Nelson

TEXTBOOK OF PEDIATRICS

Robert M. Kliegman
Joseph W. St Geme III

NATHAN J. BLUM
ROBERT C. TASKER
KAREN M. WILSON
ABIGAIL M. SCHUH
CARA L. MACK

EDITION
22

ELSEVIER

EDITION
22

Nelson

TEXTBOOK OF PEDIATRICS

Robert M. Kliegman, MD

Professor and Chair Emeritus
Department of Pediatrics
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin

NATHAN J. BLUM, MD

W.T. Grant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Developmental and Behavioral Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

ROBERT C. TASKER, MBBS, MD

Professor of Anesthesia (Pediatrics, Harvard Medical School)
Founding Chair in NeuroCritical Care
Department of Anesthesiology
Critical Care and Pain Medicine
Boston Children's Hospital
Boston, Massachusetts

KAREN M. WILSON, MD, MPH

Ruth A. Lawrence Professor of Pediatrics
Vice-Chair for Clinical and Translational Research
Department of Pediatrics
University of Rochester School of Medicine and Dentistry
Co-Director, Clinical and Translational Science Institute
Chief Research Officer, UR Medicine
Golisano Children's Hospital
Rochester, New York

Joseph W. St Geme III, MD

Professor of Pediatrics and Microbiology
Chair, Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Physician-in-Chief
Leonard and Madlyn Abramson Endowed Chair in Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

ABIGAIL M. SCHUH, MD, MMHPE

Associate Professor of Pediatrics
Division of Pediatric Emergency Medicine
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin

CARA L. MACK, MD

Professor of Pediatrics
Chief, Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin

With the assistance of

MATTHEW A. DEARDORFF, MD, PhD

Director of Translational Genomics
Division of Genomic Medicine
Department of Pathology and Laboratory Medicine
Director of Personalized Care
Children's Hospital Los Angeles
Professor of Clinical Pathology and Pediatrics
Keck School of Medicine of the University of Southern California
Los Angeles, California



ELSEVIER

To the Child's Health Care Provider
who through their expressed confidence in past editions of this book
have provided the stimulus for this revision.
May we continue to be a resource of helpful information
for clinicians who care for all of our children.

R.M. Kliegman

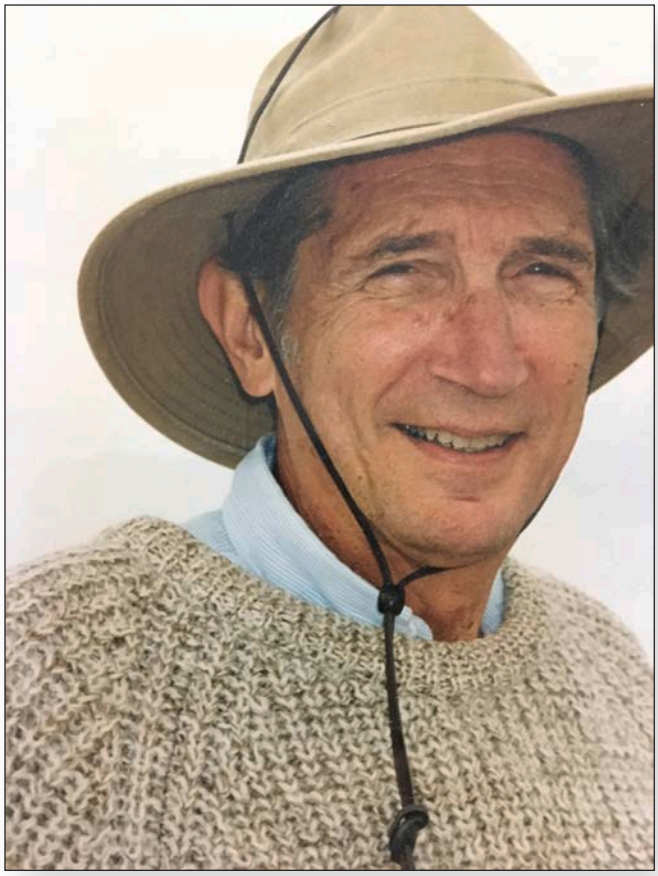

In Memory

DR. RICHARD BEHRMAN successfully served as editor of the *Nelson Textbook of Pediatrics* for 9 editions spanning over 3 decades. But more than that and without question, he excelled as an educator, a mentor, an exemplary leader in the field of pediatrics, and a role model as an investigator, clinician, department chair, dean, and director of the Packard Foundation Center for the Future of Children. Dick's career exemplifies the responsibility and critical role academic physicians must provide as child advocates by combining scholarly pursuits to advance knowledge, while seeking justice and equality for all children.

Dick always searched for expert contributors to the textbook who believed in the value of caring for all children; he recruited leading authors knowing that their approach to clinical pediatrics and to social justice would have a deeper impact and broader reach by contributing to the textbook. Because of this, *Nelson's* persists as an up-to-date authoritative global resource in not only presenting the clinical diagnosis and treatment of childhood diseases but also in identifying issues of social justice and providing solutions to improve access to health care and health outcomes. Dick's approachable intellect and intuitive nature fostered countless students, residents, and faculty allowing them to discover and nurture the best version of themselves as physicians and human beings.

Although Dick is no longer with us, his legacy persists in his selection of chapter topics and his meticulous editing of the previous chapters along with his unyielding philosophy that *Nelson* must continue to evolve while remaining a book for all children for generations to come. For those of us who know Dick as "REB" we will miss you but never forget you.

Contributors

Mark J. Abzug, MD
Professor of Pediatrics
Vice Chair for Academic Affairs
University of Colorado School of Medicine
Section of Pediatric Infectious Diseases
Children's Hospital Colorado
Aurora, Colorado
297. Nonpolio Enteroviruses

Krishna K. Acharya, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Neonatal-Perinatal Medicine
Children's Wisconsin
Milwaukee, Wisconsin
117. The Fetus
122. Nervous System Disorders
124. Transition to Newborn Pulmonary Respiration
125. Apnea
126. Respiratory Distress Syndrome (Hyaline Membrane Disease)
127. Bronchopulmonary Dysplasia
128. Transient Tachypnea of the Newborn
129. Aspiration of Foreign Material (Meconium Aspiration Syndrome, Aspiration Pneumonia)
130. Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)
131. Diaphragmatic Hernia
132. Pulmonary Air Leaks: Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium
133. Pulmonary Hemorrhage

Denise M. Adams, MD
Professor of Pediatrics
Alan R. Cohen Endowed Chair in Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Complex Vascular Anomalies Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
554. Complex Vascular Anomalies

Stewart Adelson, MD
Clinical Associate Professor
Weill Cornell Medical College
Adjunct Associate Clinical Professor
Columbia University Vagelos College of Physicians and Surgeons
New York, New York;
Senior Visiting Fellow
Yale Law School
New Haven, Connecticut
154. Gay, Lesbian, and Bisexual Adolescents

Molly C. Adrian, PhD
Associate Professor of Psychiatry and Behavioral Sciences
University of Washington School of Medicine
Attending Psychologist
Seattle Children's Hospital
Seattle, Washington
46. Self-Injurious Behavior

Shawn K. Ahlfeld, MD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Neonatology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
131.2. Paraesophageal Hernia

John J. Aiken, MD, FACS, FAAP
Professor of Surgery
Medical College of Wisconsin
Division of Pediatric General and Thoracic Surgery
Children's Wisconsin
Milwaukee, Wisconsin
391. Acute Appendicitis
394. Inguinal Hernias
420. Epigastric Hernia

Cezmi A. Akdis, MD
Professor of Immunology
University of Zurich Faculty of Medicine
Director, Swiss Institute of Allergy and Asthma Research
Zurich, Switzerland;
Christine Kühne Center for Allergy Research and Education
Davos, Switzerland
182. Allergy and the Immunologic Basis of Atopic Disease

Daniah Albokhari, MBBS
Department of Pediatrics
Division of Human Genetics
Section of Metabolism
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania;
Department of Pediatrics
Taibah University College of Medicine
Medina, Saudi Arabia
735. General Considerations in Skeletal Dysplasias
736. Disorders Involving Cartilage Matrix Proteins
737. Disorders Involving Transmembrane Receptors
738. Disorders Involving Ion Transporters
739. Disorders Involving Transcription Factors
740. Osteopetrosis and Other Disorders Involving Defective Bone Resorption
741. Other Inherited Disorders of Skeletal Development

Elizabeth M. Alderman, MD
Professor of Pediatrics
Professor of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine
Chief, Division of Adolescent Medicine
Children's Hospital at Montefiore
Bronx, New York
160. Contraception

Omar Ali, MD
Pediatric Endocrinologist
Division of Pediatric Endocrinology
Valley Children's Hospital
Madera, California
598. Hyperpituitarism
623. Hypofunction of the Testes
624. Pseudoprecocity Resulting From Tumors of the Testes
625. Gynecomastia

Wendy A. Allen-Rhoades, MD, PhD
Assistant Professor
Division of Pediatric Hematology-Oncology
Mayo Clinic
Rochester, Minnesota
549. Soft Tissue Sarcomas
550.1. Malignant Tumors of Bone

Nourah N. Almutlaq, MBBS
Division of Pediatric Endocrinology
Indiana University School of Medicine
Riley Hospital for Children
Indianapolis, Indiana
747. Hypophosphatasia
748. Hyperphosphatasia

Louella B. Amos, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pulmonary and Sleep Medicine
Children's Wisconsin
Milwaukee, Wisconsin
450. E-Cigarette or Vaping Product Use–Associated Lung Injury (EVALI)

Jason B. Anari, MD
Assistant Professor of Orthopedic Surgery
University of Pennsylvania Perelman School of Medicine
Division of Pediatric Orthopedics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
724. Common Fractures

Karl E. Anderson, MD, FACP
Professor of Internal Medicine
Director, Porphyria Laboratory and Center
University of Texas Medical Branch
Galveston, Texas
112. The Porphyrias

Sudha A. Anupindi, MD, FSAR
Professor of Radiology
Kenneth E. Fellows Endowed Chair in Radiology Quality and Safety
Associate Radiologist-in-Chief
Director of the Section of Gastrointestinal and Hepatic Imaging
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
382. Inflammatory Bowel Disease

Brian S. Appleby, MD
Professor of Neurology, Psychiatry, and Pathology
Case Western Reserve University School of Medicine
Director, National Prion Disease Pathology Surveillance Center
University Hospitals Cleveland Medical Center
Cleveland, Ohio
324. Transmissible Spongiform Encephalopathies

Stacy P. Ardoin, MD, MHS
Professor of Clinical Medicine
Division of Adult and Pediatric Rheumatology
The Ohio State University Wener Medical Center
Chief, Division of Pediatric Rheumatology
Nationwide Children's Hospital
Columbus, Ohio
199. Systemic Lupus Erythematosus
210. Vasculitis Syndromes

Alexandre Arkader, MD
Attending Surgeon
Department of Orthopaedics
Division of Oncology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
724. Common Fractures

Thaís Armangué, MD, PhD
Head of the Pediatric Neuroimmunology Unit, Service of Neurology
Sant Joan de Déu Children's Hospital
Principal Investigator at Neuroimmunology Program
IDIBAPS-Hospital Clinic
University of Barcelona
Barcelona, Spain
638.4. Autoimmune Encephalitis

Carola A.S. Arndt, MD
Professor of Pediatrics
Division of Pediatric Hematology-Oncology
Mayo Clinic
Rochester, Minnesota
549. Soft Tissue Sarcomas
550. Neoplasms of Bone

Danielle E. Arnold, MD
Assistant Research Physician
Immune Deficiency Cellular Therapy Program
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, Maryland
174. Immune Dysregulation

Adrianne R. Artis, MD
Assistant Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences
Child and Adolescent Protection Center
Children's National Hospital
Washington, DC
162. Adolescent Sexual Assault

David M. Asher, MD
Former Supervisory Medical Officer and Chief
Laboratory of Bacterial and Transmissible Spongiform Encephalopathy Agents (Retired)
Division of Emerging and Transfusion Transmitted Diseases
US Food and Drug Administration
Silver Spring, Maryland
324. Transmissible Spongiform Encephalopathies

Barbara L. Asselin, MD
Professor of Pediatrics and Oncology
University of Rochester School of Medicine and Dentistry
Department of Pediatrics
Golisano Children's Hospital and
Wilmot Cancer Institute
Rochester, New York
540. Epidemiology of Childhood and Adolescent Cancer

Christina M. Astley, MD, ScD
Assistant Professor of Pediatrics
Harvard Medical School
Attending Physician
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts
608. Autoimmune Polyglandular Syndromes

Norrell K. Atkinson, MD, FAAP
Assistant Professor of Pediatrics
Drexel University College of Medicine
Child Protection Program
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
162. Adolescent Sexual Assault

Erika F. Augustine, MD, MS
Associate Chief Science Officer
Kennedy Krieger Institute
Baltimore, Maryland
637.4. Dystonia

Marilyn C. Augustyn, MD
Professor of Pediatrics
Boston University Aram V. Chobanian & Edward Avedisian School of Medicine
Division Director, Developmental-Behavioral Pediatrics
Boston Medical Center
Boston, Massachusetts
15. Impact of Violence Exposure on Children

Leonard B. Bacharier, MD, FAAAAI
Janie Robinson and John Moore Lee Chair in Pediatrics
Professor of Pediatrics and Allergy, Immunology, and Pulmonary Medicine
Scientific Director
Center for Clinical and Translational Research
Vanderbilt University School of Medicine
Attending Physician
Division of Pediatric Allergy and Immunology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee
185. Childhood Asthma

Carlos A. Bacino, MD
Professor and Vice Chair of Clinical Affairs
Department of Molecular and Human Genetics
Medical Director, Baylor Genetics, Cytogenetics Laboratory
Baylor College of Medicine
Director, Pediatrics Genetics Clinic
Texas Children's
Houston, Texas
99. Chromosome Disorders

Zinzi D. Bailey, ScD, MSPH
Social Epidemiologist and Research Assistant Professor
University of Miami Miller School of Medicine
Managing Director
Health Equity Research Solutions, LLC
Miami, Florida
2.1. Racism and Child Health

Frances B. Balamuth, MD, PhD, MSCE
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Director of Research
Division of Emergency Medicine
Co-Director, Pediatric Sepsis Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
78. Triage of the Acutely Ill Child

Robert N. Baldassano, MD
Professor of Pediatrics
Colman Family Chair in Pediatric Inflammatory Bowel Disease
University of Pennsylvania Perelman School of Medicine
Co-Director, Center for Pediatric Inflammatory Bowel Disease
Director, CHOP Microbiome Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
382. Inflammatory Bowel Disease
383. Eosinophilic Gastroenteritis

Keith D. Baldwin, MD, MSPT, MPH
Associate Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Director, Orthopedic Trauma
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
720. The Spine
721. The Neck

Christina B. Bales, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology, and Nutrition
Medical Director, Intestinal Rehabilitation Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
376. Intestinal Atresia, Stenosis, and Malrotation

William F. Balistreri, MD
Dorothy M. M. Kersten Professor of Pediatrics
University of Cincinnati College of Medicine
Director Emeritus, Pediatric Liver Care Center
Medical Director Emeritus, Liver Transplantation
Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
402. Morphogenesis of the Liver and Biliary System
403. Manifestations of Liver Disease
404. Cholestasis
405. Metabolic Diseases of the Liver
406. Viral Hepatitis
408. Liver Disease Associated with Systemic Disorders
409. Mitochondrial Hepatopathies

Manisha Balwani, MD, MS, FACMG
Professor and Chief
Division of Medical Genetics and Genomics
Icahn School of Medicine at Mount Sinai
Department of Genetics and Genomic Sciences
New York, New York
112. The Porphyrias

Vaneeta Bamba, MD
Professor of Clinical Pediatrics
Division of Endocrinology
University of Pennsylvania Perelman School of Medicine
Medical Director, Diagnostic and Research Growth Center
Children' s Hospital of Philadelphia
Philadelphia, Pennsylvania
27. Assessment of Growth

Aleena Banerji, MD
Associate Professor of Medicine
Drug and Vaccine Allergy Center of Excellence
Director of Clinical Care
Clinical Director, Allergy and Immunology Unit
Massachusetts General Hospital
Boston, Massachusetts
189. Urticaria (Hives) and Angioedema

Janet Y. Bang, PhD
Assistant Professor of Child and Adolescent Development
San Jose State University
Connie L. Lurie College of Education
San Jose, California
53. Language Development and Communication Disorders

Nikita Barai, MD
Assistant Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, New York
152. Transitioning to Adult Care

Katherine Baranowski, MD
Assistant Professor of Pediatrics
Chief, Division of Pediatric Emergency Medicine
Rutgers University New Jersey Medical School
Newark, New Jersey
762. Nonbacterial Food Poisoning

Sarah F. Barclay, PhD
Lead Genome Analyst
TIGeR: Translational Implementation of Genomics for Rare Diseases
University of Calgary and Alberta Precision Labs
Cumming School of Medicine at University of Calgary
Calgary, Alberta, Canada
468.3. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Elizabeth Barkoudah, MD
Instructor in Neurology
Harvard Medical School
Co-Director, Cerebral Palsy and Spasticity Center
Director, Neurodevelopmental Disabilities Residency Training Program
Boston Children's Hospital
Boston, Massachusetts
638. Encephalopathies
638.1. Cerebral Palsy

Alejandra Barrero-Castillero, MD, MPH
Instructor in Pediatrics
Harvard Medical School
Division of Newborn Medicine
Boston Children's Hospital
Boston, Massachusetts
114. Overview of Morbidity and Mortality

Katherine J. Barrett, PhD
Postdoctoral Fellow
University of Colorado School of Medicine
Section of Pediatric Nutrition
Aurora, Colorado
61. Feeding Healthy Infants, Children, and Adolescents

Karyl S. Barron, MD
Deputy Director, Division of Intramural Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland
206. Amyloidosis

Donald Basel, MBBCh
Professor of Pediatrics
Chief, Division of Medical Genetics
Medical College of Wisconsin
Milwaukee, Wisconsin
744. Ehlers-Danlos Syndrome

Dorsey M. Bass, MD
Associate Professor of Pediatrics Emeritus
Stanford University School of Medicine
Division of Pediatric Gastroenterology
Lucile Salter Packard Children's Hospital
Palo Alto, California
312. Rotaviruses, Caliciviruses, and Astroviruses

Mary T. Bassett, MD, MPH
Commissioner, New York State Department of Health
Albany, New York;
FXB Professor and Director
FXB Center for Health and Human Rights
Harvard T.H. Chan School of Public Health
Boston, Massachusetts;
Associate Professor of Clinical Epidemiology
Columbia University Mailman School of Public Health
New York, New York
2.1. Racism and Child Health

Hamid Bassiri, MD, PhD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician and Fellowship Program Director
Division of Infectious Diseases
Co-Director, Immune Dysregulation Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
235. Actinomyces

Rebecca A. Baum, MD
Clinical Professor of Pediatrics
Division of General Pediatrics and Adolescent Medicine
Section of Development, Behavior, and Learning
University of North Carolina School of Medicine
Chapel Hill, North Carolina
20. Positive Parenting and Support

Edward M. Behrens, MD
Associate Professor of Pediatrics
Joseph Lee Hollander Chair in Pediatric Rheumatology
University of Pennsylvania Perelman School of Medicine
Chief, Division of Rheumatology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
207. Macrophage Activation Syndrome

Michael J. Bell, MD
Professor, Pediatrics and Critical Care Medicine
Chief, Critical Care Medicine
Children's National Medical Center
The George Washington University School of Medicine
Washington, DC
82. Neurologic Emergencies and Stabilization

Daniel K. Benjamin Jr., MD, PhD, MPH
Kiser-Arena Professor of Pediatrics
Duke Clinical Research Institute
Duke University Medical Center
Durham, North Carolina
280. Candida

Amanda E. Bennett, MD, MPH
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Associate Chief, Division of Developmental and Behavioral Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
59. Fragile X Syndromes

Jenna R.E. Bergerson, MD, MPH
Director, Allergy Immunology Consult Service
Associate Program Director, Allergy and Immunology Fellowship Training Program
Primary Immunodeficiency Clinic
Laboratory of Clinical Immunology and Microbiology
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland
175. Defects of Innate Immunity

Daniel Bernstein, MD
Alfred Woodley Salter and Mabel G. Salter Endowed Professor of Pediatrics
Division of Pediatric Cardiology
Associate Dean for Curriculum and Scholarship
Stanford University School of Medicine
Palo Alto, California
469. Cardiac Development
470. The Fetal to Neonatal Circulatory Transition
471. History and Physical Examination in Cardiac Evaluation
472. Laboratory Cardiac Evaluation
473. Epidemiology and Genetic Basis of Congenital Heart Disease
474. Evaluation and Screening of the Infant or Child With Congenital Heart Disease
475. Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions
476. Acyanotic Congenital Heart Disease: Obstructive Lesions
477. Acyanotic Congenital Heart Disease: Regurgitant Lesions
478. Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate With Cyanosis and Respiratory Distress
479. Cyanotic Congenital Heart Disease: Lesions Associated With Decreased Pulmonary Blood Flow
480. Cyanotic Congenital Heart Disease: Lesions Associated With Increased Pulmonary Blood Flow
481. Other Congenital Heart and Vascular Malformations
482. Pulmonary Hypertension
483. General Principles of Treatment of Congenital Heart Disease
493.1. Aneurysms
493.2 Arteriovenous Fistulas

Henry H. Bernstein, DO, MHCM, FAAP
Professor of Pediatrics
Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center
New Hyde Park, New York
215. Immunization Practices

Brittany J. Bice-Urbach, PhD
Assistant Professor of Pediatrics
Medical College of Wisconsin
Child Development Center
Children's Wisconsin
Milwaukee, Wisconsin
52. Math and Writing Disabilities

Brett P. Bielory, MD
Medical Director
Department of Ophthalmology
OPTUM Tri-State (NJ)
Rutherford, New Jersey;
Adjunct Clinical Surgeon
Department of Ophthalmology
New York Eye and Ear Infirmary
Mount Sinai School of Medicine
New York, New York;
Associate Professor
Department of Ophthalmology
Hackensack Meridian School of Medicine
Nutley, New Jersey
188. Ocular Allergies

Leonard Bielory, MD
Professor of Medicine, Allergy, Immunology, and Ophthalmology
Hackensack Meridian School of Medicine
Nutley, New Jersey
188. Ocular Allergies

Samra S. Blanchard, MD
Associate Professor of Pediatrics
Division Chief, Pediatric Gastroenterology
University of Maryland School of Medicine
Baltimore, Maryland
381. Peptic Ulcer Disease in Children

Eliza Blanchette, MD
Assistant Professor of Pediatrics
Renal Section, Department of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado
568. Tubular Function

Joshua A. Blatter, MD, MPH
Associate Professor of Pediatrics, Allergy, Immunology, and Pulmonary Medicine
Researcher, Patient Oriented Research Unit
Washington University School of Medicine in St. Louis
Associate Director, Pediatric Lung Transplantation Center
St. Louis Children's Hospital
St. Louis, Missouri
444. Congenital Disorders of the Lung

Archie Bleyer, MD, FRCP (Glasg)
Clinical Research Professor
Knight Cancer Center
Oregon Health & Science University
Chair, Institutional Review Board for St. Charles Health System
Portland, Oregon;
Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
543. Principles of Cancer Treatment
544. The Leukemias

Steven R. Boas, MD, FAAP, FACSM
Clinical Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Chicago, Illinois;
Director, The Cystic Fibrosis Center of Chicago
Glenview, Illinois;
Director, Illinois Sports Science Institute
President and CEO, The Cystic Fibrosis Institute
Northfield, Illinois
441. Emphysema and Overinflation
442. α1-Antitrypsin Deficiency and Emphysema
443. Other Distal Airway Diseases
467. Skeletal Diseases Influencing Pulmonary Function

Margret E. Bock, MD, MS
Associate Professor of Pediatrics
Renal Section, Department of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado
570. Nephrogenic Diabetes Insipidus

Sarah R. Boggs, MD
Associate Professor of Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia
429. Sinusitis
432. Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

Michael J. Boivin, PhD, MPH
University Distinguished Professor of Psychiatry, Neurology, and Ophthalmology
Director, Psychiatry Research Program
Michigan State University College of Human Medicine
East Lansing, Michigan
633.10. Nodding Syndrome

Julie Bonn, MD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
405. Metabolic Diseases of the Liver

Daniel J. Bonthius, MD, PhD
Clinical Professor of Neurology
Wake Forest University School of Medicine
Winston-Salem, North Carolina;
Medical Director, Pediatric Neurology
Levine Children's Hospital
Charlotte, North Carolina
318. Lymphocytic Choriomeningitis Virus

Suresh B. Boppana, MD
Hugh Dillon Professor of Pediatrics
Professor of Microbiology
University of Alabama Heersink School of Medicine
Birmingham, Alabama
302. Cytomegalovirus

Brett J. Bordini, MD, FAAP
Associate Professor of Pediatrics
Section of Hospital Medicine
Nelson Service for Undiagnosed and Rare Diseases
Medical College of Wisconsin
Milwaukee, Wisconsin
440. Plastic Bronchitis

Alexandra J. Borst, MD
Clinical Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
554. Complex Vascular Anomalies

Kristopher R. Bosse, MD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Pediatric Oncology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
541. Molecular and Cellular Biology of Cancer

Kenneth M. Boyer, MD
Professor and Woman's Board Chair Emeritus
Department of Pediatrics
Rush University Medical Center
Chicago, Illinois
336. Toxoplasmosis (Toxoplasma gondii)

Patrick W. Brady, MD, MSc
Professor of Pediatrics
University of Cincinnati College of Medicine
Research Director, Division of Hospital Medicine
James M. Anderson Center for Health Services Excellence
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
5. Safety in Healthcare for Children

Rebecca C. Brady, MD
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Adult Clinical Studies
Vaccine Research Center
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
286. Coccidioidomycosis (Coccidioides Species)

Samuel L. Brady, MS PhD, FAAPM
Associate Professor of Radiology
University of Cincinnati College of Medicine
Section Chief Clinical Medical Physicist
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
758. Biologic Effects of Ionizing Radiation on Children

Brian R. Branchford, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Hematology/Oncology
Children's Wisconsin
Associate Medical Director
Versiti Medical Sciences Institute
Associate Investigator
Versiti Blood Research Institute
Milwaukee, Wisconsin
524. Hemostasis
525. Hereditary Clotting Factor Deficiencies (Bleeding Disorders)
526. Von Willebrand Disease
528. Thrombotic Disorders in Children
529. Postneonatal Vitamin K Deficiency
530. Coagulopathy in Liver Disease
531. Acquired Inhibitors of Coagulation
533. Platelet and Blood Vessel Disorders

Amanda M. Brandow, DO, MS
Professor of Pediatrics
Section of Hematology/Oncology/Bone Marrow Transplantation
Medical College of Wisconsin
Milwaukee, Wisconsin
512. Enzymatic Defects
513. Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias
514. Hemolytic Anemias Secondary to Other Extracellular Factors
515. Polycythemia
516. Nonclonal Polycythemia
534. Anatomy and Function of the Spleen
535. Splenomegaly
536. Hyposplenism, Splenic Trauma, and Splenectomy

Erik Brandsma, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Medical Director of Medicine and Transport
Medical Director of the Infant Breathing Disorder Center
Newborn/Infant Intensive Care Unit
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
119. The High-Risk Infant

David T. Breault, MD, PhD
Associate Professor of Pediatrics
Harvard Medical School
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts
596. Diabetes Insipidus
597. Other Abnormalities of Arginine Vasopressin Metabolism and Action

Cora Collette Breuner, MD, MPH, FAAP
Professor of Pediatrics
Adjunct Professor of Orthopedics and Sports Medicine
University of Washington School of Medicine
Division of Adolescent Medicine
Department of Orthopedics and Sports Medicine
Seattle Children's Hospital
Seattle, Washington
157. Substance Use Disorder
161. Adolescent Pregnancy

Carolyn F. Bridgemohan, MD
Associate Professor of Pediatrics
Harvard Medical School
Co-Director Autism Spectrum Center
Division of Developmental Medicine
Boston Children's Hospital
Boston, Massachusetts
58. Autism Spectrum Disorder

William J. Britt, MD
Charles A. Alford Professor of Pediatrics
Professor of Microbiology
University of Alabama Heersink School of Medicine
Birmingham, Alabama
302. Cytomegalovirus

Laura Brower, MD, MSc
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Physician
Division of Hospital Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
220. Fever Without a Focus in the Neonate and Young Infant
221. Fever in the Older Child

Maria D. Brown, MD, MA
Assistant Professor of Pediatrics
The Ohio State University College of Medicine
Attending Physician
Section of Adolescent Medicine
Nationwide Children's Hospital
Columbus, Ohio
150. Adolescent Physical and Social Development

Jefferson N. Brownell, MD, MS
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
389. Disorders of Brain-Gut Interaction (Functional Gastrointestinal Disorders)

Meghen B. Browning, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Hematology-Oncology
Children's Wisconsin
Milwaukee, Wisconsin
401. Pancreatic Tumors

Nicola Brunetti-Pierri, MD
Professor of Medical Genetics
University of Naples Federico II
Naples, Italy;
Principal Investigator
Telethon Institute of Genetics and Medicine (TIGEM)
Pozzuoli, Italy
98. Integration of Genetics into Pediatric Practice

Supinda Bunyavanich, MD, MPH, MPhil
Professor of Pediatrics
Professor of Genetics & Genomic Sciences
Mount Sinai Endowed Professor in Allergy and Systems Biology
Deputy Director, Jaffe Food Allergy Institute
Icahn School of Medicine at Mount Sinai
New York, New York
183. Diagnosis of Allergic Disease

Danielle S. Burstein, MD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Pediatric Cardiology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
491. Heart Failure
492. Pediatric Heart and Heart-Lung Transplantation

Amaya L. Bustinduy, MD, PhD, MPH
Professor of Global Paediatric and Adolescent Infectious Diseases
Chair, Global Paediatric and Adolescent Infectious Diseases
Department of Clinical Research
London School of Hygiene and Tropical Medicine
London, United Kingdom
346. Schistosomiasis (Schistosoma)
347. Flukes (Liver, Lung, and Intestinal)

Jill P. Buyon, MD
Sir Deryck and Lady Va Maughan Professor of Rheumatology
New York University Grossman School of Medicine
Co-Director, Colton Center for Autoimmunity, Director, Division of Rheumatology, Director, Lupus Center
NYU Langone Health
New York, New York
199.1. Neonatal Lupus

Miguel M. Cabada, MD, MSc
Associate Professor of Medicine
Division of Infectious Diseases
The University of Texas Medical Branch at Galveston
Galveston, Texas
349. Cysticercosis
350. Echinococcosis (Echinococcus granulosus sensu lato and Echinococcus multilocularis)

Michaela Cada, MD, FRCPC, FAAP, MPH
Associate Professor of Paediatrics
University of Toronto Faculty of Medicine
Division of Hematology/Oncology
The Hospital for Sick Children
Toronto, Ontario
517. Inherited Bone Marrow Failure Syndromes With Pancytopenia

Mitchell S. Cairo, MD
Professor of Pediatrics, Medicine, Pathology, Microbiology & Immunology and Cell Biology & Anatomy
Chief, Pediatric Hematology, Oncology, and Stem Cell Transplantation
Director, WMC Cancer Center
Medical and Scientific Director, WMC Cellular and Tissue Engineering Laboratory
Medical Director, WMC Hematology Program
Vice Chairman, Department of Pediatrics
Maria Fareri Children's Hospital
Westchester Medical Center
New York Medical College
Valhalla, New York
545. Lymphoma

Diane P. Calello, MD
Professor of Emergency Medicine
Executive Director, Center for Emerging and Re-Emerging Pathogens
Rutgers University New Jersey Medical School
Executive and Medical Director
New Jersey Poison Information and Education System
Newark, New Jersey
762. Nonbacterial Food Poisoning

Lindsay H. Cameron, MD, MPH
Pediatrician, Pediatric Infectious Diseases
Texas Children's
Houston, Texas
261. Tuberculosis (Mycobacterium tuberculosis)

Angela J.P. Campbell, MD, MPH
Medical Officer
Epidemiology and Prevention Branch, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia
306. Parainfluenza Viruses

Margo Candelaria, PhD
Research Assistant Professor and Research Director
Co-Director, Parent Infant Early Childhood (PIEC) Institute for Innovation and Implementation
University of Maryland School of Social Work
Baltimore, Maryland
19. Developmental and Behavioral Theories

Laura Cannon, MD
Assistant Professor of Pediatrics
Division of Pediatric Rheumatology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
209. Sarcoidosis

Rebecca F. Carlin, MD
Assistant Professor of Pediatrics
Columbia University Vagelos College of Physicians and Surgeons
Division of Hospital Medicine
Columbia University Irving Medical Center
New York, New York
423. Sudden Infant Death Syndrome

James G. Carlucci, MD, MPH
Assistant Professor of Pediatrics
Ryan White Center for Pediatric Infectious Diseases and Global Health
Indiana University School of Medicine
Indianapolis, Indiana
218. Health Advice for Children Traveling Internationally

Michael R. Carr, MD
Associate Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Division of Cardiology
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
487. Rheumatic Heart Disease

Robert B. Carrigan, MD
Associate Professor of Clinical Orthopedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Hand and Upper Extremity Surgeon
Attending Surgeon, Hand Transplantation Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
722. The Upper Limb

Rebecca G. Carter, MD
Assistant Professor of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland
24. The Second Year
25. The Preschool Years

Gail V. Carter-Hamilton, MSN, RN, CSN
Chief Racial Equity Officer
Philadelphia Department of Public Health
Philadelphia, Pennsylvania
217. Childcare and Communicable Diseases

Abigail Case, MD
Assistant Professor of Clinical Pediatrics and Physical Medicine and Rehabilitation
Associate Fellowship Director
Attending Physician
Division of Rehabilitation Medicine
Department of Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
751. Spinal Cord Injury and Autonomic Dysreflexia Management
755. Upper and Lower Extremity Assistive Devices

Pearl W. Chang, MD
Assistant Professor of Pediatrics
University of Washington School of Medicine
Division of Hospital Medicine
Seattle Children's Hospital
Seattle, Washington
575. Urinary Tract Infections

Gisela G. Chelimsky, MD
Professor of Pediatrics
Division of Pediatric Gastroenterology
Children's Hospital of Richmond and Virginia Commonwealth University
Richmond, Virginia
84.1. Postural Tachycardia Syndrome
212. Chronic Overlapping Pain Conditions

Thomas Chelimsky, MD
Professor of Neurology
Virginia Commonwealth University
Richmond, Virginia
84.1. Postural Tachycardia Syndrome
212. Chronic Overlapping Pain Conditions

Wassim Chemaitilly, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Clinical Director
Division of Pediatric Endocrinology
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
599. Physiology of Puberty
600. Disorders of Pubertal Development

Kathleen Chiotos, MD, MSCE
Assistant Professor of Anesthesiology, Critical Care, and Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Divisions of Critical Care Medicine and Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
226. Antimicrobial Stewardship

Yvonne E. Chiu, MD
Vice Chair and Professor of Dermatology
Division of Pediatric Dermatology
Professor of Pediatrics
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin
686. Morphology of the Skin
686. Dermatologic Evaluation of the Patient
696. Eczematous Disorders
697. Photosensitivity
698. Diseases of the Epidermis
700. Diseases of the Dermis
701. Diseases of Subcutaneous Tissue

Hey Jin Chong, MD, PhD
Associate Professor of Pediatrics
University of Pittsburgh School of Medicine
Chief, Division of Pediatric Allergy and Immunology
Director, Immune Dysregulation Diagnosis and Treatment Program
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
223. Infections in Immunocompromised Persons

Stella T. Chou, MD
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Transfusion Medicine
Attending Physician, Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
495. Development of the Hematopoietic System

Lori A. Christ, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Medical Director of Intensive Care Nursery
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
119. The High-Risk Infant

John C. Christenson, MD, FAAP, FIDSA, FPIDS
Professor of Clinical Pediatrics
Ryan White Center for Pediatric Infectious Diseases and Global Health
Indiana University School of Medicine
Indianapolis, Indiana
218. Health Advice for Children Traveling Internationally

Ankur A. Chugh, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Gastroenterology
Children's Wisconsin
Milwaukee, Wisconsin
384. Celiac Disease

Theodore J. Cieslak, MD, MPH, FAAP, FIDSA
Professor of Epidemiology and Pediatrics
Co-Medical Director, Nebraska Biocontainment Unit
University of Nebraska Medical Center
Omaha, Nebraska
763. Biological and Chemical Terrorism

Donna J. Claes, MD, MS
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Nephrology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
572.2. Chronic Kidney Disease
572.3. End-Stage Kidney Disease

Thomas D. Coates, MD
Section Head, Hematology
Cancer and Blood Disease Institute
Professor of Pediatrics and Pathology
University of Southern California Keck School of Medicine
Childrens Hospital Los Angeles
Los Angeles, California
168. Neutrophils
170. Disorders of Phagocyte Function

María I. Sánchez Códez, MD
Departamento de Pediatría
Unidad de Infectología Pediátrica
Hospital Universitario Puerta del Mar
Cádiz, Spain
270. Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma urealyticum)

Susan E. Coffin, MD, MPH
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Distinguished Chair in the Department of Pediatrics
Associate Hospital Epidemiologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
217. Childcare and Communicable Diseases

Mitchell B. Cohen, MD
Katharine Reynolds Ireland Endowed Chair in Pediatrics
Professor and Chair, Department of Pediatrics
University of Alabama at Birmingham School of Medicine
Physician-in-Chief
Children's of Alabama
Birmingham, Alabama
258. Clostridioides difficile Infection

Susan S. Cohen, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Neonatal-Perinatal Medicine
Children's Wisconsin
Milwaukee, Wisconsin
117. The Fetus
122. Nervous System Disorders
124. Transition to Newborn Pulmonary Respiration
125. Apnea
126. Respiratory Distress Syndrome (Hyaline Membrane Disease)
127. Bronchopulmonary Dysplasia
128. Transient Tachypnea of the Newborn
129. Aspiration of Foreign Material (Meconium Aspiration Syndrome, Aspiration Pneumonia)
130. Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)
131. Diaphragmatic Hernia
132. Pulmonary Air Leaks: Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium
133. Pulmonary Hemorrhage

F. Sessions Cole III, MD
Assistant Vice-Chancellor for Children's Health
Park J. White Professor of Pediatrics
Professor of Cell Biology and Physiology
Washington University School of Medicine in St. Louis
Chief Medical Officer
Vice-Chairman, Department of Pediatrics
Director of Newborn Medicine
St. Louis Children's Hospital
St. Louis, Missouri
456. Diffuse Lung Diseases in Childhood

J. Michael Collaco, MD, MS, MBA, MPH, PhD
Associate Professor of Pediatrics
Eudowood Division of Pediatric Respiratory Sciences
Johns Hopkins University School of Medicine
Baltimore, Maryland
466. Bronchopulmonary Dysplasia

James W. Collins Jr., MD, MPH
Professor of Pediatrics (Neonatology)
Northwestern University Feinberg School of Medicine
Medical Director, Neonatal Intensive Care Unit
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
114.1. Race, Class, and Birth Outcomes

Joseph A. Congeni, MD
Director, Sports Medicine Center
Akron Children's Hospital
Akron, Ohio;
Professor of Pediatrics
Northeast Ohio Medical University
Rootstown, Ohio;
Clinical Associate Professor of Pediatrics and Sports Medicine
Ohio University College of Osteopathic Medicine
Athens, Ohio
730. Cervical Spine Injuries

Máire A. Conrad, MD, MS
Assistant Professor of Pediatrics
Division of Gastroenterology, Hepatology, and Nutrition
University of Pennsylvania Perelman School of Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
377. Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

Justin N. Corcoran, MD
Assistant Professor of Emergency Medicine
Medical College of Wisconsin
Medical Toxicologist
Wisconsin Poison Center
Milwaukee, Wisconsin
94. Poisoning

Alexandra M.S. Corley, MD, MPH
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Physician, Division of General and Community Pediatrics
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
12. Cultural Issues in Pediatric Care

Amanda L. Cox, MD
Associate Professor of Pediatrics
Icahn School of Medicine at Mount Sinai
Division of Pediatric Allergy and Immunology
Mount Sinai Kravis Children's Hospital
New York, New York
192. Food Allergy and Adverse Reactions to Foods

Anne M. Coyle, MD
Lewis Katz School of Medicine at Temple University
Philadelphia, Pennsylvania
718. The Knee

Tamera Coyne-Beasley, MD, MPH, FAAP, FSAHM
Professor of Pediatrics and Internal Medicine
Derrol Dawkins MD Endowed Chair in Adolescent Medicine
Vice Chair, Pediatrics for Community Engagement
Children's of Alabama
The University of Alabama at Birmingham
Birmingham, Alabama
151. Delivery of Healthcare to Adolescents
155. The Epidemiology of Adolescent Health Problems
163. Sexually Transmitted Infections

Sansanee S. Craig, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician, Division of General Pediatrics
Department of Biomedical and Health Informatics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
3. Global Child Health

Sarah M. Creighton, MD, FRCOG
Consultant Gynaecologist and Honorary Clinical Professor
Department of Women's Health
University College London Hospitals
London, United Kingdom
593. Female Genital Mutilation

Chad B. Crigger, MD, MPH
Division of Pediatric Urology
Johns Hopkins University Medical Center
Baltimore, Maryland
574. Congenital Anomalies and Dysgenesis of the Kidneys
576. Vesicoureteral Reflux
577. Obstruction of the Urinary Tract
578. Anomalies of the Bladder
579. Neuropathic Bladder
580. Enuresis and Voiding Dysfunction
581. Anomalies of the Penis and Urethra
582. Disorders and Anomalies of the Scrotal Contents
583. Trauma to the Genitourinary Tract
584. Urinary Lithiasis

James E. Crowe Jr., MD
Professor Pediatrics and Pathology, Microbiology and Immunology
Vanderbilt University School of Medicine
Director, Vanderbilt Vaccine Center
Ann Scott Carell Chair
Vanderbilt University Medical Center
Nashville, Tennessee
307. Respiratory Syncytial Virus
308. Human Metapneumovirus

Gabriel Culbert, PhD, RN
Associate Professor of Nursing
Department of Population Health Nursing Science
University of Illinois at Chicago College of Nursing
Chicago, Illinois
114.1. Race, Class, and Birth Outcomes

Steven J. Czinn, MD
Drs. Rouben and Violet Jiji Endowed Professor
Chair, Department of Pediatrics
University of Maryland School of Medicine
Director, University of Maryland Children's Hospital
Baltimore, Maryland
381. Peptic Ulcer Disease in Children

Aarti S. Dalal, DO, CEPS-P
Assistant Professor of Pediatrics
Vanderbilt University School of Medicine
Associate Director, Pediatric Electrophysiology
Division of Cardiology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee
84. Syncope
484. Disturbances of Rate and Rhythm of the Heart
485. Sudden Death

Josep Dalmau, MD, PhD
Research Professor ICREA-IDIBAPS
Service of Neurology
Hospital Clinic
University of Barcelona
Barcelona, Spain;
Adjunct Professor of Neurology
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania
638.4. Autoimmune Encephalitis

Lynn A. D'Andrea, MD
Professor of Pediatrics
Medical College of Wisconsin
Chief, Division of Pulmonary and Sleep Medicine
Children's Wisconsin
Milwaukee, Wisconsin
450. E-Cigarette or Vaping Product Use–Associated Lung Injury (EVALI)

Lara A. Danziger-Isakov, MD, MPH
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Immunocompromised Host Infectious Disease
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
284. Histoplasmosis (Histoplasma capsulatum)

Toni Darville, MD
Distinguished Professor of Pediatrics and Microbiology and Immunology
University of North Carolina School of Medicine at Chapel Hill
Chief, Division of Infectious Diseases
Vice-Chair of Pediatric Research
Department of Pediatrics
Scientific Director, Children's Research Institute
North Carolina Children's Hospital
Chapel Hill, North Carolina
238. Neisseria gonorrhoeae (Gonococcus)

Richard J. David, MD
Professor of Pediatrics
University of Illinois at Chicago College of Medicine
Co-Director, Neonatal Intensive Care Unit (retired)
Stroger Hospital of Cook County
Chicago, Illinois
114.1. Race, Class, and Birth Outcomes

Katharine Davidoff, MD
Attending Physician, Pediatric Palliative Care
Massachusetts General Hospital for Children (MGHfC)
Boston, Massachusetts
8. Pediatric Palliative Care

Loren T. Davidson, MD
Health Sciences Clinical Professor of Physical Medicine and Rehabilitation
UC Davis School of Medicine
Director, Spinal Cord Injury
Shriners Hospital for Children
Sacramento, California
752. Spasticity

Richard S. Davidson, MD
Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Children's Hospital of Philadelphia Endowed Chair in Pediatric Orthopaedic Surgery
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
715. The Foot and Toes
717. Leg-Length Discrepancy
723. Arthrogryposis

H. Dele Davies, MD, MS, MHCM
Senior Vice Chancellor for Academic Affairs
Dean for Graduate Studies
University of Nebraska Medical Center
Omaha, Nebraska
241. Chancroid (Haemophilus ducreyi)
264. Syphilis (Treponema pallidum)
265. Nonvenereal Treponemal Infections
266. Leptospira
267. Relapsing Fever (Borrelia)

Stephanie D. Davis, MD
Edward C. Curnen Jr Distinguished Professor and Chair
Department of Pediatrics
The University of North Carolina at Chapel Hill School of Medicine
Physician-in-Chief
UNC Children's Hospital
Chapel Hill, North Carolina
448.1. Hypersensitivity Pneumonia
448.2. Occupational and Environmental Lung Disease
448.3. Granulomatous Lung Disease
448.4. Eosinophilic Lung Disease
448.5. Interstitial Lung Disease

Christina Davis-Kankanamge, MD
Assistant Professor of Obstetrics and Gynecology
Baylor College of Medicine
Department of Pediatric and Adolescent Gynecology
Texas Children's
Houston, Texas
587. Vaginal Bleeding in the Prepubertal Child

Najat C. Daw, MD
Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
548. Neoplasms of the Kidney

Shannon L. Dean, MD, PhD
Assistant Professor of Neurology
Johns Hopkins University School of Medicine
Kennedy Krieger Institute
Baltimore, Maryland
637.4. Dystonia

Roberta L. DeBiasi, MD, MS
Professor of Pediatrics and Microbiology, Immunology and Tropical Medicine
The George Washington University School of Medicine
Chief, Division of Pediatric Infectious Diseases
Robert H. Parrott Professor of Pediatric Research
Children's National Hospital and Research Institute
Washington, DC
311. Coronaviruses

Shirley Delair, MD, MPH
Associate Professor of Pediatrics
Chief, Division of Pediatric Infectious Diseases
Associate Dean of Diversity, Equity and Inclusion
University of Nebraska Medical Center
Omaha, Nebraska
241. Chancroid (Haemophilus ducreyi)

Amy M. DeLaroche, MD
Assistant Professor of Pediatrics
Central Michigan University College of Medicine
Division of Emergency Medicine
Children's Hospital of Michigan
Detroit, Michigan
424. Brief Resolved Unexplained Events and Other Acute Events in Infants

Diva D. De León-Crutchlow, MD, MSCE
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Endocrinology and Diabetes
Director, Congenital Hyperinsulinism Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
113. Hypoglycemia

Helen M. Oquendo Del Toro, MD
Clinical Assistant Professor of Obstetrics and Gynecology
Division of Pediatric and Adolescent Gynecology
University of New Mexico School of Medicine
Albuquerque, New Mexico
586. Vulvovaginitis

Coralee Del Valle Mojica, MD, MPH
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
236. Nocardia

David R. DeMaso, MD
George P. Gardner and Olga E. Monks Professor of Child Psychiatry
Professor of Pediatrics
Department of Psychiatry
Harvard Medical School
Chair of Psychiatry
Department of Psychiatry and Behavioral Sciences
Boston Children's Hospital
Boston, Massachusetts
33. Psychopharmacology
34. Psychotherapy
35. Somatic Symptom and Related Disorders
36. Rumination and Pica
37. Motor Disorders and Habits
42. Disruptive, Impulse-Control, and Conduct Disorders
43. Tantrums and Breath-Holding Spells
44. Lying, Stealing, and Truancy
45. Aggression

Melina L. Dendrinos, MD
Assistant Professor of Obstetrics and Gynecology
University of Michigan Medical School
Ann Arbor, Michigan
592. Gynecologic Care for Adolescents with Special Needs

Arlene E. Dent, MD, PhD
Associate Professor of Pediatrics
Center for Global Health and Diseases
Case Western Reserve University School of Medicine
Cleveland, Ohio
337. Ascariasis (Ascaris lumbricoides)
339. Trichuriasis (Trichuris trichiura)
340. Enterobiasis (Enterobius vermicularis)
341. Strongyloidiasis (Strongyloides stercoralis)
342. Lymphatic Filariasis (Brugia malayi, Brugia timori, and Wuchereria bancrofti)
343. Other Tissue Nematodes
344. Toxocariasis (Visceral and Ocular Larva Migrans)
345. Trichinellosis (Trichinella spiralis)

Robert J. Desnick, MD, PhD
Dean for Genetic and Genomic Medicine Emeritus
Professor and Chairman Emeritus
Department of Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai
New York, New York
106.4. Lipidoses (Lysosomal Storage Disorders)
106.5. Mucolipidoses
107.6. Disorders of Glycoprotein Degradation and Structure
112. The Porphyrias

Robin R. Deterding, MD
Professor of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado
448.7. Fibrotic Lung Disease

Prasad Devarajan, MD, FAAP, FASN
Louise M. Williams Endowed Chair
Professor of Pediatrics and Developmental Biology
University of Cincinnati College of Medicine
Director of Nephrology and Hypertension
Director and CEO, Dialysis Unit and ESRD Program
Director, Biomarker Laboratory
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
560. Multisystem Disease Associated With Hematuria
561. Tubulointerstitial Disease Associated With Hematuria
562. Vascular Diseases Associated with Hematuria
563. Anatomic Abnormalities Associated With Hematuria
564. Lower Urinary Tract Causes of Hematuria
572.1. Acute Kidney Injury

Gabrielle A. deVeber, MD, MHSc
Professor of Pediatrics
University of Toronto Faculty of Medicine
Children's Stroke Program
Division of Neurology
Senior Scientist Emeritus, Research Institute
Hospital for Sick Children
Toronto, Ontario, Canada
641. Pediatric Stroke

Vineet K. Dhar, BDS, MDS, PhD
Assistant Dean, Postgraduate and Professional Studies in Dentistry
Clinical Professor and Chairman, Orthodontics and Pediatric Dentistry
Diplomate, American Board of Pediatric Dentistry
University of Maryland School of Dentistry
Baltimore, Maryland
353. Development and Developmental Anomalies of the Teeth
354. Disorders of the Oral Cavity Associated with Other Conditions
355. Malocclusion
356. Cleft Lip and Palate
357. Syndromes With Oral Manifestations
358. Dental Caries
359. Periodontal Diseases
360. Dental Trauma
361. Common Lesions of the Oral Soft Tissues
362. Diseases of the Salivary Glands and Jaws
363. Diagnostic Radiology in Dental Assessment

Julie M. Dhossche, MD
Assistant Professor of Dermatology
Oregon Health & Science University
Portland, Oregon
685. Morphology of the Skin
686. Dermatologic Evaluation of the Patient
696. Eczematous Disorders
697. Photosensitivity
698. Diseases of the Epidermis

Liliane K. Diab, MD
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Section of Pediatric Nutrition
Children's Hospital Colorado
Aurora, Colorado
64. Malnutrition in High-Resource Settings

Heather N. Di Carlo, MD
Assistant Professor of Urology
Director, Pediatric Urology Research
Johns Hopkins University Medical Center
Baltimore, Maryland
574. Congenital Anomalies and Dysgenesis of the Kidneys
576. Vesicoureteral Reflux
577. Obstruction of the Urinary Tract
578. Anomalies of the Bladder
579. Neuropathic Bladder
580. Enuresis and Voiding Dysfunction
581. Anomalies of the Penis and Urethra
582. Disorders and Anomalies of the Scrotal Contents
583. Trauma to the Genitourinary Tract
584. Urinary Lithiasis

Harry C. Dietz III, MD
Victor A. McKusick Professor of Medicine and Genetics
Departments of Pediatrics, Medicine, and Molecular Biology and Genetics
Institute of Genetic Medicine
Johns Hopkins University School of Medicine
Investigator, Howard Hughes Medical Institute
Baltimore, Maryland
743. Marfan Syndrome

Megan L. Dietze-Fiedler, MD
Pediatric and Adult Plastic Surgery
Prevea Health
Green Bay, Wisconsin
632. Deformational Plagiocephaly

Linda A. DiMeglio, MD, MPH
Professor of Pediatrics
Chief, Division of Pediatric Endocrinology
Indiana University School of Medicine
Riley Hospital for Children
Indianapolis, Indiana
747. Hypophosphatasia
748. Hyperphosphatasia

Bradley P. Dixon, MD, FASN
Associate Professor of Pediatrics and Medicine
Renal Section, Department of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado
568. Tubular Function
569. Renal Tubular Acidosis
570. Nephrogenic Diabetes Insipidus
571. Inherited Tubular Transport Abnormalities

Amy D. DiVasta, MD, MMSc
Associate Professor of Pediatrics
Harvard Medical School
Attending Physician
Division of Adolescent/Young Adult Medicine
Director, Young Women's Health Research
Boston Children's Hospital
Boston, Massachusetts
588. Breast Health

Nomazulu Dlamini, MBBS, PhD
Associate Professor of Pediatrics
University of Toronto Faculty of Medicine
Staff Physician in Neurology
Director, Children's Stroke Program
Hospital for Sick Children
Toronto, Ontario, Canada
641. Pediatric Stroke

Katherine R. Dobbs, MD
Assistant Professor of Pediatrics
Center for Global Health and Diseases
Case Western Reserve University School of Medicine
Cleveland, Ohio
337. Ascariasis (Ascaris lumbricoides)
339. Trichuriasis (Trichuris trichiura)
340. Enterobiasis (Enterobius vermicularis)
341. Strongyloidiasis (Strongyloides stercoralis)
342. Lymphatic Filariasis (Brugia malayi, Brugia timori, and Wuchereria bancrofti)
343. Other Tissue Nematodes
344. Toxocariasis (Visceral and Ocular Larva Migrans)
345. Trichinellosis (Trichinella spiralis)

Sonam N. Dodhia, MD
Department of Otolaryngology – Head and Neck Surgery
Columbia University Vagelos College of Physicians and Surgeons
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center
New York, New York
426. Acquired Disorders of the Nose

Katja Doerholt, MD
Paediatric Infectious Diseases Consultant
St George's University Hospital
Honorary Clinical Lecturer
University College London Faculty of Population Health Sciences
London, United Kingdom
346. Schistosomiasis (Schistosoma)
347. Flukes (Liver, Lung, and Intestinal)

Cara D. Dolin, MD, MPH
Assistant Professor of Obstetrics and Gynecology
University of Pennsylvania Perelman School of Medicine
Division of Maternal-Fetal Medicine
Philadelphia, Pennsylvania
116. High-Risk Pregnancies

Samuel R. Dominguez, MD, PhD
Professor of Pediatrics
University of Colorado School of Medicine
Division of Pediatric Infectious Diseases
Children's Hospital Colorado
Aurora, Colorado
311. Coronaviruses

Patricia A. Donohoue, MD
Professor and Chief, Emerita
Pediatric Endocrinology
Medical College of Wisconsin
Former Medical Director of Endocrinology
Children's Wisconsin
Milwaukee, Wisconsin
622. Development and Function of the Gonads
623. Hypofunction of the Testes
624. Pseudoprecocity Resulting From Tumors of the Testes
625. Gynecomastia
626. Hypofunction of the Ovaries
627. Pseudoprecocity Resulting From Lesions of the Ovary
628. Disorders of Sex Development

Jennifer Dow, MD, MHA, FACEP, FAWM, DiMM
Medical Director, Denali National Park and Preserve
Medical Director, National Park Service, Alaska Region
Attending Physician
Department of Emergency Medicine
Alaska Regional Hospital
Anchorage, Alaska;
Adjunct Assistant Professor of Emergency Medicine
University of Utah School of Medicine
Salt Lake City, Utah
90. Cold Injuries

Kevin J. Downes, MD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
252. Tularemia (Francisella tularensis)
253. Brucella

Daniel A. Doyle, MD
Associate Professor of Pediatrics
Sidney Kimmel Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania;
Chief, Division of Pediatric Endocrinology
Nemours Alfred I. duPont Hospital for Children
Wilmington, Delaware
610. Hormones and Peptides of Calcium Homeostasis and Bone Metabolism
611. Hypoparathyroidism
612. Pseudohypoparathyroidism
613. Hyperparathyroidism

Jefferson J. Doyle, MBBChir, PhD, MHS
Assistant Professor of Ophthalmology and Genetic Medicine
Dracopoulos Finkelstein Rising Professor in Ophthalmology
Wilmer Eye Institute
Johns Hopkins Hospital
Department of Genetic Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland
743. Marfan Syndrome

Yigal Dror, MD, FRCPC
Professor of Paediatrics
University of Toronto Faculty of Medicine
Director, Marrow Failure and Myelodysplasia
Division of Hematology/Oncology
The Hospital for Sick Children
Senior Scientist
Program in Genetics and Genome Biology Research Institute
Toronto, Ontario
517. Inherited Bone Marrow Failure Syndromes with Pancytopenia

Howard Dubowitz, MD, MS, FAAP
Professor of Pediatrics
Head, Division of Child Protection
Director, Center for Families
Department of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland
17. Abused and Neglected Children

J. Stephen Dumler, MD
Professor and Chair
Department of Pathology
Uniformed Services University of the Health Sciences
Walter Reed National Military Medical Center
Bethesda, Maryland
274. Spotted Fever Group Rickettsioses
275. Scrub Typhus (Orientia tsutsugamushi)
276. Typhus Group Rickettsioses
277. Ehrlichiosis and Anaplasmosis
278. Q Fever (Coxiella burnetii)

Andrea F. Duncan, MD, MSClinRes
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Distinguished Endowed Chair in the Department of Pediatrics
Associate Chair, Diversity and Equity, Department of Pediatrics
Medical Director, Neonatal Follow-up Program Clinic at Buerger
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
119. The High-Risk Infant

Nefertiti H. Durant, MD, MPH
Associate Professor of Pediatrics
The University of Alabama at Birmingham
Division of Adolescent Medicine
Children's of Alabama
Birmingham, Alabama
163. Sexually Transmitted Infections

Jeffrey A. Dvergsten, MD
Associate Professor of Pediatrics
Duke University School of Medicine
Division of Pediatric Rheumatology
Duke University Health System
Durham, North Carolina
195. Treatment of Rheumatic Diseases
200. Juvenile Dermatomyositis

Michael G. Earing, MD, MS
Professor of Internal Medicine and Pediatrics
Chief of Pediatric Cardiology
The University of Chicago Pritzker School of Medicine
Section Chief and Co-director Advocate Children's Hospital Heart Institute
Medical Director
Chicago Alliance for Adult Congenital Heart Disease Care
Chicago, Illinois
483.1. Congenital Heart Disease in Adults

Col. Matthew D. Eberly, MD
Associate Professor of Pediatrics
Uniformed Services University of the Health Sciences
Bethesda, Maryland
326. Primary Amebic Meningoencephalitis

Marie E. Egan, MD
Professor of Pediatrics (Respiratory) and Cellular and Molecular Physiology
Director, Cystic Fibrosis Center
Vice Chair for Research
Department of Pediatrics
Yale School of Medicine
New Haven, Connecticut
454. Cystic Fibrosis

Eric C. Eichenwald, MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief of the Division of Neonatology
Thomas Frederick McNair Scott Endowed Chair
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
121. Clinical Manifestations of Diseases in the Newborn Period
135. Meconium Ileus, Peritonitis, Intestinal Obstruction, and Gastroschisis
144. The Umbilicus

Abdul-Aziz K. Elkadri, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Gastroenterology, Hepatology and Nutrition
Children's Wisconsin
Milwaukee, Wisconsin
385. Disorders of Malabsorption

Elizabeth Englander, PhD
Professor of Psychology
Bridgewater State University
Founder and Executive Director
Massachusetts Aggression Reduction Center
Bridgewater, Massachusetts
15.1. Bullying, Cyberbullying, and School Violence

Jessica E. Ericson, MD, MPH
Associate Professor of Pediatrics
Pennsylvania State University College of Medicine
Division of Pediatric Infectious Disease
Milton S. Hershey Medical Center
Hershey, Pennsylvania
280. Candida

Elif Erkan, MD, MS
Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Nephrology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
567. Nephrotic Syndrome

Ruth A. Etzel, MD, PhD
Adjunct Professor
Milken Institute School of Public Health
George Washington University
Washington, DC
757. Overview of Environmental Health and Children

Sarah Helen Evans, MD
Professor of Clinical Pediatrics and Physical Medicine and Rehabilitation
University of Pennsylvania Perelman School of Medicine
Chief, Division of Rehabilitation Medicine
Department of Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
755. Upper and Lower Extremity Assistive Devices

Erin Faherty, MD
Assistant Professor of Clinical Pediatrics
Yale School of Medicine
Children's Heart Center
Division of Pediatric Cardiology
Yale New Haven Children's Hospital
New Haven, Connecticut
486. Infective Endocarditis

Marni J. Falk, MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Executive Director, Mitochondrial Medicine Frontier Program
Division of Human Genetics, Department of Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
108. Mitochondrial Disease Diagnosis

Itziar Familiar-Lopez, MD, PhD, MPH
Assistant Professor of Psychiatry
Michigan State University College of Human Medicine
East Lansing, Michigan
633.10. Nodding Syndrome

John H. Fargo, DO
Assistant Professor of Pediatrics
Northeast Ohio Medical University
Rootstown, Ohio;
Director, Hemostasis and Thrombosis Center
Director, Divisional Quality Improvement
Division of Pediatric Hematology/Oncology
Showers Family Center for Childhood Cancer and Blood Disorders
Akron Children's Hospital
Akron, Ohio
518. Acquired Pancytopenias

Kristen A. Feemster, MD, MPH, MSPHR, FAAP
Director of Research
Vaccine Education Center
Children's Hospital of Philadelphia
Adjunct Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania
313. Human Papillomaviruses

Katie P. Fehnel, MD
Assistant Professor of Neurosurgery
Harvard Medical School
Director, Spinal Cord Tumor Program
Boston Children's Hospital
Dana Farber Cancer Institute
Boston, Massachusetts
81. Spinal Cord Injuries in Children
646. Spinal Cord Disorders

Susan Feigelman, MD
Professor of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland
19. Developmental and Behavioral Theories
21. Assessment of Fetal Growth and Development
23. The First Year
24. The Second Year
25. The Preschool Years
26. Middle Childhood

Amy G. Feldman, MD, MSCS
Associate Professor of Pediatrics
University of Colorado School of Medicine
Program Director, Liver Transplant Fellowship
Children's Hospital Colorado
Aurora, Colorado
410. Autoimmune Hepatitis
411. Drug- and Toxin-Induced Liver Injury
412. Acute Hepatic Failure
413. Cystic Diseases of the Biliary Tract and Liver
414. Diseases of the Gallbladder
415. Portal Hypertension and Varices

Heidi M. Feldman, MD, PhD
Ballinger-Swindells Professor and Division Chief
Developmental and Behavioral Pediatrics
Stanford University School of Medicine
Service Chief, Developmental and Behavioral Pediatric Programs
Stanford Medicine Children's Health
Palo Alto, California
53. Language Development and Communication Disorders

Edward C. Fels, MD
Clinical Assistant Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts;
Rheumatology Associates
Portland, Maine
210. Vasculitis Syndromes

Eric I. Felner, MD, MSCR
Professor of Pediatrics
Division of Pediatric Endocrinology
Emory University School of Medicine
Atlanta, Georgia
594. Hormones of the Hypothalamus and Pituitary
595. Hypopituitarism

Sing-Yi Feng, MD, FAAP, FACMT
Professor of Pediatrics
University of Texas Southwestern Medical Center at Dallas
Associate Pediatric Emergency Medicine Fellowship Director
Division of Emergency Medicine, Department of Pediatrics
Children's Medical Center of Dallas
Medical Toxicologist
North Texas Poison Center
Parkland Memorial Hospital
Dallas, Texas
768. Envenomations

Thomas W. Ferkol Jr., MD
Professor of Pediatrics
Chief, Division of Pediatric Pulmonology
University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, North Carolina
455. Primary Ciliary Dyskinesia (Immotile Cilia Syndrome, Kartagener Syndrome)

Karin E. Finberg, MD, PhD
Associate Professor of Pathology
Yale School of Medicine
New Haven, Connecticut
504.1. Iron-Refractory Iron Deficiency Anemia

Jonathan D. Finder, MD
Professor of Pediatrics
The University of Tennessee Health Science Center
Attending Physician
Division of Pediatric Pulmonology
Le Bonheur Children's Hospital
Memphis, Tennessee
437. Bronchomalacia and Tracheomalacia
444. Congenital Disorders of the Lung

Kristin N. Fiorino, MD
Global Development Medical Director
AstraZeneca
Bethesda, Maryland
378. Motility Disorders and Hirschsprung Disease

Philip R. Fischer, MD
Professor of Pediatrics
Department of Pediatric and Adolescent Medicine
Mayo Clinic
Rochester, Minnesota
348. Adult Tapeworm Infections
349. Cysticercosis
350. Echinococcosis (Echinococcus granulosus sensu latu and Echinococcus multilocularis)

Anne M. Fitzpatrick, PhD, APRN
Professor of Pediatrics
Emory University School of Medicine
Atlanta, Georgia
185. Childhood Asthma

Dustin D. Flannery, DO, MSCE
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
148. Epidemiology of Infections

Nicholas L. Fleming, DO
Department of Pediatric Physical Medicine & Rehabilitation
Logan Health Children's Hospital
Kalispell, Montana
753. Birth Brachial Plexus Palsy

Veronica H. Flood, MD
Professor of Pediatrics
Medical College of Wisconsin
Interim Chief, Division of Pediatric Hematology/Oncology
Children's Wisconsin
Associate Medical Director and Investigator
Comprehensive Center for Bleeding Disorders
Versiti Blood Center of Wisconsin
Milwaukee, Wisconsin
524. Hemostasis
525. Hereditary Clotting Factor Deficiencies (Bleeding Disorders)
526. Von Willebrand Disease
529. Postneonatal Vitamin K Deficiency
530. Coagulopathy in Liver Disease
531. Acquired Inhibitors of Coagulation
533. Platelet and Blood Vessel Disorders

Francisco X. Flores, MD
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, Clinical Services and MARS Program
Division of Nephrology and Hypertension
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
558. Clinical Evaluation of the Child With Hematuria
559. Isolated Glomerular Diseases Associated With Recurrent Gross Hematuria
565. Clinical Evaluation of the Child With Proteinuria
566. Conditions Associated With Proteinuria

Joseph T. Flynn, MD, MS
Professor of Pediatrics
University of Washington School of Medicine
Chief, Division of Nephrology
Seattle Children's Hospital
Seattle, Washington
494. Systemic Hypertension

Patricia M. Flynn, MD
Senior Vice President and Medical Director
Quality and Patient Care
Deputy Clinical Director and Member
Department of Infectious Diseases
Arthur Ashe Chair in Pediatric AIDS Research
St. Jude Children's Research Hospital
Memphis, Tennessee
329. Cryptosporidium, Cystoisospora, Cyclospora, and Microsporidia

Elizabeth E. Foglia, MD, MA, MSCE
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
123. Neonatal Resuscitation and Delivery Room Emergencies

Heather C. Forkey, MD
Professor of Pediatrics
University of Massachusetts Chan Medical School
Chief, Child Protection Program (CPP)
Director, Foster Children Evaluation Service (FaCES)
Medical Director, Lifeline4Kids
UMass Memorial Children's Medical Center
Worcester, Massachusetts
10. Foster and Kinship Care

Joel A. Forman, MD
Professor of Pediatrics, Medical Education, and Environmental Medicine and Public Health
Icahn School of Medicine at Mount Sinai
Vice-Chair for Education
Interim Chief and Medical Director
Division of Pediatric Hospital Medicine
Kravis Children's Hospital
New York, New York
759. Chemical Pollutants

Alexandra F. Freeman, MD
Director, Primary Immune Deficiency Clinic
Laboratory of Clinical Immunology and Microbiology
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland
175. Defects of Innate Immunity

Deborah M. Friedman, MD
Professor Emerita of Pediatrics
New York Medical College
Valhalla, New York
199.1. Neonatal Lupus

Susan A. Friedman, MD
Clinical Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Medical Director, International Adoption Health Program
Attending Physician, Neonatal Follow Up Program
Attending Physician, Fostering Health Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
146. Fetal Alcohol Spectrum Disorder

Erika D. Friehling, MD, MS
Associate Professor of Pediatrics
Associate Vice Chair of Faculty Development
Department of Pediatrics
University of Pittsburgh School of Medicine
Division of Pediatric Hematology/Oncology
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
542. Principles of Cancer Diagnosis
543. Principles of Cancer Treatment
544. The Leukemias

Stephanie A. Fritz, MD, MSCI
Professor of Pediatrics
University of Washington School of Medicine in St. Louis
Division of Infectious Diseases
St. Louis Children's Hospital
St. Louis, Missouri
227. Staphylococcus
233. Diphtheria (Corynebacterium diphtheriae)

Donald P. Frush, MD, FACR, FAAP, FSABI
John Strohbehn Professor of Radiology
Associate Faculty, Duke Medical Physics Graduate Program
Duke University Medical Center
Durham, North Carolina
758. Biologic Effects of Ionizing Radiation on Children

Ramsay L. Fuleihan, MD
Professor of Pediatrics
Columbia University Vagelos College of Physicians and Surgeons
Clinical Director, Division of Pediatric Allergy, Immunology and Rheumatology
Columbia University Medical Center
New York, New York
165. T-Cell and Combined Deficiencies

Sheila Gahagan, MD, MPH
Professor of Clinical Pediatrics
Chief, Division of Academic General Pediatrics, Child Development, and Community Health
Martin Stein Endowed Chair, Developmental-Behavioral Pediatrics
UC San Diego School of Medicine
La Jolla, California
65. Overweight and Obesity

Patrick G. Gallagher, MD
Professor of Pediatrics, Physiology and Cell Biology
Ohio State University
Attending Physician
Nationwide Children's Hospital
Columbus, Ohio
506. Definitions and Classification of Hemolytic Anemias
507. Hereditary Spherocytosis
508. Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis and Related Disorders
509. Hereditary Stomatocytosis Syndromes
510. Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

David P. Galloway, MD
Associate Professor of Pediatrics
University of Alabama at Birmingham School of Medicine
Medical Director, Center of Advanced Intestinal Rehabilitation
Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Children's of Alabama
Birmingham, Alabama
258. Clostridioides difficile Infection

Hayley A. Gans, MD
Clinical Professor of Pediatrics
Stanford University School of Medicine
Co-Director, Pediatric Infectious Diseases Program for Immunocompromised Hosts
Division of Pediatric Infectious Diseases
Children's Hospital at Stanford
Stanford, California
293. Measles
294. Rubella
295. Mumps

Andrea K. Garber, PhD, RD
Professor of Pediatrics
Division of Adolescent and Young Adult Medicine
Chief Nutritionist, Eating Disorders Program
UC San Francisco School of Medicine
San Francisco, California
63. Refeeding Syndrome

Paula M. Gardiner, MD, MPH
Associate Professor and Associate Director of Research
Department of Family Medicine and Community Health
University of Massachusetts Chan Medical School
Worcester, Massachusetts
7. Complementary Therapies and Integrative Medicine

Luigi R. Garibaldi, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Clinical Director
Division of Pediatric Endocrinology
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
599. Physiology of Puberty
600. Disorders of Pubertal Development

Gregory M. Gauthier, MD, MS
Associate Professor of Medicine
Division of Infectious Diseases
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
285. Blastomycosis

Jeffrey S. Gerber, MD, PhD
Associate Professor of Pediatrics and Epidemiology
University of Pennsylvania Perelman School of Medicine
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
226. Antimicrobial Stewardship
254. Legionella

Anne A. Gershon, MD
Professor of Pediatrics
Columbia University Vagelos College of Physicians and Surgeons
Division of Pediatric Infectious Diseases
NewYork-Presbyterian Morgan Stanley Children's Hospital
New York, New York
300. Varicella-Zoster Virus

Saied Ghadersohi, MD
Assistant Professor of Otolaryngology - Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
438. Neoplasms of the Larynx, Trachea, and Bronchi

Kathleen A. Gibbs, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Medical Director, Newborn and Infant Chronic Lung Disease Program
Medical Director, Quality Improvement and Patient Safety, N/IICU
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
121. Clinical Manifestations of Diseases in the Newborn Period

Mark Gibson, MD
Professor (Clinical) Emeritus
Department of Obstetrics and Gynecology
Division Chief, Utah Center for Reproductive Medicine
University of Utah School of Medicine
Salt Lake City, Utah
589. Polycystic Ovary Syndrome and Hirsutism

Joseph Gigante, MD
Professor of General Pediatrics
Director of Education
Office of Faculty Development
Department of Pediatrics
Vanderbilt University Medical Center
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee
430. Acute Pharyngitis

Francis Gigliotti, MD
Professor of Pediatrics
University of Rochester Medical Center School of Medicine and Dentistry
Department of Pediatric Infectious Diseases
Golisano Children's Hospital
Rochester, New York
290. Pneumocystis jirovecii

Stephanie P. Gilley, MD, PhD
Assistant Professor in Pediatrics
University of Colorado School of Medicine
Section of Pediatric Nutrition
Children's Hospital Colorado
Aurora, Colorado
61. Feeding Healthy Infants, Children, and Adolescents
64. Malnutrition in High-Resource Settings

Walter S. Gilliam, PhD
Executive Director
Richard D. Holland Presidential Chair in Early Childhood Development
Buffett Early Childhood Institute
University of Nebraska
Omaha, Nebraska
29. Child Care

Salil Ginde, MD, MPH
Associate Professor of Internal Medicine and Pediatrics
Medical College of Wisconsin
Section of Pediatric Cardiology
Children's Wisconsin
Milwaukee, Wisconsin
483.1. Congenital Heart Disease in Adults

John A. Girotto, MD, MBA, FAAP, FACS
Professor of Surgery
Michigan State College of Human Medicine
Chief, Pediatric Plastic Surgery
Helen DeVos Children's Hospital
Grand Rapids, Michigan
632. Deformational Plagiocephaly

Samuel B. Goldfarb, MD
Professor of Pediatrics
Annalisa Marzotto Endowed Chair in Cystic Fibrosis Care
Director, Pediatric Cystic Fibrosis Program
Co-Director, University of Minnesota Cystic Fibrosis Center
Division of Pediatric Pulmonary and Sleep Medicine
University of Minnesota
Minneapolis, Minnesota
492.2. Heart-Lung and Lung Transplantation

David L. Goldman, MD
Associate Professor of Pediatrics and Microbiology and Immunology
Albert Einstein College of Medicine
Division of Pediatric Infectious Disease
The Children's Hospital at Montefiore
Bronx, New York
281. Cryptococcus neoformans and Cryptococcus gattii

Stanton C. Goldman, MD
Principal Investigator
Children's Oncology Group
Chief Medical Officer
Medical City Children's Hospital
Texas Oncology, PA
Dallas, Texas
545. Lymphoma

Oscar G. Gómez-Duarte, MD, PhD
Associate Professor of Pediatrics
Jacobs School of Medicine and Biomedical Sciences University at
Buffalo State University of New York
Buffalo, New York
242. Moraxella catarrhalis

Misty Good, MD, MS, FAAP
Associate Professor of Pediatrics
Chief, Division of Neonatal-Perinatal Medicine
University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, North Carolina
136. Necrotizing Enterocolitis

Christine M. Goodbody, MD, MBE
Assistant Professor of Orthopedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
715. The Foot and Toes
717. Leg-Length Discrepancy
723. Arthrogryposis

Denise M. Goodman, MD, MS
Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Attending Physician, Division of Critical Care Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
468.1. Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Tracey Goodman, MA
Team Lead, Life Course & Integration
EPI Unit
Department of Vaccines and Biologicals
World Health Organization
Geneva, Switzerland
215.1. International Immunization Practices

William R. Goodyer, MD, PhD
Assistant Professor of Pediatrics
Division of Pediatric Cardiology
Stanford University School of Medicine
Palo Alto, California
469. Cardiac Development

Catherine M. Gordon, MD, MS
Senior Faculty, USDA/ARS Children's Nutrition Research Center
Professor of Pediatrics
Baylor College of Medicine
Houston, Texas
746. Bone Structure, Growth, and Hormonal Regulation
749. Osteoporosis

Leslie B. Gordon, MD, PhD
Professor of Pediatrics Research
Warren Alpert Medical School of Brown University
Hasbro Children's Hospital
Providence, Rhode Island;
Department of Anesthesiology, Critical Care, and Pain Medicine
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts;
Medical Director, The Progeria Research Foundation
Peabody, Massachusetts
111. Hutchinson-Gilford Progeria Syndrome (Progeria)

Rebecca J. Gordon, MD
Instructor in Pediatrics
Harvard Medical School
Attending Physician
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts
746. Bone Structure, Growth, and Hormonal Regulation
749. Osteoporosis

Eliza Gordon-Lipkin, MD
Assistant Research Physician
Metabolism, Infection and Immunity Section
National Institutes of Health
Bethesda, Maryland
28. Developmental and Behavioral Surveillance and Screening

Michael Gorelik, MD
Assistant Professor
Division of Pediatric Otolaryngology
Children's Wisconsin
Medical College of Wisconsin
Madison, Wisconsin
434. Congenital Anomalies of the Larynx, Trachea, and Bronchi
435. Foreign Bodies in the Airway

W. Adam Gower, MD, MS
Associate Professor of Pediatrics
Division of Pediatric Pulmonology
The University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, North Carolina
448.6. Neuroendocrine Cell Hyperplasia of Infancy

Evan G. Graber, DO
Clinical Associate Professor of Pediatrics
Sidney Kimmel Medical College of
Thomas Jefferson University
Philadelphia, Pennsylvania;
Pediatric Endocrinologist
Nemours Children's Hospital–Delaware
Wilmington, Delaware
610. Hormones and Peptides of Calcium Homeostasis and Bone Metabolism
613. Hyperparathyroidism

Zachary T. Graff, MD
Assistant Professor of Pediatrics
Medical College of Wisconsin
Pediatric Leukemia and Lymphoma Program
Division of Pediatric Hematology/Oncology
Children's Wisconsin
Milwaukee, Wisconsin
539. Lymphadenopathy

Robert J. Graham, MD
Associate Professor of Anesthesiology
Harvard Medical School
Senior Associate in Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain Medicine
Boston Children's Hospital
Boston, Massachusetts
468.4. Long-term Ventilation and Technology Support: Indications, Principles, Decision-Making, Pragmatics and Home Provision

Cori M. Green, MD, MSc
Assistant Professor of Clinical Pediatrics
Director of Behavioral Health Education and Integration in Pediatrics
Weill Cornell Medicine
Associate Attending Pediatrician
NewYork-Presbyterian Phyllis and David Komansky Children's Hospital at Weill Cornell Medical Center
New York, New York
18. Strategies for Health Behavior Change

Michael Green, MD, MPH
Professor of Pediatrics, Surgery, and Clinical and Translational Science
University of Pittsburgh School of Medicine
Division of Infectious Diseases
Director, Antimicrobial Stewardship and Infection Prevention
Co-Director, Pediatric Transplant Infectious Diseases
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
223. Infections in Immunocompromised Persons

Larry A. Greenbaum, MD, PhD
Bernard Marcus Professor of Pediatrics
Director, Division of Pediatric Nephrology
Emory University School of Medicine
Executive Clinical Director
Children's Healthcare of Atlanta
Atlanta, Georgia
69. Vitamin D Deficiency (Rickets) and Excess
70. Vitamin E Deficiency
71. Vitamin K Deficiency
72. Micronutrient Mineral Deficiencies
73. Electrolyte and Acid-Base Disorders
74. Maintenance and Replacement Therapy
75. Deficit Therapy

V. Jordan Greenbaum, MD
Medical Director
International Centre for Missing and Exploited Children
Alexandria, Virginia
16. Child Trafficking for Sex and Labor

Mary V. Greiner, MD, MS
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, CHECK Foster Care Center
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
10. Foster and Kinship Care

Anne G. Griffiths, MD
Pediatric Pulmonologist
Director, Primary Ciliary Dyskinesia Center
Children's Minnesota
Children's Respiratory & Critical Care Specialists
Minneapolis, Minnesota
422. Chronic or Recurrent Respiratory Symptoms

Kenneth L. Grizzle, PhD
Associate Professor of Pediatrics
Medical College of Wisconsin
Child Development Center
Children's Wisconsin
Milwaukee, Wisconsin
52. Math and Writing Disabilities
53.1. Childhood-Onset Fluency Disorder

Judith A. Groner, MD, FAAP
Professor of Clinical Pediatrics
The Ohio State University of Medicine
Division of Primary Care Pediatrics
Nationwide Children's Hospital
Columbus, Ohio
759. Chemical Pollutants

Anete Sevciovic Grumach, MD, PhD
Clinical Immunology
University Center Faculty of Medicine ABC (CEUFMABC)
Santo Andre, SP, Brazil
173. Complement System

Seyni Gueye-Ndiaye, MD
Research Fellow in Sleep Medicine
Brigham and Women's Hospital
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts
31. Sleep Medicine

Anat Guz-Mark, MD
Attending Physician
Institute of Gastroenterology, Nutrition and Liver Disease
Schneider Children's Medical Center of Israel
Petah Tikva, Israel;
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel
388. Chronic Diarrhea

Fareeda Haamid, DO
Associate Professor of Pediatrics
The Ohio State University College of Medicine
Division of Adolescent Medicine
Nationwide Children's Hospital
Columbus, Ohio
159. Menstruation-Related Disorders

Gabriel G. Haddad, MD
Distinguished Professor of Pediatrics and Neuroscience
Chairman, Department of Pediatrics
University of California San Diego School of Medicine
Physician-in-Chief and Chief Scientific Officer
Rady Children's Hospital–San Diego
San Diego, California
421. Diagnostic Approach to Respiratory Disease

Joseph Haddad Jr., MD
Lawrence Savetsky Professor Emeritus
Columbia University Irving Medical Center
New York, New York
425. Congenital Disorders of the Nose
426. Acquired Disorders of the Nose
427. Nasal Polyps
676. General Considerations and Evaluation of the Ear
677. Hearing Loss
678. Congenital Malformations of the Ear
679. External Otitis (Otitis Externa)
682. The Inner Ear and Diseases of the Bony Labyrinth
683. Traumatic Injuries of the Ear and Temporal Bone
684. Tumors of the Ear and Temporal Bone

Matthew A. Haemer, MD
Associate Professor of Pediatrics
University of Colorado School of Medicine
Section of Pediatric Nutrition
Children's Hospital Colorado
Aurora, Colorado
61. Feeding Healthy Infants, Children, and Adolescents

Joseph F. Hagan Jr., MD, FAAP
Clinical Professor of Pediatrics
The Robert Larner, MD College of Medicine at the University of Vermont
Lakeside Pediatrics, PLLC
Burlington, Vermont
13. Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

Suraiya K. Haider, MD
Sleep Physician
Inova Children's Sleep Center
Fairfax, Virginia
451. Pleurisy, Pleural Effusions, and Empyema
461. Pneumothorax
462. Pneumomediastinum
463. Hydrothorax
464. Hemothorax
465. Chylothorax

Hana Hakim, MD, MS
Member
Department of Infectious Diseases
St. Jude Children's Research Hospital
Memphis, Tennessee
224. Infection Associated With Medical Devices

Chad R. Haldeman-Englert, MD, FACMG
Clinical Geneticist
Fullerton Genetics Center
Asheville, North Carolina
101. Signaling Pathway Disorders

Scott B. Halstead, MD
Adjunct Professor of Preventive Medicine and Biostatistics
Uniformed Services University of the Health Sciences
Bethesda, Maryland
314. Arboviral Infections
315. Dengue Fever, Dengue Hemorrhagic Fever, and Severe Dengue
316. Yellow Fever
317. Ebola and Other Viral Hemorrhagic Fevers
319. Hantavirus Pulmonary Syndrome

Lamiaa Hamie, MD, MS
Instructor in Dermatology
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin
708. Cutaneous Viral Infections
709. Arthropod Bites and Infestations

Margaret R. Hammerschlag, MD
Professor of Pediatrics and Medicine
Director, Pediatric Infectious Diseases Fellowship Training Program
Vice-Chair for Faculty Development
Department of Pediatrics
SUNY Downstate Health Sciences University
Brooklyn, New York
271. Chlamydia pneumoniae
272. Chlamydia trachomatis
273. Psittacosis (Chlamydia psittaci)

E. Adrianne Hammershaimb, MD
Instructor in Pediatrics
Division of Infectious Disease and Tropical Pediatrics
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, Maryland
387. Acute Gastroenteritis in Children

Elisa Hampton, MD
Assistant Professor of Pediatrics
Medical Director, Well Newborn Service
University of Virginia School of Medicine
Charlottesville, Virginia
22. The Newborn

Aaron Hamvas, MD
Raymond and Hazel Speck Barry Professor of Neonatology
Department of Pediatrics
Northwestern University Feinberg School of Medicine
Head, Division of Neonatology
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
456. Diffuse Lung Diseases in Childhood

Neil A. Hanchard, MBBS, Dphil
Senior Investigator
Center for Precision Health Research
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland
103. Genetics of Common Disorders

Patrick C. Hanley, MD, MSHQS
Assistant Professor of Pediatrics
Sidney Kimmel Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania;
Pediatric Endocrinologist
Nemours Alfred I. duPont Hospital for Children
Wilmington, Delaware
611. Hypoparathyroidism
612. Pseudohypoparathyroidism

Melisha G. Hanna, MD, MS
Associate Professor of Pediatrics
Renal Section, Department of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado
569. Renal Tubular Acidosis

Pooja D. Harijan, MBCHB (Leics), MRCPCH, MD (Leics)
Consultant in Pediatric Neurology
Addenbrooke's Hospital
Cambridge, United Kingdom
645. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Douglas J. Harrison, MD
Associate Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
547. Neuroblastoma

Elizabeth B. Harstad, MD, MPH
Assistant Professor of Pediatrics
Harvard Medical School
Attending Physician
Division of Developmental Medicine
Boston Children's Hospital
Boston, Massachusetts
50. Attention-Deficit/Hyperactivity Disorder

David B. Haslam, MD
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Antimicrobial Stewardship Program
Director, Microbial Genomics and Metagenomics Laboratory
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
231. Non–Group A or B Streptococci
232. Enterococcus

Fern R. Hauck, MD, MS
Spencer P. Bass, MD Twenty-First Century Professor of Family Medicine
Professor of Public Health Sciences
Departments of Family Medicine and Public Health Sciences
University of Virginia School of Medicine
Charlottesville, Virginia
423. Sudden Infant Death Syndrome

Fiona P. Havers, MD, MHS
Medical Epidemiologist
Epidemiology and Prevention Branch, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia
306. Parainfluenza Viruses

Ericka V. Hayes, MD
Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Senior Medical Director of Infection Prevention and Control
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
248. Campylobacter
249. Yersinia
263. Nontuberculous Mycobacteria
322. Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Nia J. Heard-Garris, MD, MSc
Division of Advanced General Pediatrics and Primary Care
Mary Ann & J. Milburn Smith Child Health Outreach, Research, and Evaluation Center
Ann & Robert H. Lurie Children's Hospital of Chicago
Department of Pediatrics, Northwestern University Feinberg School of Medicine
Chicago, Illinois
1. Overview of Pediatrics

Holly L. Hedrick, MD
Professor of Surgery
University of Pennsylvania Perelman School of Medicine
Attending Pediatric and Fetal Surgeon
Louise Schnaufer Endowed Chair in Pediatric Surgery
Division of Pediatric General, Thoracic and Fetal Surgery
Surgical Director, Neonatal Surgical Service
Co-Director, Neonatal Surgical Team
Director, Pulmonary Hypoplasia Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
118. Fetal Intervention and Surgery

Cheryl Hemingway, MBChB, MMed, PhD, FRCPCH(UK), FCPaed(SA)
Honorary Senior Lecturer
Imperial College London
Paediatric Neurology Consultant
Great Ormond Street Hospital for Children
London, United Kingdom
638.3. Other Encephalopathies
640. Demyelinating Disorders of the Central Nervous System

Chelsea Heneghan, MSN, CPNP-PC/AC
Nurse Practitioner
Division of Pediatric Palliative Care
Boston Children's Hospital
Boston, Massachusetts
8. Pediatric Palliative Care

Michelle L. Hernandez, MD
Professor of Pediatrics
Division of Allergy & Immunology
The University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, North Carolina
448.1. Hypersensitivity Pneumonia
448.2. Occupational and Environmental Lung Disease

Vivian P. Hernandez-Trujillo, MD
Clinical Professor of Pediatrics
Florida International University Herbert Wertheim School of Medicine
Director, Division of Allergy & Immunology
Nicklaus Children's Hospital
Allergy and Immunology Care Center of South Florida
Miami Lakes, Florida
166. B-Cell and Antibody Deficiencies

Fiorela N. Hernandez Tejada, MD
Assistant Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
547. Neuroblastoma
553. Neoplasms of the Liver

Heidi M. Herrick, MD, MSCE
Assistant Professor
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
123. Neonatal Resuscitation and Delivery Room Emergencies

Andrew D. Hershey, MD, PhD, FAAN, FAHS
Endowed Chair and Director of Neurology
Professor of Pediatrics and Neurology
University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
635. Headaches

Cynthia E. Herzog, MD
Professor of Pediatrics
Deputy Head, Division of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
551. Retinoblastoma
552. Gonadal and Germ Cell Neoplasms
553. Neoplasms of the Liver
555.2. Nasopharyngeal Carcinoma
555.3. Adenocarcinoma of the Colon and Rectum
555.5. Desmoplastic Small Round Cell Tumor

Sarah M. Heston, MD
Assistant Professor of Pediatrics
Duke University School of Medicine
Division of Infectious Diseases
Duke Children's Hospital and Health Center
Durham, North Carolina
329. Cryptosporidium, Cystoisospora, Cyclospora, and Microsporidia

Ghada Hijazi, MD, MRCPCH, FCCMG
Postdoctoral Research Associate
Department of Pediatrics
Division of Medical Genetics
Duke University Medical Center
Durham, North Carolina
107. Defects in Metabolism of Carbohydrates

Samantha V. Hill, MD, MPH
Assistant Professor of Pediatrics
The University of Alabama at Birmingham
Division of Adolescent Medicine
Children's of Alabama
Birmingham, Alabama
151. Delivery of Healthcare to Adolescents
155. The Epidemiology of Adolescent Health Problems
163. Sexually Transmitted Infections

Jessica Hochberg, MD
Associate Professor of Pediatrics
New York Medical College
Director, Hematologic Malignancy Program
Division of Pediatric Hematology, Oncology, and Stem Cell Transplant
Maria Fareri Children's Hospital at Westchester Medical Center
Valhalla, New York
545. Lymphoma

Deborah Hodes, MBBS, BSc, DRCOG, FRCPCH
Consultant Community Paediatrician
Honorary Consultant Community Paediatrician
University College London Hospitals
London, United Kingdom
593. Female Genital Mutilation

Holly R. Hoefgen, MD
Assistant Professor of Obstetrics and Gynecology
Washington University School of Medicine in St. Louis
Attending Physician
Division of Adolescent and Pediatric Gynecology
Co-Director, Integrated Care and Fertility Preservation Program
St. Louis Children's Hospital
Barnes-Jewish Hospital
St. Louis, Missouri
586. Vulvovaginitis

Lauren D. Holinger, MD, FAAP, FACS
Paul H. Holinger MD Professor of Otolaryngology – Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
438 Neoplasms of the Larynx, Trachea, and Bronchi

Cynthia M. Holland-Hall, MD, MPH
Professor of Pediatrics
The Ohio State University College of Medicine
Attending Physician
Section of Adolescent Medicine
Nationwide Children's Hospital
Columbus, Ohio
150. Adolescent Physical and Social Development
158. The Breast

Laura L. Hollenbach, MD
Assistant Professor of Obstetrics and Gynecology
University of Arkansas for Medical Sciences
Director, Division of Pediatric and Adolescent Gynecology
Arkansas Children's Hospital
Little Rock, Arkansas
591. Vulvovaginal and Müllerian Anomalies

Yolanda F. Holler-Managan, MD
Associate Professor of Pediatrics (Neurology)
Northwestern University Feinberg School of Medicine
Attending Physician
Division of Pediatric Neurology
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
630. Neurologic Evaluation

David K. Hooper, MD, MS
Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director of Kidney Transplantation
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
573. Renal Transplantation

Thomas A. Hooven, MD
Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine
Scholar, Richard King Mellon Foundation Institute for Pediatric Research
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
230. Group B Streptococcus

Julie E. Hoover-Fong, MD, PhD
Professor of Genetic Medicine and Pediatrics
McKusick-Nathans Institute of Genetic Medicine
Director, Greenberg Center for Skeletal Dysplasias
Johns Hopkins University School of Medicine
Baltimore, Maryland
735. General Considerations in Skeletal Dysplasias
736. Disorders Involving Cartilage Matrix Proteins
737. Disorders Involving Transmembrane Receptors
738. Disorders Involving Ion Transporters
739. Disorders Involving Transcription Factors
740. Osteopetrosis and Other Disorders Involving Defective Bone Resorption
741. Other Inherited Disorders of Skeletal Development

Rachel K. Hopper, MD
Clinical Associate Professor of Pediatrics
Division of Pediatric Cardiology
Stanford University School of Medicine
Palo Alto, California
482. Pulmonary Hypertension

Jeffrey D. Hord, MD
Professor of Pediatrics
Northeast Ohio Medical University
Rootstown, Ohio;
The LOPen Charities and Mawaka Family Chair, Division of Pediatric Hematology/Oncology
Showers Family Center for Childhood Cancer and Blood Disorders
Akron Children's Hospital
Akron, Ohio
518. Acquired Pancytopenias

B. David Horn, MD
Professor of Clinical Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
719. The Hip

Helen M. Horstmann, MD
Associate Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
723. Arthrogryposis

Peter J. Hotez, MD, PhD
Professor, Pediatrics and Molecular Virology and Microbiology
Texas Children's Endowed Chair of Tropical Pediatrics
Dean, National School of Tropical Medicine
Baylor College of Medicine
Houston, Texas
338. Hookworms (Necator americanus and Ancylostoma spp)

Samantha A. House, DO, MPH
Associate Professor of Pediatrics
Geisel School of Medicine at Dartmouth
Associate Professor of The Dartmouth Institute
Chief, Section of Pediatric Hospital Medicine
Dartmouth Health Children's
Lebanon, New Hampshire
439. Wheezing, Bronchiolitis, and Bronchitis

Ashley C. Howard, DO, FAAP
Assistant Professor of Pediatrics
University of Connecticut School of Medicine
Division of Infectious Diseases and Immunology
Connecticut Children's Medical Center
Hartford, Connecticut
234. Listeria monocytogenes
251. Pseudomonas, Burkholderia, and Stenotrophomonas

Mary Beth Howard, MD, MSc
Assistant Professor of Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland
77.1. Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

Evelyn K. Hsu, MD
Professor of Pediatrics
University of Washington School of Medicine
Chief, Division of Gastroenterology and Hepatology
Seattle Children's Hospital
Seattle, Washington
416. Liver Transplantation

Katherine Hsu, MD, MPH
Professor of Pediatrics
Section of Pediatric Infectious Diseases
Boston University Medical Center
Medical Director, Division of STD Prevention
Bureau of Infectious Disease and Laboratory Sciences
Massachusetts Department of Public Health
Boston, Massachusetts
238. Neisseria gonorrhoeae (Gonococcus)

Heather G. Huddleston, MD
Professor of Obstetrics, Gynecology, and Reproductive Sciences
UC San Francisco School of Medicine
San Francisco, California
589. Polycystic Ovary Syndrome and Hirsutism

Winston W. Huh, MD
Associate Professor of Clinical Pediatrics
Keck School of Medicine of USC
University of Southern California
Children's Hospital of Los Angeles
Los Angeles, California
552. Gonadal and Germ Cell Neoplasms
555.3. Adenocarcinoma of the Colon and Rectum

Stephen R. Humphrey, MD
Associate Professor of Dermatology and Pediatrics
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin
687. Principles of Dermatologic Therapy
706. Cutaneous Bacterial Infections
707. Cutaneous Fungal Infections
708. Cutaneous Viral Infections
709. Arthropod Bites and Infestations

David A. Hunstad, MD
Professor of Pediatrics and Molecular Microbiology
Washington University School of Medicine in St. Louis
St. Louis, Missouri
643. Central Nervous System Infections
644. Brain Abscess
765. Animal and Human Bites
766. Rat Bite Fever
767. Mpox (Monkeypox)

Stephen P. Hunger, MD
Professor and Jeffrey E. Perelman Distinguished Chair
Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Pediatric Oncology
Director, Center for Childhood Cancer Research
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
541. Molecular and Cellular Biology of Cancer

Carl E. Hunt, MD
Research Professor of Pediatrics
Uniformed Services University of the Health Sciences
Division of Neonatology
Walter Reed National Military Medical Center
Bethesda, Maryland;
Adjunct Professor of Pediatrics
George Washington University School of Medicine and Health Sciences
Washington, DC
423. Sudden Infant Death Syndrome

Stacey S. Huppert, PhD
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Division of Developmental Biology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
402. Morphogenesis of the Liver and Biliary System

Anna R. Huppler, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Infectious Diseases
Children's Wisconsin
Milwaukee, Wisconsin
180. Infectious Complications of Hematopoietic Stem Cell Transplantation

Hallam Hurt, MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Education Director, Neonatal Follow-up Program at Buerger Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
146. Fetal Alcohol Spectrum Disorder

Kosuke Izumi, MD, PhD
Assistant Professor of Pediatrics
Division of Genetics and Metabolism
Department of Pediatrics
University of Texas Southwestern Medical Center
Dallas, Texas
102. Chromatin Regulatory Disorders

Allison M. Jackson, MD, MPH, FAAP
Division Chief, Child & Adolescent Protection Center
Washington Children's Foundation
Endowed Professor of Child & Adolescent Protection
Children's National Hospital
Associate Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences
Washington, DC
162. Adolescent Sexual Assault

Mary Anne Jackson, MD, FAAP, FPIDS, FIDSA
Dean and Clinical Professor of Pediatrics
University of Missouri–Kansas City School of Medicine
Department of Pediatric Infectious Diseases
Children's Mercy Hospitals and Clinics
Kansas City, Missouri
674. Orbital Infections

Ashlee M. Jaffe, MD, MEd
Associate Professor of Clinical Pediatrics and Physical Medicine & Rehabilitation
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Pediatric Physical Medicine & Rehabilitation
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
751. Spinal Cord Injury and Autonomic Dysreflexia Management

Kiera M. James, PhD
Postdoctoral Scholar
Department of Psychology
University of Pittsburgh
Pittsburgh, Pennsylvania
46. Self-Injurious Behavior

Andrew B. Janowski, MD, MSCI
Assistant Professor of Pediatrics and Molecular Microbiology
Washington University School of Medicine in St. Louis
St. Louis, Missouri
643. Central Nervous System Infections
644. Brain Abscess

Brian P. Jenssen, MD, MSHP
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of General Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
157.2. Tobacco, E-Cigarettes, and Other Tobacco Products

H.A. Jinnah, MD, PhD
Professor
Departments of Neurology, Human Genetics, and Pediatrics
Emory University School of Medicine
Atlanta, University
110. Disorders of Purine and Pyrimidine Metabolism

Chandy C. John, MD, MS
Ryan White Professor of Pediatrics
Director, Ryan White Center for Pediatric Infectious Diseases and Global Health
Indiana University School of Medicine
Indianapolis, Indiana
328. Giardiasis and Balantidiasis
334. Malaria (Plasmodium)

Kari Johansen, MD, PhD
Senior Consultant in Vaccine-Preventable Diseases
Public Health Agency of Sweden
Stockholm, Sweden
215.1. International Immunization Practices

Susan L. Johnson, PhD
Professor of Pediatrics
University of Colorado School of Medicine
Section of Pediatric Nutrition
Children's Hospital Colorado
Aurora, Colorado
61. Feeding Healthy Infants, Children, and Adolescents

Brian D. Johnston, MD, MPH
Professor of Pediatrics
Adjunct Professor of Health Systems and Population Health
University of Washington School of Medicine
Chief of Service, Department of Pediatrics
Harborview Medical Center
Seattle, Washington
14. Injury Control

Artemio M. Jongco III, MD, PhD, MPH, FACP, FACAAI, FAAAAI
Clinical Associate Professor
Departments of Medicine, Pediatrics and Science Education
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Hempstead, New York;
Adjunct Assistant Professor
Institute of Molecular Medicine
Feinstein Institutes for Medical Research
Manhasset, New York
176. Approaches to Treatment of Primary Immune Deficiency Diseases

Cassandra D. Josephson, MD
Director, Cancer and Blood Disorders Institute
Director, Blood Bank, Transfusion, and Apheresis Service
Johns Hopkins All Children's Hospital
St. Petersburg, Florida;
Professor (PAR), Oncology and Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland
519. Red Blood Cell Transfusions and Erythropoietin Therapy
520. Platelet Transfusions
522. Neutrophil (Granulocyte) Transfusions
522. Plasma Transfusions
523. Risks of Blood Transfusions

Joel C. Joyce, MD
Section Chief, Pediatric Dermatology
NorthShore University Health System
Skokie, Illinois;
Clinical Assistant Professor of Dermatology
University of Chicago Pritzker School of Medicine
Chicago, Illinois
693. Hyperpigmented Lesions
694. Hypopigmented Lesions
695. Vesiculobullous Disorders
712. Nutritional Dermatoses

Soma Jyonouchi, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Allergy and Immunology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
164. Orientation to the Consideration of Inborn Errors of Immunity

Mohammad Nasser Kabbany, MD
Assistant Professor of Pediatrics
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Department of Pediatric Gastroenterology, Hepatology, and Nutrition
Cleveland Clinic Children's
Cleveland, Ohio
393. Tumors of the Digestive Tract

Marielle Kabbouche, MD, FAAN, FAHS
Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Neurology
Director, Headache Center
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
635. Headaches

Joanne Kacperski, MD, FAHS
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Neurology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
635. Headaches

Nadia A. Kadry, PhD
Biologist
US Food and Drug Administration
Center for Devices and Radiological Health
Silver Spring, Maryland
240. Haemophilus influenzae

Batul Kaj-Carbaidwala, MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Attending Physician
Department of Gastroenterology, Hepatology & Nutrition
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
408. Liver Disease Associated with Systemic Disorders

Jennifer M. Kalish, MD, PhD
Assistant Professor of Pediatrics and Genetics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Human Genetics
Lorenzo "Turtle" Sartini Jr. Endowed Chair in Beckwith-Wiedemann Syndrome Research
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
598.1. Overgrowth Syndromes

Deepak Kamat, MD, PhD, FAAP
Professor of Pediatrics
Vice Chair for Academic Affairs
Chair, Promotion and Tenure Committee
Department of Pediatrics
Joe R and Teresa Lozano Long School of Medicine
UT Health San Antonio
San Antonio, Texas
219. Fever

Alvina R. Kansra, MD
Associate Medical Director
AbbVie
North Chicago, Illinois
626. Hypofunction of the Ovaries
627. Pseudoprecocity Resulting From Lesions of the Ovary

David M. Kanter, MD
Assistant Professor of Physical Medicine and Rehabilitation
State University of New York
SUNY Upstate Medical University
Syracuse, New York
756. Health and Wellness for Children With Disabilities

Carol M. Kao, MD
Associate Professor of Pediatrics
Washington University School of Medicine in St. Louis
Division of Pediatric Infectious Diseases
St. Louis Children's Hospital
St. Louis, Missouri
227. Staphylococcus

Prasanna K. Kapavarapu, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
378. Motility Disorders and Hirschsprung Disease
390. Cyclic Vomiting Syndrome

Jacob Kattan, MD, MSCR
Assistant Professor of Pediatrics, Allergy and Immunology
Jack and Lucy Clark Department of Pediatrics
Jaffe Food Allergy Institute
Icahn School of Medicine at Mount Sinai
Mount Sinai Kravis Children's Hospital
New York, New York
183. Diagnosis of Allergic Disease

Andrea Kelly, MD, MSCE
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
27. Assessment of Growth

Desmond P. Kelly, MD
Professor of Pediatrics
University of South Carolina School of Medicine Greenville
Interim Chief Academic Executive Officer
Prisma Health
Greenville, South Carolina;
Clinical Professor
Clemson University School of Health Research
Clemson, South Carolina
49. Neurodevelopmental and Executive Function and Dysfunction

Matthew S. Kelly, MD, MPH
Associate Professor of Pediatrics
Associate Research Professor of Global Health and Molecular Genetics & Microbiology
Duke University School of Medicine
Durham, North Carolina
449. Community-Acquired Pneumonia

Michael E. Kelly, MD, PhD
Clinical Professor of Pediatrics
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Cleveland, Ohio
537. Anatomy and Function of the Lymphatic System
538. Abnormalities of Lymphatic Vessels

Sadiqa Kendi, MD, MPH, CPST
Associate Professor of Pediatrics
Boston University Chobanian & Avedisian School of Medicine
Division Chief, Pediatric Emergency Medicine
Boston Medical Center
Boston, Massachusetts
14. Injury Control

Eitan Kerem, MD
Professor of Pediatrics
Hadassah University Medical Center
Jerusalem, Israel
15.3. Effects of War on Children

Julie M. Kerr, MD
Sports Medicine Center
Akron Children's Hospital
Medical Director
University of Akron Health Services
Team Physician
Department of Intercollegiate Athletics
University of Akron
Akron, Ohio;
Clinical Associate Professor of Pediatrics
Northeast Ohio Medical University
Rootstown, Ohio
730. Cervical Spine Injuries

David A. Khan, MD
Professor of Internal Medicine and Pediatrics
University of Texas Southwestern Medical Center
Dallas, Texas
189. Urticaria (Hives) and Angioedema

Seema Khan, MD
Clinical Associate Professor of Pediatrics
Division of Pediatric Gastroenterology, Hepatology & Nutrition
Stanford University School of Medicine
The Lucile Packard Children's Hospital
Palo Alto, California
364. Embryology, Anatomy, and Function of the Esophagus
365. Congenital Anomalies
366. Obstructing Disorders of the Esophagus
367. Dysmotility
368. Hiatal Hernia
369. Gastroesophageal Reflux Disease
370. Eosinophilic Esophagitis, Pill Esophagitis, and Infective Esophagitis
371. Esophageal Perforation
372. Esophageal Varices
373. Ingestions

Ameneh Khatami, BHB, MBChB, MD
Senior Lecturer, Discipline of Child and Adolescent Health
University of Sydney
Department of Infectious Diseases and Microbiology
The Children's Hospital at Westmead
Sydney, Australia
250. Aeromonas and Plesiomonas

Ilya Khaytin, MD, PhD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Attending Physician, Divisions of Autonomic Medicine and Sleep Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute
Chicago, Illinois
468.3. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Catherine Kier, MD, FAAP, FCCP, DABSM, AE-C, ATSF
Professor of Pediatrics
Renaissance School of Medicine at Stony Brook University
Division of Pulmonology
Stony Brook Children's Hospital
Stony Brook, New York
443. Other Distal Airway Diseases

Alexandra Kilinsky, DO, MS-HPPL
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Division of Pediatric Hospital Medicine
Children's Hospital Colorado
Aurora, Colorado
215. Immunization Practices

Chong-Tae Kim, MD, PhD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Rehabilitation Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
750. Rehabilitation for Traumatic Brain Injury

Jung Won Kim, MD
Assistant Professor of Psychiatry
Department of Psychiatry
Harvard Medical School
Attending Psychiatrist
Department of Psychiatry & Behavioral Sciences
Boston Children's Hospital
Boston, Massachusetts
37. Motor Disorders and Habits

Rosa K. Kim, MD
Assistant Professor of Psychiatry and Behavioral Medicine
Division of Child and Adolescent Psychiatry
Medical Director, Wisconsin Child Psychiatry Consultation Program (WI CPCP)
Medical College of Wisconsin
Milwaukee, Wisconsin
38. Anxiety Disorders, Obsessive-Compulsive Disorder, and Posttraumatic Stress Disorder
39. Mood Disorders
40. Suicide and Attempted Suicide
47. Childhood Psychoses
48. Delirium

J. Michael King, MD, MEd
Attending Physician
Division of Rehabilitation Medicine
Associate Director, Trauma Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
750. Rehabilitation for Traumatic Brain Injury

Matthew P. Kirschen, MD, PhD
Assistant Professor
Associate Director, Pediatric Neurocritical Care
Department of Anesthesia and Critical Care Medicine
Departments of Pediatrics and Neurology
University of Pennsylvania Perelman School of Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
83. Brain Death: Death by Neurologic Criteria

Priya S. Kishnani, MD
C.L. and Su Chen Professor of Pediatrics
Chief, Division of Medical Genetics
Duke University Medical Center
Durham, North Carolina
107. Defects in Metabolism of Carbohydrates

Meghan A. Klawonn, MD
Clinical Assistant Professor of Physical Medicine and Rehabilitation
State University of New York
SUNY Upstate Medical University
Syracuse, New York
756. Health and Wellness for Children With Disabilities

Bruce L. Klein, MD
Associate Professor of Pediatrics
Johns Hopkins University School of Medicine
Director, Transport Services
Johns Hopkins Bloomberg Children's Center
Baltimore, Maryland
77.1. Interfacility Transport of the Seriously Ill or Injured Pediatric Patient
80. Acute Care of Multiple Trauma

Bruce S. Klein, MD
Professor of Pediatrics, Internal Medicine, and Medical Microbiology and Immunology
Chief, Division of Pediatric Infectious Disease
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
285. Blastomycosis

Alison S. Kliegman, MPH
Public Health Clinic Operations Director
City of Milwaukee Health Department
Milwaukee, Wisconsin
161.1. Abortion

Robert M. Kliegman, MD
Professor of Pediatrics
Nelson Service for Undiagnosed and Rare Diseases
Medical College of Wisconsin
Milwaukee, Wisconsin
134. Digestive System Disorders
137. Jaundice and Hyperbilirubinemia in the Newborn
161.1. Abortion
493.3. Generalized Arterial Calcification of Infancy (Idiopathic Infantile Arterial Calcification)
493.4. Arterial Tortuosity

Martin C.J. Kneyber, MD, PhD, FCCM
Consultant in Paediatric Intensive Care
University of Groningen Faculty of Medical Sciences
Chief, Division of Paediatric Critical Care Medicine
Beatrix Children's Hospital
Medical President-Elect, European Society for Paediatric and Neonatal Intensive Care
Groningen, Netherlands
86. Acute Care of Respiratory Distress and Failure

William C. Koch, MD
Professor of Pediatrics
Virginia Commonwealth University School of Medicine
Division of Pediatric Infectious Diseases
Children's Hospital of Richmond at VCU
Richmond, Virginia
298. Parvoviruses

Patrick M. Kochanek, MD, MCCM
Distinguished Professor of Critical Care Medicine
Ake N. Grenvik Professor of Critical Care Medicine
Vice Chair, Department of Critical Care Medicine
Professor of Anesthesiology, Pediatrics, Bioengineering, and Clinical and Translational Science
University of Pittsburgh School of Medicine
Director, Safar Center for Resuscitation Research
UPMC Children's Hospital of Pittsburgh
John G. Rangos Research Center
Pittsburgh, Pennsylvania
82. Neurologic Emergencies and Stabilization

Eric Kodish, MD
Professor of Pediatrics, Oncology and Bioethics
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Vice-Chair, Professional Staff Affairs and Faculty Development
Pediatric Institute
Cleveland Clinic
Cleveland, Ohio
6. Ethics in Pediatric Care

Stephan A. Kohlhoff, MD
Associate Professor of Pediatrics and Medicine
Chief, Division of Pediatric Infectious Diseases
SUNY Downstate Health Sciences University
Brooklyn, New York
271. Chlamydia pneumoniae
273. Psittacosis (Chlamydia psittaci)

Mark G. Kortepeter, MD, MPH, FACP, FIDSA, FASTMH
Vice President for Research
Professor of Medicine and Preventive Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland
763. Biological and Chemical Terrorism

Karen L. Kotloff, MD
Professor of Pediatrics
Head, Division of Infectious Disease and Tropical Pediatrics
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, Maryland
387. Acute Gastroenteritis in Children

Anastassios C. Koumbourlis, MD, MPH
Professor of Pediatrics
George Washington University School of Medicine and Health Sciences
Chief, Division of Pulmonary and Sleep Medicine
Director, Cystic Fibrosis Center
Children's National Medical Center
Washington, DC
446. Acute Aspiration
447. Chronic Recurrent Aspiration

Peter J. Krause, MD
Senior Research Scientist in Epidemiology (Microbial Diseases), Medicine (Infectious Diseases), and Pediatrics (Infectious Diseases)
Affiliated Faculty, Yale Institute for Global Health
Yale School of Public Health
New Haven, Connecticut
335. Babesiosis (Babesia)

Nancy F. Krebs, MD, MS
Professor and Associate Vice Chair, Academic Affairs
Department of Pediatrics
University of Colorado School of Medicine
Head, Section of Pediatric Nutrition
Children's Hospital Colorado
Aurora, Colorado
60. Nutritional Requirements
61. Feeding Healthy Infants, Children, and Adolescents
64. Malnutrition in High-Resource Settings

Richard E. Kreipe, MD, FAAAP, FSAHM, FAED
Professor Emeritus of Pediatrics
University of Rochester School of Medicine and Dentistry
Division of Adolescent Medicine
Golisano Children's Hospital
Rochester, New York
41. Eating Disorders

Steven E. Krug, MD
Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Former Head, Division of Pediatric Emergency Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
77. Emergency Medical Services for Children

Janet L. Kwiatkowski, MD, MSCE
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Hematology
Director, Thalassemia Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
511. Hemoglobinopathies

Jennifer M. Kwon, MD
Professor of Child Neurology
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
639. Neurodegenerative Disorders of Childhood

Stephan Ladisch, MD
Professor
Departments of Pediatrics and Biochemistry and Molecular Biology
George Washington University School of Medicine
Center for Cancer and Immunology Research
Center for Cancer and Blood Disorders
Children's Research Institute
Children's National Medical Center
Washington, DC
556. Histiocytosis Syndromes of Childhood

Oren J. Lakser, MD
Master Clinician
Division of Pulmonary and Sleep Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Chicago, Illinois
452. Bronchiectasis
453. Pulmonary Abscess

Leah Lalor, MD
Associate Professor of Dermatology and Pediatrics
Medical College of Wisconsin
Department of Dermatology
Division of Pediatric Dermatology
Milwaukee, Wisconsin
701.2. Lipodystrophy
705. Disorders of the Mucous Membranes
710. Acne
745. Cutis Laxa

Simon Lam, MD, FRCPC
Clinical Assistant Professor of Pediatrics
University of Calgary Cummings School of Medicine
Section of Pediatric Gastroenterology, Hepatology & Nutrition
Alberta Children's Hospital
Calgary, Alberta
404. Cholestasis

Michele P. Lambert, MD, MSTR
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Medical Director, Special Coagulation Laboratory
Associate Clinical Director, Frontier Program in Immune Dysregulation
Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
138. Blood Disorders
139. Anemia in the Newborn Infant
140. Hemolytic Disease of the Fetus and Newborn
141. Neonatal Polycythemia
142. Hemorrhage in the Newborn Infant

Christina Lampe, MD
Senior Physician
Center for Rare Diseases Giessen (ZSEGI)
Department of Pediatric Neurology, Social Pediatrics, and Epileptology
Center for Pediatrics and Adolescent Medicine
University Hospital of Giessen
Giessen, Germany
109. Mucopolysaccharidoses

Gregory L. Landry, MD
Professor Emeritus
Department of Pediatrics
University of Wisconsin – Madison
School of Medicine and Public Health
Madison, Wisconsin
727. Prevention of Injuries
728. Management of Musculoskeletal Injury
731. Heat Injuries
732. Nutrition and Endocrine Conditions in Athletes
733. Performance-Enhancing Aids
734. Specific Sports and Associated Injuries

Wendy G. Lane, MD, MPH, FAAP
Clinical Associate Professor
Departments of Epidemiology and Public Health and Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland
17. Abused and Neglected Children

A. Noelle Larson, MD
Professor of Orthopedics
Chair, Division of Community Orthopedics
Mayo Clinic
Rochester, Minnesota
550.2. Benign Tumors and Tumor-Like Processes of Bone

Phillip S. LaRussa, MD
Professor of Pediatrics
Columbia University Vagelos College of Physicians and Surgeons
Division of Pediatric Infectious Diseases
NewYork-Presbyterian Morgan Stanley Children's Hospital
New York, New York
300. Varicella-Zoster Virus

J. Todd R. Lawrence, MD, PhD
Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
718. The Knee

Brendan Lee, MD, PhD
Robert and Janice McNair Endowed Chair in Molecular and Human Genetics
Professor and Chairman
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
95. Genetics in Pediatric Medicine
96. Principles of Human Genetics
97. Patterns of Genetic Transmission
98. Integration of Genetics into Pediatric Practice
99. Chromosome Disorders
103. Genetics of Common Disorders

Erica H. Lee, PhD
Assistant Professor of Psychology in Psychiatry
Harvard Medical School
Attending Psychologist
Department of Psychiatry and Behavioral Sciences
Attending Psychologist
Department of Psychiatry and Behavioral Sciences
Boston Children's Hospital
Boston, Massachusetts
34. Psychotherapy
42. Disruptive, Impulse-Control, and Conduct Disorders
43. Tantrums and Breath-Holding Spells
44. Lying, Stealing, and Truancy
45. Aggression

Jennifer W. Leiding, MD
Adjunct Associate Professor
Johns Hopkins University
Baltimore, Maryland;
Institute for Clinical and Translational Research
Johns Hopkins All Children's Hospital
St. Petersburg, Florida
174. Immune Dysregulation

Monica E. Lemmon, MD
Associate Professor of Pediatrics and Population Health Sciences
Medical Director, Children's Clinical Research Unit
Duke University Medical Center
Durham, North Carolina
633.7. Neonatal Seizures

Daniel J. Lesser, MD
Clinical Professor of Pediatrics
University of California San Diego School of Medicine
Division of Respiratory Medicine
Rady Children's Hospital–San Diego
San Diego, California
421. Diagnostic Approach to Respiratory Disease

Steven O. Lestrud, MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Medical Director, Respiratory Care
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
468.1. Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Donald Y. M. Leung, MD, PhD
Professor of Pediatrics
University of Colorado School of Medicine
Edelstein Family Chair of Pediatric Allergy-Immunology
National Jewish Health
Denver, Colorado
186. Atopic Dermatitis (Atopic Eczema)

Michael N. Levas, MD, MS
Associate Professor of Pediatrics
Medical College of Wisconsin
Director of Social Medicine
Division of Pediatric Emergency Medicine
Medical Director, Project Ujima
Associate Director, Comprehensive Injury Center
Children's Wisconsin
Milwaukee, Wisconsin
156. Violent Behavior

Chris A. Liacouras, MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Clinical Laboratory
Medical Director, CHOP Exton Satellite
Co-Director, Center for Pediatric Eosinophilic Disorders
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
351. Normal Digestive Tract Phenomena
352. Major Symptoms and Signs of Digestive Tract Disorders
374. Normal Development, Structure, and Function of the Stomach and Intestines
375. Pyloric Stenosis and Other Congenital Anomalies of the Stomach
376. Intestinal Atresia, Stenosis, and Malrotation
377. Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct
378. Motility Disorders and Hirschsprung Disease
379. Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions
380. Foreign Bodies and Bezoars
389. Disorders of Brain-Gut Interaction (Functional Gastrointestinal Disorders)
390. Cyclic Vomiting Syndrome
417. Peritoneal Malformations
418. Ascites
419. Peritonitis

Paul H. Lipkin, MD
Professor of Pediatrics
Kennedy Krieger Institute
Johns Hopkins University School of Medicine
Baltimore, Maryland
28. Developmental and Behavioral Surveillance and Screening

Deborah R. Liptzin, MD, MS
Associate Clinical Professor of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado
448.7. Fibrotic Lung Disease

Andrew H. Liu, MD
Professor of Pediatrics
Section of Pediatric Pulmonary and Sleep Medicine
Children's Hospital Colorado
University of Colorado School of Medicine
Aurora, Colorado
185. Childhood Asthma

Mindy S. Lo, MD, PhD
Assistant Professor of Pediatrics
Harvard Medical School
Director, Rheumatology Fellowship Training Program
Boston Children's Hospital
Boston, Massachusetts
208. Kawasaki Disease

Stanley F. Lo, PhD
Professor of Pathology
Medical College of Wisconsin
Technical Director, Clinical Chemistry and Point of Care Testing
Director, Reference Standards Library
Co-Director, Biochemical Genetics Laboratory
Associate Director, Clinical Pathology
Children's Wisconsin
Milwaukee, Wisconsin
769. Laboratory Testing in Infants and Children
770. Reference Intervals for Laboratory Tests and Procedures

Sarah S. Long, MD
Professor of Pediatrics
Drexel University College of Medicine
Chief Emeritus
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
243. Pertussis (Bordetella pertussis and Bordetella parapertussis)

Katherine Lord, MD
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Inpatient Endocrinology Service
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
113. Hypoglycemia

Charles G. Macias, MD, MPH
Associate Professor of Pediatrics
Case Western Reserve University School of Medicine
Division Chief, Pediatric Emergency Medicine
Executive Director, EMS for Children Innovation and Improvement Center
Chief Quality Officer/Vice Chair Quality & Safety
University Hospitals Rainbow Babies & Children's Hospital
Cleveland, Ohio
77. Emergency Medical Services for Children

Michelle M. Macias, MD
Professor of Pediatrics
Director, SC Leadership Education in Neurodevelopmental and Related Disabilities Program
Division of Developmental-Behavioral Pediatrics
Department of Pediatrics
Medical University of South Carolina
Charleston, South Carolina
54. Augmentative and Alternative Communication

Ian R. Macumber, MD
Clinical Assistant Professor of Pediatrics
Keck School of Medicine of USC
University of Southern California
Attending Physician
Division of Nephrology
Children's Hospital Los Angeles
Los Angeles, California
494. Systemic Hypertension

Mark R. Magnusson, MD, PhD
Medical Director, Diagnostic and Complex Care Center; Spina Bifida Program; Inpatient Rehabilitation Unit; Acquired Autonomic Dysfunction Program and Clinic; Children's Hospital Home Care
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
212.1. Chronic Fatigue Syndrome

Pilar L. Magoulas, MS, CGC
Associate Professor
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
98.1. Genetic Counseling

Kathleen J. Maguire, MD
Attending Orthopaedic Surgeon
Sports Medicine and Performance Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
714. Orthopedic Evaluation of the Child

Prashant V. Mahajan, MD, MPH, MBA
Professor of Emergency Medicine and Pediatrics
Vice-Chair, Department of Emergency Medicine
Division Chief, Pediatric Emergency Medicine
C.S. Mott Children's Hospital
University of Michigan Medical School
Ann Arbor, Michigan
760. Heavy Metal Intoxication

Joseph A. Majzoub, MD
Thomas Morgan Rotch Professor of Pediatrics
Harvard Medical School
Vice Chair for Research
Department of Pediatrics
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts
596. Diabetes Insipidus
597. Other Abnormalities of Arginine Vasopressin Metabolism and Action

Petar Mamula, MD
Professor and Distinguished Endowed Chair
Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Kohl's GI Nutrition and Diagnostic Center
Co-Director, Center for Digestive, Liver and Pancreatic Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
380. Foreign Bodies and Bezoars

Colleen K. Manak, MD
Assistant Professor of Psychiatry and Behavioral Medicine
Medical College of Wisconsin
Wisconsin Child Psychiatric Consultation Program (WI CPCP)
Division of Child and Adolescent Psychiatry
Children's Wisconsin
Milwaukee, Wisconsin
39. Mood Disorders
48. Delirium

Courtney W. Mangus, MD
Assistant Professor of Pediatrics and Emergency Medicine
University of Michigan Medical School
Ann Arbor, Michigan
80. Acute Care of Multiple Trauma

Irini Manoli, MD, PhD
Clinician Associate Investigator
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland
105.6. Isoleucine, Leucine, Valine, and Related Organic Acidemias

Adnan Y. Manzur, MD, FRCPCH
Consultant Paediatric Neurologist
Dubowitz Neuromuscular Centre (DNC)
Great Ormond Street Hospital for Children
London, United Kingdom
647. Evaluation and Investigation of Neuromuscular Disorders
648. Developmental Disorders of Muscle
649. Muscular Dystrophies
650. Endocrine and Toxic Myopathies
651. Metabolic Myopathies and Channelopathies
652. Disorders of Neuromuscular Transmission and of Motor Neurons
653. Hereditary Motor-Sensory Neuropathies
654. Toxic Neuropathies

Asim Maqbool, MD
Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology, and Nutrition
Director, Center for Pancreatic Disorders
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
351. Normal Digestive Tract Phenomena
352. Major Symptoms and Signs of Digestive Tract Disorders
374. Normal Development, Structure, and Function of the Stomach and Intestines
389. Disorders of Brain-Gut Interaction (Functional Gastrointestinal Disorders)
390. Cyclic Vomiting Syndrome

Col. Ashley M. Maranich, MD, MHPE, FAAP, FIDSA
Assistant Dean for Clinical Sciences
Associate Professor of Pediatrics
Uniformed Services University of the Health Sciences
Bethesda, Maryland
282. Malassezia

Miranda Margetts, PhD
Assistant Research Professor
Center for American Indian and Rural Health Equity
Montana State University
Bozeman, Montana
591. Vulvovaginal and Müllerian Anomalies

David Margolis, MD
Professor of Pediatrics
Medical College of Wisconsin
Program Director, Bone Marrow Transplantation
Children's Wisconsin
Milwaukee, Wisconsin
177. Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation
178. Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors
179. Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease
181. Late Effects of Hematopoietic Stem Cell Transplantation

Mona Marin, MD
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia
300. Varicella-Zoster Virus

Joan C. Marini, MD, PhD
Scientist Emeritus, Section on Heritable Disorders of Bone and Extracellular Matrix
National Institute for Child Health and Development
National Institutes of Health
Bethesda, Maryland
742. Osteogenesis Imperfecta

Morri Markowitz, MD
Professor of Pediatrics and Medicine
Albert Einstein College of Medicine
Director, Lead Poisoning Prevention and Treatment Program
The Children's Hospital at Montefiore
Bronx, New York
761. Lead Poisoning

Stacene R. Maroushek, MD, PhD, MPH
Assistant Professor of Pediatrics
University of Minnesota Medical School
Divisions of Pediatric Infectious Diseases and General Pediatrics
Hennepin County Medical Center
Minneapolis, Minnesota
11. Medical Evaluation of the Foreign-Born Child
260. Principles of Antimycobacterial Therapy

Justin D. Marsh, MD
Eye Physicians of Central Florida
Maitland, Florida
658. Growth and Development of the Eye
659. Examination of the Eye
660. Abnormalities of Refraction and Accommodation
661. Disorders of Vision
662. Abnormalities of Pupil and Iris
663. Disorders of Eye Movement and Alignment
664. Abnormalities of the Lids
665. Disorders of the Lacrimal System
666. Disorders of the Conjunctiva
667. Abnormalities of the Cornea
668. Abnormalities of the Lens
669. Disorders of the Uveal Tract
670. Disorders of the Retina and Vitreous
671. Abnormalities of the Optic Nerve
672. Childhood Glaucoma
673. Orbital Abnormalities
674. Orbital Infections
675. Injuries to the Eye

Trisha L. Marshall, MD, MSc
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Hospital Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
4. Quality and Value in Healthcare for Children

Kari L. Martin, MD
Associate Professor of Dermatology and Child Health
Co-Medical Director, Dermatology Clinics
University of Missouri School of Medicine
Columbia, Missouri
688. Dermatologic Diseases of the Neonate
689. Cutaneous Defects
690. Ectodermal Dysplasias
691. Vascular Anomalies
692. Cutaneous Nevi
699. Disorders of Keratinization
702. Disorders of the Sweat Glands
703. Disorders of Hair
704. Disorders of the Nails
711. Tumors of the Skin

Vicki K. Masson, MD
Assistant Professor of Pediatrics
Renaissance School of Medicine at Stony Brook University
Division of Pulmonology
Stony Brook Children's Hospital
Stony Brook, New York
441. Emphysema and Overinflation
442. α1-Antitrypsin Deficiency and Emphysema

Dena R. Matalon, MD
Clinical Associate Professor of Pediatrics and Medical Genetics
Stanford University School of Medicine
Palo Alto, California
105.15. N-Acetylaspartic Acid (Canavan Disease)

†Reuben K. Matalon, MD, PhD
Professor of Pediatrics and Genetics
University of Texas Medical Branch
Texas Children's
Galveston, Texas
105.15. N-Acetylaspartic Acid (Canavan Disease)

Irene M.J. Mathijssen, MD, PhD, MBA-H
Professor and Head
Department of Plastic and Reconstructive Surgery
Head, Craniofacial Research
Erasmus Medical Center
Rotterdam, The Netherlands
631.10 Craniosynostosis

Sravan Kumar Reddy Matta, MD
Medical Director
Medical Safety and Pharmacovigilance
Intercept Pharmaceutical
Morristown, New Jersey
364. Embryology, Anatomy, and Function of the Esophagus
365. Congenital Anomalies
366. Obstructing Disorders of the Esophagus
367. Dysmotility
368. Hiatal Hernia
369. Gastroesophageal Reflux Disease

Elizabeth C. Maxwell, MD, MS
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
379. Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

Aletha Maybank, MD, MPH
Chief Health Equity Officer and Senior Vice President
American Medical Association
New York, New York
2.1. Racism and Child Health

Megan E. McCabe, MD, FAAP
Vice Chair for Education
Associate Professor of Pediatrics
Hackensack Meridian School of Medicine
Joseph Sanzari Children's Hospital
Hackensack, New Jersey
30. Loss, Separation, and Bereavement

Darla H. McCain, MD, MA, FAAP, NCSP
Clinical Assistant Professor of Pediatrics
University of South Carolina School of Medicine Greenville
Division of Developmental Pediatrics
Prisma Health Children's Hospital – Upstate
Greenville, South Carolina
49. Neurodevelopmental and Executive Function and Dysfunction

Susanna A. McColley, MD
Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Scientific Director, Interdisciplinary Research Partnerships
Stanley Manne Children's Research Institute
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
422.1. Extrapulmonary Diseases With Pulmonary Manifestations
460. Pulmonary Tumors

Neena McConnico, PhD
Assistant Professor of Pediatrics
Boston University Aram V. Chobanian & Edward Avedisian School of Medicine
Executive Director, Child Witness to Violence Program
Boston, Massachusetts
15. Impact of Violence Exposure on Children

Elizabeth M. McCormick, MS, LCGC
Senior Genetic Counselor
Research Coordinator, Mitochondrial Medicine Frontier Program
Division of Human Genetics, Department of Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
108. Mitochondrial Disease Diagnosis

Christine M. McDonald, ScD, MS
Assistant Professor of Pediatrics
The Benioff Center for Microbiome Medicine
UC San Francisco School of Medicine
San Francisco, California
62. Nutrition, Food Security, and Health

Margaret M. McGovern, MD, PhD
Deputy Dean for Clinical Affairs
Yale School of Medicine
CEO, Yale Medicine
New Haven, Connecticut
106.4. Lipidoses (Lysosomal Storage Disorders)
106.5. Mucolipidoses
107.6. Disorders of Glycoprotein Degradation and Structure

Sharon A. McGrath-Morrow, MD, MBA
Professor of Pediatrics
Robert Gerard Morse Endowed Chair in Pediatric Pulmonary Medicine
University of Pennsylvania Perelman School of Medicine
Associate Chief
Division of Pulmonary and Sleep Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
466. Bronchopulmonary Dysplasia

Alissa McInerney, MD, FAAP
Summit Health Allergy & Immunology
New York, New York
176. Approaches to Treatment of Primary Immune Deficiency Diseases

Jeffrey S. McKinney, MD, PhD
Professor of Pediatrics
Vice Chair for Education
Harry W. Bass Jr. Professorship in Pediatric Education
Distinguished Teaching Professor
Division of Pediatric Infectious Diseases
UT Southwestern Medical Center
Dallas, Texas
244. Salmonella

Rima McLeod, MD
Professor of Ophthalmology and Visual Science and Pediatrics
Medical Director, Toxoplasmosis Center
University of Chicago Pritzker School of Medicine
Chicago, Illinois
336. Toxoplasmosis (Toxoplasma gondii)

Marcene R. McVay-Gillam, MD, FACS, FAAP
Associate Professor of Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas;
Medical Director, Trauma Program
Medical Director, Surgery
Arkansas Children's Northwest
Springdale, Arkansas
588. Breast Health

Julia C. Meade, MD
Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine
Director, Pediatric Cancer Predisposition Program
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
542. Principles of Cancer Diagnosis
543. Principles of Cancer Treatment
544. The Leukemias

William P. Meehan III, MD
Associate Professor of Pediatrics and Orthopedics
Harvard Medical School
Director, The Micheli Center for Sports Injury Prevention
Director, Clinical Effectiveness Research Center
Director of Research
Division of Sports Medicine
Boston Children's Hospital
Boston, Massachusetts
729. Sports-Related Traumatic Brain Injury (Concussion)

†Deceased

Asuncion Mejias, MD, PhD, MSCS
Professor of Pediatrics
Pediatric Infectious Diseases Physician
Member, St Jude Faculty
Department of Infectious Diseases
St Jude Children's Research Hospital
Memphis, Tennessee
262. Hansen Disease (Mycobacterium leprae)
269. Mycoplasma pneumoniae
270. Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma urealyticum)

Peter C. Melby, MD
Professor of Internal Medicine (Infectious Diseases), Microbiology and Immunology, and Pathology
Director, Division of Infectious Diseases
Director, Center for Tropical Diseases
University of Texas Medical Branch (UTMB)
Galveston, Texas
331. Leishmaniasis (Leishmania)

Marlene D. Melzer-Lange, MD
Professor of Pediatrics
Medical College of Wisconsin
Program Director, Project Ujima
Children's Wisconsin
Milwaukee, Wisconsin
156. Violent Behavior

Jamie F. Merves, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
417. Peritoneal Malformations

Kevin B. Messacar, MD, PhD
Associate Professor of Pediatrics
University of Colorado School of Medicine
Section of Pediatric Infectious Diseases
Section of Hospital Medicine
Children's Hospital Colorado
Aurora, Colorado
297. Nonpolio Enteroviruses

Marian G. Michaels, MD, MPH
Professor of Pediatrics and Surgery
University of Pittsburgh School of Medicine
Director, Pediatric HIV Center
Co-Director, Pediatric Transplant Infectious Diseases
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
223. Infections in Immunocompromised Persons

Thomas F. Michniacki, MD
Clinical Assistant Professor of Pediatrics
University of Michigan Medical School
Division of Pediatric Hematology/Oncology
C. S. Mott Children's Hospital
Ann Arbor, Michigan
171. Leukopenia
172. Leukocytosis

Mohamad A. Mikati, MD
Wilburt C. Davison Professor of Pediatrics
Professor of Neurobiology
Chief, Division of Pediatric Neurology and Developmental Medicine
Duke University Medical Center
Durham, North Carolina
633. Seizures in Childhood
634. Conditions That Mimic Seizures

Hilary E. Miller-Handley, MD
Instructor in Pediatrics and Internal Medicine
Division of Infectious Diseases
University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
407. Liver Abscess

Jonathan W. Mink, MD, PhD, FAAN, FANA, FAAP
Frederick A. Horner MD Distinguished Professor in Pediatric Neurology
Professor of Neurology, Neuroscience, and Pediatrics
University of Rochester School of Medicine and Dentistry
Chief, Division of Child Neurology
Vice Chair, Department of Neurology
Director, University of Rochester Batten Center
University of Rochester Medical Center
Rochester, New York
637. Movement Disorders
764. Mass Psychogenic Illness

Karolyn Mirasola, MS
Speech and Language Pathologist
Child Development Center
Children's Wisconsin
Milwaukee, Wisconsin
53.1. Childhood-Onset Fluency Disorder

R. Justin Mistovich, MD, MBA
Associate Professor of Orthopaedic Surgery
Case Western Reserve University School of Medicine
Attending Physician
Director, Division of Pediatric Orthopaedic Surgery
MetroHealth Medical Center University Hospitals
Rainbow and Babies Children's Hospital
Cleveland, Ohio
720. The Spine
721. The Neck

Emma L. Mohr, MD, PhD
Assistant Professor
Department of Pediatrics
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
149. Congenital and Perinatal Infections

Diana Montoya-Williams, MD, MSHP
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Neonatology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
114. Overview of Morbidity and Mortality

Rachel Y. Moon, MD
Harrison Distinguished Teaching Professor of Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia
423. Sudden Infant Death Syndrome

Eva Morava, MD, PhD
Professor and Consultant
Departments of Clinical Genomics and Laboratory Medicine and Pathology
Mayo Clinic
Rochester, Minnesota
107.7. Congenital Disorders of Glycosylation

Megan A. Moreno, MD, MSEd, MPH
Professor and Vice Chair of Academic Affairs
Department of Pediatrics
Division Chief, General Pediatrics and Adolescent Medicine
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
15.1. Bullying, Cyberbullying, and School Violence
15.2. Media Violence

Ryan W. Morgan, MD, MTR
Assistant Professor of Anesthesiology, Critical Care, and Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
79. Pediatric Cardiorespiratory Emergencies and Resuscitation

Peter E. Morrison, DO
Assistant Professor of Neurology
University of Rochester School of Medicine and Dentistry
Co-Director, Tourette Association of America (TAA) Center of Excellence
University of Rochester Medical Center
Rochester, New York
637.1. Ataxias

Wynne Morrison, MD, MBE
Professor of Anesthesiology and Critical Care and Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Justin Michael Ingerman Center for Palliative Care
Justin Michael Ingerman Endowed Chair for Palliative Care
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
83. Brain Death: Death by Neurologic Criteria

Sagori Mukhopadhyay, MD, MMSc
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
136. Necrotizing Enterocolitis

Flor M. Munoz, MD
Associate Professor of Pediatrics
Baylor College of Medicine
Director, Transplant Infectious Diseases
Texas Children's
Houston, Texas
305. Influenza Viruses

David A. Munson, MD
Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Medical Director, Newborn/Infant Intensive Care Unit
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
120. Transport of the Critically Ill Newborn

Timothy F. Murphy, MD
SUNY Distinguished Professor of Medicine
Senior Associate Dean for Clinical and Translational Research
Director, Clinical and Translational Science Institute
Director, Community Health Equity Research Institute
Jacobs School of Medicine and Biomedical Sciences
Buffalo State University of New York
Buffalo, New York
242. Moraxella catarrhalis

Karen F. Murray, MD
Professor of Pediatrics
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Chair, Pediatrics Institute
Physician-in-Chief, Cleveland Clinic Children's
President, Cleveland Clinic Children's Hospital for Rehabilitation
Cleveland, Ohio
393. Tumors of the Digestive Tract

Thomas S. Murray, MD, PhD
Professor of Pediatrics, Infectious Disease and Global Health
Yale School of Medicine
Associate Medical Director, Infection Prevention
Yale New Haven Children's Hospital
New Haven, Connecticut
234. Listeria monocytogenes
251. Pseudomonas, Burkholderia, and Stenotrophomonas
486. Infective Endocarditis

Levent Mutlu, MD
Clinical Fellow in Gynecologic Oncology
Obstetrics, Gynecology, and Reproductive Sciences
Yale School of Medicine
New Haven, Connecticut
590. Gynecologic Neoplasms and Prevention Methods for Human Papillomavirus Infections in Adolescents

Jason M. Nagata, MD, MSc
Assistant Professor of Pediatrics
Division of Adolescent and Young Adult Medicine
UC San Francisco School of Medicine
San Francisco, California
62. Nutrition, Food Security, and Health
63. Refeeding Syndrome

Sona Narula, MD
Associate Professor of Clinical Neurology
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Pediatric Neurology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
642. Central Nervous System Vasculitis

James P. Nataro, MD, PhD, MBA
Professor and Chair
Department of Pediatrics
University of Virginia School of Medicine
Physician-in-Chief
UVA Children's Hospital
Charlottesville, Virginia
247. Cholera

Dipesh Navsaria, MD, MPH, MSLIS, FAAP
Associate Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Clinical Associate Professor of Human Development and Family Studies
University of Wisconsin School of Human Ecology
Madison, Wisconsin
13. Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

Ruth W. Nduati, MBChB, MMED, MPH
Professor of Pediatrics and Child Health
University of Nairobi Faculty of Health Sciences
Consultant Pediatrician Kenyatta National Hospital
Nairobi, Kenya
3. Global Child Health

Edward J. Nehus, MD, MS
Associate Professor of Pediatrics
Marshall University Joan C. Edwards School of Medicine
Division of Pediatric Nephrology
Hoops Family Children's Hospital at Cabell Huntington Hospital
Huntington, West Virginia
557. Introduction to Glomerular Diseases

Maureen R. Nelson, MD
Professor of Physical Medicine & Rehabilitation and of Pediatrics
Baylor College of Medicine
Medical Director, Physical Medicine & Rehabilitation
Texas Children's
Austin, Texas
753. Birth Brachial Plexus Palsy

Caitlin M. Neri, MD, MPH
Assistant Professor of Pediatrics
Boston University School of Medicine
Attending Physician
Division of Pediatric Hematology and Oncology
Medical Director, Pediatric Pain Clinic
Boston Medical Center
Boston, Massachusetts
7. Complementary Therapies and Integrative Medicine

Mary A. Nevin, MD, FAAP, FCCP
Associate Professor of Pediatrics
University of Chicago Medicine
Chicago, Illinois
457. Pulmonary Hemosiderosis
458. Pulmonary Embolism, Infarction, and Hemorrhage

Jane W. Newburger, MD
Commonwealth Professor of Pediatrics Harvard Medical School
Commonwealth Chair of Pediatrics
Associate Cardiologist-in-Chief, Academic Affairs
Boston Children's Hospital
Boston, Massachusetts
208. Kawasaki Disease

Jonathan Newmark, MD, MM, FAAN
Senior Medical Advisor
Office of Biodefense Research and Surety
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Rockville, Maryland;
Staff Neurologist
Washington DC VA Medical Center
Adjunct Assistant Professor of Neurology and Rehabilitation Medicine
George Washington University School of Medicine and Health Sciences
Washington, DC;
Adjunct Professor of Neurology
F. Edward Hebert School of Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland
763. Biological and Chemical Terrorism

Linda S. Nield, MD, FAAP
Associate Dean for Admissions
Professor of Medical Education and Pediatrics
West Virginia University School of Medicine
Morgantown, West Virginia
219. Fever

Susan Niermeyer, MD, MPH
Professor Emerita of Pediatrics and Epidemiology
University of Colorado School of Medicine and Colorado School of Public Health
Aurora, Colorado
87. Altitude-Associated Illness in Children

James J. Nocton, MD
Professor of Pediatrics
Section of Pediatric Rheumatology
Medical College of Wisconsin
Milwaukee, Wisconsin
90.1. Cold-Induced Autoinflammatory and Other Genetic Disorders
211. Musculoskeletal Pain Syndromes
700.1. Mast Cell Activation Syndrome

Lawrence M. Nogee, MD
Professor of Pediatrics
Eudowood Neonatal Pulmonary Division
Johns Hopkins University School of Medicine
Baltimore, Maryland
456. Diffuse Lung Diseases in Childhood

Corina Noje, MD
Associate Professor of Clinical Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine
Medical Director, Pediatric Transport
Johns Hopkins Bloomberg Children's Center
Baltimore, Maryland
77.1. Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

Anna H. Nowak-Wegrzyn, MD, PhD
Professor of Pediatrics
New York University Grossman School of Medicine
Director, Division of Pediatric Allergy and Immunology
Hassenfeld Children's Hospital at NYU Langone
New York, New York
191. Serum Sickness
192. Food Allergy and Adverse Reactions to Foods

Stephen K. Obaro, MD, PhD
Helen and Robert Whitley Endowed Chair of Pediatric Infectious Diseases
HSOM Assistant Dean for Global Health
University of Alabama, Birmingham
Birmingham, Alabama
265. Nonvenereal Treponemal Infections
267. Relapsing Fever (Borrelia)

Makram M. Obeid, MD
Assistant Professor of Neurology
Indiana University School of Medicine
Division of Pediatric Neurology
Riley Children's Health
Indianapolis, Indiana
634. Conditions That Mimic Seizures

Kevin P. O'Callaghan, MB BCh, BAO
Instructor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
214. Public Health Approach to Pandemics
216. Infection Prevention and Control

Joyce L. Oleszek, MD
Professor of Physical Medicine and Rehabilitation
University of Colorado School of Medicine
Children's Hospital Colorado
Denver, Colorado
752. Spasticity

Scott E. Olitsky, MD, MBA
Professor Emeritus of Ophthalmology
University of Missouri – Kansas City School of Medicine
Kansas City, Missouri
658. Growth and Development of the Eye
659. Examination of the Eye
660. Abnormalities of Refraction and Accommodation
661. Disorders of Vision
662. Abnormalities of Pupil and Iris
663. Disorders of Eye Movement and Alignment
664. Abnormalities of the Lids
665. Disorders of the Lacrimal System
666. Disorders of the Conjunctiva
667. Abnormalities of the Cornea
668. Abnormalities of the Lens
669. Disorders of the Uveal Tract
670. Disorders of the Retina and Vitreous
671. Abnormalities of the Optic Nerve
672. Childhood Glaucoma
673. Orbital Abnormalities
674. Orbital Infections
675. Injuries to the Eye

John M. Olsson, MD, CPE
Professor of Pediatrics
Division of General Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia
22. The Newborn

Meghan E. O'Neill, MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Division of Developmental Behavioral Pediatrics
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
56. Developmental Delay and Intellectual Disability

Mutiat T. Onigbanjo, MD
Assistant Professor of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland
23. The First Year
26. Middle Childhood

Robert O. Opoka, MD, PhD
Associate Dean
Undergraduate Medical Education
The Aga Khan University Medical College
Kampala, Uganda;
Adjunct Associate Professor of Pediatrics
Indiana University School of Medicine
Indianapolis, Indiana
334. Malaria (Plasmodium)

Helen M. Oquendo Del Toro, MD
Clinical Assistant Professor of Obstetrics and Gynecology
Division of Pediatric and Adolescent Gynecology
University of New Mexico School of Medicine
Albuquerque, New Mexico
586. Vulvovaginitis

Walter A. Orenstein, MD, DSc (Hon)
Professor Emeritus of Medicine, Pediatrics, and Global Health
Emory University
Associate Director, Emory Vaccines Center
Atlanta, Georgia;
Former Deputy Director for Immunization Programs
Bill & Melinda Gates Foundation
Seattle, Washington;
Former Director, National Immunization Program
Centers for Disease Control and Prevention
Atlanta, Georgia
215. Immunization Practices

Sarah H. Orkin, MD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Physician
Division of Gastroenterology, Hepatology and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
408.1. Nonalcoholic Fatty Liver Disease

Rachel C. Orscheln, MD
Professor of Pediatrics
Director, Clinical Services
Washington University School of Medicine in St Louis
Medical Director, Ambulatory Pediatric Infectious Diseases
St. Louis Children's Hospital
St. Louis, Missouri
255. Bartonella

Camile Ortega, DO
Allergy and Immunology Care Center of South Florida
Miami Lakes, Florida
166. B-Cell and Antibody Deficiencies

Timothy R. O'Toole, BS
Division of Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain Medicine
Boston Children's Hospital
Boston, Massachusetts
111. Hutchinson-Gilford Progeria Syndrome (Progeria)

Judith A. Owens, MD, MPH
Professor of Neurology
Harvard Medical School
Director of Sleep Medicine
Boston Children's Hospital
Boston, Massachusetts
31. Sleep Medicine

Seza Ozen, MD
Professor of Pediatrics
Department of Pediatric Rheumatology
Hacettepe University
Ankara, Turkey
202. Behçet Disease

Sophie Pach, MB BCHir
Research Fellow
London School of Hygiene and Tropical Medicine
London, United Kingdom
346. Schistosomiasis (Schistosoma)
347. Flukes (Liver, Lung, and Intestinal)

Lee M. Pachter, DO
Professor of Pediatrics and Population Health
Sidney Kimmel Medical College and Jefferson College of Population Health
Thomas Jefferson University
Philadelphia, Pennsylvania;
Senior Physician Scientist
Director, Mentorship and Professional Development
Institute for Research on Equity and Community Health (iREACH)
Christiana Care Health System
Wilmington, Delaware
1. Overview of Pediatrics
2. Child Health Disparities
12. Cultural Issues in Pediatric Care

Amruta Padhye, MD
Associate Professor of Pediatrics
Division of Pediatric Infectious Diseases
University of Missouri School of Medicine
Columbia, Missouri
233. Diphtheria (Corynebacterium diphtheriae)

Sindhu Pandurangi, MD, MSc
Assistant Professor of Pediatrics
Pediatric Gastroenterology, Hepatology and Nutrition
University of Texas Southwestern Medical Center
Dallas, Texas
409. Mitochondrial Hepatopathies

Suzinne Pak-Gorstein, MD, PhD, MPH
Associate Professor of Pediatrics
Adjunct Associate Professor of Global Health
University of Washington School of Medicine
Seattle, Washington
3. Global Child Health

John Palla, MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Attending Physician
Division of Pulmonary and Sleep Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
422.1. Extrapulmonary Diseases With Pulmonary Manifestations
460. Pulmonary Tumors

Tina L. Palmieri, MD, FACS, MCCM
Professor of Surgery
Chief, Division of Burn Surgery
Director, Firefighters Burn Institute
UC Davis School of Medicine
Assistant Chief of Burns
Shriners Hospital for Children Northern California
Sacramento, California
89. Burn Injuries

Jessica M. Palmieri, DO
Department of Pediatrics
Baylor College of Medicine
Section of Immunology, Allergy, and Retrovirology
Texas Children's
Houston, Texas
167. Natural Killer Cells

Diane E. Pappas, MD, JD
Professor of Pediatrics
Director of Child Advocacy
University of Virginia School of Medicine
Charlottesville, Virginia
429. Sinusitis
432. Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

John J. Parent, MD, MSCR
Associate Professor of Clinical Pediatrics
Indiana University School of Medicine
Section of Cardiology
Riley Hospital for Children at Indiana University Health
Indianapolis, Indiana
488. Diseases of the Myocardium
489. Diseases of the Pericardium
490. Tumors of the Heart

Joanna J. Parga-Belinkie, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
115. The Newborn Infant

Bijal A. Parikh, MD, PhD
Assistant Professor of Pathology and Immunology
Division of Laboratory and Genomic Medicine
Washington University School of Medicine
Director, Molecular Diagnostics Laboratory
Director, Molecular Genetic Pathology Fellowship
Barnes-Jewish Hospital
St. Louis, Missouri
321. Polyomaviruses

Alasdair P.J. Parker, MBBS (Lond), MRCP, MD, MA (Camb)
Consultant in Pediatric Neurology
Addenbrooke's Hospital
Associate Lecturer
University of Cambridge School of Clinical Medicine
Cambridge, United Kingdom
645. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Emily A. Partridge, MD, PhD, MHS
Assistant Professor of Surgery
University of Pennsylvania Perelman School of Medicine
Attending Pediatric and Fetal Surgeon
Division of Pediatric General, Thoracic and Fetal Surgery
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
118. Fetal Intervention and Surgery

Ami B. Patel, MD, MPH
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Associate Medical Director, Infection Prevention and Control
Division of Pediatric Infectious Diseases
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
229. Group A Streptococcus

Trusha Patel, MD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
380. Foreign Bodies and Bezoars

Stephen W. Patrick, MD, MPH, MS, FAAP
Associate Professor of Pediatrics and Health Policy
Director, Center for Child Health Policy
Vanderbilt University School of Medicine
Attending Neonatologist
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee
145. Neonatal Abstinence Syndrome

Briana C. Patterson, MD, MSCR
Associate Professor of Pediatrics
Emory University School of Medicine
Division of Pediatric Endocrinology
Director, Pediatric Endocrine Fellowship Program
Aflac Cancer & Blood Disorders Center of Children's Healthcare of Atlanta
Atlanta, Georgia
594. Hormones of the Hypothalamus and Pituitary
595. Hypopituitarism

Emanuele Pelosi, PhD
Assistant Research Professor
Department of Biochemistry and Molecular Biology School of Medicine
Indiana University–Purdue University Indianapolis
Indianapolis, Indiana
591. Vulvovaginal and Müllerian Anomalies

Sallie R. Permar, MD, PhD
Nancy C. Paduano Professor and Chair
Department of Pediatrics
Weill Cornell Medical College of Cornell University
Pediatrician-in-Chief
New York-Presbyterian Hospital
New York, New York
149. Congenital and Perinatal Infections

Michael Perry, MD, MRes, BA
PhD Candidate in Neuroimmunology
Cambridge Centre for Myelin Repair
University of Cambridge
Cambridge, United Kingdom;
Honorary Clinical Research Fellow in Paediatric Neurology
Great Ormond Street Hospital for Children
London, United Kingdom
638.3. Other Encephalopathies
640. Demyelinating Disorders of the Central Nervous System

Tamara T. Perry, MD, FAAP, FAAAAI
Professor of Pediatrics
Dr. & Mrs. Leeman King Endowed Chair in Pediatric Allergy
University of Arkansas for Medical Sciences
Chief of Allergy and Immunology
Arkansas Children's Hospital
Little Rock, Arkansas
184. Allergic Rhinitis

Mark J. Peters, MBChB, DPhil
Professor of Paediatric Intensive Care
Infection, Immunity & Inflammation Department
University College London – Great Ormond Street Institute of Child Health
London, United Kingdom
85. Shock

Timothy R. Peters, MD
Professor of Pediatrics
Wake Forest School of Medicine
Section of Pediatric Infectious Diseases
Wake Forest Baptist Medical Center
Winston-Salem, North Carolina
228. Streptococcus pneumoniae (Pneumococcus)

Stacy J.B. Peterson, MD
Associate Professor of Anesthesiology
Medical College of Wisconsin
Division of Pediatric Anesthesiology
Jane B. Pettit Pain and Headache Center
Children's Wisconsin
Milwaukee, Wisconsin
93. Pediatric Pain Management

Rachel A. Phelan, MD, MPH
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Hematology/Oncology/BMT
Children's Wisconsin
Milwaukee, Wisconsin
177. Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation
178. Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors
179. Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease
181. Late Effects of Hematopoietic Stem Cell Transplantation

Anna L. Pinto, MD, PhD
Assistant Professor of Neurology
Harvard Medical School
Director, Sturge Weber Clinic
Boston Children's Hospital
Boston, Massachusetts
636. Neurocutaneous Syndromes
636.3. Sturge-Weber Syndrome

Mary Pipan, MD
Director, Trisomy 21 Program
Division of Behavioral Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
57. Down Syndrome and other Abnormalities of Chromosome Number

Brittany Player, DO, MS
Division of Infectious Diseases
Medical College of Wisconsin
Children's Wisconsin
Milwaukee, Wisconsin
680. Otitis Media
681. Acute Mastoiditis

William Benjamin Prince, MD
Clinical Assistant Professor of Pediatrics
and Emergency Medicine
University of Washington School of Medicine
Division of Emergency Medicine
Seattle Children's Hospital
Seattle, Washington
88. Drowning and Submersion Injury

Mark R. Proctor, MD
Franc D. Ingraham Professor of Neurosurgery
Harvard Medical School
Neurosurgeon-in-Chief
Boston Children's Hospital
Boston, Massachusetts
81. Spinal Cord Injuries in Children
646. Spinal Cord Disorders
729. Sports-Related Traumatic Brain Injury (Concussion)

Stephanie Prozora, MD
Assistant Professor of Clinical Pediatrics
Division of Pediatric Hematology/Oncology
Pediatric Medical Director
Yale Hemophilia Treatment Center
Yale School of Medicine
New Haven, Connecticut
506. Definitions and Classification of Hemolytic Anemias
507. Hereditary Spherocytosis
508. Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis and Related Disorders
509. Hereditary Stomatocytosis Syndromes
510. Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

Howard I. Pryor II, MD
Associate Professor of Surgery
Baylor College of Medicine
Trauma Medical Director
Texas Children's
Houston, Texas;
Associate Professor of Surgery
Uniformed Services University of the Health Sciences
Walter Reed National Military Medical Center
Washington, DC
80. Acute Care of Multiple Trauma

Lee A. Pyles, MD, MS
Professor of Pediatrics
Pediatric Vice-Chair for Research
Director, Preventive Pediatric Cardiology
Division of Pediatric Cardiology
West Virginia University School of Medicine
Morgantown, West Virginia
106.3. Disorders of Lipoprotein Metabolism and Transport

Molly M. Quinn, MD
Assistant Professor of Clinical Obstetrics and Gynecology
Keck School of Medicine
University of Southern California
Los Angeles, California
589. Polycystic Ovary Syndrome and Hirsutism

Elisabeth H. Quint, MD
Professor of Obstetrics and Gynecology
University of Michigan Medical School
Ann Arbor, Michigan
592. Gynecologic Care for Adolescents with Special Needs

C. Egla Rabinovich, MD, MPH
Professor of Pediatrics
Duke University School of Medicine
Durham, North Carolina
194. Evaluation of Suspected Rheumatic Disease
195. Treatment of Rheumatic Diseases
196. Juvenile Idiopathic Arthritis
201. Scleroderma and Raynaud Phenomenon
203. Sjögren Syndrome
213. Miscellaneous Conditions Associated With Arthritis

Leslie J. Raffini, MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Medical Director, Hemostasis and Thrombosis Center
Attending Physician
Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
524. Hemostasis
527. Hereditary Predisposition to Thrombosis
528. Thrombotic Disorders in Children
532. Disseminated Intravascular Coagulation

Dristhi S. Ragoonanan, MBBS
Assistant Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
548. Neoplasms of the Kidney

Shamima Rahman, MA, BMBCh, FRCP, FRCPCH, PhD
Professor of Paediatric Metabolic Medicine
UCL Great Ormond Street Institute of Child Health
London, United Kingdom
638.2. Mitochondrial Encephalomyopathies

Shawn L. Ralston, MD, MS
Professor of Pediatrics
University of Washington School of Medicine
Chief, Division of Hospital Medicine
Seattle Children's Hospital
Seattle, Washington
439. Wheezing, Bronchiolitis, and Bronchitis

Sanjay Ram, MBBS
Professor of Medicine
University of Massachusetts Chan Medical School
Division of Infectious Diseases and Immunology
University of Massachusetts Memorial Medical Center
Worcester, Massachusetts
238. Neisseria gonorrhoeae (Gonococcus)

Octavio Ramilo, MD
Professor of Pediatrics
Chair, Department of Infectious Diseases
St Jude Children's Research Hospital
Memphis, Tennessee
269. Mycoplasma pneumoniae

Kacy A. Ramirez, MD
Associate Professor of Pediatrics
Wake Forest School of Medicine
Section of Pediatric Infectious Diseases
Wake Forest Baptist Medical Center
Winston-Salem, North Carolina
228. Streptococcus pneumoniae (Pneumococcus)

Casey M. Rand, MSDS
Research Manager and Data Scientist
Division of Autonomic Medicine
Center for Autonomic Medicine in Pediatrics
Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute
Chicago, Illinois
468.2. Congenital Central Hypoventilation Syndrome
468.3. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Sonja A. Rasmussen, MD, MS
Professor of Genetic Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland
117.4. Medications and Teratogenic Exposures

Kevin M. Rathke, MD
Clinical Associate
Department of Pediatrics
Duke University Medical Center
Durham, North Carolina
633. Seizures in Childhood

Adam J. Ratner, MD, MPH
Professor of Pediatrics and Microbiology
New York University Grossman School of Medicine
Director, Division of Pediatric Infectious Diseases
Hassenfeld Children's Hospital
New York, New York
250. Aeromonas and Plesiomonas

Lee Ratner, MD, PhD
Professor of Medicine
Professor of Molecular Microbiology and of Pathology and Immunology
Washington University School of Medicine in St. Louis
St. Louis, Missouri
323. Human T-Cell Leukemia Viruses (1 and 2)

Ann M. Reed, MD
Samuel L. Katz Distinguished Professor of Pediatrics
Chair, Department of Pediatrics
Duke University Medical Center
Physician-in-Chief
Duke Children's
Durham, North Carolina
200. Juvenile Dermatomyositis

Patrick J. Reich, MD, MSCI
Associate Professor of Pediatrics
Washington University School of Medicine in St. Louis
Division of Pediatric Infectious Diseases
Medical Director, Infection Prevention
St. Louis Children's Hospital
St. Louis, Missouri
227. Staphylococcus

Shimon Reif, MD
Chairman, Department of Pediatrics
Hadassah Medical Center
Hebrew University
Jerusalem, Israel
388.1. Diarrhea from Neuroendocrine Tumors

Megan E. Reller, MD, PhD, MPH
Associate Professor of Medicine
Duke University Medical Center
Durham North Carolina
274. Spotted Fever Group Rickettsioses
275. Scrub Typhus (Orientia tsutsugamushi)
276. Typhus Group Rickettsioses
277. Ehrlichiosis and Anaplasmosis
278. Q Fever (Coxiella burnetii)

Katherine E. Remick, MD, FAAP, FACEP, FAEMS
Associate Professor, Departments of Pediatrics and Surgery
Associate Chair for Quality, Innovation, and Outreach
Co-Director, National EMS for Children Innovation and Improvement Center
Medical Director, San Marcos Hays County EMS System
Executive Director, National Pediatric Readiness Quality Initiative
EMS Director, Pediatric Emergency Medicine Fellowship
The University of Texas at Austin Dell Medical School
Austin, Texas
77. Emergency Medical Services for Children

Allison S. Remiker, MD
Assistant Professor of Pediatrics
Section of Hematology/Oncology/Bone Marrow Transplant
Immunohematology Program Director
Medical College of Wisconsin
Attending Physician
Children's Wisconsin
Milwaukee, Wisconsin
512. Enzymatic Defects
513. Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias
514. Hemolytic Anemias Secondary to Other Extracellular Factors
515. Polycythemia
516. Nonclonal Polycythemia
534. Anatomy and Function of the Spleen
535. Splenomegaly
536. Hyposplenism, Splenic Trauma, and Splenectomy

Jorge D. Reyes, MD
Professor and Roger K. Giesecke Distinguished Chair
Department of Surgery
University of Washington School of Medicine
Chief, Division of Transplant Surgery
Seattle Children's Hospital
Seattle, Washington
386. Intestinal Transplantation in Children with Intestinal Failure
416. Liver Transplantation

Katherine M. Richardson, MD
Clinical Assistant Professor of Pediatrics
University of South Carolina School of Medicine Greenville
Division of Pediatric Infectious Diseases
Shriner's Hospital
Greenville, South Carolina
310. Rhinoviruses
428. The Common Cold

Natalie E. Rintoul, MD
Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Co-Director, Neonatal Surgical Team
Medical Director, Neonatal Surgical Service
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
118. Fetal Intervention and Surgery

A. Kim Ritchey, MD
Professor and Vice-Chair of International Affairs
Department of Pediatrics
University of Pittsburgh School of Medicine
Division of Hematology/Oncology
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
542. Principles of Cancer Diagnosis
543. Principles of Cancer Treatment
544. The Leukemias

Angela Byun Robinson, MD, MPH
Associate Professor of Pediatrics
Cleveland Clinic Lerner College of Medicine
Center for Pediatric Rheumatology and Immunology
Cleveland Clinic
Cleveland, Ohio
213. Miscellaneous Conditions Associated With Arthritis

Kristine Knuti Rodrigues, MD, MPH
Associate Professor of Pediatrics
University of Colorado School of Medicine
Department of Pediatrics
Denver Health Medical Center
Denver, Colorado
433. Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

Michael E. Rogers, DO, MPH
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
406. Viral Hepatitis

Mary E. Romano, MD, MPH
Associate Professor of Pediatrics
Division of Adolescent and Young Adult Health
Department of Pediatrics
Monroe Carell Jr. Children's Hospital at Vanderbilt
Vanderbilt University Medical Center
Nashville, Tennessee
160. Contraception

Genie E. Roosevelt, MD, MPH
Professor of Emergency Medicine
University of Colorado School of Medicine
Department of Emergency Medicine
Denver Health Medical Center
Denver, Colorado
433. Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis

Stephen M. Roper, PhD
Associate Professor of Pathology and Immunology
Division of Laboratory and Genomic Medicine
Washington University School of Medicine in St. Louis
St. Louis, Missouri
769. Laboratory Testing in Infants and Children
770. Reference Intervals for Laboratory Tests and Procedures

Stephen M. Rosenthal, MD
Professor of Pediatrics
University of California San Francisco School of Medicine
Medical Director, Child and Adolescent Gender Center
Division of Pediatric Endocrinology
UCSF Benioff Children's Hospitals
San Francisco, California
153. Gender Identity and Transgender Care

A. Catharine Ross, PhD
Professor of Nutrition
Department of Nutrition and Institute for Advancing Health Through Agriculture
College of Agriculture and Life Sciences
Texas A&M University
College Station, Texas
66. Vitamin A Deficiencies and Excess

Joseph W. Rossano, MD, MS
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Cardiology
Co-Executive Director, The Cardiac Center
Jennifer Terker Endowed Chair in Pediatric Cardiology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
491. Heart Failure
492. Pediatric Heart and Heart-Lung Transplantation

Jennifer A. Rothman, MD
Professor of Pediatrics
Director, Pediatric Comprehensive Sickle Cell Center
Division of Pediatric Hematology and Oncology
Duke University Medical Center
Durham, North Carolina
504. Iron-Deficiency Anemia
505. Other Microcytic Anemias

Alexandre T. Rotta, MD, FCCM
Professor of Pediatrics
Chief, Division of Pediatric Critical Care Medicine
Duke University Medical Center
Durham, North Carolina
86. Acute Care of Respiratory Distress and Failure

Ranna A. Rozenfeld, MD, FAAP, FCCM
Professor of Pediatrics
The Warren Alpert Medical School of Brown University
Division Director, Pediatric Critical Care Medicine
Medical Director, LifePACT Pediatric Critical Care Transport Team
Attending Physician, PICU
Hasbro Children's Hospital
Providence, Rhode Island
459. Atelectasis

Michael E. Russo, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
259. Other Anaerobic Infections

Kelsey S. Ryan, MD
Assistant Professor of Pediatrics
Division of Neonatology
Medical College of Wisconsin
Milwaukee, Wisconsin
137. Jaundice and Hyperbilirubinemia in the Newborn

Monique M. Ryan, MMed, FRACP
Formerly of University of Melbourne
Formerly of Royal Children's Hospital, Melbourne
Parkville, Victoria, Australia
655. Autonomic Neuropathies
656. Guillain-Barré Syndrome
657. Bell Palsy

Julie Ryu, MD
Professor of Pediatrics
University of California San Diego School of Medicine
Interim Chief, Division of Respiratory Medicine
Chief Research Informatics Officer
Department of Pediatrics
Rady Children's Hospital–San Diego
San Diego, California
421. Diagnostic Approach to Respiratory Disease

Sara E. Sabbagh, DO
Assistant Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Rheumatology
Children's Wisconsin
Milwaukee, Wisconsin
205. Interferonopathies

H.P.S. Sachdev, MD, FIAP, FAMS, FRCPCH
Senior Consultant
Departments of Pediatrics and Clinical Epidemiology
Sitaram Bhartia Institute of Science and Research
New Delhi, India
67. Vitamin B Complex Deficiencies and Excess
68. Vitamin C (Ascorbic Acid) Deficiency and Excess

Manish Sadarangani, BM BCh, FRCPC, DPhil
Associate Professor of Pediatrics
Division of Infectious Diseases
University of British Columbia Faculty of Medicine
Sauder Family Chair in Pediatric Infectious Diseases
Director, Vaccine Evaluation Center
Physician Lead, Family Immunization Clinic
British Columbia Children's Hospital
Vancouver, British Columbia, Canada
237. Neisseria meningitidis (Meningococcus)

Rebecca E. Sadun, MD, PhD
Assistant Professor of Rheumatology
Departments of Medicine and Pediatrics
Duke University School of Medicine
Durham, North Carolina
199. Systemic Lupus Erythematosus

Mustafa Sahin, MD, PhD
Professor of Neurology
Harvard Medical School
Director, Rosamund Stone Zander Translational Neuroscience Center
Boston Children's Hospital
Boston, Massachusetts
636. Neurocutaneous Syndromes

Martine Saint-Cyr, MD
Assistant Professor of Pediatrics
Division of Gastroenterology, Hepatology and Nutrition
Washington University School of Medicine in St. Louis
St. Louis, Missouri
60. Nutritional Requirements

Robert A. Salata, MD
Professor and Chairman
Department of Medicine
STERIS Chair of Excellence in Medicine
Founding Director, Infectious Diseases and Immunology Institute
Case Western Reserve University School of Medicine
Physician-in-Chief
University Hospitals Case Medical Center
Cleveland, Ohio
327. Amebiasis
330. Trichomoniasis (Trichomonas vaginalis)
332. African Trypanosomiasis (Sleeping Sickness; Trypanosoma brucei Complex)
333. American Trypanosomiasis (Chagas Disease; Trypanosoma cruzi)

José H. Salazar, MD, PhD
Assistant Professor of Surgery
Medical College of Wisconsin
Division of Pediatric General and Thoracic Surgery
Children's Wisconsin
Milwaukee, Wisconsin
391. Acute Appendicitis
394. Inguinal Hernias

Edsel Maurice T. Salvana, MD
Clinical Associate Professor of Medicine
University of the Philippines College of Medicine
Director, Institute of Molecular Biology and Biotechnology
National Institutes of Health
Manila, The Philippines;
Adjunct Professor of Global Health
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
327. Amebiasis
330. Trichomoniasis (Trichomonas vaginalis)
332. African Trypanosomiasis (Sleeping Sickness; Trypanosoma brucei Complex)
333. American Trypanosomiasis (Chagas Disease; Trypanosoma cruzi)

Benjamin J. Samelson-Jones, MD, PhD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
524. Hemostasis
525. Hereditary Clotting Factor Deficiencies (Bleeding Disorders)
527. Hereditary Predisposition to Thrombosis
529. Postneonatal Vitamin K Deficiency
532. Disseminated Intravascular Coagulation
533. Platelet and Blood Vessel Disorders

Julia S. Sammons, MD, MSCE
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Assistant Vice President
Office of Preparedness, Prevention and Response
Attending Physician
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
216. Infection Prevention and Control

Hugh A. Sampson, MD
Kurt Hirschhorn Professor of Pediatrics
Director Emeritus, Jaffe Food Allergy Institute
Icahn School of Medicine at Mount Sinai
Division of Pediatric Allergy
Mount Sinai Kravis Children's Hospital
New York, New York
190. Anaphylaxis
192. Food Allergy and Adverse Reactions to Foods

Chase B. Samsel, MD
Assistant Professor of Psychiatry
Department of Psychiatry
Harvard Medical School
Attending Psychiatrist
Department of Psychiatry and Behavioral Sciences
Boston Children's Hospital
Boston, Massachusetts
36. Rumination and Pica

Thomas J. Sandora, MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Senior Associate Physician in Pediatrics
Division of Infectious Diseases
Hospital Epidemiologist
Medical Director, Infection Control
Boston Children's Hospital
Boston, Massachusetts
449. Community-Acquired Pneumonia

Wudbhav N. Sankar, MD
Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Director, Young Adult Hip Preservation Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
719. The Hip

Ashok P. Sarnaik, MD
Professor and Former Interim Chair
Department of Pediatrics
Wayne State University School of Medicine
Former Pediatrician-in-Chief
Children's Hospital of Michigan
Detroit, Michigan
86. Acute Care of Respiratory Distress and Failure

Alice I. Sato, MD, PhD
Associate Professor of Pediatrics
Division of Infectious Diseases
University of Nebraska College of Medicine
Hospital Epidemiologist
Children's Nebraska
Omaha, Nebraska
264. Syphilis (Treponema pallidum)

Lisa Forbes Satter, MD
Associate Professor of Pediatrics
Baylor College of Medicine
Section of Immunology, Allergy, and Retrovirology
William T. Shearer Center for Human Immunobiology
Texas Children's
Houston, Texas
167. Natural Killer Cells

Felicia A. Scaggs Huang, MD, MS
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Associate Director, Infection Prevention and Control
Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
286. Coccidioidomycosis (Coccidioides Species)

Joshua K. Schaffzin, MD, PhD
Associate Professor of Clinical Pediatrics
University of Ottawa Faculty of Medicine
Staff Physician, Division of Infectious Diseases, Immunology, & Allergy
Children's Hospital of Eastern Ontario
Ottawa, Ontario
407. Liver Abscess

Michael S. Schechter, MD, MPH
Professor of Pediatrics
Virginia Commonwealth University School of Medicine
Chief, Division of Pulmonary Medicine
Director, Cystic Fibrosis Center
Director, UCAN Community Asthma Program
Children's Hospital of Richmond at VCU
Richmond, Virginia
454. Cystic Fibrosis

Samantha Schilling, MD, MSHP
Clinical Associate Professor of Pediatrics
Division of General Pediatrics and Adolescent Medicine
University of North Carolina School of Medicine
North Carolina Children's Hospital
Chapel Hill, North Carolina
20. Positive Parenting and Support

Mark R. Schleiss, MD
Professor of Pediatrics
American Legion and Auxiliary Heart Research Foundation Endowed Chair
Division of Pediatric Infectious Diseases and Immunology
University of Minnesota Medical School
Minneapolis, Minnesota
225. Principles of Antibacterial Therapy
256. Botulism (Clostridium botulinum)
257. Tetanus (Clostridium tetani)
292. Principles of Antiviral Therapy

W. William Schluter, MD, MSPH
Director, CDC China Country Office
US Centers for Disease Control and Prevention
Beijing, China
215.1. International Immunization Practices

Amanda C. Schondelmeyer, MD, MSc
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Physician, Division of Hospital Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
4. Quality and Value in Healthcare for Children

James W. Schroeder Jr., MD, FACS, FAAP
Professor of Otolaryngology – Head and Neck Surgery and Medical Education
Northwestern University Feinberg School of Medicine
Vice Chair, Department of Surgery
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
434. Congenital Anomalies of the Larynx, Trachea, and Bronchi
435. Foreign Bodies in the Airway
436. Laryngotracheal Stenosis and Subglottic Stenosis
438. Neoplasms of the Larynx, Trachea, and Bronchi

Elaine E. Schulte, MD, MPH, BCC
Professor of Pediatrics
Albert Einstein College of Medicine
Vice Chair, Academic Affairs and Faculty Development
Co-Director, Leadership, Engagement, Advocacy, and Diversity (L.E.A.D.) Program
Division of Academic General Pediatrics
Children's Hospital at Montefiore
Bronx, New York
9. Domestic and International Adoption

Jennifer E. Schuster, MD, MSCI
Associate Professor of Pediatrics
University of Missouri-Kansas City School of Medicine
Division of Pediatric Infectious Diseases
Children's Mercy Kansas City
Kansas City, Missouri
310. Rhinoviruses
428. The Common Cold

Marcy Schuster, PsyD
Clinic Coordinator
Elwyn Fragile X Center
Elwyn, Pennsylvania
59. Fragile X Syndromes

Mark A. Schuster, MD, PhD
Founding Dean and CEO
Professor of Health Systems Science
Kaiser Permanente Bernard J. Tyson School of Medicine
Pasadena, California
154. Gay, Lesbian, and Bisexual Adolescents

Daryl A. Scott, MD, PhD
Professor of Molecular and Human Genetics
Director, Medical Research Pathway
Baylor College of Medicine
Houston, Texas
95. Genetics in Pediatric Medicine
96. Principles of Human Genetics
97. Patterns of Genetic Transmission

John P. Scott, MD
Professor of Anesthesiology and Pediatrics
Medical College of Wisconsin
Divisions of Pediatric Anesthesiology and Pediatric Critical Care
Children's Wisconsin
Milwaukee, Wisconsin
91. Anesthesia and Perioperative Care
92. Procedural Sedation

Kristin A. Seaborg, MD
Assistant Professor of Neurology
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
639. Neurodegenerative Disorders of Childhood

Patrick C. Seed, MD, PhD, FAAP, FIDSA
Professor of Pediatrics, Microbiology and Immunology
Children's Research Fund Chair in Basic Science
Northwestern University Feinberg School of Medicine
Associate Chief Research Officer of Basic Science
Stanley Manne Children's Research Institute
Director, Host-Microbial Interactions, Inflammation, and Immunity (HMI3) Program
Ann & Robert H. Lurie Children's Hospital
Chicago, Illinois
245. Shigella
246. Escherichia coli

Janet R. Serwint, MD
Professor of Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland
30. Loss, Separation, and Bereavement

Dheeraj Shah, MD, FIAP, FAMS
Director-Professor
Department of Pediatrics
University College of Medical Sciences
Guru Teg Bahadur Hospital
New Delhi, India
67. Vitamin B Complex Deficiencies and Excess
68. Vitamin C (Ascorbic Acid) Deficiency and Excess

Samir S. Shah, MD, MSCE, MHM
Vice Chair, Clinical Affairs and Education
James M. Ewell Endowed Chair
Attending Physician, Divisions of Hospital Medicine and Infectious Diseases
Cincinnati Children's Hospital Medical Center
Professor, Department of Pediatrics
University of Cincinnati College of Medicine
Cincinnati, Ohio
220. Fever Without a Focus in the Neonate and Young Infant
221. Fever in the Older Child
725. Osteomyelitis
726. Septic Arthritis

Shivang S. Shah, MD
Assistant Professor of Pediatrics
Columbia University Vagelos College of Physicians and Surgeons
Division of Pediatric Infectious Diseases
NewYork-Presbyterian Morgan Stanley Children's Hospital
New York, New York
300. Varicella-Zoster Virus

Raanan Shamir, MD
Professor of Pediatrics
Director, Institute of Gastroenterology, Nutrition and Liver Diseases
Schneider Children's Medical Center
Chair, Eduarda and Dr. Moshe Ishay Institute for the Study of the Effects of Natural Food on Quality of Life and Human Health
Lea and Arieh Pickel Chair for Pediatric Research
Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel
388. Chronic Diarrhea

Christina M. Shanti, MD
Assistant Professor of Surgery
Wayne State University School of Medicine
Arvin I. Philippart MD Endowed Chair in Pediatric Surgical Research
Chief, Division of Pediatric Surgery
Children's Hospital of Michigan
Detroit, Michigan
392. Surgical Conditions of the Anus and Rectum

Bruce K. Shapiro, MD
Professor of Pediatrics
The Arnold J. Capute MD, MPH Chair in Neurodevelopmental Disabilities
Johns Hopkins University School of Medicine
Emeritus Vice President of Training
Kennedy Krieger Institute
Baltimore, Maryland
56. Developmental Delay and Intellectual Disability

Bennett A. Shaywitz, MD
Charles and Helen Schwab Professor in Dyslexia and Learning Development
Co-Director, Center for Dyslexia & Creativity
Chief, Child Neurology
Yale School of Medicine
New Haven, Connecticut
51. Dyslexia

Sally E. Shaywitz, MD
Audrey G. Ratner Professor in Learning Development
Co-Director, Center for Dyslexia & Creativity
Department of Pediatrics
Yale School of Medicine
New Haven, Connecticut
51. Dyslexia

Oleg A. Shchelochkov, MD
Director of Residency and Fellowship Programs
Medical Genomics and Metabolic Genetics Branch
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland
104. An Approach to Inborn Errors of Metabolism
105. Defects in Metabolism of Amino Acids

Stanford T. Shulman, MD
Emeritus Professor of Infectious Disease
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
229. Group A Streptococcus
487. Rheumatic Heart Disease

Scott H. Sicherer, MD
Elliot and Roslyn Jaffe Professor of Pediatrics, Allergy and Immunology
Director, Jaffe Food Allergy Institute
Medical Director, Clinical Research Unit
Jack and Lucy Clark Department of Pediatrics
Icahn School of Medicine at Mount Sinai
Division Chief, Pediatric Allergy
Mount Sinai Kravis Children's Hospital
New York, New York
182. Allergy and the Immunologic Basis of Atopic Disease
183. Diagnosis of Allergic Disease
184. Allergic Rhinitis
185. Childhood Asthma
186. Atopic Dermatitis (Atopic Eczema)
187. Insect Allergy
188. Ocular Allergies
189. Urticaria (Hives) and Angioedema
190. Anaphylaxis
191. Serum Sickness
192. Food Allergy and Adverse Reactions to Foods
193. Adverse and Allergic Reactions to Drugs

Jeffrey M. Simmons, MD, MSc
Chief Value Officer, VP Value and Clinical Excellence
Children's Minnesota
Minneapolis, Minnesota
4. Quality and Value in Healthcare for Children
5. Safety in Healthcare for Children

Eric A.F. Simões, MBBS, DCH, MD
Professor of Pediatrics
University of Colorado School of Medicine
Division of Pediatric Infectious Diseases
Children's Hospital Colorado
Aurora, Colorado
296. Polioviruses

Kari A. Simonsen, MD
Professor of Pediatrics
Division of Pediatric Infectious Disease
University of Nebraska Medical Center
Omaha, Nebraska
266. Leptospira

Tess S. Simpson, PhD
Assistant Professor of Physical Medicine and Rehabilitation
University of Colorado School of Medicine
Children's Hospital Colorado
Denver, Colorado
754. Meningomyelocele (Spina Bifida)

Keneisha R. Sinclair-McBride, PhD
Assistant Professor of Psychology in Psychiatry
Harvard Medical School
Attending Psychologist
Department of Psychiatry and Behavioral Sciences
Boston Children's Hospital
Boston, Massachusetts
34. Psychotherapy
42. Disruptive, Impulse-Control, and Conduct Disorders
43. Tantrums and Breath-Holding Spells
44. Lying, Stealing, and Truancy
45. Aggression

Arunjot Singh, MD, MPH
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Co-Director, Center for Celiac Disease
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
375. Pyloric Stenosis and Other Congenital Anomalies of the Stomach

Jacquelyn R. Sink, MD
Dermatologist
Northwestern Medicine Regional Medical Group
Naperville, Illinois
700. Diseases of the Dermis
701. Diseases of Subcutaneous Tissue

Bryan A. Sisk, MD, MSCI
Assistant Professor of Pediatrics, Hematology and Oncology, and General Medical Sciences
Director of Research, Bioethics Research Center
Washington University School of Medicine in St. Louis
St. Louis, Missouri
6. Ethics in Pediatric Care

Vidya Sivaraman, MD
Clinical Associate Professor of Pediatrics
Division of Pediatric Rheumatology
Nationwide Children's Hospital
Columbus, Ohio
210. Vasculitis Syndromes

Susan M. Slattery, MD, HSOR
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Attending Physician, Divisions of Autonomic Medicine and Neonatology
Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute
Chicago, Illinois
468.2. Congenital Central Hypoventilation Syndrome

Anne M. Slavotinek, MBBS, PhD
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Division of Human Genetics
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
100. Dysmorphology, Phenotyping and Sequences
101. Signaling Pathway Disorders

Jessica R. Smith, MD
Assistant Professor of Pediatrics
Harvard Medical School
Associate Medical Director, Thyroid Center
Boston Children's Hospital
Boston, Massachusetts
601. Thyroid Development and Physiology
602. Disorders of Thyroxine-Binding Globulin
603. Hypothyroidism
604. Thyroiditis
605. Goiter
606. Thyrotoxicosis
607. Carcinoma of the Thyroid
608. Autoimmune Polyglandular Syndromes
609. Multiple Endocrine Neoplasia Syndromes

Kim Smith-Whitley, MD
Executive Vice President
Head of Research and Development
Global Blood Therapeutics, Inc.
San Francisco, California
511. Hemoglobinopathies

Roland Solensky, MD
Division of Allergy & Immunology
The Corvallis Clinic
Corvallis, Oregon
193. Adverse and Allergic Reactions to Drugs

Mary Beth F. Son, MD
Associate Professor of Pediatrics
Harvard Medical School
Section Chief, Rheumatology Program Director, Services and Outreach
Boston Children's Hospital
Boston, Massachusetts
208. Kawasaki Disease

Danielle E. Soranno, MD
Associate Professor of Pediatrics
Indiana University School of Medicine
Division of Pediatric Nephrology
Riley Hospital for Children
Indianapolis, Indiana
571. Inherited Tubular Transport Abnormalities

Tina K. Sosa, MD, MSc
Assistant Professor of Pediatrics
University of Rochester Medical Center School of Medicine and Dentistry
Associate Chief Quality Officer
Division of Pediatric Hospital Medicine
Golisano Children's Hospital
Rochester, New York
5. Safety in Healthcare for Children

Carmen L. Soto-Rivera, MD
Instructor in Pediatrics
Harvard Medical School
Director, Neuroendocrine and Growth Programs
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts
596. Diabetes Insipidus
597. Other Abnormalities of Arginine Vasopressin Metabolism and Action

Laura Stout Sosinsky, PhD
Research Scientist
Research and Evaluation Group
Public Health Management Corporation
Philadelphia, Pennsylvania
29. Child Care

Emily E. Souder, MD
Attending Physician
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
243. Pertussis (Bordetella pertussis and Bordetella parapertussis)

Cristina Tomatis Souverbielle, MD
Assistant Professor
The Ohio State University College of Medicine
Division of Infectious Diseases
Nationwide Children's Hospital
Columbus, Ohio
262. Hansen Disease (Mycobacterium leprae)

Paul Spearman, MD
Albert B. Sabin Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
323. Human T-Cell Leukemia Viruses (1 and 2)

David A. Spiegel, MD
Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
720. The Spine
721. The Neck

Adiaha I.A. Spinks-Franklin, MD, MPH
Clinical Associate Professor of Pediatrics
Baylor College of Medicine
Division of Developmental-Behavioral Pediatrics
Texas Children's
Houston, Texas
2. Child Health Disparities

Alicia J. Sprecher, MD
Assistant Professor of Pediatrics
Medical College of Wisconsin
Division of Neonatal-Perinatal Medicine
Children's Wisconsin
Milwaukee, Wisconsin
117. The Fetus
122. Nervous System Disorders
124. Transition to Newborn Pulmonary Respiration
125. Apnea
126. Respiratory Distress Syndrome (Hyaline Membrane Disease)
127. Bronchopulmonary Dysplasia
128. Transient Tachypnea of the Newborn
129. Aspiration of Foreign Material (Meconium Aspiration Syndrome, Aspiration Pneumonia)
130. Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)
131. Diaphragmatic Hernia
132. Pulmonary Air Leaks: Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium
133. Pulmonary Hemorrhage

James E. Squires, MD, MS
Associate Professor of Pediatrics
Director, Pediatric Transplant Hepatology Fellowship Program
University of Pittsburgh School of Medicine
Associate Director of Hepatology
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
403. Manifestations of Liver Disease

Siddharth Srivastava, MD, PhD
Assistant Professor of Neurology
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts
636. Neurocutaneous Syndromes

Joseph W. St. Geme III, MD
Professor of Pediatrics and Microbiology and Chair of the Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chair of the Department of Pediatrics and Physician-in-Chief
Leonard and Madlyn Abramson Endowed Chair in Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
240. Haemophilus influenzae

Rachel D. St. John, MD, NCC, FAAP
Professor of Otolaryngology–Head & Neck Surgery
University of Texas Southwestern Medical Center
Director, Family-Focused Center for Deaf and Hard of Hearing Children
Children's Health Medical Center
Dallas, Texas
55. Outcomes Among Infants and Children Who Are Deaf/Hard of Hearing

Kathryn C. Stambough, MD
Assistant Professor of Obstetrics and Gynecology
University of Arkansas for Medical Sciences
Chief, Division of Pediatric and Adolescent Gynecology
Arkansas Children's Hospital
Little Rock, Arkansas
585. Gynecologic History and Physical Examination
587. Vaginal Bleeding in the Prepubertal Child

Lawrence R. Stanberry, MD, PhD
Professor of Pediatrics
Associate Dean for International Programs
Director of the Programs in Global Health
Vagelos College of Physicians and Surgeons
Columbia University
New York, New York
299. Herpes Simplex Virus

Jeffrey R. Starke, MD
Professor of Pediatrics
Faculty Senator
Baylor College of Medicine
Pediatric Infectious Diseases
Texas Children's
Houston, Texas
261. Tuberculosis (Mycobacterium tuberculosis)

Taylor B. Starr, DO, MPH
Associate Professor of Pediatrics
University of Rochester School of Medicine and Dentistry
Division of Adolescent Medicine
Golisano Children's Hospital
Rochester, New York
41. Eating Disorders

Andrew P. Steenhoff, MBBCh, DCHFAAP
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Medical Director, Global Health Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
222. Fever of Unknown Origin
287. Paracoccidioides brasiliensis
288. Sporotrichosis (Sporothrix schenckii)

Ronen E. Stein, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
382. Inflammatory Bowel Disease
383. Eosinophilic Gastroenteritis

William J. Steinbach, MD
Robert H. Fiser Jr. MD, Endowed Chair in Pediatrics
Chair, Department of Pediatrics
Associate Dean for Child Health
College of Medicine, University of Arkansas for Medical Sciences
Pediatrician-in-Chief, Arkansas Children's
Little Rock, Arkansas
279. Principles of Antifungal Therapy
283. Aspergillus
289. Mucormycosis
291. Other Pathogenic Fungi

Terri L. Stillwell, MD
Clinical Associate Professor of Pediatrics
University of Michigan Medical School
Division of Pediatric Infectious Diseases
C. S. Mott Children's Hospital
Ann Arbor, Michigan
301. Epstein-Barr Virus
309. Adenoviruses

Deborah L. Stone, MD
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland
206. Amyloidosis

Stefani Su, MD
Potomac Allergy & Asthma, P.C.
Alexandria, Virginia
176. Approaches to Treatment of Primary Immune Deficiency Diseases

Gina S. Sucato, MD, MPH
Director, Adolescent Center
Washington Permanente Medical Group
Adjunct Investigator, Kaiser Permanente
Washington Health Research Institute
Seattle, Washington
159. Menstruation-Related Disorders

Frederick J. Suchy, MD
Professor of Pediatrics
University of Colorado School of Medicine
Children's Hospital Colorado
Aurora, Colorado
410. Autoimmune Hepatitis
411. Drug- and Toxin-Induced Liver Injury
412. Acute Hepatic Failure
413. Cystic Diseases of the Biliary Tract and Liver
414. Diseases of the Gallbladder
415. Portal Hypertension and Varices

Kathleen E. Sullivan, MD, PhD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Allergy and Immunology
Frank R. Wallace Endowed Chair in Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
164. Orientation to the Consideration of Inborn Errors of Immunity

Sanjeev K. Swami, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Infectious Diseases
Director, Outpatient Infectious Diseases Clinic
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
268. Lyme Disease (Borrelia burgdorferi)

Vibha A. Szafron, MD
Department of Pediatrics
Baylor College of Medicine
Section of Immunology, Allergy, and Retrovirology
Texas Children's
Houston, Texas
167. Natural Killer Cells

Moira Szilagyi, MD, PhD
Professor of Pediatrics
David Geffen School of Medicine at UCLA
Interim Division Chief, General Pediatrics
Section Chief, Developmental/Behavioral Pediatrics
UCLA Mattel Children's Hospital
Los Angeles, California
10. Foster and Kinship Care

Dalal Taha, DO
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
143. Nonimmune Hydrops

Libo Tan, PhD
Associate Professor
Department of Human Nutrition
College of Human Environmental Sciences
University of Alabama
Tuscaloosa, Alabama
66. Vitamin A Deficiencies and Excess

Kelan G. Tantisira, MD, MPH
Professor of Pediatrics
University of California San Diego School of Medicine
Chief, Division of Respiratory Medicine
Rady Children's Hospital–San Diego
San Diego, California
421. Diagnostic Approach to Respiratory Disease

Alex M. Taylor, PsyD
Assistant Professor of Psychology
Department of Psychiatry
Harvard Medical School
Director of Neuropsychology
Brain Injury Center
Boston Children's Hospital
Boston, Massachusetts
729. Sports-Related Traumatic Brain Injury (Concussion)

Dmitry Tchapyjnikov, MD
Adjunct Assistant Professor of Pediatrics
Duke University Medical Center
Durham, North Carolina
633. Seizures in Childhood

Brenda L. Tesini, MD
Assistant Professor of Medicine and Pediatrics
University of Rochester Medical Center School of Medicine and Dentistry
Department of Pediatric Infectious Diseases
Golisano Children's Hospital
Rochester, New York
303. Roseola (Human Herpesviruses 6 and 7)
304. Human Herpesvirus 8

Jillian L. Theobald, MD, PhD
Associate Professor of Emergency Medicine
Medical College of Wisconsin
Associate Medical Director, Wisconsin Poison Center
Milwaukee, Wisconsin
94. Poisoning

Beth K. Thielen, MD, PhD
Assistant Professor of Pediatrics
Division of Pediatric Infectious Diseases
University of Minnesota Medical School
Minneapolis, Minnesota
325. Principles of Antiparasitic Therapy

Christopher S. Thom, MD, PhD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Neonatologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
138. Blood Disorders
139. Anemia in the Newborn Infant
140. Hemolytic Disease of the Fetus and Newborn
141. Neonatal Polycythemia
142. Hemorrhage in the Newborn Infant

Courtney D. Thornburg, MD, MS
Professor of Clinical Pediatrics
UC San Diego School of Medicine
La Jolla, California;
Medical Director, Hemophilia and Thrombosis Treatment Center
Rady Children's Hospital, San Diego
San Diego, California
496. Anemias
497. Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)
498. Pearson Syndrome
499. Acquired Pure Red Blood Cell Anemia
500. Anemia of Chronic Disease and Renal Disease
501. Congenital Dyserythropoietic Anemias
502. Physiologic Anemia of Infancy
503. Megaloblastic Anemias

Joel S. Tieder, MD, MPH
Professor of Pediatrics
University of Washington School of Medicine
Division of Hospital Medicine
Seattle Children's Hospital
Seattle, Washington
424. Brief Resolved Unexplained Events and Other Acute Events in Infants

Pierre Tissières, MD, PhD
Professor of Pediatrics
Director of Pediatric Intensive Care, Neonatal Medicine, and Pediatric Emergency Department
AP-HP Paris Saclay University, Bicetre Hospital
Le Kremlin-Bicetre, France
85. Shock

Victorio R. Tolentino Jr., JD, MPH, NP
Healthcare Consultant
Jackson Heights, New York;
Psychiatric Nurse Practitioner
Counseling and Wellness Services, Student Health Center
New York University
New York, New York
77.3. Principles Applicable to the Developing World

Alexis A. Topjian, MD, MSCE
Professor of Anesthesiology, Critical Care, and Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
79. Pediatric Cardiorespiratory Emergencies and Resuscitation

Richard L. Tower, MD, MS
Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Hematology/Oncology
Children's Wisconsin
Milwaukee, Wisconsin
537. Anatomy and Function of the Lymphatic System
538. Abnormalities of Lymphatic Vessels
539. Lymphadenopathy

Rebecca Trachtman, MD, MS
Assistant Professor of Pediatrics
Icahn School of Medicine at Mount Sinai
Division of Pediatric Rheumatology
Mount Sinai Kravis Children's Hospital
New York, New York
207. Macrophage Activation Syndrome

Jourdan E. Triebwasser, MD, MA
Clinical Assistant Professor of Obstetrics and Gynecology
Division of Maternal-Fetal Medicine
University of Michigan Medical School
Ann Arbor, Michigan
116. High-Risk Pregnancies

Sara K. Trowbridge, MD
Instructor in Neurology
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts
631. Congenital Anomalies of the Central Nervous System

Joseph M. Truglio, MD, MPH
Associate Professor of Medicine, Pediatrics, and Medical Education
Icahn School of Medicine at Mount Sinai
New York, New York
152. Transitioning to Adult Care

David G. Tubergen, MD
Medical Director, Host Program
MD Anderson Physicians Network
Houston, Texas
544. The Leukemias

Margaret A. Turk, MD
SUNY Distinguished Service Professor
Departments of Physical Medicine & Rehabilitation, Pediatrics, Public Health & Preventive Medicine
Vice-Chairman, Physical Medicine & Rehabilitation
State University of New York
SUNY Upstate Medical University
Syracuse, New York
756. Health and Wellness for Children With Disabilities

Joan R. Tymon-Rosario, MD
Assistant Professor
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Zucker School of Medicine
Uniondale, New York;
Northwell Health Cancer Institute
Hyde Park, New York
590. Gynecologic Neoplasms and Prevention Methods for Human Papillomavirus Infections in Adolescents

Paul J. Ufberg, DO, MBA
Medical Director, Global Medical Affairs
The Janssen Pharmaceutical Companies of Johnson & Johnson
Horsham, Pennsylvania
389. Disorders of Brain-Gut Interaction (Functional Gastrointestinal Disorders)

Christina Ullrich, MD, PhD, MPH
Assistant Professor of Pediatrics
Harvard Medical School
Senior Physician and Clinical Director
Pediatric Advanced Care Team, Psychosocial Oncology and Palliative Care
Dana-Farber Cancer Institute
Interim Director, Pediatric Palliative Care
Division of Pediatric Hematology/Oncology
Boston Children's Hospital
Boston, Massachusetts
8. Pediatric Palliative Care

Nicole Ullrich, MD, PhD
Professor of Neurology
Harvard Medical School
Director, Neurologic Neuro-Oncology
Associate Director, Clinical Trials
Neurofibromatosis Program
Boston Children's Hospital
Boston, Massachusetts
636.1. Neurofibromatosis

Taher S. Valika, MD
Assistant Professor of Otolaryngology – Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Attending Physician
Division of Otorhinolaryngology – Head and Neck Surgery
Medical Director, Aerodigestive Program
Director, Upper Airway Surgery
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois
436. Laryngotracheal Stenosis and Subglottic Stenosis

George F. Van Hare, MD
Professor of Pediatrics
Washington University School of Medicine in St Louis
Division of Pediatric Cardiology
St Louis Children's Hospital
St. Louis, Missouri
84. Syncope
484. Disturbances of Rate and Rhythm of the Heart
485. Sudden Death

Heather A. Van Mater, MD, MS
Associate Professor of Pediatrics
Duke University School of Medicine
Chief, Division of Pediatric Rheumatology
Duke University Health System
Durham, North Carolina
201. Scleroderma and Raynaud Phenomenon

Charles D. Varnell Jr., MD, MS
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Nephrology and Hypertension
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
573. Renal Transplantation

Alla Vash-Margita, MD
Associate Professor of Obstetrics, Gynecology and Reproductive Sciences
Yale School of Medicine
Chief, Division of Pediatric and Adolescent Gynecology
Yale New Haven Children's Hospital
New Haven, Connecticut
585. Gynecologic History and Physical Examination
590. Gynecologic Neoplasms and Prevention Methods for Human Papillomavirus Infections in Adolescents
591. Vulvovaginal and Müllerian Anomalies

Timothy J. Vece, MD
Professor of Pediatrics
Division of Pediatric Pulmonology
The University of North Carolina at Chapel Hill School of Medicine
Medical Director
NC Children's Airway Center
Chapel Hill, North Carolina
448.3. Granulomatous Lung Disease
448.4. Eosinophilic Lung Disease
448.5. Interstitial Lung Disease

Aarthi P. Vemana, MD
Pediatric Sleep Physician
Inova Children's Sleep Center
Fairfax, Virginia
451. Pleurisy, Pleural Effusions, and Empyema
461. Pneumothorax
462. Pneumomediastinum
463. Hydrothorax
464. Hemothorax
465. Chylothorax

Charles P. Venditti, MD, PhD
Head, Organic Acid Research Section
Senior Investigator, National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland
104. An Approach to Inborn Errors of Metabolism
105. Defects in Metabolism of Amino Acids

Sarah Vepraskas, MD
Associate Professor of Pediatrics
Section of Hospital Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin
423.1. Sudden Unexpected Postnatal Collapse/ Sudden Unexpected Early Neonatal Death

James W. Verbsky, MD, PhD
Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Rheumatology
Children's Wisconsin
Milwaukee, Wisconsin
90.1. Cold-Induced Autoinflammatory and Other Genetic Disorders
204. Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases
205. Interferonopathies

Jennifer A. Vermilion, MD
Assistant Professor of Neurology and Pediatrics
University of Rochester School of Medicine and Dentistry
Rochester, New York
637.2. Chorea, Athetosis, and Tremor

Brian P. Vickery, MD
Associate Professor of Pediatrics
Section Chief, Allergy/Immunology
Emory University School of Medicine
Director, Food Allergy Center
Emory + Children's Healthcare of Atlanta
Atlanta, Georgia
169. Eosinophils

Jerry Vockley, MD, PhD
Cleveland Family Endowed Chair in Pediatric Research
Professor of Human Genetics
University of Pittsburgh School of Medicine
Chief, Division of Genetic and Genomic Medicine
Director, Center for Rare Disease Therapy
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania
106.1. Disorders of Mitochondrial Fatty Acid β-Oxidation

Judith A. Voynow, MD
Professor of Pediatrics
Virginia Commonwealth University School of Medicine
Edwin L. Kendig Jr. Professor of Pediatric Pulmonology
Children's Hospital of Richmond at VCU
Richmond, Virginia
454. Cystic Fibrosis

Abby Walch, MD
Assistant Professor of Pediatrics
University of California San Francisco School of Medicine
Division of Pediatric Endocrinology
UCSF Benioff Children's Hospitals
San Francisco, California
153. Gender Identity and Transgender Care

Stephanie W. Waldrop, MD
Instructor in Pediatrics
University of Colorado School of Medicine
Section of Pediatric Nutrition
Children's Hospital Colorado
Aurora, Colorado
60. Nutritional Requirements

David M. Walker, MD
Associate Professor of Pediatrics
Hackensack University Medical Center
Chief, Pediatric Emergency Medicine
Joseph M. Sanarzi Children's Hospital
Hackensack, New Jersey
77.3. Principles Applicable to the Developing World

Kelly J. Walkovich, MD
Clinical Associate Professor of Pediatrics and Communicable Diseases
Division of Pediatric Hematology/Oncology
University of Michigan Medical School
Ann Arbor, Michigan
171. Leukopenia
172. Leukocytosis

Heather J. Walter, MD, MPH
Professor of Psychiatry
Department of Psychiatry
Harvard Medical School
Senior Attending Psychiatrist
Department of Psychiatry and Behavioral Sciences
Boston Children's Hospital
Boston, Massachusetts
32. Psychosocial Assessment and Psychiatric Diagnostic Evaluation
33. Psychopharmacology
34. Psychotherapy
36. Rumination and Pica
37. Motor Disorders and Habits
42. Disruptive, Impulse-Control, and Conduct Disorders
43. Tantrums and Breath-Holding Spells
44. Lying, Stealing, and Truancy
45. Aggression

Jennifer A. Wambach, MD
Associate Professor of Pediatrics
Washington University School of Medicine in St. Louis
Division of Newborn Medicine
St. Louis Children's Hospital
St. Louis, Missouri
456. Diffuse Lung Diseases in Childhood

Susan Wamithi, MD, MMed
Consultant Developmental Paediatrician
Department of Paediatrics, Child and Adolescent Health
Aga Khan University Hospital
Nairobi, Kenya
3. Global Child Health

Julie Wang, MD
Professor of Pediatrics
Jaffe Food Allergy Institute
Icahn School of Medicine at Mount Sinai
Division of Pediatric Allergy
Mount Sinai Kravis Children's Hospital
New York, New York
187. Insect Allergy
190. Anaphylaxis

Marie E. Wang, MD, MPH
Clinical Associate Professor of Pediatrics
Stanford University School of Medicine
Palo Alto, California
575. Urinary Tract Infections

Michael F. Wangler, MD
Associate Professor of Molecular and Human Genetics
Baylor College of Medicine
Jan and Dan Duncan Neurological Research Institute
Texas Children's
Houston, Texas
106.2. Disorders of Very-Long-Chain Fatty Acids and Other Peroxisomal Functions

Stephanie M. Ware, MD, PhD, FACMG
Professor of Pediatrics
Professor and Interim Chair
Department of Medical and Molecular Genetics
Director, Cardiovascular Genetics
Herman B Wells Center for Pediatric Research
Indiana University School of Medicine
Indianapolis, Indiana
488. Diseases of the Myocardium
489. Diseases of the Pericardium
490. Tumors of the Heart

Matthew C. Washam, MD, MPH
Assistant Professor of Pediatrics
The Ohio State University College of Medicine
Nationwide Children's Hospital
Columbus, Ohio
284. Histoplasmosis (Histoplasma capsulatum)

Jonathan D. Wasserman, MD, PhD
Associate Professor of Paediatrics
University of Toronto—Faculty of Medicine
Staff Physician
Division of Endocrinology
The Hospital for Sick Children
Toronto, Ontario, Canada
555.1. Thyroid Tumors
555.4. Adrenal Tumors

Ari J. Wassner, MD
Associate Professor of Pediatrics
Harvard Medical School
Medical Director, Thyroid Center
Boston Children's Hospital
Boston, Massachusetts
601. Thyroid Development and Physiology
602. Disorders of Thyroxine-Binding Globulin
603. Hypothyroidism
604. Thyroiditis
605. Goiter
606. Thyrotoxicosis
607. Carcinoma of the Thyroid
608. Autoimmune Polyglandular Syndromes
609. Multiple Endocrine Neoplasia Syndromes

Andrew M. Watson, MD
Assistant Professor of Orthopedics and Rehabilitation
Division of Sports Medicine
Team Physician
Division of Intercollegiate Athletics
University of Wisconsin – Madison
School of Medicine and Public Health
Madison, Wisconsin
727. Prevention of Injuries
728. Management of Musculoskeletal Injury
731. Heat Injuries
732. Nutrition and Endocrine Conditions in Athletes
733. Performance-Enhancing Aids
734. Specific Sports and Associated Injuries

Rachel L. Wattier, MD, MHS
Associate Professor of Clinical Pediatrics
UC San Francisco School of Medicine
Medical Director, Pediatric Antimicrobial Stewardship Program
UCSF Benioff Children's Hospital
San Francisco, California
289. Mucormycosis

David R. Weber, MD, MSCE
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Endocrinology and Diabetes
Medical Director, Center for Bone Health
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
629. Diabetes Mellitus

Jennifer Webster, DO, MSHP
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
378. Motility Disorders and Hirschsprung Disease

Debra E. Weese-Mayer, MD
Beatrice Cummings Mayer Professor of Pediatrics and Pediatric Autonomic Medicine
Northwestern University Feinberg School of Medicine
Chief, Division of Pediatric Autonomic Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute
Chicago, Illinois
468.2. Congenital Central Hypoventilation Syndrome
468.3. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Jason B. Weinberg, MD
Associate Professor of Pediatrics and Microbiology and Immunology
University of Michigan Medical School
Division of Pediatric Infectious Diseases
C. S. Mott Children's Hospital
Ann Arbor, Michigan
301. Epstein-Barr Virus
309. Adenoviruses

Jason P. Weinman, MD
Associate Professor of Radiology
University of Colorado School of Medicine
Aurora, Colorado
448.7. Fibrotic Lung Disease

Steven J. Weisman, MD
Professor of Anesthesiology and Pediatrics
Medical College of Wisconsin
Jane B. Pettit Chair in Pain Management
Children's Wisconsin
Milwaukee, Wisconsin
93. Pediatric Pain Management

Anna K. Weiss, MD, MSEd
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Associate Director for Medical Education
Division of Emergency Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
77.2. Risk Adjustment and Outcomes Measurement of Pediatric Emergency Medical Services
78. Triage of the Acutely Ill Child

Scott L. Weiss, MD, MSCE, FCCM
Associate Professor of Pediatrics and Pathology, Anatomy, and Cell Biology
Sidney Kimmel Medical College at Thomas Jefferson University
Division Chief, Critical Care Medicine
Nemours Children's Health
Wilmington, Delaware
85. Shock

Pamela F. Weiss, MD, MSCE
Associate Professor of Pediatrics and Epidemiology
University of Pennsylvania Perelman School of Medicine
Attending Physician and Clinical Research Director
Division of Rheumatology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
197. Ankylosing Spondylitis and Other Spondyloarthritides
198. Reactive and Postinfectious Arthritis

Carol C. Weitzman, MD
Co-Director Autism Spectrum Center
Boston Children's Hospital
Associate Professor, Harvard Medical School
Professor Emeritus, Yale School of Medicine
Boston, Massachusetts
58. Autism Spectrum Disorder

Lawrence Wells, MD
Associate Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Associate Director, Sports Medicine and Performance Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
713. Orthopedic Growth and Development
714. Orthopedic Evaluation of the Child
716. Torsional and Angular Deformities of the Limb
719. The Hip
724. Common Fractures

Jessica W. Wen, MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Viral Hepatitis Treatment Program
Attending Physician
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
418. Ascites
419. Peritonitis

Danielle R. Wendel, MD
Associate Professor of Pediatrics
University of Washington School of Medicine
Medical Director, Intestinal Transplant Service
Division of Gastroenterology and Hepatology
Seattle Children's Hospital
Seattle, Washington
386. Intestinal Transplantation in Children with Intestinal Failure

Steven L. Werlin, MD
Professor Emeritus of Pediatrics
Medical College of Wisconsin
Milwaukee, Wisconsin
395. Embryology, Anatomy, and Physiology of the Pancreas
396. Pancreatic Function Tests
397. Disorders of the Exocrine Pancreas
398. Treatment of Pancreatic Insufficiency
399. Pancreatitis
400. Pancreatic Fluid Collections
401. Pancreatic Tumors

Isaiah D. Wexler, MD, PhD
Associate Professor of Pediatrics
Hadassah Medical School
Attending Physician, Department of Pediatrics
Hadassah University Medical Center
Jerusalem, Israel
15.3. Effects of War on Children

Alexander S. Whitaker, MD
Instructor in Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland
21. Assessment of Fetal Growth and Development

A. Clinton White Jr., MD
Professor of Medicine
Division of Infectious Diseases
The University of Texas Medical Branch at Galveston
Galveston, Texas
348. Adult Tapeworm Infections
349. Cysticercosis
350. Echinococcosis (Echinococcus granulosus sensu lato and Echinococcus multilocularis)

Perrin C. White, MD
Professor of Pediatrics
Chief, Division of Pediatric Endocrinology
Audre Newman Rapoport Distinguished Chair in Pediatric Endocrinology
University of Texas Southwestern Medical Center
Dallas, Texas
614. Physiology of the Adrenal Gland
615. Adrenocortical Insufficiency and Altered Sensitivity to Corticosteroids
616. Congenital Adrenal Hyperplasia and Related Disorders
617. Adrenocortical Tumors and Masses
618. Virilizing and Feminizing Adrenal Tumors
619. Cushing Syndrome
620. Primary Aldosteronism
621. Pheochromocytoma

Rodney E. Willoughby Jr., MD
Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Infectious Diseases
Children's Wisconsin
Milwaukee, Wisconsin
320. Rabies

Michael Wilschanski, MD
Professor of Pediatrics
Hebrew University Hadassah School of Medicine
Director, Pediatric Gastroenterology Unit
Hadassah University Hospitals
Jerusalem, Israel
395. Embryology, Anatomy, and Physiology of the Pancreas
396. Pancreatic Function Tests
397. Disorders of the Exocrine Pancreas
398. Treatment of Pancreatic Insufficiency
399. Pancreatitis
400. Pancreatic Fluid Collections
401. Pancreatic Tumors

Susan E. Wiley, MD, FAAP
Professor of Pediatrics
University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
55. Outcomes Among Infants and Children Who Are Deaf/Hard of Hearing

Brendan A. Williams, MD
Assistant Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Sports Medicine and Performance Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
713. Orthopedic Growth and Development
716. Torsional and Angular Deformities of the Limb

Karen M. Wilson, MD, MPH
Ruth A. Lawrence Professor of Pediatrics
Vice-Chair for Clinical and Translational Research
Department of Pediatrics
University of Rochester School of Medicine and Dentistry
Strategic Director, Research Services Branch
Clinical and Translational Science Institute
Chief Research Officer, UR Medicine
Golisano Children's Hospital
Rochester, New York
759.2. Marijuana Smoke Exposure

Pamela E. Wilson, MD
Associate Professor of Physical Medicine and Rehabilitation
University of Colorado School of Medicine
Children's Hospital Colorado
Denver, Colorado
754. Meningomyelocele (Spina Bifida)

Jennifer J. Winell, MD
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
715. The Foot and Toes
716. Torsional and Angular Deformities of the Limb
719. The Hip

Peter Witters, MD, PhD
Assistant Professor of Pediatrics
Center for Metabolic Diseases
University Hospitals Leuven
Department of Development and Regeneration
Katholieke Universiteit Leuven
Leuven, Belgium
107.7. Congenital Disorders of Glycosylation

Joshua Wolf, PhD, MBBS
Associate Member
Department of Infectious Diseases
St. Jude Children's Research Hospital
Memphis, Tennessee
224. Infection Associated With Medical Devices

Joanne Wolfe, MD, MPH
Professor of Pediatrics
Harvard Medical School
Chief, Division of Pediatric Palliative Care
Department of Psychosocial Oncology and Palliative Care
Faculty Vice President for Faculty Development
Dana-Farber Cancer Institute
Director, Pediatric Palliative Care
Boston Children's Hospital
Boston, Massachusetts
8. Pediatric Palliative Care

Peter M. Wolfgram, MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Endocrinology
Children's Wisconsin
Milwaukee, Wisconsin
600.1. Delayed or Absent Puberty

Brandon T. Woods, MD, MS
Division of Critical Care Medicine
Department of Pediatrics
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, Washington
445. Pulmonary Edema

Benjamin L. Wright, MD
Associate Professor of Medicine
Division of Allergy, Asthma, and Clinical Immunology
Mayo Clinic
Scottsdale, Arizona;
Phoenix Children's Hospital
Phoenix, Arizona
169. Eosinophils

Terry W. Wright, PhD
Associate Professor of Pediatrics
Professor of Microbiology and Immunology
University of Rochester Medical Center School of Medicine and Dentistry
Department of Pediatric Infectious Diseases
Golisano Children's Hospital
Rochester, New York
290. Pneumocystis jirovecii

Eveline Y. Wu, MD, MSCR
Associate Professor of Pediatrics
Division Chief, Pediatric Rheumatology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
196. Juvenile Idiopathic Arthritis
209. Sarcoidosis
448.3 Granulomatous Lung Disease

Pablo Yagupsky, MD
Professor of Pediatrics and Clinical Microbiology (Emeritus)
Ben-Gurion University of the Negev
Department of Pediatrics
Soroka Medical Center
Beer-Sheva, Israel
239. Kingella kingae

Edward Yang, MD, PhD
Assistant Professor of Radiology
Harvard Medical School
Attending Physician
Department of Radiology
Boston Children's Hospital
Boston, Massachusetts
631. Congenital Anomalies of the Central Nervous System

Kesi C. Yang, MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania
147. Infants of Diabetic Mothers

Ming Yang, MD
Assistant Professor of Pediatrics
Division of Pediatric Endocrinology
University of Texas Southwestern Medical Center
Dallas, Texas
616. Congenital Adrenal Hyperplasia and Related Disorders

Michael Yaron, MD
Clinical Professor of Emergency Medicine
University of Colorado School of Medicine
Aurora, Colorado
87. Altitude-Associated Illness in Children

Sarah B. Younger, MD
Assistant Professor of Clinical Child Health
Medical Director, Palliative Care
University of Missouri School of Medicine
Columbia, Missouri
688. Dermatologic Diseases of the Neonate

Christopher J. Yuskaitis, MD, PhD
Assistant Professor of Neurology
Harvard Medical School
Co-Director, Infantile Spasms Program
Division of Pediatric Neurology
Boston Children's Hospital
Boston, Massachusetts
631. Congenital Anomalies of the Central Nervous System

Philip Zachariah, MD
Associate Director
Vaccine Research and Development
Pfizer, Inc
Pearl River, New York
299. Herpes Simplex Virus

Muhammad S. Zafar, MBBS
Associate Professor of Pediatrics and Neurology
Duke University Medical Center
Durham, North Carolina
633.5. Mechanisms of Seizures
633.6. Treatment of Seizures and Epilepsy

Stacey G. Zahler, DO, MS
Assistant Professor of Pediatrics
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Department of Pediatric Hematology, Oncology, and Bone Marrow Transplantation
Cleveland Clinic Children's
Cleveland, Ohio
393. Tumors of the Digestive Tract

Lauren M. Zajac, MD, MPH
Associate Professor of Environmental Medicine and Public Health and Pediatrics
Icahn School of Medicine at Mount Sinai
New York, New York
759. Chemical Pollutants

Wafik Zaky, MD
Associate Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas
546. Central Nervous System Tumors in Childhood

Jennifer A. Zaspel, MD
Assistant Professor of Psychiatry and Behavioral Medicine
Medical College of Wisconsin
Division of Child and Adolescent Psychiatry
Children's Wisconsin
Milwaukee, Wisconsin
40. Suicide and Attempted Suicide
47. Childhood Psychoses

Patricia E. Zerra, MD
Assistant Professor of Pathology/Laboratory Medicine and Pediatrics
Center for Transfusion Medicine and Cellular Therapies
Department of Laboratory Medicine and Pathology
Aflac Cancer and Blood Disorders Center
Children's Healthcare of Atlanta
Department of Pediatrics
Emory University
Atlanta, Georgia
519. Red Blood Cell Transfusions and Erythropoietin Therapy
520. Platelet Transfusions
521. Neutrophil (Granulocyte) Transfusions
522. Plasma Transfusions
523. Risks of Blood Transfusions

Amy Zhou, BA
Clinical Research Coordinator
Division of Autonomic Medicine
Center for Autonomic Medicine in Pediatrics
Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute
Chicago, Illinois
468.2. Congenital Central Hypoventilation Syndrome
468.3. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Barry S. Zuckerman, MD
Professor and Chair Emeritus, Pediatrics
Boston University Aram V. Chobanian & Edward Avedisian School of Medicine
Boston, Massachusetts
15. Impact of Violence Exposure on Children

Karen B. Zur, MD
Professor of Otorhinolaryngology – Head & Neck Surgery
University of Pennsylvania Perelman School of Medicine
Chief, Division of Otolaryngology
E. Mortimer Newlin Endowed Chair in Pediatric Otolaryngology & Human Communication
Director, Pediatric Voice Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
431. Tonsils and Adenoids

Preface

Whoever saves one life, it is considered as if they saved an entire world.

— Babylonian Talmud

The 22nd edition of *Nelson Textbook of Pediatrics* continues its tradition as an essential resource for general pediatric providers as well as pediatric subspecialists as they rely on the most current and modern approaches to diagnose and treat infants, children, and adolescents throughout the world. The 22nd edition has been thoroughly revised and updated by expert contributors and experienced editors to help the reader keep up with the huge advances in clinical care derived from basic, clinical, and population-based research. The promise that translational medicine will improve the lives of children has become a daily reality for most but not all children. Knowledge of human development, behavior, and diseases from the molecular to sociologic levels has led to greater understanding of health and illness in children and to substantial improvements in health quality for those who have access to health care. These exciting scientific advances also provide hope to effectively address prevention and treatment of new and emerging diseases threatening children and their families.

The field of pediatrics encompasses advocacy for all children throughout the world and must address societal inequalities of important resources required for normal development, as well as protection from natural and man-made disasters. Unfortunately, many children throughout the world have not benefited from the significant advances in the prevention and treatment of health-related problems. For medical advances to benefit all children and youth, good clinical practice must always be coupled with effective advocacy to overcome unconscious and systemic biases, lack of political will, and misplaced priorities.

This new edition of *Nelson Textbook of Pediatrics* attempts to provide the essential information that primary care and medical specialists, house staff, medical students, and all other care providers involved in pediatric health care throughout the world need to understand to effectively address the enormous range of biologic, psychologic, and social problems that our children and youth face. Pediatric subspecialists will benefit from the details of coexisting disorders often seen in their patients. Our goal is to be comprehensive yet concise and reader friendly, embracing both new advances in clinical science and the time-honored art of pediatric practice.

The 22nd edition is reorganized and revised from the previous edition. There are many additional chapters of new diseases, as well as substantial expansion or significant modification of others. In addition, many more tables, photographs, imaging studies, and illustrative figures, as well as up-to-date references, have been added.

This new edition has greatly benefited from the addition of two new associate editors with an extremely broad base of clinical experience: Dr. Cara Mack, Professor of Pediatrics, Gastroenterology Division Chief at the Medical College of Wisconsin, and Dr. Abigail Schuh, Associate Professor of Pediatrics, Director of Education, Section of Pediatric Emergency Medicine at the Medical College of Wisconsin.

Although, to an ill child and their family and health care provider, even the rarest disorder is of central importance, all health problems cannot possibly be covered with the same degree of detail in one general textbook of pediatrics. Thus, leading articles and subspecialty texts are referenced and should be consulted when more information is desired. In addition, as new recommendations or policies are developed, they will be updated on our website.

The outstanding value of the 22nd edition of the textbook is due to its many expert and authoritative contributors. We are all indebted to these dedicated authors for their hard work, knowledge, thoughtfulness, and outstanding judgment.

Our sincere appreciation also goes to Jennifer Shreiner, John Casey, and Sarah Barth at Elsevier and to Carolyn Redman in the Pediatric Department of the Medical College of Wisconsin. Ms. Shreiner and Ms. Redman have worked harmoniously together on five editions and are actually the editors behind the editors in maintaining the book's excellence. We also wish to thank Ms. Hayley Severson, the Clinical Services Librarian at Children's Wisconsin who has been an outstanding asset in keeping the content as well as the references as current as possible. We have all worked together to produce an edition that will be helpful to those who provide care for children and youth and to those desiring to know more about children's health worldwide.

In this edition we have had informal assistance from many faculty and house staff of the department of pediatrics at the Medical College of Wisconsin, the Perelman School of Medicine at the University of Pennsylvania, Harvard Medical School, and the University of Rochester School of Medicine and Dentistry. The help of these individuals and of the many practicing pediatricians from around the world who have taken the time to offer thoughtful feedback and suggestions is always greatly appreciated and helpful.

Last and certainly not least, we especially wish to thank our families for their patience and understanding about the great time commitment we as editors have spent reading and editing this edition.

Robert M. Kliegman, MD
Joseph W. St. Geme III, MD
Nathan J. Blum, MD
Robert C. Tasker, MBBS, MD
Karen M. Wilson, MD, MPH
Abigail M. Schuh, MD, MMHPE
Cara L. Mack, MD

The Field of Pediatrics

PART I

Chapter 1
Overview of Pediatrics

Lee M. Pachter and Nia J. Heard-Garris

Since the late 19th century, pediatrics has been the only discipline dedicated to all aspects of the care and well-being of infants, children, and adolescents, including their health—their physical, mental, social, and psychologic growth and development—and their ability to achieve full potential as adults. The importance of scientific inquiry and research discovery in pediatrics and related subspecialties was cemented by the creation of the National Institute for Child Health and Development (NICHD) in 1962. As the earliest pediatricians focused on social and environmental issues that affected health (e.g., housing, sanitation, and poverty), so too are today's pediatricians (e.g., racism, poverty, and other socioenvironmental influences). In 1959 the United Nations (UN) issued the **Declaration of the Rights of the Child**, articulating the universal presumption that children have fundamental needs and rights. However, the United States is the only UN member that has not yet ratified these rights.

The pediatrician's purpose is to advance the well-being of children, and thus pediatricians must be concerned with specific organ systems, genetics, and biologic processes and also with environmental, psychosocial, cultural, and political influences, all of which affect the health and well-being of children and their families. Pediatricians must be advocates for the individual child, their families, and communities because children cannot advocate wholly for themselves. Pediatricians must serve as advocates of all children irrespective of culture, religion, gender/gender identity, sexual orientation, race or ethnicity, ability, place of birth, or geographic boundaries. The more politically, economically, or socially disenfranchised a population is, the greater the need for advocacy for its children and for those who support children. Youth are often the most vulnerable persons in society, and thus their needs require special attention. As boundaries between nations blur through advances in media, transportation, technology, communication, and economics, a *global*, rather than a national or local, perspective for the field of pediatrics becomes both a reality and a necessity.

The interconnectedness of health issues across the world has achieved widespread recognition in the wake of new and emerging illnesses, such as COVID-19, Zika, Ebola, and severe acute respiratory syndrome (SARS), as well as familiar and persistent illnesses, such as malaria, tuberculosis, HIV/AIDS, and vaccine-preventable illness. Additionally, health issues transcend communicable disease and are influenced by global events, such as war, ethnic wars, mass shootings, bioterrorism, the burning of the Amazon rainforest, and the growing severity of wildfires, storms, drought, and hurricanes brought about by climate change to very specific events, such as the earthquake in Haiti in 2010; the displacement of families during the Syrian refugee crisis in 2016–2018; the White supremacist attack on a mosque in Christchurch, New Zealand, livestreamed in 2019; and George Floyd's and Breonna Taylor's murders in 2020.

VITAL STATISTICS ABOUT CHILDREN'S HEALTH GLOBALLY

From 1990 to 2020, the world population grew at an annual rate of 1% per year, down from 1.3% during the prior 20 years, to reach a population of nearly 8 billion people. The population growth rate continues to decline. The Pew Research Center projects the population to reach 10.9 billion people in 2100 with a growth rate of less than 0.1% at that time because of the fall in fertility rates. Africa is the only continental region that is predicted to continue to have strong population growth, as the 20 countries with the highest birthrates currently are all located in Africa. By 2100, the countries of India, China, and Nigeria are estimated to be the largest. In 2019, the average birthrate in the world was 17.9 births per 1,000 population, with a range from 46/1,000 in Niger to 6.0/1,000 in Monaco. The most populous countries—China (18.5% of the world population), India (17.7%), and the United States (4.3%)—have birthrates of 11, 18, and 11 per 1,000 population, respectively, which were all trending down from previous years. Worldwide, there are roughly 2.5 billion youth under 19 years old, which accounts for approximately one third (32%) of the world's population. The African region boasts the largest share of youth under 15 at 40% compared with 26% globally.

Despite global interconnectedness, the health of children and youth varies widely between and within regions and nations, depending on several interrelated factors. These include (1) economic conditions, (2) educational, social, and cultural considerations, (3) health and social welfare infrastructure, (4) climate and geography, (5) agricultural resources and practices, which account for nutritional resources, (6) stage of industrialization and urbanization, (7) gene frequencies for certain disorders, (8) the ecology of infectious agents and their hosts, (9) social stability, and (10) political focus and stability. Although genetics, biology, and access to affordable and quality healthcare are important determinants, social and structural influences on health outcomes—the physical environment, political and economic conditions, and social, cultural, and behavioral considerations—play as great a role, if not greater.

To ensure that the needs of children and adults worldwide were not obscured by local needs, in 2000 the international community established eight Millennium Development Goals (MDGs) slated to be achieved by 2015. Although all eight MDGs affect child well-being, MDG 4 was exclusively focused on children: to reduce the under-5 mortality rate (U5MR) by two thirds between 1990 and 2015. It was estimated that poor nutrition contributed to more than one third of the deaths worldwide in children <5 years old, so many of the efforts to reach this goal centered on increasing household food security. There has been significant progress toward this goal; the worldwide U5MR decreased by 60% between 1990 and 2021, from 93 deaths per 1,000 live births in 1990 to 38 in 2021. However, the World Health Organization (WHO) cites that between 5.2 and 5.4 million children died worldwide from preventable or treatable causes. Infants younger than 28 days account for over half the deaths, followed by children age 1-11 months, and then by children age 1-4 years old. Children in sub-Saharan Africa are 9 times more likely to die before age 5 than children in the developed areas of the world (see Fig. 3.1). School children (ages 5-9 years old) also experienced a large decline in mortality since the year 1990 related to lower prevalence of infectious diseases.

The infant mortality rate globally (2023) is 27.4 deaths per 1,000 live births, with female infants having a lower rate than male infants. The child death rates in the first year of life were highest in Afghanistan (106.8), Somalia (88.0), and Central African Republic (84.2) per 1,000 live births. In the least developed countries, as classified by the UN, this rate was 45 per 1,000, and the rate was 4 per 1,000 for high-income countries. The causes of infant and under-5 mortality differ greatly between developed and developing nations. The leading causes of under-5 mortality are preterm birth and birth-related asphyxia/trauma, pneumonia, diarrhea, and malaria (Fig. 1.1). As compared with higher-resourced countries, more children less than 5 years old in lower-resourced countries die from non–birth-related causes (see Fig. 3.4).

In developing countries, over half of the deaths in children less than 5 years old resulted from infectious and parasitic diseases, including diarrheal disease (10% of deaths) and pneumonia (15%). Neonatal

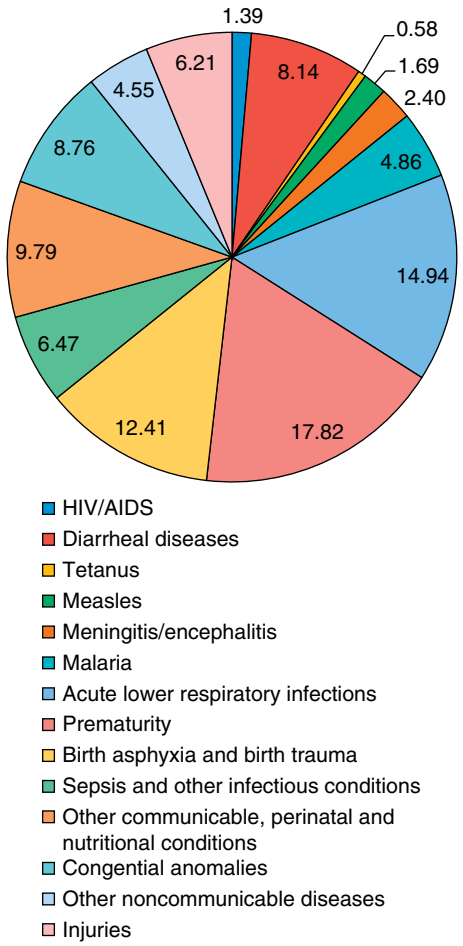

Fig. 1.1 Global causes of death under the age of 5 years.

causes contributed 12%, congenital defects 9%, and malaria, AIDS, and measles accounted for the other causes of death. In the United States, pneumonia and influenza accounted for only 2% of under-5 deaths, with only negligible contributions from diarrheal diseases and malaria (Table 1.1). Although unintentional injuries in developing countries are a proportionately less important cause of mortality than in developed countries, the absolute rates and contributions of these injuries to morbidity are substantially greater. In the United States, the top causes of unintentional injury include unintentional suffocation, drowning, motor vehicle collision, and fire. Other causes accounted for <5% of total mortality within this age-group (Tables 1.2). Violence is a significant contributor to injury-related mortality in all child age-groups (Tables 1.2 and 1.3). Globally (2023), the life expectancy at birth is 73.2 years old, with females at 76 years and males at 70.8 years.

THE CHANGING PEDIATRIC WORLD

A profound improvement in child health within industrialized nations occurred in the 20th century with the introduction of vaccines, antibiotic agents, improved hygienic practices, and attention to scientific clinical practice. Efforts to control infectious diseases were complemented by better understanding of the role of nutrition in preventing illness and maintaining health. In the United States, Canada, and parts of Europe, new and continuing discoveries in these areas led to establishment of publicly funded well-child clinics for low-income families. Although the timing of infectious disease control was uneven around the globe, this focus on control was accompanied by significant decreases in morbidity and mortality in all countries.

Later in the 20th century, with improved control of infectious diseases through more effective prevention and treatment (including the eradication of polio in the Western hemisphere), pediatric medicine in industrialized nations increasingly turned its attention to a broad spectrum of

Table 1.1 Ten Leading Causes of Death by Age Group, United States – 2018

10 leading causes of death by age group, United States – 2018

	Age groups				
Rank	<1	1–4	5–9	10–14	15–24
1	Congenital anomalies 4,473	Unintentional injury 1,226	Unintentional injury 734	Unintentional injury 692	Unintentional injury 12,044
2	Short gestation 3,679	Congenital anomalies 384	Malignant neoplasms 393	Suicide 596	Suicide 6,211
3	Maternal pregnancy comp. 1,358	Homicide 353	Congenital anomalies 201	Malignant neoplasms 450	Homicide 4,607
4	SIDS 1,334	Malignant neoplasms 326	Homicide 121	Congenital anomalies 172	Malignant neoplasms 1,371
5	Unintentional injury 1,168	Influenza and pneumonia 122	Influenza and pneumonia 71	Homicide 168	Heart disease 905
6	Placenta cord membranes 724	Heart disease 115	Chronic lower respiratory disease 68	Heart disease 101	Congenital anomalies 354
7	Bacterial sepsis 579	Perinatal period 62	Heart disease 68	Chronic lower respiratory disease 64	Diabetes mellitus 246
8	Circulatory system disease 428	Septicemia 54	Cerebro-vascular 34	Cerebro-vascular 54	Influenza and pneumonia 200
9	Respiratory distress 390	Chronic lower respiratory disease 50	Septicemia 34	Influenza and pneumonia 51	Chronic lower respiratory disease 165
10	Neonatal hemorrhage 375	Cerebro-vascular 43	Benign neoplasms 19	Benign neoplasms 30	Complicated pregnancy 151

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Courtesy Centers for Disease Control and Prevention, https://www.cdc.gov/injury/wisqars/pdf/leading_causes_of_death_by_age_group_2018-508.pdf.

noninfectious acute and chronic conditions. These included potentially lethal conditions in addition to temporarily or permanently disabling conditions. Advances occurred in the diagnosis, care, and treatment of leukemia and other neoplasms, cystic fibrosis, sickle cell disease, diseases of the newborn infant, congenital heart disease, genetic defects, rheumatic diseases, renal diseases, and metabolic and endocrine disorders.

Until the 1970s and early 1980s, children affected with sickle cell disease often died within the first 3 years of life, often from overwhelming sepsis caused by encapsulated bacteria. In the 1980s a multicenter study showed that early initiation of penicillin prophylaxis led to an 84% risk reduction for pneumococcal sepsis. Life expectancy for those with sickle cell disease increased when penicillin prophylaxis was initiated early in life. The use of prophylactic penicillin became the standard of care, increasing the importance of early detection of sickle cell disease (which led to expanding universal newborn screening) and paving the way for advances in the chronic management of the disease, including transfusion therapy, radiographic screening for silent cerebral infarctions, hydroxyurea as a disease-modifying therapy, and now, gene-altering therapies. The success of penicillin prophylaxis likely led to a more rapid rate of innovation in the diagnosis and management of the disease as a result of increased life expectancy. Today 95% of individuals born with sickle cell disease will live to their 18th birthday, and most will survive until their fifth decade.

Similarly, the treatment of acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, has also shown amazing

Table 1.2 Ten Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States – 2018

10 leading causes of injury deaths by age group highlighting unintentional injury deaths, United States – 2018

	Age groups				
Rank	<1	1–4	5–9	10–14	15–24
1	Unintentional suffocation 977	Unintentional drowning 443	Unintentional MV traffic 341	Suicide suffocation 361	Unintentional MV traffic 6,308
2	Homicide unspecified 125	Unintentional MV traffic 292	Unintentional drowning 130	Unintentional MV traffic 360	Unintentional poisoning 4,245
3	Unintentional MV traffic 80	Homicide unspecified 152	Unintentional fire/burn 99	Suicide firearm 202	Homicide firearm 4,107
4	Homicide other spec., classifiable 68	Unintentional fire/burn 123	Homicide firearm 57	Homicide firearm 134	Suicide firearm 2,995
5	Undetermined suffocation 45	Unintentional suffocation 112	Unintentional suffocation 30	Unintentional drowning 86	Suicide suffocation 2,237
6	Unintentional drowning 39	Unintentional pedestrian, other 70	Unintentional other land transport 20	Unintentional fire/burn 52	Suicide poisoning 454
7	Homicide suffocation 30	Homicide other spec., classifiable 66	Homicide unspecified 17	Unintentional suffocation 43	Unintentional drowning 431
8	Undetermined unspecified 30	Homicide firearm 54	Adverse effects 16	Unintentional other land transport 37	Homicide cut/pierce 256
9	Unintentional natural/ environment 22	Unintentional natural/ environment 38	Unintentional pedestrian, other 15	Unintentional poisoning 23	Undetermined poisoning 224
10	Two tied 18	Unintentional firearm 30	Homicide other spec., NEC[N] 14	Suicide poisoning 20	Suicide fall 205

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Courtesy Centers for Disease Control and Prevention, https://www.cdc.gov/injury/wisqars/pdf/leading_causes_of_injury_deaths_highlighting_unintentional_2018-508.pdf.

Table 1.3 Ten Leading Causes of Injury Deaths by Age Group Highlighting Violence-Related Injury Deaths, United States – 2018

10 leading causes of injury deaths by age group highlighting violence-related injury deaths, United States – 2018

	Age groups				
Rank	<1	1–4	5–9	10–14	15–24
1	Unintentional suffocation 977	Unintentional drowning 443	Unintentional MV traffic 341	Suicide suffocation 361	Unintentional MV traffic 6,308
2	Homicide unspecified 125	Unintentional MV traffic 292	Unintentional drowning 130	Unintentional MV traffic 360	Unintentional poisoning 4,245
3	Unintentional MV traffic 80	Homicide unspecified 152	Unintentional fire/burn 99	Suicide firearm 202	Homicide firearm 4,107
4	Homicide other spec., classifiable 68	Unintentional fire/burn 123	Homicide firearm 57	Homicide firearm 134	Suicide firearm 2,995
5	Undetermined suffocation 45	Unintentional suffocation 112	Unintentional suffocation 30	Unintentional drowning 86	Suicide suffocation 2,237
6	Unintentional drowning 39	Unintentional pedestrian, other 70	Unintentional other land transport 20	Unintentional fire/burn 52	Suicide poisoning 454
7	Homicide suffocation 30	Homicide other spec., classifiable 66	Homicide unspecified 17	Unintentional suffocation 43	Unintentional drowning 431
8	Undetermined unspecified 30	Homicide firearm 54	Adverse effects 16	Unintentional other land transport 37	Homicide cut/pierce 256
9	Unintentional natural/ environment 22	Unintentional natural/ environment 38	Unintentional pedestrian, other 15	Unintentional poisoning 23	Undetermined poisoning 224
10	Two tied 18	Unintentional firearm 30	Homicide other spec., NEC[N] 14	Suicide poisoning 20	Suicide fall 205

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Courtesy Centers for Disease Control and Prevention, https://www.cdc.gov/injury/wisqars/pdf/leading_causes_of_injury_deaths_highlighting_violence_2018-508.pdf.

advances. Five-year survival rates have increased from <10% in the 1960s to >90% in 2023. Cystic fibrosis has shown improvements in survival as well. In the 1960s, most children with cystic fibrosis did not live to school age. With advances in pulmonary and nutritional therapies, as well as earlier initiation of these therapies secondary to earlier identification through newborn screening, a child born with cystic fibrosis in 2010 has a projected life expectancy of 39-56 years.

These major advances in the management of chronic diseases of childhood were accomplished when significant improvement occurred in the prevention and treatment of acute infectious diseases, at least in industrial countries. This allowed human and economic resources to shift toward addressing chronic disease. However, infectious diseases continue to cause significant morbidity and mortality throughout the world. In the fall of 2021, the WHO recommended the use of the RTS,S/AS01 malaria vaccine for children in areas of moderate and high levels of transmission of *Plasmodium falciparum*, which is the most prevalent cause of malaria in Africa. This historic declaration holds great promise for improving children's health, as more than 250,000 African children under 5 die from malaria each year. The coronavirus disease 2019 (COVID-19) pandemic has proved to be an unremitting global health challenge that has not only affected health but also changed and influenced the socioeconomic lives of people throughout the world.

THE NEW NORMAL: PANDEMICS

Since **COVID-19** was first reported and identified in Wuhan, China, in 2019, it has radically and fundamentally affected both the public health and global health landscapes (see Chapters 311 and 449.1). The identification of COVID-19 and development of a vaccine unfolded over the course of 1 year, which was a testament to the importance and critical need for scientific research and rapid clinical implementation. We learned that children could present with or without symptoms and were important factors in community-based viral transmission.

Whereas many children experienced minor illnesses, others experienced more severe illnesses, which were related to underlying chronic conditions, such as asthma or the use of medical devices for children with special healthcare needs, and around 1% of children would go on to develop multiinflammatory syndrome (MIS-C). This condition could be lethal, but most children who received timely care improved. As of spring 2023, there were over 766 million cases and nearly 6.9 million deaths from COVID-19, and the United States had the highest number of cases and deaths throughout the world. Children in the United States accounted for 6 million COVID-19–positive cases, with 0.1–2.0% of children hospitalized and 0.03% leading to child deaths.

Although children were less affected by COVID-19–related illnesses than their adult counterparts, they experienced significant mental health and psychosocial challenges, grief, and loss. Over 1.5 billion

children living through the pandemic faced unprecedented learning challenges because of widespread school closures and dependence on electronic devices and stable internet connections and widening educational disparities, especially for those in poverty, children of frontline workers and single parents, and those already marginalized. Additionally, children who received nutritional support in school or received in-school or in-home services to support their learning and/or developmental needs (e.g., speech therapy, specialized teaching, or other ancillary therapies) also faced disruptions. These disruptions and stress contributed to an increase in mental and emotional health burdens, such as depression, anxiety, isolation, and fear; however, these burdens were unable to be matched with a sufficient number of mental healthcare professionals to provide needed care.

The pandemic also disproportionately affected poor families and families of color in other ways. Children in these families faced increased risk of economic hardship and instability, loss of caregivers, and other challenges. Additionally, concerns about all children's safety and welfare continued and were highlighted, as noncustodial adults had less access and exposure to children who may have experienced physical, sexual, or emotional abuse. Finally, children with special healthcare needs experienced insurmountable challenges throughout the pandemic, such as not receiving essential medicines, medical supplies, and nursing or home healthcare services because of supply chain disruptions and staffing shortages. So although children largely were spared from the illness severity, there were undoubtedly victims of the sequelae that the pandemic brought forth. Now, in partnership with parents, communities, schools, and governments, pediatricians will need to continue to advocate for and support children to mitigate COVID-19's effects on children.

THE NEW MORBIDITIES

Given the advances in public health in decreasing morbidity and mortality in infectious diseases (immunization, hygiene, antibiotics), along with technologic advances in clinical care that improved survival for many chronic illnesses, attention was given to what was described in the 1980s and 1990s as the "new morbidities"—behavioral, developmental, psychosocial conditions, and societal inequities, which have been shown to be increasingly associated with suboptimal health outcomes and quality of life. The prevention, early detection, and management of these types of child health problems should be a central focus of the field of pediatrics and require an expansion in the knowledge base regarding (1) physical and environmental factors affecting behavior, (2) normal child behavior and development, (3) health behaviors as they pertain to child health, and (4) mild, moderate, and severe behavioral and developmental disorders. Accomplishing this would require reconceptualizing professional training, improving clinical communication and interviewing skills, expanding mental health resources for children, and shifting time allocation during child health supervision visits to address these concerns. In 2001 this issue was revisited and reemphasized the need to address environmental and social aspects in addition to developmental and behavioral issues (Table 1.4). This included violence, firearms, substance use, food insecurity, and school problems, as well as poverty, unhoused (homelessness), single-parent families, divorce, social media, incarceration, and childcare. Although at first glance this list seems daunting and beyond the scope of what pediatricians typically address (i.e., physical health and development), many of these behavioral, environmental, and psychosocial problems (which all fall under what was termed the "social determinants of health" but are better characterized as the "**social and structural influences on health**") account for a large proportion of variance in health outcomes in children and youth. The role of pediatrics and the boundaries of clinical practice needed to change in order to address these salient contributors to child health and well-being. Newer models of clinical care that rely on close collaboration and coordination with other professionals committed to child welfare (e.g., social workers, psychologists, mental health providers, educators) were developed. As this model expanded, so did the role of the family, in particular the child's caregiver, from a passive recipient of professional services to a more equitable and inclusive partner in identifying the issues that needed to be addressed, as well as helping decide which therapeutic options had the "best fit" with the child, the family, and the condition.

The framing of salient child health issues under the "new morbidity" concept acknowledges that the influences on health are heterogeneous but interconnected. Biology, genetics, healthcare, behaviors, social conditions, and environmental influences should not be viewed as mutually exclusive determinants; they exert their influences through complex interactions on multiple levels. For example, epigenetic changes that result from specific social and environmental conditions illustrate the influence of context on gene expression.

Studies have demonstrated that while each of these interrelated influences are important for optimal health, development, and well-being, the greatest contributions to health outcomes occur in the behavioral, social, and environmental domains—the social and structural influences on health. From 40% to 70% of the relative variation in certain health outcomes are caused by social and economic conditions, health behaviors, and environmental factors, as well as structural inequality in the healthcare domain. Whereas traditional medical education and clinical practice emphasized the biologic and genetic determinants of health, the recognition of the new morbidities as a focus of child healthcare provision reinforced the need to address social and structural influences as a key component of pediatric care, training, and research.

The "New" New Morbidities

The new morbidities concept brought into perspective the importance of addressing the social determinants of health, as well as the increasing

Table 1.4 A Development History of the New Morbidities in Child Health*

THE NEW MORBIDITIES (1982–1993)	THE NEW MORBIDITIES REVISITED (2001)	THE "NEW "NEW MORBIDITIES (2010 TO PRESENT)
Behavioral disorders/mental health	School problems	Adverse childhood experiences (ACEs)
Family crisis	Mood and anxiety disorders	Toxic stress
Abuse and neglect	Adolescent suicide/homicide	Allostatic load
Long-term disease	Firearms in home	Chronic illnesses of lifestyle (e.g., obesity, type 2 diabetes, hypertension)
Substance abuse	School violence	Behavioral conditions (autism, ADHD, depression, anxiety)
School difficulties	Drug and alcohol abuse	Food insecurity
	HIV	Oral health
	Effects of media	Witnessing community/interpersonal violence
	Poverty	Peer victimization/bullying
	Homelessness	Discrimination
	Single-parent families	
	Effects of divorce	
	Struggle of working parents	
	Child care quality and policy	

*Each column adds further categories and refinements to prior columns.

prevalence and salience of chronic physical and behavioral health conditions in pediatric healthcare. Since then, advances in epidemiology, physiology, and epigenetics have expanded the scope of inquiry into the effects of a broad range of health influences and provided more sophisticated explanatory models for the mechanisms that explain their effects (see Table 1.4).

Racism

Although racism is known as "America's Original Sin," **racism and racial discrimination** is a worldwide problem (see Chapter 2.1). Racism can occur at the systemic/structural, interpersonal, and internal/psychologic levels. Structural racism is the hierarchical grouping of people based on physical attributes, including skin color, which assigns value to those groups and then allocates certain resources, privileges, and power to the dominant or in-group. Structural racism built on White supremacy and hegemony has been a persistent and plaguing problem for over 400 years. It is racism and racist ideology that have created and perpetuated pediatric health disparities by race (see Chapters 2 and 2.1). In the aftermath of the state-sanctioned violence against Black people, there are calls for the end of racism, police actions, and White supremacy ideology throughout the world. The field of pediatrics did not go untouched in these discussions, and numerous articles were presented about how to dismantle structural racism and equip pediatricians with the tools to do so. Importantly, pediatricians have been called to examine areas in which racism and harm are perpetuated through healthcare, through policies, practices, beliefs, and ideals. Racism along with adverse childhood experiences are some of the pressing challenges for the modern-day pediatrician in promoting equitable health access and outcomes.

The issue of racism is even more relevant by understanding that of the ~73,000,000 children in the United States, ~50% are non-White, non-Hispanic (~26% Hispanic, ~14% Black, 5% Asian, ~5% other), 20% speak a language other than English at home, and ~25% are immigrants or children of immigrants.

Adverse Childhood Experiences

Adverse childhood experiences **(ACEs)** are stressful events experienced during childhood that can have profound health consequences both in childhood and throughout the life course into adulthood. ACEs were initially defined as abuse (physical, emotional, sexual), neglect (physical and emotional), and household challenges/family dysfunction (parental spousal abuse, mental illness in household, household substance abuse, incarceration of household member, parental separation or divorce). Retrospective studies have shown a graded dose-response effect of ACEs on future adult health of those who experience the adverse event in childhood. For example, more childhood adversity is associated with significantly increased risk in later life of ischemic heart disease, chronic obstructive pulmonary disease, liver disease, depression, obesity, and cancer. People who suffer ≥6 ACEs die almost 20 years earlier than those who had not experienced ACEs.

Although the original conceptualization of ACEs included family-level psychosocial trauma, recent attempts have been made to expand the concept to include "macro" level stressors, such as those encountered in the neighborhood and community (Table 1.5). These include witnessing violence in the community, poverty, bullying and peer victimization, peer isolation, living in unsafe neighborhoods, low neighborhood social capital, living in foster care, and experiencing discrimination or racism.

ACEs and other psychosocial traumas may influence health through a number of mechanisms. ACEs are associated with adoption of risky behaviors such as substance use and early initiation of sexual activity, which in turn may increase the risk of chronic diseases such as lung cancer, liver disease, obesity, human papillomavirus (HPV) infection and cervical cancer, chronic lung disease, and premature mortality. Childhood trauma can also disrupt neurodevelopment during critical stages of brain development and contribute to social, emotional, and cognitive impairment. Finally, ACEs can result in toxic stress and lead to the dysregulation of normal physiologic processes (see Toxic Stress and Allostatic Load later).

Table 1.5 Adverse Childhood Experiences

CATEGORY	ITEMS
Abuse and neglect	Physical abuse* Physical neglect* Emotional abuse* Emotional neglect* Sexual abuse*
Family dysfunction	Intimate partner violence* Substance use in household* Mental illness in household* Parental separation or divorce* Family member incarcerated* Parental discord
Community-level adversity	Witnessing community violence Neighborhood safety Lack of neighborhood connectedness/trust Experiencing discrimination
Others	Being bullied/peer victimization Living in foster care Social isolation Low socioeconomic status/poverty

*Items included in original Kaiser ACE study.

The documentation of cumulative ACE "scores" has value from a population-based epidemiologic perspective but has *limited clinical utility*. An ACE score gives no information regarding specific adversities and traumas, nor information regarding which interventions may be required. Although ACE screening may not be the optimal approach to incorporating a trauma lens into individual clinical care, a discussion around ACEs can help the clinician to begin collaborative communication with patients and families on the importance of psychosocial stress and adversity in health and well-being in childhood and throughout the life course.

Furthermore, it becomes important to understand that individuals are not merely a sum of their traumas. Although the recognition of the importance of ACEs and **trauma-informed care** has resulted in the reframing of the question "what's wrong with you" to "what's happened to you," this needs to be seen as a transition step toward the goal of **healing-centered care**, which includes an emphasis not only on adversity but also on **assets** (Fig. 1.2). Those assets may be external (e.g., family, community, peers, mentors) or internal (e.g., resilience, positive coping strategies, locus of control). In a healing-centered model of care, the evolution of the question "what's wrong with you" to "what happened to you" gets further refined to include "what's right or positive about you."

Toxic Stress and Allostatic Load

The effects of stress are moderated by the intensity of the stress, the biologic response to the stress, and the social and physical environment in which the stress is experienced. **Toxic stress** occurs when a child experiences stressful events that are chronic, intense, or prolonged and are inadequately buffered by the child's social support system (most importantly, parents and adult caregivers). Toxic psychosocial stress influences physical health by producing allostatic load, or pathophysiologic dysregulation of normal regulatory systems. **Allostatic load** is the "wear and tear" that the body and its regulatory mechanisms experience in response to chronic, unbuffered stress. The systems that can be affected through allostatic load include the neuroendocrine, cardiovascular, immune, and metabolic systems. Dysregulation of stress hormones in the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) systems, inflammatory cytokines, hormones (e.g., insulin), immune factors (e.g., fibrinogen, C-reactive protein), and

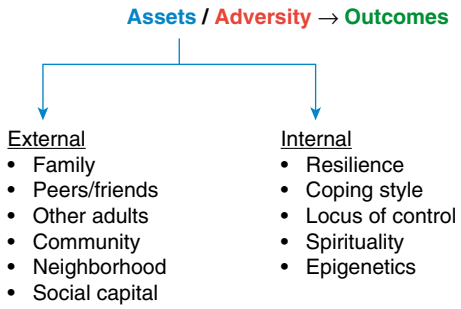

Fig. 1.2 Healing-centered care. Well-being and outcomes are a function of an individual's assets and adversities.

cardiovascular biomarkers (e.g., blood pressure) can occur from chronic stress and result in pathophysiologic conditions associated with chronic diseases. Chronic stress can also have effects at the genetic level. Studies of cellular aging have shown that chronic stress decreases telomere length, a determinant of aging on the cellular level. Epigenetic changes, including differential immune system DNA methylation, may occur after child abuse and posttraumatic stress disorder (PTSD) potentially contributing to inflammatory and immune dysregulation.*

Pediatrics, developmental psychology, basic sciences, and public health have contributed significant advances to the study of the behavioral, developmental, and social influences on child health. The influence of psychosocial stress brought about by environmental challenges, although always acknowledged as important, has taken on a new level of salience as epidemiologists have linked its occurrence to significant morbidities throughout the life course and as basic and clinical neuroscience has provided a multilevel framework for understanding how behavioral and psychosocial issues "get under the skin" to cause physiologic dysfunction and dysregulation. Such a framework can also be seen as a mechanism underlying health disparities (see Chapter 2).

Ecobiodevelopmental Framework

An **ecobiodevelopmental framework** has been proposed to integrate the overlapping influences of environmental (ecologic), biologic, and developmental factors into a model of health and illness. This model posits that ecology (or the social and physical environment) affects biology through physiologic disruptions and adaptations secondary to allostatic load mechanisms. The environment also influences development through life course science, which includes the effects of toxic exposures and childhood adversity on learning, cognitive, behavioral, and physical health throughout the life course. Stress-induced biologic responses to adversity may negatively affect development and biologic health. Biology influences development though brain maturation and neuroplasticity, which in turn are also affected by inputs from the social and physical environment. The ecobiodevelopmental framework is consistent with the biopsychosocial model while adding a longitudinal life course developmental dimension.

CHRONIC ILLNESS AND CHILDREN WITH SPECIAL HEALTHCARE NEEDS

The care of children with chronic conditions has become an increasingly larger part of clinical pediatrics for both the pediatric subspecialist and the general pediatrician. **Children and youth with special healthcare needs (CSHCN)** are defined by the U.S. Maternal and Child Health Bureau as "those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally." According to the 2018–2019 National Survey of Children's Health (NSCH), >14.1 million, or 19% of U.S. children, have a special health need. The 2009–2010 National Survey of Children with Special Health Care Needs (NS-CSHCN) reports that almost one quarter (23%) of U.S. households with children have a child with a special need. The conditions these children have are extremely heterogeneous, as shown in Table 1.6. Most of these children need specialty care in addition to primary care. In the United States, 0.4–0.7% of children fall into the category of "highest medical complexity"; these children account for 15–33% of all healthcare spending for children. Children with medical complexity account for >70% of hospital readmissions.

Table 1.6 Children with Special Healthcare Needs (CSHCN)*

HEALTH CONDITIONS
Attention-deficit/hyperactivity disorder
Depression
Anxiety problems
Behavioral or conduct problems
Autism spectrum disorder
Developmental delay
Intellectual disability
Communication disorder
Asthma
Diabetes
Epilepsy or seizure disorder
Migraines or frequent headaches
Head injury, traumatic brain injury
Heart problems, including congenital heart disease
Blood problems, including anemia or sickle cell disease
Cystic fibrosis
Cerebral palsy
Muscular dystrophy
Down syndrome
Arthritis or joint problems
Allergies

*List is not comprehensive and does not include all conditions that CSHCN may have. Adapted from Child and Adolescent Health Measurement Initiative. "2009/10 NS-CSHCN: Health Conditions and Functional Difficulties." Data Resource Center, supported by Cooperative Agreement 1-U59-MC06980-01 from the U.S. Department of Health and Human Services, Health Resources and Services Administration (HRSA). *Maternal and Child Health Bureau (MCHB)*. 2012. Available at www.childhealthdata.org. Revised 01/27/2012.

Nine of 10 CSHCN have functional difficulties in the sensory, cognitive, movement, emotional, or behavioral domains (Table 1.7). More than 65% (7.2 million) of CSHCN have conditions that affect their daily activities, and >2.3 million families experience financial difficulties because of their children's special health needs. The fact that 25% of family members of CSHCN cut back work hours or stop working because of their child's special needs highlights the social and economic impact of child chronic illness at both the individual and the national economic level.

Pediatricians are typically the "point persons" in the professional care of these children and provide data and expert opinion to procure needed services and resources to the child in the clinic, home, schools, and community. Such demands require an efficient model of chronic care.

SYSTEMS OF CARE

Population Health Approach

Because pediatric practice is increasingly spent working with patients and families who have chronic issues and conditions, new approaches to healthcare services delivery have been proposed. Whereas traditional practice models concentrate efforts toward the preventive and therapeutic needs of those patients who present for care, a **population health approach** to care refocuses efforts to emphasize the need to address health from a community- or population-level perspective, with emphasis on identifying and addressing the needs of individuals and families who do not seek regular care or whose care is episodic and suboptimal from a prevention or management standpoint. Effectiveness of such a system improves with greater collaboration between healthcare providers and payers (insurance companies) to identify gaps in care, with data surveillance systems and **electronic health records (EHRs)** and with an expanded cadre of healthcare personnel such as care coordinators, nurse practitioners, physician assistants, social workers, health navigators, and **community health workers**. Healthcare reimbursement modifications, such as incorporating value-based

Editor Note: Community members and some healthcare workers refer to this disorder as "hood disease."

Table 1.7 Functional Difficulties in Children with Special Healthcare Needs (CSHCN)*

Experiencing difficulty with…
Breathing or respiratory problem
Swallowing, digesting food, or metabolism
Blood circulation
Repeated or chronic physical pain, including headaches
Seeing even when wearing glasses or contact lenses
Hearing even when using a hearing aid or other device
Taking care of self, such as eating, dressing, or bathing
Coordination or moving around
Using his or her hands
Learning, understanding, or paying attention
Speaking, communicating, or being understood
Feeling anxious or depressed
Behavior problems such as acting out, fighting, bullying, or arguing
Making and keeping friends

*List is not comprehensive and does not include all functional difficulties that CSHCN may have.

From Child and Adolescent Health Measurement Initiative. "2009/10 NS-CSHCN: Health Conditions and Functional Difficulties." Data Resource Center, supported by Cooperative Agreement 1-U59-MC06980-01 from the U.S. Department of Health and Human Services, Health Resources and Services Administration (HRSA), *Maternal and Child Health Bureau (MCHB)*. 2012. Available at www.childhealthdata.org. Revised 01/27/2012.

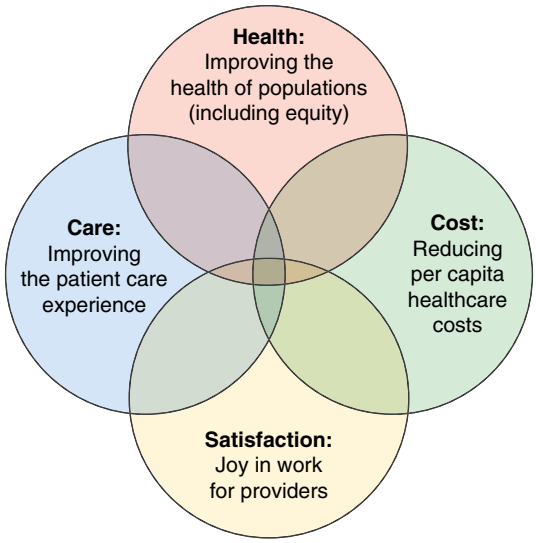

Fig. 1.3 The quadruple aim for healthcare. (*Data from Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. Ann Fam Med. 2014;12:573–576.*)

and quality-of-care–based models, if implemented correctly, may further advance a population health approach to care.

Medical Home

The concept of the **patient and family–centered medical home** (PFCMH) approach to providing care is defined as a medical home that provides care that is accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective. Patients and family members are key active participants, working with clinicians to identify priorities for and approaches to care (**shared decision-making**; see Chapter 18). A key aspect of the PFCMH is **care coordination**. Care coordination "addresses interrelated medical, social, developmental, behavioral, educational and financial needs to achieve optimal health and wellness outcomes." A care coordinator is the "point person" on the team who prospectively identifies the patient's and family's needs, concerns, and priorities for the healthcare visit, gathers pertinent information (lab results, consultations, educational plans, screening/testing results), communicates with subspecialists, and relays all important information to the clinical team before the patient/family visit. After a healthcare visit, the care coordinator works with the family to address any ongoing concerns, directs efforts to schedule follow-up appointments and referrals, and communicates information to all necessary parties. The care coordinator typically is not a physician. The intended result of care coordination is an efficient and comprehensive interaction between the pediatric team and the family, between primary care and specialty care, between ambulatory and inpatient care teams, and between the pediatric care team and the community-based supports on which the patient and family depend.

Provision of care consistent with the elements of a medical home has been associated with more accurate and early diagnosis, fewer emergency department visits and inpatient hospitalizations, lower costs, fewer unmet needs, lower out-of-pocket medical costs, less impact on parental employment, fewer school absences, and better patient satisfaction. According to the 2016 NSCH, 43% of U.S. CSHCN and 50% of U.S. children without a SHCN received coordinated, comprehensive care within a medical home.

Medical and Health Neighborhood

Although the medical home concept relates to practice transformation specific to primary care, a broadening of this concept has been proposed along two separate dimensions. The **medical neighborhood** expands the medical home concept and refers to coordinated and efficient integration between primary care pediatricians and the subspecialists, including integrated EHRs, efficient coordinated appointment scheduling, and enhanced communication. Such a system has the potential to provide a less stressful patient and family experience and could also lead to cost reduction and a decrease in medical errors.

Another expansion and modification of the medical home is the **health neighborhood** concept. The health neighborhood is based on the recognition of the importance of coordination with community-based and nonmedical providers to address comprehensively and efficiently the social and structural influences on health. Health neighborhoods include the healthcare providers (consistent with the medical home and neighborhood) but also involve services such as early intervention programs, the education system, childcare, community-based behavioral and mental health services, legal services, nutritional support services, and other clinical and community-based services that the patient and family need to access. The health neighborhood team helps families identify the needs of the patient, assists with referrals to appropriate agencies outside the healthcare system, and coordinates care.

Some nonmedical services may be co-located at the medical office. **Medical-legal partnerships** (MLPs) are collaborations between the healthcare and legal systems and embed legal aid personnel in the medical clinic. These lawyers and legal paraprofessionals can provide direct services to patients and families who have legal issues that may be affecting the child's health (e.g., housing code violations, utility shutoff, food insecurity, immigration issues, educational accommodations, guardianship). In addition to providing direct services, MLPs train healthcare personnel in the legal, social, and structural influences on health and work with physicians and others to advocate for policy change. Other nonmedical health neighborhood services that could be co-located in the medical center include supplemental nutrition assistance programs, parenting programs, behavioral health services, and family financial counseling.

Many, if not most, other services are located in the community. The health neighborhood model links families to these services and provides efficient ongoing coordination and communication. Community health workers or health navigators are paraprofessional team members who are community and culturally informed and serve as a coordinating link between the family, the medical home, and needed community services. Community health workers and health navigators can also provide patient and family education.

Expanded care models such as these have the potential to achieve what the Institute for Healthcare Improvement calls the "**quadruple aim**" for healthcare: focusing on **care** (improving the patient experience with healthcare, quality care, and satisfaction), **health** (improving the health of populations, including emphasis on equity), provider **satisfaction** ("joy in work"), and **cost** (reducing per-capita healthcare costs) (Fig. 1.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 2

Child Health Disparities

Lee M. Pachter and Adiaha I.A.Spinks-Franklin

Health and illness are not distributed equally among all members in most societies. Differences exist in historical roots, risk factors, prevalence and incidence, manifestations, severity, and outcome of health conditions, as well as in the availability and quality of healthcare. When these differences are modifiable and avoidable, they are referred to as **disparities** or **inequities**. The U.S. Department of Health and Human Services (DHHS) *Healthy People 2030* report defines *health disparity* as "a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion." The U.S. Centers for Disease Control and Prevention (CDC) define *health disparities* as "preventable differences in the burden of disease, injury, violence, or in opportunities to achieve optimal health experienced by socially disadvantaged racial, ethnic, and other population groups, and communities." Healthy People 2030 defines health equity as "the attainment of the highest level of health for all people. Achieving health equity requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities." Health and healthcare disparities occur because of unequal distribution of resources that are inherent in societies that exhibit *social stratification,* which occurs in social systems that rank and categorize people into a hierarchy of unequal status and power.

ROOT HISTORICAL CAUSES OF STRUCTURAL DETERMINANTS OF HEALTH AND HEALTH DISPARITIES

Figure 2.1 displays a categorization of the multiple determinants of health and well-being. Applying this categorization to health disparities, conceptualizations of the root causes of health disparities emphasize the most modifiable determinants of health: the physical and social environment, psychology and health behaviors, socioeconomic position and status, and access to and quality of healthcare (and the policies that place marginalized groups at greater risk based on these determinants). Differential access to these resources results in differences in *material* resources (e.g., money, education, healthcare) or *psychosocial* factors (e.g., locus of control, adaptive or risky behaviors, stress, social connectedness) that may contribute to differences in health status. This section will explore several historical social and structural root contributors to health disparities (see also Chapter 2.1).

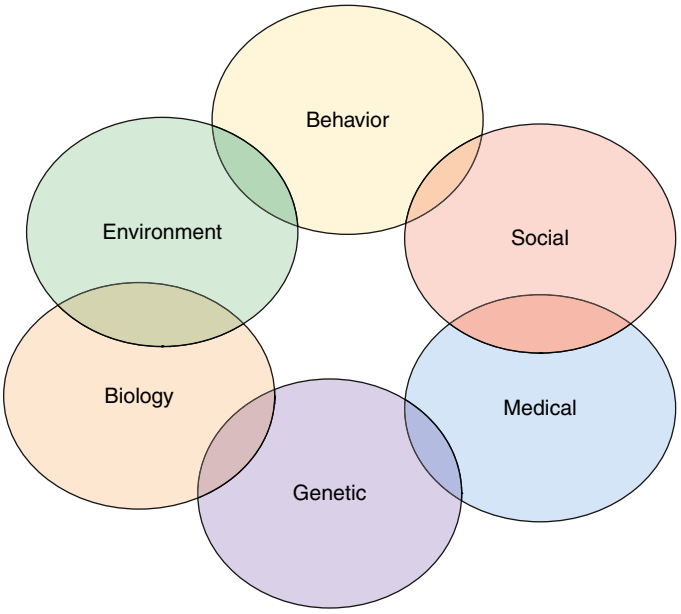

Fig. 2.1 Determinants of health.

Federal Policies and Economic Outcomes

Redlining (1933–1960)

A federally backed homeowner mortgage banking system, the Homeowners Loan Corporation (HOLC), was created in the 1930s and graded neighborhoods on credit risk for investment and mortgage lending into four color-coded levels that were outlined on city maps. The four color-coded levels were based primarily on racial and ethnic demographics rather than economic factors, with the 2 most desirable codes being for more affluent White neighborhoods. Neighborhoods defined as "Definitely Declining" were marked in yellow and were older neighborhoods with mixed ethnic makeup, including lower-income White residents and European immigrant residents, but no Black residents. Residents in these communities were allowed to get homeowner mortgages, but there was less overall economic development. Neighborhoods defined as "Hazardous" were marked in red (hence the term *redlined communities*) and were where Blacks lived, including affluent Blacks. Residents in these neighborhoods were denied homeowner mortgages and were systematically disinvested by local, state, and federal government policies.

The Federal Housing Authority (FHA), created in 1934 to be the government entity that would federally secure homeowner mortgages, created underwriting manuals for banks with rules regarding lending practices that included denying loans to Black applicants and devaluating properties in redlined neighborhoods. Therefore from the 1930s to 1960s, 98% of FHA homeowner mortgage loans were given to White Americans. This led to decades of residential housing segregation. Redlining was officially outlawed by the Fair Housing Act of 1968; however, the impact of redlining continues.

Urban Renewal (1949–1974)

After World War II, city officials and city planners across the United States described urban areas as "slums," full of poor people and in blight. At the same time, the Great Migration (1916–1970) changed the racial makeup for northern cities, when millions of rural southern Black farm workers, domestic workers, laborers, and their families left the harsh Jim Crow segregated conditions of the South and migrated to northern cities seeking a better life and improved economic conditions and opportunities. The leaders in northern destination cities sought to control and contain these southern Black Americans. The federal government passed the Housing Act of 1949 to provide funding to cities across the country to clear and redevelop the slums (called "slum clearance"). City leaders and planners used the funds to revitalize their downtown areas to woo suburban Whites for shopping and entertainment and simultaneously target redlined communities to demolish old buildings and houses and move poor Black and brown residents into public housing facilities (called "housing projects"). In 1956, the Eisenhower administration passed the Federal-Aid Highway Act of 1956 that created the national interstate system. Redlined communities were targeted for placement of these interstate highways that displaced Black and brown residents into segregated housing projects. All of these federal policies led to the following consequences affecting public health:

- **Residential housing segregation**: Fifty-plus years of discriminatory homeowner lending practices, real estate practices, and economic disinvestment have led to *hypersegregation* of neighborhoods and resources. Black and Latinx residents are more likely to live in neighborhoods where the majority of residents have incomes below the federal poverty level, which is referred to as *concentrated poverty.* Residents living in formerly redlined neighborhoods have poorer

health outcomes, including higher rates of asthma, cancer, heart disease, and premature birth and shorter life expectancies. They are at higher risk of being exposed to environmental toxins, including lead, mold, exhaust pollutants and greenhouse gases, that all contribute to poor health. Residential housing segregation has other significant health consequences for Black and Latinx American children, including living in food deserts (having few grocery stores in neighborhoods), digital deserts (lack of access to reliable high-speed internet), having fewer green spaces, and few pharmacies.

- **Economic disparities, racial wealth gap, and concentrated poverty**: Federal policies during the 1930s and 1940s created the foundation for racial wealth gaps. The Social Security Administration and the Servicemen's Readjustment Act of 1944 (the GI Bill) were established to create a middle class. The Social Security system was created to provide income to older adults. However, farmworkers and domestic workers were not included among the professionals that would pay into the Social Security system. *These occupations employed predominantly Black laborers, who did not benefit from the initial Social Security policy.* The GI Bill provided former World War II military soldiers with low-interest home, farm, and business loans; funds to pay for higher education; and unemployment assistance. White and Japanese American soldiers were granted the financial benefits from the GI Bill to buy homes and attend college. However, millions of Black soldiers were denied the GI Bill. First American (i.e., Indigenous Nations peoples) WWII veterans used the GI Bill to pay for a college education, but could not use the GI Bill to buy homes on reservations because reservation land was excluded from the GI Bill. Mexican American soldiers did not have full access to the benefits of the GI Bill for homeownership, but some were able to benefit from job training. Therefore millions of Black, Indigenous Nations peoples, and Mexican American WWII veterans did not receive all the financial and educational benefits of the GI Bill. White Americans have accumulated 10 times the wealth of Black Americans, which has transgenerational implications. Discriminatory hiring and firing practices place minoritized workers at higher risk of chronic underemployment and unemployment. Additionally, there is an ongoing racial and gendered racial pay gap between White American men and women and men and women who are Black, Asian American, Latinx American, and Indigenous Nations peoples. In 2021, for every dollar a White American man made, Asian American women made 85 cents, Black women made 63 cents, Indigenous Nations women made 60 cents, and Latina American women made 57 cents.
- **School segregation and educational underfunding**: Public schools are funded by property taxes. In hypersegregated communities with concentrated poverty, schools are underfunded, with a 2019 study reporting a $23 billion funding gap between school districts with predominantly White students and school districts with predominantly Black, Latinx, and Indigenous Nations students. This funding gap leads to schools with less qualified teachers, less rigorous curricula, and fewer extracurricular activities. Black, Latinx, and Indigenous Nations students have overpolicing and harsher school punishment practices, as discussed further in Chapter 2.1. Schools are not teaching BIPOC students self-discipline; they are overpunishing and criminalizing these students.
- **Environmental injustice**: There are racial disparities in who suffers the health consequences of climate change. Residential housing segregation and environmental policies have contributed to unequal exposure to environmental toxins. White Americans produce the majority of greenhouse gas emissions but experience less of the negative health effects of such emissions such as asthma, other chronic lung disease, cancer, and cardiovascular disease. Black and Latinx American children in hypersegregated neighborhoods are also more likely to be exposed to lead poisoning compared with their White American counterparts. Lead exposure increases the risk of health problems, including anemia, attention regulation problems, and learning problems. Increased exposure to mold and other major asthma triggers contributes to disparities in asthma outcomes among children of color and poor children. Residential housing segregation also places communities of color at risk for poor water quality and the health consequences.

Figure 2.2 illustrates the complex relations among multileveled factors and health outcomes. Historical **social stratification** factors, such as socioeconomic status (SES), race, and gender, have profound influences on environmental resources available to individuals and groups, including neighborhood factors (e.g., safety, environmental toxins, grocery stores, transportation, healthy spaces), social connectedness and support, work opportunities, and family environment. Much of the differential access to these resources results from historical discrimination on a systematic, institutional, and interpersonal level (see Chapter 2.1). Discriminatory policies place historically subordinated groups at greater risk of poorer health outcomes and psychologic functioning, including sense of control over one's life, expectations, resiliency, negative affect, and perceptions of and response to discrimination. Environmental and psychologic context then have influence over more proximal determinants of health, including health-promoting or risk-promoting behaviors; access to and quality of healthcare and health education; exposure to pathogens, toxins, and carcinogens; pathophysiologic responses to stress; and the resources available to support optimal child development.

Psychosocial Stress and Allostatic Load

An understanding of allostatic load helps explain how psychosocial stress influences disease, health outcomes, and health disparities (Fig. 2.3 and Chapter 1). *Allostasis* refers to the normal physiologic changes that occur when individuals experience a stressful event, including activation of the stress-response systems, changes in levels of inflammatory and immune mediators, cardiovascular reactivity, and metabolic and hormone activation. These are normal and adaptive responses to

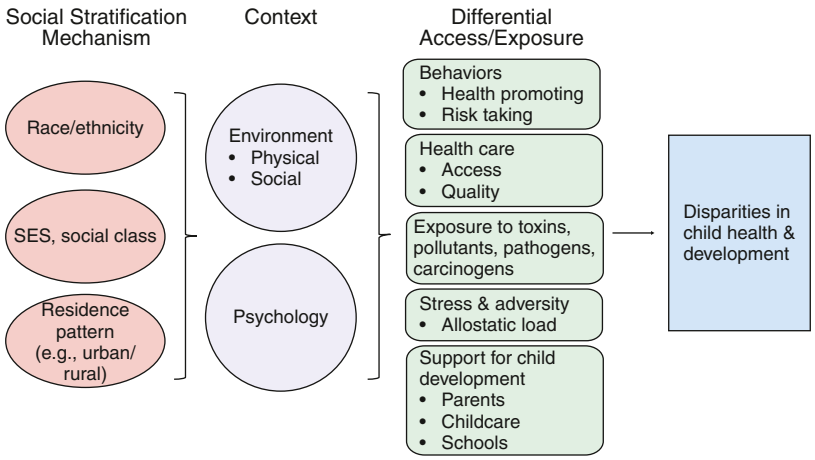

Fig. 2.2 Child health disparities. SES, Socioeconomic status. (*Data from Adler NE, Stewart J. Health disparities across the lifespan: Meaning, methods, and mechanisms. Ann NY Acad Sci. 2010;1186[1]:5–23.*)

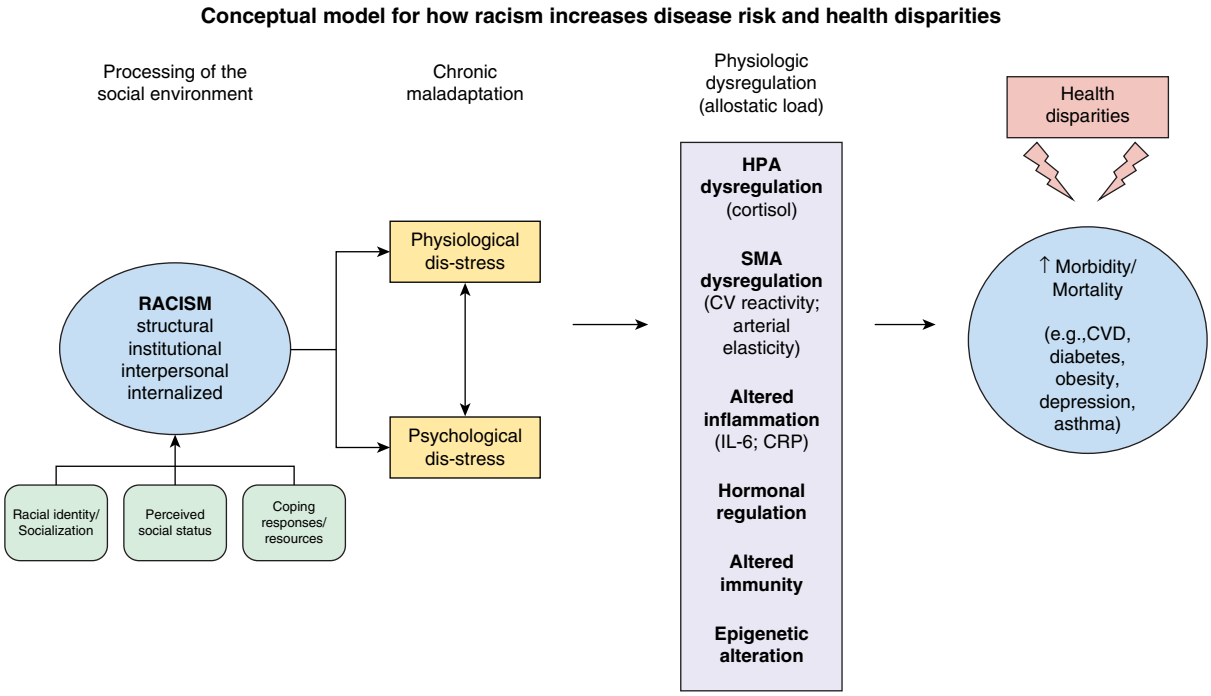

Fig. 2.3 Mechanism through which racism leads to health disparities.

stress and result in physiologic stability in the face of an external challenge. After an acute external stress or challenge, these systems revert to normal baseline states.

However, when the stressor becomes chronic and unbuffered by social supports, dysregulation of these systems may occur, resulting in pathophysiologic alterations to these responses, such as hyperactivation of the allostatic systems, or *burnout*. Over time this dysregulation contributes to increased risk of disease and dysfunction. This pathophysiologic response is called *allostatic load*.

Allostatic load may contribute to increased incidence of chronic diseases such as cardiovascular disease, stroke, diabetes, obesity, asthma, and depression. It is notable that these specific chronic diseases have increased prevalence in racial and ethnic minority groups because of long-standing historical and current discrimination and oppression that have contributed to increased psychologic distress that in turn contributes to allostatic load and the resultant disparities in these chronic diseases. Many of these conditions are noted to occur in adulthood, demonstrating the life course consequences of chronic psychosocial stress and adversity that begins in childhood. Figure 2.3 shows a model through which racism as a toxic psychosocial stressor "gets under the skin" to cause physiologic dysregulation (allostatic load), which over time leads to chronic illnesses that are known to have higher prevalence in minoritized populations (health disparities).

The allostatic load model provides a pathophysiologic mechanism through which negative structural and social determinants of health contribute to health disparities. It complements other mechanisms noted in Figure 2.2, such as differential access to healthcare; increase in health risk behaviors; and increased exposure to pathogens, toxins, and other unhealthy agents.

The Healthy Immigrant Paradox

The Healthy Immigrant Paradox refers to the epidemiologic finding that first-generation immigrants have better health than native-born counterparts regardless of age, sex, economic status, or ethnic category, but their health status declines and converges with the native-born population over time. Studies in the United States and Europe have found that most immigrants have better physical and psychologic health status than native-born people of similar ethnicity in their receiving country. There are a variety of possible explanations for this health difference, including self-selection bias among people who emigrate: being younger, more educated, and physically healthier than those in the country of origin who do not emigrate. In addition, immigrants may bring healthier cultural beliefs and practices that may contribute to better health outcomes. However, the health status of immigrant populations declines in the decades after initial migration because of a variety of complex sociopolitical and economic reasons, including denial of access to healthcare services (e.g., laws that prohibit immigrants from having access to preventive health services), having jobs with unsafe work conditions, adopting poorer health habits, and the psychologic stress of adapting to a new society (i.e., acculturation stress) (see Fig. 12.1).

The Healthy Immigrant Paradox is not universal and has been called into question by some. Many studies of the Healthy Immigrant Paradox use self-report of health status, which may be prone to bias. Not all first-generation immigrants demonstrate better health than their U.S.-born counterparts. Immigrant health status can be influenced by country-of-origin factors (e.g., war, famine), health beliefs (e.g., perceiving obesity to be a sign of wealth rather than of poor health), and racialized immigration policies in the receiving country that favor immigrants from some countries over others. Many studies of the Healthy Immigrant Paradox do not include temporary immigrant workers who often do not have the same access to resources as do longer-term immigrants.

Approximately 18.4 million, or 25% of children in the United States under age 12 years, have at least one immigrant parent. Children of immigrant parents have better health and academic outcomes compared with their U.S.-born counterparts. For example, Latinx and Asian children who are born to immigrant parents (second generation) and those brought to the United States as children (1.5 generation) have better study habits and better academic outcomes compared with third-generation U.S.-born Latinx and Asian American counterparts. Behavioral health outcomes also vary among immigrant children and their U.S.-born counterparts, where third-generation and subsequent generation children engage in more risky health behaviors.

DISPARITIES IN CHILD HEALTH AND HEALTHCARE

Tables 2.1 and 2.2 display some of the known disparities in child health and healthcare. Many health disparities may occur as a result of historical oppression and marginalization of people with policies targeting groups

Table 2.1 Child Health Disparities

HEALTH INDICATOR	RACE/ETHNICITY	FAMILY INCOME	RESIDENCE
Child health status fair or poor	Black and Hispanic > White and Asian	Poor > Not Poor	
Children with special healthcare needs (CSHCN)	Black > White > Hispanic	Poor > Not Poor	
One or more chronic health conditions	Black > White > Hispanic > Asian	Poor > Not Poor	
Asthma	Mainland Puerto Rican > Black > White and Mexican American	Poor > Not Poor	Urban > Rural
Obesity	Hispanic and Black > White and Asian	Poor > Not Poor	Rural > Urban
Infant mortality	Black > Hispanic > White	Poor > Not Poor	
Low birthweight (<2,500 g)	Black > White, Hispanic, American Indian/ Native Alaskan, Asian/Pacific Islander Mainland Puerto Rican > Mexican American	Poor > Not Poor	
Preterm birth (<37 wk)	Black > American Indian/Native Alaskan, Hispanic, White, Asian/Pacific Islander Mainland Puerto Rican > Mexican American	Poor > Not Poor	
Seizure disorder, epilepsy	Black > White, Hispanic	Poor > Not Poor	
Bone, joint, or muscle problem	White > Black, Hispanic	Poor > Not Poor	
Ever breastfed	White, Hispanic, Asian > Black	Not Poor > Poor	Urban > Rural
No physical activity in the past week	Hispanic > Black, Asian > White	Poor > Not Poor	
Hearing problem		Poor > Not Poor	
Vision problem		Poor > Not Poor	
Oral health problems (including caries and untreated caries)	Hispanic > Black > White, Asian	Poor > Not Poor	Rural > Urban
Attention-deficit/hyperactivity disorder (ADHD)	White, Black > Hispanic	Poor > Not Poor	Rural > Urban
Have ADHD but not taking medication	Hispanic, Black > White		
Anxiety problems	White > Black, Hispanic	Poor > Not Poor	
Depression		Poor > Not Poor	Rural > Urban
Behavior or conduct problem (ODD, conduct disorder)	Black > White, Hispanic	Poor > Not Poor	
Autism spectrum disorder	White > Black > Hispanic	Poor > Not Poor	
Learning disability	Black > White, Hispanic	Poor > Not Poor	Rural > Urban
Developmental delay	Black > White > Hispanic, Asian	Poor > Not Poor	
Risk of developmental delay by parental concern	Hispanic > Black and White	Poor > Not Poor	
Speech or language problems		Poor > Not Poor	
Adolescent suicide attempts (consider, attempt, needed medical attention for an attempt)	Girls: Hispanic > Black and White Boys: Hispanic and Black > White		
Adolescent suicide rate	Girls: American Indian > White, Asian/Pacific Islander, Hispanic, Black Boys: American Indian and White > Hispanic, Black, Asian/Pacific Islander		
Child maltreatment (reported)	Black, American Indian/Alaskan Native, Multiracial > White, Hispanic, Asian, Pacific Islander	Poor > Not Poor	
Flourishing	Asian American > White > Other Non-Hispanic > Black >Hispanic	Not Poor > Poor	
AIDS (adolescents)	Black > Hispanic > White		

AIDS, Acquired immunodeficiency syndrome; ODD, oppositional defiant disorder.

Table 2.2 Child Healthcare Disparities

HEALTHCARE INDICATOR	RACE/ETHNICITY	FAMILY INCOME	RESIDENCE
Did not receive any type of medical care in past 12 mo	Hispanic, Black, Asian > White	Poor > Not Poor	Rural > Urban
No well-child checkup or preventive visit in past 12 mo	Hispanic > White and Black	Poor > Not Poor	Rural > Urban
Delay in medical care	Hispanic > Black > White	Poor > Not Poor	
Unmet need in healthcare due to cost	Black > Hispanic > White > Asian	Poor > Not Poor	
No coordinated, comprehensive, or ongoing care in a medical home	Hispanic > Black and Asian > White	Poor > Not Poor	Rural > Urban
Problem accessing specialist care when needed	Hispanic and Black > White	Poor > Not Poor	
No preventative dental care visit in past 12 mo	Hispanic and Asian > Black > White	Poor > Not Poor	Rural > Urban
No vision screening in past 2 yr	Hispanic and Asian > Black and White	Poor > Not Poor	
Did not receive needed mental health treatment or counseling in past 12 mo	Black and Hispanic > White	Poor > Not Poor	
Not receiving a physician recommendation for HPV vaccination among 13- to 17-yr-old girls	Black and Hispanic > White		
Immunization rates: adolescent HPV vaccine	Girls: white > Black and Hispanic Boys: Black and Hispanic > White		

HPV, Human papillomavirus.

that are deemed to be socially, politically, geographically, and economically inferior. As a result of these targeted policies, we tend to see health disparities of people based upon racial/ethnic group, socioeconomic status (often operationalized through family income, sometimes using insurance status as a proxy), and residency patterns, such as urban and rural locale. Other stratification factors, such as ability/disability status, may also contribute to health and healthcare inequality

Child Health Disparities

Asthma

Disparities in asthma prevalence are seen by racial/ethnic group and SES. According to the CDC's 2019 National Health Interview Survey (NHIS) data, the national mean prevalence of asthma among children (<18 years old) was 7.0%. Compared with the mean, the children with the highest prevalence of asthma were Black (18.0%), Indigenous Nation/Alaskan Native (17.8%), and Hispanic (12.5%). Asthma prevalence for Asian American children was 8.2%. There are also significant regional and SES differences in asthma prevalence, with children who live below the federal poverty level having a 14.5% prevalence.

Exposure to environmental pollutants is one factor explaining these disparities in asthma prevalence. Although non-Hispanic White Americans consume the most goods and services that produce greenhouse gases (e.g., fine particulate matter), Black and Hispanic Americans have higher exposure to greenhouse gases that are associated with poor health outcomes, including asthma. Residential hypersegregation results in higher exposure to air pollution and other respiratory toxins for Black and Hispanic Americans, increasing their risk of asthma. In addition, evidence shows a correlation between exposure to traffic pollutants and having fewer local pharmacies and healthcare providers. This "triple jeopardy" is more common with Black and Hispanic children.

Obesity

In 2018, the National Center for Health Statistics found that 19.3% of all U.S. children and adolescents (ages 6-17 years) have obesity (Fig. 2.4). Obesity prevalence was highest among Hispanic children (25.6%) and non-Hispanic Black children (24.2%). The prevalence of obesity was 16.1% among non-Hispanic White children and 8.7% among non-Hispanic Asian children. The obesity prevalence among Indigenous Nation/Alaskan Native adolescents is 11.0% and among Native Hawaiian/Pacific Islanders is 26.7%. There are complex interplays between social, environmental, and behavioral influences on health that contribute to obesity disparities in the United States. Studies

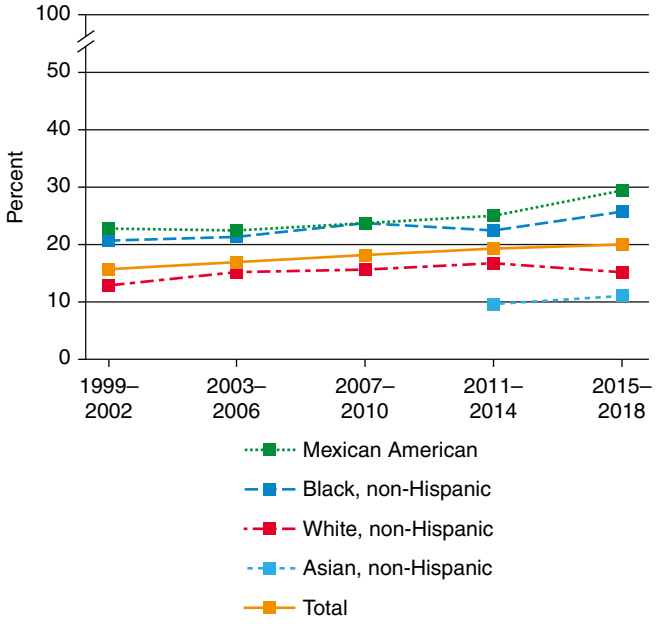

Fig. 2.4 Percentage of children ages 6-17 with obesity by race and Hispanic origin, selected years 1999–2002 through 2015–2018. (*From National Center for Health Statistics. National Health and Nutrition Examination Survey.* https://www.childstats.gov/americaschildren/surveys2.asp#nhnes.)

have found that obesity prevalence is higher in communities with high rates of poverty and communities with a majority Black population because of lack of access to grocery stores and farmers markets (food deserts), overabundance of fast-food restaurants, less access to parks and outdoor recreation areas, food marketing targeting, and higher healthy food prices. In addition, dietary patterns, access to nutritious foods, and differing cultural norms regarding body habitus may account for some of these differences.

Pregnancy Outcomes, Preterm Birth, and Infant Mortality

The highest rates of infant mortality are seen in non-Hispanic Black infants (Figs. 2.5 and 2.6). According to data from the CDC, the overall

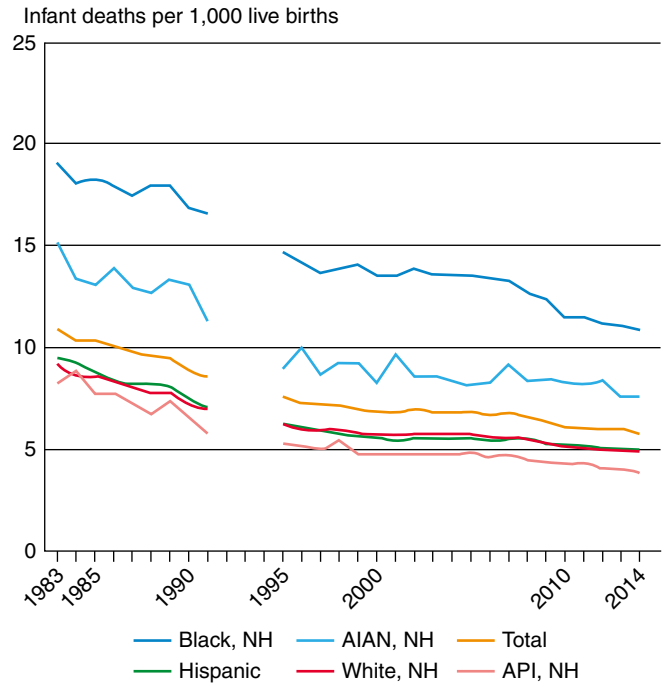

Fig. 2.5 Death rates among infants by race and Hispanic origin of mother, 1983–1991 and 1995–2014. AIAN, American Indian or Alaska Native; API, Asian or Pacific Islander; NH, non-Hispanic. (*From National Center for Health Statistics. National Vital Statistics System.* https://www.childstats.gov/americaschildren/health_fig.asp#health2. *Accessed July 2018.*)

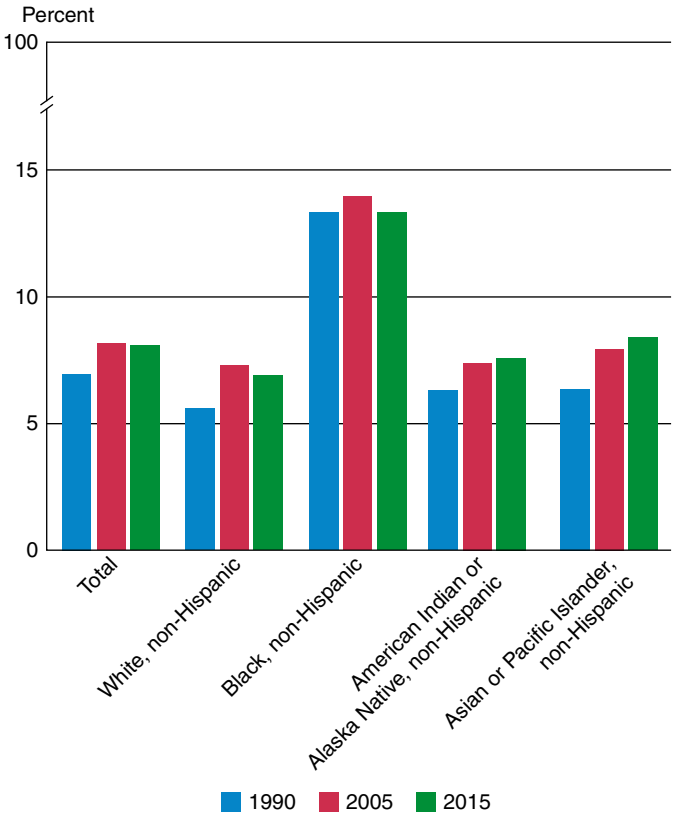

Fig. 2.6 Percentage of infants born with low birthweight by race and Hispanic origin of mother, 1990, 2005, and 2015. (*From National Center for Health Statistics. National Vital Statistics System.* https://www.childstats.gov/americaschildren/health_fig.asp#health1b. *Accessed July 2018.*)

infant mortality rate was 5.7 infants per 1,000 live births. For Black infants, the mortality rate was 10.8 infants per 1,000 live births. The top 5 causes of mortality (in order of frequency) among Black infants were low birthweight, congenital malformations, maternal complications, sudden infant death syndrome (SIDS), and unintended injuries. Black American infant mortality remains high compared with other populations, regardless of maternal education, insurance status, maternal age, and income.

Chronic experiences with structural, institutional, and interpersonal racism contribute to elevated biomarkers for stress and allostatic load, which is referred to as *weathering*—the accumulative effect of adversity on the health of individuals (see Chapter 2.1). Weathering of Black women has been associated with a risk of preterm birth and infant mortality. When examining the life-course perspective, studies suggest that early life exposure to adversity, including systemic racism, increases the risk of poor birth outcomes (see Chapter 2.1). Having a racially concordant physician significantly reduces the risk of infant mortality by 39% among Black newborns.

Infant mortality rates among Indigenous Nation/Alaskan Native populations was 8.2 infants per 1,000 live births, with the leading causes of infant death (in order of frequency) being low birthweight, congenital malformations, and maternal complications. Asian American infants had the lowest infant mortality rates, at 3.8 infants per 1,000 live births, with the leading causes of death (in order of frequency) being congenital malformations, low birthweight, maternal complications, and unintended injuries. The Asian American population was not disaggregated by country of origin, so granular details regarding this heterogenous American population were not available. Overall Hispanic infant mortality was 4.9 infants per 1,000 live births, but mortality rates varied significantly based upon country of origin from 3.8 to 5.6 per 1,000 live births. Leading causes of death among all Hispanic infants (in order of frequency) were congenital malformations, low birthweight, maternal complications, SIDS, and unintended injuries. The White American infant mortality rate was 4.6 infants per 1,000 live births, with the leading causes of infant mortality (in order of frequency) being congenital malformations, low birthweight, SIDS, unintended injuries, and maternal complications (see Chapters 114 and 114.1).

Infant mortality among the Native Hawaiian/Pacific Islander population was 9.4 infants per 1,000 live births overall. Infant mortality rates varied in the Native Hawaiian/Pacific Islander population when the data were disaggregated by country of origin from 10.1 to 22.5 per 1,000 live births. In 2017, the World Health Organization (WHO), UNICEF, and United Nations (UN) highlighted some of the social and environmental risk factors for such high infant mortality among Pacific Islanders, which include prematurity, birth complications, and severe infections (specifically, pneumonia and diarrheal illnesses). Infant mortality among Native Hawaiians was 9.4 infants per 1,000 live births, and the leading causes of infant mortality were preterm birth and low birthweight, sudden unexplained infant death, congenital anomalies, infection, and injury.

Many of the causes of infant mortality disparities can be mitigated through public policy, public health measures, and healthcare interventions that specifically target populations at highest risk, such as increased access to quality prenatal care, reducing air pollution exposure, and improving physician training to reduce implicit bias and improve communication skills.

Oral Health

Significant differences exist in oral health status and in preventive oral healthcare according to race/ethnicity, SES, and residency locale. The 2019–2020 National Survey of Children's Health (NSCH) found the prevalence of oral health problems among children (ages 1-17 years) to be 17.7% for Hispanic Americans, 16.2% for Black Americans, 15.8% for Asian Americans, 12.1% for White Americans, and 13.2% for other non-Hispanic Americans. The prevalence of oral health problems in this 2019-2020 NSCH were found to be highest among children who live in households with incomes below the federal poverty level (20.3%) compared with children who live in households making >400% of the federal poverty level (8.7%).

Data from the CDC demonstrated that overall prevalence of dental caries decreased for children age 6-11 years: from 21% in the 1994–2004 NHANES survey to 17% in the 2011–2016 survey. The children in the survey who did not show improvements in the prevalence of dental caries were younger children (ages 6-8 years), poor children (both near-poor and children living below the federal poverty level), and non-Hispanic Black children. Preventive oral healthcare may improve rates of caries and treat caries before further impairment ensues. Data from the 2014 Medical Expenditure Panel Survey revealed that being poor and lacking health insurance were the main reasons for not receiving preventive dental care.

Hearing Care

No data suggest that the prevalence of hearing loss (either congenital or acquired) is different among racial/ethnic or SES categories, but follow-up care after diagnosis of a hearing problem has been shown to be poorer in certain groups. Delays in diagnosis and treatment of hearing loss are found among children who lack health insurance, live farther away from diagnostic health centers, are poor, live in areas with specialists' shortages, live in rural areas, and have primary care providers with limited experience in caring for children with hearing loss. Much of this disparity is reduced when families have access to specialists.

Vision Problems

The parent-reported 2019–2020 NSCH found that vision problems were reported in 3.1% of Hispanic children, 1.2% of White children, 2.1% of Black children, 1.0% of Asian children, and 1.6% of children in other racial categories. Vision problems were more commonly reported among children who lived in households with an income that was less than the federal poverty level (3.4%) compared with children living in households with an income greater than 400% of the federal poverty level (0.8%). Vision problems were more commonly reported among children who did not have a medical home (2.6%) compared with children with a medical home (1.0%). Reports of vision problems in children also varied by insurance coverage type, with 0.9% of children with private health insurance, 3.0% of children with public health insurance, 3.0% of children with both public and private health insurance, and 4.1% among uninsured children.

Immunization

Disparities in immunization rates had been noted with household income status, insurance status, and residential location. In response to these socioeconomic disparities and to higher rates of measles cases in the 1980s, a number of interventions were initiated, including the creation of the **Vaccines for Children program** (VFC), which eliminated the financial barrier to immunization by providing free immunizations to at-risk groups (Medicaid-eligible, uninsured, Indigenous Nation/Alaskan Native, or underinsured and vaccinated at a federally qualified health center or rural health clinic). Although vaccination rates have improved, the 2018–2020 CDC National Immunization Survey—Child study found income, geographic, and racial disparities in infant vaccination rates. Vaccination rates were lower among infants living in households with an income below the federal poverty level and infants who lacked health insurance. Vaccination rates varied widely by state and region of the United States.

Although rates of initial *primary* vaccine series demonstrate no or decreasing disparities, other vaccination rates do show differences. Black and Hispanic adolescent females have lower human papillomavirus (HPV) vaccination rates than do Whites. Reasons for this disparity include parental concerns about safety and providers not recommending the vaccine. Of interest, Black and Hispanic male adolescents have higher rates of HPV vaccine coverage than do Whites.

Adolescent Suicide

In 2019, the CDC Youth Behavior Risk Surveillance System of 9th-12th graders reported suicide attempts by racial category, sex, and sexual orientation. The highest rate of suicide attempts was among Indigenous Nations/Alaskan Native teens (25.5%), followed by Native Hawaiian/Pacific Islanders (18.4%), multiracial teens (12.9%), Blacks (11.8%), Latinx Americans (8.9%), White Americans (7.9%), and Asian Americans (7.7%). Suicide attempts were higher among adolescent females (11.0%) than among adolescent males (6.6%). Suicide attempts vary when stratified by sexual orientation status, with the highest prevalence among bisexual teens (24.5%), followed by gay male teens (19.5%) and heterosexual teens (6.4%). Risk factors for suicide ideations and attempts include sexual assault, being bullied, substance abuse, depression, and experiences with interpersonal racial discrimination (see Chapter 40).

Child Maltreatment

In 2014, *reports* of child abuse and neglect were higher in Black (15.3 per 1,000 children), Indigenous Nation/Alaskan Native (13.4/1,000), and multiracial (10.6/1,000) children, compared with Hispanic (8.8/1,000), Pacific Islander (8.6/1,000), White (8.4/1,000), and Asian (1.7/1,000) children. Poverty, measured at the family and at the community level, is also a significant risk factor for maltreatment. Counties with high poverty concentration had >3 times the rate of child abuse deaths than counties with the lowest concentration of poverty. Additionally, it is the "criminalization" of poverty that increases the risk of poor people being reported for abuse and neglect compared to their more affluent counterparts. However, despite the fact that Black children are overrepresented in the child welfare system in the United States, race itself *should not be a marker* for child abuse or neglect. *Studies have found that Black parents are overreported for child abuse and maltreatment compared with White parents who engage in the same behavior because of historical systemic racism and implicit racial bias among those who report and caseworkers.* Latinx children's representation in the child welfare system varies by state and region, where they are overrepresented in some states, but underrepresented in other states. Indigenous Nation/Alaskan Native youth are underrepresented in the child welfare system in most states, but Alaska is the state with the highest overrepresentation of Indigenous children reported to the child welfare system. White American children are not overrepresented in the child welfare system and are often underrepresented.

Behavioral Health Disparities

Attention-Deficit/Hyperactivity Disorder (ADHD)

The 2019–2020 NSCH found the overall prevalence of ADHD among children age 3-17 years to be 8.9%. White and Black children are more often diagnosed with ADHD (10.2% and 10.5%, respectively) than are Hispanic children (6.9%), Asian American children (2.7%), and children of other non-Hispanic groups (8.5%). Other studies have shown that both Black and Hispanic children have lower odds of having an ADHD diagnosis than White children. Children reared in homes with a household income below the federal poverty level are diagnosed more often (10.9%) than those at or above the federal poverty level (8.3%). Children with two or more adverse childhood experiences (ACEs) are almost 3 times as likely to be diagnosed with ADHD (17.1%) compared with children with no ACEs (5.8%). Children without a medical home are more likely to be diagnosed with ADHD (9.7%) compared with children who have a medical home (8.0%).

Children diagnosed with ADHD have different treatment experiences. After being diagnosed with ADHD, White children, when compared with Black and Hispanic children, were more likely to be diagnosed with a coexisting anxiety disorder. Within the first year of treatment for ADHD, White children were most likely to be treated with medication or behavior therapy and Asian American children were the least likely to receive any type of treatment for ADHD.

Depression and Anxiety Disorders

According to the 2020 National Survey of Drug Use and Health, from 2004 to 2019, the reported prevalence of major depression episodes increased among all U.S. adolescents. In 2019, those with the highest reported prevalence of a major depression episode were 16- to 17-year-olds (20.2%), adolescent girls (23.0%), adolescents of two or more races (20.9%), and teens living in households with incomes above the federal poverty level (16.1%).

When stratifying by racial group, a major depression episode was found in 17.3% of Hispanic teens, 15.9% of White teens, 15.1% of Asian American teens, 12.2% of Indigenous Nation/Alaska Native teens, and

11.4% of Black teens. Differences in reported rates of depression based upon racial group may be the result of differences in the manifestation of depression symptoms, clinician treatment bias, and limited access to adequate mental healthcare.

Autism Spectrum Disorder (ASD)

Compared with White children, Black and Hispanic children are less likely to be diagnosed with ASD, and when diagnosed, are typically diagnosed at a later age and with more severe symptoms. Nonetheless, Blacks and Hispanics are typically diagnosed at a later age and with more severe symptoms. Disparities in diagnosis and timing of diagnosis are concerning given that early diagnosis provides access to therapeutic services that are most effective when initiated early. Reasons for these disparities may include differences in cultural behavioral norms, stigma, differences in parental knowledge of typical and atypical child development, poorer access to quality healthcare, and differences in the quality of provider-patient communication along with trust in providers. Recent CDC data suggest that racial and ethnic disparities in ASD diagnosis are decreasing.

Behavioral or Conduct Problems

According to the 2011–2012 NSCH, Black children age 2-17 years have higher rates of oppositional defiant disorder (ODD) or conduct disorder than do White and Hispanic children. Evidence suggests that the *overdiagnosis* of Black children with these disorders is linked to the pervasive criminalization and adultification of Black child behavior. Adults often view Black children as older, less innocent, and in less need of protection than same-age peers of other racial groups. In fact, studies have found that physicians with negative implicit racial bias are more likely to overpathologize Black child behavior and overdiagnose Black children with ODD, conduct disorder, and ADHD. The pathologizing of Black child behavior can have severe consequences, including excessive school punishment, school expulsion, and early contact with the legal system.

Developmental Delay

The 2019–2020 NSCH found that Black children age 3-17 years had higher reported rates of developmental delay (7.4%) than Hispanic children (5.3%), White children (5.4%), and other non-Hispanic children (5.4%). Children living in households with incomes below the federal poverty level were more likely to be diagnosed with a developmental delay (8.7%) than children living in households with an income at 400% of the federal poverty level (3.6%). Children experiencing two or more ACEs have a higher prevalence of developmental delay than do children with no ACEs (10.8% vs 3.8%). ACEs increase the child's allostatic load and impede neurologic development, thus placing them at increased risk of developmental delays. Evidence also suggests that physicians with negative implicit racial biases are less likely to ask Black parents and parents who speak English less fluently about their concerns regarding developmental delays and are less likely to refer the children to early intervention, and these children are less likely to receive appropriate developmental evaluations by early intervention providers.

Flourishing

In the 2019–2020 NSCH, parents reported rates of flourishing, which is overall good mental health in their children and teens. Flourishing was measured by three behaviors: learning, resilience, and self-regulation. Overall, 63.3% of parents reported their child met all three flourishing criteria. Females (66.8%) were reported as having higher flourishing than males (59.9%). The highest level of flourishing was reported among Asian American youth (73.0%), followed by White (64.8%), other non-Hispanic children (62.1%), Black (61.8%), and Hispanic (59.7%). Flourishing rates were lowest among youth who live in households with incomes lower than the federal poverty level (55.6%) and highest among youth living in families with incomes higher than 400% of the federal poverty level (70.0%).

Child Healthcare Disparities

In almost all areas, Black, Hispanic, and Indigenous Nation/Alaskan Native children have been identified as having worse access to needed healthcare, including receipt of any type of medical care within the past 12 months, well-child or preventive visits, delay in care, having an unmet need because of healthcare cost, lack of care in a medical home, problems accessing specialist care when needed, lack of preventive dental care, vision screening, mental health counseling, and recommendations for adolescent immunizations (see Table 2.2). In addition, many of these healthcare indicators are found to be worse for children living in poverty and for those living in a rural area. Disparities in access to and quality of healthcare among children of color and poor children are linked to long-standing structural barriers, systemic racist policies and practices, environmental policies, social and structural determinants of health, and healthcare provider negative implicit racial biases that influence healthcare delivery and patient-physician communication and relationships.

APPROACHES TO ERADICATING DISPARITIES: INTERVENTIONS

An example of a successful intervention that closed the disparity gap is the implementation of the VFC program, which significantly decreased the disparity in immunization rates noted among racial/ethnic groups and poor/underinsured children. This is an example of a **public health policy** approach to intervention.

Interventions need to occur at the **clinical** level as well. The almost-universal use of electronic health records (EHRs) provides a unique opportunity for collecting vital clinical and demographic data that can be helpful in identifying disparities and monitoring the success of interventions. All EHR platforms should use a standardized approach to gathering information on patient race/ethnicity, SES, primary language preferences, and health literacy. The Institute of Medicine's 2009 report *Race, Ethnicity, and Language Data: Standardization for Health Care Quality Improvement* provides best practices information about capturing these data in the health record.

The advancing science of clinical **quality improvement** can also provide a framework for identifying clinical strategies to reduce disparities in care. Use of **PDSA** (Plan-Do-Study-Act) cycles targeting specific clinical issues where health disparities exist can result in practice transformation and help reduce differential outcomes.

Another practice-level intervention that has the potential to reduce disparities in care and outcomes is the **medical home** model, providing care that is accessible, family centered, continuous, comprehensive, compassionate, coordinated, and culturally effective. The use of care coordinators and using community-based health navigators are effective tools in helping to break down the multiple social and health system barriers that contribute to disparities.

Community engagement is an essential requirement for lessening health and healthcare inequities. Health systems, practices, providers, public health, researchers, and payers need to include community voice and representation in all aspects of quality improvement, data interpretation, program design and development, and dissemination. To do less would be "working *on* people" instead of "working *with* people." To use a phrase from the disability advocacy community: *"Nothing about us without us."* Many potential interventions seem appropriate and demonstrate efficacy under ideal circumstances. However, if the intervention does not address the concerns of the end users—patients and communities—or fit the social or cultural context, it will likely be ineffective in the "real world." Only by involving the community from the beginning, including defining the issues and problems, can the likelihood of success be optimized.

At the provider level, there are opportunities for training in implicit bias and communication skills, as discussed in Chapter 2.1. *Shared decision-making* has been found to improve physician-patient relationships and health outcomes. Another strategy to address cognitive biases in physician clinical decision-making is to identify heuristic and other cognitive errors (see Tables 5.3-5.5) and use the diagnostic time-out (see Table 5.6) when a diagnosis does not fit the clinical presentation.

Population health strategies have the advantage of addressing the determinants of disparities at both the clinic and community levels. Techniques such as hotspotting, cold-casing (finding

patients and families lost to follow-up and not receiving care), and geocoding; collaborating with communities and community-based organizations; and periodic community health needs assessments identify the structural, systemic, environmental, and social factors that contribute to disparities and help guide interventions that are tailored to the local setting.

Health disparities are a consequence of social and structural determinants of health that often have developed based on historically racist policies and other practices and traditions that led to the social stratification mechanisms inherent in many modern societies. Health disparities mirror other societal disparities in education, policing, employment opportunities, and living conditions. While society grapples with the broader issues contributing to disparities, healthcare and public health can work to understand the multiple causes of these disparities and develop interventions that address the structural, clinical, and social root causes of these inequities.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

2.1 Racism and Child Health

Mary T. Bassett, Zinzi D. Bailey, and Aletha Maybank

RACISM AS A SOCIAL DETERMINANT OF HEALTH AND HEALTH INEQUITIES

An emerging body of evidence supports the role of racism in a range of adverse physical, behavioral, developmental, and mental health outcomes. Racial/ethnic inequity in health outcomes in the United States is long-standing, apparent from the first collection of vital statistics in the colonial period. However, the extensive data that document racial disparities have not settled the question of why groups of people, particularly of African and Indigenous Nations peoples ancestry, face increased odds of shorter lives and poorer health (see Tables 2.1, 2.2, and 2.3). The role of societal factors is well recognized in determining population health, but often omits racism among social determinants of health. This oversight occurs in the face of a long history of racial and ethnic subjugation in the United States that has been justified both explicitly and implicitly by racism. From the early 18th century, colonial America established racial categories that enshrined White supremacy, conferring rights specifically on White men, while denying these rights to others. This "racial" designation was social and not based on genetics. Similar, perhaps less explicit, discrimination has continued through the centuries and remains a primary contributor to racial/ethnic inequities in children's health. Current lifelong exposure to interpersonal, structural, and institutional racial discrimination and subordination has a significant impact on Black health outcomes.

For generations, racial/ethnic disparities have been documented beginning at birth and extending across life. In 2018, life expectancy at birth for Blacks was almost 4 years shorter than life expectancy of non-Hispanic Whites, influenced heavily by disparities starting at birth (Table 2.3). The **infant mortality rate** (IMR), arguably the most important measure of national health, has shown a persistent Black-White gap despite a substantial decline in U.S. IMR for all racial/ethnic groups (see Fig. 2.5). NCHS data in 2022 showed a double-digit IMR *only* among non-Hispanic Blacks, with 10.38 deaths per 1,000 live births, compared to 4.4/1,000 for non-Hispanic Whites. A troubling stagnation in IMR, with no recent decline, is found among Alaska Natives and Indigenous Nations peoples. The 2022 IMR among non-Hispanic Indigenous Nation peoples or Alaskan Native individuals, 7.68 deaths/1,000 live births, has remained essentially unchanged for almost 2 decades.

Exposures that affect infant survival occur before birth. Much of the maternal and child health literature emphasizes a higher prevalence of maternal obesity, diabetes, and substance/alcohol use before conception among Black women as individualized risk factors leading to disparities in birth outcomes (Chapter 114.1). A California study of maternal obesity found that 22.3% of pregnant Black women and 20.3% of Latina women had a body mass index (BMI) of 30-40, compared with 14.9% of White and 5.6% of Asian women. BMI >40 was more than twice as prevalent in Black (5.7%) than in White (2.6%) women. Further, in a nationally representative study of over 7 million singleton live births from the 2016 and 2017 U.S. National Vital Statistics System, although maternal prepregnancy obesity was associated with the risk of preterm birth in the general population, risk varied by maternal age and race/ethnicity. Maternal obesity among non-Hispanic Black women was inversely associated with risk of preterm birth among those younger than 30 years, but positively associated among those age 30 and older. Similar relationships were shown for non-Hispanic White and Hispanic women. Although individual risk factors such as obesity contribute to differences in birth and health outcomes, individual risk factors alone do not sufficiently explain these differences. Further, a focus on individual risk factors may contribute to a narrative that places blame on the individual without acknowledging the structural and social conditions of patients' lives influencing the prevalence of these risk factors. Proximal factors such as maternal obesity do not capture the root causes of early childhood health inequities, **social determinants of health**, which present intervention points for achieving health equity.

Achieving health equity requires examining equity in outcomes *and* also equity in process. Causes and interventions to address health inequities can be conceptualized as occurring upstream, downstream, or somewhere in between (Fig. 2.7). Downstream determinants occur on individual levels, including individual biology and specific risk factors and behaviors. In Figure 2.7, measures of health and health inequities, like life expectancy, IMR, maternal obesity, and maternal age, are at the far right and are considered downstream factors. Clinical interventions focused on downstream factors may help individuals, but do not address factors upstream that drive inequities in population health outcomes.

These upstream factors include the physical, social, work, and service environments in which people are born, grow, live, work, and age that lead to downstream outcomes. If a child lives in public housing that is systematically underresourced to eliminate common pests, that child is more likely to encounter asthma triggers, experience asthma attacks, and require emergency department care or hospitalization. Interventions could include remediating one apartment or home or increasing access to insurance; however, this is not getting at systematic mechanisms by which public housing becomes a social determinant of health. Moreover, these interventions do not address the reasons that families need public housing in the first place or why these living conditions are more prevalent among certain communities compared with others.

The distribution of these living conditions is patterned by institutional inequities in the public and private sectors and in our laws and regulations, which represent a wider set of forces and systems shaping the conditions of daily life. Social inequities, like racism, sexism, classism, heterosexism, and ableism, represent upstream social determinants of health that affect access to resources and healthy living conditions and are inequitably distributed across preexisting hierarchies of power. Resource allocation for public housing and the absence of universal access to a living wage might drive the living conditions within public housing. Focusing solely on downstream results of larger inequitable structures seldom yields sustainable change and ignores the roots of health inequities while tending to blame individuals structurally constrained by centuries of inequitable systems.

Prenatal maternal exposures to pesticides, lead, and other environmental toxins vary by race. This inequitable distribution is largely driven by racist policies and practices affecting exposures to small- and large-scale environmental hazards (see Chapter 2). The effects of persistent racism are stressful and toxic to the body, with the experience of discrimination across leading to biologic changes that persist the life span, especially for pregnant women and their children. Thus racism is an essential social determinant of racial/ethnic inequities in maternal and child health. Racism can increase cortisol levels and lead to a cascade of effects, including impaired cell function, altered fat metabolism, increased blood glucose and blood pressure, and decreased bone formation (see Chapter 1 and Fig. 2.3). This can affect a growing fetus,

Table 2.3 New Social and Health Inequities in the United States

	TOTAL	WHITE NON-HISPANIC	ASIAN*	HISPANIC OR LATINO	BLACK NON-HISPANIC†	NATIVE AMERICAN OR ALASKA NATIVE
Wealth: median household assets (2019)	$118,200	$187,300	$206,400	$31,700	$14,100	NR
Poverty: proportion living below poverty level, all ages (2019)	12.3%	9.0%	9.7%	17.2%	21.2%	24.2%
Poverty: proportion living below poverty level, children <18 yr (2019)	16.0%	10.0%	9.0% for Asians only; 18.0% for Pacific Islanders	23.0%	30.0%	30.0%
Unemployment rate (2021)	5.2%	4.6%	4.7%	6.2%	8.4%	NR
Incarceration: male inmates per 100,000 (2010)	733	450	115 for Asians only; 1,017 for Native Hawaiians and other Pacific Islanders	831	2,306	1,291
Proportion with no health insurance, age <65 yr (2018)	11.0%	7.8%	7.4%	20.1%	12.1%	28.6%
Infant mortality per 1,000 live births (2018)	5.7	4.6	3.9 for Asians only; 9.4 for Native Hawaiian and other Pacific Islander	4.9	10.8	8.2
Preterm Birth: proportion of singleton births before 37 wk gestation (2018)	8.2%	7.2%	7.1%	8.4%	11.9%	10.2%
Maternal mortality, deaths per 100,000 live births (2018)	17.4	14.9	NR	11.8	37.3	NR
Proportion of children <18 yr reporting current asthma (2018)	7.5%	5.6%	3.6%	8.0%	14.3%	NR
Self-assessed health status (age-adjusted): proportion with fair or poor health (2018)	9.0%	7.6%	8.2%	12.3%	13.5%	18.6%
Potential life lost: person-years per 100,000 before age 75 yr (2016)	7,431.7	7,021.0	3,176.8	4,926.0	10,505.2	7,360.2
Proportion reporting serious psychologic distress‡ in past 30 days, age ≥18 yr, age-adjusted (2015–2016)	3.6%	3.7%	2.1%	3.7%	3.6%	9.2%
Life expectancy at birth (2018), yr	78.7	78.6	NR	81.8	74.7	NR
Diabetes-related mortality: age-adjusted mortality per 100,000 (2018)	21.4	18.9	15.4 for Asians only; 48.1 for Native Hawaiians and other Pacific Islander	24.6	39.3	32.1
Mortality related to heart disease: age-adjusted mortality per 100,000 (2018)	163.6	168.1	82.0 for Asian alone; 161.4 for Native Hawaiian and other Pacific Islander	112.3	212.0	109.6

*Economic data and data on self-reported health and psychologic distress are for Asians only; all other health data reported combine Asians and Pacific Islanders, unless otherwise noted.
†Wealth, poverty, and potential life lost before age 75 yr are reported for the Black population only; all other data are for the Black non-Hispanic population.
‡Serious psychologic distress in the past 30 days among adults 18 yr and older is measured using the Kessler 6 scale (range: 0-24; serious psychologic distress ≥13).
NR, Not reported.
Sources: Wealth data taken from the U.S. Census; poverty data for adults taken from the Kaiser Family Foundation, and poverty data for children taken from the National Center for Education Statistics; unemployment data taken from the U.S. Bureau of Labor Statistics; incarceration data taken from the Prison Policy Initiative using U.S. Census Bureau data; data on uninsured individuals, infant mortality, self-assessed health status, potential life lost, serious psychologic distress, current asthma, preterm birth, life expectancy, diabetes-related mortality, and mortality related to heart disease taken from the National Center for Health Statistics.

leading to increased infant cortisol levels, lower birthweight (LBW), and prematurity. In New York City, White women had lower rates of adverse birth outcomes: 1.3% had preeclampsia, less than half the rate for Black women (2.9%).

Although infant deaths occur more frequently among low-income groups of all races/ethnicities, these birth outcome disparities by race/ethnicity are found also in Blacks with higher SES. College-educated Black women are more likely than White high school–educated women to have a LBW infant, a principal risk factor for infant death. Another study examined California birth certificates of pregnant Arab American women after the September 11, 2001, terrorist attacks and found that those who experienced discrimination immediately after the 9/11 attacks had a higher relative risk of giving birth to an LBW infant in the following 6 months than seen in births before this date. A similar association between exposures to discrimination-based violence and Latina mothers giving birth to LBW infants was found after the largest federal immigration incident in U.S. history in Postville, Iowa, with infants having a 24% greater risk at being LBW

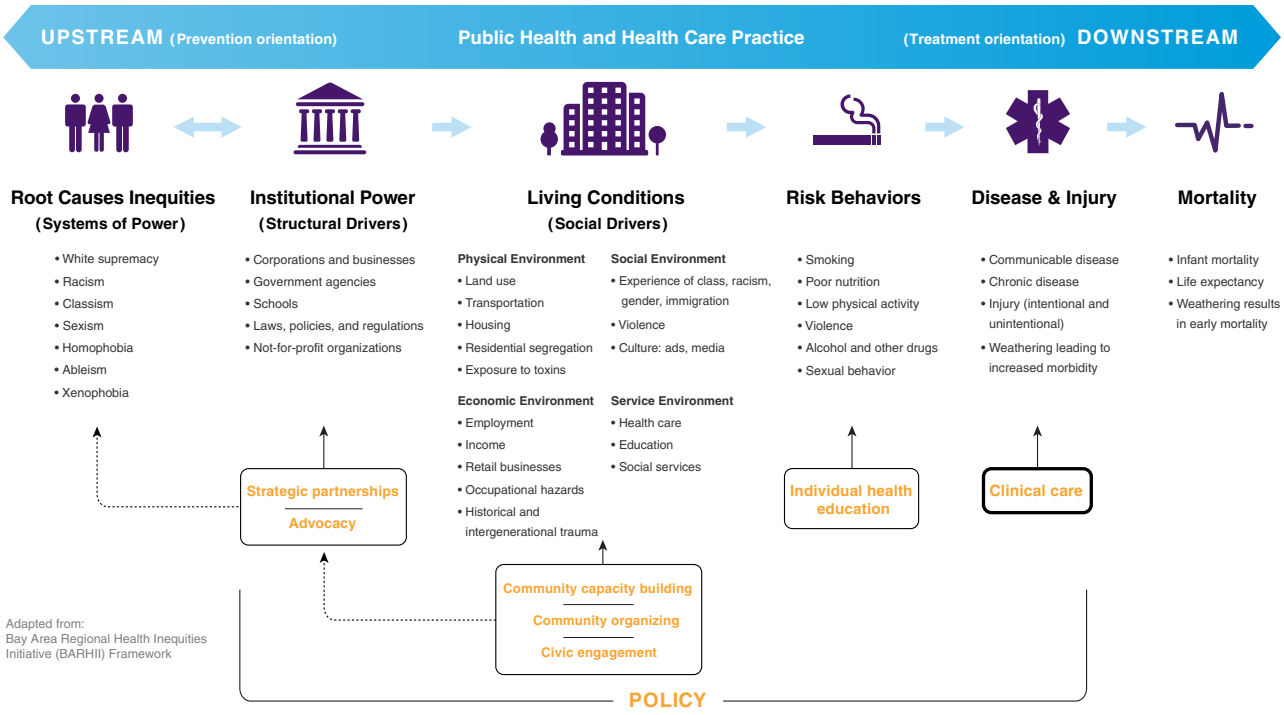

* Upstream refers to acknowledging and addressing the structural, societal, community and individual-level factors that influence health. Whereas downstream refers to the dominant approach of treating individual-level factors and/or contributors without wholly addressing structural, societal, and community factors.

Fig. 2.7 What creates health framework. *(From American Medical Association. Organizational Strategic Plan to Embed Racial Justice and Advance Health Equity, 2021–2023; adapted from the Bay Area Regional Health Inequities Initiative [BARHII] Framework.)*

at birth. These findings reinforce the critical role the physician has in explicitly asking families about potential exposures to racialized stressors and trauma.

The increased risk of disease for populations of color continues from infancy into childhood (see Table 2.1); racial/ethnic disparities are seen across almost all health indicators, with most relative gaps remaining stagnant or worsening over the past two decades. Compared with White children, Black children are about twice as likely to be diagnosed with **asthma**, more likely to be hospitalized for its treatment, and more likely to have fatal attacks. The Black-White disparity in asthma has grown steadily over time. Indigenous Nations children and youth (≤19 years) also experience negative health outcomes, with the highest rates of **unintentional injury** and mortality rates at least twice as high as for other racial/ethnic groups. Additionally, according to a 2017 NCHS brief, Latino youth age 2-19 have the highest rates of **obesity** in the 2000 CDC sex-/age-specific growth charts. The NCHS data show that 25.8% of Latino (followed by Black) children qualified as obese from 2015 to 2016. Black children are more likely to be exposed to witnessed, personal, or family **violence** (an example of an **adverse childhood experience**), and exposure to these stressful life experiences is associated with academic, behavioral, and health problems. Notably, children with more stressful life experiences have a higher likelihood of experiencing ear infections, acute respiratory infections, obesity, eczema, viral infections, and teen pregnancy.

EXPLAINING RACIAL DISPARITIES: A TAXONOMY OF RACISM

Explanations of these ubiquitous racial gaps have focused on individual factors, including variation in individual genetic constitution, behavioral risks, poverty, and access to (and use of) healthcare services. Scientists agree that "race" is a social construct that is not based on biology, despite the persistence of the idea that racial categories reflect a racially distinctive genetic makeup that has a bearing on health. In fact, the genetic variation between individuals within a particular racial/ethnic group is far greater than the variability between "races." Further, biologic ancestry is distinct and separate from the social construct of race. Despite the genetic data, many groups have been "racialized" over time. Notably, the U.S. Census Bureau's demographic classifications reflect this process. In the mid-to-late 1800s the census counted "mulattos," those of White and Black ancestry, as another race.

Starting in the late 19th century, Eastern European immigrants and Jews were considered different races. As early as 1961, the U.S. Census identified Mexicans and Puerto Ricans as "White" even as racial classification varied by geography. All states collected birth records by 1919, but there was little uniformity on how race was collected, if at all, across states. It was not until 1989, when the National Center for Health Statistics (NCHS) recommended assigning "infant race" as that of the mother and that standard guidance and categories were issued for states on collecting racial data at birth. Existing categories were changed and continue to change based on the economic, cultural, or political utility of the time, rather than actual genetic distinction.

Defining Racism

Racism has consistently structured U.S. society and is based on "White supremacy," a hierarchical idea that Whites, the *dominant* group, are intrinsically superior to other groups who are not classified as "White" No single definition of racism exists, but one useful description is *racial prejudice backed by power and resources*. This conceptualization asserts that not only must there be prejudice but

Table 2.4 Pathways Between Racism and Health and Examples

Economic injustice and social deprivation
Residential, educational, and occupational segregation to lower-quality neighborhoods, schools, and jobs (both historical de jure discrimination and contemporary de facto discrimination)
Lower salary for same work
Lower promotion rate despite comparable evaluations
Environmental and occupational health inequities
Placement of bus garages and toxic waste sites
Selective government failure to prevent lead in drinking water (per Flint, Michigan, 2015–2016)
Disproportionate exposure of workers of color to occupational hazards
Psychosocial trauma
Interpersonal racial discrimination, including microaggressions*
Exposure to racist media, including social media
Targeted marketing of health-harming substances
Legal: cigarettes; sugar sweetened beverages
Illegal: heroin; illicit opioids
Inadequate healthcare
Inadequate access to health insurance and healthcare facilities
Inadequate treatment caused by implicit or explicit racial bias
State-sanctioned violence and alienation from property and traditional lands
Police violence
Forced urban "renewal" (use of eminent domain to force relocation of urban communities of color)
Genocide and forced removal of Native Americans
Political exclusion
Voter restrictions (e.g., for ex-felons, ID requirements)
Maladaptive coping behaviors
Increased tobacco and alcohol consumption
Stereotype threat
Stigma of inferiority leading to physiologic arousal
Impaired patient-provider relationship

*Small, often unintentional racial slights/insults (e.g., a judge asking a Black defense attorney, "Can you wait outside until your attorney gets here?")

From Bailey ZD, Krieger N, Agénor M, et al. Structural racism and health inequities in the USA: Evidence and interventions. *Lancet*. 2017;389:1453–1463. Panel 2.

also an interlocking system of institutions to produce and reproduce inequities in access to and use of resources and decision-making power. Even when considering variations in health behavior, lifestyles, economic status, and healthcare use, individual-level behavioral factors do not capture how broader shared social experiences shape outcomes. **Racial domination** or racism contributes to variation in the population's access to resources and exposure to disease and to the group experience of fair treatment and opportunity. Although many groups in the United States may encounter discrimination based on race/ethnicity, most of the modest literature on health effects of racism has focused on people of African descent, leaving a need to better understand the impact of racism on people of color. Table 2.4 and Figure 2.3 describe various pathways through which racism affects health.

Although the empirical data on disparities for non-Black populations of color deserve greater research, useful frameworks exist to understand the disparities that public health has documented to date. A useful taxonomy of how racism operates in society has four categories: internalized racism, interpersonal racism, institutional racism, and structural racism. Each is relevant in considering the impact of racism on child health.

Internalized Racism

When the larger society characterizes marginalized racialized groups as "inferior," these negative assessments may be accepted by members of those groups themselves, either consciously or unconsciously. The result is *devaluation* of personal abilities and intrinsic worth, in addition to the capacity, of others also classified as being a part of a marginalized racialized group. The best-known documentation of *internalized racism* comes from the study of Kenneth and Mamie Clark known as the **doll experiment**, conducted in the 1940s. Black children, both males and females, were asked to choose between a Black doll and a White doll according to attributes described by the interviewer. In response to positive attributes (e.g., *pretty, good, smart*), most children chose the White doll. The Clarks interpreted this finding to mean that Black children had internalized the societal views of Black inferiority and White superiority, even at the expense of their personal self-image. Repeated by a New York City high school student several decades later, the findings were much the same, with 15 of 21 children endorsing positive attributes to light-skinned dolls. Multiple studies confirm that racial identity is established in young children, both Black and White, along with negative views of blackness. Developmentally, however, youth of color often explore racial identity earlier than their White counterparts. In terms of health outcomes, depending on perceived inferiority or superiority of the group, racial identification is associated with self-esteem, mastery, and depressive symptoms. Low self-esteem is independently implicated in mental health disorders and may contribute to the phenomenon of **stereotype threat**, in which personal *expectation of underperformance* correlates with prevailing social stereotypes and adversely affects actual performance.

Interpersonal Racism

How racial beliefs affect interactions between individuals has been the most-studied aspect of racism. *Interpersonal racism* refers to situations where one person from society's privileged racial group acts in a discriminatory manner that adversely affects another person or group of people. Such actions may be based on *explicit* beliefs or on *implicit* beliefs of which the perpetrating individual is not consciously aware. The experience of unfair and prejudicial treatment has *biologic* consequences, reflected in measurable increases in stress responses.

Such effects of interpersonal racism are best documented for **mental health**, where perceived unfair treatment serves as psychosocial stressors, and are less robust for physical health outcomes. A 2021 study of 10,354 U.S. children age 10 and 11 years found only 2.8% of Whites, 5.4% of Latinos, 6.2% of Asian and Pacific Islanders, 6.5% of Indigenous Nations peoples, and 10% of Blacks self-reported enduring racial discrimination. Furthermore, discriminatory experiences have been strongly and consistently linked to greater risk for anxiety, depression, conduct disorder, psychologic distress, ADHD, ODD, low self-esteem or self-worth, and challenges to psychologic adaptation and adjustment (see Chapter 2). Perceived racial discrimination can affect behavioral, mental, and physical health outcomes and is associated with increased alcohol and drug use among Indigenous Nations peoples (age 9-16 years), increased tobacco smoking for Black youth (11-19 years), higher depressive symptoms among Puerto Rican children, and insulin resistance among young females.

Understanding the enduring impact of childhood experience on adult health has increased with the study of ACEs (see Chapter 1). ACEs have well-documented cumulative negative health effects that occur across the life span and are patterned by race/ethnicity. Early experience of racism is a proxy measure for **toxic stress**. The question, "Was [child's name] ever treated or judged unfairly because of their race or ethnic group?" is included in the U.S. Census Bureau's NSCH, a random sample of over 90,000 households to assess the

health of children up to 17 years old. Children of color from low-income households, especially Latino children, were reported to have the lowest level of health. However, higher SES did not protect children exposed to racism from experiencing relatively poorer health. Children exposed to racism were also more likely (by 3.2%) to have a diagnosis of ADHD and were 2 times more likely to experience anxiety and depression.

Toxic stress increases cortisol levels in the body, increasing the risk of chronic disease. One study revealed that adolescents who reported average or high levels of perceived discrimination experienced exaggerated cortisol output in response to negative affect, whereas those reporting low levels of perceived discrimination did not experience significant reactivity to negative affect, after controlling for other stressors. Adolescents who experience racism with no support have been shown to have higher levels of blood pressure and obesity than those with emotional support, which can be protective.

Medical practice has not been exempted from occurrences of interpersonal racism. Using variation in adherence to established clinical standards in diagnostic and treatment decisions across racialized groups, researchers have been assessing interpersonal racism in physician-patient interactions. The most comprehensive review of such bias in clinical care remains the study by the U.S. Institute of Medicine, in which the discriminatory treatment was inferred from examination of clinical decision-making rather than from directly observed interactions. For virtually every condition studied, Black patients were less likely to receive recommended care. Such racial bias has been most extensively established in adults but also extends to children. A study conducted in an emergency department found pediatric patients (<21 years) were less likely to receive medically indicated pain medication if they were Black, mirroring the historical misconception of reduced pain sensitivity among Blacks. Within this context, it is unsurprising that perceived interpersonal racism has been linked to healthcare use, including delays in seeking care or filling prescriptions and distrust of the health system. When Black patients receive **concordant care** from Black healthcare providers, their communications, health outcomes, and care are improved when compared with care from White providers.

Perceived and experienced discrimination can be measured by at least six instruments (scales). Questions such as "Are you treated with less respect or courtesy than other people," "Do people act as if they are afraid of you," "Do people act as if they think you are not smart," and "Do you receive poorer service than other people," can be quantified with responses that range from *Almost everyday* to *Never*. High scores have been associated with preterm birth (see Chapter 114.1)

Institutional Racism

Interpersonal racism clearly inflicts harms, but even if completely eliminated, racial inequities would persist because of institutional and structural racism. Broadly, *institutional racism* refers to patterns of discrimination based on policy, culture, or practice and carried out by state and nonstate institutions (e.g., corporations, universities, legal systems, cultural institutions) within various sectors (e.g., housing, education, criminal justice). Key to current residential segregation are banking practices dating to the post-Depression era. As an institution, the education system has been another tragic case of how racism affects children's health. In addition, mass incarceration by the criminal justice system has dramatically increased in the United States while remaining relatively flat in other developed countries (Fig. 2.8). Over a lifetime, approximately 30% of Black men have been imprisoned.

In school, children of color can experience not only individual racism but also institutional racism, as documented by higher rates of disciplinary actions such as suspensions, and at younger ages than White children. According to a 2016 U.S. Department of Education civil rights survey, Black children, who represent only 19% of national preschool students, account for a staggering 47% of out-of-school suspensions. Black preschoolers are 3.6 times more likely to be suspended than their White peers. Black females, representing 20% of the female preschool population, account for 54% of out-of-school suspensions. Many schools have a "zero tolerance" policy for childhood behaviors, which criminalizes minor school infractions.

Unfortunately, this disparity persists as children continue through the school system: for kindergarten to grade 12 (K-12) students, Black children are 3.8 times more likely to face out-of-school suspension than White peers. This inequity is particularly harmful because the educational system feeds into the criminal justice system (school to prison pipeline). Black students are 2.2 times more likely to have either school-related arrests or law enforcement referrals than their White peers. The U.S. Department of Education survey also reveals racial inequities among children with disabilities. For K-12 children with disabilities covered under the Individuals with Disability Education Act, 21% of multiracial females were issued at least one out-of-school suspension, compared with 5% of White females.

Racial disparities in school discipline for minor infractions, disruptive behavior, or disobedience is linked to the concept of **adultification**. In this harmful, often unrecognized racial bias and social stereotype, adults and especially police view Black children (as young as 5-10 year) as older, less innocent, and more culpable than White students of the same age. Black male children are perceived as older, bigger, and more physically threatening than White peers. Black female children are viewed with similar characteristics plus a perception that Black female youth need less nurturing or protection, are more independent, and less innocent.

In addition to the threat to educational and employment prospects, school suspensions also affect children's health. A 2016 brief from the Yale Child Study Center states that early suspensions and expulsions of children harm behavioral and social-emotional development, weakening a child's overall development. Furthermore, these forms of punishment may prevent the treatment of underlying health issues, such as mental health issues or disabilities, and cause increased stress for the entire family.

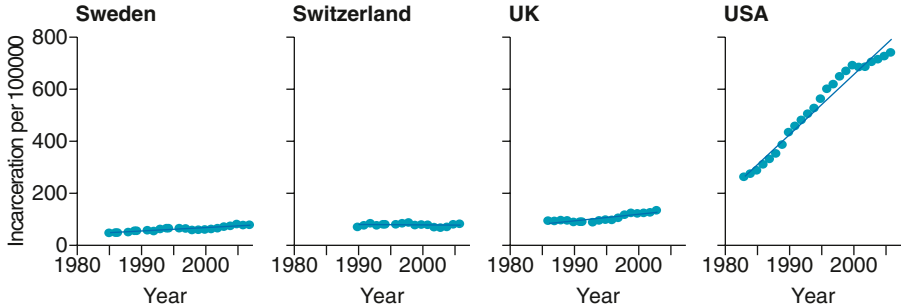

Fig. 2.8 Trends in incarceration prevalence in developed democracies, 1981–2007. (*Adapted from Wilderman C, Wang EA. Mass incarceration, public health, and widening inequality in the USA. Lancet. 2017;389:1464–1472, Fig 1.*)

Institutional racism can function without apparent individual involvement and has powerful repercussions that persist centuries later. Both medical professional organizations and educational institutions have legacies of racial discrimination rooted in *scientific racism*. In 2008 the American Medical Association (AMA) issued a formal apology for its long history, dating to the 1870s, of endorsing explicitly racist practices, including exclusion of Black physicians, silence on civil rights, and refusal to make any public statement on federally sponsored hospital segregation. In 2020, the American Academy of Pediatrics' (AAP) board of directors published an acknowledgement and apology, *Truth, Reconciliation, and Transformation: Continuing on the Path for Equity,* for the institutionalized racist and exclusionary treatment of two Black physicians, Drs. Alonzo deGrate Smith and Roland Boyd Scott, dating back to 1939 and spanning until 1945 when they were finally admitted to the AAP as the first Black members. Exclusion from medical associations also meant exclusion from gaining privileges to work at the majority of hospitals. Despite a focus on medical school desegregation in the 1960s and 1970s, the presence of Black students in medical schools is actually declining. Low enrollment has become especially critical for Black men, who in 2014 accounted for about 500 of the 20,000 medical students nationwide. If physicians hold stereotyped views about race that affect their clinical decision-making, the declining diversity of medical student bodies may well have consequences for the quality of medical care. This history of institutional racism on people of color contributes to the mistrust, apprehension, and fear projected toward the entire medical establishment.

Structural Racism

The institutional racism within medical institutions reinforces institutional racism in other sectors, creating a larger system of discrimination, *structural racism*. Structural racism can be described as "the totality of ways in which societies foster racial discrimination via mutually reinforcing systems of housing, education, employment, earnings, benefits, credit, media, healthcare, and criminal justice. These patterns and practices in turn reinforce discriminatory beliefs, values, and distribution of resources, which together affect risk of adverse health outcomes." Institutional racism and structural racism are sometimes used interchangeably, but structural racism refers to overarching patterns beyond a single institution, or even a collection of institutions. Historically, government policies and practices have been largely responsible for the creation of these structures.

De facto and de jure urban residential segregation serves as a case study for how the mechanisms of structural racism operate across multiple sectors and can affect child health and development across the life course. As described in Chapter 2 urban residential racial segregation was reinforced by the practice of **redlining** initiated by the U.S. Federal Housing Administration in 1934. This now illegal (but still covert) practice demarcated urban neighborhoods to be made ineligible for home loans based primarily on the racial composition of the neighborhood. Thus Black neighborhoods were excluded from the federally financed, post-Depression home ownership boom and remained segregated. Through this segregation, existing resources were systematically removed *(disinvestment)* and led to further impoverished communities of color.

The effects of residential segregation were not restricted to the banking or housing sectors. **Residential segregation** ties together multiple systems, driving children's access to and quality of healthcare, education, and justice, as follows:

- *Residential segregation and the healthcare system.* Healthcare institutions were explicitly racially segregated by law and inequitably resourced until passage of the 1964 Civil Rights Act. Vestiges of this segregation continue in hospital-level segregation and racial composition by hospital. In addition, institutions that provide mainly for uninsured or underserved residents are often financially unstable, leading to higher risk of closure in disinvested neighborhoods of color. On the provider level, fewer primary care and specialty physicians practice in disinvested, segregated neighborhoods, and those who are present are less likely to participate in Medicaid.
- *Residential segregation and the education system.* Schools have a similar history of racial segregation and, after a brief respite of integration peaking in 1980, the level of segregation now resembles pre–civil rights levels. School segregation is related to high-risk health behaviors. Within these schools and in their neighborhoods, Black children experience disproportionate penalization and criminalization in the educational and criminal justice systems, reinforcing institutional racism in other sectors and other forms of racism. A low-income Black child is much more likely than a low-income White child to live in a segregated neighborhood. The result is that the Black child will face not only the cumulative disadvantage in both family and neighborhood resources and experiences over time but also the initiation of chains of disadvantage during sensitive periods of childhood key for development and adult transition (e.g., early childhood, adolescence).
- *Residential segregation and the criminal justice system.* Incarceration is concentrated in overpoliced and criminalized Black communities. In the NCHS, almost 13% of Black children had a parent imprisoned during their childhood (to age 17 years), compared with about 6% of White children. Parental incarceration—which may start with a traumatic arrest in the home and later disrupt caregiving, create social stigma, deepen financial disadvantage, disconnect parents emotionally from children, and disrupt children's psychologic development—has been independently associated with a higher risk of children's antisocial behavior.

Most notably, experiences directly related to institutional and structural racism, operating through residential segregation (including financial hardship, parental imprisonment, and neighborhood violence), result in higher levels of ACEs for Blacks and Latinos than for Whites. There has been growing, consistent evidence of the lifelong association between ACEs and a range of negative physical and mental health outcomes across the life course.

Structural racism, shown here with the example of residential segregation, affects child health through various direct and indirect, overlapping pathways, including the concentration of dilapidated housing, inferior quality of the social and built environment, exposure to pollutants and toxins, limited access to high-quality primary and secondary education, few well-paying jobs, overpolicing and criminalization, adverse experiences, and limited access to quality healthcare.

OPPORTUNITIES TO ADDRESS RACISM

Racism as a determinant of health has strong empirical support, and there is promising evidence for community-wide approaches to its mitigation. Less is known about effective interventions in clinical settings. Most medical schools and subsequent training will not have prepared practitioners to examine the role of racism in their patients' lives or clinical care settings. Nonetheless, it is reasonable to expect that pediatricians can help address racism and promote racial justice in at least three ways: during individual patient encounters and at their practice sites, as members of institutions that provide medical care and training, and as respected community members.

Clinical Settings

A first step in understanding that racism affects everyone is personally assessing **implicit bias**. Such biases reflect reflexive patterns of thinking, often using racial stereotypes stemming from living in a racially stratified society. The **Project Implicit Race Implicit Association Test** (https://implicit.harvard.edu/implicit/takeatest.html) is available online, and its results are confidential. The purpose of such tests is to create awareness, not apportion blame. Nonetheless, results are usually jarring for all participants, no matter their racial identity, many of whom will uncover negative racial biases of which they were unaware. Such individual assessments may contribute to addressing interpersonal racism as it triggers self-reflection. Further, a growing number of organizations offer training in understanding common behaviors associated with implicit bias, including microaggressions (see later)

and inequitable hiring practices. Recognizing and undoing personal biases as pediatricians requires training to challenge existing thought processes and actions that are often difficult to see. Seeing and undoing personal biases are lifelong endeavors, and progress should be tracked over time.

Pediatricians and other health workers have an entrusted role in families that requires a partnership. Recognizing the strengths of families and valuing their lived experiences of internalized and interpersonal racism as expertise fosters a more collaborative clinical interaction and relationship. This expertise cannot be readily captured by pedagogy or acquired by a pediatrician in training or clinical practice. Such an approach emphasizes respect for the expertise that caregivers bring to raising their child and begins with the presumption that caregivers want to do what is best for the child. By doing this, physicians can form a collaborative relationship, rather than one based on racial stereotypes and blame. Cultural competence is a widespread concept, recognizing that *other cultures* exist that the dominant culture must learn to decode. In contrast, the concept of **cultural humility**, for which training is increasingly available, considers equality among cultures and a partnership approach to differences.

During clinical encounters with children and families, healthcare workers can use their authority to acknowledge racism. Although there is still a gap in evidence on how, when, and what, pediatricians can consider having "The Talk" with their patients who are Black, young adolescent, and male. "The Talk" is the conversation that Black parents typically initiate with their children regarding interactions with police. In doing so, the pediatrician affirms the need for such conversations to promote safety and may provide opportunities to connect families to community resources. For all young children and youth of color, pediatricians should ask patients if they have they been treated unfairly because of their race, recognizing this can be a form of **bullying**. The experience of racism at all levels can be traumatic. Trauma consists of experiences or situations that are emotionally painful and distressing and that overwhelm people's ability to cope, leaving them powerless. Pediatricians must consider adopting trauma-informed care practices that shift the paradigm from, "What is wrong with you?" to "What has happened to you?"

In addition, healthcare providers must strive for **structural competency**, which is the "trained ability to discern how a host of issues defined clinically as symptoms, attitudes, or diseases also represent the downstream implications of a number of upstream decisions," according to Johnathan M. Metzl and Helena Hansen. Consequently, it is helpful to ensure that clinical practices are aware of other social services that may enhance health and engagement with clinical care, such as a need for legal counsel to address substandard housing, counter landlord harassment, or negotiate threatened evictions (http://medical-legalpartnership.org/), or the support of literacy by prescribing or distributing children's books in order to encourage parents to read to children (http://www.reachoutandread.org/).

Institutional Settings

The healthcare institution more broadly is also a setting where racial dynamics occur. Introducing conversations about race may uncover experiences that would not otherwise be apparent. A common outcome of implicit racial bias is **microaggressions**, actions and attitudes that may seem trivial or unimportant to the perpetrators but create a cumulative burden for those who perceive them. A physician of color might be asked for identification on entering a hospital, whereas White colleagues are not so queried. These microaggressions occur in interactions among staff and with patients and may contribute to an unspoken and uncomfortable racial climate. Although such interactions rarely would violate federal discrimination standards, interaction between coworkers shapes an entire practice and can be perceived by families.

Encouraging institutions to assess the impact of race among patients and staff is a first step. Healthcare delivery institutional settings can use both data and patient accounts to examine racial effects in the practice and experience by routinely disaggregating assessment measures by race/ethnicity. Patient-reported satisfaction or quality of care might be disaggregated by race. In addition, it is important to consider racial equity within the practice's employment structure: Are there discrepancies in hiring, retention, and salaries by race? Are there proper supervision and grievance procedures, particularly around issues related to racial microaggressions? Also, consider the images and language used to discuss and represent both patients and staff, particularly when alluding to race/ethnicity. Organizations such as **Race Forward** (https://www.raceforward.org) and organizational assessment tools developed by the **Race Matters Institute** can help guide institutional assessments and internal change processes. Several local health departments have already incorporated antiracism training into staff professional development and introduced internal reforms to drive organizational change. Because institutional reform is closely associated with other models of productive practices, including quality improvement, collective impact, community engagement, and community mobilization, application of an antiracism lens should be judged by its contributions to organizational effectiveness and on its moral merits.

Education or training institutions have a special role in ensuring a workforce that is both diverse and informed. Patterns of student admissions should be scrutinized, as should the curriculum. The recruitment of Black healthcare workers will enhance the benefits of racially concordant care between Black providers and patients.

Although many medical schools now include diversity training and provide instruction on cultural competency, such instruction is often brief (and sometimes delivered online). By contrast, approaches based on structural competency, cultural humility (see Chapter 12), and **cultural safety** have been implemented in health professionals' training in such countries as Canada and New Zealand. These approaches emphasize the value of gaining knowledge about structural racism, internalized scripts of racial superiority and inferiority, and the cultural and power contexts of health professionals and their patients or clients. Health professionals benefit from the scholarship of diverse disciplines about the origins and perpetuation of, and remedies to counter, racism. Finding class time for these topics encounters a *biomedical bias* that is widespread in medical education, although arguably successful medical practice also requires a host of skills in addition to a firm grounding in pathophysiology and recommended treatments. Racism results in damaging disparities that cause ill health and shorten lives, which justifies the teaching hours committed to its understanding.

Pediatricians as Advocates for Antiracist Practices and Systems

Physicians are respected members of communities and wield the power, privilege, and responsibility for dismantling structural racism. A conceptual review of structural racism highlights the promise of place-based interventions that target geographically defined communities, to engage residents and a range of institutions (across sectors) in order to ensure equitable access to resources and services, remediating the processes set in motion decades earlier. Clinicians play a role in advocating with the halls of medicine in linking patients to services, programming, and other resources and advocating for responsiveness in addressing gaps. Over time, concentrated efforts across sectors in targeted areas have shown improvement in a host of social outcomes, including health outcomes. Similarly, providing access to higher-quality housing, either with housing vouchers or housing lotteries, had unexpected positive health impacts. These findings are encouraging, as are the social policy interventions and systemic change, including legislation such as the Civil Rights Act, the advent of Medicare and Medicaid, and tenement regulations, associated with the narrowing of racial gaps.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 3

Global Child Health

Suzinne Pak-Gorstein, Ruth W. Nduati, Sansanee S. Craig, and Susan Wamithi

GLOBAL BURDEN AND TRENDS IN CHILD HEALTH

The **under-5 mortality rate (U5MR)**, also known as the **child mortality rate**, serves as a reliable gauge of child well-being. It measures the outcome of a country's health system and reflects a nation's social and economic development. The global U5MR fell by 61% between the years 1990 and 2020. Despite these gains, in 2019 an estimated *5.3 million children under 5 years of age died worldwide,* which is equivalent to 37.1 *deaths per 1,000 live births,* or nearly *13,700 child deaths each day*. The burden of the world's child mortality disproportionately falls upon low- and middle-income populations of Africa and Asia (Fig. 3.1), with 82% of all child deaths in the world occurring in just two regions: sub-Saharan Africa (55%) and South Asia (27%), compared to the less than 1% of child deaths occurring in high-income countries (HICs). Consequently, a child born in sub-Saharan Africa is over 15 times more likely to die by age 5 years compared to a child born in an HIC.

Improvements in child mortality have been uneven globally, regionally, and nationally. Significant disparities in child mortality persist and are concentrated in specific regions of Africa and Asia. The countries with the highest child mortality gap between the richest and the poorest in 2019 were Nigeria, Guinea, and the Central African Republic. In Nigeria in 2019 while the national rate of child mortality was 117 deaths per 1,000 live births, at the subnational level, the rates ranged from 58 to 261 deaths per 1,000 live births.

Although the number of child deaths has decreased dramatically over the past 3 decades, the early years of life remain one of a child's most vulnerable periods. Among the under-5 child deaths, nearly half occurred within their first month of life (2.4 million deaths in 2019). This estimate of **neonatal deaths** (<1 month of age) translates into 17.9 per 1,000 live births. Declines in neonatal mortality occurred at slower rates, so that in 2019 the neonatal deaths made up 48% of all under-5 deaths (Fig. 3.2).

Neonatal deaths account for a smaller percentage of child mortality in low- and middle-income countries (LMICs) compared to HICs (Fig. 3.3), but the absolute risk of death remains significantly higher. A child in sub-Saharan Africa or in Southern Asia is nine times more likely to die in the first month of life than a child born in an HIC.

An estimated 2 million **stillborn** deaths (≥28 completed weeks' gestation) burden families worldwide every year, which correlates to 13.9 deaths per 1,000 births. This translates into a stillborn baby

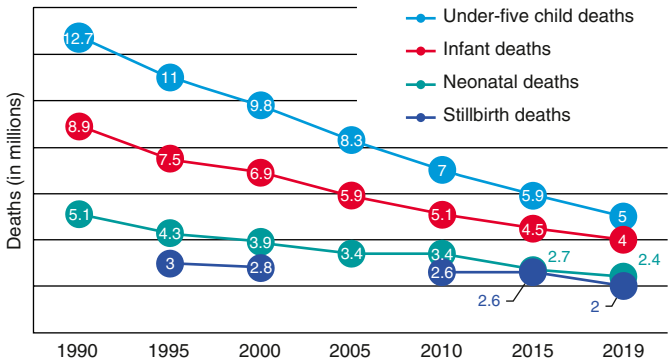

Fig. 3.2 Deaths for under-5 children, infants, neonates, and stillbirths between 1990 and 2019. (*Data from United Nations Inter-agency Group for Child Mortality Estimation – UN IGME 2020; Stillbirth estimates for 1995 and 2009 from Cousens 2011 [2010 rate is from 2009]; year 2000 rates from Lawn 2012, and 2015 rate of 2.6 million is from Blencowe 2016.*)

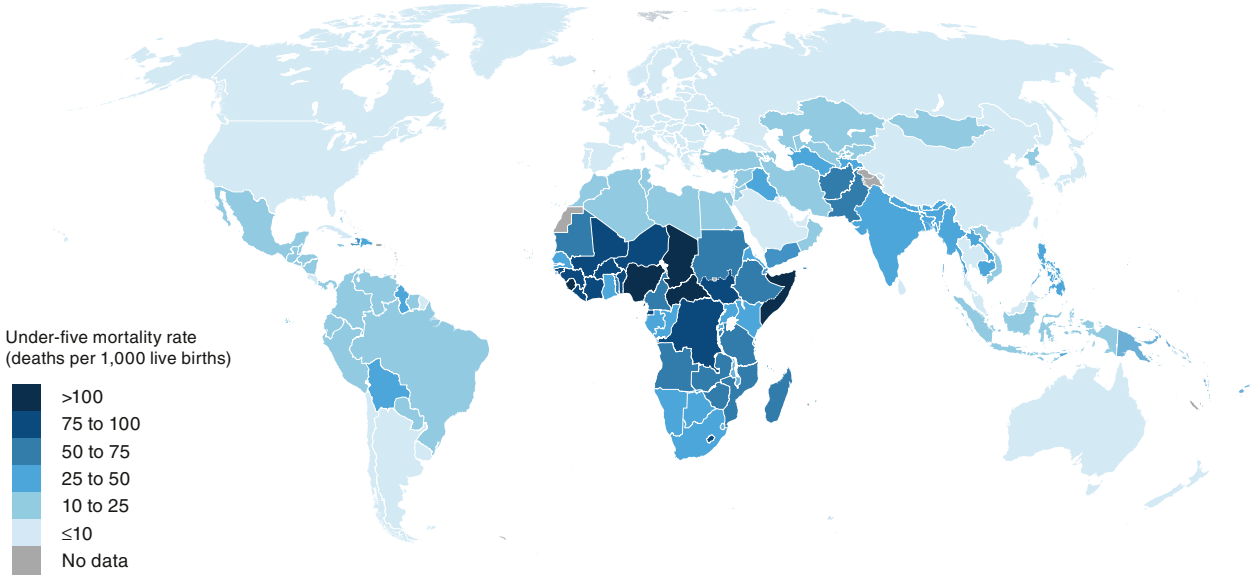

Fig. 3.1 Under-5 mortality rate (probability of dying by age 5 per 1,000 live births) by country, 2019. Note: The classification is based on unrounded numbers. This map does not reflect a position by UN IGME agencies on the legal status of any country or territory or the delimitation of any frontiers. (*From United Nations Inter-agency Group for Child Mortality Estimation [UN IGME]. Levels & Trends in Child Mortality: Report 2020, Estimates developed by the United Nations Inter-agency Group for Child Mortality Estimation. New York: United Nations Children's Fund, 2020. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/unpd_2020_levels-and-trends-in-child-mortality-igme-.pdf.*)

for every 72 births, or one every 16 seconds. These figures are likely an underestimate because stillbirths are underreported, reflecting the low prioritization of this vulnerable age group. Before 2006, no organization published global, regional, or country-specific stillbirth rates. Progress to reduce stillbirths has been slow, with the annual rate of reduction estimated to be half that for neonatal deaths between 2000 and 2019. Almost all stillbirths occur in LMICs (98%), with three-quarters in sub-Saharan Africa and South Asia.

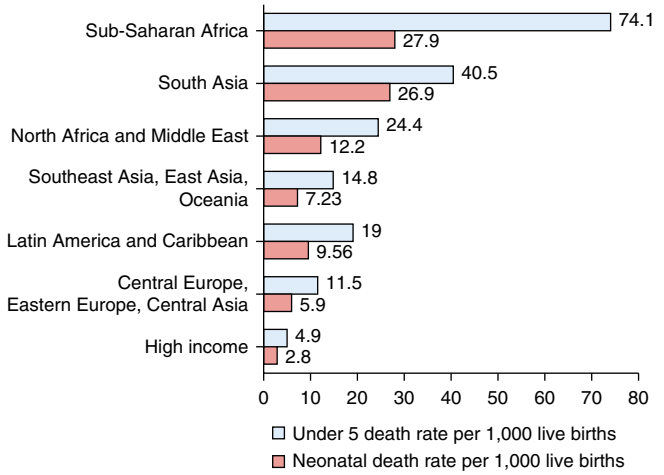

Fig. 3.3 Under-5 child and neonatal death rates per 1,000 live births, 2019. (*Data from GBD 2019 Under-5 Mortality Collaborators. Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: All-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019.* Lancet. *2021;398:870–905.*)

Most childhood deaths are caused by conditions that could be prevented or managed through improved access to simple, low-cost interventions. The **most common causes of child death** are preterm birth complications, intrapartum-related events, pneumonia, and diarrhea (Fig. 3.4). Of all under-5 child deaths, 2.61 million were the result of infectious diseases and 21.7% of all child deaths were vaccine-preventable. **Neonatal disorders** accounted for an estimated 46% of the deaths in children younger than the age of 5 years. In contrast, child deaths from infections in developed countries are less common, where injuries and congenital malformations account for higher proportions of under-5 deaths. **Undernutrition**, including fetal growth restriction, stunting and wasting, and micronutrient deficiencies, contributes up to 45% of under-5 deaths and poor childhood development in LMICs. Undernutrition has an enormous impact on child mortality because of the vicious cycle between nutrition and infection whereby lowered immunity and mucosal damage from inadequate dietary intake lead to increased susceptibility to pathogen invasion, while recurrent illnesses impair the child's appetite and ability to absorb adequate calories and nutrients. In addition, undernutrition early in life can have long-lasting consequences, including impaired cognitive ability and reduced school and work performance.

Infants who start out life with a **low birthweight** are at high risk of death, contributing 60–80% of all neonatal deaths. Most of these

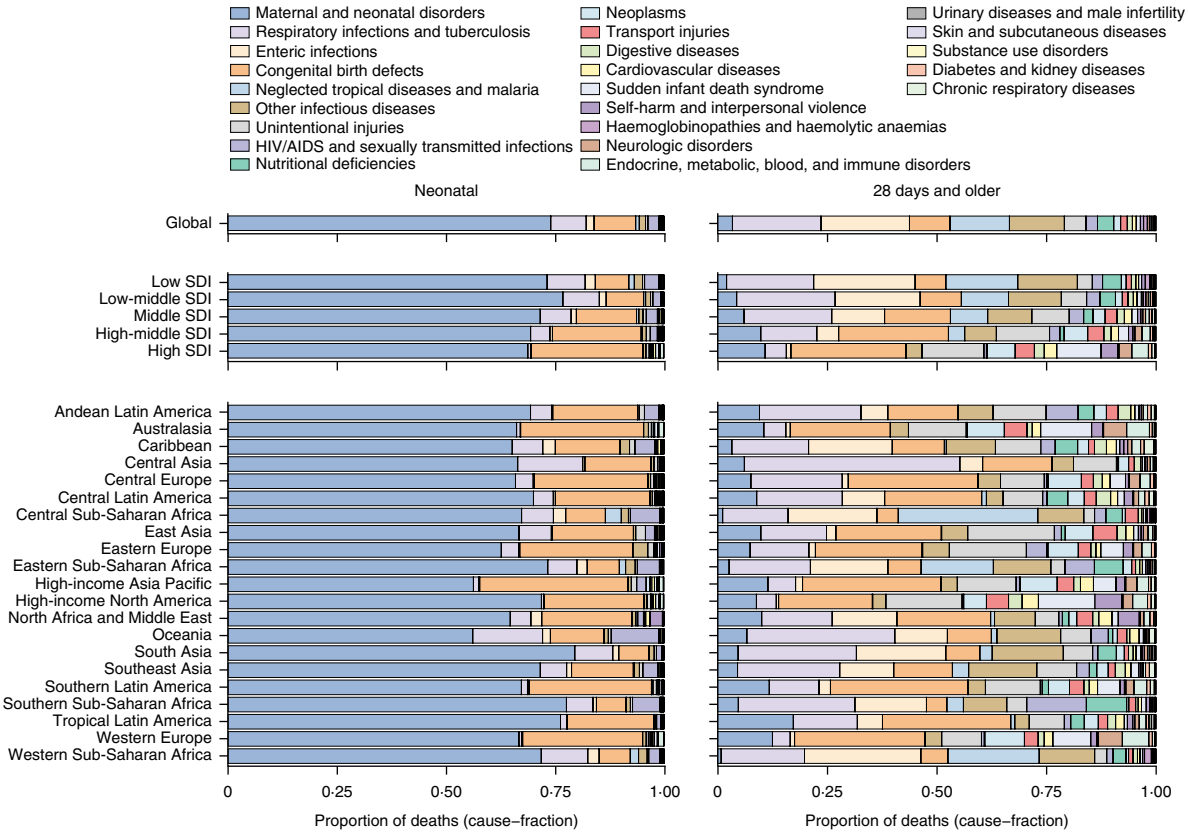

Fig. 3.4 Neonatal and remaining under-5 cause-specific mortality by region and SDI. Values presented are cause fractions: the proportion of total age-specific deaths with a particular underlying cause of death. Causes are presented at Level 2 in the hierarchy, with other noncommunicable diseases disaggregated to include congenital birth defects, sudden infant death syndrome, hemoglobinopathies and hemolytic anemias, endocrine, metabolic, blood, and immune disorders, and urinary diseases and male infertility separately. Total under-5 mortality is split at 28 days to include neonatal (<28 days) separately from children between 28 days and 5 years of age. SDI, Sociodemographic Index. (*From GBD 2019 Under-5 Mortality Collaborators. Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: All-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019.* Lancet *2021;398:870–905. Fig. 3, p. 887.*)

infants are premature (born before 37 weeks of pregnancy) or suffered from fetal growth restriction. About half of **stillbirths** take place during labor, ranging from 10% in developed regions to 59.3% in South Asia, which reflects the role that timely, high-quality care around delivery can play to prevent many deaths.

Mortality among older children age 5-14 is low compared with the younger cohort, although 1 million children in this age group died in 2016, which is equivalent to 3,000 children dying every day. Infectious diseases play a smaller role in deaths among these older children, with injuries from causes such as drowning and road traffic trauma accounting for more than a quarter of the deaths and noncommunicable diseases for about another quarter.

Child health should not be assessed based on mortality rates alone. Children surviving illness are often left with lifelong disabilities, burdening their families and affecting their economic productivity. Approximately 1 in 10 children are born with or acquire a disability, and 80% of these disabled children live in LMICs. Neonatal disorders, infectious diseases, protein-energy and micronutrient deficiencies, hemoglobinopathies, and injuries are leading causes of disability in children. Child deaths can also lead to disability in the surviving mother. For example, a woman who has a stillbirth is at risk of an obstetric fistula or death, with an estimated 78–98% of women with obstetric fistula having had a stillbirth. Also, perinatal loss and child death is a psychologic trauma. Stillbirth, neonatal death, and child loss can lead to posttraumatic stress disorder, depression, anxiety, guilt, and in some settings shame and social stigma, particularly in the mother, with significant impact on the health and well-being of the family.

Adolescents age 10-19 years who have benefited from the gains in child survival grow up to find themselves in social settings where less attention and fewer resources are devoted to their well-being compared to their earlier years of growth. The paucity of support during this time of transition into adulthood diminishes the impact that child survival can have on their lives. *Adolescents made up 18% of the world's population, approximately 1.8 billion individuals, in 2010, and the adolescent population is expected to increase to over 2 billion in the year 2050.* The vast majority of adolescents, 88%, live in LMICs. In 2050, sub-Saharan Africa is projected to have more adolescents than any other region. Although adolescent mortality rates are far lower than their younger age cohorts, in low-income countries adolescents face a lack of educational and employment opportunities and increased risk of injuries and violence, HIV and AIDS, mental health problems, adolescent marriage, and teenage pregnancy—preventing them from attaining their potential as they transition into adulthood. The decade of adolescence is a critical period when poverty and inequity frequently transfer to the next generation. *The intergenerational transmission of poverty is most apparent among undereducated adolescent females.* In many parts of the world poor teenage females are likely to be married early, risking premature childbearing, higher rates of maternal mortality, and contributing to infant and child undernutrition.

THE SOCIAL DETERMINANTS OF CHILD HEALTH AND THE COVID-19 PANDEMIC

The gross national income level accounts for much of the differences in child mortality rates observed between countries; however, other significant factors affect child health. For example, although the wealth of the United States places it in the 7th position with respect to gross domestic product (GDP) per capita (2022) in the world, the U.S. child mortality rate is ranked 47th in the world, at 6.5 deaths out of 1,000 live births, which is higher than Cuba (5.1), Canada (4.9), the UK (4.3), the Czech Republic (3.2), and Japan (2.5). In addition, *national estimates of mortality mask differences in health status among subpopulations within the same country.* In Burkina Faso, the child mortality rate is 43.7 per 1,000 live births among children born to mothers with no education, whereas it is 16.7 per 1,000 among children born to mothers with at least secondary education. Similarly, in 2016 the child mortality rate in Bolivia was 18.6 per 1,000 live births for children in the highest wealth quintile, whereas it was 55.1 per 1,000 for children living in the lowest quintile.

Child health is influenced by socioeconomic factors that operate at multiple levels of society. Disparities in these socioeconomic factors translate into child health inequities as reflected by high rates of disease, poor nutrition, and disability. The immediate, underlying, and basic structural determinants of disease, malnutrition, and disability are outlined in Figure 3.5. Preventive and curative medical interventions focus on the immediate causes of poor health; however, inequities in child mortality and morbidity will persist unless the basic and underlying determinants of health are addressed.

Socioeconomic and Political Roots of Disparities in Global Health

The root influences on a child's health often lie in the economic and political environments in which the child is born (see Figs. 3.4 and 3.5). Growth of economies during the first half of the 20th century was associated with dramatic health improvements, with falling mortality rates and rising life expectancy across all regions. However, the second half of the 20th century was characterized by growing disparities in global economies and health between and within many countries. According to the **World Inequality Report** (http://wir2018.wid.world/) between 1980 and 2016 the richest 1% of the world reaped twice as much of the world's income as the poorest 50% of the world (27% of income growth compared with 12%). Although almost all countries report population-level income inequalities, a few such as the United States have seen income disparities at historical proportions. For example, since 1980 the bottom half of Americans captured only 3% of the total growth. Growing income inequalities translate into greater differences in health outcomes, such as life expectancy, between the rich and poor in the United States (Fig. 3.6). More aggressive redistribution of wealth through taxes and transfers, labor protections, and

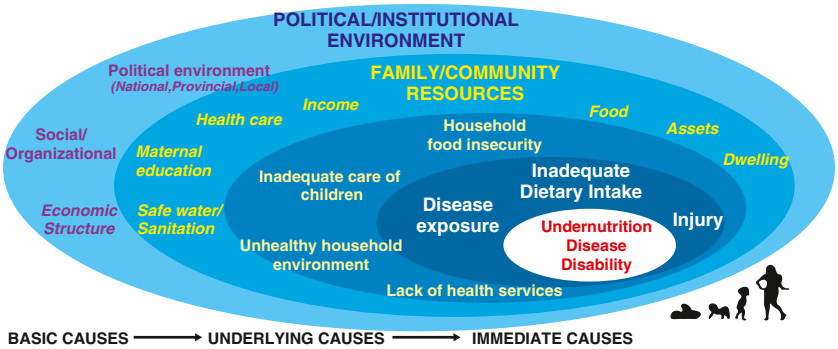

Fig. 3.5 Socioecologic model – Basic, underlying, and immediate determinants of child health.

universal access to education and health care contribute to Europe's significantly lower levels of income disparities.

Evidence supports the notion that inequalities are not just a human rights issue, but are detrimental to economic growth. Wealthier households spend a smaller percentage of their own income, thereby dampening demand and slowing down economies. Poorer households face greater challenges to invest in health and educational opportunities, translating into less human capital and obstacles to be productive and contribute to the economy. In extreme cases, inequalities can threaten social unrest, which further undermines economic activity.

Global disparities have grown between many wealthy and low-income countries, in large part because of **austerity measures**, including structural adjustment programs, imposed on many postcolonial countries by the International Monetary Fund (IMF) and World Bank. To receive loans and pay off their debt, many of these countries were required to take on austerity measures that transformed their economies to produce cash crops and export natural resources to HICs, rather than supporting local industries and investing in human capital and social services. The focus on cash economies rather than health and social service systems limited their ability to provide services to their growing poor population and further hindered responses to the spread of communicable diseases such as HIV/AIDS and the growing prevalence of noncommunicable diseases.

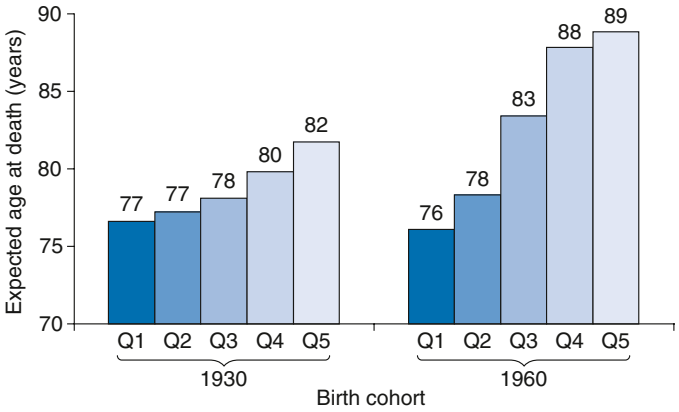

Fig. 3.6 Projected life expectancy for U.S. men at age 50 for 1930 and 1960 birth cohorts by income quintile – Q1 (poorest) to Q5 (richest). (*From Bor J, Cohen GH, Galea S. Population health in an era of rising income inequality: USA, 1980–2015, Lancet. 2017;389:1475–1490, Fig. 5b; with data from National Academies of Sciences, Engineering, and Medicine*. The Growing Gap in Life Expectancy by Income: Implications for Federal Programs and Policy Responses. *Washington, DC: National Academies Press;2015.*)

The COVID-19 Pandemic

The emergence of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) leading to the global pandemic of coronavirus disease 2019 (COVID-19) resulted in over 6 million deaths from COVID-19 and over 499 million cases of COVID-19 infection in the world (see Chapter 311). Children and adolescents tend to experience less severe illness and fewer deaths from SARS-CoV-2 compared to adults, which may lead to lower rates of testing among children and contribute to transmission.

Childhood COVID-19 infections have not affected countries equally, with early evidence showing pediatric deaths from COVID-19 to be significantly greater in LMICs compared to HICs. One study estimated 2.77 pediatric deaths/1 million children in LMICs compared to 1.32/million children in HICs and higher rates of death among infants <1 year of age, at 0.07%, in HICs versus 1.30% in LMICs. Although some LMICs' settings are protected from COVID-19 infection by having a younger demographic profile, lower prevalence of the chronic conditions predisposing to severe infection, and less international transport especially in remote, low-income regions, they also suffer from limited personal protective equipment, poor ventilation of indoor spaces, and inequitable distribution of COVID-19 vaccines. Marginalized groups in these nations who are infected face inadequate medical support and supplies, which can greatly elevate their risk of death and disability. Furthermore, poor availability of testing leads to a large number of deaths and infections being underreported.

The pandemic has significantly strained the already weak health and public health systems in LMICs, raising grave concerns about the risk for youth with chronic conditions. COVID-19 impact has led to disruptions in routine childhood vaccinations, lack of medical supplies, shortages of a health workforce, and reduced delivery of lifesaving services such as cardiac surgery. One estimate showed that 90% of countries report disruptions in essential health services such as essential medicines, routine childhood immunizations, and diagnostics, although some mitigation efforts are in place.

COVID-19 and Social Determinants of Health

COVID-19 affects child and adolescent health indirectly through the rippling effects on the world's economies and disruption of national systems in public health, healthcare, food, and education, all which are feared to be more of a threat than the pandemic itself (Fig. 3.7).

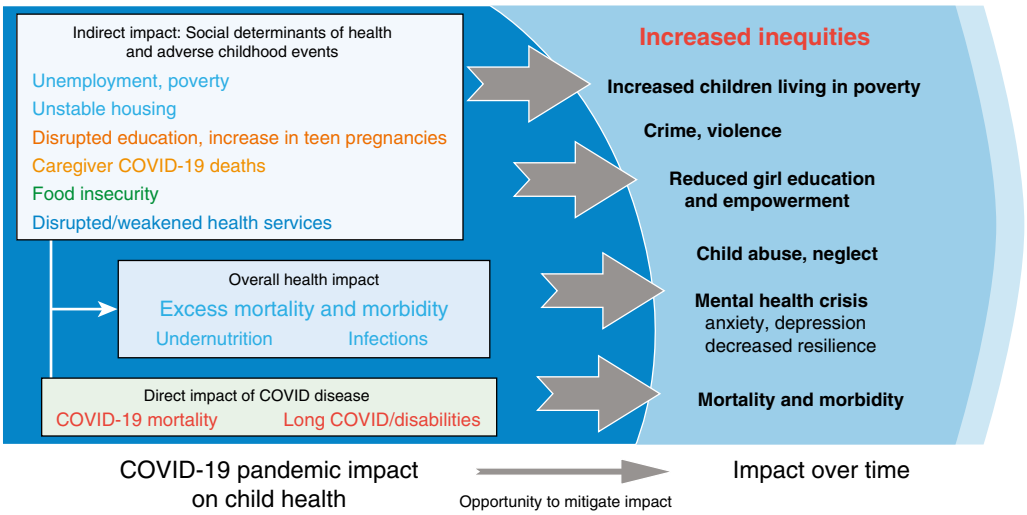

Fig. 3.7 Direct and indirect effects of the COVID-19 pandemic on child and adolescent health over time.

The economic crisis precipitated by the COVID pandemic lockdown and supply chain disruptions places the greatest strain on low-income communities, increasing the proportion of children who live in extreme poverty and face housing instability. An estimated additional 100 million children are estimated to have fallen into extreme poverty worldwide, which is the first increase in this indicator in 20 years. Pre-existing disparities have widened during the pandemic both within countries and globally between LMICs and HICs.

The COVID pandemic has stressed the social fabric of communities around the world so that the most marginalized and vulnerable bear the brunt of its full impact. Many racial and ethnic minority groups are unequally affected by COVID-19, with significantly higher rates of illness and death from COVID-19. Vulnerable communities that existed before the pandemic living in poverty, those employed in the informal sectors (e.g., street vendors), living within close proximity to others, unable to afford being able to stay safe at home, lacking protective gear at work, and without access to healthcare and health insurance are all at greater risk for COVID-19 infections.

Children in LMICs are particularly vulnerable because of the prolonged shutdown of schools, resulting in loss of education without access to technologic online solutions to engage in the educational curriculum. The loss of safe school environments has also been attributed to further widening gender inequities, and several countries reported a surge in adolescent pregnancies, domestic violence, and child abuse after closures.

Furthermore, the number of children affected by COVID-19–associated orphanhood and caregiver death has been estimated to have increased by 90%. The loss of a mother is associated with increased child mortality, especially when maternal death occurs in the first year of the child's life. In regions where rates of maternal death were already high, the impact of COVID-19 leading to loss of a mother or another caregiver can have devastating impact on the lives of children in the short and long term.

An epidemic of poor mental health has followed the COVID-19 pandemic for parents and their children; as the pandemic has progressed, the prevalence of depression and anxiety symptoms among adolescents has escalated. The impact on mental health is not surprising because of the extraordinary disruption of routines, recreation, family income, peer interaction, and school support. The pandemic further halted mental health services in 93% of countries worldwide as the demand for mental health services increased in settings where online mental health services are not an option.

Sustainable Development Goals

The prioritization and planning of global development and international aid has been guided by international goals. In 2015, world leaders agreed to 17 goals, the **Sustainability Development Goals (SDGs)**, to improve global well-being by 2030 (Fig. 3.8). The SDGs were built on the eight **Millennium Development Goals (MDGs)**, which were concrete, specific, and measurable targets set by the United Nations in 2000 to eradicate poverty, hunger, illiteracy, and disease by 2015.

The SDGs have become even more critical to countries planning for ways to mitigate the future impact of the COVID-19 pandemic on child health, particularly among marginalized communities and LMICs. The SDGs highlight recommended interventions for countries to meet their goals in the setting of the challenges created by the COVID-19 pandemic such as optimizing digital centers to increase access to public services, with an emphasis on targeting solutions for communities with low internet connectivity. There have been setbacks in progress towards meeting the 17 SDGs because of the COVID pandemic, highlighting the need to prioritize programs such as routine immunization services, malaria bed net distribution, family planning, and antenatal care services to prevent further negative impacts on child health.



Fig. 3.8 Sustainable development goals. (*Courtesy United Nations Department of Public Information, 2016. United Nations Sustainable Development Goals website: https://www.un.org/sustainabledevelopment/. The content of this publication has not been approved by the United Nations and does not reflect the views of the United Nations or its officials or Member States.*)

SDG-3 is to ensure healthy lives and promote well-being for all at all ages. It includes health-related subtargets, including to reduce U5MR to 25 deaths per 1,000 live births and neonatal mortality rate to 12 deaths per 1,000 live births by 2030. The other 16 SDGs focus mainly on social and economic determinants and the environment. This reflects an important shift to broaden the global targets to include upstream determinants of health, including health systems, and socioeconomic, gender-based, political, and environmental factors. As a social movement to support sustainable development, the SDGs were founded on the recognition that the world's environment, economic and social development, and human health are interconnected and dependent. The SDGs were formulated with core principles and values for economic development, environmental sustainability, and social inclusion for all.

The **Global Strategy for Women's, Children's and Adolescent's Health 2016–2030** maps out the strategies to achieve the SDGs by centering on the goal of health for all women, children, and adolescents using evidence-based approaches, backed by innovative and sustainable financing mechanisms. An important component of the Global Strategy is the inclusion of adolescents as central to the 2030 Agenda for Sustainable Development. In alignment with the SDGs, the Global Strategy focuses on three pillars of action: (1) **ending preventable deaths** among women, children, and adolescents, (2) **ensuring their health and well-being** by ending malnutrition and ensuring access to family planning, reducing exposure to pollution, and achieving universal health coverage, and (3) **expanding enabling environments** by efforts such as eradicating extreme poverty, ensuring good-quality education, eliminating violence against females, enhancing research and technologic capabilities, and encouraging innovation.

In addition to being much broader in scope, the Global Strategy focuses on equity in that the strategy is meant to apply to all people, including the marginalized and difficult-to-reach populations, in all situations, including during crisis. Health insurance coverage would not be assessed based simply on the national average of coverage but also by how well the increases in coverage benefit all population groups regardless of income or educational level.

EVIDENCE-BASED INTERVENTIONS AND INNOVATIONS TO ADDRESS CHILD HEALTH INEQUITIES

Estimates suggest that most of the 5.6 million annual deaths in children younger than 5 could be averted by increasing implementation of proven low-cost interventions (Table 3.1). Childhood deaths from diarrheal illness and pneumonia can be prevented by simple

Table 3.1 Essential Interventions Across the Continuum of Care to Improve Child Survival

HEALTH AND MULTISECTOR ACTIONS

- Ensuring food security for the family (or mother and child)
- Maternal education
- Safe drinking water and sanitation
- Handwashing with soap
- Reduced household air pollution
- Health education in schools

AGE-SPECIFIC ACTIONS

PREVENTION	TREATMENT
Adolescence and Pre-Pregnancy • Family planning • Preconception care	
Pregnancy • Appropriate care for normal and high-risk pregnancies (maternal tetanus vaccination)	• Antenatal steroids for premature births • Intermittent preventive treatment for malaria

Childbirth
• Maternal intrapartum care and monitoring
• Skilled delivery
  • Thermal care for all newborns
  • Clean cord and skin care
  • Early initiation and exclusive breastfeeding within the first hour
	• Newborn resuscitation (e.g., Healthy Babies Breathe)
	• Premature: Surfactant administration, continuous positive airway pressure (CPAP), treatment of jaundice, feeding support for small/preterm infants
	• Kangaroo mother care

Postnatal Period • Appropriate postnatal visits	• Extra care for small and sick babies (kangaroo mother care, treatment of infection, support for feeding, and management of respiratory complications) • Antibiotics for newborns at risk and for treatment of bacterial infections (PROM, sepsis, meningitis, pneumonia)

Infancy and Childhood
• Exclusive breastfeeding for 6 mo and continued breastfeeding up to at least 2 yr with appropriate complementary feeding from 6 mo
• Monitoring and care for child growth and development
• Routine immunization for childhood diseases
• Micronutrient supplementation, including vitamin A, from 6 mo
• Prevention of childhood diseases
  • Malaria (insecticide-treated bed nets)
  • Pneumonia
  • Diarrhea (rotavirus immunization)
  • Meningitis (meningococcal/Hib/pneumococcal vaccine)
  • Measles (vaccine)
• Prevention of mother-to-child transmission
	• Case management of severe acute malnutrition
	• Management of childhood diseases
	  • Malaria (antimalarials)
	  • Pneumonia (case management, antibiotics)
	  • Diarrhea (ORS, zinc supplement, continued feeding)
	  • Meningitis (case management, antibiotics)
	  • Measles (vitamin A supplement)
	• Comprehensive care of children exposed to or infected with HIV (highly active antiretroviral therapy [HAART])

Data from UNICEF, Were WM, Daelmans B, Bhutta Z, et al. Children's health priorities and interventions. *BMJ*. 2015;351:h4300.

measures such as vaccinations and exclusive breastfeeding until 6 months of age. Deaths related to undernutrition, which predisposes children to infectious diseases, may be prevented by proper infant and young child feeding practices, micronutrient supplementation, and community-based screening and management of malnutrition.

Addressing the SDGs to improve the health of mothers, children, and adolescents takes a **life-course approach**. Figure 3.9 displays estimates of coverage for essential interventions across the continuum of care, indicating the wide range of coverage rates within countries that will need to be addressed if SDGs are to be attained.

Vaccine-Preventable Diseases

Vaccines prevent an estimated 2.5 million deaths per year among children under 5 years of age. One study predicted a reduction in 120 million deaths among children born between 2000 and 2030 with vaccination programs. Yet in 2019 an estimated 1.15 million under-5 deaths were the result of vaccine-preventable diseases, with 99% of these children who died living in LMICs. Top contributors were *Streptococcus pneumoniae* and rotavirus, followed by *Bordetella pertussis,* measles virus, *Haemophilus influenzae* B (Hib), and influenza virus.

The WHO Expanded Program on Immunization (EPI) has resulted in a dramatic reduction in deaths, illness, and disability from many of these diseases, in addition to the near elimination of poliomyelitis. Recommendations for routine immunizations have continued to grow with the development of new vaccines that have demonstrated significant lifesaving potential in industrialized countries (Table 3.2). The vulnerability of these programs was demonstrated during the pandemic as global vaccine coverage dropped from 86% in 2019 to 83% in 2020, with an estimated 23 million under the age of 1 year who did not receive basic vaccines in 2020—the highest number since 2009.

In 2015, 86% of the world's infants were vaccinated with 3 doses of DTP. Although vaccines are very effective in improving child survival, rates of coverage are low in many countries. In 2016, a total of 19.5 million did not receive all routine lifesaving vaccinations, and 90,000 deaths were reported due to measles alone. Lifesaving vaccines are still not available in many countries, but progress has been made to expand availability to new countries every year. The lowest number of wild poliovirus cases were reported in 2016 (37 cases). The significant declines in immunization coverage caused by the COVID-19 pandemic have increased the risk for a resurgence of these vaccine-preventable infections amidst weakened healthcare systems.

Reaching Every Child, Everywhere

Global vaccine organizations aim for universal coverage of immunizations but face challenges within countries to attain this goal. Other lifesaving interventions have met barriers to attaining universal coverage. Oral rehydration therapy has been the evidence-based intervention to prevent dehydration from diarrheal disease since the 1970s, yet only 2 in 5 children under 5 with diarrheal illness receive this treatment. The determinants of whether or not a child receives a lifesaving intervention are multifactorial. Characteristics of a healthcare system, the social attitudes and practices, and political climate affect whether universal coverage can be reached for evidence-based essential interventions. Innovations to strengthen vaccine coverage to reach every child in every district of a country range from programs such as **Reaching Every Child through Quality Improvement (REC-QI)**, using community mapping techniques, to the integration of service delivery mechanisms and strengthening the health system with improved surveillance.

Effective Delivery Strategies: Integrated Management of Childhood Illness

Weak health systems impede the ability of countries to deliver cost-effective interventions and lifesaving health messages for children. Such systems are characterized by insufficient numbers of health workers, low-quality training and supervision, and poorly functioning supply chains. The provision of child health services may focus on a single level such as the health facility, but effective and lasting improvements can only be achieved with the integration of delivery at all levels, such as adequate referrals and follow-up between community, clinic, and health facility. As countries resume health services after the COVID-19 pandemic, an important component will be community-based, lifesaving outreach services such as mass immunization, vitamin A campaigns, and community-based health promotion activities (Fig. 3.10).

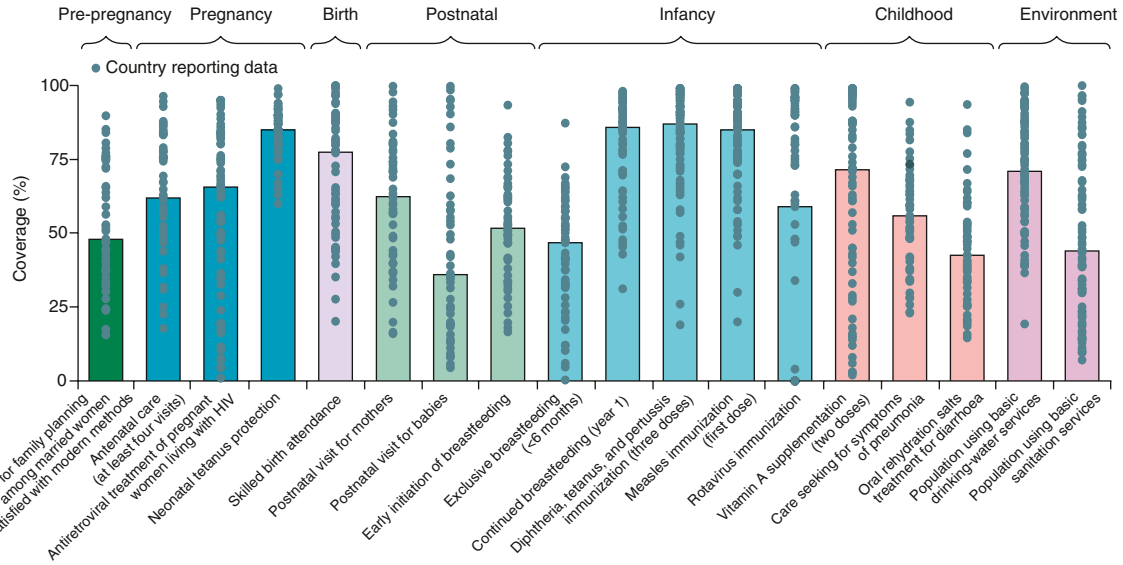

Fig. 3.9 Coverage of interventions across the continuum of care based on the most recent data since 2012 in countdown countries. Bars show median national coverage of interventions, whereas the dots show country-specific data. (*From Countdown to 2030 Collaboration. Countdown to 2030: Tracking progress towards universal coverage for reproductive, maternal, newborn, and child health.* Lancet. *2018;391:1538–1548. Fig. 1.*)

Table 3.2 Routine Childhood Immunizations Recommended by the World Health Organization (2021)*

ANTIGEN		AGE OF 1ST DOSE	DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES		BOOSTER DOSE	CONSIDERATIONS
				1ST TO 2ND	2ND TO 3RD		
BCG		As soon as possible after birth	1				Birth dose and HIV; universal vs selective vaccination; co-administration; vaccination of older age groups; pregnancy
Hepatitis B	Option 1	As soon as possible after birth (<24hr)	3	4 wk (min) with DTPCV1	4 wk (min) with DTPCV2		Premature and low birth weight; co-administration and combination vaccine; high risk groups
	Option 2	As soon as possible after birth High risk groups	4	4 wk (min) with DTPCV1	4 wk (min) with DTPCV2		
Polio	bOPV + IPV "Preferred schedule" (fractional Salk-IPV permitted)	bOPV 6 wk IPV 14 wk	5 (3 bOPV and 2 IPV)	bOPV 4 wk (min) (e.g. with DTPCV2) IPV ≥ 4 mo (min) (e.g. with MCV)	bOPV 4 wk (min) (e.g. with DTPCV3)		bOPV birth dose; type of vaccine; fractional dose IPV; transmission and importation risk; local epidemiology, programmatic implications and feasibility for "early" option
	bOPV+IPV "Early option" (full dose IPV only)	bOPV 6 wk IPV 6 wk	5 (3 bOPV and 2 IPV)	bOPV 4 wk (min) (e.g. with DTPCV2) IPV 14 wk (min) (e.g. with DTPCV3)	bOPV 4 wk (min) (e.g. with DTPCV3)		
	IPV / bOPV Sequential	8 wk (IPV 1st) bOPV (4–8 wk after 2nd IPV)	4 (2 IPV followed by ≥ 2 bOPV)	IPV (4–8 wk)	bOPV (4–8 wk)†		
	IPV-only	6–8 wk	3	4–8 wk	4–8 wk	IPV booster (6 mo after 3rd dose) is needed when 1st dose given at < 8 wk	Only for countries in polio-free regions with a very low risk of importation and sustained high routine immunization coverage (DTP3> 90%)
	Alternative IPV-only (fractional permitted)	≥14 wk	2	≥ 4 mo (e.g. with MCV)			

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

ANTIGEN		AGE OF 1ST DOSE	DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES		BOOSTER DOSE	CONSIDERATIONS
				1ST TO 2ND	2ND TO 3RD		
DTP-containing vaccine		6 wk (min)	3	4 wk (min) – 8 wk	4 wk (min) – 8 wk	3 boosters 12–23 mo (DTP containing vaccine); 4–7 yr (Td/DT containing vaccine); and 9–15 yr (Td)	Delayed/ interrupted schedule Combination vaccine; Maternal immunization
***Haemophilus influenzae* type b**	Option 1	6 wk (min) 59 mo (max)	3	4 wk (min) with DTPCV2	4 wk (min) with DTPCV3		Single dose if >12 mo of age; not recommended for children > 5 yr; delayed/interrupted schedule; co-administration and combination vaccine
	Option 2		2–3	8 wk (min) if only 2 doses 4 wk (min) if 3 doses	4 wk (min) if 3 doses	At least 6 mo (min) after last dose	
Pneumococcal (conjugate)	Option 1 3p+0	6 wk (min)	3	4 wk (min)	4 wk		Schedule options (3p+0 vs 2p+1);vaccine options; HIV+ and preterm neonate booster; vaccination in older adults
	Option 2 2p+1	6 wk (min)	2	8 wk (min)		9–18 mo	
Rotavirus		6 wk (min) with DTP1	2 or 3 depending on product	4 wk (min) with DTPCV2	For three dose series – 4 week (min) with DTPCV3		Not recommended if >24 mo
Measles		9 or 12 mo (6 mo min)	2	4 wk (min)			Co-administration live vaccines; combination vaccine; HIV early vaccination; pregnancy
Rubella		9 or 12 mo with measles containing vaccine	1				Achieve and sustain 80% coverage; co-administration and combination vaccine; pregnancy
HPV		As soon as possible from 9 yr (females only)	1–2	6–12 mo			Target 9–14 yr old females; off-label 1 dose schedule; MACs with intro; pregnancy; HIV and immunocompromised

*Please see WHO reference for specific vaccine recommendations for children residing in certain regions and in high-risk populations and more detailed footnotes. https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/table_2_feb_2023_english.pdf?sfvrsn=3e27ab48_11&download=true.

†Interval between 3rd and 4th, bOPV (4–8 wk).

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

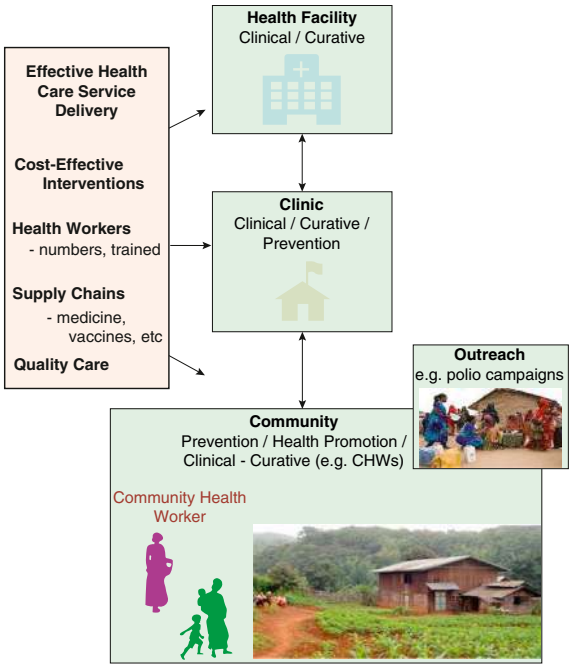

Fig. 3.10 Health services delivery systems.

Community-based interventions are effective in extending healthcare delivery, are low cost, improve healthcare-seeking behavior, and can reduce infant and child mortality and morbidity. They may include **community health workers (CHWs)**, who are members of a community without formal medical training chosen to provide basic health and medical care to their community, as discussed in more detail later.

The lack of integration of programs that deliver individual interventions results in missed opportunities. Children may receive immunizations from one health worker at one encounter, but go somewhere else to obtain oral rehydration solution (ORS) for diarrheal illness and yet elsewhere for treatment of malnutrition. Past programs focused on a single disease and set of interventions, whereas most children present with overlapping signs and symptoms to community-level health facilities with limited diagnostic tools such as laboratories or radiography.

The **Integrated Management of Childhood Illnesses (IMCI)** was launched in the mid-1990s by UNICEF and the World Health Organization (WHO) as an approach to reduce child death, illness, and disability and to promote improved growth and development in countries struggling with high child mortality rates. The IMCI was designed to increase coverage of evidence-based, high-impact interventions that tackle the top causes of child mortality by integrating health promotion, illness prevention, and disease treatment.

The IMCI contains both preventive and curative elements that are set forth through a series of clinical algorithms and guidelines for case management (Fig. 3.11 provides an example) and implemented by families, communities, and providers at health facilities. One key component of the IMCI strategy is to train CHWs to use the algorithms to identify signs of common childhood illness and to decide when a child needs referral to a health facility. IMCI trains CHWs to instruct parents on home management of ill children, including ORS and zinc for diarrhea, antimalarial medicine for febrile children who test positive for malaria, and antibiotics for children with signs of pneumonia. CHWs can schedule follow-up visits for ill children. They also promote use of bed nets, handwashing, and proper infant and young child feeding. In 2003, the IMCI guidelines underwent minor transitions, including the addition of newborn care under 1 week of age, so that it was renamed Integrated Management of Newborn and Childhood Illnesses (IMNCI).

Over 100 countries have adopted the IMNCI and implement some or all of its components that include not only improving health workers' skills but also strengthening health systems and improving family and community practices. After 20 years of implementation, a recent review of the IMNCI strategy noted that it was associated with a 15% reduction in child mortality when activities were properly implemented in health facilities and communities. However, the implementation of IMNCI was found to be uneven between and within countries. In many countries the resources for CHW training and supervision, supply of medications, and referrals were limited or absent. The IMNCI was only successful in those countries with strong government leadership and a commitment to implement IMNCI in partnership with support from groups such as UNICEF and the WHO. The success of IMNCI required an adequate health system and a systematic approach to planning and implementation.

Social Protection Programs: Conditional and Unconditional Cash Transfers

Financial incentives are widely used to improve healthcare coverage, alleviate poverty, and improve access to child health services. In industrialized countries, cash transfers are a common mechanism for ensuring that the poorest, most marginalized subgroups of the population, particularly with children, receive adequate support to meet their basic needs. Before the COVID-19 pandemic, cash transfer schemes were increasingly being used in LMICs to support population needs, and COVID-19 led to an enormous elevation of social protection efforts as a critical response to mitigate the far-reaching impact of the pandemic on vulnerable communities. Many lessons have been learned during this escalation of social protection programs, which provides hope for continued support of families in need, in addition to an expansion of services to mitigate the projected increases in children living in extreme poverty.

Out-of-pocket expenses by households form the major share of total health expenditure in most LMICs. Many social protection programs serve a dual purpose of reducing financial barriers and strengthening service delivery. Financial incentives may include cash transfers, microcredit, vouchers, and user fee removal and health insurances. **Financial incentive programs may be unconditional**, provided to eligible families without any requirements or expectations, based on the belief that families will use this type of financial support for their children's best interests. **Other incentives are conditional on health promotion behavior targeting child health**, such as the provision of cash or vouchers only to those families who participate in mother groups to learn about breastfeeding practices, visiting clinics for child vaccinations and growth monitoring, engaging in deworming, and ensuring that their children receive vitamin A and iron supplementation. Some social protection programs are also directed towards educational improvement by making cash transfers conditional on child school enrollment, attendance, and occasionally on some measure of academic performance.

Expansions of innovations that have been scaled up quickly during the pandemic protected millions of families such as through mobile cash transfer programs that take advantage of data and technology to better target those in need. Certain countries with a large proportion of children at risk are projected to have a protracted recovery period. Efforts have been taken to identify and provide international support for these countries and communities (Fig. 3.12).

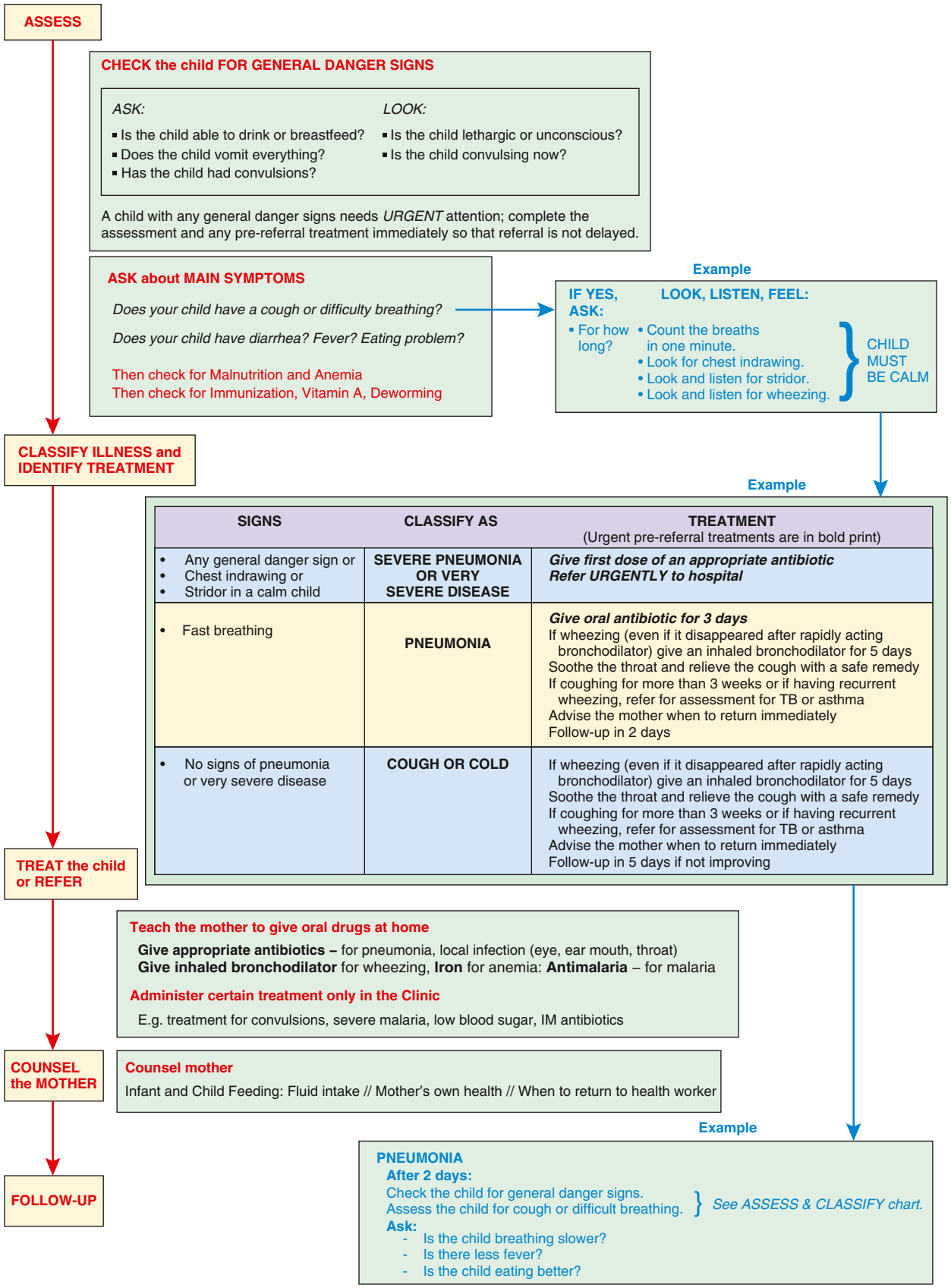

Fig. 3.11 Integrated management of childhood illnesses (IMCI) Generic IMCI table for appraisal of respiratory symptoms, with each algorithm tailored to the specific country context before implementation.

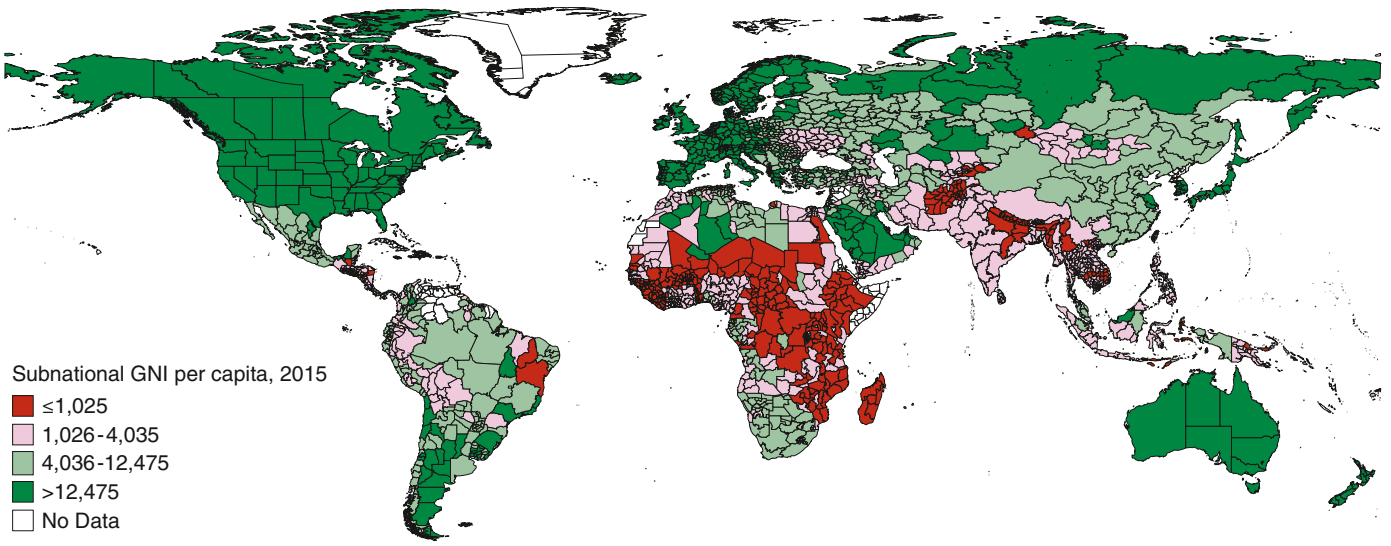

Fig. 3.12 Subnational poverty "hotspots" for extreme poverty (2015), based on GNI per capita. (*From Desai R, Kharas H, Ozdogan S. Poverty hotspots and the correlates of subnational development.* Brookings Institution. *Dec. 2020. Global working paper #149. https://www.brookings.edu/wp-content/uploads/2020/12/Poverty-hotspots_final.pdf.*)

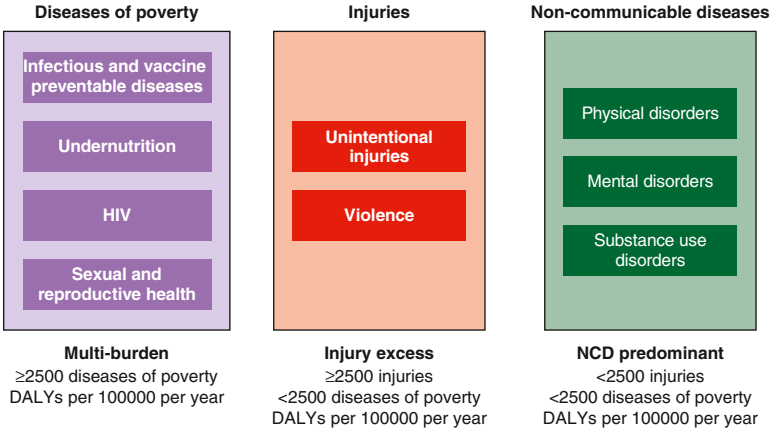

Fig. 3.13 Country categorization based on adolescent burden of disease. Categorization into 3 groups according to adolescent burden of disease and reflecting passage through epidemiologic transition. DALYs, Disability-adjusted life-years; NCD, noncommunicable diseases. (*From Patton GC, Sawyer SM, Santelli JS, et al. Our future: A Lancet commission on adolescent health and wellbeing.* Lancet. *2016;387:2423–2478, Fig. 7.*)

CHALLENGES IN GLOBAL HEALTH

Adolescent health. The Global Strategy, which directs countries to attain their SDGs, has called upon countries to focus efforts to support adolescent health given the potential role in breaking the intergenerational cycle of poverty. One challenge to attaining these health goals will be to effectively advocate for governments to invest in this age group as a means to improve national productivity and the economy. Considerable gaps in data on adolescents pose one of the biggest challenges to promoting their health and their rights. Data on early adolescents age 10-14 is relatively scarce, thus limiting the knowledge of this crucial period. Efforts to promote youth participation in delineating their health priorities are essential to the design of effective interventions.

One critical strategy to support adolescents is to improve completion of secondary school education, particularly among girls. The development of adolescents' capacities and values through education can empower an entire generation to become economically independent, to become positive contributors to society, and to break out of the cycle of poverty.

Other threats to adolescent health include mental health, substance abuse, sexual and reproductive health, and noncommunicable diseases (NCDs) such as obesity, which vary depending on country (Fig. 3.13). The surge in adolescent pregnancies that has been reported in several countries during the COVID-19 pandemic places particular emphasis on the need to strengthen youth access to sexual and reproductive education and services.

A common theme for these threats is that interventions to combat these issues must attempt to influence individual behavior and attitudes while promoting healthy lifestyles. It is estimated that around 20% of the world's adolescents have a mental health or behavioral problem, and this has only increased since the COVID-19 pandemic. Depression is the single largest contributor to the global burden of disease for people age 15-19, and suicide is one of the three leading causes of mortality among people age 15-35. Efforts to tackle these problems will require an interdisciplinary approach, with more research needed to identify and evaluate interventions to effectively influence adolescent behavior in LMIC settings.

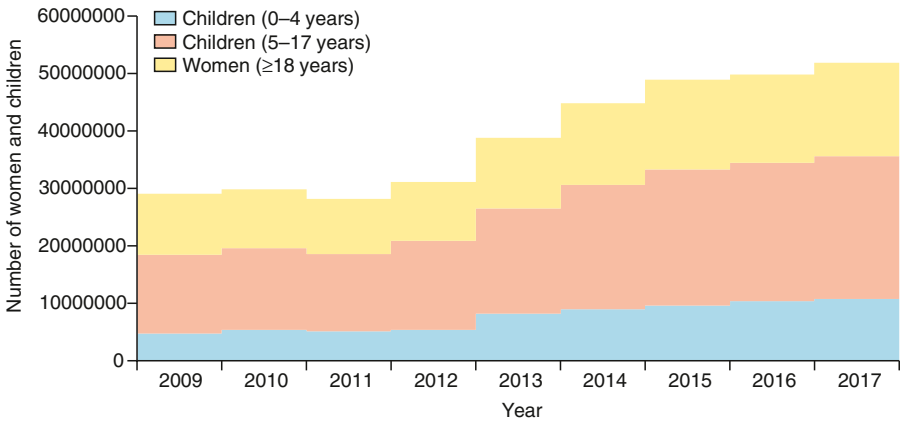

Fig. 3.14 Estimated number of children and women displaced by conflict, 2009–2017. (*From Bendavid E, Boerma T, Akseer N, et al. The effects of armed conflict on the health of women and children.* Lancet. *2021;397:522–530, Fig. 2, p. 524.*)

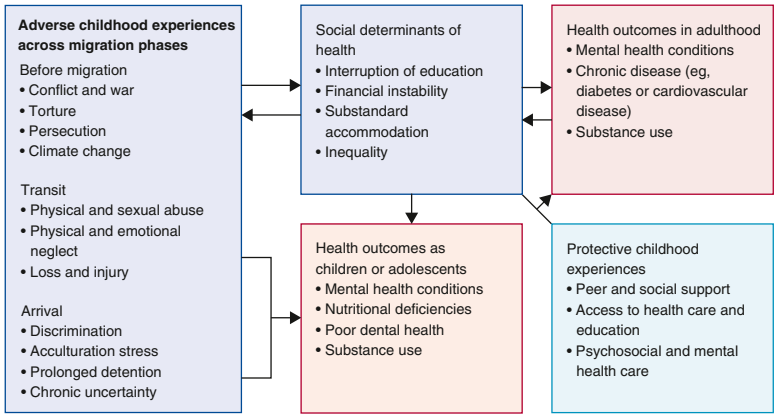

Fig. 3.15 Intersection between adverse childhood experiences during migration and social determinants of health and their long-term effects. Protective childhood experiences can act as a buffer so that adverse health conditions of childhood and adolescence are less prolonged and less severe in adulthood. (*From Maioli SC, Bhabbha J, Wickramage K, et al. International migration of unaccompanied minors: Trends, health risks, and legal protection.* Lancet Child Adolescent. *2021;5:882–895.*)

Climate change. Climate change is the most urgent and alarming long-term threat to child health and well-being in this century. Contributing to environmental degradation, the loss of natural resources and change in climate undermine food and water sources. Climate change and an increased frequency and severity of humanitarian crises have already adversely affected children's health and nutrition. Advocacy at local, national, and international levels to reduce greenhouse gas emissions are needed.

Conflict, emergency situations, and migration. During times of crisis, children, adolescents, and women are most vulnerable (Fig. 3.14). Although the youngest are the most likely to perish because of disease or injuries, all children suffer as a result of food shortages, poor water and sanitation, interrupted education, and family separation or displacement. Approximately 281 million migrants live outside their countries of birth, which includes 35 million young children and adolescents under the age of 20 who have migrated either with their parents or are unaccompanied. Many other children are affected by migration through parental separation because of deportation or emigration.

Children and adolescents crossing borders are often not entitled to the same protections and rights as those who reside in a given country, leaving them at greater risk of discrimination and exploitation. A rights-based approach to migration is required to reinforce the steady buildup of support and attention to migration issues at the international and national levels. This approach must also address the long-term social and health consequences and the root causes of migration (e.g., instability, inequality, discrimination, poverty) in the country of origin and should incorporate policies specifically targeted for young children, adolescents, young women, and vulnerable populations, including those left behind when family members migrate away (Fig. 3.15).

Health information and communications technology. The widespread proliferation of health information and communications technology (HICT) has transformed health care. Social media and mobile apps can be used to raise awareness and build skills, especially in LMICs, where other channels of public health messages may not be readily accessible.

The dissemination of HICT has not been equitable. The majority of LMICs are still in the early stages of adoption. Many healthcare settings in LMICs rely exclusively on paper-based records or simple electronic data-capture tools such as spreadsheets for disease surveillance, reporting, and research. Barriers to implementing HICT in LMICs include lack of health data infrastructures, reliable internet and electricity, workforce training, tools that fit local healthcare needs and culture, and sustainable funding. A further challenge is the need to ensure privacy and security while standardizing the format in which health data are captured to permit sharing of health information across facilities to reduce costly inefficiencies and to improve quality of care. Balanced partnerships between health care and technology communities across low-, middle-, and high-income countries are needed to share knowledge, foster innovation, and strengthen health information systems to advance equitable health outcomes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 4

Quality and Value in Healthcare for Children

Trisha L. Marshall, Amanda C. Schondelmeyer, and Jeffrey M. Simmons

THE NEED FOR IMPROVEMENT IN QUALITY AND VALUE

Adults and children receive recommended evidence-based care only about half the time. The gap between knowledge and practice widens to a *chasm* in part because of variations in practice and disparities in care from doctor to doctor, institution to institution, geographic region to geographic region, and socioeconomic group to socioeconomic group. Furthermore, it is estimated that it routinely takes more than a decade for new knowledge to be adopted into clinical practice.

In addition to appropriate care that patients do not receive, the U.S. healthcare systems also deliver much care that is unnecessary and waste many resources in doing so. This overuse or waste is one **key driver** of the disproportionate costs of care in the United States compared with other developed countries' delivery systems (in 2016, the United States spent about twice as much per capita, adjusting for gross domestic product [GDP], on healthcare compared to the average of peer wealthy nations). It is estimated that more than one quarter of all U.S. healthcare spending is waste. Gaps in appropriate care, combined with overuse and high costs, have driven conversations about the need to improve the value of care, which would mean better quality at lower overall costs. **Choosing Wisely**, an initiative initially sponsored by the American Board of Internal Medicine Foundation and subsequently endorsed by the American Academy of Pediatrics (AAP), asked medical societies to identify overused practices that clinicians could then make collective efforts to address.

WHAT ARE QUALITY AND VALUE?

The National Academy of Medicine (NAM) defines *quality* of healthcare as "the degree to which healthcare services for individuals and populations increases the likelihood of desired health outcomes and are consistent with current professional knowledge." To measure healthcare quality, they identified *Six Dimensions of Quality*: **effectiveness**, **efficiency**, **equity**, **timeliness**, **patient safety**, and **patient-centered care**. Healthcare services need to be *effective,* which means that they should result in benefits and be grounded in evidence whenever possible. Healthcare services also need to be *efficient,* which incorporates the idea of avoiding waste and improving system cost efficiencies, and the services should be *safe* for patients. Healthcare services must be *timely,* thus incorporating the need for appropriate access to care (see Chapter 5). Healthcare services should be *equitable,* which highlights the importance of minimizing variations as a result of race, ethnicity, gender, geographic location, and socioeconomic status (SES). Healthcare quality should be *patient centered,* which underscores the importance of identifying and incorporating individual patient needs, preferences, and values in clinical decision-making. In pediatrics, the patient-centered dimension extends to family-centeredness, so that the needs, preferences, and values of parents and other child caregivers are considered in care decisions and system design.

This framework emphasizes the concept that all Six Dimensions of Quality need to be met for the provision of *high-quality* healthcare. Collectively, the Six Dimensions of Quality represent *quality* in the overall *value* proposition of quality per cost. Value remains a critical concept, though difficult to measure accurately.

The evolving healthcare system requires physicians, healthcare providers, hospitals, and healthcare organizations to partner together and with patients to define, measure, and improve the overall quality and value of care delivered. Concrete examples of the evolving U.S. perspective include the widespread adoption of **Maintenance of Certification** (MOC) requirements by medical-certifying bodies, which require providers to engage in activities that improve care in their practices, and the core quality measurement features and population health incentives of the **Patient Protection and Affordable Care Act (ACA)** of 2010. The ACA also established the **Patient-Centered Outcomes Research Institute (PCORI)** to develop a portfolio of effectiveness and implementation research that requires direct engagement of patients and families to partner in setting research priorities, formulating research questions, and designing studies that will directly affect the needs of patients to improve the value of the research.

Although significant progress has been made along many dimensions of quality, a notable gap is the lack of progress on addressing inequities in healthcare. Disparities in healthcare based on racial or ethnic background, SES, and for patients and families with limited English proficiency are well documented and include inequities in access to care, treatment of pain, and in number of adverse events experienced during acute hospitalizations (see Chapter 2).

FRAMEWORKS FOR QUALITY IMPROVEMENT

Quality improvement (QI) science is a predominant method used to close gaps and improve value. Initially focused on improving performance and reliability in care processes, more recently, in part inspired by the Institute for Healthcare Improvement's **Triple Aim** approach, QI is also being used to improve value for *populations* of patients by focusing more on *outcomes* defined by patients' needs. The Triple Aim included (1) improving the patient experience of care, (2) improving the health of populations, and (3) reducing per capita cost of healthcare. The **Quadruple Aim** approach adds the fourth dimension of healthcare worker experience, or *joy in work,* to focus delivery systems on the need to consider the resilience and safety of the clinical workforce in order to maintain the delivery of high-value care.

Quality is broader in scope than QI. Many quality measurement systems have attempted to be more transparent with clinicians and patients about costs of care. Because more direct costs have been shifted to patients and families through widespread adoption of high-deductible insurance plans (i.e., families experience lower upfront insurance coverage costs but pay for certain acute healthcare expenses out-of-pocket until the preset deductible is met), better awareness of costs has become a more important driver of improvement in value, in part by reducing overuse.

The applied science of QI currently in use in healthcare is also firmly grounded in the classic scientific method of observation, hypothesis, and planned experimentation. There are four key features of the applied science of QI: appreciation of systems, understanding variation, knowledge theory, and psychology of change. In addition to this theoretical framework, statistical analytic techniques have evolved to better evaluate variable systems over time. Although each derives key features from this applied scientific foundation, multiple QI methodologies are currently in use in healthcare. At their most parsimonious level, each method can be described as a three-step model: *Data → Information → Improvement.* Quality needs to be measured. Data obtained from measurement needs to be converted into meaningful information that can be analyzed, compared, and reported. Information must then be *actionable* to achieve improvements in clinical practice and health systems' processes. Some common approaches to conducting QI in healthcare, many of which originated in manufacturing, include Model for Improvement, Six Sigma, and Lean methodologies. These approaches are not mutually exclusive and share common features and tools. The Model for Improvement is an overarching framework

for improvement. Six Sigma focuses largely on reducing variation in processes, and Lean focuses on eliminating waste.

Model for Improvement

The Model for Improvement is structured around three key questions: (1) What are we trying to accomplish? (2) How will we know that a change is an improvement? and (3) What change can we make that will result in improvement? Clarifying the first question, the *goal,* is critical and is often a step skipped by clinicians, who typically already have change ideas in mind. The second question is about defining measures, with an emphasis on practicality and efficiency. The third question is about defining testable ideas for improvement, which are subsequently tested using a framework of rapid cycle improvement, also known as the **plan-do-study-act (PDSA) cycle** (Fig. 4.1A). The PDSA cycle is typically aimed at testing small care process changes in iterative, rapid cycles. After discrete testing periods, results are analyzed, and the next cycle of change testing is planned and implemented (i.e., multiple PDSA cycles, often called a PDSA *ramp,* build on previous learning from PDSAs; see Fig. 4.1B). Valuable information can be obtained from PDSA cycles that are successful, and those that are not, to help plan the next iteration of the PDSA cycle. The PDSA cycle specifically requires that improvements be data driven. Many clinicians attempt to make changes for improvement in their practice based on clinical intuition rather than on interpretation of empirical data. Data can be either quantitative or qualitative in nature.

One successful QI collaborative using the Model for Improvement in the outpatient setting is related to improvements in remission rates and reduction in systemic corticosteroid use among children with inflammatory bowel disease (IBD, Crohn disease, or ulcerative colitis). This work was supported by the **ImproveCareNow Network** (https://improvecarenow.org/), a learning health system. A *learning health system* is a collaborative endeavor organized around communities of patients, clinicians, and researchers working together to integrate research with QI (i.e., knowledge dissemination and implementation) to improve care delivery while advancing clinical research. For the IBD network, outpatient gastroenterology practices standardized treatment approaches to align with existing evidence through QI interventions adapted to local circumstances. Therapeutic decisions for individual patients remained at the discretion of physicians and their patients.

Six Sigma

Six Sigma is related to the reduction in *undesirable variation in processes.* Six Sigma attempts to provide a structured approach to unwanted variations in healthcare processes. Six Sigma approaches have been successfully used in healthcare to improve processes in both clinical and nonclinical settings.

Lean Methodology

Lean methodology focuses on reducing waste within a process in a system. Figure 4.2A illustrates the steps in the process of a patient coming to the emergency department (ED). After the initial registration, the patient is seen by a nurse and then the physician. In a busy ED, a patient may need to wait for hours before registration is complete and the patient is placed in the examination room. This wait time is a waste from the perspective of the patient and the family. Incorporating the registration process after placing the patient in the physician examination room can save time and minimize waste (see Fig. 4.2B). Lean methods have been successfully used in several outpatient and inpatient settings with resulting improvements in efficiency. Lean principles have also been adopted as a core strategy for many children's hospitals and health systems with the goal of improving efficiencies, including access, while reducing waste. These efforts can improve aspects of quality while also

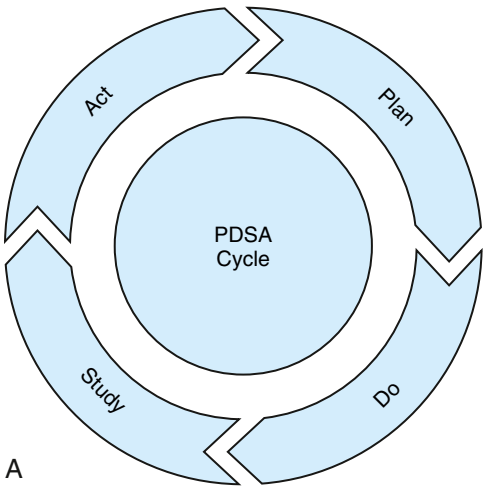

A

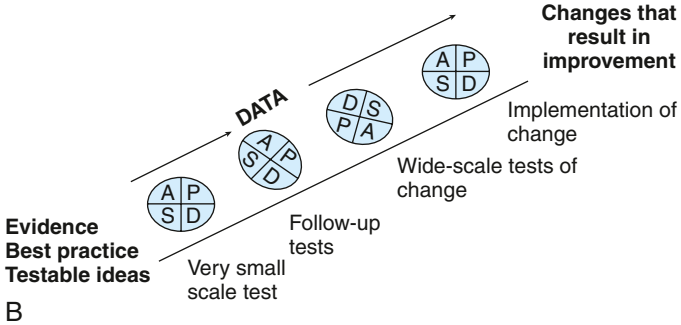

B

Fig. 4.1 A, The plan-do-study-act (PDSA) cycle. B, Use of PDSA cycles: a ramp. (*From Langley GJ. The Improvement Guide: A Practical Guide to Enhancing Organizational Performance. San Francisco: Jossey-Bass:1996. Copyright 1996 by Gerald J. Langley, Kevin M. Nolan, Thomas W. Nolan, L. Norman, and Lloyd P. Provost.)*

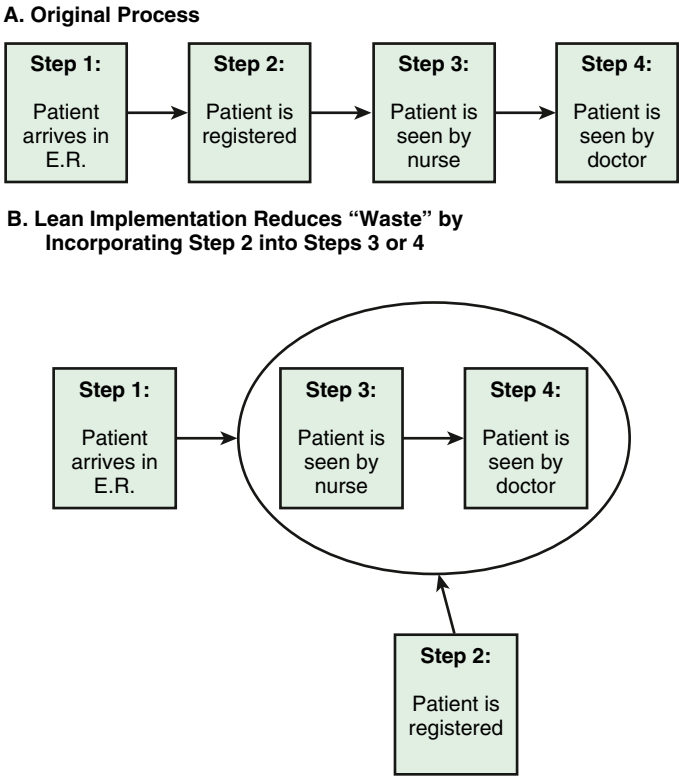

Fig. 4.2 A and B, Lean methodology—waste reduction.

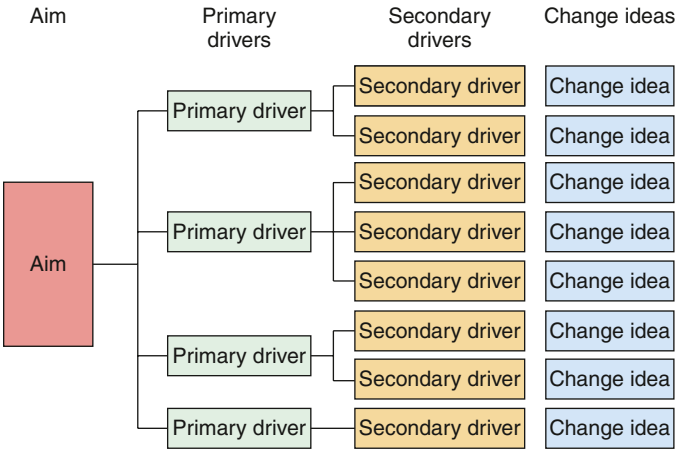

Fig. 4.3 Key driver diagram: theory of how to achieve an aim.

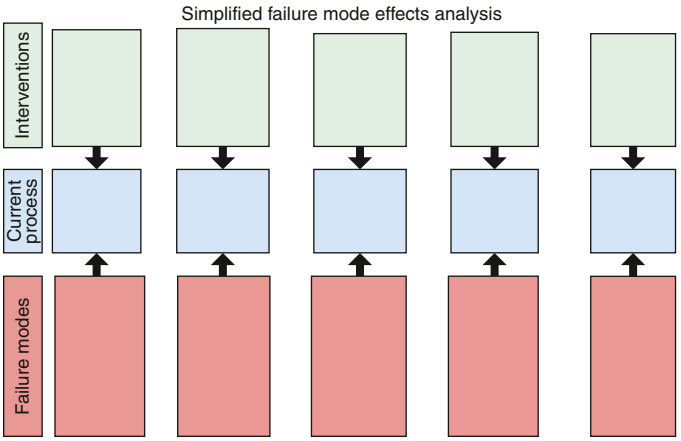

Fig. 4.4 Failure modes and effects analysis (FMEA).

typically reducing costs. Another key principle of Lean methods is the empowerment of the workforce and frontline leaders to make changes that reduce hassles for them and for patients.

Tools for Organizing Quality Improvement Theory and Execution

QI efforts need to be organized around a theory of how the desired changes in outcome will be achieved. Multiple tools are available to help organize a QI team's thinking and execution. These tools typically help teams organize work into discrete projects or phases, and some of them also help teams develop change ideas.

Key driver diagrams (KDDs) are a tool to organize the theory of learning that underpins a QI project (Fig. 4.3), using the Model for Improvement. Important aspects of a KDD include a statement of the specific aim or improvement goal; a list of the key themes, or drivers, that are theorized to require improvement in order to achieve the aim; and lastly a list of the discrete change ideas or initiatives to be tested to determine whether or not they affect discrete drivers, and therefore the overall aim. Because most system outcomes are driven by multiple factors, a KDD allows a QI team to depict a theory that addresses multiple factors. Similarly, Lean and Six Sigma projects use a tool called an A3 that, in addition to organizing the theory of a project, also prompts teams to assess the current state and consider timelines and personnel for planned change (examples are available at https://www.lean.org/common/display).

There are additional QI tools to help assess the current state of a system to better understand how to improve it. One, the **failure modes and effects analysis (FMEA)**, also helps teams develop change ideas (Fig. 4.4). Starting with a map of the processes in the current system, FMEA then asks teams to investigate and brainstorm the many ways discrete processes can go wrong—the *failure modes*. Once failure modes are identified, teams begin to develop discrete interventions or countermeasures to address the failures (see Chapter 5). A similar tool, the **fishbone** or **cause-and-effect** diagram, is organized around key components in a system (e.g., people, material, machines) and helps a team catalog how deficiencies in each component can affect the overall outcome of a system.

Another tool to help teams prioritize action is a **Pareto chart**, which organizes system deficiencies in terms of their prevalence (Fig. 4.5). A Pareto chart typically displays the individual prevalence of discrete problems, determined by baseline analysis of data, as well as the cumulative prevalence, helping teams see which problems should be addressed first to maximize impact on the overall outcome.

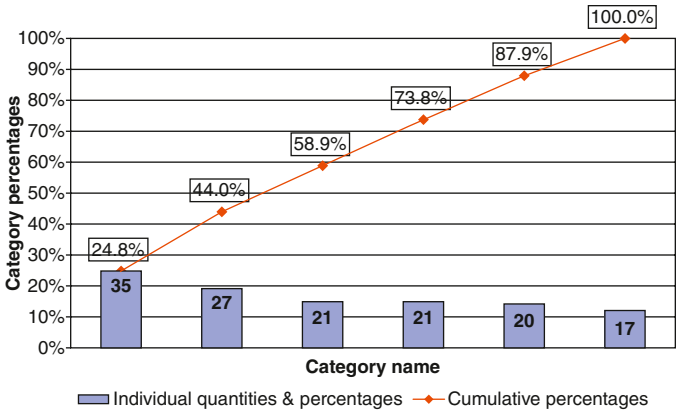

Fig. 4.5 Pareto chart.

Table 4.1 Properties of Robust Quality Measures

ATTRIBUTE	RELEVANCE
Validity	Indicator accurately captures the concept being measured.
Reliability	Measure is reproducible.
Feasibility	Data can be collected using paper or electronic records.
Usability	Measure is useful in clinical practice.

MEASURING QUALITY

Robust quality indictors should have clinical and statistical relevance. *Clinical relevance* ensures that the indicators are meaningful to patient care from the standpoint of patients and clinicians. *Statistical relevance* ensures that the indicators have measurement properties to allow an acceptable level of accuracy and precision. These concepts are captured in the national recommendations that quality measures must meet the criteria of being valid, reliable, feasible, and usable (Table 4.1). **Validity** of quality measures refers to the measure being an estimate of the true concept of interest. **Reliability** refers to the measure being reproducible and providing the same result if retested. It is important that quality measures are **feasible** in practice, with an emphasis on how the data supporting the measures are collected. Quality measures must be **usable**, which means that they should be clinically meaningful. The Agency for Healthcare Research and Quality (AHRQ) and the National Quality Forum have provided specific criteria to be considered when developing quality measures.

Several categories of quality measures can be used to measure the performance of healthcare systems: structure, process, outcome, and balancing. **Structure** refers to the *organizational characteristics* in healthcare delivery. Examples of organizational characteristics are the number of physicians and nurses in an acute care setting and the availability and use of systems such as electronic health records (EHRs). **Process** measures estimate how services are provided; examples are the percentage of families of children with asthma who receive an asthma action plan as part of their office visit and the percentage of hospitalized children who have documentation of pain assessments as part of their care. **Outcome** measures refer to the final health status of the child; examples are risk-adjusted survival in an intensive care unit setting, birthweight-adjusted survival in the neonatal intensive care unit (NICU) setting, and the functional status of children with chronic conditions such as cystic fibrosis. **Balancing measures** are often used to ensure changes in processes or systems do not have unintended consequence. If a healthcare system is actively working to reduce hospital length of stay for common conditions, it would be beneficial to ensure that hospital readmission rates are not increasing.

It is important to distinguish between measures for accountability and measures for improvement. Measures, particularly measures for accountability that may be linked to attribution and payment, must be based on a rigorous process (Fig. 4.6). This can be resource-intensive and time-consuming. In contrast, measures for improvement serve a different purpose—to track incremental improvements linked to specific QI efforts. These may not undergo rigorous testing, and they often have limited applicability beyond the specific QI setting.

Quality data can be quantitative and qualitative. *Quantitative* data includes numerical data, which can be *continuous* (patient satisfaction scores represented as a percentage, with higher numbers indicating better satisfaction) or *categorical* (patient satisfaction scores from a survey using a Likert scale indicating satisfactory, unsatisfactory, good, or superior care). Data can also be *qualitative* in nature, which includes nonnumerical data. Examples of qualitative data can include results from open-ended surveys related to the experience of care in a clinic or hospital setting.

Data measuring quality of care can be obtained from a variety of sources, which include chart reviews, patient surveys, existing administrative data sources (i.e., billing data), disease and specialty databases, and patient registries, which track individual patients over time. Sources of data vary in terms of reliability and accuracy, which will influence *rigor* and therefore appropriate-use cases for the data; many national databases invest significant resources in implementing processes to improve data reliability and accuracy. Data quality can become a significant impediment when using data from secondary sources, which can adversely affect the overall quality evaluation.

Health information technology (HIT) is a critical component in the effort to improve quality. EHRs have resulted in an unprecedented rise in available healthcare data, including traditional, structured data fields such as patient demographic and billing diagnosis codes, as well as unstructured data such as written clinician documentation in notes and imaging studies. The 21st Century Cures Act aims to facilitate the exchange and use of electronic health information "without special effort" on the part of the user. The Cures Act was designed to address concerns about interoperability and usability of electronic health systems, which can be barriers to care, improvement, and research.

The potential applications of big data in quality improvement are far reaching and include advancements in clinical informatics designed to better predict, manage, and treat common illnesses and provide effective, evidence-based, real-time, clinical decision-making support. For example, the Hospital for Sick Children at the University of Toronto is using a real-time data gathering and analysis framework to detect subtle changes on infant heart monitors that may predict potential cases of late-onset neonatal sepsis.

ANALYZING QUALITY DATA

The classic statistical approach from a research paradigm has been applied to quality data for comparing trends over time and differences before and after an intervention. Another approach from an improvement science paradigm uses techniques such as run charts and statistical process control (SPC) charts to track data longitudinally to assess for changes in a system over time. There are several advantages to using run or SPC charts when analyzing quality

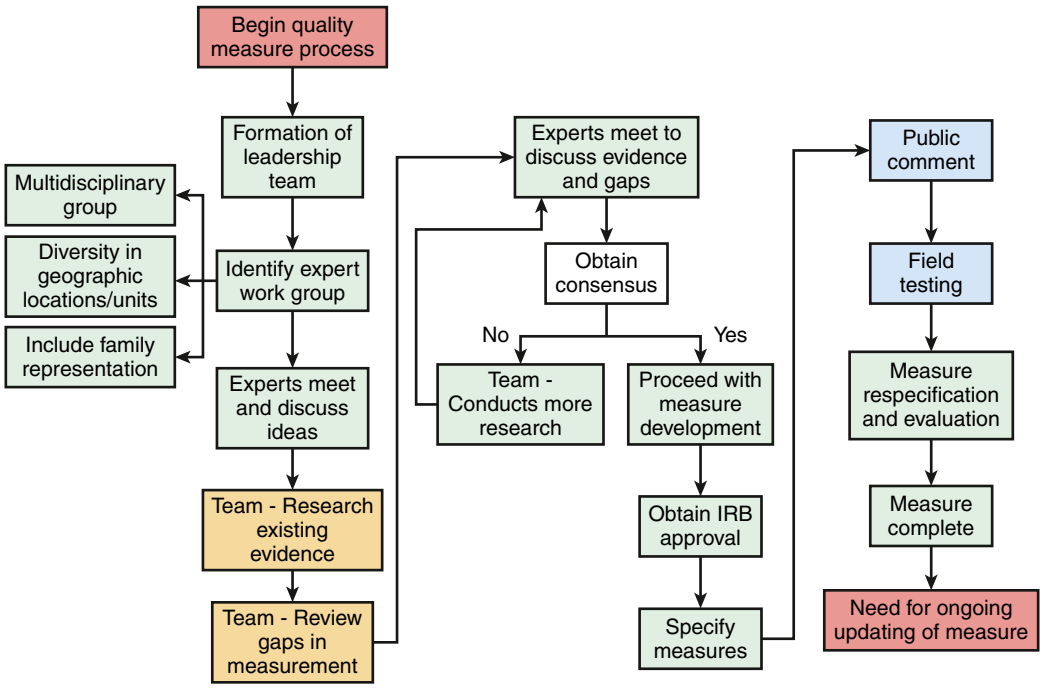

Fig. 4.6 Development of a rigorous quality measure.

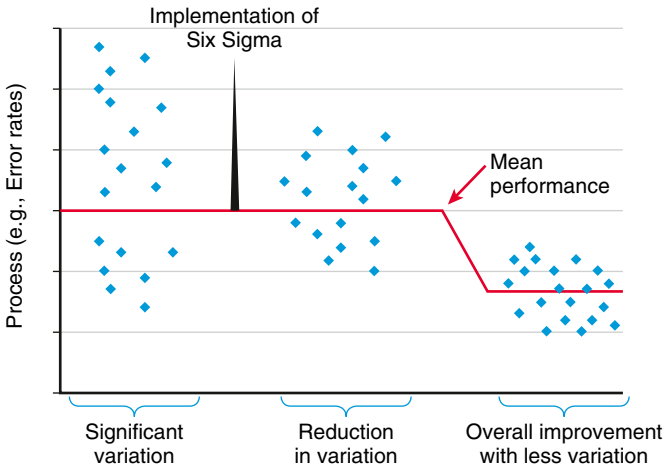

Fig 4.7 Run or SPC chart with common cause and special cause variation.

data—for example, these tools allow evaluation of the effectiveness of various interventions in near real time. Additionally, when using an SPC chart QI teams can also more clearly assess how variation in a process or system is changing over time. Two types of variations are important to distinguish between. **Random variation**, also called *common cause variation,* refers to the variation that is inherent in a process and is expected in any system. In contrast, **special cause variation** refers to nonrandom variation that can affect a process and implies something in the system has been perturbed. When tracking infection rates in a nursery, for example, a sudden increase in the infection rates may be secondary to a planned or unexpected change in a product or supply critical to infection prevention. This would represent a special cause variation; once the supply issue is resolved or mitigated, the system perturbation is resolved, and the infection rates will likely go back to the baseline level. Alternatively, improvement ideas are intended to perturb the system positively such that outcomes improve, ideally without exacerbating the variation in the system (Fig. 4.7). Both run and SPC charts have established rules to assess for special cause variation or a statistically significant change in a process or system over time.

EXPANDING INDIVIDUAL QUALITY IMPROVEMENT INITIATIVES TO SCALE

Despite the success of individual QI projects, the overall progress to achieve large-scale improvements to reach all children across the spectrum of geographic location and SES remains limited. This contributes to the health disparities that persist for children, with significant differences in access and quality of care. A potential factor that limits the full impact of QI is the lack of strategic alignment of improvement efforts with hospitals, health systems, and across states.

This challenge can be viewed from a system standpoint in being able to conduct and expand QI from a micro level (individual projects), to the meso level (regional), to the macro level (national and international). The learning from individual QI projects for addressing specific challenges can be expanded to the regional level by ensuring that there is optimal leadership, opportunity for education, and adoption of improvement science (Fig. 4.8). To further expand the learning to a national and international level, it is important to leverage implementation science to allow a strategic approach to the identification of the key factors that influence success. To leverage fully the synergies in order to impact the quality of care delivered to children, it is important for national and international healthcare organizations to collaborate effectively from a knowledge management and improvement standpoint (Table 4.2).

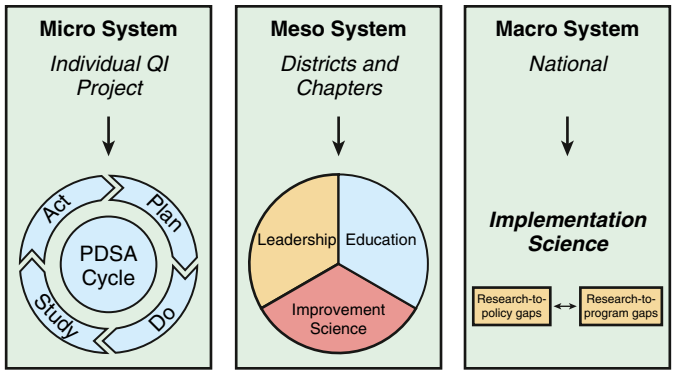

Fig. 4.8 Progressing from small scale to large scale quality improvement.

COMPARING AND REPORTING QUALITY

At the health system level, there is an increasing emphasis on quality reporting in healthcare in the United States. Many states have mandatory policies for the reporting of quality data. This reporting may be tied to reimbursement using the approach of pay-for-performance (P4P), which implies that reimbursements by insurers to hospitals and physicians will be partially based on the quality metrics. An extension of the P4P concept relates to the implementation of the policy of **nonreimbursable hospital-acquired conditions**, formerly called *never events* by the Centers for Medicare and Medicaid Services (CMS). CMS has identified a list of hospital-acquired conditions, which are specific quality events that will result in no payment for subsequent care provided to patients, such as wrong-site surgery, central line–associated bloodstream infections (CLA-BSIs), and pressure ulcers. This approach has not yet been widely implemented for pediatric patients.

There are growing, internet-based, commercial platforms for sharing information about patient and family experiences of care with specific clinical sites and specific providers. Many children's hospitals have also developed their own websites for voluntarily reporting their quality information, including ratings of care experiences. Although greater transparency may provide a competitive advantage to institutions, the underlying policy goal of transparency is to improve the quality of care being delivered and for families to be able to make informed choices in selecting hospitals and providers for their children.

When comparing quality measures across clinical settings, it is important to perform risk adjustments. **Risk adjustment** is the statistical concept that uses measures of underlying severity or risk so that the outcomes can be compared in a meaningful manner. The importance of risk adjustment was highlighted in the pediatric intensive care unit (PICU) setting many years ago. The unadjusted mortality rate for large tertiary care centers was significantly higher than that for smaller hospital settings. However, after **severity of illness** risk adjustment, it was subsequently shown that the risks in tertiary-care, large PICUs were higher because patients had, in general, greater severity of illness. Although this concept is intuitive for most clinicians, the use of severity of illness models allows mathematical estimates of patient severity using physiologic and laboratory data and permits meaningful comparisons of the outcomes across institutions, which may care for patient populations varying in complexity and acuity.

At the individual physician level, quality measures may also be used for purposes of certification as part of the MOC process. In the past, specialty and subspecialty certification in medicine, including pediatrics, was largely based on demonstrating a core fund of knowledge by being successful on an examination. Further, no specific evidence of competency in actual practice needed to be demonstrated beyond successful completion of a training program. However, significant variation in practice patterns among

Table 4.2 National Organizations Involved in Pediatric Quality Improvement (QI)

ORGANIZATION	ROLE	ACTIVITIES
American Academy of Pediatrics (AAP)	Represents more than 60,000 pediatricians and pediatric subspecialists worldwide	Resources for QI to improve health for all children, best practices, advocacy, policy, research and practice, and medical home
American Board of Pediatrics (ABP)	Certifying board for pediatrics and pediatric subspecialties	Certification policies and resources for activities such as Maintenance of Certification (MOC)
American Medical Association (AMA)	Physician member association	Physician Consortium for Performance Improvement (PCPI)—physician-led initiative
Children's Hospital Association (CHA)	Formerly the National Association of Children's Hospitals and Related Institutions and the Child Health Corporation of America	Databases, QI collaboratives, and policy
Institute for Healthcare Improvement (IHI)	QI organization for adult and pediatric care	QI collaboratives, QI educational workshops and materials
National Initiative for Child Health Quality (NICHQ)	QI organization for pediatric care	QI training, improvement networks
The Joint Commission (TJC)	Hospital accreditation organization	Unannounced surveys to evaluate quality of care in hospitals
National Committee for Quality Assurance (NCQA)	QI organization	Healthcare Effectiveness Data and Information Set (HEDIS) and quality measures for improvement
National Quality Forum (NQF)	Multidisciplinary group including healthcare providers, purchasers, consumers, and accrediting bodies	Endorsing national quality measures, convening expert groups, and setting national priorities

physicians who are board certified has demonstrated how medical knowledge is important, but not sufficient, for the delivery of high-quality care. In response, the American Board of Medical Specialties, including its member board, the American Board of Pediatrics, implemented the MOC process in 2010. Within the MOC process, there is a specific requirement (Part IV) for the physician to demonstrate the assessment of their quality of care and implementation of improvement strategies as part of recertification in pediatrics and pediatric subspecialties. Lifelong learning and the translation of learning into practice are the basis for the MOC process and an essential competency for physicians' professionalism. This concept has also filtered in to graduate medical education, as demonstrated by the Accreditation Council for Graduate Medical Education requirement for residency programs to incorporate QI curriculum to ensure that systems-based practice and QI are part of the overall competencies within accredited graduate medical training programs.

IMPLICATIONS OF THE U.S. HEALTHCARE REFORM FOR QUALITY

Regarding quality of healthcare for children, healthcare reform efforts had three key implications. First, expanded insurance coverage optimized access and include expanded coverage for young adults to age 26 years. Second, various initiatives related to quality, safety, patient-centered outcomes research, and innovation were implemented and funded. For example, the AHRQ funded a national effort to establish 7 centers of excellence through the **Pediatric Quality Measurement Program** (PQMP) to improve existing pediatric quality measures and create new measures that can be used by states and in a variety of other settings to evaluate quality of care for children. Third, reform advocated a paradigm shift in the existing model of healthcare delivery from vertical integration toward a model of *horizontal* integration. This has led to the creation and rapid growth of integrated delivery systems and risk-sharing relationships through **accountable care organizations (ACOs)**. Population health outcomes from these changes remain uncertain, although it appears healthcare cost inflation may have slowed somewhat.

Another area of increasing emphasis is **population health**. This is important because it expands the traditional role of physicians to improve quality of care for individual patients to also improve the quality of care for larger populations. Populations can be defined by geographic constraints or disease/patient condition. Efforts to link payment and reimbursement for care delivery by physicians and health systems are being increasingly tied to measurable improvements in population health and demonstration of improved value. To achieve a meaningful improvement in population outcome, physician practices will need to embrace the emerging paradigm of practice transformation, whose many facets include the adoption of a **medical home**, the seamless connectivity across the primary care and subspecialty continuum, and a strong connection between the medical and social determinants of healthcare delivery. To implement successful practice transformation, health systems are increasingly striving to evolve to serve children across the entire range of the care continuum, including preventive and primary care and acute hospital care, and to partner with community organizations for enhancing social supports. In addition, new risk-sharing payment models are being developed, such as value-based purchasing, which represent a financial risk-sharing model across primary and subspecialty care and hospitals.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 5

Safety in Healthcare for Children

Patrick W. Brady, Tina K. Sosa, and Jeffrey M. Simmons

Children may be harmed by the healthcare that aims to make them better. Such harms include central line–associated bloodstream infections (CLA-BSIs) and medication errors. In 1991 the Harvard Medical Practice Study reviewed adult medical records from New York State and found that adverse events occurred in an estimated 3.7% of hospitalizations. Most events gave rise to serious disability, and 13.6% led to death. The National Academy of Medicine estimated that as many as 98,000 Americans per year die in the hospital from medical errors.

Although fewer data are available for children, it is evident that children experience substantial healthcare-related harm. Nationally, hospitalized children experience approximately 1,700 CLA-BSIs and 84,000 adverse drug events each year. Although the evidence is less robust, and not without controversy, substantial progress has been reported, particularly in **healthcare-associated conditions (HACs)**. Less strong epidemiologic estimates are available for adverse events in the ambulatory environment, but these events are likely more common than reported.

The **Solutions for Patient Safety (SPS)** collaborative includes >145 children's hospitals across the United States and Canada (http://www.solutionsforpatientsafety.org) and uses a learning network model to pursue the aim of eliminating serious harm across all children's hospitals. In addition, healthcare has recognized the high rates of healthcare worker injury and the critical role that the safety of healthcare providers plays in outcomes, burnout, and safe patient care.

ERROR VS HARM

Clinical leaders, improvers, and researchers often employ measures of error and harm to understand and improve safety, but the differences between these two measures can lead to confusion. **Errors** occur when a member of the healthcare team does the wrong thing *(error of commission)* or fails to do the right thing *(error of omission)*; errors of omission (e.g., not arriving at the right diagnosis) are considerably more difficult to measure. **Harm**, as defined by the Institute for Healthcare Improvement, is "unintended physical injury resulting from or contributed to by medical care (including the absence of indicated medical treatment), that requires additional monitoring, treatment, or hospitalization, or that results in death." Most errors in healthcare do not lead to harm; harm may be both preventable and nonpreventable (Fig. 5.1). A physician may erroneously fail to add a decimal point in a medication order for an aminoglycoside antibiotic, ordering a dose of 25 mg/kg rather than the intended dose of 2.5 mg/kg. If this error is caught by the computerized order entry system or the pharmacist, this would be an error with no resultant harm. If this error was not caught and reached the patient, who suffered acute kidney injury, this would be *preventable* harm since evidence shows that pharmacist review can reduce the risk of these errors 10-fold. Alternatively, if a patient received a first lifetime dose of amoxicillin and had anaphylaxis requiring hospital admission, this harm would be considered *nonpreventable* since no valid predictive tests are available for antibiotic allergy. Furthermore, the concept of **latent risk**, independent of any actual error, is inherent in any system where patients can be harmed. Among errors that do not lead to harm, **near misses** that do not reach patients—or high-risk situations that do not lead to harm because of good fortune or mitigation—are important learning opportunities about safety threats.

Several classification systems exist to rate harm severity, including the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) Index for medication-related harm and the severity scales for all-cause harm. **Serious safety events (SSEs)** are deviations from expected practice followed by death or severe harm. The SPS collaborative has SSE elimination as its primary goal. **Sentinel events** or **never events**, such as a wrong-site surgery, are also targets of external reporting and for elimination through quality improvement (QI) initiatives (see Chapter 4). Increasingly, health systems are using a *composite serious harm index,* which combines a variety of preventable HACs (e.g., CLA-BSIs) to examine system safety performance over time across various patient populations and sites of care.

SAFETY FRAMEWORKS

Safety frameworks are conceptual models and tools to help clinicians, improvers, and researchers understand the myriad contributors to safe healthcare and safety events. Healthcare is delivered in a complex system with many care providers and technologies, such as electronic health records and continuous physiologic monitors. The Donabedian framework, which links structure, process, and outcome, can be a very useful tool. The **Systems Engineering Initiative for Patient Safety (SEIPS)** model, developed by human factors engineers, cognitive psychologists, and physicians, provides more detailed tools to understand the work system and the complex interactions between people (including the patient and family) and task work and technology and the environment. The SEIPS 3.0 model uses the concept of the "patient journey" to describe a patient's interactions with multiple complex and separate care settings over time. Other available safety frameworks include those from the Institute for Healthcare Improvement. The "Swiss cheese" model illustrates how multiple components of an organization's defenses prevent failures from leading to harm, but harm may occur when multiple defenses fail at the same time (Fig. 5.2).

Traditionally, safety science and improvement have focused on identifying *what went wrong* (near misses, errors, and harm) and then tried to understand and improve the system of care that led to these events (Safety-I framework). There is increasing focus on *what goes right*. This framework, called *Safety-II,* brings focus on the much greater number of things that go right and how people act every day to create safety in complex and unpredictable systems. Safety-II seeks to learn from people, the greatest source of system resilience, particularly in the midst of high levels of risk and stress, as often seen in healthcare.

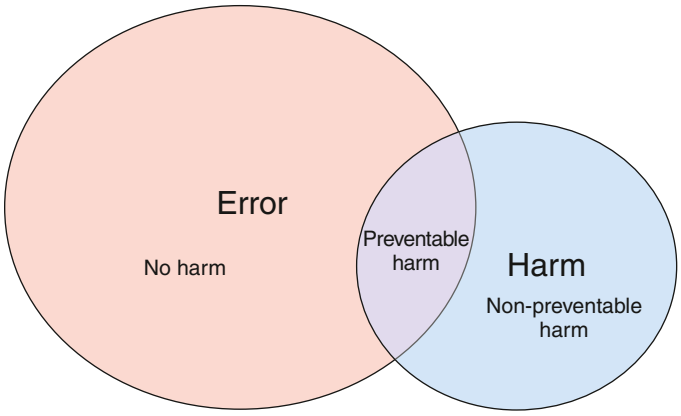

Fig. 5.1 Overlap between error and harm.

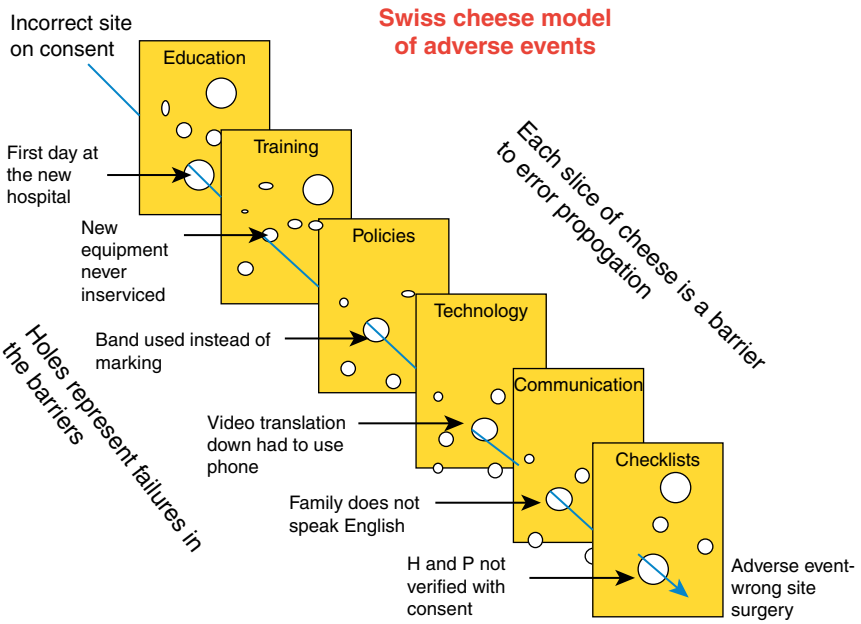

Fig. 5.2 The Swiss cheese model of adverse events. (*From Stein JE, Heiss K. The Swiss cheese model of adverse event occurrence—Closing the holes.* Semin Pediatr Surg. *2015;24[6]:278–282.)*

IDENTIFYING AND ANALYZING HARM, ERRORS, AND LATENT THREATS

Health systems use a toolbox of processes to discover, understand, and mitigate unsafe conditions.

Incident Reporting Systems

Many health systems and hospitals offer employees access to a system to report errors, harms, or near misses. Most frequently, these are anonymous so that healthcare workers feel safe to submit an event in which they may have been involved or when the harm involved someone in a position of authority. Ideally, these systems facilitate smooth and efficient entry of enough information for further review but avoid excessive burden of time or cognitive load on the reporter. **Incident reporting** systems likely work best in the presence of a strong safety culture and when employees have some confidence that the event will be reviewed and actions taken. The chief limitation of incident reporting systems is that incident reports dramatically *underreport* safety events. Thus other mechanisms must also be in place to learn about safety. **Trigger tool** systems use *triggers,* such as the need for an antidote to an opioid overdose or the transfer of a patient to higher-level care, to facilitate targeted medical record review by trained nurses and physicians to elucidate any errors or system risks.

Simulation

Simulation is an excellent tool to better understand system and latent threats. *High-fidelity simulation,* which involves the use of a manikin that can reproduce or mimic human anatomy and physiology, can allow clinicians to practice technical skills such as intubation in a safe environment. Perhaps more importantly, simulation can help clinical teams improve nontechnical skills such as using closed-loop communication and sharing a mental model (e.g., a team leader states, "I believe this patient has septic shock. We are rapidly infusing fluids and giving antibiotics. Blood pressure is normal for age. What other thoughts does the team have?"). It is often easier and more feasible to give feedback in a simulated scenario versus a real event.

Low-fidelity simulation does not require costly simulated patients and may have advantages in identifying latent threats in the hospital or clinic. For example, a simulated scenario on a medical-surgical unit might identify that nurses do not know where to find a mask for continuous positive airway pressure (CPAP) to support an infant with respiratory failure. Identifying—and then mitigating—this latent threat in a simulated environment is preferable to doing so in an acutely deteriorating child.

Event Analysis

Several types of event analysis, including root cause analysis, apparent cause analysis, and common cause analysis, can help teams understand—and later mitigate—the causes of adverse events. Each model has its own strengths and weaknesses. **Root cause analysis (RCA)** is a robust and time-intensive process to ascertain the most fundamental, or *root*, causes of a safety event. The Joint Commission requires the use of RCA on sentinel events. Most health systems reserve this methodology primarily for sentinel events, because RCAs can take months to complete and require convening a multidisciplinary team of experts. The safety event and its antecedents are reviewed in detail with a focus not on human behavior, but instead on systems, hazards, and latent errors. The RCA team works to go beyond the event (e.g., enteral formula feeds connected to and administered through a central line) to the proximal causes (e.g., "feeding tube and intravenous tubing are visually identical and are easily attached") and root cause (e.g., "organization lacks a system to assess human factors risks as new equipment is procured and put into practice"). When root causes are identified and tied to robust improvement action plans, safety can be substantially improved (e.g., "we will design feeding tubing and intravenous tubing to be distinct and incompatible"). In addition to the time-intensive nature of RCAs, *hindsight bias* is a risk and needs to be managed carefully by the team. Additional challenges with RCAs include the potential to *overfit solutions*—designing protocols or procedures that may have reduced the risk of the specific safety event reviewed but also introduce new problems and increase the probability of other safety threats—as well as difficulties in spreading solutions to different care areas that often have different needs, processes, and goals.

Apparent cause analysis, common cause analysis, and failure modes and effects analysis are complementary learning methods. **Apparent cause analysis** is performed by a smaller multidisciplinary team to look primarily for proximal causes, making it feasible for events that occur often (e.g., the wrong medication is sent from the pharmacy). Importantly, in each analysis the team works to determine how likely it is that such an event will occur in the

future and how widespread the proximate causes are in the microsystem. **Common cause analysis** seeks to aggregate learning across multiple events. A similar common cause, such as poor handoff procedures, may lead to different safety events (e.g., a missed laboratory check and a delayed diagnosis); common cause analysis aids leaders in determining this. **Failure mode and effects analysis (FMEA)** is a powerful tool that clinicians use to describe a process and identify *failure modes,* or ways in which each step might fail. A more robust and quantitative form of FMEA rates potential failure modes in three categories: probability of event occurring, its severity, and its ability to be detected. The product of these, called the *risk priority number,* can help a team identify which failure modes may lead to the greatest harm and thus which to target first.

SAFETY CULTURE

A broad and supportive safety culture likely drives both patient and employee safety outcomes. An organization with a mature safety culture fosters a culture of learning and treats errors as opportunities to improve the system, rather than as the personal failures of individual clinicians. *Just culture* differentiates the mistakes and wrong decisions that a clinician makes commensurate with their training and experience from willful violations and gross or repeated patterns of negligence. A safety culture prioritizes clear and consistent communication and teamwork and aims to ease authority gradients (described later). Several tools are available to measure safety culture, including the Safety Attitudes Questionnaire and the Agency for Healthcare Research and Quality (AHRQ) surveys on Patient Safety Culture. A strong safety culture supports transfer of responsibility within disciplines at handoffs and across disciplines (e.g., when a nurse is calling a physician with a new concern). Structured communication tools such as the **Situation-Background-Assessment-Recommendation** (SBAR) approach are valued in a safety culture, as are safety behaviors such as "repeat back or write back," when a critical laboratory result is shared and repeated back by the receiving clinician.

Authority gradients are quite real in healthcare. In a culture of safety, both junior and senior clinicians work together across disciplines to speak up when concerns are identified, to ask questions, and not to proceed if there is uncertainty about safe patient care. Health system leaders have a critical role in supporting this culture, orienting new employees to its importance, and stepping in if authority gradients or disruptive behaviors contribute to safety events or unsafe conditions. To address the adverse impact of the healthcare hierarchy on providing safe care, recent efforts have focused on *psychologic safety.* Psychologic safety is defined as the ability to raise concerns and ask questions without the fear of negative consequences for self-image, status, or career. This concept is critical for multiple aspects of safety culture, including establishing a shared mental model, event reviews and debriefs, addressing professionalism concerns, and effectively partnering with patients and families to pursue safety goals.

RELIABILITY SCIENCE, HUMAN FACTORS ENGINEERING, AND HIGH-RELIABILITY ORGANIZATIONS

Reliability in healthcare is defined as the measurable capability of a process, procedure, or health service to perform its intended function in the required time under commonly occurring conditions. Most processes in healthcare organizations currently perform at **Level 1** reliability, meaning a success rate of only 80–90%. To achieve **Level 2** performance (≤5 failures/100 opportunities), processes must be *intentionally designed* with tools and concepts based on the principles of **human factors engineering** and **reliability science**. These processes include creating intentional redundancy, such as independent verification on high-risk medication dosing, and making the default action the desired action based on evidence, such as a default to an influenza vaccination for high-risk patients with asthma. Performance at **Level 3** (≤5 failures/1,000 opportunities) requires a well-designed system with low variation and cooperative relationships and a state of "mindfulness," with attention to processes, structure, and their relationship to outcomes.

Healthcare can learn important safety lessons from disciplines such as human factors engineering and cognitive psychology. Industries that better leverage learnings from these disciplines—and robustly identify and mitigate threats and use simulation—include commercial aviation and nuclear power, termed *high-reliability organizations*. These organizations achieve exemplary safety records under dynamic and high-risk conditions through consistent application of five tenets: (1) a preoccupation with failure—surprises and errors are thought of as learning opportunities, and learnings spread quickly through the organization, (2) reluctance to simplify interpretations—serious safety events receive an RCA, (3) sensitivity to operations—proactive assessments and huddles target risks to patients and the organization, (4) a commitment to resilience—errors do not disable, and high-risk, uncommon scenarios are negotiated, and (5) deference to expertise—leaders defer to frontline experts when their knowledge is required.

SERIOUS HARM EVENTS AND HEALTHCARE-ASSOCIATED CONDITIONS

Substantial improvement in patient safety has occurred through improvement teams targeting *serious harm* events. The **serious harm event rate** is a composite metric that groups preventable HACs into one number (usually a rate per at-risk patient-days), so that an organization or collaborative can track progress on a variety of conditions with one metric and chart. Table 5.1 lists frequently targeted HACs. Commonalities among successful improvement teams targeting these HACs include multidisciplinary team membership, clear outcome definitions and measurement, learning systems around each HAC, and attention to both process and outcome measures. Many of the successes with CLA-BSIs were associated with targeted improvements to reliably adhere to a line insertion bundle and a line maintenance bundle. Figure 5.3 illustrates coincident improvements in process measures and outcomes measure in a hypothetical CLA-BSI project. In this case, after improvement interventions targeted two process measures known to be important in CLA-BSI risk—the line insertion and the line maintenance bundles—the QI team saw improvement in both measures and coincident reduction in CLA-BSIs.

A safety culture and experienced improvement teams are consistent drivers of success. A **learning network model**, as used in SPS, is effective in bringing project teams together from different hospitals to discuss lessons learned and common barriers faced and negotiated.

SAFETY OPPORTUNITIES AND GAPS

In addition to HACs, several other safety events are the targets of active study and improvement. Unrecognized clinical deterioration in hospitalized children, diagnostic error, poor handoffs across multiple stakeholders, and alarm/alert fatigue lead to substantial and preventable harm. There are also important considerations for improving safety in unique sites of care, including the surgical and ambulatory environments. Additionally, it is increasingly clear that patient safety improvements might be limited if the field does not also target improved occupational safety of those who provide care.

Clinical Deterioration

The deterioration of hospitalized patients is rarely a sudden and unpredictable event; rather, it is often preceded by abnormal vital signs and concerns from patients, families, and clinicians. **Rapid response systems** are designed to detect deterioration and then deploy teams with critical care expertise to provide treatment or escalate care to an intensive care unit (ICU). Although variation remains in how these teams

Table 5.1 Common Healthcare-Associated Conditions (HACs) Targeted in Quality Improvement Efforts with Interventions

HAC	DEFINITION	COST PER EVENT	POTENTIALLY EFFECTIVE INTERVENTIONS
Central line–associated bloodstream infections	Laboratory-confirmed bloodstream infection with central line in place at time of or 48 hr before onset of event (details at https://www.cdc.gov/nhsn)	$55,646	Line insurance bundle (e.g., handwashing, chlorhexidine scrub), maintenance bundle (catheter care, change dressing, discuss daily if catheter is needed)
Catheter-associated urinary tract infections	Urinary tract infection where an indwelling urinary catheter was in place >2 days on day of event (details at https://www.cdc.gov/nhsn)	$7,200	Protocols for reviewing and removing catheters daily, clear indications for inserting catheters, physician champions, audit and feedback of data
Adverse drug events	Harm associated with any dose of a drug (details at http://www.nccmerp.org/types-medication-errors)	$3,659	Pharmacist review of medication order, computerized physician order entry, co-ordering of laxatives in patients on opiates
Peripheral IV infiltrates	Moderate or serious harm (e.g., diminished pulses, >30% swelling) associated with a peripheral IV infiltrate (details at http://www.solutionsforpatientsafety.org)	—	Hourly reviews of IV status, limitations on use of desiccants through peripheral IVs, remove IVs when no longer needed
Pressure injuries	Localized damage to skin and/or underlying soft tissue usually over a bony prominence or related to a device (details at http://www.solutionsforpatientsafety.org)	—	Screening of high-risk patients (e.g., Braden Q Scale), regular turning of low-mobility patients, regular inspection and skin care; specialized device padding
Surgical site infections	Infection of incision or deep tissue space after operative procedure (details at https://www.cdc.gov/nhsn)	—	Surgical checklist, antimicrobial prophylaxis within 60 min before incision, preoperative baths, postoperative antibiotic redosing
Venous thromboembolism	Blood clot in deep vein, stratified as central line–associated vs not (details at https://www.cdc.gov/nhsn)	$27,686	Screening for high-risk patients, removal of central line catheters when no longer needed, targeted prophylaxis

are activated and staffed, all U.S. children's hospitals have some version of a rapid response system. The initiation of rapid response teams is associated with a significant reduction in codes outside the ICU and in-hospital mortality.

Pediatric early warning scores (PEWS) are used in many large children's hospitals to identify deteriorating patients by assigning scores based on the degree of abnormalities in different body systems. Different versions of PEWS are often employed, but all include scores driven by age-based vital signs and nursing assessments in areas such as mental status and perfusion. Importantly, PEWS take these diverse exam elements and combine them into a single score, which when coupled with clear, expected actions (e.g., evaluation by physician at score of 5, evaluation by rapid response team at score of 7) may better detect deterioration and improve safety outcomes.

PEWS are one method of improving a clinician's *situation awareness*—the sense of what is going on around the clinician, the notion of what is important, and the anticipation of future consequences. Maintaining situation awareness can be challenging in dynamic, high-risk environments such as healthcare. Work at several children's hospitals to improve situation awareness has been associated with sustained and significant reductions in unrecognized clinical deterioration. This improvement work first designed systematic and proactive identification of *watcher* patients, or those a nurse, physician, or patient family felt were close to the edge of deterioration. These high-risk patients are discussed at multidisciplinary bedside "huddles," and specific treatment plans and predictions are outlined. Concerns are more fully addressed through the rapid response team and at hospital-wide safety huddles and safety rounds. To gain a better sense of organization safety and performance threats, many hospitals in the SPS collaborative employ a daily safety or operations brief, where leaders from a variety of service lines (e.g., inpatient, pharmacy, perioperative care) can discuss unexpected events and rapidly develop solutions and follow-up plans to mitigate emerging threats that cross disciplines. Event debriefs and reviews are particularly relevant for instances of clinical deterioration. They serve multiple purposes, including the emotional processing of an event, a discussion of the process of care and team performance, and the development of action plans to improve care in the future. The Pediatric Resuscitation Quality Collaborative (pediRES-Q: https://www.pedires-q.org/) classifies debriefs into two types: (1) "hot" debriefs, which occur minutes to hours after the event and allow for emotional processing and educational discussion, and (2) "cold" debriefs, which occur days to weeks after the event and allow for a comprehensive, multidisciplinary review of all data and feedback. Current research and improvement efforts in this area are focused on developing successful frameworks to guide discussions and action plan development, such as formal processes for classifying and reviewing cardiac arrest events in the pediatric ICU.

Cardiopulmonary arrest rates outside of the ICU are useful metrics to evaluate the performance of rapid response systems in adult patients. Given that these events are quite rare in pediatrics, and increasingly so since the implementation of rapid response systems, the identification of valid, more frequent proximal metrics is a focus of research efforts. Table 5.2 describes proximal metrics to arrest and the types of code events used to identify risk factors for unrecognized deterioration and evaluate rapid response system effectiveness in pediatrics.

Diagnostic Error

Diagnostic error is recognized as an increasingly common and impactful event, with 10–15% of diagnoses estimated to be incorrect. There are two systems of clinical decision-making. **System 1** is fast, instinctual, and largely unconscious. **System 2** is slow, effortful, cognitive, and calculating. System 1 and its *heuristics* or *biases* allow for quick—almost automatic—decision-making, often by associating new information with existing patterns or beliefs (e.g., that red object on the right side of the road is a stop sign; I should stop). However, system 1 thinking can be dangerous in diagnosis, particularly when new data are unconsciously made to fit the preconceived pattern and

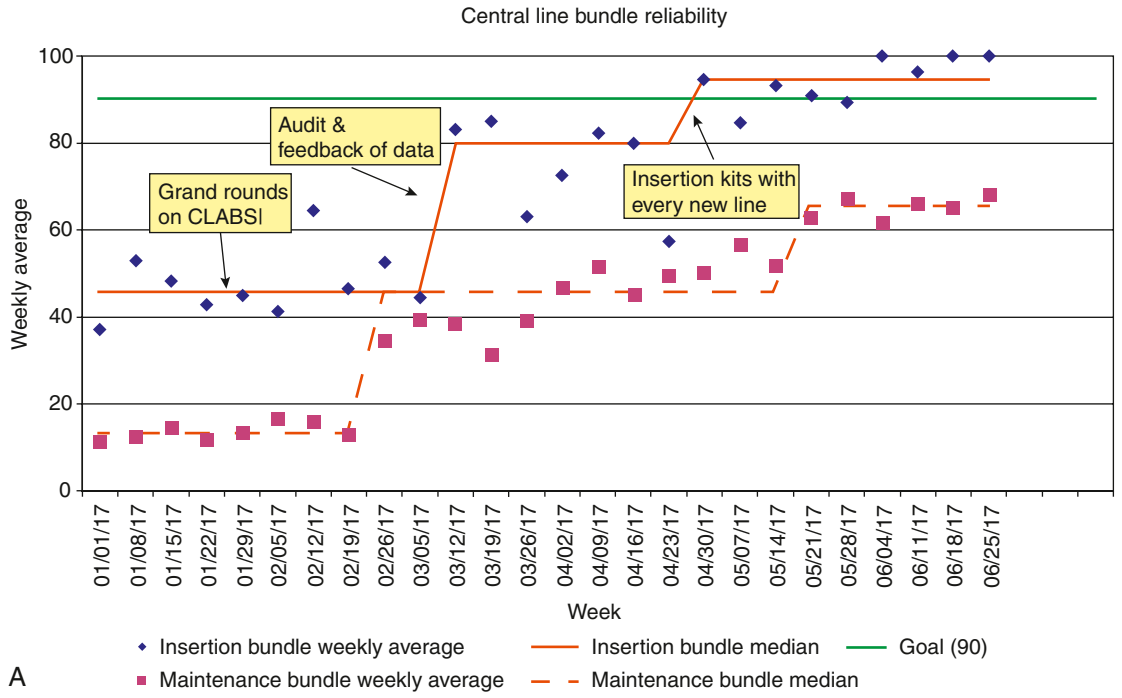

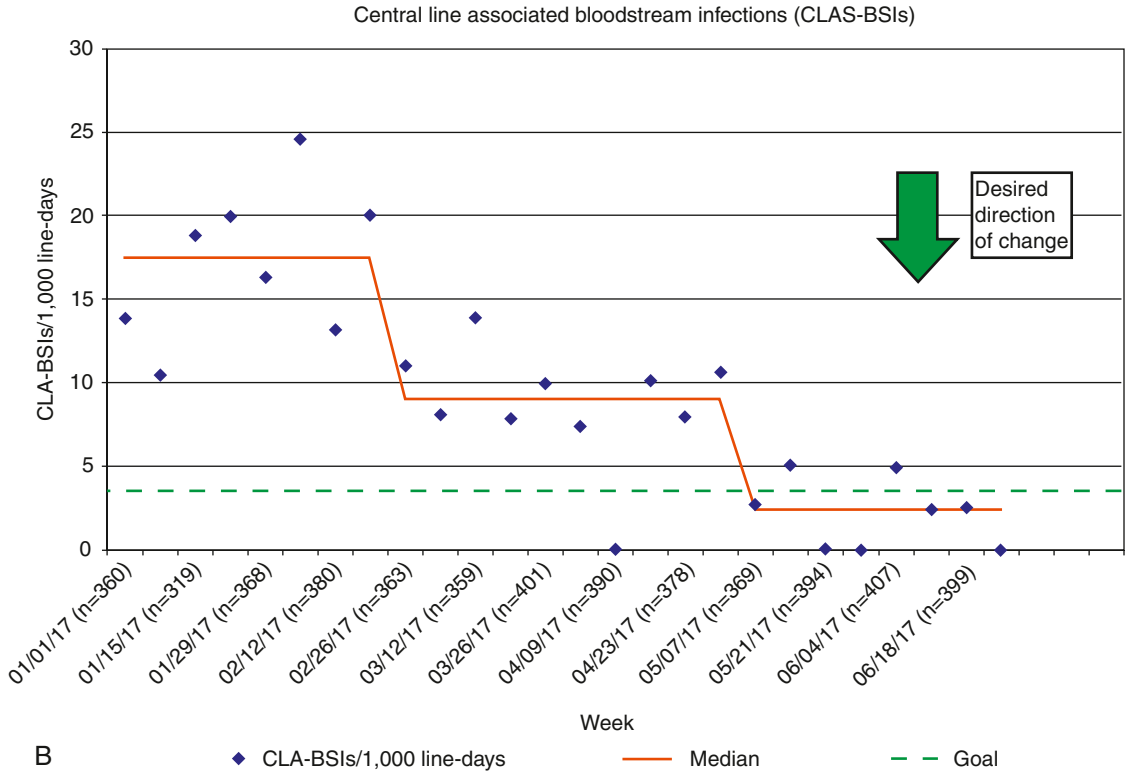

Fig. 5.3 Quality improvement interventions targeted process improvement in the **A,** line insertion bundle, where performance improved from 46% to 95%, and **B,** line maintenance bundle, where performance improved from 13% to 66%. Coincident with the improved bundle performance, the rate of CLA-BSIs fell from 17.6 to 2.5 per 1,000 line-days.

are not seen as disconfirming. Research in this area aims to better understand how well-described cognitive biases (e.g., premature closure, availability bias) play out in clinical care and what system-based strategies can mitigate their effects (Tables 5.3 to 5.5). There are ongoing efforts to move clinicians from system 1 to system 2 thinking, such as being explicit on uncertainty (e.g., patients admitted from the emergency department [ED] as "uncertain diagnosis") or using decision aids to prompt revisiting provisional diagnoses such as the diagnostic time-out or team-based (collective intelligence) thinking (Tables 5.6 and 5.7). Safety culture is critical to both the open acknowledgment of diagnostic uncertainty and the willingness to discuss and learn from diagnostic error when it occurs.

The 2015 National Academy of Medicine (NAM) report entitled *Improving Diagnosis in Health Care* emphasized the centrality of

Table 5.2 Metrics to Identify Risk Factors for Unrecognized Deterioration Outside of the ICU and Evaluate Rapid Response System Performance

METRIC	REFERENCE	DEFINITION	STRENGTHS	LIMITATIONS
Unplanned ICU transfer	Baker 2009 Reese 2015	All patients unexpectedly admitted to the ICU from a lower level of care in the hospital Transfer to the ICU from the inpatient ward that was not expected or previously coordinated (such as a planned ICU admission postoperatively)	More common than code events and other proximal metrics to arrest High sensitivity for unrecognized deterioration	Low specificity for unrecognized deterioration Often requires time-intensive manual review of ICU transfers Site-specific parameters, including definition adjustments, and the acuity of patients cared for outside of the ICU
Critical deterioration event	Bonafide 2012	Noninvasive ventilation, intubation, or vasopressor initiation within 12 hr after ICU transfer	More common than emergency transfers and code events High sensitivity for unrecognized deterioration Increased specificity as compared with unplanned ICU transfers Objective criteria facilitating use in multicenter studies and collaboratives	Less specific than emergency transfers; may include patients with promptly recognized deterioration Often requires time-intensive manual review of ICU transfers
Emergency transfer	Brady 2013	Intubation, inotropic support, or 3 or more fluid boluses in the first hour after arrival or before ICU transfer	More common than code events High specificity for unrecognized deterioration Objective criteria facilitating use in multicenter studies and collaboratives Feasible to track in near-real time	Less common than critical deterioration events and unplanned ICU transfers
Significant clinical deterioration event	Parshuram 2018	Death, cardiopulmonary resuscitation, tracheal intubation, vasoactive medications, or ≥60 mL/kg fluid boluses in the 12 hr before transfer, or death, cardiopulmonary resuscitation, tracheal intubation, or ECMO initiation within 1 hr after ICU transfer	More common than code events Objective criteria facilitating use in multicenter studies and collaboratives	Complex definition not inclusive of all interventions and outcomes associated with acute deterioration events Often requires time-intensive manual review of ICU transfers
Code event: Cardiopulmonary arrests (CPAs)	Children's Hospital Association	Pulselessness or pulse with inadequate perfusion necessitating chest compressions and/or electric shock	High specificity for unrecognized deterioration Objective criteria facilitating use in multicenter studies and collaboratives Feasible to track in near-real time	Less common than proximal metrics to arrest Low sensitivity for inadequately recognized, subacute cases of deterioration
Code event: Acute respiratory compromise (ARC)	Children's Hospital Association	Respiratory insufficiency with bag-valve mask or invasive airway interventions, followed by a transfer to a higher level of care for sustained airway support	High specificity for unrecognized deterioration Objective criteria facilitating use in multicenter studies and collaboratives Feasible to track in near-real time	Less common than proximal metrics to arrest Low sensitivity for inadequately recognized, subacute cases of deterioration Not inclusive of all nonrespiratory etiologies of deterioration

communication to patients and families in the diagnostic process while introducing a diagnostic process model with several important outcomes (Fig. 5.4). The diagnostic process occurs with iterative cycles of information gathering, its integration and interpretation, and the formulation of a working diagnosis. The NAM report brought particular emphasis to the diagnostic team, which includes doctors and nurses in different practice contexts (e.g., the ED and primary care), as well as pharmacists, respiratory therapists, patients, and families. Strategies that aim to leverage the diagnostic team, as opposed to simply the cognition of busy individuals, may be particularly well poised to improved patient-level and system-diagnostic outcomes.

Handoffs/I-PASS

There is a growing evidence base on the consequences of poor handoffs and on complex interventions to improve handoffs and resultant safety outcomes. The best-studied handoff is resident-to-resident shift handoff in teaching hospitals. Use of the **I-PASS** mnemonic—*i*llness severity, *p*atient summary, *a*ction list, *s*ituation awareness and contingency planning, and *s*ynthesis by receiver—and the surrounding educational quality improvement curriculum was associated with a significant 23% reduction in medical errors and 30% reduction in adverse events in a nine-hospital study. Related work has described improved communication by targeting ICU-to-floor, operating room–to–ICU, and inpatient medical team–to–primary care handoffs.

Alarm/Alert Fatigue

Alarm fatigue, when a healthcare provider is subject to so many interruptions that a potentially relevant alarm is not heard, is also an area of active research and improvement. In the hospital, many physiologic monitor alarms occur each day (up to 400 per patient

Table 5.3 Cognitive Biases Related to Heuristic Failure

BIASES	DEFINITION
Anchoring	Locking into a diagnosis based on initial presenting features, failing to adjust diagnostic impressions when new information becomes available
Confirmation bias	Looking for and accepting only evidence that confirms a diagnostic impression, rejecting or not seeking contradictory evidence
Diagnostic momentum	Perpetuating a diagnostic label over time, usually by multiple providers both within and across healthcare systems, despite the label being incomplete or inaccurate
Expertise bias/yin-yang out	Believing that a patient who has already undergone an extensive evaluation will have nothing more to gain from further investigations, despite the possibility that the disease process or diagnostic techniques may have evolved so as to allow for appropriate diagnosis
Overconfidence bias	Believing one knows more than one does, acting on incomplete information or hunches, and prioritizing opinion or authority, as opposed to evidence
Premature closure	Accepting the first plausible diagnosis before obtaining confirmatory evidence or considering all available evidence: "When the diagnosis is made, thinking stops"
Unpacking principle	Failing to explore primary evidence or data in its entirety and subsequently failing to uncover important facts or findings, such as accepting a biopsy report or imaging study report without reviewing the actual specimen or image; especially important in undiagnosed and rare diseases

From Bordini BJ, Stephany A, Kliegman R. Overcoming diagnostic errors in medical practice. *J Pediatr.* 2017;185:19–25, Table I.

Table 5.4 Cognitive Biases Related to Errors of Attribution

BIASES	DEFINITION
Affective bias	Allowing emotions to interfere with a diagnosis, either positively or negatively; dislikes of patient types ("frequent flyers").
Appeal to authority	Deferring to authoritative recommendations from senior, supervising, or "expert" clinicians, independent of the evidentiary support for such recommendations.
Ascertainment bias	Maintaining preconceived expectations based on patient or disease stereotypes.
Attribution error	Placing undue importance on the perceived internal characteristics or motivations of others, whether they are the patient, the patient's family, or other members of the evaluation team.
Countertransference	Being influenced by positive or negative subjective feelings toward a specific patient.
Outcome bias	Minimizing or overemphasizing the significance of a finding or result, often based on subjective feelings about a patient, a desired outcome, or personal confidence in one's own clinical skills. The use of "slightly" to describe abnormal results.
Psych-out bias	Maintaining biases about people with presumed mental illness.

From Bordini BJ, Stephany A, Kliegman R. Overcoming diagnostic errors in medical practice. *J Pediatr.* 2017;185:19–25, Table II.

Table 5.5 Cognitive Biases Related to Errors of Context

BIASES	DEFINITION
Availability bias	Basing decisions on the most recent patient with similar symptoms, preferentially recalling recent and more common diseases.
Base-rate neglect	Prioritizing specific information (e.g., a laboratory value) pertaining to a case while ignoring general base rate information about the prevalence of disease in populations (pretest probability).
Framing effect	Being influenced by how or by whom a problem is described or by the context in which the evaluation takes place.
Frequency bias	Believing that common things happen commonly and usually are benign in general practice.
Hindsight bias	Reinforcing diagnostic errors once a diagnosis is discovered despite these errors. May lead to a clinician overestimating the efficacy of his or her clinical reasoning and may reinforce ineffective techniques.
Posterior probability error	Considering the likelihood of a particular diagnosis in light of a patient's chronic illness. New headaches in a patient with a history of migraines may in fact be a tumor.
Representative bias	Basing decisions on an expected typical presentation. Not effective for atypical presentations. Overemphasis on disease-diagnostic criteria or "classic" presentations. "Looks like a duck, quacks like a duck."
Sutton's slip	Ignoring alternative explanations for "obvious" diagnoses (Sutton's law is that one should first consider the obvious).
Thinking in silo	Restricting diagnostic considerations to a particular specialty or organ system. Each discipline has a set of diseases within its comfort zone, which reduces diagnostic flexibility or team-based communication.
Zebra retreat	Lacking conviction to pursue rare disorders even when suggested by evidence.

From Bordini BJ, Stephany A, Kliegman R. Overcoming diagnostic errors in medical practice. *J Pediatr.* 2017;185:19–25, Table III.

in some environments), and nurses exposed to a high volume of alarms respond more slowly to them. Interventions currently being studied include removing monitors from patients unlikely to benefit from them, designing smart alarms that alert only when certain scenarios occur (e.g., bradycardia in the context of hypoxia), and using advanced communication technology to safely escalate true alarms while ignoring nonactionable alarms. **Alert fatigue** is related to alarm fatigue but refers to clinicians not processing an alert, such as a medication interaction from the electronic health record, when receiving a large burden of alerts often regarded as nonactionable.

Table 5.6 Diagnostic Time-Out

- Identify the clinical issues, dilemmas, or concerns needing a time-out.
- Remove all previous diagnoses and reexamine all laboratory studies, imaging, and other information, including the history and physical exam.
- Did we consider the risks of heuristic (intuitive) thinking?
- Do we have biases?
- What are the diseases we must not miss?

From Bordini BJ, Basel D. Disease mimics: An approach to undiagnosed diseases. In: Kliegman RM, Toth H, Bordini BJ, Basel D. (eds). *Nelson Pediatric Symptom-Based Diagnosis*. 2nd ed. Philadelphia: Elsevier; 2023: Table 1.6.

Surgical Safety

Initially, in response to the problem of wrong-patient or wrong-site surgeries, perioperative leaders developed a set of safety strategies often termed the *tenets of surgical safety,* which are endorsed by the World Health Organization (https://www.who.int/patientsafety/safesurgery/en/). The tenets are implemented as several discrete checklists at key points, or "time-outs," in the workflow around a procedure or surgery. Several studies have demonstrated reduced harm to patients, and surgical checklists are adopted widely throughout surgical and procedural environments. Typically, checklists are used at three key times during a procedure: before induction of anesthesia, before skin incision or insertion of a device into any body cavity or orifice, and before a patient leaves the procedural area or operating room. Key aspects of the impact of this approach include multidisciplinary active participation, visual display of the checklist or other key tools as references, and attention to hierarchies and team-based communication. An evolving area of surgical and procedural safety is the use of simulation and video-based procedure review to improve surgical technique and perioperative team function and to identify latent threats.

Ambulatory Safety

Adverse drug events and medication dosing errors are the best-studied safety events in the outpatient environment. A study of children receiving chemotherapy used direct observation by a trained nurse at home and found approximately 70 errors per 100 patients, many of which were serious or significant. Families often make dosing errors

Table 5.7 Solutions to Avoid Diagnostic Errors

1. Enhancing foundational knowledge in medical education
   - Teach symptoms and their differential pathophysiology, not just diseases.
   - Emphasize red flags and must-not-miss diagnoses.
2. Minimizing errors related to heuristic failure
   - Build understanding of system 1 and system 2 thought processes and the risks of heuristic failure.
   - Actively model and encourage counterfactual reasoning and hypothesis generation to enhance system 2 skills.
3. Mitigating errors of attribution
   - Increase awareness of biases toward specific patients by promoting self-reflection.
   - Use a team-based approach and diagnostic strategies that actively dispel biases.
4. Avoiding errors of context
   - Solicit input across a variety of specialties when appropriate.
   - Consciously acknowledge the risk of thinking in silo and actively seek explanations outside of one's specialty.
5. Optimizing data gathering, analysis, and hypothesis generation
   - Develop differential diagnoses based on pathophysiology; consider alternatives and competing options.
   - Realize that diagnostic criteria for certain diseases do not account for atypical disease manifestations.
   - Rely on objective individual data, not just disease prevalence rates, when considering the pretest likelihood of a particular diagnosis.
   - Avoid diagnostic momentum and question-accumulated diagnostic labels, regardless of who applied the label.
6. Improving hypothesis testing
   - Know the limitations of laboratory tests (i.e., false positives and negatives).
   - Do not be so quick to "rule out" a diagnosis: consider the posttest likelihood of a disease in terms of a probabilistic analysis that applies specifically to the patient.
   - Acknowledge that the initial "working" diagnosis may not always be the final diagnosis.
   - Rely on evidence-based data and avoid authority- or overconfidence-based errors.
   - Recognize that a diagnosis is an iterative and interactive process that should not be bounded by premature closure or anchoring. Be open to both confirmatory and nonconfirmatory data.
   - Both know and accept what you do not know.
7. Critical solutions for complex and undiagnosed and rare-disease patients
   - Maintain healthy skepticism, especially with patients who come prediagnosed.
   - Analyze historical diagnostic data methodically and thoroughly and unpack all data completely. Examine actual studies, such as tissue specimens and imaging investigations, and do not rely on written reports.
   - Question the working diagnosis when findings or the clinical course does not fit.
   - Realize that patients can have more than one disease process.
   - Incorporate all data and avoid minimizing the significance of abnormal results. Do not ignore contradictory clinical, laboratory, or imaging data.
   - Never say "never" or "it cannot be."
   - Use a systematic team-based approach to enhance debiasing, broaden the collective knowledge base, and minimize context-related errors.
   - Be aware that patients with undiagnosed and rare diseases may have an atypical or rare manifestation of a recognizable common disease or may have a rare disease.
   - Use extensive literature review and search strategies based on the patient's phenotype and individual findings and hypotheses.

From Bordini BJ, Stephany A, Kliegman R. Overcoming diagnostic errors in medical practice. *J Pediatr*. 2017;185:19–25, Table V.

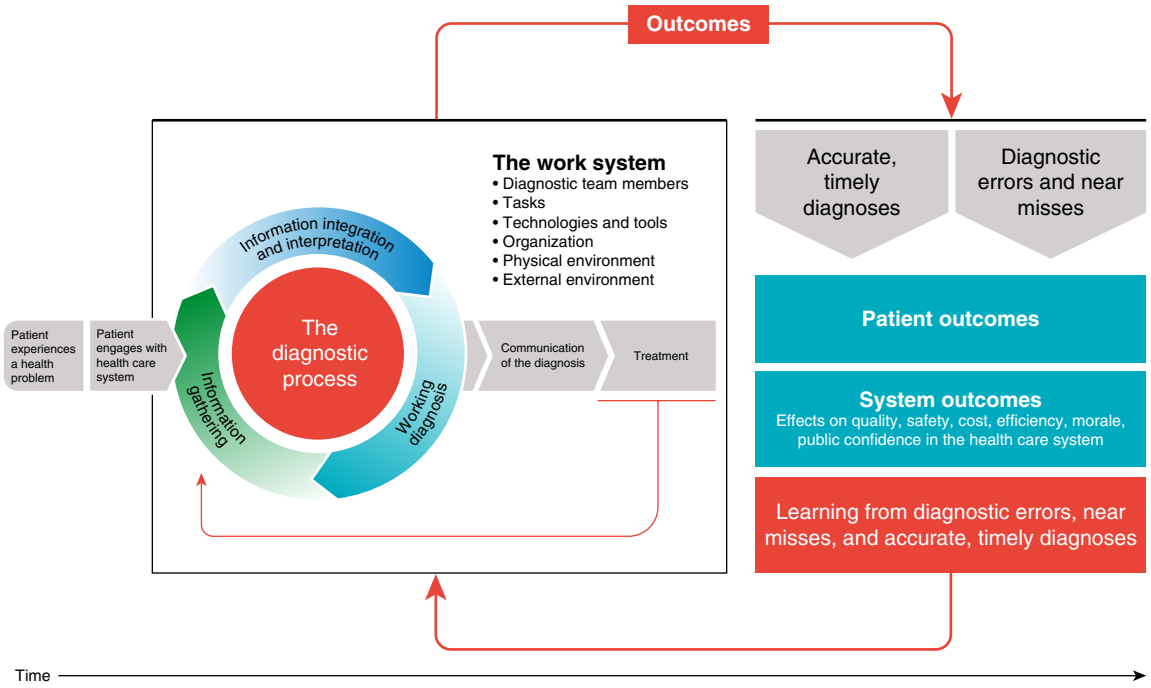

Fig. 5.4 Outcomes from the diagnostic process. (*From National Academies of Sciences, Engineering, and Medicine. 2015. Improving Diagnosis in Health Care https://doi.org/10.17226/21794.*)

in administering liquid medications, particularly when using kitchen spoons rather than dosing syringes. A health literacy–informed pictogram reduces the rates of these errors Additional ambulatory safety threats include delays in diagnosis or treatment caused by mishandling of laboratory or imaging results and failures in care coordination.

Occupational Safety

The provision of healthcare can be a dangerous profession, with injury rates that surpass those of coal miners. The magnitude of this challenge and efforts to improve workplace safety have gained considerable attention over the past several years. Nurses and physicians still typically view a needlestick injury or back strain from lifting a patient as simply "part of the job." A culture of safety should include employee safety, and health systems should have mechanisms for employees to report injuries, near misses, and threats. Focused improvement efforts might include the roll-out of safer needle systems, education on safe processes, and easy access to lifts for larger children with limited mobility. Violence and patient interaction injuries, often from children with psychiatric disease or developmental disabilities, are a growing source of harm to clinicians. Education for clinicians on de-escalation techniques, behavioral specialist engagement in bedside care, and implementation of standardized behavior response teams are active areas of improvement and study as we consider how to best support patients with behavioral needs admitted to the medical unit.

EMERGING AREAS OF SAFETY RESEARCH AND IMPROVEMENT

Safe and Equitable Care

The authors of *Crossing the Quality Chasm* stated that healthcare should target 6 aims for improvement: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity. These aims are not independent, and we are just beginning to critically examine the relationship between safety and equity. Existing evidence suggests that there are disparities in safety for several groups of pediatric patients, including Black and Latino children, for children whose families do not primarily speak English, and for children on public insurance. In pediatric surgery, one study found that Black children had over three times the odds of dying in the postoperative period, nearly 20% relative greater odds of postoperative complications, and 7% relative higher odds of developing serious adverse events as compared to White children, even while controlling for multiple variables, including racial variation in preoperative morbidity. A systematic review of the evidence in pediatric appendicitis found that social, racial, and economic inequities exist in the rate of misdiagnosis, laparoscopic versus open approach, length of stay, and appendiceal perforation rate. In pediatric severe sepsis, a recent large retrospective study found evidence of an increased odds of death for Black children as compared to White children, particularly in the Western and Southern United States. This study also described longer hospital stays for Hispanic and Black children as compared with White children. Disparities also affect adverse events for hospitalized children, with one multicenter study reporting that hospitalized Latino children experience higher rates of adverse events as compared to non-Latino White children, and publicly insured children experience higher rates of preventable adverse events as compared to those who are privately insured. The Institute for Healthcare Improvement notes that "there can be no quality without equity," and the field of pediatric patient safety is increasingly focused on health equity as a critical and essential outcome measure.

Learning from Patient and Family Partnerships

Another important area of current and growing research involves how healthcare providers can partner with patients and families to improve the safety of care. Families often identify a wide number of errors and safety events that clinicians fail to report. More important than families simply reporting mistakes are early efforts to engage families more broadly and deeply to co-produce healthcare that is efficient, effective, and safe. This is particularly important for the growing population of children with complex chronic disease, for whom family caregivers are critical in identifying deviations from baseline in their children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 6

Ethics in Pediatric Care

Eric Kodish and Bryan A. Sisk

Pediatric ethics is the branch of bioethics that analyzes moral aspects of decisions made relating to the healthcare of children. In general terms, the **autonomy**-driven framework of adult medical ethics is replaced by a **beneficent** paternalism in pediatrics. Pediatric ethics is distinctive because the pediatric clinician has an independent fiduciary obligation to act in a younger child's **best interest** that takes moral precedence over the wishes of the child's parent(s). For older children, the concept of **assent** suggests that the voice of the patient must be heard. These factors create the possibility of conflict among child, parent, and clinician. The approach to the ethical issues that arise in pediatric practice *must* include respect for parental responsibility and authority balanced with a child's developing capacity and autonomy. Heterogeneity of social, cultural, and religious views about the role of children adds complexity.

Additional features of ethical decision-making include **nonmaleficence** (do no harm) and **justice** (treating patients with the same condition equally).

ASSENT AND PARENTAL PERMISSION

The doctrine of *informed consent* has limited direct application to children and adolescents who lack decisional capacity. The capacity for informed decision-making in healthcare involves the ability to understand and communicate, to reason and deliberate, and to analyze conflicting elements of a decision using a set of personal values. The age at which a competent patient may legally exercise voluntary and informed consent for medical care varies from state to state, and there may be exceptions related to specific conditions (sexually transmitted infections, family planning, drug or alcohol abuse).

In contrast to decisions about one's own care, a parent's right to direct a child's medical care is more limited. For this reason, the term *parental consent* is misleading. The concept of parental permission (rather than consent) reflects a *surrogate* or *proxy* decision made by a parent on behalf of a child. It is constrained by the child's best interest, even if this places the clinician in conflict with the parent. In any given instance, the decision of what is or is not in a child's best interest may be difficult, especially given the diverse views of acceptable child rearing and child welfare. Parents are (and should be) granted wide discretion in raising their children. In cases involving a substantial risk of harm, the moral focus should be on avoiding or preventing harm to the child, not on a parental right to decide. Although the term *best interests* may be too high of a threshold requirement, a minimum standard of *basic interests* is ethically obligatory.

Respect for children must account for both a child's vulnerability and developing capacity. This respect encompasses both the protective role of parental permission and the developmental role of **child assent** (the child's affirmative agreement). Understanding the concept of assent is one of the major conceptual challenges in pediatric ethics. The **dissent** (or disagreement) of a child is the opposite of assent and is also morally relevant. Pediatric ethics *requires* clinicians and parents to override a child's dissent when a proposed intervention is essential to the child's welfare. Otherwise, assent should be solicited and dissent honored. In seeking younger children's assent, a clinician should help them understand their condition, tell them what they can expect, assess their understanding and whether they feel pressured to assent, and solicit their willingness to proceed. All efforts must be made to delineate situations in which the test or procedure will be done regardless of the child's assent/dissent, and in such cases the charade of soliciting assent should be avoided. There is an important distinction between soliciting assent and respectfully informing a child that a test or procedure will take place regardless of the child's decision. Optimally, an educational process can transpire (if time allows) to gain the trust and assent of the child-patient. When this cannot occur, pediatric ethics requires that clinicians apologize to a child for acting to override dissent.

Older children or adolescents (<18 years) may have the cognitive and emotional capacity to participate fully in healthcare decisions. If so, the adolescent should be provided with the same information given to an adult patient. In such situations the patient may be able to provide informed consent ethically but not legally. The adolescent's parent(s) remain in a guiding and protective role. The process of communication and negotiation will be more complex should disagreement arise between the parent and adolescent. Pediatricians can be effective intercessors when these situations arise, making use of communication skills in a respectful way that uses an ethical framework.

TREATMENT OF CRITICALLY ILL CHILDREN

Infants, children, and adolescents who become critically ill may recover fully, may die, or may survive with new or increased limitations of function. Uncertainty about outcomes can make planning goals of care difficult or, if misunderstandings among patient, families, and medical staff occur, may drive conflict over treatment proposals. *Ethical issues* that arise during critical illness include balancing benefits, burdens, and harms of therapy in the face of uncertainty; maintaining a helpful degree of transparency and communication about medical standards of care at an institution; understanding and respecting religious and cultural differences that affect requests for or refusal of treatments; defining limits of therapy based on assessments of medical futility; recognizing the moral equivalence of not starting an ineffective treatment and stopping (although the two acts may seem very different to families and even to clinicians); and controversies such as withholding medically administered nutrition and hydration.

Transitioning the Goals of Care

Most acutely ill children who die in an intensive care unit do so after a decision has been made to forgo or withdraw **life-sustaining medical treatment (LSMT)**, and the same may apply in the chronically ill population. LSMT is justified when the anticipated benefit outweighs the burdens to the patient; it is important to note that the availability of technology does not in and of itself obligate its use. Decisions to use, limit, or withdraw LSMT should be made after careful consideration of all pertinent factors recognizable by both family and medical staff, including medical likelihood of particular outcomes, burdens on the patient and family, religious and cultural decision-making frameworks, and input by the patient when possible (Table 6.1). Although fear of legal repercussions may sometimes drive treatment and medical advice, ultimately decisions should be based on what is thought to be best for the patient.

The concept of **futility** has been used to support unilateral forgoing of LSMT against the wishes of patients and families by holding that clinicians should not provide futile (or useless) interventions. If *medical futility* is defined narrowly as the impossibility of achieving a desired physiologic outcome, forgoing a particular intervention is ethically justified. However, this approach may not adequately engage professionals and families in understanding facts and values that might allow the same therapy to reach other goals and may leave medical and family stakeholders in permanent conflict. Guidance from critical care groups recommend restricting use of the word *futility* to situations of strict physiologic futility, and instead use process guidelines to evaluate and manage situations of *potentially inappropriate treatment*. If agreement cannot be reached through clear and compassionate communication efforts, further input should be sought from an ethics consultant or committee.

Communication about life-threatening or life-altering illness is challenging and requires skills learned through both modeling and practice. These *skills* include choosing a setting conducive to what may become one or more long conversations; listening carefully to children's and families' hopes, fears, understanding, and expectations; explaining medical information and uncertainties simply and clearly without complicated terms and concepts; conveying concern and openness to discussion; and being willing to share the burdens of decision-making with families by giving clear recommendations. Discussing difficult topics with children requires an understanding of child development and can be aided by professionals such as child psychologists or child life specialists. Such conversations and their outcomes have a major impact on the future care of the patient, on

Table 6.1 Approach to Termination of Medical Treatments for Adults (≥18 yr) and Children

CONSIDERATION	DISCUSSION
Is there a legal right to refuse medical interventions?	**YES.** The U.S. Supreme Court declared that competent patients ≥18 yr have a constitutionally protected right to refuse unwanted medical treatments. **NO.** In neonates and children, if the treatment is in the best interest of the child, the family cannot refuse beneficial treatments (see later).
What interventions can be legally and ethically terminated?	Any and all interventions (including respirators, antibiotics, pacemakers, ECMO, intravenous or enteral nutrition and hydration) can be legally and ethically terminated.
Is there a difference between withholding life-sustaining interventions and withdrawing them?	**NO.** The consensus is that there is no legal or ethical difference between withholding and withdrawing medical interventions. Stopping a treatment once begun is just as ethical as never having started it.
Whose view about terminating life-sustaining interventions prevails if there is a conflict between the family and physician?	If continued treatment is not beneficial (futile), there is no obligation to continue such care. At times, involvement of an ethics committee or the courts is necessary. In most circumstances, the parents agree with the healthcare team (shared decision-making).
Are advance care directives legally enforceable?	**YES.** As a clear expression of the patient's wishes, they are a constitutionally protected method for patients to exercise their right to refuse medical treatments. In almost all states, clear and explicit oral statements are legally and ethically sufficient for decisions about withholding or withdrawing medical interventions. This is true for patients over 18 yr old. Mature, competent adolescents (≥16 yr) may provide assent and consent to refuse care, but this is not universally accepted.

ECMO, Extracorporeal membrane oxygenation.
Modified from Emanuel EJ. Bioethics in the practice of medicine. In: Goldman L, Schafer AI (eds). *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020: Table 2.2.

families, and on medical staff. For this reason, ongoing evaluation of goals and communication about them is needed with families and within complex medical teams as the course of the illness unfolds.

Experts recognize that good medical care involves providing for communication, symptom management, and a range of supportive services from the onset of acute illness. In this way, if an illness proves to be life-limiting despite intensive therapies, the elements of palliative care are already in place. This concept has had difficulty gaining traction, especially in critical care settings, because of the mistaken conflation of broadly defined palliative measures with hospice care. **Palliative care** interventions focus on the relief of symptoms and conditions that may detract from quality of life regardless of the impact on a child's underlying disease process, and as such are important whether care is focused on cure or on transitioning to end-of-life care (see Chapter 8). Some interventions regarded as life-sustaining, such as chemotherapy, may be ethically acceptable in the end-of-life setting if their use decreases pain and suffering.

Withholding and Withdrawing Life-Sustaining Treatment

Limitation of interventions or withdrawal of existing therapies is ethically permissible if congruent with a plan of care focused on **comfort** and **improved quality** at the end of life rather than cure. The prevailing view in Western medical ethics is that there is no moral distinction between withholding or withdrawing interventions that are not medically indicated (see Table 6.1). Uncertainty in predicting a child's response to treatment may drive the initiation and continuation of interventions that are subsequently determined to be no longer aligned with the goals of care. It is important to continually evaluate the results of these treatments and the evolution of the illness to recognize whether such interventions continue to be the best medical and moral choices. Maintaining the focus on the child rather than on the interests of parents or medical staff should be the primary driver of decision-making.

The decision about whether to attempt **cardiopulmonary resuscitation** (CPR) may become an issue to discuss with parents of children living with life-threatening or terminal conditions. All elements of end-of-life care approaches, including resuscitation status, should be supportive of agreed-on goals of care. It is imperative that decisions and plans are effectively communicated to all caregivers in order to avoid denying medically effective interventions and measures to ensure comfort. Orders about resuscitation status should clarify the plan regarding intubation and mechanical ventilation, the use of cardiac medications, chest compressions, cardioversion, blood products, antibiotics, and dialysis. Because goals of care may change over time, a medical order regarding resuscitation is not irrevocable. Clinicians may assume that the absence of a **do-not-attempt-resuscitation (DNAR)** order obligates them to perform CPR. This action may not be ethically obligatory if resuscitative efforts will not achieve the desired physiologic end-point. In all cases, treatments should be tailored to the child's clinical condition, balancing benefits and burdens to the patient. Resuscitation should not be performed solely to mollify parental distress at the tragic time of the loss of their child.

Artificial Hydration and Nutrition

Issues surrounding withholding or withdrawing artificial hydration and nutrition are controversial, and interpretations are affected by parental religious and medical beliefs. Any adult or child who is fully dependent on the care of others will die as a result of not receiving hydration and nutrition. Case law has supported the withholding of artificially administered nutrition and hydration in the setting of adult vegetative or permanently unconscious patients who can be shown to have previously expressed a wish not to be maintained in such a state. This requires a valid advance directive or for a surrogate decision maker to speak on behalf of the patient's known wishes. Because infants and many children have not reached a developmental stage in which such discussions would have been possible, decisions about stopping artificially administered nutrition and hydration as a limitation of treatment are more problematic. These decisions should be based on what families and caregivers decide best support comfort. In the child who is imminently dying, unaware of hunger, does not tolerate enteral feedings, and in whom family and staff agree that IV nutrition and hydration only prolong the dying process, it may be ethically permissible to withhold or withdraw these treatments based on a benefit-burden analysis.

The Doctrine of Double Effect

Treatment decisions at the end of life may include limitations of certain LSMT or may involve the use of analgesic or sedative medications that some fear may shorten life, thereby causing death. The doctrine of double effect (**DDE**) holds that an action with both good and bad effects is morally justifiable if the good effect is the only one intended and the bad effect is foreseen and accepted, but not desired. In pediatrics, DDE is most commonly applied in end-of-life cases when upward titration of medication (opiates) necessary to relieve pain, anxiety, or air hunger can be expected to result in a degree of respiratory depression. In such cases, meeting a clinician's obligation to relieve suffering is the intended effect, and this

obligation to the patient outweighs the acknowledged but unavoidable side effect. Choosing medications that adequately relieve symptoms with minimal adverse effects would be ethically preferable, but absent these options, the obligation to provide comfort at the end of life outweighs the foreseeable occurrence of unavoidable side effects. Hastening death as a primary intention is not considered to be morally acceptable.

Providing pain medication guided by the DDE should not be confused with active euthanasia. The distinction is clear:

- In **active euthanasia**, causing death is chosen as a means of relieving the symptoms that cause suffering.
- Under DDE, adequate management of pain, anxiety, or air hunger is recognized as an obligation to dying patients and is provided by careful titration of medications in response to symptoms. If death occurs sooner as a result, this is accepted.

In both cases the patient dies, and in both cases suffering ends, but immediate death is the intended consequence only in the case of euthanasia. Codes of ethics and legislation in many states support the obligation to provide pain and symptom relief at the end of life, even if this requires increasing doses of medication.

NEONATAL ETHICS

As neonatal care has evolved, the limits of viability of extremely premature infants are continuing to change. This introduces new elements of uncertainty to decision-making, often in emotionally fraught circumstances such as a precipitous premature delivery. In cases of uncertain prognosis, parental desires should determine the decision-making, while clinicians should help parents recognize when treatments are inappropriate; this should result in a shared decision-making approach to developing plans of care.

The federal **Child Abuse Prevention and Treatment Act** of 1984 (CAPTA), which became known as "Baby Doe Regulations," required state child protective services agencies to develop and implement mechanisms to report to a specific government agency treatment that the reporter believed was withheld from infants on the basis of disability. Exceptions were (1) an infant is chronically and irreversibly comatose; (2) if providing a treatment would merely prolong dying, would not be effective in ameliorating or correcting all the infant's life-threatening conditions, or would be futile in terms of the infant's survival; and (3) if the treatment would be virtually futile and inhumane. This legislation pertains *only* to infants and is intended to prevent discrimination on the basis of disability alone. One consequence of the legislation was a shift from potential undertreatment to widespread overtreatment (LSMT that does not serve the interests of the child) of severely disabled newborns. As parental involvement in decision-making is again taking a more central role, and as palliative care approaches in infants have become more available and skilled, balanced approaches to valuing the lives of disabled infants should be considered. Understanding institutional, regional, state, and national regulations related to care of infants is important in order to practice within regulatory frameworks while respecting the values of the family and pursuing the interests of the patient.

Active euthanasia of severely suffering disabled newborns has been legalized in The Netherlands and Belgium, using protocols designed to minimize the risk of abuse and maximize transparency. It is currently illegal in the United States, and although controversy surrounds the subject, the predominant view is that active euthanasia is not ethically acceptable in the care of infants and children, instead favoring palliative treatment (including pain management) and limiting escalation of treatment (see Chapter 8).

DECLARING DEATH AND ORGAN DONATION

Donation of solid organs necessary to support life can occur after a patient is declared dead based on either irreversible cessation of function of the brain and brainstem (death by neurologic criteria, or *brain death*) or a predetermined period of cardiac asystole called *circulatory death* (see Chapter 83). To avoid a potential conflict of interest by surgeons or others caring for a potential organ recipient, the request for organ donation should be separated from the clinical discussion of either brain death or withdrawal of LSMT. Although clinicians may be the first to enter discussion about death and organ donation with family members during conversations about outcomes and options, detailed discussion of organ donation should be done by other individuals who are specifically trained for this purpose. This decoupling of clinical decision-making from a request for organ donation by trained individuals, perhaps by providing families with expert information without a perceived conflict of interest, has been associated with improved donation rates.

Death by Neurologic Criteria

Death by neurologic criteria (**DNC**), commonly referred to as brain death (**BD**), may be difficult for families to understand when the child appears to be breathing (although on a ventilator), pink, and warm to the touch and when language such as "life support" is used at the bedside by staff. Studies also document clinician misunderstanding of the diagnosis of **BD/DNC**. For these reasons, strict criteria adhering to nationally accepted guidelines must be used to determine when irreversible cessation of brain and brainstem function (coma, brainstem areflexia, apnea) has occurred and adequately document these findings (see Chapter 83).

RELIGIOUS OR CULTURAL OBJECTIONS TO TREATMENT

Differences in religious beliefs or cultural norms may lead to conflict among patients, families, and medical caregivers over the approach to medical care. Pediatricians need to remain sensitive to and maintain an attitude of respect for these differences yet recognize that an independent obligation exists to provide safe and effective medical treatment to the child. An adult with decision-making capacity is recognized as having the right to refuse treatment on religious or cultural grounds, but children who have not yet developed this capacity are considered a vulnerable population with a right to treatment. In situations that threaten the life of the child or that may result in substantial harm, legal intervention should be sought if reasonable efforts toward collaborative decision-making are ineffective. If a child's life is imminently threatened, medical intervention is ethically justified despite parental objections.

PEDIATRIC ETHICS COMMITTEES AND ETHICS CONSULTATION

Most hospitals have *institutional ethics committees* to assist with policy development, education, and case consultation. When these committees serve institutions caring for children, they may be referred to as *pediatric ethics committees*. Because of the important differences in approach between adult and pediatric ethics, member expertise on this committee should include those with special insight into the unique ethical issues arising in the care of children. Such committees generally provide ethics consultation advice without mandating action or being determinative. For the vast majority of decisions involving the medical treatment of children (including forgoing LSMT), pediatric clinicians and parents are in agreement about the desirability of the proposed intervention. Because of the ethical importance of assent, the views of older children should also be given considerable weight.

Pediatric ethics committees typically perform at least three different functions: (1) the drafting and review of institutional policy on such issues as DNAR orders and forgoing LSMT, (2) the education of healthcare professionals, patients, and families about ethical issues in healthcare, and (3) case consultation and conflict resolution. Although the process of *case consultation* may vary, ideally the committee (or consultant) should adopt a collaborative approach that uncovers all the readily available and relevant facts, considers the values of those involved, and balances the relevant interests, while arriving at a recommendation based on a consistent ethical analysis. One helpful approach involves consideration of the 4 following elements: (1) medical indications, (2) patient preferences, (3) quality of life, and (4) contextual features. Another framework based on principles would suggest attention to respect for persons, beneficence/nonmaleficence, and justice.

Pediatric ethics committees often play a constructive role when parents and medical staff cannot agree on the proper course of action. Over the past several decades, these committees have acquired considerable influence and are increasingly recognized by state courts as an important aid in decision-making. The membership, policies, and procedures of a pediatric ethics committee should conform to accepted professional standards.

NEWBORN SCREENING

The *Oxford Dictionary of Public Health* defines screening as "the identification of a previously unrecognized disease or disease precursor, using procedures or tests that can be conducted rapidly and economically on large numbers of people with the aim of sorting them into those who may have the condition(s) … and those who are free from evidence of the condition(s)." Several programs, such as newborn screening for inborn errors of metabolism (see Chapter 104; e.g., phenylketonuria and hypothyroidism), are rightly counted among the triumphs of contemporary pediatrics. The success of such programs sometimes obscures serious ethical issues that continue to arise in proposals to screen for other conditions for which the benefits, risks, and costs have not been clearly established. Advances in genetics and technology have led to exponential growth in the number of conditions for which screening programs might be considered, with insufficient opportunity to study each proposed testing program (see Chapter 95).

The introduction of screening efforts should be done in a carefully controlled manner that allows for the evaluation of the costs (financial, medical, and psychologic) and benefits of screening, including the effectiveness of follow-up and treatment protocols. New programs should be considered *experimental* until the risks and benefits can be carefully evaluated. Screening tests that identify candidates for treatment must have demonstrated sensitivity, specificity, and high predictive value, lest individuals be falsely labeled and subject to possibly toxic treatments or to psychosocial risks. As newborn screening tests are being developed, parents should be given the opportunity to exercise informed parental permission or refusal. However, once a particular screening test has been clearly demonstrated to benefit the individual or public health, a formal, active parental permission process may not be ethically obligatory.

A persistent ethical issue is whether screening should be (1) voluntary ("opt in"), (2) routine, with the ability to "opt out" or refuse, or (3) mandatory. A **voluntary** approach entails an informed decision by parents before screening. Concern is often expressed that seeking parental permission is ethically misguided for tests of clear benefit, such as phenylketonuria screening, because refusal would constitute neglect. **Routine** testing with an opt-out approach requires an explicit refusal of screening by parents who object to this intervention. The principal ethical justification for **mandatory** screening is the claim that society's obligation to promote child welfare through early detection and treatment of selected conditions supersedes any parental right to refuse this simple and low-risk medical intervention. Parental permission is clearly required when there is a research agenda (i.e., for incorporating experimental tests into established screening programs).

GENETICS, GENOMICS, AND PRECISION MEDICINE

Genetics refers to the study of particular genes, and **genomics** describes the entirety of an individual's genetic material. Genomics has been made possible by technologic advances that allowed the rapid and inexpensive sequencing now used in clinical care. The development of **precision medicine** is in large part predicated on genomic science and may have a major impact on the practice of pediatrics in the future. Efforts to undertake whole-genome sequencing of newborns may yield actionable information to benefit the child, but also carry the risk of stigmatization, false positives, and unwanted information that could lead to anxiety and psychologic distress.

Genetic testing of young children for late-onset disorders such as the *BRCA1* and *BRCA2* breast cancer risk genes has also been the subject of some ethical controversy. Knowledge of increased risk status may lead to lifestyle changes that can reduce morbidity and the risk of mortality or may precipitate adverse emotional and psychologic responses and discrimination. Because many adults choose not to be tested for late-onset disorders, one cannot assume that a child would want or will benefit from similar testing. Genetic testing of young children for late-onset disorders is generally inappropriate unless such testing will result in interventions that have been shown to reduce morbidity and mortality when initiated in childhood. Otherwise, such testing should be deferred until the child has the capacity to make an informed and voluntary choice.

Precision medicine promises to enhance treatment and public health outcomes in the future. Yet the success of precision medicine will depend on whose data are used to develop and refine artificial intelligence algorithms that will inform care. A large body of literature has begun to explore racial and ethnic disparities in precision medicine, with the goal of ensuring advances will benefit all people. However, children represent another group that is at risk of exclusion from these benefits. Historically, the rarity of many childhood illnesses, protective regulations, and financial disincentives have limited the development of effective treatments for many childhood diseases. Legislation such as the "Research to Accelerate Cures and Equity for Children Act" (RACE Act) has begun to mandate greater representation of children in clinical trials. If similar steps are not taken in pediatric precision medicine, we run the risk of creating a new generation of therapeutic orphans.

ADOLESCENT HEALTHCARE

Adolescent Assent and Consent

Many adolescents are more like adults than children in their capacity to understand healthcare issues and to relate them to their life goals (see Chapter 150). Teenagers may lack legally defined competency, yet they may have developed the capacity to meet the elements of informed consent for many aspects of medical care (see Chapter 151). There are also public health reasons for allowing adolescents to consent to their own healthcare with regard to reproductive decisions, such as contraception, abortion, and treatment of sexually transmitted infections. Strict requirements for parental permission may deter adolescents from seeking healthcare, with serious implications for their health and other community interests.

Counterbalancing these arguments are legitimate parental interests to maintain responsibility and authority for child rearing, including the opportunity to influence the sexual attitudes and practices of their children. Others claim that access to treatment such as contraception, abortion, or needle exchange programs implicitly endorses sexual activity or drug use during adolescence. Pediatricians should not impose their own moral beliefs in these disputes. Rather, they should provide unbiased evidence-based information and nonjudgmental support. One guiding principle should be encouragement of children and adolescents to begin taking responsibility, with guidance, for their own health. This requires some input from parents or guardians but also some privacy during decision-making as adolescents achieve developmentally anticipated separation from parental control.

Communication, Privacy, and Confidentiality

Exchanging information is a core function of communication in pediatric and adolescent care. As adolescents mature, their need to exchange information about sensitive topics can increase, complicating the triadic clinician-parent-child relationship. For example, adolescents might wish to start oral contraception or seek treatment for a sexually transmitted infection without their parents' knowledge. The confidentiality of conversations about reproductive health and sexually transmitted infections between adolescents and clinicians is often protected by state laws, although the scope of protections in these laws varies widely. A recent federal law that mandates increased transparency in medical care will further complicate this sensitive communication.

The 21st Century Cures Act included a rule that requires healthcare organizations to provide electronic health information (EHI) to patients in easily accessible platforms. This mandate went into effect in April 2021. As a result of this law, adolescents now have access to their EHI. For preadolescent patients, healthcare organizations provide proxy access to parents. When children reach adolescence, approaches to provision of EHI access vary greatly. Some sites allow parental access to adolescent EHI that has been filtered for confidential information. Other sites revoke parental access, but allow adolescents the option of permitting proxy consent. Still other sites permanently revoke parental access once a child has reached adolescence. This new transparency will likely provide benefits, but could also generate new ethical risks to preserving the confidentiality of adolescent patients. Pediatricians must be cognizant of this tension when creating clinical documentation that might be visible to parents and adolescent patients.

Chronic Illness

The normal process of adolescent development involves gradually separating from parents, establishing self-confidence, asserting individuality, developing strong peer relationships, solidifying an ability to function independently outside the family, and taking on increasing autonomy in healthcare decisions. Most developmentally typical children older than age 14 years understand the implications of well-explained medical options as well as the average adult, and their input into their own care should be respected. For children living with chronic illness, the ability to make medical decisions for themselves may either occur earlier than for those who have been previously healthy or may occur later if, because of illness, they have not been able to achieve normal developmental milestones or psychologic maturity. The clinician's role involves assessment of the individual adolescent patient's ability to understand the medical situation, to support the patient's efforts to express wishes regarding medical treatment, to value and encourage parental support and involvement, and to foster cooperation and mutual understanding. This may be difficult in situations in which parents and adolescents disagree about life-sustaining treatments such as organ transplantation or chemotherapy, but many such conflicts may be resolved by exploring the reasons for the disagreement. Overriding an adolescent's wishes should be done very infrequently and only after careful consideration of the potential consequences of unwanted interventions.

Decisions in Terminally Ill Adolescents

Most adolescents share end-of-life decision-making with family members, although communication may be challenging because of a growing sense of independence. Open communication and flexibility about treatment preferences may help teens cope with fears and uncertainties. Development of an age-appropriate advance directive may support the patient's emerging autonomy by clarifying the adolescent's wishes while fostering a collaborative process among the patient, family, and medical caregivers. From the time of diagnosis of a life-threatening condition through the end-of-life phase, children should be included in a developmentally tailored process of communication and shared decision-making that builds a foundation of mutual respect and trust. Some experts believe that most adolescents are not yet fully capable of making a decision to forgo life-sustaining treatment. Careful case-by-case evaluation is required to make this determination, and assistance from developmental psychologists and ethics consultants may be helpful.

RESEARCH

The central ethical challenge of pediatric research is the need to balance protection of children from research risk against the ethical imperative of conducting studies to better the lives of future children. *Research* is defined in the federal regulations as "a systematic investigation designed to develop or contribute to generalizable knowledge." For any research to be performed, the risks should be minimized and reasonable with respect to any anticipated benefits to the participants and the importance of the resulting knowledge. That some children derive a direct benefit from participation in research must also be considered, making it important to distinguish research with the prospect of direct benefit from nontherapeutic pediatric research. *Because children are a vulnerable population, there are restrictions on the research risks to which a child may be exposed,* in contrast to the risk level acceptable for research with consenting adults**.** These restrictions function by limiting the type of research that institutional review boards (IRBs) are permitted to approve and by specifying the conditions under which parents have the moral and legal authority to permit a child to participate in research.

Nontherapeutic research in children is the most ethically controversial because it holds no expected direct benefit for the individual. The prohibition against using a person (especially a child) solely as a means to an end has led some to argue that children should *never* be used in nontherapeutic research. The more widely held opinion is that children may be exposed to a limited degree of risk with IRB approval, parental permission, and assent if the child is capable. The federal regulations allow healthy children to participate in minimal-risk research regardless of the potential benefit to the child. More controversially, the regulations also state that children with a disorder or condition may be exposed to slightly more than minimal risk in nontherapeutic research if the child's experience is similar to everyday life with the condition and the anticipated knowledge is of vital importance for understanding the condition.

In pediatric research with the prospect of direct benefit, the risks must be justified by the anticipated benefit to the child, and the balance of anticipated benefit to the risk should be at least as favorable as that presented by available alternatives. *In our opinion, the welfare of an individual child must always come before the scientific goals of the research study.*

U.S. regulations for the protection of human research participants rest on two foundations: (1) independent review of the ethics and science of the research by an IRB **before** (2) voluntary and informed consent of the participant. Although it is not amenable to regulation, the *integrity* of the investigator is probably the most important element contributing to the protection of human research participants. The standard for informed consent in a research setting is higher than for clinical care because the risks and benefits are typically less clear, the investigator has a conflict of interest, and humans have historically been subjected to unauthorized risks when strict requirements for consent were not respected.

Adolescents who are competent may sometimes consent to be research participants. Younger children may participate in a process of assent, but this does not imply that a child's signature on an assent document is necessarily a legal or ethical requirement. Children should be given the opportunity to dissent, particularly for nontherapeutic research, when there cannot be a claim that participation is in the child's interest. In the United States, national regulations require that reasonable efforts be made at least to inform children who are capable of understanding that participation is *not* part of their care, and therefore they are free to refuse to participate. In the rare case that the research offers a direct benefit to the child that would not otherwise be available, the regulations do not require child assent but only parental permission.

In addition to the protection that informed consent or parental permission is intended to provide, virtually all research involving humans in the United States is reviewed by an IRB, as required by federal regulations for institutions receiving federal research funds and for drug research regulated by the U.S. Food and Drug Administration. For research that carries more than a minor increase over minimal risk without prospect of benefit to the child such that a local IRB cannot provide approval, there is a process for federal review of research that "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." Ultimately, the U.S. Secretary of Health and Human Services has the authority to approve such research.

JUSTICE AND PEDIATRIC ETHICS

The most serious ethical problem in U.S. healthcare may be *inequality* in access to healthcare. Children are particularly vulnerable to this disparity, and pediatricians have a moral obligation to advocate for children as a class. Because children do not vote and do not have financial resources at their disposal, they are subject to a greater risk of being uninsured or underinsured. This lack of adequate and affordable healthcare has serious consequences in terms of death, disability, and suffering. The per capita proportion of healthcare funding spent on adults greatly exceeds that spent on children, and Medicare is available to all adults who turn 65 years old, whereas Medicaid is limited to those beneath a specific income level. Pediatricians should be familiar with policy issues around the economics of child healthcare so that they will be better able to advocate for their own patients.

Beyond access to healthcare, structural social inequalities also have profound impacts on child health and well-being. Systemic racism and structural disadvantages can affect every aspect of pediatric care, from infant mortality and neonatal care delivery to asthma outcomes and surgical complications. Furthermore, social inequality and adverse childhood experiences (ACEs) have been linked to greater incidence of chronic diseases, substance abuse, increased encounters with the justice system, and lower executive functioning. Pediatricians should take active steps to acknowledge and attempt to mitigate the effect of these inequalities on their patients through individual, local, and national advocacy efforts.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 7

Complementary Therapies and Integrative Medicine

Paula M. Gardiner and Caitlin M. Neri

Integrative medicine focuses on promoting physical, mental, emotional, spiritual, social, and educational well-being in the context of a medical home in a healthy family and community. The foundations of integrative medicine are health-promoting practices such as optimal nutrition and dietary supplements to prevent deficiencies, avoidance of addictive substances (e.g., nicotine, illicit drugs), physical activity, adequate sleep, a healthy environment, and supportive social relationships. Evidence-based **complementary therapies** such as dietary supplements, massage, chiropractic, other forms of bodywork, yoga, meditation practices, hypnosis, guided imagery, biofeedback, and acupuncture may also be used.

Not including multivitamins and mineral supplements such as iron and calcium, an estimated 10–40% of healthy children and >50% of children with chronic conditions use integrative medicine in the United States. The prevalence could be even higher because these treatments usually occur without disclosure to the children's primary care physician. Common therapies include dietary supplements, deep breathing, guided imagery, meditation, biofeedback, hypnosis, yoga, acupuncture, massage, and aromatherapy.

Use of complementary therapies is most common among youth with chronic, incurable, or recurrent conditions such as cancer, depression and other mental health conditions, asthma, autism, headaches, abdominal pain, and other chronic painful conditions. In a 2017 study of freestanding children's hospitals, 92% offered complementary services, 38% had a specific complementary center on-site, and 60% had policies related to supplement use during hospitalization. Integrative therapies are being used in pediatric cancer symptom management and chronic pain clinics. Practice often includes supplements (e.g., probiotics) and mind-body techniques (e.g., hypnotherapy, biofeedback) with traditional medical management for these common pediatric conditions.

DIETARY SUPPLEMENTS

Under the 1994 U.S. Dietary Supplement Health and Education Act, a **dietary supplement** is a product taken by mouth that contains a *dietary ingredient* intended to supplement the diet. These may include vitamins, minerals, herbs or other botanical, amino acids, and substances such as enzymes, organ tissues, glands, and metabolites. Dietary supplements are the most frequently used complementary therapies for children and adolescents (Table 7.1). Some uses are common and recommended, such as vitamin D supplements for breastfed infants and probiotics to prevent antibiotic-associated diarrhea, whereas other uses are more controversial, such as using herbal products to treat otitis media.

In the United States, dietary supplements do not undergo the same stringent evaluation and postmarketing surveillance as prescription medications. Although they may not claim to prevent or treat specific medical conditions, product labels may make *structure-function* claims. A label may claim that a product "promotes a healthy immune system," but it may not claim to cure the common cold.

According to the 2017–2018 National Health and Nutrition Examination Survey (NHANES), 34% of children and adolescents used any dietary supplement in the past 30 days, with multivitamin-mineral products the most common (24%). Use of dietary supplements is most common among children whose families have higher income and education and whose parents use supplements, among older children, and among those with chronic conditions.

Despite this widespread use, many patients and their parents who use dietary supplements do not talk with their physician about their use. Several guidelines have called for more complete dietary supplement history taking by healthcare professionals. The Joint Commission recommends that this information be included in the medication reconciliation process.

DIETARY SUPPLEMENT SAFETY

Dietary supplements may have safety issues in children, but toxicity is much less common with nonprescription dietary supplements than with prescription medications. Toxicity depends on dose, use of other therapies, and the child's underlying medical condition (see Table 94.20). Current use of a dietary supplement (e.g., ephedra for weight loss) may not reflect its traditional use (e.g., ephedra as a component of a traditional Chinese medicine tea in small doses to improve allergic or respiratory symptoms). Moreover, herbs that are apparently safe for most adults may be more hazardous in specific conditions (e.g., newborns, patients with impaired renal or hepatic function), under special circumstances (e.g., after organ transplantation or other surgery), or when combined with prescription medications. Some natural products are toxic in and of themselves. Even when a product is safe when used correctly, it can cause mild or severe toxicity when used incorrectly. Although peppermint is a commonly used and usually benign gastrointestinal spasmolytic included in after-dinner mints, it can exacerbate gastroesophageal reflux.

Table 7.1 Commonly Used Dietary Supplements in Pediatrics

PRODUCT	USES
VITAMINS	
B_2 (riboflavin)	Migraine headache prophylaxis
B_6 (pyridoxine)	Pyridoxine-dependent epilepsy; neuropathy; nausea associated with pregnancy
B_9 (folate)	Prevention of neural tube defects
D	Prevention of rickets; treatment of vitamin D deficiencies
Multivitamins	General health promotion
MINERALS	
Iodine (salt)	Prevent goiter and intellectual disability
Iron	Prevent and treat iron-deficiency anemia
Magnesium	Constipation, asthma, migraine prevention
Zinc	Diarrhea in nutrient-poor populations
HERBS*	
Aloe vera	Mild burns
Chamomile	Mild sedative, dyspepsia
Echinacea	Prevention of upper respiratory infections
Ginger	Nausea
Lavender (aromatherapy)	Mild sedative
Peppermint	Irritable bowel syndrome
Tea tree oil	Antibacterial (acne remedies), pediculicide (lice)
OTHER	
Melatonin	Insomnia
Omega-3 fatty acids	ADHD, allergies, inflammation, anxiety and mood disorders
Probiotics	Antibiotic-associated diarrhea; *Clostridium difficile*–associated diarrhea; constipation; irritable bowel syndrome; pouchitis; inflammatory bowel disorders

ADHD, Attention-deficit/hyperactivity disorder.
*See text; potentially useful evidence base not established for many herbs.

Although there are good manufacturing practices for dietary supplements in the United States, dietary supplement labels might not accurately reflect the contents or concentrations of ingredients. Because of natural variability, variations of 10-fold to 1,000-fold have been reported for several popular herbs, even across lots produced by the same manufacturer. Herbal products may be contaminated with pesticides or microbial agents or toxins, or the wrong herb may be misidentified during harvesting. Products from some countries (e.g., Ayurvedic products from South Asia) might contain toxic levels of mercury, cadmium, arsenic, or lead, either from unintentional contamination during manufacturing or from intentional additions by producers who believe that these metals have therapeutic value. Approximately 30–40% of Asian patent medicines include potent pharmaceuticals, such as analgesics, antibiotics, hypoglycemic agents, or corticosteroids; typically the labels for these products are not written in English and do not note the inclusion of pharmaceutical agents. Even conventional mineral supplements, such as calcium, have been contaminated with lead or had significant problems with product variability.

Many families use supplements concurrently with medications, posing hazards of interactions (Table 7.2). Using the same principles of drug-drug interactions can help determine if a supplement-drug interaction is a concern. For example, St. John's wort induces CYP3A4 activity of the cytochrome P450 enzyme system and thus can enhance elimination of most drugs that use this pathway, including digoxin, cyclosporine, protease inhibitors, oral contraceptives, and numerous antibiotics, leading to subtherapeutic serum levels.

DIETARY SUPPLEMENT EFFICACY

Evidence about the effectiveness of dietary supplements to prevent or treat pediatric problems is mixed, depending on the product used and condition treated. Some herbal products may be helpful adjunctive treatments for common childhood problems; some herbs have proved helpful for colic (fennel and the combination of chamomile, fennel, vervain, licorice, and balm mint), nausea (ginger), irritable bowel syndrome (peppermint), and diarrhea (probiotics).

MASSAGE AND CHIROPRACTIC

Massage is usually provided at home by parents and in clinical settings by professional massage therapists, physical therapists, and nurses. **Infant massage** is routinely provided in many neonatal intensive care units to promote growth and development in preterm infants. Massage also has been demonstrated to be beneficial for pediatric patients with asthma, insomnia, colic, cystic fibrosis, or juvenile arthritis and patients undergoing cancer therapy. **Massage therapy** is generally safe. Professional massage practice is regulated by state government and may be in the form of a license, registration, or certification. More than 44 states license massage therapists, with licensure being the strictest form of regulation, making it illegal for any nonlicensed professional to practice massage therapy.

Chiropractic healthcare deals with the diagnosis, treatment, and prevention of disorders of the neuromusculoskeletal system and their effects on general health. Currently, >70,000 chiropractors have licensure in the United States, with licensure in all 50 states. Most medical insurance companies cover chiropractic care. Children and families seek chiropractic care for common childhood conditions such as asthma, infantile colic, nocturnal enuresis, constipation, and headache. A consensus update on chiropractic care in children found no evidence for the effectiveness of chiropractic care for such common childhood conditions. With respect to safety, the evidence is also limited; however, published cases of serious adverse events in infants and children receiving chiropractic care are rare. Unfortunately, although rare, complications of cervical manipulation include vertebrobasilar dissection with resultant stroke and rupture of a syringomyelia with resultant paralysis. If children and families are seeking chiropractic care, it is appropriately done following consultation with the child's pediatric primary care provider to ensure patient safety. In addition, chiropractors often give medical advice beyond their expertise; up to 30% believe vaccines have significant side effects.

MIND-BODY THERAPIES

Mind-body therapies such as slow, deep breathing, meditation, guided imagery, biofeedback, hypnosis, tai chi, and yoga are also frequently used complementary therapies in pediatrics. These practices can be learned informally through books, online videos, compact discs, digital video discs, smartphone apps, or classes and in therapeutic sessions with health professionals, such as psychologists and social workers (Table 7.3). Substantial research suggests that such practices can aid in reducing anxiety, insomnia, and stress-related conditions, including migraine headaches and functional abdominal pain. These therapies can also help patients struggling with chronic pain.

ACUPUNCTURE

Modern acupuncture incorporates treatment traditions from China, Japan, Korea, France, and other countries. In the United States, acupuncturists are licensed to practice in 47 states. Acupuncture can be delivered to pediatric patients in hospital and clinic settings to treat a variety of ailments. Acupuncture is particularly useful for children experiencing pain, and acupuncture services are offered alongside conventional medicine and psychology by >50% of North American academic pediatric chronic pain programs. The technique that has undergone the most scientific study involves penetrating the skin

Table 7.2 Common Herbal Dietary Supplement (HDS)–Drug Interactions

HDS	DRUGS	POTENTIAL CONSEQUENCES/REACTIONS
Aloe vera	Glibenclamide (glyburide)	↑ Oral aloe vera gel can cause additive glycemic-lowering effects when taken concurrently with a hypoglycemic agent
Bitter orange	Phenelzine	↑ Risk of hypertensive crisis
Garlic	Ritonavir	↓ Effect of ritonavir
	Saquinavir	↓ Effect of saquinavir
Licorice	Warfarin	↑ Risk of bleeding
Grapefruit	Calcium channel blockers	Grapefruit juice has been found to increase the bioavailability of certain drugs by inhibition of the cytochrome P450 (CYP) 3A4 isozyme in the liver and gut wall
Melatonin	Zolpidem	↑ Sedative effects
Valerian	Alprazolam, phenobarbital	↑ Central nervous system depression
Goldenseal	Inhibition of CYP2D6 and CYP3A4	May affect approximately 50% of common pharmaceutical agents
St. John's wort	Cyclosporine, tacrolimus, warfarin, protease inhibitors, digoxin, theophylline, venlafaxine, oral contraceptives	May decrease drug effectiveness

↓, Decreasing; ↑, increasing.

Table 7.3 Commonly Used Mind-Body Practices in Pediatrics

PRACTICE	USES
Biofeedback	Preventing migraine headaches; reducing stress and anxiety; encopresis/constipation treatment; treatment of stress incontinence; neurofeedback is adjunctive for ADHD
Deep breathing	Relaxation; stress management
Guided imagery	Stress management; anxiety reduction; pain relief
Hypnosis	Correcting habit disorders; preventing headaches; managing pain
Meditation	Stress management; improving concentration
Tai chi	Improving balance, coordination, concentration, and discipline
Yoga	Improving balance, coordination, and concentration

ADHD, Attention-deficit/hyperactivity disorder.

with thin, solid, metallic needles manipulated by hand or by electrical stimulation. Variants include rubbing (**shiatsu**), heat (**moxibustion**), lasers, magnets, pressure (**acupressure**), or electrical currents.

Although pediatric patients may be averse to needles, when approached in a developmentally appropriate way by an acupuncturist trained in pediatrics, children are often amenable to acupuncture and report that it is helpful. Acupuncture can offer significant benefits in the treatment of recurrent headache, anxiety, back and other types of pain, depression, abdominal pain, and nausea. Infections and bleeding are rare but can occur, and more serious complications, such as pneumothorax, occur in <1 in 30,000 treatments.

CANNABIS

Because marijuana has been legalized in many states for both recreational (adult) use and medical use, caregivers and families may inquire about the potential health benefits of cannabis for both children and adults. There are significant safety concerns in adolescents and young adults, because detrimental effects of marijuana on the developing brain have been documented. One systematic review of 90 studies, including 9,441 adolescents and young adults, provided preliminary evidence for functional and structural alterations in frontoparietal, frontolimbic, frontostriatal, and cerebellar regions among adolescent cannabis users.

It is important to note that in some children with severe refractory epilepsy, oral cannabidiol, a nonpsychoactive component in marijuana, improves seizure control. Outside of prescription cannabidiol, the purity and regulation of marijuana and its commercially available component products are variable. Most of the pediatric literature on cannabis describes an increase in accidental ingestions in young children, presumably in association with the increase in products now available for adult use; this is an additional safety risk for pediatricians to consider.

INTERNET RESOURCES

American Academy of Pediatrics Section on Integrative Medicine: https://www.aap.org/en/community/aap-sections/integrative-medicine/about-soim/

Academic Consortium Integrative Medicine and Health: http://www.imconsortium.org/

National Institutes of Health, National Center for Complementary and Integrative Health: https://nccih.nih.gov/

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 8

Pediatric Palliative Care

Katharine Davidoff, Chelsea Heneghan, Joanne Wolfe, and Christina Ullrich

According to the World Health Organization (WHO), "Palliative care for children is the active total care of the child's body, mind and spirit and also involves giving support to the family. Optimally, this care begins when a life-threatening illness or condition is diagnosed and continues regardless of whether or not a child receives treatment directed at the underlying illness." Provision of palliative care applies to children with a wide variety of serious illnesses, including cancer, cystic fibrosis, complex or severe cardiac disease, neurodegenerative disorders, severe malformations, and trauma with life-threatening sequelae (Table 8.1). Many children who benefit from integration of palliative care approaches have **complex chronic conditions and are supported by advanced medical technology that allows them to live longer**. These children, who often survive health crises followed by the renewed need for rehabilitative and life-prolonging treatments, are best served by a system that is flexible and responsive to changing needs and blended goals of care.

Although often mistakenly understood as synonymous with *end-of-life care,* **the scope and potential benefits of palliative care are applicable *throughout the illness trajectory*.** Palliative care emphasizes ascertaining and aligning with goals of care, which may be congruent with maximal treatment aimed at sustaining or prolonging life, optimization of quality of life, communication, and symptom control.

The mandate of pediatric clinicians to attend to children's physical, mental, and emotional health and development includes the provision of palliative care for those who live with a significant possibility of death before adulthood (Fig. 8.1). As such, all pediatric clinicians benefit from using basic (primary) palliative care principles when approaching the care of children living with serious illness. At the same time, such comprehensive physical, psychologic, social, and spiritual care benefits from an interdisciplinary approach.

The philosophy of palliative care can be successfully integrated into any hospital setting, including the ICU, when the focus of care also includes the prevention or amelioration of suffering and improving comfort and quality of life. All interventions that affect the child and family need to be assessed in relationship to these goals. This proactive approach asks the question, "What can we offer that will improve the quality of this child's life and provide the most meaning and sense of control and choice for their family?" instead of, "What therapies are we no longer going to offer this patient?" Staff may benefit from education, support, and guidance on the basic principles of pediatric palliative care, while using specialty-trained pediatric palliative care providers when available for additional support and expertise. *Regardless of the care setting, comprehensive palliative care requires an interdisciplinary approach that may include nurses, physicians, psychologists, psychiatrists, social workers, chaplains/clergy, child life specialists, and trained volunteers.*

GOALS OF CARE AND DECISION-MAKING

In the course of a child's serious illness, a series of important decisions may arise in relation to location of care, medications with risks and benefits, not starting or discontinuing life-prolonging treatments, experimental treatments in research protocols, and use of integrative therapies. Guided discussions around **goals of care** for the child provide opportunities to support decision-making. This is often accomplished

Table 7.3 Commonly Used Mind-Body Practices in Pediatrics

PRACTICE	USES
Biofeedback	Preventing migraine headaches; reducing stress and anxiety; encopresis/constipation treatment; treatment of stress incontinence; neurofeedback is adjunctive for ADHD
Deep breathing	Relaxation; stress management
Guided imagery	Stress management; anxiety reduction; pain relief
Hypnosis	Correcting habit disorders; preventing headaches; managing pain
Meditation	Stress management; improving concentration
Tai chi	Improving balance, coordination, concentration, and discipline
Yoga	Improving balance, coordination, and concentration

ADHD, Attention-deficit/hyperactivity disorder.

with thin, solid, metallic needles manipulated by hand or by electrical stimulation. Variants include rubbing (**shiatsu**), heat (**moxibustion**), lasers, magnets, pressure (**acupressure**), or electrical currents.

Although pediatric patients may be averse to needles, when approached in a developmentally appropriate way by an acupuncturist trained in pediatrics, children are often amenable to acupuncture and report that it is helpful. Acupuncture can offer significant benefits in the treatment of recurrent headache, anxiety, back and other types of pain, depression, abdominal pain, and nausea. Infections and bleeding are rare but can occur, and more serious complications, such as pneumothorax, occur in <1 in 30,000 treatments.

CANNABIS

Because marijuana has been legalized in many states for both recreational (adult) use and medical use, caregivers and families may inquire about the potential health benefits of cannabis for both children and adults. There are significant safety concerns in adolescents and young adults, because detrimental effects of marijuana on the developing brain have been documented. One systematic review of 90 studies, including 9,441 adolescents and young adults, provided preliminary evidence for functional and structural alterations in frontoparietal, frontolimbic, frontostriatal, and cerebellar regions among adolescent cannabis users.

It is important to note that in some children with severe refractory epilepsy, oral cannabidiol, a nonpsychoactive component in marijuana, improves seizure control. Outside of prescription cannabidiol, the purity and regulation of marijuana and its commercially available component products are variable. Most of the pediatric literature on cannabis describes an increase in accidental ingestions in young children, presumably in association with the increase in products now available for adult use; this is an additional safety risk for pediatricians to consider.

INTERNET RESOURCES

American Academy of Pediatrics Section on Integrative Medicine: https://www.aap.org/en/community/aap-sections/integrative-medicine/about-soim/

Academic Consortium Integrative Medicine and Health: http://www.imconsortium.org/

National Institutes of Health, National Center for Complementary and Integrative Health: https://nccih.nih.gov/

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 8

Pediatric Palliative Care

Katharine Davidoff, Chelsea Heneghan, Joanne Wolfe, and Christina Ullrich

According to the World Health Organization (WHO), "Palliative care for children is the active total care of the child's body, mind and spirit and also involves giving support to the family. Optimally, this care begins when a life-threatening illness or condition is diagnosed and continues regardless of whether or not a child receives treatment directed at the underlying illness." Provision of palliative care applies to children with a wide variety of serious illnesses, including cancer, cystic fibrosis, complex or severe cardiac disease, neurodegenerative disorders, severe malformations, and trauma with life-threatening sequelae (Table 8.1). Many children who benefit from integration of palliative care approaches have **complex chronic conditions and are supported by advanced medical technology that allows them to live longer**. These children, who often survive health crises followed by the renewed need for rehabilitative and life-prolonging treatments, are best served by a system that is flexible and responsive to changing needs and blended goals of care.

Although often mistakenly understood as synonymous with *end-of-life care,* **the scope and potential benefits of palliative care are applicable *throughout the illness trajectory*.** Palliative care emphasizes ascertaining and aligning with goals of care, which may be congruent with maximal treatment aimed at sustaining or prolonging life, optimization of quality of life, communication, and symptom control.

The mandate of pediatric clinicians to attend to children's physical, mental, and emotional health and development includes the provision of palliative care for those who live with a significant possibility of death before adulthood (Fig. 8.1). As such, all pediatric clinicians benefit from using basic (primary) palliative care principles when approaching the care of children living with serious illness. At the same time, such comprehensive physical, psychologic, social, and spiritual care benefits from an interdisciplinary approach.

The philosophy of palliative care can be successfully integrated into any hospital setting, including the ICU, when the focus of care also includes the prevention or amelioration of suffering and improving comfort and quality of life. All interventions that affect the child and family need to be assessed in relationship to these goals. This proactive approach asks the question, "What can we offer that will improve the quality of this child's life and provide the most meaning and sense of control and choice for their family?" instead of, "What therapies are we no longer going to offer this patient?" Staff may benefit from education, support, and guidance on the basic principles of pediatric palliative care, while using specialty-trained pediatric palliative care providers when available for additional support and expertise. *Regardless of the care setting, comprehensive palliative care requires an interdisciplinary approach that may include nurses, physicians, psychologists, psychiatrists, social workers, chaplains/clergy, child life specialists, and trained volunteers.*

GOALS OF CARE AND DECISION-MAKING

In the course of a child's serious illness, a series of important decisions may arise in relation to location of care, medications with risks and benefits, not starting or discontinuing life-prolonging treatments, experimental treatments in research protocols, and use of integrative therapies. Guided discussions around **goals of care** for the child provide opportunities to support decision-making. This is often accomplished

Table 8.1 Conditions Appropriate for Pediatric Palliative Care

CONDITIONS FOR WHICH CURATIVE TREATMENT IS POSSIBLE BUT MAY NOT SUCCEED
Advanced or progressive cancer or cancer with a poor prognosis
Complex and severe congenital or acquired heart disease
CONDITIONS FOR WHICH THERE IS INTENSIVE LONG-TERM TREATMENT AIMED AT PROLONGING LIFE AND MAINTAINING QUALITY OF LIFE, BUT PREMATURE DEATH IS STILL POSSIBLE
Cystic fibrosis
Severe immunodeficiency
High-risk solid-organ transplant candidates and/or recipients (e.g., lung, multivisceral)
Chronic or severe respiratory failure
Muscular dystrophy
Complex multiple congenital malformation syndromes
Primary pulmonary hypertension
Severe chromosomal disorders (aneuploidy, deletions, duplications)
PROGRESSIVE CONDITIONS FOR WHICH THERE IS NO CURATIVE OPTION AND IN WHICH TREATMENT IS ALMOST EXCLUSIVELY PALLIATIVE AFTER DIAGNOSIS
Progressive metabolic disorders (Tay-Sachs disease)
Batten disease
Severe forms of osteogenesis imperfecta
CONDITIONS INVOLVING SEVERE, NONPROGRESSIVE DISABILITY, CAUSING EXTREME VULNERABILITY TO HEALTH COMPLICATIONS
Severe cerebral palsy with recurrent infection or difficult-to-control symptoms
Severe neurologic sequelae of infectious disease
Hypoxic or anoxic brain injury
Brain malformations (e.g., holoprosencephaly, lissencephaly)

Adapted from The Together for Short Lives (formerly the Association for Children's Palliative Care [ACT]) Life-limiting/Life-threatening Condition Categories. http://www.togetherforshortlives.org.uk/professionals/childrens_palliative_care_essentials/approach.

by eliciting parent (and child) understanding of the child's condition and asking open-ended questions that explore the parent's and child's hopes, worries, and family values. Goals-of-care conversations include what is most important for them as a family, considerations of their child's clinical condition, and their values and beliefs, including cultural, religious, and spiritual considerations (see Chapters 2 and 12). Table 8.2 presents specific questions that can effectively guide these discussions, and Figure 8.2 provides a basic framework illustrating a palliative-minded approach to care, anchored by eliciting goals of care and aligning care with those goals. The conversation should also include a review of previous discussions, active listening to concerns and issues as they are raised, opportunities to repeat back elements of the discussion to ensure clarity, and provision of honest, factual answers even in areas of uncertainty. As a provider, it is imperative to consider one's own views and implicit biases before entering into discussions with families who may identify with different cultures, races, or other social determinants (see Chapters 2, 3, and 12).

Decision-making should be focused on the goals of care, as opposed to limitations of care: "This is what we can offer," instead of, "There is nothing more we can do." Rather than meeting specifically to discuss discontinuing life-prolonging therapies or a do-not-resuscitate (DNR) order, a more general discussion centered on the goals of care will naturally lead to considering which interventions are in the child's best interests and can present an opportunity for the clinicians to make recommendations based on these goals. By offering medical recommendations based on family goals and the clinical reality, the team can decrease the burden of responsibility for decision-making that parents carry.

Conflicts in decision-making can occur within families, within healthcare teams, between the child and family, and between the family and care team (see Chapter 6). For children who are developmentally unable to provide guidance in decision-making (neonates, very young children, or children with severe cognitive impairment), parents and healthcare professionals may come to different conclusions as to what is in the child's best interests. Decision-making around the care of adolescents presents specific challenges, given the shifting boundary that separates childhood from adulthood. In some families and cultures, open disclosure and

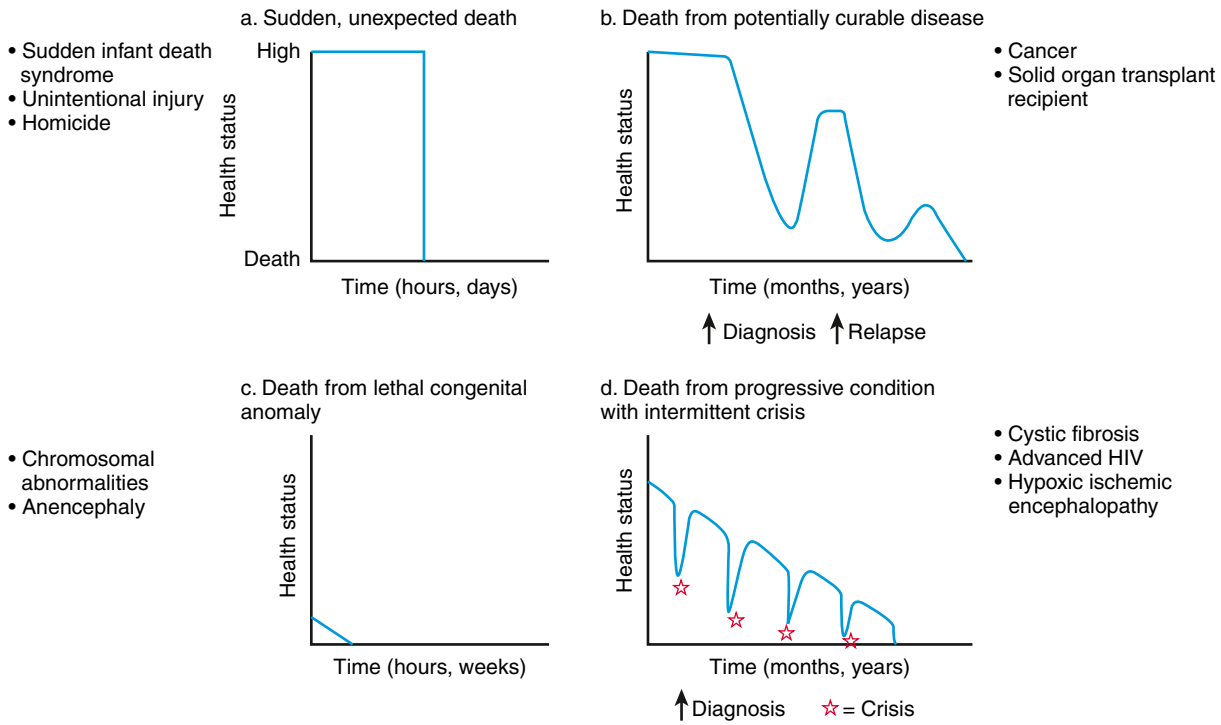

Fig. 8.1 Typical illness trajectories for children with life-threatening illness. (*From Field M, Behrman R [eds]. When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families. Washington, DC: National Academies Press;2003: 74.*)

autonomy are secondary to maintaining the integrity of the family (see Chapter 12). Although frequently encountered, differences in opinion are often manageable for all involved when lines of communication are kept open, team and family meetings are held, and the goals of care are clear.

ADVANCE CARE PLANNING

Although accurate prognostication is a particular challenge in pediatrics, the medical team often recognizes a poor prognosis before the prognosis is understood by parents or the child. This delay may impede informed decision-making about how the child lives at the end of life. Given the inherent prognostic uncertainty of a serious, life-threatening diagnosis, discussions concerning resuscitation, symptom control, and end-of-life care planning should be initiated when the physician recognizes that a significant possibility of patient mortality exists. Having these conversations in the midst of a crisis is not ideal. Whenever possible, they should occur well in advance of the crisis or when the patient has recovered from a crisis but is at high risk for others.

Patients and families are most comfortable being cared for by physicians and other care providers with whom they have an established relationship. Even in the face of long-standing and highly connected relationships, clinicians often hold assumptions about parent prognostic awareness, as well as parent readiness and willingness to have such discussions. In an attempt to protect families, clinicians may avoid conversations they perceive as promoting distress or hopelessness. However, parents greatly value honesty, and in fact such conversations can promote parent hopefulness and trust and connection with the care team. At times, a *consultative* specialty palliative care team provides the family with an opportunity to engage in sensitive conversations that may not as readily occur with the primary team, at least initially.

The population of individuals who die before reaching adulthood includes a disproportionate number of nonverbal and preverbal children and adolescents who are developmentally unable to make autonomous care decisions. Although parents are usually the primary decision-makers, these youth should be as fully involved in discussions and decisions about their care as appropriate for their developmental status. Using communication experts, child life therapists, chaplains, social workers, psychologists, and psychiatrists to allow children to express themselves through art, play, music, talk, and writing will enhance the provider's knowledge of the child's understanding and hopes. Tools such as **Five Wishes** (for adults), **Voicing My Choices** (for adolescents), and **My Wishes** (for school-age children) have in practice been useful in helping to introduce advance care planning to children, adolescents, and their families (www.agingwithdignity.org/index.php).

Table 8.2 Five Basic Questions to Guide the "Goals of Care" Conversation

PHRASING FOR ADULT OR OLDER ADOLESCENT	PHRASING FOR CHILD
Tell us about your child as a person. What does your child enjoy?	Tell me about yourself before you got sick.
What is your understanding of your child's illness/condition?	Why are you in the hospital? What do you understand about your illness?
In light of your understanding, what is most important to you regarding your child's care?	What do you want others to know or do for you when taking care of you?
What are you hoping for? What are your worries?	I wonder if there is anything that is worrying you or that is keeping you up at night. Is there anything you wish you could talk about?
What gives you strength in the face of your child's illness/condition?	What helps you get through the day? What helps you feel good?

Resuscitation Status

Many parents do not understand the legal mandate requiring attempted resuscitation for cardiorespiratory arrest unless a written DNR order is in place. In broaching this topic, rather than asking parents if they want to forgo cardiopulmonary resuscitation (CPR) for their child (and placing the burden of decision-making on them), discuss whether or not resuscitative interventions are likely to benefit the child. It is important to make recommendations based on overall goals of care and medical knowledge of potential benefit and/or harm of these interventions. Once the goals of therapy are agreed on, the physician is required to write a formal order. Out-of-hospital DNR verification forms are available which, if completed on behalf of the child, affirm that rather than initiating resuscitative efforts, emergency response teams are obligated to provide appropriate symptom management intended to support

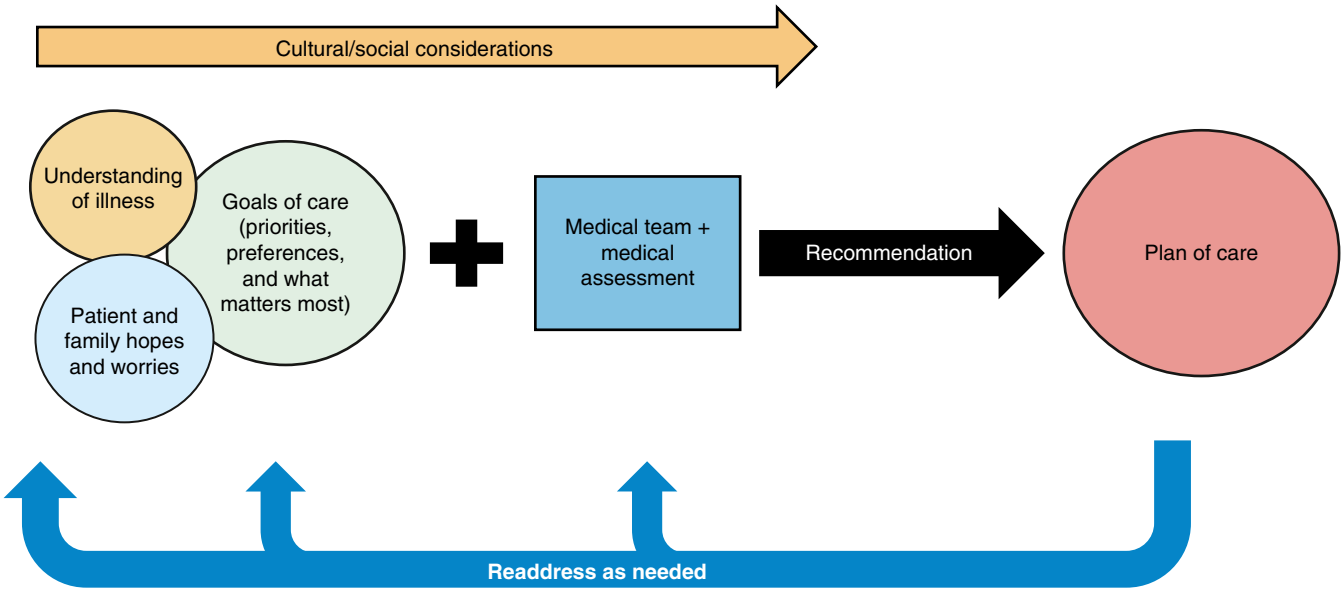

Fig. 8.2 A framework for creating plans of care with a palliative-minded approach, anchored by patient/family goals of care.

comfort and relief of suffering with appropriate interventions when called to the scene.

All states have implemented the **physician orders for life treatment (POLST) system**. A POLST order is completed for children with life-threatening illness, creating actionable orders for interventions to pursue versus avoid based on the expressed parent's and/or child's wishes (polst.org). It is usually helpful to frame discussions about POLST as ways for parents to maintain some control by communicating their goals and care preferences so their wishes may be honored, irrespective of the setting. It may also be beneficial to write a letter that delineates decisions regarding resuscitation interventions and supportive care measures to be undertaken for the child, particularly if POLST are not available. The letter should be as detailed as possible, including recommendations for comfort medications and contact information for the care team best known to the patient. Such a letter, given to the parents, with copies to the involved care team and institutions, can be a useful communication aid, especially in times of crisis. In any case, if a child dies in the home setting and the parents opt to use an out-of-hospital DNR verification form or POLST, plans to pronounce the child and provide support for the family must be in place. If the child has been referred to hospice, the hospice usually fulfills those responsibilities.

CARE SETTINGS

Pediatric palliative care should be provided across settings, including hospital, outpatient, and home, as well as pediatric nursing facilities and sometimes inpatient hospice locations. **Home care** for the child with a life-threatening illness requires 24 hour/day access to experts in pediatric palliative care, a team approach, and an identified coordinator who serves as a link among hospitals, the community, and specialists and who may assist in preventing or arranging for hospital admissions, respite care, and increased home care support as needed based on the child's clinical condition and goals of care. Adequate home care support and respite care, although sorely needed, is often not readily available, given gaps in staffing or the high-tech skills required to care for these children. Furthermore, families may view using respite care as a personal failure, or they may worry that others cannot adequately care for their child's special needs or potential rapid escalation of symptoms.

In the United States, the healthcare and reimbursement structure, combined with frequent use of medical technology (e.g., home ventilatory support) or continuous home nursing, historically precluded formal enrollment of children on the hospice benefit when they were otherwise eligible (i.e., had estimated prognosis of ≤6 months). Section 2302 of the Patient Protection and Affordable Care Act (ACA), the Concurrent Care for Children Requirement (CCCR), eliminated the requirement that Medicaid patients <21 years old forgo curative or life-prolonging therapies to be eligible for hospice. Although Medicaid programs in every state are required to provide concurrent curative/life-prolonging treatment and hospice services for hospice-eligible children, development of systems to make such concurrent care a reality has been slow. A limitation of the CCCR is that it does not expand access to hospice for children with life-threatening illness who do not meet hospice eligibility criteria (i.e., have a prognosis that cannot be estimated to be <6 months) or those not receiving Medicaid.

A number of state-based pediatric palliative care coalitions have formed to improve access to home-based pediatric hospice/palliative care services, using strategies such as Medicaid waivers or state plan amendments to increase coverage for hospice services. A growing number of home care agencies have also developed palliative care programs that serve as a bridge to hospice services for children not yet meeting hospice eligibility criteria. Some hospices have adopted an **open hospice** model with more flexible eligibility criteria. However, provision of hospice or palliative care for children is often also limited by the availability of clinicians who have training or experience in caring for seriously ill children. Furthermore, there are only a few inpatient facilities in existence within the United States that provide end-of-life care exclusively to pediatric patients.

At the end of life, children and families may need intensive support. About half of pediatric deaths occur in acute care hospitals, and end-of-life care may otherwise be provided in the home, pediatric nursing facility, or hospice house. Families need to feel safe and well cared for and given permission, if possible, to choose the location of care. In tertiary care hospitals, most children die in the neonatal and pediatric ICUs. In some instances, when death at home for a child in the ICU is preferred, transport and even extubation at home may be possible, if clinical and logistical circumstances permit it and support it.

COMMUNICATION AND ANTICIPATORY GUIDANCE

Parents

For parents (parents defined as any primary caregivers for children), **compassionate communication** with medical providers who understand their child's illness, treatment options, and family beliefs and goals is the cornerstone of caring for children with serious illness. During this time, one of the most significant relationships is that with the child's primary care clinician, who often has an enduring relationship with the child and family, including healthy siblings. Although a family's goals may change with the child's evolving clinical condition and other variable factors, *parents need to know that their child's primary care clinician will not abandon them as the goals of care evolve.* A flexible approach rooted in ongoing communication and guidance that incorporates understanding of the family's values, goals, and religious, cultural, spiritual, and personal beliefs is of paramount importance.

Pediatricians should recognize the important role they have in continuing to care for the child and family, because the primary goal of treatment may simultaneously be prolongation of life as well as comfort, relief of suffering, and promoting quality of life. Regular meetings between the care team and the family are essential to reassess and manage symptoms, explore the impact of illness on immediate family members, and provide anticipatory guidance. At these meetings, important issues with lifelong implications for parents and their child may be discussed. Such discussions should be planned with care, ensuring that adequate time for in-depth conversation is allotted; a private, physical setting is arranged; devices are silenced; and both parents and others who might be identified by the family as primary supports are present. Strategies for facilitating conversations related to goals of care and decision-making are detailed later.

Families may look to their pediatrician for assurance that all treatment options have been explored. Assisting a patient's family to arrange a second opinion may be helpful. Listening to families and children speak about the future even in the face of a poor prognosis may help keep the focus on living even while the child may be dying. Hoping for a miracle can coexist for parents even as they are facing and accepting the reality of death.

Parents also need to know about the availability of home care, respite services, web-based support (e.g., www.courageousparentsnetwork.org), educational materials, and support groups. Responding to parental requests or need for counseling referrals for themselves, other children, or the family is essential. Also, attending to the concrete needs of families (e.g., financial, insurance, housing) can be paramount in freeing them from worries that might interfere or compete with their ability to be fully present in their child's care.

When closer to the patient's end of life, although broaching the topic may seem daunting, exploration of how parents envision their child's death, addressing their previous loss experiences (most often with death of an adult relative) and any misconceptions, is often a great relief. *Learning about cultural, spiritual, and family values regarding pain management, suffering, and the preferred place of end-of-life care is essential* (see Chapters 2 and 12). Even mentioning funeral arrangements, possible autopsy, and organ/tissue donation pre-emptively can be helpful to give parents choices and know that these considerations can be discussed without fear. A major worry of many parents is how to involve and communicate with siblings, as well as the child, about the likelihood of impending death.

Ratings of "high satisfaction" with physician care have been directly correlated with receiving **clear communication** around end-of-life issues, delivered with sensitivity and caring; such communication included speaking directly to the child when appropriate. Communication may be complicated by **mutual protection** in which the child

wants to protect his or her parents, and likewise the parents want to protect their child, from painful information, sadness, or fear. Honoring the uniqueness of the child and understanding and respecting the family's communication style, values, spirituality, and culture are critical in these highly sensitive conversations. Evidence shows that parents who have open conversations with their child about death and dying do not regret having done so, whereas many parents who do not engage in these conversations regret avoiding them.

In communications with the child and family, the physician should avoid giving specific estimates of survival length, even when the child or family explicitly asks for them. These predictions are invariably inaccurate because population-based statistics do not predict the course for individual patients. A more honest approach may be to explore *ranges of time in general terms* (days to weeks, weeks to months, months to years) while recognizing that children with serious illness are also susceptible to acute events that cause rapid deterioration. The physician can also ask parents what they might do differently if they knew how long their child would live, then assist them in thinking through the options relating to their specific concerns (e.g., suggest celebrating upcoming holidays or important events earlier to take advantage of times when the child may be feeling better). It is generally wise to suggest that relatives who wish to visit might do so earlier rather than later, given the unpredictable trajectory of many conditions.

For the child and family, the integration of "bad news" is a *process,* not an event, and when done sensitively, does not take away hope or alter the relationship between the family and physician. The physician should expect that some issues previously discussed may not be fully resolved for the child and parents (e.g., DNR orders, artificial nutrition or hydration) and may need to be revisited over time. Parents of a child with a chronic illness may reject the reality of an impending death because past predictions may not have been accurate. Whether they are parents of a child with a chronic illness or a child whose death is the result of an accident or sudden catastrophic illness, they may experience great anxiety, guilt, or despair.

The Child

Truthful communication that takes into account the child's developmental stage and unique lived experience can help to address the fear and anxiety commonly experienced among children with serious illness. Responding in a developmentally appropriate fashion (Table 8.3) to a child's questions about death (e.g., "What's happening to me?" or "Am I dying?") requires a careful exploration of what is already known by the child, what is really being asked *(the question behind the question),* and why the question is being asked at this particular time and in this setting. It may signal a need to be with someone who is comfortable listening to such unanswerable questions. Many children find nonverbal expression much easier than talking; art, play therapy, and storytelling may be more helpful than direct conversation.

A child's perception of death depends on his or her conceptual understanding of *universality* (that all things inevitably die), *irreversibility* (that dead people cannot come back to life), *nonfunctionality* (that being dead means that all biologic functions cease), and *causality* (that there are objective causes of death).

Very young children may struggle with the concepts of irreversibility and nonfunctionality. For young school-age children, who are beginning to understand the finality of death, worries may include *magical thinking* in which their thoughts, wishes, or bad behavior might be the underlying cause for their illness. Older children seek more factual information to gain some control over the situation.

Children's fears of death are often centered on the concrete fear of being separated from parents and other loved ones and what will happen to their parents rather than themselves. This can be true for teens and young adults as well. This fear may be responded to in different ways: some families may give reassurance that loving relatives will be waiting, and others use religious concepts to refer to an eternal spiritual connection.

Adolescents may have a conceptual understanding of death similar to that of adults, but working with the adolescent with life-threatening illness presents unique concerns and issues. The developmental work of adolescence includes separating from their parents, developing strong peer relationships, and moving toward independent adulthood. For this population, the teenager's developmental need to separate is complicated by the increasing dependence both physically and emotionally on their parents. Providing space for these conversations and communicating openly and honestly supports independence while also meeting the adolescent's individual need.

In addition to developmental considerations, understanding related to the child's life experiences, the length of the child's illness, the understanding of the nature and prognosis of the illness, the child's role in the family, and the complex relationship between the child and their parents as primary caretakers should be considered in communication with children.

The question of whether and when to involve adolescents in decision-making arises particularly often. There is no one answer to this question. Instead, numerous considerations should be taken into account, including the adolescent's chronological age, developmental stage, adolescent preference with regard to such participation, and the family's preferred approach to communication and decision-making.

Parents have an instinctive and strong desire to protect their children from harm. When facing the death of their child, many parents attempt to keep the reality of impending death hidden from their child, hoping the child can be protected from the harsh reality. Although it is important to respect parental wishes, it is also true that most children already have a sense of what is happening to their bodies, even when it has been purposely left unspoken. Children may blame themselves for their illness and the resulting hardships for their loved ones. *Perpetuating the myth that "everything is going to be all right" takes away the chance to explore fears and provide reassurance.* Assisting parents to understand that the key to honest communication is not telling a child he or she is dying, but opening the door to conversation and validating what the child *already knows*. Honest communication also allows opportunities for memory and legacy making and saying goodbye.

School is the work of childhood and adolescence and is important in optimizing quality of life for a child seeking normalcy in the face of illness. Finding ways to help children and their families to maintain these connections through modification of the school day and exploring options to promote educational and social connections into the home or into the hospital room can be meaningful in the event that a child is not well enough to attend school. Video conferencing can be readily arranged from almost any setting.

The Siblings

Siblings are at special risk both during their sibling's illness and after the death. Because of the extraordinary demands placed on parents to meet the needs of their ill child, healthy siblings may feel their own needs are not being acknowledged or fulfilled. These feelings of neglect may then trigger guilt about their own good health and resentment toward their parents and ill sibling. Younger siblings may react to the stress by becoming seemingly oblivious to the turmoil around them. Some younger siblings may feel guilty for wishing the affected child would die so they could get their parents back (magical thinking). Parents need to know that these are normal responses, and siblings should be encouraged to maintain the typical routines of daily living. Siblings who are most involved with their sick sibling before death usually adjust better both at the time of and after the death. Acknowledging and validating sibling feelings, being honest and open, and appropriately involving them in the life of their sick sibling provide a good foundation for the grief process. It is often helpful to identify a person in the family (e.g., caring aunt) or school (e.g., counselor) to offer confidential and supportive opportunities for the sibling to reflect on their family experience, particularly as parents may be too overwhelmed to provide this at crucial times.

The Staff

Inadequate support for the staff providing palliative care can result in depression, emotional withdrawal, and other symptoms. Offering educational opportunities and emotional support in the form of both

Table 8.3 Developmental Questions, Thoughts, and Concepts of Dying, with Responsive Strategies

TYPICAL QUESTIONS AND STATEMENTS ABOUT DYING	THOUGHTS THAT GUIDE BEHAVIOR	DEVELOPMENTAL UNDERSTANDING OF DEATH	STRATEGIES AND RESPONSES
MONTHS TO 3 YR OF AGE			
"Mommy, don't cry." "Daddy, will you still tickle me when I'm dead?"	Child has limited understanding of events, future and past, and of the difference between living and nonliving.	Child may have "sense" that something is wrong. Death is often viewed as continuous with life (analogous to being awake and being asleep).	Optimize comfort and consistency; familiar persons, objects, routines. Use soothing songs, words, and touch. "I will always love you." "I will always take care of you." "I will tickle you forever."
AGE 3-5 YR			
"I did something bad and so I will die." "Can I eat anything I want in heaven?"	Concepts are simple and reversible. Variations between reality and fantasy.	Child may see death as temporary and reversible and not universal. Child may feel responsible for illness. Death may be perceived as an external force that can get you.	Assure child that illness is not their fault. Provide a consistent care team. Promote honest, simple language. Use books to explain the life cycle and promote questions and answers. "You did not do anything to cause this." "You are so special to us, and we will always love you." "We know (God, Jesus, Grandma, Grandpa) are waiting to see you."
AGE 5-10 YR			
"How will I die?" "Will it hurt?" "Is dying scary?"	Child begins to demonstrate organized, logical thought. Thinking becomes less esoteric. Child begins to problem-solve concretely, reason logically, and organize thoughts coherently. However, child has limited abstract reasoning.	Child begins to understand death as real and permanent. Death means that your heart stops, your blood does not circulate, and you do not breathe. It may be viewed as a violent event. Child may not accept death could happen to himself or herself or to anyone he or she knows, but starts to realize that people they know will die.	"Tell me why you are asking." Be honest and provide specific details if they are requested. Help and support the child's need for control. Permit and encourage the child's participation in decision-making. "We will work together to help you feel comfortable. It is very important that you let us know how you are feeling and what you need. We will always be with you, so you do not need to be afraid."
AGE 10-18 YR			
"I'm afraid if I die my mom will just break down." "I'm too young to die. I want to get married and have children." "Why is God letting this happen?"	Abstract thoughts and logic possible. Body image is important. Child needs peer relationships for support and for validation. Child expresses altruistic values, such as staying alive for family (parents, siblings) and donating organs/tissue. Disbelief that they are dying.	Understand death as irreversible, inevitable, and universal. Child needs reassurance of continued care and love. Search for meaning and purpose of life.	Reinforce child's/adolescent's self-esteem, sense of worth, and self-respect. Allow need for privacy, independence, access to friends and peers. Tolerate expression of strong emotions and permit participation in decision-making. "I can't imagine how you must be feeling. Despite it all, you are doing an incredible job. I wonder how I can help?" "What's most important to you now?" "What are your hopes … your worries?" "You have taught me so much; I will always remember you."

Adapted from Hurwitz C, Duncan J, Wolfe J. Caring for the child with cancer at the close of life, *JAMA*. 2003;292:2141–2149.

informal opportunities to express emotions or formal debriefs/check-ins for staff at various stages of caring for a child with life-threatening illness can be helpful in bettering patient/family care and preventing staff from experiencing compassion fatigue, burnout, and long-term repercussions, including leaving the field.

The Pediatric Clinician

Although optimal palliative care for children entails an interdisciplinary care team approach, pediatric clinicians are well positioned to support children and their families, particularly when they have a long-standing relationship with multiple family members. A primary care clinician who has cared for a family over time may already know and care for other family members, understand pre-existing stressors for the family, and be familiar with coping strategies used by family members. For this reason, trusted primary care clinicians may be best suited to explore goals of care, provide difficult news in a compassionate manner, and support families throughout the trajectory of illness. Specialty training is not needed to provide expert primary palliative care; rather, a motivation to guide decisions based on family goals and values and understanding of the community supports available are a sufficient starting point. Pediatric clinicians are familiar with the process of eliciting concerns and providing anticipatory guidance for parents, as well as developmentally appropriate explanations for children. Those interested in developing skillful communication techniques surrounding serious illness have many resources available, including VitalTalk (vitaltalk.org).

Symptom Management

Intensive symptom management is another cornerstone of pediatric palliative care. Alleviation of symptoms reduces suffering of the child and family and allows them to focus on other concerns and participate in meaningful experiences. Despite increasing attention to symptoms and pharmacologic and technical advances in medicine, children often suffer from multiple symptoms. Figure 8.3 provides key elements and general approaches to managing symptoms.

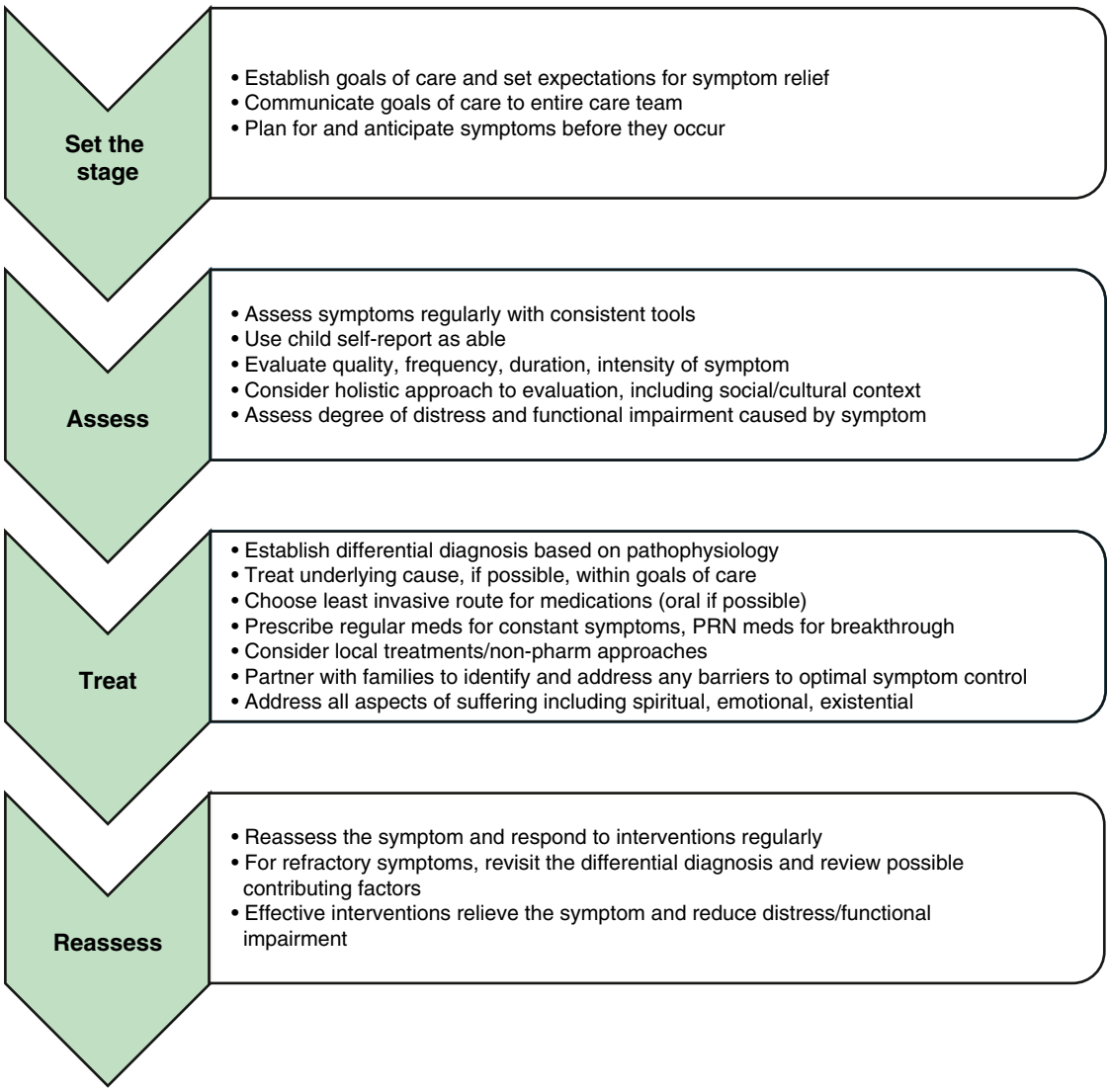

Fig. 8.3 Key elements of effective symptom management.

Pain is a complex sensation triggered by actual or potential tissue damage and influenced by cognitive, behavioral, emotional, social, and cultural factors. Effective pain relief is essential to prevent *central sensitization,* a central hyperexcitation response that may lead to hypersensitivity and escalating pain, and to diminish a stress response that may have a variety of physiologic effects. Assessment tools include self-report tools for children who can communicate their pain verbally and tools based on behavioral cues for children who are unable to do so because of their age, medical condition, or a neurodevelopmental disorder. Figure 8.4 and Tables 8.4 and 8.5 address management of pain (see also Chapter 93).

Many children with life-threatening illness experience pain that requires **opioids** for adequate relief at some point in their illness trajectory. The WHO pain guidelines recommend the first step for mild pain and the second step for moderate to severe pain (Fig. 8.4). Prescribing *codeine* should be avoided because of its side effect profile and lack of superiority over nonopioid analgesics. Furthermore, relatively common genetic polymorphisms in the *CYP2D6* gene lead to wide variation in codeine metabolism. Specifically, 10–40% of individuals carry polymorphisms causing them to be *poor metabolizers* who cannot convert codeine to its active form, *morphine,* and therefore are at risk for inadequate pain control. Others are *ultrametabolizers* who may even experience respiratory depression from rapid generation of morphine from codeine. It is therefore preferable to use a known amount of the active agent, morphine. Federal and state health agencies in the United States have put forth considerable effort in establishing guidelines for opioid prescribing. Before prescribing opioids, create an opioid agreement with patients and families, check the state's electronic prescription monitoring program, and limit opioid prescription for minors to 7 days or less for *initial* opioid prescription.

It is important to explore with families and members of the care team misconceptions that they may have regarding opioids, such as respiratory depression, addiction, dependence, the symbolic meaning of starting an opioid such as methadone or morphine and/or a morphine drip, and the potential for opioids to hasten death. *There is no association between administration or escalation of opioids and length of survival.* In fact, evidence supports longer survival in individuals with symptoms that are well controlled. Collaboration with specialty palliative care and/or hospice care teams can help guide complex symptom management.

Children with serious illness and medical complexity often experience a multitude of nonpain symptoms. A combination of both pharmacologic (see Table 8.4) and nonpharmacologic (see Table 8.5) interventions is often optimal. **Fatigue** is one of the most common symptoms in children with advanced illness. Children

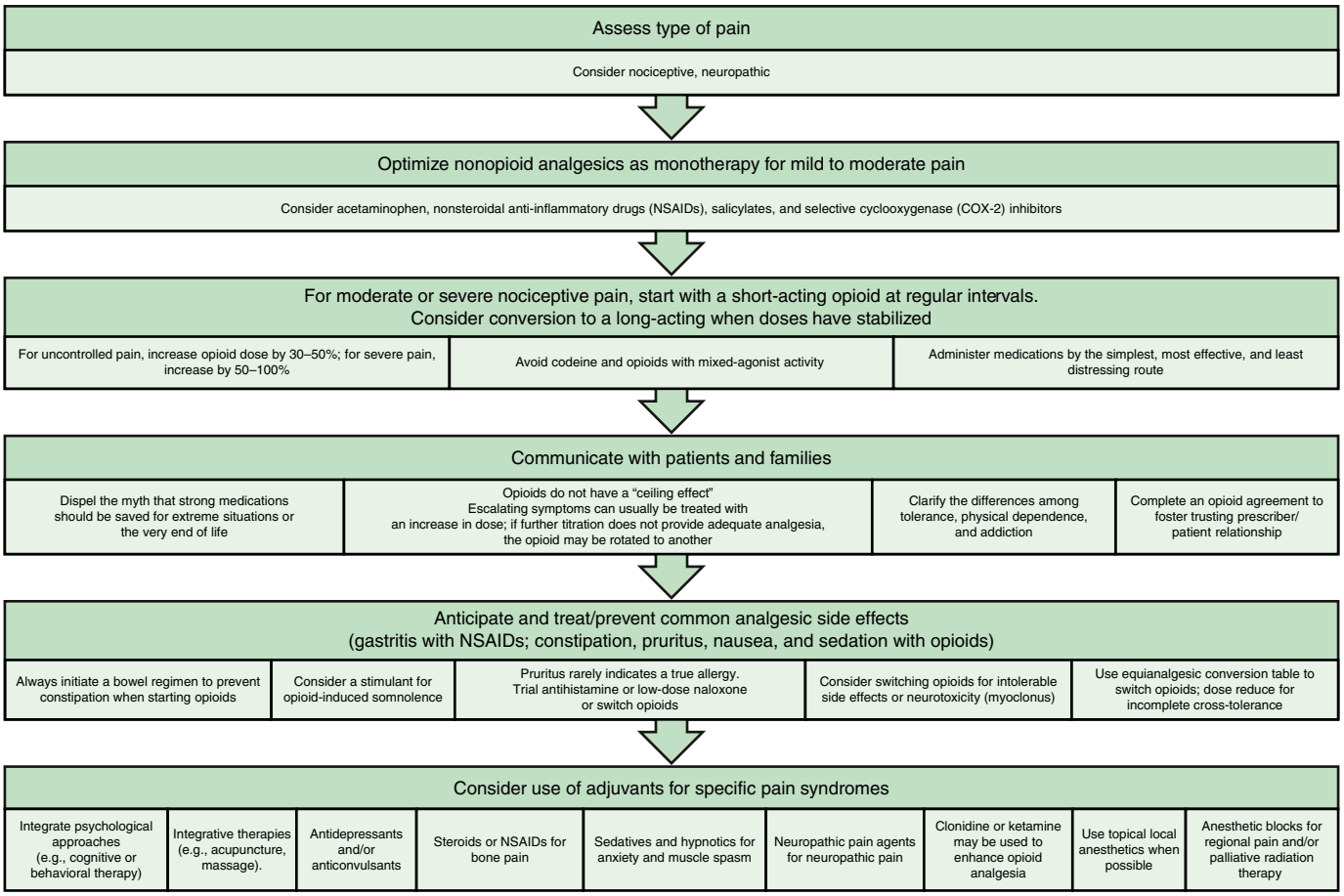

Fig. 8.4 Guidelines for pain management related to life-threatening illness.

Table 8.4 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pain—mild	Acetaminophen	15 mg/kg PO q4h, max 3 g/day or 40 mg/kg/day	Available PO (including liquid), PR, or IV
	Ibuprofen	10 mg/kg PO q6h	PO (including liquid) only; avoid if risk of bleeding; use only in infants ≥6 mo. Use with caution in congestive heart failure. Chewable tablets contain phenylalanine.
	Naproxen	5mg/kg PO q12h	Avoid if risk of bleeding; may cause nephrotoxicity.
	Celecoxib	1-2 mg/kg (max 100-200 mg) PO q12-24h	Selective cyclooxygenase (COX-2) inhibitor has low risk of gastritis and low antiplatelet activity.
	Ketorolac	0.5 mg/kg (15-30 mg) IV q6h, max 24h dose 120 mg	Do not use longer than 5 days; may cause nephrotoxicity.
Pain—moderate/severe	Morphine immediate release (i.e., MSIR)	0.3 mg/kg PO q4h if <50 kg 15 mg PO q4h if >50 kg*† 0.05-0.1 mg/kg IV q2-4h	Also available in IV/SC formulation. Reduce dose in renal/hepatic impairment.‡§
	Oxycodone	0.1 mg/kg PO q4h if <50 kg 5-10 mg PO q4h if >50 kg*†	No injectable formulation. Longer half-life than morphine. Reduce dose in renal/hepatic impairment.‡§
	Hydromorphone	0.05 mg/kg PO q4h if <50 kg 2-4 mg PO q4h if >50 kg*† 0.015 mg/kg IV q2-4h	Also available in IV/SC formulation. Injectable form very concentrated, facilitating subcutaneous delivery. Preferred drug in liver impairment.‡§
	Fentanyl	0.5-1.5 µg/kg IV/SC q30min*†	Rapid infusion may cause chest wall rigidity. Preferred drug in renal impairment.‡§

Continued

Table 8.4 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pain—sustained-release formulations	MS Contin Kadian (contains sustained-release pellets) Oramorph	Total daily dose of MSIR divided bid-tid	Do not crush MS Contin. For those unable to swallow pills, Kadian capsules may be opened and contents mixed with food, but *cannot be chewed*. Kadian contents may be mixed in 10 mL water and given via 16-French G-tube. Larger-dose formulation may not be suitable for small children.§
	Oxycontin	Total daily dose of oxycodone divided bid-tid	Do not crush.§
	Transdermal fentanyl patch	Divide total 24 hr PO morphine dose by 2 to determine starting dose of transdermal fentanyl. No data exist on the equianalgesic conversion from transdermal fentanyl to any oral opioid.	Smallest patch size may be too high for small children. Patches are for children >2 yr. Apply to upper back in young children. Patch may **not** be cut. Typically for patients taking at least 60 mg morphine/day or its equivalent. Not appropriate when dosage changes are frequent or for opioid-naïve patients. Fever >40°C results in higher serum concentrations.§
	Methadone	Starting dose 0.1-0.2 mg/kg PO bid. May give tid if needed. Recommend consultation with experienced clinician for equivalence dosing from other opioids.*†	Only opioid with immediate and prolonged effect; available as a liquid; do not adjust dose more often than every 72 hr because prolonged biologic half-life is greater than therapeutic half-life. Knowledge of methadone pharmacokinetics is needed for converting to and from doses of other opioids. Also available IV/SC. May cause QT interval prolongation (consider ECG), especially in adults on >200 mg/day or in those at risk for QT prolongation. Interacts with several antiretroviral, antiepileptic agents.§
Pain—Neuropathic	Gabapentin	Start at 5 mg/kg/day at bedtime and gradually increase to 10-15 mg/kg/day divided tid; titrate up by 5 mg/kg/day q3-4 days as needed, but not to exceed 50-75 mg/kg/day (3,600 mg/day)	May cause neuropsychiatric events in children (aggression, emotional lability, hyperkinesia), usually mild but may require discontinuation of gabapentin. May cause dizziness, drowsiness, tremor, nystagmus, ataxia, and swelling.
	Nortriptyline	0.5 mg/kg PO at bedtime (max 150 mg/day). Begin at lower dose and titrate every 3-4 days until therapeutic effect or max dose.	Fewer anticholinergic side effects than amitriptyline. May cause constipation, sedation, postural hypotension, and dry mouth. May cause QT interval prolongation (consider ECG). At higher doses, monitor ECG and plasma levels.
	Pregabalin	Start at 1 mg/kg/dose PO at bedtime for 3 days, then increase to 1 mg/kg/dose bid. Increase every 3 days to 3 mg/kg/dose PO bid (max 6 mg/kg/dose).	See gabapentin.
	Methadone	See previous listing	See previous listing.
Dyspnea	Morphine, immediate release (i.e., MSIR)	0.1 mg/kg PO q4h prn*†	All opioids may relieve dyspnea. For dyspnea, the starting dose is 25–35% of the dose that would be administered for pain.§
	Lorazepam	0.025-0.05 mg/kg IV/PO q6h, up to 2 mg/dose	See previous listing For anxiety contributing to dyspnea
Respiratory secretions	Scopolamine patch	1.5 mg patch, change q72h (for children >8-12 yr old)	Excessive drying of secretions can cause mucus plugging of airways. Good for motion-induced nausea and vomiting. Handling patch and contacting eye may cause anisocoria and blurry vision. May fold patches, but do not cut them. Anticholinergic side effects possible.
	Glycopyrrolate	0.04-0.1 mg/kg PO q4-8h	Powerful antisialagogue. Excessive drying of secretions can cause mucus plugging of airways. Anticholinergic side effects possible. Quaternary ammonium structure limits its ability to cross lipid membranes, such as the blood-brain barrier (in contrast to atropine, scopolamine, and hyoscyamine sulfate), so may exert fewer central anticholinergic effects.
	Hyoscyamine sulfate	PO/SL: *2-12 yr*: 0.0625-0.125 mg q4h as needed; max daily dosage 0.75 mg *or* timed release 0.375 mg q12h; max daily dosage 0.75 mg *>12 yr-adult*: 0.125-0.25 mg q4h as needed; max daily dosage 1.5 mg *or* timed release 0.375-0.75 mg q12h; max daily dosage 1.5 mg	Anticholinergic side effects possible, including sedation. May be given sublingually.
	Atropine	1-2 gtt SL q4-6h prn	Give 0.5% ophthalmic drops sublingually.

Table 8.4 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Nausea	Metoclopramide	0.1-0.2 mg/kg/dose q6h, up to 10 mg/dose (prokinetic and mild nausea dosing). For chemotherapy-associated nausea, 0.5-1 mg/kg q6h prn PO/IV/SC; give with diphenhydramine and continue diphenhydramine for 24 hr after last dose of high-dose metoclopramide to prevent extrapyramidal reaction.	Helpful when dysmotility is an issue; may cause extrapyramidal reactions, particularly in children after IV administration of high doses. Contraindicated in complete bowel obstruction or pheochromocytoma. Avoid concomitant use with olanzapine.
	Ondansetron	0.15 mg/kg dose IV/PO q8h prn. No single IV dose should exceed 16 mg because of risk of QT prolongation.	Significant experience in pediatrics. Good empirical therapy for nausea in palliative care population. Oral dissolving tablet contains phenylalanine. Higher doses used with chemotherapy, although single 32 mg IV dose is no longer available (risk for QT prolongation). Consider ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or in patients taking other medications with the potential to cause QT prolongation. May cause constipation.
	Dexamethasone	0.1 mg/kg/dose tid PO/IV; max dose 10 mg/day	Also helpful with hepatic capsular distension, bowel wall edema, anorexia, increased ICP. May cause mood swings or psychosis.
	Lorazepam	See previous listing.	Helpful for anticipatory nausea
	Dronabinol	<6 *yr*: No dosing information; use with caution 6-12 *yr*: 2.5-5 mg/dose PO q6h prn or scheduled >*12 years:* 5-7.5 mg/dose PO q6h prn or scheduled; max dosage (escalating): 5 mg 4 times/day (20 mg/day)	Available in 2.5 and 5 mg capsules and 5 mg/mL liquid. May remove liquid contents from capsules for children who cannot swallow capsules. Avoid in patients with sesame oil hypersensitivity or history of schizophrenia. May cause euphoria, dysphoria, strange dreams, or other mood changes. Tolerance to CNS side effects usually develops in 1-3 days of continuous use. Avoid in patients with depression or mania.
	Scopolamine patch	See previous listing	See previous listing
	Olanzapine	4-6 yr: 1.25 mg PO daily 6-12 yr: 2.5 mg PO daily ≥12 yr: 5 mg daily; doses may be titrated to max of 10 mg/day	Little evidence to guide antiemetic dosing. Ranges largely derived from olanzapine dosing for other purposes. Avoid concomitant use with metoclopramide.
Anxiety	Lorazepam	See previous listing	See previous listing
Agitation/ delirium	Haloperidol	0.01 mg/kg PO tid prn for acute onset: 0.025-0.050 mg/kg PO, may repeat 0.025 mg/kg in 1 hr prn	May cause extrapyramidal reactions, which can be reversed with diphenhydramine or Cogentin. Safety not established in children <3 yr.
Sleep disturbance/ insomnia	Trazodone	Children 6-18 yr: 0.75-1 mg/kg/dose, given bid-tid if needed If >18 yr, start at 25-50 mg/dose, given bid-tid if needed Max dose 150 mg/dose	Potentially arrhythmogenic
Fatigue	Methylphenidate	0.3 mg/kg/dose (2.5-5 mg) titrated as needed, up to 60 mg/day	Rapid antidepressant effect; also improves cognition. Administer before meals to avoid appetite suppression. Use with caution in children at risk for cardiac arrhythmia. Available as liquid and chewable tablet and transdermal patch.
Pruritus	Diphenhydramine	0.5-1 mg/kg q6h IV/PO (100 mg max per day)	Indicated for histamine-mediated itch. May reverse phenothiazine-induced dystonic reactions. Topical formulation on large areas of the skin or open area may cause toxic reactions. May cause paradoxical reaction in young children. Typically ineffective for opioid-associated pruritus.
	Hydroxyzine	0.5-1 mg/kg q6h IV/PO (600 mg max per day)	
	Naloxone	0.25-2 mcg/kg/hr continuous IV infusion	Low-dose continuous infusion indicated for opioid-induced itch
	Nalbuphine	0.02 mg/kg (1.5 mg) IV q6h PRN	For opioid-induced itch
Constipation	Docusate	40-150 mg/day PO in 1-4 divided doses	Stool softener available as liquid or capsule

Continued

Table 8.4 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
	MiraLAX	<10 kg: ¼ scoop (4.25 g) daily <5 yr: 1/2 scoop (8.5 g) in 4 oz water daily *>5 yr*: 1 scoop (17 g) in 8 oz water daily	Tasteless powder may be mixed in beverage of choice. Now available over the counter.
	Lactulose	5-10 mL PO up to q2h until bowel movement or 15-30 mL PO bid	Bowel stimulant; dosing q2h may cause cramping.
	Senna	2.5-5 mL PO daily (for children >27 kg)	Bowel stimulant; available as granules
	Dulcolax (bisacodyl)	3-12 yr: 5-10 mg PO daily >12 yr 5-15 mg PO daily	Available in oral or rectal formulation
	Pediatric Fleets Enema	*2-4 yr*: Administer one half contents of one 2.25 oz pediatric enema *5-11 yr*: Administer contents of one 2.25 oz pediatric enema ≥*12 yr* and adolescents: Administer contents of one 4.5 oz enema as single dose	May repeat ×1 if needed. Do not use in neutropenic patients.
	Methylnaltrexone	10 mg/dose 10-20 kg: 2 mg SC 21-33 kg: 4 mg SC 34-46 kg: 6 mg SC 47-62 kg: 8 mg SC 63-114 kg: 12 mg SC ≥115 kg: 0.15 mg/kg SC Administer 1 dose every other day as needed; max 1 dose/24 hr	Peripherally acting opioid antagonist for opioid-induced constipation. Usually works within 30-60 min of administration. May cause cramping.
Muscle spasm	Diazepam	Oral/IM/IV: *<50 kg*: 0.05 mg/kg q6h (titrate to 0.2 mg/kg/dose max) *>50 kg*: 2.5 mg q6h (titrate to 10 mg/dose max)	May be irritating if given by peripheral IV line.
	Baclofen	5 mg PO tid, increase by 5 mg/dose as needed. Max 80 mg/day.	Helpful with neuropathic pain and spasticity; abrupt withdrawal may result in hallucinations and seizures; not for children <10 yr
Seizures	Lorazepam	0.1 mg/kg IV/PO/SL/PR repeat q10min × 2	
	Diazepam	0.1 mg/kg IV/PO q6h (max 5 mg/dose if <5 yr; max 10 mg/dose if >5 yr)	May be given PR as Diastat (0.2 mg/kg/dose q15min ×3 doses)
Neuroirritability	Gabapentin	See previous listing	
	Clonidine	Oral or transdermal patch: Initial dosing: 5 mcg/kg/day; divide daily dose into q8-12h for enteral dosing, or round daily dose to nearest ¼ patch size for transdermal dosing (max initial dose 100 mcg/day) Increase gradually if needed by 2.5 mcg/kg/day; max dose 25 mcg/kg/day (up to max 0.6 mg/day). May switch from oral to transdermal route once optimal oral dose is established. Transdermal dose is equivalent to the total oral daily dose (e.g., if total oral dose is 0.1 mg/day, apply 1 patch [delivers 0.1 mg/day]). Change patch every 7 days.	Transdermal patch may contain metal (e.g., aluminum) that may cause burns if worn during MRI scan. Remove patch before MRI. Patch may be cut into 1/4 or 1/2 fractions based on dose needed.
	Clonazepam	<10 yr or <30 kg: initial dose 0.01-0.03 mg/kg/day divided tid ≥10 yr (≥30 kg): initial dose up to 0.25 mg PO tid; may increase by 0.5-1 mg/day every 3 days Maintenance dose: 0.05-0.2 mg/kg/day up to 20 mg/day	
Appetite stimulation	Dronabinol	See previous listing	See previous listing
	Cyproheptadine	Children ≥2 yr and adolescents: 0.08 mg/kg PO q8h; if no benefit in 5 days, increase dose by 0.04-0.08 mg/kg/dose Max daily dose: ≤6 yr: 12 mg/day; 7-14 yr: 16 mg/day; ≥15 yr: 32 mg/day	Potent antihistamine and serotonin antagonist

*Infants <6 mo should receive 25–30% of the usual opioid starting dose.
†Although the usual opioid starting dose is presented, the dose may be titrated as needed. There is no ceiling/maximum dose for opioids.
‡Breakthrough dose is 10% of 24 hr dose. See Chapter 76 for information regarding titration of opioids.
§Side effects from opioids include constipation, respiratory depression, pruritus, nausea, urinary retention, and physical dependence.
Note: Some medications or dosing may not apply to infants (≤12 mo). Verify suitability and dosing of all medications before administering to neonates.
IV, Intravenous(ly); PO, by mouth; PR, rectally; prn, as needed; gtt, drops; SC, subcutaneously; bid, twice daily; tid, 3 times daily; *q4h*, every 4 hours; q30min, every 30 minutes; CNS, central nervous system; ECG, electrocardiogram; ICP, intracranial pressure.
Adapted from Ullrich C, Wolfe J. Pediatric pain and symptom control. In Walsh TD, Caraceni AT, Fainsinger R, et al (eds): *Palliative Medicine*. Philadelphia: Saunders, 2008.

Table 8.5 Nonpharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	APPROACH TO MANAGEMENT
Pain	Prevent pain when possible by limiting unnecessary painful procedures, providing sedation, and giving preemptive analgesia before a procedure (e.g., including sucrose for procedures in neonates). Address coincident depression, anxiety, sense of fear, or lack of control. Consider guided imagery, relaxation, hypnosis, art/pet/play therapy, acupuncture/acupressure, cognitive behavioral therapy (CBT), physical therapy, biofeedback, massage, heat/cold, yoga, transcutaneous electric nerve stimulation, and distraction.
Dyspnea or air hunger	Wipe and/or suction oral secretions if present; positioning; comfortable loose clothing; fan to provide cool, blowing air. Limit volume of intravenous fluids; consider diuretics if fluid overload/pulmonary edema present. Behavioral strategies, including breathing exercises, guided imagery, relaxation, music, and distraction.
Fatigue	Sleep hygiene (establish a routine, promote habits for restorative sleep). Regular, gentle exercise; prioritize or modify activities. Address potentially contributing factors (e.g., anemia, depression, side effects of medications). Aromatherapy*: peppermint, rosemary, basil.
Nausea/vomiting	Consider dietary modifications (bland, soft, adjust timing/volume of foods or feeds). Aromatherapy*: ginger, peppermint, lavender, acupuncture/acupressure.
Constipation	Increase fiber in diet, encourage fluids, ambulation (if possible).
Oral lesions/ dysphagia	Oral hygiene and appropriate liquid, solid, and oral medication formulation (texture, taste, fluidity). Treat infections, complications (mucositis, pharyngitis, dental abscess, esophagitis).
	Oropharyngeal motility study and speech (feeding team) consultation.
Anorexia/cachexia	Manage treatable lesions causing oral pain, dysphagia, or anorexia. Support caloric intake during phase of illness when anorexia is reversible. Acknowledge that anorexia/cachexia is intrinsic to the dying process and may not be reversible. Prevent/treat coexisting constipation.
Pruritus	Moisturize skin. Trim child's nails to prevent excoriation. Try specialized anti-itch lotions. Apply cold packs. Counterstimulation, distraction, relaxation.
Diarrhea	Evaluate/treat if obstipation. Assess and treat infection. Dietary modification.
Depression	Psychotherapy, behavioral techniques, setting attainable daily goals. Aromatherapy*: bergamot, lavender.
Anxiety	Psychotherapy (individual and family), behavioral techniques. Aromatherapy*: clary sage, angelica, mandarin, lavender.
Agitation/terminal restlessness	Evaluate for organic or drug causes. Educate family. Orient and reassure child; provide calm, nonstimulating environment; use familiar music, verse, voice, touch. Aromatherapy*: frankincense, ylang.

*Best if aromatherapy is administered by a practitioner trained in aromatherapy use and safety and if child has choice of essential oil aroma that stimulates positive response.
From Sourkes B, Frankel L, Brown M, et al. Food, toys, and love: Pediatric palliative care. *Curr Probl Pediatr Adolesc Health Care*. 2005;35:345–392.

may experience fatigue as a physical symptom (e.g., weakness or somnolence), a decline in cognition (e.g., diminished attention or concentration), and impaired emotional function (e.g., depressed mood or decreased motivation). Because of its multidimensional and incapacitating nature, fatigue can prevent children from participating in meaningful or pleasurable activities, thereby impairing quality of life. Fatigue is usually multifactorial in etiology. A careful history may reveal contributing physical factors (uncontrolled symptoms, medication side effects), psychologic factors (anxiety, depression), spiritual distress, or sleep disturbance. It is important to explore a patient's sleep history and encourage behavioral interventions such as optimizing sleep hygiene (e.g., instituting a regular bedtime routine, limiting screens and physical activity before bed), and sticking to regular sleep and wake times as much as feasible. If biobehavioral approaches remain ineffective, pharmacologic approaches such as trazodone may be considered. Interventions to reduce fatigue include treatment of contributing factors, exercise, behavior modification strategies, and pharmacologic agents. Challenges to effectively addressing fatigue include the common belief that fatigue is inevitable, lack of communication between families and care teams about it, and limited awareness of potential interventions for fatigue.

Dyspnea (the *subjective* sensation of shortness of breath) results from a mismatch between afferent sensory input to the brain and the outgoing motor signal from the brain. It may stem from respiratory causes (e.g., airway secretions, obstruction, infection) or other factors (e.g., cardiac) and may also be influenced by psychologic factors (e.g., anxiety). Respiratory parameters such as respiratory rate and oxygen saturation correlate unreliably with the degree of dyspnea. Therefore giving oxygen to a cyanotic or hypoxic child who is otherwise quiet and relaxed may relieve staff discomfort while having no impact on patient distress and may also add burden if the child cannot tolerate the mask or cannula. *Dyspnea can be relieved with the use of regularly scheduled plus as-needed doses of*

opioids. Opioids work *directly* on the brainstem to reduce the sensation of respiratory distress, as opposed to relieving dyspnea by sedation. The dose of opioid needed to reduce dyspnea is as little as 25% of the amount that would be given for analgesia. Nonpharmacologic interventions, including guided imagery or hypnosis to reduce anxiety, or cool, flowing air, aimed toward the face, are also frequently helpful in alleviating dyspnea. Although oxygen may relieve hypoxemia-related headaches, it is no more effective than blowing room air in reducing the distressing sensation of shortness of breath.

As death approaches, a buildup of secretions may result in noisy respiration sometimes referred to with the outdated term "death rattle." Patients at this stage are usually unconscious, and noisy respirations are often more distressing for others than for the child. It is often helpful to discuss this anticipated phenomenon with families in advance, and if it occurs, to point out the child's lack of distress from it. Nonpharmacologic interventions include positional changes, and if treatment is needed, an anticholinergic medication, such as glycopyrrolate, may reduce secretions.

Neurologic symptoms include **seizures** that are often part of the antecedent illness but may increase in frequency and severity toward the end of life. A plan for managing seizures should be made in advance, and anticonvulsants should be readily available in the event of seizure. Parents can be taught to use rectal diazepam at home. Increased **neuroirritability** accompanies some neurodegenerative disorders; it may be particularly disruptive because of the resultant break in normal sleep–wake patterns and the difficulty in finding respite facilities for children who have prolonged crying or difficulty consoling. Such neuroirritability may respond to gabapentin. Judicious use of sedatives, benzodiazepines, clonidine, nortriptyline, or methadone may also reduce irritability without inducing excessive sedation; such treatment can dramatically improve the quality of life for both child and caregivers. **Increased intracranial pressure** and **spinal cord compression** are most often encountered in children with brain tumors or metastatic and solid tumors. Depending on the clinical situation and the goals of care, radiation therapy, surgical interventions, and steroids are potential therapeutic options.

Delirium is an underrecognized brain disorder characterized by waxing and waning attention, confusion, and disorientation. Agitation may occur along with features of hypomania. Although delirium as a whole is often not diagnosed, the hypomanic form is particularly underrecognized. Delirium has a range of causes, including electrolyte imbalances, organ dysfunction, sleep–wake cycle disturbances, and results of medications such as anticholinergics and benzodiazepines. Environmental strategies to calm and orient the child while addressing potentially contributing factors are helpful. In some patients, antipsychotic/neuroleptic medications are indicated (see Chapters 33 and 47).

Feeding and hydration issues can raise ethical questions that evoke intense emotions in families and medical caregivers alike. Options that may be considered to artificially support nutrition and hydration in a child who can no longer feed by mouth include nasogastric and gastrostomy feedings or intravenous nutrition or hydration (see Chapter 60). These complex decisions require evaluating the risks and benefits of artificial feedings and taking into consideration the child's functional level and prognosis. At times, it may be appropriate to initiate a trial of tube feedings, with the understanding that they may be discontinued at a later stage of the illness. A commonly held but unsubstantiated belief is that artificial nutrition and hydration are comfort measures, without which a child may suffer from starvation or thirst. The sensation of thirst may be alleviated by careful efforts to keep the mouth moist and clean. There are also deleterious side effects to artificial hydration in the form of increased secretions, need for frequent urination, edema, and exacerbation of dyspnea. For these reasons, it is important to educate families about anticipated decreases in appetite/thirst and therefore little need for nutrition and hydration as the child approaches death. In addition, exploring the meaning that provision of nutrition and hydration may hold for families, as well as helping families anticipate the changes in their child's appearance and exploring alternative ways that they may love and nurture their child, may ease distress around this issue.

Nausea and vomiting may be caused by medications or toxins, irritation to or obstruction of the gastrointestinal tract, motion, and emotions. Drugs such as metoclopramide, 5-hydroxytryptamine antagonists, corticosteroids, olanzapine, and aprepitant may be used and should be chosen depending on the underlying pathophysiology and neurotransmitters involved. Vomiting may accompany nausea but may also occur without nausea, as with increased intracranial pressure. **Constipation** is commonly encountered in children with neurologic impairment or children receiving medications that impair gastrointestinal motility (most notably opioids). Stool frequency and quantity should be evaluated in the context of the child's diet and usual bowel pattern. Children using scheduled opioids should routinely be placed on an osmotic laxative (polyethylene glycol) in addition to a stimulant laxative agent (e.g., senna). For some patients, parenteral methylnaltrexone is also helpful in relieving opioid-induced constipation. **Diarrhea** may be particularly difficult for the child and family and may be treated with loperamide (an opioid that does not cross the blood-brain barrier), and in some cases, cholestyramine or octreotide may be indicated. Paradoxical diarrhea, a result of overflow resulting from constipation, should also be included in the differential diagnosis.

Hematologic issues include consideration of anemia and thrombocytopenia or bleeding. If the child has symptomatic anemia (weakness, dizziness, shortness of breath, tachycardia), red blood cell transfusions may be considered. Platelet transfusions may be an option if the child has symptoms of bleeding. Teabags on the gums and topical agents such as Amicar may be used for mucosal bleeding. It is important to provide anticipatory education that although distressing to see, bleeding is not painful. Life-ending hemorrhage is disturbing for all concerned, and a plan involving environment intervention such as dark sheets and the use of fast-acting sedatives should be prepared in advance if such an event is a possibility.

Skin care issues include primary prevention of problems by ongoing and timely assessment (including observation of indwelling lines and tubes) and frequent turning and repositioning and alleviating pressure wherever possible (e.g., elevating heels off the bed with pillows). Pruritus may be secondary to systemic disorders or drug therapy. Treatment includes avoiding excessive use of drying soaps, using moisturizers, trimming fingernails, and wearing loose-fitting clothing, in addition to administering topical or systemic corticosteroids. Oral antihistamines and other specific therapies may also be indicated (e.g., cholestyramine in biliary disease). Opioids can cause histamine release from mast cells, but this does not account for most of the pruritus caused by opioids. Given that opioid-induced pruritus is generally not histamine-mediated, the mainstay of treatment includes rotating opioids or instituting a low dose of opioid antagonist (nalbuphine or naloxone) rather than an antihistamine.

Children with life-threatening illness may experience psychologic symptoms such as **anxiety** and **depression**. Such symptoms are frequently multifactorial and sometimes interrelated with uncontrolled symptoms such as pain and fatigue. Diagnosing depression in the context of serious illness may pose challenges because neurovegetative symptoms may not be reliable indicators. Instead, expressions of hopelessness, helplessness, worthlessness, and guilt may be more useful. Interventions and opportunities for children to explore worries, hopes, and concerns in an open, supportive, and nonjudgmental setting are equally, if not more, important approaches to psychologic distress. Skilled members from a variety of disciplines, including psychology, social work, chaplaincy, child life, and expressive therapy, may help children and their families in this regard. Such opportunities may

create positive moments in which meaning, connection, and new definitions of hope are found. Pharmacologic agents such as antidepressants may be helpful, although their effect is often preceded by a significant lag phase. Because of its immediate and positive effect on mood, *methylphenidate* may be an effective antidepressant for children at the end of life, when there may not be time for a traditional antidepressant to take effect.

Discussions with adolescent patients, or with the parents of any ill child, about possible therapies or interventions should include **integrative therapies** such as massage therapy, Reiki, acupuncture, clinical aromatherapy, prayer, and nutritional supplements. Many families use integrative therapy but do not bring it up with their physician unless explicitly asked (see Chapter 7). Although largely unproven, some of these therapies are inexpensive and provide relief to individual patients. Other therapies may be expensive, painful, intrusive, and even toxic. By initiating a conversation and inviting discussion in a nonjudgmental way, the clinician can offer advice on the safety of different therapies and may help avoid expensive, dangerous, or burdensome interventions. Medical marijuana (**cannabis**) for pediatric use has been legalized by some states, and pediatricians are increasingly asked about it. In such cases, it is most helpful to use this opportunity to engage in a broader conversation about symptoms and symptom management, even in states where use of cannabis for pediatric medicinal purposes is legal.

Intensive Symptom Management

At the end of life, when intensive efforts to relieve the symptom have been exhausted, or when efforts to address suffering are incapable of providing relief with acceptable toxicity/morbidity or in an acceptable time frame, **palliative sedation** may be considered. Palliative sedation may relieve suffering from refractory symptoms by reducing a child's level of consciousness. It is most often used for intractable pain, dyspnea, or agitation, but is not limited to these distressing indications. It is imperative that parents, staff, and primary clinicians discuss the indications and goals for sedation before initiation of this therapy, as well as questions or concerns about this therapy, and to engage in ongoing discussions after initiation of sedation.

The doctrine of double effect (DDE) is often invoked to justify escalation of symptom-relieving medications or palliative sedation for uncontrolled symptoms at the end of life. Use of DDE emphasizes the risk of hastening death posed by escalating opioids or sedation, which is theoretical and unproven (see Chapter 6). There is mounting evidence that patients with well-controlled symptoms live longer.

Approaching End of Life and Bereavement

As death seems imminent, the major task of the physician and team is to help the child have as many good days as possible and not suffer. If patient and family preference is to remain at home and clinical status and community supports allow this, if not already in place, a referral **for hospice care** (usually provided in the *home,* rather than a hospice facility) may provide the most comprehensive care for the child and family. Gently preparing the family for what to expect and offering choices, when possible, will allow them a sense of control in the midst of tragic circumstances. Before death, it can be very helpful to discuss the following:

- ◆ Support of siblings or other family members
- ◆ Resuscitation status
- ◆ Limiting technology when no longer beneficial to the child
- ◆ Cultural, spiritual, or religious needs
- ◆ Location of death
  - Who will pronounce if death occurs at home
  - Offering siblings choice and appropriate support to attend
- ◆ Autopsy and/or tissue/organ donation
  - Builds a legacy, benefits others, and informs science and family

Offered the opportunity, families will often tolerate thinking and speaking about their hopes and fears regarding their child's end of life, and some even express relief when the door to such a conversation is opened by the care team. It may help to let the family know these conversations are not about *whether* the child will die, but *how* the child may die.

Families gain tremendous support from having a physician and team who will continue to stay involved in the child's care. If the child is at home or hospitalized, regular phone calls or visits, assisting with symptom management, and offering emotional support is invaluable for families.

In an intensive care setting, where technology can be overwhelming and put distance between the child and parent, the physician can offer discontinuation of that which is no longer benefiting the child or adding to quality of life. Less invasive ways to control symptoms, such as subcutaneous infusions or topical applications, may be helpful. Parents may be afraid to ask about holding their child or sleeping next to their child. They may need reassurance and assistance in holding, touching, and speaking with their child, despite tubes and technology, even if the child appears unresponsive.

It is believed that hearing and the ability to sense touch are often present until death; all family members should be encouraged to continue interacting with their loved one through the dying process as they feel comfortable. Parents may be afraid to leave the bedside so that their child will not die alone. Offering parents other supports such as chaplaincy/clergy, social work, and extended family members may be helpful. In most instances the moment of death cannot be predicted. Some propose that children wait to die until their parents are ready, an important event has passed, or they are given permission. The care team need not dispute this, nor the hope for a miracle often held by families until the child takes the last breath.

For the family, the moment of death is an event that is recalled in detail for years to come, and thus enhancing opportunity for dignity and limited suffering is essential. Research suggests that improved symptom control and easing of difficult moments at the time of death may lessen the long-term distress of bereaved parents. Clinical experience has shown that families often find solace in clinician presence, whether at home or in the hospital. After death, families should be given the option of remaining with their child for as long as they would like and should be prepared for changes in the child's body. During this time, physicians and other professionals may ask permission to say goodbye. The family may be invited to bathe and dress the body as a final act of caring for the child.

The clinician's decision to attend the funeral is a personal one. Participation may serve the dual purpose of showing respect and helping the provider cope with a personal sense of loss. If unable to attend services, families report highly valuing the importance of receiving a call, card, or note from the physician. To know that their child made a difference and will not be forgotten is often very important to families in their bereavement. Furthermore, bereaved parents cite ongoing support from their child's healthcare teams and medical institutions after the death of their child as essential sources of support during their grief journeys. Many families benefit from community-based bereavement support groups, which are often offered through hospice organizations, or individual grief counseling.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 9

Domestic and International Adoption

Elaine E. Schulte

Adoption is a social, emotional, and legal process that provides a new family for a child when the family of origin is unable or unwilling to parent. In the United States, about 1.5 million children <18 years of age are adopted; 2–4% of American families have adopted. In the United States, approximately 135,000 children are adopted every year. Of these, 59% are from the child welfare (foster) system, 25% are from other countries, and 15% are voluntarily relinquished American babies. The remaining numbers are from private agencies, American Indigenous Nations, stepparent, or other forms of kinship care. Because of changing policies toward adoption and social change in several of the sending countries, the number of international adoptions has decreased dramatically over the last 15 years. Public agencies support approximately 50% of total annual adoptions in the United States, private agencies facilitate 25% of adoptions, and independent practitioners (e.g., lawyers) handle 15% of adoptions. Compared to 19% of the general population, approximately 39% of adopted children have special healthcare needs.

DOMESTIC ADOPTION

The **Adoption and Safe Families Act** (P.L. 105-89) requires children in foster care to be placed with adoptive families if they cannot be safely returned to their families within a reasonable time. In fiscal year (FY) 2020 there were an estimated 407,000 children in foster care and 117,000 waiting for adoption. Of the 224,000 who exited foster care, 48% were reunited with parent(s) or primary caretaker(s) and 25% were adopted. Of the 53,500 children who were adopted in 2021, 55% were adopted by their foster parent(s) and 34% were adopted by relatives (see Chapter 10).

Many children awaiting adoption are less likely to be adopted because they are of school age, are part of a sibling group, are members of historically oppressed racial/ethnic groups, or have considerable physical, emotional, or developmental needs. A number of policy efforts are aimed at increasing adoption opportunities for these children, including federal adoption subsidies, tax credits, recruitment efforts to identify ethnically diverse adults willing to adopt, increased preplacement services, and expanding adoption opportunities to single adults, older couples, and gay/lesbian partners.

Same-sex couple adoption is legal in more than a dozen countries worldwide. Although legislation regarding same-sex couple adoption varies by state, increasing numbers of gay and lesbian partners have been able to adopt. Current estimates suggest that over 2 million children, including 5% of all adopted children, are raised by gay or lesbian parents. Adopted children include those adopted domestically, those from foster care, and internationally adopted children. There is good evidence that children raised by same-sex couples are as physically or psychologically healthy, capable, and successful as those raised by opposite-sex couples. Pediatricians can advocate for adopted children by supporting gay and lesbian parents.

Open adoption, usually through an agency or privately, occurs when the birth mother arranges to continue to be involved, although in a limited manner, with the legally adopted family. This may occur through surrogacy or, more often, in an unplanned pregnancy.

INTERCOUNTRY ADOPTION

Along with foster care adoptions, **international adoptions** are a way of providing stable, long-term care to vulnerable children throughout the world. There is concern that in some countries of origin, the rapid growth of international adoption has outpaced regulation and oversight to protect vulnerable children and families. Opportunities for financial gain have led to abuses, including the sale and abduction of children, bribery, and financial coercion of families, but the extent and scope of the potential concern are difficult to ascertain. Increasing global efforts, such as the **Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption**, have promoted political cooperation between nations and established international law to reduce the potential for child abduction and child trafficking and to ensure that the best interests of the child are paramount in decision-making. Participating nations, including the United States, are working to address the myriad of sociopolitical conditions that create the need for out-of-family care and are working to support children within their nation's borders. International adoption is increasingly considered a measure of last resort if the child cannot be cared for within his or her family of origin (including extended relatives), the immediate community, or the larger national culture. As a result, children adopted internationally into the United States are more likely to enter their families at older ages or with complex medical, developmental, or social-emotional needs.

In 2021, US families adopted 1,785 children from other countries (compared to a peak of 22,884 in 2004). Children from Bulgaria, Columbia, India, Nigeria, South Korea, and Ukraine represented 65% of children adopted internationally into the United States; 2021 marked the first year since 1984 where no children where adopted from China. Although individual experiences vary, most children placed for international adoption have some history of poverty and social hardship in their home countries, and most are adopted from orphanages or institutional settings. Many young infants are placed into **orphanage care** shortly after birth. Some older children have experienced family disruption resulting from parental illness, war, or natural disasters. Still others enter orphanage care after determination of significant abuse or neglect within their biologic families. The effects of **institutionalization** and other life stresses may affect all areas of growth and development. As a result, many children require specialized support and understanding to overcome the impact of stress and early adversity and to reach their full potential.

ROLE OF PEDIATRICIANS

Preadoption Medical Record Reviews

Preadoption medical record reviews are important for both domestic and international adoptions. Adoption agencies are making increased efforts to obtain biologic family health information and genetic histories to share with adoptive families before adoption. Such information often becomes increasingly relevant as the child ages. The unique medical and developmental needs of adopted children have led to the creation of specialty clinics throughout the United States, which may be a valuable resource for adoptive families at all stages in the adoption process and throughout the adopted child's life. When available, adoption medicine pediatricians can help prospective adoptive parents understand the health and developmental history of a child and available background information from birth families in order to assess actual and potential medical and psychosocial risk factors to support adult decision-making about the family's ability to parent the waiting child.

Under the Hague Convention, U.S. agencies that arrange international adoptions must make efforts to obtain accurate and complete health histories on children awaiting adoption. The nature and quality of medical and genetic information, when available, vary greatly. Incongruous translation and use of medical terminology and medications that are unfamiliar to U.S.-trained physicians are common. Results of specific diagnostic studies and laboratory tests performed outside the United States should not be relied on and *should be repeated* once the child arrives in the United States. Paradoxically, review of the child's medical records may raise more questions than provide answers. Each medical diagnosis should be considered carefully before being rejected or accepted. Country-specific growth curves should be avoided because they do not reflect the demographic of institutionalized

Table 9.1 Recommended Screening Tests for International Adoptees on U.S. Arrival

SCREENING TESTS
Complete blood cell count, including eosinophil count
Thick and thin smear for malaria if from endemic area
Vitamin D level
TSH, T_4
Iron, ferritin
Blood lead level
Newborn universal screening (age ≤6 mo)
Vision and hearing screening
Dental screening
Developmental testing
Immunization records or titers (alternative plan: revaccinate)
OTHER SCREENING TESTS TO CONSIDER BASED ON CLINICAL FINDINGS AND AGE OF CHILD
Stool cultures or NAAT for bacterial pathogens in the presence of diarrhea and fever
Glucose-6-phosphate dehydrogenase deficiency (based on heritage)
Sickle cell test or hemoglobin electrophoresis (based on heritage)
Urine pregnancy test
INFECTIOUS DISEASE SCREENING
(see Table 9.2)

NAAT, Nucleic acid amplification test; TSH, thyroid-stimulating hormone.

Table 9.2 Infectious Disease Screening for Internationally Adopted Children

CONDITION OR TEST	INTERNATIONALLY ADOPTED CHILDREN
HEPATITIS A VIRUS (ACUTE INFECTION)	
Hepatitis A IgM antibody	All
HEPATITIS B VIRUS	
Hepatitis B surface antigen (HBsAg)	All[a]
Hepatitis B surface antibody (anti-HBs)	All[a]
Hepatitis B core antibody (anti-HBc)	All[a]
HEPATITIS C VIRUS	
Hepatitis C antibody	All[a]
SYPHILIS	
Nontreponemal test (RPR, VDRL, or ART)	All
Treponemal test (TPPA, MHA-TP, or FTA-ABS)	All
HUMAN IMMUNODEFICIENCY VIRUS	
Human immunodeficiency virus 1 and 2 antibody	All[a]
TUBERCULOSIS	
Tuberculin skin test (TST)	All[a]
or	
Interferon-γ release assay	≥2 yr
INTESTINAL PARASITES	
Microscopic evaluation of stool for ova and parasites	All (3 specimens)
Giardia intestinalis and *Cryptosporidium* antigen	All (1 specimen)
BACTERIAL ENTERIC INFECTION	
In children with diarrhea: bacterial stool culture	All
CHAGAS (ENDEMIC AREAS)	
Trypanosoma cruzi serologic testing	All
Complete blood count	All
EOSINOPHILIA WITH NEGATIVE STOOL OVA AND PARASITE FOR HELMINTHS	
Strongyloides serologic testing	All
Schistosoma serologic testing (endemic countries)[b]	
LYMPHATIC FILARIASIS (ENDEMIC AREAS)	
Filaria serology	≥2 yr
CHAGAS (ENDEMIC AREAS)	
Trypanosoma cruzi serologic testing	All
MALARIA SCREENING (ENDEMIC AREAS)	
Malaria polymerase chain reaction	Not recommended
HEMATURIA (SCHISTOSOMIASIS)	
Urinalysis	Not recommended

[a]Consider reassessing 6 months after arrival.
[b]Some experts recommend serologic testing regardless of whether eosinophilia is present.
ART, Automated reagin test; FTA-ABS, fluorescent treponemal antibody absorption; MHA-TP, microhemagglutination–*Treponema pallidum;* RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory.
https://wwwnc.cdc.gov/travel/yellowbook/2020/family-travel/international-adoption.

children. Instead, *serial growth* data should be plotted on U.S. standard growth curves; this may reveal a pattern of poor growth because of malnutrition or other chronic illness. Photographs or video files may provide the only objective information from which medical status can be determined. Full-face photographs may reveal dysmorphic features consistent with fetal alcohol syndrome (see Chapter 146) or findings suggestive of other congenital disorders.

Frank interpretations of available information should be shared with the prospective adoptive parents. The role of the healthcare provider is not to comment on the advisability of an adoption, but to inform the prospective parents of any significant medical, developmental, and behavioral health needs identified now or anticipated in the future.

Postadoption Medical Care

Arrival Visit: International Adoption

All internationally adopted children should have a thorough medical evaluation shortly after arriving in the United States. Many children may have acute or chronic medical problems that are not always immediately evident, including malnutrition, growth deficiencies, stool pathogens, anemia, elevated blood lead, dental decay, strabismus, birth defects, developmental delay, feeding and sensory difficulty, and social-emotional concerns. *All children who are adopted from other countries should undergo comprehensive screening for infectious diseases and disorders of growth, development, vision, and hearing* (Tables 9.1 and 9.2). Regardless of test results before arrival, all children should be screened for tuberculosis with either a tuberculin skin test (TST) or interferon-γ release assay (IGRA). If the child's purified protein derivative (PPD) skin test is negative, it should be repeated in 4-6 months; children may have false-negative tests because of poor nutrition. Additional tests (e.g., malaria) should be ordered depending on the prevalence of disease in the child's country of origin (see Chapter 11). **Immunization records** should be carefully reviewed. Internationally adopted children frequently have incomplete records or have been vaccinated using alternative schedules. Pediatricians may choose to check titers to determine which vaccines need to be given, or they can *choose to reimmunize* the child.

Growth Delays

Physical growth delays are common in internationally adopted children and may represent the combined result of many factors, such as unknown/untreated medical conditions, malnutrition, and psychologic deprivation. It is more important to monitor growth over time, including preplacement measurements, because trend data may provide a more objective assessment of the child's nutritional and medical status. Children who present with low height for age (**growth stunting**) may have a history of inadequate nutrition and chronic adversity. Although most children experience a significant catch-up in physical growth after adoption, many remain shorter than their peers who did not experience early adversity.

Developmental Delays

Many children adopted internationally exhibit delays in at least one area of development, but most exhibit significant gains within the first 12 months after adoption. Children adopted at older ages are likely to have more variable outcomes. In the immediate postadoption period, it may be impossible to determine with any certainty whether developmental delays will be transient or long-lasting. Careful monitoring of development within the first years of adoption can identify a **developmental trend** over time that may be more predictive of long-term functioning than assessment at any specific point in time. When in doubt, it is better to *refer early* for developmental intervention, rather than wait to see if the children will catch up (see Chapter 28).

Language Development

For both domestic and international adoptees, genetic or biologic risk factors for poor language development may be identified preadoptively, but it is unlikely that international adoptees will have had these delays identified before adoption. These children typically have not had an assessment in their native language and have had little exposure to English. If assessment in their native language is not available, it may not be possible to fully assess their language abilities until they have had a chance to learn English. Regardless of the age at adoption, most internationally adopted children will reach age-expected language skills over time.

If a child has language delays, referral to early intervention or the school district should be made. Clinicians may need to work with these groups to help them understand the unique circumstances surrounding an adopted child's language development. For example, English language acquisition in internationally adopted children depends on the age of adoption and native language skills. Placing the recently adopted, school-age child in an English as a second language class may not be sufficient if the child's language development in the primary language has been atypical.

Eating Concerns

Initial concerns about eating, sleep regulation, and repetitive (e.g., self-stimulating or self-soothing) behaviors are common, especially among children adopted after a high degree of neglect or developmental trauma. Feeding behaviors of international adoptees may be linked to orphanage feeding practices or limited exposure to textured or solid foods during later infancy/toddlerhood. Children who have experienced chronic lack of food may not have developed an awareness of *satiation cues,* leading to hoarding or frequent vomiting. **Feeding concerns** often subside gradually with introduction of age-appropriate foods and parental support for positive feeding practices. Many children who were adopted after significant malnutrition may eat an excessive amount of food. Unless the child is eating to the point of vomiting (which would indicate little awareness of satiation cues), it is generally best to allow them to eat until satiation. Typically, within several months, the child will regulate food intake appropriately. Occasionally, additional support from a speech pathologist or feeding specialist is warranted to address possible sensory, physical, or psychologic issues around proper feeding.

Sleep Concerns

Sleep is often disrupted as the child reacts to changes in routines and environments. Efforts to create continuity between the preadoption and postadoption environment can be helpful. Within the first 3-6 months, as the child's emotional self-regulation improves, many sleep concerns subside. Similarly, stereotypical behaviors, such as rocking or head banging, often diminish within the first few months after adoption.

Social and Emotional Development

Dyadic interactions between child and caretaker are a critical component to later regulatory functioning and social-emotional development. The amount and quality of individualized caretaking that children have received before their adoption, whether international, domestic, or through the foster care system, is usually unknown. In many cases, entry into a secure, stable home setting with consistent childcare routines is sufficient to support the child's emerging social-emotional development. Pediatricians can help parents remember that adoption is part of the child's identity. Throughout one's childhood, prior experiences or biologic disposition may result in behavior that is confusing to the adoptive parents. The child's reactions may be subtle or difficult to interpret, interfering with the parents' ability to respond in a sensitive manner. In these circumstances, additional behavioral health support may be helpful to foster the emerging relationships and behavioral regulation in the newly formed family.

Racial Identity Development

Transracial adoption (where the racial background of the child differs from that of the parent/parents) accounts for a significant percentage of adoptions each year in the United States. In most of these adoptive placements, children of color have been adopted by White parents. Racial identity development, including ways to understand and respond to discrimination, is increasingly recognized as important in the overall development of children. Surveys of adults adopted transracially indicate that racial identity is of central importance at many ages and tends to increase in significance during young adulthood. Integrating race/ethnicity into identity can be a complex process for all children, but it may be especially complicated when they are raised in a family where racial differences are noted. Adults raised within interracial families have noted the value of attending racially diverse schools and of having adult role models (e.g., teachers, doctors, coaches) who share their racial background. Parents who adopt transracially are often encouraged to support interactions within diverse communities and to discuss race (and associated discrimination) often within the family. Black children raised by White families in White communities may have been sheltered from overt racism but need to be taught that many others (including law enforcement officers) will regard them as Black with all the intense biases associated with race (see Chapter 2.1).

Adoption culture camps are another option for transracial Black children to experience their racial heritage and meet children with similar experiences. In addition, there are Asian (Chinese, Korean) heritage camps that provide a similar cultural experience for internationally adopted children.

Toxic Stress

The cumulative amount of unsupported early adversity (e.g., numerous years within international orphanage care, extensive abuse/neglect before removal from the biologic family, or multiple foster care placements) experienced by a child before adoption, referred to as *toxic stress,* can affect both immediate placement stability and long-term physical health and emotional well-being (see Chapter 2). The degree of presumed toxic stress may be helpful in interpreting a child's behavior and supporting family functioning.*

Family Support

The unique aspects to adoptive family formation can create familial stress and affect child and family functioning. Some adoptive families may have to address infertility, creation of a multiracial family, disclosure of adoptive status, concerns and questions the child may have about their preadoptive experiences and biologic origins, and ongoing scrutiny by adoption agencies. With gay/lesbian parents, there are often additional psychosocial stressors, including continued barriers to legal recognition of both parents in a gay/lesbian partnership that can negatively affect family functioning. Although most families acclimate well to adoption-related stressors, some parents experience postadoption depression and may benefit from additional mental health support to ease the family's transition.

Adoption Narrative

Families are encouraged to speak openly and repeatedly about adoption with their child, beginning in the toddler years and continuing through adolescence. Creating a *lifebook* for the adopted child provides a way to support family communication about the child's

* See video at https://www.youtube.com/watch?v=rVwFkcOZHJw

history and significant relationships (including members of the family of origin) and to document the child's important life transitions (e.g., through foster care or immigration to the United States). It is common, and normal, for children to have questions about adoption and their preadoptive experiences and biologic family throughout their development. An increase in cognitive understanding between ages 7 and 10 years can sometimes increase adoption-related questions and distress. Youth who have questions about biologic family members are increasingly able to access information via social media and web-based searching, raising the importance of ongoing open communication about adoption. Pediatricians may need to respond to increased concerns and questions when the adoptee's health and genetic history is incomplete or unknown. It is important to remember that, at any time, concerns about development, behavior, and social-emotional functioning may or may not be related to the child's adoption history.

The vast majority of adopted children and families adjust well and lead healthy, productive lives. Adoptions infrequently disrupt; disruption rates are higher among children adopted from foster care, which research associates with their age at adoption and a history of multiple placements before adoption. With increased understanding of the needs of families who adopt children from foster care, agencies are placing greater emphasis on the preparation of adoptive parents and ensuring the availability of a full range of postadoption services, including physical health, mental health, and developmental services for their adopted children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 10

Foster and Kinship Care

Mary V. Greiner, Heather C. Forkey, and Moira Szilagyi

The placement of children in out-of-home care has served the needs of children in many societies worldwide throughout history. The institution of foster care was developed in the United States as a temporary resource for children during times of family crisis and is rooted in the principle that children fare best when raised in family settings. The mission of foster care is to provide for the safety, permanency, and well-being of children while assisting their families with services to promote reunification.

EPIDEMIOLOGY

The number of children in foster care worldwide is unknown, although it has been estimated that 8 million may be in foster and **congregate care**. On September 30, 2021, approximately 391,098 children in the United States resided in foster care, down from a high of 511,318 in care in 2005. Early in the millennium, foster care numbers decreased despite an increase in maltreatment reports, as child welfare offered families more preventive services and placement with relatives (**kinship care**) or nonrelative caregivers as an alternative to court-ordered removal. Higher rates of children in care, reaching 437,337 in 2018, appear to be related to the opioid epidemic. Over the last 10 years, reunification rates and adoption of children from foster care have increased. Nationally, approximately 44% of children live with a nonrelative foster caregiver, 35% of children are in placement with a relative, 9% are in congregate (group) care, and 2% are in supervised independent living.

Approximately 37% of children in foster care in the United States are younger than 5 years, and 28% are older than 12 years. Most children are White (44%), 22% are Black, 22% are Hispanic of any race, and 8% are identified as 2 or more races. Child welfare agencies have been attending to the drivers of disparities rooted in implicit bias and structural racism for nearly 2 decades. Despite efforts to address disparities, Black, Latinx, and Indigenous children are overrepresented in foster care compared with their representation in the population at large. The average length of stay in foster care continues to decline (median in 2021, 14.9 months), though 33% of children spend >2 years in care as of 2021. Approximately half of children achieve reunification, and 25% are adopted and 9% reside with relatives. Among the remaining children, 8% emancipate between ages 18 and 21. There were 368 deaths reported in foster care in FY 2021.

Placement instability (multiple placements) is associated with poor outcomes for children in foster care, including poor educational outcomes and increased behavioral and mental health issues as well as delayed permanency (i.e., reunification, adoption). The majority of children in foster care for longer than 2 years have three or more placements. Important predictors of multiple placements include older age, longer time in custody, history of sexual or physical abuse, and behavioral and physical health challenges.

Youth who emancipate (e.g., age out) from foster care face additional challenges. Approximately 75% have graduated from high school or obtained a GED. By age 24, only 5% have graduated from any 2- or 4-year college and only half are employed. 39% have experienced homelessness or "couch surfing." 81% of males and 57% of females have been arrested. Two thirds of females and one half of males report they have had at least one child. Extended foster care to age 21 benefits youth in foster care, although it does not eliminate all risks.

LEGISLATION IN THE UNITED STATES

In the United States, the **Adoption and Safe Families Act** (P.L. 105-89) requires that a permanency plan be made for each child no later than 12 months after entry into foster care and that a petition to terminate parental rights typically be filed when a child has been in foster care for at least 15 of the previous 22 months. The **Fostering Connections and Promoting Adoptions Act** of 2009 (P.L. 110-351) focused on incentives for guardianship and adoption, supports for young adults at the age of emancipation, and rights of U.S. Indigenous Nation children to caregiving within their tribe. This act also contained a clause requiring states to develop and coordinate healthcare systems for children in foster care in collaboration with Medicaid and pediatricians. In 2018 the **Family First Prevention Services Act** was signed into law. This legislation emphasizes providing evidence-based mental health and substance abuse services for families whose children are at imminent risk of entering foster care, addresses the need for children in care to be provided with appropriate evidence-based mental health services, and has incentives to move children in care from congregate to family settings.

EARLY CHILDHOOD TRAUMA LEADS TO POOR HEALTH OUTCOMES

Children in foster care have high rates of **early childhood trauma** and adversity. More than 60% are placed in foster care for neglect, 12% for physical abuse, 4% for sexual abuse, and 5% are abandoned. Parental alcohol and other **substance use** is a known factor in 42% of removals and are likely underestimated. Parental alcohol and substance use also contributes to prenatal substance exposures for their children. **Violence** in the home is common, with many children having experienced intimate partner and/or community violence.

Removal from the family of origin may compound prior trauma experiences, although some children experience relief at removal from a chaotic, abusive, or dangerous home. No matter the circumstances of removal, most children miss their family, worry about their family, and long for reunification. Separation, loss and grief, unpredictable contact with family of origin, placement changes, the process of terminating parental rights, and the sheer uncertainty of foster care may further erode a child's well-being.

Childhood trauma is correlated with poor developmental, behavioral, and health outcomes. Early trauma and chronic stress adversely affect the neurobiology of the developing brain, especially those areas involved in attention, emotional regulation, memory, executive function, and cognition. As a result, shortened attention span, hyperactivity or dissociation, poorer cognitive function, aggression, and memory issues are problems encountered frequently among children in foster care. Evidence-based mental health trauma treatment is recommended for children who are symptomatic. Additionally, evidence shows that foster care–specific interventions, such as specially trained foster caregivers and mentoring for adolescents in foster care, can improve outcomes, although replication and dissemination of these evidence-based interventions is limited.

HEALTH ISSUES

Experiencing multiple childhood adversities and receiving fragmented and inadequate health services before placement into foster care mean that children enter foster care with a high prevalence of chronic medical, mental health, developmental, dental, and educational problems. Thus they are defined as *children with special healthcare needs* (CSHCN). The greatest single healthcare need of this population is for high-quality, evidence-based, **trauma-informed** mental health services to address the impacts of prior and ongoing trauma, loss, and unpredictability. In addition, children in foster care have higher rates of asthma, growth failure, obesity, vertically transmitted infections, hearing and vision loss, dental decay, and neurologic conditions than the general pediatric population. Adolescents need access to reproductive health and substance use services. Up to 60% of children <5 years old have a developmental delay in at least one domain, and >40% of school-age children qualify for special education services. Unfortunately, educational difficulties persist despite improvements in school attendance and performance after placement in foster care. Each placement change that is accompanied by a change in school sets children back academically by about 4 months. Federal legislation requires child welfare to maintain children in their school of origin when possible, even if child welfare has to provide transportation to ensure this.

Although children in foster care are CSHCN, they often lack access to the services they need. Most public and private child welfare agencies do not have formal arrangements for accessing the needed array of health services and rely on local physicians and health clinics funded by Medicaid. Health histories are often sparse at admission because many have lacked regular care, or their family of origin may not be available, and information sharing between medical and child welfare settings is often very limited. Once children enter foster care, there is often a diffusion of responsibility for obtaining healthcare services across caregivers and child welfare. Foster caregivers usually receive little information about a child's healthcare needs, but they are typically expected to decide when and where children receive medical treatment. Child welfare professionals are responsible for ensuring that a child's health needs are addressed, but coordination across multiple healthcare providers can be daunting. Although child welfare can consent to routine care and even some procedures, the child's parents or family of origin may retain some medical decision-making rights unless parental rights have been terminated. Complexity in legal responsibility for making healthcare treatment decisions and access to health information may delay or result in the denial of healthcare services.

HEALTHCARE FOR CHILDREN AND ADOLESCENTS IN FOSTER CARE

The American Academy of Pediatrics (AAP) has published detailed healthcare standards for children in foster care, available on the *Healthy Foster Care America* website. The AAP recommends that children receive healthcare services in a medical home setting, where comprehensive healthcare is continuous over time. Compassionate, culturally competent healthcare that is trauma-informed means that health staff should understand, recognize, and respond to symptoms and risk factors of traumatic stress and provide an environment that offers physical, emotional, and psychologic safety for children and caregivers. In foster care, attention must be paid to the effects of past trauma and the impact of ongoing uncertainty and loss on a child's health and well-being, as well as that of their birth and foster/kinship caregivers.

The **trauma-informed office** is one in which symptoms such as dysregulation of sleep, behavioral problems, developmental delays, poor school function, and somatic complaints are recognized as potential effects of childhood trauma. Understanding the child's psychosocial context and history, as well as that of the caregiver, and exploring their strengths, assets, and challenges are the foundation of a trauma-informed approach. The office should have resources for education of families and child welfare professionals and ideally the ability to make warm hand-offs to community resources. Integrated trauma-informed pediatric mental health services are ideal, with referrals to community mental health services when needed, in collaboration with caregivers, child welfare, and educators. **Continuity of care** is very important for the child in foster care and includes ongoing monitoring and management of progress and care.

Several recommendations are specific to the care of children and youth in foster care (Table 10.1). Children should be seen early and often when they first enter a new placement to identify all their health issues and to support the child and caregivers through a major transition that involves considerable loss and adjustment, including the development of an attachment relationship with a new caregiver and the promotion of the child and family of origin relationship.

It is recommended that every child in foster care have comprehensive medical, dental, developmental, and mental health assessments within 30 days of entering foster care. Almost every child in foster care deserves a full mental health evaluation to assess for the impact of trauma and loss on emotional well-being. *Psychotropic medication* should only be considered, after a thorough, high-quality, trauma-informed mental health evaluation by a pediatric-trained mental health professional. The healthcare provider should remember that the impact of trauma on the developing brain can mimic other mental health disorders, including attention-deficit/hyperactivity disorder, anxiety, and depression (see Chapters 38, 39, and 50). Childhood trauma may impair cognition, executive function, and memory (see Chapter 49), so that children <6 years of age benefit from a comprehensive developmental assessment, whereas older children often benefit from a comprehensive psychoeducational assessment. The child welfare professional should provide consents for healthcare and any available health history and encourage the appropriate involvement of the family of origin. This can be facilitated with electronic medical records, though multiple sources of information may need to be identified, as most children have experienced fragmented care. The primary care provider can help child welfare professionals and caregivers by obtaining and interpreting the results of these assessments. Pediatricians, caregivers, and child welfare professionals should share information to ensure the best healthcare delivery.

Foster/kinship caregivers are the major therapeutic intervention of the foster care system, and pediatricians are in a unique position to provide them with appropriate education and support. Important topics include positive parenting strategies, supporting children through transitions, providing a consistent and nurturing environment, and helping children heal from past trauma and adversity (Table 10.2). All caregivers may need extensive education

Table 10.1 Healthcare Needs and Guidance for Pediatricians Caring for Children in Foster Care

HEALTH NEED	HEALTHCARE RISKS	GUIDANCE FOR PEDIATRICIANS
Health supervision Physical health and growth Nutrition Vision/hearing Immunizations Anticipatory guidance	Food insecurity and malnutrition, leading to poor growth (failure to thrive) or obesity Vision/hearing deficits Behind on immunizations or overvaccinated with poor records Increased lead exposures Increased communicable diseases	See early and often with entry into foster care and placement changes, screening within the first week, and comprehensive evaluation within 1 mo After stabilization, visits every month for first 6 mo of age; every 3 mo from 6 mo to 2 yr; twice yearly after age 2 Support child, caregivers at placement, and family of origin Communicate and collaborate with child welfare professionals and legal professionals Maintain a comprehensive medical record despite changes in placement
Evaluation and monitoring for abuse/neglect	History of abuse and neglect at entry into foster care Abuse/neglect during out-of-home placement	Examine and document full physical examination, including skin, joint range of motion, and genital examination Laboratory testing for sexually transmitted infections (STIs), pregnancy, consideration of history of commercial sexual exploitation
Oral health	Poor dental hygiene Untreated dental disease	Examine teeth, apply fluoride when applicable, teach oral hygiene Connect with dental services by first birthday or first tooth, whichever comes first
Developmental delay/academic concern	Early adversity and environmental exposures with decreased supports lead to decreased rates of kindergarten readiness, literacy, and high school graduation School disruptions with placement changes	Developmental screening with low threshold for referral to early intervention and developmental therapies Recommend preschool programming (i.e., Head Start) and early education programs Clarification of ability to stay in school of origin (best interests determination), role of foster caregiver or education surrogate with role in requesting and approving educational plan Support child in obtaining IEP/504 plans for learning and/or behavior when needed
Mental health concerns	Placement into foster care is a trauma on top of whatever trauma that child has already experienced Placement disruptions cause further trauma Increased rates of mental health diagnoses Overlap/overrepresentation with juvenile justice	Maintain a trauma-informed medical office: Understand and educate children, families, and other healthcare professionals on the impact of early childhood adversities, trauma, and ongoing uncertainties of foster care on the developing child All children in foster care should have mental health evaluations, including screening for trauma symptoms Integrate pediatric care with behavioral health when possible Close psychiatric medication monitoring to prevent overuse; any medication should be accompanied by trauma-informed therapy Immediate referral for psychiatric emergency (i.e., suicide or violent behavior)
Medical complexity	Face challenges with chronic disease management caused by disruptions in care May be dependent on medical technologies Information sharing with foster caregiver and child welfare can improve care, follow-up	Need medical home to serve as hub for involved specialties Education required for child welfare professional to understand needs Extra care must be taken with placement changes to ensure appropriate medications, supplies, technology, etc., move with child and new caregivers are trained and prepared to meet needs; information sharing and transfer of medical information to be considered Assist with supports (e.g., SSI, special education)
Transition to adulthood	Adolescents more likely to be in nonfamilial settings, such as group homes and independent living with less adult support Sexual health risks, including earlier sexual debut and earlier transition to parenting Substance use risks, earlier initiation At risk for disengagement with healthcare system	Identify supports, such as mentors and educational/employment opportunities (i.e., Job Corps) Regular STI screening to include contraception and safe sex ounseling with support for LGBTQ+ individuals Screen for intimate partner violence Regular substance use screening with brief intervention and/or referral to treatment when appropriate Partner with adolescent medicine and transition medicine when available Support youth in foster care who are parents Warm handoff to adult healthcare providers to avoid disruptions

Table 10.2 Trauma-Informed Anticipatory Guidance for Children in Foster Care

SITUATION	ANTICIPATORY GUIDANCE FOR FOSTER CAREGIVERS
Preparing for visits with family of origin	Educate foster/kinship caregivers about impact of visitation on children and ways to improve the experience for children Create standard routines before visit Send familiar object with child to visit Have child draw picture or card to give family of origin Reassure child that foster/kinship caregiver will be there when child returns from visits Advise all caregivers to minimize conflict with and negativity toward each other Ideally, visits with family of origin are coached by trained professionals
Returning from visits and other transitions	Greet child warmly and help with unpacking Reassure safety with welcoming words, creating safe spaces in home (tent in the child's room, child's own special chair, lovey object) Establish reentry rituals, such as quiet play, reading together, active play, having a healthy snack
Relationship with family of origin	Encourage child welfare professional to have family of origin keep child's rituals and routines consistent with those in foster/kinship home (vice versa when appropriate) Focus on family of origin's positive qualities; maintain a neutral or positive affect
Affirming and building on child's strengths	Encourage participation in child-directed play Time-in with child Encourage participation in normalizing activities (e.g., hobbies, sports) "Catch the child being good," praising positive behaviors Give specific praise Practice attentive listening Provide child with words for emotions Ignore negative behavior or redirect unless there is a safety issue
Preparing for court dates	Foster/kinship caregiver, child welfare professional or law guardian should explain purpose of court hearings to child in simple terms Anticipate that court outcomes may disrupt child and reassure safety; return to routines as quickly as possible
School	If changing schools, visit school together a few times and meet teacher Check in regularly (weekly or monthly depending on need) with child's teacher Address need for any additional evaluation and supports, including IEP or specialized setting
Adolescence	Identify what issues demand firm limits and guidelines (e.g., curfews, no smoking, party at a friend's house), what issues are not important and can be left up to teen (e.g., hair length and color), and what issues are ideal for negotiation (e.g., transportation to school function, style of dress) Encourage responsible decision-making by recognizing and complimenting it Encourage and support after-school activities Teach driving when age and developmentally appropriate Encourage teen to seek employment and teach job skills Support skills in financial awareness and money management Help teen to identify mentors and focus on the future

about behavioral and emotional problems within the context of the child's trauma history to remove blame and promote healing. Minimizing conflict among parents/caregivers is extremely important because children ideally have affection and loyalty for all their caregivers. Clinicians can promote resilience by focusing on child, caregiver, and family of origin strengths. For teens and young adults in foster care, the pediatrician can provide anticipatory guidance around education, identity formation in the face of past trauma, independent decision-making, health promotion including reproductive health, healthy relationships, and developing the skills and competencies needed for a successful future life. The pediatrician can advocate for placement stability in a nurturing and responsive family setting where caregivers possess the appropriate skills to help children and youth heal.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 11

Medical Evaluation of the Foreign-Born Child

Stacene R. Maroushek

More than 210,000 foreign-born children (≤16 years old) enter the United States each year as asylees (asylum seekers), refugees, and immigrants, including international adoptees (see Chapter 9). This number does not include undocumented children living and working in the United States, the U.S.-born children of foreign-born parents, or the approximately 2.7

million nonimmigrant visitors ≤16 years old who legally enter the United States annually with temporary visas. With the exception of internationally adopted children, pediatric guidelines for screening these newly arrived children are sparse. The diverse countries of origin and patterns of infectious disease, the possibility of previous high-risk living circumstances (e.g., refugee camps, orphanages, foster care, rural/urban poor), the limited availability of reliable healthcare in many economically developing countries, the generally unknown past medical histories, and interactions with parents who may have limited English proficiency and/or varied educational and economic experiences make the medical evaluation of immigrant children a challenging but important task.

Before admission into the United States, all immigrant children are required to have a medical examination performed by a physician designated by the U.S. Department of State in their **country of origin**. This examination is limited to completing legal requirements for screening for certain communicable diseases and examination for serious physical or mental problems that would prevent issuing a permanent residency visa. This evaluation is *not* a comprehensive assessment of the child's health, and except in limited circumstances, laboratory or radiographic screening for infectious diseases *is not required* for children <15 years old. After entry into the United States, health screenings of refugees, but not other immigrants, are recommended to be done by the resettlement state. There is limited tracking of refugees as they move to different cities or states. Thus many foreign-born children have had minimal prearrival or postarrival screening for infectious diseases or other health issues.

Immunization requirements and records also vary depending on entry status. Internationally adopted children who are younger than 10 years are exempt from Immigration and Nationality Act regulations pertaining to immunization of immigrants before arrival in the United States. Adoptive parents are required to sign a waiver indicating their intention to comply with U.S.-recommended immunizations, whereas older immigrants need only show evidence of up-to-date, not necessarily complete, immunizations before application for permanent resident (green card) status after arrival in the United States.

Infectious diseases are among the most common medical diagnoses identified in immigrant children after arrival. Children may be asymptomatic; therefore diagnoses must be made by screening tests in addition to history and physical examination. Because of inconsistent perinatal screening for hepatitis B and hepatitis C viruses, syphilis, and HIV and the high prevalence of certain intestinal parasites and tuberculosis, all foreign-born children should be screened for these infections on arrival in the United States. Table 9.2 and Table 11.1 list suggested screening tests for infectious diseases for international adoptees or immigrants/refugees, respectively. Table 11.2 lists incubation periods of common internationally acquired diseases. In addition to these infections, other medical and developmental issues, including hearing, vision, dental, and mental health assessments; evaluation of growth and development; nutritional assessment; lead exposure risk; complete blood cell count with red blood cell indices; microscopic urinalysis; newborn screening (this could also be done in nonneonates) and/or measurement of thyroid-stimulating hormone concentration; and examination for congenital anomalies (including fetal alcohol syndrome) should be considered as part of the initial evaluation of any immigrant child.*

Children should be examined within 1 month of arrival in the United States, or earlier if there are immediate health concerns, but foreign-born parents may not access the healthcare system with their children unless prompted by illness, school vaccination, or other legal requirements. *It is important to assess the completeness of previous medical screenings at any first visit with a foreign-born child.*

Clinicians should be aware of potential diseases in high-risk immigrant children and their clinical manifestations. Some diseases, such as central nervous system cysticercosis, may have incubation periods as long as several years and thus may not be detected during initial screening. On the basis of findings at the initial evaluation, consideration should be given to a repeat evaluation 6 months after arrival. In most cases, the longer the interval from arrival to development of a clinical syndrome, the less likely the syndrome can be attributed to a pathogen acquired in the country of origin.

Table 11.1 Infectious Disease Screening for Refugee Children

CONDITION OR TEST	REFUGEE CHILDREN
HEPATITIS A VIRUS (ACUTE INFECTION)	
Hepatitis A IgM antibody	Not recommended
HEPATITIS B VIRUS	
Hepatitis B surface antigen (HBsAg)	All
Hepatitis B surface antibody (anti-HBs)	All
Hepatitis B core antibody (anti-HBc)	All
HEPATITIS C VIRUS	
Hepatitis C antibody	Some
SYPHILIS	
Nontreponemal test (RPR, VDRL, or ART)	≥15 yr
Treponemal test (TPPA, MHA-TP, or FTA-ABS)	Not recommended
HUMAN IMMUNODEFICIENCY VIRUS	
Human immunodeficiency virus 1 and 2 antibody	≥13 yr
Recommended	<13 yr
TUBERCULOSIS	
Tuberculin skin test (TST)	All
or	
Interferon-γ release assay	≥2 yr
INTESTINAL PARASITES	
Microscopic evaluation of stool for ova and parasites	All (two specimens)*
Giardia intestinalis and *Cryptosporidium* antigen	All (one specimen)*
BACTERIAL ENTERIC INFECTION	
In children with diarrhea: bacterial stool culture	All
CHAGAS (ENDEMIC AREAS)	
Trypanosoma cruzi serologic testing	All
Complete blood count	All
EOSINOPHILIA WITH NEGATIVE STOOL OVA AND PARASITE FOR HELMINTHS	
Strongyloides serologic testing	All
Schistosoma serologic testing (endemic countries)*	
LYMPHATIC FILARIASIS (ENDEMIC AREAS)	
Filaria serology	All
CHAGAS (ENDEMIC AREAS)W	
Trypanosoma cruzi serologic testing	All
MALARIA SCREENING (ENDEMIC AREAS)	
Malaria polymerase chain reaction	All without pretreatment
HEMATURIA (SCHISTOSOMIASIS)	
Urinalysis	All

*Some experts recommend serologic testing regardless of whether eosinophilia is present.

ART, Automated reagin test; FTA-ABS, fluorescent treponemal antibody absorption; MHA-TP, microhemagglutination–*Treponema pallidum;* RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory.

Modified from Staat MA. Infectious disease considerations in international adoptees and refugees. In: Cherry JD, Harrison GJ, Kaplan SL, et al. (eds): *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 8th ed. Philadelphia: Elsevier; 2019: Table 233.1, p. 2310.

* For the most up-to-date guidelines based on country of origin/birth, see: https://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/domestic-guidelines.html.

Table 11.2 Incubation Periods of Common Travel-Related Infections*

SHORT INCUBATION (<10 DAYS)	MEDIUM INCUBATION (10-21 DAYS)	LONG INCUBATION (>21 DAYS)
Malaria	Malaria	Malaria
Arboviruses including dengue, yellow fever, Japanese encephalitis, Zika, chikungunya	Flaviviruses: tick-borne encephalitis and Japanese encephalitis	Schistosomiasis
Hemorrhagic fevers: Lassa, Ebola, South American arenaviruses	Hemorrhagic fevers: Lassa, Ebola, Crimean-Congo	Tuberculosis
Respiratory viruses including severe acute respiratory syndrome	Acute HIV infection	Acute HIV infection
Typhoid and paratyphoid	Typhoid and paratyphoid	Viral hepatitis
Bacterial enteritis	*Giardia*	Filariasis
Rickettsia: spotted fever group—Rocky Mountain spotted fever, African tick typhus, Mediterranean spotted fever, scrub typhus, Q fever	*Rickettsia*: flea-borne, louse-borne, and scrub typhus, Q fever, spotted fevers (rare)	*Rickettsia:* Q fever
Bacterial pneumonia including *Legionella*	Cytomegalovirus	Secondary syphilis
Relapsing fever	*Toxoplasma*	Epstein-Barr virus including mononucleosis
Amoebic dysentery	Amoebic dysentery	Amoebic liver disease
Meningococcemia	Histoplasmosis	Leishmaniasis
Brucella (rarely)	*Brucella*	*Brucella*
Leptospirosis	Leptospirosis	Bartonellosis (chronic)
Fascioliasis	Babesiosis	Babesiosis
Rabies (rarely)	Rabies	Rabies
African trypanosomiasis (acute), East African (rarely)	East African trypanosomiasis (acute)	West African trypanosomiasis (chronic)
	Hepatitis A (rarely)	Cytomegalovirus
	Measles	

*Diseases that commonly have variable incubation periods are shown more than once. However, most diseases may rarely have an atypical incubation period, and this is not shown here.

HIV, Human immunodeficiency virus.

From Freedman DO. Infections in returning travelers. In: Bennett JE, Blaser MJ, Dolin R, et al (eds): *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders;2015: Table 324-2.

COMMONLY ENCOUNTERED INFECTIONS

Hepatitis B

See also Chapter 406.

The prevalence of hepatitis B surface antigen (HBsAg) in refugee children ranges from 4% to 14%, depending on the country of origin, age, and year studied. Prevalence of markers of past hepatitis B virus (HBV) infection is higher. HBV infection is most prevalent in immigrants from Asia, Africa, and some countries in Central and Eastern Europe, as well as the former Soviet Union (e.g., Bulgaria, Romania, Russia, Ukraine), but also occurs in immigrants born in other countries. All immigrant children, even if previously vaccinated, coming from high-risk countries (HBsAg seropositivity >2%) should undergo serologic testing for HBV infection, including both HBsAg and antibody to HBsAg (anti-HBs), to identify current or chronic infection, past resolved infection, or evidence of previous immunization. Because HBV has a long incubation period (6 weeks to 6 months), the child may have become infected at or near the time of migration, and initial testing might be falsely negative. Therefore strong consideration should be given to a repeated evaluation 6 months after arrival for all children, especially those from highly endemic countries. Chronic HBV infection is indicated by persistence of HBsAg for >6 months. Children with HBsAg-positive test results should be evaluated to identify the presence of chronic HBV infection, which occurs in >90% of infants infected at birth or in the first year of life and in 30% of children exposed at ages 1-5 years. Once identified as being infected, additional testing should be done to assess for biochemical evidence of severe or chronic liver disease or liver cancer.

Hepatitis A

See Chapter 406.

Hepatitis C

See also Chapter 406.

The decision to screen children should depend on history (e.g., receipt of blood products; traditional percutaneous procedures such as tattooing, body piercing, circumcisions, or other exposures to reused, unsterile medical devices) and the prevalence of hepatitis C virus (HCV) infection in the child's country of origin. Children from Eastern Mediterranean and Western Pacific countries, Africa, China, and Southeast Asia should be considered for HCV infection screening. All children coming from Egypt, which has the highest known HCV seroprevalence (12% nationally and 40% in some villages), should be tested for hepatitis C.

Intestinal Pathogens

Fecal examinations for ova and parasites (O&P) by an experienced laboratory will identify a pathogen in 8–86% of immigrants and refugees. The prevalence of intestinal parasites varies by country of origin, time period when studied, previous living conditions (including water quality, sanitation, and access to footwear), and age, with toddler/young school-aged children being the most affected. If documented predeparture treatment was given, an eosinophil count should be performed. An absolute eosinophil count of >400 cells/μL, if persistently elevated for 3-6 months after arrival, should prompt further investigation for tissue-invasive parasites such as *Strongyloides* (see Chapter 341) and *Schistosoma* (see Chapter 346) species (if no predeparture ivermectin or praziquantel was given). If no documented predeparture treatment was given and screening eosinophils are >400 cells/μL, two stool O&P specimens obtained from separate morning stools should be examined by the concentration method *or* empiric ivermectin and praziquantel given. If the child is symptomatic, including evidence of poor physical growth, but no eosinophilia is present, a single stool specimen should also be sent for *Giardia lamblia* (see Chapter 328.1) and *Cryptosporidium parvum* (see Chapter 329) antigen detection. All potentially pathogenic parasites found should be treated appropriately. All nonpregnant refugees >2 years of age coming from sub-Saharan Africa and Southeast Asia should be presumptively treated with predeparture albendazole.

Tuberculosis

See also Chapter 261.

Tuberculosis (TB) commonly is encountered in immigrants from all countries because *Mycobacterium tuberculosis* infects approximately 30% of the world's population. Latent TB infection rates can be up to 60% in populations of refugee children from some regions of North Africa and the Middle East. Since 2007, TB *Technical Instructions for Medical Evaluation of Aliens* have required that children ages 2-14 years undergo a TB skin test or interferon-γ release assay if they are medically screened

in countries where the TB rate is ≥20 cases per 100,000 population. If the testing is positive, a chest radiograph is required. If the chest film suggests TB, cultures and three sputum smears are required, all before arrival in the United States. Check with the Centers for Disease Control and Prevention, Division of Global Migration and Quarantine, for the latest information (www.cdc.gov/ncidod/dq/technica.htm).

Congenital Syphilis

See Chapter 264.

HIV Infection

See Chapter 322.

IMMUNIZATIONS

See Chapter 215.

Immigrant children and adolescents should receive immunizations according to the recommended schedules in the United States for healthy children and adolescents. Some immigrants will have written documentation of immunizations received in their birth or home country. Although immunizations such as bacille Calmette-Guérin (BCG), diphtheria and tetanus toxoids and pertussis (DTP), poliovirus, measles, and HBV vaccines often are documented, other immunizations, such as *Haemophilus influenzae* type b, mumps, and rubella vaccines, are given less frequently, and *Streptococcus pneumoniae,* human papillomavirus, meningococcal, and varicella vaccines are given rarely. When doubt exists, an equally acceptable alternative is to reimmunize the child. Because the rate of more serious local reactions after DTP vaccine increases with the number of doses administered, serologic testing for antibody to tetanus and diphtheria toxins before reimmunizing, or if a serious reaction occurs, can decrease risk.

In children older than 6 months with or without written documentation of immunization, testing for antibodies to diphtheria and tetanus toxoid may be considered to determine whether the child has protective antibody concentrations. If the child has protective concentrations, the immunization series should be completed as appropriate for that child's age. In children older than 12 months, measles, mumps, rubella, and varicella antibody concentrations may be measured to determine whether the child is immune; these antibody tests should not be performed in children younger than 12 months because of the potential presence of maternal antibody.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 12

Cultural Issues in Pediatric Care

Lee M. Pachter and Alexandra M.S. Corley

Pediatricians live and work in a multicultural world. Among the world's nearly 8 billion people residing in over 200 countries, more than 6,000 languages are spoken. As the global population becomes more mobile, population diversity increases in all countries. In the United States, sources of ethnic and cultural diversity come from indigenous groups, such as Indigenous Nation peoples and Alaskan and Hawaiian natives, groups from U.S. territories such as Puerto Rico, recent immigrant groups, those whose heritage originates from the African diaspora and arrived to U.S. soil forcibly via the middle passage of the transatlantic slave trade, and others whose families and communities migrated to the United States from Europe and Asia generations ago but who have retained cultural identification. U.S. census estimates suggest that in 2020, nearly 40% of the U.S. population self-identified as belonging to an ethnic group other than non-Hispanic white. Immigrants comprise 15.4% of the U.S. population. Based on recent estimates, 25% of children in the United States are either new immigrants or first-generation US citizens. Immigrants from China and India account for the largest groups coming to the United States, followed by those from Mexico and Latin America. This national and international diversity allows for a heterogeneity of experience that enriches the lives of everyone. Much of this diversity is based on varied cultural orientation.

WHAT IS CULTURE?

The concept of *culture* does not refer exclusively to ethnic categorizations. A common definition of **cultural group** is *a collective that shares common heritage, worldviews, beliefs, values, attitudes, behaviors, practices, and identity*. Cultural groups can be based on identities such as gender (cis, trans, nonbinary), sexual orientation (gay, lesbian, straight, bisexual), age (teen culture), being deaf or hearing impaired (deaf culture; see Chapter 55), and having neurodevelopmental differences (neurodiversity). Those who identify in such groups, to a certain extent, may share common worldviews, attitudes, beliefs, values, practices, and identities with others in the group.

As a part of their shared experiences, many cultural groups face oppression, which can affect their health. Therefore these cultural groups require focused consideration from healthcare providers, and we must critically examine societal factors like racism, sexism, ableism, and other forms of discrimination at the structural (institutional), interpersonal, and psychologic levels as root causes of health disparities (see Chapters 2 and 2.1). These premises are particularly relevant in a white supremacy and hegemony-based society such as the United States and previously colonized nations.

Medical professionals can also be considered as belonging to a specific cultural group. Those who identify with the **culture of medicine** share common theories of well-being and disease, acceptance of the biomedical and biopsychosocial models of health, and common practices and rituals. As with other cultural groups, physicians and other healthcare professionals have a distinct language and share a common history, including experiencing similar preparatory courses that must be mastered for entrance into training for the profession (a rite of passage) and a degree of socioeconomic privilege. Medical professionals subscribe to common norms in medical practice. Young physicians learn a way to describe health and illness that requires a new common vocabulary and an accepted structure for communicating a patient's history. These common beliefs, orientations, and practices are often not shared by those outside of medicine. Therefore *any clinical interaction between a healthcare provider and a patient can be a potential cross-cultural interaction*—between the culture of medicine and the culture of the patient—regardless of the ethnicity or socioeconomic status of the participants. A culturally informed and sensitized approach to clinical communication is a fundamental skill required of *all* medical professionals, regardless of the demographic makeup of one's patient population.

Culture, Identity, and Intersectionality

We are all members of multiple cultural groups. Our identification with different groups can be dynamic. How we identify may depend on the context in which we find ourselves and may change over time. A gay Latino physician may feel, at different times and in different situations, greatest affinity with Latino culture, the culture of medicine, the "minority" culture in the United States, or his gay identity. An immigrant from India may initially feel great connection with her Indian culture and heritage, which may wane during periods of assimilation into American cultural life, then increase again at other points in life. Alternatively, there may be identities that are not as flexible; a dark-skinned person will never be able to "pass" as White. An obese person will not have the "thin privilege" of their underweight counterpart. In addition, multiple cultural identities can intersect. **Intersectionality** is a concept that expresses the *interconnected nature of the different social categorizations an individual may be connected to and how those identities interact to create systems*

of disadvantage and/or privilege. Considering intersectionality helps to understand how people who are members of multiple disenfranchised groups may experience harm as a result of either identity or both simultaneously. For example, a Black woman's experience with navigating both racism and sexism might differ from how her White female colleague deals with sexism alone. Culturally informed clinicians should never assume to understand the cultural identity or experiences of a person based solely on their perception of ethnic, racial, or group affiliation.

Intracultural Variability

There can be significantly different beliefs, values, and behaviors among members of the same cultural group. There is as much variability *within* cultures as there is *between* cultures. The sources of this variability include differences in personal psychology and philosophy, family beliefs and practices, social context, and other demographic differences, as well as **acculturation**, defined as the changes in beliefs and practices resulting from continuous interactions with another culture. The literature on acculturation and health outcomes shows varied effects of cultural change on health and well-being. These differences are in part caused by overly simplistic ways of measuring acculturation in public health and health services research. The use of *acculturation proxies* such as generational status (recent immigration, first generation) and socioeconomic status as measures of acculturation do not allow for an understanding of the complex behavioral changes that occur during shifts in cultural orientation. Often, acculturation is seen as a linear process where individuals move from unacculturated to acculturated or assimilated into the host culture. This simplistic view does not consider the reality that acculturation is *multidimensional* and includes the degree to which an individual continues to identify with her original culture-of-origin identity, the degree to which the host cultural orientation is adopted, and how inviting and welcoming the host culture is. These are separate and independent processes (Fig. 12.1). One can become *bicultural* (adopting the host culture while retaining aspects of the original culture), *assimilated* (host culture is adopted, but original culture is not retained), *separated* (original cultural orientation is retained, but host culture is not greatly adopted), or *marginalized* (does not adopt host culture and does not retain original culture). These variations in the acculturation process are determined not only by the individual going through the cultural change process but also by the degree of acceptance of diversity in the host culture. In theory, individuals who best adapt to the multicultural society are those who are **bicultural** because they retain the strengths and assets of their heritage culture while being able to positively adjust to host cultural norms. However, historically and in the present day, people from various cultural groups have taken on acculturation in a variety of ways for different reasons (e.g., survival, safety, wealth attainment). The acculturative process can be a source of stress and may have a negative impact on health and contribute to health disparities. It is worth noting that the acculturation process is one that the majority culture often has little awareness of or participation in. Members of the majority culture should strive for cultural awareness as a foundation for a culturally informed practice.

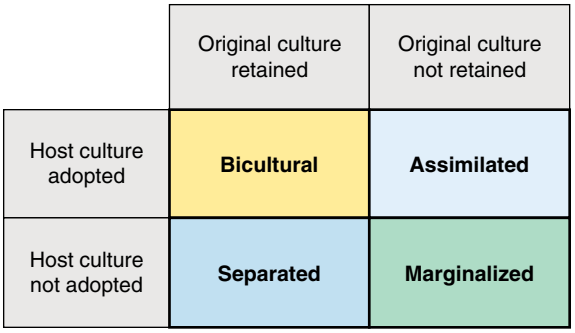

Fig. 12.1 Multidimensional model of acculturation. *(Adapted from Berry J. Immigration, acculturation, and adaptation. Appl Psychol 1997;46:5–68.)*

CULTURALLY INFORMED CARE

Physicians and patients bring to their interactions diverse orientations from multiple cultural systems. These different belief systems and practices could have significant implications for the delivery of healthcare and the receipt of health information. Consequently, physician cultural awareness, sensitivity, and humility are critical to successful patient-provider interaction.

The culturally informed physician (1) attempts to understand and respect the beliefs, values, attitudes, and lifestyles of all patients; (2) understands that health and illness are influenced by beliefs and practices originating from cultural orientation, linguistic considerations, religious and spiritual beliefs, and other socially constructed affiliations; (3) has insight into their own cultural biases and does not see cultural issues as something that only affects the patient; (4) is sensitive to how differences in power and privilege may affect the quality of the clinical encounter; (5) recognizes that in addition to the physiologic aspects of disease, the culturally and psychologically constructed meaning of illness and health is a central clinical issue; and (6) is sensitive to the role of intersectionality and intragroup variations in beliefs and practices and avoids stereotyping based on group affiliation. These core components of culturally informed care are important for interactions with *all* patients, regardless of socioeconomic status or ethnicity.

Becoming culturally informed is a developmental process. Figure 12.2 displays a framework that includes a continuum of perceptions and orientations to cultural awareness. Individuals in the *denial* stage perceive their own cultural orientation as the true one, with other cultures either undifferentiated or unnoticed. In the *defensive* stage, other cultures are acknowledged but regarded as inferior to one's own culture. The *minimization* stage is characterized by beliefs that fundamental similarities among people outweigh any differences and downplays the role of culture as a source of human variation. The mistaken idea that one should be "color blind" is an example of a common belief of individuals in the minimization stage and ignores the important historical adverse sociopolitical events faced by Black or other minoritized peoples.

As one moves to the *acceptance* stage, cultural differences are acknowledged. Further expansion and understanding lead to *adaptation,* where one not only acknowledges differences but can shift frames of reference and have a level of comfort outside one's own cultural frame. This eventually leads to further comfort with different worldviews seen at the *integration* stage, where individuals respect cultural differences and can comfortably interact across cultures with humility and respect.

Understanding Culture in the Context of Healthcare

Cultural orientation is just one of many different perspectives that individuals draw on as they make health and healthcare decisions. Individual psychology, past experiences (including racism), religious and spiritual views, social position, socioeconomic status (poverty), and family norms all can contribute to a person's health beliefs and practices as well as trust in the healthcare system.

Trust is essential to the patient–healthcare provider relationship. However, because of historical or current experiences, many cultures do not trust the healthcare system. In the past, Black people have been subjected to involuntary sterilization and not being treated for syphilis (the notorious Tuskegee study). Currently, Black people have received unequal pain relief and have experienced episodes of implicit and explicit racism in our healthcare system. These experiences create mistrust.

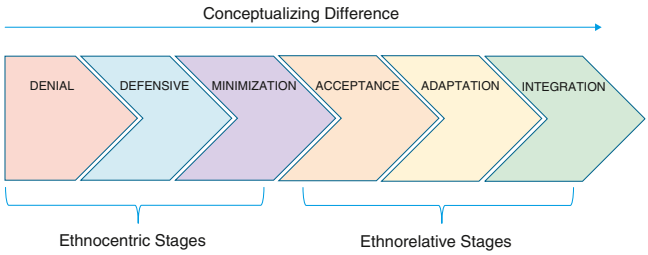

Fig. 12.2 Development of intercultural awareness. *(Adapted from Bennett MJ. A developmental approach to training for intercultural sensitivity. Int J Intercultural Relations. 1986;10:179–196.)*

The concept of intersectionality also contributes to the variability of beliefs and practices any individual subscribes to. These beliefs and practices can also change over time and may be expressed differently in different situations and circumstances. Because of the significant variability in health beliefs and behaviors seen among members of the same cultural group, an approach to cultural competency that emphasizes a "knowledge set" of specific cultural health practices in different cultural groups could lead to false assumptions and stereotyping. Knowledge is important, but it only goes so far. *Instead, an approach that focuses on the healthcare provider acquiring skills and attitudes relating to open and effective communication is a preferable approach to culturally effective and informed care.* Such an approach does not rely on rote knowledge of facts that may be stereotypical or outdated. Instead, it provides a toolbox that can be used in all circumstances. The following skills can lead to a culturally informed approach to care:

1. *Don't assume.* Presupposing that a particular patient may have certain beliefs or may act in a particular way based on stereotypic cultural group affiliation could lead to incorrect assumptions. Sources of intracultural diversity are varied. Multiple cultural identities can intersect and can contribute to a diversity of experiences.
2. *Practice humility.* Cultural humility has been described as "the ability to maintain an interpersonal stance that is 'other'-oriented (or open to the other) in relation to aspects of cultural identity." Cultural humility goes beyond cultural competency in that it requires the clinician to self-reflect and acknowledge that one's own cultural orientation enters any transaction with a patient.
   Cultural humility aims to address power imbalances between the dominant (hospital-medical) privileged culture and the patient. It incorporates the patient's life experiences. It creates a collaborative partnership between practitioner and patient. It also pushes the provider to critically examine their own biases and presuppositions.
   Cultural competency is an approach that typically focuses on the patient's culture, whereas cultural humility acknowledges that both physicians and patients have cultural orientations and that a successful relationship requires give and take among those differing perspectives. Cultural humility also includes an understanding that differences in social power, which are inherent in the physician-patient relationship, need to be understood and addressed so that open communication can occur.
3. *Understand and address privilege.* Members of the majority culture have certain privileges and benefits that are often unrecognized and unacknowledged. For example, they are more likely to be positively represented in media such as movies and television. Compared with minoritized groups, those in the majority culture have less chance of being followed by security guards at stores, stopped by the police, or having their bags checked. They have a greater chance of having a positive reception in a new neighborhood or of finding food in the supermarket that is consistent with their heritage. They have a lower likelihood of having to deal with the burden of racism and the acculturation process. These privileges typically go unnoticed by members of the majority culture, but their absence is painfully recognized by members of oppressed cultural groups. The culturally informed physician should try to be mindful of these privileges and power differentials and how they may influence their interactions with patients. Addressing such privilege might involve proactively centering traditionally silenced voices.
4. *Be inquisitive.* Because of the significant amount of intracultural diversity of beliefs and practices noted earlier, the only way to know a particular patient's approach to health and illness is through direct and effective communication. Asking about the patient's/family's perspective in an inquisitive and respectful manner will usually be met with open and honest responses, as long as the patient does not feel looked down on and the questions are asked in genuine interest. Obtaining a **health beliefs history** on *all* patients is an effective way of understanding clinical issues from the patient's and family's perspective (Table 12.1). The health beliefs history gathers information on the patient's views on the identification of health problems, causes, susceptibility, signs and symptoms, concerns, treatment, and expectations. Responses gathered from the health beliefs history can be helpful in guiding care plans and health education interventions.

Table 12.1 The Health Beliefs History

- What do you think is wrong with your child?
- Why do you think your child has gotten it (the illness)?
- What do you think caused it?
- Why do you think it started when it did?
- What do you think is happening inside the body?
- What are the symptoms that make you know your child has this illness?
- What problems does this illness cause your child?
- What are you most worried about with this illness?
- How long do you think it will last?
- How do you treat it?
- What will happen if it is not treated?
- What do you expect from the treatments?

Data from Kleinman A, Eisenberg L, Good B. Culture, illness and care: Clinical lessons from anthropologic and cross-cultural research. *Ann Intern Med.* 1978;88:251–258.

5. *Be flexible.* As members of the culture of medicine, clinicians have been educated and acculturated to the biomedical model as the optimal approach to health and illness. Patients and families may have health beliefs and practices that do not fully fit the biomedical model. Traditional beliefs and practices may be used in tandem with biomedical approaches without posing harm. An individual's approach to health rarely is exclusively biomedical or traditional and is often a combination of multiple approaches. The health beliefs history provides clinicians with information regarding nonbiomedical beliefs and practices that may be held by the patient. Culturally informed physicians should be flexible and find ways of integrating nonharmful traditional beliefs and practices into the medical care plan to make that plan fit the patient's needs and worldview, while still reaching the desired health outcome. This will likely result in better adherence to treatment and prevention.
   Obtaining a health beliefs history for a child with asthma, for example, may reveal that the family uses an **alternative remedy** when the symptoms first occur. If the symptoms do not resolve after giving the remedy, the family administers standard medical care. In this case, if the alternative remedy is safe and has no significant likelihood of causing adverse effects, the culturally informed physician might say, "I'm not sure if the remedy you're using is helpful or not, but I can say that if used as you described, it's not likely to be harmful. So, if you think it may work, feel free to try it. But instead of waiting to give the prescription medicine until after you see if the remedy works, why don't you give it at the same time you give the remedy? Maybe they'll work well together." This approach shows respect for the family-held beliefs and practices while increasing timely adherence to the biomedical therapy.

At times, an alternative therapy may be contraindicated or may have adverse effects. In this case it is advisable to recommend against the therapy, but whenever possible, one should attempt to replace the therapy with another, safer, culturally acceptable treatment. If a parent is giving a child tea containing harmful ingredients to treat a cold, the culturally informed physician could recommend stopping the practice and explain the concerns, but then recommend replacing the harmful tea with something safer that fits the family's cultural belief system, such as an herbal tea with no harmful ingredients. This requires an awareness and background knowledge of the cultural belief system, and this approach increases the chances that the family will follow through on the recommendation and feel that their beliefs are respected.

Awareness-Assessment-Negotiation Model

Providing care in the multicultural context can be challenging, but it offers opportunities for creativity and can result in improved long-term physician-patient relationships, which will ultimately improve the quality and outcomes of healthcare. Culturally informed care combines knowledge with effective communication skills, an open attitude, and the qualities of flexibility and humility.

The culturally informed physician should first become **aware** of common health beliefs, practices, and communication styles

of patients in the practice. Reading literature on particular groups could increase awareness, but with the caution that such information may be biased, outdated, or not specific to the local context. The best approach to becoming aware of specific health beliefs and practices is to ask—enter into conversations with patients, families, and community members. One might say, "Other families have shared with me that there are ways of treating this illness [or staying healthy] that work for them, but doctors do not know about them. Sometimes they are recommended by grandparents or others in the community. They may be effective. Have you heard of any of these?" This approach shows genuine interest and openness, is not based on presumptions, and does not ask about behaviors or practices, only if the patient has heard of these practices. If the question elicits a positive response, the conversation can then continue, including asking whether the patient has personally tried any of the therapies, under what circumstances, and if they thought it was helpful. This approach shows respect for the patient as an individual and avoids stereotyping all members of a particular group as monolithic in their cultural beliefs and practices.

The information obtained should be seen only as common ways that members of a community *may* interpret health-related issues. Assuming that all members subscribe to similar beliefs and practices would be incorrect and potentially damaging by promoting stereotypes. Because the unit of measurement in clinical care is the individual patient and family, clinicians must **assess** to what extent a specific patient may act on these general beliefs and under what circumstances. The health beliefs history can help the physician become aware of the specific beliefs and practices that a patient holds and allow one to tailor the care to the individual patient.

Once the patient's explanatory model is elicited and understood, the clinician should be able to assess the congruity of this model and the biomedical model, finding similarities. Then the process of **negotiating** can occur. Integrating patient-held approaches to health with evidence-based biomedical standards of care will help place care within the lifestyle and worldview of patients, leading to increased adherence to medical care plans, better physician-patient communication, enhanced long-term therapeutic relationships, better health outcomes, and improved patient (and physician) satisfaction. When there is a needed behavioral change, counseling for a patient or family should follow motivational interviewing best practices (see Chapter 18).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 13

Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

Joseph F. Hagan Jr. and Dipesh Navsaria

Health supervision visits from birth to age 21 are the platform for a young person's healthcare. Routine, scheduled care of well infants, children, and adolescents is an essential prevention effort for children and youth worldwide. The provision of **well care** in the medical home fosters strong relationships between the clinic or practice and the child and family, enabling the provision of appropriate surveillance, screening, and sick care.

To ensure the optimal health of the developing child, pediatric care in the United States and other countries evolved into regularly scheduled visits to ensure adequate nutrition, to detect and immunize against infectious diseases, and to observe the child's development. To foster optimal child healthy development, it is also wise to assess the child's or adolescent's emotional-behavioral health, their parents' mental health, their relational health, and their social determinants of health.

Well-child care focuses on the health and well-being of the child, but as children live in families of many varieties, it must also address that context by evaluating the needs, strengths, opportunities, and challenges of the identified family, including parents and other adults. Answering parents' questions while creating an environment where parents feel comfortable asking is an important feature of the well-child visit. Promoting family-centered care and partnership with parents increases the ability to elicit parental concerns, especially about their child's development, learning, behavior, and social needs. Addressing of needs may be as straightforward as supportive listening, or may include validation, and referral to an appropriate resource whether in the community or the adult's own medical home. Such two-generation approaches benefit both the parent and the child.

Ever-present and lying just beneath the surface of arguably of every pediatric encounter is the phenomenon of *relational health*. What is the health of the relationships within the family unit? Is the child surrounded by safe, stable, nurturing relationships? Or are they subject to unbuffered threats to their well-being? Are caregivers confident of their caregiving abilities? Do they have the capacity to do it well? This assessment followed by efforts to bolster relational health within families will act as a strong support to child development that has significant implications for the life course.

Contemporary analysis of changes in the population's health, coupled with the recognition that early life experiences and social factors affect health along the entire life course, call for a supportive environment providing positive childhood experiences that enhance the trajectory for child development and health. But stressful circumstances impair development, and **adverse childhood experiences** (ACEs) early in life increase the risk of disease (see Chapter 1). Adults who experienced abuse, violence, or other stressors as children have an increased risk for depression, heart disease, and other morbidities. Biology informs us that **ubuffered stress** leads to increased heart rate and blood pressure and increased levels of inflammatory cytokines, cortisol, and other stress hormones, all of which impair brain activity, immune status, and cardiovascular function. These impacts of stress present causal models of how ACEs, including those that could have been prevented, increase health risk and negatively affect the life course.

Preventive care for children, youth, and families offers great opportunity for health cost savings as a component of contemporary U.S. health reform activities. A thriving society and economy requires educated and healthy citizens and workers. For children to have a successful, meaningful, and useful educational experience, they must have physical, cognitive, and emotional health. Educational success in particular is tied to early childhood developmental competence. Well-child care plays a vital role in promoting adult health, a concept endorsed by business leaders as essential to building the human infrastructure of the U.S. economy and society.

THE PERIODICITY SCHEDULE AND GUIDELINES

The frequency and content for well-child care activities are derived from evidence-based practice and research. In addition, federal agencies and professional organizations, such as the American Academy of Pediatrics (AAP), have developed evidence-informed, expert consensus guidelines for care. The *Recommendations for Preventive Pediatric Health Care,* or **Periodicity Schedule**, is a compilation of

recommendations listed by age-based visits (Fig. 13.1). It is intended to guide practitioners of pediatric primary care to perform certain services and intentionally make observations at age-specific visits; it designates the standard for *preventive services* for U.S. children and youth and is referred to as such in some legislation. It is updated annually and is available online.

Comprehensive guides for care of well infants, children, and adolescents have been developed based on the Periodicity Schedule to expand and further recommend how practitioners might accomplish the tasks outlined. The current guideline standard is *The Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents*, fourth edition (https://brightfutures.aap.org/Pages/default.aspx). These guidelines were developed by the AAP under the leadership of the Maternal Child Health Bureau of the U.S. Department of Health and Human Services, in collaboration with the National Association of Pediatric Nurse Practitioners, American Academy of Family Physicians, American Medical Association, American Academy of Pediatric Dentistry, Family Voices, and others.

TASKS OF WELL-CHILD CARE

The well-child encounter aims to promote the physical and emotional well-being of children and youth. Child health professionals, including pediatricians, family medicine physicians, nurse practitioners, and physician assistants, take advantage of the opportunity well-child visits provide to elicit parental questions and concerns, gather relevant family and individual health information, perform a physical examination, and initiate screening tests. The tasks of each well-child visit include the following:

1. Disease detection
2. Disease prevention
3. Health promotion
4. Anticipatory guidance

To achieve these outcomes, healthcare professionals employ techniques to screen for disease—or for the risk of disease—and provide advice about healthy behaviors. These activities lead to the formulation of appropriate anticipatory guidance and health advice.

Clinical detection of disease in the well-child encounter is accomplished by a careful physical examination and both surveillance and screening. In well-child care, **surveillance** occurs in every health encounter and is enhanced by repeated visits and observations with advancing developmental stages. It relies on the experience of a skilled clinician performing intentional observation over time facilitated and informed by the observations offered by parents. **Screening** is a more formal process using a validated assessment tool that has known sensitivity and specificity. For example, anemia *surveillance* is accomplished through taking a dietary history and seeking signs of anemia in the physical examination. Anemia *screening* is done by hematocrit or hemoglobin tests. Developmental *surveillance* relies on the observations of parents and the assessment of clinicians in pediatric healthcare who are knowledgeable about child development. Table 13.1 shows the age at which 75% or more of children would be expected to achieve a developmental milestone across multiple streams of development. Developmental *screening* involves trained personnel scoring and interpreting a structured developmental screening tool completed by parents (see Chapter 28).

The second essential action of the well-child encounter, **disease prevention**, may include both *primary prevention* activities applied to a whole population and *secondary prevention* activities aimed at patients with specific risk factors. For example, counseling about reducing fat intake is appropriate for all children and families. However, counseling is intensified for overweight and obese youth or in the presence of a family history of hyperlipidemia and its sequelae. The child and adolescent healthcare professional needs to individualize disease prevention strategies to the specific patient, family, and community.

Health promotion and **anticipatory guidance** activities distinguish the well-child health supervision visit from all other encounters with the healthcare system. Disease detection and disease prevention activities are germane to all interactions of children with physicians and other healthcare clinicians, but health promotion and anticipatory guidance shift the focus to wellness and to the strengths of the family (e.g., what is being done well and how this might be improved). This approach is an opportunity to help the family address relationship issues; broach important safety topics; access needed services; and engage with extended family, school, neighborhood, and community and spiritual organizations. This is a prime area for relational health to be conceptually housed in the mind of the skilled clinician.

It is not possible to cover all the topics suggested by comprehensive guidelines such as *Bright Futures* in the average 18-minute well-child visit. Child health professionals must prioritize the most important topics to cover. Consideration should be given to a discussion of the following:

- First and foremost, the agenda the parent or child brings to the health supervision visit.
- The topics where evidence suggests counseling is effective in behavioral change.
- The topics where there is a clear rationale for the issue's critical importance to health, such as sleep environment to prevent sudden unexpected infant death (SUID) or attention to diet and physical activity.
- A summary of the child's progress in emotional, cognitive, and social development; physical growth; and strengths.
- Issues that address the questions, concerns, or specific health problems relevant to the individual family.
- Community-specific problems that could significantly affect the child's health (e.g., neighborhood violence from which children need protection or the absence of bike paths that would promote activity).

INFANCY AND EARLY CHILDHOOD

Nutrition, physical activity, sleep, safety, and emotional, social, and physical growth, along with parental well-being, are critical for all children. For each well-child visit, there are topics specific to individual children based on their age, family situation, chronic health condition, or a parental concern, such as sleep environment to prevent SUID, activities to promote healthy weight, and fences around swimming pools. Attention should also be focused on the family milieu and other social determinants of health, including screening for parental depression (especially maternal postpartum depression) and other mental illness, family violence, substance abuse, nutritional inadequacy, and lack of housing. It is equally important to identify, acknowledge, and empower family strengths. These issues are essential to the care of young children.

Evidence-based approaches such as early literacy assessment and promotion (e.g., Reach Out and Read) provide a structure for enquiry, surveillance, and parent coaching efficiently within the health supervision visit.

It is important to identify children with developmental disorders as early as possible. Developmental surveillance at every visit combined with a structured developmental screening, neuromuscular screening, and autism screening at certain visits enhances early diagnosis, especially for mild to moderate delays or autism spectrum disorders for which early intervention is believed to be associated with reduced morbidity.

MIDDLE CHILDHOOD AND ADOLESCENCE

As the child enters school-age years, additional considerations emerge. Attention to their developing autonomy requires fostering a clinician-patient relationship that begins to separate from the clinician–child-family relationship, with increasing needs for privacy and confidentiality as the child ages. As gender awareness develops, supportive and nonjudgmental care that is inclusive of the array of gender identities and sexual orientations found in youth is essential, particularly for LGBTQ+ youth.

The six health behaviors that most significantly affect adolescent and adult morbidity and mortality are inadequate physical activity, poor nutrition, sexuality-related behaviors, substance use and abuse (including tobacco and vaporized nicotine), unintentional injury–related behaviors, and intentional injury–related behaviors. New morbidities related to social media affect all contemporary youth, starting at remarkably young ages. Children are particularly

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Recommendations for Preventive Pediatric Health Care

Bright Futures/American Academy of Pediatrics

Bright Futures
prevention and health promotion for infants, children, adolescents, and their families™

Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving nurturing parenting, have no manifestations of any important health problems, and are growing and developing in a satisfactory fashion. Developmental, psychosocial, and chronic disease issues for children and adolescents may require more frequent counseling and treatment visits separate from preventive care visits. Additional visits also may become necessary if circumstances suggest concerns.

These recommendations represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

Refer to the specific guidance by age as listed in the *Bright Futures Guidelines* (Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents.* 4th ed. American Academy of Pediatrics; 2017).

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

The Bright Futures/American Academy of Pediatrics Recommendations for Preventive Pediatric Health Care are updated annually.

Copyright © 2023 by the American Academy of Pediatrics, updated April 2023.

No part of this statement may be reproduced in any form or by any means without prior written permission from the American Academy of Pediatrics except for one copy for personal use.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

	INFANCY								EARLY CHILDHOOD							MIDDLE CHILDHOOD						ADOLESCENCE										
AGE[1]	Prenatal[2]	Newborn[3]	3-5 d[4]	By 1 mo	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo	30 mo	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y	19 y	20 y	21 y
HISTORY Initial/Interval	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
MEASUREMENTS																																
Length/Height and Weight		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Head Circumference		●	●	●	●	●	●	●	●	●	●	●																				
Weight for Length		●	●	●	●	●	●	●	●	●	●																					
Body Mass Index[5]												●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood Pressure[6]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SENSORY SCREENING																																
Vision[7]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	★	●	★	●	★	●	★	★	●	★	★	★	★	★	★
Hearing		●[8]	●[9] →	→	→	★	★	★	★	★	★	★	★	★	●	●	●	★	●	★	●	←	←	●[10] →	→	←	←	● →	←	←	● →	→	→
DEVELOPMENTAL/SOCIAL/BEHAVIORAL/ MENTAL HEALTH																																
Maternal Depression Screening[11]				●	●	●	●																									
Developmental Screening[12]								●			●		●																			
Autism Spectrum Disorder Screening[13]											●	●																				
Developmental Surveillance		●	●	●	●	●	●		●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Behavioral/Social/Emotional Screening[14]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tobacco, Alcohol, or Drug Use Assessment[15]																						★	★	★	★	★	★	★	★	★	★	★
Depression and Suicide Risk Screening[16]																							●	●	●	●	●	●	●	●	●	●
PHYSICAL EXAMINATION[17]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PROCEDURES[18]																																
Newborn Blood		●[19]	●[20] →	→																												
Newborn Bilirubin[21]		●																														
Critical Congenital Heart Defect[22]		●																														
Immunization[23]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Anemia[24]						★			●	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Lead[25]							★	★	● or ★[26]		★	● or ★[26]		★	★	★	★															
Tuberculosis[27]				★			★		★			★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Dyslipidemia[28]												★			★		★		★	←	● →	★	★	★	★	★	←	←	←	● →	→	→
Sexually Transmitted Infections[29]																						★	★	★	★	★	★	★	★	★	★	★
HIV[30]																						★	★	★	★	● →	→	→	→	→	→	→
Hepatitis B Virus Infection[31]		★ →	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Hepatitis C Virus Infection[32]																													● →	→	→	→
Sudden Cardiac Arrest/Death[33]																						★ →	→	→	→	→	→	→	→	→	→	→
Cervical Dysplasia[34]																																●
ORAL HEALTH[35]							●[36]	●[36]	★		★	★	★	★	★	★	★															
Fluoride Varnish[37]							←	←	←	←	●	←	←	←	← →																	
Fluoride Supplementation[38]							★	★	★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★				
ANTICIPATORY GUIDANCE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

KEY: ● = to be performed ★ = risk assessment to be performed with appropriate action to follow, if positive ←★ or ●→ = range during which a service may be provided

Fig. 13.1 Recommendations for preventive pediatric healthcare. The AAP updates the *Periodicity Schedule* annually. The current *Periodicity Schedule* should be consulted at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf. (*From Bright Futures/American Academy of Pediatrics. Copyright 2022, American Academy of Pediatrics. Elk Grove Village, IL.* https://www.aap.org/en-us/documents/periodicity_schedule.pdf.)

1. If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up to date at the earliest possible time.
2. A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding, per "The Prenatal Visit" (https://doi.org/10.1542/peds.2018-1218).
3. Newborns should have an evaluation after birth, and breastfeeding should be encouraged (and instruction and support should be offered).
4. Newborns should have an evaluation within 3 to 5 days of birth and within 48 to 72 hours after discharge from the hospital to include evaluation for feeding and jaundice. Breastfeeding newborns should receive formal breastfeeding evaluation, and their mothers should receive encouragement and instruction, as recommended in "Breastfeeding and the Use of Human Milk" (https://doi.org/10.1542/peds.2011-3552). Newborns discharged less than 48 hours after delivery must be examined within 48 hours of discharge, per "Hospital Stay for Healthy Term Newborn Infants" (https://doi.org/10.1542/peds.2015-0699).
5. Screen, per "Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report" (https://doi.org/10.1542/peds.2007-2329C).
6. Screening should occur per "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents" (https://doi.org/10.1542/peds.2017-1904). Blood pressure measurement in infants and children with specific risk conditions should be performed at visits before age 3 years.
7. A visual acuity screen is recommended at ages 4 and 5 years, as well as in cooperative 3-year-olds. Instrument-based screening may be used to assess risk at ages 12 and 24 months, in addition to the well visits at 3 through 5 years of age. See "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians" (https://doi.org/10.1542/peds.2015-3596) and "Procedures for the Evaluation of the Visual System by Pediatricians" (https://doi.org/10.1542/peds.2015-3597).
8. Confirm initial screen was completed, verify results, and follow up, as appropriate. Newborns should be screened, per "Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs" (https://doi.org/10.1542/peds.2007-2333).
9. Verify results as soon as possible, and follow up, as appropriate.
10. Screen with audiometry including 6,000 and 8,000 Hz high frequencies once between 11 and 14 years, once between 15 and 17 years, and once between 18 and 21 years. See "The Sensitivity of Adolescent Hearing Screens Significantly Improves by Adding High Frequencies" (https://www.sciencedirect.com/science/article/abs/pii/S1054139X16000483).
11. Screening should occur per "Incorporating Recognition and Management of Perinatal Depression Into Pediatric Practice" (https://doi.org/10.1542/peds.2018-3259).
12. Screening should occur per "Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening" (https://doi.org/10.1542/peds.2019-3449).
13. Screening should occur per "Identification, Evaluation, and Management of Children With Autism Spectrum Disorder" (https://doi.org/10.1542/peds.2019-3447).
14. Screen for behavioral and social-emotional problems per "Promoting Optimal Development: Screening for Behavioral and Emotional Problems" (https://doi.org/10.1542/peds.2014-3716), "Mental Health Competencies for Pediatric Practice" (https://doi.org/10.1542/peds.2019-2757), "Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders" (https://pubmed.ncbi.nlm.nih.gov/32439401), and "Screening for Anxiety in Adolescent and Adult Women: A Recommendation From the Women's Preventive Services Initiative" (https://pubmed.ncbi.nlm.nih.gov/32510990). The screening should be family centered and may include asking about caregiver emotional and mental health concerns and social determinants of health, racism, poverty, and relational health. See "Poverty and Child Health in the United States" (https://doi.org/10.1542/peds.2016-0339), "The Impact of Racism on Child and Adolescent Health" (https://doi.org/10.1542/peds.2019-1765), and "Preventing Childhood Toxic Stress: Partnering With Families and Communities to Promote Relational Health" (https://doi.org/10.1542/peds.2021-052582).
15. A recommended assessment tool is available at http://crafft.org.
16. Screen adolescents for depression and suicide risk, making every effort to preserve confidentiality of the adolescent. See "Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part I. Practice Preparation, Identification, Assessment, and Initial Management" (https://doi.org/10.1542/peds.2017-4081), "Mental Health Competencies for Pediatric Practice" (https://doi.org/10.1542/peds.2019-2757), "Suicide and Suicide Attempts in Adolescents" (https://doi.org/10.1542/peds.2016-1420), and "The 21st Century Cures Act & Adolescent Confidentiality" (https://www.adolescenthealth.org/Advocacy/Advocacy-Activities/2019-(1)/NASPAG-SAHM-Statement.aspx).
17. At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped. See "Use of Chaperones During the Physical Examination of the Pediatric Patient" (https://doi.org/10.1542/peds.2011-0322).
18. These may be modified, depending on entry point into schedule and individual need.
19. Confirm initial screen was accomplished, verify results, and follow up, as appropriate. The Recommended Uniform Screening Panel (https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/regulations (https://www.babysfirsttest.org/) establish the criteria for and coverage of newborn screening procedures and programs.
20. Verify results as soon as possible, and follow up, as appropriate.
21. Confirm initial screening was accomplished, verify results, and follow up, as appropriate. See "Hyperbilirubinemia in the Newborn Infant ≥35 Weeks' Gestation: An Update With Clarifications" (https://doi.org/10.1542/peds.2009-0329).
22. Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per "Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease" (https://doi.org/10.1542/peds.2011-3211).
23. Schedules, per the AAP Committee on Infectious Diseases, are available at https://publications.aap.org/redbook/pages/immunization-schedules. Every visit should be an opportunity to update and complete a child's immunizations.
24. Perform risk assessment or screening, as appropriate, per recommendations in the current edition of the AAP *Pediatric Nutrition: Policy of the American Academy of Pediatrics* (Iron chapter).
25. For children at risk of lead exposure, see "Prevention of Childhood Lead Toxicity" (https://doi.org/10.1542/peds.2016-1493) and "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention" (https://www.cdc.gov/nceh/lead/docs/final_document_030712.pdf).
26. Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas.
27. Tuberculosis testing per recommendations of the AAP Committee on Infectious Diseases, published in the current edition of the AAP *Red Book: Report of the Committee on Infectious Diseases*. Testing should be performed on recognition of high-risk factors.
28. See "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents" (http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm).
29. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the AAP *Red Book: Report of the Committee on Infectious Diseases*.
30. Screen adolescents for HIV at least once between the ages of 15 and 21, making every effort to preserve confidentiality of the adolescent, as per "Human Immunodeficiency Virus (HIV) Infection: Screening" (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/human-immunodeficiency-virus-hiv-infection-screening); after initial screening, youth at increased risk of HIV infection should be retested annually or more frequently, as per "Adolescents and Young Adults: The Pediatrician's Role in HIV Testing and Pre- and Postexposure HIV Prophylaxis" (https://doi.org/10.1542/peds.2021-055207).
31. Perform a risk assessment for hepatitis B virus (HBV) infection according to recommendations per the USPSTF (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening) and in the 2021–2024 edition of the AAP *Red Book: Report of the Committee on Infectious Diseases*, making every effort to preserve confidentiality of the patient.
32. All individuals should be screened for hepatitis C virus (HCV) infection according to the USPSTF (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening) and Centers for Disease Control and Prevention (CDC) recommendations (https://www.cdc.gov/mmwr/volumes/69/rr/rr6902a1.htm) at least once between the ages of 18 and 79. Those at increased risk of HCV infection, including those who are persons with past or current injection drug use, should be tested for HCV infection and reassessed annually.
33. Perform a risk assessment, as appropriate, per "Sudden Death in the Young: Information for the Primary Care Provider" (https://doi.org/10.1542/peds.2021-052044).
34. See USPSTF recommendations (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/cervical-cancer-screening). Indications for pelvic examinations prior to age 21are noted in "Gynecologic Examination for Adolescents in the Pediatric Office Setting" (https://doi.org/10.1542/peds.2010-1564).
35. Assess whether the child has a dental home. If no dental home is identified, perform a risk assessment (https://www.aap.org/en/patient-care/oral-health/oral-health-practice-tools/) and refer to a dental home. Recommend brushing with fluoride toothpaste in the proper dosage for age. See "Maintaining and Improving the Oral Health of Young Children" (https://doi.org/10.1542/peds.2014-2984).
36. Perform a risk assessment (https://www.aap.org/en/patient-care/oral-health/oral-health-practice-tools/). See "Maintaining and Improving the Oral Health of Young Children" (https://doi.org/10.1542/peds.2014-2984).
37. The USPSTF recommends that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prevention-of-dental-caries-in-children-younger-than-age-5-years-screening-and-interventions1). Once teeth are present, apply fluoride varnish to all children every 3 to 6 months in the primary care or dental office based on caries risk. Indications for fluoride use are noted in "Fluoride Use in Caries Prevention in the Primary Care Setting" (https://doi.org/10.1542/peds.2020-034637).
38. If primary water source is deficient in fluoride, consider oral fluoride supplementation. See "Fluoride Use in Caries Prevention in the Primary Care Setting" (https://doi.org/10.1542/peds.2020-034637).

Fig. 13.1 cont'd

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 13.1 Developmental Milestones Across Streams of Development

AGE	STREAMS OF DEVELOPMENT			
	LANGUAGE	COGNITIVE	MOTOR	SOCIAL EMOTIONAL
2 mo	• Makes sounds other than crying • Reacts to loud sounds	• Watches you as you move • Looks at a toy for several seconds	• Holds head up when on tummy • Opens hands briefly	• Calms when spoken to or picked up • Looks at face • Seems happy to see parent • Smiles when parent talks to them
4 mo	• Makes cooing sounds • Makes sounds back when talked to • Turns head towards sound of parent's voice	• If hungry, opens mouth when sees breast or bottle • Looks at hands with interest	• Holds head steady without support when being held • Uses arms to swing at toys • Brings hands to mouth • Pushes up onto elbows/ forearms when on tummy	• Smiles to get parent's attention • Chuckles responsively • Attempts to get parent's attention using eye contact, movement, or sounds
6 mo	• Takes turns making sounds • Sticks tongue out and blows (e.g., raspberries) • Makes squealing noises	• Puts things in mouth to explore them • Reaches to grab a toy • Closes lips when does not want more food	• Rolls from tummy to back • Pushes up with straight arms when on tummy • Leans on hands for support when sitting	• Knows familiar people • Likes to look at self in a mirror • Laughs
9 mo	• Makes babbling sounds • Lifts arms up to be picked up	• Looks for objects when dropped out of sight • Bangs 2 things together	• Gets to a sitting position on one's own • Transfers things between hands • Uses fingers to "rake" food • Sits without support	• Is shy or clingy around strangers • Makes several facial expressions like happy, sad, angry, or surprised • Looks when you call name • Smiles or laughs when playing peek-a-boo
12 mo	• Waves "bye-bye" • Has name for parent such as "mama" or "dada" • Understands "no" (not just tone of voice)	• Puts something in a container, like a block in a cup • Looks for things they see you hide	• Pulls up to stand • Walks holding on to furniture • Drinks from a cup without a lid as parent holds it • Picks things up between thumb and pointer finger	• Plays games with parent, like pat-a-cake
15 mo	• Approximates saying 1 or 2 words besides "mama" or "dada" • Looks at a familiar object when named • Follows directions given with gesture • Points to request object or help (e.g., proto-imperative pointing)	• Tries to use things the right way, like a phone, cup, or book • Stacks at least 2 small objects, like blocks	• Takes a few steps on own • Able to finger feed	• Copies other children playing • Shows parent an object they like • Claps when excited • Hugs stuffed doll or other toy • Shows parent affection
18 mo	• Says 3 or more words besides "mama" or "dada" • Follows 1-step directions without a gesture • Points to show interest (e.g., proto-declarative pointing)	• Copies parent doing chores • Plays with toys in a simple way, like pushing a toy car	• Walks on own • Scribbles • Drinks from a cup without a lid, may spill sometimes • Tries to use a spoon • Climbs on and off a couch or chair without help	• Checks in when moving away from parent • Puts hands out to be washed • Looks at a book with parent • Helps with dressing by pushing arm through sleeve or lifting up foot
2 yr	• Points to pictures in book on request • Says at least 2 words together (e.g., more milk) • Points to 2 or more body parts on request • Uses more gestures than just waving and pointing (e.g., blowing a kiss, nodding yes)	• Holds something while using the other hand (e.g., holding container and taking lid off) • Tries to use knobs, switches, or buttons on toys • Plays with more than 1 toy at the same time (e.g., putting toy food on toy plate)	• Kicks a ball • Runs • Walks (not climbs) up a few stairs with or without help • Eats with a spoon	• Notices when others are hurt or upset, like pausing or looking sad when someone is crying • Looks at parent's face to see how to react in a new situation
2½ yr	• Says about 50 words • Says 2 or more words, with 1 action word (e.g., doggie run) • Names things in a book when you point and ask, "What is this?" • Says words like "I," "me," or "we"	• Engages in pretend play • Shows simple problem-solving skills (e.g., using a stool to reach something) • Follows 2-step instructions • Knows at least 1 color	• Uses hands to twist things (e.g., turning doorknobs or lids) • Takes off some clothes on own • Jumps off the ground with both feet • Turns book pages, 1 at a time, when read to	• Plays next to other children and at times with them • Shows what he or she can do by saying, "Look at me!" • Follows simple routines when told (e.g., clean-up time)

Table 13.1 Developmental Milestones Across Streams of Development—cont'd

AGE	STREAMS OF DEVELOPMENT			
3 yr	• Has conversation using at least 2 back-and-forth exchanges • Asks "who," "what," "where," or "why" questions • Says what action is happening in a picture or book (e.g., running, eating) • Says first name when asked • Talks well enough for others to understand most of the time	• Imitates drawing a circle • Avoids touching hot objects, like a stove, when warned	• Strings items together, like large beads or macaroni • Puts on some clothes on own • Uses a fork	• Calms down within 10 min after parent leaves (e.g., at childcare drop-off) • Notices other children and joins them to play
4 yr	• Says sentences with 4 or more words • Talks about at least 1 thing that happened during the day • Answers simple questions (e.g., what is a coat for?)	• Names a few colors • Tells what comes next in a well-known story • Draws a person with 3 or more body parts	• Catches a large ball most of the time • Serves themselves food or pours water, with adult supervision • Unbuttons some buttons • Holds crayon or pencil between fingers and thumb (not a fist)	• Pretends to be something else during play (e.g., teacher, dog) • Asks to play with children • Comforts others who are hurt or sad • Likes to be a "helper" • Changes behavior based on location (e.g., library, playground)
5 yr	• Tells a story they heard or made up with at least 2 events • Answers simple questions about a book or story • Keeps a conversation going with more than 3 back-and-forth exchanges • Uses or recognizes simple rhymes (e.g., bat-cat, ball-tall)	• Counts to 10 • Names some numbers between 1 and 5 when you point to them • Uses words about time, like yesterday, tomorrow, morning, or night • Pays attention for 5 to 10 min during activities • Writes some letters in name • Names some letters when they are pointed to	• Buttons some buttons • Hops on 1 foot	• Follows rules or takes turns when playing games with other children • Sings, dances, or acts • Does simple chores at home

Adapted from Centers for Disease Control Developmental Milestones: https://www.cdc.gov/ncbddd/actearly/milestones/index.html. Accessed March 19, 2022.

vulnerable to advertising of unhealthy products and behaviors because of immature skills in critical thinking and impulse control. Emotional well-being and early diagnosis and treatment of mental health problems are crucially important, with attention to the developmental tasks of adolescence: competence at school and other activities, connection to friends and family, autonomy, empathy, and a sense of self-worth.

Children and Youth with Special Healthcare Needs

This set of frameworks must be directed at *all children*, including children and youth with special healthcare needs (CYSHCN). CYSHCN are no different from other children in their need for guidance about healthy nutrition, physical activity, progress in school, connection with friends, a healthy sense of self-efficacy, and avoidance of risk-taking behaviors. The existence of frequent visits to the medical home or specialists to address the special health needs sometimes masks the lack of general health supervision care. The coordination of specialty consultation, medication monitoring, and functional assessment, which should occur in their periodic visits, needs to be balanced with a discussion of the child's unique ways of accomplishing the emotional, social, and developmental tasks of childhood and adolescence. Comprehensive, integrated care planning for CYSHCN should support partnerships between family-centered medical homes and families and youth through goal setting and negotiating next steps. In this process, chronic condition management and health surveillance (including adolescent engagement and planning for transition to adult care) occur within an effective patient care relationship, partnering to improve health outcomes and efficiencies of current and future care provision.

OFFICE INTERVENTION FOR BEHAVIORAL AND MENTAL HEALTH ISSUES

One fifth of primary care encounters with children are for a behavioral or mental health problem or sickness visits complicated by a mental health issue. Pediatricians and other primary care clinicians seeing children must have reasonable comfort with and knowledge for diagnosis, treatment, and referral criteria for attention-deficit/hyperactivity disorder (see Chapter 50), depression and other mood disorders (see Chapter 39), anxiety (see Chapter 38), and conduct disorder (see Chapter 42), as well as an understanding of the pharmacology of the frequently prescribed psychotropic medications. Familiarity with available local mental health services and clinicians and knowledge of the types of services indicated are important for effective consultation or referral. With new understanding of the impact of lifestyle on mood disorders and anxiety, encouragement of behavioral change to implement regular exercise, a healthy diet, avoidance of substances, and judicious use of media has become an important responsibility of the primary care clinician. **Motivational interviewing** (see Chapter 18) provides a structured approach that has been designed to help patients and parents identify the discrepancy between their desire for health and

the outcomes of their current behavioral choices. It also allows the clinician to use proven strategies that lead to a patient-initiated plan for change.

Strength-Based Approaches and Framework

Questions about school or extracurricular accomplishments or competent personal characteristics should be integrated into the content of the well child visit. Such inquiries set a positive context for the visit, deepen the partnership with the family, acknowledge the child's healthy development, and facilitate discussing social-emotional development with children and their parents. There is a strong relationship between appropriate social-emotional development (e.g., children's strong connection to their family, social friends, and mentors; competence; empathy; appropriate autonomy) and decreased participation in all the risk behaviors of adolescence (related to drugs, sex, and violence). An organized approach to the identification and encouragement of a child's strengths during health supervision visits provides both the child and the parent with an understanding of how to promote healthy achievement of the developmental tasks of childhood and adolescence. It also provides an opportunity to assess and comment on the relational health in the family. CYSHCN often have a different timetable, but they have an equal need to be encouraged to develop strong family and peer connections, competence in a variety of arenas, ways to do things for others, and appropriate independent decision-making.

Family Support Programs

Family support can range from the informal, to the highly formalized, to the referral to other agencies. Informal supports can be incorporated easily into existing assessment or anticipatory guidance. More formalized programs incorporate clinician and clinic staff training and guidance for the family while still operating within the existing framework of the well-child visit, such as Reach Out and Read. Even more structured are programs such as HealthySteps or Video Interaction Project, which address deeper needs for support through additional personnel and time. Finally, agencies external to the medical home, like evidence-based home visiting, can offer even greater intensity or flexibility of service.

This continuum of offerings allows a clinician to "tune" the intensity of services to meet the needs of a family while maintaining the support and connection of the medical home in the face of the reality of families who have needs far beyond what can be addressed immediately. Family support programs should be selected and offered based on available evidence and strong elements of reproducibility, scalability, and clarity. Advocacy for funding for family support programs is also imperative.

Office System Change for Quality Improvement

To facilitate the effective delivery of preventive services for children and youth, screening schedules and parent handouts, flow sheets, registries, and parent and youth previsit questionnaires are available in *The Bright Futures Guidelines Toolkit*. These efforts are part of a larger national effort that is built on a coordinated team approach in the office setting and the use of continuous measurement for improvement.

EVIDENCE

Available evidence should be used in developing health-promotion and disease-detection recommendations. Revisions to the AAP Periodicity Schedule undergo rigorous evidence assessment; however, many highly valued well-child care activities have not been evaluated for efficacy. Lack of evidence is most often related to absence of systematic study and does not necessarily mean lack of benefit. Thus the clinical encounter with the well child is also guideline and recommendation driven and requires the integration of clinician goals, family needs, and community realities in seeking better health for the child. The evidence and rationale for recommendations in the Periodicity Schedule (see Fig. 13.1) and *Bright Futures Guidelines* regarding well-child care activities are a balance of evidence from research, clinical practice guidelines, professional recommendations, expert opinion, experience, and knowledge of the needs of the patient population in the context of community assets and challenges. Clinical or counseling decisions and recommendations may also be based on local legislation (e.g., seat belts), on commonsense measures not likely to be studied experimentally (e.g., lowering water heater temperatures, use of car seats), or on the basis of relational evidence (e.g., television watching associated with violent behavior in young children). Most importantly, sound clinical and counseling decisions are responsive to family needs and desires and support patient-centered decision-making.

CARING FOR THE CHILD AND YOUTH IN THE CONTEXT OF THE FAMILY AND COMMUNITY

A successful primary care practice for children incorporates families, is family centered, and embraces the concept of the medical home. To be considered a **medical home**, a primary care practice must certify that their care is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. In a medical home, a clinician works in partnership with the family and patient to ensure that all medical and nonmedical needs of the child are met. Through this partnership, the child healthcare professional helps the family/patient access and coordinate specialty care, educational services, out-of-home care, family support, and other public and private community services that are important to the overall health of the child and family.

Health promotion activities occur not only in the medical home but also through community members and other health and education professionals. To be most effective, communication and coordination around providing accurate, consistent information is key, with a clear understanding of the important role that the community plays in supporting healthy behaviors among families. Communities where children and families feel safe and valued and have access to positive activities and relationships provide the important base that the healthcare professional can build on and refer to for needed services that support health but are outside the realm of the healthcare system or primary care medical home. It is important for the medical home and community agencies to identify mutual resources, communicate well with families and each other, and partner in designing service delivery systems. This interaction is the practice of **community pediatrics**, whose unique feature is its concern for all the population: those who remain well but need preventive services, those who have symptoms but do not receive effective care, and those who do seek medical care in a physician's office or hospital.

Contemporary and future health supervision of children and adolescents must evolve to improve the delivery of this comprehensive care, which is critical to the healthy development of every child, their family, and their community. Relevant practice models for delivery of health supervision care will continue to evolve to provide comprehensive care and partnership with medical and community services to serve their patients and families. Such models will appropriately broaden the sphere of primary care pediatrics and foster partnerships in community care. Pediatric clinicians should also advocate not only for individual patients but also for system change for the betterment of this and future generations.

Health reform is key to this work to assure that an evidence-based, comprehensive system of health supervision is supported. Payment modalities might vary, but payment must recognize that the work of healthcare and the essential work of those providing preventive care to children is poorly recognized, supported, and remunerated by most existing payment systems. The success of accountable care organizations and any other current or future healthcare system can and should require strengthening and broadening primary care preventive services. This reform must acknowledge and embrace the already existing reality that preventive care is so much more than merely height, weight, and immunizations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 14

Injury Control

Brian D. Johnston and Sadiqa Kendi

In all high-income countries of the world, and increasingly in many low- and middle-income countries, injuries are the most common cause of death during childhood and adolescence beyond the first few months of life (Table 14.1 and Fig. 14.1). Injuries represent one of the most important causes of preventable pediatric morbidity and mortality in the United States. Identification of risk factors for injuries has led to the development of successful programs for prevention and control. Strategies for injury prevention and control should be pursued by the pediatrician in the office, emergency department (ED), hospital, and community setting.

Injuries have identifiable risk and protective factors that can be used to define prevention strategies. The term *accident* implies a chance event occurring without pattern or predictability. In fact, most injuries occur under predictable circumstances to children and families known to be at risk. *Most injuries are preventable.*

Reduction of morbidity and mortality from injuries can be accomplished not only through *primary* prevention (averting the event or injury) but also through *secondary* and *tertiary* prevention. The latter two approaches include appropriate **emergency medical services** (EMS) for injured children; **regionalized trauma care** for the child with multiple injuries, severe burns, or traumatic brain injury; and **specialized pediatric rehabilitation** services to optimize functional recovery after injury.

Injury control also encompasses *intentional injuries* (assaults and self-inflicted injuries). These injuries are important in adolescents and young adults, and in some populations, these rank first or second as causes of death in these age-groups. Many of the same principles of injury control can be applied to these problems; for example, limiting access to firearms may reduce unintentional shootings and also homicides and suicides.

SCOPE OF THE PROBLEM

Mortality

In the United States, injuries cause 41% of deaths among 1- to 4-year-old children and 3.2 times more deaths than the next leading cause, congenital anomalies. For the rest of childhood and adolescence up to age 19 years, 65% of deaths are a result of injuries, more than all other causes combined. In 2019, injuries caused 13,384 deaths (16.4 deaths per 100,000 population) among individuals ≤19 years old in the United States, resulting in more years of potential life lost than any other cause. **Unintentional injuries** remained the leading cause of death among those <24 years old in 2019 (see Table 14.1).

Motor vehicle injuries lead the list of injury deaths among school-age children and adolescents and are the second leading cause of injury death for those age 1-4 years. In children and adults, motor vehicle *occupant* injuries account for most of these deaths. During adolescence, occupant injuries are the leading cause of injury death, accounting for >50% of unintentional trauma mortality in this age-group.

Drowning ranks second overall as a cause of unintentional injury deaths among those age 1-19 years, with peaks in the preschool and later teenage years (see Chapter 88). In some areas of the United States, drowning is the leading cause of injury death for preschool-age children. The causes of drowning deaths vary with age and geographic area. In young children, bathtub and swimming pool drowning predominates, whereas in older children and adolescents, drowning occurs in natural bodies of water while swimming or boating.

Fire- and burn-related deaths account for 3% of all unintentional trauma deaths, with the highest rates among those <5 years of age (see Chapter 89). Most deaths are a result of house fires and are caused by smoke inhalation or asphyxiation rather than severe burns. Children and elderly persons are at greatest risk for these deaths when they cannot independently escape from burning buildings.

Suffocation represents approximately 87% of all unintentional deaths in children <1 year old. Some cases result from choking on food items, such as hot dogs, candy, grapes, and nuts. Nonfood items that can cause choking include undersized infant pacifiers, small balls, and latex balloons. An increasing number of infant suffocation deaths represent sleep-related mortality in the presence of unsafe bedding or crib bumpers, or when co-sleeping with an impaired adult. In previous years these might have been classified as sudden infant death syndrome (see Chapter 423).

Homicide is the third leading cause of injury death in children 1-4 years old and in adolescents (15-19 years old) (Fig. 14.2). Homicide in the pediatric age-group falls into two patterns: infant (child) and adolescent. Child homicide involves children <5 years old and represents child abuse (see Chapter 17). The perpetrator is usually a caretaker; death is generally the result of blunt trauma to the head and/or abdomen. The adolescent pattern of homicide involves peers and acquaintances and is caused by firearms in 77.6% of cases. The majority of these deaths involve handguns. Children between these two age-groups experience homicides of both types.

Suicide is rare in children <10 years old; however, the rate increases greatly after age 10 years, with the result that suicide is now the second leading cause of death for 10- to 19-year-olds. Approximately 50.6% of teenage suicides involve firearms (see Chapter 40).

There has been a sharp and substantial increase in unintentional **poisoning** deaths among teens and young adults. In 2019, unintentional poisonings were the second leading cause of injury deaths among 15- to 24-year-olds. Many of these were from prescription analgesic and opioid medications such as fentanyl.

Nonfatal Injuries

Most childhood injuries do not result in death. Approximately 12% of children and adolescents receive medical care for an injury each year in hospital EDs, and at least as many are treated in physicians' offices. Of these, 2% require inpatient care, and 55% have at least short-term disability because of their injuries.

The distribution of nonfatal injuries is very different from that of fatal trauma (Fig. 14.3). **Falls** are the leading cause of both ED visits and hospitalizations. **Bicycle-related trauma** is the most common type of sports and recreational injury, accounting for approximately 300,000 ED visits annually. **Nonfatal injuries** may be associated with severe morbidity such as anoxic encephalopathy from near-drowning, scarring and disfigurement from burns, and persistent neurologic deficits from head injury, leading to substantial changes in the quality of life for victims and their families. In 2010, nonfatal injuries to U.S. children <19 years old resulted in >$32 billion in direct medical and lifetime work-loss costs.

Global Child Injuries

Child injuries are a global public health issue, and prevention efforts are necessary in low-, middle-, and high-income countries. Between 1990 and 2010 there was a 53% decrease in mortality of people of all ages from communicable, maternal, neonatal, and nutritional disorders, whereas injury mortality decreased by only 16% (Fig. 14.4).

Worldwide, almost 1 million children and adolescents die from injuries and violence each year, and >90% of these deaths are in low- and middle-income countries. As child mortality undergoes an epidemiologic transition because of better control of infectious diseases and malnutrition, injury increasingly becomes a leading cause of death for children in the developing world, as it now is in all industrialized countries. Drowning is the fifth most common cause of death for 5- to 9-year-old children globally, and in some countries, such as Bangladesh, it is the leading cause of death among children 1-4 years old, with a rate over 50 times greater than that in the United States.

An estimated 1 billion people do not currently have immediate access to roads; as industrialization and motorization spread, the incidence of motor vehicle crashes, injuries, and fatalities will climb.

Table 14.1 Injury Deaths in the United States, 2019 (N [rate per 100,000])

CAUSE OF DEATH	<1 YEAR	1-4 YEARS	5-9 YEARS	10-14 YEARS	15-19 YEARS	0-19 YEARS
All causes	20,921 (553.0)	3,676 (23.3)	2,333 (11.6)	3,164 (15.2)	10,258 (48.7)	40,352 (49.4)
All injuries	1,645 (43.48)	1,494 (9.46)	915 (4.53)	1,536 (7.39)	7,794 (37.02)	13,384 (16.40)
All unintentional	1,266 (33.47)	1,149 (7.28)	714 (3.54)	778 (3.74)	3,537 (16.80)	7,444 (9.12)
Motor vehicle occupant	16 (0.42)	67 (0.42)	91 (0.45)	106 (0.51)	654 (3.11)	934 (1.14)
Pedestrian	7 (0.19)	158 (1.00)	78 (0.39)	94 (0.45)	225 (1.07)	562 (0.69)
Drowning	34 (0.90)	378 (2.39)	133 (0.66)	100 (0.48)	216 (1.03)	861 (1.05)
Fire and burn	8 (0.21)	76 (0.48)	71 (0.35)	40 (0.19)	35 (0.17)	230 (0.28)
Poisoning	14 (0.37)	27 (0.17)	12 (0.06)	21 (0.10)	692 (3.29)	766 (0.94)
Pedal cyclist	0 (0.00)	4 (0.03)	13 (0.06)	26 (0.13)	53 (0.25)	96 (0.12)
Firearm	2 (0.05)	24 (0.15)	9 (0.04)	16 (0.08)	66 (0.31)	117 (0.14)
Fall	7 (0.19)	23 (0.15)	14 (0.07)	14 (0.07)	55 (0.26)	113 (0.14)
Suffocation	1,095 (28.94)	139 (0.88)	33 (0.16)	28 (0.13)	40 (0.19)	1,335 (1.64)
All intentional	263 (6.95)	284 (1.80)	167 (0.83)	725 (3.49)	4,123 (19.58)	562 (6.81)
Suicide	0 (0.00)	0 (0.00)	12 (0.06)	534 (2.57)	2,210 (10.50)	2,756 (3.38)
Firearm suicide	*0 (0.00)*	*0 (0.00)*	*0 (0.00)*	*172 (0.83)*	*995 (4.73)*	*1,167 (1.43)*
Homicide	263 (6.95)	284 (1.80)	155 (0.77)	191 (0.92)	1,877 (8.91)	2,770 (3.39)
Firearm homicide	*10 (0.26)*	*47 (0.30)*	*68 (0.34)*	*144 (0.69)*	*1,754 (8.33)*	*2,023 (2.48)*
Undetermined intent	116 (3.07)	61 (0.39)	34 (0.17)	33 (0.16)	134 (0.64)	378 (0.46)

Injury data from Centers for Disease Control and Prevention (CDC): Web-based Injury Statistics Query and Reporting System (WISQARS) (website). National Center for Injury Prevention and Control, CDC (producer). https://www.cdc.gov/injury/wisqars/.
All cause mortality data from Centers for Disease Control and Prevention, National Center for Health Statistics.
Underlying Cause of Death 1999-2019 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. http://wonder.cdc.gov/ucd-icd10.html. Accessed June 4, 2021.

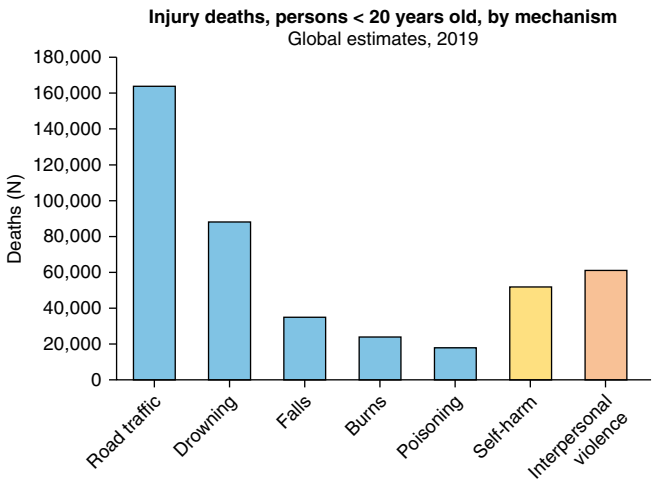

Fig. 14.1 Global injury deaths, persons <20 years old, by mechanism, in 2019. (*From Global Burden of Disease Collaborative Network, Global Burden of Disease Study 2019 [GBD 2019] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2020. Available from* http://ghdx.healthdata.org/gbd-results-tool.)

The rate of child injury death in low- and middle-income countries is threefold higher than that in high-income countries and reflects both a higher incidence of many types of injuries and a much higher case fatality rate in those injured because of a lack of access to emergency and surgical care. As in high-income countries, prevention of child injuries and consequent morbidity and mortality is feasible with multifaceted approaches, many of which are low cost and of proven effectiveness.

PRINCIPLES OF INJURY CONTROL

Injury prevention once centered on attempts to pinpoint the innate characteristics of a child that result in greater frequency of injury. Most now discount the theory of the "accident-prone child." For example, although longitudinal studies have demonstrated an association between attention-deficit/hyperactivity disorder (ADHD; see Chapter 50) and increased rates of injury, the sensitivity and specificity of these traits as a test to identify individuals at high risk for injury are extremely low. The concept of *accident proneness* is counterproductive in that it shifts attention away from more modifiable factors, such as product design or the built environment. It is more appropriate to examine the physical and social environment of children with frequent rates of injury than to try to identify personality traits or temperaments, which are difficult to modify.

Efforts to control injuries include education or persuasion, changes in product design, and modification of the social and physical environment. Efforts to persuade individuals, particularly parents, to change their behaviors have constituted the greater part of injury control efforts. Speaking with parents specifically about using child car seat restraints and bicycle helmets, installing smoke detectors, and checking the tap water temperature is likely to be more successful than offering well-meaning but too-general advice about supervising the child closely, being careful, and childproofing the home. This **information should be geared to the developmental stage of the child and presented in moderate doses in the form of anticipatory guidance** at well-child visits. Table 14.2 lists topics to discuss at each developmental

stage. It is important to acknowledge that there are many barriers to prevention adherence beyond simple knowledge acquisition; pediatricians should be familiar with low-cost sources for safety equipment such as bicycle helmets, smoke detectors, trigger locks, and car seats in their community.

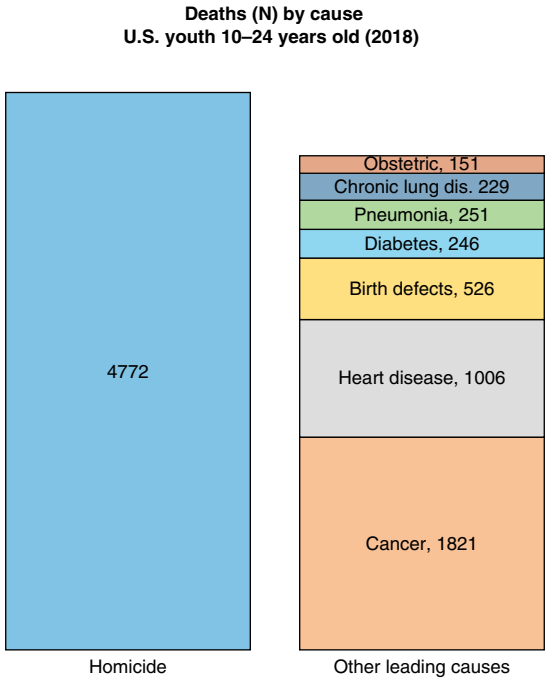

Fig. 14.2 Chart showing third leading cause of death (homicide) among persons aged 10-24 years compared with fourth through tenth leading causes of death in the same age-group in the United States in 2018. Does not include the two leading causes of death among persons aged 10-24 years in 2018: unintentional injuries (12,736 deaths) and suicide (6,807). (*Data from Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.* (https://www.cdc.gov/injury/wisqars/LeadingCauses_images.html. *Accessed July 12, 2021.*)

The most successful injury prevention strategies generally are those involving **changes in product design**. These passive interventions protect all individuals in the population, regardless of cooperation or level of skill, and are likely to be more successful than measures that require repeated behavioral actions by the parent or child. The most important and effective product changes have been in motor vehicles, in which protection of the passenger compartment, use of airbags, and development of crash avoidance and driving support technologies have had large effects on injury risk. Reducing the factory-set water heater temperature, installing smoke detectors, and using child-resistant caps on medicines and household products are other examples of effective product modifications. Many interventions require both active and passive measures: smoke detectors provide passive protection when fully functional, but behavior change is required to ensure periodic battery changes and proper testing.

Modification of the environment often requires greater changes than individual product modification but may be very effective in reducing injuries. Safe roadway design, decreased traffic volume and speed limits in neighborhoods, and elimination or safe storage of guns in households are examples of such interventions. Included in this concept are changes in the social environment through legislation, such as laws mandating child seat restraint and seatbelt use, zero-tolerance laws for alcohol-impaired driving, and graduated driver's licensing laws.

Prevention campaigns combining two or more of these approaches have been particularly effective in reducing injuries. The classic example is the combination of legislation and education to increase child seat restraint and seatbelt use; other examples are programs to promote bike helmet use among school-aged children and improvements in occupant protection in motor vehicles.

RISK FACTORS FOR CHILDHOOD INJURIES

Major factors associated with an increased risk of injuries to children include age, sex, socioeconomic status, rural-urban location, and the environment.

Age

Infants are especially vulnerable to sleep-related suffocation and to abusive head trauma. Toddlers are at the greatest risk for burns, drowning, and falling. Poisonings become another risk as these

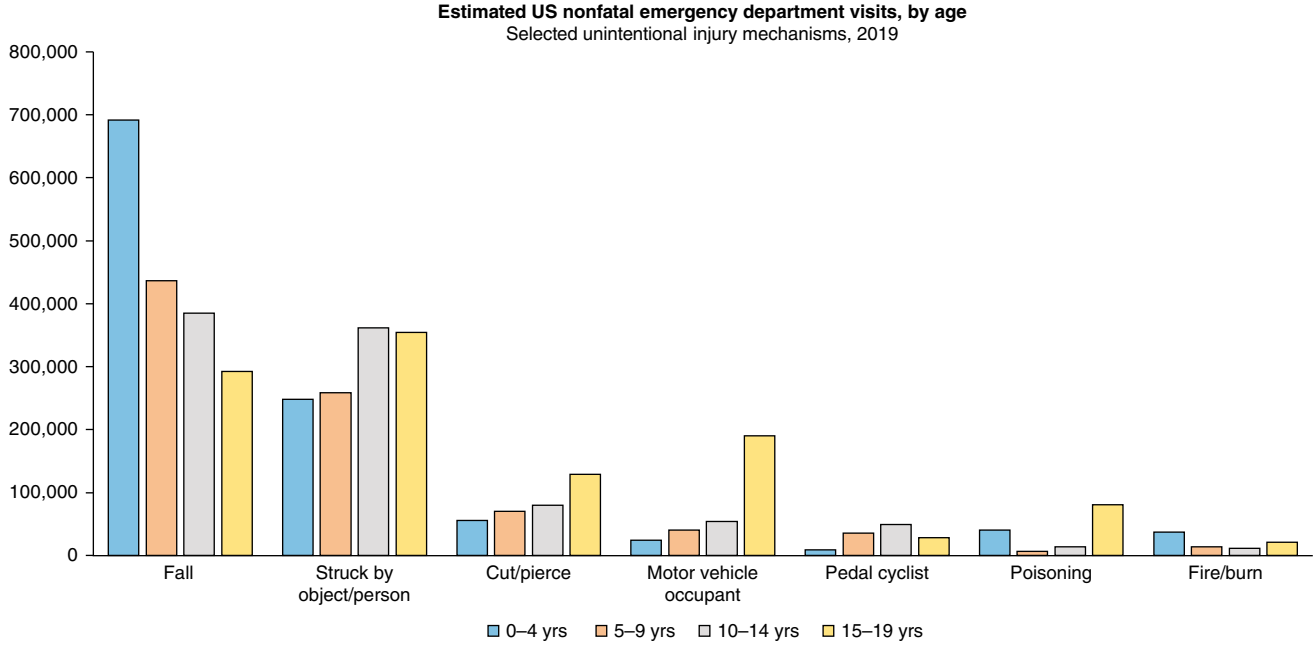

Fig. 14.3 Estimated U.S. nonfatal emergency department visits, by age for selected unintentional injury mechanisms, 2019. (*Injury data from Centers for Disease Control and Prevention [CDC]. Web-based Injury Statistics Query and Reporting System (WISQARS) (website); National Center for Injury Prevention and Control, CDC (producer).* https://www.cdc.gov/injury/wisqars/nonfatal.html. *Accessed July 12, 2021.*)

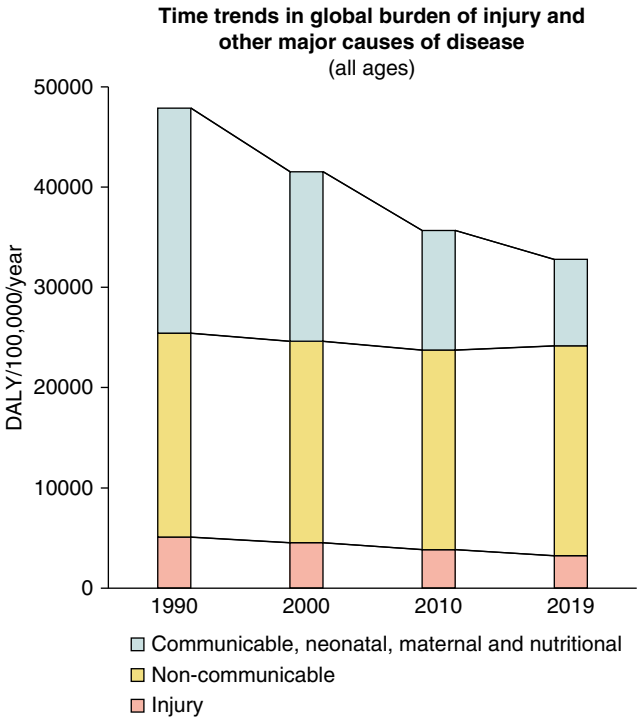

Fig. 14.4 Rates of disability-adjusted life-years (DALYs) lost per 100,000 per year by major grouping of cause. (*Data from Institute for Health Metrics and Evaluation; GBD data visualization site,* https://vizhub.healthdata.org/gbd-compare/. *Accessed July 14, 2021.*)

children acquire mobility and exploratory behavior. Young school-age children are at greatest risk for pedestrian injuries, bicycle-related injuries (the most serious of which usually involve motor vehicles), motor vehicle occupant injuries, burns, and drowning. During the teen years, there is a greatly increased risk from motor vehicle occupant trauma, a continued risk from drowning and burns, and the new risk of intentional trauma. Sports- and recreation-related injuries, including concussion, become more common, and more serious, as children age. Work-related injuries associated with child labor, especially for 14- to 16-year-olds, are an additional risk.

Injuries occurring at a particular age represent a period of vulnerability during which a child or an adolescent encounters a new task or hazard that they may not have developed the cognitive, socioemotional, or physical skills to handle successfully. Toddlers do not have the judgment to know that medications can be poisonous or that some houseplants are not to be eaten; they do not understand the hazard presented by a swimming pool or an open second-story window. For young children, parents may inadvertently set up this mismatch between the skills of the child and the demands of the task. Many parents expect young school-age children to walk home from school, the playground, or the local convenience store, tasks for which most children are not developmentally ready. Likewise, the lack of skills and experience to handle many tasks during the teenage years contributes to an increased risk of injuries, particularly motor vehicle injuries. The high rate of motor vehicle crashes among 15- to 17-year-olds is caused primarily by inexperience, but also reflects their level of cognitive development and emotional maturity. Alcohol, other drugs, and distraction from mobile phone use substantially add to these limitations.

Age also influences the severity of injury and the risk of long-term disability. Young school-age children have an incompletely developed pelvis. In a motor vehicle crash, a seatbelt does not anchor onto the pelvis but rides up onto the abdomen, resulting in the risk of serious abdominal injury. Proper restraint for 4- to 8-year-old children requires the use of booster seats. Children <2 years old have much poorer outcomes from traumatic brain injuries than older children and adolescents, partly related to the unique severity of abusive head trauma.

Table 14.2 Injury Prevention Topics for Anticipatory Guidance by the Pediatrician

NEWBORN
Car seats
Tap water temperature
Smoke detectors
Sleep safety
INFANT
Car seats
Tap water temperature
Bath safety
Choking prevention
TODDLER AND PRESCHOOLER
Car seats and booster seats
Water safety
Poison prevention
Fall prevention
PRIMARY SCHOOL CHILD
Pedestrian skills training
Water skills training
Booster seats and seat belts
Bicycle and sports helmets
Safe storage of firearms in the home
MIDDLE SCHOOL CHILD
Pedestrian skills training
Seatbelts
Safe storage of firearms in the home
Water skills training
Sports safety and concussion prevention
HIGH SCHOOL AND OLDER ADOLESCENT
Seatbelts
Alcohol and drug use, especially while driving and swimming
Driving risks and readiness
Safe storage of firearms
Sports safety and concussion prevention
Occupational injuries

Gender

Beginning at 1-2 years of age and continuing throughout the life span, males have higher rates of fatal injury than do females. During childhood, this does *not* appear to be primarily a result of developmental differences between the genders, differences in coordination, or differences in muscle strength. Variation in *exposure* to risk may account for the male predominance in some types of injuries. Although males in all age-groups have higher rates of bicycle-related injuries, adjusting for exposure reduces this excess risk. Gender differences in rates of pedestrian injuries do *not* appear to be caused by differences in the amount of walking but rather reflect differences in *behavior* between young females and males; whether these are genetic or the result of gender socialization is uncertain. Greater risk-taking behavior, combined with greater frequency of alcohol use, may lead to the disproportionately high rate of motor vehicle crashes among teenage males. The rate of violence-related injuries is higher among males because of their higher rates of aggression and risk-taking behaviors.

Socioeconomic Status

Poverty is one of the most important risk factors for childhood injury. Mortality from fires, motor vehicle crashes, and drowning is 2-4 times higher in poor children. Death rates have an inverse relationship to income level: the higher the income level, the lower the death rate. Many other identified injury risk factors, such as single-parent families,

teenage parents, multiple care providers, family stress, and having multiple siblings, are also mediated primarily through their strong association with poverty.

Rural-Urban Location

Injury rates are generally higher in rural than in urban areas. Homicide rates are higher in urban areas, as is violent crime in general. However, suicide among adolescents is higher in rural than in urban areas. Case fatality from injury is generally twice as high in rural areas than in urban areas, reflecting both the increased severity of some injuries (e.g., motor vehicle crashes occurring at higher speeds) and poorer access to EMS and definitive trauma care. Some injuries are unique to rural areas, such as agricultural injuries to children and adolescents.

Environment

Poverty increases the risk of injury to children at least in part through its effect on the environment. Children who are poor are at increased risk for injury because they are exposed to more hazards in their living environments. They may live in poor housing, which is more likely to be dilapidated and less likely to be protected by smoke detectors. The roads in their neighborhoods are more likely to be major thoroughfares. Their neighborhoods are more likely to experience higher levels of violence, and they are more likely to be victims of assault than children and adolescents living in the suburbs. The focus on the environment is also important because it directs attention away from relatively immutable factors, such as family dynamics, child temperament, and race and directs efforts toward factors that can be changed through interventions.

Ethnic Disparities

In the United States, Indigenous Nation children have the highest death rate from unintentional injuries, followed by Black, Hispanic, and White children. These discrepancies are even more pronounced for some injuries. The homicide rate for Black children aged 15-19 years was 34.86 per 100,000 population in 2019 compared with 7.67/100,000 for Indigenous Nations and Alaskan Natives and 3.86/100,000 for Whites and 2.72/100,000 for Asians. The suicide rate for Indigenous Nation youth was 2.1 times the rate for Whites and 3.2 times the rate for Blacks. Disparities in fatal drowning rates vary by age, with highest rates in the 1- to 4-year-old age group in Indigenous Nation and Alaskan Native children (4.1/100,000) and in the 5- to 9- and 10- to 14-year-old age-groups in Black children (1.5/100,000 and 1.6/100,000, respectively). Indigenous Nation teenagers 15-19 years old are at the highest risk for suicide, followed by White males; Black females have the lowest rate of suicide in this age-group.

It is important to acknowledge racial disparities in injury rates and recognize that the underlying risk factors are racism and social determinants of health (such as socioeconomic status, the educational status of parents, natural and built environment conditions, and access to timely high-quality trauma care), rather than race itself.

MECHANISMS OF INJURY

Motor Vehicle Injuries

Motor vehicle injuries are the leading cause of serious and fatal injuries for children and adolescents. Large and sustained reductions in motor vehicle crash injuries can be accomplished by identifiable interventions.

Occupants

Injuries to passenger vehicle occupants are the predominant cause of motor vehicle deaths among children and adolescents. The peak injury and death rate for both males and females in the pediatric age-group occurs between 15 and 19 years (see Table 14.1). Proper restraint use in vehicles is one of the most effective methods for preventing serious or fatal injury in children involved in motor vehicle crashes. Table 14.3 shows the recommended restraints at different ages. Figure 14.5 provides examples of car safety seats.

Much attention has been given to child occupants <8 years old. Use of child-restraint devices, infant car seats, and booster seats can be expected to reduce fatalities by 71% and the risk of serious injuries by 67% in this age-group. All 50 states and the District of Columbia have laws mandating their use, although the upper age limit for booster seat requirements varies by state. Physician reinforcement of the positive benefits of child seat restraints has been successful in improving parent acceptance.

Table 14.3 Recommended Child-Restraint Methods

	INFANTS	TODDLERS (1-3)	YOUNG CHILDREN
Recommended age/weight requirements	Birth to 1 yr or below weight limit of seat.	Older than 1 yr and weight 20-40 lb.	Weight 40-80 lb and height under 4 ft 9 in; generally, between 4 and 8 yr of age.
Type of seat	Infant-only or Rear-facing convertible.	Convertible or Forward-facing harness seat.	Forward-facing car seat with harness and tether until height or weight limit allowed by manufacturer. Then, belt-positioning booster seat.
Seat position	Rear-facing only. Place in back seat of vehicle.	Rear-facing as long as possible, until height or weight limit allowed by manufacturer. Then forward facing. Place in back seat of vehicle.	Forward-facing. Always in back seat of vehicle.
Notes	Children should use rear-facing seat until at least 1 yr and at least 20 lb. Harness straps should be at or below shoulder level.	Harness straps should be at or above shoulder level. Most seats require top strap for forward-facing use.	Belt-positioning booster seats must be used with both lap and shoulder belts. Make sure that lap belt fits low and tightly across lap/upper thigh area and that shoulder belt fits snugly, crossing chest and shoulder to avoid abdominal injuries.

Data from the National Highway Traffic Safety Administration, https://www.nhtsa.gov/equipment/car-seats-and-booster-seats.

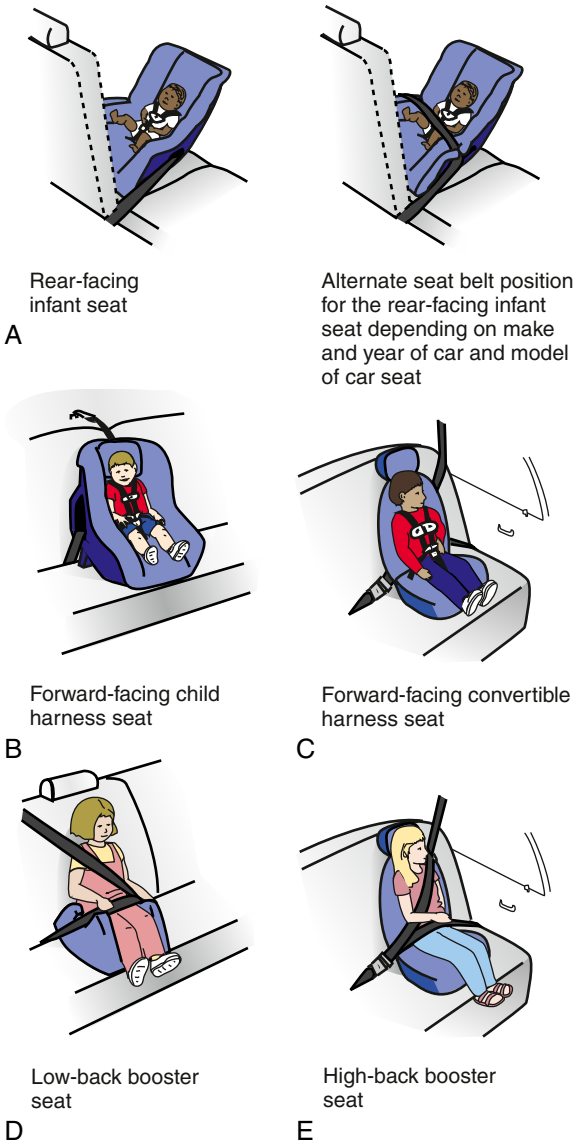

Fig. 14.5 Car safety seats. A, Rear-facing infant seat. B, Forward-facing child harness seat. C, Forward-facing convertible harness seat. D, Low-back booster seat. E, High-back booster seat. (*From Ebel BE, Grossman DC. Crash proof kids? An overview of current motor vehicle child occupant safety strategies. Curr Probl Pediatr Adolesc Health Care. 2003;33:33–64. Source: NHTSA.*)

A detailed guide and list of acceptable devices is available from the American Academy of Pediatrics (AAP)* and the National Highway Traffic Safety Administration (NHTSA).† Infants may use an infant seat within the height and weight guidelines of the seat or may be placed in a convertible infant-toddler child-restraint device. Infants and toddlers should remain rear facing until at least 2 years old and up to the weight and height limits of their seat. Once toddlers outgrow the rear-facing limits of their seat, they can be placed in a forward-facing child harness seat until it is outgrown. Emphasis must be placed on the correct use of these seats, including placing the seat in the right direction, routing the belt properly, and ensuring that the child is buckled into the rear seat of the car correctly. Government regulations specific to automobile and product design, including the Lower Anchors and Tethers for Children (LATCH) system, have made the fit between car seats and the car easier, quicker, and less prone to error.

Older children are often not adequately restrained. Many ride in the rear seat restrained with lap belts only. **Booster seats** have been shown to decrease the risk of injury by 59% and should be used by children once they outgrow their forward-facing child harness seat until at least 8 years of age and 4 ft 9 in (145 cm) tall. Many states have extended their car seat laws to include children of booster seat age as well. Shoulder straps placed behind the child or under the arm do not provide adequate crash protection and may increase the risk of serious injury. The use of lap belts alone has been associated with an increased risk of seatbelt-related injuries, especially fractures of the lumbar spine and hollow-viscus injuries of the abdomen. These flexion-distraction injuries of the spine are often accompanied by injuries to the abdominal organs.

The rear seat is clearly much safer than the front seat for both children and adults. One study of children <15 years old found that the risk of injury in a crash was 70% lower for children in the rear seat compared with those sitting in the front seat. Frontal **airbags** present a risk of serious or fatal injury from the airbag itself for children <13 years. Side airbags also pose a risk for children who are in the front seat and are leaning against the door at the time of a crash. **The safest place for children is in the rear middle seat, properly restrained for their age and size.** Educational and legislative interventions to increase the number of children traveling in the rear seat have been successful.

Children riding in the rear bed of pickup trucks are at special risk for injury because of the possibility of ejection from the truck and resultant serious injury. Preschool or younger children riding in a **school bus** should use a proper child restraint system. Older children (usually >65 lb) can ride safely in a large (>16 passenger) school bus because of compartmentalization of the bus. Smaller buses require child restraint systems with seat belts, and seat belts are recommended for all new school buses.

Transportation of **premature infants** presents special challenges. The possibility of oxygen desaturation, sometimes associated with bradycardia, among premature infants while in child seat restraints has led the American Association of Pediatrics (AAP) to recommend an observed trial of infants born at <37 weeks of gestational age in the seat before discharge and the use of oxygen or alternative restraints for infants who experience desaturation or bradycardia, such as seats that can be reclined and used as a car bed.

Teenage Drivers

Drivers 15-17 years old have more than twice the rate of collisions compared with motorists 18 years and older. Formal driver education courses for young drivers appear to be ineffective as a primary means of decreasing the number of collisions. The risk of serious injury and mortality is directly related to the speed at the time of the crash and inversely related to the size of the vehicle. Small, fast cars greatly increase the risk of a fatal outcome in the event of a crash.

The number of passengers traveling with teen drivers influences the risk of a crash. The risk of death for 17-year-old drivers is 50% greater when driving with one passenger compared with driving alone; this risk is 2.6-fold higher with two passengers and 3-fold higher with three or more passengers.

Teens driving at night are overrepresented in crashes and fatal crashes, with nighttime crashes accounting for >33% of teen motor vehicle fatalities. Almost 50% of fatal crashes involving drivers <18 years old occur in the 4 hours before or after midnight. Teens are 5-10 times more likely to be in a fatal crash while driving at night compared with driving during the day. The difficulty of driving at night combined with the inexperience of teen drivers appears to be a deadly combination.

Another risk factor for motor vehicle crashes for people of all ages, including teens, is **distracted driving**. Distracting events can include *visual* distraction (taking eyes from the forward roadway), *manual* distraction (removing hands from vehicle controls), or *cognitive* distraction (taking attention from navigating the vehicle or responding to critical events). **Electronic devices** present all three modes of distraction in combination and are increasingly recognized as a major threat to driver safety, especially among teens. The recent uptick in motor vehicle fatality rates per vehicle mile driven is generally believed to be caused by distracted driving.

* http://www.healthychildren.org/english/safety-prevention/on-the-go/pages/car-safety-seats-information-for-families.aspx.
† https://www.nhtsa.gov/equipment/car-seats-and-booster-seats.

In 2017, 39.2% of teen drivers reported they had texted or emailed while driving in the last 30 days. Dialing on a cell phone increases the risk of a crash almost threefold, and texting may increase the risk as much as sixfold. Although most states have banned text messaging for all drivers, the effect of state laws on prohibiting such behavior while driving is unknown. Parents should set limits on the use of these devices by their teens; technologic interventions that can block cell phone signals in a moving vehicle are also available and should be considered by parents for their teens.

Newer vehicles are increasingly equipped with driver assistance technology, electronic stability control, and automated crash avoidance systems. Despite the potential to reduce road traffic crashes and injury, these technologies are not yet prevalent in the vehicular fleet. In addition, there is evidence that many drivers do not understand the use, or limitations, of these technologies.

Graduated driver's licensing (GDL) programs consist of a series of steps over a designated period before a teen can receive full, unrestricted driving privileges. In a three-stage graduated license, the student driver must first pass vision and knowledge-based tests, followed by obtaining a learner's permit, and once a specific age has been achieved and driving skills advanced, the student driver is eligible to take the driving test. Once given a provisional license, the new driver will have a specified time to do low-risk driving. GDL usually places initial restrictions on the number of passengers (especially teens) allowed in the vehicle and limits driving at night. The number of crashes decreases 10–30% among the youngest drivers in states with a GDL system. The characteristics of GDL programs vary substantially across states. Optimal safety benefits depend on parent monitoring and engagement with teens around driving restrictions and responsibilities. Parent–teen driving contracts are available and help to facilitate these discussions.

Alcohol use is a major cause of motor vehicle trauma among adolescents. The combination of inexperience in driving and inexperience with alcohol is particularly dangerous. Approximately 20% of all deaths from motor vehicle crashes in this age-group are the result of alcohol intoxication, with impairment of driving seen at blood alcohol concentrations (BACs) as low as 0.05 g/dL. In 2019, approximately 16.7% of adolescents reported riding with a driver who had been drinking, and 5.4% reported driving after drinking. All states have adopted a *zero-tolerance policy* to adolescent drinking while driving, which defines any measurable alcohol content as legal intoxication. All adolescent motor vehicle injury victims should have their BAC measured in the ED and should be screened for high-risk alcohol use with a validated screening test (e.g., CRAFFT (https://crafft.org/); Alcohol Use Disorders Identification Test [AUDIT]) to identify those with alcohol abuse problems (see Chapter 157.1). Individuals who have evidence of alcohol abuse should not leave the ED or hospital without plans for appropriate alcohol abuse treatment. Interventions for problem drinking can be effective in decreasing the risk of subsequent motor vehicle crashes. Even brief interventions in the ED using motivational interviewing can be successful in decreasing adolescent problem drinking.

Another cause of impaired driving is **marijuana use**. In 2017, nearly 20% of high school students reported using marijuana in the prior 30 days, and 50% of current teen users reported driving after use. Marijuana is currently legal (2021) for adult use in 19 U.S. states and for medical use in 27 states, while being considered in many others; the effects of this on adolescent injury remain to be determined. Marijuana is often co-ingested with alcohol or other drugs, and blood thresholds for biologic impairment have not been standardized. It is therefore difficult to estimate the independent effect of marijuana on crash risk.

All-Terrain Vehicles

All-terrain vehicles (ATVs) in many parts of the United States are an important cause of injuries to children and adolescents. These vehicles can attain high speeds, especially with low-weight children, and are prone to rollover because of their high center of gravity. Orthopedic and head injuries are the most common serious injuries seen among children involved in ATV crashes. Helmets can significantly decrease the risk and severity of head injuries among ATV riders, but current use is very low. Voluntary industry efforts to decrease the risk of injuries appear to have had little effect in making ATVs safer. The AAP recommends that children <16 years old should not ride or drive ATVs.

Bicycle Injuries

Each year in the United States, approximately 122,000 children and adolescents are treated in EDs for bicycle-related injuries, making this one of the most common reasons that children with trauma visit EDs. The majority of severe and fatal bicycle injuries involve **head trauma**. A logical step in the prevention of these head injuries is the use of helmets. **Helmets** are very effective, reducing the risk of all head injury by 85% and the risk of traumatic brain injury by 88%. Helmets also reduce injuries to the mid and upper face by as much as 65%. Pediatricians can be effective advocates for the use of bicycle helmets and should incorporate this advice into their anticipatory guidance schedules for parents and children. Appropriate helmets are those with a firm polystyrene liner that fits properly on the child's head. Parents should avoid buying a larger helmet to give the child "growing room." If a crash occurs and the helmet is struck, it should be replaced.

Promotion of helmet use can and should be extended beyond the pediatrician's office. Community education programs spearheaded by coalitions of physicians, educators, bicycle clubs, and community service organizations have been successful in promoting the use of bicycle helmets to children across the socioeconomic spectrum, resulting in helmet use rates of ≥70% with a concomitant reduction in the number of head injuries. Passage of bicycle helmet laws also leads to increased helmet use.

Consideration should also be given to other types of preventive activities, although the evidence supporting their effectiveness is limited. Bicycle paths are a logical method for separating bicycles and motor vehicles.

Ski- and Snowboard-Related Head Injuries

The increasing use of helmets in snow sports, such as skiing and snowboarding, is encouraging because head injuries are the most common cause of death in these sports, and helmets reduce the risk of head injury by ≥50%. Use of helmets does not result in skiers or snow boarders taking more risks and should be encouraged in all snow sports at all ages, not just for young children.

Pedestrian Injuries

Pedestrian injuries are a major cause of traumatic death for children and adolescents in the United States and in most high-income countries. In low-income countries, a much higher proportion of road traffic fatalities are pedestrians, especially among 5- to 14-year-olds. Although case fatality rates are <5%, serious nonfatal injuries constitute a much larger problem, resulting in 29,233 ED visits in 2019 for children and adolescents. Pedestrian injuries are the most important cause of traumatic coma in children and a frequent cause of serious lower-extremity fractures, particularly in school-age children.

Most pedestrian injuries occur during the day, with a peak in the after-school period; thus improved lighting or reflective clothing would be expected to prevent few injuries. Surprisingly, approximately 30% of pedestrian injuries occur while the individual is in a marked crosswalk, reflecting a false sense of security and decreased vigilance in these areas. The risk of pedestrian injury is greater in neighborhoods with high traffic volumes, speeds >25 miles/hr, absence of play space adjacent to the home, household crowding, and low socioeconomic status.

One important risk factor for childhood pedestrian injuries is the developmental level of the child. Children <5 years old are at risk for being run over in the driveway. Few children <9 or 10 years of age have the developmental skills to successfully negotiate traffic under all circumstances. Young children have poor ability to judge the distance and speed of traffic and are easily distracted by playmates or other factors in the environment. Many parents are not aware of this mismatch between the abilities of the young school-age child and the skills needed to cross streets safely. The use of mobile phones and devices has become increasingly common while walking and can increase the risk of being struck by a motor vehicle.

Prevention of pedestrian injuries is difficult but should consist of a multifaceted approach. Education of the child in pedestrian safety should be initiated at an early age by the parents and continue into the school-age years. Younger children should be taught never to cross streets when alone; older children should be taught (and practice how) to negotiate quiet streets with little traffic. Major streets should not be crossed alone until the child is at least 10 years of age and has been observed to follow safe practices.

Legislation and police enforcement are important components of any campaign to reduce pedestrian injuries. Right-turn-on-red laws increase the hazard to pedestrians. In many cities, few drivers stop for pedestrians in crosswalks, a special hazard for young children. Engineering changes in roadway design are extremely important as passive prevention measures. Most important are measures to slow the speed of traffic and to route traffic away from schools and residential areas; these efforts are endorsed by parents and can decrease the risk of injuries and death by 10–35%. Other modifications include networks of one-way streets, proper placement of transit or school bus stops, sidewalks in urban and suburban areas, striping in rural areas to delineate the edge of the road, "road diets" to reduce lanes of traffic pedestrians must cross, and curb parking regulations. Comprehensive traffic "calming" schemes using these strategies have been very successful in reducing child pedestrian injuries in Sweden, the Netherlands, Germany, and increasingly, the United States.

Falls

Falls are the leading cause of **nonfatal injury** in children and adolescents. Altogether, there were 1.8 million falls that led to ED visits in 2019 for children and adolescents; approximately 2.9% of these visits led to a hospitalization or transfer. There have been relatively few in-depth analytic studies of falls, except in particular circumstances, such as playground injuries. Strategies to prevent falls depend on the environmental circumstances and social context in which they occur. *Window falls* have been successfully prevented with the use of devices that prevent egress, and injuries from *playground falls* can be mitigated through the use of proper surfacing, such as woodchips or other soft, energy-absorbing materials. Alcohol may also contribute to falls among teenagers, and these injuries can be reduced by general strategies to reduce teen alcohol use.

Fire- and Burn-Related Injuries

See Chapter 89.

Poisoning

See Chapter 94.

Drowning

See Chapter 88.

Traumatic Brain Injury

See Chapter 82.

Firearm Injuries

Injuries to children and adolescents involving firearms occur in three different situations: unintentional injury, suicide attempt, and assault. The injury may be fatal or may result in permanent sequelae.

Firearm related deaths (all causes) for youths (1-19 years) in 2020 was ~5.62 per 100,000 population. The rate was 17.4 for Black youths, compared to 3.4 for White youths. Firearm homicides represent 60% of firearm-related deaths in youths. In 2020, firearm-related deaths exceeded motor vehicle collisions as the leading cause of death for children and adolescents. **Unintentional firearm injuries** and deaths have continued to decrease and accounted for 426 deaths to children 0-18 years old in 2019, representing only a very small fraction of all firearm injuries among children and adolescents. The majority of these deaths occur to teens during hunting or recreational activities.

Suicide is the second most common cause of death from all causes in both males and females aged 10-19 years. During the 1950s to 1970, suicide rates for children and adolescents more than doubled; firearm suicide rates peaked in 1994 and decreased by 59% from this peak by 2010 before gradually increasing, paralleling increases in the overall suicide rate. The difference in the rate of suicide death between males and females is related to the differences in method used during attempts. Females die less often in suicide attempts because they use less lethal means (mainly drugs) and perhaps have a lower degree of intent. The use of firearms in a suicidal act results in an approximately 90% case fatality rate.

Homicides are third only to motor vehicle crashes and suicide among causes of death in teenagers >15 years old. In 2019, 2,023 adolescents aged 15-19 years were homicide victims; Black teenagers accounted for 64% of the total, making homicides the most common cause of death among this group. Over 85% of homicides among teenage males involved firearms, mostly handguns.

In the United States, approximately 32% of adults reported owning a gun in 2020, including 36% of adults who had children under 18 in the household. Home ownership of guns increases the risk of adolescent suicide 3- to 10-fold and the risk of adolescent homicide up to 4-fold. In homes with guns, the risk to the occupants is far greater than the chance that the gun will be used against an intruder; for every death occurring in self-defense, there may be 1.3 unintentional deaths, 4.6 homicides, and 37 suicides.

Handguns account for approximately 30% of the firearms in use today, yet they are involved in 80% of criminal and other firearm misuse. Of all firearms, **handguns** pose the greatest risk to children and adolescents. Access to handguns by adolescents is surprisingly common and is not restricted to those involved in gang or criminal activity. Stricter policies to reduce youth access to handguns, rather than all firearms, would appear to be the most appropriate focus of efforts to reduce shooting injuries in children and adolescents (Fig. 14.6).

Locking and unloading guns and storing ammunition locked in a different location substantially reduce the risk of a suicide or unintentional firearm injury among youth by up to 73%. Because up to 30% of handgun-owning households have at least one firearm stored unsafely, one potential approach to reducing these injuries could focus on improving household firearm storage practices where children and youth reside or visit. The evidence regarding the effectiveness of office-based counseling to influence firearm storage practice is mixed; the most effective programs are those in which safe storage devices are dispensed along with advice.

Adolescents with mental health conditions and alcoholism are at particularly high risk for firearm injury. In the absence of conclusive evidence, physicians should continue to work with families to eliminate access to guns in these households.

Violent Behavior and Aggression

Although the current rates of homicide are much lower than at their peak in the late 1980s and early 1990s, the problem of violence and assault remains large. The origins of adult and teen violence occur during childhood. Almost all adults who commit violent acts have a history of violent behavior during childhood or adolescence. Longitudinal studies following groups of individuals from birth have found that aggression occurs early and that most children learn to control this aggression in childhood. Children who later become violent adolescents and adults do not learn to control this aggressive behavior.

The most successful interventions for violence target young children and their families. These include home visits by nurses and paraprofessionals beginning in the prenatal period and continuing for the first few years of life to provide support and guidance to parents, especially parents without other resources. Enrollment in early childhood education programs (e.g., Head Start) beginning at age 3 years has been shown to be effective in improving school success, keeping children in school, and decreasing the chance that the child will experience delinquency in adolescence. School-based interventions, including curricula to increase the social skills of children and improve the parenting skills of caregivers, have long-term effects on violence and risk-taking behavior. Early identification of behavior problems by primary care pediatricians can best be accomplished through the routine use of formal screening tools. Interventions in adolescence, such as family therapy, multisystemic therapy, and therapeutic foster care, can decrease problem behavior and a subsequent decline into delinquency and violence.

PSYCHOSOCIAL CONSEQUENCES OF INJURIES

Many children and their parents have substantial psychosocial sequelae from trauma. Studies in adults indicate that 10–40% of hospitalized injured patients will have **posttraumatic stress disorder** (PTSD; see Chapter 38). Among injured children involved in motor vehicle

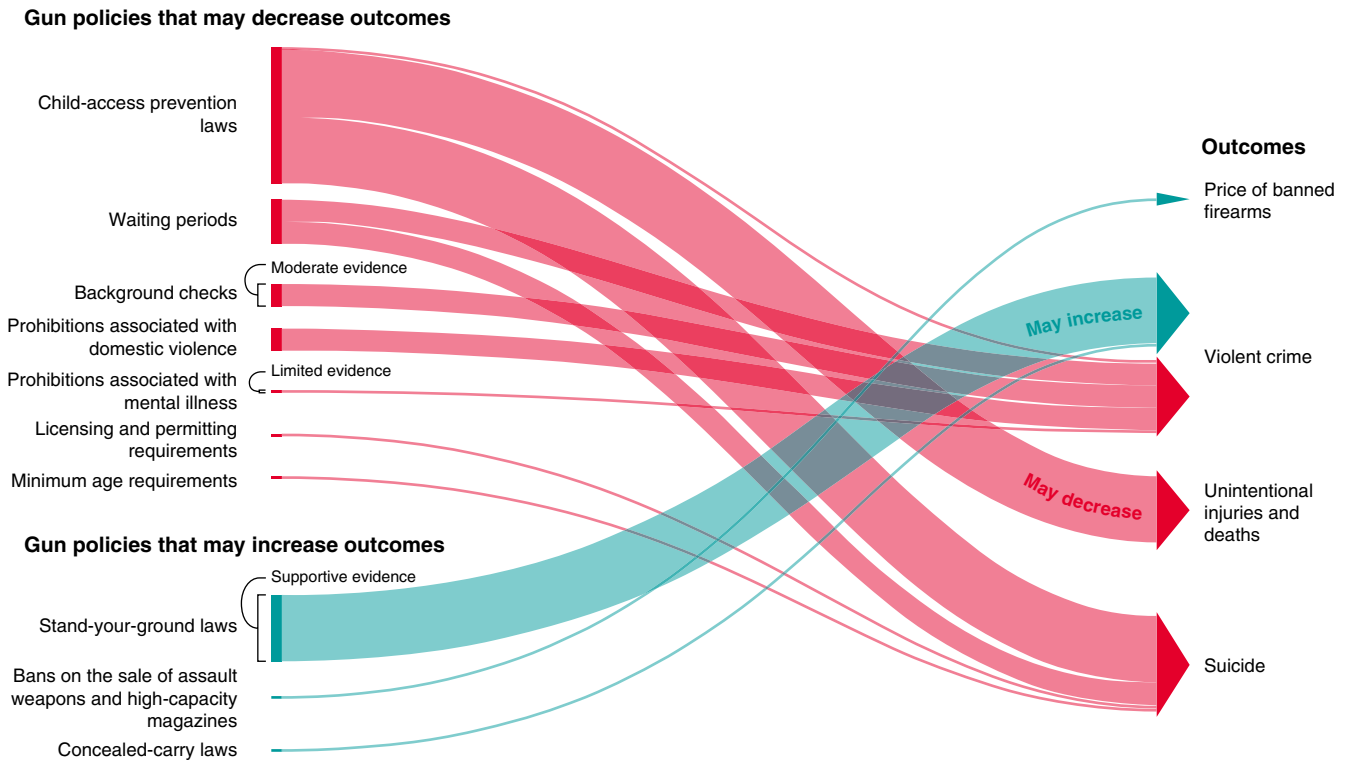

Fig. 14.6 Gun policy–based outcomes. (*Adapted from Gun Policy in America/RAND*. https://www.rand.org/research/gun-policy.html.)

crashes, 90% of families will have symptoms of **acute stress disorder** after the crash, although the diagnosis of acute stress disorder is poorly predictive of later PTSD. Standardized questionnaires that collect data from the child, the parents, and the medical record at the time of initial injury can serve as useful screening tests for later development of PTSD. Early mental health intervention, with close follow-up, is important for the treatment of PTSD and for minimizing its effect on the child and family.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 15

Impact of Violence Exposure on Children

Marilyn C. Augustyn, Neena McConnico, and Barry S. Zuckerman

The reach of violence—whether as the victim, perpetrator, or witness, whether in person or through the media—is far, deep, and long-standing across the globe. In the home, it is estimated that 80–95% of children and youth witness such aggression. In general, the types of violence children are exposed to increases in severity as children grow older. *Exposure to violence* disrupts the healthy development of children in a myriad of ways. Pediatric clinicians must be aware of violence exposure and competent to address its impact on children and families under their care (**trauma-informed care**). Trauma-informed care gives pediatric clinicians the tools to assess childhood trauma and adversity experiences as well as practical guidance, resources, and interventions. Clinicians also have a wider responsibility to advocate on local, state, national, and international levels for safer environments in which all children can grow and thrive (see Fig. 14.6).

We know that many traumatic events during childhood can have immediate and long-term impact (**adverse childhood experiences;** see Chapter 1). Adversity in the first years of life may deleteriously affect the course of human development throughout the life span, and **witnessing violence** is one such adversity. Because bystanders who witness violence can have permanent emotional and behavioral effects due to neurophysiologic alterations, healthcare providers may not fully appreciate their distress and thereby miss an opportunity to provide needed interventions. For children not living in war zones, the source of first exposure to violence is often **intimate partner violence (IPV)**. In the United States alone, >1 in 15 children witness IPV each year, and worldwide approximately 275 million children are exposed to IPV yearly. Exposure to IPV in infancy and toddlerhood affects attachment relationships, and school-aged youth who witness IPV have difficulties in developing and maintaining friendships, have difficulty in school, may abuse drugs and alcohol, and may develop mental health problems.

Another source of witnessed violence is **community violence**, a serious problem in the United States that disproportionately affects children from low-income areas. Approximately 22% of children witness violence in their family or in their community each year; *witnessed violence* includes assaults and bullying, sexual victimization, maltreatment by a caregiver, and theft or vandalism. Almost 60% of children will experience or witness violence during childhood. Witnessing acts of violence may be a significant stressor in children's lives. Witnessed community violence is related to internalizing problems such as depression and posttraumatic stress disorder (PTSD), as well as externalizing problems, including delinquent behavior, aggression, and substance abuse.

The most ubiquitous source of witnessing violence for U.S. children is **media violence**, sometimes referred to as **virtual violence**. This form

of violence is not experienced physically; rather it is experienced in realistic ways through technology and ever more intense and realistic games. There is an ever-widening array of screens that are part of children's everyday lives, including computers, tablets, and cell phones, in addition to long-standing platforms, such as televisions and movies. Tragic events, including mass shootings and acts of terrorism, have increased the specter of fear among children as these events are reenacted for them on the multiple screens they encounter. Although exposure to media/virtual violence cannot be equated to exposure to real-life violence, many studies confirm that media/virtual violence *desensitizes* youth to the meaning and impact of violent behavior. Violent video game exposure may be associated with increased aggressive behavior; increased aggressive cognitions; increased aggressive affect, increased desensitization, and decreased empathy; and increased physiologic arousal. Violent video game use is a risk factor for adverse outcomes; however, insufficient data exist to examine any potential link between violent video game use and delinquency or criminal behavior. Table 15.1 lists interventions to reduce exposure to media violence.

IMPACTS OF VIOLENCE

All types of violence have a profound impact on health and development, physiologically, psychologically, and behaviorally potentially leading to the challenges mentioned earlier. It may influence how children view the world and their place in it. Children can come to see the world as a dangerous and unpredictable place. This fear may thwart their exploration of the environment, which is essential to learning in childhood. Youth may experience overwhelming terror, helplessness, and fear, even if they are not immediately in danger. Young children are most vulnerable to threats that involve the safety (or perceived safety) of their caretakers. Chronic exposure to violence predisposes children to subsequent mental health problems and can have a deleterious effect on learning and neurodevelopment. High exposure to violence in older youth correlates with poorer performance in school, symptoms of anxiety and depression, and lower self-esteem. Violence, particularly IPV, can also teach youth especially powerful early lessons about the role of violence in relationships. Violence may change the way that children view their future; they may believe that they could die at an early age and thus take more risks, such as drinking alcohol, abusing drugs, not wearing a seatbelt, and not taking prescribed medication. Violence exposure is an important childhood adversity that is known to increase the risk for poor health in adults.

Some children exposed to severe and/or chronic violence may suffer from PTSD, exhibiting constricted emotions, difficulty concentrating, autonomic disturbances, and reenactment of the trauma through play or action (see Chapter 38). Based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for PTSD in children ≤6 years old, >50% of preschoolers may experience clinically significant symptoms of PTSD after exposure to IPV. Although young children may not fully meet these criteria, certain behavioral changes are associated with exposure to trauma, such as sleep disturbances, aggressive behavior, new fears, and increased anxiety about separations (clinginess). A challenge in treating and diagnosing pediatric PTSD is that a child's caregiver exposed to the same trauma may be suffering from it as well.

Table 15.1 Public Health Recommendations to Reduce Effects of Media Violence on Children and Adolescents

1. Parents should:
- Be made aware of the risks associated with children viewing violent imagery, as it promotes aggressive attitudes, antisocial behavior, fear, and desensitization.
- Review the nature, extent, and context of violence in media available to their children before children view it.
- Assist children's understanding of violent imagery appropriate to their developmental level.
- Be aware and monitor social media access/use of youth

2. Professionals should:
- Offer support and advice to parents who allow their children unsupervised access to extreme violent imagery, as this could be seen as a form of emotional abuse and neglect.
- Educate all young people in critical film appraisal in terms of realism, justification, and consequences.
- Exercise greater control over access to inappropriate violent media entertainment by young people in secure institutions.
- Use violent film material in anger management programs under guidance.

3. Media producers should:
- Reduce violent content and promote antiviolence themes and publicity campaigns.
- Ensure that when violence is presented, it is in context and associated with remorse, criticism, and penalty.
- Ensure that violent action is not justified or its consequences understated.

4. Policymakers should:
- Monitor the nature, extent, and context of violence in all forms of media and implement appropriate guidelines, standards, and penalties.
- Ensure that education in media awareness is a priority and a part of school curricula.

From Browne KD, Hamilton-Giachritsis C. The influence of violent media on children and adolescents: A public-health approach. *Lancet.* 2005;365:702–710.

Diagnosis and Follow-Up

The simplest way to recognize whether violence exposure has affected a family is to screen both the caregivers and the youth (after approximately 8 years of age) on a regular basis. This practice is particularly important during pregnancy and the immediate postpartum period, when women may be at highest risk for being abused. It is important to assure families that they are not being singled out, but that all families are asked about their exposure to violence. In the case of IPV, it is important to ask the caregivers separately to maintain safety and mitigate risk for the caregiver who is being abused.

A direct approach may be useful: "Violence is a major problem in our world today and one that impacts everyone in our society. So I ask all my patients and families about violence that they experienced growing up as well as now. . . ." This can take the form of a three-generation family history of violence exposure. In other cases, beginning with general questions and then moving to the specific may be helpful: "Do you feel safe in your home and neighborhood? Has anyone ever hurt you or your child?" When violence has affected the child, it is important to gather details about symptoms, behaviors, and protective factors that support resilience.

The pediatric clinician can effectively counsel many parents and children who have been exposed to violence. Regardless of the type of violence to which the child has been exposed, the following components are part of the guidance: (1) careful review of the facts and details of the event, (2) referring to support services, (3) providing information about the symptoms and behaviors common in youth exposed to violence, (4) assistance in restoring a sense of stability to the family in order to enhance the youth's feelings of safety, and (5) helping caregivers talk to their children about the event. Families should be referred to a mental health professional when (1) the violence is significant, (2) symptoms are chronic (>6 months) or not improving, (3) if the violent event involved the death or departure of a parent, (4) if the caregivers are unable to empathize with the child, or (5) if the ongoing safety of the child is a concern.

Visit Elsevier Ebooks+ at eBooks.Health.Elsevier.com to read this chapter.

15.1 Bullying, Cyberbullying, and School Violence

Megan A. Moreno and Elizabeth Englander

BULLYING AND CYBERBULLYING

Bullying behavior affects people throughout the life span, but much of the focus has been on children and adolescents. In the past, bullying was sometimes considered a rite of passage or was written off as "kids being kids." However, it is well recognized that bullying can have profound short- and long-term negative consequences on all those involved, including perpetrators, targets, and bystanders. The consequences of bullying can affect a child's social experiences, academic progress, and health.

Bullying is defined as any unwanted aggressive behavior by another youth or group of youths that involves an actual or perceived power imbalance and is repeated multiple times or is highly likely to be repeated. Generally, sibling aggression and dating violence are excluded, but research has associated these problems with *peer bullying*. Digital technology was initially viewed as a context in which bullying can occur. **Cyberbullying** is not merely bullying that occurs through electronic communications, but rather a type of bullying with distinct elements, such as the potential for a single event to "go viral" and the use of technology as a tool to achieve power imbalance.

It is thought that bullying and cyberbullying are more alike than dissimilar and that surveillance efforts, as well as prevention and intervention approaches, should address both types of bullying.

Bullying Roles and Nomenclature

Bullying represents a dynamic social interaction in which an individual may play different roles at different stages. A child can be a perpetrator of bullying, a target of bullying, a witness or bystander, or simply a child whose environment is affected by pervasive bullying. In any bullying experience, the roles that each child plays may be fluid, such that a target of bullying may then become a perpetrator, or vice versa. Thus common nomenclature has evolved to refer to children as *perpetrators* of bullying or *targets* of bullying to represent a present state, rather than labeling a child as a bully or a victim, which suggests a static role and may affect that child's self-image.

Epidemiology

Bullying is a widespread problem during childhood and adolescence. Current estimates suggest that school-based bullying likely affects 18–31% of children and youth and that cyberbullying affects 7–15% of youth. Apparent rates of bullying are influenced by the questions that are asked; the word "bully" is stigmatized, and absent that label, youth are more willing to acknowledge having engaged in activities that can be categorized as bullying. Estimates of bullying prevalence are typically based on self-reported victimization (not perpetration), but here too, language can influence results. Targets of other types of social conflict may overestimate or underestimate their bullying victimization unless precise language is used during assessment.

Risk Factors

Certain groups are more vulnerable to bullying, including youth who are lesbian, gay, bisexual, transgender, and questioning (LGBTQ+); immigrant and ethnic/racial minoritized youth; obese youth; and youth with disabilities. However, it is important to recognize that although these individual risk factors exist, the context and situation can also present unique risk factors. Some studies have found that Black children are bullied more often than Latinos, whereas other studies have found no group differences. Contextual factors, such as the school climate or prevalence of a particular ethnic group in a school setting, may be important factors in a given bullying situation. The 2019 Youth Risk Behavior Survey found that White teens were much more likely than Black teens to report experiencing any bullying. Thus it is important to recognize that any individual being bullied is embedded within a situation that is within a larger social context. This *person by situation by context* approach is useful to consider in identifying why bullying takes place in some situations but not others.

Bullying may occur with other high-risk behaviors. Students who carry weapons, smoke, and drink alcohol are at higher risk for engaging in bullying. Negative parenting behavior is related to a moderately increased risk of becoming a *bully/victim* (youth who are both perpetrators and targets) and small to moderate effects on being targeted for bullying at school.

Some risk factors may be specific to cyberbullying. Among preadolescent children, more access to technology (e.g., cell phone ownership) predicts cyberbullying behaviors and some types of digital victimization. Also, communications through digital technology can be misperceived as hostility, and those misperceptions can in turn increase electronic forms of bullying.

Consequences of Bullying

Involvement in any type of bullying is associated with poorer psychosocial adjustment; perpetrators, targets, and those both perpetrator and target report greater health problems and poorer emotional and social adjustment. Consequences of both traditional and cyber forms of bullying are particularly significant in the areas of physical health, mental health, and academic achievement. Being the target of bullying is typically viewed as particularly stressful. The impact of this stress has been shown to affect the developing brain and to be associated with changes to the stress response system, which confers an increased risk for future health and academic difficulties. The long-term consequences of being bullied as a child include increased risk for depression, poor self-esteem, and abusive relationships. Negative outcomes for perpetrating bullying include higher risks of depression and substance abuse. Mental health consequences for both perpetrator and target include, across types of bullying, increased risks of depression, poor self-esteem, increased suicidality, and anxiety. Academic difficulties include increased risk of poor school performance, school failure, and dropping out.

SCHOOL VIOLENCE

Epidemiology

School violence is a significant problem in the United States. Almost 40% of U.S. schools report a least one violent incident to police, with >600,000 victims of violent crime per year. Among 9th to 12th graders, 8% were threatened or injured on school property in the last 12 months, and 14% were involved in a physical fight over the last year. Still, school-associated violent deaths are rare. Seventeen homicides of children aged 5-18 years occurred at school during the 2009–2010 school year. Of all youth homicides, <2% occur at school. Although urban schools experience more episodes of violence, the rare rampage gun violence that happens in rural and suburban schools demonstrates that no region is immune to lethal violence.

Risk Factors

Bullying and weapon carrying may be important precursors to more serious school violence. Among perpetrators of violent deaths at school, 20% had been bullying victims, and 6% carried a weapon to school in the last 30 days. Nonlethal violence, mental health problems, racial tensions, student attacks on teachers, and the effects of rapid economic change in communities can all lead to school violence. Individual risk factors for violence include prior history of violence, drug, alcohol, or tobacco use, association with delinquent peers, poor family functioning, poor grades in school, and poverty in the community.

Family risk factors include early childbearing, low parental attachment and involvement, authoritarian or permissive parenting styles (see Chapter 20), and poverty. There is more school violence in areas with higher crime rates and more street gangs, which take away students' ability to learn in a safe environment and leave many children with traumatic stress and grief reactions.

TREATMENT AND PREVENTION OF BULLYING AND SCHOOL VIOLENCE

Pediatric providers are in a unique position to screen, treat, and advocate for reducing the impact of bullying and school violence by assisting those affected and seeking to prevent further occurrences.

Signs and Symptoms

Signs of a child being involved in bullying or exposed to school violence include physical complaints such as insomnia, stomachaches, headaches, and new-onset enuresis. **Psychologic symptoms**, such as depression (see Chapter 39), loneliness, anxiety (see Chapter 38), and suicidal ideation, may occur. **Behavioral changes**, such as irritability, poor concentration, school avoidance, and substance abuse, are common. **School problems**, such as academic failure, social problems, and lack of friends, can also occur. Additional vigilance is warranted for those children who represent vulnerable groups for bullying and aggression, including youth with disabilities; obesity; or minority, immigrant, or LGBTQ+ status.

Screening for Bullying

Assessing bullying and cyberbullying involvement is an important part of pediatric visits. Several tools can be helpful for clinicians, including the *Bright Futures Guidelines,* which recommend screening at each well-child visit. In these discussions, begin by normalizing the conversation; for example, practitioners can let the patient know that bullying is a topic they discuss with all their patients. It is advisable to define bullying based on the uniform definition but using readily understandable and developmentally appropriate language. Physicians can ask patients if they have had experiences where there was repeated cruelty or "mean actions" between peers, either as a target of that cruelty or seeing the cruelty, or even being angry or mean toward others. Asking a patient if he or she is a bully is not likely to generate either trust or an honest answer. Asking about exposures to peer victimization or school violence is also important. Throughout these discussions, it is critical to provide support and empathy while engaging a patient.

One tool to help providers begin and navigate these discussions is a *Practice Enhancement Tool* developed by the **Massachusetts Aggression Reduction Center** (MARC) and Children's Hospital Boston (Fig. 15.1). It begins by defining bullying in readily understandable language and then asks, "Is there any one kid, or a bunch of kids, that pick on you or make you feel bad over and over again?" The tool also guides the practitioner in asking about problematic digital experiences and asks whom the child has spoken to about the problem and whether that has helped. Finally, it guides the practitioner through emphasizing the usefulness of talking about social problems and discusses how the physician can assist the patient.

Children who are aggressive, overly confident, lacking in empathy, or have persistent conduct problems may need careful screening. It is important to bear in mind that bullying is a dynamic process, and a child may be involved as both a perpetrator and a target at different time points. The physical, behavioral, psychologic, and academic symptoms of bullying may overlap with other conditions, such as medical illness, learning problems, and psychologic disorders. Thus labeling the behavior as *bullying* rather than the child as a "bully" is recommended.

Management of bullying and school violence involves several steps. First, ensure that all parties understand the relevant information (the patient, parents, and school). Second, assess a child's need for specialized counseling or social skills interventions. Extracurricular activities (e.g., drama clubs, mentoring programs, sports) can be discussed as avenues to help increase the child's social skills and self-esteem. Third, ensure that the patient has adequate support, including at home and at school. Peers are a particularly effective source of support, and patients can be encouraged to spend time with friends, but parents and educators are also important sources of emotional support. Many children benefit from planning their actions in unstructured settings (e.g., discussing where they could sit during lunch), whereas some benefit from role-playing. Finally, the clinician should identify safety issues, such as suicidal ideation and plans, substance abuse, and other high-risk behaviors.

When bullying or cyberbullying is suspected or confirmed, the parents and child should be offered education and resources. Some resources include the government-supported website www.stopbullying.gov, as well as MARC. Both provide free downloadable literature that can be offered to parents and families.

Addressing cases of bullying or exposure to violence in clinic often requires a cross-disciplinary approach. Involving teachers or school counselors, as well as outside referrals to psychologists, social workers, or counselors, may be warranted. Parental mental health and resource risk factors should also be addressed.

Prevention

Pediatric clinicians can reasonably expect their patients' schools to provide violence and bullying prevention programs. Rather than focusing on only changing a target of bullying, successful interventions use whole-school approaches that involve multiple stakeholders. **School climate** has been shown to have significant effects on bullying prevalence, so these approaches are essential to primary prevention. These broad-based programs simultaneously include school-wide rules and sanctions, teacher training, classroom curriculum, and high levels of student engagement. Addressing access to firearms, involving community organizations and parents, and supporting youth mental health are important in creating a safe school climate.

Prevention programs for cyberbullying are at a nascent stage, reflecting uncertainty about the prevalence of the practice, who is perpetrating it and from where, and how students respond when they are victimized. Many schools have established cyberbullying policies and are increasingly involved with teaching youth about guidelines for appropriate online interactions and monitoring for cyberbullying problems. As of 2016, 23 states included cyberbullying in their state antibullying laws, and 48 states included "electronic harassment." Although legal remedies are frequently not the most productive answer to bullying and cyberbullying incidents, pediatric clinicians should be aware of local laws and be prepared to refer parents to more information about these laws when necessary. Studies suggest that preventive interventions designed to address bullying have effects on cyberbullying, and vice versa.

The American Academy of Pediatrics (AAP) provides a free online **Family Media Use Plan** that allows families to develop rules for digital media use and prompts for discussions about safety and online relationships with the goal of preventing negative consequences of online behavior and interactions. The tool is designed for ongoing discussions with family members about online experiences and family rules and values.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

15.2 Media Violence

Megan A. Moreno

Today's youth are growing up in a media-rich environment of both traditional and digital media. *Traditional* media includes television (TV), radio, and periodicals; *digital* media includes online content that promotes interactive and social engagement. The online world allows youth instant access to entertainment, information, and knowledge; social contact; and marketing. Social and interactive media allow users to act as both creators and consumers of content. Examples include applications (apps), social media, multiplayer video games, YouTube videos, and video blogs (vlogs).

One of the earliest studies that has been linked to media effects on aggression and violence was the "bobo doll" experiment in which children who observed an aggressive adult model were more likely to be aggressive toward a doll afterward. It has been widely accepted that media exposure can affect behavior; the advertising industry is grounded in the concept that media exposure can change purchasing behavior. Exposure to sexual content in media has been linked to earlier sexual initiation; exposure to pro-alcohol content

MARC/BACPAC Pediatric Questionnaire: **Bullying & Cyberbullying**

Date of office visit:_____

Child's name: _____	Gender: ☐Male ☐Female
Child's grade: _____	Child's age: _____ years _____ months
IEP? ☐Yes ☐No	Neurodev / Psych Dx (if established): _____

Parent present during interview? ☐Yes ☐No

Subjective complaints (eg, H/A, tics, sleep):

_____

_____

BEGIN BY STATING:

"You probably know that grownups today are very worried about bullying. I'd like to ask you a little bit about that, but I want to make sure you understand what I mean. When I ask about bullying, I mean another kid (or group of kids) who picks on someone or is mean to them on purpose, over and over again – not just one time."

1. Do you see bullying happen at your school?

☐ **Yes** ☐ **No**

2. Is there any one kid or a bunch of kids that pick on you or make you feel bad over and over again?

☐ **Yes** (inquire as to the frequency):

(_____ times daily; _____ times a week; _____ times a month; _____ times a year).

IF NO, SKIP TO **#3**

If YES:
Where does this happen? (check all that apply):

☐ classroom ☐ lunchroom ☐ hallways
☐ stairwell ☐ bathroom ☐ locker-room
☐ playground ☐ bus ☐ other: _____

What did he or she do to you? (check all that apply):

☐ made fun of me ☐ kids laughed ☐ name-calling
☐ rumors ☐ made up lies ☐ got me in trouble
☐ pushed, shoved, hit, threw stuff ☐ other:_____

3. How about on the computer at home? Has anyone been mean to you or made fun of you on the internet?

☐ **Yes** (Details):

_____

_____

If **NO** to both **#2** and **#3, END HERE.** Otherwise, continue.

Copyright ©2013: Peter C. Raffalli, MD, Elizabeth Englander, PhD

Fig. 15.1 MARC/BACPAC* pediatric questionnaire on bullying and cyberbullying. *Massachusetts Aggression Reduction Center and Bullying and Cyberbullying Prevention and Advocacy Collaborative. (*Copyright 2013 Peter C. Raffalli, MD, and Elizabeth Englander, PhD.*)

Continued

MARC/BACPAC Pediatric Questionnaire: **Bullying & Cyberbullying**

4. It's very important that you understand that if you are being bullied that it is *never* your fault. Bullying is wrong and people should *never* bully others. Have you told any adults about the kids that are bothering you?

☐ **Yes** (Who have you told?)

- ☐ Parent
- ☐ Teacher
- ☐ Other: _____

If Yes.....Were the adults able to stop the bullying?

☐ **Yes** ☐ **No**

If Yes.....Did talking about it make you feel better?

☐ **Yes** ☐ **No** ("That's ok. Sometimes talking does help though.")

5. "Sometimes it feels good just to talk about things. I wish you and I had more time to talk about it today. Would you like to have a chance to talk about it sometime soon?"

☐ **Yes** (if YES, refer to):

_____

_____

☐ **No**

IF NO...

..."Would you like me to try to help? As your doctor, I can talk with the school officials and try to make sure that the bullying stops. While I cannot promise that everything will be better, I know that if we do nothing the bullying will likely continue and probably get worse. I want you to be happy and safe at school — is it okay with you if I talk to your school about this?"

☐ **Yes**
(Who would you like me to talk to? Principal / Nurse / Counselor / Teacher / Other: _____)

☐ **No**

Copyright ©2013: Peter C. Raffalli, MD, Elizabeth Englander, PhD

Fig. 15.1 cont'd

MARC/BACPAC Pediatric Questionnaire: **Bullying & Cyberbullying**

Guide to the bullying/cyberbullying checklist/interview

"Warm up" questions: briefly acknowledge these but do not discuss at length. No need to note the child's answers.

- Are the kids in your school friendly?
- Tell me about one child at your school who you like.
- Tell me about one child at your school who is not friendly.

(Brief acknowledgement, e.g.: "Ok" or "that's good.")

Note: It's fine to skip the warm-up questions if you have already chatted with the child.

Websites for parents/ teachers/students:

The Massachusetts Aggression Reduction Center (MARC): **MARCcenter.org**

Bullying And Cyberbullying Prevention and Advocacy Collaborative (BACPAC) at Boston Children's Hospital: **bostonchildrens.org/BACPAC**

Stop Bullying Now from the U.S. government: **stopbullying.gov**

When a child is being bullied

There are three venues through which you can help this child:

1. **BY GIVING THEM A "SAFE ADULT" AT SCHOOL THEY CAN ALWAYS SPEAK WITH (EG, THE SCHOOL NURSE, THE SCHOOL ADJUSTMENT COUNSELOR);**
2. **BY GIVING THEIR PARENTS GUIDANCE ABOUT HOW TO COPE (THROUGH HANDOUTS, WEBSITES); AND**
3. **BY OFFERING THEM SUPPORT FROM YOURSELF.**

If child consents to your involvement, seek written parental consent to share information with the school in writing. The more details the child can provide as to who, what, where, how, the more power the school will have to act. Explain this to the child/parent and do your best to gently get details for your letter to the school. If child or parent will not consent to communication with school, provide advice / handouts (**MARCcenter.org**) to help the parent advocate themselves for their child with the school. Always document in your note the conversation in the office.

Copyright ©2013: Peter C. Raffalli, MD, Elizabeth Englander, PhD

Fig. 15.1 cont'd

has been linked to earlier alcohol initiation. However, applying these same constructs to media violence has been controversial. Some suggest that other concepts may be important to consider, such as "dose-response" effects of media or gene-environment interactions.

There are three main types of media in which children may be exposed to violence: video games, traditional media, and social media. **Violent video game** exposure is associated with several outcomes, including increases in composite aggression score, aggressive behavior, aggressive cognitions, aggressive affect, and desensitization; decreased empathy; and increased physiologic arousal. Several mechanisms for these outcomes have been studied. These have included evaluating links between video game violence and the limbic or reward areas of the brain, as well as through other cognitive processes, including skill acquisition, cognitive control, and attention.

Traditional media such as movies and TV often model violent behavior for the purposes of entertainment. Media violence does not always portray the real human cost or suffering caused by violence. Special effects can make virtual violence more believable and appealing than in the real world. For some children, exposure to media violence can lead to anxiety, depression, posttraumatic stress disorder, or sleep disorders and nightmares. Repeated exposure to the behavioral scripts provided by entertainment media can lead to increased feelings of hostility, expectations for aggression, desensitization to violence, and increased likelihood of interacting and responding to others with violence.

Social media presents similar risks of exposure to virtual violence, but because of the interactive nature of the medium, this content can feel more personal, relevant, or targeted. Social media combines peer and media effects and thereby represents a powerful motivator of behavior, whether content created by adolescents themselves or content they find and share with peers. The Facebook Influence Model describes 13 distinct constructs in which social media may influence users, such as establishing *social norms* and connection to identity. Thus exposure to violent content on social media may have an influence in promoting a social norm or connecting this type of content to one's own identity.

SCREENING

It is important for pediatricians to screen and counsel patients and families about media use and exposure to violent content. Both the quantity and the quality of media are critical factors in media effects on children. When heavy media use by a child is identified, pediatricians should evaluate the child for aggressive behaviors, fears, or sleep disturbances and intervene appropriately.

RECOMMENDATIONS (SEE TABLE 15.1)

Pediatricians can counsel parents to help their children **avoid exposure to any form of media violence under age 8 years**. These younger children do not have the capacity to distinguish fantasy from reality.

Parents should **select and co-view media with their children**, including playing video games with them, watching movies together, and co-viewing social media content. Parents can then assess these games and shows in regard to what they are teaching about communication and interactions with others.

Parents should **feel empowered to place restrictions** on games or shows that reward shooting, killing, or harming other people. Media are powerful teachers, and parents can make choices about how much violence they want their children to learn. Parents can use industry ratings, such as from the Motion Picture Association of America and the Entertainment Software Ratings Board for movies and TV, as well as resources such as Commonsense Media (which also includes video game reviews), to guide media selections.

Visit Elsevier Ebooks+ at eBooks.Health.Elsevier.com to read this chapter.

15.3 Effects of War on Children

Isaiah D. Wexler and Eitan Kerem

The adverse consequences of war on children are devastating and long-lasting—death, injury, loss of family members, conflict-associated sexual violence, food insecurity, forced relocation (prejudice and discrimination in the receiving country), coercive conscription, child abduction, and psychologic trauma. Human rights organizations and the Secretary General of the United Nations annually detail the extent and impact of war on children. These reports clearly establish that war is a global phenomenon associated with a staggering intensity of human rights violations involving children. Approximately 426 million live in a conflict zone, and ~1.6 billion children (0-18 years) live in a conflict-affected country (Fig. 15.2). The recent onset of large-scale hostilities between Russia and Ukraine in 2022 has had a significant impact on children, especially displacement.

During the last decade, there has been an increase in armed conflict–associated exploitation in the form of **human trafficking**, slavery, forced marriages, prostitution, and child labor. **Displacement** and forced relocation are on the rise as a result of the increasing number of intrastate conflicts, especially in the Middle East and Africa. In 2020, UNHCR **(Office of the United Nations High Commissioner for Refugees)** reported the

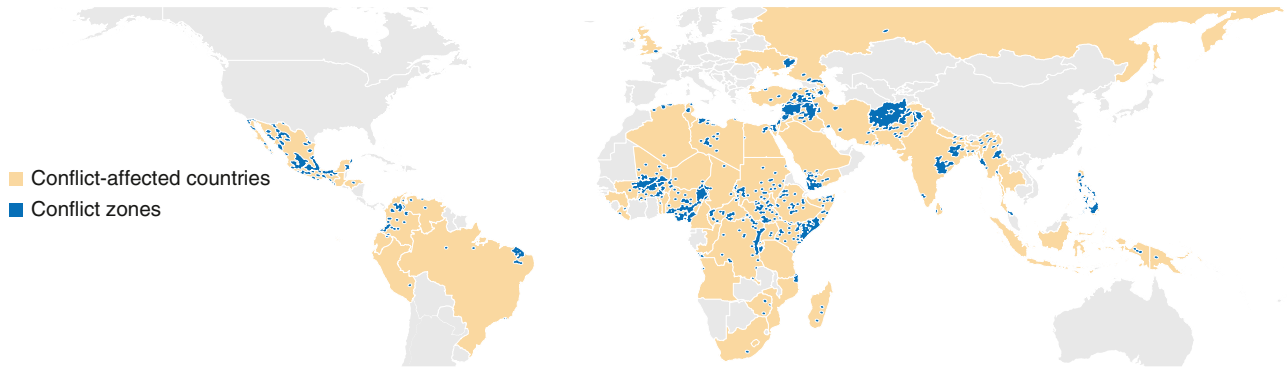

Fig. 15.2 Conflict-affected countries and conflict zones, 2019. Overlays of the conflict-affected countries with the conflict zones where actual fighting took place in 2019. Conflicts are usually concentrated in limited geographical areas within countries. (*From Østby G, Rustad SA, Tollefsen AF. Children affected by armed conflict, 1990–2019. Conflict Trends, vol 6. Oslo: PRIO;2020: Figure 1. https://www.prio.org/publications/12527.*)

astounding statistic of 82.4 million people forcibly displaced worldwide, with most of the refugees being sheltered in developing countries that lack adequate resources to deal with large-scale humanitarian crises. In Ukraine, the United Nations Office for the Coordination of Humanitarian Affairs reported that 2 million children had been internally displaced at the end of 2022. Reemergence of polio or cholera and the increased virulence of tuberculosis have been associated with conflict-affected regions and large population displacements. The COVID-19 pandemic that began in 2020 has worsened the existing situation, with widespread disruption of health and educational services provided by domestic healthcare systems and humanitarian organizations.

Mortality and morbidity related to the long-term effects of war and civil strife are as significant as those occurring during actual fighting. War and violence are rarely listed as leading causes of childhood mortality, but the regions with the highest levels of child mortality, especially among children <5 years of age, are the same locations involved in military conflicts. Nations experiencing conflict often devote substantial portions of their budgets to military expenditures at the expense of the healthcare infrastructure; a substantial proportion of deaths attributed to malnutrition, environmentally related infectious disease, or inadequate immunization are related to the effects of war. Children experiencing the trauma of wartime violence are at risk for long-term health sequelae, with greater risk for obesity, hypertension, stroke, and cardiovascular disease.

During wartime, customary patterns of behavior are forced to change, overcrowding is frequent, and essential resources, such as water and food staples, may be polluted or contaminated. There is a growing understanding that war and climate change are linked. Armed conflict can worsen the impact of spreading desertification, and competition for scarce resources can serve as a stimulus for war.

The morbidity of children exposed to conflicts is significant and long-term (Table 15.2). Many more children are physically harmed than killed. Children bear the psychologic scars of war resulting from exposure to violent events, loss of primary caregivers, and forced removal from their homes. Impressment of children into service as **soldiers** is a form of *exploitation* associated with long-term problems of adjustment. Child soldiers often lack the appropriate education and socialization, and thus their moral compass is often misaligned. They are often incapable of understanding the sources of conflict or why they have been targeted. Their thought processes are more concrete; it is easier for them to dehumanize their adversaries. Children, who themselves are exposed to violence and cruelty, frequently become the worst perpetrators of atrocities.

After cessation of hostilities, children are still at risk for life-endangering injuries from **landmines**, unexploded ordinance, and other explosive remnants of war. Before the signing of the international treaty to ban landmines in 1997, an estimated 20,000-25,000 casualties occurred annually from landmines. Despite the ban, there are still a significant amount of casualties reported, with over 7,000 casualties in 2020 according to *Landmine and Cluster Munition Monitor*, a nongovernmental organization monitoring adherence to the international treaty. Approximately 30% of these casualties occur in children, with a predominance of males. The continued proliferation of small arms and light weapons, which are easily handled by children, also continues to take its toll on human life and hinders stabilization in post conflict societies.

SUSCEPTIBILITY OF CHILDREN IN TIMES OF WAR

Children do not have the physical or intellectual capabilities to defend themselves. It is easier for adults to victimize children than other adults. Older children's curiosity, desire for adventure, and imperfect assessment of risk often lead them to participate in dangerous behavior. Younger children, because of their small size and immature physiology, are more susceptible to disease and starvation and are more likely to sustain fatal injuries from ballistic projectiles and explosive devices such as mines. **Blast injuries**, a common cause of violence-related injuries, have a more devastating impact on children than on adults. Specific types of military engagement can have a disproportionate effect on children. In a survey of war-related mortality in Iraq from 2003 to 2008, it was found that approximately 10% of the violence-related fatalities were children. Most children succumbed to either small arms gunfire or suicide bombs (35%). Data collected during the Syrian civil war from 2011 to 2016 showed that 17% of the approximately 100,000 fatal civilian casualties were children, with over 70% of male children succumbing as a result of artillery shelling or aerial bombardments.

Table 15.2 Impact of War on Children

PHYSICAL
Death
Sexual violence (pregnancy, genital trauma, STIs)
Amputations and fractures
Head trauma
Ballistic wounds
Blast injuries
Burns
Chemical- and biologic-induced respiratory disease
Malnutrition and starvation
Infectious disease
Toxicity from polluted natural resources
Torture
PSYCHOSOCIAL
Abduction
Displacement
Loss of caregivers and family members (orphaned)
Child assuming adult roles (labor, parenting sibling)
Separation from community
Lack of education
Inappropriate socialization
Acute stress reaction
Posttraumatic stress disorder
Depression
Maladaptive behavior
EXPLOITATION
Conscription as soldiers
Coerced involvement in terrorist activities
Prostitution
Slavery
Forced adoption

STI, Sexually transmitted infection.

During times of war, there is a breakdown of social inhibitions and cultural norms. Exploitation of children, such as forced marriages or involuntary conscription, are rationalized as being beneficial for the greater cause. Aberrant behavior such as rape, torture, and pillaging, which would be inconceivable in times of peace, is common during war. Children may be attacked, kidnapped, or used as human shields.

The changing nature of war has adversely affected children. Conventional warfare in which armies of professional soldiers representing different countries battle each other has become less common since World War II, with the notable exception of the Russia-Ukraine war **Intrastate conflicts** in the form of civil war or insurgency predominate. In 2020, there were over 50 active intrastate armed conflicts in the world, as documented by the *Uppsala Conflict Data Program* (UCDP). These conflicts are often rooted in factious ethnic, political, or religious ideologies, and the participants are frequently nonprofessional irregulars who lack discipline and accountability to higher echelons and are directed by those who do not acknowledge or respect international accords governing warfare. Often the military resources of the antagonists are disproportionate, leading the weaker protagonist to develop compensatory

tactics that can include guerrilla, paramilitary, and terrorist activities, while the stronger side often resorts to the disproportionate use of force. Low-intensity conflicts have become more common. These types of conflicts are often characterized by military activities targeting civilian populations with the goal of disrupting normal routines and generating publicity for the perpetrators. Sites of violence can be remote from the battleground when one or both parties to a conflict resort to terrorist activities.

Terrorism and organized urban-based **gang warfare** have become prevalent. Violence perpetrated by terrorist groups or gangs is designed to coerce and intimidate both individuals and entire societies. Children are often intended victims of political- or religious-motivated violence because this serves to maximize the impact of terrorism. The destruction of the New York City World Trade Center Towers in 2001 and the nearly 3,000 fatalities showed that highly organized and motivated terrorists have few inhibitions and can strike anywhere. **Biologic** and **chemical** weapons of mass destruction have been employed, with the most recent example being the use of poisonous gases in the Syrian civil war. Children are more susceptible to chemical and biologic toxins because of their higher respiratory rates, more permeable skin, and other developmental vulnerabilities (see Chapter 763).

The media and the internet have had a significant role in exacerbating the effects of war on children. Media coverage of war and terrorist events is extensive and visual, and social media promulgated via the internet is a convenient tool for disseminating **propaganda** and graphic video material designed to recruit volunteers and shock opponents. Children, more impressionable than adults, often view this material uncontrolled. Uncensored pictures of victims, unbridled violence, people in shock, or family members searching through ruins for relatives may traumatize children and even encourage inappropriate behavior. Overt broadcast propaganda glorifying war and violence may sway children to participate in militaristic or antisocial activities (see Chapter 15.2).

Table 15.3 Manifestations of Stress Reactions in Children and Adolescents Exposed to Armed Conflict

CHILDREN ≤6 YR
Excessive fear of separation
Clinging behavior
Uncontrollable crying or screaming
Freezing (persistent immobility)
Sleep disorders
Terrified affect
Regressive behavior
Expressions of helplessness and passivity
CHILDREN 7-11 YR
Decline in school performance
Truancy
Sleep disorders
Somatization
Depressive affect
Abnormally aggressive or violent behavior
Irrational fears
Regressive and childish behavior
Expressions of fearfulness, withdrawal, and worry
ADOLESCENTS 12-17 YR
Decline in school performance
Sleep disturbances
Flashbacks
Emotional numbness
Antisocial behavior
Substance abuse
Revenge fantasies
Suicidal ideation
Withdrawal

PSYCHOLOGIC IMPACT OF WAR

Exposure to war and violence can have a significant impact on a child's psychosocial development. Displacement, loss of caregivers, physical suffering, and the lack of appropriate socialization all contribute to abnormal child development. Often the reactions are age specific (Table 15.3). Preschoolers may have an increase in somatic complaints and sleep disturbances and display acting-out behaviors such as tantrums or excessively clinging behavior. School-aged children may show regressive behavior such as enuresis and thumb sucking. They, too, have an increase in somatic complaints; there is often a negative impact on school performance. For teenagers, psychologic withdrawal and depression are common. Adolescents often exhibit trauma-stimulated acting-out behavior. Motivated by the desire for revenge, they may be quick to join in the violence and contribute to the continuation of conflict.

There is an increased incidence of both **acute stress reactions** and **posttraumatic stress disorder** (PTSD; see Chapter 38). The true incidence is difficult to assess because of the heterogeneous nature of war, degree of exposure to violence, and methodologic challenges related to the precise characterization of PTSD. Risk factors for having a more serious psychologic response to a violent event include severity of the incident, personal involvement (physical injury, proximity, loss of a relative), prior history of exposure to traumatic events, female gender, and a dysfunctional parental response to the same event. Children may develop PTSD many years after the traumatic event. Children do not have to be directly exposed to violent activity, and media coverage of terrorist events may be sufficient to trigger PTSD-like symptomatology.

The trauma experienced by children during war can have lifelong effects. Studies on children imprisoned in concentration camps or evacuated from their homes in London during the Battle of Britain show that these individuals were at greater risk for PTSD, anxiety disorders, and a higher level of dissatisfaction with life when surveyed decades after the traumatic events. Depression is often a comorbid condition associated with PTSD among children exposed to armed conflict. Trauma may have a **transgenerational effect**, with biologic stress responses and environmental influences causing children of PTSD victims to display a wide variety of psychologic disorders. On the positive side, children are more resilient than adults. With appropriate support from family and community, together with timely and intensive psychologic intervention, children can recover and lead normal, productive lives despite the searing trauma that they may have experienced.

EFFORTS TO PROTECT CHILDREN FROM THE EFFECTS OF WAR

International Conventions

War and terror violate the human rights of children, including the right to life, the right to be nurtured and protected, the right to develop appropriately, the right to be with family and community, and the right to a healthy existence. Several international treaties and conventions have been ratified, beginning with the **Fourth Geneva Convention** (1949) that set forth guidelines regarding appropriate treatment of children in times of war. The **United Nations Convention on the Rights of the Child** (1990) delineated specific human rights inherent to every child (defined as any individual younger than 18 years) and the subsequent **First Optional Protocol** (2000), which prohibits conscripting or recruiting children for military activities. The **Third Optional Protocol** in 2014 established methods for communicating complaints of human rights violations involving children to the United Nations Committee on the Rights of the Child and sets up procedures by which the committee can

conduct inquiries into alleged human rights violations among signatory nations. The **Rome Statute of the International Criminal Court** enacted in 2002 declared that the conscription or enlistment of children younger than 15 years is a prosecutable war crime. Despite these conventions and better documentation, human rights violations have not abated. In the past decade there has even been an upswing in the recruitment of child soldiers as combatants by nonstate armed groups (NSAGs).

Although these treaties and conventions define the extent of protection afforded to children, the means of enforcement available to the international community is limited. Individuals, motivated by religious fervor, nationalistic zeal, or ethnic xenophobia, are unlikely to curb their activities because of fear of prosecution. These treaties better serve in heightening awareness regarding the protected status of children in wartime, and perhaps deter high-ranking leaders who fear being held accountable for war crimes.

Humanitarian Efforts

Several organizations, either nongovernmental or under UN auspices, are involved in mitigating the effects of war on children. The International Red Cross, UNICEF, UNHCR, International Rescue Committee, World Health Organization (WHO), and Médicins Sans Frontières (Doctors Without Borders) have had a significant impact on reducing violence-related casualties in war-torn regions. During the Russia-Ukraine war, many countries sent medical teams including pediatricians to Ukraine and neighboring countries hosting refugees to provide assistance. The infusion of humanitarian aid into developing countries often improves overall mortality and morbidity by increasing the level of medical and social services available to the general population. Other organizations, such as Amnesty International, Stockholm International Peace Research Institute, and Physicians for Human Rights, actively monitor human rights abuses involving children and other civilian groups. In 2005 the UN Security Council approved the establishment of a monitoring and reporting system designed to protect children exposed to war. UN-led task forces conduct active surveillance in war-stricken regions reporting on the **six grave violations against children during armed conflict:** the killing or injuring of children, recruitment of child soldiers, attacks directed against schools or hospitals, sexual violence against children, abduction of children, and denial of humanitarian access for children.

ROLE OF PEDIATRICIANS AND ALLIED HEALTH PROFESSIONALS

War is a chronic condition, and health providers need to be prepared to treat childhood casualties resulting from military or terrorist activity, as well as caring for children suffering from the aftermath of war or related violence. Community and hospital pediatricians need to be involved in community disaster planning. General disaster planning should not ignore the unique needs and requirements of children; in planning for a possible chemical attack, appropriate resuscitation equipment suitable for children needs to be stockpiled. The signs of biologic infection, chemical intoxication, or radiation injury are different for children, and pediatricians and emergency personnel need to be aware of these differences (see Chapters 758 and 763). Surveys of pediatricians and other healthcare providers indicate that many feel unprepared for bioterrorism attacks. Professional organizations (e.g., WHO, American Academy of Pediatricians [AAP], Centers for Disease Control and Prevention [CDC]) have published position papers, and the AAP *Red Book* presents guidelines for treating specific pathogens likely to be used in **biologic warfare**. In regions where violent terrorist activity is likely, pediatricians, nurses, and rescue personnel should obtain certification provided by Red Cross Basic and Advanced Trauma Life Support programs. The U.S. Department of Health and Human Services sponsors a *Technical Resources, Assistance Center, and Information Exchange* (TRACIE) website that includes information for health service providers related to disaster management and preparedness for incidents involving children (asprtracie.hhs.gov).

Pediatricians need to be aware of the potential effects of war and terror on parents and children. Loss or separation from parents or caregivers has a devastating impact on children (see Chapter 30). Parents, who themselves are under tremendous strain, may not be sensitive to the effects that the same stressors have on their children. Parents and caregivers must be made cognizant of the effect that media coverage can have on their children and their role in the intermediation of the repetitive broadcast of real-time acts of violence and incendiary communications designed to enlist support for specific causes. Pediatricians should draw out both parents and children and encourage them to talk freely about their feelings. Child healthcare providers can be instrumental in educating parents to be more aware of inappropriate responses by children to war and violence. When necessary, pediatricians can serve their families by referring them to appropriate support services.

Just as it is important to administer first aid for physical trauma, it is also critical to provide psychologic first aid to victims of trauma. An excellent source of online information for both providers and caregivers is the **U.S. government–sponsored National Child Traumatic Stress Network** (nctsn.org). In day-to-day patient interactions, a pediatrician is most likely to confront situations related to stress reactions such as PTSD or depressive disorders. Recognition of PTSD is essential so that early treatment can be initiated. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) stipulates that for a diagnosis of PTSD, there has to be manifestations from each of four symptom clusters: *intrusion, avoidance, negative alterations in cognitions and mood,* and *alterations in arousal and reactivity*. DSM-5 also established a special preschool subtype of PTSD that has the same four symptom clusters but with specific manifestations typical of preschoolers exposed to trauma. Clues to the presence of PTSD and acute anxiety reactions include changes in behavior, school performance, affect, and sleep patterns and an increase in somatic complaints. Even when the triggering event is neither temporally nor physically proximate, it should not dissuade the pediatrician from making an appropriate referral to mental health professionals who are expert in childhood stress disorders.

Medical professional standards demand that the physician treat all patients equitably without regard to their background. Both international law and professional medical societies ban physicians from actively participating in **torture** or other activities that infringe on human rights, including those of children. It is difficult to countenance any situation in which a health professional, even acting as a representative of their country, might directly or indirectly injure a minor. On the positive side, many pediatricians and other physicians have treated children during war either as members of the armed services or volunteers, often under adverse conditions, refusing to abandon their patients even when it has put their own lives at risk. Pediatricians and pediatric organizations have been at the forefront in advocating for peaceful coexistence, assisting in relief efforts, and attempting to alleviate the disparities in healthcare resulting from war.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 16

Child Trafficking for Sex and Labor

V. Jordan Greenbaum

Human trafficking violates the fundamental human rights of affected children, adolescents, and adults and affects families, communities, and societies. Trafficked persons originate from countries worldwide and may belong to any racial, ethnic, religious, socioeconomic, or cultural group. They may be of any gender. According to the United Nations *Protocol to Prevent, Suppress and Punish Trafficking in Persons,* **child trafficking** refers to the "recruitment, transportation, transfer, harboring or receipt of a person" under 18 years old for purposes of exploitation. Two major types of trafficking involve **forced labor** and **sexual exploitation** (Table 16.1). Whereas adult sex trafficking requires demonstration of force, fraud, coercion, deception, or the abuse of power as a means of exploitation, these are *not* required for persons younger than 18 years. Interpretation of the international protocol varies across the globe; U.S. law does not require movement of a victim to qualify as human trafficking. In addition, minors who "consent" to commercial sex in the absence of a third party (trafficker) are victims of commercial sexual exploitation, because their age precludes true informed consent.

Child trafficking may occur within the confines of the child's home country (*domestic* trafficking) or may cross national borders (*international,* or *transnational,* trafficking). Globally, individuals tend to be trafficked within their own country or to a country in the same region. In the United States, most identified children and adolescents experiencing *sex trafficking* are U.S. citizens or legal residents; few statistical data exist on minors who are trafficked for labor. Variations in definitions of terms, problems with data collection, and underrecognition of affected individuals complicate estimates of the prevalence of human trafficking, but the International Labour Organization estimates that approximately 3.3 million children and adolescents across the globe experienced forced labor in 2021, of whom approximately 1.7 million were subjected to commercial sexual exploitation. In a global study of officially identified trafficked persons, the United Nations Office on Drugs and Crime estimated that approximately 19% were girls and 15% boys. However, laws that define sexual exploitation in terms of females and women, as well as cultural views regarding gender roles, lead to underreporting of males, especially as victims of sex trafficking, so their numbers may be higher than estimated.

Table 16.1 Types of Exploitation Included in Child Trafficking

Sexual Exploitation
Prostitution of a child
Production of child sexual exploitation materials (child pornography)
Exploitation in context of travel and tourism
Having a minor perform sex acts in a sexual venue (e.g., strip club)
Child marriage or forced marriage
Live online sexual abuse
Labor Exploitation
Agriculture, manufacturing, textiles, food/hospitality services
Domestic work
Construction
Magazine sales
Health and beauty
Cleaning services
Forced Begging
Forced Criminality
Forced Engagement in Armed Conflict
Illegal Adoption

Factors creating vulnerability to human trafficking exist at the individual, relationship, community, and societal levels (Table 16.2). **Age** is an important risk factor for adolescents because they are at a stage in their development at which they have limited life experience, a desire to demonstrate their independence from parental control, and a level of brain maturation that favors risk-taking and impulsive behaviors over careful situational analysis and other executive functions. They are also very interested in social media and are savvy at internet use, which render them susceptible to online recruitment and solicitation.

Recruitment of children and adolescents for labor or sex trafficking often involves false promises of romance, job opportunities, or a better life. Individuals may remain in their exploitative situation for a number of reasons, including **fear of violence** to themselves or their loved ones should they attempt to leave their situation; **guilt and shame** for believing the fraudulent recruitment scheme or engaging in illegal and/or socially condemned activities; **humiliation** and fear of criticism by authorities; **debt bondage** (believing they owe the trafficker exorbitant amounts of money and cannot leave until the debt is paid); and fear of **arrest** and/or **deportation**. Many children and adolescents do not view their situation as exploitative. Females who believe their trafficker is a boyfriend may view their commercial sexual activities as demonstrations of their love; males engaging in commercial sex to obtain shelter or food while living on the street may feel they are exploiting buyers rather than being victimized themselves. Traffickers may use violence, economic manipulation, and psychologic manipulation to control individuals.

CLINICAL PRESENTATION

Children and adolescents who experience trafficking may seek medical care for any of the myriad physical and emotional conditions associated with exploitation. They may present with traumatic injuries inflicted by traffickers, buyers, or others or injuries related to unsafe working conditions. They may present with a history of sexual assault or symptoms/signs of sexually transmitted infections (STIs) and infections related to overcrowded, unsanitary conditions. They may request testing for HIV or complain of signs/symptoms of HIV or infections endemic to their home country (e.g., malaria, schistosomiasis, tuberculosis). Other clinical presentations may involve pregnancy and complications of pregnancy or abortion; malnutrition and/or dehydration; exhaustion; conditions related to exposure to toxins, chemicals, and dust; and signs and symptoms of posttraumatic stress disorder (PTSD), major depression, suicidality, behavioral problems including aggression, and somatization. Some children and adolescents may have preexisting chronic medical conditions that have been inadequately treated before or during the exploitation (e.g., diabetes, seizure disorder, asthma). Individuals who are trafficked may also seek medical care for their children.

Many of the same factors that prevent children and adolescents from leaving their exploitative conditions also preclude them from disclosing their situation to others. Most affected individuals presenting for medical care at clinics, hospitals, and emergency departments do not spontaneously self-identify as trafficked persons. Consequently, it is incumbent on the medical professional to be aware of risk factors so that those being trafficked and those at risk may be recognized and offered services. A trafficked individual may present to a medical facility alone, in the company of a parent/guardian (who may or may not be aware of the trafficking situation), a friend or other person not involved in the trafficking, a person working for the trafficker (who may pose as a friend or relative),

Table 16.2 Risk Factors for Child Trafficking

INDIVIDUAL
Member of marginalized group (e.g., racial, ethnic, sexual minority, caste)
History of sexual/physical abuse or neglect
Limited education
Unaccompanied immigrant status
Substance misuse
Homeless/runaway status; told to leave home
History of child welfare and/or juvenile justice involvement (U.S., sex trafficking)
Untreated mental or behavioral health condition
RELATIONSHIP
Family poverty
Family violence, substance misuse, or other dysfunction
Forced migration
Family/peers involved in trafficking
Intolerance of LGBTQ+ status
Significantly older intimate partner
COMMUNITY
Limited resources (economic, educational, social support)
Tolerance of trafficking/exploitation
Natural disaster
Community violence
Limited knowledge of trafficking/exploitation
Increased tourism, travel to area
SOCIETAL
Cultural beliefs about roles and rights of children
Gender bias/discrimination
Cultural beliefs and practices that marginalize and disempower groups (e.g., transphobia, xenophobia)
Tolerance of exploitation
Systemic racism and discrimination
Tolerance of violence
Societal/economic/health inequity and inequality
Social or political upheaval
Inadequate laws regarding trafficking; corruption

LGBTQ+, Lesbian, gay, bisexual, transgender, queer/questioning, and other.

Table 16.3 Potential "Red Flags" for Child Trafficking

RED FLAGS AT PRESENTATION
Chief complaint of acute physical or sexual assault
Chief complaint of suicide attempt or ideation
Patient accompanied by unrelated adult or juvenile
Patient or parent accompanied by domineering person who appears in hurry to leave
Patient or parent appears intimidated or fearful
Patient or accompanying person provides inconsistent or unlikely history of events
Patient unfamiliar with city/town, cannot provide address where staying
PHYSICAL FINDINGS
Patient withdrawn and with flat affect, fearful, very anxious, intoxicated, or with inappropriate affect
Evidence of remote or acute inflicted injury (suspicious burns, bruising, signs of strangulation, fractures, closed head injury, thoracoabdominal trauma)
Evidence of preventable work injury, toxic exposure, overuse injury, or untreated injury
Malnutrition with or without dehydration
Poor dentition and/or dental trauma
Late presentation of illness/injury

or the trafficker. Traffickers may be male or female, adult or juvenile, and they may be family members, acquaintances, friends, or strangers. On occasion, children and adolescents are brought in by law enforcement or child protective services because of concerns of trafficking. Table 16.3 lists potential "red flags" for labor or sex trafficking. In some cases, the red flag may be the **chief complaint**, which may involve a condition frequently associated with trafficking (e.g., STI symptoms/signs, especially with history of prior STI, and a preventable work-related injury such as a toxic exposure). The practitioner may become concerned about possible trafficking on recognizing the presence of one or more **risk factors** (e.g., runaway status, recent migration and current work in a sector known for labor trafficking).

APPROACH TO THE PATIENT AT RISK FOR TRAFFICKING

When interacting with a patient who may have experienced labor or sex trafficking, the medical provider should use a **trauma-informed, human rights–based, culturally appropriate, and gender-sensitive approach** (Table 16.4). This involves an awareness that trauma experienced by a young person may influence the child's thoughts about themselves and others, their beliefs and perceptions of the world, and their behavior. Hostility, withdrawal, or distrust may be reactions to trauma and should be met with a sensitive, nonjudgmental, empathic response by the provider. Physical safety of the patient and staff are critical, and protocols should be in place to address security issues that may arise if the trafficker is on the premises. Psychologic safety of the patient may be facilitated by separating them from any accompanying person when obtaining the medical history, conducting the visit in a warm, child-friendly environment, and taking adequate time to build rapport and begin to establish trust. When interpretation is needed, a professional interpreter should be used. This person needs to be trained in trauma-informed care and should not be from the same community as the patient. When possible, the patient's preference for gender of clinician and interpreter should be respected.

Respect for the **patient's rights** is essential, including the right to an explanation regarding the purpose of the questions being asked and the reasons for, and elements of, the examination and diagnostic evaluation. Informed assent by the patient for all steps of the process should be obtained whenever possible. Every attempt should be made to understand and respect cultural, gender-based, and religious factors that may affect the individual's views of their bodies, their condition, and their desired treatment.

The limits of confidentiality should be explained in a way the patient understands so that they are able to choose what information to disclose. This should occur before asking sensitive questions. As appropriate to developmental stage and the context of the visit, the provider should discuss how sensitive information is to be documented in the individual's medical record and work collaboratively to honor the patient's preferences and desire for privacy and confidentiality (within the bounds of laws, policies, and the need to ensure appropriate continuity of care).

Currently, there are limited child trafficking screening tools designed for the healthcare setting. The Short Screen for Child Sex Trafficking (SSCST) is validated for youth 11-17 years who present to emergency departments, child abuse clinics, and teen clinics; this tool screens for risk factors associated with sex trafficking; a positive screen indicates a child is at risk, and additional follow-up questions are needed to assess the level of risk and to determine next steps (e.g., specific service referrals, mandatory reporting). It does not screen for labor trafficking. The Quick Youth Indicators of Trafficking (QYIT) is a short screen designed for young adults

Table 16.4 Elements of a Human Rights–Based, Trauma-Informed Approach to Patient Care

BASIC RIGHTS
Best interest of the child to be primary concern in all actions involving the child
Protection from discrimination because of gender, race, ethnicity, culture, socioeconomic status, disability, religion, language, country of origin, or other status
Right to express views and be heard appropriate to the child's age and development
Right to obtain information relevant to the child to be given in a way that the child can understand
Right to privacy and confidentiality
Right to the highest attainable standard of health and to access healthcare services
Right to dignity and self-respect
Right to consideration of special needs (e.g., age, disability)
Right to respect of cultural and religious beliefs and practices
TRAUMA-INFORMED CARE
A strength-based approach that facilitates patient resilience and empowerment.
Obtain medical history in a private, safe place, outside the presence of persons accompanying the patient to the visit.
Explain all processes in way the patient understands, and obtain assent for each step; discuss the limits of confidentiality and mandated reporting.
Encourage the patient to express views and to participate in decision-making regarding referrals and care.
Foster the patient's sense of control during the evaluation.
Ask only the questions needed to assess safety, health, and well-being. Avoid asking irrelevant questions about trauma to avoid unnecessarily triggering anxiety and distress.
Minimize retraumatization during history, examination, and diagnostic testing (avoid triggers of stress when possible).
Monitor for signs of distress, both verbal and nonverbal.
Allow the patient to choose the gender of the provider, if feasible.
Have trained personnel present during the examination to assist with providing support and reassurance.
Avoid making promises the provider cannot fulfill.
Put information gathered to good use.
Work with the child to conduct a safety assessment and create a plan.
Be prepared to make referrals and offer resources.

(18-25) seeking services at a homeless shelter; it screens for both labor and sex trafficking.

When a provider is speaking with a child at perceived risk for trafficking, additional questions may be asked once trust has been established. These should be asked using a trauma-informed approach. For example,

- "Many children who are living on the street have a hard time getting money for food and shelter. Sometimes they have to exchange sex to get what they need. Has this ever happened to you or anyone you know?"
- When asking about sexual history: "Has anyone ever asked you or forced you to have sex with another person? Do you feel comfortable telling me about it?"
- "If you feel comfortable, can you tell me a little bit about your job? Is the work you do what you expected when you agreed to the job? Are you allowed to keep all of the money you earn or send it home? Where, and with whom, do you live? When you are not working, are you allowed to come and go from the place you stay?"

Such questions may open the door to a discussion of exploitation and facilitate the provider identifying appropriate resources and referrals.

All elements of the medical history and review of systems are important, but special attention should be paid to reproductive history (including sexual orientation and gender identity, prior history of sex partners, STIs, pregnancy and terminations, and condom use); injury history; substance use/misuse; and mental health history and current symptoms. Rates of substance misuse, PTSD, depression, and suicidality are very high among individuals experiencing human trafficking, and questioning may highlight the need for emergency care or nonurgent referrals. It also provides an opportunity for anticipatory guidance aimed at harm reduction: a discussion of condom use, STIs, HIV/AIDS, and substance use may prove invaluable, because many youth lack accurate information on these topics. It is important to identify any chronic conditions, especially if untreated, and to assess vaccination status. Many individuals who have experienced trafficking have had very poor healthcare in the past and lack basic primary care. It is important to ask questions about signs/symptoms of infections endemic to the child's home country or to countries in which the child has been trafficked (e.g., tuberculosis, dengue, malaria; see Chapter 11).

EXAMINATION AND DIAGNOSTIC TESTING

A thorough physical examination allows the provider to assess and treat acute and chronic medical conditions, collect forensic evidence (as appropriate), assess nutritional and developmental status, and document recent and remote injuries. Diagnostic testing may identify pregnancy, STIs, HIV seroconversion, nonsexually transmitted infections, vitamin and mineral deficiencies, anemia, toxic exposures, and drug or alcohol use. A sexual assault evidence kit may reveal trace evidence or DNA from offenders. Informed assent for the exam, assault kit, and diagnostic tests is important, as is careful explanation of each step during the process and monitoring of the patient for signs of distress and anxiety. Those who have been sex-trafficked may experience particular distress during the anogenital examination, the oral exam, and when injuries are photographed. A trauma-trained chaperone is very helpful in providing comfort and support to the patient. The examination should be conducted outside the presence of anyone suspected of being involved in the trafficking situation. After the exam the provider should explain the results, ask the patient if they have any questions about the exam, and give them the opportunity to discuss concerns about their bodies. Individuals who experience trafficking may harbor anxiety about a variety of issues, including possible infertility, future health, or possible permanent damage from work-related injuries and toxic conditions.

Providers may follow U.S. Centers for Disease Control and Prevention (CDC) guidelines on STI testing and prophylaxis. Additional resources on laboratory testing for sexually and nonsexually transmitted diseases may be obtained from the CDC (https://www.cdc.gov/) or World Health Organization (WHO) websites (http://www.who.int/en/). In general, STIs of greatest relevance include *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis,* HIV, syphilis, and hepatitis B and C viruses. Methods of testing and decisions to treat (e.g., positive test results vs prophylaxis vs syndromic treatment) will depend on national guidelines and on medical resources, which may be limited in some countries or regions. However, consideration should be given to the high likelihood that the patient may be lost to follow-up after the visit, so the decision to delay treatment until test results are available may lead to lack of needed medication. Testing and treatment decisions need to be outlined in a protocol. Emergency contraception and other methods of birth control (especially long-acting reversible contraception) should be discussed with the patient as feasible.

Many individuals who have been trafficked (and children of trafficked adults) have experienced nutritional deprivation, lack of immunizations, and general poor health, especially if they are from low-resource countries or are born into the trafficking situation. Guidance on **medical screening** and care for immigrant children (see Chapter 11) also may be obtained from the CDC (https://www.cdc.gov/immigrantrefugeehealth/guidelines/refugee-guidelines.html) or American Academy of Pediatrics

(AAP) *Red Book* or *Immigrant Child Health Toolkit* (https://aapca1.org/resource/aap-immigrant-child-health-toolkit/). Consideration should be given to vaccine-preventable diseases (including tetanus if there are open wounds) and common diseases in the patient's home country. Trafficked individuals may have iron deficiency, hemoglobinopathies, vitamin D deficiency, and undiagnosed vision or hearing problems. Crowded, unhygienic living conditions during the trafficking period raise the risks of tuberculosis, scabies, and diarrheal illnesses. Toxic levels of lead or chemicals may be present, and vitamin/mineral deficiencies should be considered. A **developmental or educational assessment** is important, given the high likelihood of poor primary care in the past and possible harsh living conditions.

Documentation of overall health and identified injuries is extremely important and should be detailed and accurate. Body diagrams and photographs (if not traumatizing to the patient) are helpful, as are written descriptions of injury location, type (e.g., contusion, laceration), size, shape, and color. All photographs should include patient identifiers and a measuring instrument when possible. Distance photographs to establish injury location may be supplemented with close-up photographs from various angles. Physical signs of untreated illness, malnutrition, and other conditions need to be documented carefully. When documenting the medical history, direct quotes should be used when possible (quotes of provider and of patient statements). Records, including written, video, audio, and photographic records, should be stored in a secure health information system, with limited access and password protection. Strict protocols for patient confidentiality and privacy should be established and followed.

REFERRALS AND RESOURCES

Before discharge, the provider should ensure the patient understands the results of the evaluation and has the opportunity to ask questions. A **risk assessment** should be done by the provider or other qualified staff, to include a discussion with the individual of safety concerns (involving current risks and perceived risks after discharge). The provider should engage the patient in establishing a **treatment plan** as developmentally appropriate. Transparency and shared decision-making are key elements of a trauma-informed approach. Healthcare providers must comply with mandatory reporting laws in their state or country, but in doing so, should make every effort to avoid causing harm to the patient or their family. If a mandatory report is necessary, this should be discussed with the patient before making the call to authorities, so the individual is aware of actions being taken. For nonmandated referrals, patient permission is needed.

For those practicing within the United States, assistance on interpreting laws, working with individuals who may have been trafficked, making reports to authorities, and identifying local referral sources may be obtained by contacting the **National Human Trafficking Hotline** (1-888-373-7888). The hotline has trained staff to assist trafficked persons and professionals alike, including interpreters for over 200 languages. Additional assistance may be obtained by contacting state or local law enforcement and antitrafficking task forces or local child advocacy centers (free-standing or hospital-based facilities that provide services for children and families who have experienced child abuse and/or neglect). In other countries, "helplines" and "hotlines" may be used to seek assistance for those who are being trafficked and those at risk. It is important for the healthcare provider to be aware of local, state, and national resources for individuals experiencing human trafficking.

Affected patients have numerous needs that extend beyond the range of the healthcare provider's ability to respond. A multidisciplinary team approach is needed to ensure the child is provided with necessary food, shelter, crisis management, language interpretation, immigration assistance, mental health and medical care, educational needs, and other services. Such a team may include local victim service providers, shelter staff, behavioral health professionals, child protective services (CPS) workers, law enforcement, child advocacy center staff, representatives of sexual assault crisis centers, and victim advocates. Potential health-related referrals may be found in Table 16.5. To increase the likelihood that the patient and family will obtain the services they desire, it is helpful for the provider to make a "warm handoff" to a referral agency, either contacting agency staff directly or allowing the patient/trusted caregiver to make the call to the agency before leaving the health facility.

Table 16.5 Potential Health Referrals for Trafficked Persons

Behavioral health assessment and treatment (emergent or nonurgent): trauma-focused, preferably conducted by a professional trained in trauma therapies*
Substance use assessment/treatment
Obstetrician/gynecologist
Specialized medical service
Primary medical home (for immunizations including HPV; HIV PrEP; periodic STI testing; monitoring of growth and development; family planning and reproductive health; anticipatory guidance; and nutrition/hygiene counseling)
Physical therapy, occupational therapy
Developmental assessment
Dentist
Optometrist or audiologist
Resources for LGBTQ+ individuals
HIV clinic
Child advocacy center (for second opinion on anogenital exam; forensic interview, behavioral health services)

*Appropriate therapy may differ with victims from varied cultures; there is a limited evidence base for the effectiveness of behavioral health therapy for children experiencing trafficking. However, in the United States, therapies with an evidence base for child sexual assault/abuse are often adapted for use.

HPV, Human papillomavirus; HIV PrEP: human immunodeficiency virus pre-exposure prophylaxis; STI, sexually transmitted infection; LGBTQ+, lesbian, gay, bisexual, transgender, queer/questioning, and other.

Children and adolescents who experience trafficking may face considerable **discrimination** and **social stigma** from the public and from professionals. They may be viewed as "consenting" participants, "illegal immigrants" who somehow "deserve" maltreatment, or "bad" youth who are responsible for their own actions. They may face discrimination related to risk factors such as poverty, gender identity, or systemic racism. In some countries, laws on sexual exploitation do not include boys, and cultural beliefs foster the attitude that males cannot be victimized. This complicates service provision and support for male patients who have experienced trafficking. Variations in the age of consent may result in a child being considered an adult in one country and a child in another, the former condition limiting access to adequate support or increasing the likelihood of being viewed as a criminal offender. For these reasons and others, it is important for the healthcare provider to advocate for the patient's best interests when interacting with other professionals and emphasize the need for comprehensive, sustained, trauma-informed services.

If responsible for long-term care of the patient, the provider should consider that treatment needs change over time, so treatment plans must be reevaluated periodically. Continuity of care is important but can be challenging when the individual is moved to another city, is transported back to the home country, or is retrafficked. Ongoing communication with external agencies and other healthcare providers can be extremely helpful, along with assignment of a case manager to help ensure referrals are in place in destination towns or villages.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 17

Abused and Neglected Children

Howard Dubowitz and Wendy G. Lane

The abuse and neglect (maltreatment) of children are pervasive problems worldwide, with short- and long-term physical and mental health, cognitive, social, and economic consequences. Primary care professionals (PCPs) serving children have an important role in helping address this problem. In addition to their responsibility to identify maltreated children and help ensure their protection, health, and well-being, PCPs can also play vital roles related to prevention, treatment, and advocacy. While securing a child's safety is a priority, the child welfare system also aims to improve families' functioning and enable them to adequately care for their children.

DEFINITIONS

Abuse is defined as acts of commission, neglect as acts of omission. The U.S. government offers a minimal definition of child abuse as "any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm." Many states include other household members and a broader set of circumstances. Children may face situations in which no actual harm has occurred and no imminent risk of serious harm is evident, yet potential harm is a concern. Many states include *potential harm* in their child abuse laws. This is critical to preventing maltreatment, although predicting harm is inherently difficult. Two aspects should be considered: the likelihood and the severity of the potential harm.

Physical abuse includes beating, shaking, burning, drowning, suffocating, and biting. Physical punishment remains controversial, although it is increasingly being prohibited. The Global Initiative to End All Physical Punishment of Children reported that 62 countries have banned physical punishment in all settings, including the home; 135 have done so for schools, and governments in 27 other countries have committed to full prohibition. In the United States, physical punishment in the home remains lawful in all states, and 20 still permit it in schools.

The threshold for when physical punishment should be considered as abuse is unclear. One can consider any injury beyond transient redness such as from a slap as abuse. Proponents of physical punishment suggest that if parents spank a child, it should be limited to the buttocks, be over clothing, and should never involve the head and neck. When parents use objects other than a hand, the potential for serious harm increases. Acts of serious violence (e.g., throwing a hard object, slapping an infant's face) should be seen as abusive even if no injury ensues; significant potential harm exists. Although some PCPs think that hitting is acceptable under limited conditions, almost all prefer more constructive approaches to discipline. The American Academy of Pediatrics issued a policy statement clearly opposing the use of physical punishment. Although many agree that hitting a child should never be accepted, and research has amply documented the potential harm, there remains a reluctance in the United States to label hitting as abuse—unless there is an injury. Clearly the emotional impact of being hit may leave the most worrisome and lasting scars, long after the bruises fade and the fractures heal.

Neglect refers to omissions in care resulting in actual or potential harm. Omissions include inadequate healthcare, education, supervision, or protection from hazards in the environment and unmet physical needs (e.g., clothing, food) and inadequate emotional support. A preferable alternative to focusing on caregiver omissions is to instead consider the *basic needs* (or rights) of children (e.g., adequate food, clothing, shelter, healthcare, education, nurturance). Neglect occurs when a need is not adequately met and results in actual or potential harm, whatever the reasons. A broad definition concerned with children's needs fosters a more comprehensive understanding of what contributes to neglect in addition to the potential parental role. A child-focused definition also offers a more constructive approach to ensure a child's needs are adequately met in contrast to one that narrowly focuses on and blames parents. A child whose health is jeopardized or harmed by not receiving necessary care experiences medical neglect. This view enables professionals to approach the problem in terms of what the child needs, rather than focusing on what parents did badly. Not all such situations necessarily require a referral to child protective services (CPS); less intrusive initial efforts may be appropriate.

Psychologic abuse includes verbal abuse and humiliation and acts that scare or terrorize a child. Although this form of abuse may be extremely harmful to children, resulting in problems such as depression, anxiety, poor self-esteem, and lack of empathy, CPS seldom becomes involved because of the difficulty in proving such allegations. PCPs should still carefully consider this form of maltreatment, even if the concern fails to reach a legal or agency threshold for referral. These children and families can still benefit from counseling and other services. Many children experience more than one form of maltreatment; CPS is more likely to address psychologic abuse in the context of other forms of maltreatment.

INCIDENCE AND PREVALENCE

Abuse and neglect mostly occur behind closed doors and often remain a dark, well-kept secret. Rates of maltreatment are thus difficult to estimate. Nevertheless, the problem is globally prevalent.

Global Situation

The World Health Organization (WHO) estimates that nearly 3 in 4 children, or 300 million children aged 2-4 years, regularly suffer physical punishment and/or psychologic violence at the hands of parents. In addition, as many as 1 in 5 women and 1 in 13 men report having been sexually abused as a child. Less international research has been done on child neglect. Nevertheless, neglect too is clearly a global problem. For example, a large study (n = 41,194) of Balkan countries found lifetime rates of neglect ranging from 23% in Romania to 48% in Bosnia. Among Hong Kong adults, 45% reported a history of childhood neglect. Rates as high as 94% of children for emotional neglect and 89% for physical neglect were found in Burundi, a country severely affected by civil war and political violence. Varying definitions, policies, and practices concerning child maltreatment preclude comparing rates across countries.

United States

There were 4.4 million reports to CPS involving 7.9 million children in the United States in 2019. Of the 656,000 children with substantiated reports (8.9 per 1,000 children), 75% experienced neglect (including 2.3% medical neglect), 17.5% physical abuse, 9.3% sexual abuse, and 6.8% psychologic maltreatment. Neglect is by far the most common form of maltreatment referred to CPS, involving 7 per 1,000 children. Although there had been a welcome decline in rates beginning in the early 1990s, rates increased in 2014 and 2015 and stayed stable until the COVID-19 pandemic, when reports of physical abuse increased. Medical personnel made 11% of all reports. Sources other than official CPS statistics indicate that the incidence of maltreatment is far greater than what gets reported to CPS. In a community survey, for example, 3% of parents reported using very severe violence (e.g., hitting with fist, burning, using gun or knife) toward their child in the prior year.

ETIOLOGY

Child maltreatment seldom has a single cause; rather, multiple and interacting biopsychosocial risk factors at four levels usually interact and contribute to the problem. At the individual level, a child's disability or behavioral challenges or a parent's depression or substance use predispose a child to maltreatment. At the familial level, intimate partner (or domestic) violence jeopardizes children's health and development. Influential community factors include stressors such as dangerous neighborhoods with few supports or recreational facilities. Professional inaction may contribute to neglect, such as when the treatment plan is not clearly communicated or risk factors are ignored. Broad societal factors, such as poverty and its many associated burdens, also contribute significantly to maltreatment. The WHO estimates the rate of child homicide is approximately twofold higher in low-income compared to high-income countries (2.58 vs 1.21 per 100,000 population). Nevertheless, children at all income levels can be maltreated, and PCPs need to guard against biases concerning minoritized and low-income families.

In contrast, protective factors, such as family supports or a parent's concern for their child, may buffer risk factors and protect children from maltreatment. Deliberately identifying and incorporating protective factors is vital to intervening effectively. One can say to a parent who did not fill a prescription, for example, "I can see how much you love [child's name]. What can we do to keep them out of the hospital?" In sum, child maltreatment results from a complex interplay among risk and protective factors. A single parent who has a colicky baby and who recently lost their job has multiple risk factors, but a loving grandparent may be protective. A good assessment and understanding of both risk and protective factors guide an appropriate response.

OUTCOMES

All forms of child maltreatment jeopardize children's physical and emotional health and their cognitive and social development, manifesting in a wide array of possible problems—in the short and the long term. Problems in adolescence and adulthood include health risk behaviors (e.g., smoking, alcohol, and substance use), mental health problems (e.g., anxiety, depression, suicide attempt), and physical health problems (e.g., heart disease, cancer). Maltreated children are also at risk for becoming maltreating parents. The impact of neuroendocrine stress responses to child abuse and neglect on the developing brain may partly explain some of these sequelae.

Some maltreated children appear to be resilient and function relatively well, perhaps owing to protective factors or interventions. Still, PCPs and parents need to be sensitive to the possibility of later problems ("sleeper effects"). The benefits of intervention have been found in even the most severely neglected children, such as those rescued from Romanian orphanages in the early 1990s, who were adopted—the earlier, the better. That said, resilience is a relative concept, and few severely maltreated children escape unscathed.

CLINICAL MANIFESTATIONS

Child abuse and neglect can manifest in a myriad of ways (Table 17.1). A critical element of physical abuse is the lack of a plausible history other than inflicted trauma. The onus is on the clinician to carefully consider the differential diagnosis and not jump to conclusions.

Bruises are the most common manifestation of physical abuse. Features suggestive of abuse include (1) bruising in a preambulatory infant (occurring in just 2% of such infants), (2) bruising of padded and less exposed areas (buttocks, cheeks, ears, neck, genitalia), (3) patterned bruising conforming to the shape of an object (Fig. 17.1), and (4) multiple bruises, especially if clearly of different ages. Earlier suggestions for estimating the age of bruises, however, have long been discredited. It is very difficult to precisely age bruises. The **TEN-4 FACESp** mnemonic is useful for when to suspect abuse in children under 4 years of age: torso, ear, neck, frenulum, angle of jaw, cheeks [fleshy], eyelids, subconjunctivae, and patterned, as well as *any* bruise in children under 4 months, helps identify suspicious bruises. This prediction rule is 95.6% sensitive and 87.1% specific for identifying abuse.

Table 17.1 Injury Patterns

METHOD OF INJURY/ IMPLEMENT	PATTERN OBSERVED
Grip/grab	Relatively round marks that correspond to fingertips and/or thumb
Closed-fist punch	Series of round bruises that correspond to the knuckles of the hand
Slap	Parallel, linear bruises (usually petechial) separated by areas of central sparing
Belt/electrical cord	Loop marks or parallel lines of petechiae (the width of the belt/cord) with central sparing, may see triangular marks from the end of the belt, small circular lesions caused by the holes in the tongue of the belt, and/or a buckle pattern
Rope	Areas of bruising interspersed with areas of abrasion
Other objects/ household implements	Injury in shape of object/implement (e.g., rods, switches, and wires cause linear bruising)
Human bite	Two arches forming a circular or oval shape, may cause bruising and/or abrasion
Strangulation	Petechiae of the head and/or neck, including mucous membranes; may see subconjunctival hemorrhages
Binding/ligature	Marks around the wrists, ankles, or neck; sometimes accompanied by petechiae or edema distal to the ligature mark
Punishment by kneeling on salt or other rough substance	Abrasions/burns, especially to knees
Hair pulling	Traumatic alopecia; may see petechiae on underlying scalp or swelling or tenderness of the scalp (from subgaleal hematoma)
Tattooing or intentional scarring	Abusive cases have been described but can also be a cultural phenomenon (e.g., Māori body ornamentation); may also be a symbol of ownership in a youth being sexually trafficked

In nonmobile infants, bruises are considered a **sentinel injury** because of the low likelihood of noninflicted injury. Bruises are the most common injury to be missed or misdiagnosed among children who later present with fatal or near-fatal injuries. Other sentinel injuries include oropharyngeal injuries in children <6 months of age and subconjunctival hemorrhage in healthy children under 4 years of age.

Conditions such as birthmarks, including slate gray nevus (congenital dermal melanocytosis or Mongolian spots), can be confused with bruises and abuse. Other mimics are noted in Table 17.2. These skin markings are not tender and do not rapidly change color or size. An underlying medical explanation for bruises may exist, such as blood dyscrasias (hemophilia) or connective tissue disorders (Ehlers-Danlos syndrome). The history or examination usually provides clues to these conditions. Hemorrhagic edema of infancy and IgA vasculitis (Henoch-Schönlein purpura) is the most common vasculitis in young

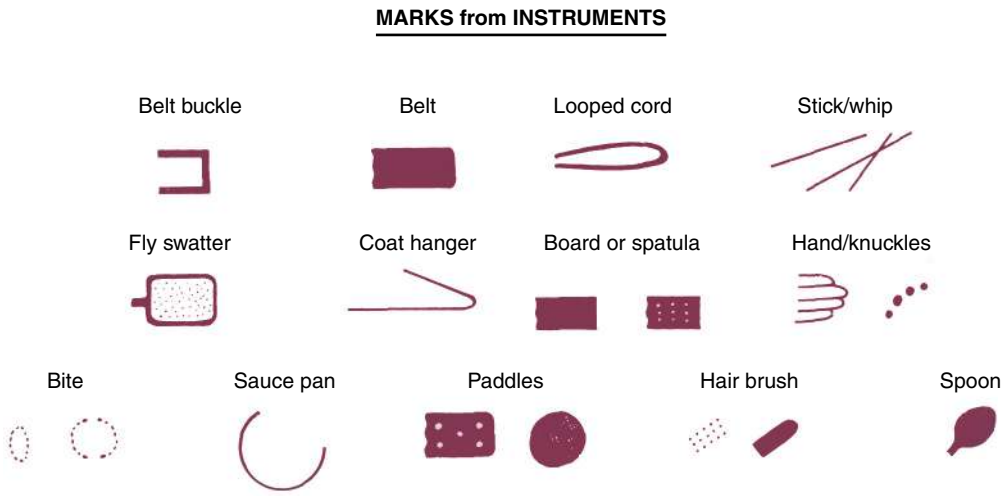

Fig. 17.1 A variety of instruments may be used to inflict injury on a child. Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury.

children, and may be confused with abuse. The pattern and location of bruises caused by abuse are usually different from those caused by a coagulopathy. Noninflicted bruises are characteristically anterior and over bony prominences, such as shins and foreheads. However, the *presence of a medical disorder does not preclude abuse*.

Cultural practices can cause bruising. Cao gio, or coining, is a Southeast Asian folkloric therapy. A hard object is vigorously rubbed on the skin, causing petechiae or purpura. *Cupping* is another approach, popular in the Middle East. A heated glass is applied to the skin, often on the back. As it cools, a vacuum forms, leading to perfectly circular bruises. The context here is important, and such circumstances should not be considered abusive (see Chapter 12).

A careful history of bleeding problems in the patient and first-degree relatives is needed. If a bleeding disorder is suspected, a complete blood count, including platelet count, prothrombin time, and partial thromboplastin time, should be obtained. More extensive testing, such as for factors VIII, IX, and XIII activity and von Willebrand disease, should be considered in consultation with a hematologist.

Bites have a characteristic pattern of one or two opposing arches with multiple bruises. They can be inflicted by an adult, another child, an animal, or the patient. Forensic odontologists developed guidelines for distinguishing adult from child and human from animal bites. However, several recent studies have identified problems with the accuracy and consistency of bite mark analysis.

Burns may be inflicted, noninflicted, or the result of inadequate supervision. Scalding burns may result from immersion or splash. *Immersion burns,* when a child is forcibly held in hot water, show a clear delineation between the burned and healthy skin and uniform depth (Fig. 17.2). They may have a sock or glove distribution. Splash marks are usually absent, unlike when a child inadvertently encounters hot water. Symmetric burns are strongly suggestive of abuse, as are burns of the buttocks and perineum. Although most often noninflicted, splash burns may also result from abuse. Burns from hot objects such as curling irons, radiators, steam irons, metal grids, hot knives, and cigarettes leave patterns indicating the object (Fig. 17.3). A child is likely to try to rapidly escape from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and suggest abuse.

Several conditions mimic abusive burns, such as brushing against a hot radiator, car seat burns, congenital insensitivity to pain syndromes, and folk remedies such as moxibustion. Impetigo may resemble cigarette burns. Cigarette burns are usually 7-10 mm across, whereas impetigo has lesions of varying size. Noninflicted cigarette burns are usually oval and superficial.

Neglect frequently contributes to childhood burns. Children left home alone may be burned in house fires. A parent taking drugs may cause a fire and be unable to protect a child. Exploring children left unattended may pull hot liquids onto themselves. Liquids cool as they flow downward so that the burn is most severe and broad proximally, often in an inverted triangle pattern. If the child is wearing a diaper or clothing, the fabric may absorb the hot water and cause burns worse than otherwise expected. Burns through clothing tend to have an irregular pattern. Some circumstances are difficult to foresee, and a single burn resulting from a momentary lapse in supervision should not automatically be construed as neglect.

Concluding whether a burn was inflicted depends on the history, burn pattern, and the child's capabilities. A delay in seeking healthcare may result from the burn initially appearing minor, before blistering or becoming infected. This circumstance may represent reasonable behavior and should not be automatically deemed neglectful. A scene investigation by law enforcement is often valuable (e.g., testing the water temperature).

Fractures that strongly suggest abuse include those of the posterior ribs, scapula, sternum, and spinous processes and classic metaphyseal lesions—especially in young children (Table 17.3). These fractures all require more force than would be expected from a minor fall or routine handling and activities of a child. Rib and sternal fractures rarely result from cardiopulmonary resuscitation, even when performed by untrained adults. The recommended two-finger or two-thumb technique for infants may, however, produce anterolateral rib fractures. Most common in abused infants are rib (Fig. 17.4), metaphyseal (Fig. 17.5), and skull fractures. Femoral and humeral fractures in nonambulatory infants are also very worrisome for abuse. In contrast, with increasing mobility and running, toddlers can fall with enough rotational force to cause a spiral, femoral fracture. Multiple fractures in various stages of healing are suggestive of abuse. In some circumstances, such as when there are multiple or repeated fractures or a family history of such, underlying medical conditions need to be considered. Clavicular, femoral, supracondylar humeral, and distal extremity fractures in children older than 2 years are most likely noninflicted unless they are multiple or accompanied by other signs of abuse. Few fractures are pathognomonic of abuse; all must be considered together with the history and child's development.

The differential diagnosis includes conditions that increase susceptibility to fractures, such as osteopenia and osteogenesis imperfecta, metabolic and nutritional disorders (e.g., scurvy, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, and neoplasia (see Table 17.2). Some have pointed to possible rickets and low but subclinical levels of vitamin D as being responsible for fractures thought to be due to abuse. The evidence, however, refutes this supposition. Features of congenital or metabolic conditions

Table 17.2 Mimics of Nonaccidental Trauma

CUTANEOUS LESIONS
Accidental trauma
Congenital coagulation defects (hemophilia, von Willebrand disease)
Acquired coagulation defects (aplastic anemia, ITP, leukemia, vitamin K deficiency)
Ehlers-Danlos syndrome
Vitamin C deficiency
Impetigo
Vasculitis (IgA vasculitis: Henoch-Schönlein purpura)
Dermal melanocytosis (Mongolian spots)
Cupping
Coining
Spooning
SKELETAL LESIONS
Osteogenesis imperfecta
Obstetric trauma
Caffey disease
Rickets (not just low 25-hydroxy-vitamin D levels)
Hyper-IgE syndrome
Recurrent multifocal osteomyelitis
Skeletal dysplasias
HEAD TRAUMA
Birth trauma
Hemophilia
Factor XIII deficiency
Vitamin K deficiency (malabsorption)
Cobalamin C defect
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Glutaric aciduria type I
Menkes syndrome
Vasculitis (primary CNS, systemic)
Benign enlargement of subarachnoid spaces

ITP, Immune thrombocytopenic purpura; IgA, immunoglobulin A; IgE, immunoglobulin E; CNS, central nervous system.

associated with noninflicted fractures include family history of recurrent fractures after minor trauma, abnormally shaped cranium, dentinogenesis imperfecta, blue sclera, impaired hearing, craniotabes, ligamentous laxity, bowed legs, hernia, and translucent skin. *Subperiosteal new bone formation* is a nonspecific finding seen in infectious, traumatic, and metabolic disorders. In young infants, new bone formation may be a normal physiologic finding; it is usually bilateral, symmetric, and less than 2 mm in depth.

The evaluation of a fracture should include a skeletal survey in children less than 24 months of age when abuse seems possible (Table 17.4). Multiple radiographs with different views are needed; "babygrams" (one or two films of the entire body) should be avoided. If a fracture is found or when the survey is normal but concern for an occult injury remains, a follow-up survey should be completed 2 weeks later, as it may reveal fractures not apparent initially. Omission of skull, spine, and pelvis films on repeat survey reduces radiation exposure while still capturing most occult fractures.

In corroborating the history and the injury, the age of a fracture can be crudely estimated (Table 17.5). Soft tissue swelling subsides in 2-21 days. Subperiosteal new bone is visible within 4-21 days. Loss of definition of the fracture line and visible soft callus formation occur on a similar timeline. Hard callus is visible between 14 and 90 days. These ranges are shorter in infancy and longer in children with poor nutritional status or a chronic underlying disease. Fractures of flat bones such as the skull do not form a callus and cannot be aged, although soft tissue swelling indicates recency (i.e., within the prior week).

Abusive head trauma (AHT) results in significant morbidity and mortality. Abusive injury may be caused by direct impact, asphyxia, shaking, or a combination. Subdural hematomas (Fig. 17.6); retinal hemorrhages, especially when extensive and involving multiple layers; brain parenchymal injury; and fractures (often rib and classic metaphyseal lesions) strongly suggest AHT, especially when they occur together. Infants' poor neck muscle tone and relatively large heads make them vulnerable to acceleration-deceleration forces if severely shaken, leading to AHT. Children may lack external signs of injury, even with serious intracranial trauma. The clinical presentation varies, ranging from nonspecific lethargy, to vomiting (without diarrhea), changing neurologic status or seizures, or coma. In all preverbal children, the possibility of AHT should be considered when children present with these signs or symptoms.

Acute intracranial trauma is best evaluated via CT. CT helps identify bone and soft tissue injury. Some centers use fast-sequence MRI to reduce radiation exposure, but the sensitivity may not be as good as CT. MRIs are helpful in differentiating extraaxial fluid, determining the approximate time of injuries, assessing parenchymal injury, and identifying vascular anomalies. Neck imaging may identify spinal subdural blood and ligamentous, spinal cord, and nerve root injuries. MRIs are best obtained 5-7 days after an acute injury. Other causes of subdural hemorrhage in infants include arteriovenous malformations, coagulopathies, birth trauma, tumor, and infections (see Table 17.2). Glutaric aciduria type 1 can present with intracranial bleeding and should be considered. When AHT is suspected, possible injuries elsewhere—especially skeletal and abdominal—should be ruled out.

Retinal hemorrhages are an important marker of AHT (Fig. 17.7). Whenever AHT is being considered, a dilated indirect eye examination by a pediatric ophthalmologist should be performed. Although retinal hemorrhages can be found in other conditions, hemorrhages that are multiple, involve more than one retinal layer, and extend to the periphery are very suspicious for abuse. The mechanism is likely repeated acceleration-deceleration caused by shaking. Traumatic retinoschisis points strongly to abuse.

With other causes of retinal hemorrhages, the pattern is usually different from that seen in child abuse. After birth, many newborns have them, but they disappear by 2-6 weeks. Coagulopathies (particularly leukemia), retinal diseases, carbon monoxide poisoning, and glutaric aciduria may be responsible. Severe noninflicted direct crush injury to the head can rarely cause an extensive hemorrhagic retinopathy. Cardiopulmonary resuscitation rarely, if ever, causes retinal hemorrhages in infants and children; if present, there are only a few hemorrhages in the posterior pole. Hemoglobinopathies, diabetes mellitus, routine play, minor noninflicted head trauma, and vaccinations do not appear to cause retinal hemorrhage in children. Severe coughing or seizures rarely cause retinal hemorrhages that could be confused with AHT.

The dilemma frequently posed is whether minor, everyday forces can explain the findings seen in AHT. Simple linear skull fractures in the absence of other suggestive evidence can be explained by a short fall, although even that is unusual (1–2%); underlying brain injury from short falls is exceedingly rare. Timing of brain injuries in cases of abuse is not precise. In fatal cases, however, the trauma most likely occurred very soon before the child became symptomatic.

Other manifestations of AHT may be seen. *Raccoon eyes* are associated with subgaleal hematomas after traction on the anterior hair and scalp or a blow to the forehead. Neuroblastoma can present similarly. Bruises from attempted strangulation may be visible on the neck. Choking or suffocation can cause hypoxic brain injury, often with no external signs.

Oral lesions may present as bruised lips, bleeding, torn frenulum, and dental trauma or multiple caries (neglect).

Abdominal trauma also accounts for significant morbidity and mortality in abused children. Young children are especially vulnerable because of their relatively large abdomens and lax abdominal musculature. A forceful blow or kick can cause hematomas of solid organs (liver, spleen, kidney) from compression against the spine, as well as hematomas (duodenal) or rupture (stomach) of hollow organs. Intra-abdominal bleeding may result from trauma to an organ or from



Fig. 17.2 Immersion injury patterns. A, Sparing of flexural creases. B, Immersion "sock" burn. C, Immersion "glove" burn. D, Immersion buttocks burn. *(From Jenny C. Child abuse and neglect: diagnosis, treatment, and evidence. Philadelphia: Saunders;2011: Fig. 28-3, p. 225.)*

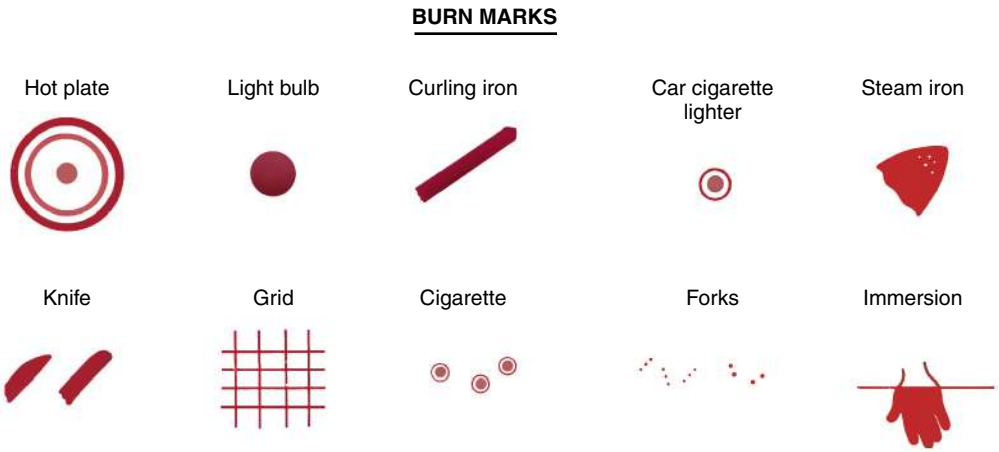

Fig. 17.3 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly or for a long time.

Table 17.3 Specificity of Radiologic Findings

HIGH SPECIFICITY*
Classic metaphyseal lesions
Rib fractures, especially posteromedial
Scapular fractures
Spinous process fractures
Sternal fractures
MODERATE SPECIFICITY
Multiple fractures, especially bilateral
Fractures of different ages
Epiphyseal separations
Vertebral body fractures and subluxations
Digital fractures
Complex skull fractures
Pelvic fractures
COMMON BUT LOW SPECIFICITY
Subperiosteal new bone formation
Clavicular fractures
Long bone shaft fractures
Linear skull fractures

*Highest specificity applies in infants
From Kleinman PK. *Diagnostic imaging of child abuse,* 3rd ed. Cambridge, UK: Cambridge University Press;2015: 24.

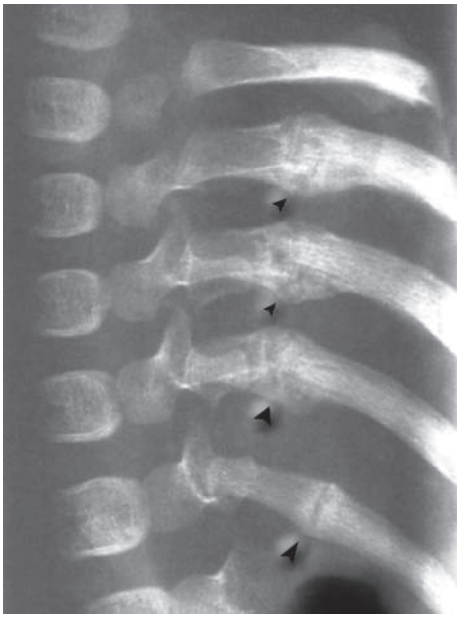

Fig. 17.4 High detail oblique view of the ribs of a 6-month-old infant shows multiple healing posteromedial rib fractures *(arrowheads).* The level of detail in the image is far greater that what would be present on a standard chest radiograph. *(From Dwek JR. The radiographic approach to child abuse. Clin Orthop Relat Res. 2011;469:776–789, Fig. 4.)*

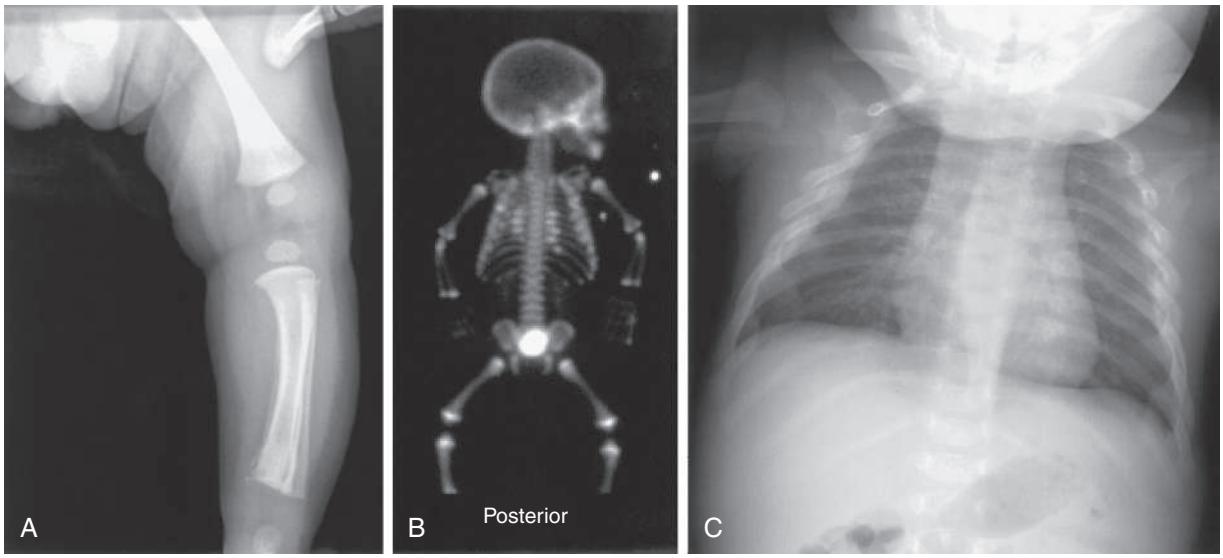

Fig. 17.5 **A,** Metaphyseal fracture of the distal tibia in a 3-month-old infant admitted to the hospital with severe head injury. There is also periosteal new bone formation of the tibia, perhaps from previous injury. **B,** Bone scan of the same infant. The initial chest x-ray showed a single fracture of the right posterior fourth rib. A radionuclide bone scan performed 2 days later revealed multiple previously unrecognized fractures of the posterior and lateral ribs. **C,** Follow-up radiograph 2 weeks later showed multiple healing rib fractures. This pattern of fractures is highly specific for child abuse. The mechanism of these injuries is usually violent squeezing of the chest.

Table 17.4 Radiologic Skeletal Survey for Infants and Children under 2 Years of Age*

- Anteroposterior (AP) and lateral views of skull (Townes view optional; add if any fracture seen)
- Lateral spine (cervical spine [C-spine] may be included on skull radiographs; AP spine is included on AP chest and AP pelvis views to include entire spine)
- AP view, right posterior oblique, left posterior oblique view of chest-rib technique
- AP pelvis
- AP view of each femur
- AP view of each leg
- AP view of each humerus
- AP view of each forearm
- Posteroanterior (PA) view of each hand
- AP (dorsoventral) view of each foot

*Images are checked by a radiologist before the patient leaves. Poorly positioned or otherwise suboptimal images should be repeated. Lateral views are added for positive or equivocal findings in the extremities. Coned views of positive or equivocal findings (i.e., at ends of long bones, ribs) may be obtained.
Adapted from Coley BD. *Caffey's pediatric diagnostic imaging*, 12th ed. Philadelphia: Mosby;2013: Box 144-1, p. 1588.

Table 17.5 Timetable of Radiologic Changes in Children's Fractures*

CATEGORY	EARLY	PEAK	LATE
1. SPNBF	4-10 days	10-14 days	14-21 days
2. Loss of fracture line definition, days		10-14 days	14-21 days
3. Soft callus		10-14 days	14-21 days
4. Hard callus	14-21 days	21-42 days	42-90 days

The time points tend to increase from early infancy into childhood.
*Repetitive injuries may prolong all categories.
SPNBF, Subperiosteal new bone formation.
From Kleinman PK. *Diagnostic imaging of child abuse*, 3rd ed. Cambridge, UK: Cambridge University Press;2015: p. 215.

shearing of a vessel. More than one organ may be affected. Children may present with cardiovascular failure or an acute abdomen, often after a delay in care. Bilious vomiting without fever or peritoneal irritation suggests a duodenal hematoma, often the result of abuse.

The manifestations of abdominal trauma are often subtle, even with severe injuries. Bruising of the abdominal wall is unusual, and symptoms may evolve slowly. Delayed perforation may occur days after the injury; bowel strictures or a pancreatic pseudocyst can develop weeks or months later. PCPs should consider screening for occult abdominal trauma when other evidence of physical abuse exists. Screening should include liver and pancreatic enzyme levels and testing urine for blood. When results indicate possible injury or if there is concern about possible splenic, adrenal, or hepatic injury, an abdominal CT is indicated.

Neglect is the most prevalent form of child maltreatment, with potentially severe and lasting sequelae. It may manifest in many ways, depending on which basic needs are not adequately met. Nonadherence to medical treatment, for example, may aggravate the condition, as may a delay in seeking healthcare. Inadequate food may manifest as impaired growth; inattention to obesity is also a problem. Poor hygiene may contribute to infected cuts or lesions. Inadequate supervision contributes to injuries and ingestions. Children's needs for mental healthcare, dental care, and other healthcare may be inadequately met, manifesting as neglect. Educational needs, particularly for children with learning disabilities, are often not adequately met.

GENERAL PRINCIPLES FOR ASSESSING POSSIBLE PHYSICAL ABUSE AND NEGLECT

The heterogeneity of circumstances in situations of child maltreatment precludes specific detailing of varied assessments. The following are useful general principles:

- Given the complexity and possible ramifications of determining child maltreatment, an **interdisciplinary assessment** is optimal, with input from all involved professionals. Consultation with a physician expert in child abuse pediatrics is recommended.
- A thorough **history** should be obtained from the parent(s), optimally via separate interviews.
- Verbal children should be interviewed separately in a developmentally appropriate manner. **Open-ended questions** (e.g., "Tell me what happened") are best. Some children need more directed

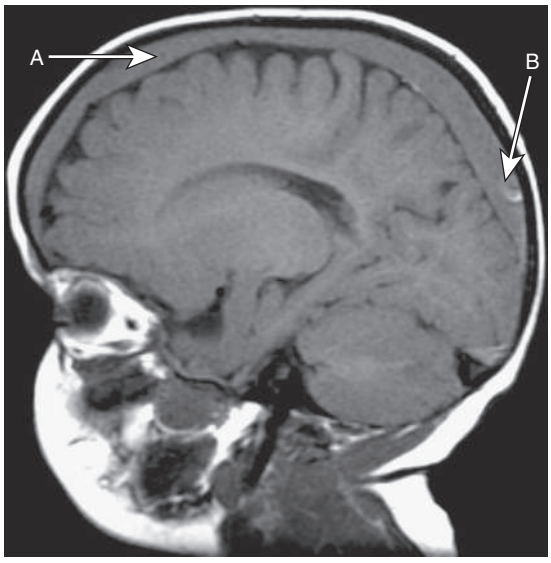

Fig. 17.6 CT scan indicating intracranial bleeding. *A*, Older blood. *B*, New blood.

questioning (e.g., "How did you get that bruise?"); others need multiple-choice questions. Leading questions must be avoided (e.g., "Did your daddy hit you?").

- A thorough **physical examination** is necessary.
- Careful **documentation** of the history and physical is essential. Verbatim quotes are valuable, including the question that prompted the response. Photographs are helpful.
- For **abuse**, the assessment should answer these questions: What is the evidence for concluding abuse? Have other diagnoses been ruled out? What is the likely mechanism of the injury? When did the injury likely occur?
- For **neglect**, the assessment should answer these questions: Do the circumstances indicate that the child's needs have not been adequately met? Is there evidence of actual harm? Is there evidence of potential harm and on what basis? Suboptimal treatment adherence may not be ideal but lead to few or no consequences. What is the nature of the neglect? Is there a pattern of neglect?
- It may be **difficult to be certain** regarding the likelihood of abuse or neglect. The use of "possible" or "probable" is recommended when uncertain. Inadequacies in the care children receive naturally fall along a continuum, requiring a range of responses tailored to the individual family's situation. Legal considerations or CPS practice may discourage PCPs from labeling many circumstances as neglect. Even if neglect does not meet a threshold for referring to CPS, professionals can still help ensure children's needs are adequately met.
- Are there indications of **other forms of maltreatment**? Has there been prior CPS involvement?
- A child's **safety** is a paramount concern. What is the risk of imminent harm and of what severity?
- What is contributing to the maltreatment? Consider the categories described in the section on etiology.
- What **strengths/resources** are there? This is as important as identifying problems.
- What **treatment or services** do the child and family need? What interventions have been tried and with what results? Knowing the nature of these interventions can be useful, especially from the parent's perspective.
- What is the **prognosis**? Is the family motivated to improve the circumstances and accept help, or are they resistant? Are needed resources, formal and informal, available?
- Are there **other children** in the home who should be assessed for maltreatment?

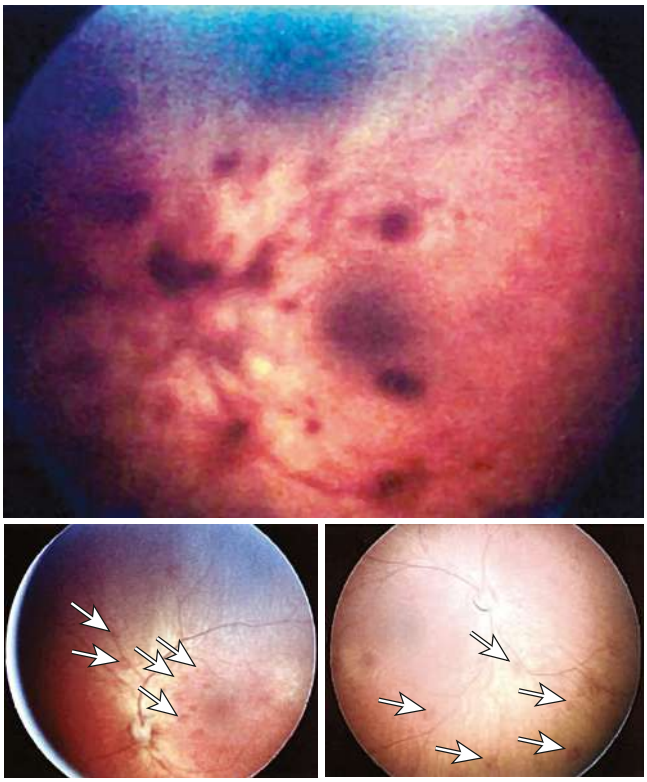

Fig. 17.7 Retinal hemorrhages. *Arrows* point to hemorrhages of varying sizes.

GENERAL PRINCIPLES FOR ADDRESSING PHYSICAL ABUSE AND NEGLECT

The heterogeneity of circumstances also precludes specific details regarding how to address different types of maltreatment. The following are general principles:

- Treat any medical problems.
- Help ensure the child's safety, often in conjunction with CPS; this is a priority. In some instances, hospitalization is the prudent approach.
- Convey concerns of maltreatment to parents, kindly but forthrightly. Avoid blaming. It is natural to feel anger towards parents of maltreated children, but they need support and deserve respect.
- Have a means of addressing the difficult emotions child maltreatment can evoke in us. Self-care is important.
- Be empathic and state interest in helping or suggest another healthcare professional.
- Know the laws and/or local CPS policies on referring child maltreatment. In the United States, the legal threshold for referring is typically "reason to believe" (or "reason to suspect"); one does not need to be certain. Physical abuse and moderate to severe neglect warrant a referral. In less severe neglect, less intrusive interventions may be an appropriate initial response. For example, if an infant's mild failure to gain sufficient weight is caused by an error in mixing the formula, parent education and perhaps a visiting nurse should be tried. In contrast, severe growth faltering may require hospitalization, and, if the contributing factors are particularly serious (e.g., a psychotic mother), out-of-home placement may be needed. CPS can assess the home environment and provide valuable insights.
- Referring child maltreatment to public agencies is never easy. Parental inadequacy or culpability is at least implicit, and parents may become angry. PCPs should supportively inform families directly of the referral to CPS; it can be explained constructively as an effort to clarify the situation and provide help, as well as a professional (and legal) responsibility. Words matter, and "referral" avoids the stigma of "report," and it is what we commonly

do in healthcare. Explaining what the ensuing process is likely to entail (e.g., a visit from a CPS worker and sometimes a police officer) may ease a parent's anxiety. Parents are frequently concerned that they might lose their child. PCPs can cautiously reassure parents that CPS is responsible for helping children and families and that, in most instances, children remain with their parents. When CPS does not accept a referral or when it is not substantiated, they may still facilitate supportive services such as food, shelter, parenting resources, and childcare. PCPs can be a useful liaison between the family and the public agencies and should try to remain involved after referring to CPS.

- Help address contributory factors, prioritizing those that are most important to the family and amenable to being remedied. Concrete needs should not be overlooked; accessing food programs, obtaining health insurance, enrolling children in preschool, and help finding housing can make a valuable difference. Parents may need their own problems addressed to enable them to adequately care for their children.
- Establish specific objectives (e.g., no hitting, diabetes will be adequately controlled), with measurable outcomes (e.g., urine dipsticks, hemoglobin A_{1c}). Similarly, advice should be specific and limited to a few reasonable steps. A written (and perhaps signed) contract can help establish the agreed-upon plan and help ensure it pans out.
- Engage the family in developing the plan—solicit their input and agreement. Motivational interviewing (MI) offers a fundamentally different approach to working with parents (and older children and teens), forging a partnership, and understanding their perceptions of an issue and how they think they can address it. Knowledge and skills regarding MI can enhance the effectiveness of PCPs (see Chapter 18).
- Deliberately identify protective factors or strengths—within and outside the family; there are always some. Incorporating these in one's approach is a valuable way to engage parents and ensure plans get implemented.
- Encourage informal supports (e.g., family, friends; invite fathers to office visits). This is where most people get their support, not from professionals. Consider support available through a family's religious affiliation.
- Consider children's specific needs. Too often, maltreated children do not receive needed services.
- Be knowledgeable about community resources and facilitate appropriate referrals. Consider how to help ensure referrals pan out.
- Provide support, follow-up, and review of progress, and adjust the plan if needed.
- Recognize that maltreatment often requires long-term intervention with ongoing support and monitoring.

PREVENTION OF PHYSICAL ABUSE AND NEGLECT

An important aspect of prevention is that many of the efforts to strengthen families and support parents should promote children's health, development, well-being, and safety and prevent maltreatment. Medical responses to child maltreatment have typically occurred after the fact; preventing the problem is preferable. PCPs can help in several ways. An ongoing relationship offers opportunities to develop trust and knowledge of a family's circumstances. Astute observation of parent–child interactions can reveal useful information.

Parent and child education regarding medical conditions helps to ensure implementation of the treatment plan and to prevent neglect. Possible barriers to treatment should be addressed. Practical strategies such as writing down the plan can help. In addition, anticipatory guidance helps with positive parenting (see Chapter 20), diminishing the risk of maltreatment. Hospital-based programs that educate parents about caring for a crying infant and the risks of shaking may help prevent AHT.

Screening for and addressing major psychosocial risk factors for maltreatment such as parental depression, substance use, intimate partner violence, major stress, and helping address identified problems, often via referrals, can help prevent maltreatment. Primary care offers excellent opportunities to screen briefly for psychosocial problems. The traditional organ system–focused review of systems can be expanded to probe areas such as feelings about the child, the parent's own functioning, the relationship, possible depression, disciplinary approaches, stressors, and supports. The Safe Environment for Every Kid (SEEK) model offers an evidence-informed approach for pediatric primary care to identify and help address prevalent adverse childhood experiences (ACEs) (e.g., exposure to intimate partner violence, parental depression, or substance use) or social determinants of health (e.g., food insecurity, severe parental stress) that are also risk factors for child maltreatment. This approach should incorporate working with protective factors and use of MI principles in developing a plan jointly with the family.

Obtaining information directly from children or youth is also important, especially given that separate interviews with teens have become the norm. Any concerns identified on such screens require at least a brief assessment and initial management, which may lead to a referral for further evaluation and treatment. More frequent office visits can be scheduled for support and counseling while monitoring the situation. Other key family members (e.g., father, a grandparent) might be invited to participate, thereby encouraging informal support. Some practices arrange parent groups through which problems and solutions are shared. PCPs also need to recognize their limitations and facilitate referrals to other community resources.

ADVOCACY

PCPs can assist in understanding what contributed to a child's maltreatment. When advocating for the best interest of the child and family, addressing contributory factors at the individual, family, and community levels is optimal. At the individual level, an example of advocating on behalf of a child is explaining to a parent that an active toddler is behaving normally and not intentionally annoying the parent. Encouraging a parent to seek help dealing with a violent spouse, saying, for example, "You and your life are very important"; asking about substance use; and helping parents obtain health insurance for their children are all forms of advocacy.

Efforts to improve family functioning, such as encouraging fathers' involvement in the lives of their children, are also examples of advocacy. Remaining involved after a referral to CPS and helping ensure needed services are provided is advocacy as well. In the community, PCPs can be influential advocates for improving resources devoted to children and families. These include parenting programs, services for abused women and children, and recreational facilities. They can be strong advocates for policies and programs at the local, state, and national levels to benefit children and families. The problems underpinning child maltreatment, such as poverty, parental stress, substance use, and limited child-rearing resources, require policies and programs that enhance families' abilities to care for their children at least adequately. Examples in the United States include Medicaid, the Supplemental Nutrition Assistance Program (SNAP), the Women, Infants, and Children (WIC) program, paid family and medical leave, the Earned Income Tax Credit (EITC), and childcare subsidies.

Child maltreatment is a complex problem without simple solutions. Through partnerships with parents and colleagues in child protection, mental health, education, and law enforcement, PCPs can make an enormous difference in the lives of many children and families.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

17.1 Sexual Abuse

Wendy G. Lane and Howard Dubowitz

See also Chapter 162.

Approximately 18% of females and 7% of males in the United States are sexually abused at some point during childhood. Primary care professionals (PCPs) serving children can play several roles in addressing sexual abuse, including identification, referring to child protective services (CPS) and/or law enforcement, testing for and treating sexually transmitted infections, providing support and reassurance, and providing guidance to prevent future sexual abuse. In many jurisdictions throughout the United States, PCPs play a mostly triage role, with the definitive medical evaluation conducted by a child abuse specialist.

DEFINITION

Sexual abuse has been defined as "the involvement of dependent, developmentally immature children and adolescents in sexual activities which they do not fully comprehend, to which they are unable to give consent, or that violate the social taboos of family roles." Sexual abuse includes exposure to sexually explicit materials, oral-genital contact, genital-to-genital contact, genital-to-anal contact, and genital fondling. Any touching of "private parts" by parents or caregivers in a context other than necessary care is inappropriate. It is important to note that sexual abuse does not have to involve direct touching or physical contact by the perpetrator. Showing pornography to a child, filming or photographing a child in sexually explicit poses, and encouraging or forcing a child to perform sex acts on another all constitute sexual abuse. When these acts occur for financial gain or in exchange for something of value, it is considered sexual exploitation. Recruiting, enticing, harboring, transporting, providing, obtaining, and/or maintaining a minor for the purpose of engaging in sexual acts are forms of sex trafficking (see Chapter 16), a subset of sexual exploitation.

Some legal definitions distinguish sexual abuse from sexual assault; the former being committed by a parent or caregiver or household member, and the latter being committed by someone without a custodial or any relationship to the child. For this chapter, the term *sexual abuse* encompasses abuse, assault, and exploitation.

PRESENTATION OF SEXUAL ABUSE

Because physical findings are uncommon and behavioral findings are often nonspecific, a more reliable means of identifying sexual abuse is through a child's history. Some children provide a clear, spontaneous description of abuse to a trusted adult. Other children provide less clear histories, such as not wanting to visit a particular person's home or vaguely saying "something bad happened." Preschool-aged children and those with limited language skills may be developmentally unable to provide details about sexual acts or timing. Such lack of detail may unfortunately dissuade adults from trusting the account and referring. Because PCPs are mandated reporters, they should have a low threshold for referring young children.

Sexual abuse may be discovered when another person witnesses the abuse or discovers evidence such as sexually explicit photographs or videos. There are also children, with and without symptoms, who will not be identified at any point during their childhood, and perhaps never.

Behavioral changes may be the first indication of possible abuse. Children may exhibit **sexually explicit behavior** outside the norm for their age and developmental level. It can be tricky to distinguish normal from concerning behavior, especially given children's increasing and prevalent exposure to sexual material and information over recent decades. For preschool- and school-age children, behavior thought to be normal includes curiosity about their own body and differences between boys and girls. Touching their own genitals, masturbation, and undressing in front of others are also common. Worrisome sexual behavior includes compulsive masturbation (i.e., continuing in public areas even after being told to stop), attempting to perform sex acts on adults or other children, or asking adults or children to perform sex acts on them. Teen sexual behavior thought to be normal includes interest in media with sexual themes, looking up sexual information on the internet, demanding more privacy, masturbation, and sexual contact with teens of the same or opposite sex. Worrisome teenage behaviors include sexual promiscuity, engaging in prostitution, and engaging in sexual acts with younger children or with animals. Sexting has become common among teenagers and requires a discussion between parents and teens about its risks. Sexting that involves extortion or trafficking is very concerning; in many states trafficking requires mandated reporting to CPS.

It is important to recognize that in addition to sexual abuse, some sexualized behavior could also result from other exposure (e.g., a child who enters their parents' bedroom at night to find their parents having sex), from neglect (e.g., parents watching pornographic movies where a child can see them), from exposure to sexual behavior by other children who may have been abused or exposed to inappropriate sexual behavior or materials, or from information discussed and shared by peers.

A number of other behavior changes, although not specific for sexual abuse, are common among children who have been sexually abused. These include social withdrawal, acting out, increased clinginess or fearfulness, distractibility, learning difficulties, and behavioral regression such as secondary enuresis. Teenagers may become depressed, experiment with drugs or alcohol, or run away from home. Therefore sexual abuse should usually be considered when addressing a wide variety of child behavior and mental health problems.

Physical signs of sexual abuse are uncommon and are seen in only about 5% of children who undergo medical examination, usually soon after the abuse occurred. The absence of physical findings can often be explained by the type and timing of sexual contact. Abusive acts such as fondling or even digital penetration may not cause any injury. In addition, many children do not disclose abuse until days, weeks, months, or even years after the abuse occurred. Because genital injuries usually heal within days, injuries are generally not seen by the time a child presents for medical evaluation. Clearly, a normal genital exam does not rule out the possibility or probability of abuse and should not influence the decision to refer to CPS. Physical findings that may indicate sexual abuse include genital or anal pain, anogenital bleeding, or discharge. Sexually transmitted infections (STIs), including gonorrhea, chlamydia, and trichomonas beyond the neonatal period, are highly suspicious for abuse. Pregnancy, too, may be the result of abuse. Rarely, there are physical signs of healed trauma, such as a complete hymenal transection (i.e., part of the posterior hymen is missing).

All 50 U.S. states mandate that professionals refer suspected sexual abuse to CPS, and many require reporting of sex trafficking. The specific criteria or threshold for "reason to suspect" is generally not defined by state law. Clearly, referrals do not require certainty that abuse occurred. Therefore it may be appropriate to refer a child with worrisome sexual behavior when no alternative explanation is plausible and the child does not clearly confirm or deny abuse.

THE ROLE OF THE PCP IN ASSESSING AND ADDRESSING POSSIBLE SEXUAL ABUSE

Speaking with parents about possible abuse: When a parent raises concern for sexual abuse, PCPs should have the child leave the room before obtaining additional information from the parent alone to avoid influencing the child. The child healthcare professional should gather details regarding the parent's concern to help discriminate between possible sexual abuse and other behavioral or health issues. For example, parents may be worried about a child's normal sexual behavior, or they may assume that a nonspecific finding such as vulvar irritation is the result of abuse. In these situations, reassurance and treatment

of the medical issue may suffice. PCPs should document the parental concerns, clearly indicating the source of the information. If a child reported abuse to a parent, documentation should include what questions the parent asked to elicit the disclosure or what triggered it. Additional evaluation should include a review of systems for behavioral and urogenital problems. Parents should be asked whether there are other children in the home, school, or childcare who may have been exposed to the alleged offender; this information should be shared with CPS, as these children may benefit from a precautionary interview or exam at the local child advocacy center (CAC). Parents who have experienced sexual abuse themselves may disclose this information to the child healthcare professional, and they may have a heightened concern about abuse of their children and the sequelae. In these situations, the PCP should discuss mental health services for the parent. Some states require reporting of sexual abuse even when the survivor is an adult.

Speaking with children about possible abuse: Children with suspected sexual abuse may present to the PCP's office with a clear history of abuse or more subtle indicators. A private, brief conversation between PCP and child provides an opportunity for the child to speak in their own words. Doing this may be especially important when the parent does not believe or support the child. Telling parents that a private conversation is standard in such circumstances can be reassuring.

When speaking with a child, it is essential to **first establish rapport**, starting with general and open-ended questions; for example: "Tell me about school" and "What are your favorite things to do?" It helps to explain the purpose of the evaluation and why it is being done. For example, "Your mom is worried that someone may have hurt you and we want to make sure you're healthy and safe." Questions about sexual abuse should focus on **a minimally adequate history** (i.e., gathering enough information to determine if sexual abuse may have happened and whether there is a need to refer to CPS). If a referral is made to CPS, a multidisciplinary investigation will likely be initiated, including an extensive forensic interview. Questions should also be nonleading (e.g., avoid asking questions such as "who touched you there?"). It helps to explain that sometimes children are hurt or bothered by others and that one wonders whether that might have happened to the child. Open-ended questions, such as "Can you tell me more about that?" allow the child to add information and clarification in their own words. The PCP should document the child's statements in quotation marks and the source. Documenting the questions that elicited the child's response should clarify whether questions were leading or not. Very young children and those with developmental delay may lack the verbal skills to describe what happened. In this situation, the parent's history may provide enough information to warrant a CPS referral without interviewing the child.

Medical referral: Because delayed disclosure is common, most children do not need an urgent expert medical evaluation (Fig. 17.8). Indications for one include recent abuse (i.e., within the past 3-5 days), current pain or bleeding, and severe child or parental emotional distress. It is optimal for children suspected of having been sexually abused to be evaluated in a child-friendly setting and by professionals skilled in this field. Because emergency departments may not have a child abuse expert and can be busy, noisy, and lacking in privacy, examination at an alternative location such as a CAC or outpatient clinic is preferable, when possible. If the exam is not urgent, it is best that the evaluation be done at a time when the child is not tired and cranky.

Referring PCPs should be familiar with the triage procedures in their communities, including the referral sites for both acute and nonacute evaluations, timeframes for when an evaluation is considered acute, and whether there are different referral sites for prepubertal and postpubertal children. Depending on the jurisdiction, the site may be an emergency department, a CAC, or an outpatient clinic. For the *prepubertal child,* if abuse is thought to have occurred in the previous 72 hours and history suggests direct contact, forensic evidence collection (e.g., external genital, vaginal, anal, and oral swabs, sometimes referred to as a *rape kit*) may be indicated, and the

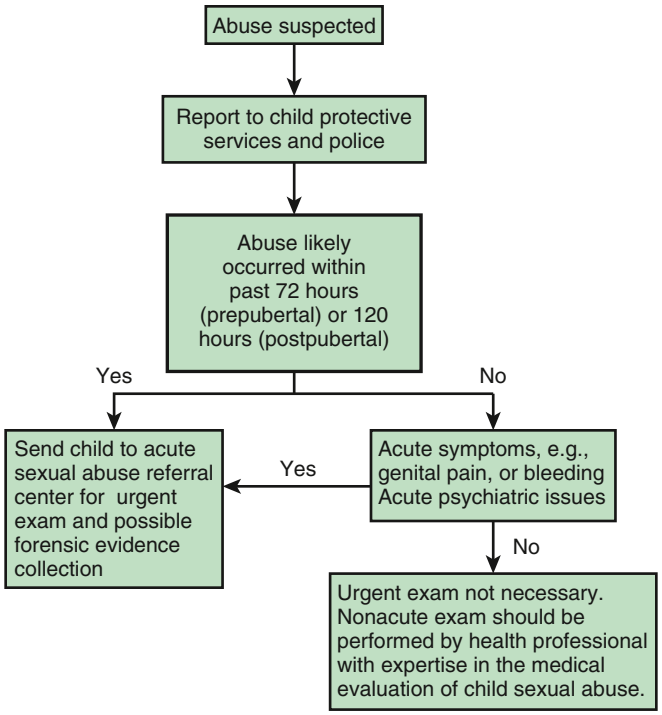

Fig. 17.8 Triage protocol for children with suspected sexual abuse.

child should be referred to a site equipped to do this. Some centers may have shorter or longer cutoffs (e.g., 24 hours or 5 days). If the last suspected incident of abuse occurred more than 72 hours prior, the likelihood of recovering forensic evidence is extremely low, making forensic evidence collection unnecessary. For *postpubertal females,* it is recommended that forensic evidence be collected up to 120 hours after the abuse—as for adult women. The extended timeframe relates to semen possibly remaining in the postpubertal vaginal vault for more than 72 hours. Some jurisdictions extend the time for collecting forensic evidence up to 10-15 days if there has been penetration and possible ejaculation. The National Institute of Justice suggests considering a 9-day time frame based on one study.

Physical examination of the child with suspected sexual abuse: Children suspected of having been sexually abused may benefit from a brief evaluation and examination of their anogenital area to determine whether and when an expert medical evaluation is needed. Unfortunately, many physicians are unfamiliar with genital anatomy, particularly in the prepubertal girl (Figs. 17.9 and 17.10). Nevertheless, signs of trauma such as bruising, abrasions, and bleeding or of infection may be apparent. Because about 95% of children who undergo a medical evaluation after sexual abuse have normal exams, the role of the PCP is often simply to be able to distinguish a normal exam from findings indicative of common medical concerns (e.g., diaper dermatitis) or trauma, or to reassure a parent whose preschooler is touching themself. Unsuspected injuries or medical problems such as labial adhesions, imperforate hymen, or urethral prolapse may be identified. In addition, reassurance about the child's physical health may often allay anxiety for the child and family.

When concerns about sexual abuse arise because of genital findings or complaints, it is important to assess for and rule out medical problems that can be confused with abuse. Several genital findings may raise concern about abuse but often have alternative explanations. For example, genital redness in a prepubertal child is usually caused by nonspecific vulvovaginitis, diaper dermatitis, or infection with a nonsexually transmitted organism such as staphylococcus or

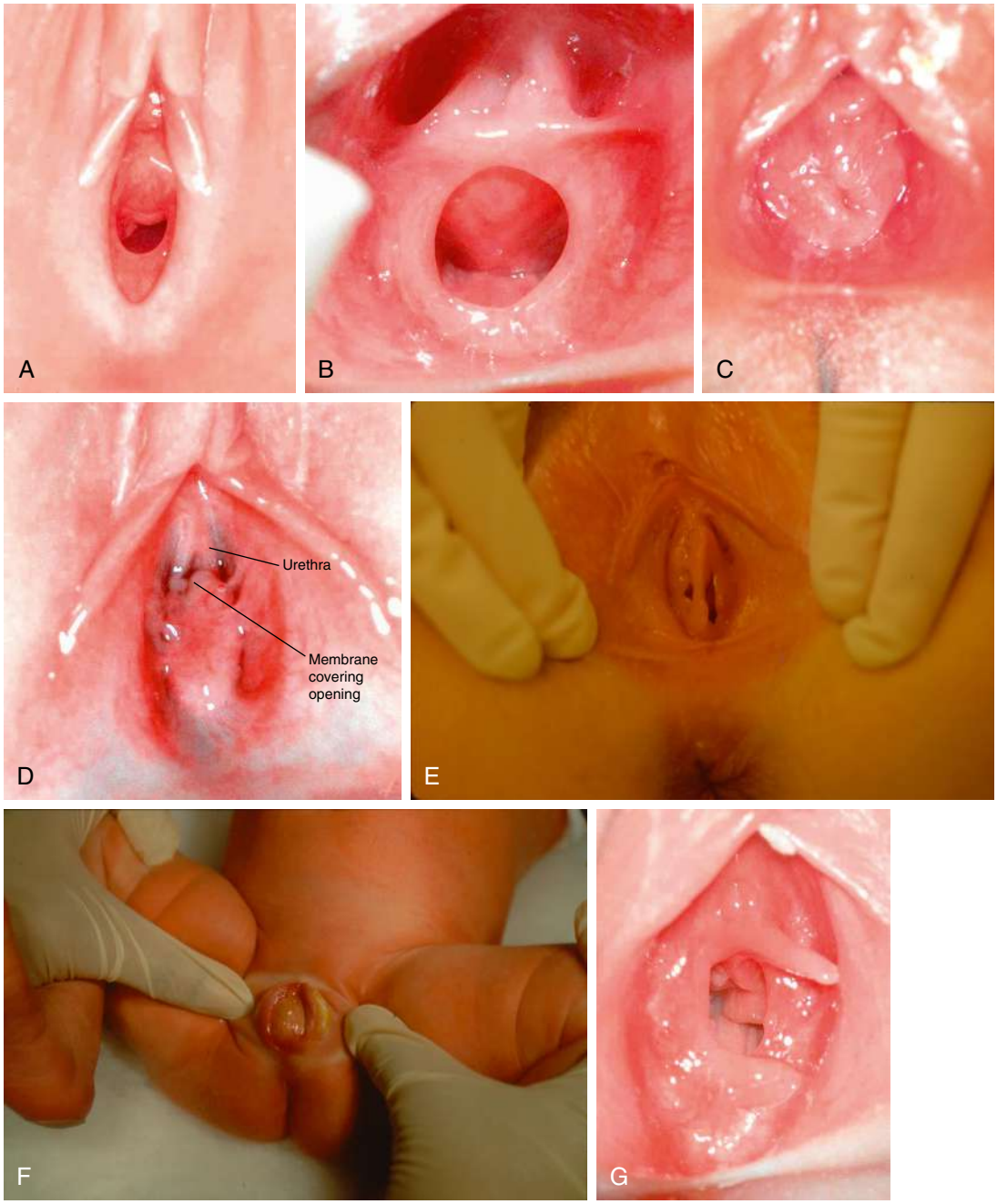

Fig. 17.9 Types of hymens. **A,** Crescentic. **B,** Annular. **C,** Redundant. **D,** Microperforate. **E,** Septated. **F,** Imperforate. **G,** Hymeneal tags. *(A-D and G from McCann JJ, Kerns DL. The Anatomy of Child and Adolescent Sexual Abuse. St. Louis: InterCorp, 1999; E and F from Perlman SE, Nakajima ST, Hertweck SP. Clinical Protocols in Pediatric and Adolescent Gynecology. London: Parthenon Publishing Group, 2004. Figs. 25.5 and 25.9.)*

group A streptococcus. It is often apparent that the diffuse redness is unlikely to be the result of trauma. Lichen sclerosis is an uncommon cause of redness and usually presents with vulvar and/or perianal atrophy and hypopigmentation, often in a figure 8 pattern. Vaginal discharge can be caused by STIs, but also by poor hygiene, foreign body, the onset of puberty, or infection with *Salmonella, Shigella,* or *Yersinia*. Genital ulcers can be caused by herpes simplex virus (HSV) and syphilis, but also by Epstein-Barr virus, varicella-zoster, Crohn's disease, and Behçet's disease. Genital bleeding can be caused by urethral prolapse, vaginal foreign body, or noninflicted trauma.

The medical exam should begin with a general exam of the child. Doing so enables the child to become comfortable with the exam process before the genital exam and may identify other evidence of maltreatment or health problems. For prepubertal children, the parent should be present to provide comfort and reassurance. Older children should be given the option of having a parent present. The American Academy of Pediatrics (AAP) recommends that whenever "private" parts are examined (i.e., genitals, breast, anus), a chaperone should be present. In prepubertal children, this can be a parent. For adolescents, the chaperone should be a clinical staff member, unless the teen objects. If so, the PCP may have a parent be present if all three

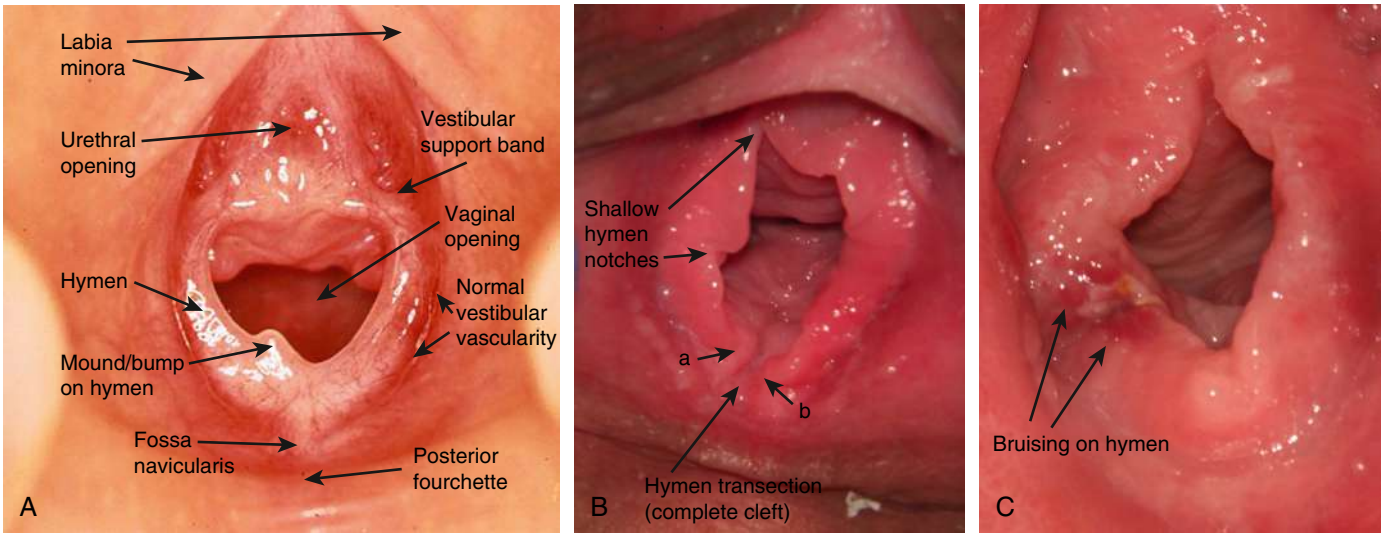

Fig. 17.10 **A,** Photograph taken with a camera attached to colposcope at 10× magnification. Note the increased vascularity and redness in the vestibule adjacent to the hymen on the right and left. This is a normal finding and not to be mistaken for signs of trauma. **B,** Photograph taken with a camera attached to colposcope at 10×magnification shows the appearance of the hymen in an adolescent. Shallow notches in the hymen are evident at the 9 and 11 o'clock positions, as well as hymen transection at approximately 7 o'clock. There is no hymen tissue between *arrow a and arrow b,* confirming that the defect extends all the way through the hymen tissue. **C,** Photograph taken with a camera attached to a colposcope shows bruising of the hymen at the 7 to 8 o'clock position and the suggestion of a possible hymen laceration. Examination of additional positions and other examination techniques would be required to determine if a hymen laceration is also present at this location. (*From Adams JA, Kellog ND, Moles R. Medical care for children who may have been sexually abused: an update for 2016. J Pediatr Adolesc Gynecol. 2015;17(4):255–263. Figs. 1, 2, and 4.)*

are amenable. The PCP may decline to do an exam if the teen refuses a chaperone.

The female genital exam is done with the child in the frog-leg supine position or the adolescent in the lithotomy position. Labial separation and labial traction, with gentle tugging apart and down of the labia majora, provide a view of the hymen. Any suspected abnormalities should be confirmed by also examining the child in the prone knee-chest position. Supine knee-chest is the best way to examine the anus. Internal vaginal and anal exams are rarely needed. If there is significant bleeding or a persistent discharge, a referral to an expert in child abuse is recommended.

Referral to a child abuse specialist: Referral to a child abuse specialist will help ensure that findings indicative or suggestive of abuse are appropriately identified and documented. It is considered the standard of care to use a colposcope or camera for the genital exam to magnify the genital and anal tissues for improved visualization and to take photographs or video as potential evidence and for peer review. Child abuse experts can identify mimics of sexual abuse, test for and treat STIs, and address child or parental concerns.

Testing for STIs: Testing for STIs is not indicated for most children but is warranted in certain situations (Table 17.6). *Culture* was considered the gold standard for diagnosing vaginal gonorrhea (Chapter 238) and chlamydia (Chapter 272) infections in children. Nucleic acid amplification testing (NAAT) for gonorrhea and chlamydia by either vaginal swab or urine in prepubertal girls is as, or more, sensitive than culture. Guidelines from the Centers for Disease Control and Prevention (CDC) allow for such NAAT testing as an alternative to culture. Because obtaining vaginal swabs can be uncomfortable, particularly for prepubertal girls, urine testing is preferable, using a Food and Drug Administration (FDA)–approved assay. Although the FDA has not approved NAATs for the diagnosis of gonorrhea or chlamydia infections of the throat or anus, they may be used if the laboratory has performed internal validation with reference standards. Although little data on the use of urine NAAT testing in prepubertal boys are available, the CDC has indicated that there is no reason to suspect that test performance in children and youth would be different from adults. Thus urine testing of them too appears adequate.

Table 17.6 Indications for STI Screening in Children with Suspected Sexual Abuse

1. The child has experienced penetration or has evidence of recent or healed penetrative injury to the genitals, anus, or oropharynx.
2. The child has been abused by a stranger.
3. The child has been abused by an assailant known to be infected with an STI or at high risk for STIs (e.g., injecting drug user, men who have sex with men, persons with multiple sexual partners, or person with a history of STIs).
4. The child has a sibling, other relative, or another person in the household with an STI.
5. The child lives in an area with a high rate of STIs in the community.
6. The child has signs or symptoms of STIs (e.g., vaginal discharge or pain, genital itching or odor, urinary symptoms, or genital lesions or ulcers).
7. The child or parent requests STI testing.
8. The child is unable to verbalize details of the assault.

STI, Sexually transmitted infection.
From Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep.* 2021;70(4):1–184.

For all NAAT testing in females and males, the child should *not* receive presumptive treatment at the time of testing. Instead, a positive NAAT test should be confirmed by repeating the test on the original sample or on a new sample. Whereas the CDC previously recommended confirmatory testing with a different FDA-approved assay, the 2021 Sexually Transmitted Infection Treatment Guidelines no longer require this. Gonorrhea and chlamydia in prepubertal children rarely cause ascending infection; thus waiting for a definitive diagnosis before treatment holds little risk for pelvic inflammatory disease.

Testing for *Trichomonas vaginalis* is by culture, NAAT, or wet mount. Wet mount requires the presence of vaginal secretions, viewing must be immediate for optimal results, and sensitivity is only

Table 17.7 Implications of Commonly Encountered Sexually Transmitted or Sexually Associated Infections for Diagnosis and Reporting of Sexual Abuse Among Infants and Prepubertal Children

INFECTION	EVIDENCE FOR SEXUAL ABUSE	SUGGESTED ACTION
Gonorrhea*	Diagnostic†	Report†
Syphilis*	Diagnostic	Report†
HIV§	Diagnostic	Report†
*Chlamydia trachomatis**	Diagnostic†	Report†
*Trichomonas vaginalis**	Diagnostic	Report†
Anogenital herpes	Suspicious	Consider report†,¶
Condylomata acuminata (anogenital warts)*	Suspicious	Consider report†,¶,**
Anogenital molluscum contagiosum	Inconclusive	Medical follow-up
Bacterial vaginosis	Inconclusive	Medical follow-up

*If unlikely to be perinatally acquired and vertical transmission, which is rare, is excluded.
†Reports should be made to the local or state agency mandated to receive reports of suspected child abuse or neglect
§If unlikely to have been acquired perinatally or through transfusion.
¶Unless a clear history of autoinoculation exists.
**Report if evidence exists to suspect abuse, including history, physical examination, or other identified infections. Lesions appearing for the first time in a child aged >5 yr are more likely to have been caused by sexual transmission.
From Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep.* 2021;70(4):1–184. Adapted from Kellogg N, American Academy of Pediatrics Committee on Child Abuse and Neglect. The evaluation of sexual abuse in children. *Pediatrics.* 2005;116:506–512; Adams JA, Farst KJ, Kellogg ND. Interpretation of medical findings in suspected child abuse: An update for 2018. *J Pediatr Adolesc Gynecol.* 2018;31:225–231.

44–68%; therefore false-negative tests are common. NAAT tests for *Trichomonas* should only be performed using FDA-approved products. Positive tests should be confirmed using the same sample or a repeat collection. Point-of-care tests for *Trichomonas*, done at the PCP's office, have not been validated for prepubertal children and should not be used.

Obtaining a blood sample for HIV, syphilis, and hepatitis B testing should be considered, particularly if there has been vaginal or anal penetration with pain, bleeding, or ejaculation. To limit painful procedures, some experts begin with genital, anal, and/or throat testing and do the blood testing if the earlier testing is positive. Because HIV testing identifies antibodies to the virus, it may take several months for seroconversion—repeat testing at 6 weeks and 3 months after the last suspected exposure is indicated. Repeat testing for syphilis and hepatitis B is also recommended at the same intervals.

INTERPRETATION OF FINDINGS

History: A clear disclosure of abuse by a child or adolescent, particularly with details that can be corroborated, is strong evidence that abuse has occurred. A strong denial could indicate that abuse did not occur, but could also be the result of fear, threats from the perpetrator, or pressure from family members to remain silent. Limited language skills or a long length of time since the abuse occurred may limit the specificity of the disclosure. Alternatively, a vague disclosure may lead a parent to assume abuse when none has occurred. Infrequently, a child may be coached by a parent to describe abuse, sometimes in the context of a custody dispute. More commonly, an abusive parent will allege coaching to protect themself and enable ongoing access to the child.

Findings indicative of trauma: Abrasions, lacerations, and bruising of the labia, vulva, penis, scrotum, perianal tissues, or perineum indicate recent trauma. Hymenal bruising and lacerations and deep perianal lacerations (vs superficial fissures) indicate penetrating trauma. Anogenital scars indicate older trauma. Hymnal scars often appear as changes in the usual anatomy and pallor. It is noteworthy that such findings that are exactly midline are likely normal embryonic remnants. A complete transection of the hymen all the way to the base below 3 and 9 o'clock in the supine position (i.e., absence or gap of hymenal tissue posteriorly) is considered diagnostic for penetrating trauma (see Fig. 17.10). For all these findings, the cause of injury must be elucidated through the child and parent history, as trauma may also be the result of a noninflicted injury or consensual sexual activity. If there is any concern that the finding may be the result of sexual abuse, CPS should be notified, and a medical evaluation should be performed by a medical specialist with expertise in child sexual abuse.

STIs: A number of STIs raise serious concern for abuse (Table 17.7). In a prepubertal child, **gonorrhea**, **trichomonas**, or **syphilis** beyond the neonatal period indicates that the child had contact with infected genital secretions, almost always as a result of sexual abuse. There is some evidence to indicate that **chlamydia** in children up to 3 years of age may be perinatally acquired. Chlamydia in children older than 3 years is diagnostic of contact with infected genital secretions almost always because of abuse. **HIV** is diagnostic for sexual abuse if other means of transmission have been excluded. Because of the potential for human papillomavirus (HPV) transmission, either perinatally or through nonsexual contact, the presence of **genital warts** has a low specificity for sexual abuse. Nevertheless, the possibility of abuse should be briefly probed with the family, especially in children whose warts first appear beyond 5 years of age. **Type 1 or 2 herpes simplex virus (HSV)** in the anogenital area is concerning for sexual abuse, but not diagnostic given other possible routes of transmission. PCPs should consider referring patients with HPV and HSV to CPS.

Integration of Information

Because most sexually abused children have normal exams, it is often not possible to make a diagnosis of sexual abuse by the exam alone. Ideally, the determination of abuse should be made as part of a multidisciplinary team process, where information from interviews, medical evaluation, forensic kit, and laboratory test results are integrated. Determinations by CPS as to whether abuse occurred may not align directly with a decision to prosecute alleged offenders because criminal cases require a higher level of proof (beyond a reasonable doubt) than do CPS cases, which rely on the preponderance of evidence (i.e., more likely than not).

Recommendations for Children and Families

At the conclusion of the medical evaluation, the PCP should let the child and parent know that the child is physically healthy but should also explain to them why a normal exam does not rule out abuse. It is often helpful to reinforce that in most cases, what is most important in determining whether sexual abuse occurred is what the child has said. When there are findings indicative of abuse, these should also be clearly explained. Of note, injuries to the anogenital area typically heal without complications, and most STIs respond well to treatment. Thus comforting and reassuring children and families is generally appropriate, even when injuries and/or infection occurs. PCPs should tell children that the abuse was not their fault and encourage parents to be supportive of their child. Although most children will not need medical follow-up, a visit with their PCP can be helpful to monitor psychosocial progress and to support the child and family. Some will need repeat HIV, syphilis, and hepatitis B testing. Hepatitis B and HPV vaccination (for children ≥9 years) should be given if the child has not been adequately vaccinated. Most children and their parents benefit from therapy or counseling. A mental health evaluation for other children in the home should be considered; the stress of coping with abuse and its ramifications can be difficult for the entire family. Parents are often very stressed by the sexual abuse of their child, even when it is uncertain what happened. This is compounded by the legal processes and implications. If emotional or behavior problems arise later, the PCP should try to refer the child to a mental health professional with experience in addressing trauma.

SEXUAL ABUSE PREVENTION

PCPs can play a role in the prevention of sexual abuse by educating parents and children about sexual safety at well-child visits. During the genital exam the PCP can inform the child that only the doctor and select adult caregivers should be permitted to see their "private parts" and that a trusted adult should be told if anyone else attempts to do so. Parents and children should be encouraged to use correct terms (vagina, vulva, penis, breasts) to demystify the genitals. The pediatrician can teach parents, children, and youth how to minimize the opportunity for perpetrators to access children, for example, by limiting one-adult/one-child situations outside the home (e.g., in daycare or school) and being sensitive to another adult's unusual interest in young children. In addition, PCPs can model for parents talking with children about what to do if confronted with a potentially abusive situation. Some examples include telling children to say "no," to leave, and to tell a parent and/or another trusted adult. Conversations with children of all ages can include a discussion of consent before touching another person. Conversations with teens can include information about statutory rape and electronic dissemination of sexual photos, along with their risks. Finally, PCPs can encourage open communication between parents and children; children need to hear that their parent is there to protect them and will not be angry with them if they hear something bad. Instead, they need to know.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

17.2 Factitious Disorder Imposed on Another: Medical Child Abuse (Munchausen Syndrome by Proxy)

Howard Dubowitz and Wendy G. Lane

Munchausen syndrome describes situations in which adults falsify their own symptoms to obtain healthcare. In *Munchausen syndrome by proxy,* a parent, typically a mother, simulates or causes signs and/or symptoms in her child, resulting in unnecessary healthcare. Several terms describing this phenomenon focus on the abuse or neglect experienced by a child, including *pediatric condition falsification, caregiver-fabricated illness in a child,* and **medical child abuse (MCA)**. **Factitious disorder imposed on another (FDIA)** is a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) psychiatric diagnosis focused on the psychopathology in the responsible parent attempting to meet their own psychologic needs. FDIA may encompass all other titles. In some instances, such as partial suffocation, "child abuse" may be most appropriate.

Because milder forms of MCA often go undetected, its incidence is unclear, although 0.5-2 per 100,000 children is commonly cited, and it appears to be a global problem. The core dynamic is that a parent falsely presents a child for healthcare. This may be via fabricating a history, such as reporting seizures or apnea that never occurred. A parent may directly cause a child's illness, for example, by exposing a child to a toxin, medication, or infectious agent (e.g., injecting stool into an intravenous line) or smothering a child. Signs or symptoms may also be manufactured, such as when a parent withholds medication or alters laboratory samples or temperature measurements. Parents may also withhold information about normal procedures or testing done elsewhere. Preverbal children are usually involved, although older children may be convinced by parents that they have a particular problem and become dependent on the increased attention; this may lead to feigning symptoms. They may also be coached to corroborate false histories. Each of these actions may lead clinicians to suspect a health problem and thus to provide unnecessary healthcare, including intrusive tests and surgeries.

When to suspect FDIA/MCA? Consideration of MCA may be triggered when the described symptoms, their course, test results, or response to standard treatment is incompatible with any known disease or condition. The reported symptoms may be repeatedly noted by only one parent or occur only when one caregiver is alone with the child. Other risk indicators include parents who appear to need a lot of attention from physicians or who insist that the child cannot cope without them. They may refuse to leave the bedside for days.

Parents with experience in a medical field may be adept at constructing plausible presentations, although the internet provides other parents with easy access to medical information. A convincing seizure history may be offered, as a normal electroencephalogram cannot fully rule out the possibility of a seizure disorder. Even after extensive testing fails to lead to a diagnosis or treatment proves ineffective, clinicians may think they are confronting a new or rare disease and may unwittingly contribute to unnecessary testing and to a parent's belief that a real problem exists. Efforts to carefully pursue a diagnosis along with difficulty accepting uncertainty may lead clinicians to persist with testing. Clinicians generally rely on and trust parents to provide an accurate history. As with other forms of child maltreatment, accurate diagnosis of MCA requires that professionals maintain a healthy skepticism under certain circumstances; this can be difficult. Clinicians, including mental health experts, may think that they are skilled at detecting deception. Most do poorly when attempting to do so during a clinical interview.

At a systems level, limited communication among treating professionals may delay the diagnosis of MCA. The "problems" often recur repeatedly over several years. The time from first presentation until the diagnosis is made averages about 2 years. Ultimately, a diagnosis of MCA rests on clear evidence of a child repeatedly being subjected to unnecessary tests and treatment, primarily stemming from a parent's exaggeration, fabrication, or induction of symptoms or signs suggesting an illness or condition.

CLINICAL MANIFESTATIONS

Mothers are the most frequent perpetrators of MCA. They may present as devoted or even model parents who form close relationships with members of the healthcare team. Although appearing very interested in their child's condition, they may be distant emotionally. Negative test results may meet with disappointment, and they may insist on further evaluation. They may have a history

of Munchausen syndrome, though not necessarily diagnosed as such.

MCA varies in nature and severity. Males and females are equally involved. Most of the victims are infants and toddlers, but approximately 25% of cases occur in children over 6 years of age. Siblings are commonly affected. Approximately 6–9% of cases are fatal, with fatalities most often the result of poisoning or suffocation. It is important to note that children who really do have health problems can also be victims of MCA; up to 30% of patients with MCA have been found to have a medical problem. Many medical or behavioral conditions can be falsified. The following are examples of relatively common ways MCA presents:

Bleeding may be caused by adding dyes to samples, adding blood (e.g., from the mother) to the child's sample, or giving the child an anticoagulant (e.g., warfarin). Blood group testing may be needed.

Seizures are easy to fabricate and difficult to rule out. A parent may report that another physician diagnosed seizures, and the myth may be perpetuated if there is no effort to confirm the original "diagnosis." Alternatively, seizures may be induced by toxins, medications (e.g., insulin), water, or salt. Clinicians need to be familiar with the substances available to families and their risks.

Apnea may be falsified or created by partial suffocation. A history of a sibling with the same problem, perhaps dying from it, should raise concern. Parents of children hospitalized for a brief resolved unexplained event (BRUE) have been videotaped attempting to suffocate their child while in the hospital.

Gastrointestinal problems such as vomiting and diarrhea are common. Forced ingestion of medications such as ipecac may induce chronic vomiting, or laxatives may cause diarrhea. Toxicology testing is indicated in such circumstances.

Allergies may be fabricated. Sometimes, allergies may be diagnosed or considered, and a parent persists in viewing this as a problem even after it has subsequently been ruled out.

Urinary tract infections and hematuria account for about 25% of cases.

Behavior problems such as self-harm or harming others, learning disabilities, hyperactivity, or autism may be falsely described.

EVALUATION AND DIAGNOSIS

It is critical that clinicians consider the possibility of MCA in their differential diagnosis when facing the previously noted presentations. Further, it helps to focus on the actual or potential harm to a child, rather than the parent's possible motivation. Once MCA is suspected, gathering and critically reviewing **all** the child's medical records from all sources is an onerous but critical first step, best done by someone knowledgeable about MCA. Child protective services (CPS) can help gather the records, and a hospital-based child protection team might be able to review the case. Important documentation at each health contact includes date, location, reason for contact, reported signs/symptoms as stated by the caregiver, objective observations documented by the physician, conclusions/diagnosis made, treatment provided, effectiveness of treatment, and other comments or observations. It is important to confer with other treating physicians about what specifically was conveyed to the family; they may have been reluctant to document concerns in the child's record. A parent may report that a certain test was done at the insistence of a physician, when they, in fact, had demanded it. It is also sometimes necessary to confirm the exact basis for a given diagnosis, rather than simply accepting a parent's account (e.g., seizure).

Depending on the nature of the presenting problem, hospitalization may be needed. Verbal children should be interviewed alone, and the family history should probe for unusual and frequent illnesses. Close observation of a child can be valuable. There may be a history of poor appetite and vomiting, yet the child is observed to eat well without problems. Symptoms may only be described when the parent is present and otherwise noted to be absent. In some instances, such as BRUEs, covert video surveillance accompanied by monitoring (to rapidly intervene if a parent attempts to suffocate a child) can be valuable. In addition to helping clarify the diagnosis, video surveillance can identify a true medical problem. It is prudent to consult with risk management and hospital legal staff before initiating surveillance. Specimens should be carefully collected, with no opportunity for tampering with them. Similarly, temperature measurements should be closely observed.

Coordination among treating professionals is essential, especially as some may side with the parent and resent even the possibility of MCA being raised. Ideally, parents should not be informed of the evaluation for MCA until the diagnosis is made. Doing so could influence their behavior and jeopardize establishing the diagnosis. In summarizing the review of health records and gathering additional information, careful and chronologic documentation is important. This includes who witnessed symptoms, direct information from other clinicians who made diagnoses, what guidance was given to the family, whether a parent insisted on testing or treatment, and suspected tampering with equipment or records as well as other concerning behavior. It may be necessary to block parents at least temporarily from accessing part of the electronic health record.

The diagnosis of MCA hinges on a child receiving unnecessary healthcare that is actually or potentially harmful and that is instigated by a parent or caregiver. Three questions to be answered in considering MCA include:

1. Are the history, signs, and symptoms credible?
2. Is the child receiving unnecessary and harmful or potentially harmful medical care?
3. If so, who is instigating the evaluations or treatments?

Comprehensive practice guidelines regarding MCA are available from the American Academy of Pediatrics (AAP) and the American Professional Society on the Abuse of Children (APSAC). In addition, consultation with a board-certified child abuse pediatrician is strongly recommended.

Related circumstances: In assessing possible MCA, several other circumstances should be considered in addition to a true health problem. Some parents may be extremely anxious and genuinely concerned about a possible problem. There may be many reasons underpinning the vulnerable child syndrome, such as the death of neighbor's child or something read on the internet. Alternatively, parents may believe something told to them by a trusted clinician despite subsequent evidence to the contrary and efforts to correct the earlier misdiagnosis (e.g., persistent belief that the child has multiple food allergies). Secondary gain, such as qualifying for a disability benefit, may be the impetus for malingering. A child's anxiety, especially in the context of complex medical conditions, may lead to psychosomatic symptoms and consideration of MCA. In addition, parents of such children may be extremely stressed, and this may contribute to an approach that is overly medicalized (e.g., reluctance to wean a child off medication). There is also a need to discern commonly used hyperbole (e.g., exaggerating the height of a fever) to evoke concern and perhaps justify a clinic visit. Whatever the possible underlying dynamics, children who receive unnecessary healthcare as a result of parental actions can be diagnosed with MCA.

TREATMENT

MCA is a form of child abuse or neglect and needs to be referred to CPS even when one is less than certain of the diagnosis; law enforcement may also need to be involved. CPS staff often lack knowledge of and experience with MCA and may need to be educated regarding this condition. Once the diagnosis of MCA is

established, the medical team and CPS should determine the treatment and safety plan, which may require out-of-home placement and should include mental healthcare for the offending parent; psychiatric decompensation and maternal suicide have been reported. Further medical care should be carefully coordinated through one primary care professional. CPS should be encouraged to meet with the family only after the medical team has informed the offending parent of the diagnosis, together with the other parent or another supportive adult if possible. Direct CPS involvement with the family during the assessment may jeopardize clarifying the diagnosis. If the plan is to place the child out-of-home, it is optimal that CPS plan the necessary steps in advance. Parents often respond with resistance, denial, and threats. It may be prudent to have hospital security in the vicinity in case of physical aggression or an attempt to remove the child from the hospital against medical advice. CPS should assess the safety of other children in the home. All family members may be affected by an MCA diagnosis; mental healthcare is recommended specifically for the parent involved with FDIA.

Assessing and addressing MCA can be time intensive and challenging. Clinicians may face the dilemma of when to accept that all plausible diagnoses have been reasonably ruled out, the circumstances fit MCA, and when testing and treatment should cease. The likelihood of MCA must be balanced with concerns about possibly missing an important diagnosis. Consultation with a child abuse pediatrician is recommended for making the diagnosis and for helping plan ongoing healthcare if the child remains in or returns to the home. Good communication among treating clinicians is needed to adequately monitor the situation; long-term monitoring may be needed.

OUTCOMES

There may be lasting physical harms associated with unnecessary and sometimes invasive evaluations and interventions, including scarring, surgical complications, brain damage, and death. There are also potentially serious and lasting social and psychologic sequelae as a result of missing school and extracurricular activities and viewing themselves as disabled. Victims of MCA may be overly compliant or aggressive and may develop poor self-esteem, posttraumatic stress disorder, and eating problems. Indirectly, other family members and friends, professionals, and even community members may be affected. Recidivism has been reported in 17–50% of cases. Successful treatment of the abusive parent appears rare and hinges on acknowledging their role and being willing and able to change their behavior.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 18

Strategies for Health Behavior Change

Cori M. Green

To improve the health of children, pediatricians often ask patients and caregivers to make behavioral changes. These may be lifestyle changes to manage a chronic condition (e.g., obesity, asthma), adherence with the recommended timing and frequency of medications, or recommendations to seek assistance from other health providers (e.g., dieticians; mental health providers; physical, occupational, or speech therapists). However, change is difficult and can cause distress, and families often express reluctance or ambivalence to change because of perceived barriers. When families do not believe change is needed or possible, pediatricians may become discouraged or uncomfortable in providing care. This can make it difficult for clinicians to form an alliance with families, which is central to finding a solution to most problems identified in the medical setting.

Many healthcare problems may require complex, multifaceted interventions, but the first step is always to engage the family in identifying the healthcare problem driving the need for behavior change. Once a problem is identified and agreed on, clinicians and families need to set an achievable goal and identify specific behaviors that can help families reach their goal. It is important to be specific and precise about the actual behavior and not simply identify the *category* of the behavior. When counseling a patient on weight loss for obesity, for example, one might discuss three possible approaches: making dietary changes, increasing exercise, and decreasing screen time. The choice of which behavior to focus on should come from the patient but needs to be specific. It is not enough for the patient to state he or she will exercise more. Instead, the clinician should help the patient identify a more specific goal, such as playing basketball with friends 3 times a week at the park near home. This takes into account the action, context, setting, and time of the new behavioral goal. Specific examples of problems that would necessitate a behavior change to improve outcomes are used throughout the chapter.

UNIFIED THEORY OF BEHAVIOR CHANGE

There are several theories of health-related behavior change. Each highlights a different concept, but frameworks that unite these theories suggest that the factor most predictive of whether one will perform a behavior is the *intention* to do so. The **unified theory of behavior change** examines behavior along two dimensions: influences on intent and moderators of the intention-behavior relationship (Fig. 18.1). Five main factors that influence one's decision to perform a behavior are expectancies, social norms/normative influences, self-concept/self-image, emotions, and self-efficacy. Table 18.1 provides specific examples on how to explore influences of intent when guiding families in decision-making, such as deciding to start a stimulant medication for a child diagnosed with attention-deficit/hyperactivity disorder (ADHD). It is not necessary to ask about each influence, but these principles are particularly useful when guiding patients who may be resistant to change.

Once a decision to make a change is made, four factors determine whether an intention leads to carrying out the behavior: knowledge and skills, environmental facilitators and constraints, salience of the behavior, and habits. The pediatrician can help ensure intent leads to behavior change by addressing these factors during the visit. In the ADHD example, the clinician can help the family build their knowledge by providing handouts on stimulants, nutritional pamphlets on how to minimize the appetite-suppressant effects of the medication on weight, and information on how the family can explain to others the need for medication. Asking about morning routines will help identify potential barriers in remembering to take the medication. Lastly, clinicians can help families think about cues for remembering to give the medication in the morning, because their morning routines, or habits, will have to be adjusted to adhere to this medication.

By using these principles of behavior change, clinicians can guide their patients toward change during an encounter by ensuring they leave with (1) a strong positive intention to perform the behavior; (2) the perception that they have the skills to accomplish it; (3) a belief that the behavior is socially acceptable and consistent with their self-image; (4) a positive feeling about the behavior; (5) specific strategies in overcoming potential barriers in performing the behavior; and (6) a set of identified cues and enablers to help build new habits.

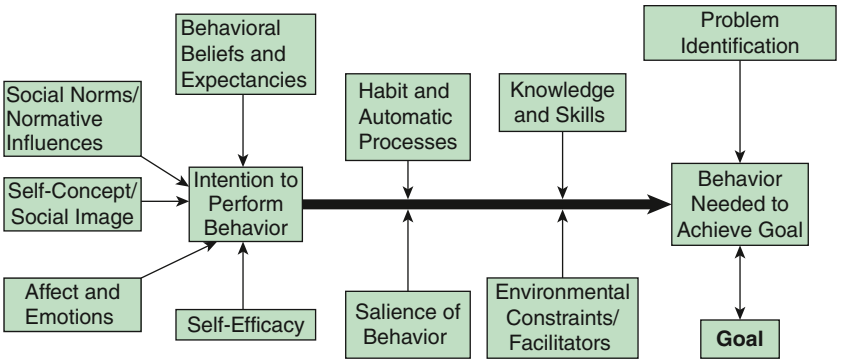

Fig. 18.1 The five constructs that influence one's intent to perform a behavior and the four influences that determine whether an intent will lead to performing the behavior. Problem identification (*box* at upper right) is where the process of thinking about health behavior changes begins. A clinician can then help the patient decide which behavior can help them meet the health goal. Once this is decided, to help with behavior change, clinicians should think about intent, influences of intent, and the factors that may facilitate or impede intent from leading to action.

Table 18.1 Influences of Intent and Possible Use During a Patient Encounter (Specifically, Starting a Stimulant for ADHD)

INFLUENCE OF INTENT	STRATEGIES TO ENGAGE FAMILIES USING INFLUENCES OF INTENT	POSSIBLE FACTORS INFLUENCING THE DECISION*
Beliefs and expectancies Perceived advantages and disadvantages of performing a behavior.	Ask questions about their beliefs and experiences. "What do you know already know about stimulants?" "Have you heard about other children's experiences taking stimulants?" "What do you expect will happen if your child takes a stimulant?" Ask permission to give information addressing their prior beliefs or experiences. "Is it all right if I give you some information addressing your concerns?"	"I know that stimulants helped my nephew do better in school." "I heard stimulants stunt children's growth."
Social norms Pressures to (or not) perform a behavior because of what is standard among social groups.	Share information about the normative nature of the behavior and ways to cope if performing a behavior that is not the social norm. "I have a lot of patients who have improved in school after starting a stimulant."	"Do other parents give their children stimulants if they are diagnosed with ADHD?" "What would my mother think if she found out my child was taking a stimulant?"
Self-concept/self-image Overall sense of self and whether behavior is congruent with that and with the image they want to project to others.	Interact with family in a partnering, supportive, respectful manner. Identify strengths. Reframe any negative images they foresee may happen with the behavior. "I am sure your in-laws will be so happy when your child is doing better in school."	"Am I a good parent if I give my child medications that affect their brain?" "What will other parents at school think if I allow my child to start a stimulant? What will my in-laws think?"
Emotions Emotional reactions to performing behaviors in terms of intensity and direction (positive or negative).	Allow patients to express their feelings. Suggest ways to manage negative or avoidant feelings. "Many parents are scared to start stimulants at first. However, once their child is succeeding in school, they realize the benefits outweighed the risks. Let's talk more about your fears."	"I am so nervous about my child starting to take a stimulant." "I am so upset with how my child is doing in school and really do not know what to do next." "I am so relieved that there is a medication that may help improve my child's grades and chance of going to college."
Self-efficacy Perceived confidence they can perform the behavior.	Provide information, model the behavior, encourage success, and teach skills. Explore what obstacles they foresee and how confident they are they can overcome obstacles. Help strategize ways to overcome obstacles. "Do you feel confident you will be able to get your child to take the medication?" "Let's brainstorm how we can prevent any of the side effects." "Many of my patients have a large breakfast before taking the medication. Can I help you figure out how to fit that into your schedule?"	"Will I be able to remember to give my child this medication every day?" "Will I be able to make sure my child has a large breakfast in the morning before taking the medication?"

ADHD, Attention-deficit/hyperactivity disorder.
*Statements and questions are examples of what caregivers may be thinking.

Table 18.2 Stages of Change and Strategies for Counseling*

STAGE/DEFINITION	GOAL AND STRATEGY	SPECIFIC EXAMPLES
Precontemplation Not considering change. May be unaware that a problem exists.	Establish a therapeutic relationship. Increase awareness of need to change.	"I understand you are only here because your parents are worried and that you don't feel that smoking marijuana is a big deal." "Can I ask if smoking marijuana has created any problems for you now? I know your parents were worried about your grades." "It's up to you to decide if and when you are ready to cut back on smoking marijuana." "Is it okay if I give you some information about marijuana use?" "I know it can be hard to change a habit when you feel under pressure. It is totally up to you to decide if cutting back is right for you. Is it okay if I ask you about this during our next visit?"
Contemplation Beginning to consider making a change, but still feeling ambivalent about making a change.	Identify ambivalence. Help develop discrepancy between goals and current behaviors. Ask about pros and cons of changing problem behavior. Support patient toward making a change.	"I'm hearing that you do agree that sometimes your marijuana use does get in the way, especially with school. However, it helps relax you and it would be hard to make a change right now." "What would be one benefit of cutting back? What would be a drawback to cutting back? Do you think your smoking will cause problems in the future?" "After talking about this, if you feel you want to cut back, the next step would be to think about how to best do that. We wouldn't need to jump right into a plan. Why don't you think about what we discussed, and we can meet next week if you are ready to make a plan?"
Preparation Preparing for action. Reduced ambivalence and exploration of options for change.	Help patient set a goal and prepare a concrete plan. Offer a menu of choices. Identify supports and barriers.	"It's great that you are thinking about ways to cut back on your smoking. I understand your initial goal is to stop smoking during the week." "I can give you some other options of how to relax and reduce stress during the week." "We need to figure out how to react to your friends after school who you normally smoke with." "Do you have other friends who you can see after school instead, who would support this decision?"
Action Taking action; actively implementing plan.	Provide positive feedback. Identify unexpected barriers and create coping strategies.	"Congratulations on cutting back. Have you noticed any differences in your schoolwork? I'm so happy to hear your grades improved." "Has it been difficult to not see your friends after school? How have you reacted when they get annoyed you don't want to smoke with them?" "Let's continue to track your progress."
Maintenance Continues to change behavior and maintains healthier lifestyle.	Reinforce commitment and affirm ability to change. Create coping plans when relapse does occur. Manage triggers.	"You really are committed to going to a good college and improving your grades. I'm so happy the hard work has paid off." "I understand that it was hard to say no to smoking with your friends last week when it was someone's birthday. How did you feel after? Are there triggers that we can think about preventing in the future?"

*This table uses an example of an adolescent who is initially resistant to cutting back on smoking marijuana. His parents caught him smoking in his room and arranged for him to see the pediatrician.

Adapted from *Implementing Mental Health Priorities in Practice: Substance Use,* American Academy of Pediatrics. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/substance-use.aspx.

TRANSTHEORETICAL MODEL OF HEALTH BEHAVIOR CHANGE

It is difficult to counsel families to change a behavior when they may not agree there is a problem or when they are not ready to build an intention to change. The **transtheoretical model of health behavior change** places an individual's motivation and readiness to change on a continuum. The premise of this model is that behavior change is a process, and as someone attempts to change, they move through five stages (although not always in a linear fashion): *precontemplation* (no current intention of making a change), *contemplation* (considering change), *preparation* (creating an intention, planning, and committing to change), *action* (has changed behavior for a short time), and *maintenance* (sustaining long-term change). Assessing a patient's stage of change and then targeting counseling toward that stage can help build a *therapeutic alliance,* in contrast to counseling a patient to do something she or he is not ready for, which can disrupt the therapeutic alliance and lead to resistance. Table 18.2 further describes stages of change and gives examples for counseling that target the adolescent's stage of change in reducing marijuana smoking.

COMMON FACTORS APPROACH

Conversations around behavior change are most effective when they take place in a context of a trusting, mutually respectful relationship. The traditional medical model assumes that patients and their families come with questions and needs and that the pediatrician's job is to offer specific advice and advocate for its acceptance. This approach fails when families are reluctant, ambivalent, demoralized, or unfamiliar with the healthcare system or the treatment choices offered. A context more supportive of behavior change can be developed when clinicians use communication strategies that facilitate collaboration and building a therapeutic alliance.

The **common factors approach** is an evidence-based communication strategy that is effective in facilitating behavior change. The skills central to a common factors approach are consistent across multiple forms of psychotherapy and therefore can be considered transdiagnostic. Common factors and processes can be viewed as generic aspects of treatment that can be used across a wide range of symptoms to build a therapeutic alliance between the physician and patient. This alliance predicts outcomes of counseling more than the specific modality of treatment. The common factors approach has been implemented and

Table 18.3 Hope, Empathy, Language, Loyalty, Permission, Partnership, Plan (HEL^{2}P^3)*

SKILL	EXAMPLES
Hope for improvement: Develop strengths.	"I have seen other children like you with similar feelings of sadness, and they have gotten better."
Empathy: Listen attentively.	"It must be hard for you that you no longer get pleasure in playing soccer."
Language: Use family's language. Check understanding.	"Let me make sure I understand what you are saying. You no longer feel like doing things that made you happy in the past?"
Loyalty: Express support and commitment.	"You are free to talk to me about anything while we work through this."
Permission: Ask permission to explore sensitive subjects. Offer advice.	"I would like to ask more questions that you may find more sensitive, is that okay?" "Is it okay with you if I give you my opinion on what may be the problem here?"
Partnership: Identify and overcome barriers.	"Can we discuss together possible solutions to overcoming your discomfort in getting therapy?"
Plan: Establish a plan, or at least a first step the family can take.	"If we work together, maybe we can think through solutions for the problems you identified."

*This table illustrates the **interpersonal skills** highlighted in the common factors approach. In this example the clinician is responding to an adolescent struggling with depression and resistant to seeking help.

Adapted with data from Foy JM, Kelleher KJ, Laraque D. American Academy of Pediatrics Task Force on Mental Health. Enhancing pediatric mental health care: Strategies for preparing a primary care practice. *Pediatrics.* 2010;125 Suppl 3:S87–S108.

studied in pediatric primary care for children with mental health problems. Children who were treated by pediatricians trained in the common factors approach had improved functioning compared to those who saw pediatricians without this training.

A common factors approach distinguishes between the impact of the patient-provider alliance and the pediatrician's use of skills that influence patient behavior change across a broad range of conditions. Interpersonal skills that help build alliances with patients include showing empathy, warmth, and positive regard. Skills that influence behavior change include a clinician's ability to provide optimism, facilitate treatment engagement, and maintain the focus on achievable goals. This can be done by clearly explaining the condition and treatment approaches while keeping the discussion focused on immediate and practical concerns.

Interpersonal Skills: HEL^{2}P^3

The interpersonal skills that facilitate an effective bond between the patient and clinician can be remembered by the HEL^{2}P^3 mnemonic (Table 18.3). These skills include providing **hope**, **empathy**, and **loyalty**; using the patient's **language**; **partnering** with the family; asking **permission** to raise more sensitive questions or to give advice; and creating a **plan** that is initiated by the family. These interpersonal skills should help operationalize the common factors approach by increasing a patient's optimism, feelings of well-being, and willingness to work toward improved health, while also targeting feelings of anger, ambivalence, and hopelessness.

Structuring a patient encounter using common factors to facilitate behavior change uses these steps: eliciting concerns while setting an agenda and agreeing on the nature of the problem; establishing a plan; and responding to anger and demoralization and emphasizing hope.

Elicit Concerns: Set the Agenda and Agree on the Problem

The first step of the visit is to elicit both the child's and the parent's concerns and agree on the focus for the visit. This can be accomplished by using open-ended questions and asking "anything else?" until nothing else is disclosed. It is important to show you have time and are interested in their concerns by making eye contact, listening attentively, minimizing distractions, and responding with empathy and interest. Engage both the child and the parent by taking turns eliciting their concerns. It is helpful to summarize their story to reassure them you have heard and understand what they are saying. Keep the session organized, and manage rambling by gently interrupting, paraphrasing, asking for additional concerns, and refocusing the conversation. These same principles apply for telehealth visits. Make sure you are looking into the camera and use exaggerated responses. It is particularly helpful to frequently summarize the child's and parents' concerns, voice observations, and use reflective statements during telehealth visits so the family does see that you are listening to them.

By the end of this step in the visit, all parties should feel reassured that their problems were heard and accurately described. The next step is to agree on the problem to be addressed during that visit. If the parent and child do not agree on the issue, try to find a common thread that will address the concerns of both.

Establish a Plan

Once a problem is agreed on, the clinician can partner with families to develop acceptable and achievable plans for treatment or further evaluation. Families should take the lead in developing goals and the strategies to attain them, and information should be given in response to patients' expressed needs. Pediatricians can involve families by offering choices and asking for feedback. Advice should be given only after asking a family's permission to do so. If the family asks for advice, the clinician should respond by considering principles of behavior change, as described earlier. Advice should be tailored toward the family's willingness to act, concerns for barriers, and attitudes and should be as specific and practical as possible. Once an initial plan is established, it is important to partner in monitoring responses and to provide continued support.

Respond to Anger and Demoralization and Emphasize Hope

The common factors approach is particularly helpful in engaging families in situations where anger and demoralization could prevent patients from being able to use the clinician's advice. Focusing the conversation on goals for the future and how to achieve them is more productive than discussing how problems began. This "solution-focused therapy" approach grew out of the need for clinicians to help people in a brief encounter. Hopelessness can be relieved by pediatricians helping patients to identify and build on strengths and past success, reframing events and feelings, and breaking down overwhelming goals into small, concrete steps that are more readily accomplished. In general, pediatricians can use the **elicit-provide-elicit model**. After eliciting a concern or hearing about patients' goals, ask if they want to hear your thoughts about the situation. Provide guidance in a neutral way, and then ask the family what they think about what you just stated.

Table 18.4 provides an example of how to use common factors in practice using a scenario of an adolescent female who has been teased for using albuterol before physical education class for her exercise-induced asthma. The clinician in the scenario attempts to address both the patient's and her mother's concerns.

Table 18.4 Common Factors Approach in Practice*

GOAL	SPECIFIC SKILLS	EXAMPLES
Elicit child's and parents' concerns.	Use open-ended questions and ask, "What else?" until nothing else is listed, while engaging both parties and demonstrating empathy.	"Hi, Jacqueline and Mrs. Smith. How have things been since last time? What are your biggest concerns for today?" "What else do you think we should put on the agenda for today?" "I am sorry to hear that you have had more asthma symptoms around gym time, Jacqueline. I'd like to ask you a few more questions to get a better understanding of what has changed, if that's okay with you." "I understand this is upsetting you, Mrs. Smith, and that you worry that Jacqueline is not going to the nurse before gym to use her inhaler pump anymore. Let's hear from Jacqueline."
	Agree on the problem.	"Can we all agree that managing the asthma symptoms around gym time is the most pressing issue for today? Should we focus on that today?"
	Manage rambling.	"What you're saying is really important, but I want to be sure we have time to talk about controlling your daughter's asthma symptoms during gym. Is it okay if we go back to that topic?"
Partner with families to find acceptable forms of treatment.	Develop acceptable plans for treatment of further diagnoses.	"I believe we can develop a plan to help deal with this. Is it okay to start talking about next steps?" "I am happy to give suggestions on how to more easily use your inhaler before gym, without the other kids noticing. But what were you thinking, Jacqueline?" "Let's brainstorm how you would respond to your classmates if they see you using your inhaler."
	Address barriers to treatment.	"Is there anything that makes you worry that this may not work?"
Increase expectations that treatment will be helpful.	Respond to hopelessness, anger, and frustration.	"I realize it wasn't your choice to come here, Jacqueline, but I'm interested in hearing how you feel about this issue." "It must be really hard for you, Jacqueline, when the kids tease you about your inhaler. Discussing this with your mom and me was very brave, and now we can help you." "It must be frustrating for the school nurse to call you in the middle of the day at work, Mrs. Smith." "I would be angry, too, if I felt my mom didn't understand how it felt when I got teased for going to the nurse's office."
	Emphasize hope.	"We've managed difficult things before. Remember when Jacqueline kept getting admitted for her asthma when she was younger? We have come a long way since then, and I'm sure we can manage this as well."

*Jacqueline is an adolescent female who has had asthma since she was an infant. Despite multiple hospitalizations as an infant, her asthma had been under control except for during exercise, including physical education (PE) class. She had been going to the nurse's office to take albuterol before PE class, but recently she had been teased for having to take medication before PE. She has begun to skip treatments to avoid the teasing. However, her mother has now been called a few times to pick her up from school because of her asthma symptoms. Jacqueline's caregiver is a single parent who cannot miss work and is very frustrated. She was not aware of the bullying Jacqueline has undergone.
This scenario is adapted from the American Academy of Pediatrics curricula on common factors. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Module-1-Brief-Intervention.aspx.

MOTIVATIONAL INTERVIEWING

Motivational interviewing (MI) is a goal-oriented, supportive counseling style that complements the HEL^{2}P^3 framework and is useful when patients or families remain ambivalent about making health-related behavior changes. MI is designed to enhance intrinsic motivation in patients by exploring their perspectives and ambivalence. It is also aligned with the transtheoretical model's continuum of change, where the clinician not only tailors counseling to a patient's stage of change but does so with the goal of moving the patient toward the next stage. It is particularly effective for those not interested in change or not ready to make a commitment. MI has been shown to be an effective intervention strategy for decreasing high-risk behaviors, improving chronic disease control, and increasing adherence to preventive health measures.

MI is a collaborative approach in which the pediatrician respects patients' perspectives and treats them as the "expert" on their values, beliefs, and goals. *Collaboration, acceptance, compassion,* and *evocation* are the foundation of MI and are referred to as the "spirit" of the approach. The clinician is a "guide," respecting patients' autonomy and their ability to make their own decision to change. The pediatrician expresses genuine concern and demonstrates that he or she understands and validates the patient's or family's struggle. Using open-ended questions, the pediatrician evokes the patient's own motivation for change.

Expressing empathy facilitates behavior change by accepting the patient's beliefs and behaviors. This contrasts with *direct persuasion,* which often leads to resistance. The pediatrician must reinforce that ambivalence is normal and use skillful reflective listening, showing the patient an understanding of the situation.

Developing a discrepancy between current behaviors (or treatment choices) and treatment goals motivates change and helps move the patient from the precontemplative stage to the contemplative stage or from the contemplative stage to preparation, as described in the transtheoretical model. Through MI the clinician can guide patients in understanding that their current behaviors may not be consistent with their stated goals and values.

Rolling with resistance, or not pushing back when suggestions are declined, is a strategy again to align with the patient. Resistance is

Table 18.5 Counseling for Obesity Using a Motivational Interviewing (MI) Approach

ACTION	SPECIFIC SKILLS	EXAMPLES
Engagement*	**O**pen-ended questions	"Now that we have finished the majority of the visit, I'd like to talk about your weight. Is that okay? How do you feel about your size?" "How do you feel about Jimmy's weight?" (directed toward caregiver)
	Affirmations	"You definitely have shown how strong you are having dealt with kids teasing you about your size." "Remember when you were having difficulties with your schoolwork? You were able to make a few changes, and now you are doing well. I am confident we can do the same with your weight."
	Reflective listening	"You are feeling like your son is the same size as everyone in your family, and you aren't concerned right now." "I hear that as a working parent, watching TV before bed really works for your family." "You're not terribly excited about having to think of ways to cook differently."
	Summary statements	"So far, we have discussed how challenging it would be to lose weight and make changes for the whole family, but you are willing to consider some simple changes."
Focusing	Set the agenda.	"We could talk about increasing the amount of exercise Jimmy has every week, reducing screen time, or making a dietary change. What do you think would work best?" "Great, so we will talk about soda. What do you like about it? How many times a week do you drink it?"
Evocation	Reinforce any change talk. Change ruler.	"Those are great reasons for thinking about cutting back on soda." "On a scale of 1 to 10, how confident are you (or how important is it) that you can cut back on soda?" "A 5. Why didn't you answer a 3?" "What would it take to bring it to a 7?"
Planning	Focus on how to make the change, not "why" anymore. Be concrete.	"Maybe completely eliminating soda is too difficult right now. Do you want to think of a couple of times during the week where you can reward yourself with a soda?" "What will you drink after school instead of soda?"

*OARS is used to engage the patient and build rapport.
Adapted from *Changing the Conversation About Childhood Obesity,* American Academy of Pediatrics, Institute for Healthy Childhood Weight. https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/Changing-the-conversation-about-Childhood-Obesity.aspx.

usually a sign that a different approach is needed. As necessary, the clinician can ask permission to give new perspectives.

Self-efficacy, or a patient's belief in her or his ability to perform the behavior, is a key element for change and a powerful motivator. Clinicians can express confidence in the patient's ability to achieve change and support the patient's self-efficacy.

The process by which MI is used in a patient encounter involves the following four parts:

1. *Engagement* is the rapport-building part of the encounter. In addition to using the skills presented in the HEL^{2}P^3 framework, the MI approach highlights the use of open-ended questions, affirmations, reflective listening, and summaries (**OARS**). **Open-ended questions** should be inviting and probing, enabling the patient to think through and come to a better understanding of the problem and elicit their internal motivation. **Affirmations** provide positive feedback, express appreciation about a patient's strengths, and can reinforce autonomy and self-efficacy. **Reflective listening** demonstrates that the clinician understands the patient's thoughts and feelings without judgement or interruption. It should be done frequently and can encourage the patient to be more open. **Summarizing** the conversation in a succinct way reinforces that you are listening, pulls together all information, and allows the patient to hear his or her own motivations and ambivalence.
2. *Focusing* the visit is done to clarify the patient's priorities and stage of readiness and to identify the problem where there is ambivalence. If a patient remains resistant to change, ask permission to give information or share ideas and then ask for feedback on what they think about what you said. In the **elicit-ask-elicit model**, a clinician can deliver information about an unhealthy behavior or lifestyle decision in a nonpaternalistic manner.
3. *Evocation* is when the clinician assesses their patients' reasons for change and helps them to explore advantages, disadvantages, and barriers to change. It is important to reinforce the patient's **change talk.** Examples of change talk include an expression of desire ("I want to…"), ability ("I can…"), reasons ("There are good reasons to…"), or a need for change ("I need to…"). Clinicians can use "readiness rulers" by asking their patients to rate on a scale from 1 to 10 how important and confident they are in making a change. The clinician should then respond by asking why the patient did not choose a lower number and should follow up by asking what it would take to bring it to a higher number.
4. The *planning* stage is similar to that described in the discussion of a common factors approach and occurs once a patient is in the preparation stage on the continuum of change. A clinician can guide their patient through this stage by having them write down responses to statements such as, "The changes I want to make are…," "The most important reasons to make this change are…," "Some people who can support me are…," and "They can help me by…." A concrete plan should include specific actions and a way to factor in accountability and rewards. Table 18.5 uses a visit for counseling about obesity to demonstrate the process of MI.

SHARED DECISION-MAKING

Shared decision-making (SDM) has many similarities to the processes previously described in that it emphasizes moving clinicians away from a paternalistic approach in dictating treatment to one where patients and clinicians collaborate in making a medical decision, particularly when multiple evidence-based treatment options exist. The overall goal is to approach medical decisions using patient-centered strategies that are based on the best evidence available while aligning with family values. By definition, (1) SDM must involve two parties (clinician and patient/family); (2) information must be exchanged in both directions; (3) both parties must be aware of all treatment options; and (4) the clinician and patient/family must both bring their own knowledge and values equally into the decision-making

process. This approach is only possible when there is more than one management strategy and SDM does not put a patient at risk.

SDM is often facilitated by using evidence-based decision aids such as pamphlets, videos, web-based tools, or educational workshops. Condition-specific or more generic decision aids have been created and facilitate the process of SDM. Studies in adults show that such aids improve knowledge and satisfaction, reduce decisional conflict, and increase the alignment between patient preferences and treatment options. Although SDM is widely used and has been studied in adult populations, it is more complicated in pediatric settings because the caregiver (a surrogate for the patient) is also involved in decision-making. It important to involve the child or adolescent in SDM, as the more they are involved in SDM, the better their outcomes may be. Options must be explained in a developmentally appropriate way. Then both the parent and clinician need to assess how much the patient truly understands regarding their stated preference.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Growth, Development, and Behavior

PART II

Chapter 19

Developmental and Behavioral Theories

Margo Candelaria and Susan Feigelman

The field of pediatrics is dedicated to optimizing the growth and development of each child. Pediatricians require knowledge of normal growth, development, and behavior to effectively monitor children's progress, identify delays or abnormalities in development, help obtain needed services, and counsel parents and caretakers. To alter factors that increase or decrease risk and resilience, pediatricians need to understand how biologic and social forces interact within the parent–child relationship, within the family, and between the family and the larger society. Growth is an indicator of overall well-being, status of chronic disease, and interpersonal and psychologic stress. By monitoring children and families over time, pediatricians are uniquely situated to observe the interrelationships between physical growth and cognitive, motor, and emotional development. Observation is enhanced by familiarity with developmental and behavioral theories that inform one about typical patterns of development and provide guidance for prevention or intervention for behavior problems. Familiarity with theories of health behavior may assist clinicians in guiding patients and families in disease management and wellness care.

BIOPSYCHOSOCIAL MODEL AND ECOBIODEVELOPMENTAL FRAMEWORK: MODELS OF DEVELOPMENT

The **medical model** presumes that a patient presents with signs and symptoms and a physician focuses on diagnosing and treating diseases of the body. This model neglects the social and psychologic aspect of a person who exists in the larger realm of the family and society. In the **biopsychosocial model**, societal and community systems are simultaneously considered along with more proximal systems that make up the person and the person's environment (Fig. 19.1). A patient's symptoms are examined and explained in the context of the patient's existence. This multidimensional model can be used to understand health and both acute and chronic disease, and this model has been increasingly used to develop care models over the past few decades.

With the advances in neurology, genomics (including epigenetics), molecular biology, and the social sciences, a broader model, the **ecobiodevelopmental framework**, has emerged. This framework emphasizes how the ecology of childhood (social and physical environments) interacts with biologic processes to determine outcomes and life trajectories. Early influences, particularly those producing **toxic levels of stress**, affect the individual through their impact on the body's stress response systems, brain development, and modification of gene expression. Epigenetic changes, such as DNA methylation and histone acetylation, may be influenced by early life experiences (the environment) and impact gene expression without changing the DNA sequence. These changes can produce long-lasting effects on the health and well-being of the individual and may be passed on to future generations (Fig. 19.2).

Critical to learning and remembering (and therefore development) is **neuronal plasticity**, which permits the central nervous system to reorganize neuronal networks in response to environmental stimulation, both positive and negative. An overproduction of neuronal precursors eventually leads to about 100 billion neurons in the adult brain. Each neuron develops on average 15,000 synapses by 3 years of age. During early childhood, synapses in frequently used pathways are preserved, whereas less-used ones atrophy, a process termed *pruning*. Changes in the strength and number of synapses and reorganization of neuronal circuits also play important roles in brain plasticity. Increases or decreases in synaptic activity result in persistent increases or decreases in synaptic strength. Thus experience (**environment**) has a direct effect on the physical and therefore functional properties of the brain. Children with different talents and temperaments (already a combination of genetics and environment) further elicit different stimuli from their varying environments.

Periods of rapid development generally correlate with periods of great changes in synaptic numbers in relevant areas of the brain. Accordingly, sensory deprivation during the time when synaptic changes should be occurring has profound effects. The effects of strabismus leading to amblyopia occur quickly during early childhood; patching the eye with good vision to reverse amblyopia is less effective in late childhood (see Chapter 663). Early experience is particularly important because learning proceeds more efficiently along established synaptic pathways. However, some plasticity of the brain continues into adolescence, with further development of the prefrontal cortex, which is important in decision-making, future planning, and emotional control; neurogenesis persists in adulthood in certain areas of the brain.

Early traumatic experiences modify the expression of stress mediators (in particular the hypothalamic-pituitary-adrenal axis) and neurotransmitters, leading to changes in brain connectivity and function. These effects may be persistent, leading to alterations and dysfunction in the stress response throughout life. Chronic stress has negative effects on cognitive functions, including memory and emotional regulation. Positive and negative experiences do not determine the ultimate outcome but shift the probabilities by influencing the child's ability to respond adaptively to future stimuli.

There is increasing evidence that positive experiences and relationships can buffer the impact of negative or traumatic experience and toxic stress. In fact, there is a recent call for pediatrics to recognize and promote relational health as a protective factor. By promoting positive relationships, labeled safe, stable, and nurturing relationships (SSNRs) within primary care, healthcare providers can work with families to build relational health, thereby combatting the deleterious effects of toxic stress and promoting resilience. Pediatric care can do this by employing a public health approach, partnering with families and communities, to build healthy relationships by connecting to and integrating with primary, secondary, and tertiary prevention programs. This can include embedding interventions within primary care and creating robust referral networks to connect families to needed services.

Biologic Influences

Biologic influences on development include genetics, in utero exposure to teratogens, the long-term negative effects of low birthweight (neonatal morbidities plus increased rates of subsequent adult-onset obesity, coronary heart disease, stroke, hypertension, and type 2 diabetes), postnatal illnesses, exposure to hazardous substances, and maturation. Adoption and twin studies consistently show that heredity accounts for approximately 40% of the variance in IQ and in other personality traits, such as sociability and desire for novelty, whereas shared environment accounts for another 50%. The negative effects on development of prenatal exposure to teratogens, such as mercury and alcohol, and of postnatal insults, such as meningitis and traumatic brain injury, have been extensively studied (see Chapters 117, 122, and 146). Any chronic illness can affect growth and development, either directly or through changes in factors such as nutrition, parenting, school attendance, peer interactions, or self-esteem.

Most children follow similar motor developmental sequences despite great variability in child-rearing practices. The attainment of skills such as the use of complex sentences is less tightly bound to a

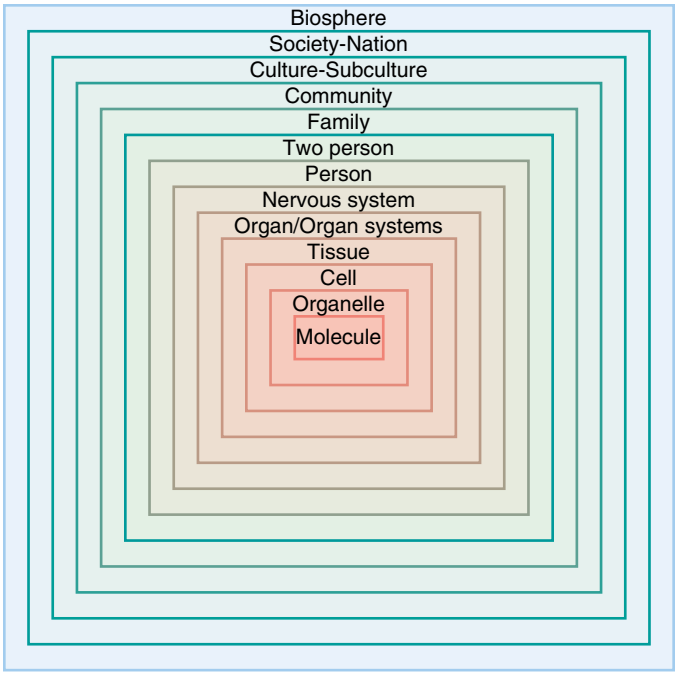

Fig. 19.1 Continuum and hierarchy of natural systems in the biopsychosocial model. *(From Engel GL. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980;137:535–544.)*

maturational schedule. Maturational changes also generate behavioral challenges at predictable times. Decrements in growth rate and sleep requirements around 2 years of age often generate concern about poor appetite and refusal to nap. Although it is possible to accelerate many developmental milestones (toilet training a 12 month old or teaching a 3 year old to read), *the long-term benefits of such precocious accomplishments are questionable.*

In addition to physical changes in size, body proportions, and strength, maturation brings about hormonal changes. Sexual differentiation, both somatic and neurologic, begins in utero. Both stress and reproductive hormones affect brain development as well as behavior throughout development. Steroid production by the fetal gonads leads to differences in brain structures between males and females.

Temperament describes the stable, early-appearing individual variations in behavioral dimensions, including emotionality (crying, laughing, sulking), activity level, attention, sociability, and persistence. The classic theory proposes nine dimensions of temperament (Table 19.1). These characteristics lead to three common constellations: (1) the easy, highly adaptable child, who has regular biologic cycles; (2) the difficult child, who is inflexible, moody, and easily frustrated; and (3) the slow-to-warm-up child, who needs extra time to adapt to new circumstances. Various combinations of these clusters also occur. Temperament has long been described as biologic or "inherited." Monozygotic twins are rated by their parents as temperamentally similar more often than are dizygotic twins. Estimates of heritability suggest that genetic differences account for 20–60% of the variability of temperament within a population. The remainder of the variance is attributed to the child's environment. Maternal prenatal stress and anxiety is associated with child temperament, possibly through stress hormones. However, certain polymorphisms of specific genes moderate the influence of maternal stress on infant temperament. Children who are easily frustrated, fearful, or irritable may elicit negative parental reactions, making these children even more susceptible to negative parenting behaviors and to poor adjustment to adversity. Longitudinal twin studies of adult personality indicate that changes in personality over time largely result from dissimilar environmental influences, whereas stability of temperament appears to result from genetic factors.

The concept of temperament can help parents understand and accept the characteristics of their children without feeling responsible for having caused them. Children who have difficulty adjusting to change may have behavior problems when a new baby arrives or at the time of school entry. In addition, pointing out the child's temperament may allow for adjustment in parenting styles. Behavioral and emotional problems may develop when the temperamental characteristics of children and parents are in conflict. If parents who keep an irregular schedule have a child who is not readily adaptable, behavioral difficulties are more likely than if the child has parents who have predictable routines.

Psychologic Influences: Attachment and Contingency

The influence of the child-rearing environment dominates most current models of development. Infants in hospitals and orphanages, devoid of opportunities for attachment, have severe developmental deficits. **Attachment** refers to a biologically determined tendency of a young child to seek proximity to the parent during times of stress and to the relationship that allows securely attached children to use their parents to reestablish a sense of well-being after a stressful experience. Insecure attachment may be predictive of later behavioral and learning problems.

At all stages of development, children progress optimally when they have adult caregivers who pay attention to their verbal and nonverbal cues and respond accordingly. In early infancy, such contingent responsiveness to signs of overarousal or underarousal helps maintain infants in a state of quiet alertness and fosters autonomic self-regulation. **Consistent contingent responses** (reinforcement depending on the behavior of the other) to nonverbal gestures create the groundwork for the shared attention and reciprocity that are critical for later language and social development.

Social Factors: Family Systems and the Ecologic Model

Contemporary models of child development recognize the critical importance of influences outside the mother–child dyad. Fathers play critical roles, both in their direct relationships with their children and in supporting mothers. As traditional nuclear families become less dominant, the influence of other family members and caregivers (grandparents, foster and adoptive parents, same-sex partners) becomes increasingly important. Furthermore, the presence of nurturing and stable caregivers, in or out of the nuclear family, can help to buffer the impact of a parent who may struggle with mental illness, substance use, or other afflictions. As children grow within their larger ecosystem, it is important to recognize and include all relevant caregivers in the child's care.

Families function as systems, with internal and external boundaries, subsystems, roles, and rules for interaction. In families with rigidly defined parental subsystems, children may be denied any decision-making, exacerbating rebelliousness. In families with poorly defined parent–child boundaries, children may be required to take on responsibilities beyond their years or may be recruited to play a spousal role.

Family systems theory recognizes that individuals within systems adopt implicit roles. Although birth order does not have long-term effects on personality development, within families the members take on different roles. One child may be the troublemaker, whereas another is the negotiator and another is quiet. Changes in one person's behavior affects every other member of the system; roles shift until a new equilibrium is found. The birth of a new child, attainment of developmental milestones such as independent walking, the onset of nighttime fears, diagnosis of a chronic illness, or death of a family member are all changes that require renegotiation of roles within the family and have the potential for healthy adaptation or dysfunction.

The family system, in turn, functions within the larger systems of extended family, subculture, culture, and society. Bronfenbrenner's ecologic model depicts these relationships as concentric circles, with the parent–child dyad at the center (with associated risks and protective factors) and the larger society at the periphery. Changes at any level are reflected in the levels above and below. Furthermore, these systems and their interactions change over time, with some influences being persistent and chronic and others being temporary. The shift from an industrial economy to one based on service and information and the influence of systemic racism are examples of how society has profound effects on families and children. Understanding the child's greater ecosystem is important to understand their family and the context of their

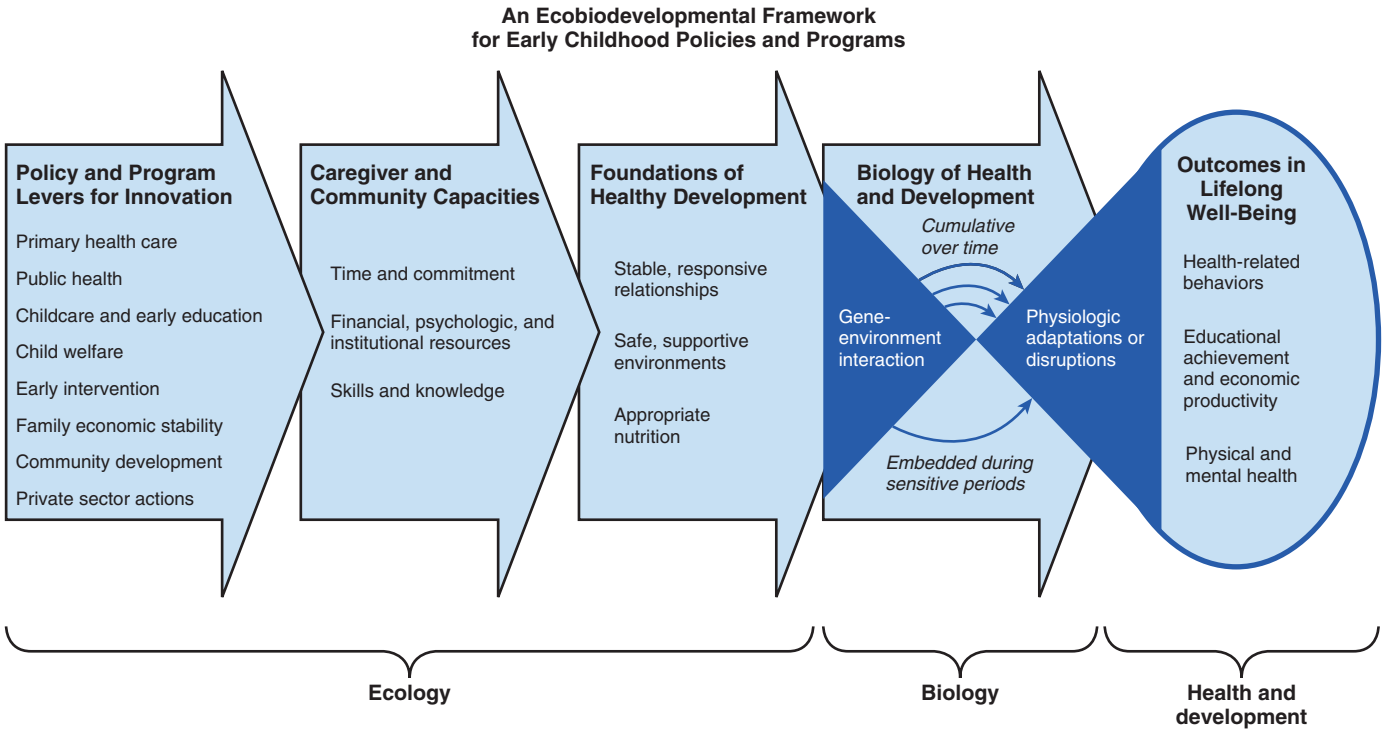

Fig. 19.2 Ecobiodevelopmental framework for early childhood policies and programs. (*Adapted from Center on the Developing Child. The foundations of lifelong health are built in early childhood. 2010; Available at: http://www.developingchild.harvard.edu.*)

Table 19.1 Temperamental Characteristics: Descriptions and Examples

CHARACTERISTIC	DESCRIPTION	EXAMPLES*
Activity level	Amount of gross motor movement	"She's constantly on the move." "He would rather sit still than run around."
Rhythmicity	Regularity of biologic cycles	"He's never hungry at the same time each day." "You could set a watch by her nap."
Approach and withdrawal	Initial response to new stimuli	"She rejects every new food at first." "He sleeps well in any place."
Adaptability	Ease of adaptation to novel stimulus	"Changes upset him." "She adjusts to new people quickly."
Threshold of responsiveness	Intensity of stimuli needed to evoke a response (e.g., touch, sound, light)	"He notices all the lumps in his food and objects to them." "She will eat anything, wear anything, do anything."
Intensity of reaction	Energy level of response	"She shouts when she is happy and wails when she is sad." "He never cries much."
Quality of mood	Usual disposition (e.g., pleasant, glum)	"He does not laugh much." "It seems like she is always happy."
Distractibility	How easily diverted from ongoing activity	"She is distracted at mealtime when other children are nearby." "He doesn't even hear me when he is playing."
Attention span and persistence	How long a child pays attention and sticks with difficult tasks	"He goes from toy to toy every minute." "She will keep at a puzzle until she has mastered it."

*Typical statements of parents, reflecting the range for each characteristic from very little to very much.
Based on data from Chess S, Thomas A. *Temperament in Clinical Practice.* New York: Guilford; 1986.

growth. Factors such as poverty, systemic racism, access to education, transportation, food, housing, parental employment, and local support systems are influential factors in a child's well-being. Whenever possible, identifying community supports and assets for families can help promote health and development.

Unifying Concepts: The Transactional Model, Risk, and Resilience

The **transactional model** proposes that a child's status at any point in time is a function of the interaction between biologic and social influences. The influences are bidirectional: biologic factors, such as temperament and health status, affect the child-rearing environment and are affected by it. A premature infant may cry little and sleep for long periods; the infant's depressed parent may welcome this behavior, setting up a cycle that leads to poor nutrition and inadequate growth. The child's failure to thrive may reinforce the parent's sense of failure as a parent. At a later stage, impulsivity and inattention associated with early, prolonged undernutrition may lead to aggressive behavior. The cause of the aggression in this case is not the prematurity, the undernutrition, or the maternal depression, but the interaction of all these factors (Fig. 19.3). Conversely, children with biologic risk factors may nevertheless do

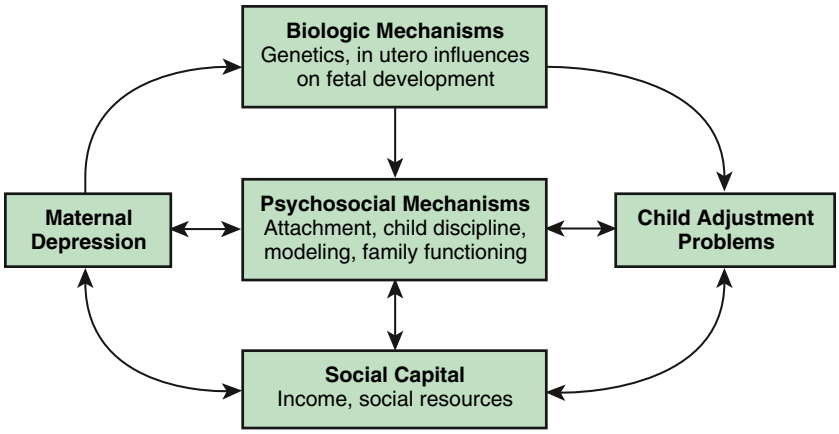

Fig. 19.3 Theoretical model of mutual influences on maternal depression and child adjustment. *(From Elgar FJ, McGrath PJ, Waschbusch DA, et al. Mutual influences on maternal depression and child adjustment problems, Clin Psychol Rev 2004;24:441–459.)*

well developmentally if the child-rearing environment is supportive. Premature infants with electroencephalographic evidence of neurologic immaturity may be at increased risk for cognitive delay. When parent–child interactions are optimal, risk of developmental disability is reduced.

An estimate of developmental risk can begin with risk factors, such as low income, low literacy, and lack of neighborhood resources. Stress and anxiety in pregnancy are associated with cognitive, behavioral, and emotional problems in the child. Early stress may have effects on aging mediated by shortening of telomere length, a link to health disparities. Risk for negative outcomes over time increases exponentially as a result of declining plasticity and accumulation of risk factors (both behavioral and environmental). Interventions are most effective in young children; over time, risk increases as the ability to change decreases.

Children growing up in poverty experience multiple levels of developmental risk: increased exposure to biologic risk factors, such as environmental lead and inadequate nutrition; lack of stimulation in the home; and decreased access to interventional education and therapeutic experiences. As they respond by withdrawal or acting out, they further discourage positive stimulation from those around them. Children of adolescent mothers are also at risk. When early intervention programs provide timely, intensive, comprehensive, and prolonged services, at-risk children show marked and sustained upswings in their developmental trajectory. Early identification of children at developmental risk, along with early intervention to support parenting, is critically important (see Chapter 20). Promoting relational health and identifying supportive community resources and interventions can buffer the negative impact of environmental risk factors.

Children can have appropriate developmental trajectories despite childhood trauma. **Resilience** is the ability to withstand, adapt to, and recover from adversities. There are several modifiable resilience factors: a positive appraisal or outlook and good executive functioning (see Chapter 49); nurturing parenting; good maternal mental health, self-care skills, and consistent household routines; and an understanding of trauma. The personal histories of children who overcome poverty often include at least one trusted adult (parent, grandparent, teacher) with whom the child has a special, supportive, close relationship. Pediatric providers are positioned to target and bolster resilience in their patients and families.

Developmental Domains and Theories of Emotion and Cognition

Child development can also be tracked by the child's developmental progress in particular domains, such as gross motor, fine motor, social, emotional, language, and cognition. Within each of these categories are *developmental* sequences of changes leading up to particular attainments. Development in the gross motor domain, from rolling to creeping to independent walking, are clear. Others, such as the line leading to the development of conscience, are subtler.

The concept of a developmental line implies that a child passes through successive stages. Several developmental theories are based on stages as qualitatively different epochs in the development of emotion and cognition (Table 19.2). In contrast, behavioral theories rely less on qualitative change and more on the gradual modification of behavior and accumulation of competence.

Psychoanalytic Theories

At the core of **Freudian theory** is the idea of body-centered (or broadly, "sexual") drives; the emotional health of both the child and the adult depends on adequate resolution of conflicts brought about by these drives. Although Freudian ideas have been challenged, they opened the door to subsequent theories of development.

Erikson recast Freud's stages in terms of the emerging personality (see Table 19.2). The child's sense of basic trust develops through the successful negotiation of infantile needs. As children progress through these psychosocial stages, different issues become salient. It is predictable that a toddler will be preoccupied with establishing a sense of autonomy, whereas a late adolescent may be more focused on establishing meaningful relationships and an occupational identity. Erikson recognized that these stages arise in the context of Western European societal expectations; in other cultures, the salient issues may be quite different.

Erikson's work calls attention to the intrapersonal challenges facing children at different ages in a way that facilitates professional intervention. Knowing that the salient issue for school-age children is industry vs inferiority, pediatricians inquire about a child's experiences of mastery and failure and (if necessary) suggest ways to ensure adequate successes.

Cognitive Theories

Cognitive development is best understood through the work of **Piaget**. A central tenet of Piaget's work is that cognition changes in *quality,* not just quantity (see Table 19.2). During the sensorimotor stage, an infant's thinking is tied to immediate sensations and a child's ability to manipulate objects. The concept of "in" is embodied in a child's act of putting a block into a cup. With the arrival of language, the nature of thinking changes dramatically; symbols increasingly take the place of objects and actions. Piaget described how children actively construct knowledge for themselves through the linked processes of **assimilation** (taking in new experiences according to existing schemata) and **accommodation** (creating new patterns of understanding to adapt to new information). In this way, children are continually and actively reorganizing cognitive processes.

There have been challenges to some of the Piaget's basic concepts. Children may reach the stages at variable ages. Of undeniable

Table 19.2 Classic Developmental Stage Theories

	INFANCY (0-1 YR)	TODDLERHOOD (2-3 YR)	PRESCHOOL (3-6 YR)	SCHOOL AGE (6-12 YR)	ADOLESCENCE (12-20 YR)
Freud: psychosexual	Oral	Anal	Phallic/oedipal	Latency	Genital
Erikson: psychosocial	Basic trust vs mistrust	Autonomy vs shame and doubt	Initiative vs guilt	Industry vs inferiority	Identity vs role diffusion
Piaget: cognitive	Sensorimotor	Sensorimotor	Preoperational	Concrete operations	Formal operations
Kohlberg: moral	—	Preconventional: avoid punishment/obtain rewards (stages 1 and 2)	Conventional: conformity (stage 3)	Conventional: law and order (stage 4)	Postconventional: moral principles

importance is Piaget's focus on cognition as a subject of empirical study, the universality of the progression of cognitive stages, and the image of a child as actively and creatively interpreting the world. Piaget's work is of special importance to pediatricians for three reasons: (1) Piaget's observations provide insight into many puzzling behaviors of infancy, such as the common exacerbation of sleep problems at 9 and 18 months of age; (2) Piaget's observations often lend themselves to quick replication in the office, with little special equipment; and (3) open-ended questioning, based on Piaget's work, can provide insights into children's understanding of illness and hospitalization.

However, other studies have found that even young children and infants are "natural scientists" and able to integrate new information through experimentation. Young children's learning is highly similar to the scientific thought process, including inductive reasoning, making predictions, and hypothesis testing. Hypotheses and conclusions about the world are constantly being revised based on the child's experience. When children are faced with evidence that conflicts with expected outcomes (**expectancy violation**), they are motivated to explore and resolve ambiguities. Children can alter their beliefs when given new evidence. That children utilize probabilistic models and exploration to resolve unexpected outcomes has strong implications for the advancement of educational theory.

Based on cognitive development, **Kohlberg** developed a theory of moral development in six stages, from early childhood through adulthood. Preschoolers' earliest sense of right and wrong is egocentric, motivated by externally applied controls. In later stages, children perceive equality, fairness, and reciprocity in their understanding of interpersonal interactions through perspective taking. Most youth will reach stage 4, conventional morality, by mid-to late adolescence. The basic theory has been modified to distinguish morality from social conventions. Whereas moral thinking considers interpersonal interactions, justice, and human welfare, social conventions are the agreed-on standards of behavior particular to a social or cultural group. Within each stage of development, children are guided by the basic precepts of moral behavior, but they also may take into account local standards, such as dress code, classroom behavior, and dating expectations. There is a broader understanding of moral development of even young infants and children theorizing an innate capacity to relate to others. Moral development can be found in very young infants, toddlers, and preschoolers who have a concept of self in relation to others, empathy and caring for others, and may incorporate their cultural context in a way that influences how and when moral development occurs.

Behavioral Theory

This theoretical perspective distinguishes itself by its lack of concern with a child's inner experience. Its focus is on observable behaviors and measurable factors that either increase or decrease the frequency with which these behaviors occur. No stages are implied; children, adults, and indeed animals all respond in the same way. In its simplest form, the behaviorist orientation asserts that behaviors that are reinforced occur more frequently; behaviors that are punished or ignored occur less frequently. Reinforcement may be further divided into *positive* reinforcement, when a reward or attention increases the chance of a behavior occurring, and *negative* reinforcement, when removal of an aversive stimulus increases the frequency of the behavior. A teacher who allows students who complete the homework Monday through Thursday not to have an assignment on Friday is using negative reinforcement to motivate homework completion during the week.

The strengths of behavioral theory are its simplicity, wide applicability, and conduciveness to scientific verification. A behavioral approach lends itself to interventions for various common problems, such as temper tantrums, aggressive preschool behavior, and eating disorders, in which behaviors are broken down into discrete units. In cognitively limited children and children with autism spectrum disorder, behavioral interventions using **applied behavior analysis** approaches have demonstrated the ability to teach new, complex behaviors. Applied behavior analysis has been particularly useful in the treatment of early-diagnosed autism spectrum disorder (see Chapter 58). However, when misbehavior is symptomatic of an underlying emotional, perceptual, or family problem, an exclusive reliance on behavior therapy risks leaving the cause untreated. Behavioral approaches can be taught to parents for application at home.

Theories Used in Behavioral Interventions

An increasing number of programs or interventions (within and outside the physician's office) are designed to influence health behaviors; some of these models are based on behavioral or cognitive theory or may have attributes of both. The most commonly employed models are the Health Belief Model, Theory of Reasoned Action, Theory of Planned Behavior, Social Cognitive Theory, and Transtheoretical Model, also known as Stages of Change Theory (see Chapter 18). Pediatricians should be aware of these models and their similarities and differences (Table 19.3). Interventions based on these theories have been designed for children and adolescents in community, clinic, and hospital-based settings.

Motivational interviewing (MI) is a technique often used in clinical settings to bring about behavior change (Chapter 18). Briefly, the goal is to enhance an individual's motivation to change behavior by exploring and overcoming ambivalence. The therapist is a partner rather than an authority figure and recognizes that, ultimately, the patient has control over his or her choices. Pediatric providers can learn brief MI techniques.

Statistics Used in Describing Growth and Development

See Chapter 27.

In everyday use, the term *normal* is synonymous with *healthy*. In a statistical sense, *normal* means that a set of values generates a

Table 19.3 Similar or Identical Elements Within Six Theories of Health Behavior

CONCEPT	GENERAL TENET OF "ENGAGING IN THE BEHAVIOR IS LIKELY IF..."	HEALTH BELIEF MODEL	THEORY OF REASONED ACTION	THEORY OF PLANNED BEHAVIOR	SOCIAL COGNITIVE THEORY	TRANS-THEORETICAL MODEL (STAGES OF CHANGE)	SOCIAL NORMS THEORY
ATTITUDINAL BELIEFS							
Appraisal of positive/ negative aspects of the behavior and expected outcome	Positive aspects outweigh negative aspects	Benefits vs. barriers; health motive	Behavioral beliefs and evaluation of those beliefs (attitudes)		Outcome expectation; expectancies	Pros, cons (decision balance)	Perceptions of peer attitudes and behaviors
SELF-EFFICACY/BELIEF ABOUT CONTROL OVER THE BEHAVIOR							
Belief in one's ability to perform the behavior; confidence	Belief that one can perform the behavior	Self-efficacy	—	Perceived behavioral control	Self-efficacy	Self-efficacy/ temptation	—
NORMATIVE AND NORM-RELATED BELIEFS AND ACTIVITIES							
Belief that others are supportive of the behavior	Belief that others support the behavior change	Cues from media, friends	Normative beliefs and motivation to comply (subjective norms)		Social support	Helping relationships (process of change)	Misperceptions of actual vs. perceived norms
Belief that others are engaging in the behavior	Other people are engaging in the behavior	—	—	—	Social environment; modeling	Social liberation (process of change)	Misperceptions of actual vs. perceived norms
Responses that increase or decrease the likelihood of engaging in the behavior; reminders	Receives positive reinforcement	Cues to action	—	—	Reinforcement	Reinforcement management/ stimulus control	Change in perceptions through media; social messaging
RISK-RELATED BELIEFS AND EMOTIONAL RESPONSES							
Belief that one is at risk if not engaging in the behavior; consequences may be severe	Belief that one is at risk for negative outcome or disease	Perceived susceptibility/ severity (perceived threat)	—	—	Emotional coping responses/ expectancies about environmental cues	Dramatic relief (process of change)	—
INTENTION/COMMITMENT/PLANNING							
Intending or planning to perform the behavior/ setting goals	Forms strong intentions to engage in the behavior/makes a commitment	—	Behavioral intentions		Self-control/ self-regulation	Contemplation/ preparation/; self-liberation (process of change)	Understanding actual norms leads to change

Adapted from Noar SM, Zimmerman RS. Health behavior theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? Health Educ Res. 2005; 20:275-290, Table 1.

Table 19.4 Relationship Between Standard Deviation (SD) and Normal Range for Normally Distributed Quantities

OBSERVATIONS INCLUDED IN THE NORMAL RANGE		PROBABILITY OF A "NORMAL" MEASUREMENT DEVIATING FROM THE MEAN BY THIS AMOUNT	
SD	%	SD	%
±1	68.3	≥1	16.0
±2	95.4	≥2	2.3
±3	99.7	≥3	0.13

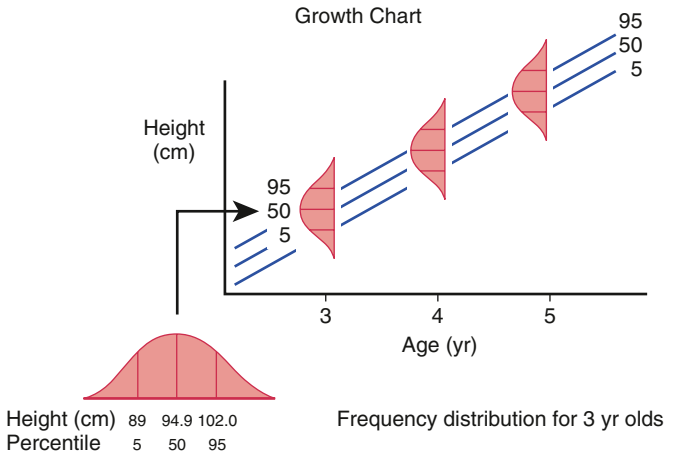

Fig. 19.4 Relationship between percentile lines on the growth curve and frequency distributions of height at different ages.

normal (bell-shaped or gaussian) distribution. This is the case with anthropometric quantities, such as height and weight, and with many developmental measures, such as IQ. For a **normally distributed measurement**, a histogram with the quantity (height, age) on the *x* axis and the frequency (the number of children of that height, or the number who stand on their own at that age) on the *y* axis generates a bell-shaped curve. In an ideal bell-shaped curve, the peak corresponds to the arithmetic **mean** (average) of the sample, as well as to the median and the mode. The **median** is the value above and below which 50% of the observations lie; the **mode** is the value with the highest number of observations. Distributions are termed *skewed* if the mean, median, and mode are not the same number.

The extent to which observed values cluster near the mean determines the width of the bell and can be described mathematically by the **standard deviation (SD)**. In the ideal normal curve, a range of values extending from 1 SD below the mean to 1 SD above the mean includes approximately 68% of the values, and each "tail" above and below that range contains 16% of the values. A range encompassing ±2 SD includes 95% of the values (with the upper and lower tails each comprising approximately 2.5% of the values), and ±3 SD encompasses 99.7% of the values (Table 19.4 and Fig. 19.4).

For any single measurement, its distance away from the mean can be expressed in terms of the number of SDs (also called a ***z* score**); one can then consult a table of the normal distribution to find out what percentage of measurements fall within that distance from the mean. Software to convert anthropometric data into *z* scores for epidemiologic purposes is available. A measurement that falls "outside the normal range" (arbitrarily defined as 2, or sometimes 3, SDs on either side of the mean) is atypical, but not necessarily indicative of illness. The further a measurement (height, weight, IQ) falls from the mean, the greater is the probability that it represents not simply normal variation, but rather a different, potentially pathologic condition.

Another way of relating an individual to a group uses percentiles. The **percentile** is the percentage of individuals in the group who have achieved a certain measured quantity (e.g., height of 95 cm) or a developmental milestone (e.g., walking independently). For anthropometric data, the percentile cutoffs can be calculated from the mean and SD. The 5th, 10th, and 25th percentiles correspond to −1.65 SD, −1.3 SD, and −0.7 SD, respectively. Figure 19.4 demonstrates how frequency distributions of a particular parameter (height) at different ages relate to the percentile lines on the growth curve.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 20

Positive Parenting and Support

Rebecca A. Baum and Samantha Schilling

No single force may be more important to a child's development than the environment in which they are raised. Many factors, both positive and negative, contribute to this environment. Parenting practices provide a foundation to promote healthy child development, protect against adverse outcomes, and foster resilience. The term **positive parenting** describes an approach to parenting that achieves these goals.

THE IMPORTANCE OF PARENTING

Interactions between parents and their children provide stimulation that promotes the development of language, early cognitive skills, and school readiness. Less frequent participation in interactive parenting practices, such as reading aloud to children, eating family meals, and participating in family outings, predicts an increased risk of developmental delay in low-income families. Interventions that increase parents' reading to children promote positive developmental outcomes such as early language and literacy development.

The affective nature of the parent–child interaction is important for both cognitive and social emotional development. Persistent maternal depression has been linked to decreases in child IQ scores at school entry. Early exposure to positive parenting has been associated with lower rates of childhood depression, risky behavior, delinquency, injuries, behavior problems, and bullying, and with increased likelihood of empathy and prosocial behavior. The beneficial effects of early maternal sensitivity on social competence have been found to persist into adulthood, contributing to the growing evidence that early parent–child interactions have a long-term impact.

Positive parenting practices, such as using a warm, supportive approach during conflict, and negative practices, such as maternal aggression, have been associated with MRI changes in adolescent brain development in males. Animal models have been used to demonstrate the detrimental effects of stressful early life experiences. Offspring raised in these environments were more likely to exhibit fearful behavior and had differences in brain architecture and in epigenetic changes that alter gene expression. Importantly in these animal models, increased maternal nurturing could protect against these changes.

THE ROLE OF THE FAMILY

Parenting occurs in the context of the family, and yet a "one size fits all" approach to understanding families does not suffice. To understand the influence of the family environment on parenting practices, it is important to appreciate the evolving diversity among U.S. families with respect to culture, race/ethnicity, and family makeup. The U.S. population continues to become more racially/ethnically diverse (61.1% in 2020 vs 54.9% in 2010). Over the last several decades, the percentage of children raised in single-parent homes has continued to grow to nearly 25% in 2020, up from 9% in 1960. It is also important to appreciate that many families face disparities in health and developmental outcomes related to racism and other forms of discrimination that may occur on the basis of religion, sexuality/gender, disability, and socioeconomic status among other factors. For many children these factors interact to further increase risk for disparities in outcomes. Children living in single-parent homes experience poverty at a higher rate than those living in two-parent homes.

Chronic stress and adverse experiences in childhood can have far-reaching consequences that negatively affect health and developmental outcomes (see Chapters 1 and 2). However, parenting—in the form of safe, stable, and nurturing relationships (SSNRs)—has been suggested as one of a number of strategies that can promote resilience and buffer adversity and turn potentially toxic stress responses into tolerable or positive responses.

PARENTING STYLES

Parenting practices are significantly influenced by culture, defined as a pattern of social norms, values, language, and behavior shared by a group of individuals. Approaches to self-regulation, for example, vary across cultures with respect to promoting attention, compliance, delayed gratification, executive function, and effortful control. In examining parent practices, it is important to recognize the role of structural racism and bias on the design and interpretation of parenting research.

Three styles of parenting have been described: authoritative, authoritarian, and permissive. Each style has varying approaches to parental control and responsiveness. A fourth style, neglectful parenting, has also been suggested. **Authoritative parenting** describes a parenting style that is warm, responsive, and accepting but that also sets expectations for behavior and achievement. Differences are approached with reasoning and discussion rather than by exerting control. **Authoritarian parenting** is characterized by a high degree of parental control in which obedience is expected. Punishment is often employed to foster compliance rather than verbal discussion. **Permissive parenting** refers to an approach characterized by warmth and acceptance with the child's autonomy being highly valued, but with few rules or expectations. This contrasts with **neglectful parenting,** similarly characterized by few rules or expectations but also by limited parental warmth or responsiveness.

An authoritative parenting style is most likely to be associated with positive child outcomes across multiple domains, including educational achievement and social-emotional competence. Parental supervision, consistency, and open communication reduce risky behaviors in adolescents. Harsh, inconsistent, and coercive discipline and physical punishment have been associated with increases in emotional and behavioral problems. Child physical abuse is often preceded by corporal punishment. In addition to a higher rate of aggression and behavioral problems, children who have experienced physical punishment have been found to have lower IQs and smaller prefrontal cortexes compared to those who have not. Much of the initial research on parenting styles was based on select U.S. populations (White middle-class families).

CHILD TEMPERAMENT

As evidenced by the effects of family structure, culture/ethnicity, and economics, parenting does not occur in isolation. The child also brings to the parent–child relationship their own personality, or **temperament,** a collection of traits that stay relatively constant over time (see Chapter 19). The initial temperament research identified nine traits: activity level, predictability of behavior, reaction to new environments, adaptability, intensity, mood, distractibility, persistence, and sensitivity. Most infants (65%) fit into one of three groups, easy (40%), difficult (10%), and slow to warm up (15%), and these patterns are relatively stable over time. Although variations in temperament traits are part of normal human variations, certain behavioral difficulties have been associated with certain temperament types. For example, a difficult temperament has been associated with the development of externalizing behavior (e.g., acting out, disruptive, and aggressive behavior) and, not surprisingly, a slow-to-warm-up temperament with internalizing behavior (e.g., anxious and moody behavior).

Temperament traits are relatively stable, but how the child functions is affected by the environment, especially by parenting and the "goodness of fit" between the parent and child. Children with difficult temperament characteristics respond more negatively to neglectful parenting, and children of all temperament groups respond positively to responsive and sensitive parenting. Moreover, childhood traits such as low adaptability, impulsivity, and low frustration tolerance may lead some parents to engage in more negative parenting practices. These findings illustrate the interactive nature between parent and child, with parental behavior shaping child behavior, and vice versa.

CHILD BEHAVIORAL PROBLEMS

Emotional and behavioral problems are common in childhood. Early behavioral problems impact at least one in five children under age 5 in the United States and are associated with impairments in multiple domains, including family, academic, and social functioning, which often continue into adulthood. Emotional and behavioral problems have been associated with single-parent households and poverty. Children in underserved populations experience life circumstances and structural barriers to care that place them at greater risk of behavior problems and unmet needs. High rates of socioeconomic disadvantage, inadequate social infrastructure, neighborhood exposure to violence, repetitive experiences of discrimination, and chronic exposure to racism among minoritized children can have significant adverse effects on children's physical and mental health. Although negative parenting may contribute to and exacerbate such problems, positive parenting practices have been shown to buffer against poor outcome for children growing up in such adversity.

Other risk factors for the development of challenging behavior include trauma and developmental problems. **Adverse childhood experiences (ACEs)**, defined as abuse and neglect, caregiver substance use, caregiver mental health problems, and domestic violence or criminality, are often present during childhood (see Chapter 1). In the National Survey of Child and Adolescent Well-Being there was a cumulative relationship between emotional and behavioral problems and ACE exposure, with children exposed to four or more ACEs being almost five times more likely to have internalizing problems than children not exposed to ACEs. A similar relationship was found for externalizing problems. Studies involving children with developmental disabilities suggest emotional and behavioral problems occur more frequently in this group than in typically developing children. These children may have delays in self-regulation and communication skills as well as increased family stress, which contribute to the increased likelihood of behavioral challenges.

DEFINING POSITIVE PARENTING

The precise definition of the components of positive parenting is lacking. Positive parenting must ensure the child's safety, health, and nutrition as well as developmental promotion. Common attributes of positive parenting include caring, leading, providing, teaching, and communicating with the child in a consistent and unconditional manner. To account for the long-term goals of successful parenting in promoting optimal emotional, behavioral, and developmental outcomes, some suggest the term **purposeful parenting** and related characteristics (Table 20.1). The characterization of an ideal approach to parenting will evolve with ever-changing societal norms, but key components such as those in Table 20.1 will likely remain fundamental.

PARENTING AS AN INTERVENTION

The influence of parenting practices on child behavior, development, and overall adjustment has led to efforts to teach parenting as a method of primary prevention. The Video Interaction Project (VIP) uses a coaching and education model with recorded parent–child interactions to foster positive parenting behavior. These parenting behaviors range from reading aloud to encouraging interactive play. In an urban, low-income, primary care setting, parent and child outcomes for the VIP group were compared to those from a lower-intensity intervention (parent mailings encouraging positive parenting behaviors) and a control group. VIP produced the most robust impacts on socioemotional outcomes, including decreased distress with separation, hyperactivity, and externalizing behavior in toddlers.

Table 20.1 Components of Purposeful Parenting

ATTRIBUTE	DEFINING ACTIONS
Protective	Ensure the child's emotional, developmental, and physiologic needs are met. Provide a safe environment. Balance the need for safety with the child's need for exploration and independence.
Personal	Show unconditional love and acceptance. Be kind and gentle. Avoid name-calling and harsh language. Label emotions and behaviors to help children understand their feelings. Teach and model helpful behavior rather than just saying "no."
Progressive	Adapt parenting skills and discipline to meet the child's developmental needs. Learn about child development to know what to expect. Notice and praise new skills and desirable behaviors.
Positive	Be warm, supportive, and optimistic, even during times of misbehavior. Avoid harsh or physical punishments. Provide encouragement and reward effort, not just a positive result.
Playful	Enjoy child-led time together to encourage exploration, foster creativity, and learn new skills. Read together.
Purposeful	Take care of your needs as a parent. Keep the long-term goals of parenting in mind. Preferentially use teaching instead of punishment to encourage desirable behavior. Be consistent with routines and expectations. Try to understand the reason behind the child's behavior.

Adapted from the work of Andrew Garner and the Ohio Chapter, American Academy of Pediatrics. http://ohioaap.org/wp-content/uploads/2013/07/BPoM_PurposefulParenting.pdf.

Table 20.2 Parent Training Program Components

COMPONENT	ACTIVITIES
Knowledge about child development and behavior	Providing developmentally appropriate environment Learning about child development Promoting positive emotional development
Positive parent–child interactions	Learning the importance of positive, non–discipline-focused interactions Using skills that promote positive interactions Providing frequent positive attention
Responsiveness and warmth	Responding sensitively to the child's emotional needs Providing appropriate physical contact and affection
Emotional communication	Using active listening to foster communication Helping children identify and express emotion
Disciplinary communication	Setting clear, appropriate, and consistent expectations Establishing limits and rules Choosing and following through with appropriate consequences
Discipline and behavior management	Understanding child misbehavior Understanding appropriate discipline strategies Using safe and appropriate monitoring and supervision practices Using reinforcement techniques Using problem solving for challenging behavior Being consistent
Promoting children's social skills and prosocial behavior	Teaching children to share, cooperate, and get along with others Using good manners
Promoting children's cognitive or academic skills	Fostering language and literacy development Promoting school readiness

Adapted from U.S. Centers for Disease Control and Prevention: *Parent training programs: insight for practitioners*, Atlanta, CDC;2009.

Positive parenting as a public health intervention has resulted in decreased rates of substantiated child maltreatment cases, out-of-home placements, and child maltreatment injuries. Other effective public health approaches include home-visiting programs, which have been deployed to at-risk families in an effort to improve maternal and child outcomes. The Maternal, Infant and Early Childhood Home Visiting Program, authorized as part of the Affordable Care Act of 2010 and again in 2015, is part of the Medicare Access and Children's Health Insurance Program (CHIP) Reauthorization Act. A key component of home-visiting programs is the promotion of positive parenting behavior to foster child developmental and school readiness. Group parenting programs have been deployed as primary prevention to promote emotional and behavioral adjustment in young children. There is moderate-quality evidence that group-based parenting programs may improve parent–child interactions. These programs typically employ praise, encouragement, and affection and have been associated with improved self-esteem and social and academic competence.

Parenting behaviors have also been employed as an *intervention* to treat emotional and behavioral problems in young children. Parenting interventions such as Incredible Years, Triple P Positive Parenting Program, New Forrest Parenting Program, and Child Adult Relationship Enhancement in Primary Care are effective for at least short-term improvements in child conduct problems, parental mental health, and parenting practices. Also called *parent training programs*, most teach the importance of play, rewards, praise, and consistent discipline and allow parents to practice new skills. This active-learning component distinguishes parent training programs from educational programs, which have been shown to be less effective.

Teaching emotional communication skills and positive parent–child interaction skills are associated with parent training programs that demonstrate a greater increase in parenting skills (Table 20.2). Several components are associated with programs that show greater improvements in child externalizing behavior including teaching parents to interact positively and respond consistently to their children as well as to use time-out correctly. All successful programs require parents to practice parenting skills during the program.

Parents have been found to benefit from participation in parenting programs. Before their participation, parents experienced a loss of control, self-blame, social isolation, and difficulty dealing with their child's emotional and behavioral problems, all of which improved after participation. The few studies that have assessed the long-term efficacy of parent-training programs suggest overall positive child outcomes but also periods of relapse during which the use of positive parenting skills decreased. Use of social supports is associated with positive child outcomes and may be an important program component when considering long-term success.

THE ROLE OF THE PEDIATRICIAN

Pediatricians and other pediatric practitioners have a primary responsibility to support the needs of parents and their children. Numerous programs and interventions have been developed to be delivered effectively and efficiently in the primary care setting.

The American Academy of Pediatrics (AAP) publishes Bright Futures and the associated Guidelines for Preventive Care to standardize child health promotion and prevention in primary care. A substantial amount of the content in Bright Futures maps to the positive-parenting domains of safety, feeding, developmental promotion, and protection. Implementing Bright Futures guidelines in health supervision visits is an important way for pediatric practitioners to support the promotion of positive parenting in practice. The AAP's policy statement titled Preventing Childhood Toxic Stress: Partnering with Families and Communities to Promote Relational Health describes the importance of the parent–child relationship in building the foundation for healthy child development as well as buffering the effects of more significant stressors.

Reading aloud to children is a powerful strategy to promote language development, early literacy, and positive parent–child interaction. The Reach Out and Read program is a primary care–based intervention that trains practitioners to encourage parents to read with their child and provides books to at-risk families. In the absence of a formal partnership with Reach Out and Read, practitioners should promote the benefits of reading aloud to children and support parents in their efforts to develop habits that incorporate reading into daily routines.

In addition to VIP described earlier, other primary care models to promote parenting have been studied. The Healthy Steps for Young Children program is a strengths-based approach delivered in the primary care setting from infancy to age 3 years. Healthy Steps promotes changes in parents' knowledge, beliefs, and psychologic health and changes in parenting behaviors using a variety of methods delivered in the office setting by the practitioner and Healthy Steps specialists and through home visits. Extensive evaluations have shown improvements in parental well-being, parenting practices, and parent–child attachment and decreased child behavior problems. Another promising approach uses community health workers and nurses to provide parenting education and allow mothers to practice parenting skills outside the office setting.

If participation in a formal parenting program is not possible, pediatric practitioners can still implement a systematic approach to support the needs of parents and their children. Practitioners can take advantage of materials in the public domain from national organizations devoted to child and family health, such as ZERO TO THREE (https://www.zerotothree.org/) and AAP (https://www.aap.org/). The U.S. Centers for Disease Control and Prevention (CDC) also provides evidenced-based parenting resources (https://www.cdc.gov/parents/essentials/index.html). Additional components include early identification of parents' concerns, addressing concerns in a supportive and nonjudgmental way, and providing linkage to treatment services when appropriate.

Parents want more information about child development, but parents of children with behavior problems often feel stigmatized and isolated. Practitioners are encouraged to be supportive and optimistic in their interactions with families and to develop a partnership aimed at promoting parent and child health (see Chapter 18). Practitioners may also encourage parents to practice new skills briefly in the office setting before trying a new skill at home. Active modeling by the practitioner using "teachable moments" may also be effective.

DISCIPLINE/PUNISHMENT

Discipline is meant to teach children to learn good behavior and thus enhance child development. There are many positive parenting approaches to discipline that help avoid confrontations and to also correct behavior without conflict or physical punishment (Tables 20.3 and 20.4) (see Chapters 25 and 26). In addition, parents should teach by example; rather than prompting a child to say thank you, the parents saying thank you is a behavior that an imitating child will follow. Furthermore, when possible, give the child a choice between positive activities, thus enhancing autonomy and preventing conflict. In verbal children, it is helpful to engage the child in problem solving by asking "how can *we* make this better?"

Table 20.3 UNICEF Approach to Positive Discipline

- Create one-on-one times for engagement
- Praise good behavior
- Set clear and realistic expectations
- Distract to a more positive activity
- Calm (not shouting) realistic consequences (if/then)

Data from United Nations Children's Fund (UNICEF). *How to discipline your child the smart and healthy way.* https://www.unicef.org/parenting/child-care/how-discipline-your-child-smart-and-healthy-way.

Table 20.4 CDC Time-Out Steps

1. Identify behavior and give warning
2. Explain why time-out
3. Go to time-out space
   - No talking
   - No playing
   - No lecturing
   - No scolding
   - No excuses from child
   - Ignore protesting or promise to be good
   - Time for both parent and child to calm down
4. End time-out
5. Explain why there was a time-out
6. Praise next positive behavior

Time-out duration rule is ~1 minute per child age in years

Adapted from U.S. Centers for Disease Control and Prevention (CDC). *Using discipline and consequences.* https://www.cdc.gov/parents/essentials/consequences/index.html. Accessed 14 March 2022.

Corporal (physical) punishment is viewed as a violation of the child's right of protection by the United Nations Convention on the Rights of Children. It is viewed by the CDC as a form of child abuse. Corporal punishment is the use of force to produce harm, pain, or discomfort in a dependent child for the purpose of correcting behavior or showing disapproval. It may be manifest by hitting, striking, smacking, slapping, whupping, pinching, kicking, shaking, burning/scalding, pulling hair, washing the mouth with soap or other harmful substances, forcing the child to assume a painful or prolonged posture/position, or using an object to inflict harm. Parents who use corporal punishment may have experienced this punishment as a child. Use of corporal punishment is also associated with adults who misuse drugs, are depressed, or experience intimate partner violence.

The consequences of corporal punishment to the child include worsening behavioral problems including aggression and adverse effects on cognitive development and mental health (anxiety, depression). In addition, corporal punishment does not correct the behavior. Furthermore, there may be a dose-response relationship between the frequency of corporal punishment and adverse child behaviors and development.

For age-related approaches to discipline see Chapters 24, 25, and 26.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 21

Assessment of Fetal Growth and Development

Alexander S. Whitaker and Susan Feigelman

The developing fetus is affected by social and environmental influences, including maternal nutritional status, substance use (both legal and illicit), and psychologic trauma. Correspondingly, the psychologic alterations experienced by the parents during the gestation profoundly impact the lives of all members of the family. The complex interplay among these forces and the somatic and neurologic transformations occurring in the fetus influence growth and behavior at birth, through infancy, and potentially throughout the individual's life.

SOMATIC DEVELOPMENT

Embryonic Period

Table 21.1 lists milestones of prenatal development. By 6 days postconception age, as implantation begins, the embryo consists of a spherical mass of cells with a central cavity (the *blastocyst*). By 2 weeks, implantation is complete and the uteroplacental circulation has begun; the embryo has two distinct layers, *endoderm* and *ectoderm*, and the amnion has started to form. By 3 weeks, the third primary germ layer *(mesoderm)* has appeared, along with a primitive neural tube and blood vessels. Paired heart tubes have begun to pump.

During weeks 4-8, lateral folding of the embryologic plate, followed by growth at the cranial and caudal ends and the budding of arms and legs, produces a human-like shape. Precursors of skeletal muscle and vertebrae (somites) appear, along with the branchial arches that will form the mandible, maxilla, palate, external ear, and other head and neck structures. Lens placodes appear, marking the site of future eyes; the brain grows rapidly. By the end of week 8, as the embryonic period closes, the rudiments of all major organ systems have developed; the crown-rump length is 3 cm.

Fetal Period

From the ninth week on (fetal period), somatic changes consist of rapid body growth as well as differentiation of tissues, organs, and organ systems. Figure 21.1 depicts changes in body proportion. By week 10, the face is recognizably human. The midgut returns to the abdomen from the umbilical cord, rotating counterclockwise to bring the stomach, small intestine, and large intestine into their normal positions. By week 12, the gender of the external genitals becomes clearly distinguishable. Lung development proceeds, with the budding of bronchi, bronchioles, and successively smaller divisions. By weeks 20-24, primitive alveoli have formed and surfactant production has begun; before that time, the absence of alveoli renders the lungs useless as organs of gas exchange.

During the third trimester, weight triples and length doubles as body stores of protein, fat, iron, and calcium increase.

NEUROLOGIC DEVELOPMENT

During the third week, a neural plate appears on the ectodermal surface of the trilaminar embryo. Infolding produces a neural tube that will become the central nervous system and a neural crest that will become the peripheral nervous system. Neuroectodermal cells differentiate into neurons, astrocytes, oligodendrocytes, and ependymal cells, whereas microglial cells are derived from mesoderm. By the fifth week, the three main subdivisions of forebrain, midbrain, and hindbrain are evident. The dorsal and ventral horns of the spinal cord have begun to form, along with the peripheral motor and sensory nerves. Myelination begins at midgestation and continues for years.

By the end of the embryonic period (week 8), the gross structure of the nervous system has been established. On a cellular level, neurons migrate outward to form the six cortical layers. Migration is complete by the sixth month, but differentiation continues. Axons and dendrites form synaptic connections at a rapid pace, making the central nervous system vulnerable to teratogenic or hypoxic influences throughout gestation. Figure 21.2 shows rates of increase in DNA (a marker of cell number), overall brain weight, and cholesterol (a marker of myelinization). Epigenetic modifications are made in the presence of fetal gonadal steroids, directing masculinization of the male brain. The prenatal and postnatal peaks of DNA probably represent rapid growth of neurons and glia, respectively. The glial cells are important in shaping the brain and neuronal circuits. The various types of glial cells are needed for the formation of axonal myelin sheaths, a range of functions in the formation and maintenance of neural pathways, and removal of waste (the brain has no lymphoid system for this task).

By the time of birth, the structure of the brain is complete. However, many cells will undergo *apoptosis* (cell death). Synapses will be pruned back substantially, and new connections will be made, largely as a result of experience. Many psychiatric and developmental disorders are thought to result at least in part from disruptions in the **functional connectivity** of brain networks. Disorders of connectivity may begin during fetal life; MRI studies provide a developmental timetable for such connections that lend support to the possible role of disruptions in the establishment of such connections.

BEHAVIORAL DEVELOPMENT

No behavioral evidence of neural function is detectable until the third month. Reflexive responses to tactile stimulation develop in a craniocaudal sequence. By weeks 13-14, breathing and swallowing motions appear. The grasp reflex appears at 17 weeks and is well developed by 27 weeks. Eye opening occurs around 26-28 weeks. By midgestation, the full range of neonatal movements can be observed.

During the third trimester, fetuses respond to external stimuli with heart rate elevation and body movements, which can be observed with ultrasound (see Chapter 117). Reactivity to auditory (vibroacoustic) and visual (bright light) stimuli vary, depending on their behavioral state, which can be characterized as quiet sleep, active sleep, or awake. Individual differences in the level of fetal activity are usually noted by mothers. Fetuses will preferentially turn to light patterns in the configuration of the human face. Fetal movement is affected by maternal medications and diet, increasing after ingestion of caffeine. Behavior may be entrained to the mother's diurnal rhythms: asleep during the day, active at night. Abnormal fetal movement patterns are found in neonates with subsequent muscular or neurologic abnormalities.

Fetal movement increases in response to a sudden auditory tone but decreases after several repetitions. This demonstrates **habituation**, a basic form of learning in which repeated stimulation results in a response decrement. If the tone changes in pitch, the movement increases again, which is evidence that the fetus distinguishes between a familiar, repeated tone and a novel tone. Habituation improves in older fetuses and decreases in neurologically impaired or physically stressed fetuses. Similar responses to visual and tactile stimuli have been observed.

PSYCHOLOGIC CHANGES IN PARENTS

Many psychologic changes occur during pregnancy. An unplanned pregnancy may be met with anger, denial, or depression. Ambivalent feelings are common, whether or not the pregnancy was planned. Elation at the thought of producing a baby and the wish to be the perfect parent compete with fears of inadequacy and of the lifestyle changes that parenting will impose. Parents of an existing child may feel protective of the child, worried that the child may feel less valued. Old conflicts may resurface as a woman psychologically identifies with her own mother and with herself as a child. The father-to-be faces similar mixed feelings, and problems in the parental relationship may intensify.

Tangible evidence that a fetus exists as a separate being, whether as a result of ultrasonic visualization or awareness of fetal movements known as *quickening* (at 16-20 weeks), often heightens a

woman's feelings. Parents worry about the fetus's healthy development and mentally rehearse what they will do if the child is malformed, including their response to evidence of abnormality through ultrasound, amniocentesis, or other fetal laboratory tests. Toward the end of pregnancy, a woman becomes aware of patterns of fetal activity and reactivity and begins to ascribe to her fetus an individual personality and an ability to survive independently. Appreciation of the psychologic vulnerability of the expectant parents and of the powerful contribution of fetal behavior facilitates supportive clinical intervention.

Table 21.1 Milestones of Prenatal Development

WK	DEVELOPMENTAL EVENTS
1	Fertilization and implantation; beginning of *embryonic* period
2	Endoderm and ectoderm appear (bilaminar embryo)
3	First missed menstrual period; mesoderm appears (trilaminar embryo); somites begin to form
4	Neural folds fuse; folding of embryo into human-like shape; arm and leg buds appear; crown-rump length 4-5 mm
5	Lens placodes, primitive mouth, digital rays on hands
6	Primitive nose, philtrum, primary palate
7	Eyelids begin; crown-rump length 2 cm
8	Ovaries and testes distinguishable
9	*Fetal* period begins; crown-rump length 5 cm; weight 8 g
12	External genitals distinguishable
20	Usual lower limit of viability; weight 460 g; length 19 cm
25	Third trimester begins; weight 900 g; length 24 cm
28	Eyes open; fetus turns head down; weight 1,000-1,300 g
38	Term

THREATS TO FETAL DEVELOPMENT

Mortality and morbidity are highest during the prenatal period (see Chapter 114). An estimated 50% of all pregnancies end in spontaneous abortion, including 10–15% of all clinically recognized pregnancies. The majority occur in the first trimester. Many spontaneous abortions occur as a result of chromosomal abnormalities, most commonly aneuploidies.

Teratogens associated with gross physical and mental abnormalities include various infectious agents (e.g., toxoplasmosis, rubella, syphilis, Zika virus), chemical agents (e.g., mercury, thalidomide, antiepileptic medications, retinoids, ethanol), high temperature, and radiation (see Chapters 117 and 758).

Teratogenic effects may also result in decreased growth and cognitive or behavioral deficits that only become apparent later in life. Nicotine has vasoconstrictor properties and may disrupt dopaminergic and serotonergic pathways. Prenatal exposure to cigarette smoke is associated with lower birthweight, stunting, and smaller head circumference. It is also associated with changes in neonatal neurodevelopmental assessments; later, these children are at increased risk for learning problems, attention and behavior disorders, and other long-term health effects. Alcohol is a common teratogen affecting physical development, cognition, and behavior (see Chapter 146). Prenatal exposure to opiates can result in neonatal abstinence syndrome (NAS) characterized by irritability, poor feeding, tremors and temperature instability in newborn infants. Affected infants may require treatment with low-dose opiates to abate the symptoms. School-age children with a history of NAS are significantly more likely to have educational disabilities, even when controlling for external factors such as maternal educational attainment and gestational age.

The effects of prenatal exposure to cocaine, also occurring through alternations in placental blood flow and in direct toxic effects to the developing brain, have been followed in several cohorts and are less dramatic than previously believed. Exposed adolescents show small but significant effects in behavior and functioning but may not show cognitive impairment. Associated risk factors including alcohol and tobacco use, and postnatal environments frequently characterized by toxic stress, may explain some of the observed negative developmental outcomes. (see Chapters 1, 15, and 17).

The association between an inadequate nutrient supply to the fetus and low birthweight has been recognized for decades; this adaptation

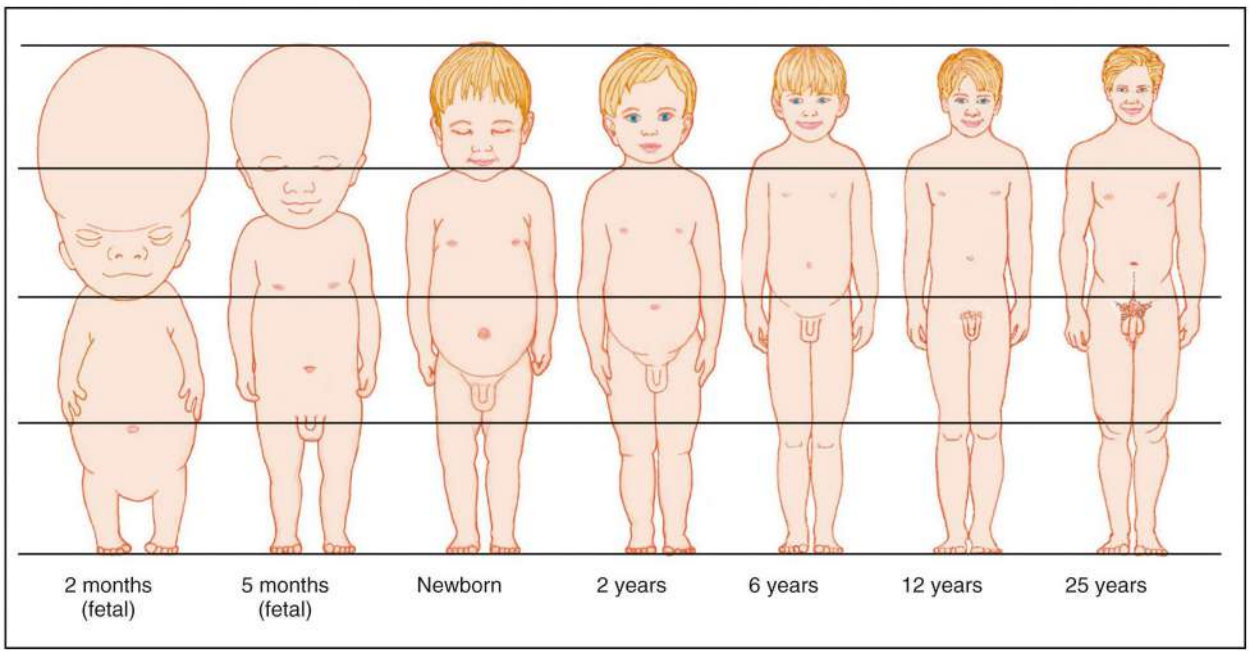

Fig. 21.1 Changes in body proportions. Approximate changes in body proportions from fetal life through adulthood. *(From Leifer G. Introduction to Maternity & Pediatric Nursing. Philadelphia: WB Saunders;2011: pp 347–385, Fig. 15-2.)*

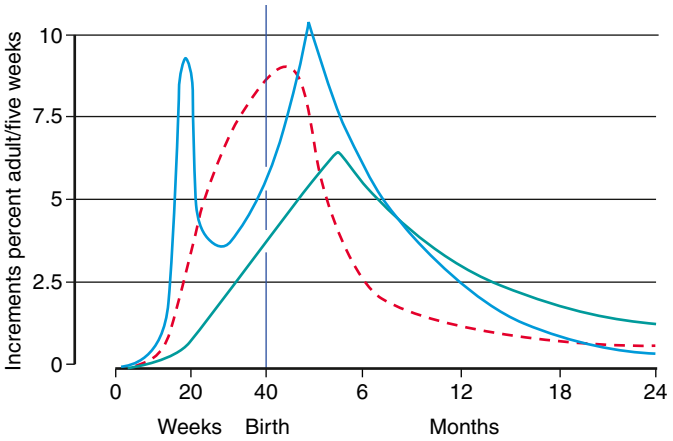

Fig. 21.2 Velocity curves of the various components of human brain growth. *Blue line,* DNA; *red line,* brain weight; *green line,* cholesterol. *From Brasel JA, Gruen RK. In Falkner F, Tanner JM, eds: Human Growth: a comprehensive treatise. New York: Plenum Press; 1986: pp 78–95.*

on the part of the fetus presumably increases the likelihood that the fetus will survive until birth. For any potential fetal insult, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol, timing of exposure, and the mother's diet may explain the variability in fetal alcohol effects. Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the first trimester (**organogenesis**) (http://www.epa.gov/children/children-are-not-little-adults details critical periods and specific developmental abnormalities).

Fetal adaptations or responses to an adverse situation in utero, termed **fetal programming** or **developmental plasticity**, have lifelong implications. Fetal programming may prepare the fetus for an environment that matches that experienced in utero. Fetal programming in response to some environmental and nutritional signals in utero increases the risk of cardiovascular disease, diabetes, and obesity in later life. These adverse long-term effects appear to represent a mismatch between environmental conditions faced by a fetus or neonate and the conditions that the individual will confront later in life. A fetus deprived of adequate calories may or may not face famine as a child or adolescent. One proposed mechanism for fetal programming is epigenetic imprinting, in which one of two alleles is turned off through environmentally induced epigenetic modification (see Chapter 97). Many environmental factors have been found to play a role in producing epigenetic modifications that are both transgenerational (direct effect on the developing fetus) and intergenerational (changes in the germ cells that will affect future generations).

Just as the fetal adaptations to the in utero environment may increase the likelihood of later metabolic conditions, the fetus adapts to the mother's psychologic distress. In response to the stressful environment, physiologic changes involving the hypothalamic-pituitary-adrenal axis and the autonomic nervous system occur. Dysregulation of these systems may explain the associations observed in some but not all studies between maternal distress and negative infant outcomes. These negative outcomes include low birthweight, spontaneous abortion, prematurity, and decreased head circumference. In addition, children born to mothers experiencing high stress levels have been found to have higher rates of inattention, impulsivity, conduct disorders, and negative cognitive changes. Although these changes may have been adaptive in primitive cultures, they are maladaptive in modern societies, leading to psychopathology. Genetic variability, timing of stress during sensitive periods, and the quality of postnatal parenting can attenuate or exacerbate these associations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 22

The Newborn

Elisa Hampton and John M. Olsson

See also Chapter 115.

Regardless of gestational age, the newborn (neonatal) period begins at birth and includes the first month of life. During this time, marked physiologic transitions occur in all organ systems, and the infant learns to respond to many forms of external stimuli. Because infants thrive physically and psychologically only in the context of their social relationships, any description of the newborn's developmental status has to include consideration of the parents' role as well.

PARENTAL ROLE IN PARENT–INFANT ATTACHMENT

Parenting a newborn infant requires dedication because a newborn's needs are urgent, continuous, and often unclear. Parents must attend to an infant's signals and respond empathically. Many factors influence parents' ability to assume this role.

Prenatal Factors

Pregnancy is a period of psychologic preparation for the profound demands of parenting. Expectant parents may experience ambivalence, particularly (but not exclusively) if the pregnancy was unplanned. Financial concerns, physical illness, prior miscarriages or stillbirths, or other crises may interfere with future bonding. For adolescent parents, the demand that they relinquish their own developmental agenda, such as an active social life, may be especially burdensome.

The transition to parenthood is a unique developmental phase, and a stressful one. Lifetime experiences of parents, particularly traumatic ones, may affect their approaches to developing a nurturing relationship with their infant (Table 22.1). It has been shown that an increasing number of adverse childhood experiences (ACEs) may be associated with increased parental stress, a more authoritarian style of parenting, increased risk for child abuse, and greater insecurity in parent–child attachment (bonding). Identifying parental ACEs and addressing them with community resources, including parenting classes, parent aides, and parent support groups may help provide parents with the resilience to mitigate the effects of ACEs.

Table 22.1 Prenatal Risk Factors for Attachment

Recent death of a loved one
Previous loss of or serious illness in another child
Prior removal of a child
History of depression or serious mental illness
History of infertility or pregnancy loss
Troubled relationship with parents
Financial stress or job loss
Marital discord or poor relationship with the other parent
Recent move or no community ties
No friends or social network
Unwanted pregnancy
No good parenting model
Experience of poor parenting
Drug and/or alcohol use
Extreme immaturity

From Dixon SD, Stein MT. *Encounters With Children: Pediatric Behavior and Development.* 4th ed. Philadelphia: Mosby, 2006. p 131.

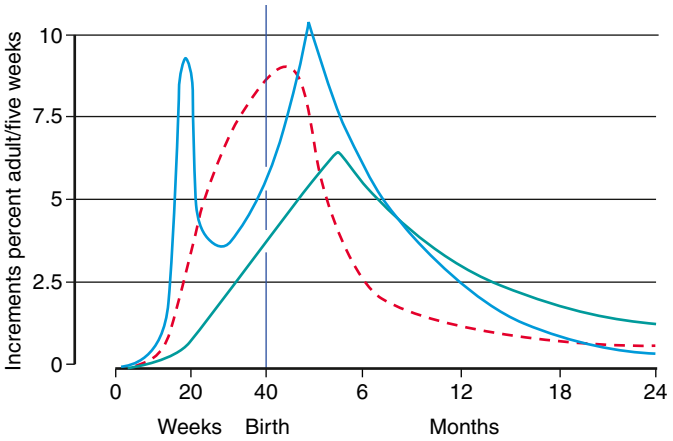

Fig. 21.2 Velocity curves of the various components of human brain growth. *Blue line,* DNA; *red line,* brain weight; *green line,* cholesterol. *From Brasel JA, Gruen RK. In Falkner F, Tanner JM, eds: Human Growth: a comprehensive treatise. New York: Plenum Press; 1986: pp 78–95.*

on the part of the fetus presumably increases the likelihood that the fetus will survive until birth. For any potential fetal insult, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol, timing of exposure, and the mother's diet may explain the variability in fetal alcohol effects. Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the first trimester (**organogenesis**) (http://www.epa.gov/children/children-are-not-little-adults details critical periods and specific developmental abnormalities).

Fetal adaptations or responses to an adverse situation in utero, termed **fetal programming** or **developmental plasticity**, have lifelong implications. Fetal programming may prepare the fetus for an environment that matches that experienced in utero. Fetal programming in response to some environmental and nutritional signals in utero increases the risk of cardiovascular disease, diabetes, and obesity in later life. These adverse long-term effects appear to represent a mismatch between environmental conditions faced by a fetus or neonate and the conditions that the individual will confront later in life. A fetus deprived of adequate calories may or may not face famine as a child or adolescent. One proposed mechanism for fetal programming is epigenetic imprinting, in which one of two alleles is turned off through environmentally induced epigenetic modification (see Chapter 97). Many environmental factors have been found to play a role in producing epigenetic modifications that are both transgenerational (direct effect on the developing fetus) and intergenerational (changes in the germ cells that will affect future generations).

Just as the fetal adaptations to the in utero environment may increase the likelihood of later metabolic conditions, the fetus adapts to the mother's psychologic distress. In response to the stressful environment, physiologic changes involving the hypothalamic-pituitary-adrenal axis and the autonomic nervous system occur. Dysregulation of these systems may explain the associations observed in some but not all studies between maternal distress and negative infant outcomes. These negative outcomes include low birthweight, spontaneous abortion, prematurity, and decreased head circumference. In addition, children born to mothers experiencing high stress levels have been found to have higher rates of inattention, impulsivity, conduct disorders, and negative cognitive changes. Although these changes may have been adaptive in primitive cultures, they are maladaptive in modern societies, leading to psychopathology. Genetic variability, timing of stress during sensitive periods, and the quality of postnatal parenting can attenuate or exacerbate these associations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 22

The Newborn

Elisa Hampton and John M. Olsson

See also Chapter 115.

Regardless of gestational age, the newborn (neonatal) period begins at birth and includes the first month of life. During this time, marked physiologic transitions occur in all organ systems, and the infant learns to respond to many forms of external stimuli. Because infants thrive physically and psychologically only in the context of their social relationships, any description of the newborn's developmental status has to include consideration of the parents' role as well.

PARENTAL ROLE IN PARENT–INFANT ATTACHMENT

Parenting a newborn infant requires dedication because a newborn's needs are urgent, continuous, and often unclear. Parents must attend to an infant's signals and respond empathically. Many factors influence parents' ability to assume this role.

Prenatal Factors

Pregnancy is a period of psychologic preparation for the profound demands of parenting. Expectant parents may experience ambivalence, particularly (but not exclusively) if the pregnancy was unplanned. Financial concerns, physical illness, prior miscarriages or stillbirths, or other crises may interfere with future bonding. For adolescent parents, the demand that they relinquish their own developmental agenda, such as an active social life, may be especially burdensome.

The transition to parenthood is a unique developmental phase, and a stressful one. Lifetime experiences of parents, particularly traumatic ones, may affect their approaches to developing a nurturing relationship with their infant (Table 22.1). It has been shown that an increasing number of adverse childhood experiences (ACEs) may be associated with increased parental stress, a more authoritarian style of parenting, increased risk for child abuse, and greater insecurity in parent–child attachment (bonding). Identifying parental ACEs and addressing them with community resources, including parenting classes, parent aides, and parent support groups may help provide parents with the resilience to mitigate the effects of ACEs.

Table 22.1 Prenatal Risk Factors for Attachment

Recent death of a loved one
Previous loss of or serious illness in another child
Prior removal of a child
History of depression or serious mental illness
History of infertility or pregnancy loss
Troubled relationship with parents
Financial stress or job loss
Marital discord or poor relationship with the other parent
Recent move or no community ties
No friends or social network
Unwanted pregnancy
No good parenting model
Experience of poor parenting
Drug and/or alcohol use
Extreme immaturity

From Dixon SD, Stein MT. *Encounters With Children: Pediatric Behavior and Development.* 4th ed. Philadelphia: Mosby, 2006. p 131.

Social support during pregnancy, particularly support from the partner and close family members, is also important. Family support can promote resilience in the face of ACEs as described earlier.

Many decisions have to be made by parents in anticipation of the birth of their child. One important choice is how the infant will be nourished. Among the important benefits of **breastfeeding** is its promotion of bonding. Providing breastfeeding education for the parents during prenatal pediatric or obstetric care can increase maternal confidence in breastfeeding after delivery, reduce stress during the newborn period, and promote increased breastfeeding rates and duration (see Chapter 61).

Peripartum and Postpartum Influences

The continuous presence of a support person during labor results in shorter labor and fewer obstetric complications (including cesarean section). These beneficial effects may be even more pronounced when the support person is specially trained and present solely for the purpose of continuous support (a **doula**). Early skin-to-skin contact between mothers and infants immediately after birth is associated with an increased rate and longer duration of breastfeeding. Most new parents value even a brief period of uninterrupted time in which to get to know their new infant, and increased mother–infant contact over the first days of life may improve long-term mother–child interactions. Nonetheless, early separation, although predictably very stressful, does not inevitably impair a mother's ability to bond with her infant.

Postpartum mood and anxiety disorder (PMAD) may occur in the first week or up to 6 months after delivery and can adversely affect neonatal growth and development. Screening tools, such as the **Edinburgh Postnatal Depression Scale (EPDS)**, are available for use during neonatal and infant visits to the pediatric provider. Screening mothers for PMAD is recommended at the 1, 2, 4, and 6 month well child visit. PMAD is also seen in partners of postpartum women, but peaks later at 3-6 months. Pediatric providers should consider screening partners at the 6 month well child visit using the EPDS. A score of 10 or higher, or a positive response to question 10 (suicidal thoughts), in either postpartum women or their partners warrants referral for evaluation (Table 22.2).

THE INFANT'S ROLE IN PARENT–INFANT ATTACHMENT

The in utero environment contributes greatly but not completely to the future growth and development of the fetus. Abnormalities in maternal-fetal placental circulation and maternal glucose metabolism or the presence of maternal infection can result in abnormal fetal growth. Infants may be small or large for gestational age as a result. These abnormal growth patterns not only predispose infants to an increased requirement for medical intervention, but they also may affect their ability to respond behaviorally to their parents.

Physical Examination

Examination of the newborn should include an **evaluation of growth** (see Chapter 21) and an **observation of behavior**. The average term newborn weighs approximately 3.4 kg (7.5 lb); boys are slightly heavier than girls. The average length and head circumference are about 50 cm (20 in) and 35 cm (14 in), respectively, in term infants. Each newborn's growth parameters should be plotted on growth curves specific for that infant's gestational age to determine the appropriateness of size. Specific growth charts for conditions associated with variations in growth patterns have also been developed. It is important to note that in the United States, significant disparities exist in low birthweight (<2,500 g) rates with higher rates in low socioeconomic status (SES) groups and in minoritized populations.

The infant's response to being examined may be useful in assessing its vigor, alertness, and tone. Observing how the parents handle their infant, their comfort, and affection is also important. The order of the physical examination should be from the least to the most intrusive maneuvers. Assessing visual tracking and response to sound and noting changes of tone with level of activity and alertness are very helpful. Performing this examination and sharing impressions with parents is an important opportunity to facilitate bonding (see Chapter 115).

Interactional Abilities

Soon after birth, neonates are alert and ready to interact and nurse. This first alert-awake period may be affected by maternal analgesics and anesthetics or fetal hypoxia. Neonates are nearsighted, having a fixed focal length of 8-12 inches, approximately the distance from the breast to the mother's face, as well as an inborn visual preference for faces. Hearing is well developed, and infants preferentially turn toward a female voice. These innate abilities and predilections increase the likelihood that when a mother gazes at her newborn, the baby will gaze back. The initial period of social interaction, usually lasting about 40 minutes, is followed by a period of somnolence. After that, briefer periods of alertness or excitation alternate with sleep. If a mother misses her baby's first alert-awake period, she may not experience as long a period of social interaction for several days. The hypothalamic-midbrain-limbic-paralimbic-cortical circuits of the parent's brain together support responses to the infant that are critical for effective parenting (e.g., emotion, attention, motivation, empathy, decision-making).

Modulation of Arousal

Adaptation to extrauterine life requires rapid and profound physiologic changes, including aeration of the lungs, rerouting of the circulation, and activation of the intestinal tract. The necessary behavioral changes are no less profound. To obtain nourishment, to avoid hypo- and hyperthermia, and to ensure safety, neonates must react appropriately to an expanded range of sensory stimuli. Infants must become aroused in response to stimulation, but not so overaroused that their behavior becomes disorganized. Underaroused infants are not able to feed and interact; overaroused infants show signs of **autonomic instability**, including flushing or mottling, perioral pallor, hiccupping, vomiting, uncontrolled limb movements, and inconsolable crying.

Behavioral States

The organization of infant behavior into discrete behavioral states may reflect an infant's inborn ability to regulate arousal. *Six states* have been described: quiet sleep, active sleep, drowsy, alert, fussy, and crying. In the **alert state**, infants visually fixate on objects or faces and follow them horizontally and (within a month) vertically; they also reliably turn toward a novel sound, as if searching for its source. When overstimulated, they may calm themselves by looking away, yawning, or sucking on their lips or hands, thereby increasing parasympathetic activity and reducing sympathetic nervous system activity. The behavioral state determines an infant's muscle tone, spontaneous movement, electroencephalogram pattern, and response to stimuli. In **active sleep**, an infant may show progressively less reaction to a repeated heelstick (habituation), whereas in the **drowsy state**, the same stimulus may push a child into fussing or crying.

Mutual Regulation

Parents actively participate in an infant's state regulation, alternately stimulating and soothing. In turn, they are regulated by the infant's signals, responding to cries of hunger with a letdown of milk (or with a bottle). Such interactions constitute a system directed toward furthering the infant's physiologic homeostasis and physical growth. At the same time, they form the basis for the emerging psychologic relationship between parent and child. Infants come to associate the presence of the parent with the pleasurable reduction of tension (as

Table 22.2 Edinburgh Postnatal Depression Scale

INSTRUCTIONS FOR USERS

1. The mother is asked to underline the response that comes closest to how she has been feeling in the previous 7 days.
2. All 10 items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others.
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.
5. The Edinburgh Postnatal Depression Scale may be used at 6-8 wk to screen postnatal women. The child health clinic, a postnatal checkup, or a home visit may provide a suitable opportunity for its completion.

EDINBURGH POSTNATAL DEPRESSION SCALE

Name:

Address:

Baby's age:

Because you have recently had a baby, we would like to know how you are feeling. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

Here is an example, already completed.

I have felt happy:

Yes, all the time
Yes, most of the time
No, not very often
No, not at all

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all
2. I have looked forward with enjoyment to things
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never

4. I have been anxious or worried for no good reason
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often

*5. I have felt scared or panicky for no very good reason
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all

*6. Things have been getting on top of me
   - Yes, most of the time I haven't been able to cope at all
   - Yes, sometimes I haven't been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever

*7. I have been so unhappy that I have had difficulty sleeping
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all

*8. I have felt sad or miserable
   - Yes, most of the time
   - Yes, quite often
   - Not very often
   - No, not at all

*9. I have been so unhappy that I have been crying
   - Yes, most of the time
   - Yes, quite often
   - Only occasionally
   - No, never

*10. The thought of harming myself has occurred to me
   - Yes, quite often
   - Sometimes
   - Hardly ever
   - Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom. Items marked with an asterisk (*) are reverse-scored (i.e., 3, 2, 1, and 0). The total score is calculated by adding the scores for each of the 10 items. Users may reproduce the scale without further permission provided they respect copyright (which remains with the *British Journal of Psychiatry*) by quoting the names of the authors, the title, and the source of the paper in all reproduced copies.

Adapted from Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150:782–786; reproduced from Currie ML, Rademacher R. The pediatrician's role in recognizing and intervening in postpartum depression. *Pediatr Clin North Am*. 2004;51(3):785–xi.

in feeding) and show this preference by calming more quickly for their parent than for a stranger. This response in turn strengthens a parent's sense of efficacy and their connection with their baby.

IMPLICATIONS FOR THE PEDIATRICIAN

The pediatrician can support healthy newborn development in several ways.

Optimal Practices

A **prenatal pediatric visit** allows pediatricians to assess both the strengths of the expectant parents and any needs they may have in anticipation of the birth of their infant. This should include assessment of social determinants of health and may consist of addressing needs such as baby supplies, financial assistance, and parental mental health support. **Supportive hospital policies** include the use of birthing rooms rather than operating suites and delivery rooms; encouraging the partner or a trusted relative or friend to remain with the mother during labor or the provision of a professional doula; the practice of giving the newborn infant to the mother immediately after drying and a brief assessment; keeping the newborn with the mother rather than in a central nursery; and avoiding in-hospital distribution of infant formula. Such policies ("Baby Friendly Hospital") have been shown to significantly increase breastfeeding rates (see Chapter 115.3). After discharge, **home visits** by nurses and lactation counselors can reduce early feeding problems and identify emerging medical conditions in either mother or baby. Infants requiring transport to another hospital should be brought to see the mother first, if at all possible. Timing of hospital discharge should be individualized for each maternal–infant dyad based on the mode of delivery, presence or absence of specific risk factors, and any problems identified during the birth hospitalization. Some healthy term newborns may be discharged before 48 hours of life, and these newborns should be evaluated with a follow up visit by 3-5 days after birth and within 48-72 hours after discharge. The timing of the first visit for newborns with a longer initial hospital stay will depend on the newborn's specific issues and identified needs.

Assessing Parent–Infant Interactions

During a feeding or when infants are alert and face-to-face with their parents, it is normal for the dyad to appear absorbed in one another. Infants who become overstimulated by the parent's voice or activity may turn away or close their eyes, leading to a premature termination of the encounter. Alternatively, the infant may be ready to interact, but the parent may appear preoccupied. Asking a new mother about her own emotional state, and inquiring specifically about a history of depression, facilitates referral for therapy, which may provide long-term benefits to the child.

Teaching About Individual Competencies

The **Newborn Behavior Assessment Scale (NBAS)** provides a formal measure of an infant's neurodevelopmental competencies, including state control, autonomic reactivity, reflexes, habituation, and orientation toward auditory and visual stimuli. This examination can also be used to demonstrate to parents an infant's capabilities and vulnerabilities. Parents might learn that they need to undress their infant to increase the level of arousal or to swaddle the infant to reduce overstimulation by containing random arm movements. The NBAS can be used to support the development of positive early parent–infant relationships. Demonstration of the NBAS to parents in the first week of life has been shown to correlate with improvements in the caretaking environment months later.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 23

The First Year

Mutiat T. Onigbanjo and Susan Feigelman

The prenatal period and the first year of life provide the platform for remarkable growth and development, setting the trajectory for a child's life. **Neural plasticity**, the ability of the brain to be shaped by experience, both positive and negative, is at its peak. Total brain volume doubles in the first year of life and increases by an additional 15% over the second year. Total brain volume at age 1 month is approximately 36% of adult volume but by age 1 year is approximately 72% (83% by 2 years) (Fig. 23.1).

The acquisition of seemingly "simple" skills, such as swallowing, reflects a series of intricate and highly coordinated processes involving multiple levels of neural control distributed among several physiologic systems whose nature and relationships mature throughout the first year of life. Substantial learning of the basic tools of language (phonology, word segmentation) occurs during infancy. Speech processing in older individuals requires defined and precise neuronal networks; the infant brain possesses a structural and functional organization similar to that of adults, suggesting that structural neurologic processing of speech may guide infants to discover the properties of their native language. Myelination of the cortex begins at 7-8 months' gestation and continues into adolescence and young adulthood. It proceeds posterior to anterior, allowing progressive maturation of sensory, motor, and finally associative pathways. Given the importance of iron, cholesterol, and other nutrients in myelination, adequate stores throughout infancy are critical (see Chapter 61). Insufficient interactions with caregivers or the wider environment may alter experience-dependent processes that are critical to brain structure development and function during infancy. Although for some processes, subsequent stimulation may allow catch-up; as the periods of plasticity close during the rapid developmental changes occurring in infancy, more permanent deficits may result.

The infant acquires new competences in all developmental domains. The concept of **developmental trajectories** recognizes that complex skills build on simpler ones; it is also important to realize how development in each domain affects functioning in all the others. All growth parameters should be plotted using the World Health Organization charts, which show how children from birth through 72 months "should" grow under optimal circumstances (see Figs. 24.1 and 24.2). Table 23.1 presents an overview of key milestones by domain; Table 23.2 presents similar information arranged by age. Table 23.3 presents age at time of x-ray appearance of centers of ossification. Parents often seek information about "normal development" during this period and should be directed to reliable sources, including the American Academy of Pediatrics website (www.healthychildren.org) or the Center for Disease Control website (www.cdc.gov/ncbddd/actearly/milestones/index.html).

AGE 0-2 MONTHS

In the full-term infant, **myelination** is present by the time of birth in the dorsal brainstem, cerebellar peduncles, and posterior limb of the internal capsule. The cerebellar white matter acquires myelin by 1 month of age and is well myelinated by 3 months. The subcortical white matter of the parietal, posterior frontal, temporal, and calcarine cortex is partially myelinated by 3 months of age. In this period the infant experiences tremendous growth. Physiologic changes allow the establishment of effective feeding routines and a predictable sleep–wake cycle. The social interactions that occur as parents and infants accomplish these tasks lay the foundation for cognitive and emotional development.

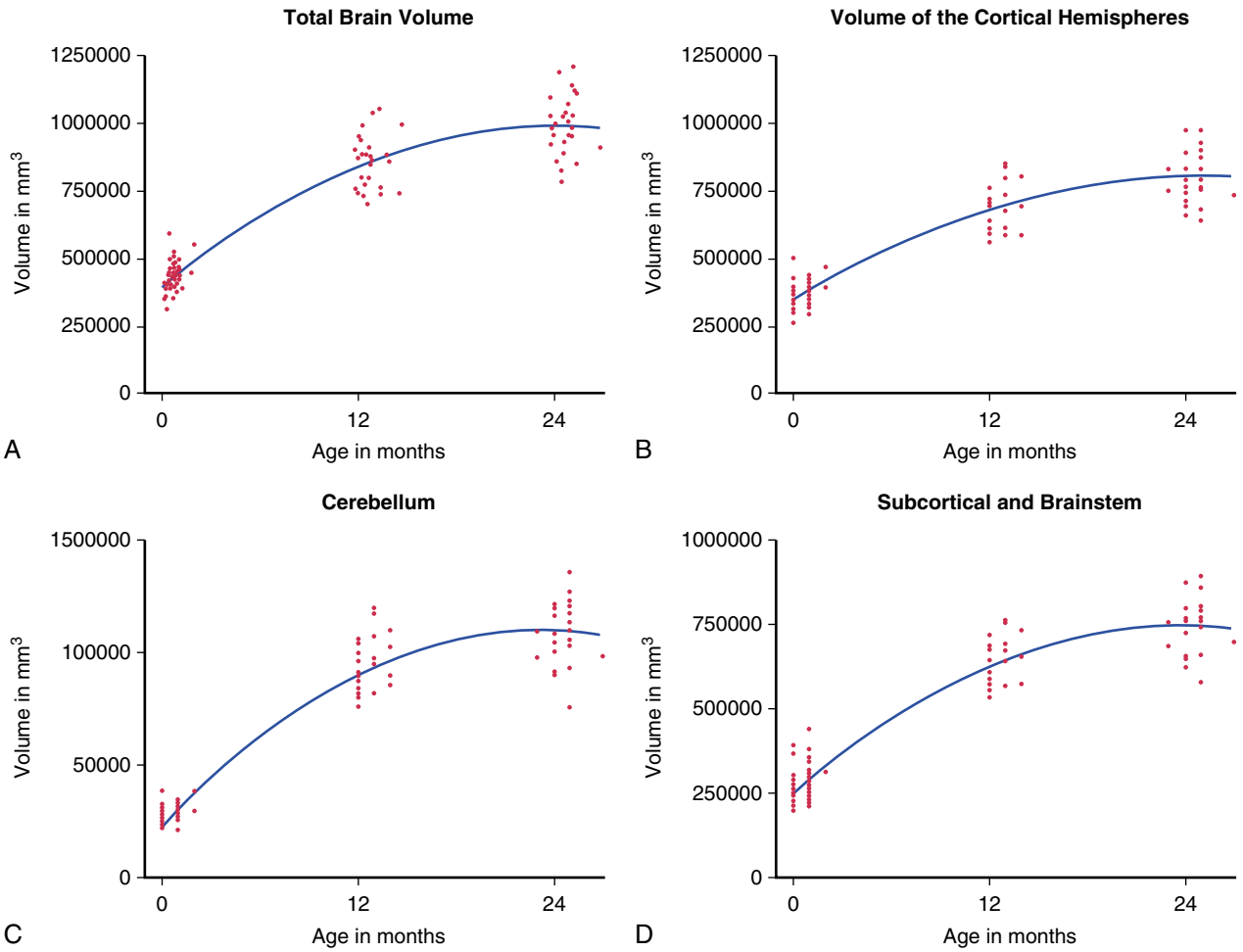

Fig. 23.1 Scatterplots showing brain growth in the first 2 years of life. A, Total brain volume by age at scan. B, Cortical hemispheres. C, Cerebellum. D, Subcortical region and brainstem. *(From Knickmeyer RC, Gouttard S, Kang C, et al. A structural MRI study of human brain development from birth to 2 years. J Neurosci. 2008;28:12176–12182.)*

Physical Development

A newborn's weight may initially decrease 10% (vaginal delivery) to 12% (cesarean section) below birthweight in the first week as a result of excretion of excess extravascular fluid and limited nutritional intake. Nutrition improves as colostrum is replaced by higher-fat content breast milk, infants learn to latch on and suck more efficiently, and mothers become more comfortable with feeding techniques. Infants regain or exceed birthweight by 2 weeks of age and should grow at approximately 30 g (1 oz) per day during the first month (see Table 27.1). This is the period of fastest postnatal growth. Arms are held to the sides. Limb movements consist largely of uncontrolled writhing, with apparently purposeless opening and closing of the hands. Smiling occurs involuntarily. Eye gaze, head turning, and sucking are under better control and thus can be used to demonstrate infant perception and cognition. An infant's preferential turning toward the mother's voice is evidence of recognition memory.

Six **behavioral states** have been described (see Chapter 22). Initially, sleep and wakefulness are evenly distributed throughout the 24 hour day (Fig. 23.2). Neurologic maturation accounts for the consolidation of sleep into blocks of 5 or 6 hours at night, with brief awake, feeding periods. Learning also occurs; infants whose parents are consistently more interactive and stimulating during the day learn to concentrate their sleeping during the night.

Cognitive Development

Infants can differentiate among patterns, colors, and consonants. They can recognize facial expressions (smiles) as similar, even when they appear on different faces. They also can match abstract properties of stimuli, such as contour, intensity, or temporal pattern, across sensory modalities. Infants at 2 months of age can discriminate rhythmic patterns in native vs nonnative language. Infants appear to seek stimuli actively, as though satisfying an innate need to make sense of the world. These phenomena point to the integration of sensory inputs in the central nervous system. Caretaking activities provide visual, tactile, olfactory, and auditory stimuli, all of which support the development of cognition. Infants **habituate** to the familiar, attending less to repeated stimuli and increasing their attention to novel stimuli.

Emotional Development

The infant is dependent on the environment to meet its needs. The consistent availability of a trusted adult to meet the infant's urgent needs creates the conditions for **secure attachment**. Basic **trust vs mistrust,** the first of Erikson's psychosocial stages (see Chapter 19), depends on attachment and reciprocal maternal bonding. Crying occurs in response to stimuli that may be obvious (a soiled diaper) but are often obscure (see Chapter 23.1). Infants who are consistently picked up and held in response to distress cry less at 1 year and show less aggressive behavior at 2 years. Infants of adolescent mothers who are trained to carry their babies demonstrate secure attachment. Infants cry in response to the cry of another infant, which has been interpreted as an early sign of empathy.

Implications for Parents and Pediatricians

Success or failure in establishing feeding and sleep cycles influences parents' feelings of competence. When things go well, the parents' anxiety and ambivalence, as well as the exhaustion of the early weeks, decrease. Infant issues (e.g., colic) or familial conflict may prevent this from occurring. With physical recovery from delivery and hormonal

Table 23.1 Developmental Milestones in First 2 Years of Life

MILESTONE	AVERAGE AGE OF ATTAINMENT (MO)	DEVELOPMENTAL IMPLICATIONS
GROSS MOTOR		
Holds head steady while sitting	2	Allows more visual interaction
Pulls to sit, with no head lag	3	Muscle tone
Brings hands together in midline	3	Self-discovery of hands
Asymmetric tonic neck reflex gone	4	Can inspect hands in midline
Sits without support	6	Increasing exploration
Rolls back to stomach	6.5	Truncal flexion, risk of falls
Walks alone	12	Exploration, control of proximity to parents
Runs	16	Supervision more difficult
FINE MOTOR		
Grasps rattle	3.5	Object use
Reaches for objects	4	Visuomotor coordination
Palmar grasp gone	4	Voluntary release
Transfers object hand to hand	5.5	Comparison of objects
Thumb-finger grasp	8	Able to explore small objects
Turns pages of book	12	Increasing autonomy during book time
Scribbles	13	Visuomotor coordination
Builds tower of two cubes	15	Uses objects in combination
Builds tower of six cubes	22	Requires visual, gross, and fine motor coordination
COMMUNICATION AND LANGUAGE		
Smiles in response to face, voice	1.5	More active social participant
Monosyllabic babble	6	Experimentation with sound, tactile sense
Inhibits to "no"	7	Response to tone (nonverbal)
Follows one-step command with gesture	7	Nonverbal communication
Follows one-step command without gesture	10	Verbal receptive language (e.g., "Give it to me")
Says "mama" or "dada"	10	Expressive language
Points to objects	10	Interactive communication
Speaks first real word	12	Beginning of labeling
Speaks 4-6 words	15	Acquisition of object and personal names
Speaks 10-15 words	18	Acquisition of object and personal names
Speaks two-word sentences (e.g., "Mommy shoe")	19	Beginning grammatization, corresponds with 50-word vocabulary
COGNITIVE		
Stares momentarily at spot where object disappeared	2	Lack of object permanence (out of sight, out of mind; e.g., yarn ball dropped)
Stares at own hand	4	Self-discovery, cause and effect
Bangs two cubes	8	Active comparison of objects
Uncovers toy (after seeing it hidden)	8	Object permanence
Egocentric symbolic play (e.g., pretends to drink from cup)	12	Beginning symbolic thought
Uses stick to reach toy	17	Able to link actions to solve problems
Pretend play with doll (e.g., gives doll bottle)	17	Symbolic thought

normalization, the mild postpartum "blues" that affects many mothers passes. If the mother continues to feel sad, overwhelmed, or anxiety, the possibility of moderate to severe **postpartum depression or anxiety,** found in 20–25% of postpartum women, needs to be considered. Major depression that arises during pregnancy or in the postpartum period threatens the mother–child relationship and is a risk factor for later cognitive and behavioral problems. Postpartum depression is often reported in mothers and can also occur in fathers. It can present over the course of a year with symptoms of depression or irritability. The pediatrician may be the first professional to encounter the depressed parent and should be instrumental in assisting the parent in seeking treatment (see Chapter 22).

AGE 2–6 MONTHS

At about age 2 months, the emergence of voluntary (social) smiles and increasing eye contact mark a change in the parent–child relationship, heightening the parents' sense of being loved reciprocally. During the next months, an infant's range of motor and social control and cognitive engagement increases dramatically. Mutual regulation takes the form of complex social interchanges, resulting in strong mutual attachment and enjoyment. Routines are established. Parents are less fatigued.

Physical Development

Between 3 and 4 months of age, the rate of growth slows to approximately 20 g/day (see Table 27.1 and Figs. 24.1 and 24.2). By age 4 months, birthweight is doubled. Early reflexes that limited voluntary movement recede (e.g., **primitive reflexes**; see Chapter 630). Disappearance of the asymmetric tonic neck reflex means that infants can begin to examine objects in the midline and manipulate them with both hands. Waning of the early grasp reflex allows infants both to hold objects and to let them go voluntarily. A novel object may elicit purposeful, although inefficient, reaching. The quality of spontaneous movements also changes, from larger (proximal) writhing to smaller, circular (distal) movements that have been described as "fidgety." Abnormal or absent fidgety movements may constitute a risk factor for later neurologic abnormalities.

Increasing control of truncal flexion makes intentional rolling possible. Once infants can hold their heads steady while sitting, they can

Table 23.2 Emerging Patterns of Behavior During the First Year of Life*

NEONATAL PERIOD (0-4 WK)	
Prone:	Lies in flexed attitude; turns head from side to side; head sags on ventral suspension
Supine:	Generally flexed and a little stiff
Visual:	May fixate face on light in line of vision; doll's eye movement (oculocephalic reflex) of eyes on turning of the body
Reflex:	Moro response active; stepping and placing reflexes; grasp reflex active
Social:	Visual preference for human face
AT 1 MO	
Prone:	Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension
Supine:	Tonic neck posture predominates; supple and relaxed; head lags when pulled to sitting position
Visual:	Watches person; follows moving object
Social:	Body movements in cadence with voice of other in social contact; beginning to smile
AT 2 MO	
Prone:	Raises head slightly farther; head sustained in plane of body on ventral suspension
Supine:	Tonic neck posture predominates; head lags when pulled to sitting position
Visual:	Follows moving object 180 degrees
Social:	Smiles on social contact; listens to voice and coos
AT 3 MO	
Prone:	Lifts head and chest with arms extended; head above plane of body on ventral suspension
Supine:	Tonic neck posture predominates; reaches toward and misses objects; waves at toy
Sitting:	Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded
Reflex:	Typical Moro response has not persisted; makes defensive movements or selective withdrawal reactions
Social:	Sustained social contact; listens to music; says "aah, ngah"
AT 4 MO	
Prone:	Lifts head and chest, with head in approximately vertical axis; legs extended
Supine:	Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth
Sitting:	No head lag when pulled to sitting position; head steady, tipped forward; enjoys sitting with full truncal support
Standing:	When held erect, pushes with feet
Adaptive:	Sees raisin, but makes no move to reach for it
Social:	Laughs out loud; may show displeasure if social contact is broken; excited at sight of food
AT 7 MO	
Prone:	Rolls over; pivots; crawls or creep-crawls (Knobloch)
Supine:	Lifts head; rolls over; squirms
Sitting:	Sits briefly, with support of pelvis; leans forward on hands; back rounded
Standing:	May support most of weight; bounces actively
Adaptive:	Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; rakes at raisin
Language:	Forms polysyllabic vowel sounds
Social:	Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact
AT 10 MO	
Sitting:	Sits up alone and indefinitely without support, with back straight
Standing:	Pulls to standing position; "cruises" or walks holding on to furniture
Motor:	Creeps or crawls
Adaptive:	Grasps objects with thumb and forefinger; pokes at things with forefinger; picks up pellet with assisted pincer movement; uncovers hidden toy; attempts to retrieve dropped object; releases object grasped by other person
Language:	Repetitive consonant sounds ("mama," "dada")
Social:	Responds to sound of name; plays peek-a-boo or pat-a-cake; waves bye-bye
AT 1 YR	
Motor:	Walks with one hand held; rises independently, takes several steps (Knobloch)
Adaptive:	Picks up raisin with unassisted pincer movement of forefinger and thumb; releases object to other person on request or gesture
Language:	Says a few words besides "mama," "dada"
Social:	Plays simple ball game; makes postural adjustment to dressing

*Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others.
Data from Knobloch H, Stevens F, Malone AF. *Manual of Developmental Diagnosis.* Hagerstown, MD: Harper & Row;1980.

gaze across at things rather than merely looking up at them, opening up a new visual range. They can begin taking food from a spoon. At the same time, maturation of the visual system allows greater depth perception.

In this period, infants achieve stable state regulation and regular sleep–wake cycles. Total sleep requirements are approximately 14-16 hours per 24 hours, with about 9-10 hours concentrated at night and 2 naps per day. Approximately 70% of infants sleep for a 6-8 hour stretch by age 6 months (see Fig. 23.2). By 4-6 months, the sleep electroencephalogram shows a mature pattern, with demarcation of rapid eye movement and three stages of non–rapid eye movement sleep. The sleep cycle remains shorter than in adults (50-60 minutes vs approximately 90 minutes). As a result, infants arouse to light sleep or wake frequently during the night, setting the stage for behavioral sleep problems (see Chapter 31).

Cognitive Development

The overall effect of these developments is a qualitative change. At 4 months of age, infants are described as "hatching" socially, becoming interested in a wider world. During feeding, infants no longer focus exclusively on the mother, but become distracted. In the mother's arms, the infant may literally turn around, preferring to face outward.

Table 23.3 Time of Radiographic Appearance of Centers of Ossification in Infancy and Childhood

MALES: AGE AT APPEARANCE*	BONES AND EPIPHYSEAL CENTERS	FEMALES: AGE AT APPEARANCE*
HUMERUS, HEAD		
3 wk		3 wk
CARPAL BONES		
2 mo ± 2 mo	Capitate	2 mo ± 2 mo
3 mo ± 2 mo	Hamate	2 mo ± 2 mo
30 mo ± 16 mo	Triangular†	21 mo ± 14 mo
42 mo ± 19 mo	Lunate†	34 mo ± 13 mo
67 mo ± 19 mo	Trapezium†	47 mo ± 14 mo
69 mo ± 15 mo	Trapezoid†	49 mo ± 12 mo
66 mo ± 15 mo	Scaphoid†	51 mo ± 12 mo
No standards available	Pisiform†	No standards available
METACARPAL BONES		
18 mo ± 5 mo	II	12 mo ± 3 mo
20 mo ± 5 mo	III	13 mo ± 3 mo
23 mo ± 6 mo	IV	15 mo ± 4 mo
26 mo ± 7 mo	V	16 mo ± 5 mo
32 mo ± 9 mo	I	18 mo ± 5 mo
FINGERS (EPIPHYSES)		
16 mo ± 4 mo	Proximal phalanx, 3rd finger	10 mo ± 3 mo
16 mo ± 4 mo	Proximal phalanx, 2nd finger	11 mo ± 3 mo
17 mo ± 5 mo	Proximal phalanx, 4th finger	11 mo ± 3 mo
19 mo ± 7 mo	Distal phalanx, 1st finger	12 mo ± 4 mo
21 mo ± 5 mo	Proximal phalanx, 5th finger	14 mo ± 4 mo
24 mo ± 6 mo	Middle phalanx, 3rd finger	15 mo ± 5 mo
24 mo ± 6 mo	Middle phalanx, 4th finger	15 mo ± 5 mo
26 mo ± 6 mo	Middle phalanx, 2nd finger	16 mo ± 5 mo
28 mo ± 6 mo	Distal phalanx, 3rd finger	18 mo ± 4 mo
28 mo ± 6 mo	Distal phalanx, 4th finger	18 mo ± 5 mo
32 mo ± 7 mo	Proximal phalanx, 1st finger	20 mo ± 5 mo
37 mo ± 9 mo	Distal phalanx, 5th finger	23 mo ± 6 mo
37 mo ± 8 mo	Distal phalanx, 2nd finger	23 mo ± 6 mo
39 mo ± 10 mo	Middle phalanx, 5th finger	22 mo ± 7 mo
152 mo ± 18 mo	Sesamoid (adductor pollicis)	121 mo ± 13 mo
HIP AND KNEE		
Usually present at birth	Femur, distal	Usually present at birth
Usually present at birth	Tibia, proximal	Usually present at birth
4 mo ± 2 mo	Femur, head	4 mo ± 2 mo
46 mo ± 11 mo	Patella	29 mo ± 7 mo
FOOT AND ANKLE‡		

*To nearest month.
†Except for the capitate and hamate bones, the variability of carpal centers is too great to make them very useful clinically.
‡Standards for the foot are available, but normal variation is wide, including some familial variants, so this area is of little clinical use.
Values represent mean ± standard deviation, when applicable.
The norms present a composite of published data from the Fels Research Institute, Yellow Springs, OH (Pyle SI, Sontag L. *AJR Am J Roentgenol.* 1943, 49:102), and unpublished data from the Brush Foundation, Case Western Reserve University, Cleveland, OH, and the Harvard School of Public Health, Boston, MA. Compiled by Lieb, Buehl, and Pyle.

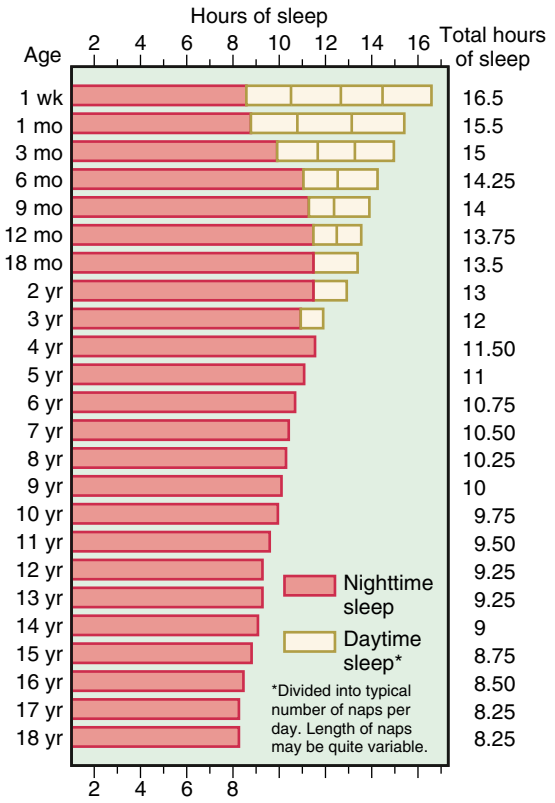

Fig. 23.2 Typical sleep requirements in children. *(From Ferber R. Solve Your Child's Sleep Problems, New York: Simon & Schuster; 1985.)*

Infants at this age also explore their own bodies, staring intently at their hands; vocalizing; blowing bubbles; and touching their ears, cheeks, and genitals. These explorations represent an early stage in the understanding of cause and effect as infants learn that voluntary muscle movements generate predictable tactile and visual sensations. Learning and memory involving the hippocampus can be demonstrated at 3 months. These activities have a role in the emergence of a sense of self, separate from the parents. This is the first stage of personality development. Infants come to associate certain sensations through frequent repetition. The proprioceptive feeling of holding up the hand and wiggling the fingers always accompanies the sight of the fingers moving. Such "self" sensations are consistently linked and reproducible at will. In contrast, sensations that are associated with "other" occur with less regularity and in varying combinations. The sound, smell, and feel of the parent sometimes appear promptly in response to crying, but sometimes do not. The satisfaction that the mother or another loving adult provides continues the process of attachment.

Emotional Development and Communication

Babies interact with increasing sophistication and range. They have an innate ability for facial expressions that, over time, become the functional expressions of emotion (anger, joy, interest, fear, disgust, and surprise). Infants can discriminate and imitate facial expressions, when paired with vocalizations, of adults as well as other infants. Initiating games (singing, hand games) increases social development. Such face-to-face behavior reveals the infant's ability to share emotional states, the first step in the development of communication. Infants of depressed parents show a different pattern, spending less time in coordinated movement with their parents and making fewer efforts to reengage. Rather than anger, they show sadness and a loss of energy when the parents continue to be unavailable.

Implications for Parents and Pediatricians

Motor and sensory maturation makes infants at 3-6 months exciting and interactive. Some parents experience their 4-month-old child's outward turning as a rejection, secretly fearing that their infants no longer love them. For most parents, this is a happy period and they may excitedly report that they can hold conversations with their infants, taking turns vocalizing and listening. Pediatricians share in the enjoyment, as the baby coos, makes eye contact, and moves rhythmically. Infants who do not show this reciprocal language and movements are at risk for autism spectrum disorder or other developmental disabilities (see Chapters 56 and 58). If this visit does not feel joyful and relaxed, causes such as social

stress, family dysfunction, parental mental illness, or problems in the infant–parent relationship should be considered. Parents can be reassured that responding to an infant's emotional needs cannot spoil the infant. Giving vaccines and drawing blood while the child is seated on the parent's lap or nursing at the breast increases pain tolerance.

AGE 6–12 MONTHS

With achievement of the sitting position, increased mobility, and new skills to explore the world around them, 6-12 month old infants show advances in cognitive understanding and communication, and new tensions arise in regard to attachment and separation. Infants develop will and intentions, characteristics that most parents welcome but still find challenging to manage.

Physical Development

Growth slows more (see Table 27.1 and Figs. 24.1 and 24.2). By the first birthday, birthweight has tripled, length has increased by 50%, and head circumference has increased by 10 cm (4 in). The ability to sit unsupported (6-7 months) and to pivot while sitting (around 9-10 months) provides increasing opportunities to manipulate several objects at a time and to experiment with novel combinations of objects. These explorations are aided by the emergence of a thumb-finger grasp (8-9 months) and a neat pincer grasp by 12 months. Voluntary release emerges at 9 months. Many infants begin crawling and pulling to stand around 8 months, followed by cruising. Some walk by 1 year. Motor achievements correlate with increasing myelinization and cerebellar growth. These gross motor skills expand infants' exploratory range and create new physical dangers, as well as opportunities for learning. Tooth eruption occurs, usually starting with the mandibular central incisors. Tooth development (see Table 353.1) reflects skeletal maturation and bone age, although there is wide individual variation.

Cognitive Development

The 6-month-old infant has discovered his hands and will soon learn to manipulate objects. At first, everything is mouthed. In time, novel objects are picked up, inspected, passed from hand to hand, banged, dropped, and then mouthed. Each action represents a nonverbal idea about what things are for (in Piagetian terms, a *schema*; see Chapter 19). The complexity of an infant's play, how many different schemata are brought to bear, is a useful index of cognitive development at this age. The pleasure, persistence, and energy with which infants tackle these challenges suggest the existence of an intrinsic drive or mastery motivation. Mastery behavior occurs when infants feel secure; those with less secure attachments show limited experimentation and less competence.

A major milestone is the achievement by 9 months of **object permanence** (**constancy**), the understanding that objects continue to exist, even when not seen. At 4-7 months of age, infants look down for a yarn ball that has been dropped but quickly give up if it is not seen. With object constancy, older infants persist in searching. They will find objects hidden under a cloth or behind the examiner's back. Peek-a-boo brings unlimited pleasure as the child magically brings back the other player. Events seem to occur as a result of the child's own activities.

Emotional Development

The advent of object permanence corresponds with qualitative changes in social and communicative development. Infants look back and forth between an approaching stranger and a parent and may cling or cry anxiously, demonstrating **stranger anxiety**. Separations often become more difficult. Infants who have been sleeping through the night for months begin to awaken regularly and cry, as though remembering that the parents are nearby or in the next room (see Chapter 31).

A new demand for **autonomy** also emerges. Poor weight gain at this age often reflects a struggle between an infant's emerging independence and parent's control of the feeding situation. Use of the two-spoon method of feeding (one for the child and one for the parent), finger foods, and a high chair with tray table can avert potential problems. Tantrums make their first appearance as the drives for autonomy and mastery come in conflict with parental controls and the infant's still-limited abilities.

Communication

Infants at 7 months of age are adept at nonverbal communication, expressing a range of emotions and responding to vocal tone and facial expressions. At about 9 months of age infants become aware that emotions can be shared between people; they show parents toys as a way of sharing their happy feelings. Between 8 and 10 months of age, babbling takes on a new complexity, with multisyllabic sounds ("ba-da-ma") called **canonical babbling**. Babies can discriminate between languages. Infants in bilingual homes learn the characteristics and rules that govern two different languages. Social interaction (attentive adults taking turns vocalizing with the infant) profoundly influences the acquisition and production of new sounds. The first true word (i.e., a sound used consistently to refer to a specific object or person) appears in concert with an infant's discovery of object permanence. Picture books now provide an ideal context for verbal language acquisition. With a familiar book as a shared focus of attention, a parent and child engage in repeated cycles of pointing and labeling, with elaboration and feedback by the parent. Often infants learn a gesture to communicate before the can say the word (e.g., waving bye-bye before saying "bye-bye"), and there is limited evidence that the addition of sign language may support infant development while enhancing parent–infant communication.

Implications for Parents and Pediatricians

With the developmental reorganization that occurs around 9 months of age, previously resolved issues of feeding and sleeping reemerge. Pediatricians can prepare parents at the 6 month visit so that these problems can be understood as the result of developmental progress and not regression. Parents should be encouraged to plan ahead for necessary, and inevitable, separations (e.g., babysitter, daycare). Routine preparations may make these separations easier. Dual parent employment has not been consistently found to be harmful or beneficial for long-term cognitive or social-emotional outcomes. Introduction of a **transitional object** may allow the infant to self-comfort in the parents' absence. The object cannot have any potential for asphyxiation or strangulation.

Infants' wariness of strangers often makes the 9 month examination difficult, particularly if the infant is temperamentally prone to react negatively to unfamiliar situations. Initially, the pediatrician should avoid direct eye contact with the child. Time spent talking with the parent and introducing the child to a small, washable toy will be rewarded with more cooperation. The examination can be continued on the parent's lap when feasible. Encourage parents to read, play, and communicate with their infant.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

23.1 Infant Crying and Colic

Mutiat T. Onigbanjo and Susan Feigelman

Crying or fussiness is present in all babies but reaches medical attention in about 20% of infants younger than 2 months. Although usually a transient and normal infant behavior, crying is often associated with parental concern and distress. On average, babies cry 2 hours per day, peaking at 6 weeks of age. Premature infants will have peak crying at 6 weeks corrected age (Fig. 23.3). Small-for-gestational-age and premature babies may be at higher risk. The peak period of infant crying usually occurs in the evenings and early part of the night. Excessive crying or fussiness persisting longer than 3-5 months may be associated with behavioral problems in an older child (anxiety, aggression, hyperactivity), decreased duration of breastfeeding, or postnatal depression, but it is uncertain which is the cause or effect. Most infants with crying/fussiness do not have gastroesophageal reflux, lactose intolerance, constipation, or cow's milk protein allergy.

Acute-onset uncontrollable crying could be caused by a medical condition. Potentially overlooked conditions to consider include corneal abrasion, tourniquet effect of a hair wrapped around a digit or

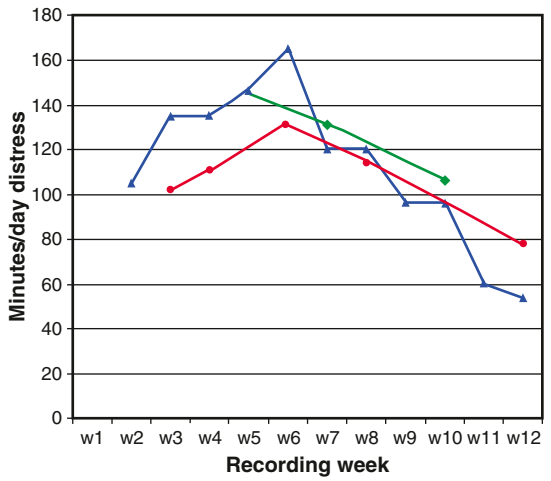

Fig. 23.3 Crying amounts and patterns from three North American studies illustrating similarities in crying pattern. *(From Barr RG, Trent RB, Cross J. Age-related incidence curve of hospitalized shaken baby syndrome cases: convergent evidence for crying as a trigger to shaking. Child Abuse Negl. 2006;30:7–16.)*

penis, occult fracture, urinary tract infection, acute abdomen including inguinal hernia, or anomalous coronary artery. Breastfeeding mothers should be asked about medications, drugs, and diet. Gastrointestinal distress can result from a maternal diet high in cruciferous vegetables. Most of the time, the etiology of a serious problem can be discovered with a careful history and physical examination.

Crying is a normal part of neurobehavioral development. Infants have various signals for their needs and for getting attention from a caregiver. These behaviors progressively increase in intensity in many infants, from changes in breathing and color, to postural and movement changes, and then to calm vocalizations. These precry cues, if not attended to, will eventually lead to active crying. Some infants may go directly to crying, perhaps based on temperament; these infants may be less easily consolable, more intense, or more responsive to sensory stimuli. Management of crying/fussiness should include teaching caregivers about precry cues and responding to the signal for feeding in a calm, relaxed manner. If sensory overstimulation is a factor, creating a nondistracting, calm environment may help, as well as swaddling. When lack of sensory stimulation is present, parent–infant skin-to-skin contact and carrying the infant may be beneficial. In all situations, reassurance that this is both normal and transient, with only 5% of infants persisting beyond 3 months of age, helps the family cope. Teaching families about expectations for normal crying behavior can reduce emergency department visits.

The emotional significance of any experience depends on both the individual child's temperament and the parent's responses (see Table 19.1); differing feeding schedules produce differing reactions. Hunger generates increasing tension; as the urgency peaks, the infant cries, the parent offers the breast or bottle, and the tension dissipates. Infants fed "on demand" consistently experience this link among their distress, the arrival of the parent, and relief from hunger. Most infants fed on a fixed schedule quickly adapt their hunger cycle to the schedule. Those who cannot adapt, because they are temperamentally prone to irregular biologic rhythms, experience periods of unrelieved hunger as well as unwanted feedings when they already feel full. Similarly, infants who are fed at the parents' convenience, with neither attention to the infant's hunger cues nor a fixed schedule, may not consistently experience feeding as the pleasurable reduction of tension. Infants with early dysregulation often show increased irritability and physiologic instability (spitting, diarrhea, poor weight gain) as well as later behavioral problems. Infants with excess crying after 4-6 months may have neurobehavioral dysregulation and may be at higher risk of other behavior problems (sleep, behavior, feeding).

Colic is characterized by the "rule of 3." It occurs in a healthy, thriving infant beginning in the second or third week of life with crying that lasts at least 3 hours per day, occurs at least 3 days per week, lasts for more than 3 weeks, and resolves by 3 or 4 months of age. It is equally common in breastfed and bottle-fed infants, although prevalence is variable (up to 20%). There is no racial, socioeconomic status, or gender risk for colic. Colic is a diagnosis of exclusion following a careful history and physical examination. Few cases will be found to have an organic etiology. Although all babies have crying episodes, colicky babies cry excessively and are difficult to settle. The fussiness is not associated with hunger or any other form of discomfort. Colicky babies may be more reactive to the same stimulus and may cry louder than other babies. Although crying periods are a normal developmental phenomenon, babies with colic can cause parents to become anxious, distraught, frustrated, and sleep deprived. Mothers are at higher risk for postpartum depression if they report inconsolable crying episodes lasting more than 20 minutes. Depression may lead to cessation of breastfeeding. The risk of abuse increases as frustrated parents may use aggressive means in an attempt to quiet the child, resulting in the **shaken baby syndrome**.

There is no specific treatment for colic, but practitioners should provide advice and reassurance to parents. Parents must be counseled about the problem, the importance of implementing a series of calm, systematic steps to soothe the infant, and having a plan for stress relief, such as timeout for parents and substitute caregivers. Parents can be advised that colic is self-limited with no adverse effects on the child. Public health programs, such as the **Period of PURPLE Crying** (http://purplecrying.info/) and **Take 5 Safety Plan for Crying**, are invaluable tools for parents. These programs inform parents that all babies go through periods of crying, deflecting parental guilt and self-recrimination. Most importantly, parents are reminded that it is better to allow the baby to cry than engage in shaking that leads to head trauma. Although babies with colic will have inconsolable periods when there is no relief, parents can try some simple steps. Predictable daily schedules may help, ensuring the baby has adequate sleep. Parents should provide appropriate stimulation throughout the day when baby is in an alert/awake period. The sleep environment should be free of stimulation. Swaddling, rocking, white noise, and movement (e.g., stroller, car ride) help some babies settle. Infants who are carried by a parent show different physiologic changes than when held in a sitting position, although there is no evidence that continuous carrying is effective in colic management. A study in a hunter-gatherer society showed that children who are continuously carried by their mothers display similar crying periods as those in Western societies.

Some studies have found differences in **fecal microflora (dysbiosis)** between babies with excess crying and controls. Results include fewer bifidobacteria and lactobacilli and more coliform bacteria such as *Escherichia coli*. None has been conclusive, however, and each study was found to have limitations such as lack of precise inclusion criteria, lack of blinded observers, and variability in outcome measurements.

If the child appears to have gastrointestinal symptoms, breastfeeding mothers may try elimination of milk, beans, and cruciferous vegetables from their diets. In allergic families, mothers may try a stricter elimination of food allergens (milk, egg, wheat, nuts, soy, and fish), although nutritional status should be monitored. For formula-fed infants, changing from milk-based to soy-based or other lactose-free formulas had no effect in most studies. A protein hydrolysate formula may moderately improve symptoms.

The cause of colic in not known, and no medical intervention has been consistently effective. Colic has been described as a "functional gastrointestinal disorder" and has been associated with maternal migraines, as well as later development of **migraine** in the child. Simethicone has not been shown to be better than placebo. Anticholinergic medications should not be used in infants younger than 6 months. Early studies of probiotics look promising, but evidence is insufficient to recommend their routine use. Among various complementary therapies, certain **herbal teas**, sugar solutions, Gripe water (containing herbal supplements), chamomile and fennel extract may have benefit, but the evidence is weak. Baby massage may be helpful, but chiropractic manipulation should not be performed in young children. Acupuncture was effective in one trial and singing while in utero may produce babies who cry less.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 24

The Second Year

Rebecca G. Carter and Susan Feigelman

The second year of life is a time of rapid growth and development, particularly in the realms of social-emotional and cognitive skills as well as motor development. The toddler's newly found ability to walk allows separation and independence; however, the toddler continues to need secure attachment to the parents. At approximately 18 months of age, the emergence of symbolic thought and language causes a reorganization of behavior, with implications across many developmental domains.

AGE 12–18 MONTHS

Physical Development

Although overall rate of growth continues to decline, the toddler continues to experience considerable brain growth and myelination in the second year of life, resulting in an increase in head circumference of 2 cm over the year (Figs. 24.1 and 24.2). Toddlers have relatively short legs and long torsos, with exaggerated lumbar lordosis and protruding abdomens.

Most children begin to walk independently at about 12-15 months of age. Early walking is not associated with advanced development in other domains. Infants initially toddle with a wide-based gait, with the knees bent and the arms flexed at the elbow; the entire torso rotates with each stride; the toes may point in or out, and the feet strike the floor flat. The appearance is that of genu varum (**bowleg**). Subsequent refinement leads to greater steadiness and energy efficiency. After several months of practice, the center of gravity shifts back and the torso stabilizes, while the knees extend and the arms swing at the sides for balance. The feet are held in better alignment, and the child is able to stop, pivot, and stoop without toppling over (see Chapters 713 and 714).

Cognitive Development

Exploration of the environment increases in parallel with improved dexterity (reaching, grasping, releasing) and mobility. Learning follows the precepts of Piaget's **sensorimotor stage** (see Chapter 19). Toddlers manipulate objects in novel ways to create interesting effects, such as stacking blocks or filling and dumping buckets. Playthings are also more likely to be used for their intended purposes (combs for hair, cups for drinking). Imitation of parents and older siblings or other children is an important mode of learning. Make-believe play (**symbolic play**) centers on the child's own body, such as pretending to drink from an empty cup (Table 24.1; see also Table 23.1).

Emotional Development

Infants who are approaching the developmental milestone of taking their first steps may be irritable. Once they start walking, their predominant mood changes markedly. Toddlers are often elated with their new ability and with the power to control the distance between themselves and their parents. Exploring toddlers will orbit around their trusted adults, moving away and then returning for a reassuring touch before moving away again. A child with **secure attachment** will use the trusted adult as a secure base from which to explore independently. Proud of their accomplishments, the child illustrates Erikson's **stage of autonomy and separation** (see Chapter 19). The toddler who is overly controlled and discouraged from active exploration may feel doubt, shame, anger, and insecurity. All children will experience tantrums, reflecting their inability to delay gratification, suppress or displace anger, or verbally communicate their emotional states. Children may form secure attachments with parents as well as other trusted adults, thereby reinforcing the value of quality childcare if parents are employed out of the home.

Linguistic Development

Receptive language precedes *expressive* language. By the time infants speak their first words around 12 months of age, they already respond appropriately to several simple statements, such as "no," "bye-bye," and "give me." By 15 months, the average child points to major body parts and uses four to six words spontaneously and correctly. Toddlers also enjoy **polysyllabic jargoning** (see Tables 23.1 and 24.1) and do not seem upset that no one understands. Most communication of wants and ideas continues to be nonverbal (e.g., by pointing, facial expressions).

Implications for Parents and Pediatricians

Parents who cannot recall any other milestone tend to remember when their child began to walk, perhaps because of the symbolic significance of walking as an act of independence and because of the new demands that the ambulating toddler places on the parent. All toddlers should be encouraged to explore their environment; however, a child's ability to wander out of sight also increases the risks of injury and the need for supervision, making recommendations regarding **childproofing** an integral focus of physician visits.

Parents must understand the importance of exploration. Rather than limiting movement, parents should place toddlers in safe environments or substitute one activity for another. In the office setting, many toddlers are comfortable exploring the examination room, but cling to the parents under the stress of the examination. Children who become more, not less, distressed in their parents' arms or who avoid their parents at times of stress may be insecurely attached. Young children who, when distressed, turn to strangers rather than parents for comfort are particularly worrisome. Children raised in environments with extreme and/or chronic levels of stress (**toxic stress**) have increased vulnerability to disease that continues into adulthood (see Chapter 1). These effects can be mediated by fostering elements of resiliency including introduction of a supportive or encouraging trusted adult. The conflicts between independence and security manifest in issues of **discipline**, temper tantrums, toilet training, and changing feeding behaviors. Parents should be counseled on these matters within the framework of normal development.

Parents may express concern about poor food intake as growth slows. The growth chart should provide reassurance. Many children still take two daytime naps, although the duration steadily decreases and may start to condense to one longer nap (see Fig. 23.2).

AGE 18–24 MONTHS

Physical Development

Motor development during this period is reflected in improvements in balance and agility and the emergence of running and stair climbing. Height and weight increase at a steady rate during this year, with a gain of 5 in and 5 lb. By 24 months, children are about half their ultimate adult height. Head growth slows slightly, with 85% of adult head circumference achieved by age 2 years, leaving only an additional 5 cm (2 in) gain over the next few years (see Fig. 24.1 and Table 27.1).

Cognitive Development

At approximately 18 mo of age, several cognitive changes coalesce, marking the conclusion of the sensorimotor period. These can be observed during *self-initiated play*. **Object permanence,** which was first demonstrated around 9 months of age (see Chapter 23), is now firmly established; toddlers anticipate where an object will end up, even though the object was not visible while it was being moved. Cause and effect are better understood, and toddlers demonstrate flexibility in problem solving (e.g., using a stick to obtain a toy that is out of reach, figuring out how to wind a mechanical toy). Symbolic transformations in play are no longer tied to the toddler's own body; thus a doll can be "fed" from an empty plate. As with the reorganization that occurs at 9 months (see Chapter 23), the cognitive changes at 18 months correlate with important changes in the emotional and linguistic domains (see Table 24.1).

Emotional Development

The relative independence of the preceding half-year often gives way to increased clinginess at about 18 months. This stage, described as "rapprochement," may be a reaction to growing awareness of the possibility of separation. Many parents report that they cannot go anywhere without having a small child attached to them. **Separation anxiety** will manifest at bedtime. Many children use a special blanket or stuffed toy as a **transitional object**, which functions as a symbol of the absent parent. The transitional object remains important until the transition to symbolic thought

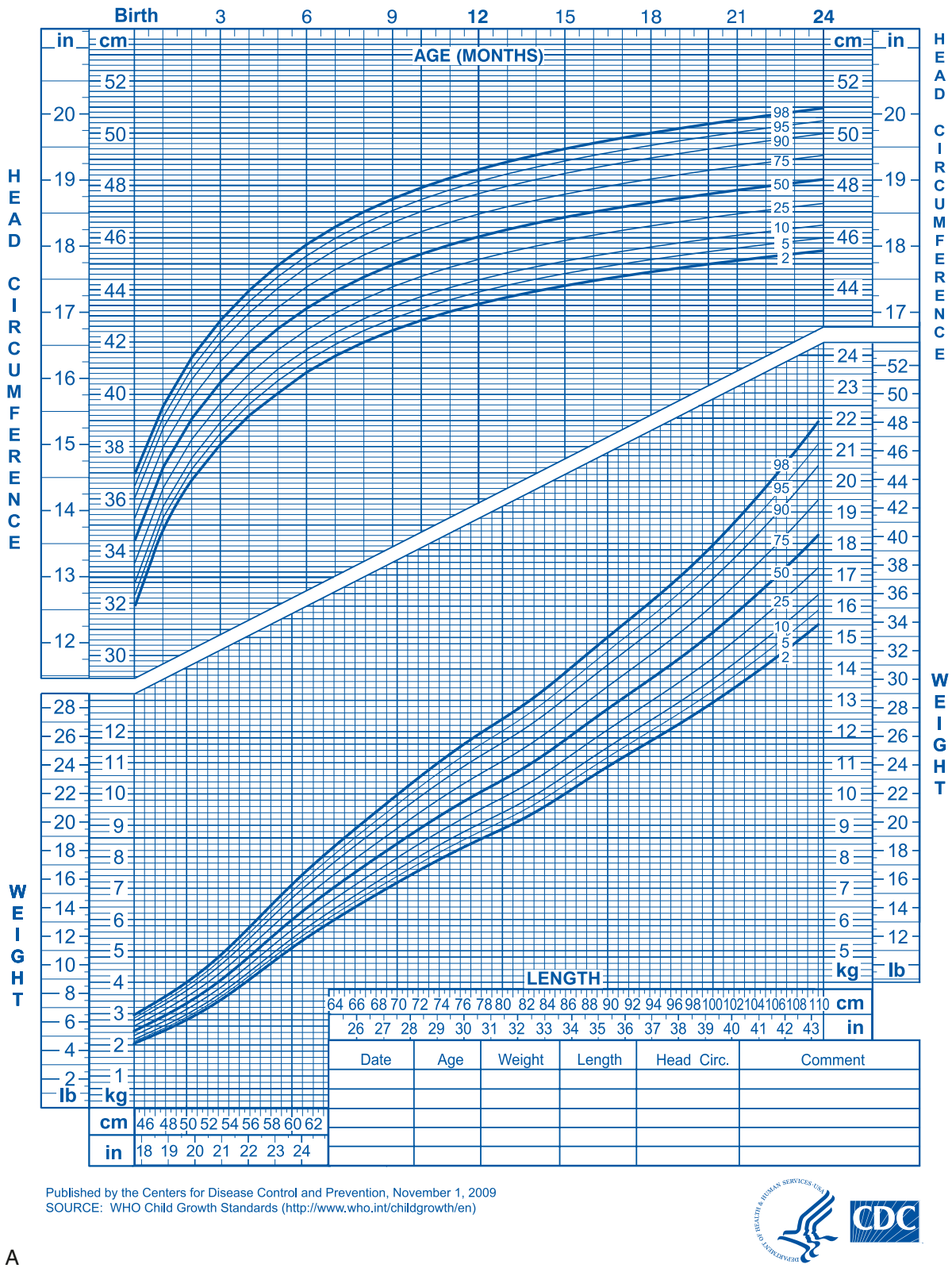

A

Fig. 24.1 World Health Organization growth charts. A, Weight for length and head circumference for age for boys, birth to 24 months. B, Weight for length and head circumference for age for girls, birth to 24 months. *(Courtesy World Health Organization: WHO Child Growth Standards, 2021.)*

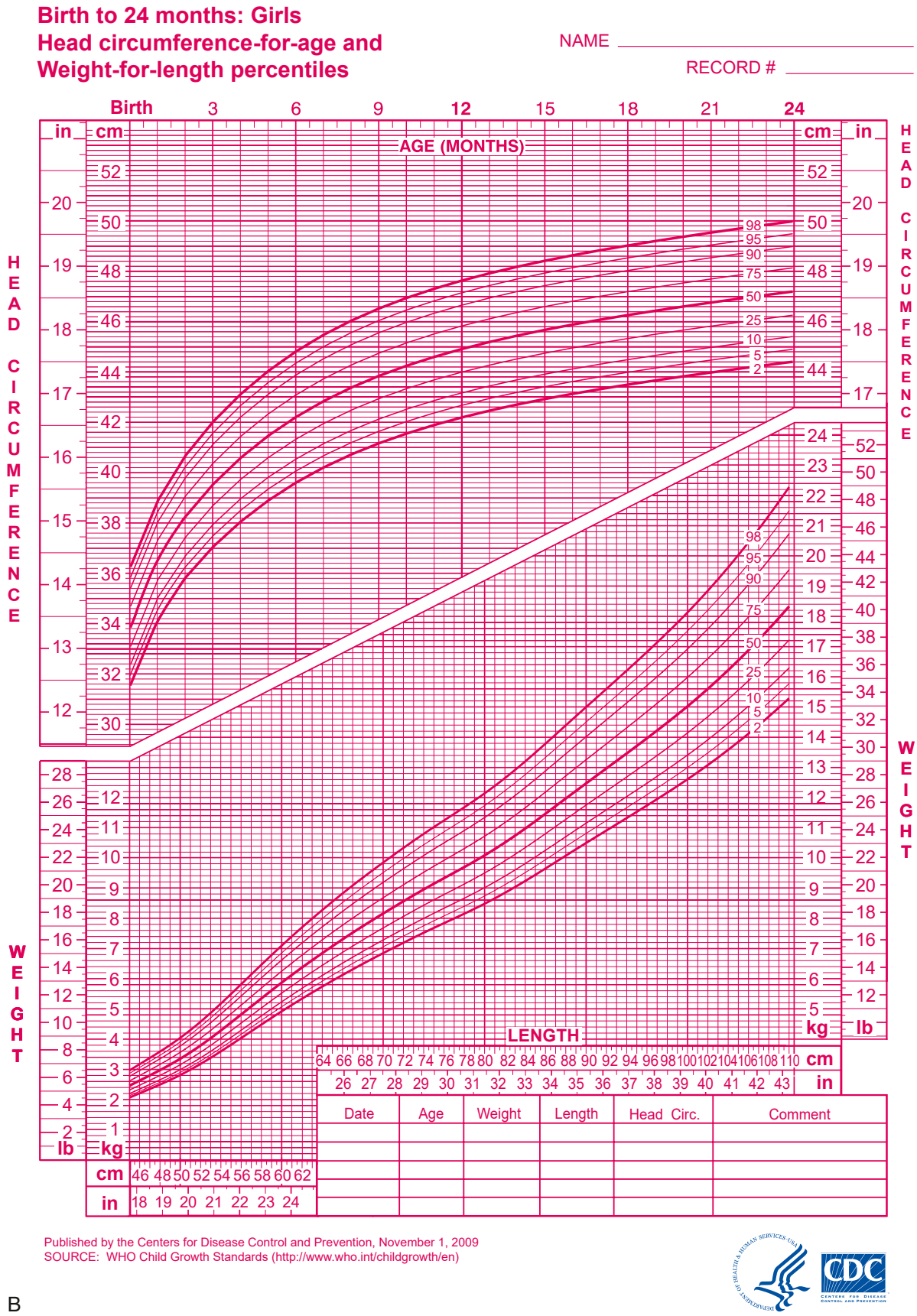

B

Fig. 24.1, cont'd

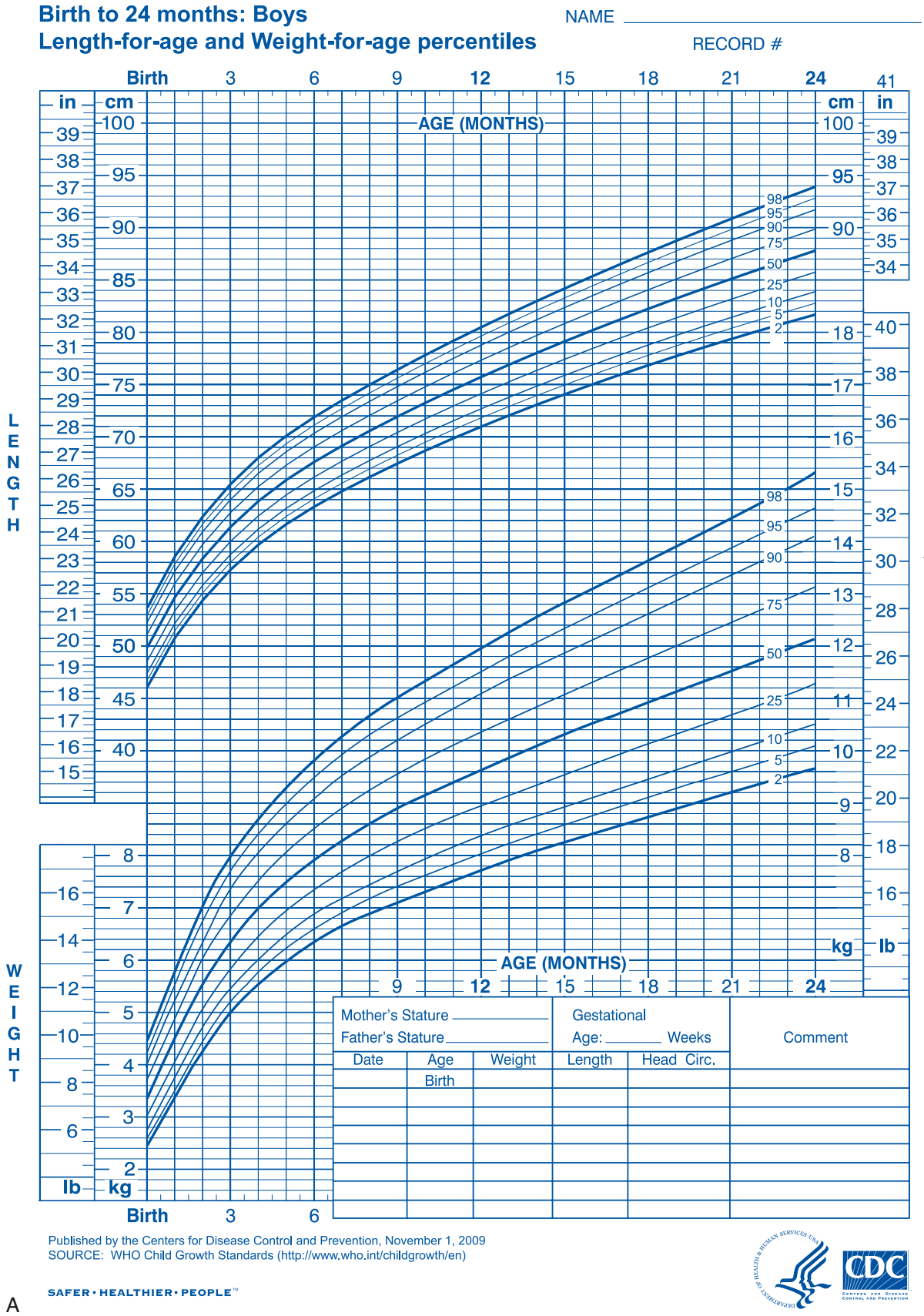

A

Fig. 24.2 World Health Organization growth charts. **A,** Length for age and weight for age for boys, birth to 24 months. **B,** Length for age and weight for age for girls, birth to 24 months. *(Courtesy World Health Organization: WHO Child Growth Standards, 2021.)*

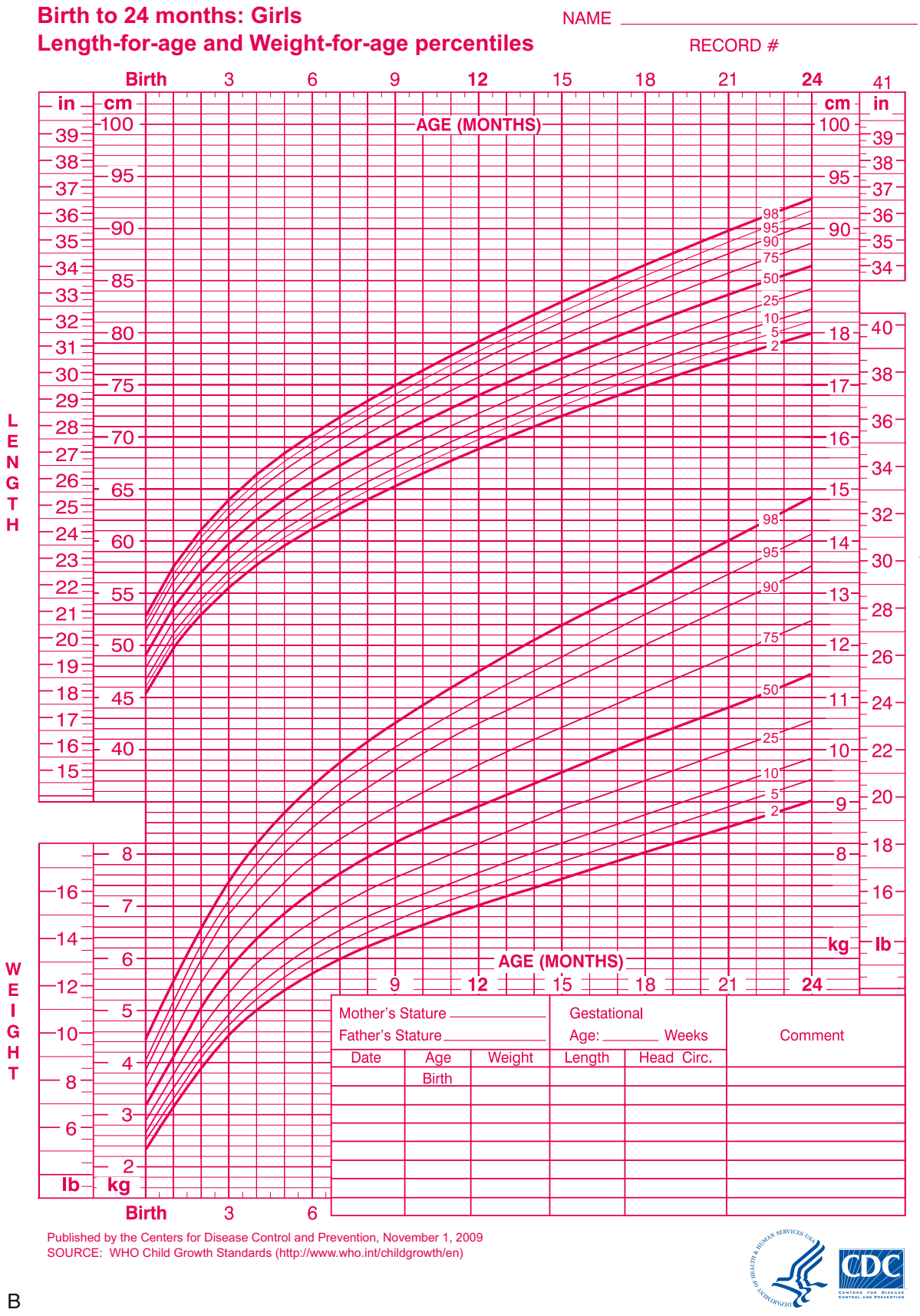

B

Fig. 24.2, cont'd

Table 24.1	Emerging Patterns of Behavior from 1-5 Years of Age
15 MO	
Motor:	Walks alone; crawls up stairs
Adaptive:	Makes tower of 3 cubes; makes a line with crayon; inserts raisin in bottle
Language:	Jargon; follows simple commands; may name a familiar object (e.g., ball); responds to his/her name
Social:	Indicates some desires or needs by pointing; hugs parents
18 MO	
Motor:	Runs stiffly; sits on small chair; walks up stairs with 1 hand held; explores drawers and wastebaskets
Adaptive:	Makes tower of 4 cubes; imitates scribbling; imitates vertical stroke; dumps raisin from bottle
Language:	10 words (average); names pictures; identifies 1 or more parts of body
Social:	Feeds self; seeks help when in trouble; may complain when wet or soiled; kisses parent with pucker
24 MO	
Motor:	Runs well, walks up and down stairs, 1 step at a time; opens doors; climbs on furniture; jumps
Adaptive:	Makes tower of 7 cubes (6 at 21 mo); scribbles in circular pattern; imitates horizontal stroke; folds paper once imitatively
Language:	Puts 3 words together (subject, verb, object)
Social:	Handles spoon well; often tells about immediate experiences; helps to undress; listens to stories when shown pictures
30 MO	
Motor:	Goes up stairs alternating feet
Adaptive:	Makes tower of 9 cubes; makes vertical and horizontal strokes, but generally will not join them to make cross; imitates circular stroke, forming closed figure
Language:	Refers to self by pronoun "I"; knows full name
Social:	Helps put things away; pretends in play
36 MO	
Motor:	Rides tricycle; stands momentarily on 1 foot
Adaptive:	Makes tower of 10 cubes; imitates construction of "bridge" of 3 cubes; copies circle; imitates cross
Language:	Knows age and gender; counts 3 objects correctly; repeats 3 numbers or a sentence of 6 syllables; most of speech intelligible to strangers
Social:	Plays simple games (in "parallel" with other children); helps in dressing (unbuttons clothing and puts on shoes); washes hands
48 MO	
Motor:	Hops on 1 foot; throws ball overhand; uses scissors to cut out pictures; climbs well
Adaptive:	Copies bridge from model; imitates construction of "gate" of 5 cubes; copies cross and square; draws man with 2-4 parts besides head; identifies longer of 2 lines
Language:	Counts 4 pennies accurately; tells story
Social:	Plays with several children, with beginning of social interaction and role-playing; goes to toilet alone
60 MO	
Motor:	Skips
Adaptive:	Draws triangle from copy; names heavier of 2 weights
Language:	Names 4 colors; repeats sentence of 10 syllables; counts 10 pennies correctly
Social:	Dresses and undresses; asks questions about meaning of words; engages in domestic role-playing

Data derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others. After 6 yr, the Wechsler Intelligence Scales for Children (WISC-IV) and other scales offer the most precise estimates of cognitive development. To have their greatest value, they should be administered only by an experienced and qualified person.

has been completed and the symbolic presence of the parent fully internalized. Despite the attachment to the parent, the child's use of "no" is a way of declaring independence. Individual differences in **temperament**, in both the child and the parents, play a critical role in determining the balance of conflict vs cooperation in the parent–child relationship. As effective language emerges, conflicts often become less frequent.

Self-conscious awareness and internalized standards of behavior first appear at this age. Toddlers looking in a mirror will, for the first time, reach for their own face rather than the mirror image if they notice something unusual on their nose. They begin to recognize when toys are broken and may hand them to their parents to fix. Language becomes a means of impulse control, early reasoning, and connection between ideas. When tempted to touch a forbidden object, they may tell themselves "no, no." This is the very beginning of the formation of a conscience. The fact that they often go on to touch the object anyway demonstrates the relative weakness of **internalized inhibitions** at this stage.

Linguistic Development

Perhaps the most dramatic developments in this period are linguistic. Labeling of objects coincides with the advent of symbolic thought. After the realization occurs that words can stand for objects or ideas, a child's vocabulary grows from 10-15 words at 18 months to between 50 and 100 at 2 years. After acquiring a vocabulary of about 50 words, toddlers begin to combine them to make simple sentences, marking the beginning of grammar. At this stage, toddlers understand **two-step commands**, such as "Give me the ball and then get your shoes." Language also gives the toddler a sense of control over the surroundings, as in "night-night" or "bye-bye." The emergence of verbal language marks the end of the sensorimotor period. As toddlers learn to use symbols to express ideas and solve problems, the need for cognition based on direct sensation and motor manipulation wanes.

Implications for Parents and Pediatricians

With children's increasing mobility, physical limits on their explorations become less effective; words become increasingly important for behavior control as well as cognition. Children with delayed language acquisition often have greater behavior problems and frustrations due to problems with communication. Language development is facilitated when parents and caregivers use clear, simple sentences; ask questions; pause to allow time to process and generate verbal responses and respond to children's incomplete sentences and gestural communication with the appropriate words. Television and distracted screen-time viewing, as well as television as background noise, decreases parent–child verbal interactions, whereas looking at picture books and engaging the child in two-way conversations stimulates language development. In the world of constant access to tablets, phones, and screens, parents and children have more distractions from direct language engagement. Even educational programing needs to be limited on screens to reinforce face-to-face contact with caregivers during language acquisition; solo media use should be avoided in this age. As an introduction to this topic, the provider can ask "What are your child's favorite activities?" and "What activities do you like to do with your child?"

Performing most of the physical examination in the parent's lap may help allay fears of separation and **stranger anxiety**. Avoid direct eye contact initially and introduce all tools used during the exam such as the otoscope for the patient to explore before use. Save the more invasive portions of the exam to the end (i.e., ears, throat, etc.). Pediatricians can help parents understand the resurgence of problems with separation and the appearance of a transitional object as developmental phenomenon. Methods of **discipline** should be discussed; effective alternatives to corporal punishment will usually be appreciated (see Chapter 20 and Tables 20.3 and 20.4). Helping parents to understand and adapt to their children's different temperamental styles can constitute an important intervention (see Table 19.1). Developing daily routines is helpful to all children at this age. Rigidity in those routines reflects a need for mastery over a changing environment. Parents should also institute systems to help prepare their child during times of transition from one activity or setting to another to help foster a sense of trust and communication.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 25

The Preschool Years

Rebecca G. Carter and Susan Feigelman

The emergence of language and exposure of children to an expanding social sphere represent the critical milestones for children age 2-5 years. As toddlers, children learn to walk away and come back to the secure adult. As preschoolers, they explore emotional separation, alternating between stubborn opposition and cheerful compliance, between bold exploration and clinging dependence. Increasing time spent in classrooms and playgrounds strengthens a child's ability to adapt to new rules and relationships. Emboldened by their growing array of new skills and accomplishments, preschool children also are increasingly cognizant of the constraints imposed on them by the adult world and their own limited abilities.

STRUCTURAL DEVELOPMENT OF THE BRAIN

The preschool brain experiences dramatic changes in its anatomic and physiologic characteristics, with increases in cortical area, decreases in cortical thickness, and changing cortical volume. These changes are not uniform across the brain and vary by region. Gray and white matter tissue properties change dramatically, including diffusion properties in the major cerebral fiber tracts. Dramatic increases occur in brain metabolic demands. In general, more brain regions are required in younger than in older children to complete the same cognitive task. This duplication has been interpreted as a form of "scaffolding," which is discarded with increasing age. The preschool brain is characterized by growth and expansion of synapses that will be followed in later years by "pruning."

PHYSICAL DEVELOPMENT

Somatic and brain growth slows by the end of the second year of life, with corresponding decreases in nutritional requirements and appetite, and the emergence of "picky" eating habits (see Table 27.1). Increases of approximately 2 kg (4-5 lb) in weight and 7-8 cm (2-3 in) in height per year are expected. Birthweight quadruples by 2.5 years of age. An average 4 year old weighs 40 lb and is 40 in tall. The head will grow only an additional 5-6 cm between ages 3 and 18 years. Current growth charts, with growth parameters, can be found on the U.S. Centers for Disease Control and Prevention website (http://www.cdc.gov/growthcharts/) and in Chapter 27. Children with early **adiposity rebound** (increase in body mass index) are at increased risk for adult obesity.

The preschooler has genu valgum (**knock-knees**) and mild pes planus (**flatfoot**). The torso slims as the legs lengthen. Growth of sexual organs is commensurate with somatic growth. Physical energy peaks, and the need for sleep declines to 11-13 hours per 24 hours, with the child eventually dropping the nap (see Fig. 23.2). Visual acuity reaches 20/30 by age 4 years and 20/20 by school age. All 20 primary teeth have erupted by 3 years of age (see Chapter 353).

Most children walk with a mature gait and run steadily before the end of their third year (see Table 24.1). Beyond this basic level, there is wide variation in ability as the range of motor activities expands to include throwing, catching, and kicking balls; riding on bicycles; climbing on playground structures; dancing; and other complex pattern behaviors. Stylistic features of gross motor activity, such as tempo, intensity, and cautiousness, also vary significantly. Although toddlers may walk with different styles, **toe walking** should not persist.

The effects of such individual differences on cognitive and emotional development depend in part on the demands of the social environment and alignment with their caregivers' temperaments. Energetic, coordinated children may thrive emotionally with parents or teachers who encourage physical activity; lower-energy, more cerebral children may thrive with adults who value quiet play.

Handedness is usually established by the third year. Frustration may result from inability to properly teach skills based on child's hand preference. Variations in fine motor development reflect both individual proclivities and different opportunities for learning. Children who are restricted from drawing with crayons, for example, develop a mature pencil grasp later.

Bowel and bladder control emerge during this period, with "readiness" for toileting having large individual and cultural variation. Females tend to potty "train" faster and earlier than males. Bed-wetting is common up to age 5 years (see Chapter 580). Many children master toileting with ease, particularly once they are able to verbalize their bodily needs. For others, **toilet training** can involve a protracted power struggle. Refusal to defecate in the toilet or potty is relatively common, associated with constipation, and can lead to parental frustration. Defusing the issue with a temporary cessation of training (and a return to diapers) often allows toilet mastery to proceed. Parents should focus on positive reinforcement and avoid negative reactions during the toilet training process.

Implications for Parents and Pediatricians

The normal decrease in appetite at this age may cause parental concern about nutrition; growth charts should reassure parents that the child's intake is adequate. Children normally modulate their food intake to match their somatic needs according to feelings of hunger and satiety. Daily intake fluctuates, at times widely, but intake over a week is relatively stable. Parents should provide a predictable eating schedule, with three meals and two snacks per day, allowing the child to choose how much to eat. This will avoid power struggles and allows the child to respond to satiety cues. However, it is important to obtain thorough diet histories for children at this age to advise parents about healthy choices and encourage physical activity to decrease long-term obesity risks and improve learning and cognitive development.

Highly active children face increased risks of injury, and parents should be counseled about safety precautions. Parental concerns about possible hyperactivity may reflect inappropriate expectations, heightened fears, or true overactivity. Children who engage in ongoing impulsive activity with no apparent regard for personal safety or those harming others on a regular basis should be evaluated further.

Assessment of motor skills must take into account a child's exposure history. Before diagnosing a motor delay based on screening tools, pediatricians should explore any limitations to a child's exposure and encourage parents to seek opportunities to work on these skills. Children should be followed closely at this age; referral to therapies should be pursued when true delays are identified given the proven benefits of early intervention.

LANGUAGE, COGNITION, AND PLAY

These three domains all involve **symbolic function**, a mode of dealing with the world that emerges during the preschool period.

Language

Our understanding of the acquisition of language is evolving. Preschool children command significant computational skills and understanding of statistical patterns that allow them to learn about both language and causation. The 2- and 3-year-old child employs frequency distributions to identify phonetic units distinguishing words in his or her native language from other languages.

Language development occurs most rapidly between 2 and 5 years of age. Vocabulary increases from 50-100 words to more than 2,000. Sentence structure advances from telegraphic phrases ("baby cry") to sentences incorporating all the major grammatical components (see Chapter 53). As a rule of thumb, between ages 2 and 5 years, the number of words the child puts in a typical sentence should, at a minimum, equal the child's age (2 by age 2 years, 3 by age 3 years, and so on). By 21-24 months, most children are using possessives ("my ball"), progressives (the "-ing" construction, as in "I playing"), questions, and negatives. By age 4 years, most children can count to 4 and use the past tense; by age 5 years, they can use the future tense. Young children do not use figurative speech; they will comprehend only the literal meaning of words. Referring to an object as "light as a feather" may produce a quizzical look on a child.

It is important to distinguish between **speech** (the production of intelligible sounds) and **language**, which refers to the underlying mental act. Language includes both expressive and receptive functions. *Receptive* language (understanding) varies less in its rate of acquisition than does *expressive* language; therefore it has greater prognostic importance (see Chapters 28 and 53).

Language acquisition depends critically on environmental input. Key determinants include the amount and variety of speech directed toward children and the frequency with which adults ask questions and encourage verbalization. Children raised in poverty typically perform lower on measures of language development than children from economically advantaged families, who tend to be exposed to many more words in the preschool period. Interventions aimed at increasing access to books in the home can temper these differences and improve language and pre-reading skills in the preschool child.

Although experience influences the rate of language development, many linguists believe that the basic mechanism for language learning is "hard-wired" in the brain. Children do not simply imitate adult speech; they abstract the complex rules of grammar from the ambient language, generating implicit hypotheses. Evidence for the existence of such implicit rules comes from analysis of grammatical errors, such as the overgeneralized use of "-s" to signify the plural and "-ed" to signify the past ("We seed lots of mouses.").

Language is linked to both cognitive and emotional development. Language delays may be the first indication of an intellectual disability, autism spectrum disorder, or child neglect or maltreatment. Language plays a critical part in the regulation of behavior through internalized "private speech" in which a child repeats adult prohibitions, first audibly and then mentally. Language also allows children to express feelings, such as anger or frustration, without acting them out; consequently, language-delayed children may show higher rates of tantrums and other externalizing behaviors.

Preschool language development lays the foundation for later success in school. Approximately 35% of U.S. children may enter school lacking the language skills that are the prerequisites for acquiring literacy. Children from socially and economically disadvantaged backgrounds have an increased risk of school problems, making early detection, along with referral and enrichment in programs such as Head Start, highly crucial for later development. Although children typically learn to read and write in elementary school, critical foundations for literacy are established during the preschool years. Through repeated early exposure to written words, children learn about the uses of writing (telling stories or sending messages) and about its form (left to right, top to bottom). Early errors in writing, like errors in speaking, reveal that literacy acquisition is an active process involving the generation and revision of hypotheses. **Bilingual children** may initially appear to lag behind their monolingual peers in acquiring language. They learn the differing rules governing both languages, and generally have the same number of total words between the languages. Bilingual children do not follow the same course of language development as monolingual children, but rather create a different system of language cues. Several cognitive advantages have been repeatedly demonstrated among bilingual compared to monolingual children.

Picture books have a special role in familiarizing young children with the printed word and in the development of verbal language. Children's vocabulary and receptive language improve when their parents or caregivers consistently read to them. Reading aloud with a young child is an interactive process in which a parent repeatedly focuses the child's attention on a particular picture, asks questions, and then gives the child feedback (**dialogic reading**). The elements of shared attention, active participation, immediate feedback, repetition, and graduated difficulty make such routines ideal for language learning. Programs in which physicians provide books to preschool children have shown improvement in language skills among the children (e.g., Reach Out and Read).

The period of rapid language acquisition is also when **developmental dysfluency** and **stuttering** are most likely to emerge (see Chapter 53.1); these can be traced to activation of the cortical motor, sensory, and cerebellar areas. Common difficulties include pauses and repetitions of initial sounds. Stress or excitement exacerbates these difficulties, which generally resolve on their own. Although 5% of preschool children will stutter, it will resolve in 80% of those children by age 8 years. Children with stuttering should be referred for evaluation if it is severe, persistent, or associated with anxiety, or if parental concern is elicited. Treatment includes guidance to parents to reduce pressures associated with speaking.

Cognition

The preschool period corresponds to Piaget's **preoperational** (prelogical) **stage,** characterized by magical thinking, egocentrism, and thinking that is dominated by perception, not abstraction (see Table 19.2). **Magical thinking** includes confusing coincidence with causality, *animism* (attributing motivations to inanimate objects and events), and unrealistic beliefs about the power of wishes. A child might believe that people cause it to rain by carrying umbrellas, that the sun goes down because it is tired, or that feeling resentment toward a sibling can actually make that sibling sick. **Egocentrism** refers to a child's inability to take another's point of view and does not connote selfishness. A child might try to comfort an adult who is upset by bringing the adult a favorite stuffed animal. After 2 years of age, the child develops a concept of herself or himself as an individual and senses the need to feel "whole."

Piaget demonstrated the dominance of **perception** over logic. In one experiment, water is poured back and forth between a tall, thin vase and a low, wide dish, and children are asked which container has more water. Typically, preschool-age children choose the one that looks larger (usually the tall vase), even when the examiner points out that no water has been added or taken away. Such misunderstandings reflect young children's developing hypotheses about the nature of the world, as well as their difficulty in attending simultaneously to multiple aspects of a situation. Preschool children also are able to understand **causal relationships**; this adds to our understanding of the ability of preschool children to engage in abstract thinking (see Chapter 19).

Imitation, central to the learning experience of preschool children, is a complex act because of differences in the size of the operators (the adult and the child), different levels of dexterity, and even different outcomes. A child who watches an adult unsuccessfully attempt a simple act (unscrew a lid) will imitate the action, but often with the intended outcome and not the demonstrated (failed) outcome. Thus "imitation" goes beyond the mere repetition of observed movements.

By age 3 years, children have self-identified their sex and are actively seeking understanding of the meaning of **gender identification**. There is a developmental progression from rigidity (males and female have strict gender roles) in the early preschool years to a more flexible realistic understanding (males and females can have a variety of interests that are not gender specific). Parents can facilitate this flexibility by eliminating gender-based expectations and expanding play options.

Play

Play involves learning, physical activity, socialization with peers, and practicing adult roles. Play increases in complexity and imagination, from simple imitation of common experiences, such as shopping and putting baby to bed (2 or 3 years of age), to more extended scenarios involving singular events, such as going to the zoo or going on a trip (3 or 4 years of age), to the creation of scenarios that have only been imagined, such as flying to the moon (4 or 5 years of age). By age 3 years, **cooperative play** is seen in activities such as building a tower of blocks together; later, more structured **role-play activity**, as in playing house, is seen. Play also becomes increasingly governed by rules, from early rules about asking (rather than taking) and sharing (2 or 3 years of age), to rules that change from moment to moment, according to the desires of the players (4 and 5 years of age), to the beginning of the recognition of rules as relatively immutable (5 years of age). Electronic forms of play (games) are best if interactive and educational and should remain limited in duration.

Play also allows for resolution of conflicts and anxiety and for creative outlets. Children can vent anger safely (reprimanding a doll), take on superpowers (dinosaur and superhero play), and obtain things that

are denied in real life (an imaginary friend or stuffed animal). Creativity is particularly apparent in drawing, painting, and other artistic activities. Themes and emotions that emerge in a child's drawings often reflect the emotional issues of greatest importance for the child.

Difficulty distinguishing fantasy from reality colors a child's perception of what the child views in the media, through programming and advertising. Twenty-five percent of young children have a television set or tablet in their bedroom; screen time in the bedroom is associated with more hours of watching. The number of hours that most preschoolers watch screens exceeds guidelines (1 hr/day for 2-5 year olds). Interactive quality educational programming in which children develop social relationships with the characters can increase learning if paired with adult interaction around the storyline. Exposure to commercial programming with violent content is associated with behavior problems, and because children younger than 8 years are not able to comprehend the concept of persuasive intent, they are more vulnerable to advertising.

Implications for Parents and Pediatricians

The significance of language as a target for assessment and intervention cannot be overestimated, because of its central role as an indicator of cognitive and emotional development and a key factor in behavioral regulation and later school success. As language emerges, parents can support emotional development by using words that describe the child's feeling states ("You sound angry right now") and urging the child to use words to express rather than act out feelings. Active imaginations will come into play when children offer explanations for misbehavior. A parent's best way of dealing with untruths is to address the event, not the child, and have the child participate in "making things right."

Parents should have a regular time each day for reading or looking at books with their children. Programs such as **Reach Out and Read,** in which clinicians give out picture books along with appropriate guidance during primary care visits, have been effective in increasing reading aloud and thereby promoting language development, particularly in lower-income families. TV and similar media should be limited to 1 hr/day of quality programming for children age 2-5 years, and parents should be watching the programs with their children and debriefing their young children afterward. At-risk children, particularly those living in poverty, can better meet future school challenges if they have early high-quality child care and learning experiences (e.g., Head Start).

Preoperational thinking constrains how children understand experiences of illness and treatment. Children begin to understand that bodies have "insides" and "outsides." Children should be given simple, concrete explanations for medical procedures and given some control over procedures if possible. Children should be reassured that they are not to blame when receiving a vaccine or venipuncture, and parents should be discouraged from making threats about needles if their child is not cooperating with the exam. An adhesive bandage will help to make the body "whole" again in a child's mind.

The active imagination that fuels play and the magical, animist thinking characteristic of preoperational cognition can also generate intense fears. More than 80% of parents report at least one fear in their preschool children. Refusal to take baths or to sit on the toilet may arise from the fear of being washed or flushed away, reflecting a child's immature appreciation of relative size. Attempts to demonstrate rationally that there are no monsters in the closet often fail, inasmuch as the fear arises from preoperational thinking. However, this same thinking allows parents to be endowed with magical powers that can banish the monsters with "monster spray" or a night-light. Parents should acknowledge the fears, offer reassurance and a sense of security, and give the child some sense of control over the situation. Use of the **Draw-a-Person**, in which a child is asked to draw the best person the child can, may help elucidate a child's viewpoint.

Emotional and Moral Development

Emotional challenges facing preschool children include accepting limits while maintaining a sense of self-direction, reigning in aggressive and sexual impulses, and interacting with a widening circle of adults and peers. At 2 years of age, behavioral limits are predominantly external; by 5 years of age, these controls need to be internalized if a child is to function in a typical classroom. Success in achieving this goal relies on prior emotional development, particularly the ability to use internalized images of trusted adults to provide a secure environment in times of stress. The love a child feels for important adults is the main incentive for the development of self-control.

Children learn what behaviors are acceptable and how much power they wield vis-à-vis important adults by testing limits. **Limit testing** increases when it elicits attention, even though that attention is often negative, and when limits are inconsistent. Testing often arouses parental anger or inappropriate solicitude as a child struggles to separate, and it gives rise to a corresponding parental challenge: letting go. Excessively tight limits can undermine a child's sense of initiative, whereas overly loose limits can provoke anxiety in a child who feels that no one is in control.

Control is a central issue. Young children cannot control many aspects of their lives, including where they go, how long they stay, and what they take home from the store. They are also prone to lose internal control, that is, to have **temper tantrums**. Fear, overtiredness, hunger, inconsistent expectations, or physical discomfort can also evoke tantrums. Tantrums normally appear toward the end of the first year of life and peak in prevalence between 2 and 4 years of age. Tantrums lasting more than 15 minutes or regularly occurring more than three times per day may reflect underlying medical, emotional, developmental, or social problems. Parents likely will not be able to reason or teach in the context of an active tantrum, and should offer emotional support during these times, sticking to short and concise explanations ("I can't let you hit"). Lessons about their behavior or discussions about strategies for future challenges should be delayed until the child is calm and able to engage.

Preschool children normally experience complicated feelings toward their parents that can include strong attachment and possessiveness toward the parent of the opposite sex, jealousy and resentment of the other parent, and fear that these negative feelings might lead to abandonment. These emotions, most of which are beyond a child's ability to comprehend or verbalize, often find expression in highly labile moods. The resolution of complicated feelings (a process extending over years) involves a child's unspoken decision to identify with the parents rather than compete with them. Play and language foster the development of emotional controls by allowing children to express emotions and role-play.

Curiosity about genitals and adult sexual organs is normal, as is **masturbation**. Excessive masturbation interfering with normal activity, acting out sexual intercourse, extreme modesty, or mimicry of adult seductive behavior all suggest the possibility of sexual abuse or inappropriate exposure (see Chapter 17.1). Modesty appears gradually between 4 and 6 years of age, with wide variations among cultures and families. Parents should begin to teach children about "private" body areas before school entry.

Moral thinking is constrained by a child's cognitive level and language abilities but develops as the child builds their identity with trusted adults. Beginning before the second birthday, the child's sense of right and wrong stems from the desire to earn adult approval and avoid negative consequences. The child's impulses are tempered by external forces; the child has not yet internalized societal rules or a sense of justice and fairness. Over time, as the child internalizes parental admonitions, words are substituted for aggressive behaviors. Finally, the child accepts personal responsibility. Actions will be viewed by damage caused, not by intent. Empathic responses to others' distress arise during the second year of life, but the ability to consider another child's point of view remains limited throughout this period. In keeping with a child's inability to focus on more than one aspect of a situation at a time, fairness is taken to mean equal treatment, regardless of circumstance. A 4 year old will acknowledge the importance of taking turns but will complain if he or she "didn't get enough time." Rules tend to be absolute, with guilt assigned for bad outcomes, regardless of intentions.

Implications for Parents and Pediatricians

The importance of the preschooler's sense of control over his or her body and surroundings have implications for practice. Preparing the

patient by letting the child know how the visit will proceed is reassuring. Tell the child what will happen, but do not ask permission unless you are willing to deal with a "no" answer. A brief introduction to "private parts" is warranted before the genital examination.

The visit of the 4 or 5 year old should be entertaining, because of the child's ability to communicate, as well as the child's natural curiosity. Physicians should realize that all children are occasionally difficult. Guidance emphasizing appropriate expectations for behavioral and emotional development and acknowledging normal parental feelings of anger, guilt, and confusion should be part of all visits at this time. Parents should be queried about daily routines and their expectations of child behavior. Providing children with **acceptable choices** (all options being acceptable to the parent) and encouraging independence in self-care activities (feeding, dressing, and bathing) will reduce conflicts.

Although some cultures condone the use of physical **punishment** for disciplining of young children, it is not a consistently effective means of behavioral control (Chapter 20). As children habituate to repeated spanking, parents have to spank ever harder to achieve the desired response, increasing the risk of serious injury. Sufficiently harsh punishment may acutely inhibit undesired behaviors, but at great long-term psychologic cost. Children may mimic the physical punishment that they receive; children who are spanked will have more aggressive behaviors later. Whereas spanking is the use of force, externally applied, to produce behavior change, **discipline** is the process that allows the child to internalize controls on behavior. Alternative discipline strategies should be offered, such as the "countdown" for transitions along with consistent limit setting, "time-outs" and "time-ins" (fun activities with caregiver present and interacting), clear communication of rules, and frequent approval with positive reinforcement of productive play and behavior (see Chapter 20 and Tables 20.3 and 20.4). Punishment should be immediate, specific to the behavior, and time limited. *Time-out for approximately 1 minute per year of age is very effective if children are getting sufficient time in.* A kitchen timer or digital phone alarm allows the parent to step back from the situation; the child is free when the timer rings. Although one strategy might not work for all children uniformly, consistency is integral to healthy learning and growth.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 26

Middle Childhood

Mutiat T. Onigbanjo and Susan Feigelman

Middle childhood (6-11 years of age) is the period in which children increasingly separate from parents and seek acceptance from teachers, other adults, and peers. Children begin to feel under pressure to conform to the style and ideals of the peer group. Self-esteem becomes a central issue, as children develop the cognitive ability to consider their own self-evaluations and their perception of how others see them. For the first time, they are judged according to their ability to produce socially valued outputs, such as getting good grades, playing a musical instrument, or hitting home runs.

PHYSICAL DEVELOPMENT

Growth occurs *discontinuously,* in three to six irregularly timed spurts each year, but varies both within and among individuals. Growth during the period averages 3-3.5 kg (6.6-7.7 lb) and 6-7 cm (2.4-2.8 in) per year (Fig. 26.1). The head grows only 2 cm in circumference throughout the entire period, reflecting a slowing of brain growth. Myelination continues into adolescence, with peak gray matter at 12-14 years. Body habitus is more erect than previously, with long legs compared with the torso.

Growth of the midface and lower face occurs gradually. Loss of deciduous (baby) teeth is a more dramatic sign of maturation, beginning around 6 years of age. Replacement with adult teeth occurs at a rate of about four per year, so that by age 9 years, children will have eight permanent incisors and four permanent molars. Premolars erupt by 11-12 years of age (see Chapter 353). Lymphoid tissues hypertrophy and reach maximal size, often giving rise to impressive tonsils and adenoids.

Muscular strength, coordination, and stamina increase progressively, as does the ability to perform complex movements, such as dancing or shooting baskets. Such higher-order motor skills are the result of both maturation and training; the degree of accomplishment reflects wide variability in innate skill, interest, and opportunity.

Physical fitness has declined among school-age children. Sedentary habits at this age are associated with increased lifetime risk of obesity, cardiovascular disease, lower academic achievement, and lower self-esteem. The number of overweight children and the degree of overweight have been increasing (see Chapter 65). Only 15% of middle and junior high schools require physical education classes at least three days per week. One quarter of youth do not engage in any free-time physical activity, despite the recommendation for at least 1 hour of physical activity per day.

Perceptions of **body image** develop early during this period; children as young as 5 and 6 years may express dissatisfaction with their body image; by ages 8 and 9 years many of these youth report trying to diet, often using ill-advised regimens. Loss-of-control (binge) eating occurs among approximately 6% of children at this age.

Before puberty the sensitivity of the hypothalamus and pituitary changes, leading to increased gonadotropin synthesis. Interest in gender differences and sexual behavior increases progressively until puberty. Although this is a period when sexual drives are limited, masturbation is common, and children may be interested in differences between genders. Rates of maturation differ by geography, ethnicity, and country. Sexual maturity occurs earlier for both sexes in the United States. Differences in maturation rates have implications for differing expectations of others based on sexual maturation.

Implications for Parents and Pediatricians

Middle childhood is generally a time of excellent health. However, children have variable sizes, shapes, and abilities. Children of this age compare themselves with others, eliciting feelings about their physical attributes and abilities. Fears of being "abnormal" can lead to avoidance of situations in which physical differences might be revealed, such as gym class or medical examinations. However, all children, including those with disabilities, should participate in gym classes. Those with physical disabilities may face special stresses; medical, social, and psychologic risks tend to occur together.

Children should be asked about risk factors for **obesity**. Participation in physical activity, including organized sports or other organized activities, can foster skill, teamwork, and fitness as well as a sense of accomplishment, but pressure to compete when the activity is no longer enjoyable has negative effects. Counseling on establishing healthy eating habits and limited screen time should be given to all families. Prepubertal children should not engage in high-stress, high-impact sports, such as power lifting or tackle football, because skeletal immaturity increases the risk of injury and concussions may have long-term sequelae (see Chapter 729).

COGNITIVE DEVELOPMENT

The thinking of early elementary school-age children differs qualitatively from that of preschool children. In place of the magical, egocentric, and perception-bound cognition of preschool children, school-age children increasingly apply rules based on observable phenomena, factor in multiple dimensions and points of view, and interpret their perceptions using physical laws. Piaget documented this shift from preoperational to **concrete** (logical) **operations** (see Chapter 19). When 5 year olds watch a ball of clay being rolled into a snake, they might insist that the snake has "more" because it is longer. In contrast, 7 year olds typically reply that the ball and the snake must weigh the same because nothing has been added or taken away or because the

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____

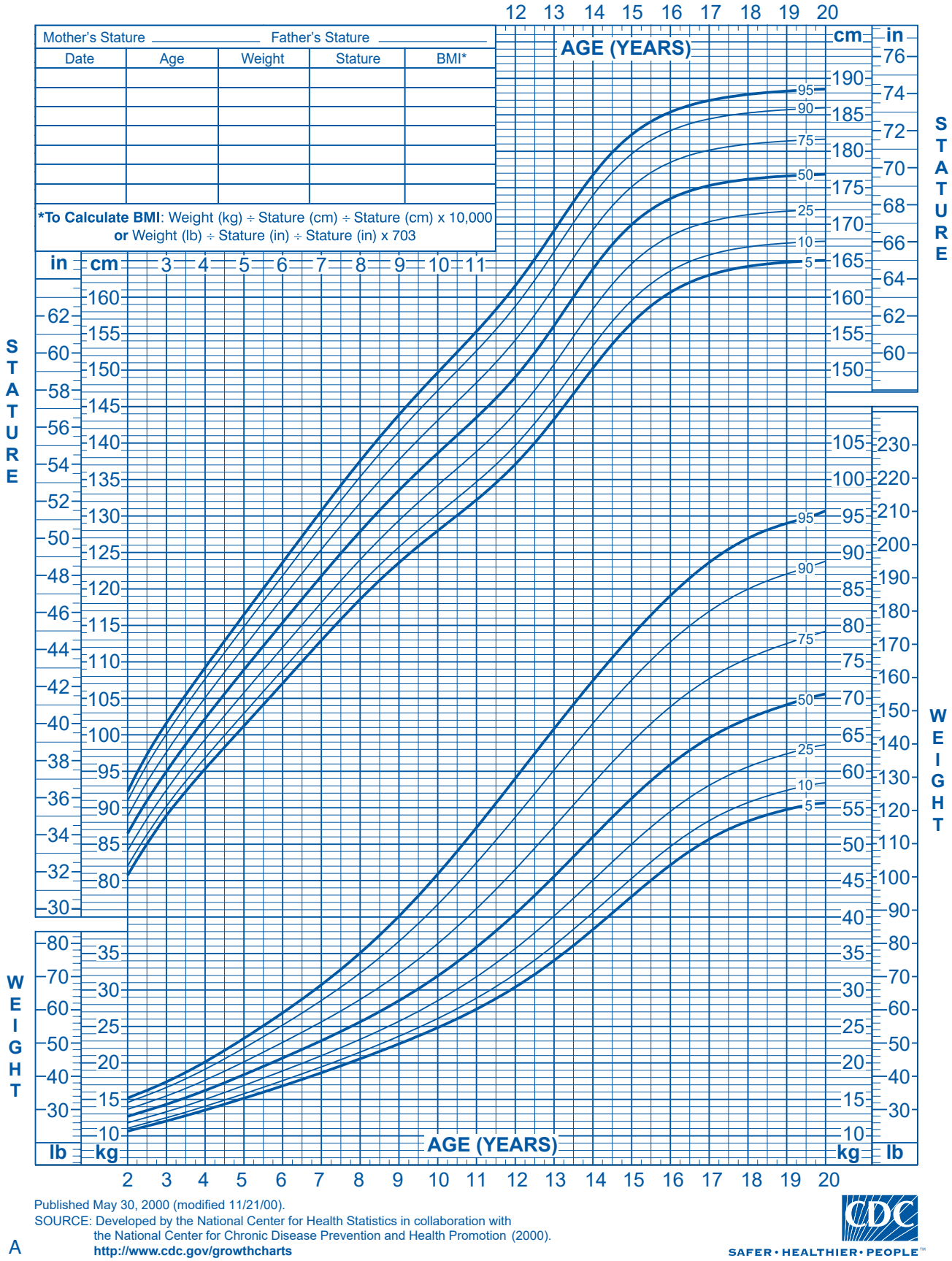

A

Fig. 26.1 A, Stature (height) for age and weight for boys, age 2-20 years. B, Stature (height) for age and weight for girls, age 2-20 years. *(Courtesy National Center for Health Statistics, in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. http://www.cdc.gov/growthcharts.)*

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____

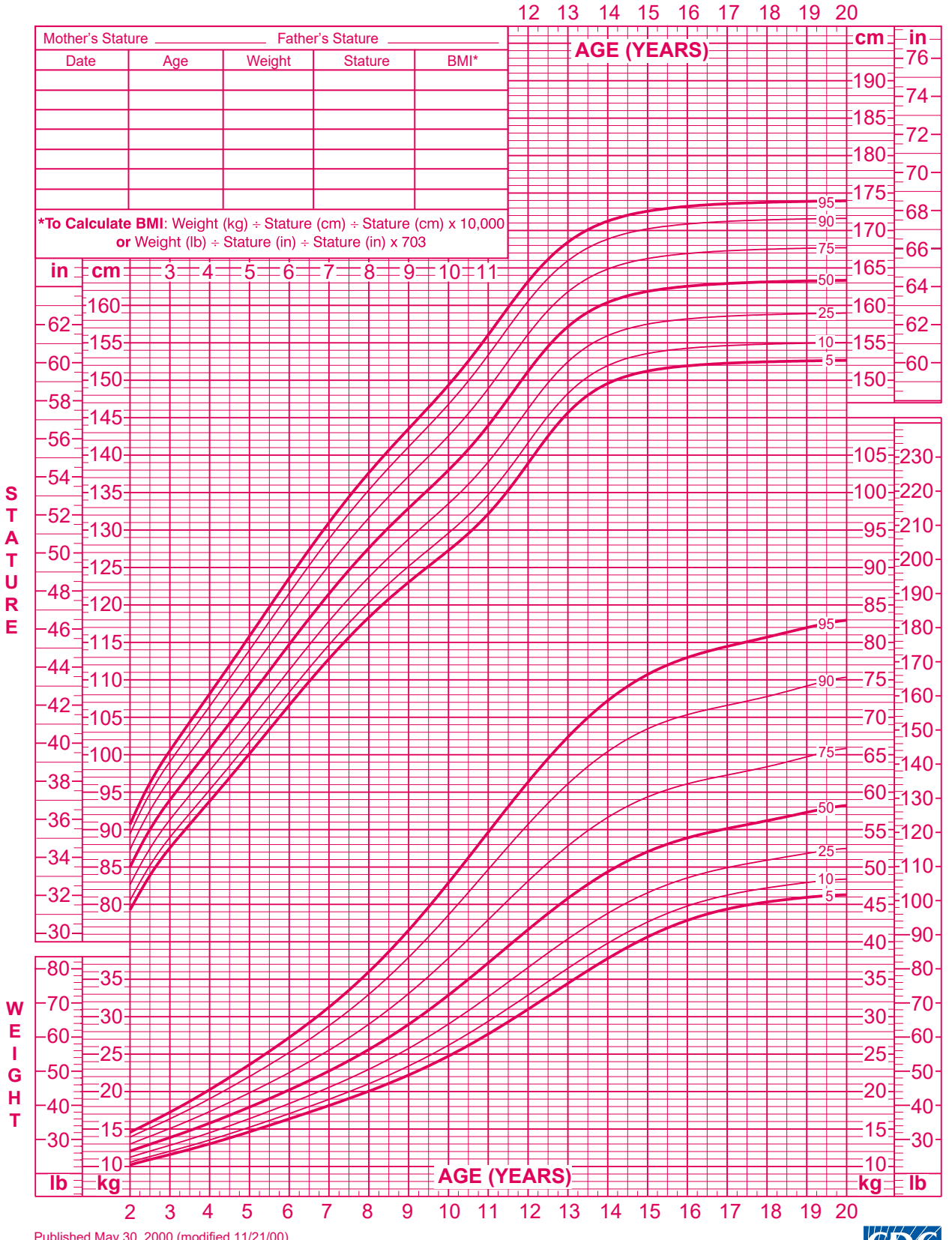

Published May 30, 2000 (modified 11/21/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

B

CDC SAFER • HEALTHIER • PEOPLE™

Fig. 26.1, cont'd

Table 26.1 Selected Perceptual, Cognitive, and Language Processes Required for Elementary School Success

PROCESS	DESCRIPTION	ASSOCIATED PROBLEMS
PERCEPTUAL		
Visual analysis	Ability to break a complex figure into components and understand their spatial relationships	Persistent letter confusion (e.g., between *b*, *d*, and *g*); difficulty with basic reading and writing and limited "sight" vocabulary
Proprioception and motor control	Ability to obtain information about body position by feel and unconsciously program complex movements	Poor handwriting, requiring inordinate effort, often with overly tight pencil grasp; special difficulty with timed tasks
Phonologic processing	Ability to perceive differences between similar-sounding words and to break down words into constituent sounds	Delayed receptive language and reading skill; attention and behavior problems secondary to not understanding directions; delayed acquisition of letter-sound correlations (phonetics)
COGNITIVE		
Long-term memory, both storage and recall	Ability to acquire skills that are "automatic" (i.e., accessible without conscious thought)	Delayed mastery of the alphabet (reading and writing letters); slow handwriting; inability to progress beyond basic mathematics
Selective attention	Ability to attend to important stimuli and ignore distractions	Difficulty following multistep instructions, completing assignments, and behaving well; problems with peer interaction
Sequencing	Ability to remember things in order; facility with time concepts	Difficulty organizing assignments, planning, spelling, and telling time
LANGUAGE		
Receptive language	Ability to comprehend complex constructions, function words (e.g., if, when, only, except), nuances of speech, and extended blocks of language (e.g., paragraphs)	Difficulty following directions; wandering attention during lessons and stories; problems with reading comprehension; problems with peer relationships
Expressive language	Ability to recall required words effortlessly (word finding), control meanings by varying position and word endings, and construct meaningful paragraphs and stories	Difficulty expressing feelings and using words for self-defense, with resulting frustration and physical acting out; struggling during "circle time" and in language-based subjects (e.g., English)

snake is both longer and thinner. This cognitive reorganization occurs at different rates in different contexts. In the context of social interactions with siblings, young children often demonstrate an ability to understand alternate points of view long before they demonstrate that ability in their thinking about the physical world. Understanding time and space constructs occurs in the later part of this period.

The concept of **school readiness** has evolved. The American Academy of Pediatrics recommends following an "interactional relational" model in which the focus is on the child, the environment, and the resulting interactions. This model explicitly asserts that all children can learn and that the educational process is reciprocal between the child and the school. It is developmentally based, recognizing the importance of early experiences for later development. Rather than delaying school entry, high-quality early-education programs may be the key to ultimate school success.

School makes increasing cognitive demands on the child. Mastery of the elementary curriculum requires that many perceptual, cognitive, and language processes work efficiently (Table 26.1), and children are expected to attend to many inputs at once. The first 2-3 years of elementary school are devoted to acquiring the fundamentals: reading, writing, and basic mathematics skills. By third grade, children need to be able to sustain attention through a 45-minute period, and the curriculum requires more complex tasks. The goal of reading a paragraph is no longer to decode the words, but to understand the content; the goal of writing is no longer spelling or penmanship, but composition. The volume of work increases along with the complexity.

Cognitive abilities interact with a wide array of attitudinal and emotional factors in determining classroom performance. These factors include *external rewards* (eagerness to please adults and approval from peers) and *internal rewards* (competitiveness, willingness to work for a delayed reward, belief in one's abilities, and ability to risk trying when success is not ensured). Success predisposes to success, whereas failure impacts self-esteem and reduces self-efficacy, diminishing a child's willingness to take future risks.

Children's intellectual activity extends beyond the classroom. Beginning in the third or fourth grade, children increasingly enjoy strategy games and wordplay (puns and insults) that exercise their growing cognitive and linguistic mastery. Many become experts on subjects of their own choosing, such as sports trivia, or develop hobbies, such as special card collections. Others become avid readers or take on artistic pursuits. Whereas board and card games were once the usual leisure-time activity of youth, video, computer, and other electronic games currently fill this need.

Implications for Parents and Pediatricians

Pediatricians have an important role in preparing their patients for school entrance by promoting health through immunizations, adequate nutrition, appropriate recreation, and screening for physical, developmental, and cognitive disorders. The American Academy of Pediatrics recommends that pediatric providers promote the "5 Rs" of early education: (1) reading as a daily family activity; (2) rhyming, playing, and cuddling together; (3) routines and regular times for meals, play, and sleep; (4) reward through praise for successes; and (5) reciprocal nurturing relationships.

Concrete operations allow children to understand simple explanations for illnesses and necessary treatments, although they may revert to prelogical thinking when under stress. A child with pneumonia may be able to explain about white cells fighting the "germs" in the lungs but may still secretly harbor the belief that the sickness is a punishment for disobedience.

As children are faced with more abstract concepts, academic and classroom behavior problems emerge and come to the pediatrician's attention. Referrals may be made to the school for remediation or to community resources (medical or psychologic) when appropriate. The causes may be one or more of the following: deficits in perception (vision and hearing); specific learning disabilities (see Chapters 51 and 52); global cognitive delay (intellectual disability; Chapter 56); deficits in attention and executive function (Chapters 49 and 50);

and attention deficits secondary to family dysfunction, depression, anxiety, or chronic illness. Children whose learning style does not fit the classroom culture may have academic difficulties and need assessment before failure sets in. Simply having a child repeat a failed grade rarely has any beneficial effect and often seriously undercuts the child's self-esteem. In addition to finding the problem areas, identifying each child's strengths is important. Educational approaches that value a wide range of talents ("multiple intelligences") beyond the traditional reading, writing, and mathematics may allow more children to succeed.

The change in cognition allows the child to understand "if/when" clauses. Increased responsibilities and expectations accompany increased rights and privileges. Discipline strategies should move toward negotiation and a clear understanding of consequences, including removal of privileges for infringements.

SOCIAL, EMOTIONAL, AND MORAL DEVELOPMENT

Social and Emotional Development

In middle childhood, energy is directed toward creativity and productivity. Changes occur in three spheres: the home, the school, and the neighborhood. Of these, the home and family remain the most influential. Increasing independence is marked by the first sleepover at a friend's house and the first time at overnight camp. Parents should make demands for effort in school and extracurricular activities, celebrate successes, and offer unconditional acceptance when failures occur. Regular chores, associated with an allowance, provide an opportunity for children to contribute to family functioning and learn the value of money. These responsibilities may be a testing ground for psychologic separation, leading to conflict. Siblings have critical roles as competitors, loyal supporters, and role models.

The beginning of school coincides with a child's further separation from the family and the increasing importance of teacher and peer relationships. Social groups tend to be same-sex, with frequent changing of membership, contributing to a child's growing social development and competence. Popularity, a central ingredient of self-esteem, may be won through possessions (having the latest electronic gadgets or the right clothes), as well as through personal attractiveness, accomplishments, and actual social skills. Children are aware of racial differences and are beginning to form opinions about racial groups that impact their relationships. **Gender identification**, which began in early childhood, continues to evolve and can have significant implications for peer relationships and self-awareness.

Some children conform readily to the peer norms and enjoy easy social success. Those who adopt individualistic styles or have visible differences may be teased or bullied. Children with deficits in social skills may go to extreme lengths to win acceptance, only to meet with repeated failure. Attributions conferred by peers, such as funny, stupid, bad, or fat, may become incorporated into a child's self-image and affect the child's personality, as well as school performance. Parents may have their greatest effect indirectly, through actions that change the peer group (changing the child's school or encouraging involvement in structured after-school activities). Children who identify with a gender different from their sex of birth, or whose manner and dress reflect those more typically seen as "opposite" their birth sex, may be subject to teasing or **bullying** (Chapter 153). This can magnify the confusion for these children, who are formulating their own concept of "self."

In the neighborhood, real dangers, such as busy streets, bullies, violence, and strangers, tax school-age children's common sense and resourcefulness (see Chapter 15). Interactions with peers without close adult supervision call on increasing conflict resolution skills. Media exposure to adult materialism, sexuality, substance use, and violence may be frightening, reinforcing children's feeling of powerlessness in the larger world. Compensatory fantasies of being powerful may fuel the fascination with heroes and superheroes. A balance between fantasy and an appropriate ability to negotiate real-world challenges indicates healthy emotional development.

Moral Development

Although by age 6 years most children will have a **conscience** (internalized rules of society), they vary greatly in their level of moral development. For younger children, many still subscribe to the notion that rules are established and enforced by an authority figure (parent or teacher), and decision-making is guided by self-interest (avoidance of negative and receipt of positive consequences). The needs of others are not strongly considered in decision-making. As they grow older, most will recognize not only their own needs and desires but also those of others, although personal consequences are still the primary driver of behavior. Social behaviors that are socially undesirable are considered wrong. By age 10-11 years, the combination of peer pressure, a desire to please authority figures, and an understanding of **reciprocity** (treat others as you wish to be treated) shapes the child's behavior.

Implications for Parents and Pediatricians

Children need unconditional support as well as realistic demands as they venture into a world that is often frightening. A daily query from parents over the dinner table or at bedtime about the good and bad things that happened during the child's day may uncover problems early. Parents may have difficulty allowing the child independence or may exert excessive pressure on their children to achieve academic or competitive success. Children who struggle to meet such expectations may have behavior problems or psychosomatic complaints.

Many children face stressors that exceed the normal challenges of separation and success in school and the neighborhood. Approximately 50% of all marriages in the United States end in divorce. In addition, domestic violence, parental substance abuse, and other adverse childhood experiences (**ACEs**) may also impair a child's ability to use home as a secure base for refueling emotional energies. In many neighborhoods, random violence makes the normal development of independence extremely dangerous. Older children may join gangs as a means of self-protection and a way to attain recognition and to belong to a cohesive group. Children who bully others and those who are victims of bullying should be evaluated, because bullying is associated with mood disorders, family problems, and school adjustment problems. Parents should reduce exposure to hazards where possible. Because of the risk of unintentional firearm injuries to children, parents should be encouraged to ask parents of playmates whether a gun is kept in their home and, if so, how it is secured.

Pediatrician visits are infrequent in this period; therefore each visit is an opportunity to assess children's functioning in all contexts (home, school, neighborhood). Maladaptive behaviors, both internalizing and externalizing, occur when children do not have safe, secure attachments to adults and stress in any of these environments overwhelms the child's coping responses, becoming "toxic stress." Because of continuous exposure and the strong influence of media (programming and advertisements) on children's beliefs and attitudes, parents must be alert to exposures from television and internet. Youth 8-12 years of age spend over 6 hr/day with a variety of media; half have a TV in their bedroom. Parents should be advised to remove the TV from their children's rooms, limit viewing to 2 hr/day, and monitor what programs children watch. Nearly all children have exposure to mobile technology. Some computer screen time may be necessary for schoolwork and virtual learning. However, the widespread use of **social media** may have detrimental effects including risky health behaviors, cyberbullying, targeted advertisements, and low self-esteem. The **Draw-a-Person** (for ages 3-10 years, with instructions to "draw a complete person") and **Kinetic Family Drawing** (beginning at age 5 years, with instructions to "draw a picture of everyone in your family doing something") are useful office tools to assess a child's functioning.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 27

Assessment of Growth

Vaneeta Bamba and Andrea Kelly

Growth can be considered a vital sign in children, and aberrant growth may be the first sign of an underlying pathologic condition. The most powerful tool in growth assessment is the **growth chart** (Figs. 24.1, 24.2, 26.1, and 27.1), used in combination with accurate measurements of height, weight, head circumference, and calculation of the **body mass index (BMI).**

TECHNIQUES TO MEASURE GROWTH

Growth assessment requires accurate and precise measurements. For infants and toddlers age <2 years, weight, length, and head circumference are obtained. **Head circumference** is measured with a flexible tape measure starting at the supraorbital ridge around to the occipital prominence in the back of the head, locating the maximal circumference. **Height** and **weight** measures should be performed with the infant naked, and ideally, repeated measures will be performed on the same equipment. **Recumbent length** is most accurately measured by two examiners (one to position the child). Hair ornaments and hairstyles that interfere with measurements and positioning should be removed. The child's head is positioned against an inflexible measuring board in the **Frankfurt plane**, in which the outer canthi of the eyes are in line with the external auditory meatus and are perpendicular to the long axis of the trunk. Legs should be fully extended, and feet are maintained perpendicular to the plane of the supine infant. For older children (>2 years) who can stand unassisted, standing heights should be obtained without shoes, using a stadiometer with the head in the Frankfurt plane, and the back of the head, thoracic spine, buttocks, and heels approximating the vertical axis of one another and the stadiometer.

Measurements obtained using alternative means, such as marking examination paper at the foot and head of a supine infant or using a tape measure or wall growth chart with a book or ruler on the head can lead to inaccuracy and render the measurement useless.

Measurements for height and weight should be plotted on the age-appropriate growth curve. Comparing measurements with previous growth trends, repeating measures that are inconsistent, and plotting results longitudinally are essential for monitoring growth. Calculation of interim linear height velocity, such as centimeters per year (cm/yr), allows more precise comparison of growth rate to the norm (Table 27.1).

If a child is growing faster or more slowly than expected, measurement of body proportions, which follow a predictable sequence of changes with development, are useful. The head and trunk are relatively large at birth, with progressive lengthening of the limbs throughout development, particularly during puberty. The **upper-to-lower body segment ratio** (**U/L ratio**) provides an assessment of truncal growth relative to limb growth. The **lower-body segment** is defined as the length from the top of the symphysis pubis to the floor, and the **upper-body segment** is the total height minus the lower-body segment. The U/L ratio equals approximately 1.7 at birth, 1.3 at 3 years, and 1.0 after 7 years. Higher U/L ratios are characteristic of short-limb dwarfism, as occurs with Turner syndrome or bone disorders, whereas lower ratios suggest hypogonadism or Marfan syndrome.

Arm span also provides assessment of proportionality and is measured as the distance between the tips of the middle fingers while the patient stands with the back against the wall with arms outstretched horizontally at a 90-degree angle to the trunk. This span should be close to height, although the proportion changes with age.

GROWTH CURVES

The American Academy of Pediatrics (AAP) and the U.S. Centers for Disease Control and Prevention (CDC) recommend use of the 2006 World Health Organization (WHO) growth curves for children age 0-24 months and the 2000 CDC growth curves for children age 2-19 years (https://www.cdc.gov/growthcharts). There are five standard gender-specific charts: (1) weight for age, (2) height (length and stature) for age, (3) head circumference for age, (4) weight for height (length and stature) for infants, and (5) BMI for age (see Fig. 27.1; see also Figs. 24.1, 24.2, and 26.1). Clinicians should confirm that the correct CDC and WHO growth charts are used in electronic medical records to ensure accurate characterization of growth.

The WHO curves describe growth differently than the CDC curves (Fig. 27.2). The WHO curves are **growth standards** that describe how children grow under optimal conditions, whereas the CDC curves are **growth references** that describe how children grew in a specific time and place. The WHO growth curves are based on longitudinal growth studies in which cohorts of newborns were chosen from six countries (Brazil, Ghana, India, Norway, Oman, United States) using specific inclusion and exclusion criteria; all infants were breastfed for at least 12 months and were predominantly breastfed for the first 4 months of life. They were measured regularly from birth to 23 months during 1997–2003. In contrast, the CDC curves are based on cross-sectional data from different studies during different time points. Growth curves for children age 2-59 months were based on the National Health and Nutrition Examination Survey (NHANES), which included a cross section of the U.S. population. These data were supplemented with additional participants in a separate nutrition surveillance study.

Several deficiencies of the older charts have been corrected, such as the overrepresentation of bottle-fed infants and the reliance on a local dataset for the infant charts. The disjunction between length and height when transitioning from the infant curves to those for older children is improved.

Each chart is composed of percentile curves, which indicate the percentage of children at a given age on the *x* axis whose measured value falls below the corresponding value on the *y* axis. The 2006 WHO growth curves include values that are 2 standard deviations (SD) above and below median (2nd and 98th percentiles), whereas the 2000 CDC growth curves include 3rd and 97th percentiles. On the WHO weight chart for boys ages 0-24 months (see Fig. 24.2A), the 9 month age line intersects the 25th percentile curve at 8.3 kg, indicating that 25% of 9-month-old males in the WHO cohorts weigh less than 8.3 kg (75% weigh more). Similarly, a 9-month-old male weighing more than 11 kg is heavier than 98% of his peers. The median or 50th percentile is also termed the **standard value,** in the sense that the standard length for a 7-month-old female is 67.3 cm (see Fig. 24.2B). The weight-for-length charts (see Fig. 24.1) are constructed in an analogous fashion, with length or stature in place of age on the *x* axis; the median or standard weight for a female measuring 100 cm is 15 kg.

Extremes of height or weight can also be expressed in terms of the age for which they would represent the standard or median. For instance, an 18-month-old female who is 74.9 cm (2nd percentile) is at the 50th percentile for a 13 month old. Thus the height age is 13 months. Weight age can similarly be expressed.

In assessing adolescents, caution must be used in applying cross-sectional charts. Growth during adolescence is linked temporally to the onset of puberty, which varies widely. Normal variations in the timing of the growth spurt can lead to misdiagnosis of growth abnormalities. By using cross-sectional data based on chronologic age, the charts combine youth who are at different stages of maturation. Data for 12-year-old males include both earlier-maturing males who are at the peak of their growth spurts and later-maturing ones who are still growing at their prepubertal rate. The net results are an artificially blunted growth peak, and the appearance that adolescents grow more gradually and for a longer duration than in actuality.

When additional insight is necessary, growth charts derived from longitudinal data, such as the **height velocity charts** of Tanner and colleagues, are recommended. The longitudinal component of these velocity curves is based on British children from the 1950s and 1960s, and cross-sectional data from U.S. children were superimposed. Height velocity curves based on longitudinal data from a multiethnic study conducted at five U.S. sites included SD scores for height velocity for

2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703

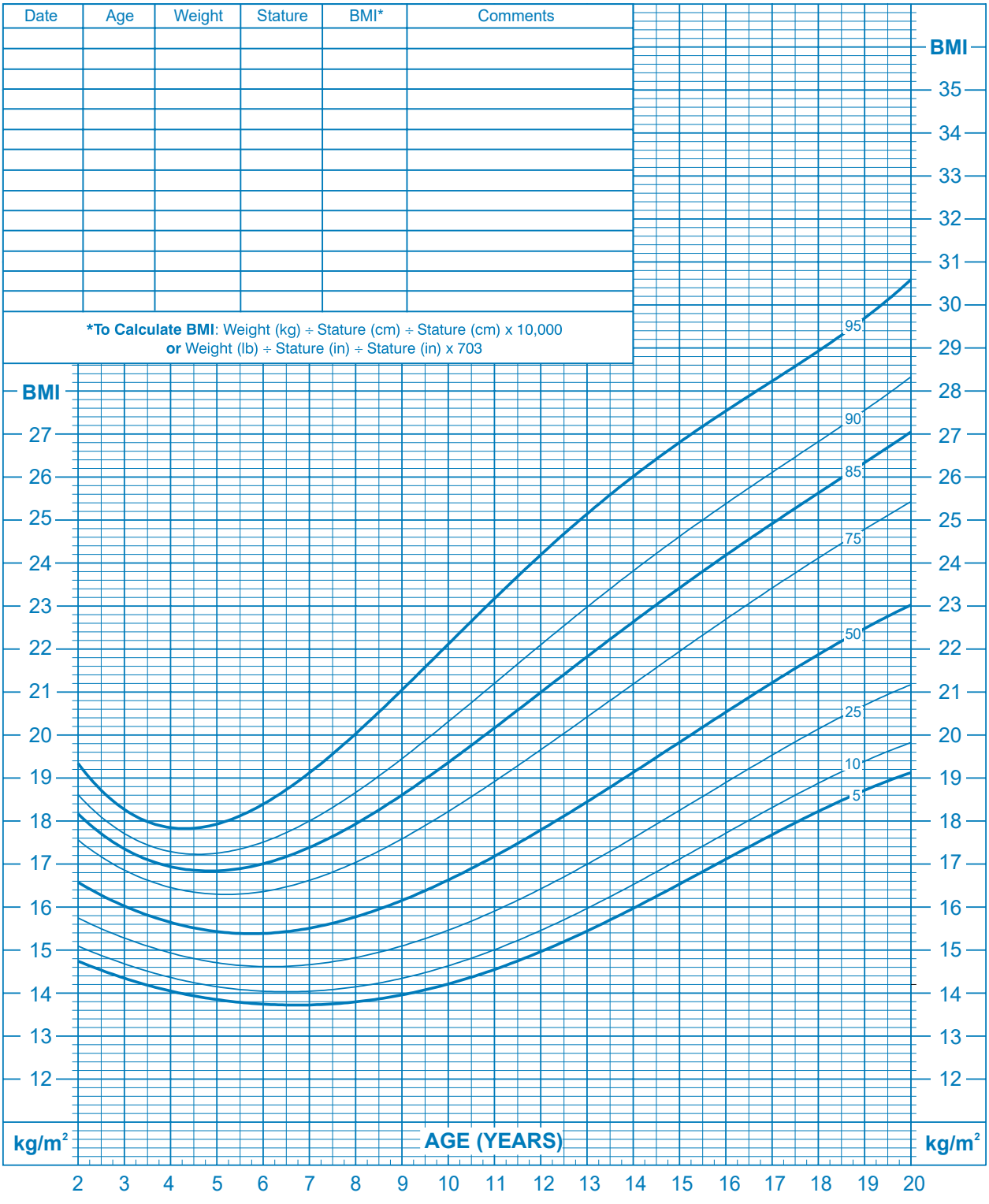

Published May 30, 2000 (modified 10/16/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC SAFER • HEALTHIER • PEOPLE™

A

Fig. 27.1 A, Body mass index (BMI) percentiles for boys, age 2-20 years.

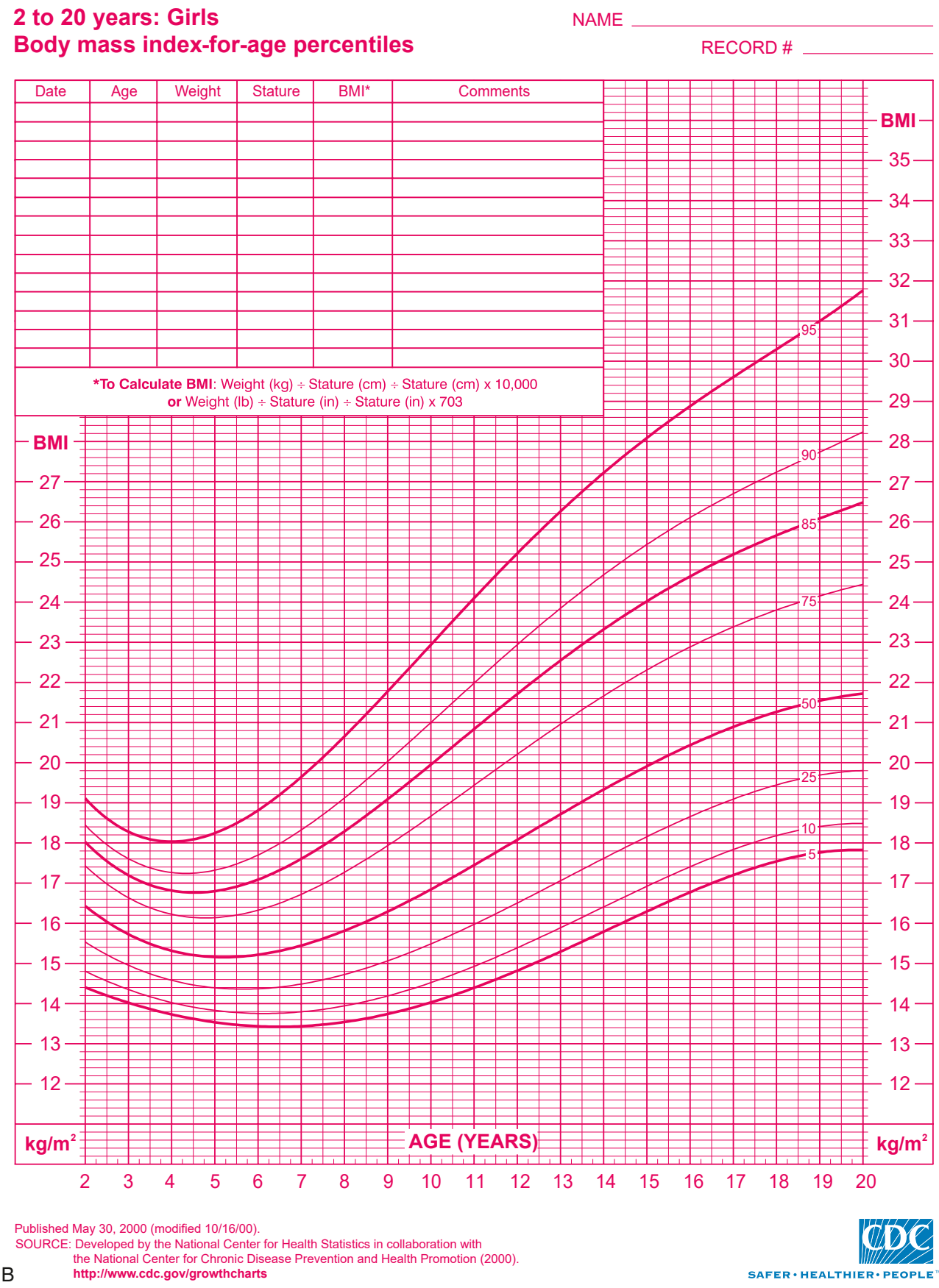

B

Fig. 27.1 Cont'd B, BMI percentiles for girls, age 2-20 years. *Official Centers for Disease Control and Prevention [CDC] growth charts, as described in this chapter.) The 85th to 95th percentile is at risk for overweight; >95th percentile is overweight; <5th percentile is underweight. Technical information and interpretation and management guides are available at www.cdc.gov/nchs. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000 (http://www.cdc.gov/growthcharts).*

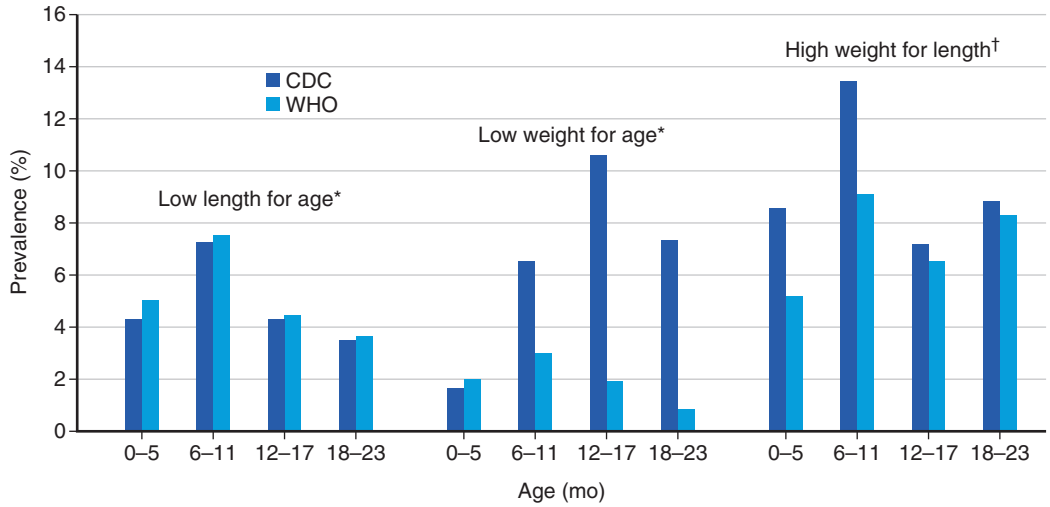

Fig. 27.2 Comparison of World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth chart prevalence of low length for age, low weight for age, and high weight for length among children age <24 months, United States, 1999–2004. *, ≤5th percentile on the CDC charts; ≤2.3rd percentile on the WHO charts. †, ≥95th percentile on the CDC charts; ≥97.7th percentile on the WHO charts. *(Data from the National Health and Nutrition Examination Survey, 1999–2004; from Grummer-Strawn LM, Reinold C, Krebs NF: Centers for Disease Control and Prevention: Use of World Health Organization and CDC growth charts for children ages 0-59 months in the United States, MMWR Recomm Rep 2010;59[RR-9]:1–15.)*

Table 27.1 Growth Velocity and Other Growth Characteristics by Age

INFANCY	CHILDHOOD	ADOLESCENCE
Birth-12 mo: 24 cm/yr 12-24 mo: 10 cm/yr 24-36 mo: 8 cm/yr	6 cm/yr Slowly decelerates before pubertal onset Height typically does not cross percentile lines	Sigmoid-shaped growth Adolescent growth spurt accounts for about 15% of adult height Peak height velocity Girls: 8 cm/yr Boys: 10 cm/yr

earlier- and later-maturing adolescents to facilitate the identification of poor or accelerated linear growth.

Specialized growth charts have been developed for U.S. children with various conditions, including very low birthweight (VLBW), small for gestational age, trisomy 21, Turner syndrome, and achondroplasia, and should be used when appropriate.

Facilitating identification of obesity, the charts include curves for plotting BMI for ages 2-20 years rather than weight for height (see Fig. 27.1). Methodologic steps have ensured that the increase in the prevalence of obesity has not unduly raised the upper limits of normal. BMI can be calculated as weight in kilograms/(height in meters)^2 or weight in pounds/(height in inches)^2 × 703, with fractions of pounds and inches expressed as decimals. Because of variable weight and height gains during childhood, BMI must be interpreted relative to age and sex; the BMI percentile provides a more standardized comparison. For example, a 6-year-old girl with a BMI of 19.7 kg/m^2 (97th percentile) is obese, whereas a 15-year-old female with BMI of 19.7 kg/m^2 (50th percentile) is normal weight.

Normal Growth

Height is highly correlated with genetics, specifically parental height. Calculation of sex-adjusted **midparental height** is important when assessing growth in a child to avoid misclassification of abnormal growth. The average difference in stature between males and females is 5 inches (13 cm); therefore 5 inches (13 cm) is subtracted from the father's height before averaging with mother's height in a female, whereas 5 inches (13 cm) is added to the mother's height before averaging with the father's height in a male:

- Males: [(Maternal height + 5 inches) + Paternal height]/2
- Females: [Maternal height + (Paternal height − 5 inches)]/2

Furthermore, generally 4 inches (2 SD) is applied above and below this value to provide a *genetic target height range*. For example, if the mother is 63 inches tall and the father 70 inches tall, the daughter's sex-adjusted midparental height is 64 inches ± 4 inches, for a target height range of 60-68 inches. The son of these same parents would have a sex-adjusted midparental height of 69 inches, with a range of 65-73 inches. Note that these general guidelines do not address extreme differences between parental heights that may affect individual target height range.

Growth can be divided into four major phases: fetal, infantile, childhood, and adolescence. Growth rate varies by age (see Table 27.1). Different factors are of different importance in each phase, and the various contributors to poor growth may feature more in one phase than another. Long-term height may be permanently compromised if one entire phase is characterized by poor growth. Therefore early detection and prevention are critical. **Fetal growth** is the fastest growth phase, with maternal, placental, fetal, and environmental factors playing key roles. Birthweight does not necessarily correlate with adult height, although factors that inhibit fetal growth may have long-lasting effects, as seen in children with intrauterine growth retardation. **Infantile growth** is particularly sensitive to nutrition as well as congenital conditions. Genetic height gradually becomes influential; indeed, crossing of percentiles in the first 2 years of life is common as children begin to approach their genetic potential. **Childhood growth** is often the most steady and predictable. During this phase the height percentile is fairly consistent in otherwise healthy children.

Adolescent growth is associated with a decrease in growth velocity before the onset of puberty; this deceleration tends to be more pronounced in males. During pubertal development, sex hormones

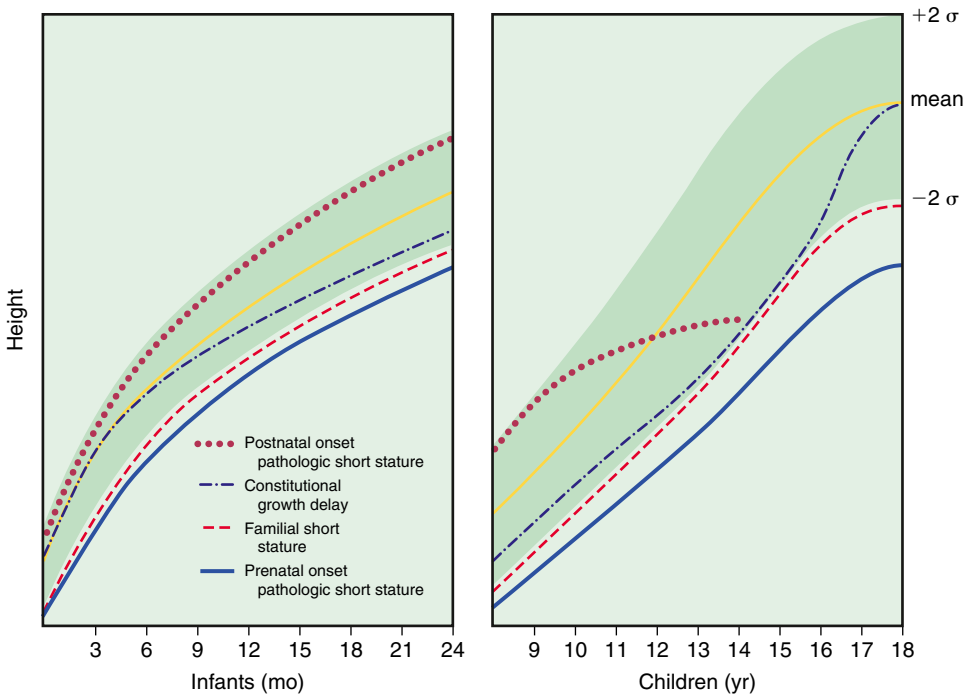

Fig. 27.3 Height-for-age growth curves of the four general causes of proportional short stature: postnatal onset pathologic short stature, constitutional growth delay, familial short stature, and prenatal onset short stature. *(From Mahoney CP: Evaluating the child with short stature, Pediatr Clin North Am 1987;34:825.)*

(testosterone and estrogen) are the primary drivers of growth and enhance growth hormone secretion, thereby facilitating pubertal growth acceleration. Females typically experience growth acceleration during Tanner stage 3 for breast development, whereas this acceleration occurs during Tanner stage 4 for pubic hair development in males. Males not only achieve greater height velocities than females during puberty, but also grow approximately 2 years longer than females, both of which contribute to the taller average height of adult males compared with adult females.

Abnormal Growth

Growth is a dynamic process. A child measured at the 5th percentile for stature may be growing normally, may be failing to grow, or may be recovering from growth failure, depending on the trajectory of the growth curve (Fig. 27.3). Growth failure must be distinguished from short stature. **Growth failure** is defined as achievement of height velocity that is less than expected for a child's age and sex (and pubertal development if relevant) or a downward crossing of more than 2 percentile lines for height on the growth chart. **Short stature** is defined as growing either below expected genetic potential or growing below −2 SD for age and sex. For some children, however, growth parameters ≤2 SD may be normal, and differentiating appropriately small vs. pathologically small is crucial. Midparental height, ethnicity, and other factors that may be inherent in the child's genetic height potential are important considerations in the assessment of growth. For children with particularly tall or short parents, overdiagnosing and underdiagnosing growth disorders are risks if parental heights are not considered. In the setting of familial short stature or tall stature, more specialized charts can help determine whether a child is even shorter or taller than expected for parental heights, to prevent misdiagnosis of growth disorders.

For **premature infants**, overdiagnosis of growth failure can be avoided by using growth charts developed specifically for this population. A cruder method, subtracting the weeks of prematurity from the postnatal age when plotting growth parameters, does not capture the variability in growth velocity that VLBW infants demonstrate. Although VLBW infants may continue to show **catch-up growth** through early school age, most achieve weight catch-up during the second year and height catch-up by 3-4 years, barring medical complications (see Chapter 119).

Abnormal growth may be caused by a variety of factors, including congenital conditions, systemic disease, endocrine disorders, nutritional deficiency (see Chapter 62), psychosocial conditions, constitutional delay, or familial disorders (Tables 27.2 and 27.3). In congenital pathologic short stature, an infant may or may not be born small, but growth gradually tapers throughout infancy (see Fig. 27.3). Causes include chromosome or genetic abnormalities (Turner syndrome, skeletal dysplasia, trisomy 21; see Chapters 57 and 99), perinatal infection, extreme prematurity, and teratogens (phenytoin, alcohol) (see Chapters 117.4 and 146). Linear growth deceleration with or without changes in weight can occur at the onset or as a result of a systemic illness or chronic inflammation. Medications such as high-dose glucocorticoids may also impact growth. Analysis of growth patterns requires consideration of weight status. Poor linear growth in the setting of decreasing BMI suggests a nutritional or gastrointestinal issue, whereas *poor linear growth* in the context of good or robust BMI may suggest a hormonal condition (hypothyroidism, growth hormone deficiency, cortisol excess).

Not all decreased growth is abnormal; variations of growth include constitutional growth (and pubertal) delay and familial short stature. In **constitutional growth delay**, weight and height decrease near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence with achievement of normal adult height. In **familial short stature**, both the infant/child and the parent(s) are small; growth runs parallel to and just below the normal curves.

Although **tall or accelerated growth** may be a variation of normal, unexpected increase in growth may also signal an underlying condition (see Table 27.3). Typically, obese individuals grow more quickly than their peers because of peripheral aromatization of estrogen and effects on bone maturation. Despite early taller stature, obese children are not ultimately taller than anticipated for genetic height. Early onset of puberty, growth hormone excess, and sex steroid exposure can also lead to accelerated growth. Several of these conditions may ultimately lead to short stature in adulthood. Genetic conditions associated with tall stature and overgrowth include Sotos, Klinefelter, and Marfan syndromes (see Chapter 598 and 598.1).

Table 27.2 Common Causes of Decreased Growth and Short Stature

Variation of normal
Familial short stature
Constitutional delay
Delayed puberty
Nutrition and gastrointestinal conditions
Malnutrition
Celiac disease
Inflammatory bowel disease
Genetic conditions
Turner syndrome
Prader-Willi syndrome
22q deletion syndrome
Trisomy 21
Skeletal dysplasias: achondroplasia, SHOX haploinsufficiency, osteogenesis imperfecta
Endocrine conditions
Hypothyroidism
Growth hormone deficiency
Poorly controlled diabetes mellitus
Poorly controlled diabetes insipidus
Metabolic bone disease: rickets, hypophosphatasia
Glucocorticoid excess
Psychosocial causes
Renal conditions
Renal tubular acidosis
Nephrotic syndrome
Medications
Glucocorticoids
Inappropriate sex steroid exposure
Antiepileptic medications

Table 27.3 Common Causes of Increased Growth and Tall Stature

Variation of normal
Constitutional tall stature
Familial tall stature
Endocrine conditions
Growth hormone excess
Precocious puberty (ultimate height may be decreased)
Congenital adrenal hyperplasia
Obesity
Genetic conditions
Marfan syndrome
Klinefelter syndrome
Sotos syndrome

Evaluation of Abnormal Growth

Evaluation of abnormal growth should include confirmation that the data are accurate and plotted correctly. Comparisons should be made with previous measurements. If poor or rapid growth or short or tall stature is a concern, a radiograph of the left hand and wrist to show the **bone age** can provide information about skeletal maturation. Skeletal development represents physiologic rather than chronologic age. Reference standards for bone maturation facilitate estimation of bone age (see Table 23.3). A delayed bone age (skeletal age younger than chronologic age) suggests catch-up potential for linear growth. Advanced bone age suggests a rapid maturation of the skeleton that may lead to earlier cessation of growth. Bone age should be interpreted with the guidance of a pediatric endocrinologist. Skeletal age correlates well with stage of pubertal development and may be helpful in predicting adult height in early- or late-maturing adolescents. In familial short stature the bone age is normal (comparable to chronologic age), whereas constitutional delay, endocrinologic short stature, and undernutrition may be associated with delay in bone age comparable to the height age.

Laboratory testing is also useful in assessment of growth and may be tailored to suspected etiology based on the patient history and physical examination. Initial assessment includes comprehensive metabolic panel, complete blood count, sedimentation rate, C-reactive protein, thyroid-stimulating hormone, thyroxine, celiac panel, and insulin-like growth factor (IGF)-I and IGF-BP3, which are surrogate markers for growth hormone secretion (see Chapter 595). A karyotype to exclude Turner syndrome is an essential component of the evaluation of short stature in females and should be performed even in the absence of characteristic physical features (see Chapter 626.1). If there is concern for abnormal timing of puberty contributing to growth pattern, gonadotropins (luteinizing hormone, follicle-stimulating hormone), and estradiol or testosterone may also be assessed. A urinalysis can provide additional information about renal function. Evaluation by a pediatric nutritionist for caloric needs assessment may be useful in patients with malnutrition, underweight status, or slow weight gain. Additional testing and referral to specialists should be performed as indicated.

OTHER GROWTH CONSIDERATIONS

Obesity

Obesity affects large numbers of children (see Chapter 65). The CDC defines *obesity* as BMI ≥95th percentile for age and sex, and *overweight* as BMI 85th to <95th percentile for age and sex. Although widely accepted as the best clinical measure of underweight and overweight, BMI may not provide an accurate index of adiposity because it does not differentiate lean tissue and bone from fat. In otherwise healthy individuals, lean body mass is largely represented by BMI at lower percentiles. BMI >80–85% largely reflects increased body fat with a nonlinear relationship between BMI and adiposity. In the setting of chronic illness, increased body fat may be present at low BMI, whereas in athletes, high BMI may reflect increased muscle mass. Measurement of the triceps, subscapular, and suprailiac skinfold thickness have been used to estimate adiposity. Other methods of measuring fat, such as hydrodensitometry, bioelectrical impedance, and total body water measurement, are used in research, but not in clinical evaluation, but whole body dual-energy x-ray absorptiometry (DXA) is beginning to emerge as a tool for measuring body fat and lean body mass.

Dental Development

Dental development includes mineralization, eruption, and exfoliation (Table 27.4). Initial mineralization begins as early as the second trimester (mean age for central incisors, 14 weeks) and continues through 3 years of age for the primary (deciduous) teeth and 25 years of age for the secondary (permanent) teeth. Mineralization begins at the crown and progresses toward the root. Eruption begins with the central incisors and progresses laterally. Exfoliation begins at about 6 years of age and continues through 12 years. Eruption of the permanent teeth may follow exfoliation immediately or may lag by 4-5 months. The timing of dental development is poorly correlated with other processes of growth and maturation. **Delayed eruption** is usually considered when no teeth have erupted by approximately 13 months of age (mean ± 3 SD). Common causes include congenital or genetic disorders, endocrine disorders (e.g., hypothyroidism, hypoparathyroidism), familial conditions, and (the most common) idiopathic conditions. Individual teeth may fail to erupt because of mechanical blockage (crowding, gum fibrosis). Causes of **early exfoliation** include hypophosphatasia, histiocytosis X, cyclic neutropenia, leukemia, trauma, and idiopathic factors. Nutritional and metabolic disturbances, prolonged illness, and certain medications (tetracycline) frequently result in discoloration or malformations of the dental enamel. A discrete line of pitting on the enamel suggests a time-limited insult.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 27.4 Chronology of Human Dentition of Primary (Deciduous) and Secondary (Permanent) Teeth

	CALCIFICATION		AGE AT ERUPTION		AGE AT SHEDDING	
	BEGINS AT	COMPLETE AT	MAXILLARY	MANDIBULAR	MAXILLARY	MANDIBULAR
PRIMARY TEETH						
Central incisors	5th fetal mo	18-24 mo	6-8 mo	5-7 mo	7-8 yr	6-7 yr
Lateral incisors	5th fetal mo	18-24 mo	8-11 mo	7-10 mo	8-9 yr	7-8 yr
Cuspids (canines)	6th fetal mo	30-36 mo	16-20 mo	16-20 mo	11-12 yr	9-11 yr
First molars	5th fetal mo	24-30 mo	10-16 mo	10-16 mo	10-12 yr	10-12 yr
Second molars	6th fetal mo	36 mo	20-30 mo	20-30 mo	10-12 yr	11-13 yr
SECONDARY TEETH						
Central incisors	3-4 mo	9-10 yr	7-8 yr	6-7 yr		
Lateral incisors	Max, 10-12 mo Mand, 3-4 mo	10-11 yr	8-9 yr	7-8 yr		
Cuspids (canines)	4-5 mo	12-15 yr	11-12 yr	9-11 yr		
First premolars (bicuspids)	18-21 mo	12-13 yr	10-11 yr	10-12 yr		
Second premolars (bicuspids)	24-30 mo	12-14 yr	10-12 yr	11-13 yr		
First molars	Birth	9-10 yr	6-7 yr	6-7 yr		
Second molars	30-36 mo	14-16 yr	12-13 yr	12-13 yr		
Third molars	Max, 7-9 yr Mand, 8-10 yr	18-25 yr	17-22 yr	17-22 yr		

Mand, Mandibular; max, maxillary.
Adapted from a chart prepared by P.K. Losch, Harvard School of Dental Medicine, who provided the data for this table.

Chapter 28

Developmental and Behavioral Surveillance and Screening

Eliza Gordon-Lipkin and Paul H. Lipkin

In healthy development, a child will acquire new skills beginning prenatally and extending into at least young adulthood. The roots of this acquisition of skills lie in the development of the nervous system, with additional influences from the health status of other organ systems and the physical and social environment in which the development occurs. *Development* and its milestones are divided into the "streams" of gross motor, fine motor, language (expressive and receptive), social language, and self-help. *Behavior* can be categorized into observable, spontaneous, and responsive behaviors in the settings of home, school, and community.

Although typical development is associated with wide variability in the age of skill acquisition in each of these streams, specific developmental and behavioral disorders are seen in approximately 1 of 6 children and may affect the health, function, and well-being of the child and family for a lifetime. These disorders include relatively less common conditions that often cause severe impairments, such as cerebral palsy and autism, and relatively common conditions such as attention-deficit/hyperactivity disorder, speech language disorders, and behavioral and emotional disorders that affect as many as 25% of children. The more common conditions are generally perceived as "less severe," but these too can have major short-term and long-term impact on the child's health and daily functioning in the home, school, and community and can affect lifelong well-being. Because of their high prevalence in children; their impact on health, social, and economic status; and their effect on the child, the home, and the community, these disorders require the attention of the pediatrician throughout childhood. In addition, both the child and the family benefit from the early identification and treatment of many of these conditions, including the most severe. It is therefore incumbent on the primary care clinician to conduct regular **developmental surveillance** and periodic **developmental screening** at health supervision visits aimed at early identification and treatment.

Among the many types of developmental or behavioral conditions, the most common include *language problems,* affecting at least 10% of children (see Chapter 53); *behavior or emotional disorders,* affecting up to 25% of children, with 6% considered serious; *attention-deficit/hyperactivity disorder,* affecting 10% of children (Chapter 50); and *learning disabilities,* affecting up to 10% (Chapters 51 and 52). Less common and more disabling are the intellectual disabilities (1–2%; Chapter 56); autism spectrum disorders (1 in 36 children; Chapter 58); cerebral palsy and related motor impairments (0.3%, or 1 in 345 children; Chapter 638.1); hearing impairment, also referred to as deafness, hard-of-hearing, or hearing loss (0.12%; Chapters 55 and 677); and nonrefractive vision impairment (0.8%; Chapter 661).

DEVELOPMENTAL AND BEHAVIORAL SURVEILLANCE

General health surveillance is a critical responsibility of the primary care clinician and is a key component of health supervision visits. Regular developmental and behavioral surveillance should be performed at every health supervision visit from infancy through young adulthood. Surveillance of a child's development and behavior includes both obtaining historical information on the child and family and making observations at the office visit (Tables 28.1 and 28.2).

Key historical elements include (1) eliciting and attending to the parents' or caregivers' concerns around the child's development or behavior; (2) obtaining a history of the child's developmental skills and behavior at home, with peers, in school, and in the community; and (3) identifying the risks, strengths, and protective factors for development and behavior in the child and family, including the social determinants of health. During the office visit, the clinician should make and document direct observations of the child's developmental skills and behavioral interactions. Skills in all streams of development should be considered along with observations of related neurologic functioning made on physical examination.

With this history and observation, the clinician should create and maintain a longitudinal record of the child's development and behavior for tracking the child across visits. It is often helpful to obtain information from and share information with other professionals involved

Table 28.1 Key Components of Developmental and Behavioral Surveillance

HISTORY
1. Parental developmental concerns
2. Developmental history
   a. Streams of developmental milestone achievement
      i. Gross motor
      ii. Fine motor
      iii. Verbal speech and language
         (1) Expressive
         (2) Receptive
      iv. Social language and self-help
   b. Patterns of abnormality
      i. Delay
      ii. Dissociation
      iii. Deviation or deviant development
      iv. Regression
3. Behavior history
   a. Interactions
      i. Familiar settings (e.g., home, school): parents, siblings, other familiar people, peers, other children
      ii. Interaction in unfamiliar settings (e.g., community): unfamiliar adults and children
   b. Patterns of abnormality
      i. Noncompliance, disruption (including tantrums), aggression, impulsivity, increased activity, decreased attention span, decreased social engagement, decreased auditory or visual attention
      ii. Deviation or atypical behaviors
         (1) Repetitive play, rituals, perseverative thought or action, self-injury
4. Risk factor identification: medical, family, and social history (including social determinants of health)
5. Protective factor identification (also including social determinants)

DEVELOPMENTAL OBSERVATION
1. Movement: gross and fine motor skills
2. Verbal communication: expressive speech and language, language understanding
3. Social engagement and response
4. Behavior: spontaneous and responsive with caregiver and with staff
5. Related neurologic function on physical examination

Table 28.2 Red Flags in Developmental Screening and Surveillance

These indicators suggest that development is significantly delayed or disordered and that the child should be referred to a developmental pediatrician or pediatric neurologist. Any delay in achieving a milestone at the 75th percentile may be considered a red flag and merits further evaluation, vigilant surveillance, or repeat screening.

POSITIVE INDICATORS

Presence of any of the following:
- Loss of developmental skills at any age
- Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age (simultaneous referral to pediatric ophthalmology)
- Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment)
- Persistently low muscle tone or floppiness (check creatine kinase)
- No speech by 15 mo, especially if the child does not try to communicate by other means, such as gestures (simultaneous referral for urgent hearing test)
- Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone
- Persistent toe walking
- Multiple organ involvement
- Head circumference above the 99.6th centile or below 0.4th centile; also, if circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to parental head circumference

NEGATIVE INDICATORS

Activities that the child cannot do:
- Sit unsupported by 12 mo
- Walk by 18 mo (check creatine kinase)
- Walk other than on tiptoes
- Run by 24 mo
- Hold object placed in hand by 4 mo (corrected for gestation)
- Reach for objects by 6 mo (corrected for gestation)
- Points to show you something interesting by 18 months

Adapted from Horridge KA. Assessment and investigation of the child with disordered development. *Arch Dis Child Educ Pract Ed.* 2011;96:9–20; Zubler JM, Wiggins LD, Macias MM, et al. Evidence-informed milestones for developmental surveillance tools. Pediatrics. 2022;149(3):e2021052138.

with the child, including childcare professionals, home visitors, teachers, after-school providers, and developmental therapists. This provides a complete picture of the child's development and behavior and allows collaborative tracking of the child's progress.

The Developmental and Behavioral Histories

Developmental surveillance includes tracking a child's achievement of milestones, which represent key readily recognizable skills that usually occur in a predictable sequence and at predictable age ranges during childhood. The developmental skill areas can be divided into **gross motor**, **fine motor**, **speech and language** (expressive and receptive), **social language**, and **self-help**. Tracking milestones will reveal that most children achieve the milestones in a typical pattern and within typical age ranges. However, the pediatrician or the parent may recognize concerning patterns of development, such as delay, dissociation, deviation, or regression.

Developmental delay occurs when development is occurring in its usual sequence but at a slower rate, with milestones achieved later than the normal range (see Chapter 56). Delay can occur in a single area of development or across several streams and can be expressed as a *developmental quotient* (DQ). The DQ is calculated by dividing the age at which the child is functioning developmentally (*developmental age*; DA) by *chronologic age* (CA) and multiplying by 100 (DQ = DA/CA × 100). A DQ of 100 indicates that the child is developing at the mean or average rate, whereas a DQ below 70 is associated with delays of 2 or more standard deviations from the mean and suggests a significant delay that requires further evaluation.

Developmental dissociation indicates delay in a single stream with typical development in other streams. A child with autism may have delays in verbal or social language but normal motor skills. *Deviation or deviant development* is defined by development occurring out of sequence, as when a child stands before sitting (as in diplegic cerebral palsy) or has better expressive vocabulary than receptive understanding of words (language and autism spectrum disorders). *Regression* refers to a loss of skills. It may also be identified earlier or more subtly by a slowing or lack of advancement in skills. Although regression is uncommon in most developmental disabilities, regression is described in as many as 25% of children with autism and is also seen in rarer neurologic disorders, such as Rett syndrome and Duchenne muscular dystrophy.

Behavioral surveillance is conducted by obtaining a history of a child's behavior and interactions across settings, including home, daycare, school, and community, and in situations such as eating, sleeping, and play. In addition, interactions may differ based on who the child is with (parent or guardian, sibling, peers, teachers, strangers). Concerns may include limited engagement or socializing, compliance, tantrums, aggression, destruction, impulsivity, high activity level, decreased auditory or visual attention, and short attention span. Deviations from

Table 28.3 Standardized Tools for General Developmental Screening

SCREENING TEST*	AGE RANGE	ITEMS (NO.)	ADMIN TIME (MIN)	PUBLICATION INFORMATION
Ages & Stages Questionnaires-3 (ASQ3)[1]	2-66 mo	30	10-15	Paul H. Brookes Publishing www.agesandstages.com
Parents' Evaluation of Developmental Status (PEDS)[2]	0-8 yr	10	2-10	Ellsworth & Vandermeer Press 877-296-9972 www.pedstest.com
Parents' Evaluation of Developmental Status: Developmental Milestones (PEDS:DM) Screening Version[2]	0-8 yr	6-8 items at each age level	4-6	Ellsworth & Vandermeer Press 877-296-9972 www.pedstest.com
Survey of Well-Being of Young Children (SWYC)[3-6]	*Dev:* 1-65 mo *Autism:* 16-35 mo	*Dev:* 10 *Autism:* 7	*Dev:* <5 *Autism:* <5	www.theswyc.org

*Key reference sources:
[1]Squires J, Potter L, Bricker D. *The ASQ User's Guide*, 3rd ed, Baltimore, MD, Paul H. Brookes Publishing, 2009.
[2]Glascoe FP, Marks KP, Poon JK, et al. (eds). *Identifying and addressing developmental-behavioral problems: a practical guide for medical and non-medical professionals, trainees, researchers and advocates*. Nolensville, TN: PEDStest.com, 2013.
[3]Sheldrick RC, Perrin EC. Evidence-based milestones for surveillance of cognitive, language, and motor development. *Acad Pediatr*. 2013, 13(6):577–556.
[4]Smith N, Sheldrick R, Perrin E. An abbreviated screening instrument for autism spectrum disorders. *Infant Ment Health J*. 2012;34(2):149–155.
[5]Salisbury LA, Nyce JD, Hannum CD, et al. Sensitivity and specificity of 2 autism screeners among referred children between 16 and 48 months of age. *J Dev Behav Pediatr*. 2018;39(3):254–258.
[6]Publications and user's manual available at www.theswyc.org.

usual behavior may also occur, including repetitive play, ritualistic behaviors, perseverative thoughts or actions, and self-injury.

Observation

Observations of the child's developmental skills and behavioral interactions should be made in the examining room, with documentation in the medical record, and combined with the examination of other neurologic functioning, such as muscle tone, reflexes, and posture.

Developmental observations may include a child's gross and fine motor movements, both on the floor and on the examination table. Spoken language and response to others' communications, as well as interactions and engagement with the parent or guardian, should be noted. If siblings are in the room, the interaction between the child and a sibling may also be informative. Impulsivity, attention problems, tantrums, noncompliance, oppositionality, and aggression may be observed along with interactions with the clinician, but one should inquire about whether these behaviors are seen in *other settings*, given the possible unfamiliarity or discomfort of the child with the healthcare professional or in healthcare settings.

If inquiring about and observing the child's development and behavior suggests normal or typical patterns of development and behavior, discussions can be held about future milestones and usual behavior management strategies employable at home. If problems or concerns are identified by the parent or clinician, however, formal developmental screening, evaluation, or management should be considered, along with early follow-up and review.

DEVELOPMENTAL AND BEHAVIORAL SCREENING

Periodic episodic screening for developmental and behavioral conditions should be conducted on every child, as done for other health conditions such as anemia, lead poisoning, hearing, and congenital metabolic disorders. Developmental and behavioral screenings are centered on administration of low-cost, brief, and standardized tests in the primary care setting. These tests can be implemented by health assistants at age-determined visits, with interpretation of the results and referral or treatment initiation by the primary care clinician as indicated.

The American Academy of Pediatrics provides recommendations and guidelines on age-specific developmental screening for implementation in the primary care medical home. Developmental screening using a formal, validated, and standardized test is recommended during health supervision visits at 9, 18, and 30 months. Tests recommended at these ages screen development across all the streams. In addition, an autism screening test is recommended at the 18 and 24 month visits. Tables 28.3 and 28.4 provide recommended screening tests for general development and for autism. It is also recommended that a child have a screening test administered any time that a parent, guardian, or child health or early childhood professional has concerns identified during developmental surveillance, or through screening performed at early childhood programs. Although routine formal screening before the child's entry into elementary school is not included in current guidelines, the primary care clinician should be vigilant about surveillance regarding development at the 4 or 5 year old visit and perform formal screening if concerns are identified, because of the potential impact on learning and school services.

Each of the screening visits offers special opportunities to identify specific developmental conditions. At the 9 month screening, critical areas of development are vision, hearing, gross motor, fine motor, and receptive language. It is at this age that disabilities may be identified in vision or hearing, as well as cerebral palsy and other neuromotor disorders. At 18 months, expressive language and social language development are particularly important areas. Conditions identified at this age may include those considered at 9 months, although in milder forms, as well as autism spectrum, language, and intellectual disorders. By the 30 month visit, the child's behavioral interactions become an additional area of focus, with problems emerging tied to attention and disruptive behavior disorders. Although universal screening is not recommended at later ages, developmental surveillance may identify children in need of screening or evaluation for problems in learning, attention, and behavior.

Additional screening for *behavioral conditions* should be considered, although there is currently no recommended consensus on the ages at which behavioral screening should occur. One possibility would be to provide behavioral screening at the 30 month, 4 or 5 year, and 8 year visits to identify problems emerging in the toddler, preschool, and early elementary years. For older children, visits during preadolescent or adolescent ages also offer an opportunity for surveillance and possible screening for behavioral and emotional problems meriting professional assistance or intervention. Table 28.5 provides recommended behavior screening tools.

Evidence-Based Tools

Tables 28.3, 28.4, and 28.5 show a range of measures useful for early identification of developmental and behavioral problems. Because well-child visits are brief and with broad agendas (health

Table 28.4 Standardized Tools for Language and Autism Screening

SCREENING TEST*	AGE RANGE	ITEMS (NO.)	ADMIN TIME (MIN)	PUBLICATION INFORMATION
Communication and Symbolic Behavior Scales: Developmental Profile (CSBS-DP): Infant Toddler Checklist[1]	6 mo-6 years (for language function 6-24 mo)	24	5-10	Paul H. Brookes Publishing 800-638-3775 www.brookespublishing.com
Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F)[2]	16-48 mo	20 plus follow-up interview	5-10	www.mchatscreen.com
Screening Tool for Autism in Toddlers and Young Children (STAT)[3,4]	24-35 mo	12 (avg)	20-30	https://stat.vueinnovations.com
Social Communication Questionnaire (SCQ)[5,6]	4+ yr	40 (avg)	5-10	Western Psychological Services www.wpspublish.com

*Key reference sources:
[1]Wetherby AM, Prizant BM. *Communication and Symbolic Behavior Scales: developmental profile*. Baltimore, MD: Paul H. Brookes Publishing, 2002.
[2]Robins DL, Casagrande K, Barton M, et al. Validation of the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F). *Pediatrics*. 2014;133(1):37–45.
[3]Stone WL, Coonrod EE, Ousley O. Brief report: screening tool for autism in 2-year-olds (STAT): development and preliminary data. *J Autism Dev Disord*. 2000;30:607–612
[4]Stone WL, Coonrod EE, Turner LM, Pozdol SL. Psychometric properties of the STAT for early autism screening. *J Autism Dev Disord*. 2004;34:691–701.
[5]Rutter M, Bailey A, Lord C: *The Social Communication Questionnaire (SCQ) Manual*. Los Angeles; Western Psychological Services, 2003.
[6]Corsello C, Hus V, Pickles A, et al. Between a ROC and a hard place: decision making and making decisions about using the SCQ. *J Child Psychol Psychiatry*. 2007;48(9):932–940.

Table 28.5 Standardized Tools for General Behavioral Screening

SCREENING TEST*	AGE RANGE	ITEMS (NO.)	ADMIN TIME (MIN)	PUBLICATION INFORMATION
Ages & Stages Questionnaire: Social-Emotional-2 (ASQ:SE-2) (2015)[1,2]	2-72 mo	9 age-specific forms with 19-33 items	10	Paul H. Brookes Publishing 800-638-3775 www.agesandstages.com
Brief Infant Toddler Social Emotional Assessment (BITSEA)[3]	12-36 mo	42	7-10	Mapi Research Trust https://eprovide.mapi-trust.org/
Pediatric Symptom Checklist–17 items (PSC-17b)[4]	4-16 yr PSC-35 Youth self-report: ≥11 yr	17	<5	Massachusetts General Hospital https://www.massgeneral.org/psychiatry/treatments-and-services/pediatric-symptom-checklist
Strengths and Difficulties Questionnaire (SDQ)[5]	4-17 yr 3-4 yr old version available Youth self-report 11-16 yr	25; 22 for 3-4 yr olds	5-10	www.sdqinfo.org

*Key reference sources:
[1]Squires J, Bricker DD, Twombly E. *Ages & Stages Questionnaires: Social-Emotional-2 (ASQ:SE-2): a parent-completed, child-monitoring system for social-emotional behaviors*. Baltimore, MD: Paul H. Brookes Publishing, 2016.
[2]Briggs RD, Stettler EM, Johnson Silver E, et al. Social-emotional screening for infants and toddlers in primary care. *Pediatrics*. 2012;129(2):1–8.
[3]Briggs-Gowan MJ, Carter AS, McCarthy K, et al. Clinical validity of a brief measure of early childhood social–emotional/behavioral problems. *J Pediatr Psychol*. 2013;38(5):557–587.
[4]Murphy JM, Stepanian S, Riobueno-Naylor A, et al. Implementation of an electronic approach to psychosocial screening in a network of pediatric practices. *Acad Pediatr*. 2021;21(4):702–709.
[5]Stone LL, Otten R, Engels RC, et al. Psychometric properties of the parent and teacher versions of the Strengths and Difficulties Questionnaire for 4- to 12-year-olds: a review. *Clin Child Fam Psychol Rev*. 2010;13(3):254–274.

surveillance and screening, physical examination, immunization, anticipatory guidance, safety and injury prevention, and developmental promotion), tools relying on parent completion with office staff administration and scoring are well suited for primary care settings. Such tests may be completed in advance of appointments, either online or in writing, whether at home or while waiting for the pediatric visit to begin. If a test is scored in advance of the visit, the pediatric clinician can enter the room with results in hand for review and discussion, including a description of the child's development and behavior compared with peers, general information on child development and behavior, any areas of concern, referrals needed, and information to share with the child's daycare, preschool, or other community providers, when applicable.

Screening Test Properties

Each of the tests provided in Tables 28.3 to 28.5 meets accepted psychometric test criteria. The test has standardized questions or milestones with norms based on administration to parents of a large sample of children with typical development. These norms allow comparison of an individual child's performance on the test with that of the large sample of typically developing children. In addition, the tests demonstrate accepted standards of *reliability*, or the ability to produce consistent results; *predictive validity*, or the ability to predict later test performance or development; *sensitivity*, or accuracy in the identification of delayed development or disability; and *specificity*, or accuracy in the identification of children who are not delayed. Some of the screening tests are general, evaluating multiple areas of development or behavior (sometimes referred to as "broad band"). Others are domain specific, evaluating one area of development (e.g., language), or disorder specific, aimed at identifying a specific developmental disorder (sometimes referred to as "narrow band").

BEYOND SURVEILLANCE AND SCREENING

Comprehensive Evaluation

When a developmental or behavioral concern is identified through surveillance or screening, the primary care clinician's role is to

ensure that the child receives an appropriate diagnostic evaluation, related medical testing, and indicated developmental interventions and medical treatment. When a concern is identified, a full diagnostic evaluation should be performed by a professional with appropriate training and experience. In the case of developmental concerns, this may be a pediatric specialist, such as a neurodevelopmental pediatrician/neurologist or a developmental-behavioral pediatrician, or a related developmental professional, depending on resources in the local community. Related professionals may include early childhood educators, psychologists, speech/language pathologists, audiologists, physical therapists, and occupational therapists, many of whom are available through the local early intervention system. Such an evaluation would typically include more detailed standardized developmental testing. The primary care physician should ensure that hearing and vision assessments are completed. For the child with motor concerns, the physician should pay particular attention to the motor and neurologic evaluation. Children with language delays should have hearing, speech, language, and learning skills (e.g., reading, phonics) evaluated.

The primary care clinician should also perform a comprehensive medical evaluation of the child to identify any related health conditions. Physical examination including head circumference should be reviewed to identify growth abnormalities and dysmorphic features. For the child with motor delay and decreased or normal muscle tone, serum creatine kinase and thyroid function testing are recommended to rule out muscular dystrophy and thyroid disease, respectively. When there is increased tone, MRI or referral to a neurologist should be considered. For the child with suspected autism or intellectual disability (or global developmental delay), chromosomal microarray and fragile X testing are recommended (see Chapter 56).

Referral and Intervention

Children with significant developmental delays or an identified developmental disability are entitled to and usually benefit from early intervention with therapy services directed at delayed or atypical development. The U.S. Individuals with Disabilities Education Act (IDEA) entitles any child with a disability or developmental delay to receive local education and related services, including therapy, from as early as birth, for known or high-risk conditions that lead to such delay or disability, through age 21 years. These interventions enhance the child's development through early intervention and family support as well as individualized public education with the goal of improving long-term functional outcomes and reducing public costs. The pediatric provider should therefore refer every child with developmental concerns to the local early intervention program or agency (ages 0-3 years), public school program (≥ 3 years), and/or local therapy providers. Typical service needs include special education for the child with intellectual or learning concerns, physical or occupational therapy for children with motor delays, speech language therapy for the child with language or social communication difficulties, and behavioral therapy services for the child with social engagement or other behavior problems.

Likewise, the child with specific behavior concerns should be referred to an appropriate pediatric or behavioral health professional who can perform a thorough evaluation and assist the family to alleviate the problems or concerns. Such professionals may include those trained in developmental-behavioral pediatrics, neurodevelopmental disabilities, adolescent medicine, child and adolescent psychiatry, pediatric psychology, psychiatric advanced practice nursing, and social work. Such an evaluation is similar to developmental evaluation in its aim of determining a diagnosis, as well as developing a treatment program that may include psychotherapeutic and medication management. Associated medical or developmental disorders should be considered and further evaluated as needed.

Ongoing Management

Children with developmental or behavioral disorders should be identified as *children with special healthcare needs* in the medical home, with a program of chronic condition management initiated by the clinical program staff, including its medical and nonmedical staff. In doing so, the clinician and family should work together to outline the child's short- and long-term goals and management plan. This includes a program of regular monitoring and follow-up of the child's development and behavior, referrals, treatment, and surveillance for identification and treatment of related medical, developmental, or behavioral comorbidities that may arise. Some children and families may warrant assignment of a case manager or care navigator either within the medical home or in a related local agency. The pediatric clinician or other medical home staff should participate in care coordination activities as needed and assist the family and other professionals in decision-making on medical care, therapies, and educational services.

The family can be further assisted during the screening and referral phases or later with ongoing care by referral to support service programs, such as respite care, parent-to-parent programs, and advocacy organizations. Some children may qualify for additional state or federal benefit programs, including insurance, supplemental security income, and state programs for children with special healthcare needs. Families often seek out information, support, or connection to other families with similarly affected children and find benefit in local or national networks (e.g., Family Voices, Family to Family Health Information centers) and condition-specific associations.

Implementation

The principles and professional guidelines for developmental-behavioral surveillance and screening have been solidified to identify children with developmental disabilities, including the specific conditions of intellectual disability, autism spectrum disorder, motor disorders, and behavioral-emotional problems. Specific algorithms are included in these guidelines to assist the clinician with implementation. However, primary care clinicians have reported difficulties in putting these into practice, with obstacles and barriers identified and policy changes made to ensure that screening and referral can be implemented. (See Bibliography online for specific guidelines.)

Implementation projects have identified key factors for successful incorporation of developmental surveillance and screening into practice. Successful office-based screening requires development of a comprehensive office-based system that extends from the child's home to the front office and into the clinic visit, rather than solely centered on the time in the clinic room. This requires utilizing office and medical support staff for scheduling, advance test distribution, and initiation of the surveillance and screening procedures before the health supervision visit. The practice must choose screening tests that are not only valid for screening of the specific condition at the recommended ages, but also appropriate to the population being served (including reading level and language). The tests chosen should be able to be completed by the caregiver in a short time and at low cost. Staff training on billing and coding for these procedures ensures appropriate payment.

Practice systems should also be developed for referral and tracking of children who have problems identified through screening. This should include systems for referral to early intervention, community therapy, developmental professionals, and medical consultants. Office representatives or the clinician should establish working relationships with local community programs and resources to assist the child and family.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 29

Child Care

Laura Stout Sosinsky and Walter S. Gilliam

Child care impacts the health and development of children and the economic stability of families. For too many young children and their families, affordable high-quality child care is not accessible. Pediatricians have a role in helping children receive safe, enriching care in high-quality early childhood education (ECE) settings that allows parents to be able to work.

As an environment in which children learn, grow, and play, child care is a component of the social determinants of health. The majority of young children regularly spend time in at least one nonparental child care arrangement. Routine exposure to high-quality child care provides an opportunity for early education in language, early literacy, math, and social skills, as well as for teaching children health-promoting behaviors and for identifying early signs of delays or special needs. Inadequate child care supply and poor availability block these opportunities for many children, disproportionately those from low-resourced families. Instead, many young children are exposed to a patchwork of child care arrangements that are unstable, unaffordable, and often poorly resourced, adding stress that harms child and family well-being.

Child care provision is affected by many factors, derived from family demand, child care supply, and child/family policy. With increasing movement of mothers into the workplace across the globe, the prime reason most families use child care is to support employment of both parents. After childbirth, unpaid maternity leave is the typical situation among U.S. mothers. The U.S. federal leave program allows for 12 weeks of unpaid job-protected leave during pregnancy or after childbirth, but only covers approximately 50% of the workforce because companies with <50 employees, with part-time employees, and those working in informal labor markets are exempt. Several states and cities have passed paid family leave laws.

In part because of the financial burden of an unpaid maternity leave, many mothers return to work, and their children may begin child care in the first few weeks after birth. In a 2000 Family and Medical Leave Act survey, only 10% of respondents reported taking more than 60 days for maternity leave. Approximately 44% of mothers in 2005–2007 were working by the time their first child was 3-4 months of age, and approximately 63% of mothers were working by the time their first child was 12 months. Some mothers face work requirements if they are receiving public benefits because of the reforms to welfare passed by the U.S. Congress in 1996. Many mothers feel strong financial motivation or even pressure to work, especially in single-parent households, or have strong incentive to work for short- and long-term financial security. Employment is not the only factor driving child care use; young children of *unemployed* mothers spend on average 21 hours per week in child care. Many parents want their children to have child care experiences for the potential benefits that early learning environments can give to their children. Given these realities, child care quality is of great concern, yet the quality of child care and early education environments varies widely, and the supply of high-quality child care is largely deemed inadequate.

The COVID-19 pandemic revealed the fragility of America's child care system. Relative to adults, young children have been far less likely to suffer severe medical complications from coronavirus infection, and rates of transmission in child care facilities that followed mitigation protocols have been low. However, the downstream effects of the pandemic on young children have been acute. Burdensome child care cost and access barriers became exaggerated. Parents of young children report significant concerns about their children's safety and education during the pandemic and describe significant disruptions and impacts on families' well-being. Estimates indicate that 1 in every 500 U.S. children have experienced COVID-19 orphanhood or the loss of a caregiving grandparent, further highlighting a crisis in early childhood caregiving.

QUALITY, PROVISION, REGULATION, AND ACCESS

Child Care Quality

High-quality child care is characterized by warm, responsive, and stimulating interactions between children and child care providers. These caregivers express positive feelings toward the children; are emotionally involved, engaged, and aware of the child's needs and sensitive and responsive to their initiations; speak directly with children in a manner that is elaborative and stimulating while being age-appropriate; and ask questions and encourage children's ideas and verbalizations. Structural quality features of the setting, including ratio of children to adults, group size, and caregiver education and training, act indirectly on child outcomes by facilitating high-quality interactions. It would be highly unlikely, if not impossible, for even the most sensitive and stimulating provider to engage in high-quality interactions with each child, if, for example, the provider was the sole caregiver of 10 toddlers.

Poor-quality child care settings and unsafe environments that do not meet children's basic physical and emotional needs can result in developmental delays tied to lack of healthy relationships with adults or developmentally inappropriate activities, toxic stress, neglect, or injury or death from fire, building hazards, disease, and inadequate staff oversight. State regulations put a "floor" on structural quality and basic staff indicators to mitigate risks and safeguard health and safety. Although structural indicators are more easily monitored in licensing, some but not all research suggests only modest relationships of structural indicators with child outcomes. When it comes to process quality, a body of studies demonstrates small-to-modest associations with short-term child development and some evidence of long-term impacts.

The early childhood field is focusing increasingly on effective practices, evidence-based curricula, and programs that are reported to have moderate-to-large effects on child outcomes. Some specific teacher practices are related to gains in academic and social-emotional skills among preschool students. Evidence-informed and evaluated ECE curricula with aligned professional development can have substantial impacts on child outcomes across several developmental domains. Primary caregiving, the practice in infant and toddler classrooms of assigning one teacher the primary responsibility for the care of a small group of children and developing relationships with their families, is consistent with research showing that infants who experience stable, consistent, sensitive and responsive care develop more secure attachment relationships and more positive developmental outcomes. Family engagement, in which early educators partner with families to share their unique knowledge of each child to build positive and goal-oriented relationships, relates to gains in preschool children's social and early academic skills and reduced problem behaviors.

Integration of Health and Safety Within Quality Practices

The American Academy of Pediatrics (AAP), the American Public Health Association, and the National Resource Center for Health and Safety in Child Care and Early Education provide health and safety guidelines in *Caring for Our Children (CFOC): National Health and Safety Performance Standards; Guidelines for Early Care and Education Programs, 4th ed.* (https://nrckids.org/CFOC; 2019). These national standards represent the best evidence on quality practices and address health and safety as an integrated component of early care and education. The intent is for the guidelines to serve as a resource for states and other entities to improve health and safety standards in licensing and quality rating improvement systems. An additional objective is for the various monitoring agencies and mechanisms to work together to collaboratively safeguard children and minimize or eliminate the duplication and burden of complicated and sometimes conflicting procedures and requirements.

The current guidelines include sections in 10 areas (Table 29.1). The National Resource Center also provides updated online resources: (1) up-to-date CFOC Standards Online Database (https://nrckids.org/CFOC and (2) a crosswalk of COVID-19 questions with CFOC

Table 29.1 *Caring for Our Children* Performance Standards: Chapters and Topics

1. **Staffing:** Child-staff ratio, group size, minimum age; background checks (criminal history, sex offender registry, and child abuse and neglect registry checks), qualifications, professional development, training
2. **Program Activities for Healthy Development:** Developmental activities (general and by age), supervision and discipline, parent/guardian relationships, health education
3. **Health Promotion and Protection:** Health promotion in child care (health checks and supervision, physical activity, limiting screen time, safe sleep, oral health); hygiene (diapering, hand hygiene, exposure to bodily fluids); cleaning, sanitizing, and disinfecting; tobacco and drug use; animals; emergency procedures; child abuse and neglect; sun safety and insect repellent; strangulation hazards; management of illness
4. **Nutrition and Food Service:** General and by age, meal service, seating, and supervision, nutrition learning experiences for children and for parents/guardians, food safety, and more
5. **Facilities, Supplies, Equipment, and Environmental Health:** Space per child, exits, ventilation, lighting, noise, furnishings, equipment, and more
6. **Play Areas/Playgrounds and Transportation:** Playground equipment, water play areas, toys
7. **Infectious Diseases:** Immunizations, respiratory tract infections, enteric (diarrheal) infections and hepatitis A virus, skin and mucous membrane infections, blood-borne infections, herpes viruses, interaction with state or local health departments, judicious use of antibiotics
8. **Children with Special Healthcare Needs and Disabilities:** Inclusion, service plans, coordination and documentation, periodic reevaluation, assessment of facilities for children with special needs, additional standards
9. **Administration:** Governance, policies, human resources, records
10. **Licensing and Community Action:** Regulatory policy, licensing agency, facility licensing, health department responsibilities and role, caregiver/teacher support, public policy issues and resource development

From the American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education. Caring for Our Children: National Health and Safety Performance Standards; *Guidelines for Early Care and Education Programs*. 4th ed., Itasca, IL: American Academy of Pediatrics; 2019. (https://nrckids.org/CFOC/TOC).

standards (https://nrckids.org/files/CFOC.Crosswalk.pdf) to help child care health consultants and providers learn how the CFOC standards address provision of safe and healthy early care and education environments during the COVID-19 pandemic.

Child Care Settings and Use

Public early education programs (such as Head Start and targeted state-funded prekindergarten programs) have historically been designed as policy mechanisms to close the school readiness gap among children with fewer resources, whereas child care has been seen as necessary when parents (usually mothers) work while their children are young. Despite these historical "silos," all early care and education settings serve both purposes: they are early learning environments for children and necessary supports for working parents.

Quality of care matters for all child care settings, but there are key differences in the structure and provision of care that influence organizational and business operations, regulatory mandates, and accessibility and affordability for families.

Child care settings vary widely and fall into four broad categories from the least to the most formal:

1. Relative or friend cares for a child in the relative's or friend's home or in the child's home
2. Nonrelative care who comes to the child's home, such as nannies, babysitters, or au pairs
3. Home-based child care in which an individual runs a child care business in their own home and cares for a few or several children, often including children of mixed ages, siblings, or the provider's own children
4. Center-based care, provided in nonresidential facilities for children grouped by age, including preschools, prekindergarten programs, Head Start centers, and child care centers.

Child care centers and early education programs are administered by a wide array of businesses and organizations, including for-profit providers or companies, religious organizations, public and private schools including early childhood special education programs, nonprofits and other community organizations, cooperatives, employer-based child care, and public agencies. Increasingly, publicly funded prekindergarten programs contract with existing community-based centers and home-based providers for program delivery. With a few exceptions (such as faith-affiliated child care), center-based child care programs must satisfy state licensing laws for safety practices. For other child care options, governmental oversight for health and safety is rarer; many home-based child care programs are licensed, whereas many others are unknown to regulatory agencies, and family, friend, and nanny care are almost never regulated. Child care licensing and regulation is described in the next section.

Approximately 59% of children 5 years and younger and not yet in kindergarten were in at least 1 weekly nonparental child care arrangement, as reported by their parents in the U.S. Census Bureau's 2019 National Household Education Surveys Program. Forty-two percent of children less than 1 year of age, 55% of 1-2 year olds, and 74% of 3-5 year olds were in nonparental care. Nearly 60% of those in at least one child care arrangement were in a center-based arrangement, 38% were in relative care, and 20% were in nonrelative care in a private home; children may have been in more than one type of arrangement. Center-based arrangements were most common among preschoolers, whereas relative care arrangements were most common among infants.

Child Care Closures

The COVID-19 pandemic accelerated a worsening trend of child care closures. In 2012, there were approximately 129,000 center-based programs serving 6.98 million children from birth through age 5. Between 2014 and 2017, the number of licensed child care programs of all types in the United States decreased to approximately 109,000 centers. The number of listed home-based providers (which includes licensed or otherwise regulated providers) decreased by about 25% between 2012 and 2019.

In response to COVID-19, by April 2020 new state public health requirements resulted in closing 70% of U.S. child care centers; more than 35% of child care workers became unemployed. Reasons for this include COVID-19 outbreaks and preventative health protocols such as social distancing with limits in group sizes and child:staff ratios. As the pandemic continued, reasons for new or even permanent closures included staffing shortages as well as business models that cannot support a program's financial survival at low enrollment rates. However, child masking within the first year of the pandemic was associated with a 13-14% reduction in child care closure rates.

Licensing, Regulation, Monitoring, and Accreditation

State and territory licensing agencies enumerate which providers are subject to licensing to legally operate and monitor those providers' compliance with foundational, mandated regulations to protect children's safety, health, and well-being. Many states and territories also offer systems of child care monitoring that are usually voluntary in nature, such as quality rating and improvement systems (QRIS), and various professional organizations offer voluntary accreditation systems to assess whether providers meet higher-quality standards, often (but not always) requiring licensure as a prerequisite to participation.

Licensing

Licensing and regulatory requirements establish the minimum requirements necessary to protect the health and safety of children in

child care. Typically, these include basic health and safety standards such as sanitary practices, child and provider vaccinations, access to a healthcare professional, and facilities and equipment hazards and safety, as well as basic structural and caregiver characteristics such as background checks, the ratio of children to staff, group sizes, and minimum caregiver education and training requirements. Most child care centers and preschools and many family child care providers are subject to state licensing and regulation. All states regulate child care centers, as does the District of Columbia, and most states regulate family child care providers.

Pediatricians are encouraged to learn about their own state's child care licensing rules. Large differences between states mean large differences in allowable levels of quality. The most common child:staff ratios are 4:1 for infants, 6:1 for toddlers, and 10:1 for preschoolers. However, some states permit ratios that are 5:1 or 6:1 for infants 9 months of age or younger.

State and territory child care licensing regulations are maintained in a searchable National Database of Child Care Licensing Regulations (https://childcareta.acf.hhs.gov/licensing) by the National Center on Early Childhood Quality Assurance (NCECQA). The site provides a tool for searching state and territory licensing regulations and agency contact information. Licensing requirements are frequently updated.

Unlicensed settings and even licensed providers in states with low licensing and regulatory standards may be providing care at quality levels below professional recommendations. Moreover, various types of programs may be exempt from licensure, such as faith-affiliated child care programs, and exemptions are specific to each state; as many as one third of child care centers are legally exempt in some states. Centers are often exempted if care is offered by other organizations such as school districts that provide external oversight. The smallest homes (three or four children in care) are often license-exempt, encompassing relative, friend, and neighbor caregivers as well as babysitters, nannies, and au pairs. Some of these providers and the families who use them may not even think of themselves as providing "child care." The Child Care Development Block Grant (CCDBG) reauthorization in 2014 required states and territories to expand their monitoring of legally exempt providers to protect the health and safety of children receiving subsidized child care. Most states require exempt centers and family child care homes to meet some licensure requirements such as background checks and to receive an annual inspection to receive child care subsidy payments.

Other Quality Monitoring Systems

Several voluntary public and private initiatives require that child care settings meet their own sets of guidelines and regulations in areas considered critical to effective practice and child outcomes to receive either state or federal funding. These diverse initiatives include those that focus on nutrition (the Child and Adult Care Food Program [CACFP]), inclusion (the Individuals with Disabilities Education Act [IDEA]), and financial assistance to low-income working parents (child care subsidies through the CCDBG). Most states have quality initiatives called QRIS. Publicly funded early education programs, including the federal Head Start and Early Head Start program as well as state and local public prekindergarten have their own program performance standards.

Participating providers benefit in ways that may include technical assistance supports, professional development, and additional funding often tied to the numbers of children served under the program. About 75% of early care and education centers report receiving funds from multiple sources. Providers may also value earning a public-facing "seal of approval" to help families learn about higher-quality programs.

These programs all monitor eligibility and compliance with program standards. For example, Head Start and most of the state prekindergarten programs that restrict enrollment to low-income families require verification of family eligibility (although some states' and cities' prekindergarten programs are universally available to all preschool-age children regardless of family income). Other eligibility standards include verification of parental employment for child care subsidies or verification of nutritious food for low-income families for receipt of CACFP funds. Other monitoring may cover staffing, meals and snacks, curricula and teaching, and other areas of service delivery. QRIS systems work within the infrastructure of the early care and education system to assess, incentivize, and support higher levels of quality. Examples of incentives and supports include tiered subsidy reimbursement systems in which participating providers who achieve levels of quality beyond basic licensing requirements are entitled to higher subsidy payments, public funding to facilitate accreditation, professional development systems and coaching, and program assessments and technical assistance.

Accreditation

A smaller portion of providers become accredited by National Association for the Education of Young Children (NAEYC), National Association for Family Child Care (NAFCC), or other organizations by voluntarily meeting high-quality, developmentally appropriate, professionally recommended standards. The accreditation process goes beyond health and safety practices and structural and caregiver characteristics to examine the quality of child–caregiver interactions. Evidence indicates that child care programs that complete voluntary accreditation through NAEYC provide an environment that better facilitates children's overall development, but few providers are accredited. This is partly the result of a lack of knowledge, resources, and incentives for providers to improve quality, but it may also be partly because of expenses providers incur in becoming accredited.

Child Care Access

As one social determinant of health, access to affordable high-quality child care that supports child development and meets family needs is critical.

Access to child care goes beyond simple "supply" (numbers of available slots) and "demand" (numbers of young children needing extrafamilial care). Barriers to access include aspects of affordability, hours of operation, location, transportation, and culturally or linguistically appropriate care. Barriers to access to high-quality child care are pervasive among families in which caregivers work irregular, fluctuating, or nontraditional work schedules, families with infants and toddlers, families for whom English is not the primary language spoken at home, and families with children with disabilities or special needs.

Two thirds of children 5 years of age and younger have both parents in the workforce or in school or training programs. Nearly 30% of low-income mothers of children under 6 years of age work nonstandard hours, but child care supply during nonstandard or irregular hours is extremely limited. Over 30% of parents with children in weekly care report that the arrangement does not cover the hours needed for work very well. Many more report that they are not in the workforce or school, or not working the hours or shifts that they need or want, due to lack of affordable accessible child care.

SCREENING AND SUPPORT FOR CHILD DEVELOPMENT AND HEALTH

Child Care and Child Behavior

Before the COVID-19 pandemic, about 192,000 U.S. young children were being expelled or suspended from child care programs annually for concerns rising from developmentally typical crying and temper tantrums to physical aggression to violations of various "zero tolerance policies," such as bringing a water gun to child care. In fact, young children are expelled from child care and preschool programs at a rate more than 3 times that for kindergarten through 12th graders. Young children experiencing any number of adverse childhood events are at significantly increased odds of preschool expulsion, such as exposure to domestic or community violence, family mental illness and substance abuse, poverty, parental divorce, and parental incarceration. These disciplinary exclusions are disproportionately applied to young males and to children of color; implicit biases account for at least some of these disproportionalities. These early disciplinary exclusions predict later negative school attitudes, academic failure and grade retention, and later expulsions and suspensions, as well as a 10-fold increase in high-school dropout rates and an 8-fold increase in later incarceration.

State efforts to reduce early childhood exclusionary discipline include early childhood mental health consultation (ECMHC) models to support child care providers, who are often not well trained in managing child behavior, as well as build capacity to raise child care quality for all children. ECMHC links a mental health professional with an early education and care provider in an ongoing problem-solving and capacity-building relationship. ECMHC has been shown to be effective in statewide randomized controlled trials, and now exist in several states and cities. Because this is a rapidly evolving area of support, clinicians wishing to provide guidance to parents of young children at risk of early disciplinary exclusion should consider inquiring about the existence of an ECMHC system within their state or locality by contacting their state early childhood department and/or state/local child care resource and referral agency. Local regulations may limit or prohibit the exclusion of children in response to behaviors that may be a symptomatic expression of a diagnosed disability or special education need, providing a potential method for safeguarding a child's ability to receive early care and education, as described in the next section.

Children with Special Needs

Children with cognitive, physical, or emotional disabilities who require special care and instruction often require particular attention when it comes to their participation in most child care settings. Guiding principles of services for children with disabilities advocate supporting children in natural environments, including child care. Furthermore, the Americans with Disabilities Act and Section 504 of the Rehabilitation Act of 1973 prohibit discrimination against children and adults with disabilities by requiring equal access to offered programs and services.

Child care can be, and often is, utilized for delivery of support services to children with special needs and/or for linking families to services such as early intervention. Furthermore, clinicians can draw on child care providers for important evaluative data regarding a child's well-being, as these providers have extensive daily contact with the child and may have broad, professional understanding of normative child development. Child care providers often conduct screenings for developmental milestones and delays using standardized instruments. A child care provider may be the first to identify a child's potential language delay. Child care providers are also necessary and valuable partners in the development and administration of early intervention service plans. However, many child care providers and settings are unprepared to identify or administer services for children with special needs.

Children with special needs may be eligible for special educational services under IDEA. The purpose of this law is to provide "free appropriate public education," regardless of disability or chronic illness, to all eligible children, birth to 21 years of age, in a natural and/or least-restrictive environment. Eligible children include those with mental, physical, or emotional disabilities who, because of their disability or chronic illness, require special instruction to learn. As a part of these services, a formal plan of intervention is to be developed by the service providers, families, and the children's healthcare providers. Federal funds are available to implement a collaborative early intervention system of services for eligible infants and toddlers between the ages of birth and 3 years and their families. These services include screening, assessment, service coordination, and collaborative development of an **individualized family service plan (IFSP).** The IFSP describes early intervention services for the child's health, therapeutic, and educational needs and supports needed by the family. An understanding of the child's routines and real-life opportunities and activities, such as eating, playing, interacting with others, and working on developmental skills, is crucial to enhancing a child's ability to achieve the functional goals of the IFSP. Therefore it is critical that child care providers be involved in IFSP development or revision, with parental consent. Child care providers should also become familiar with the child's IFSP and understand the providers' role and the resources available to support the family and child care provider. Additionally, IDEA provides support for eligible children 3 years of age and older to receive services through the local school district. This includes development of a written **individualized education program (IEP)**, with implementation being the responsibility of the local education agency in either a public or private preschool setting. As with IFSPs, child care providers should become familiar with the preschooler's special needs as identified in the IEP and may become involved, with parental consent, in IEP development and review meetings. In cases where children may have or be at risk of developmental delays, a diagnosis is important for obtaining and coordinating services and further evaluation. To this end, clinicians can partner with child care providers to screen and monitor children's behavior and development. Even if a young child is not being provided special educational services, special accommodations may be requested for any child whose access to child care is being adversely impacted by a diagnosable developmental or behavioral disability through Section 504 of the Rehabilitation Act of 1973.

Sick Children and Control of Infectious Disease

When children are ill, they may be excluded from out-of-home child care and under state licensure child care programs are required to exclude children with certain conditions. Children in child care are of an age that places them at increased risk for acquiring infectious diseases. Participation in group settings elevates exposure, leading to increased infections, especially during the first year of child care exposure and especially with infants. Children enrolled in such settings have a higher incidence of illness (upper respiratory tract infections, otitis media, diarrhea, hepatitis A infections, skin conditions, and asthma) than those cared for at home, especially in the preschool years; these illnesses have no long-term adverse consequences. Child care providers that follow child care licensure guidelines for handwashing, diapering, and food handling, and manage child illness appropriately, can reduce communicable illnesses.

CFOC (2019) and its up-to-date online supplement and the AAP (Table 29.2) offer guidelines and recommendations regarding the conditions under which sick children should and should not be excluded from group programs. State laws typically mirror these guidelines but may be stricter in some states. Although exclusion from child care due to mild illness is often unnecessary, their summary of guidelines states that a child should be excluded temporarily from care if the signs or symptoms of the illness does any of the following:

- Prevents the child from participating in daycare activities
- Results in a level of care that is greater than the staff can provide
- Poses a contagion risk of serious diseases to other children and staff

For COVID-19 exposure or symptoms or recovery go to https://www.cdc.gov/coronavirus/2019-nCoV/index.html

Health checks should be performed on each child every day. If symptoms develop during child care but do not require exclusion, written or verbal communication after the daycare is appropriate. Emergencies must be addressed with 911 calls and immediate notification of the family. If nonemergent but requiring exclusion, the parents should be notified to take the child home. Parents should have a backup plan when exclusions occur. *Return to child care is usually permissible without a primary healthcare visit.*

CFOC also provides guidelines for control of infectious disease outbreaks and for exclusion of any child or staff member who is suspected of contributing to transmission of the illness, who is not adequately immunized when there is an outbreak of a vaccine-preventable disease, or when the circulating pathogen poses an increased risk to the individual.

During the first 3 months of the COVID-19 pandemic in the United States, exposure to child care was not associated with an elevated risk of COVID-19 transmission to adult child care providers within the context of the considerable efforts that were employed to reduce transmission. Although enhanced hand hygiene and surface disinfecting were the most common transmission mitigation methods, many child care programs also engaged in daily symptom screening and temperature checks, social distancing efforts, and cohorting (i.e., keeping groups of children separate to help control the speed of transmission). Despite Centers for Disease Control and Prevention (CDC) guidance, masking of adults and children were rarely employed; federal guidance and requirements in several states, child care provider COVID-19 vaccination rates in June 2021 were only 78.2%. COVID-19 modifications and

Table 29.2 Signs and Symptoms for Consideration of Exclusion or Inclusion in Child Care

SIGN OR SYMPTOM	COMMON CAUSES	COMPLAINTS OR WHAT MIGHT BE SEEN	NOTIFY HEALTH CONSULTANT	NOTIFY PARENT	TEMPORARILY EXCLUDE?	IF EXCLUDED, READMIT WHEN
Cold symptoms	*Viruses* (early stage of many viruses) • Adenovirus • Coronavirus • Enterovirus • Influenza virus • Parainfluenza virus • Respiratory syncytial virus (RSV) • Rhinovirus Bacteria • Mycoplasma • Pertussis	• Coughing • Runny or stuffy nose • Scratchy throat • Sneezing • Fever • Watery eyes	Not necessary unless epidemics occur (i.e., RSV or vaccine-preventable disease like measles or varicella [chickenpox])	Yes	No, unless • Fever accompanied by behavior change. • Child looks or acts very ill. • Child has difficulty breathing. • Child has blood-red or purple rash not associated with injury. • Child meets routine exclusion criteria.	Exclusion criteria are resolved.
Cough (cough is a body response to something that is irritating tissues in the airway anywhere from the nose to the lungs)	• Common cold • Lower respiratory infection (e.g., pneumonia, bronchiolitis) • Croup • Asthma • Sinus infection • Bronchitis • Pertussis • Noninfectious causes like allergies	• Dry or wet cough • Runny nose (clear, white, or yellow-green) • Sore throat • Throat irritation • Hoarse voice, barking cough • Coughing fits	Not necessary unless the cough is due to a vaccine-preventable disease, such as pertussis	Yes	No, unless • Severe cough. • Rapid or difficult breathing. • Wheezing if not already evaluated and treated. • Cyanosis (i.e., blue color of skin or mucous membranes). • Pertussis is diagnosed and not yet treated. • Fever with behavior change. • Child meets routine exclusion criteria.	Exclusion criteria are resolved.
Diaper rash	• Irritation by rubbing of diaper material against skin wet with urine or stool • Infection with yeast or bacteria	• Redness • Scaling • Red bumps • Sores • Cracking of skin in diaper region	Not necessary	Yes	No, unless • Oozing sores that leak body fluids outside the diaper. • Child meets routine exclusion criteria.	Exclusion criteria are resolved.
Diarrhea	• Usually viral, less commonly bacterial or parasitic • Noninfectious causes such as dietary (drinking too much juice), medications, inflammatory bowel disease, or cystic fibrosis	• Frequent loose or watery stools compared with child's normal pattern. (Note that exclusively breastfed infants normally have frequent unformed and somewhat watery stools or may have several days with no stools.) • Abdominal cramps • Fever • Generally not feeling well • Vomiting occasionally present	Yes, if one or more cases of bloody diarrhea or two or more children in same group with diarrhea within a week	Yes	Yes, if • Directed by the local health department as part of outbreak management. • Stool is not contained in the diaper for diapered children. • Diarrhea is causing "accidents" for toilet-trained children. • Stool frequency exceeds 2 stools above normal during the time the child is in the program because this may cause too much work for teachers/caregivers and make it difficult to maintain good sanitation. • Blood/mucus in stool. • Black stools. • No urine output in 8 hours. • Jaundice (i.e., yellow skin or eyes). • Fever with behavior change. • Looks or acts very ill. • Child meets routine exclusion criteria.	• Cleared to return by healthcare provider for all cases of bloody diarrhea and diarrhea caused by Shiga toxin-producing *Escherichia coli, Shigella*, or *Salmonella* serotype Typhi until negative stool culture requirement has been met. • Diapered children have their stool contained by the diaper (even if the stools remain loose) and toilet-trained children do not have toileting accidents. • Stool frequency is no more than 2 stools above normal during the time the child is in the program, or what has become normal for that child when the child seems otherwise well. • Exclusion criteria are resolved.

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 29.2 Signs and Symptoms for Consideration of Exclusion or Inclusion in Child Care—cont'd

SIGN OR SYMPTOM	COMMON CAUSES	COMPLAINTS OR WHAT MIGHT BE SEEN	NOTIFY HEALTH CONSULTANT	NOTIFY PARENT	TEMPORARILY EXCLUDE?	IF EXCLUDED, READMIT WHEN
Difficult or noisy breathing	• Common cold • Croup • Epiglottitis • Bronchiolitis • Asthma • Pneumonia • Object stuck in airway • Exposed to a known trigger of asthma symptoms (e.g., animal dander, pollen)	• Common cold: stuffy/runny nose, sore throat, cough, or mild fever • Croup: barking cough, hoarseness, fever, possible chest discomfort (symptoms worse at night), or very noisy breathing, especially when breathing in • Epiglottitis: gasping noisily for breath with mouth wide open, chin pulled down, high fever, or bluish (cyanotic) nails and skin; drooling, unwilling to lie down • Bronchiolitis and asthma: child is working hard to breathe; rapid breathing; space between ribs looks like it is sucked in with each breath (retractions); wheezing; whistling sound with breathing; cold/cough; irritable and unwell. Takes longer to breathe out than to breathe in. • Pneumonia: deep cough, fever, rapid breathing, or space between ribs looks like it is sucked in with each breath (retractions) • Object stuck in airway: symptoms similar to croup (listed previously) • Exposed to a known trigger of asthma symptoms: a known trigger and breathing that sounds or looks different from what is normal for that child	Not necessary except for epiglottitis	Yes	Yes, if • Fever with behavior change. • Child looks or acts very ill. • Child has difficulty breathing. • Rapid or difficult breathing. • Wheezing if not already evaluated and treated. • Cyanosis (i.e., blue color of skin or mucous membranes). • Cough interferes with activities. • Breath sounds can be heard when the child is at rest. • Child has blood-red or purple rash not associated with injury. • Child meets routine exclusion criteria.	Exclusion criteria are resolved.
Earache	• Bacteria • Often occurs in context of common cold virus	• Fever • Pain or irritability • Difficulty hearing • "Blocked ears" • Drainage • Swelling around ear	Not necessary	Yes	No, unless child meets routine exclusion criteria.	Exclusion criteria are resolved.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 29.2 Signs and Symptoms for Consideration of Exclusion or Inclusion in Child Care—cont'd

SIGN OR SYMPTOM	COMMON CAUSES	COMPLAINTS OR WHAT MIGHT BE SEEN	NOTIFY HEALTH CONSULTANT	NOTIFY PARENT	TEMPORARILY EXCLUDE?	IF EXCLUDED, READMIT WHEN
Eye irritation, pinkeye	• Bacterial infection of the membrane covering one or both eyes and eyelids (bacterial conjunctivitis) • Viral infection of the membrane covering one or both eyes and eyelids (viral conjunctivitis) • Allergic irritation of the membrane covering one or both eyes and eyelids (allergic conjunctivitis) • Chemical irritation of the membrane covering the eye and eyelid (irritant conjunctivitis) (e.g., swimming in heavily chlorinated water, air pollution, smoke exposure)	• Bacterial infection: pink color of the "whites" of eyes and thick yellow/green discharge. Eyelid may be irritated, swollen, or crusted. • Viral infection: pinkish/red color of the whites of the eye; irritated, swollen eyelids; watery discharge with or without some crusting around the eyelids; may have associated cold symptoms. • Allergic and chemical irritation: red, tearing, itchy, puffy eyelids; runny nose, sneezing; watery/stringy discharge with or without some crusting around the eyelids.	Yes, if two or more children have red eyes with watery discharge	Yes	*For bacterial conjunctivitis* No. Exclusion is no longer required for this condition. Healthcare providers may vary on whether to treat this condition with antibiotic medication. The role of antibiotics in treatment and preventing spread is unclear. Most children with pinkeye get better after 5 or 6 days without antibiotics. *For other eye problems* No, unless child meets other exclusion criteria. *Note:* One type of viral conjunctivitis spreads rapidly and requires exclusion. If two or more children in the group have watery red eyes without any known chemical irritant exposure, exclusion may be required and health authorities should be notified to determine whether the situation involves the uncommon epidemic conjunctivitis caused by a specific type of adenovirus. Herpes simplex conjunctivitis (red eyes with blistering/vesicles on eyelid) occurs rarely and would also require exclusion if there is eye watering.	• *For bacterial conjunctivitis,* once parent has discussed with healthcare provider. Antibiotics may or may not be prescribed. • Exclusion criteria are resolved.
Fever	• Any viral, bacterial, or parasitic infection • Vigorous exercise • Reaction to medication or vaccine • Other noninfectious illnesses (e.g., rheumatoid arthritis, malignancy)	Flushing, tired, irritable, decreased activity *Notes:* • Fever alone is not harmful. When a child has an infection, raising the body temperature is part of the body's normal defense against germs. • Rapid elevation of body temperature sometimes triggers a febrile seizure in young children; this usually is outgrown by age 6 yr. The first time a febrile seizure happens, the child requires medical evaluation. These seizures are frightening but are usually brief (less than 15 minutes) and do not cause the child any long-term harm. Parents should inform their child's healthcare provider every time the child has a seizure, even if the child is known to have febrile seizures. Warning: *Do not* give aspirin. It has been linked to an increased risk of Reye syndrome (a rare and serious disease affecting the brain and liver).	Not necessary	Yes	No, unless • Behavior change or other signs of illness in addition to fever or child meets other routine exclusion criteria. • Unable to participate. • Care would compromise staff's ability to care for other children. *Note:* A temperature considered meaningfully elevated above normal, although not necessarily an indication of a significant health problem, for infants and children older than 2 mo is above 101°F (38.3°C) from any site (axillary, oral, or rectal). *Get medical attention* when infants younger than 4 mo have unexplained fever. In any infant younger than 2 mo, a temperature above 100.4°F (38.0°C) is considered meaningfully elevated and requires that the child get medical attention immediately, within an hour if possible. The fever is not harmful; however, the illness causing it may be serious in this age group.	Exclusion criteria are resolved.

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 29.2 Signs and Symptoms for Consideration of Exclusion or Inclusion in Child Care—cont'd

SIGN OR SYMPTOM	COMMON CAUSES	COMPLAINTS OR WHAT MIGHT BE SEEN	NOTIFY HEALTH CONSULTANT	NOTIFY PARENT	TEMPORARILY EXCLUDE?	IF EXCLUDED, READMIT WHEN
Headache	• Any bacterial/viral infection • Other noninfectious causes	• Tired and irritable • Can occur with or without other symptoms	Not necessary	Yes	No, unless child meets routine exclusion criteria. *Note:* Notify healthcare provider in case of sudden, severe headache with vomiting or stiff neck that might signal meningitis. It would be concerning if the back of the neck is painful or the child cannot look at his or her belly button (putting chin to chest)—different from soreness in the side of the neck.	Exclusion criteria are resolved.
Itching	• Ringworm • Chickenpox • Pinworm • Head lice • Scabies • Allergic or irritant reaction (e.g., poison ivy) • Dry skin or eczema • Impetigo	• Ringworm: itchy ring-shaped patches on skin or bald patches on scalp. • Chickenpox: blister-like spots surrounded by red halos on scalp, face, and body; fever; irritable. • Pinworm: anal itching. • Head lice: small insects or white egg sheaths that look like grains of sand (nits) in hair. • Scabies: severely itchy red bumps on warm areas of body, especially between fingers or toes. • Allergic or irritant reaction: raised, circular, mobile rash; reddening of the skin; blisters occur with local reactions (poison ivy, contact reaction). • Dry skin or eczema: dry areas on body. More often worse on cheeks, in front of elbows, and behind knees. In infants, may be dry areas on face and anywhere on body but not usually in the diaper area. If swollen, red, or oozing, think about infection. • Impetigo: areas of crusted yellow, oozing sores. Often around mouth or nasal openings or areas of broken skin (insect bites, scrapes).	Yes, for infestations such as lice and scabies; if more than one child in group has impetigo or ringworm; for chickenpox	Yes	*For chickenpox:* Yes, until lesions are fully crusted *For ringworm, impetigo, scabies, and head lice:* Yes, at the end of the day Children should be referred to a healthcare provider at the end of the day for treatment. *For pinworm, allergic or irritant reactions like hives, and eczema:* No, unless appears infected as a weeping or crusty sore *Note:* Although exclusion for these conditions is not necessary, families should seek advice from the child's health professional for how to care for these health problems. *For any other itching:* No, unless the child meets routine exclusion criteria.	• Exclusion criteria are resolved. • On medication or treated as recommended by a healthcare provider if treatment is indicated for the condition. For conditions that require application of antibiotics to lesions or taking antibiotics by mouth, the period of treatment to reduce risk of spread to others is usually 24 hours. For most children with insect infestations or parasites, readmission as soon as the treatment has been given is acceptable.
Mouth sores	• Oral thrush (yeast infection) • Herpes or coxsackie-virus infection • Canker sores	• Oral thrush: white patches on tongue, gums, and along inner cheeks • Herpes or coxsackievirus infection: pain on swallowing; fever; painful, white/red spots in mouth; swollen neck glands; fever blister, cold sore; reddened, swollen, painful lips • Canker sores: painful ulcers inside cheeks or on gums	Not necessary	Yes	No, unless • Drooling steadily related to mouth sores. • Fever with behavior change. • Child meets routine exclusion criteria.	Exclusion criteria are resolved.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 29.2 Signs and Symptoms for Consideration of Exclusion or Inclusion in Child Care—cont'd

SIGN OR SYMPTOM	COMMON CAUSES	COMPLAINTS OR WHAT MIGHT BE SEEN	NOTIFY HEALTH CONSULTANT	NOTIFY PARENT	TEMPORARILY EXCLUDE?	IF EXCLUDED, READMIT WHEN
Rash	Many causes • Viral: roseola infantum, fifth disease, chickenpox, herpesvirus, molluscum contagiosum, warts, cold sores, shingles (herpes zoster), and others • Skin infections and infestations: ringworm (fungus), scabies (parasite), impetigo, abscesses, and cellulitis (bacteria) • Scarlet fever (strep infection) • Severe bacterial infections: meningococcus, pneumococcus, *Staphylococcus* (methicillin-susceptible *S. aureus*; methicillin-resistant *S. aureus*), *Streptococcus* • Noninfectious causes: allergy (hives), eczema, contact (irritant) dermatitis, medication related, poison ivy	• Skin may show similar findings with many different causes. Determining cause of rash requires a competent healthcare provider evaluation that takes into account information other than just how rash looks. However, if the child appears well other than the rash, a healthcare provider visit is not necessary. • Viral: usually signs of general illness such as runny nose, cough, and fever (except not for warts or molluscum). Some viral rashes have a distinctive appearance. • Minor skin infections and infestations: see Itching. • More serious skin infections: redness, pain, fever, pus. • Severe bacterial infections: rare. These children usually have fever with a rapidly spreading blood-red rash and may be very ill. • Allergy may be associated with a raised, itchy, pink rash with bumps that can be as small as a pinpoint or large welts known as hives. See also Itching for what might be seen for allergy or contact (irritant) dermatitis or eczema.	For outbreaks, such as multiple children with impetigo within a group	Yes	No, unless • Rash with behavior change or fever. • Has oozing/open wound. • Has bruising not associated with injury. • Has joint pain and rash. • Rapidly spreading blood-red rash. • Tender, red area of skin, especially if it is increasing in size or tenderness. • Child meets routine exclusion criteria. • Diagnosed with a vaccine-preventable condition, such as chickenpox.	• On antibiotic medication for required period (if indicated). • Infestations (lice and scabies) and ringworm can be treated at the end of the day with immediate return the following day. • Exclusion criteria are resolved.
Sore throat (pharyngitis)	• Viral: common cold viruses that cause upper respiratory infections • Strep throat	• Viral: verbal children will complain of sore throat; younger children may be irritable with decreased appetite and increased drooling (refusal to swallow). Often see symptoms associated with upper respiratory illness, such as runny nose, cough, and congestion. • Strep throat: signs of the body's fight against infection include red tissue with white patches on sides of throat, at back of tongue (tonsil area), and at back wall of throat. Unlike viral pharyngitis, strep throat infections are *not* accompanied with cough or runny nose in children older than 3 yr. • Tonsils may be large, even touching each other. Swollen lymph nodes (sometimes called "swollen glands") occur as body fights off the infection.	Not necessary	Yes	No, unless • Inability to swallow. • Excessive drooling with breathing difficulty. • Fever with behavior change. • Child meets routine exclusion criteria. *Note:* Most children with red back of throat or tonsils, pus on tonsils, or swollen lymph nodes have viral infections. If strep is present, 12 hours of antibiotics is required before return to care. However, tests for strep infection are not often necessary for children younger than 3 yr because these children do not develop rheumatic heart disease, which is the primary reason for treatment of strep throat.	• Able to swallow. • On medication at least 12 hours (if strep). • Exclusion criteria are resolved.

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 29.2 Signs and Symptoms for Consideration of Exclusion or Inclusion in Child Care—cont'd

SIGN OR SYMPTOM	COMMON CAUSES	COMPLAINTS OR WHAT MIGHT BE SEEN	NOTIFY HEALTH CONSULTANT	NOTIFY PARENT	TEMPORARILY EXCLUDE?	IF EXCLUDED, READMIT WHEN
Stomachache	• Viral gastroenteritis or strep throat • Problems with internal organs of the abdomen such as intestine, colon, liver, bladder • Nonspecific, behavioral, and dietary causes • If combined with hives, may be associated with a severe allergic reaction	• Viral gastroenteritis or strep throat: Vomiting and diarrhea or cramping are signs of a viral infection of the stomach or intestine. Strep throat may cause stomachache with sore throat, headache, and possible fever. In children older than 3 yr, if cough or runny nose is present, strep is very unlikely. • Problems with internal organs of the abdomen: persistent severe pain in abdomen. • Nonspecific stomachache: vague complaints without vomiting/diarrhea or much change in activity.	If multiple cases in same group within 1 week	Yes	No, unless • Severe pain causing child to double over or scream. • Abdominal pain after injury. • Bloody/black stools. • No urine output for 8 hours. • Diarrhea (see Diarrhea). • Vomiting (see Vomiting). • Yellow skin/eyes. • Fever with behavior change. • Looks or acts very ill. • Child meets routine exclusion criteria.	• Pain resolves. • Able to participate. • Exclusion criteria are resolved.
Swollen glands (properly called swollen lymph nodes)	• Normal body defense response to viral or bacterial infection in the area where lymph nodes are located (i.e., in the neck for any upper respiratory infection) • Bacterial infection of lymph nodes that is more than the normal response to infection near where the lymph nodes are located	• Normal lymph node response: swelling at front, sides, and back of the neck and ear; in the armpit or groin; or anywhere else near an area of an infection. Usually, these nodes are less than 1 inch across. • Bacterial infection of lymph nodes: swollen, warm lymph nodes with overlying pink skin, tender to the touch, usually located near an area of the body that has been infected. Usually these nodes are larger than 1 inch across.	Not necessary	Yes	No, unless • Difficulty breathing or swallowing. • Red, tender, warm glands. • Fever with behavior change. • Child meets routine exclusion criteria.	• Child is on antibiotics (if indicated). • Exclusion criteria are resolved.
Vomiting	• Viral infection of the stomach or intestine (gastroenteritis) • Coughing strongly • Other viral illness with fever • Noninfectious causes: food allergy (vomiting, sometimes with hives), trauma, dietary and medication related, headache	Diarrhea, vomiting, or cramping for viral gastroenteritis	For outbreak	Yes	Yes, if • Vomited more than 2 times in 24 hours • Vomiting and fever • Vomiting with hives • Vomit that appears green/bloody • No urine output in 8 hours • Recent history of head injury • Looks or acts very ill • Child meets routine exclusion criteria.	• Vomiting ends. • Able to participate. • Exclusion criteria are resolved.

From Aronson SS, Shope TR, (eds). *Managing Infectious Diseases in Child Care and Schools: a quick reference guide.* 4th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2017.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

considerations are itemized in the Crosswalk (https://nrckids.org/files/CFOC.Crosswalk.pdf) and include, for example, discussion of daily symptom checks for children as well as daily screening procedures and exclusion criteria for staff.

Most families need to arrange to keep sick children at home necessitating staying home from work or having backup plans with an alternative caregiver. Alternative care arrangements outside the home for sick children are relatively rare but may include either (1) care in the child's own center, if it offers special provisions designed for the care of ill children (sometimes called the **infirmary model** or **sick daycare**), or (2) care in a center that serves only children with illness or temporary conditions. Although it is important that such arrangements emphasize preventing further spread of disease, one study found no occurrence of additional transmission of communicable disease in children attending a sick center.

Protection and Promotion of Child Health

Child care has a role in protecting and promoting child health and well-being. Child care providers are often the first to notice signs of child abuse and neglect and are a major source of child welfare referrals. Findings of increased health-related issues in the first year of child care are likely a testament to early detection benefits provided by child care providers.

Sudden Infant Death Syndrome

A disproportionate number of sudden infant death syndrome (SIDS) deaths occur in child care centers or family-based child care homes. Infants who are back-sleepers at home but are put to sleep on their front in child care settings have a higher risk of SIDS. Providers and parents should be made aware of the importance of placing infants on their backs to sleep.

Asthma and Respiratory Illness

Children enrolled in prekindergarten may have a greater risk of asthma diagnosis during prekindergarten but a lower risk in the years following prekindergarten, when compared with children who were not exposed to prekindergarten. Enrollment in prekindergarten may increase the early detection of asthma symptoms.

A 10-year follow-up of a birth cohort has found no association between child care attendance and respiratory infections, asthma, allergic rhinitis, or skin-prick test reactivity. Another study found that in the first year of elementary school, children who had attended child care had fewer absences from school, half as many episodes of asthma, and less acute respiratory illness than their peers who had never attended child care. These results are perhaps related to protection against respiratory illness through early exposure or a shift in the age-related peak of illness, although selection of illness-prone children into homecare may play a role. Other factors include children in child care potentially being less exposed to passive smoking than children at home.

Vision and Hearing Problems

Children enrolled in a citywide universal prekindergarten program had higher probability of diagnosis of vision problems, receipt of treatment for hearing or vision problems, and receiving an immunization. These effects were not offset by lower rates in the kindergarten year, suggesting that identification and treatment of these conditions was accelerated by enrollment in universal prekindergarten. As hearing and vision problems could potentially delay learning and cause behavioral problems, early detection and treatment is beneficial for future health and school readiness.

Obesity and Promotion of Healthy Behaviors

There is insufficient research on longitudinal associations between child care, diet, and physical activity behaviors. Some limited research suggests a negative or mixed association between child care exposure and healthy behaviors, but the strength of these associations, and whether any causal implications exist, are difficult to tease apart. Other research suggests that child care center-based interventions are generally found to be effective in improving physical activity and may be effective at improving dietary behaviors.

The CDC identifies child care settings as one of the best places to reach young children with obesity prevention efforts. Through their Spectrum of Opportunities framework (https://www.cdc.gov/obesity/strategies/childcareece.html), they outline how a state's early care and education system can embed recommended standards and support for obesity prevention, including nutrition, infant feeding, physical activity, and screen time.

ROLE OF PEDIATRIC PROVIDERS

Consultation, Referrals, and Screening to Improve Access

Many parents are first-time purchasers of child care with little experience and very immediate needs; they may select care in a market that does little to provide them with useful information about child care arrangements. To inform their child care decisions, parents may turn to their child's healthcare provider as the only professional with expertise in child development with whom they have regular and convenient contact. Primary care clinicians should screen for child care just as they do for other social determinants of health, asking about child care arrangements and offering information about resources to help find and pay for child care to reinforce the importance of child care and increase the chances that children are enrolled in high-quality settings.

It is difficult for many parents to find high-quality child care that they can accept and afford. Many parents also worry how their child will fare in child care (e.g., they may worry that their child will feel distressed by the group settings, suffer from separation from the parents, or even be subjected to neglect or abuse). Practical concerns of transportation, scheduling to cover their work or school hours, and reliability are also common. The reliability of the arrangement is often rated as a "very important" selection factor by a higher proportion of parents than any other factor, followed by availability and staff qualifications. Among those who reported difficulty finding child care, cost was most often the primary reason, followed by lack of open slots, quality, then location or other reasons. Worries about finding quality child care are especially likely among parents with greater barriers to child care access and fewer personally accessible family and community resources. With the coronavirus pandemic, parents may be worried about the transmission of COVID-19 and about sporadic disruptions in service caused by quarantines or temporary closures, and unfounded fears about the safety of vaccines or facial masks.

Primary care practices can share information with parents about publicly available sources of information to help them find or pay for child care (Table 29.3). For example, they can

- Refer low-income parents to Head Start, which serves 3-4 year old children, or Early Head Start programs, which serves low-income expecting families and their children until their child's third birthday
- Refer low-income working parents to apply for child care subsidies and financial assistance in their state or county
- Refer parents to their local child care resource and referral agency for help finding and selecting child care; these can be located via the national association, Child Care Aware of America (www.childcareaware.org/families)

Some parents may think of child care only as babysitting focusing mainly on whether the child is safe and warm and may not fully appreciate the potential consequences of unenriched care for their child's cognitive, linguistic, and social development. These parents may be less likely to select a high-quality child care arrangement. Healthcare providers can help parents understand the importance for their child's development of selecting high-quality care by describing how it looks and providing referrals and tips on how to find and select high-quality child care. Families facing socioeconomic challenges accessing high-quality care should be referred to available resources listed previously and in Table 29.3.

When a healthcare provider talks with a parent about a child care arrangement, it also is important to consider the individual child's health concerns, dispositions, and physiologic responses to the environment. Like all environments, child care is experienced differently

Table 29.3 Child Care Information Resources

ORGANIZATION	SPONSOR	WEBSITE AND CONTACT INFORMATION
All Our Kin		https://allourkin.org/
Caring for Our Children: National Resource Center for Health and Safety in Child Care and Early Education (NRC)	American Academy of Pediatrics, the American Public Health Association, and the National Resource Center for Health and Safety in Child Care and Early Education	*Caring for Our Children, National Health and Safety Performance Standards* https://nrckids.org/CFOC
Child Care Aware of America		http://www.childcareaware.org
Healthy Child Care America	American Academy of Pediatrics	http://www.healthychildcare.org
HealthySteps	Zero to Three	https://www.healthysteps.org/
National Association for the Education of Young Children (NAEYC)		http://www.naeyc.org
National Association for Family Child Care		https://nafcc.org/
National Black Child Development Institute		https://www.nbcdi.org/
National Database of Child Care Licensing Regulations	National Center on Early Childhood Quality Assurance (NCECQA) funded by the U.S. Department of Health and Human Services, Administration for Children and Families.	https://childcareta.acf.hhs.gov/licensing
National Indian Child Care Association		https://www.nicca.us/
Office of Child Care (OCC)	U.S. Department of Health and Human Services, Administration for Children & Families	http://www.acf.hhs.gov/programs/occ
Office of Child Care Technical Assistance Network (CCTAN)	U.S. Department of Health and Human Services, Administration for Children & Families, Office of Child Care	https://childcareta.acf.hhs.gov/
UnidosUS		https://www.unidosus.org/
Zero to Three		https://www.zerotothree.org/

by different children. When an environment lacks adequate support for a child's unique needs, healthy development can be compromised. Some children may be more vulnerable to low-quality child care (or particularly responsive to high-quality child care), such as children with difficult or fearful temperaments, especially if their home environments are characterized by more risk factors, such as poverty or high conflict with a parent. Clinicians can help parents determine how to adjust child care arrangements to best meet their child's specific needs (e.g., allergies, eating and sleeping habits, temperament, and stress-regulation capacities).

Children Who Are Expelled from Child Care

A provider may tell a parent that they will not continue to serve a child because of the child's behaviors. Such expulsions are prohibited in some regulated child care settings, such as Head Start and many state-funded prekindergarten programs. In addition to complete termination of a child's child care arrangement (expulsion), children are sometimes told that they cannot attend for a certain number of days (suspension) or have their hours of care reduced, sent home from care early, or excluded in other ways. Regardless of the form of the exclusion or its stated reason, the result is often extremely stressful for the child and family, and often the child care provider too. Indeed, parents may lose their jobs due to the resulting lack of reliable child care or resort to dangerous alternatives, such as leaving the child unattended or in an unsafe arrangement. Healthcare providers should play an important role during child care expulsions by supporting families' efforts to find alternative care, perhaps through a referral to their local child care resource and referral agency, assessing for any potentially contributory underlying developmental or behavioral concerns, and asking parents about the safety of any alternative care arrangements. (See Standard 2.2.0.8 [Preventing Expulsions, Suspensions, and Other Limitations in Services] of Caring for Our Children, as well as the most recent policy statement on this issue by the AAP.)

Supporting Parents Regarding Children's Health

Parents frequently may ask primary care clinicians about sick children, exposure to and prevention of risks in child care, and support for children with special needs in child care. When children are ill, parents should be advised to follow guidelines for inclusion and temporary exclusion (see CFOF, CDC, and state guidelines) (see Table 29.2). Parents may disagree with child care staff about whether a child meets or does not meet the exclusion criteria, as a substantial amount of work absenteeism is due to a child illness, showing the impact of lost child care on parental employment. However, professional guidelines in CFOC state that if the reason for exclusion relates to the child's ability to participate or the caregiver's ability to provide care for the other children, the caregiver should not be required to accept responsibility for the care of the child.

Primary care clinicians should emphasize that parents of infants ensure that child care providers put infants on their backs to sleep to prevent SIDS and follow vaccination schedules, including COVID-19 vaccination as it is available to children of younger ages. Most states require compliance with scheduled vaccinations for children to participate in licensed group child care settings. As of October 2021, only three states (Connecticut, Illinois, New Jersey, and Washington) plus the District of Columbia required child care providers to be vaccinated against COVID-19 and/or participate in regular testing.

Helping Families of Children with Special Needs

Healthcare providers should work with parents and communicate with other service providers and early intervention staff to identify problems, remove access barriers, and coordinate service delivery for children with special needs. They should also encourage involvement of parents and child care providers in developing special education plans such as IEPs and IFSPs. Federal law emphasizes the central role of the family in the development of these plans, and the team writing this plan must consist of the parent or legal guardian and other professionals

that may be involved in the provision of these services, including child care providers. Healthcare providers have an important role to play on these IFSP teams and may attend meetings at the request of the family. Many children with developmental or other special needs that would qualify them for early childhood special education services will present with health concerns, making the healthcare professionals an essential part of adequate early education planning. Additionally, healthcare professionals may support a child's civil rights to access public services such as preschool when their access or ability to participate fully in the program are at risk of limitation due to a diagnosable disability, health, or mental health condition. Often this may require writing a letter stating the nature of the medical condition and the types of accommodations that may improve the child's ability to participate more fully in the range of activities offered by the program. By supporting a child's civil rights under Section 504 of the Rehabilitation Act of 1973 and the Americans with Disabilities Act of 1990, clinicians can and should play an integral role for safeguarding the rights of their patients.

Consulting and Partnering with Child Care Providers

Most state regulations mandate that licensed programs have a formal relationship with a healthcare provider. They can provide consultation to child care providers about measures to protect and maintain the health and safety of children and staff. This may include consultation regarding promoting practices to prevent SIDS; preventing and reducing the spread of communicable disease; reducing allergen, toxin, and parasite exposure; ensuring vaccinations for children and staff; removing environmental hazards; and preventing injuries. In some cases pediatricians have provided ongoing health and mental health consultation to child care programs, such through highly successful programs like HealthySteps (https://www.healthysteps.org/) and "Docs for Tots" (https://docsfortots.org/).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 30

Loss, Separation, and Bereavement

Megan E. McCabe and Janet R. Serwint

All children will experience involuntary separations, whether from illness, death, or other causes, from loved ones at some time in their lives. Relatively brief separations of children from their parents usually produce minor transient effects, but more enduring and frequent separation may cause sequelae. The potential impact of each event must be considered in light of the age, stage of development, and experiences of the child; the particular relationship with the absent person; and the nature of the situation.

SEPARATION AND LOSS

Separations may be from temporary causes, such as vacations, parental job requirements, natural disasters or civil unrest, or parental or sibling illness requiring hospitalization. More long-term separations occur as a result of divorce, placement in foster care, or immigration, whereas permanent separation may occur because of death. The initial reaction of young children to separation of any duration may involve crying, such as a tantrum type, protesting type, and a quieter, sadder type. Children's behavior may appear subdued, withdrawn, fussy, or moody, or they may demonstrate resistance to authority. Specific problems may include poor appetite, behavior issues such as acting against caregiver requests, reluctance to go to bed, sleep problems, or regressive behavior, such as requesting a bottle or bed-wetting. School-age children may experience impaired cognitive functioning and poor performance in school. Some children may repeatedly ask for the absent parent and question when the absent parent will return. The child may go to the window or door or out into the neighborhood to look for the absent parent; a few may even leave home or their place of temporary placement to search for their parents. Other children may not refer to the parental absence at all.

A child's response to reunion may surprise or alarm an unprepared parent. A parent who joyfully returns to the family may be met by wary or cautious children. After a brief interchange of affection, children may seem indifferent to the parent's return. This response may indicate anger at being left or wariness that the event will happen again, or the young child may feel, as a result of **magical thinking** (see Chapter 25), as if the child caused the parent's departure. For example, if the parent who frequently says "Stop it, or you'll give me a headache" is hospitalized, the child may feel at fault and guilty. Because of these feelings, children may seem more closely attached to the present parent than to the absent one, or even to the grandparent or babysitter who cared for them during their parent's absence. Some children, particularly younger ones, may become more clinging and dependent than they were before the separation, while continuing any regressive behavior that occurred during the separation. Such behavior may engage the returned parent more closely and help to reestablish the bond that the child felt was broken. Such reactions are usually transient, and within 1-2 weeks, children will have recovered their usual behavior and equilibrium. Recurrent separations may tend to make children wary and guarded about reestablishing the relationship with the repeatedly absent parent, and these traits may affect other personal relationships. Parents should be advised not to try to modify a child's behavior by threatening to leave.

DIVORCE

More sustained experiences of loss, such as divorce or placement in foster care, can give rise to the same kinds of reactions noted earlier, but they are more intense and possibly more lasting. Currently in the United States, approximately 40% of first marriages end in divorce. Divorce has been found to be associated with negative parent functioning, such as parental depression and feelings of incompetence; negative child behavior, such as noncompliance and whining; and negative parent–child interaction, such as inconsistent discipline, decreased communication, and decreased affection. Greater childhood distress is associated with greater parental distress. Continued parental conflict and loss of contact with the noncustodial parent is common.

Two of the most important factors that contribute to morbidity of the children in a divorce include *parental psychopathology* and *disrupted parenting* before the separation. The year after the divorce is the period when problems are most apparent; these problems tend to dissipate over the next 2 years. Depression may be present up to 5 years later, and educational or occupational decline may occur even 10 years later. It is difficult to sort out all confounding factors. Children may suffer when exposed to parental conflict that continues after divorce and that in some cases may escalate. The degree of *interparental conflict* may be the most important factor associated with child morbidity. A continued relationship with the noncustodial parent when there is minimal interparental conflict is associated with more positive outcomes.

School-age children may become depressed, may seem indifferent, or may be extremely angry. Other children appear to deny or avoid the issue, behaviorally or verbally. Most children cling to the hope that the actual placement or separation is not real and only temporary. The child may experience guilt by feeling that the loss, separation, or placement represents rejection and perhaps punishment for misbehavior. Children may protect a parent and assume guilt, believing that their own "badness" caused the parent to depart. Children who feel that their misbehavior caused their parents to separate may have the fantasy that their own trivial or recurrent behavioral patterns caused their parents to become angry at each other. A child might perceive that outwardly

blaming parents is emotionally risky; parents who discover that a child harbors resentment might punish the child further for these thoughts or feelings. Some children have behavioral or psychosomatic symptoms and unwittingly adopt a "sick" role as a strategy they hope will reunite their parents.

In response to divorce of parents and the subsequent separation and loss, older children and adolescents usually show intense anger. Five years after the breakup, approximately 30% of children report intense unhappiness and dissatisfaction with their life and their reconfigured family; another 30% show clear evidence of a satisfactory adjustment; and the remaining children demonstrate a mixed picture, with good achievement in some areas and faltering achievement in others. After 10 years, approximately 45% do well, but 40% may have academic, social, or emotional problems. As adults, some are reluctant to form intimate relationships, fearful of repeating their parents' experience.

Parental divorce has a moderate long-term negative impact on the adult mental health status of children, even after controlling for changes in economic status and problems before divorce. Good adjustment of children after a divorce is related to ongoing involvement with two psychologically healthy parents who minimize conflict and to the siblings and other relatives who provide a positive support system. Divorcing parents should be encouraged to avoid adversarial processes and to use a trained mediator to resolve disputes if needed. Joint-custody arrangements may reduce ongoing parental conflict, but children in joint custody may feel overburdened by the demands of maintaining a strong presence in two homes.

When the primary care provider is asked about the effects of divorce, parents should be informed that different children may have different reactions, but that the parents' behavior and the way they interact will have a major and long-term effect on the child's adjustment. The continued presence of both parents in the child's life, with minimal interparental conflict, is most beneficial to the child.

MOVE/FAMILY RELOCATION

A significant proportion of the U.S. population changes residence each year. The effects of this movement on children and families are frequently overlooked. For children, the move is essentially involuntary and out of their control. When changes in family structure such as divorce or death precipitate moves, children face the stresses created by both the precipitating events and the move itself. Parental sadness surrounding the move may transmit unhappiness to the children. Children who move lose their old friends, the comfort of a familiar bedroom and house, and their ties to school and community. They not only must sever old relationships but also are faced with developing new ones in new neighborhoods and new schools. Children may enter neighborhoods with different customs and values, and because academic standards and curricula vary among communities, children who have performed well in one school may find themselves struggling in a new one. Frequent moves during the school years are likely to have adverse consequences on social and academic performance.

Migrant children and children who emigrate from other countries present with special circumstances. These children not only need to adjust to a new house, school, and community, but also need to adjust to a new culture and in many cases a new language. Because children have faster language acquisition than adults, they may function as translators for the adults in their families. This powerful position may lead to role reversal and potential conflict within the family. In the evaluation of migrant children and families, it is important to ask about the circumstances of the migration, including legal status, violence or threat of violence, conflict of loyalties, and moral, ethical, and religious differences.

Parents should prepare children well in advance of any move and allow them to express any unhappy feelings or misgivings. Parents should acknowledge their own mixed feelings and agree that they will miss their old home while looking forward to a new one. Visits to the new home in advance are often useful preludes to the actual move. Transient periods of regressive behavior may be noted in preschool children after moving, and these should be understood and accepted. Parents should assist the entry of their children into the new community, and whenever possible, exchanges of letters and visits with old friends should be encouraged.

SEPARATION BECAUSE OF HOSPITALIZATION

Potential challenges for hospitalized children include coping with separation; adapting to the new hospital environment; adjusting to multiple caregivers; seeing very sick children; and sometimes experiencing the disorientation of intensive care, anesthesia, and surgery. To help mitigate potential problems, a preadmission visit to the hospital can help by allowing the child to meet the people who will be offering care and ask questions about what will happen. Parents of children <5-6 years old should room with the child if feasible. Older children may also benefit from parents or other family members staying with them while in the hospital, depending on the severity of their illness. Creative and active recreational or socialization programs with child life specialists, chances to act out feared procedures in play with dolls or mannequins, and liberal visiting hours, including visits from siblings, are all helpful. Sensitive, sympathetic, and accepting attitudes toward children and parents by the hospital staff are very important. Healthcare providers need to remember that parents have the best interest of their children at heart and know their children the best. Whenever possible, school assignments and tutoring for hospitalized children should be available to engage them intellectually and prevent them from falling behind in their scholastic achievements.

The psychologic aspects of illness should be evaluated from the outset, and physicians should act as a model for parents and children by showing interest in a child's feelings, allowing them a venue for expression, and demonstrating that it is possible and appropriate to communicate about discomfort. Continuity of medical personnel may be reassuring to the child and family.

MILITARY FAMILIES

More than 2 million children live in military families in the United States, and approximately 50% of them obtain medical care in the community rather than at a military medical facility. Children whose parents are serving in the military may experience loss and separation in multiple ways. These include frequent relocations, relocation to foreign countries, and duty-related separation from parents. The most impactful experiences have been repeated wartime deployments of parents and the death of parents during military service. All branches of the military have increased their focus on preparing and supporting military families for a service member's deployment to improve family coping. Military families composed of young parents and young children are at risk for child maltreatment in the context of repeated or prolonged deployments.

PARENTAL/SIBLING DEATH

Approximately 5–8% of U.S. children will experience parental death; rates are much higher in parts of the world more directly affected by war, AIDS, and natural disasters. Anticipated deaths from chronic illness may place a significant strain on a family, with frequent bouts of illness, hospitalization, disruption of normal home life, absence of the ill parent, and perhaps more responsibilities placed on the child. Additional strains include changes in daily routines, financial pressures, and the need to cope with aggressive treatment options.

Children can and should continue to be involved with the sick parent or sibling, but they need to be prepared for what they will see in the home or hospital setting. The stresses that a child will face include visualizing the physical deterioration of the family member, helplessness, and emotional lability. Forewarning the child that the family member may demonstrate physical changes, such as appearing thinner or losing hair, will help the child to adjust. These warnings combined with simple yet specific explanations of the need for equipment, such as a nasogastric tube for nutrition, an oxygen mask, or a ventilator, will help lessen the child's fear. Children should be honestly informed of what is happening, in language they can understand, allowing them choices, but with parental involvement in decision-making. They should be encouraged, but not forced, to see their ill family member. Parents who are caring for a dying spouse or child may be too emotionally depleted

to be able to tend to their healthy child's needs or to continue regular routines. Children of a dying parent may suffer the loss of security and belief in the world as a safe place, and the surviving parent may be inclined to impose his or her own need for support and comfort onto the child. However, the well parent and caring relatives must keep in mind that children need to be allowed to remain children, with appropriate support and attention. Sudden, unexpected deaths lead to more anxiety and fear because there is no time for preparation, and explanations for the death can cause uncertainty. Examples of this may be death of a parent due to a motor vehicle crash, homicide or suicide, sudden health-related issue such as a myocardial infarction or stroke, or from infection such as the recent COVID pandemic. Providing support to the child is paramount to allow him or her to express sorrow and grief and to have stability in the child's remaining relationships.

GRIEF AND BEREAVEMENT

Grief is a personal, emotional state of bereavement or an anticipated response to loss, such as a death. Common reactions include sadness, anger, guilt, fear, and at times, relief. The normality of these reactions needs to be emphasized. Most bereaved families remain socially connected and expect that life will return to some new, albeit different, sense of normalcy. The pain and suffering imposed by grief should never be automatically deemed "normal" and thus neglected or ignored. In **uncomplicated grief** reactions, the steadfast concern of the pediatrician can help promote the family's sense of well-being. In more distressing reactions, as seen in traumatic grief of sudden death, the pediatrician may be a major, first-line force in helping children and families address their loss.

Participation in the care of a child with a life-threatening or terminal illness is a profound experience. Parents experience much anxiety and worry during the final stages of their child's life. In one study, 45% of children dying from cancer died in the pediatric intensive care unit, and parents report that 89% of their children suffered "a lot" or "a great deal" during the last month of life. Physicians consistently underreport children's symptoms compared with parents' reports. Better ways are needed to provide care for dying children. Providers need to maintain honest and open communication, provide appropriate pain management, and meet the families' wishes as to the preferred location of the child's death, in some cases in their own home. Inclusion of multiple disciplines, such as hospice, clergy, nursing, pain service, child life specialists, social work, and pet therapy, often helps to support patients and families fully during this difficult experience.

The practice of withholding information from children and parents regarding a child's diagnosis and prognosis has generally been abandoned, because physicians have learned that protecting parents and patients from the seriousness of their child's condition does not alleviate concerns and anxieties. Even very young children may have a real understanding of their illness. Children who have serious diseases and are undergoing aggressive treatment and medication regimens, but who are told by their parents that they are okay, are not reassured. These children understand that something serious is happening to them, and they are often forced to suffer in silence and isolation because the message they have been given by their parents is to not discuss it and to maintain a cheerful demeanor. Children have the right to know their diagnosis and should be informed early in their treatment. The content and depth of the discussion needs to be tailored to the child's personality and developmental level of understanding. Parents have choices as to how to orchestrate the disclosure. Parents may want to be the ones to inform the child themselves, may choose for the pediatric healthcare provider to do so, or may do it in partnership with the pediatrician.

A **death**, especially the death of a family member, is the most difficult loss for a child. Many changes in normal patterns of functioning may occur, including loss of love and support from the deceased family member, a change in income, the possible need to relocate, less emotional support from surviving family members, altering of routines, and a possible change in status from sibling to only child. Relationships between family members may become strained, and children may blame themselves or other family members for the death of a parent or sibling. Bereaved children may exhibit many of the emotions discussed earlier as a result of the loss, in addition to behaviors of withdrawal into their own world, sleep disturbances, nightmares, and symptoms such as headache, abdominal pains, or possibly symptoms similar to those of the family member who has died. Children 3-5 years of age who have experienced a family bereavement may show regressive behaviors such as bed-wetting and thumb sucking. School-age children may exhibit nonspecific symptoms, such as headache, abdominal pain, chest pain, fatigue, and lack of energy. Children and adolescents may also demonstrate enhanced anxiety if these symptoms resemble those of the family member who died. Bereavement may be measured by various published scales (Table 30.1). Behavioral patterns of *persistent complex bereavement disorder* are noted in Table 30.2.

Table 30.1 Example Items from the Three Grief Measurement Tools Assessed Through Cognitive Interviewing

CORE BEREAVEMENT ITEMS (CBI)
Do you experience images of the events surrounding your loved one's death? Do thoughts of your loved one make you feel distressed?
Do you find yourself pining for/yearning for your loved one?
Do reminders of your loved one such as photos, situations, music, places, etc., cause you to feel loneliness?
Do reminders of your loved one such as photos, situations, music, places, etc. cause you to cry about your loved one?
Response options: A lot of the time; Quite a bit of the time; A little bit of the time; Never
GRIEF COGNITIONS QUESTIONNAIRE FOR CHILDREN (GCQ-C)
Since my loved one died, I think of myself as a weak person.
I should have seen to it that he/she would not have died.
I blame myself for not having cared for him/her better than I did. It is not nice toward him/her, when I will begin to feel less sad. My life is worthless since he/she died.
Response options: Hardly ever; Sometimes; Always
INTRUSIVE GRIEF THOUGHTS SCALE (IGTS)
(During the past 4 wk) How often did you think about the death of your loved one?
How often did you find yourself thinking how unfair it is that your loved one died, even though you didn't want to think about it?
How often did you have trouble falling asleep because you were thinking about your loved one's death? How often have you had bad dreams related to your loved one's death?
How often did you have trouble doing things you like because you were worrying about how you and your family will get along?
Response options: Several times a day; About once a day; Once or twice a week; Less than once a week; Not at all

From Taylor TM, Thurman TR, Nogela L. Every time that month comes, I remember: using cognitive interviews to adapt grief measures for use with bereaved adolescents in South Africa. *J Child Adolesc Mental Health.* 2016;28(2):163–174, Table 1, p 166.

The presence of secure and stable adults who can meet the child's needs and who permit discussion about the loss is most important in helping a child to grieve. The pediatrician should help the family understand this necessary presence and encourage the protective functioning of the family unit (Table 30.3). More frequent visits to the healthcare professional may be necessary to address these symptoms and provide reassurance when appropriate. Suggested availability of clergy or mental health providers can provide additional support and strategies to facilitate the transitions after the death.

Death, separation, and loss as a result of **natural catastrophes** and **human-made disasters** have become increasingly common events in children's lives. Exposure to such disasters occurs either directly or indirectly, where the event is experienced through the media. Examples of **indirect exposure** include scenes of earthquakes, hurricanes, tsunamis, tornadoes, and terrorist attacks. Children who experience personal loss in disasters tend to watch more media coverage than children who do not. Children without a personal loss watch as a way of participating in the event and may thus experience repetitive exposure to traumatic scenes and stories. The loss and devastation for a child who personally lives through a disaster are significant; the effect of the simultaneous occurrence of disaster

Table 30.2 Developmental Manifestations of Persistent Complex Bereavement Disorder in Children and Adolescents: Developmental Considerations and Symptom Manifestation in Youth

CRITERION A	**CHILD HAS EXPERIENCED THE DEATH OF A LOVED ONE**
CRITERION B	
B1: Expression of persistent yearning or longing for the deceased	Children have an evolving understanding of the permanence of death, particularly among young children; behavioral expressions of separation distress from surviving caregivers are common, as are reunification fantasies (i.e., wanting to die to be reunited with the parent in the afterlife)
B2: Intense sorrow or emotional pain	Children focus on the more salient immediate physical environment rather than their own internal state; young children often have difficulties expressing inner mood; overt expressions of emotional pain might be interspersed within seemingly normal mood, which can lead to others incorrectly assuming they are not grieving
B3: Preoccupation with the person who died	Children might become distressed when separated from the deceased parent's belongings; it is common for youth to seek out physical connections to their parent, including sleeping in the parent's bed, or wearing their clothing or jewelry
B4: Preoccupation with the circumstances of the death	Young children might reenact the death through play, sometimes with alternate (i.e., counterfactual) actions that depict what children feel they or others could have done to prevent the death; reenacting might also take the form of drawing disturbing scenes or aspects of the death
CRITERION C	
C3: Difficulties related to positive reminiscing about the deceased	Children's ability to reminisce matures with development and is often facilitated by surviving caregivers
C4: Bitterness or anger related to the loss	Youth might show overall irritability, oppositional behavior, and problem behavior in the context of bereavement; externalizing behaviors are often precipitated by changes to the youth's daily routine that are a result of the parent's absence (including others assuming the deceased parent's roles)
C5: Maladaptive self-appraisals in relation to the deceased or the death	Youth, particularly adolescents, might become preoccupied by a perceived accountability (e.g., blaming others or oneself for their parent's death); in young children, this might manifest as magical thinking that their own thoughts or actions caused their parents to die
C6: Excessive avoidance of reminders of the loss	Avoidance might not always be under a child's control (e.g., a parent might choose not to bring the child to the gravesite, which prevents the child from confronting that reminder)
C7: Desire not to live so that they can be with the deceased	Children and adolescents often experience suicidal ideation as a means of reunification fantasies, and their reduced understanding of the complexities of death might exacerbate this mindset among young children; suicidal ideation associated with reunification fantasies might not be accompanied by intent or planning; adolescents might engage in risk-taking behaviors (e.g., substance use, reckless driving)
C8: Difficulty trusting other people since the death	Children might have difficulty establishing relationships with new caregivers, which is often reflective of difficulty with new life circumstances, rather than lack of trust; youth might also display overt anger or oppositional and defiant behaviors toward the surviving or new caregiver
C9: Feeling alone or detached from others since the death	Youth often report feelings of alienation from other peers who have not experienced a similar loss, particularly when reminders of this difference are salient (e.g., seeing other classmates' parents coming to a school event); children and adolescents might conceal their own grief reactions to protect their caregivers from additional distress
C10: Feeling that life is meaningless or empty without the deceased or the belief that they cannot function without the deceased	Developmental regressions (e.g., regression in toileting or language among young children; loss of study skills or emotion regulation in adolescents) are common, as are disruptions to sleep and appetite patterns; adolescents can show a lack of engagement in preparations for adulthood (e.g., applying to jobs)
C11: Confusion about their role in life or a diminished sense of their identity	Youth can express sadness over lost opportunities they were planning to experience with their deceased caregiver (e.g., riding a bicycle, walking down the aisle at their wedding); adolescents might show disorganization, lack of direction, or both

The letters and numbers refer to the symptom within each diagnostic criterion (e.g., criterion B, 4th symptom). Persistent complex bereavement disorder symptom criteria and descriptions have been adapted to the context of parental death.

From Kentor RA, Kaplow JB. Supporting children and adolescents following parental bereavement: guidance for health-care professionals. *Lancet Child Adolesc.* 2020;4:889–898, p 891.

and personal loss complicates the bereavement process as grief reactions become interwoven with posttraumatic stress symptoms (see Chapter 38). After a death resulting from aggressive or traumatic circumstances, access to expert help may be required. Under conditions of threat and fear, children seek proximity to safe, stable, protective figures.

It is important for parents to grieve with their children. Some parents want to protect their children from their grief, so they put on an outwardly brave front or do not talk about the deceased family member or traumatic event. Instead of the desired protective effect, the child receives the message that demonstrating grief or talking about death is wrong, leading the child to feel isolated, grieve privately, or delay grieving. The child may also conclude that the parents did not really care about the deceased because they seem to have forgotten the person so easily or demonstrate no emotion. The parents' efforts to avoid talking about the death may cause the parents to isolate themselves from their children at a time when the children most need them. Children need to know that their parents love them and will continue to protect them. Children need opportunities to talk about their relative's death and associated memories. A surviving sibling may feel guilty simply because he or she survived, especially if the death was the result of an accident that involved both children. Siblings' grief, especially when compounded by feelings of guilt, may manifest as regressive behavior or anger. Parents should be informed of this possibility and encouraged to discuss it with their children.

Table 30.3 Recommendations for Healthcare Professionals for Helping Children After Bereavement

- Help children and families recognize that there is no correct way to grieve and that every child grieves differently
- Help caregivers recognize that child grief is not the same as adult grief, and children express their grief reactions in very different ways
- Help caregivers understand that the circumstances of the death can play a major role in children's grief reactions, and deaths by homicide or suicide might be especially difficult for children (therefore could require more intensive mental healthcare)
- Empower caregivers by explaining they can be instrumental in facilitating adaptive grief in their children by providing empathy, reassurance, and a listening ear, and talking openly about the deceased person with their child
- Help caregivers to use language accessible to children when talking about the death, meaning that they should use simple and straightforward language that is appropriate for the child's developmental stage, and let the child ask questions as opposed to providing a lot of detailed information
- Provide accurate information to children about the cause of death; children can become preoccupied with thoughts about contagion (e.g., "will I catch cancer too?") or worries about the caregiver's level of suffering (e.g., "did it hurt when my dad had a stroke?"), and healthcare professionals can help children understand the circumstances of the death and assist in alleviating some of these concerns
- Never underestimate the importance of simply bearing witness to a child's grief; our society often sends children messages that it is not okay to talk about their own grief, and in allowing them the space to do that, healthcare professionals can help to both normalize and validate their reactions.

From Kentor RA, Kaplow JB. Supporting children and adolescents following parental bereavement: guidance for health-care professionals. *Lancet Child Adolesc.* 2020;4:889–898, p 896.

DEVELOPMENTAL PERSPECTIVE

Children's responses to death reflect the family's current culture, their past heritage, their experiences, and the sociopolitical environment. Personal experience with terminal illness and dying may also facilitate children's comprehension of death and familiarity with mourning. Developmental differences exist in children's efforts to make sense of and master the concept and reality of death and profoundly influence their grief reactions.

Children younger than 3 years have little or no understanding of the concept of death. Despair, separation anxiety, and detachment may occur at the withdrawal of nurturing caretakers. Young children may respond in reaction to observing distress in others, such as a parent or sibling who is crying, withdrawn, or angry. Young children also express signs and symptoms of grief in their emotional states, such as irritability or lethargy, and in severe cases, mutism. If the reaction is severe, failure to thrive may occur.

Preschool children are in the preoperational cognitive stage, in which communication takes place through play and fantasy (see Chapter 25). They do not show well-established cause-and-effect reasoning. They may feel that death is reversible, analogous to someone going away. In attempts to master the finality and permanence of death, preschoolers frequently ask unrelenting, repeated questions about when the person who died will be returning. This makes it difficult for parents, who may become frustrated because they do not understand why the child keeps asking and do not like the constant reminders of the person's death. The primary care provider has a very important role in helping families understand the child's struggle to comprehend death. Preschool children typically express magical explanations of death events, sometimes resulting in guilt and self-blame ("He died because I wouldn't play with him"; "She died because I was mad at her"). Some children have these thoughts but do not express them verbally because of embarrassment or guilt. Parents and primary care providers need to be aware of magical thinking and must reassure preschool children that their thoughts had nothing to do with the outcome. Children of this age are often frightened by prolonged, powerful expressions of grief by others. Children conceptualize events in the context of their own experiential reality, and therefore consider death in terms of sleep, separation, and injury. Young children express grief intermittently and show marked affective shifts over brief periods.

Younger school-age children think concretely, recognize that death is irreversible, but believe it will not happen to them or affect them, and begin to understand biologic processes of the human body ("You'll die if your body stops working"). Information gathered from the media, peers, and parents forms lasting impressions. Consequently, they may ask candid questions about death that adults will have difficulty addressing ("He must have been blown to pieces, huh?").

Children approximately 9 years and older do understand that death is irreversible and that it may involve them or their families. These children tend to experience more anxiety, overt symptoms of depression, and somatic complaints than do younger children. School-age children are often left with anger focused on the loved one, those who could not save the deceased, or those presumed responsible for the death. Contact with the primary care clinician may provide great reassurance, especially for the child with somatic symptoms, and particularly when the death followed a medical illness. School and learning problems may also occur, often linked to difficulty concentrating or preoccupation with the death. Close collaboration with the child's school may provide important diagnostic information and offer opportunities to mobilize intervention or support.

At **12-14 years of age**, children begin to use symbolic thinking, reason abstractly, and analyze hypothetical, or "what if," scenarios systematically. Death and the end of life become concepts rather than events. Teenagers are often ambivalent about dependence and independence and may withdraw emotionally from surviving family members, only to mourn in isolation. Adolescents begin to understand complex physiologic systems in relationship to death. Because they are often egocentric, they may be more concerned about the impact of the death on themselves than about the deceased or other family members. Fascination with dramatic, sensational, or romantic death sometimes occurs and may find expression in *copycat behavior,* such as cluster suicides, as well as *competitive behavior,* to forge emotional links to the deceased person ("He was my best friend"). Somatic expression of grief may revolve around highly complex syndromes such as eating disorders (see Chapter 41) or conversion reactions (Chapter 35), as well as symptoms limited to the more immediate perceptions (stomachaches). *Quality of life* takes on meaning, and the teenager develops a focus on the future. Depression, resentment, mood swings, rage, and risk-taking behaviors can emerge as the adolescent seeks answers to questions of values, safety, evil, and fairness. Alternately, adolescents may seek philosophic or spiritual explanations ("being at peace") to ease their sense of loss. The death of a peer may be especially traumatic.

Families often struggle with how to inform their children of the death of a family member. The answer depends on the child's developmental level. It is best to avoid misleading euphemisms and metaphor. A child who is told that the relative who died "went to sleep" may become frightened of falling asleep, resulting in sleep problems or nightmares. Children can be told that the person is "no longer living" or "no longer moving or feeling." Using examples of pets that have died sometimes can help children gain a more realistic idea of the meaning of death. Parents who have religious beliefs may comfort their children with explanations, such as, "Your sister's soul is in heaven," or "Grandfather is now with God," provided those beliefs are honestly held. If these are not religious beliefs that the parents share, children will sense the insincerity and experience anxiety rather than

the hoped-for reassurance. Children's books about death can provide an important source of information, and when read together, these books may help the parent to find the right words while addressing the child's needs.

ROLE OF THE PEDIATRIC HEALTHCARE PROVIDER IN GRIEF

The pediatric healthcare provider who has had a longitudinal relationship with the family will be an important source of support in the disclosure of bad news and in critical decision-making, during both the dying process and the bereavement period (see Table 30.3). The involvement of the healthcare provider may include being present at the time the diagnosis is disclosed, at the hospital or home at the time of death, being available to the family by phone during the bereavement period, sending a sympathy card, attending the funeral, and scheduling a follow-up visit. Attendance at the funeral sends a strong message that the family and their child are important, respected by the healthcare provider, and can also help the pediatric healthcare provider to grieve and reach personal closure about the death. A family meeting 1-3 months later may be helpful because parents may not be able to formulate their questions at the time of death. This meeting allows the family time to ask questions, share concerns, and review autopsy findings (if one was performed), and allows the healthcare provider to determine how the parents and family are adjusting to the death.

Instead of leaving the family feeling abandoned by a healthcare system that they have counted on, this visit allows them to have continued support. This is even more important when the healthcare provider will be continuing to provide care for surviving siblings. The visit can be used to determine how the mourning process is progressing, detect evidence of marital discord, and evaluate how well surviving siblings are coping. This is also an opportunity to evaluate whether referrals to support groups or mental health providers may be of benefit. Continuing to recognize the child who has died is important. Families appreciate the receipt of a card on their child's birthday, around holidays, or the anniversary of their child's death.

The healthcare provider needs to be an *educator* about disease, death, and grief. The pediatrician can offer a safe environment for the family to talk about painful emotions, express fears, and share memories. By giving families permission to talk and modeling how to address children's concerns, the clinician demystifies death. Parents often request practical help. The healthcare provider can offer families resources, such as literature (both fiction and nonfiction), referrals to therapeutic services, and tools to help them learn about illness, loss, and grief. In this way the physician reinforces the sense that other people understand what they are going through and helps to normalize their distressing emotions. The healthcare provider can also facilitate and demystify the grief process by sharing basic tenets of **grief therapy**. There is no single right or wrong way to grieve. Everyone grieves differently; mothers may grieve differently than fathers, and children mourn differently than adults. Helping family members to respect these differences and reach out to support each other is critical. Grief is not something to "get over," but a lifelong process of adapting, readjusting, and reconnecting.

Parents may need help in knowing what constitutes **normal grieving**. Hearing, seeing, or feeling their child's presence may be a normal response. Vivid memories or dreams may occur. The healthcare provider can help parents to learn that, although their pain and sadness may seem intolerable, other parents have survived similar experiences, and their pain will lessen over time.

Healthcare providers are often asked whether children should attend the **funeral** of a parent or sibling. These rituals allow the family to begin their mourning process. Children >4 years old should be given a choice. If the child chooses to attend, the child should have a designated, trusted adult who is not part of the immediate family and who will stay with the child, offer comfort, and be willing to leave with the child if the experience proves to be overwhelming. If the child chooses not to attend, the child should be offered additional opportunities to share in a ritual, go to the cemetery to view the grave, tell stories about the deceased, or obtain a keepsake object from the deceased family member as a remembrance.

In the era of regionalized tertiary care medicine, the primary care provider and medical home staff may not be informed when one of their patients dies in the hospital. Yet, this communication is critically important. Families assume their primary care provider has been notified and often feel hurt when they do not receive some symbol of condolence. Because of their longitudinal relationship with the family, primary care providers may offer much needed support. There are practical issues, such as the need to cancel previously made appointments and to alert office and nursing staff so that they are prepared should the family return for a follow-up visit or for ongoing health maintenance care with the surviving siblings. Even minor illnesses in the surviving siblings may frighten children. Parents may contribute to this anxiety because their inability to protect the child who has died may leave them with a sense of guilt or helplessness. They may seek medical attention sooner or may be hypervigilant in the care of the siblings because of guilt over the other child's death, concern about their judgment, or the need for continued reassurance. A primary care visit can do much to allay their fears.

Clinicians must remain vigilant for risk factors in each family member and in the family unit as a whole. Primary care providers, who care for families over time, know bereft patients' premorbid functioning and can identify those at current or future risk for physical and psychiatric morbidity. Providers must focus on symptoms that interfere with a patient's normal activities and compromise a child's attainment of developmental tasks. Symptom duration, intensity, and severity, in context with the family's culture, can help identify **complicated grief** reactions in need of therapeutic attention (see Table 30.2). Descriptive words such as "unrelenting," "intense," "intrusive," or "prolonged" should raise concern. Total absence of signs of mourning, specifically an inability to discuss the loss or express sadness, also suggests potential problems.

No specific sign, symptom, or cluster of behaviors identifies the child or family in need of help. Further assessment is indicated if the following occur: (1) persistent somatic or psychosomatic complaints of undetermined origin (headache, stomachache, eating and sleeping disorders, conversion symptoms, symptoms related to the deceased's condition, hypochondriasis); (2) unusual circumstances of death or loss (sudden, violent, or traumatic death; inexplicable, unbelievable, or particularly senseless death; prolonged, complicated illness; unexpected separation); (3) school or work difficulties (declining grades or school performance, social withdrawal, aggression); (4) changes in home or family functioning (multiple family stresses, lack of social support, unavailable or ineffective functioning of caretakers, multiple disruptions in routines, lack of safety); and (5) concerning psychologic factors (persistent guilt or blame, desire to die or talk of suicide, severe separation distress, disturbing hallucinations, self-abuse, risk-taking behaviors, symptoms of trauma such as hyperarousal or severe flashbacks, grief from previous or multiple deaths). Children who are intellectually impaired may require additional support.

TREATMENT

Suggesting interventions outside the natural support network of family and friends can often prove useful to grieving families. Bereavement counseling should be readily offered if needed or requested by the family. Interventions that enhance or promote attachments and security, as well as give the family a means of expressing and understanding death, help to reduce the likelihood of future or prolonged disturbance, especially in children. Collaboration between pediatric and mental health professionals can help determine the timing and appropriateness of services.

Interventions for children and families who are struggling to cope with a loss in the community include gestures such as sending a card or offering food to the relatives of the deceased and teaching children the etiquette of behaviors and rituals around bereavement and mutual support. Performing community service or joining

charitable organizations, such as fund-raising in memory of the deceased, may be useful. In the wake of a disaster, parents and older siblings can give blood or volunteer in search and recovery efforts. When a loss does not involve an actual death (e.g., parental divorce, geographic relocation), empowering the child to join or start a "divorced kids' club" in school or planning a "new kids in town" party may help. Participating in a constructive activity moves the family away from a sense of helplessness and hopelessness and helps them find meaning in their loss.

Psychotherapeutic services may benefit the entire family or individual members. Many support or self-help groups focus on specific types of losses (sudden infant death syndrome, suicide, widow/widowers, AIDS) and provide an opportunity to talk with other people who have experienced similar losses. Family, couple, sibling, or individual counseling may be useful, depending on the nature of the residual coping issues. Combinations of approaches may work well for children or parents with evolving needs. A child may participate in family therapy to deal with the loss of a sibling and use individual treatment to address issues of personal ambivalence and guilt related to the death.

The question of **pharmacologic intervention** for grief reactions often arises. Explaining that medication does not cure grief and often does not reduce the intensity of some symptoms (separation distress) can help. Although medication can blunt reactions, the psychologic work of grieving still must occur. The physician must consider the patient's premorbid psychiatric vulnerability, current level of functioning, other available supports, and the use of additional therapeutic interventions. Medication as a first line of defense rarely proves useful in normal or uncomplicated grief reactions. In certain situations (severe sleep disruption, incapacitating anxiety, intense hyperarousal), an anxiolytic or antidepressant may help to achieve symptom relief and provide the patient with the emotional energy to mourn. Medication used in conjunction with some form of psychotherapy, and in consultation with a psychopharmacologist, has optimal results.

Children who are **refugees** and may have experienced war, violence, or personal torture, while often resilient, may experience posttraumatic stress disorder if exposures were severe or repeated (see Chapters 15.3 and 38). Sequelae such as depression, anxiety, and grief need to be addressed, and mental health therapy is indicated. Cognitive-behavioral therapy, use of journaling and narratives to bear witness to the experiences, and use of translators may be essential.

SPIRITUAL ISSUES

Responding to patients' and families' spiritual beliefs can help in comforting them during family tragedies. Offering to call members of pastoral care teams or their own spiritual leader can provide needed support and can aid in decision-making. Families have found it important to have their beliefs and their need for hope acknowledged in end-of-life care. The majority of patients report welcoming discussions on spirituality, which may help individual patients cope with illness, disease, dying, and death. In addressing spirituality, physicians need to follow certain guidelines, including maintaining respect for the patient's beliefs, following the patient's lead in exploring how spirituality affects the patient's decision-making, acknowledging the limits of their own expertise and role in spirituality, and maintaining their own integrity by not saying or doing anything that violates their own spiritual or religious views. Healthcare providers should not impose their own religious or nonreligious beliefs on patients, but rather should listen respectfully to their patients. By responding to spiritual needs, clinicians may better aid their patients and families in end-of-life care and bereavement and take on the role of healers.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 31
Sleep Medicine

Judith A. Owens and Seyni Gueye-Ndiaye

BASICS OF SLEEP AND CHRONOBIOLOGY

Sleep and wakefulness are a highly complex and intricately regulated neurobiologic system that both influences and is influenced by all physiologic systems in the body, as well as by the environment and sociocultural practices. The concept of **sleep regulation** is based on what is usually referred to as the "two-process model" because it requires the simultaneous operation of two basic, highly coupled processes that govern sleep and wakefulness. The **homeostatic process** ("Process S"), regulates the length and depth of sleep and is thought to be related to the accumulation of adenosine and other sleep-promoting chemicals ("somnogens"), such as cytokines, during prolonged periods of wakefulness. This sleep pressure appears to build more quickly in infants and young children, thus limiting the duration that wakefulness can be sustained during the day and necessitating periods of daytime sleep (i.e., naps). The endogenous **circadian rhythms** ("Process C") influence the internal organization of sleep and the timing and duration of daily sleep–wake cycles and govern predictable patterns of alertness throughout the 24-hour day.

The "master circadian clock" or "circadian pacemaker" that controls sleep–wake patterns, of which melatonin secretion is the principal biomarker, is located in the suprachiasmatic nucleus in the anterior hypothalamus. In addition, "circadian clocks" are present in virtually every cell in the body, which in turn govern the timing of multiple other physiologic systems (e.g., cardiovascular reactivity, hormone levels, renal and pulmonary functions). Because the human circadian clock is slightly longer than 24 hours, intrinsic circadian rhythms must be synchronized or "entrained" to the 24 hour-day cycle by environmental cues called *zeitgebers.* The **dark-light cycle** is the most powerful of the zeitgebers; light signals are transmitted to the suprachiasmatic nucleus via the circadian photoreceptor system within the retina (functionally and anatomically separate from the visual system), which switch the pineal gland's production of the hormone melatonin off (light) or on (dark). Circadian rhythms are also synchronized by other external time cues, such as timing of meals and clock time.

Sleep propensity, the relative level of sleepiness or alertness experienced at any given time during a 24-hour period, is partially determined by the homeostatic *sleep drive*, which in turn depends on the duration and quality of previous sleep and the amount of time awake since the last sleep period. Interacting with this *sleep homeostat* is the 24-hour cyclic pattern or rhythm characterized by clock-dependent periods of maximum sleepiness and maximum alertness. There are two periods of maximum sleepiness, one in the late afternoon (approximately 3:00-5:00 PM) and one toward the end of the night (around 3:00-5:00 AM), and two periods of maximum alertness, one in mid-morning and one in the evening just before the onset of natural sleep, the so-called forbidden zone or second-wind phenomenon, which allows for the maintenance of wakefulness in the face of an accumulated sleep drive.

There are significant health, safety, and performance consequences of failure to meet basic sleep needs, termed *insufficient/inadequate sleep* or **sleep loss**. Sufficient sleep is a biologic imperative, necessary for optimal brain and body functioning. **Slow-wave sleep (SWS)** (i.e., N3, delta, or deep sleep) appears to be the most restorative form of sleep; it is entered relatively quickly after sleep onset, is preserved in the face of reduced total sleep time and increases (rebounds) after a night of restricted sleep. These restorative properties of sleep may be linked to the "glymphatic system," which increases clearance of metabolic waste

products, including β-amyloid, produced by neural activity in the awake brain. **Rapid eye movement (REM)** sleep (stage R or "dream" sleep) appears to be involved in numerous important brain processes, including completion of vital cognitive functions (e.g., consolidation of memory), promoting the plasticity of the central nervous system (CNS), and protecting the brain from injury. Sufficient amounts of these sleep stages are necessary for optimal cognitive functioning and emotional and behavioral self-regulation.

Partial sleep loss (i.e., sleep restriction) on a chronic basis accumulates in a **sleep debt** and over several days produces deficits equivalent to those seen under conditions of one night of total sleep deprivation. If the sleep debt becomes large enough and is not voluntarily repaid by obtaining sufficient recovery sleep, the body may respond by overriding voluntary control of wakefulness. This results in periods of decreased alertness, dozing off, and unplanned napping, recognized as *excessive daytime sleepiness (EDS)*. The sleep-restricted individual may also experience very brief (several seconds) repeated daytime microsleeps, of which the individual may be completely unaware, but which nonetheless may result in significant lapses in attention and vigilance. There is also a relationship between the amount of sleep restriction and performance on cognitive tasks, particularly those requiring sustained attention and higher-level cognitive skills (*executive functions*; see Chapter 49), with a decay in performance correlating with declines in sleep amounts.

It has also been recognized that what may be globally described as "deficient" sleep involves alterations in both amount and *timing* of sleep. Misalignment of intrinsic circadian rhythms with extrinsic societal demands, such a shift work and early school start times, is associated with deficits in cognitive function and self-regulation, increased emotional and behavioral problems and risk-taking behaviors, and negative impacts on health, such as increased risk of cardiovascular disease, obesity, and metabolic dysfunction.

Insufficient quantity of sleep, mistimed sleep, and poor-quality sleep frequently result in EDS and decreased daytime alertness levels. Sleepiness in children may be recognizable as drowsiness, yawning, and other classic "sleepy behaviors" as well as resumption of napping in older children and extending sleep when given the opportunity such as on weekends. If a child can sleep more, they need more sleep. EDS can also manifest as mood disturbance, including irritability, emotional lability, low frustration tolerance and depressed or negative mood; fatigue and daytime lethargy, including increased somatic complaints (headaches, gastrointestinal disturbances); cognitive impairment, including problems with memory, attention, concentration, decision-making, and problem solving; daytime behavior problems, including hyperactivity, impulsivity, and noncompliance; and academic problems, including chronic tardiness related to insufficient sleep and school failure. While sleepiness and fatigue may overlap in their clinical presentation, sleepiness is characterized by the propensity to fall asleep, particularly under conditions of low stimulation (e.g., riding in the car), while fatigue is often described as a state of low energy, decreased motivation, and "exhaustion."

DEVELOPMENTAL CHANGES IN SLEEP

Sleep disturbances, as well as many characteristics of sleep itself, have some distinctly different features in children from sleep and sleep disorders in adults. Changes in sleep architecture and the evolution of sleep patterns and behaviors reflect the physiologic/chronobiologic, developmental, and social/environmental changes that are occurring across childhood. These trends may be summarized as the gradual assumption of more adult sleep patterns as children mature (Figs. 31.1 and 31.2):

1. Sleep is *the* primary activity of the brain during early development; for example, by age 2 years, the average child has spent 9,500 hours (approximately 13 months) asleep vs 8,000 hours awake, and between 2 and 5 years, the time asleep is equal to the time awake.
2. There is a gradual decline in the average 24-hour sleep duration from infancy through adolescence, which involves a decrease in both diurnal and nocturnal sleep amounts. The decline in daytime sleep (scheduled napping) results in termination of naps typically by age 5 years, although there is clearly considerable variability in the age at which children cease napping. There is also a gradual continued decrease in nocturnal sleep amounts into late adolescence; however, adolescents still require 8-10 hours of sleep per night.
3. There is also a decline in the relative percentage of REM sleep from birth (50% of sleep) through early childhood into adulthood (25–30%), and a similar initial predominance of SWS that peaks in early childhood, drops off abruptly after puberty (40–60% decline), and then further decreases over the life span. This SWS preponderance in early life has clinical significance; for example, the high prevalence of partial arousal parasomnias (sleepwalking and sleep terrors) in preschool- and early school–age children is related to the relative increased percentage of SWS in this age-group.
4. The within-sleep *ultradian cycle* lengthens from about 50 minutes in the term infant to 90-110 minutes in the school-age child. This has clinical significance in that typically a brief arousal or awakening occurs during the night at the termination of each ultradian cycle. As the length of the cycles increase, there is a concomitant decrease in the number of these end-of-cycle arousals (night wakings).
5. A gradual shift in the circadian sleep–wake rhythm to a delayed (later) sleep onset and offset time, linked to pubertal stage rather than chronologic age, begins with pubertal onset in middle childhood and accelerates in early to mid-adolescence. This biologic phenomenon often coincides with environmental factors, which further delay bedtime and advance wake time and result in insufficient sleep duration, including exposure to electronic "screens" in the evening, social networking, academic and extracurricular demands, and early (before 8:30 AM) high school start times. In addition, the accumulation of the homeostatic sleep drive across the day slows and both sensitivity and exposure to evening light increases (especially blue spectrum light from electronic devices) during adolescence, conspiring to further delay sleep onset.
6. Increasing irregularity of sleep–wake patterns is typically observed across childhood into adolescence; this is characterized by increasingly larger discrepancies between school night and non–school night bedtimes and wake times, and increased "weekend oversleep" in an attempt to compensate for chronic weekday sleep insufficiency. This phenomenon, often referred to as "social jet lag," not only fails to adequately address performance deficits associated with insufficient sleep on school nights but further exacerbates the normal adolescent phase delay and results in additional circadian disruption (analogous to that experienced by shift workers).

Table 31.1 lists normal developmental changes in children's sleep.

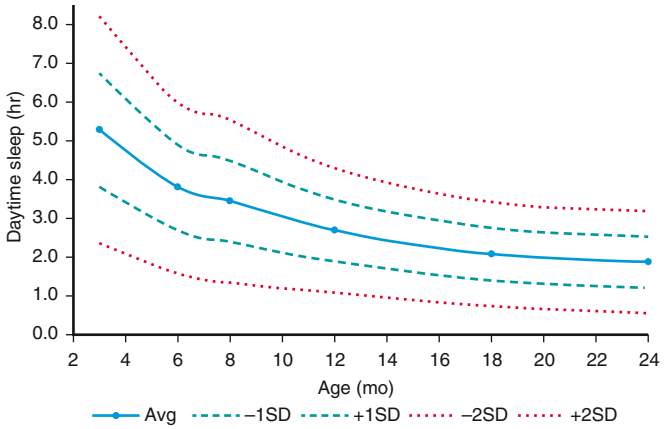

Fig. 31.1 Daytime sleep duration in infants ages 3-24 mo. SD, Standard deviation. *(From Paavonen EJ, Saarenpää-Heikkilä O, Morales-Munoz, I, et al. Normal sleep development in infants: findings from two large birth cohorts.* Sleep Med. *2020;69:145–154. Fig. 2, p 149.)*

COMMON SLEEP DISORDERS

Childhood sleep problems may be conceptualized as resulting from (1) inadequate duration of sleep for age and sleep needs (insufficient sleep quantity); (2) disruption and fragmentation of sleep (poor

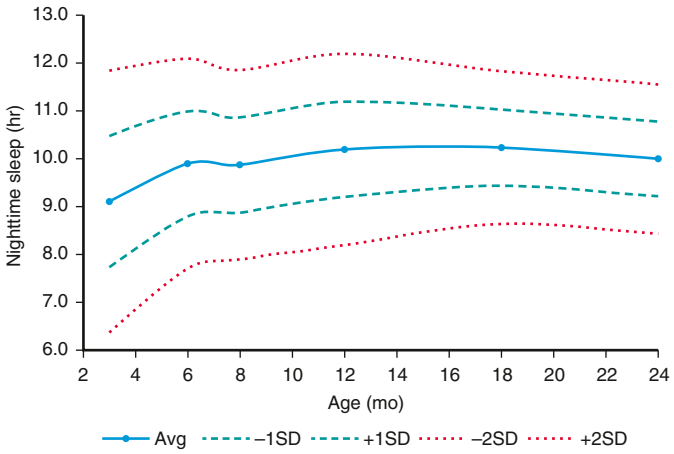

Fig. 31.2 Nighttime sleep duration in infants ages 3-24 mo. SD, Standard deviation. *(From Paavonen EJ, Saarenpää-Heikkilä O, Morales-Munoz, I, et al. Normal sleep development in infants: findings from two large birth cohorts.* Sleep Med. *2020;69:145–154. Fig. 3, p 149.)*

sleep quality) as a result of frequent, repetitive, and brief arousals during sleep; (3) misalignment of sleep–wake timing with circadian rhythms; or (4) CNS-mediated **hypersomnia** (EDS and increased sleep needs). Insufficient sleep is usually the result of difficulty initiating *(delayed sleep onset)* or maintaining sleep *(prolonged night wakings)* but, especially in older children and adolescents, may also represent a conscious lifestyle decision to sacrifice sleep in favor of competing priorities, such as homework and social activities. The underlying causes of delayed sleep onset/prolonged night wakings or sleep fragmentation may in turn be related to primarily behavioral factors (e.g., bedtime resistance resulting in shortened sleep duration) or medical causes (e.g., **obstructive sleep apnea [OSA]** causing frequent, brief arousals).

Certain pediatric populations are relatively more vulnerable to acute or chronic sleep problems. These include children with chronic illnesses or pain conditions (e.g., cystic fibrosis, asthma, idiopathic juvenile arthritis) and acute illnesses (e.g., otitis media); children taking stimulants (e.g., psychostimulants, caffeine), sleep-disrupting medications (e.g., corticosteroids), or daytime-sedating medications (some anticonvulsants, α-agonists); hospitalized children; and children with a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, and anxiety disorders. Children with neurodevelopmental disorders such as autism, intellectual disability, blindness, and some chromosomal syndromes (e.g., Smith-Magenis, fragile X) have especially high rates of sleep disturbances for a wide variety of reasons. They may have comorbid medical issues or may be taking sleep-disrupting medications, may be more prone to nocturnal seizures, may be less easily entrained by environmental cues and thus more vulnerable to circadian disruption, and are more likely to have psychiatric and behavioral comorbidities that further predispose them to disrupted sleep. Children from low socioeconomic households or minoritized racial and ethnic groups, as well as children in alternative care such as foster placement, are more likely to experience, are less likely to be diagnosed and treated, and are more vulnerable to the negative impact of sleep disorders resulting in significant sleep health disparities.

Insomnia of Childhood

Insomnia is defined as difficulty initiating and/or maintaining sleep that occurs despite age-appropriate time and opportunity for sleep and results in some degree of impairment in daytime functioning for the child and/or family (ranging from fatigue, irritability, lack of energy, and mild cognitive impairment to effects on mood, school performance, and quality of life). Insomnia may be of a short-term and transient nature (usually related to an acute event) or may be characterized as long-term and chronic. Insomnia is a set of *symptoms* with many possible etiologies (e.g., pain, medication, medical/psychiatric conditions, learned behaviors). As with many behavioral issues in children, insomnia is often primarily defined by parental concerns rather than by objective criteria and therefore should be viewed in the context of family (maternal depression, stress), child (temperament, developmental level), and environmental (cultural practices, sleeping space) considerations.

While current terminology (*Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, 2015; *International Classification of Sleep Disorders,* 3rd edition, 2014) groups most types of insomnia in both children and adults under a single category of Chronic Insomnia Disorder, the descriptor of Behavioral Insomnia of Childhood and its subtypes (Sleep Onset Association and Limit Setting) remains a useful construct in clinical practice, particularly for young children (0-5 years). One of the most common presentations of insomnia found in infants and toddlers is the **sleep-onset association type.** In this situation the child learns to fall asleep only under certain conditions or associations, which typically require parental presence, such as being rocked or fed, and does not develop the ability to self-soothe. During the night, when the child experiences the type of brief arousal that normally occurs at the end of an ultradian sleep cycle or awakens for other reasons, the child is not able to get back to sleep without those same associations being present. The infant then "signals" the parent by crying (or coming into the parents' bedroom if the child is ambulatory) until the necessary associations are provided. The presenting complaint is typically one of prolonged night waking requiring caregiver intervention and resulting in insufficient sleep (for both child and caregiver).

Management of **night wakings** should include establishment of a set sleep schedule and bedtime routine and implementation of a behavioral program. The treatment approach typically involves a program of rapid withdrawal (extinction) or more gradual withdrawal (graduated extinction) of parental assistance at sleep onset and during the night. **Extinction** ("cry it out") involves putting the child to bed at a designated bedtime, "drowsy but awake," to maximize sleep propensity and then systematically ignoring any protests by the child until a set time the next morning. Although it has considerable empirical support, extinction is often not an acceptable choice for families. **Graduated extinction** (aka "check-ins," "Ferber method," "sleep training") involves gradually weaning the child from dependence on parental presence; typically, the parent leaves the room at "lights out" and then returns or "checks" periodically at fixed or successively longer intervals during the sleep–wake transition to provide *brief* reassurance until the child falls asleep. The exact interval between checks is generally determined by the parents' tolerance for crying and the child's temperament; the goal is to allow enough time between checks for the child to fall asleep independently while avoiding extended time intervals that result in continued escalation of protest behaviors such as screaming and

Table 31.1 Normal Developmental Changes in Children's Sleep

AGE CATEGORY	SLEEP DURATION* AND SLEEP PATTERNS	ADDITIONAL SLEEP ISSUES	SLEEP DISORDERS

Newborn (0-2 mo)	• Total sleep: 10-19 hr per 24 hr (average, 13-14.5 hr), may be higher in premature babies.
	• Bottle-fed babies generally sleep for longer periods (2-5 hr bouts) than breastfed babies (1-3 hr).
	• Sleep periods are separated by 1-2 hr awake.
	• No established nocturnal-diurnal pattern in first few wk; sleep is evenly distributed throughout the day and night, averaging 8.5 hr at night and 5.75 hr during day.
		• American Academy of Pediatrics issued a revised recommendation in 2016 advocating against bed-sharing in the first year of life, instead encouraging proximate but separate sleeping surfaces for mother and infant for at least the first 6 mo and preferably first year of life.
		• Safe sleep practices for infants:
		  • Place baby on his or her back to sleep at night and during nap times.
		  • Place baby on a firm mattress with well-fitting sheet in safety-approved crib.
		  • Do not use pillows or comforters.
		  • Standards require crib bars to be no farther apart than 2 3/8 in.
		  • Make sure baby's face and head stay uncovered and clear of blankets and other coverings during sleep.
			• Most sleep issues perceived as problematic at this stage represent a discrepancy between parental expectations and developmentally appropriate sleep behaviors.
			• Newborns who are extremely fussy and persistently difficult to console, as noted by parents, are more likely to have underlying medical issues such as colic, gastroesophageal reflux, and formula intolerance.

Infant (2-12 mo)	• Recommended sleep duration (4-12 mo) is 12-16 hr (note that there is great individual variability in sleep times during infancy).	• Sleep regulation or self-soothing involves the infant's ability to negotiate the sleep–wake transition, both at sleep onset and following normal awakenings throughout the night. The capacity to self-soothe begins to develop in the first 12 wk of life and is a reflection of both neurodevelopmental maturation and learning. • Sleep consolidation, or "sleeping through the night," is usually defined by parents as a continuous sleep episode without the need for parental intervention (e.g., feeding, soothing) from the child's bedtime through the early morning. Infants develop the ability to consolidate sleep between 6 wk and 3 mo.	• Behavioral insomnia of childhood; sleep-onset association type • Sleep-related rhythmic movements (head banging, body rocking)
Toddler (1-2 yr)	• Recommended sleep amount is 11-14 hr (including naps). • Naps decrease from two to one nap at average age of 18 mo.	• Cognitive, motor, social, and language developmental issues impact sleep. • Nighttime fears develop; transitional objects and bedtime routines are important.	• Behavioral insomnia of childhood, sleep-onset association type • Behavioral insomnia of childhood, limit-setting type
Preschool (3-5 yr)	• Recommended sleep amount is 10-13 hr (including naps). • Overall, 26% of 4 yr olds and just 15% of 5 yr olds nap.	• Persistent cosleeping tends to be highly associated with sleep problems in this age-group. • Sleep problems may become chronic.	• Behavioral insomnia of childhood, limit-setting type • Sleepwalking, sleep terrors, nighttime fears/nightmares, obstructive sleep apnea syndrome
Middle childhood (6-12 yr)	• Recommended sleep amount is 9-12 hr.	• School and behavior problems may be related to sleep problems. • Media and electronics, such as television, computer, video games, and the internet, increasingly compete for sleep time. • Irregularity of sleep–wake schedules reflects increasing discrepancy between school and non–school night bedtimes and wake times.	• Nightmares • Obstructive sleep apnea syndrome • Insufficient sleep
Adolescence (13-18 yr)	• Recommended sleep amount is 8-10 hr. • Later bedtimes; increased discrepancy between sleep patterns on weekdays and weekends	• Puberty-mediated phase delay (later sleep onset and wake times), relative to sleep–wake cycles in middle childhood • Earlier required wake times • Environmental competing priorities for sleep	• Insufficient sleep • Delayed sleep–wake phase disorder • Narcolepsy • Restless legs syndrome/ periodic limb movement disorder

*All recommended sleep amounts from Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2016;12:785–786.

gagging/vomiting. This allows the infant or child to develop the skills necessary for self-soothing at bedtime and also during the night. Sleep training is typically not instituted until about 6 months of age, but the practice of putting the infant to sleep "drowsy but awake" starting at 3-4 months to encourage self-soothing may avoid the need for later intervention. In older infants and young children, the introduction of more appropriate sleep associations that will be readily available to the child during the night (transitional

objects, such as a blanket or toy), in addition to positive reinforcement (stickers for remaining in bed), is often beneficial. As healthy, normally growing full-term infants no longer need night feedings from a nutritional standpoint, if the child has become habituated to awaken for nighttime feedings (learned hunger), these feedings should be eliminated (either "cold turkey" or by gradually decreasing volume and the milk:water ratio). Parents must be consistent in applying behavioral interventions to avoid inadvertent, intermittent reinforcement of night wakings. They should also be forewarned that crying behavior often temporarily escalates at the beginning of treatment *(postextinction burst)*.

Bedtime problems, including stalling and refusing to go to bed, are more common in preschool-age and older children. This type of insomnia is frequently related to inadequate **limit setting** at bedtime such as an inability or unwillingness to set consistent bedtime rules, and enforce a regular bedtime. In some cases, caregivers have adopted an inconsistent approach to night wakings that involves intermittently allowing the child to share their bed. This type of sleep problem may be associated with parental difficulty in setting limits or managing behavior in general and may be exacerbated by a child's tendency to engage in oppositional behavior. In some cases, the child's resistance at bedtime is the result of an underlying problem in falling asleep that is caused by other factors (medical conditions such as asthma or medication use; a sleep disorder such as restless legs syndrome; anxiety) or a mismatch between the child's intrinsic circadian rhythm ("night owl") and parental expectations regarding an "appropriate" bedtime.

Successful treatment of limit-setting sleep problems generally involves a combination of parent education regarding appropriate limit setting, decreased parental attention for bedtime-delaying behavior, establishment of bedtime routines, and positive reinforcement (sticker charts) for appropriate behavior at bedtime and during the night. For problematic night wakings, it is essential for caregivers to have a consistent response (e.g., returning the child to their bedroom after *every* night waking). Other behavioral management strategies that have empirical support include **bedtime fading**, or temporarily setting the bedtime closer to the actual sleep-onset time and then gradually advancing the bedtime to an earlier target bedtime. Older children may benefit from being taught relaxation techniques to help themselves fall asleep or back to sleep more readily. Following the principles of healthy sleep practices for children is essential (Table 31.2).

A third type of childhood insomnia is related to a mismatch between parental expectations regarding time in bed and the child's intrinsic sleep needs. If, as illustrated in Figure 31.3, a child's typical sleep time is 10 hours but the "sleep window" is set for 12 hours (7 PM to 7 AM), the result is likely to be a prolonged sleep onset of 2 hours, an extended period of wakefulness during the night, or early morning waking (or a combination); these periods are usually characterized by "normal" wakefulness in the child that is not accompanied by excessive distress. This situation is important to recognize because the solution (reducing the time in bed to actual sleep time) is typically simple and effective.

Another form of insomnia that is more common in older children and adolescents has often been referred to as *psychophysiologic, primary,* or *learned* insomnia. **Primary insomnia** occurs mainly in adolescents and is characterized by a combination of learned sleep-preventing associations and heightened physiologic arousal resulting in a complaint of sleeplessness and decreased daytime functioning. A hallmark of primary insomnia is excessive worry about sleep and an exaggerated concern of the potential daytime consequences. The physiologic arousal can be in the form of cognitive **hypervigilance**, such as "racing" thoughts; in many individuals with insomnia, an increased baseline level of arousal is further intensified by this secondary anxiety about sleeplessness. Treatment usually involves educating the adolescent about the principles of healthy sleep practices (Table 31.3), institution of a consistent sleep–wake schedule, avoidance of daytime napping, instructions to use the bed for sleep only and to get out of bed if unable to fall asleep *(stimulus control)*, restricting time in bed to the actual time asleep *(sleep restriction)*, addressing maladaptive cognitions about sleep, and teaching relaxation techniques to reduce anxiety (cognitive behavioral therapy for insomnia [CBT-I]).

Table 31.2 Basic Principles of Healthy Sleep for Children

1. **Have a set bedtime and bedtime routine** for your child.
2. **Bedtime and wake-up time should be about the same time on school nights and non–school nights.** There should not be more than about 1 hr difference from one day to another.
3. **Make the hour before bed shared quiet time.** Avoid high-energy activities, such as rough play, and stimulating activities, such as watching television or playing computer games, just before bed.
4. **Don't send your child to bed hungry.** A *light* snack (e.g., milk and cookies) before bed is a good idea. Heavy meals within 1 hr or 2 of bedtime, however, may interfere with sleep.
5. **Avoid products containing caffeine for at least several hours before bedtime.** These include caffeinated sodas, coffee, tea, and chocolate.
6. **Make sure your child spends time outside every day,** whenever possible, and is involved in regular exercise.
7. **Keep your child's bedroom quiet and dark.** A low-level night light is acceptable for children who find completely dark rooms frightening.
8. **Keep your child's bedroom at a comfortable temperature during the night (<24°C [75°F]).**
9. **Don't use your child's bedroom for time-out or punishment.**
10. **Keep the television out of your child's bedroom.** Children can easily develop the bad habit of "needing" the television to fall asleep. It is also much more difficult to control your child's viewing if the set is in the bedroom.

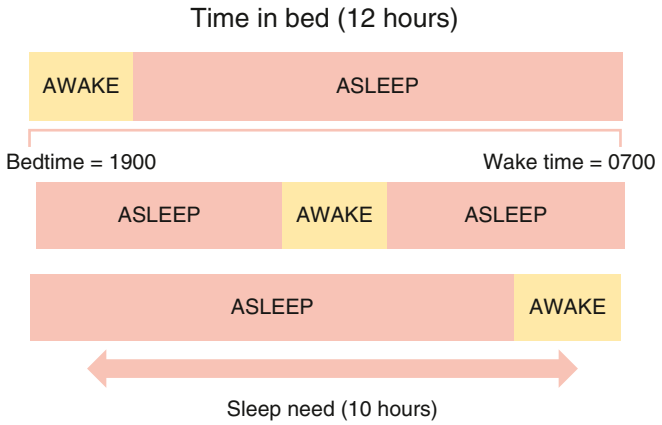

Fig. 31.3 Mismatch between sleep needs/duration and time in bed, resulting in insomnia.

The keys to successful behavioral sleep interventions involve forming an alliance with the family, negotiating tailored solutions that are more likely to be effective if families can be successful in implementing them, and setting appropriate agreed-on treatment goals with planned follow-up. Behavioral treatments for insomnia, even in young children, appear to be highly effective and well tolerated. Several studies have failed to demonstrate long-term negative effects of behavioral strategies such as "sleep training" on parent–child relationships and attachment, psychosocial-emotional functioning, and chronic stress. It should also be emphasized that, as in adults, behavioral interventions are the *first-line treatment* for insomnia in children, and in general, hypnotic medications or supplements such as melatonin are infrequently needed and should only be used as an adjunct to behavioral therapy to treat insomnia in typically developing and healthy children. If cognitive behavior therapy and sleep hygiene practices are ineffective in children with autism spectrum disorders or ADHD, melatonin may be an additional effective therapy.

Table 31.3 Basic Principles of Healthy Sleep for Adolescents

1. **Wake up and go to bed at about the same time** every night. Bedtime and wake-up time should not differ from school to non–school nights by more than approximately 1 hr.
2. **Avoid sleeping in on weekends** to "catch up" on sleep. This makes it more likely that you will have problems falling asleep.
3. If you take **naps**, they should be **short** (no more than 1 hr) and **scheduled in the early to mid-afternoon.** However, if you have a problem with falling asleep at night, napping during the day may make it worse and should be avoided.
4. **Spend time outside** every day. Exposure to sunlight helps to keep your body's internal clock on track.
5. **Exercise regularly.** Exercise may help you fall asleep and sleep more deeply.
6. **Use your bed for sleeping only.** Don't study, read, listen to music, or watch television on your bed.
7. **Make the 30-60 min before bedtime a quiet or wind-down time.** Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don't study, watch exciting/scary movies, exercise, or get involved in "energizing" activities just before bed.
8. Eat regular meals, and **don't go to bed hungry.** A light snack before bed is a good idea; eating a full meal within 1 hr before bed is not.
9. **Avoid** eating or drinking products containing **caffeine** from dinnertime to bedtime. These include caffeinated sodas, coffee, tea, and chocolate.
10. **Do not use alcohol.** Alcohol disrupts sleep and may cause you to awaken throughout the night.
11. Smoking (e.g., cigarettes) disturbs sleep. Although you should not smoke at all, if you do, **do not smoke at least 2 hr before bed.**
12. **Do not use sleeping pills, melatonin, or other nonprescription sleep aids** to help you sleep unless specifically recommended by your doctor. These can be dangerous, and the sleep problems often return when you stop taking the medicine.

Obstructive Sleep Apnea

Sleep disordered breathing (SDB) in children encompasses a broad spectrum of respiratory disorders that occur exclusively in sleep or that are exacerbated by sleep, including primary snoring and upper airway resistance syndrome, as well as apnea of prematurity (see Chapter 125) and central apnea (see Chapter 468.2). OSA, the most important clinical entity within the SDB spectrum, is characterized by repeated episodes of prolonged upper airway obstruction during sleep despite continued or increased respiratory effort, resulting in complete *(apnea)* or partial (*hypopnea*; ≥30% reduction in airflow accompanied by ≥3% O_2 desaturation and/or arousal) cessation of airflow at the nose and/or mouth, as well as disrupted sleep. Both intermittent hypoxia and the multiple arousals resulting from these obstructive events likely contribute to significant metabolic, cardiovascular, and neurocognitive-neurobehavioral morbidity.

Primary snoring is defined as snoring without associated ventilatory abnormalities on overnight **polysomnogram (PSG)** (e.g., no apneas or hypopneas, hypoxemia, hypercapnia) or respiratory-related arousals and is a manifestation of the vibrations of the oropharyngeal soft tissue walls that occur when an individual attempts to breathe against increased upper airway resistance during sleep. Although generally considered nonpathologic, primary snoring in children may still be associated with subtle breathing abnormalities during sleep, including evidence of increased respiratory effort, which in turn may be associated with adverse neurodevelopmental outcomes that may be similar to those associated with OSA.

Etiology

OSA results from an anatomically or functionally narrowed upper airway; this typically involves some combination of decreased upper airway patency (upper airway obstruction and/or decreased upper airway diameter), increased upper airway collapsibility (reduced pharyngeal muscle tone), and decreased drive to breathe in the face of reduced upper airway patency (reduced central ventilatory drive) (Table 31.4). Upper airway obstruction varies in degree and level (i.e., nose, nasopharynx/oropharynx, hypopharynx) and is most frequently caused by adenotonsillar hypertrophy, although tonsillar size does not necessarily correlate with degree of obstruction, especially in older children. Other causes of airway obstruction include allergies associated with chronic rhinitis or nasal obstruction; craniofacial abnormalities, including hypoplasia or displacement of the maxilla and mandible; gastroesophageal reflux with resulting pharyngeal reactive edema (see Chapter 369); nasal septal deviation (Chapter 425); and velopharyngeal flap cleft palate repair. Reduced upper airway tone may result from neuromuscular diseases, including hypotonic cerebral palsy and muscular dystrophies (see Chapter 649), or hypothyroidism (Chapter 603). Reduced central ventilatory drive may be present in some children with Arnold-Chiari malformation (see Chapter 631.09); rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (Chapter 65); and meningomyelocele (Chapter 631.04). In other situations, the etiology is mixed; individuals with Down syndrome (see Chapter 57), because of their facial anatomy, hypotonia, macroglossia, and central adiposity, as well as the increased incidence of hypothyroidism, are at particularly high risk for OSA, with some estimates of prevalence as high as 70%.

Table 31.4 Anatomic Factors That Predispose to Obstructive Sleep Apnea Syndrome and Hypoventilation in Children

NOSE
Anterior nasal stenosis
Choanal stenosis/atresia
Deviated nasal septum
Seasonal or perennial rhinitis
Nasal polyps, foreign body, hematoma, mass lesion
NASOPHARYNGEAL AND OROPHARYNGEAL
Adenotonsillar hypertrophy
Macroglossia
Cystic hygroma
Velopharyngeal flap repair
Cleft palate repair
Pharyngeal mass lesion
CRANIOFACIAL
Micrognathia/retrognathia
Midface hypoplasia (e.g., trisomy 21, Crouzon disease, Apert syndrome)
Mandibular hypoplasia (Pierre Robin, Treacher Collins, Cornelia de Lange syndromes)
Craniofacial trauma
Skeletal and storage diseases
Achondroplasia
Storage diseases (e.g., glycogen; Hunter, Hurler syndromes)

Although children with OSA may be of normal weight, a large percentage are overweight or obese, and many of these children are school-age or younger. There is a significant correlation between weight and SDB (e.g., habitual snoring, OSA, sleep-related hypoventilation). Although adenotonsillar hypertrophy also plays an important etiologic role in overweight/obese children with OSA, mechanical factors related to an increase in the amount of adipose tissue in the throat (pharyngeal fat pads), neck (increased neck circumference), and chest wall and abdomen can increase upper airway resistance, worsen gas exchange, and increase the work of breathing, particularly in the supine position and during REM sleep. A component of blunted central ventilatory drive in response to hypoxia/hypercapnia and hypoventilation may occur as well (see Chapter 468.2), particularly in children with morbid or syndrome-based (e.g., Prader-Willi) obesity. Overweight and obese children and adolescents are at particularly high risk for

metabolic and cardiovascular complications of SDB, such as insulin resistance and systemic hypertension. Morbidly obese children are also at increased risk for postoperative complications as well as residual OSA after adenotonsillectomy.

Epidemiology

Overall prevalence of parent-reported snoring in the pediatric population is approximately 8%; "always" snoring is reported in 1.5–6%, and "often" snoring in 3–15%. When defined by parent-reported symptoms, the prevalence of OSA is 4–11%. The prevalence of pediatric OSA as documented by overnight sleep studies using ventilatory monitoring procedures (e.g., in-lab polysomnography, home studies) is 1–4% overall, with a reported range of 0.1–13%. Prevalence is also affected by the demographic characteristics such as age (increased prevalence between 2 and 8 years), gender (more common in males, especially after puberty), ethnicity (increased prevalence in African American and Asian children), history of prematurity, and family history of OSA.

Pathogenesis

The upregulation of inflammatory pathways, as indicated by an increase in peripheral markers of inflammation (e.g., C-reactive protein, interleukins), appears to be linked to metabolic dysfunction (e.g., insulin resistance, dyslipidemia, alterations in neurohormone levels such as leptin) in both obese and nonobese children with OSA. Systemic inflammation and arousal-mediated increases in sympathetic autonomic nervous system activity with altered vasomotor tone may be key contributors to increased cardiovascular risk due to alterations in vascular endothelium in both adults and children with OSA. Other potential mechanisms that may mediate cardiovascular sequelae in adults and children with OSA include elevated systemic blood pressure and ventricular dysfunction. Mechanical stress on the upper airway induced by chronic snoring may also result in both local mucosal inflammation of adenotonsillar tissues and subsequent upregulation of inflammatory molecules, most notably leukotrienes.

One of the primary mechanisms by which OSA is believed to exert negative influences on cognitive function appears to involve repeated episodic arousals from sleep leading to sleep fragmentation and sleepiness. Equally important, intermittent hypoxia may lead directly to systemic inflammatory vascular changes in the brain. Levels of inflammatory markers such as C-reactive protein and interleukin-6 are elevated in children with OSA and are also associated with cognitive dysfunction.

Clinical Manifestations

The clinical manifestations of OSA may be divided into sleep-related and daytime symptoms. The most common nocturnal manifestations of OSA in children and adolescents are loud, frequent, and disruptive snoring; breathing pauses; choking or gasping arousals; restless sleep; and nocturnal diaphoresis. Many children who snore do not have OSA, but few children with OSA do not snore (caregivers may not be aware of snoring in older children and adolescents). Children, like adults, tend to have more frequent and more severe obstructive events in REM sleep and when sleeping in the supine position. Children with OSA may adopt unusual sleeping positions, keeping their necks hyperextended to maintain airway patency. Frequent arousals associated with obstruction may result in nocturnal awakenings but are more likely to cause fragmented sleep.

Daytime symptoms of OSA include mouth breathing and dry mouth, chronic nasal congestion or rhinorrhea, hyponasal speech, morning headaches, difficulty swallowing, and poor appetite. Children with OSA may have *secondary enuresis,* postulated to result from the disruption of the normal nocturnal pattern of atrial natriuretic peptide secretion by changes in intrathoracic pressure associated with OSA. Partial arousal parasomnias (sleepwalking and sleep terrors) may occur more frequently in children with OSA, related to the frequent associated arousals and an increased percentage of SWS.

One of the most important but frequently overlooked sequelae of OSA in children is the effect on mood, behavior, learning, and academic functioning. The neurobehavioral consequences of OSA in children include daytime sleepiness with drowsiness, difficulty in morning waking, and unplanned napping or dozing off during activities, although evidence of frank hypersomnolence tends to be less common in children compared to adults with OSA (except in very obese children or those with severe disease). Mood changes include increased irritability, mood instability and emotional dysregulation, low frustration tolerance, and depression or anxiety. Behavioral issues include both "internalizing" (i.e., increased somatic complaints and social withdrawal) and "externalizing" behaviors, including aggression, impulsivity, hyperactivity, oppositional behavior, and conduct problems. There is substantial overlap between the clinical impairments associated with OSA and the diagnostic criteria for ADHD, including inattention, poor concentration, and distractibility (see Chapter 50).

Many of the studies that have looked at changes in behavior and neuropsychologic functioning in children after treatment (usually adenotonsillectomy) for OSA have found significant improvement in outcomes, both short term and long term, including daytime sleepiness, mood, behavior, academics, and quality of life. However, most studies failed to find a dose-dependent relationship between OSA in children and specific neurobehavioral-neurocognitive deficits, suggesting that other factors may influence neurocognitive outcomes, including individual genetic susceptibility, racial/ethnic background, environmental influences (e.g., passive smoking exposure), and comorbid conditions, such as obesity, shortened sleep duration, and other sleep disorders.

Diagnosis

The 2012 revised American Academy of Pediatrics clinical practice guidelines provide excellent information for the evaluation and management of uncomplicated childhood OSA (Table 31.5). No physical examination findings are truly pathognomonic for OSA, and most healthy children with OSA appear normal; however, certain physical examination findings may suggest OSA. Growth parameters may be abnormal (obesity, or less frequently, failure to thrive), and there may be evidence of chronic nasal obstruction (hyponasal speech, mouth breathing, septal deviation) and signs of atopic disease (i.e., "allergic shiners"). Oropharyngeal examination may reveal enlarged tonsils, excess soft tissue in the posterior pharynx, and a narrowed posterior pharyngeal space, as well as craniofacial features associated with an increased risk of obstruction including "adenoidal facies" with open mouth posture and long/asymmetric face, midface hypoplasia, retrognathia and micrognathia, forward head posture (best appreciated by inspection of the frontal and lateral facial profile), and teeth crowding, narrow arched palate, and tongue tie (short frenulum). In severe cases the child may have evidence of pulmonary hypertension, right-sided heart failure, and cor pulmonale; systemic hypertension may occur, especially in obese children.

Because no combination of clinical history and physical findings can accurately predict which children with snoring have OSA, the gold standard for diagnosing OSA remains an in-lab overnight **PSG**. Overnight PSG is a technician-supervised, monitored study that documents physiologic variables during sleep; sleep staging, arousal measurement, cardiovascular parameters, and body movements (electroencephalography [EEG], electrooculography, chin and leg electromyography [EMG], electrocardiogram, body position sensors, and video recording), and a combination of breathing monitors (oronasal thermal sensor and nasal air pressure transducer for airflow), chest/abdominal monitors (e.g., inductance plethysmography for respiratory effort, pulse oximeter for O_2 saturation, end-tidal or transcutaneous CO_2 for CO_2 retention, snore microphone). The PSG parameter most often used in evaluating for sleep-disordered breathing is the **apnea-hypopnea index (AHI)**, which indicates the number of apneic and hypopneic (both obstructive and central) events per hour of sleep. There are no universally accepted PSG normal reference values or parameters for diagnosing OSA in children, and it is still unclear which parameters best predict morbidity. Normal preschool- and school-age children generally have a total AHI <1.5 (obstructive AHI <1), and this is the most widely used cutoff value for OSA in children ≤12 years old; in older adolescents the adult cutoff of an AHI ≥5 is generally used. When AHI is between one and five obstructive events per hour, assessment of

Table 31.5 American Academy of Pediatrics Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome

Key Action Statement 1: Screening for OSA
As part of routine health maintenance visits, clinicians should inquire whether the child or adolescent snores. If the answer is affirmative or if a child or adolescent presents with signs or symptoms of OSA, clinicians should perform a more focused evaluation. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 2A: Polysomnography
If a child or adolescent snores on a regular basis and has any of the complaints or findings of OSA, clinicians should either (1) obtain a polysomnogram (Evidence Quality: Grade A; Recommendation Strength: Recommendation) *or* (2) refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation. (Evidence Quality: Grade D; Recommendation Strength: Option.)
Key Action Statement 2B: Alternative Testing
If polysomnography is not available, clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography. (Evidence Quality: Grade C; Recommendation Strength: Option.)
Key Action Statement 3: Adenotonsillectomy
If a child is determined to have OSA, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery, the clinician should recommend adenotonsillectomy as the first line of treatment. If the child has OSA but does not have adenotonsillar hypertrophy, other treatment should be considered (see Key Action Statement 6). Clinical judgment is required to determine the benefits of adenotonsillectomy compared with other treatments in obese children with varying degrees of adenotonsillar hypertrophy. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 4: High-Risk Patients Undergoing Adenotonsillectomy
Clinicians should monitor high-risk patients undergoing adenotonsillectomy as inpatients postoperatively. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5: Reevaluation
Clinicians should clinically reassess all patients with OSA for persisting signs and symptoms after therapy to determine whether further treatment is required. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5B: Reevaluation of High-Risk Patients
Clinicians should reevaluate high-risk patients for persistent OSA after adenotonsillectomy, including those who had a significantly abnormal baseline polysomnogram, have sequelae of OSA, are obese, or remain symptomatic after treatment, with an objective test (see Key Action Statement 2), or refer such patients to a sleep specialist. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 6: CPAP
Clinicians should refer patients for CPAP management if symptoms/signs or objective evidence of OSA persists after adenotonsillectomy or if adenotonsillectomy is not performed. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 7: Weight Loss
Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSA is overweight or obese. (Evidence Quality: Grade C; Recommendation Strength: Recommendation.)
Key Action Statement 8: Intranasal Corticosteroids
Clinicians may prescribe topical intranasal corticosteroids for children with mild OSA in whom adenotonsillectomy is contraindicated or for children with mild postoperative OSA. (Evidence Quality: Grade B; Recommendation Strength: Option.)

CPAP, Continuous Positive Airway Pressure; OSA, obstructive sleep apnea.
Adapted from Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2012;130:576–584.

additional PSG parameters (e.g., elevated CO_2 indicating obstructive hypoventilation, O_2 desaturation, respiratory-related arousals), clinical judgment regarding risk factors for SDB, presence and severity of clinical symptoms, and evidence of daytime sequelae should determine further management.

Treatment

No universally accepted guidelines exist regarding the indications for treatment of pediatric SDB, including primary snoring and OSA. Recommendations largely emphasize weighing what is known about the potential cardiovascular, metabolic, and neurocognitive sequelae of SDB in children in combination with the individual healthcare professional's clinical judgment. The decision of whether and how to treat OSA specifically in children depends on several parameters, including severity (nocturnal symptoms, daytime sequelae, sleep study results), duration of disease, and individual patient variables such as age, comorbid conditions, and underlying etiologic factors. In the case of moderate (AHI 5-10) to severe (AHI >10) disease, the decision to treat is usually straightforward, and most pediatric sleep experts recommend that any child with AHI >5 should be treated. However, a large randomized trial of early adenotonsillectomy vs watchful waiting with supportive care demonstrated that 46% of the control group children normalized on PSG (vs 79% of early adenotonsillectomy group) during the 7 month observation period. In addition, it is worth emphasizing that the child with habitual snoring (≥3×/week) but without polysomnographic evidence of OSA may also experience adverse neurobehavioral and neurocognitive outcomes; ongoing studies are examining whether these children may benefit from more aggressive treatment such as adenotonsillectomy.

In the majority of cases of pediatric OSA, adenotonsillectomy is the first-line treatment in any child with significant adenotonsillar hypertrophy, even in the presence of additional risk factors such as obesity. Adenotonsillectomy (or adenotonsillotomy, which is considered a less invasive procedure and may be indicated in some children) in uncomplicated cases generally (70–90% of children) results in complete resolution of symptoms; regrowth of adenoidal tissue after surgical removal occurs in some cases. Groups considered at high risk include young children (<3 years) as well as those with severe OSA documented by PSG, significant clinical sequelae of OSA (e.g., failure to thrive), or associated medical conditions, such as craniofacial syndromes, morbid obesity, and hypotonia. All patients should be reevaluated postoperatively to determine whether additional evaluation, a repeat PSG, and treatment are required. The American Academy of Sleep Medicine recommends that in high-risk groups (children with obesity, craniofacial anomalies, Down syndrome, or moderate-severe OSA) or in children with continued symptoms of OSA, a follow-up sleep study about 6 weeks after adenotonsillectomy is indicated. Also, a number of studies have suggested that children who are underweight, normal weight, or overweight/obese at baseline all tend to *gain weight* after adenotonsillectomy, and thus clinical vigilance is required during follow-up.

It should be noted that in cases of residual OSA postadenotonsillectomy, additional diagnostic evaluation to identify other sites of obstruction may be necessary to more specifically tailor treatment. An example of this type of advanced diagnostic tool is **drug-induced sleep**

endoscopy (DISE), a powerful method for studying the airway in a sleeping patient in real time. DISE provides direct visualization of the spontaneously breathing airway under light anesthesia and facilitates identification of obstructive lesions. Site of obstruction with potential surgical corrections include lingual (resection) tonsils, tongue base (reductions), turbinate (reduction), and supraglottoplasty.

Additional treatment measures that may be appropriate include weight loss, **positional therapy** (attaching a firm object, such as a tennis ball, to the back of a sleep garment to prevent the child from sleeping in the supine position), and aggressive treatment of additional risk factors when present, such as asthma, seasonal allergies, and gastroesophageal reflux. Evidence suggests that intranasal corticosteroids and leukotriene inhibitors may be helpful in reducing upper airway inflammation in mild OSA. Other surgical procedures (e.g., uvulopharyngopalatoplasty) and maxillofacial surgery (e.g., mandibular distraction osteogenesis) are seldom performed in children. Oral appliances, such as mandibular advancing devices and palatal expanders, may be considered in select cases, particularly in those children with craniofacial risk factors as mentioned earlier, and consultation with a pediatric dentist or orthodontist is recommended. Neuromuscular reeducation or repatterning of the oral and facial muscles with exercises to address abnormal tongue position and low upper airway tone (i.e., **myofunctional therapy**) have been shown to be beneficial in addressing pediatric OSA as well as alleviating chewing and swallowing problems in children able to cooperate with the behavioral program.

Continuous or **bilevel positive airway pressure (CPAP** or **BiPAP)** is the most common treatment for OSA in adults and can be used successfully in children and adolescents. Positive airway pressure (PAP) may be recommended if removing the adenoids and tonsils is not indicated, if there is residual disease following adenotonsillectomy, or if there are major risk factors not amenable to surgery (obesity, hypotonia). PAP delivers humidified, warmed air through an interface (mask, nasal pillows) that, under pressure, effectively "splints" the upper airway open. Optimal pressure settings (that abolish or significantly reduce obstructive respiratory events without increasing arousals or central apneas) are determined in the sleep lab during a full-night PAP titration. Careful attention should be paid to education of the child and family, and desensitization protocols should usually be implemented to increase the likelihood of adherence. Efficacy studies at the current pressure and retitrations should be conducted periodically with long-term use (at least annually) or in association with significant weight changes or resurgence of SDB symptoms. High-flow nasal cannula therapy may be another approach. A novel treatment for OSA in adults is hypoglossal nerve stimulation; case series suggest this may be an effective treatment in selected pediatric cases, especially in children with Down syndrome.

Parasomnias

Parasomnias are episodic nocturnal behaviors that often involve cognitive disorientation and autonomic and skeletal muscle disturbance. Parasomnias may be further characterized as occurring primarily during non-REM sleep (partial arousal parasomnias) or in association with REM sleep, including nightmares, hypnogogic hallucinations, and sleep paralysis; other common parasomnias include sleep-talking and hypnic jerks or "sleep starts."

Etiology

Partial arousal parasomnias represent a dissociated sleep–wake state, the neurobiology of which remains unclear, although genetic factors and an intrinsic oscillation of subcortical-cortical arousal with sleep have been proposed. These episodic events, which include sleepwalking, sleep terrors, and confusional arousals, are more common in preschool- and school-age children because of the relatively higher percentage of SWS in younger children. Partial arousal parasomnias typically occur when SWS predominates, in the first third of the night. In contrast, **nightmares**, which are much more common than partial arousal parasomnias but are often confused with them, tend to be concentrated in the last third of the night, when REM sleep is most prominent. Any factor associated with an increase in the relative percentage of SWS (certain medications, previous sleep restriction) may increase the frequency of events in a predisposed child. There appears to be a genetic predisposition for both sleepwalking and sleep terrors. Partial arousal parasomnias may also be difficult to distinguish from nocturnal seizures. Table 31.6 summarizes similarities and differences among these nocturnal arousal events.

Epidemiology

Many children sleepwalk on at least one occasion; the lifetime prevalence by age 10 years is 13%. **Sleepwalking** (somnambulism) may persist into adulthood, with the prevalence in adults of

Table 31.6 Key Similarities and Differentiating Features Between Non-REM and REM Parasomnias as Well as Nocturnal Seizures

	CONFUSIONAL AROUSALS	SLEEP TERRORS	SLEEPWALKING	NIGHTMARES	NOCTURNAL SEIZURES
Time	Early	Early	Early-mid	Late	Any
Sleep stage	SWA	SWA	SWA	REM	Any
EEG discharges	–	–	–	–	+
Scream	–	++++	–	++	+
Autonomic activation	+	++++	+	+	+
Motor activity	–	+	+++	+	++++
Awakens	–	–	–	+	+
Duration (min)	0.5-10; more gradual offset	1-10; more gradual offset	2-30; more gradual offset	3-20	5-15; abrupt onset and offset
Postevent confusion	+	+	+	–	+
Age	Child	Child	Child	Child, young adult	Adolescent, young adult
Genetics	+	+	+	–	±
Organic CNS lesion	–	–	–	–	++++

CNS, Central nervous system; EEG, electroencephalogram; REM, rapid eye movement; SWA, slow-wave arousal.
From Avidan A, Kaplish N. The parasomnias: epidemiology, clinical features and diagnostic approach. *Clin Chest Med.* 2010;31:353–370.

approximately 4%. The prevalence is approximately 10 times greater in children with a family history of sleepwalking. The peak prevalence of **sleep terrors** (or night terrors) is 34% at age 1-5 years, decreasing to 10% by age 7; the age at onset is usually between 4 and 12 years. Because of the common genetic predisposition, the likelihood of developing sleepwalking after age 5 is almost twofold higher in children with a history of sleep terrors. Although sleep terrors can occur at any age from infancy through adulthood, most individuals outgrow sleep terrors by adolescence. **Confusional arousals** may be accompanied by (and often precede in onset) episodes sleepwalking and sleep terrors; prevalence rates have been estimated at >15% in children age 3-13 years.

Clinical Manifestations

The partial arousal parasomnias have several features in common. Because they typically occur at the transition out of "deep" sleep or SWS, partial arousal parasomnias have clinical features of both the *awake* (ambulation, vocalizations) and the *sleeping* (high arousal threshold, unresponsiveness to environment) states, usually with amnesia for the events. External (noise) or internal (obstruction) factors may trigger events in some individuals. The duration is typically a few minutes (sleep terrors) up to 30-40 minutes (confusional arousals). Sleep terrors are sudden in onset and characteristically involve a high degree of autonomic arousal (tachycardia, diaphoresis, dilated pupils). Confusional arousals typically arise more gradually from sleep, may involve thrashing around, mumbling, and other vocalizations, but usually not displacement from bed, and are often accompanied by slow mentation, disorientation, and confusion on forced arousal from SWS or on waking in the morning. Sleepwalking may be associated with safety concerns (e.g., falling out of windows, wandering outside). The child's avoidance of, or increased agitation with, comforting by parents or prolongation of events by attempts at awakening are also common to all partial arousal parasomnias.

Treatment

Management of partial arousal parasomnias involves some combination of parental education and reassurance, healthy sleep practices, and avoidance of exacerbating factors such as sleep restriction and caffeine. Particularly in the case of sleepwalking, it is important to institute safety precautions such as use of gates in doorways and at the top of staircases, locking of outside doors and windows, and installation of parent notification systems such as bedroom door alarms. **Scheduled awakening** is a behavioral intervention that involves having the parent wake the child 15-30 minutes before the time of night that the first parasomnia episode typically occurs and is most likely to be successful in situations where partial arousal episodes occur on a nightly basis. Pharmacotherapy is rarely necessary but may be indicated in cases of frequent or severe episodes despite nonpharmacologic interventions and absence of treatable underlying sleep disorders exacerbating partial arousal parasomnias such as OSA or **periodic limb movement disorder (PLMD),** high risk of injury, violent behavior, or serious disruption to the family. The primary pharmacologic agents used are potent SWS suppressants, primarily benzodiazepines and tricyclic antidepressants.

Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder, Restless Sleep Disorder, and Rhythmic Movement Disorder

Although some of these sleep disorders share common features (e.g., movements of specific body parts such as extremities vs whole body movements) and pathogenesis (e.g., iron deficiency), each has a distinctive set of diagnostic criteria, epidemiology and clinical management, and may differ in the degree of disruption to sleep quality and quantity and related daytime consequences.

Although most of these sleep-related movement disorders do not require overnight polysomnographic evaluation for diagnosis (PLMD is a notable exception), a videotaped episode by caregivers in the home setting can prove very valuable in helping to differentiate sleep-related movements from nocturnal seizures. Such sleep-related seizures usually arise from the frontal and/or temporal lobes. Ambulatory EEG, in-patient video-EEG monitoring and overnight video PSG with chin and leg EMG recording may be necessary to establish a diagnosis of a sleep-related movement disorder.

Restless Legs Syndrome/Periodic Limb Movement Disorder

Restless legs syndrome (RLS), also termed *Willis-Ekbom disease*, is a primary disorder of the CNS sensorimotor network characterized by an almost irresistible urge to move the legs, often accompanied by uncomfortable sensations in the lower extremities. Both the urge to move and the sensations are usually worse at rest and in the evening and are at least partially relieved by movement, including walking, stretching, and rubbing, but only if the motion continues. RLS is a clinical diagnosis that is based on the presence of these key symptoms (Table 31.7).

PLMD is characterized by periodic, repetitive, brief (0.5-10 seconds), and highly stereotyped limb jerks typically occurring at 20-40 second intervals. These movements occur primarily during sleep, usually occur in the legs, and frequently consist of rhythmic extension of the big toe and dorsiflexion at the ankle. Although there may be clinical complaints of kicking movements in sleep or restless sleep, the diagnosis of **periodic limb movements (PLMs)** requires overnight PSG to document the characteristic limb movements with anterior tibialis EMG leads. However, like adults, children also show considerable individual night-to-night variability of PLMs, and a single-night PSG may not always reflect the true severity.

Etiology

RLS has a clear genetic component, with a sixfold to sevenfold increase in prevalence in first-degree relatives of RLS patients. The mode of inheritance is complex, and several genetic loci have been identified *(MEIS1, BTBD9, MAP2K5)*. Low serum iron levels (even without anemia) in both adults and children may be an important etiologic factor for the presence and severity of both RLS symptoms and PLMs. As a marker of decreased iron stores, serum ferritin levels in both children and adults with RLS are frequently low (<50 µg/mL). The postulated underlying mechanism is related to the role of iron as a cofactor in tyrosine hydroxylation, a rate-limiting step in dopamine

Table 31.7 Diagnostic Criteria for Restless Legs Syndrome

A. An urge to move legs, usually accompanied by or in response to uncomfortable and unpleasant sensations in the legs, characterized by the following:
   1. The urge to move the legs begins or worsens during periods of rest or inactivity.
   2. The urge to move the legs is partially or totally relieved by movement.
   3. The urge to move the legs is worse in the evening or at night than during the day, or occurs only in the evening or at night.

B. The symptoms in Criterion A occur at least 3 times per week and have persisted for at least 3 mo.

C. The symptoms in Criterion A are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

D. The symptoms in Criterion A are not attributable to another mental disorder or medical condition (e.g., arthritis, leg edema, peripheral ischemia, leg cramps) and are not better explained by a behavioral condition (e.g., positional discomfort, habitual foot tapping).

E. The symptoms are not attributable to the physiologic effects of a drug or abuse or medication (e.g., akathisia).

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed, Arlington, VA: American Psychiatric Association; 2013. p 410.

synthesis; in turn, dopaminergic dysfunction has been implicated, particularly in the genesis of the sensory component of RLS, as well as in PLMD. Certain medical conditions, including diabetes mellitus, end-stage renal disease, cancer, idiopathic juvenile arthritis, hypothyroidism, and pregnancy, may also be associated with RLS/PLMD, as are specific medications (e.g., antidepressants, including tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, first-generation sedating antihistamines, and dopamine receptor antagonists, such as Compazine and metoclopramide), as well as caffeine.

Epidemiology

Survey studies estimate the prevalence rates of RLS in the pediatric population as between 1 and 6%; approximately 2% of 8-17 year olds meet the criteria for "definite" RLS. Prevalence rates of PLMs >5 per hour in clinical populations of children referred for sleep studies range from 5–27%; in survey studies of PLM symptoms, rates are 8–12%. About 40% of adults with RLS have symptoms before age 20 years; 20% report symptoms before age 10. Familial cases usually have a younger age of onset. Several studies in referral populations have found that PLMs occur in as many as 25% of children diagnosed with ADHD.

Clinical Manifestations

In addition to the urge to move the legs and the sensory component (paresthesia-like, tingling, burning, itching, crawling), most RLS episodes are initiated or exacerbated by rest or inactivity, such as lying in bed to fall asleep or riding in a car for prolonged periods. Children may describe the sensory symptoms as a funny feeling, tickling, hurting, or pain or bugs, spiders, ants, or goosebumps in the legs. Sometimes, the child may draw pins, needles, tiny sand particles, and bugs over his or her legs when asked to depict the symptoms. An "informal" suggested clinical immobilization test (SCIT) (i.e., "If I asked you to lie perfectly still sitting on your bed at bedtime, would you be able to do it?") can be helpful in eliciting RLS complaints. A unique feature of RLS is that the timing of symptoms also appears to have a circadian component, in that they often peak in the evening hours. Some children may complain of "growing pains," although this is considered a nonspecific feature. Because RLS symptoms are usually worse in the evening, bedtime struggles and difficulty falling asleep are two of the most common presenting complaints. In contrast to patients with RLS, individuals with PLMs are usually unaware of these movements, but children may complain of morning muscle pain or fatigue; these movements may result in arousals during sleep and consequent significant sleep disruption. Parents of children with RLS/PLMD may report that their child is a restless sleeper and kicks a bed partner.

The differential diagnosis includes growing pains, leg cramps, neuropathy, arthritis, myalgias, nerve compression ("leg fell asleep"), and dopamine antagonist–associated akathisia.

Treatment

Because of the frequent co-occurrence and overlap in underlying pathophysiology and risk factors for RLS and PLMD, management strategies for both disorders are similar. The clinical decision to treat RLS and PLMs is based on the severity of symptoms, sleep disturbances, and effect on daytime functioning. An acronym that summarizes the management approach for RLS/PLMD in children is AIMS. This includes the following:

- *A*voidance of drugs/substances which may exacerbate RLS/PLMD (including caffeine, nicotine, alcohol)
- *I*ron supplementation
- *M*uscles: increased physical activity, massage, application of heat/cold, muscle relaxation and biofeedback
- *S*leep: regular and adequate sleep

Treatment with iron supplementation is indicated if serum ferritin is <50 ng/mL. Administration of oral supplements for ferritin levels >75-100 μg/L, at least in adults, are likely ineffective because of low absorption. It should be kept in mind that ferritin is an acute-phase reactant and thus may be falsely elevated (i.e., normal) in the setting of a concomitant illness. In addition, the ferritin level should be drawn, if possible, in the early morning after avoiding a dinner with a high iron content (e.g., red meat) on the previous evening. A typical iron regimen is ferrous fumarate or sulfate as an oral tablet or liquid: 3-6 mg/kg of elemental iron/day × 3 months with 200 mg vitamin C on an empty stomach while avoiding calcium-containing foods that may slow absorption. Ferritin levels should be repeated after 3 months to assess response and avoid iron overload.

If ferritin levels are very low or levels fail to improve after treatment with iron, these children may require referral to hematology for evaluation of their iron deficiency (e.g., occult blood loss, malabsorption). Although pediatric data regarding IV iron for RLS/PLMD are largely lacking, there are studies examining the role of IV iron therapy (e.g., ferric carboxymaltose, iron dextran) in the treatment of severe iron deficiency or with iron malabsorption in adults. Potential advantages of IV therapy include rapid response and avoidance of malabsorption/tolerance/compliance issues.

Treatment with pharmacologic agents may be indicated in children with moderate-severe RLS symptoms and PLMD, who did not respond to the previously mentioned measures. Currently, there are no Food and Drug Administration (FDA)-approved pharmacologic agents for RLS/PLMD in children. Dopaminergic medication is considered the first line of treatment for RLS in adults. Other classes of medications used to treat PLS/PLMD include α-agonists, opiates, benzodiazepines, and bupropion.

Restless Sleep Disorder

Restless sleep disorder **(RSD)** has both clinical and PSG features *distinct* from RLS and PLMD. Clinical descriptors include a complaint of "restless sleep" typically reported by a parent, caregiver, or bedpartner; the visible body movements, involving *large muscle groups of the whole body, all four limbs, arms, legs, or head* during sleep, may be characterized further as frequent repositioning disruption of the bedsheets, falling out of bed and being found in a completely different position compared to the position in which they fell asleep. Diagnostic criteria also include objective documentation on videography of increased levels of nocturnal activity and gross body movements with a total movement index during sleep that exceeds five per hour of sleep. RSD has also been found to be associated with low serum iron levels with symptomatic improvement following iron supplementation.

Sleep-related rhythmic movements, including head banging, body rocking, and head rolling, are characterized by repetitive, stereotyped, and rhythmic movements or behaviors that involve large muscle groups. These behaviors typically occur with the transition to sleep at bedtime, but also at nap times and after nighttime arousals. Children are thought to engage in these behaviors as a means of soothing themselves to (or back to) sleep. These behaviors are very common, with about two thirds of all infants having some type, typically beginning before 12 months and usually disappearing by preschool age. In most cases, rhythmic movement behaviors are benign, because sleep is not significantly disrupted, and associated significant injury is rare; however, these behaviors can potentially affect the sleep of a family member room-sharing and/or caregivers in nearby sleeping spaces. In addition, caregivers are often concerned about these behaviors as potentially being harmful to the child or possibly indicative of an underlying neurologic or neurodevelopmental disorder (e.g., autism). However, these behaviors typically occur in normally developing children and in the majority of cases do not indicate some underlying neurologic or psychologic problem. Usually, the most important aspect in management of sleep-related rhythmic movements is reassurance to the family that this behavior is normal, common, benign, and self-limited. Safety may be an important concern, and appropriate measures such as tightening of crib bolts and guardrails on the bed should be taken to prevent injury; noise dampening measures such as moving the bed away from adjoining walls may be helpful. If there are concerns about an associated sleep disorder, seizure disorder, or risk of injury referral to a sleep specialist may be considered.

Central Disorders of Hypersomnolence: Narcolepsy type 1, Narcolepsy type 2, Idiopathic Hypersomnia

Hypersomnia is a clinical term that is used to describe a group of disorders characterized by recurrent episodes of EDS, reduced baseline alertness, and/or prolonged nighttime sleep periods that interfere with normal daily functioning (Table 31.8). The many potential causes of EDS can be broadly grouped as "extrinsic" (e.g., secondary to insufficient and/or fragmented sleep) or "intrinsic" (e.g., resulting from an increased need for sleep).

Table 31.8 Diagnostic Criteria for Narcolepsy

A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least 3 times per week over the past 3 mo.
B. The presence of at least one of the following:
   1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few times per month:
      a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
      b. In children or individuals within 6 mo of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
   2. Hypocretin deficiency, as measured using CSF hypocretin-1 immunoreactivity values (less than or equal to one third of values obtained in healthy subjects tested using the same assay, or ≤110 pg/mL). Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
   3. Nocturnal sleep polysomnography showing REM sleep latency ≤15 min, or a multiple sleep latency test showing a mean sleep latency ≤ 8 min and two or more sleep-onset REM periods.

Specify whether:

Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive polysomnography/multiple sleep latency test are met, but no cataplexy is present (Criterion B1 not met).

Narcolepsy with cataplexy but without hypocretin deficiency: In this rare subtype (<5% of narcolepsy cases), Criterion B requirements of cataplexy and positive polysomnography/multiple sleep latency test are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

Autosomal dominant cerebellar ataxia, deafness, and narcolepsy: This subtype is caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations and is characterized by late-onset (age 30-40 yr) narcolepsy (with low or intermediate CSF hypocretin-1 levels), deafness, cerebellar ataxia, and eventually dementia.

Autosomal dominant narcolepsy, obesity, and type 2 diabetes: Narcolepsy, obesity, and type 2 diabetes are low; CSF hypocretin-1 levels have been described in rare cases and are associated with a mutation in the myelin oligodendrocyte glycoprotein gene.

Narcolepsy without cataplexy but with hypocretin deficiency: This subtype is for narcolepsy that develops secondary to medical conditions that cause infectious (e.g., Whipple disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.

Severity:

Mild: Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

Moderate: Cataplexy once daily or every few days, disturbed nocturnal sleep and need for multiple naps daily.

Severe: Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (i.e., movements, insomnia, and vivid dreaming).

CSF, Cerebrospinal fluid; REM, rapid eye movement.
From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed, Arlington, VA: American Psychiatric Association; 2013. pp 372–373.

Narcolepsy

Narcolepsy is a chronic, lifelong CNS disorder, typically presenting in adolescence and early adulthood, characterized by profound daytime sleepiness resulting in significant functional impairment. More than half of patients with narcolepsy also present with **cataplexy** (type 1 narcolepsy), defined as the sudden, brief, partial, or complete loss of skeletal muscle tone, typically triggered by strong emotion (e.g., laughter, surprise, anger), with retained consciousness. Other symptoms frequently associated with narcolepsy, including hypnogogic/hypnopompic (immediately before falling asleep/awakening) visual, auditory, or perceptual hallucinations, and sleep paralysis, may be conceptualized as representing the "intrusion" of REM-related phenomena (dream mentation, loss of motor tone) into the waking state. Other REM-related features include observance of eye movements and twitches at sleep onset and vivid dreams. Somewhat paradoxically, increased sleep fragmentation is a common feature. Rapid weight gain, especially near symptom onset, may be observed, and young children with narcolepsy have been reported to develop precocious puberty.

Etiology

The genesis of narcolepsy with cataplexy (type 1) is thought to be related to a specific deficit in the hypothalamic orexin/hypocretin neurotransmitter system involving the selective loss of cells that secrete hypocretin/orexin in the lateral hypothalamus. *Hypocretin* neurons stimulate a range of wake-promoting neurons in the brainstem, hypothalamus, and cortex and basal forebrain that produce neurochemicals to sustain the wake state and prevent lapses into sleep.

The development of narcolepsy may involve autoimmune mechanisms, possibly triggered by streptococcal, influenza virus, H1N1, and other viral infections, likely in combination with a genetic predisposition and environmental factors. A 12-13–fold increase in narcolepsy type 1 cases, especially in children, was reported in parts of Europe in 2009–2010 following immunization with the AS03 adjuvanted H1N1 influenza vaccine. Human leukocyte antigen testing also shows a strong association with narcolepsy; the majority of individuals with this antigen (~25% of the general population) do not have narcolepsy, but most (>90%) patients with narcolepsy with cataplexy are HLA-DQB1*0602–positive. Patients with narcolepsy without cataplexy (type 2) are increasingly thought to have a significantly different underlying pathophysiology; they are much less likely to be HLA-DQB1*0602–positive (4–50%), and cerebrospinal fluid (CSF) hypocretin levels are normal in most patients.

Although most cases of narcolepsy are considered idiopathic (autoimmune), **secondary narcolepsy** can be caused by lesions to the posterior hypothalamus induced by traumatic brain injury, tumor, stroke, and neuroinflammatory processes such as poststreptococcal pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS; see Chapter 229), as well as by neurogenetic diseases such as Prader-Willi syndrome (Chapter 99.7), Niemann-Pick type C (Chapter 106.4), myotonic dystrophy (Chapter 649.6), Angelman syndrome, autosomal dominant cerebellar ataxia-deafness-narcolepsy (ADCA-DN), Moebius syndrome, and Norrie disease.

Epidemiology

Narcolepsy is a rare disorder with a prevalence of approximately 1 in 2000 with equal sex distribution; however, specific countries (e.g., Japan) appear to have relatively higher prevalence rates. The risk of developing narcolepsy with cataplexy in a first-degree relative of a narcoleptic patient is estimated at 1–2%. This represents an increase of 10-40–fold compared to the general population, but the risk remains very low, reinforcing the likely role for other etiologic factors.

Clinical Manifestations and Diagnosis

The typical onset of symptoms of narcolepsy is in adolescence and early adulthood, although symptoms may initially present in school-age and even younger children. The early manifestations of narcolepsy are often ignored, misinterpreted, or misdiagnosed as other medical, neurologic, or psychiatric conditions, and the appropriate diagnosis is frequently delayed for years. The onset may be abrupt or slowly progressive.

The most prominent clinical manifestation of narcolepsy is profound daytime sleepiness, characterized by both an increased baseline level of daytime drowsiness and the repeated occurrence of sudden and unpredictable sleep episodes. These "sleep attacks" are often described as "irresistible," in that the child or adolescent is unable to stay awake despite considerable effort and occur even in the context of normally stimulating activities (e.g., during meals, in conversation). Very brief (several seconds) sleep attacks may also occur in which the individual may "stare off," appear unresponsive, or continue to engage in an ongoing activity *(automatic behavior)*. EDS may also be manifested by increased nighttime sleep needs and extreme difficulty waking in the morning or after a nap.

Cataplexy is considered virtually pathognomonic for narcolepsy but can develop several years after the onset of EDS. Manifestations are triggered by strong positive (laughing, joy) or negative (fright, anger, frustration) emotions and predominantly include facial slackening, head nodding, jaw dropping, and less often, knees buckling or complete collapse with falling to the ground. The cataplectic attacks are typically brief (seconds to minutes), the patient is awake and aware, and episodes are fully reversible, with complete recovery of normal tone when the episode ends. A form of cataplexy unique to children known as **cataplectic facies** is characterized by prolonged tongue protrusion, ptosis, slack jaw, slurred speech, grimacing, and gait instability. Additionally, children may have positive motor phenomenon similar to dyskinesias or motor tics, with repetitive grimacing and tongue thrusting. The cataplectic attacks are typically brief (seconds to minutes) but in children may last for hours or days (**status cataplecticus**). The differential diagnosis of cataplexy includes syncope, seizures, cataplexy-like episodes in *KCNA1* pathologic variants (ataxia-myokymia syndrome), hyperekplexia, hypo and hyperkalemic periodic paralysis syndromes, and pseudocataplexy.

Hypnogogic/hypnopompic hallucinations usually involve vivid visual but also auditory and sometimes tactile sensory experiences during transitions between sleep and wakefulness, either at sleep offset (hypnopompic) or sleep onset (hypnogogic). **Sleep paralysis** is the inability to move or speak for a few seconds or minutes at sleep onset or offset and often accompanies the hallucinations. Other symptoms associated with narcolepsy include disrupted nocturnal sleep, impaired cognition, inattention and ADHD-like symptoms, and behavioral and mood dysregulation.

Several pediatric screening questionnaires for EDS, including the modified Epworth Sleepiness Scale, help to guide the need for further evaluation in clinical practice when faced with the presenting complaint of daytime sleepiness. Physical examination should include a detailed neurologic assessment. Overnight PSG and a multiple sleep latency test (MSLT) are strongly recommended components in the evaluation of a patient with profound unexplained daytime sleepiness or suspected narcolepsy. The purpose of the overnight PSG is to evaluate for primary sleep disorders (e.g., OSA) that may cause EDS. The MSLT involves a series of five opportunities to nap (20 min long), during which patients with narcolepsy demonstrate a pathologically shortened mean sleep-onset latency (≤8 minutes, typically <5 minutes) as well as at least two periods of REM sleep occurring immediately after sleep onset. Alternatively, a diagnosis of type 1 narcolepsy can be made by findings of low CSF hypocretin-1 concentration (typically ≤110 pg/mL) with a standardized assay.

Treatment

In general, the management of pediatric narcolepsy is best done in conjunction with a pediatric sleep specialist. An individualized narcolepsy treatment plan usually involves education, good sleep hygiene, behavioral changes, and medication. Scheduled naps during the day are often helpful. Wake-promoting medications such as modafinil or armodafinil may be prescribed to control the EDS, although these are not approved for use in children by the U.S. FDA, and potential side effects include rare reports of Stevens-Johnson syndrome and reduced efficacy of hormone-based contraceptives. Psychostimulants are approved for ADHD in children and can be used for EDS; side effects include appetite suppression, mood lability, and cardiovascular effects. Antidepressants (serotonin reuptake inhibitors, tricyclic antidepressants, venlafaxine) may be used to reduce cataplexy. Sodium oxybate, which is approved for use in children, is a unique drug that appears to have a positive impact on daytime sleepiness, cataplexy, and nocturnal sleep disruption; reported side effects include dizziness, weight loss, enuresis, exacerbation of OSA, depression, and risk of respiratory depression, especially when combined with CNS depressants, including alcohol. Pitolisant has a novel mechanism as a histamine (H_3) receptor agonist and has been shown to improve cataplexy and EDS in adult patients with narcolepsy. Preliminary results in children have been encouraging. Solriamfetol, a norepinephrine-dopamine reuptake inhibitor, is another alertness-enhancing drug recently approved in adults. The goal for the child should be to allow the fullest possible return of normal functioning in school, at home, and in social situations.

Idiopathic Hypersomnia

Idiopathic hypersomnia **(IH)** is a central sleep disorder, presenting in adolescence and young adults, characterized by chronic and EDS, but without cataplexy or REM sleep intrusions. Patients typically present with prolonged nocturnal sleep duration and severe sleep inertia, making it difficult to arouse from nocturnal sleep or daytime naps. Patients often report transient periods of confusion and "sleep drunkenness" on awakening, sleep paralysis, and hypnagogic hallucinations. Unlike patients with narcolepsy, daytime naps tend to be long (more than 1 hour) and unrefreshing. The prevalence in the general population is not known because of challenges with diagnostic evaluation, but is estimated to be approximately 20-50 cases per million. The pathogenesis also is not well understood; however, some cases were documented to be precipitated by viral illnesses, suggesting a possible autoimmune process. A diagnosis of IH requires daily periods of irrepressible need to sleep or daytime lapses into sleep for at least 3 months, absence of cataplexy, and exclusion of other causes including insufficient sleep. Diagnosis is made by PSG followed by an MSLT showing mean sleep latency of <8 minutes and less than two sleep-onset REM periods (SOREMPs) on MSLT or no SOREMPs if the REM sleep latency preceding PSG is 15 minutes or less. When the mean sleep latency on the MSLT is >8 minutes, a 24-hour PSG or 2-week actigraphy to ensure a total 24-hour sleep time ≥660 minutes is needed. Treatment is mostly derived from experience with medications to treat EDS in narcolepsy. Wakeful promoting medications such as modafinil, armodafinil, methylphenidate, amphetamines, and oxybate are treatment options. Behavior modifications such as scheduled naps are not generally helpful.

Kleine-Levin syndrome (KLS) may mimic IH and manifests with recurrent episodes of hypersomnia (Table 31.9). KLS may resolve overtime; some reports support the use of parenteral steroids during an episode.

Table 31.9 Diagnostic Criteria for Kleine-Levin Syndrome

CRITERIA A–E MUST BE MET

A. The patient experiences at least two recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks.
B. Episodes recur usually more than once a year and at least once every 18 months.
C. The patient has normal alertness, cognitive function, behavior, and mood between episodes.
D. The patient must demonstrate at least one of the following during episodes:
E. Cognitive dysfunction.
F. Altered perception.
G. Eating disorder (anorexia or hyperphagia).
H. Disinhibited behavior (such as hypersexuality).
I. The hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.

From Afolabi-Brown O, Mason II TBA. Kleine-Levin syndrome. *Pediatr Respir Rev.* 2018;25:9–13, Table 1, p 10.

Delayed Sleep–Wake Phase Disorder

Delayed sleep–wake phase disorder (**DSWPD**), a circadian rhythm disorder, involves a significant, persistent, and intractable phase shift in sleep–wake schedule (later sleep onset and wake time) that conflicts with the individual's normal school, work, and lifestyle demands. DSWPD may occur at any age but is most common in adolescents and young adults.

Etiology

Individuals with DSPD may start out as "night owls"; that is, they have an underlying biologic predisposition/circadian-based "eveningness" chronotype that results in a propensity for staying up relatively late at night and sleeping until late in the morning or early afternoon, and in extreme cases, a complete "day-night reversal." Although these patients struggle to get up in time for school or work, they usually revert to their preferred sleep schedule on weekends, holidays, and summer vacations. The underlying pathophysiology of DSWPD is still unknown, although some theorize that it involves an intrinsic abnormality in the circadian oscillators that govern the timing of the sleep period.

Epidemiology

Studies indicate that the prevalence of DSWPD may be as high as 7–16% in adolescents and young adults.

Clinical Manifestations

The most common clinical presentation of DSWPD is sleep-initiation insomnia when the individual attempts to fall asleep at a "socially acceptable" desired bedtime and experiences very delayed sleep onset (often after 1-2 AM), accompanied by daytime sleepiness. Patients may also report extreme difficulty arising in the morning even for desired activities, with pronounced confusion on waking *(sleep inertia)*, and caregivers often complain of the need for multiple reminders or even the complete failure to awaken the adolescent in time to attend school. Sleep maintenance is generally not problematic, and no sleep-onset insomnia is experienced if bedtime coincides with the preferred sleep-onset time. Patients may also develop "secondary" psychophysiologic insomnia as a result of spending prolonged time in bed attempting to fall asleep. School tardiness and frequent absenteeism with a decline in academic performance often occur, and there may be school-related disciplinary action (i.e., suspension, truancy label) or a need to justify home-based schooling/tutoring that motivate families to seek help. It is important to recognize that there may also be issues related to family dynamics and comorbid anxiety, depression, or learning disabilities that provide a motivation to avoid attending school and perpetuate the sleep schedule problems, as well as reducing adherence to interventions.

Treatment

The treatment of DSWPD usually has three components, all directed toward the goals of shifting the sleep–wake schedule to an earlier, more desirable time and maintaining the new schedule. The initial step involves shifting the sleep–wake schedule to the desired earlier times, usually with gradual (i.e., in 15-30 minute increments every few days) alternating advancement of rise time in the morning and bedtime in the evening. More significant phase delays (i.e., larger difference between current sleep onset and desired bedtime) may require *chronotherapy,* which involves delaying bedtime and wake time by 2-3 hours every 24 hours "forward around the clock" until the target bedtime is reached. Because melatonin secretion is highly sensitive to light, exposure to light in the morning (either natural light or a "light box," which typically produces light at around 10,000 lux) and avoidance of evening light exposure (especially from screens emitting predominantly blue light, such as computers and laptops) are often beneficial. Exogenous oral melatonin supplementation may also be used; larger, mildly sedating doses (5 mg) are typically given 30 minutes before bedtime, but some studies have suggested that physiologic doses of oral melatonin (0.3-0.5 mg) administered in the afternoon or early evening (5-7 hours before the habitual sleep-onset time or 2 hours before the desired bedtime) may be more effective in advancing the sleep phase.

SLEEP HEALTH SUPERVISION

It is especially important for pediatricians to screen for and recognize sleep disorders in children and adolescents during routine healthcare encounters. The well-child visit is an opportunity to educate parents about normal sleep and to teach strategies to prevent sleep problems from developing (primary prevention) or becoming chronic, if problems already exist (secondary prevention). Developmentally appropriate screening for sleep disturbances should take place in the context of every well-child visit and should include a range of potential sleep problems; Table 31.10 outlines a simple sleep screening algorithm called the "BEARS." Because parents may not always be aware of sleep problems, especially in older children and adolescents, it is also important to question the child directly about sleep concerns. The recognition and evaluation of sleep problems in children require both an understanding of the association between sleep disturbances and daytime consequences (e.g., irritability, inattention, poor impulse control) knowledge of risk factors for the wide variety of sleep disorders (e.g., obesity, positive family history, medications), and familiarity with the developmentally appropriate differential diagnoses of common presenting sleep complaints (difficulty initiating and maintaining sleep, episodic nocturnal events). An assessment of sleep patterns and possible sleep problems should be part of the initial evaluation of every child presenting with behavioral or academic problems, especially ADHD.

Effective preventive measures include educating parents of newborns about normal sleep amounts and patterns. The ability to regulate sleep begins to develop in the first 8-12 weeks of life. Thus it is important to recommend that parents put their 2-4 month old infants to bed "drowsy but awake" if they want to avoid dependence on parental presence at sleep onset and foster the infant's ability to self-soothe. Other important sleep issues include discussing the importance of regular bedtimes, bedtime routines, and transitional objects for toddlers, and providing parents and children with basic information about healthy sleep practices, recommended sleep amounts at different ages, and signs that a child is not getting sufficient sleep.

The cultural and family context within which sleep problems in children occur should be considered. For example, bed-sharing of infants and parents is a common and accepted practice in many racial/ethnic groups, and these families may not share the goal of independent self-soothing in young infants. *Anticipatory guidance* needs to balance cultural awareness with the critical importance of "safe sleep" conditions in sudden infant death syndrome prevention (i.e., sleeping in the supine position, avoidance of bed-sharing but encouragement of room-sharing in the first year of life) (see Chapter 423). On the other hand, the institution of cosleeping by parents as an attempt to address a child's underlying sleep problem (so-called reactive cosleeping), rather than as a conscious family decision, is likely to yield only a temporary respite from the problem and may set the stage for more significant sleep issues.

EVALUATION OF PEDIATRIC SLEEP PROBLEMS

The clinical evaluation of a child presenting with a sleep problem involves obtaining a careful medical history to assess for potential medical causes of sleep disturbances, such as allergies, concomitant medications, and acute or chronic pain conditions. A developmental history is important because of the increased risk of sleep problems in children with neurodevelopmental disorders. Assessment of the child's current level of functioning (school, home) is a key part of evaluating possible mood, behavioral, and neurocognitive sequelae of sleep problems. Current sleep patterns, including the usual sleep duration and sleep–wake schedule, are often best assessed with a **sleep diary,** in which a parent (or adolescent) records daily sleep behaviors for an extended period (1-2 weeks). A review of sleep habits, such as bedtime routines, daily caffeine intake, and the

Table 31.10 BEARS Sleep Screening Algorithm

The BEARS instrument is divided into five major sleep domains, providing a comprehensive screen for the major sleep disorders affecting children 2-18 yr old. Each sleep domain has a set of age-appropriate "trigger questions" for use in the clinical interview.
B = Bedtime problems
E = Excessive daytime sleepiness
A = Awakenings during the night
R = Regularity and duration of sleep
S = Snoring

	DEVELOPMENTALLY APPROPRIATE TRIGGER QUESTIONS		
	TODDLER, PRESCHOOL (2-5 YR)	**SCHOOL-AGE (6-12 YR)**	**ADOLESCENT (13-18 YR)**
1. Bedtime problems	Does your child have any problems going to bed? Falling asleep?	Does your child have any problems at bedtime? (P) Do you any problems going to bed? (C)	Do you have any problems falling asleep at bedtime? (C)
2. Excessive daytime sleepiness	Does your child seem overtired or sleepy a lot during the day? Does your child still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (P) Do you feel tired a lot? (C)	Do you feel sleepy a lot during the day? In school? While driving? (C)
3. Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P) Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)	Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)
4. Regularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	What time does your child go to bed and get up on school days? Weekends? Do you think your child is getting enough sleep? (P)	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)
5. Snoring	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	Does your teenager snore loudly or nightly? (P)

C, Child; P, parent.

sleeping environment (e.g., temperature, noise level), may reveal environmental factors that contribute to the sleep problems. Nocturnal symptoms that may be indicative of a medically based sleep disorder, such as OSA (loud snoring, choking or gasping, sweating) or PLMs (restless sleep, repetitive kicking movements), should be elicited. Home video recording may be helpful in the evaluation of potential parasomnia episodes and the assessment of snoring and increased work of breathing in children with OSA. An overnight sleep study (PSG) is not routinely warranted in the evaluation of a child with sleep problems unless there are symptoms suggestive of OSA or PLMs, unusual features of episodic nocturnal events, or unexplained daytime sleepiness.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Behavioral and Psychiatric Disorders

PART III

Chapter 32

Psychosocial Assessment and Psychiatric Diagnostic Evaluation

Heather J. Walter

It is estimated that 20% of children living in the United States experience a mental illness in a given year; mental illness is more prevalent than leukemia, diabetes, and AIDS combined. More money is spent on mental disorders than on any other childhood illness, including asthma, trauma, and infectious diseases. Although nearly one in five youths suffers from a psychiatric disorder, 75–85% do not receive specialty mental health services; rather most services are delivered in nonspecialty sectors (primary care, schools, child welfare, juvenile justice), where mental health expertise may be limited. Untreated or inadequately treated psychiatric disorders persist over decades, become increasingly intractable to treatment, impair adherence to medical treatment regimens, and incur progressively greater social, educational, and economic consequences over time.

AIMS OF PSYCHOSOCIAL ASSESSMENT IN THE PEDIATRIC SETTING

A psychosocial assessment in the pediatric setting should determine whether there are signs and symptoms of cognitive, developmental, emotional, behavioral, or social difficulties and characterize those signs and symptoms sufficiently to determine their appropriate management. The focus of the assessment varies with the nature of the presenting problem and the clinical setting. Under emergency circumstances, the focus may be limited to an assessment of "dangerousness to self or others" for the purpose of determining the safest level of care. In routine circumstances (well-child visits), the focus may be broader, involving a screen for symptoms, distress, and functional impairment in the major psychosocial domains. The challenge for the pediatric practitioner will be to determine as accurately as possible whether the presenting signs and symptoms are likely to meet criteria for a psychiatric disorder and whether the severity and complexity of the disorder suggest referral to a mental health specialist or management in the primary care setting.

PRESENTING PROBLEMS

Infants may come to clinical attention because of problems with eating and/or sleep regulation, concerns about failure to gain weight, poor social responsiveness, limited vocalization, apathy or disinterest, and response to strangers that is excessively fearful or overly familiar. Psychiatric disorders most commonly diagnosed during this period are rumination and reactive attachment disorders.

Toddlers are assessed for concerns about sleep problems, language delay, motor hyperactivity, extreme misbehavior, extreme shyness, inflexible adherence to routines, difficulty separating from parents, struggles over toilet training, dietary issues, and testing limits. Developmental delays and more subtle physiologic, sensory, and motor processing problems can be presented as concerns. Problems with "goodness of fit" between the child's temperament and the parents' expectations can create relationship difficulties that also require assessment (see Chapter 19). Mental health disorders most commonly diagnosed during this period are developmental delays, autism spectrum disorder (ASD) and reactive attachment disorders.

Presenting problems in **preschoolers** include elimination difficulties, sibling jealousy, difficulty forming friendships, self-destructive impulsiveness, multiple fears, nightmares, refusal to follow directions, rigidity, somatization, speech that is difficult to understand, and temper tantrums. Mental health disorders most commonly diagnosed in this period are ASD, communication, oppositional, attention-deficit/hyperactivity (ADHD), anxiety (separation, selective mutism), reactive attachment, and sleep disorders.

Older children are brought to clinical attention because of concerns about angry or sad mood, bed-wetting, overactivity, impulsiveness, distractibility, learning problems, arguing, defiance, nightmares, school refusal, bullying or being bullied, worries and fears, somatization, communication problems, tics, and withdrawal or isolation. Mental health disorders most commonly diagnosed during this period are ADHD, oppositional, anxiety (phobias), elimination, somatic symptom, specific learning, and tic disorders.

Adolescents are assessed for concerns about the family situation, experimentation with sexuality and drugs, delinquency and gang involvement, friendship patterns, issues of independence, identity formation, self-esteem, and morality. Mental health disorders most often diagnosed during this period are anxiety (panic, social anxiety), depressive, bipolar, psychotic, obsessive-compulsive, impulse control, conduct, substance-related, and eating disorders.

GENERAL PRINCIPLES OF THE PSYCHOSOCIAL INTERVIEW

Psychosocial interviewing in the context of a routine pediatric visit requires adequate time and privacy. The purpose of this line of inquiry should be explained to the child and parents ("to make sure things are going OK at home, at school, and with friends"), along with the limits of confidentiality. Thereafter, the first goal of the interview is to build rapport with both the child and the parents (see Chapters 18 and 34 for further discussion of strategies for engaging families).

With the parents, this rapport is grounded in respect for the parents' knowledge of their child, their role as the central influence in their child's life, and their desire to make a better life for their child. Parents often feel anxious or guilty because they believe that problems a child is experiencing imply that their parenting skills are inadequate. Parents' experiences of their own childhood influence the meaning a parent places on a child's feelings and behavior. A good working alliance allows mutual discovery of the past as it is active in the present and permits potential distortions to be modified more readily. Developmentally appropriate overtures can facilitate rapport with the child. Examples include playing peek-a-boo with an infant, racing toy cars with a preschooler, commenting on sports with a child who is wearing a baseball cap, and discussing music with a teenager who is wearing a rock band T-shirt.

After an overture with the child, it is helpful to begin with **family-centered interviewing,** in which the parent is invited to present any psychosocial concerns (learning, feelings, behavior, peer relationships) about the child. With adolescent patients, it is important to conduct a separate interview to give the adolescent an opportunity to confirm or refute the parent's presentation and to present the problem from his or her perspective. Following the family's undirected presentation of the primary problem, it is important to shift to direct questioning to clarify the duration, frequency, and severity of symptoms, associated distress or functional impairment, and the developmental and environmental context in which the symptoms occur.

Because of the high degree of **comorbidity** of psychosocial problems in children, after eliciting the presenting problem, the pediatric practitioner should then briefly screen for problems in all the major

Table 32.1 Mental Health Action Signs

- Feeling very sad or withdrawn for more than 2 weeks
- Seriously trying to harm or kill yourself, or making plans to do so
- Sudden overwhelming fear for no reason, sometimes with a racing heart or fast breathing
- Involvement in many fights, using a weapon, or wanting to badly hurt others
- Severe out-of-control behavior that can hurt yourself or others
- Not eating, throwing up, or using laxatives to make yourself lose weight
- Intense worries or fears that get in the way of your daily activities
- Extreme difficulty in concentrating or staying still that puts you in physical danger or causes school failure
- Repeated use of drugs or alcohol
- Severe mood swings that cause problems in relationships
- Drastic changes in your behavior or personality

From The Action Signs Project. *Center for the Advancement of Children's Mental Health* at Columbia University.

developmentally appropriate categories of cognitive, developmental, emotional, behavioral, and social disturbance, including problems with mood, anxiety, attention, behavior, substance use, eating, elimination, social relatedness, language, and learning. This can be preceded by a transition statement such as, "Now I'd like to ask about some other issues that I discuss with all parents and kids. Have there been any problems with attention, learning, behavior, sad mood…" etc.

A useful guide for this area of inquiry is provided by the **11 Action Signs** (Table 32.1), designed to give frontline clinicians the tools needed to recognize early symptoms of mental disorders. *Functional impairment* can be assessed by inquiring about symptoms and function in the major life domains, including home and family, school, peers, and community. These domains are included in the **HEADSS** (Home, Education, Activities, Drugs, Sexuality, Suicide/Depression) Interview Guide, often used in the screening of adolescents (Table 32.2).

The nature and severity of the presenting problem(s) can be further characterized through a **standardized self-, parent-, or teacher-informant symptom rating scale**; Table 32.3 lists selected scales in the public domain. A rating scale is a type of measure that provides a relatively rapid assessment of a specific construct with an easily derived numerical score that is readily interpreted. The use of symptom rating scales can ensure efficient, systematic coverage of relevant symptoms, quantify symptom severity, and document a baseline against which treatment effects can be measured. Functional impairment also can be assessed with self- and other-reported rating scales.

Clinical experience and methodologic studies suggest that parents and teachers are more likely than the child to report externalizing problems (disruptive, impulsive, overactive, or antisocial behavior). Children may be more likely to report anxious or depressive feelings, including suicidal thoughts and acts, of which the parents may be unaware. Discrepancies across informants are common and can shed light on whether the symptoms are pervasive or contextual. Although concerns have been raised about children's competence as self-reporters (because of limitations in linguistic skills, self-reflection, emotional awareness, ability to monitor behavior, thoughts, and feelings, tendency toward social desirability), children and adolescents can both be reliable and valid self-reporters.

Pediatric practitioners are encouraged to become familiar with the psychometric characteristics and appropriate use of at least one **general (broad-band) psychosocial screening instrument**, such as the *Strengths and Difficulties Questionnaire* (SDQ)* or the *Pediatric Symptom Checklist* (PSC)† to identify potential mental health problems. If the clinical interview or broad-band symptom rating scale suggests difficulties in one or more specific symptom areas, the clinician can follow with a psychometrically sound, corresponding **narrow-band**

Table 32.2 HEADSS Screening Interview for Taking a Rapid Psychosocial History

PARENT INTERVIEW

Home
- How well does the family get along with each other?

Education
- How well does your child do in school?

Activities
- What does your child like to do?
- Does your child do anything that has you really concerned?
- How does your child get along with peers?

Drugs
- Has your child used drugs or alcohol?

Sexuality
- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/Depression
- Has your child ever been treated for an emotional problem?
- Has your child ever intentionally tried to hurt him/herself or made threats to others?

ADOLESCENT INTERVIEW

Home
- How do you get along with your parents?

Education
- How do you like school and your teachers?
- How well do you do in school?

Activities
- Do you have a best friend or group of good friends?
- What do you like to do?

Drugs
- Have you used drugs or alcohol?

Sexuality
- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/Depression
- Everyone feels sad or angry some of the time. How about you?
- Did you ever feel so upset that you wished you were not alive or so angry you wanted to hurt someone else badly?

HEADSS, Home, Education, Activities, Drugs, Sexuality, Suicide/Depression.
From Cohen E, MacKenzie RG, Yates GL. HEADSS, a psychosocial risk assessment instrument: implications for designing effective intervention programs for runaway youth. *J Adolesc Health.* 1991;12:539–544.

instrument, such as the *Vanderbilt ADHD Diagnostic Rating Scale* or *Swanson Nolan and Pelham (SNAP)-IV-26* for attention and behavior problems; the *Center for Epidemiological Studies Depression Scale for Children* (CES-DC), *Mood and Feelings Questionnaire* (MFQ), or *Patient Health Questionnaire-9* (PHQ-9) for depression; or the *Screen for Child Anxiety Related Emotional Disorders* (SCARED) or the *Generalized Anxiety Disorder-7* (GAD-7) for anxiety.

Children and adolescents scoring above focused symptom rating scale cutpoints in most cases should undergo a mental health assessment, because scores above cutpoints are highly correlated with clinically significant psychiatric disorders. Youths scoring just below or only slightly above cutpoints may be appropriate for preventive intervention (anticipatory guidance) in the pediatric primary care setting. Youths scoring moderately above cutpoints for disorders commonly presenting in pediatric primary care (e.g., anxiety, depression, ADHD) may be appropriate for treatment in primary care. Youths scoring greatly above cutpoints for anxiety, depression, and ADHD, or youths presenting with symptoms of psychiatric disorders nearly always characterized by severity and complexity (e.g., bipolar, psychotic, obsessive-compulsive,

* http://www.sdqinfo.org/py/sdqinfo/b0.py.
† http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf.

Table 32.3 Selected List of Mental Health Rating Scales in the Public Domain

INSTRUMENTS	FOR AGES (YR)	INFORMANT: NUMBER OF ITEMS	TIME TO COMPLETE (MIN)	AVAILABLE AT
BROAD-BAND/GENERALIZED				
Pediatric Symptom Checklist (PSC)	4-18	Parent: 35, 17 Youth: 35, 17	5-10	https://www.massgeneral.org/psychiatry/treatments-and-services/pediatric-symptom-checklist
Strengths and Difficulties Questionnaire (SDQ)	4-18	Parent, Teacher, Child: 25	5	https://www.sdqinfo.org
NARROW-BAND/FOCUSED				
Anxiety				
Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED)	8-18	Parent, Child: 41	5	https://www.pediatricbipolar.pitt.edu/resources/instruments
Generalized Anxiety Disorder-7 (GAD-7)	12-18	Youth: 7	1	https://www.phqscreeners.com
Attention and Behavior				
Vanderbilt ADHD Diagnostic Rating Scale	6-12	Parent: 55 Teacher: 43	10	https://www.nichq.org/resource/nichq-vanderbilt-assessment-scales
Swanson Nolan and Pelham (SNAP)-IV 26	6-18	Parent and Teacher: 26	5	http://www.shared-care.ca/files/Scoring_for_SNAP_IV_Guide_26-item.pdf
Autism				
Modified Checklist for Autism in Toddlers (M-CHAT)	16-30 mo	Parent: 23	5-10	https://mchatscreen.com
Depression				
Center for Epidemiological Studies Depression Scale for Children (CES-DC)	6-18	Child: 20	5	https://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf
Mood and Feelings Questionnaire (MFQ)	7-18	Parent: 34 Child: 33	<5	https://devepi.duhs.duke.edu/measures/the-mood-and-feelings-questionnaire-mfq/
Patient Health Questionnaire–9 (PHQ-9)	12/13+	9	<5	https://www.phqscreeners.com

ADHD, Attention-deficit/hyperactivity disorder.

posttraumatic stress, eating) may be most appropriate for treatment in specialty care.

The **safety** of the child in the context of the home and community is of paramount importance. The interview should sensitively assess whether the child has been exposed to any frightening events, including abuse, neglect, bullying, marital discord, or domestic or community violence; whether the child shows any indication of dangerousness to self or others or a severely altered mental status (psychosis, intoxication, delirium, rage, hopelessness); or whether the child (if age appropriate) has been involved in any **risky behavior**, including running away, staying out without permission, truancy, gang involvement, experimentation with substances, and unprotected sexual encounters. The interview also should assess the capacity of the parents to adequately provide for the child's physical, emotional, and social needs or whether parental capacity has been diminished by psychiatric disorder, family dysfunction, or the sequelae of disadvantaged socioeconomic status. Any indications of threats to the child's safety should be immediately followed by thorough assessment and protective action.

DIAGNOSIS

There is variability in the level of confidence pediatric practitioners perceive in diagnosing mental health problems in children and adolescents in accordance with *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. Pediatric practitioners who have familiarity with psychiatric diagnostic criteria may feel confident diagnosing certain disorders, particularly the more common neurodevelopmental, elimination, and eating disorders (ADHD, anxiety, autism spectrum, tics, enuresis, encopresis, anorexia). The disorders about which some pediatric practitioners might have less diagnostic confidence include the disruptive/impulse control/conduct, anxiety, depressive, bipolar, psychotic, obsessive-compulsive, trauma-related, somatic symptom, and substance-related disorders. Pediatric practitioners may prefer to use the "unspecified" diagnosis option in the context of diagnostic uncertainty until clarification is achieved, often through consultation with or referral to a mental health clinician.

While focusing on the specific psychiatric manifestations and their appropriate treatment, the practitioner must also take into consideration secondary etiologies (systemic illnesses, substance and medication use [Tables 32.4 and 32.5]) producing psychiatric symptoms. Disease-specific therapy combined with psychopharmacology is often necessary when a systemic disorder is identified.

PSYCHIATRIC DIAGNOSTIC EVALUATION

The objectives of the psychiatric diagnostic evaluation of the child and adolescent, generally conducted by a behavioral health specialist, are to determine whether **psychopathology or developmental risk** is present and if so, to establish an explanatory formulation and a differential diagnosis, and to determine whether treatment is indicated and, if so, to develop a treatment plan and facilitate the parents' and child's involvement in the plan. The aims of the diagnostic evaluation are to clarify the reasons for the referral, to obtain an accurate accounting of the child's developmental functioning and the nature and extent of the child's psychosocial difficulties, functional impairment, and subjective distress, and to identify potential individual, family, or environmental factors that might account for, influence, or ameliorate these difficulties. The issues relevant to diagnosis and treatment planning can span genetic, constitutional, and temperamental factors, individual psychodynamics, cognitive, language, and social skills, family patterns of interaction and child-rearing practices, and community, school, and socioeconomic influences.

Table 32.4 Medical (Secondary) and Psychiatric (Primary) Causes of Psychosis and/or Depression

CATEGORY	DISORDERS
Psychiatric	Schizophrenia Schizoaffective Schizophreniform Brief psychotic Major depression Bipolar Postpartum
Head trauma	Traumatic brain injury Subdural hematoma
Infectious	Viral infections/encephalitides (HIV infection/encephalopathy, herpes encephalitis, cytomegalovirus, Epstein-Barr virus, COVID-19) Lyme disease Cerebral malaria Endocarditis Neurosyphilis Whipple disease
Inflammatory	Autoimmune encephalitis: NMDAR, limbic, others (see Table 32.5) Systemic lupus erythematosus Sjögren syndrome Hashimoto encephalopathy (steroid-responsive encephalopathy associated with autoimmune thyroiditis [SREAT]) Sydenham chorea Sarcoidosis Celiac disease
Neoplastic	Primary or secondary cerebral neoplasm Paraneoplastic encephalitis: ovarian teratoma-associated autoimmune encephalitis Systemic neoplasm Pheochromocytoma
Endocrine or acquired metabolic	Hepatic encephalopathy Uremic encephalopathy Hypo/hyperparathyroidism Hypo/hyperthyroidism Addison disease Cushing disease Vitamin deficiency: vitamin B_{12}, folate, niacin, vitamin C, thiamine Gastric bypass–associated nutritional deficiencies Hypoglycemia Hyponatremia
Vascular	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Other vasculitis syndromes Stroke
Degenerative	Idiopathic basal ganglia calcifications, Fahr disease Neuroacanthocytosis Neurodegeneration with brain iron accumulation (NBIA) Tuberous sclerosis Huntington disease Corticobasal ganglionic degeneration Multisystem atrophy, striatonigral degeneration, olivopontocerebellar atrophy
Demyelinating, dysmyelinating	Multiple sclerosis Acute disseminated encephalomyelitis Adrenoleukodystrophy Metachromatic leukodystrophy
Inherited metabolic	Wilson disease Posterior horn syndrome Tay-Sachs disease (adult onset) Neuronal ceroid lipofuscinosis Niemann-Pick disease type C Acute intermittent porphyria Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
Inherited metabolic (cont'd)	Mitochondrial neurogastrointestinal encephalopathy (MNGIE) Cerebrotendinous xanthomatosis Homocystinuria Ornithine transcarbamylase deficiency Phenylketonuria
Syndromes	Williams Prader-Willi Marfan Fragile X Deletion 22q11.2 Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation (ROHHAD) Klinefelter
Epilepsy	Ictal Interictal Postictal Postepilepsy surgery Lafora progressive myoclonic epilepsy Complex partial (temporal lobe)
Substance induced (medications)	Analgesics Acyclovir Androgens (anabolic steroids) Antiarrhythmics Anticonvulsants Anticholinergics Antihypertensives Antineoplastic agents β-Blocking agents Cefepime Clarithromycin Cyclosporine Dextromethorphan Dopamine agonists Ketamine Fluoroquinolones Metronidazole Sulfamethoxazole-trimethoprim Oral contraceptives Sedatives/hypnotics Selective serotonin reuptake inhibitors (SSRIs) (serotonin syndrome) Steroids
Substance induced	Alcohol Amphetamines Cocaine LSD Marijuana and synthetic cannabinoids Methylenedioxymethamphetamine (MDMA, Ecstasy) Phencyclidine Mescaline Psilocybins (mushrooms)
Drug withdrawal syndromes	Alcohol Barbiturates Benzodiazepines Amphetamines SSRIs
Toxins	Heavy metals: lead, mercury, arsenic Carbon monoxide Inhalants Organophosphates St. John's wort
Other	Normal-pressure hydrocephalus Ionizing radiation Decompression sickness Narcolepsy

From Byrne R, Elsner G, Beattie A. Emotional and behavioral symptoms. In Kliegman RM, Toth H, Bordini BJ, Basel D (eds): *Nelson Pediatric Symptom-Based Diagnosis: Common Diseases and their Mimics*, 2nd ed. Philadelphia: Elsevier, 2023. Table 31.4, p. 514–515.

Table 32.5 Antigenic Targets in Autoimmune Encephalitis with Associated Psychiatric Features

COMMONLY TARGETED ANTIGENS	ANTIGEN DESCRIPTION OR EPITOPE	MAIN ENCEPHALOPATHY SYNDROME AND PSYCHIATRIC FEATURES	OTHER ASSOCIATED NEUROLOGIC DISORDERS	MAIN PSYCHIATRIC FEATURES
NMDAR	Ligand-gated ion channel	Encephalopathy (frequently extralimbic manifestation)	Post–herpes simplex encephalitis relapse with chorea; pediatric dyskinetic encephalitis lethargica; idiopathic epilepsy; immunotherapy-responsive dementia	Anxiety, agitation, bizarre behavior, catatonia, delusional or paranoid thoughts, and visual or auditory hallucinations; also movement disorder, seizures, autonomic instability
LGI1	VGKC-associated and AMPAR-associated secreted molecule	Limbic encephalitis with or without faciobrachial dystonic seizures; prominent hyponatremia	Morvan syndrome, neuromyotonia, epilepsy, REM sleep behavior disorder; rarely isolated movement disorder (parkinsonism, dystonia, chorea)	Confusion, hallucinations, depression
CASPR2	VGKC-associated adhesion molecule	Morvan syndrome: peripheral nerve hyperexcitability, autonomic instability, encephalopathy	Limbic encephalitis, neuromyotonia, epilepsy; rarely isolated movement disorder (chorea, myoclonus)	Confusion, hallucinations, agitation, delusions
AMPAR	Ligand-gated ion channel	Limbic encephalitis	NA	Personality change, psychosis, apathy, agitation, confabulation
$GABA_AR$	Ligand-gated ion channel	Limbic encephalitis with refractory seizures	Varied presentations	Confusion, anxiety, affective changes (including depression), hallucinations, catatonia
$GABA_BR$	Ligand-gated ion channel	Limbic encephalitis with refractory status epilepticus	Opsoclonus-myoclonus; cerebellar ataxia; PERM	Psychosis, agitation, catatonia
Hu	Intracellular RNA-binding protein	Limbic encephalitis or limbic encephalomyelitis occurring with small cell lung cancer	Painful sensory neuropathy; cerebellar ataxia	Confusion, depression, less commonly hallucinations
Ma2	Intracellular protein involved in mRNA processing or biogenesis	Limbic encephalitis occurring with testicular germ cell tumors; REM sleep disorder is common; frequent short-term memory problems	Visual dysfunction, gait disturbance, hypokinesia	Confusion and anxiety, including obsessions and compulsions
D2R	Metabotropic receptor	So-called basal ganglia encephalitis with prominent movement disorder (i.e., dystonia, parkinsonism, chorea, tics)	Sydenham chorea, PANDAS	Agitation, depression, psychosis, emotional lability
DPPX	Auxiliary subunit of Kv4.2 potassium channels	Limbic encephalitis with enteropathy	PERM	Amnesia, delirium, psychosis, depression
MGluR5	Metabotropic glutamate receptor	So-called Ophelia syndrome: limbic encephalitis in association with Hodgkin lymphoma	Paraneoplastic limbic encephalitis without lymphoma, or nonparaneoplastic limbic encephalitis; immunotherapy-responsive prosopagnosia	Depression, anxiety, delusions, visual and auditory hallucinations, personality change, anterograde amnesia
GFAP	Intracellular (cytosolic) glial intermediate filament protein	Corticosteroid-responsive meningoencephalitis or encephalitis, with or without myelitis; presents with subacute onset of memory loss and confusion	NA	Occurred in 29% in one study but not described in detail; psychosis and behavioral changes reported

AMPAR, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; D2R, dopamine receptor D2; DPPX, dipeptidyl-peptidase-like protein-6; $GABA_AR$, γ-aminobutyric acid type A receptor; $GABA_BR$, γ-aminobutyric acid type B receptor; GFAP, glial fibrillary acidic protein; LGI1, leucine-rich glioma-inactivated 1; MGluR5, metabotropic glutamate receptor 5; NA, not applicable; NMDAR, N-methyl-D-aspartate receptor; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PERM, progressive encephalomyelitis with rigidity and myoclonus; REM, rapid eye movement; VGKC, voltage-gated potassium channel.

Modified from Pollak TA, Lennox BR, Muller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. *Lancet Psychiatry.* 2020;7(1):93–108.

The focus of the evaluation is developmental; it seeks to describe the child's functioning in various realms and to assess the child's adaptation in these areas relative to that expected for the child's age and phase of development. The developmental perspective extends beyond current difficulties to vulnerabilities that can affect future development and as such are important targets for preventive intervention. Vulnerabilities may include **subthreshold or subsyndromal difficulties** that, especially when manifold, often are accompanied by significant distress or impairment and as such are important as potential harbingers of future problems.

Throughout the assessment, the clinician focuses on identifying a realistic balance of vulnerabilities and strengths in the child, in the parents, and in the parent–child interactions. From this strength-based approach, over time a hopeful family narrative is co-constructed to frame the child's current developmental progress and predict the child's ongoing progress within the scope of current risk and protective factors.

As described earlier a **psychiatric** assessment conducted by a pediatric primary care practitioner generally will be a brief **psychosocial** assessment focused on obtaining sufficient information to triage the case to the appropriate level of care. A brief assessment can comprise both administration of a focused (narrow-band) symptom rating scale to assess symptom severity and a focused clinical interview. The focused clinical interview can comprise four dimensions: **history** (onset, duration, response to prior treatment, family history), **severity** (as derived from the focused rating scale and verbal query about the degree of distress and/or impairment associated with the symptom[s]), **complexity** (brief review of psychiatric comorbidities and medical or social complexities), and **safety** (ascertainment of imminent and substantial risk of harm). With this information, the pediatrician can provisionally diagnose the case and triage the case to primary care (for preventive intervention or treatment of mild to moderate presentations of common disorders [e.g., ADHD, anxiety, depression]), or to specialty behavioral healthcare (for severe presentations of these disorders or for other psychiatric disorders nearly always characterized by severity and complexity).

In the specialty care setting, although the scope of the evaluation will vary with the clinical setting (e.g., emergency room vs medical floor vs psychiatric clinic), a **comprehensive psychiatric diagnostic evaluation** typically has 12 major components:

- Presenting problem(s) and the context in which they occur
- Review of psychiatric symptoms
- History of psychiatric treatment
- Medical history
- Developmental history
- Educational history
- Family history
- Mental status examination
- Biopsychosocial clinical formulation
- *DSM, Fifth Edition* (DSM-5) diagnosis
- Risk assessment
- Treatment plan

For infants and young children, the presenting problem and historical information is derived from parents and other informants. As children mature, they become increasingly important contributors to the information base, and they become the primary source of information in later adolescence. Information relevant to formulation and differential diagnosis is derived in multiple ways, including directive and nondirective questioning, interactive play, and observation of the child alone and together with the caregiver(s).

The **explication of the presenting problem(s)** includes information about onset, duration, frequency, setting, and severity of symptoms, associated distress and/or functional impairment, and predisposing, precipitating, perpetuating, and ameliorating contextual factors. The **symptom review** assesses potential comorbidity in the major domains of child and adolescent psychopathology. The **history of psychiatric treatment** includes gathering information about prior emergency mental health assessments, psychiatric hospitalizations, day treatment, psychotherapy, pharmacotherapy, and nontraditional treatments.

The **medical history** includes information about the source of primary care, the frequency of health supervision, past and current medical illnesses and treatments, and the youth and family's history of adherence to medical treatment. A systematic review of organ or functional systems facilitates the identification of abnormalities that require investigation or monitoring by the pediatric practitioner, as well as the identification of cautionary factors related to the prescription of psychotropic medication. The **developmental history** includes information about the circumstances of conception, pregnancy, or adoption, pre-, peri-, or postnatal insults, attachment and temperament, cognitive, motor, linguistic, emotional, social, and moral development, health habits, sexuality, substance use (as age appropriate), coping and defensive structure, future orientation, and perceived strengths. The **educational history** includes schools attended, typical grades, attendance, behavior, classroom accommodations, special education services, disciplinary actions, social relationships, extracurricular activities, and barriers to learning. The **family history** assesses family composition, sociodemographic and neighborhood characteristics, domiciliary arrangements, parenting capacities, family function, medical/psychiatric histories of family members, and cultural/religious affiliations.

The **mental status examination** assesses appearance, relatedness, cognition, communication, mood, affective expression, behavior, memory, orientation, and perception.

The comprehensive psychiatric evaluation culminates in a biopsychosocial formulation, diagnosis, and risk assessment. The **biopsychosocial formulation** is derived from an assessment of *vulnerabilities* and *strengths* in the biologic, psychologic, and social domains and serves to identify targets for intervention and treatment. In the *biologic* domain, major vulnerabilities include a family history of psychiatric disorder as well as a personal history of pre-, peri-, or postnatal insults, cognitive or linguistic impairments, chronic physical illness, and a difficult temperament. In the *psychologic* domain, major vulnerabilities include failure to achieve developmental tasks, unresolved unconscious conflicts, and maladaptive coping and defensive styles. In the *social* domain, major vulnerabilities include parental incapacity, unskilled parenting, family dysfunction, social isolation, inadequate school setting, absence of supportive community structures, and sociodemographic disadvantage. Major strengths include cognitive and linguistic capability, physical health and vigor, stable, moderate temperamental characteristics, and stable supportive parenting, family, peer, and community structures. The biopsychosocial formulation can be organized to reflect *predisposing*, *precipitating*, *perpetuating*, and *protective (ameliorating) factors (the "4 Ps")* influencing the development of the observed psychopathology.

The **diagnosis** is made in accordance with the nomenclature in DSM-5. This nomenclature categorizes cross-sectional phenomenology into discrete clinical syndromes and seeks to improve diagnostic accuracy at the expense of theories of causation. By DSM-5 convention, if diagnostic criteria are met, the diagnosis is given (except where hierarchical rules apply); consequently, psychiatric comorbidity is a common occurrence. The **risk assessment** includes a careful assessment of risk status, including suicidality, homicidality, assaultiveness, self-injuriousness, acute mental status changes, and involvement in risky behavior or situations.

The comprehensive psychiatric diagnostic evaluation culminates in a **treatment plan** that brings the broad array of targeted interventions to the service of the child. Diagnoses drive the choice of evidence-based psychotherapeutic and psychopharmacologic treatments. The formulation drives the selection of interventions targeted at biologic, psychologic, and social vulnerabilities and strengths. Many of these treatments and interventions are described in the succeeding chapters.

SPECIAL CONSIDERATIONS IN THE DIAGNOSTIC EVALUATION OF INFANTS AND YOUNG CHILDREN

Evaluation of infants and young children with challenging behaviors includes the domains of physiology, temperament, language and motor development, affective behavior, social behavior, and communication. Although much of the information in these domains will be derived from parent report, much also can be gleaned from nonverbal behavior and observation of the parent–child interaction. Observations should include predominant affective tone of parent and child (positive, negative, apathetic), involvement in the situation (curiosity, disinterest), social responsiveness (mutuality of gaze, auditory responsiveness), and reactions to transitions (including separation).

A screen for maternal depression* is critical at this stage, as is an assessment of the mother's (or other caregiver's) ability to respond rapidly on a contingent basis to the child's expressed needs, regulate the child's rapid shifts of emotion and behavior, and provide a stimulus shelter to prevent the child from being overwhelmed.

Standardized screening instruments (Ages and Stages Questionnaires, Brief Infant-Toddler Social & Emotional Assessment, Early Childhood Screening Assessment, Modified Checklist for Autism in Toddlers, Parents' Evaluation of Developmental Status, and Survey of Well-being of Young Children) designed for this age-group can be helpful in systematizing the evaluation. In addition, the Infant, Toddler and Preschool Mental Status Exam (ITP-MSE) is a reference tool that describes how traditional categories of the mental status examination can be adapted to observations of young children. Additional categories, including sensory and state regulation, have been added that reflect important areas of development in young children.

Diagnostic systems that are more age appropriate than DSM-5 have been developed for infants and young children. These systems include the *Research Diagnostic Criteria–Preschool Age* (RDC-PA) and *Zero to Three Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood-Revised* (DC: 0-3R). The DC: 0-3R includes a relationship classification that assesses the range of interactional adaptation in each parent–child relationship and regulation disorders of sensory processing that identify a range of constitutionally and maturationally based sensory reactivity patterns, motor patterns, and behavior patterns that together can dysregulate a child internally and impact the child's interactions with caregivers.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

*See http://www.medicalhomeportal.org/clinical-practice/screening-and-prevention/maternal-depression for several examples.

Chapter 33

Psychopharmacology

David R. DeMaso and Heather J. Walter

Psychopharmacology is the first-line treatment for several child and adolescent mental health disorders (e.g., attention-deficit/hyperactivity [ADHD], schizophrenia spectrum, and bipolar disorders) and is used adjunctively with psychosocial treatments for other disorders (or comorbid conditions), including anxiety, depressive, autism spectrum, trauma-related, and obsessive-compulsive disorders. Before prescribing a psychotropic medication, primary care practitioners (PCPs) should review full prescribing information for each medication (in package inserts or at reliable websites such as the National Institutes of Health *DailyMed**) to obtain complete and up-to-date information about indications, contraindications, warnings, interactions, and precautions.

*https://dailymed.nlm.nih.gov/dailymed/index.cfm.

It is helpful for PCPs to be guided by principles for effective use of psychotropic medications in their medication assessment and management (Table 33.1). These principles involve a series of interconnected steps, including conducting a focused behavioral health assessment, **establishing target symptom(s)** and appropriate level of care, deciding on a medication and a monitoring plan, obtaining treatment assent/consent, and implementing treatment. In following this approach, PCPs are well positioned to provide safe and effective first-line psychopharmacology for common mental health conditions (e.g., ADHD, anxiety, depression) with moderate symptom presentations. Severe/complex presentations likely are better served through consultation with and/or referral to a behavioral health specialist.

Questions remain about the quality of the evidence supporting the use of many psychotropic medications in children and adolescents. In general, cognitive, emotional, and behavioral symptoms are targets for medication treatment when (1) there is no or insufficient response to available evidence-based psychosocial interventions, (2) the patient's symptoms are severe and the patient is experiencing significant distress or functional impairment, and/or (3) the patient's symptoms convey significant risk of harm. Common target symptoms include agitation, aggression, anxiety, depression, mania, hyperactivity, inattention, impulsivity, obsessions, compulsions, and psychosis (Table 33.2). All these symptoms can be quantitatively measured with standardized rating scales to establish baseline symptom severity and facilitate "treating to target."

STIMULANTS AND OTHER ADHD MEDICATIONS

Stimulants are sympathomimetic drugs that act both in the central nervous system (CNS) and peripherally by enhancing dopaminergic and noradrenergic transmission (Table 33.3). Strong evidence (approximate effect size 1.00, large) exists for the effectiveness of these medications for the treatment of ADHD (Chapter 50); stimulants also are effective for the management of aggression. In some cases, stimulants have been used as monotherapy for fatigue or malaise associated with chronic physical illnesses.

No major differences in efficacy or tolerability have been found between different classes of stimulants, and no consistent patient profile identifies those who will respond preferentially to one class over another. The most common (generally dose-dependent) side effects of stimulants include headache, stomachache, appetite suppression, weight loss, blood pressure (BP) and heart rate increases, and delayed sleep onset. Less common side effects include irritability (more prominent in younger children), aggression, social withdrawal, and rarely, hallucinations (visual or tactile).

Stimulants have been associated with elevations in mean BP (<5 mm Hg) and pulse (<10 beats/min); a subset of individuals (5–10%) may have greater increases. The rate of sudden death in pediatric patients taking stimulants is comparable to children in the general population; the hazard ratio for serious cardiovascular (CV) events is 0.75 (although up to a twofold increase in risk could not be ruled out). Moreover, a case series analysis of children with a CV incident and treatment with methylphenidate demonstrated an increased risk of arrhythmia (incidence rate ratio, 1.61) that was highest in the presence of congenital heart disease. The U.S. Food and Drug Administration (FDA) recommends that stimulants should be avoided in the presence of structural cardiac abnormalities (e.g., postoperative tetralogy of Fallot, coronary artery abnormalities, subaortic stenosis, hypertrophic cardiomyopathy) and patient symptoms (syncope, palpitations, arrhythmias) or family history (e.g., unexplained sudden death) suggestive of CV disease. In these circumstances, cardiology consultation is recommended before prescribing. Routine electrocardiograms (ECGs) are not recommended in the absence of cardiac risk factors.

The α-adrenergic agents **clonidine** and **guanfacine** are presynaptic adrenergic agonists that appear to stimulate inhibitory presynaptic autoreceptors in the CNS (see Table 33.3). The extended release formulations of both agents have FDA approval for ADHD. The extended-release formulation of guanfacine has strong evidence (approximate effect size 0.80, large) for the monotherapy of ADHD. Extended-release guanfacine also has moderate evidence for effective treatment

Table 33.1 Principles for Effective Use of Psychotropic Medications

- **Identify potential target symptoms using broad mental health screening instruments (e.g., Pediatric Symptom Checklist [PSC-17])**
- **Conduct focused behavioral health (BH) assessment to establish target symptoms and appropriate level of care**
  - Focused symptom rating scales, e.g.,
    - Patient Health Questionnaire-9 (PHQ-9)
    - Mood and Feelings Questionnaire (MFQ)
    - Screen for Child Anxiety Related Disorders (SCARED)
    - Generalized Anxiety Disorder-7 (GAD-7)
    - Vanderbilt ADHD Diagnostic Rating Scales
    - Swanson Nolan and Pelham-IV-26 (SNAP-IV-26)
  - Focused clinical interview to determine symptom history, severity (from focused rating scale score), complexity (psychiatric comorbidities, medical or psychosocial complexity), and safety (imminent risk of substantial harm)
    - If insufficient information is available to render a precise diagnosis for a symptom cluster, consider applying Unspecified Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) psychiatric diagnosis
  - Rule out alternative explanations (medical, medication, substance, or developmental "masqueraders") for target symptoms (may require specialty referral)
- **Establish appropriate level of care based upon findings from focused BH assessment**
  - Subclinical to mild presentation: triage to brief preventive intervention (e.g., anticipatory guidance)
  - Moderate presentation: triage to primary care for basic psychopharmacology and/or brief psychosocial intervention
  - Severe presentation: triage to specialty behavioral healthcare for comprehensive diagnostic evaluation, advanced psychopharmacology, and/or specialized psychotherapy
- **Rule out relative or absolute contraindications to medication use, e.g.,**
  - Medical conditions
  - Drug interactions
  - Inability to monitor (e.g., unreliable parent/guardian, patient residing out of town)
  - Concern about drug diversion in the context of substance abuse or antisocial behavior
- **Counsel about factors potentially contributing to symptom presentation or affecting response to medication**
  - Inadequate nutrition, physical activity, sleep, recreation, stress management; substance use
- **Consider response to previous medication trials**
  - Favorable and adverse effects
- **Develop comprehensive treatment plan as indicated**
  - Psychotherapy and/or medication
  - Home and/or school interventions
- **Obtain informed consent from parent/guardian and assent from patient**
  - Nature of the condition needing treatment
  - Nature and purpose of proposed treatment and the probability that it will succeed
  - Risks and benefits of the proposed treatment
  - Alternatives to the proposed treatment, and their attendant risks and benefits
  - Prognosis with and without the proposed treatment
- **Select evidence-based medication and prescribe an adequate dose for an adequate duration; whenever possible, U.S. Food and Drug Administration (FDA)-approved medications for the given indication should be prioritized**
  - Titrate to effective tolerated dose within established dosage range
  - Consider the period of time needed for each medication to achieve maximum effect
  - "Start low, go slow"
- **Explain details of medication management**
  - Name of medication
  - When to administer
  - Who should administer (e.g., parent, older teen)
  - How to administer (e.g., with food, swallowed whole)
  - Time to onset
  - Duration of action
  - How to store medication
  - Review of side effects and what to do if each should occur
  - How response to medication will be monitored (e.g., focused symptom rating scales, height/weight, pulse/blood pressure, side effect checks)
  - Special safety instructions (e.g., suicidal thoughts, severe agitation)
  - What the next step will be if medication is ineffective or not tolerated
  - How long medication likely will need to be taken if effective
  - Consider providing parent with standardized Medication Guide, such as those found at https://dailymed.nlm.nih.gov/dailymed/index.cfm
- **Monitor medication compliance and physical/laboratory parameters as indicated**
- **Monitor response to treatment**
  - Periodic readministration of focused symptom rating scale(s); adjust dose as indicated to achieve remission
- **Taper and discontinue ineffective medication before substituting alternative medication, or have clear rationale for using medication combinations**
- **Plan for medication discontinuation after symptom-free and high-functioning interval**

of ADHD with comorbid oppositional defiant disorder (ODD), favorably affecting both symptom clusters, as well as for the treatment of agitation in autism.

Sedation, somnolence, headache, abdominal pain, hypotension, bradycardia, cardiac conduction abnormalities, dry mouth, depression, and confusion are potential side effects of clonidine and guanfacine. Abrupt withdrawal can result in rebound hypertension; overdose can result in bradycardia and hypotension leading to hospitalization or death.

Atomoxetine is a selective inhibitor of presynaptic norepinephrine reuptake that increases dopamine and norepinephrine in the prefrontal cortex (see Table 33.3). It is less effective for the treatment of ADHD (approximate effect size 0.60, medium) than stimulants, but atomoxetine has a longer duration of action (approximately 24 hours). Atomoxetine can have an onset of action within 1-2 weeks of starting treatment, but there is an incrementally increasing response for up to 4-6 weeks or longer. Common side effects include nausea, headache, abdominal pain, insomnia, somnolence, erectile dysfunction, irritability, fatigue,

Table 33.2 Target Symptom Approach to Psychopharmacologic Management

TARGET SYMPTOM	MEDICATION CONSIDERATIONS
Aggression	Stimulant α-Agonist Antipsychotic (only if aggression is severe or dangerous)
Agitation	Antipsychotic (only if agitation is severe or dangerous) Anxiolytic
Anxiety	Antidepressant Anxiolytic (only for acute situational anxiety)
Depression	Antidepressant
Hyperactivity, inattention, impulsivity	Stimulant α-Agonist Selective norepinephrine reuptake inhibitor
Mania	Antipsychotic Lithium
Obsessions, compulsions	Antidepressant
Psychosis	Antipsychotic
Tics	α-Agonist Antipsychotic (only if tics are severe/disabling)

Adapted from Shaw RJ, DeMaso DR. *Clinical Manual of Pediatric Consultation-Liaison Psychiatry*. Washington, DC: American Psychiatric Press, 2020: 443.

decreased appetite, weight loss, and dizziness, along with nonclinical increases in heart rate and BP. Potential serious neuropsychiatric reactions include psychosis, mania, panic attacks, aggressive behavior, depression, seizures, and suicidal thinking. Atomoxetine carries an FDA warning regarding the risk of suicidal thinking and the need to monitor this closely. Atomoxetine also has been associated with rare hepatotoxicity and should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Because of the risk of sudden death, atomoxetine generally should be avoided in youth with known serious structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, or other serious cardiac problems.

Viloxazine is a second selective norepinephrine reuptake inhibitor that was approved for ADHD by the FDA in 2021. It has once daily dosing, reaches steady state by day 2, and has a similar side effect profile to atomoxetine (including FDA warnings on suicidality and increases in heart rate and blood pressure).

ANTIDEPRESSANTS

Antidepressant drugs act on presynaptic and postsynaptic receptors affecting the release and reuptake of brain neurotransmitters, including norepinephrine, serotonin, and dopamine (Table 33.4). There is moderate evidence for the effectiveness of antidepressant medications in the treatment of anxiety and obsessive-compulsive disorders (approximate effect size 0.70, medium) and weaker evidence for the treatment of depressive disorders (approximate effect size 0.30, small). Suicidal thoughts have been reported during treatment with all antidepressants. The overall risk difference of suicidal thoughts/behaviors across randomized controlled trials (RCTs) of all antidepressants and all indications has been reported as 0.7%, corresponding to a *number needed to harm* of 143. All antidepressants carry an FDA warning for suicidality; careful monitoring is recommended during the initial stages of treatment and following dose adjustments.

The **selective serotonin reuptake inhibitor (SSRI)** fluoxetine outperforms all other antidepressants (both SSRI and non-SSRI) studied and is the only SSRI separating from placebo in studies of depressed *preadolescents*. Side effects to SSRIs generally manifest in the first few weeks of treatment, and many will resolve with time. More common side effects include nausea, irritability, insomnia, appetite changes, weight loss/gain, headaches, dry mouth, dizziness, bruxism, diaphoresis, tremors, akathisia, and restlessness. A small proportion of youth taking SSRIs, particularly younger children, develop **behavioral activation** (motor or mental restlessness, increased impulsivity, disinhibited behavior, talkativeness, insomnia) that can be confused with mania, but the activation symptoms typically resolve when the dose is decreased or the medication discontinued. Because the likelihood of activation events has been associated with higher antidepressant plasma levels, slow up-titration and close monitoring (particularly in younger children) is warranted and underscores the importance of educating parents/guardians and patients in advance about this potential side effect.

Sexual side effects are common, including decreased libido, anorgasmia, and erectile dysfunction. There is an increased risk of bleeding, especially when used with aspirin or nonsteroidal antiinflammatory drugs (NSAIDs).

SSRIs can be associated with abnormal heart rhythms, and citalopram causes dose-dependent QT interval prolongation, contraindicating doses >40 mg/day. Patients with diabetes may experience hypoglycemia during SSRI treatment and hyperglycemia on discontinuation. **Discontinuation symptoms** (e.g., dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania) are common with short-acting SSRIs (sertraline, citalopram, escitalopram), leading to a recommendation for divided doses if these medications are used at higher doses and graduated reduction if discontinued.

Serotonin syndrome results from excessive agonism of the CNS and peripheral nervous system serotonergic receptors and can be caused by prescribing multiple serotonergic medications concomitantly (Chapter 94). Symptoms can arise within 24-48 hours and are characterized by *mental status changes* (confusion, agitation, anxiety), *neuromuscular hyperactivity* (tremors, clonus, hyperreflexia, muscle rigidity), and *autonomic hyperactivity* (hypertension, tachycardia, arrhythmias, tachypnea, diaphoresis, shivering, vomiting, diarrhea). Advanced symptoms include fever, seizures, arrhythmias, and unconsciousness, which can lead to fatalities. Treatment is hospital based and includes discontinuation of all serotonergic agents and supportive care with continuous cardiac monitoring. Monoamine oxidase inhibitors (MAOIs) play a role in most cases of serotonin syndrome and should be avoided in combination with any other serotonergic drug, including another MAOI. Moreover, caution should be exercised when combining two or more non-MAOI serotonergic drugs, including antidepressants, opioids and other pain medications, stimulants, cough/cold/allergy medications, and other over-the-counter products. Caution entails starting the second non-MAOI serotonergic drug at a low dose, increasing the dose slowly, and monitoring for symptoms, especially in the first 24-48 hours after dosage changes. Adolescents should be informed that certain recreational drugs (e.g., dextromethorphan, "ecstasy") are highly serotonergic and can cause serious interactions with antidepressants.

The **non-SSRI antidepressants** include duloxetine, venlafaxine, bupropion, and mirtazapine (see Table 33.4). These medications all lack rigorous evidence to support their effectiveness in children and adolescents and as such should not be considered first-line options.

Duloxetine and venlafaxine are **serotonin-norepinephrine reuptake inhibitors (SNRIs)**. *Duloxetine* has FDA approval for treatment of generalized anxiety disorder in children and adolescents but typically is not as effective for anxiety as the SSRIs. Studies of duloxetine for depression in youth have been negative. There is some evidence in adults that duloxetine can be useful for fibromyalgia and chronic musculoskeletal pain, an effect that has also been observed in children and adolescents. Common side effects of duloxetine include nausea, diarrhea, decreased weight, and dizziness. Increases in heart rate and BP have been noted; BP should be monitored at each visit and with each dosage change. In addition, there have been reports of hepatic failure, sometimes fatal; duloxetine should be discontinued and not resumed in patients who develop jaundice or other evidence of liver dysfunction. Duloxetine also has been associated with severe skin reactions (erythema multiforme and Stevens-Johnson syndrome).

Table 33.3 Select Medications for Attention-Deficit/Hyperactivity Disorder Symptoms

GENERIC [BRAND] (HOW SUPPLIED) DURATION OF ACTION	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	SUGGESTED DAILY STARTING DOSE (MG)	USUAL DAILY THERAPEUTIC DOSAGE RANGE (MG)*
Methylphenidate [Concerta] (18, 27, 36, 54 mg caps) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	18	Age 6-12: 18-54; Age >12: 18-72
Dexmethylphenidate [Focalin XR]† (5, 10, 15, 20 mg caps) 10-12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	5	5-30
Serdexmethylphenidate/ dexmethylphenidate [Azstarys]† (26.1 mg/5.2 mg, 39.2 mg/7.8 mg, 52.3 mg/10.4 mg) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	26.1 /5.2	26.1 /5.2-52.3/10.4
Methylphenidate suspension, extended release [Quillivant XR] (25 mg/5 mL) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	10	10-60
Dextroamphetamine/ amphetamine [Adderall XR]† (5, 10, 15, 20, 25, 30 mg caps) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	2.5-5	5-30
Lisdexamfetamine [Vyvanse]† (10, 20, 30, 40, 50, 60, 70 mg caps; 10, 20, 30, 40, 50, 60 mg chewable tabs) 12-14 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	10	10-70
Amphetamine suspension extended release [Dyanavel XR] (2.5/mL) 13 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	2.5-5	2.5-20
Methylphenidate [Metadate CD]† (10, 20, 30, 40, 60 mg caps) 8 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	10	10-60
Methylphenidate [Ritalin LA]† (10, 20, 30, 40 mg caps) 8 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	10	10-60
Dextroamphetamine [Dexedrine Spansule]† (5, 10, 15 mg spansules) 6-8 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	5	5-40
Dexmethylphenidate [Focalin] (2.5, 5, 10 mg tabs) 4-5 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	2.5-5	5-20
Methylphenidate [Ritalin] (5, 10, 20 mg tabs) 4 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	2.5-5	5-60
Methylphenidate [Methylin] (5 mg/5 mL, 10 mg/5 mL) 4 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	2.5-5	5-60
Dextroamphetamine/ amphetamine [Adderall] (5, 10, 15, 20, 30 mg tabs) 4-5 hr	ADHD (3+)	Inattention Hyperactivity Impulsivity	Age 3-5: 2.5 Age ≥6: 5	Age 6-12: 5-30; Age >12: 5-40

Continued

Table 33.3 Select Medications for Attention-Deficit/Hyperactivity Disorder Symptoms—cont'd

GENERIC [BRAND] (HOW SUPPLIED) DURATION OF ACTION	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	SUGGESTED DAILY STARTING DOSE (MG)	USUAL DAILY THERAPEUTIC DOSAGE RANGE (MG)*
Dextroamphetamine [Dexedrine] (5, 10, 15, mg caps) 4 hr	ADHD (3+)	Inattention Hyperactivity Impulsivity	Age 3-5: 2.5 Age ≥6: 5	5-40
Atomoxetine [Strattera]† (10, 18, 25, 40, 60, 80, 100 mg caps) 24 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	<70 kg: 0.5 mg/kg/day >70 kg: 40	<70 kg: 0.5-1.2 mg/kg/day >70 kg: 40-100
Viloxazine [Qelbree]† (100, 150, 200 mg ER caps) 24 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	Age 6-11: 100 Age ≥12: 200	Age 6-11: 100-400 Age ≥11: 200-400
Clonidine [Kapvay] (0.1 mg tabs) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	0.05	25-40kg: 0.05-0.2 41-45kg: 0.05-0.3 >45kg: 0.05-0.4
Guanfacine [Intuniv] (1, 2, 3, 4 mg tabs) 24 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	1	25-40kg: 1-2 41-45kg: 1-3 >45kg: 1-4
Clonidine [Catapres] (0.1, 0.2, 0.3 mg tabs) 4 hr	None	Inattention Hyperactivity Impulsivity	0.05	25-40 kg: 0.05-0.2 41-45 kg: 0.05-0.3 >45 kg: 0.05-0.4
Guanfacine [Tenex] (1, 2 mg tabs) 6 hr	None	Inattention Hyperactivity Impulsivity	0.5	25-40 kg: 0.5-2 mg 41-45 kg: 0.5-3 mg >45 kg: 0.5-4 mg

*Doses shown in table may exceed maximum recommended dose for some children.
†Capsule contents may be sprinkled on soft food.
ADHD, Attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration.

Bupropion, a **norepinephrine-dopamine reuptake inhibitor (NDRI)**, appears to have an indirect mixed-agonist effect on norepinephrine and dopamine transmission. No rigorous studies of bupropion for anxiety or depression have been conducted with children or adolescents, although some evidence suggests that bupropion may be effective for smoking cessation and ADHD in youth. Common side effects include irritability, nausea, anorexia, headache, and insomnia. Dose-related seizures (0.1% risk at 300 mg/day and 0.4% risk at 400 mg/day) have occurred with bupropion, so it is contraindicated in those with epilepsy, eating disorders, or at risk for seizures.

Venlafaxine has only negative trials for the treatment of depression in children and adolescents but does have some favorable evidence for the treatment of anxiety. Side effects are similar to SSRIs, including hypertension, irritability, insomnia, headaches, anorexia, nervousness, and dizziness, and dropout rates are high in clinical trials of venlafaxine. BP should be monitored at each visit and with each dosage change. Discontinuation symptoms are more pronounced with venlafaxine than the other non-SSRI antidepressants. In addition, suicidal thinking and agitation may be more common with venlafaxine than with other antidepressants, requiring close monitoring. In light of the substantial adverse effects, venlafaxine likely should be considered to be a third-line medication.

Mirtazapine is both a noradrenergic and a specific serotonergic antidepressant. Mirtazapine has only negative trials for the treatment of depression in youth and has no rigorous evidence of effectiveness for any other child or adolescent psychiatric disorder. Mirtazapine is associated with a risk for substantial weight gain and, more rarely, hypotension, elevated liver enzymes, agranulocytosis, and QT prolongation. Although its sedating properties have led to its adjunctive use for insomnia in adults with depressive/anxiety disorders, there is no evidence for use of mirtazapine in childhood sleep disorders.

The **tricyclic antidepressants (TCAs)** have mixed mechanisms of action; for example, clomipramine is primarily serotonergic, and imipramine is both noradrenergic and serotonergic. With the advent of the SSRIs, the lack of efficacy studies, particularly in depression, and more serious side effects, the use of TCAs in children and adolescents has substantially declined. *Clomipramine* has been used in the treatment of obsessive-compulsive disorder (see Table 33.4). TCAs also have been used for neuropathic pain. TCAs cause both blood pressure and heart rate increases and are class I antiarrhythmics with quinidine-like properties that are potentially fatal in overdose. Anticholinergic symptoms (e.g., dry mouth, blurred vision, constipation) are the most common side effects.

Anxiolytic agents, including lorazepam, clonazepam, and hydroxyzine, have been effectively used for the *short-term* relief of the symptoms of *acute* anxiety (see Table 33.4). They are less effective as chronic (>4 months) anxiolytic medications, particularly when used as monotherapy. Chronic use carries a significant risk of physical and psychologic dependence.

ANTIPSYCHOTICS

Based on their mechanism of action, antipsychotic medications can be divided into first-generation (blocking dopamine D_2 receptors) and second-generation (mixed dopaminergic and serotonergic antagonists) agents (Table 33.5).

The **second-generation antipsychotics (SGAs)** have relatively strong antagonistic interactions with 5-HT_2 receptors and perhaps more variable activity at central adrenergic, cholinergic, and histaminic sites, which might account for the varying side effects, particularly metabolic, noted among these agents. The SGAs have moderate evidence for the treatment of agitation in autism and for the treatment of schizophrenia, bipolar disorder, and aggression. Haloperidol is a

Table 33.4 Select Medications for Depression and Anxiety in Children and Adolescents

GENERIC [BRAND] (HOW SUPPLIED)	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	SUGGESTED DAILY STARTING DOSE (MG)	USUAL DAILY THERAPEUTIC DOSAGE RANGE (MG)*
Citalopram [Celexa] (10, 20, 40 mg tabs)	None	Depression Anxiety Obsessions Compulsions	Age 6-12: 10 Age 13-17: 20	10-40
Escitalopram [Lexapro] (5, 10, 20 mg tabs)	Depression (12-17) Anxiety (7-17)	Depression Anxiety Obsessions Compulsions	10	5-20
Fluoxetine [Prozac] (10, 20, 40, 60 mg tabs)	Depression (8-17) OCD (7-17)	Depression Anxiety Obsessions Compulsions	Age 6-12: 10 Age 13-17: 20	Depression: 10-20 Anxiety, OCD: 10-60
Sertraline [Zoloft] (25, 50, 100 mg tabs)	OCD (6-17)	Depression Anxiety Obsessions Compulsions	Age 6-12: 12.5-25 Age 13-17: 25-50	25-200
Duloxetine [Cymbalta] (20, 30, 60 mg tabs)	Anxiety (7-17)	Depression Anxiety	30	30-60
Venlafaxine [Effexor XR] (37.5, 75, 150 mg caps)	None	Depression Anxiety	37.5	37.5-225
Bupropion [Wellbutrin XL] (150, 300 mg tabs)	None	Depression	150	150-300
Mirtazapine [Remeron] (15, 30, 45 mg tabs)	None	Depression	7.5	7.5-45
Clomipramine [Anafranil] (25, 50, 75 mg caps)	OCD (10-17)	Obsessions Compulsions	25	25-200
Lorazepam [Ativan] (0.5, 1, 2 mg tabs)	None	Acute anxiety	0.5	0.5-2
Clonazepam [Klonopin] (0.5, 1, 2 mg tabs)	None	Panic	0.5	0.5-1
Hydroxyzine [Vistaril] (25, 50 mg caps)	Anxiety	Acute anxiety	Age <12: 12.5-25 Age >12: 25-50	Age <12: 25-50 Age >12: 50-100

*Doses shown in table may exceed maximum recommended dose for some children.

high-potency **first-generation antipsychotic** that is most commonly used in treatment of agitation and schizophrenia.

The antipsychotic agents have significant side effects, including sedation, extrapyramidal symptoms, hyperprolactinemia, anticholinergic, seizures, orthostasis, CV effects, weight gain, hyperlipidemia, metabolic syndrome, glucose abnormalities, hematologic effects (e.g., leukopenia, neutropenia), and elevated liver transaminases (Table 33.6). They have an FDA warning for increased risk of diabetes. Youth appear to be more sensitive to sedation, extrapyramidal side effects (except akathisia), withdrawal dyskinesia, prolactin abnormalities, weight gain, hepatotoxicity, and metabolic abnormalities. The development of diabetes or tardive dyskinesia appears less prevalent than in adults, although this may be a function of short follow-up periods because these side effects may not emerge until adulthood.

The management of adverse effects should be proactive with baseline assessment and ongoing monitoring (Table 33.7). Abnormal movements (dystonia, akathisia, tardive dyskinesia) need periodic assessment using a standardized instrument such as the *Abnormal Involuntary Movement Scale* (AIMS). The need for antiparkinsonian agents may be a consideration, particularly for patients at risk for acute dystonia or who have a previous history of dystonic reactions. CV effects include prolongation of the QTc interval, tachycardia, orthostatic hypertension, and pericarditis. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline ECG with subsequent monitoring should be considered, along with cardiology consultation before prescribing. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

The **cytochrome P450 (CYP)** enzymes metabolize the antipsychotics and as such necessitate that the PCP and psychiatrist are alert for potential drug-drug interactions that may impact the serum levels of all patient medications. CYP3A4 is mainly relevant to lurasidone, quetiapine, olanzapine, and haloperidol, whereas CYP2D6 predominately clears aripiprazole and risperidone. Asenapine is metabolized by CYP1A2 as well as direct glucuronidation by UGT1A4. Because <10% of paliperidone undergoes CYP first-pass metabolism, there is a lower likelihood of drug-drug interactions.

Primary prevention strategies to manage weight and metabolic dysfunction include educating the youth and family about healthy lifestyle behaviors and selecting an agent that has the lowest likelihood of impacting metabolic status. Secondary strategies would include intensifying healthy lifestyle instructions, consideration of switching agents, and a weight loss treatment program. Consideration

Table 33.5 Select Medications for Psychosis, Mania, Irritability, Agitation, Aggression, and Tourette Disorder in Children and Adolescents

GENERIC (BRAND)	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	SUGGESTED DAILY STARTING DOSE	USUAL DAILY THERAPEUTIC DOSAGE RANGE (MG)*
Aripiprazole [Abilify]	Bipolar (10-17) Schizophrenia (13-17) Irritability in autism (6-17) Tourette (6-17)	Mania Psychosis Irritability Aggression Agitation Vocal/motor tics	Bipolar, schizophrenia: 2 Autism: 2 Tourette: 2	Bipolar, schizophrenia: 10-30 Autism: 5-15 Tourette: 5-20
Olanzapine [Zyprexa] Available in dissolvable and IM prep	Bipolar (13-17) Schizophrenia (13-17)	Mania Psychosis Agitation	2.5	2.5-20
Quetiapine [Seroquel]	Bipolar (10-17) Schizophrenia (13-17)	Mania Psychosis Agitation	25 mg bid	Bipolar: 400-600 Schizophrenia: 400-800
Risperidone [Risperdal] Available in liquid and dissolvable prep	Bipolar (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Mania Psychosis Irritability Aggression Agitation	Bipolar, schizophrenia: 0.5 Autism: <20 kg: 0.25 ≥20 kg: 0.5	Bipolar, schizophrenia: 1-6 Autism: 0.5-3
Paliperidone [Invega] Available in IM prep	Schizophrenia (12-17)	Psychosis	3	<51 kg: 3-6 ≥51 kg: 3-12
Lurasidone [Latuda]	Schizophrenia (13-17) Depressive episodes with Bipolar (13-17)	Psychosis	Schizophrenia: 40 Bipolar: 20	Schizophrenia: 40-80 Bipolar: 20-80
Asenapine [Saphris]	Bipolar (10-17)	Mania Psychosis	2.5 twice daily	5-20
Haloperidol [Haldol] Available in liquid and IM prep	Psychosis Severe behavioral disorders Agitation (3-17) Tourette disorder	Mania Psychosis Irritability Aggression Agitation Vocal/motor tics	0.05 mg/kg/day	0.05-0.15 mg/kg/day
Lithium carbonate Available in liquid prep	Bipolar (12-17)	Mania	Acute mania: 1800 mg/day Target level: 1.0-1.5 mEq/L	Long-term control: 900-1200 mg/day Target level: 0.6-1.2 mEq/L

*Doses shown in table may exceed maximum recommended dose for some children.

of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds the 90th percentile of body mass index (BMI) for age, or a change of 5 BMI units in youth who were obese at the initiation of treatment. Tertiary strategies, where diabetes, hypertension, obesity, or another metabolic abnormality has occurred, require more intensive weight reduction interventions, changing medication, and consultation with a medical subspecialist. Metformin has been found to be an effective treatment for antipsychotic-induced weight gain in children with autism spectrum disorder. Extrapyramidal adverse effects are generally dose- and titration rate–dependent and may respond to dose or titration rate reductions. More disabling effects may benefit from adjunctive treatment (e.g., anticholinergics, antihistamines).

Neuroleptic malignant syndrome is a rare, potentially fatal reaction that can occur during antipsychotic therapy (see Chapter 94). The syndrome generally manifests with fever, muscle rigidity, autonomic instability, and delirium. It is associated with elevated serum creatine phosphokinase levels, a metabolic acidosis, and high end-tidal CO_2 excretion. It has been estimated to occur in 0.2–1% of patients treated with dopamine-blocking agents. Malnutrition and dehydration in the context of an organic brain syndrome and simultaneous treatment with lithium and antipsychotic agents (particularly haloperidol) can increase the risk. Mortality rates may be as high as 20–30% as a result of dehydration, aspiration, kidney failure, and respiratory collapse. Differential diagnosis of neuroleptic malignant syndrome includes infections, heat stroke, malignant hyperthermia, lethal catatonia, agitated delirium, thyrotoxicosis, serotonin syndrome, drug withdrawal, and anticholinergic or amphetamine, ecstasy, and salicylate toxicity.

MOOD STABILIZERS

Because of their limited evidence of effectiveness and concerns about safety, mood-stabilizing medications (see Table 33.5) have limited use in the treatment of child and adolescent psychiatric disorders. For the treatment of bipolar mania in adolescents, antipsychotics are considered first-line therapy.

Of the mood stabilizers, **lithium** alone has rigorous support for the treatment of bipolar mania. Lithium's mechanism of action is not well understood; proposed theories relate to neurotransmission, endocrine effects, circadian rhythm, and cellular processes. Common side effects include polyuria and polydipsia, hypothyroidism,

Table 33.6 Relative Side Effects for Select Antipsychotic Medications

ADVERSE EFFECT	ARIPIPRAZOLE [ABILIFY]	OLANZAPINE [ZYPREXA]	QUETIAPINE [SEROQUEL]	RISPERIDONE [RISPERDAL]	PALIPERIDONE [INVEGA]	LURASIDONE [LATUDA]	HALOPERIDOL [HALDOL]
Akathisia	++	++	+	++	++	++	+++
Parkinsonism	+	++	+	++	++	++	+++
Dystonia	+	+	+	++	++	++	+++
Tardive dyskinesia	+	+	+	++	++	++	+++
Hyperprolactinemia	+	++	+	+++	+++	+	+++
Anticholinergic	+	++	+/++	++	+	+	+
Seizures	+	++	++	+	+	+	+
Orthostasis	+	++	++	++	++	+	+
QT interval	+	++	+	+	+	+	++
Weight gain	+	+++	++	++	++	+	+
Hyperlipidemia	+	+++	++	+++	++	++	+
Glucose abnormalities	+	+++	++	++	+	+	+
Sedation	+	++	++	+	+	++	+

+= Seldom; ++ = sometimes; +++ = often.
Adapted from Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry*. 2020;177(9):868–872.

Table 33.7 Metabolic Monitoring Parameters Based on ADA/APA Consensus Guidelines

	BASELINE	WEEK 4	WEEK 8	WEEK 12	EVERY 3 MO THEREAFTER	ANNUALLY
Medical history*	X			X		X
Body mass index	X	X	X	X	X	X
Waist circumference	X			X		X
Blood pressure	X			X		X
Fasting glucose and Hemoglobin A_{1c}	X			X		X
Fasting lipid panel	X			X		X

*Personal/family history of obesity, hypertension, and cardiovascular disease.
From American Diabetes Association. American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.

hyperparathyroidism, weight gain, nausea, abdominal pain, diarrhea, acne, and CNS symptoms (sedation, tremor, somnolence, memory impairment). Periodic monitoring of lithium levels along with thyroid and renal function is needed. Lithium serum levels of 0.8-1.2 mEq/L are targeted for acute episodes, and levels of 0.6-0.9 mEq/L are targeted for maintenance therapy. Acute overdose (level >1.5 mEq/L) manifests with neurologic symptoms (e.g., tremor, ataxia, nystagmus, hyperreflexia, myoclonus, slurred speech, delirium, coma, seizures) and altered renal function. Toxicity is enhanced when dehydrated or with drugs that affect renal function, such as NSAIDs or angiotensin-converting enzyme (ACE) inhibitors. Neuroleptic malignant syndrome has been reported in patients concurrently taking antipsychotic drugs and lithium.

MEDICATION USE IN PHYSICAL ILLNESS

There are special considerations in the use of psychotropic medications with physically ill children. Between 80% and 95% of most psychotropic medications are protein bound; the exceptions are lithium (0%), methylphenidate (10–30%), and venlafaxine (25–30%). As a result, psychotropic levels may be directly affected because albumin binding is reduced in many physical illnesses. Metabolism is primarily through the liver and gastrointestinal (GI) tract, with excretion via the kidney. Therefore dosages may need to be adjusted in children with hepatic or renal impairment.

Hepatic Disease

In general, it is necessary to use lower doses of medications for patients with hepatic disease. Initial dosing of medications should

be reduced, and titration should proceed slowly. In acute hepatitis, there is generally no need to modify dosing because metabolism is only minimally altered. In chronic hepatitis and cirrhosis, hepatocytes are destroyed, and doses may need to be modified.

In steady-state situations, changes in protein binding can result in elevated unbound medication, resulting in increased drug action even in the presence of normal serum drug concentrations. Albumin and α_1 glycoproteins produced in the liver may be reduced with infectious and inflammatory hepatic disease, whereas surgery, trauma, and cirrhosis may result in elevated protein levels. Because it is often difficult to predict changes in protein binding, it is important to maintain attention to the clinical effects of psychotropic medications and not rely exclusively on serum drug concentrations.

Medications with high baseline rates of liver clearance (e.g., haloperidol, sertraline, venlafaxine) are significantly affected by hepatic disease. For drugs that have significant hepatic metabolism, intravenous (IV) administration may be preferred because parenteral administration avoids first-pass liver metabolic effects, and the dosing and action of parenteral medications are similar to those in patients with normal hepatic function.

Gastrointestinal Disease

GI disease primary affects drug absorption. Examples that impact absorption include conditions affecting GI motility, surgical alterations of the GI tract, short bowel syndrome, or celiac disease. Any condition that diverts blood away from the GI tract (e.g., congestive heart failure, shock) may also reduce absorption.

Psychotropic medications have the potential to cause GI side effects. Medications with anticholinergic side effects can slow GI motility, affecting absorption and causing constipation. SSRIs increase gastric motility and can cause diarrhea. SSRIs can increase the risk of GI bleeding, especially when administered with NSAIDs. Extended-release or controlled-release preparations of medications can reduce GI side effects, particularly where gastric distress is related to rapid increases in plasma drug concentrations. Using extended-release medication preparations may reduce these side effects.

Renal Disease

In general, initial dosages of medication should be reduced or dosing intervals lengthened in renal failure. The rule of two thirds is that dosages should be reduced by one third of the normal dosage for a patient with renal insufficiency. However, most psychotropic medications, with the exceptions of lithium and gabapentin, do not require significant dosing adjustments in kidney failure. It is important to monitor serum concentrations in renal insufficiency, particularly for medications with a narrow therapeutic index. Cyclosporine can elevate serum lithium levels by decreasing lithium excretion. Although TCAs have been largely supplanted by SSRIs, patients with kidney failure and those on dialysis appear to be more sensitive to their side effects, possibly because of the accumulation of hydroxylated tricyclic metabolites.

Because most psychotropic medications are highly protein bound, they are not significantly cleared by dialysis. Lithium is essentially completely removed by dialysis, and the common practice is to administer lithium after dialysis. Patients on dialysis often have significant fluid shifts and are at risk for dehydration, with neuroleptic malignant syndrome more likely in these situations.

Cardiac Disease

Antipsychotics, TCAs, and citalopram (>40 mg/day) can lead to prolongation of the QTc interval, with increased risk of ventricular tachycardia and ventricular fibrillation, particularly in patients with structural heart disease. Patients with a baseline QTc interval of >440 msec should be particularly considered at risk. The normal QTc value in children is 400 msec (±25-30 msec). A QTc value that exceeds 2 standard deviations (SDs; >450-460 msec) is considered too long and may be associated with increased mortality. An increase in the QTc from a baseline of >60 msec is also associated with increased mortality.

There is increased risk of morbidity and mortality in patients with preexisting cardiac conduction problems. Patients with Wolff-Parkinson-White syndrome who have a short PR interval (<0.12 sec) and widened QRS interval associated with paroxysmal tachycardia are at high risk for life-threatening ventricular tachycardia that may be exacerbated by the use of antipsychotics, TCAs, and citalopram.

Respiratory Disease

Anxiolytic agents can increase the risk of respiratory suppression in patients with pulmonary disease. SSRIs are the first-line medications to consider in treating disabling anxiety. Possible airway compromise caused by acute laryngospasm should be considered when dopamine-blocking antipsychotic agents are used.

Neurologic Disease

Psychotropic medications can be used safely with epilepsy following consideration of potential interactions among the medication, the seizure disorder, and the anticonvulsant. Any behavioral toxicity of anticonvulsants used either alone or in combination should be considered before proceeding with psychotropic treatment. Simplification of combination anticonvulsant therapy or a change to another agent can result in a reduction of behavioral or emotional symptoms and obviate the need for psychotropic intervention. Clomipramine and bupropion possess significant seizure-inducing properties and should be avoided when the risk of seizures is present.

Principles for Psychotropic Prescribing in Primary Care

In the context of a severe and prolonged shortage of child and adolescent psychiatrists (CAPs), PCPs are increasingly managing behavioral health conditions in primary care. The principles for effective use of psychotropic medications outlined in the beginning of this chapter can be used by PCPs to guide their medication assessment and management (see Table 33.1). This approach emphasizes **baseline assessment with standardized symptom rating scales** to identify target symptoms and their level of severity, **prioritizing FDA-approved medications** for the target symptom and patient age range, adherence to recommendations regarding therapeutic dosage ranges, using a **follow-up symptom rating scale assessment** to monitor medication response, continuing the medication trial for sufficient duration, and switching to an alternative FDA-approved medication if the first medication trial is ineffective.

PCPs can access support for psychotropic prescribing through the development of collaborative relationships with CAPs who can provide timely consultation for questions/advice; interim management until stable; and ongoing care for patients with severe, complex, unsafe, or treatment-refractory conditions. Ideally, consultation with a CAP should occur if one is considering using psychotropic medications with very young children, multiple psychotropic medications, medication doses outside of therapeutic range, or non–FDA-approved medications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 34

Psychotherapy

Erica H. Lee, Keneisha R. Sinclair-McBride, David R. DeMaso, and Heather J. Walter

PSYCHOTHERAPY

Psychotherapy is the first-line treatment for many child and adolescent psychiatric disorders (e.g., posttraumatic stress disorder [PTSD], depression, anxiety, behavior, substance-related) because for these disorders, psychotherapy produces outcomes greater than or equal to pharmacotherapy, with less risk of harm. Even with disorders (e.g., schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder [ADHD]) for which medication is typically the first-line treatment, adjunctive psychotherapy can convey additional benefit.

Psychotherapy is moderately effective in reducing psychiatric symptomatology and achieving remission of illness. In a 2017 multilevel meta-analysis of almost 500 randomized trials over 5 decades, there was a 63% probability that a youth receiving psychotherapy fared better than a youth in a control condition. Effects varied across multiple moderators. The mean posttreatment and follow-up effect sizes were highest for anxiety, followed by behavior/conduct, ADHD, and depression, and lowest for multiple concurrent comorbidities. Effect sizes varied according to outcome measure informant, with youth and parents generally reporting larger effects than teachers.

A variety of psychotherapeutic modalities have been developed, with varying levels of effectiveness (Table 34.1). Differences between therapeutic approaches may be less pronounced in practice than in theory. The quality of the therapist-patient alliance is consistently one of the most important predictors of treatment outcome. A positive working relationship, expecting change to occur, facing problems assertively, increasing mastery, and attributing change to the participation in the therapy have all been associated with effective therapy, irrespective of the specific psychotherapeutic modality.

All psychotherapy interventions involve a series of interconnected steps, including performing an assessment, constructing working diagnoses and an explanatory formulation, deciding on treatment and a monitoring plan, obtaining treatment assent/consent, implementing treatment, terminating treatment, and following for symptom recurrence. Psychotherapists ideally develop a treatment plan by combining evidence-based therapies with clinical judgment and patient/family preference to collaboratively arrive at a specific intervention plan for the individual patient.

Behavior Therapy

Behavior therapy is based on both classic (Pavlovian) and operant (Skinnerian) conditioning. Both approaches address the **antecedent stimuli** and **consequent outcomes** of problematic thoughts or behaviors. The treatment begins with a behavioral assessment along with a functional analysis of the setting, immediately preceding events, and real-world outcomes of the behavior to identify the settings in which the behavior occurs and/or the reason the child engages in the behavior. Often the function of problematic behavior is to **gain access to attention** or a **tangible item** the child wants or to **avoid a task or stressful situation.** The goal is to teach the child a more adaptive response using tools such as positive and negative reinforcement; social and tangible rewards; response cost/consequences; shaping, modeling, and prompting; systematic desensitization; and aversive conditioning.

Behavior therapy has shown particular effectiveness with oppositional behavior, obsessive-compulsive, autism spectrum disorder, and substance use disorders, and ADHD.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is based on social and cognitive learning theories and extends behavior therapy to address the influence of cognitive processes on behavior. CBT is a short-term, problem- and goal-oriented treatment centered on correcting problematic patterns in thinking and behavior that lead to emotional difficulties and functional impairments. The CBT therapist seeks to help the patient identify and change cognitive distortions (e.g., learned helplessness, irrational fears); identify and incrementally approach aversive situations; and identify and practice distress-reducing behavior. **Self-monitoring** (daily thought records), **self-instruction** (brief sentences asserting thoughts that are comforting and adaptive), and **self-reinforcement** (rewarding oneself for adaptive behaviors) are key tools used to facilitate achievement of the CBT goals.

CBT has good-quality evidence for the treatment of anxiety, obsessive-compulsive disorder (OCD), behavior disorders, substance abuse, and insomnia, and fair evidence for the treatment of depression. For many childhood psychiatric disorders, CBT alone provides outcomes comparable to psychotropic medication alone, and the combination of both may convey additional benefit in symptom and harm reduction. Modified versions of CBT have shown applicability to the treatment of other disorders.

Trauma-Focused Cognitive-Behavioral Therapy

Trauma-focused cognitive-behavioral therapy (TF-CBT) is designed to process and master the psychologic, behavioral, and physiologic consequences of a specific traumatic experience. It involves a combination of education about the broad effects of trauma exposure; teaching effective relaxation, affective modulation, and cognitive coping and processing skills; creating a trauma narrative to foster understanding; mastering trauma reminders; enhancing future safety and development; and teaching parents how to support youth with trauma exposure. TF-CBT is considered the first-line treatment for PTSD.

Dialectical Behavioral Therapy

Dialectical behavioral therapy (DBT) is a modality targeted at emotional and behavioral dysregulation by synthesizing or integrating the seemingly opposite strategies of acceptance and change. *Dialectic conflicts* (wanting to die vs wanting to live) often exist in the same patient. **The four skills modules—*mindfulness* (the practice of being fully aware and present in the moment), *distress tolerance* (how to tolerate emotional pain), *interpersonal effectiveness* (how to maintain self-respect and effective communication in relationships with others), and *emotion regulation* (how to manage complex emotions)—are balanced in terms of acceptance and change.** The treatment targets, in order of priority within a given session, are life-threatening behaviors, such as suicidal and self-injurious behaviors or communications; therapy-interfering behaviors, such as coming late to sessions, canceling appointments, and being uncollaborative in working toward treatment goals; quality-of-life behaviors, including relationship and occupational problems and financial crises; and skills acquisition to help patients achieve their goals. DBT has good-quality evidence for self-injurious thoughts and behaviors and has shown promise for the treatment of bipolar disorder and other manifestations of emotional-behavioral dysregulation.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) focuses on resolving interpersonal difficulties that lead to psychologic distress and maladaptive behaviors. Patients are viewed as having strengths and vulnerabilities that determine the manner in which they cope with or respond to an interpersonal crisis (stressor). The main goals of IPT include expanding social support, decreasing interpersonal stress, enhancing the processing of emotions, and improving social functioning within significant relationships. The interpersonal inventory, a detailed review of the patient's significant relationships, both current and past, with their emotional valence, leads to a formulation linking the interpersonal situations to the emotional/behavior symptoms. Various techniques (linking emotions/behaviors to interpersonal events, communication and problem-solving training, perspective-taking, role adaptation) are utilized to resolve interpersonal difficulties. IPT is a well-established treatment for adolescent depression.

Table 34.1 Effective Psychotherapies for Specific Behavioral Health Disorders

DISORDER	WELL-ESTABLISHED*	PROBABLY EFFICACIOUS†
Anorexia	Family therapy: behavioral	Family therapy: systemic Individual psychodynamic psychotherapy
Anxiety, children under 8	Family-based CBT	Group parent CBT ± group child CBT
Anxiety	CBT ± parent component ± medication	Family psychoeducation Parent/child CBT Relaxation, assertiveness training
Attention-deficit/hyperactivity	BPT Behavioral classroom management Behavioral peer interventions Organization (executive function) training	Combined training interventions
Autism	Individual, comprehensive ABA Teacher-implemented focused ABA + DSP	Individual, focused (communication) ABA ± DSP Focused DSP parent training
Behavior, child	Group BPT Individual BPT with child component	Modifications of Group BPT‡ Individual BPT alone or with other modifications Self-directed parent behavior therapy Group child behavior therapy ± teacher training Individual child behavior therapy ± parent component Group/individual child-centered play therapy
Behavior, adolescent	Behavioral therapy + CBT + family therapy	CBT
Bipolar	Family skill building + psychoeducation	DBT
Depression, child	None	None
Depression, adolescent	Individual/group CBT Individual IPT	Group IPT
Obsessive-compulsive	Family-focused CBT	Individual CBT
Posttraumatic stress	Individual/group trauma-focused CBT ± parent component	Group CBT + parent component EMDR
Substance use	Individual/group/family CBT ± MET Family-based treatment, ecologic ± CBT ± MET	Family-based treatment, behavioral Motivational interviewing/MET Family-based treatment, ecologic + contingency management Family-based treatment, behavioral, ecologic, contingency management + MET MET + CBT + contingency management
Self-injurious thoughts and behaviors	DBT-adolescents (deliberate self-harm, suicidal ideation)	DBT—adolescents (nonsuicidal self-injury, suicide attempt) Individual/family CBT (suicide attempt) Family therapy (suicide attempt) Interpersonal therapy—adolescents (suicidal ideation) Individual psychodynamic therapy (deliberate self-harm) Parent training (self-injurious thoughts and behaviors (suicidal and nonsuicidal)

*Two or more consistent randomized controlled trials demonstrating superiority of treatment over control groups; conducted by independent investigators working at different research settings.
†Same as in the previous footnote, but lacking independent investigator criterion.
‡Modifications of Group Behavioral Parent Training that are probably efficacious include adding child components or family problem-solving strategies
CBT, Cognitive-behavioral therapy; BPT, behavioral parent training; ABA, applied behavioral analysis; DSP, developmental social-pragmatic; DBT, dialectical behavioral therapy; IPT, interpersonal psychotherapy; EMDR, eye movement desensitization and reprocessing; MET, motivational enhancement treatment.
Adapted from Society of Clinical Child and Adolescent Psychology. Concerns, symptoms and disorders. https://effectivechildtherapy.org/concerns-symptoms-disorders/. Accessed July 13, 2021.
Criteria derived from Southam-Gerow MA, Prinstein MJ. Evidence base updates: The evolution of the evaluation of psychological treatments for children and adolescents. *J Clin Child Adol Psychol*. 2014;43(1):1–6.

Psychodynamic Psychotherapy

At the core of psychodynamic psychotherapy lies a dynamic interaction between different dimensions of the mind, conscious and unconscious. This approach is based on the belief that much of one's mental activity occurs outside one's awareness. The patient is often unaware of internal conflicts because threatening or painful emotions, impulses, and memories are repressed to avoid experiencing psychologic pain. Behavior is then controlled by what the patient does not know about himself or herself. Therapy objectives are to increase self-understanding and acceptance of painful conflicting feelings, and to develop realistic relationships between self and others. A fundamental difference of this modality is its nondirective approach to allow a patient's characteristic patterns of thinking and behavior to emerge over time. The relationship between the patient and the therapist can play a key role in identifying these patterns, as they are recapitulated in the therapeutic environment. The therapist can then analyze and interpret the manifest pattern so that self-understanding and a corrective emotional experience can be fostered.

Psychodynamic psychotherapy has shown applicability for the treatment of self-injurious thoughts and behaviors as well as anxiety,

depression, and maladaptive aspects of personality. Brief, time-limited psychodynamic psychotherapy can be appropriate for youth who are in acute situational distress. Long-term therapy can be appropriate when the biologic or social factors destabilizing the child's adaptation and development are chronic, or the psychologic difficulties are complex, or if entrenched conflicts and developmental interferences are present.

Supportive Psychotherapy

Supportive psychotherapy aims to minimize levels of emotional distress through the provision of individual and contextual support. The goal is to reduce symptoms, and treatment is focused on the "here and now." The therapist is active and helpful in providing the patient with symptomatic relief by helping the patient to contain and manage anxiety, sadness, and anger. The therapist provides support and encouragement ("coaching") to bolster a patient's existing coping mechanisms, facilitates problem solving, and provides social and instrumental support for ameliorating or lessening contextual precipitants. CBT-informed techniques are often combined with supportive psychotherapy. Probably the most common psychotherapy employed by therapists, supportive psychotherapy has shown comparable results to CBT in a number of research studies, particularly those targeting depression.

Family Therapy

The core premise in family therapy is that **dysfunctional family** interaction patterns precipitate and/or perpetuate an individual's emotional or behavioral difficulties. Family dysfunction can take a variety of forms, including enmeshment, disengagement, role-reversal or confusion, and maladaptive communication patterns. Family therapy begins with an assessment of the family system, including observing patterns of interaction; assessing family beliefs and the meanings attached to behaviors; defining social and cultural contexts; exploring the presenting problem in the context of individual and family development; assessing the family's style of dealing with problems; and identifying family strengths and weaknesses.

Family therapy techniques are drawn from two major theoretical models: structural and behavioral. **Structural family therapy** develops structures believed to foster well-functioning families, including clear and flexible boundaries between individuals, well-defined roles, and an appropriate balance between closeness and independence. **Behavioral family therapy** focuses on behavioral sequences that occur in daily life and attempts to interrupt unhelpful behavioral patterns and strengthen positive behavioral patterns through effective communication and problem solving.

Family therapy has shown established applicability in anorexia nervosa, behavior problems, and substance use and may be a promising treatment for depression and bipolar disorder.

Parenting Interventions

See Chapters 20 and 42 for more details.

Parenting interventions seek to improve both the parent–child relationship and parenting skills using the principles of behavior therapy previously described. These interventions can be provided in individual or group therapy formats. Core relationship recommendations include spending quality time with the child to foster a strong parent–child bond, increasing positive verbal interaction, showing physical affection, and engaging in child-directed play. Core parenting skills include increasing reinforcement of positive behaviors; decreasing reinforcement of negative behaviors; ignoring merely annoying behaviors; applying logical consequences for dangerous/destructive behaviors; and making parental responses predictable, contingent, and immediate. Parenting interventions have shown applicability for behavior disorders and ADHD.

Common Elements of Evidence-Based Psychotherapies

A major challenge for the practitioner is selecting the "right intervention" for the "right person" in the "right setting," and delivering the intervention in the "right way" (to meet the needs of patients and families). This challenge has led to an interest in identifying **common practice elements** across efficacious evidence-based therapies that could be "matched" in a flexible way to patients of a certain age, gender, and race/ethnicity who have certain psychiatric disorders. Table 34.2 provides the major practice elements for three of the most common child and adolescent psychiatric disorders: anxiety, depression, and disruptive behaviors. These practice elements, when made available to patients with psychiatric disorders in a system of care, are estimated to be relevant to approximately two thirds of the patients. Six of the practice elements—psychoeducation of the parent, problem-solving skills, relaxation skills, self-monitoring, cognitive/coping skills, and psychoeducation of the child—are applicable to all three disorders and as such could be considered "**core competencies**" for both mental health specialists as well as primary care practitioners (PCPs) interested in delivering brief psychotherapeutic interventions in the context of anticipatory guidance (see Discussion of Common Factors in Chapter 18).

Psychoeducation is the education of the parent and child about the cause, course, prognosis, and treatment of the disorder. Problem solving includes techniques, discussions, or activities designed to bring about solutions to targeted problems, with the intention of imparting skills for how to approach and solve future problems in a similar manner. Relaxation includes techniques designed to create and maintain the physiologic relaxation response. Self-monitoring is the repeated measurement of a target emotional or behavioral metric by the child or parent to establish goals for treatment and monitor progress toward mastery. Cognitive/coping skills consist of techniques designed to alter interpretations of events through examination of the child's reported thoughts, accompanied by exercises designed to test the validity of the reported thoughts.

Modular Therapy Packages

Of considerable importance to day-to-day clinical work is the manner in which common therapy practice elements are selected, sequenced, repeated, or selectively applied. This **coordination of psychotherapeutic elements** is particularly relevant for patients presenting with multiple concurrent psychiatric disorders whose primary concern may shift between sessions. The *Modular Approach to Therapy for Children* (MATCH) is a multi-disorder intervention system that incorporates treatment procedures (practice elements) and treatment logic (coordination) corresponding to efficacious interventions for childhood anxiety, depression, traumatic stress, and behavior problems, with modifications to allow the system to operate as a single protocol. Compared with standard manualized treatments for individual disorders and with usual care, the modular package outperformed both comparators on multiple clinical and service outcome measures when assessed over a 2-year period, although additional, independently derived evidence is needed to determine the conditions under which it is most effective and categorize this treatment approach as well established.

Treatment Engagement Interventions

Treatment engagement is conceptualized as a multidimensional construct targeting cognitive, attendance, and adherence domains. Research has identified several key factors addressing these domains that are associated with treatment engagement: accessibility promotion, psychoeducation about services, appointment reminders, assessment of treatment barriers, patient assessment, setting of positive expectations, modeling, homework assignments, rapport building, cultural acknowledgement, and goal setting (Table 34.3). To promote treatment engagement, the first 10 of these factors can be addressed by the PCP and the medical home team as soon as a mental health problem is identified that would benefit from treatment (see Chapter 18 for further discussion).

Psychotherapy in the Medical Home

Recognizing that up to one half of visits to PCPs involve a mental health problem and that an estimated one fifth of pediatric patients have a functionally impairing psychiatric disorder, in the context of limited access to specialty mental health services in community or hospital settings a number of models have been developed to deliver

Table 34.2 Practice Elements in Interventions for Three Common Child and Adolescent Psychiatric Disorders

	ANXIETY DISORDERS	DEPRESSION	DISRUPTIVE BEHAVIOR
Directed play			X
Limit setting			X
Time-out			X
Cost response			X
Activity scheduling		X	
Maintenance		X	X
Skill building		X	
Social skills training		X	X
Therapist praise/rewards			X
Natural and logical consequences	X		X
Communication skills	X		X
Assertiveness training	X		
Parent monitoring	X		X
Modeling	X		
Ignoring	X		X
Parent praise	X		X
Problem solving	X	X	X
Parent coping	X		X
Psychoeducation, parent	X	X	X
Relaxation	X	X	X
Tangible rewards	X		X
Self-monitoring	X	X	X
Cognitive/coping	X	X	X
Psychoeducation, child	X	X	X
Exposure	X		

Adapted from Chorpita BF, Daleiden EL, Weisz JR. Identifying and selecting the common elements of evidence based interventions: a distillation and matching model. *Ment Health Serv Res.* 2005;7(1):5–20.

psychotherapy in primary care. Two prominent models, both originally developed for adult populations, are collaborative care and primary care behavioral health.

Collaborative care, which spans a spectrum ranging from coordinated to co-located to integrated, provides mental healthcare for patients through a collaboration between mental health specialists and PCPs. In integrated collaborative care, patients' mental health problems are managed in the medical home setting by an interdisciplinary care team of PCPs, mental health clinicians, and care coordinators supported by a consulting psychiatrist. The PCP is the "team captain"; the mental health clinician maintains a population registry, provides brief, focused psychosocial interventions, and monitors treatment response; the care coordinator facilitates external referrals; and the consulting psychiatrist provides input regarding evidence-based psychiatric diagnosis and treatment. The four critical elements of integrated collaborative care are that it is team-driven, population-focused, measurement-guided, and evidence-based. These elements guide a treatment approach in which the patient perceives a seamless integration of medical and mental healthcare.

In children and adolescents, randomized controlled trials (RCTs) have shown that integrated collaborative care for child behavior problems, adolescent depression, and adolescent substance use is associated with more favorable treatment adherence, symptom reduction, disorder remission, and consumer satisfaction outcomes than usual care, with or without specialty referral. In a meta-analysis of collaborative care RCTs, larger effects were observed for treatment trials targeting diagnoses and elevated symptoms relative to prevention trials and for mental health diagnoses relative to substance-related diagnosis, as well as for integrated models relative to other types of collaborative mental healthcare.

Primary care behavioral health employs a mental health clinician (psychologist, social worker, mental health counselor) in the primary care setting to provide focused assessment of patients with mental health, health behavior, and substance use problems, and short-term therapy as well as health/mental health promotion and prevention interventions. Mental health clinicians typically collaborate with PCPs to develop treatment plans, monitor patient progress, and flexibly provide care to meet patients' changing needs. The model uses a "wide net" approach aimed at serving the entire primary care population, with emphasis on brief, focused interventions.

The results of **brief interventions**, particularly applicable to the fast-paced medical home setting, are encouraging. Interventions lasting only one session, particularly those utilizing CBT techniques, can be effective for mild presentations of multiple child psychiatric disorders, particularly anxiety and behavior problems in children (vs adolescents). These interventions can greatly expand capacity to

Table 34.3 Selected Psychotherapy Engagement Elements

ELEMENT	DEFINITION
Accessibility promotion	Any strategy used to make services convenient and accessible to proactively encourage and increase participation in treatment; e.g., hiring a co-located therapist or referring to a local community-based therapist with whom the practice has an ongoing collaborative relationship
Psychoeducation about services	Provision of information about services or the service delivery system; e.g., type of therapy being recommended, information about the therapist, session frequency and duration
Appointment reminders	Providing information about the day, time, and location of the therapy office for the initial appointment via mail, text, phone, email, etc., to increase session attendance
Assessment of treatment barriers	Discussion to elicit and identify barriers that hinder participation in treatment; e.g., transportation, scheduling, childcare, previous experiences with therapy, stigma
Assessment	Measurement of the patient's strengths/needs through a variety of methods; e.g., mental health screening instruments, interviews, recorded reviews during which the referring practitioner can motivate treatment engagement
Modeling	Demonstration of a desired behavior to promote imitation and performance of that behavior by client
Expectation setting	Instillation of hope regarding the efficacy of therapy and the patient's ability to participate successfully in treatment
Homework assignment	Therapeutic tasks given to the patient to complete outside the therapy session to reinforce or facilitate knowledge or skills that are consistent with the treatment plan
Goal setting	Selection of a therapeutic goal for the purpose of making a plan to achieve that goal
Rapport building	Strategies used to strengthen the relationship between therapist and patient
Cultural acknowledgment	Exploration of an individual's culture; e.g., race/ethnicity, age, sexual orientation, gender identity

Adapted from Lindsey MA, Brandt NE, Becker KD, et al. Identifying the common elements of treatment engagement interventions in children's mental health services. *Clin Child Fam Psychol Rev.* 2014;17(3):283–298; Becker KD, Lee BR, Daleiden EL, Lindsey M, Brandt NE, Chorpita BF. The common elements of engagement in children's mental health services: which elements for which outcomes?. *J Clin Child Adolesc Psychol.* 2015;44(1):30–43; and Becker KD, Boustani M, Gellatly R, Chorpita BF. Forty Years of Engagement Research in Children's Mental Health Services: Multidimensional Measurement and Practice Elements. *J Clin Child Adolesc Psychol.* 2018;47(1):1–23.

provide mental health support to those patients with emerging mild mental health problems, with the goal of preventing escalation into full-blown psychiatric disorders if problems are left untreated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 35

Somatic Symptom and Related Disorders

David R. DeMaso

Medically unexplained physical symptoms are common in children and adolescents. Although frequently chronic and disabling, these symptoms do not often result in referrals for mental health assessment and treatment (see Chapter 212). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) somatic symptom and related disorders (SSRDs) are those conditions in which the physical symptoms are unexplained or for which the patient's response to the underlying medical condition is disproportionate and debilitating.

The SSRDs include somatic symptom disorder (Table 35.1), conversion disorder (Table 35.2), factitious disorders (Table 35.3), illness anxiety disorder (Table 35.4), and other specified/unspecified somatic symptom disorders (Table 35.5), as well as psychologic factors affecting other medical conditions (Table 35.6). With the exception of illness anxiety disorder (with high level of anxiety about health in the absence of significant somatic symptoms) and psychologic factors affecting other medical conditions (with psychologic and/or behavioral factors adversely affect a pediatric condition), SSRDs are classified on the basis of physical symptoms associated with clinically significant distress and impairment, with or without the presence of a diagnosed medical condition.

Most patients with SSRDs are seen by primary care practitioners or by pediatric subspecialists, who may make specialty-specific diagnoses such as visceral hyperalgesia, chronic fatigue syndrome, psychogenic syncope, or noncardiac chest pain. Even within psychiatry, SSRDs are variously referred to as functional or psychosomatic disorders or as medically unexplained symptoms. The nosologic heterogeneity across the pediatric subspecialties contributes to the varying diagnostic labels. There is a significant overlap in the symptoms and presentation of patients with somatic symptoms who have received different diagnoses from different specialties. Moreover, SSRDs share similarities

Table 35.1 DSM-5 Diagnostic Criteria for Somatic Symptom Disorder

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns, as manifested by at least one of the following:
   1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
   2. Persistent high level of anxiety about health and symptoms.
   3. Excessive time and energy devoted to these symptoms or health concerns.
C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo).

Specify if:

With predominant pain (previously known as "pain disorder" in DSM IV-TR): for individuals whose somatic symptoms predominantly involve pain.

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (>6 mo).

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 311. Copyright 2013. American Psychiatric Association.

Table 35.2 DSM-5 Diagnostic Criteria for Conversion Disorder or Functional Neurologic Symptom Disorder

A. One or more symptoms of altered voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurologic or medical conditions.
C. The symptom is not better explained by another medical or mental disorder.
D. The symptom causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type: weakness or paralysis, abnormal movements, swallowing symptoms, speech symptom, attacks/seizures, anesthesia/sensory loss, special sensory symptom (e.g., visual, olfactory, hearing), or mixed symptoms.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 318. Copyright 2013. American Psychiatric Association.

Table 35.3 DSM-5 Diagnostic Criteria for Factitious Disorders

FACTITIOUS DISORDER IMPOSED ON SELF

A. Falsification of physical or psychologic signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Specify if: single episode or recurrent episodes.

FACTITIOUS DISORDER IMPOSED ON ANOTHER (PREVIOUSLY "FACTITIOUS DISORDER BY PROXY")

A. Falsification of physical or psychologic signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
B. The individual presents another individual (victim) to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note: The perpetrator, not the victim, receives this diagnosis.

Specify if: single episode or recurrent episodes.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 324. Copyright 2013. American Psychiatric Association.

Table 35.4 DSM-5 Diagnostic Criteria for Illness Anxiety Disorder

A. Preoccupation with having or acquiring a serious illness.
B. Somatic symptoms are not present, or, if present, are only mild in intensity. If another medical condition is present or there is a high risk for developing a medical condition (e.g., strong family history is present), the preoccupation is clearly excessive or disproportionate.
C. There is a high level of anxiety about health, and the individual is easily alarmed about personal health status.
D. The individual performs excessive health-related behaviors (e.g., repeatedly checks his or her body for signs of illness) or exhibits maladaptive avoidance (e.g., avoids doctor appointments and hospitals).
E. Illness preoccupation has been present for at least 6 months, but the specific illness that is feared may change over that time.
F. The illness-related preoccupation is not better explained by another mental disorder.

Specify whether: care-seeking type or care-avoidant type.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 315. Copyright 2013. American Psychiatric Association.

Table 35.5 DSM-5 Diagnostic Criteria for Other Specified/Unspecified Somatic Symptom and Related Disorders

OTHER SPECIFIED

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the *somatic symptom and related disorders diagnostic class.*

Examples of presentations that can be specified using the "other specified" designation include the following:

1. Brief somatic symptom disorder: duration of symptoms is <6 mo.
2. Brief illness anxiety disorder: duration of symptoms is <6 mo.
3. Illness anxiety disorder without excessive health-related behaviors: Criterion D for illness anxiety disorder is not met (see Table 35.4).
4. Pseudocyesis: a false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy.

UNSPECIFIED

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in functioning predominate but do not meet criteria for any of the other disorders in the *somatic symptom and related disorders* diagnostic class.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 327. Copyright 2013. American Psychiatric Association.

in etiology, pathophysiology, neurobiology, psychologic mechanisms, patient characteristics, and management and treatment response, which is indicative of a single spectrum of somatic disorders.

It is helpful for all healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered physically or psychologically based. In contrast, a developmental biopsychosocial continuum of disease better characterizes these illnesses as occurring across a spectrum ranging from a predominantly biologic to a predominantly psychosocial etiology. Indeed, there is a neurobiologic component to the related **functional neurologic disorders**, especially related to pain symptoms (see Chapters 212 and 389).

SOMATIZATION

The term *somatization* is defined as a pattern of seeking medical help for physical symptoms that cannot be fully explained by pathophysiologic mechanisms but are nevertheless attributed to physical disease by the sufferer. It has been described as the propensity to express psychologic distress through somatic complaints. It is thought to occur universally in young children (but occurs in every age group) who have not yet developed the cognitive and a linguistic skill needed to comprehend and communicate their feelings.

Between 10% and 30% of children worldwide experience physical symptoms that are seemingly unexplained by a physical illness, with recurrent somatic complaints generally falling into cardiovascular, gastrointestinal, pain, and pseudoneurologic symptom clusters (Chapter 212). The prevalence of somatization is roughly equal among school-age males and females with a rise in adolescence, at which point somatic complaints in females are five times greater than those in males. Youth with a history of somatization are more likely to experience emotional/behavioral difficulties, be absent from school, and perform poorly academically. There are high rates of anxiety and depressive disorders in youth with SSRDs. Youth with conversion disorder, specifically

Table 35.6 DSM-5 Diagnostic Criteria for Psychologic Factors Affecting Other Medical Conditions

A. A medical symptom or condition (other than a mental disorder) is present.
B. Psychologic or behavioral factors adversely affect the medical condition in one of the following ways:
   1. The factors have influenced the course of the medical condition, as shown by a close temporal association between the psychologic factors and the development or exacerbation of, or delayed recovery from, the medical condition.
   2. The factors interfere with the treatment of the medical condition (e.g., poor adherence).
   3. The factors constitute additional well-established health risks for the individual.
   4. The factors influence the underlying pathophysiology, precipitating or exacerbating symptoms or necessitating medical attention.
C. The psychologic and behavioral factors in Criterion B are not better explained by another mental disorder (e.g., panic disorder, major depressive disorder, posttraumatic stress disorder).

Specify if: mild, moderate, severe, or extreme.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 322. Copyright 2013. American Psychiatric Association.

nonepileptic seizures, have increased rates of comorbid psychopathology including internalizing disorders and posttraumatic stress disorders. Somatization is common in cultures that accept physical illness but not psychologic symptoms as a reason for disability.

RISK FACTORS FOR SOMATIZATION

Genetic and biologic factors, stressful life events, personality traits and coping styles, cognitive and learning difficulties, learned complaints, family factors, and sociocultural background are potential risk factors that have been associated with pediatric somatization.

Genetic and Biologic Factors

Somatization clusters in families with increased rates in first-degree relatives of patients with SSRDs. The concordance rates for somatization approximate 29% in monozygotic twin studies. Genetic factors have been hypothesized to contribute to the development of personality traits that may predispose to somatization when combined with environmental factors. Neuroimaging studies have found neuronal areas (premotor and supplementary motor cortexes, the middle frontal gyrus, the anterior cingulate cortex, the insula, and the posterior cingulate cortex) to differ between patients with SSRDs.

Stressful Life Events

Stressful life events, including childhood trauma, physical/sexual abuse, bullying, and exposure to natural disasters have all been associated with somatization. Youth with SSRDs have shown high rates of comorbid anxiety, suicidal histories, family psychiatric histories, bullying, learning difficulties, and significant life events.

Personality Traits and Coping Styles

Somatization has been postulated to occur in patients who are unable to verbalize emotional distress and instead use physical symptoms as a means of expression. Physical symptoms have been called a form of body language for children who have difficulty expressing emotions verbally. Examples include individuals who have difficulties with disclosing traumatic events and high-achieving children who cannot admit they are under too much pressure. *Alexithymia* has been used to describe individuals with somatic concerns who do not have a verbal vocabulary to describe their feelings. Somatic complaints have also been linked to *somatosensory amplification,* which is the tendency to experience normal somatic sensations as "intense, noxious and disturbing." When present, patients are hypervigilant to their own bodily sensations, overreact to these sensations, and interpret them as indicating physical illness.

Cognitive and Learning Difficulties

Children with difficulties learning and using academic skills, particularly in the context of high parental expectations, are associated with increased rates of somatization. Compared with unaffected siblings, youth with "functional" neurologic disorders have been found to score lower on tests of full-scale IQ, vocabulary level, and mathematics as well as to have more learning difficulties. Between 40% and 60% of patients with psychogenic nonepileptic seizures are reported to have learning and subtle language problems.

Learned Complaints

In operant conditioning learning, attention and sympathy from others and/or decrease in responsibilities *(secondary gain)* can reinforce somatic complaints. If somatic symptoms are reinforced (i.e., increased parental attention and/or avoidance of unpleasant school pressures) early in the course of an SSRD the likelihood increases that the somatic complaints will become more ingrained and less amenable to change. Social learning theory suggests that somatic symptoms may be a result of "modeling" or "observational learning" within the family. Family members with similar physical complaints *(symptom model)* are commonly found in SSRDs.

Family Factors

In family systems theory, somatization can serve the function of drawing attention away from other areas of tension with a family. It has been suggested that children in families with significant conflict may develop somatic complaints as a mechanism to avoid any emotional expression that may exacerbate family conflict.

Sociocultural Background

SSRDs have been reported to be more common in rural areas and among individuals of lower socioeconomic status. Spells or visions are common aspects of culturally sanctioned religious and healing rituals, and falling down with loss or alteration in consciousness is a feature in a variety of culture-specific syndromes.

ASSESSMENT

The diagnosis of SSRD must be based on the presence of somatic symptoms that are distressing and/or result in significant impairment of daily life. These somatic symptoms must be accompanied by excessive thoughts, feelings, and behaviors related to these symptoms and/or associated health concerns. SSRDs are not diagnoses of exclusion; the mere absence of a medical explanation is insufficient to make the diagnosis.

The assessment of suspected SSRDs should include an assessment of biologic, psychologic, social, and developmental realms, both separately and in relation to each other. A collaborative healthcare approach between pediatric practitioners and mental health clinicians is indicated to ensure that all realms are considered in the assessment of medically unexplained physical symptoms (Table 35.7)

Medical Assessment

A comprehensive medical workup to rule out serious physical illness is necessary, but must be carefully balanced with efforts to avoid unnecessary and potentially harmful tests and procedures. Certain medical conditions are notoriously overlooked and should be carefully considered as part of the diagnostic workup for problematic somatic symptoms (Table 35.8).

The presence of a medical condition does not exclude the possibility of somatization playing an important role in the presentation. Somatic symptoms early in a disease course that can be directly attributed to a specific physical illness (e.g., acute respiratory illness) may evolve into psychologically based symptoms, particularly in situations where the patient may experience benefit from adopting the sick role. Symptoms may not follow known physiologic principles or anatomic patterns and may respond to suggestion or placebo. Physical findings may occur secondary to the effects of the SSRD, especially when chronic or severe (e.g., deconditioning, disuse atrophy from prolonged immobilization, nutritional deficiency, gastroparesis and constipation from chronic poor oral intake).

Table 35.7 Key Elements to Consider in the Psychiatric Assessment of Somatic Symptoms and Related Disorders in Children and Adolescents

MEDICAL FINDINGS SUGGESTIVE OF SSRDS
- Absence of findings despite thorough medical workup
  - Lack of electrical evidence on video-electroencephalographic monitoring
- Inconsistent findings on examination
  - Sensory changes inconsistent with anatomic distribution (e.g., splitting at the midline, loss of sensation of entire face but not scalp, discrepancy between pain and temperature sensation, absence of Romberg sign)
  - Absence of functional impairment despite claims of profound weakness (e.g., impairment of fine motor function on testing, yet able to dress and undress)
  - Face-hand test (deflecting falling arm from face)
  - Hoover sign (patient pushes down with "paretic" leg when attempting to raise unaffected leg and fails to press down with unaffected leg when raising "paretic" leg)
  - Astasia-abasia (staggering gait, momentarily balancing, but never actually falling)
  - Dragging a "weak" leg as though it were a totally lifeless object instead of circumduction of the leg
  - Psychogenic deafness responding to unexpected words or noises
  - Tunnel vision
  - Movement disorder with normal concurrent electroencephalogram
  - Symptoms suggestive of conversion seizures (see Table 634.3).
  - Increased symptoms in the presence of family or medical staff
  - Periods of normal function when distracted
- Temporal relationship between onset of symptom and psychosocial stressor

PSYCHIATRIC FINDINGS SUGGESTIVE OF SSRDS
- Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns
- Co-occurring psychiatric disorder
- Learning difficulties and academic failure
- Stressful life events (including childhood trauma and bullying)
- Symptom model(s)

FAMILY BELIEFS REGARDING SOMATIC SYMPTOMS
- Belief in a single undiagnosed primary medical cause
  - Investment in further medical workup
  - Fear about serious medical illness
- Belief in the role of environmental triggers
- Belief in the role of psychologic factors
- Beliefs regarding symptom management
  - Awareness of nonpharmacologic approaches
  - Belief that the child should rest and be excused from usual responsibilities

FAMILY MEDICAL HISTORY
- Family history of unexplained somatic symptoms
- Pattern of reinforcement of illness behavior in the family

IMPACT OF SOMATIC SYMPTOMS
- Emotional (e.g., depression/anxiety vs la belle indifférence)
- Family (e.g., disruption of work schedule, impact on marital relationship, impact on distraction from family conflict)
- Social and peer relationships
- Academic (e.g., absenteeism, placement in home teaching)

REINFORCEMENT OF SOMATIC SYMPTOMS
- Reinforcement by parents
  - Medical journals and diaries of symptoms kept by parents
  - Parent home from work
- Increased attention from family/friends
- Increased attention from medical providers
- Avoidance of school, social, or athletic stressor

SSRD, Somatic symptoms and related disorder.
From Shaw RJ, DeMaso DR. *Clinical Manual of Pediatric Consultation-Liaison Psychiatry.* American Psychiatric Press; 2020:250–252.

Table 35.8 Selected Medical Conditions to Consider in the Differential Diagnosis of Youth Presenting with Disabling Somatic Symptoms

AIDS	Hyperparathyroidism
Acquired myopathies	Hyperthyroidism
Acute intermittent porphyria	Juvenile idiopathic arthritis
Angina	Lyme disease
Autoinflammatory (recurrent fever) syndromes	Migraine headaches
Basal ganglia disease	Mitochondrial disorders
Brain tumors	Multiple sclerosis
Cardiac arrhythmias	Myasthenia gravis
Chronic systemic infections	Narcolepsy
Ehlers-Danlos syndrome	Optic neuritis
Fabry disease	Periodic paralysis
Gaucher disease	Postural orthostatic hypertension syndrome
Guillain-Barré syndrome	Polymyositis
Hereditary neuropathies	Seizure disorders
Hereditary angioedema	Small fiber neuropathy
	Superior mesenteric artery syndrome
	Systemic lupus erythematosus

Modified from Shaw RJ, DeMaso DR. *Clinical Manual of Pediatric Consultation-Liaison Psychiatry.* American Psychiatric Press; 2020:248.

Psychosocial Assessment

If somatization is suspected, a mental health consultation should be included early in the diagnostic workup. This can be a difficult step for many families given their belief that there is a medical cause for their child's problem. A common response is for the family to react adversely and think that their child's symptoms are not being taken seriously. It is helpful for the pediatric practitioner to frame the consultation as a routine part of the medical workup as well as an opportunity to assess the level of stress connected with the current physical symptoms. The practitioner can communicate that the mental health consultation will be used to gain a more complete understanding of the origins of their child's distress, what perpetuates it, and which treatments are likely to be most effective.

The mental health assessment should include a careful assessment of psychosocial stressors, comorbid depression or anxiety disorders, individual and family histories of somatization, the presence of a model of illness behavior, and evidence of secondary gain resulting from the symptoms. The assessment should provide the pediatric practitioner(s) with a biopsychosocial explanation of the child's symptoms (diagnosis and formulation), which will inform the development of a comprehensive biopsychosocial management plan.

Differential Diagnoses

The primary differential diagnosis is between an SSRD and a physical illness. *Importantly, however, these disorders are not mutually exclusive and often coexist.* Depressive and anxiety disorders frequently include the presence of physical symptoms, which tend to remit with treatment of the primary depressive or anxiety symptoms, and which appear distinct from physical complaints seen in SSRDs. Distinguishing features of other physical complaint disorders are noted in Table 35.9. Chronic pain syndromes may be caused by fibromyalgia and small fiber autonomic neuropathy and complex regional pain syndrome (see Chapter 211).

MANAGEMENT

Effective management of SSRDs begins with the development of a positive working relationship between the patient, family, pediatric practitioner, and mental health clinician based on a shared understanding of the diagnosis, formulation, and a management plan that generally incorporates a number of different treatment modalities.

The *formulation of the problem is the crucial first step.* Patients and their families routinely present with the belief that their symptoms are caused by a medical illness alone. This view needs to be reframed from this narrow medical model view to a comprehensive biopsychosocial understanding. With the completion of medical and psychosocial assessments, a joint meeting of the pediatric practitioner(s) and

Table 35.9 Features of Conditions Characterized by Patient's Physical Complaints

	ILLNESS ANXIETY DISORDER	SOMATIC SYMPTOM DISORDER	CONVERSION DISORDER FUNCTIONAL NEUROLOGIC DISORDER
Presenting complaint	Primary concern is the development of a serious illness—does not require specific symptoms	Primary concern is a specific symptom; generally presents with a more specific physical complaint There are no objective physical findings other than those related to deconditioning	Presents with new-onset neurologic or physical symptom; patient may or may not be concerned about this new symptom
Medical correlation to complaint	Generally present with more vague complaints than a specific symptom; not usually explained by medical workup In the presence of a known disease, the complaint does not correlate to the natural history of the disorder in severity, duration, or dysfunction	Patient can have a medical explanation for their symptom; however, the worry about the seriousness of the symptom is disproportionate or excessive	Physical and neurologic findings do not correlate with patient's presentation Neurologic manifestations involve aspects of CNS where voluntary control is exercised
Course of disease	Often associated with other anxiety disorders; can be chronic	Chronic; rarely remits	Generally acute onset; can recur with same or different presenting symptom(s)

CNS, Central nervous system
Modified from Byrne R, Elsner G, Beattie A. Emotional and behavioral symptoms. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis: Common Diseases and their Mimics*. 2nd ed. Elsevier; 2023:Table 31.14, p. 530.

mental health clinician (as well as any involved pediatric specialists) should be arranged to reach and ensure a consensus on the diagnosis and treatment plan and facilitate adequate and consistent communication among all providers.

The next step is an "informing conference or meeting" that includes both the managing pediatric practitioner and the family. It is important in this meeting that this practitioner present the medical and psychosocial findings together to the patient and the family in a supportive and nonjudgmental manner. If patients and their families believe that the practitioner understands and empathizes with the degree of distress the somatic symptoms have produced, then they are more likely to be active participants in treatment. Depending on the comfort and expertise of the pediatric practitioner and the severity of the SSRD, the mental health clinician may or may not elect to attend this meeting.

After complete medical investigations yield no unifying results, labeling the symptoms as "psychiatric" may be problematic because it can shift the search for the cause onto family functioning, resulting in children and parents feeling blamed for the symptoms. The goal is to avoid such labeling and instead help the family move toward an understanding of the *mind-body connection and to shift their approach from searching for the cause of the symptoms to increasing child functioning*. Providing mind-body examples, such as facial flushing when embarrassed, hand shaking when frightened, or phantom limb pain, will help the patient and family understand how the brain may produce physical symptoms.

Treatment

With child and family acceptance of a biopsychosocial understanding, an integrated medical and psychosocial treatment approach focused on the development and implementation a treatment plan to improve the patient's functioning, and not a continued search for a cause of the presenting symptoms, can be implemented. It is helpful to establish realistic goals that emphasize improvements in *functioning* rather than the illusion that the symptoms can be completely removed. Those patients with mild-moderate presentations can be treated effectively in the primary or specialty pediatric care setting with appropriate mental health follow-up, whereas those with severe presentations and high complexity are better managed in the psychiatry specialty care setting.

Role of the Pediatric Practitioner

The pediatric practitioner serves an important role in providing ongoing monitoring and treatment for possible physical illness in addition to the recommended mental health interventions. Frequent, brief, and ongoing pediatric visits can be scheduled as a means of helping avoid unnecessary medical investigations and procedures. This arrangement permits the patient to receive attention from their pediatric practitioner without having to develop somatic symptoms. Furthermore it may reassure the family that the team is continuing to monitor for symptoms that would require further evaluation and helps ensure that any further medical evaluation is directed by a clinician knowledgeable about the previous symptoms and evaluations. It is generally more helpful for the practitioner to attend to a patient's *anxiety* in relation to their physical symptoms rather than the symptoms themselves. This approach has been shown to reduce overall healthcare utilization and to improve patient satisfaction.

Using Rehabilitation Approach

A rehabilitative approach *acknowledges* the reality of the symptoms, *emphasizes* the necessary involvement of mind and body in the recovery process, and *shifts the focus* from "cure" to "return to normal functioning" while allowing youth to "save face" through the promotion of physical recovery as the primary goal. A rehabilitative approach includes the use of intensive physical and occupational therapy that emphasizes the recovery of function. This approach can be combined with a behavioral modification program, with incentives for improvements in functioning, while removing secondary gain for illness behavior.

In severely disabled patients, it may be preferable to recommend admission to an inpatient medical-psychiatric treatment program that specializes in SSRDs. Another useful option to consider is that of day treatment or partial hospitalization programs. Multidisciplinary inpatient rehabilitation programs have much to offer these patients because they are designed to support both physical and psychologic recovery. Families are generally reassured that multidisciplinary staff can continue to monitor physical symptoms, thus ensuring that any missed diagnoses will be recognized quickly.

Youth with a high level of impairment often miss a significant amount of school. Communication with the school is often crucial in coordinating a successful reintegration. In addition to discussions with the school guidance counselor and/or nurse, a letter for the school providing education and recommended approaches for the patient's symptoms can be beneficial. These interventions can be formalized by having the school work with the family to develop either a 504 plan for accommodations needed in regular education settings, or an individualized educational plan (IEP) if the child needs special education services. Ongoing communication between the school and the pediatric practitioner for monitoring of further symptoms is recommended.

Psychotherapy and Psychopharmacology

Meta-analyses have shown that psychologic treatments improve symptom load, disability, and school attendance in youth suffering from various somatic symptoms including functional abdominal symptoms, fatigue, tension-type headache, and musculoskeletal pain. **Cognitive-behavioral therapy** (CBT) interventions modify symptom experience and restore central nervous system abnormalities associated with functional impairment. CBT techniques (e.g., relaxation training, biofeedback, hypnosis) can be used to teach patients the control they can have over certain physiologic processes, such as autonomic system activity. Cognitive restructuring is effective in addressing and altering dysfunctional thoughts regarding symptoms and their implications for functioning. Treatments that encourage active coping strategies and emotional expression and modulation are helpful in reducing symptoms and improving functioning. Modifying parental response patterns that are overprotective and potentially reinforcing (e.g., allowing the child to sleep late or to stay home from school in response to symptoms) help to decrease disability.

Psychopharmacologic treatment may be considered when psychiatric comorbidities are present, specifically, depressive and anxiety disorders. A combination of pharmacotherapy, physical therapy, and psychologic interventions in multicomponent management programs has been shown to be effective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 36

Rumination and Pica

Chase B. Samsel, Heather J. Walter, and David R. DeMaso

36.1 Rumination Disorder

Chase B. Samsel, Heather J. Walter, and David R. DeMaso

Rumination disorder is the repeated regurgitation of food, in which the regurgitated food may be rechewed, reswallowed, or spit out, for a period of at least 1 month following a period of normal functioning. Regurgitation is typically frequent and daily; it does not occur during sleep. It is not caused by an associated gastrointestinal illness or other medical conditions (e.g., gastroesophageal reflux, pyloric stenosis). It does not occur exclusively during the course of anorexia nervosa, bulimia nervosa, binge-eating disorder, or avoidant/restrictive food intake disorder. If the symptoms occur in the context of an intellectual or other neurodevelopmental disorder, the symptoms must be sufficiently severe to warrant additional clinical attention.

Weight loss and failure to make expected weight are common features in infants with rumination disorder. Infants may display a characteristic position of straining and arching the back with the head held back while making sucking movements with their tongue. In infants and older individuals with intellectual disability, the rumination behavior may appear to have a self-soothing or self-stimulating function. Malnutrition may occur in older children and adults, particularly when the regurgitation is associated with restricted food intake (which may be designed to avoid regurgitation in front of others). They may attempt to hide the regurgitation behavior or avoid eating among others.

EPIDEMIOLOGY

Originally thought of as a disorder predominantly seen in infants and those with intellectual disability, rumination disorder has also been recognized in healthy individuals across the life span and can be overlooked in adolescents. In otherwise healthy children, rumination disorder typically appears in the first year of life, generally between ages 3 and 12 months. The disorder can have an episodic course or can occur continuously until treatment is initiated. In infants the disorder frequently remits spontaneously but can be protracted with problematic and even life-threatening malnutrition. Additional complications related to the secondary effects of malnutrition include growth delay and negative effects on development and learning potential.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Risk factors for rumination disorder in infants and young children include a disturbed relationship with primary caregivers, lack of an appropriately stimulating environment, neglect, stressful life situations, learned behavior reinforced by pleasurable sensations, distraction from negative emotions, and inadvertent reinforcement (attention) from primary caregivers. Risk factors for rumination disorder in adolescents include similar early childhood factors along with female gender and comorbid anxiety and depression. The differential diagnosis includes congenital gastrointestinal system anomalies, pyloric stenosis, Sandifer syndrome, gastroparesis, hiatal hernia, increased intracranial pressure, diencephalic tumors, adrenal insufficiency, and inborn errors of metabolism. Older children and adults with anorexia nervosa or bulimia nervosa may also engage in regurgitation because of concerns about weight gain. The diagnosis of rumination disorder is appropriate only when the severity of the disturbance exceeds that routinely associated with a concurrent physical illness or mental disorder.

TREATMENT

The first step in treatment begins with a behavioral analysis to determine whether the disorder serves a self-stimulation purpose and/or is socially motivated. The behavior may begin as self-stimulation, but it subsequently becomes reinforced and maintained by the social attention given to the behavior. The central focus of behavioral treatment is to reinforce correct eating behavior while minimizing attention to rumination. Diaphragmatic breathing and postprandial gum chewing, when used as a competing response, have been shown to be helpful. Aversive conditioning techniques (e.g., withdrawal of positive attention, introducing bitter/sour flavors when regurgitating) are considered when a child's health is jeopardized but can be more reasonable and useful in adolescents. Additional techniques shown to be useful in adolescents include reswallowing all regurgitation, use of paradoxical intention, and guided progressive food trials.

Successful behavioral treatment requires the child's primary caregivers to be involved in the intervention. The caretakers need education and counseling on responding adaptively to the child's behavior as well as altering any maladaptive responses. No current evidence supports a psychopharmacologic intervention for rumination disorder. In more severe or intractable cases (e.g., severe dehydration, malnutrition), an intensive integrated medical-behavioral treatment program on a medical or medical-psychiatric unit may be necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

36.2 Pica

Chase B. Samsel, Heather J. Walter, and David R. DeMaso

Pica involves the persistent eating of nonnutritive, nonfood substances (e.g., paper, soap, plaster, charcoal, clay, wool, ashes, paint, earth) over a period of at least 1 month. The eating behavior is inappropriate to the developmental level (e.g., the normal mouthing and tasting of objects in infants and toddlers), and therefore a minimum age of 2 years is suggested. The eating behavior is not part of a culturally supported or socially normative practice. A diagnosis of pica may be assigned in the presence of any other feeding and eating disorder.

EPIDEMIOLOGY

Pica can occur throughout life but occurs most frequently in childhood. It is more common in those with intellectual disability and autism spectrum disorders, and to a lesser degree in obsessive-compulsive and schizophrenic disorders. The prevalence of pica is unclear, although it appears to increase with the severity of an intellectual disability. It usually remits in childhood but can continue into adolescence and adulthood. **Geophagia** (eating earth) is associated with pregnancy and is not seen as abnormal in some cultures (e.g., rural or preindustrial societies in parts of Africa and India). Children with pica are at increased risk for lead poisoning, iron-deficiency anemia, mechanical bowel problems, intestinal obstruction, intestinal perforations, dental injury, and parasitic infections. Pica can be fatal based on substances ingested.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Numerous etiologies have been proposed but not proved, ranging from psychosocial causes to physical ones. They include nutritional deficiencies (e.g., iron, zinc, calcium), low socioeconomic factors (e.g., lead paint exposure), child abuse and neglect, family disorganization (e.g., poor supervision), mental disorder, learned behavior, underlying (but undetermined) biochemical disorder, and cultural and familial factors. The differential diagnosis includes anorexia nervosa, factitious disorder, and nonsuicidal self-injury. A separate diagnosis of pica should be made only if the eating behavior is sufficiently severe enough to warrant additional clinical attention.

TREATMENT

Combined behavioral, social, and medical approaches are generally indicated for pica. Assessment for neglect and family supervision combined with psychiatric assessment for concurrent mental disorders and developmental delay are important in developing an effective intervention strategy for pica. Behavioral interventions, particularly applied behavioral analysis in patients with intellectual disability or autism spectrum disorders, are increasingly found to be helpful. The sequelae related to an ingested item can require specific treatment (e.g., lead toxicity, iron-deficiency anemia, parasitic infestation). Ingestion of hair can require medical or surgical intervention for a gastric bezoar.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 37 Motor Disorders and Habits

Jung Won Kim, Heather J. Walter, and David R. DeMaso

Motor disorders are interrelated sets of psychiatric symptoms characterized by abnormal motor movements and associated phenomena. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), they include tic, stereotypic movement, and developmental coordination disorders. **Tic disorders** (Tourette, persistent motor or vocal tic, provisional tic, other specified/unspecified tic) and **stereotypic movement disorders** (SMDs) are addressed in this chapter. **Habits** present as repetitive and often problematic motor behaviors (e.g., thumb sucking, nail biting, teeth grinding). When the problems cause significant distress or impairment they are discussed as **body-focused repetitive behavior disorder** in the Obsessive Compulsive and Related Disorders section of DSM-5.

37.1 Tic Disorders

Jung Won Kim, Heather J. Walter, and David R. DeMaso

Tourette disorder (TD), **persistent (chronic) motor or vocal tic disorder (PTD)**, and **provisional tic disorders** are characterized by involuntary, rapid, repetitive, and single or multiple motor and/or vocal/phonic tics that wax and wane in frequency but have persisted for >1 year since the first tic onset (<1 year for provisional tic disorder) (Table 37.1). PTD is differentiated from TD in that PTD is limited to either motor or vocal tics (not both), whereas TD has both motor and vocal tics at some point in the illness (although not necessarily concurrently). The tic disorders are hierarchical in order (i.e., TD followed by PTD followed by provisional tic disorder), such that once a tic disorder at one level of the hierarchy is diagnosed, a lower-hierarchy diagnosis cannot be made. **Other specified/unspecified tic disorders** are presentations in which symptoms characteristic of a tic disorder that cause significant distress or impairment predominate but do not meet the full criteria for a tic or other neurodevelopmental disorder.

DESCRIPTION

Tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations. *Simple motor tics* (e.g., eye blinking, neck jerking, shoulder shrugging, extension of the extremities) are fast, brief movements involving one or a few muscle groups. *Complex motor tics* involve sequentially and/or simultaneously produced, relatively coordinated movements that can seem purposeful (e.g., brushing back one's hair bangs, tapping the foot, imitating someone else's movement [**echopraxia**], or making a sexual or obscene gesture [**copropraxia**]). *Simple vocal tics* (e.g., throat clearing, sniffing, coughing) are solitary, meaningless sounds and noises. *Complex vocal tics* involve recognizable word or utterances (e.g., partial words [syllables], words out of context, obscenities or slurs [**coprolalia**], repeating one's own sounds or words [**palilalia**], or repeating the last heard word or phrase [**echolalia**]).

Table 37.1 DSM-5 Diagnostic Criteria for Tic Disorders

TOURETTE DISORDER
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for >1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington disease, postviral encephalitis).
PERSISTENT (CHRONIC) MOTOR OR VOCAL TIC DISORDER
A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.
B. The tics may wax and wane in frequency but have persisted for >1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington disease, postviral encephalitis).
E. Criteria have never been met for Tourette disorder.
Specify if:
With motor tics only
With vocal tics only
PROVISIONAL TIC DISORDER
A. Single or multiple motor and/or vocal tics.
B. The tics have been present for <1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington disease, postviral encephalitis).
E. Criteria have never been met for Tourette disorder or persistent (chronic) motor or vocal tic disorder.

Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization. Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p 81. Copyright ©2013. American Psychiatric Association. All Rights Reserved.

Sensory phenomena (premonitory urges) that precede and trigger the urge to tic have been described. Individuals with tics can suppress them for varying periods of time, particularly when external demands exert their influence, when deeply engaged in a focused task or activity, or during sleep. Tics are often suggestible and are worsened by anxiety, excitement, or exhaustion. Parents have described increasing frequency of tics at the end of the day.

CLINICAL COURSE

Onset of tics is typically between ages 4 and 6 years. The frequency of tics tends to wax and wane with peak tic severity between ages 10 and 12 years and marked attenuation of tic severity in most individuals (65%) by age 18-20 years. A small percentage will have worsening tics into adulthood. New onset of tics in adulthood is very rare and most often is associated with exposure to drugs or insults to the central nervous system. Tics manifest similarly in all age groups, with changes in affected muscle groups and vocalizations that occur over time. Some individuals may have tic-free periods of weeks to months.

EPIDEMIOLOGY

Prevalence rates for all tics range from 6–18% for males and 3–11% for females, with the rate of TD alone estimated as 0.8%. In general, PTD/TD has a male preponderance with a gender ratio varying from 2:1 to 4:1.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other repetitive movements of childhood (Table 37.2). Tics may be difficult to differentiate from stereotypies. Although stereotypies may resemble tics, **stereotypies** are typically rhythmic movements and do not demonstrate the change in body location or movement type over time that is typical of tics. **Compulsions** may be difficult to differentiate from tics when tics have premonitory urges. Tics should be differentiated from a variety of developmental and benign movement disorders (e.g., benign paroxysmal torticollis, Sandifer syndrome, benign jitteriness of newborns, shuddering attacks). Although tics may present in various neurologic illnesses (e.g., Wilson disease, neuroacanthocytosis, Huntington syndrome, various frontal-subcortical brain lesions), it is rare for tics to be the only manifestation of these disorders (Table 37.3).

Individuals presenting with tics in the context of declining motor or cognitive function should be referred for neurologic assessment. Substances/medications that are reported to worsen tics include selective serotonin reuptake inhibitors (SSRIs), lamotrigine, and cocaine. If tics develop in close temporal relationship to the use of a substance or medication and then remit when use of the substance is discontinued, a causal relationship is possible. Stimulants do not commonly increase tics.

COMORBIDITIES

Comorbid psychiatric disorders are common, often with both patient and family viewing the accompanying condition as more problematic than the tics. There is a bidirectional association between PTD/TD (especially TD) and obsessive-compulsive disorder (OCD), with 20–60% of TD patients meeting OCD criteria and 20–40% of OCD patients reporting tics (Fig. 37.1). Attention-deficit/hyperactivity disorder (ADHD) occurs in approximately 50% of all childhood PTD/TD, but estimates in clinically referred patients suggest much higher rates (60–80%). PTD/TD is often accompanied by behavior problems, including poor frustration tolerance, temper outbursts, and oppositionality. Learning disabilities have been found in >20% of these patients. Concurrent anxiety and depression have also been observed. Some patients with PTD/TD will display symptoms of autism spectrum disorder (ASD); careful assessment is required to determine which disorder is primary.

ETIOLOGY

Tics are proposed to be the result of dysfunctional corticostriatal-thalamocortical motor pathways in the basal ganglia, striatum, and frontal lobes associated with abnormalities in the dopamine, serotonin, and norepinephrine neurotransmitter systems. Male predominance in PTD/TD may be attributable to influences of sex hormones on the neurodevelopment of these motor pathways, as reflected by the effects of antiandrogens in the treatment of TD.

Family studies suggest a 10-100–fold increased risk of PTD/TD among first-degree relatives compared to rates in the general population. Twin studies also support a genetic link, with approximately 80% of monozygotic twins and 30% of dizygotic twins showing concordance for PTD/TD. Candidate-gene association and nonparametric linkage studies have not identified specific susceptibility genes for PTD/TD.

Autoimmune-mediated mechanisms have been hypothesized as having a potential etiologic role in *some* tic disorders. The **pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)** designation describes cases of acute childhood onset of OCD and/or tics following a streptococcal infection. Pediatric acute-onset neuropsychiatric syndrome **(PANS)** describes a subtype of acute childhood-onset OCD (tics are not a required feature) in which a link to a prior streptococcal infection is not evident, suggesting that other infectious agents may be responsible. In addition to a diagnosis of OCD and tics, children with PANS/PANDAS may potentially have separation anxiety, nightmares, personality change, oppositional behaviors, and deterioration in math skills and handwriting. Although some studies suggest a prior history of infections may increase the risk for developing tic disorder, this remains controversial.

Premorbid stress has been hypothesized to act as a sensitizing agent in the pathogenesis of TD among susceptible individuals by affecting stress-responsive biologic systems such as the hypothalamic-pituitary-adrenal axis.

Table 37.2 Repetitive Movements of Childhood

MOVEMENT	DESCRIPTION	TYPICAL DISORDERS WHERE PRESENT
Tics	Sudden rapid, recurrent, nonrhythmic, stereotyped, vocalization or motor movement	Transient tics, Tourette disorder, persistent tic disorder
Dystonia	Involuntary, sustained, or intermittent muscle contractions that cause twisting and repetitive movements, abnormal postures, or both	*DYT1* gene, Wilson disease, myoclonic dystonia, extrapyramidal symptoms caused by dopamine-blocking agents
Chorea	Involuntary, random, quick, jerking movements, most often of the proximal extremities, that flow from joint to joint. Movements are abrupt, nonrepetitive, and arrhythmic and have variable frequency and intensity	Sydenham chorea, Huntington chorea
Stereotypies	Stereotyped, rhythmic, repetitive movements or patterns of speech, with lack of variation over time	Autism, stereotypic movement disorder, intellectual disability
Compulsions	A repetitive, excessive, meaningless activity or mental exercise that a person performs in an attempt to avoid distress or worry	Obsessive-compulsive disorder, anorexia, body dysmorphic disorder, trichotillomania, excoriation disorder
Myoclonus	Shocklike involuntary muscle jerk that may affect a single body region, one side of the body, or the entire body; may occur as a single jerk or repetitive jerks	Hiccups, hypnic jerks, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, mitochondrial encephalopathies, metabolic disorders
Akathisia	Unpleasant sensations of "inner" restlessness, often prompting movements in an effort to reduce the sensations	Extrapyramidal adverse effects from dopamine-blocking agents; anxiety
Volitional behaviors	Behavior that may be impulsive or caused by boredom, such as tapping peers or making sounds (animal noises)	Attention-deficit/hyperactivity disorder, oppositional defiant disorder, sensory integration disorders

Adapted from Murphy TK, Lewin AB, Storch EA, Stock S. American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry. 2013;52(12):1341–1359.*

SEQUELAE

Many individuals with mild to moderate tics express minimal to no distress or functional impairment and may even be unaware of their tics. Even individuals with moderate to severe tics can experience minimal functional impairment, but psychologic distress may occur. Infrequently, the presence of tics can lead to social isolation, social victimization, inability to work or attend school, or impaired quality of life. TD/PTD is associated with increased risk of suicide. Suicidal behavior should be monitored, particularly in those with persistent tics, history of suicide attempts, and psychiatric comorbidities.

SCREENING

Pediatric practitioners should routinely screen for unusual movements (e.g., sudden twitches or jerks, eye blinking, neck twisting, muscle tightening, shoulder shrugging, or involuntary gestures) or vocalizations (e.g., utter involuntary sounds, like grunts, yelps, squeaks, or throat clears). Often families are unaware that frequent sniffing, coughing, or blinking may be indicative of tics, attributing these behaviors to medical problems (e.g., allergies, visual problems). A careful assessment of the timing, triggers, and specific characteristics may differentiate tics from other medical problems. If differentiation is difficult, a referral to a pediatric specialist in the affected system is warranted.

ASSESSMENT

If the screening suggests the presence of a tic disorder, a more comprehensive evaluation should ensue, including the age of onset, types of tics, tic frequency, alleviating and aggravating factors, and a family history of tics. Parent rating scales specific for tics (e.g., the *Motor Tic, Obsessions and Compulsions, Vocal Tic Evaluation Survey* [MOVES] and *Autism-Tics, ADHD and other Comorbidities inventory* (A-TAC) can supplement the assessment. For clinician-rated tic severity, the most comprehensive, reliable, and valid instrument is the *Yale Global Tic Severity Scale* (YGTSS), though its relatively long administration makes routine use in clinical practice problematic (https://candapediatricmedicalhomes.files.wordpress.com/2017/02/yale-global-tic-severity-scale.pdf).

A medical workup should be considered for new-onset tics, particularly for presentations characterized by sudden onset, atypicality, or mental status abnormalities. Basic laboratory measures (hemogram, renal/hepatic function panel, thyroid panel, and ferritin, along with urine drug screen for adolescents) should be considered. For new, sudden onset, or severe symptom exacerbation, pediatric practitioners may assess for concurrent acute infection (e.g., culture, rapid viral tests). Electroencephalography and brain imaging are not routinely recommended for isolated tics and should be reserved for patients with other neurologic findings that might suggest an autoimmune encephalitis syndrome (limbic encephalitis). Comorbid psychiatric disorders (e.g., OCD, ADHD, ASD) should be investigated.

TREATMENT

The decision to treat tics is made with the child and family based on the level of impairment and distress caused by the tics. If tics are mild in severity, the pediatric practitioner can provide the family with education, often with no need for further intervention.

Patient and family education should include common symptom presentations, implications of concurrent conditions, course and prognosis, and treatment options (including no treatment). The patient's typical exacerbating and alleviating factors should be outlined. Pediatric practitioners can also direct the patient and family to informational websites, including the Tourette Association of America (www.tourette.org).

Almost 75% of children with TD/PTD receive some form of classroom accommodation (e.g., directions to ignore tics and permission to leave the room as needed). The accommodations may need to be formalized in an individualized education plan (IEP) if a child needs special education services or a 504 plan if the child just needs accommodations in the regular classroom.

Table 37.3 Etiology of Tics

PRIMARY CAUSES
Sporadic
Transient motor or phonic (<1 year), chronic motor or phonic tics (>1 year), adult-onset recurrent) tics, Tourette disorder, primary dystonia
Inherited
Tourette disorder, Huntington disease, primary dystonia, neuroacanthocytosis syndromes, neurodegeneration with brain iron accumulation (type 1) (pantothenate kinase associated neurodegeneration), tuberous sclerosis, Wilson disease, Duchenne muscular dystrophy
SECONDARY CAUSES
Infections
Encephalitis, Creutzfeldt-Jakob disease, neurosyphilis, Sydenham chorea, PANS
Drugs
Amphetamines, methylphenidate, levodopa, cocaine, carbamazepine, phenytoin, phenobarbital, lamotrigine, antipsychotics, and other dopamine receptor-blocking drugs
Toxins
Carbon monoxide, wasp venom
Developmental
Static encephalopathy, intellectual disability syndromes, chromosomal abnormalities, autistic spectrum disorders
Chromosomal Disorders
Down syndrome, Klinefelter syndrome, XYY karyotype, fragile X, triple X, and 9p mosaicism, partial trisomy 16, 9p monosomy, citrullinemia, Beckwith-Wiedemann syndrome
Other Causes
Head trauma, stroke, cardiopulmonary bypass with hypothermia, neurocutaneous syndromes, schizophrenia, neurodegenerative diseases
RELATED DISORDERS
• Stereotypies/habits/mannerisms • Self-injurious behaviors • Motor restlessness • Akathisia • Compulsions • Hyperekplexia • Jumping Frenchman (startle response)

PANS, Pediatric acute neuropsychiatric syndrome.
Modified from Jankovic J. Differential diagnosis and etiology of tics. In: Cohen DJ, Goetz, CG, Jankovic J, eds. Tourette Syndrome. Lippincott Williams & Wilkins, 2001:Table 2.2, p. 18.

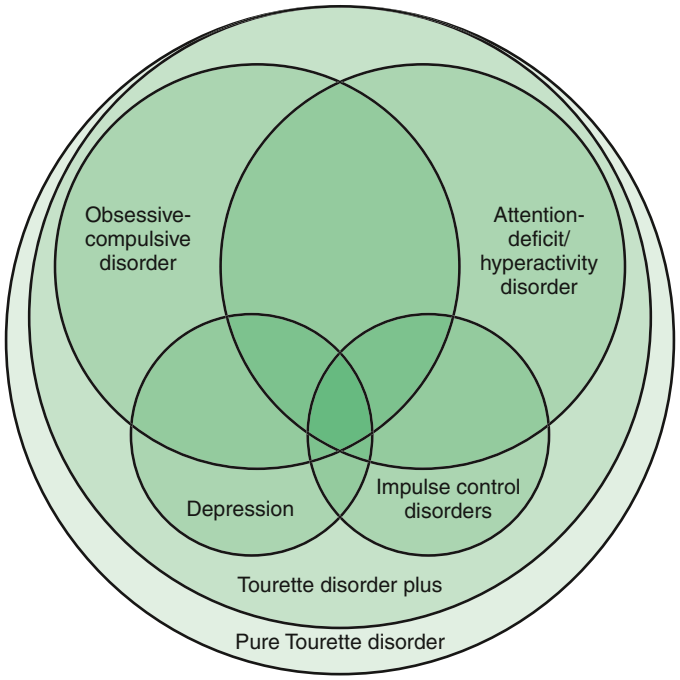

Fig. 37.1 Schematic representation of the behavioral spectrum in Tourette disorder. The size of each area is proportional to the estimated prevalence of the symptoms; the background color intensity is proportional to the complexity of the clinical presentation. *(From Cavanna AE, Seri S. Tourette's syndrome. BMJ. 2013;347:f4964.)*

Referral to a *behavioral treatment specialist* should be considered when tics are distressing or functionally impairing. The behavioral interventions with the strongest empirical support are habit reversal therapy (HRT) and comprehensive behavioral intervention for tics (CBIT). The basic components of HRT include premonitory urge awareness training and building a competing response to the urge to tic (Table 37.4). Based on HRT, CBIT additionally includes relaxation training and a functional intervention designed to mitigate against tic-generating situations. A course of HRT/CBIT treatment typically takes several months or 8-10 sessions. CBIT has been found to reduce significantly the severity of tics compared to education and supportive therapy.

Medications should be considered when the tics are causing severe impairment in the quality of life or when psychiatric comorbidities are present. The only U.S. Food and Drug Administration (FDA)–approved medications to treat TD in children and adolescents are two first-generation antipsychotics (haloperidol, pimozide) and one second-generation antipsychotic (aripiprazole). α-Agonists (clonidine, guanfacine) are also considered as first-line agents because of their more favorable side effect profile compared with the antipsychotic medications (see Chapter 33).

Youths with tic disorders may benefit from SSRIs for the treatment of comorbid obsessive-compulsive, anxiety, or depressive disorders. Augmentation of SSRIs with an atypical antipsychotic has been a consideration in patients with concurrent tic disorders and OCD responding poorly to an SSRI alone. The presence of tics does not preclude the use of stimulants to address comorbid ADHD. Treatment of tics and comorbid ADHD with a combination of α-agonists and stimulants (e.g., clonidine with methylphenidate) decreases tics. Close clinical monitoring is required for possible exacerbation of tics during stimulant treatment. Anger and rage outbursts are common particularly among youth with severe tics (up to 80% in clinically referred samples). Behavioral therapies (cognitive-behavioral therapy [CBT], parent management training; see Chapter 34) that address anger management may be useful.

A systematic review indicated high confidence of efficacy for CBIT; moderate confidence for medications, such as haloperidol, risperidone, aripiprazole, clonidine; and low confidence for medications, such as ziprasidone, guanfacine, and topiramate. No evidence exists to differentiate the effectiveness of HRT/CBIT alone vs combined with pharmacotherapy as tic disorder treatment options. There is no rigorous scientific evidence to support the use of deep brain stimulation, repetitive magnetic stimulation, or dietary supplements in the treatment of TD or PTD.

In severe presentations, pediatric practitioners should consider seeking consultations from and/or making referrals to pediatric tic disorder specialists (i.e., behavioral psychologist, pediatric neurologist, developmental-behavioral pediatrician, or child and adolescent psychiatrist) in determining a treatment regimen.

37.2 Stereotypic Movement Disorder

Jung Won Kim, Heather J. Walter, and David R. DeMaso

Stereotypic movement disorder (SMD) is defined in DSM-5 as a neurodevelopmental disorder characterized by repetitive, seemingly driven, and apparently purposeless motor behavior *(stereotypy)* that interferes with social, academic, or other activities and may result in self-injury. The onset of SMD is the early developmental period (often before age 3 years), and the symptoms are not attributable to the physiologic effects of a substance or neurologic condition and are not better explained by another neurodevelopmental or mental disorder. The disorder is considered *mild* if symptoms are easily suppressed by sensory stimulation or distraction, and *severe* if continuous monitoring and protective measures are required to prevent serious injury, with *moderate* falling between mild and severe.

DESCRIPTION

Examples of stereotypic movements include hand shaking or waving, body rocking, head banging, self-biting, and hitting one's own body. The presentation depends on the nature of the stereotypic movement and level of the child's awareness of the behavior. Among typically developing children, the repetitive movements may be stopped when attention is directed to the movements or when the child is distracted from performing them. Among youth with intellectual disability, the behaviors may be less responsive to such efforts. Each individual presents with their own uniquely patterned behavior. Stereotypic movements may occur many times during a day, lasting a few seconds to several minutes or longer. The behaviors may occur in multiple contexts, including when the individual is excited, stressed, fatigued, or bored.

CLINICAL COURSE

Stereotypic movements typically begin before age 3 years. In those who develop complex motor stereotypies, the great majority exhibit these symptoms before 24 months. In most typically developing youth, these movements resolve over time. Among those with intellectual disability, the stereotyped behaviors may persist for years, although the pattern may change over time.

EPIDEMIOLOGY

Simple stereotypic movements are common in typically developing young children. Some children may bang their head on their mattress as they are falling asleep or may sit and rock when bored or overstimulated. Self-injurious habits, such as self-biting or head banging, can occur in up to 25% of typically developing toddlers (often during tantrums), but they are *almost invariably* associated with developmental delay in youth older than 5 years. *Complex* stereotypic movements are much less common (approximately 3–4%). Between 4% and 16% of patients with intellectual disability engage in stereotypic movements.

COMORBIDITY

Stereotypic movements are a common manifestation of a variety of neurogenetic disorders, such as Lesch-Nyhan, Rett, fragile X, Cornelia de Lange, and Smith-Magenis syndromes.

DIFFERENTIAL DIAGNOSIS

According to DSM-5, stereotypic movements must be differentiated from normal development, ASDs, tic disorders, OCDs, and other neurologic/medical conditions. Simple stereotypic movements occurring in the context of typical development usually resolve with age. Stereotypic movements may be a presenting symptom of ASD, but SMD does not include the deficits in the social communication characteristic of ASD. When ASD is present, SMD is diagnosed only when there is self-injury or when the stereotypic behaviors are sufficiently severe to become a focus of treatment. Typically, SMD has an earlier age of onset than the tic disorders. SMD is distinguished from OCD by the absence of obsessions as well as the nature of the repetitive behaviors, which in OCD are purposeful (e.g., in response to obsessions). The diagnosis of stereotypic movements requires the exclusion of mannerisms, paroxysmal dyskinesias, and benign hereditary chorea. A neurologic history and examination are required to assess features suggestive of other disorders, such as myoclonus, dystonia, and chorea.

ETIOLOGY

There is a possible evolutionary link between repetitive abnormal grooming-like behaviors and early human experience with adversity. Brain regions implicated in this model (e.g., amygdala, hippocampus) are those involved in navigating human experience through unpredictable, anxiety-provoked emotional states, as well as regions (e.g., nucleus accumbens) related to pleasure and reward seeking. The latter involves the hypothesis that individuals experience some level of gratification from performing the stereotypic behavior.

Social isolation with insufficient stimulation (e.g., severe neglect) is a risk factor for self-stimulation that may progress into stereotypies, particularly repetitive rocking or spinning. Environmental stress may trigger stereotypic behaviors. Repetitive self-injurious behavior may be a behavioral phenotype in neurogenetic syndromes (e.g., Lesch-Nyhan, Rett, and Cornelia de Lange syndromes). Lower cognitive functioning is also linked to greater risk of stereotypic behaviors.

TREATMENT

The initial approach to mild stereotypy is for the primary caretakers to ignore the undesired behavior, encourage substitute behavior, and not convey worry to their child. These behaviors may disappear with time and elimination of attention in young children. However, in children with intellectual disability or ASDs, stereotypies may be more refractory to treatment than in typically developing children and may necessitate referral to a behavioral psychologist, developmental-behavioral pediatrician, or child and adolescent psychiatrist for behavioral and/or psychopharmacologic management. The pediatric practitioner should consider and rule out neglect of the child, which can be associated with repetitive rocking, spinning, or other stereotypic movements.

Behavior therapy is the mainstay of treatment, using a variety of strategies, including habit reversal, relaxation training, self-monitoring, contingency management, competing responses, and negative practice. The environment should also be modified to reduce risk of injury to those engaging in self-injurious behavior.

Atypical antipsychotic medications may be helpful in reducing stereotypic movements in youth with ASD. Patients with anxiety and obsessive-compulsive behaviors treated with SSRIs may show improvement in their stereotypic movements.

HABITS

Habits involve an action or pattern of behavior that is repeated often. Habits are common in childhood and range from usually benign and transient behaviors (e.g., thumb sucking, nail biting) to more problematic (e.g., trichotillomania, bruxism). In DSM-5, habits are not included as a diagnostic category because they are not viewed as disorders causing clinically significant distress or impairment in functioning. When they do cause distress or impairment or are associated with repeated attempts by the individual to stop the behavior they are discussed as body-focused repetitive behavior disorder. HRT has been effective as a first-line treatment approach (see Table 37.4).

Table 37.4 Components of Habit Reversal Training

INCREASE INDIVIDUAL'S AWARENESS OF HABIT
Response description—have individual describe behavior to therapist in detail while reenacting the behavior and looking in a mirror.
Response detection—inform individual of each occurrence of the behavior until each occurrence is detected without assistance.
Early warning—have individual practice identifying earliest signs of the target behavior.
Situation awareness—have individual describe all situations in which the target behavior is likely to occur.
TEACH COMPETING RESPONSE TO HABIT
The competing response must result in isometric contraction of muscles involved in the habit, be capable of being maintained for 3 min, and be socially inconspicuous and compatible with normal ongoing activities but incompatible with the habit (e.g., clenching one's fist, grasping and clenching an object). For vocal tics and stuttering, deep relaxed breathing with a slight exhale before speech has been used as the competing response.
SUSTAIN COMPLIANCE
Habit inconvenience review—have individual review in detail all problems associated with target behavior.
Social support procedure—family members and friends provide high levels of praise when a habit-free period is noted.
Public display—individual demonstrates to others that he or she can control the target behavior in situations in which the behavior occurred in the past.
FACILITATE GENERALIZATION—SYMBOLIC REHEARSAL PROCEDURE
For each situation identified in situation awareness procedure, individual imagines himself or herself beginning the target behavior but stopping and engaging in the competing response.

From Carey WB, Crocker AC, Coleman WL, et al., eds. *Developmental-Behavioral Pediatrics*. 4th ed. Philadelphia: Saunders; 2009:639.

Thumb Sucking

Thumb sucking is common in infancy and occurring in as many as 25% of children age 2 years and 15% of children age 5 years. Thumb sucking beyond 5 years of age may be associated with sequelae (e.g., paronychia, anterior open bite). As with other rhythmic patterns of behavior, thumb sucking is self-soothing. Basic behavioral management, including encouraging parents to ignore thumb sucking and instead focus on praising the child for substitute behaviors, is often an effective treatment. Simple reminders and reinforcers can also be considered; giving the child a sticker or other reward for each block of time that they do not thumb suck. In rare cases, mechanical devices placed on the thumb or in the mouth to prevent thumb sucking or noxious agents (bitter salves) placed on the thumb may be part of the treatment plan.

Bruxism

Bruxism or teeth grinding is common (5–30% of children), can begin in the first 5 years of life, and may be associated with daytime anxiety. Persistent bruxism can manifest as muscular or temporomandibular joint pain. Untreated bruxism can cause problems with dental occlusion. Helping the child find ways to reduce anxiety might relieve the problem; bedtime can be made more relaxing by reading or talking with the child and allowing the child to discuss fears. Praise and other emotional support are useful. Persistent bruxism requires referral to a dentist given the risk for dental occlusion.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 38

Anxiety Disorders, Obsessive-Compulsive Disorder, and Post-traumatic Stress Disorder

Rosa K. Kim

Anxiety is not necessarily pathologic, is seen across the life span, and can be adaptive (e.g., the anxiety one might feel during life-threatening situations). It has both a cognitive-behavioral component, expressed in worrying and wariness, and a physiologic component, mediated by the autonomic nervous system. Anxiety is characterized as *pathologic* (e.g., a disorder) when it becomes disabling, interferes with social interactions, or derails normal development.

Anxiety disorders are some of the most common psychiatric disorders in childhood. The point prevalence worldwide is nearly 7%, and the estimated lifetime prevalence in the United States is approximately 20–30%. Anxiety disorders are often comorbid with other psychiatric and medical disorders, and they can have physical manifestations, such as weight loss, palpitations, tremors, muscle cramps, paresthesias, hyperreflexia, and abdominal distress (Table 38.1). Although onset can be acute, the course is generally chronic with periods of fluctuating severity. The potential consequences of untreated anxiety include impairments in social, educational, and overall functioning. Because anxiety is both a normal phenomenon and, when highly activated, strongly associated with impairment, the clinician is tasked with differentiating between normal anxiety and abnormal anxiety across development (Fig. 38.1).

The median age of onset is 11 years. However, there are known periods of typical onset during specific developmental phases for both normal and pathologic anxiety. Normal stranger anxiety begins around 7-9 months of age. Preschoolers typically have specific fears related to the dark, animals, and imaginary situations. **Separation anxiety** can occur during the preschool years. Although most school-aged children abandon the imaginary fears of early childhood, some replace them with fears of bodily harm or other worries, reaching the level of a **specific phobia** (Table 38.2). Some characteristics of obsessive-compulsive disorder (OCD) can be considered typical in early school-ages, but OCD often has its onset in the mid–school-aged years (Table 38.3). **Social anxiety** occurs in later grade-school ages and early adolescence (Table 38.4) as the value of peer relationships increases. **Generalized anxiety**, **panic**, and **agoraphobia** tend to occur during the teen and young adult years (Tables 38.5 to 38.7).

Genetic or temperamental factors contribute more to the development of some anxiety disorders, whereas environmental factors are closely linked to the cause of others. Specifically, behavioral inhibition (sensitivity to novel stimuli) appears to be a heritable tendency and is linked with social phobia, generalized anxiety, and selective mutism. **OCD** and other disorders associated with OCD-like behaviors, such as Tourette syndrome and other tic disorders, tend to have high genetic risk as well (see Chapter 37.1). Environmental factors, such as parent–infant attachment and exposure to trauma, contribute more to **separation anxiety disorder** and posttraumatic stress disorder (**PTSD**) (Table 38.8). Parental anxiety disorder is associated with an increased risk of anxiety disorder in offspring.

Table 38.1 Mental and Somatic Disorders that are Frequently Comorbid or Difficult to Distinguish in Anxiety Disorder

	EXAMPLES OF OVERLAPPING SYMPTOMS	KEY CLINICAL INSIGHTS TO RECOGNIZE
MENTAL DISORDERS		
Major depressive disorder	Fatigue, anxiety, worry, or agitation	Major depressive disorder is the highest comorbidity in anxiety disorder and associated with higher severity, suicidality, disability and chronicity; clinicians must comprehensively assess because major depressive disorder comorbidity requires more intensive pharmacologic treatment and a different form of psychotherapy treatment (e.g., cognitive-behavioral therapy for depression rather than for anxiety disorder)
Bipolar disorder	Agitation, irritability, or racing thoughts	Anxiety is often present in bipolar disorder and is associated with rapid cycling; targeting anxiety could aid in mood stabilization; bipolar disorder requires focus on mood stabilization and considerate use of medication, which could induce mania (especially antidepressants)
Obsessive-compulsive disorder*	Extreme worry or inability to relax	People who have obsessive-compulsive disorder engage in ritualistic, repetitive behavior to deal with their fears, which is absent in anxiety disorder; these people often realize that their behavior is irrational and inappropriate
Posttraumatic stress disorder*	Avoidance, hyperarousal, or anxiety-laden intrusive memories	The intense experience of anxiety in posttraumatic stress disorder is specifically in response to a psychologic trauma (e.g., abuse, war, or accident); specific psychotherapies focused on the trauma associated with the posttraumatic stress disorder should be used
Health anxiety* (hypochondriasis)	Anxiety or worry from bodily responses	Anxiety is specifically related to preoccupation with having or acquiring a serious, undiagnosed medical illness
Substance use (e.g., illicit drugs, alcohol, or benzodiazepines) disorder	Tremor, sweating, palpitations, or panic attacks (during withdrawal or in some cases intoxication)	When suspected, clinicians should conduct a psychiatric interview of substance use disorders, with potential breath, urine, or plasma drug screening; comorbidity of alcohol or benzodiazepine abuse with anxiety disorder is considerable
SOMATIC DISORDERS		
Cardiac disease	Chest pain or palpitations (which is also common in panic disorder)	Clinical evaluation, including electrocardiogram, assessment of plasma troponin concentration, or Holter monitoring
Thyroid disease (e.g., hyperthyroidism)	Palpitations, tremor, panic attacks, or persistent anxiety	Laboratory assessment of plasma thyroid-stimulating hormone
Respiratory disease (e.g., asthma)	Shortness of breath	Clinical evaluation with a pulmonary function test
Pheochromocytoma or other disorders that result in sudden blood pressure increase	Panic attacks or bodily sensations	Blood pressure monitoring over 24 hr or hormone assessment (e.g., in blood or urine)
Epilepsy	Anxiety symptoms as part of aura or start of seizure	Clinical evaluation or neurologic referral when the causes of symptoms are unclear

*In previous classifications of the *Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases*, these disorders were included in the classification of anxiety disorders. In current classifications (e.g., the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* and the 11th edition of the *International Classification of Diseases)*, they are integrated in different classifications.

From Penninx BWJH, Pine DS, Holmes EA, Reif A. Anxiety disorders. *Lancet*. 2021;397:914–926:Table 2, p. 917.

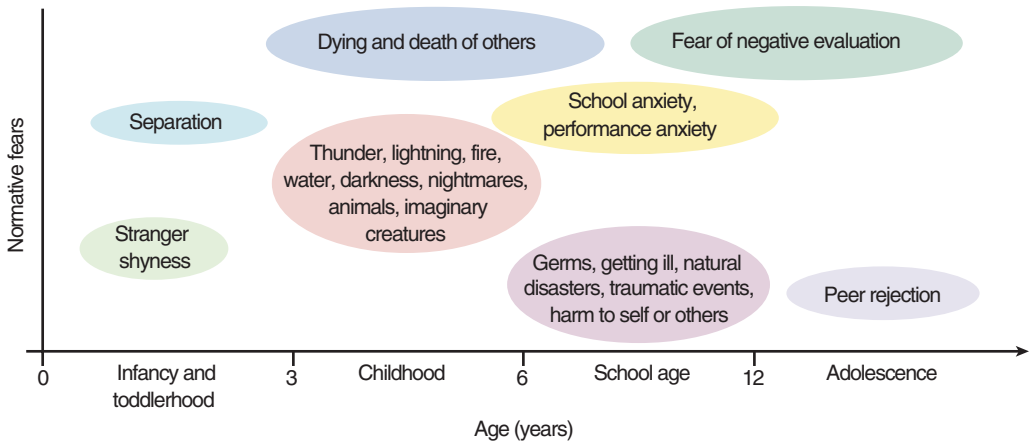

Fig. 38.1 Normative fears throughout childhood and adolescence. *(From Craske MG, Stein MB. Anxiety. Lancet. 2016;388[10063]:3048–3059.)*

Table 38.2 DSM-5 Diagnostic Criteria for Specific Phobia

A. Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.

B. The phobic object or situation almost always provokes immediate fear or anxiety.

C. The phobic object or situation is actively avoided or endured with intense fear or anxiety.

D. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.

E. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

G. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety, and avoidance or situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive disorder); remainders of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).

Specify if:

Code based on the phobic stimulus:

Animal (e.g., spiders, insects, dogs).

Natural environment (e.g., heights, storms, water).

Blood-injection-injury (e.g., needles, invasive medical procedures).

Situational (e.g., airplanes, elevators, enclosed places).

Other (e.g., situations that may lead to choking or vomiting; in children, e.g., loud sounds or costumed characters).

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp 197–198. Copyright 2013. American Psychiatric Association.

Table 38.4 DSM-5 Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)

A. Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).

B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).

C. The social situations almost always provoke fear or anxiety.

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The fear, anxiety, or avoidance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.

J. If another medical condition (e.g., Parkinson disease, obesity, disfigurement from burns or injury) is present, the anxiety or avoidance is clearly unrelated or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp 202-203. Copyright 2013. American Psychiatric Association.

Table 38.3 DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):

1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):

1. Repetitive behaviors (e.g., handwashing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hr/day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating disorder, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if:

With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.

With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.

With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.

Specify if:

Tic-related: The individual has a current or past history of a tic disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p 237. Copyright 2013. American Psychiatric Association.

Table 38.5 DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 mo):

Note: Only one item is required in children.

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or other medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, remainders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p 222. Copyright 2013. American Psychiatric Association.

Table 38.6 DSM-5 Diagnostic Criteria for Panic Disorder

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating.
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heart sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealizations (feeling or unreality) or depersonalization (being detached from oneself).
12. Fear of losing control or "going crazy."
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as one of the four required symptoms.

B. At least one of the attacks has been followed by 1 mo (or more) of one or both of the following:

1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).
D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; or in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. pp 208-209. Copyright 2013. American Psychiatric Association..

ASSESSMENT

There is no recommendation for routine screening of children and adolescents for anxiety disorders. Freely available general screening instruments such as the Pediatric Symptom Checklist and Strengths and Difficulties Questionnaire can be used to identify anxiety concerns in primary care and school settings. Rating scales can be used to support diagnosis and to follow response to treatment, but they are not diagnostic on their own. Commonly used anxiety rating scales include the Screen for Child Anxiety Related Emotional Disorders (SCARED), the Spence Children's Anxiety Scale (SCAS), the Preschool Anxiety Scale, the Generalized Anxiety Disorder-7 (GAD-7), and the Patient Reported Outcomes Measurement Information System (PROMIS) Pediatric Short Form-Anxiety-8a.

Symptoms of anxiety are typically identified through the clinical interview by asking questions about "worries," "fears," and "stress" or by the patient and family's spontaneous report. The interview must be developmentally sensitive, and further discussions with the family may reveal environmental reinforcements, including the caregiver's parenting style and enabling of avoidance behaviors.

Because some degree of anxiety is considered normal, it is important to clarify when the symptom severity reaches the point of being pathologic and to differentiate between the subtypes (Table 38.9). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) has specific criteria for each type of anxiety with requirements for frequency, duration, and extent of functional impairment.

DIFFERENTIAL DIAGNOSIS AND COMORBIDITIES

In addition to determining whether diagnostic criteria are met for a specific anxiety disorder, it is also crucial to rule out alternative explanations. The differential diagnosis includes numerous medical conditions and medication-induced anxiety (Table 38.10). Anxiety disorders also frequently occur with not just other anxiety subtypes but also other psychiatric comorbidities, notably depression and substance use disorders (Table 38.11; see Table 38.1).

TREATMENT OF ANXIETY

Cognitive-Behavioral Therapy (CBT)

Cognitive-behavioral therapy (CBT) is a therapy that targets the cognitions, behaviors, and physiologic symptoms of anxiety, with a particular focus on the interconnections between the three. Its framework typically involves homework assignments for practicing the skills in real-life environments. The goal is to achieve functional improvement within approximately 18 sessions. Because it is a skills-based treatment, CBT is thought to be a durable treatment, an important consideration when treating children and adolescents. It is specifically recommended to patients 6-18 years old with social anxiety, generalized anxiety, separation anxiety, specific phobia, and panic disorder.

Specialized training and experience are paramount to the effective delivery of this treatment modality, and it is worth taking the time to ensure that patients identify therapists with the training and experience to provide rigorous CBT. CBT typically should incorporate graduated exposure, in which stepwise mastery of a hierarchy of fearful stimuli results in desensitization.

Table 38.7 DSM-5 Diagnostic Criteria for Agoraphobia

A. Marked fear or anxiety about two (or more) of the following five situations:
   1. Using public transportation (e.g., automobiles, buses, trains, ships, planes).
   2. Being in open spaces (e.g., parking lots, marketplaces, bridges).
   3. Being in enclosed places (e.g., shops, theaters, cinemas).
   4. Standing in line or being in a crowd.
   5. Being outside of the home alone.

B. The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of a developing panic-like symptoms or other incapacitating or embarrassing symptoms (e.g., fear or falling in the elderly, fear of incontinence).

C. The agoraphobic situations almost always provoke fear or anxiety.

D. The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important area of functioning.

H. If another medical condition (e.g., inflammatory bowel disease, Parkinson disease) is present, the fear, anxiety, or avoidance is clearly excessive.

I. The fear, anxiety, or avoidance is not better explained by the symptoms or another mental disorder—for example, the symptoms are not confined to specific phobia or situational type; do not involve only social situations (as in social anxiety disorder); and are not related exclusively to obsessions (as in obsessive-compulsive disorder), reminders or traumatic events (as in posttraumatic stress disorder), or fear of separation (as in separation anxiety disorder).

Note: Agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp 217-218. Copyright 2013. American Psychiatric Association.

Table 38.8 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder

POSTTRAUMATIC STRESS DISORDER

Note: The following criteria apply to adults, adolescents, and children older than 6 yr. For children 6 yr and younger, see corresponding criteria below.

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).

Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: In children older than 6 yr, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

   2. Recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic event(s).

Note: In children, there may be frightening dreams without recognizable content.

   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the more extreme expression being a complete loss or awareness of present surroundings.)

Note: In children, trauma-specific reenactment may occur in play.

   4. Intense or prolonged psychologic distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
   5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
   1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
   2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
   1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
   2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
   3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
   4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
   5. Markedly diminished interest or participation in significant activities.

Table 38.8 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder—cont'd

6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed by verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 mo.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:
1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

POSTTRAUMATIC STRESS DISORDER FOR CHILDREN 6 YEARS AND YOUNGER

A. In children 6 yr and younger, exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers.

Note: Witnessing does not include events that are only in electronic media, television, movies, or pictures.

3. Learning that the traumatic event(s) occurred to a parent or caregiving figure.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: Spontaneous and intrusive memories may not necessarily appear distressing and may be expressed as play reenactment.

2. Recurrent distressing dreams in which the content and/or effect of the dream is related to the traumatic event(s).

Note: It may not be possible to ascertain that the frightening content is related to the traumatic event.

3. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play.
4. Intense or prolonged psychologic distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s):

PERSISTENT AVOIDANCE OF STIMULI
1. Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections or the traumatic event(s).
2. Avoidance of or efforts to avoid people, conversations, or interpersonal situations around recollections of the traumatic event(s).

NEGATIVE ALTERATIONS IN COGNITIONS
3. Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
4. Markedly diminished interest or participation in significant activities, including constriction of play.
5. Socially withdrawn behavior.
6. Persistent reduction in expression of positive emotions.

D. Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal and physical aggression toward people or objects (including extreme temper tantrums).
2. Hypervigilance.
3. Exaggerated startle response.
4. Problems with concentration.
5. Sleep disturbance (e.g., difficulty falling asleep or staying asleep or restless sleep).

E. The duration of the disturbance is more than 1 mo.

F. The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior.

G. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication or alcohol) or another medical condition.

Continued

Table 38.8 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder—cont'd

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp 271-274. Copyright 2013. American Psychiatric Association.

Table 38.9 Core Diagnostic Features and Characteristics for Anxiety Disorders

	SELECTIVE MUTISM	SEPARATION ANXIETY	SPECIFIC PHOBIA	SOCIAL ANXIETY DISORDER	AGORAPHOBIA	PANIC DISORDER	GENERALIZED ANXIETY DISORDER
Core emotions or cognitions	Consistent failure to speak in situations for which there is an expectation to speak, despite language competence	Unrealistic, persistent fear or anxiety about separation from, or loss of, attachment figure, or adverse events occurring to them	Marked, excessive, and unreasonable fear or anxiety of circumscribed objects or situations (e.g., animals, natural forces, blood injection, or places)	Marked, excessive, and unreasonable fear or anxiety of scrutiny or negative judgement by other people	Marked, excessive, and concerning fear of leaving home, entering closed or open public places, crowds, or transportation	Recurrent, unexpected panic attacks with sustained mental (e.g., fear, fear of losing control, or feeling of alienation) manifestations	Marked, uncontrollable, and anxious worry and fears about everyday events and problems
Physical symptoms	No physical symptoms	Nightmares and symptoms of distress	No physical symptoms	Blushing, fear of vomiting, urgency or fear of micturition or defecation	No physical symptoms	Multiple symptoms (e.g., palpitations, dyspnea, diaphoresis, chest pain, dizziness, paresthesia, or nausea)	Restlessness, fatigue, irritability, difficulty concentrating, muscle tension, sleep disturbance, or autonomic arousal
Behavior	Disturbance interferes with (educational) achievement or social communication	Reluctance to leave attachment figure; disturbance impairs social, school, or other functioning	Avoidance of circumscribed objects or situations; disturbance impairs social, school, work, or other functioning	Avoidance of social interactions and situations; disturbance impairs social, school, work, or other functioning	Avoidance of fear-inducing situations; disturbance impairs social, school, work, or other functioning	Changed behavior in maladaptive ways related to the attacks; disturbance impairs social, school, work or other functioning	Disturbance impairs social, school, work, or other functioning
Required symptom duration	>1 month (beyond first school month)	>1 mo (childhood; 4-18 yr); >6 months (adulthood; 18 yr or older)	>6 mo	>6 mo	>6 mo	>1 mo	>6 mo
Median age of onset	Childhood (<5 yr)	Childhood (around 6 yr)	Childhood (around 8 yr)	Early adolescence (around 13 yr)	Late adolescence (around 20 yr)	Adulthood (around 25 yr)	Adulthood (around 30 yr)

For OCD see Table 38.3; for PTSD see Table 38.8.

Characteristics and features for anxiety disorders were based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) *and International Classification of Diseases* (11th Edition).

From Penninx BWJH, Pine DS, Holmes EA, Reif A. Anxiety disorders. *Lancet.* 2021;397:914–926. Table 1, p. 915.

Table 38.10 Differential Diagnosis of Anxiety Disorders

GENERAL	PSYCHIATRIC	MEDICAL
Shyness	Substance use (including caffeine) Substance use withdrawal Body dysmorphic disorder ADHD (distractibility, restlessness) ASD (social withdrawal, social skills deficits, distractibility) MDD (distractibility, insomnia, somatic symptoms) Bipolar disorder Delusional disorder Learning disorders (worry about school performance) ODD (refusal to do activity)	Antihistamines Bronchodilators Nasal decongestants Steroids Dietary supplements Stimulants Hyperthyroidism Allergic reactions Asthma Cardiac conditions Autoimmune encephalitis Chronic pain Headaches CNS disease Diabetes Dysmenorrhea Lead intoxication Hypoglycemia Hypoxia Pheochromocytoma Mast cell disorders Carcinoid syndrome Hereditary angioedema Systemic lupus erythematosus

Table 38.11 Psychiatry and Medical Comorbidities of Anxiety

PSYCHIATRIC	MEDICAL
Depression ADHD Bipolar disorder Eating disorder Learning disorder Language disorder Substance-related disorders	Somatic symptoms Headaches GI disorders Asthma Allergies

component of treatment, and specific plans for anxiety management can be included in a child's 504 plan or individualized education plan (IEP).

The therapy with the most evidence for PTSD is a subtype of CBT called trauma-focused CBT (**TF-CBT**). Given that standard anxiety medications are less effective in PTSD, it is particularly crucial that clinicians refer these patients to trauma-focused therapy. In TF-CBT, the therapist amplifies stress management techniques in preparation for exposure-based interventions with the goal of achieving mastery over trauma triggers. In small adult trials, ketamine- or 3,4-methyl enedioxymethamphetamine (MDMA)-assisted therapy have shown benefit. There is insufficient evidence to currently recommend either therapy.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) as a class are effective in treating anxiety. The available options include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone. Despite randomized clinical trials (RCTs) providing support for the safety and effectiveness of this medication class, no specific SSRIs are U.S. Food and Drug Administration (FDA)–approved for anxiety in children. SSRIs are generally well tolerated, with the most common side effects involving xerostomia, gastrointestinal upset, headache, somnolence or insomnia, dizziness, fatigue, and changes in appetite (see Chapter 33).

RCTs in children and adolescents with PTSD found no significant difference between SSRI and placebo. SSRIs may be considered in pediatric patients with PTSD who have comorbid conditions responsive to SSRIs, including depression, affective numbing, and anxiety (see Table 33.5).

All of the SSRIs carry a "black box" warning for suicidal thinking and behavior through age 24 years, and this specific risk must be discussed with the patient and caregiver and documented before initiation. Other potential adverse effects include behavioral activation, hypomanic or manic symptoms, and serotonin syndrome (see Chapter 33).

Combination Treatment

The combination of CBT and an SSRI is generally thought to be better than either treatment alone for moderate to severe anxiety. It is important to continue recommending CBT even after the decision has been made to start pharmacologic treatment.

Serotonin-Norepinephrine Reuptake Inhibitors

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) and has an FDA indication for the treatment of generalized anxiety disorder in children ages 7-17. However, it is still considered a second-line treatment as SSRIs tend to be more effective. The other SNRI options are venlafaxine and desvenlafaxine. Potential side effects of duloxetine include xerostomia, diaphoresis, abdominal discomfort, gastrointestinal distress, headache, tremor, sedation or insomnia, decreased appetite, and weight loss. Of note, it is less likely to cause behavioral activation than the SSRIs.

α-Agonists

Clonidine and guanfacine are α-agonists and may be helpful for PTSD by targeting sleep disturbances like nightmares, persistent physiologic arousal, and exaggerated startle response.

OBSESSIVE-COMPULSIVE DISORDER AND PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

Obsessive-compulsive symptoms can be effectively treated with SSRIs (sertraline, fluoxetine). If the patient's symptoms prove to be treatment-refractory to the standard options, then one might consider fluvoxamine and/or clomipramine, which is a heterocyclic antidepressant. These are indicated when a patient has failed two or more SSRI trials. Habit reversal training is an important nonpharmacologic treatment modality for OCD as well.

A proportion of *abrupt-onset OCD* cases are attributed to an immune response that targets the brain (pediatric acute-onset neuropsychiatric syndrome [PANS]). The immune response may be brought about by

Table 38.12 Diagnostic Criteria for Pediatric Acute-Onset Neuropsychiatric Syndrome

CRITERION 1
Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake.
CRITERION 2
Concurrent presence of additional neuropsychiatric symptoms with similarly severe and acute onset from at least two of the following seven categories: 1. Anxiety. 2. Emotional lability or depression. 3. Irritability, aggression, or severely oppositional behaviors. 4. Behavioral (developmental) regression. 5. Deterioration in school performance. 6. Sensory or motor abnormalities. 7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.
CRITERION 3
Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder, autoimmune encephalitis, or others. The diagnostic workup of patients with suspected PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scans, lumbar puncture, electroencephalograms, or other diagnostic tests.

PANS, Pediatric acute-onset neuropsychiatric syndrome.
Modified from Johnson M, Fernell E, Preda I, et al. Paediatric acute-onset neuropsychiatric syndrome in children and adolescents: an observational cohort study. *Lancet Child Adolesc Health.* 2019;3(3):175–180.

infections (commonly, but not exclusively, streptococcal infections) or other mechanisms that activate the immune system.

There are no DSM-5 diagnostic criteria for PANS. One suggested approach to PANS diagnostic criteria is noted in Table 38.12. Of note is the *abrupt-sudden onset* of OCD, the presence of additional psychiatric disorders (e.g., anxiety, depression, emotional lability), and the requirement to rule out other disorders like Sydenham chorea.

If PANS is suspected, a comprehensive evaluation is warranted primarily to rule out neurologic and medical conditions (see Table 38.12). Children with an abrupt onset of psychiatric *and* neurologic findings should be evaluated with MRI, electroencephalogram (EEG), and blood plus cerebrospinal fluid (CSF) autoimmune encephalitis antibody testing. Children with a sudden onset of only psychiatric symptoms (OCD, tics, anxiety) do not require extensive testing except for testing for a group A streptococcus, unless they have severe and disabling psychiatric features, The latter group should be evaluated to rule out the disorders noted in Table 38.12. Once diagnosed, clinicians should prioritize the target symptoms of the individual patient and select treatments accordingly. The three realms of PANS treatment are psychotherapeutic, antimicrobial, and immunomodulatory. Because behavioral interventions take time to work, psychiatric interventions should begin expeditiously for symptomatic relief. Antibiotics may eliminate the underlying source of neuroinflammation, and immunomodulatory options can help treat immune system disturbances.

SPECIFIC PHOBIAS

Specific phobias may not typically require treatment with an SSRI and may be better targeted with *exposure response prevention* therapies and with *premedicating* with a β blocker before an anticipated exposure. The exception to this is needle phobia; premedication with a β blocker is not indicated in this instance because of the risk of exacerbating the vasovagal response. Physical maneuvers, such as crossing the legs and tensing the muscles, may be effective in needle phobia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 39

Mood Disorders

Colleen K. Manak and Rosa K. Kim

Mood disorders encompass several different entities on the spectrum between depression and mania. Mood disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in emotional self-regulation. Classically, the mood disorders have been divided into depressive and bipolar disorders, representing the two emotional polarities, *dysphoric* ("low") and *euphoric* ("high") mood. Mood disorders in children and adolescents are highly prevalent and are the most common psychiatric illnesses seen after attention-deficit/hyperactivity disorder (ADHD) and anxiety. Primary care is often their first point of contact when seeking treatment.

39.1 Depressive Disorders

Colleen K. Manak and Rosa K. Kim

Depressive disorders include major depressive, persistent depressive, disruptive mood dysregulation, other specified/unspecified depressive, premenstrual dysphoric, and substance/medication-induced disorders, as well as depressive disorder caused by another medical condition (Fig. 39.1).

DESCRIPTION

Major depressive disorder (MDD) is characterized by a distinct period of at least 2 weeks (an *episode*) in which there is a depressed or irritable mood and/or loss of interest or pleasure in almost all activities that is present for most of the day, nearly every day (Table 39.1 and Fig. 39.2). Major depression is associated with characteristic vegetative and cognitive symptoms, including disturbances in appetite, sleep, energy, and activity level; impaired concentration; thoughts of worthlessness or guilt; and suicidal thoughts or actions. Major depression is considered *mild* if few or no symptoms in excess of those required to make the diagnosis are present, and the symptoms are mildly distressing, manageable, and result in minor functional impairment. Major depression is considered *severe* if symptoms substantially in excess of those required to make the diagnosis are present, and the symptoms are highly distressing, unmanageable, and markedly impair function. *Moderate* major depression is intermediate in severity (Fig. 39.3).

Persistent depressive disorder is characterized by depressed or irritable mood for more days than not, for at least 1 year (in children and adolescents). This chronic form of depression is associated with characteristic vegetative and cognitive symptoms; however, the cognitive symptoms of persistent depression are less severe (e.g., low self-esteem rather than worthlessness, hopelessness rather than suicidality). Persistent depressive disorder is characterized as mild, moderate, or severe (Table 39.2).

Overall, the clinical presentation of major and persistent depressive disorders in children and adolescents is similar to that in adults. The prominence of the symptoms can change with age: irritability and somatic complaints may be more common in children, and energy, activity level, appetite, and sleep disturbances may be more common in adolescents. Because of the cognitive and linguistic immaturity of young children, symptoms of depression in that age group may be more likely to be observed than self-reported.

The core feature of **disruptive mood dysregulation disorder (DMDD)** is severe, persistent irritability evident most of the day, nearly every day, for at least 12 months in multiple settings (at home, at school, with peers). The irritable mood is interspersed

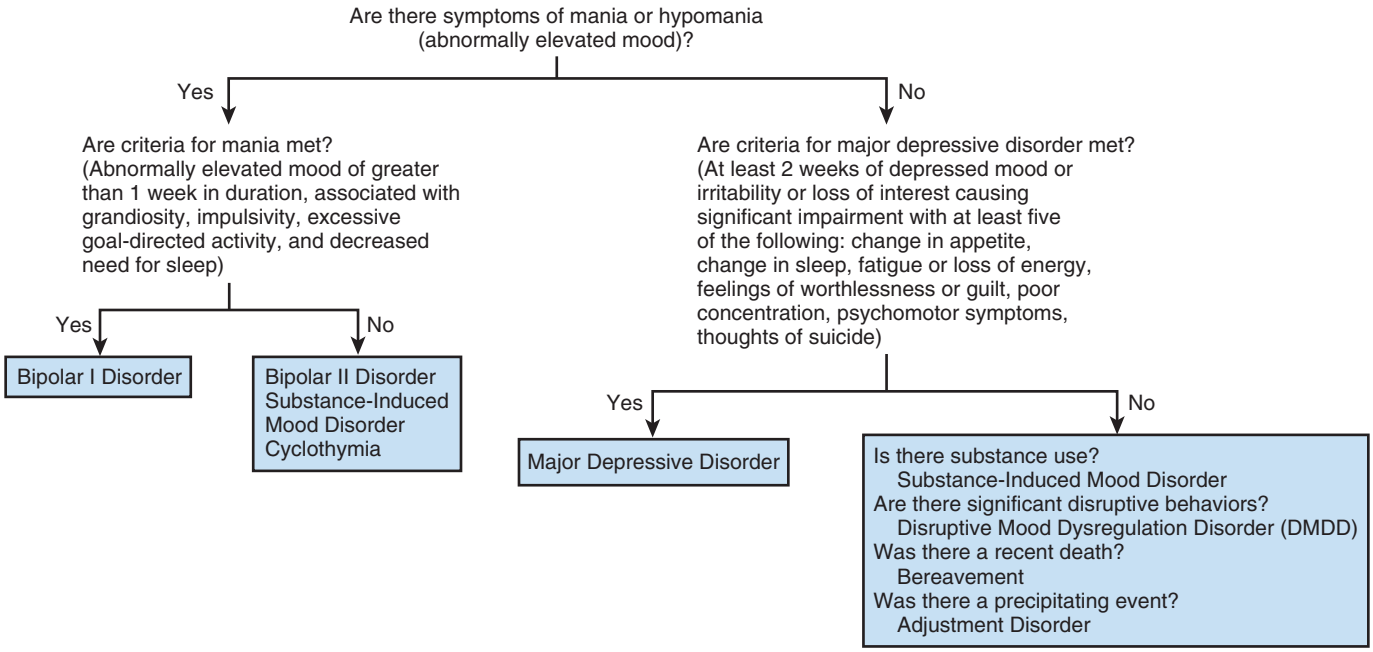

Fig. 39.1 Evaluation of mood disorders. *(From Kliegman RM, Lye, PS, Bordini BJ, et al., eds. Nelson Pediatric Symptom-Based Diagnosis. Elsevier, 2018; Fig, 27.2, p. 426.)*

Table 39.1 DSM-5 Diagnostic Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   1. Depressed most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).

Note: In children and adolescents, can be irritable mood.

   1. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   2. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

Note: In children, consider failure to make expected weight gain.

   1. Insomnia or hypersomnia nearly every day.
   2. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   3. Fatigue or loss of energy nearly every day.
   4. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   5. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   6. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiologic effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. pp. 125–126. Copyright 2013. American Psychiatric Association.

with frequent (≥3 times/week) and severe temper outbursts (verbal rages, physical aggression; Table 39.3). This diagnosis is intended to characterize more accurately the extreme irritability, which some investigators had considered a *developmental* presentation of bipolar disorder, and to distinguish extreme irritability from the milder presentations characteristic of oppositional defiant disorder (ODD) and intermittent explosive disorder. Table 39.4 highlights some of the similarities and differences between the various mood disorders and also factors that distinguish mood disorders from grief experienced in response to loss.

Other specified/unspecified depressive disorder (subsyndromal depressive disorder) applies to presentations in which symptoms characteristic of a depressive disorder are present and cause clinically significant distress or functional impairment but do not meet the full criteria for any of the disorders in this diagnostic class.

EPIDEMIOLOGY

The current prevalence of depressive disorder in the United States among 3-17 year olds is approximately 3.2%; the lifetime prevalence rates increase to 4.9% for ages 6-17 and to 12.8% for 12-17 year olds. The male:female ratio (excluding DMDD) is approximately 1:1 during childhood and beginning in early adolescence rises to 1:1.5-3.0 by adulthood.

Based on rates of chronic and severe persistent irritability, which is the core feature of DMDD, the overall 6 month to 1 year prevalence has been estimated in the 2–5% range. In three community samples, the 3-month prevalence rate of DMDD ranged from 0.8–3.3%, with the highest rates occurring in preschoolers (although *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [DSM-5] does not permit this diagnosis until age 6 years). Approximately 5–10% of children and adolescents are estimated to have subsyndromal (unspecified) depression.

ETIOLOGY AND RISK FACTORS

Models of vulnerability to depressive disorders are grounded in genetic and environmental pathways. Genetic studies have demonstrated the heritability of depressive disorders, with monozygotic twin studies finding concordance rates of 40–65%. In families, both bottom-up (children to parents) and top-down (parents to children) studies have shown a two- to four–fold bidirectional increase in depression among first-degree relatives. Cerebral variations in structure and function (particularly serotonergic), the function of the hypothalamic-pituitary-adrenal axis, difficult temperament/personality (i.e., negative affectivity), and ruminative, self-devaluating cognitive style have been implicated as components of biologic vulnerability. The great majority of depressive disorders arise in youth with long-standing psychosocial difficulties, among the most predictive of which are physical/sexual abuse, neglect, chronic illness, school difficulties (bullying, academic failure), social isolation, family or marital disharmony, divorce/separation, parental psychopathology, and domestic violence. Longitudinal studies demonstrate the greater importance of environmental influences in children who become depressed than in adults who become depressed. Factors shown to be protective against the development of depression include better family function, a prosocial peer group, higher IQ, greater educational aspirations, a positive relationship with a caregiver, and closer caregiver supervision, monitoring, and involvement.

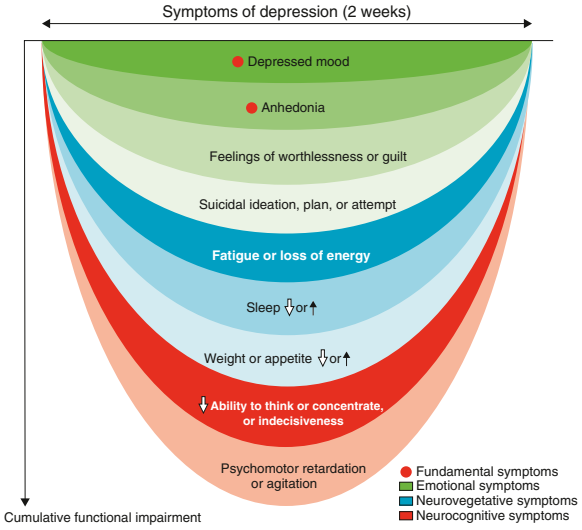

Fig. 39.2 Defining major depressive disorder. Key symptoms of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM)-5 for major depressive disorder. For a diagnosis of major depressive disorder, the individual needs to present with five or more of any of the symptoms nearly every day during the same 2-week period, provided at least one of these symptoms is a fundamental one. The clinical symptoms of major depressive disorder are usually accompanied by functional impairment. The greater the number and severity of symptoms (as opposed to particular symptoms), the greater the probability of the functional impairment they are likely to confer. The symptoms of depression can be grouped into emotional, neurovegetative, and neurocognitive domains. Importantly sleep, weight, and appetite are usually diminished in depression but can also be increased, and suicidal ideation, plans, or an attempt should be documented whenever depression is suspected. *(From Malhi GS, Mann JJ. Depression. Lancet. 2018;392[10161]:2299–2312:Fig. 1, p. 2300.)*

SCREENING AND DIAGNOSIS

Screening

Adolescents presenting in the primary care setting should be queried, along with their caregiver(s), about depressed mood as part of the routine clinical interview. A typical screening question would be, "Everyone feels sad or angry some of the time; how about you (or your teen)?" The caregivers of younger children can be queried about overt signs of depression, such as tearfulness, irritability, boredom, or social isolation. A number of standardized screening instruments widely used in the primary care setting (e.g., *Pediatric Symptom Checklist*, *Strengths and Difficulties Questionnaire*, *Vanderbilt ADHD Diagnostic Rating Scales*) have items specific to sad mood and as such can be used to focus the interview. Additionally, screening tools specific to depression, such as the *Patient Health Questionnaire-9* (*PHQ-9*) and *Beck Depression Inventory*, can be utilized as part of routine screening (Table 39.5).

The role of universal depression screening using standardized depression-specific instruments is unclear. A Cochrane review found that the use of depression screening in primary care has little or no impact on the recognition, management, or outcome of depression. Nonetheless, the U.S. Preventive Services Task Force (USPSTF) recommends the universal use of depression screening instruments, but only among adolescents and only when systems are in place to ensure adequate follow-up. Targeted screening of known high-risk groups (e.g., youth who are homeless, refugees, attracted to the same sex, involved with child welfare or juvenile justice), or youth experiencing known psychosocial adversities or self-reporting a dysphoric mood, may be a higher-yield case-finding strategy than universal screening.

Assessment

Youth (and/or their caregivers) presenting in the primary care setting who self-report, or respond affirmatively to queries about a distressing life experience or a depressed or irritable mood should be offered the opportunity to talk about the situation with the pediatric practitioner (separately with the older youth). By engaging in active listening (e.g.,

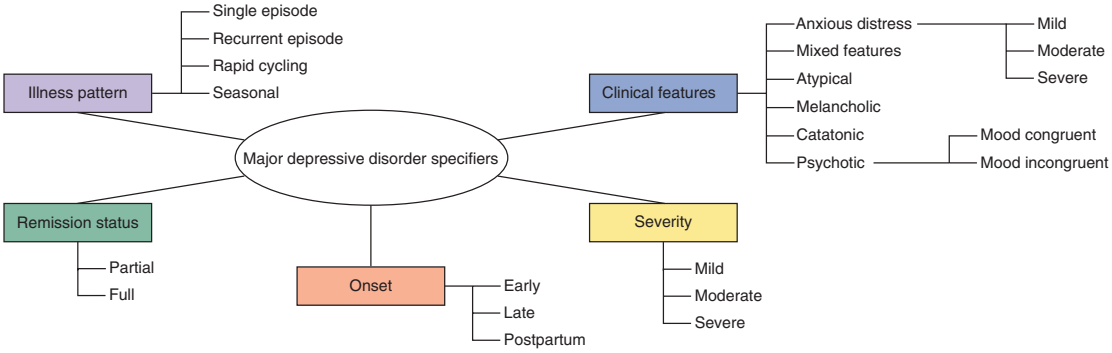

Fig. 39.3 Major depressive disorder specifiers. Episodes of major depression can be described in greater depth by specifiers (outlined in *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [DSM-5]) that provide additional information regarding the pattern of the illness and its clinical features. Specifiers can also indicate the severity of the episode, when it first emerged (onset), and whether it has remitted (status). For example, in clinical practice, a typical episode of depression can be described as suffering from a recurrence of depression that is moderately severe with melancholic features and has partly remitted in response to initial treatment. *(From Malhi GS, Mann JJ. Depression. Lancet. 2018;392[10161]:2299–2312:Fig. 2, p. 2301.)*

Table 39.2 DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 yr.

Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr.

B. Presence, while depressed, of two (or more) of the following:
   1. Poor appetite or overeating.
   2. Insomnia or hypersomnia.
   3. Low energy or fatigue.
   4. Low self-esteem.
   5. Poor concentration or difficulty making decisions.
   6. Feelings of hopelessness.

C. During the 2 yr period (1 yr for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 mo at a time.

D. Criteria for a major depressive disorder may be continuously present for 2 yr.

E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include four symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 yr but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp. 168–169. Copyright 2013. American Psychiatric Association.

Table 39.3 DSM-5 Diagnostic Criteria for Disruptive Mood Dysregulation Disorder

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.

B. The temper outbursts are inconsistent with developmental level.

C. The temper outbursts occur, on average, three or more times per week.

D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).

E. Criteria A-D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A-D.

F. Criteria A and D are present in at least two of three settings (i.e., at home, at school, with peers) and are severe in at least one of these.

G. The diagnosis should not be made for the first time before age 6 yr or after age 18 yr.

H. By history or observation, the age at onset of Criteria A-E is before 10 yr.

I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.

J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).

Note: The diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.

K. The symptoms are not attributable to the physiologic effects of a substance or to another medical or neurologic condition.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p. 156. Copyright 2013. American Psychiatric Association.

"I hear how upset you have been feeling; tell me more about what happened to make you feel that way"), the clinician can begin to assess the onset, duration, context, and severity of the symptoms and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., suicidality, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 weeks to conduct a depression assessment. At this follow-up visit, to assist with decision-making about appropriate level of care, a depression-specific screening or standardized rating scale can be administered to assess symptom severity (see Table 39.5), and additional risk factors can be explored.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric disorders, general medical conditions, and medications can generate symptoms of depression or irritability and must be distinguished from the depressive disorders. The psychiatric disorders include autism spectrum disorder (ASD), ADHD, and bipolar, anxiety, trauma- and stressor-related, disruptive/impulse control/conduct, and substance-related disorders. Medical conditions include neurologic disorders (including autoimmune encephalitis), endocrine disorders (including hypothyroidism and Addison disease), infectious diseases, tumors, anemia, uremia, failure to thrive, chronic fatigue disorder, and pain disorder. Medications include narcotics, chemotherapy agents, β blockers, corticosteroids, and contraceptives. The diagnosis of a depressive disorder should be made after these and other potential explanations for the observed symptoms have been ruled out.

COMORBIDITY

Major and persistent depressive disorders often co-occur with other psychiatric disorders. Depending on the setting and source of referral, 40–90% of youths with a depressive disorder have other psychiatric disorders, and up to 50% have two or more comorbid diagnoses. The most common comorbid diagnosis is an **anxiety disorder** and as such may reflect a common diathesis; other common comorbidities include ADHD and disruptive behavior, eating, and substance use disorders. The development of depressive disorders can both lead to and follow the development of comorbid disorders.

DMDD may occur with other psychiatric disorders, including other depressive disorders, ADHD, conduct disorder, and substance use disorders. Because the symptoms of DMDD overlap in part with symptoms of bipolar disorder, ODD, and intermittent explosive disorder, by DSM-5 convention, hierarchical diagnostic rules apply. Thus bipolar disorder takes precedence over DMDD if a manic/hypomanic episode

Table 39.4 A Comparison of Features of Depression, Persistent Depressive Disorder, Disruptive Mood Dysregulation Disorder, and Grief in Children with Developmental Considerations

	MAJOR DEPRESSIVE DISORDER	PERSISTENT DEPRESSIVE DISORDER	DISRUPTIVE MOOD DYSREGULATION DISORDER	GRIEF
Core feature(s)	Sadness, irritability, anhedonia	Sadness, irritability, anhedonia	Irritability and anger with behavioral outbursts (verbal, physical)	Sadness in response to the loss/death of a loved one
Duration	2 weeks with symptoms nearly every day	1 year with symptoms more days than not	1 year with outbursts at least three times/week	Ongoing, can continue/ recur indefinitely (e.g., around anniversaries, birthdays, holidays)
Associated symptoms	Changes in appetite, sleep, energy and activity level; impaired concentration; hopelessness, worthlessness and guilt; suicidal ideations/ actions	Changes in appetite, sleep, energy and activity level; impaired concentration; hopelessness, worthlessness and guilt; suicidal ideations/actions	Persistent irritability between episodes	Anger; guilt; regret; anxiety; intrusive images; overwhelmed; lonely
Age considerations	Younger children may be irritable and complain of somatic symptoms		Cannot be diagnosed before age 6 or after age 18	Developmental level and understanding of death can influence grief symptoms

Table 39.5 Depression-Specific Rating Scales

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE (YR)	ITEMS (NO.)
Beck Depression Inventory	Youth	13+	21
Beck Depression Inventory for Youth	Youth	7-14	20
Center for Epidemiologic Studies-Depression-Children	Youth	6-18	20
Children's Depression Rating Scale-Revised	Youth, Parent, Clinician	6-18	47
Children's Depression Inventory, Second Edition	Youth, Parent, Teacher	7-17	28/17/12
Depression Self-Rating Scale	Youth	7-13	18
Mood and Feelings Questionnaire	Youth, Parent	7-18	33-34
Patient Health Questionnaire-9	Youth	12/13+	9
Preschool Feelings Checklist	Parent	3-5.6	20
PROMIS Emotional Distress-Depressive Symptoms	Youth, Parent	8-17 (youth report) or 5-17 (parent report)	8/6
Reynolds Child Depression Scale	Youth	8-13	30
Reynolds Adolescent Depression Scale, Second Edition	Youth	11-20	30

has ever occurred, and DMDD takes precedence over ODD and intermittent explosive disorder if full criteria for DMDD are met.

TREATMENT

Treatment decisions should be guided by the understanding that depression in youth is highly responsive to placebo (50–60%) or brief nonspecific intervention (15–30%). The goal of treatment is **remission,** defined as a period of at least 2 weeks with no or very few depressive symptoms, and ultimately **recovery,** defined as a period of at least 2 months with no or very few depressive symptoms. Assessment of remission and recovery can be aided using the depression-specific standardized rating scales, in which remission is defined as scores below the scale-specific clinical cut point.

For *mild symptoms* (manageable and not functionally impairing) and in the absence of major risk factors (e.g., suicidality; psychosis; substance use; history of depression, mania, or traumatic exposures; parental psychopathology, particularly depression; severe family dysfunction), **guided self-help** (anticipatory guidance) with watchful waiting and scheduled follow-up may suffice. Guided self-help can include provision of educational materials (e.g., pamphlets, books, workbooks, apps, internet sites) that provide information to the youth about coping adaptively with stressful situations, as well as advice to caregivers about strengthening the caregiver–child relationship and modifying triggering exposures (e.g., taking action against bullying, increasing opportunities for social interaction and support, protecting child from exposure to marital discord). Additional self-help activities that have shown promise in improving mild depressive symptoms include behavioral activation (e.g., physical exercise, social engagement, participation in a hobby), mindfulness (e.g., yoga, meditation), and a regular sleep schedule.

For youths who *continue* to have mild depression after a few weeks of guided self-help, supportive therapy by a mental health professional may be an appropriate subsequent step. For youths who have not responded to approximately 4–8 weeks of supportive psychotherapy, or who from the outset exhibit moderate to severe, comorbid, or recurrent depression or suicidality, or who have a history of mania, traumatic exposures, or severe family dysfunction or psychopathology,

assessment and treatment by a child-trained mental health clinician should be obtained.

For *moderate* to *severe depression*, specific manualized psychotherapies, antidepressant medication, or a combination of both should be considered. There is insufficient evidence on which to base definitive conclusions about the relative effectiveness of these treatments.

Psychotherapies

Clinical trials of acute treatments have generated support for the efficacy of cognitive-behavioral therapy (CBT)/behavioral activation therapy and interpersonal therapy as monotherapies in depressed youth, but overall effect sizes are modest. CBT focuses on identifying and correcting cognitive distortions that may lead to depressed mood and teaches problem-solving, behavior activation, social communication, and emotional regulation skills to combat depression. Interpersonal therapy focuses on enhancing interpersonal problem solving and social communication to decrease interpersonal conflicts. Each of these therapies typically involves 8-12 weekly visits. Limited evidence suggests that family therapy may be more effective than no treatment in decreasing depression and improving family functioning. Manualized CBT treatment as well as alternative therapy modalities such as play therapy are also available for younger children.

Pharmacologic Treatment

Two selective serotonin reuptake inhibitors (SSRIs), fluoxetine and escitalopram, are the only antidepressants approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression in youth; fluoxetine alone is approved for preadolescents. Other SSRIs, with the exception of paroxetine, which has been shown to be ineffective in children, are frequently used off-label and may be considered for use in depressed children and teens despite the lack of FDA approval.

There are several considerations to keep in mind when starting an SSRI, including family history of response to SSRIs, comorbid medical conditions, and other concurrent medications. Fluoxetine should be given in the morning, given its propensity to be activating for some patients; escitalopram is preferentially dosed in the evening as it can be sedating. Sertraline has the advantage of a very wide dosing range, which can be helpful when small dosing changes are preferred.

All SSRIs carry a "black box" warning for increased suicidal thinking in patients under age 25 that must be discussed with all patients and caregivers before starting an SSRI. The risk for this side effect is highest when initiating treatment and when making dose adjustments. All SSRIs can cause *akathisia*, an uncomfortable feeling of internal restlessness; this side effect is more common in children than it is in adults. Gastrointestinal upset and headaches are among the most common side effects; they typically self-resolve after a few weeks. However, they may recur when dose increases are made. Education around the expected course and resolution of these side effects can be helpful when providing informed consent and may lead to improved adherence in the early phase of treatment. Sexual side effects of SSRIs, including decreased libido and difficulty reaching orgasm, are also important considerations and should be addressed with patients before treatment initiation.

If the first trial of an SSRI is unsuccessful, a trial of a second SSRI should be considered. An adequate trial of an SSRI requires that a sufficient dose be achieved and that it be continued for a reasonable amount of time. Given the length of time it takes for SSRIs to take full effect, an adequate trial would be at least 6-8 weeks at a target dose. Trials may end early if patients experience intolerable side effects. For patients who do not respond to two adequate trials of an SSRI, it is appropriate to consider referral to a psychiatrist for further management.

Clinical severity, comorbidity, family conflict, low drug concentration, nonadherence, anhedonia, sleep difficulties, subsyndromal manic symptoms, and child maltreatment have all been related to treatment resistance. Approximately 50% of depressed youth failing to respond to the first SSRI respond after switching to a second antidepressant plus CBT, vs approximately 40% who respond to a second medication alone. For youth with psychotic depression, augmenting the antidepressant with an atypical antipsychotic medication should be considered, while monitoring closely for side effects.

Because of the high rate of recurrence, successful treatment should continue for 6-12 months. The findings from one trial suggested that the addition of relapse-prevention CBT to ongoing medication management reduces the risk of relapse more than medication management alone, even after the end of treatment. When treatment concludes, all antidepressants (except possibly fluoxetine because of its long half-life) should be discontinued gradually to avoid withdrawal symptoms (gastrointestinal upset, disequilibrium, sleep disruption, flulike symptoms, sensory disturbances). Patients with recurrent (two or more episodes), chronic, or severe major depression may require treatment beyond 12 months.

Ketamine or esketamine, glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonists have demonstrated efficacy in treating treatment resistant depression in adults.

There are no rigorous studies evaluating the effectiveness of pharmacologic or psychosocial treatment approaches to persistent depressive disorder or DMDD. The aforementioned treatments for MDD may prove helpful in persistent depressive disorder. In suspected cases of DMDD, child and adolescent psychiatry consultation may be helpful to clarify diagnosis and suggest treatment approaches.

LEVEL OF CARE

Most children and adolescents with mild to moderate depressive disorders can be safely and effectively treated as outpatients, provided that a clinically appropriate schedule of visits can be maintained through the phases of treatment. Inpatient treatment should be considered for youth who present with a substantial risk of suicide, serious self-harm, or self-neglect, or when the family is not able to provide an appropriate level of supervision or follow-up with outpatient treatment recommendations, or when comprehensive assessment for diagnostic clarity is needed. When considering inpatient admission for a young person with depression, the benefits of inpatient treatment need to be balanced against potential detrimental effects, such as separation from family and community support.

CLINICAL COURSE

Major depression may first appear at any age, but the likelihood of onset greatly increases with puberty. Incidence appears to peak in the 20s. The median duration of a major depressive episode is about 5-8 months for clinically referred youth and 3-6 months for community samples. The course is quite variable in that some individuals rarely or never experience remission, whereas others experience many years with few or no symptoms between episodes. Persistent depressive disorder often has an early and insidious onset and, by definition, a chronic course (average untreated duration in both clinical and community samples: 3.5 years).

Depressed children appear to be more likely to develop nondepressive psychiatric disorders in adulthood than depressive disorders. However, depression in adolescents has a probability of recurrence reaching 50–70% after 5 years. The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence; other negative prognostic factors include more severe symptoms, longer time to remission, history of maltreatment, and comorbid psychiatric disorders. Up to 20% of depressed adolescents develop a bipolar disorder; the risk is higher among adolescents who have a high genetic risk for bipolar disorder, who have psychotic depression, or who have had pharmacologically induced mania.

SEQUELAE

Approximately 60% of youths with MDD report thinking about suicide; 30% attempt suicide. Youths with depressive disorders are also at high risk of substance abuse, impaired family and peer relationships, early pregnancy, legal problems, educational and occupational underachievement, and poor adjustment to life stressors, including physical illness.

Children with DMDD have displayed elevated rates of social impairments, school suspension, and service use. Irritability in adolescence has predicted the development of major depressive and dysthymic disorders and generalized anxiety disorder (but not bipolar disorder) 20 years later, as well as lower educational attainment and income.

PREVENTION

Experimental trials have sought to demonstrate the effectiveness of psychologic or educational strategies in preventing the onset of depressive disorders in children and adolescents. These programs generally have provided information about the link between depressed mood, thoughts, and behaviors, as well as training in skills intended to modify these thoughts and behaviors. A Cochrane review found small effects of these programs on depression symptoms when implemented universally vs no intervention, with selective programs targeted at high-risk groups performing better than universal programs; however, the effect of prevention programs was null compared with attention controls.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

39.2 Bipolar Disorders

Colleen K. Manak and Rosa K. Kim

The bipolar and related disorders include bipolar I, bipolar II, cyclothymic, and other specified/unspecified bipolar and related disorders, as well as bipolar and related disorder caused by another medical condition.

A **manic episode** is characterized by a distinct period of at least 1 week in which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy that is present for most of the day, nearly every day (or any duration if hospitalization is necessary). The episode is associated with characteristic cognitive and behavioral symptoms, including disturbances in self-regard, speech, attention, thought, activity, impulsivity, and sleep (Table 39.6). To diagnose **bipolar I disorder**, criteria must be met for at least one manic episode, and the episode must not be better explained by a psychotic disorder. The manic episode may be preceded and may be followed by hypomanic or major depressive episodes. Bipolar I disorder is rated as mild, moderate, or severe in the same way as the depressive disorders.

To diagnose **bipolar II disorder**, criteria must be met for at least one hypomanic episode and at least one major depressive episode. A **hypomanic episode** is similar to a manic episode but is briefer (at least 4 days) and less severe (causes less impairment in functioning, is not associated with psychosis, and would not require hospitalization) (Table 39.7). In bipolar II disorder, there must never have been a manic disorder, the episodes must not be better explained by a psychotic disorder, and the symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania must cause clinically significant distress or functional impairment. Bipolar II disorder is also rated as mild, moderate, or severe.

Cyclothymic disorder is characterized by a period of at least 1 year (in children and adolescents) in which there are numerous periods with hypomanic and depressive symptoms that do not meet criteria for a hypomanic episode or a major depressive episode, respectively (Table 39.8).

EPIDEMIOLOGY

The lifetime prevalence of bipolar disorder I among adults in the United States varies from 0.8–1.6%, and bipolar II carries a lifetime prevalence of around 1.1%. Bipolar I disorder affects males and females equally, whereas bipolar II disorder is more common in females. Lifetime rates of mania among youth have ranged from 0.1–1.7%. The estimated annual number of U.S. office-based visits of youth with a diagnosis of bipolar disorder increased from 25 per 100,000 population in 1994-1995 to 1,003/100,000 in 2002-2003. U.S. hospital discharge diagnoses increased from 1.4 to 7.3/10,000 in 9-13-year-old children and from 5.1 to 20.4 per 10,000 in 14-19 year olds. These increases were not found in U.K. diagnoses or hospital discharges, raising questions about whether bipolar disorder was being over-diagnosed in the United States, with resultant increases in prescribing of antipsychotic and mood-stabilizing medications.

Table 39.6 DSM-5 Diagnostic Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non–goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p. 124. Copyright 2013. American Psychiatric Association.

ETIOLOGY AND RISK FACTORS

Twin studies suggest the heritability of bipolar disorder may be 60–90%; shared and unique environmental factors may account for 30–40% and 10–20%, respectively. Offspring of parents with bipolar disorders are at high risk for early-onset bipolar disorders as well as anxiety and behavioral disorders and mood dysregulation. There is an average 10-fold increased risk among adult relatives of individuals with bipolar disorder, with the magnitude of risk increasing with the degree of kinship. Bipolar disorder and schizophrenia likely share a common genetic origin, reflected in familial co-aggregation of the two disorders.

Studies to date suggest key roles for the amygdala, anterior paralimbic cortices, and their connections in the emotional dysregulation of bipolar disorder. Some of these abnormalities are apparent by adolescence, whereas others appear to progress over adolescence into young adulthood.

Dysthymic (sad), *cyclothymic* (labile), or *hyperthymic* (irritable) temperaments may presage eventual bipolar disorder. Premorbid anxiety and dysphoria also are common. Environmental factors such as irritable and negative parenting styles, physical and sexual abuse, poor social support, and prenatal alcohol exposure may interact with genetic vulnerability to produce early onset of bipolar illness as well as negative prognostic indicators. *Affective lability,* in particular, has been associated with high levels of childhood trauma, and gradual sensitization to stressors has been linked to episode recurrence.

SCREENING

Cardinal manic symptoms of elation, increased energy, and grandiosity occurring in adolescents as a discrete episode representing an unequivocal and uncharacteristic change in functioning should alert pediatric practitioners to the possibility of bipolar disorder. High scores on parent-completed versions of mania-specific rating scales (e.g., *General Behavior Inventory, Child Mania Rating Scale, Young Mania Rating Scale*) have been associated with increased likelihood of a bipolar diagnosis. However, screening tools for bipolar disorder have suboptimal psychometric properties when applied to young people. Because of the complexity of diagnosing and treating bipolar disorders, any suspected cases should be referred to the specialty mental health setting for comprehensive assessment and treatment.

Table 39.7 DSM-5 Diagnostic Criteria for a Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least four consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non–goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The disturbance is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A-F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p. 124. Copyright 2013. American Psychiatric Association.

PRESENTATION

In adolescents, the clinical manifestations of mania are similar to those in adults; psychosis (delusions, hallucinations) often is an associated symptom (see Chapter 47). Mood in a manic episode is often described as euphoric, excessively cheerful, high, or "feeling on top of the world." During the episode, the adolescent may engage in multiple new projects that are initiated with little knowledge of the topic and often at unusual hours (middle of the night). Inflated self-esteem is usually present, ranging from uncritical self-confidence to marked grandiosity, and may reach delusional proportions. The adolescent may sleep little, if at all, for days and still feel rested and full of energy. Speech can be rapid, pressured, and loud and characterized by jokes, puns, amusing irrelevancies, and theatricality. Frequently there is a "flight of ideas," evidenced by an almost continuous flow of accelerated speech, with abrupt shifts from one topic to another. Distractibility is evidenced by an inability to censor irrelevant extraneous stimuli, which often prevents an individual with mania from engaging in a rational conversation. The expansive mood, grandiosity, and poor judgment often lead to reckless involvement in activities with high potential for personal harm.

Controversy surrounds the applicability of the diagnostic criteria for mania to prepubertal children. It may be developmentally normal for children to be elated, expansive, grandiose, or talkative, reducing the specificity of these symptoms to this disorder. In addition, the distractibility, overactivity, impulsivity, and irritability formerly ascribed to bipolar disorder by some investigators may be better explained by a diagnosis of ADHD, with or without comorbid ODD. The presentation of severe and pervasive irritability formerly diagnosed as "bipolar disorder" may be better captured by the diagnosis of DMDD.

DIFFERENTIAL DIAGNOSIS

Numerous psychiatric disorders, general medical conditions, and medications can generate manic-like symptoms and must be distinguished from the bipolar and related disorders. The psychiatric disorders include ADHD, ODD, and intermittent explosive, posttraumatic stress, depressive, anxiety, substance abuse, and borderline personality disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, and vitamin deficiencies. Medications include androgens, bronchodilators, cardiovascular medications, corticosteroids, chemotherapy agents, thyroid preparations, and certain psychiatric medications (benzodiazepines, antidepressants, stimulants). The diagnosis of a bipolar disorder should be made after these other explanations for the observed symptoms have been ruled out. Substance-induced mood disorder should also be considered and ruled out in patients presenting with mania.

Table 39.8 A Comparison of Bipolar I and II and Cyclothymia in Children and Adolescents

	BIPOLAR I	BIPOLAR II	CYCLOTHYMIA
Core feature(s)	One manic episode	One hypomanic episode AND one major depressive episode	Symptoms of hypomania and depression, without meeting full criteria for a manic, hypomanic or depressive episode
Duration	Mania: 7 days	Hypomania: 4 days Depressive episode: 14 days	1 year
Associated symptoms	Depressive episodes, hypomanic episodes, psychosis		Chronic disruption in mood patterns

For bipolar II disorder, the main differential is unipolar depression (MDD) or cyclothymic disorder, which are ruled out by the lack of a hypomanic episode and by not meeting full criteria for either a major depressive or hypomanic episode, respectively.

COMORBIDITY

The most common simultaneous comorbidities (ADHD, ODD, conduct disorder, anxiety) may be difficult to distinguish from mania because of considerable symptom overlap. Substance use also is a common comorbidity in adolescents, and presentations that appear to be manic may remit when the substances of abuse are discontinued.

TREATMENT

Pharmacologic Treatment

Medication is the primary treatment for mania (Table 39.9). Studies have demonstrated the superiority of antipsychotics over mood stabilizers in the treatment of mania. Risperidone and olanzapine are the most efficacious agents; quetiapine, risperidone, and olanzapine ranked as the most tolerable agents. The choice of antipsychotic medication is based on factors such as side effect profiles, comorbidities, adherence, and positive response of a family member.

Among traditional mood stabilizers, only lithium is FDA approved for the treatment of bipolar disorder from age 12 years; its efficacy and tolerability compared to placebo has been demonstrated in randomized controlled trials (RCTs). There also is evidence that lithium reduces the risk of suicide and total deaths in patients with both unipolar and bipolar depressive disorder.

Given the co-occurrence of sleep disturbance with bipolar disorders, the use of medications to help regulate sleep can have a significant benefit on mood and functioning. Medications to promote sleep, including benzodiazepines, benzodiazepine receptor agonists, and melatonin receptor agonists have some evidence for the treatment of sleep in bipolar disorder in adults. When treating children and adolescents, it is important to monitor for paradoxical activation/disinhibition when using benzodiazepines.

Medication trials should be systematic and their duration sufficient (generally 6-8 weeks) to determine effectiveness. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Because these medications are associated with significant side effects, careful monitoring of baseline and follow-up indices is imperative (see Chapter 33).

The regimen needed to stabilize acute mania should be maintained for 12-24 months. Maintenance therapy is often needed for adolescents with bipolar I disorder, and some patients need lifelong medication. Any attempts to discontinue prophylactic medication should be done gradually while closely monitoring the patient for relapse.

Antidepressants *alone* should not be prescribed for depressive symptoms in confirmed cases of bipolar I disorder because of the risk of manic switch. For treatment of depression in bipolar II, antidepressant medication may be used cautiously. Comorbid ADHD can be treated with a stimulant once a mood stabilizer has been initiated.

Table 39.9 U.S. Food and Drug Administration–Approved Treatments for Bipolar Disorder in Youth

MEDICATION	INDICATION (APPROVED AGES)
Aripiprazole	Mania (10-17 yr)
Asenapine	Mania/mixed episode (10-17 yr)
Lithium	Acute mania/bipolar maintenance (7-17 yr)
Lurasidone	Bipolar depression (10-17 yr)
Olanzapine	Mania/mixed episode (13-17 yr)
Quetiapine	Mania (10-17 yr)
Risperidone	Mania/mixed episode (10-17 yr)

Psychotherapies

Psychotherapy is a potentially important adjunctive treatment for bipolar disorders. Therapies with some evidence of efficacy, primarily as adjunctive to pharmacotherapy, include multifamily psychoeducational psychotherapy and family-focused treatment, child and family–focused CBT, dialectical behavioral therapy, and interpersonal and social rhythm therapy. Active components of these therapies include family involvement and psychoeducation, along with self-regulation, cognitive restructuring, communication, problem-solving, and emotion regulation skills. Factors that adversely influence response to therapy include high-conflict families and sleep impairment, suggesting the importance of targeting these factors in treatment. Sleep hygiene is an important factor in the treatment of mania, and there is support for the use of CBT in treating insomnia related to bipolar disorder. Ensuring patients get adequate rest will help with recovery and the prevention of future episodes of mania.

LEVEL OF CARE

Most youths with bipolar disorders can be safely and effectively treated as outpatients, provided that an appropriate schedule of visits and laboratory monitoring can be maintained through the course of treatment. Youths who are suicidal, homicidal, psychotic, or present an intentional danger to themselves or others typically require inpatient care.

Clinical Course and Prognosis

The mean age of onset of the first manic episode is approximately 18 years old for bipolar I disorder. Premorbid problems are common in bipolar disorder, especially temperamental difficulties with mood and behavioral regulation. Premorbid anxiety also is common. The early course of adolescent-onset bipolar I disorder appears to be more chronic and refractory to treatment than adult-onset bipolar disorder. Comorbidity predicts functional impairment, and age at onset predicts duration of episodes. Sleep impairment and family conflict are inversely related to favorable treatment response, suggesting important targets for treatment. The bipolar disorders are highly recurrent, and 70–80% of bipolar I patients will have additional mood episodes. Recurrent episodes can approximate 4 in 10 years, with the interepisode interval shortening as the patient ages. Although the majority of patients with bipolar I return to a fully functional level between episodes, approximately 30% continue to be symptomatic and functionally impaired between episodes.

The initial presentation of bipolar I disorder is often a major depressive episode. Switching from a depressive episode to a manic episode by adulthood may occur in 10–20% of youth, both spontaneously and during depression treatment. Factors that predict the eventual development of mania in depressed youth include a depressive episode characterized by rapid onset, psychomotor retardation, and psychotic features; a family history of affective disorders, especially bipolar disorder; and a history of mania or hypomania after antidepressant therapy.

The mean age of onset of bipolar II disorder is 20 years old. The illness most often begins with a depressive episode and is not recognized as bipolar II disorder until a hypomanic episode occurs, in about 12% of individuals with the initial diagnosis of major depression. Many individuals experience several episodes of major depression before experiencing the first recognized hypomanic episode. Anxiety, substance misuse, or eating disorders may also precede the onset of bipolar II, complicating its detection. About 5–15% of individuals with bipolar II disorder will ultimately develop a manic episode, which changes the diagnosis to bipolar I disorder.

Depression in bipolar I or II usually has an earlier age of onset, more frequent episodes of shorter duration, an abrupt onset and offset, is linked to comorbid substance misuse, and is triggered by stressors. Atypical symptoms such as hypersomnia, lability, and weight instability are also common in bipolar depression, reported in up to 90% of cases vs 50% in unipolar depression. Psychosis, psychomotor retardation, and catatonia are also more characteristic of bipolar depression,

whereas somatic complaints are more frequent in unipolar depression. A family history of mania is also a relevant discriminating factor.

Provision of clinical services is poor for youth with bipolar disorder. In one healthcare system study spanning 2-year follow-up after diagnosis, despite complex drug regimens, medication appointments were infrequent, averaging one visit every 2 months. More than 50% of patients needed one or more hospitalizations, and almost half had psychiatric emergency department visits. In a national study, 38% of youths diagnosed with bipolar disorder had received no treatment at all.

SEQUELAE

Bipolar disorder has one of the higher rates of suicide among mental health diagnoses, with a lifetime risk of suicide in individuals with bipolar disorder estimated to be at least 15 times that of the general population. Factors associated with suicide attempts include female gender, young age at illness onset, depressive polarity of first illness episode or current or most recent episode, comorbid anxiety disorder, any comorbid substance use disorder, borderline personality disorder, and first-degree family history of suicide. In contrast, completed suicides are associated with male sex and a first-degree family history of suicide. Despite patients with bipolar disorder having normal or even superior cognition before diagnosis, bipolar disorder has been associated with decrements in executive function and verbal memory. Youths with bipolar disorder are also at high risk for substance abuse, antisocial behavior, impaired academic performance, impaired family and peer relationships, and poor adjustment to life stressors.

PREVENTION

Although empirical support is sparse, one study demonstrated the effectiveness of family-focused treatment vs an educational control in hastening and sustaining recovery from mood symptoms in a high-familial-risk cohort of youths with subsyndromal symptoms of mania. Family-focused treatment is a manualized psychoeducational intervention designed to reduce family stress, conflict, and affective arousal by enhancing communication and problem solving between youths and their caregivers. Pharmacologic interventions for subsyndromal mania have produced equivocal results.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 40

Suicide and Attempted Suicide

Jennifer A. Zaspel and Rosa K. Kim

Youth suicide is a major public health concern. In 2021, suicide was the second leading cause of death in adolescents and young adults (aged 10-24 years) and the tenth leading cause of death for all ages. The rates of emergency department (ED) visits for psychiatric chief complaints have also increased over time, with a 2.5-fold increase in suicide-related visits in adolescents. There are numerous genetic, psychiatric, social, cultural, and environmental risk factors for suicidal behavior (Fig. 40.1). There are also many protective factors and interventions that can reduce rates of self-injury and suicide. Knowledge of these risk factors and protective factors may facilitate identification and treatment in youths at highest risk for intentional harm to themselves.

EPIDEMIOLOGY

Suicide rates for children and adolescents have been increasing over time, with the overall suicide rates increasing by 35% since 1999. It is estimated that 46% of people who die by suicide were diagnosed with a psychiatric condition at the time of their death. Linear trends in suicide attempts from 2009–2019 have also increased and specifically among certain demographic groups. A better understanding of which groups are at risk for suicide and parasuicidal behavior can help pediatricians identify and support those who are at risk (Table 40.1).

Suicidal Ideation and Attempts

More than 30% of 9th-12th grade students in the United States felt so sad or hopeless almost every day for 2 or more weeks in a row during the previous year that they stopped doing usual activities. During that same period, 18.8% of the students reported that they had seriously considered attempting suicide, and 8.9% reported that they had attempted suicide one or more times. A suicide attempt in the previous year that resulted in an injury, poisoning, or overdose that had to be treated by a physician or nurse was reported by 2.5% of students.

Ingestion is the most common method of attempted suicide. The 15–19-year-old age-group is the most likely to intentionally harm themselves by ingestion, receive treatment in the ED, and survive. Attempts are more common in adolescent females than males and in Hispanic females than their non-Hispanic counterparts. LGBTQ+ and bullied youths also have disproportionately high rates of suicidal ideation and suicide attempts (see Chapter 154). Prior self-harm (self-injury) from poisoning, drowning, firearms, fires, asphyxiation (hanging), and traffic injury are risk factors for suicide. Repeated episodes of self-harm are a higher risk factor than a single episode (see Chapter 46). Attempters who have made prior suicide attempts, who used a method other than ingestion, who have a plan, who have no regret, and who still want to die are at increased risk for completed suicide. Nonetheless, a significant number of children and adolescents who have completed suicide had no previous attempts.

Suicide Completions

In the United States, completed suicide is very rare before age 10. Rates of completed suicide increase steadily across adolescence into young adulthood, peaking in the early 20s. The male-to-female ratio for completed suicide rises with age from 3:1 in children to approximately 4:1 in those aged 15-24 and greater than 6:1 among those ages 20-24. Although exact rates have changed over time, firearms, suffocation, and poisoning remain the most common methods of suicide (Fig. 40.2).

For both male and female youth ages 15-24, suicide rates remain highest among Indigenous American and Indigenous Alaskan youth and White youth relative to Black, Asian or Pacific Islander, and Hispanic youth. However, rates have been rising for both Black and Asian or Pacific Islander youth, with the rates in Black males increasing 47% between 2013 and 2019 (12.2/100,000 to 17.9/100,000 individuals) and Asian or Pacific Islander males increasing 40% between 2013 and 2019 (12.0/100,000 to 16.8/100,000 individuals). Similar increases have also been seen in female youth in these groups in this time, with a rate increase of 59% among Black female youth (2.7 to 4.3/100,000) and 42% among Asian or Pacific Islander (3.6 to 5.1/100,000). In 2021, the combined (male and female, age 10-24) suicide rates among Indigenous youths increased ~16% (over 2018 rates); Increases were also noted among Black youths (~36%) and Hispanic youths (~8%).

RISK FACTORS

Multiple risk factors predispose youth to suicide (see Fig. 40.1, Table 40.1). Dynamic risk factors are those that change over time and are most amenable to risk mitigation through treatment, resources, and support. Static risk factors are those that increase an individual's risk of suicide attempt and completion but are not amenable to direct intervention. They include genetic factors, demographic information, an individual's past psychiatric history, family psychiatric history, and history of suicidal and parasuicidal behavior. The risk associated with each factor varies, with the highest risk associated with a personal

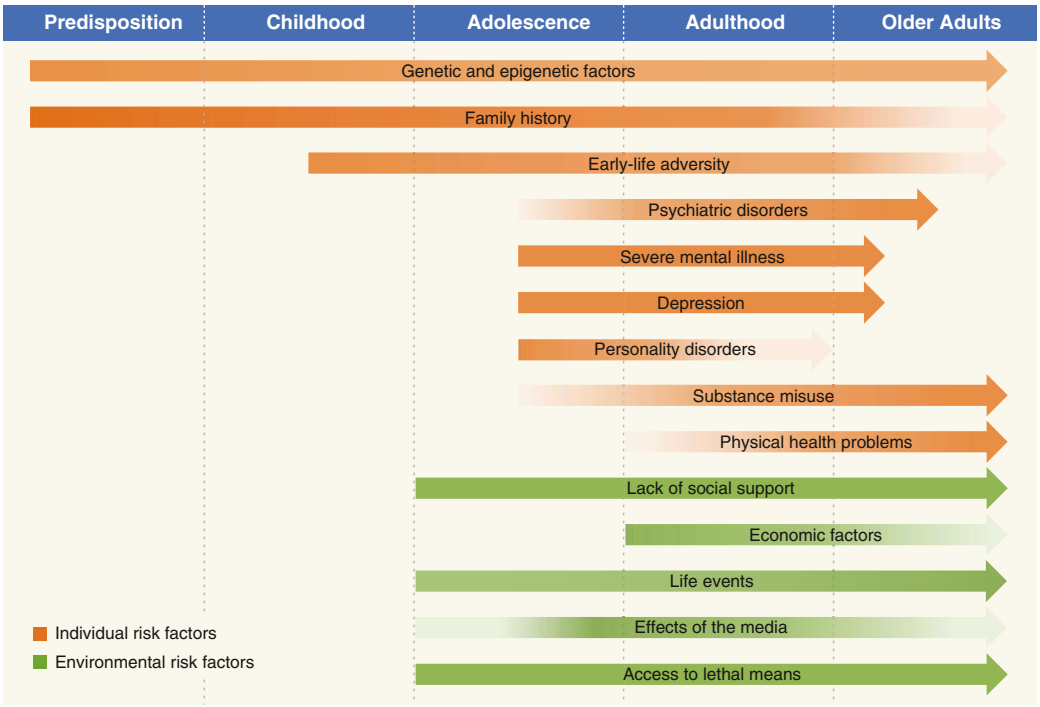

Fig. 40.1 Risk factors for suicide and the strength of the association throughout life. The strength of the association between each risk factor and suicide is indicated by the shading (darker shading indicates a stronger association). *(From Fazel S, Runeson B. Suicide [published correction appears in. N Engl J Med. 2020 Mar 12;382:1078]; N Engl J Med. 2020;382:266–274:Fig. 1, p 267.)*

history of a suicide attempt. Risk is also cumulative, with childhood adversity leading to an increased lifetime risk of suicide.

Access to Firearms

Firearms are the most lethal method of suicide completion; the death rate with respect to firearms is approximately 80–90%, whereas the death rate is only 1.5–4% for drug overdoses. Firearms have long been the most common method of completed suicide across all ages and genders and have become the most common method of suicide completion for adolescent males (see Fig. 40.2). Limiting access to lethal means, in particular firearms, reduces rates of completed suicide.

Suicide Contagion

Suicide attempts may also be precipitated by exposure to news of another person's suicide or by reading about or viewing a suicide portrayed in a romantic light in the media. Media coverage of suicide is linked to fluctuating incidence rates of suicides, particularly among adolescents. Glorification of suicide whether in news or in fictional media has been associated with an increase in suicides. When media coverage includes a detailed description of specific means used, the use of that particular method may increase in the overall population.

Preexisting Psychiatric Illness

Approximately 90% of youths who complete suicide have a preexisting psychiatric illness, most often major depression. Among females, chronic anxiety, especially panic disorder, also is associated with suicide attempts and completion. Among males, conduct disorder and substance use confer increased risk. Comorbidity of a substance use disorder, a depressive disorder, and/or conduct disorder are linked to suicide by firearm. Schizophrenia spectrum disorders are linked to suicide attempts and completions (see Chapter 47.1).

Suicidal and Parasuicidal Behavior

History of a previous suicide attempt is recognized as the strongest predictive risk factor for future suicidal behavior. Individual definitions of suicide attempts can vary; therefore parasuicidal behavior should be explored when considering past attempts. Some patients may not consider an aborted attempt or interrupted attempt an actual suicide attempt, but these behaviors carry considerable risk, as do researching suicide methods, preparatory acts, rehearsals, giving away possessions, and making arrangements for responsibilities (e.g., finding someone else to care for a pet or family member in their planned absence).

Nonsuicidal self-injury (NSSI) is the direct and deliberate destruction of one's own body tissue with the *absence of intent to die* (see Chapter 46). The most common self-harm behavior is cutting or carving, but other behaviors include scratching, burning, punching or hitting oneself, biting, and others. NSSI is common among adolescents, especially females. Up to 47.4% of youth with a diagnosis of depression engage in NSSI, and lifetime prevalence rates of NSSI are between 17% and 60%. Although the intent of these behaviors may not be to cause death, they are important to note, as they are strong predictors of future suicidality if left untreated. Seventy percent of adolescents who engaged in NSSI report a lifetime suicide attempt, and 55% reported multiple attempts. Individuals who are most likely to engage in NSSI are those who have a family member or close friend who have engaged in self-harm and those who believe that peers engage in self-harm.

Protective Factors

Protective factors (Table 40.2) can provide a counterbalance for those contemplating suicide. Internal protective factors are those that are inherent to the individual. External protective factors are typically dependent on relationships and interactions with others. Protective factors, even if present, may not counteract significant acute risk.

ASSESSMENT AND INTERVENTION

All suicidal ideation (including planning) and suicide attempts should be taken seriously and require a thorough assessment by a child-trained mental health clinician to evaluate the youth's current state of mind, ongoing risk of harm, and next best steps in treatment. Emergency mental health assessment is needed for immediate threat to self (i.e., active suicidal ideation with plan and intent); urgent mental health assessment (48-72 hours) is needed for severe psychiatric symptoms, significant change in overall functioning, and suicidal ideation without intent or plan. Routine mental health assessment is appropriate for mild to moderate psychiatric symptoms without suicidal ideation.

Pediatric practitioners should expect the mental health clinician to evaluate the presence and degree of suicidality and underlying risk factors. The reliability and validity of child interviewing are affected by

Table 40.1 Dynamic and Static Risk Factors for Suicide in Children and Adolescents

DYNAMIC RISK FACTORS	
Psychiatric symptoms	Anhedonia Feelings of hopelessness, helplessness, or worthlessness Impulsivity Insomnia Command hallucinations Agitation Anxiety or panic Poor coping
Changes in psychiatric treatment	Recent discharge from a psychiatric hospital Change in treatment plan Change in treatment team
Psychosocial stressors or precipitants	Events that can cause humiliation, shame, or despair (e.g., loss of a relationship, death of a loved one, housing insecurity, academic problems, newly diagnosed medical condition) Ongoing medical illness Substance intoxication Family turmoil/chaos/conflict Social isolation Bullying or being bullied Pending legal situation Suicide in the community (contagion)
STATIC RISK FACTORS	
Demographics	Age: 14-25 Sex: male Race: White, Indigenous American, and Native Alaskan LGBTQ+ identification
Preexisting and/or current psychiatric illness	Mood disorder Psychotic disorder Substance abuse disorder ADHD Eating disorder Posttraumatic stress disorder Cluster B personality traits/disorders Conduct disorder or behaviors (antisocial behavior, aggression) History of trauma, abuse, or neglect
Past suicidal and parasuicidal behavior	Previous suicide attempts Aborted or interrupted suicide attempts Nonsuicidal self-injury (self-harm) thoughts and/or action
Family history	Psychiatric illness Psychiatric hospitalization Suicide attempts and completions

ADHD, Attention-deficit/hyperactivity disorder.

children's level of cognitive development as well as their understanding of the relationship between their emotions and behavior. Confirmation of the youth's suicidal behavior can be obtained from information gathered by interviewing others who know the child or adolescent. A discrepancy between patient and parent reports is not unusual, with both children and adolescents more likely to disclose suicidal ideation and suicidal actions than their parents.

Suicide Inquiry

In the mental health assessment, suicidal ideation is assessed by explicit questions posed in a nonjudgmental, noncondescending, matter-of-fact approach. The clinician should explore all aspects of suicidal ideation (i.e., frequency, intensity), suicide plan, parasuicidal behaviors like preparatory acts or writing notes, and intent associated with their thoughts. The assessment of a suicide attempt should also include a detailed exploration of the hours immediately preceding an attempt to identify precipitants as well as the circumstances of the attempt itself to better understand the patient's intent and potential lethality. It is important to recognize that suicidal ideation is dynamic in nature and should be considered on an individual basis; a patient should be compared to their own baseline when assessing for risk of harm to self.

Children Under 12 Years

Although suicidal ideation and attempts are less frequent in children under 12 than older teens and adults, they do occur. A developmental approach must be taken, as children vary in their understanding of death, moral reasoning, and cognitive reasoning based on age and whether they are following a typical developmental trajectory. A young child may not recognize that their means are not lethal, but that fact should not discount their intent.

Unlike adolescents, Black male *children* are most likely to complete suicide, most often by hanging or strangulation. Children who are at risk of suicide may be less likely to demonstrate classical symptoms of depression than teens and are more likely to attempt at home. Children who die by suicide have higher rates of attention-deficit/hyperactivity disorder (ADHD), emphasizing the importance of impulsivity in suicide attempts. Relationship problems are the most common precipitating circumstance, but the specific relationship differs along developmental lines. Younger adolescents are more likely to have had relationship problems with peers or a significant other, whereas children are more likely to have had relationship problems with family.

Determining Risk

The calculation of the level of risk of harm to self is complex, requiring a determination across a spectrum of risk. At the low end of the risk spectrum are youth with thoughts of death or wanting to die but without suicidal thoughts, intent, or plan. Those with specific suicide plans, preparatory acts or suicide rehearsals, low probability of being found during an attempt, and clearly articulated intent are at the high end. A history of suicide attempts, presently impaired judgment, and poor social support further exacerbates the heightened risk. Among adolescents who consider self-harm, those who carry out self-injury are more likely to have family or friends who have engaged in self-harm. When considering all aspects of a suicide risk assessment, positive responses to a suicide inquiry carry more weight and concern than risk factors alone.

Levels of Psychiatric Care

For youth who are an imminent danger to themselves (i.e., have active thoughts of killing themselves with plan and intent), inpatient level of psychiatric care is necessary to ensure safety, clarify diagnoses, and plan comprehensive treatment. These patients can be hospitalized voluntarily or involuntarily. It is helpful for the pediatric practitioner to have an office protocol to follow in these situations. This protocol should take into consideration state laws regarding involuntary hospitalization, transportation options, nearest emergency assessment site, necessary forms for hospitalization, and available emergency mental health consultants.

For those youth suitable for treatment in the outpatient setting (e.g., suicidal ideation without plan or intent, intact mental status, few or no other risk factors for suicidality, willing and able to participate in outpatient treatment; has caregivers able to provide emotional support, supervision, safeguarding, and adherence to follow-up), an appointment should be scheduled within a few days with a mental health clinician. Ideally, this appointment should be scheduled before leaving the assessment venue. A procedure should be in place to contact the family to encourage mental health follow-up and provide additional support or resources, if needed. Some

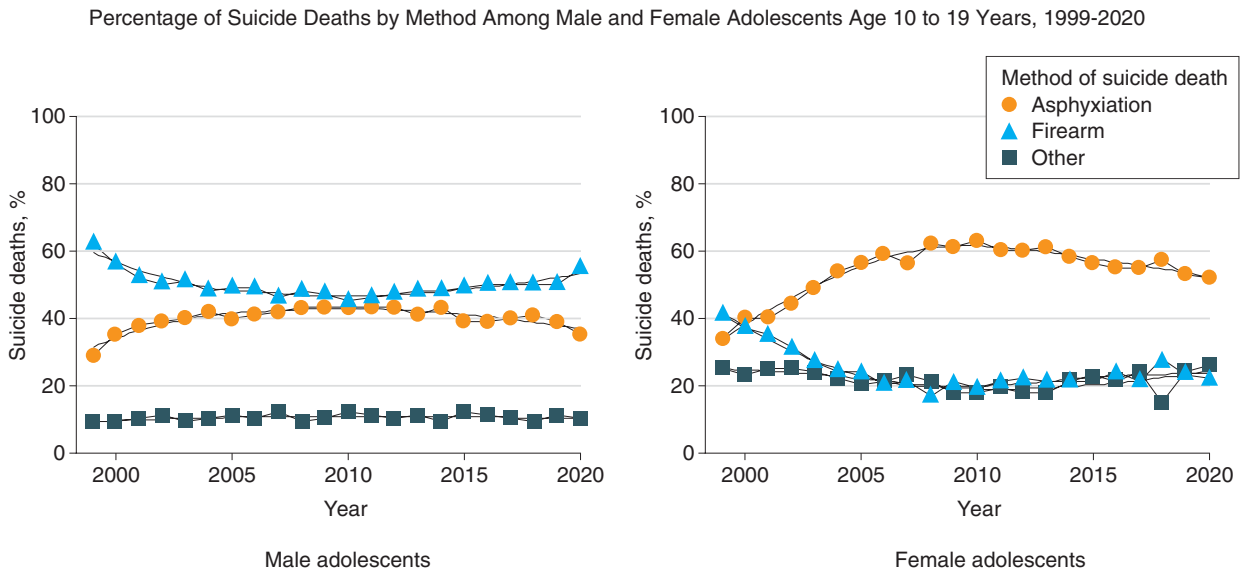

Fig. 40.2 Percentage of suicide deaths by method among male and female adolescents, age 10 to 19 years, 1999-2020. Locally estimated scatterplot smoothing regression estimated percentages of suicide deaths by method with 95% CIs. *Asphyxiation* includes suicide deaths involving hanging, strangulation, and suffocation; *Firearm* includes suicide deaths involving firearm use; and *Other* includes suicide deaths involving poisoning, drowning, fall, fire, and cuts. *(Data from Centers for Disease Control and Prevention. Multiple cause of death: 1999-2020 request form. Updated July 27, 2022. Accessed July 11, 2022.* https://wonder.cdc.gov/wonder/help/mcd.html.*)*

Table 40.2 Protective Factors Against Suicide in Children and Adolescents

PROTECTIVE FACTORS	
Internal protective factors	Positive coping skills Frustration tolerance Religious faith Fear of consequences of an attempt (e.g., disfigurement, hospitalization, effects on family/friends) Future oriented thinking Fear of lost opportunities
External protective factors	Responsibilities for others (e.g., other children in the home, pets) Positive therapeutic or mentoring relationships (e.g., physician, therapist, teacher, coach) Social supports Living with others

Table 40.3 Warning Signs of Suicide

Seek help as soon as possible by contacting a mental health professional or by calling the National Suicide Prevention Lifeline at **1-800-273-TALK** if you or someone you know exhibits any of the following signs:

- Threatening to hurt or kill oneself or talking about wanting to hurt or kill oneself.
- Looking for ways to kill oneself by seeking access to firearms, available pills, or other means.
- Talking or writing about death, dying, or suicide when these actions are out of the ordinary for the person.
- Feeling hopeless.
- Feeling rage or uncontrolled anger or seeking revenge.
- Acting reckless or engaging in risky activities, seemingly without thinking.
- Feeling trapped, "like there's no way out."
- Increasing alcohol or drug use.
- Withdrawing from friends, family, and society.
- Feeling anxious, agitated, or unable to sleep, or sleeping all the time.
- Experiencing dramatic mood changes.
- Seeing no reason for living, or having no sense of purpose in life.

Developed by the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA). https://www.nimh.nih.gov/health/publications/warning-signs-of-suicide

evidence suggests that quick and consistent follow-up with a team approach, including both primary care and mental health, can be helpful in enhancing treatment plan engagement among patients who are suicidal.

Safety Planning

Safety planning is a brief psychosocial intervention that has been shown to reduce suicidal behavior and increase engagement in treatment. Safety plan development consists of working ideally with both the patient and their caregivers to identify individual warning signs and symptoms related to self-harm and suicidal behavior, outlining healthy coping skills and people or places that can provide distraction, identifying loved ones and professionals who can be contacted during a crisis, and agreeing on ways to make the home environment safe (e.g., removing firearms, locking up medications). *Studies have repeatedly refuted the efficacy of safety or suicide contracts in mitigating risk of completing suicide, and some have shown them to be harmful to the therapeutic relationship.*

PREVENTION

The previously mentioned risk factors associated with suicide are relatively common and individually not strong predictors of suicide. The assessment is complicated by patients who may attempt to conceal their suicide thoughts and by those who express suicidal thoughts without serious intent. Suicide screening has been challenging because most screening instruments have variable sensitivity and specificity. In addition, the follow-up mental health evaluations for those who screen positive has been poor.

Prevention strategies in the pediatric medical home include training staff to recognize and respond to the warning signs of suicide (Table 40.3), screening for and treating depression, educating

patients/parents about warning signs for suicide, and restricting access to lethal means. Pediatric practitioners should consider counseling parents to remove firearms from the home entirely or securely lock guns and ammunition in separate locations. Anecdotal evidence suggests youths frequently know where guns and keys to gun cabinets are kept, even though parents may think they do not. The same recommendation applies to restricting access to potentially lethal prescription and nonprescription medications (e.g., containers of >25 acetaminophen tablets) and alcohol. These approaches emphasize the importance of restriction of access to means of suicide to prevent self-harm.

SCREENING AND EARLY TREATMENT

In 2022, the U.S. Preventive Services Task Force (USPSTF) concluded that there is insufficient evidence to recommend universal suicide screening in the primary care setting for children and adolescents. The American Academy of Pediatrics does recommend universal suicide screening for all children ≥12 years old. In addition, in 2018 the American Academy of Pediatrics and the USPFTS (2022) recommended annual universal depression screening for youths 12 and older, which often includes suicide screening as part of validated tools. Pediatric practitioners should also consider suicide potential and the need for mental health assessment in the

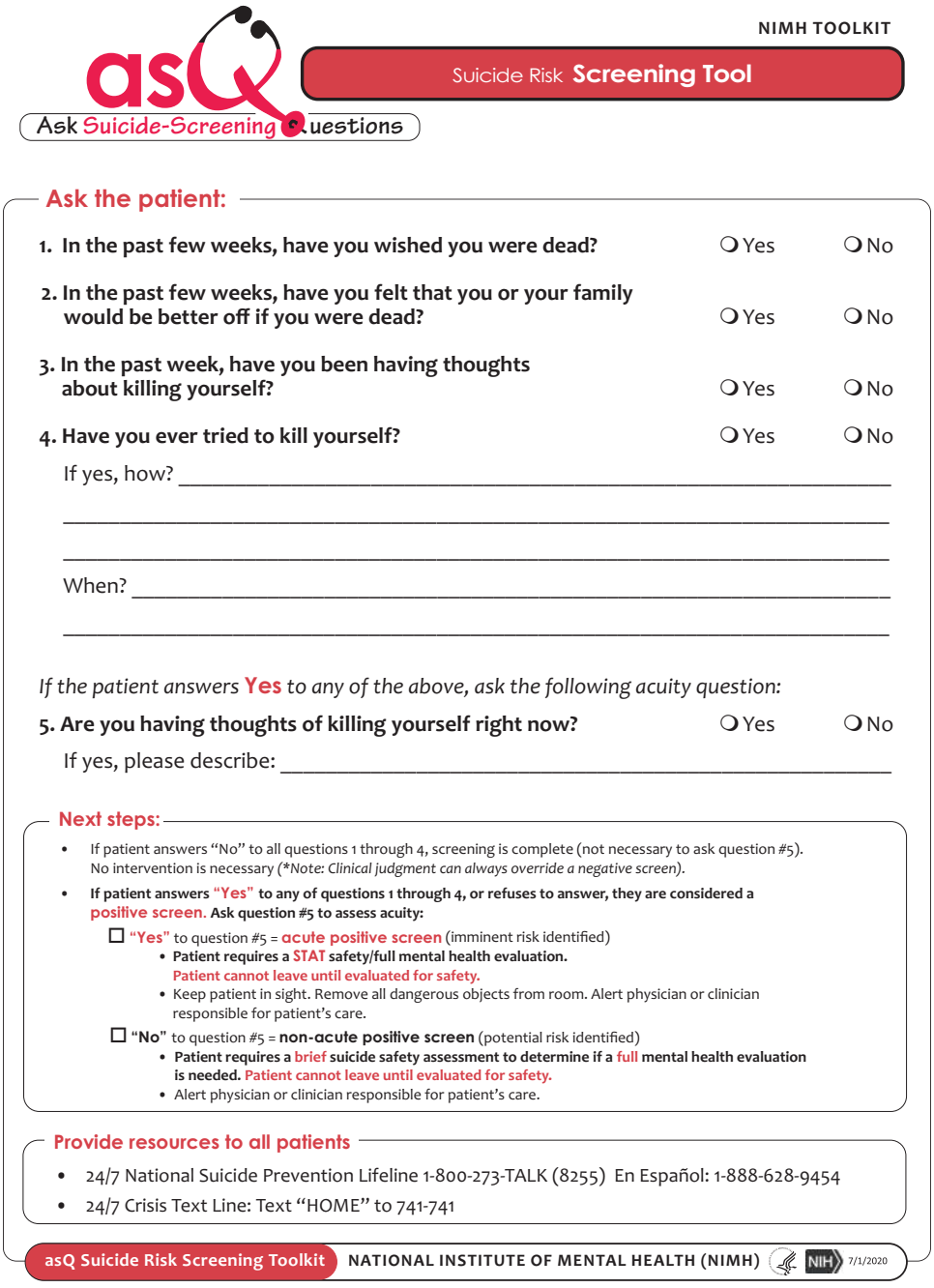

NIMH TOOLKIT

asQ Ask Suicide-Screening Questions

Suicide Risk **Screening Tool**

Ask the patient:

1. **In the past few weeks, have you wished you were dead?** ❍ Yes ❍ No
2. **In the past few weeks, have you felt that you or your family would be better off if you were dead?** ❍ Yes ❍ No
3. **In the past week, have you been having thoughts about killing yourself?** ❍ Yes ❍ No
4. **Have you ever tried to kill yourself?** ❍ Yes ❍ No

If yes, how? _____

_____

_____

When? _____

_____

If the patient answers **Yes** *to any of the above, ask the following acuity question:*

5. **Are you having thoughts of killing yourself right now?** ❍ Yes ❍ No

If yes, please describe: _____

Next steps:

- If patient answers "No" to all questions 1 through 4, screening is complete (not necessary to ask question #5). No intervention is necessary *(*Note: Clinical judgment can always override a negative screen).*
- **If patient answers "Yes" to any of questions 1 through 4, or refuses to answer, they are considered a positive screen. Ask question #5 to assess acuity:**
  - ☐ **"Yes"** to question #5 = **acute positive screen** (imminent risk identified)
    - **Patient requires a STAT safety/full mental health evaluation. Patient cannot leave until evaluated for safety.**
    - Keep patient in sight. Remove all dangerous objects from room. Alert physician or clinician responsible for patient's care.
  - ☐ **"No"** to question #5 = **non-acute positive screen** (potential risk identified)
    - **Patient requires a brief suicide safety assessment to determine if a full mental health evaluation is needed. Patient cannot leave until evaluated for safety.**
    - Alert physician or clinician responsible for patient's care.

Provide resources to all patients

- 24/7 National Suicide Prevention Lifeline 1-800-273-TALK (8255) En Español: 1-888-628-9454
- 24/7 Crisis Text Line: Text "HOME" to 741-741

asQ Suicide Risk Screening Toolkit | NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH) | NIH | 7/1/2020

Fig. 40.3 Ask Suicide-Screening Questions—Suicide Risk Screening Tool. (ASQ Tool courtesy National Institute of Mental Health. National Institutes of Health, Bethesda, Maryland. Accessed at https://www.nimh.nih.gov/research/research-conducted-at-nimh/asq-toolkit-materials, May 9, 2022.)

Table 40.4 Columbia Suicide Severity Rating Scale Screener

1. Have you wished you were dead or wished you could go to sleep and not wake up?
2. Have you actually had any thoughts about killing yourself?
If "Yes" to 2, answer questions 3, 4, 5, and 6.
If "No" to 2, go directly to question 6.
3. Have you thought about how you might do this?
4. Have you had any intention of acting on these thoughts of killing yourself, as opposed to you having the thoughts but you definitely would not act on them?
5. Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
6. Have you done anything, started to do anything, or prepared to do anything to end your life?
RESPONSE PROTOCOL TO SCREENING (BASED ON LAST ITEM ANSWERED "YES")
Item 1—Mental Health Referral at discharge
Item 2—Mental Health Referral at discharge
Item 3—Care Team Consultation (Psychiatric Nurse) and Patient Safety Monitor/Procedures
Item 4—Psychiatric Consultation and Patient Safety Monitor/Procedures
Item 5—Psychiatric Consultation and Patient Safety Monitor/Procedures
Item 6—If over 3 months ago, Mental Health Referral at discharge
If 3 months ago or less, Psychiatric Consultation and Patient Safety Monitor

From Posner K. Columbia Lighthouse Project. The Columbia-Suicide Severity Rating Scale (C-SSRS) Screener–Recent. https://cssrs.columbia.edu/the-columbia-scale-c-ssrs/risk-identification/

context of concerning information elicited in child/parent psychosocial histories (e.g., HEADSS Psychosocial Risk Assessment; see Chapter 32, Table 32.2), general screening measure scores out of the normal range (e.g., Pediatric Symptom Checklist Internalizing Sub-Scale; see Table 28.5), or self-reported statements or behaviors from patients and parents. The Ask Suicide-Screening Questionnaire (ASQ) is a validated four-item measure shown in the ED setting to have high sensitivity and negative predictive value in identifying youth at risk for suicide ideation and behavior (Fig. 40.3). Other common screening tools are the Columbia Suicide Severity Rating Scale (C-SSRS) Screener (Table 40.4) and the Patient Health Questionnaire (PHQ-2/PHQ-9). These scales have also been used in the emergency room setting.

Through follow-up office visits, pediatric practitioners can help support and facilitate the implementation of psychotherapies that target the *specific psychiatric disorders* and the emotional dysphoria or behavioral dysregulation that accompany suicidal ideation or behavior. In conjunction with a child and adolescent psychiatrist, psychotropic medications may be used as indicated to treat underlying psychiatric disorders. Both dialectical behavioral therapy and cognitive behavioral therapy are effective in reducing harm but must be combined with appropriate psychopharmacology of an underlying disorder. Pediatric practitioners also can encourage social connectedness to peers and to community organizations, as well as promote help-seeking (e.g., talking to a trusted adult when distressed) and wellness behaviors. In the event of a completed suicide, pediatricians can offer support to the family, particularly by monitoring for pathologic bereavement responses in siblings and parents.

SCHOOL RESOURCES

Screening for suicide in schools is also fraught with problems related to low specificity of screening instruments, paucity of referral sites, and variable acceptability among school administrators. Gatekeeper (e.g., student support personnel) training appears effective in improving skills among school personnel and is highly acceptable to administrators but has not been shown to prevent suicide. School curricula (e.g., Signs of Suicide) have shown some preventive potential by teaching students to recognize the signs of depression and suicide in themselves and others and providing them with specific action steps necessary for responding to these signs. Peer helpers have not generally been shown to be efficacious.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 41
Eating Disorders

Taylor B. Starr and Richard E. Kreipe

Eating disorders (EDs) are characterized by body dissatisfaction related to overvaluation of a thin body ideal, associated with dysfunctional patterns of cognition and weight control behaviors that result in significant biologic, psychologic, and social complications. EDs can develop in individuals of any age, gender, sexual orientation, ethnicity, or cultural background. Early intervention in EDs improves outcome.

DEFINITIONS

Anorexia nervosa (AN) involves significant overestimation of body size and shape, with a relentless pursuit of thinness that, in the **restrictive** subtype, typically combines excessive dieting and compulsive exercising. In the **binge-purge** subtype, patients might intermittently overeat and then attempt to rid themselves of calories by vomiting or taking laxatives, still with a strong drive for thinness (Table 41.1).

Bulimia nervosa (BN) is characterized by episodes of eating large amounts of food in a brief period, followed by compensatory vomiting, laxative use, exercise, or fasting to rid the body of the effects of overeating in an effort to avoid obesity (Table 41.2).

Children and adolescents with EDs may not fulfill criteria for AN or BN in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and may fall into a subcategory of **Other Specified Feeding and Eating Disorders (OSFED)**. Youth with these subthreshold conditions merit close monitoring over time because they may be early in the course of an illness.

Avoidant/restrictive food intake disorder **(ARFID)** involves limiting food intake based on the subjective qualities of food (e.g., appearance, color, smell, taste, texture or consistency), fear of adverse consequences of eating (e.g., choking, gagging or vomiting), or lack of interest in eating, but without concern about body image, weight, shape, or size. However, significant unintended weight loss or nutritional deficiencies and problems with social interactions can occur as a result (Table 41.3).

Binge eating disorder (BED), in which binge eating is not followed regularly by any compensatory behaviors (vomiting, laxatives), is a stand-alone category in DSM-5 but shares many features with obesity (see Chapter 65).

Table 41.1 DSM-5 Diagnostic Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.
Specify whether:
Restricting type (ICD-10-CM code F50.01): During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.
Binge-eating/purging type (ICD-10-CM code F50.02): During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
Specify if:
In partial remission: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.
In full remission: After full criteria for anorexia nervosa were previously met, none of the criteria has been met for a sustained period of time.
Specify current severity:
The minimum level of severity is based, for adults, on current BMI (see the following) or, for children and adolescents, on BMI percentile. **The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used.** The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.
Mild: BMI ≥17 kg/m^2 **Moderate**: BMI 16-16.99 kg/m^2 **Severe**: BMI 15-15.99 kg/m^2 **Extreme**: BMI <15 kg/m^2

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. pp. 338–339. Copyright 2013. American Psychiatric Association.

Table 41.2 DSM-5 Diagnostic Criteria for Bulimia Nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: 1. Eating, in a discrete period of time (e.g., within any 2 hr period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances. 2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
B. Recurrent inappropriate compensatory behaviors to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.
Specify if:
In partial remission: After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time.
In full remission: After full criteria for bulimia nervosa were previously met, none of the criteria has been met for a sustained period of time.
Specify current severity:
The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see the following). The level of severity may be increased to reflect other symptoms and the degree of functional disability.
Mild: An average of 1-3 episodes of inappropriate compensatory behaviors per week.
Moderate: An average of 4-7 episodes of inappropriate compensatory behaviors per week.
Severe: An average of 8-13 episodes of inappropriate compensatory behaviors per week.
Extreme: An average of 14 or more episodes of inappropriate compensatory behaviors per week.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p. 345. Copyright 2013. American Psychiatric Association.

EPIDEMIOLOGY

The classic presentation of AN is an early to middle adolescent female of above-average intelligence and socioeconomic status who is a conflict-avoidant, risk-aversive perfectionist and is struggling with disturbances of anxiety and/or mood. BN tends to emerge in later adolescence, sometimes evolving from AN, and is typified by impulsivity and features of borderline personality disorder associated with depression and mood swings. ARFID typically presents in late childhood, is more common in males, and more often co-occurs with anxiety disorders and autism spectrum disorder. The 0.5–1% and 3–5% incidence rates among younger and older adolescent females for AN and BN, respectively, probably reflect ascertainment bias in sampling and underdiagnosis in cases not fitting the common profile. The same may be true of the significant gender disparity, in which female patients account for approximately 85% of patients with diagnosed EDs.

No single factor causes the development of an ED; sociocultural studies indicate a complex interplay of culture, ethnicity, gender, peers, and family. The gender dimorphism is presumably related to females having a stronger relationship between body image and self-evaluation, as well as the influence of the Western culture's thin body ideal. Ethnicity appears to moderate the association between risk factors and disordered eating, with African American and Caribbean females reporting lower body dissatisfaction and less dieting than Hispanic and non-Hispanic White females. Because peer acceptance is central to healthy adolescent growth and development, especially in early adolescence, when AN tends to have its initial prevalence peak, the potential influence of peers on EDs is significant, as are the relationships among peers, body image, and eating. Teasing by peers or by family members (especially males) may be a contributing factor for overweight females.

Table 41.3 DSM-5 Diagnostic Criteria for Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following: 1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children). 2. Significant nutritional deficiency. 3. Dependence on enteral feeding or oral nutritional supplements. 4. Marked interference with psychosocial functioning.
B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.
D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.
Specify if:
In remission: After full criteria for avoidant/restrictive food intake disorder were previously met, the criteria have not been met for a sustained period of time.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p. 334. Copyright 2013. American Psychiatric Association.

Family influence in the development of EDs is even more complex because of the interplay of environmental and genetic factors; shared elements of the family environment and immutable genetic factors account for approximately equal amounts of the variance in disordered eating. There are associations between parents' and children's eating behaviors; dieting and physical activity levels suggest parental reinforcement of body-related societal messages. The influence of inherited genetic factors on the emergence of EDs during adolescence is also significant, but not directly. Rather, the risk for developing an ED appears to be mediated through a genetic predisposition to *anxiety* (see Chapter 38), *depression* (see Chapter 39), or *obsessive-compulsive traits* that may be modulated through the internal milieu of puberty. There is no evidence to support the outdated notion that parents or family dynamics cause an ED; rather, the family dynamics may represent responses to having a family member with a potentially life-threatening condition. The supportive influence on recovery of parents as nurturing caregivers cannot be overestimated.

PATHOLOGY AND PATHOGENESIS

The emergence of EDs coinciding with the processes of adolescence (e.g., puberty, identity, autonomy, cognition) indicates the central role of development. EDs may be viewed as a final common pathway, with a number of *predisposing* factors that increase the risk of developing an ED, *precipitating* factors often related to developmental processes of adolescence triggering the emergence of the ED, and *perpetuating* factors that cause an ED to persist. A history of sexual trauma is more common in children with BN, and when present with any ED makes recovery more difficult. EDs often begin with dieting but gradually progress to unhealthy habits that lessen the negative impact of associated psychosocial problems to which the affected person is vulnerable because of premorbid biologic and psychologic characteristics, family interactions, and social climate. When persistent, the biologic effects of starvation and malnutrition (e.g., true loss of appetite, hypothermia, gastric atony, amenorrhea, sleep disturbance, fatigue, weakness, depression), combined with the psychologic rewards of increased sense of mastery and reduced emotional reactivity, actually maintain and reward pathologic ED behaviors.

This positive reinforcement of behaviors and consequences, generally viewed by parents and others as negative, helps to explain why persons with an ED characteristically deny that a problem exists and resist treatment. With significantly low caloric intake, patients initially exhibit extreme irritability, but over time experience emotional "numbness," which reinforces continued caloric restriction. Although noxious, purging can be reinforcing because of a reduction in anxiety triggered by overeating; purging also can result in short-term, but reinforcing, improvement in mood related to changes in neurotransmitters. In addition to an imbalance in neurotransmitters, most notably serotonin and dopamine, alterations in functional anatomy also support the concept of EDs as brain disorders. The cause-and-effect relationship in central nervous system (CNS) alterations in EDs is not clear, nor is their reversibility.

CLINICAL MANIFESTATIONS

Except for ARFID, in which weight loss is *unintentional,* a central feature of EDs is the overestimation of body size, shape, or parts (e.g., abdomen, thighs) leading to intentional weight control practices to reduce weight (AN) or prevent weight gain (BN). Associated practices include severe restriction of caloric intake and behaviors intended to reduce the effect of calories ingested, such as compulsive exercising or purging by inducing vomiting or taking laxatives. Eating and weight loss habits commonly found in EDs can result in a wide range of energy intake and output, the balance of which leads to a wide range in weight, from extreme loss of weight in AN to fluctuation around a normal to moderately high weight in BN. Reported eating and weight control habits thus inform the initial primary care approach (Table 41.4).

Although weight control patterns guide the initial pediatric approach, an assessment of common symptoms and findings on physical examination is essential to identify targets for intervention. When reported symptoms of excessive weight loss (feeling tired and cold; lacking energy; orthostasis; difficulty concentrating) are explicitly linked by the clinician to their associated physical signs (hypothermia with acrocyanosis and slow capillary refill; loss of muscle mass; bradycardia with orthostasis), it becomes more difficult for the patient to deny that a problem exists. Furthermore, awareness that bothersome symptoms can be eliminated by healthier eating and activity patterns can increase a patient's motivation to engage in treatment. Tables 41.5 and 41.6 detail common symptoms and signs that should be addressed in a pediatric assessment of a suspected ED.

DIFFERENTIAL DIAGNOSIS

In addition to identifying symptoms and signs that deserve targeted intervention for patients who have an ED, a comprehensive history and physical examination are required to rule out other conditions in the differential diagnosis. Weight loss can occur in any condition with increased *catabolism* (e.g., hyperthyroidism, malignancy, occult chronic infection) or *malabsorption* (e.g., **celiac disease**) or in other disorders (Addison disease, type 1 diabetes mellitus, stimulant abuse), but these illnesses are generally associated with other findings and are not usually associated with decreased caloric intake. Patients with **inflammatory bowel disease** can reduce intake to minimize abdominal cramping; eating can cause abdominal discomfort and early satiety in AN because of gastric atony associated with significant weight loss, not malabsorption. Likewise, signs of weight loss in AN might include hypothermia, acrocyanosis with slow capillary refill, and neutropenia similar to some features of sepsis, but the overall picture in EDs is one of relative cardiovascular stability compared with sepsis. **Endocrinopathies** are also in the differential of EDs. With BN, voracious appetite in the face of weight loss might suggest diabetes mellitus, but blood glucose levels are normal or low in EDs. Adrenal insufficiency mimics many physical symptoms and signs found in restrictive AN but is associated with elevated potassium levels and hyperpigmentation. Thyroid disorders may be considered, because of changes in weight, but the overall presentation of AN includes symptoms of both underactive and

Table 41.4 Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder (ED)

	PROMINENT FEATURE		CLINICAL COMMENTS REGARDING ED HABITS	
HABIT	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high because of very low caloric density of intake as a result of "diet" and nonfat choices	Variable, but calories normal to high; intake in binges is often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body is an essential feature of diagnosis	Inconsistent balance of intake, exercise, and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; emphasis on "healthy food choices" with reduced caloric density Monotonous, limited "good" food choices, often leading to vegetarian or vegan diet Strong feelings of guilt after eating more than planned leads to exercise and renewed dieting	Aware of calories and fat, but less regimented in avoidance than AN Frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan Reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner Volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to "rules" governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because "unhealthy"	Snack "comfort foods" can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially "healthy" Beliefs and "rules" about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being "weak" or "lazy"	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with "diets" often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive Shame and guilt prominent afterward	Often "subjective" (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive May excel in dance, long-distance running	Less predictable May be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs ED	Males often use exercise as means of "purging"
Vomiting	Characteristic of binge-purge subtype May chew, then spit out, rather than swallow, food as a variant	Most common habit intended to reduce effects of overeating Can occur after meal as well as a binge	Physiologic and emotional instability prominent	Strongly "addictive" and self-punishing, but does not eliminate calories ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly "addictive," self-punishing, but ineffective means to reduce weight (calories are absorbed in small intestine, but laxatives work in colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, Anorexia nervosa; BN, bulimia nervosa.

Table 41.5 Symptoms Commonly Reported by Patients with an Eating Disorder (ED)

	DIAGNOSIS		
SYMPTOMS	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**	**CLINICAL COMMENTS REGARDING ED SYMPTOMS**
Body image	Feels fat, even with extreme emaciation, often with specific body distortions (e.g., stomach, thighs); strong drive for thinness, with self-efficacy closely tied to appraisal of body shape, size, and/or weight	Variable body image distortion and dissatisfaction, but drive for thinness is less than desire to avoid gaining weight	Challenging patient's body image is both ineffective and countertherapeutic clinically Accepting patient's expressed body image but noting its discrepancy with symptoms and signs reinforces concept that patient can "feel" fat but also "be" too thin and unhealthy
Metabolism	Hypometabolic symptoms include feeling cold, tired, and weak and lacking energy May be both bothersome and reinforcing	Variable, depending on balance of intake and output and hydration	Symptoms are evidence of body's "shutting down" in an attempt to conserve calories with an inadequate diet Emphasizing reversibility of symptoms with healthy eating and weight gain can motivate patients to cooperate with treatment
Skin	Dry skin, delayed healing, easy bruising, gooseflesh Orange-yellow skin on hands	No characteristic symptom; self-injurious behavior may be seen	Skin lacks good blood flow and ability to heal in low weight Carotenemia with large intake of β-carotene foods; reversible
Hair	Lanugo-type hair growth on face and upper body Slow growth and increased loss of scalp hair	No characteristic symptom	Body hair growth conserves energy Scalp hair loss can worsen during refeeding "telogen effluvium" (resting hair is replaced by growing hair) Reversible with continued healthy eating
Eyes	No characteristic symptom	Subconjunctival hemorrhage	Caused by increased intrathoracic pressure during vomiting
Teeth	No characteristic symptom	Erosion of dental enamel Decay, fracture, and loss of teeth	Intraoral stomach acid resulting from vomiting etches dental enamel, exposing softer dental elements
Salivary glands	No characteristic symptom	Enlargement (no to mild tenderness)	Caused by chronic binge eating and induced vomiting, with parotid enlargement more prominent than submandibular; reversible
Heart	Dizziness, fainting in restrictive subtype Palpitations more common in binge-purge subtype	Dizziness, fainting, palpitations	Dizziness and fainting due to postural orthostatic tachycardia and dysregulation at hypothalamic and cardiac level with weight loss, as a result of hypovolemia with binge-purge Palpitations and arrhythmias often caused by electrolyte disturbance Symptoms reverse with weight gain and/or cessation of binge-purge
Abdomen	Early fullness and discomfort with eating Constipation Perceives contour as "fat," often preferring well-defined abdominal musculature	Discomfort after a binge Cramps and diarrhea with laxative abuse	Weight loss is associated with reduced volume and tone of GI tract musculature, especially the stomach Laxatives may be used to relieve constipation or as a cathartic Symptom reduction with healthy eating can take weeks to occur
Extremities and musculoskeletal	Cold, blue hands and feet	No characteristic symptoms Self-cutting or burning on wrists or arms	Energy-conserving low body temperature with slow blood flow most notable peripherally Quickly reversed with healthy eating
Nervous system	No characteristic symptom	No characteristic symptom	Neurologic symptoms suggest diagnosis other than ED
Mental status	Depression, anxiety, obsessive-compulsive symptoms, alone or in combination	Depression; PTSD; borderline personality disorder traits	Underlying mood disturbances can worsen with dysfunctional weight control practices and can improve with healthy eating AN patients might report emotional "numbness" with starvation preferable to emotionality associated with healthy eating

AN, Anorexia nervosa; ED, eating disorder; GI, gastrointestinal; PTSD, posttraumatic stress disorder.

Table 41.6 Signs Commonly Found in Patients with Eating Disorder Relative to Prominent Feature of Weight Control

PHYSICAL SIGN	PROMINENT FEATURE		CLINICAL COMMENTS RELATED TO ED SIGNS
	RESTRICTIVE INTAKE	BINGE EATING/PURGING	
General appearance	Thin to cachectic, depending on balance of intake and output Might wear bulky clothing to hide thinness and might resist being examined	Thin to overweight, depending on the balance of intake and output through various means	Examine in hospital gown Weight loss more rapid with reduced intake and excessive exercise Binge eating can result in large weight gain, regardless of purging behavior Appearance depends on balance of intake and output and overall weight control habits
Weight	Low and falling (if previously overweight, may be normal or high); may be falsely elevated if patient drinks fluids or adds weights to body before being weighed	Highly variable, depending on balance of intake and output and state of hydration Falsification of weight is unusual	Weigh in hospital gown with no underwear, after voiding (measure urine SG) Remain in gown until physical exam completed to identify possible fluid loading (low urine SG, palpable bladder) or adding weights to body
Metabolism	Hypothermia: temp <35.5°C (95.9°F), pulse <60 beats/min Slowed psychomotor response with very low core temperature Hypoglycemia Hypokalemia Amenorrhea Delayed puberty	Variable, but hypometabolic state is less common than in AN	Hypometabolism related to disruption of hypothalamic control mechanisms as a result of weight loss Signs of hypometabolism (cold skin, slow capillary refill, acrocyanosis) most evident in hands and feet, where energy conservation is most active Metabolic acidosis or alkalosis
Skin	Dry, scaly Increased prominence of hair follicles Orange or yellow hands Hair loss	Calluses over proximal knuckle joints of hand (Russell sign)	Carotenemia with large intake of β-carotene foods Russell sign: maxillary incisors abrasion develops into callus with chronic digital pharyngeal stimulation, usually on dominant hand
Hair	Lanugo-type hair growth on face and upper body Scalp hair loss, especially prominent in parietal region	No characteristic sign	Body hair growth conserves energy Scalp hair loss "telogen effluvium" can worsen weeks after refeeding begins, as hair in resting phase is replaced by growing hair
Eyes	No characteristic sign	Subconjunctival hemorrhage	Increased intrathoracic pressure during vomiting
Teeth	Caries	Eroded dental enamel and decayed, fractured, missing teeth	Perimolysis (dental erosions) worse on lingual surfaces of maxillary teeth, is intensified by brushing teeth without preceding water rinse
Salivary glands	No characteristic sign	Enlargement, relatively nontender	Parotid > submandibular involvement with frequent and chronic binge eating and induced vomiting
Throat	No characteristic sign	Absent gag reflex	Extinction of gag response with repeated pharyngeal stimulation
Heart	Bradycardia, hypotension, and orthostatic pulse differential >25 beats/min	Hypovolemia if dehydrated	Changes in AN resulting from central hypothalamic and intrinsic cardiac function Orthostatic changes less prominent if athletic, more prominent if associated with purging
Abdomen	Scaphoid, organs may be palpable but not enlarged, stool-filled left lower quadrant Constipation Transaminitis	Increased bowel sounds if recent laxative use	Presence of organomegaly requires investigation to determine cause Constipation prominent with weight loss Pancreatitis Esophageal or gastric ulceration or perforation
Extremities and musculoskeletal system	Cold, acrocyanosis, slow capillary refill Edema of feet Loss of muscle, subcutaneous, and fat tissue Osteopenia	No characteristic sign, but may have rebound edema after stopping chronic laxative use	Signs of hypometabolism (cold) and cardiovascular dysfunction (slow capillary refill and acrocyanosis) in hands and feet Edema, caused by capillary fragility more than hypoproteinemia in AN, can worsen in early phase of refeeding
Nervous system	No characteristic sign Peripheral neuropathy	No characteristic sign	Water loading before weigh-ins can cause acute hyponatremia
Mental status	Anxiety about body image, irritability, depressed mood, oppositional to change	Depression, evidence of PTSD, more likely suicidal than AN	Mental status often improves with healthier eating and weight; SSRIs only shown to be effective for BN

AN, Anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; PTSD, posttraumatic stress disorder; SG, specific gravity; SSRIs, selective serotonin reuptake inhibitors.

overactive thyroid, such as hypothermia, bradycardia, and constipation, as well as weight loss and excessive physical activity, respectively.

In the CNS, craniopharyngiomas and Rathke pouch tumors can mimic some of the findings of AN, such as weight loss and growth failure, and even some body image disturbances, but the latter are less fixed than in typical EDs and are associated with other findings, including evidence of increased intracranial pressure. **Mitochondrial neurogastrointestinal encephalomyopathy**, caused by a mutation in the *TYMP* gene, presents with gastrointestinal dysmotility, cachexia, ptosis, peripheral neuropathy, ophthalmoplegia, and leukoencephalopathy. Symptoms begin during the second decade of life and are often initially diagnosed as AN. Early satiety, vomiting, cramps, constipation, and pseudoobstruction result in weight loss often before the neurologic features are noticed (see Chapter 638.2). Acute or chronic oromotor dysfunction and obsessive-compulsive disorder may mimic an ED. Fear of choking may lead to **avoidance-restrictive food intake disorder**.

Any patient with an atypical presentation of an ED, based on age, sex, or other factors not typical for AN or BN, deserves a scrupulous search for an alternative explanation. In ARFID, disturbance in the neurosensory processes associated with eating, not weight loss, is the central concern and must be recognized for appropriate treatment. Patients can have both an underlying illness and an ED. The core features of dysfunctional eating habits (body image disturbance and change in weight) can co-occur with conditions such as diabetes mellitus, where patients might manipulate their insulin dosing to lose weight.

LABORATORY FINDINGS

Because the diagnosis of an ED is made clinically, there is no confirmatory laboratory test. Laboratory abnormalities, when found, are the result of malnutrition secondary to weight control behaviors or medical complications; studies should be chosen based on history and physical examination. A routine screening battery typically includes complete blood count, erythrocyte sedimentation rate (should be normal), and biochemical profile. Common abnormalities in ED include low white blood cell count with normal hemoglobin and differential; hypokalemic, hypochloremic metabolic alkalosis from severe vomiting; mildly elevated liver enzymes, cholesterol, and cortisol levels; low gonadotropins and blood glucose with marked weight loss; and generally normal total protein, albumin, and renal function. An electrocardiogram (ECG) may be useful when profound bradycardia or arrhythmia is detected; the ECG usually has low voltage, with nonspecific ST or T-wave changes. Although prolonged QTc has been reported, prospective studies have not found an increased risk for this. Nonetheless, when a prolonged QTc is present in a patient with ED, it may increase the risk for ventricular dysrhythmias.

COMPLICATIONS

No organ is spared the harmful effects of dysfunctional weight control behaviors, but the most concerning targets of medical complications are the heart, brain, gonads, and bones. Some **cardiac** findings in EDs (e.g., sinus bradycardia, hypotension) are *physiologic* adaptations to starvation that conserve calories and reduce afterload. Cold, blue hands and feet with slow capillary refill that can result in tissue perfusion insufficient to meet demands also represent energy-conserving responses associated with inadequate intake. All these acute changes are reversible with restoration of nutrition and weight. Significant orthostatic pulse changes, ventricular dysrhythmias, or reduced myocardial contractility reflect myocardial impairment that can be lethal. In addition, with extremely low weight, **refeeding syndrome** (a result of the rapid drop in serum phosphorus, magnesium, and potassium with excessive reintroduction of calories, specifically carbohydrates), is associated with acute tachycardia and heart failure and neurologic symptoms (see Chapter 63). With long-term malnutrition, the myocardium appears to be more prone to tachyarrhythmias, the second most common cause of death in these patients after suicide. In BN, dysrhythmias can also be related to electrolyte imbalance.

Clinically, the primary CNS area affected acutely in EDs, especially with weight loss, is the **hypothalamus.** Hypothalamic dysfunction is reflected in problems with thermoregulation (warming and cooling), satiety, sleep, autonomic cardioregulatory imbalance (orthostasis), and endocrine function (reduced gonadal and excessive adrenal cortex stimulation), all of which are reversible. Anatomic studies of the brain in ED have focused on AN, with the most common finding being increased ventricular and sulcal volumes that normalize with weight restoration. Persistent gray matter deficits following recovery, related to the degree of weight loss, have been reported. Elevated medial temporal lobe cerebral blood flow on positron emission tomography, similar to that found in psychotic patients, suggests that these changes may be related to body image distortion. Also, visualizing high-calorie foods is associated with exaggerated responses in the visual association cortex that are similar to those seen in patients with specific phobias. Patients with AN might have an imbalance between serotonin and dopamine pathways related to neurocircuits in which dietary restraint reduces anxiety.

Reduced **gonadal** function occurs in male and female patients; it is clinically manifested in AN as amenorrhea in female patients and erectile dysfunction in males. It is related to understimulation from the hypothalamus as well as cortical suppression related to physical and emotional stress. Amenorrhea precedes significant dieting and weight loss in up to 30% of females with AN, and most adolescents with EDs perceive the absence of menses positively. The primary health concern is the negative effect of decreased ovarian function and estrogen on **bones**. Decreased bone mineral density (BMD) with osteopenia or the more severe osteoporosis is a significant complication of EDs (more pronounced in AN than BN). Data do not support the use of sex hormone replacement therapy because this alone does not improve other causes of low BMD (low body weight, lean body mass, low insulin-like growth factor-1, high cortisol).

TREATMENT

Principles Guiding Primary Care Treatment

The approach in primary care should facilitate the acceptance by the ED patient (and parents) of the diagnosis and initial treatment recommendations. A **nurturant-authoritative** approach using the biopsychosocial model is useful. A pediatrician who explicitly acknowledges that the patient may disagree with the diagnosis and treatment recommendations and may be ambivalent about changing eating habits, while also acknowledging that recovery requires strength, courage, willpower, and determination, demonstrates *nurturance*. Parents also find it easier to be nurturing once they learn that the development of an ED is neither a willful decision by the patient nor a reflection of poor parenting. Framing the ED as a "maladaptive coping mechanism" for a complex variety of issues with both positive and negative aspects avoids blame or guilt and can prepare the family for professional help that will focus on strengths and restoring health, rather than on the deficits in the adolescent or the family.

The *authoritative* aspect of a physician's role comes from expertise in health, growth, and physical development. A goal of primary care treatment should be attaining and maintaining health, not merely weight gain, although weight gain is a means to the goal of wellness. Providers who frame themselves as consultants to the patient with authoritative knowledge about health can avoid a countertherapeutic authoritarian stance. Primary care health-focused activities include monitoring the patient's physical status, setting limits on behaviors that threaten the patient's health, involving specialists with expertise in EDs on the treatment team, and continuing to provide primary care for health maintenance, acute illness, or injury.

The **biopsychosocial model** uses a broad ecologic framework, starting with the biologic impairments of physical health related to dysfunctional weight control practices, evidenced by symptoms and signs. Explicitly linking ED behaviors to symptoms and signs can increase motivation to change. In addition, there are usually unresolved psychosocial conflicts in both the intrapersonal (self-esteem, self-efficacy) and the interpersonal (family, peers, school)

domains. Weight control practices initiated as coping mechanisms become reinforced because of positive feedback. That is, external rewards (e.g., compliments about improved physical appearance) and internal rewards (e.g., perceived mastery over what is eaten or what is done to minimize the effects of overeating through exercise or purging) are more powerful to maintain behavior than negative feedback (e.g., conflict with parents, peers, and others about eating) is to change it. Thus, when definitive treatment is initiated, more productive alternative means of coping must be developed.

Nutrition and Physical Activity

The primary care provider generally begins the process of prescribing nutrition, although a dietitian should be involved eventually in the meal planning and nutritional education of patients with AN or BN. Framing food as fuel for the body and the source of energy for daily activities emphasizes the health goal of increasing the patient's energy level, endurance, and strength. For patients with AN and low weight, the nutrition prescription should work toward gradually increasing weight at the rate of about 0.5-1 lb/week, by increasing energy intake by 100-200 kcal increments every few days, toward a target of approximately 90% of average body weight for sex, height, and age. Weight gain will not occur until intake exceeds output, and eventual intake for continued weight gain can exceed 4,000 kcal/day, especially for patients who are anxious and have high levels of thermogenesis from nonexercise activity. Stabilizing intake is the goal for patients with BN, with a gradual introduction of "forbidden" foods while also limiting foods that might trigger a binge.

When initiating treatment of an ED in a primary care setting, the clinician should be aware of common cognitive patterns. Patients with AN typically have all-or-none thinking (related to perfectionism) with a tendency to overgeneralize and jump to catastrophic conclusions, while assuming that their body is governed by rules that do not apply to others. These tendencies lead to the dichotomization of foods into good or bad categories, having a day ruined because of one unexpected event, or choosing foods based on rigid self-imposed restrictions. These thoughts may be related to neurocircuitry and neurotransmitter abnormalities associated with executive function and rewards. Weight loss in the absence of body shape, size, or weight concerns should raise suspicion about ARFID, because the emotional distress associated with "forced" eating is not associated with gaining weight, but with the neurosensory experience of eating.

A standard nutritional balance of 15–20% calories from protein, 50–55% from carbohydrate, and 25–30% from fat is appropriate. The fat content may need to be lowered to 15–20% early in the treatment of AN because of continued fat phobia. With the risk of low BMD in patients with AN, calcium and vitamin D supplements are often needed to attain the recommended 1,300 mg/day intake of calcium. Refeeding can be accomplished with frequent small meals and snacks consisting of a variety of foods and beverages (with minimal diet or fat-free products), rather than fewer high-volume high-calorie meals. Some patients find it easier to take in part of the additional nutrition as canned supplements (medicine) rather than food. Regardless of the source of energy intake, the risk for refeeding syndrome (e.g., see the previous section on "Complications") increases with the degree of weight loss and the rapidity of caloric increases (see Chapter 63). Therefore, if the weight has fallen below 80% of expected weight for height, refeeding should proceed carefully (not necessarily slowly) and possibly in the hospital (Table 41.7).

Patients with AN tend to have a highly structured day with restrictive intake, in contrast to BN, which is characterized by a lack of structure, resulting in chaotic eating patterns and binge-purge episodes. All patients with AN, BN, or ED-NOS benefit from a daily structure for healthy eating that includes three meals and at least one snack a day, distributed evenly over the day, based on balanced meal planning. Breakfast deserves special emphasis because it is often the first meal eliminated in AN and is often avoided the morning after a binge-purge episode in BN. In addition to structuring meals and snacks, patients should plan structure in their activities. Although overexercising is common in AN, completely prohibiting exercise can lead to further restriction of intake or to surreptitious exercise; inactivity should be limited to situations in which weight loss is dramatic or there is physiologic instability. Also, healthy exercise (once a day, for no more than 30 min, at no more than moderate intensity) can improve mood and make increasing calories more acceptable. Because patients with AN often are unaware of their level of activity and tend toward progressively increasing their output, exercising without either a partner or supervision is not recommended.

Table 41.7 Potential Indications for Inpatient Medical Hospitalization of Patients with Anorexia Nervosa

PHYSICAL AND LABORATORY
Heart rate <50 beats/min
Other cardiac rhythm disturbances
Blood pressure <80/50 mm Hg
Postural hypotension resulting in >10 mm Hg decrease or >25 beats/min increase
Hypokalemia
Hypophosphatemia
Hypoglycemia
Dehydration
Body temperature <36.1°C (97°F)
<80% healthy body weight
Hepatic, cardiac, or renal compromise
PSYCHIATRIC
Suicidal intent and plan
Very poor motivation to recover (in family and patient)
Preoccupation with ego-syntonic thoughts
Coexisting psychiatric disorders
MISCELLANEOUS
Requires supervision after meals and while using the restroom
Failed day treatment

Primary Care Treatment

Follow-up primary care visits are essential in the management of EDs. Close monitoring of the response of the patient and the family to suggested interventions is required to determine which patients can remain in primary care treatment (patients with early, mildly disordered eating), which patients need to be referred to individual specialists for co-management (mildly progressive disordered eating), and which patients need to be referred for interdisciplinary team management (EDs). Between the initial and subsequent visits, the patient can record daily caloric intake (food, drink, amount, time, location), physical activity (type, duration, intensity), and emotional state (e.g., angry, sad, worried) in a journal that is reviewed jointly with the patient in follow-up. Focusing on the recorded data helps the clinician to identify dietary and activity deficiencies and excesses, as well as behavioral and mental health patterns, and helps the patient to become objectively aware of the relevant issues to address in recovery.

Given the tendency of patients with AN to overestimate their caloric intake and underestimate their activity level, before reviewing the journal record it is important at each visit to measure weight, without underwear, in a hospital gown after voiding; urine specific gravity; temperature; and blood pressure and pulse in supine, sitting, and standing positions as objective data. In addition, a targeted physical examination focused on hypometabolism, cardiovascular stability, and mental status, as well as any related symptoms, should occur at each visit to monitor progress (or regression).

Referral to Mental Health Services

In addition to referral to a registered dietitian, mental health and other services are important elements of treatment of ED patients. Depending on availability and experience, these services can be provided by a psychiatric social worker, psychologist, or psychiatrist, who should team with the primary care provider. ARFID presents the challenge of working with patients' negative experiences of eating, or fear of trauma such as vomiting or choking, while also addressing inadequate nutritional needs. Although patients with AN often are prescribed a selective serotonin reuptake inhibitor (SSRI) because of depressive symptoms, there is no evidence of efficacy for patients at low weight; food remains the initial treatment of choice to treat depression in AN. SSRIs, very effective in reducing binge-purge behaviors regardless of depression, are considered a standard element of therapy in BN. SSRI dosage in BN, however, may need to increase to an equivalent of >60 mg of fluoxetine to maintain effectiveness.

Cognitive-behavioral therapy, which focuses on restructuring "thinking errors" and establishing adaptive patterns of behavior, is more effective than interpersonal or psychoanalytic approaches in ED patients. **Dialectical behavioral therapy**, in which distorted thoughts and emotional responses are challenged, analyzed, and replaced with healthier ones, with an emphasis on "mindfulness," requires adult thinking skills and is useful for older patients with BN. **Group therapy** can provide much needed support, but it requires a skilled clinician. Combining patients at various levels of recovery who experience variable reinforcement from dysfunctional coping behaviors can be challenging if group therapy patients compete with each other to be "thinner" or take up new behaviors such as vomiting.

The younger the patient, the more intimately the parents need to be involved in therapy. The only treatment approach with evidence-based effectiveness in the treatment of AN in children and adolescents is **family-based treatment**, exemplified by the Maudsley approach. This three-phase intensive outpatient model helps parents play a positive role in restoring their child's eating and weight to normal, then returns control of eating to the child, who has demonstrated the ability to maintain healthy weight, and then encourages healthy progression in the other domains of adolescent development. Features of effective family treatment include (1) an agnostic approach in which the cause of the disease is unknown and irrelevant to weight gain, emphasizing that parents are *not* to blame for EDs; (2) parents being actively nurturing and supportive of their child's healthy eating while reinforcing limits on dysfunctional habits, rather than an authoritarian "food police" or complete hands-off approach; and (3) reinforcement of parents as the best resource for recovery for almost all patients, with professionals serving as consultants and advisors to help parents address challenges.

Referral to an Interdisciplinary Eating Disorder Team

The treatment of a child or adolescent diagnosed with an ED is ideally provided by an interdisciplinary team (physician, nurse, dietitian, mental health provider) with expertise treating pediatric patients. Because such teams, often led by specialists in adolescent medicine at medical centers, are not widely available, the primary care provider might need to convene such a team. Adolescent medicine–based programs report encouraging treatment outcomes, possibly related to patients entering earlier into care and the stigma that some patients and parents may associate with psychiatry-based programs. Specialty centers focused on treating EDs are generally based in psychiatry and often have separate tracks for younger and adult patients. The elements of treatment noted earlier (cognitive-behavioral, dialectical behavioral, family-based), as well as individual and group treatment, should all be available as part of interdisciplinary team treatment. Comprehensive services ideally include intensive outpatient and partial hospitalization as well as inpatient treatment. Regardless of the intensity, type, or location of the treatment services, the patient, parents, and primary care provider are essential members of the treatment team. A recurring theme in effective treatment is helping patients and families reestablish connections that are disrupted by the ED.

Inpatient medical treatment of EDs is generally limited to patients with AN to stabilize and treat life-threatening starvation and to provide supportive mental health services. Inpatient medical care may be required to avoid refeeding syndrome in severely malnourished patients, provide nasogastric tube feeding for patients unable or unwilling to eat, or initiate mental health services, especially family-based treatment, if this has not occurred on an outpatient basis (see Table 41.7). Admission to a general pediatric unit is advised only for short-term stabilization in preparation for transfer to a medical unit with expertise in treating pediatric EDs. Inpatient psychiatric care of EDs should be provided on a unit with expertise in managing often challenging behaviors (e.g., hiding or discarding food, vomiting, surreptitious exercise) and emotional problems (e.g., depression, anxiety). Suicidal risk is small, but patients with AN might threaten suicide if made to eat or gain weight in an effort to "get their parents to back off."

An ED **partial hospital program** offers outpatient services that are less intensive than round-the-clock inpatient care. Generally held 4-5 days/week for 6 to 9 hours each session, partial hospital program services typically are group based and include eating at least two meals as well as opportunities to address issues in a setting that more closely approximates "real life" than inpatient treatment. That is, patients sleep at home and are free-living on weekends, exposing them to challenges that can be processed during the 25-40 hours each week in program, as well as sharing group and family experiences.

Supportive Care

In relation to pediatric EDs, support groups are primarily designed for parents. Because their daughter or son with an ED often resists the diagnosis and treatment, parents often feel helpless and hopeless. Because of the historical precedent of blaming parents for causing EDs, parents often express feelings of shame and isolation (www.maudsleyparents.org). Support groups and multifamily therapy sessions bring parents together with other parents whose families are at various stages of recovery from an ED in ways that are educational and encouraging. Patients often benefit from support groups after intensive treatment or at the end of treatment because of residual body image or other issues after eating and weight have normalized.

PROGNOSIS

With early diagnosis and effective treatment, ≥80% of youth with AN recover: They develop normal eating and weight control habits, resume menses, maintain average weight for height, and function in school, work, and relationships, although some still have poor body image. With weight restoration, fertility returns as well, although the weight for resumption of menses (approximately 92% of average body weight for height) may be lower than the weight for ovulation. The prognosis for BN is less well established, but outcome improves with multidimensional treatment that includes SSRIs and attention to mood, past trauma, impulsivity, and any existing psychopathology. Since the diagnosis of ARFID was only established in 2013, little is known about its long-term prognosis, although anecdotal evidence suggests that weight restoration is not actively resisted as it is in AN.

PREVENTION

Given the complexity of the pathogenesis of EDs, prevention is difficult. Targeted preventive interventions can reduce risk factors in older adolescents and college-age women. Universal prevention efforts to promote healthy weight regulation and discourage unhealthy dieting have not shown effectiveness in middle school students. Programs that include recovered patients or focus on the problems associated with EDs can inadvertently normalize or even glamorize EDs and should be discouraged.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 42

Disruptive, Impulse-Control, and Conduct Disorders

Erica H. Lee, Keneisha R. Sinclair-McBride, David R. DeMaso, and Heather J. Walter

The disruptive, impulse-control, and conduct disorders (CDs) are interrelated sets of psychiatric symptoms characterized by a core deficit in self-regulation of anger, aggression, defiance, and antisocial behaviors that typically begin in childhood or adolescence. These disorders include oppositional defiant, intermittent explosive, conduct, and other specified/unspecified disruptive/impulse-control/CDs, as well as pyromania, kleptomania, and antisocial personality disorder. Although all involve difficulty with both emotional and behavioral self-regulation, the disorders vary by the relative intensity of problems with emotional regulation (e.g., anger outbursts) vs behavioral regulation (e.g., defiance, aggression, violating the rights of others or societal norms).

DESCRIPTION

Oppositional defiant disorder (ODD) is characterized by a persistent pattern lasting at least 6 months of **angry/irritable mood, argumentative/defiant behavior, and/or vindictiveness** exhibited during interaction with at least one individual who is not a sibling (Table 42.1). For preschool children, the behavior must occur on most days, whereas in school-age children, the behavior must occur at least once a week. The severity of the disorder is considered *mild* if symptoms are confined to only one setting (e.g., at home, at school, at work, with peers), *moderate* if symptoms are present in at least two settings, and *severe* if symptoms are present in three or more settings.

Intermittent explosive disorder (IED) is characterized by **recurrent verbal or physical aggression** that is grossly disproportionate to the provocation or to any precipitating psychosocial stressors (Table 42.2). The outbursts, which are impulsive and/or anger-based rather than premeditated and/or instrumental, typically onset rapidly, last <30 minutes, and frequently occur in response to a minor provocation by a close intimate.

CD is characterized by a repetitive and persistent pattern over at least 12 months of **serious aggressive, destructive, and/or rule-violating behavior** in which the basic rights of others or major age-appropriate societal norms or rules are violated (Table 42.3). The symptoms of CD are divided into four major categories: aggression to people and animals, destruction of property, deceitfulness or theft, and serious rule violations (e.g., truancy, running away). Three subtypes of CD (which have different prognostic significance) are based on the age of onset: childhood-onset type, adolescent-onset type, and unspecified. A small proportion of individuals with CD exhibit characteristics (lack of remorse/guilt, callous/lack of empathy, unconcerned about performance, shallow/deficient affect) that qualify for the "with limited prosocial emotions" specifier. CD is classified as *mild* when few if any symptoms over those required for the diagnosis are present, and the symptoms cause relatively minor harm to others. CD is classified as *severe* if many symptoms over those required for the diagnosis are present, and the symptoms cause considerable harm to others. *Moderate* severity is intermediate between mild and severe.

Other specified/unspecified disruptive/impulse-control/CD (subsyndromal disorder) applies to presentations in which symptoms characteristic of the disorders in this class are present and cause clinically significant distress or functional impairment, but do not meet full diagnostic criteria for any of the disorders in this class.

EPIDEMIOLOGY

The prevalence of ODD is approximately 3%, and in preadolescents is more common in males than females (1.4:1). One-year prevalence rates for IED and CD approximate 3% and 4%, respectively. For CD, prevalence rates rise from childhood to adolescence and are higher among males than females.

CLINICAL COURSE

Oppositional behavior can occur in all children and adolescents at times, particularly during the toddler and early teenage periods when autonomy and independence are normative developmental tasks. Oppositional behavior becomes a concern when it is frequent, intense, persistent, and pervasive and when it affects the child's social, family, and/or academic life. Some of the earliest manifestations of oppositionality are stubbornness (3 years), defiance and temper tantrums (4-5 years), and argumentativeness (6 years). Approximately 65% of children with ODD exit from the diagnosis after a 3-year follow-up; earlier age at onset of oppositional symptoms conveys a poorer prognosis. ODD often precedes the development of CD and there is an approximately 30% higher likelihood of CD when ODD is comorbid with attention-deficit/hyperactivity disorder (ADHD). ODD also increases the risk for the development of depressive and anxiety disorders. The defiant, argumentative, and vindictive symptoms carry most of the risk for CD, whereas the angry, irritable mood symptoms carry most of the risk for depression and anxiety.

IED usually begins in late childhood or adolescence and appears to follow a persistent course over many years, with recurrent periods of impulsive and aggressive outbursts.

The onset of CD may occur as early as the preschool years, but the first significant symptoms usually emerge during the period from middle childhood through middle adolescence; onset is rare after age 16 years. Symptoms of CD vary with age as the individual develops increased physical strength, cognitive abilities, and sexual maturity. Symptoms that emerge first tend to be less serious (e.g., lying), while those emerging later tend to be more severe (e.g., sexual or physical assault). Severe behaviors emerging at an early age convey a poor prognosis. In the majority of individuals, the disorder remits by adulthood; in a substantial fraction, antisocial personality disorder develops. Individuals with CD also are at risk for the later development of mood, anxiety, posttraumatic stress, impulse-control, psychotic, somatic symptom, and substance-related disorders.

DIFFERENTIAL DIAGNOSIS

The disorders in this diagnostic class share a number of characteristics with each other as well as with disorders from other classes, and as such must be carefully differentiated. ODD can be distinguished from CD by the absence of physical aggression and destructiveness and by the presence of angry, irritable mood. ODD can be distinguished from IED by the lack of serious aggression toward others (e.g., physical assault). IED can be distinguished from CD by the lack of predatory aggression and other, nonaggressive symptoms of CD.

The oppositionality seen in ODD, the explosivity seen in IED, and the aggression/destructiveness seen in CD must be distinguished from those symptoms occurring in the context of other psychiatric disorders, particularly ADHD, depression, and bipolar, substance-related, autism spectrum, or psychotic disorders.

COMORBIDITY

Rates of ODD are much higher in children with ADHD, which suggests shared temperamental risk factors. Depressive, anxiety, and substance-related disorders are most often comorbid with IED. ADHD and ODD are both common in individuals with CD, and this comorbid presentation predicts worse outcomes. CD may also occur with anxiety, depressive, bipolar, learning, language, and substance-related disorders.

SEQUELAE

The disruptive, impulse-control, and CDs are associated with a wide range of psychiatric disorders in adulthood and with many other adverse outcomes, such as suicidal behavior, physical injury,

Table 42.1 DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least four symptoms from any of the following categories, and exhibited during interaction with at least one individual who is not a sibling:

ANGRY/IRRITABLE MOOD
1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

ARGUMENTATIVE/DEFIANT BEHAVIOR
4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

VINDICTIVENESS
8. Has been spiteful or vindictive at least twice within the past 6 mo.

Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 yr, the behavior should occur on most days for a period of at least 6 mo unless otherwise noted (Criterion A8). For individuals 5 yr or older, the behavior should occur at least once per week for at least 6 mo, unless otherwise noted (Criterion A8). Although these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp. 462–463. Copyright 2013. American Psychiatric Association.

Table 42.2 DSM-5 Diagnostic Criteria for Intermittent Explosive Disorder

A. Recurrent behavioral outbursts representing a failure to control aggressive impulses as manifested by either of the following:
1. Verbal aggression (e.g., temper tantrums, tirades, verbal arguments or fights) or physical aggression toward property, animals, or other individuals, occurring twice weekly, on average, for a period of 3 mo. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.
2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring with a 12 mo period.

B. The magnitude of aggressiveness expressed during the recurrent outbursts is grossly out of proportion to the provocation or to any precipitating psychosocial stressors.

C. The recurrent aggressive outbursts are not premeditated (i.e., they are impulsive and/or anger-based) and are not committed to achieve some tangible objective (e.g., money, power, intimidation).

D. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or as associated with financial or legal consequences.

E. Chronologic age is at least 6 yr (or equivalent developmental level).

F. The recurrent aggressive outbursts are not better explained by another mental disorder (e.g., major depressive disorder, bipolar disorder, disruptive mood dysregulation disorder, a psychotic disorder, antisocial personality disorder, borderline personality disorder) and are not attributable to another medical condition (e.g., head trauma, Alzheimer disease) or to the physiologic effects of a substance (e.g., a drug of abuse, a medication). For children ages 6-18 yr, aggressive behavior that occurs as part of an adjustment disorder should not be considered for this diagnosis.

Note: This diagnosis can be made in addition to the diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, or autism spectrum disorder when recurrent impulsive aggressive outbursts are in excess of those usually seen in these disorders and warrant clinical attention.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. p. 466. Copyright 2013. American Psychiatric Association.

delinquency and criminality, legal problems, substance use, unplanned pregnancy, social instability, marital failure, and academic and occupational underachievement.

ETIOLOGY AND RISK FACTORS

At the individual level, a number of neurobiologic markers (lower heart rate and skin conductance reactivity, reduced basal cortisol reactivity, abnormalities in the prefrontal cortex and amygdala, serotonergic abnormalities) have been variously associated with aggressive behavior disorders. Other biologic risk factors include pre-, peri-, and postnatal insults; cognitive and linguistic impairment, particularly language-based learning deficits; difficult temperamental characteristics, particularly negative affectivity, emotional reactivity, poor frustration tolerance, and impulsivity; certain personality characteristics (novelty seeking, reduced harm avoidance, and reward dependence); and certain cognitive characteristics (cognitive rigidity, hostile attributions for ambiguous social cues).

At the family level, a consistently demonstrated risk factor is ineffective parenting. Parents of behaviorally disordered children are more inconsistent in their use of rules, issue more and unclear commands, are more likely to respond to their child based on their own mood rather than the child's behavior, are more likely to utilize a harsh or neglectful parenting style, are less likely to monitor their children's whereabouts, and are relatively unresponsive to their children's prosocial behavior. Complicating this association is the consistent finding that temperamentally difficult children are more likely to elicit negative parenting responses, including physical punishment, which can exacerbate anger and oppositionality in the child. Other important family-level influences include impaired parent–child attachment, child maltreatment (physical and sexual abuse, neglect), exposure to marital conflict and domestic violence, family poverty and crime, frequent changes in caregivers, and family genetic liability (family history of the disorders in this class along with substance use, depressive, bipolar, schizophrenic, somatization, and personality disorders, as well as ADHD, have all been shown to be associated with the development of behavior disorders).

Peer-level influence on the development of behavior problems includes peer rejection in childhood and antisocial peer groups. Neighborhood influences include social processes such as collective efficacy, social control, and exposure to violence. Culturally, it is helpful to consider the context in which undesirable behaviors occur to better understand their function.

PREVENTION

An effective conduct problem prevention program was *Fast Track*, a multicomponent school-based intervention comprising a classroom curriculum targeted at conflict resolution and interpersonal skills, parent training, and interventions targeted at the school environment. Implemented in grades 1 through 10, former program participants at age 25 had a lower prevalence of any externalizing, internalizing, or substance

Table 42.3 DSM-5 Diagnostic Criteria for Conduct Disorder

A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least 3 of the following 15 criteria in the past 12 mo from any of the following categories, with at least one criterion present in the past 6 mo:
AGGRESSION TO PEOPLE AND ANIMALS 1. Often bullies, threatens, or intimidates others. 2. Often initiates physical fights. 3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun). 4. Has been physically cruel to people. 5. Has been physically cruel to animals. 6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery). 7. Has forced someone into sexual activity.
DESTRUCTION OF PROPERTY 8. Has deliberately engaged in fire setting with the intention of causing serious damage. 9. Has deliberately destroyed others' property (other than by fire setting).
DECEITFULNESS OR THEFT 10. Has broken into someone else's house, building, or car. 11. Often lies to obtain good or favors or to avoid obligations (i.e., "cons" others). 12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).
SERIOUS VIOLATIONS OF RULES 13. Often stays out at night despite parental prohibitions, beginning before age 13 yr. 14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period. 15. Is often truant from school, beginning before age 13 yr.
B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.
C. If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. pp. 469–471. Copyright 2013. American Psychiatric Association.

abuse problem than program nonparticipants. Program participants also had lower violent and drug crime conviction scores, lower risky sexual behavior scores, and higher well-being scores. Another useful prevention program, the *Seattle Social Development Project*, was also a multicomponent school-based intervention with teacher, parent, and student components targeting classroom management, interpersonal problem solving, child behavior management, and academic support skills. Implemented in grades 1 through 6, outcomes at age 19 years demonstrated that the intervention decreased lifetime drug use and delinquency for participant males compared with males in comparator communities but had no significant effects on females.

SCREENING/CASE FINDING

The parents of children presenting in the primary care setting should be **queried about angry mood or aggressive, defiant, or antisocial behavior as part of the routine clinical interview**. A typical screening question would be, "Does [name] have a lot of trouble controlling [his/her] anger or behavior?" A number of standardized broad-band screening instruments widely used in the primary care setting (e.g., *Pediatric Symptom Checklist*, *Strengths and Difficulties Questionnaire*) have items specific to angry mood and aggressive behavior, and as such can also be used to identify problems in this domain.

EARLY INTERVENTION

Youth (and/or their parents) presenting in the primary care setting who self-report or respond affirmatively to queries about difficulties managing angry mood or aggressive or antisocial behavior should be afforded the opportunity to talk about the situation with the pediatric practitioner (separately with older youth as indicated). By engaging in **active listening** (e.g., "I hear how you have been feeling. Tell me more about what happened to make you feel that way"), the pediatric practitioner can establish therapeutic rapport and begin to assess the onset, duration, context, severity, and complexity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., homicidality, assaultiveness, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within a few weeks to conduct a behavior assessment. At this follow-up visit, to assist with decision-making about appropriate level of care, a focused symptom rating scale can be administered (Table 42.4) and additional risk factors explored (e.g., see the previous section on "Etiology and Risk Factors").

For mild symptoms (manageable by the parent and not functionally impairing) and in the absence of major risk factors, guided self-help (anticipatory guidance) and monitoring with a scheduled follow-up may suffice. Guided self-help can include provision of educational materials (pamphlets, books, videos, workbooks, internet sites) that provide information to the youth about dealing with anger-provoking situations, and advice to parents about strengthening the parent–child relationship, effective parenting strategies, and the effects of adverse environmental exposures on the development of behavior problems. In a Cochrane review, media-based parenting interventions had a moderate positive effect on child behavior problems, either alone or as an adjunct to medication. An example of a self-help program for parents is the *Positive Parenting Program* (*Triple P*; http://www.triplep-parenting.com), online version, in which parents can purchase 6-8 modules of instruction addressing techniques for positive parenting and strategies for encouraging good behavior, teaching new emotional and behavioral skills, and managing misbehavior with youth from toddlers to teens (see Chapter 20).

If a mental health clinician has been **co-located or integrated into the primary care setting**, all parents of young children (universal prevention), as well as the parents of youth with mild behavior problems (indicated prevention), could be provided with a brief version of **behavioral parent training**. For example, *Incredible Years* (http://www.incredibleyears.com) has a 4-8 session universal prevention version to help parents promote their 2–6-year-old children's emotional regulation, social competence, problem solving, and reading readiness. A randomized trial in pediatric practices found that *Incredible Years* significantly improved parenting practices and 2–4-year-olds' disruptive behaviors compared to a wait-list control. *Incredible Years*' positive effects on parenting and child behavior have been found for populations diverse in race, cultural background, and socioeconomic status. Similarly, the *Triple P* program has seminar (three, 90 minute sessions), brief (15-30 min consultations), and primary care (four, 20-30 minute consultations) versions for the parents of youth from birth to the teenage years, specifically designed for implementation in the primary care setting. The *Triple P* interventions, supported by an extensive evidence base, focus on strengthening the parent–child relationship, identifying and monitoring the frequency of a problem behavior, and implementing and reviewing the effects of a targeted behavior plan. Meta-analyses have found that gains from *Triple P* are maintained over time.

TREATMENT

For youth who continue to have mild to moderate behavior problems after several weeks of guided self-help or a brief course of behavioral parent training, or who from the outset exhibit moderate to severe symptoms, or who have a history of maltreatment or severe family dysfunction or psychopathology, assessment and treatment in the specialty mental health setting by a child-trained mental health clinician should be provided.

The youth's problem behavior may predominantly occur at home, at school, with peers, or in the community, or it may be pervasive. If possible, interventions need to address each context specifically, rather than assuming generalizability of treatment. Thus, for behaviors mostly manifested in the home setting, behavioral parent training would be the treatment of

Table 42.4 Selected Anger/Aggression Rating Scales

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE (YR)	NO. OF ITEMS
Children's Aggression Scale	Parent, Teacher	5-18	33 (P), 23 (T)
Eyberg Child Behavior Inventory	Parent	2-16	36
Outburst Monitoring Scale	Parent	12-17	20
Sutter-Eyberg Student Behavior Inventory–Revised	Teacher	2-16	38
Vanderbilt ADHD Diagnostic Rating Scales	Parent, Teacher	6-12	55 (P), 43 (T)

choice, whereas for behaviors manifested mostly at school, consultation with the teacher regarding an assessment for a 504 plan or individualized education plan (IEP) can be useful. School-based services can include a functional behavioral analysis to determine the function of the problematic behavior for the child, and development of a behavioral intervention plan to direct the child toward alternative positive behaviors that can achieve the same goal. School-based services should be considered whenever a child is subjected to repeated disciplinary action in school or suspensions for misbehavior. When there are pervasive problems, including aggression toward peers, **cognitive-behavioral therapy (CBT)** with the child/teen can be employed in addition to the other interventions.

Behavioral parent training has been extensively studied for the treatment of youth problem behavior. These programs work by reshaping negative family patterns that may trigger or reinforce problem behaviors. They are typically 10-15 weeks in duration and focus on some combination of the following components: understanding social learning principles, developing a warm supportive relationship with the child, encouraging child-directed interaction and play, providing a predictable structured household environment, setting clear and simple household rules, consistently praising and materially or socially rewarding positive behavior, consistently ignoring annoying behavior (followed by praise when the annoying behavior ceases), giving effective commands, and consistently giving consequences (e.g., time-out, loss of privileges) for dangerous or destructive behavior. Other important targets for parenting training include understanding developmentally appropriate moods and behavior, managing difficult temperamental characteristics, fostering the child's social and emotional development, and protecting the child from traumatic exposures. Parent training can be implemented with families in individual or group formats. Specific parent training programs include *Incredible Years* and *Triple P,* described earlier, and *Parent–Child Interaction Therapy*, *Helping the Noncompliant Child,* and *Parent Management Training Oregon.* Predictors of nonresponse to these interventions have included greater initial symptom severity as well as involvement of the parent with child protection services.

Difficulty with adherence to the complete treatment regimen has limited the effectiveness of parent training programs. Estimates of premature termination are as high as 50–60%, and termination within five treatment sessions is not uncommon. Predictors of premature termination have included single-parent status, low family income, low parental education levels, young maternal age, minority group status, and life stresses.

CBT for youth with disruptive behavior also has been extensively studied. Common CBT techniques for disruptive behavior include identifying the antecedents and consequences of disruptive or aggressive behavior, learning strategies for recognizing and regulating anger expression, problem-solving and cognitive restructuring (perspective-taking) techniques, and modeling and rehearsing socially appropriate behaviors that could replace angry or aggressive reactions. Programs typically are delivered in 16-20 weekly sessions.

Multicomponent treatments for serious behavior disorders such as CD target the broader social context. **Multidimensional Treatment Foster Care**, delivered in a foster care setting for 6-9 months, typically includes foster parent training and support; family therapy for biologic parents; youth anger management, social skills, and problem-solving training; school-based behavioral interventions and academic support; and psychiatric consultation and medication management, when needed. **Multisystemic Therapy**, typically lasting 3-5 months, generally includes social competence training, parent and family skills training, medications, academic engagement and skills building, school interventions and peer mediation, mentoring and after-school programs, and involvement of child-serving agencies. Due to the strength of the supporting evidence, these multicomponent programs have been designated "well-established" treatments for adolescents involved in the juvenile justice system. Predictors of nonresponse to multicomponent treatments have included higher frequency of rule-breaking behavior and predatory aggression, higher psychopathy scores, and comorbid mood disorders.

Psychosocial interventions should be considered the first-line intervention; pharmacotherapy may provide benefit, particularly if psychosocial treatment has not led to adequate improvement. Three classes of medication, stimulants, α_2-adrenergic agonists, and atypical antipsychotics, have evidence for the management of impulsive, anger-driven aggressive behavior, although none is approved by the U.S. Food and Drug Administration (FDA) for this indication, except irritability/aggression in autism. Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist or developmental-behavioral pediatrician.

There are favorable effects of stimulants on oppositional behavior, anger outbursts, and aggression in youths, with or without comorbid ADHD. The doses of stimulants used for aggression are similar to those used for ADHD. An extended-release α_2-adrenergic agonist (guanfacine) is efficacious for oppositionality comorbid with ADHD, with a dose of 1-4 mg/day, dosed according to weight. There is evidence for efficacy of risperidone in reducing aggression and conduct problems in children age 5-18 years. The suggested usual daily dose of risperidone for severe aggression is 1.5-2 mg for children and 2-4 mg for adolescents, titrating up as needed and tolerated from starting doses of 0.25 mg (children) or 0.5 mg (adolescents). The use of this class of medication should be reserved for severe presentations in which the safety of self and/or others is compromised.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 weeks for atypical antipsychotics; shorter for stimulants and α-agonists) to determine the agent's effectiveness. The short-term goal of medication treatment is to achieve at least a 50% reduction in aggressive symptoms, as assessed by a focused symptom rating scale (see Table 42.4); the ultimate goal is to achieve symptom remission (below clinical cutpoint on the rating scale). A second medication of the same class can be considered if there is insufficient evidence of response to the maximal tolerated dose. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Discontinuation of the medication should be considered after a symptom-free interval.

LEVEL OF CARE

Most children and adolescents with a behavior disorder can be safely and effectively treated in the outpatient setting. Youths with intractable CD may benefit from residential or specialized foster care treatment, where more intensive treatments can be provided.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 43

Tantrums and Breath-Holding Spells

Keneisha R. Sinclair-McBride, Erica H. Lee, David R. DeMaso, and Heather J. Walter

Temper tantrums are common during early childhood. They are typically developmentally normative expressions of children's frustration with their own limitations or anger about not being able to get their way. It is important for parents to recognize the different triggers for tantrums to determine the best course of action to prevent or manage this behavior as it arises. Dealing with tantrum behavior can become very frustrating for parents and these feelings should be validated, while also helping make sure parents are aware that many tantrums can be averted by awareness or attunement to certain cues given by their child. In particular, parents should be aware that when a child is tired, hungry, or has to make a transition, it can be expected that the child will be more likely to have a tantrum because limit setting or unmet expectations may feel particularly overwhelming in these circumstances. In this case, it is advised that parents plan ahead and take a preventive stance by being aware of triggers and minimizing the potential for a tantrum. Parents should not make a tired or hungry child accompany them on an extended outing unless absolutely necessary. Additionally, depending on the child's developmental level, it is helpful to have a clear discussion ahead of time about the expectations in certain scenarios. An example of setting expectations to help prevent a tantrum is: "When we go into the store I need you to (1) stay with me, (2) keep your hands to yourself, and (3) not whine for treats. If you can do these three things, we can pick one treat to bring home." When children are able to demonstrate good control, their behavior should be acknowledged, praised, and rewarded when appropriate. This will increase the likelihood that they will engage in the desired response more often, even in situations they find frustrating.

When children tantrum as an expression of anger or sadness in not getting their way, parents may feel inclined to give in or respond to the negative behavior with yelling or threats. Unfortunately, these responses can reinforce and even escalate the oppositional behavior. Parents should attempt to avert defiance by giving the child choices (e.g., you can walk to the car on your own two feet or I can carry you). Active ignoring can be used for mild tantrum behaviors because paying attention, even negative attention, can be reinforcing. If a child is tantruming in a way that is unsafe, they can be removed from the unsafe situation and given a consequence by being placed in time-out. If the tantrum was to avoid a task, the child should be required to complete the task once time-out is over.

Breath-holding spells occasionally occur during a tantrum and can be frightening to parents. These are reflexive events in which the crying child becomes apneic, pale, or cyanotic, may lose consciousness, and occasionally will have a brief seizure. Parents are best advised to ignore breath holding during a tantrum once it has started. Without reinforcement, breath-holding generally disappears.

Subtypes of breath-holding spells include cyanotic, pallid, or mixed episodes. Cyanotic spells are the dominant type. Pallid spells may be similar to vasovagal-related syncopal events in older children and may be initiated by similar stimuli. Iron deficiency with or without anemia may be present, and some children with breath-holding spells respond to iron therapy. There is no increased risk of seizure disorders in children who have had a short seizure during a breath-holding spell. Medical conditions to rule-out in breath-holding spells (usually pallid) include seizures, Chiari crisis, familial dysautonomia, cardiac arrhythmias, cataplexy, hereditary hyperekplexia, and other central nervous system lesions.

The first key to the management of temper tantrums and breath-holding spells is to help parents intervene before the child is highly distressed. The parent can be instructed to calmly remind the child of the expected behavior and the potential consequence if the expected behavior does not occur. In addition, distraction to another activity or conversation may help. If the child does not comply, he or she should be placed in time-out for a period approximating 1 min for each year of age. Parents should state the reason the child is being placed in time-out beforehand in a calm and neutral tone, but they should not discuss the reasons during time-out. Once the time-out is over and the child is calm, it may be helpful for parents to discuss with the child the reasons for the child's frustration and their expectations for how the child will respond in the future.

Time-out can be effectively used in children up to approximately 10 years of age. Parents should also be advised to be mindful of their own reactions to their child's tantrum behavior to avoid an escalation of the child's behavior caused by an angry parental response.

If behavioral measures such as time-out fail, pediatricians must assess other aspects of parent–child interactions, such as the frequency of positive interactions, the consistency of parental responses to child behavior, and the ways that parents handle anger, before making further recommendations. In the absence of frequent positive parent–child interactions, time-out may not be effective, and inconsistent responding to problem behavior increases the likelihood of the negative behavior continuing. Children can be frightened by the intensity of their own angry feelings and by angry feelings they arouse in their parents. Parents should model the anger control that they want their children to exhibit. Some parents are unable to see that if they lose control themselves, their own angry behavior does not help their children to behave differently. Advising parents to calmly provide simple choices will help the child to feel more in control and to develop a sense of autonomy. Providing the child with options also typically helps reduce the child's feelings of anger and shame, which can later have adverse effects on social and emotional development. Providing choice also reduces power struggles between the parent and child and can aid in enhancing the parent–child relationship and building problem-solving skills.

When tantrum behavior, including breath holding, does not respond to parent coaching or is accompanied by head banging or high levels of aggression, referral for a mental health evaluation is indicated. Further evaluation is also recommended if tantrum behavior persists into the latency period and preteen years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 44

Lying, Stealing, and Truancy

Keneisha R. Sinclair-McBride, Erica H. Lee, David R. DeMaso, and Heather J. Walter

Young children lie for a multitude of reasons. Lies for this age group can be considered developmentally normative attempts at understanding language, communication, rules, and expectations. In early childhood, lying often occurs as a child experiments with language. By observing the reactions of parents, preschoolers learn about expectations for honesty in communication. Lying can also be a form of fantasy for children, who often describe things as they wish them to be rather than as they are. To avoid an unpleasant confrontation, a child who has not followed a rule or met an expectation may lie. At this stage, children often do not understand that lying only postpones a confrontation. Parents should keep in mind that lying behavior in this age group is rarely malicious or premeditated.

In *older children*, lying is generally an effort to cover up actions that do not fit into the child's conceptualization of themselves. Children in this age group may lie as an attempt to maintain self-esteem. Of course, lying is also often used to avoid a negative consequence for misbehavior. Older children are also more likely to intentionally leave out critical parts of a story in an attempt to deceive or avoid a negative consequence. Lying can also be promoted by poor adult modeling. Many children and adolescents lie to avoid adults' disapproval. If children and teens are responded to in harsh and punitive ways, they may lie to avoid this. Alternatively, lying may be used as a method of rebellion, especially in adolescence. Lying about forbidden activities, social media use, or other behaviors may be an attempt to continue to break the rules without detection. Chronic lying can occur in combination with several other antisocial behaviors and is a sign of underlying psychopathology or family dysfunction.

Parents should address lying by giving the child a clear message of what is acceptable. Sensitivity and support combined with limit setting are necessary for a successful intervention. Although habitual lying can become frustrating for parents, they should be discouraged from making accusations or focusing on catching their child in a lie and instead should work toward creating an atmosphere that makes it easier for their child to tell the truth. Parents should let the child know that telling the truth about a difficult situation will allow the parents to help them better problem-solve the issue at hand. Should a situation arise where a child has lied and the parents are aware of the true details, the lie should be confronted while providing the facts of what is known and also stating the desired or expected behavior. This should be done in a calm, neutral manner. For example, if a parent is aware that a child played video games instead of doing homework and the child denies it, the parent can state, "I notice that your homework is incomplete and that you are playing without permission. Our rule is that you complete homework first. There will be no more video games for the rest of the week." This response reminds the child how he can meet his goals in an acceptable way and an appropriate consequence can then be given. Parents should be encouraged to address the expectations for their home and children in a family meeting or in regular discussions with their child outside the context of the child's lying.

Regardless of age or developmental level, when lying becomes a common way of managing conflict, intervention is warranted. If this behavior cannot be resolved through the parents' understanding of the situation and the child's understanding that lying is not a reasonable alternative, a mental health evaluation is indicated.

STEALING

Many children steal something at some point in their lives. Often, when very *young children* steal, the behavior is an impulsive action to acquire something they want. A common example is the child who takes candy or a toy from the store shelf. If a parent notices this behavior, they can use the situation as a teaching opportunity to explain that community and family expectations are that we have to pay for things at the store and not take them without permission. It should not be expected that a very young child will be aware of all the rules around shopping or stealing. It may also be difficult for a child who has been used to being able to freely take whatever she wants to be aware of all the expected behaviors across different settings. When preschoolers and school-age children begin to steal frequently even after they have been told not to, the behavior may be a response to stressful environmental circumstances and requires further exploration and evaluation.

For some *older children*, stealing can be an expression of anger or revenge for perceived frustrations with parents or other authority figures. In such instances, stealing becomes one way the child and adolescent can manipulate and attempt to control their world. Stealing can also be learned from adults. Some children will report that the behavior is "exciting" for them, and they may also engage in the behavior for peer approval. In some cases, youth living in poverty may engage in the behavior as a survival mechanism.

Kleptomania, an impulse-control disorder, may begin in adolescence and is characterized by an intense impulse to steal objects that may not be rationally needed by the patient. There are often comorbid disorders such as anxiety, eating disorders, substance misuse, and depression. Treatment includes cognitive-behavioral therapy (CBT) in addition to various drugs such as lithium, naltrexone, and selective serotonin reuptake inhibitors (SSRIs).

Parents should work with their children to rectify stealing through restitution. Parents should require that their child return stolen items or pay for them with their own money (i.e., allowance or gift money). When this is not possible, another reasonable consequence should be given, such as losing a privilege or completing additional chores. When stealing is part of a pattern of broader conduct problems, referral for a mental health evaluation is warranted.

TRUANCY

Truancy and running away are never developmentally appropriate. Truancy may represent an unsafe environment of disorganization within the home including lack of appropriate supervision or older children being required to caretake for younger siblings. Truancy can also be a sign of developing conduct problems or behavioral health problems including depression or anxiety. When truancy occurs in younger children, there are usually psychosocial concerns with the parents or adult caretakers in the home that prevent them from following through with the required demands of getting their children to school each day. Families struggling with housing and food insecurity may have difficulties having their children attend school regularly. Parents with intellectual disability or their own mental health or substance abuse problems may become overwhelmed with managing the home and caring for their children; thus they might not consistently ensure their child gets to school. In addition, children might decide to remain at home to take care of parents who are impaired.

Truancy is more common in *preteens and adolescents* and can be a function of multiple factors, including but not limited to learning difficulties, social anxiety, depression, traumatic exposure, bullying, peer pressure, and substance use. In any of these cases, the child should be referred for further evaluation to assess the barriers to returning to school. Best practices for dealing with truancy resulting from school avoidance and anxiety include addressing the underlying psychologic symptoms causing the school avoidance and empowering parents, children, and school staff to work on a consistent plan for a return to school.

Younger children may threaten running away out of frustration or a desire to "get back at" parents. Older children who run away are almost always expressing a serious underlying problem within themselves or their family, including violence, abuse, and neglect. Adolescent runaways are at high risk for substance abuse and other risk-taking behaviors as well as at risk for being victims of abuse (e.g., sexual exploitation).

Youth exhibiting truancy or running away should be referred for a mental health evaluation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 45

Aggression

Keneisha R. Sinclair-McBride, Erica H. Lee, David R. DeMaso, and Heather J. Walter

Aggressive behavior is a serious symptom associated with significant morbidity and mortality. Early intervention is indicated for persistent aggressive behavior given that children may not simply "grow out of" this pattern of behavior. Aggressive tendencies are heritable, although environmental factors can promote aggression in susceptible children. Both enduring and temporary stressors affecting a family can increase aggressive behavior in children. Aggression in childhood is correlated with both poverty and chaotic family situations, including chronic unemployment, family discord, and exposure to community and domestic violence, criminality, and psychiatric disorders. Children born to teenage mothers and parents with limited resources and support are also at risk. Males are reported to be more aggressive than females. A difficult temperament and later aggressiveness are related. When children with temperament difficulties are responded to with punitive discipline strategies within the family environment, it can set up a cycle of increasing aggression. Aggressive children often misinterpret social cues in such a way that they perceive hostile intent in ambiguous or benign interactions, and then may react with verbal or physical aggression toward peers and parents.

It is important to differentiate the causes and motives for childhood aggression. Intentional aggression may be primarily instrumental (i.e., to achieve an end), primarily hostile (i.e., to inflict physical or psychologic pain), or primarily impulsive. Impulsive aggression can often be effectively managed with simple behavioral interventions at home. Children who are callous, not empathetic, and more consistently aggressive require intervention in the specialty mental health setting (see Chapter 42). These children are at high risk for suspension from school and eventual school failure. Because learning disorders are common in this population, aggressive children should be referred for screening. Aggressive behavior is often present in a variety of other psychologic conditions, including attention-deficit/hyperactivity and oppositional defiant, intermittent explosive, conduct, and disruptive mood dysregulation disorders (see Chapters 39 and 42).

Aggressive behavior in males is relatively consistent from the preschool period through adolescence. Without effective intervention, a male with a high level of aggressive behavior between 3 and 6 years of age has a high probability of carrying this behavior into adolescence. The developmental progression of aggression among females is less well studied. Fewer females show physically aggressive behavior in early childhood. However, interpersonal coercive behavior, especially in peer relationships, is seen in females. This behavior may be related to the development of physical aggression for females in adolescence (e.g., fighting) or other conduct problems (e.g., stealing).

Children exposed to aggressive models on television, in video games, or in play have more aggressive behavior compared with children not exposed to these models. Parents' anger and aggressive or harsh punishment can model behavior that children may imitate when they are physically or psychologically hurt. Parents' abuse may be transmitted to the next generation by several modes: children imitate aggression that they have witnessed; abuse can cause neurologic damage, which itself predisposes the child to violence; and internalized rage often results from abuse.

Aggressive behavior in youth is often oriented toward peers through bullying (see Chapter 15.1). Although it is developmentally normative for children to engage in some teasing behavior, bullying has a more serious tone. Bullying is defined as unwanted aggressive behavior in which there is a real or perceived imbalance of power or strength between the bully and the victim. Typically, it involves a pattern of behavior repeated over time. Although most often perceived as physical aggression, bullying can take on a variety of forms, including relational bullying, the most common form engaged in by females. Cyberbullying is a particular risk during the middle and high school years because of increased exposure and access to multiple social media platforms at this developmental stage. Parents should be advised to closely monitor their child's social media and maintain open communication with their children. Children may bully others because of impulse-control and social skills deficits, strong need for power and negative dominance, satisfaction in causing harm to others, or psychologic or material rewards. Children who bully are at risk for a variety of negative school and psychologic outcomes.

Victims of bullying are particularly at risk for negative outcomes, especially if the behavior is not addressed by adults. Victimization experiences are associated with school avoidance and school dropout, social isolation, somatic symptoms, and increased psychologic problems such as depression and anxiety. There have been numerous cases of suicide in children who reported a prior history of being bullied. Should a concern arise around bullying in the school setting, parents should be advised to reach out to their child's teacher, school counselor, and school administrative staff to have the bullying behavior addressed. Many schools also have a bullying intervention protocol that can be implemented, and state departments of education have antibullying policies with formal protocols to address concerns. Given the significant psychologic risks for both victims and perpetrators of bullying, it is essential that all children who are persistently involved in these incidents be referred for mental health evaluation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 46

Self-Injurious Behavior

Kiera M. James and Molly C. Adrian

Self-injurious behaviors, or deliberate engagement in self-inflicted harm, comprise both **suicidal behaviors** and **nonsuicidal self-injury (NSSI)** (see Chapter 40). NSSI, specifically, involves intentional self-inflicted damage to bodily tissue without the intent to die, though it can unintentionally result in significant harm or even death.

Suicidal behaviors and NSSI are both transdiagnostic behaviors occurring in the context of numerous psychiatry disorders as well as in the absence of any diagnosis at all. Nonetheless, the vast majority of youth who engage in NSSI meet diagnostic criteria for a psychiatry disorder. Self-injurious behavior may also be associated with developmental disabilities often as a manifestation of stereotypic movement disorder (Chapter 37.2).

Chapter 45

Aggression

Keneisha R. Sinclair-McBride, Erica H. Lee, David R. DeMaso, and Heather J. Walter

Aggressive behavior is a serious symptom associated with significant morbidity and mortality. Early intervention is indicated for persistent aggressive behavior given that children may not simply "grow out of" this pattern of behavior. Aggressive tendencies are heritable, although environmental factors can promote aggression in susceptible children. Both enduring and temporary stressors affecting a family can increase aggressive behavior in children. Aggression in childhood is correlated with both poverty and chaotic family situations, including chronic unemployment, family discord, and exposure to community and domestic violence, criminality, and psychiatric disorders. Children born to teenage mothers and parents with limited resources and support are also at risk. Males are reported to be more aggressive than females. A difficult temperament and later aggressiveness are related. When children with temperament difficulties are responded to with punitive discipline strategies within the family environment, it can set up a cycle of increasing aggression. Aggressive children often misinterpret social cues in such a way that they perceive hostile intent in ambiguous or benign interactions, and then may react with verbal or physical aggression toward peers and parents.

It is important to differentiate the causes and motives for childhood aggression. Intentional aggression may be primarily instrumental (i.e., to achieve an end), primarily hostile (i.e., to inflict physical or psychologic pain), or primarily impulsive. Impulsive aggression can often be effectively managed with simple behavioral interventions at home. Children who are callous, not empathetic, and more consistently aggressive require intervention in the specialty mental health setting (see Chapter 42). These children are at high risk for suspension from school and eventual school failure. Because learning disorders are common in this population, aggressive children should be referred for screening. Aggressive behavior is often present in a variety of other psychologic conditions, including attention-deficit/hyperactivity and oppositional defiant, intermittent explosive, conduct, and disruptive mood dysregulation disorders (see Chapters 39 and 42).

Aggressive behavior in males is relatively consistent from the preschool period through adolescence. Without effective intervention, a male with a high level of aggressive behavior between 3 and 6 years of age has a high probability of carrying this behavior into adolescence. The developmental progression of aggression among females is less well studied. Fewer females show physically aggressive behavior in early childhood. However, interpersonal coercive behavior, especially in peer relationships, is seen in females. This behavior may be related to the development of physical aggression for females in adolescence (e.g., fighting) or other conduct problems (e.g., stealing).

Children exposed to aggressive models on television, in video games, or in play have more aggressive behavior compared with children not exposed to these models. Parents' anger and aggressive or harsh punishment can model behavior that children may imitate when they are physically or psychologically hurt. Parents' abuse may be transmitted to the next generation by several modes: children imitate aggression that they have witnessed; abuse can cause neurologic damage, which itself predisposes the child to violence; and internalized rage often results from abuse.

Aggressive behavior in youth is often oriented toward peers through bullying (see Chapter 15.1). Although it is developmentally normative for children to engage in some teasing behavior, bullying has a more serious tone. Bullying is defined as unwanted aggressive behavior in which there is a real or perceived imbalance of power or strength between the bully and the victim. Typically, it involves a pattern of behavior repeated over time. Although most often perceived as physical aggression, bullying can take on a variety of forms, including relational bullying, the most common form engaged in by females. Cyberbullying is a particular risk during the middle and high school years because of increased exposure and access to multiple social media platforms at this developmental stage. Parents should be advised to closely monitor their child's social media and maintain open communication with their children. Children may bully others because of impulse-control and social skills deficits, strong need for power and negative dominance, satisfaction in causing harm to others, or psychologic or material rewards. Children who bully are at risk for a variety of negative school and psychologic outcomes.

Victims of bullying are particularly at risk for negative outcomes, especially if the behavior is not addressed by adults. Victimization experiences are associated with school avoidance and school dropout, social isolation, somatic symptoms, and increased psychologic problems such as depression and anxiety. There have been numerous cases of suicide in children who reported a prior history of being bullied. Should a concern arise around bullying in the school setting, parents should be advised to reach out to their child's teacher, school counselor, and school administrative staff to have the bullying behavior addressed. Many schools also have a bullying intervention protocol that can be implemented, and state departments of education have antibullying policies with formal protocols to address concerns. Given the significant psychologic risks for both victims and perpetrators of bullying, it is essential that all children who are persistently involved in these incidents be referred for mental health evaluation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 46

Self-Injurious Behavior

Kiera M. James and Molly C. Adrian

Self-injurious behaviors, or deliberate engagement in self-inflicted harm, comprise both **suicidal behaviors** and **nonsuicidal self-injury (NSSI)** (see Chapter 40). NSSI, specifically, involves intentional self-inflicted damage to bodily tissue without the intent to die, though it can unintentionally result in significant harm or even death.

Suicidal behaviors and NSSI are both transdiagnostic behaviors occurring in the context of numerous psychiatry disorders as well as in the absence of any diagnosis at all. Nonetheless, the vast majority of youth who engage in NSSI meet diagnostic criteria for a psychiatry disorder. Self-injurious behavior may also be associated with developmental disabilities often as a manifestation of stereotypic movement disorder (Chapter 37.2).

Although NSSI and suicidal behavior are distinct constructs based on the *intent* of the behavior, they are also highly comorbid. Research exploring the attitudes of youth who have engaged in NSSI indicates that there is a strong identification with suicide and death for this population, which makes NSSI a significant clinical issue and risk factor that cannot be ignored or minimized. Although some youth engage in repeated NSSI without ever attempting suicide, studies suggest that 50–75% of adolescents who have a history of NSSI will make a suicide attempt at some point.

NSSI has been documented in children as young as 7 years of age, with rates increasing from childhood (~8%) to adolescents (~18%), and decreasing during adulthood (~5.5%). Although traditionally thought to be more prevalent in females than males, NSSI occurs in both sexes. Emerging research suggests that, if present at all, gender differences in rates of NSSI are more likely in clinical than community populations. Notably, however, rates of NSSI are particularly high among transgender and gender nonconforming teens with up to 55% reporting past-year engagement in NSSI. There are no significant ethnicity or class differences among youth who engage in NSSI. Youth identified as those with the highest risk include females ages 15-19 and males 20-24.

Cutting is the most commonly reported form of NSSI. For those youth who engage in NSSI for the first time, approximately 20% will repeat the behavior within the same year; cutting is the most commonly repeated method of NSSI. Other methods of NSSI include scratching, burning, carving, piercing, hitting or punching, biting, picking at wounds, and digging nails into the skin. The most common areas of injury are the arms, legs, and torso, though NSSI may also occur on other parts of the body (e.g., breasts, genitals, groin, neck). Objects used in cutting include razors, scissors, broken glass, hard plastic, knives, staples, paper clips, or any other objects sharp enough to cause injury. Importantly, there are gender differences in methods such that females are more likely to engage in cutting, scratching, biting, hair pulling, and wound picking whereas males are more likely to engage in burning and self-battery, including hitting and head banging.

Youth often report exposure to NSSI before engaging in the behavior. Some youth report that they have friends who self-injure (e.g., cut) to attempt to alleviate negative emotions. Others may view stories of their peers' engagement in NSSI on websites and social media. Impressionable youth have also reported learning about NSSI for the first time from celebrities who have engaged in the behavior.

NSSI is associated with depression, anxiety, peer (bullying) victimization, social isolation, low self-esteem, substance abuse, eating disorders, impulsivity, poor school performance, delinquency, and neglectful or highly punitive parenting practices, as well as trauma, including a history of physical or sexual abuse. The behavior may begin as an impulsive response to internal distress for younger children, but for those who are older, the behavior can take on a self-reinforcing function. Youth may feel a sense of *relief* or *mastery* over negative emotions once the behavior has been completed. Some youth report that they engage in NSSI when feeling intense negative emotions, overwhelmed, or panicked to regulate their emotions. Others engage in the behavior when they are feeling numb, to "feel something" again. NSSI may also serve as a *distraction* from emotional pain, provide a sense of *control* over the body, or be used as a form of *self-punishment* for a perceived wrongdoing. NSSI may also function to *communicate* distress or strength or provide peer group *affiliation*. Youth often report that they are unable to resist the urge to engage in the behavior and will continue to feel increasing levels of distress until they engage in NSSI. Others plan or schedule the behavior, building it into their routine. Youth who view NSSI as an effective, private, and necessary coping strategy tend to have more dependence on the behavior and more resistance to stopping it.

Some adolescents and young adults engage in repeated NSSI for years without disclosing the behavior. Due to the shame associated with this stigmatized behavior, youth will often go to great lengths to keep it a secret. Some wear bracelets to cover scars on their arms or wear long sleeves in summer to hide the scarring. They report feeling ashamed of the behavior and fear rejection or disappointment from family and friends should they find out. At times, fear of being rejected or a disappointment to others can increase feelings of depression and anxiety and can serve to perpetuate the behavior. In contrast, others are more open about showing their scars and sharing their behavior with others. In either case, the behavior is a way to communicate or manage some level of *distress*. Many youth who engage in NSSI may never be seen in a hospital emergency department or by a mental health professional. Factors that protect against engagement in NSSI include a lack of awareness of, or exposure to, NSSI; an aversion to physical pain; an aversion to NSSI-related stimuli (e.g., blood); a positive view of the self; the use of other more adaptive emotion regulation strategies; and social norms. *Youth with repetitive NSSI should be referred to behavioral health services.* Effective treatment strategies include conducting a functional analysis around NSSI behavior, identifying and teaching alternative emotion regulation strategies, and reducing access to means to harm oneself. Reduction of NSSI has been observed with dialectical behavior therapy for adolescents, cognitive-behavioral therapy, cognitive analytic therapy, and mentalization-based therapy for adolescents. There are no psychopharmacologic treatments that have demonstrated efficacy; thus behavioral approaches should be prioritized.

Parents should be advised to monitor youth social media access and be aware of their peer group. Maintaining open communication can assist parents in recognizing an increase in concerning behaviors or patterns of behaviors. Parents should talk with their child about strategies for managing strong emotions and provide emotion coaching to support their child through experiences of distress. They should also be encouraged to talk with their child about their use of and exposure to drugs and alcohol as substance use can be associated with NSSI. Learning that their child has been engaging in self-injury can be frightening for parents because they are unsure of what to do or why their child is engaging in this behavior. It is important that parents receive psychoeducation about NSSI to reduce common misconceptions that make it difficult to understand their child's engagement in NSSI and respond effectively. Such information should be digestible and accurate, including written suggestions and examples. Parents should also seek mental health services for their child. *It is recommended that the child receive a full assessment for risk of suicide when NSSI is a concern.*

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) has classified NSSI as a condition requiring further study before consideration for possible placement in forthcoming editions of DSM. Proposed diagnostic criteria include self-inflicted injury without suicidal intent occurring on 5 or more days in the past year, with lack of suicidal intent either stated by the individual or inferred by the individual's repeated engagement in a behavior not likely to result in death. The individual expects that the self-injurious behavior will relieve a negative feeling or thought, resolve an interpersonal difficulty, or induce a positive feeling state. The self-injurious behavior is associated with interpersonal difficulties or negative feelings or thoughts, preoccupation with the intended behavior that is difficult to control, or frequent thoughts about the intended behavior. The proposed criteria also specify that the behavior is not socially sanctioned (e.g., body piercing, tattooing) and is not restricted to skin picking or nail biting. The behavior must be associated with significant *distress* or functional impairment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 47

Childhood Psychoses

Jennifer A. Zaspel and Rosa K. Kim

Psychosis is a severe disruption of thought, perception, and behavior resulting in *loss of reality testing*. Psychosis can occur as part of a mood disorder, such as major depressive disorder or bipolar I disorder; between mood disorder episodes, as in schizoaffective disorder; or without mood disorder episodes, as in schizophrenia. Transient psychotic episodes can arise during times of psychologic or physiologic stress in patients who are vulnerable because of personality, developmental, or genetic disorders. **Positive symptoms**, including delusions, hallucinations, disorganized thinking, and grossly disorganized behavior, are key features that define psychoses across disorders, likely because of shared pathophysiologic mechanisms. **Negative symptoms**, on the other hand, are most typical of schizophrenia.

Delusions are fixed, unchangeable, false beliefs held despite conflicting evidence. They may include a variety of themes, including persecutory, referential (the belief that irrelevant events or details in the world are related directly to oneself), somatic, religious, and grandiose. Delusions are considered bizarre if they are clearly implausible. **Hallucinations** are vivid, clear, perceptual disturbances that occur without external stimulus and have the full force and impact of normal perceptions. They may occur in any sensory modality; auditory hallucinations are the most common associated with psychosis. **Disorganized thinking** is inferred from an individual's speech by examining their thought process and thought content and is typically severe enough to impair one's ability to communicate. **Grossly disorganized behavior** may range from childlike silliness to unpredictable agitation to catatonic behavior. **Negative symptoms** include diminished emotional expression, avolition (decreased drive to perform purposeful tasks), alogia (lack of speech), anhedonia, and social withdrawal. Negative symptoms account for a substantial portion of the long-term morbidity associated with schizophrenia.

Given the centrality of hallucinations and delusions in making a diagnosis of a psychotic illness, their differentiation from developmentally normal fantasy is essential. When children are imagining, they control the fantasy and do not have the perceptual experience of seeing and hearing. When children are hallucinating, they do not control the hallucination. Almost two thirds of children will endorse at least one psychotic-like experience, most often a hallucination. When not persistent or accompanied by distress, these experiences are not usually a cause for concern. The largest population-based study to date evaluating psychotic symptoms and neurocognition in youth 11-21 years old found that those who endorsed more psychotic-like experiences than is typical for their age had reduced accuracy across neurocognitive domains, reduced global functioning, and increased risk of depression, anxiety, behavioral disorders, substance use, and suicidal ideation. Thus psychotic-like symptoms that are frequent, distressing, and cause impairment signal a need for further evaluation and monitoring; however, only a small minority of these children will develop persisting psychotic illnesses.

47.1 Schizophrenia Spectrum Disorders

Jennifer A. Zaspel and Rosa K. Kim

Schizophrenia spectrum and other psychotic disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) include brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder, psychotic disorder caused by another medical condition, catatonia associated with another mental disorder, catatonic disorder due to another medical condition, unspecified catatonia, delusional disorder, schizotypal personality disorder, and other specified/unspecified schizophrenia spectrum and other psychotic disorders.

DESCRIPTION

The **schizophrenia spectrum** and other psychotic disorders are primarily characterized by the presence of symptoms of psychosis, specifically delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior, and negative symptoms. **Brief psychotic disorder** is characterized by the duration of one or more of these symptoms for at least 1 day but less than 1 month followed by complete resolution. Emergence of symptoms may or may not be preceded by an identifiable stressor (Table 47.1). Although brief, the level of impairment in this disorder may be severe enough that supervision is required to ensure that basic needs are met and that the individual is protected from the consequences of poor judgment and cognitive impairment.

If two or more psychotic symptoms persist for between 1 and 6 months, the condition is called **schizophreniform disorder** (Table 47.2). To meet DSM-5 criteria for **schizophrenia**, two or more psychotic symptoms must have been present for a significant portion of time for at least 1 month (unless suppressed by treatment), and the level of psychosocial functioning must either be markedly below the level achieved before the onset or there is failure to achieve the expected level of functioning. In addition, there must be continuous signs of the disturbance for at least 6 months (Table 47.3).

Individuals with schizophrenia can display inappropriate affect, dysphoric mood, disturbed sleep patterns, and lack of interest in eating, or food refusal. Depersonalization, derealization, somatic concerns, and anxiety and phobias are common. Cognitive deficits are observed, including decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed. These individuals may have no

Table 47.1 DSM-5 Diagnostic Criteria for Brief Psychotic Disorder

A. Presence of one (or more) of the following symptoms. At least one of these must be (1), (2), or (3):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (e.g., frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior

Note: Do not include a symptom if it is a culturally sanctioned response.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 mo, with eventual full return to premorbid level of functioning.

C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With marked stressor(s) (brief reactive psychosis): If symptoms occur in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

Without marked stressor(s): If the symptoms do not occur in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

With postpartum onset: If onset is during pregnancy or within 4 wk postpartum.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p 94. Copyright 2013. American Psychiatric Association.

Table 47.2 DSM-5 Diagnostic Criteria for Schizophreniform Disorder

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (e.g., frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (i.e., diminished emotional expression or avolition)

B. An episode of the disorder lasts at least 1 mo but less than 6 mo. When the diagnosis must be made without waiting for recovery, it should qualified as "provisional."

C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

D. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With good prognostic features: This specifier requires the presence of at least two of the following features: onset of prominent psychotic symptoms within 4 wk of the first noticeable change in usual behavior or functioning; confusion or perplexity; good premorbid social and occupational functioning; and absence of blunted or flat affect.

Without good prognostic features: This specifier is applied if two or more of the previous features have not been present.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. pp 96–97. Copyright 2013. American Psychiatric Association.

Table 47.3 DSM-5 Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (e.g., frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (i.e., diminished emotional expression or avolition)

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved before the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least a month (or less if successfully treated).

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. pp 99–100. Copyright 2013. American Psychiatric Association.

insight or awareness of their disorder, which is a predictor of nonadherence to treatment, higher relapse rates, and poorer prognosis. Hostility and aggression can be associated with schizophrenia, although spontaneous or random assault is uncommon. Aggression is more frequent for younger males and for individuals with a history of violence, nonadherence with treatment, substance abuse, and impulsivity.

The essential features of schizophrenia are the same in childhood as in adulthood, but it is more difficult to make the diagnosis. In children, delusions and hallucinations may be less elaborate, visual hallucinations may be more common, and disorganized speech may be better attributed to an autism spectrum or communication disorder. In youth with schizophrenia, the most frequent psychotic symptoms are auditory hallucinations (82%), delusions (78%), thought disorder (66%), disorganized or bizarre behavior (53%), and negative symptoms (50%). Childhood-onset schizophrenia tends to represent a more severe form of the disorder spectrum, with more genetic risk factors, more brain abnormalities, and more prominent prepsychotic developmental disorders.

EPIDEMIOLOGY

Brief psychotic disorder is reported to account for 9% of first-onset psychosis in the United States and is more common in females than males. The incidence of schizophreniform disorders in the United States appears as much as fivefold less than that of schizophrenia. The lifetime prevalence of schizophrenia is approximately 0.3–0.7%, although variations are reported by race/ethnicity, across countries, and by geographic origin for immigrants. The male-to-female ratio is approximately 1.4:1. Males generally have poorer premorbid adjustment, lower educational achievement, more prominent negative symptoms, and more cognitive impairment than females. Childhood (preadolescent)-onset is exceedingly rare, with an incidence of less than 0.04%, and 2:1 ratio in males versus females.

CLINICAL COURSE

Brief psychotic disorder most often appears in adolescence or early adulthood, with the average age of onset in the mid-30s but can occur throughout the life span. A diagnosis of brief psychotic disorder requires *full remission* within 1 month of onset and gradual return to premorbid level of function. The age of onset of schizophreniform disorder is similar to that of schizophrenia. Recovery from an episode of the disorder is within 6 months; however, about 65% of patients relapse and eventually receive a diagnosis of schizophrenia or schizoaffective disorder. Abrupt onset, confusion, absence of blunted affect, and good premorbid functioning predict a better outcome in schizophreniform disorder.

Schizophrenia typically develops between the late teens and the mid-30s; onset before adolescence is rare. The peak age at onset for the first psychotic episode is in the early to mid-20s for males and in the late 20s for females. The onset may be abrupt or insidious, but most individuals manifest a slow and gradual development of symptoms, with about 50% of individuals complaining of depressive symptoms. The predictors of course and outcome are largely unexplained. The course is favorable in approximately 20% of cases; a small number of individuals are reported to recover completely. However, many remain chronically ill, with exacerbations and remissions of active symptoms, whereas others experience

progressive deterioration. Most individuals diagnosed with schizophrenia require some form of daily living support. Positive symptoms tend to diminish over time, and negative symptoms are the most persistent, along with cognitive deficits.

It is important to recognize hallmark phases in the assessment and management of schizophrenia. In the **prodrome phase**, most patients experience functional deterioration over the course of months (e.g., social withdrawal, idiosyncratic preoccupations, unusual behaviors, academic failure, deteriorating self-care skills, and/or dysphoria) before the onset of overt psychotic symptoms. The **acute phase** is characterized by prominent positive symptoms and deterioration in functioning and is the phase in which most patients present for care. During the **recovery phase**, negative symptoms and disorganization may persist as active psychosis remits. The **residual phase** has minimal to no positive symptoms, although negative symptoms may cause continued impairment. Some patients will experience **chronic impairment** despite adequate treatment.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the psychotic disorders is broad and includes reactions to substances/medications (dextromethorphan, LSD, hallucinogenic mushrooms, psilocybin, peyote, cannabis, stimulants, inhalants, corticosteroids, anesthetics, anticholinergics, antihistamines, amphetamines); medical conditions causing psychotic-like symptoms (Table 47.4; see Table 32.4); and other psychiatric disorders (depressive, bipolar, obsessive-compulsive, factitious, body dysmorphic, posttraumatic stress, autism spectrum, communication, personality). The differential diagnosis can be difficult because many conditions that can be mistaken for psychosis also increase the risk for it.

There are many indications that suggest psychotic symptoms may be related to a physical illness rather than a primarily psychiatric illness (Table 47.5). When psychotic symptoms are caused by identifiable medical conditions, there are often impairments in attention, orientation, recent memory, and intellectual function. Hallucinations associated with medical illness are more often tactile or visual, whereas auditory hallucinations are more common in primary psychotic disorders. Patients whose hallucinations are caused by medical illness are more likely to recognize that they do represent reality. A positive family or prior personal history of psychosis or other serious psychiatric illnesses is less likely to be present.

Autoimmune encephalitis caused by anti–*N*-methyl-D-aspartate (NMDA) receptor or other autoantibodies may manifest with psychosis, anxiety, depression, agitation, aggression, delusions, catatonia, visual or auditory hallucinations, disorientation, and paranoia in combination with sleep disturbances, autonomic dysfunction, dyskinesias, movement disorders, seizures, memory loss, and a depressed level of consciousness (Fig. 47.1; see Table 32.5). The cerebrospinal fluid (CSF) and MRI are usually, but not always, abnormal. The constellation of a relatively rapid onset psychosis and encephalitic features should suggest the diagnosis, although at presentation, behavioral problems may be the dominant feature (see Chapter 638.4; Table 47.6). A small number of patients present with purely psychiatric symptoms without other neurologic findings.

Determining when identifiable medical conditions are causing delirium with prominent psychotic symptoms may be difficult

Table 47.4 Possible Causes of Secondary Psychosis

	EXAMPLES	INVESTIGATIONS
Trauma	Traumatic head injury	CT, MRI
Autoimmune disorders	Systemic lupus erythematosus, NMDA receptor encephalitis and others	Autoantibody titers
Cytogenetic/congenital disorders	Velocardiofacial syndrome, agenesis of corpus callosum	Karyotyping, MRI
Toxic/substance-induced disorders	PCP, MDMA, LSD, cannabis, alcohol, cocaine, synthetic cannabinoids (bath salts) Lead, mercury or arsenic poisoning, ginseng, St. John's Wort, ma huang	Careful medication history; urine screen for drugs, heavy metal screen; trial off the offending agent
Iatrogenic disorders	Antimalarials, steroids, isoniazid	Careful medication history; trial off the offending agent
Cerebrovascular disorders	Stroke, subdural hematomas	CT, MRI
Space-occupying disorders	Cerebral tumors	CT, MRI
Metabolic disorders	Pheochromocytoma, metachromatic leukodystrophy, Wilson disease, adult Tay-Sachs disease, acute intermittent porphyria	Urinary catecholamines; arylsulfatase-A levels, copper and ceruloplasmin levels
Dietary disorders	Pellagra, B_{12} deficiency; thiamine deficiency	B_{12}, folate, thiamine levels
Sepsis/infectious disorders	Neurosyphilis, toxoplasmosis, HIV disease, encephalitis	RPR to rule out syphilis; HIV antibody titers; glucose, protein in CSF
Unknown cause/degenerative/demyelinating disorders	Lewy body dementia, Parkinson disease, Huntington disease, multiple sclerosis, Friedreich ataxia	MRI, CT, EEG, evoked potentials
Seizure disorders	Partial complex seizures, temporal lobe epilepsy	EEG, including sleep deprivation; telemetric EEG as indicated
Endocrine disorders	Hyperthyroidism, hypothyroidism, hyperparathyroidism	Serum calcium, thyroid/parathyroid hormone levels

CSF, Cerebrospinal fluid; EEG, electroencephalography; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; RPR, rapid plasma reagin.

Modified from Keshavan MS, Kaneko Y. Secondary psychoses: An update. *World Psychiatry*. 2013;12(1):4–15:Table 1, p 5.

Table 47.5 Red Flags and Features Suggesting Secondary Etiologies of Psychosis

ATYPICAL FEATURES
- Normal before event
- Very early (≤13 yr) age of onset
- Acute or subacute onset (days, ≤1 mo)
- Catatonia
- Dyskinesias
- Isolated misidentification delusion (Capgras syndrome)
- Depressed level of consciousness; disorientation; somnolence
- Cognitive and recent memory decline
- Poor orientation
- Intractability despite adequate therapy
- Rapidly progressive and/or fluctuating (polymorphic) symptoms
- Multimodal hallucinations: visual, auditory, olfactory, gustatory
- Poor response to antipsychotics

HISTORY
- Infectious prodrome (fever)
- New or worsening headache; change in headache pattern
- Paresthesias
- Past, current substance misuse
- Recent onset incontinence
- Anorexia/weight loss
- Risk factors for cerebrovascular disease or central nervous system infections
- Malignancy
- Immunocompromised status
- Head trauma
- Seizures
- Hepatobiliary disorders
- Systemic lupus erythematosus/other autoimmune diseases
- Biologic relatives with similar medical complaints
- Aphasia, mutism, dysarthria

PHYSICAL EXAMINATION
- Autonomic hyperactivity: tachycardia, hypertension, mydriasis, sleep disturbance
- Incoordination, or gait difficulty; nystagmus
- Toxidrome
- Abnormal neurologic exam: upper and lower motor neuron focal findings
- Movement disorder
- Neuroendocrine changes

DIAGNOSTIC ABNORMALITIES
- Abnormal electroencephalogram (extreme delta brush, diffuse slowing)
- Abnormal cerebrospinal fluid (pleocytosis: greater than 5 lymphocytes)
- Positive urine toxicology
- Screening laboratory tests including *N*-methyl-D-aspartate receptor and other antibodies
- Abnormal neuroimaging studies (unilateral or bilateral hippocampal/medial temporal lobe hyperdensities: limbic encephalitis)
- Hyponatremia

Modified from Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*. 2nd ed. Elsevier, 2023: Table 31.9, p 526

and is more fully explored in Chapter 48. In general, **delirium** is hallmarked by fluctuating levels of consciousness and is often associated with abnormalities in the neurologic exam and vital signs. Psychosis may be present in patients with delirium, but it will be accompanied by clear signs and symptoms of physical illness.

The diagnosis of a psychotic disorder should be made only after other explanations for the observed symptoms have been thoroughly considered. Mistakenly diagnosing psychosis when it is not present can lead to inappropriate use of antipsychotics with their attendant risks. The persistence, frequency, and form of possible psychotic symptoms, as well as the degree of accompanying distress and functional regression, need to be considered in determining the likelihood of an underlying psychotic pathophysiology.

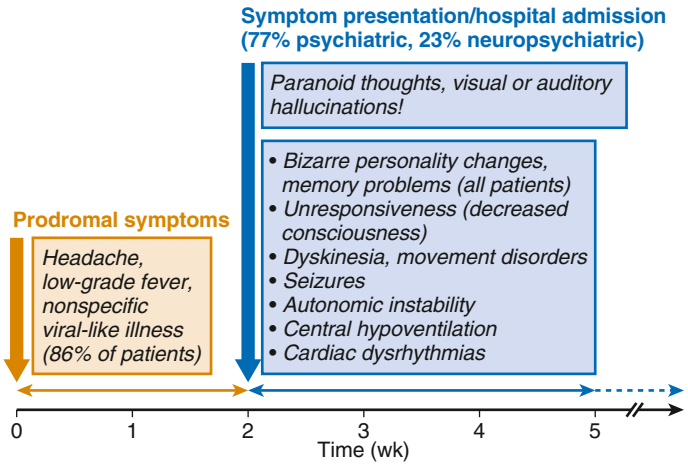

Fig. 47.1 Clinical characteristics of patients with anti–NMDA-receptor encephalitis. (*Modified from Wandinger KP, Saschenbrecker S, Stoecker W, Dalmau J. Anti-NMDA-receptor encephalitis: A severe, multistage, treatable disorder presenting with psychosis. J Neuroimmunol. 2011;231:86–91. Fig 2.*)

Table 47.6 Proposed Diagnostic Criteria for Autoimmune Psychosis

For a diagnosis of possible autoimmune psychosis:

The patient must have current psychotic symptoms of abrupt onset (rapid progression of <3 months) with at least one of the following:
- Currently or recently diagnosed with a tumor
- Movement disorder (catatonia or dyskinesia)
- Adverse response to antipsychotics, raising suspicion of neuroleptic malignant syndrome (rigidity, hyperthermia, or raised creatine kinase)
- Severe or disproportionate cognitive dysfunction
- A decreased level of consciousness
- The occurrence of seizures that are not explained by a previously known seizure disorder
- A clinically significant autonomic dysfunction (abnormal or unexpectedly fluctuant blood pressure, temperature, or heart rate)

If a patient has possible autoimmune psychosis, they should be investigated as per section 5 ("Consensus multimodal approach to the systematic investigation of patients with suspected autoimmune psychosis"), including electroencephalography, MRI, serum autoantibodies, and CSF analysis (including CSF autoantibodies). The results should lead to a diagnosis of non-autoimmune psychosis or probable/definite autoimmune psychosis.

For a diagnosis of probable autoimmune psychosis:

The patient must have current psychotic symptoms of abrupt onset (rapid progression of <3 mo) with at least one of the seven clinical criteria listed previously for possible autoimmune psychosis and at least one of the following:
- CSF pleocytosis of >5 white blood cells/μL
- Bilateral brain abnormalities on T2 weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes

Or two of the following:
- Electroencephalogram encephalopathic changes (i.e., spikes, spike-wave activity, or rhythmic slowing [intermittent rhythmic delta or theta activity] focal changes, or extreme delta brush
- CSF oligoclonal bands or increased IgG index
- The presence of a serum antineuronal antibody detected by cell-based assay

After exclusion of alternative diagnoses.

For a diagnosis of definite autoimmune psychosis:

The patient must meet the criteria for probable autoimmune psychosis with IgG class antineuronal antibodies in CSF.

Note that these criteria do not exclude a diagnosis being made in a patient with an acute onset (<3 mo) of psychosis, even if that patient has had a previous psychotic, other psychiatric, or encephalopathic episode that resolved.

From Pollak TA, Lennox BR, Müller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin [published correction appears in *Lancet Psychiatry*. 2019 Dec;6(12):e31]. *Lancet Psychiatry*. 2020;7(1):93–108: Panel 1, p 100.

COMORBIDITY

Among youth with schizophrenia, rates of comorbidity are approximately 34% for posttraumatic stress disorder, 34% for attention-deficit/hyperactivity and/or disruptive behavior disorders, and 32% for substance abuse/dependence. At least 10–20% of children diagnosed with schizophrenia have intellectual delays; it is unclear if this is related to the impact of the illness on cognitive testing. Children with schizophrenia also demonstrate impairments in language, communication, and information processing. Co-occurring *rates* of schizophrenia and autism spectrum disorder (ASD) are higher than would be expected in general populations; childhood-onset schizophrenia has been linked to ASD, with an estimated 30–50% of cases preceded by a diagnosis of an ASD.

SEQUELAE

Follow-up studies of early-onset schizophrenia suggest moderate to severe impairment across the life span. Poor outcome is predicted by low premorbid functioning, insidious onset, higher rates of negative symptoms, childhood onset, and low intellectual functioning. When followed into adulthood, youth with schizophrenia demonstrated greater social deficits, lower levels of employment, and lower likelihood of independent living, relative to those with other childhood psychotic disorders.

Approximately 5–10% of individuals with schizophrenia die by suicide or accidental death directly related to behaviors caused by psychotic thinking, approximately 20% attempt suicide on one or more occasions, and many more have suicidal ideation. Life expectancy is reduced in individuals with schizophrenia because of associated medical conditions; a shared vulnerability for psychosis and medical disorders may explain some of the medical comorbidity of schizophrenia.

ETIOLOGY AND RISK FACTORS

Etiologic evidence for schizophrenia supports a neurodevelopmental and neurodegenerative model, with multiple genetic and environmental risks having important roles. It has been hypothesized that although psychotic disorders have their origins in early development, it is not until youth are in their mid-teens that the underlying neural structures manifest the disabling functional deficits and resultant psychotic symptoms.

Genetic Factors

The lifetime risk of developing schizophrenia is 5-20 times higher in first-degree relatives of affected probands than the general population. Concordance rates of 40–60% and 5–15% have been reported in monozygotic and dizygotic twins, respectively. Genome-wide association studies have implicated variants in >100 different genes that are statistically significant but individually only demonstrate small increases in the risk for schizophrenia. The risk for schizophrenia increases with increasing burden of these risk alleles; approximately 30% of the risk is attributable to common genetic variants. Rare variants of larger effect have also been implicated as increasing risk. Some rare copy number variants, where segments of the genome encompassing many genes are either duplicated or deleted, increase the risk of schizophrenia more markedly, with odds ratios of 2-25. Although these copy number variants may be responsible for 0.5–1.0% of typical adolescent/adult-onset schizophrenia, data indicate that they are responsible for about 12% of schizophrenia cases with onset before age 13 years.

Environmental Factors

In utero exposure to maternal famine, advanced paternal age, prenatal infections, obstetric complications, marijuana use, and immigration have been hypothesized to contribute to the development of schizophrenia. Cannabis use in teens is associated with a higher risk of eventually developing psychosis, but it is difficult to determine whether this is related to drug effects or an unmasking of underlying disease potential. Environmental exposures may mediate disease risk through direct neurologic damage, gene-environment interactions, epigenetic effects, or de novo mutations. There is no evidence that psychologic or social factors alone cause schizophrenia. Rather, environmental factors potentially interact with biologic risk factors to mediate the timing of onset, course, and severity of an acute episode. Expressed emotion within the family setting can influence the onset and exacerbation of acute episodes and relapse rates.

NEUROANATOMIC ABNORMALITIES

Increased lateral ventricle volumes, along with reductions in hippocampus, thalamus, and frontal lobe volumes, have been reported in schizophrenia. Youth with schizophrenia have reductions in gray matter volumes and reduced cortical folding. Neurotransmitter systems, particularly central nervous system dopamine circuits, are hypothesized to have a key role in the pathophysiology of schizophrenia. The dopamine hypothesis is derived in part from the identification of D_2 receptor blockade as the mechanism for the action of antipsychotic medications. On neurologic exam, those with schizophrenia are often found to have deficits in smooth-pursuit eye movements and autonomic responsivity.

PREVENTION

There has been significant interest in prospectively identifying youth at risk for schizophrenia spectrum and other psychotic disorders to provide early intervention before the development of a chronic psychotic disorder. Those considered to be at clinically high risk may express a variety of unusual or odd beliefs. They may have unusual perceptual experiences, including frank hallucinations, but retain insight into their unreality. Their speech and behavior may be unusual, but not overtly disorganized. Individuals who had been socially active may become withdrawn. The symptoms are described as present at least once per week for the past month and have begun or worsened over the past year. Although the symptoms are less severe and more transient than in a psychotic disorder, 20–40% of patients with these attenuated symptoms appear to go on to a psychotic disorder within several years of symptom presentation. There is evidence that premorbid lower cognitive and social skills as well as a history of substance abuse contribute to the risk of developing a schizophrenia spectrum disorder.

Some evidence indicates that antipsychotic medication may delay conversion to a psychotic disorder and ameliorate attenuated symptoms in active treatment, yet there appear to be no lasting effects after the medication is withdrawn. Additionally, the known adverse effects of antipsychotics argue against their being used broadly to prevent psychosis in these patients, given that about 65% do not go on to develop a psychotic disorder.

Antidepressants have been associated with symptomatic improvement in adolescents who are at risk of developing a schizophrenia spectrum disorder. Psychologic interventions, including social skills, cognitive, and interaction training programs, as well as educational family interventions and cognitive-behavioral therapy (CBT), are reported to improve symptoms and psychosocial functioning in youth with early symptoms and decrease the rate of conversion to psychosis.

Despite improvements in diagnostic predictive validity, significant concern remains regarding a high false-positive rate that may cause individuals to be stigmatized or exposed to unnecessary treatment. In this context, youth with early symptoms suggestive of psychosis should be referred to a child and adolescent psychiatrist or other qualified mental health specialist.

SCREENING

There are no validated tools for screening for schizophrenia spectrum disorders in children or adolescents. A widely accepted premorbid phenotype for childhood-onset schizophrenia has yet to be established.

Of children with childhood-onset schizophrenia, 67% show disturbances in social, motor, and language functioning, as well as learning disabilities. Many meet criteria for comorbid ASDs, mood disorders, and anxiety disorders.

Pediatric practitioners can make general inquiries of youth and their parents regarding problems with thinking or perceptions, including hallucinations and delusions. For younger children, the clinician must ensure that the child understands the questions. True psychotic symptoms are generally confusing to the individual. Highly descriptive, detailed, organized, and situation-specific reports are less likely to represent true psychosis. Overt evidence of psychosis is not always present on mental status examination, but in the absence of this, the validity of symptom reports should be scrutinized. Given the strong genetic component of schizophrenia spectrum disorders, a thorough family history is key in supporting the workup of psychosis in children. Youth presenting with possible psychosis warrant assessment and treatment by a child and adolescent psychiatrist or other qualified mental health specialist.

ASSESSMENT

The diagnostic assessment of schizophrenia in youth is uniquely complicated; misdiagnosis is common. Most children who report hallucinations do not meet criteria for schizophrenia, and many do not have a psychotic illness. The persistence, frequency, and form of possible psychotic symptoms; the presence of distress; functional impairment; and insight need to be considered in arriving at a diagnosis. Expertise in childhood psychopathology and experience in assessing reports of psychotic symptoms in youth are important prerequisite skills for clinicians evaluating youth for psychosis. Comprehensive diagnostic assessments, which reconcile mental status findings with the rigorous application of diagnostic criteria, help improve accuracy.

All children who present with psychotic symptoms should receive a thorough pediatric and neurologic evaluation to focus on ruling out nonpsychiatric causes of psychosis (see Tables 47.4 and 32.4). There is no neuroimaging or laboratory test that establishes a diagnosis of schizophrenia spectrum disorders; these diagnostic tests are instead used to further assist with the medical evaluation while also establishing baseline laboratory parameters for monitoring medication therapy. Routine laboratory testing typically includes blood counts; basic metabolic panel; and assessment of liver, renal, and thyroid function. More extensive evaluation is indicated for atypical presentations, such as a gross deterioration in cognitive and motor abilities, focal neurologic symptoms, or delirium (see Table 47.5). Neuroimaging may be indicated when neurologic deficits are present, or EEG may be indicated for a clinical history suggestive of seizures or encephalopathy. Toxicology screens are indicated for acute onset or exacerbations of psychosis when exposure to drugs of abuse cannot be ruled out. Genetic testing is indicated if there are associated dysmorphic or syndromic features. Tests to rule out specific syndromes or diseases are indicated for clinical presentations suggestive of a specific syndrome (e.g., amino acid screens for inborn errors of metabolism, ceruloplasmin for Wilson disease, porphobilinogen for acute intermittent porphyria, neuronal antibodies for autoimmune encephalitis). Neuropsychologic testing cannot establish the diagnosis but may be important for documenting cognitive deficits for academic planning.

TREATMENT

Treatment goals include decreasing psychotic symptomatology, directing the child toward a developmentally typical trajectory, and reintegrating the child into the home and community. Children and families facing schizophrenia spectrum disorders require an array of mental health services to address their psychologic, social, educational, and cultural needs. Given the insidious onset and chronic course of these disorders, the patient must be followed longitudinally, with periodic reassessment to hone diagnostic accuracy and tailor services to meet the patient's and family's needs. Integrated psychopharmacologic, psychotherapeutic, psychoeducational, and case management services are often necessary.

Psychoeducation about the illness with an assessment of the potential role of stigma in treatment participation is critical for improving adherence with treatment recommendations. Assessing a child's strengths and vulnerabilities as well as available environmental resources is critical in devising an effective treatment plan. School and community liaison work to develop and maintain a day-to-day schedule for the patient is important. Specialized educational programs should be considered within the school system. Cognitive remediation has led to some promising gains in planning ability and cognitive flexibility. Effective and collaborative communication among the family, the pediatrician, a child and adolescent psychiatrist, and other mental health providers increases the potential for the patient's optimal functioning.

Pharmacotherapy

First-generation (typical) and second-generation (atypical) antipsychotic medications are effective in reducing psychotic symptoms. Antipsychotics appear to outperform placebo and to have approximately equal effectiveness, except for ziprasidone and clozapine, which may be less and more effective than the others, respectively. Risperidone, aripiprazole, quetiapine, olanzapine, and lurasidone are FDA-approved second-generation antipsychotics for treating schizophrenia in patients 13 years and older, and paliperidone for those 12 years and older. Several first-generation antipsychotics are also FDA-approved for children and adolescents. The choice of which agent to use first is typically based on FDA approval status, side effect profile, patient and family preference, clinician familiarity, and cost. Although clozapine is effective in treating both positive and negative symptoms, it has a risk for agranulocytosis and seizures, which limits its use to those patients with *treatment-resistant* disorders. Ziprasidone and paliperidone are associated with QT prolongation; this finding along with the inferior effectiveness of ziprasidone limits its use with children and adolescents. All antipsychotics carry some degree of risk of sedation, weight gain, and extrapyramidal symptoms (see Chapter 33).

Most patients require long-term treatment and are at significant risk of relapse if their medication is discontinued. However, more than 75% of youth with schizophrenia discontinue their medication within 6 months. Common reasons for discontinuation include lack of efficacy, intolerable side effects, and general lack of adherence with treatment plan. Many patients will continue to experience some degree of positive or negative symptoms, requiring ongoing treatment. Patients should maintain regular physician contact to monitor symptom course, side effects, and adherence. Depot or long-acting injectable antipsychotics have not been studied well in pediatric age groups and have inherent risks with long-term exposure to adverse side effects. They are typically only considered when there is a well-documented history of psychotic symptoms as well as poor medication adherence.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) may be used with severely impaired adolescents if medications are either not helpful or cannot be tolerated. It has not been systematically studied in children, but its use is supported in adults with schizophrenia, typically in combination with antipsychotic therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

47.2 Non-Schizophrenia Spectrum Psychotic Disorders

Jennifer A. Zaspel and Rosa K. Kim

Beyond the schizophrenia spectrum of psychotic disorders, substance/medication-induced psychotic disorder (Table 47.7) and psychotic disorder due to another medical condition (Table 47.8) can be seen in pediatric populations.

The hallmark features of **substance/medication-induced psychosis** are delusions and hallucinations that develop within the context of substance exposure: typically a drug of abuse, a medication, or a toxin exposure (see Tables 47.4 and 32.4 for a brief list). Synthetic cannabinoids (bath salts) are a common drug producing psychotic effects. A substance-induced psychosis is distinguished from a primary psychotic disorder by examining the onset and course of symptoms; the onset of a primary psychosis may precede substance exposure and may occur during periods of sustained abstinence. Once they arise, psychotic symptoms may be present as long as substance exposure is continued. Although the prevalence of substance/medication-induced psychotic disorder in the general population is unknown, it is estimated that 7–25% of individuals presenting with a first episode of psychosis meet criteria for this diagnosis. Symptoms can be managed with antipsychotics until they remit, which often happens shortly after the offending substance is removed. Patients can develop a schizophrenia spectrum disorder following substance exposure, but this tends to occur in individuals who are at high risk for developing a primary psychotic disorder regardless of substance exposure.

Psychosis due to **another medical condition** (see Table 47.8) is also characterized by prominent hallucinations or delusions, but history, physical exam, and laboratory findings support a direct pathophysiologic connection between these symptoms and another medical condition (see Tables 32.4, 47.4, 47.5, and 47.8). Any sensory modality can be affected by hallucinations. The hallucinations vary in complexity depending on their etiology, and their description may be highly suggestive of a particular diagnosis, like olfactory hallucinations in temporal lobe epilepsy. Associations between delusions and medical conditions tend to be less specific. The list of medical conditions that can cause psychosis is long, and includes epilepsy, strokes, neoplasms, endocrine disorders, genetic syndromes like velocardiofacial syndrome, autoimmune disorders, and the permanent sequelae of toxic exposures (see Tables 32.4 and 47.4). Notably, delirium is excluded from psychosis due to another medical condition. When narrowing the differential between schizophrenia spectrum disorders, psychosis due to another medical condition, and any other etiology, it is important to consider the timeline of symptoms, the presence of features that are atypical for a primary psychosis, and the possibility of substance or medication exposure. Treatment of the underlying medical condition may or may not require adjunctive antipsychotic treatment for management of psychosis, and the course and prognosis of the psychosis will likely depend on the etiology.

A notable example of psychosis due to another medical condition is **psychosis associated with epilepsy.** The disorder manifests with delusions or hallucinations associated with poor insight, and can be further differentiated into ictal, interictal, and postictal psychosis. Ictal-induced psychosis is a form of **nonconvulsive status epilepticus**, usually a complex partial status that can last for hours to days and is associated with periods of impaired consciousness. Brief interictal psychosis can last days to weeks and is associated with paranoia, delusions, and auditory hallucinations. Chronic interictal psychosis resembles schizophrenia and manifests with paranoia, visual hallucinations, and catatonia. Postictal psychosis is the most common type (observed in 2–7% of patients with epilepsy) and lasts up to 1 week and then spontaneously remits. The diagnosis requires a strong index of suspicion and EEG monitoring. Treatment requires appropriate anticonvulsant drugs and, if the psychosis persists, initiating low-dose antipsychotic medication.

Table 47.7 DSM-5 Diagnostic Criteria for Substance/Medication Induced Psychotic Disorder

A. Presence of one or both of the following symptoms:
   1. Delusions
   2. Hallucinations
B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):
   1. The symptoms of Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
   2. The involved substance/medication is capable of producing the symptoms in Criterion A.
C. The disturbance is not better explained by a psychotic disorder that is not substance/medication induced.
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With onset during intoxication: If the criteria are met for intoxication with the substance and the symptoms develop during intoxication.

With onset during withdrawal: If the criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp 110–115. Copyright 2013. American Psychiatric Association. .

Table 47.8 DSM-5 Diagnostic Criteria for Psychotic Disorder Due to Another Medical Condition

A. Prominent hallucinations or delusions.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiologic consequence of another medical condition.
C. The disturbance is not better explained by another mental disorder.
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify whether:

With delusions: If delusions are the predominant symptom.

With hallucinations: If hallucinations are the predominant symptom.

From the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. pp 115–116. Copyright 2013. American Psychiatric Association. .

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography..

47.3 Catatonia in Children and Adolescents

Jennifer A. Zaspel and Rosa K. Kim

Catatonia is a constellation or syndrome of psychomotor features, the most notable of which are decreased purposeful motor activity, decreased engagement in interviews and physical exams, or excessive and peculiar motor activity. The most characteristic symptoms are waxy flexibility and bizarre poses, but these may or may not be present (Table 47.9). Diagnosis can be challenging, as psychomotor disturbances can range from unresponsiveness to agitation. Catatonia has been associated with a broad array of conditions affecting children, adolescents, and adults, including psychotic, affective, drug-related, autoimmune, encephalitic, and neurodevelopmental conditions (Table 47.10). Autoimmune encephalitis may be the most common etiology in childhood. In addition, catatonia *(autism shut down syndrome)* may complicate ASD (Chapter 58).

Table 47.9 Catatonia

Excitement: Extreme hyperactivity; constant motor unrest, which is apparently nonpurposeful
Immobility/stupor: Extreme hypoactivity, immobility; minimally responsive to stimuli
Mutism: Verbally unresponsive or minimally responsive
Staring: Fixed gaze, little or no visual scanning of environment, decreased blinking
Posturing/catalepsy: Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting)
Grimacing: Maintenance of odd facial expressions
Echopraxia/echolalia: Mimics of examiner's movements/speech
Stereotypy: Repetitive, non–goal-directed motor activity (e.g., finger play; repeatedly touching, patting, or rubbing self)
Mannerisms: Odd, purposeful movements (hopping or walking tiptoe, saluting passersby, exaggerated caricatures of mundane movements)
Verbigeration: Repetition of phrases or sentences
Rigidity: Maintenance of a rigid posture despite efforts to be moved
Negativism: Apparently motiveless resistance to instructions or to attempts to move/examine the patient; contrary behavior does the opposite of the instruction
Waxy flexibility: During reposturing of the patient, offers initial resistance before allowing themselves to be repositioned (similar to that of bending a warm candle)
Withdrawal: Refusal to eat, drink, or make eye contact
Impulsivity: Suddenly engaging in inappropriate behavior (e.g., runs down the hallway, starts screaming, or takes off clothes) without provocation; afterward, cannot explain
Automatic obedience: Exaggerated cooperation with examiner's request, or repeated movements that are requested once
Passive obedience *(mitgehen)*: Raising arm in response to light pressure of finger, despite instructions to the contrary
Negativism *(gegenhalten)*: Resistance to passive movement that is proportional to strength of the stimulus; response seems automatic rather than willful
Ambitendency: Appears stuck in indecisive, hesitant motor movements
Grasp reflex: Striking the patient's open palm with two extended fingers of the examiner's hand results in automatic closure of the patient's hand
Perseveration: Repeatedly returns to the same topic or persists with the same movements
Combativeness: Belligerence or aggression, usually in an undirected manner, without explanation
Autonomic abnormality: Abnormality of body temperature (fever), blood pressure, pulse rate, respiratory rate, inappropriate sweating

From Dhossche DM, Wachtel LE. Catatonia is hidden in plain sight among different pediatric disorders: A review article. *Pediatr Neurol*. 2010;43:307–315.

Table 47.10 Conditions Associated with Catatonia

Psychotic Disorders
- Paranoid schizophrenia, catatonic schizophrenia, psychosis, autism, Prader-Willi syndrome, intellectual impairment

Mood Disorders
- Bipolar disorder: manic or mixed episodes

Major Depressive Disorder

Medical Conditions
- Hyper-hypothyroidism, euthyroid autoimmune thyroiditis, Addison disease, infections, electrolyte imbalances, pathogenic variants in *SCN2A* gene, systemic lupus erythematosus

Neurologic Conditions
- Epilepsy, strokes, traumatic brain injury, multiple sclerosis, infectious and autoimmune encephalitis, acute disseminated encephalomyelitis, neuromyelitis optica spectrum

Drugs
- Withdrawal: benzodiazepines, L-dopa, gabapentin
- Overdose: LSD, PCP, cocaine, MDMA (Ecstasy), disulfiram, levetiracetam

LSD, Lysergic acid; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; PCP, phencyclidine. Adapted from Weder ND, Muralee S, Penland H, Tampi RR. Catatonia: A review. *Ann Clin Psychiatry*. 2008;20(2):97–107:Table 2.

Table 47.11 DSM-5 Criteria for Catatonia Due to Another Medical Condition

A. The clinical picture is dominated by three (or more) of the following symptoms:
   1. Stupor (i.e., no psychomotor activity; not actively relating to environment).
   2. Catalepsy (i.e., passive induction of a posture held against gravity).
   3. Waxy flexibility (i.e., slight, even resistance to positioning by examiner).
   4. Mutism (i.e., no, or very little, verbal response [*Note:* not applicable if there is an established aphasia]).
   5. Negativism (i.e., opposing or not responding to instructions or external stimuli).
   6. Posturing (i.e., spontaneous and active maintenance of a posture against gravity).
   7. Mannerism (i.e., odd, circumstantial caricature of normal actions).
   8. Stereotypy (i.e., repetitive, abnormally frequent, non–goal-directed movements).
   9. Agitation, not influenced by external stimuli.
   10. Grimacing.
   11. Echolalia (i.e., mimicking another's speech).
   12. Echopraxia (i.e., mimicking another's movements).

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiologic consequence of another medical condition.
C. The disturbance is not better explained by another mental disorder (e.g., a manic episode).
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other areas of functioning.

Coding note: Include the name of the medical condition in the name of the mental disorder (e.g., F06.1 catatonic disorder due to hepatic encephalopathy). The other medical condition should be coded and listed separately immediately before the catatonic disorder due to the medical condition (e.g., K71.90 hepatic encephalopathy; F06.1 catatonic disorder due to hepatic encephalopathy)

Adapted from Weder ND, Muralee S, Penland H, Tampi RR. Catatonia: A review. *Ann Clin Psychiatry*. 2008;20(2):97–107:Table 2.

The exact pathophysiology of catatonia is unknown, but neuroanatomic, neuroendocrine, immunologic, and neurotransmitter-based theories have all been proposed based on the various underlying etiologies of catatonia. Morbidity and mortality are high in adults who have experienced catatonia and are presumed to be high in pediatric populations based on limited data primarily because of the severity of an underlying illness that could cause catatonia. Patients with schizophrenia spectrum disorders and catatonia tend to be more impaired than those who do not experience catatonia, and suicide rates are estimated to be 500-fold higher than in the general population.

Catatonia is defined as 3 or more of the 12 symptoms listed in Table 47.11 and can be described by both etiology and presentation. The DSM-5 broadly splits etiology into presentations related to mental disorders and presentations related to another medical condition, the diagnosis of which must be supported by the patient's history, physical exam, and any accompanying laboratory findings. Pediatric prevalence rates range from 0.6–17% in child psychiatric inpatients and up to 17% in medically hospitalized children, but rates are difficult to determine due to underdiagnosis of the condition. Catatonia can be further subdivided into three presentation categories: stuporous, excited, and malignant. **Stuporous** presentations are characterized by immobility, mutism, staring, and rigidity, whereas **excited** presentations include prolonged periods of psychomotor agitation. **Malignant catatonia** is an emergent condition, presenting with hyperthermia, hypertension, rhabdomyolysis, and psychomotor agitation in addition to the psychiatric and motor

Table 47.12 Standard Examination of Catatonia

The method described here is used to complete the 23-item Bush-Francis Catatonia Rating Scale (BFCRS) and the 14-item Bush-Francis Catatonia Screening Instrument (BFCSI). Item definitions on the two scales are the same. The BFCSI measures only the presence or absence of the first 14 signs.

Ratings are based solely on observed behaviors during the examination, with the exception of completing the items for "withdrawal" and "autonomic abnormality," which may be based on directly observed behavior or chart documentation.

As a general rule, only items that are clearly present should be rated. If the examiner is uncertain as to the presence of an item, rate the item as "0."

PROCEDURE

1. Observe the patient while trying to engage in a conversation.
2. The examiner should scratch his or her head in an exaggerated manner.
3. The arm should be examined for cogwheeling. Attempt to reposture and instruct the patient to "keep your arm loose." Move the arm with alternating lighter and heavier force.
4. Ask the patient to extend his or her arm. Place one finger beneath his or her hand and try to raise it slowly after stating, "Do not let me raise your arm."
5. Extend the hand stating, "Do not shake my hand."
6. Reach into your pocket and state, "Stick out your tongue. I want to stick a pin in it."
7. Check for grasp reflex.
8. Check the chart for reports from the previous 24-hour period. Check for oral intake, vital signs, and any incidents.
9. Observe the patient indirectly, at least for a brief period each day, regarding the following:
   - Activity level
   - Abnormal movements
   - Abnormal speech
   - Echopraxia
   - Rigidity
   - Negativism
   - Waxy flexibility
   - Gegenhalten
   - Mitgehen
   - Ambitendency
   - Automatic obedience
   - Grasp reflex

Gegenhalten, Resistance to movements that is equal and opposite to the pressure exerted by examiner; *mitgehen*, extreme mitmachen where even slightest pressure moves limb; mitmachen, passive movement of extremity despite instruction not to move.

From Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. *Acta Psychiatr Scand.* 1996;93(2):129–136.

symptoms seen in catatonia. The differential diagnosis for this type includes neuroleptic malignant syndrome or serotonin syndrome (see Chapter 33). Most children will present with a stuporous clinical picture, whereas the remaining cases present as excited or malignant, 19% and 5%, respectively. The severity of symptoms can be measured and tracked using the Bush-Francis Catatonia Rating Scale, a validated tool that accompanies a standardized physical examination and observation of patient behavior (Table 47.12). The diagnostic approach is driven by the search for the underlying cause for catatonia and the monitoring of its potentially dangerous effects on the body.

Beyond supportive care and discontinuation of any precipitating agents, treatment of catatonia should be expeditious to reduce the medical sequelae of prolonged symptoms. Benzodiazepines, in particular lorazepam, are typically first-line pharmacologic treatment for catatonia. Low-dose lorazepam is often trialed as a confirmatory "challenge" for patients with suspected catatonia, where a positive result is improvement or even resolution of symptoms within hours of administration of the medication. If the initial challenge test does reverse symptoms, increasing doses of lorazepam are indicated, with careful monitoring to avoid side effects (Fig. 47.2). Rapid withdrawal of benzodiazepines can, in turn, precipitate catatonia in those who are susceptible. The use of antipsychotics in catatonia is controversial, as they have been associated with an increased incidence of malignant catatonia or neuroleptic malignant syndrome. ECT has also been used in both adults and children, though it is underutilized due to caretaker and ethical concerns. Its use is typically recommended when other viable treatment options have either not been successful or cannot be safely administered. It has been successful in treating refractory catatonia in children with autism.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

47.4 Hallucinations of Childhood

Jennifer A. Zaspel and Rosa K. Kim

Hallucinations are perceptions that occur in the absence of identifiable external stimuli. Nondiagnostic hallucinations are those that fall within the realm of normal human experience, such as hearing footsteps, knocking, or one's name being called. **Hypnogogic** and **hypnopompic** hallucinations are experienced as one transitions into and out of sleep, respectively, and on their own carry no psychopathologic implications. In younger children, reported hallucinations can reflect a developmentally appropriate blurring between fantasy and reality, especially regarding dreams and imaginary friends. Children are also more susceptible to perceptual distortions or **illusions** (misinterpretations of external stimuli) but may communicate these phenomena to adults in a way that most would interpret as hallucinations. The first clinical task in evaluating youth who report hallucinations is to sort out those associated with severe mental illness from those derived from other causes (Fig. 47.3).

Acute phobic hallucinations are benign, common, and typically occur in otherwise healthy preschool children. The hallucinations are often visual or tactile, last 10-60 minutes, and most often occur at night. The children are quite frightened and might complain that bugs or snakes are crawling over themselves and attempt to remove them. The child's fear is not alleviated by reassurance by the parents or physician, and the child is not amenable to reason. Findings on physical and mental status examinations are otherwise normal, and the cause is unknown. Symptoms can persist for 1-3 days, slowly abating over 1-2 weeks.

In children with nonpsychotic hallucinations, all other symptoms of psychosis are absent. Nonpsychotic hallucinations typically occur in the context of severe traumatic stress, developmental difficulties, social and emotional deprivation, parents whose own psychopathology promotes a breakdown in the child's sense of reality, cultural beliefs in mysticism, and unresolved mourning. Auditory hallucinations of voices telling the child to do "bad things" may be associated with disruptive behavior disorders in an unconscious attempt to distance oneself from undesirable behaviors. Hearing a voice invoking suicide is often associated with depression. Trauma-related hallucinations are commonly associated with posttraumatic stress disorder and are likely a representation of flashbacks. Auditory and visual hallucinations may similarly be endorsed in complex bereavement. The content of the hallucinations is often relevant in understanding the underlying psychopathology and developmental issues.

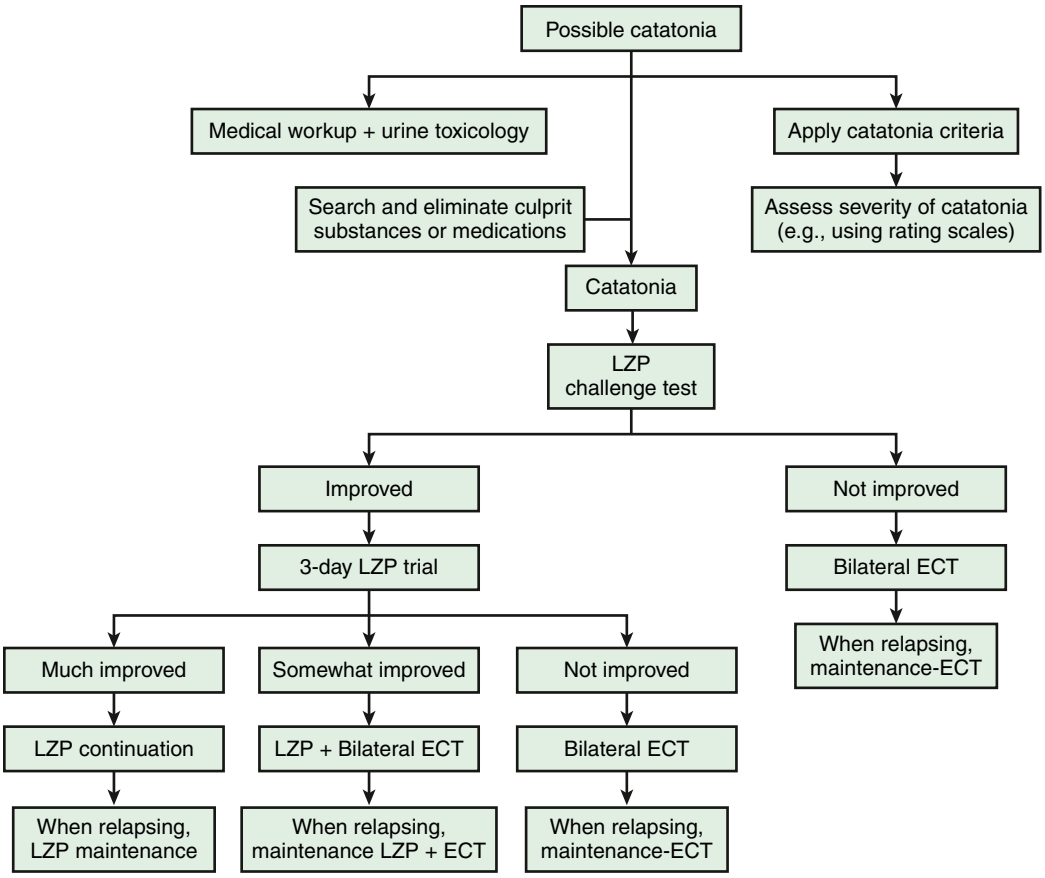

Fig. 47.2 Algorithm for the evaluation, diagnosis, and treatment of catatonia in children and adolescents. ECT, Electroconvulsive therapy; LZP, lorazepam. (*From Dhossche DM, Wilson C, Wachtel LE. Catatonia in childhood and adolescents: Implications for the DSM-5. Prim Psychiatry. 2010;17:23–26.*)

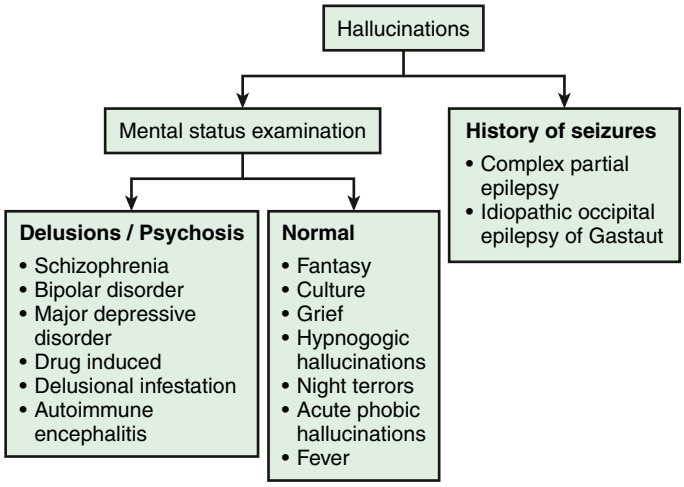

Fig. 47.3 Algorithm for the evaluation of hallucinations.

The evaluation of the underlying condition directs the type of treatment needed. Diagnostic nonpsychotic hallucinations suggest the need for disorder-specific psychotherapy and adjunctive medication, if indicated. CBT focused on helping the youth understand the origin of the hallucinations and on developing coping strategies for stressful situations may be helpful for older children and adolescents.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 48

Delirium

Colleen K. Manak and Rosa K. Kim

Delirium is defined as a disorder of **awareness** and **attention** and is characterized by its waxing and waning nature. It is not a primary psychiatric diagnosis and instead occurs secondary to an underlying medical condition, though at the time of initial presentation the underlying cause is often unknown. The symptoms of delirium are similar between adults and children. Delirium in children carries risks of adverse outcomes, including death, if it is not treated. Untreated delirium can serve to prolong the recovery course of comorbid and underlying conditions; the clinical features of delirium, including agitation, aggression, and confusion, can often interfere with necessary medical care. Delirium in children and adolescents is associated with a 12.5–29% mortality rate. Quick recognition, diagnosis, and treatment of delirium and its underlying cause is essential in ensuring the best outcome for patients.

DIAGNOSIS

Criteria for the diagnosis of delirium are included in the DSM-5 under Neurocognitive Disorders (Table 48.1). Delirium presents with an **acute onset**, developing quickly over the course of hours to days and symptoms tend to **wax and wane.** This fluctuation of symptoms can be dramatic over the course of a day, with a patient appearing

Table 48.1 DSM-5 Diagnostic Criteria for Delirium

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p. 596. Copyright 2013. American Psychiatric Association.

Table 48.2 DSM-5 Delirium Subtypes

Hyperactive delirium	Increased psychomotor activity and mood lability • Confusion • Psychosis • Disorientation • Agitation • Hypervigilance • Hyper-alertness • Combativeness • Loud, pressured speech • Behavioral dysregulation • Pulling at lines/catheters
Hypoactive delirium	Decreased psychomotor activity • Sluggishness • Lethargy • Stupor • Confusion • Apathy
Mixed delirium	Normal level of psychomotor activity • Poor attention • Decreased awareness • Rapid fluctuation of activity level

Adapted from Meagher D, Moran M, Raju B, et al. A new data-based motor subtype schema for delirium. *J Neuropsychiatry Clin Neurosci.* 2008;20(2):185–193:Fig 1.

relatively well from a cognitive perspective during one assessment, and then seeming acutely altered at the next. At the core of delirium is an alteration in attention and awareness, and a disturbance in cognition. Patients with delirium will struggle to focus and sustain attention. They are often disoriented, showing confusion about where they are, poor orientation to time, and sometimes disorientation to self. In addition to these core features, delirium often presents with symptoms that have the potential to be mistaken for psychosis or mania. People with delirium may hallucinate, engage in bizarre or purposeless movements, and show alterations in their sleep–wake cycles.

Delirium can be further categorized into subtypes (Table 48.2). The **hyperactive** subtype is characterized by increased motor activity, loss of control of activity, restlessness, and wandering. The **hypoactive** subtype presents with reduction in activity, speed of actions, awareness of surroundings, quantity and speed of speech, and alertness. It is possible for patients to present with both hyperactive and hypoactive symptoms over the course of 24 hours, classified as having a **mixed motor subtype**. There has been emerging evidence of a fourth group, identified as the **no motor subtype**, in which they do not show characteristics of either hyper- or hypoactive subtypes.

Although these subtypes are often seen in both pediatric and adult delirium, diagnosing delirium in children can pose challenges not present in adult populations. Developmental differences, especially in young children, necessitate alternative approaches to assessing and diagnosing delirium. Bedside staff and caregivers can provide helpful insight into behaviors and cognitive changes, such as changes in attention, increased fussiness over baseline, and difficulty soothing, which might be missed by clinicians who are unable to evaluate symptoms of delirium using traditional methods (Fig. 48.1).

EPIDEMIOLOGY

The prevalence rate of pediatric delirium is an estimated to be 13–44% among *hospitalized* children, with higher rates seen in patients who are admitted to the intensive care unit (ICU) and/or those being mechanically ventilated. Increased risk for delirium may be associated with the underlying medical condition, prolonged hospitalization (especially ICU admission), young age, neurocognitive and developmental disorders, and a personal history of delirium. Potentially modifiable risk factors include polypharmacy, deep sedation, the use of benzodiazepines and anticholinergic medications, disrupted sleep, pain, sensory deprivation, and lack of familiar environment or caregivers. Delirium can occur at any age and has been observed in infants in the NICU.

ETIOLOGY

Although nearly any medical condition that requires hospitalization can lead to delirium, there are diagnoses that are more commonly associated with delirium (Table 48.3). Similarly, there are several drugs that are associated with the development of delirium in children including benzodiazepines, anticholinergic medications, sedatives, opiates, steroids, and some illicit substances (synthetic cathinone, synthetic cannabinoids).

ASSESSMENT

A thorough review of the medical record helps to identify predisposing and precipitating factors including exposures, changes in behavior, recent illness, and surgeries. If a reasonable cause is unable to be found on history, a further medical work-up is usually indicated.

It is possible for children with known psychiatric illnesses to develop delirium in response to medical stress. Having a comorbid psychiatric diagnosis should not delay the diagnosis of delirium. Psychiatric illnesses that can be confused with delirium include psychosis, mania, depression, and catatonia (Table 48.4). Key factors to look for in the history of patients with delirium are an acute onset without prodrome or other previous concern for worsening behavioral functioning, variable symptoms from moment to moment, and deficits in attention and orientation.

One of the factors that complicates assessment of delirium in children is the developmental level of the child. A young child will be unable to answer some of the standard assessment questions (e.g., questions about orientation), which means that a fair amount of the assessment will come from the bedside staff and the child's primary caregivers. More standard assessment strategies can be utilized in older children and adolescents.

In the patient interview, a good assessment will strive to evaluate affect, thought process, thought content, attention, and orientation to make the diagnosis of delirium. Because the nature of delirium is waxing and waning, it would not be atypical to have a seemingly normal exam in a patient one suspects to have delirium. Performing multiple assessments over the course of time is important to making an accurate diagnosis. In delirium, patients can have a disruption in their normal affect and may appear restricted or dysthymic.

Cornell Assessment of Pediatric Delirium (CAPD)

RASS score _____ (if –4 or –5 do not proceed)

Please answer the following questions based on your interactions with the patient over the course of your shift:

	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never 0	**Rarely 1**	**Sometimes 2**	**Often 3**	**Always 4**	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive–very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					TOTAL	

A

The Preschool Confusion Assessment Method for the ICU (psCAM-ICU)

1 Acute change or fluctuating course of mental status
- Is there an **acute change** from mental status baseline? (Y or N)
- Has the patient's mental status **fluctuated** during the past 24 hours? (Y or N)

If *"YES"* to *EITHER* question then Feature 1 is present → Move on to **Feature 2**

No → **STOP Delirium absent**

Yes ↓

2 Inattention → Show alternating pictures/mirrors and give verbal prompts
- Attends to **7 or less** pictures/mirrors?
- Patient does **not** maintain spontaneous eye opening in between verbal prompts

If *"YES"* to *EITHER* question then Feature 2 is present → Move on to **Feature 3**

No

Yes ↓

3 Altered level of consciousness (LOC)
- Does the patient currently have an **altered LOC**? (i.e. not alert and calm)

If *"YES"* then Feature 3 is present → **DELIRIUM PRESENT**

If *"NO"* then Feature 3 is **not** present → Move on to **Feature 4**

Yes → **Delirium present**

No ↓

4 Disorganized brain
- Does the patient have a **sleep-wake cycle disturbance**? (Any of the following)
  - Sleeps mostly during the day
  - Has difficulty getting to sleep
  - Does not awaken easily to stimulation
  - Sleeps little at night

If *"YES"* then Feature 4 is present → **DELIRIUM PRESENT**

Yes

No → **Delirium absent**

B

Fig. 48.1 Screening tools for the assessment of delirium. A, Cornell Assessment of Pediatric Delirium (CAPD). B, The Preschool Confusion Assessment Method for the ICU (psCAM-ICU). The short-form (clinical) psCAM-ICU is used to assess for delirium in infants and children who are at least responsive to voice. RASS, Richmond Agitation and Sedation Scale. (A *from Traube C, Silver G, Kearney J, et al. Cornell Assessment of Pediatric Delirium: A valid, rapid, observational tool for screening delirium in the PICU*. Crit Care Med. 2014;42:656–663;* B *from Smith HA, Gangopadhyay M, Goben CM, et al. The Preschool Confusion Assessment Method for the ICU: Valid and Reliable Delirium Monitoring for Critically Ill Infants and Children. Crit Care Med. 2016;44:592–600:Fig. 2.*)

Table 48.3	Etiologies of Pediatric Delirium (CRITICAL CARE mnemonic)
Cardiovascular	Anemia, shock, vasculitis, hypertensive encephalopathy
Respiratory	Respiratory insufficiency, respiratory failure, pneumothorax
Infection	Sepsis, encephalitis, urinary tract infection, meningitis, fever, pneumonia, tracheitis, cellulitis, surgical site infection, COVID-19
Toxins	Polypharmacy, heavy metals, drug:drug interactions
Inflammatory process	Autoimmune and rheumatologic disease
CNS pathology	Stroke, seizure, head trauma, intracranial bleed, tumor, anoxic brain injury
Abuse, withdrawal, sedation	Alcohol, benzodiazepines, opioids, barbiturates, prolonged/excessive sedation
Liver	Liver insufficiency, hepatic failure, hyperammonemia
Catheters, central line infections	Invasive device or procedure complications
Alimentation	Electrolyte imbalance, nutritional deficiencies, dehydration
Renal	Renal insufficiency or failure
Endocrinopathies	Glycemic disturbance, thyroid disease, parathyroid disease, adrenal disease

Adapted from Malas N, Brahmbhatt K, McDermott C, Smith A, Ortiz-Aguayo R, Turkel S. Pediatric delirium: Evaluation, management, and special considerations. *Curr Psychiatry Rep*. 2017;19(9):65.

Thought processes are often disorganized, tangential, or circumstantial and may seem loosely associated with, or not at all related to, the reality of what is going on in the moment. Patient with delirium may also be perseverative in their thought content, with difficulty moving away from a subject or becoming highly fixated on, or preoccupied with, one thing. They may have altered thought content, with hallucinations. Visual hallucinations especially are one of the hallmark alterations of thought content associated with delirium. Attention is frequently impacted in delirium, with patients demonstrating decreased attention, with an impaired ability to attend to a conversation or a situation. Orientation in people with delirium is often altered, especially with regards to orientation to place and time. Although all of these changes are observed to wax and wane during the course of delirium, changes in orientation can be the most striking, with patients sometimes going from being fully oriented to quite confused in the span of hours.

RATING SCALES

There are multiple rating scales that have been created to help to screen for delirium, particularly in critical care or intensive care setting (see Fig. 48.1). The Cornell Assessment for Pediatric Delirium (CAPD), Pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU), Preschool Confusion Assessment Method for the ICU (psCAM-ICU), and Richmond Agitation Sedation Scale (RASS) are all scales that are frequently used to help monitor for delirium. The CAPD, pCAM-ICU, and psCAM-ICU have all been validated for use in the pediatric population. Rating scales are not diagnostic on their own but can be useful for identifying patients at risk for delirium and for following response to treatment.

MEDICAL EVALUATION

Delirium is a clinical diagnosis and can be made with history and physical exam alone. There are no tests that are routinely recommended in

Table 48.4	Differential Diagnosis of Delirium			
CLINICAL FEATURE	**DELIRIUM**	**PSYCHOSIS**	**DEPRESSION**	**CATATONIA**
Course	Acute onset, hours, days or more	Insidious onset over many months, prodrome	Insidious onset, at least 2 wk, often over months	Onset variable
Attention	Markedly impaired attention and arousal	Normal to mild impairment	Mild impairment	Variable difficulty with attention and arousal
Fluctuation	Characterized by a waxing and waning course; disturbed day/night cycle	Absent	Absent	Less likely to fluctuate, motor signs may show more fluctuation
Perception	Misperceptions; hallucinations (visual, fleeting); paramnesia	Hallucinations, auditory with personal reference	May have mood-congruent hallucinations	May have hallucinations, especially if secondary to primary psychosis
Speech and language	Abnormal clarity, speed and coherence; disjointed and dysarthric; misnaming; characteristic dysgraphia	Disorganized with bizarre theme	Decreased amount of speech	Mutism; echolalia
Other cognition	Disorientation to time, place; recent memory and visuospatial abnormalities	Disorientation to person; concrete interpretations	Mental slowing; indecisiveness; memory retrieval difficulty	Global disorientation
Behavior	Lethargy; nonsystematized delusions; emotional lability	Systematized delusions; paranoia; bizarre behavior	Depressed mood; anhedonia; lack of energy; sleep and appetite disturbance	Stupor; catalepsy; negativism; posturing; stereotypy; agitation not influenced by external stimuli; grimacing; echopraxia
Electroencephalogram	Diffuse slowing; low voltage fast activity; specific patterns	Normal	Normal	Normal, focal abnormalities or generalized slowing

the evaluation for delirium, rather clinicians should be guided by the history and medical concerns. There are times when laboratory, imaging, and other testing modalities can be helpful particularly in patients with suspected delirium when the underlying medical etiology of delirium is unknown.

Central nervous system imaging may be recommended to help identify underlying processes that may be contributing to delirium; brain imaging on its own is not a tool that can diagnose delirium and is not recommended for the sole purpose of diagnosis.

Electroencephalogram (EEG) is one of the few tools that can be used to help confirm a delirium diagnosis if there is diagnostic ambiguity or uncertainty. Various studies have found 65–86% of children with delirium have *abnormal* EEGs. Findings associated with delirium typically include some degree of diffuse background slowing and disorganization. This EEG finding has been shown to effectively discriminate between children with delirium and healthy controls. However, these EEG findings are nonspecific and are not sufficient to diagnose delirium. Another caveat when utilizing EEG in the evaluation of delirium is the reality that several of the underlying causes of delirium, including metabolic derangement, seizures, infections, and intoxication, can also lead to EEG changes in the absence of delirium (see Table 48.3).

DIFFERENTIAL DIAGNOSIS

Both medical and psychiatric disorders may share or mimic some of the symptoms of delirium and can sometimes lead to complications when trying to make the diagnosis. **Catatonia**, **depression**, and **psychosis** are some of the more frequently occurring diagnoses that can be confused for delirium in children and especially adolescents (see Table 48.4; see Chapter 47). In particular, catatonia can be difficult to separate from delirium, especially because the two can co-occur. It is important to attempt to clarify the diagnosis because treatment of delirium and catatonia is different; the treatment for one can exacerbate the other. To help distinguish between the two, it is often helpful to assess for motor signs seen in catatonia that are not typically present in delirium (see Chapter 47.3). Additionally, catatonia is less likely to present with a waxing and waning course. The Bush-Francis Rating Scale can be used to help diagnose catatonia (see Table 47.12).

Delirium can also mimic psychosis, frequently presenting with hallucinations and sometimes delusions. One of the most profound differences between the two is the onset; delirium has an acute onset compared with the prodromal nature of a first episode of psychosis. It would be unusual for primary psychosis to develop over the course of days. However, this is characteristic of delirium. Hallucinations in delirium are often visual, whereas primary psychotic illnesses typically present with predominantly auditory hallucinations. Delusional thought content in delirium often lacks any internal structure or interconnectedness, while delusions in primary psychotic disorders are frequently structured around a common theme.

Patients with depression may have some characteristics of delirium. The course and onset can help to distinguish depression from delirium; with depression the timing of onset is often closer to that of delirium. Depression does not demonstrate a waxing and waning course, and while cognition can be affected, it is often slowed with some memory problems, whereas orientation remains intact.

TREATMENT

Nonpharmacologic Interventions

Nonpharmacologic interventions are a mainstay in both delirium treatment and prevention. The goal behind these interventions is to provide a supportive environment and to provide sensory and environmental modifications to help offset the challenges posed by the need for hospital-based care and treatment. Strategies such as frequent reorientation, adherence to normal routines, clustering care, and maintaining a normal sleep–wake cycle are all frequently implemented to prevent or manage delirium (Table 48.5)

Table 48.5 Nonpharmacologic Management of Delirium

Environmental modifications	• Maintain lighting consistent with the time of day • Minimize noise • Familiar objects • Visible clock, calendar
Sensory modifications	• Have appropriate sensory aides available (glasses, hearing aids) • Soft, calming music • Minimize lines, catheters, restraints • Maintain comfortable position and body alignment
Caregiver interventions	• Frequent reorientation • Fewer care team providers/different faces • Cluster cares to minimize interruptions • Promote normal sleep/wake schedule • Presence of familiar caregivers

Pharmacologic Treatment

Pharmacologic management of delirium focuses on both utilizing medications to help manage the symptoms of delirium while the underlying process is being treated and removing medications that may precipitate or worsen delirium.

Antipsychotics

Medications for the behavioral symptoms of delirium target disruptive behaviors that pose a danger to the patient and caregivers and interfere with necessary medical care. Although these medications do not treat the underlying cause of delirium, they can help to decrease distress and lead to a shorter overall course. Antipsychotic medications are the mainstay of treatment for the behavioral and psychiatric symptoms of delirium. Both first- and second-generation antipsychotics are effective, and the choice of medication is based on what other medical needs are co-occurring. It is recommended to "start low and go slow" to arrive at an effective dose. Although typically used only for a short course (days to weeks), it remains important to consider adverse effects of antipsychotic medications (see Chapter 33). All antipsychotics can cause QTc prolongation; thus it is recommended that electrocardiogram (ECG) monitoring be considered at the onset of and throughout the treatment. For a patient who is unable to take medications by mouth, intramuscular (IM) or intravenous (IV) haloperidol can be used. IV haloperidol is more potent than IM or oral haloperidol; switching between formulations and modes of administration must be done carefully. For patients who can take medications by mouth, second-generation antipsychotics are typically the preferred choice. Risperidone, quetiapine, and olanzapine have all been shown to be effective in treating children and adolescents with delirium. Risperidone and olanzapine are available in an oral disintegrating tablet, and quetiapine is available in a liquid solution, which makes them easy to administer for patients who are dependent on a nasogastric tube for nutrition. Choice of medication is often dependent on what is available in the treatment setting, and the preferred route of administration. In chronically ill medical patients, inquiring about a past history of delirium and treatment can be helpful in guiding medication choices.

Other Medications

Melatonin has some utility in the management of delirium as it can help to promote a normal circadian rhythm and the return to a healthy sleep–wake cycle. Trazodone has also been shown to have some benefit for patients who are struggling with nocturnal sleep maintenance.

Medications to Avoid

In addition to adding medications for the treatment of delirium, eliminating unnecessary or potentially deliriogenic medications is equally important. *Benzodiazepines worsen delirium and should be avoided as much as possible in patients at risk of developing delirium.* They should not be used to treat agitation in delirious patients. Anticholinergic medications are also known to potentiate delirium and should also be avoided. Minimizing polypharmacy to the extent possible can help to

eliminate potentially deliriogenic medications and aid in the *prevention of delirium*.

Pain Medications

Opiate pain medications can be associated with worsening delirium and should be used with care in patients at risk for delirium. Complicating this is the reality that untreated or undertreated pain can also be associated with the development and perpetuation of delirium, so ensuring adequate pain control will help to manage, and in some cases, prevent delirium.

Course and Sequelae

Course

The resolution of delirium can be variable. Some patients improve quickly once the underlying cause is identified and treated, while others may take weeks to months to show full resolution of symptoms. Patients who have delirium related to complex medical issues, such as autoimmune encephalitis, or prolonged hospital stays, may have longer lasting delirium. When symptoms improve, antipsychotic medications can be weaned; patients do not need to be on them long term.

Sequelae

Patients who have delirium are more likely to have subsequent episodes of delirium. There is evidence that patients with delirium go on to have impaired cognitive functioning compared to patients who have never had an episode of delirium.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Learning and Developmental Disorders

PART IV

Chapter 49

Neurodevelopmental and Executive Function and Dysfunction

Desmond P. Kelly and Darla H. McCain

TERMINOLOGY AND EPIDEMIOLOGY

A **neurodevelopmental function** is a basic brain process needed for learning and productivity and involves the following core neurodevelopmental domains: sensory, motor, language, visual-spatial/visual-perceptual, intellectual, memory, social cognition, and executive function. **Executive function (EF)** is a broad term used to describe specific neurocognitive processes involved in the regulating, guiding, organizing, and monitoring of thoughts and actions to achieve a specific goal. Processes considered to be "executive" in nature include inhibition/impulse control, cognitive/mental flexibility, emotional control, initiation skills, planning, organization, working memory, and self-monitoring.

Neurodevelopmental variation refers to differences in neurodevelopmental functioning. Wide variations in these functions exist within and between individuals. These differences can change over time and need not represent pathology or abnormality.

Neurodevelopmental and/or executive dysfunctions reflect any disruptions or weaknesses in these processes, which may result from neuroanatomic disturbance or neuropsychologic malfunctioning.

Neurodevelopmental and/or executive dysfunction places a child at risk for developmental, cognitive, emotional, behavioral, psychosocial, and adaptive challenges. Preschool-age children with neurodevelopmental or executive dysfunction may manifest delays in developmental domains such as language, motor, self-help, or social-emotional development and self-regulation. For the school-age child, an area of particular focus is academic skill development. It is at this age that disorders of learning are often diagnosed. The *Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition* (DSM-5) classifies disorders of learning within the group of neurodevelopmental disorders as **specific learning disorder (SLD)**, with separate specifiers recognizing impairments in reading, written expression, and mathematics. In the *International Classification of Diseases, Tenth Edition* (ICD-10), neurodevelopmental disorders include **specific developmental disorders of scholastic skills** with specific reading disorder, mathematics disorder, and disorder of written expression. **Dyslexia** is a term used more frequently by neurologists and by some advocacy groups to describe reading disorders. **Disorders of EF** have traditionally been viewed as a component of **attention-deficit/hyperactivity disorder (ADHD)**, which is also classified in DSM-5 as a neurodevelopmental disorder. **Frontal lobe and executive function deficit** is a recognized diagnostic term used primarily by neuropsychologists.

There are no prevalence estimates specifically for neurodevelopmental dysfunction, but overall estimates for learning disorders range from 5% to 10% or more with a similar range reported for ADHD. These disorders frequently co-occur. The range in prevalence is related to differences in criteria used for classification and diagnosis, the overlap and interaction of neurodevelopmental variations, and differing methods of assessment.

ETIOLOGY AND PATHOGENESIS

Neurodevelopmental and executive dysfunction may result from a broad range of etiologic factors, including genetic, medical, psychologic, environmental, and sociocultural influences.

A high degree of **heritability** is reported in learning and attention disorders, with estimates ranging from 45% to 80%, but identification of specific gene associations is elusive. Neurodevelopmental dysfunctions generally fall along a continuum of traits with disorders becoming evident at extremes of dimensions or thresholds of dysfunction. The same genetic and early environmental risk factors that are associated with a disorder such as ADHD also predict trait levels in the general population. Specific genes have been identified as associated with reading disorders, including the *DYX2* locus on chromosome 6p22 and the *DYX3* locus on 2p12. Neuroimaging studies have confirmed links between gene variations and variations in cortical thickness in areas of the brain known to be associated with learning and academic performance, such as the temporal regions. Chromosomal abnormalities can lead to unique patterns of dysfunction, such as visual-spatial deficits in females diagnosed with Turner syndrome (see Chapter 99.4) or executive and language deficits in children with fragile X syndrome (see Chapter 99.6). Chromosome 22q11.2 deletion syndrome (see Chapter 99.3) has been associated with predictable patterns of neurodevelopmental and executive dysfunction that can be progressive, including a higher prevalence of intellectual disability and deficits in visual-spatial processing, attention, **working memory** (e.g., the ability to hold and manipulate information over short periods), verbal learning, arithmetic, and language.

Perinatal factors, including very low birthweight, severe intrauterine growth restriction, perinatal hypoxic-ischemic encephalopathy, and prenatal exposure to substances such as alcohol and drugs or infections, may independently disrupt neurodevelopment or exacerbate genetic vulnerabilities. Increased risk of neurodevelopmental and executive dysfunction has also been associated with environmental toxins, including lead (see Chapter 761); drugs such as cocaine; infections such as meningitis, HIV, and Zika; and brain injury associated with intraventricular hemorrhage, periventricular leukomalacia, or head trauma. The negative academic impact of concussion in children and adolescents, although usually temporary, has been well characterized, including impaired concentration and slowed processing speed. Repeated injuries have a much higher likelihood of long-term negative neurocognitive effects.

Early **psychologic trauma** may result in both structural and neurochemical changes in the developing brain, which may contribute to neurodevelopmental and executive dysfunction. Exposure to trauma, abuse, or other adverse experiences in early childhood in the absence of positive experiences—primarily safe, stable, and nurturing relationships—can lead to diminished regulatory influences mediated by key brain regions (hippocampus and prefrontal cortex) and may influence right hemisphere function with associated risk for problems with information processing, memory, focus, and self-regulation. Environmental and sociocultural deprivation can also lead to, or potentiate, neurodevelopmental and executive dysfunction, and numerous studies have indicated that parent/caregiver executive functioning affects the development of EFs in children.

Investigations of neuroanatomic substrates have yielded important information about the underlying **pathogenesis** in neurodevelopmental and executive dysfunction. Differences have been demonstrated in the left parietotemporal and left occipitotemporal brain regions of individuals with dyslexia compared to those without reading difficulties (see Chapter 51). Studies have also described the neural circuitry, primarily in the parietal cortex, underlying mathematical competencies such as the processing of numerical magnitude and mental arithmetic. The associations between executive dysfunction and the *prefrontal/frontal cortex* have been established, and injury to the frontal lobe regions often

result in dysfunction of executive abilities (e.g., poor inhibitory control). Although the prefrontal/frontal cortex may be the primary control region for EFs, there is considerable interconnectivity between the brain's frontal regions and other areas, such as *arousal* systems (reticular activating system), *motivational and emotional* systems (limbic system), *cortical association* systems (posterior/anterior; left/right hemispheres), and *input/output* systems (frontal motor/posterior sensory areas).

CORE NEURODEVELOPMENTAL FUNCTIONS

The neurodevelopmental processes that are critical to a child's successful functioning may best be understood as falling within **core neurodevelopmental domains** that are highly integrated.

Sensory and Motor Function

Sensory development begins well before birth in the primary visual, auditory, and somatosensory cortical regions along with the olfactory and gustatory cortices. This neurodevelopmental process is crucial in helping children experience, understand, and manipulate their environments. Sensory development progresses in association with environmental exposure and with the development of other cognitive processes, such as motor development. Through sensory experiences, children's brains mature as new neuronal pathways are created and existing pathways are strengthened.

There are three distinct, yet related, forms of **neuromotor** ability: fine motor, graphomotor, and gross motor coordination. **Fine motor function** reflects the ability to control the muscles that produce small, exact movements. Deficits in fine motor function can disrupt the ability to communicate in written form and to excel in artistic and crafts activities and can interfere with learning a musical instrument or mastering a computer keyboard.

Graphomotor function refers to the specific motor aspects of written output. Several subtypes of graphomotor dysfunction can significantly impede writing. Children who harbor weaknesses of visualization during writing have trouble picturing the configurations of letters and words as they write (orthographics), with poorly legible written output and inconsistent spacing between words. Others have weaknesses in orthographic memory and may labor over individual letters and prefer printing (manuscript) to cursive writing. Some exhibit signs of finger agnosia and have trouble localizing their fingers while they write, needing to keep their eyes very close to the page and applying excessive pressure to the pencil. Others struggle to produce the highly coordinated motor sequences needed for writing. It is important to emphasize that a child may show excellent fine motor dexterity (as revealed in mechanical or artistic domains) but very poor graphomotor fluency (with labored or poorly legible writing).

Gross motor function refers to control of large muscles. Children with gross motor incoordination often have problems in processing "outer spatial" information to guide gross motor actions. Affected children may be inept at catching or throwing a ball because they cannot form accurate judgments about trajectories in space. Others demonstrate diminished body position sense. They do not efficiently receive or interpret proprioceptive and kinesthetic feedback from peripheral joints and muscles. They are likely to evidence difficulties when activities demand balance and tracking of body position and movement. Others are unable to meet the motor planning demands of complex motor procedures such as those needed for dancing, gymnastics, or swimming.

The term **dyspraxia** relates to difficulty in developing an ideomotor plan and activating coordinated and integrated visual-motor actions to complete a task or solve a motor problem, such as assembling a model or learning a new movement.

Developmental coordination disorder is categorized in DSM-5 as a motor disorder where the learning and execution of coordinated motor skills is below age level given the child's opportunity for skill learning, and the motor difficulties significantly interfere with activities of daily living, academic productivity, and play.

Language

Language is one of the most critical and complex cognitive functions and can be broadly divided into **receptive** (auditory comprehension/understanding) and **expressive** (speech and language production and/or communication) functions (see Chapter 53). Children who primarily experience receptive language problems may have difficulty understanding verbal information, following instructions and explanations, and interpreting what they hear. Expressive language weaknesses can result from problems with speech production and/or problems with higher-level language development. **Speech production difficulties** include oromotor problems affecting articulation, verbal fluency, and naming. Some children have trouble with sound sequencing within words. Others find it difficult to regulate the rhythm or prosody of their verbal output. Their speech may be dysfluent, hesitant, and inappropriate in tone. Problems with **word retrieval** can result in difficulty finding exact words when needed (as in a class discussion) or substituting definitions for words (circumlocution).

The basic components of language include **phonology** (ability to process and integrate the individual sounds in words), **semantics** (understanding the meaning of words), **syntax** (mastery of word order and grammatical rules), **discourse** (processing and producing paragraphs and passages), **metalinguistics** (ability to think about and analyze how language works and draw inferences), and **pragmatics** (social understanding and application of language). Children who evidence higher-level expressive language impediments have trouble formulating sentences, using grammar appropriately, and organizing spoken (and possibly written) narratives.

To one degree or another, all academic skills are taught largely through language, and thus it is not surprising that children who experience language dysfunction often experience problems with academic performance. In fact, some studies suggest that up to 80% of children who present with a specific learning disorder also experience language-based weaknesses. Additionally, the role of language in executive functioning cannot be understated, because language serves to guide cognition and behavior.

Visual-Spatial/Visual-Perceptual Function

Important structures involved in the development and function of the visual system include the retina, the optic nerves, the brainstem (control of automatic responses, e.g., pupil dilation), the thalamus (e.g., lateral geniculate nucleus for form, motion, color), and the primary (visual space and orientation) and secondary (color perception) visual processing regions located in and around the occipital lobe. Other brain areas, although considered to be outside of the primary visual system, are also important to visual function, helping to process *what* is seen (temporal lobe) and *where* it is located in space (parietal lobe).

Critical aspects of visual processing development in the child include appreciation of **spatial** relations (ability to perceive objects accurately in space in relation to other objects), visual discrimination (ability to differentiate and identify objects based on their individual attributes, e.g., size, shape, color, form, position), and visual closure (ability to recognize or identify an object when the entire object cannot be seen). Visual-spatial processing dysfunctions are rarely the cause of reading disorders, but some investigations have established that deficits in orthographic coding (visual-spatial analysis of character-based systems) can contribute to reading disorders. Spelling and writing can emerge as a weakness because children with visual processing problems usually have trouble with the precise visual configurations of words. In mathematics, these children often have difficulty with visual-spatial orientation, with resultant difficulty aligning digits in columns when performing calculations and difficulty managing geometric material. In the social realm, intact visual processing allows a child to make use of visual or physical cues when communicating and interpreting the paralinguistic aspects of language. Secure visual functions are also necessary to process proprioceptive and kinesthetic feedback and to coordinate movements during physical activities.

Intellectual Function

A useful definition of **intellectual function** is the capacity to think in the abstract, reason, problem-solve, and comprehend. Intelligence is viewed as a global construct composed of more specific cognitive

functions (e.g., auditory and visual-perceptual processing, spatial abilities, processing speed, and working memory).

The expression of intellect is mediated by many factors, including language development, sensorimotor abilities, genetics, heredity, environment, and neurodevelopmental function. When an individual's measured intelligence is >2 standard deviations below the mean (a standard score of <70 on most IQ tests) and accompanied by significant weaknesses in adaptive skills, the diagnosis of **intellectual disability** may be warranted (see Chapter 56). Functionally, some common characteristics distinguish children with intellectual disability from those with average or above-average abilities. Typically, those at the lowest end of the spectrum (e.g., profound or severe intellectual disability) are incapable of independent function and require a highly structured environment with constant aid and supervision. At the other end of the spectrum are those with unusually well-developed intellect ("gifted"). Stronger intellect has been associated with better-developed concept formation, critical thinking, problem solving, understanding and formulation of rules, brainstorming and creativity, and *metacognition* (ability to "think about thinking"). Although high levels of intellectual functioning offer many opportunities, they can also be associated with functional challenges related to socialization, learning, and communication style.

Individuals whose intellect falls in the below-average range (sometimes referred to as the "borderline" or "slow learner" range) tend to experience greater difficulty processing and managing information that is abstract, making connections between concepts and ideas, and generalizing information (e.g., may be able to comprehend a concept in one setting but be unable to carry it over and apply it in different situations). In general, these individuals tend to do better when information is presented in more concrete and explicit terms (with repetition) and when working with rote information (e.g., memorizing specific material).

Memory

Memory is a term used to describe the complex, cognitive mechanism by which information is acquired, retained, and recalled. Major brain areas involved in memory processing include the hippocampus, fornix, temporal lobes, and cerebellum, with connections in and between most brain regions. Memory consists of multiple distinct and interconnected subsystems that are categorized based on the length of time information is stored (e.g., short-term memory, long-term memory), type of information stored (e.g., events, facts, procedures, emotional associations, conditioned reflexes), modality of the information (e.g., visual, auditory, olfactory), and whether memories are consciously recalled (**explicit memory**) or unconsciously recalled (**implicit memory**). Information processing models also include **working memory** as a distinct component.

Memory formation begins with sensory input (e.g., auditory, visual, tactile) that is identified, or **registered**, and subsequently **encoded**. Encoding is a mental process that transforms perceptual input into a representational code for the memory system. Information in **short-term memory** is transferred into **long-term memory** through the process of **consolidation** and **storage**. Information capacity in short-term memory is limited and brief, lasting for seconds to minutes, whereas information in long-term memory is potentially unlimited in terms of capacity and can be available for hours or as long as a life span.

Once information finds its way into long-term memory, it must be accessed. In general, information can be retrieved spontaneously (a process known as **free recall**) or with the aid of cues (**cued or recognition recall**). With deliberate, repeated practice, children can develop **automaticity**, the ability to instantaneously and effortlessly access information that has been learned in the past. Automaticity frees cognitive resources to process other information and promote learning. For example, automaticity in decoding words allows a child to focus on the meaning of the text.

Social Cognition

The development of effective social skills is heavily dependent on secure **social cognition**, which consists of mental processes that allow an individual to understand and interact with the social environment. Although some evidence shows that social cognition exists as a discrete area of neurodevelopmental function, multiple cognitive processes are involved with social cognition. These include the ability to recognize, interpret, and make sense of the thoughts, communications (verbal and nonverbal), and actions of others; the ability to understand that others' perceptions, perspectives, and intentions might differ from one's own (commonly referred to as "theory of mind"); the ability to use language to communicate with others socially (pragmatic language); and the ability to make inferences about others and the environment based on contextual information. It can also be argued that social cognition involves processes associated with memory and EFs, such as flexibility and shifting. Children with autism spectrum disorder harbor deficits in social cognition (see Chapter 58).

Executive Function

EF involves multiple skills (Table 49.1) that begin development early in life (early indications of inhibitory control and even working memory have been found in infancy), mature significantly during the preschool years, and continue to develop through adolescence and well into adulthood. Some studies suggest that secure EF may be more important than intellectual ability for academic success and have revealed that a child's ability to delay gratification early in life predicts competency, attention, self-regulation, frustration tolerance, aptitude, physical and mental health, and even risk for substance dependency in adolescence and adulthood. Conversely, deficits in other areas of neurodevelopment, such as language development, affect EF.

Attention is far from a unitary, independent, or specific brain function. This may be best illustrated through the phenotype associated with ADHD (see Chapter 50). Disordered attention can result from faulty mechanisms in and across subdomains of attention. These subdomains include *selective* attention (ability to focus attention on a particular stimulus and to discriminate relevant from irrelevant information), *divided* attention (ability to orient to more than one stimulus at a given time), *sustained* attention (ability to maintain one's focus), and *alternating* attention (capacity to shift focus between stimuli).

Attention problems in children can manifest at any point, from arousal through output. Children with diminished alertness and

Table 49.1 Symptom Expression of Executive Dysfunction

EXECUTIVE FUNCTION DEFICIT	SYMPTOM EXPRESSION
Inhibitory control	Impulsivity/poor behavioral regulation Interrupts "Blurts things out"
Shifting	Problems with transitioning from one task/activity to another Unable to adjust to unexpected change Repeats unsuccessful problem-solving approaches
Initiation	Difficulty independently beginning tasks/activities Lacks initiative Difficulty developing ideas or making decisions
Working memory	Challenges following multistep instruction (e.g., only completes one of three steps) Forgetfulness
Organization and planning	Fails to plan ahead Work is often disorganized Procrastinates and does not complete tasks "Messy" child
Self-monitoring	Fails to recognize errors and check work Does not appreciate impact of actions on others Poor self-awareness
Emotional control	Experiences behavioral and emotional outbursts (e.g., tantrums) Easily upset/frustrated Frequent mood changes

arousal can exhibit signs of mental fatigue in a classroom or when engaged in any activity requiring sustained focus. They are apt to have difficulty directing and sustaining their concentration, and their efforts may be erratic and unpredictable, with extreme performance inconsistency. Weaknesses in determining saliency often result in allocating cognitive resources to the wrong stimuli, at home, in school, and socially, and missing important information. **Distractibility** can take the form of listening to extraneous noises instead of a teacher, staring out the window, or constantly thinking about the future. Attention dysfunction can affect the output of work, behavior, and social activity. It is important to appreciate that most children with attentional dysfunction also have other forms of neurodevelopmental dysfunction that can be associated with academic disorders (with some estimates suggesting up to 60% comorbidity).

Inhibitory control (IC) can be described as one's ability to restrain, resist, and not act (cognitively or behaviorally/emotionally) on a thought. IC may also be seen as one's ability to stop thoughts or ongoing actions. Deficits in this behavioral/impulse regulation mechanism are a core feature of the **combined** or **hyperactive impulsive** presentation of ADHD and have a significant adverse impact on a child's overall functioning. In everyday settings, children with weak IC may exhibit difficulties with self-control and self-monitoring of their behavior and output (e.g., impulsivity), may not recognize their own errors or mistakes, and often act prematurely and without consideration of the potential consequences of their actions. In the social context, disinhibited children may interrupt others and demonstrate other impulsive behaviors that often interfere with interpersonal relationships. The indirect consequences of poor IC can include challenges with behavior, emotional regulation, and academic functioning and have adverse impacts on social interactions and safety.

Shifting is the ability to transition from one activity, topic, or aspect of a problem to another when needed. Effective shifting allows a child to flexibly move through their day, tolerating changes in schedule and routine. Additionally, shifting allows a child to change strategies when working a problem and adjust to changes in topics when conversing with others. Children with difficulties in shifting can become quickly upset in novel situations (e.g., when presented with a substitute teacher) and show marked resistance to change in routine. They can get stuck on one problem-solving strategy, which compromises their work efficiency. Socially, problems with shifting can result in one-sided conversations, negatively affecting a child's ability to build and maintain friendships.

Initiation refers to the ability to independently begin an activity, a task, or thought process (e.g., problem-solve). Children who present with initiation difficulties often have trouble "getting started." This can be exhibited behaviorally, such that the child struggles to start on physical activities like getting out of bed or beginning chores. Cognitively, weaknesses in initiation may manifest as difficulty coming up with ideas or generating plans. In school, children who have poor initiation abilities may be slow or unable to start homework assignments or tests. In social situations, initiation challenges may cause a child to have difficulty beginning conversations, calling on friends, or going out with friends.

Deficits in "primary" initiation are relatively rare and are often associated with significant neurologic conditions and treatments (e.g., traumatic brain injury, anoxia, effects of radiation treatment in childhood cancer). More often, initiation deficits are secondary to other executive problems (e.g., disorganization) or behavioral (e.g., oppositional/defiant behaviors), developmental (e.g., autism spectrum disorder), or emotional (e.g., depression, anxiety) disorders.

Working memory (WM) can be defined as the ability to hold, manipulate, and store information for short periods. In its simplest form, WM involves the interaction of short-term verbal and visual processes (e.g., memory, phonologic awareness, and spatial skills) with a centralized control mechanism that is responsible for coordinating all the cognitive processes involved (e.g., temporarily suspending information in memory while manipulating it). Ultimately, this function enables new information arriving in short-term memory to be linked to prior knowledge or procedures held in long-term memory. As such, working memory is critical to be able to complete multistep problems and more complex instructions and tasks. WM capacity can double or triple between the preschool years and adolescence. In the classroom, a child with a weakness in working memory might appear inattentive or careless when completing their work. When doing math, a child with WM dysfunction might have difficulty carrying a number and following the expected procedure. When reading a paragraph, a child might not recall key facts or be able to integrate information when reading, particularly long paragraphs. For writing tasks, a child might leave out ideas they intended to express while they are recalling grammar rules, such as placing a comma, and working on spelling a word correctly.

Planning refers to the ability to effectively generate, sequence, and put into motion the steps and procedures necessary to realize a specific goal. In real-world settings, children who struggle with planning are typically described by caregivers and teachers as being inept at independently gathering what is required to solve a problem or as unable to complete more weighty assignments. These children commonly exhibit poor time management skills.

Organization is an ability that represents a child's proficiency in arranging, ordering, classifying, and categorizing information. Planning and organizing depend on **discrimination** ability, which refers to the child's ability to determine what is and is not valuable when trying to problem-solve or organize. Common daily life challenges associated with organizational difficulties in childhood include problems with gathering and managing materials or items. When children struggle with organization, indirect consequences may include becoming overwhelmed with information and being unable to complete a task or activity. Effective organization is a vital component in learning (more specifically, in memory/retention); many studies, along with clinical experience, have shown that poor organization significantly affects how well a child recalls information.

Self-monitoring involves awareness and assessment of one's actions, whether it be a work product (e.g., writing an essay) or social interaction with another. This EF allows one to evaluate and make necessary corrections. Children with difficulty in self-monitoring fail to recognize errors in their work and struggle with editing. When interacting with others, they may not realize how their verbal and nonverbal behaviors are being perceived, ultimately missing opportunities to correct their behavior and resulting in poor social interactions.

Emotional control is the ability to regulate emotions in order to realize goals and direct one's behavior, thoughts, and actions. It has been well established that affective/emotional states have an impact on many aspects of functioning. Conversely, executive function or dysfunction often contributes to modulation of affect. Although emotional control is highly interrelated with different EFs (e.g., disinhibition, self-monitoring), separating it conceptually facilitates an appreciation for and recognition of the often-overlooked role that a child's emotional state plays in cognitive and behavioral functioning. Children with weak emotional control may exhibit explosive outbursts, poor temper/anger control, and oversensitivity. Understanding a child's emotional state is vital to understanding its impact not only on executive functioning but also on functioning as a whole (e.g., socially, mentally, behaviorally, academically).

Any discussion involving emotional control should also recognize **motivation**. *Motivation/effort* may be defined as the reason or reasons one acts or behaves in a certain way. Less motivated children are less likely to engage and utilize all their abilities. Such a disposition not only interferes with application of executive skills but also results in less-than-optimal performance and functioning. The less success a child feels, the less likely the child is to put forth effort and to persevere when things become more challenging. If a child's initial efforts are met with a negative reaction, the likelihood that the child will continue putting forth adequate effort diminishes. If left unchecked, a child's overall level of functioning will likely be compromised. More importantly, the child's sense of personal efficacy (e.g., self-esteem) and competence may suffer.

CLINICAL MANIFESTATIONS

The symptoms and clinical manifestations of neurodevelopmental and executive dysfunction differ with age. **Preschool-age children**

might present with delayed language development, including problems with articulation, vocabulary development, word finding, and rhyming. They often experience early challenges with learning colors, shapes, letters, numbers, the alphabet, and days of the week. Children with visual processing deficits may have difficulty learning to draw and write and have problems with art activities. These children might also have trouble discriminating between left and right. They might encounter problems recognizing letters and words. Difficulty following instructions, overactivity, and distractibility may be early symptoms of emerging executive dysfunction. Difficulties with fine motor development (e.g., grasping crayons/pencils, coloring, drawing) and social interaction may develop. These manifestations should be considered as potential "red flags" for future learning challenges (see "Assessment and Diagnosis").

School-age children with neurodevelopmental and executive dysfunctions can vary widely in clinical presentations. Their specific patterns of academic performance and behavior represent final common pathways of neurodevelopmental strengths and deficits interacting with environmental, social, or cultural factors; temperament; educational experience; and intrinsic resilience (Table 49.2). Children with language weaknesses might have problems integrating and associating letters and sounds, decoding words, deriving meaning, and being able to comprehend passages. Children with early signs of a mathematics weakness might have difficulty with concepts of quantity or with adding or subtracting without using concrete representation (e.g., their fingers when calculating). Difficulty learning time concepts and confusion with directions (right/left) might also be observed. Poor fine motor control and coordination and poor planning can lead to writing problems. Attention and behavioral regulation weaknesses observed earlier can continue, and together with other EF weaknesses (e.g., organization, initiation skills), further complicate the child's ability to acquire and generalize new knowledge. Children with weaknesses in WM may struggle to remember the steps necessary to complete an activity or problem-solve. In social settings, these children often have difficulty keeping up with more complex conversations.

Table 49.2 Neurodevelopmental Dysfunction Underlying Academic Disorders*

ACADEMIC DISORDER	POTENTIAL UNDERLYING NEURODEVELOPMENTAL DYSFUNCTION
Reading	Language • Phonologic processing • Verbal fluency • Syntactic and semantic skills Memory • Working memory Sequencing Visual-spatial Attention
Written expression, spelling	Language • Phonologic processing • Syntactic and semantic skills Graphomotor Visual-spatial Memory • Working memory Sequencing Attention
Mathematics	Visual-spatial Memory • Working memory Language Sequencing Graphomotor Attention

*Isolated neurodevelopmental dysfunction can lead to a specific academic disorder, but more often there is a combination of factors underlying weak academic performance. In addition to the dysfunction in neurodevelopmental domains as listed in the table, the clinician must also consider the possibility of limitations of intellectual and cognitive abilities or associated social and emotional problems.

In **middle school children** the substantial increase in cognitive, academic, and regulatory demands can cause further difficulties for those with existing neurodevelopmental and executive challenges. In reading and writing, middle school children might present with transposition and sequencing errors; might struggle with root words, prefixes, and suffixes; might have difficulty with written expression; and might avoid reading and writing altogether. Challenges completing word problems in math are common. Difficulty with recall of information might also be experienced. Although observable in both lower and more advanced grades, behavioral, emotional, and social difficulties tend to become more salient in middle school children who experience cognitive or academic problems.

High school students can present with deficient reading comprehension, written expression, and slower processing efficiency. Difficulty in answering open-ended questions, dealing with abstract information, and deploying executive control (e.g., self-monitoring, organization, planning, self-starting) is often reported.

Academic Problems

Reading disorders (see Chapter 51) can stem from a number of neurodevelopmental dysfunctions, as described earlier (see Table 49.2). Most often, language and auditory processing weaknesses are present, as evidenced by poor phonologic processing that results in deficiencies at the level of decoding individual words and, consequently, a delay in *automaticity* (e.g., acquiring a repertoire of words readers can identify instantly) that causes reading to be slow, laborious, and frustrating. Deficits in other core neurodevelopmental domains might also be present. Weak WM might make it difficult for a child to hold sounds and symbols in mind while breaking down words into their component sounds, or might cause reading comprehension problems. Some children experience temporal-ordering weaknesses and struggle with reblending phonemes into correct sequences. Memory dysfunction can cause problems with recall and summarization of what was read. Some children with higher-order cognitive deficiencies have trouble understanding what they read because they lack a strong grasp of the concepts in a text. Although rare as a cause of reading difficulty, problems with visual-spatial functions (e.g., visual perception) can cause children difficulty in recognizing letters. It is not unusual for children with reading problems to avoid reading practice, and a delay in reading proficiency becomes increasingly pronounced and difficult to remediate.

Spelling and writing impairments share many related underlying processing deficits with reading, so it is not surprising that the two disorders often occur simultaneously in school-age children (see Table 49.2). Core neurodevelopmental weaknesses that underlie *spelling difficulties* include phonologic and decoding difficulties, orthographic problems (coding letters and words into memory), and morphologic deficits (use of suffixes, prefixes, and root words). Problems in these areas can manifest as phonetically poor, yet visually comparable, approximations to the actual word (*faght* for *fight*), spelling that is phonetically correct but visually incorrect (*fite* for *fight*), and inadequate spelling patterns (*plade* for *played*). Children with memory disorders might misspell words because of coding weaknesses. Others misspell because of poor auditory WM that interferes with their ability to process letters. Sequencing weaknesses often result in transposition errors when spelling.

Writing difficulties have been classified as **disorder of written expression**, or **dysgraphia** (see Table 49.2). Although many of the same dysfunctions described for reading and spelling can contribute to problems with writing, written expression is the most complex of the language arts, requiring synthesis of many neurodevelopmental functions (e.g., auditory, visual-spatial, memory, executive; see Chapter 52.2). Weaknesses in these functions can result in written output that is difficult to comprehend, disjointed, and poorly organized. The child with WM challenges can lose track of what the child intended to write. Attention deficits can make it difficult for a child to mobilize and sustain the mental effort, pacing, and self-monitoring demands necessary for writing. In many cases, writing is laborious because of an underlying *graphomotor dysfunction* (e.g., fluency does not keep pace

with ideation and language production). Thoughts may also be forgotten or underdeveloped during writing because the mechanical effort is so taxing.

Weaknesses in mathematical ability, known as **mathematics disorder** or **dyscalculia**, involve the assimilation of both procedural knowledge (e.g., calculations) and higher-order cognitive processes (e.g., WM) (see Table 49.2). There are many reasons why children struggle with mathematics (see Chapter 52.1). It may be difficult for some to grasp and apply math concepts effectively and systematically; good mathematicians are able to use both verbal and perceptual conceptualization to understand such concepts as fractions, percentages, equations, and proportion. Children with language dysfunctions have difficulty in mathematics because they have trouble understanding their teachers' verbal explanations of quantitative concepts and operations and are likely to experience frustration in solving word problems and in processing the vast network of technical vocabulary in math. Mathematics also relies on visualization. Children who have difficulty forming and recalling visual imagery may be at a disadvantage. They might experience problems writing numbers correctly, placing value locations, and processing geometric shapes or fractions. Children with executive dysfunction may be unable to focus on fine detail (e.g., operational signs), might take an impulsive approach to problem solving, engage in little or no self-monitoring, forget components of the problem, or commit careless errors. When a child's memory system is weak, the child might have difficulty recalling appropriate procedures and automatizing mathematical facts (e.g., multiplication tables). Moreover, children with mathematical disabilities can have superimposed mathematics **phobias**; anxiety over mathematics can be especially debilitating.

Nonacademic Problems

The impulsivity and lack of effective self-monitoring of children with executive dysfunction can lead to unacceptable actions that were unintentional. Children struggling with neurodevelopmental dysfunction can experience excessive performance anxiety, sadness, or clinical depression; declining self-esteem; and chronic fatigue. Some children may lose motivation and feel no need to exert effort and develop future goals. These children may be easily led toward dysfunctional interpersonal relationships, detrimental behaviors (e.g., delinquency, substance abuse), and the development of mental health disorders, such as mood disorders (see Chapter 39) or conduct disorder (see Chapter 42).

ASSESSMENT AND DIAGNOSIS

Pediatricians have a critical role in identifying and treating the child with neurodevelopmental or executive dysfunction (Fig. 49.1). They have knowledge of the child's medical and family history and social-environmental circumstances and have the benefit of longitudinal contact over the course of routine health visits. Focused **surveillance and screening** will facilitate early identification of developmental-behavioral and preacademic difficulties and interventions to facilitate optimal outcomes.

A **family history** of a parent who still struggles with reading or time management or an older sibling who has failed at school should spur an increased level of monitoring. **Risk factors** in the medical history, such as extreme prematurity or chronic medical conditions, should likewise be flagged. Children with low birthweight and those born prematurely who appear to have been spared more serious neurologic problems might only manifest academic problems later in their school career. **Nonspecific physical complaints** or unexpected **changes in behavior** might be presenting symptoms. Warning signs might be subtle or absent, and parents might have concerns about their child's learning progress but may be reluctant to share these with the pediatrician unless prompted, such as through completion of **standardized developmental screening questionnaires** or direct questioning regarding possible concerns. Concerns voiced to parents or caregivers by daycare, preschool, or early elementary teachers might be the first indicators of neurodevelopmental dysfunctions. There should be a low threshold for initiating further school performance screening and assessment if there are any concerns or "red flags" (see "Clinical Manifestations").

In elementary school, review of **school report cards** and teacher comments can provide very useful information. In addition to patterns of grades in the various academic skill areas, it is also important to review ratings of classroom behavior and work habits. Group-administered **standardized tests** provide further information, although interpretation is required because poor scores could result from a learning disorder, ADHD, emotional problems, lack of motivation, or some combination. Conversely, a discrepancy between above-average scores on standardized tests and unsatisfactory classroom performance could signal motivation, adjustment issues, or instructional mismatches. Challenges related to **homework**, such as excessive time to complete, can provide further insight regarding EFs, academic skill, and behavioral factors or factors related to the home environment.

Underlying or associated medical problems should be ruled out. Any suspicion of sensory difficulty should warrant referral for **vision or hearing testing**. The influence of chronic medical problems or potential side effects of medications should be considered. **Sleep deprivation** is increasingly being recognized as a contributor to academic problems, especially in middle and high school. **Substance use** must always be a consideration as well, especially in the adolescent previously achieving well who has shown a rapid decline in academic performance.

The physician should be alert for **dysmorphic physical features**, minor congenital anomalies, or constellations of physical findings (e.g., cardiac and palatal anomalies in 22q11.2 deletion syndrome) and should perform a detailed **neurologic examination**, including an assessment of fine and gross motor coordination and any involuntary movements or soft neurologic signs. Genetic testing is often recommended for children with intellectual disability or autism spectrum disorder; electroencephalogram and brain MRI are generally not indicated in the absence of specific medical findings or a family history.

Early signs of **executive dysfunction** can also be subtle and easily overlooked or misinterpreted. Informal inquiry might include questions about how children complete schoolwork or tasks, how organized or disorganized they are, how much guidance they need, whether they think through problems or respond and react too quickly, what circumstances or individuals affect their ability to employ EFs, how easily they begin tasks and activities, and how well they plan, manage belongings, and control their emotions.

Pediatricians who are interested in performing further assessment before referral, or who are practicing in areas where psychologic testing resources are limited, can use **standardized rating scales and inventories** or brief, individually administered tests to narrow potential diagnoses and guide next steps in diagnosis and treatment. Such instruments, completed by the parents, teachers, and the child (if old enough), can provide information about emotions and behavior, patterns of academic performance, and traits associated with specific neurodevelopmental dysfunctions (see Chapter 32). Screening instruments such as the *Pediatric Symptom Checklist* and behavioral questionnaires such as the *Child Behavior Checklist* (CBCL) and *Behavior Assessment System for Children, Third Edition* (BASC-3) can aid in evaluation.

EFs can be further assessed by instruments such as the *Behavior Rating Inventory of Executive Function, Second Edition* (BRIEF-2), which provides a comprehensive measure of real-world behaviors that are closely tied to executive functioning in children age 5-18 years. Tests that can be directly administered to gauge intellectual and language functioning include the *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2) and *Peabody Picture Vocabulary Test, Fifth Edition* (PPVT 5; assessing receptive vocabulary). A relatively brief test of academic skills is the *Wide Range Achievement Test5* (WRAT5). It should be recognized that these are midlevel tests that can provide descriptive estimates of function but are not diagnostic.

Children who are struggling academically are entitled to evaluations in school. Such assessments are guaranteed in the United States under Public Law 101-476, the **Individuals with Disabilities Education Act (IDEA)**. One increasingly common type of evaluation model supported by IDEA is referred to as a **Response to Intervention (RtI)** model (see Chapter 52.1). In this model, students who are struggling with academic skills are initially provided research-based instruction. If a child does not respond to this instruction, an individualized

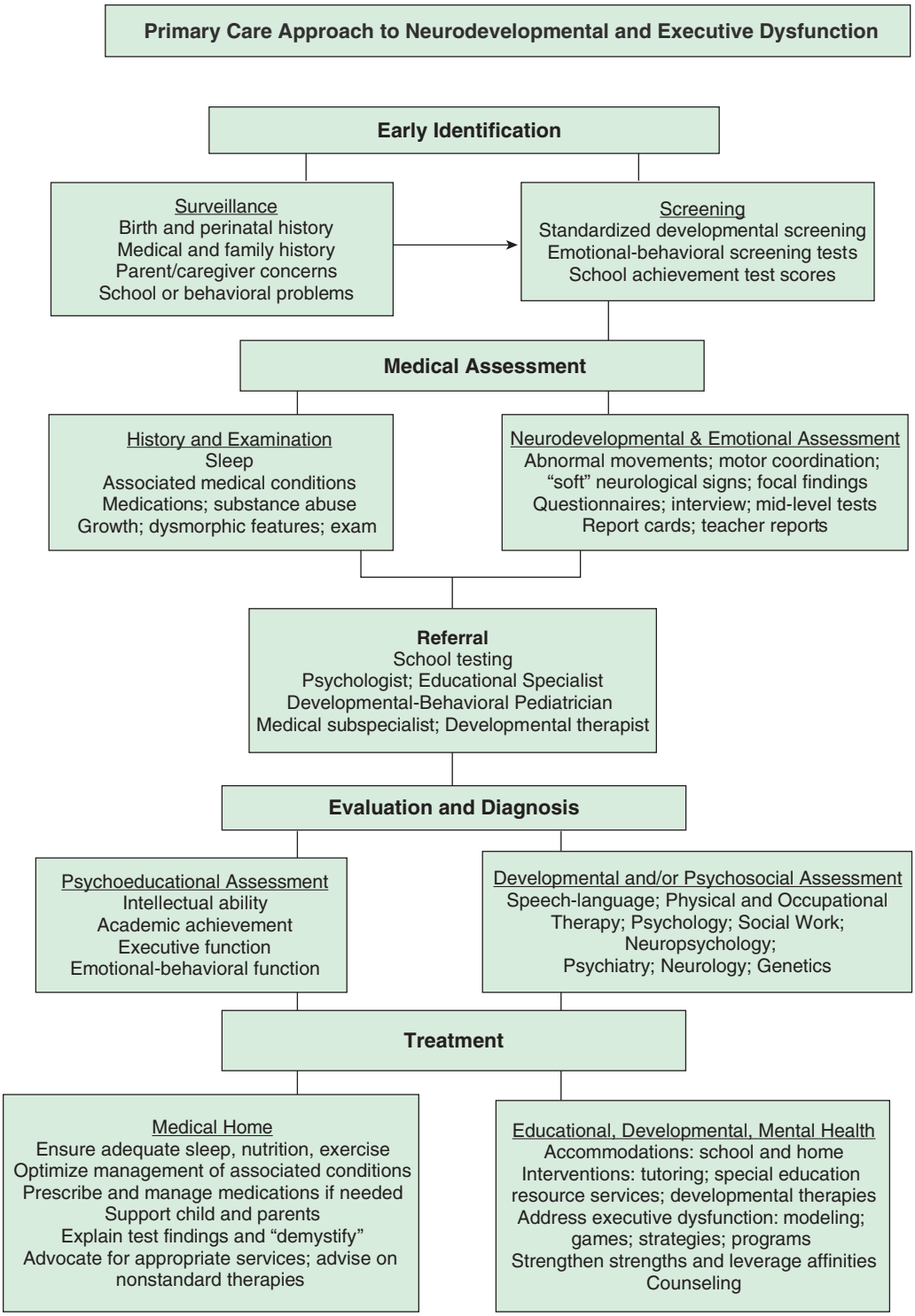

Fig. 49.1 Algorithm showing components of a primary care approach to identification, diagnosis, and comprehensive multidisciplinary management of neurodevelopmental and executive dysfunction.

evaluation by a multidisciplinary team is conducted. Children found to have attentional dysfunction and other disorders might qualify for educational accommodations in the regular classroom under Section 504 of the Rehabilitation Act of 1973 (**504 Plan**) or might qualify for an **individualized education program (IEP)**.

The pediatrician should advise and support parents regarding steps to request evaluations by the school. Multidisciplinary evaluations are focused primarily on determining whether a student meets the eligibility criteria for special education services and to assist in developing an IEP for those eligible for these services. **Independent evaluations** can provide second opinions outside the school setting. The multidisciplinary team should include a psychologist and preferably an educational diagnostician who can undertake a detailed analysis of academic skills and subskills to pinpoint where breakdowns are occurring in the processes of reading, spelling, writing, and mathematics. Other professionals should become involved, as needed, such as a speech-language pathologist, occupational therapist, and social worker. A mental health specialist can be valuable in identifying family-based issues or psychiatric disorders that may be complicating or aggravating neurodevelopmental dysfunctions.

In some cases, more in-depth examination of a child's **neurocognitive status** is warranted. This is particularly true for children who

present with developmental or cognitive difficulties in the presence of a medical condition (e.g., epilepsy, traumatic brain injury, childhood cancers/brain tumors, genetic conditions). A **neuropsychologic evaluation** involves comprehensive assessment to understand brain functions across domains. Neuropsychologic data are often analyzed together with other tests, such as MRI, to look for supporting evidence of any areas of difficulty (e.g., memory weaknesses associated with temporal lobe anomalies). Neuropsychologists can also provide more in-depth evaluation of EFs. Assessment of EFs is typically completed in an examination setting using tools specifically designed to identify any weaknesses in these functions. Although few tools are currently available to assess EF in preschool-age children, the assessment of school-age children is better established. Problems with EFs should be evaluated across measures and in different settings, particularly within the context of the child's daily demands.

TREATMENT

Treatment for neurodevelopmental and executive dysfunction involves a **multimodal, multidisciplinary "cross-sector" approach to foster optimal outcomes.** This process begins with **demystification**, which involves educating the child and family about the nature of the child's delay or dysfunction while also identifying a child's strengths. The explanation of the dysfunction should be provided in nontechnical language, communicating a sense of optimism for improvement with appropriate intervention. Children need to have their affinities, potentials, and talents identified clearly and emphasized as an integral component of the long-term treatment plan. It is as important to **augment strengths** as it is to attempt to **remedy deficiencies**. Athletic skills, artistic inclinations, creative talents, and mechanical abilities are among the potential assets of certain students who are underachieving academically. Parents and school personnel need to create opportunities for such students to build on these assets. These well-developed personal assets can ultimately have implications for the transition into young adulthood, including career or college selection.

In the clinic setting, the pediatrician plays an important role as a **consultant and advocate** in overseeing and monitoring the implementation of a comprehensive multidisciplinary management plan for children with neurodevelopmental dysfunctions. The primary care provider should **identify and treat any underlying or associated medical problems** that might contribute to neurodevelopmental and EF dysfunction, such as iron deficiency, elevated lead levels, and sleep problems, including inadequate sleep related to poor sleep hygiene or poor quality of sleep (e.g., obstructive sleep apnea). Additionally, the pediatrician will need to monitor for **conditions that often co-occur** with neurodevelopmental delays and executive dysfunction or that may develop over time, including anxiety, depression, and substance use disorder.

Bypass Strategies (Accommodations)

Numerous techniques can enable a child to circumvent neurodevelopmental dysfunctions. Such strategies are typically used in the regular classroom and can be incorporated into a 504 Plan or IEP. Accommodations change *how* the child learns, allowing them to access material and meet the same expectations as their peers. Examples of accommodations include using large print for those with visual impairment and using a frequency modulation (FM) system for students with hearing impairment. For children with learning disorders, accommodations may include using a calculator while solving mathematical problems, writing essays with a word processor and use of spellcheck, or presenting oral instead of written reports. Children with executive dysfunction might benefit from being seated near the teacher to minimize distractions and taking tests untimed. These bypass strategies do not cure neurodevelopmental dysfunctions, but they minimize their academic and nonacademic effects and can provide a scaffold for more successful academic achievement.

Curriculum Modifications

Many children with neurodevelopmental dysfunctions require alterations in the school curriculum to succeed, especially as they progress through secondary school. A modification changes *what* the child is taught or expected to learn. Modifications include a student learning different material (e.g., continuing to work on addition and subtraction facts while peers move on to fractions) and instructors assigning grades using a different standard. In high school and college, students with memory weaknesses might need to work with an advisor to select courses that avoid an inordinate cumulative memory load in any single semester. For adolescents with learning disorders, the timing of foreign language learning and the selection of mathematics and science courses are critical to their academic success.

Remediation/Targeted Intervention

Interventions can be implemented at home and in school to strengthen academic skills. **Early identification** is critical so that appropriate instructional interventions can be introduced to minimize the long-term effects of academic disorders. Any interventions should be empirically supported (e.g., phonologically based reading intervention has been shown to significantly improve reading skills in school-age children). **Remediation** may take place in a resource room or learning center at school and is usually limited to children who have met the educational criteria for special education services described earlier. Reading specialists, mathematics tutors, and other professionals can use diagnostic data to select techniques that use a student's neurodevelopmental strengths to improve decoding skills, writing ability, or mathematical computation skills. Remediation need not focus exclusively on specific academic areas. Many students need assistance in acquiring study skills, cognitive strategies, and productive organizational habits.

Speech-language pathologists offer intervention for children with various forms of language disability. **Occupational therapists** focus on sensorimotor skills, including the motor skills of students with writing problems, and **physical therapists** address gross motor incoordination.

Treatment of Executive Dysfunction

Interventions to strengthen EFs can be implemented throughout childhood but are most effective if started at a young age. Preschool-age children first learn EFs by way of the **modeling, boundaries, and rules** observed and put in place by their parents/caregivers, and this modeled behavior must gradually become "internalized" by the child. Early **play** has been shown to be effective in promoting executive skills in younger children with games such as peek-a-boo (WM); pat-a-cake (WM and IC); follow the leader, Simon Says, and "Ring Around the Rosie" (self-control); imitation activities (attention and impulse control); matching and sorting games (organization and attention); and imaginary play (attention, WM, IC, self-monitoring, cognitive flexibility).

In school-age children it is crucial to establish consistent **cognitive and behavioral routines** that foster and maximize independent, goal-oriented problem solving and performance through mechanisms that include modification of the child's environment, modeling and guidance with the child, and positive reinforcement strategies. Interventions should promote **generalization** (teaching executive routines in the context of a problem, not as a separate skill) and should move from the external to the internal (from "external support" with active and directive modeling to an "internal process"). An intervention could proceed from external modeling of multistep problem-solving routines and external guidance in developing and implementing everyday routines, to practicing application and use of routines in everyday situations, to a gradual fading of external support and cueing of internal generation and use of executive skills. Such approaches should make the child a part of intervention planning, should avoid labeling, reward effort not outcomes, make interventions positive, and hold the child responsible for his or her efforts. Studies have consistently shown that a **combination of medication and behavioral treatments** are most effective, although evidence for long-term efficacy is lacking. It is important that any treatment plans aimed at bolstering attention and EF also include interventions that address the specific deficits associated with any comorbid diagnoses.

In addition to behavioral approaches, **cognitive training**, both computerized and noncomputerized, has been shown to strengthen the cognitive skills on which one is trained. Some computerized training

programs show lasting improvements in WM skills in children, though benefits are narrow and limited only to the aspects of WM specifically trained. Recently, game-based digital therapy has been shown to improve attention in children with ADHD-inattentive type and combined type. Noncomputerized cognitive training has shown greater improvements in EF than any type of computerized cognitive training. This may be the result of instructor-trainee interaction. Also evidencing positive outcomes are curriculum-based **classroom programs**, such as the *Tools of the Mind* (Tools) and *Promoting Alternative Thinking Strategies* (PATHS), which have been shown to improve IC.

Emerging evidence suggests **physical activity** can improve EF. Children who are more physically active and have better aerobic fitness have been shown to have better EF than children who are sedentary. Although plain aerobic exercise (e.g., walking, running) has not been found to improve EF, encouraging findings have been noted when an activity involves aerobic exercise and is also cognitively demanding. Basketball and dance, for example, are high in physical exertion while also requiring cognitive engagement through motor coordination and planning. In contrast, resistance training has not been shown to improve EF.

Approaches that use **mindfulness techniques** are also gaining prominence. Mindfulness practices incorporating movement (e.g., tai chi) improve EF better than those performed in a seated position. **Martial arts** such as taekwondo, which stresses discipline and self-regulation, have demonstrated improvements that generalize in many aspects of EFs and attention (e.g., sustained focus).

COUNSELING AND PARENT TRAINING PROGRAMS

The pediatrician is often in a close, trusting relationship with families and is well-positioned to identify adverse home factors that may require additional supports, including counseling and parent training. When academic difficulties are complicated by family problems or identifiable psychiatric disorders, **psychotherapy** may be indicated. Mental health professionals may offer long-term or short-term therapy. Such intervention may involve the child alone or the entire family. **Cognitive-behavioral therapy** is especially effective for mood and anxiety disorders. It is essential that the therapist have a firm understanding of the nature of a child's neurodevelopmental dysfunctions. Formal **parenting interventions** have also demonstrated strong evidence for effectiveness. Four programs that have the most empirical support are the *Triple P, Parent-Child Interaction Therapy* (PCIT), *Incredible Years,* and *New Forest Parenting Programme*.

Table 49.3 outlines interventions to target the specific components of EF. Although interventions may target each component separately, success will be determined by how well treatments can be integrated across settings and generalized to other areas of function. Whenever possible, working with more than one EF simultaneously is encouraged as a means of scaffolding intervention and building on previously mastered skills.

Medication

Psychopharmacologic agents may be helpful in lessening the toll of some neurodevelopmental dysfunctions. Most often, **stimulants** are used in the treatment of children with attention deficits. Although most children with attention deficits have other associated dysfunctions, such as language disorders, memory problems, motor weaknesses, or social skill deficits, medications such as methylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts, as well as nonstimulants such as α_2-**adrenergic agonists** and **atomoxetine**, can be important adjuncts to treatment by helping some children focus more selectively and control their impulsivity. When depression or excessive anxiety is a significant component of the clinical picture,

Table 49.3 Executive Function Categories: Presenting Symptoms, Suggested Dysfunction, and Potential Interventions

SYMPTOM/PRESENTING COMPLAINT	SUSPECTED AREA OF DYSFUNCTION	POSSIBLE "REAL-WORLD" INTERVENTIONS
Acts before thinking Interrupts Poor behavioral and/or emotional control	Inhibitory control	Increase structure in environment to set limits for inhibition problems. Make behavior and work expectations clear and explicit; review with child. Post rules in view; point to them when child breaks rule. Teach response-delay techniques (e.g., counting to 10 before acting).
Cannot follow multistep instructions Forgetful	Working memory	Repeat instructions as needed. Keep instructions clear and concise. Provide concrete references.
Struggles starting assignments/tasks Lacks initiative/motivation Has trouble developing ideas/strategies	Initiation	Increase structure of tasks. Establish and rely on routine. Break tasks into smaller, manageable steps. Place child with partner or group for modeling and cueing from peers.
Does not plan ahead Uses trial-and-error approach	Planning	Practice with tasks with only a few steps first. Teach simple flow charting as a planning tool. Practice with planning tasks (e.g., mazes). Ask child to verbalize plan before beginning work. Ask child to verbalize second plan if first does not work. Ask child to verbalize possible consequences of actions before beginning. Review incidents of poor planning/anticipation with child.
Work/belongings is/are "messy" Random/haphazard problem solving Procrastinates/does not complete tasks	Organization	Increase organization of classroom and activities to serve as model, and help child grasp structure of new information. Present framework of new information to be learned at the outset, and review again at the end of a lesson. Begin with tasks with only a few steps and increase gradually.
Gets "stuck" Trouble transitioning Does not adapt to change	Flexibility/shifting	Increase routine to the day. Make schedule clear and public. Forewarn of any changes in schedule. Give "2-minute warning" of time to change. Make changes from one task to the next or one topic to the next, clear and explicit. Shifting may be a problem of inhibiting, so apply strategies for inhibition problems.

antidepressants or **anxiolytics** may be helpful. Other medications may improve behavioral control (see Chapter 33). Children receiving medication need regular follow-up visits that include a history to check for side effects, a review of current behavioral checklists, a complete physical examination, and appropriate modifications of the medication dose. Periodic trials off medication are recommended to establish whether the medication is still necessary.

Nonstandard Therapies

Pediatricians should be aware of nonstandard therapies that purport to treat neurodevelopmental and executive dysfunction or components therein. A variety of treatment methods for neurodevelopmental dysfunctions have been proposed that currently have little to no known scientific evidence of efficacy. This list includes dietary interventions (vitamins, elimination of food additives or potential allergens), neuromotor programs or medications to address vestibular dysfunction, eye exercises, filters, tinted lenses, and various technologic devices. Parents should be cautioned against expending the excessive amounts of time and financial resources usually demanded by these remedies. In many cases, it is difficult to distinguish the nonspecific beneficial effects of increased support and attention paid to the child from the purported target effects of the interventions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 50

Attention-Deficit/ Hyperactivity Disorder

Elizabeth B. Harstad

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common and extensively studied neurobehavioral disorders of childhood and is among the most prevalent chronic health conditions affecting school-age children. ADHD is characterized by inattention, including increased distractibility and difficulty sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor overactivity and restlessness (Table 50.1, Fig. 50.1). Definitions vary in different countries. In the International Classification of Diseases (ICD) 2022 update from ICD-10 to ICD-11, hyperkinetic disorder was replaced with ADHD, which aligns with *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) terminology. Under ICD-11, the essential features of ADHD are described, but without giving age of onset, duration, or minimum number of symptoms needed for the diagnosis as specified in DSM-5 (Table 50.2). Children with ADHD may experience academic underachievement, problems with interpersonal relationships with family members and peers, and low self-esteem. ADHD often coexists with other emotional, behavioral, language, and learning disorders. Evidence also suggests that for many people, the disorder continues, with varying manifestations across the life cycle, leading to significant underemployment and unemployment, social dysfunction, and increased risk of antisocial behaviors (e.g., substance abuse), difficulty maintaining relationships, encounters with the law, and death from suicide or accidents (Figs. 50.2 and 50.3).

EPIDEMIOLOGY

Studies of the prevalence of ADHD worldwide have generally reported that 5–10% of school-age children are affected, although rates vary considerably by country, perhaps in part because of differing sampling and testing techniques and a varying symptom threshold for diagnosis. ADHD is more common in males than in females (male to female ratio 4:1 for the predominantly hyperactive-impulsive presentation and 2:1 for the predominantly inattentive presentation). Many children with ADHD will have coexisting diagnoses, including learning disabilities, mood disorders, and/or language disorders. Children with high intellectual quotient (IQ) are just as likely to have ADHD as those with average IQ, but children with below-average IQ have increased risk of having coexisting ADHD.

ETIOLOGY

There is no single etiology identified for ADHD; many factors play a role in its development. A genetic contribution to the etiology of ADHD is well established. Twin studies show 70–80% heritability, and there is a 5- to 10-fold increased risk for ADHD among first-degree relatives of those with ADHD. However, there are many ways in which genetic variants contribute to ADHD; it is thought that ADHD is a polygenic disorder in which multiple common genetic variants act together to increase the risk for ADHD.

Structural and functional abnormalities of the brain have been identified in children with ADHD. These include dysregulation of the frontal subcortical circuits; small cortical volumes in this region or more widespread throughout the brain; and abnormalities of the cerebellum, particularly midline/vermian elements. There is a median of a 3-year delay in attainment of peak cortical thickness in prefrontal regions of the brain in those with ADHD. Although neuroimaging studies have advanced knowledge related to ADHD, neuroimaging does not typically have a role in the clinical diagnosis or inform ongoing management.

Brain catecholamine metabolism, specifically for dopamine and norepinephrine, appears to play a role in the pathophysiology of ADHD. Animal studies suggest that an imbalance between these systems (specifically a decrease in inhibitory dopamine activity and increase in norepinephrine activity) contributes to ADHD. These findings are supported by human studies showing that individuals with ADHD have an increase in dopamine transporter density (which clears away dopamine too quickly) compared to non-ADHD controls. Additionally, studies showing that stimulant medications work to treat ADHD by increasing the amount of available dopamine and norepinephrine at the synapse support a role for catecholamine metabolism in the etiology of ADHD.

Some environmental factors also may contribute to the pathogenesis of ADHD. Prenatal exposure to tobacco smoke or alcohol is associated with increased risk for ADHD. Prematurity, including even late-preterm birth, is also associated with increased risk for ADHD. Maternal mental illness increases the risk for ADHD in offspring, and research indicates underlying maternal mental illness itself, rather than treatment of the mental illness, is the associated risk factor. Diet is not thought to play a role in the pathogenesis of ADHD for most children with the condition. A small subset of children with ADHD may be uniquely sensitive to certain foods, sugars, or additives, but this remains controversial, as studies reporting these findings are typically small and often not rigorously designed.

CLINICAL MANIFESTATIONS

Development of the DSM-5 criteria for ADHD has occurred mainly in field trials with children 5-12 years of age (see Table 50.1). The DSM-5 criteria state that the inattentive or hyperactive-impulsive behaviors must be developmentally inappropriate (substantially different from that of other children of the same age and developmental level), must begin before age 12 years, must be present for at least 6 months, must be present in two or more settings, and must not be secondary to another disorder. To meet criteria for ADHD, the symptoms must interfere with social, academic, or occupational functioning.

antidepressants or **anxiolytics** may be helpful. Other medications may improve behavioral control (see Chapter 33). Children receiving medication need regular follow-up visits that include a history to check for side effects, a review of current behavioral checklists, a complete physical examination, and appropriate modifications of the medication dose. Periodic trials off medication are recommended to establish whether the medication is still necessary.

Nonstandard Therapies

Pediatricians should be aware of nonstandard therapies that purport to treat neurodevelopmental and executive dysfunction or components therein. A variety of treatment methods for neurodevelopmental dysfunctions have been proposed that currently have little to no known scientific evidence of efficacy. This list includes dietary interventions (vitamins, elimination of food additives or potential allergens), neuromotor programs or medications to address vestibular dysfunction, eye exercises, filters, tinted lenses, and various technologic devices. Parents should be cautioned against expending the excessive amounts of time and financial resources usually demanded by these remedies. In many cases, it is difficult to distinguish the nonspecific beneficial effects of increased support and attention paid to the child from the purported target effects of the interventions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 50

Attention-Deficit/ Hyperactivity Disorder

Elizabeth B. Harstad

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common and extensively studied neurobehavioral disorders of childhood and is among the most prevalent chronic health conditions affecting school-age children. ADHD is characterized by inattention, including increased distractibility and difficulty sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor overactivity and restlessness (Table 50.1, Fig. 50.1). Definitions vary in different countries. In the International Classification of Diseases (ICD) 2022 update from ICD-10 to ICD-11, hyperkinetic disorder was replaced with ADHD, which aligns with *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) terminology. Under ICD-11, the essential features of ADHD are described, but without giving age of onset, duration, or minimum number of symptoms needed for the diagnosis as specified in DSM-5 (Table 50.2). Children with ADHD may experience academic underachievement, problems with interpersonal relationships with family members and peers, and low self-esteem. ADHD often coexists with other emotional, behavioral, language, and learning disorders. Evidence also suggests that for many people, the disorder continues, with varying manifestations across the life cycle, leading to significant underemployment and unemployment, social dysfunction, and increased risk of antisocial behaviors (e.g., substance abuse), difficulty maintaining relationships, encounters with the law, and death from suicide or accidents (Figs. 50.2 and 50.3).

EPIDEMIOLOGY

Studies of the prevalence of ADHD worldwide have generally reported that 5–10% of school-age children are affected, although rates vary considerably by country, perhaps in part because of differing sampling and testing techniques and a varying symptom threshold for diagnosis. ADHD is more common in males than in females (male to female ratio 4:1 for the predominantly hyperactive-impulsive presentation and 2:1 for the predominantly inattentive presentation). Many children with ADHD will have coexisting diagnoses, including learning disabilities, mood disorders, and/or language disorders. Children with high intellectual quotient (IQ) are just as likely to have ADHD as those with average IQ, but children with below-average IQ have increased risk of having coexisting ADHD.

ETIOLOGY

There is no single etiology identified for ADHD; many factors play a role in its development. A genetic contribution to the etiology of ADHD is well established. Twin studies show 70–80% heritability, and there is a 5- to 10-fold increased risk for ADHD among first-degree relatives of those with ADHD. However, there are many ways in which genetic variants contribute to ADHD; it is thought that ADHD is a polygenic disorder in which multiple common genetic variants act together to increase the risk for ADHD.

Structural and functional abnormalities of the brain have been identified in children with ADHD. These include dysregulation of the frontal subcortical circuits; small cortical volumes in this region or more widespread throughout the brain; and abnormalities of the cerebellum, particularly midline/vermian elements. There is a median of a 3-year delay in attainment of peak cortical thickness in prefrontal regions of the brain in those with ADHD. Although neuroimaging studies have advanced knowledge related to ADHD, neuroimaging does not typically have a role in the clinical diagnosis or inform ongoing management.

Brain catecholamine metabolism, specifically for dopamine and norepinephrine, appears to play a role in the pathophysiology of ADHD. Animal studies suggest that an imbalance between these systems (specifically a decrease in inhibitory dopamine activity and increase in norepinephrine activity) contributes to ADHD. These findings are supported by human studies showing that individuals with ADHD have an increase in dopamine transporter density (which clears away dopamine too quickly) compared to non-ADHD controls. Additionally, studies showing that stimulant medications work to treat ADHD by increasing the amount of available dopamine and norepinephrine at the synapse support a role for catecholamine metabolism in the etiology of ADHD.

Some environmental factors also may contribute to the pathogenesis of ADHD. Prenatal exposure to tobacco smoke or alcohol is associated with increased risk for ADHD. Prematurity, including even late-preterm birth, is also associated with increased risk for ADHD. Maternal mental illness increases the risk for ADHD in offspring, and research indicates underlying maternal mental illness itself, rather than treatment of the mental illness, is the associated risk factor. Diet is not thought to play a role in the pathogenesis of ADHD for most children with the condition. A small subset of children with ADHD may be uniquely sensitive to certain foods, sugars, or additives, but this remains controversial, as studies reporting these findings are typically small and often not rigorously designed.

CLINICAL MANIFESTATIONS

Development of the DSM-5 criteria for ADHD has occurred mainly in field trials with children 5-12 years of age (see Table 50.1). The DSM-5 criteria state that the inattentive or hyperactive-impulsive behaviors must be developmentally inappropriate (substantially different from that of other children of the same age and developmental level), must begin before age 12 years, must be present for at least 6 months, must be present in two or more settings, and must not be secondary to another disorder. To meet criteria for ADHD, the symptoms must interfere with social, academic, or occupational functioning.

Table 50.1 DSM-5 Diagnostic Criteria for ADHD

A. A persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms of inattention have persisted for ≥6 mo to a degree that is inconsistent with development level and that negatively affects directly on social and academic/occupational activities:
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
   b. Often has difficulty sustaining attention in tasks or play activities.
   c. Often does not seem to listen when spoken to directly.
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not the result of oppositional behavior or failure to understand instructions).
   e. Often has difficulty organizing tasks and activities.
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork, homework).
   g. Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, tools).
   h. Is often easily distracted by extraneous stimuli.
   i. Is often forgetful in daily activities.
2. **Hyperactivity/impulsivity:** Six (or more) of the following symptoms of inattention have persisted for ≥6 mo to a degree that is inconsistent with development level and that negatively affects directly on social and academic/occupational activities.
   a. Often fidgets with hands or feet or squirms in seat.
   b. Often leaves seat in classroom or in other situations in which remaining seated is expected.
   c. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness).
   d. Often has difficulty playing or engaging in leisure activities quietly.
   e. Is often "on the go" or often acts as if "driven by a motor."
   f. Often talks excessively. Impulsivity.
   g. Often blurts out answers before questions have been completed.
   h. Often has difficulty awaiting turn.
   i. Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Several inattentive or hyperactive/impulsive symptoms were present before 12 yr of age.

C. Several inattentive or hyperactive/impulsive symptoms are present in two or more settings (e.g., at school [or work] or at home) and are documented independently.

D. There is clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. Symptoms do not occur exclusively during the course of schizophrenia, or another psychotic disorder, and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

CODE BASED ON TYPE

314.01 Attention-deficit/hyperactivity disorder, combined presentation: if both Criteria A1 and A2 are met for the past 6 mo.

314.00 Attention-deficit/hyperactivity disorder, predominantly inattentive presentation: if Criterion A1 is met but Criterion A2 is not met for the past 6 mo.

314.01 Attention-deficit/hyperactivity disorder, predominantly hyperactive-impulsive presentation: if Criterion A2 is met but Criterion A1 is not met for the past 6 mo.

Specify if:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and if the symptoms result in no more than minor impairments in social and occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, Text Revision, Washington, DC: American Psychiatric Association; 2000, and *Fifth Edition* (Copyright 2013 American Psychiatric Association.)

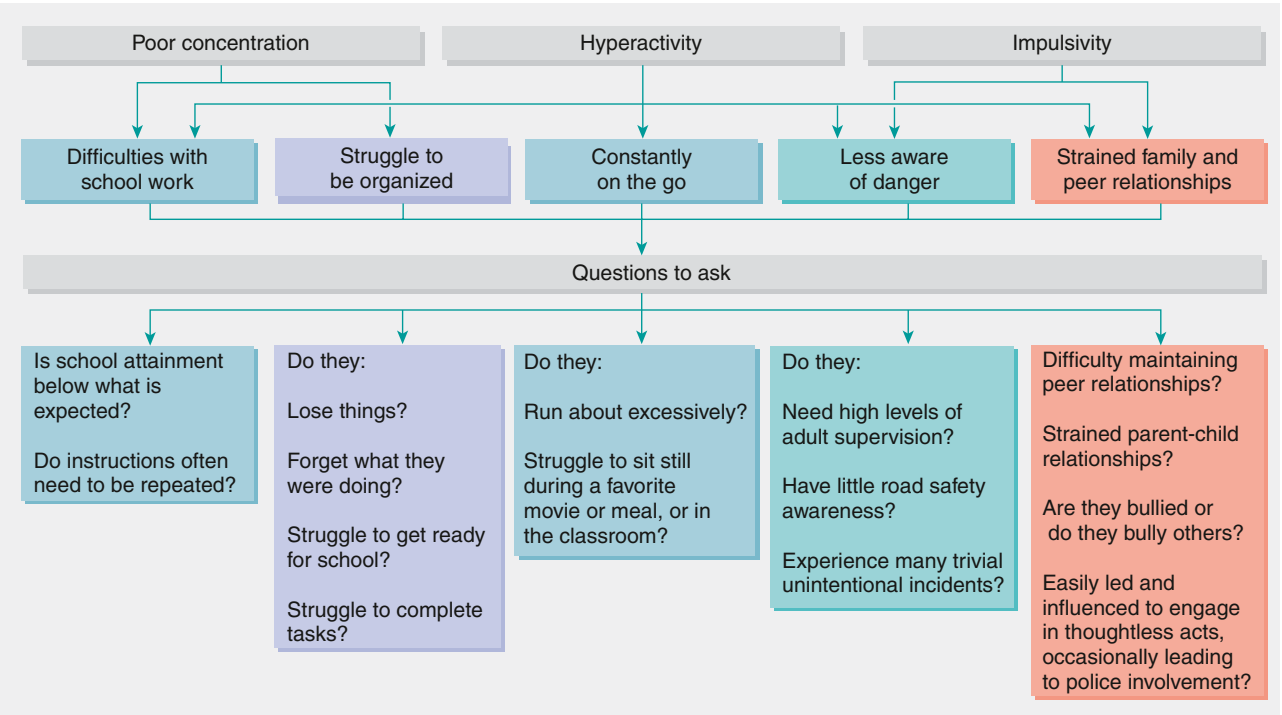

Fig. 50.1 How to assess children for attention-deficit/hyperactivity disorder. *(From Verkuijl N, Perkins M, Fazel M. Childhood attention-deficit/hyperactivity disorder. BMJ. 2015;350:h2168, Fig. 2, p. 146.)*

Table 50.2 Differences Between U.S. and European Criteria for ADHD or HKD

DSM-5 ADHD	ICD-10 HKD	ICD-11 ADHD*
SYMPTOMS		
Either or both of the following: • At least 6 of 9 inattentive symptoms • At least 6 of 9 hyperactive or impulsive symptoms	*All of the following:* • At least 6 of 8 inattentive symptoms • At least 3 of 5 hyperactive symptoms • At least 1 of 4 impulsive symptoms	*No minimum numbers of symptoms but must have:* • Persistent pattern (≥6 mo) of inattention and/or hyperactivity-impulsivity that has a direct negative impact on academic, occupational, or social functioning
PERVASIVENESS Some impairment from symptoms is present in one or more settings	Criteria are met for one or more settings	Symptoms must be evident across multiple situations or settings but are likely to vary according to the structure and demands of the setting

*ICD-11 went into effect on January 1, 2022.
ADHD, Attention-deficit/hyperactivity disorder; HKD, hyperkinetic disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-10, International Classification of Diseases, Tenth Edition.
Modified from Biederman J, Faraone S. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366:237–248.

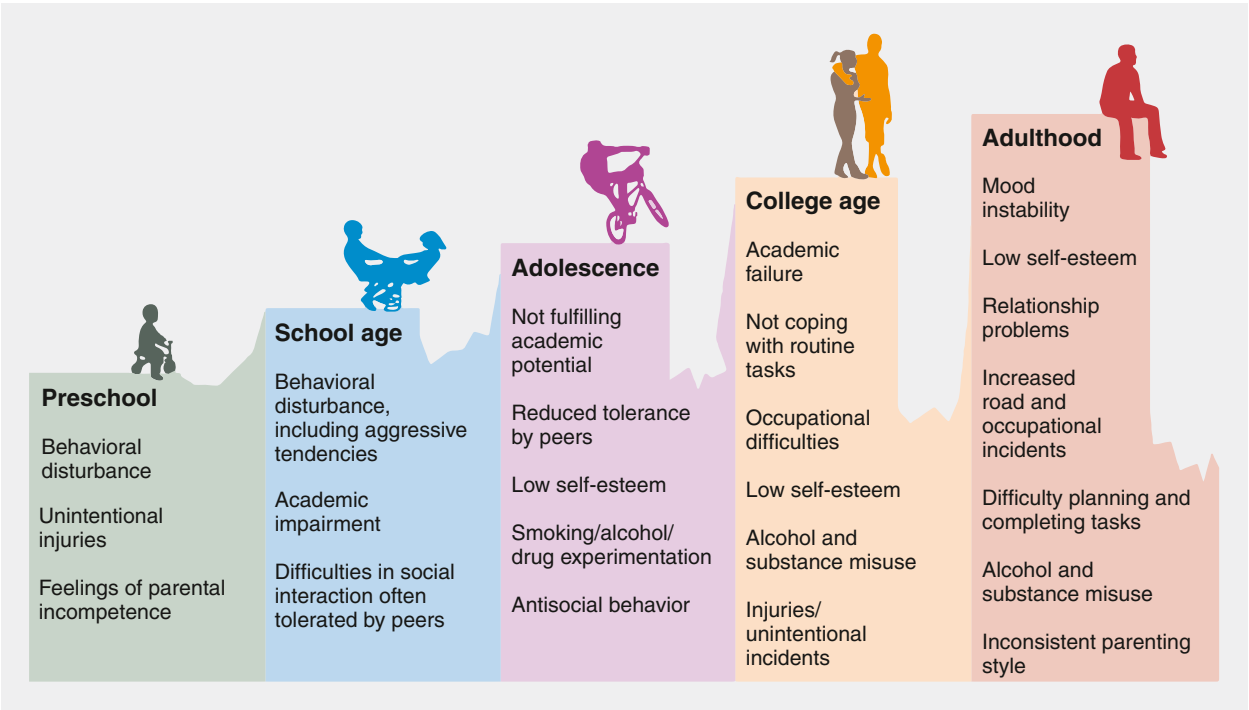

Fig. 50.2 Possible developmental impacts of attention-deficit/hyperactivity disorder. *(From Verkuijl N, Perkins M, Fazel M. Childhood attention-deficit/hyperactivity disorder. BMJ. 2015;350:h2168, Fig. 1, p. 145.)*

DSM-5 identifies three presentations of ADHD: the inattentive presentation, hyperactive-impulsive presentation, and combined presentation. Clinical manifestations of ADHD may change with age; thus the specific ADHD presentation for an individual may not be stable over time but describes current symptomatology (see Fig. 50.2). The symptoms may vary from motor restlessness and aggressive and disruptive behavior, which are common in preschool children, to disorganized, distractible, and inattentive symptoms, which are more typical in older adolescents and adults. Although hyperactivity generally decreases in late childhood and adolescence, symptoms of impulsivity and inattention often persist. Females with ADHD are relatively more likely than males to be diagnosed with the inattentive presentation, and this presentation is more commonly associated with internalizing symptoms (anxiety and low mood).

DIAGNOSIS

An evaluation for ADHD should be initiated in any child ≥4 years of age with symptoms of inattention, hyperactivity, and/or impulsivity (Fig. 50.4). This evaluation includes a careful history and clinical interview to rule in ADHD or to identify other causes or contributing factors, completion of behavior rating scales by different observers from at least two settings (e.g., teacher and parent), and a physical examination. It is important to systematically gather and evaluate information from a variety of sources, including the child, parents, teachers, and, when appropriate, other caretakers or professionals involved in the child's care.

The evaluation for ADHD may require several office visits. A thorough assessment should be conducted at the time of initial diagnosis, and reevaluation should occur if there are worsening or new symptoms, given the common occurrence of coexisting conditions.

Clinical Interview and History

The clinical interview allows a comprehensive understanding of whether the symptoms meet the diagnostic criteria for ADHD and to assess for coexisting conditions. The interview should collect information about the history and duration of presenting problems, the child's attainment of developmental milestones, school performance, social skills, mood, sleep, medical illnesses, sensory impairments, or

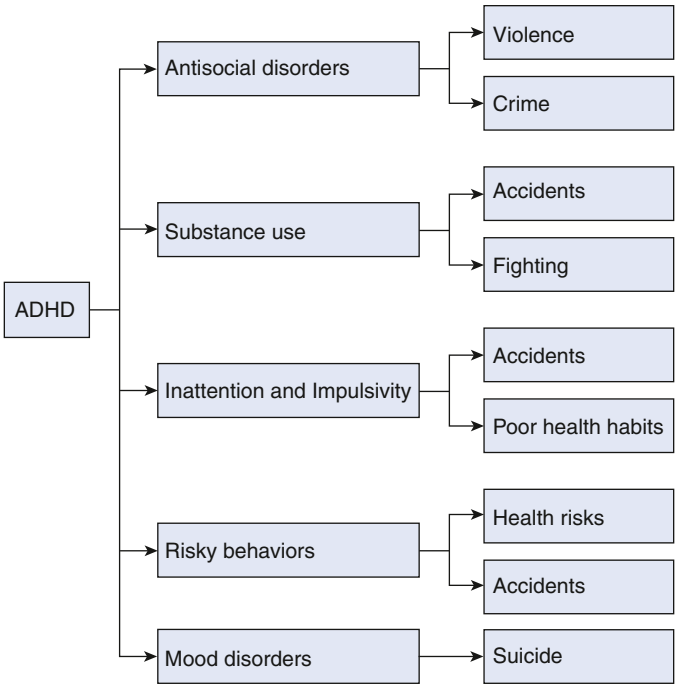

Fig. 50.3 Pathways to premature death in persons with attention-deficit/hyperactivity disorder (ADHD). *(From Faraone SV. Attention deficit hyperactivity disorder and premature death. Lancet. 2015;385:2132–2133.)*

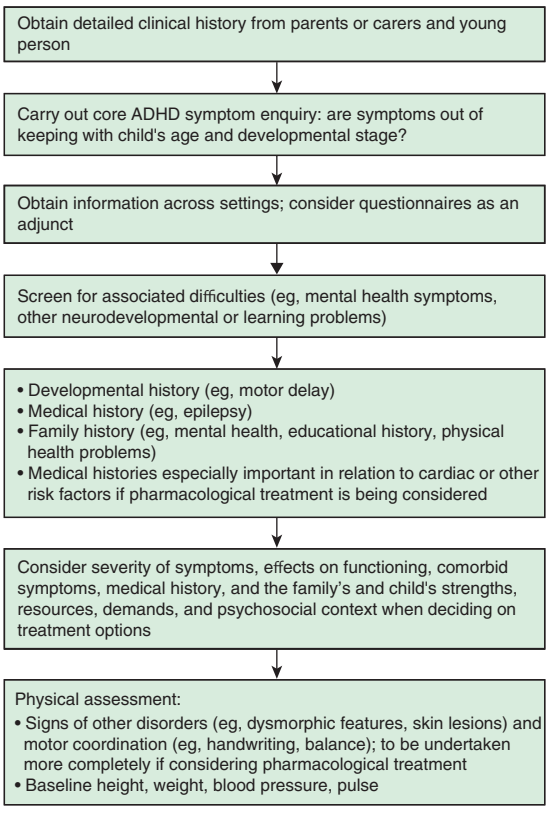

Fig. 50.4 Summary of the clinical assessment process for ADHD. ADHD, Attention-deficit/hyperactivity disorder. *(From Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387[10024]:1240–1250, Fig. 2.)*

medication use that might affect the child's functioning. Disruptive social factors, such as family discord, situational stress, and abuse or neglect, can result in hyperactive or anxious behaviors. A family history of first-degree relatives with ADHD, mood or anxiety disorders, learning disability, antisocial disorder, or alcohol or substance abuse might indicate an increased risk of ADHD and coexisting conditions.

Behavior Rating Scales

Behavior rating scales can help to elicit information about ADHD symptoms across contexts (i.e., home and school). The *Vanderbilt ADHD Rating Scale* (which has parent and teacher versions) is a commonly used screening measure for ADHD in primary care. It has specific questions about inattention and hyperactivity/impulsivity that correspond directly with the DSM-5 ADHD diagnostic criteria and questions about overall performance to assess for functional impairment, as well as subscales for some common coexisting conditions (anxiety/depression and oppositional behaviors/conduct disorder). Additional ADHD-specific rating scales include the *Conners 3 ADHD Index* and *ADHD Rating Scale 5*, among others that can be used. Broadband rating scales (such as *Achenbach Child Behavior Checklist* [CBCL] or *Behavioral Assessment Scale for Children* [BASC] or *Conners 3 Full Length Forms*) can be useful in assessing for coexisting conditions. Electronic capture of rating scale information is increasingly available and may facilitate completion and scoring. Rating scales provide information about the type, frequency, and severity of ADHD or other behavioral/mood symptoms, but interpretation requires clinical judgement. Contextual factors (such as triggers for a certain behavior, responses to a behavior that may inadvertently reinforce it) should be considered when interpreting rating scales. When there are discrepancies between results of rating scales for parents and teachers, the context and level of support provided in each setting should be assessed. ADHD rating scales can help with both the initial diagnostic assessment and with monitoring treatment response over time. Although there is no universal standard to use as a criterion for a positive response to treatment in terms of rating scale results, a decrease in ADHD symptom scores by 25% or more is generally considered significant improvement. However, improvement in functional outcomes may be more important to consider than changes in symptom scores. For children on medication, it is important to consider if the medication was "active" when the child was observed (i.e., stimulant medication may work to reduce ADHD symptoms during the school day, but the symptoms may return as the medication wears off in the afternoon/evening when the child is home).

Physical Examination, Laboratory, and Other Assessments

Most children with ADHD will have a normal physical exam, but one should be conducted as part of the diagnostic evaluation. Particular attention should be paid to cardiac and neurologic evaluations, thyroid, hearing and vision, and assessment for dysmorphic features that may signify an underlying condition, such as fetal alcohol syndrome. A child's behavior in the clinic visit may not represent the child's usual behaviors, as some children may be able to remain focused or calm for brief periods and others may exhibit more impulsivity or high activity level when nervous in the context of a clinic visit. Laboratory tests and brain imaging are not routinely recommended as part of an ADHD assessment. The presence of hypertension, ataxia, or asymmetric neurologic examination or symptoms of a sleep, seizure, or thyroid disorder may prompt further diagnostic tests. Lead levels could be considered if there are other factors associated with risk for lead toxicity. The clinician should identify possible vision or hearing problems. Computerized attentional tasks and quantitative electroencephalographic assessments are not needed to make the diagnosis. They are subject to high rates of false-positive and false-negative results and thus are of limited utility in the diagnostic assessment.

Educational testing should be considered if there are concerns about academic progress, as specific learning disabilities in reading,

mathematics, or written expression often coexist with ADHD (see Chapters 51 and 52). If there has been slow attainment of developmental milestones, intelligence or developmental testing should be conducted. If there are concerns about a child's social communication skills combined with restricted, repetitive behaviors or interests, a clinical assessment for autism spectrum disorder may be indicated (see Chapter 58).

Differential Diagnosis and Coexisting Conditions

Given that the symptoms of ADHD can overlap with other conditions, a broad differential diagnosis should be considered. For ease of presentation, the differential diagnosis for ADHD can be grouped into specific categories of developmental, psychiatric, medical, and psychosocial (Table 50.3). Children at either end of the developmental/cognitive level (i.e., with significant cognitive delays or with superior intelligence) can appear inattentive and/or distracted and sometimes also disruptive if the material in school or expectations at home are not appropriate for their developmental level. In differentiating impulsivity and challenging behaviors associated with ADHD versus an externalizing disorder (oppositional defiant disorder [ODD] or conduct disorder), consider whether the child "acts without thinking" and/or is more reactive (easily upset over demands for sustained attention or other small triggers), which would be more consistent with ADHD, versus proactively looks to aggress, fight, and challenge authority, which may be indicative of an externalizing disorder. Tic disorders can both present with some symptoms similar to ADHD (e.g., fidgeting, squirming, making sounds that seem impulsive) and also commonly coexist with ADHD. For cases in which ADHD symptoms are reported in one setting but not another, psychosocial causes should be considered, such as unrealistic classroom expectations, distress at home, or untoward parenting strategies. However, clinicians should be aware that inappropriate parenting strategies may be the result of the child's ADHD, as parents try anything (often unsuccessfully) to help their child. These parents are in need of parenting and behavioral supports, without feeling blamed for their child's symptoms.

Sleep disorders, including those secondary to chronic upper airway obstruction from enlarged tonsils and adenoids, often result in behavioral and emotional symptoms that can resemble or exacerbate ADHD (see Chapter 31). Periodic leg movements of sleep/restless legs syndrome have been associated with symptoms of inattention, and inquiry regarding this should be made during the history. Behavioral and emotional disorders can cause disrupted sleep patterns as well.

Mental health disorders: Depression and anxiety disorders can cause many of the same symptoms as ADHD (inattention, restlessness, inability to focus and concentrate on work, poor organization, forgetfulness) but can also coexist with ADHD (see Chapters 38 and 39). Obsessive-compulsive disorder can mimic ADHD, particularly when recurrent and persistent thoughts, impulses, or images are intrusive, interfering with normal daily activities. Adjustment disorders secondary to major life stresses (death of a close family member, parents' divorce, family violence, parents' substance abuse, or a move) or parent–child relationship disorders involving conflicts over discipline, overt child abuse and/or neglect, or overprotection can result in symptoms similar to those of ADHD.

When considering a new diagnosis in an adolescent patient, there should be an opportunity to interview the adolescent privately, and the adolescent should be specifically asked about mood symptoms and psychosocial stressors; frequent digital media use; and screened for use of alcohol, marijuana, and illicit substances.

Table 50.3 Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD)

GENERAL CATEGORY	SPECIFIC CONDITIONS, CAUSES
Developmental	Low developmental level/cognitive abilities Very high cognitive abilities Specific learning disabilities in reading, mathematics, or written expression Communication or language disorder Autism spectrum disorder Fetal alcohol syndrome
Psychiatric	Anxiety/depression Oppositional defiant disorder/conduct disorder Bipolar disorder/disruptive mood dysregulation disorder Substance use disorder Posttraumatic stress disorder/adjustment disorder
Medical	Sleep disorder, obstructive sleep apnea Hearing or vision impairment Specific medications, such as some antiepileptics or high-dose steroids Thyroid disorders Tic disorders Posttraumatic head injury or encephalitis Genetic conditions, such as fragile X, Klinefelter syndrome, Turner syndrome, tuberous sclerosis, and neurofibromatosis
Psychosocial	Response to abuse, neglect Response to distress in home, inappropriate expectations or parenting practices Response to inappropriate classroom setting

TREATMENT

Overall Treatment Approach

ADHD is considered a chronic condition and should be managed as such, with education about ADHD at the time of diagnosis and regular follow-up visits to monitor and treat symptoms. Parent support groups with appropriate professional consultation to such groups can be very helpful. Treatment of ADHD should be multimodal and involve behavioral therapy, school-based supports, and/or medications. The treatment plan should be developed in collaboration with the child (if developmentally appropriate) and family. The recommended initial treatments for ADHD vary by age.

Preschool-age children: For children up until 6 years of age, the recommended first-line treatment is evidence-based parent- and/or teacher-administered behavior therapy. If behavior interventions do not provide significant improvements and there is moderate to severe impairment in the child's functioning as a result of ADHD symptoms, medication should be considered. If behavioral interventions are not available, the risks of medication should be compared with risks of not treating ADHD symptoms.

School-age children and adolescents: For children ages 6 years old and older, ADHD medications should be considered first-line treatment, along with behavior and educational interventions. Organizational skills training, coaching, or cognitive-behavioral therapy may be helpful for adolescents and adults.

Behaviorally Oriented Treatments

Behavioral interventions should be an integral part of the treatment plan for all children with ADHD. Behavioral interventions involve modifying the environment and empowering caregivers with strategies to promote positive behaviors and minimize negative behaviors. Behavioral strategies typically focus on promoting a limited number of well-defined appropriate behaviors, using positive reinforcement with increased adult attention, tangible rewards, or access to privileges. A token economy in which a child earns (or loses) tokens that can be exchanged for rewards may be used. Any rules should be clearly defined and consistently enforced. Behavioral parent training, also known as *parent training in behavioral management,* is a well-established combination of behavioral interventions shown to reduce problematic behaviors and improve adaptive skills for children with ADHD. It involves teaching parents how to use behavior modification strategies to address specific behaviors, with a strong emphasis on positive reinforcement (described earlier) while ignoring or, if necessary, systematically implementing appropriate consequences for maladaptive behaviors. Treatments geared toward behavioral management for ADHD often occur in the time frame of 8-12 sessions but may sometimes require more sessions.

Although there is much less research published on psychosocial treatments for adolescents with ADHD, behavioral parent training can be modified to focus on improving communication between parents and adolescents with ADHD, developing a behavioral contract, and problem-solving around challenging situations. For children and adolescents with ADHD and coexisting anxiety disorders and/or depression, cognitive-behavioral therapy may help address anxiety or low mood.

At least 60 minutes of moderate to vigorous exercise is recommended for the general health of all children ≥6 years old, and some studies indicate exercise may reduce ADHD symptoms in children; thus encouraging regular exercise is reasonable. Interventions including cognitive training, electroencephalogram (EEG) biofeedback, and diet modification do not have the level of evidence needed to recommend them for most children.

Educational Supports and Accommodations

Behavioral classroom management strategies can be used by teachers to implement strategies within the whole classroom that will help children with ADHD. These include clear expectations and consistency in follow-through, positive reinforcement for work completion and on-task behaviors, and appropriate consequences when rules are not followed. Additionally, children with ADHD may benefit from individualized educational supports and accommodations, such as preferential seating near the source of instruction and away from distractions, motor breaks as needed, frequent teacher check-ins, being able to take tests in a less distracting environment, and an individualized positive behavior plan. A daily report card or communication log can be used to facilitate regular communication between the parents and teachers. A daily report card is individually designed for each child to include target problem behaviors in academic and/or social domains in the classroom (e.g., following directions, turning in work, getting along with others). The teacher provides a rating for each behavior on the report card, which is sent home daily, and the child is given home-based rewards for meeting goals set for the ratings from school.

Children with ADHD often need explicit instruction in organization and executive functioning skills and may not develop these skills at the same pace as non-ADHD peers. The use of an agenda book to record assignments, color coding for different classes, and teacher check-ins regularly to help with organization may be helpful for some children, and others may require a higher level of more individualized instruction in the executive functioning domains of staying organized, planning, initiating tasks, shifting gears, and self-monitoring.

Children with ADHD and coexisting learning disorders, communication or developmental delays, significant mental health or oppositional challenges, or autism spectrum disorder often need more specialized educational supports than those that can be provided through accommodations in a general classroom. In the United States, these children would qualify to have an individualized educational plan (IEP) developed through the public school system.

Medications

Before medication initiation, a history and physical examination and an assessment for baseline sleep, eating, and mood should be conducted because these need to be monitored for a child on medication. Children with ADHD and their families should be educated on the benefits, risks, and side effects of medication, with a discussion about goals and expectations for medication treatment. It is common for a child to need to try several trials of different medications or doses to find the optimal ADHD pharmacologic treatment that both reduces core ADHD symptoms and is well tolerated. ADHD rating scales can be used to assess for medication effectiveness and side effects, both at initiation and during medication maintenance, and should be collected from parents and teachers when possible.

The types of medications used to treat ADHD fall into one of the following three categories: stimulants, norepinephrine reuptake inhibitors, and α_2-adrenergic agonists. Stimulants are the most commonly used medications to treat ADHD and have been used to treat this condition since the 1930s. Stimulant medications have a slightly larger treatment effect size (standardized mean difference) than nonstimulants (approximately 1.0 for stimulants versus approximately 0.7 for both norepinephrine reuptake inhibitors and α_2-adrenergic agonists). Although stimulants are generally recommended as the first-line ADHD medication, nonstimulant medications may be considered in the context of active substance use disorder for an adolescent with ADHD or household family member or if there is a strong family desire for a nonstimulant medication. Stimulants have been found to have relatively high rates of adverse effects (particularly moodiness and irritability) in preschool-age children and in children with intellectual disability or autism spectrum disorder, leading some physicians to choose nonstimulant medication in these situations, as described later.

When starting a stimulant, the clinician can select either a methylphenidate-based or an amphetamine-based medication. The decision about which stimulant medication to use for a specific child or adolescent with ADHD is often based on factors such as duration of action (short, intermediate, long acting), preparation (pills, capsules that can be swallowed whole or whose contents can be "sprinkled" into food, chewable tablets, and liquids), and clinician preference or insurance company formularies. Stimulant medications have a rapid onset of action (ranging from about 20 minutes to up to an hour, depending on the formulation), and most leave the system within 3-12 hours, depending on if they are short, intermediate, or long acting. A child who responds poorly to one stimulant medication may do well with a different medication in that class or the other class (methylphenidate versus amphetamine). Stimulant medications should be initiated at the lowest available dose and titrated upward, assessing for both effectiveness and side effects, until reaching a dose that reduces ADHD symptoms and has minimal to no side effects. Common side effects of stimulant medication include decreased appetite, headaches, stomachaches, and difficulty falling asleep. If mood lability occurs, it should be noted whether this is while the stimulant medication is active (which may indicate that a different medication should be tried instead) or as the medication is wearing off (also called *rebound* and may indicate that a short-acting preparation should be replaced by a longer-acting preparation or a low dose of a short-acting preparation should be added about 30 minutes before the onset of the rebound symptoms).

Height, weight, pulse, and blood pressure should be periodically monitored. Stimulants may be associated with a slight reduction in linear growth, although studies of the impact of stimulants on adult height range from findings of a slight impact to no significant difference. Children with decreased appetite from stimulants and difficulty with weight gain can be counseled to increase caloric intake later in the day when the appetite returns. Significant reductions (i.e., crossing two lines on the growth curve) in either height or weight for a child on stimulant medication may prompt changing to a different ADHD medication.

Before starting stimulants, children should be screened for symptoms or signs suggestive of a cardiomyopathy, coronary artery disease, cardiac arrhythmias, or a family history of cardiac arrhythmias or sudden death under 50 years of age, and if these symptoms are present, an electrocardiogram and/or evaluation by a cardiologist to determine if it is safe to start these medications is recommended. Most children with tics can be treated with stimulant medication, but occasionally these medications may exacerbate tics. In these cases, the risks and benefits of continuing versus changing or stopping the medication should be considered.

Treatment of ADHD with stimulant medication is associated with reduced substance use risks. However, stimulant medications themselves are controlled substances with potential for misuse, diversion, and abuse. Therefore clinicians should regularly counsel adolescent patients about this risk, the importance of taking the medication only as prescribed, and about safe medication storage practices (e.g., keeping medication in a secure location).

Two types of selective norepinephrine reuptake inhibitors are approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD in children and adolescents: atomoxetine and viloxazine. These medications take up to 4 weeks to achieve effectiveness and should be taken consistently to be effective. Both atomoxetine and viloxazine have common side effects of fatigue, decreased appetite, nausea, vomiting, and irritability and a rare potential for suicidal thinking and behaviors for which the child must be monitored.

α_2-Adrenergic agonist medications include guanfacine and clonidine. Long-acting preparations of both have U.S. FDA approval for the treatment of ADHD in children ≥6 years old either as monotherapy or an adjunctive therapy with stimulant medication. Short-acting preparations are sometimes used off-label to treat young (<6-year-old) children with ADHD (especially those with coexisting autism spectrum disorder or sleep disorders). α_2-Adrenergic agonists may take up to 2 weeks to achieve an initial response. These medications can also treat motor and vocal tics and so may be a reasonable choice in a child with a coexisting tic disorder. Common side effects of α_2-adrenergic agonists can include sedation, headaches, and hypotension, and they should be stopped gradually because abrupt discontinuation could result in rapid increase in blood pressure.

Medication alone may not be sufficient to treat ADHD in children, particularly when children have additional psychiatric disorders, developmental disabilities, or significant psychosocial challenges. When children do not respond to medication, it may be appropriate to refer them to a mental health specialist. Consultation with a child psychiatrist, developmental-behavioral pediatrician, or psychologist can be beneficial to determine the next steps for treatment, including adding other components and supports to the overall treatment program. Evidence suggests that children who receive careful medication management, accompanied by frequent treatment follow-up, all within the context of an educational, supportive relationship with the primary care provider, are likely to experience behavioral gains.

PROGNOSIS

More than half of individuals with a childhood diagnosis of ADHD will manifest a mental health condition (e.g., anxiety, depression, substance use disorders) in adulthood. Approximately one third to two thirds of those diagnosed with ADHD in childhood will continue to manifest significant symptoms of ADHD in adulthood. In children with ADHD, a reduction in hyperactive behavior often occurs with age. Other symptoms associated with ADHD can become more prominent with age, such as inattention, impulsivity, and disorganization, and these exact a heavy toll on adolescent and young adult functioning. Adolescents and young adults with ADHD have an increased likelihood of risk-taking behaviors (early sexual activity, delinquent behaviors, motor vehicle accidents, substance use), seizures, psychosis, educational underachievement or employment difficulties, and relationship difficulties. With proper treatment, the risks associated with ADHD, including injuries, can be significantly reduced. Consistent treatment with medication and adjuvant therapies appears to lower the risk of adverse outcomes, such as substance abuse.

SECONDARY PREVENTION

Parent training can lead to significant improvements in ADHD symptoms and oppositional behaviors in preschool and school-age children with ADHD. To the extent that parents, teachers, physicians, and policymakers support efforts for earlier detection, diagnosis, and treatment, prevention of long-term adverse effects of ADHD on affected children's functioning can be considered within the lens of secondary prevention of the long-term effects of untreated or ineffectively treated ADHD on children and youth.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 51

Dyslexia

Sally E. Shaywitz and Bennett A. Shaywitz

DEFINITION

Dyslexia has always been defined as an unexpected difficulty in reading, which has been codified in U.S. Federal law (First Step Act of 2018, PL: 115–391) as the most up-to-date, evidence-based definition of dyslexia: "The term *dyslexia* means an unexpected difficulty in reading for an individual who has the intelligence to be a much better reader, most commonly caused by a difficulty in the phonological processing (the appreciation of the individual sounds of spoken language), which affects the ability of an individual to speak, read, and spell." In typical readers, development of reading and intelligence quotient (IQ) are dynamically linked over time. In dyslexic readers, however, a developmental uncoupling occurs between reading and IQ (Fig. 51.1), such that reading achievement is significantly below what would be expected given the individual's IQ.

The uncoupling between reading achievement and IQ provides the long-sought empirical evidence for the seeming paradox between cognition and reading in individuals with developmental dyslexia, and this discrepancy is recognized in the federal definition as unexpected difficulty in reading. However, clinicians may see other approaches to diagnosis. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) describes specific learning disorder with impairment in reading for children with reading skills significantly below those expected for the child's age where the deficits are not explained by intellectual disability, sensory deficits, neurologic disorders, or psychosocial adversity. This definition can be problematic in failing to differentiate primary problems with reading comprehension from the reading problems experienced by children with dyslexia despite strong evidence that the two are distinct. Further, excluding children with psychosocial adversity is concerning because children who struggle with reading due to psychosocial adversity suffer similar adverse long-term consequences and have been shown to benefit from interventions designed to help children with dyslexia.

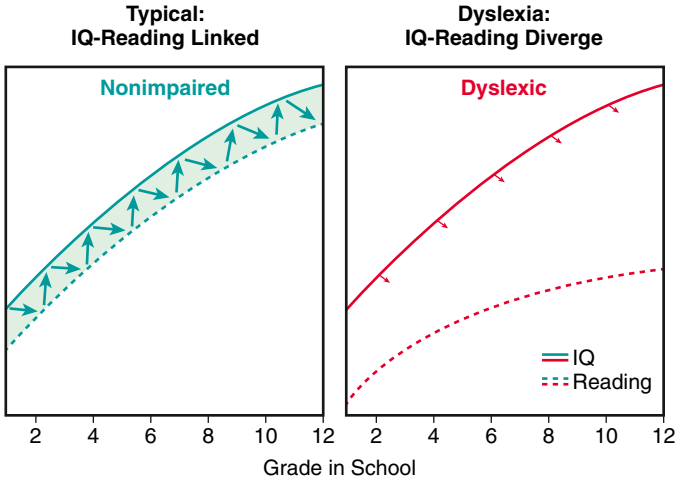

Fig. 51.1 Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia. *Left,* In typical readers, reading and IQ development are dynamically linked over time. *Right,* In contrast, reading and IQ development are dissociated in dyslexic readers, and one does not influence the other. *(Copyright Sally Shaywitz, MD. Adapted from Shaywitz S, Shaywitz J. Overcoming Dyslexia, 2nd ed. New York: Vintage Books;2020: 103.)*

EPIDEMIOLOGY

Dyslexia is the most common of the learning disabilities, affecting 80–90% of children identified as having a learning disability. Dyslexia may be the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 20% in unselected population-based samples to much lower rates in school-identified samples. The low prevalence rate in school-identified samples may reflect the reluctance of schools to screen, assess, and identify dyslexia. Dyslexia occurs with equal frequency in males and females in survey samples in which *all* children are assessed. Despite such well-documented findings, schools continue to identify more males than females, probably reflecting the more rambunctious behavior of males who come to the teacher's attention because of misbehavior, whereas females with reading difficulty, who are less likely to be misbehaving, are also less likely to be noticed and identified by the schools. Dyslexia fits a dimensional model in which reading ability and disability occur along a *continuum*.

PATHOGENESIS

Evidence from a number of lines of investigation indicates that dyslexia reflects deficits within the language system, and more specifically, within the **phonologic component** of the language system engaged in processing the sounds of speech. Individuals with dyslexia have difficulty developing an awareness that spoken words can be segmented into smaller elemental units of sound (phonemes), an essential ability given that reading requires that the reader map or link printed symbols to their sounds. Increasing evidence indicates that disruption of attentional mechanisms may also play an important role in reading difficulties.

Functional brain imaging in both children and adults with dyslexia demonstrates an inefficient functioning of left hemisphere posterior brain systems, a pattern referred to as the *neural signature of dyslexia* (Fig. 51.2). These differences can be observed before the start of formal reading instruction, suggesting they represent a biologic predisposition to reading difficulties as opposed to a result of inadequate instruction. Although functional magnetic resonance imaging (fMRI) consistently demonstrates differences between *groups* of dyslexic compared to typical readers, brain imaging is not able to reliably differentiate an *individual* case of a dyslexic reader from a typical reader and thus is not useful in diagnosing dyslexia.

CLINICAL MANIFESTATIONS

Reflecting the underlying phonologic weakness, children and adults with dyslexia manifest problems in both spoken and written language. Spoken language difficulties are typically manifest by mispronunciations, lack of glibness, speech that lacks fluency with many pauses or hesitations and "ums," word-finding difficulties with the need for time to summon an oral response, and the inability to come up with a verbal response quickly when questioned; these reflect *sound-based,* not semantic or knowledge-based, difficulties.

Struggles in decoding and word recognition can vary according to age and developmental level. The cardinal signs of dyslexia observed in school-age children and adults are a labored, effortful approach to reading involving decoding, word recognition, and text reading. Listening comprehension is typically robust. Older children improve reading accuracy over time, but without commensurate gains in reading fluency; they remain slow readers. Difficulties in spelling typically reflect the phonologically based difficulties observed in oral reading. Handwriting is often affected as well.

History often reveals early subtle language difficulties in dyslexic children. During the preschool and kindergarten years, at-risk children display difficulties playing rhyming games and learning the names for letters and numbers. Kindergarten assessments of these language skills can help identify children at risk for dyslexia. Although a dyslexic child enjoys and benefits from being read to, the child might avoid reading aloud to the parent or reading independently.

Dyslexia may coexist with attention-deficit/hyperactivity disorder (see Chapter 50); this comorbidity has been documented in both referred samples (40% comorbidity) and nonreferred samples (15% comorbidity).

DIAGNOSIS

A large achievement gap between typical and dyslexic readers is evident as early as first grade and persists (Fig. 51.3). These findings provide strong evidence and impetus for early screening and identification of and early intervention for young children at risk for dyslexia. One source of potentially powerful and highly accessible screening information is their teacher's judgment about the child's reading and reading-related skills. Evidence-based screening can be carried out as early as kindergarten, and also in grades 1-3, by the child's teacher. Their teachers' responses to a small set of questions (10-12 questions) predict a pool of children who are at risk for dyslexia with a high degree of accuracy. This evidence-based screening takes less than 10 minutes, is completed on a tablet, and is extremely efficient and economical. Children

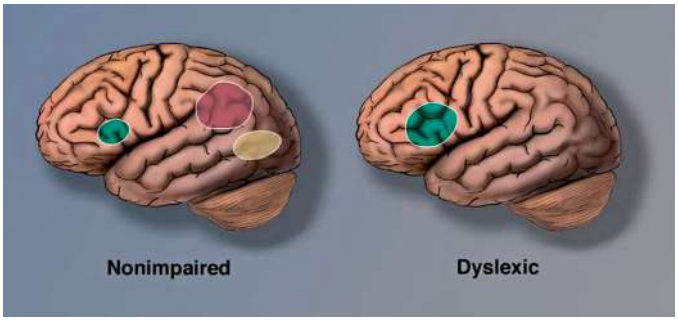

Fig. 51.2 A neural signature for dyslexia. Image on left shows left hemisphere brain systems in typical (nonimpaired) readers. The three systems for reading are an anterior system in the region of the inferior frontal gyrus (Broca's area), serving articulation and word analysis, and two posterior systems: one in the occipitotemporal region serving word analysis and a second in the occipitotemporal region (the word-form area) serving the rapid, automatic, fluent identification of words. In dyslexic readers (*right* image), the two posterior systems are functioning inefficiently and appear underactivated. This pattern of underactivation in left posterior reading systems is referred to as the neural signature for dyslexia. *(Copyright Sally Shaywitz, MD. Adapted from Shaywitz S. Shaywitz J. Overcoming Dyslexia, 2nd ed. New York: Vintage Books;2020: 78.)*

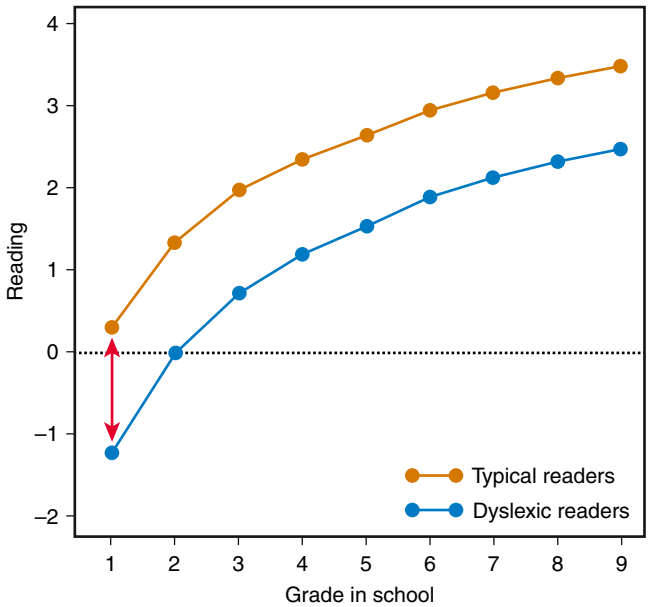

Fig. 51.3 Reading from grades 1 through 9 in typical and dyslexic readers. The achievement gap between typical and dyslexic readers is evident as early as first grade and persists through adolescence. *(Copyright Sally Shaywitz, MD. Adapted from Shaywitz S. Shaywitz J. Overcoming Dyslexia, 2nd ed. New York: Vintage Books;2020: 56.)*

found to be at risk will then have further assessment and, if diagnosed as dyslexic, should receive evidence-based intervention.

Dyslexia is a clinical diagnosis, and history is especially critical. The clinician seeks to determine through history, observation, and psychometric assessment if there are unexpected difficulties in reading (based on the person's intelligence, chronologic/grade, level of education, or professional status) and associated linguistic problems at the level of phonologic processing. No single test score is pathognomonic of dyslexia. The diagnosis of dyslexia should reflect a thoughtful synthesis of all clinical data available.

Dyslexia is distinguished from other disorders that can prominently feature reading difficulties by the unique, circumscribed nature of the *phonologic deficit,* one that does not intrude into other linguistic or cognitive domains. A core assessment for the diagnosis of dyslexia in children includes tests of language, particularly phonology; reading, including real and pseudowords; reading fluency; spelling; and tests of intellectual ability. Additional tests of memory, general language skills, and mathematics may be administered as part of a more comprehensive evaluation of cognitive, linguistic, and academic function.

For informal screening, in addition to a careful history, the primary care physician in an office setting can listen to the child read aloud from the child's own grade-level reader. Keeping a set of graded readers available in the office serves the same purpose and eliminates the need for the child to bring in schoolbooks. **Oral reading** is a sensitive measure of reading accuracy and fluency. The most consistent and telling sign of a reading disability in an accomplished young adult is slow and laborious reading and writing. In attempting to read aloud, most children and adults with dyslexia display an effortful approach to decoding and recognizing single words, an approach in children characterized by hesitations, mispronunciations, and repeated attempts to sound out unfamiliar words. In contrast to the difficulties they experience in decoding single words, persons with dyslexia typically possess the vocabulary, syntax, and other higher-level abilities involved in comprehension.

Fluency forms the bridge between decoding, that is, reading a word accurately, and comprehension, understanding what is read. Fluent reading is reading accurately and rapidly, with good intonation (prosody) indicating an understanding of the text. The failure either to recognize or to measure the lack of fluency in reading is perhaps the most common error in the diagnosis of dyslexia, especially in older children and accomplished young adults. Simple word identification tasks will not detect dyslexia in a person who is accomplished enough to be in honors high school classes or to graduate from college or obtain a graduate degree. Tests relying on the accuracy of word identification alone are inappropriate to use to diagnose dyslexia because they show little to nothing of the *struggle* to read. Because they assess reading accuracy but not automaticity or prosody, the types of reading tests used for school-age children might provide misleading data on bright adolescents and young adults. Among the most critical tests are those that are *timed;* they are the most sensitive in detecting dyslexia in a bright adult. Few standardized tests for young adult readers are administered under timed and untimed conditions; the *Nelson-Denny Reading Test* is an exception. The helpful *Test of Word Reading Efficiency* (TOWRE) examines simple word reading under timed conditions, and the Achievement Improvement Monitoring System (AIMSweb) and Dynamic Indicators of Basic Early Literacy Skills (DIBELS) measure reading connected text under timed conditions. Any scores obtained on testing must be considered relative to peers with the same degree of education or professional training.

IS FAMILY HISTORY HELPFUL IN DIAGNOSING DYSLEXIA?

Although dyslexia is familial, family history is not effective as a screening measure for dyslexia and does not improve the classification accuracy provided by an evidence-based early screening measure.

Genome-wide association studies (GWASs) in children with dyslexia have demonstrated that a large number of genes are involved, each producing a small effect. Complex traits such as reading are the work of thousands of genetic variants working in concert (see Chapter 103). Thus pediatricians should be wary of recommending any genetic test to their patients that purports to diagnose dyslexia in infancy or before language and reading have even emerged. It is unlikely that a single gene or even a few genes will reliably identify people with dyslexia. Rather, dyslexia is best explained by multiple genes, each contributing a small amount toward the expression of dyslexia.

MANAGEMENT

The management of dyslexia demands a life-span perspective. Early in life the focus is on **remediation** of the reading problem. Applying knowledge of the importance of early language, including phonologic skills and vocabulary, leads to significant improvements in children's reading accuracy, even in predisposed children. As a child matures and enters the more time-demanding setting of middle and then high school, the emphasis shifts to the important role of providing accommodations. Based on the work of the National Reading Panel, evidence-based reading intervention methods and programs are identified. Effective intervention programs provide systematic instruction in five key areas: phonemic awareness, phonics, fluency, vocabulary, and comprehension strategies. These programs also provide ample opportunities for writing, reading, and discussing literature.

Taking each component of the reading process in turn, effective interventions improve phonemic awareness: the ability to focus on and manipulate phonemes (speech sounds) in spoken syllables and words. The elements found to be most effective in enhancing **phonemic awareness**, reading, and spelling skills include teaching children to manipulate phonemes with letters, focusing the instruction on one or two types of phoneme manipulations rather than multiple types, and teaching children in small groups. Providing instruction in phonemic awareness is necessary, but not sufficient, to teach children to read. Effective intervention programs include teaching **phonics**, or making sure that the beginning reader understands how letters are linked to sounds (phonemes) to form letter-sound correspondences and spelling patterns. The instruction should be explicit and systematic; phonics instruction enhances children's success in learning to read, and systematic phonics instruction is more effective than instruction that teaches little or no phonics or that teaches phonics casually or haphazardly. Important but often overlooked is starting children on reading connected text early on, optimally at or near the beginning of reading instruction. Reading connected text is critical in building vocabulary and increasing background knowledge—both important in improving reading comprehension.

Fluency is of critical importance because it allows the automatic, rapid recognition of words. Although it is generally recognized that fluency is an important component of skilled reading, it is often overlooked in teaching. One approach is to have a child practice oral reading with a teacher or parent providing positive and helpful feedback. Here practice is critical. Interventions for vocabulary development and reading comprehension are not as well established. The most effective methods to teach reading comprehension involve teaching vocabulary and strategies that encourage active interaction between the reader and the text. Emerging science indicates that it is not only teacher content knowledge but the teacher's skill in engaging the student and focusing the student's attention on the reading task at hand that is required for effective instruction.

The interventions described here can be provided in multiple settings, but specialized schools for children with dyslexia that provide intensive intervention over 4 years or more have been very effective. Typically, these schools are costly, although increasingly offering scholarships. Some school districts are considering developing public schools specializing in educating children with dyslexia.

For those in high school, college, and graduate school, provision of **accommodations** most often represents a highly effective approach to dyslexia. Imaging studies now provide neurobiologic evidence of the need for extra time for dyslexic students; accordingly, college students with a childhood history of dyslexia require extra time in reading and writing assignments and in examinations. Many adolescent and adult students have been able to improve their reading accuracy, but without commensurate gains in reading speed. The accommodation of extra time reconciles the individual's often high cognitive ability and slow reading, so that the exam is a measure of that person's ability rather than disability. Another important accommodation is helping the student access text-to-speech programs. Excellent text-to-speech programs and apps are available for Apple and Android systems and the PC and include Voice Dream Reader, Immersive Reader (available for free in all Microsoft Office programs, including Word, OneNote, and PowerPoint), Kurzweil Firefly, Read & Write Gold, Read: OutLoud, and Natural Reader. Voice-to-text programs are also helpful, often part of the suite of programs, as well as the popular Dragon Dictate. Voice-to-text is found on many smartphones. Other helpful accommodations include the use of laptop computers with spelling checkers, access to lecture notes, tutorial services, and a separate quiet room for taking tests.

In addition, the impact of the primary phonologic weakness in dyslexia mandates special consideration during oral examinations so that students are not graded on their lack of glibness or speech hesitancies, but on their content knowledge. Unfortunately, speech hesitancies or difficulties in word retrieval often are wrongly confused with insecure content knowledge. The major difficulty in dyslexia—reflecting problems accessing the sound system of spoken language—causes great difficulty learning a second language. As a result, an often-necessary accommodation is a waiver or partial waiver of the foreign language requirement; the dyslexic student may enroll in a course taught in English on the history or culture of a non–English-speaking country.

PROGNOSIS

Application of evidence-based methods to young children, when provided with sufficient intensity and duration, can result in improvements in reading accuracy and, to a much lesser extent, fluency. Improvements in fluency can be effected with frequent practice in reading aloud with the helpful input of a teacher or parent. As noted earlier, accommodations are critical in allowing the dyslexic child to demonstrate his or her knowledge.

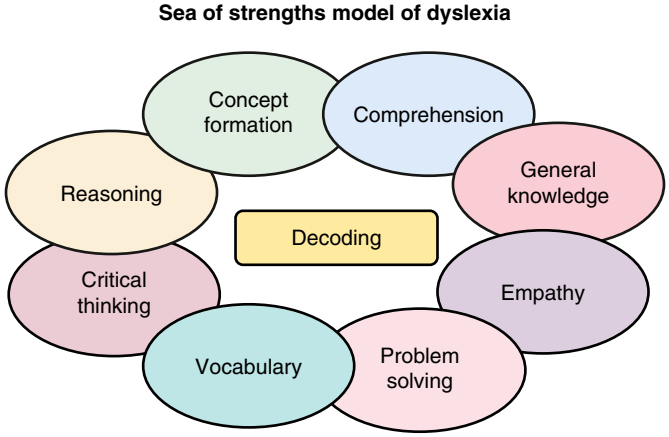

Fig. 51.4 Sea of strengths model of dyslexia. In dyslexia, a circumscribed, encapsulated weakness in decoding is surrounded by a sea of strengths in higher-level thinking and reasoning. The weakness in decoding masks what are often excellent thinking and comprehension skills. *(Copyright Sally Shaywitz, MD. Adapted from Shaywitz S. Shaywitz J. Overcoming Dyslexia, 2nd ed. New York: Vintage Books;2020: 141.)*

A person who is dyslexic experiences through life aligns with our Sea of Strengths model of dyslexia (Fig. 51.4). This model indicates that in dyslexia there is a weakness in decoding reflecting the difficulties connecting letters to sounds, a weakness that is very visible early on when learning to read. At the same, this weakness is surrounded by a sea of strengths in higher-level cognitive, big-picture thinking, including reasoning, problem solving, vocabulary, empathy, concept formation, and critical thinking. It is this sea of strengths that comes to the fore and supports a positive future as a person with dyslexia matures. The sea of strengths was very "visible" in a recent report examining the academic and social experiences in college and outcomes in the workplace 5 or more years after graduation in Yale graduates with dyslexia compared with a matched group of Yale graduates who were typical readers. Dyslexic college graduates did not differ from typical graduates either in college or in the workplace. Parents of dyslexic children often ask about their child's future. These findings should reassure those pediatricians and parents that dyslexic students can succeed all along the developmental pathway throughout school, and now through college and the workplace. With proper support, dyslexic children can succeed in a range of future occupations that might seem out of their reach, including medicine, law, journalism, and writing.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 52
Math and Writing Disabilities

52.1 Math Disabilities

Kenneth L. Grizzle and Brittany J. Bice-Urbach

Data from the U.S. National Center for Educational Statistics for 2009 showed that 69% of U.S. high school graduates had taken algebra 1, 88% geometry, 76% algebra 2/trigonometry, and 35% precalculus. These percentages are considerably higher than those from 20 years earlier. However, concerns remain about the limited mathematics literacy level for children, adolescents, and those entering the workforce; poor math skills predict numerous social, employment, and emotional challenges. The need for number and math literacy extends beyond the workplace and into daily lives, and weaknesses can negatively affect daily functioning. Research into the etiology and treatment of **math disabilities** falls behind the study of reading disabilities (see Chapter 51), and yet the database needed to effectively identify, treat, and minimize the impact of math challenges on daily functioning and education is growing.

MATH LEARNING DISABILITY DEFINED

Understanding learning challenges associated with mathematics requires a basic appreciation of domain-specific terminology and operations. The *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) has published diagnostic criteria for learning disorders. Specific types of learning challenges are subsumed under the broad term of **specific learning disorder (SLD)**. The DSM-5 identifies

the following features of a SLD with an **impairment in math**: difficulties mastering number sense, number facts, or fluent calculation and difficulties with math reasoning. Symptoms must be present for a minimum of 6 months and persist despite interventions to address the learning challenges. **Number sense** refers to a basic understanding of quantity, number, and operations and is represented as nonverbal and symbolic. Examples of number sense include an understanding that each number is 1 more or 1 less than the previous or following number, knowledge of number words and symbols, and the ability to compare the relative magnitude of numbers and perform simple arithmetic calculations.

The DSM-5 definition can be contrasted with an **education-defined learning disability in mathematics**. Two math-related areas are identified as part of the **Individuals with Disabilities Education Act (IDEA)**: mathematics calculation and mathematics problem solving. Operationally, this is reflected in age-level competency in arithmetic and math calculation, word problems, interpreting graphs, understanding money and time concepts, and applying math concepts to solve quantitative problems. The federal government allows states to choose the way a *learning disability* (LD) is identified if the procedure is "research based." Referred to specifically in the IDEA as methods for identifying an LD are a **discrepancy model** and "use of a process based on the child's response to scientific, research-based intervention." The former refers to identifying an LD based on a pronounced discrepancy between intellectual functioning and academic achievement. The latter, referred to as a **response to intervention (RtI)** model, requires school systems to screen for a disability, intervene using evidence-based treatments for the identified disability, closely monitor progress, and make necessary adjustments to the intervention as needed. If a child is not responding adequately, a multidisciplinary team is created, and an evaluation is then completed to determine whether the child qualifies for special education programming. Not responding to the interventions alone does not result in automatic qualification for services outside of regular education. Rather, it is a three-step process: lack of adequate progress to the interventions, an evaluation of the area(s) of concern, and then determination by the team if an **individualized educational plan (IEP)** is needed. The IEP team typically consists of teachers, special education teacher, school psychologist, school district representative, parents, and, depending on their age, the student.

It is important that primary care providers understand the RtI process because many states require or encourage this approach to identifying LDs. Confusion can be avoided by helping concerned parents understand that a school may review their child's records, screen the skills of concern, and provide intervention with close progress monitoring before initiating the process for an IEP. Traditional psychoeducation testing (IQ and achievement) may only be completed if a child has not responded well to specific interventions. The RtI approach is a valuable, empirically supported way to approach and identify a potential LD but is very different from a medical approach to diagnosis and treatment. First and foremost, this allows for early intervention, which has been shown repeatedly to decrease the likelihood of a later identified LD. Intervening early also allows educators to avoid the "wait to fail" model that all too often waited for children to enter third or fourth grade before receiving needed services.

Terminology

The term **dyscalculia**, often used in medicine and research but seldom used by educators, is reserved for children with a SLD in math when there is a pattern of deficits in learning arithmetic facts and accurate, fluent calculations. The term **math learning disability (MLD)** is used generically here, with dyscalculia used when limiting the discussion to children with deficient math calculation skills. A distinction is also made between children with a MLD and those who are **low achieving (LA) in math**; both groups have received considerable research focus. Although not included in either definition provided earlier, research into math deficits often require that individuals identified with MLD have math achievement scores below the 10th percentile across multiple grade levels. These children start out poorly in math and continue poor performance across grades, despite interventions. LA math students consistently score below the 25th percentile on math achievement tests across grades, often showing the same weak math-related characteristics as those with MLD but with less severity. Complicating the identification of MLD and its differentiation from LA math students is the variability in relative complexity of math concepts that may result in short-lived math difficulties.

EPIDEMIOLOGY

Prevalence

Depending on how MLD is defined and assessed, the prevalence varies. Based on findings from multiple studies, approximately 7% of children will show a MLD profile before high school graduation. An additional 10% of students will be identified as LA. Because research in the area typically requires that individuals show deficits for consecutive years, the respective prevalence estimates are lower than the 10th percentile cutoff for being identified as having an MLD or the 25th percentile cutoff for being identified as LA. It is not unusual for children to score below the criterion one year and then above the criterion in subsequent years. Males are at greater risk to experience MLD.

Risk Factors

Genetics

The heritability of math skills is estimated to be approximately 0.50. The heritability or genetic influence on math skills is consistent across the continuum from high to low math skills. This research emphasizes that although math skills are learned across time, the stability of math performance is the result of genetic influences. Math heritability appears to be the product of multiple genetic markers, each having a small effect.

Medical/Genetic Conditions

Numerous genetic syndromes are associated with math problems. Although most children with **fragile X syndrome** have an *intellectual disability* (ID), approximately 50% of females with the condition do not. Of those without an ID, ≥75% have a math disability by the end of third grade and are already scoring below average in mathematics in kindergarten and first grade. For females with fragile X MLD, weak working memory seems to play an important role. The frequency of MLD in **Turner syndrome (TS)** is the same as that found in females with fragile X syndrome. A consistent finding is females with TS complete math calculations at significantly slower speed than typically developing students. Although females with TS have weak calculation skills, their ability to complete math problems not requiring explicit calculation is similar to that of their peers. The percentage of children with **22q11.2 deletion syndrome** (22q11.2ds) with MLD is not clear. Younger children with this genetic condition (6-10 years old) showed similar number sense and calculation skills as typically developing children but weaker math problem solving. Older children with 22q11.2ds showed slower speed in their general number sense and calculations, but accuracy was maintained. Weak counting skills and magnitude comparison have been found in this group of children, suggesting weak visual-spatial processing. Children with **myelomeningocele** are at greater risk for math difficulties than their unaffected peers. Almost 30% of these children have MLD without an additional diagnosed learning disorder, and >50% have both math and reading learning disorders. Although broad, deficits are most pronounced in speed of math calculation and written computation.

Comorbidities

It is estimated that 30–70% of those with MLD will also have a reading disability. This is especially important because children with MLD are less likely to be referred for additional educational assistance and intervention than students with reading problems. Unfortunately, children identified with both learning challenges perform poorer across psychosocial and academic measures than children with MLD alone. Having a MLD places a child at greater risk for not only other learning challenges but also psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder, generalized anxiety disorder, and major depressive disorder.

Individuals with MLD have been found to have increased social isolation and difficulties developing social relationships in general.

CAUSES OF MATH LEARNING DISABILITY

There is a consensus that individuals with MLD are a heterogeneous group, with multiple potential broad and specific deficits contributing to their learning difficulties. Research into the causes of MLD has focused on math-specific processes and broad cognitive deficits, with an appreciation that these two factors are not always independent.

Broad Cognitive Processes

Intelligence

Intelligence affects learning, but if intellectual functioning were the primary driver of poor math performance, the math skills of low-IQ children would be similar or worse than individuals with MLD. On the contrary, children with MLD have significantly poorer math achievement than children with low IQ. Children with MLD have severe deficits in math not accounted for by their cognitive functioning. Individuals with lower cognition may have difficulty learning mathematics, but their math skills are likely to be commensurate with their intelligence.

Memory

Working memory (WM) refers to the ability to keep information in mind while using the information in other mental processes. WM is composed of three core systems: the central executive, the language-related phonologic loop, and the visual-based sketch pad. The central executive coordinates the functioning of the other two systems. All three play a role in various aspects of learning and in the development and application of math skills in particular; children with MLD have shown deficits in each area.

Committing math facts to and/or retrieving facts from memory has consistently been found to be problematic for children with MLD. This is not necessarily limited to inaccurate retrieval of facts but also speed of retrieval, independent of broader speed of processing deficits. Unfortunately, unlike some typically developing peers who may be slower but accurate in their fact retrieval, students with MLD are often slow and inaccurate. Weak fact encoding or retrieval alone do not determine an MLD diagnosis. Many math curricula in the United States do not include development of math facts as a part of the instructional process, resulting in children not knowing basic facts.

Processing Speed

Individuals with MLD are often slower to complete math problems than their typically developing peers, a result in part of their poor fact retrieval rather than broader speed of processing deficits. However, young children later identified with a MLD when beginning school have numerical-processing speed that is considerably slower than same-age same-grade peers. This is reflected in the time required to recognize numbers, correctly order fractions, and complete word problems.

Problem Solving

Not only do children with MLD struggle to quickly and accurately engage in numerical-related activities, in part because of these difficulties, they commonly rely on less efficient and laborious problem-solving practices. This is seen in children relying on finger counting beyond second grade, use of repeated adding for multiplication facts, pronounced difficulty moving beyond reliance on manipulatives, and drawing objects to help with calculation. Difficulties with math processes across multiple levels can result in math being a time-intensive and time-consuming process for kids with MLD.

Executive Skills

Difficulties with executive functioning (EF) can lead to challenges in multiple areas of a child's life, academic and nonacademic (see Chapter 49). Performance in math is but one example. EF refers to skills including but not limited to sustained attention, managing impulses, cognitive and behavioral flexibility, and WM. Anyone who has worked with children diagnosed with ADHD, a group of kids notorious for having EF challenges, can appreciate the impact these behaviors could potentially have on math. Deficits in WM, auditory and visual, can negatively affect a child's development of math skills. A child approaching a word problem exemplifies the impact of various executive skills on math. The child must keep in memory the content read and integrate it with what they know about the topic and possible operation to apply, all the while not responding to the irrelevant information contained within the passage. Creating a mental representation of the problem requires use of the visual sketch pad (visual WM).

Math-Specific Processes

Number Sense

The term *number sense* has been defined in different ways, though the general agreement is that the concept refers to an intuitive preverbal ability to identify an approximation of items within a set that precedes formal math instruction. This is seen in the ability to recognize and manipulate nonsymbolic properties without having to apply a name to the process—for example, recognizing that a box of three dots is fewer than a box containing five dots. Unlike their peers, children with MLD are more likely to count the number of items within the comparison rather than recognizing the apparent difference.

Math is a symbolic process and cannot be efficiently learned and mastered without understanding this numerical skill. There is considerable evidence that young children who struggle to develop symbolic numerical representation, in contrast to number sense, are at considerable risk to have difficulty developing higher-level math skills. Examples of symbolic representations range from recognizing that the numeral 4 and word *four* reflect a quantity and quickly recognizing the larger (or smaller) of two numbers, all the way to understanding fractions and more complex notations.

Procedural Errors

The type of errors made by children with a, MLD are typical for any child, the difference being that children with a LD show a 2- to 3-year lag in understanding the concept. An example of a common error a first-grade child with a, MLD might make when "counting on" is to undercount: "6 + 2= ?"; "6, 7" rather than starting at 6 and counting an additional two numbers. As children with math deficits get older, it is common to subtract a larger number from a smaller number. For example, in the problem "63 − 29 = 46," the child makes the mistake of subtracting 3 from 9. Another common error is not decreasing the number in the 10s column when borrowing: "64 − 39 = 35." For both adding and subtracting, there is a lack of understanding of the commutative property of numbers and a tendency to use repeated addition rather than fact retrieval. It is not that children with an MLD do not develop these skills, it is that they develop them much later than their peers, thereby making the transition to complicated math concepts much more challenging.

Unlike dyslexia, in which deficits have been isolated and identified as causal (see Chapter 51), factors involved in the development of a MLD are much more heterogeneous. Alone, none of the processes previously outlined fully account for MLD, although all have been implicated as problematic for those struggling with math.

TREATMENT AND INTERVENTIONS

The most effective interventions for MLD are those that include explicit instruction on solving specific types of problems and that take place over several weeks to several months. Skill-based instruction is a critical component; general math problem solving will not carry over across various math skills unless the skill is part of a more complex math concept. Clear, comprehensive guidelines for effective interventions for students struggling with math have been provided by the U.S. Department of Education in the form of a *Practice Guide* released through the What Works Clearinghouse. This document gives excellent direction in the identification and treatment of children with math difficulties in the educational system. Although not intended for medical personnel or parents, the guide is available free of charge and can be helpful for parents when talking to teachers about their child's learning. Table 52.1 lists additional resources for parents concerned about their young child's development of math facts.

Table 52.1 Parent Resources for the Child with Math Learning Disability

Let's Talk About Math. Available from http://www.zerotothree.org/parenting-resources/early-math-video-series. Accessed September 19, 2021.

Mixing in Math. Available from https://www.terc.edu/mixinginmath/. Accessed September 19, 2021.

PBS Parents. Math resources available to parents through the Public Broadcasting Service website. Accessed September 19, 2021.
http://www.pbs.org/parents/earlymath/index.html
http://www.pbs.org/parents/education/math/

Understood: Math. Available from https://www.understood.org/topics/en/math.

U.S. Department of Education. *Helping your child learn mathematics*. Available from https://www2.ed.gov/parents/academic/help/math/index.html. Accessed September 19, 2021.

Table 52.2 Risk Factors for a Specific Learning Disability Involving Mathematics

The child is at or below the 20th percentile in any math area, as reflected by standardized testing or ongoing measures of progress monitoring.

The teacher expresses concerns about the child's ability to "take the next step" in math.

There is a positive family history for math learning disability (this alone will not initiate an intervention).

Parents think they have to "reteach" math concepts to their child.

Awareness that most public school systems have implemented some form of an RtI model to identify LDs allows the primary care physician to encourage parents to return to the school seeking an intervention to address their child's concern. Receiving special education services in the form of an IEP may be necessary for some children. However, the current approach to identifying children with an LD allows school systems to intervene earlier, when problems arise, and potentially avoid the need for an IEP. Pediatricians with patients whose parents have received feedback from school with any of the risk factors outlined in Table 52.2 should encourage the parents to discuss an intervention plan with the child's teacher.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

52.2 Writing Disabilities

Kenneth L. Grizzle and Brittany J. Bice-Urbach

Oral language is a complex process that typically develops in the absence of formal instruction. In contrast, *written language* requires instruction in acquisition (word reading), understanding (reading comprehension), and expression (spelling and composition). Unfortunately, despite reasonable pedagogy, a subset of children struggle with development in one or several of these areas. The disordered output of written language is currently referred to within the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) as a **specific learning disorder with impairment in written expression** (Table 52.3).

Various terminology has been used when referring to individuals with writing deficits; this subchapter uses the term **impairment in written expression (IWE)** rather than "writing disorder" or "disorder of written expression." **Dysgraphia** is often used when referring to children with writing problems, sometimes synonymously with IWE, though the two are related but distinct conditions. Dysgraphia is primarily a deficit in motor output (paper/pencil skills), and IWE is a conceptual weakness in developing, organizing, and elaborating on ideas in writing.

The diagnoses of IWE and dysgraphia are made largely based on phenotypical presentation; spelling, punctuation, grammar, clarity, and organization are factors to consider with IWE concerns. Aside from these potentially weak writing characteristics, however, no other guidelines are offered. Based on clinical experience and research into the features of writing samples of children with disordered writing skills, one would expect to see limited output, poor organization, repetition of content, and weak sentence structure and spelling despite the child taking considerable time to produce a small amount of content. For those with comorbid dysgraphia, the legibility of their writing product will also be poor, sometimes illegible.

Table 52.3 DSM-5 Diagnostic Criteria for Specific Learning Disability with Impairment in Written Expression

A. Difficulties learning and using academic skills that have persisted for at least 6 months, despite the provision of interventions that target those difficulties.
Difficulties with written expression (e.g., makes multiple grammatical or punctuation errors within sentences; employs poor paragraph organization; written expression of ideas lacks clarity).

B. The affected academic skills are substantially and quantifiably below those expected for the individual's chronologic age and cause significant interference with academic or occupational performance or with activities of daily living, as confirmed by individually administered standardized achievement measures and comprehensive clinical assessment. For individuals age 17 years and older, a documented history of impairing learning difficulties may be substituted for the standardized assessment.

C. The learning difficulties begin during school-age years but may not become fully manifest until the demands for those affected academic skills exceed the individual's limited capacities (e.g., as in timed tests, reading or writing lengthy complex reports for a tight deadline, excessively heavy academic loads).

D. The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurologic disorders, psychosocial adversity, lack of proficiency in the language of academic instruction, or inadequate educational instruction.

315.2 (F81.81) With impairment in written expression:
Spelling accuracy
Grammar and punctuation accuracy
Clarity or organization of written expression
Specify current severity:

Mild: Some difficulties learning skills in one or two academic domains, but of mild enough severity that the individual may be able to compensate or function well when provided with appropriate accommodations or support services, especially during the school years.

Moderate: Marked difficulties learning skills in one or more academic domains, so that the individual is unlikely to become proficient without some intervals of intensive and specialized teaching during the school years. Some accommodations or supportive services at least part of the day at school, in the workplace, or at home may be needed to complete activities accurately and efficiently.

Severe: Severe difficulties learning skills, affecting several academic domains, so that the individual is unlikely to learn those skills without ongoing intensive individualized and specialized teaching for most of the school years. Even with an array of appropriate accommodations or services at home, at school, or in the workplace, the individual may not be able to complete all activities efficiently.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association; 2013:66–67.

EPIDEMIOLOGY

The incidence of IWE is estimated at 6.9–14.7%, with the relative risk for IWE ~2.5 times higher for males than for females. The risk for writing problems is much greater among select populations; >50% of children with oral language disorders reportedly have IWE. The relationship between attention-deficit/hyperactivity disorder (ADHD) and learning disorders in general is well established, including IWE estimates in the 60% range for the combined and inattentive presentations of ADHD. Because of the importance of working memory (WM) and other executive functions in the writing process, any child with weakness in these areas will likely find the writing process difficult (see Chapter 49).

SKILL DEFICITS ASSOCIATED WITH IMPAIRED WRITING

Written language, much like reading, occurs along a developmental trajectory that can be seamless as children master skills critical to the next step in the process. Mastery of motor control that allows a child to produce letters and letter sequences frees up cognitive energy to devote to spelling words and eventually stringing words into sentences, paragraphs, and complex composition. Early in the development of each individual skill, considerable cognitive effort is required, although ideally the lower-level skills of motor production, spelling, punctuation, and capitalization (referred to as **writing mechanics** or **writing conventions**) will gradually become automatic and require progressively less mental effort. This effort can then be devoted to higher-level skills, such as planning, organization, application of knowledge, and use of varied vocabulary. For children with writing deficits, breakdowns can occur at one, some, or every stage.

Transcription

Among preschool and primary grade children, there is a wide range of what is considered "developmentally typical" as it relates to letter production and spelling. However, evidence indicates that poor writers in later grades are slow to produce letters and write their name in preschool and kindergarten. Weak early spelling and reading skills (letter identification and phonologic awareness; see Chapter 51) and weak oral language have also been found to predict weak writing skills in later elementary grades. Children struggling to master early **transcription** skills tend to write slowly, or when writing at reasonable speed, the legibility of their writing degrades. Output in quantity and variety is limited, and vocabulary use in poor spellers is often restricted to words they can spell.

As children progress into upper elementary school and beyond, a new set of challenges arises. They are now expected to have mastered lower-level transcription skills, and the focus turns to the application of these skills to more complex text generation. In addition to transcription, this next step requires the integration of additional cognitive skills that have yet to be tapped by young learners.

Oral Language

Language, though not speech, has been found to be related to writing skills. Writing difficulties are associated with deficits in both expression and comprehension of oral language. Writing characteristics of children with **specific language impairment (SLI)** can differ from their unimpaired peers early in the school experience and persist through high school (see Chapter 53). In preschool and kindergarten, as a group, children with language disorders show poorer letter production and ability to print their name. Poor spelling and weak vocabulary also contribute to the poor writing skills. Beyond primary grades, the written narratives of SLI children tend to be evaluated as "lower quality with poor organization" and weaker use of varied vocabulary.

Pragmatic language and higher-level language deficits also negatively affect writing skills. **Pragmatic language** refers to the social use of language, including though not limited to greeting and making requests, adjustments to language used to meet the need of the situation or listener, and following conversation rules verbally and nonverbally. Higher-level language goes beyond basic vocabulary, word form, and grammatical skills and includes making inferences, understanding and appropriately using figurative language, and making cause-and-effect judgments. Weaknesses in these areas, with or without intact foundational language, can present challenges for students in all academic areas that require writing. For example, whether producing an analytic or narrative piece, the writer must understand the extent of the reader's background knowledge and in turn what information to include and omit, make an argument for a cause-and-effect relationship, and use content-specific vocabulary or vocabulary rich in imagery and nonliteral interpretation.

Executive Functions

Writing is a complicated process and, when done well, requires the effective integration of multiple processes. Executive functions (EFs) are a set of skills that include planning, problem solving, monitoring, and adjusting as needed (see Chapter 49). Three recursive processes have consistently been reported as involved in the writing process: *translation* of thought into written output, *planning,* and *reviewing.* Coming up with ideas, although challenging for many, is simply the first step when writing a narrative (story). Once an idea has emerged, the concept must be developed to include a plot, characters, and storyline and then coordinated into a coherent whole that is well organized and flows from beginning to end. Even if one develops ideas and begins to write them down, *persistence* is required to complete the task, which requires *self-regulation.* Effective writers rely heavily on EFs, and children with IWE struggle with this set of skills. Poor writers seldom engage in the necessary planning and struggle to self-monitor and revise effectively.

Working Memory

WM refers to the ability to hold, manipulate, and store information for short periods. The more space available, the more memory can be devoted to problem solving and thinking tasks. Nevertheless, there is limited space in which information can be held, and the more effort devoted to one task, the less space is available to devote to other tasks. WM has consistently been shown to play an important role in the writing process, because weak WM limits the

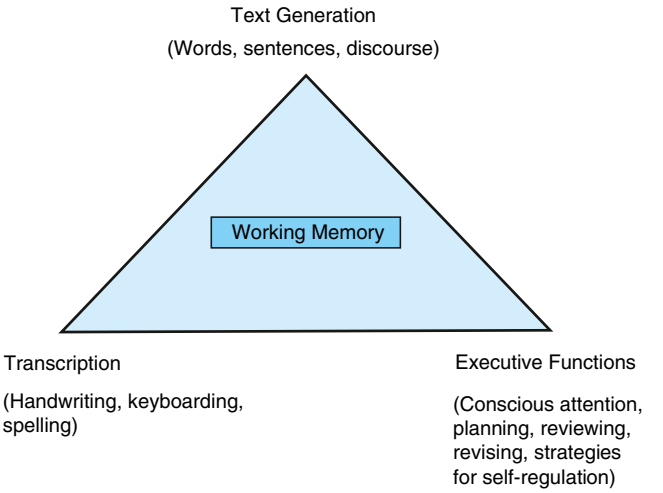

Fig. 52.1 Simple view of writing. *(From Berninger VW. Preventing written expression disabilities through early and continuing assessment and intervention for handwriting and/or spelling problems: Research into practice. In: Swanson HL, Harris KR, Graham S [eds]. Handbook of Learning Disabilities. New York: The Guilford Press;2003.)*

space available. Further, when writing skills that are expected to be *automatic* continue to require effort, precious memory is required, taking away what would otherwise be available for higher-level language.

The **Simple View of Writing** is an approach that integrates each of the four ideas just outlined to describe the writing process (Fig. 52.1). At the base of the triangle are transcription and EFs, which support, within WM, the ability to produce text. Breakdowns in any of these areas can lead to poor writing, and identifying where the deficit(s) are occurring is essential when deciding to treat the writing problem. For example, children with weak **graphomotor** skills (e.g., dysgraphia) must devote considerable effort to the accurate production of written language, thereby increasing WM use devoted to lower-level transcription and limiting memory that can be used for developing discourse. The result might be painfully slow production of a legible story or a passage that is largely illegible. If, on the other hand, a child's penmanship and spelling have developed well but their ability to persist with challenging tasks or to organize their thoughts and develop a coordinated plan for their paper is limited, one might see very little information written on the paper despite considerable time devoted to the task. Lastly, even when skills residing at the base of this triangle are in place, students with a language disorder will likely produce text that is more consistent with their language functioning than their chronologic grade or age.

TREATMENT

Poor writing skills can improve with effective treatment. Weak graphomotor skills may not necessarily require intervention from an **occupational therapist (OT)**, although *Handwriting Without Tears* is a curriculum frequently used by OTs when working with children with poor penmanship. An empirically supported writing program has been developed by Berninger, but it is not widely used inside or outside school systems *(PAL Research-Based Reading and Writing Lessons)*. Her research suggests that for children with dysgraphia, lower-level transcription skills should be emphasized to the point of becoming automatic. The connection between transcription skills and composition should be included in the instructional process; that is, children need to see how their work at letter production is related to broader components of writing. Further, because of WM constraints that frequently affect the instructional process for students with learning disorders, all components of writing should be taught within the same lesson. Building upon Berninger's sequencing of skills, Otaiba, Gillespie-Rouse, and Baker summarized features of effective handwriting instruction for kids who struggle: direct instruction on letter formation that is modeled and followed using verbal and visual instruction; retrieving letters from memory using such strategies as a child viewing the letter, covering, and reproducing the letter; children identifying their own errors; newly learned letters are integrated into word and sentence context and then into a child's own writing product; integration of multisensory strategies; and handwriting interventions included practice, occurred regularly, and were relatively brief but meaningful (children learned that writing had a purpose beyond accurately producing letters).

Explicit instruction of writing composition strategies combined with implementation and coaching in self-regulation will likely produce the greatest gains for students with writing deficits beyond transcription. Emphasis will vary depending on the deficit specific to the child. A well-researched and well-supported intervention for poor writers is **self-regulated strategy development (SRSD)**. The six stages in this model include developing and activating a child's background knowledge, introducing and discussing the strategy that is being taught, modeling the strategy for the student, assisting the child in memorization of the strategy, supporting the child's use of the strategy during implementation, and independent use of the strategy. SRSD can be applied across various writing situations and is supported until the student has developed mastery. The model can emphasize the areas most needed by the child.

An additional excellent resource is entitled *Teaching Elementary School Students to Be Effective Writers* and is found within the What Works Clearinghouse maintained by the U.S. Department of Education's Institute of Education Science.

Educational Resources

Children with identified learning disorders can potentially qualify for formal education programming through special education or a Section 504 plan. **Special education** is guided on a federal level by the **Individual with Disabilities Education Act (IDEA)** and includes development of an **individual education plan** (IEP) (see Chapter 49). The processes involved in pursuing an IEP are somewhat complex and outlined in the chapter on math learning disability (MLD). A **504 plan** provides accommodations to help children succeed in the regular classroom. Accommodations that might be provided to a child with IWE, through an IEP or a 504 plan, include dictation to a scribe when confronted with lengthy writing tasks; additional time to complete exams that require writing; and use of technology such as keyboarding, speech-to-text software, and writing devices that record teacher instruction.

Speech-to-text capability is available on most smartphones, which can be helpful for students from a functional standpoint. Educational resources that can be accessed inside and outside the classroom are often readily available for all children but may need to be included as an accommodation for a child with dysgraphia. Examples of easily available software include Voice Dictation in Google Docs and Dictation in Microsoft Word, both available at no cost. More sophisticated apps that can be purchased include Co:Writer for Chrome, Read & Write, and Kurzweil 3000. Kurzweil 3000 is a comprehensive assistive technology device that, in addition to speech-to-text and text-to-speech, offers multiple valuable resources for students with any type of literacy-based learning disability. Editing is a critical component of the writing process and, for children struggling with written expression, can present quite a challenge. Microsoft Word has built-in spelling and grammar correction suggestions, as do other word processing programs such as Pages and Google Docs. Apps for use when using the internet are also available to help with spelling, grammar, and writing mechanics. One example—though there are others—is Grammarly. When recommending that parents pursue assistive technology for their child as a potential accommodation, the physician should emphasize the importance of instruction to mastery of the device being used. Learning to use technology effectively requires considerable time and is initially likely to require additional effort, which can result in frustration and avoidance.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 53

Language Development and Communication Disorders

Janet Y. Bang and Heidi M. Feldman

There are over 6,000 languages in the world, each with a distinct set of symbols, defined as words or signs that signify objects, actions, ideas, or relationships. By combining symbols in novel ways, humans can create an infinite number of meanings. Human communication (Table 53.1) encompasses language, speech, nonverbal gestures, and written language. Typically developing children learn language skills seemingly without effort or explicit education early in the course of development. However, there is wide variation in how and when children learn and use language, speech, and communication. Globally, families differ in the specific languages and number of languages they speak and in the ways in which they communicate to convey their beliefs, values, and circumstances. Children vary in their rates of learning language and the highest level of skills they attain. Milestones within each domain (language, speech, communication) signify the unfolding steps by which new structures and skills come into children's language abilities (Table 53.2 and Fig. 53.1). Some children require explicit education or clinical support to learn language or to make their speech easily interpretable.

TYPICAL DEVELOPMENT

Development of Phonology

Every language is made up of an inventory of **speech sounds** or **phonemes** (see Table 53.1), and the number of speech sounds varies across languages (e.g., Hawaiian = 13, Cantonese = more than 36, English = 46). **Speech perception** depends on the physical structures of the ear and the auditory processing system. Fetuses detect sound as early as 28 weeks' gestation, and within 5 days after birth, infants can demonstrate the ability to discriminate vowel sounds (i.e., English vs Swedish) and show preferences for their own prenatal monolingual or bilingual language environments (i.e., English vs Tagalog-English). Infants develop their speech sound perception, built on the ability to track the statistical probabilities of sound combinations (e.g., *b* + *a* is more prevalent in language than *b* + *d*), segment sounds and words from a stream of speech, and become attuned to the speech sounds in their respective language or languages. Older children or adults learning a new language need to learn a new speech sound inventory.

Speech production involves activating the physical structures of the respiratory tract and oral cavity, such as the lips, tongue, and vocal cords, all of which work in concert. Infants begin producing nonspeech **cooing** sounds at 4-6 weeks. By 6-8 months, many infants engage in canonical **babbling** (e.g., *bababa*) followed by variegated babbling (e.g., *badadeda*). Infants who are exposed to **sign language** from birth demonstrate manual babbles at around the same time as hearing infants begin vocal babbles. These skills lay the stage for infants' first words and subsequent word combinations. Speech production continues to develop throughout early childhood, with easier consonant sounds maturing early, around age 3 (e.g., in English *p, b, m, h, w*) and difficult sounds (e.g., in English *l, s, r, v, ch, th*) maturing late, typically by around age 7.

Development of the Lexicon, Morphology, and Syntax

It is difficult to pinpoint when in development children typically understand their first word, but many children may say their first words by around 1 year; English-speaking families in the United States report first words appearing as young as 7 and as late as 15 months. Children's first words mark their expressive skills in their **lexicon** (see Table 53.1), and first words may come from a variety of categories (e.g., people, objects, and greetings). Many children recognize their own name between 7 and 15 months old. Initial word learning is typically very slow, but the rate of acquisition of new words gradually accelerates. Expressive lexical errors are common at this age and can include overextensions (e.g., all edible objects are "*apples*") or underextensions (e.g., only one specific spoon is labeled "*spoon*"). Between 1 and 2 years, children build a lexicon of over 50 words. The **vocabulary spurt** is rapid acceleration in word learning, usually after children reach 50 words in expressive language and coincident with the beginning of two-word phrases.

By approximately 2 years, children begin to demonstrate their developing understanding of **morphology** and **syntax** (see Table 53.1). Morphology and syntax rules differ by language. Children's receptive syntax skills are evident when they can follow simple directions or answer *wh-* questions. Notable expressive morphologic milestones in English include the use of the present progressive tense (e.g., "*go-ing*") and the plural -s (e.g., *dog-s*). Expressive syntax skills are evident via children's early creative word combinations, starting with two-word combinations, which are likely to vary from adult models (e.g., in English "*me down!*" or "*ick eggs!*"). By 3 years, children begin to produce sentences as long as five words and with increasingly complex grammar, such as negation (e.g., in English "*I no want to*") and questions (e.g., "*What he do?*"). As in these examples, lexical, morphologic, and/or syntax errors in understanding and production are common during this early phase of syntactic development. Morphologic or syntax errors in production may consist of overgeneralizations (e.g., in English, generalizing the "*-ed*" ending to all verbs such as "*runned*" rather than "*ran*"; in Spanish, Italian, or French, using the masculine articles with feminine nouns). By 4-5 years, children are able to use sentences with adult-like grammar (e.g., in English "*I fell because I was running too fast.*"), although they may still make mistakes (e.g., in English "*I gots 1 game and he got 3 games.*"). Children also engage in longer, coherent, connected discourse, such as telling or retelling stories and recounting the steps of a familiar activity, such as taking a bath.

Development of Pragmatics

Pragmatic skills begin in infancy. The ability to attend to and follow another's **eye gaze** develops as early as 3-4 months old. As young as 3 months old, children can engage in **protoconversations**, turn-taking patterns with caregivers that resemble early conversations. Responsive, contingent interactions between caregivers and children provide infants the opportunity to experience, imitate, and practice the timing, rhythm, and rate of nonverbal pragmatic skills, such as facial expressions, body language, and intonation. By 6 months, many infants can passively follow the adult's line of visual regard, resulting in a joint reference to the same objects and events in the environment. The ability to share the same experience is critical to the development of further language, social, and cognitive skills as infants "map" specific meanings onto their experiences. By 10-13 months, many infants can actively show, give, and point to objects. Children vary widely in when these skills first appear; English-speaking families have reported pointing skills as early as 6 months and as late as 16 months.

An important facet of typical communication development and a building block of conversational turn-taking skills includes establishing a **joint focus of attention**, a sharing of the topic of conversation with a communicative partner, both in comprehension (e.g., infants turn their heads to the object an adult is pointing at) and in production (e.g., a child saying "look at that dog over there," then looking back at their caregiver and expressing a desire for a dog). Conversation skills are important for forming relationships and especially strong social bonds and friendships. As children reach school age and adolescence, they develop **nonliteral** or **figurative language skills** (see Table 53.1), including hints, idioms, metaphors, hyperbole, humor, and sarcasm. In lexical development, understanding often occurs before production; in children's humor development, children's production may precede full understanding of their meaning. Another notable milestone of

Table 53.1 Definitions of Basic Terms in Communication, Language, and Speech

TERM	DEFINITION	EXAMPLES
Communication	• Broad umbrella term that encompasses understanding and producing language, speech, nonverbal communicative gestures, and written language	• Humans share ideas using verbal or signed speech and language • Nonverbal communicative gestures include nodding one's head up and down to convey "yes" in some cultures
Language	• Verbal, signed, written, or other systems that use arbitrary but conventional, rule-governed symbols to communicate about objects, events, and ideas in the past, present, and future	• Verbal symbols include words (e.g., *apple* in English or *manzana* in Spanish, both of which represent a red, tasty fruit) • Signed symbols include the word *apple* in American Sign Language, produced by the twist of the knuckle of the index finger on the cheek
Speech	• Perception of the meaningful units of sounds that comprise verbal language and production of these sounds by coordinating the mouth, tongue, airflow, and vibration of the vocal folds	• Speech sounds or phonemes make a difference in meaning (e.g., *b, p, a, i,* and *t* affect the meaning of *bat, bit, pat,* and *pit*) • Speech does not include all vocal sounds, such as coughs or throat clearing • Phonemes in sign language are based on spatial, temporal features, such as hand shape
Receptive language	• Hearing and understanding verbal or sign language	• Recognizing own name • Following two-step directions
Expressive language	• Speaking using verbal or sign language	• Speaking first words or signs in a sign language • Telling stories
Phonology	• The system of relationships among speech sounds or phonemes that constitute a fundamental component of language	• Understanding *seetheredball* can be segmented into *see the red ball* • Babbling, consonant-vowel combinations that use phonemes
Lexicon	• All of the words or vocabulary of a person or a language	• The lexicon of the mathematician may vary from the lexicon of the lawyer
Morphology	• Units of meaning that can be combined to form vocabulary	• In English *dogs* is made of two morphemes, *dog* and the plural *-s; untie* is made of *un-* and *tie*
Syntax	• Grammar and word order to make sentences	• In English word order, *the dog chases the cat,* while in Hindi word order, *the cat the dog chases*
Pragmatics	• Verbal and nonverbal communication skills that govern how language and communication are used in context • Includes intonation, facial expression, and body language	• Use of eye contact and gestures to make a point forcefully • The timing and responsiveness between communication partners (e.g., engaging, responding, and maintaining reciprocal exchanges)
Nonliteral or figurative language skill	• Meaning of a word or phrase that is not literal but understood in context	• Hints (e.g., a teacher saying, "*I think I hear children talking*") • Idioms (e.g., "*Give me a hand*") • Metaphor (e.g., "*You are my sunshine*") • Hyperbole (e.g., "*That's the biggest thing I've ever seen!*")
Advanced language skills	• Ability to listen, speak, read, write, and reason using language	• Academic language • Ability to debate and deliver speeches
Literacy skills	• Skills required for reading and writing	• Reading an alphabetic language requires awareness of the sounds of language, print, and the relationship between letters and sounds • Spelling is a literacy skill
Bilingualism and multilingualism	• Ability to speak and/or sign two or more languages	• Ability to communicate verbally in Chinese and English • Ability to communicate verbally in English and to use American Sign Language • Ability to use Chinese, English, and American Sign Language
Biliteracy and multiliteracy	• Ability to read and write in two or more languages	• Ability to read and write Chinese, Spanish, and English
Phonologic processes	• Errors in speech production that affect more than a single sound and are based on violations of predictable, rule-based features	• Fronting, when a sound that should be made in the back of the mouth (cat) is made in the front of the mouth (tat) • Cluster reduction, when a consonant cluster (as in stop) is reduced to a single consonant (top)

Table 53.2 Speech, Language, and Communication Milestones from Birth to 5 Years, Based on Typically Developing Children Acquiring a Single Verbal Language

HEARING AND UNDERSTANDING	SPEAKING
BIRTH TO 3 MO	
• Startles at loud sounds • Recognizes voices and quiets if crying • Turns head toward sounds • Watches faces • Quiets or smiles when spoken to	• Makes pleasure sounds (cooing, gooing) • Cries differently for different needs
4-6 MO	
• Moves eyes in direction of sounds • Responds to changes in tone of voice • Notices music and sounds • Recognizes familiar people and things at a distance	• Vocalizes differently to show excitement, being tired, or in pain • Makes sounds when alone and when playing • Makes babbling sounds that are speechlike and uses consonant sounds, such as *p, b,* and *m* • Reaches for toys or objects • Engages in turn-taking and protoconversations
7-12 MO	
• Listens when spoken to • Turns and looks in direction of sounds • Enjoys social games, such as peek-a-boo and pat-a-cake • Responds to own name • Recognizes words for common items, such as *cup, shoe,* and *juice* • Begins to respond to simple requests *(Come here; Want more?)* or *No* • Looks when an adult points at something	• Uses speech sounds or gestures to get and keep attention and to respond to others • Imitates different speech sounds and gestures • Babbles with long and short groups of sounds, such as *bababa upup bibi,* and mixes different syllables, such as *badadeda* • Says one or two words *(bye-bye, dada, mama)* • Points to or shows things to spontaneously share interest with familiar people • Uses gestures such as waving for *hi* and *bye* or shaking head for *no*
1-2 YR	
• Listens to simple stories, songs, and rhymes • Follows simple commands and understands simple questions *(Roll the ball; Kiss the baby; Where's your shoe?)* • Points to things when asked or when named such as body parts and objects	• Learns to say more words every month • Uses some one- and two-word questions *(Where kitty? Go bye-bye? What's that?)* • Combines two words in their own ways *(more cookie, no juice, mommy book)* • Uses consonant sounds such as *p, b, m, h,* and *w* in English
2-3 YR	
• Understands differences in meaning (e.g., go–stop, in–on, big–little, up–down) • Follows two-step requests *(Get the book and put it on the table.)*	• Often asks for or directs attention to objects by naming them • Has a word for almost everything • Uses prepositions like *in, on,* and *under* • Often uses two- to three-word "sentences" • Speech is mostly understood by familiar listeners • Uses consonant sounds such as *k, g, f, t, d,* and *n* in English
3-4 YR	
• Understands simple *who, what, where,* and *why* questions • Understands words for colors like *red, blue,* or *green* and shapes like *circle* or *square* • Responds when you call from another room	• Uses pronouns like *I, you, me, we,* and *they* • Uses sentences that have four or more words with more complex grammar such as negative *(I no want to)* and questions • Talks about activities outside the home • Usually understood by people outside the family
4-5 YR	
• Hears and understands most of what is said at home and in school • Pays attention to a short story and answers simple questions about it • Understands words for time like *yesterday, today,* and *tomorrow* • Understands words for order like *first, next,* and *last* • Follows longer directions such as *(Find an animal you like, draw a circle around it, and bring the paper to me)*	• Uses sentences that include details (I like to read my books) and different action words like jump or play; may still make some grammar mistakes (I gots one game and he got three games) • Tells simple stories using mostly full sentences • Communicates easily with other children and adults • Says most sounds correctly except a few that are harder to say, such as *l, s, r, v, z, ch, sh,* and *th* in English

Milestones may not apply to bilingual children, children exposed to sign languages, children learning a second language, and children with language and learning disorders
For Spanish translations and more information, including activities for families:
• American Speech-Language-Hearing Association: http://www.asha.org/public/speech/development/chart.htm
• The American Academy of Pediatrics: https://healthychildren.org/English/Pages/default.aspx
• Centers for Disease Control and Prevention Milestones checklist: https://www.cdc.gov/ncbddd/actearly/milestones/index.html
Adapted from the American Speech-Language-Hearing Association (2021), the American Academy of Pediatrics (2009), and the Centers for Disease Control and Prevention Milestones checklist (2021).

pragmatic skills is the ability to adapt how to narrate events or stories for different audiences (e.g., friends vs teachers).

Advanced Language Skills

Once children enter school, they continue to develop new vocabulary and use increasingly complex sentence constructions to communicate about abstract, hypothetical, and imaginary topics. By adolescence, many students in Westernized school systems are required to deliver expository speeches or to debate. Formal schooling also affords new situations to communicate with a broader network of individuals, including teachers, coaches, and supervisors. The diversity of the situations requires nuanced attention to social rules and conventions and increases exposure to diverse forms of nonliteral language use, though proficiency in the use of nonliteral language varies by the language and culture of the speaker and addressee. Finally, the introduction of formal schooling presents children with the demands of acquiring

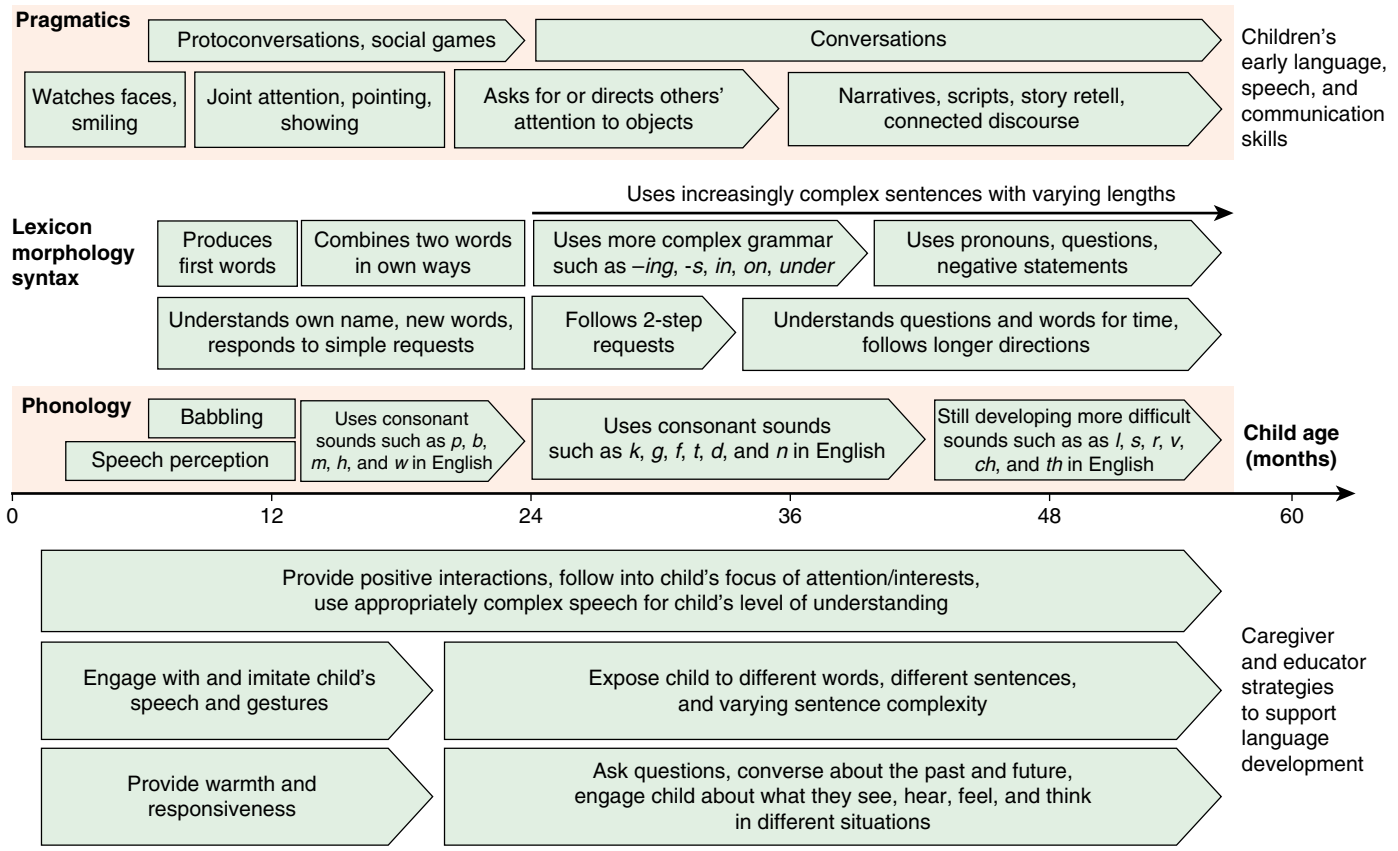

Fig. 53.1 Timeline of children's early language, speech, and communication skills and caregivers' and educators' strategies to support that development. The timing and width of boxes for the child skills are adapted from milestones from the American Speech-Language-Hearing Association, The American Academy of Pediatrics, and the Centers for Disease Control and Prevention. More information on milestones can also be seen in Table 53.1. Caregivers and educators should be encouraged to engage with the child using the language with which they are most comfortable because children, even children with delays, are capable of becoming bilingual. Specific child skills and caregiver/educator strategies may vary according to language and cultural practices.

literacy skills (see Table 53.1), those skills required for reading and writing. Early oral language skills are a robust predictor of children's early reading skills, and early oral language and reading skills are in turn predictors of children's writing skills (see Chapters 51 and 52.2). Language skills become critical to support high-level school- and work-related literacy skills.

BILINGUALISM AND MULTILINGUALISM

Worldwide, learning more than one language is more common than learning just one; many regions and countries in the world are home to individuals who routinely speak two or more languages. The timing of exposure, balance between languages, and level of skill in each language in dual-language or multilanguage learners varies across situations. **Simultaneous bilinguals** refers to those regularly exposed to both languages prenatally or from birth. **Sequential bilinguals** refers to those exposed to the second language after the first language, often when they enter school, though the timing of when the second language is introduced varies. Once children learn two languages, the balance in skill level between them may vary. For example, a child who was born in Nigeria, exposed to Igbo, and then immigrated to Greece at age 5 years will initially be more proficient in Igbo than in Greek. As the child attends school in Greece, Greek proficiency will improve (likely also supported through the introduction of reading and writing in a Greek monolingual school environment), and thus the balance will shift and the child may become more proficient in Greek over Igbo. A high level of skill across all domains of phonology, lexicon, syntax, and pragmatics is considered an ideal picture of bilingualism, but this ideal is not always the case or necessary for many bilingual learners. Bilingual learners often demonstrate **code-switching**, that is, alternating between languages, or **code-mixing**, mixing their languages together, especially when speaking with other bilingual speakers. A distinction between **conversational** and **academic** language skills may be made in reference to bilinguals. Bilingual speakers may master conversational language, the language used to communicate casually with family or friends, but remain less skilled in academic language, the complex, technical, and specialized vocabulary and syntax required in academic or work settings, particularly when school is presented in a language different from the language of the home. Some bilingual learners may experience **language attrition**, a reduction in the proficiency in one language over time. Factors within the child, family (e.g., one caregiver/one language, caregivers speaking both languages), community (e.g., availability of bilingual schooling, minority vs majority language of the community, perceived prestige of a language), and policy (e.g., national acknowledgement of multiple languages or requirements of accessibility of documents in school or business sectors) contribute to proficiency in both languages.

Bilingualism or multilingualism is typical language development for many children and not an adequate explanation for language delays as long as the child's skills in both languages are assessed. Even children with language and developmental disorders, such as intellectual disability and autism spectrum disorder, may be successful bilingual or multilanguage learners. It is difficult to predict developmental trajectories in bilingual development because of the wide variety of factors associated with the level of skill in different domains. *Children in homes with two or more languages who show delays in language development (considering the accumulated accomplishments in all languages) should be promptly referred for evaluation.*

DRIVERS OF VARIATION IN TYPICAL LANGUAGE DEVELOPMENT

Genetic

Similarities in language abilities across members of the same family suggest that genetic factors contribute to individual differences in language abilities. Genetic factors have been studied more often in the context of disorders of language learning than in the context of normal variation (see below).

Environment

Interactions between young children and their caregivers that are positive, responsive, and warm allow children to practice their early word learning (e.g., social games, routines). Living in stable home environments is better for language development than living in an unstable condition. The Bucharest Early Intervention Project conducted a randomized controlled trial to examine the role of being raised in a home (foster care) versus in institutionalized care in Romanian orphanages that were providing infants with low levels of responsive interactions. Children taken from the orphanages and placed in foster care by age 15 months had language skills that were similar to typically developing peers at 30 and 42 months in the same Romanian community living with their biologic families; children placed in foster care after 24 months had persistent expressive language delays.

The role of caregivers specifically is one of the few levers available to influence language outcomes in clinical practice and public programs. Positive links have been found between variability in socioeconomic backgrounds and children's later language skills; caregivers have been shown to mediate this link. Caregivers' **child-directed speech** refers to changes to caregivers' prosody (intonation patterns), phonology, grammar, and lexicon when engaging with young children. This child-directed speech has been measured across a wide variety of features, which can be broadly categorized into measures of quantity (e.g., total number of words spoken), quality (e.g., number of different words spoken), and interaction (e.g., warmth and responsiveness). Taken together, these factors constitute **language nutrition**, which, like dietary nutrition, is associated with rates of growth. However, the causal links between caregivers' child-directed speech and children's language outcomes are still unclear in children with typical development or language delays or disorders. Meta-analyses of interventions targeting improved language nutrition to date have generally reported either null effects or small to moderate positive effects on children's language skills. The specific role of book-sharing interventions to support children's language development is also mixed among different meta-analyses. Wide heterogeneity across intervention studies, including the method of delivery (e.g., one-on-one coaching vs caregiver groups), intensity (e.g., 1 hour per week for 12 weeks vs two 45-minute visits), measures of caregiver-child interaction, and child language outcomes, may contribute to differences in results. Caregivers' mental health has been found to be an important mediator of child outcomes; higher caregiver depression has been linked to poorer children's language outcomes.

Greater amounts of screen time and early age of screen time are negatively related to children's early language skills. However, high-quality screen-time practices (e.g., co-viewing, educational programs) are positively related to children's language skills; effect sizes are small to moderate.

Misattributions of Language Delay

Several common conditions have been erroneously implicated as an adequate explanation for language delays and disorders. Typically developing twins learn to talk at the same age as typically developing single-born children. Birth-order effects on language development have not been consistently found. **Ankyloglossia** (tongue-tie), an extremely tight lingual frenulum, does not prevent the acquisition of speech, but ankyloglossia may be the result of abnormalities associated with disorders of speech, such as neural injury and cerebral palsy. Frequent ear infections and serous otitis media in early childhood *do not* result in persisting language disorder. Prompt placement of tympanostomy tubes for chronic serous otitis media *does not* lead to better skills than watchful waiting. Biologic sex differences have been found in many studies of language development. Though males are generally slower to develop than females, the differences do not usually rise to the level of being clinically apparent. However, males are more likely to develop language disorders than females. Based on these findings, *children with moderate to severe delays in the development of language and speech deserve a prompt evaluation, even if they are males, non–first born children, twins, tongue-tied toddlers, and/or children with chronic otitis media.*

LANGUAGE, SPEECH, AND COMMUNICATION DISORDERS

Impairment in language, speech, and communication may occur in isolation or may be associated with other conditions.

Isolated Language Disorders with or Without Accompanying Speech Disorders

Clinical Presentation

Primary disorders of speech and language development are significant difficulties found in the absence of major cognitive, sensory, or motor dysfunction. The literature uses the term **specific language impairment** (SLI) or **language impairment**, the term we use here, also called *developmental language disorder* or *developmental dysphasia.* Children with language impairment typically perform >1.25-1.5 standard deviations below the mean on standardized language assessments. The *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) criteria for a language disorder are provided in Table 53.3. Many children with language impairment eventually become competent language users, though they may show persistent and subtle difficulties with skills related to phonology, lexicon, and/or syntax. As adolescents and adults, compared to peers, they are generally less proficient at producing stories, descriptions, and scripts of everyday events, collectively known as **oral narratives**. Their narratives tend to be shorter, including fewer prepositions, main story ideas, and devices fostering cohesion. Children with language impairment may have significant difficulty in higher-level language skills (see Table 53.1), reasoning skills (e.g., drawing correct inferences and conclusions), the ability to take another person's perspective, and the ability to paraphrase and rephrase. Some children with language impairment show difficulties with social interaction because social interactions are often mediated by verbal language. Young children with language impairment may interact more successfully with older children or adults, who can adapt their communication to match the child's level of function, than with peers.

Epidemiology

Over 15% of 2-year-olds may not produce a vocabulary of 50 words or two-word utterances; estimates may vary for children exposed to two or more languages. Almost half of preschool-age children, age 3-5 years old, who qualify for special education meet eligibility based only on speech-language impairment. By age 5, approximately 6% of children are identified as having a speech impairment alone, 5% as having both speech and language impairment, and 8% as having language impairment alone. Males are nearly twice as likely to have an identified speech or language impairment as females.

Etiology

Genetic factors appear to play a major role in influencing how children learn to talk. A family history may identify current or past speech or language problems in up to 30% of first-degree relatives of proband children. Concordance rate for low language test scores and/or a history of speech therapy within twin pairs is about 50% in dizygotic pairs and 90% in monozygotic pairs. Consistent pathogenic genetic variations have not been identified. Instead, multiple genetic regions and epigenetic changes may result in heterogeneous genetic pathways causing language disorders. Several single-nucleotide polymorphisms (SNPs) involving noncoding regulatory genes, including *CNTNAP2* (contactin-associated-protein-like-2) and *KIAA0319,* are strongly associated with early language acquisition and are also thought to

affect early neuronal structural development. Several chromosomal **copy number variants** (see Chapter 96) have also been associated with abnormalities of language and speech; these variants may be associated with distinctive physical features (e.g., tall stature in Klinefelter syndrome) or neurobehavioral conditions (e.g., autistic features). Environmental, hormonal, and nutritional factors may exert **epigenetic** influences by dysregulating gene expression. These forces result in aberrant sequencing of the onset, growth, and timing of language development.

All of the family, community, and sociopolitical factors that appear to contribute to variation in typical language learning may contribute to the rate of learning in children with disorders. Improving the quality of the verbal environment, and in particular the quantity and quality of child-directed speech (see above), may moderate the impact of genetic and epigenetic factors.

Pathogenesis

Language functioning is widely distributed across the brain through interconnected neural networks. Frank neurologic injury is typically absent in children with language impairment. Language disorders have been attributed to a fundamental difficulty in the brain's capacity to process complex information rapidly. Limitations in the amount of information that can be stored in verbal working memory (see Chapter 49) may also limit the rate at which language information is processed. Electrophysiologic studies show abnormal latency in the early phase of auditory processing in children with language impairment. Neuroimaging studies identify an array of anatomic abnormalities, implicated in language processing. MRI scans in children with language impairment may reveal white matter lesions and volume loss, ventricular enlargement, focal gray matter heterotopia within the right and left parietotemporal white matter, abnormal morphology of the inferior frontal gyrus, atypical patterns of asymmetry of language cortex, or increased thickness of the corpus callosum in a minority of affected children. Postmortem studies of children with language disorders found evidence of atypical symmetry in the plana temporale and cortical dysplasia in the region of the sylvian fissure. A high rate of atypical perisylvian asymmetries has been documented in the parents of children with language impairment.

Language Disorders Associated with Cognitive Impairment and Intellectual Disability

Speech and language impairment may be the first indication of a global neurodevelopmental disorder. **Global developmental delay** or **early developmental impairment** is defined as delays in two or more domains. Children with substantial delays in adaptive function and scores 2 or more standard deviations below the mean on intelligence testing may meet criteria for **intellectual disability** (see Chapter 56). Most children with a mild intellectual disability learn to communicate adequately, though they are likely to encounter difficulties with higher-level language skills (see Table 53.1). Children with an IQ as low as 25 may eventually acquire a small lexicon and ability to combine words. Specific genetic syndromes have distinctive language profiles: in Down syndrome, verbal skills are more impaired than nonverbal skills; in William syndrome, language skills may be relatively preserved compared to nonverbal skills; in fragile X syndrome, unusual word or sound repetition may be present.

Autism Spectrum Disorder

A disordered pattern of language, speech, and communication development characterizes autism spectrum disorder (ASD) (see Chapter 58). The core characteristics of ASD are persistent difficulties in social communication and social interaction relative to age expectations and restricted, repetitive patterns of behavior, interests, or activities. Children with ASD show a wide range of language and communication abilities. At the severe end, language and speech may be extremely limited (nonverbal). Approximately 30–50% of children with ASD also meet criteria for intellectual disability, which contributes to the challenges of developing communication skills. Parents report regression in language and social skills (**autistic regression**) in approximately 20–25% of children with ASD, usually between 12 and 36 months of age. The cause of the regression is not known; it is associated with an increased risk for intellectual disability and severe ASD. Individuals with ASD who are high functioning may have large vocabularies and use grammatically correct sentences but have unusual or impaired social-pragmatic features, such as odd intonation patterns, off-topic comments, and atypical conversational skills. For example, they may engage in long monologues about a topic of special interest, without considering the interest of their conversational partner. Some individuals with ASD have highly specialized, isolated, "savant" skills, such as calendar calculations or **hyperlexia** (the precocious ability to recognize written words beyond expectation based on general intellectual ability).

DSM-5 identified **social (pragmatic) communication disorder (SPCD)** as a category of communication disorder distinct from ASD (see Table 53.3). Symptoms of SPCD include extreme literalness and inappropriate verbal and social interactions. Socially appropriate use and understanding of figurative language (see Table 53.1) depends on correct interpretation of the meaning and the context of language and the ability to draw proper inferences, skills limited in SPCD. SPCD has been recognized as a symptom of a wide range of disorders, including right-hemisphere brain injury and nonverbal learning disabilities.

Hearing Impairment

Hearing loss may be caused by a sensorineural loss, a conductive loss, or a mixed picture in one or both ears. Although it is not possible to accurately predict the impact of hearing loss on a child's verbal language development, the type, degree, and laterality of hearing loss; the age of onset; and the duration of the auditory impairment before amplification play important roles (see Chapter 55). Newborn screening programs are designed to identify congenital hearing loss but fail to identify children with progressive or acquired hearing loss or deafness after birth. *Any child who shows a speech or language problem should have a hearing assessment by an audiologist, even if they passed their newborn hearing screen.*

Conductive hearing loss occurs when sounds cannot get through the outer and middle ear to stimulate the auditory nerve. In children, the most common cause of conductive hearing loss is **acute** or **chronic serous otitis media**. Otitis media is typically transient and may increase the sound threshold at which children can detect tones or understand language. Persistent fluid in the middle ear may be treated with **tympanostomy or ventilation tubes**. However, treatment of chronic serous otitis media with tympanostomy tubes does not improve outcomes in the domains of speech and language, cognition, academic skills, or psychosocial functioning from preschool years through middle childhood.

Neurologic Conditions

Epilepsy Syndromes

Children with Landau-Kleffner syndrome or verbal auditory agnosia have a history of typical language development until they experience a regression in their ability to comprehend spoken language—verbal auditory agnosia—along with the development of seizures, usually between 3 and 7 years of age. Expressive language skills also typically deteriorate. An electroencephalogram (EEG) may show a distinct pattern of status epilepticus in sleep (continuous spike wave in slow-wave sleep), and up to 80% of children with Landau-Kleffner syndrome eventually exhibit clinical seizures. Use of antiepileptic medication, corticosteroids, and intravenous gamma globulin has led to varying results. The prognosis for return of typical language ability is uncertain, even if seizures resolve.

Epileptic interictal discharges are more frequently found on EEGs of children with language impairments than EEGs of otherwise typically developing children. The discharges are likely a manifestation of an underlying disorder of brain, distinct from the language impairment. Only when seizure symptoms or regression in language ability is present is a routine EEG recommended in the evaluation for a child with speech and/or language impairment.

Table 53.3 DSM-5 Diagnostic Criteria for Communication Disorders

LANGUAGE DISORDER

A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following:
   1. Reduced vocabulary (word knowledge and use).
   2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology).
   3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation).
B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination.
C. Onset of symptoms is in the early developmental period.
D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurologic condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

SPEECH SOUND DISORDER

A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages.
B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination.
C. Onset of symptoms is in the early developmental period.
D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurologic conditions.

SOCIAL (PRAGMATIC) COMMUNICATION DISORDER

A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following:
   1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context.
   2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language.
   3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction.
   4. Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meanings of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation).
B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination.
C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities).
D. The symptoms are not attributable to another medical or neurologic condition or to low abilities in the domains of word structure and grammar and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders, 5th ed.* Washington, DC: American Psychiatric Association; 2013:42, 44, 47–48.

Cerebellar Mutism Syndrome

In the aftermath of operations for tumors in the posterior fossa, such as **medulloblastoma**, many children lose the ability to speak. Fortunately, though the presentation is initially profound, most children recover the ability to use language. **Cerebellar mutism syndrome** demonstrates that the cerebellum probably plays a fundamental role in language and communication. The syndrome is thought to result from damage to the superior cerebellar peduncle that connects the cerebellum to language centers in the frontal lobes.

Stroke

Strokes in childhood can occur prenatally, in the perinatal period, or at any time in childhood. As in adults, a brain territory frequently affected is supplied by the middle cerebral artery resulting in damage to the **left frontal and temporal lobes** that are associated with language function in adults. However, young children with stroke show greater plasticity of language function than do adults with similar brain injuries. Many children with left hemisphere stroke go on to demonstrate typical or near-typical language functions. Functional imaging studies document that these children activate uninjured regions of the left hemisphere around the stroke or homologous regions in the right hemisphere. This demonstrates that though under usual circumstances the left hemisphere serves language, alternative networks can substitute in the case of early injury. The quality of the home language environment is strongly associated with the language skills of children with strokes.

Metabolic and Neurodegenerative Disorders (see Part IX and Chapter 639)

Regression of language development may accompany loss of neuromotor function at the outset of a number of metabolic diseases, including lysosomal storage disorders (metachromatic leukodystrophy), peroxisomal disorders (adrenal leukodystrophy), ceroid lipofuscinosis (Batten disease), and mucopolysaccharidosis (Hunter disease, Hurler disease). A creatine transporter deficiency was identified as an X-linked disorder that manifests with language delay in males and with mild learning disability in female carriers.

Hydrocephalus (see Chapter 631.11)

Children with hydrocephalus may be described as having cocktail-party syndrome. In this syndrome, children may use sophisticated words, but their comprehension of abstract concepts is limited, pragmatic conversational skills are weak, their analyses are superficial, and/or they appear to be carrying on a monologue.

Language in the Context of Psychologic or Mental Health Conditions

Selective Mutism

In **selective mutism**, children do not speak in specific social situations, such as school or other settings outside the home, though they speak normally in certain settings, such as within their home or when they are alone with their parents. Other symptoms include excessive shyness, withdrawal, dependency on parents, and oppositional behavior. Most cases of selective mutism are the manifestation of a chronic pattern of **anxiety**. Children with selective mutism often report that they want to speak in social settings but are too afraid, worried, or distressed to do so. The family history is often positive for anxiety symptoms. Children with selective mutism may also have a language or speech impairment, contributing to their sense of distress in speaking. Treatment of selective mutism generally uses evidence-based approaches to reducing general anxiety, including cognitive-behavioral therapy and/or selective serotonin reuptake inhibitors in conjunction with speech-language therapy.

Schizophrenia

A characteristic of schizophrenia is abnormal communication, including highly disorganized language that is difficult to follow and frequent changes in topic (see Chapter 47.1). This communication challenge accompanies the thought disturbance that is the hallmark of schizophrenia. Schizophrenia usually presents in individuals in adolescence or young adulthood. The communication disorder is linked to other features of schizophrenia, including slower processing speed, poorer cognitive control, and weaker working memory relative to typically developing peers.

Adverse Psychosocial Conditions

Orphanages

An estimated 8 million children worldwide are living in residential care or orphanages, despite recognition of the severe adverse impacts of institutionalization on children's health and development. Children in orphanages have poor receptive and expressive language skills, most likely the result of limited language exposure and lack of consistent warm relationships with caring adults. Children from orphanages may be adopted. In an international adoption, the children typically face a new challenge: learning a different language (see Chapter 9). Outcomes for internationally adopted children are mixed; meta-analyses suggest trends for stronger language outcomes when children are adopted before the age of 1 year than after 1 year. However, findings were not statistically significant, likely because of the wide variety of challenges that the children face and difficulty identifying appropriate comparison groups.

Foster Care

Approximately 30–75% of the children 6 years of age or younger in foster care are delayed, and therefore **assessing language skills for them is imperative** (see Chapter 10). An important contribution to the language delay in many children in foster care, like that of children in orphanages, is the lack of consistently warm, responsive parenting that is fundamental to language nutrition. Encouraging foster parents to increase language nutrition may positively affect the language skills of children in foster care.

High-Stress, Low-Verbal Environments

Children from homes where they may experience stressors, such as food insecurity, housing insecurity, poor childcare facilities, and high levels of community violence, are at risk for slower language development relative to peers in stable environments. All of these factors may contribute to initial delays in physical and cognitive development, with language development being one of the most noticeable to track developmental progress. If language delays persist, the chances that the children will catch up with others from more resourced environments, even if their circumstance change, are limited. Thus, what begins as a delay may end up as a disorder. Referral of children from stressed, low-verbal environments to public and community-based prevention programs designed to provide stability and to enhance language input may improve the children's outcomes.

SPEECH DISORDERS

Structural Anomalies of the Organs of Speech

Cleft Lip and Palate

Cleft lip is a split in the formation of the lip. **Cleft palate** is a split in the hard and/or soft palate (see Chapter 356). These conditions often occur together but may occur separately. Cleft lip or palate is the most common structural abnormality at birth in the United States. The cleft is often easy to see but may be subtle if isolated to the soft palate. A child with isolated cleft lip may have minimal speech problems. A child with cleft palate is likely to have speech difficulties, including **hypernasal speech** in which air escapes through the nose, making it difficult to produce consonants that need pressure to build in the mouth for proper execution (e.g., *b, k,* and *s*). In addition, children with cleft palate may have severe and persistent serous otitis media, leading to moderate to severe conductive hearing loss beyond the frequency and complications of children with an intact palate. Therefore most children with cleft palate need long-term therapy with a speech-language pathologist (SLP). Cleft palate may occur in isolation, called **nonsyndromic cleft palate**, or in conjunction with other malformations, called **syndromic cleft palate**. **Velocardiofacial syndrome (VCFS)** is an autosomal dominant condition that results from a deletion on the long arm of chromosome 22 (deletion22q11) and may include cleft palate. Many different phenotypes are associated with this deletion, demonstrating the complex relationship of genes, anatomic structure, and function. The prognosis for speech and language in such cases is dependent on the specific syndrome associated with the cleft palate.

Velopharyngeal Insufficiency

Velopharyngeal insufficiency (**VPI**) is an abnormality of the soft palate, such that the soft palate cannot regulate the flow of air between the mouth and nose in speech. It may occur as part of cleft palate or may be an isolated finding. VPI may not be apparent in early development when the adenoids are large and bolster the soft palate. As the adenoids regress, it may become clear that the soft palate is not closing off the passage to the nose, creating hypernasal speech. Evaluation of the intactness of the soft palate is important before adenoidectomy because removal of the adenoids can bring on VPI suddenly. Surgery or use of prosthetic devices may be required for individuals who cannot be helped by speech therapy.

Speech Sound Disorders

Speech sound disorders is an umbrella term that refers to difficulties with perception, motor production, or phonologic representation of speech sounds and/or speech segments (see Table 53.3). Speech sound disorders may be organic in origin, including neurologic conditions, structural conditions, or sensory conditions. Speech sound disorders are considered **functional** when no known cause can be identified. Speech sound disorders may be accompanied by subtle difficulties in speech perception.

Phonologic Disorders

Phonologic disorders are functional speech sound disorders that affect linguistic aspects of speech. **Phonologic processes** (see Table 53.1) are errors in speech production based on violations of predictable, rule-based features of speech. These phonologic processes are typical at young ages and resolve at specific ages. Phonologic processes become disorders when they persist to older ages and impair intelligibility.

Articulation Disorders

Articulation disorders focus on errors (such as distortions and substitutions) in production of individual speech sounds regardless of where in a word or phrase the sound occurs. Articulation errors are not the result of neuromotor impairment, but rather seem to reflect an inability to correctly process the words they hear. As a result, they lack understanding of how to fit sounds together properly to create words. Children with articulation or other speech sound disorders are at risk for later reading and learning disability.

Childhood Apraxia of Speech

In childhood apraxia of speech (CAS), difficulty in planning and coordinating movements for speech sound production results in inconsistent distortions or errors of speech sounds, even vowel sounds. The same word may be pronounced differently each time, making intelligibility poor. Intelligibility also tends to decline as the length and complexity of the child's speech increase. Consonants may be deleted and sounds transposed. As they try to talk spontaneously or imitate others' speech, children with CAS may display oral groping or struggling. Children with CAS frequently have a history of early feeding difficulty, limited sound production as infants, and/or delayed onset of spoken words. They may point, grunt, or develop an elaborate gestural communication system in an attempt to overcome their verbal difficulty. Apraxia may be limited to verbal motor skills, may extend to oral-motor function, or may be a more generalized problem affecting fine and/or gross motor coordination. Childhood apraxia of speech may co-occur with disorders of language and learning.

Dysarthria

This motor speech disorder often originates from neuromotor disorders, such as cerebral palsy, muscular dystrophy, myopathy, and facial palsy. Dysarthria is characterized by lack of strength and muscular control and manifests as slurring of words and distorting vowels. Speech patterns are often slow and labored. Feeding difficulty, drooling, open-mouth posture, and protruding tongue may accompany the dysarthric speech.

Disorders of Fluency, Voice, and Resonance

Stuttering

Under normal circumstances, most people do not speak smoothly all the time, but rather repeat words or sounds, hesitate to find a word, pause, add "uh" or "you know" to the flow of speech, or repeat a sound or word more than once. These disruptions are called **dysfluencies** and are discussed further in Chapter 53.1. **Stuttering** in children over age 4 that lasts longer than 6 months, includes repetition of individual sounds, and/or creates emotional distress should be evaluated by a speech and language pathologist.

Voice

A **voice disorder** is an abnormality in voice quality, pitch, and loudness that is unexpected or inappropriate for an individual's age, gender, cultural background, or geographic location. Voice disorders can be subdivided into organic and functional. **Organic voice disorders** are physiologic in nature and result from alterations in respiratory, laryngeal, or vocal tract mechanisms. **Aerodigestive disorders** cover congenital or acquired conditions of the aerodigestive tract; they include abnormalities of the **airway** (pharynx and larynx), **pulmonary tract** (trachea, bronchi, and lungs), and **upper digestive tract** (esophagus). These structural problems may affect respiratory and swallowing functions and speech, especially voice. **Functional voice** disorders result from improper or inefficient use of the vocal mechanism in the context of normal physical structure. Psychologic stress can also lead to habitual and maladaptive voice quality, known as **psychogenic voice disorders**. These categories may overlap. Vocal nodules result from behavioral voice misuse that leads to repeated trauma to the vocal folds and structural changes to the vocal fold tissue.

ASSESSMENT OF LANGUAGE AND SPEECH DISORDERS

Screening

Developmental surveillance at each well-child visit should include specific questions about typical language developmental milestones and observations of the child's behavior. Clinical judgment, defined as eliciting and responding to parents' concerns, can detect many children with speech and language challenges. The American Academy of Pediatricians (AAP) recommends clinicians employ standardized developmental screening questionnaires and observation checklists at select well-child visits (see Chapter 28). However, the U.S. Preventive Services Task Force reviewed screening for language impairment in young children in primary care settings and found inadequate evidence to support screening in the absence of parental or clinician concern about children's speech, language, hearing, or development. At present, when parents, other caregivers, or physicians are concerned about speech or language development, the child should be referred for a diagnostic evaluation and intervention.

Diagnostic Evaluation

A developmental delay indicates abnormally slow timing relative to same-age peers in the development of the skill. A language delay becomes a language disorder when it persists to school age; is functionally impactful in terms of communication, social skills, or learning and cognition; or is qualitatively different from normal patterns or sequences of development. Language and communication skills should be interpreted within the context of that child's overall cognitive, social, and physical abilities. A multidisciplinary evaluation of a child with language delay or disorder is often warranted. At a minimum, the diagnostic evaluation should include psychologic or neurodevelopmental evaluation, including an assessment of social skills, a speech-language evaluation, an audiologic assessment, and a pediatric examination.

Psychologic or Neurodevelopmental Evaluation

The two main goals for the psychologic evaluation of a young child with a communication disorder are to assess nonverbal cognitive ability and social skills. A broad-based cognitive assessment is important to determine the breadth and severity of developmental difficulties. At a minimum, the child should have an assessment of both verbal and nonverbal skills. As children reach school age, they may be assessed with an intelligence test and an assessment of adaptive function to determine if they meet criteria for intellectual disability (see Chapter 56). If the child has findings of global developmental delay or intellectually disability, their language and speech skills should be evaluated within that context. Language and speech disorders may coexist with other conditions, so that the psychologic evaluation at all ages should consider mental health conditions, such as anxiety, mood disorder, and attention-deficit/hyperactivity disorder (ADHD) and, at older ages, learning challenges.

A child's social behaviors must be assessed to determine whether the child meets diagnostic criteria for ASD (see Chapter 58). Children with language impairment may display an interest in social interaction, even if they may have difficulty socializing because of limitations in communication skills, such as difficulties initiating conversation or taking turns. Children with ASD do not display social interest in typical ways. However, the distinction may be challenging in the context of a clinical evaluation when the child needs to interact only with professional adults and not with peers. Observational tests include specific maneuvers, such as calling the child's name, making exaggerated gestures, and attempting to engage the child in a reciprocal interaction around blowing bubbles, to make this distinction.

Speech and Language Evaluation

A certified SLP should perform a speech and language evaluation on a child with delays or difficulties in language and speech. A typical evaluation includes assessment of language, speech, and the physical mechanisms associated with speech production. Both expressive and receptive language (see Table 53.1) are assessed, using a combination of standardized measures, informal interactions, and pertinent observations. All components of language are assessed, including phonology, lexicon, morphology, syntax, and pragmatics (see Table 53.1). Speech assessment similarly uses a combination of standardized measures and informal observations and includes assessment of speech sounds, fluency, voice, and resonance. Assessment of physical structures includes oral structures and function, respiratory function, and vocal quality.

Audiologic Assessment (see Chapter 677)

In many settings, an SLP works in conjunction with an audiologist, who can do an appropriate hearing evaluation of the child. If an audiologist is not available in that setting, a separate referral should be made. No child is too young for a hearing evaluation. Passive methods can be used in children who are young or unable to cooperate with testing. Repeat assessment with an active assessment can be accomplished at older ages. A referral for full hearing evaluation is appropriate whenever there is suspicion of language or speech impairment.

Pediatric Evaluation

History and physical examination should focus on the identification of potential contributors to the child's language and communication difficulties. A family history of delay in talking, need for speech and language therapy, or academic difficulty can suggest a genetic predisposition to language disorders. Pregnancy history might reveal risk factors for prenatal developmental anomalies, such as polyhydramnios or decreased fetal movement patterns. Small size for gestational age at birth, symptoms of neonatal encephalopathy, or early and persistent oral-motor feeding difficulty may presage speech and language difficulty. Developmental history should focus on the age when various language skills were mastered and the sequences and patterns of milestone acquisition. *Regression or loss of acquired skills should raise immediate concern.*

Physical examination should include measurement of height (length), weight, and head circumference, even in children over age 2 years. The skin should be examined for lesions consistent with phakomatosis (see Chapter 636). Anomalies of the head and neck, such as white forelock and hypertelorism (Waardenburg syndrome), ear malformations (Goldenhar syndrome), facial and cardiac anomalies (Williams syndrome, VCFS), retrognathism of the chin (Pierre Robin anomaly), or cleft lip/palate, are associated with hearing and speech abnormalities. Neurologic examination might reveal muscular hypertonia or hypotonia, both of which can affect neuromuscular control of speech. Generalized muscular hypotonia, with increased range of motion of the joints, is frequently seen in children with language impairment. The reason for this association is not clear, but it might account for the fine and gross motor clumsiness often seen in these children. However, mild hypotonia is not a sufficient explanation for the impairment of receptive and expressive language. Language impairment may be a component of a syndrome or other recognizable condition. The physical examination gathers information to make other diagnoses.

No routine diagnostic studies are indicated for isolated language disorders with the exception of the hearing assessment. When language delay is a part of a generalized cognitive or physical disorder, referral for further genetic evaluation, genetic testing (e.g., fragile X testing, microarray, whole exome or whole genome sequencing), neuroimaging studies, and EEG should be considered.

Treatment of Language and Speech Disorders

Disorders of language and speech are often treated by SLPs working alone or as part of a multidisciplinary team with others, such as early intervention specialists or occupational therapists. SLPs may work in hospital in-patient and out-patient settings. More commonly, they work in schools and early intervention programs. The nature and intensity of treatment are predicated on the nature and cause of the language or speech disorder and the explicit objectives of treatment. **Childhood apraxia of speech** typically requires that the child participate in four or five short sessions per week to achieve intelligible speech, whereas language impairment disorder may require once- or twice-weekly therapy in a peer-group setting to increase communicative attempts. Speech-language therapy for young children is typically play-based. Even drills are couched in naturally occurring, enjoyable, or fun activities. Group therapy with other young children is often well suited to children with language and communication disorders because children practice their emerging skills with peers in naturalistic settings. A strong family component to therapy is important to leverage the limited time that therapists can spend with children. Caregivers can be taught to use effective techniques designed to meet the objectives of the treatment program. For children who do not develop useful verbal language, the SLP may consider the use of assistive and augmentative communication (AAC; see Chapter 54), which may use high-technology devices, such as voice-generating computer programs, or low-technology solutions, such as sign language or picture exchanges. The use of AAC allows the nonverbal child to communicate within the human community. Several systematic reviews and meta-analyses provide compelling data that speech-language therapy is effective for improving many aspects of language and speech. Therefore a timely referral for treatment with an SLP is recommended over watchful waiting for many children with delays and disorders of language and speech.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

53.1 Childhood-Onset Fluency Disorder

Kenneth L. Grizzle and Karolyn Mirasola

Dysfluent speech describes speech, language, and voice behaviors that interrupt the production and fluency of sounds, words, and thoughts. All speakers produce dysfluent speech, but not all dysfluent speech is stuttering. The words *stuttering, stammering,* and *dysfluency* are often used interchangeably. *Stutter* is used informally, particularly in the United States, to describe when an individual is struggling to express themself and may speak in a halting manner. *Stammering* is used in the United Kingdom in place of stuttering (Table 53.4). It is important for clinicians to have a general understanding about what stuttering is and when to counsel and refer families to speech-language pathologists (SLPs). It is important to distinguish between stuttered and nonstuttered dysfluencies and other fluency disorders and to identify concomitant symptoms.

DIAGNOSIS

In the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5), the term *stuttering* has been removed from the diagnostic classification, and the disorder is referred to as **childhood-onset fluency disorder** (Table 53.5). Note that impact on functional behavior is a component of the psychiatric diagnosis. In contrast, communication disorder specialists would consider anxiety and avoidance of various activities as concomitant symptoms, but not necessarily a requirement for the diagnosis of stuttering.

Child-onset stuttering (formerly known as developmental stuttering) is a speech disorder that often begins in the preschool period

Table 53.4 Terminology Related to Childhood-Onset Fluency Disorder

TERM	DEFINITION
Stuttering	A speech disorder manifested through abnormal speech patterns referred to as *dysfluencies*
Childhood-onset fluency disorder	Term used in DSM-5 that is synonymous with *stuttering*
Stammering	The clinical term used in the United Kingdom rather than stuttering; stammering also used informally to describe halting speech
Cluttering	A speech disorder characterized by an excessively rapid and irregular rate of speech
Dysfluency	Speech disruptions that can occur in normal or disordered speech

Table 53.5 DSM-5 Diagnostic Criteria for Childhood-Onset Fluency Disorder

A. Disturbances in the normal fluency and time patterning of speech that are inappropriate for the individual's age and language skills, persist over time, and are characterized by frequent and marked occurrences of one (or more) of the following:
   1. Sound and syllable repetitions.
   2. Sound prolongations of consonants and vowels.
   3. Broken words (e.g., pauses within a word).
   4. Audible or silent blocking (filled or unfilled pauses in speech).
   5. Circumlocutions (word substitutions to avoid problematic words).
   6. Words produced with an excess of physical tension.
   7. Monosyllabic whole-word repetitions (e.g., "I-I-I-I see him").

B. The disturbance causes anxiety about speaking or limitations in effective communication, social participation, or academic or occupational performance, individually or in any combination.

C. The onset of symptoms is in the early developmental period.
Note: Later-onset cases are diagnosed as 307.0 [F98.5] adult-onset fluency disorder.

D. The disturbance is not attributable to a speech-motor or sensory deficit, dysfluency associated with neurologic insult (e.g., stroke, tumor, trauma), or another medical condition and is not better explained by another mental disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders. 5th ed.* Washington, DC: American Psychiatric Association; 2013:45–46.

and is not associated with stroke, traumatic brain injury, or other possible medical conditions. Stuttering behaviors can occur in typically developing children who do not have a speech disorder and in this situation are more accurately referred to as *developmental dysfluencies*. During the toddler and preschool years, children often produce repetition of sounds, syllables, or words, particularly at the beginning of sentences (normal dysfluencies). These developmental dysfluencies occur between the ages of 2.5 and 4 years old when the language, motor, and emotional systems are developing. These dysfluencies may occur as the child struggles to try to express more complex ideas in a rapid and precise manner.

Child-onset stuttering disorder also typically begins between 2 and 4 years of age. Onset of symptoms varies from pronounced stuttering within a few days to gradual worsening of symptoms across months. Symptoms may ebb and flow, including disappearing for weeks before returning, especially among young children. From 40% to 75% of young children who stutter will stop spontaneously, typically within months of starting. Although predicting which child will stop stuttering is difficult, risk factors for persisting include stuttering for >1 year, continued stuttering after age 6 years, and experiencing other speech or language problems. Additionally, certain types of dysfluencies are typically seen only in child-onset stuttering disorder.

Types of Dysfluencies

Dysfluencies interrupt the normal flow of speech through repeated or prolonged sounds, syllables, or words. Types of dysfluency that are *not* exclusive to children who stutter include *interjections* ("well, uhh, umm"), hesitations (pause), *revisions* ("I thought . . . I mean"), and *phrase repetitions* ("Did you say—Did you say"). In addition, the perspective of the speaker and cause of the dysfluency differ between true stuttering disorders and other types of dysfluency. The dysfluencies might sound the same but occur for different reasons. For example, a typically developing child with dysfluency may talk around a word or use a completely different word because of issues with word retrieval, complex thought formulation, or distractibility. But for children who stutter, they may talk around a word or retrieve a completely different word because even though they know exactly what they want to say, they are unable to produce or "get" the sounds out. This highlights the notion that stuttering is about more than what the listener observes. The "moment of stuttering" is different because something occurs that only the person who stutters can perceive.

Dysfluencies that occur in child-onset stuttering vary in type, frequency, and longevity. Specifically, children who stutter show greater part-word repetition ("b-b-b-b-but"), single-syllable word repetition ("My, my, my"), sound prolongation ("MMMMMM-an"), and in more severe cases, blocking. Blocking is a dysfluent behavior that is identified by a fleeting or sometimes lengthy blockage of the flow of air at the level of the vocal folds or articulators (tongue, teeth, and lips). Typically, the child has initiated an articulatory posture (tongue is in the position to produce "k"), but she is unable to release any air and/or phonation (i.e., voice). Often in response to this inability to produce sounds or words, the child will develop secondary behaviors that recruit movement from other parts of the body that the child feels they have more "control" over.

These types of behaviors and movements exist only within child-onset stuttering disorder. They are referred to as *secondary characteristics,* or physical concomitants that often occur as a response to stuttering. Common secondary characteristics include movements of the head (head turning or jerking), face (eye blinking/squinting, grimacing, opening or tightly closing the jaw), neck (tightening), and limbs (stomping feet, slapping hand); an increase in body tension; and irregular patterns of inhalations and exhalations.

Emotional Symptoms and Stuttering

Fear and anxiety are **emotional symptoms** associated with stuttering. Many people experience some level of fear and anxiety related to speaking in front of a group, but children who stutter often experience high levels of fear and anxiety related to all speaking situations, especially ones that occur with newer or unfamiliar people (e.g., ordering at a restaurant, calling a store to ask about store hours, introducing oneself). Along with their own feelings interfering with speech production, the reactions of those around them may also increase the anxiety of children who stutter. Negative interactions or comments may inhibit a child's future attempts to interact verbally with another person or in a group setting. Consider also the potential **social challenges** associated with entering a classroom for the first time, transitioning to middle/high school/college, beginning a job, dating, and so on. Not surprisingly, just as avoiding production of a perceived sound or word is common, *avoidance* of situations and people is a common way of coping with the anxiety created by the fear of stuttering. These avoidance behaviors indicate a need for intervention.

Differential Diagnosis

Although many dysfluencies are often referred to as stuttering, it is important to recognize that there are different types of fluency disorders. Cluttering is a fluency disorder that may occur with or separate from stuttering but is different in form and cause. Stuttering and cluttering have been identified to exist on a continuum. Unlike stuttering, for which distinct episodes can be identified and even counted, **cluttering** affects the entire speech output and is often diagnosed around age 7 years or later. In addition to elevated repetitions of partial words (as in stuttering), whole words, and phrases, those who clutter show speech bursts that are often choppy, and articulation can be slurred and imprecise. In addition, there is often an increase in disorganization of their language, unusual prosody, and listener perception of a fast rate of talking. The level of awareness of how their speech affects those listening, unlike children who stutter, is minimal for those who clutter. In fact, children with a cluttering disorder often experience a decrease in their dysfluent behaviors when they are speaking in front of a group because of an increased focus on their speech, whereas the impact for children who stutter is exactly the opposite.

In addition to cluttering, neurogenic (result of a stroke, head trauma, or other neurologic damage) and psychogenic (associated with psychologic trauma) stuttering also exist, though they rarely occur in childhood. Stuttering can also be confused with dysfluent speech that occurs for other neurologic reasons (e.g., Tourette syndrome, cerebral palsy, spasmodic dysphonia).

Epidemiology

Approximately 5% of children experience stuttering, with the highest rates among young children. Seldom does a child begin stuttering before 2 years of age or after 12 years; in fact, the mean age of onset is 2-4 years, and most children stop stuttering within 4 years of onset. Symptoms will disappear within 4 weeks for a minority of children. Stuttering is more common in males than in females, and the magnitude of the difference increases as children get older. The ratio among children <5 years is approximately 2:1 and jumps to 4:1 among adolescents and young adults.

Genetics

There is convergent evidence of a genetic link for childhood-onset fluency disorder. Concordance rates among monozygotic twins range from 20% to 83%, and for dizygotic twins, 4–19%. Family aggregation studies suggest increased incidence of approximately 15% among first-degree relatives of those affected, three times higher than the 5% rate for the general population. The variance in risk for stuttering attributed to genetic effects is high, ranging from 70% to 85%. Although evidence is limited, stuttering appears to be a polygenic condition, and several genes increase susceptibility.

Brain Structure and Function

Brain structure and function abnormalities found among individuals who stutter include deficits in white matter in the left hemisphere, overactivity in the right cortical region, and underactivity in the auditory cortex. Abnormal basal ganglia activation has also been identified.

EVALUATION

Comorbidities

Despite the widely held belief in a high degree of comorbidity between childhood-onset fluency disorder and other communication disorders, research to date does not necessarily support this association. SLPs consistently report high rates of comorbidity, although this would be expected in clinical samples. Speech sound (phonologic) disorders are the most commonly reported comorbidities, occurring in 30–40% of children seen by SLPs. However, studies have not found greater incidence of phonologic disorders among those who stutter compared to a control group. Similarly, SLPs report a much higher percentage of children with language disorders among their patients who stutter than the approximately 7% expected in the population at large, yet studies find the language functioning among individuals who stutter is no different than in the general population. The same pattern holds for learning disorders (LDs).

Children who stutter seem to experience more anxiety than their nonstuttering peers, although research is limited. The frequency of reported anxiety increases with age. Social anxiety and generalized anxiety disorder are common among adolescents who stutter. Although one should not assume that an individual who stutters will have an increased risk for any specific psychiatric disorder, assessing for anxiety is important, as children who stutter frequently avoid situations that demand speaking, as discussed earlier in the chapter.

Children who stutter have consistently been found to be bullied more than peers. In one study, these children were almost four times more likely to be bullied than their nonstuttering counterparts. About 45% of children who stuttered reported having been the victim of bullying.

Referral to Speech and Language Pathology

In deciding who to refer to an SLP, it is important to distinguish developmental dysfluencies from stuttering. In addition to the risks noted in Table 52.5, indications for referral include three or more dysfluencies per 100 syllables (b-b-but; th-th-the; you, you, you), secondary characteristics denoting escape or avoidance behaviors (pauses, head nod, blinking), discomfort or anxiety while speaking, family history of stuttering or other speech-language disorders, and suspicion of an associated neurologic or psychotic disorder. Most children with persistent stuttering after age 4 years should be evaluated by an SLP.

As a part of the evaluation, the SLPs will be able to address the many pressing concerns and worries of a parent whose child is stuttering. The outcome of a speech-language evaluation for stuttering should accomplish the following:

1. Obtain a strong family history related to the existence of speech and language disorders in general and more specifically related to stuttering and dysfluencies.
2. Interview the parent or child about the child's stress when speaking in various situations.
3. Record a speech sample to analyze the type, frequency, and complexity of the dysfluent behaviors and secondary characteristics that the child is producing.
4. Differentiate between developmental dysfluency behaviors, other causes of dysfluent behaviors, and a child-onset dysfluency disorder (aka stuttering).
5. Develop a plan with the family that involves a combination of direct and indirect speech and language therapy, parent education, and home programming.

TREATMENT

A true stuttering disorder is a lifelong condition. To date, no evidence supports the use of a pharmacologic agent to treat stuttering in children and adolescents, and there is no cure for stuttering. However, treatment in preschool-age children has been shown to improve stuttering. In fact, speech-language therapy is most effective when initiated during the preschool period. The broad focus of therapy allows for minimizing the adverse effects of the condition.

Based on the child's age, types and frequency of stuttered behaviors, severity of secondary characteristics, and impact on the child's qualify of life, the SLP will decide if a less direct or more direct therapeutic intervention is recommended.

Less direct therapy focuses on manipulating the situation and environment while allowing the child to experience increased fluency. Most preschool children respond to interventions taught by SLPs that are accompanied by behavioral feedback strategies implemented by parents and teachers. It is important to recognize that parental pressure or speaking pressure does not cause stuttering. A less direct therapy approach involves working with the caregiver to accomplish the following:

1. Limit situations and expectations that cause increased dysfluencies and stress
2. Demonstrate and model how to adjust speaking rate and complexity of language rather than reprimanding children for their speech errors or asking them to slow down
3. Increase opportunities for the child to experience fluent communication

More direct therapy is recommended and implemented when less direct therapy did not have an impact on the stuttering behaviors, the child has increasing worries related to stuttering, the child has a high risk of continuing to stutter, or the child is older and has been stuttering for some time. One of the overarching goals of the therapy implemented by an SLP is to help the child experience increased fluency and strategies to learn how to "stutter" better.

Therapy that is more direct adds the following elements:

1. Awareness and education: Recognizing and accepting that their speech is different, identifying and naming types of speech, nonjudgmentally noting episodes of stuttering using selected words and phrases (which are often accompanied by pictures) that were developed with and practiced by the child ("That was a bit bumpy"), appreciating others' reaction to the child when stuttering, managing secondary behaviors, admitting they are a person who stutters, and addressing avoidance behaviors as a result of the stress and anxiety they are experiencing.
2. Fluency-shaping behaviors: Regulating rate of speech and breathing and helping the child gradually progress from the fluent production of syllables to more complex sentences. The child should be involved in opportunities to identify speech disfluencies, implement self-correction, and respond to requests ("Can you say that again?").

Because stuttering rarely disappears, the thrust of therapy is often to "improve" the type of stuttering, decrease the occurrences of stuttering, and develop strategies for coping with the fear and anxiety that will continue to occur in various speaking opportunities.

Appreciating that dysfluency is a broad term and stuttering can be one of the causes for this behavior allows pediatricians to have a more accurate understanding of the symptoms, causes, and treatments associated with dysfluencies. Being armed with this information allows the provider to include in their referral to an SLP an accurate description of symptomology, which will be beneficial in the planning and execution of their initial evaluation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 54

Augmentative and Alternative Communication

Michelle M. Macias

Children must develop communicative competence to interact with others, to influence their environment, and to participate fully in society. If children are not able to effectively communicate, they will have minimal means to express what they need, exchange information with others, and develop social skills and relationships. Some children are unable to communicate effectively through natural means, including speech, gestures, or writing (see Chapter 53). These children with **complex communication needs (CCNs)** have more independent function through **augmentative and alternative communication (AAC)** methods to meet their communication needs and to avoid significant restrictions on their participation in all aspects of life.

AAC interventions have been helpful for individuals with no speech, limited speech, and those at risk for speech-language disorders; this includes individuals who rely on speech but need augmentation to enhance speech, those recovering from a traumatic brain injury, and those who may have temporary conditions affecting communication. AAC has changed from an emphasis on providing the means to express needs and wants to the recognition that communication must also foster exchange of information, development of social relationships, and participation in social routines. In addition, there is recognition that communication needs extend beyond face-to-face interactions and also include written communication in the school setting and even social media in peer communities.

DEFINITIONS

According to the American Speech-Language-Hearing Association (ASHA), AAC is "an area of clinical practice that addresses the needs of individuals with significant and complex communication disorders characterized by impairments in speech-language production and/or comprehension, including spoken and written modes of communication." AAC encompasses the communication methods used to supplement or replace speech or writing for those with impairments in the production or comprehension of spoken or written language. In pediatrics, AAC is used by youth with a wide range of speech and language impairments, including cerebral palsy (CP), traumatic brain injury, intellectual disabilities, autism spectrum disorder (ASD), and apraxia of speech. In addition, children and adolescents hospitalized in intensive care units can benefit from AAC.

AAC is **augmentative** when used to supplement existing speech and **alternative** when used in place of speech that is absent or not functional. AAC uses a wide variety of electronic and nonelectronic techniques from low technology to high technology, including manual signs, gestures, tangible objects, line drawings, picture communication boards and letter boards, and speech-generating devices. The term **assistive technology (AT)** is a more general term describing systems and devices that alleviate the effects of a disability and improve function, for example, bracing for a child with a neuromotor impairment as well as AAC.

Prevalence

Across countries, the overall prevalence of AAC use ranges from approximately 1.2% to 1.5% of the population; worldwide up to 0.6% of the school-age population has a severe speech impairment. A national survey of U.S. special educators reported that approximately 18% of students served in special education use a form of AAC for communication, with 7% using gestural modes, 6.5% using pictorial supports, and 4.8% using a speech-generating device (SGD). However, not all U.S. children with developmental disabilities or children with special healthcare needs have their communication needs met. The more severe a child's communication deficit, the more likely the child would benefit from AAC support.

Across particular pediatric populations, it has been estimated that 25–50% of children with ASD have limited speech and would benefit from AAC. Up to 45% of children with CP use AAC either exclusively or to supplement speech. Several studies have found that in intensive care units ~30% of patients had communication breakdowns and met AAC candidacy criteria, although alternative communication modes were rarely used.

Goals of Communicative Interactions and AAC Interventions

The ultimate goal of AAC is to enable individuals to effectively engage in interactions and participate in activities of their choosing. Broadly speaking, the goals of AAC interventions are to assist individuals with meeting their current communication needs and prepare them to meet their future communication needs. Communicative interactions can be said to fulfill four purposes: (1) communicate needs/wants, (2) transfer information, (3) social closeness, and (4) social etiquette. It is important to remember that adequacy of communication depends on the personal goals of the person using AAC, and the definition of success may vary by the professionals involved.

Most children with complex communication needs demonstrate some ability to communicate using speech, although some are entirely nonverbal. The effectiveness of natural speech for communication can be divided into 10 levels (Meaningful Use of Speech Scale; Robbins & Osberger):

1. Makes vocal sounds in communicative exchanges
2. Gets another person's attention using speech
3. Uses various vocal sounds depending on the intention and content of messages

Uses speech for communication about:

1. Known topics with familiar people
2. Known topics with unfamiliar people
3. New topics with familiar people
4. New topics with unfamiliar people
5. Messages that are understood by familiar people
6. Messages that are understood by unfamiliar people
7. Clarification messages as needed when communication breakdown occurs

AAC Systems

An "**AAC system**" refers to the integrated group of components used to support and enhance communication. These components include the specific forms of AAC, selection techniques, and strategies for use.

Individuals with complex communication needs must have access to a wide range of means to enhance their communication and participate fully within social and educational contexts. This may include **unaided AAC**, which does not require an external tool and requires some degree of motor control (e.g., gestures, sign language, finger spelling, speech approximations), or **aided AAC**, which requires either an electronic or a nonelectronic tool. Nonelectronic aided forms are referred to as **low-tech aided AAC** and include options such as communication boards/books, picture-exchange communication systems (PE or PECS, pictures, photographs), or visual schedules. Electronic forms are referred to as **mid-tech or high-tech AAC** systems and include traditional speech-generating devices (SGDs) or voice output communication aids (VOCAs), recordable devices, and computer/tablet options and applications ("apps"). SGDs/VOCAs include multiple options. **Single-level devices** have pictures/words on a single-level display, whereas **multilevel devices** can have vocabulary programmed on more than one level. **Static display devices** keep the same display, and the user can sequence symbols or words to generate a message. **Dynamic display devices** are usually those with a touch screen for the display in which pages can change using navigation keys and link buttons. **Text-to-speech devices** enable the user to spell messages that convert to synthesized speech. Some dynamic display devices include text-to-speech

Table 54.1 Types of Augmentative and Alternative Communication

	LOW TECH	MID-HIGH TECH
Unaided	• Sign language • Gestures	—
Aided	• Communication boards/books • Picture exchange systems • Visual schedules • Eye-gaze picture board • Simple single-message speech output devices	• Voice output communication aids (VOCAs)/speech-generating devices (SGDs) with prestored recordings of natural speech or computer-generated speech • Specialized software on electronic tablet, smartphone • Spelling and/or symbol systems to represent language

Unaided systems: Do not require special materials or equipment; rely on user's body to covey messages.
Aided systems: Require the use of tools or equipment; can require power or no power.

and use symbols as well as text. Table 54.1 provides examples of the range of AAC systems.

Mobile technology (e.g., iPad) and greater use of social media tools have increased acceptance of AAC and reduced attitudinal barriers to AAC use. However, the increased diversity of communication tools also means increased operational demands, given that each tool is designed with different representations, organizations, and layouts of information as well as different access techniques (e.g., swiping, tapping). Each design may reflect different motor, cognitive, perceptual, and linguistic learning demands. A combination of gestures/signs, low-technology systems, mobile technology devices, and SGDs can provide AAC users with the most effective communication options to suit their needs.

AAC Teams

AAC teams serving individuals with CCNs are the groups of people that guide the AAC intervention decision-making process and implement communication supports. Team members include the children and adolescents with CCN themselves, parents/caregivers, and professionals playing a variety of roles.

Children with CCN. The most important member of the team is the individual relying on AAC techniques. The role may change in response to the individual's maturation and capability, but to the extent possible, the child or adolescent should participate in the decision-making process regarding goals, social relationships, and support options related to the AAC system and interventions.

AAC facilitators. The term *facilitator* refers to parents/family members, friends, professionals, and frequent communication partners who assume some responsibility for keeping the AAC system operational and/or supporting the person with CCN to use it effectively. They support communication interactions by coaching, serving as interpreters, and/or helping resolve communication breakdowns. Importantly, the role of facilitator is to support independent communication by the individual with CCN, not to communicate *for* the individual.

AAC specialists. AAC specialists provide direct AAC intervention services by instructing and educating about AAC and designing and implementing AAC interventions. AAC specialists work with clinicians and educators, such as speech-language pathologists, occupational therapists, teachers, and pediatric healthcare providers who provide clinical and educational services to youth with CCN.

AAC Assessment

AAC assessment involves gathering information so that informed decisions can be made about the adequacy of current communication, the communication needs, the AAC techniques that are most appropriate, how to provide instruction in AAC techniques, and how to evaluate outcomes. Proper evaluation and support for the use of AAC devices are of paramount importance.

Studies comparing acquisition of communication skills reveal few differences in terms of how quickly many children can learn to use some of the available AAC options. For example, PEC and sign language comparison studies vary—some show PECs were acquired more easily than signing, and others suggest both PECs and signing were acquired at an equal pace. Studies comparing PECs with SGDs similarly vary in terms of effectiveness of device use.

Physicians, therapists, and other professionals who prescribe AAC must make sure the child (and family) receives training and monitoring for using the device and that the device is accessible across settings in which the child functions (e.g., home, school, community activities). A substantial number of AAC devices are abandoned shortly after implementation without support for their use. AAC assessment and intervention is a dynamic process, and usually ongoing, as often the children and adolescents requiring the AAC system are unable to speak or write because of physical, cognitive, language, and/or sensory impairments. Assessment generally consists of four phases as outlined here:

Phase 1: Referral. The "finder" role is an important role for pediatric healthcare providers. They may be the impetus for recognizing that a child has a CCN and that an AAC intervention may be helpful. They then assist the patient and their family by initiating a referral to an appropriate resource. The pediatric provider can support the AAC funding application by certifying a medical diagnosis and signing a prescription for the recommended service. Although the role is episodic, it is nonetheless a key role in the AAC assessment and treatment process.

Phase 2: Initial Assessment. The goal of this phase is to gather information to design an AAC intervention to match the child's existing needs and capabilities. The AAC specialist(s) assesses the child's current communication interaction needs and his or her physical, cognitive, language, and sensory abilities. This typically focuses on enabling communicative interactions between the child and familiar AAC facilitators. The intervention is refined as the child learns about the operational requirements of the AAC system and the AAC team gathers information on how well the system works for the child. Demonstrations and simulators are available to help with training before the actual equipment is ordered.

Phase 3: Assessment for Other Settings. The goal is to develop a solid communication system that supports the child with CCN in a variety of environments, including home, school, and recreational environments. A child must have access to a system that allows educational and social participation.

Phase 4: Follow-Up Assessment. This involves maintaining a comprehensive AAC system that accommodates the child's changing capabilities. The communication equipment must be examined regularly to assess the needs of new communication partners, detect replacement/repair needs, and reassess the child's capabilities as they change.

Specific Assessment Details

Assess Current Communication. The initial step is to assess the effectiveness of the child's current communication system. The assessment of communication access focuses on the operational and social aspects of communicative competence. A child with spastic quadriplegia, for example, may be unable to use eye gaze consistently and therefore operationally unable to use an eye-gaze AAC system. On the other hand, a minimally verbal adolescent with ASD may be able to operate an electronic AAC device but never use it to initiate a social interaction.

Some questions to ask regarding current communication behaviors in children with CCN include the following:

- What are the various methods your child uses to communicate? Examples: words/speech, vocalizations, gestures, signing, communication board, eye gaze, typing, and so on.
- What body part is used for each technique (e.g., left/right hand, eyes)?
- On a scale of 1 to 5, how accurately and efficiently is your child able to use this technique?
- On a scale of 1 to 5, how well is your child able to use this technique in an interactive, socially appropriate manner?

Screening Tools. Various screening instruments exist that help document communication behaviors. These include the Communication Matrix; the Inventory of Potential Communicative Acts (IPCA); and the Social Communication, Emotional Regulation, Transactional Support (SCERTS) Model Assessment, among others. The Communication Matrix focuses on individuals using any form of communication (presymbolic or AAC), and the IPCA focuses primarily on presymbolic communicators with physical and/or developmental disabilities. The SCERTS Model Assessment focuses on communication and social regulation behaviors in verbal and nonverbal children with ASD.

Assess Potential to Use or Increase Speech. A key issue in AAC assessment for children with CCN is whether AAC is needed to augment insufficient speech or serve as a replacement for speech. Parents are often concerned that using an AAC device will negatively affect speech development, as the child will have access to an "easier" alternative. The use of AAC techniques does not inhibit natural speech; conversely, AAC may enhance spoken language by supporting the development of communicative competence and language skills.

Assess Potential for Environmental Adaptations. Modifications of physical spaces or structures may be relatively straightforward or more complex, depending on the specific situation. For example, at home, furniture rearrangement or renovations to adapt the home to accommodate AAC devices may be necessary. In the school, desks/tables may need to be raised/lowered or a vertical workspace may need to be created with a slanted board.

Specific Issues Regarding AAC for Children with Disabilities

Cerebral Palsy

Communication impairments are commonly seen in children with CP, both related to impaired (motor) speech intelligibility and language disorders (see Chapter 638.1). The incidence of dysarthria varies depending on the type of CP and degree of motor impairment. Language impairments are associated with intellectual functioning and hearing loss, if present.

More than any other disability, communication interventions for children with CP require a multidisciplinary team approach. The wide variety of motor impairments entails the involvement of occupational and physical therapists, orthotics specialists, rehabilitation engineers, and speech-language pathologists. Positioning and seating adaptations may need to be developed for optimum stability and to allow efficient movement to access the AAC system. The team must consider the wide range of options available and what is necessary to optimally match the child with the system being used. Although up to half of children with CP may be able to access the AAC device through use of a finger, others will need alternative access techniques, including chin pointers, joysticks, optical indicators, or switches.

Emphasis on AAC needs to be balanced with other developmental interventions, including speech-language therapy, motor development training, and academic instruction. Some will require extensive motor training to be able to use alternative access methods such as eye tracker, head mouse, or a switch for scanning. Although speech, gestures, and facial expressions may be affected as a result of motor impairment, patients should still be encouraged in using these natural modes for communication. A balanced approach supports the use of multimodal systems, which can vary according to the situation. A child with CP may be able to communicate effectively with family members using natural speech and gestures but may need to rely on AAC techniques with unfamiliar partners.

Long-term planning for adulthood is essential, given the need to rely on AAC devices and techniques that can accommodate the range of demands that are communicative in nature, including interpersonal, academic, and employment demands. Without advance planning, AAC systems are unlikely to meet all these demands, or the individual will not have all the skills required to use the systems.

Intellectual Disability

As defined by the American Association on Intellectual and Developmental Disabilities (AAIDD), intellectual disability (ID; see Chapter 57) is characterized by "significant limitations both in intellectual functioning and adaptive behavior as expressed in conceptual, social, and practical skills." Appropriate supports, including AAC supports, can have a significant impact on the ability of individuals with ID to live and learn successfully in inclusive environments typical of their same-age peers. At least 30% of school-age individuals requiring AAC supports have an ID. One of the main barriers that exists for children with ID is simply recognizing that the use of AAC can be beneficial and that AAC use should be generalized across settings and not just used in highly structured settings such as school.

Although most youth with ID do not engage in socially inappropriate behaviors, problem behaviors occur more frequently in this population compared to those without ID. Many individuals with ID do not use speech as their primary mode of communication, and problem behaviors can be exacerbated by difficulty communicating. Many of the strategies used to support individuals with ID involve AAC strategies such as visual schedules or those used to teach choice making and functional communication training.

The nature of interventions directed at both natural speech development and AAC varies considerably given the diversity of syndromes and conditions that result in ID. Many individuals with ID may have multiple diagnoses that affect the nature of their intervention needs.

Autism Spectrum Disorder

ASD (see Chapter 58) is a highly variable disorder; individuals with ASD experience a wide range of complex issues related to language and communication, which presents challenges regarding speech-based and AAC interventions. Individuals with ASD *and* ID may require more extensive educational, behavioral, and community supports compared with those without ID, but those without ID still require supports in the core area of social communication. **Language forms** are the language structures and vocabulary (e.g., grammar, syntax). **Language function** refers to what individuals do with language as they engage and interact with others. Because ASD affects the nature of communication as a social mediator, it is important that AAC interventions emphasize the function, or pragmatic aspects of communication, as well as the communication aspects related to the form of language.

Interventions must start at the individual's level of social, communicative, and cognitive development and build skills in a natural developmental progression. The development of dynamic, interactive communication is critical, and the child with ASD needs to learn to use communication skills related to functional activities in daily life. The developmental profiles of youth with ASD are often characterized by an uneven distribution of skills. Children with ASD often perform much better with object permanence and tool use (causality) than those areas requiring interpersonal interaction, such as gestural or vocal imitation, symbolic understanding, or language comprehension. Therefore AAC interventions must be geared to the child's social and linguistic abilities rather than the child's object abilities (e.g., fine motor skills or object manipulation skills). Manual sign or pictorial systems (PECS) are often recommended for nonverbal children with ASD. This often presumes that the problem is only one of output and that communicative intent is intact; however, the child may not have the language or the social base on which communication must be built. Therefore interventions should initially build imitation, joint attention, and natural gestural communication skills before initiating formal language-based AAC or speech approaches.

SGDs and other speech-output technologies can be used effectively in children with ASD to teach both communication and literacy skills. SGDs can act as a "social bridge" to familiar and unfamiliar communicative partners. They can be programmed with whole messages (e.g., "do you want to play") in addition to single words and phrases and thereby increase communicative efficiency and decrease potential communication breakdowns. These output devices are available via touch-screen tablet and mobile devices.

Childhood Apraxia of Speech

ASHA defines childhood apraxia of speech (CAS) as a neurologic speech-sound disorder "in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits." Given consensus on diagnostic criteria is lacking, ASHA recommends that the term "suspected CAS" be used. There is consensus on motor speech behaviors in three areas: (1) inconsistent errors on consonants and vowels in repeated syllables or words; (2) lengthened, disrupted transitions between sounds and syllables; and (3) inappropriate prosody of speech (see Chapter 53).

Given CAS is primarily a motor speech disorder, AAC is usually a secondary intervention, with the primary intervention focused on improving natural speech production. Because children with CAS often evidence significant language delays related to the inability to practice language, it is important to provide them with AAC modalities early on. The use of AAC will not inhibit speech development and production, and generally use of AAC supports result in increased mean length of utterances for the child.

Children with suspected CAS who benefit from traditional AAC are those who primarily speak in single words, have largely unintelligible speech, and are not able to effectively communicate with family members, peers, and teachers. The children benefit from a wide range of AAC, from unaided techniques including gestures and signs and aided techniques such as PECS communication books and/or SGD. It is important that the AAC device facilitates both language development and social competence. The AAC system should be designed so that the child learns to create longer and more complex messages that are grammatically accurate.

Children with suspected CAS who can produce single-word utterances but struggle with multiword speech often benefit from AAC speech supplementation. This supplementation may be in the form of key symbol supplementation, in which they point to key symbols in conjunction with speech. This can help with topic setting—when the child introduces a new topic of conversation, they point to a symbol, which helps narrow the range of possibilities for the communication partner. Often children with suspected CAS prefer to use natural speech and unaided approaches, using aided AAC techniques only when communication breakdown occurs.

Special Considerations

Reimbursement and Funding. The AAC specialist (usually a speech-language pathologist) should be familiar with public and private funding options. Funding can come from schools, third-party payers (private or public insurance companies), or philanthropic sources. Low-tech AAC systems are usually developed by a speech-language pathologist and do not usually require additional funding. SGDs are considered durable medical equipment (DME), and funding can vary immensely. Coverage will need to be verified based on the patient's specific needs and insurance. Pediatric care providers are often asked to sign prescriptions and/or write letters of medical necessity for an AAC device. This should be done only after conferring with the AAC team members, especially the speech-language pathologist. The letter should include that the pediatric provider received the evaluation reports, reviewed the recommendations, and agrees that the recommended AAC devices are medically necessary for treatment of the child's CCN associated with the specific diagnosis. SGD vendors are often able to assist with funding questions.

The Assistive Technology Act. The Assistive Technology Act of 2004 provides all U.S. states and territories with federal funding to increase access to AT devices and services. This information can be found at the National Assistive Technology Act Technical Assistance and training (AT3) Center (https://www.at3center.net/stateprogram).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 55

Outcomes Among Infants and Children Who Are Deaf/Hard of Hearing

Susan E. Wiley and Rachel D. St. John

See also Chapter 677.

Approximately 3 in every 1,000 infants in the United States are *born* deaf or hard of hearing (D/HH). Additionally, for infants who pass the newborn hearing screening, there are a number of risk factors for developing *delayed-onset* hearing loss at any time during infancy and childhood. Given that the large majority of deaf infants are born to hearing parents, there is the potential for a developmental crisis when an infant or child does not have an accessible shared language in common with their parents.

Acquisition of one's first language is a phenomenon of early development (see Chapter 53). The first months and years of a child's life are critical to developing an intact native language. When the process of language acquisition is delayed or fragmented, as can happen with an infant who is D/HH, it can have a significant and permanent effect on overall lifetime cognitive development. Timely identification and support of infants and children who are D/HH, including the provision of early access to language, is critical to the lifetime trajectory of outcomes, including language, pragmatics, academic success, executive functioning, and psychosocial well-being.

DEAF CULTURE

It is important to recognize that we as authors do not speak for Deaf individuals or parents of D/HH children but seek to bring awareness of some fundamental norms as a starting point for increasing familiarity and collaboration with these groups. Readers are encouraged to explore the resources cited in this chapter, as well as information provided by Deaf individuals and parents of D/HH children themselves.

Among individuals in America who are D/HH, there is a subset who self-designate as culturally Deaf (intentionally spelled with an uppercase D) who share American Sign Language (ASL) as their primary means of communication and a set of beliefs and traditions that are transmitted across generations. In the United States, the National Association of the Deaf is the organizational body that supports and represents this cultural Deaf community, with a mission "to preserve, protect and promote the civil, human and linguistic rights of deaf and hard of hearing people in the United States of America."

There is a potential conflict between the "hearing" medical community and the culturally Deaf community, with the medical community traditionally operating from a pathology model (identify and fix the problem) and the Deaf community operating from a sociocultural one (there is no problem in need of fixing). Hearing parents and professionals whose societal existence is grounded in listening and spoken language often view being D/HH as a limitation to interpersonal connection, education, and vocation. Deaf individuals, who achieve virtually all the same milestones as hearing individuals do by using a visual language medium, do not view being D/HH as a loss. Among culturally Deaf individuals, the terms "hearing loss" and "hearing impaired" are often viewed as inaccurate and potentially offensive. For those who were born deaf, the experience of hearing is something they never had and therefore have never missed. It is not something that holds them back, but instead is a source of maintaining a positive self-identity and pride in one's culture and community.

Hearing clinicians caring for deaf infants and children or members of the Deaf community must practice with the cultural humility necessary to appreciate the perspectives of the Deaf community (see Chapter 2).

Table 55.1 Common False Assumption About Deaf or Hard of Hearing (D/HH) Infants and Children

FALSE ASSUMPTION	ALTERNATIVE APPROACH
Being D/HH causes language delay.	Often, the parent and deaf infant do not share a common language, creating a language barrier leading to delays. Early identification (by 1-3 mo of age) and intervention by 6 mo of age are critical for language development.
Passing newborn hearing screening tests means one does not need to be concerned about hearing.	Many factors can cause delayed-onset hearing loss. A full audiologic evaluation is indicated for any caregiver concern about hearing or for delays in language development—a "wait and see" approach is never indicated.
All behavioral symptoms or developmental delays are caused by the hearing loss.	Young neurotypical deaf children with adequate access to language through amplification and spoken language, sign language, or both should not be expected to have challenges in development, behavior, or social engagement. Referral for evaluation is essential if these symptoms are present.
Sign language is a last resort for communication for D/HH infants or children.	American Sign Language (ASL) is a full and complex language with a clear syntax and grammar structure. Learning sign language can promote language development when children cannot access spoken language during a period when this input is critical for cortical brain development.

Including access to Deaf individuals as part of healthcare teams involved in the care of D/HH infants and children is an important first step in including this cultural perspective in health service delivery and decision-making.

It is also important to recognize the concept of **intersectionality** (the interconnected nature of social categorizations such as race, ethnicity, class, and gender), which plays a role in the Deaf community. Being Deaf and Black is not just the sum of the experiences of Deaf individuals and Black individuals—the two constructs existing simultaneously in the same person makes for a unique life experience. Intersectionality is recognized within the context of the **Deaf Plus** community because those individuals do not simply experience life as a Deaf person who also happens to have an additional condition. The interplay of these aspects of individuals is a critical part of identity formation, self-esteem, cultural engagement, potential experiences of disadvantage/discrimination, and personhood in general.

EARLY DETECTION AND LANGUAGE DEVELOPMENT

Deaf children who are born to deaf/signing parents are natively exposed to sign language from the first day of life and subsequently can be expected to acquire sign language milestones in a predictable manner similar to typically developing hearing children acquiring spoken language milestones. Deaf children of signing parents achieve their first signs, vocabulary expansion, combining of two discrete sign concepts, progression to more complex phrases and sentences, and other language-related milestones at expected ages if assessed in sign language. However, more than 90% of deaf infants are born to hearing parents who most often do not sign fluently. This creates an immediate and significant loss of a shared intact language. Families will turn to professionals for advice on making decisions regarding language, education, amplification technology, and social engagement. Sometimes these clinicians make false assumptions that delay detection or intervention for children who are D/HH (Table 55.1).

Clinicians should be aware that although language delay may be a presenting symptom in a D/HH child, being deaf in and of itself does not inherently cause delayed language development. Rather, the inability for a parent and an infant to share a common accessible language creates a barrier to the development of language. This is why early identification and support are critical for D/HH infants to support language access, whether to spoken language through amplification and therapy or access to sign language (or both). Even children who have passed their newborn hearing screening who have language delays must have a full audiologic evaluation, as a substantial number of factors can contribute to delayed-onset hearing loss (DOHL) at any time during early, middle, or late childhood. Parental concern about language delay or responsiveness of their child is a sensitive, but not specific, indicator of possible hearing loss. It is important to respond to parental concerns of hearing or language with referrals for hearing assessment, language evaluation, and age-appropriate therapeutic support systems.

Clinicians should also consider the possibility of hearing loss in young children with other behavioral changes. An older child may report a sudden dramatic hearing loss. However, younger children may not have the linguistic capacity or awareness to describe loss of hearing and may present instead with changes in behavior (being upset, aggressive, withdrawn). Some children with a progressive or sudden change in hearing status may appear to have a behavioral condition such as attention-deficit/hyperactivity disorder (ADHD) or may be described as defiant. Children with unidentified hearing changes and children with ADHD can share behaviors—they are perceived as not paying attention, they often are not aware of what is happening in the moment, they may not respond as expected when being addressed, and they may not focus on the things that are being discussed.

Another problematic issue known as **diagnostic overshadowing** can occur when all developmental or behavioral challenges are attributed to one cause (in this case, hearing status) when the symptoms should suggest the possibility of another disorder. For example young neurotypical D/HH children who have adequate access to language (through amplification technology and spoken language, sign language, or a combination of both) should not automatically be expected to have substantial challenges with language development, behavior, and social engagement. If clinicians reflexively attribute delays in social and language development to the fact that the child is D/HH, they may miss the diagnosis of a developmental disorder when they would not have missed the diagnosis in a hearing child.

Sign language has many benefits for D/HH infants and children and should not be regarded as an inferior last resort only to be used if spoken language efforts are not successful. ASL is a full and complex language. Much of the grammatical structure and concept complexity in ASL is conveyed through spatial placement of signs and body movements. Body movements can include body lean and eyebrow shift to indicate a question, furrowing of the brow and pursing of lips to convey negation, and shifting of body position in space to define multiple individuals involved in conversation, to name a few.

The active discouragement of using visual language with any D/HH child is a developmental disservice, particularly so with the profoundly deaf infant whose hearing level is too low to benefit from traditional hearing aids. For these infants, a cochlear implant is likely the only potential route for accessing spoken language input, and the earliest that the Food and Drug Administration (FDA) currently approves cochlear implantation is 9 months of age. There remains a number of children who are not achieving such early ages of cochlear implantation. Lack of access to sign language can mean up to a year or more of complete lack of accessible linguistic input during a period of cortical development when language input is critical; that lack of language input can in turn affect infant bonding with parents. Even after cochlear implantation, it takes a substantial amount of therapy (auditory-verbal/listening and speech-language therapy) to build spoken language skills.

INTERVENTIONS

Supporting children who are D/HH requires a combination of a proactive approach to care, ongoing monitoring for delays in all developmental domains, and timely recognition and intervention of gaps that can occur because of the impact of hearing status on language and overall development.

There is a tendency, especially for those who are not familiar with D/HH children, to assume that a child who does not hear will have reduced developmental outcomes compared to their hearing peers. There is robust evidence supporting the importance of early identification and intervention for long-term outcomes in children who are D/HH. A child's developmental and learning potential should not be defined by their hearing; clinicians should encourage and support families' high expectations for a child's development regardless of hearing status.

The medical home can fill a critical role in supporting a family's journey, though often primary care providers have relatively few children who are D/HH in their practice and may not be well-versed in how to monitor the medical and psychosocial needs of a D/HH child. This prompts the need to seek out information from a variety of sources and link families with reputable information. Because D/HH is a low-incidence condition, it is challenging for one setting (early intervention–based, school-based, clinical-based) to include a variety of children and match appropriate communication approaches. Interventions can be categorized in a variety of ways. A framework for various communication approaches is commonly used for understanding how to support language development in children who are D/HH (Table 55.2), including technology and environmental modifications.

Communication Approaches

Often different approaches to communication are presented as a choice to make during the early years of critical language growth. Many communication approaches have passionate national organizations advocating for a specific approach (Table 55.3). The educational philosophy known as total communication is often misunderstood to mean using both signing and spoken language; however, it refers to incorporating an array of communication modalities (formal signs and fingerspelling, gestures, body language, lip reading, speaking, listening), with the goal of optimizing language development that is tailored to be most effective for the individual child.

We have chosen to refer to the national organizations and the Centers for Disease Control and Prevention (CDC) to guide definitions of communication approaches (see Table 55.2). Each approach has specific components needed for successful implementation and language outcomes. The overall goal to support communication development can be an unfolding journey. Choices and strategies that worked well for a child in early childhood may not be as effective as the child matures, particularly as social engagement and academic demands evolve with age and advancement in school. Thus it is important for families to recognize that communication needs can change over time, prompting a shift from a prior decision to an alternative approach.

Technology

Hearing Aids

Hearing aid technology is very refined. Hearing aids are essentially minicomputers that take sound from the environment and are programmed to adjust how this sound is processed and delivered to the ear. Hearing aids have a number of different features that can augment the quality of sound a child will hear. Hearing aids can analyze the sounds coming into the device and preferentially reduce background noise. They can compress sound waves to preferentially make soft sounds louder and try to avoid distortion of loud sounds (wide dynamic range compression). Hearing aids can have microphones that can receive sound from many directions or focus primarily on sounds coming from in front of a child. A hearing aid can also carry a variety of programs for different listening settings. This allows a child to have a different program for a quiet environment compared to a noisy environment. Technology can also include Bluetooth to link to other devices. There are a number of apps to help monitor battery life and adjust the program for the setting through the app. Follow-up care with audiology is important to ensure continued supports for any amplification used and to monitor for changes in hearing. For children with conductive hearing changes, **bone conduction aids** may be indicated. These devices bypass the outer and middle ear, conducting sound through the skull directly to the cochlea and auditory nerve. When children are 5 years or older, they can be considered for a surgically implanted bone conduction aid called a *bone-anchored hearing aid* (BAHA). These devices also have the capacity to link to a frequency modulation (FM) system.

It is helpful to remember that even with advancements in technology, what children hear with hearing aids is not the same as what people hear with a typically functioning auditory system. It is equally important to consider environmental supports to optimize

Table 55.2 Communication Approaches for Children Who Are Deaf and Hard of Hearing (D/HH)

COMMUNICATION MODALITY	DESCRIPTION	CITATION/ORGANIZATION
American Sign Language (ASL)	ASL is the recognized sign language of the deaf community in the United States. ASL conforms to linguistic principles and is distinct from English.	National Association of the Deaf (https://www.nad.org/about-us/position-statements/position-statement-on-american-sign-language)
Conceptually Accurate Signed English (CASE)	Using conventional ASL signs in an English word order.	https://www.cdc.gov/ncbddd/hearingloss/parentsguide/building/case.html
Manually coded English	Signing Exact English is an example of a manually coded English. It is a sign system that matches signs with the English language and includes manual representation of all components of the English language.	www.signingexactenglish.com
Fingerspelling/Rochester method	The Rochester method was intended to support English literacy and uses fingerspelling for all words.	
Cued Speech	Cued Speech is a visual communication system that uses eight handshapes in four different placements near the face in combination with the mouth movements of speech to make the sounds of spoken language look different from each other.	National Cued Speech Association (https://www.mdaap.org/pdf/CuedSpeech.pdf)
Spoken language and listening	Children learn to listen and talk with the support of hearing technology such as hearing aids, assistive listening devices (such as an FM system), or cochlear implants. Auditory-oral approaches include gestures, listening, speech/lip reading, and spoken speech. Auditory-verbal relies on listening and spoken speech.	Communication Options (https://www.agbell.org/Families/Communication-Options) Centers for Disease Control and Prevention: How People with Hearing Loss Learn Language (https://www.cdc.gov/ncbddd/hearingloss/language.html)

Table 55.3 Resources for Families and Professionals

NATIONAL ORGANIZATIONS: FAMILY SUPPORT	
Hand and Voices (www.handsandvoices.org)	Supports families and children without a platform providing a specific mode of communication.
National Association for the Deaf	Advocates for use of American Sign Language and represents the culturally Deaf community.
Alexander Graham Bell Association for the Deaf and Hard of Hearing (www.agbell.org)	Advocates for people who are D/HH to hear and use spoken language.
Beginnings (www.ncbegin.org)	Promotes language accessibility through cued speech (see Table 55.2).
American Society for Deaf Children (www.deafchildren.org)	
DEAF HISTORY AND CULTURE	
The National Association of the Deaf	https://www.nad.org/about-us/
Deaf Heritage: A Narrative History of Deaf America	This 1981 book by Jack Gannon, a Deaf author and historian, is often referred to as a canon of Deaf culture in the United States. The book covers a number of events throughout history, including the establishment of schools for the deaf and the inception of the National Association of the Deaf and explores topics such as American Sign Language, Deaf artists, Deaf sports, and seminal Deaf publications.
Through Deaf Eyes	A 2007 documentary covering close to 200 years of being Deaf in the United States in a 2-hour run time through a diversity of interviews, movie shorts, and stories that capture the events that have affected Deaf lives throughout American history (https://www.youtube.com/watch?v=PL5d8kyZUQk).
DEAF MENTORS	
The National Center for Hearing Assessment and Management	Houses a directory of D/HH adult involvement programs by state (https://www.infanthearing.org/dhhadultinvolvement/states/index.html)
SKI HI Deaf Mentor Program	Curriculum for infants and young children who are D/HH (http://www.deaf-mentor.skihi.org)
Hand and Voices Deaf and HH Mentor/Guide/Role Model Programs	https://handsandvoices.org/fl3/topics/dhh-involvement/programs.html
American Society for Deaf Children: Deaf ASL Ambassadors Program	https://deafchildren.org/knowledge-center/asl-resources/sign-on/
PRACTICE GUIDELINES	
American Academy of Pediatrics Early Hearing Detection and Intervention Program	https://www.aap.org/en/patient-care-pages-in-progress/early-hearing-detection-and-intervention/
EHDI National Technical Resource Center	https://www.infanthearing.org
The Joint Committee on Infant Hearing	www.jcih.org

listening environments. Contralateral routing of signal aids (CROS) can be helpful for children with unilateral profound deafness. This amplification system uses a transmitter at the ear that does not hear and routes it to a receiver on the typically hearing ear. Assisted listening devices such as FM systems are used to help address problems hearing in background noise and when speakers are farther away. This system has a small transmitter with a microphone. The speaker wears the transmitter, and this then links directly into headphones or a personal amplification system (hearing aid or cochlear implant). FM systems are traditionally used in the classroom setting, although they may be employed in other settings that tend to have competing background noise such as restaurants or when the focus on a particular individual speaking is important. The teacher may also use a transmitter with microphone that links to a number of speakers around the room (**soundfield system**). In this way, the accommodation is available to all students in the classroom, may benefit children easily distracted by background noise as well as the D/HH student, and does not single out the D/HH child alone.

Cochlear Implants

Cochlear implants are surgically implanted devices that bring direct electrical stimulation to the cochlea. These devices are FDA-approved for children 9 months and older with profound sensorineural hearing loss and in lesser degrees of hearing changes (70 dB or more) when children are not receiving adequate benefit from traditional amplification. A period of hearing aid trial is recommended before implantation. In children with hearing loss caused by meningitis, it is important to monitor for bony changes in the cochlea via imaging. Early signs of ossification would prompt earlier cochlear implantation to ensure the electrodes are in an optimal position to stimulate the auditory nerve. Even for children who are bilaterally profoundly deaf, there can be reasons that a cochlear implant is not appropriate. For example, absence of an auditory nerve would preclude pursuing an implant.

Often pediatric cochlear implant centers use a multidisciplinary approach to determining cochlear implant candidacy and to ensure strong follow-up support. In the past, children with developmental disabilities were deemed not appropriate for cochlear implantation, as results were thought to be limited. Although outcomes can vary in this group of children, a developmental disability alone does not preclude receiving benefit from the device. Ensuring global developmental supports, addressing potential expectations and outcomes, and linking children and families to resources can help children gain benefit from access to sound.

Coordination of care and follow-up is essential in all children with cochlear implants. They initially will see audiologists at frequent intervals to program the implant, and speech therapy is a critical and ongoing component of fostering success with an implant. At the age of 2 years, they should receive the 23-valent pneumococcal vaccine to ameliorate the increased risk of meningitis. The

medical home can play an important role in managing this additional immunization, as well as in monitoring medical issues and developmental progress.

Early implantation has been associated with better hearing, speech perception, and spoken language outcomes, as it ensures early stimulation of the auditory cortex necessary for the development of spoken language. Although FDA approval is for children 9 months and older, there are situations where earlier implantation is indicated, and many in the field of pediatric audiology and pediatric otology are advocating for earlier implantation. Unilateral deafness is another emerging indication for cochlear implantation in children.

Other Supports and Factors Influencing Amplification Decisions

The cost of amplification devices can be quite high. Many insurance plans do not cover hearing aids, though more cover costs associated with BAHAs and cochlear implants. Services and coverages vary by state and insurance plan. Families often need to obtain insurance or additional coverage to cover replacement costs associated with damage or loss of the device. Technology updates can also add further expenses.

There are also many day-to-day factors that affect a child's acceptance of amplification. In early childhood there is rapid growth of the skull and ear canal. With hearing aids, children often need to return to audiology frequently to resize the ear molds to ensure a good fit. Children also can become very adept at removing their hearing aids. Young children in daycare are particularly vulnerable to potentially losing their amplification when rolling, crawling, or playing or when naturally curious peers and playmates attempt to take them. Parents, caregivers, and teachers routinely checking on hearing aids/cochlear implants is a critical support to using amplification technology successfully in young children.

A number of environmental supports can be helpful. For families seeking a spoken language approach, it is helpful to decrease background sounds. Turning off TVs and devices can help children be able to listen and hear what is said. Children often struggle hearing speakers from a distance. This affects incidental learning, as they have fewer opportunities to "overhear" peripheral conversations. Families are often coached in ways to optimize their child's listening environment and ways to highlight spoken language and concepts.

Technologic support can include captioning on the television, video-relay with sign language interpreters, texting, speech-to-text, visual fire alarms, and vibrating alarms. These types of technologies are often not covered through insurance, although some state agencies have programs to help defray costs. Other accommodations for communication access can include sign language interpreters, cued speech interpreters, and open captioning. The Americans with Disabilities Act ensures children, adolescents, and adults have the legal right to communication access. This is particularly important in medical settings. Family members should not be asked to serve as interpreters for the child, as this limits the ability for the parent to listen and be part of the conversation or may limit the child's access to the conversation at hand.

LANGUAGE LEARNING

Language is a critical component of the human condition and allows connection with others. The United Nations has recognized communication as a human right. Communication happens in many ways that can include behavior, nonverbal communication, tone, facial expressions, words, and sentences. These aspects of communication are universal irrespective of mode of communication.

Promoting language development needs to focus on far more than the ear and hearing. As in typical children, the quality and quantity of communication are important (see Chapter 53). Additionally, children who are D/HH are at high risk of missing learning via "the unwritten curriculum": social and cultural learning that occurs incidentally and passively. Hearing children repeatedly overhear conversations that do not directly include them but are related to them, such as when their parents talk to the pediatrician about their care or how the parents interface with office staff when they schedule the next appointment. D/HH children are vulnerable to missing years, if not decades, of incidental learning regarding everyday interactions. Direct teaching of incidental information, or making the implicit explicit, is a tenet of supporting the language development of children and youth who are D/HH. In the medical setting, this can be addressed for the signing D/HH child by having a sign language interpreter present to ensure the child can build an understanding of their own health history and expand health literacy, even if they may be too young to engage in the conversation directly. Although it may feel more comfortable and efficient to get information directly from parents, it is critical for the provider to engage the child directly as much as possible to maximize their involvement in their own plan of care. Addressing incidental learning for children who are D/HH should occur regardless of mode of communication.

As families hold an important role in their child's language development, building and empowering families in the development of skills and strategies is an important component of early intervention. Within the field of early intervention, coaching parents on how to engage and interact with their child to promote optimal development has been noted to be effective for a number of populations of children. Communication is interactional, and coaching puts the family in the position of providing the intervention and thus builds skills to support their child.

When a Child Is Not Progressing

If a child's language development is not progressing, it is necessary to reevaluate factors that could contribute to language development. Factors to consider include problems with devices that have not been fully optimized, aspects of access to language, and coexisting medical, developmental, or behavioral conditions impacting learning.

In evaluating a child's access to language, consider how the child is learning, the language environment, and whether a child is getting a quality language model for learning. If a communication modality is pursued that cannot be supported across the environments the child is in (e.g., school, home, community-based organizations), the D/HH child can lag behind their peers. Overt problematic scenarios include a deaf child without good acoustic access attempting to learn spoken language or a child learning sign language but with limited sign language proficiency in their home, community, and school environments. Regression of language should prompt reevaluation of hearing and consideration of brain-centered as opposed to hearing-centered problems with learning.

A child's response to a communication approach may be affected by broader developmental issues. A child may have a unique learning profile and benefit from alternative approaches to language-based learning. Whereas children who are D/HH often have strong visual problem-solving skills, some children who are D/HH are stronger in the auditory domain. Although it should not be automatically assumed that a D/HH child will have developmental delay, up to 40% also have a developmental disability or condition that can affect progress. Early recognition of a child's broader needs can help ensure children receive effective interventions for all of their needs.

ACADEMIC CONSIDERATIONS

The Individuals with Disabilities Education Act (IDEA) ensures a free, appropriate public education for all students with disabilities, including those who are D/HH. This law recognizes the right to be educated within the least restrictive environment (LRE), or to the maximum extent that is appropriate, education with their peers who do not have disabilities. This must be balanced with the individual student's communication, linguistic, academic, social, emotional, and cultural needs. Because of the varied settings and range of communication support needs, as well as the diversity of individual student strengths, endorsing one specific educational setting is not possible or appropriate.

Reading and literacy skills are associated with language fluency levels and tend to be improved by early age of identification and intervention. Standardized achievement testing from the early

2000s demonstrated that only half of D/HH high school graduates were reading above a fourth-grade level. However, these data are old and do not control for varying factors across students such as coexisting medical or developmental conditions, delays in identification and early language access, and varying teaching methodologies. Academic outcomes are likely to be optimized with early identification and support of language in infants who are D/HH and with the prompt recognition of, and support for, other developmental or behavioral challenges that may interfere with learning.

PSYCHOSOCIAL WELL-BEING

An important consideration for any individual is psychosocial well-being. Because the population of D/HH individuals is heterogenous, it is difficult to make overarching statements regarding mental health and wellness. Hearing loss in the elderly has been associated with depression. This is due—at least in part—to the loss of connection and communication with others. Similar effects can be seen across the life span for deaf individuals who did not develop enough formal language to communicate effectively. Studies have linked a lack of language proficiency with in-patient psychiatric care in adults and psychosocial difficulties in children. A large-scale study in Taiwan spanning over a decade estimated an 11.1% lifetime prevalence of clinically diagnosed unspecified anxiety disorder in the D/HH group, which was twice the incidence in the hearing control group.

A phenomenon described by some D/HH individuals, **deaf anxiety**, is related to interpersonal challenges a D/HH individual can experience when interfacing with a largely hearing society. Although advances in technology with hearing aids and cochlear implants continue to improve access to audiologic input, it is important to consider that these are tools with inherent limitations—they are not an equivalent "replacement" for natural hearing. D/HH adults have described fears such as missing/misunderstanding information, concern with appearing not to be interested in or not paying attention to someone speaking, disproportionately increased difficulty when dealing with noisy environments, and worry about missing significant information in nonaccessible environments such as being unaware that a fire alarm has gone off if there is no visual indicator in addition to the sound alarm.

The experiences of a deaf person in a predominantly hearing world contribute to the critical journey of identity formation for D/HH children as they become young adults. Deaf children, regardless of their success with technology, are still deaf. When a child takes off their hearing aids or cochlear implants to take a bath, swim, or rest, they are deaf. The technology does not change who they are fundamentally. Supporting families in their efforts to understand, accept, and value their child as a deaf individual can provide resilience for identity formation in adolescence. There also needs to be recognition that families are necessarily thrust into a position of making decisions for their young D/HH child with the knowledge they have at the time and may have concerns about how their child as an emerging adult may feel later on about those decisions. Families can benefit tremendously from access to programs that can connect them with other deaf children, deaf adults, and community resources that support a variety of ways to exist as a successful deaf individual.

DEAF PLUS

It is helpful to recognize that some of the risks associated with being D/HH are also risks for other conditions that impact functioning in children who are D/HH (Table 55.4). It is important to look beyond hearing status as the reason for delays so as not to miss other factors contributing to a child's slow rate of progress. Delayed recognition of these factors causes delays in accessing effective intervention strategies. Conversely, the presence of specific coexisting conditions should not be assumed to predict functioning or decisions about communication. A child who is deaf and also has cerebral palsy should not be assumed to be unable to use sign language because of impact on hand/arm movements, as these children may use sign language receptively for language understanding quite well. The need for individually tailored care and education plans is particularly critical in children who are Deaf Plus.

Table 55.4 Rates and Types of Disabilities Among Children Who Are D/HH and Within the General Population

TYPE OF DISABILITY	D/HH (%)	GENERAL POPULATION (%)
No developmental disability	60	83
Cognitive/intellectual disability	8.3	1
Cerebral palsy	8	0.3
Blindness and vision impairment	5.5	0.3
Attention-deficit/hyperactivity disorder	5.4	9
Specific learning disability	8	7
Autism spectrum disorders	7	1.7

Children who are D/HH have vision changes at nearly twice the rates compared to the general population. Vision differences are important to detect, as children who are D/HH often rely on their vision for accessing information. Even among children who receive effective amplification and good acoustic access to information, some reliance on lip reading and visual attention to the speaker can enhance a child's ability to process information. There are no specific standards regarding the timing and frequency of ophthalmologic evaluations and monitoring intervals, but it is important for all children who are D/HH to have regular monitoring of vision and eye health with a pediatric eye care specialist.

For children who have both hearing and vision changes (**DeafBlind**), intervention strategies can be increasingly complex. IDEA specifically defines DeafBlindness as "concomitant hearing and visual impairments, the combination of which causes such severe communication and other developmental and educational needs that they cannot be accommodated in special education programs solely for children with deafness or children with blindness." When the two conditions are present simultaneously, there are additional challenges to be considered regarding language access and acquisition. Each state has a federally funded DeafBlind project that provides resources and technical assistance to support children identified as DeafBlind. For children who are DeafBlind, many are advocating for interveners. Interveners are more than interpreters: they facilitate communication and inclusion and address social and emotional needs within educational settings.

FAMILY JOURNEY

Each family has a unique narrative to their overall family experience, as well as a specific pathway to supporting the growth and development of their D/HH child. Some families experience profound grief around the loss of an expected parenting story. Many families speak of being overwhelmed initially by an immense amount of information and pressured to make crucial decisions in a timely manner. Others move into an advocacy model and have their own unique take on the parenting journey. One

Table 55.5 Approaches in the Medical Home to Support the Family Journey

FAMILY JOURNEY THEMES	CONSIDERATIONS AND STRATEGIES
Family-centered decision-making: Ensure families are central in decision-making	Before the visit: • Physician reflection on their own knowledge, expertise, and biases At the visit: • Listen to family concerns actively and address concerns, referring to others when outside provider expertise is necessary
Families' need for **informed** choice	Before the visit: • Recognize that each family and child are unique and decisions may vary across families • Recognize that decisions may change over the life span of the child • Recognize the passion across communication modalities, which drive potential biases in information and guidance At the visit: • Listen actively to understand the family's values and intended goals and outcomes • Collaboratively seek information from a variety of reputable sources and discuss potential biases across various "experts" in the field (see resource list) • Incorporate the family's values in an action plan together • Refer to experts as appropriate
Family-to-family support: Because having a child who is D/HH can feel isolating and professionals do not carry the same day-to-day experiences, family-to-family connection is an important component of support	Before the visit: • Recognize the importance of family-to-family support • Identify resources to link families with other families (see resources) During the visit: • Discuss the possible isolation families face • Determine interest and readiness for family networking • Share resources that they can rely on when ready to reach out
Access to D/HH adults: To support the family's recognition of what success can be and to provide children with a conceptual framework for D/HH individuals as adults	Before the visit: • Recognize families may be experiencing grief over the loss of their child's expected future and that experiences with other individuals who are D/HH may be limited or nonexistent • Identify resources to link families with Deaf adults and Deaf mentoring programs (see Table 55.3) During the visit: • Discuss family's hopes and fears • Highlight the importance of high expectations for their child • Discuss ways to promote identity, connection, and independence for their child
Child interactions and supports	Before the visit: • Recognize the variability and uniqueness of children who are D/HH in terms of capabilities, skills, and opportunities At the visit: • Engage D/HH children directly rather than rely solely on family members for interpreting communication; for children who use sign language, access to an interpreter is a right under the Americans with Disabilities Act • Recognize children's strengths and resilience • Ensure children have access to their own health information (at their developmental level) and have the opportunity for inclusion in decisions as appropriate • Advocate with children and families to have high expectations for skills, recognizing that often medical and educational settings use a deficit model (the child must be behind) to access supports

simply has to take a look at some of the family stories that are available in the public realm to appreciate the diversity of the family experience in raising a D/HH child.

A number of parent support organizations are available to families, some of which are organized around specific communication philosophies (see Table 55.3).

The pediatrician may be the first medical professional that families turn to if there is concern about language development and/or hearing. Although these physician/family relationships are often just as diverse as the families themselves, some universal concepts start to emerge when listening to parent stories (Table 55.5). Recognizing these themes and identifying ways to partner and support families is a critical role of the medical home.

ACKNOWLEDGMENTS

The authors extend their gratitude to Chris Moreland, MD, and Robert Nutt, MD, for their input from the deaf adult/deaf professional perspective, and to Lauren Tyra, PhD, for her input from the perspective of a parent of a deaf child.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 56

Developmental Delay and Intellectual Disability

Meghan E. O'Neill and Bruce K. Shapiro

Intellectual disability (ID) refers to a heterogeneous group of disorders that have in common deficits of adaptive and intellectual function and an age of onset before maturity is reached. In Europe, the term *learning disability* is often used to describe ID.

DEFINITION

Contemporary conceptualizations of ID emphasize adaptive functioning and social interaction rather than test scores in isolation. The definition of ID requires significant impairment in general intellectual function (reasoning, memory, learning, problem solving) and adaptive behavior, with severity defined by limitations in adaptive functioning or levels of needed support. This focus encourages the development of individual treatment plans characterizing the supports needed to enhance functioning. Consistent across these definitions is onset of symptoms before adulthood (18-22 years of age). Children with ID have a nonprogressive disorder; loss of developmental milestones or progressive symptoms with a downward developmental trajectory suggest another disorder.

Significant impairment in adaptive behavior reflects the degree to which cognitive dysfunction directly contributes to impairments in daily functioning at home, at school and work, and in the community. **Adaptive behavior** refers to the skills required for people to function in their everyday lives, and individuals with deficits require more support than same-age peers for optimal participation. The American Association on Intellectual and Developmental Disabilities (AAIDD) and *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) classifications of adaptive behavior address three broad sets of skills: conceptual, social, and practical. **Conceptual skills** include language, reading, writing, time, number concepts, and self-direction. **Social skills** include interpersonal skills, personal and social responsibility, self-esteem, gullibility, naiveté, and ability to follow rules, obey laws, and avoid victimization. Representative **practical skills** involve performance of activities of daily living (dressing, feeding, toileting/bathing, mobility), instrumental activities of daily living (e.g., housework, managing money, taking medication, shopping, preparing meals, using phone and mail systems), occupational skills, and maintenance of a safe environment. For a deficit in adaptive behavior to be present, a significant delay in at least one of the three skill areas must be present. The rationale for requiring only one area is the empirically derived finding that people with ID can have varying patterns of ability and may not have deficits in all three areas.

The requirement for adaptive behavior deficits is the most controversial aspect of the diagnostic formulation. The controversy centers on two broad areas: whether impairments in adaptive behavior are necessary for the construct of ID and what to measure. The adaptive behavior criterion may be irrelevant for many children; adaptive behavior is impaired in virtually all children who have IQ scores <50. The major utility of the adaptive behavior criterion is to confirm ID in children with IQ scores in the 60-75 range, especially considering the historical overdiagnosis of ID among individuals of color with typical adaptive functioning and biased IQ testing results. It should be noted that deficits in adaptive behavior are often found in disorders such as autism spectrum disorder (ASD; see Chapter 58) and attention-deficit/hyperactivity disorder (ADHD; see Chapter 50) in the presence of typical intellectual function, often mediated by significant difficulties with executive functioning, self-directedness, or maladaptive behaviors. In contrast, deficits of adaptive functioning in ID are primarily attributable to the individual's overall cognitive limitations.

The issues of measurement are important as well. The independence of the three domains of adaptive behavior has not been validated. The relationship between adaptive behavior and IQ performance is insufficiently explored. Many adults with IQ scores in the 60-75 range do not have significant impairments in practical skills. Adaptive behavior deficits also must be distinguished from *maladaptive behavior* (e.g., aggression, self-injury, inappropriate sexual behavior).

Significant impairment in general intellectual function refers to performance on an individually administered test of intelligence that is approximately 2 standard deviations (SDs) below the mean. Generally, these tests provide a standard score that has a mean of 100 and SD of 15 points, so that IQ scores <70 would meet these criteria. If the standard error of measurement is considered, the upper limits of significantly impaired intellectual function may extend to an IQ of 75. Using a score of 75 to delineate ID might double the number of children with this diagnosis, but the requirement for impairment of adaptive skills limits the false positives. Children with ID often show a variable pattern of strengths and weaknesses. Not all their subtest scores on IQ tests fall into the significantly impaired range.

Onset before age 22 years or adulthood distinguishes dysfunctions that originate during the developmental period from those that begin in adulthood. The diagnosis of ID may be made after 22 years of age, but the cognitive and adaptive dysfunction must have been manifested before age 22 years. Age of onset may be relevant to qualification for certain benefits programs that require a diagnosis of ID.

Intellectual disability as nonprogressive. Individuals with ID will acquire new developmental milestones over time, although at a slower rate than unaffected children. A slowing trajectory is not uncommon as individuals with ID get older. This should be distinguished from *regression* of milestones, which involves true loss of previously acquired skills and demands additional and often more extensive etiologic workup. Sometimes regression is seen in the context of the child's larger medical picture, such as loss of mobility with increasing spasticity and contractures in children with comorbid cerebral palsy (CP) or loss of language skills in the setting of new seizures. Alternatively, regression could suggest a **progressive encephalopathy** caused by an *inborn error of metabolism* or a *neurodegenerative disorder* (see Chapters 104 and 639). Prompt identification is essential, as some of these conditions are treatable or modifiable and some necessitate conversations about future reproductive risk.

Global developmental delay (GDD) is a term often used to describe young children with delays across multiple domains of development that have not yet resulted in a diagnosis of ID. In DSM-5, GDD is a diagnosis given to children <5 years of age who display significant delay (>2 SDs) in acquiring early childhood developmental milestones in two or more domains of development. These domains include receptive and expressive language; gross and fine motor function; cognition, social and personal development; and activities of daily living. Typically, it is assumed that delay in two domains will be associated with delay across all domains evaluated, including cognitive and intellectual abilities. Longitudinal studies following outcomes of children with GDD are sparse but suggest that that upwards of 80% of children with early global delays continue to experience development challenges through the school-age years. However, not all children who meet criteria for a GDD diagnosis at a young age go on to meet criteria for ID later in childhood. Reasons for the lack of concordance between GDD and later diagnosis of ID include lower reliability and predictive validity of developmental testing in children under 5-6 years of age; a positive change in developmental trajectory with maturation or possibly with intervention; reclassification to a different disability category (autism, ADHD, developmental coordination disorder); or imprecise use of the GDD diagnosis initially. Conversely, in patients with more severe early delays, the GDD term is often used beyond the point when the child could be reclassified as having ID, such as when a child has persistently and markedly low developmental quotients on multiple assessments and despite intervention during the first few years of life.

It is important to distinguish the medical diagnosis of GDD from the federal disability classification of "developmental delay" that may be used by education agencies under the Individuals with Disabilities Education Act (IDEA). This classification requires that a child have delays in only one domain of development with subsequent need for special education. Each state determines its own precise definition and terms of eligibility under the broader definition outlined by IDEA, and many states use the label for children up to 9 years of age.

Table 56. 1 Genetic Testing Guidelines for ID/GDD and/or ASD

ORGANIZATION	RECOMMENDATION(S) FOR GENETIC TESTING

Autism and Intellectual Disability Committee of the American Academy of Child and Adolescent Psychiatry (AACAP)	• CMA in all individuals with ID/GDD and/or ASD
	• FMR1 repeat analysis in males and females with ID or a family history of ID
	• Depending on history and physical examination, consider:
	  • PTEN testing if head circumference (HCM) is more than 2.5 SD above the mean for age in a child with ID/GDD and/or ASD
	  • MECP2 testing for Rett syndrome in females with severe ID
	  • Karyotype if a chromosomal syndrome is suspected
	• If other investigations do not provide an etiology and there are unresolved clinical findings, consider ES and mitochondrial DNA testing

American Academy of Pediatrics (AAP)	• If a comprehensive history and exam are indicative of a specific syndrome or disorder, proceed with specific testing in patients with ASD and/or ID/GDD • In all individuals with ASD and ID/GDD without specific findings, consider CMA and FMR1 CGG repeat analysis • In females with ASD and/or ID/GDD without specific findings, consider MECP2 testing • In males with ID/GDD without specific findings, consider an X-linked ID panel (XLID) • If an etiology is not identified, consider a referral to genetics for additional workup, including possible ES
International Standard Cytogenomic Array (ISCA) Consortium	• CMA is the first-tier genetic test in patients with GDD/ID, ASD, and/or multiple congenital anomalies

American College of Medical Genetics (ACMG)	• After a detailed family history and physical examination, proceed with specific testing for patients with ASD if a syndrome is suspected or if features are suggestive of a mitochondrial or metabolic condition
	• If family history and physical exam are not suggestive of a specific diagnosis, metabolic, or mitochondrial condition, proceed with CMA for all patients with ASD and FMR1 repeat analysis for all males with ASD
	• If CMA (in males and females) and FMR1 repeat analysis (in males) are not diagnostic, consider:
	  • MECP2 sequencing in all females with ASD
	  • MECP2 duplication testing in males with ASD if phenotype is suggestive
	  • PTEN testing in patients with ASD if HCM is more than 2.5 SD above the mean for age
	  • FMR1 repeat analysis in females with ASD and additional features suggestive of fragile X (e.g., family history and phenotype)

American College of Medical Genetics (ACMG)	• CMA is the first-tier genetic test in patients with multiple congenital anomalies that are not indicative of a specific genetic syndrome and those with nonsyndromic ID/GDD and ASD
Multidisciplinary Expert Consensus Panel	• ES in all individuals with ID and/or ASD • If ES is nondiagnostic and does not include copy number variant analysis, proceed with CMA • If ES (and CMA if needed) is nondiagnostic, reanalysis of data from testing should be undertaken periodically
American Academy of Neurology (AAN) and Child Neurology Society (CNS)	• High-resolution karyotype and FMR1 repeat analysis for patients with ASD that also have ID, family history of fragile X and/or ID, or dysmorphic features • After obtaining a detailed medical, developmental, and family history for patients with ID/GDD, if a specific etiology is considered, perform appropriate testing such as single gene testing, metabolic testing, or XLID panel • If a specific etiology is not suspected, perform CMA (or, if not possible, karyotype and subtelomeric FISH) for all individuals with ID/GDD, MECP2 testing for females with moderate to severe ID/GDD, and FMR1 repeat analysis in all individuals with mild ID/GDD • If these and other etiologic workups are negative, consider a referral to genetics

From Savatt JM, Myers SM. Genetic testing in neurodevelopmental disorders. *Front Pediatr*. 2021;9:526779, Table 3.

ETIOLOGY

Numerous identified causes of ID may occur prenatally, during delivery, postnatally, or later in childhood. These include infection, trauma, prematurity, hypoxia-ischemia, toxic exposures, metabolic dysfunction, endocrine abnormalities, malnutrition, and genetic abnormalities. Most people with ID will not have a readily identifiable underlying diagnosis based on prenatal or perinatal history or dysmorphology, meriting further medical and genetic evaluation. Practice guidelines recommend that an etiologic workup be pursued in all children with ID or GDD when there is not a readily apparent explanation for the child's presentation (Tables 56.1 and 56.2). It is anticipated that these diagnostic guidelines change because genome sequencing studies have identified severe monogenic etiologies in previously difficult to diagnose developmental disorders despite extensive previous recommended evaluations.

Among children with milder GDD, yield of etiologic workup will likely be lower in comparison to children with more significant delays or disability. With increases in etiologic testing among all children with ID and advancement of technologic capabilities of testing, the number of identified biologic and genetic causes of ID is continuing to increase rapidly. There are slightly over 100 disorders (all of which are metabolic in nature) for which treatment may ameliorate the core symptoms of ID (see https://www.treatable-id.org/), but these conditions account for a relatively small percentage of children with ID (Table 56.3). However, there are several reasons beyond disease modification that should prompt providers to seek etiologic answers in patients with ID. These include insight into possible associated medical or behavioral comorbidities; information on prognosis and life expectancy; estimation of recurrence risk for family planning counseling, potential validation, and closure for the family; increased access to services or specific supports; and better understanding of underlying pathology with the hope for new treatment options. When surveyed, families of children with ID with no identified underlying etiology almost universally report that they would want to know of an etiologic diagnosis if given the choice. Expanded testing will contribute to the growing pathophysiologic understanding of how ID occurs mechanistically and serves as an opportunity for future targeted treatment opportunities and clinical trial development.

Mild and more severe forms of ID have different but overlapping risk factors and etiologies. Nongenetic risk factors that are often associated with mild ID include low socioeconomic status, low maternal education levels, residence in a developing country, malnutrition, and poor access to healthcare. The most common biologic causes of, or risk factors for, mild ID include intrauterine growth restriction; prematurity; perinatal insults; intrauterine exposure to drugs of abuse (including alcohol); postnatal exposure to neurotoxic substances (including lead); some sex chromosomal abnormalities; and some genetic syndromes with multiple, major, or minor congenital anomalies (e.g., 22q11 deletion syndrome, sex chromosomal abnormalities, Noonan syndrome). Familial clustering is common.

Table 56.2 Genetic Tests Commonly Used in Evaluation of Neurodevelopmental Disorders

TEST	RESULTS/VARIANTS DETECTED	DETECTION LIMITATIONS
Chromosomal microarray (CMA)	• Copy number variants (CNV) (generally >250 kb but could be smaller if region is specifically targeted) • Regions of homozygosity*	• Repetitive DNA sequences, including trinucleotide repeat expansions (e.g., *FMR1* repeat expansion) • Balanced chromosomal rearrangements • Sequence-level variants in the exome/genome • Mitochondrial variants • Epigenetics alterations (e.g., methylation abnormalities, uniparental heterodisomy) • Low-level mosaicism
Exome sequencing (ES)	• Sequence-level variants in the coding region (exome) • Copy number variants**	• Repetitive DNA sequences, including trinucleotide repeat expansions (e.g., *FMR1* repeat expansion) • Balanced chromosomal rearrangements • Smaller copy number variants, including deletions/duplications involving one to two exons • Mitochondrial variants • Epigenetics alterations (e.g., methylation abnormalities) • Intronic/noncoding variants • Variants in regions of the exome that are not well-covered by sequencing
FMR1 CGG repeat testing	• CGG repeat number in the *FMR1* gene	• Sequence-level variants in *FMR1* or elsewhere in the exome/genome • Copy number variants • Balanced chromosomal rearrangements • Exon-level deletions/duplications • Mitochondrial variants • Epigenetics alterations (e.g., methylation abnormalities)

*Single-nucleotide polymorphism–based chromosomal microarray (SNP-CMA)
**Several laboratories are now calling CNVs as a routine part of ES, and this trend will continue to expand.
From Savatt JM, Myers SM. Genetic testing in neurodevelopmental disorders. *Front Pediatr*. 2021;9:526779, Table 2.

Table 56.3 Conditions in Which Early Treatment May Significantly Improve the Course of the Disease

CONDITION	TREATMENT
Galactosemia	Lactose-free diet
Fructosemia	Fructose-free diet
Phenylketonuria	Phenylalanine-free diet
Maternal phenylketonuria	Phenylalanine-free diet during pregnancy
Maple syrup urine disease	Diet restricted in branched-chain amino acids + dialysis or exchange transfusion
Hypoglycemia from any cause	Prevent hypoglycemia and/or provide glucose
Lead intoxication	Separate child from source of lead; chelation therapy
Hypothyroidism	Thyroid replacement
Recurrent otitis media	Antibiotic prophylaxis, pressure-equalizing tubes
Malnutrition	Adequate nutrition
Increased intracranial pressure (e.g., hydrocephalus, neoplasm)	Shunt ventricles or cystic structure
Congenital HIV infection	Prenatal/postnatal treatment with AZT (zidovudine)
Congenital toxoplasmosis	Prenatal treatment with spiramycin, pyrimethamine, and sulfonamide
Dopa-responsive dystonia	Responds to levodopa; may be misdiagnosed as cerebral palsy
Biotinidase deficiency	Oral biotin
Biotin-thiamine–responsive basal ganglia disease	Biotin, thiamine
Wilson disease	Copper chelation; liver transplant
Cerebral folate disorder	Folinic acid

CONDITION	TREATMENT
Creatine disorders	Creatine monohydrate
Vitamin B_{12} deficiency	Vitamin B_{12}
Cerebral glucose transporter defect	Ketogenic diet
Metachromatic leukodystrophy	BMT
Niemann-Pick disease	BMT, liver transplantation, implanted amniotic epithelial cells
Adrenoleukodystrophy	BMT
Glycogen storage disease type IV	Liver transplantation
Menkes disease	Parenteral copper histidinate
Lesch-Nyhan syndrome	Allopurinol + BMT
Krabbe disease	BMT
α-Mannosidosis	ERT: velmanase alfa
Aspartylglucosaminuria	BMT
Gaucher disease type III	ERT: Ceredase; SRT: Cerdelga; PCT: Mucosolvan
Hunter syndrome (MPS II)	ERT: Elaprase
Hurler syndrome (MPS I)	ERT: Aldurazyme
Sanfilippo syndrome A (MPS IIIa)	SRT: Genistein
Sanfilippo syndrome B (MPS IIIb)	SRT: Genistein
Sanfilippo syndrome C (MPS IIIc)	SRT: Genistein
Sanfilippo syndrome D (MPS IIId)	SRT: Genistein
Sly syndrome (MPS VII)	ERT: Mepsevii
Neuronal ceroid lipofuscinosis type II	ERT: Brineura

BMT, Bone marrow transplant; ERT, enzyme replacement therapy; MPS, mucopolysaccharidosis; PCT, pharmacologic chaperone therapy; SRT, substrate reduction therapy.
From Muriello M. Neurocognitive and developmental regression. In: Kliegman RM, Toth H, Bordini BJ, Basel D (eds). *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 28.10, p. 481.

Table 56.4 Identification of Causes in Children with Significant Intellectual Disability

CAUSE	EXAMPLES	% OF TOTAL
Chromosomal disorder	Trisomies 21, 18, 13 Deletions 1p36, 4p, 5p, 11p, 12q, 17p, others Microdeletions Klinefelter, 47,XXX, and Turner syndromes	~20
Genetic syndrome	Fragile X, Prader-Willi, Angelman, and Rett syndromes	~20
Nonsyndromic autosomal mutations	Variations in copy number; de novo mutations in *SYNGAP1*, *GRIK2*, *TUSC3*, oligosaccharyl transferase, and others	~10
Developmental brain abnormality	Hydrocephalus ± meningomyelocele; schizencephaly, lissencephaly	~8
Inborn errors of metabolism or neurodegenerative disorder	Phenylketonuria, ceroid lipofuscinosis, Tay-Sachs disease, other storage diseases	~7
Congenital infections	HIV, toxoplasmosis, rubella, cytomegalovirus, syphilis, herpes simplex, Zika virus	~3
Familial intellectual disability	Environment, syndromic, or genetic	~5
Perinatal causes	Hypoxic-ischemic encephalopathy, meningitis, intraventricular hemorrhage, periventricular leukomalacia, fetal alcohol syndrome	4
Postnatal causes	Trauma (abuse), meningitis, nutritional deficiencies, hypothyroidism	~4
Unknown		20

Adapted from Stromme P, Hayberg G. Aetiology in severe and mild mental retardation: A population-based study of Norwegian children. *Dev Med Child Neurol.* 2000;42:76–86.

In children with more severe ID, a biologic cause (usually with prenatal onset) can be identified in about three fourths of all cases. Causes include chromosomal (e.g., Down, Wolf-Hirschhorn, and deletion 1p36 syndromes) and other genetic and epigenetic disorders (e.g., fragile X, Rett, and Angelman syndromes), abnormalities of brain development (e.g., lissencephaly), and inborn errors of metabolism and mitochondrial disorders (e.g., mucopolysaccharidoses, mitochondrial respiratory chain complex disorders) (Table 56.4). *Nonsyndromic* severe ID may be a result of inherited or de novo gene mutations, as well as microdeletions or microduplications. Currently, >1,300 single genes have been associated with ID. Inherited genetic abnormalities may be mendelian (autosomal dominant de novo, autosomal recessive, X-linked) or nonmendelian (imprinting, methylation, mitochondrial defects; see Chapter 97). De novo mutations may also cause other phenotypic features such as seizures or autism; the presence of these features suggests more pleotropic manifestations of genetic mutations. Consistent with the finding that disorders altering early embryogenesis are the most common and severe, the earlier the problem occurs in development, the more severe its consequences tend to be.

EPIDEMIOLOGY

ID is one of the most common causes of disability in children globally. The prevalence of ID depends on the definition, method of ascertainment, and population studied, both in terms of geography and age. According to the statistics of a normal distribution, 2.5% of the population should have ID (based on IQ alone), and 75% of these individuals should fall into the mild to moderate range. Variability in rates across populations likely results from the heavy influence of external environmental factors and definitional differences on the prevalence of mild ID. The prevalence of severe ID is relatively stable. Globally, the prevalence of ID has been estimated to be approximately 16.4 per 1,000 persons in low-income countries, approximately 15.9/1,000 for middle-income countries, and approximately 9.2/1,000 in high-income countries. A meta-analysis of worldwide studies from 1980 to 2009 yielded an overall prevalence of 10.4/1,000. ID occurs more in boys than in girls, at 2:1 in mild ID and 1.5:1 in severe ID. In part this may be a consequence of the many X-linked disorders associated with ID, the most common being fragile X syndrome (see Chapter 59).

In the United States the prevalence of ID in school-age children ranges from 1.1% to 1.8%. There are several reasons why fewer children are identified as having mild ID than predicted from statistics. Professionals might miss or defer the diagnosis and "give the benefit of the doubt" to the child and await repeated confirmatory testing over time because it is more challenging to diagnose mild ID than the more severe forms. Other reasons that contribute to the discrepancy between predicted and observed prevalence are use of instruments that underidentify young children with mild ID, children diagnosed as having ASD without their ID being recognized or addressed, misdiagnosis as a language disorder or specific learning disability, and a disinclination to make the diagnosis in minoritized students because of concern about biased assessments that historically led to overdiagnosis. In some cases, behavioral disorders may divert the focus from the cognitive dysfunction.

Beyond potential under diagnosis of mild ID, the number of children with mild ID may be decreasing because of public health and education measures to prevent prematurity and provide early intervention and Head Start programs. However, although the number of school children who receive services under a federal disability classification of ID has decreased since 1999, when *developmental delay* is included in analysis of the data, the numbers have not changed appreciably.

The prevalence of *severe ID* has not changed significantly since the 1940s, accounting for 0.3–0.5% of the population. Many of the causes of severe ID involve genetic or congenital brain malformations that can neither be anticipated nor treated at present, though trends toward more expanded prenatal screening (and subsequent termination) may alter this balance, as seen with the decreasing incidence of Down syndrome. Additionally, expanded newborn screening with early treatment has virtually eliminated ID caused by phenylketonuria and congenital hypothyroidism. However, continued high prevalence of fetal exposure to alcohol and illicit drugs, improved survival of very low birthweight premature infants, and increasing overall maternal age during pregnancy (contributing to increased rates of genetic abnormalities) have counterbalanced this effect.

PATHOLOGY AND PATHOGENESIS

The limitations in our knowledge of the neuropathology of ID are demonstrated by the finding that 10–20% of brains of persons with severe ID appear normal on standard neuropathologic study. Many of the brains that appear abnormal show only mild, nonspecific changes that correlate poorly with the degree of ID, including microcephaly, gray matter heterotopias in the subcortical white matter, unusually regular columnar arrangement of the cortex, and neurons that are more tightly packed than usual. Only a minority of the brains show more specific changes in dendritic and synaptic organization, with dysgenesis of dendritic spines or cortical pyramidal neurons or impaired growth of dendritic trees. CNS maturation is defined by genetic, molecular, autocrine, paracrine, and endocrine influences. Receptors, signaling molecules, and genes are critical to brain development.

As the ability to identify genetic aberrations that correspond to particular phenotypes expands through the use of next-generation sequencing, more will be elucidated about the pathogenesis of ID at a genetic and molecular level. This expanding pathophysiologic knowledge base may serve as a framework with which to develop targeted therapies to bypass or correct newly identified defects. For example, use of histone deacetylase (HDAC) inhibitors has been shown to rescue structural and functional neural deficits in mouse models of Kabuki syndrome, a disorder of histone methylation that leads to variable levels of ID and characteristic facial features. Similarly, there is growing interest in the role of mammalian target of rapamycin (mTOR) inhibitor use preventing seizures, neurodevelopmental disabilities, retinal tumors, cutaneous tumors, and other manifestations seen in tuberous sclerosis (see Chapter 636.2).

CLINICAL MANIFESTATIONS

Early diagnosis of ID facilitates earlier intervention, identification of abilities, realistic goal setting, monitoring for potential comorbid conditions, easing of parental anxiety, and greater inclusion of the child in the community. Children with ID may first come to the pediatrician's attention because of dysmorphisms (often in infancy), associated developmental disabilities, or failure to meet age-appropriate developmental milestones (Tables 56.5 and 56.6). Physical exam findings are nonspecific, but constellations of dysmorphisms may be consistent with certain genetic syndromes. With the advent of more sophisticated genetic testing, the limitations of dysmorphology have become more apparent given the phenotypic variability seen with many genetic causes of ID.

Most children with ID lag behind peers in their acquisition of developmental skills. In early infancy, failure to meet age-appropriate expectations can include a lack of visual or auditory responsiveness, unusual muscle tone (hypotonia or hypertonia), or posture and feeding difficulties. Between 6 and 18 months of age, gross motor delay (lack of sitting, crawling, walking) is the most common concern. Language delay and behavior problems are common concerns after 18 months of age (see Table 56.6). For some children with mild ID, the diagnosis remains

Table 56.5 Physical Examination of a Child with Suspected Developmental Disabilities

ITEM	POSSIBLE SIGNIFICANCE
General appearance	May indicate significant delay in development or obvious syndrome
STATURE	
Short stature	Malnutrition, many genetic syndromes are associated with short stature (e.g., Turner, Noonan)
Obesity	Prader-Willi syndrome
Large stature	Sotos syndrome, Sotos-like syndromes
HEAD	
Shape	Flat occiput: Down syndrome, Zellweger syndrome; prominent occiput: trisomy 18 Delayed closure of sutures: hypothyroidism, hydrocephalus Craniosynostosis: Crouzon syndrome, Pfeiffer syndrome Delayed fontanel closure: hypothyroidism, Down syndrome, hydrocephalus, skeletal dysplasia
Macrocephaly	Alexander syndrome, Canavan disease, Sotos syndrome, gangliosidosis, hydrocephalus, mucopolysaccharidosis, subdural effusion
Microcephaly	Virtually any condition that can restrict brain growth (e.g., malnutrition, Angelman syndrome, Cornelia de Lange syndrome, fetal alcohol effects)
FACE	
Specific measurements may provide clues to inherited, metabolic, or other diseases	Midface hypoplasia: fetal alcohol syndrome, Down syndrome Triangular facies: Russell-Silver syndrome, Turner syndrome Coarse facies: mucopolysaccharidoses, Sotos syndrome Prominent nose and chin: fragile X syndrome Flat facies: Apert syndrome, Stickler syndrome Round facies: Prader-Willi syndrome Hypotelorism or hypertelorism; slanted or short palpebral fissure; unusual nose, maxilla, and mandible
Nose	Anteverted nares/synophrys: Cornelia de Lange syndrome Broad nasal bridge: fetal drug effects, fragile X syndrome Low nasal bridge: achondroplasia, Down syndrome Prominent nose: Rubenstein Taybi, Coffin-Lowry syndrome, Smith-Lemli-Opitz syndrome
Mouth	Long philtrum/thin vermilion border: fetal alcohol effects Cleft lip and palate: isolated or part of a syndrome Micrognathia: Pierre Robin sequence, trisomies, Stickler syndrome Macroglossia: hypothyroidism, Beckwith-Wiedemann syndrome
Teeth	Anodontia: ectodermal dysplasia Notched incisors: congenital syphilis Late dental eruption: Hunter syndrome, hypothyroidism Talon cusps: Rubinstein-Taybi syndrome Wide-spaced teeth: Cornelia de Lange syndrome, Angelman syndrome

Table 56.5 Physical Examination of a Child with Suspected Developmental Disabilities—cont'd

ITEM	POSSIBLE SIGNIFICANCE
EYES	
Set	Hypertelorism: fetal hydantoin syndrome, Waardenburg syndrome Hypotelorism: holoprosencephaly sequence, maternal phenylketonuria effect
Prominent	Crouzon, Seckel, Apert syndrome; Beckwith-Wiedemann syndrome and fragile X syndromes
Iris/sclera	Brushfield spots: Down syndrome Lisch nodules: neurofibromatosis Blue sclera: osteogenesis imperfecta, Turner syndrome, hereditary connective tissue disorders
Cataract	Galactosemia, Lowe syndrome, prenatal rubella, hypothyroidism
Cherry-red spot in macula	Gangliosidosis (GM_1), metachromatic leukodystrophy, mucolipidosis, Tay-Sachs disease, Niemann-Pick disease, Farber lipogranulomatosis, sialidosis type III
Chorioretinitis	Congenital infection with cytomegalovirus, toxoplasmosis, Zika virus, or rubella
Corneal cloudiness	Mucopolysaccharidosis types I and II, Lowe syndrome, congenital syphilis
EARS	
Low-set or malformed pinnae	Trisomies such as Down syndrome, Rubinstein-Taybi syndrome, CHARGE syndrome, cerebrooculofacioskeletal syndrome, Treacher Collins syndrome, fetal phenytoin effects
Hearing	Loss of acuity in mucopolysaccharidosis; hyperacusis in many encephalopathies
HEART	
Structural anomaly or hypertrophy	CHARGE syndrome, velocardiofacial syndrome, glycogenosis type II, fetal alcohol effects, mucopolysaccharidosis type I; chromosomal anomalies such as Down syndrome; maternal PKU; chronic cyanosis may impair cognitive development
LIVER	
Hepatomegaly	Fructose intolerance, galactosemia, glycogenosis types I-IV, mucopolysaccharidosis types I and II, Niemann-Pick disease, Tay-Sachs disease, Zellweger syndrome, Gaucher disease, ceroid lipofuscinosis, gangliosidosis
GENITALIA	
Macroorchidism	Fragile X syndrome
Hypogenitalism	Prader-Willi, Klinefelter, and CHARGE syndromes
EXTREMITIES	
Hands, feet; dermatoglyphics, creases	May indicate a specific entity such as Rubinstein-Taybi syndrome or may be associated with chromosomal anomaly Short limbs: achondroplasia, rhizomelic chondrodysplasia Small hands: Prader-Willi syndrome Clinodactyly: trisomies, including Down syndrome Polydactyly: trisomy 13, ciliopathies Broad thumb: Rubinstein-Taybi syndrome Syndactyly: de Lange syndrome Smith Lemli Opitz Transverse palmar crease: Down syndrome Joint laxity: Down syndrome, fragile X syndrome, Ehlers-Danlos syndrome Phocomelia: Cornelia de Lange syndrome
Joint contractures	Signs of muscle imbalance around the joints (e.g., with meningomyelocele, cerebral palsy, arthrogryposis, muscular dystrophy; also occurs with cartilaginous problems such as mucopolysaccharidosis) Williams syndrome
SKIN	
Café-au-lait spots	Neurofibromatosis, Legius syndrome, tuberous sclerosis, chromosomal aneuploidy, ataxia-telangiectasia, multiple endocrine neoplasia type 2b Fanconi anemia, Gaucher disease Syndromes: basal cell nevus; McCune-Albright, Silver-Russell, Bloom, Chediak-Higashi, Hunter, Bannayan-Riley-Ruvalcaba, Maffucci syndromes
Seborrheic or eczematoid rash	PKU, histiocytosis
Hemangiomas and telangiectasia	Sturge-Weber syndrome, Bloom syndrome, ataxia-telangiectasia; Klippel Trenaunay Weber
Hypopigmented macules, streaks, adenoma sebaceum	Tuberous sclerosis, hypomelanosis of Ito
Hair	Hirsutism: De Lange syndrome, mucopolysaccharidosis, fetal phenytoin effects, cerebrooculofacioskeletal syndrome, trisomy 18, Hurler syndrome Low hairline: Klippel-Feil sequence, Turner syndrome Sparse hair: Menkes disease, argininosuccinic acidemia, biotin deficiency Abnormal hair whorls/posterior whorl: chromosomal aneuploidy (e.g., Down syndrome) Hypertrichosis cubiti (elbows): Wiedemann-Steiner, MacDermot-Patton-Williams syndromes Abnormal eyebrow patterning: Cornelia de Lange syndrome

Continued

Table 56.5 Physical Examination of a Child with Suspected Developmental Disabilities—cont'd

ITEM	POSSIBLE SIGNIFICANCE
Nails	Hypoplastic or dysplastic: fetal alcohol, trisomies, Coffin Siris syndrome
NEUROLOGIC	
Asymmetry of strength and tone	Focal lesion, hemiplegic cerebral palsy
Hypotonia	Prader-Willi, Down, and Angelman syndromes; gangliosidosis; early cerebral palsy; muscle disorders (dystrophy or myopathy)
Hypertonia	Neurodegenerative conditions involving white matter, cerebral palsy, trisomy 18
Ataxia	Ataxia-telangiectasia, metachromatic leukodystrophy, Angelman syndrome
Spine	Sacral dimple/hairy patch: spina bifida
OTHER	
Neck	Webbed neck/low posterior hairline: Turner syndrome, Noonan syndrome
Chest	Shield-shaped chest: Turner syndrome Inverted nipples; congenital disorders of glycosylation

CHARGE, Coloboma, heart defects, atresia choanae, retarded growth, genital anomalies, ear anomalies (deafness); CATCH-22, cardiac defects, abnormal face, thymic hypoplasia, cleft palate, hypocalcemia, defects on chromosome 22; PKU, phenylketonuria.
Modified from Simms M. Intellectual and developmental disability. In: Kliegman RM, Lye PS, Bordini BJ, et al, (eds). *Nelson Pediatric Symptom-Based Diagnosis*. Philadelphia: Elsevier; 2018: Table 24.11, p. 376.

Table 56.6 Common Presentations of Intellectual Disability by Age

AGE	AREA OF CONCERN
Newborn	Dysmorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding, breathing)
Early infancy (2-4 mo)	Failure to interact with the environment Concerns about vision and hearing impairments
Later infancy (6-18 mo)	Gross motor delay
Toddlers (2-3 yr)	Language delays or difficulties
Preschool (3-5 yr)	Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing
School age (>5 yr)	Academic underachievement Behavior difficulties (e.g., attention, anxiety, mood, conduct)

uncertain during the early years and becomes clearer as the demands of the school setting increase.

With increasing expectations for independence at home and socially, limitations among those with mild ID become more salient. Older school-age children and adolescents with mild ID are typically up to date on current trends and are conversant as to "who," "what," and "where." It is not until the "why" and "how" questions are asked that their limitations become apparent. If allowed to interact at a superficial level, their mild ID might not be appreciated, even by professionals such as healthcare providers. Because of the stigma associated with ID, adolescents may refer to themselves as learning disabled, dyslexic, language disordered, or slow learners. Some people with ID emulate their social milieu to be accepted. Adolescents with mild ID are both at high risk of being bullied and of being taken advantage of from a social perspective.

ETIOLOGIC EVALUATION

ID is one of the most frequent reasons for referral to pediatric genetic providers, with separate but similar etiologic evaluation guidelines (see Table 56.1). ID is a diagnosis of great clinical heterogeneity, with only a subset of syndromic etiologies identifiable through classic dysmorphology. If diagnosis is not made after conducting an appropriate history and physical examination, chromosomal microarray and testing for fragile X syndrome are often the recommended first steps in the etiologic evaluation of ID. Other testing to consider in the etiologic evaluation include exome or whole genome sequencing, neuroimaging, metabolic testing, and electroencephalography (Fig. 56.1).

Decisions to pursue an etiologic diagnosis should be based on the medical and family history, physical examination, and the family's wishes. Table 56.7 summarizes clinical practice guidelines and the yields of testing to assist in decisions about evaluating the child with GDD or ID. Yield of testing tends to increase with worsening severity of delays (see also Tables 56.1 and 56.2).

Microarray analysis has replaced a karyotype as first-tier testing, given that it discerns abnormalities that are far below the resolution of a karyotype. Microarray analysis will detect copy number variations but may result in identification of variants of unknown significance or benign variants and therefore should be used in conjunction with a genetic consultation. Karyotyping has a role when concerns for trisomy, inversions, balanced insertions, and reciprocal translocations are present. If microarray analysis is not diagnostic, whole exome sequencing (WES) increases the diagnostic yield in children with nonsyndromic severe ID, especially when associated conditions such as autism, epilepsy, or movement disorders are present. WES will identify nucleotide sequence variants within the coding region of genes which affect protein function, missing structural and noncoding variants, and trinucleotide repeat disorders. *Starting with WES may be more cost-effective and may substantially reduce time to diagnosis with higher ultimate yields compared with the traditional diagnostic pathway.* Whole genome sequencing, which identifies variants within both exons and introns, represents the most comprehensive sequencing option, providing roughly 3,000 times more data than a microarray. Multimodal genome-wide analysis has identified monogenic etiologies in difficult to diagnose patients when previous testing did not reveal a diagnosis.

Molecular genetic testing for fragile X syndrome is currently recommended, although a relatively low diagnostic yield has led some to suggest that this should not be considered a first-line test for all children with ID or GDD. Yields are highest in males with moderate ID, unusual physical features, and/or a family history of ID or for females with more subtle cognitive deficits associated with severe shyness and a relevant family history, including premature ovarian failure or later-onset tremor-ataxia symptoms (see Chapter 59). For children with a strong history of X-linked ID, specific testing of genes or the entire chromosome may be revealing. Testing for Rett syndrome (methyl CpG–binding protein 2 [MECP2]) should be considered in females with moderate to severe disability, though WES may supplant this.

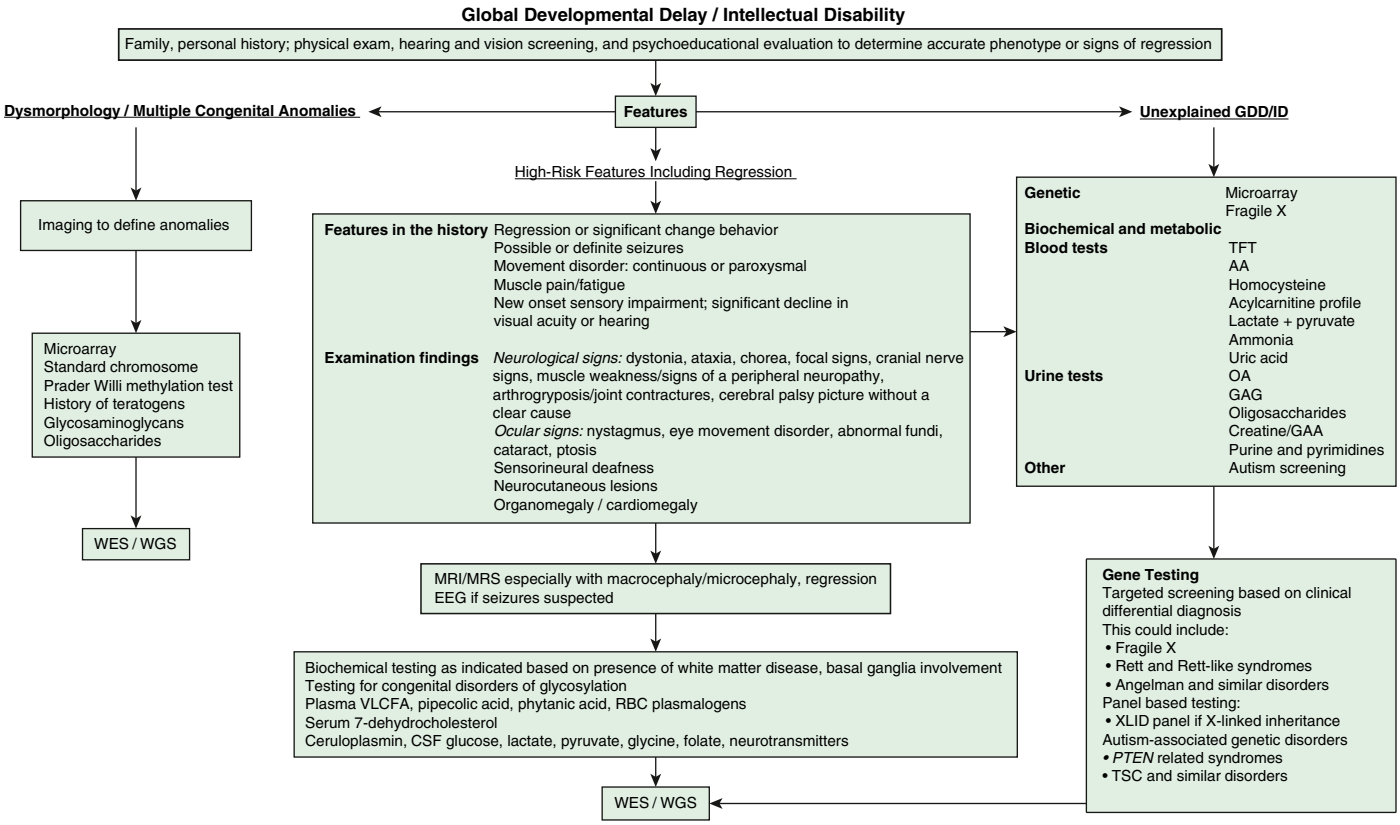

Fig. 56.1 Algorithm for the evaluation of the child with unexplained global developmental delay (GDD) or intellectual disability (ID). AA, Amino acids; ASD, autistic spectrum disorder; CK, creatine kinase; CSF, cerebrospinal fluid; FBC, full blood count; GAA, guanidinoacetic acid; GAG, glycosaminoglycans; LFT, liver function test; OA, organic acids; TFT, thyroid function tests; TSC, tuberous sclerosis complex; U&E, urea and electrolytes; VLCFA, very long-chain fatty acids; WES, whole exome sequencing; WGS, whole genome sequencing; XLID, X-linked intellectual disability genes.

A child with a **progressive neurologic disorder, developmental regression, or acute behavioral changes** needs metabolic investigation, as shown in Figure 56.1. Some advocate for metabolic testing to be done more frequently in children with ID because of the possibility of detecting a condition that could be treatable (Fig. 56.2, Tables 56.3 and 56.8), though with expanded newborn screening many of these conditions can be identified at birth. This is most relevant for children born in countries without widespread newborn screening initiatives, especially when there is a history of consanguinity. In the absence of a specific indication, an **electroencephalogram (EEG)** is typically of low diagnostic utility and should be reserved for evaluation of clinical events that may represent seizures or when significant language regression occurs, which may be concerning for Landau-Kleffner syndrome. **MRI of the brain** may provide useful information in directing the care of a child with microcephaly or macrocephaly, change in head growth trajectory, asymmetric head shape, new or focal neurologic findings, or seizures. MRI can detect a significant number of subtle markers of cerebral dysgenesis in children with ID, but these markers do not usually suggest a specific etiologic diagnosis, and the risk of anesthesia may outweigh the potential benefits in young children without any additional concerning signs or symptoms.

Some children with subtle physical or neurologic findings can also have determinable biologic causes of their ID (see Tables 56.5 and 56.6). How intensively one investigates the cause of a child's ID is based on the following factors:

- What is the degree of delay, and what is the age of the child? If milder or less pervasive delays are present, especially in a younger child, etiologic yield is likely to be lower.
- Is the medical history, family history, or physical exam suggestive of a specific disorder, increasing the likelihood that a diagnosis will be made? Are the parents planning on having additional children, and does the patient have siblings? If so, one may be more likely to intensively seek disorders for which prenatal diagnosis or a specific early treatment option is available.
- Is there a potentially treatable disorder?
- What are the parents' wishes? Some parents have little interest in searching for the cause of the ID, whereas others become so focused on obtaining a diagnosis that they have difficulty following through on interventions until a cause has been found. The entire spectrum of responses must be respected, and supportive guidance should be provided.

DIFFERENTIAL DIAGNOSIS

One of the important roles of pediatricians is the early recognition and diagnosis of cognitive deficits. Developmental surveillance should be multifaceted. Parents' concerns and observations about their child's development should be listened to carefully. Medical, genetic, and environmental risk factors should be recognized. Infants at high risk (prematurity, maternal substance abuse, perinatal insult) should be registered in newborn follow-up programs in which they are evaluated periodically for developmental lags in the first 2 years of life; they should be referred to early intervention programs as appropriate. Developmental milestones should be recorded routinely during healthcare maintenance visits. The American Academy of Pediatricians (AAP) has formulated a schema for developmental surveillance and screening at 9, 18, 24, and 30 months of age, including general developmental and autism screens (see Chapter 28).

Table 56.7 Suggested Evaluation of the Child with Intellectual Disability (ID) or Global Developmental Delay (GDD)

TEST	COMMENT
In-depth history	Includes prenatal, perinatal, and postnatal events (including seizures); developmental attainments; and three-generation pedigree in family history (focusing on neurologic or developmental abnormalities, miscarriages, consanguinity, etc.)
Physical examination	Particular attention to minor or subtle dysmorphisms; growth issues; neurocutaneous findings; eye and skull abnormalities; hepatosplenomegaly; and neurologic examination for focality Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A ~15% yield overall Better resolution than with karyotype; may identify up to twice as many abnormalities as karyotyping Often included in exome testing
Karyotype	No longer a first-line test Reserve use when concerned for trisomic/monosomic conditions, inversions and balanced insertions, or reciprocal translocations
Fragile X screen	Combined yield of 2%, preselection on clinical grounds can increase yield to 7.6%
Next-generation gene sequencing	Detects inherited and de novo point mutations, especially in nonsyndromic severe intellectual disability Whole exome sequencing gives an additional yield of about 30–40% Pilot studies of whole genome sequencing (WGS) reveal additional yield of about 15%
Neuroimaging	MRI preferred; positive findings increased by abnormalities of skull contour or microcephaly and macrocephaly or focal neurologic examination (30–40% if indicated, 10–14% if screening) Identification of specific etiologies is rare; most conditions that are found do not alter the treatment plan; need to weigh risk of sedation against possible yield
Thyroid (T_4, TSH)	Near 0% in settings with universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure (e.g., low socioeconomic status, home built before 1950)
Metabolic testing	Yield of 0.2–4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and capillary blood gas Focused testing based on clinical findings is warranted if lack of newborn screen results or suggestive history/exam (e.g., regression, consanguinity, hepatosplenomegaly, course facies) Tandem mass spectrometry newborn screening has allowed for identification of many disorders in the perinatal period and has decreased yield in older children; other disorders have emerged, such as congenital disorders of glycosylation (yield 1.4%) and disorders of creatine synthesis and transport (yield 2.8%)
MECP2 for Rett syndrome	1.5% of females with criteria suggestive of Rett (e.g., acquired microcephaly, loss of skills) 0.5% of males
EEG	May be deferred in absence of history of seizures or significant language regression
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype; new technology may be available for evaluation

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG–binding protein 2; T_4, thyroxine; TSH, thyroid-stimulating hormone.
Data from Michelson DJ, Shevell MI, Sheer EH, et al. Evidence report. Genetic and metabolic testing on children with global developmental delay: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of Child Neurology. *Neurology*. 2011;77:1629–1635; Curry CJ, Stevenson RE, Aughton D, et al. Evaluation of mental retardation: Recommendations of a Consensus Conference: American College of Medical Genetics. *Am J Med Genet*. 1997;12:72:468–477; Shapiro BK, Batshaw ML. Mental retardation. In: Burg FD et al: *Gellis and Kagan's Current Pediatric Therapy,* 18th ed, Philadelphia: Saunders; 2005; and Shevell M, Ashwal S, Donley D, et al. Practice parameter: Evaluation of the child with global developmental delay. *Neurology*. 2003;60:367–380.

Before making the diagnosis of ID, other disorders that affect cognitive abilities and adaptive behavior should be considered. These include conditions that mimic ID and others that involve ID as an associated impairment. Sensory deficits (severe hearing and vision loss), communication disorders, refractory seizure disorders, poorly controlled mood disorders, or unmanaged severe attention deficits can mimic ID; certain progressive neurologic disorders can appear as ID before regression is appreciated. Approximately half of children with **cerebral palsy** (see Chapter 638.1) and one third of children with **autism spectrum disorder** (see Chapter 58) also have ID. Differentiation of isolated CP from ID relies on motor skills being more affected than cognitive skills and on the presence of pathologic reflexes and tone changes. Importantly, cognitive testing may be limited because of motor and communication impairments in CP such that an accurate diagnostic assessment often hinges on evaluation by a professional with experience with this population.

In ASD, social communication and social adaptive skills are more affected than nonverbal reasoning skills, whereas in ID, there are usually more equivalent deficits in social, fine motor, adaptive, and cognitive skills. The discrepancy between social communication abilities and overall developmental abilities and the presence, severity, and intensity of restricted and repetitive behaviors differentiates whether an individual has ID alone or a comorbid diagnosis of ASD. Among toddlers with ASD, those with lower verbal and nonverbal cognitive test scores in conjunction with poor adaptive skills have an 85–90% chance of being classified as having ID in adulthood. However, across all levels of cognition in ASD, there is a significant trend toward much lower adaptive functioning than would be expected otherwise.

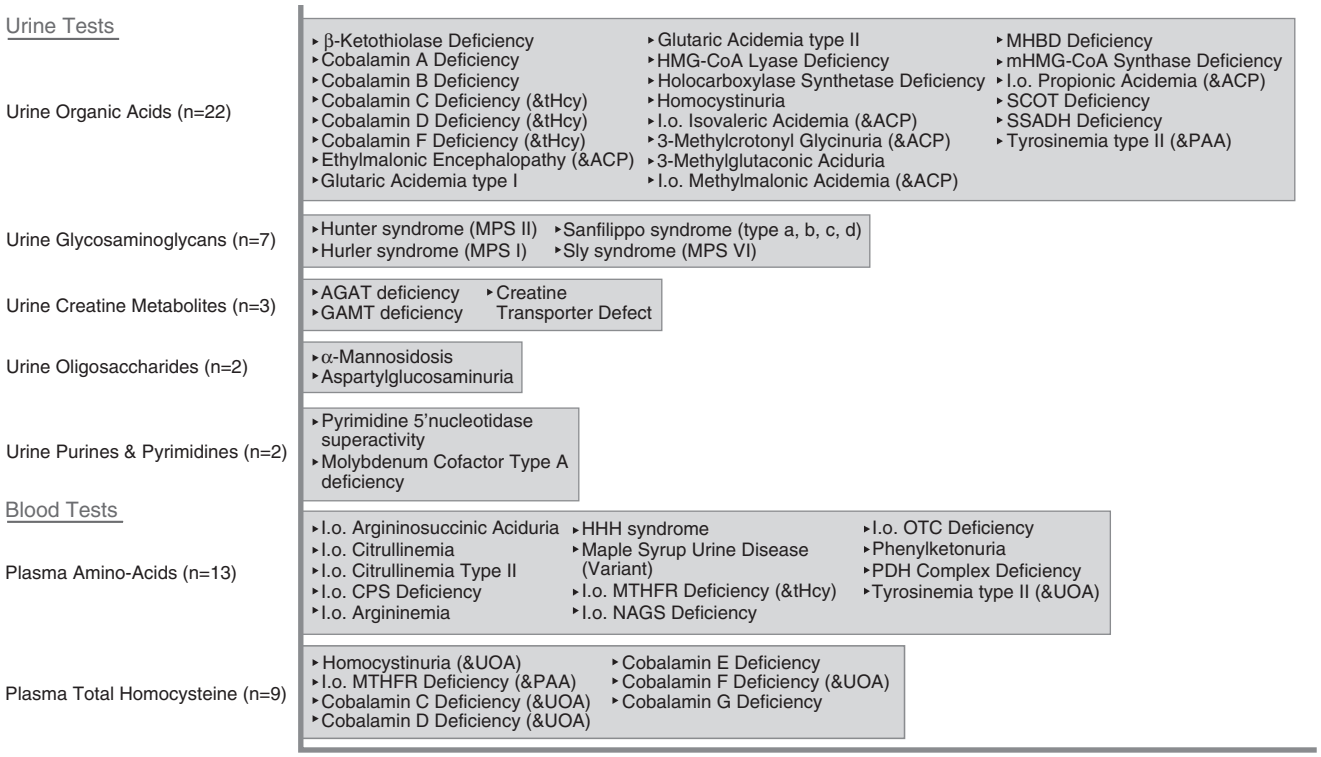

Fig. 56.2 Summary of treatable inherent errors of metabolism (IEM) that can be detected by metabolic tests in affected children, each of which is affordable and accessible and has the potential to identify at least 2 IEM (and up to 22). Each bar represents the yield of the specific screening test and lists the number and types of treatable IEM it can identify. PAA, Plasma amino acids; tHcy, total homocysteine; ACP, plasma acylcarnitine profile; UOA, urine organic acids. *(From van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: A systematic literature review. Mol Genet Metab. 2012;105:368–381, Fig. 1, p. 374.)*

Table 56.8 Treatable Intellectual Disability Endeavor (TIDE) Diagnostic Protocol

***TIER* 1: NONTARGETED METABOLIC SCREENING TO IDENTIFY 54 (60%) TREATABLE IEM**	
Blood	Plasma amino acids, total homocysteine, acylcarnitine profile, copper, ceruloplasmin
Urine	Organic acids, purine and pyrimidines, creatine metabolites, oligosaccharides, glycosaminoglycans, amino acids (when indicated)
***TIER* 2: CURRENT PRACTICE ADHERING TO INTERNATIONAL GUIDELINES* (ONE OR MORE OF THE FOLLOWING)**	
Blood	Cytogenetic testing (array CGH), thyroid studies, complete blood count, lead, metabolic testing, fragile X, targeted gene sequencing/molecular panel
Diagnostics	Brain MRI and 1H spectroscopy (where available)
Referrals	Audiology, ophthalmology
TIER 3: TARGETED WORKUP TO IDENTIFY 35 (40%) TREATABLE IEM REQUIRING SPECIFIC TESTING According to patient's symptomatology and clinician's expertise Use of digital tools (www.treatable-id.org)	
Blood	Plasma cholestanol, 7-dehydroxycholesterol:cholesterol ratio, pipecolic acid and urine α-amino adipic semialdehyde (AASA), very-long-chain fatty acids Plasma vitamin B_{12} and folate, serum lactate to pyruvate ratio, whole blood manganese
CSF	Lactate to pyruvate ratio, amino acids, neurotransmitters, CSF to plasma glucose ratio
Urine	Urine deoxypyridinoline
Other	Enzyme activities (leukocytes): arylsulfatase A, biotinidase, glucocerebrosidase, fatty aldehyde dehydrogenase CoQ measurement: fibroblasts Molecular analysis: *CA5A, NPC1, NPC2, SC4MOL, SLC18A2, SLC19A3, SLC30A10, SLC52A2, SLC52A3, PDHA1, DLAT, PDHX, SPR, TH* genes

*Low threshold for ordering tests.
IEM, Inborn errors of metabolism; CSF, cerebrospinal fluid; CGH, comparative genomic hybridization; CoQ, coenzyme Q (ubiquinone).
Adapted from Van Karnebeek CD, Stockler-Ipsiroglu S. Early identification of treatable inborn errors of metabolism in children with intellectual disability: The Treatable Intellectual Disability Endeavor protocol in British Columbia. *Paediatr Child Health.* 2014;19(9):469–471.

DIAGNOSTIC PSYCHOLOGIC TESTING

The formal diagnosis of ID requires the administration of individual tests of intelligence and adaptive functioning.

The *Bayley Scales of Infant and Toddler Development, Fourth Edition* (BSID-4), the most used infant intelligence test, provides an assessment of cognitive, language, motor, behavior, social-emotional, and general adaptive abilities between 16 days and 42 months of age. The BSID-4 correlates more strongly with other standardized tests of cognition and motor development than did prior versions of the test and permits the differentiation of infants with severe ID from typically developing infants, but it is less helpful in distinguishing between a typical child and one with mild ID.

The most used intelligence tests for children older than 3 years are the Wechsler Scales, although others are also used. The *Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition* (WPPSI-IV) is used for children with mental ages of 2.5-7.6 years. The *Wechsler Intelligence Scale for Children, Fifth Edition* (WISC-V) is used for children who function above a 6-year-old mental age. Both scales contain numerous subtests in the areas of verbal and performance skills. Although children with ID usually score low on all subscales, they occasionally score in the average range in one or more performance areas. Among children who have marked language or verbal limitations, tests like the *Differential Ability Scales-II (DAS-II)* or the *Leiter International Performance Scale,* Third Edition (Leiter-3) may be used to optimally capture nonverbal performance skills.

Several normative scales are used in practice to evaluate adaptive functioning, often through questionnaire or interview formats, with information being attained from caregivers and educators in multiple different environments when possible (home, school, work). For example, the *Vineland Adaptive Behavior Scale* (VABS-3) uses semi-structured interviews with parents and caregivers/teachers to assess adaptive behavior in four domains: communication, daily living skills, socialization, and motor skills. Other tests of adaptive behavior include the *Adaptive Behavior Assessment System* (ABAS-3), the *Woodcock-Johnson Scales of Independent Behavior–Revised,* and the *AAIDD Diagnostic Adaptive Behavior Scale* (DABS). There is usually (but not always) a good correlation between scores on the intelligence and adaptive scales in ID. However, it is important to recognize that adaptive behavior can by influenced by environmentally based opportunities and by family or cultural expectations. Basic practical adaptive skills (feeding, dressing, hygiene) are more responsive to remedial efforts than is the IQ score itself. The trajectory of adaptive skill acquisition may not be consistent over time because of the underlying condition, response to interventions, and environmental expectations.

COMPLICATIONS AND ASSOCIATED CONDITIONS

Children with ID have higher rates of vision, hearing, neurologic, orthopedic, and behavioral or emotional disorders than typically developing children (Table 56.9). These problems are often detected later in children with ID. If untreated, the associated impairments may adversely affect the individual's outcome more than the ID itself.

The more severe the ID, the greater the number and severity of associated impairments. Knowing the cause of the ID can help predict which associated impairments are most likely to occur. For example, fragile X syndrome (see Chapter 59) and fetal alcohol syndrome (see Chapter 146) are associated with a high rate of behavioral disorders and may be amenable to certain treatments. Children with fetal alcohol syndrome may have a less robust response to stimulant use, whereas preliminary data suggest that children with fragile X syndrome may see behavioral improvements with the use of metformin. Other genetic conditions may have well-established medical comorbidities that should be screened for throughout the life span. For example, Down syndrome (see Chapter 57) has many medical complications (hypothyroidism, hearing and vision impairments, obstructive sleep apnea, congenital heart disease, atlantoaxial subluxation). Such associated impairments can require ongoing physical therapy, occupational therapy, speech-language therapy, behavioral therapy, adaptive and mobility equipment, glasses, hearing aids, and medication or other medical management. Failure to identify and treat these impairments can hinder successful habilitation and result in difficulties in the school, home, and neighborhood environment.

Special attention should be given to screening for accidental injury, neglect, and abuse. Children with ID have a greater risk of preventable death from accidental injury. They are more likely to be victims of frequent, continual abuse at the hands of multiple abusers and are more frequently abused by unrelated or unfamiliar perpetrators compared to typically developing peers. Up to 15–30% of children with ID are victims of sexual abuse, with female teens with ID being at highest risk. Abuse may precipitate the onset of maladaptive behaviors and changes in mood. As such, a high index of suspicion must be maintained, with the knowledge that even individuals with severe ID may be able to reliably disclose victimization and abuse.

Table 56.9 Conditions Associated with ID

MEDICAL/PHYSICAL CONDITIONS	DEVELOPMENTAL/ PSYCHIATRIC CONDITIONS
Cerebral palsy/severe motor impairment	Attention-deficit/hyperactivity disorder
Seizures	Emotional disorders (anxiety, mood disorders, posttraumatic stress disorder)
Endocrine abnormalities (e.g., hypothyroidism, short stature)	Obsessive-compulsive disorder
GI issues (constipation, reflux)	Behavioral disorders (self-injurious behavior, aggression, adjustment disorder, disruptive behavior)
Dysphagia	Autism spectrum disorder
Other organ system anomalies (e.g., congenital heart disease, malformations)	Eating and feeding disorders
Hearing loss	Psychotic disorders
Vision impairment (refractive error, cataracts, strabismus)	Movement disorders (tics, stereotypies,)
Dental caries	Developmental coordination disorder
Lead poisoning from associated pica	Learning disabilities (difficulties not explained by cognition alone)
Sleep disorders (OSA, behavioral sleep dysfunction)	Substance abuse
Obesity	Victimization (bullying, sexual abuse, physical abuse)

GI, Gastrointestinal; OSA, obstructive sleep apnea.

PREVENTION

Examples of primary programs to prevent ID include the following:

- Increasing the public's awareness of the adverse effects of alcohol and other drugs of abuse on the fetus (the most common preventable cause of ID in the Western world is fetal alcohol exposure).
- Encouraging safe sexual practices, preventing teen pregnancy, and promoting early prenatal care with a focus on preventive programs to limit transmission of diseases that may cause congenital infection (syphilis, toxoplasmosis, cytomegalovirus, HIV).
- Preventing traumatic injury by encouraging the use of safety technologies (car seats, window locks, helmets, gun locks).
- Preventing poisonings by teaching parents about securing medications and potential poisons.

- Implementing immunization programs to reduce the risk of ID caused by encephalitis, meningitis, and congenital infection.

Presymptomatic detection of certain disorders can result in treatment that prevents adverse consequences. State newborn screening by tandem mass spectrometry (now detecting >60 rare genetic disorders in most states), newborn hearing screening, and preschool lead poisoning prevention programs are examples. Additionally, screening for comorbid conditions can help to limit the extent of disability and maximize the level of functioning in certain populations. Annual thyroid, vision, and hearing screening in a child with Down syndrome is an example of presymptomatic testing in a disorder associated with ID.

TREATMENT

Although the core symptoms of ID can be prevented in some conditions, they are generally not treatable once ID is diagnosed. Many associated impairments are amenable to intervention and therefore benefit from early identification. Most children with an ID do not have a behavioral or emotional disorder as an associated impairment, but challenging behaviors (aggression, self-injury, oppositional defiant behavior) and internalizing disorders (mood and anxiety disorders) occur with greater frequency in this population than among children with typical intelligence. These behavioral and emotional disorders are the primary cause for out-of-home placements, increased family stress, reduced employment prospects, and decreased opportunities for social inclusion. Some behavioral and emotional disorders are difficult to diagnose in children with more severe ID because of the child's limited abilities to understand, communicate, interpret, or generalize. Other disorders are masked by the ID. The detection of ADHD (see Chapter 50) in the presence of moderate to severe ID may be difficult, as may be discerning a thought disorder (psychosis) in someone with autism and ID.

Behavioral disorders in ID often result from a mismatch between the child's abilities and the demands of the situation, organic problems, and family difficulties. These behaviors may represent attempts by the child to communicate, gain attention, gain access to desired tangibles, escape certain demands, exert control, or avoid frustration. Determining the antecedents, functions, and consequences of behavior can help in developing an effective behavior intervention plan. The most formal iteration of this is a functional behavioral assessment carried out by a well-trained behavior analyst. In assessing the challenging behavior, one must also consider whether it is inappropriate for the child's *mental or developmental age,* rather than the *chronological age.* However, if the behavior is dangerous to the individual or the external world, intervention is required regardless of whether it is "appropriate" for their developmental age. When intervention is needed, an environmental change, such as a more appropriate classroom setting, may improve certain behavior problems. Behavior management techniques and parent training are valuable; psychopharmacologic agents may be appropriate in certain situations, such as aggression or self-injurious behaviors with high levels of intensity and frequency.

No medication has been found that improves the core symptoms of ID. However, several agents are being tested in specific disorders with known biologic mechanisms (e.g., mTOR inhibitors in tuberous sclerosis and PTEN disorder), with the hope for future pharmacologic options that could alter the natural course of cognitive impairment seen in patients with these disorders. Medication is most useful in the treatment of associated behavioral and psychiatric disorders that do not respond to initial behavioral approaches and environmental manipulation. Additionally, underlying medical disorders and abuse/neglect should be considered as part of the differential before medication initiation in patients with self-injury, aggression, irritability, or significant disruptive behaviors.

Medications used among individuals with ID generally target specific associated symptom complexes, including inattention, impulsivity, and hyperactivity (stimulant medications and alpha-agonists); self-injurious behavior and aggression (antipsychotics); anxiety, obsessive-compulsive disorder, and depression (selective serotonin reuptake inhibitors); and sleep-related dysfunction (melatonin, alpha-agonists, gabapentin, trazodone). Even if a medication proves successful, its use should be reevaluated at least yearly to assess the need for continued treatment of the target behaviors and improvements in functional goals. Generally, medications should be started at a low dose and increased slowly, with frequent assessments of whether benefits outweigh any adverse effects. Adverse effects and idiosyncratic responses to medications may be more common in this population.

PRIMARY CARE, SUPPORTIVE CARE, AND MANAGEMENT

Each child with ID needs a medical home with a primary care clinician who is readily accessible to the family to answer questions, help coordinate care, and discuss concerns. Healthcare clinicians can have effects on patients and their families that are still felt decades later. The role of primary care includes involvement in prevention efforts, early diagnosis, identification and management of associated deficits, longitudinal developmental surveillance and screening, referral for appropriate diagnostic and therapeutic services, interdisciplinary management, provision of anticipatory guidance (see Chapter 13), and advocacy for the child and family. The management strategies for children with an ID should be multimodal, with efforts directed at all aspects of the child's life: health, education, social and recreational activities, behavior problems, and associated impairments. Support for parents and siblings should also be provided (Table 56.10). A strengths-based approach focusing on optimizing participation in all aspects of life tends to be more beneficial than an exclusive focus on cognitive or academic skill attainment. Goals of overall care should include maximizing the individual's independent functioning, identifying effective communication strategies, preserving and enhancing physical fitness and well-being, supporting positive relationship building, and ensuring opportunities for the individual to participate fully in the community and find purpose and enjoyment in life activities. Goals should be individualized, flexible, appropriate, and attainable.

The AAP has published a series of guidelines and/or toolkits for health supervision of children with specific disorders associated with ID (Down syndrome, fragile X syndrome, Williams syndrome, fetal alcohol spectrum disorder). Another source for disorder-specific information can be found at https://www.medicalhomeportal.org/diagnoses-and-conditions.

Goals should be considered and programs adjusted as needed during the primary care visit. Decisions should also be made about what additional information is required for future planning or to explain why the child is not meeting expectations. Other evaluations, such as formal neuropsychologic or educational testing, can be helpful for diagnostic clarification, attaining more appropriate school-based supports, understanding strengths and challenges, or assisting with the process of transition at various time points.

Interdisciplinary Management

The primary care clinician has the responsibility for consulting with other disciplines to make the diagnosis of ID and coordinate treatment services. Consultant services may include speech-language pathology, physical therapy, occupational therapy, psychology, audiology, nutrition, nursing, and social work, as well as medical specialties such as neurodevelopmental disabilities, neurology, genetics, physical medicine and rehabilitation, psychiatry, developmental-behavioral pediatrics, and surgical specialties. Contact with early intervention and school personnel is equally important to help prepare and assess the adequacy of the child's individual family service plan or individual education plan. The family should be an integral part of the planning and direction of this process. Care should be family centered and culturally sensitive; for older children, their participation in planning and decision-making should be promoted to whatever extent possible. Goal setting should be appropriate, individualized, and achievable

Table 56.10 Resource List for Families by Category

Advocacy	Consortium for Citizens with Disabilities	http://www.c-c-d.org/
	The Arc	https://thearc.org/
	American Association on Intellectual and Developmental Disabilities	https://www.aaidd.org/
	Council for Exceptional Children	https://exceptionalchildren.org/
	The National Disability Rights Network	https://www.ndrn.org/
	Ollibean	https://ollibean.com/
	TASH	https://tash.org/
	National Association for Councils on Developmental Disabilities	https://www.nacdd.org/
Assistive Technology	Rehabilitation Engineering and Assistive Technology Society of North America	www.resna.org
	AT Network	www.atnet.org
	Association of Assistive Technology Act Programs (ATAP)	www.ataporg.org
	Guide to Software Accessibility for the Disabled	ithare.com/guide-to-software-accessibility-for-the-disabled/
Behavior and Mental Health	National Association for the Dually Diagnosed (NADD)	www.thenadd.org
	Behavior Analyst Certification Board	www.bacb.com
	Challenging behaviors in I/DD informational article	https://milnepublishing.geneseo.edu/instruction-in-functional-assessment/chapter/chapter-1-challenging-behaviors-of-individuals-with-developmental-disabilities/
	Challenging Behaviors Toolkit	https://www.autismspeaks.org/sites/default/files/2018-08/Challenging%20Behaviors%20Tool%20Kit.pdf
Early Intervention	Zero to Three	www.zerotothree.org/
	Pathways.org	https://pathways.org/
	First Signs Campaign	http://www.firstsigns.org/
	Early intervention overview	https://www.parentcenterhub.org/ei-overview/
	CDC Early intervention information	https://www.cdc.gov/ncbddd/actearly/parents/states.html
	CDC developmental milestones	https://www.cdc.gov/ncbddd/actearly/milestones/index.html
Special Education and Inclusion	Parent Training and Information Centers (PTIs)	https://www.parentcenterhub.org/find-your-center/
	Iris Center (Inclusion)	https://iris.peabody.vanderbilt.edu/
	Understood.org	https://www.understood.org/pages/en/learning-thinking-differences/
	WrightsLaw.com	http://www.wrightslaw.com/advoc/ltrs/inclusion_right_suzanne.htm
	Institute for Community Inclusion	http://www.communityinclusion.org
	Kids Included Together	https://www.kit.org/what-we-do/inclusion-resources/
	Kidstogether.org	http://www.kidstogether.org/
Postsecondary Education	PACER Center	www.PACER.org/transition
	National Center for College Students with Disabilities	https://www.nccsdonline.org/
	DREAM: Disability Rights, Education, Activism, and Mentoring	https://www.dreamcollegedisability.org/
	Guide to Paying for College for People with Disabilities	https://lendedu.com/blog/paying-for-college-for-people-with-disabilities/
	Affordable Colleges Online College Resources for Students with Disabilities	https://www.affordablecollegesonline.org/college-resource-center/resources-for-students-with-disabilities/

Table 56.10 Resource List for Families by Category—cont'd

Transition, Vocational Training, Employment, and Community Participation	The Arc	https://thearc.org/
	Best Buddies International	https://www.bestbuddies.org/
	Easter Seals	https://www.easterseals.com/EasterSeals.com
	Got Transition	https://www.gottransition.org/
	Project SEARCH	https://www.projectsearch.us/Project SEARCH
	Recruit Disability job listings	https://www.recruitdisability.org/
	Rehabilitation Services Administration	https://rsa.ed.gov/
	Work Incentives Planning and Assistance Project Fact Sheet	https://www.ssa.gov/disabilityresearch/wi/generalinfo.htm
	Respectability	https://www.respectability.org/resources/Job-Seekers-Disabilities/
	Employer assistance and Resource Network on Disability Inclusion	https://askearn.org/
	What Can You Do? Resources for Employers	https://www.whatcanyoudocampaign.org/where-to-learn-more/resources-for-employers/
Recreation	Special Olympics	https://www.specialolympics.org/
	Summer camp locator	https://www.veryspecialcamps.com/
Parent and Family Resources	Family Voices	https://familyvoices.org/lfpp/f2fs/
	Parents Helping Parents	https://www.php.com/
	Eparent.com	http://www.eparent.com
	Community Parent Resource Centers (CPRCs)	https://www.parentcenterhub.org/find-your-center/
	Summer camp options for siblings of children with I/DD	https://www.veryspecialcamps.com/summer/siblings-camps/
Government Initiatives and Services	Policy information on SSI for children with disabilities	https://www.cbpp.org/research/social-security/ssi-a-lifeline-for-children-with-disabilities
	Supplemental security income and social security disability insurance – beneficiaries with I/DD	https://www.ssa.gov/policy/docs/ssb/v77n1/v77n1p17.html
	Centers for Medicare and Medicaid Services	http://www.cms.gov
	Home- and community-based waiver programs	https://www.medicaid.gov/medicaid/home-community-based-services/index.html
	Achieving a Better Life Experience (ABLE) Accounts – ABLE national resource center	https://www.ssa.gov/ssi/spotlights/spot-able.htmlhttps://www.ssa.gov/ssi/spotlights/spot-able.html https://www.ablenrc.org/
	Association of University Centers on Disabilities	http://www.aucd.org/directory/directory.cfm
	Administration for Community Living	https://acl.gov/www.acl.gov/programs/aidd/index.aspx.
	Division on Developmental Disabilities (DDD)	http://daddcec.org/Home.aspxwww.acl.gov/programs/aidd/index.aspx.
	National Association of States Directors of Developmental Disabilities Services (NASDDDS)	http://www.nasddds.orgwww.nasddds.org http://daddcec.org/Home.aspx
	Division on Developmental Disabilities (DDD)	Individual state websites
Disorder-Specific Groups	Epilepsy	http://www.epilepsyfoundation.org
	Autism	www.autismspeaks.org www.autism-society.org
	Cerebral Palsy	https://www.yourcpf.org/
	There are other disorder-specific groups that are too numerous to list here, which include large national networks for more common syndromes such as Down syndrome (e.g., http://www.ndss.org, https://www.ndsccenter.org/) or fragile X syndrome (http://www.fragilex.org) and smaller support groups for more rare disorders (many of which can be located through the unique website at https://rarechromo.org/).	

Continued

Table 56.11 Severity of Intellectual Disability and Adult-Age Functioning

LEVEL	SUPPORT LEVEL	FUNCTIONAL AGE EQUIVALENT AS ADULT	ADULT ADAPTATION
Mild	Intermittent	9-11 yr	Reads at fourth- to fifth-grade level; simple multiplication and division; can write a simple list or letter; completes job application; basic independent job skills (arrive on time, stay at task, interact with coworkers); uses public transportation, might qualify for driver's license; keeps house, cooks using recipes; challenges with planning and money management; at risk of being manipulated by others; may need support for making decisions in healthcare, shopping, finances, and raising a family.
Moderate	Limited	6-8 yr	Sight-word reading; copies information (e.g., address from card to job application); matches written number to number of items; recognizes time on clock; communicates; some independence in self-care; housekeeping with supervision or cue cards; meal preparation, can follow picture recipe cards; job skills learned with much repetition; employment in a supported environment; use of public transportation with some supervision; successful friendships attained, but social judgment and life decisions require support.
Severe	Extensive	3-5 yr	Little understanding of written language or number, time, and money concepts; needs extensive supports for problem solving; trainable in some basic activities of daily living, but needs some level of continuous support and supervision for most activities; might communicate wants and needs with use of basic words, phrases, gestures, or with the use of augmentative and alternative communication techniques; trainable in some basic activities of daily living.
Profound	Pervasive	<3 yr	Dependent for self-care, continence, communication needs with supports required for all activities of everyday living; co-occurring physical and sensory limitations are common; may use objects in a goal-directed fashion for recreation or self-care; limited understanding of symbolic communication, but may understand some gestures and emotional cues; uses nonverbal expressions; might need complete custodial or nursing care.

Data from World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th revision. Geneva: WHO; 2011 and American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association.

Periodic Reevaluation

The child's abilities and the family's needs change over time. As the child grows, more information must be provided to the child and family, goals must be reassessed, and programming needs should be adjusted. A periodic review should include information about the child's health status and the child's functioning at home, at school, and in other community settings. Other information, such as psychologic or educational testing, may be helpful. Reevaluation should be undertaken at routine intervals (every 6-12 months during early childhood), at any time the child is not meeting expectations, or when the child is moving from one service delivery system to another. This is especially true during the transition to adulthood, beginning at age 16, as mandated by the IDEA Amendments of 2004, and lasting through age 21, when care should be transitioned to adult-based systems and providers (see Chapter 152).

Federal and Education Services

Education is the single most important discipline involved in the treatment of children with an ID. In the United States, the IDEA, Part B, mandates a free and appropriate public education (FAPE) in the least restrictive environment (LRE) for all school-age children (3-21 years of age). Additionally, Part C mandates early intervention services from birth through 36 months of age to be delivered in a natural environment (usually home) for all qualifying infants and toddlers. The developmental and educational program for children with GDD or ID must be relevant to the child's unique needs and address the child's individual strengths and challenges. The child's developmental level, requirements for support, and goals for independence provide a basis for early intervention services to establish an **individualized family service plan (IFSP),** which focuses on the family's needs to help them optimize the development of their child. For children over 36 months of age, the school system develops an **individualized education program (IEP)**, which focuses on the child's educational needs. Inclusive education seeks to support the right of every child, regardless of ability, to participate in a broad range of activities and contexts as full members of families, communities, and societies with an effort to maximize access, participation, and supports. Research on inclusion reveals benefits for individuals with disabilities and for typically developing children. As such, to the maximum extent appropriate, children with disabilities should be educated with children who do not have disabilities. In general, removal from the regular educational environment should occur only when the nature or severity of the child's disability is such that education in regular classes with the use of supplementary aids and services cannot be achieved satisfactorily, not simply because significant curriculum modifications are needed. Children who are educated in more inclusive settings, regardless of overall developmental level, tend to have higher rates of community participation as adults. Behavioral challenges are the most limiting factor in terms of full inclusion, both in school and within the community, emphasizing the importance of implementing early and consistent behavior management strategies.

Beyond education services, families of children with ID often are eligible for federal or state-provided social services. All states offer developmental disabilities programs that provide home and

community-based services to eligible children and adults, potentially including in-home supports, care coordination services, residential living arrangements, vocational and employment support programs, and additional therapeutic options. A variety of Medicaid waiver programs are also offered for children with disabilities within each state. Children with ID who live in low-income-status households can qualify to receive supplemental security income (SSI), but many of these families do not receive the benefits to which they are eligible.

Leisure and Recreational Activities

The child's social and recreational needs should be addressed. Although young children with ID are generally included in play activities with children who have typical development, adolescents with ID often do not have opportunities for enriching social interactions. Community participation among adults with ID is much lower than that of the typical population even though these individuals tend to have the same preferences and wishes for leisure activities as their nondisabled peers. Individuals with ID experience high rates of marginalization, especially from involvement in formal recreational programs, often because of insufficient resources to accommodate participation, difficulties with expenses and transportation, and so forth. To reduce isolation, ideas for inclusion in leisure activities should be explored with families, including church group involvement, Boy and Girl Scout chapters, 4H clubs, local park district programs, and musical opportunities like choir and instrumental lessons. Participation in sports should be encouraged (even if the child is not competitive) because it offers many benefits, including weight management, development of physical coordination, maintenance of cardiovascular fitness, and improvement of self-image. Inclusion in class trips, dances, dating, and other social events should be encouraged. International programs such as Special Olympics and Best Buddies International seek to enhance inclusion and visibility of individuals with disabilities and can be a valuable resource.

Family Counseling

Many families adapt well to having a child with ID, but some have emotional or social difficulties. The risks of parental depression and child abuse and neglect are higher in this group of children than in the general population. The factors associated with good family coping and parenting skills include stability of the marriage, good parental self-esteem, limited number of siblings, higher socioeconomic status, lower degree of disability or associated impairments (especially behavioral), parents' appropriate expectations and acceptance of the diagnosis, supportive extended family members, and availability of community programs and respite care services. In families in whom the emotional burden of having a child with ID is great, family counseling, parent support groups, sibling support groups and camps, respite care, and home health services should be an integral part of the treatment plan.

Transition to Adulthood

The transition to adulthood can present a stressful and chaotic time for the adolescent with ID and their family (see Chapter 152). A successful transition correlates with better quality of life but requires significant advanced planning. The transition process for those with ID extends beyond medical care and needs to include education and employment, health and well-being, finances and independence, and social and community life. Specific issues include:

- Decision-making (supported decision-making, guardianship, power of attorney)
- Accessing and securing social benefits for which the person is eligible (e.g., SSI, Medicaid)
- The choice of living arrangements and necessary supports (independent living, shared living arrangements, or living with parents; community-integrated living arrangements; group homes)
- Estate planning for the parents (ABLE accounts, special needs trust)
- Postsecondary training (vocational choices, postsecondary education – pacer.org)
- Community participation and involvement in leisure activities (e.g., community service and volunteering activities, religious groups, Special Olympics, Best Buddies, local clubs)

Successful transition is difficult to achieve because of policies, systems, and services that are not comprehensive or coordinated. In moving from child to adult care, families tend to find that services are less readily available, more fragmented, and more difficult to navigate across multiple agencies and jurisdictions.

Transition planning is a required element of the IEP process by age 16 years, and options for continued education or entry into the workforce after high school should be thoroughly considered, with the greater goal of ultimate community-based employment. Postsecondary education possibilities might involve community college or vocational training. In 2008, the U.S. Higher Education Opportunity Act (HEOA) granted students with ID access to federal financial aid to attend colleges with **Comprehensive Transition Programs** (CTPs), which are designed for postsecondary students with ID to continue academic, career and technical, and independent living instruction to prepare for employment. As of 2019, more than 265 nondegree postsecondary programs for students with ID exist nationwide in the United States.

Although employment is a critical element of life adaptation for persons with ID, only 15% are estimated to have jobs, with significant gaps in pay and compensation compared to workers without disability. Employment selection should be "customized" to the individual's interests and abilities. Options may include participation in competitive employment, supported employment, high school–to–work transition programs, job-coaching programs, and consumer-directed voucher programs.

Self-Advocacy

The self-advocacy movement represents an important effort by persons with ID and other disabilities to advocate for maximal autonomy and self-determination in all aspects of life. This movement is a part of the greater disabilities rights movement and represents a resistance to historical systemic injustices experienced by individuals with ID, including neglect, abuse, nonautonomy, marginalization, incarceration, sterilization, and isolation. Self-advocacy stresses that individuals with ID should be able to speak for themselves, should be involved maximally in decision-making, should be treated as equal and fully included in society, and should be given as much control over their own self-direction as possible. This movement emphasizes the tenet of "nothing about us without us" and has led to nationwide changes in terms of policy and medical and legal nomenclature. Above all, the self-advocacy movement has sought to redefine the approach to disability, moving toward a social model of acceptance, equality, accommodation, and inclusion, putting the onus on society to change its attitudes and practices rather than calling on the individual with ID to change.

OUTCOMES

In children with severe ID or ID requiring significant supports, the prognosis is often evident by early childhood. Mild ID might not always be a lifelong disorder. Children might meet criteria for GDD at an early age, but later the disability can evolve into a more specific developmental disorder (language disorder, autism, ADHD, specific learning disability, or borderline intelligence). Others with a diagnosis of mild ID during their school years may develop sufficient adaptive behavior skills that they no longer fit the diagnosis as adolescents or young adults, or the effects of maturation and plasticity may result in children moving from one diagnostic category to another (from

moderate to mild ID). Conversely, some children who have a diagnosis of a specific learning disability or communication disorder might not maintain their rate of cognitive growth and may fall into the range of ID over time.

The apparent higher prevalence of ID in low- and middle-income countries is of concern, given the limitations in available resources. **Community-based rehabilitation (CBR)** is an effort promoted by the World Health Organization (WHO) over the past 4 decades as a means of making use of existing community resources for persons with disabilities in low-income countries, with the goal of increasing inclusion and participation within the community. CBR is now being implemented in >90 countries, although the efficacy of such programs has not been established.

The long-term outcome of persons with ID depends on the underlying cause; degree of cognitive and adaptive deficits; presence of associated medical, developmental, and behavioral impairments; capabilities of the families and schools; and availability of community supports, services, and training provided to the child and family (see Table 56.10). As adults, many persons with mild ID can gain economic and social independence with functional literacy, but they may need periodic support or supervision (especially when under social, economic, or health-related stress). Most live successfully in the community, either independently or in supervised settings. Many will marry, some will have children, and meaningful and long-lasting relationships can be expected.

For persons with moderate ID, the goals of education are to enhance adaptive abilities and "survival" academic and vocational skills, so they are better able to live and function in the adult world (Table 56.11). The concept of supported employment has been very beneficial to these individuals; the person is trained by a coach to do a specific job in the setting where the person is to work, bypassing the need for a "sheltered workshop" experience and resulting in successful work adaptation in the community and meaningful inclusion. These persons generally live at home with family or in a supervised setting in the community, such as a **community integrated living arrangement (CILA)** where different levels of supervision and support are provided depending on the needs of the individuals. There has been a strong movement away from institutionalized living, defined as residence in a facility of four or more people who did not choose to live together.

As adults, people with severe to profound ID usually require extensive to pervasive supports (see Table 56.11). These individuals often have associated impairments, such as CP, behavioral disorders, epilepsy, or sensory impairments, that further limit their adaptive functioning. They can perform simple tasks in supervised settings. Most people with this level of ID can live in the community with appropriate supports, though some may require a higher level of "institutional care" that is best provided though smaller community-run group home settings.

The life expectancy of people with mild ID is similar to the general population, with a mean age at death in the early 70s. However, persons with severe and profound ID have a decreased life expectancy at all ages, presumably from associated serious neurologic or medical disorders, with a mean age at death in the mid-50s. Given that persons with ID are living longer and have high rates of comorbid health conditions in adulthood (e.g., obesity, hypertension, diabetes), ID is now one of the costliest ICD-10 diagnoses, with an average lifetime cost of 1-2 million dollars per person. Thus the priorities for pediatric primary care are to improve healthcare delivery systems during childhood; facilitate the transition of care to adult providers; and ensure high-quality, integrated, community-based services for all persons with ID.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 57

Down Syndrome and Other Abnormalities of Chromosome Number

Mary Pipan

PRINCIPLES OF CARING FOR CHILDREN WITH COMPLEX GENETIC DISORDERS

Down syndrome (trisomy 21) is the most common genetic cause of intellectual disability, with an incidence of 1 in 700 live births in the United States. Many of the principles of care for individuals with Down syndrome generalize to other complex genetic disorders. Genetic disorders generally affect all cells in the body, and hence tend to be multisystemic disorders. Trisomy 21's multisystem effects require monitoring of all organ systems for potential related issues.

Chromosome 21 is the smallest human autosome, which likely accounts for the relatively high fetal survival rate in trisomy 21. The clinical manifestations of *other* trisomies and aneuploidies are shown in Tables 57.1 and 57.2 and Figs. 57.1, 57.2, and 57.3. Fetuses with other

Table 57.1 Chromosomal Trisomies (13, 18) and Their Clinical Findings

TRISOMY 13	TRISOMY 18
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60–80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arrhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples
EXTREMITIES	
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over third, fifth over fourth; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth restriction Renal abnormalities 1-year survival <10%	Severe developmental delays and prenatal and postnatal growth restriction Premature birth, polyhydramnios Inguinal or abdominal hernias 1-year survival <10%

ASD, Atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
From Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics,* 4th ed. Philadelphia: Saunders;2002: 142.

Table 57.2 Other Rare Aneuploidies and Partial Autosomal Aneuploidies

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Growth and mental deficiency are variable. The majority of patients are mosaics. Deep palmar and plantar furrows are characteristic. Joint contractures are present.
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaics. Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%).
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible.
Tetrasomy 12p	46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)	Known as Pallister-Killian syndrome Sparse anterior scalp hair (more so temporal region), eyebrows, and eyelashes; prominent forehead; chubby cheeks; long philtrum with thin upper lip and cupid-bow configuration; polydactyly; streaks of hyperpigmentation and hypopigmentation



Fig. 57.1 Several physical manifestations of trisomy 18. **A,** Typical profile reveals prominent occiput and low-set, posteriorly rotated malformed auricles. **B,** Clenched hand showing typical pattern of overlapping fingers. **C,** Rocker-bottom feet. *(Courtesy Kenneth Garver, MD, Pittsburgh, PA.)*



Fig. 57.2 Trisomy 13 syndrome. Note sloping forehead with variable defect in facial development. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 1 A-C, p. 16.)*



Fig. 57.3 Trisomy 13. A and B, Note hyperconvex nails and postaxial polydactyly. C, Aplasia cutis congenita over posterior occiput. D, Scrotalization of the phallus. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 2, p. 17.)*

full autosomal trisomies are not always viable, but partial trisomy and quatrosomy (trisomy or quatrisomy of only part of the chromosome) or mosaic trisomy (only part of the cell lines contain the aneuploidy) can be viable.

The Down syndrome phenotype can occur as a result of full trisomy 21 (95%), partial trisomy 21 (part of the 21st chromosome in triplicate), mosaic trisomy 21, or translocation. Maternal nondisjunction in meiosis is the most common cause of trisomy 21. Paternal origin accounts for less than 10%.

Chromosome abnormalities affect not only the product and function of that particular group of genes but can have upstream and downstream effects on other gene products in linked pathways. The over 314 triplicate genes in Down syndrome are known to affect the products and metabolic activity of genes from every other chromosome. Possible phenotype (condition) gene relationships in trisomy 21 are noted in Figure 57.4.

The link between children's physical health, development, and behavior becomes obvious when caring for children with complex genetic disorders. Children with developmental disabilities often cannot adequately communicate the symptoms of illness. Challenging behaviors can also interfere with adequate assessment and intervention. Too often, sources of distress, developmental challenges, and behavioral issues are attributed to the genetic disorder and dismissed by family, medical, and educational caregivers. Providing care for genetically complex children requires health and other providers to consider a range of potential differential diagnoses when presented with a change in behavior, a plateau or regression in development, or a new physical complaint.

Trisomy 21 affects brain development across the life span, leading to differences in brain anatomy, neurotransmission, and connectivity that affect processing, glial cell function, infrastructure support, energy metabolism, and in adults, the formation of amyloid plaques leading to high risk for early Alzheimer disease. Alterations in brain development and functioning affect learning, behavior, and emotions, leading to an increased incidence of neurobehavioral and psychiatric disorders such as autism spectrum disorders (ASDs), attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and depression.

It is important for the clinician to understand that children with genetic disorders are genetically more closely related to their biologic family than they are to other children with similar disorders. Children with Down syndrome will have similar patterns of familial heritability for heritable traits and medical conditions as their biologic siblings. Individuals with genetic disorders need to be seen as children/persons first who happen to have a genetic disorder. Using person-first language (child with Down syndrome, *not* Downs child) helps everyone focus on this principle.

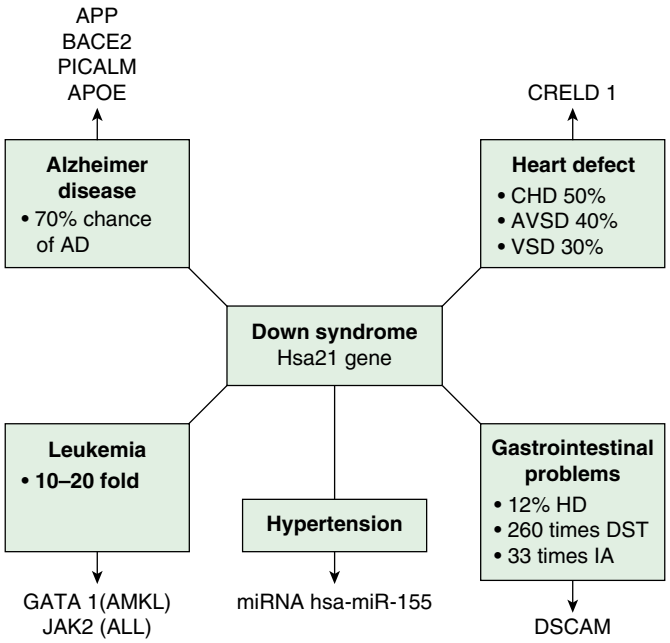

Fig. 57.4 Various conditions associated with Down syndrome with its causative genes. DST, Duodenal stenosis; IA, imperforate anus; HD, Hirschsprung disease; CHD, congenital heart disease; AVSD, atrioventricular septal defects; VSD, ventricular septal defect; AD, Alzheimer disease. *(From Asim A, Kumar A, Muthuswamy S, et al. Down syndrome: An insight of the disease. J Biomed Sci. 2015;22:41, Fig. 1.)*

CLINICAL CHARACTERISTICS

Children with Down syndrome are at increased risk for a variety of congenital anomalies and comorbid medical conditions. Typically, they have a characteristic facial appearance and other physical characteristics that allow clinical recognition of trisomy 21 in the newborn period (Figs. 57.5 and 57.6 and Table 57.3).

The increased risk for a variety of medical conditions continues throughout the life span (Table 57.4). The American Academy of Pediatrics (AAP) has developed Down Syndrome Health Supervision Guidelines for clinicians caring for children with trisomy 21 (Table 57.5). Individuals with Down syndrome often have significant communication deficits, which can result in difficulty reporting pain and discomfort; clinicians need to pay attention to the caregiver's observation of changes in behavior when evaluating the level of pain or illness. Paying close attention to subtle cues on exam



Fig. 57.5 Down syndrome in the neonatal period. **A,** Brushfield spots. **B,** Loose nuchal skin. **C,** Wide space between toes 1 and 2. **D,** Poor tone. **E** and **F,** Accentuation of typical face when crying. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 3, p. 7.)*



Fig. 57.6 Appearance of two 2-year-old children with trisomy 21. The facial appearance of children with trisomy 21 is often characterized by a low nasal bridge, small nose, small ears, up-slanting almond-shaped eyes, and epicanthal folds. *(Photos courtesy of Children's Hospital of Philadelphia.)*

Table 57.3 Clinical Features of Trisomy 21 in the Neonatal Period

CENTRAL NERVOUS SYSTEM
Hypotonia*
Developmental delay
Poor Moro reflex*

CRANIOFACIAL
Brachycephaly with flat occiput
Flat face*
Upward slanted palpebral fissures*
Epicanthal folds
Speckled irises (Brushfield spots)
Three fontanels
Delayed fontanel closure
Frontal sinus and midfacial hypoplasia
Mild microcephaly
Short, hard palate
Small nose, flat nasal bridge
Protruding tongue, open mouth
Small dysplastic ears*

CARDIOVASCULAR
Endocardial cushion defects
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Aberrant subclavian artery
Pulmonary hypertension

MUSCULOSKELETAL
Joint hyperflexibility*
Short neck, redundant skin*
Short metacarpals and phalanges
Short fifth digit with clinodactyly*
Single transverse palmar creases*
Wide gap between first and second toes
Pelvic dysplasia*
Short sternum
Two sternal manubrium ossification centers

GASTROINTESTINAL
Duodenal atresia
Annular pancreas
Tracheoesophageal fistula
Hirschsprung disease
Imperforate anus
Neonatal cholestasis

CUTANEOUS
Cutis marmorata

*Hall's criteria to aid in diagnosis.

Table 57.4 Frequency of Medical Conditions in Trisomy 21

SYSTEM	CONDITION	ESTIMATED FREQUENCY (IF KNOWN)
EYE		
	Cataracts (birth/later)	1.4%/5–37 %
	Glaucoma	1%
	Nystagmus	18–30%
	Strabismus	19–34%
	Refractive errors	80%
	Astigmatism	67–74%
	Nasolacrimal duct obstruction	11–30%
ENT		
	Stenotic ear canals	50%
	Choanal atresia	
	Bifid uvula/mucosal cleft	5%
	Laryngomalacia	
	Middle ear effusions	50–90%
	Adeno/tonsillar hypertrophy	
	Hearing loss	37–78%
DENTAL		
	Tooth agenesis	54–58%
	Malocclusion	>70%
	Periodontal disease	~100% under 30 years
ENDOCRINE		
	Congenital hypothyroidism	1:113 to 1:141 live births
	Acquired hypothyroidism	13–34%
	Subclinical hypothyroidism	7–40%
	Hyperthyroidism	6.5%
	Type 1 diabetes mellitus	0.3–1%
CARDIAC		
	Congenital heart disease	44–54%
	AV canal defects	42% (of CHD)
	VSD	22–35%
	ASD	8–16%
	Tetralogy of Fallot	2–4%
	Acquired mitral, tricuspid, or aortic regurgitation PDA	5–7%

Table 57.4 Frequency of Medical Conditions in Trisomy 21—cont'd

SYSTEM	CONDITION	ESTIMATED FREQUENCY (IF KNOWN)
PULMONARY		
	Pulmonary hypertension	1–5%
	Subglottic stenosis	6%
	Tracheo/laryngomalacia	33% (of ENT-referred population)
	Tracheal bronchus	
	Obstructive sleep apnea	~50%
GASTROINTESTINAL		
	Esophageal atresia	0.5–0.9%
	Duodenal malformations	4%
	Rectoanal malformations	1%
	Hirschsprung disease	3%
	Celiac disease	5–9.8%
	GERD	14–40%
	Constipation	30–49%
GENITOURINARY		
	Renal/urinary tract findings	Up to 25%
HEMATOLOGY/ONCOLOGY		
	Transient myeloproliferative disease (TMD)	5–10%
	Acute megakaryoblastic leukemia (AMKL)	10–20% with TMD, first 4 years of life
	Acute lymphocytic leukemia	0.1–0.2%
ORTHOPEDICS		
	Atlantoaxial instability (AAI)	9–27%
	Symptomatic AAI	1–2%
	Recurrent joint dislocations (shoulder, knee, elbow, thumb)	1–7%
	Pes planus	91%
	Juvenile idiopathic arthritis	~1%
DERMATOLOGY		
	Alopecia/vitiligo	1–11%
	Hidradenitis suppurativa	2%
	Xerosis/eczema	
	Seborrheic dermatitis	
	Psoriasis	0.5–8%
NEUROLOGY		
	Infantile spasms	2–5%
	Seizure disorders	8% (lifetime)
	Strokes and moyamoya	
	Autism spectrum disorder	7–16%
	Early onset Alzheimer disease	~50% >50 yr
	Down syndrome disintegrative disorder	<1%

ENT, Ear/nose/throat; AV, atrioventricular; CHD, congenital heart disease; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; GERD, gastroesophageal reflux disease.

and asking direct questions about specific areas of pain or discomfort can be helpful (e.g., "Does your throat hurt?" while pointing to or touching their throat).

Ophthalmology

The red reflex should be evaluated in the newborn period with a thorough ophthalmologic exam in the first 6 months of life and then annually until age 5, then every 2-3 years thereafter. Children with DS are at higher risk for cataracts, glaucoma, nystagmus, strabismus, astigmatism, refractive error, accommodative error, blepharitis, and keratoconus. Visual acuity and visual processing are foundational for development.

Ear, Nose, and Throat

The pinna and external ear canals are often small with a predisposition to cerumen impaction. Middle ear effusion occurs in the majority of children, starting in infancy, and may require referral to an ear/nose/throat (ENT) specialist for better visualization because of stenotic ear canals. Chronic nasal congestion, choanal atresia, adeno/tonsillar hypertrophy, laryngo/tracheomalacia, subglottic stenosis, and laryngeal cleft all can affect feeding and breathing, including contributing to sleep apnea. Most children with DS require regular ENT follow-up.

Many children with DS have some degree of hearing loss (HL). Most commonly this is conductive HL associated with middle ear effusion. Smaller numbers have mixed or sensorineural HL. Hearing is foundational for speech development. Hearing should be screened in the newborn period and with audiologic assessment between 6 and 9 months and every 6 months thereafter until an accurate ear-specific audiologic evaluation is obtained, then annually. Hearing assessment through auditory brainstem responses (requiring sedation) may be needed if audiologic evaluation is inconclusive. Lack of parental concern about hearing should not preclude obtaining audiologic assessment. Aggressive treatment of otitis media and middle ear effusion reduces the frequency of hearing loss.

Dental

Children with DS often have delayed tooth eruption, malformed teeth, microdontia, permanent tooth agenesis, tooth impaction, malocclusion, and supernumerary teeth. Periodontal disease is

Table 57.5 Summary of Down Syndrome-Specific Care

Action	Pre-natal	Birth up to 1 mo	1 mo up to 1 yr	1 yr up to 5 yr	5 yr up to 12 yr	12 yr up to 21 yr
1. Confirm DS diagnosis with either CVS or amniocentesis prenatally or karyotype postnatally						
2. Review recurrence risk and offer the family referral to a clinical geneticist or genetic counselor.						
3. Offer parent-to-parent and support group information to the family.						
4. Use CDC DS-specific growth charts to monitor weight, length, weight-for-length, head circumference, or BMI. Use standard charts for BMI after age 10 years.		All healthcare visits				
5. Order an echo, to be read by a pediatric cardiologist.						
6. Feeding assessment or video study if any: marked hypotonia, underweight (<5th %ile weight-for-length or BMI), slow feeding or choking with feeds, recurrent or persistent abnormal respiratory symptoms, desaturations with feeds		Any visit				
7. Obtain objective hearing assessment (may be in NBS protocols) and follow EHDI protocols.			Up to 6 mo			
8. If TM can't be visualized, refer to otolaryngologist for exam with microscope until reliable TM and tympanometry exams are possible		Every 3-6 mo				
9. Car safety seat evaluation before hospital discharge.						
10. CBC with differential		By day 3				
11. If TAM, make caregivers aware of risk/signs of leukemia (e.g., easy bruising/bleeding, recurrent fevers, bone pain)						
12. TSH		At birth (if not in NBS)	Every 5-7 mo	Annually, and every 6 mo if antithyroid antibodies ever detected		
13. RSV prophylaxis based on AAP guidelines.		Annually		Through 2 yr		
14. Discuss cervical spine-positioning for procedures and atlantoaxial stability precautions.		All HMV		Biennially		
15. Assess for CAM use, discourage any unsafe CAM practices.		All HMV				
16. Refer children to early intervention for speech, fine motor or gross motor therapy.		Any visit	Up to 3 yr			
17. If middle ear disease occurs, obtain developmentally-appropriate hearing evaluation.			When ear clear	After treatment		
18. Rescreen hearing with developmentally-appropriate methodology (BAER, behavioral, ear-specific).			Start at 6mo, every 6 mo until established normal bilaterally by ear-specific testing, then annually			
19. Refer to ophthalmologist with experience and expertise in children with disabilities.			By 6 mo			
20. CBC with differential if easy bruising or bleeding, recurrent fevers, or bone pain			Any visit			
21. Assess for sleep-disordered breathing; if present, refer to physician with expertise in pediatric sleep disorders.			At least once by 6 mo, then all subsequent HMV thereafter			
22. Ensure child is receiving developmental therapies, and family understands and is following therapy plan at home.		All HMV				
23. CBC with differential and either (1) a combination of ferritin and CRP, or (2) a combination of serum iron and Total Iron Binding Capacity				Annually		
24. If a child has sleep problems and a ferritin less than 50 mcg/L, the pediatrician may prescribe iron supplement.				Any visit		
25. Vision screening			All HMV, use developmentally-appropriate criteria	Photoscreen (all HMV); if unable, refer to ophthalmologist annually	Photoscreen (all HMV); if unable, refer to ophthalmologist biennially	Visual acuity or photoscreening at all HMV, or ophthalmology-determined schedule
26. If a child has myelopathic symptoms, obtain neutral C-spine plain films (see text for details).				Any visit		
27. Obtain polysomnogram.				Between 3-5 yr		
28. Prepare family for transition from early intervention to preschool.				At 30 mo		
29. Discuss sexual exploitation risks.				At least once	At least once	At least once
30. Make developmentally-appropriate plans for menarche, contraception (advocate/offer LARC), and STI prevention.					As developmentally-appropriate, then all subsequent HMV	
31. Discuss risk of DS if patient were to become pregnant.					At least once	At least once
32. Assess for any developmental regression.			All HMV			
33. Discuss and facilitate transitions: education, work, finance, guardianship, medical care, independent living					All HMV starting at 10 yr	

	Do once at this age
	Do if not done previously
	Repeat at indicated intervals
(border)	See report for end point

Abbreviations: DS, Down syndrome; CVS, Chorionic villus sampling; HMV, Health Maintenance Visit; BMI, Body mass index; CDC, Centers for Disease Control; EHDI, Early Hearing Detection and Intervention; NBS, Newborn screen; CAM, Complementary and alternative medicine; BAER, Brainstem auditory evoked response; TM, Tympanic membrane; TAM: transient abnormal myelopoiesis

From Bull MJ, Trotter T, Santoro SL, et al. Health supervision for children and adolescents with Down syndrome. *Pediatrics*. 2022;149(5):e2022057010.

seen in the majority of individuals with DS. Starting oral health preventive programs young, close supervision and support of dental hygiene and chemical adjuvants improve outcomes. Children with DS should first see a pediatric dentist at age 1 year and follow up at least every 6 months. For children who do not tolerate dental examinations or procedures, sedated examinations may be necessary, preferably in a hospital with anesthesiologists familiar with caring for patients with DS.

Endocrine

Children with DS are at risk for congenital and acquired hypothyroidism (HT) and hyperthyroidism (Graves disease [GD]). Thyroid testing should be done at birth as part of newborn screening. Acquired HT and GD are autoimmune disorders with elevated thyroid antibodies. Thyroid-stimulating hormone (TSH) testing can detect both HT and hyperthyroidism and should be checked by 6 months, at 1 year, and then annually thereafter. Most cases of thyroid disorders are asymptomatic and would be missed without screening. Compensated HT refers to mild elevations in TSH with normal T_4, requiring continued monitoring. Low TSH can indicate Graves disease. Children with DS who have GD can develop HT, and those with HT can develop GD. Thyroid disorder should be considered as part of the differential diagnoses with mood or behavior changes, slowing of growth, exophthalmos, high blood pressure, or tachycardia.

Type 1 diabetes mellitus (DM) is more common in children with DS. Screening for type 2 DM, especially in obese individuals, should follow similar guidelines to the typically developing (TD) population.

Cardiac

Congenital heart disease (CHD) affects about half of all children with DS, including atrioventricular (AV) canal defects, atrial septal defect (ASD), ventricular septal defect (VSD), tetralogy of Fallot (TOF), patent ductus arteriosus (PDA), and patent foramen ovale (PFO). All children with DS should have an infant echocardiogram even with a normal physical examination. Cardiology follow-up will be based on echocardiogram findings. Signs of heart failure such as failure to thrive, tachypnea, easy fatigue, or sweating with feeds require expedited referral back to cardiology. Pulmonary hypertension can also occur in children with DS related to congenital heart defects or to respiratory illness. Later in adolescence and adulthood, clinicians should be aware of the increased risk for valvular heart disease and endocarditis.

Pulmonary

Respiratory infections are the most common cause for hospital admission of children with DS without CHD and are a common cause of mortality in children with CHD. Respiratory compromise may present with subtle signs of respiratory distress such as tachypnea, intercostal retraction, shortness of breath, and easy fatigue with exertion. The lack of overt distress may lead clinicians to underestimate the level of respiratory compromise. Both anatomy and immunodeficiency associated with DS can lead to increased risk for upper and lower respiratory infections. Macro and micro pulmonary structural anomalies have been reported. Gastroesophageal reflux disease, swallowing dysfunction, and upper airway differences (including transesophageal [TE] fistula) increase the risk of aspiration.

Sleep

The estimated prevalence of obstructive sleep apnea (OSA) ranges from 31% to 79%, and onset occurs from infancy through adulthood. A sleep study before the age of 4 years is recommended. Clinicians should consider ordering a sleep study at any age, with chronic signs of respiratory compromise when awake or asleep or daytime symptoms of nonrestorative sleep. There is some evidence that OSA causes difficulties in cognitive, behavioral, and adaptive functioning in children with DS. Obesity increases the risks for OSA in many children with DS.

Neurology

Children with DS ages 6-18 months are at increased risk for infantile spasms (IS). The outcome is often better with treatment than the non–DS population with ID but is variable, ranging from no obvious sequelae to ongoing seizure disorders, ASD, and more severe intellectual disability. In addition to the classic signs of IS, change in mental status in an infant or toddler or a plateau or regression in development should lead to prompt neurologic evaluation, including an electroencephalogram (EEG). Children with trisomy 21 are at increased risk for other seizure disorders. There is an increased risk for strokes possibly related to CHD, vascular malformations (including moyamoya syndrome), and other risk factors.

Gastrointestinal

Most children with DS have structural or functional gastrointestinal (GI) comorbidities, many of which can affect individuals across the life span. There is evidence of abnormalities in enteric nerves affecting microanatomy and nerve function. Congenital anomalies include esophageal atresia, TE fistula and duodenal atresia, stenosis, and webs, Hirschsprung disease, and anorectal malformations. Constipation and gastroesophageal reflux disease (GERD) are frequent causes of irritability, GI discomfort, feeding issues, toileting refusal, and incontinence. There appears to be a strong association between GERD, pneumonia, and OSA. Children with DS are also at higher risk of celiac disease, which can cause GI, nutritional, and behavioral issues. The AAP guidelines do not recommend routine celiac screening, but rather to maintain a high index of suspicion with GI complaints, growth faltering, or behavioral concerns. Many others, however, have performed routine screening because many patients with DS who have celiac disease are asymptomatic; there may be a lag of 2-3 years before symptoms appear.

Nutrition/Obesity

In infancy and early childhood, dysphagia, GI conditions, cardiac, and respiratory complications may cause failure to thrive. Weight faltering can continue for older children because of the same issues but may be more intermittent. Because of the high rates of dysphagia in infants with DS, video swallow studies should be considered when there is any sign of weight faltering, aspiration, feeding difficulties, or recurrent respiratory infections. Thickened formulas, low-flow bottles/nipples, or slower paced feeding may be required. Nasogastric (NG) or gastric tube (GT) supplementation to assure adequate nutrition may be needed. Many babies with DS can successfully breastfeed, and clinicians need to be encouraging but watchful for growth faltering.

Obesity becomes more prominent in early childhood and extending into adulthood. In school-age children with DS, those at 50% or greater on DS-specific BMI charts are in the obese range. Thus to gauge the level of overweight for children with DS, the Centers for Disease Control and Prevention (CDC) curves for BMI should be used. When children with DS gain more autonomy in feeding, overeating can become a problem. Many do not appear to satiate and will continue to eat as long as food is presented or will seek food. Caregivers therefore cannot rely on the child's satiety to determine caloric sufficiency. Decreased basal metabolic rates (reduced caloric needs) and lower physical activity can also contribute to obesity. Anticipatory guidance regarding healthy nutritional practices, meal and snack limits, and active lifestyle choices should be part of well-child visits from a young age.

Genitourinary

Renal and urinary tract abnormalities, including ureteropelvic junction obstruction, vesicoureteral reflux, renal hypoplasia, obstructive uropathy and posterior urethral valves, hypospadias,

Table 57.6 Neurodevelopmental, Neurobehavioral, and Psychiatric Characteristics of Trisomy 21

MOTOR SKILLS	
Gross motor skills	0-24 mo: Mild delays initially which widen with age At 2 years 25% walking
Oromotor	Dysphagia 0-6 mo: 50% Self-feeding delays: 70%
Fine motor skill	Early skills delays: ~75% Bimanual skill delays: 100%
SPEECH AND LANGUAGE	
Intelligibility	Frequently unintelligible (parent report): 5-21 yr: 54–57% Motor speech impairment: Delay: 27% Articulation: 60% Apraxia: 33% Dysfluency: Stuttering: 10–45% Cluttering (abnormally rapid or irregular pace or both): 80%
Language	Receptive: Similar to mental age–matched controls Expressive: More delayed relative to mental age–matched controls Syntax: More impaired than expressive vocabulary Pragmatics: Same variety of language functions as mental age–matched peers; may be less likely to ask for clarification
SOCIAL AND EMOTIONAL DEVELOPMENT	
	High sociability Joint attention compared with mental age–matched peers Strong imitation skills Pro-social empathetic responses to others in distress Underexpression of emotional distress Less frequent and shorter social referencing Reduced ability to read facial expressions More restricted repetitive behaviors and interests Average social motivation but lower social cognition
COGNITION	
	Intellectual disability: Mild: ~25% Moderate: ~50% Severe: ~25% Decline in IQ throughout childhood (slowing in developmental progress relative to same-age peers) Strengths: Implicit memory, visual spatial sequencing, visual spatial construction, and nonverbal memory Weaknesses: Working memory capacity, explicit memory, verbal processing, auditory short-term memory, complex visual spatial skills, executive functioning
Oppositional behaviors	70%
Aggression	4–15%
Self-injurious behavior	18%
Autism spectrum disorders	15–20%
ADHD	14–40%
Anxiety disorders	10–22%
Obsessive-compulsive disorders	0.5–4.5%
Depression	5–11%
Catatonia/Down syndrome disintegrative disorder	Multiple case series and case reports

IQ, Intelligence quotient; ADHD, attention-deficit/hyperactivity disorder.

asymptomatic renal pelvic dilatation, kidney ectopia, proteinuria and hematuria, immunoglobulin A (IgA) nephropathy, and focal segmental glomerulosclerosis, occur more frequently than in the general population. There are no current guidelines for regular surveillance, but clinicians need to maintain a high index of suspicion.

Sexuality and Reproductive Health

Males and females with DS undergo puberty at similar ages to peers. In males, after puberty, testicular volume decreases and gonadal dysfunction worsens with age. Males are infertile, with few exceptions. Females with DS are fertile, having a 33% chance of having a child with DS. Menstrual problems, including irregular periods, and premenstrual irritability are common reasons for use of oral contraceptives. Most females manage menstrual periods well, but there may be difficulties with hygiene. Menopause tends to occur early.

Individuals with DS are at increased risk for sexual abuse, and caregivers should discuss appropriate and inappropriate contact and relationships from an early age. Sexuality education should be included in their educational curriculum. Clinicians should discuss sexuality, birth control, and reproductive issues at health maintenance visits.

Hematology-Oncology

AAP guidelines recommend a complete blood cell count (CBC) with differential for all newborns with DS. Neonates with DS commonly have hematologic abnormalities, including peripheral blasts, neutrophilia, thrombocytopenia, or polycythemia. Five to ten percent of neonates with DS have transient myeloproliferative disorder (TMD) (also called *transient abnormal myelopoiesis* [TAM]), which is associated with pathologic variants in *GATA1*. Typically, this resolves spontaneously within the first 1-3 months of life, but 10–20% will develop acute megakaryocytic leukemia (AMKL) in the first 4 years of life. AMKL is sensitive to treatment in most cases and has a good prognosis.

Children with DS are ~20 times more likely to get acute lymphoblastic leukemia (ALL) (1 in 900-1,000) than the typical population, which is associated with pathologic variants in *JAK2*. Treatment trials show lower response rates, higher recurrence rate, and higher treatment-related mortality.

Annual hemoglobin screening for anemia is recommended throughout childhood with additional testing for ferritin and C-reactive protein (CRP) when iron deficiency is suspected. The incidence of anemia in DS may be similar or increased compared with the general population. Other common CBC findings include macrocytosis, low white blood cell (WBC) count, and polycythemia, the clinical significance of which is unknown.

Immunology/Allergy

Individuals with DS are more susceptible to infections because of mild to moderate T- and B-cell lymphopenia, with a decrease in naive lymphocytes, impaired mitogen-induced T-cell proliferation, reduced specific antibody responses to immunizations, and defects of neutrophil chemotaxis. Nonimmunologic anatomic factors also contribute to the increased risk of respiratory infections. Children with DS with significant numbers of serious infections or difficulty clearing infections need further immunologic evaluation.

Autoimmune disorders are also more common, including thyroid disorders, celiac disease, alopecia areata, vitiligo, type 1 DM, juvenile idiopathic arthritis, and systemic lupus erythematosus.

Musculoskeletal

Individuals with DS have short stature across the life span and stop growing sooner than typical peers, the mechanism of which is unclear. Growth hormone is rarely deficient. Ligamentous laxity is common, especially in the ankles and feet. Inflammatory arthritis is underrecognized, and scoliosis is more common. Joint instability is most apparent in the neck (atlantoaxial instability [AAI]), hips, and knees. Joint pain and impaired mobility can contribute to motor skills deficits, impede independence, and add to behavioral difficulties.

Radiographic screening for AAI is not recommended because flexion/extension neck x-rays are not predictive for future neurologic risk. Signs and symptoms of AAI occur because of compression of the spinal cord from slippage of the C1 or C2 vertebrae, which can occur after an injury or anesthesia but can also be seen spontaneously. Neck pain, stiffness, and/or myelopathic signs and symptoms (e.g., change in gait, bowel, or bladder pattern or weakness) should prompt referral to orthopedics or neurosurgery. Universal neck precautions are recommended for all children with DS, assuming that all are at risk for injury from AAI, including limited participation in any activities that would be associated with forcible neck movement such as contact sports, diving, and universal cervical precautions with intubation procedures/surgery. Children with DS should be secured in rear-facing car seats until 40 pounds and may need harness-style car restraints over 40 pounds.

Hip instability resulting in recurrent (often painless and voluntary) hip dislocation and patellar instability can impair ambulation and may require surgical interventions.

Dermatology

Although causing minor morbidity, dermatologic problems can be highly distressing to patients and families due to appearance (e.g., alopecia), discomfort (e.g., eczema, hidradenitis), or intractability (e.g., onychomycosis). Common conditions include folliculitis, hidradenitis suppurativa, eczematous and seborrheic dermatitis, autoimmune alopecia and vitiligo, fungal infections including tinea pedis and onychomycosis, angular cheilitis, and hyperkeratosis.

DEVELOPMENTAL AND BEHAVIORAL CHARACTERISTICS

Development and behavior concerns are almost universal. Some concerns are easily explained and remediated and are responsive to appropriate therapeutic or behavioral interventions, but others may indicate an underlying neurobehavioral disorder such as autism, ADHD, depression, or anxiety (Table 57.6). Thinking through the categories that follow will help clinicians understand this complexity and direct families to appropriate resources.

Motor Skills

Children with DS often have marked delays in motor skills in early development related to hypotonia, ligamentous laxity, and lack of coordination.

Acquisition of early gross motor skills is foundational for postural control, feeding, visual motor development, socialization, and communication. Without stimulation and support, infants with DS may persist in lax postural control, further adding to motor delays. Through toddler and childhood many gradually improve but have persistent deficits in motor control and coordination and more difficulty with speed and complex postural changes, as well as persistent hypotonia. **Physical therapy** in the first years of life concentrates on core strengthening and ensuring acquisition of adaptive motor planning that supports effective ambulation. Gait abnormalities and persistent low core strength often require ongoing physical therapy. Developing physical literacy in recreational fitness activities, such as swimming, and community sports can also support health and well-being in school-age and adult years.

Oromotor skills are often delayed, with dysphagia in half of infants, requiring feeding therapy, thickening of formula, low-flow nipples, pacing between swallows, and sometimes supplemental enteral feeding. **Feeding therapy** helps young children learn to handle food boluses, chew, and drink from a cup.

Fine motor skills are also delayed, although they seem to be acquired in the same sequence as typically developing peers, but with a wider age range of acquisition. Most unaffected children are able to write their name between 60 and 72 months, but in children with DS, this usually occurs between 120 and 216 months. **Occupational therapy** often helps remediate or compensate for motor difficulties interfering with independence in activities of daily living.

Speech and Language Skills

Individuals with DS often have difficulty speaking clearly enough to be readily comprehensible to listeners across the life span resulting in communication breakdowns, which can be frustrating to both parties. Typical children are 90–100% intelligible by age 4 years. In individuals with DS over 50% of parents reported frequent difficulties in intelligibility over the age of 5 years into adulthood, and almost all qualify for a diagnosis of a motor speech disorder. Differences in voice quality, articulation, phonology, fluency, prosody, and motor coordination (apraxia) all contribute to making speech hard to understand (see Chapter 53). The complexity of speech impairments in children with DS requires **speech therapy** evaluation with targeted interventions for each individual.

Children with DS relative to children matched for nonverbal skills show similar abilities in receptive vocabulary but impairments in expressive vocabulary, syntax, grammar, and verbal short-term

memory indicative of a specific language impairment (SLI). The frequency of such impairments requires comprehensive language assessment for all children with DS. The language impairment may be associated with decreased ability to express thoughts and feelings verbally and use of fewer words in answer to questions or to carry on a conversation.

Misunderstandings may occur if the individual refers to past events in the present tense or thinks that something described as a future event will happen immediately. Verbal short-term memory deficits affect comprehension of more complex language (e.g., multistep instructions, complex sentences, conversation, and narrative) and reading comprehension. Visual, contextual, and multisensory supports incorporated into both receptive and expressive language can be helpful.

Speech and language intervention has been shown to be effective, especially when of higher intensity; focused on individual needs and targeted skills; and when taking into account the individual's age, interests, and motivators. Use of **applied behavior analysis** to teach communication skills improves outcomes. Incorporating interventions across contexts (classroom, home, and community settings) and into pragmatic language situations outside of structured learning settings (e.g., peer interaction, conversation) supports generalization of skills learned in therapy. For some individuals with DS, speech and language intervention will be required through school and possibly into adulthood.

Social and Emotional Development

Social and emotional development occurs as a complex transactional process between the child and their social partners. Children with developmental delays will likely also have delays in their social interactions, social communication, and play. Children with DS often have a strong orientation toward sociability. From early infancy, mutual gaze in babies with DS emerges more slowly but once established tends to last longer, with sometimes strong preferences for looking at people as opposed to toys and other objects. Development of joint attention is commensurate with developmental age-matched peers and may be a relative strength. Strong imitation skills are noted in children with DS. Children with DS show stronger pro-social empathetic responses to others' distress, but their own expression of distress tends to be dampened (often described as high pain tolerance or, in older children, a perceived reluctance to acknowledge feelings of distress).

There are relative weaknesses in social development, which can help explain some of the social difficulties caregivers encounter. Children with DS have been shown to socially reference less frequently, with shorter glances toward others, and some have more difficulty interpreting the facial expressions of others. Older children with DS have more restricted repetitive behaviors and interests, including rigidity and insistence on sameness. Despite typical social motivation, they may have difficulties with social cognition and difficulty gaining and maintaining friendships. Having friends has been associated with improved quality of life in children with DS. Most adolescents are happy with their level of friendships, but friends may include helpers and adult companions. Leisure time is often spent at home with family or by themselves, and socializing with same-age peer-friends occurs predominantly in the context of common educational or community activities. Building healthy sustained friendships with both TD peers and those with developmental disabilities often requires active ongoing caregiver and community support to prevent social isolation and loneliness as children transition to adulthood.

Cognition

Individuals with DS have varied degrees of intellectual and learning disabilities. Intelligence quotient (IQ) scores of adults with DS are mostly in the 40s-60s, and tests of adaptive functioning typically have standard scores in the low 50s. In children with DS, IQ scores tend to decline with age because progress is slower than same-age peers, and deficits are more marked in higher-level thinking. Thus the gap between children with DS and same-age peers widens with age. An actual plateau in functioning before mid-adolescence or a decline at any age is not typical and should prompt thorough etiologic evaluation.

IQ scores are of limited value for intervention planning, as they provide limited information about relative strengths and weaknesses. Children with DS often have relative strengths in areas of imitation, implicit memory, visual spatial sequencing, visual spatial construction, and nonverbal memory. Relative weaknesses tend to occur in working memory capacity, explicit memory, verbal processing, auditory short-term memory, more complex visual spatial skills (mental rotation, closure, wayfinding), and executive functioning (see Chapter 49). Recognizing a child's individual learning profile and building on strengths while supporting weaknesses will help caregivers, teachers, and therapists work together to teach children effectively to their potential.

Children's reading skills are generally commensurate with their nonverbal mental age. Many children with DS can learn to read, some phonologically, some orthographically. Reading comprehension largely relies on language comprehension skills and is often more difficult.

Mathematics is much more difficult because of weak working memory, language deficits, and fine motor skills. Math interventions generally include direct instruction, modeling, guided and repeated practice, and use of concrete materials.

Neurobehavioral Challenges and Disorders

Autism Spectrum Disorder

Due to the sociability associated with children with DS, ASDs have been underrecognized in the past but are estimated to occur in 15–20% of children with DS. Studies also have shown that autism symptoms are not attributable to the degree of developmental disability and that individuals with DS and ASD are distinct from those with DS alone. *Children with DS who show high levels of repetitive behavior, maladaptive behaviors (e.g., aggression, self-injury, destructive behaviors), social isolation, or difficulty with reciprocal social interaction should be referred for further evaluation, even when overtly sociable.* Children with ASD require specialized behavioral and educational interventions with an emphasis on functional communication, social and play skills development, and sensory-based supports (see Chapter 58).

ADHD

The reported incidence of ADHD in children with DS varies greatly, from 14% to 44%. Inattention, impulsivity, and hyperactivity, the core symptoms of ADHD, are nonspecific, and it can be difficult to differentiate all the factors contributing to these symptoms in children with DS (see Chapter 50). From a clinical perspective, the diagnosis of ADHD relies on reports of ADHD symptoms from two different settings (usually parent and teacher) and dysfunction caused by the ADHD symptoms in areas such as learning, socialization, and safety. Medication use in ADHD has been shown to be effective in children with DS, but the response rates are lower than in typical peers with ADHD. Further, there are higher rates of significant side effects, with some children showing decline in behavior and cognitive performance on medication.

Aggression and Self-Injurious Behaviors

Aggressive behavior is more common in children with many genetic disorders, including DS. The estimated incidence in DS is 4–15%, which is higher than the general population but less than many other genetic syndromes. Aggression disproportionately affects quality of life for the individual and family members and may result in the use of medications and more restrictive educational placements. These behaviors occur more often in males and in individuals with ASD, ADHD, or poor communication skills. Self-injurious behavior (SIB) occurs in

~18%. Individuals with DS who engage in SIB are likely to have lower cognitive and communication ability (may be nonverbal), more repetitive behaviors, higher levels of activity and impulsivity, and fewer social interactions. Assessment of aggression or SIB should include a functional behavioral analysis (FBA) along with overall skills assessment with emphasis on communication. New onset or escalation of aggression or SIB should also include careful assessment for potential sources of pain or discomfort that may exacerbate these behaviors. Behavioral interventions designed based on the results of the FBA should be the initial intervention. Medications may be needed to address symptoms of ADHD, irritability, mood, or anxiety.

Oppositional Behaviors

Disobedience and stubbornness are common. In some cases, this behavior may relate, at least in part, to differences in cognitive processing. Children with DS have difficulty shifting attention or disengaging from activities. They often desire sameness and resist changes to routine or to the way they think things should be done. Difficulties with language comprehension or frustration with a task or trying to express oneself may result in behaviors that are seen as oppositional. When combined with difficulty problem solving, low frustration tolerance, and emotional dysregulation, disruptive or sometimes verbally or physically aggressive behaviors may result. Before diagnosing a child as having oppositional defiant disorder (see Chapter 42), clinicians should try to understand potential comprehension or skill deficits that may be contributing to the behavior. If the child has difficulty with transitions, interventions to help them shift activities more easily such as transition routines, warnings, or countdowns may be most helpful. Visual schedules can also be helpful to prepare the child for what is next, as can providing some additional time for the transition. Simplifying language can help avert communication frustration.

Anxiety

There is an increased prevalence of anxiety disorder in children with DS compared with typical peers. Generally, anxiety disorders are diagnosed based on verbal descriptions of fear or worry and the impact of the fear or worrying on functioning or individual distress. Whereas some individuals with DS have the language skills to describe these experiences, others do not. Clinicians often need to rely on the history from caregivers and contextual cues. Behavioral reactions to anxiety can result in flight-or-fight responses. Thus anxiety could manifest with aggressive or escape/avoidance behaviors. Cognitive-behavioral therapy or exposure therapies can be helpful, and medication management is sometimes needed when anxiety is overwhelming or affects sleep or daytime functioning. Evidence for effectiveness of intervention in DS specifically is sparse.

Obsessive-Compulsive or Perseverative Behaviors

Children and adults with DS often need specific things to be a certain way or may have repetitive patterns of behavior that can seem obsessive or compulsive. They may spend many minutes arranging pillows on their bed, need all doors in the house to be shut, make long lists, or perseveratively ask about upcoming events. These behaviors can be associated with anxiety, and the possibility of increased anxiety should be investigated if there are sudden increases in intensity or frequency of these behaviors.

Depression

The prevalence of depression in DS ranges from 4% to 11%, with most studies being done in adults. This may be an underestimation, as depression in individuals with intellectual disability can be difficult to diagnose because of limited abilities to self-report internal mood states. Behavioral symptoms can include anxiety, increases in obsessive-compulsive behaviors, depressed affect, crying for no reason, lack of emotion, social isolation, anhedonia, irritability with increases in outbursts or aggression, sleep disturbance, psychomotor retardation, low self-esteem, catatonia, and psychosis. Clinicians need to consider potential contributing factors, including medical factors, recent life stressors, trauma, and family history. Anecdotally, interventions that involve reengagement in previously enjoyed activities and treatment with selective serotonin reuptake inhibitors (SSRIs) can be effective.

Catatonia (Also Known as Down Syndrome Disintegrative Disorder or Down Syndrome Regression Disorder)

Older children and young adults can experience a sudden regression in communication, socialization, and daily living skills associated with psychomotor retardation, negative mood or mood lability, refusal to participate in activities, social withdrawal, and insomnia with signs and symptoms of catatonia on the Bush Frances Catatonia Scale (see Chapter 47.3). Patients should undergo a medical evaluation for mental status change. Contributing etiologic factors include stressful events, depression, anxiety, or high physiologic stress. Treatment consists of addressing the underlying suspected cause and may include a trial of Ativan and then electroconvulsive therapy (ECT) if Ativan is unsuccessful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 58

Autism Spectrum Disorder

Carolyn F. Bridgemohan and Carol C. Weitzman

DEFINITION

Autism spectrum disorder (ASD) is a neurobiologic disorder with onset in early childhood. The key features are impairment in social communication and social interaction and restricted and repetitive behaviors. The presentation of ASD can vary significantly from one individual to another, as well as over the course of development for a particular child. There is currently no diagnostic biomarker for ASD. Accurate diagnosis therefore requires careful review of the history and direct observation of the child's behavior.

DIAGNOSTIC CRITERIA AND SYMPTOMS

The diagnostic criteria in the *Diagnostic and Statistical Manual, Fifth Edition* (DSM-5) focus on symptoms in two primary domains: (1) social communication and social interaction and (2) restricted interests and repetitive behaviors (Table 58.1). To meet criteria for ASD, the symptoms need to have been present since the early developmental period, significantly affect functioning, and not be better explained by the diagnosis of intellectual disability (ID) or global developmental delay (GDD; Chapter 56). Table 58.2 provides associated features not included in the DSM-5 criteria.

Symptoms can present in infancy, with reduced response to name and unusual use of objects being strong predictors for risk of ASD. However, symptoms before age 12 months are not as reliably predictive of later diagnosis. Individuals with milder severity may not present

Table 58.1 DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity.
   2. Deficits in nonverbal communicative behaviors used for social interaction.
   3. Deficits in developing, maintaining, and understanding relationships.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects, or speech.
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.
   3. Highly restricted, fixated interests that are abnormal in intensity or focus.
   4. Hyperreactivity or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.

C. Symptoms must be present in the early developmental period (may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. (Copyright 2013). American Psychiatric Association, pp. 50–51.

Table 58.2 Associated Features of Autism Not in DSM-5 Criteria

Atypical language development and abilities
- Age <6 yr: frequently disordered and delayed in comprehension; two thirds have difficulty with expressive phonology and grammar
- Age ≥6 yr: disordered pragmatics, semantics, and morphology, with relatively intact articulation and syntax (i.e., early difficulties are resolved)

Motor abnormalities: motor delay; hypotonia; catatonia; deficits in coordination, movement preparation and planning, praxis, gait, and balance

For version with full references, see American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington DC: American Psychiatric Association; 2013. Adapted from Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet*. 2014;383:896–910.

until preschool or school age, when the social demands for peer interaction and group participation are higher.

Social Communication and Social Interaction

Individuals with ASD have difficulty understanding and engaging in social relationships. The problems are pervasive and affect three major areas: social-emotional reciprocity, nonverbal communication, and understanding of social relationships. The presentation can vary with severity and developmental functioning. A diagnosis of ASD requires the presence of symptoms from all three categories (Table 58.3).

Social-Emotional Reciprocity

Reduced social interactions in ASD may range from active avoidance or reduced social response to having an interest in, but lacking ability to initiate or sustain, an interaction with peers or adults. A young child with ASD may not respond when their name is called, may exhibit limited showing and sharing behaviors, and may prefer solitary play. In addition, the child may avoid attempts by others to play and may not participate in activities that require taking turns, such as peek-a-boo and ball play. An older child with ASD may have an interest in peers but may not know how to initiate or join in play. The child may have trouble understanding the rules of conversation and may either talk at length about an area of interest or abruptly exit the interaction. Younger children often have limited capacity for imaginative or pretend play. Older children may engage in play and conversation but lack flexibility and may be highly directive to peers. Some children with ASD interact well with adults but struggle to interact with same-age peers.

Nonverbal Communicative Behavior

Difficulties with nonverbal communication may manifest as reduced or overly intense use of eye contact and gestures such as pointing. Children may also show reduced awareness or response to the eye gaze or pointing of others. They may use eye contact only when communicating a highly preferred request or may have difficulty coordinating the use of nonverbal with verbal communication. Children with ASD may have limited range of facial social-communicative expression or expressed emotion.

Developing, Maintaining, and Understanding Relationships

Children with ASD have limited insight regarding social relationships. They may have difficulty understanding the difference between a true friend and a casual acquaintance, and even when the definitions are well understood, there may still be difficulty in developing and maintaining more intimate relationships They have trouble picking up on the nuances of social interactions and understanding social expectations for polite behavior. They may have reduced understanding of personal boundaries and may stand too close to others. In addition, they can have trouble understanding and inferring others' emotions and are less likely to share emotion or enjoyment with others. Adolescents and young adults have difficulty engaging in group interactions and navigating romantic relationships.

Restrictive and Repetitive Behavior

A diagnosis of ASD requires the presence of two of the four symptoms of restrictive and repetitive patterns of behavior discussed next.

Stereotyped Motor Movements or Speech

Stereotyped (or stereotypic) movements and repetitive behaviors may include hand flapping, finger movements, body rocking and lunging, jumping, running and spinning, and repetitive speech such as echoing words immediately after they are said. Repetitive patterns of play may be present, such as lining up objects, repetitively turning light switches on and off or opening and closing doors, spinning objects, or arranging toys in a specific manner. These repetitive patterns may not be seen in very young toddlers but may develop as they get older. Stereotyped movements can change over time and in older children are seen more often in individuals with lower cognitive functioning.

Insistence on Sameness

Children with ASD have difficulty tolerating transitions or change. They may insist on certain routines or schedules and can become very distressed with unexpected events or new situations. They may repeat scripts from shows or movies or watch the same portion of a video repeatedly. Intolerance for change can cause significant impairment and irritability and have an effect on child and family function.

Restricted Interests

This symptom may manifest as interests that seem of greater intensity when compared to same-age peers. Younger children may play with a limited range of toys or may insist on retaining a small object in each hand. Older children may have a strong preference for a particular story or movie. The area of interest may be shared by peers (e.g., Disney movies, Legos, Thomas the Train) but *unusual* in its intensity. Other affected children may have interests that are both intense and

Table 58.3 Signs and Symptoms of Possible Autism in Preschool Children (or Equivalent Mental Age)

Spoken Language
- Language delay (in babbling or using words; e.g., using <10 words by age 2 yr).
- Regression in, or loss of, use of speech.
- Spoken language (if present) may include unusual features, such as vocalizations that are not speechlike; odd or flat intonation; frequent repetition of set words and phrases (echolalia); reference to self by name or "you" or "she" or "he" beyond age 3 yr.
- Reduced and/or infrequent use of language for communication (e.g., use of single words, although able to speak in sentences).

Responding to Others
- Absent or delayed response to name being called, despite normal hearing.
- Reduced or absent responsive social smiling.
- Reduced or absent responsiveness to other people's facial expressions or feelings.
- Unusually negative response to the requests of others ("demand avoidance" behavior).
- Rejection of cuddles initiated by parent or caregiver, although the child may initiate cuddles.

Interacting with Others
- Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space.
- Reduced or absent social interest in others, including children of own age—may reject others; if interested in others, child may approach others inappropriately, seeming to be aggressive or disruptive.
- Reduced or absent imitation of others' actions.
- Reduced or absent initiation of social play with others; plays alone.
- Reduced or absent enjoyment of situations that most children like (e.g., birthday parties).
- Reduced or absent sharing of enjoyment.

Eye Contact, Pointing, and Other Gestures
- Reduced or absent use of gestures and facial expressions to communicate (although may place an adult's hand on objects).
- Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication.
- Reduced or absent social use of eye contact (assuming adequate vision).
- Reduced or absent "joint attention" (when one person alerts another to something by means of gazing, finger pointing, or other verbal or nonverbal indication for the purpose of sharing interest). This would be evident in the child from lack of:
  - Gaze switching
  - Following a point (looking where the other person points to—may look at hand)
  - Using pointing at or showing objects to share interest

Ideas and Imagination
- Reduced or absent imagination and variety of pretend play.

Unusual or Restricted Interests and/or Rigid and Repetitive Behaviors
- Repetitive "stereotypic" movements such as hand flapping, body rocking while standing, spinning, and finger flicking.
- Repetitive or stereotyped play (e.g., opening and closing doors).
- Overfocused or unusual interests.
- Excessive insistence on following own agenda.
- Extremes of emotional reactivity to change or new situations; insistence on things being "the same."
- Overreaction or underreaction to sensory stimuli, such as textures, sounds, or smells.
- Excessive reaction to the taste, smell, texture, or appearance of food, or having extreme food fads.

Adapted from Baird G, Douglas HR, Murphy MS. Recognizing and diagnosing autism in children and young people: Summary of NICE guidance. *BMJ*. 2011;343:d6360, Box 1, p. 901.

unusual, such as an interest in brands of vehicles, license plate numbers, or fans and heating systems. These interests interfere with social interactions; a child may only want to talk about their area of interest or may insist that peers act out a particular story in a rigid and inflexible manner.

Hyporeactivity or Hyperreactivity to Sensory Input

Children with ASD may be overly sensitive to sensory input, such as noise, smells, or texture. Children may scream or react strongly when they hear a siren or vacuum and may gag and choke with certain foods or odors. They may refuse to wear certain clothing or may become very distressed with bathing or with cutting nails and hair. Conversely, some affected children seem to crave sensory input. They may engage in repetitive jumping or hugging and may smell or lick objects or people. Young children may inappropriately touch the face or hair of others.

Diagnosing ASD with DSM-5 criteria can be challenging in very young children because of reduced expression of repetitive behaviors, particularly stereotyped behavior and intense interests. Studies monitoring development in high-risk young children who have an older sibling with ASD indicate these additional symptoms may emerge over time. This creates a dilemma for specialty clinicians evaluating very young children for ASD, because they may not be able to endorse sufficient symptoms to make an early diagnosis and access specialized intervention services.

Severity Levels Defined in DSM-5

Severity levels in ASD are based on the level of support the individual requires in each of the major domains impacted—social communication and restricted interests and repetitive behavior. Levels range from "needing support" (level 1), to "needing substantial support" (level 2), to "needing very substantial support" (level 3) (Table 58.4).

Specifiers Defined in DSM-5

A formal diagnosis of ASD also includes documenting associated conditions, including whether the individual has cognitive and/or language impairment; any related medical, genetic, or environmental factors; and any other neurodevelopmental or behavioral health conditions, including catatonia (Table 58.5). This process helps to better characterize the presentation in an individual child and ensures that the diagnosis has been made by considering the symptoms in the context of the child's current cognitive and language abilities.

EPIDEMIOLOGY

The prevalence of ASD is estimated at 1 in 36 persons by the U.S. Centers for Disease Control and Prevention (CDC). This information comes from prevalence data of 8-year-olds derived from 11 sites participating in the Autism and Developmental Disabilities Network (ADDM) and shows a greater than 300% increase in prevalence since systematic surveillance began in the year 2000. The increased prevalence relates, at least in part, to improved diagnosis and case finding, as well as inclusion of less severe presentations within the autism *spectrum*. There is a 4:1 male predominance, although new emerging information suggests that the prevalence in females may be higher than previously believed. Females with ASD often use "camouflaging," which is intentionally or unconsciously hiding social communication difficulties by mimicking the facial expressions of others, having more effective compensatory behaviors, and displaying less clearly unusual preoccupying interests. All of these things, including clinician bias, may decrease girls with ASD being diagnosed. The prevalence is increased in siblings (up to 18% recurrence rate) and particularly in identical twins. There are no racial or ethnic differences in prevalence. Individuals from racial minorities and lower socioeconomic status are at risk for later

Table 58.4 DSM-5 Severity Levels for Autism Spectrum Disorder

SEVERITY LEVEL	SOCIAL COMMUNICATION	RESTRICTED, REPETITIVE BEHAVIORS
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. *For example,* a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. *For example,* a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. *For example,* a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

From the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (Copyright 2013). American Psychiatric Association, p. 52.

diagnosis, although the most recent prevalence data suggest that this gap is closing.

ETIOLOGY

The etiology of ASD is thought to result from disrupted neural connectivity and is primarily impacted by genetic variations affecting early brain development. Animal models and studies of individuals with ASD indicate changes in brain volume and neural cell density in the limbic system, cerebellum, and frontotemporal regions. One study documented changes in early brain development, characterized as "hyperexpansion of cortical surface area," at age 6-12 months on brain MRI, which correlated with later development of impaired social skills. Functional studies show abnormalities of processing information, particularly related to foundational social skills such as facial recognition. The disruptions in early brain development likely are responsive to treatment. Early developmental therapies in young children with ASD have demonstrated the capacity for normalization of electrophysiologic response to visual stimuli, including faces.

Numerous genes involved in brain development and synaptic function have been associated with ASD. Pathogenic variants that include large genetic deletions or duplications and small sequencing changes have been implicated; these can be inherited or occur de novo. Heterozygous mutations in genes, such as present in deletion or duplication of 15q11.2 or 16p11.2, may have variable expression within a family. Rare recessive mutations have been implicated in some populations with high levels of consanguinity. Patients with a number of genetic syndromes (e.g., fragile X, Down, Smith-Lemli-Opitz, Rett, Angelman, Timothy, Joubert), as well as disorders of metabolism and mitochondrial function have higher rates of ASD than the general population (Tables 58.5, 58.6, and 58.7).

There is also possible evidence for environmental contributions to ASD. Older maternal or paternal age may increase the risk of ASD. In addition, factors influencing the intrauterine environment, such as maternal obesity or overweight, short interval from prior pregnancy, premature birth, and certain prenatal infections (e.g., rubella, cytomegalovirus), are associated with ASD. Population-level associations have been investigated for environmental toxins such as organophosphates, pesticides, air pollution, and volatile organic compounds. An epigenetic model is considered one explanation for the etiology; individuals with genetic vulnerability may be more sensitive to environmental factors influencing early brain development.

Despite frequent concerns from families that vaccines or the preservatives in vaccines lead to ASD, *there is no evidence to support this claim.* Multiple research studies and meta-analyses have failed to show an association of vaccines with ASD.

No biomarkers are available yet, but there is emerging evidence from neuroimaging findings, electrophysiologic testing, and eye tracking that hold the promise for presymptomatic detection along with accurate clinical diagnosis and prognostic assessment.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ASD is complex because many conditions in the differential can also occur with ASD. The most important conditions to consider in young children are language disorder (see Chapter 53), ID or GDD (Chapter 56), and hearing loss (Chapter 55). Children with **language disorder** may have impairments in social communication and play; their social and play skills, however, are typically on par with their language level. In addition, they do not have associated restricted and repetitive behavior or atypical use of language, such as scripting. The diagnosis of **social communication disorder** is also distinguished from ASD by the lack of restrictive and repetitive behaviors. Children with **ID** or **GDD** may have delays in social and communication skills as well as stereotyped behavior. However, social and communication skills are typically commensurate with their cognitive and adaptive functioning. Children with **hearing loss** may present with some "red flags" for ASD, such as poor response to name. However, they typically develop nonverbal communication and play skills as expected and do not have stereotyped or restricted behavior patterns.

In older children, disorders of attention, learning, and mood regulation must be considered in the differential diagnosis of ASD. Children with **attention-deficit/hyperactivity disorder (ADHD)** may present with reduced eye contact and response to name caused by poor attention rather than lack of social awareness. Children with ADHD, however, do not have associated impairments in shared enjoyment and social reciprocity or repetitive behaviors. Children with **social anxiety** or other anxiety disorders may present with some symptoms suggestive of ASD. Shy children may have reduced eye contact and social initiation. Anxious children can be resistant to change and prefer familiar routines. Children with anxiety, however, typically will have preserved social interest and insight and will not exhibit high levels of stereotyped behaviors. **Reactive attachment disorder** can be difficult to distinguish from ASD, particularly in younger children with a history of prolonged

Table 58.5 Common Co-occurring Conditions in Autism Spectrum Disorder (ASD)

COMORBIDITY	INDIVIDUALS WITH AUTISM AFFECTED	COMMENTS
DEVELOPMENTAL DISORDERS		
Intellectual disability	~45%	Prevalence estimate is affected by the diagnostic boundary and definition of intelligence (e.g., whether verbal ability is used as a criterion). In individuals, discrepant performance between subtests is common.
Language disorders	Variable	An autism-specific language profile (separate from language disorders) exists, but with substantial interindividual variability.
Tic disorders	14–38%	~6.5% have Tourette syndrome.
Motor abnormality	≤79%	See Table 58.2.
GENERAL MEDICAL DISORDERS		
Epilepsy	35-46%	Increased frequency in individuals with intellectual disability or genetic syndromes. Two peaks of onset: early childhood and adolescence. Increases risk of poor outcome.
Gastrointestinal problems	9–70%	Common symptoms include chronic constipation, abdominal pain, chronic diarrhea, cyclic vomiting, and gastroesophageal reflux. Associated disorders include gastritis, esophagitis, gastroesophageal reflux disease, inflammatory bowel disease, celiac disease, Crohn disease, and colitis.
Immune dysregulation	≤38%	Associated with allergic and autoimmune disorders.
Genetic disorders	10–20%	Collectively called *syndromic autism.* Examples include fragile X syndrome (21–50% of individuals affected have autism), Rett syndrome (most have autistic features but with profiles different from idiopathic autism), tuberous sclerosis complex (24–60%), Down syndrome (5–39%), phenylketonuria (5–20%), CHARGE syndrome* (15–50%), Angelman syndrome (50–81%), Timothy syndrome (60–70%), and Joubert syndrome (~40%).
Sleep disorders	50–80%	Insomnia is the most common.
BEHAVIORAL HEALTH DISORDERS		
Any behavioral health disorder	70–90%	
ADHD	40–70%	
Anxiety	~40%	Common across all age-groups. Most common are social anxiety disorder (13–29% of individuals with autism) and generalized anxiety disorder (13–22%). High-functioning individuals are more susceptible (or symptoms are more detectable).
Catatonia	Unknown	Autism shutdown disorder similar to Down syndrome disintegrative disorder (see Chapters 47.3 and 57).
Depression	12–70%	Common in adults, less common in children. High-functioning adults who are less socially impaired are more susceptible (or symptoms are more detectable).
Obsessive-compulsive disorder (OCD)	7–24%	Shares the repetitive behavior domain with autism that could cut across nosologic categories. Important to distinguish between repetitive behaviors that do not involve intrusive, anxiety-causing thoughts or obsessions (part of autism) and those that do (and are part of OCD).
Psychotic disorders	12–17%	Mainly in adults. Most commonly recurrent hallucinosis. High frequency of autism-like features (even a diagnosis of ASD) preceding adult-onset (52%) and childhood-onset schizophrenia (30–50%).
Substance use disorders	≤16%	Potentially because individual is using substances as self-medication to relieve anxiety.
Oppositional defiant disorder	16–28%	Oppositional behaviors could be a manifestation of anxiety, resistance to change, stubborn belief in the correctness of own point of view, difficulty seeing another's point of view, poor awareness of the effect of own behavior on others, or no interest in social compliance.
Eating disorders	10-21%	Avoidant/restrictive food intake may lead to nutrient deficiencies and poor growth.
PERSONALITY DISORDERS†		
Paranoid personality disorder	0–19%	Could be secondary to difficulty understanding others' intentions and negative interpersonal experiences.
Schizoid personality disorder	21–26%	Partly overlapping diagnostic criteria.
Schizotypal personality disorder	2–13%	Some overlapping criteria, especially those shared with schizoid personality disorder.
Borderline personality disorder	0–9%	Could have similarity in behaviors (e.g., difficulties in interpersonal relationships, misattributing hostile intentions, problems with affect regulation), which requires careful differential diagnosis. Could be a misdiagnosis of autism, particularly in females.
Obsessive-compulsive personality disorder	19–32%	Partly overlapping diagnostic criteria.
Avoidant personality disorder	13–25%	Could be secondary to repeated failure in social experiences.

Continued

Table 58.5 Common Co-occurring Conditions in Autism Spectrum Disorder (ASD)—cont'd

COMORBIDITY	INDIVIDUALS WITH AUTISM AFFECTED	COMMENTS
BEHAVIORAL DISORDERS		
Aggressive behaviors	≤68%	Often directed toward caregivers rather than noncaregivers. Could be a result of empathy difficulties, anxiety, sensory overload, disruption of routines, and difficulties with communication.
Self-injurious behaviors	≤50%	Associated with impulsivity and hyperactivity, negative affect, and lower levels of ability and speech. Could signal frustration in individuals with reduced communication, as well as anxiety, sensory overload, or disruption of routines. Could also become a repetitive habit. Could cause tissue damage and need for restraint.
Pica	~36%	More likely in individuals with intellectual disability. Could be a result of a lack of social conformity to cultural categories of what is deemed edible, or sensory exploration, or both.
Suicidal ideation or attempt	11–14%	Risks increase with concurrent depression and behavioral problems and after being teased or bullied.

*Coloboma of the eye; heart defects; atresia of the choanae; retardation of growth and development, or both; genital and urinary abnormalities, or both; and ear abnormalities and deafness.
†Particularly in high-functioning adults.
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
Adapted from Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet*. 2014;383:896–910.

Table 58.6 Syndromes with Autistic-Like Behaviors

CHROMOSOME DELETIONS	OTHER SYNDROMES
1q21	2q37 monosomy
7q11.28	Angelman
16p11.2	Bardet-Biedl
17q12	Cardiofaciocutaneous
2q23.1 (*MBD5**)	CHARGE association
12q24.3	Cohen
Cri-du-chat (5p15.2-p15.33)	Congenital rubella
22q deletion syndrome	Cornelia de Lange
Jacobsen (11q23.2)	Costello
Phelan-McDermid (*SHANK3*; 22q13)	*FOXG1* variants
Pitt-Hopkins (18q21.2)	Fragile X
	Hypomelanosis of Ito
CHROMOSOME DUPLICATIONS	Joubert
15q11.1-q13.3	Kleefstra (*EHMT1*)
7q11.23	Lujan-Fryns
18q12.2	Moebius sequence
16p11.2	Muscle-eye brain disease
1q21.1	Myotonic dystrophy
22q11.2	Neurofibromatosis
Potocki-Lupski (17p11.2)	Nonsyndromic intellectual disability due to *SYNGAP1* variants
EPILEPSY ENCEPHALOPATHIES, EPILEPSY	Noonan
Cortical dysplasia focal epilepsy	Oculoauriculovertebral spectrum (including Goldenhar)
SCN1A-related syndromes (Dravet, Lennox Gastaut, others)	Partial monosomy 1p36
Early myoclonic encephalopathies (Ohtahara: *STXBP1*, *ARX*, *SIK1*)	Partial tetrasomy 15
SCN2A-related syndromes (West, others)	Prader-Willi
SLC6A1 myotonic-atonic epilepsy	PTEN variants
HCN1-related epilepsies	Rett complex (female >> male)
CDKL5	Ring chromosome 14
SCN8A	*SETD1B* variants
PCDH19	Sex chromosome aneuploidies
SCL35A2-related disorders	Sashi-Pena (*ASXL2*)
Epilepsy-aphasia spectrum (Landau-Kleffner; *GRIN2A*; continuous spike wave during low-wave sleep)	Smith-Lemli-Opitz
	Smith-Magenis
Juvenile myoclonic epilepsy (*RING2*)	Sotos
	Timothy
	Tolchin-Le Caignec (TOLCAS)
	Trisomy 21
	Tuberous sclerosis
	WAGR
	Wiedemann-Steiner (*KMT2A*)
	Williams

*Italics denoted affected gene
Modified from Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 32.6, p. 537.

Table 58.7 Inborn Errors of Metabolism with Autistic-Like Behavior

Adenylosuccinate lyase deficiency
Biotinidase deficiency
Cerebral creatinine deficiency
Cerebral folate deficiency
Ceroid lipofuscinosis (infantile)
Cystathionine β-synthase deficiency
Dihydropyrimidinase deficiency
Disorders of creatine transport or metabolism
Homocystinuria
Lesch-Nyhan syndrome
Methylenetetrahydrofolate reductase deficiency
Mitochondrial disorders
Mucopolysaccharidosis
Phenylketonuria (untreated)

Modified from Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 32.8, p. 539.

neglect or trauma. However, social behaviors in these children generally improve with positive caretaking.

The differentiation of ASD from **obsessive-compulsive disorder (OCD)**, tics, and stereotyped behaviors can sometimes be challenging. In general, stereotyped behaviors may be calming or preferred, whereas tics and compulsive routines generally are distressing to the individual. Children with OCD have intense interests, as well as repetitive behaviors and rituals, but do not have impairment in social communication or interaction. Children with **stereotypic movement disorder** will not have impaired social skills or other types of restricted and repetitive behaviors. Children with **Landau Kleffner syndrome (LKS)** present with a loss of skills in language comprehension (auditory verbal agnosia) and verbal expression (aphasia) associated with onset of epileptic seizures during sleep (see Chapter 53). In contrast to ASD, children with LKS usually present with typical early development followed by loss of language function at age 3-6 years.

CO-OCCURRING CONDITIONS

Between 35% and 50% of individuals with ASD have ID, ranging in severity from mild to severe (see Table 58.5). An additional 23% of children have intellectual functioning in the borderline range (IQ = 71-85), and approximately 40% of individuals with ASD are nonverbal. ID is associated with higher rates of both identified genetic conditions and epilepsy. Children with ASD often have associated language impairments, including delays in expressive, receptive, and pragmatic (social) language skills. Language function can range

widely from nonverbal status to age appropriate. Gastrointestinal (GI) problems such as cyclic vomiting, constipation, esophagitis, and gastroesophageal reflux disease (GERD) are reported in up to 70% of children with ASD. Epilepsy occurs in up to 35–46% of children with ASD and presents in two peaks: in early childhood and in adolescence. Children with ID, female gender, and lower gestational age are at higher risk for having seizures.

Overall, between 70% and 90% of children with ASD are identified as having a co-occurring behavioral health condition, with ADHD being the most common, occurring in between 40% and 70% of children with ASD. There are higher rates of anxiety (~40%) and mood disorders in ASD, particularly during adolescence. Children with ASD are also at increased risk for being bullied and may present with secondary irritability, anxiety, or depression. Adolescents may develop gender-nonconforming roles, gender variance, and transgender identities; this may also lead to being bullied. Children with ASD are at high risk for suicidal ideation and attempts. **Catatonia** can also occur, most commonly developing during the teenage years, and may present with changes in activity level, unusual movements, and behavioral regression or loss of skills (Chapter 47.3).

Sleep problems, including delayed sleep onset, frequent night waking, and abnormal sleep architecture, are reported in 50–80% of children with ASD. There is some evidence for baseline abnormalities in melatonin secretion. The use of screen-based activities such as television, computers, or tablets before bedtime can inhibit melatonin secretion.

Children with ASD commonly have high rates of feeding and toileting problems resulting from resistance to change, sensory sensitivity, and repetitive behavior patterns. Many children with ASD have **restrictive feeding patterns** and food selectivity. DSM-5 introduced the diagnosis of avoidant and restrictive food intake disorder (ARFID) that, although not specific to children with ASD, describes a pattern of a severely disturbed eating experience resulting in nutritional deficiency or inadequate weight gain and may affect as many as 21% of children with ASD. Restrictive eating patterns may lead to nutritional deficiencies, such as scurvy, rickets, anemia, or protein malnutrition. Children with ASD also have higher rates of overweight, possibly because of diets higher in carbohydrates, reduced physical activity, use of food rewards to regulate behavior, and side effects from medications used for managing mood and behavior. As many as 25% of preschool-age children with ASD have pica (eating of nonfood items), and this tends to persist in children with co-occurring ID.

Self-injury and aggression are common in ASD patients, but most common in individuals with lower cognitive function and limited language. Sleep deprivation, nutritional deficits, pain, epilepsy, and medication side effects may contribute to these behaviors.

Wandering frequently co-occurs with ASD, with nearly 50% of children between 4 and 10 years of age reported as trying to elope. In children who were missing long enough to call the police, approximately 66% were at risk for traffic-related injury and nearly 30% had near-drowning events, which is the leading cause of death in children who wander.

SCREENING

The American Academy of Pediatrics recommends screening for ASD for *all* children at age 18 months and 24 months (see Chapter 28). Screening should also occur when there is increased risk for ASD, such as a child with an older sibling who has ASD, or whenever there is concern for possible ASD. Screening can be done by a parent checklist or direct assessment. The most frequently used screening tool is the *Modified Checklist for Autism, Revised/Follow-Up Interview* (MCHAT-R/FU), a 20-item parent report measure, with additional standardized parent interview completed for intermediate scores. The MCHAT-R/FU can be used from age 16-30 months. Children who score ≥8 or between 3 and 7 after the parent interview are at high risk for a diagnosis of ASD or some developmental delay. The Parent's Observation of Social Interaction (POSI) is another commonly used autism specific screener. It includes seven items.

ASSESSMENT

Diagnostic assessment optimally should include medical evaluation and assessment of the child's cognitive, language, and adaptive function. Developmental-behavioral pediatricians, neurodevelopmental disability specialists, neurologists, psychiatrists, and psychologists are qualified to make a formal diagnosis of ASD. Other specialists, including speech-language pathologists and occupational therapists, should also be included depending on the child's age and the presenting concerns.

Assessment of ASD includes direct observation of the child to evaluate social-communicative skills and behavior. Informal observation can be supplemented with structured diagnostic tools such as the *Autism Diagnostic Observation Schedule, Second Edition* (ADOS-2) or the Toddler module (ADOS-T). These structured play-based assessments provide social prompts and opportunities to evaluate the frequency and quality of a child's social responsiveness to, initiation, and maintenance of social interactions, the capacity for joint attention and shared enjoyment; the child's behavioral flexibility; and the presence of repetitive patterns of behavior and preoccupying interests. These measures also provide some understanding of a child's insight about social relationships and emotional awareness. The ADOS-2 and ADOS-T are not required for accurate diagnosis and do not stand alone, but rather can be used to augment a careful history and observation. The *Childhood Autism Rating Scale, Second Edition* (CARS-2) is a 15-item direct clinical observation instrument that can assist clinicians in the diagnosis of ASD. The *Autism Diagnostic Interview-Revised* (ADI-R) is a lengthy clinical interview tool that is used primarily in research settings because it takes several hours to administer. Other tools include standardized rating scales, such as the Social Responsiveness Scale or the Social Communication Questionnaire, that parents and teachers can complete to report on the child's social skills and behaviors. There is an emergence of the use of telehealth to assess children with ASD, and preliminary studies have suggested that 80% of children could be determined to have or not have ASD with reasonable certainty.

Medical evaluation should include a thorough history and detailed physical examination of the child, including direct behavioral observations of communication and play. In addition, the examination should include measurement of head circumference, careful evaluation for dysmorphic features, and screening for tuberous sclerosis with Wood lamp exam. Children with ASD should have genetic testing, an audiology examination to rule out hearing loss, and in children with pica, a lead test (Table 58.8).

There are currently several specialty-specific clinical guidelines for genetic evaluation of children diagnosed with ASD. Genetic testing is shown to impact clinical decision-making, but no studies have evaluated the impact of genetic testing on the outcome for the child. The American College of Medical Genetics recommends a tiered approach to genetic testing.

Initial Etiologic Assessment

All children with ASD should have a **chromosomal microarray (CMA)**. CMA will be positive in 10–15% of individuals with ASD. The rate is increased to almost 30% in individuals who have complex presentations, such as associated microcephaly, dysmorphic features, congenital anomalies, or seizures. CMA technology will identify copy number variants but not DNA sequencing errors, balanced translocations, or abnormalities in trinucleotide repeat length. *Fragile X DNA testing is recommended for all males with ASD.* Fragile X testing should also be considered in females with physical features suggestive of fragile X syndrome or with a family history of fragile X, X-linked pattern of ID, tremor/ataxia, or premature ovarian failure (see Chapter 59).

Second Tier Etiologic Assessment

Females with ASD should have testing for pathologic variants in the *MeCP2* gene. Males who have hypotonia, drooling, and frequent respiratory infections should have *MeCP2* deletion/duplication testing. All individuals with ASD and a head circumference greater than 2.5

Table 58.8 Medical and Genetic Evaluation of Children with Autism Spectrum Disorder

PHYSICAL EXAMINATION
Dysmorphic physical features
Muscle tone and reflexes
Head circumference
Wood lamp examination for tuberous sclerosis
DIAGNOSTIC TESTING
Chromosomal microarray (CMA) in all individuals
Fragile X DNA test in males
Audiology and vision evaluation
Lead test in children with pica
ADDITIONAL TARGETED GENETIC TESTING
Fragile X DNA test in females with symptoms suggestive of fragile X, family history of X-linked intellectual disability, tremor, ataxia, or premature ovarian failure
MeCP2 sequencing in females
PTEN testing if head circumference >2.5 standard deviations (SD) above the mean
MeCP2 deletion/duplication testing in males with significant developmental regression, drooling, respiratory infections, and hypotonia
Karyotype if unable to obtain CMA or if balanced translocation suspected
ADDITIONAL TARGETED DIAGNOSTIC TESTING
Electroencephalogram (EEG) in children with seizures, staring spells, or developmental regression
Brain MRI in children with dysmorphology, microcephaly, focal neurologic findings, seizures, severe hypotonia, or developmental regression
Metabolic testing in children with developmental regression, hypotonia, seizures, food intolerance, cyclic vomiting, lethargy, hearing loss, ataxia, or course facial features
Exome or genome sequencing if atypical features are present (behavioral or dysmorphic) (see Table 56.1)

Data from Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* 2013;15(5):399–407 and Lord C, Charman T, Havdahl A, et al. The Lancet Commission on the future of care and clinical research in autism. *Lancet.* 2022;399:271–326.

standard deviations (SD) above the mean should have testing for pathologic variants in the *PTEN* gene because there is a risk for hamartoma tumor disorders (Cowden, Proteus-like, Bannayan-Riley-Ruvakaba syndromes) in these individuals. Cytogenetic testing (karyotype) has a lower yield than CMA. Karyotype is recommended if microarray is not available and in children with suspected balanced translocation, such as history of multiple prior miscarriages.

Further medical diagnostic testing is indicated by the child's history and presentation. Brain imaging (MRI) is indicated in cases of microcephaly, significant developmental regression, seizures, or focal findings on neurologic examination. Because of the high rate (up to 25%) of macrocephaly in ASD, imaging is not indicated for macrocephaly alone. MRI is not recommended for minor language regression (loss of a few words) during the second year of life that is often described in toddlers with ASD. Children with concern for seizures, spells, or developmental regression should have an electroencephalogram (EEG). Metabolic screening is indicated for children with signs of a metabolic or mitochondrial disorder, such as developmental regression, weakness, fatigue, lethargy, cyclic vomiting, or seizures (see Table 58.7 and Chapters 56 and 104).

Next-Generation Sequencing

Whole exome sequencing (WES) can identify single-nucleotide variants, including pathogenic loss of function mutations and missense mutations; studies have identified a molecular diagnosis in nearly 30% of individuals tested because of the presence of a neurodevelopmental disorder. If the initial genetic testing is negative, clinicians should consider ordering this test in conjunction with genetic counseling to aid in understanding results.

TREATMENT AND MANAGEMENT

Approaches to Intervention

The primary treatment for ASD is done outside the medical setting and includes developmental and educational programming (Fig. 58.1). Numerous resources have been developed that can help families in the complex process of treatment planning (Table 58.9). Intensive behavioral therapies have the strongest evidence to date. Earlier age at initiation of treatment and higher intensity of treatment are associated with better outcomes, although recent studies comparing two different treatments at different levels of intensity (15 vs 25 hr/wk) did not show significant differences between groups in any of the outcomes assessed. Programming must be individualized, and no approach is successful for all children. In addition, research treatments are often conducted with a high level of intensity and fidelity that is difficult to scale up or reproduce in community settings. Higher cognitive, play, and joint attention skills and lower symptom severity at baseline are predictors for better outcomes in core symptoms, intellectual function, and language function.

There are many evidence-based approaches to treating children with ASD, with three main approaches identified. The intervention with the strongest evidence base is **applied behavioral analysis (ABA)**, which is based on the principles of direct incremental teaching of skills within a traditional behavioral framework using reinforcement of desired behavior, careful data collection, and analysis and adjustment of the treatment program based on review of data. The second is **developmental relationship-based intervention (DRBI)**, which includes parent-mediated interventions that focus on building warm, meaningful interaction to improve communication, learning, and problem solving. The best-known approach in this category is **Floortime.** The third approach is the **naturalistic developmental behavioral intervention**, which builds upon ABA to incorporate more choices for children and is implemented in natural situations. Comprehensive models integrating behavioral and developmental approaches that build on key foundational skills, such as joint attention, shared enjoyment, and reciprocal communication, show strong evidence of efficacy for young children, particularly toddlers, with ASD. Examples include the *Early Start Denver Model* (ESDM), *Joint Attention Symbolic Play Engagement and Regulation* (JASPER), and *Social Communication/Emotional Regulation/Transactional Support* (SCERTS).

Educational approaches such as the *Treatment and Education of Autistic and Communication Handicapped Children* (TEACCH) incorporate structured teaching, visual supports, and adjustment of the environment to the individual needs of students with ASD, such as difficulty with communication, understanding time, and need for routine. These approaches have demonstrated efficacy for improved cognitive and adaptive skills. For older children with more severe symptoms, approaches that use behavioral principles in addition to adjusting the environment may be most effective.

Speech and language therapy can help build vocabulary, comprehension, and pragmatic skills. Children with ASD benefit from visual supports for comprehension, understanding expectations, and communicating their needs. **Augmentative communication** approaches using photographs or picture icons can improve comprehension and ability to communicate (see Chapter 54). There are a range of options with varying levels of complexity, flexibility, and technology. Using augmentative communication does not inhibit acquisition of verbal language. On the contrary, supporting a child's language development with augmentative supports can facilitate the development of spoken language, even in older children.

Additional strategies to build social skills are used for school-age children and adolescents and may be administered in the school or community setting by a variety of specialists, including speech therapists, psychologists, and counselors. **Social skills programs** that include training peer mentors have higher rates of efficacy.

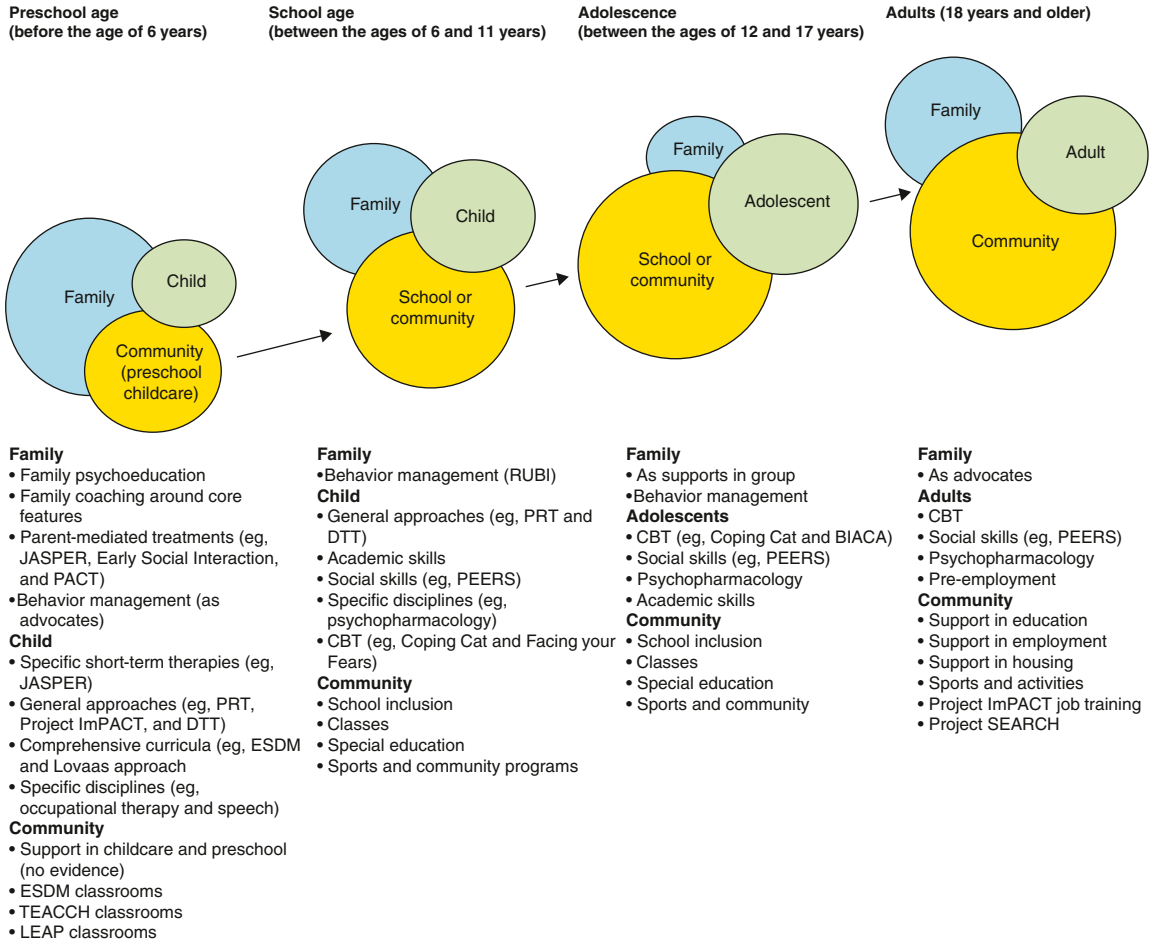

Fig. 58.1 Sources of support and locations of treatment. The size of each ellipse represents the extent of care or intervention received. BIACA, Behavioral Interventions for Anxiety in Children with Autism; CBT, cognitive-behavioral therapy; DTT, discrete trial training; ESDM, Early Start Denver Model; ImPACT, Improving Parents as Communication Teachers; JASPER, Joint Attention, Symbolic Play, Engagement, and Regulation approach; LEAP, Learning Experiences and Alternative Program for Preschoolers and their Parents; PACT, Preschool Autism Communication Trial; PEERS, Program for the Education and Enrichment of Relational Skills; PRT, Pivotal Response Treatment; RUBI, Research Units in Behavioral Intervention; TEACCH, Treatment and Education of Autistic and Related Communication Handicapped Children program. *(From Lord C, Charman T, Havdahl A, et al. The Lancet Commission on the future of care and clinical research in autism. Lancet. 2022;399:271–326, Fig. 6, p. 287.)*

Table 58.9 Autism Resources for Families

Autism Speaks First 100 Days kit https://www.autismspeaks.org/family-services/tool-kits/100-day-kit
Autism Speaks Toolkits–dental, transition, guardianship https://www.autismspeaks.org/family-services/tool-kits
AACAP Autism Spectrum Disorder Parent's Medication Guide https://www.aacap.org/App_Themes/AACAP/Docs/resource_centers/autism/Autism_Spectrum_Disorder_Parents_Medication_Guide.pdf
Sexuality information for individuals with developmental disability http://vkc.mc.vanderbilt.edu/healthybodies/

Occupational and physical therapy may be indicated for individuals with motor delay and difficulty acquiring adaptive skills such as dressing and toileting.

For some high school students with ASD, training in life skills and vocational skills is critical for maximizing independence in adulthood. Training may focus on basic self-care (e.g., dressing, hygiene), functional academics (e.g., money management, banking skills), learning to fill out a job application, and understanding how to behave with strangers and in work settings. Social skills and job coaching may be needed even for adolescents with strong cognitive and academic function, because they may struggle with social perception and may be vulnerable to exploitation by others.

There continue to be disparities in regard to accessing care, with racially and ethnically minoritized groups and children from low-income families showing less access to acute care and specialized, community and educational services, when compared with higher-income and White families.

Co-occurring Conditions

Additional medical or behavioral health treatment is often required for the management of co-occurring conditions in ASD. Seizures occur in up to 35% of children with ASD and should be managed with appropriate antiepileptic therapy (see Chapter 633). GI problems (e.g., cyclic vomiting, constipation, esophagitis, GERD) may present with nonspecific irritability, sleep disturbance, self-injury, aggression, and signs of pain or discomfort, such as crying, and can be managed with the same approaches used in typically

Table 58.10 Common Pharmacologic Treatments in Autism Spectrum Disorder (ASD)

TARGET SYMPTOM	MEDICATION CLASS*	EFFECTS	SIDE EFFECTS	MONITORING
Hyperactivity and/or Inattention	Stimulants	Decreased hyperactivity, impulsivity, improved attention	Activation, irritability, emotional lability, lethargy/social withdrawal, stomach ache, reduced appetite, insomnia, increased stereotypy	Height, weight, BP, HR
	α_2-Agonists	Decreased hyperactivity, impulsivity, improved attention	Drowsiness, irritability, enuresis, decreased appetite, dry mouth, hypotension	Height, weight, BP, HR
	Selective norepinephrine reuptake inhibitor	Decreased hyperactivity, impulsivity, improved attention	Irritability, decreased appetite, fatigue, stomach ache, nausea, vomiting, racing heart rate	Height, weight, BP, HR
Anxiety	Selective serotonin reuptake inhibitors	Decreased anxiety	Activation, hyperactivity, inattention, sedation, change in appetite, insomnia, stomachache, diarrhea Citalopram: prolonged QTc interval	Weight, BP, HR
Irritability	Atypical antipsychotics (risperidone, aripiprazole)	Decreased irritability, aggression, self-injurious behavior, repetitive behavior, hyperactivity	Somnolence, weight gain, extrapyramidal movements, drooling, tremor, dizziness, vomiting, gynecomastia	Weight, BP, HR Monitor CBC, cholesterol, ALT, AST, prolactin, glucose or hemoglobin A_{1c}
Insomnia	Melatonin	Shortened sleep onset	Nightmares, enuresis	—

*Specific medication names are provided in parentheses when there is a Food and Drug Administration (FDA)–approved indication for the use of the medication to treat the symptom in children with ASD. Further information about these medications is available in Chapter 33.
BP, Blood pressure; HR, heart rate; CBC, complete blood count; ALT, alanine transaminase; AST, aspartate transaminase.

developing children. Children with pica should have lead and iron levels monitored.

Management of co-occurring attention and mood disorders is similar to that for typically developing children. Strategies to increase structure and organization in the environment and use of visual supports (e.g., schedules) can improve attention and reduce anxiety. Some children with ASD benefit from modified cognitive-behavioral therapy to address anxiety and OCD. (see Chapter 31).

Strategies to promote **sleep hygiene** and use of behavioral approaches, such as structured bedtime routines, can address delayed sleep onset. Other medical problems, such as epilepsy or GERD, can also contribute to poor sleep and should be treated directly. In cases refractory to behavioral approaches, medications may be used.

Structured behavioral approaches for delayed toilet training in concert with treatment to prevent constipation are often needed for children with ASD. For children with highly restrictive diets, nutrition counseling and behaviorally based feeding therapy may be needed to address poor caloric intake or lack of nutritional quality. Because of limited diets, children with ASD may be at risk for low levels of calcium, vitamins C and D, and iron. Children who are overweight may still have poor nutrition as a result of restrictive diets.

Irritability is a nonspecific symptom and can be a reflection of pain, anxiety, distress, or lack of sleep. Children with ASD are prone to irritability because of their difficulty tolerating change and their limited communication skills. Management of irritability includes evaluating carefully for medical problems that may be causing pain and for any factors in the child's home or school environment that may be causing distress. Possible causes of distress range from common experiences such as changes in the routine to undisclosed abuse or bullying. Treatment should be targeted first at any underlying cause. Medications are often used to treat irritability in ASD, but should only be used after appropriate behavioral and communication supports have been implemented.

Pharmacology

There are currently no medications that treat the core symptoms of ASD. Medications can be used to target specific co-occurring conditions or symptoms (Table 58.10; see also Table 58.5). Families should be cautioned, however, that the effect size may be lower and the rate of medication side effects higher in children with ASD.

Preliminary data suggested that intranasal therapy with neuropeptide oxytocin may improve social functioning in children with ASD, particularly those with low pretreatment oxytocin levels, but a recent randomized trial did not demonstrate any effect of oxytocin on social or cognitive functioning.

There is evidence to support the use of stimulant medications, atomoxetine, and α-agonists for ADHD in ASD. Selective serotonin reuptake inhibitors (SSRIs) can be used for anxiety and OCD and in adolescents may also be useful for depression. Benzodiazepines may be useful for situational anxiety, for example, triggered by dental and medical procedures or air travel. Medications used to treat ADHD and anxiety may result in activation or irritability in ASD and require careful monitoring.

Melatonin can be used to improve sleep onset but will not address night waking. Clonidine or trazodone may be used for sleep onset and maintenance. No medications are specifically labeled for treatment of insomnia in ASD.

The α-adrenergic agonists may be helpful in children who present with significant behavioral dysregulation. There are two atypical antipsychotic medications that have U.S. Food and Drug Administration (FDA) recommendation for irritability and aggression in children with ASD. Both risperidone and aripiprazole have several studies documenting efficacy for reducing irritability, aggression, and self-injury. Secondary improvements in attention and repetitive behavior were also noted. Side effects include weight gain and metabolic syndrome, as well as tardive dyskinesia and extrapyramidal movements. Careful laboratory monitoring is recommended. Mood-stabilizing antiepileptic medications have also been used to treat irritability.

Complementary and Alternative Medicine

Families of children with ASD often use complementary and alternative medicine (CAM) approaches. These treatments can include supplements, dietary changes, and body or physical treatments. There is limited evidence to inform families, who often learn about these treatments from friends and family members, alternative medicine providers, or the internet. For most therapies, evidence is insufficient to show benefit. There is strong evidence that secretin and facilitated communication are not effective. Some therapies, such as hyperbaric oxygen, chelation, and high-dose vitamins, are potentially harmful. For children with restrictive diets, taking a daily multivitamin and 400 IU vitamin D may be indicated, although there is no evidence to support megadoses of vitamins. Similarly, for children with evidence of gluten sensitivity, a trial of a gluten-free diet may be indicated. However, current evidence does not support this as a treatment for all children with ASD. There is an interest in the use of cannabidiol (CBD) to treat core autism symptoms or co-occurring problems such as anxiety, ADHD, or sleep problems, but there is currently no evidence to support this therapy.

When discussing CAM with a family, it is best to use open and collaborative communication, encouraging them to share their current practices and any questions. Specifically ask if they use any herbal treatments, supplements, or other therapies, such as acupuncture, massage, or chiropractic treatment, and what they have observed since trying the treatment. Provide accurate information regarding potential benefit and risk for any treatment. Educate about "red flags" such as treatments that are marketed as a cure for multiple conditions, that report no risk of side effects, or that are marketed by the clinician recommending the treatment. Encourage families to identify a target symptom, "try one thing at a time," and monitor response carefully.

Transition

Navigating a successful transition to adult care is a key role for the pediatric provider. This process should ideally start as early as age 12-13 years. Parents are faced with a complex and disconnected system of diverse agencies that they need to navigate. Use of structured-visit templates and care coordinators can help ensure that families and their youth with ASD are able to make appropriate decisions about secondary and postsecondary educational programming, vocational training, guardianship, finances, housing, and medical care. High school educational programming should include individualized and meaningful vocational training, as well as instruction regarding sexuality, relationships, safety—particularly internet safety and abuse prevention—finances, travel training, and general self-advocacy. More than half of young adults with ASD remain unemployed and unenrolled in higher education 2 years after high school graduation. Individuals with ASD who are of average cognitive intellectual functioning will need help accessing supports for college or postsecondary skills training and may benefit from referral to their state vocational rehabilitative services and personal life coaches or counselors. Families who have adult children with more significant cognitive disability need information about the range of adult disability services; how to apply for supplemental security income (SSI); and the process for considering guardianship, medical and financial conservatorship, or supported decision making for their adult child. These decisions are complex and must be individualized for the adult with ASD and the family.

OUTCOME

ASD is a lifelong condition. Although a minority of individuals no longer meet criteria for the diagnosis, most will make progress but continue to have some impairment in social, behavioral, learning, language, or emotional functioning as adults. Adult outcome studies are sobering, indicating that many adults with ASD are socially isolated, lack gainful employment or independent living, and have higher rates of depression and anxiety. It is not clear if these data can be extrapolated to younger children currently receiving intensive educational therapies. There is a growing network of adult self-advocates who promote the unique strengths in individuals with ASD. Outcome, as measured by developmental progress and functional independence, is better for individuals who have higher cognitive and language skills and lower ASD severity at initial diagnosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography

Chapter 59

Fragile X Syndromes

Amanda E. Bennett and Marcy Schuster

Fragile X syndrome (FXS) is a genetic disorder associated with intellectual, learning, and behavioral symptoms and some specific physical characteristics. In FXS an expansion of >200 CGG repeats on the distal long arm of chromosome Xq27.3 silences the *FMR1* gene, which leads to a deficiency in fragile X mental retardation protein (FMRP) and affects synaptic function throughout much of the brain. It is the most common heritable cause of intellectual disability and has a prevalence rate of approximately 1 in 4,000 males and 1 in 7,000 females. Like many X-linked disorders, males with fragile X tend to present with more features and more significant impairments than females.

On average, unaffected individuals have 30 CGG repeats in the untranslated region of the *FMR1* gene. Those with 55-200 repeats are described as having the premutation. Females with the premutation are at increased risk of expansion of the number of CGG repeats causing FXS in their children (Table 59.1). When males with the premutation alleles pass them to daughters, they typically remain as premutation alleles. Those with premutation alleles may also have clinical manifestations (Tables 59.2 and 59.3).

Fragile XE syndrome (FRAXE) resembles FXS and manifests within a variable spectrum of intellectual and learning disabilities. The involved gene *(AFF2)* results in an expansion of CCG trinucleotide repeats and is inherited as an X-linked disorder. Symptoms also include aggressive behaviors, agitation, autistic behaviors, clumsiness, and delayed speech and language development. *This form of FXS will not usually be detected with standard fragile X testing.*

EVALUATION AND DIAGNOSIS

The phenotype of FXS early in life can be nonspecific with symptoms such as developmental delay, including motor and language delays, and autistic-like behaviors, such as repetitive motor mannerisms, sensory sensitivities, and deficits in eye contact. Manifestations in early to middle childhood often include problems with learning, attention-deficit/hyperactivity disorder (ADHD), anxiety, and aggressive behaviors. The physical features become more pronounced during or after puberty and include macroorchidism, hyperextensible finger joints, and characteristic facial features, including a long face, large ears, and a prominent square jaw (Fig. 59.1). Females affected with FXS show varying degrees of intellectual disability and/or learning disabilities, and they may present with symptoms of ADHD and anxiety as well.

Children with FXS are at increased risk for ophthalmologic, feeding, and orthopedic problems, as well as recurrent otitis media in early childhood. Females are at increased risk for precocious puberty.

Adolescents should be monitored for seizures and heart murmurs, and adults with FXS are at increased risk for mitral valve prolapse. Adults are also at risk for intention tremor and ataxia and premature menopause, which can also occur in those with the premutation. Table 59.3 includes phenotypic features, clinical signs, and their typical age of onset.

Family History and Premutation Carriers

Collecting a detailed family history can help identify potential risk factors for FXS. Individuals with premutation triplet repeat expansions have been found to have a variety of clinical manifestations. **Fragile X–associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disorder** that most commonly affects males over age 50 years. Females are less commonly affected and tend to have mild disease. Symptoms include an intention tremor followed by ataxia that may manifest as needing support when walking or with a wide-based gait. Females with premutation triple repeat expansions are at risk for developing **fragile X–associated premature ovarian insufficiency (FXPOI)**. Women with this condition undergo menopause approximately 5 years earlier than women without the condition, but symptoms are variable, with the most severely affected experiencing irregular or absent menstrual periods before age 40 and often infertility. A variety of neuropsychiatric symptoms, including anxiety, ADHD, social deficits, or autism spectrum disorder (ASD), have also been associated with the premutation. Asking about family members for a history of developmental, behavioral, or learning problems or adult family members with early menopause, fertility challenges, or adult-onset neurologic problems may help to identify risk for a positive fragile X test in a child with developmental or behavioral concerns. Asymptomatic siblings or other family members may benefit from testing to determine premutation status, which can also be associated with the symptoms noted earlier. See Table 59.3 for additional information about clinical symptoms in **premutation carriers**.

Table 59.1 Risk of Expansion of a Premutation to a Full Mutation in Male Offspring Based on Maternal Number of CGG Triplet Repeats

MATERNAL CGG TRIPLET REPEAT NUMBER	RISK FOR EXPANSION OF PREMUTATION TO FULL MUTATION
59-69	37%
70-79	65%
80-89	70%
90-99	95%
100 or more	100%

CGG triplet repeat, Cytosine-guanine-guanine trinucleotide repeat.
From Fragile X Syndrome. *Clinical Overview. Elsevier Point of Care*. https://www.clinicalkey.com/#!/content/clinical_overview/67-s2.0-c9588237-6031-4f21-b273-34970f89cd2e. Updated June 14, 2021. Copyright Elsevier. All rights reserved; with data from Hersh JH et al. Health supervision for children with fragile X syndrome. *Pediatrics*. 2011;127(5):994–1006, Table 1; and Saul RA et al. FMR1-related disorders. In: Pagon RA et al, eds. *GeneReviews [internet]*. University of Washington; 1993–2018.

Diagnostic Testing

A diagnosis of FXS is possible through PCR and Southern blot analysis of a patient's blood. Positive DNA testing shows an expansion of >200 trinucleotide CGG repeats inside an area of the *FMR1* gene on the X chromosome. Diagnostic testing that reports methylation status of the gene region is preferred because methylation status is inversely correlated with cognitive functioning. Because the physical features of FXS are not always apparent in early childhood, diagnostic testing is recommended for any child who presents with global developmental delay, intellectual disability, or ASD (see Chapters 56 and 58). Any positive test for fragile X should include genetic counseling to inform of inheritance risk, phenotypic variability, and medical conditions associated with FXS and premutation status. Specific gene (*AFF2*) testing for FRAXE should be considered if CGG repeat testing is negative.

Table 59.2 Phenotypic and Genetic Effect of Number of CGG Repeats

VARIATION TYPE	CGG ALLELE SIZE	TYPICAL PHENOTYPE	GENETIC CONSEQUENCES
Full mutation	More than 200 repeats	Males are affected with fragile X syndrome About 50% of females are affected with fragile X syndrome	Repeat expansion and methylation typically result in partial or complete silencing of *FMR1* Females usually benefit from having two X chromosomes, because usually one of them is unaffected (i.e., no expanded CGG repeats) and X-inactivation does not silence all copies of it
Premutation	About 55-200 repeats	Patients typically have normal intellect, and some may have mild manifestations associated with fragile X syndrome Carriers may be at increased risk for fragile X–associated tremor ataxia syndrome and *FMR1*-related primary ovarian insufficiency	FMRP expression is usually not significantly impaired; however, larger mutations may have lowered expression Alleles are at risk for CGG expansion during maternal gametogenesis, and offspring are at risk for fragile X syndrome
Intermediate (gray zone)	About 45-54 repeats	Patient does not have fragile X syndrome caused by CGG repeats	A minority of intermediate/gray zone alleles may have minor instability; however, expansion of CGG repeats is unlikely, and if it occurs, it will not reach full mutation number within a single generation
Normal	About 5-44 repeats	Patient does not have fragile X syndrome caused by CGG repeats	No meiotic or mitotic instability is present; alleles are transmitted without any change in repeat number

FMR1 gene, FMRP translational regulator 1; FMRP, fragile X mental retardation protein.
From Fragile X Syndrome. *Clinical Overview. Elsevier Point of Care*. https://www.clinicalkey.com/#!/content/clinical_overview/67-s2.0-c9588237-6031-4f21-b273-34970f89cd2e. Updated June 14, 2021. Copyright Elsevier. All rights reserved; with data from Hersh JH et al. Health supervision for children with fragile X syndrome. *Pediatrics*. 2011;127(5):994–1006, Table 1; and Saul RA et al. FMR1-related disorders. In: Pagon RA et al, eds. *GeneReviews [internet]*. University of Washington; 1993–2018.

Table 59.3 Clinical Features of Fragile X Syndrome and Premutation Carriers

COGNITIVE, BEHAVIORAL, AND PHYSICAL CHARACTERISTICS	AGE REPORTED
FULL MUTATION FRAGILE X SYNDROME (>200 CGG REPEATS)	
Hypotonia	Infancy
Reflux	Infancy
Poor suck	Infancy
Developmental delay/intellectual disability (96% males, 64% females)	Early childhood
Autism (46% males, 16% females)	Early childhood
Attention problems (84% males, 67% females)	Early childhood
Hyperactivity (66% males, 30% females)	Early childhood
Anxiety (70% males, 56% females)	Early childhood
Aggression (38% males, 14% females)	Early childhood
Self-injurious behaviors (41% males, 10% females)	Early childhood
Depression (12% males, 22% females)	Early childhood
Recurrent otitis media (>60%)	Early childhood
Seizures (18% males, 7% females)	Early childhood
Strabismus (20%)	Early childhood
Sleep disturbances	Early childhood
Flat feet	Early childhood
Low muscle tone	Early childhood
Hyperextensible joints	Early childhood
Large prominent ears	Early/middle childhood
Elongated face	Early/middle childhood
Large testes	Adolescence
Obesity (30%)	Adolescence
Mitral valve prolapse	Adulthood
Cognitive decline/parkinsonism (17%)	Adulthood
Perseveration	Adulthood
PREMUTATION CARRIERS (55-200 CGG REPEATS)	
Attention problems	Early childhood
Autism spectrum disorder	Early childhood
Seizures	Early childhood
Anxiety	Adolescence
Depression	Adulthood
Hypertension	Adulthood
Sleep disturbances	Adulthood
Migraine	Adulthood
Fibromyalgia	Adulthood
Hypothyroidism	Adulthood
Fragile X–associated primary ovarian insufficiency (FXPOI) (~20%)	Adulthood
Fragile X–associated tremor ataxia syndrome (FXTAS) (40% males, 16% females)	Later adulthood

Data from National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. Data and Statistics on Fragile X Syndrome, 2021; Hagerman RJ, Berry-Kravis E, Hazlett HC, et al. Fragile X syndrome. *Nat Rev Dis Primers.* 2017;3:17065; Hersh JH, Saul RA; Committee on Genetics. Health supervision for children with fragile X syndrome. *Pediatrics.* 2011;127(5):994–1006; Wheeler A, Raspa M, Hagerman R, Mailick M, Riley C. Implications of the FMR1 Premutation for Children, Adolescents, Adults, and Their Families. *Pediatrics.* 2017;139(Suppl 3):S172–S182.

MANAGEMENT OF FRAGILE X SYNDROME

Management of FXS in children often requires a multidisciplinary approach focused on monitoring for and managing developmental and/or behavioral symptoms. In addition to health supervision visits with a primary care clinician, many children with FXS benefit from ongoing care with a medical professional with experience or knowledge of FXS. Families will also benefit from accessing educational and behavioral health resources in the community.

Educational

Many individuals with FXS will require educational support to meet their needs starting from a young age. **Early intervention** services, including speech therapy, occupational therapy, physical therapy, and special instruction, are often vital components of addressing developmental delays. As a child ages and ongoing assessment occurs, special education support through an **individualized education plan (IEP)** may be warranted (See Chapter 49). There are interventions shown to be specific to the learning needs of individuals with FXS. Biologic males typically demonstrate strengths in receptive language, verbal labeling, simultaneous processing, imitation, and daily living activities. Biologic females typically demonstrate areas of strength in vocabulary, comprehension, reading, writing, spelling, and short-term visual memory. These advantages should be explored when educational interventions are being developed. Areas often in need of interventions for individuals with FXS include improving complex problem solving, maintaining attention, improving impulse control, understanding spatial relationships, and math concepts.

Environmental modifications and adaptive technologies can be an asset for an individual with FXS. This can include a modified keyboard and/or mouse and touch-screen computer options integrated into classroom lessons. A quiet environment with minimal distractions can help improve focus on tasks. Small group and one-on-one instruction for teaching new tasks can minimize anxiety and improve generalization of skills to the larger classroom. Teaching students to request breaks when feeling overwhelmed can minimize overall frustration. Visual schedules, manipulatives, clutter-free areas, and social stories are all interventions to improve compliance and learning.

Behavioral

Individuals with FXS can present with a variety of cognitive and behavioral challenges. ASD is diagnosed in between 50% and 60% of individuals with FXS. ASD is characterized by deficits in communication and social skills along with restricted interests and/or repetitive behaviors that interfere with one's daily life (see Chapter 58). Individuals with FXS can struggle with making eye contact, engaging in conversations, and expressing wants and needs. Often individuals with FXS want social contact but may avoid it due to anxiety. Hyperarousal is a common behavioral symptom, particularly in social situations where eye contact is expected, suggesting the presence of significant sensory aversions. Behavioral interventions that include skill development and anxiety management can be helpful in addressing social skills deficits. Other sensory-aversive behaviors can be related to auditory, visual, or tactile stimuli. Tantrums, and occasionally aggression, can emerge when children with FXS are overstimulated.

Sensory-seeking behaviors can also be present in individuals with FXS. These may include repetitive movements, narrowed interests, rigid routines, and atypical sensory exploration. Behaviors such as rocking, pacing, and jumping could occur to obtain sensory input. Individuals with FXS can become extremely anxious if a routine is changed or if a preferred activity is interrupted. Teaching coping strategies along with the recognition of triggers for anxiety can be helpful as a behavior management strategy.

Individuals with FXS can present with deficits in attention and focus, impulsivity, and/or hyperactivity, particularly during childhood. This can lead to a diagnosis of ADHD (see Chapter 50). These deficits can affect learning in school and require specialized

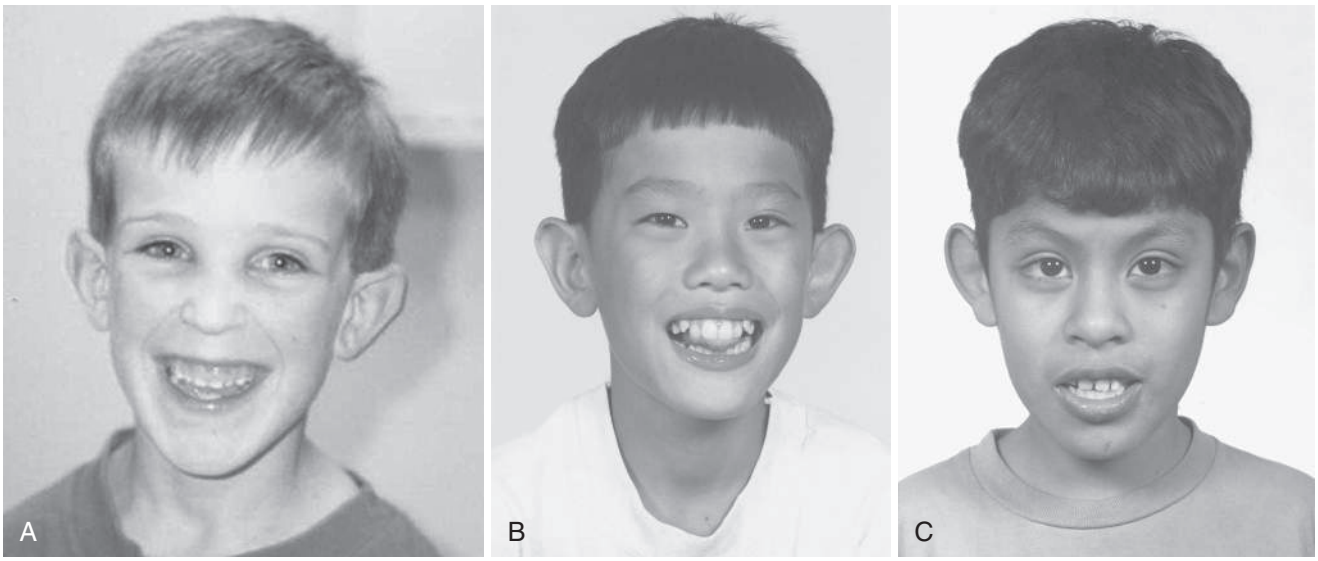

Fig. 59.1 Boys with fragile X syndrome. Note the long faces, prominent jaws, and large ears and the similar characteristics of children from different ethnic groups: European (**A**), Asian (**B**), and Latin American (**C**). *(From Jorde, LB, Carey JC, Bamshad MJ. Medical Genetics, 6th ed. Philadelphia: Elsevier; 2020: Fig. 5.20.)*

instruction or classroom accommodations to help improve focus and participation.

Individuals with FXS can present with aggressive behavior directed toward themselves and toward others. These behaviors are seen in approximately 50% of males with FXS and tend to increase with age. Individuals who exhibit ongoing aggression also typically present with more significant intellectual impairment, communication delays, and anxiety. Aggression can put a strain on caregivers or lead to injury and therefore often emerges as a primary focus of treatment.

Behavior management techniques vary depending on a child's needs. If an ASD diagnosis is present, applied behavioral analysis (ABA) programs are often integrated into treatment. ABA promotes multiple areas of development, including language, emotion, and cognition. ABA focuses on tracking specific behaviors through observation and data collection, learning their antecedents (the event or environment before the behavior occurred), and managing their consequences (the response others have after the behavior occurs) through a structured approach. Most interventions for unwanted behaviors (e.g., aggression or self-injury) aim to change the antecedents to reduce the likelihood of the behavior occurring or to change the consequence in order to make the behavior less rewarding for the individual. Interventions that aim to increase a desired behavior (e.g., complying with an instruction or toilet training) will incorporate environmental changes to remind and encourage the behavior and identify rewarding consequences that can be delivered after the behavior has occurred. ABA interventions delivered during daily living activities, community participation, and family interactions allow for optimal skill development. Special education programs often include similar behavior management techniques throughout the early childhood for individuals with FXS.

Medical

In addition to educational and behavioral management, many children with FXS may present with certain medical conditions and may require additional monitoring or care by a specialist (see Table 59.3). Monitoring in infancy and early childhood should emphasize assessment for orthopedic, growth, and/or feeding concerns. Because young children with FXS are more susceptible to otitis media and may lack communication skills to convey discomfort, a full physical examination, including ear examination, is recommended if a child presents with acute behavior changes. Young children should also be routinely screened for ophthalmologic problems, such as strabismus or astigmatism, and monitored for symptoms related to connective tissue problems, such as hypermobile joints or inguinal hernias. Seizures are more prevalent in children with FXS; symptoms concerning for any type of seizure should be investigated with electroencephalogram (EEG) when the child is both awake and asleep. Although risk for mitral valve prolapse is not typically increased until adulthood, examination for murmurs, clicks, or changes in blood pressure should be performed regularly. Sleep disturbances commonly reported among children with FXS include delayed sleep onset, frequent night waking, and occasionally obstructive sleep apnea. Screening for sleep concerns should be done at every visit, and parents should be counseled on behavioral strategies to address sleep onset and waking challenges (see Chapter 31). Concerns for apnea or snoring may require further evaluation by a sleep specialist or with polysomnography. Medications to help address sleep concerns may include melatonin or clonidine, neither of which is currently approved by the Food and Drug Administration (FDA) for use in children with FXS.

There are currently no approved treatments for the core symptoms of FXS, but many individuals will benefit from medication to address some of the commonly co-occurring behavioral symptoms associated with absence of FMRP. If behavioral strategies are not sufficient to address hyperactivity or impulsivity, a young child (<5 years) may benefit from a trial of an α_2-adrenergic agonist, such as clonidine or guanfacine. School-aged children with FXS often show improvements in hyperactivity, impulsivity, and/or attention problems when treated with a stimulant, but side effects such as irritability or aggression may occur. Selective serotonin reuptake inhibitors (SSRIs) can be safe and effective in reducing anxiety, obsessive-compulsive symptoms, and sometimes aggression in young children with FXS; one trial of sertraline in young children with FXS demonstrated improvements in visual reception and fine motor coordination in 2- to 6-year-olds. Additional analyses demonstrated improvements in expressive language skills for children with FXS and ASD. Treatment with an atypical antipsychotic, such as risperidone or aripiprazole, may be needed in cases of severe anxiety, aggression, or mood instability that have not responded to other medications.

Neurobiologic studies of FXS have identified overactivation of brain glutamate pathways and underactivation of gamma-aminobutyric acid (GABA) pathways leading to studies of

medications targeting these pathways in the hopes that they would improve cognitive outcomes. Although some studies in animal models were encouraging, human trials have yet to demonstrate consistent benefits. Some clinical trials are ongoing.

In addition to continued monitoring for cardiac, seizure, sleep, and behavioral symptoms, health supervision in late childhood and adolescence should also include discussion of adult transition issues, including vocational training, accessing state-specific adult disability services, and transition to adult medical care.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Nutrition

PART V

Chapter 60

Nutritional Requirements

Martine Saint-Cyr, Stephanie W. Waldrop, and Nancy F. Krebs

Nutrition for infants, children, and adolescents should maintain current weight and support normal growth and development. Growth during infancy is rapid, critical for neurocognitive development, and has the highest energy and nutrient requirements relative to body size compared with any other period of growth. It is followed by growth during childhood, when 60% of total growth occurs, and finally by puberty. Nutrition and growth during the first 3 years of life predict adult stature and some health outcomes. Although the antecedents are numerous and occur earlier, the major risk period for linear **growth faltering or stunting** (length- or height-for-age z score ≤-2) is between 6 and 24 months of age. Therefore it is critical to identify nutrient deficiencies promptly and to address them aggressively early in life, because missing them can impart lasting adverse effects on later growth and development.

Dietary intake should meet **energy requirements,** as well as provide the essential macronutrients and micronutrients needed for sustaining the function of multiple vital processes. Nutrient deficiencies can limit growth, impair immune function, affect neurodevelopment, and increase morbidity and mortality. Worldwide, malnutrition and undernutrition are the leading causes of acquired immunodeficiency and a major factor underlying morbidity and mortality in children <5 years of age.

The transition in food supply and the type of nutrition chosen in many developing countries from a traditional to Western diet has resulted in increased life expectancy and adult stature. It is associated with decreases in the incidence of communicable diseases. Unfortunately, the Western diet, characterized by high energy density, more refined grains, and highly processed foods, is also frequently accompanied by decreased physical activity and increases in the incidence and prevalence of noncommunicable diseases such as type 2 diabetes, cardiovascular (CV) disease, obesity, inflammatory bowel disease (IBD), and certain cancers. Consequently, it is important to view the impact of diet and nutrition on health from various perspectives: to prevent deficiency, to promote adequacy, and to prevent or reduce the risk for acquiring diseases associated with excess intakes, such as obesity, diabetes, and CV disease.

Advances in our understanding of the roles of some nutrients such as vitamin D, polyunsaturated fatty acids (PUFAs), and fiber have changed our focus from recommendations about preventing deficiency to recommendations about nutritional intake associated with optimal health. The 2006 World Health Organization (WHO) growth charts, recommended *for all infants and children until age 2 years,* are not only descriptive but also prescriptive on how children with adequate nutrition and healthcare should grow. Identifying and providing appropriate and adequate nutrition in infancy and childhood are critical to supporting normal growth and development, as well as providing the foundation for lifelong health and well-being.

DIETARY REFERENCE INTAKES

The **dietary reference intakes (DRI)** were established by the Food and Nutrition Board of the U.S. Institute of Medicine (IOM), currently known as the National Academy of Medicine (NAM), to provide guidance on the nutrient needs for individuals and groups across different life stages and according to gender (Tables 60.1-60.3 and see Tables 60.5 and 60.6).

The DRI represent a series of indicators that are used as a basis for macronutrient and micronutrient intake recommendations for healthy populations within the United States and Canada. The DRI also serve as an estimation of the Dietary Guidelines for Americans 2020-2025 (DGA) Daily Nutritional Goals. DRI indicators include the estimated

Table 60.1 Equations to Estimate Energy Requirements

INFANTS AND YOUNG CHILDREN: EER (KCAL/DAY) = TEE + ED	
0-3 mo	EER = (89 × weight [kg] − 100) + 175
4-6 mo	EER = (89 × weight [kg] − 100) + 56
7-12 mo	EER = (89 × weight [kg] − 100) + 22
13-36 mo	EER = (89 × weight [kg] − 100) + 20
CHILDREN AND ADOLESCENTS 3-18 YR: EER (KCAL/DAY) = TEE + ED	
BOYS	
3-8 yr	EER = 88.5 − (61.9 × age [yr] + PA × [(26.7 × weight [kg] + (903 × height [m])] + 20
9-18 yr	EER = 88.5 − (61.9 × age [yr] + PA × [(26.7 × weight [kg] + (903 × height [m])] + 25
GIRLS	
3-8 yr	EER = 135.3 − (30.8 × age [yr] + PA [(10 × weight [kg] + (934 × height [m])] + 20
9-18 yr	EER = 135.3 − (30.8 × age [yr] + PA [(10 × weight [kg] + (934 × height [m])] + 25

EER, Estimated energy requirement; TEE, total energy expenditure; ED, energy deposition (energy required for growth /new tissue accretion).
PA indicates the physical activity coefficient:
For boys:
PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4); PA = 1.13 (low active, estimated physical activity level 1.4-1.6); PA = 1.26 (active, estimated physical activity level 1.6-1.9); PA = 1.42 (very active, estimated physical activity level 1.9-2.5)
For girls:
PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4); PA = 1.16 (low active, estimated physical activity level 1.4-1.6); PA = 1.31 (active, estimated physical activity level 1.6-1.9); PA = 1.56 (very active, estimated physical activity level 1.9-2.5)
Adapted from Kleinman RE (ed). *Pediatric Nutrition Handbook,* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2013.

Table 60.2 Acceptable Macronutrient Distribution Ranges

AMDA (% OF ENERGY)		
MACRONUTRIENT	**AGE 1-3 YR**	**AGE 4-18 YR**
Fat	30-40	25-35
ω6 PUFAs (linoleic acid)	5-10	5-10
ω3 PUFAs (α-linolenic acid)	0.6-1.2	0.6-1.2
Carbohydrate	45-65	45-65
Protein	5-20	10-30

PUFAs, Polyunsaturated fatty acids.
Adapted from Otten JJ, Hellwig JP, Meyers LD (eds). *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC: Institute of Medicine, National Academies Press; 2006.

Table 60.3 Dietary Reference Intakes: Macronutrients

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
TOTAL DIGESTIBLE CARBOHYDRATE				
RDA based on its role as the primary energy source for the brain AMDR based on its role as a source of kcal to maintain body weight	*Infants* 0-6 mo 7-12 mo *Children* >1 yr *Pregnancy* ≤18 yr 19-30 yr	 60* 95* 130 175 175	Major types: starches and sugars, grains, and vegetables (corn, pasta, rice, potatoes, and breads) are sources of starch. Natural sugars are found in fruits and juices. Sources of added sugars: soft drinks, candy, fruit drinks, desserts, syrups, and sweeteners.†	No defined intake level for potential adverse effects of total digestible carbohydrate is identified, but the upper end of the AMDR was based on decreasing risk of chronic disease and providing adequate intake of other nutrients. It is suggested that the maximal intake of added sugars be limited to providing no more than 10% of energy.
TOTAL FIBER				
Improves laxation, reduces risk of coronary artery (heart) disease, assists in maintaining normal blood glucose levels	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr	 ND ND 19* 25* 31* 38* 38* 26* 26* 25* 28* 28*	Includes dietary fiber naturally present in grains (e.g., oats, wheat, unmilled rice) and functional fiber synthesized or isolated from plants or animals and shown to be of benefit to health.	Dietary fiber can have variable compositions; therefore it is difficult to link a specific source of fiber with a particular adverse effect, especially when phytate is also present in the natural fiber source. As part of an overall healthy diet, a high intake of dietary fiber will not produce deleterious effects in healthy persons. Occasional adverse GI symptoms are observed when consuming some isolated or synthetic fibers, but serious chronic adverse effects have not been observed because of the bulky nature of fibers. Excess consumption is likely to be self-limiting; therefore UL was not set for individual functional fibers.
TOTAL FAT				
Energy source When found in foods, is a source of ω3 and ω6 PUFAs Facilitates absorption of fat-soluble vitamins	*Infants* 0-6 mo 7-12 mo 1-18 yr	 31* 30* Insufficient evidence to determine AI or EAR; see AMDR, Table 60.2.	*Infants:* Human milk or infant formula *Older children:* Butter, margarine, vegetable oils, whole milk, visible fat on meat and poultry products, invisible fat in fish, shellfish, some plant products such as seeds and nuts, bakery products.	UL is not set because there is no defined intake of fat at which adverse effects occur. High fat intake will lead to obesity. Upper end of AMDR is also based on reducing risk of chronic disease and providing adequate intake of other nutrients.† Low fat intake (with high carbohydrate) has been shown to increase plasma triacylglycerol concentrations and decrease HDL cholesterol.
ω6 POLYUNSATURATED FATTY ACIDS				
Essential component of structural membrane lipids, involved with cell signaling Precursor of eicosanoids Required for normal skin function	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr *Lactation* ≤18 yr 19-21 yr	 4.4* 4.6* 7* 10* 12* 16* 17* 10* 11* 12* 13* 13* 13* 13*	Nuts, seeds; vegetable oils such as soybean, safflower, corn oil.	There is no defined intake of ω6 level at which adverse effects occur. Upper end of AMDR is based on the lack of evidence that demonstrates long-term safety and human in vitro studies that show increased free radical formation and lipid peroxidation with higher amounts of ω6 fatty acids. Lipid peroxidation is thought to be a component of atherosclerotic plaques.

Continued

Table 60.3 Dietary Reference Intakes: Macronutrients—cont'd

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
ω3 POLYUNSATURATED FATTY ACIDS				
Involved with neurologic development and growth Precursor of eicosanoids	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr *Lactation* ≤18 yr 19-21 yr	 0.5* 0.5* 0.7* 0.9* 1.2* 1.6* 1.6* 1.0* 1.1* 1.1* 1.4* 1.4* 1.3* 1.3*	Vegetable oils (e.g., soybean, canola, flaxseed oil); fish oils, fatty fish, walnuts†; smaller amounts in meats and eggs.	No defined intake levels for potential adverse effects of ω3 PUFAs are identified. Upper end of AMDR is based on maintaining appropriate balance with ω6 fatty acids and the lack of evidence that demonstrates long-term safety, along with human in vitro studies that show increased free radical formation and lipid peroxidation with higher amounts of PUFAs. Because the longer-chain *n*-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are biologically more potent than their precursor, linolenic acid, much of the work on adverse effects of this group of fatty acids has been on DHA and EPA. Lipid peroxidation is thought to be a component in the development of atherosclerotic plaques.
SATURATED AND TRANS FATTY ACIDS				
The body can synthesize its needs for saturated fatty acids from other sources.		No dietary requirement	Saturated fatty acids are present in animal fats (meat fats and butter fat) and coconut and palm kernel oils. Trans fat: stick margarines, foods containing hydrogenated or partially hydrogenated vegetable shortenings	There is an incremental increase in plasma total and LDL cholesterol concentrations with increased intake of saturated or trans fatty acids; therefore saturated fat intake should be limited to <10% with no trans fat.†‡
CHOLESTEROL		No dietary requirement	Sources: liver, eggs, foods that contain eggs (e.g., cheesecake, custard pie)	
PROTEIN AND AMINO ACIDS‡				
Major structural component of all cells in the body Functions as enzymes, in membranes, as transport carriers, and as some hormones During digestion and absorption, dietary protein is broken down to amino acids, which become the building blocks of these structural and functional compounds Nine indispensable amino acids must be provided in the diet; the body can make the other amino acids needed to synthesize specific structures from other amino acids	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr ≥19 yr *Females* 9-13 yr ≥14 yr ≤18 yr 19-21 yr Pregnancy and lactation	 9.1* **11.0** **13** **19** **34** **52** **56** **34** **46** **46** **71**	Proteins from animal sources (e.g., meat, poultry, fish, eggs, milk, cheese, yogurt) provide all nine indispensable amino acids in adequate amounts and are considered "complete proteins." Protein from plants, legumes, grains, nuts, seeds, and vegetables tend to be deficient in ≥1 of the indispensable amino acids and are called "incomplete proteins." Vegan diets adequate in total protein content can be made "complete" by combining sources of incomplete protein, which lack different indispensable amino acids.	No defined intake levels for potential adverse effects of protein are identified. Upper end of AMDR was based on complementing AMDR for carbohydrate and fat for the various age-groups. Lower end of AMDR is set at approximately the RDA.

Note: Starred (*) numbers are Adequate Intake (AI) **bold** numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97–98% of members in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

AMDR is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. With consumption in excess of the AMDR, there is a potential for increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients.

ND amounts are not determinable because of a lack of data regarding adverse effects in this age-group and concern with regard to a lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

†2015–2020 Dietary Guidelines for Americans. U.S. Department of Health and Human Services. https://health.gov/dietaryguidelines/2015/.

‡Based on 1.5 g/kg/day for infants, 1.1 g/kg/day for 1-3 yr, 0.95 g/kg/day for 4-13 yr, 0.85 g/kg/day for 14-18 yr, 0.8 g/kg/day for adults, and 1.1 g/kg/day for pregnant (using pre-pregnancy weight) and lactating women.

AI, Adequate intake; AMDR, acceptable macronutrient distribution range; EAR, estimated average requirement; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ND, not determinable; PUFAs, polyunsaturated fatty acids; RDA, recommended dietary allowance; UL, upper limit of normal.

Institute of Medicine. 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. https://doi.org/10.17226/10490.
Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, DC.

average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL) (Figs. 60.1 and 60.2). In addition, the concept of the DRI is also applicable to the estimated energy requirement (EER) and the acceptable macronutrient distribution range (AMDR).

The EAR is an estimated average of the daily nutrient intake required to meet the nutritional needs of 50% of the population; it is applied to the assessment of a population's intake. The RDA provides an estimate of the minimum daily average intake for a nutrient that meets the nutritional needs for more than 97% of individuals in a population, and it can be used as a guideline for individuals to avoid deficiency. When an EAR cannot be derived, an RDA cannot be calculated; therefore an **adequate intake (AI)** is developed as a guideline for individuals based on the best available data and scientific consensus. The UL denotes the highest average daily intake with no associated adverse health effects for almost all individuals in a given population. Figure 60.2 shows the relationships among EAR, RDA, and UL.

ENERGY

Energy balance constitutes both caloric intake, most often derived from food, *and* metabolic caloric expenditure. An imbalance between energy intake and energy expenditure can lead to undesirable health consequences. *Inadequate* energy intake can lead to weight faltering, catabolism of body tissues (e.g., fat and muscle), diminished immunity, and increased morbidity and mortality. For infants, children, and adolescents, acute or chronic energy deficits can adversely affect

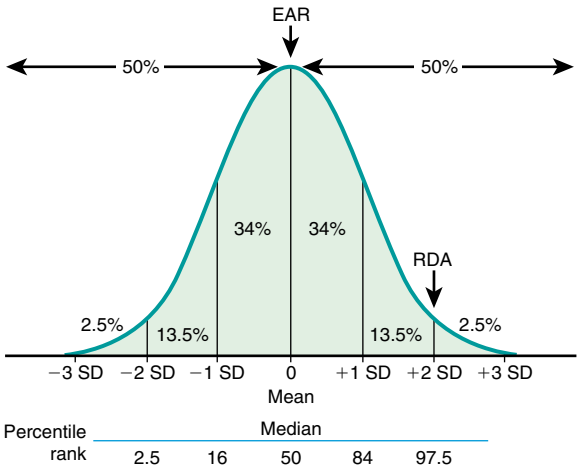

Fig. 60.1 Dietary reference intakes. Normal requirement distribution of hypothetical nutrient showing percentile rank and placement of the estimated average requirement (EAR) and the recommended dietary allowance (RDA) on the distribution; SD, standard deviation.

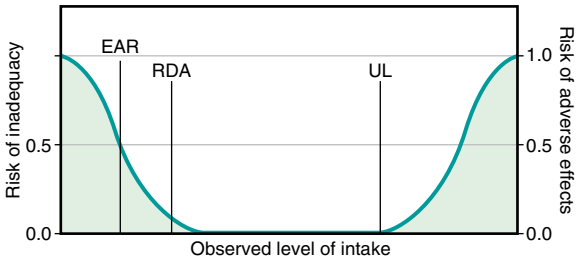

Fig. 60.2 Dietary reference intakes: The relationship among the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL). This figure shows that the EAR is the intake at which the risk of inadequacy is estimated to be 0.5 (50%). The RDA is the intake at which the risk of inadequacy would be very small, only 0.02-0.03 (2–3%). At intakes between the RDA and the UL, the risk of inadequacy and of excess are estimated to be close to 0.0. At intakes above the UL, the potential risk of adverse effects can increase.

motor, cognitive, and behavioral development. *Excess* energy intake can increase the risk for obesity and obesity-related metabolic disease. Energy balance in adults is associated with maintenance of weight status. Positive energy balance is required in children to support growth. Components of energy expenditure in adults include the *basal metabolic rate* (BMR), which is primarily determined by lean body mass; the *thermal effect* of food (e.g., energy required for digestion and absorption); *energy* for thermoregulation; and *energy* for physical activity. Energy needs are increased during infancy, childhood, pregnancy, and lactation, necessitating increased energy intakes during these life stages.

The 2020–2025 DGA provides important nutrition and health topics applicable to each life stage, including data on estimates of caloric intake for healthy persons. The exact daily caloric requirement varies according to an individual's age, gender, height, weight, and physical activity, among other factors. Weight loss, weight maintenance, and weight gain depend on calories consumed and calories expended in the context of caloric needs.

The **estimated energy requirement (EER)** for infants, children, and adolescents is the average dietary energy intake predicted to maintain energy balance, ensure adequate growth and development, and provide for a desirable level of physical activity. It considers age, gender, weight, stature, and level of physical activity (see Table 60.1). The EER was determined based on empirical research in healthy persons at different levels of physical activity and is estimated by equations that account for both *total energy expenditure* (TEE) and *energy deposition* (ED) for healthy growth. EERs for infants, relative to body weight, are approximately twice those for adults because of the increased metabolic rate and energy requirements for weight maintenance and growth.

The EER was not devised for, and does not necessarily apply to, children with acute or chronic diseases who may have altered energy requirements due to chronic infection or inflammation, malabsorption, febrile illnesses, chronic lung disease, congenital heart disease, or other conditions. In these situations, **energy requirements** are typically higher when compared with healthy matched peers. Conversely, in some conditions, individuals may be hypometabolic and thus require less energy than expected (e.g., hypothyroidism, hypothalamic obesity conditions, Down syndrome, and certain syndromic or monogenic obesity disorders). Individual energy needs for healthy persons based on age, gender, height, weight, activity level, pregnancy, or lactation status can be approximated using online tools, such as the DRI Calculator for Healthcare Professionals, available at https://www.nal.usda.gov/human-nutrition-and-food-safety/dri-calculator.

Dietary nutrients that provide energy include *fats* (approximately 9 kcal/g), *carbohydrates* (4 kcal/g), and *protein* (4 kcal/g). These nutrients are called **macronutrients**. If alcohol is consumed, it also contributes to energy intake (7 kcal/g). The EER does not specify the relative energy contributions of macronutrients. Once the minimal intake of each macronutrient is attained (e.g., sufficient protein intake to meet specific amino acid requirements, sufficient fat intake to meet linoleic acid and α-linolenic acid needs for brain development), the remainder of the intake is used to meet energy requirements, with some degree of freedom and interchangeability among fat, carbohydrate, and protein. This forms the basis for the **acceptable macronutrient distribution ranges (AMDRs)**, expressed as a function of total energy intake (see Table 60.2).

FAT

Fat is the most calorically dense macronutrient, providing approximately 9 kcal/g. For infants, human milk and formula are the main dietary sources of fat, whereas older children obtain fat from animal products, vegetable oils, margarine, and nuts and seeds. The AMDR for fats is 30–40% of total energy intake for children 1-3 years and 25–35% for children 4-18 years of age. In addition to being energy dense, lipids provide essential fatty acids that have structural and functional roles (e.g., cholesterol moieties are precursors for cell membranes, hormones, and bile acids). Fat intake also facilitates absorption of fat-soluble vitamins (vitamins A, D, E, and K). Both roles are relevant to neurologic and ocular development (see Table 60.3).

Dietary fats include phospholipids; free fatty acids; monoglycerides, diglycerides, and triglycerides; and sterols. **Triglycerides** are the most common form of dietary fat and are composed of one glycerol molecule with three fatty acids. They are found in both animal and vegetable fats. In addition, simple sugars (i.e., refined grains and high-sugar drinks) can be converted to triglycerides in the liver. In general, dietary fatty acids can be classified as saturated, unsaturated, and more specifically, as monounsaturated or polyunsaturated. Dietary saturated fatty acids, found primarily in animal fat and dairy products as well as some vegetable fats (e.g., coconut and palm oil), can be synthesized endogenously by the body and thus are not required in the diet. **Medium-chain triglycerides (e.g., MCT oil)** are beneficial for those suffering from malabsorptive disorders resulting in steatorrhea because of their direct absorption from the gastrointestinal (GI) tract into the bloodstream via the portal vein, bypassing the need for pancreatic and biliary secretory components. The dietary saturated fatty acids most commonly consumed include myristic (C14), palmitic (C16), and steric acid (C18).

Trans fatty acids are a type of unsaturated fat having undergone hydrogenation that alters the configuration of its double bond(s). They are found primarily in processed foods such as margarines and shortenings and are nonessential. A small amount of naturally occurring trans fats can be found in animal products and human breast milk. **Monounsaturated fatty acids** are typically found in certain plants and their derived oils (e.g., avocado oil, olive oil, canola) and in some animal fats. Because monounsaturated fatty acids can be synthesized by the liver, they are considered nonessential to the diet. **Polyunsaturated fatty acids (PUFAs)** are fatty acids not able to be synthesized de novo in the body and are necessary for maintenance of growth, skin integrity, aspects of central nervous system development, and other essential physiologic functions such as regulation of gene transcription, immunity, and inflammation. These dietary essential fatty acids include linoleic (C18:2,W6,9) and linolenic acid (C18:3,W3,6,9), and they are discussed in more detail later.

Neither monounsaturated nor polyunsaturated fatty acids contribute adversely to plasma cholesterol levels. However, dietary saturated fatty acids (found primarily in animal fat and dairy products), trans fats (found in hydrogenated margarines and oils), and **cholesterol** increase the low-density lipoprotein (LDL) fraction of serum cholesterol, which is a risk factor for the development of atherosclerosis. Autopsy studies demonstrate that atherosclerosis begins early in childhood, even in infancy. Therefore dietary advice to optimize CV health should be given starting from age 2 years, when sufficient fat intake to sustain growth and brain development is less of a concern. **It is recommended that saturated fat make up less than 10% of total daily calories in the diet for those age 2 years and above**, with increased focus on consumption of monounsaturated and polyunsaturated fats. **Dietary trans fatty acids are to be avoided**, particularly artificial trans fatty acids in the form of partially hydrogenated oils, which are no longer considered Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA). Figure 60.3 shows the dietary contributions of saturated fat for those age 1 year and above.

Because saturated and monounsaturated fats can be synthesized endogenously to support adequate structural and physiologic requirements, there is no AI or RDA set for these dietary components. Trans fats, which *have no known health benefits in humans,* also do not have an AI or RDA defined. A UL has not been set for cholesterol, saturated, or trans fats because there is a continuous positive linear association between intake of these fats and increased risk for CV disease, without a threshold level. Diets low in saturated fats without trans fats are therefore preferred. **For optimal CV health in the general population, rather than limiting fat intake, advice should focus in most cases**

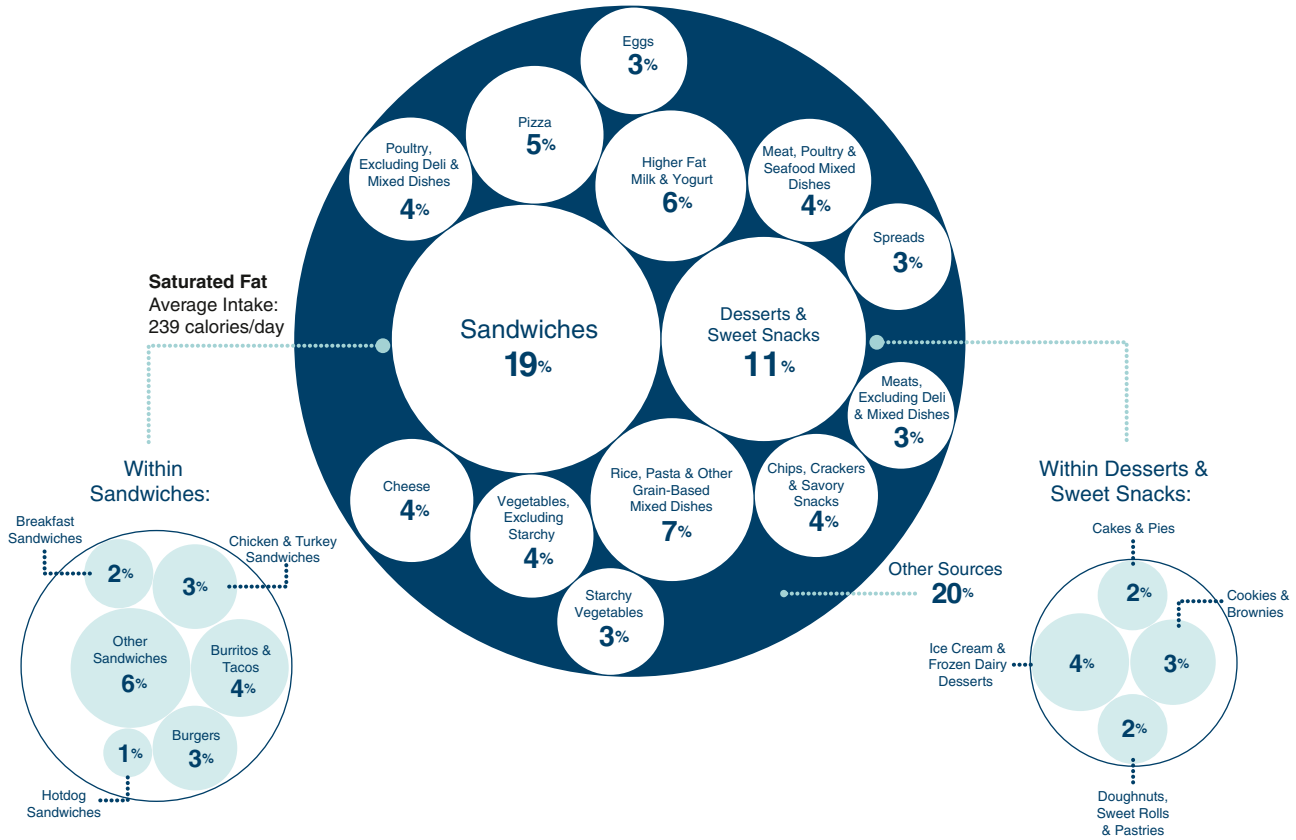

Fig. 60.3 Top sources and average intakes of saturated fat: U.S. population age 1 year and older. Estimates based on 2-day dietary intake data, weighted, from What We Eat in America (WWEIA), National Health and Nutrition Examination Survey (NHANES), 2013-2016. (*From Dietary Guidelines for Americans. 2020-2025, Chapter 1: Nutrition and Health Across the Lifespan. Fig. 1.11. https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf.*)

on changing the type of fat consumed. Because of their high energy density, excessive intake of all types of fatty acids has the potential to increase the risk of obesity.

Humans are incapable of synthesizing the precursor ω3 (α-linolenic acid [ALA]) and ω6 (linoleic acid [LA]) long-chain PUFAs and depend on diet for these two essential fatty acids. Walnut, canola, and flaxseed oil are good sources of ALA. Good sources of LA include safflower and sunflower oil. Essential fatty acids are enzymatically elongated and desaturated into longer-chain fatty acids (LC-PUFAs) that serve essential physiologic roles in the body. ALA can be converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). LA is converted to arachidonic acid (ARA). The conversion of ALA to EPA and DHA and of LA to ARA is influenced by many factors, including type and amounts of dietary fats and by enzymatic substrate affinity among competing ω3, ω6, ω9, saturated, and trans fatty acids. Approximately 0.5% of dietary ALA is converted to DHA, and 5% of ALA intake is converted to EPA; therefore dietary intake of LC-PUFAs is an important determinant of serum and tissue DHA and EPA status.

LC-PUFAs such as DHA and ARA have a variety of cellular structural and functional roles; they influence membrane fluidity and gene expression and modulate the inflammatory response. ARA and DHA are present in breast milk and reflect maternal intake. They are often supplemented in infant formulas and are important for optimal growth and development. DHA is highly concentrated in the retina and is involved in the visual evoked response in infants.

Risk factors for **essential fatty acid deficiency** (i.e., deficiency of ALA and LA) include severe fat malabsorption, prematurity, and administration of fat-free parenteral nutrition. Deficiency can develop within 2-4 weeks of inadequate intake. Essential fatty acid deficiency of LA is associated with desquamating skin rashes, alopecia, thrombocytopenia, impaired immunity, and growth deficits, but is rare in the general population. Deficiency of ALA has been associated with paresthesias, weakness, impaired gait, impaired vision, hemorrhagic folliculitis, and impaired wound healing.

The biologic activity and health benefits of ALA are thought to be derived from its elongation products EPA and DHA. Consistent with the findings of limited conversion of ALA to EPA and DHA, the DRI stipulates that up to 10% of the AI for ω3 PUFA (ALA being the major dietary constituent) can be replaced by DHA and EPA to support normal neural development and growth. The ratio of dietary intake of each type of PUFA influences their relative amounts in different tissue compartments. **A dietary ω6:ω3 PUFA ratio of 4-5:1 may be associated with improved health outcomes, compared with the current 15-30:1 ratio typically observed in U.S. diets**. In general, ω6 fatty acids tend to have more proinflammatory effects and ω3 fatty acids more antiinflammatory effects, which have potential implications for adjunctive nutritional management of chronic inflammatory conditions.

PROTEIN

Protein and amino acids have structural and functional roles in every cell in the body. Dietary protein intake is required to maintain and replenish the turnover of protein and to meet amino acid needs for growth. Dietary protein also provides approximately 4 kcal/g as an energy substrate when intake is in excess of needs or derived from endogenous sources during periods of catabolism. Inadequate energy intake or inadequate protein intake increases catabolism of body protein reservoirs (i.e., lean body mass) for energy and free amino acids required to support normal physiologic function. Without adequate daily dietary protein intake, endogenous sources will be mobilized at the expense of function. Negative energy balance (weight loss) is associated with an obligatory negative nitrogen balance. Nitrogen from protein turnover is primarily excreted in urine and stool.

Increased protein intake of up to 20–30% may be required during hypermetabolic states, as well as in those infants and children recovering from malnutrition. Certain conditions may require a modest increase in protein intake, including conditions with high protein turnover, such as cystic fibrosis, inflammatory conditions, critical illnesses, extensive burn injuries, compensated liver disease, and postsurgical states including bariatric surgery (e.g., laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass). Premature infants also require increased protein intakes due to increased needs related to accelerated growth rates. In addition, athletes engaging in resistance, muscle-building training may have increased total protein needs of approximately 1.2-2.0 g/kg/day to prevent loss of lean body mass and to maintain nitrogen balance. Importantly, the increased protein intake in these situations must occur in the context of adequate energy intake in order for protein deposition to occur, thus ensuring that protein is not used or catabolized for energy. Moderate to severe protein-energy malnutrition (PEM), although relatively rare in the non-institutionalized U.S. population, is more common in low-resource settings. Mild PEM occurs more commonly in the United States, leading children not to meet weight targets on growth curves. PEM impairs brain, immune system, and intestinal mucosal functions (see Chapters 62 and 64).

The DRI for protein is provided in Table 60.3. Numerous factors influence dietary requirements for protein, including gender, age, growth stage, pregnancy, lactation, the presence of illness, the nutritional adequacy of an individual's diet, and genetics. The most important determinant of protein requirements is energy intake because insufficient energy intake will lead to protein catabolism to maintain energy balance, effectively increasing protein intake requirements. The EAR and RDA take into account protein required for growth and maintenance, but the RDA accounts for variation in requirements for a particular population that may exist as a result of differences in maintenance needs, protein accrual rates, and the efficiency of dietary protein accrual. Thus the RDA exceeds the EAR and most protein needs for individuals of a specific group.

The average intake of protein from poultry, meat, eggs, nuts, seeds, and soy products differs by age and gender. According to the 2020–2025 DGA and based on National Health and Nutrition Examination Survey (NHANES) data from 2015 to 2016, the average daily intake of protein for males and females age 2-4 years and 5-8 years is within recommended ranges. In children age 9-13 years, average protein intake barely meets the lower end of recommended intake for both males and females. For adolescents 14 years of age and above, males have average daily protein intakes within the recommended range; that for females falls short of the minimum recommended daily intake. A UL for protein has not been set because of insufficient data; however, excessively high intakes can result in increased urinary calcium excretion that may increase the risk of renal calculi. **Intake of protein or specific amino acids needs to be limited in some health conditions**, such as renal disease, decompensated liver disease, and metabolic diseases such as phenylketonuria and maple syrup urine disease, in which specific amino acids can be toxic. Conclusive evidence for harm in *otherwise healthy* individuals from high protein intakes is lacking. Protein intake necessary to meet micronutrient needs, especially during the first 2 years of postnatal life, will typically exceed recommended protein intakes, thus requiring micronutrient supplementation to prevent insufficiency or deficiency.

The amino acid content of dietary protein is also important. The standard by which a protein's quality is judged is its ability to support adequate growth. Certain amino acids are **indispensable/essential**, and humans depend on dietary sources to meet adequacy and prevent deficiency. Certain amino acids are termed **conditionally indispensable**, meaning they can be endogenously produced but require an exogenous source (i.e., diet) in certain disease conditions or during a certain life stage. An example would be the increased requirements for cysteine, tyrosine, and arginine in newborns because of enzyme immaturity (Table 60.4). DRI recommendations regarding protein intake assume adequate provision of indispensable amino acids and high digestibility. Human milk contains both the indispensable and conditionally indispensable amino acids and therefore meets the protein requirements for infants. Breast milk is considered the optimal protein source for infants and is the reference amino acid composition by which biologic quality is determined for infants. If a single amino acid in a food protein source is low or absent but is required to support normal metabolism, that specific amino acid becomes the limiting nutrient in that food. Animal protein, unlike plant protein, contains sufficient indispensable

Table 60.4 Indispensable, Dispensable, and Conditionally Indispensable Amino Acids in the Human Diet

INDISPENSABLE	DISPENSABLE	CONDITIONALLY INDISPENSABLE*	PRECURSORS OF CONDITIONALLY INDISPENSABLE
Histidine†	Alanine	Arginine	Glutamine/glutamate, aspartate
Isoleucine	Aspartic acid	Cysteine	Methionine, serine
Leucine	Asparagine	Glutamine	Glutamic acid/ammonia
Lysine	Glutamic acid	Glycine	Serine, choline
Methionine	Serine	Proline	Glutamate
Phenylalanine		Tyrosine	Phenylalanine
Threonine			
Tryptophan			
Valine			

**Conditionally indispensable* is defined as requiring a dietary source when endogenous synthesis cannot meet metabolic need.
†Although histidine is considered indispensable, unlike the other 8 indispensable amino acids, it does not fulfill the criteria of reducing protein deposition and inducing negative nitrogen balance promptly on removal from the diet.
Adapted from Otten JJ, Hellwig JP, Meyers LD (eds). *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC: Institute of Medicine, National Academies Press; 2006.

amino acids and typically is more digestible (>95%) than plant-source proteins (70–80%).

To ensure appropriate growth and to promote satiety, children should consume the recommended amount of protein. Specific recommendations for appropriate dietary protein sources to meet indispensable amino acid requirements are available for groups adopting specific diets, such as vegetarians and vegans. Including mixtures of protein sources (e.g., legumes and corn) and using a variety of food sources to provide all of the required amino acids are strategies advocated for vegetarians and vegans (see Chapter 61).

CARBOHYDRATES

Carbohydrates are abundant in many foods, including cereals, grains, fruits, and vegetables, and provide approximately 4 kcal/g of energy. Dietary carbohydrates include *monosaccharides,* which contain one sugar molecule (e.g., glucose, fructose, galactose); *disaccharides,* which contain two sugar molecules (e.g., sucrose, lactose, maltose); *oligosaccharides* or *polysaccharides,* which contain multiple sugar molecules in a chain or complex configuration (e.g., starch, nonstarch polysaccharides like fiber); and *sugar alcohols.* Dietary carbohydrates are absorbed across the intestinal epithelium and converted to glucose in the liver. Glucose serves as the essential energy source for erythrocytes and the central nervous system and is a major energy source for all other cells. The requirements for carbohydrates are based on the average minimum amount of glucose used by the brain. Chronic low carbohydrate intake (e.g., less than 10% of total caloric intake) results in ketosis. Although a UL for carbohydrates has not been set, a maximal intake of <10% of total energy intake from *added* sugars, such as syrups and other caloric *sweeteners,* has been proposed in the 2020–2025 DGA.

Added sugars do not contribute essential nutrients and function to sweeten foods and beverages. Naturally occurring sugars, such as in milk (lactose) or fruits (fructose), are not included. Higher intakes of added sugar can displace other **macronutrients and micronutrients** and increase the risk for nutrient deficiency and excessive energy intake. There is no benefit from consuming added sugars as discretionary calorie intake. The excess calories from added sugars may displace more nutrient-dense foods and make it difficult to meet nutrient needs while remaining within the recommended total caloric intake.

The recommended AMDR for carbohydrates is based on data suggesting a risk for coronary artery disease (CAD) with diets high in refined carbohydrates and low in fat (see Table 60.2). These diets, compared with diets with higher fat intake, result in high triglyceride levels, low high-density lipoprotein (HDL) cholesterol, and small LDL cholesterol particles and are associated with an increased risk of CAD, especially in sedentary overweight individuals. Diets within the AMDR for carbohydrates and fats minimize the risks of diabetes, obesity, and CAD. Diets with less than the minimum AMDR for carbohydrate most likely do not meet the AI for fiber (see Table 60.3).

Most carbohydrates are present as starches or sugars in food. Simple sugars (monosaccharides and disaccharides) are often added to foods and beverages during food preparation, processing, and packaging to enhance their palatability and also act as preservatives. Sugar-sweetened beverages, including nondiet soft drinks, juice drinks, iced tea, and sport drinks, are major contributors to added sugars in the diet of U.S. children and adolescents (Fig. 60.4). Added sugars are associated with increased risk for obesity, diabetes, and dental caries. Fructose is one such added sugar in the form of *high-fructose corn syrup,* which is ubiquitous in the U.S. diet. Added fructose increases HDL and triglyceride production in the liver and serum uric acid, which increases systolic blood pressure and is associated with nonalcoholic fatty liver disease and metabolic syndrome. Excessive fructose intake, such as in the form of fruit juices, may be associated with diarrhea, abdominal pain, and failure to thrive in children. Fructose consumed in whole fruits rarely contributes to these side effects because its systemic absorption and metabolic effects are mitigated by the fact that it is complexed with fiber.

The **glycemic index** is a measure of peak blood glucose concentration 2 hours after ingestion of a given food compared with a reference standard (slice of white bread). The glycemic index has predictable effects on blood glucose, hemoglobin A_{1C}, insulin, triglycerides, and HDL cholesterol. *Lower-glycemic-index foods are recommended and may reduce the risk of insulin resistance and CV disease.* Examples of low-glycemic-index foods include oat bran, muesli, barley, carrots, nonstarchy vegetables, and most fruits.

FIBER

Fiber consists of *nondigestible* carbohydrates (i.e., nonstarch polysaccharides and nonpolysaccharides such as lignins), mostly derived from plant sources, such as whole grains, fruits, and vegetables, that escape digestion and reach the colon almost 100% intact. Fiber can be classified as fermentable and nonfermentable. Fermentable fibers are found in beans, fruits, and products containing oats or psyllium, and nonfermentable fiber is found in whole grains and vegetables. The DRI classification considers total fiber intake to be composed of **dietary fiber** (nondigestible carbohydrates and lignins intrinsic to plants that are fermented by colonic bacteria) and **functional fiber** (nondigestible carbohydrates isolated from plants or manufactured for use as dietary supplements). Although functional fibers may improve constipation and glucose absorption, they do not contain the other beneficial phytochemicals and nutrients of naturally occurring fiber found in whole foods. Functional fibers have been added to cereals, salad dressings, soups, baked goods, and meal replacements with the aim of increasing fiber intake.

Dietary fiber may help reduce intestinal cell dysplasia by diluting toxins, carcinogens, and tumor promoters; decreasing transit time, thereby reducing colonic mucosal exposure; and promoting toxin expulsion in the fecal stream. Dietary fiber that is resistant to colonic

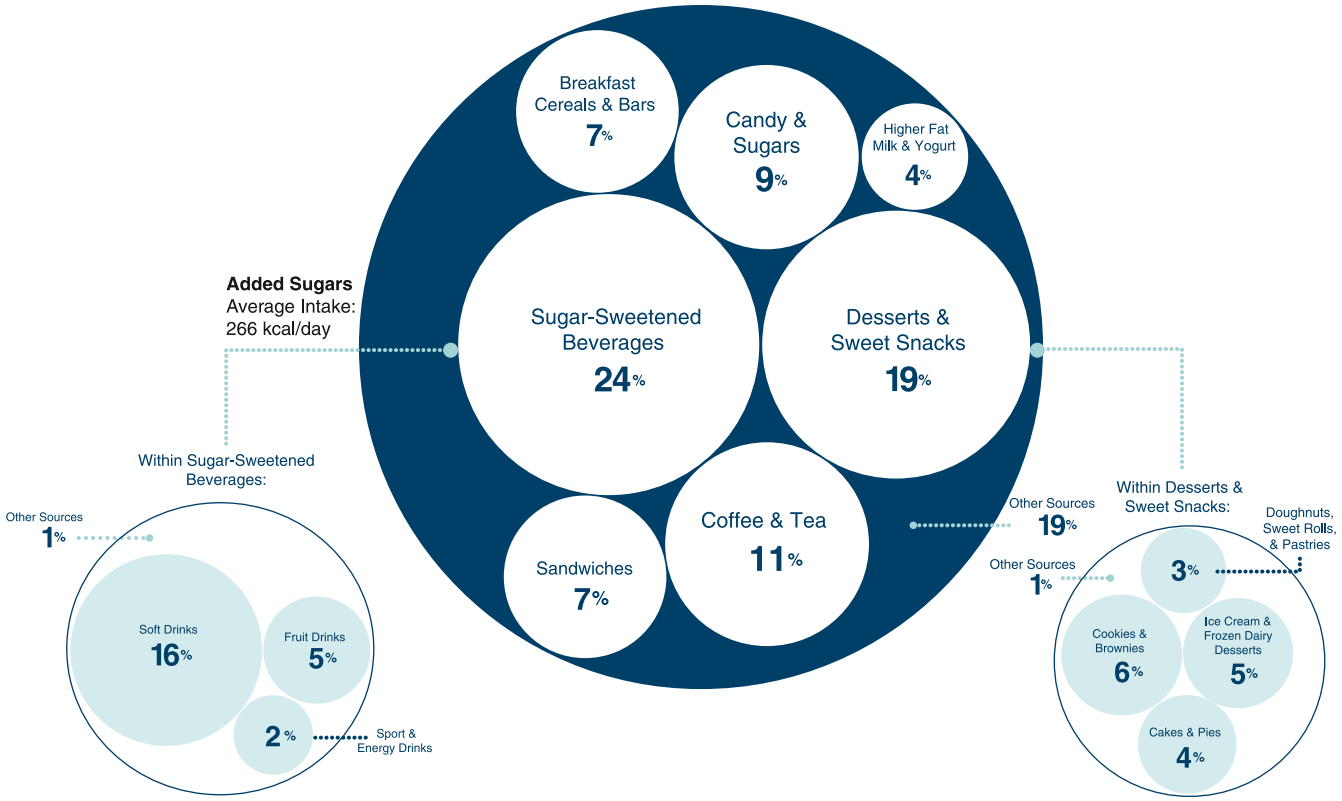

Fig. 60.4 Top sources and average intakes of added sugars: U.S. population age 1 year and older. Estimates based on 2-day dietary intake data, weighted, from What We Eat in America (WWEIA), NHANES, 2013-2016. (*From the Dietary Guidelines for Americans, 2020-2025, Chapter 1: Nutrition and Health Across the Lifespan. Fig. 1.10.* https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf.)

degradation may also play a role in maintaining and promoting stool bulk and in regulating intraluminal pressure and colonic wall resistance, disordered colonic motility, or both. Lack of certain types of dietary fiber is associated with constipation and diverticulosis.

All types of dietary fiber slow gastric emptying and promote satiety, and thus may help to regulate appetite. Dietary fiber may decrease the rate of release and absorption of simple sugars and may help regulate blood sugar concentration by lowering postprandial blood glucose levels. Dietary fiber has a low glycemic index and may have a beneficial effect on insulin sensitivity. Fiber also binds luminal cholesterol and reduces absorption and enterohepatic circulation of the cholesterol in bile salts (e.g., with the intake of more viscous forms of dietary fiber, such as pectin). Guar gum, oat products, and pectin (i.e., fermentable/viscous fiber) lower serum cholesterol, whereas nonfermentable/nonviscous fiber (e.g., flax, wheat bran) may reduce serum triglycerides. Fiber such as psyllium, resistant dextrins, and resistant starch may lower both serum LDL cholesterol and triglycerides. Low fiber intake in Western society has been associated with the increasing incidence and prevalence of diabetes, obesity, CV disease, colon cancer, and IBD.

There is a dynamic interplay between the colonic bacterial milieu and the diet. The metabolic fate of fiber is influenced primarily by colonic bacteria, which render it susceptible to fermentation, depending on the structure of the fiber (e.g., pectin, oat bran). Common by-products of colonic fermentation include carbon dioxide, methane (in addition to other gases), **oligofructose** (also known as a *prebiotic,* a substrate that nourishes beneficial commensal GI microbiota), and **short-chain fatty acids (SCFAs)**. The common SCFAs produced by fermentation include acetate, butyrate, and propionate. SCFAs influence colonic physiology by stimulating colonic blood flow and fluid and electrolyte uptake. Butyrate is the preferred fuel for the colonocyte and may have a role in maintaining the normal phenotype in these cells. Good sources of fiber include beans, peas, leafy and cruciferous vegetables, fruits, and whole grains. The observed benefits of diets rich in fruits and vegetables may be mediated by the fiber they contain and also by the other compounds and micronutrients (e.g., polyphenols, carotenoids) they contain.

Data are insufficient to establish an EAR for dietary fiber. AI for dietary fiber has been established based on the intake levels associated with reducing risk for CV disease and in lowering or normalizing serum cholesterol (see Table 60.3). Several recommendations address dietary fiber intake in children based on body weight or as a proportion of daily calories consumed. The IOM recommends an AI for fiber of 14 g per 1,000 kcal of energy consumed (see Table 60.3), which for younger children may be unrealistic to achieve. *The equation for the range of recommended daily fiber intake in grams = Age (years) + 5 to 10 grams per day.* The recommendations do not specify type of fiber and predate the newer definitions of fiber.

A UL has not been established for fiber, which is not thought to be harmful to human health. Some types of fiber, such as fermentable oligosaccharides, may exert symptoms on the basis of their digestibility, by-product formation, and interactions with GI microbiota. Excessive intake of **fermentable oligosaccharides** (e.g., fructooligosaccharides such as onions), **disaccharides** (e.g., lactose), **monosaccharides** (e.g., fructose), and **polyols** (e.g., sorbitol) (aka **FODMAPs**) is associated with increased risk for GI symptoms along the functional abdominal pain, functional GI disorders (IBS), and IBD. **Restricted intake or substitution with lower-FODMAP foods may be beneficial.** Substitutions within the same food groups can shift from a high-FODMAP diet to a low-FODMAP diet, which may provide GI symptom relief. For example, substituting cucumber for celery would be exchanging a high-FODMAP food for a low-FODMAP food. Dietary management for some conditions may put certain children at risk of low fiber intake. Gluten-free diets used for celiac disease are often low in fiber. In such cases, gluten-free sources of fiber should be recommended, such as tapioca, flax, corn, rice, sorghum, and quinoa.

MICRONUTRIENTS

See Chapters 66-72.

Vitamins and minerals, the dietary **micronutrients**, are essential for growth and development and contribute to a host of physiologic functions. Many U.S. children may have suboptimal intake of iron, zinc, potassium, calcium, and vitamins D, E, and K, and excess intake of sodium. Dietary recommendations for micronutrients were originally established to prevent deficiency and currently also include the impact of micronutrients on long-term health outcomes (Table 60.5). Food fortification is an effective strategy to prevent some nutrient deficiencies and has been successfully implemented to prevent iodine, folate, and vitamin D deficiencies.

The DRI for 0-6 months for all micronutrients are AIs, because data are considered to be insufficient to establish an EAR on which an RDA would be based. The AI for the first 6 months of postnatal life is based on the daily mean nutrient intake supplied by human milk for healthy, full-term infants who are exclusively breastfed. For approximately the first 6 months of postnatal life for healthy term infants, an adequately nourished mother produces human milk with adequate amounts of the majority of micronutrients; exceptions are iron and zinc, concentrations of which are unrelated to maternal intake. In the early postnatal months, infants rely on body stores and iron available from the relatively high erythron (especially with delayed cord clamping), and thus the actual dietary requirement for iron is very modest. Infants born prematurely and/or with evidence of fetal growth restriction are likely to have low iron stores at birth and thus may need exogenous iron earlier than 6 months. Zinc concentrations in human milk decline sharply over the first 3-4 months of lactation and are insufficient to meet needs by approximately 6 months. Thus after about 6 months, sources of both iron and zinc are required from complementary foods, such as pureed meats, fortified foods (e.g., infant cereals), or from supplements.

Iron

Iron requirements are relatively higher during infancy and early childhood than later in life and are higher for menstruating females than for males of similar age-groups (see Chapter 72). Iron from animal protein is more bioavailable than that found in animal-source foods such as milk or plant sources because it is already incorporated into heme moieties in blood and muscle. Iron deficiency is the most common micronutrient deficiency in the world and is associated with iron-deficiency anemia and neurocognitive deficits in some children.

Zinc

Zinc deficiency is estimated to affect millions of children in low-resource settings and is associated with increased risk for impaired linear growth (stunting), impaired immune function, and increased risk for respiratory and diarrheal diseases. In high-resource settings, mild deficiency may occur in older infants and toddlers if dietary choices do not include meat or fortified products. Whole grains, legumes, and other high-protein plant sources contain good amounts of zinc, but the absorption bioavailability will be lower compared to animal-source foods.

Vitamin D

Vitamin D insufficiency is more common than previously thought in infants and children. Vitamin D is central to calcium and bone metabolism but is also an important determinant of various nonosseous health outcomes (see Chapter 69). Children of all ages with darker skin and those who do not consume fortified dairy products should be considered for screening for vitamin D deficiency. The DRI for vitamin D is based on its effects on calcium status and bone health. The goal is to achieve serum 25-hydroxyvitamin D levels >50 nmol/L (30 ng/dL). Breast milk is a poor source of vitamin D. The American Academy of Pediatrics (AAP) recommends total vitamin D intake of 400 IU/day for infants (0 to <12 months). A supplement is recommended for all breastfed infants to ensure sufficient intake. The RDA of vitamin D is currently 600 units daily for healthy children 1-18 years of age.

Calcium

Calcium is key to bone health. Adequacy is determined in part by bone mineral content and bone mineral density (BMD). The main storage organs for calcium are the bones and teeth. Bone mineral accretion occurs primarily during childhood, with peak bone mass being achieved by the second to third decade of life. Calcium recommendations include a change from an AI to RDA, in terms of strength of evidence for recommendations, and increased UL in 9- to 18-year-olds (Table 60.6). There are no adequate biomarkers to assess calcium status in healthy children because serum calcium is tightly regulated (regardless of intake and total body calcium) by changes in parathyroid hormone and calcitriol levels. Maintaining adequate serum calcium level despite inadequate intake could come at the expense of BMD. Therefore in the long term, reduced BMD could serve as a surrogate marker of chronic calcium intake and status. It is important to note other determinants of BMD are age, gender, genetic-ethnic factors, hormonal status, physical activity, and weight. Assessments of calcium status should include calcium intake in the diet. It is also important to educate families on additional and alternative sources of calcium (including calcium supplementation) if calcium intake is determined to be low.

Electrolytes

Potassium (K^+) and sodium (Na^+) are the main intracellular and extracellular cations, respectively, and are involved in transport of fluids and nutrients across the cellular membrane. The AI for potassium is related to its effects in maintaining a healthy blood pressure, reducing risk for nephrolithiasis, and supporting bone health. Moderate potassium deficiency occurs even in the absence of hypokalemia and can result in increased blood pressure, stroke, and other CV disease.

For people at increased risk of hypertension and who are salt sensitive, reducing sodium intake and increasing potassium intake is advised. Leafy green vegetables, vine fruits (e.g., tomatoes, eggplant, zucchini, pumpkin), and root vegetables (e.g., yams, beets) are good sources of potassium (see Table 60.6). People with impaired renal function may need to reduce potassium intake, because hyperkalemia can increase the risk for fatal cardiac arrhythmias among these patients.

Most dietary sodium (i.e., sodium chloride, or table salt) in the United States is found in processed foods, breads, and condiments (Fig. 60.5). Sodium salt (NaCl) is added to foods to serve as a preservative and enhance palatability. Sodium has an AI, but given the risk of table salt–related hypertension, an UL has also been set. The UL threshold may be even lower in certain populations, who on average may be more sodium salt sensitive, and for those with hypertension or preexisting renal disease. Dietary sodium intake also displaces potassium intake. Elevated sodium:potassium ratios can increase the risk for nephrolithiasis. Intakes of <2,300 mg sodium (approximately 1 tsp of table salt) per day are recommended. The average daily salt intake for most people in the United States and Canada exceeds both the AI and UL. *For populations with or at risk of hypertension and renal disease, sodium intake should be decreased to <1,500 mg/day and potassium intake increased to >4,700 mg/day.* For persons with hypertension, additional dietary guidelines are available from the **Dietary Approaches to Stop Hypertension (DASH) eating plan.**

WATER

The daily water requirement and water content as a proportion of body weight are highest in infants and decrease with age. Water intake is achieved with liquid and food intake, and losses include excretion in the urine and stool, as well as insensible and evaporative losses through the skin and respiratory tract. An AI has been established for water (see Table 60.6). Special considerations are required by life stages and by BMR, physical activity, body proportions (surface area to volume), environment, and underlying medical conditions. Breast milk and infant formula provide adequate water, and additional water or other fluid intake is not required until complementary foods are introduced. Water contains no calories, but the concern is that additional water intake in young infants will decrease breast milk intake and displace the intake of essential nutrients during this phase of rapid rate of growth and high metabolic activity. The relatively higher fluid needs of

Table 60.5 Dietary Reference Intakes for Vitamins

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Biotin (vitamin B_7)	Coenzyme in synthesis of fat, glycogen, and amino acids	*Infants* (μg/day)			Liver, smaller amounts in fruits and meats	Limited data to support adverse effects with excess; however, high intakes still should be taken with precaution.	None
		0-6 mo	5*	ND			
		7-12 mo	6*	ND			
		Children (μg/day)					
		1-3 yr	8*	ND			
		4-8 yr	12*	ND			
		Males (μg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Females (μg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Pregnancy (μg/day)					
		≤18 yr	30*	ND			
		19-21 yr	30*	ND			
		Lactation (μg/day)					
		≤18 yr	35*	ND			
		19-21 yr	35*	ND			
Choline	Precursor for acetylcholine, phospholipids, and betaine	*Infants* (mg/day)			Milk, liver, eggs, peanuts	Fishy body odor, sweating, salivation, hypotension, hepatotoxicity	Patients with trimethylaminuria, renal disease, liver disease, depression, and Parkinson disease may be at risk for adverse effects with intakes at the UL. AIs have been set for choline, but there are little data to assess whether a dietary supply of choline is needed at all stages of the life cycle because the choline requirement might be met by endogenous synthesis at some of these stages.
		0-6 mo	125*	ND			
		7-12 mo	150*	ND			
		Children (mg/day)					
		1-3 yr	200*	1,000			
		4-8 yr	250*	1,000			
		Males (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	550*	3,000			
		19-21 yr	550*	3,500			
		Females (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	400*	3,000			
		19-21 yr	425*	3,500			
		Pregnancy (mg/day)					
		≤18 yr	450*	3,000			
		19-21 yr	450*	3,500			
		Lactation (mg/day)					
		≤18 yr	550*	3,000			
		19-21 yr	550*	3,500			

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Folate (folic acid, vitamin B_9, folacin); pteroyl-polyglutamates given as dietary folate equivalents (DFEs) 1 DFE = 1 µg food folate = 0.6 µg folate from fortified food, or as supplement consumed with food = 0.5 µg of supplement taken on empty stomach	Coenzyme in metabolism of nucleic and amino acids Prevents megaloblastic anemia	*Infants* (µg/day)			Enriched cereal, grains, dark leafy vegetables, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	Masks neurologic complications in people with vitamin B_{12} deficiency. No adverse effects with folate from food or supplements have been reported; however, high intakes still should be taken with precaution. UL applies to synthetic forms obtained from supplements and/or fortified foods.	Poor intake associated with neural tube defects; therefore all women who can become pregnant should consume, in addition to intake of food folate from a varied diet, 400 µg/day from supplements or fortified foods.
		0-6 mo	65*	ND			
		7-12 mo	80*	ND			
		Children (µg/day)					
		1-3 yr	**150**	300			
		4-8 yr	**200**	400			
		Males (µg/day)					
		9-13 yr	**300**	600			
		14-18 yr	**400**	800			
		19-21 yr	**400**	1,000			
		Females (µg/day)					
		9-13 yr	**300**	600			
		14-18 yr	**400**	800			
		19-21 yr	**400**	1,000			
		Pregnancy (µg/day)					
		≤18 yr	**600**	800			
		19-21 yr	**600**	1,000			
		Lactation (µg/day)					
		≤18 yr	**500**	800			
		19-21 yr	**500**	1,000			
Niacin (vitamin B_3) Includes nicotinic acid amide, nicotinic acid (pyridine-3 carboxylic acid), and derivatives that exhibit biologic activity of nicotinamide Given as niacin equivalents (NE) 1 mg niacin = 60 mg tryptophan Age 0-6 mo: preformed niacin (not NE).	Coenzyme or cosubstrate in many biologic reduction and oxidation reactions, thus required for energy metabolism	*Infants* (mg/day)			Meat, fish, poultry, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	No evidence of adverse effects from consuming naturally occurring niacin in food. Adverse effects from niacin-containing supplements can include flushing and GI distress. UL for niacin applies to synthetic forms obtained from supplements, fortified food, or a combination of these.	Extra niacin may be required by persons treated with hemodialysis or peritoneal dialysis or those with malabsorption syndrome.
		0-6 mo	2*	ND			
		7-12 mo	4*	ND			
		Children (mg/day)					
		1-3 yr	**6**	10			
		4-8 yr	**8**	15			
		Males (mg/day)					
		9-13 yr	**12**	20			
		14-18 yr	**16**	30			
		19-21 yr	**16**	35			
		Females (mg/day)					
		9-13 yr	**12**	20			
		14-18 yr	**14**	30			
		19-21 yr	**14**	35			
		Pregnancy (mg/day)					
		≤18 yr	**18**	30			
		19-21 yr	**18**	35			
		Lactation (mg/day)					
		≤18 yr	**17**	30			
		19-21 yr	**17**	35			

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Pantothenic acid (vitamin B_5)	Coenzyme in fatty acid metabolism	*Infants* (mg/day)			Chicken, beef, potatoes, oats, cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli, whole grains	Doses greater than 10 mg/day may cause mild diarrhea or mild intestinal distress; therefore high intakes should be taken with precaution.	Doses are age-dependent and if the patient is pregnant or lactating.
		0-6 mo	1.7*	ND			
		7-12 mo	1.8*	ND			
		Children (mg/day)					
		1-3 yr	2*	ND			
		4-8 yr	3*	ND			
		Males (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Females (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Pregnancy (mg/day)					
		≤18 yr	6*	ND			
		19-21 yr	6*	ND			
		Lactation (mg/day)					
		≤18 yr	7*	ND			
		19-21 yr	7*	ND			
Riboflavin (vitamin B_2)	Coenzyme in numerous redox reactions	*Infants* (mg/day)			Organ meats, milk, bread products, fortified cereals	No adverse effects associated with vitamin B_2 consumption from food or supplements have been reported; however, high intakes still should be taken with precaution.	None
		0-6 mo	0.3*	ND			
		7-12 mo	0.4*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.3**	ND			
		19-21 yr	**1.3**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.6**	ND			
		19-21 yr	**1.6**	ND			

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Thiamin (vitamin B_1,)	Coenzyme in metabolism of carbohydrates and branched-chain amino acids	*Infants* (mg/day)			Enriched, fortified, or whole-grain products, bread and bread products, mixed foods whose main ingredient is grain, ready-to-eat cereals	No adverse effects associated with vitamin B_1 consumption from food or supplements have been reported; however, high intakes still should be taken with precaution.	Persons being treated with hemodialysis or have a malabsorption syndrome may have increased needs for vitamin B_1.
		0-6 mo	0.2*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.2**	ND			
		19-21 yr	**1.2**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
Vitamin A Includes provitamin A carotenoids that are dietary precursors of retinol Given as retinol activity equivalents (RAEs) 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin To calculate RAEs from REs of provitamin A carotenoids in food, divide REs by 2 For preformed vitamin A in food or supplements and for provitamin A carotenoids in supplements, 1 RE = 1 RAE	Required for normal vision, gene expression, reproduction, embryonic development, and immune function	*Infants* (μg/day)			Liver, dairy products, fish, dark-colored fruit, leafy vegetables	Teratologic effects, liver toxicity (from preformed vitamin A only).	Persons with high alcohol intake, preexisting liver disease, hyperlipidemia, or severe protein malnutrition may be susceptible to the adverse effects of excess preformed vitamin A intake. β-Carotene supplements are advised only to serve as a provitamin A source for persons at risk for vitamin A deficiency.
		0-6 mo	400*	600			
		7-12 mo	500*	600			
		Children (μg/day)					
		1-3 yr	**300**	600			
		4-8 yr	**400**	900			
		Males (μg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**900**	2,800			
		19-21 yr	**900**	3,000			
		Females (μg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**700**	2,800			
		19-21 yr	**700**	3,000			
		Pregnancy (μg/day)					
		≤18 yr	**750**	2,800			
		19-21 yr	**770**	3,000			
		Lactation (μg/day)					
		≤18 yr	**1,200**	2,800			
		19-21 yr	**1,300**	3,000			

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Pyridoxine (vitamin B_6) Comprises a group of six related compounds: pyridoxal, pyridoxine, pyridoxamine, and 5′-phosphates (PLP, PNP, PMP)	Coenzyme in metabolism of amino acids, glycogen, and sphingoid bases	*Infants* (mg/day)			Fortified cereals, organ meats, fortified soy-based meat substitutes	No adverse effects associated with vitamin B_6 from food have been reported; however, high intakes still should be taken with precaution. Sensory neuropathy, ataxia, and nausea have occurred from high intakes (>1,000 mg/day) of supplemental forms.	Deficiencies often occur when other B vitamins in the body are low, particularly vitamin B_{12} and folic acid. Risk of developing deficiency is associated with conditions such as kidney disease, celiac disease, inflammatory bowel disease, rheumatoid arthritis, and alcohol use.
		0-6 mo	0.1*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	30			
		4-8 yr	**0.6**	40			
		Males (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.3**	80			
		19-21 yr	**1.3**	100			
		Females (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.2**	80			
		19-21 yr	**1.3**	100			
		Pregnancy (mg/day)					
		≤18 yr	**1.9**	80			
		19-21 yr	**1.9**	100			
		Lactation (mg/day)					
		≤18 yr	**2.0**	80			
		19-21 yr	**2.0**	100			
Cobalamin (vitamin B_{12})	Coenzyme in nucleic acid metabolism Prevents megaloblastic anemia	*Infants* (μg/day)			Fortified cereals, meat, fish, poultry		Because 10–30% of older people malabsorb food-bound vitamin B_{12}, those >50 yr are advised to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}.
		0-6 mo	0.4*	ND			
		7-12 mo	0.5*	ND			
		Children (μg/day)					
		1-3 yr	**0.9**	ND			
		4-8 yr	**1.2**	ND			
		Males (μg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Females (μg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Pregnancy (μg/day)					
		≤18 yr	**2.6**	ND			
		19-21 yr	**2.6**	ND			
		Lactation (μg/day)					
		≤18 yr	**2.8**	ND			
		19-21 yr	**2.8**	ND			

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin C (ascorbic acid, dehydroascorbic acid)	Cofactor for reactions requiring reduced copper or iron metalloenzyme and as a protective antioxidant	*Infants* (mg/day)			Citrus fruit, tomatoes, tomato juice, potatoes, brussels sprouts, cauliflower, broccoli, strawberries, cabbage, spinach	GI disturbances, kidney stones, excess iron absorption	Smokers require additional 35 mg/day of vitamin C over that needed by nonsmokers. Nonsmokers regularly exposed to tobacco smoke should ensure they meet the RDA for vitamin C.
		0-6 mo	40*	ND			
		7-12 mo	50*	ND			
		Children (mg/day)					
		1-3 yr	**15**	400			
		4-8 yr	**25**	650			
		Males (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**75**	1,800			
		19-21 yr	**90**	2,000			
		Females (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**65**	1,800			
		19-21 yr	**75**	2,000			
		Pregnancy (mg/day)					
		≤18 yr	**80**	1,800			
		19-21 yr	**85**	2,000			
		Lactation (mg/day)					
		≤18 yr	**115**	1,800			
		19-21 yr	**120**	2,000			
Vitamin E (α-tocopherol) α-tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, RRS-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements	A metabolic function has not yet been identified. Vitamin E's major function appears to be as a nonspecific chain-breaking antioxidant.	*Infants* (mg/day)			Vegetable oil, unprocessed cereal grains, nuts, fruit, vegetables, meat	No evidence of adverse effects from consuming vitamin E naturally occurring in food. Adverse effects from supplements may include hemorrhagic toxicity. UL applies to any form of α-tocopherol obtained from supplements, fortified foods, or a combination of these.	Persons receiving anticoagulant therapy are at risk of excess bleeding when taking vitamin E supplements in doses greater than 1,000 mg/day.
		0-6 mo	4*	ND			
		7-12 mo	5*	ND			
		Children (mg/day)					
		1-3 yr	**6**	200			
		4-8 yr	**7**	300			
		Males (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Females (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Pregnancy (mg/day)					
		≤18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Lactation (mg/day)					
		≤18 yr	**19**	800			
		19-21 yr	**19**	1,000			

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin K	Coenzyme during synthesis of many proteins involved in blood clotting and bone metabolism	*Infants* (μg/day)			Green vegetables (collards, spinach, salad greens, broccoli), brussels sprouts, cabbage, plant oil, margarine	No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals; however, high intakes still should be taken with precaution.	Patients receiving anticoagulant therapy or taking long-term antibiotics should monitor vitamin K intake.
		0-6 mo	2.0*	ND			
		7-12 mo	2.5*	ND			
		Children (μg/day)					
		1-3 yr	30*	ND			
		4-8 yr	55*	ND			
		Males (μg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	120*	ND			
		Females (μg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	90*	ND			
		Pregnancy (μg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			
		Lactation (μg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			

Note: Starred (*) numbers are adequate intake (AI) and **bold** numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97–98% of members in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, or inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data on adverse effects in this age-group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*RDA for vitamin D in IU/day: 400 if <1 yr age, 600 if >1 yr, lactating, or pregnant.

AI, Adequate intake; GI, gastrointestinal; ND, not determinable; PLP, pyridoxal phosphate; PMP, pyridoxamine phosphate; PNP, pyridoxine phosphate; RDA, recommended dietary allowance; UL, upper limit of normal.

Data from Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride, 1997; Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline, 1998; Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids, 2000; Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc, 2001; Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids, 2002/2005; Dietary reference intakes for calcium and vitamin D, 2011. These reports may be accessed via www.nap.edu

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.6 Dietary Reference Intakes for Select Micronutrients and Water

NUTRIENT	FUNCTION	LIFE STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Sodium	Maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted meats, bread, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table. Salt is about 40% sodium by weight.	Hypertension, increased risk of cardiovascular disease and stroke	AI is set based on ability to obtain a nutritionally adequate diet for other nutrients and to meet the needs for sweat losses for persons engaged in recommended levels of physical activity. Persons engaged in activity at higher levels or in humid climates resulting in excessive sweating might need more than the AI. UL applies to apparently healthy persons without hypertension; it thus may be too high for persons who already have hypertension.
		0-6 mo	120	ND			
		7-12 mo	370	ND			
		Children					
		1-3 yr	1,000	1,500			
		4-8 yr	1,200	1,900			
		Males					
		9-13 yr	1,500	2,200			
		14-21 yr	1,500	2,300			
		Females					
		9-13 yr	1,500	2,200			
		13-21 yr	1,500	2,300			
		Pregnancy and Lactation					
		≥14 yr	1,500	2,300			
Chloride	With sodium, maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added table salt, benzoate, phosphate; salted meats, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table. Salt is about 60% chloride by weight.	In concert with sodium, results in hypertension	Chloride is lost, usually with sodium, in sweat and in vomiting and diarrhea. AI and UL are equimolar in amount to sodium because most of sodium in diet comes as table salt.
		0-6 mo	180	ND			
		7-12 mo	570	ND			
		Children					
		1-3 yr	1,500	2,300			
		4-8 yr	1,900	2,900			
		Males					
		9-13 yr	2,300	3,400			
		14-21 yr	2,300	3,600			
		Females					
		9-13 yr	2,300	3,400			
		13-21 yr	2,300	3,600			
		Pregnancy and Lactation					
		≥14 yr	2,300	3,600			
Potassium	Maintains fluid volume inside/outside of cells and thus normal cell function; acts to blunt the rise of blood pressure in response to excess sodium intake and decrease markers of bone turnover and recurrence of kidney stones	*Infants*			Fruits and vegetables, dried peas, dairy products, meats, nuts	None documented from food alone, but potassium from supplements or salt substitutes can result in hyperkalemia and possibly sudden death if excess is consumed by persons with chronic renal insufficiency (kidney disease) or diabetes	Persons taking drugs for cardiovascular disease such as ACE inhibitors, ARBs, or potassium-sparing diuretics should be careful not to consume supplements containing potassium and might need to consume less than the AI.
		0-6 mo	400	None set			
		7-12 mo	700				
		Children					
		1-3 yr	3,000	No UL			
		4-8 yr	3,800				
		Males					
		9-13 yr	4,500				
		14-21 yr	4,700				
		Females					
		9-13 yr	4,500				
		13-21 yr	4,700				
		Pregnancy					
		≥14 yr	4,700				
		Lactation					
		≥14 yr	5,100				

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.6 Dietary Reference Intakes for Select Micronutrients and Water—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin D (calciferol) 1 µg calciferol = 40 IU vitamin D DRI values are based on absence of adequate exposure to sunlight.	Maintains serum calcium and phosphorus concentrations	*Infants (µg/day)**			Fish liver oils, flesh of fatty fish, liver, eggs from hens that have been fed vitamin D, fortified milk products, fortified cereals	Elevated plasma 25(OH)D concentration causing hypercalcemia	Patients receiving glucocorticoid therapy might require additional vitamin D.
		0-6 mo	10	25			
		7-12 mo	10	38			
		*Children (µg/day)**					
		1-3 yr	15	63			
		4-8 yr	15	75			
		*Males (µg/day)**					
		9-21 yr	15	100			
		*Females (µg/day)**					
		9-21 yr	15	100			
		*Pregnancy (µg/day)**					
		≤18 yr	15	100			
		Lactation (µg/day)					
		≤18 yr	15	100			
		19-21 yr	15	100			
Calcium	Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation	*Infants*			Milk, cheese, yogurt, corn tortillas, calcium-set tofu, Chinese cabbage, kale, broccoli	Kidney stones, hypercalcemia, milk alkali syndrome, renal insufficiency	Amenorrheic women (exercise or anorexia nervosa induced) have reduced net calcium absorption.
		0-6 mo	200	1,000			
		7-12 mo	260	1,500			
		Children					
		1-3 yr	700	2,500			
		4-8 yr	1,000	2,500			
		Males					
		9-18 yr	1,300	3,000			
		19-21 yr	1,000	2,500			
		Females					
		9-18 yr	1,300	3,000			
		19-21 yr					
		Pregnancy					
		≤18 yr	1,300	3,000			
		19-21 yr	1,000	2,500			
		Lactation					
		≤18 yr	1,300	3,000			
		19-21 yr	1,000	2,500			

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.6 Dietary Reference Intakes for Select Micronutrients and Water—cont'd

NUTRIENT	FUNCTION	LIFE STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Iron	Critical component of enzymes, cytochromes, myoglobin, and hemoglobin	*Infants*			Heme sources: meat, poultry, fish Nonheme sources: dairy, eggs, plant-based foods like whole grains, nuts, seeds, legumes, and leafy greens, breads, cereals, breakfast foods	GI distress	Persons with decreased gastric acidity may be at increased risk for deficiency. Cow's milk is a poor source of bioavailable iron and is not recommended for children <1 yr old. Neurocognitive deficits have been reported in infants with iron deficiency. RDA for females increases with menarche related to increased losses during menstruation. Vegans and vegetarians might require iron supplementation or intake of iron-fortified foods. GI parasites can increase iron losses via GI bleeds. Iron supplements can interfere with zinc absorption, and vice versa; if supplements are being used, the doses should be staggered.
		0-6 mo	0.27	40			
		7-12 mo	**11**	40			
		Children					
		1-3 yr	**7**	40			
		4-8 yr	**10**	40			
		Males					
		9-13 yr	**8**	40			
		14-18 yr	**11**	45			
		19-21 yr	**8**	45			
		Females					
		9-13 yr	**8**	40			
		14-18 yr	**15**	45			
		19-21 yr	**18**	45			
		Pregnancy					
		≤18 yr	**27**	45			
		19-21 yr	**27**	45			
		Lactation					
		≤18 yr	**10**	45			
		19-21 yr	**9**	45			
Zinc	Essential for proper growth and development; important catalyst for 100 specific enzymes	*Infants*			Meats, shellfish, legumes, fortified cereals, whole grains	Acutely, zinc supplements cause GI irritation and headache; chronic effects of zinc supplementation include impaired immune function, changes in lipoprotein and cholesterol levels, and reduced copper status.	Zinc supplements interfere with iron absorption, and vice versa; therefore if supplements are being used, the doses should be staggered. Zinc deficiency can be associated with stunting or impaired linear growth.
		0-6 mo	2	4			
		7-12 mo	**3**	5			
		Children					
		1-3 yr	**3**	7			
		4-8 yr	**5**	12			
		Males					
		9-13 yr	**8**	23			
		14-18 yr	**11**	34			
		19-21 yr	**11**	40			
		Females					
		9-13 yr	**8**	23			
		14-18 yr	**9**	34			
		19-21 yr	**8**	40			
		Pregnancy					
		≤18 yr	**12**	34			
		19-21 yr	**11**	40			
		Lactation					
		≤18 yr	**13**	34			
		19-21 yr	**12**	40			

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 60.6 Dietary Reference Intakes for Select Micronutrients and Water—cont'd

Water	Maintains homeostasis in the body Allows transport of nutrients to cells and removal and excretion of waste products of metabolism	*Infants* (L/day)		None set	All beverages, including water Moisture in foods High-moisture foods include watermelon, meats, and soups	No UL because normally functioning kidneys can handle >0.7 L (24 oz) of fluid per hour. Symptoms of water intoxication include hyponatremia, which can result in heart failure, and rhabdomyolysis (skeletal muscle tissue injury), which can lead to kidney failure.	Recommended intakes for water are based on median intakes of generally healthy persons who are adequately hydrated. Persons can be adequately hydrated at levels above or below the AIs provided; AIs provided are for total water in temperate climates. All sources can contribute to total water needs: beverages (tea, coffee, juice, soda, drinking water) and moisture found in foods. Moisture in food accounts for about 20% of total water intake. Thirst and consumption of beverages at meals are adequate to maintain hydration.
		0-6 mo	0.7				
		7-12 mo	0.8				
		Children					
		1-3 yr	1.3				
		4-8 yr	1.7				
		Males (L/day)					
		9-13 yr	2.4				
		14-18 yr	3.3				
		≥19 yr	3.7				
		Females (L/day)					
		9-13 yr	2.1				
		14-18 yr	2.3				
		≥19 yr	2.7				
		Pregnancy (L/day)					
		≥14 yr	3.0				
		Lactation (L/day)					
		≥14 yr	3.8				

Note: **Bold** numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97–98% of members in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of a group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, or inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data on adverse effects in this age-group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Vitamin D RDA in IU/day: 400 if <1 yr, 600 if >1 yr of age or pregnant or lactating.

ACE, Angiotensin-converting enzyme; AI, adequate intake; ARB, angiotensin receptor blocker; GI, gastrointestinal; ND, not determinable; RDA, recommended dietary allowance; UL, upper limit of normal.

Data from Food and Nutrition Board, U.S. Institute of Medicine. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (http://www.nap.edu/openbook.php?record_id=10925); and Ross AC, U.S. Institute of Medicine, Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes: Calcium, Vitamin D. Washington, DC: National* Academies Press; 2011: pp. xv, 536

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

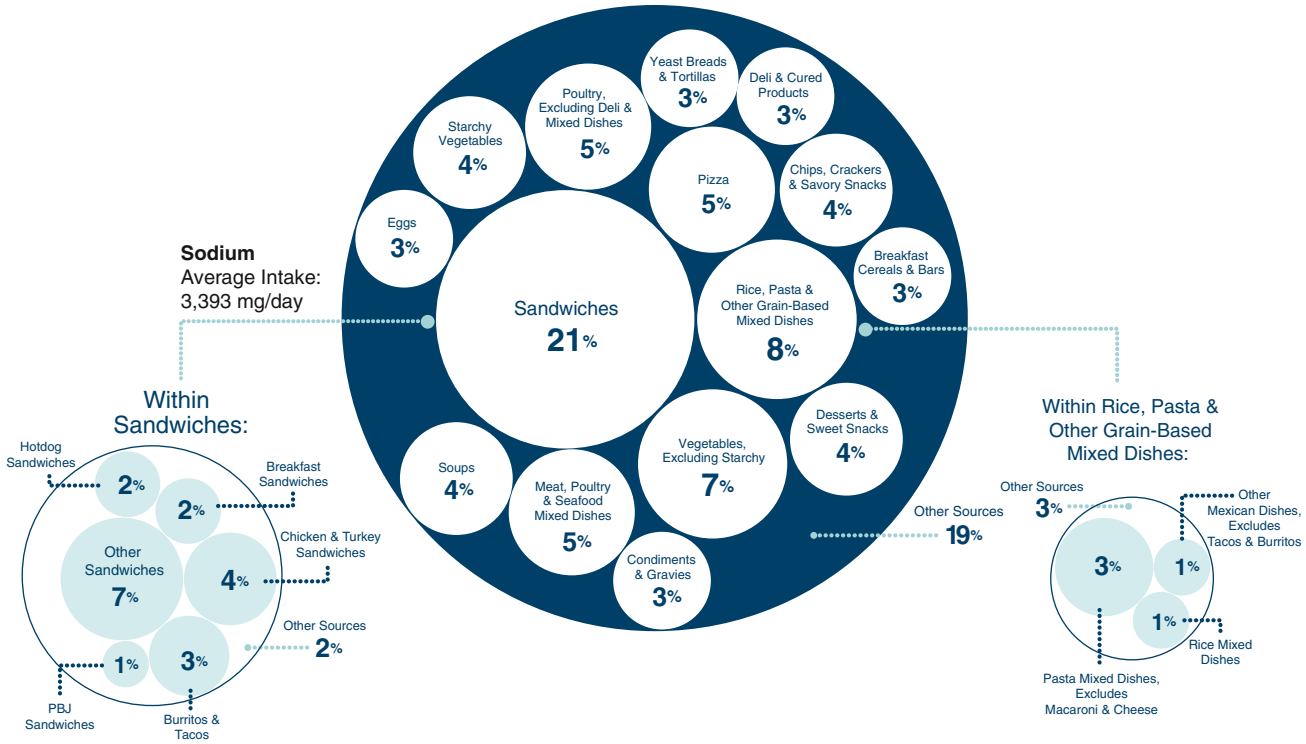

Fig. 60.5 Top sources and average intakes of sodium: U.S. population age 1 and older. Estimates based on 2-day dietary intake data, weighted, from What We Eat in America (WWEIA), National Health and Nutrition Examination Survey (NHANES), 2013-2016. (*From Dietary Guidelines for Americans. 2020-2025, Chapter 1: Nutrition and Health Across the Lifespan. Fig 1.12.* https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf.)

Table 60.7 Growth Chart Comparisons for Measuring Growth from Birth to 20 Years

GROWTH CHART	AGE RANGE	GROWTH METRICS	INSUFFICIENT GROWTH PERCENTILE	EXCESSIVE GROWTH PERCENTILE	BMI STATUS PERCENTILE
World Health Organization, 2006	Birth to 2 yr	Weight, length, weight-for-length, and head circumference	<2.3rd	>97.7th	—
U.S. Centers for Disease Control and Prevention, 2000	2-20 yr	Weight, height, body mass index (BMI)	<5th	>95th	Under (<5th) Normal (5-85th) Over (85-95th) Obese (>95th) Severe obesity (≥120% of 95th or ≥35 kg/m^2)

infants and young children can be explained in part by the high ratio of body surface area to volume in infancy, high respiratory rate, and rapid growth.

The consequences of inadequate fluid intake include impaired thermoregulation and heat dissipation, reduced activity tolerance and performance, and reduced intravascular fluid and dehydration. Inadequate fluid intake may be reflected by decreased urine output. These deficits can result in an increased compensatory heart rate, hypotension, and syncope, and if uncorrected, renal injury or nephrolithiasis. "Free water" is defined as water in the body that can be removed by ultrafiltration and in which substances can be dissolved. Excess free water intake is usually better tolerated by healthy adults than by younger children, who are at increased risk for water intoxication. Hyponatremia can result when water and sodium are out of balance, such as excess free water intake coupled with inadequate sodium intake. Fluid intake requirements and restrictions are also influenced by any underlying renal and hormonal disorders, including diabetes, the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and diabetes insipidus.

MEASURING NUTRITIONAL ADEQUACY

The U.S. Centers for Disease Control and Prevention (CDC) and AAP recommend the use of the WHO charts to monitor growth of all infants and children (human milk–fed and infant formula–fed) from birth to 2 years, and the use of the CDC 2000 growth charts for children 2-20 years (see Chapters 19 and 27). The WHO growth charts are derived from longitudinal and cross-sectional data obtained from a sample of healthy breastfed infants and children (0-2 years) who were receiving adequate nutritional intake and medical care in Brazil, Ghana, India, Norway, Oman, and the United States. Consequently, the WHO/CDC 0-2 year growth charts are considered *standards* and describe the ideal growth of adequately nourished healthy children under best-care practices. The CDC 2-20 year charts are considered *references* and describe the population's average growth and distribution.

In the clinical setting, the 2.3rd and 97.7th percentiles on the WHO growth charts are used to identify *insufficient* and *excessive* growth from birth to 2 years, respectively. In contrast, the 5th and 95th percentiles are recommended for the equivalent identification in the CDC growth charts from 2 to 20 years (Table 60.7). Note that length, weight, and

weight-for-length are used in the WHO growth charts from birth to 2 years. *Body mass index* (BMI) can be calculated but is not recommended for use in children <2 years. Stature, weight, and BMI are used in the CDC 2000 growth charts from 2 to 20 years of age. These charts can be used to categorize children as *underweight* (<5th BMI percentile), normal weight (5-85th), overweight (85-95th), and obese (≥95th BMI percentile).

Severe obesity is defined as BMI ≥120% of the 95th percentile or BMI ≥35 kg/m^2 (whichever is lower). This assessment corresponds to approximately the 99th percentile or a BMI *z* score ≥2.33. Severe obesity that exceeds the 99th percentile is tracked on a specialized percentile curve for obesity. Furthermore, adult classification is used for BMI ≥27 kg/m^2 in adolescents over age 18 for consideration of medication and bariatric surgery.

It is important to consider the limitations in the use of WHO and CDC growth charts for certain populations such as premature infants, children with certain genetic disorders (e.g., Turner syndrome, Down syndrome, Wolf-Hirschhorn syndrome, achondroplasia) and children with cerebral palsy. Specific growth charts addressing the unique growth characteristics of these children are available from various resources, including the AAP.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 61

Feeding Healthy Infants, Children, and Adolescents

Katherine J. Barrett, Stephanie P. Gilley, Matthew A. Haemer, Nancy F. Krebs, and Susan L. Johnson

Early feeding experiences can support the development of healthy eating habits, optimal growth and development, and prevention of chronic disease throughout the life course. Childhood nutrition is known to play a role in the origin of adult diseases such as type 2 diabetes, hypertension, obesity, and metabolic syndrome. To support development and to prevent chronic disease, appropriate feeding practices are best established in the neonatal period and continued throughout childhood and adolescence to adulthood. Healthful feeding in children requires partnerships between family members, the healthcare system, schools, the community, and policy makers.

FEEDING DURING THE FIRST YEAR OF LIFE

Breastfeeding

The American Academy of Pediatrics (AAP) and World Health Organization (WHO) have declared breastfeeding and the administration of human milk to be the ideal practice for infant feeding and nutrition. Breastfeeding has documented short- and long-term medical and neurodevelopmental advantages and rare contraindications (Tables 61.1, 61.2, and 61.3). The AAP and the WHO recommend that infants be exclusively fed human breast milk for approximately 6 months. Breastfeeding ideally should be continued with the introduction of complementary foods until 24 months of age or longer, if mutually desired by the mother and infant. We recognize that there are some lactating individuals who do not identify as women/mothers and may prefer the use of other terms, including the use of chestfeeding in lieu of breastfeeding. This is a consideration that a practitioner may need to make when speaking to a family member who uses these alternative terms. The success of breastfeeding initiation and continuation depends on multiple factors, such as education about breastfeeding, hospital breastfeeding practices and policies, routine and timely follow-up care, family and societal support, and the health of the mother (Tables 61.4 and 61.5). Breastfeeding support from both professionals and lay individuals has a positive impact on breastfeeding success, and the importance of such support cannot be overstated.

Table 61.1 Selected Beneficial Properties of Human Milk Compared with Infant Formula

FACTOR	ACTION
ANTIBACTERIAL FACTORS	
Secretory IgA	Specific antigen-targeted antiinfective action
Lactoferrin	Immunomodulation, iron chelation, antimicrobial action, antiadhesive, trophic for intestinal growth
κ-Casein	Antiadhesive, bacterial flora
Oligosaccharides	Prevention of bacterial attachment
Cytokines	Antiinflammatory, epithelial barrier function
GROWTH FACTORS	
Epidermal growth factor	Luminal surveillance, repair of intestine
Transforming growth factor (TGF)	Promotes epithelial cell growth (TGF-β) Suppresses lymphocyte function (TGF-β)
Nerve growth factor	Promotes neural growth
ENZYMES	
Platelet-activating factor (PAF)–acetylhydrolase	Blocks action of PAF
Glutathione peroxidase	Prevents lipid oxidation
Nucleotides	Enhance antibody responses, bacterial flora

Adapted from Hamosh M. Bioactive factors in human milk. *Pediatr Clin North Am.* 2001;48:69–86.

Feedings are initiated soon after birth unless medical conditions preclude them. Mothers can be encouraged to feed at both breasts at each feeding, starting with the breast offered second at the last feeding. For optimal milk production, it is preferable to fully empty the first breast before moving to the second breast, rather than partially emptying both sides. It is not unusual for an infant to fall asleep after the first breast and refuse the second. Table 61.6 summarizes patterns of milk supply in the first week. Pacifiers may help prevent sudden infant death syndrome in breastfed infants, but it is not recommended to introduce until breastfeeding is well established and should not be used to try to increase time between feeds or in lieu of a feed in a baby showing hunger cues.

Breastfeeding is a learned skill for both mother and infant, and support from a provider knowledgeable in breastfeeding is critical, especially as milk production is established in the first few weeks postpartum. It is helpful to instruct new mothers about infant hunger cues and correct nipple latch, positioning of the infant on the breast, and feeding frequency. It is also suggested that someone trained in lactation observe a feeding to evaluate positioning, latch, milk transfer, maternal responses, and infant satiety. Attention to these issues during the newborn period allows dialog with the mother and family and can prevent problems that could occur with improper technique or knowledge of breastfeeding. Discussions about normal infant feeding, infant elimination patterns, breast engorgement, breast care, and maternal nutrition are important aspects of the hospital discharge process. A follow-up appointment with a lactation specialist is recommended within 24-48 hours after hospital discharge. The AAP recommends that exclusively breastfed infants start supplementation with vitamin D (10 mcg, or 400 IU) by 2 weeks of life.

Table 61.2 Absolute and Relative Contraindications to Breastfeeding Because of Maternal Health Conditions

MATERNAL HEALTH CONDITION	DEGREE OF RISK
HIV and HTLV infection	In the United States, breastfeeding is contraindicated. In other settings, health risks of not breastfeeding must be weighed against the risk of transmitting the virus to the infant.
Tuberculosis infection	Direct breastfeeding is contraindicated until completion of approximately 2 wk of appropriate maternal therapy.
Varicella-zoster infection	Infant should not have direct contact with active lesions. Infant should receive immune globulin.
Herpes simplex infection	Breastfeeding is contraindicated with active herpetic lesions of the breast.
CMV infection	May be found in milk of mothers who are CMV seropositive. Transmission through human milk causing symptomatic illness in term infants is uncommon.
Hepatitis B infection	Infants routinely receive hepatitis B immune globulin and hepatitis B vaccine if mother is HBsAg positive. No delay in initiation of breastfeeding is required.
Hepatitis C infection	Breastfeeding is not contraindicated.
COVID-19	Maternal infection is not a contraindication for breastfeeding or feeding expressed milk.
Ebola	Confirmed maternal Ebola infection is a contraindication to breastfeeding and expressed milk.
Brucellosis	Active untreated brucellosis is a contraindication to breastfeeding and expressed milk.
Live vaccines	Smallpox and yellow fever live-virus vaccines are contraindicated for breastfeeding mothers.
Alcohol intake	Limit maternal alcohol intake to <0.5 g/kg/day (for a woman of average weight—this is the equivalent of 2 cans of beer, 2 glasses of wine, or 2 oz of liquor).
Cigarette smoking	Discourage cigarette smoking, but smoking is not a contraindication to breastfeeding.
Marijuana usage	Metabolites, including tetrahydrocannabinol, are detectable in breast milk. Marijuana usage is not recommended but is not a strict contraindication to breastfeeding.
Chemotherapy, radiopharmaceuticals	Breastfeeding is generally contraindicated.

CMV, Cytomegalovirus; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.
Adapted from Schanler RJ, Krebs NF, Mass SB (eds). *Breastfeeding Handbook for Physicians*, 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014: 223–226.

Table 61.3 Conditions for Which Human Milk May Have a Protective Effect

INFANT		MOTHER
• Diarrhea • Otitis media • Urinary tract infection • Necrotizing enterocolitis • Septicemia • Infant botulism • Insulin-dependent diabetes mellitus • Celiac disease	• Crohn disease • Lymphoma • Leukemia • Recurrent otitis media • Atopy • Hospitalizations for respiratory illness • Sudden infant death syndrome • Obesity	• Uterine atony • Breast cancer • Ovarian cancer • Cardiovascular disease • Obesity • Type 2 diabetes

Table 61.4 Ten Hospital Practices to Encourage and Support Breastfeeding*†

1. Have a written breastfeeding policy that is routinely communicated to all healthcare staff.
2. Train all healthcare staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help women initiate breastfeeding within 1 hour of birth.
5. Show women how to breastfeed and how to maintain lactation, even if they are separated from their newborns.
6. Give newborns no food or drink other than breast milk unless medically indicated.
7. Practice rooming-in; allow mothers and newborns to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no pacifiers or artificial nipples to breastfeeding infants.‡
10. Foster the establishment of breastfeeding support groups and refer to them on discharge from the hospital or birth center.

COMPONENTS OF SAFE POSITIONING FOR THE NEWBORN WHILE SKIN-TO-SKIN**

1. Infant's face can be seen.
2. Infant's head is in "sniffing" position.
3. Infant's nose and mouth are not covered.
4. Infant's head is turned to one side.
5. Infant's neck is straight, not bent.
6. Infant's shoulders and chest face mother.
7. Infant's legs are flexed.
8. Infant's back is covered with blankets.
9. Mother-infant dyad is monitored continuously by staff in the delivery environment and regularly on the postpartum unit.
10. When mother wants to sleep, infant is placed in bassinet or with another support person who is awake and alert.

*The 1994 report of the Healthy Mothers, Healthy Babies National Coalition Expert Work Group recommend that the UNICEF-WHO Baby Friendly Hospital Initiative be adapted for use in the United States as the United States Breastfeeding Health Initiative, using the adapted 10 hospital practices noted.
†Data from Baby-Friendly USA. Guidelines and evaluation criteria for facilities seeking baby-friendly designation. Sandwich, MA: Baby Friendly USA; 2010. Available at https://www.babyfriendlyusa.org/for-facilities/practice-guidelines/. Accessed 10 November 2022. From ACOG Committee Opinion. Optimizing support for breastfeeding as part of obstetric practice. *Obstet Gynecol.* 2018;132(4):e187–e195, Boxes 1 and 2, pp. e191–e192.
‡The American Academy of Pediatrics endorsed the UNICEF-WHO Ten Steps to Successful Breastfeeding, but does not support a categorical ban on pacifiers because of their role in reducing the risk of sudden infant death syndrome and their analgesic benefit during painful procedures when breastfeeding cannot provide the analgesia.
**Data from Ludington-Hoe SM, Morgan K. Infant assessment and reduction of sudden unexpected postnatal collapse risk during skin-to-skin contact. *Newborn Infant Nurs Rev.* 2014;14:28–33.

Nipple pain is one of the most common complaints of breastfeeding mothers in the immediate postpartum period. Poor infant positioning and improper latch are the most common reasons for nipple pain beyond the mild discomfort felt early in breastfeeding. If the problem persists and the infant refuses to feed, evaluation for **nipple candidiasis** is indicated. If candidiasis is present, the nipples can be treated with an antifungal cream that is wiped off of the breast before feeding, and the infant is treated with an oral antifungal medication.

Tongue-tie (ankyloglossia) has been associated with nipple pain, poor latching, and poor weight gain in breastfed and bottle-fed infants. Ankyloglossia is defined as a lingual frenulum that attaches close to the anterior tongue tip and is estimated to be present in 4–11% of newborns. *Frenotomy* is a minor surgical procedure with few complications

Table 61.5 Recommendations on Breastfeeding Management for Healthy Term Infants

1. Exclusive breastfeeding for about 6 months
   - Breastfeeding preferred; alternatively, expressed mother's milk or donor breast milk
   - To continue for 2 years or beyond as long as mutually desired by mother and child
   - Complementary foods rich in iron, zinc, and other micronutrients should be introduced at about 6 mo of age
2. Peripartum policies and practices that optimize breastfeeding initiation and maintenance should be compatible with the AAP and Academy of Breastfeeding Medicine Model Hospital Policy and include the following:
   - Direct skin-to-skin contact with mothers immediately after delivery until the first feeding is accomplished and encouraged throughout the postpartum period
   - Delay in routine procedures (weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis) until after the first feeding is completed
   - Delay in administration of intramuscular vitamin K until after the first feeding is completed but within 6 hr of birth
   - Ensure 8-12 feedings at the breast every 24 hr
   - Ensure formal evaluation and documentation of breastfeeding by trained caregivers (including position, latch, milk transfer, examination) at least once for each nursing shift
   - Give no supplements (water, glucose water, commercial infant formula, or other fluids) to breastfeeding newborn infants unless medically indicated using standard evidence-based guidelines for the management of hyperbilirubinemia and hypoglycemia
   - Avoid routine pacifier use in the postpartum period
   - Begin daily oral vitamin D drops (400 IU) at hospital discharge
3. All breastfeeding infants should be seen by a pediatrician within 48-72 hr after discharge from the hospital
   - Evaluate hydration and elimination patterns
   - If weight >7% below birthweight or there is additional weight loss on day 5 or later, providers should consider more frequent follow-ups and/or referral to a lactation consultant.
   - Discuss maternal/infant issues
   - Observe feeding
4. Mother and infant should sleep in proximity to each other to facilitate breastfeeding
5. Pacifier should be offered, while placing infant in back-to-sleep-position, no earlier than 3-4 weeks of age and after breastfeeding has been established

From American Academy of Pediatrics (AAP). Breast-feeding and the use of human milk. *Pediatrics.* 2012;129:e827–e841.

Table 61.6 Patterns of Milk Supply

DAY OF LIFE	MILK SUPPLY
Day 1	Some milk (~5 mL) may be expressed.
Days 2-4	Lactogenesis; milk production increases.
Day 5	Milk present; fullness and leaking are felt.
Day 6 onward	Breasts should feel "empty" after feeding.

Adapted from Neifert MR. Clinical aspects of lactation: promoting breastfeeding success. *Clin Perinatol.* 1999;26:281–306.

and has been used as a treatment option for ankyloglossia with increasing frequency despite *insufficient evidence* that it improves breastfeeding outcomes, making its use somewhat controversial. Most infants with ankyloglossia have no feeding problems, and most infants with nursing problems do not have ankyloglossia. Providing a feeding evaluation and assessment of latch while monitoring weight over the course of 2-3 weeks may be more valuable than proceeding immediately to frenotomy. During that time many feeding issues resolve, thus avoiding unnecessary frenotomy.

Engorgement may occur in the second stage of lactogenesis (typically days 3-10 postpartum) and is characterized by the breasts feeling firm, overfilled, and sometimes painful. Incomplete removal of milk as a result of ineffective breastfeeding technique or infant illness can cause engorgement. Breastfeeding immediately at signs of infant hunger can prevent this from occurring. To reduce engorgement, breasts may be softened before infant feeding with a combination of hot compresses and manual expression of milk. To reduce inflammation and pain, between feedings mothers can wear a supportive bra, apply cold compresses, and take oral nonsteroidal antiinflammatory drugs (NSAIDs).

Mastitis occurs in 2–3% of lactating women and is usually unilateral, manifesting with localized warmth, tenderness, edema, and erythema after the second postdelivery week. Sudden onset of breast pain, myalgia, and fever with fatigue, nausea, vomiting, and headache can also occur. Organisms implicated in mastitis include *Staphylococcus aureus, Escherichia coli,* group A streptococcus, *Haemophilus influenzae, Klebsiella pneumoniae,* and *Bacteroides* species. Diagnosis is confirmed by physical examination. Treatment is with oral antibiotics (most commonly dicloxacillin or cephalexin) and analgesics, while at the same time promoting breastfeeding or emptying of the affected breast. A **breast abscess** is a much less common complication of mastitis, but it is a more serious infection that requires intravenous antibiotics and incision and drainage, along with continued breast emptying. Washing hands thoroughly before breastfeeding or pumping, especially after changing the baby's diapers, can help minimize risk for breast infections.

Insufficient milk intake, dehydration, and jaundice in the infant can occur within the first weeks of life. In fact, retrospective studies suggest higher rates of hospitalization—primarily caused by jaundice and poor weight gain—in the first month of life for breastfed versus formula-fed babies, highlighting the *critical importance of lactation support*. Breastfed neonates feed 8-12 times a day. Signs that milk intake is not adequate include lethargy, delayed stooling, decreased urine output, weight loss >10% of birthweight, hypernatremic dehydration, inconsolable crying, and increased hunger. Insufficient milk intake may be caused by inadequate milk production and/or health conditions in the infant that prevent proper breast stimulation. Careful attention to prenatal history can identify maternal factors associated with low milk production (for example, obesity, type 2 diabetes, postpartum hemorrhage, or failure of breasts to enlarge during pregnancy or within the first few days after delivery). Excess weight loss or failure to return to birthweight by 7-10 days in an exclusively breastfed infant should trigger an evaluation of breastfeeding effectiveness. Direct observation of breastfeeding can help identify improper technique, and test weighs (weighing the infant before and after feeding) may help assess milk transfer. If a large volume of milk is expressed manually after breastfeeding, the infant might not be extracting enough milk, eventually leading to decreased milk output. Late preterm infants (34-36 weeks) are at particular risk for insufficient milk intake because of weak suck, difficulty coordinating suck and swallow patterns, or medical issues.

Breastfeeding jaundice, also referred to as *suboptimal intake jaundice,* is related to insufficient fluid intake during the first week of life and is a common reason for hospital readmission of healthy breastfed infants (see Chapter 137). Breastfeeding jaundice is associated with dehydration and hypernatremia. Treatment may require supplementation with expressed maternal breast milk, donor milk, or infant formula**.** ***Breast milk*** **jaundice** is a different disorder that causes persistently high serum indirect bilirubin in thriving, healthy, well-fed infants. Breast milk contains inhibitors of glucuronyl transferase and causes enhanced absorption of bilirubin from the gut. Breast milk jaundice becomes evident later than breastfeeding jaundice and generally declines in the second to third week of life. Infants with severe or persistent jaundice or a direct hyperbilirubinemia need evaluation for other medical causes (see Chapter 137). Persistently high bilirubin levels may require treatment with phototherapy without cessation of breastfeeding or changing from breast milk to infant formula for 24-48 hours if phototherapy is not available or if a rapid reduction in total serum bilirubin is urgently needed. Breastfeeding can resume after the decline in serum bilirubin. Parents can be encouraged to continue collecting breast milk during the period the infant is taking formula.

Breast milk collection by pumping is a common practice when the mother and baby are separated and when families wish for other caregivers to engage in infant feeding. Electric breast pumps are generally more efficient and better tolerated by mothers than manual pumps or hand-expression, but not all insurance companies cover electric pumps. Good handwashing and hygiene are important during all steps of pumping. Collection kits should be cleaned with hot soapy water, rinsed, and air-dried after each use. Glass or plastic containers can be used to collect the milk. Fresh milk can be stored at room temperature for up to 4 hours and in the refrigerator for up to 4 days. Expressed breast milk can be frozen and used for up to 6-12 months; frozen milk should be used within 24 hours of thawing. Human milk should never be microwaved. **Paced bottle feeding** helps support breastfeeding during bottle feeds by matching the slower pace of direct breastfeeding.

Growth of the breastfed infant differs from that of the formula-fed infant; the infant's risk for excess weight gain during late infancy may be associated with bottle feeding (whether formula or expressed human milk). The WHO growth charts are based on growth patterns of healthy breastfed infants through the first year of life. The infants were selected based on being breastfed, having good healthcare, an absence of socioeconomic constraints, and nonsmoking mothers, so that they reflect the growth pattern of breastfed infants in optimal conditions and can be used as prescriptive standards rather than as normative reference curves. Charts are available for growth monitoring. The Centers for Disease Control and Prevention (CDC) recommends use of the WHO growth charts for infants from birth to 2 years and CDC growth charts for ages 2 to 20 years (see Chapter 27).

Formula Feeding

Despite efforts to promote exclusive breastfeeding through 6 months, only ~55% of women in the United States continue any breastfeeding at 6 months. Parental preferences are the most common reason for using infant formula and may relate to return to work, perceived poor milk supply, lack of support, or other factors. Most parents make their infant feeding choices early in pregnancy. However, infant formula is also indicated for infants whose intake of breast milk is contraindicated for infant factors (e.g., inborn errors of metabolism) or maternal factors (see Table 61.2). In addition, infant formula may be used as a supplement to support inadequate weight gain in breastfed infants, though often formula is used to supplement based upon caregiver perception of benefit rather than medical necessity.

Infant formulas marketed in the United States are safe and nutritionally adequate as the sole source of nutrition for healthy infants for the first 6 months of life. Infant formulas are available in ready-to-feed, concentrated liquid, and powder forms. Ready-to-feed products generally provide 19-20 kcal/30 mL (1 oz) and approximately 64-67 kcal/100 mL. Concentrated liquid products, when diluted according to instructions, and powder formulas, when mixed according to instructions (typically 2 ounces of water plus one scoop of powder), will result in similar caloric density.

Although infant formulas are manufactured in adherence to good manufacturing practices and are regulated by the U.S. Food and Drug Administration (FDA), there are potential safety issues. Ready-to-feed and concentrated liquid formulas are commercially sterile, but powder preparations are not. Although the number of bacterial colony-forming units per gram (CFU/g) of powder formula is generally lower than allowable limits, outbreaks of infections with *Cronobacter sakazakii* (previously *Enterobacter sakazakii*) have been documented, especially in premature infants. The powder preparations can contain other coliform bacteria but have not been linked to disease in healthy term infants. Care must be taken to follow the mixing instructions to avoid overdilution or underdilution, to use clean water, and to use the specific scoops provided by the manufacturer because scoop sizes vary. Water that has been boiled must cool fully to prevent degradation of heat-labile nutrients, specifically vitamin C. Well water should be tested regularly for bacteria and toxin contamination. Testing may also identify high lead concentrations in water flowing through pipes installed before 1986. Municipal water can contain variable concentrations of fluoride, and if the concentrations are higher than 2.0 mg/L, use of bottled water that is defluoridated is preferred to avoid possible toxicity and tooth discoloration.

Proper handwashing is important before preparing formula for the infant. Formula storage guidelines vary based on preparation. Once opened, ready-to-feed and concentrated liquid containers can be covered and stored in the refrigerator for no longer than 48 hours. Manufacturer guidelines recommend storing powder formula in a cool, dry place but not in the refrigerator; once opened, cans can be covered with the original plastic cap or aluminum foil, and the powdered product used within 4 weeks. The CDC recommends using prepared formula within 24 hours, regardless of type. The CDC further recommends using formula within 2 hours of removal from the refrigerator and within 1 hour from the start of a feed. Prepared formula stored in the refrigerator can be warmed by placing the container in warm water for about 5 minutes. Formula should *never* be heated in a microwave because it can heat unevenly and result in burns, despite appearing to be at the right temperature when tested.

Formula feedings are ideally provided ad libitum, with the goal of achieving growth and development to the child's genetic potential. The usual intake to allow a weight gain of 20-30 g/day in the first 2-3 months of life is approximately 140-180 mL/kg/day, although some may require intake outside this range. The average rate of weight gain declines from 3 to 12 months of age (see Chapters 27 and 64). **Overfeeding** with resultant rapid weight gain increases the risk for developing obesity and is to be prevented. **Paced bottle feeding** may help avoid overfeeding.

COW'S MILK PROTEIN–BASED FORMULAS

Intact cow's milk protein–based formulas are appropriate for most term infants. There are nutritional differences between formula and breast milk, although the effects of these differences on long-term health are unknown. Formulas contain 10-35 times higher iron compared with breast milk and higher zinc, sodium, and vitamin D. Most formulas in the United States also contain considerably higher protein than in mature breast milk. This concentration is designed to meet the needs of the youngest infants but may lead to excess protein intake for older infants and has been associated with increased risk of obesity. In contrast, breast milk protein content decreases over time to match needs. Protein concentration and composition differences between human milk and cow's milk–based formulas result in different plasma amino acid profiles in infants on different feeding patterns, but clinical significance has not been demonstrated.

Fat provides 40–50% of the energy in cow's milk–based formulas and is primarily from plant and animal oils. Fat blends are better absorbed than dairy fat and provide saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs). All infant formulas are supplemented with long-chain PUFAs, specifically docosahexaenoic acid (DHA) and arachidonic acid (ARA). DHA and ARA are found at varying concentrations in human milk and vary by geographic region and maternal diet. The DHA and ARA added to formulas are derived from single-cell microfungi and microalgae and are classified as "generally recognized as safe" (GRAS) for use in infant formulas at approved concentrations and ratios. Long-term studies are lacking on the relationship between routine supplementation of formula with long-chain PUFAs and physical, neurodevelopmental, or visual outcomes of term infants.

Lactose is the major carbohydrate in breast milk and in standard cow's milk–based formulas for term infants. Formulas for term infants may also contain modified starch or other complex carbohydrates like prebiotic oligosaccharides similar to those in human milk.

SOY PROTEIN–BASED FORMULAS

Soy protein–based formulas on the market are all free of cow's milk–based protein and lactose. They meet the vitamin, mineral, and electrolyte guidelines from the AAP and the FDA for feeding term infants. In term infants, although soy protein–based formulas have been used to provide nutrition resulting in normal growth patterns, there are few indications for use in place of cow's milk–based formula. Indications for soy formula include galactosemia, preference for a vegetarian diet, and hereditary lactase deficiency, because

soy-based formulas are lactose free. Most healthy infants with acute gastroenteritis can be managed after rehydration with continued use of breast milk or cow's milk–based formulas and do not require a lactose-free formula. However, soy protein–based formulas may be indicated when documented secondary lactose intolerance occurs. Soy protein–based formulas have no advantage over cow's milk protein–based formulas as a supplement for the breastfed infant, unless the infant has one of the indications noted previously. Soy protein–based formulas are *contraindicated for preterm infants* because of concerns about protein quality and aluminum content. The routine use of soy protein–based formula has no proven value in the prevention or management of infantile colic, fussiness, or atopic disease. Infants with documented cow's milk protein–induced enteropathy or enterocolitis often are also sensitive to soy protein and should be fed using an extensively hydrolyzed or amino acid–based formula.

PROTEIN HYDROLYSATE FORMULAS

Protein hydrolysate formulas may be partially hydrolyzed, containing oligopeptides with a molecular weight of <5,000 daltons (range 3,000-10,000 Da), or extensively hydrolyzed, containing peptides with a molecular weight <3,000 Da. These formulas are lactose free and can include medium-chain triglycerides, making them useful in infants with gastrointestinal malabsorption caused by cystic fibrosis, short bowel syndrome, prolonged diarrhea, or hepatobiliary disease. **Partially hydrolyzed protein** formulas have fat blends similar to cow's milk–based formulas, and carbohydrates are supplied by corn maltodextrin or corn syrup solids. Because the protein is only partially hydrolyzed, these formulas are not appropriate for infants who are allergic to cow's milk protein. There is insufficient evidence to recommend use of hydrolyzed formulas to prevent atopic dermatitis or other atopic diseases in high-risk infants. **Extensively hydrolyzed formulas** are recommended for infants intolerant to cow's milk or soy proteins.

AMINO ACID FORMULAS

Amino acid (elemental) formulas are peptide-free formulas that contain mixtures of essential and nonessential amino acids. They are designed for infants with cow's milk–based protein allergy who fail to thrive on extensively hydrolyzed protein formulas. The effectiveness of amino acid formulas to prevent atopic disease has not been studied.

OTHER FLUIDS IN INFANTS AND TODDLERS

Neither breastfed nor formula-fed infants require additional water unless dictated by a specific condition involving excess water loss, such as diabetes insipidus. Vomiting and spitting up are common in healthy infants. When weight gain and general well-being are noted, no change in formula is necessary. Whole cow's milk can impair iron absorption and is not recommended for infants younger than 12 months. Nondairy, very low-protein milks are also inadequate to meet infant nutritional needs. Prune or apple juice may be used in small amounts for treatment of constipation, but juice is not recommended for routine consumption in infants. Infants with vomiting caused by gastroenteritis may need to consume an oral electrolyte solution but will need close monitoring and ideally will consume the solution for less than 24 hours. Goat milk is not an appropriate substitution for formula. Goat milk has been shown to cause significant electrolyte disturbances and anemia because it has low folic acid concentrations. Likewise, homemade formulas, which typically involve a combination of raw cow, raw goat, or plant-based milk, cod liver oil, molasses, and other ingredients, cannot be considered safe for infant feeding. Mixing homemade formula incorrectly can put unnecessary stress on a newborn's kidneys and intestines and may not provide sufficient calories or micronutrients. Infants and young children are also particularly susceptible to infections such as *Escherichia coli*, *Campylobacter*, *Listeria*, *Brucella*, and *Salmonella* found in **raw or unpasteurized milk**.

COMPLEMENTARY FEEDING

The timely introduction of complementary foods (solid and liquid foods other than breast milk or formula, also called **weaning foods**) during infancy is important for nutritional and developmental reasons (Table 61.7). The AAP recommends exclusive breastfeeding for about the first 6 months, after which nutrient requirements cannot be met by breastfeeding alone. Table 61.7 summarizes the AAP recommendations for introducing complementary foods, though nearly 25% of parents do not adhere to current guidelines (e.g., introducing complementary foods too early or introducing inappropriate foods, such as cow's milk, in children under 12 months).

Complementary foods should be introduced around 6 months and be varied to ensure adequate macronutrient and micronutrient intake. Although there is not currently evidence to promote a recommended order in which to introduce foods, information about important nutrients is included here. Additionally, a wide variety of textures is important for oral motor development, typically starting with pureed or very soft (easy to mash with the gums) foods. This is also a good time to establish consistent eating routines, including providing predictable meal and snack times for solid foods, eating in a safe dedicated space (such as in a highchair at the family table), and eating with family members to the extent possible. Continued breastfeeding up to 24 months of age and use of infant formula until 12 months is encouraged.

Some complementary foods are more nutritionally beneficial than others. *Iron- and zinc-rich foods* (such as fortified infant cereals, age-appropriate meats, eggs, and legumes) are especially important for breastfed infants, whose iron and zinc stores decline over time and are not sufficiently replaced through consumption of breast milk. Yogurt and cheese (including soy-based products) without added sugars are appropriate for infants receiving complementary foods, but full-fat cow's milk as a replacement for infant milk is inappropriate before 12 months. In addition to honey and unpasteurized consumables, foods and beverages with added sugars and those high in sodium are not recommended. Overconsumption of energy-dense complementary foods (e.g., cakes, cookies, fried foods, and sugar-sweetened beverages) can lead to excessive weight gain in infancy, increasing the risk of obesity in childhood.

Early introduction of peanuts and eggs around 4-6 months helps to prevent the development of food allergies. Although data are limited for other highly allergenic foods, the strength of current evidence suggests that introducing other allergenic foods early in complementary

Table 61.7 Important Principles for Weaning

- Begin around 6 mo of age.
- Introduce one new food at a time.
- Choose foods that provide key nutrients and help meet energy needs.
- Iron-containing foods (meat, iron-supplemented cereals) are required, especially for breastfed infants.
- Zinc intake should be encouraged with foods such as meat, dairy products, and fortified infant cereal.
- Phytate intake should be low to enhance mineral absorption.
- By 7-8 mo infants should be consuming foods from all food groups.
- Between 9 and 12 mo of age, encourage a cup rather than a bottle.
- Fluids other than breast milk, formula, and water should be discouraged.
- Breast milk can continue up to 24 mo of age; cow's milk can be introduced at 12 mo of age and up to 24 oz/day of cow's milk can be consumed if breastfeeding is discontinued.
- Give no more than 4 oz/day of 100% fruit juice; no sugar-sweetened beverages.
- Encourage routine mealtimes and responsive feeding, watching for and responding to the child's hunger and satiety cues.

Adapted from American Academy of Pediatrics. *Pediatric Nutrition Handbook*, 8th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2019.

feeding may prevent IgE-mediated food allergies. The most recent guidelines from the American Academy of Allergy, Asthma, and Immunology recommend early introduction of the top 9 highly allergenic foods (dairy, soy, eggs, peanuts, tree nuts, sesame, wheat, fish, and shellfish) for all children, especially those at higher risk for atopic disease. For more information, see Chapter 192.

TRANSITION TO MILK

Whole cow's milk can be introduced at 12 months, and formula-fed children are transitioned to milk at this time. In children 12-24 months, for whom overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk may be appropriate. Otherwise, whole milk is recommended until age 24 months, after which changing to 1% milk helps reduce overall dietary intake of fat if this is a concern. The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) does not provide 2% or whole milk for children over 24 months unless authorized by a medical provider. Regardless of the type, all animal milk consumed should be pasteurized because of the infection risk with raw or unpasteurized milk, as discussed earlier.

Nondairy alternatives to milk from plant-based (e.g., soy, hemp, pea, oat, rice) and nut-based (e.g., almond, cashew, peanut) sources are popular. When counseling parents, it is important to emphasize that the overall nutritional content and quality of plant-based milk alternatives is not equivalent to cow's milk. Although most are fortified with vitamin A, vitamin D, and calcium, only some soy-, hemp-, and pea-based milk alternatives have comparable protein content, and all products have inferior protein quality. Many plant-based products have added oils and sugars. No nondairy alternative milks are appropriate substitutions for infant formula or breast milk in infants. Nut-based milks may be suitable for toddlers ≥12 months of age without allergies who have an otherwise adequate diet. Nondairy (vegan) milks vary between products; a careful assessment of ingredients, including protein and micronutrient fortification, must be determined.

RESPONSIVE FEEDING

Responsive feeding begins in infancy and is associated with desirable growth outcomes. Responsive feeding refers to recognizing and responding to children's signs of hunger and satiety in a timely and developmentally appropriate manner. Parents are encouraged to learn to recognize signs of hunger (e.g., child leans forward or reaches for food, or opens mouth when offered food) and satiety (e.g., child closes mouth or turns away from food) in infants who receive solid foods so that they can respond appropriately.

The period from 6 months to 15 months is characterized by acquisition of self-feeding skills as the infant learns to grasp finger foods, use a spoon, and eat soft foods (Table 61.8). Around 12 months of age, the child learns to drink from a cup, and bottle weaning around 12-15 months is recommended. To prevent dental caries, bedtime bottles should be discouraged, and it is best that cups contain only water outside of mealtimes. Sugar-sweetened beverages and 100% fruit juice are not recommended for infants less than 12 months. Cups without a lid or with a straw rather than a hard spout are preferred.

Baby-led weaning (BLW) typically refers to allowing infants to self-feed soft (often well-cooked) solid or table foods from the very beginning of complementary feeding. Presently, many parents are choosing to give their infants finger foods rather than, or in combination with, purees. There is little evidence that BLW leads to improved nutrient status, weight gain, or food acceptance longitudinally. In general, all food textures, including purees, are encouraged to be included in the infant's diet. Parents should be counseled on avoidance of foods that are common choking hazards.

FEEDING TODDLERS AND PRESCHOOL-AGED CHILDREN

Toddlerhood is a period when eating behaviors and healthful habits can be established, and it is often a confusing and anxiety-generating period for parents. Important goals of early childhood nutrition are to offer foods that are developmentally appropriate and to begin to foster healthful eating habits that will last a lifetime. Growth after the first year slows dramatically, appetite decreases, motor activity increases, and children naturally become leaner until they reach an adiposity nadir at 4-6 years. Using growth charts to illustrate adequate growth and provide guidance about typical behavior and eating habits can help allay parents' concerns if they are explained in a way that parents can understand (Table 61.9). Eating behavior can be erratic, and children can appear distracted from eating as they explore the environment. Young children may consume a limited variety of foods, and it is common for children to "like" a particular food for a period and then reject the favored food. It can take many offers before children become familiar with and decide to try a novel food, and it is important to help children learn about food without expectations regarding how much they will eat.

Table 61.8 Feeding Skills Birth to 36 Months

AGE (mo)	FEEDING/ORAL SENSORIMOTOR SKILLS
Birth to 4-6	Nipple feeding, breast or bottle Hand on bottle during feeding (2-4 mo) Maintains semiflexed posture during feeding Promotion of infant-parent interaction
6-9 (transition feeding)	Head and neck control Feeding more in upright position Spoon-feeding thin, pureed foods Both hands to hold bottle Finger feeding of easily dissolvable solids introduced Vertical munching of easily dissolvable solids
9-12	Cup drinking Eats lumpy, mashed food Finger feeding for easily dissolvable solids Chewing includes rotary jaw action
12-18	Self-feeding; grasps spoon with whole hand Holds cup with two hands Drinking with four to five consecutive swallows Holding and tipping bottle
>18-24	Swallowing with lip closure Self-feeding predominates Chewing broad range of food Up-down tongue movements
24-36	Circulatory jaw rotations Chewing with lips closed One-handed cup holding and open cup drinking with no spilling Using fingers to fill spoon Eating wide range of solid food Total self-feeding, using fork

Adapted from Arvedson JC. Swallowing and feeding in infants and young children. *GI Motility Online*. 2006. https://doi.org/10.1038/gimo17.

Recommended Intake and Serving Sizes

Toddlers and preschool-aged children usually eat three healthy meals and one to two snacks daily. Recommended daily amounts for each food group can be found in Table 61.10. Toddlers and preschool children often fail to meet the recommended servings of fruits, vegetables, and fiber, whereas intakes of food with fat and added sugar are excessive. Recommended serving sizes of fruits, vegetables, and grains are approximately the size of the child's fist, and a serving size of protein can be the size of the child's palm. It is important to be mindful that some children become overwhelmed when large portions are offered, fearing that they will be expected to finish the entire portion. If parents are concerned about their children eating enough vegetables, giving vegetables at the beginning of the meal has been shown, in some circumstances, to be an effective strategy for increasing vegetable consumption in preschool children. Milk continues to be an important

Table 61.9 Suggested Language for Discussing Growth Charts with Families

UNDERWEIGHT	NORMAL WEIGHT	OVERWEIGHT OR OBESE
• Looking at how your child's weight is matched for their height, only 2 of 100 children are at a weight that is lower at the same height. • Your child's weight for their height is lower than what is generally thought to be healthy. • BMI looks at the way height and weight are balanced with each other. Currently your child's BMI is too low, which has a higher risk of developing health problems related to weight.	• Looking at how your child's weight is matched for their height, 75 of 100 children are at a weight that is lower at the same height. • Your child's weight and height are matched for each other in a way that is generally thought to be healthy. • If you were to line up 100 children of the same age by weight, your child would be right in the middle.	• Looking at how your child's weight is matched for their height, 99 of 100 children are at a weight that is lower at the same height. • Your child's weight for their height is heavier than what is generally thought to be healthy. • BMI looks at the way height and weight are balanced with each other. Currently your child's BMI is too high, which has a higher risk of developing health problems related to weight.

Table 61.10 Recommended Daily Amounts for Children

	TODDLERS AGES 12-23 MO	CHILDREN AGES 2-8 YR	CHILDREN AGES 9 YR AND OLDER
Calories per day*	700-1,000	1,000-1,400	1,600-3,200
Vegetables	⅔-1 cup	1-1½ cups	2-4 cups
Fruits	½-1 cup	1-1½ cups	1½-2½ cups
Grains	1¾-3 ounces	3-5 ounces	5-10 ounces
Dairy	1⅔-2 cups	2-2½ cups	3 cups
Protein foods	2 ounces	2-4 ounces	5-7 ounces
Oils	9-13 grams	15-17 grams	22-51 grams

*Calorie needs may be higher for children who are active far above typical levels for age. Additionally, calorie needs may change on a daily basis as children experience illness, growth spurts, and variations in activity.

Adapted from the U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans, 2020-2025*, 9th Edition. December 2020. Available at DietaryGuidelines.gov.

source of nutrition, particularly protein, fat, calories, and vitamin D, and it is recommended that children consume up to 2-3 cups (16-24 ounces) per day (see Table 61.10). Sugar-sweetened beverages like soda, sports drinks, sweetened tea, or fruit punch are not recommended. Toddlers ages 12 months and older can be given up to 4 oz/day of 100% fruit juice. Grapefruit juice can affect medications metabolized by CYP34A (e.g., antifungals such as fluconazole and ketoconazole, antiretrovirals, erythromycin, clarithromycin, fluoxetine, and amiodarone).

Feeding Practices

In the second year of life, self-feeding is learned, becomes the norm with time, and provides more opportunities for the family to eat together. Self-feeding also provides the child with the autonomy to self-regulate their intake. Child feeding is an interactive process, especially because children receive cues regarding appropriate eating behaviors from parents. Parents are encouraged to notice and comment on positive and ignore negative eating behaviors unless the behavior jeopardizes the health and safety of the child. Parents should avoid pressuring young children to eat, particularly pressuring them to eat larger, adult-sized portions. Instead, parents are encouraged to focus on acceptance of a wide variety of healthful foods. In addition, parents are encouraged to eat the same foods with their toddlers to model positive eating behaviors such as trying and consuming healthful foods.

The 2-year-old child can progress from small pieces of soft finger foods to prepared table foods with care. They can also learn how to eat with utensils (as culturally appropriate) over the preschooler period. The young child is not capable of completely chewing and swallowing chewy or hard foods, and hard foods present a choking risk. Hard candies, nuts, popcorn, and raw carrots should be avoided before age 4 years. Foods like hot dogs, sausages, and grapes can be sliced lengthwise to avoid choking. Caregivers should always be vigilant and present during feeding, and the child placed in a highchair or booster seat. The AAP discourages eating in the presence of distractions such as television, tablets, mobile devices, and other screens and eating in a car where an adult cannot adequately observe and assist the child.

FEEDING SCHOOL-AGED CHILDREN AND ADOLESCENTS

MyPlate

The U.S. Department of Agriculture (USDA) MyPlate (www.myplate.gov) is a basis for building an optimal diet for children and adults (Fig. 61.1). MyPlate is based on the 2020 **Dietary Guidelines for Americans**. MyPlate provides a visual representation of the different food groups and portion sizes designed for the general public. The website provides recipes, weight management strategies, and tools to track calories and physical activity goals. A personalized eating plan based on these guidelines provides, on average over a few days, all the essential nutrients necessary for health and growth, while limiting nutrients associated with chronic disease development. MyPlate can also be used as an interactive tool for customized recommendations based on age, sex, physical activity, and for some populations, weight and height. Print materials from the USDA are also available for families without internet access.

The MyPlate model emphasizes making half the plate vegetables and fruits, prioritizing whole grains, and eating protein from both animal and plant sources. A separate dairy section is included. Physical activity recommendations to achieve a healthful energy balance are not visually displayed but are provided on the website. MyPlate has removed foods that have low nutritional value, such as sugar-sweetened beverages and sweetened baked goods.

In the United States, the vast majority of children and adolescents do not consume a diet that follows the recommendations of MyPlate. The intake of high-calorie/low-nutrient-density foods is much higher than recommended, with frequent consumption of sugar-sweetened beverages (e.g., soda, juice drinks, iced tea, sport drinks), snack foods,

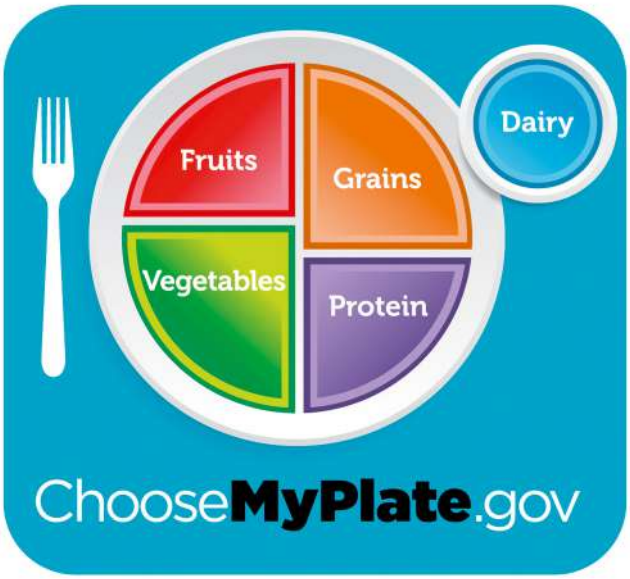

Fig. 61.1 MyPlate food guide. *(From U.S. Department of Agriculture: http://www.myplate.gov/.)*

Table 61.11 Revised National School Lunch Program and School Breakfast Program Recommendations

1. Portion sizes of food are to be based on age-grade groups.
2. School lunches and breakfasts will have a minimum and maximum calorie level, maximum saturated fat content, and a maximum sodium content.
3. Foods must contain zero grams of trans fat per serving.
4. The inclusion of unsaturated vegetable oils is encouraged within calorie limits.
5. Vegetables and fruits are not interchangeable.
6. Vegetable offerings at lunch must include cup equivalent of the following: dark-green vegetables, bright-orange vegetables, and legumes.
7. No more than half of fruit servings may be in the form of juice.
8. At least one half of bread/grain offered must be whole grain.
9. Milk must be fat free if flavored and either fat free or 1% fat if plain.
10. Students must select a fruit option at breakfast with their meal and either a fruit or a vegetable at lunch for the meal to be reimbursable.

Adapted from the National Academies of Engineering, Science and Medicine. *School Meals: Building Blocks for Healthy Children*. Washington, DC: National Academies Press; 2010.

high-fat meat (e.g., bacon, sausage), and high-fat dairy products (e.g., cheese, ice cream). Intake of dark-green and orange vegetables (vs fried white potatoes), whole fruits, reduced-fat dairy products, and whole grains is typically lower than recommended (see Table 61.10 for recommendations). Other common unhealthful eating habits include consuming larger-than-recommended portion sizes; preparing foods with added fat, sugar, or salt; skipping breakfast and/or lunch; grazing; consuming packaged snack foods; and following fad diets. MyPlate offers a helpful and customer-friendly tool to assist pediatricians counseling families on optimal eating plans for short- and long-term health.

Diet quality tends to decline with child age, and ensuring that children and adolescents consume sufficient nutrient-dense foods is a challenge for many parents. The vast majority of children and adolescents consume more than the recommended amounts of added sodium, saturated fats, and added sugars, with ~17% of calorie intake coming from highly processed packaged foods. Frequent snacking and consumption of sugar-sweetened beverages are major contributors to this excess and are valuable targets for dietary counseling. Among adolescents, night eating may be an important source of lower-quality food intake that may be missed during a standard diet recall. In the United States, nearly 85% of adolescents consume caffeinated beverages. Although moderate consumption (up to 2.5 mg/kg/day, equivalent to 6 ounces of coffee for a 30-kg child) is generally considered safe, higher levels of caffeine consumption are associated with impaired sleep and with negative physiologic, emotional, and behavioral outcomes.

NUTRITION ISSUES OF IMPORTANCE ACROSS PEDIATRIC AGES

Eating at Home

At home, parents control much of what children and adolescents eat because they typically shop for groceries and monitor which foods are available in the household. Home food availability is associated with child dietary intake: availability of foods such as fruits, vegetables, and dairy has been associated with intake of those foods, whereas availability of foods such as sugar-sweetened beverages is associated with lower diet quality. Parents can help to influence children's healthy food choices by modeling healthful eating behaviors themselves. Dietary counseling includes encouraging parents to make healthier food choices available and attractive at home and part of routine family meals. Improved diet quality for children is associated with regular family meals while sitting at a table (vs eating alone or watching a TV or other screen), perhaps because of increased opportunities for *positive parenting* during meals. Although there are many reasons families may be unable to provide an ideal meal setting (busy schedules, parents working multiple jobs, no kitchen table), family meals at predictable times are encouraged to the extent families are able.

Another important aspect of *food parenting* is helping children learn to be mindful of and respond to internal cues of hunger and satiety. This can be a challenge for some families who have children with a propensity to overeat or to eat in response to nonhunger signals (such as eating as an emotional response). Parents can support their children to eat at a slower pace and to chew their food properly. Useful strategies when the child is still hungry after a meal include a 15- to 20-minute pause (to allow the child to engage in another activity) before providing a second serving or offering foods that are insufficiently consumed, such as vegetables, whole grains, or fruits.

Eating in Childcare and School Settings

Many U.S. toddlers and preschool children attend formal or informal childcare and receive meals and snacks in this setting. There is wide variation in the quality of food offered (if food is provided) and level of mealtime supervision. Parents are encouraged to assess the quality of the food and supervision by asking questions, visiting the center, and taking part in parent committees. Free or reduced-price snacks and meals are provided in childcare centers for low- and medium-income communities through the **USDA Child and Adult Care Food Program**. Participating programs are required to provide meals and snacks that meet meal regulations set by the USDA, enabling a certain level of food quality. However, many centers and schools still struggle to provide high-quality meals and snacks due to cost.

The National School Lunch Program and the School Breakfast Program provide low-cost meals to millions of children. Guidelines for meals are taken from the Dietary Guidelines for Americans. Recommendations include the use of age-grade portion sizes and the amounts of vegetables and fruits, grains, and fats (Table 61.11). Among the necessary components of these programs are training and equipment for school food service staff, school community engagement, parent education, and food industry involvement. Parents are encouraged to assist their child with food choices at school. If children bring their lunch from home, lunch should include, at a minimum, a fruit and/or vegetable, a whole grain, and a protein source. Parents can be directed to www.myplate.gov for healthful lunch ideas. Additionally, parents are encouraged to be aware of school and classroom parties and work with teachers and other parents to ensure children have access to healthy choices.

Eating Outside the Home

The number of meals eaten outside the home or brought home from takeout restaurants continues to increase among all age-groups in the United States. The increased convenience of this meal pattern is undermined by the generally lower nutritional value of the meals compared with home-cooked meals. Typically, meals from fast-food or casual restaurants are of large portion size; are dense in calories; and contain large amounts of saturated fat, salt, and sugar and low amounts of whole grains, fruits, and vegetables. Although an increasing number of restaurants offer healthier alternatives, the vast majority of what is consumed at restaurants does not fit MyPlate recommendations. Parents are encouraged to evaluate menu labels when available, select the healthiest available options, and consider sharing meals to supplement children's meals, which often comprise highly palatable options with low nutrient density.

With increasing age, more meals and snacks are also consumed during peer social gatherings at friends' houses and parties. When a large part of a child's or adolescent's diet is consumed on these occasions, diet quality can suffer because food offerings are typically of low nutritional value. Parents and pediatricians need to guide children and teens in navigating these occasions while maintaining a healthful diet and enjoying meaningful social interactions. These occasions may also be opportunities for teens to consume alcohol; consequently, adult supervision is important.

Food Environment

Environmental and social challenges can make it difficult for families to make healthful food choices. Although *taste* is the main determinant of food choice, many other complex factors influence that choice, including cost, availability, accessibility, convenience, and marketing strategies, including shelf placement and special pricing. Recognizing the context of food and lifestyle choices can help providers understand lack of changes or "poor adherence" to dietary recommendations and can decrease the frustration often experienced by the pediatricians who might otherwise "blame the victim" for behavior that is not entirely under their control. Local and national efforts to improve access to fresh and unprocessed foods are ongoing but often struggle to address broader issues such as cost or time to prepare foods at home.

Responsive Feeding and Contingent Feeding Practices

Responsive feeding entails recognizing and responding to children's hunger and satiety cues in an age-appropriate and developmentally appropriate way across all stages of childhood and adolescence (Table 61.12). It also includes providing routines and structure with clear expectations (e.g., providing meals and snacks at scheduled intervals with a variety of healthy foods to choose from) and a warm emotional context that promotes positive interactions about food and eating. Responsive feeding strategies can include encouraging children to eat foods that are healthful, teaching them about various foods, and involving them in the selection and preparation of meals. Allowing children to select (within reason) how much to eat of each offered food encourages children to listen to internal cues of hunger and satiety.

It is common for parents to use food as a reward or sometimes withdraw preferred foods as punishment. Most parents use this practice occasionally, and some use it systematically, starting at young ages. The practice is also commonly used in other settings, such as in childcare, school, or even athletics. Although it is a good idea to limit some unhealthful but desirable foods to special occasions, using food as a reward can be problematic. Making access to food contingent on an accomplishment increases the desirability of that food. Conversely, pressuring children to consume some healthful foods renders those foods less desirable. Therefore phrases such as, "Finish your vegetables, and you will get ice cream for dessert" can result in establishing unhealthful eating habits once the child has more autonomy in food choices. Parents are encouraged to choose items other than food as rewards, such as stickers, inexpensive toys or sporting equipment, additional time for a favorite activity, special family events, or collectible items. Similar types of behavior are also seen in schools and extracurricular events, and parents are encouraged to work with teachers and coaches to identify appropriate alternative rewards.

Table 61.12 Responsive Feeding Recommendations

WAYS TO PROMOTE RESPONSIVE FEEDING	WHAT TO AVOID
• Have set meal and snack times and a consistent place to eat. • Select and provide healthful snack and meal options. • Allow child to decide what to eat and how much. • Sit and eat with the child. • Encourage child to try what is on the plate. • Notice when child attempts to try a food: "You tried your broccoli," or "good job trying your broccoli."	• Allow child to "graze" or eat small bites throughout the day. • Allow child to eat whatever they want. • Make child eat all of the food on their plate. • Leave child to eat by themselves. • Offer the child a (food) reward for eating their food. • Offer person praise to child: "You are a good person for trying your broccoli."

Cultural Considerations in Nutrition and Feeding

Food choices, food preparation, eating patterns, and infant feeding practices all have very deep cultural roots. Beliefs, attitudes, and practices related to food and eating are some of the most important components of cultural identity (Fig. 61.2). In multicultural societies, high dietary variability can be observed. In a world where global marketing forces tend to reduce geographic differences in the types and brands of food that are available, most families are still influenced by their cultural background, especially during family meals at home. Therefore pediatricians are encouraged to become familiar with the dietary characteristics of various cultures in their community, so that they can identify the potential nutritional benefits and concerns related to their patients' diets and address concerns in a nonjudgmental way.

Vegetarianism

Vegetarianism is the practice of following a diet that excludes animal flesh foods, including beef, pork, poultry, fish, and shellfish. There are several variations on the vegetarian diet, some of which also exclude eggs and/or some products produced from animal labor, such as dairy products and honey. Another expression used for different varieties of vegetarianism is **plant-based diets**.

It is important to ask parents or adolescents about their diets when they report following a vegetarian, vegan, or plant-based diet, because these terms may mean different restrictions for different families. Vegetarian and vegan diets, with extensive knowledge and forethought, can be safely followed by children. Some people practice diets that are even more restrictive, such as those that exclude foods from the allium family (e.g., onion, garlic, chives) or include only raw foods cooked below a certain temperature. The safety of these *more restrictive diets,* which can be very limited in macronutrients and micronutrients, has not been studied in children, and these more restrictive diets are not recommended. Although being on a vegetarian or vegan diet does not appear to increase the risk of an eating disorder, some teenagers with disordered eating may choose such diets to aid in limiting their caloric intake.

Vegetarianism, or following a plant-based diet, is considered a healthful and viable diet: both the U.S. Academy of Nutrition and Dietetics and the Dietitians of Canada have found that a properly planned and well-balanced vegetarian diet can satisfy the nutritional goals for all stages of life. Recommendations for healthy vegetarian dietary patterns at all ages can be found in the 2020 Dietary Guidelines for Americans. Families may benefit from consultation with a registered dietitian to ensure all nutrient requirements are being met.

Compared with meat-based diets, vegetarian diets tend to have lower intakes of saturated fat, cholesterol, and animal protein and relatively higher levels of complex carbohydrates, fiber, magnesium, potassium,

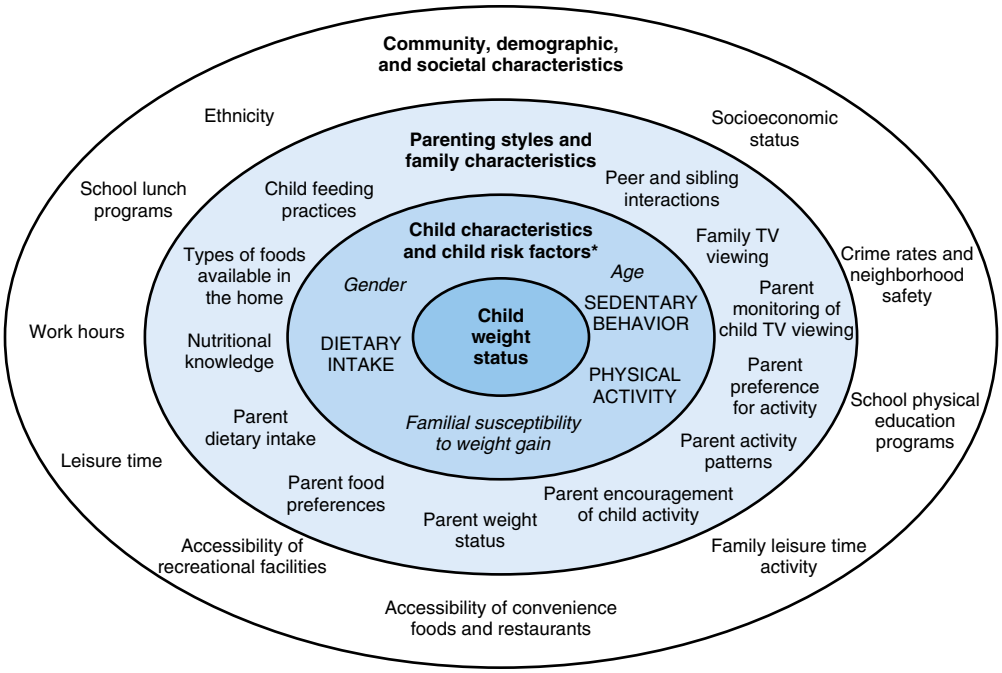

Fig. 61.2 A conceptual framework of the context of food and lifestyle choices. Child risk factors (shown in uppercase lettering) refer to child behaviors associated with the development of overweight. Characteristics of the child (shown in italic lettering) interact with child risk factors and contextual factors to influence the development of overweight (i.e., moderator variables). *(From Davison KK, Birch LL. Childhood overweight: a contextual model and recommendations for future research. Obes Rev. 2001;2:159–171. © 2001 The International Association for the Study of Obesity.)*

folate, vitamins C and E, and phytochemicals. Vegetarians tend to have a lower body mass index, cholesterol level, and blood pressure and are at decreased risk for cancer and ischemic heart disease. Specific nutrients of concern in vegetarian diets include the following:

- **Iron** (see Chapter 72): Vegetarian diets may have similar levels of iron intake as nonvegetarian diets, but iron from plant sources has lower bioavailability than iron from meat sources. Additionally, iron absorption may be inhibited by other dietary constituents, such as phytate (found in leafy green vegetables and whole grains). Iron stores are lower in vegetarians and vegans than in nonvegetarians, and iron deficiency is more common in vegetarian and vegan women and children. Plant-based foods rich in iron include iron-fortified cereals, black beans, cashews, kidney beans, lentils, oatmeal, raisins, black-eyed peas, soybeans, sunflower seeds, chickpeas, molasses, chocolate, and tempeh. Iron absorption from plants is increased when consumed with vitamin C–containing foods (e.g., bell peppers, citrus fruits, strawberries, tomatoes, broccoli). Periodic monitoring of iron stores may be valuable in vegan and vegetarian children and adolescents with low iron intake.
- **Vitamin B_{12}:** Plants are not a good source of B_{12} (see Chapter 67.7). Vegetarians may consume vitamin B_{12} through dairy products and eggs; vegans need fortified foods or supplements. Breastfeeding by B_{12}-unsupplemented vegan mothers can place an infant at risk for vitamin B_{12} deficiency. Only some infant liquid multivitamins contain B_{12}. Vegan children and adolescents may need assessment of vitamin B_{12} levels if supplementation is inconsistent.
- **Fatty acids:** Vegetarians and vegans may be at risk for insufficient eicosapentaenoic acid (EPA) and DHA. The inclusion of sources of linolenic acid (a precursor of EPA and DHA), such as walnuts, soy products, flaxseed oil, and canola oil, is recommended.
- **Calcium and vitamin D:** Without supplementation, vegan diets can be low in calcium and vitamin D, putting vegans at risk for impaired bone mineralization (see Chapter 69). Monitoring serum 25-hydroxyvitamin D levels can identify patients with deficiency (<30 ng/mL) and start supplementation. Calcium sources include leafy greens with low oxalate, such as broccoli, kale, and Chinese cabbage. Calcium and vitamin D are found in some fortified plant-based milks and yogurts and some brands of orange juice.
- **Zinc:** The bioavailability of zinc in plant sources tends to be low because of the presence of phytates and fiber that inhibit zinc absorption (see Chapter 72). Zinc is found in soy products, legumes, grains, cheese, and nuts.
- **Iodine:** Plant-based diets can be low in iodine, and vegetarians and vegans who do not consume iodized salt or sea vegetables (which have variable iodine content) may be at risk of iodine deficiency. The exclusive use of noniodized salt such as Himalayan, sea, or kosher salts could further increase that risk. Iodized salt is not typically used in processed foods such as crackers, although some bread products are fortified with iodine.

Families may also choose to restrict specific foods in the form of elimination diets to prevent allergies or to treat real or presumed gastrointestinal disorders. Figure 61.3 provides an approach to elimination/restrictive diets.

Organic Food

Organic food is defined as produce and ingredients grown without the use of synthetic pesticides, synthetic fertilizers, sewage sludge, genetically modified organisms, or ionizing radiation. Animals that produce organic meat, poultry, eggs, and dairy products are not given antibiotics or growth hormones. In the United States, certification must be obtained, and USDA regulations must be followed to market food as "organic."

Genetically modified organisms (GMOs) in themselves are not thought to be harmful to consume. However, GMOs are modified to be resistant to the effects of herbicides, including glyphosate and 2,4-dichlorophenoxyacetic acid (2,4-D), which give GMOs a selective growth advantage and facilitate use of these chemicals. Glyphosate and 2,4-D have been designated by the International Agency for Research on Cancer as probable and possible human carcinogens, respectively. Therefore higher concentrations of these chemicals in GMO foods are of concern.

Parents may prefer organic foods to feed children secondary to concerns regarding chemical and hormonal content of animals and produce. Although nutritional differences between organic and conventional foods have been reported (e.g., higher levels of PUFAs, α-tocopherol, and iron and lower levels of cadmium, selenium, and

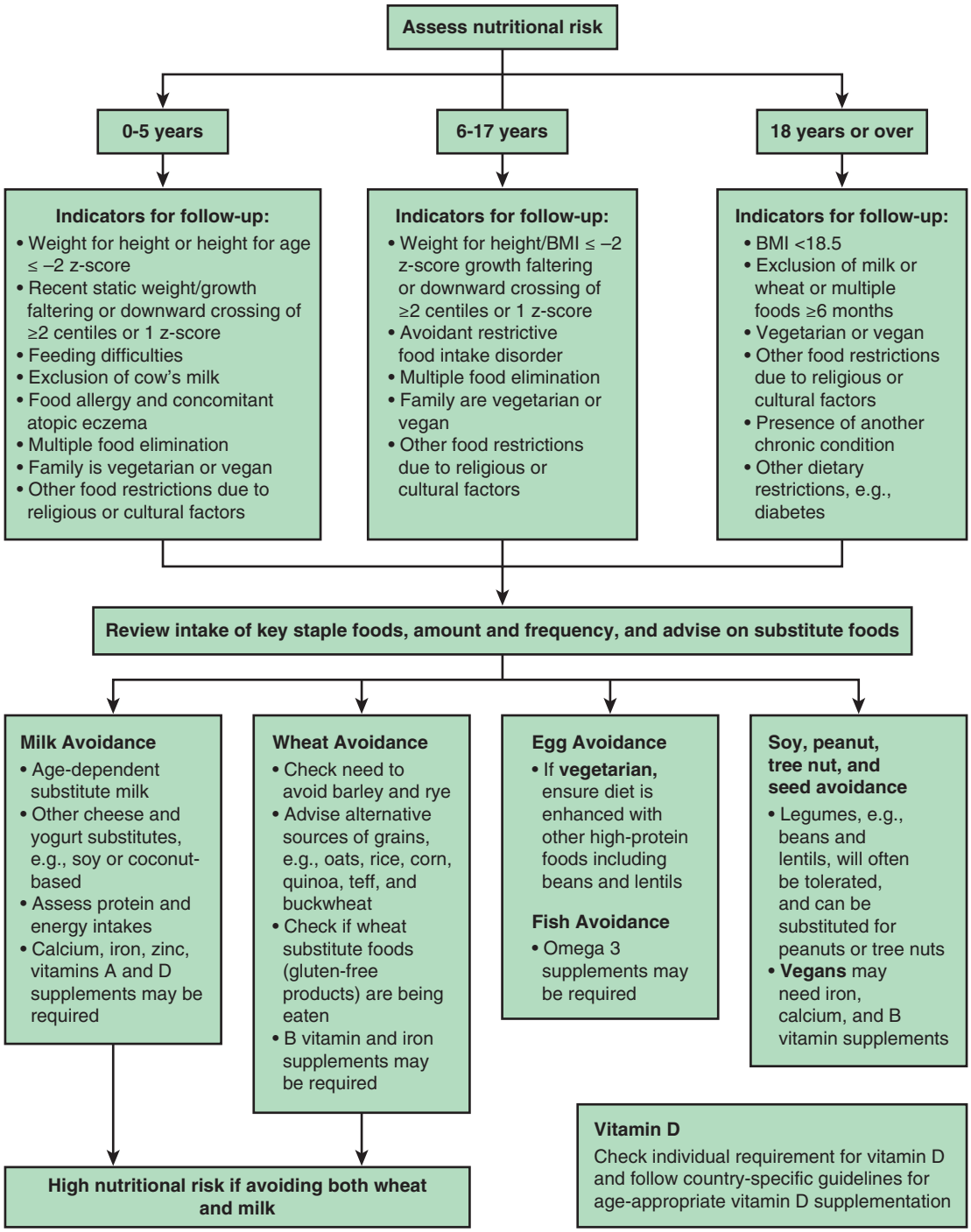

Fig. 61.3 Approach to evaluate risk for adverse elimination diets. BMI, Body mass index. *(Modified from Skypala IJ, McKenzie R. Nutritional issues in food allergy. Clin Rev Allergy Immunol. 2019;57:166–178, Fig. 1, p. 172.)*

iodine), they may not be clinically relevant. Similarly, children consuming organic foods have lower levels of pesticides in their urine compared with those consuming nonorganic foods, but it remains unclear whether such a reduction is clinically meaningful. However, other chemicals in the environment, such as the endocrine disruptors bisphenol-A and phthalates (found in plastics), are best avoided. A high frequency of organic food ingestion has been associated with a lower risk of cancer in adults.

Nutritional Supplements

The use of nutritional supplements as complementary or alternative medicine is increasing, despite limited data on safety and efficacy, especially in children. Many parents assume that if a food or supplement is "natural" or "organic," there is no potential for risk and some potential for benefit. However, adverse effects of some dietary supplements have been documented, and some supplements have been discovered to contain common allergens. In the United States, dietary supplements, including botanical and herbal products, are regulated differently from medications. Manufacturers do not have to prove safety or efficacy before marketing the supplement; the potential for adverse effects, inefficacy, unnecessary cost, and contamination is therefore high. It can be difficult to compete against the aggressive marketing of food supplements. Medical professionals must also compete against advice from people without a scientific background and those with significant conflicts of interest, particularly on the internet.

Pediatricians may be asked whether a child needs to receive a daily multivitamin. Many children do not follow all the guidelines of MyPlate, and parents and pediatricians may be tempted to use multivitamin supplements to fill gaps. The average U.S. diet provides more than a sufficient amount of most nutrients. Therefore multivitamins are recommended only where there is concern for dietary inadequacy, especially when intake of one of the major food groups is very limited or absent (fruits, vegetables, proteins, whole grains, dairy or equivalent). Using vitamin supplements as a support while working to expand dietary variety can help avoid micronutrient deficiencies in cases of dietary restriction whether due to food selectivity or for health, cultural, or religious reasons.

Food Safety

Food safety issues are an important aspect of feeding infants, children, and adolescents. In addition to choking hazards and food allergies, pediatricians and parents need to be aware of food safety issues related to infectious agents and environmental contaminants. **Food poisoning** with bacteria, viruses, or their toxins is most common with raw or undercooked food, such as meat, poultry, eggs, and seafood, or cooked foods that have not been handled or stored properly. Unwashed fruits and vegetables may also be contaminated. The specific bacteria and viruses involved in food poisoning are described in Chapter 259. Many chemical contaminants, such as heavy metals, pesticides, and organic compounds, are present in various foods, usually in small amounts. Because of concerns regarding their child's neurologic development and cancer risk, many questions arise from parents, especially after media coverage of isolated incidents. A recurring debate is the balance between the benefits of seafood for the growing brain and cardiovascular health and the risk of mercury contamination from consuming large, predatory fish species. The **Food Safety Modernization Act** provides the FDA with authority to have stricter control over food production and distribution, including requirements that manufacturers develop food safety plans. A good source of information for patients and parents can be found at www.foodsafety.gov. Other reliable sources of information include the websites of the U.S. Environmental Protection Agency (EPA), FDA, and CDC.

Preventive Nutrition Counseling in Pediatric Primary Care

An important part of the primary care well child visit focuses on nutrition and growth because most families turn to pediatric healthcare providers for guidance on child nutrition. Preventive nutrition is one of the cornerstones of preventive pediatrics and a critical aspect of anticipatory guidance. The first steps of nutrition counseling are nutritional status assessments, primarily achieved through growth monitoring and dietary intake assessment. Although **dietary assessment** is somewhat simple in infants who have a relatively monotonous diet, it is more challenging at older ages. The goals of dietary assessment in the primary care setting need to include an idea of the eating patterns (time, location, and environment) and usual diet. A basic assessment of the child's intake includes evaluating meal routine, dietary diversity (ensuring that a child eats foods from all food groups, namely vegetables, fruits, whole grains, sources of iron and protein, and low-fat or nonfat dairy products), and consumption of sugar-sweetened beverages, including 100% fruit juice. Pediatricians can encourage regularly scheduled meals and one or two healthy snacks (depending on the child's age) with avoidance of grazing, particularly on foods and beverages that are energy dense but of low nutritional value. For more ambitious goals of dietary assessment, referral to a registered dietitian with pediatric experience is recommended.

After understanding the child's usual diet, existing or anticipated nutritional problems can be addressed, such as diet quality, dietary habits, and portion size. Most nutritional issues, such as overeating or poor food choices, are not solely the result of lack of parents' knowledge but can be the result of access, availability, and economic factors. Therefore nutrition education alone is insufficient in these situations, and pediatricians need to acquire training in behavior-modification techniques such as motivational interviewing (see Chapter 18) or refer to specialists to assist their patients in engaging in healthful feeding and eating behaviors. The physical, cultural, and family environment in which the child lives must be considered so that nutrition counseling is relevant and changes feasible (see Fig. 61.2). The phone app ChangeTalk from the AAP provides free training on motivational interviewing for the prevention and treatment of pediatric obesity.

One important aspect of nutrition counseling is providing families with sources of additional information and behavioral change tools. Although some handouts are available from government agencies, the AAP, and other professional organizations for families without internet access, an increasing number of families rely on the internet to find nutrition information. Therefore pediatricians need to become familiar with common websites so that they can point families to reliable and unbiased sources of information. Perhaps the most useful websites for children are the AAP and USDA MyPlate sites and those of the CDC, FDA, National Institutes of Health, The National Academies, and Food and Nutrition Board for government sources. Other professional resources include the American Heart Association and Academy of Nutrition and Dietetics. Unfortunately, there are websites that provide biased or even dangerous information. Examples include dieting sites, sites that openly promote dietary supplements or other food products, and the sites of "nonprofit" organizations that are mainly sponsored by food companies or that have other social or political agendas.

Food Security and U.S. Food Assistance Programs

Food insecurity is defined as the state of being without reliable access to a sufficient quantity of affordable, nutritious food. In 2016, minoritized households were 1.5 to almost 2 times more likely to be food insecure than the national average of 12.3%. Children in food-insecure homes are more likely to have medical problems, including asthma and depression, and are more likely to seek emergency medical care. Patients from all backgrounds can experience food insecurity, and selective screening risks reinforcing bias and missing children in need. Answering "often true" or "sometimes true" (versus "never") to the following two-question screen has a sensitivity of 97% and specificity of 83% for identifying food insecurity: For the last 12 months: (1) "We worried whether our food would run out before we got money to buy more." (2) "The food we bought just didn't last, and we didn't have money to get more."

Several programs exist in the United States to help meet the needs of families experiencing food insecurity. One of the most utilized federal programs is the **Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)**. This program provides nutrition supplements to a large proportion of pregnant and postpartum women and children up to their fifth birthday. One of its strengths is that families regularly visit a WIC nutritionist, who can be a useful resource for nutritional counseling. For older children, federal programs provide school lunches, breakfasts, and after-school meals, as well as daycare and summer nutrition. Lower-income families are also eligible for the **Supplemental Nutrition Assistance Program (SNAP)**, formerly known as the Food Stamp Program. This program provides funds directly to families to purchase various food items in regular food stores. **Food insecurity screening should be universal in clinical settings.** Eligibility criteria for both WIC and SNAP can be found on the programs' federal websites.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 62

Nutrition, Food Security, and Health

Jason M. Nagata and Christine M. McDonald

MALNUTRITION AS THE INTERSECTION OF FOOD INSECURITY AND HEALTH INSECURITY

Undernutrition is usually an outcome of three factors, often in combination: household food supply insecurity, suboptimal childcare practices, and restricted access to or use of health and water/sanitation services. In famine and emergency settings, food shortage is the foremost factor, but in many countries with widespread undernutrition, food production or access to food might not be the most limiting factor. More important causes might be repeated childhood infections, especially diarrheal diseases associated with an unsanitary environment, poor infant and young child feeding practices, or various challenges that may prevent families from using quality maternal and child health services. Figure 62.1 shows some of the many causal factors on the pathway to undernutrition and how they extend from household and community levels to national/international levels. Inequitable distribution of resources because of political, economic, and agricultural policies often denies families their right to adequate land, water, food, healthcare, education, and a safe environment, all of which can influence nutritional status.

Families with few economic resources who know how to care for their children and are enabled to do so can often use available food and health services to produce well-nourished children. If food resources and health services are not available in a community, not used, or not accessible to some families, children might become undernourished. Undernutrition is not confined to low-income countries. It has been noted in chronically ill patients in neonatal and pediatric intensive care units in high-income countries and among patients with burns, human immunodeficiency virus (HIV) infection, tuberculosis, cystic fibrosis, chronic diarrhea syndromes, malignancies, bone marrow transplantation, and inborn errors of metabolism (see Chapter 64). Severe malnutrition has been reported in affluent communities in infants whose families believe in fad diets and in infants with food allergies fed nutritionally inadequate foods such as rice "milk," which has a very low protein and micronutrient content (Figs. 62.2 and 62.3; also see Fig. 61.3).

FOOD SECURITY

Food security exists when all people, at all times, have access to sufficient, safe, nutritious food to maintain a healthy and active life. Four main dimensions of food security can be identified: availability, access, utilization, and stability. **Availability** refers to the *supply* of food, reflecting the level of food production, food stocks, and net trade. **Access** is typically defined at the household level, reflecting purchasing power, household food production, and food/cash transfers received through social "safety net" programs. The **utilization** dimension recognizes that even when a household has access to food, it is not necessarily shared equitably within a household. **Stability** refers to being "food secure" at all times: Examples of situations that affect stability are the "lean seasons" before a harvest, natural disasters, political unrest, and rising food prices. To be food secure, all four dimensions must be met simultaneously.

Measuring Food Insecurity

The most commonly used measurement of food insecurity is *undernourishment* (chronic hunger), which is the proportion of the population who are unable to meet daily energy requirements for light activities. It is an estimate calculated by the **Food and Agriculture Organization (FAO)** based on country-level food balance sheets. It does not take nutrient adequacy into account, but has the advantage of being available for almost all countries annually (although with a time lag) and assists in monitoring global trends. In addition, FAO measures food access by asking individuals about their experiences over the last 12 months, such as whether they ran out of food or skipped meals. The responses are graded from mild to severe food insecurity. This relatively simple monitoring tool, the **Food Insecurity Experience Scale**, provides timely information to guide decision-making at national and local levels.

In 2020, the FAO estimated that between 720 and 811 million people, or approximately 9.9% of the world's population, were undernourished. More than half of the world's undernourished were found in

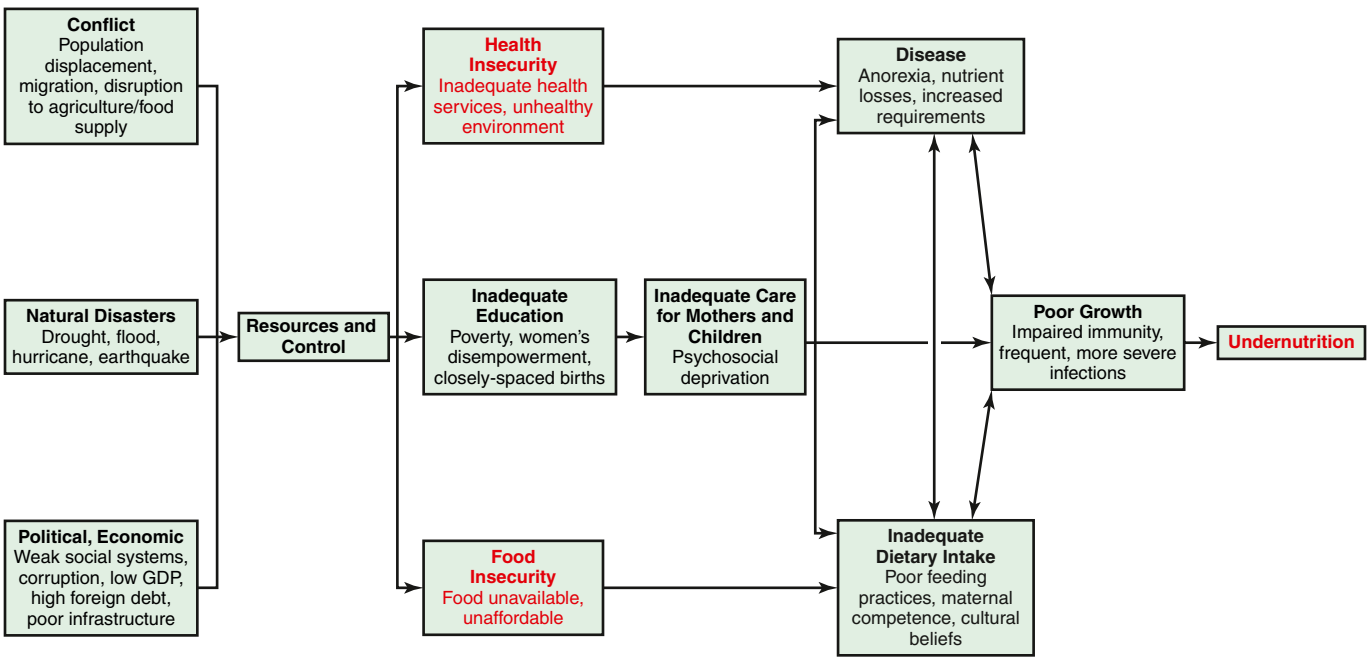

Fig. 62.1 Basic, underlying, and immediate causes of undernutrition.



Fig. 62.2 A 14-month-old girl with "flaky paint" dermatitis. *(From Katz KA, Mahlberg MH, Honig PJ, et al. Rice nightmare: Kwashiorkor in 2 Philadelphia-area infants fed Rice Dream beverage. J Am Acad Dermatol. 2005;52:S69–S72.)*



Fig. 62.3 Paired, transverse, homogeneous, and smooth bordered lines noted in all fingernails suggestive of Muehrcke lines in an infant fed diluted cow's milk since birth. Muehrcke lines are an apparent leukonychia most often associated with hypoalbuminemia. *(From Williams V, Jayashree M. Muehrcke lines in an infant. J Pediatr. 2017;189:234.)*

Asia, and more than one third were found in Africa. The majority are rural poor people subsisting on small plots of land or hired as laborers and urban poor people who lack the means to grow or buy food. Alongside the 768 million people who are underfed are 1.9 billion who are overweight or obese, reflecting global inequalities and the "double burden of malnutrition" in low- and middle-income countries.

Nutrition, Food Security, and Poverty

Household food security tracks income closely. With rising incomes, very poor households first increase their dietary energy intake to avert hunger. If incomes rise further, there is a shift to more expensive staple foods and then to a more varied diet with a greater proportion of energy from animal sources, fruits/vegetables, and fats/sugars and less from cereals, roots, and tubers. National economic growth tends to be accompanied by reductions in stunting, but economic growth can pass by poor persons if they work in unaffected sectors or are unable to take advantage of new opportunities because of lack of education, access to credit, or transportation, or if governments do not channel resources accruing from economic growth to healthcare, education, social protection, and other public services and infrastructure. There is good evidence that economic growth reduces poverty but does not necessarily reduce undernutrition.

Table 62.1 Global Food Security and Nutrition Targets

ZERO HUNGER CHALLENGE OBJECTIVES	WORLD HEALTH ASSEMBLY GLOBAL NUTRITION TARGETS FOR 2025
1. Access to an adequate and stable food supply for all 2. Elimination of stunting in children <2 yr, and no malnutrition in pregnancy and early childhood 3. Sustainable food systems 4. Doubling of smallholder productivity and income, particularly for women 5. No loss or waste of food and responsible consumption	1. A 40% reduction in the number of stunted children <5 yr 2. A 50% reduction in anemia in women of reproductive age 3. A 30% reduction in low birthweight 4. No increase in childhood overweight 5. Increase exclusive breastfeeding rates to at least 50% in the first 6 mo 6. Reduce and maintain childhood wasting to <5%

Food Security and Nutrition Targets

The period of the Millennium Development Goals (MDGs) ended in 2015. All developing regions except sub-Saharan Africa achieved the target to halve the proportion of people living in extreme poverty, with the proportion falling from 47% in 1990 to 14% in 2015. Reductions in hunger were broadly consistent with those of poverty reduction, and rates of undernourishment in developing regions fell from 23% in 1990 to 13% in 2015. The prevalence of underweight among children under 5 years (another MDG indicator of "hunger") fell from 29% in 1990 to 15% in 2015 for the developing regions combined. Rural children are almost twice as likely to be underweight as urban children, and the poorest quintile is almost 3 times as likely to be underweight as the richest quintile.

Eradicating poverty and hunger continue to be core targets of the **Sustainable Development Goals**, as agreed by 193 countries of the United Nations General Assembly in September 2015, and are to be achieved by 2030. In addition, in 2012 the World Health Assembly agreed to six global nutrition targets to be reached by 2025, measured against a 2010 baseline, and the United Nations Secretary-General launched the **Zero Hunger Challenge** with five objectives that "would boost economic growth, reduce poverty and safeguard the environment" and "would foster peace and stability" (Table 62.1).

Future Food Security

Between now and 2050 the world's population is expected to exceed 9 billion, and an increase in the food supply of 70–100% will be needed to feed this larger, more urban, and more affluent populace. Over this same period, the world's food supply is expected to diminish unless action is taken. Accelerating the decline in fertility rates and reducing overconsumption are basic but difficult actions to bridge the gap between increasing demand and diminishing supply. Equally challenging actions include limiting climate disruption, increasing the efficiency of food production, reducing waste, and reducing the demand for meat and dairy foods. The COVID-19 pandemic significantly disrupted food systems and exacerbated food insecurity globally.

- *Limit climate disruption.* Drought, floods, and other extreme weather events are becoming more prevalent and destroy crops and livestock, often on a huge scale. Rising sea levels will lead to loss of productive land through inundation and salinization. Acidification of oceans will reduce marine harvests. Because curbing greenhouse gas emissions is essential to minimize climate disruption, the goals are (1) to cut fossil fuel use by at least half of present levels by 2050 so as to reduce carbon dioxide (CO_2) emissions and (2) change livestock husbandry and agronomic practices to reduce methane and nitrous oxide (N_2O) emissions.
- *Increase efficiency of food production.* Expanding the area of agricultural land to any large extent (e.g., by deforestation) is not a sustainable option because of adverse consequences on ecosystems and biodiversity, although some expansion of food production could be

achieved by switching good-quality land away from first-generation biofuels. For example, almost 40% of the U.S. corn harvest in 2016–2017 went to biofuels. Efforts to increase the intensity of production need to be environmentally sustainable. These include optimizing yields by soil and water conservation, removal of technical and financial constraints faced by farmers, and breeding resource-efficient crops and livestock that are also climate resilient and pest/disease resistant.

- *Reduce waste.* Approximately 30–40% of food is wasted, between harvesting and the market, during retail, at home, and in the food service industry. Better transport and storage facilities in developing countries, less stringent sell-by dates, lower cosmetic standards for fruits and vegetables, and ending supersized portions would help reduce waste.
- *Change diets.* As wealth increases, so does the demand for processed foods, meat, dairy products, and fish. About one third of global cereal production is fed to animals, so reducing consumption of meat from grain-fed livestock and increasing the proportion derived from the most efficient sources (pigs and poultry) would allow more people to be fed from the same amount of land.

UNDERNUTRITION

The greatest risk of undernutrition (underweight, stunting, wasting, and micronutrient deficiencies) occurs in the first 1,000 days, from conception to 24 months of age, and this early effect on growth and development can have adverse consequences on health, intellectual ability, school achievement, work productivity, and earnings in later life. Governments and agencies are therefore advised to focus interventions on this critical window of opportunity.

Measurement of Undernutrition

The term **malnutrition** encompasses both ends of the nutrition spectrum, undernutrition as well as overweight and obesity. Many poor nutritional outcomes begin in utero and are manifest as low birthweight (LBW, <2,500 g). Preterm birth and fetal growth restriction are the two main causes of LBW, with prematurity relatively more common in richer countries and fetal growth restriction relatively more common in lower-income countries.

Nutritional status is often assessed in terms of anthropometry (Table 62.2). International standards of normal child growth under optimum conditions from birth to 5 years have been established by the World Health Organization (WHO). To compile the standards, longitudinal data from birth to 24 months of healthy, breastfed, term infants were combined with cross-sectional measurements of children ages 18-71 months. The standards allow normalization of anthropometric measures in terms of *z* scores (standard deviation [SD] scores). A *z* score is the child's height (weight) minus the median height (weight) for the child's age and sex divided by the relevant SD. The standards are applicable to all children everywhere, having been derived from a large, multicountry study reflecting diverse ethnic backgrounds and cultural settings.

Height-for-age (or length-for-age for children <2 years) is a measure of linear growth, and a deficit represents the cumulative impact of adverse events, usually in the first 1,000 days from conception, that result in *stunting,* or chronic undernutrition. A low height-for-age typically reflects socioeconomic disadvantage. A low **weight-for-height**, or *wasting*, usually indicates acute malnutrition. Conversely, a high weight-for-height indicates *overweight*. **Weight-for-age** is the most commonly used index of nutritional status, although a low value has limited clinical significance because it does not differentiate between wasting and stunting. Weight-for-age has the advantage of being somewhat easier to measure than indices that require height measurements. In humanitarian emergencies and some community or outpatient settings, **mid-upper arm circumference** is used as a screening tool to identify wasted children (Fig. 62.4).

Body mass index (BMI) is calculated by dividing weight in kilograms by the square of height in meters. For children, BMI is age and gender specific. **BMI-for-age** can be used from birth to 20 years and is a screening tool for *thinness* (less than −2 SD), *overweight* (between +1 SD and +2 SD), and *obesity* (greater than +2 SD). To diagnose obesity, additional measures of adiposity are desirable because a high BMI can result from high muscularity and not only from excess subcutaneous fat.

Table 62.2 Classification of Undernutrition

CLASSIFICATION	INDEX	GRADING
Gomez (underweight)	90–75% of median weight-for-age	Grade 1 (mild)
	75–60%	Grade 2 (moderate)
	<60%	Grade 3 (severe)
Waterlow (wasting)	90–80% of median weight-for-height	Mild
	80–70%	Moderate
	<70%	Severe
Waterlow (stunting)	95–90% of median height-for-age	Mild
	90–85%	Moderate
	<85%	Severe
WHO (wasting)	< −2 to > −3 SD weight-for-height	Moderate
	< −3	Severe
WHO (stunting)	< −2 to > −3 SD height-for-age	Moderate
	< −3	Severe
WHO (wasting) (for age-group 6-59 mo)	115-125 mm mid-upper arm circumference	Moderate
	<115 mm	Severe

SD, Standard deviation; WHO, World Health Organization.



Fig. 62.4 Measuring mid-upper arm circumference. *(Courtesy Nyani Quarmyne/Panos Pictures.)*

Micronutrient deficiencies are another dimension of undernutrition. Those of particular public health significance are vitamin A, iodine, iron, and zinc deficiencies.

Vitamin A deficiency is caused by a low intake of retinol (in animal foods) or its carotenoid precursors, mainly beta-carotene (in orange-colored fruits and vegetables and dark-green leaves) (see Chapter 66). The prevalence of *clinical deficiency* is assessed from symptoms and signs of xerophthalmia (principally night blindness and Bitot spots). *Subclinical deficiency* is defined as serum retinol concentration ≤0.70 µmol/L. Vitamin A deficiency is the leading cause of preventable blindness in children. It is also associated with a higher morbidity and mortality among young children.

Iodine deficiency is the world's leading cause of preventable intellectual impairment (see Chapter 72). An enlarged thyroid (goiter) is a sign of deficiency. Severe deficiency in pregnancy causes fetal loss and permanent damage to the brain and central nervous system in surviving offspring (cretinism). It can be prevented by iodine supplementation before conception or during the first trimester of pregnancy. Postnatal iodine deficiency is associated with impaired mental function and growth stunting. The median urinary iodine concentration in children age 6-12 years is used to assess the prevalence of deficiency in the general population, and a median of <100 µg/L indicates insufficient iodine intake.

Iron-deficiency anemia is common in childhood either from low iron intakes or poor absorption, or as a result of illness or parasite infestation (see Chapter 72). Women also have relatively high rates of anemia as a result of menstrual blood loss, pregnancy, low iron intake, poor absorption, and illness. Hemoglobin cutoffs to define anemia are 110 g/L for children 6-59 months, 115 g/L for children 5-11 years, and 120 g/L for children 12-14 years. Cutoffs to define anemia are 120 g/L for nonpregnant women, 110 g/L for pregnant women, and 130 g/L for men.

Zinc deficiency increases the risk of morbidity and mortality from diarrhea, pneumonia, and possibly other infectious diseases (see Chapter 72). Zinc deficiency also has an adverse effect on linear growth. Deficiency at the population level is assessed from dietary zinc intakes or serum zinc concentrations. For children under 10 years of age, serum zinc cutoffs of <65 µg/dL and <57 µg/dL are used to define zinc deficiency according to whether the blood sample was obtained in the morning or afternoon, respectively. For females 10 years of age or older, cutoffs of <70 µg/dL, <66 µg/dL, and <59 µg/dL are used depending on whether the blood sample was obtained in the morning in a fasted state, the morning in a nonfasted state, or in the afternoon in a nonfasted state, respectively.

Prevalence of Undernutrition

It is estimated that approximately 14.6% of births worldwide in 2015 were LBW. Rates of LBW are highest (48%) in southern Asia, which are twice those of sub-Saharan Africa. Globally, in 2015, 14% of children <5 years of age were *underweight* (weight-for-age < −2 SD). The global prevalence of *stunting* (height-for-age < −2 SD) has declined from 33% in 2000 to 22% in 2017, with the greatest reductions occurring in Asia. Stunting prevalence is highest in the African region (30%). *Wasting* (weight-for-height < −2 SD) affects 7% of children <5 years, with minimal change in prevalence over the past 2 decades. These figures represent 149 million stunted children and 50 million wasted children under 5 years of age. Asia carries most of the global burden of underweight children because of the combination of large population size and high prevalence. In 2017, 55% of all stunted children and 69% of all wasted children lived in Asia. Africa carries most of the remaining global burden.

Approximately 29% of children under 5 years of age in low- and middle-income countries (LMICs) suffer from vitamin A deficiency. Nationally representative data on the zinc status of children are sparse, but an estimated 17% of the global population is believed to be at risk of inadequate zinc intake. The estimated prevalence of anemia in children and women of reproductive age in 2016 was 42% and 33%, respectively. Iron deficiency is considered to be the primary cause of anemia in 25–42% and 50–60% of anemia cases among children and women, respectively. Universal salt iodization has made great strides in reducing the global burden of iodine deficiency. However, mild to moderate iodine deficiency remains a public health concern in 25 countries.

Consequences of Undernutrition

The most profound consequence of undernutrition is premature death (Table 62.3). Fetal growth restriction together with suboptimal breastfeeding in the first month of life contribute to 19% of all deaths in children <5 years (1.3 million deaths/year). When the effects of stunting, wasting, and deficiencies of vitamin A and zinc are also considered, these six items jointly contribute to 45% of global child deaths (3.1 million deaths/year), and many more are disabled or stunted for life. Anemia contributes to over one quarter of maternal deaths.

Table 62.3 Global Deaths in Children <5 Years Attributed to Nutritional Conditions

CONDITION	ATTRIBUTABLE DEATHS	% OF TOTAL DEATHS <5 YR
(a) Fetal growth restriction (<1 mo)	817,000	11.8
(b) Stunting (1-59 mo)	1,017,000	14.7
(c) Wasting (1-59 mo)	875,000	12.6
(d) Zinc deficiency (12-59 mo)	116,000	1.7
(e) Vitamin A deficiency (6-59 mo)	157,000	2.3
(f) Suboptimal breastfeeding (0-23 mo)	804,000	11.6
Joint effects of (a) + (f)	1,348,000	19.4
Joint effects of all 6 factors	3,097,000	44.7

From Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low- and middle-income countries. *Lancet.* 2013;382:427–451.

The risk of child death from infectious diseases increases even with mild undernutrition, and as the severity of undernutrition increases, the risk increases exponentially (Table 62.4). Undernutrition impairs immune function and other host defenses; consequently, childhood infections are more severe and longer lasting and more likely to be fatal than the same illnesses in well-nourished children. Infections can adversely affect nutritional status, and young children can quickly enter a cycle of repeated infections and ever-worsening malnutrition. Even for the survivors, physical and cognitive damage as a result of undernutrition can affect their future health and economic well-being. For females, the cycle of undernutrition is passed on to the next generation when undernourished women give birth to LBW babies.

Fetal growth restriction and early childhood undernutrition have consequences for adult chronic illness. LBW is associated with an increased risk of hypertension, stroke, and type 2 diabetes in adults. This increased risk is thought to reflect "fetal programming," a process by which fetal undernutrition leads to permanent changes in the structure and metabolism of organs and systems that manifest as disease in later life. The risk is exacerbated by low weight gain during the first 2 years of life. The increased risk of adult chronic disease from undernutrition early in life is a particular challenge to LMICs with rapid economic growth.

Stunting before age 3 years is associated with poorer motor and cognitive development and altered behavior in later years. The developmental quotient (DQ; see Chapter 28) is reduced by 6-13 points. Iodine and iron deficiencies also lead to loss of cognitive potential. Indications are that children living in areas of chronic iodine deficiency have an average reduction in intelligence quotient (IQ) of 12-13.5 points compared with children in iodine-sufficient areas. Iron deficiency has a detrimental effect on the motor development of children <4 years and on cognition of school-aged children. The estimated deficit is 1.73 IQ points for each 10 g/L decrease in hemoglobin concentration.

Undernutrition can have substantial economic consequences for survivors and their families. The consequences can be quantified in five categories: (1) increased costs of healthcare, either neonatal care for LBW babies or treatment of illness for infants and young children; (2) productivity losses (and thus reduced earnings) associated with smaller stature and muscle mass; (3) productivity losses from reduced cognitive ability and poorer school performance; (4) increased costs of chronic diseases associated with fetal and early child malnutrition; and

Table 62.4 Hazard Ratios for All-Cause and Cause-Specific Deaths Associated with Stunting, Wasting, and Underweight in Children <5 Years

STANDARD DEVIATION (SD) SCORE	DEATHS				
	ALL	PNEUMONIA	DIARRHEA	MEASLES	OTHER INFECTIONS
HEIGHT/LENGTH-FOR-AGE					
< −3	5.5	6.4	6.3	6.0	3.0
−3 to < −2	2.3	2.2	2.4	2.8	1.9
−2 to < −1	1.5	1.6	1.7	1.3	0.9
≥ −1	1.0	1.0	1.0	1.0	1.0
WEIGHT-FOR-LENGTH					
< −3	11.6	9.7	12.3	9.6	11.2
−3 to < −2	3.4	4.7	3.4	2.6	2.7
−2 to < −1	1.6	1.9	1.6	1.0	1.7
≥ −1	1.0	1.0	1.0	1.0	1.0
WEIGHT-FOR-AGE					
< −3	9.4	10.1	11.6	7.7	8.3
−3 to < −2	2.6	3.1	2.9	3.1	1.6
−2 to < −1	1.5	1.9	1.7	1.0	1.5
≥ −1	1.0	1.0	1.0	1.0	1.0

From Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low- and middle-income countries. *Lancet.* 2013;382:427–451.

(5) consequences of maternal undernutrition on future generations. The impact of nutrition on earnings appears to be independent of the effects of childhood deprivation.

Interventions for Undernutrition

Interventions to address child undernutrition can be divided into those that address immediate causes *(nutrition-specific interventions)* and those that address underlying or indirect causes *(nutrition-sensitive interventions)* (Table 62.5). In the short-term, nutrition-specific interventions (e.g., salt iodization) can have substantial impact even in the absence of economic growth, and micronutrient interventions (supplementation and fortification) are consistently ranked as the most cost-effective investment. However, there is increased attention to nutrition-sensitive interventions as the best means of sustainably eliminating malnutrition and to multisectoral policies that harness the synergism between the two types of interventions (e.g., cross-sectoral linkages among agriculture, nutrition, and health).

To reduce the adverse consequences of undernutrition on mortality, morbidity, and cognitive development, interventions must encompass both fetal and postnatal periods. Preventing LBW is essential, with emphasis on prevention of low maternal BMI and anemia, and in the longer term, prevention of low maternal stature. Maternal height is a strong predictor of birth outcomes, and approximately 6.5 million small-for-gestational age (SGA) or preterm births are associated with maternal short stature each year. Other measures include smoking cessation, birth spacing, delaying pregnancy until after 18 years of age, and intermittent preventive treatment of malaria in malaria-endemic areas. In the postnatal period, promotion and support of exclusive breastfeeding is a high priority. Although the Baby Friendly Hospital Initiative has a marked benefit on rates of exclusive breastfeeding in hospitals, postnatal counseling from community workers or volunteers is needed to facilitate continuation of exclusive breastfeeding at home for 6 months (see Chapter 61). Most studies show a lower risk of HIV transmission with exclusive breastfeeding than with mixed breastfeeding. The risk of HIV transmission by breastfeeding is approximately 5–20% depending on duration, but can be reduced to <2% with antiretroviral drugs. Even without antiretroviral drugs, exclusively breastfed children of HIV-infected mothers in low-income countries have lower mortality than nonbreastfed children, because the latter are at increased risk of death from diarrhea and pneumonia.

Table 62.5 Examples of Nutrition-Specific and Nutrition-Sensitive Interventions

NUTRITION-SPECIFIC INTERVENTIONS	NUTRITION-SENSITIVE INTERVENTIONS
• Promotion and support for exclusive breastfeeding for 6 mo, and continued breastfeeding for at least 2 yr • Promotion of adequate, timely, and safe complementary feeding from 6 mo • Increased micronutrient intake through dietary diversity • Micronutrient supplements for pregnant women (iron/folate) and young children (vitamin A, iron, zinc) in deficient areas • Zinc supplements to children during and after diarrhea (10-20 mg/day for 2 wk) • Prevention and treatment of severe acute malnutrition • Crop biofortification, food fortification, salt iodization • Reduced heavy physical activity in pregnancy	• Increased access to affordable, nutritious food; smallholder agriculture; credit and microfinance • Postharvest food processing and preservation • Vaccination against neonatal and childhood illness; access to healthcare • Improved water/sanitation and hygiene (e.g., handwashing with soap) • Education; women's empowerment; gender equality • Social protection (e.g., cash transfers) • Malaria prevention (vector control/bednets); intermittent preventive treatment during pregnancy and in children 3-59 mo • Birth spacing; delaying pregnancy until after 18 yr of age

Interventions to improve infant feeding must be designed for the local setting and thus require careful formative research during their development. Messages should be few, feasible, and

culturally appropriate. For complementary feeding, the introduction of nutrient-rich energy-dense mixtures of foods at 6 months of age and responsive feeding are often emphasized. Where adequate complementary feeding is difficult to achieve and subclinical deficiencies are common, high-dose vitamin A supplementation every 6 months in children 6-59 months of age reduces all-cause mortality and death caused by diarrhea by 12%, and zinc supplementation can reduce 1- to 4-year mortality by 18%, diarrhea incidence by 13%, and pneumonia by 19%. Monitoring of child growth provides an early alert to a nutrition or health problem but is only worthwhile if accompanied by good counseling and growth promotion activities. The impact of growth monitoring and promotion will depend on coverage, intensity of contact, health worker performance and communication skills, adequacy of resources, and the motivation and ability of families to follow agreed actions.

Other Nutritional Interventions

Treatment of vitamin and mineral deficiencies is discussed in Chapters 66-72. Treatment of LBW and intrauterine growth restriction is discussed in Chapter 119.

SEVERE ACUTE MALNUTRITION

Severe acute malnutrition is defined as severe wasting and/or bilateral edema. *Severe wasting* is extreme thinness diagnosed by a weight-for-length (or height) < −3 SD of the WHO Child Growth Standards. In children ages 6-59 months, a mid-upper arm circumference <115 mm also denotes severe acute malnutrition: a color-banded tape (see Fig. 62.4) is a convenient way of screening children in need of treatment.

Bilateral edema is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 seconds. A pit (dent) remaining under each thumb indicates bilateral edema.

This definition of severe acute malnutrition distinguishes wasted/edematous children from those who are stunted because stunted children (although underweight) are not a priority for acute clinical care because their deficits in height and weight cannot be corrected in the short term. The previous name *protein-energy malnutrition* is avoided because it oversimplifies the complex, multifactorial etiology. Other terms are *marasmus* (severe wasting), *kwashiorkor* (characterized by edema), and *marasmic-kwashiorkor* (severe wasting and edema).

Children with severe acute malnutrition have had a diet insufficient in energy and nutrients relative to their needs. The magnitude of the deficits will differ depending on the duration of inadequacy, quantity and diversity of food consumed, presence of antinutrients (e.g., phytate), individual variation in requirements, and number and severity of coexisting infections and their duration. Infections can lead to profound nutrient deficits and imbalances: For example, amino acids are diverted to form acute-phase proteins, potassium, magnesium, vitamin A, and zinc are lost through diarrhea, and losses of glycine and taurine are linked to small bowel bacterial overgrowth. Ingested microbes can cause villous atrophy and loss of nutrients from maldigestion and malabsorption, as well as disruption of gut barrier function leading to microbial translocation, chronic immune activation, and altered gut microbiome (environmental enteric dysfunction). Deficits can also arise from increased nutrient utilization in response to toxins (e.g., cysteine and methionine to detoxify dietary cyanogens).

Children affected by severe acute malnutrition may have different clinical presentations and metabolic disturbances due to variations in the type and extent of deficits and imbalances in their bodies. This heterogeneity is a result of diverse pathways that lead to severe acute malnutrition. Children who develop edematous malnutrition are more likely than nonedematous children to have had exposures that generate oxidative stress and/or to have greater deficits in free radical–scavenging antioxidants (glutathione; vitamins A, C, and E; and essential fatty acids) or cofactors (zinc, copper, selenium).

Table 62.6 Clinical Signs of Malnutrition

SITE	SIGNS
Face	Moon face (kwashiorkor), simian facies (marasmus)
Eye	Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periorbital edema
Mouth	Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement
Teeth	Enamel mottling, delayed eruption
Hair	Dull, sparse, brittle hair; hypopigmentation; flag sign (alternating bands of light and normal color); broomstick eyelashes; alopecia
Skin	Loose and wrinkled (marasmus); shiny and edematous (kwashiorkor); dry, follicular hyperkeratosis; patchy hyperpigmentation and hypopigmentation ("crazy paving" or "flaky paint" dermatoses); erosions; poor wound healing
Nails	Koilonychia; thin and soft nail plates, fissures, or ridges
Musculature	Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)
Skeletal	Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies
Abdomen	Distended: hepatomegaly with fatty liver; ascites may be present
Cardiovascular	Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy
Neurologic	Global developmental delay, loss of knee and ankle reflexes, impaired memory
Hematologic	Pallor, petechiae, bleeding diathesis
Behavior	Lethargic, apathetic, irritable on handling
Gastrointestinal tract	Atrophy of small intestine mucosa, lactase deficiency common

Modified from Grover Z, Ee LC. Protein energy malnutrition. *Pediatr Clin North Am.* 2009;56:1055–1068.

Clinical Manifestations of Severe Acute Malnutrition (Table 62.6)

Severe wasting is most visible on the thighs, buttocks, and upper arms and over the ribs and scapulae, where loss of fat and skeletal muscle is greatest (Fig. 62.5). Wasting is preceded by failure to gain weight and then by weight loss. The skin loses turgor and becomes loose as subcutaneous tissues are broken down to provide energy. The face may retain a relatively normal appearance, but eventually becomes wasted and wizened. The eyes may be sunken from loss of retroorbital fat, and lacrimal and salivary glands may atrophy, leading to lack of tears and a dry mouth. Weakened abdominal muscles and gas from bacterial overgrowth of the upper gut may lead to a distended abdomen. Severely wasted children are often fretful and irritable.

In **edematous malnutrition** the edema is most likely to appear first in the feet and then in the lower legs. It can quickly develop into generalized edema affecting also the hands, arms, and face (Fig. 62.6). Skin changes typically occur over the swollen limbs and include dark, crackled peeling patches ("flaky paint" dermatosis) with pale skin underneath that is easily infected (see Figs. 62.2 and 62.6). The hair is sparse, easily pulled out, and may lose its curl. In dark-haired children, the hair may turn pale or reddish. The liver is often enlarged with fat. Children with edema are uncomfortable, irritable and/or apathetic, and often refuse to eat.



Fig. 62.5 Child with severe wasting.



Fig. 62.6 Child with generalized edema.

Pathophysiology

When a child's intake is insufficient to meet daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy and prolong life. This process is called *reductive adaptation*. Fat stores are mobilized to provide energy. Later, protein in muscle, skin, and the gastrointestinal tract is mobilized. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs, and reducing inflammatory and immune responses. These changes have important consequences:

- The liver makes glucose less readily, making the child more prone to hypoglycemia. It produces less albumin, transferrin, and other transport proteins. It is less able to cope with excess dietary protein and to excrete toxins.
- Heat production is less, making the child more vulnerable to hypothermia.
- The kidneys are less able to excrete excess fluid and sodium, and fluid easily accumulates in the circulation, increasing the risk of fluid overload.
- The heart is smaller and weaker and has a reduced output, and fluid overload readily leads to death from cardiac failure.
- Sodium builds up inside cells because of leaky cell membranes and reduced activity of the sodium-potassium pump, leading to excess body sodium, fluid retention, and edema.
- Potassium leaks out of cells and is excreted in urine, contributing to electrolyte imbalance, fluid retention, edema, and anorexia.
- Loss of muscle protein is accompanied by loss of potassium, magnesium, zinc, and copper.
- The gut produces less gastric acid and enzymes. Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.
- Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.
- Immune function is impaired, especially cell-mediated immunity. The usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection.
- Red blood cell mass is reduced, releasing iron, which requires glucose and amino acids to be converted to ferritin, increasing the risk of hypoglycemia and amino acid imbalances. If conversion to ferritin is incomplete, unbound iron promotes pathogen growth and formation of free radicals.
- Micronutrient deficiencies limit the body's ability to deactivate free radicals, which cause cell damage. Edema and hair/skin changes are outward signs of cell damage.

When prescribing treatment, it is essential to take these changes in function into account. Otherwise, organs and systems will be overwhelmed, and death will rapidly ensue.

Principles of Treatment

Figure 62.7 shows the 10 steps of treatment, which are separated into two phases: stabilization and rehabilitation. These steps apply to all clinical forms and all geographic locations, including North America and Europe. The aim of the **stabilization** phase is to repair cellular function, correct fluid and electrolyte imbalance, restore homeostasis, and prevent death from the interlinked triad of hypoglycemia, hypothermia, and infection. The aim of the **rehabilitation** phase is to restore wasted tissues (i.e., catch-up growth). It is essential that treatment proceeds in an ordered progression and that the metabolic machinery is repaired before any attempt is made to promote weight gain. Pushing ahead too quickly risks inducing the potentially fatal "refeeding syndrome" (see Chapter 63).

Caregivers bring children to health facilities because of illness, rarely because of their malnutrition. A common mistake among healthcare providers is to focus on the illness and treat as for a well-nourished child. This approach ignores the deranged metabolism in malnourished children and can be fatal. Such children should be considered as severely malnourished with a complication, and

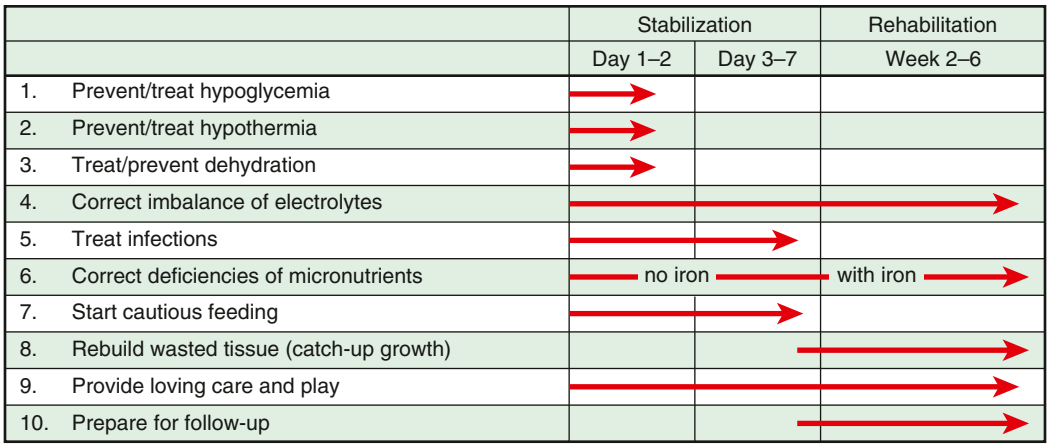

Fig. 62.7 The 10 steps of treatment for severe acute malnutrition and their approximate time frames.

Table 62.7 Emergency Treatment in Severe Malnutrition

CONDITION	IMMEDIATE ACTION
Shock • Lethargic or unconscious *and* • Cold hands *Plus* either: • Slow capillary refill (>3 sec) *or* • Weak fast pulse	1. Give oxygen. 2. Give sterile 10% glucose (5 mL/kg) rapidly by IV injection. 3. Give IV fluid at 15 mL/kg over 1 hr, using: • Ringer lactate with 5% dextrose *or* • Half-normal saline* with 5% dextrose *or* • Half-strength Darrow solution with 5% dextrose • If all these are unavailable, Ringer lactate 4. Measure and record pulse and respirations at the start and every 10 min. If there are signs of improvement (pulse and respiration rates fall), repeat IV drip, 15 mL/kg for 1 more hr. Then switch to oral or nasogastric rehydration with ReSoMal, 5-10 mL/kg in alternate hr (see Table 62.8 step 3). If there are no signs of improvement, assume septic shock and: 1. Give maintenance fluid IV (4 mL/kg/hr) while waiting for blood. 2. Order 10 mL/kg fresh whole blood and transfuse slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood. 3. Give furosemide, 1 mg/kg IV at start of transfusion.
Hypoglycemia Blood glucose <3 mmol/L	See Table 62.8 step 1 for treatment.
Severe dehydration	Do *not* give IV fluids except in shock. See Table 62.8 step 3 for treatment.
Very severe anemia Hgb <4 g/dL	If very severe anemia (or Hgb 4-6 g/dL *and* respiratory distress): 1. Give whole blood 10 mL/kg slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood. 2. Give furosemide 1 mg/kg IV at the start of the transfusion.
Emergency eye care Corneal ulceration	If corneal ulceration: 1. Give vitamin A immediately (age <6 mo: 50,000 IU; 6-12 mo: 100,000 IU; >12 mo: 200,000 IU) 2. Instill 1 drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out.

*Some would recommend 5% dextrose in normal saline.
Hgb, Hemoglobin; IV, intravenous(ly).

treatment should follow the 10 steps. *Two other potentially fatal mistakes are to treat edema with a diuretic and to give a high-protein diet in the early phase of treatment.*

Emergency Treatment

Table 62.7 summarizes emergency treatment for malnourished children with shock and other emergency conditions. Note that treatment of shock in these children is different (less rapid, smaller volume, different fluid) from treatment of shock in well-nourished children. However, shock from dehydration and shock from sepsis often coexist and are difficult to differentiate on clinical grounds. Thus the physician must be guided by the response to treatment: children with dehydration respond to IV fluid, whereas those with septic shock will not respond. Because severely malnourished children can quickly succumb to fluid overload, they must be monitored closely.

Stabilization

Table 62.8 summarizes the therapeutic directives for stabilization steps 1-7 (see Fig. 62.7). Giving broad-spectrum antibiotics (Table 62.9) and feeding frequent small amounts of F75 (a specially formulated low-lactose milk with 75 kcal and 0.9 g protein per 100 mL to which potassium, magnesium, and micronutrients are added) will reestablish metabolic control, treat edema, and restore appetite. The parenteral route should be avoided; children who lack appetite should be fed by nasogastric tube, because nutrients delivered within the gut lumen help in its repair. Table 62.10 provides recipes for preparing the special feeds and their nutrient composition. Of the two recipes for F75, one requires no cooking, and the other is cereal based and has a lower osmolality, which may benefit children with persistent diarrhea. F75 is also commercially available; maltodextrins replace some of the sugar, and potassium, magnesium, minerals, and vitamins are already added.

Table 62.8 Therapeutic Directives for Stabilization of Malnourished Children

STEP	PREVENTION	TREATMENT
1. Prevent/treat hypoglycemia blood glucose <3 mmol/L.	Avoid long gaps without food and minimize need for glucose: 1. Feed immediately. 2. Feed every 3 hr day and night (2 hr if ill). 3. Feed on time. 4. Keep warm. 5. Treat infections (they compete for glucose). *Note:* Hypoglycemia and hypothermia often coexist and are signs of severe infection.	**If conscious:** 1. Give 10% glucose (50 mL), or a feed (see step 7), or 1 tsp sugar under tongue, whichever is quickest. 2. Feed every 2 hr for at least first day. Initially give ¼ of feed every 30 min. 3. Keep warm. 4. Start broad-spectrum antibiotics. **If unconscious:** 1. Immediately give sterile 10% glucose (5 mL/kg) rapidly by IV. 2. Feed every 2 hr for at least first day. Initially give ¼ of feed every 30 min. Use nasogastric (NG) tube if unable to drink. 3. Keep warm. 4. Start broad-spectrum antibiotics.
2. Prevent/treat hypothermia axillary <35°C (95°F); rectal <35.5°C (95.9°F).	Keep warm and dry and feed frequently. 1. Avoid exposure. 2. Dress warmly, including head, and cover with blanket. 3. Keep room hot; avoid drafts. 4. Change wet clothes and bedding. 5. Do not bathe if very ill. 6. Feed frequently day and night. 7. Treat infections.	Actively rewarm. 1. Feed. 2. Skin-to-skin contact with caregiver ("kangaroo technique") or dress in warmed clothes, cover head, wrap in warmed blanket, and provide indirect heat (e.g., heater; transwarmer mattress; incandescent lamp). 3. Monitor temperature hourly (or every 30 min if using heater). 4. Stop rewarming when rectal temperature is 36.5°C (97.7°F).
3. Prevent/treat dehydration.	Replace stool losses. 1. Give ReSoMal after each watery stool. ReSoMal (37.5 mmol Na/L) is a low-sodium rehydration solution for malnutrition.	Do *not* give IV fluids unless the child is in shock. 1. Give ReSoMal 5 mL/kg every 30 min for first 2 hr orally or NG tube. 2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour. 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins). 4. Stop when rehydrated (≥3 signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate).
4. Correct electrolyte imbalance—deficit of potassium and magnesium, excess sodium.		1. Give extra potassium (4 mmol/kg/day) and magnesium (0.6 mmol/kg/day) for at least 2 wk (see Table 62.12). *Note:* Potassium and magnesium are already added in Nutriset F75 and F100 packets.
5. Prevent/treat infections.	Minimize risk of cross-infection. 1. Avoid overcrowding. 2. Wash hands. 3. Give measles vaccine to unimmunized children age >6 mo.	Infections are often silent. Starting on first day, give broad-spectrum antibiotics to all children. 1. For antibiotic choices/schedule, see Table 62.9. 2. Ensure all doses are given, and given on time. 3. Cover skin lesions so that they do not become infected. *Note:* Avoid steroids because they depress immune function.
6. Correct micronutrient deficiencies.	*Note:* Folic acid, multivitamins, zinc, copper, and other trace minerals are already added in Nutriset F75 and F100 packets.	Do *not* give iron in the stabilization phase. 1. Give vitamin A on day 1 (<6 mo 50,000 units; 6-12 mo 100,000 units; >12 mo 200,000 units) if child has any eye signs of vitamin A deficiency or has had recent measles. Repeat this dose on days 2 and 14. 2. Give folic acid, 1 mg (5 mg on day 1). 3. Give zinc (2 mg/kg/day) and copper (0.3 mg/kg/day). These are in the electrolyte/mineral solution and Combined Mineral Vitamin mix (CMV) and can be added to feeds and ReSoMal. 4. Give multivitamin syrup or CMV.
7. Start cautious feeding.		1. Give 8-12 small feeds of F75 to provide 130 mL/kg/day, 100 kcal/kg/day, and 1-1.5 g protein/kg/day. 2. If gross edema, reduce volume to 100 mL/kg/day. 3. Keep a 24-hr intake chart. Measure feeds carefully. Record leftovers. 4. If child has poor appetite, coax and encourage to finish the feed. If unfinished, reoffer later. Use NG tube if eating ≤80% of the amount offered. 5. If breastfed, encourage continued breastfeeding but also give F75. 6. Transfer to F100 when appetite returns (usually within 1 wk) and edema has been lost or is reduced. 7. Weigh daily and plot weight.

Dehydration status is easily misdiagnosed in severely wasted children, because the usual signs (e.g., slow skin pinch, sunken eyes) may be present even without dehydration. Rehydration must therefore be closely monitored for signs of fluid overload. Serum electrolyte levels can be misleading because of sodium leaking from the blood into cells and potassium leaking out of cells. Keeping the intake of electrolytes and nutrients constant (see Table 62.8) allows systems to stabilize more quickly than adjusting intake in response to laboratory results.

Table 62.11 provides a recipe for the special rehydration solution used in severe malnutrition (ReSoMal). Therapeutic **Combined Mineral Vitamin mix (CMV)** contains electrolytes, minerals, and vitamins and is added to ReSoMal and feeds. If unavailable, potassium, magnesium, zinc, and copper can be added as an electrolyte/mineral stock solution (Table 62.12 provides a recipe), and a multivitamin supplement can be given separately.

Rehabilitation

The signals for entry to the rehabilitation phase are reduced or minimal edema and return of appetite. A controlled transition over 3 days is recommended to prevent refeeding syndrome (see Chapter 63). After the transition, unlimited amounts should be given of a high-energy, high-protein milk formula such as F100 (100 kcal and 3 g protein per 100 mL), or a **ready-to-use therapeutic food**

Table 62.9 Recommended Antibiotics for Malnourished Children*

	GIVE
If no complications	Amoxicillin, 25 mg/kg PO twice daily for 5 days
If complications (shock, hypoglycemia, hypothermia, skin lesions, respiratory or urinary tract infections, or lethargy/sickly)	Gentamicin, 7.5 mg/kg IV or IM once daily for 7 days *and* Ampicillin, 50 mg/kg IV or IM every 6 hr for 2 days, then amoxicillin, 25-40 mg/kg PO every 8 hr for 5 days

If specific infections are identified, add appropriate antibiotics.
For persistent diarrhea or small bowel overgrowth, add metronidazole, 7.5 mg/kg PO every 8 hr for 7 days.
*Local resistance patterns may require these to be adjusted: Ensure that there is gram-negative coverage.
PO, Orally; IM, intramuscularly; IV, intravenously.

Table 62.11 Recipe for Rehydration Solution for Malnutrition (ReSoMal)

INGREDIENT	AMOUNT
Water	2 L
WHO ORS	One 1-L sachet*
Sucrose	50 g
Electrolyte/mineral solution†	40 mL

ReSoMal contains 37.5 mmol sodium and 40 mmol potassium/L.
*Sachet contains 2.6 g sodium chloride, 2.9 g trisodium citrate dihydrate, 1.5 g potassium chloride, and 13.5 g glucose.
†See Table 62.12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).
WHO ORS, World Health Organization Oral Rehydration Solution.

Table 62.10 Recipes for Milk Formulas F75 and F100

	F75[B] (STARTER)	F75[C] (STARTER) (CEREAL-BASED)	F100[D] (CATCH-UP)
Dried skimmed milk (g)	25	25	80
Sugar (g)	100	70	50
Cereal flour (g)	—	35	—
Vegetable oil (g)	30	30	60
Electrolyte/mineral solution (mL)[a]	20	20	20
Water: make up to (mL)	1000	1000	1000
Content/100 mL			
Energy (kcal)	75	75	100
Protein (g)	0.9	1.1	2.9
Lactose (g)	1.3	1.3	4.2
Potassium (mmol)	4.0	4.2	6.3
Sodium (mmol)	0.6	0.6	1.9
Magnesium (mmol)	0.43	0.46	0.73
Zinc (mg)	2.0	2.0	2.3
Copper (mg)	0.25	0.25	0.25
% Energy from protein	5	6	12
% Energy from fat	32	32	53
Osmolality (mOsm/L)	413	334	419

Whisk at high speed to prevent oil from separating out.
[a]See Table 62.12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).
[b]A comparable F75 can be made from 35 g dried whole milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1,000 mL or from 300 mL full-cream cow's milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1,000 mL.
[c]This lower-osmolality formula may be helpful for children with dysentery or persistent diarrhea. Cook for 4 min.
[d]A comparable F100 can be made from 110 g dried whole milk, 50 g sugar, 30 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL or from 880 mL full-cream cow's milk, 75 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1,000 mL.

Table 62.12 Recipe for Concentrated Electrolyte/Mineral Solution*

INGREDIENT	g	mol/20 mL
Potassium chloride: KCl	224.0	24 mmol
Tripotassium citrate	81.0	2 mmol
Magnesium chloride: $MgCl_2 \cdot 6H_2O$	76.0	3 mmol
Zinc acetate: Zn acetate$\cdot 2H_2O$	8.2	300 µmol
Copper (cupric) sulfate: $CuSO_4 \cdot 5H_2O$	1.4	45 µmol
Water: make up to	2500 mL	

Add 20 mL when preparing 1 L of feed or ReSoMal.
*Make fresh each month. Use cooled boiled water.

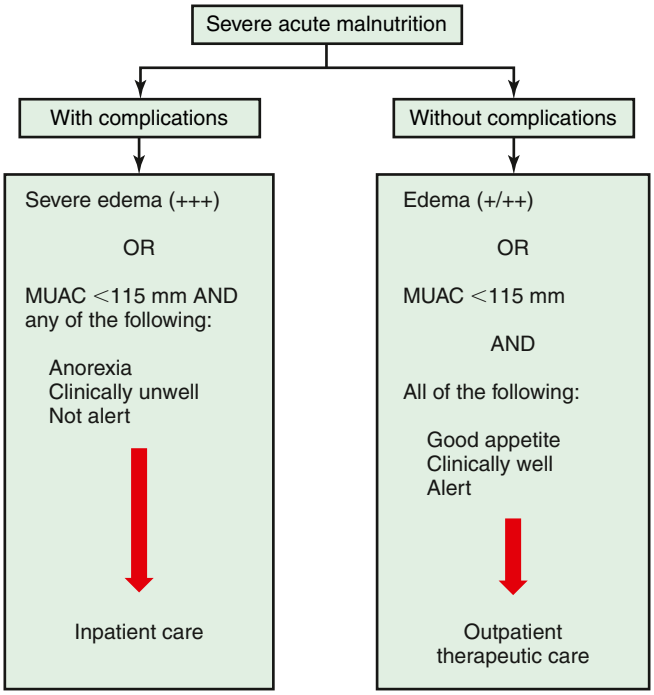

Fig. 62.8 Flow diagram for inpatient care *(left)* and outpatient care *(right)* in the child with severe acute malnutrition. MUAC, Mid-upper arm circumference.

(RUTF), or family foods modified to have comparable energy and protein contents.

To make the transition, for 2 days replace F75 with an equal volume of F100, then increase each successive feed by 10 mL until some feed remains uneaten (usually at about 200 mL/kg/day). After this transition, give 150-220 kcal/kg/day and 4-6 g protein/kg/day and continue to give potassium, magnesium, and micronutrients. Add iron (3 mg/kg/day). If breastfed, encourage continued breastfeeding. Children with severe malnutrition have developmental delays, so loving care, structured play, and sensory stimulation during and after treatment are essential to aid recovery of brain function.

Community-Based Treatment

Many children with severe acute malnutrition can be identified in their communities before medical complications arise. If these children have a good appetite and are clinically well, they can be rehabilitated at home through community-based management of acute malnutrition, which has the added benefit of reducing their exposure to nosocomial infections and providing continuity of care after recovery. It also reduces the time caregivers spend away from home and their opportunity costs and can be cost-effective for health services.

Figure 62.8 shows the criteria for inpatient and outpatient care. To maximize coverage and compliance, community-based therapeutic care has 4 main elements: community mobilization and sensitization, active case finding, therapeutic care, and follow-up after discharge.

Community-based therapeutic care comprises steps 8-10 (see Fig. 62.7), plus a broad-spectrum antibiotic (step 5). RUTF is usually provided, especially in times of food shortage. RUTF is specially designed for rehabilitating children with severe acute malnutrition at home. It is high in energy and protein and has electrolytes and micronutrients added. The most widely used RUTF is a thick paste that contains milk powder, peanuts, vegetable oil, and sugar. Pathogens cannot grow in it because of its low moisture content. Hospitalized children who have completed steps 1-7 can be transferred to community-based care for completion of their rehabilitation, thereby reducing their hospital stay to about 7-10 days.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 63

Refeeding Syndrome

Jason M. Nagata and Andrea K. Garber

Refeeding syndrome occurs in response to reintroduction of nutrition in the malnourished patient. Rapid electrolyte and fluid shifts in response to the surge of insulin brought on by the presence of nutrients can lead to numerous medical complications shown in Table 63.1 and may progress to life-threatening outcomes, including coma, heart failure, and sudden death. Early accounts of the syndrome were among starved survivors of wartime sieges and concentration camps and among prisoners of war when given sudden access to unlimited food. Refeeding syndrome occurs as a result of oral, enteral, or parenteral (highest risk) feeding of malnourished individuals, especially in the setting of aggressive refeeding. Patient populations at risk for refeeding syndrome include those with anorexia nervosa and other restrictive eating disorders, chronic conditions causing malnutrition (cancer, congenital heart disease), malabsorptive syndromes (inflammatory bowel disease, cystic fibrosis), cerebral palsy, bariatric surgery, and bowel resections (Table 63.2).

In malnourished patients with anorexia nervosa, cases of refeeding syndrome have been documented during refeeding. Risk is greatest within the first 7 days of the start of feeding and is primarily indicated by serum hypophosphatemia (<3.0 ng/dL); hypokalemia (<3.5 mmol/L) and hypomagnesemia (<1.8 mg/dL) are also seen. Studies have identified low weight, but not the caloric load, as the primary risk factor for refeeding syndrome.

An increase in the supply of energy (usually carbohydrates) is accompanied by an increase in sodium pump activity, and too sudden a supply risks causing a rapid release of accumulated sodium from cells, causing expansion of extracellular and plasma volumes. At the same time, there is increased cellular uptake of glucose, potassium, magnesium, and phosphate. Reactivation of metabolic pathways for adenosine triphosphate (ATP) production further depletes serum phosphorus.

For decades, the key to preventing the syndrome was believed to be lower-calorie refeeding with cautious advancement. Diets starting at 1,000-1,200 calories per day were recommended by multiple organizations in the United States. Diets as low as 500 calories per day were recommended in Europe. These cautious approaches are *still recommended* for patients with extreme malnutrition (<60% of median body mass index for age and sex) and children in developing

Table 63.1 Clinical Signs and Symptoms of Refeeding Syndrome

HYPOPHOSPHATEMIA	HYPOKALEMIA	HYPOMAGNESEMIA	VITAMIN/THIAMINE DEFICIENCY	SODIUM RETENTION	HYPERGLYCEMIA
Cardiac Hypotension Decreased stroke volume *Respiratory* Impaired diaphragm contractility Dyspnea Respiratory failure *Neurologic* Paresthesia Weakness Confusion Disorientation Lethargy Areflexic paralysis Seizures Coma Hematologic Leukocyte dysfunction Hemolysis Thrombocytopenia *Other* Death	*Cardiac* Arrhythmias *Respiratory* Failure *Neurologic* Weakness Paralysis *Gastrointestinal* Nausea Vomiting Constipation *Muscular* Rhabdomyolysis Muscle necrosis *Other* Death	*Cardiac* Arrhythmias *Neurologic* Weakness Tremor Tetany Seizures Altered mental status Coma *Gastrointestinal* Nausea Vomiting Diarrhea *Other* Refractory hypokalemia and hypocalcemia Death	Encephalopathy Lactic acidosis Death	Fluid overload Pulmonary edema Cardiac compromise	*Cardiac* Hypotension *Respiratory* Hypercapnia Failure *Other* Ketoacidosis Coma Dehydration Impaired immune function

Data from Kraft MD, Btaiche IF, Sacks GS. Review of RFS. *Nutr Clin Pract.* 2005;20:625–633. From Fuentebella J, Kerner JA. Refeeding syndrome. *Pediatr Clin North Am.* 2009;56:1201–1210.

Table 63.2 Refeeding Syndrome: National Institutes for Clinical Excellence (NICE) Guidelines for Management of Refeeding Syndrome

PATIENTS AT RISK FOR REFEEDING SYNDROME	
ONE OR MORE OF THE FOLLOWING	—OR— TWO OR MORE OF THE FOLLOWING
• BMI <16 kg/m^2	• BMI <18.5 kg/m^2
• Unintentional weight loss of >15% in the previous 3-6 mo	• Unintentional weight loss of >10% in the previous 3-6 mo
• Little or no nutritional intake for >10 days	• Little or no nutritional intake for >5 days
• Low levels of potassium, phosphorus, or magnesium before refeeding	• History of alcohol or drug use, including insulin, chemotherapy, antacids, or diuretics

From Sachs K, Andersen D, Sommer J, Winkelman A, Mehler PS. Avoiding medical complications during the refeeding of patients with anorexia nervosa. *Eat Disord.* 2015;23(5):411–421, Table 1, p. 414.

nations, where the World Health Organization (WHO) guidelines for the treatment of malnutrition are still in place (see Chapter 62). However, the majority of patients hospitalized in the United States are adolescents with acute, moderate malnutrition. In this patient population, studies have demonstrated the feasibility of higher-calorie refeeding beginning >1,400 calories per day. A randomized clinical trial has demonstrated the efficacy and safety of starting with 2,000 calories per day in hospitalized adolescents with moderate malnutrition secondary to anorexia nervosa. In the United States, meal-based refeeding is most common, with food served on bedside trays, whereas higher-calorie refeeding by nasogastric tube is reported in Australia. Electrolyte shifts are much lower than expected using these protocols; serum electrolyte levels can be monitored daily in hospital settings and decreased electrolyte levels may be corrected with supplementation.

The following guidance is a suggestion for possible electrolyte repletion for refeeding syndrome in adolescents with eating disorders. For hypophosphatemia: Phos-Na-K 1 packet (250 mg) tid for phosphorous 2.5-2.9 mg/dL; Phos-Na-K 2 packets (500 mg) tid for phosphorous 2.0-2.4 mg/dL; IV Na-K-Phos 0.24 mmol/kg max 15 mmol/dose, and consider intensive care consultation for phosphorous <2.0 mg/dL. For hypokalemia: extended release KCl 20 mEq PO for potassium 3.1-3.4 mmol/L (recheck in 8-12 hours); extended release KCl 40 mEq PO for potassium 2.5-3.0 mmol/L (recheck in 8-12 hours); extended release KCl 40 mEq PO stat for potassium 2.2-2.4 mmol/L; and IV KCl and consider intensive care consultation for potassium <2.2 mmol/L. For hypomagnesemia: Mag-oxide 1 tablet (133-200 mg elemental Mg each) bid for magnesium 1.3-1.7 mg/dL; Mag-oxide 2 tablets (133-200 mg elemental Mg each) bid for magnesium 1.0-1.2 mg/dL; and IV Mg-SO_4 @50 mg/kg; max 2 g/dose and consider intensive care consultation for magnesium <1.0 mg/dL. Declining electrolytes but within the normal range generally do not need to be treated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 64

Malnutrition in High-Resource Settings

Liliane K. Diab, Stephanie P. Gilley, and Nancy F. Krebs

See Chapter 62 for malnutrition in low- and middle-income countries. **Malnutrition** refers to **undernutrition** and is defined as an imbalance between nutrient requirements and intake or delivery that then results in deficits—of energy, protein, or micronutrients—that negatively affect growth and development. Malnutrition may be illness related or nonillness related, or both. Illness-related malnutrition may be caused by one or more diseases, infections, or congenital anomalies and by injury or surgery. Nonillness-related causes include environmental, psychosocial, or behavioral factors. Often, one cause may be primary and exacerbated by another. Patients with malnutrition may present with growth deceleration, or actual weight loss, as measured by anthropometric parameters, including weight, length/height, skinfolds, and mid-upper arm circumference (see Chapter 62). **Wasting** is defined as being too thin for height (weight for length or body mass index [BMI] *z* score less than −2). **Stunting** is defined as being too short for age (height or length *z* score less than −2).

U.S. data suggest 10% of children seen by primary care physicians are diagnosed with growth faltering. Malnutrition is a primary diagnosis in 1–5% of all hospital admissions. The prevalence of malnutrition in hospitalized patients is ~25%; malnutrition in children can contribute to poor outcomes, especially in intensive care units.

Although **failure to thrive (FTT)** has classically been the term used to describe children who are not meeting weight gain targets based on growth curves, the term *malnutrition* more accurately describes this cohort of children and removes perceived accusations or blame from the diagnosis.

CLINICAL MANIFESTATIONS

The degree of malnutrition can be assessed by inadequate weight-for-corrected age, failure to gain adequate weight over time (weight gain velocity), height velocity, weight-for-length or BMI depending on age, and developmental outcomes (see Chapter 62). These growth and anthropometric parameters are measured longitudinally and plotted on growth charts appropriate for the child's sex, age (corrected if premature), and, if known, genetic disorders, such as trisomy 21 or Turner syndrome. The American Academy of Pediatrics (AAP) and the U.S. Centers for Disease Control and Prevention (CDC) recommend the 2006 World Health Organization (WHO) standards for infants up to 2 years of age who are measured supine for length. The CDC 2000 growth references are recommended for children and adolescents (age 2-20 years) when measured with a standing height. The severity of malnutrition (mild, moderate, or severe) may be determined by plotting the *z* score (standard deviation [SD] from the mean) for each of these anthropometric values on the age- and sex-appropriate growth chart (Table 64.1). Most electronic health records are able to calculate and plot the *z* scores for measured anthropometrics. *Z* scores can also be obtained by entering measurements in electronic applications such as peditools.org. In infants less than 6 months old, a slow or slowing weight gain velocity can indicate malnutrition even if weight/length is preserved. The presence of bilateral pitting edema and low albumin triggers concern for **edematous malnutrition** (kwashiorkor) in the absence of an alternative explanation (such as heart, liver, or renal disease). Edema in the setting of malnutrition automatically classifies as **severe malnutrition** (see Table 64.1).

ETIOLOGY AND DIAGNOSIS

The most common mechanisms of pediatric malnutrition are nonillness related and are secondary to insufficient calorie intake, whether the result of low maternal breast milk supply, psychosocial factors such as food insecurity, or feeding difficulties. Picky eating, although common in young children, can occasionally be so restrictive as to result in malnutrition and/or micronutrient deficiencies. **Avoidant restrictive food intake disorder** is one risk factor and is often seen in children with autism, food aversions, or those on elimination diets for fear of food allergies or gluten sensitivity (Fig. 61.3) (Table 64.2). The most important illness-related

Table 64.1 Comprehensive Malnutrition Indicators

INDICATORS*	SEVERE MALNUTRITION	MODERATE MALNUTRITION	MILD MALNUTRITION
Weight-for-length *z* score	≤−3	−2.0 to −2.99	−1.0 to −1.99†
BMI-for-age *z* score	≤−3	−2.0 to −2.99	−1.0 to −1.99†
Length *z* score	≤−3	No data	No data
Mid-upper arm circumference	≤−3	−2.0 to −2.99	−1.0 to −1.99
†Weight gain velocity (<2 years of age)	<75% of the norm for expected weight gain	<50% of the norm for expected weight gain	<25% of the norm for expected weight gain
†Weight loss (2-20 yr of age)	>10% of UBW	>7.5% UBW	>5% UBW
†Deceleration in weight-for-length/height or BMI-for-age	Deceleration across 3 *z* score lines	Deceleration across 2 *z* score lines	Deceleration across 1 *z* score line
†Inadequate nutrient intake	≤25% of estimated energy/protein need	26–50% of estimated energy/protein need	51–75% of estimated energy/protein need
^Edema	Present	Absent	Absent

Use clinical judgment when applying these diagnostic criteria.
*It is recommended that when a child meets more than one malnutrition acuity level, the highest acuity level is used for diagnosis to ensure that appropriate evaluation, monitoring, and treatment are provided.
^The presence of bilateral pitting edema and low albumin is diagnostic for kwashiorkor, which is severe malnutrition regardless of any other indicator(s).
†Needs additional positive diagnostic criteria to make a malnutrition diagnosis.
BMI, Body mass index; UBW, usual body weight.
Adapted with modifications from Becker PJ, Nieman Carney L, Corkins MR, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *J Acad Nutr Diet.* 2014;114(12):1988–2000.

cause of insufficient growth is inability to consume sufficient calories or starvation. The differential diagnosis in this case is broad and includes many health conditions such as cardiac and neurologic diseases. Oral aversion can sometimes be a manifestation of eosinophilic esophagitis or dysphagia. Other causes of malnutrition are (1) increased nutrient losses (e.g., protein-losing enteropathy, chronic diarrhea); (2) increased metabolic demands, as seen in extensive burn injuries, congenital heart disease, and thyroid disorders; (3) altered nutrient digestion, absorption, or utilization (e.g., cystic fibrosis, short bowel syndrome, celiac disease); and (4) some chromosome abnormalities that can be associated with poor growth such as Russel Silver syndrome. More than one mechanism can exist simultaneously (Fig. 64.1). *Chronic malnutrition* is defined as malnutrition having a duration of ≥3 months (see Chapter 62).

Table 64.2 DSM-5 Diagnosis of Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
   1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).
   2. Significant nutritional deficiency.
   3. Dependence on enteral feeding or oral nutritional supplements.
   4. Marked interference with psychosocial functioning.

B. The disturbance is not better explained by lack of available food or by associated culturally sanctioned practice.

C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.

D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. p. 947. Copyright 2013. American Psychiatric Association.

A complete history includes information regarding the onset of the growth faltering, a detailed review of systems, past medical history, and family history including parents' heights and growth patterns. The perinatal history is also important to identify children who are born small for gestational age (SGA). SGA infants who are asymmetric (birthweight is disproportionally more depressed than length or head circumference) have a better prognosis for catch-up growth than do infants who have symmetric intrauterine growth restriction. A detailed nutritional history should include unusual nutritional beliefs and the quantity, quality, and frequency of meals. A comprehensive physical examination can help elucidate possible underlying etiologies and manifestations of micronutrient deficiencies to guide laboratory or imaging evaluation if indicated (Table 64.3 and see Table 62.6). Tanner staging cannot be used as a marker for nutritional status, but it is influenced and often delayed by malnourishment. Puberty will usually resume progression when the malnourished state improves. A reasonable initial screen should include a complete blood count, a comprehensive metabolic panel (CMP), and urinalysis.

Additional measurements that are useful for classifying the severity of malnutrition and following the progress of the acutely malnourished child are mid-upper arm circumference (MUAC) and triceps skin folds (TSF). MUAC can be used as an independent anthropometric tool to screen for and diagnose malnutrition (depletion of subcutaneous fat stores) when obtaining an accurate length or height is difficult. The MUAC is used as a predictor of malnutrition-related mortality by the WHO (increased risk of death from malnutrition if less than 11.5 cm in infants and children 6-64

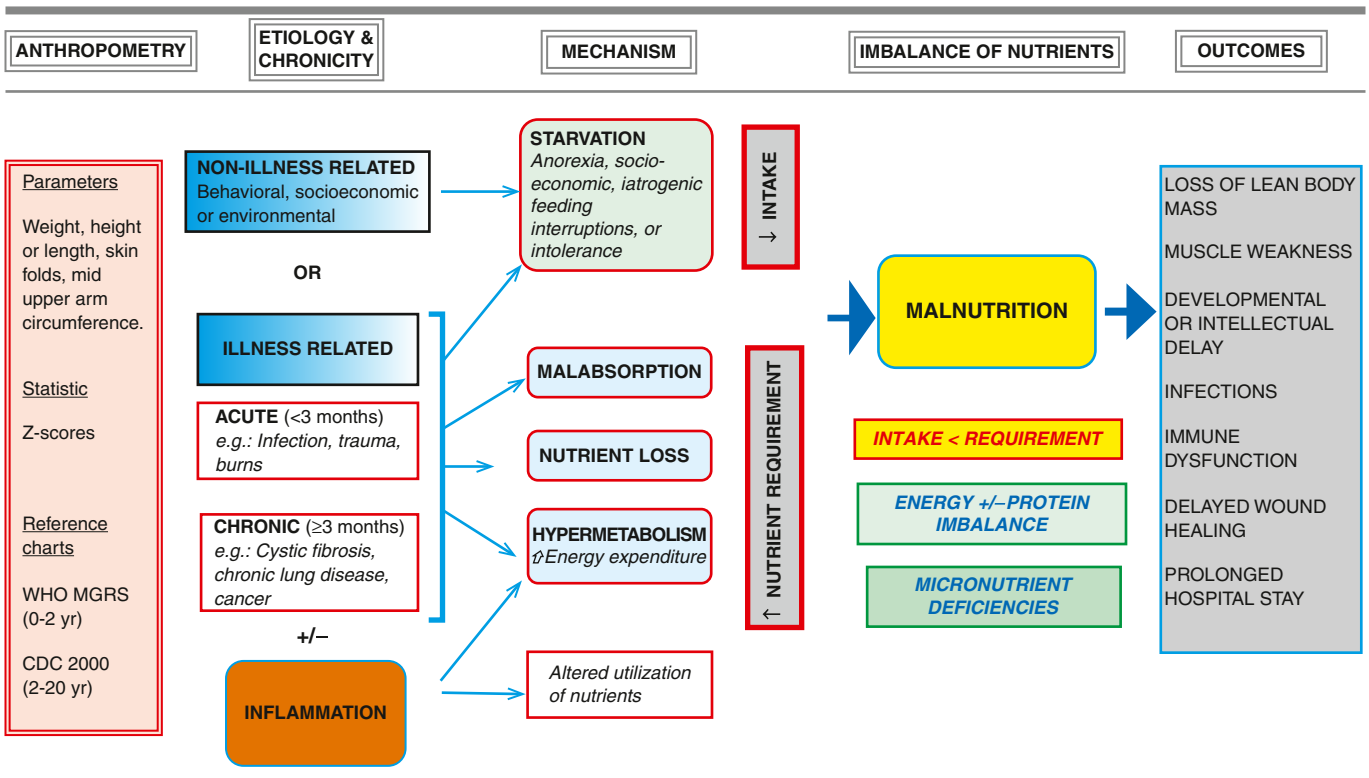

Fig. 64.1 Defining malnutrition in hospitalized children (ASPEN). CDC, Centers for Disease Control and Prevention; MGRS, Multicenter Growth Reference Study; WHO, World Health Organization. *(From Mehta NM, Corkins MR, Lyman B, et al. Defining pediatric malnutrition: A paradigm shift toward etiology-related definitions.* J Parenter Enteral Nutr. 2013;37[4]:460-481.*)*

Table 64.3 Approach to Malnutrition Based on Review of Systems

CAUSE	HISTORY AND PHYSICAL EXAMINATION	DIAGNOSTIC CONSIDERATION	WORKUP
Psychosocial	Lack of structure, poor sleep, permissive or intrusive feeding, feeding difficulties and food refusal starting in infancy	Low caloric intake secondary to home feeding environment; in extreme cases need to consider child neglect or abuse Avoidant restrictive food intake disorder (ARFID)	May need blood tests to check for certain micronutrient deficiencies based on diet history
CNS	Developmental delay, poor feeding, vomiting, large head circumference, abnormal neurologic exam	Brain tumor, intracranial bleeding (consider child abuse)	Referral to developmental pediatrics or neurology, MRI, EEG, specific test for neuromuscular function
Gastrointestinal	Chronic vomiting or diarrhea, fatty stool, crying with feedings, nocturnal cough, snoring, history of travel to/from developing countries	Malabsorption, intestinal parasites, milk protein intolerance, pancreatic insufficiency, cystic fibrosis, celiac disease, immunodeficiency, inflammatory bowel disease, small bowel bacterial overgrowth	May need referral to gastroenterology; stool studies (reducing substance, occult blood, fat stain), upper GI with small bowel follow-through; may need endoscopic evaluation
Cardiac	Slow feeding, dyspnea, diaphoresis with feeding, restless sleep, heat murmur	Congenital heart disease, heart failure	Referral to cardiology, ECG, echocardiogram
Genetic	May have a positive family history of developmental delay; often facies typical of a syndrome, skeletal abnormalities, heart murmur; consider in symmetric IUGR.	Noonan syndrome, William syndrome, Turner syndrome, Russel Silver syndrome	Specific genetic testing
Pulmonary	Dyspnea, tachypnea, recurrent wheezing, pulmonary infections	Asthma, aspiration, food allergies, cystic fibrosis, immunodeficiency, neuroendocrine hyperplasia of infancy	Chest x-ray, sweat chloride test; specialty referral
Renal	History of recurrent UTI, abnormal urinalysis, elevated BUN and creatinine	UTI, renal tubular acidosis	General chemistry with BUN and creatinine, urinalysis, urine and serum osmolality
Endocrine	Hypothyroidism is associated with decreased activity level; diabetes is associated with polyuria and polydipsia; growth hormone deficiency is associated with decreased linear growth velocity	Hypothyroidism, type 1 diabetes, growth hormone deficiency	Thyroid function tests, blood glucose and urinalysis, pituitary function tests

BUN, Blood urea nitrogen; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; IUGR, intrauterine growth restriction; UTI, urinary tract infection.

Adapted from Carrasco MM, Wolford JE. Child abuse and neglect. In Zitelli BJ, McIntire SC, Nowalk AJ, eds. *Atlas of Pediatric Physical Diagnosis*, 7th ed. Philadelphia: Elsevier; 2018, Table 6.6.

months of age). TSF is a measure of subcutaneous fat and is a sensitive indicator of total body fat. Both MUAC and TSF are especially useful tools for nutrition status assessment in children with altered body composition such as low muscle mass due to cerebral palsy. However, TSF needs to be done by experienced providers to minimize errors. MUAC and TSF charts are available on the WHO website.

TREATMENT

While an illness-related etiology of malnutrition is being investigated, caloric supplementation can occur simultaneously. Both the medical workup and the initiation of supplemental oral feeds can occur in the outpatient setting with close follow-up. Consider including a speech or occupational therapist for a suck-and-swallow evaluation if the history suggests difficulty with oral feeds. Hospitalization may be indicated for cases of severe malnutrition because of the potential for refeeding syndrome (see Chapter 63), or if a child with mild to moderate malnutrition has not responded after 2-3 months of outpatient management. Hospitalization may include initiation of nasogastric tube feeds, further diagnostic and laboratory evaluation, assessment and observed implementation of adequate nutrition, and evaluation of the parent-child feeding interaction. The type of caloric supplementation is based on the age of the child, the severity of malnutrition, and the underlying medical condition. Every effort to maximize the breastfeeding relationship in breastfed infants should be made, ideally involving lactation support, expressing breast milk to increase supply if low, and fortification of maternal milk if indicated.

Feeding style is equally important to caloric intake. Parents should be encouraged to respond to the child's cues of hunger and satiety and to have a structured schedule for meals and snacks (every 2-3 hours). A responsive feeding style that respects the toddler's autonomy but retains parental control over food choices helps establish healthy feeding habits (see Chapter 61). Grazing behaviors with frequent small snacks interfere with eating at mealtimes. Commonly used spill-proof and squeezable packaging foster eating "on the go" and has been associated with poor self-regulation of energy intake.

Use of liquid **oral nutritional supplements** resulted in significantly better catch-up growth in children with moderate to severe malnutrition (Tables 64.4 and 64.5). Oral nutritional supplements are most helpful when monitored and balanced with food intake. Start with 30-40 kcal per kg per day and serve them in small amounts simultaneously with meals to allow intake of age-appropriate food. However, children with oral motor difficulties may need to consume a larger proportion of calories in a liquid form.

Table 64.4 Nutritional Supplements

CATEGORY	BRAND EXAMPLES	FEATURES AND COMMENTS
ORAL SUPPLEMENTS		
Standard, cow's milk protein	Boost Kid Essentials 1.0 or 1.5 (with or without fiber) PediaSure 1.0 or 1.5 (with or without fiber) Nutren Jr 1.0 (with or without fiber) Kate Farms Pediatric Standard 1.2 *EnfaGrow *Nido *Scandishake	May or may not contain lactose.
Semi-elemental	Kate Farms Pediatric Peptide 1.5 PediaSure Peptide 1.0 or 1.5 Peptamen Jr	Used for malabsorption. Contains MCT.
Elemental	EleCare Junior Neocate Splash Neocate Jr Puramino Peptamen Jr	Used for malabsorption or severe protein allergy. Contains MCT.
Soy protein	Bright Beginnings Soy Pediasmart Soy	Cow-milk protein free.
Clear liquid	*Boost Breeze *Ensure Clear	Clear liquid, fruit flavored, fat free; cow's milk protein source. For supplemental nutrition *only;* none are a complete nutrition supplement.
Wound healing supplement	Juven Arginaid	Arginaid: L-Arginine only. Juven: Arginine glutamine, and betahydroxy-betamethylbutyrate.
TUBE FEEDING		
Standard, cow's milk protein	Boost Kid Essentials 1.0, 1.5 Nutren Junior PediaSure 1.0	Isotonic, most available with or without additional fiber.
High calorie	Boost Kid Essentials 1.5 *(1.5 kcal/mL)* PediaSure 1.5 *(1.5 kcal/mL)* Kate Farms Pediatric Peptide 1.5 *(1.5 kcal/mL)*	For increased caloric needs or fluid restriction.
Food-based formulas	Compleat Pediatric *(1.0 kcal/mL)* Compleat Pediatric Reduced Calorie *(0.6 kcal/mL)* Compleat Pediatric Organic Blends *(1.2 kcal/mL)* PediaSure Harvest *(1.0 kcal/mL)* Kate Farms Pediatric Standard *(1.2 kcal/mL)* Nourish *(1.13 kcal/mL)*	

List of products is not exhaustive and does not imply endorsement. Pediatric formulas are appropriate for children ages 1-11 years and are not appropriate for use in infants. After 11 years, adult formulations (not listed) may be used.
*Does not provide complete sole source of nutrition.
Adapted from Pediatric Nutrition Handbook/internal guide at Children's Hospital Colorado.

The response to feeding depends on the specific diagnosis, medical treatment, and severity of malnutrition. The same anthropometric measures used to diagnose malnutrition can be used to measure progress and recovery from the malnourished state. Target recovery growth is 150% of the normal rate of weight gain for age (Table 64.6). Many children with malnutrition require empiric micronutrient supplementation with zinc (and thiamine, if concerns about refeeding). Iron deficiency is also common in young children, but supplementation is most effective if initiated after resolution of any acute inflammatory processes (such as infection) and is typically not initiated until after 1-2 weeks of successful weight restoration. Additional supplementation for other micronutrients such as vitamin D and vitamin A can be considered based on symptoms and laboratory evaluation.

Interventions for contributing psychosocial factors are ideally targeted to the underlying issue, such as maternal depression or insufficient funds for food. Some children who develop feeding aversion behaviors will require treatment by a specialized feeding team. If abuse or purposeful neglect is a concern, the family should be referred to the child protective services team.

Kwashiorkor has a specific set of treatment guidelines from the WHO, including empiric antibiotics and avoidance of intravenous fluids and rapid repletion, as this can precipitate heart failure. Treatment of kwashiorkor in a low-resource setting is discussed in more detail in Chapter 62. In a high-resource setting, treatment may involve continuous feeds of a semi-elemental formula through a nasogastric tube to stabilize blood sugars in conjunction with close monitoring of electrolytes.

Table 64.5 Calorie Boosters for Oral and Enteral Feeding

	Kcal/g	Kcal/Tbsp	FEATURES AND COMMENTS
CARBOHYDRATE (CHO)			
Cornstarch	3.8	33	Can add to formula or water to treat hypoglycemia in glycogen storage disease or other disorders; dose per weight, age, and glucose levels; suggested starting dose of 0.5 g per kg per feed.
Infant rice cereal	—	15	Thickens formula, not human milk; start with 1 teaspoon rice cereal/oz formula (adds 5 kcal/oz, dilutes other nutrients). Not recommended to administer through feeding tube.
FAT			
MCT oil	8.3	116	7.7 kcal/mL; does not mix well, can administer as small bolus.
Heavy whipping cream		50	3.3 kcal/mL can be added to milk or nutritional supplements.
Butter		100	Easy to mix and use in a variety of foods.
PROTEIN			
Beneprotein	3.6	16.7	100% whey protein; 1 packet = 1 scoop = 7 g weight, 6 g protein, 25 kcal; can add to formula, human milk, food, or beverages.
COMBINATION			
Duocal	4.9	42	Hydrolyzed corn starch and fat (35% MCT); can add to formula, human milk, food, or beverages.
MCT Procal	6.6	—	1 packet (16 g) = 105 kcal, 10 g MCT, 2 g protein. For altered fat absorption or metabolism. Contains MCT and milk protein; can add to formula, food, and beverages.
Carnation Instant Breakfast			1 packet (36 g) = 140 kcal

Table 64.6 Weight Gain Velocity (0-2 Years of Age, g/day)

AGE (MONTHS)	EXPECTED GROWTH (g/DAY)	CATCH-UP GROWTH (g/DAY)
Preterm infant	30-40	
0-3	20-30	30-45
3-6	15-20	20-30
6-9	10-15	15-20
9-12	10	15
12-24	6	10

PROGNOSIS

Malnutrition, regardless of cause, can potentially have a detrimental effect on physical and intellectual growth and development, especially in infants younger than 2 years old. Early diagnosis and treatment of acute malnutrition may avoid long-term consequences. Multiple studies point to a negative impact of chronic malnutrition and stunting on intelligence quotient (IQ) later in life. Pediatric medical providers are encouraged to approach nutritional status in children as a controllable factor that can have a profound influence on brain function throughout life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 65

Overweight and Obesity

Sheila Gahagan

EPIDEMIOLOGY

Obesity is an important pediatric public health problem associated with risk of complications in childhood and increased morbidity and mortality throughout adult life. Obesity is linked to more deaths than underweight. In 2016, according to the World Health Organization (WHO), 39% of adults aged 18 years and older were overweight and 13% were obese.

In the United States, child and adolescent obesity prevalence has increased by 300% over the past 40 years. In 2017–2018, the U.S. prevalence of pediatric obesity was 19.3%, affecting about 14.4 million children and adolescents. Obesity prevalence increases by age-group, with 13.4% of 2- to 5-year-olds, 20.3% of 6- to 11-year-olds, and 21.2% of 12- to 19-year-olds affected. Some U.S. populations have higher rates of childhood obesity than others do. Prevalence of obesity in children was 25.6% among Hispanic children, 24.2% among non-Hispanic Black children, 16.1% in non-Hispanic White children, and 8.7% in non-Hispanic Asian children. Higher maternal education confers protection against childhood obesity across all ethnic groups.

The first 1,000 days, the period from conception to age 2 years, are a modifiable period related to risk for childhood obesity. Recommendations for the first 1,000 days include (1) a healthy and nutritious diet during pregnancy; (2) good care for all mothers during pregnancy; (3) exclusive breastfeeding for 6 months; (4) nurturing and responsive care for infants and toddlers; (5) the right foods introduced to babies at the right time; (6) water and other healthy beverages with no added sugars for toddlers; (7) a healthy and nutritious diet for babies and toddlers; (8) the right knowledge and skills for parents and caregivers to properly nourish young children; (9) consistent access to enough nutritious food for families of young children; and (10) societal investments in the well-being of every baby and toddler (for further information see https://thousanddays.org/resource/nourishing-americas-future/).

Parental obesity correlates with a higher risk for obesity in the children. Prenatal factors, including high preconceptual weight, gestational weight gain, high birthweight, and maternal smoking, are associated with increased risk for later obesity. Paradoxically, intrauterine growth restriction with early infant catch-up growth is associated with the development of central adiposity and adult-onset cardiovascular (CV) risk. Breastfeeding is modestly protective for obesity based on dose and duration. Infants with high levels of negative reactivity (temperament) are more at risk for obesity than those with better self-regulation. The incidence of obesity in children was noted to increase during the COVID-19 pandemic.

BODY MASS INDEX

Obesity, or increased adiposity, is defined using the **body mass index (BMI)**, an excellent proxy for more direct measurement of body fat. BMI = weight in kg/(height in meters)^2. Adults with a BMI ≥30 meet the criterion for obesity, and those with a BMI 25-30 fall in the overweight range. During childhood, levels of body fat change beginning with high adiposity during infancy. Body fat levels decrease for approximately 5.5 years until the period called *adiposity rebound,* when body fat is typically at the lowest level. Adiposity then increases until early adulthood (Fig. 65.1). Consequently, obesity and overweight are defined using BMI percentiles for children ≥2 years old and weight/length percentiles for infants <2 years old. The criterion for **obesity** is BMI ≥95th percentile, and for **overweight** is BMI between 85th and 95th percentiles.

ETIOLOGY

Humans have the capacity to store energy in adipose tissue, allowing improved survival in times of famine. Simplistically, obesity results from an imbalance of caloric intake and energy expenditure. Even incremental but sustained caloric excess results in excess adiposity. Individual adiposity is the result of a complex interplay among genetically determined body habitus, appetite, nutritional intake, **physical activity (PA)**, and energy expenditure. Environmental factors determine levels of available food, preferences for types of foods, levels of PA, and preferences for types of activities. Food preferences play a role in the consumption of energy-dense foods. Humans innately prefer sweet and salty foods and tend initially to reject bitter flavors, common to many vegetables. Repeated exposure to healthy foods promotes their acceptance and liking, especially in early life. This human characteristic to adapt to novel foods can be used to promote healthy food selection.

Environmental Changes

Over more than 4 decades, the food environment changed dramatically related to urbanization and the food industry as fewer families routinely prepare meals. Foods prepared by a food industry have higher levels of calories, simple carbohydrates, and fat. The price of many foods has declined relative to the family budget. These changes, in combination with marketing pressure, have resulted in larger portion sizes and increased snacking between meals. The increased consumption of high-carbohydrate beverages, including sodas, sport drinks, fruit punch, and juice, adds to these factors.

According to the National Center for Health Statistics, fast food is consumed by 36.3% of 2- to 19-year-old U.S. children each day and by two thirds of children every week. A typical fast-food meal can contain 2,000 kcal and 84 g of fat. Many children consume four servings of high-carbohydrate beverages per day, resulting in an additional 560 kcal of low nutritional value. Sweetened beverages have been linked to increased risk for obesity. The dramatic increase in the use of high-fructose corn syrup to sweeten beverages and prepared foods is another important environmental change, leading to availability of inexpensive calories.

Since World War II, levels of PA in children and adults have declined. According to the 2017 National Health and Nutrition Examination Survey (NHANES) survey, 26.1% of adolescents met PA guidelines of 60 minutes of PA per day. Only 20% met guidelines for aerobic PA and muscle strengthening. The persistence of low levels of PA is related to many factors, including changes in the built environment, more reliance on cars, lower levels of active transportation, safety issues, and increasingly sedentary lifestyles. Many sectors of society do not engage in PA during leisure time. For children, budgetary constraints and pressure for academic performance have led to less time devoted to physical education in schools. Perception of poor neighborhood safety also leads to lower levels of PA. Furthermore, screens (televisions, tablets, smartphones, computers) offer compelling sedentary activities that do not burn calories.

Sleep plays a role in the risk for obesity. Over the past 4 decades, children and adults have decreased the amount of time spent sleeping. Reasons for these changes may relate to increased time at work, increased time watching television, and a generally faster pace of life. Chronic partial sleep loss can increase risk for weight gain and obesity, with the impact possibly greater in children than in adults. In studies of young, healthy, lean men, short sleep duration was associated with decreased leptin levels and increased ghrelin levels, along with increased hunger and appetite. *Sleep debt* also results in decreased glucose tolerance and insulin sensitivity related to alterations in glucocorticoids and sympathetic activity. Some effects of sleep debt might relate to *orexins,* peptides synthesized in the lateral hypothalamus that can increase feeding, arousal, sympathetic activity, and neuropeptide Y activity.

Genetics

Genetic determinants also have a role in individual susceptibility to obesity (Table 65.1). Findings from genome-wide association studies explain a very small portion of interindividual variability in obesity.

2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703

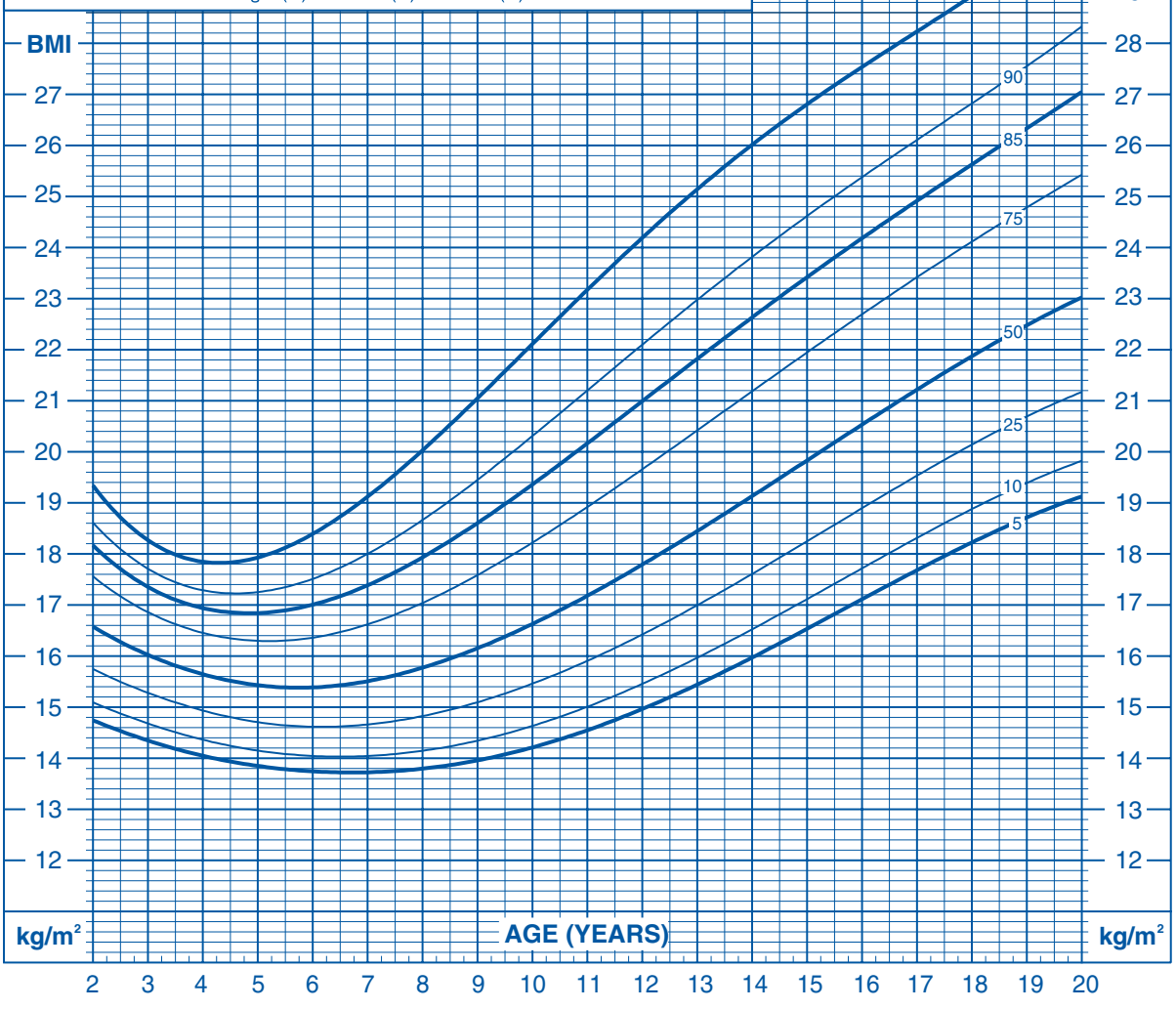

Published May 30, 2000 (modified 10/16/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

SAFER • HEALTHIER • PEOPLE™

A

Fig. 65.1 A, Body mass index (BMI)-for-age profiles for boys and men.

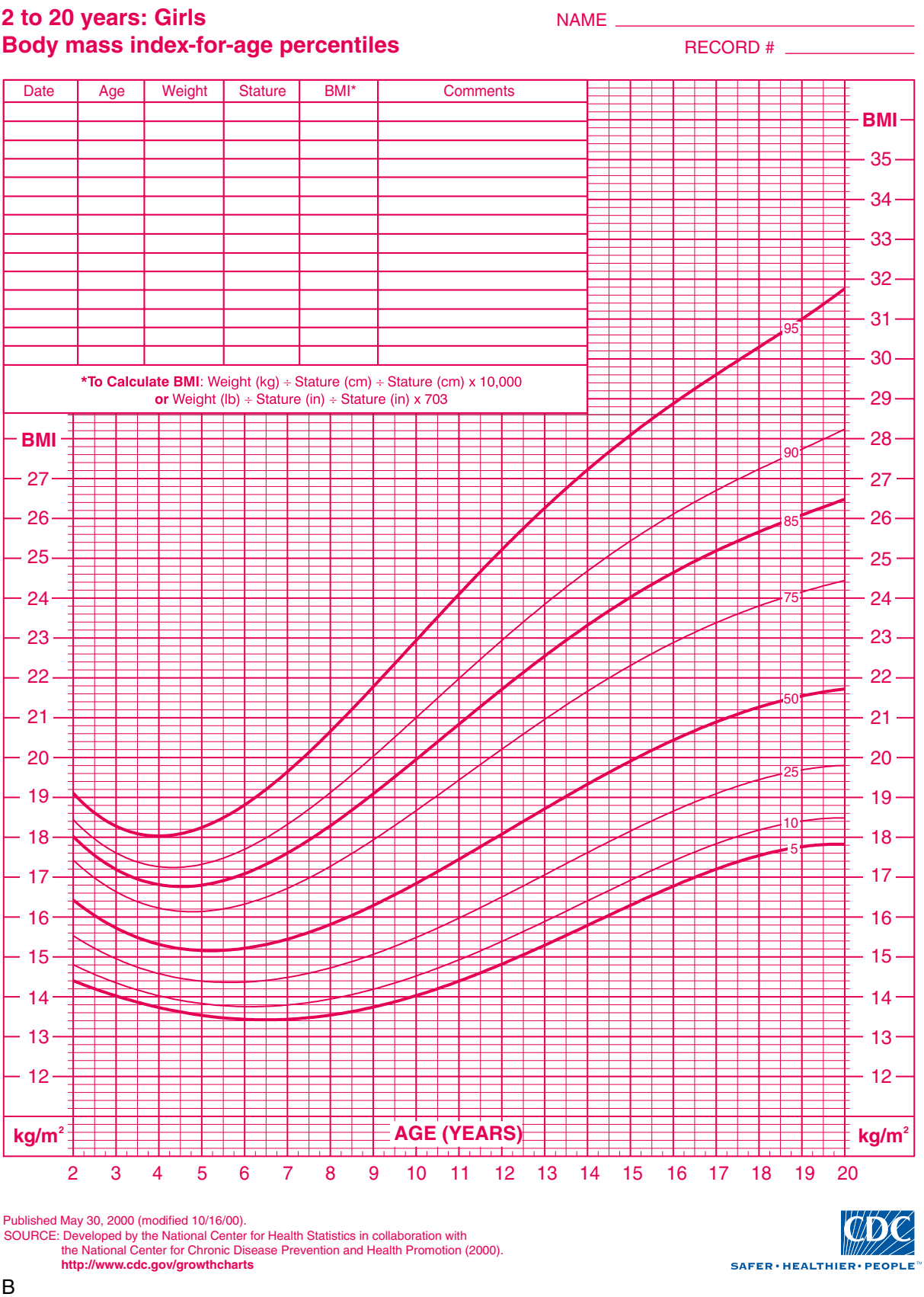

B

Fig. 65.1, cont'd B, BMI-for-age profiles for girls and women. *Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. See* www.cdc.gov/growthcharts.

Table 65.1 Endocrine and Genetic Causes of Obesity

DISEASE	SYMPTOMS	LABORATORY
ENDOCRINE		
Cushing syndrome	Central obesity, hirsutism, moon face, hypertension	Dexamethasone suppression test
GH deficiency	Short stature, slow linear growth	Evoked GH response, IGF-1
Hyperinsulinism	Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome	Insulin level
Hypothyroidism	Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT_4
Pseudohypoparathyroidism	Short metacarpals, subcutaneous calcifications, dysmorphic facies, intellectual disability, short stature, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion
GENETIC/SYNDROMIC		
Albright hereditary osteodystrophy	Short stature, skeletal defects, PTH resistance	*GNAS* gene, in syndromic but also in isolated nonsyndromic obesity
Alström syndrome	Cognitive impairment, retinitis pigmentosa, insulin-resistant diabetes mellitus, hearing loss, hypogonadism, cardiomyopathy	*ALMS1* gene
Bardet-Biedl syndrome	Retinitis pigmentosa, renal abnormalities, polydactyly, syndactyly, hypogonadism	~21 different genes
BDNF/TrkB deficiency	Hyperactivity, impaired concentration, limited attention span, impaired short-term memory and pain sensation	*BDNF/TrkB* gene
Biemond syndrome	Cognitive impairment, iris coloboma, hypogonadism, polydactyly	
Carpenter syndrome	Polydactyly, syndactyly, cranial synostosis, intellectual disability	*RAB23* gene, located on chromosome 6 in humans
Cohen syndrome	Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, intellectual disability, microcephaly, decreased visual activity, neutropenia, joint laxity	*VPS13B* gene (often called *COH1*) at locus 8q22
Deletion 9q34	Early-onset obesity, intellectual disability, brachycephaly, synophrys, prognathism, behavior and sleep disturbances	Deletion 9q34
Down syndrome	Short stature, dysmorphic facies, intellectual disability	Trisomy 21
ENPP1 gene	Insulin resistance, childhood obesity	Gene on chromosome 6q
Fragile X	Long facies, large, prominent ears, macroorchidism, autism	*FMR1*; CGG repeat expansion >200
Fröhlich syndrome	Hypothalamic tumor	
FTO gene polymorphism, plus upstream regulatory and downstream activation genes	Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression	Homozygous for *FTO* AA allele
Kabuki syndrome	Characteristic facies, intellectual disability, visceral and skeletal malformations	*KMT2D, MLL2, ALR, KABUK1*
Kleefstra syndrome	Intellectual disability, autism-like behavior, hypotonia, cardiac defects	*EHMT1*
KSR2 deficiency	Mild hyperphagia and reduced basal metabolic rate, insulin resistance often with acanthosis nigricans, irregular menses, early development of type 2 diabetes mellitus	*KSR2* gene
Leptin or leptin receptor gene deficiency	Early-onset severe obesity, infertility (hypogonadotropic hypogonadism), hyperphagia, infections	Leptin
Leptin variant (antagonistic)	Hyperphagia, obesity; treatment with high dose recombinant leptin	High leptin levels
Melanocortin 4 receptor gene mutation	Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia; **most common known genetic cause of obesity;** homozygous worse than heterozygous	*MC4R* variant
MEHMO	Intellectual disability, epilepsy, hypogonadism, microcephaly, obesity	Xp22.13-p21.1
MORM	Intellectual disability, obesity, retinal dystrophy, micropenis	*INPP5E*
PCSK1 deficiency	Small bowel enteropathy, hypoglycemia, hypothyroidism, ACTH deficiency, diabetes insipidus	*PCSK1* gene
Prader-Willi syndrome	Neonatal hypotonia, slow infant growth, small hands and feet, intellectual disability, hypogonadism, hyperphagia leading to severe obesity, paradoxically elevated ghrelin	Partial deletion of chromosome 15 or loss of paternally expressed genes: *MKRN3, ZNF127, MAGEL2, SNRPN*
Proopiomelanocortin (POMC) deficiency	Obesity, red hair, pale skin, adrenal insufficiency due to ACTH deficiency, hyperproinsulinemia, hyperphagia, cholestatic jaundice	Loss-of-function of *POMC* gene
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD); ROHHADNET (with neuroendocrine tumor)	Often confused with congenital central hypoventilation syndrome (CCHS); presentation ≥1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, GH deficiency, pain insensitivity, hypothermia, precocious puberty, and neural crest tumors	Unknown genes May be a paraneoplastic disorder
Rubinstein-Taylor syndrome	Short stature, visual impairment, scoliosis, dysmorphic facies	*CREBBP, EP300*
SH2B1 deficiency	Hyperphagia, disproportionate hyperinsulinemia, early speech and language delay that often resolves, behavioral problems including aggression	*SH2B1* gene
SIM1 deficiency (Prader-Willi–like)	Hyperphagia with autonomic dysfunction (characterized by low systolic blood pressure), speech and language delay, neurobehavioral abnormalities including autistic-type behaviors	*SIM1*gene
Smith-Magenis syndrome	Intellectual disability, delayed speech, facial dysmorphology	*RAI1*
TUB deficiency	Retinal dystrophy, deafness	*TUB* gene
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment	XO chromosome
WAGRO	Wilms tumor, aniridia, genitourinary anomalies, mental retardation, obesity	*BDNF*

ACTH, Adrenocorticotropic hormone; cAMP, cyclic adenosine monophosphate; FT_4, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

One important example, the *FTO* gene at 16q12, is associated with adiposity in childhood, probably explained by increased energy intake. Monogenic forms of obesity have also been identified, including **melanocortin-4 receptor (**MC4R**)** deficiency, associated with early-onset obesity and food-seeking behavior. Pathogenic variants in *MC4R* are a common cause of **monogenetic** obesity but a rare (0.1%) cause of obesity in general. Deficient activation of *MC4R* is also seen in patients with **proopiomelanocortin (POMC)** deficiency, a prohormone precursor of adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH), resulting in adrenal insufficiency, light skin, red hair, hyperphagia, and obesity. Leptin releases MSH, which can then activate MC4R, affecting appetite.

In addition, evidence suggests that appetitive traits are moderately heritable. Some genes associated with appetite also relate to weight, and vice-versa. In addition, there are genetic conditions associated with obesity, such as **Prader-Willi syndrome**, which results from absence of paternally expressed imprinted genes in the 15q11.2-q13 region. Prader-Willi syndrome is characterized by insatiable appetite and food seeking. In the era of genomic medicine, it will be increasingly possible to identify risks according to specific genes and consider gene-environment interactions. Epigenetic environmental modification of genes may have a role in the development of obesity, especially during fetal and early life.

Endocrine and Neural Physiology

Monitoring of "stored fuels" and short-term control of food intake (appetite and satiety) occurs through neuroendocrine feedback loops linking adipose tissue, the GI tract, and the CNS (Figs. 65.2 and 65.3). GI hormones, including cholecystokinin, glucagon-like peptide 1, peptide YY (PYY), and vagal neuronal feedback, promote satiety. *Ghrelin* stimulates appetite. Adipose tissue provides feedback regarding energy storage levels to the brain through hormonal release of adiponectin and leptin. These hormones act on the arcuate nucleus in the hypothalamus and on the solitary tract nucleus in the brainstem and in turn activate distinct neuronal networks. Adipocytes secrete *adiponectin* into the blood, with reduced levels in response to obesity and increased levels in response to fasting. Reduced adiponectin levels are associated with lower insulin sensitivity and adverse CV outcomes. *Leptin* is directly involved in satiety; low leptin levels stimulate food intake, and high leptin levels inhibit hunger in animal models and in healthy human volunteers. However, the negative feedback loop from leptin to appetite may be more adapted to preventing starvation than excess intake.

Numerous neuropeptides in the brain, including PYY agouti-related peptide, and orexin, appear to affect appetite stimulation, whereas melanocortins and α-melanocortin–stimulating hormone are involved in satiety (see Fig. 65.3). The neuroendocrine control of appetite and weight involves a negative feedback system, balanced between short-term control of appetite and long-term control of adiposity (including leptin). PYY reduces food intake via the vagal-brainstem-hypothalamic pathway. Developmental changes in PYY are evident, as infants have higher PYY levels than school-aged children and adults. Obese children have lower fasting levels of PYY than adults. Weight loss may restore PYY levels in children, even though this does not happen in adults. In addition, patients homozygous for the *FTO* obesity-risk allele demonstrate poor regulation of the orexigenic hormone acyl-ghrelin and have poor postprandial appetite suppression.

COMORBIDITIES

Complications of pediatric obesity occur during childhood and adolescence and persist into adulthood. An important reason to prevent and treat pediatric obesity is the increased risk for morbidity and mortality later in life. Males who are overweight during adolescence are twice as likely to die from CV disease as those who have normal weight. More immediate comorbidities include type 2 diabetes, hypertension, hyperlipidemia, and **nonalcoholic fatty liver disease** (NAFLD) (Table 65.2). Insulin resistance increases with increasing adiposity and independently affects lipid metabolism and CV health. **Metabolic syndrome** (central obesity, hypertension, glucose intolerance, and hyperlipidemia) increases the risk for CV morbidity and mortality. NAFLD has been reported in 34% of patients treated in a pediatric obesity clinic. NAFLD is the most common chronic liver disease in U.S. children and adolescents. It can present with advanced fibrosis or nonalcoholic steatohepatitis and may result in cirrhosis and hepatocellular carcinoma. Insulin resistance is often associated. NAFLD is also independently associated with increased risk of CV disease.

Obesity may also be associated with chronic inflammation. Adiponectin, a peptide with antiinflammatory properties, occurs in reduced levels in obese patients compared with insulin-sensitive, lean persons. Low adiponectin levels correlate with elevated levels of free fatty acids and plasma triglycerides in addition to a high BMI, and high adiponectin levels correlate with peripheral insulin sensitivity. Adipocytes secrete peptides and cytokines into the circulation, and proinflammatory peptides such interleukin (IL)-6 and tumor necrosis factor (TNF)-α occur in higher levels in obese patients. Specifically, IL-6 stimulates production of CRP in the liver. CRP is a marker of inflammation and might link obesity, coronary disease, and subclinical inflammation.

Some complications of obesity are mechanical, including obstructive sleep apnea and orthopedic complications. Orthopedic complications include Blount disease and slipped femoral capital epiphysis (see Chapters 718 and 719.4).

Mental health problems can coexist with obesity, with the possibility of bidirectional effects. These associations are modified by gender, ethnicity, and socioeconomic status. Self-esteem may be lower in obese adolescent females than in nonobese peers. Some studies have found an association between obesity and adolescent depression. There is considerable interest in the co-occurrence of eating disorders and obesity. Obese youth are also at risk for bullying.

IDENTIFICATION

Overweight and obese children are often identified as part of routine medical care. The child and family may be unaware that the child has increased adiposity. They may be unhappy with the medical provider for raising this issue and may respond with denial or apparent lack of concern. It is often necessary to begin by helping the family understand the importance of healthy weight for current and future health. Forging a good therapeutic relationship is important because obesity intervention requires a chronic disease management approach. Intervention and successful resolution of this problem require considerable effort by the family and the child over an extended period in order to change eating and activity behaviors.

EVALUATION

The evaluation of the overweight or obese child begins with examination of the growth chart for weight, height, and BMI trajectories; consideration of possible medical causes of obesity; and detailed exploration of family eating, nutritional, and activity patterns. A complete pediatric history is used to uncover comorbid disorders. The family history focuses on the adiposity of other family members and the family history of obesity-associated disorders. The physical examination adds data that can lead to important diagnoses. Laboratory testing is guided by the need to identify comorbidities.

Examination of the **growth chart** reveals the severity, duration, and timing of obesity onset. Children who are overweight (BMI in 85th-95th percentile) are less likely to have developed comorbid conditions than those who are obese (BMI ≥95th percentile). Those with a BMI ≥99th percentile are most likely to have coexisting medical problems. Once obesity severity is determined, the BMI trajectory is examined to elucidate when the child became obese. Several periods during childhood are considered *sensitive* periods, or times of increased risk for developing obesity, including infancy, adiposity rebound (when body fat is lowest at approximately age 5.5 years), and adolescence. An abrupt change in BMI might signal the onset of a medical problem or a period of family or personal stress for the child. Examination of the weight trajectory can further reveal how the problem developed. A young child might exhibit high weight and high height because linear growth can increase early in childhood if a child consumes excess energy. At some point the weight percentile exceeds the height percentile, and the child's BMI climbs into the obese range. Another example

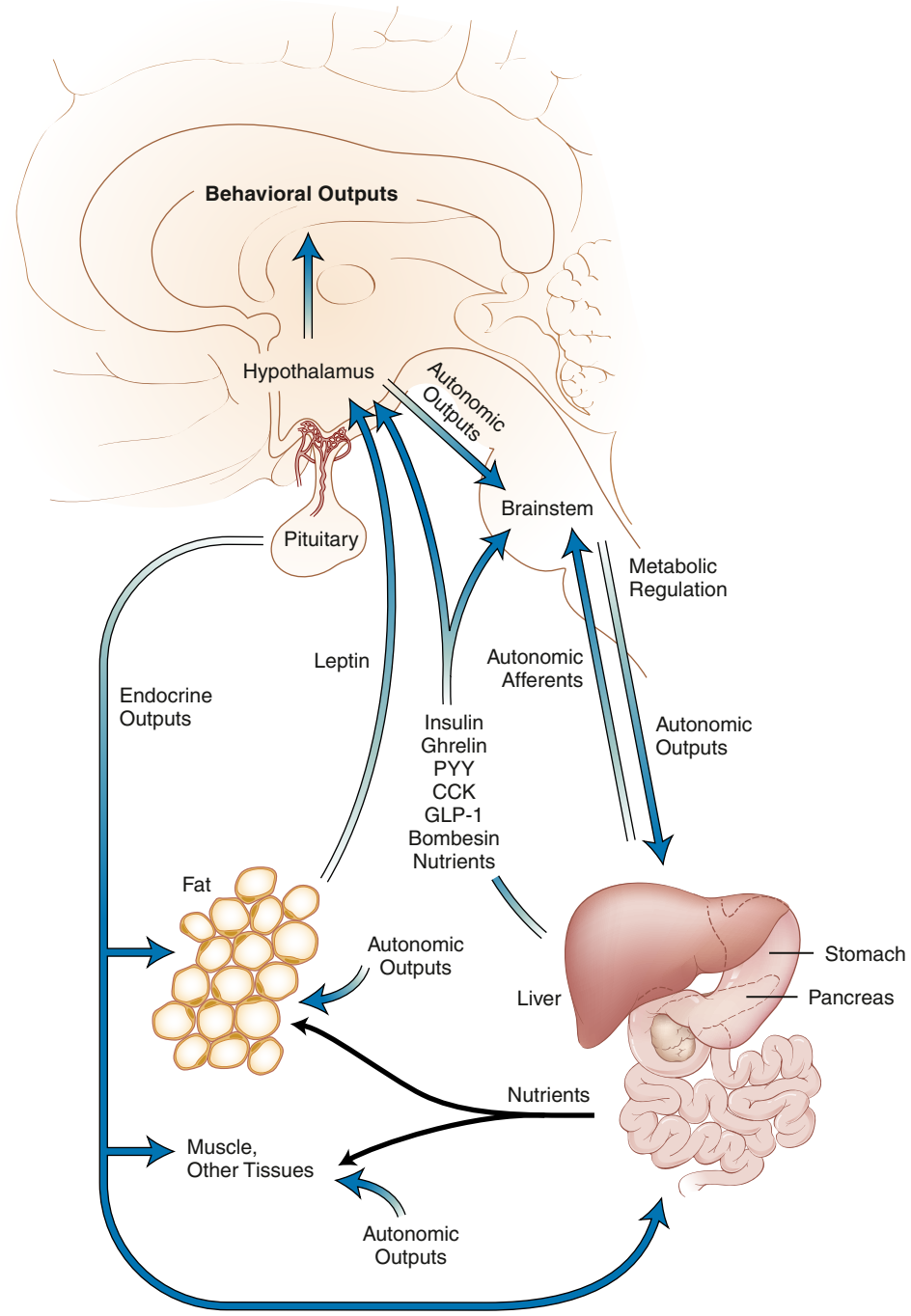

Fig. 65.2 Regulation of energy homeostasis by the brain-gut-adipose axis. CCK, Cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY. *(From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016, p. 1610.)*

is a child whose weight rapidly increases when they reduce their activity level and consume more meals away from home. Examination of the height trajectory can reveal endocrine problems, which often occur with slowing of linear growth.

Consideration of possible medical causes of obesity is essential, even though endocrine, syndromic, and monogenetic causes are rare (see Table 65.1). Growth hormone deficiency, hypothyroidism, and Cushing syndrome are examples of endocrine disorders that can lead to obesity. In general, these disorders manifest with slow linear growth. Because children who consume excessive amounts of calories tend to experience accelerated linear growth, short stature warrants further evaluation. Genetic disorders associated with obesity may manifest extreme hyperphagia, or they can have coexisting dysmorphic features, cognitive impairment, vision and hearing abnormalities, or short stature. In some children with congenital disorders such as myelodysplasia or muscular dystrophy, lower levels of PA can lead to secondary obesity. Some medications, such as atypical antipsychotics, can cause excessive appetite and hyperphagia, resulting in obesity (Table 65.3). Rapid weight gain in a child or adolescent taking one of these medications might require its discontinuation. Poor linear growth and rapid changes in weight gain are indications for evaluation of possible medical causes.

Exploration of family eating, nutritional, and activity patterns begins with a description of regular meal and snack times and family habits for walking, bicycle riding, active recreation, and **screen time** (TV, computer, video games). It is useful to request a 24-hour dietary recall with special attention to intake of fruits, vegetables, and water, as well as high-calorie foods and high-carbohydrate beverages. When possible, evaluation by a nutritionist is extremely helpful. This information will form the basis for incremental changes in eating behavior, caloric intake, and PA during the intervention.

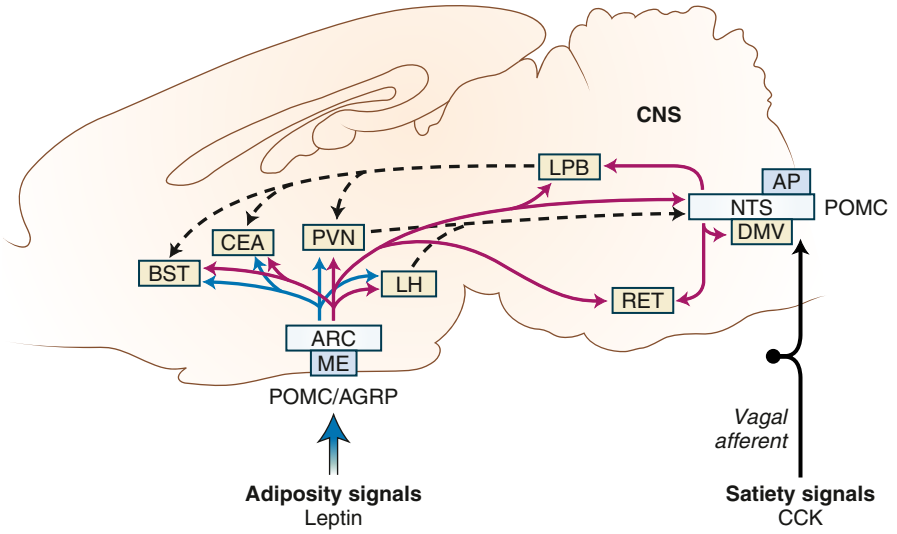

Fig. 65.3 Brain structures involved in energy homeostasis. Receipt of long-term adipostatic signals and acute satiety signals by neurons in arcuate nucleus and brainstem, respectively. Pale-blue boxes indicate nuclei containing proopiomelanocortin (POMC) neurons; tan boxes indicate nuclei containing melanocortin-4 receptor (MC4R) neurons that may serve to integrate adipostatic and satiety signals; and darker-blue boxes show some circumventricular organs involved in energy homeostasis. Magenta arrows designate a subset of projections of POMC neurons; blue arrows show a subset of projections of agouti-related peptide (AGRP) neurons. AP, Area postrema; ARC, arcuate nucleus; BST, bed nucleus of stria terminalis; CCK, cholecystokinin; CEA, central nucleus of amygdala; CNS, central nervous system; DMV, dorsal motor nucleus of vagus; LH, lateral hypothalamic area; LPB, lateral parabrachial nucleus; ME, median eminence; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus of hypothalamus; RET, reticular formation. *(Modified from Fan W, Ellacott KL, Halatchev IG, Takahashi K, Yu P, Cone RD. Cholecystokinin-mediated suppression of feeding involves the brainstem melanocortin system. Nat Neurosci. 2004;7[4]:335–336.)*

Table 65.2 Obesity-Associated Comorbidities

DISEASE	POSSIBLE SYMPTOMS	LABORATORY CRITERIA
CARDIOVASCULAR		
Dyslipidemia	HDL <40, LDL >130, total cholesterol >200 mg/dL	Fasting total cholesterol, HDL, LDL, triglycerides
Hypertension	SBP >95% for sex, age, height	Serial testing, urinalysis, electrolytes, blood urea nitrogen, creatinine
ENDOCRINE		
Type 2 diabetes mellitus	Acanthosis nigricans, polyuria, polydipsia	Fasting blood glucose >110, hemoglobin A_{1c}, insulin level, C-peptide, oral glucose tolerance test
Metabolic syndrome	Central adiposity, insulin resistance, dyslipidemia, hypertension, glucose intolerance	Fasting glucose, LDL and HDL cholesterol
Polycystic ovary syndrome	Irregular menses, hirsutism, acne, insulin resistance, hyperandrogenemia	Pelvic ultrasound, free testosterone, LH, FSH
GASTROINTESTINAL		
Gallbladder disease	Abdominal pain, vomiting, jaundice	Ultrasound
Nonalcoholic fatty liver disease (NAFLD)	Hepatomegaly, abdominal pain, dependent edema, ↑ transaminases Can progress to fibrosis, cirrhosis	AST, ALT, ultrasound, CT, or MRI
NEUROLOGIC		
Pseudotumor cerebri	Headaches, vision changes, papilledema	Cerebrospinal fluid opening pressure, CT, MRI
Migraines	Hemicrania, headaches	None
ORTHOPEDIC		
Blount disease (tibia vara)	Severe bowing of tibia, knee pain, limp	Knee radiographs
Musculoskeletal problems	Back pain, joint pain, frequent strains or sprains, limp, hip pain, groin pain, leg bowing	Radiographs
Slipped capital femoral epiphysis	Hip pain, knee pain, limp, decreased mobility of hip	Hip radiographs
PSYCHOLOGIC		
Behavioral complications	Anxiety, depression, low self-esteem, disordered eating, signs of depression, worsening school performance, social isolation, problems with bullying or being bullied	Child Behavior Checklist, Children's Depression Inventory, Peds QL, Eating Disorder Inventory 2, subjective ratings of stress and depression, Behavior Assessment System for Children, Pediatric Symptom Checklist
PULMONARY		
Asthma	Shortness of breath, wheezing, coughing, exercise intolerance	Pulmonary function tests, peak flow
Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems	Polysomnography, hypoxia, electrolytes (respiratory acidosis with metabolic alkalosis)

ALT, Alanine transaminase; AST, aspartate transaminase; CT, computed tomography; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; Peds QL, Pediatric Quality of Life Inventory; SBP, systolic blood pressure.

Table 65.3 Medications Associated with Obesity

Prednisone and other glucocorticoids
Thioridazine
Olanzapine
Clozapine
Quetiapine
Risperidone
Lithium
Amitriptyline and other tricyclic antidepressants
Paroxetine
Valproate
Carbamazepine
Gabapentin
Cyproheptadine
Propranolol and other β blockers



Fig. 65.4 Acanthosis nigricans. *From Gahagan S. Child and adolescent obesity. Curr Probl Pediatr Adolesc Health Care. 2004;34:6–43.*

Table 65.4 Normal Laboratory Values for Recommended Tests

LABORATORY TEST	NORMAL VALUE
Glucose	<110 mg/dL
Insulin	<15 mU/L
Hemoglobin A_{1c}	<5.7%
AST (age 2-8 yr)	<58 U/L
AST (age 9-15 yr)	<46 U/L
AST (age 15-18 yr)	<35 U/L
ALT	<35 U/L
Total cholesterol	<170 mg/dL
LDL	<110 mg/dL
HDL	>45 mg/dL
Triglycerides (age 0-9 yr)	<75 mg/dL
Triglycerides (age 10-19 yr)	<90 mg/dL

AST, Aspartate transaminase; ALT, alanine transaminase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
From Children's Hospital of Wisconsin. *The NEW (nutrition, exercise and weight management) kids program.* http://www.chw.org/display/displayFile.asp?docid=33672&filename=/Groups/NEWKids/NewKidsReferral.PDF.

Initial assessment of the overweight or obese child includes a complete review of bodily systems, focusing on the possibility of comorbid conditions (see Table 65.2). Developmental delay and visual and hearing impairment can be associated with genetic disorders. Difficulty sleeping, snoring, or daytime sleepiness suggests sleep apnea. Abdominal pain might suggest NAFLD. Symptoms of polyuria, nocturia, or polydipsia may be the result of type 2 diabetes. Hip or knee pain can be caused by secondary orthopedic problems, including Blount disease and slipped capital femoral epiphysis. Irregular menses may be associated with polycystic ovary syndrome. Acanthosis nigricans can suggest insulin resistance and type 2 diabetes (Fig. 65.4).

The family history begins with identifying other obese family members. Parental obesity is an important risk for child obesity. If all family members are obese, focusing the intervention on the entire family is reasonable. The child may be at increased risk for developing type 2 diabetes if a family history exists. Identification of a family history of hypertension, CV disease, or metabolic syndrome indicates increased risk for developing these obesity-associated conditions. If the clinician helps the family to understand that childhood obesity increases the risk for developing these chronic diseases, this educational intervention might serve as motivation to improve their nutrition and PA.

Physical examination should be thorough, focusing on possible comorbidities (see Table 65.2). Careful screening for hypertension using an appropriately sized blood pressure cuff is important. Systematic examination of the skin can reveal acanthosis nigricans, suggesting insulin resistance, or hirsutism, suggesting polycystic ovary syndrome. Tanner staging can reveal premature adrenarche secondary to advanced sexual maturation in overweight and obese females.

Laboratory testing for fasting plasma glucose, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol, and liver function tests are recommended as part of the initial evaluation for newly identified pediatric obesity (Table 65.4). Overweight children (BMI 85th-95th percentile) who have a family history of diabetes mellitus or signs of insulin resistance should also be evaluated with a fasting plasma glucose test. Other laboratory testing should be guided by history or physical examination findings. Figure 65.5 provides a recommended approach to categorization, evaluation, and treatment.

INTERVENTION

Evidence shows that some interventions result in modest but significant and sustained improvement in body mass. Based on behavior change theories (see Chapter 18), treatment includes specifying target behaviors, self-monitoring, goal setting, stimulus control, and promotion of self-efficacy and self-management skills. **Behavior changes** associated with improving BMI include drinking lower quantities of sugar-sweetened beverages, consuming higher-quality diets, increasing exercise, decreasing screen time, and self-weighing. Most successful interventions have been *family based* and consider the child's developmental age. "Parent-only" treatment may be as effective as "parent–child" treatment. Because obesity is multifactorial, not all children and adolescents will respond to the same approach. For example, *loss-of-control eating,* associated with weight gain and obesity, predicts poor outcome in response to family-based treatment. Furthermore, clinical treatment programs are expensive and not widely available. Therefore interest has grown in novel approaches such as internet-based treatments and guided self-help.

It is important to begin with clear recommendations about **appropriate caloric intake** for the obese child (Table 65.5). Working with a dietitian is essential. Meals should be based on fruits, vegetables, whole grains, lean meat, fish, and poultry. Prepared foods should be chosen for their nutritional value, with attention to calories and fat. Foods that provide excessive calories and low nutritional value should be reserved for infrequent treats. The World Health Organization recommends avoiding artificial sweeteners (aspartame, sucralose, stevia).

Weight reduction diets in adults generally do not lead to sustained weight loss. Therefore the focus should be on changes that can be maintained for life. Attention to eating patterns is helpful. Families should be encouraged to plan *family meals,* including breakfast. It is almost impossible for a child to make changes in nutritional intake and eating patterns if other family members do not make the same changes.

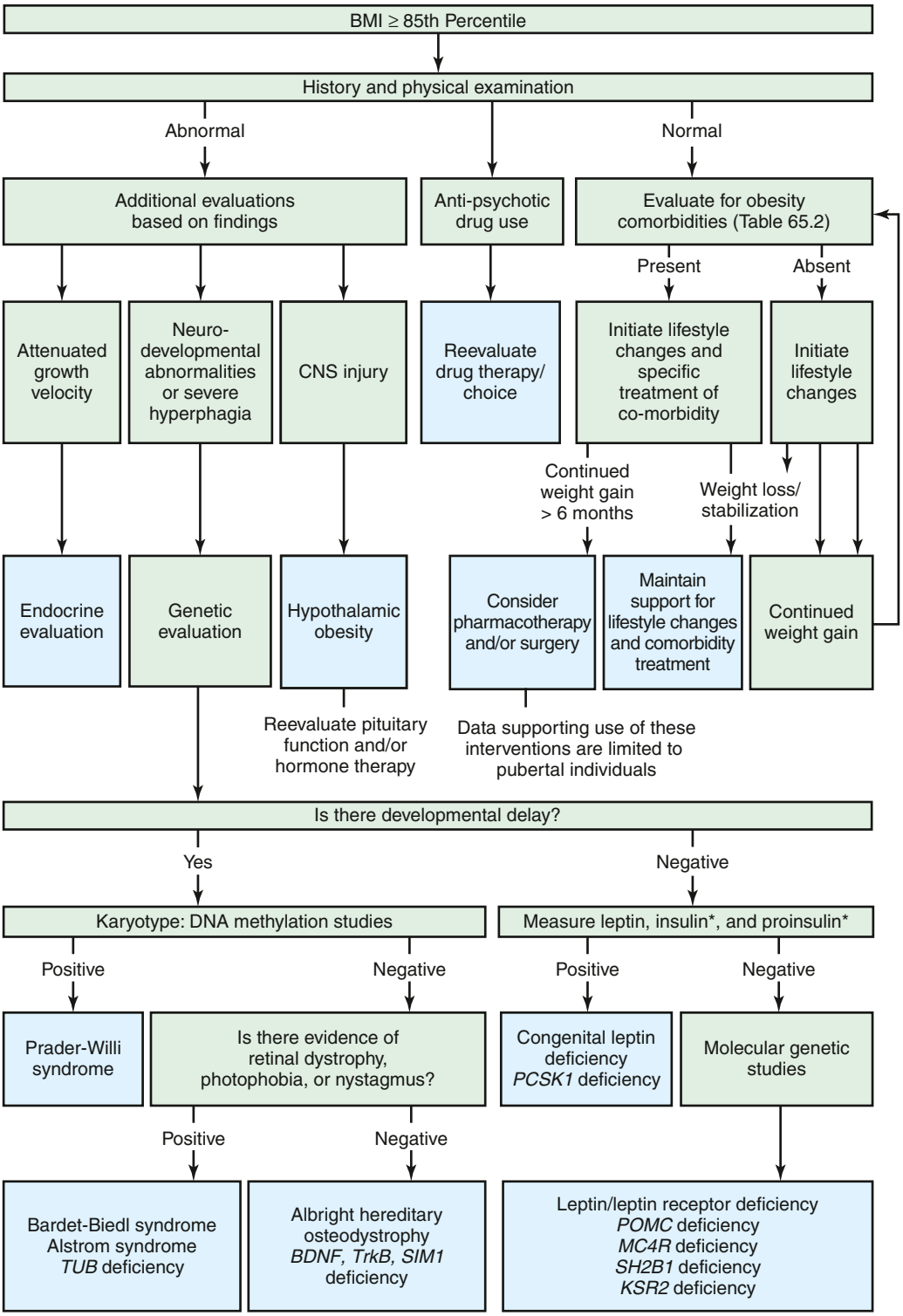

Fig. 65.5 Diagnostic and treatment algorithm for the evaluation of the overweight or obese child. *Measure insulin and proinsulin in patients with clinical features of PCSK1 deficiency. BMI, Body mass index; CNS, central nervous system. *(From Farooqi SOR, O'Rahilly S. Genetic obesity syndromes. In Grant S, ed. The Genetics of Obesity. New York: Springer; 2014, pp. 23–32; originally adapted from August GP, Caprio S, Fennoy I, et al. Prevention and treatment of pediatric obesity: An Endocrine Society clinical practice guideline based on expert opinion. J Clin Endocrinol Metab. 2008;93:4576–4599.)*

Dietary needs also change developmentally; adolescents require greatly increased calories during their growth spurts, and adults who lead inactive lives need fewer calories than active, growing children.

Psychologic strategies are helpful. The **"traffic light" diet** groups foods into those that can be consumed without any limitations (green), in moderation (yellow), or reserved for infrequent treats (red) (Table 65.6). The concrete categories are very helpful to children and families. This approach can be adapted to any ethnic group or regional cuisine. **Motivational interviewing** begins with assessing how ready the patient is to make important behavioral changes. The professional then engages the patient in developing a strategy to take the next step toward the ultimate goal of healthy nutritional intake.

Table 65.5 Recommended Caloric Intake Designated by Age and Gender

LIFE-STAGE GROUP	AGE (YR)	RELATIVELY SEDENTARY LEVEL OF ACTIVITY (KCAL)	MODERATE LEVEL OF ACTIVITY (KCAL)	ACTIVE (KCAL)
Child	2-3	1,000	1,000-1,400	1,000-1,400
Female	4-8	1,200	1,400-1,600	1,400-1,800
	9-13	1,600	1,600-2,000	1,800-2,200
	14-18	1,800	2,000	2,400
Male	4-8	1,400	1,400-1,600	1,600-2,000
	9-13	1,800	1,800-2,200	2,000-2,600
	14-18	2,200	2,400-2,800	2,800-3,200

Adapted from U.S. Department of Agriculture. Dietary guidelines for Americans, 2005. http://www.health.gov/DIETARYGUIDELINES/dga2005/document/html/chapter2.htm.

Table 65.6 "Traffic Light" Diet Plan

FEATURE	GREEN LIGHT FOODS	YELLOW LIGHT FOODS	RED LIGHT FOODS
Quality	Low-calorie, high-fiber, low-fat, nutrient-dense	Nutrient-dense, but higher in calories and fat	High in calories, sugar, and fat
Types of food	Fruits, vegetables	Lean meats, dairy, starches, grains	Fatty meats, sugar, sugar-sweetened beverages, fried foods
Quantity	Unlimited	Limited	Infrequent or avoided

This method allows the professional to take the role of a coach, helping the child and family reach their goals. Other behavioral approaches include family rules about where food may be consumed (e.g., "not in the bedroom").

Increasing PA without decreasing caloric intake is unlikely to result in weight loss. However, **aerobic exercise** training improves metabolic profiles in obese children and adolescents. Furthermore, it can increase aerobic fitness and decrease percent body fat even without weight loss. Therefore increasing PA can decrease risk for CV disease, improve well-being, and contribute to weight loss. Increased PA can be accomplished by walking to school, engaging in PA during leisure time with family and friends, or enrolling in organized sports. Children are more likely to be active if their parents are active; family PA is recommended. When adults lose significant weight, they may regain that weight despite eating fewer calories. The body may adapt to weight loss by reducing the basal metabolic rate (BMR), thus requiring fewer calories. One approach to this phenomenon is to increase PA.

Active pursuits can replace more sedentary activities. The American Academy of Pediatrics recommends that screen time be restricted to no more than 2 hours/day for children >2 years old and that children <2 years old not watch television. Screen time in general, and TV watching in particular, is often associated with eating and poorer-quality diets, as many highly caloric food products are marketed directly to children during child-oriented television programs.

Pediatric healthcare providers should assist families to develop goals to change nutritional intake and PA. They can also provide the child and family with needed information. The family should not expect immediate lowering of BMI percentile related to behavioral changes, but can instead count on a gradual decrease in the rate of BMI percentile increase until it stabilizes, followed by a gradual decrease. Referral to multidisciplinary, comprehensive pediatric weight management programs is ideal for obese children whenever possible.

Pharmacotherapy for weight loss in the pediatric population is understudied. Randomized controlled trials (RCTs) have evaluated many medications, including metformin, orlistat, sibutramine, and exenatide (Table 65.7). Available medications result in modest weight loss or BMI improvement, even when combined with behavioral interventions. Various classes of drugs are of interest, including those that decrease energy intake or act centrally as **anorexiants**, those that affect the availability of nutrients through intestinal or renal tubular reabsorption, and those that affect metabolism. One U.S. Food and Drug Administration (FDA)–approved medication for obesity in children <16 years old is *orlistat,* which decreases absorption of fat, resulting in modest weight loss. Complications include flatulence, oily stools, and spotting. This agent offers little benefit to severely obese adolescents.

Saxenda *(liraglutide)* and semaglutide are also FDA approved for chronic weight management among pediatric patients aged 12 and older who are obese. Both drugs are glucagon-like peptide-1 receptor agonists, are approved for children ≥12 years old, and have been effective in reducing weight. In addition, semaglutide improves adverse cardiometabolic features associated with obesity. Adverse reactions include headache, abdominal pain, emesis, and diarrhea. Long-term therapy may increase the risk of medullary thyroid carcinoma and pancreatitis. This class of medication has produced the most significant weight loss of drug-treated obesity.

Because multiple redundant neural mechanisms act to protect body weight, promoting weight loss is extremely difficult. Thus there is considerable interest in combining therapies that simultaneously target multiple weight-regulating pathways. One promising example is the combination of *amylin analogs* (decreases food intake and slows gastric emptying) with *leptin,* which has no anorexigenic effects when given alone. This combination requires injection and is in clinical trials in adults. Another FDA-approved drug for adults is *lorcaserin,* a selective serotonin 2α receptor agonist. Some medications approved for the treatment of type 2 diabetes, such as other glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, are being evaluated for treatment of obesity in adults. Establishing long-term safety and tolerability

Table 65.7 Medications for Weight Management with Mechanism of Action, Availability, and Dosing

MEDICATION	MECHANISM OF ACTION	AVAILABLE FOR CHRONIC USE		MEAN PERCENTAGE WEIGHT LOSS		ADVANTAGES	DISADVANTAGES
		USA	EU	PLACEBO	DRUG		
Phentermine, 15-30 mg PO	Sympathomimetic	For short-term use	No	Not stated in label	Not stated in label	Inexpensive	Side effect profile; no long-term data*
Orlistat, 120 mg PO tid before meals	Pancreatic lipase inhibitor	Yes	Yes	−2.6%†	−6.1%†	Not absorbed; long-term data*	Modest weight loss; side effect profile
Lorcaserin, 10 mg PO bid	5-HT_{2c} serotonin agonist with little affinity for other serotonergic receptors	Yes	No	−2.5%	−5.8%	Mild side effects; long-term data*	Expensive; modest weight loss
Phentermine/topiramate ER, 7.5 mg/46 mg or 15 mg/92 mg PO indicated as rescue (requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Yes	No	−1.2%	−7.8% (mid-dose) −9.8% (full dose)	Robust weight loss; long-term data*	Expensive; teratogen
Naltrexone SR/bupropion SR, 32 mg/360 mg PO (requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Yes	Yes	−1.3%	−5.4%	Reduces food craving; long-term data*	Moderately expensive; side effect profile
Liraglutide, 3.0 mg injection (requires titration)	GLP-1 receptor agonist	Yes	Yes	−3%	−7.4% (full dose)	Side effect profile; long-term data*	Expensive; injectable
Semaglutide, 2.4 mg once weekly injection	GLP-1 receptor agonist	Yes	Yes	−1%	−10 to −15%	As above	As above

Information is from US product labels, except where noted. The data supporting these tables are derived from the prescribing information labeling approved by the US Food and Drug Administration.
*Data from randomized controlled trials lasting >52 wk.
†Assuming the average patient in the orlistat and placebo groups weighed 100 kg at baseline.
ER, Extended release; GLP-1, glucagon-like peptide-1; SR, sustained release; PO, orally; bid, twice daily; tid, 3 times daily.
Adapted from Bray GA, Frühbeck G, Ryan DH, Wilding JPH. Management of obesity. *Lancet*. 2016;387:1947–1965, p. 1950.

in children is a challenge because medications of interest have CNS effects or interfere with absorption of nutrients. Teratologic effects must be considered for use in adolescent females. *Setmelanotide*, which binds to and activates *MC4R*, is approved to treat proopiomelanocortin deficiency, leptic receptor deficiency, and proprotein subtilisin/kexin type 1 disorder. **Hormone replacement therapy** is available for patients with leptin deficiency and may become available for patients with POMC deficiency.

In some cases, it is reasonable to refer adolescents for **bariatric surgery** evaluation. The American Pediatric Surgical Association guidelines recommend that surgery be considered only in children with complete or near-complete skeletal maturity, a BMI ≥40, and a medical complication resulting from obesity, *after* they have failed 6 months of a multidisciplinary weight management program. Surgical approaches include the Roux-en-Y and the adjustable gastric band (Fig. 65.6). Endoscopically placed space-occupying fluid or air-filled gastric balloons(s) is approved for adults and may be a nonsurgical intervention. In obese adults, bariatric surgery reduces the risk of developing type 2 diabetes mellitus. In obese adult patients with existing type 2 diabetes, bariatric surgery improves diabetic control. Nutritional complications of bariatric surgery include malabsorption and vitamin (A, B_1, B_2, B_6, B_{12}, D, E, K) and mineral (copper, iron) deficiencies that require supplementation.

PREVENTION

Prevention of child and adolescent obesity is essential for public health in the United States and most other countries (Tables 65.8 and 65.9). Efforts by pediatric providers can supplement national and community public health programs. The National Institutes of Health (NIH) and U.S. Centers for Disease Control and Prevention (CDC) recommend a variety of initiatives to combat the current obesogenic environment, including promotion of breastfeeding, access to fruits and vegetables, walkable communities, and 60 minutes/day of activity for children. The U.S. Department of Agriculture (USDA) sponsors programs promoting 5.5 cups of fruits and vegetables per day. Incentives for the food industry to promote consumption of healthier foods should be considered. Marketing of unhealthy foods to children is now being regulated. Changes in federal food programs are expected, including commodity foods, the Women, Infant, and Children Supplemental Food Program (WIC), and school lunch programs, to meet the needs of today's children.

Pediatric prevention efforts begin with careful monitoring of weight and BMI percentiles at healthcare maintenance visits. Attention to changes in BMI percentiles can alert the pediatric provider to increasing adiposity before the child becomes overweight or obese. All families should be counseled about healthy nutrition for their children, because the current prevalence of overweight and obesity in adults is 65%. Therefore approximately two thirds of all children can be considered at risk for becoming overweight or obese at some time in their lives. Those who have an obese parent are at increased risk. Prevention efforts begin with promotion of *exclusive breastfeeding for 6 months* and total breastfeeding for 12 months. Introduction of infant foods at 6 months should focus on cereals, fruits, and vegetables. Lean meats, poultry, and fish may be introduced later in the first year of life. Parents should be specifically counseled to *avoid introducing highly sugared beverages and foods in the first*

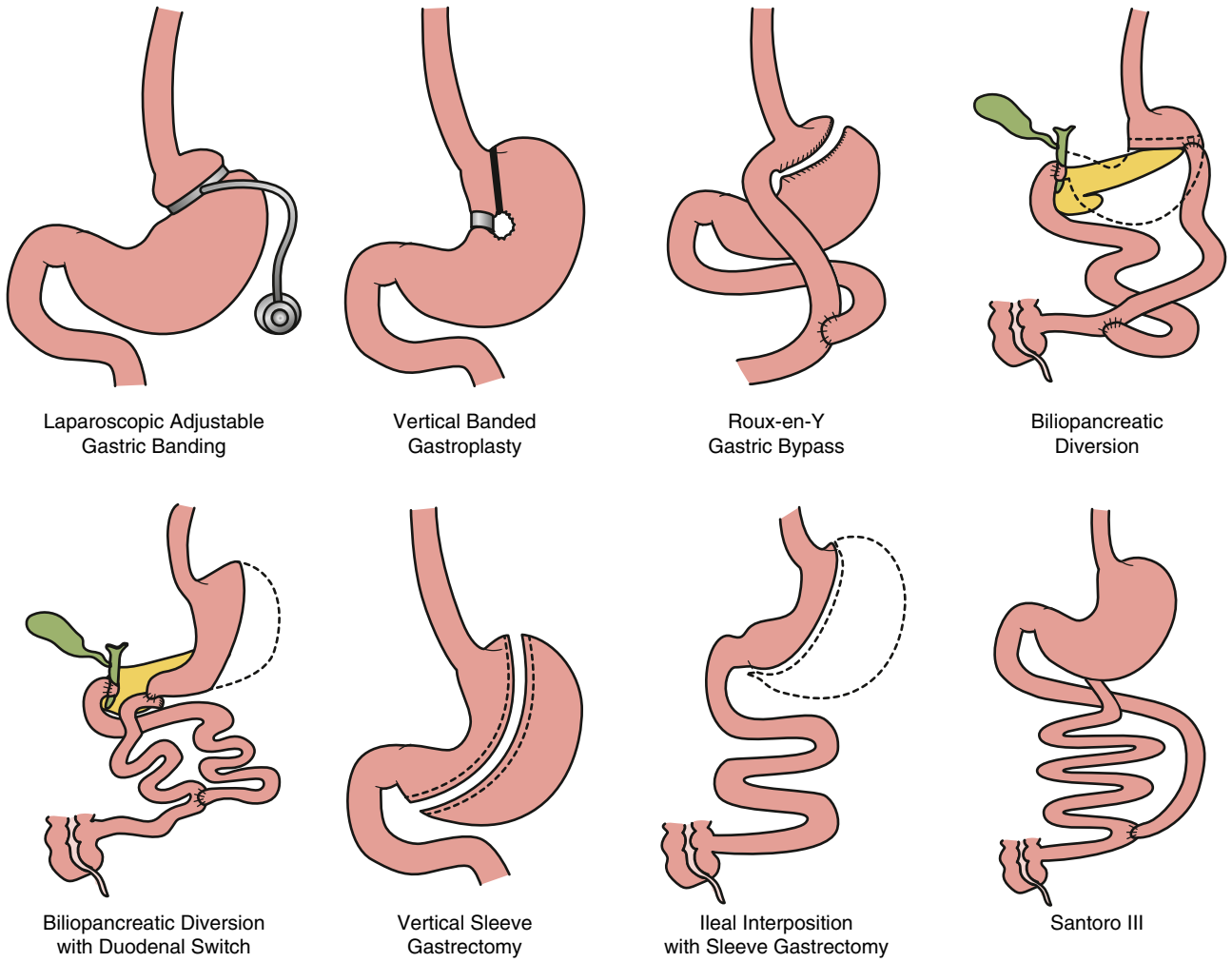

Fig. 65.6 Bariatric surgical procedures, including laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, and vertical sleeve gastrectomy techniques.

year of life. Instead, they should expose their infants and young children to a rich variety of fruits, vegetables, grains, lean meats, poultry, and fish to facilitate acceptance of a diverse and healthy diet. Parenting matters, and authoritative parents are more likely to have children with a healthy weight than those who are authoritarian or permissive. Families who eat regularly scheduled meals together are less likely to have overweight or obese children. Child health professionals can address a child's nutritional status and provide expertise in child growth and development.

Child health professionals can also *promote PA* during regular healthcare maintenance visits. Parents who spend some of their leisure time in PA promote healthy weight in their children. Beginning in infancy, parents should be cognizant of their child's developmental capability and need for PA. Because TV, computer, and video game time can replace health-promoting PA, physicians should counsel parents to limit screen time for their children. Snacking during TV watching should be discouraged. Parents can help their children to understand that television commercials intend to sell a product. Children can learn that their parents will help them by responsibly choosing healthy foods.

Because obesity is determined by complex multifactorial conditions, prevention will take efforts at multiple levels of social organization. Successful programs include **EPODE** (Ensemble Prévenons l'Obésité Des Enfants), a multilevel prevention strategy that began in France and has been adopted by more than 500 communities in 6 countries. **Shape Up Somerville** is a citywide campaign to increase daily PA and healthy eating in Somerville, Massachusetts, since 2002. The **"Let's Move"** campaign was championed by former First Lady Michelle Obama. Because community and environmental factors are related to pediatric obesity risk, changes in local environments, daycare centers, schools, and recreational settings can have a public health impact. Programs can empower families to adopt practices that promote healthy lifestyles for children and adolescents. The most successful programs are comprehensive and rely on four strategies: political commitment to change, resources to support social

Table 65.8 Proposed Suggestions for Preventing Obesity

PREGNANCY
- Normalize body mass index (BMI) before pregnancy.
- Do not smoke.
- Maintain moderate exercise as tolerated.
- In women with gestational diabetes, provide meticulous glucose control.
- Monitor gestational weight gain within Institute of Medicine (IOM) recommendations.

POSTPARTUM AND INFANCY
- Breastfeeding: exclusive for 4-6 mo; continue with other foods for 12 mo.
- Postpone introduction of baby foods to 4-6 mo and juices to 12 mo.

FAMILIES
- Eat meals as a family in a fixed place and time.
- Do not skip meals, especially breakfast.
- Do not allow television during meals.
- Use small plates and keep serving dishes away from the table.
- Avoid unnecessary sweet or fatty foods and sugar-sweetened drinks.
- Remove televisions from children's bedrooms; restrict times for TV viewing and video games.
- Do not use food as a reward.

SCHOOLS
- Eliminate candy and cookie sales as fundraisers.
- Review the contents of vending machines and replace with healthier choices; eliminate sodas.
- Avoid financial support for sports teams from beverage and food industries.
- Install water fountains and hydration stations.
- Educate teachers, especially physical education and science faculty, about basic nutrition and the benefits of physical activity (PA).
- Educate children from preschool through high school on appropriate diet and lifestyle.
- Mandate minimum standards for physical education, including 60 min of strenuous exercise 5 times weekly.
- Encourage "the walking school bus": groups of children walking to school with adult supervision.

COMMUNITIES
- Increase family-friendly exercise and safe play facilities for children of all ages.
- Develop more mixed residential-commercial developments for walkable and bicyclable communities.
- Discourage the use of elevators and moving walkways.
- Provide information on how to shop and prepare healthier versions of culture-specific foods.

HEALTHCARE PROVIDERS
- Explain the biologic and genetic contributions to obesity.
- Give age-appropriate expectations for body weight in children.
- Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.

INDUSTRY
- Mandate age-appropriate nutrition labeling for products aimed at children (e.g., "red light/green light" foods, with portion sizes).
- Encourage marketing of interactive video games in which children must exercise to play.
- Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals.
- Reduce portion size (drinks and meals).

GOVERNMENT AND REGULATORY AGENCIES
- Classify childhood obesity as a legitimate disease.
- Find novel ways to fund healthy lifestyle programs (e.g., with revenues from food and drink taxes).
- Subsidize government-sponsored programs to promote the consumption of fresh fruits and vegetables.
- Provide financial incentives to the industry to develop more healthful products and to educate the consumer on product content.
- Provide financial incentives to schools that initiate innovative PA and nutrition programs.
- Allow tax deductions for the cost of weight loss and exercise programs.
- Provide urban planners with funding to establish bicycle, jogging, and walking paths.
- Ban advertising of fast foods, non-nutritious foods, and sugar-sweetened beverages directed at preschool children, and restrict advertising to school-aged children.
- Ban toys as gifts to children for purchasing fast foods.

Adapted from Speiser PW, Rudolf MCJ, Anhalt H, et al. Consensus statement: Childhood obesity. *J Clin Endocrinol Metab*. 2005;90:1871–1887.

Table 65.9 Anticipatory Guidance: Establishing Healthy Eating Habits in Children

- Do not punish a child during mealtimes with regard to eating. The emotional atmosphere of a meal is very important. Interactions during meals should be pleasant and happy.
- Do not use foods as rewards.
- Parents, siblings, and peers should model healthy eating, tasting new foods, and eating a well-balanced meal.
- Children should be exposed to a wide range of foods, tastes, and textures.
- New foods should be offered multiple times. Repeated exposure leads to acceptance and liking.
- Forcing a child to eat a certain food will decrease the child's preference for that food. Children's wariness of new foods is normal and should be expected. Offering a variety of foods with low-energy density helps children balance energy intake.
- Parents should control what foods are in the home. Restricting access to foods in the home will increase rather than decrease a child's desire for that food.
- Children tend to be more aware of satiety than adults, so allow children to respond to satiety and stop eating. Do not force children to "clean their plate."

Adapted from Benton D. Role of parents in the determination of food preferences of children and the development of obesity. *Int J Obes Relat Metab Disord*. 2004;28:858–869.

marketing and changes, support services, and evidence-based practices. Community-wide programs are important because neighborhood environmental factors (e.g., poverty) have been associated with obesity in its residents. There is considerable interest in focusing these efforts early in the life cycle. Beginning obesity prevention during pregnancy and engaging health systems, early childhood programs, and community systems to support healthier life cycles is an approach with great promise.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 66

Vitamin A Deficiencies and Excess

Libo Tan and A. Catharine Ross

OVERVIEW OF VITAMIN A

Vitamin A is a fat-soluble micronutrient that cannot be synthesized de novo by mammals; thus it is an obligatory dietary factor. The term **vitamin A** is generally used to refer to a group of compounds that possess the biologic activity of all-*trans* retinol (Fig. 66.1). Vitamin A is recognized as being essential for all vertebrates for normal vision, reproduction, cell and tissue differentiation, and immune system functions. Vitamin A plays critical roles in neonatal development. It is required for normal embryonic development, hematopoiesis, and growth and differentiation of many types of cells.

Vitamin A can be obtained from the diet from preformed vitamin A (retinyl esters, such as retinyl palmitate) primarily in foods of animal origin. Organ meats (especially liver and kidney) are very rich in vitamin A, whereas other meats, milk, and cheese contain moderate levels. Other sources of vitamin A include several provitamin A carotenoids, which are found naturally in many fruits and vegetables, especially yellow-orange vegetables (pumpkin, squash, sweet potato) and leafy green vegetables (chard, spinach, broccoli). One of the most abundant carotenoids is β-carotene. Several *cultivars,* or biofortified forms, of sweet potatoes have been introduced to elevate carotene intake in areas of the world where vitamin A deficiency still is prevalent. α-carotene and oxygenated carotenoids, such as β-cryptoxanthin, found in oranges, also possess vitamin A activity, but at a lower bioactivity. In the body, these precursors are used for the synthesis of two essential metabolites of vitamin A. **All-*trans* retinoic acid** is the form required for cell differentiation and regulation of gene transcription and is the most bioactive form of vitamin A; **11-*cis* retinal** is the form required for vision as the light-absorbing chromophore of the visual pigments rhodopsin and iodopsin.

METABOLISM OF VITAMIN A

Vitamin A compounds in foods must first be released through normal digestive processes. Retinyl esters must first be hydrolyzed in the intestinal lumen to liberate unesterified retinol for absorption across the mucosal barrier. Once in the enterocyte, most of the retinol is reesterified, forming new retinyl esters for inclusion in chylomicrons. Approximately 70–90% of dietary preformed vitamin A is absorbed provided there is approximately 10 g of fat in the meal; otherwise, the absorption efficiency is lower. Chronic intestinal disorders or lipid malabsorption can result in vitamin A deficiency. Provitamin-A carotenoids are transported from the intestinal lumen into the enterocytes by specific transporters and then either incorporated intact into chylomicrons or cleaved to form *retinal,* a precursor for retinol; β-carotene becomes retinol through this process. The estimated efficiency of absorption of carotenoids is 20–50%, lower than for preformed vitamin A. Moreover, the efficiency is reduced when the body's vitamin A status is high, and because vitamin A status may vary, there is significant interindividual variability in absorption efficiency. The carotene cleavage enzyme β-carotene monooxygenase, present in the enterocyte and in other tissues at lower levels, exhibits certain single nucleotide polymorphisms (SNPs) that, at least in vitro, reduce the efficiency of conversion of β-carotene to retinol. Clinical studies suggest a similar effect in vivo.

Once retinol is esterified in the enterocyte, retinyl ester is then packaged into nascent chylomicrons, which are secreted into the lymphatic vessels, enter the systemic circulation, and are then transported to and taken up by various tissues. When vitamin A status is adequate, in most mammals, including humans, the liver

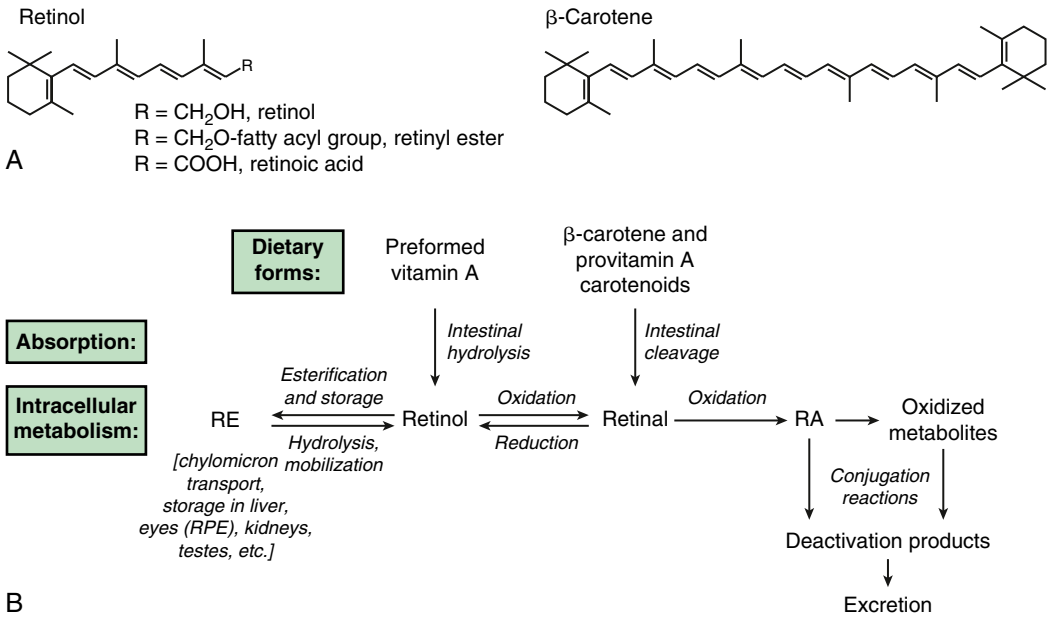

Fig. 66.1 A, Vitamin A structures. B, Overview of vitamin A metabolism. RA, All-*trans* retinoic acid; RE, retinyl ester; RPE, retinal pigment epithelium.

is the major site of chylomicron vitamin A uptake and storage, with potentially high levels of retinyl esters within hepatic stellate cells (HSCs). As vitamin A status deteriorates into the deficient range, vitamin A stores are mobilized from the HSCs, such that the released retinol can be taken up and used by extrahepatic tissues. Circulating retinol is bound to a specific transport protein, retinol-binding protein (RBP), which in turn binds to the thyroid hormone transport protein, transthyretin (TTR); this complex delivers plasma retinol (and the thyroid hormone) to a large number of vitamin A target tissues. The major physiologic mediator of retinol uptake by cells in many tissues is Stra6, a widely expressed multitransmembrane domain protein that functions as a cell surface receptor for retinol bound to RBP. Stra6 is not significantly expressed in the liver, but a homologous receptor may perform the similar function. Within target tissues, retinol is either esterified into retinyl esters for storage or oxidized into retinoic acid for function. In the eye, 11-*cis*-retinal is formed and bound to the protein rhodopsin (rods) or iodopsin (cones), where it functions as a light-sensing receptor.

Inflammation Causing Low Plasma Retinol

Inflammation is a cause of reduced levels of plasma retinol as a result of reduced synthesis of RBP and TTR. This condition may mimic a lack of vitamin A, but will not be corrected by supplementation. In U.S. adults, those with moderately elevated levels of CRP, indicative of mild inflammation, had lower average plasma retinol levels. The extent to which inflammation is a factor in low plasma retinol in children is uncertain but likely significant in acute infectious diseases such as measles, and possibly in chronic inflammatory conditions such as cystic fibrosis.

FUNCTIONS OF VITAMIN A AND MECHANISMS OF ACTION

Except for its role in vision, the pleiotropic actions of this micronutrient are mediated by all-*trans*-retinoic acid (RA), which is a ligand for specific nuclear transcription factors, **retinoic acid receptor (RAR)** and **retinoid X receptor (RXR)**, that regulate the expression of several hundred genes. When an RAR is activated by RA, an RAR-RXR complex is formed, which binds to and activates specific DNA sequences present in retinoid-responsive genes, RAREs and RXREs. Genes can be either induced or repressed, depending on additional co-activators or co-repressors recruited to the RAR-RXR complex. Retinoid-regulated genes are involved in several fundamental biologic activities, including regulation of cell division, death, and differentiation. The term *retinoids* is now applied to both natural and synthetic compounds with vitamin A activity, although it is most often used in the context of vitamin A and RA acting at the gene level. Numerous synthetic retinoids have gained clinical acceptance in the treatment of skin disorders and certain cancers.

During embryonic development, RA is among the most important signaling molecules that determine body patterning (morphogenesis). Many physiologic processes are sensitive to a deficiency or excess of vitamin A or RA, including reproduction, growth, bone development, and the functions of the respiratory, gastrointestinal, hematopoietic, and immune systems. Vitamin A supplementation may be particularly important in developing countries, where it reduces morbidity and mortality, presumably by enhancing immune function and host defense, from various infectious diseases, including measles (see Chapter 293).

Vitamin A plays a critical role in vision, mediated by 11-*cis* retinal. The human retina contains two distinct photoreceptor systems: the *rods,* in which rhodopsin senses light of low-intensity, and the *cones,* in which iodopsins detect different colors; 11-*cis*-retinal is the prosthetic group on both these visual proteins. The mechanism of vitamin A action is similar for rods and cones, based on *photoisomerization* of 11-*cis* to all-*trans* retinal (change shape when exposed to light), which initiates signal transduction via the optic nerve to the brain, resulting in visual sensation. After isomerization (also known as *photobleaching*), a series of reactions serves to regenerate the 11-*cis* retinal for resynthesis of rhodopsin and iodopsin, as is necessary for an efficient visual process. Accessory cells, including retinal pigment epithelium (RPE) cells and Müller cells, are involved in this recycling process.

VITAMIN A DEFICIENCY

If the growing child has a well-balanced diet and obtains vitamin A from foods rich in vitamin A or provitamin A (Table 66.1), the risk of vitamin A deficiency is small. However, even subclinical vitamin A deficiency can have serious consequences.

Deficiency states in developed countries are rare, except in some impoverished populations (see Chapter 62) or after mistakes in food preparation or with fad diets or restrictive/elimination diets, but are common in many developing countries and often associated with global malnutrition. In the clinical setting, vitamin deficiencies can also occur as complications in children with various chronic disorders or diseases. Information obtained in the medical history related to dietary habits can be important in identifying the risk of such nutritional problems. Except for vitamin A, toxicity from excess intake of vitamins is rare. Table 66.1 summarizes the food sources, functions, and deficiency and excess symptoms of the vitamin.

Vitamin A Status in Neonates

Neonates begin life with low levels of vitamin A in plasma, liver, and extrahepatic tissues compared with those in adults. Normal plasma levels of retinol are 20-50 μg/dL in infants and increase gradually as children become older. Median serum retinol values are 1.19 μmol/L in both males and females ages 4-8 years; 1.4 and 1.33 μmol/L in males and females, respectively, ages 9-13; and 1.71 and 1.57 μmol/L in males and females, ages 14-18 (for conversion, 1 μmol/L = 28.6 μg/dL). Values of 1.96 and 1.85 μmol/L are found in 19- to 30-year-old adult men and women, respectively. Figure 66.2 shows the distribution of serum retinol concentrations in U.S. children. Few healthy children are severely vitamin A deficient, but the 5th percentile of children 4-8 years and 9-13 years of age, respectively, in the National Health and Examination Survey (NHANES) fell below 1.05 μmol/L, which is interpreted as mild vitamin A deficiency.

Retinol levels are even lower in neonates in developing countries, where vitamin A intakes may be low and vitamin A deficiency is a common nutritional problem. Lower vitamin A stores and plasma retinol concentrations are also seen in low birthweight infants and in preterm newborns, and poor vitamin A status (plasma retinol concentrations <0.35 μmol/L) may contribute to the development of chronic lung disease, such as bronchopulmonary dysplasia (BPD; see Chapter 127).

Clinical Manifestations of Vitamin A Deficiency

The most obvious symptoms of vitamin A deficiency are associated with changes in epithelial cell morphology and functions. In the intestines, mucus-secreting goblet cells are affected, and loss of an effective barrier against pathogens can cause diarrhea or impairment of epithelial barrier function. Similarly, mucus secretion by the epithelium is essential in the respiratory tract for the disposal of inhaled pathogens and toxicants. Characteristic epithelial changes result from vitamin A deficiency, including proliferation of basal cells, hyperkeratosis, and formation of stratified cornified squamous epithelium. Squamous metaplasia of the renal pelvis, ureters, vaginal epithelium, and the pancreatic and salivary ducts can lead to increased infections in these areas. In the urinary bladder,

Table 66.1 Vitamin A Characteristics

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
Retinol (vitamin A_1); 1 μg retinol = 3.3 IU vitamin A = 1 RAE Provitamins A: the plant pigments α-, β-, and γ-carotenes and cryptoxanthin have partial retinol activity: 12 μg β-carotene, or 24 μg other provitamin A carotenoids = 1 μg retinol	Fat-soluble; heat-stable; destroyed by oxidation, drying Bile necessary for absorption Stored in liver Protected by vitamin E	In vision, as retinal, for synthesis of the visual pigments rhodopsin and iodopsin In growth, reproduction, embryonic and fetal development, bone growth, immune and epithelial functions, via retinoic acid as a ligand for specific nuclear transcription factors, regulating genes involved in many fundamental cellular processes	Nyctalopia Photophobia, xerophthalmia, Bitôt spots, conjunctivitis, keratomalacia leading to blindness Faulty epiphyseal bone formation Defective tooth enamel Keratinization of mucous membranes and skin Stunted growth Impaired resistance to infection, anemia, reproductive failure, fetal abnormalities	Anorexia, slow growth, drying and cracking of skin, enlargement of liver and spleen, swelling and pain of long bones, bone fragility, increased intracranial pressure, alopecia, carotenemia Fetal abnormalities	Liver, fish liver oils Dairy products, except skim milk Egg yolk, fortified margarine, fortified skim milk Carotenoids from plants: green vegetables, yellow fruits, and vegetables

RAE, Retinol activity equivalent.

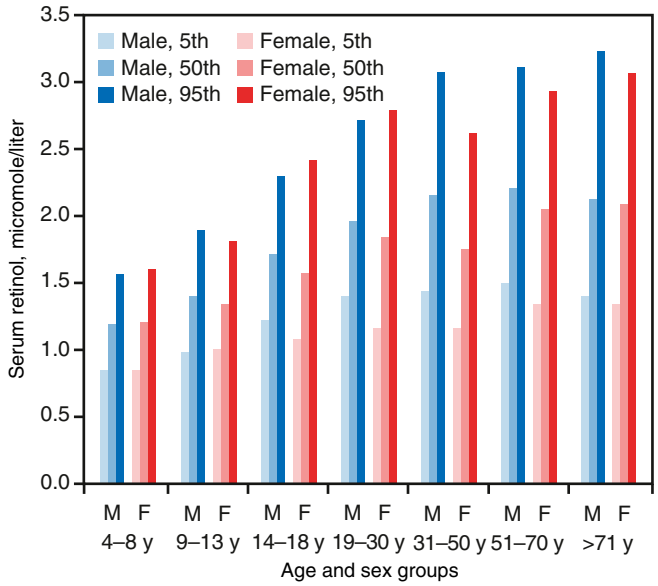

Fig. 66.2 Distribution of serum retinol concentrations in U.S. children and adults by age and sex in the National Health and Nutrition Examination Survey (NHANES).

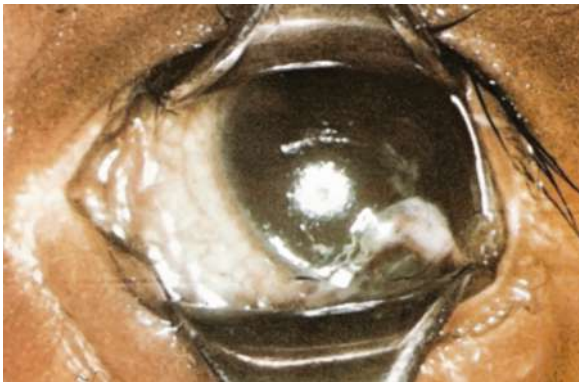

Fig. 66.3 Advanced xerophthalmia with an opaque, dull cornea and some damage to the iris in a 1-yr-old boy. *(From Oomen HAPC. Vitamin A deficiency, xerophthalmia and blindness. Nutr Rev. 1974;6:161–166.)*

loss of epithelial integrity can result in pyuria and hematuria. In the skin, vitamin A deficiency manifests as dry, scaly, hyperkeratotic patches, typically on the arms, legs, shoulders, and buttocks. The combination of defective epithelial barriers to infection, low immune response, and lowered response to inflammatory stress, all from insufficient vitamin A, can cause poor growth and serious health problems in children.

The most characteristic and specific signs of vitamin A deficiency are *eye lesions,* but these may manifest rather late in the progression of vitamin A deficiency, develop insidiously, and rarely occur before age 2 years. An earlier symptom of vitamin A deficiency is delayed dark adaptation as a result of reduced resynthesis of rhodopsin; this may progress to **night blindness**. Photophobia is a common symptom. The RPE, one of the structural elements of the retina, undergoes keratinization. When the RPE degenerates, the rods and cones have no support and eventually break down, resulting in blindness.

As vitamin A deficiency progresses, the corneal and conjunctival epithelial tissues of the eye become severely altered because of a lack of sufficient RA for normal epithelial cell differentiation. The cornea protects the eye from the environment and is also important in light refraction. Stages in vitamin A deficiency include corneal keratinization and opacity, susceptibility to infection, and formation of dry, scaly layers of cells (**xerophthalmia**) (Figs. 66.3 and 66.4). The conjunctival membrane undergoes keratinization and may develop foamy-appearing plaques (**Bitôt spots**; Fig. 66.5). When lymphocytes infiltrate the cornea in later stages of infection, it degenerates irreversibly (**keratomalacia** and **corneal ulceration**), resulting in irreversible blindness. These eye lesions are primarily diseases of

the young and are a major cause of blindness in developing countries. Although rates of xerophthalmia have fallen, the number of affected children is still too high. Treatment with vitamin A, up to the stage of keratomalacia, is effective in rapidly repleting the individual and saving vision.

Other clinical signs of vitamin A deficiency include poor overall growth, diarrhea, susceptibility to infections, anemia, apathy, intellectual impairment, and increased intracranial pressure, with wide separation of the cranial bones at the sutures. There may be vision problems as a consequence of bone overgrowth causing pressure on the optic nerve.

Malnutrition, particularly protein deficiency, can cause vitamin A deficiency through impaired synthesis of retinol transport protein. In developing countries, subclinical or clinical zinc deficiency can increase the risk of vitamin A deficiency. There is also some evidence of marginal zinc intakes in U.S. children.



Fig. 66.4 Recovery from xerophthalmia, showing a permanent eye lesion. *(From Bloch CE. Blindness and other disease arising from deficient nutrition [lack of fat soluble A factor]. Am J Dis Child. 1924;27:139.)*

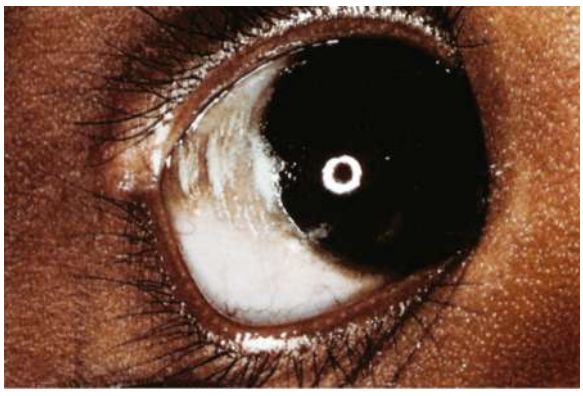

Fig. 66.5 Bitôt spots with hyperpigmentation seen in a 10-mo-old Indonesian boy. *(From Oomen HAPC. Vitamin A deficiency, xerophthalmia and blindness. Nutr Rev 1974;6:161–166.)*

Diagnosis

Dark adaptation tests can be used to assess early-stage vitamin A deficiency. Although Bitôt spots develop relatively early, those related to active vitamin A deficiency are usually confined to preschool-age children. Xerophthalmia is a very characteristic lesion of vitamin A deficiency. For detection of less severe deficiency (marginal vitamin A status), methods include conjunctival impression cytology, relative dose response, and modified relative dose response tests. A diet history is useful in suggesting or ruling out low intake as a cause of symptoms. Marginal vitamin A status is relatively prevalent among pregnant and lactating women in low-resource (and therefore poor dietary intake) areas of the world. Although plasma retinol level is not a completely accurate indicator of vitamin A status, various guidelines have been proposed for categorizing vitamin A status based on serum retinol. In children, plasma retinol <0.35 μmol/L is considered *very deficient,* 0.35-0.7 μmol/L *deficient,* 0.7-1.05 μmol/L *marginal,* and >1.05 μmol/L *adequate.* It has long been thought that a liver vitamin A concentration >20 μg/g is needed to support a normal rate of secretion of retinol-RBP into plasma, and therefore normal delivery of retinol to peripheral tissues.

Epidemiology and Public Health Issues

Vitamin A deficiency and xerophthalmia still occur throughout much of the developing, income-poor world and are linked to undernourishment and complicated by illness. Various public health programs to provide large doses of vitamin A periodically have been instituted. Vitamin A supplementation is considered part of the strategy of the World Health Organization (WHO) Millennium Development Goals to reduce <5 year mortality. Neonatal supplementation may be most effective in populations with a high incidence of maternal vitamin A deficiency. Other strategies being tested include improving the content of β-carotene in staple foods through plant breeding (biofortification).

Dietary Reference Intakes for the Healthy Population

Table 66.2 summarizes the dietary reference intakes for infants and children. Dietary reference intake values include the estimated average requirement (EAR), which is the mean biologic requirement for the nutrient for the age/sex-group of interest; the recommended dietary allowance (RDA), which is set to cover the physiologic needs of >97% of the population (thus the needs of many people are more than met by consuming the RDA); and the upper level

Table 66.2 Dietary Reference Intakes for Vitamin A in Children

AGE RANGE	RECOMMENDED DIETARY ALLOWANCE (RDA)*	UPPER LEVEL (UL)*	COMMENTS
0-6 mo	400	600	The recommended intake for infants is an adequate intake, based on the amount of vitamin A normally present in breast milk.
7-12 mo	500	600	
1-3 yr	300	600	The UL applies only to preformed vitamin A (retinol).
4-8 yr	400	900	
9-13 yr	600	1,700	
14-18 yr	900, male; 700, female	2,800	

*μg retinol equivalents per day.

of normal (UL), an intake level above which risk of adverse effects may increase; the UL pertains only to chronic consumption of preformed vitamin A. The RDA is expressed as retinol activity equivalents (RAEs; 1 RAE = 1 μg all-*trans* retinol; equivalents for provitamin-A in foods = 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin). From infancy to age 18 years, the RDA increases as a result of increased body size, becoming higher for males than for females during adolescence. During pregnancy the RDA is 750-770 μg, and during lactation it increases to 1,200-1,300 μg to ensure sufficient vitamin A content during breastfeeding.

It is noteworthy that, especially for young children, the UL is only about two times higher than the RDA. This suggests that for children whose diet is good, care should be taken not to overuse dietary supplements (vitamin-mineral supplements) containing preformed vitamin A and/or to avoid excessive consumption of foods that are very rich in vitamin A, such as liver.

Vitamin A for Treatment of Deficiency

A daily supplement of 1,500 μg of vitamin A is sufficient for treating latent vitamin A deficiency, after which intake at the RDA level should be the goal. In children without overt signs of vitamin A deficiency but suspected low reserves of vitamin A, rates of morbidity and mortality, as from viral infections such as measles, have been reduced by a weekly dose of vitamin A at the RDA level. More often, higher doses of 30-60 mg of retinol (100,000-200,000 IU/child) are given once or twice, under careful monitoring to avoid toxicity associated with excess vitamin A. Xerophthalmia is treated by giving 1,500 μg/kg body weight orally for 5 days, followed by intramuscular injection of 7,500 μg of vitamin A in oil, until recovery.

HYPERVITAMINOSIS A

Chronic hypervitaminosis A results from excessive ingestion of preformed vitamin A (retinol or retinyl ester), generally for several weeks or months. Hypervitaminosis A is most often caused by vitamin A–containing supplements or food faddism, including high intakes of organ meats. Chronic daily intakes of 15,000 μg and 6,000 μg can be toxic in adults and children, respectively. Because there is no antidote for hypervitaminosis A, and vitamin A is readily stored in liver and other tissues, it is most important to prevent toxicity. Symptoms may subside rapidly on withdrawal of the vitamin, but the rate of improvement depends on the amount of vitamin A stored in tissues. Extreme hypervitaminosis A is fatal. Signs of subacute or chronic toxicity can include headache; vomiting (early signs); anorexia; dry, itchy, desquamating skin; and seborrheic cutaneous lesions. With chronic hypervitaminosis A, one may observe fissuring at the corners of the mouth; alopecia and coarsening of the hair; bone abnormalities, including swelling and resorption; enlargement of the liver and spleen; diplopia; increased intracranial pressure; dryness of the mucous membranes; and desquamation of the palms and the soles of the feet. Radiographs may show *hyperostosis* affecting several long bones, especially in the middle of the shafts (Fig. 66.6). Manifestations of hypervitaminosis A may also include nonspecific changes in affect, including severe headache, irritability, stupor, and limited motion. Serum levels of vitamin A are elevated, mostly in the form of retinyl esters carried in lipoproteins, which may result in tissue damage and release of liver enzymes into plasma. Hypercalcemia and/or liver cirrhosis may be present. Hypervitaminosis A is distinct from cortical hyperostosis (see Chapter 741).

In young children, signs of vitamin A toxicity include vomiting and bulging fontanels, neither of which is specific. Combined with anorexia, pruritus, and a lack of weight gain, vitamin A toxicity should be considered. Less common symptoms include diplopia, papilledema, cranial nerve palsies, and other symptoms suggesting **pseudotumor cerebri**.

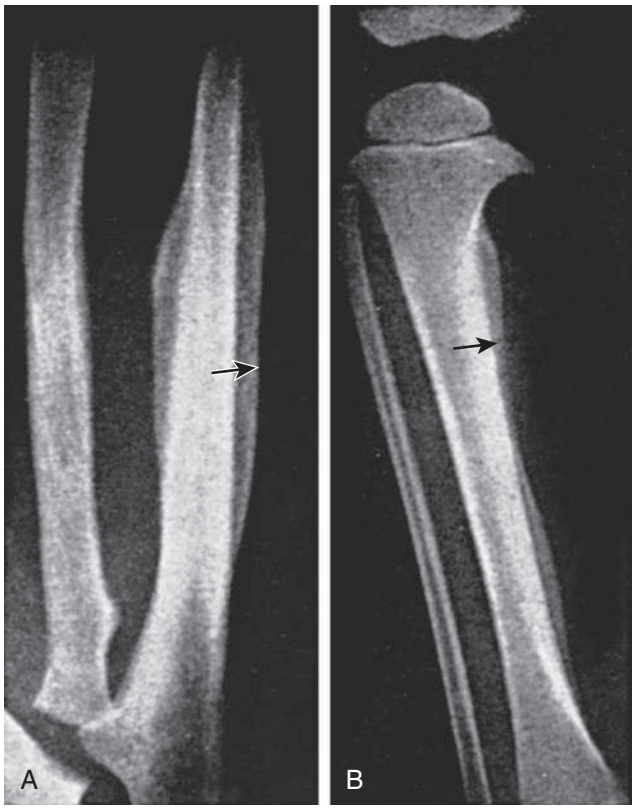

Fig. 66.6 Hyperostosis of the ulna and tibia in 21-mo-old infant, resulting from vitamin A positioning. **A**, Long, wavy cortical hyperostosis of the ulna *(arrow)*. **B**, Long, wavy cortical hyperostosis of the right tibia *(arrow)*, with a striking absence of metaphyseal changes. *(From Caffey J. Pediatric X-Ray Diagnosis, 5th ed. Chicago: Year Book;1967: 994.)*

If high levels of vitamin A or synthetic retinoids are taken early in pregnancy, **severe congenital malformations** may occur in the fetus. **Teratogenicity** has been associated with therapeutic doses (0.5-1.5 mg/kg) of oral 13-*cis*-retinoic acid (e.g., Accutane), generally taken for the treatment of acne or cancer, during the first trimester of pregnancy. A high incidence (>20%) of spontaneous abortions and birth defects, including characteristic craniofacial abnormalities, has prompted the U.S. Food and Drug Administration (FDA) to enact more stringent prescription regulations for such drugs in women of childbearing age to attempt to reduce these birth defects.

Carotenoids, even in high doses, *are not* associated with toxicity but can cause yellowing of the skin (**carotenodermia**), including palms of the hands, and high levels in serum (carotenemia); this relatively benign state disappears slowly when carotene intake is reduced. Children with liver disease, diabetes mellitus, or hypothyroidism are more susceptible. Food faddism, such as excessive consumption of carotene-rich foods and juices, may be a cause of carotenodermia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 67

Vitamin B Complex Deficiencies and Excess

H.P.S. Sachdev and Dheeraj Shah

Vitamin B complex includes a number of water-soluble nutrients, including thiamine (vitamin B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate (B9), cobalamin (B12), biotin (B7), and pantothenic acid (B5). *Choline* and *inositol* are also considered parts of the B complex and are important for normal body functions, but specific deficiency syndromes have not been attributed to a lack of these factors in the diet (Table 67.1).

B-complex vitamins serve as coenzymes in many metabolic pathways that are functionally closely related. Consequently, a lack of one of the vitamins has the potential to interrupt a chain of chemical processes, including reactions that are dependent on other vitamins, and ultimately can produce diverse clinical manifestations. Because diets deficient in any one of the B-complex vitamins are often poor sources of other B vitamins, manifestations of several vitamin B deficiencies usually can be observed in the same person. *It is therefore a general practice in a patient who has evidence of deficiency of a specific B vitamin to treat with the entire B-complex group of vitamins.*

Table 67.1 Water-Soluble Vitamins

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	DIETARY REFERENCE INTAKES BY AGE	
						RDA*	EAR**
Thiamine (vitamin B1)	Coenzyme in carbohydrate metabolism Nucleic acid synthesis Neurotransmitter synthesis	Neurologic (dry beriberi): irritability, peripheral neuritis, muscle tenderness, ataxia Cardiac (wet beriberi): tachycardia, edema, cardiomegaly, cardiac failure	3-5 mg/day PO thiamine for 6 wk	Polished rice–based diets Malabsorptive states Severe malnutrition Malignancies Alcoholism	Meat, especially pork; fish; liver Rice (unmilled), wheat germ; enriched cereals; legumes	0-6 mo: 0.2 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Females: 1.0 mg/day Males: 1.2 mg/day	1-3 yr: 0.4 mg/day 4-8 yr: 0.5 mg/day 9-13 yr: 0.7 mg/day 14-18 yr: Females: 0.9 mg/day Males: 1.0 mg/day
Riboflavin (vitamin B2)	Constituent of flavoprotein enzymes important in redox reactions: amino acid, fatty acid, and carbohydrate metabolism and cellular respiration	Glossitis, photophobia, lacrimation, corneal vascularization, poor growth, cheilosis	3-10 mg/day PO riboflavin	Severe malnutrition Malabsorptive states Prolonged treatment with phenothiazines, probenecid, or OCPs	Milk, milk products, eggs, fortified cereals, green vegetables	0-6 mo: 0.3 mg/day 7-12 mo: 0.4 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Females: 1.0 mg/day Males: 1.3 mg/day	1-3 yr: 0.4 mg/day 4-8 yr: 0.5 mg/day 9-13 yr: 0.8 mg/day 14-18 yr: Females: 0.9 mg/day Males: 1.1 mg/day
Niacin (vitamin B3)	Constituent of NAD and NADP, important in respiratory chain, fatty acid synthesis, cell differentiation, and DNA processing	Pellagra manifesting as diarrhea, symmetric scaly dermatitis in sun-exposed areas, and neurologic symptoms of disorientation and delirium	50-300 mg/day PO niacin	Predominantly maize-based diets Anorexia nervosa Carcinoid syndrome	Meat, fish, poultry Cereals, legumes, green vegetables	0-6 mo: 2 mg/day 7-12 mo: 4 mg/day 1-3 yr: 6 mg/day 4-8 yr: 8 mg/day 9-13 yr: 12 mg/day 14-18 yr: Females: 14 mg/day Males: 16 mg/day	1-3 yr: 5 mg/day 4-8 yr: 6 mg/day 9-13 yr: 9 mg/day 14-18 yr: Females: 11 mg/day Males: 12 mg/day
Pyridoxine (vitamin B6)	Constituent of coenzymes for amino acid and glycogen metabolism, heme synthesis, steroid action, neurotransmitter synthesis	Irritability, convulsions, hypochromic anemia Failure to thrive Oxaluria	5-25 mg/day PO for deficiency states 100 mg IM or IV for pyridoxine-dependent seizures	Prolonged treatment with INH, penicillamine, OCPs	Fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, potatoes	0-6 mo: 0.1 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 1.0 mg/day 14-18 yr: Females: 1.2 mg/day Males: 1.3 mg/day	1-3 yr: 0.4 mg/day 4-8 yr: 0.5 mg/day 9-13 yr: 0.8 mg/day 14-18 yr: Females: 1.0 mg/day Males: 1.1 mg/day

Table 67.1 Water-Soluble Vitamins—cont'd

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	DIETARY REFERENCE INTAKES BY AGE	
						RDA*	EAR**
Biotin (vitamin B7)	Cofactor for carboxylases, important in gluconeogenesis, fatty acid and amino acid metabolism	Scaly periorificial dermatitis, conjunctivitis, alopecia, lethargy, hypotonia, and withdrawn behavior	1-10 mg/day PO biotin	Consumption of raw eggs for prolonged periods Parenteral nutrition with infusates lacking biotin Valproate therapy	Liver, organ meats, fruits	0-6 mo: 5 µg/day 7-12 mo: 6 µg/day 1-3 yr: 8 µg/day 4-8 yr: 12 µg/day 9-13 yr: 20 µg/day 14-18 yr: 25 µg/day	Not established
Pantothenic acid (vitamin B5)	Component of coenzyme A and acyl carrier protein involved in fatty acid metabolism	Experimentally produced deficiency in humans: irritability, fatigue, numbness, paresthesias (burning feet syndrome), muscle cramps		Isolated deficiency extremely rare in humans	Beef, organ meats, poultry, seafood, egg yolk Yeast, soybeans, mushrooms	0-6 mo: 1.7 mg/day 7-12 mo: 1.8 mg/day 1-3 yr: 2 mg/day 4-8 yr: 3 mg/day 9-13 yr: 4 mg/day 14-18 yr: 5 mg/day	Not established
Folic acid (vitamin B9)	Coenzymes in amino acid and nucleotide metabolism as an acceptor and donor of 1-carbon units	Megaloblastic anemia Growth stunting, glossitis Neural tube defects in progeny	0.5-1 mg/day PO folic acid	Malnutrition Malabsorptive states Malignancies Hemolytic anemias Anticonvulsant therapy	Enriched cereals, beans, leafy vegetables, citrus fruits, papaya	0-6 mo: 65 µg/day 7-12 mo: 80 µg/day 1-3 yr: 150 µg/day 4-8 yr: 200 µg/day 9-13 yr: 300 µg/day 14-18 yr: 400 µg/day	1-3 yr: 120 µg/day 4-8 yr: 160 µg/day 9-13 yr: 250 µg/day 14-18 yr: 330 µg/day
Cobalamin (vitamin B12)	As deoxyadenosylcobalamin, acts as cofactor for lipid and carbohydrate metabolism As methylcobalamin, important for conversion of homocysteine to methionine and folic acid metabolism	Megaloblastic anemia, irritability, developmental delay, developmental regression, involuntary movements, hyperpigmentation	500-1,000 µg IM or oral vitamin B12	Vegan diets Malabsorptive states Crohn disease Intrinsic factor deficiency (pernicious anemia)	Organ meats, seafood, poultry, egg yolk, milk, fortified ready-to-eat cereals	0-6 mo: 0.4 µg/day 7-12 mo: 0.5 µg/day 1-3 yr: 0.9 µg/day 4-8 yr: 1.2 µg/day 9-13 yr: 1.8 µg/day 14-18 yr: 2.4 µg/day	1-3 yr: 0.7 µg/day 4-8 yr: 1.0 µg/day 9-13 yr: 1.5 µg/day 14-18 yr: 2.0 µg/day
Ascorbic acid (vitamin C)	Important for collagen synthesis, metabolism of cholesterol and neurotransmitters Antioxidant functions and nonheme iron absorption	Scurvy manifesting as irritability, tenderness and swelling of legs, bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, and poor wound healing	100-200 mg/day PO ascorbic acid for up to 3 mo	Predominantly milk-based (non–human milk) diets Severe malnutrition	Citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, leafy green vegetables	0-6 mo: 40 mg/day 7-12 mo: 50 mg/day 1-3 yr: 15 mg/day 4-8 yr: 25 mg/day 9-13 yr: 45 mg/day 14-18 yr: Females: 65 mg/day Males: 75 mg/day	1-3 yr: 13 mg/day 4-8 yr: 22 mg/day 9-13 yr: 39 mg/day 14-18 yr: Females: 56 mg/day Males: 63 mg/day

*For healthy breastfed infants, the values represent adequate intakes (AI), that is, the mean intake of apparently "normal" infants. For biotin and pantothenic acid also, the values represent AI, as the RDA has not been established.

**Values have not been established for infants (0-12 mo).

PO, Orally; IM, intramuscularly; IV, intravenously; INH, isoniazid; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OCP, oral contraceptive pill; RDA, recommended dietary allowance (average daily nutrient intake level estimated to meet the requirements of nearly all the healthy individuals); EAR, estimated average requirement (average daily nutrient intake level estimated to meet the requirements of 50% of the healthy individuals).

From The National Academies Press. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (https://www.nap.edu/catalog/6015/dietary-reference-intakes-for-thiamin-riboflavin-niacin-vitamin-b6-folate-vitamin-b12-pantothenic-acid-biotin-and-choline) and Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (https://www.nap.edu/catalog/9810/dietary-reference-intakes-for-vitamin-c-vitamin-e-selenium-and-carotenoids)

67.1 Thiamine (Vitamin B1)

H.P.S. Sachdev and Dheeraj Shah

Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate catabolism such as pyruvate dehydrogenase, transketolase, and α-ketoglutarate. These enzymes also play a role in the hexose monophosphate shunt that generates nicotinamide adenine dinucleotide phosphate (NADP) and pentose for nucleic acid synthesis. Thiamine is also required for the synthesis of acetylcholine (ACh) and γ-aminobutyric acid (GABA), which have important roles in nerve conduction. Thiamine is absorbed efficiently in the gastrointestinal (GI) tract and

Table 67.2 Genetic Pathogenic Variants Affecting Thiamine Metabolism

DISEASE	VARIANT	PROTEIN	AGE AT ONSET	CLINICAL SYMPTOMS	MANAGEMENT (DOSE)
TRMA/Rogers syndrome	*SLC19A2*	THTR1	Birth to adolescence	Megaloblastic anemia, diabetes mellitus, sensorineural deafness, optic atrophy, congenital heart defects, short stature	Thiamine (50-200 mg/day)
Biotin–thiamine-responsive basal ganglia disease	*SLC19A3*	THTR2	Birth to adolescence	*Episodic* encephalopathy associated with febrile illness, seizures, external ophthalmoplegia, dysphagia, gait ataxia, bilateral lesions of the basal ganglia	Biotin (5-10 mg/kg/day), thiamine (up to 40 mg/kg/day)
Amish lethal microcephaly/ THMD3	*SLC25A19*	Mitochondrial TPP carrier	Birth	*Episodic* encephalopathy associated with lactic acidosis and alpha-ketoglutaric aciduria, microcephaly, delayed psychomotor development, seizures, increased urinary lactate	Phenobarbital (for seizures) and physical therapy High-fat diet
Thiamine metabolism dysfunction syndrome 4/THMD4 (progressive polyneuropathy type)	*SLC25A19*	MTPC	Adolescence	*Episodic* encephalopathy associated with febrile illness, transient neurologic dysfunction, residual weakness, progressive axonal polyneuropathy, bilateral striatal degeneration	High-dose (600 mg/day) thiamine may prevent acute episodes
Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type) THMD5	*TPK1*	Thiamine phosphokinase 1	Early childhood	*Episodic* encephalopathy (Leigh-like) associated with high serum and CSF lactate with progressive neurologic and motor dysfunctions (gait disturbances, ataxia, dystonia, and spasticity, which, in some cases, may result in loss of ability to walk) triggered by infections Cognitive function usually preserved; some developmental delay; some patients may recover from some neurologic deficits; in others, the outcome is fatal.	Oral thiamine (100-200 mg/day)

Modified from Dhir S, Tarasenko M, Napoli E, Giulivi C. Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. *Front Psychiatry*. 2019;10:207, Table 1.

may be deficient in persons with GI or liver disease. The requirement of thiamine is increased when carbohydrates are taken in large amounts and during periods of increased metabolism, such as fever, muscular activity, hyperthyroidism, pregnancy, and lactation. Alcohol affects various aspects of thiamine transport and uptake, contributing to the deficiency in alcoholics.

Pork (especially lean), fish, and poultry are good **dietary sources** of thiamine. Main sources of thiamine for vegetarians are rice, oat, wheat, and legumes. Most ready-to-eat breakfast cereals are enriched with thiamine. Thiamine is water soluble and heat labile; most of the vitamin is lost when the rice is repeatedly washed and the cooking water is discarded. The breast milk of a well-nourished mother provides adequate thiamine; breastfed infants of thiamine-deficient mothers are at risk for deficiency. Thiamine antagonists (coffee, tea, carbonated caffeinated beverages) and thiaminases (fermented fish) may contribute to thiamine deficiency. Most infants and older children consuming a balanced diet obtain an adequate intake of thiamine from food and do not require supplements.

THIAMINE DEFICIENCY

Deficiency of thiamine is associated with severely malnourished states, including malignancy and after surgery. The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (**oriental beriberi**); it can also arise if highly refined wheat flour forms a major part of the diet, in persons with alcoholic use disorder, and in food faddists (occidental beriberi). Thiamine deficiency has often been reported from inhabitants of refugee camps consuming the polished rice–based monotonous diets and in breastfed infants of mothers on a predominantly polished rice–based diet. Low thiamine concentrations are also noted during critical illnesses.

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss, responding in varying degrees to thiamine treatment. The syndrome occurs because of pathologic variants of the *SLC19A2* gene, encoding a thiamine transporter protein, leading to abnormal thiamine transportation and cellular vitamin deficiency (Table 67.2). Another dependency state, **biotin-thiamine–responsive basal ganglia disease (BTBGD)**, results from pathologic variants of the *SLC19A3* gene (see Table 67.2). It classically presents in children with recurrent episodes of subacute encephalopathy manifesting as lethargy, dystonia, rigidity, dysphagia, and convulsions and responds to combined treatment with biotin (5-10 mg/kg/day) and thiamine (up to 40 mg/kg/day). An infantile form manifesting with acidosis, lethargy, poor feeding, and infantile spasms is also described. Other genetic disorders are noted in Table 67.2. Thiamine and related vitamins may improve the outcome in children with Leigh encephalomyelopathy.

Clinical Manifestations

Thiamine deficiency can develop within 2-3 months of a deficient intake. Early symptoms of thiamine deficiency are nonspecific, such as fatigue, apathy, irritability, depression, drowsiness, poor mental concentration, anorexia, nausea, and abdominal discomfort. As the condition progresses, more specific manifestations of **beriberi** develop, such as peripheral neuritis (manifesting as tingling, burning, and paresthesias of the toes and feet), decreased deep tendon reflexes, loss of vibration sense, tenderness and cramping of the leg muscles, heart failure, and psychologic disturbances. Patients can have ptosis of the eyelids and atrophy of the optic nerve. Hoarseness or aphonia caused by paralysis of the laryngeal nerve is a characteristic sign. Muscle atrophy and tenderness of the nerve trunks are followed by ataxia, loss of coordination, and loss of deep sensation. Later signs include increased intracranial pressure, meningismus, and coma. The clinical picture of nutritional thiamine deficiency is usually divided into a dry (**neuritic**) type and a wet (**cardiac**) type. The disease is wet or dry depending on the amount of fluid that accumulates in the body because of cardiac and renal dysfunction, even though the exact cause for this edema is unknown. Many cases of thiamine deficiency show a mixture of both features and are more properly termed **thiamine deficiency with cardiopathy and peripheral neuropathy**. A fulminant form of beriberi (**Shoshin beriberi**) manifesting acutely with severe metabolic acidosis, hypotension, and cardiogenic shock has also been described.

The classic clinical triad of **Wernicke encephalopathy**—mental status changes, ocular signs, and ataxia—is rarely reported in infants and young children with severe deficiency secondary to malignancies or feeding of defective formula. An epidemic of life-threatening thiamine deficiency was seen in infants fed a defective soy-based formula that had undetectable thiamine levels. Manifestations included emesis, lethargy, restlessness, ophthalmoplegia, abdominal distention, developmental delay, failure to thrive (malnutrition), lactic acidosis, nystagmus, diarrhea, apnea, seizures, and auditory neuropathy. An acute presentation with tachycardia, aphonia/hoarse cry, pulmonary hypertension, and severe metabolic acidosis responding to parenteral thiamine has been reported in infants of mothers consuming polished and frequently washed rice.

Death from nutritional thiamine deficiency usually is secondary to cardiac involvement. The initial signs are cyanosis and dyspnea, but tachycardia, enlargement of the liver, loss of consciousness, and convulsions can develop rapidly. The heart, especially the right side, is enlarged. The electrocardiogram (ECG) shows an increased QT interval, inverted T waves, and low voltage. These changes, as well as the cardiomegaly, rapidly revert to normal with treatment, but without prompt treatment, cardiac failure can develop rapidly and result in death. In fatal cases of beriberi, lesions are principally located in the heart, peripheral nerves, subcutaneous tissue, and serous cavities. The heart is dilated, and fatty degeneration of the myocardium is common. Generalized edema or edema of the legs, serous effusions, and venous engorgement are often present. Degeneration of myelin and axon cylinders of the peripheral nerves, with Wallerian degeneration beginning in the distal locations, is also common, particularly in the lower extremities. Lesions in the brain include vascular dilation and hemorrhage.

Diagnosis

The diagnosis is often suspected based on clinical setting and compatible symptoms. A high index of suspicion in children presenting with unexplained cardiac failure may sometimes be lifesaving. Objective biochemical tests of thiamine status include measurement of erythrocyte transketolase activity and the thiamine pyrophosphate effect. The biochemical diagnostic criteria of thiamine deficiency consist of low erythrocyte transketolase activity and high thiamine pyrophosphate effect (normal range: 0–14%). Urinary excretion of thiamine or its metabolites (thiazole or pyrimidine) after an oral loading dose of thiamine may also be measured to help identify the deficiency state. A diagnostic approach to genetic thiamine deficiencies is noted in Table 67.3. MRI changes of nutritional and genetic thiamine deficiency in infants are characterized by bilateral symmetric hyperintensities of the basal ganglia and frontal lobe, in addition to the lesions in the mammillary bodies, periaqueductal region, and thalami described in adults (Fig. 67.1).

Table 67.3 Suggested Criteria for the Diagnosis of Inherited Thiamine Defects with Prominent Neurologic Involvement

REQUIRED

1. Clinical criteria
   a. *SLCI9A3*: Acute or recurrent episodes of encephalopathy (decreased consciousness, irritability) with two or more of the following: (a) dystonia, (b) hypotonia, (c) bulbar dysfunction, (d) ataxia, and (e) seizures. Of note, 16% of patients may have an insidious onset of symptoms (psychomotor regression, clumsy or abnormal gait, and stiff limbs).
   b. *SLC25AI9*: Acute or recurrent episodes of encephalopathy with (a) progressive peripheral neuropathy or (b) severe congenital microcephaly with brain malformations.
   c. *TPK1*: Acute or recurrent episodes of encephalopathy, with two or more of the following: (a) dystonia, (b) hypotonia, (c) ataxia, (d) seizures, and (e) developmental delay. Of note, some patients may have a nonepisodic early-onset global developmental delay.
2. Biochemical criteria
   a. Normal total thiamine blood levels
   b. Low free-thiamine in CSF and/or fibroblasts (SLC19A3)
   c. Low TPP in blood, muscle, and/or fibroblasts (TPK1)
   d. High excretion of alpha-ketoglutaric acid in urine (common in TPK1 and SLC25A19, rare in SLC19A3)
3. Radiologic criteria
   a. MRI pattern compatible with Leigh syndrome (SLC19A3, SLC25A19, TPK1) or Wernicke encephalopathy (SLC19A3)
      i. *SLC19A3*: Symmetric T2W hyperintensity of caudate, putamen, cortico/subcortical areas, and/or ventromedial thalamus. No involvement of mammillary bodies. Diffuse T2W hyperintensity of brain white matter (single adult patient reported).
      ii. *SLC25A19*: Symmetric T2W hyperintensity in the caudate and putamen.
      iii. TPK1: Symmetric T2W hyperintensity in basal ganglia and cerebellum (dentate nuclei).
4. Therapeutic criteria
   a. Clinical improvement after thiamine supplementation

SUPPORTIVE

1. Consanguinity
2. Trigger event (e.g., infection, vaccination, trauma, intense physical activity)
3. Absence of predisposing factors of beriberi or Wernicke encephalopathy
4. Absence of systemic features of mitochondrial disease (cardiomyopathy, arrhythmia/conduction defects, renal tubulopathy, or dysmorphic features)
5. Increased lactate in blood and/or CSF or presence of a lactate peak on MRS
6. Normal OXPHOS and PDHc activity in muscle and fibroblast

CSF, Cerebrospinal fluid; MRI, magnetic resonance imaging; OXPHOS, oxidative phosphorylation: PDHc, pyruvate dehydrogenase complex; MRS, magnetic resonance spectroscopy; TPP, thiamine pyrophosphate; T2W, T2-weighted.

From Marcé-Grau A, Martí-Sánchez L, Baide-Mairena H, Ortigoza-Escobar JD, Pérez-Dueñas B. Genetic defects of thiamine transport and metabolism: A review of clinical phenotypes, genetics, and functional studies. *J Inherit Metab Dis.* 2019;42(4):581–597, Table 3, p. 586.

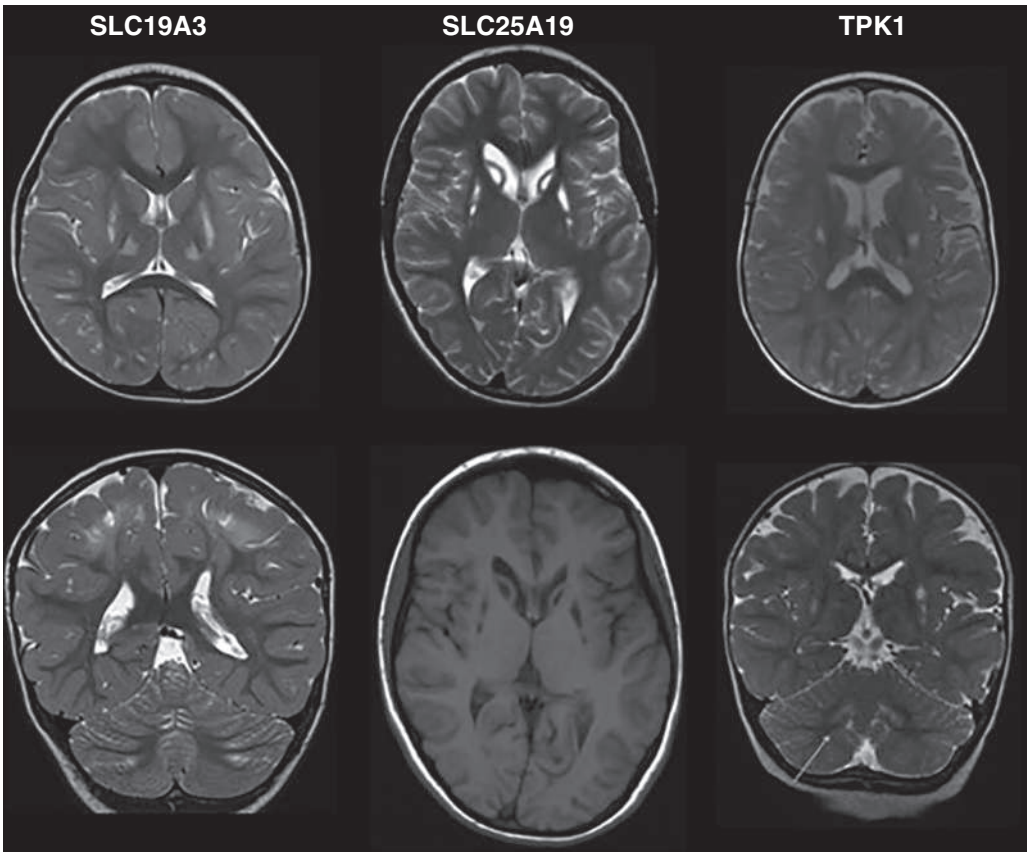

Fig. 67.1 MRI patterns in patients with inherited thiamine defects. *SLC19A3*, Axial and coronal T2-weighted images show bilateral symmetric involvement of the putamen and thalamus along with patchy cortical and subcortical hyperintensities. *SLC25A19*, Axial T2-weighted and T1-weighted images show cystic necrosis of the caudate and putamen. *TPK1*, Axial and coronal T2-weighted spin-echo images show involvement of the posterior putamen and dentate nuclei *(gray arrow). (Modified from Ortigoza-Escobar JD, Alfadhel M, Molero-Luis M, et al. Thiamine deficiency in childhood with attention to genetic causes: Survival and outcome predictors. Ann Neurol. 2017;82[3]:317-330, Fig. 3, p. 322.)*

Prevention

A maternal diet containing sufficient amounts of thiamine prevents thiamine deficiency in breastfed infants, and infant formulas marketed in all developed countries provide recommended levels of intake. During complementary feeding, adequate thiamine intake can be achieved with a varied diet that includes meat and enriched or whole-grain cereals. When the staple cereal is polished rice, special efforts need to be made to include legumes and/or nuts in the ration. Thiamine and other vitamins can be retained in rice by **parboiling**, a process of steaming the rice in the husk before milling. Improvement in cooking techniques, such as not discarding the water used for cooking, minimal washing of grains, and reduction of cooking time, helps to minimize the thiamine losses during the preparation of food. Thiamine supplementation should be ensured during total parenteral nutrition (TPN).

Treatment

In the absence of GI disturbances, oral administration of thiamine is effective. Children with cardiac failure, convulsions, or coma should be given 10-50 mg of thiamine intramuscularly (IM) or intravenously (IV) daily for the first week. This treatment should then be followed by 3-5 mg/day of thiamine orally (PO) for at least 6 weeks. The response is dramatic in infants and in those having predominantly cardiovascular manifestations, whereas the neurologic response is slow and often incomplete. Epilepsy, mental disability, and language and auditory problems of varying degrees have been reported in survivors of severe infantile thiamine deficiency.

Patients with beriberi often have other B-complex vitamin deficiencies; therefore all other B-complex vitamins should also be administered. **Treatment of TRMA syndrome and other genetic pathogenic variants of thiamine metabolism require higher dosages (Table 67.2).** The anemia responds well to thiamine administration, and insulin for associated diabetes mellitus can also be discontinued in many patients with TRMA syndrome. Patients with BTBGD need lifelong supplementation.

THIAMINE TOXICITY

There are no reports of adverse effects from consumption of excess thiamine by ingestion of food or supplements. A few isolated cases of pruritus and anaphylaxis have been reported in patients after parenteral administration of vitamin B1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

67.2 Riboflavin (Vitamin B2)

H.P.S. Sachdev and Dheeraj Shah

Riboflavin is part of the structure of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide, which participate in oxidation-reduction (redox) reactions in numerous metabolic pathways and in energy production via the mitochondrial respiratory chain. Specific transporter proteins direct riboflavin intracellularly for these functions. Riboflavin is stable to heat but is destroyed by light. Milk and dairy products, eggs, organ meats, legumes, and mushrooms are rich dietary sources of riboflavin. Most commercial cereals, flours, and breads are enriched with riboflavin.

RIBOFLAVIN DEFICIENCY

The causes of riboflavin deficiency (**ariboflavinosis**) are mainly related to malnourished and malabsorptive states, including GI infections. Treatment with some drugs, such as probenecid, phenothiazine, doxorubicin, or oral contraceptives (OCs), can also cause the deficiency. Phototherapy for hyperbilirubinemia can contribute to deficiency as the side chain of the vitamin is photochemically destroyed because it is involved in the photosensitized oxidation of bilirubin to more polar excretable compounds.

Brown-Vialetto-Van Laere syndrome (BVVLS) and Fazio-Londe syndrome are clinically overlapping conditions related to **riboflavin transporter deficiency (RTD)**. Pathologic variants (autosomal recessive) of the *SLC52A1* (type 1), *SLC52A2* (type 2), and *SLC52A3* (type 3) genes, which encode intestinal human riboflavin transporter proteins, have been demonstrated in these disorders characterized by *progressive* neurologic deterioration, peripheral neuropathy, hypotonia, ataxia, sensorineural hearing loss (usually the first symptom), optic atrophy, pontobulbar palsy, and respiratory insufficiency. Age of onset is variable; the later the onset, the milder the symptoms. Treatment with high doses (10-80 mg/kg/day) of riboflavin lead to clinical improvement in the majority of cases, especially if treated early in the disease course. Prophylaxis with riboflavin has been demonstrated to be effective in the reduction of frequency of headache in adult migraine; the evidence is insufficient in children and adolescents.

Clinical Manifestations

Clinical features of nutritional riboflavin deficiency include cheilosis, glossitis, keratitis, conjunctivitis, photophobia, lacrimation, corneal vascularization, and seborrheic dermatitis. Cheilosis begins with pallor at the angles of the mouth and progresses to thinning and maceration of the epithelium, leading to fissures extending radially into the skin (Fig. 67.2). In glossitis the tongue becomes smooth, with loss of papillary structure (Fig. 67.3). Normochromic, normocytic anemia may also be seen because of the impaired erythropoiesis. A low riboflavin content of the maternal diet has been linked to congenital heart defects, but the evidence is weak.

Diagnosis

Most often, the diagnosis is based on the clinical features of angular cheilosis in a malnourished child, who responds promptly to riboflavin supplementation. A functional test of riboflavin status is done by measuring the activity of erythrocyte glutathione reductase (EGR), with and without the addition of FAD. An EGR activity coefficient (ratio of EGR activity with added FAD to EGR activity without FAD) of >1.4 is used as an indicator of deficiency. Urinary excretion of riboflavin <30 μg/24 hr also suggests low intake.

Riboflavin transporter deficiency may be detected by genetic testing.

Prevention

Table 67.1 lists the recommended daily allowance of riboflavin for infants, children, and adolescents. Adequate consumption of milk, milk products, and eggs prevents riboflavin deficiency. Fortification of cereal products is helpful for those who follow vegan diets or who are consuming inadequate amounts of milk products for other reasons.

Treatment

Treatment includes oral administration of 3-10 mg/day of riboflavin, often as an ingredient of a vitamin B–complex mix. The child should also be given a well-balanced diet, including milk and milk products.

RIBOFLAVIN TOXICITY

No adverse effects associated with riboflavin intake from food or supplements have been reported, and the upper safe limit for consumption has not been established. Although the photosensitizing property of vitamin B2 suggests some potential risks, limited absorption in high-intake situations precludes such concerns.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 67.2 Clinical photograph of a child showing angular cheilosis with ulceration and crusting in riboflavin deficiency. *(Courtesy National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India.)*



Fig. 67.3 Papillary atrophy, inflammation, and ulceration of the tongue as seen in riboflavin deficiency. *(From Zappe HA, Nuss S, Becker K, et al. Riboflavin deficiency in Baltistan.* http://www.rzuser.uni-heidelberg.de/%7Ecn6/baltista/ribofl_e.htm.*)*

67.3 Niacin (Vitamin B3)

H.P.S. Sachdev and Dheeraj Shah

Niacin (nicotinamide or nicotinic acid) forms part of two cofactors, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are important in several biologic reactions, including the respiratory chain, fatty acid and steroid synthesis, cell differentiation, and DNA processing. Niacin is rapidly absorbed from the stomach and the intestines and can also be synthesized from tryptophan in the diet.

Major dietary sources of niacin are meat, fish, and poultry for nonvegetarians and cereals, legumes, and green leafy vegetables for vegetarians. Enriched and fortified cereal products and legumes also are major contributors to niacin intake. Milk and eggs contain little niacin but are good sources of tryptophan, which can be converted to NAD (60 mg tryptophan = 1 mg niacin).

NIACIN DEFICIENCY

Pellagra, the classic niacin deficiency disease, occurs chiefly in populations where corn (maize), a poor source of tryptophan, is the major foodstuff. A severe dietary imbalance, such as in anorexia nervosa and in war or famine conditions, also can cause pellagra. Pellagra is rare outside the African subcontinent; however, consumption of a highly restrictive diet, such as in autism, has led to some resurgence in high-income countries. Pellagra can also develop in conditions associated with disturbed tryptophan metabolism, such as carcinoid syndrome and Hartnup disease.



Fig. 67.4 A, Symmetric, well-demarcated, erythematous, eroded plaques with desquamation over hands and forearms. B, Brownish plaques with desquamation in the distribution of neck collar (Casal necklace) because of pellagra in a child with autism on highly restrictive diet. *(From Zaenglein A, Martin A, Carlson L, Williams KE. Pellagra secondary to selective eating in a child with autism. Pediatr Dermatol. 2020;37:698–700.)*

Clinical Manifestations

The early symptoms of pellagra are vague: anorexia, lassitude, weakness, burning sensation, numbness, and dizziness. After a long period of deficiency, the classic triad of dermatitis, diarrhea, and dementia appears. **Dermatitis**, the most characteristic manifestation of pellagra, can develop suddenly or insidiously and may be initiated by irritants, including intense sunlight. The lesions first appear as symmetric areas of erythema on exposed surfaces, resembling sunburn, and might go unrecognized. The lesions are usually sharply demarcated from the surrounding healthy skin, and their distribution can change frequently. The lesions on the hands and feet often have the appearance of a glove or stocking (Fig. 67.4A). Similar demarcations can also occur around the neck (**Casal necklace**) (see Fig. 67.4B). In some cases, vesicles and bullae develop (wet type). In others there may be suppuration beneath the scaly, crusted epidermis; in still others the swelling can disappear after a short time, followed by desquamation (Fig. 67.5). The healed parts of the skin might remain pigmented. The cutaneous lesions may be preceded by or accompanied by stomatitis, glossitis, vomiting, and diarrhea. Swelling and redness of the tip of the tongue and its lateral margins is often followed by intense redness, even ulceration, of the entire tongue and the papillae. Central nervous system symptoms include depression, disorientation, insomnia, and delirium.

The classic symptoms of pellagra usually are not well developed in infants and young children, but anorexia, irritability, anxiety, and apathy are common. Young patients might also have sore tongues and lips and usually have dry scaly skin. Diarrhea and constipation can alternate, and anemia can occur. Children who have pellagra often have evidence of other nutritional deficiency diseases.

Diagnosis

Because of lack of a good functional test to evaluate niacin status, the diagnosis of deficiency is usually made from the physical signs of glossitis, GI symptoms, and a symmetric dermatitis. Rapid clinical response to niacin is an important confirmatory test. A decrease in the concentration and/or a change in the proportion of the niacin metabolites N^1-methylnicotinamide and 2-pyridone in the urine provide biochemical evidence of deficiency and can be seen before the appearance of overt signs of deficiency. Histopathologic changes from the affected skin include dilated blood vessels without significant inflammatory infiltrates, ballooning of the keratinocytes, hyperkeratosis, and epidermal necrosis.



Fig. 67.5 Clinical manifestations of niacin deficiency before (A) and after (B) therapy. *(From Weinsier RL, Morgan SL. Fundamentals of Clinical Nutrition. St Louis: Mosby; 1993:99.)*

Prevention

Adequate intake of niacin is easily met by consumption of a diet that consists of a variety of foods and includes meat, eggs, milk, and enriched or fortified cereal products. The dietary reference intake (DRI) is expressed in milligram niacin equivalents (NE) in which 1 mg NE = 1 mg niacin or 60 mg tryptophan. The DRI is summarized in Table 67.1.

Treatment

Children usually respond rapidly to treatment. A liberal and varied diet should be supplemented with 50-300 mg/day of niacin; in severe cases or in patients with poor intestinal absorption, 100 mg may be given IV. The diet should also be supplemented with other vitamins, especially other B-complex vitamins. Sun exposure should be avoided during the active phase of pellagra, and the skin lesions may be covered with soothing applications. Other coexisting nutrient deficiencies such as iron-deficiency anemia should be treated. Even after successful treatment, the diet should continue to be monitored to prevent recurrence.

NIACIN TOXICITY

No toxic effects are associated with the intake of naturally occurring niacin in foods. Shortly after the ingestion of large doses of nicotinic acid taken as a supplement or a pharmacologic agent, a person often experiences a burning, tingling, and itching sensation, as well as flushing on the face, arms, and chest. Large doses of niacin also can have nonspecific GI effects and can cause cholestatic jaundice or hepatotoxicity. Tolerable upper intake levels for children are 10 mg/day for 1-3 years, 15 mg/day for 4-8 years, 20 mg/day for 9-13 years, and 30 mg/day for 14-18 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

67.4 Vitamin B6 (Pyridoxine)

H.P.S. Sachdev and Dheeraj Shah

Vitamin B6 includes a group of closely related compounds: pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives. **Pyridoxal 5′-phosphate (PLP)** and, to a lesser extent, pyridoxamine phosphate function as coenzymes for many enzymes involved in amino acid metabolism, neurotransmitter synthesis, glycogen metabolism, and steroid action. If vitamin B6 is lacking, glycine metabolism can lead to oxaluria. The major excretory product in the urine is 4-pyridoxic acid.

The vitamin B6 content of human milk and infant formulas is adequate. Good food sources of the vitamin include fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, and certain vegetables. Large losses of the vitamin can occur during high-temperature processing of foods or milling of cereals, whereas parboiling of rice prevents its loss.

VITAMIN B6 DEFICIENCY

Because of the importance of vitamin B6 in amino acid metabolism, high protein intake can increase the requirement for the vitamin; the recommended daily allowances are sufficient to cover the expected range of protein intake in the population. The risk of deficiency is increased in persons taking medications that inhibit the activity of vitamin B6 (e.g., isoniazid, penicillamine, corticosteroids, phenytoin, carbamazepine), in young women taking oral progesterone-estrogen contraceptives, and in patients receiving maintenance dialysis.

Clinical Manifestations

The vitamin B6 deficiency symptoms seen in infants are listlessness, irritability, seizures, vomiting, and failure to thrive. Peripheral neuritis is a feature of deficiency in adults but is not usually seen in children. EEG abnormalities have been reported in infants and in young adults in controlled depletion studies. Skin lesions include cheilosis, glossitis, and seborrheic dermatitis around the eyes, nose, and mouth. Microcytic anemia can occur in infants but is not common. Oxaluria, oxalic acid bladder stones, hyperglycinemia, lymphopenia, decreased antibody formation, and infections also are associated with vitamin B6 deficiency.

Several types of vitamin B6 **dependence syndromes**, presumably resulting from errors in metabolism or transport of PLP or pyridoxine, respond to large doses of pyridoxine. These syndromes include pyridoxine-dependent epilepsy, a vitamin B6–responsive anemia, xanthurenic aciduria, cystathioninuria, and homocystinuria. Pyridoxine-dependent epilepsy involves pathologic variants in the *ALDH7A1* gene causing deficiency of antiquitin, an enzyme involved in dehydrogenation of α-aminoadipic semialdehyde. Pathologic variants of the genes *PROSC*, which encodes a PLP binding protein, and *PNPO* encoding for the pyridoxamine 5-phosphate oxidase enzyme also cause epilepsy responsive to PLP or high doses of pyridoxine. Neonatal epileptic encephalopathy and hypophosphatasia are associated with impaired import of PLP into the neuronal cells, and seizures occurring in these conditions also respond to pyridoxine therapy.

Diagnosis

The activity of aspartate (glutamic-oxaloacetic) transaminase (AST) and alanine (glutamic-pyruvic) transaminase (ALT) is low in vitamin B6 deficiency; tests measuring the activity of these enzymes before and after the addition of PLP may be useful as indicators of vitamin B6 status. Abnormally high xanthurenic acid excretion after tryptophan ingestion also provides evidence of deficiency. Plasma PLP assays are being used more often, but factors such as inflammation, renal function, and hypoalbuminemia can influence the results. Ratios between substrate-product pairs (e.g., PAr index, 3-hydroxykynurenine/xanthurenic acid ratio, oxoglutarate/glutamate ratio) may attenuate such influence. Quantification of a large number of metabolites, using mass spectrometry–based metabolomics, are being evaluated as functional biomarkers of pyridoxine status.

Vitamin B6 deficiency or dependence should be suspected in all infants with **seizures**. If more common causes of infantile seizures have been eliminated, 100 mg of pyridoxine can be injected, with EEG monitoring if possible. If the seizure stops, vitamin B6 deficiency should be suspected. In older children, 100 mg of pyridoxine may be injected IM while the EEG is being recorded; a favorable response of the EEG suggests pyridoxine deficiency.

Prevention

Deficiency is unlikely in children consuming diets that meet their energy needs and contain a variety of foods. Parboiling of rice prevents the loss of vitamin B6 from the grains. The dietary reference intake for vitamin B6 is shown in Table 67.1. Infants whose mothers have received large doses of pyridoxine during pregnancy are at increased risk for seizures from pyridoxine dependence, and supplements during the first few weeks of life should be considered. Any child receiving a pyridoxine antagonist, such as isoniazid, should be carefully observed for neurologic manifestations; if these develop, vitamin B6 should be administered or the dose of the antagonist should be decreased.

Treatment

Intramuscular or intravenous administration of 100 mg of pyridoxine is used to treat convulsions caused by vitamin B6 deficiency. One dose should be sufficient if adequate dietary intake follows. For pyridoxine-dependent children, daily doses of 2-10 mg IM or 10-100 mg PO may be necessary.

VITAMIN B6 TOXICITY

Adverse effects have not been associated with high intakes of vitamin B6 from food sources. However, ataxia and sensory neuropathy have been reported with dosages above 200 mg/day in adults taking vitamin B6 supplements for several months. Tolerable upper intake levels for children are 30 mg/day for 1-3 years, 40 mg/day for 4-8 years, 60 mg/day for 9-13 years, and 80 mg/day for 14-18 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

67.5 Biotin

H.P.S. Sachdev and Dheeraj Shah

Biotin (vitamin B7 or vitamin H) functions as a cofactor for enzymes involved in carboxylation reactions within and outside mitochondria. These biotin-dependent carboxylases catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism.

There is limited information on the biotin content of foods; biotin is believed to be widely distributed, making a deficiency unlikely. *Avidin* found in raw egg whites acts as a biotin antagonist. Signs of biotin deficiency have been demonstrated in persons who consume large amounts of raw egg whites over long periods. Deficiency also has been described in infants and children receiving enteral and parenteral nutrition formula that lacks biotin. Treatment with valproic acid may result in a low biotinidase activity and/or biotin deficiency.

The clinical findings of biotin deficiency include scaly periorificial dermatitis, conjunctivitis, thinning of hair, and alopecia (Fig. 67.6). Central nervous system (CNS) abnormalities seen with biotin deficiency are lethargy, hypotonia, seizures, ataxia, and withdrawn behavior. Biotin deficiency can be successfully treated using 1-10 mg of biotin orally daily. The dietary reference intake for biotin is shown in Table 67.1. No toxic effects have been reported with very high doses.

Biotin-responsive basal ganglia disease or **biotin and thiamine–responsive basal ganglia disease** is a rare childhood neurologic disorder characterized by encephalopathy, seizures, extrapyramidal manifestations, altered signals in basal ganglia (bilateral involvement of caudate nuclei and putamen with sparing of globus pallidus) on MRI, and homozygous pathologic variation in the *SLC19A3* gene (see Table 67.2). Chapter 105 describes conditions involving deficiencies in the enzymes holocarboxylase synthetase and biotinidase that respond to treatment with biotin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

67.6 Folate

H.P.S. Sachdev and Dheeraj Shah

Folate exists in different chemical forms (Fig. 67.7). **Folic acid** (pteroylglutamic acid) is the synthetic form used in fortified foods and supplements. Naturally occurring folates in foods retain the core chemical structure of pteroylglutamic acid but vary in their state of reduction, the single-carbon moiety they bear, or the length of the glutamate chain. These polyglutamates are broken down and reduced in the small intestine to dihydrofolates and tetrahydrofolates, which are involved as coenzymes in amino acid and nucleotide metabolism as acceptors and donors of 1-carbon units. Folate is important for CNS development during embryogenesis.

Rice and cereals are rich dietary sources of folate, especially if enriched. Beans, leafy vegetables, and fruits such as oranges and papaya are good sources as well. The vitamin is readily absorbed from the small intestine and is broken down to monoglutamate derivatives by mucosal polyglutamate hydrolases. A high-affinity proton-coupled folate transporter (PCFT) seems to be essential for absorption of folate in the intestine and in various cell types at low pH. The vitamin is also synthesized by colonic bacteria, and its half-life is prolonged by enterohepatic recirculation.

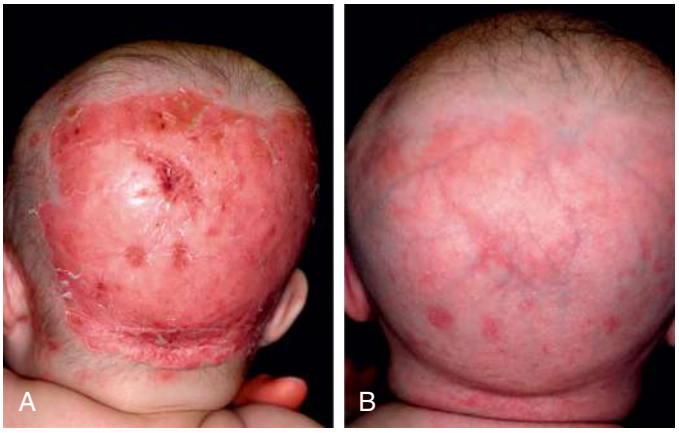

Fig. 67.6 A, Scalp rash in an infant with biotin deficiency before treatment with biotin. B, After 3 weeks of biotin treatment. *(From Ito T, Nishie W, Fujita Y, et al. Infantile eczema caused by formula milk. Lancet. 2013;381:1958.)*

FOLATE DEFICIENCY

Because of folate's role in protein, DNA, and RNA synthesis, the risk of deficiency is increased during periods of rapid growth or increased cellular metabolism. Folate deficiency can result from poor nutrient content in the diet, inadequate absorption (celiac disease, inflammatory bowel disease), increased requirement (sickle cell anemia, psoriasis, malignancies, periods of rapid growth as in infancy and adolescence), or inadequate use (long-term treatment with high-dose nonsteroidal antiinflammatory drugs; anticonvulsants such as phenytoin and phenobarbital; methotrexate). Rare causes of deficiency are hereditary folate malabsorption, inborn errors of folate metabolism (methylene tetrahydrofolate reductase, methionine synthase reductase, and glutamate formiminotransferase deficiencies), and cerebral folate deficiency. A loss-of-function pathologic variant in the gene coding for PCFT is the molecular basis for hereditary folate malabsorption. A high-affinity blocking autoantibody against the membrane-bound folate receptor in the choroid plexus preventing its transport across the blood-brain barrier is the likely cause of **infantile cerebral folate deficiency**.

Clinical Manifestations

Folic acid deficiency results in megaloblastic anemia and hypersegmentation of neutrophils. Nonhematologic manifestations include glossitis, listlessness, and growth retardation not related to anemia. An association exists between low maternal folic acid status and neural tube defects, primarily spina bifida and anencephaly, and the role of periconceptional folic acid in their prevention is well established (see Chapter 503.1).

Hereditary folate malabsorption manifests at 1-3 months of age with recurrent or chronic diarrhea, failure to thrive (malnutrition), oral ulcerations, neurologic deterioration, megaloblastic anemia, and opportunistic infections. **Cerebral folate deficiency** manifests at 4-6 months of age with irritability, microcephaly, developmental delay, cerebellar ataxia, pyramidal tract signs, choreoathetosis, ballismus, seizures, and blindness as a result of optic atrophy. 5-Methyltetrahydrofolate levels are normal in serum and red blood cells (RBCs) but greatly depressed in the cerebrospinal fluid (CSF).

Diagnosis

The diagnosis of folic acid deficiency anemia is made in the presence of macrocytosis along with low folate levels in serum or RBCs. Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150-600 ng/mL of packed cells. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation also are seen.

Cerebral folate deficiency is associated with low levels of 5-methyltetrahydrofolate in CSF and normal folate levels in the plasma

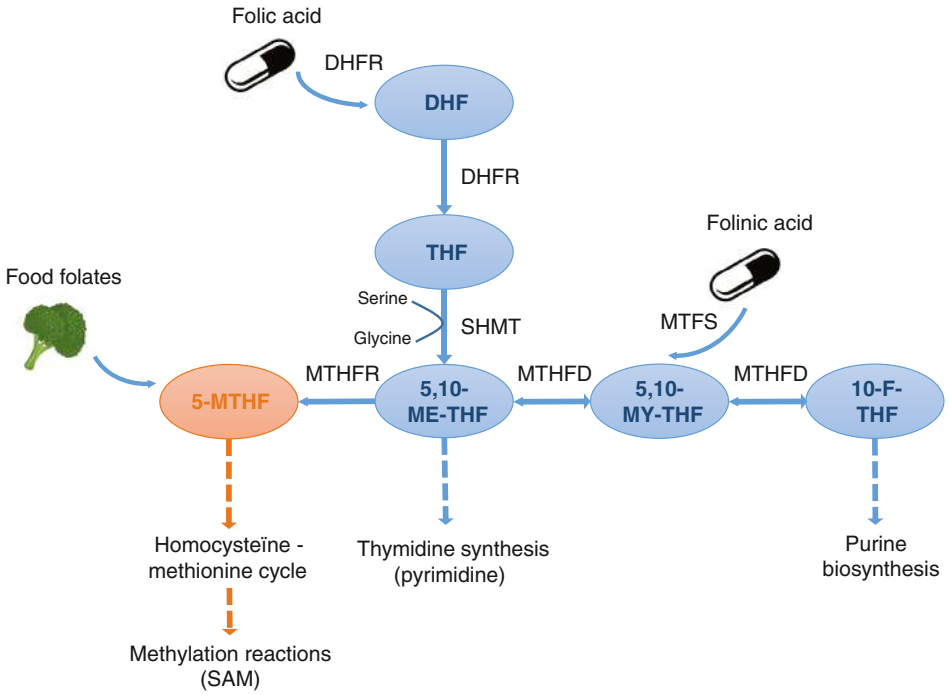

Fig. 67.7 Simplified scheme of folate metabolism; 5-MTHF is the predominant form in which dietary folate enters the circulation. Synthetic folic acid first has to be metabolized in two steps to the biologically active form THF, whereas the biologically derived folinic acid is already reduced and easily converted to 5,10-methenyl-THF. Serine is an important one carbon donor and allows entry of THF into the active one-carbon pool of intermediates by way of 5,10-methylene-THF, which functions as a cofactor for the synthesis of thymidine. 5,10-Methylene-THF can be metabolized to 5-MTHF for the remethylation of homocysteine to methionine, or it can be converted to 10-formyl-THF for use in purine synthesis.1 DHF, dihydrofolate; DHFR, dihydrofolate reductase; THF, tetrahydrofolate; 5-MTHF, 5-methyltetrahydrofolate; SAM, S-adenosylmethionine; 5,10-ME-THF, 5,10-methylene-THF; 5,10-MYTHF, 5,10-methenyl-THF; 10-F-THF, 10-formyl-THF; MTFS, 5,10-methenyltetrahydrofolate synthetase. *(From Lubout CMA, Goorden SMI, van den Hurk K, et al. Successful treatment of hereditary folate malabsorption with intramuscular folinic acid. Pediatr Neurol. 2020;102:62-66, Fig. 2, p. 64.)*

and RBCs. Pathologic variants of the *PCFT* gene are demonstrated in hereditary folate malabsorption.

Prevention

Breastfed infants have better folate nutrition than nonbreastfed infants throughout infancy. Consumption of folate-rich foods and food fortification programs are important to ensure adequate intake in children and in women of childbearing age. The dietary reference intakes (DRIs) for folate are 65 µg of dietary folate equivalents (DFE) for infants 0-6 months of age and 80 µg of DFE for infants 6-12 months. (1 DFE = 1 µg food folate = 0.6 µg of folate from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach.) For the DRIs in older children, see Table 67.1. All women desirous of becoming pregnant should consume 400-800 µg folic acid daily; the dose is 4 mg/day in those having delivered a child with a neural tube defect. To be effective, supplementation should be started at least 1 month before conception and continued through the first 2-3 months of pregnancy. The benefit of periconceptional folate supplementation in prevention of congenital heart defects, orofacial clefts, childhood cancers, and autism spectrum disorders are unclear. Preconceptional folate supplementation continued throughout pregnancy may marginally reduce the risk of delivering a preterm or small-for-gestational-age infant. Providing iron and folic acid tablets for prevention of anemia in children and pregnant women is a routine strategy in at-risk populations. Mandatory fortification of cereal flours with folic acid coupled with health education programs has been associated with a substantial reduction in incidence of neural tube defects in many countries.

Treatment

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. Folic acid therapy should be continued for 3-4 weeks or until a definite hematologic response has occurred. Maintenance therapy with 0.2 mg/day of folate is adequate. Prolonged treatment with oral or parenteral folinic acid is required in cerebral folate deficiency, and the response may be incomplete. High-dose intravenous folinic acid may help in refractory cases. Treatment of hereditary folate malabsorption may be possible with intramuscular folinic acid; some patients may respond to high-dose oral folinic acid therapy.

FOLATE TOXICITY

No adverse effects have been associated with consumption of the amounts of folate normally found in fortified foods. Tolerable upper intake levels for children are 300 µg/day for 1-3 years, 400 µg/day for 4-8 years, 600 µg/day for 9-13 years, and 800 µg/day for 14-18 years. Excessive intake of folate supplements might obscure and potentially delay the diagnosis of vitamin B12 deficiency. Massive doses given by injection have the potential to cause neurotoxicity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

67.7 Vitamin B12 (Cobalamin)

H.P.S. Sachdev and Dheeraj Shah

Vitamin B12, in the form of deoxyadenosylcobalamin, functions as a cofactor for isomerization of methylmalonyl-CoA to succinyl-CoA, an essential reaction in lipid and carbohydrate metabolism. Methylcobalamin is another circulating form of vitamin B12 and is essential for methyl group transfer during the conversion of homocysteine to methionine. This reaction also requires a folic acid cofactor and is important for protein and nucleic acid biosynthesis. Vitamin B12 is important for hematopoiesis, CNS myelination, and mental and psychomotor development (Fig. 67.8).

Dietary sources of vitamin B12 are almost exclusively from animal foods. Organ meats, muscle meats, seafood (mollusks, oysters, fish), poultry, and egg yolk are rich sources. Fortified ready-to-eat cereals and milk and their products are the important sources of the vitamin for vegetarians. Human milk is an adequate source for breastfeeding infants if the maternal serum B12 levels are adequate. Vitamin B12 is absorbed from ileum at alkaline pH after binding with intrinsic factor. Enterohepatic circulation, direct absorption, and synthesis by intestinal bacteria are additional mechanisms helping to maintain the vitamin B12 nutriture.

VITAMIN B12 DEFICIENCY

Deficiency of vitamin B12 caused by inadequate dietary intake occurs primarily in persons consuming strict vegetarian or vegan diets. Prevalence of vitamin B12 deficiency is high in predominantly vegetarian or lactovegetarian populations. Breastfeeding infants of B12-deficient mothers are also at risk for significant deficiency. Malabsorption of B_{12} occurs in celiac disease, ileal resections, Crohn disease, *Helicobacter pylori* infection, and autoimmune atrophic gastritis (pernicious anemia). Obesity, type 1 diabetes, and use of metformin and proton pump inhibitors histamine (H_2) receptor antagonists and misuse of nitrous oxide—usually in the form of inhaling aerosol whipped cream (whippits)—may increase the risk of deficiency. **Hereditary intrinsic factor deficiency** and **Imerslund-Gräsbeck disease** are inborn errors of metabolism leading to vitamin B12 malabsorption. Pathologic variants of the hereditary intrinsic factor gene cause hereditary intrinsic factor deficiency, whereas pathologic variation in any of the two subunits (cubilin and amnionless) of the intrinsic factor receptor cause Imerslund-Gräsbeck disease. Maternal vitamin B12 deficiency may produce neonatal B12 deficiency, which may be detected by elevated levels of homocysteine and methylmalonic acid on the newborn screen.

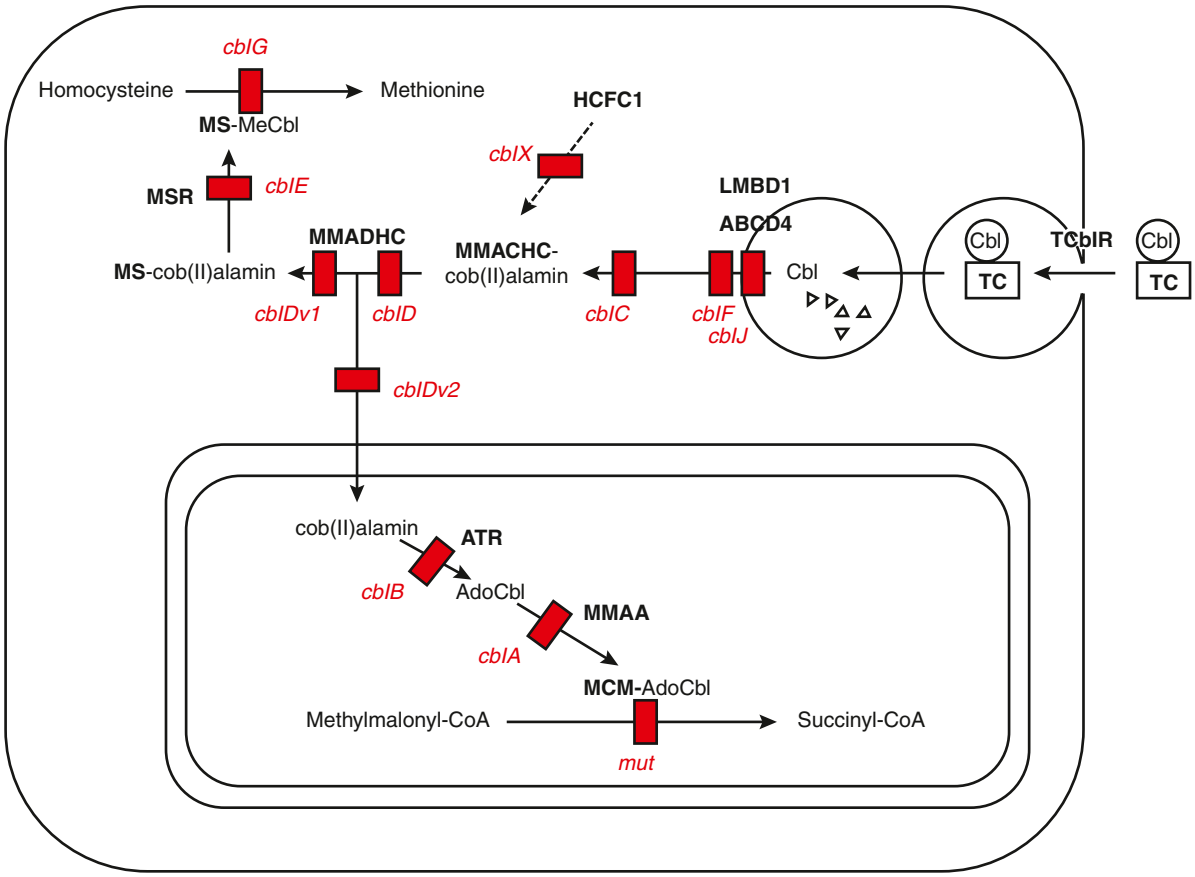

Fig. 67.8 Scheme of cobalamin (Cbl) metabolism. The sites affected by methylmalonyl-CoA mutase deficiency *(mut)* and inborn errors of cobalamin metabolism (*cblA-cblG, cblJ,* and *cblX*) are shown in *red.* The cblA disorder is caused by defects in the MMAA protein; the cblB disorder by defects in the cob(I)alamin adenosyltransferase (MMAB) protein; the cblC disorder by defects in the MMACHC protein; the cblD, cblD variant 1 *(cblDv1),* and cblD variant 2 *(cblDv2)* disorders are caused by defects in the MMADHC protein; cblE disorder is caused by defects in the methionine synthase reductase (MSR) protein; cblG disorder by defects in the methionine synthase (MS) protein; cblJ disorder by pathologic variants in the ABCD4 protein; cblX disorder by pathologic variation in the HCFC1 protein, and the mut disorder by defects in methylmalonyl-CoA mutase (MCM). The protein affected in the cblF disorder is unknown. MCM-AdoCbl, Holomethylmalonyl-CoA mutase (mutase with bound adenosylcobalamin); MS-cob(II)alamin, methionine synthase with bound cob(II)alamin; MS-MeCbl, holomethionine synthase (synthase with bound methylcobalamin); TC, transcobalamin. *(From Orkin SH, Fisher DE, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood, 8th ed. Philadelphia: Elsevier; 2015:318.)*



Fig. 67.9 MRI of the cervical spine illustrating a long segment of T2 hyperintensity involving the dorsal column of virtually the entire cervical spinal cord consistent with a diagnosis of subacute combined degeneration from vitamin B12 deficiency. *(From Stockton L, Simonsen C, Seago S. Nitrous oxide-induced vitamin B12 deficiency. Proc [Bayl Univ Med Cent]. 2017;30[2]:171–172.)*



Fig. 67.10 Hyperpigmentation of (A) knuckles and (B) soles in an adolescent female with severe anemia and vitamin B12 deficiency.

Clinical Manifestations

The hematologic manifestations of vitamin B12 deficiency are similar to manifestations of folate deficiency and are discussed in Chapter 503.2. Irritability, hypotonia, developmental delay, developmental regression, and involuntary movements (predominantly coarse tremors) are the common neurologic symptoms in infants. Older children with vitamin B12 deficiency may show poor growth and poor school performance, whereas sensory deficits, paresthesias, peripheral neuritis, and psychosis are seen in adolescents and adults (Fig. 67.9). Hyperpigmentation of the knuckles, palms, and soles is another common observation with B12 deficiency in children and adolescents (Fig. 67.10).

Diagnosis

See Chapter 503.2.

Vitamin B12 deficiency may be present with vitamin B12 levels in the normal or low normal range and without macrocytosis. Ancillary testing of methylmalonic acid and homocysteine levels may enhance the diagnosis.

Treatment

The hematologic symptoms respond promptly to parenteral administration of 250-1,000 µg vitamin B12. Children with severe deficiency and those with neurologic symptoms need repeated doses, daily or on alternate days in the first week, followed by weekly for the first 1-2 months and then monthly. Children with only hematologic presentation recover fully within 2-3 months, whereas those with neurologic disease need at least 6 months of therapy. Children with a continuing malabsorptive state and those with inborn errors of vitamin B12 malabsorption need lifelong treatment. Daily treatment with high-dose (500-1,000 µg) oral vitamin B12 preparations has also been shown to be equally effective in correcting biochemical vitamin B12 deficiency in a few trials in children, but data are inadequate to support use of the oral route in children with neurologic manifestations and severe anemia. The sublingual route has recently been explored in infants and children and has been found to be effective in normalizing serum vitamin B12 levels.

Prevention

Vitamin B12 dietary reference intakes (DRIs) are shown in Table 67.1. In pregnancy the DRI is 2.6 µg/day and in lactation 2.8 µg/day. Pregnant and breastfeeding women should ensure an adequate consumption of animal products to prevent cobalamin deficiency in infants. Strict vegetarians, especially vegans, should ensure regular consumption of vitamin B12. Food fortification with the vitamin helps to prevent deficiency in predominantly vegetarian populations. Though metabolic derangements suggestive of vitamin B12 deficiency are present in a high proportion of infants and children from low-income country settings, routine supplementation with vitamin B12 does not seem to significantly improve their growth, development, or hemoglobin status.

Toxicity

Administration of therapeutic doses, both in oral and parenteral forms, is usually safe. Transient erythroderma and chromaturia have been reported with administration of adult-equivalent doses of intravenous hydroxycobalamin in a child. Acneiform eruptions, palpitations, headache, and insomnia have been occasionally reported in young adults receiving repeated high parenteral doses.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 68

Vitamin C (Ascorbic Acid) Deficiency and Excess

Dheeraj Shah and H.P.S. Sachdev

Vitamin C is important for synthesis of collagen at the level of hydroxylation of lysine and proline in precollagen. It is also involved in neurotransmitter metabolism (conversion of dopamine to norepinephrine and tryptophan to serotonin), cholesterol metabolism (conversion of cholesterol to steroid hormones and bile acids), and the biosynthesis of carnitine. Vitamin C functions to maintain the iron and copper atoms, cofactors of the metalloenzymes, in a reduced (active) state. Vitamin C is an important antioxidant (electron donor) in the aqueous milieu of the body. Vitamin C enhances nonheme iron absorption, the transfer of iron from transferrin to ferritin, and the formation of tetrahydrofolic acid and thus can affect the cellular and immunologic functions of the hematopoietic system. Though vitamin C has antiinflammatory and immunomodulating effects, there is no evidence of clinical benefit of vitamin C supplementation in pediatric critical illnesses and respiratory tract infections, including COVID-19.

DIETARY NEEDS AND SOURCES OF VITAMIN C

Humans depend on dietary sources for vitamin C. An adequate intake is 40 mg for ages 0-6 months and 50 mg for 6-12 months. For older children, the recommended dietary allowance is 15 mg for ages 1-3 years, 25 mg for 4-8 years, 45 mg for 9-13 years, and 65-75 mg for 14-18 years. The recommended dietary allowances during pregnancy and lactation are 85 mg/day and 120 mg/day, respectively. The requirement for vitamin C is increased during infectious and diarrheal diseases. Children exposed to smoking or environmental tobacco smoke also require increased amounts of foods rich in vitamin C. The best food sources of vitamin C are citrus fruits and fruit juices, peppers, berries, melons, guava, kiwifruit, tomatoes, cauliflower, and green leafy vegetables. Vitamin C is easily destroyed by prolonged storage, overcooking, and processing of foods.

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands. The brain ascorbate content in the fetus and neonate is markedly higher than the content in the adult brain, a finding probably related to its function in neurotransmitter synthesis.

When a mother's intake of vitamin C during pregnancy and lactation is adequate, the newborn will have adequate tissue levels of vitamin C related to active placental transfer, subsequently maintained by the vitamin C in breast milk or commercial infant formulas. Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy. Infants consuming pasteurized or boiled animal milk are at significant risk of developing deficiency if the other sources of vitamin C are also lacking in the diet. Neonates whose feeding has been delayed because of a clinical condition can also have ascorbic acid deficiency. For patients receiving total parenteral nutrition (TPN), 80 mg/day is recommended for full-term infants and 25 mg/kg/day for preterm infants. Parents and children who choose a limited (selective) diet or those on fad diets are at risk for vitamin C deficiency.

VITAMIN C DEFICIENCY

A deficiency of vitamin C results in the clinical presentation of **scurvy**. Children fed predominantly heat-treated (ultrahigh-temperature or pasteurized) milk or unfortified formulas and not receiving fruits and fruit juices are at significant risk for symptomatic disease. In the last decade, most cases of scurvy from North America and Europe have been reported in children with developmental and behavioral disorders, *especially autism spectrum disorders,* on highly restrictive diets. Such dietary patterns occur mainly due to severe self-imposed dietary restrictions due to child preference or parental belief in unsubstantiated claims of benefit of such restrictions in autism and other developmental disorders. In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, the cortex is thin, and the trabeculae become brittle and fracture easily.

Clinical Features

The early manifestations of vitamin C deficiency are irritability, loss of appetite, low-grade fever, musculoskeletal pain, and tenderness in the legs. These signs and symptoms are followed by leg swelling—most marked at the knees and the ankles—and **pseudoparalysis**. The infant might lie with the hips and knees semiflexed and the feet rotated outward. Subperiosteal hemorrhages in the lower-limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. A "rosary" at the costochondral junctions and depression of the sternum are other typical features (Fig. 68.1). The angulation of scorbutic beads is usually sharper than that of a rachitic rosary. Gum changes are seen in older children after teeth have erupted, manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors (Fig. 68.2). **Anemia**, a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies, including iron, vitamin B_{12}, and folate. Hemorrhagic manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the characteristic perifollicular hemorrhages (Fig. 68.3). Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.

Laboratory Findings and Diagnosis

The diagnosis of vitamin C deficiency is usually based on the characteristic clinical picture, the radiographic appearance of the long bones, and a history of poor vitamin C intake. A high index of suspicion is required in children on restrictive diets, particularly those with autism and other developmental disorders, and they should be evaluated for scurvy whenever they present with difficulty in walking or bone pains. The typical radiographic changes occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of *pencil outlining* of the diaphysis and epiphysis. The *white line of Fränkel,* an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring (Fig. 68.4). The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line at the metaphysis. This zone of rarefaction *(Trümmerfeld zone),* a linear break in the bone that is proximal and parallel to the white line, represents an area of debris of broken-down bone trabeculae and connective tissue. A *Pelkan spur* is a lateral prolongation of the white line and may be present at the cortical ends. Epiphyseal separation can occur along the line of destruction, with either linear displacement or compression of the epiphysis against the shaft (Fig. 68.5). Subperiosteal hemorrhages are not visible using plain radiographs during the active phase of scurvy. However, during healing, the elevated periosteum becomes calcified and radiopaque (see Fig. 68.5), sometimes giving a dumbbell or club shape to the affected bone. MRI can demonstrate both acute and healing subperiosteal hematomas along with periostitis, metaphyseal changes (Fig. 68.4), and heterogeneous bone marrow signal intensity, even in the absence of changes in plain radiographs. Gelatinous transformation of bone marrow on aspiration has been reported in children with suspected malignancy.



Fig. 68.1 Sharp angulation of beading at costochondral junction (scorbutic rosary) in scurvy. (*Courtesy Dr. J.D. MacLean, McGill Centre for Tropical Diseases, Montreal.)*



Fig. 68.2 Clinical photograph showing inflamed marginal gingiva in scurvy. (*From Agarwal A, Shaharyar A, Kumar A, Bhat MS, Mishra M. Scurvy in pediatric age group: a disease often forgotten? J Clin Orthop Trauma. 2015;6:101–107, Fig. 1, p. 103.)*

Biochemical tests are not very useful in the diagnosis of scurvy, because they do not reflect the tissue status. A plasma ascorbate concentration of <0.2 mg/dL usually is considered deficient. Leukocyte concentration of vitamin C is a better indicator of body stores, but this measurement is technically more difficult to perform. Leukocyte concentrations of ≤10 μg/10^8 white blood cells are considered deficient and indicate latent scurvy, even in the absence of clinical signs of deficiency. Saturation of the tissues with vitamin C can be estimated from the urinary excretion of the vitamin after a test dose of ascorbic acid. In healthy children, 80% of the test dose appears in the urine within 3-5 hours after parenteral administration. Generalized nonspecific aminoaciduria is common in scurvy, whereas plasma amino acid levels remain normal.

Differential Diagnosis

Scurvy is often misdiagnosed as infectious or juvenile idiopathic arthritis, osteomyelitis, nonaccidental trauma (child abuse), malignancy, or acrodynia. The early irritability and bone pain are sometimes attributed to nonspecific pains or other nutritional deficiencies. Copper deficiency results in a radiographic picture similar to that of scurvy. Henoch-Schönlein purpura, (IgA vasculitis) thrombocytopenic purpura, or leukemia is sometimes suspected in children presenting with hemorrhagic manifestations.

Treatment

Vitamin C supplements of 100-200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within 1 week in most cases, but the treatment should be continued for up to 3 months for complete recovery.





Fig. 68.3 Scurvy. **A,** Perifollicular hemorrhages. **B,** Corkscrew hairs with perifollicular hyperkeratotic papules. (*Modified from Lipner S. A classic case of scurvy. Lancet. 2018;392[10145]:431.)*

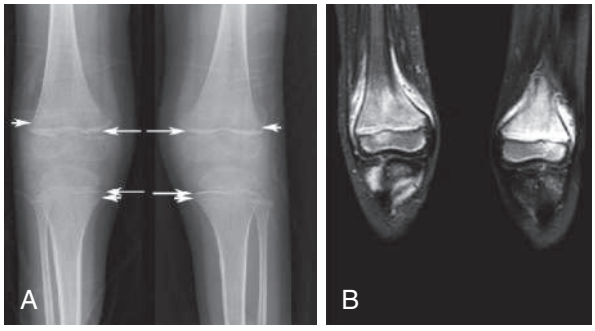

Fig. 68.4 **A,** Radiograph of the knee in scurvy demonstrates a radiodense band at the chondroosseous junction (Fränkel line; *long arrows*) and a translucent band in the metaphysis (Trümmerfeld zone; *short arrows*) of the distal femora and the proximal tibiae. **B,** Magnetic resonance imaging (coronal fat saturation T2-weighted imaging) of the knee demonstrates ill-defined T2 hyperintensities in the metaphyses and juxtaosseous soft tissue. The diaphysis was spared. (*From Seya M, Handa A, Hasegawa D, et al. Scurvy: from a selective diet in children with developmental delay. J Pediatr. 2016;177:331, Fig. A and B, p. 331.)*

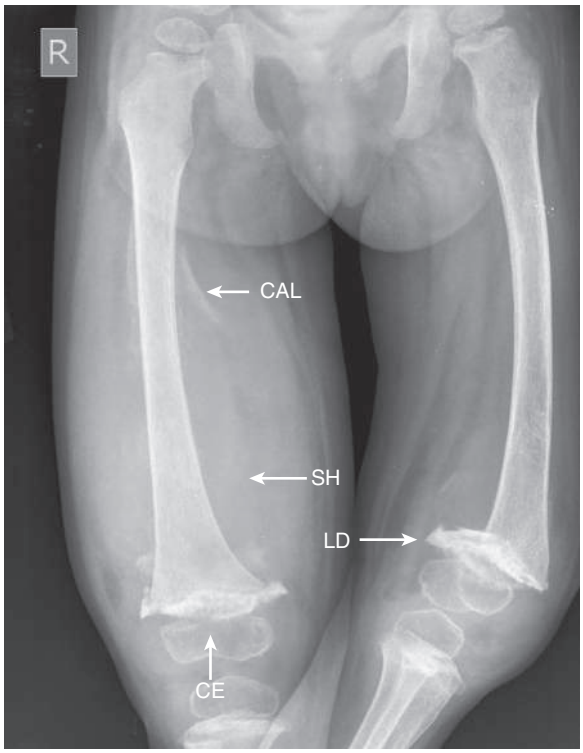

Fig. 68.5 Large subperiosteal hematoma (SH) with areas of calcification (CAL) is seen along the shaft of the right femur of a child with advanced scurvy. Epiphyseal separation is seen in both knees, with linear displacement (LD) in the left knee and compression (CE) against the shaft in the right knee.

Prevention

Breastfeeding protects against vitamin C deficiency throughout infancy. In children consuming milk formula, fortification with vitamin C must be ensured. Children consuming heat-treated milk or plant-based beverages (e.g., almond milk, soy milk) should consume adequate vitamin C–rich foods in infancy. Dietary or medicinal supplements are required in children on restrictive diets deficient in vitamin C, severely malnourished children, and those with chronic debilitating conditions (e.g., malignancies, neurologic disorders). Providing antenatal supplements of vitamin C to smoking mothers may mitigate some of the harmful effects of smoking on fetal and infant lung development and function.

VITAMIN C TOXICITY

Daily intake of <2 g of vitamin C is generally without adverse effects in adults. Larger doses can cause gastrointestinal problems, such as abdominal pain and osmotic diarrhea. Hemolysis has rarely been reported after high doses of ascorbic acid. Megadoses of vitamin C should be avoided in patients with a history of urolithiasis or conditions related to excessive iron accumulation, such as thalassemia and hemochromatosis. Data are sparse regarding vitamin C toxicity in children. The following values for tolerable upper intake levels are extrapolated from data for adults based on body weight differences: ages 1-3 years, 400 mg; 4-8 years, 650 mg; 9-13 years, 1,200 mg; and 14-18 years, 1,800 mg.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 69

Vitamin D Deficiency (Rickets) and Excess

Larry A. Greenbaum

RICKETS

Bone consists of a protein matrix called *osteoid* and a mineral phase, principally composed of calcium and phosphate, mostly in the form of *hydroxyapatite*. **Osteomalacia** occurs with inadequate mineralization of bone osteoid in children and adults. **Rickets** is a disease of growing bone caused by unmineralized matrix at the growth plates in children only before fusion of the epiphyses. Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate, the growth plate thickens. Circumference of the growth plate and metaphysis is also greater, increasing bone width at the growth plates and causing classic clinical manifestations, such as widening of the wrists and ankles. The general softening of the bones causes them to bend easily when subject to forces such as weight bearing or muscle pull. This softening leads to a variety of bone deformities.

Rickets is principally caused by vitamin D deficiency. Although largely corrected through public health measures that provided children with adequate vitamin D, rickets remains a persistent problem in developed countries, especially in children with restrictive diets (autism) or elimination diets (fear of allergies). It remains a significant problem in developing countries and may be secondary to nutritional vitamin D deficiency and inadequate intake of calcium (Table 69.1).

Etiology

There are many causes of rickets, including vitamin D disorders, calcium deficiency, phosphorus deficiency, and distal renal tubular acidosis (Table 69.2).

Clinical Manifestations

Most manifestations of rickets are a result of skeletal changes (Table 69.3). **Craniotabes** is a softening of the cranial bones and can be detected by applying pressure at the occiput or over the parietal bones. The sensation is similar to the feel of pressing into a Ping-Pong ball and then releasing. Craniotabes may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis. It is a normal finding in many newborns, especially near the suture lines, but typically disappears within a few months of birth. Widening of the costochondral junctions results in a **rachitic "rosary,"** which feels like the beads of a rosary as the examiner's fingers move along the costochondral junctions from rib to rib (Fig. 69.1). Growth plate widening is also responsible for the enlargement at the wrists and ankles (Fig. 69.2). The horizontal depression along the lower anterior chest known as the *Harrison groove* occurs from pulling of the softened ribs by the diaphragm during inspiration. Softening of the ribs also impairs air movement and predisposes patients to atelectasis and pneumonia. Valgus or varus deformities of the legs are common; **windswept deformity** occurs when one leg is in extreme valgus and the other is in extreme varus (Fig. 69.3).

The clinical presentation of rickets may vary based on the etiology. Changes in the lower extremities tend to be the dominant feature in X-linked hypophosphatemic rickets. Symptoms secondary to hypocalcemia occur only in those forms of rickets associated with decreased serum calcium.

Table 69.1 Physical and Metabolic Properties and Food Sources of Vitamins D, E, and K

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
VITAMIN D					
Vitamin D3 (3-cholecalciferol), which is synthesized in the skin, and vitamin D2 (from plants or yeast) are biologically equivalent; 1 μg = 40 IU vitamin D	Fat-soluble, stable to heat, acid, alkali, and oxidation; bile necessary for absorption; hydroxylation in the liver and kidney necessary for biologic activity	Necessary for GI absorption of calcium; also increases absorption of phosphate; direct actions on bone, including mediating resorption	Rickets in growing children; osteomalacia; hypocalcemia can cause tetany and seizures	Hypercalcemia, which can cause emesis, anorexia, pancreatitis, hypertension, arrhythmias, CNS effects, polyuria, nephrolithiasis, renal failure	Exposure to sunlight (UV light); fish oils, fatty fish, egg yolks, and vitamin D–fortified formula, milk, cereals, bread
VITAMIN E					
Group of related compounds with similar biologic activities; α-tocopherol is the most potent and most common form	Fat-soluble; readily oxidized by oxygen, iron, rancid fats; bile acids necessary for absorption	Antioxidant; protection of cell membranes from lipid peroxidation and formation of free radicals	Red cell hemolysis in premature infants; posterior column and cerebellar dysfunction; pigmentary retinopathy	Unknown	Vegetable oils, seeds, nuts, green leafy vegetables, margarine
VITAMIN K					
Group of naphthoquinones with similar biologic activities; K_1 (phylloquinone) from diet; K_2 (menaquinones) from intestinal bacteria	Natural compounds are fat-soluble; stable to heat and reducing agents; labile to oxidizing agent, strong acids, alkali, light; bile salts necessary for intestinal absorption	Vitamin K–dependent proteins include coagulation factors II, VII, IX, and X; proteins C, S, Z; matrix Gla protein, osteocalcin	Hemorrhagic manifestations; long-term bone and vascular health	Not established; analogs (no longer used) caused hemolytic anemia, jaundice, kernicterus, death	Green leafy vegetables, liver, certain legumes and plant oils; widely distributed

CNS, Central nervous system; GI, gastrointestinal; UV, ultraviolet.

Table 69.2 Causes of Rickets

VITAMIN D DISORDERS
- Nutritional vitamin D deficiency
- Congenital vitamin D deficiency
- Secondary vitamin D deficiency
- Malabsorption
- Increased degradation
- Decreased liver 25-hydroxylase
- Vitamin D–dependent rickets types 1A and 1B
- Vitamin D–dependent rickets types 2A and 2B
- Chronic kidney disease

CALCIUM DEFICIENCY
- Low intake
  - Diet
  - Premature infants (rickets of prematurity)
- Malabsorption
  - Primary disease
  - Dietary inhibitors of calcium absorption

PHOSPHORUS DEFICIENCY
- Inadequate intake
  - Premature infants (rickets of prematurity)
  - Aluminum-containing antacids

RENAL LOSSES
- X-linked hypophosphatemic rickets*
- Autosomal dominant hypophosphatemic rickets*
- Autosomal recessive hypophosphatemic rickets types 1, 2, and 3*
- Hereditary hypophosphatemic rickets with hypercalciuria
- Hypophosphatemic rickets with nephrolithiasis and osteoporosis types 1 and 2
- Overproduction of fibroblast growth factor-23
  - Tumor-induced rickets*
  - McCune-Albright syndrome*
  - Epidermal nevus syndrome (cutaneous skeletal hypophosphatemia syndrome)*
  - Neurofibromatosis*
  - Fanconi syndrome
  - Dent disease
  - Distal renal tubular acidosis

*Disorders secondary to excess fibroblast growth factor-23.

Table 69.3 Clinical Features of Rickets

GENERAL
- Failure to thrive (malnutrition)
- Listlessness
- Protruding abdomen
- Muscle weakness (especially proximal)
- Hypocalcemic dilated cardiomyopathy
- Fractures (pathologic, minimal trauma)
- Increased intracranial pressure

HEAD
- Craniotabes
- Frontal bossing
- Delayed fontanel closure (usually closed by 2 yr)
- Delayed dentition
  - No incisors by age 10 mo
  - No molars by age 18 mo
- Caries
- Craniosynostosis

CHEST
- Rachitic rosary
- Harrison groove
- Respiratory infections and atelectasis*

BACK
- Scoliosis
- Kyphosis
- Lordosis

EXTREMITIES
- Enlargement of wrists and ankles
- Valgus or varus deformities
- Windswept deformity (valgus deformity of one leg with varus deformity of other leg)
- Anterior bowing of tibia and femur
- Coxa vara
- Leg pain

HYPOCALCEMIC SYMPTOMS†
- Tetany
- Seizures
- Stridor caused by laryngeal spasm

*These features are most frequently associated with the vitamin D deficiency disorders.
†These symptoms develop only in children with disorders that produce hypocalcemia (see Table 69.4).



Fig. 69.1 Rachitic "rosary" in a child with rickets. *(Courtesy Dr. Thomas D. Thacher, Rochester, MN.)*



Fig. 69.2 Hands and forearms of a young child with rickets show prominence above the wrist, resulting from flaring and poor mineralization of lower end of the radius and ulna. *(From Bullough PG. Orthopaedic Pathology, 5th ed. St Louis: Mosby: 2010: Fig 8-31.)*



Fig. 69.3 Windswept deformity of the legs in an older child with rickets. *(From Rickets and osteomalacia. In Hochberg MC, Silman AJ, Smolen JS, et al., eds. Rheumatology, 4th ed. London: Mosby; 2008: Fig 192-6.)*

The chief complaint in a child with rickets is quite variable. Many children present because of skeletal deformities, whereas others have difficulty walking owing to a combination of deformity and weakness. Other common presenting complaints include failure to thrive (malnutrition) and symptomatic hypocalcemia (see Chapters 610-612).

Radiology

Rachitic changes are most easily visualized on posteroanterior radiographs of the wrist, although characteristic rachitic changes can be seen at other growth plates (Figs. 69.4 and 69.5). Decreased calcification leads to thickening of the growth plate. The edge of the metaphysis loses its sharp border, which is described as *fraying*. The edge of the metaphysis changes from a convex or flat surface to a more concave surface. This change to a concave surface is termed *cupping* and is most easily seen at the distal ends of the radius, ulna, and fibula. There is widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

Diagnosis

The diagnosis of rickets is based on the presence of classic radiographic abnormalities. It is supported by physical examination findings, history, and laboratory results consistent with a specific etiology (Table 69.4).

Clinical Evaluation

Because the majority of children with rickets have a nutritional deficiency, the initial evaluation should focus on a **dietary history**, emphasizing intake of both vitamin D and calcium. Most children in industrialized nations receive vitamin D from formula, fortified milk, or vitamin supplements. Along with the amount, the exact composition of the formula or milk is pertinent, because rickets has occurred in children given products that are called "milk" (e.g., soy milk) but are deficient in vitamin D and minerals.

Cutaneous synthesis mediated by sunlight exposure is an important source of vitamin D. It is important to ask about time spent outside, sunscreen use, and clothing, especially if there may be a cultural reason for increased covering of the skin. Because winter sunlight is ineffective at stimulating cutaneous synthesis of vitamin D, the season is an additional consideration. Children with increased skin pigmentation are at increased risk for vitamin D deficiency because of decreased cutaneous synthesis.

The presence of **maternal** risk factors for nutritional vitamin D deficiency, including diet and sun exposure, is an important consideration when a neonate or young infant has rachitic findings, especially if the infant is breastfed (Table 69.5). Determining a child's intake of dairy products, the main dietary source of calcium, provides a general sense of calcium intake. High dietary fiber can interfere with calcium absorption.

The child's **medication** use is relevant, because certain medications, such as the anticonvulsants phenobarbital and phenytoin, increase degradation of vitamin D, and phosphate binders or aluminum-containing antacids interfere with the absorption of phosphate.

Malabsorption of vitamin D is suggested by a history of liver or intestinal disease. Undiagnosed liver or intestinal disease should be suspected if the child has gastrointestinal (GI) symptoms, although occasionally rickets is the presenting complaint. Fat malabsorption is often associated with diarrhea or oily stools, and there may be signs or symptoms suggesting deficiencies of other fat-soluble vitamins (A, E, and K; see Chapters 66, 70, and 71).

A history of **renal disease** (proteinuria, hematuria, urinary tract infections) is an additional significant consideration, given the importance of chronic kidney disease as a cause of rickets. Polyuria can occur in children with chronic kidney disease or Fanconi syndrome.

Children with rickets might have a history of dental caries, poor growth, delayed walking, waddling gait, pneumonia, and hypocalcemic symptoms.

The family history is critical, given the large number of **genetic causes** of rickets, although most of these causes are rare. Along with bone disease, it is important to inquire about leg deformities,

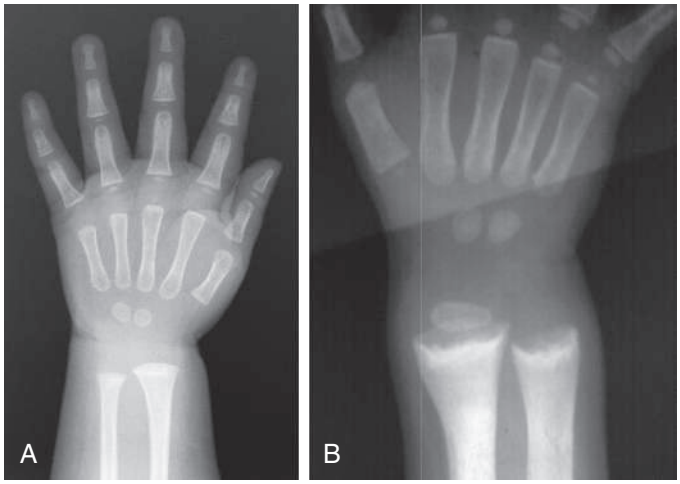

Fig. 69.4 Radiographs of the wrist in normal child (A) and child with rickets (B), who has metaphyseal fraying and cupping of the distal radius and ulna.

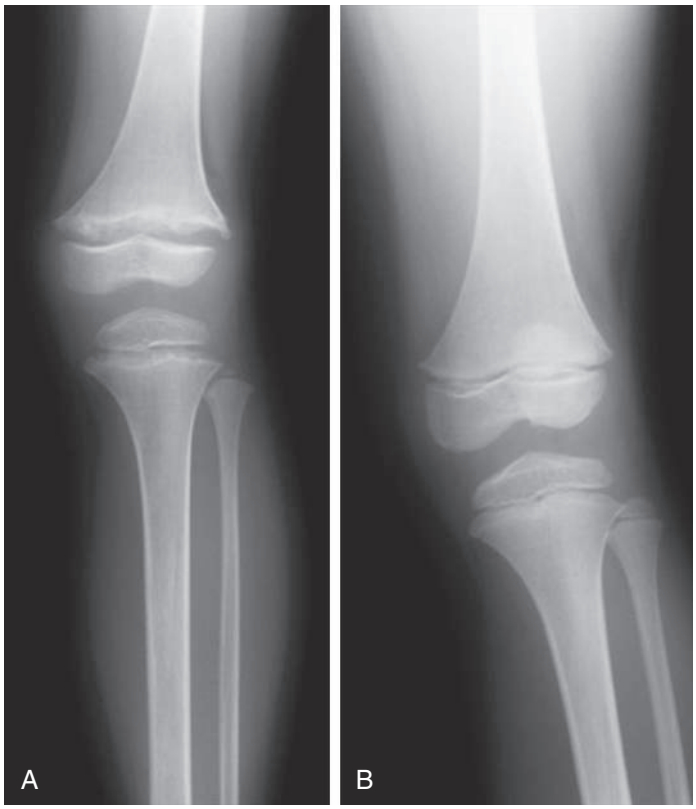

Fig. 69.5 Radiographs of the knees in 7-year-old female with distal renal tubular acidosis and rickets. **A,** At initial presentation, there is widening of the growth plate and metaphyseal fraying. **B,** Dramatic improvement after 4 months of therapy with alkali.

Table 69.4 Laboratory Findings in Various Disorders Causing Rickets

DISORDER	Ca	Pi	PTH	25-(OH)D	1,25-$(OH)_2$D	ALP	URINE Ca	URINE Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
VDDR, type 1A	N, ↓	↓	↑	N	↓	↑	↓	↑
VDDR, type 1B	N, ↓	↓	↑	↓	N	↑	↓	↑
VDDR, type 2A	N, ↓	↓	↑	N	↑↑	↑	↓	↑
VDDR, type 2B	N, ↓	↓	↑	N	↑↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
XLH*	N	↓	N, ↑	N	RD	↑	↓	↑
ADHR*	N	↓	N	N	RD	↑	↓	↑
HHRH	N	↓	N, ↓	N	↑	↑	↑	↑
ARHR, type 1 or type 2*	N	↓	N	N	RD	↑	↓	↑
Tumor-induced rickets†	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dent's disease	N	↓	N	N	N	↑	↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

*Elevated fibroblast growth factor-23 (FGF-23).
†FGF-23 elevated in some patients.
ADHR, Autosomal dominant hypophosphatemic rickets; ALP, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ↓, decreased; ↑, increased; ↑↑, extremely increased.

Table 69.5 Risk Factors for Nutritional Rickets and Osteomalacia and Their Prevention

MATERNAL FACTORS
Vitamin D deficiency
Dark skin pigmentation
Full body clothing cover
High latitude during winter/spring season
Other causes of restricted sun (UVB) exposure (e.g., predominant indoor living, disability, pollution, cloud cover)
Low–vitamin D diet
Low-calcium diet
Poverty, malnutrition, special diets
INFANT/CHILDHOOD FACTORS
Neonatal vitamin D deficiency secondary to maternal deficiency/vitamin D deficiency
Lack of infant supplementation with vitamin D
Prolonged breastfeeding without appropriate complementary feeding from 6 mo
High latitude during winter/spring season
Dark skin pigmentation and/or restricted sun (UVB) exposure (e.g., predominant indoor living, disability, pollution, cloud cover)
Avoidant restrictive food intake disorder
Low–vitamin D diet
Low-calcium diet
Poverty, malnutrition, special diets
PREVENTIVE MEASURES
Sun exposure (UVB content of sunlight depends on latitude and season)
Vitamin D supplementation
Strategic fortification of the habitual food supply
Normal calcium intake

Adapted from Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab.* 2016;101:394–415, p. 401.

difficulties with walking, or unexplained short stature, because some parents may be unaware of their diagnosis. Undiagnosed disease in the mother is not unusual in X-linked hypophosphatemia. A history of an unexplained sibling death during infancy may be present in the child with cystinosis, the most common cause of Fanconi syndrome in children.

The physical examination focuses on detecting manifestations of rickets (see Table 69.3). It is important to observe the child's gait, auscultate the lungs to detect atelectasis or pneumonia, and plot the patient's growth. *Alopecia* suggests vitamin D–dependent rickets type 2.

The initial **laboratory tests** in a child with rickets should include serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D (1,25-D), creatinine, and electrolytes (see Table 69.4 for interpretation). Urinalysis is useful for detecting the glycosuria seen with Fanconi syndrome. Evaluation of urinary excretion of calcium (24-hour collection for calcium or calcium:creatinine ratio) is helpful if hereditary hypophosphatemic rickets with hypercalciuria or Dent disease is suspected. Direct measurement of other fat-soluble vitamins (A, E, and K) or indirect assessment of deficiency (prothrombin time for vitamin K deficiency) is appropriate if malabsorption is a consideration.

VITAMIN D DISORDERS

Vitamin D Physiology

Vitamin D can be synthesized in skin epithelial cells and therefore technically is not a vitamin. Cutaneous synthesis is normally the most important source of vitamin D and depends on the conversion of 7-dehydrocholesterol to vitamin D3 (3-cholecalciferol) by ultraviolet B (UVB) radiation from the sun. The efficiency of this process is decreased by melanin; therefore more sun exposure is necessary for vitamin D synthesis in people with increased skin pigmentation. Measures to decrease sun exposure, such as covering the skin with clothing or applying sunscreen, also decrease vitamin D synthesis. Children who spend less time outside have reduced vitamin D synthesis. The winter sun away from the equator is ineffective at stimulating vitamin D synthesis.

There are few natural dietary sources of vitamin D. Fish liver oils have a high vitamin D content. Other good dietary sources include fatty fish and egg yolks. Most children in industrialized countries receive vitamin D via fortified foods, especially formula and milk (both of which contain 400 IU/L) and some breakfast cereals and breads. Supplemental vitamin D may be vitamin D2 (which comes from plants or yeast) or vitamin D3. Breast milk has a low vitamin D content, approximately 12-60 IU/L.

Vitamin D is transported bound to vitamin D–binding protein to the liver, where 25-hydroxlase converts vitamin D into 25-hydroxyvitamin D (25-D), the most abundant circulating form of vitamin D. Because there is little regulation of this liver hydroxylation step, measurement of 25-D is the standard method for determining a patient's vitamin D status. The final step in activation occurs in the kidney, where the enzyme 1α-hydroxylase adds a second hydroxyl group, resulting in 1,25-D. The 1α-hydroxylase is upregulated by PTH and hypophosphatemia and inhibited by hyperphosphatemia and 1,25-D. Most 1,25-D circulates bound to vitamin D–binding protein.

1,25-Dihydroxyvitamin D acts by binding to an intracellular receptor, and the complex affects gene expression by interacting with vitamin D response elements. In the intestine, this binding results in a marked increase in calcium absorption, which is highly dependent on 1,25-D. There is also an increase in phosphorus absorption, but this effect is less significant because most dietary phosphorus absorption is vitamin D independent. 1,25-D also has direct effects on bone, including mediating resorption. 1,25-D directly suppresses PTH secretion by the parathyroid gland, thus completing a negative feedback loop. PTH secretion is also suppressed by the increase in serum calcium mediated by 1,25-D. 1,25-D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.

Nutritional Vitamin D Deficiency

Vitamin D deficiency remains the most common cause of rickets globally and even occurs in industrialized countries. Because vitamin D can be obtained from dietary sources or from cutaneous synthesis, most patients in industrialized countries have a combination of risk factors that lead to vitamin D deficiency.

Etiology

Vitamin D deficiency most frequently occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the first or second months of life unless there is severe maternal vitamin D deficiency. Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis. Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements. Cutaneous synthesis can be limited because of the ineffectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices; and decreased cutaneous synthesis because of increased skin pigmentation.

The effect of skin pigmentation explains why most cases of nutritional rickets in the United States and Northern Europe occur in breastfed children of African descent or other dark-pigmented populations. The additional impact of the winter sun is supported by such infants more often presenting in the late winter or spring. In some groups, complete covering of infants or the practice of not taking infants outside has a significant role, explaining the occurrence of rickets in infants living in areas of abundant sunshine, such as the Middle East. Because the mothers of some infants can

have the same risk factors, decreased maternal vitamin D can also contribute, both by leading to reduced vitamin D content in breast milk and by lessening transplacental delivery of vitamin D. Rickets caused by vitamin D deficiency can also be secondary to dietary practices, such as vegan diets that use unfortified soy milk or rice milk. Children with restrictive food habits (autism) or food elimination diets (fear of allergies) may be at risk for vitamin D deficiency.

Clinical Manifestations

The clinical features are typical of rickets (see Table 69.3), with a significant minority presenting with symptoms of hypocalcemia. Prolonged laryngospasm is occasionally fatal. These children have an increased risk of pneumonia and muscle weakness leading to a delay in motor development.

Laboratory Findings

Table 69.4 summarizes the principal laboratory findings. Hypocalcemia is a variable finding because the elevated PTH acts to increase the serum calcium concentration. The hypophosphatemia is caused by PTH-induced renal losses of phosphate, combined with a decrease in intestinal absorption.

The wide variation in 1,25-D levels (low, normal, or high) is secondary to the upregulation of renal 1α-hydroxylase caused by concomitant hypophosphatemia and hyperparathyroidism. Because serum levels of 1,25-D are much lower than the levels of 25-D, even with low levels of 25-D, there is often enough 25-D still present to act as a precursor for 1,25-D synthesis in the presence of upregulated 1α-hydroxylase. The level of 1,25-D is only low when there is severe vitamin D deficiency.

Some patients have a metabolic acidosis secondary to PTH-induced renal bicarbonate wasting. There may also be generalized aminoaciduria.

Diagnosis and Differential Diagnosis

The diagnosis of nutritional vitamin D deficiency is based on the combination of a history of poor vitamin D intake and risk factors for decreased cutaneous synthesis, radiographic changes consistent with rickets, and typical laboratory findings (see Table 69.4). A normal PTH level almost never occurs with vitamin D deficiency and suggests a primary phosphate disorder.

Treatment

Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus. There are two strategies for administration of vitamin D. With **stoss therapy**, vitamin D (300,000-600,000 IU) is administered orally (preferred) or intramuscularly as 2-4 doses over 1 day (vitamin D3 is preferred to D2 because of the longer half-life of D3). Because the doses are observed, stoss therapy is ideal in patients in whom adherence to therapy is questionable. The alternative strategy is daily vitamin D with a minimum dose of 2,000 IU/day for a minimum of 3 months. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 year old or 600 IU/day if >1 year old. It is important to ensure that children receive adequate dietary calcium (minimum of 500 mg/day) and phosphorus; this dietary intake is usually provided by milk, formula, and other dairy products, although calcium supplements may be needed in some patients.

Children who have symptomatic hypocalcemia might need intravenous (IV) calcium acutely, followed by oral calcium supplements, which typically can be tapered over 2-6 weeks in children who receive adequate dietary calcium. Transient use of IV or oral 1,25-D (**calcitriol**) is often helpful in reversing hypocalcemia in the acute phase by providing active vitamin D during the delay, as supplemental vitamin D is converted to active vitamin D. Calcitriol doses are typically 0.05 μg/kg/day. IV calcium is initially given as an acute bolus for symptomatic hypocalcemia (20 mg/kg calcium chloride or 100 mg/kg calcium gluconate). Some patients require a continuous IV calcium drip, titrated to maintain the desired serum calcium level. These patients should transition to enteral calcium, and most infants require approximately 1,000 mg of elemental calcium.

Prognosis

Most children with nutritional vitamin D deficiency have an excellent response to treatment, with radiologic healing occurring within a few months. Laboratory test results should also normalize rapidly. Many of the bone malformations improve dramatically, but children with severe disease can have permanent deformities and short stature. Rarely, patients benefit from orthopedic intervention for leg deformities, although this is generally not done until the metabolic bone disease has healed, there is clear evidence that the deformity will not self-resolve, and the deformity is causing functional problems.

Prevention

Most cases of nutritional rickets can be prevented by universal administration of 400 IU of vitamin D to infants <1 year old. Older children with risk factors for inadequate intake should receive 600 IU/day. Vitamin D may be administered as a component of a multivitamin or as a vitamin D supplement.

Congenital Vitamin D Deficiency

Congenital rickets is quite rare in industrialized countries and occurs when there is severe maternal vitamin D deficiency during pregnancy. Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies. These newborns can have symptomatic hypocalcemia, intrauterine growth restriction, and decreased bone ossification, along with classic rachitic changes (craniotabes, large fontanelle, fractures). In addition, neonates with congenital rickets may have bone pain, weakness, elevated PTH and ALP levels, and hypocalcemia with low serum 25-hydroxyvitamin D levels. Subtler maternal vitamin D deficiency can have an adverse effect on neonatal bone density and birthweight, cause a defect in dental enamel, and predispose infants to neonatal hypocalcemic tetany. Treatment of congenital rickets includes vitamin D supplementation and adequate intake of calcium and phosphorus. Use of prenatal vitamins containing vitamin D (600 IU) prevents this entity.

Secondary Vitamin D Deficiency

Etiology

Along with inadequate intake, vitamin D deficiency can result from inadequate absorption, decreased hydroxylation in the liver, and increased degradation. Because vitamin D is fat soluble, its absorption may be decreased in patients with a variety of liver and GI diseases, including cholestatic liver disease, defects in bile acid metabolism, cystic fibrosis and other causes of pancreatic dysfunction, celiac disease, and Crohn disease. Malabsorption of vitamin D can also occur with intestinal lymphangiectasia and after intestinal resection.

Severe liver disease, which usually is also associated with malabsorption, can cause a decrease in 25-D formation as a result of insufficient enzyme activity. Because of the large reserve of 25-hydroxlase activity in the liver, vitamin D deficiency caused by liver disease usually requires a loss of >90% of liver function. A variety of medications increase the degradation of vitamin D by inducing the cytochrome P450 (CYP) system. Rickets from vitamin D deficiency can develop in children receiving anticonvulsants (e.g., phenobarbital, phenytoin) or antituberculosis medications (e.g., isoniazid, rifampin).

Treatment

Treatment of vitamin D deficiency attributable to malabsorption requires high doses of vitamin D. Because of its better absorption, 25-D (25-50 μg/day or 5-7 μg/kg/day) is superior to vitamin D3. The dose is adjusted based on monitoring of serum levels of 25-D. Alternatively,

patients may be treated with 1,25-D, which also is better absorbed in the presence of fat malabsorption, or with parenteral vitamin D. Children with rickets as a result of increased degradation of vitamin D by the CYP system require the same acute therapy as indicated for nutritional deficiency (discussed earlier), followed by long-term administration of high doses of vitamin D (e.g., 1,000 IU/day), with dosing titrated based on serum levels of 25-D. Some patients require as much as 4,000 IU/day.

Vitamin D–Dependent Rickets, Type 1

Children with vitamin D–dependent rickets **type 1A**, an autosomal recessive disorder, have pathologic gene variants in *CYP27B,* which encodes the renal 1α-hydroxylase, preventing conversion of 25-D into 1,25-D. These patients normally present during the first 2 years of life and can have any of the classic features of rickets (see Table 69.3), including symptomatic hypocalcemia. They have normal levels of 25-D but low levels of 1,25-D (see Table 69.4). Occasionally, 1,25-D levels are at the lower limit of normal, inappropriately low given the high PTH and low serum phosphorus levels, both of which should increase the activity of renal 1α-hydroxylase and cause elevated levels of 1,25-D. As in nutritional vitamin D deficiency, renal tubular dysfunction can cause a metabolic acidosis and generalized aminoaciduria.

Vitamin D–dependent rickets **type 1B** is secondary to pathologic variants in the gene (*CYP2R1*) for the principal 25-hydroxylase. Patients have low levels of 25-D but normal levels of 1,25-D (see Table 69.4).

Treatment

Vitamin D–dependent rickets type 1A responds to long-term treatment with 1,25-D (calcitriol). Initial doses are 0.25-2 μg/day, and lower doses are used once the rickets has healed. Especially during initial therapy, it is important to ensure adequate intake of calcium. The dose of calcitriol is adjusted to maintain a low-normal serum calcium level, a normal serum phosphorus level, and a high-normal serum PTH level. Targeting a low-normal calcium concentration and a high-normal PTH level avoids excessive dosing of calcitriol, which can cause hypercalciuria and nephrocalcinosis. Therefore patient monitoring includes periodic assessment of urinary calcium excretion, with a target of <4 mg/kg/day.

Vitamin D–dependent rickets type 1B may respond to pharmacologic doses of vitamin D2 (3,000 U/day) as a result of alternative enzymes with 25-hydroxylase activity or residual activity of the abnormal protein.

Vitamin D–Dependent Rickets, Type 2

Patients with vitamin D–dependent rickets **type 2A** have pathologic variants in *VDR,* the gene encoding the vitamin D receptor, preventing a normal physiologic response to 1,25-D. Levels of 1,25-D are extremely elevated in this autosomal recessive disorder (see Table 69.4). Most patients present during infancy, although rickets in less severely affected patients might not be diagnosed until adulthood. Less severe disease is associated with a partially functional vitamin D receptor. Approximately 50–70% of children have **alopecia**, which tends to be associated with a more severe form of the disease and can range from alopecia areata to alopecia totalis. Epidermal cysts are a less common manifestation.

Vitamin D–dependent rickets **type 2B** appears to result from overexpression of a hormone response element–binding protein that interferes with the actions of 1,25-D. Alopecia may be present.

Treatment

Some patients respond to extremely high doses of vitamin D2 (25-D or 1,25-D), especially patients without alopecia. This response is caused by a partially functional vitamin D receptor in patients with vitamin D–dependent rickets type 2A, but may also occur in vitamin D–dependent rickets type 2B. All patients should be given a 3- to 6-month trial of high-dose vitamin D and oral calcium. The initial dose of 1,25-D should be 2 μg/day, but some patients require doses as high as 50-60 μg/day. Calcium doses are 1,000-3,000 mg/day. Patients who do not respond to high-dose vitamin D may be treated with long-term IV calcium, with possible transition to very high-dose oral calcium supplements. Treatment of patients who do not respond to vitamin D is difficult.

Chronic Kidney Disease

With chronic kidney disease, there is decreased activity of 1α-hydroxylase in the kidney, leading to diminished production of 1,25-D. In chronic kidney disease, unlike the other causes of vitamin D deficiency, patients have hyperphosphatemia as a result of decreased renal excretion (see Table 69.4 and Chapter 572.2).

Treatment

Therapy requires the use of a form of vitamin D that can act without 1-hydroxylation by the kidney (calcitriol), which both permits adequate absorption of calcium and directly suppresses the parathyroid gland. Because hyperphosphatemia is a stimulus for PTH secretion, normalization of the serum phosphorus level through a combination of dietary phosphorus restriction and use of oral phosphate binders is as important as the use of activated vitamin D.

CALCIUM DEFICIENCY

Pathophysiology

Rickets secondary to inadequate dietary calcium is a significant problem in some countries in Africa, although there are cases in other regions of the world, including industrialized countries. Because breast milk and formula are excellent sources of calcium, this form of rickets develops after children have been weaned from breast milk or formula and is more likely to occur in children who are weaned early. Rickets develops because the diet has low calcium content, typically <200 mg/day if <12 months old or <300 mg/day if >12 months old. The child has minimal intake of dairy products or other sources of calcium. In addition, because of reliance on grains and green leafy vegetables, the diet may be high in phytate, oxalate, and phosphate, which decrease absorption of dietary calcium. In industrialized countries, rickets caused by calcium deficiency can occur in children who consume an unconventional diet. Examples include children with milk allergy who have low dietary calcium and children who transition from formula or breast milk to juice, soda, or a calcium-poor soy drink, without an alternative source of dietary calcium.

This type of rickets can develop in children who receive IV nutrition without adequate calcium. Malabsorption of calcium can occur in celiac disease, intestinal abetalipoproteinemia, and after small bowel resection. There may be concurrent malabsorption of vitamin D.

Clinical Manifestations

Children with calcium deficiency have the classic signs and symptoms of rickets (see Table 69.3). Presentation can occur during infancy or early childhood, although some cases are diagnosed in teenagers. Because calcium deficiency occurs after the cessation of breastfeeding, it tends to occur later than the nutritional vitamin D deficiency that is associated with breastfeeding. In Nigeria, nutritional vitamin D deficiency is most common at 4-15 months of age, whereas calcium deficiency rickets typically occurs at 15-25 months.

Diagnosis

Laboratory findings include increased levels of ALP, PTH, and 1,25-D (see Table 69.4). Calcium levels may be normal or low, although symptomatic hypocalcemia is uncommon. There is decreased urinary excretion of calcium, and serum phosphorus levels may be low as a result of renal wasting of phosphate from secondary hyperparathyroidism. In some children, there is coexisting nutritional vitamin D deficiency, with low 25-D levels.

Treatment

Treatment focuses on providing adequate calcium, typically as a dietary supplement (doses of 700 [age 1-3 years], 1,000 [4-8 years],

and 1,300 [9-18 years] mg/day of elemental calcium are effective). Vitamin D supplementation is necessary if there is concurrent vitamin D deficiency (discussed earlier). Prevention strategies include discouraging early cessation of breastfeeding and increasing dietary sources of calcium. In countries such as Kenya, where many children have diets high in cereal with negligible intake of cow's milk, school-based milk programs have been effective in reducing the prevalence of rickets.

PHOSPHORUS DEFICIENCY

Inadequate Intake

With the exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus, because phosphorus is present in most foods. Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease), but if rickets develops, the primary problem is usually malabsorption of vitamin D and/or calcium.

Isolated malabsorption of phosphorus occurs in patients with long-term use of **aluminum-containing antacids**. These compounds are very effective at chelating phosphate in the GI tract, leading to decreased absorption. This decreased absorption results in hypophosphatemia with secondary osteomalacia in adults and rickets in children. This entity responds to discontinuation of the antacid and short-term phosphorus supplementation.

Fibroblast Growth Factor-23

Fibroblast growth factor-23 (**FGF-23**) is a humoral mediator that decreases renal tubular reabsorption of phosphate and therefore decreases serum phosphorus. FGF-23, synthesized by osteocytes, also decreases the activity of renal 1α-hydroxylase, resulting in a decrease in the production of 1,25-D. Increased levels of FGF-23 cause many of the renal phosphate-wasting diseases (see Table 69.2).

X-Linked Hypophosphatemic Rickets

Among the genetic disorders causing rickets because of hypophosphatemia, X-linked hypophosphatemic rickets (**XLH**) is the most common, with a prevalence of 1/20,000. The defective gene is on the X chromosome, but female carriers are affected, so it is an X-linked–dominant disorder.

Pathophysiology

The pathologic variants are in a gene called *PHEX* because it is a *ph*osphate-regulating gene with homology to *e*ndopeptidases on the *X* chromosome. The product of this gene appears to have an indirect role in inactivating FGF-23. Thus pathologic variants in *PHEX* lead to increased levels of FGF-23. Because the actions of FGF-23 include inhibition of phosphate reabsorption in the proximal tubule, phosphate excretion is increased. FGF-23 also inhibits renal 1α-hydroxylase, leading to decreased production of 1,25-D.

Clinical Manifestations

These patients have rickets, but abnormalities of the lower extremities and poor growth are the dominant features. Delayed dentition and tooth abscesses are also common. Some patients have hypophosphatemia and short stature without clinically evident bone disease.

Laboratory Findings

Patients have high renal excretion of phosphate, hypophosphatemia, and increased ALP; PTH and serum calcium levels are normal (see Table 69.4). Hypophosphatemia normally upregulates renal 1α-hydroxylase and should lead to an increase in 1,25-D, but these patients have low or inappropriately normal levels of 1,25-D.

Treatment

Burosumab is a monoclonal antibody to FGF-23 that is approved for treating XLH in children >1 year, although cost may limit its availability in low-resourced countries. Outcomes are better and side effects decreased when compared with conventional therapy. The dose of burosumab is titrated to normalize the serum phosphorus; it is contraindicated in patients with severe renal impairment.

Conventional treatment is a combination of oral phosphorus and 1,25-D (calcitriol). The daily need for phosphorus supplementation is 1-3 g of elemental phosphorus divided into four or five doses. Frequent dosing helps to prevent prolonged decrements in serum phosphorus because there is a rapid decline after each dose. In addition, frequent dosing decreases diarrhea, a complication of high-dose oral phosphorus. Calcitriol is administered at 30-70 ng/kg/day in two doses.

Complications of conventional treatment occur when there is not an adequate balance between phosphorus supplementation and calcitriol. Excess phosphorus, by decreasing enteral calcium absorption, leads to secondary hyperparathyroidism, with worsening of the bone lesions. In contrast, excess calcitriol causes hypercalciuria and nephrocalcinosis and can even cause hypercalcemia. Therefore laboratory monitoring of treatment includes serum calcium, phosphorus, ALP, PTH, and urinary calcium, as well as periodic renal ultrasound to evaluate patients for nephrocalcinosis. Because of variation in the serum phosphorus level and the importance of avoiding excessive phosphorus dosing, normalization of ALP levels is a more useful method of assessing the therapeutic response than measuring serum phosphorus. For children with significant short stature, growth hormone is an effective option. Children with severe deformities might need osteotomies, but these procedures should be done only when treatment has led to resolution of the bone disease.

Prognosis

The response to therapy is usually good, although frequent dosing can lead to problems with compliance with conventional therapy. Girls generally have less severe disease than boys, probably because of the X-linked inheritance. Short stature can persist despite healing of the rickets. Adults generally do well with less aggressive treatment, and options include burosumab, conventional treatment, and no treatment. Adults with bone pain, poorly healing fractures, or other symptoms improve with treatment.

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets (**ADHR**) is much less common than XLH. There is incomplete penetrance and variable age of onset. Patients with ADHR have a pathologic variant in the gene encoding FGF-23 *(FGF23)*. The pathologic variant prevents degradation of FGF-23 by proteases, leading its level to increase. The actions of FGF-23 include decreased reabsorption of phosphate in the renal proximal tubule, which results in hypophosphatemia, and inhibition of 1α-hydroxylase in the kidney, causing a decrease in 1,25-D synthesis.

In ADHR, as in XLH, abnormal laboratory findings are hypophosphatemia, elevated ALP level, and a low or inappropriately normal 1,25-D level (see Table 69.4). Treatment is similar to the conventional approach with phosphate supplementation and calcitriol used in XLH. However, iron deficiency, which upregulates FGF-23 synthesis, should be corrected if present.

Autosomal Recessive Hypophosphatemic Rickets

Autosomal recessive hypophosphatemic rickets (**ARHR**) **type 1** is an extremely rare disorder caused by pathologic variants in the *DMP1* gene. ARHR **type 2** occurs in patients with pathologic variants in *ENPP1*. Pathologic variants in *ENPP1* also cause generalized arterial calcification of infancy. **Raine syndrome**, also called **ARHR type 3**, is an autosomal recessive disorder caused by pathologic variants in *FAM20C* and is an osteosclerotic bone dysplasia that is often fatal in the neonatal period. However, patients who survive into childhood may develop rickets.

The three types of ARHR are associated with elevated levels of FGF-23, leading to renal phosphate wasting, hypophosphatemia, and low or inappropriately normal levels of 1,25-D. Treatment is similar to the approach used in XLH, although monitoring for arterial calcification is prudent in patients with *ENPP1* pathologic variants.

Hereditary Hypophosphatemic Rickets with Hypercalciuria

Hereditary hypophosphatemic rickets with hypercalciuria (**HHRH**) is a rare disorder that is mainly found in the Middle East.

Pathophysiology

This autosomal recessive disorder is caused by pathologic variants in the gene for a sodium-phosphate co-transporter in the proximal tubule *(SLC34A3)*. The renal phosphate leak causes hypophosphatemia, which then stimulates production of 1,25-D. The high level of 1,25-D increases intestinal absorption of calcium, suppressing PTH. Hypercalciuria ensues as a result of the high absorption of calcium and the low level of PTH, which normally decreases renal excretion of calcium.

Clinical Manifestations

The dominant symptoms of HHRH are rachitic leg abnormalities (see Table 69.3), muscle weakness, and bone pain. Patients can have short stature, with a disproportionate decrease in the length of the lower extremities. The severity of the disease varies, and some family members have no evidence of rickets but have kidney stones secondary to hypercalciuria.

Laboratory Findings

Laboratory findings include hypophosphatemia, renal phosphate wasting, elevated serum ALP levels, and elevated 1,25-D levels. PTH levels are low (see Table 69.4).

Treatment

Therapy for HHRH patients relies on oral phosphorus replacement (1-2.5 g/day of elemental phosphorus in five divided doses). Treatment of the hypophosphatemia decreases serum levels of 1,25-D and corrects the hypercalciuria. The response to therapy is usually excellent, with resolution of pain, weakness, and radiographic evidence of rickets.

Hypophosphatemic Rickets with Nephrolithiasis and Osteoporosis Types 1 and 2

Hypophosphatemic rickets with nephrolithiasis and osteoporosis type 1 is an autosomal recessive disorder caused by pathologic variants of *SL34A1,* which encodes a phosphate transporter in the proximal tubule. Pathologic variants in the same gene can also cause Fanconi syndrome and infantile hypercalcemia. Hypophosphatemic rickets with nephrolithiasis and osteoporosis type 2 is an autosomal dominant disorder resulting from pathologic variants in *SLC9A3R1* that cause renal phosphate wasting. Laboratory findings and treatment for these disorders are similar to HHRH, with the exception of the features of Fanconi syndrome (see later and Chapter 569) in some patients with the type 1 disorder.

Overproduction of FGF-23

Tumor-induced osteomalacia is more common in adults; in children it can produce classic rachitic findings. Most tumors are mesenchymal in origin and are usually benign, small, and located in bone. These tumors secrete FGF-23 and produce a biochemical phenotype similar to XLH, including urinary phosphate wasting, hypophosphatemia, elevated ALP levels, and low or inappropriately normal 1,25-D levels (see Table 69.4). Curative treatment is excision of the tumor. If the tumor cannot be removed, treatment is identical to that for XLH, including use of burosumab.

Renal phosphate wasting leading to hypophosphatemia and rickets (or osteomalacia in adults) is a potential complication in **McCune-Albright syndrome**, an entity that includes the triad of polyostotic fibrous dysplasia, hyperpigmented macules, and polyendocrinopathy (see Chapter 600.06). Affected patients have inappropriately low levels of 1,25-D and elevated ALP levels. The renal phosphate wasting and inhibition of 1,25-D synthesis are related to the polyostotic fibrous dysplasia. Patients have elevated FGF-23, presumably caused by the dysplastic bone. Hypophosphatemic rickets can also occur in children with isolated polyostotic fibrous dysplasia. Although it is rarely possible, removal of the abnormal bone can cure this disorder in children with McCune-Albright syndrome. Most patients receive the same conventional treatment as children with XLH, with case reports describing off-label treatment with burosumab. Bisphosphonate treatment decreases the pain and fracture risk associated with the bone lesions.

Rickets is an unusual complication of **epidermal nevus syndrome**, which is caused by somatic pathologic variants (Ras family of genes and others). It is called **cutaneous skeletal hypophosphatemia syndrome** when associated with hypophosphatemic rickets or osteomalacia (see Chapter 692). Excessive production of FGF-23 causes renal phosphate wasting and an inappropriately normal or low level of 1,25-D. The timing of presentation with rickets varies from infancy to early adolescence. Hypophosphatemia and rickets have resolved after excision of the epidermal nevi in some patients, but not in others. In most the skin lesions are too extensive to be removed, necessitating treatment with phosphorus supplementation and 1,25-D. Rickets caused by phosphate wasting is an extremely rare complication in children with **neurofibromatosis** (see Chapter 636.1).

Fanconi Syndrome

Fanconi syndrome is secondary to generalized dysfunction of the renal proximal tubule (see Chapter 569.1). There are renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the proximal tubule. Some patients have partial dysfunction, with less generalized losses. The most clinically relevant consequences are hypophosphatemia caused by phosphate losses and proximal renal tubular acidosis caused by bicarbonate losses. Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution. Failure to thrive is a consequence of both rickets and renal tubular acidosis. Treatment is dictated by the etiology (see Chapter 569).

Dent Disease

Dent disease is an X-linked disorder usually caused by pathologic variants in the gene encoding a chloride channel expressed in the kidney *(CLCN5)*. Some patients have pathologic variants in the *OCRL1* gene, which can also cause Lowe syndrome (see Chapter 571.3). Affected males have variable manifestations, including hematuria, nephrolithiasis, nephrocalcinosis, rickets, and chronic kidney disease. Almost all patients have low-molecular-weight proteinuria and hypercalciuria. Other, less universal abnormalities are aminoaciduria, glycosuria, hypophosphatemia, and hypokalemia. Rickets occurs in approximately 25% of patients, and it responds to oral phosphorus supplements. Some patients also need 1,25-D, but this treatment should be used cautiously because it can worsen the hypercalciuria.

RICKETS OF PREMATURITY

Rickets in very low birthweight infants has become a significant problem as the survival rate for this group of infants has increased (see Chapter 119.2).

Pathogenesis

The transfer of calcium and phosphorus from mother to fetus occurs throughout pregnancy, but 80% occurs during the third trimester. Premature birth interrupts this process, with rickets developing when the premature infant does not have an adequate supply of calcium and phosphorus to support mineralization of the growing skeleton.

Most cases of rickets of prematurity occur in infants with a birthweight <1,000 g. It is more likely to develop in infants with lower

birthweight and younger gestational age. Rickets occurs because unsupplemented breast milk and standard infant formula do not contain enough calcium and phosphorus to supply the needs of the premature infant. Other risk factors include cholestatic jaundice, a complicated neonatal course, prolonged use of parenteral nutrition, the use of soy formula, and medications such as diuretics and corticosteroids.

Clinical Manifestations

Rickets of prematurity occurs 1-4 months after birth. Infants can have nontraumatic fractures, especially of the legs, arms, and ribs. Most fractures are not suspected clinically. Because fractures and softening of the ribs lead to decreased chest compliance, some infants have respiratory distress from atelectasis and poor ventilation. This rachitic respiratory distress usually develops >5 weeks after birth, distinguishing it from the early-onset respiratory disease of premature infants. These infants have poor linear growth, with negative effects on growth persisting beyond 1 year of age. An additional long-term effect is enamel hypoplasia. Poor bone mineralization can contribute to dolichocephaly. There may be classic rachitic findings, such as frontal bossing, rachitic rosary (see Fig. 69.1), craniotabes, and widened wrists and ankles (see Table 69.3). Most infants with rickets of prematurity have no clinical manifestations, and the diagnosis is based on radiographic and laboratory findings.

Laboratory Findings

Because of inadequate intake, the serum phosphorus level is low or low-normal in patients with rickets of prematurity. The renal response is appropriate, with conservation of phosphate leading to a low urine phosphate level; tubular reabsorption of phosphate is >95%. Most patients have normal levels of 25-D unless there has been inadequate intake or poor absorption (discussed earlier). The hypophosphatemia stimulates renal 1α-hydroxylase, so levels of 1,25-D are high or high-normal. These high levels can contribute to bone demineralization because 1,25-D stimulates bone resorption. Serum levels of calcium are low, normal, or high, and patients often have hypercalciuria. Elevated serum calcium levels and hypercalciuria are secondary to increased intestinal absorption and bone dissolution caused by elevated 1,25-D levels and inability to deposit calcium in bone because of an inadequate phosphorus supply. The hypercalciuria indicates that phosphorus is the limiting nutrient for bone mineralization, although increased provision of phosphorus alone often cannot correct the mineralization defect; increased calcium is also necessary. Thus there is an inadequate supply of calcium and phosphorus, but the deficiency in phosphorus is greater.

Alkaline phosphatase levels are often elevated, but some affected infants have normal levels. In some cases, normal ALP levels may be secondary to resolution of the bone demineralization because of an adequate mineral supply despite the continued presence of radiologic changes, which take longer to resolve. However, ALP levels may be normal despite active disease. No single blood test is 100% sensitive for the diagnosis of rickets. The diagnosis should be suspected in infants with ALP >5-6 times the upper limit of normal (UL) for adults (unless there is concomitant liver disease) or phosphorus <5.6 mg/dL. The diagnosis is confirmed by radiologic evidence of rickets, which is best seen on radiographs of the wrists and ankles. Films of the arms and legs might reveal fractures. The rachitic rosary may be visible on chest radiograph. Unfortunately, radiographs cannot show early demineralization of bone because changes are not evident until there is >20–30% reduction in the bone mineral content.

Diagnosis

Because many premature infants have no overt clinical manifestations of rickets, screening tests are recommended. These tests should include weekly measurements of calcium, phosphorus, and ALP. Periodic measurement of the serum bicarbonate concentration is also important because metabolic acidosis causes dissolution of bone. At least one screening radiograph for rickets at 6-8 weeks of age is appropriate in infants who are at high risk for it; additional films may be indicated in high-risk infants.

Prevention

Provision of adequate amounts of calcium, phosphorus, and vitamin D significantly decreases the risk of rickets of prematurity. Parenteral nutrition is often necessary initially in very premature infants. In the past, adequate parenteral calcium and phosphorus delivery was difficult because of limits secondary to insolubility of these ions when their concentrations were increased. Current amino acid preparations allow higher concentrations of calcium and phosphate, decreasing the risk of rickets. Early transition to enteral feedings is also helpful. These infants should receive either human milk fortified with calcium and phosphorus or preterm infant formula, which has higher concentrations of calcium and phosphorus than standard formula. Soy formula should be avoided because there is decreased bioavailability of calcium and phosphorus. Increased mineral feedings should continue until the infant weighs 3-3.5 kg. These infants should also receive approximately 400 IU/day of vitamin D through formula and vitamin supplements.

Treatment

Therapy for rickets of prematurity focuses on ensuring adequate delivery of calcium, phosphorus, and vitamin D. If mineral delivery has been good and there is no evidence of healing, it is important to screen for vitamin D deficiency by measuring serum 25-D. Measurement of PTH, 1,25-D, and urinary calcium and phosphorus may be helpful in some cases.

DISTAL RENAL TUBULAR ACIDOSIS

Distal renal tubular acidosis usually manifests with failure to thrive. Patients have a metabolic acidosis with an inability to acidify the urine appropriately. Hypercalciuria and nephrocalcinosis are typically present. The many etiologies include autosomal recessive and autosomal dominant forms. Rickets is variable and responds to alkali therapy (see Fig. 69.5 and Chapter 569.2).

HYPERVITAMINOSIS D

Etiology

Hypervitaminosis D is caused by excessive intake of vitamin D. It can occur with long-term high intake or with a substantial, acute ingestion (see Table 69.1). Most cases are secondary to misuse of prescribed or nonprescription vitamin D supplements, but other cases have been secondary to accidental overfortification of milk, contamination of table sugar, and inadvertent use of vitamin D supplements as cooking oil. The recommended upper limits for long-term vitamin D intake are 1,000 IU for children <1 year old and 2,000 IU for older children and adults.

Hypervitaminosis D can also result from excessive intake of synthetic vitamin D analogs (25-D, 1,25-D). Vitamin D intoxication is never secondary to excessive exposure to sunlight, probably because ultraviolet irradiation can transform vitamin D3 and its precursor into inactive metabolites.

Pathogenesis

Although vitamin D increases intestinal absorption of calcium, the dominant mechanism of the hypercalcemia is excessive bone resorption.

Clinical Manifestations

The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia. GI manifestations include nausea, vomiting, poor feeding, constipation, abdominal pain, and pancreatitis.

Possible cardiac findings are hypertension, decreased QT interval, and arrhythmias. The central nervous system effects of hypercalcemia include lethargy, hypotonia, confusion, disorientation, depression, psychosis, hallucinations, and coma. Hypercalcemia impairs renal concentrating mechanisms, which can lead to polyuria, dehydration, and hypernatremia. Hypercalcemia can also lead to acute kidney injury, nephrolithiasis, and nephrocalcinosis, which can result in chronic kidney disease. Deaths are usually associated with arrhythmias or dehydration.

Laboratory Findings

The classic findings in vitamin D intoxication are hypercalcemia, elevated levels of 25-D (>100 ng/mL), hypercalciuria, and suppressed PTH. Hyperphosphatemia is also common. Hypercalciuria can lead to nephrocalcinosis, which is visible on renal ultrasound. Hypercalcemia and nephrocalcinosis can lead to renal insufficiency.

Surprisingly, levels of 1,25-D are usually normal. This may result from downregulation of renal 1α-hydroxylase by the combination of low PTH, hyperphosphatemia, and a direct effect of 1,25-D. The level of free 1,25-D may be high because of displacement from vitamin D–binding proteins by 25-D. Anemia is sometimes present; the mechanism is unknown.

Diagnosis and Differential Diagnosis

The diagnosis is based on the presence of hypercalcemia and an elevated serum 25-D level, although children with excess intake of 1,25-D or another synthetic vitamin D preparation have normal levels of 25-D. With careful sleuthing, there is usually a history of excess intake of vitamin D, although in some situations (overfortification of milk by a dairy), the patient and family may be unaware.

The differential diagnosis of vitamin D intoxication focuses on **other causes of hypercalcemia**. Hyperparathyroidism produces hypophosphatemia, whereas vitamin D intoxication usually causes hyperphosphatemia. Williams syndrome is often suggested by phenotypic features and accompanying cardiac disease. Idiopathic infantile hypercalcemia occurs in children taking appropriate doses of vitamin D. Subcutaneous fat necrosis is a common cause of hypercalcemia in young infants; skin findings are usually present. The hypercalcemia of familial benign hypocalciuric hypercalcemia is mild, asymptomatic, and associated with hypocalciuria. Hypercalcemia of malignancy is an important consideration. Hypercalcemia may occur on a ketogenic diet. High intake of calcium can also cause hypercalcemia, especially in the presence of renal insufficiency. Inquiring about calcium intake should be part of the history in a patient with hypercalcemia. Occasionally, patients are intentionally taking high doses of calcium and vitamin D.

Treatment

The treatment of vitamin D intoxication focuses on control of hypercalcemia. Many patients with hypercalcemia are dehydrated as a result of polyuria from nephrogenic diabetes insipidus, poor oral intake, and vomiting. Rehydration lowers the serum calcium level by dilution and corrects prerenal azotemia. The resultant increased urine output increases urinary calcium excretion. Urinary calcium excretion is also increased by high urinary sodium excretion. The mainstay of the initial treatment is aggressive therapy with normal saline, often in conjunction with a loop diuretic to further increase calcium excretion; this is often adequate for treating mild or moderate hypercalcemia. More significant hypercalcemia usually requires other therapies. Glucocorticoids decrease intestinal absorption of calcium by blocking the action of 1,25-D. There is also a decrease in the levels of 25-D and 1,25-D. The usual dosage of prednisone is 1-2 mg/kg/24 hr.

Calcitonin, which lowers calcium by inhibiting bone resorption, is a useful adjunct, but its effect is usually not dramatic. There is an excellent response to IV or oral bisphosphonates in vitamin D intoxication. Bisphosphonates inhibit bone resorption through their effects on osteoclasts. Hemodialysis using a low or zero dialysate calcium can rapidly lower serum calcium in patients with severe hypercalcemia that is refractory to other measures.

Along with controlling hypercalcemia, it is imperative to eliminate the source of excess vitamin D. Additional sources of vitamin D such as multivitamins and fortified foods should be eliminated or reduced. Avoidance of sun exposure, including the use of sunscreen, is prudent. The patient should also restrict calcium intake.

Prognosis

Most children make a full recovery, but hypervitaminosis D may be fatal or can lead to chronic kidney disease. Because vitamin D is stored in fat, levels can remain elevated for months, necessitating regular monitoring of 25-D, serum calcium, and urine calcium.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 70

Vitamin E Deficiency

Larry A. Greenbaum

Vitamin E is a fat-soluble vitamin and functions as an antioxidant, but its precise biochemical functions are not known. Vitamin E deficiency can cause hemolysis or neurologic manifestations and occurs in premature infants, in patients with malabsorption, and in an autosomal recessive disorder affecting vitamin E transport. Because of its role as an antioxidant, there is considerable research on vitamin E supplementation in chronic illnesses.

PATHOGENESIS

The term *vitamin E* denotes a group of 8 compounds with similar structures and antioxidant activity. The most potent member of these compounds is α-**tocopherol**, which is also the main form in humans. The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine (see Table 69.1).

The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals. Other antioxidants, such as ascorbic acid, enhance the antioxidant activity of vitamin E. The importance of other functions of vitamin E is still being delineated.

Premature infants are particularly susceptible to vitamin E deficiency because there is significant transfer of vitamin E during the last trimester of pregnancy. Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis, potentially causing anemia. The risk of symptomatic vitamin E deficiency was increased by the use of formulas for premature infants that had a high content of polyunsaturated fatty acids (PUFAs). These formulas led to a high content of PUFAs in red blood cell membranes, making them more susceptible to oxidative stress, which could be ameliorated by vitamin E. Oxidative stress was augmented by aggressive use of iron supplementation; iron increases the production of oxygen radicals. The incidence of hemolysis as a result of vitamin E deficiency in premature infants decreased secondary to the use of formulas with a lower content of PUFAs, less aggressive use of iron, and provision of adequate vitamin E.

Because vitamin E is plentiful in common foods, primary dietary deficiency is rare except in premature infants and in severe, generalized malnutrition. Vitamin E deficiency does occur in children with fat malabsorption secondary to the bile acid needed for vitamin E absorption. Although symptomatic disease is most common in children with cholestatic liver disease, it can occur in patients with

cystic fibrosis, celiac disease, short bowel syndrome, and Crohn disease. The autosomal recessive disorder **abetalipoproteinemia** causes fat malabsorption, and vitamin E deficiency is a common complication (see Chapter 106).

In **ataxia with isolated vitamin E deficiency (AVED)**, a rare autosomal recessive disorder, there are pathologic variants in *TTPA*, the gene for α-tocopherol transfer protein. Patients with this disorder are unable to incorporate vitamin E into lipoproteins before their release from the liver, leading to reduced serum levels of vitamin E. There is no associated fat malabsorption, and absorption of vitamin E from the intestine occurs normally.

CLINICAL MANIFESTATIONS

A severe, progressive neurologic disorder occurs in patients with prolonged vitamin E deficiency. Clinical manifestations do not appear until after 1 year of age, even in children with cholestasis since birth. Patients may have cerebellar disease, posterior column dysfunction, and retinal disease. Loss of deep tendon reflexes is usually the initial finding. Subsequent manifestations include limb ataxia (intention tremor, dysdiadochokinesia), truncal ataxia (wide-based, unsteady gait), dysarthria, ophthalmoplegia (limited upward gaze), nystagmus, decreased proprioception (positive Romberg test), decreased vibratory sensation, and dysarthria. Some patients have pigmentary retinopathy. Visual field constriction can progress to blindness. Cognition and behavior can also be affected. Myopathy and cardiac arrhythmias are less common findings.

In premature infants, hemolysis as a result of vitamin E deficiency typically develops during the second month of life. Edema may also be present.

LABORATORY FINDINGS

Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present. Therefore vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal in older children and adults; <0.6 mg/g is abnormal in infants <1 year. Premature infants with hemolysis caused by vitamin E deficiency also often have elevated platelet counts.

Neurologic involvement can cause abnormal somatosensory evoked potentials and nerve conduction studies. Abnormalities on electroretinography can precede physical examination findings in patients with retinal involvement.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Premature infants with unexplained hemolytic anemia after the first month of life, especially if thrombocytosis is present, either should be empirically treated with vitamin E or should have serum vitamin E and lipid levels measured. Children with neurologic findings and a disease that causes fat malabsorption should have their vitamin E status evaluated.

Because children with AVED do not have symptoms of malabsorption, a correct diagnosis requires a high index of suspicion. **Friedreich ataxia** has been misdiagnosed in some patients (see Chapter 637.1). Children with unexplained ataxia should be screened for vitamin E deficiency.

TREATMENT

For correction of deficiency in neonates, the dose of vitamin E is 25-50 units/day for 1 week, followed by adequate dietary intake. Children with deficiency as a result of malabsorption should receive 1 unit/kg/day, with the dose adjusted based on levels; ongoing treatment is necessary. Children with AVED normalize their serum vitamin E levels with high doses of vitamin E and require ongoing treatment.

PROGNOSIS

The hemolytic anemia in infants resolves with correction of the vitamin E deficiency. Some neurologic manifestations of vitamin E deficiency may be reversible with early treatment, but many patients have little or no improvement. Importantly, treatment prevents progression.

PREVENTION

Premature infants should receive sufficient vitamin E through formula or breast milk fortifier and formula without a high content of PUFAs. Children at risk for vitamin E deficiency as a result of malabsorption should be screened for deficiency and given adequate vitamin E supplementation. Vitamin preparations with high content of all the fat-soluble vitamins are available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 71

Vitamin K Deficiency

Larry A. Greenbaum

Vitamin K is necessary for the synthesis of clotting factors II, VII, IX, and X; deficiency of vitamin K can result in clinically significant bleeding. Vitamin K deficiency typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency can affect long-term bone and vascular health (see Chapters 142 and 529).

PATHOGENESIS

Vitamin K is a group of compounds that have a common naphthoquinone ring structure (see Table 69.1). **Phylloquinone**, called *vitamin K_1*, is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin K_1 is the form used to fortify foods and as a medication in the United States. *Vitamin K_2* is a group of compounds called **menaquinones**, which are produced by intestinal bacteria. There is uncertainty regarding the relative importance of intestinally produced vitamin K_2. Menaquinones are also present in meat, especially liver, and cheese. A menaquinone is used pharmacologically in some countries.

Vitamin K is a cofactor for γ-glutamyl carboxylase, an enzyme that performs posttranslational carboxylation, converting glutamate residues in proteins to **γ-carboxyglutamate (Gla)**. The Gla residues, by facilitating calcium binding, are necessary for protein function.

The classic Gla-containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX, and X. Vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S). Based on the presence of reduced levels of Gla, these proteins appear more sensitive than the coagulation proteins to subtle vitamin K deficiency. Evidence suggests that mild vitamin K deficiency might have a deleterious effect on long-term bone strength and vascular health.

Because it is fat soluble, vitamin K requires the presence of bile salts for its absorption. Unlike other fat-soluble vitamins, there are

limited body stores of vitamin K. In addition, there is high turnover of vitamin K, and the vitamin K–dependent clotting factors have a short half-life. Thus symptomatic vitamin K deficiency can develop within weeks when there is inadequate supply because of low intake or malabsorption.

There are three forms of **vitamin K deficiency bleeding (VKDB)** of the newborn (see Chapter 142). **Early VKDB** was formerly called *classic hemorrhagic disease of the newborn* and occurs at 1-14 days of age. Early VKDB is secondary to low stores of vitamin K at birth as a result of the poor transfer of vitamin K across the placenta and inadequate intake during the first few days of life. In addition, there is no intestinal synthesis of vitamin K_2 because the newborn gut is sterile. Early VKDB occurs mostly in breastfed infants as a consequence of the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

Late VKDB most often occurs at 2-12 weeks of age, although cases can occur up to 6 months after birth. Almost all cases are in breastfed infants because of the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, α_1-antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4-10 per 100,000 newborns.

The third form of VKDB of the newborn occurs **at birth** or shortly thereafter. It is secondary to maternal intake of medications (warfarin, phenobarbital, phenytoin) that cross the placenta and interfere with vitamin K function.

VKDB as a result of fat malabsorption can occur in children of any age. Potential etiologies include cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short bowel syndrome). Prolonged diarrhea can cause vitamin K deficiency, especially in breastfed infants. Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

Beyond infancy, low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin K_2–producing bacteria can cause vitamin K deficiency. This scenario is especially common in the intensive care unit. Vitamin K deficiency can also occur in patients who receive total parenteral nutrition (TPN) without vitamin K supplementation.

CLINICAL MANIFESTATIONS

In early VKDB, the most common sites of bleeding are the gastrointestinal (GI) tract, mucosal and cutaneous tissue, umbilical stump, and the postcircumcision site; intracranial bleeding is less common. GI blood loss can be severe enough to require a transfusion. In contrast, the most common site of bleeding in late VKDB is intracranial, although cutaneous and GI bleeding may be the initial manifestation. Intracranial bleeding can cause convulsions, permanent neurologic sequelae, or death. In some patients with late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive (malnutrition). Older children with vitamin K deficiency can present with bruising, mucocutaneous bleeding, or more serious bleeding.

Laboratory Findings

In patients with bleeding as a result of vitamin K deficiency, the prothrombin time (PT) is prolonged. The PT must be interpreted based on the patient's age because it is normally prolonged in newborns (see Chapters 142 and 524). The partial thromboplastin time (PTT) is usually prolonged, but may be normal in early deficiency. Factor VII has the shortest half-life of the coagulation factors and is the first to be affected by vitamin K deficiency, but isolated factor VII deficiency does not affect PTT. The platelet count and fibrinogen level are normal.

When there is mild vitamin K deficiency, the PT is normal, but there are elevated levels of the undercarboxylated forms of the proteins that are normally carboxylated in the presence of vitamin K. These undercarboxylated proteins are called *proteins induced by vitamin K absence* (PIVKA). Measurement of undercarboxylated factor II (PIVKA-II) can be used to detect mild vitamin K deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels do not always reflect tissue stores.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K, which stops the active bleeding. Other possible causes of bleeding and a prolonged PT include disseminated intravascular coagulation (DIC), liver failure, and rare hereditary deficiencies of clotting factors. DIC, which is usually secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K. Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

Coumarin derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the common anticoagulant **warfarin** or with ingestion of rodent poison, which contains a coumarin derivative. High doses of salicylates also inhibit vitamin K regeneration, potentially leading to a prolonged PT and clinical bleeding.

TREATMENT

Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hours and normalize within 24 hours. For rapid correction in adolescents, the parenteral dose is 2.5-10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh-frozen plasma (FFP), which corrects the coagulopathy rapidly. Children with vitamin K deficiency caused by malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/week to 5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

PREVENTION

Administration of either oral or parenteral vitamin K soon after birth prevents early VKDB of the newborn. In contrast, a single dose of oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular (IM) injection of vitamin K (1 mg), the current practice in the United States, is almost universally effective, except in children with severe malabsorption. This increased efficacy of the IM form is thought to be the result of a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated. Oral vitamin K is a less effective alternative for parents who refuse IM vitamin K, but multiple doses are necessary and rely on home administration.

Discontinuing the offending medications before delivery can prevent VKDB attributable to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If parenteral vitamin K does not correct the coagulopathy rapidly, the child should receive FFP.

Children who are at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 72

Micronutrient Mineral Deficiencies

Larry A. Greenbaum

Micronutrients include vitamins (see Chapters 66-71) and trace elements. By definition, a **trace element** is <0.01% of the body weight. Trace elements have a variety of essential functions (Table 72.1), although the evidence is not always strong (chromium). With the exception of iron deficiency, trace element deficiency is uncommon in developed countries, but some deficiencies (iodine, zinc, selenium) are important public health problems in a number of developing countries. Because of low nutritional requirements and plentiful supply, deficiencies of some of the trace elements are extremely rare in humans and typically occur in patients receiving unusual diets or prolonged total parenteral nutrition without adequate delivery of a specific trace element. Trace element deficiencies can also occur in children with short bowel syndrome or malabsorption. Excess intake of trace elements is uncommon, but can result from environmental exposure or overuse of supplements (see Table 72.1).

For a number of reasons, children are especially susceptible to trace element deficiency. First, growth creates an increased demand for most trace elements. Second, some organs are more likely to sustain permanent damage because of trace element deficiency during childhood. The developing brain is particularly vulnerable to the consequences of certain deficiency states (iron, iodide). Similarly, adequate fluoride is most critical for dental health during childhood. Third, children, especially in the developing world, are more prone to gastrointestinal disorders that can cause trace element deficiencies because of malabsorption.

A normal diet provides adequate intake of most trace elements. However, the intake of certain trace elements varies significantly in different geographic locations. Iodide-containing food is plentiful near the ocean, but inland areas often have inadequate sources, leading to goiter and **hypothyroidism**. **Iodine deficiency** is not a problem in the United States because of the widespread use of iodized salt; however, symptomatic

Table 72.1 Trace Elements

ELEMENT	PHYSIOLOGY	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	DIETARY SOURCES
Chromium	Potentiates the action of insulin	Impaired glucose tolerance, peripheral neuropathy, and encephalopathy	Unknown	Meat, grains, fruits, and vegetables
Copper	Absorbed via specific intestinal transporter Circulates bound to ceruloplasmin Enzyme cofactor (superoxide dismutase, cytochrome oxidase, and enzymes involved in iron metabolism and connective tissue formation)	Microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, depigmentation of hair and skin	Acute: nausea, emesis, abdominal pain, coma, and hepatic necrosis Chronic toxicity (liver and brain injury) occurs in **Wilson disease** (see Chapter 405.2) and secondary to excess intake (see Chapter 405.3)	Vegetables, grains, nuts, liver, margarine, legumes, corn oil
Fluoride	Incorporated into bone	Dental caries (see Chapter 358)	Chronic: dental fluorosis (see Chapter 353)	Toothpaste, fluoridated water
Iodine	Component of thyroid hormone (see Chapter 580)	Hypothyroidism (see Chapters 601 and 603)	Hypothyroidism and goiter (see Chapters 603 and 605); maternal excess can cause congenital hypothyroidism and goiter (see Chapter 603.1)	Saltwater fish, iodized salt
Iron	Component of hemoglobin, myoglobin, cytochromes, and other enzymes	Anemia (see Chapter 504), decreased alertness, impaired learning	Acute (see Chapter 94): nausea, vomiting, diarrhea, abdominal pain, and hypotension Chronic excess usually secondary to hereditary disorders (see Chapter 511); causes organ dysfunction	Meat, fortified foods Deficiency can also result from blood loss (hookworm infestation, menorrhagia)
Manganese	Enzyme cofactor	Hypercholesterolemia, weight loss, decreased clotting proteins*	Neurologic manifestations, cholestatic jaundice	Nuts, meat, grains, tea
Molybdenum	Enzyme cofactor (xanthine oxidase and others)	Tachycardia, tachypnea, night blindness, irritability, coma*	Hyperuricemia and increased risk of gout	Legumes, grains, liver
Selenium	Enzyme cofactor (prevents oxidative damage)	Cardiomyopathy (**Keshan disease**), myopathy	Nausea, diarrhea, neurologic manifestations, nail and hair changes, garlic odor	Meat, seafood, whole grains, garlic
Zinc	Enzyme cofactor Constituent of zinc-finger proteins, which regulate gene transcription	Decreased growth, dermatitis of extremities and around orifices, impaired immunity, poor wound healing, hypogonadism, diarrhea Supplements are beneficial in diarrhea and improve neurodevelopmental outcomes	Abdominal pain, diarrhea, vomiting Can worsen copper deficiency	Meat, shellfish, whole grains, legumes, cheese

*These deficiency states have been reported only in case reports associated with parenteral nutrition or highly unusual diets.

iodine deficiency (goiter, hypothyroidism) is common in many developing countries. Selenium content of the soil and consequently of food is also quite variable. Dietary **selenium deficiency** (associated with cardiomyopathy) occurs in certain locations, such as some parts of China.

The consequences of severe isolated trace mineral deficiency are illustrated in certain genetic disorders. The manifestations of **Menkes disease** are caused by pathologic variants in the gene coding for a protein that facilitates intestinal copper absorption (see Chapters 639.5 and 703). These pathologic variants result in severe copper deficiency; subcutaneous copper is an effective treatment. Nutritional copper deficiency has been reported in children receiving unsupplemented parenteral nutrition and in children on a ketogenic diet (with associated neutropenia and anemia). The recessive disorder **acrodermatitis enteropathica** is secondary to malabsorption of zinc (see Chapter 712). These patients respond dramatically to zinc supplementation.

Children can have apparently asymptomatic deficiencies of certain trace elements but still benefit from supplementation. As an example, zinc is highly effective in treating children before or during diarrheal illnesses in the developing world.

Zinc deficiency is quite common in the developing world and is often associated with malnutrition or other micronutrient deficiencies (iron). Chronic zinc deficiency is associated with dwarfism, hypogonadism, dermatitis, and T-cell immunodeficiency. Diets rich in phytates bind zinc, impairing its absorption. Zinc supplementation in at-risk children reduces the incidence and severity of diarrhea, pneumonia, and possibly malaria. In developing countries, children who have diarrhea may benefit from zinc supplementation, especially if there is underlying malnutrition.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Fluid and Electrolyte Disorders

PART VI

Chapter 73 Electrolyte and Acid-Base Disorders

73.1 Composition of Body Fluids

Larry A. Greenbaum

TOTAL BODY WATER

Total body water (TBW) as a percentage of body weight varies with age (Fig. 73.1). The fetus has very high TBW, which gradually decreases to approximately 75% of birthweight for a term infant. Premature infants have higher TBW than term infants. During the first year of life, TBW decreases to approximately 60% of body weight and remains at this level until puberty. At puberty, the fat content of females increases more than that in males, who acquire more muscle mass than females. Because fat has very low water content and muscle has high water content, by the end of puberty TBW in males remains at 60%, but TBW in females decreases to approximately 50% of body weight. The high fat content in overweight children causes a decrease in TBW as a percentage of body weight. During dehydration, TBW decreases and thus is a smaller percentage of body weight.

FLUID COMPARTMENTS

TBW is divided between two main compartments: **intracellular fluid (ICF)** and **extracellular fluid (ECF)**. In the fetus and newborn, the ECF volume is larger than the ICF volume (see Fig. 73.1). The normal postnatal diuresis causes an immediate decrease in the ECF volume. This is followed by continued expansion of the ICF volume, which results from cellular growth. By 1 year of age, the ratio of ICF volume to ECF volume approaches adult levels. The ECF volume is approximately 20–25% of body weight, and the ICF volume is approximately 30–40% of body weight, close to twice the ECF volume (Fig. 73.2). With puberty, the increased muscle mass of males causes them to have a higher ICF volume than females. There is no significant difference in the ECF volume between postpubertal females and males.

The ECF is further divided into the plasma water and the interstitial fluid (see Fig. 73.2). The *plasma water* is 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants; in premature newborns it is approximately 10% of body weight. The volume of plasma water can be altered by pathologic conditions, including dehydration, anemia, polycythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia. The *interstitial fluid,* normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis. An increase in interstitial fluid also occurs in patients with ascites or pleural effusions.

There is a delicate equilibrium between the intravascular fluid and the interstitial fluid. The balance between hydrostatic and

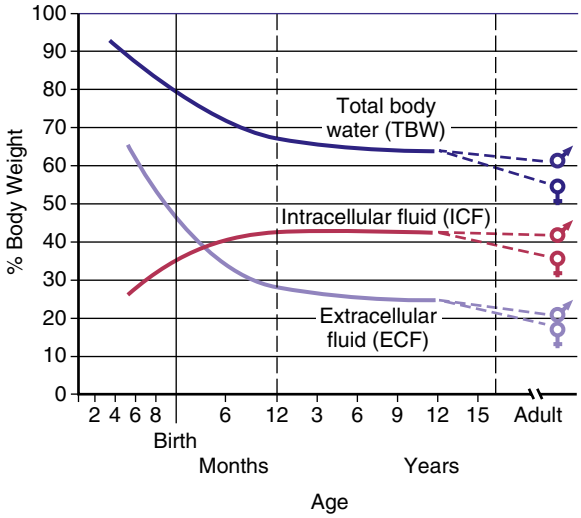

Fig. 73.1 Total body water, intracellular fluid, and extracellular fluid as a percentage of body weight as a function of age. *(From Winters RW. Water and electrolyte regulation. In: Winters RW, ed. The Body Fluids in Pediatrics. Little, Brown; 1973.)*

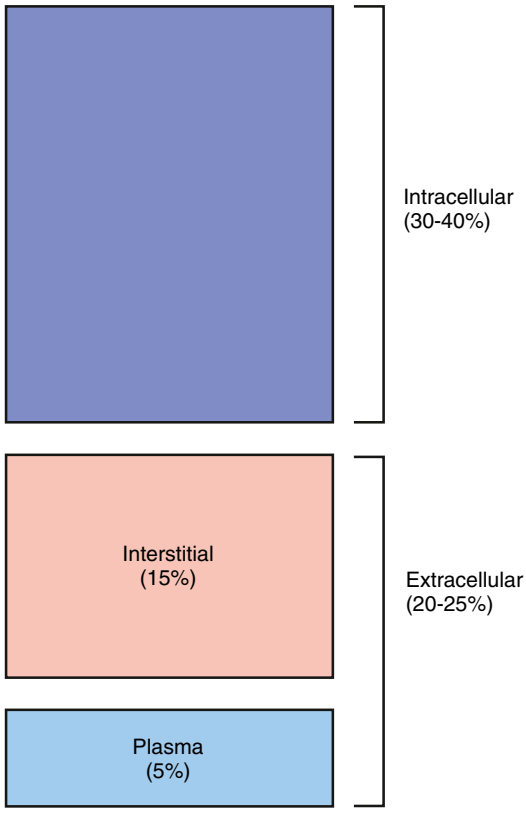

Fig. 73.2 Compartments of total body water, expressed as percentages of body weight, in an older child or adult.

oncotic forces regulates the intravascular volume, which is critical for proper tissue perfusion. The *intravascular fluid* has a higher concentration of albumin than the interstitial fluid, and the consequent oncotic force draws water into the intravascular space. The maintenance of this gradient depends on the limited permeability of albumin across the capillaries. The hydrostatic pressure of the intravascular space, which is caused by the pumping action of the heart, drives fluid out of the intravascular space. These forces favor movement into the interstitial space at the arterial ends of the capillaries. The decreased hydrostatic forces and increased oncotic forces, which result from the dilutional increase in albumin concentration, cause movement of fluid into the venous ends of the capillaries. Overall, there is usually a net movement of fluid out of the intravascular space to the interstitial space, but this fluid is returned to the circulation via the *lymphatics*.

An imbalance in these forces may cause expansion of the interstitial volume at the expense of the intravascular volume. In children with hypoalbuminemia, the decreased oncotic pressure of the intravascular fluid contributes to the development of **edema**. Loss of fluid from the intravascular space may compromise the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially likely in diseases in which capillary leak occurs because the loss of albumin from the intravascular space is associated with an increase in the albumin concentration in the interstitial space, further compromising the oncotic forces that normally maintain intravascular volume. In contrast, with **heart failure**, there is an increase in venous hydrostatic pressure from expansion of the intravascular volume, which is caused by impaired pumping by the heart, and the increase in venous pressure causes fluid to move from the intravascular space to the interstitial space. Expansion of the intravascular volume and increased intravascular pressure also cause the edema that occurs with acute glomerulonephritis.

ELECTROLYTE COMPOSITION

The composition of the solutes in the ICF and ECF are very different (Fig. 73.3). **Sodium** (Na^+) and **chloride** (Cl^-) are the dominant cation and anion, respectively, in ECF. The sodium and chloride concentrations ([Na^+], [Cl^-]) in the ICF are much lower. **Potassium** (K^+) is the most abundant cation in the ICF, and its concentration ([K^+]) within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is largely determined by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations (Na^+ and K^+) relies on activity of the Na^+,K^+-adenosine triphosphatase (ATPase) pump and membrane ion channels.

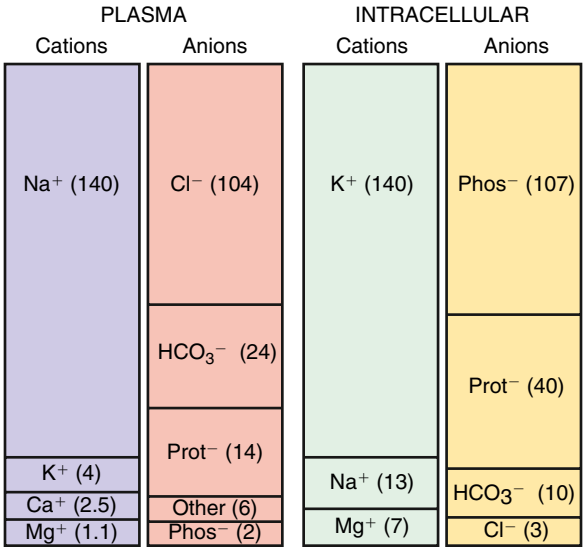

Fig. 73.3 Concentrations of the major cations and anions in the intracellular space and the plasma, expressed in mEq/L.

The difference in the electrolyte compositions of the ECF and the ICF has important ramifications in the evaluation and treatment of electrolyte disorders. Serum concentrations of electrolytes ([Na^+], [K^+], and [Cl^-]) do not always reflect total body content. Intracellular [K^+] is much higher than the serum concentration. A shift of K^+ from the **intracellular space (ICS)** can maintain a normal or even an elevated serum [K^+] despite massive losses of K^+ from the ICS. This effect is seen in diabetic ketoacidosis, in which significant K^+ depletion is masked by transmembrane shift of K^+ from the ICF to the ECF. Therefore, for K^+ and phosphorus, electrolytes with a high intracellular concentration, serum level may not reflect total body content. Similarly, the serum **calcium** concentration ([Ca^{2+}]) does not reflect total body content of Ca^{2+}, which is largely contained in bone (see Chapter 69).

OSMOLALITY

The ICF and the ECF are in **osmotic equilibrium** because the cell membrane is permeable to water. If the osmolality in one compartment changes, then water movement leads to a rapid equalization of osmolality, with a shift of water between the ICS and **extracellular space (ECS)**. Clinically, the primary process is usually a change in the osmolality of the ECF, with resultant shift of water into the ICF if ECF osmolality decreases, or vice versa if ECF osmolality increases. The *ECF osmolality* can be determined and *usually equals ICF osmolality*. **Plasma osmolality**, normally 285-295 mOsm/kg, is measured by the degree of freezing-point depression. The plasma osmolality can also be *estimated* by a calculation based on the following formula:

$$\text{Osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

Glucose and blood urea nitrogen (BUN) are reported in mg/dL. Division of these values by 18 and 2.8, respectively, converts the units into mmol/L. Multiplication of the [Na^+] value by 2 accounts for its accompanying anions, principally Cl^- and bicarbonate. The calculated osmolality is usually slightly lower than measured osmolality.

Urea is not confined to the ECS because it readily crosses the cell membrane, and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated [Na^+] causes a shift of water from the ICS, with **uremia** there is no osmolar gradient between the two compartments and consequently no movement of water. The only exception is during **hemodialysis**, when the decrease in extracellular urea is so rapid that intracellular urea does not have time to equilibrate. **Disequilibrium syndrome** during hemodialysis may result in a shift of water into brain cells and lead to severe symptoms. Ethanol, because it freely crosses cell membranes, is another ineffective osmole. Hence, the effective osmolality can be calculated as follows:

$$\text{Effective osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18$$

The *effective osmolality* determines the osmotic force that is mediating the shift of water between the ECF and the ICF.

Hyperglycemia causes an increase in the plasma osmolality because it is not in equilibrium with the ICS. During hyperglycemia, there is shift of water from the ICS to the ECS. This shift causes dilution of the Na^+ in the ECS, causing hyponatremia despite elevated plasma osmolality. The magnitude of this effect can be calculated as follows:

$$[Na]_{corrected} = [Na]_{measured} + 1.6 \times ([glucose] - 100 \text{ mg/dL})/100$$

where $[Na]_{measured}$ = Na^+ concentration measured by the clinical laboratory and $[Na]_{corrected}$ = corrected Na^+ concentration (the Na^+ concentration if the glucose concentration were normal and its accompanying water moved back into the cells). The $[Na]_{corrected}$ is the more reliable indicator of the ratio of total body Na^+ to TBW, the usual determinant of the $[Na^+]$.

Normally, measured osmolality and calculated osmolality are within 10 mOsm/kg. However, there are some clinical situations in which this difference does not occur. The presence of **unmeasured osmoles** causes measured osmolality to be significantly elevated in comparison with the calculated osmolality. An **osmolal gap** is present when the difference between measured osmolality exceeds calculated osmolality by >10 mOsm/kg. Examples of unmeasured osmoles include ethanol, ethylene glycol, methanol, sucrose, sorbitol, and mannitol. These substances increase measured osmolality but are not part of the equation for calculating osmolality. The presence of an osmolal gap is a clinical clue to the presence of unmeasured osmoles and may be diagnostically useful when there is clinical suspicion of poisoning with methanol or ethylene glycol.

Pseudohyponatremia is a second situation in which there is discordance between measured osmolality and calculated osmolality. Lipids and proteins are the solids of the serum. In patients with elevated serum lipids or proteins, the water content of the serum decreases because water is displaced by the larger amounts of solids. Some instruments measure $[Na^+]$ by determining the amount of Na^+ per liter of serum, including the solid component. When the solid component increases, there is a decrease in $[Na^+]$ per liter of serum, despite a normal concentration when based on the amount of Na^+ per liter of serum water. *It is the concentration of Na^+ in serum water that is physiologically relevant.* A similar problem occurs when using instruments that require dilution of the sample before measurement of Na^+ (indirect potentiometry). In both situations, the plasma osmolality is normal despite the presence of pseudohyponatremia, because the method for measuring osmolality is not appreciably influenced by the percentage of serum that is composed of lipids and proteins. Pseudohyponatremia is diagnosed by the finding of a normal measured plasma osmolality despite hyponatremia. This laboratory artifact does not occur if the $[Na^+]$ in water is measured directly with an ion-specific electrode, as with arterial blood gas (ABG) analyzers. **Pseudohypernatremia** may occur in patients with very low levels of serum proteins by a similar mechanism.

When there are no unmeasured osmoles and pseudohyponatremia is not a concern, the calculated osmolality provides an accurate estimate of the plasma osmolality. Measurement of plasma osmolality is useful for detecting or monitoring unmeasured osmoles and confirming the presence of true hyponatremia. Whereas many children with high plasma osmolality are dehydrated—as seen with hypernatremic dehydration or diabetic ketoacidosis—high osmolality does not always equate with dehydration. A child with salt poisoning or uremia has an elevated plasma osmolality but may be volume overloaded.

POINT-OF-CARE TESTING

Point-of-care (POC) testing offers a number of advantages, including rapid turnaround and usually smaller blood sample volume required. POC devices may provide more accurate results in certain situations, such as pseudohyponatremia (see earlier) and pseudohyperkalemia (see Chapter 73.4). However, the agreement between POC and the laboratory is variable, and thus caution is needed when interpreting results. Because of bias, POC and laboratory results should not be used on an alternating basis when following critical trends (e.g., during correction of hypernatremia or hyponatremia; see Chapter 73.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

73.2 Regulation of Osmolality and Volume

Larry A. Greenbaum

The regulation of plasma **osmolality** and the intravascular **volume** is controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance. When present, volume depletion takes precedence over regulation of osmolality, and retention of water contributes to the maintenance of intravascular volume.

REGULATION OF OSMOLALITY

The plasma osmolality is tightly regulated and maintained at 285-295 mOsm/kg. Modification of water intake and excretion maintains normal plasma osmolality. In the steady state, the combination of water intake and water produced by the body from oxidation balances water losses from the skin, lungs, urine, and gastrointestinal (GI) tract. Only water intake and urinary losses can be regulated.

Osmoreceptors in the hypothalamus sense plasma osmolality (see Chapter 594). An elevated effective osmolality leads to secretion of **antidiuretic hormone (ADH)** by neurons in the supraoptic and paraventricular nuclei in the hypothalamus. The axons of these neurons terminate in the posterior pituitary. Circulating ADH binds to its V_2 receptors in the collecting duct cells of the kidney and causes insertion of water channels (aquaporin-2) into the renal collecting duct cells. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. Urine concentration increases and water excretion decreases. Urinary water losses cannot be eliminated because there is obligatory excretion of urinary solutes, such as urea and sodium. The regulation of ADH secretion is tightly linked to plasma osmolality, responses being detectable with a 1% change in osmolality. ADH secretion virtually disappears when plasma osmolality is low, allowing excretion of maximally dilute urine. The resulting loss of free water (i.e., water without Na^+) corrects plasma osmolality. ADH secretion is not an all-or-nothing response; there is a graded adjustment as the osmolality changes.

Water intake is regulated by hypothalamic osmoreceptors, which stimulate thirst when the serum osmolality increases. Thirst occurs with a small increase in the serum osmolality. *Control of osmolality is subordinate to maintenance of an adequate intravascular volume.* When volume depletion is present, both ADH secretion and thirst are stimulated, regardless of the plasma osmolality. The sensation of thirst requires moderate volume depletion but only a 1–2% change in the plasma osmolality.

A number of conditions can limit the kidney's ability to excrete adequate water to correct low plasma osmolality. In the **syndrome of inappropriate antidiuretic hormone (SIADH)**, ADH continues to be produced despite a low plasma osmolality (see Chapters 73.3 and 597).

The glomerular filtration rate (GFR) affects the kidney's ability to eliminate water. With a decrease in the GFR, less water is delivered to

the collecting duct, limiting the amount of water that can be excreted. The impairment in the GFR must be quite significant to limit the kidney's ability to respond to an excess of water.

The **minimum urine osmolality** is approximately 30-50 mOsm/kg. This places an upper limit on the kidney's ability to excrete water; sufficient solute must be present to permit water loss. Massive water intoxication may exceed this limit, whereas a lesser amount of water is necessary in the child with a diet that has very little solute. This can produce severe hyponatremia in children who receive little salt and have minimal urea production as a result of inadequate protein intake. Volume depletion is an extremely important cause of decreased water loss by the kidney despite a low plasma osmolality. This "appropriate" secretion of ADH occurs because volume depletion takes precedence over the osmolality in the regulation of ADH.

The **maximum urine osmolality** is approximately 1,200 mOsm/kg. The obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute kidney injury. An increase in urinary solute and thus water losses occurs with an **osmotic diuresis**, which results classically from glycosuria in diabetes mellitus as well as iatrogenically after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child. This limits the ability to conserve water and makes such a patient more vulnerable to hypernatremic dehydration. Very high fluid intake, as seen with **psychogenic polydipsia**, can dilute the high osmolality in the renal medulla, which is necessary for maximal urinary concentration. If fluid intake is restricted in patients with this condition, the kidney's ability to concentrate the urine may be somewhat impaired, although this defect corrects after a few days without polydipsia. This may also occur during the initial treatment of central diabetes insipidus with desmopressin acetate; the renal medulla takes time to achieve its normal maximum osmolality.

REGULATION OF VOLUME

An appropriate intravascular volume is critical for survival; both volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The principal extracellular anion, Cl^-, is also necessary, but for simplicity, Na^+ balance is considered the main regulator of volume status because body content of sodium and that of chloride usually change proportionally, given the need for equal numbers of cations and anions. In some situations, Cl^- depletion is considered the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion).

The kidney determines sodium balance because there is little homeostatic control of sodium intake, even though **salt craving** does occasionally occur, typically in children with chronic renal salt loss. The kidney regulates Na^+ balance by altering the percentage of filtered Na^+ that is resorbed along the nephron. Normally, the kidney excretes <1% of the Na^+ filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output match intake, with the kidney having the capacity to adapt to large variations in sodium intake. When necessary, urinary sodium excretion can be reduced to virtually undetectable levels or increased dramatically.

The most important determinant of renal Na^+ excretion is the volume status of the child; it is the effective intravascular volume that influences urinary Na^+ excretion. The *effective intravascular volume* is the volume status that is sensed by the body's regulatory mechanisms. Heart failure is a state of volume overload, but the effective intravascular volume is low because poor cardiac function prevents adequate perfusion of the kidneys and other organs. This explains the avid renal Na^+ retention often present in patients with heart failure.

The **renin-angiotensin system** is an important regulator of renal Na^+ excretion. The juxtaglomerular apparatus produces renin in response to decreased effective intravascular volume. Specific stimuli for renin release are decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β_1-adrenergic agonists, which increase in response to intravascular volume depletion. Renin, a proteolytic enzyme, cleaves angiotensinogen, producing angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption *and* stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron—specifically, the late distal convoluted tubule and the collecting duct—aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasoconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion.

Volume expansion stimulates the synthesis of **atrial natriuretic peptide (ANP)**, which is produced by the atria in response to atrial wall distention. Along with increasing the GFR, ANP inhibits Na^+ resorption in the medullary portion of the collecting duct, facilitating an increase in urinary Na^+ excretion.

Volume overload occurs when Na^+ intake exceeds output. Children with kidney failure have impaired ability to excrete Na^+. The GFR is low at birth, limiting a newborn's ability to excrete a Na^+ load. In other situations, there is a loss of the appropriate regulation of renal Na^+ excretion. This loss of regulation occurs in patients with excessive aldosterone, as seen in primary hyperaldosteronism or renal artery stenosis, where excess renin production leads to high aldosterone levels. In acute glomerulonephritis, even without significantly reduced GFR, the normal intrarenal mechanisms that regulate Na^+ excretion malfunction, causing excessive renal retention of Na^+ and volume overload.

Renal retention of Na^+ occurs during volume depletion, but this appropriate response causes the severe excess in total body Na^+ that is present in heart failure, liver failure, nephrotic syndrome, and other causes of hypoalbuminemia. In these diseases, the effective intravascular volume is decreased, causing the kidney and the various regulatory systems to respond, leading to renal Na^+ retention and edema formation.

Volume depletion usually occurs when Na^+ losses exceed intake. The most common etiology in children is gastroenteritis. Excessive losses of sodium may also occur from the skin in children with burns, in sweat from patients with cystic fibrosis, or after vigorous exercise. Inadequate intake of Na^+ is uncommon except in neglect, in famine, or with an inappropriate choice of liquid diet in a child who cannot take solids. Urinary Na^+ wasting may occur in a range of renal diseases, from renal dysplasia to tubular disorders, such as Bartter syndrome. The neonate, especially if premature, has a mild impairment in the ability to conserve Na^+. Iatrogenic renal Na^+ wasting takes place during diuretic therapy. Renal Na^+ loss occurs as a result of derangement in the normal regulatory systems. An absence of aldosterone, seen most frequently in children with **congenital adrenal hyperplasia** caused by 21-hydroxylase deficiency, causes sodium wasting (see Chapter 616).

Isolated disorders of water balance can affect volume status and Na^+ balance. Because the cell membrane is permeable to water, changes in TBW influence both the extracellular volume and the intracellular volume. In isolated water loss, as occurs in diabetes insipidus, the impact is greater on the ICS because it has a greater volume than the ECS. Thus, compared with other types of dehydration, hypernatremic dehydration has less impact on plasma volume; most of the fluid loss comes from the ICS. Yet, significant water loss eventually affects intravascular volume and will stimulate renal Na^+ retention, even if total body Na^+ content is normal. Similarly, with acute water intoxication or SIADH, there is an excess of TBW, but most is in the ICS. However, there is some effect on the intravascular volume, which causes renal excretion

of Na^+. Children with SIADH or water intoxication have high urine Na^+ concentration despite hyponatremia. This finding reinforces the concept of independent control systems for water and Na^+, but the 2 systems interact when pathophysiologic processes dictate, and control of effective intravascular volume always takes precedence over control of osmolality.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

73.3 Sodium

Larry A. Greenbaum

SODIUM METABOLISM

Body Content and Physiologic Function

Sodium is the dominant cation of the ECF (see Fig. 73.3), and it is the principal determinant of extracellular osmolality. Na^+ is therefore necessary for the maintenance of intravascular volume. Less than 3% of Na^+ is intracellular. More than 40% of total body Na^+ is in bone; the remainder is in the interstitial and intravascular spaces. The low intracellular [Na^+], approximately 10 mEq/L, is maintained by Na^+,K^+-ATPase, which exchanges intracellular Na^+ for extracellular K^+.

Sodium Intake

A child's diet determines the amount of Na^+ ingested—a predominantly cultural determination in older children. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Children in the United States tend to have very high salt intakes because their diets include a large amount of "junk" food or fast food. Infants receive sodium from breast milk (approximately 7 mEq/L) and formula (7-13 mEq/L, for 20 calorie/oz formula).

Sodium is readily absorbed throughout the GI tract. Mineralocorticoids increase sodium transport into the body, although this effect has limited clinical significance. The presence of glucose enhances sodium absorption because of the presence of a co-transport system. This is the rationale for including sodium and glucose in oral rehydration solutions (see Chapter 387).

Sodium Excretion

Sodium excretion occurs in stool and sweat, but the kidney regulates Na^+ balance and is the principal site of Na^+ excretion. There is some Na^+ loss in stool, but it is minimal unless diarrhea is present. Normally, sweat has 5-40 mEq/L of sodium. Sweat [Na^+] is increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism. The higher sweat losses in these conditions may cause or contribute to Na^+ depletion.

Sodium is unique among electrolytes because water balance, not Na^+ balance, usually determines its concentration. When the [Na^+] increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of ADH, which leads to renal conservation of water. Both these mechanisms increase the water content of the body, and the [Na^+] returns to normal. During hyponatremia, the decrease in plasma osmolality stops ADH secretion, and consequent renal water excretion leads to an increase in the [Na^+]. Even though water balance is usually regulated by osmolality, volume depletion does stimulate thirst, ADH secretion, and renal conservation of water. Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of Na^+ by the kidney is not regulated by the plasma osmolality. The patient's effective plasma volume determines the amount of sodium in the urine. This is mediated by a variety of regulatory systems, including the renin-angiotensin-aldosterone system and intrarenal mechanisms. In hyponatremia or hypernatremia, the underlying pathophysiology determines the amount of urinary Na^+, not the serum [Na^+].

Table 73.1 Causes of Hypernatremia

EXCESSIVE SODIUM
Improperly mixed formula
Excess sodium bicarbonate
Ingestion of seawater or sodium chloride
Intentional salt poisoning (child abuse or fictitious disorder inflicted on another)
Intravenous hypertonic saline
Sodium phosphate enemas
Hyperaldosteronism
WATER DEFICIT
Nephrogenic Diabetes Insipidus
Acquired
X-linked (OMIM 304800)
Autosomal recessive (OMIM 125800)
Autosomal dominant (OMIM 125800)
Central Diabetes Insipidus
Acquired*
Autosomal recessive (OMIM 125700/600955)
Autosomal dominant (OMIM 125700)
Wolfram syndrome (OMIM 222300/604928/598500)
Hypothalamic neurogenic (essential) adipsic hypernatremia
Increased Insensible Losses
Premature infants
Radiant warmers
Phototherapy
Inadequate Intake
Ineffective breastfeeding
Child neglect or abuse
Adipsia (lack of thirst)
WATER AND SODIUM DEFICITS
Gastrointestinal Losses
Diarrhea
Emesis/nasogastric suction
Osmotic cathartics (lactulose)
Cutaneous Losses
Burns
Excessive sweating
Renal Losses
Osmotic diuretics (mannitol)
Diabetes mellitus
Chronic kidney disease (dysplasia and obstructive uropathy)
Polyuric phase of acute tubular necrosis
Postobstructive diuresis

*Acquired: central diabetes insipidus from CNS malformations, trauma, meningitis, tumor, infiltration, unknown.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

HYPERNATREMIA

Hypernatremia is a [Na^+] >145 mEq/L, although it is sometimes defined as >150 mEq/L. Mild hypernatremia is common in children, especially among infants with gastroenteritis. Hypernatremia in hospitalized patients may be iatrogenic, which is caused by inadequate water administration or, less often, by excessive Na^+ administration. Moderate or severe hypernatremia has significant morbidity because of the underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

Etiology and Pathophysiology

There are three basic mechanisms of hypernatremia (Table 73.1). *Sodium intoxication* may be iatrogenic in a hospital setting because of correction of metabolic acidosis with sodium bicarbonate. Baking soda, a putative home remedy for upset stomach, is another source of sodium bicarbonate; the hypernatremia is accompanied by a profound metabolic alkalosis. Hypernatremia may develop following sodium phosphate emesis. In hyperaldosteronism, there is renal retention of sodium and resultant hypertension; hypernatremia may not be present or is usually mild.

The classic causes of hypernatremia from a *water deficit* are **nephrogenic** and **central diabetes insipidus** (see Chapters 570 and 596). Hypernatremia develops in diabetes insipidus only if the patient does not have access to water or cannot drink adequately because of immaturity, neurologic impairment, emesis, or anorexia. Infants are at high risk because of their inability to control their own water intake. Central diabetes insipidus and the genetic forms of nephrogenic diabetes insipidus typically cause massive urinary water losses and very dilute urine. The water losses are less dramatic, and the urine often has the same osmolality as plasma when nephrogenic diabetes insipidus is secondary to intrinsic renal disease (obstructive uropathy, renal dysplasia, sickle cell disease).

The other causes of a water deficit are also secondary to an imbalance between losses and intake. Newborns, especially if premature, have high insensible water losses. Losses are further increased if the infant is placed under a radiant warmer or with the use of phototherapy for hyperbilirubinemia. The renal concentrating mechanisms are not optimal at birth, providing an additional source of water loss. Ineffective breastfeeding, often in a primiparous mother, can cause severe hypernatremic dehydration. **Adipsia**, the absence of thirst, is usually secondary to damage to the hypothalamus, such as from trauma, tumor, hydrocephalus, or histiocytosis. Primary adipsia (**essential hypernatremia**) is rare but is seen in children with central nervous system (CNS) malformations (septo-optic dysphasia, holoprosencephaly, optic nerve hypoplasia).

When hypernatremia occurs in conditions with *deficits of sodium and water,* the water deficit exceeds the sodium deficit. This occurs only if the patient is unable to ingest adequate water. Diarrhea results in depletion of both Na^+ and water. Because diarrhea is hypotonic—typical Na^+ concentration of 35-65 mEq/L—water losses exceed Na^+ losses, potentially leading to hypernatremia. Most children with gastroenteritis do not have hypernatremia because they drink enough hypotonic fluid to compensate for stool water losses (see Chapter 387). Fluids such as water, juice, and formula are more hypotonic than the stool losses, allowing correction of the water deficit and potentially even causing hyponatremia. Hypernatremia is most likely to occur in the child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.

Osmotic agents, including mannitol, and glucose in diabetes mellitus, cause excessive renal losses of water and Na^+. Because the urine is hypotonic ($[Na^+]$ of approximately 50 mEq/L) during an osmotic diuresis, water loss exceeds Na^+ loss, and hypernatremia may occur if water intake is inadequate. Certain chronic kidney diseases, such as renal dysplasia and obstructive uropathy, are associated with tubular dysfunction, leading to excessive losses of water and Na^+. Many children with such diseases have disproportionate water loss and are at risk for hypernatremic dehydration, especially if gastroenteritis supervenes. Similar mechanisms occur during the polyuric phase of acute kidney injury and after relief of urinary obstruction (postobstructive diuresis). Patients with either condition may have an osmotic diuresis from urinary losses of urea and an inability to conserve water because of tubular dysfunction.

Clinical Manifestations

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms (see Chapter 75). Children with hypernatremic dehydration tend to have better preservation of intravascular volume because of the shift of water from the ICS to the ECS. This shift maintains blood pressure and urine output and allows hypernatremic infants to be less symptomatic initially and potentially to become more dehydrated before medical attention is sought. Breastfed infants with hypernatremia are often profoundly dehydrated, with failure to thrive (malnutrition). Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated, hypernatremic infant has a "doughy" feel.

Hypernatremia, even without dehydration, causes central nervous system (CNS) symptoms that tend to parallel the degree of $[Na^+]$ elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever, although many patients have an underlying process that contributes to the fever. Hypernatremia is associated with hyperglycemia and mild hypocalcemia; the mechanisms are unknown. Beyond the sequelae of dehydration, there is no clear direct effect of hypernatremia on other organs or tissues, except the brain.

Brain hemorrhage is the most devastating consequence of *untreated* hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, leading to a decrease in brain volume. This decrease can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhages. Seizures and coma are possible sequelae of the hemorrhage, although seizures are more common during correction of hypernatremia. The cerebrospinal fluid protein is often elevated in infants with significant hypernatremia, probably because of leakage from damaged blood vessels. Neonates, especially if premature, seem especially vulnerable to hypernatremia and excessive sodium intake. There is an association between rapid or hyperosmolar sodium bicarbonate administration and the development of intraventricular hemorrhages in neonates. Even though **osmotic demyelination syndrome (ODS)**, which includes central pontine myelinolysis and extrapontine myelinolysis, is classically associated with overly rapid correction of hyponatremia, it can occur in children with hypernatremia (see "Treatment"). Thrombotic complications occur in severe hypernatremic dehydration, including stroke, dural sinus thrombosis, peripheral thrombosis, and renal vein thrombosis. This is secondary to dehydration and possibly hypercoagulability associated with hypernatremia.

Diagnosis

The etiology of hypernatremia is usually apparent from the history. Hypernatremia resulting from water loss occurs only if the patient does not have access to water or is unable to drink. In the absence of dehydration, it is important to ask about sodium intake. Children with excess salt intake do not have signs of dehydration, unless another process is present. Severe Na^+ intoxication causes signs of volume overload, such as pulmonary edema and weight gain. **Salt poisoning** is associated with an elevated fractional excretion of Na^+, whereas hypernatremic dehydration causes a low fractional excretion of Na^+. Gastric sodium concentrations are often elevated in salt poisoning. In hyperaldosteronism, hypernatremia is usually mild or absent and is associated with edema, hypertension, hypokalemia, and metabolic alkalosis.

When there is isolated water loss, the signs of volume depletion are usually less severe initially because much of the loss is from the ICS. When pure water loss causes signs of dehydration, the hypernatremia and water deficit are usually severe. In the child with renal water loss, either central or nephrogenic diabetes insipidus, the urine is inappropriately dilute and urine volume is not low. The urine is maximally concentrated and urine volume is low if the losses are extrarenal or caused by inadequate intake. With extrarenal causes of loss of water, the urine osmolality should be >1,000 mOsm/kg. When diabetes insipidus is suspected, the evaluation may include measurement of ADH and a water-deprivation test, including a trial of desmopressin acetate (synthetic ADH analog) to differentiate between nephrogenic diabetes insipidus and central

diabetes insipidus (see Chapters 570 and 596). A water-deprivation test is unnecessary if the patient has simultaneous documentation of hypernatremia and poorly concentrated urine (osmolality lower than that of plasma). In children with central diabetes insipidus, administration of desmopressin acetate increases the urine osmolality above the plasma osmolality, although maximum osmolality does not occur immediately because of the decreased osmolality of the renal medulla as a result of the chronic lack of ADH. In children with nephrogenic diabetes insipidus, there is no response to desmopressin acetate. *Hypercalcemia or hypokalemia may produce a nephrogenic diabetes insipidus–like syndrome.*

With combined Na^+ and water deficits, analysis of the urine differentiates between renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, concentrated urine, and Na^+ retention (urine $[Na^+]$ <20 mEq/L, fractional excretion of Na^+ <1%). With renal causes, the urine volume is not appropriately low, the urine is not maximally concentrated, and the urine $[Na^+]$ may be inappropriately elevated.

Treatment

As hypernatremia develops, the brain generates **idiogenic osmoles** to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum $[Na^+]$ is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the two compartments. The resultant brain swelling may manifest as seizures or coma.

Because of the associated dangers, *chronic hypernatremia should not be corrected rapidly.* The goal is to decrease the serum $[Na^+]$, but avoid a decrease of more than 10 mEq/L every 24 hours. The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum $[Na^+]$ value so that fluid therapy can be adjusted to provide adequate correction, neither too slow nor too fast. If a child has seizures because of brain edema secondary to rapid correction, administration of hypotonic fluid should be stopped. An infusion of 3% saline can acutely increase the serum $[Na^+]$, reversing the cerebral edema.

Chapter 75 outlines a detailed approach to the child with hypernatremic dehydration. Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly with 5% dextrose in water (D5W) because idiogenic osmoles have not had time to accumulate. This fact balances the high morbidity and mortality rates associated with hypernatremia with the dangers of overly rapid correction. When hypernatremia is severe and is caused by sodium intoxication, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening the volume overload. In this situation, dialysis allows for removal of the excess Na^+, with the precise strategy dependent on the mode of dialysis. In less severe cases, the addition of a loop diuretic increases the removal of excess Na^+ and water, decreasing the risk of volume overload. With Na^+ overload, hypernatremia is corrected with Na^+-free intravenous (IV) fluid (D5W).

Hyperglycemia from hypernatremia is not usually a problem and is not treated with insulin because the acute decrease in glucose may precipitate cerebral edema by lowering plasma osmolality. Rarely, the glucose concentration of IV fluids must be reduced (from 5% to 2.5% dextrose in water). The secondary hypocalcemia is treated as needed.

It is important to address the underlying cause of the hypernatremia, if possible. The child with central diabetes insipidus should receive desmopressin acetate. Because this treatment reduces renal excretion of water, excessive intake of water must be avoided to prevent both overly rapid correction of the hypernatremia and the development of hyponatremia. Over the long-term, reduced sodium intake and the use of medications can somewhat ameliorate the water losses in nephrogenic diabetes insipidus (see Chapter 570). The daily water intake of a child receiving tube feeding may need to be increased to compensate for high losses. The patient with significant ongoing losses, such as through diarrhea, may need supplemental water and electrolytes (see Chapter 74). Sodium intake is reduced if it contributed to the hypernatremia.

HYPONATREMIA

Hyponatremia, a very common electrolyte abnormality in hospitalized patients, is a serum sodium level <135 mEq/L. Both total body sodium and TBW determine the serum sodium concentration. Hyponatremia exists when the ratio of water to Na^+ is increased. This condition can occur with low, normal, or high levels of body Na^+. Similarly, body water can be low, normal, or high.

Etiology and Pathophysiology

Table 73.2 lists the causes of hyponatremia. **Pseudohyponatremia** is a laboratory artifact present when the plasma contains very high concentrations of protein (multiple myeloma, intravenous immune globulin [IVIG] infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). It does not occur when a direct ion-selective electrode determines the $[Na^+]$ in undiluted plasma, a technique that is used by ABG analyzers or POC instruments (see Chapter 73.1). In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. **Hyperosmolality,** as may occur with hyperglycemia, causes a low $[Na^+]$ because water moves down its osmotic gradient from the ICS into the ECS, diluting the $[Na^+]$. However, because the manifestations of hyponatremia are a result of the low plasma osmolality, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia. When the etiology of the hyperosmolality resolves, such as hyperglycemia in diabetes mellitus, water moves back into the cells, and the $[Na^+]$ rises to its "true" value. Mannitol or sucrose, a component of IVIG preparations, may cause hyponatremia because of hyperosmolality.

Classification of hyponatremia is based on the patient's volume status. In **hypovolemic hyponatremia,** the child has lost Na^+ from the body. The water balance may be positive or negative, but Na^+ loss has been higher than water loss. The pathogenesis of the hyponatremia is usually a combination of Na^+ loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and this fluid contains Na^+. Most fluid that is lost has a lower $[Na^+]$ than that of plasma. Viral diarrhea fluid has an average $[Na^+]$ of 50 mEq/L. Replacing diarrhea fluid, which has $[Na^+]$ of 50 mEq/L, with formula, which has only approximately 7-10 mEq/L of Na^+, reduces the serum $[Na^+]$. Intravascular volume depletion interferes with renal water excretion, the body's usual mechanism for preventing hyponatremia. The volume depletion stimulates ADH synthesis, resulting in renal water retention. Volume depletion also decreases the GFR and enhances water resorption in the proximal tubule, thereby reducing water delivery to the collecting duct.

Diarrhea as a result of gastroenteritis is the most common cause of hypovolemic hyponatremia in children. Emesis causes hyponatremia if the patient takes in hypotonic fluid, either IV or enterally, despite the emesis. Most patients with emesis have either a normal $[Na^+]$ or hypernatremia. Burns may cause massive losses of isotonic fluid and resultant volume depletion. Hyponatremia develops if the patient receives hypotonic fluid. Losses of sodium from sweat are especially high in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, although high losses can also occur in a hot climate. Third space losses are isotonic and can cause significant volume depletion, leading to ADH production and water retention, which can cause hyponatremia if the patient receives hypotonic fluid. In diseases that cause volume depletion through extrarenal Na^+ loss, the urine Na^+ level should be low (<10 mEq/L) as part of the renal response to maintain the intravascular volume. The only exceptions are diseases that cause both extrarenal and renal Na^+ losses: adrenal insufficiency and pseudohypoaldosteronism.

Table 73.2 Causes of Hyponatremia

PSEUDOHYPONATREMIA
Hyperlipidemia
Hyperproteinemia
HYPEROSMOLALITY
Hyperglycemia
Iatrogenic (mannitol, sucrose, glycine)
HYPOVOLEMIC HYPONATREMIA
Extrarenal Losses
Gastrointestinal (emesis, diarrhea)
Skin (sweating or burns)
Third space losses (bowel obstruction, peritonitis, sepsis)
Renal Losses
Thiazide or loop diuretics
Osmotic diuresis
Postobstructive diuresis
Polyuric phase of acute tubular necrosis
Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)
Autosomal recessive polycystic kidney disease (OMIM 263200)
Tubulointerstitial nephritis
Obstructive uropathy
Cerebral salt wasting
Proximal (type II) renal tubular acidosis (OMIM 604278)*
Lack of aldosterone effect (high serum potassium):
Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Urinary tract obstruction and/or infection
Addison disease
EUVOLEMIC HYPONATREMIA
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)
Desmopressin acetate
Glucocorticoid deficiency
Hypothyroidism
Antidepressant medications
Water intoxication
Iatrogenic (excess hypotonic intravenous fluids)
Feeding infants excessive water products
Swimming lessons
Tap water enema
Child abuse
Psychogenic polydipsia
Diluted formula
Beer potomania
Exercise-induced hyponatremia
HYPERVOLEMIC HYPONATREMIA
Heart failure
Cirrhosis
Nephrotic syndrome
Acute, chronic kidney injury
Capillary leak caused by sepsis
Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Table 73.3 Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Absence of:
  Renal, adrenal, or thyroid insufficiency
  Heart failure, nephrotic syndrome, or cirrhosis
  Diuretic ingestion
  Dehydration
- Urine osmolality >100 mOsm/kg (usually > plasma)
- Serum osmolality <280 mOsm/kg and serum sodium <135 mEq/L
- Urine sodium >30 mEq/L
- Reversal of "sodium wasting" and correction of hyponatremia with water restriction

Renal Na^+ loss may occur in a variety of situations. In some situations the urine $[Na^+]$ is >140 mEq/L; thus hyponatremia may occur without any fluid intake. In many cases, the urine Na^+ level is less than the serum $[Na^+]$; hence, the intake of hypotonic fluid is necessary for hyponatremia to develop. In diseases associated with urinary Na^+ loss, the urine Na^+ level is >20 mEq/L despite volume depletion. This may not be true if the urinary Na^+ loss is no longer occurring, as is frequently the case if diuretics are discontinued. Because loop diuretics prevent generation of a maximally hypertonic renal medulla, the patient can neither maximally dilute nor concentrate the urine. The inability to maximally retain water provides some protection against severe hyponatremia. The patient receiving thiazide diuretics can concentrate the urine and is at higher risk for severe hyponatremia. Osmotic agents, such as glucose during diabetic ketoacidosis, cause loss of both water and Na^+. Urea accumulates during kidney failure and then acts as an osmotic diuretic after relief of urinary tract obstruction and during the polyuric phase of acute tubular necrosis. Transient tubular damage in these conditions further impairs Na^+ conservation. The serum $[Na^+]$ in these conditions depends on $[Na^+]$ of the fluid used to replace the losses. Hyponatremia develops when the fluid is hypotonic relative to the urinary losses.

Renal salt wasting occurs in hereditary kidney diseases, such as juvenile nephronophthisis and autosomal recessive polycystic kidney disease. Obstructive uropathy, most often a result of posterior urethral valves, produces salt wasting, but patients with the disease may also have hypernatremia as a result of impaired ability to concentrate urine and high-water loss. Acquired tubulointerstitial nephritis, usually secondary to either medications or infections, may cause salt wasting, along with other evidence of tubular dysfunction. CNS injury may produce cerebral salt wasting, which is theoretically caused by the production of a natriuretic peptide that causes renal salt wasting. In type II **renal tubular acidosis (RTA)**, usually associated with Fanconi syndrome (see Chapter 569.1), there is increased excretion of Na^+ and bicarbonate in the urine. Patients with Fanconi syndrome also have glycosuria, aminoaciduria, and hypophosphatemia because of renal phosphate wasting.

Aldosterone is necessary for renal Na^+ retention and for the excretion of K^+ and acid. In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the block of aldosterone production results in hyponatremia, hyperkalemia, and metabolic acidosis. Decreased aldosterone secretion may be seen in Addison disease (adrenal insufficiency). In pseudohypoaldosteronism, aldosterone levels are elevated, but there is no response because of either a defective Na^+ channel or a deficiency of aldosterone receptors. A lack of tubular response to aldosterone may occur in children with urinary tract obstruction, especially during an acute urinary tract infection.

In **hypervolemic hyponatremia,** there is an excess of TBW and Na^+, although the increase in water is greater than the increase in Na^+. In most conditions that cause hypervolemic hyponatremia, there is a decrease in the *effective blood volume*, resulting from third space fluid loss, vasodilation, or poor cardiac output. The regulatory systems sense a decrease in effective blood volume and attempt to retain water and Na^+ to correct the problem. ADH causes renal water retention, and the kidney, under the influence of aldosterone and other intrarenal mechanisms, retains sodium. The patient's

sodium concentration decreases because water intake exceeds sodium intake and ADH prevents the normal loss of excess water.

In these disorders, there is low urine [Na^+] (<10 mEq/L) and an excess of both TBW and Na^+. The only exception is in patients with kidney failure and hyponatremia. These patients have an expanded intravascular volume, and hyponatremia can therefore appropriately suppress ADH production. Water cannot be excreted because very little urine is being made. Serum Na^+ is diluted through ingestion of water. Because of renal dysfunction, the urine [Na^+] may be elevated, but urine volume is so low that urine Na^+ excretion has not kept up with Na^+ intake, leading to sodium overload. The urine [Na^+] in kidney failure varies. In patients with acute glomerulonephritis, because it does not affect the tubules, the urine Na^+ level is usually low, whereas in patients with acute tubular necrosis, it is elevated because of tubular dysfunction.

Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia.** These patients typically have an excess of TBW and a slight decrease in total body Na^+. Some of these patients have an increase in weight, implying that they are volume overloaded. Nevertheless, from a clinical standpoint, they usually appear normal or have subtle signs of fluid overload. In SIADH the secretion of ADH is not inhibited by either low serum osmolality or expanded intravascular volume (see Chapter 597). The result is that the child with SIADH is unable to excrete water. This results in dilution of the serum Na^+ and hyponatremia. The expansion of the extracellular volume because of the retained water causes a mild increase in intravascular volume. The kidney increases Na^+ excretion to decrease intravascular volume to normal; thus the patient has a mild decrease in body Na^+. SIADH typically occurs with disorders of the CNS (infection, hemorrhage, trauma, tumor, thrombosis, Guillain-Barré syndrome), but lung disease (infection, asthma, positive pressure ventilation) and malignant tumors (producing ADH) are other potential causes. A variety of medications may cause SIADH, including recreational use of 3,4 -methylenedioxymethylamphetamine (MDMA, or "Ecstasy"), opiates, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate), tricyclic antidepressants, vincristine, cyclophosphamide, and selective serotonin reuptake inhibitors (SSRIs). The diagnosis of SIADH is one of exclusion, because other causes of hyponatremia must be eliminated (Table 73.3). Because SIADH is a state of intravascular volume expansion, low serum uric acid and BUN levels are supportive of the diagnosis. A rare gain-of-function pathogenic variant in the renal ADH receptor causes **nephrogenic syndrome of inappropriate antidiuresis**. Patients with this X-linked disorder appear to have SIADH but have undetectable levels of ADH.

Hyponatremia in hospitalized patients is frequently caused by inappropriate production of ADH and administration of hypotonic IV fluids (see Chapter 74). Causes of inappropriate ADH production include stress, medications such as narcotics or anesthetics, nausea, and respiratory illness. The synthetic analog of ADH, desmopressin acetate, causes water retention and may cause hyponatremia if fluid intake is not appropriately limited. The main uses of desmopressin acetate in children are for the management of central diabetes insipidus and nocturnal enuresis.

Excess water ingestion can produce hyponatremia. In these cases, [Na^+] decreases as a result of dilution. This decrease suppresses ADH secretion, and there is a marked water diuresis by the kidney. Hyponatremia develops only because the intake of water exceeds the kidney's ability to eliminate water. This condition is more likely to occur in infants because their lower GFR limits their ability to excrete water.

Hyponatremia may develop in infants <6 months of age when caregivers offer water to their infant as a supplement, during hot weather, or when they run out of formula. Hyponatremia may result in transient seizures, hypothermia, and poor tone. With cessation of water intake, the hyponatremia rapidly corrects. *Infants <6 months of age should not be given water to drink; infants 6-12 months of age should not receive >1-2 ounces. If the infant appears thirsty, the parent should offer formula or breastfeed the child.*

In some situations the water intoxication causes acute hyponatremia and is caused by a massive **acute water load**. Causes include infant swimming lessons, inappropriate use of hypotonic IV fluids, water enemas, and forced water intake as a form of child abuse. Chronic hyponatremia occurs in children who receive water but limited sodium and protein. The minimum urine osmolality is approximately 50 mOsm/kg; the kidney can excrete 1 L of water only if there is enough solute ingested to produce 50 mOsm for urinary excretion. Because Na^+ and urea (a breakdown product of protein) are the principal urinary solutes, a lack of intake of Na^+ and protein prevents adequate water excretion. This occurs with the use of diluted formula or other inappropriate diets. Subsistence on beer, a poor source of Na^+ and protein, causes hyponatremia because of the inability to excrete the high water load ("beer potomania"). **Exercise-induced hyponatremia**, reported frequently during marathons, is caused by excessive water intake, salt losses from sweat, and secretion of ADH.

The pathogenesis of the hyponatremia in glucocorticoid deficiency (adrenal insufficiency) is multifactorial and includes increased ADH secretion. In hypothyroidism there is an inappropriate retention of water by the kidney, but the precise mechanisms are not clearly elucidated.

Cerebral salt wasting, an uncommon disorder in children, may be confused with SIADH and is often associated with CNS injury or lesions. Cerebral salt wasting produces renal salt losses and hypovolemia (orthostatic hypotension and elevated hematocrit, BUN, or creatinine). Hypovolemia is not seen in SIADH.

Clinical Manifestations

Hyponatremia causes a decrease in the osmolality of the ECS. Because the ICS then has a higher osmolality, water moves from the ECS to the ICS to maintain osmotic equilibrium. The increase in intracellular water causes cells to swell. Although cell swelling is not problematic in most tissues, it is dangerous for the brain, which is confined by the skull. As brain cells swell, there is an increase in intracranial pressure (ICP), which impairs cerebral blood flow. Acute, severe hyponatremia can cause brainstem herniation and apnea; respiratory support is often necessary. Brain cell swelling is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may have hypothermia and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness; rhabdomyolysis can occur with water intoxication.

The symptoms of hyponatremia are mostly a result of the decrease in extracellular osmolality and the resulting movement of water down its osmotic gradient into the ICS. Brain swelling can be significantly obviated if the hyponatremia develops gradually, because brain cells adapt to the decreased extracellular osmolality by reducing intracellular osmolality. This reduction is achieved by extrusion of the main intracellular ions (K^+, Cl^-) and a variety of small organic molecules. This process explains why the range of symptoms in hyponatremia is related to both the serum [Na^+] and its rate of decrease. A patient with chronic hyponatremia may have only subtle neurologic abnormalities with a serum [Na^+] of 110 mEq/L, but another patient may have seizures because of an acute decline in serum [Na^+] from 140 to 125 mEq/L.

Diagnosis

The history usually points to a likely etiology of the hyponatremia. Most patients with hyponatremia have a history of volume depletion. Diarrhea and diuretic use are common causes of hyponatremia in children. A history of polyuria, perhaps with enuresis, and/or salt craving is present in children with primary kidney diseases or absence of aldosterone effect. Children may have signs or symptoms suggesting a diagnosis of hypothyroidism or adrenal insufficiency (see Chapters 603 and 615). Brain injury raises the possibility of SIADH or cerebral salt wasting, with the caveat that SIADH is much more likely. Liver disease, nephrotic syndrome, kidney failure, or congestive heart failure may be

acute or chronic. The history should include a review of the patient's intake, both IV and enteral, with careful attention to the amounts of water, Na^+, and protein.

The traditional first step in the diagnostic process is determination of the plasma osmolality. This is done because some patients with a low serum [Na^+] do not have low osmolality. The clinical effects of hyponatremia are secondary to the associated low osmolality. Without a low osmolality, there is no movement of water into the ICS.

A patient with hyponatremia can have a low, normal, or high osmolality. A normal osmolality in combination with hyponatremia occurs in pseudohyponatremia. Children with elevation of serum glucose concentration or of another effective osmole (mannitol) have a high plasma osmolality and hyponatremia. The presence of a low osmolality indicates "true" hyponatremia. Patients with low osmolality are at risk for neurologic symptoms and require further evaluation to determine the etiology of the hyponatremia.

In some situations, true hyponatremia is present despite a normal or elevated plasma osmolality. The presence of an ineffective osmole, usually urea, increases the plasma osmolality, but because urea has the same concentration in the ICS, it does not cause fluid to move into the ECS. There is no dilution of the serum Na^+ by water, and the [Na^+] remains unchanged if the ineffective osmole is eliminated. Most importantly, the ineffective osmole does not protect the brain from edema caused by hyponatremia. Therefore a patient may have symptoms of hyponatremia despite having a normal or increased osmolality because of uremia.

In patients with true hyponatremia, the next step in the diagnostic process is to clinically evaluate the volume status. Patients with hyponatremia can be hypovolemic, hypervolemic, or euvolemic. The diagnosis of volume depletion relies on the usual findings with dehydration (see Chapter 75), although subtle volume depletion may not be clinically apparent. Children with hypervolemia are edematous on physical examination. They may have ascites, pulmonary edema, pleural effusion, or hypertension.

Hypovolemic hyponatremia can have renal or nonrenal causes. The urine [Na^+] is very useful in differentiating between renal and nonrenal causes. When the losses are nonrenal and the kidney is working properly, there is renal retention of Na^+, a normal homeostatic response to volume depletion. Thus the urinary [Na^+] is low, typically <10 mEq/L, although Na^+ conservation in neonates is less avid. When the kidney is the cause of the Na^+ loss, the urine [Na^+] is >20 mEq/L, reflecting the defect in renal Na^+ retention. The interpretation of the urine Na^+ level is challenging with diuretic therapy because it is high when diuretics are being used but low after the diuretic effect is gone. This becomes an issue only when diuretic use is surreptitious. The urine [Na^+] is not useful if a metabolic alkalosis is present; the urine [Cl^-] must be used instead (see Chapter 73.7).

Differentiating among the nonrenal causes of hypovolemic hyponatremia is usually facilitated by the history. Although the renal causes are more challenging to distinguish, a high serum [K^+] is associated with disorders in which the Na^+ wasting is caused by absence of or ineffectiveness of aldosterone.

In the patient with hypervolemic hyponatremia, the urine [Na^+] is a helpful parameter. It is usually <10 mEq/L, except in the patient with kidney failure.

Treatment

The management of hyponatremia is based on the pathophysiology of the specific etiology. The management of all causes requires judicious monitoring and avoidance of an overly quick normalization of the serum [Na^+]. A patient with severe symptoms (seizures), no matter the etiology, should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium. *Hypoxia worsens cerebral edema,* and *hyponatremia may exacerbate hypoxic cell swelling.* Therefore pulse oximetry should be monitored and hypoxia aggressively corrected.

With all causes of hyponatremia, it is important to avoid overly rapid correction, which may cause *osmotic demyelination syndrome (ODS)*, which includes central pontine myelinolysis and extrapontine myelinolysis. This syndrome, which occurs within several days of rapid correction of hyponatremia, produces neurologic symptoms, including confusion, agitation, flaccid or spastic quadriparesis, and death. There are usually characteristic pathologic and radiologic changes in the brain. Despite severe symptoms, full recovery does occur in some patients.

ODS is more common in patients who are treated for *chronic* hyponatremia than for acute hyponatremia. Presumably, this difference is based on the adaptation of brain cells to the hyponatremia. The reduced intracellular osmolality, an adaptive mechanism for chronic hyponatremia, makes brain cells susceptible to dehydration during rapid correction of the hyponatremia, which may be the mechanism of ODS. Even though ODS is rare in pediatric patients, it is advisable to avoid correcting the serum [Na^+] by >10 mEq/L/24 hr or >18 mEq/L/48 hr. Desmopressin is a potential option if the serum [Na^+] is increasing too rapidly. This guideline *does not* apply to acute hyponatremia, as may occur with water intoxication, because the hyponatremia is more often symptomatic, and the adaptive decrease in brain osmolality has not had time to occur. The consequences of brain edema in acute hyponatremia exceed the small risk of ODS.

Patients with hyponatremia can have severe neurologic symptoms, such as seizures and coma. The seizures associated with hyponatremia generally are poorly responsive to anticonvulsants. The child with hyponatremia and severe symptoms needs treatment that will quickly reduce cerebral edema. This goal is best accomplished by increasing the extracellular osmolality so that water moves down its osmolar gradient from the ICS to the ECS.

Intravenous hypertonic saline rapidly increases serum [Na^+], and the effect on serum osmolality leads to a decrease in brain edema. Each mL/kg of 3% NaCl increases the serum [Na^+] by approximately 1 mEq/L. A child with active symptoms often improves after receiving 4-6 mL/kg of 3% NaCl.

The child with **hypovolemic hyponatremia** has a deficiency in Na^+ and may have a deficiency in water. The cornerstone of therapy is to replace the Na^+ deficit and any water deficit present. The first step in treating any dehydrated patient is to restore the intravascular volume with isotonic saline. Ultimately, complete restoration of intravascular volume suppresses ADH production, thereby permitting excretion of the excess water. Chapter 75 discusses the management of hyponatremic dehydration.

The management of **hypervolemic hyponatremia** is difficult; patients have an excess of both water and Na^+. Administration of Na^+ leads to worsening volume overload and edema. In addition, patients are retaining water and Na^+ because of their ineffective intravascular volume or renal insufficiency. The cornerstone of therapy is water and Na^+ restriction, because patients have volume overload. Diuretics may help by causing excretion of both Na^+ and water. Vasopressin receptor antagonists (**vaptans**), by blocking the action of ADH and causing a water diuresis, are effective in correcting the hypervolemic hyponatremia caused by heart failure. Vaptans are contraindicated if there are moderate to severe CNS symptoms.

Hyponatremic patients with low albumin from nephrotic syndrome have a better response to diuretics after an infusion of 25% albumin; the [Na^+] often normalizes as a result of expansion of the intravascular volume. A child with heart failure may have an increase in renal water and Na^+ excretion if there is an improvement in cardiac output. This improvement will "turn off" the regulatory hormones causing renal water (ADH) and Na^+ (aldosterone) retention. The patient with kidney failure cannot respond to any of these therapies except fluid restriction. Insensible fluid losses eventually result in an increase in the [Na^+] as long as insensible and urinary losses are greater than intake. A more definitive approach in children with kidney failure is to perform dialysis, which removes water and Na^+.

In **isovolumic hyponatremia** there is usually an excess of water and a mild Na^+ deficit. Therapy is directed at eliminating the excess water. The child with acute excessive water intake loses water in the urine

because ADH production is turned off as a result of the low plasma osmolality. Children may correct their hyponatremia spontaneously over 3-6 hours. For acute, symptomatic hyponatremia as a result of water intoxication, hypertonic saline may be needed to reverse cerebral edema. For chronic hyponatremia from poor solute intake, the child needs an appropriate formula, and excess water intake should be eliminated.

Children with **iatrogenic hyponatremia** caused by the administration of hypotonic IV fluids should receive 3% saline if symptomatic. Subsequent management is dictated by the patient's volume status. The hypovolemic child should receive isotonic IV fluids. The child with nonphysiologic stimuli for ADH production should undergo fluid restriction. Prevention of this iatrogenic complication requires judicious use of IV fluids (see Chapter 74).

Specific hormone replacement is the cornerstone of therapy for the hyponatremia of hypothyroidism or cortisol deficiency. Correction of the underlying defect permits appropriate elimination of the excess water.

SIADH is a condition of excess water, with limited ability of the kidney to excrete water. The mainstay of its therapy is fluid restriction with normal sodium intake. Furosemide and NaCl supplementation are effective in the patient with SIADH and *severe* hyponatremia. Even in a patient with SIADH, furosemide causes an increase in water and Na^+ excretion. The loss of Na^+ is somewhat counterproductive, but this Na^+ can be replaced with hypertonic saline. Because the patient has a net loss of water and the urinary losses of Na^+ have been replaced, there is an increase in the $[Na^+]$, but no significant increase in blood pressure. Vaptans, which block the action of ADH and cause a water diuresis, are effective at correcting **euvolemic hyponatremia**, but overly rapid correction is a potential complication. Vaptans are not appropriate for treating symptomatic hyponatremia because it can take a few hours before the water diuresis occurs.

Treatment of chronic SIADH is challenging. Fluid restriction in children is difficult for nutritional and behavioral reasons. Other options are long-term furosemide therapy with Na^+ supplementation, an oral vaptan (tolvaptan), or oral urea.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

73.4 Potassium

Larry A. Greenbaum

POTASSIUM METABOLISM

Body Content and Physiologic Function

The intracellular $[K^+]$, approximately 150 mEq/L, is much higher than the plasma $[K^+]$ (see Fig. 73.3). The majority of body K^+ is contained in muscle. As muscle mass increases, there is an increase in body K^+. Thus an increase in body K^+ occurs during puberty, and it is more significant in males. The majority of extracellular K^+ is in bone; <1% of total body K^+ is in plasma.

Because most K^+ is intracellular, the plasma concentration does not always reflect the total body K^+ content. A variety of conditions alter the distribution of K^+ between the intracellular and extracellular compartments. Na^+,K^+-ATPase maintains the high intracellular $[K^+]$ by pumping Na^+ out of the cell and K^+ into the cell. This activity balances the normal leak of K^+ out of cells via potassium channels that is driven by the favorable chemical gradient. Insulin increases K^+ movement into cells by activating Na^+,K^+-ATPase. Hyperkalemia stimulates insulin secretion, which helps mitigate the hyperkalemia. Acid-base status affects K^+ distribution, probably via K^+ channels and the Na^+,K^+-ATPase. A decrease in pH drives potassium extracellularly; an increase in pH has the opposite effect. β-Adrenergic agonists stimulate the Na^+,K^+-ATPase, increasing cellular uptake of K^+. This increase is protective, in that hyperkalemia stimulates adrenal release of catecholamines. α-Adrenergic agonists and exercise cause a net movement of K^+ out of the ICS. An increase in plasma osmolality, as with mannitol infusion, leads to water movement out of the cells, and K^+ follows as a result of solvent drag. The serum $[K^+]$ increases by approximately 0.6 mEq/L with each 10 mOsm rise in plasma osmolality.

The high intracellular concentration of K^+, the principal intracellular cation, is maintained through Na^+,K^+-ATPase. The resulting chemical gradient is used to produce the resting membrane potential of cells. K^+ is necessary for the electrical responsiveness of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. The changes in membrane polarization that occur during muscle contraction or nerve conduction make these cells susceptible to changes in serum $[K^+]$. The ratio of intracellular to extracellular K^+ determines the threshold for a cell to generate an action potential and the rate of cellular repolarization. The intracellular $[K^+]$ affects cellular enzymes. K^+ is necessary for maintaining cell volume because of its important contribution to intracellular osmolality.

Potassium Intake

Potassium is plentiful in food. Dietary consumption varies considerably, even though 1-2 mEq/kg is the recommended intake. The intestines normally absorb approximately 90% of ingested K^+. Most absorption occurs in the small intestine, whereas the colon exchanges body K^+ for luminal Na^+. Regulation of intestinal losses normally has a minimal role in maintaining potassium homeostasis, although kidney failure, aldosterone, and glucocorticoids increase colonic secretion of K^+. The increase in intestinal losses in the setting of kidney failure and hyperkalemia, which stimulates aldosterone production, is clinically significant, helping to protect against hyperkalemia.

Potassium Excretion

Some loss of K^+ occurs in sweat but is normally minimal. The colon has the ability to eliminate some K^+. In addition, after an acute K^+ load, much of the K^+ (>40%) moves intracellularly, through the actions of epinephrine and insulin, which are produced in response to hyperkalemia. This process provides transient protection from hyperkalemia, but most ingested K^+ is eventually excreted in the urine. The kidneys principally regulate long-term K^+ balance, and they alter excretion in response to a variety of signals. K^+ is freely filtered at the glomerulus, but 90% is resorbed before reaching the distal tubule and collecting duct, the principal sites of K^+ regulation that have the ability to absorb and secrete K^+. The amount of tubular secretion regulates the amount of K^+ that appears in the urine. The plasma $[K^+]$ directly influences secretion in the distal nephron. As the $[K^+]$ increases, secretion increases.

The principal hormone regulating potassium secretion is **aldosterone**, which is released by the adrenal cortex in response to increased plasma K^+. Its main site of action is the cortical collecting duct, where aldosterone stimulates Na^+ movement from the tubule into the cells. This movement creates a negative charge in the tubular lumen, facilitating K^+ excretion. In addition, the increased intracellular Na^+ stimulates the basolateral Na^+,K^+-ATPase, causing more K^+ to move into the cells lining the cortical collecting duct. Glucocorticoids, ADH, a high urinary flow rate, and high Na^+ delivery to the distal nephron also increase urinary K^+ excretion. Insulin, catecholamines, and urinary ammonia decrease K^+ excretion. Whereas ADH increases K^+ secretion, it also causes water resorption, decreasing urinary flow. The net effect is that ADH has little overall impact on K^+ balance. Alkalosis causes potassium to move into cells, including the cells lining the collecting duct. This movement increases K^+ secretion, and because acidosis has the opposite effect; acidosis decreases K^+ secretion.

The kidney can dramatically vary K^+ excretion in response to changes in intake. Normally, approximately 10–15% of the filtered load is excreted. In an adult, excretion of K^+ can vary from 5-1,000 mEq/day.

HYPERKALEMIA

Hyperkalemia—because of the potential for lethal arrhythmias—is one of the most alarming electrolyte abnormalities.

Etiology and Pathophysiology

Three basic mechanisms cause hyperkalemia including increased intake, cellular shifts, and decreased excretion; spurious lab values are also commonly seen (Table 73.4). In the individual patient, the etiology is sometimes multifactorial.

Spurious hyperkalemia or **pseudohyperkalemia** is very common in children because of the difficulties in obtaining blood specimens. This laboratory result is usually caused by hemolysis during a heelstick or phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, either of which causes local potassium release from muscle.

The serum $[K^+]$ is normally 0.4 mEq/L higher than the plasma value, secondary to K^+ release from cells during clot formation. This phenomenon is exaggerated with thrombocytosis because of K^+ release from platelets. For every 100,000/m^3 increase in the platelet count, the serum $[K^+]$ rises by approximately 0.15 mEq/L. This phenomenon also occurs with the marked white blood cell (WBC) count elevations sometimes seen with leukemia. Elevated WBC counts, typically >200,000/m^3, can cause a dramatic elevation in the measured serum $[K^+]$. Analysis of a plasma sample usually provides an accurate result. It is important to analyze the sample promptly to avoid K^+ release from cells, which occurs if the sample is stored in the cold, or cellular uptake of K^+ and spurious hypokalemia, which occurs with storage at room temperature. Pneumatic tube transport can cause pseudohyperkalemia if cell membranes are fragile (leukemia). Occasionally, heparin causes lysis of leukemic cells and a false elevation of the plasma sample; a blood gas syringe has less heparin and may provide a more accurate reading than a standard tube. There are rare genetic disorders causing in vitro leakage of K^+ from red blood cells (RBCs) that may causes familial **pseudohyperkalemia** (autosomal dominant; *ABCB6* gene).

Because of the kidney's ability to excrete K^+, it is unusual for excessive intake, by itself, to cause hyperkalemia. This condition can occur in a patient who is receiving large quantities of IV or oral K^+ for excessive losses that are no longer present. Frequent or rapid blood transfusions can acutely increase the $[K^+]$ because of the K^+ content of blood, which is variably elevated. Increased intake may precipitate hyperkalemia if there is an underlying defect in K^+ excretion.

The ICS has a very high $[K^+]$, so a shift of K^+ from the ICS to the ECS can have a significant effect on the plasma $[K^+]$. This shift occurs with metabolic acidosis, but the effect is minimal with an organic acid (lactic acidosis, ketoacidosis). A respiratory acidosis has less impact than a metabolic acidosis. Cell destruction, as seen with rhabdomyolysis, tumor lysis syndrome, tissue necrosis, or hemolysis, releases K^+ into the extracellular milieu. The K^+ released from RBCs in internal bleeding, such as hematomas, is resorbed and enters the ECS.

Normal doses of succinylcholine or β blockers and fluoride or digitalis intoxication all cause a shift of K^+ out of the intracellular compartment. *Succinylcholine should not be used during anesthesia in patients at risk for hyperkalemia.* β Blockers prevent the normal cellular uptake of K^+ mediated by binding of β-agonists to the β_2-adrenergic receptors. K^+ release from muscle cells occurs during exercise, and levels can increase by 1-2 mEq/L with high activity. With an increased plasma osmolality, water moves from the ICS, and K^+ follows. This process occurs with hyperglycemia, although in nondiabetic patients the resultant increase in insulin causes K^+ to move intracellularly. In diabetic ketoacidosis (DKA), the absence of insulin causes potassium to leave the ICS, and the problem is compounded by the hyperosmolality. The effect of hyperosmolality causes a transcellular shift of K^+ into the ECS after mannitol or hypertonic saline infusions. **Malignant hyperthermia**, which is triggered by some inhaled anesthetics, causes muscle release of potassium (see Chapter 651.2). **Hyperkalemic periodic paralysis** is an autosomal dominant disorder caused by pathogenic variants in *SCN4A*, the gene for a Na^+ channel. It results in episodic cellular release of K^+ and attacks of paralysis (see Chapter 651.1).

Table 73.4 Causes of Hyperkalemia

SPURIOUS LABORATORY VALUE
Hemolysis
Tissue ischemia during blood drawing
Thrombocytosis
Leukocytosis
Familial pseudohyperkalemia (OMIM 609153)
INCREASED INTAKE
Intravenous or oral
Blood transfusions
TRANSCELLULAR SHIFTS
Acidosis
Rhabdomyolysis
Tumor lysis syndrome
Tissue necrosis
Hemolysis/hematomas/gastrointestinal bleeding
Succinylcholine
Digitalis intoxication
Fluoride intoxication
β-Adrenergic blockers
Exercise
Hyperosmolality
Insulin deficiency
Malignant hyperthermia (OMIM 145600/601887/601888)
Hyperkalemic periodic paralysis (OMIM 170500)
DECREASED EXCRETION
Kidney failure
Primary adrenal disease
Acquired Addison disease
21-Hydroxylase deficiency (OMIM 201910)
3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
Lipoid congenital adrenal hyperplasia (OMIM 201710)
Adrenal hypoplasia congenita (OMIM 300200)
Aldosterone synthase deficiency (OMIM 203400/610600)
Adrenoleukodystrophy (OMIM 300100)
Hyporeninemic hypoaldosteronism
Urinary tract obstruction
Sickle cell disease (OMIM 603903)
Kidney transplant
Lupus nephritis
Renal tubular disease
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Pseudohypoaldosteronism type II (OMIM 614491/614492/614495)
Bartter syndrome, type 2 (OMIM 241200)
Urinary tract obstruction
Kidney transplant
Medications
Renin inhibitors
Angiotensin-converting enzyme inhibitors
Angiotensin II blockers
Potassium-sparing diuretics
Calcineurin inhibitors
Nonsteroidal antiinflammatory drugs
Trimethoprim
Heparin
Drospirenone (in some oral contraceptives)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

The kidneys excrete most of the daily K^+ intake, so a decrease in kidney function can cause hyperkalemia. Newborn infants in general, and especially premature infants, have decreased kidney function at birth; thus they are at increased risk for hyperkalemia despite an absence of intrinsic renal disease. Neonates also have decreased expression of K^+ channels, further limiting K^+ excretion.

A wide range of primary **adrenal disorders**, both hereditary and acquired, can cause decreased production of aldosterone, with secondary hyperkalemia (see Chapters 615 and 616). Patients with these disorders typically have metabolic acidosis and salt wasting with hyponatremia. Children with subtle adrenal insufficiency may have electrolyte problems only during acute illnesses. The most common form of **congenital adrenal hyperplasia**, 21-hydroxylase deficiency, typically manifests in male infants as hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion. Females with this disorder usually are diagnosed as newborns because of their ambiguous genitals; treatment prevents the development of electrolyte problems.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, a result of kidney damage, can lead to decreased aldosterone production. **Hyporeninemia** occurs in many kidney diseases, with some of the more common pediatric causes listed in Table 73.4. These patients typically have hyperkalemia and a metabolic acidosis, without hyponatremia. Some of these patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in K^+ excretion is more extreme than expected for the degree of renal insufficiency.

A variety of **renal tubular disorders** impair renal excretion of K^+. Children with **pseudohypoaldosteronism type 1** have hyperkalemia, metabolic acidosis, and salt wasting (kidney, colon, sweat) leading to hyponatremia and volume depletion; aldosterone values are elevated. In the autosomal recessive variant, there is a defect in the renal Na^+ channel that is normally activated by aldosterone. Patients with this variant have severe symptoms (failure to thrive, diarrhea, recurrent respiratory infections, miliaria-rubra like rash), beginning in infancy. Patients with the autosomal dominant form have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. **Pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension),** also called **Gordon syndrome,** is an autosomal dominant disorder characterized by hypertension caused by salt retention and impaired excretion of K^+ and acid, leading to hyperkalemia and hyperchloremic metabolic acidosis. Pathogenic variants in at least four genes (*WNK4*, *WNK1*, *KLHL3*, *CUL3)* may cause Gordon syndrome. Patients may respond well to thiazide diuretics. In **Bartter syndrome**, caused by pathogenic variants in the potassium channel *ROMK* (type 2 Bartter syndrome), there can be transient hyperkalemia in neonates, but hypokalemia subsequently develops (see Chapter 571.1).

Acquired renal tubular dysfunction, with an impaired ability to excrete K^+, occurs in a number of conditions. These disorders, all characterized by **tubulointerstitial disease,** are often associated with impaired acid secretion and a secondary metabolic acidosis. In some affected children, the metabolic acidosis is the dominant feature, although a high K^+ intake may unmask the defect in K^+ handling. The tubular dysfunction can cause renal salt wasting, potentially leading to hyponatremia. Because of the tubulointerstitial damage, these conditions may also cause hyperkalemia as a result of hyporeninemic hypoaldosteronism.

The risk of hyperkalemia resulting from medications is greatest in patients with underlying renal insufficiency. The predominant mechanism of medication-induced hyperkalemia is impaired renal excretion, although ACE inhibitors may worsen hyperkalemia in anuric patients, probably by inhibiting GI potassium loss, which is normally upregulated in renal insufficiency. The hyperkalemia caused by trimethoprim is especially problematic at higher doses. Potassium-sparing diuretics may easily cause hyperkalemia because they are often used in patients receiving oral K^+ supplements. Oral contraceptives containing drospirenone, which blocks the action of aldosterone, may cause hyperkalemia and should not be used in patients with decreased renal function.

Clinical Manifestations

The most important effects of hyperkalemia result from the role of K^+ in membrane polarization. The cardiac conduction system is usually the dominant concern. Changes in the electrocardiogram (ECG) begin with peaking of the T waves. This is followed, as K^+ level increases, by ST-segment depression, an increased PR interval, flattening of the P wave, and widening of the QRS complex (Fig. 73.4). However, the correlation between K^+ level and ECG changes is poor. This process can eventually progress to ventricular fibrillation. Asystole may also occur. Some patients have paresthesias, fasciculations, weakness, and even an ascending paralysis, but cardiac toxicity usually precedes these clinical symptoms, emphasizing the danger of assuming that an absence of symptoms implies an absence of danger. Chronic hyperkalemia is generally better tolerated than acute hyperkalemia.

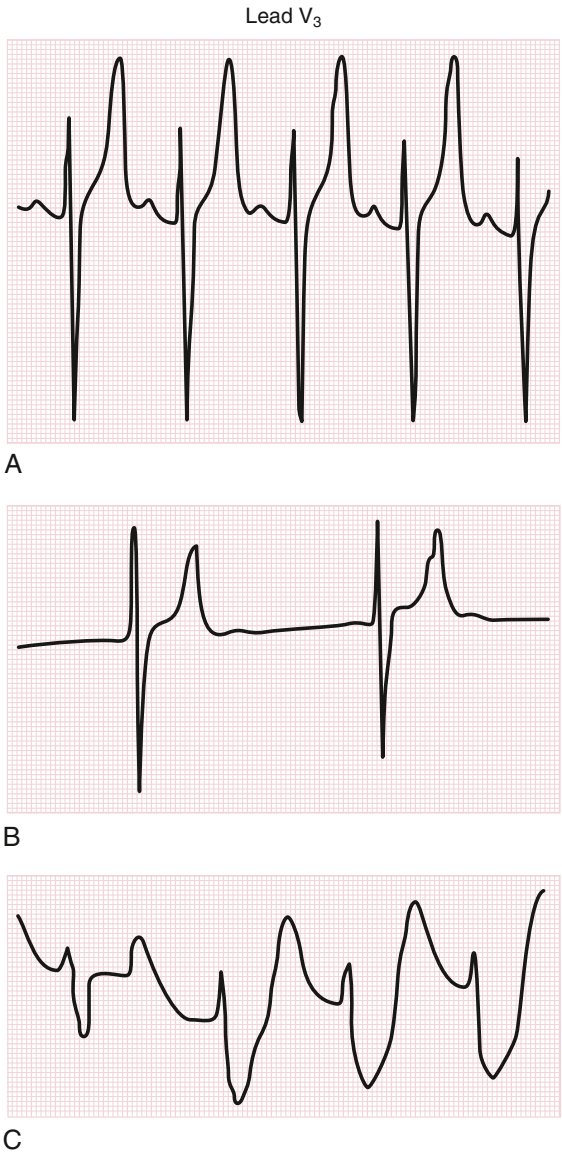

Fig. 73.4 The effects of progressive hyperkalemia on the electrocardiogram. All of the ECGs are from lead V_3. **A,** Serum potassium concentration ($[K^+]$) = 6.8 mEq/L; note the peaked T waves together with normal sinus rhythm. **B,** Serum $[K^+]$ = 8.9 mEq/L; note the peaked T waves and absent P waves. **C,** Serum $[K^+]$ >8.9 mEq/L; note the classic sine wave with absent P waves, marked prolongation of the QRS complex, and peaked T waves. *(From Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Elsevier; 2020. Fig. 109.2, p. 727.)*

Diagnosis

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is very common in children, so obtaining a second potassium measurement is often appropriate. If there is a significant elevation of WBC or platelet count, the second measurement should be performed on a plasma sample that is evaluated promptly. The history should initially focus on potassium intake, risk factors for transcellular shifts of K^+, medications that cause hyperkalemia, and signs of renal insufficiency, such as oliguria and edema. Initial laboratory evaluation should include creatinine, BUN, and assessment of the acid-base status. Many etiologies of hyperkalemia cause **metabolic acidosis**, which worsens hyperkalemia through the transcellular shift of K^+ out of cells. Decreased kidney function is a common cause of the combination of metabolic acidosis and hyperkalemia, also seen in diseases associated with aldosterone insufficiency or aldosterone resistance. Children with absent or ineffective aldosterone often have hyponatremia and volume depletion because of salt wasting. Genetic diseases, such as congenital adrenal hyperplasia and pseudohypoaldosteronism, usually manifest in infancy and should be strongly considered in the infant with hyperkalemia and metabolic acidosis, especially if hyponatremia is present.

It is important to consider the various etiologies of a transcellular K^+ shift. In some of these disorders, the K^+ level continues to increase, despite the elimination of all K^+ intake, especially with concurrent renal insufficiency. This increase is potentially seen in tumor lysis syndrome, hemolysis, rhabdomyolysis, and other causes of cell death. All these entities can cause concomitant hyperphosphatemia and hyperuricemia. **Rhabdomyolysis** produces an elevated creatinine phosphokinase (CPK) value and hypocalcemia, whereas children with hemolysis have hemoglobinuria and a decreasing hematocrit. For the child with diabetes, elevated blood glucose and acidosis suggest a transcellular shift of K^+.

Treatment

The plasma K^+ level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. High serum $[K^+]$ and the presence of ECG changes require vigorous treatment. An additional source of concern is the patient in whom plasma K^+ levels are rising despite minimal intake. This situation can happen if there is cellular release of K^+ (tumor lysis syndrome), especially in the setting of diminished excretion (kidney failure).

The first action in a child with a concerning elevation of plasma $[K^+]$ is to stop all sources of additional K^+ (oral, IV). Washed RBCs can be used for patients who require blood transfusions. If the $[K^+]$ is >6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Peaked T waves are the first sign of hyperkalemia, followed by a prolonged PR interval, and when most severe, prolonged QRS complex. Life-threatening ventricular arrhythmias may also develop. The treatment of hyperkalemia has two basic goals: (1) to stabilize the heart to prevent life-threatening arrhythmias and (2) to remove K^+ from the body. The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes) but do not remove K^+ from the body. **Calcium** stabilizes the cell membrane of heart cells, preventing arrhythmias; it is given IV over a few minutes, and its action is almost immediate. Calcium should be given over 30 minutes in a patient receiving digitalis because the calcium may cause arrhythmias. **Bicarbonate** causes potassium to move intracellularly, lowering the plasma $[K^+]$; it is most efficacious in a patient with a metabolic acidosis. **Insulin** causes K^+ to move intracellularly but must be given with **glucose** to avoid hypoglycemia. The combination of insulin and glucose works within 30 minutes. Nebulized **albuterol**, by stimulation of β_1-adrenergic receptors, leads to rapid intracellular movement of K^+. This has the advantage of not requiring an IV route of administration, allowing it to be given concurrently with the other measures.

It is critical to begin measures that remove K^+ from the body. In patients who are not anuric, a **loop diuretic** increases renal excretion of K^+. A high dose may be required in a patient with significant renal insufficiency. **Sodium polystyrene sulfonate** (**SPS**; Kayexalate) is an exchange resin that is given either rectally or orally. **Patiromer** and **sodium zirconium cyclosilicate** are oral exchange resins for treating hyperkalemia. Some patients require **dialysis** for acute K^+ removal. Dialysis is often necessary if the patient has either severe kidney failure or an especially high rate of endogenous K^+ release, as is sometimes present with tumor lysis syndrome or rhabdomyolysis. Hemodialysis rapidly lowers plasma $[K^+]$. Peritoneal dialysis is not nearly as quick or reliable, but it is usually adequate as long as the acute problem can be managed with medications and the endogenous release of K^+ is not high.

Long-term management of hyperkalemia includes reducing intake through dietary changes and eliminating or reducing medications that cause hyperkalemia (see Chapter 572). Some patients require medications to increase potassium excretion, such as SPS, patiromer, sodium zirconium cyclosilicate, and loop or thiazide diuretics. Some infants with chronic kidney disease may need to start dialysis to allow adequate caloric intake without hyperkalemia. It is unusual for an older child to require dialysis principally to control chronic hyperkalemia. The disorders caused by aldosterone deficiency respond to replacement therapy with fludrocortisone.

HYPOKALEMIA

Hypokalemia is common in children, with most cases related to gastroenteritis.

Etiology and Pathophysiology

There are four basic mechanisms of hypokalemia (Table 73.5). **Spurious hypokalemia** occurs in patients with leukemia and very elevated WBC counts if plasma for analysis is left at room temperature, permitting the WBCs to take up K^+ from the plasma. With a transcellular shift, there is no change in total body K^+, although there may be concomitant potassium depletion resulting from other factors. Decreased intake, extrarenal losses, and renal losses are all associated with total body K^+ depletion. In addition, seasonal pseudo-hypokalemia is seen during warm summer months as a laboratory phenomenon when blood samples are exposed to a warm environment. On immediate retesting, the potassium level is normal. This should not be confused with a pseudo-Bartter syndrome (hypokalemic, hypochloremic, alkalosis) seen in children with cystic fibrosis in a very warm environment due to excessive sweating.

Because the intracellular $[K^+]$ is much higher than the plasma level, a significant amount of K^+ can move into cells without greatly changing the intracellular $[K^+]$. **Alkalemia** is one of the more common causes of a transcellular shift. The effect is much greater with a *metabolic* alkalosis than with a respiratory alkalosis. The impact of exogenous insulin on K^+ movement into the cells is substantial in patients with DKA. Endogenous insulin may be the cause when a patient is given a bolus of glucose. Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of K^+. Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations. Children with **hypokalemic periodic paralysis,** a rare autosomal dominant disorder, have acute cellular uptake of K^+ (see Chapter 651). **Thyrotoxic periodic paralysis,** which is more common in Asians, is an unusual initial manifestation of hyperthyroidism. Affected patients have dramatic hypokalemia as a result of a transcellular shift of potassium. Hypokalemia can occur during refeeding syndrome (see Chapters 63 and 385.7).

Inadequate K^+ intake occurs in **anorexia nervosa**; accompanying bulimia and laxative or diuretic abuse exacerbates the K^+ deficiency.

Table 73.5 Causes of Hypokalemia

SPURIOUS LABORATORY VALUE
High white blood cell count

TRANSCELLULAR SHIFTS
Alkalemia
Insulin
α-Adrenergic agonists
Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
Hypokalemic periodic paralysis (OMIM 170400)
Thyrotoxic period paralysis
Refeeding syndrome

DECREASED INTAKE
Anorexia nervosa

EXTRARENAL LOSSES
Diarrhea
Laxative abuse
Sweating
Sodium polystyrene sulfonate (Kayexalate) or clay ingestion

RENAL LOSSES
With Metabolic Acidosis
Distal renal tubular acidosis (OMIM 179800/602722/267300/611590)
Proximal renal tubular acidosis (OMIM 604278)*
Ureterosigmoidostomy
Diabetic ketoacidosis

Without Specific Acid-Base Disturbance
Tubular toxins: amphotericin, cisplatin, aminoglycosides
Interstitial nephritis
Diuretic phase of acute tubular necrosis
Postobstructive diuresis
Hypomagnesemia
High urine anions (e.g., penicillin or penicillin derivatives)

With Metabolic Alkalosis
Low urine chloride
- Emesis or nasogastric suction
- Chloride-losing diarrhea (OMIM 214700)
- Cystic fibrosis (OMIM 219700)
- Low-chloride formula
- Posthypercapnia
- Previous loop or thiazide diuretic use

High urine chloride and normal blood pressure
- Gitelman syndrome (OMIM 263800)
- Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
- Autosomal dominant hypoparathyroidism (OMIM 146200)
- EAST syndrome (OMIM 612780)
- Autosomal dominant kidney hypomagnesemia due to *RRAGD* variant (OMIM not assigned)
- Loop and thiazide diuretics (current)

High urine chloride and high blood pressure
- Adrenal adenoma or hyperplasia
- Glucocorticoid-remediable aldosteronism (OMIM 103900)
- Hyperaldosteronism type II (OMIM 605635)
- Familial hyperaldosteronism type III (OMIM 613677)
- Familial hyperaldosteronism type IV (OMIM 617027)
- Renovascular disease
- Renin-secreting tumor
- 17β-Hydroxylase deficiency (OMIM 202110)
- 11β-Hydroxylase deficiency (OMIM 202010)
- Cushing syndrome
- 11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
- Licorice ingestion
- Liddle syndrome (OMIM 177200)
- Early-onset autosomal dominant hypertension with exacerbation in pregnancy (OMIM 605115)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.
EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Sweat losses of K^+ can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of K^+ (discussed later). Diarrheal fluid has a high concentration of K^+, and hypokalemia because of diarrhea is usually associated with metabolic acidosis resulting from stool losses of bicarbonate. In contrast, normal acid-base balance or mild metabolic alkalosis is seen with laxative abuse. Intake of potassium-binding resins (SPS) or ingestion of clay because of pica increases stool losses of potassium.

Urinary potassium wasting may be accompanied by a **metabolic acidosis** (proximal or distal RTA). In DKA, although it is often associated with normal plasma [K^+] from transcellular shifts, there is significant total body K^+ depletion from urinary losses because of the osmotic diuresis, and the K^+ level may decrease dramatically with insulin therapy (see Chapter 629). Both the polyuric phase of acute tubular necrosis and postobstructive diuresis cause transient, highly variable K^+ wasting and may be associated with metabolic acidosis. Tubular damage, which occurs either directly from medications or secondary to interstitial nephritis, is often accompanied by other tubular losses, including magnesium, Na^+, and water. Such tubular damage may cause a secondary RTA with metabolic acidosis. Isolated magnesium deficiency causes renal K^+ wasting. Penicillin is an anion excreted in the urine, resulting in increased K^+ excretion because the penicillin anion must be accompanied by a cation. Hypokalemia from penicillin therapy occurs only with the *sodium* salt of penicillin, not with the potassium salt.

Urinary K^+ wasting is often accompanied by a **metabolic alkalosis**. This condition is usually associated with increased aldosterone, which increases urinary K^+ and acid losses, contributing to the hypokalemia and the metabolic alkalosis. Other mechanisms often contribute to both the K^+ losses and the metabolic alkalosis. With emesis or nasogastric suction, there is gastric loss of K^+, but this is minimal given the low K^+ content of gastric fluid, approximately 10 mEq/L. More important is the gastric loss of hydrochloric acid (HCl), leading to metabolic alkalosis and a state of volume depletion. The kidney compensates for metabolic alkalosis by excreting bicarbonate in the urine, but there is obligate loss of K^+ and Na^+ with the bicarbonate. The volume depletion raises aldosterone levels, further increasing urinary K^+ losses and preventing correction of metabolic alkalosis and hypokalemia until the volume depletion is corrected.

Urinary chloride (Cl^-) is low as a response to the volume depletion. Because the volume depletion is secondary to Cl^- loss, this is a **state of Cl^- deficiency**. There were cases of Cl^- deficiency resulting from infant formula deficient in Cl^-, which caused a metabolic alkalosis with hypokalemia and low urine [Cl^-]. Current infant formula is not deficient in Cl^-. A similar mechanism occurs in cystic fibrosis because of Cl^- loss in sweat. In **congenital chloride-losing diarrhea**, an autosomal recessive

disorder, there is high stool loss of Cl^-, leading to metabolic alkalosis, an unusual sequela of diarrhea. Because of stool K^+ losses, Cl^- deficiency, and metabolic alkalosis, patients with congenital chloride-losing diarrhea have hypokalemia.

During respiratory acidosis, there is renal compensation, with retention of bicarbonate and excretion of Cl^-. After the respiratory acidosis is corrected, the patients have Cl^- deficiency and post–hypercapnic alkalosis with secondary hypokalemia. Patients with Cl^- deficiency, metabolic alkalosis, and hypokalemia have a urinary $[Cl^-]$ of <10 mEq/L. Loop and thiazide diuretics lead to hypokalemia, metabolic alkalosis, and Cl^- deficiency. During treatment, these patients have high urine chloride levels resulting from the effect of the diuretic. However, after the diuretics are discontinued, there is residual Cl^- deficiency, the urinary $[Cl^-]$ is appropriately low, and neither the hypokalemia nor the alkalosis resolves until the Cl^- deficiency is corrected.

The combination of metabolic alkalosis, hypokalemia, high urine $[Cl^-]$, and normal blood pressure is characteristic of Bartter syndrome, Gitelman syndrome, and current diuretic use. Patients with any of these conditions have high urinary losses of Cl^- despite a state of relative volume depletion with secondary hyperaldosteronism with high plasma renin. Bartter and Gitelman syndromes are autosomal recessive disorders caused by defects in tubular transporters (see Chapter 571). **Bartter syndrome** is usually associated with hypercalciuria, and often with nephrocalcinosis, whereas children with **Gitelman syndrome** have low urinary calcium losses but hypomagnesemia because of urinary magnesium losses. Some patients with Bartter syndrome have hypomagnesemia. A transient antenatal form of Bartter syndrome is associated with severe polyhydramnios and pathogenic variants in *MAGED2*.

Some patients with hypoparathyroidism and hypocalcemia caused by activating pathogenic variants of the calcium-sensing receptor (**autosomal dominant hypoparathyroidism**) have hypokalemia, hypomagnesemia, and metabolic alkalosis. The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism. **EAST syndrome**, an autosomal recessive disorder caused by pathologic variants in the gene for a potassium channel in the kidney, inner ear, and brain, consists of *e*pilepsy, *a*taxia, *s*ensorineural hearing loss, and *t*ubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).

In the presence of *high aldosterone levels*, there is urinary loss of K^+, hypokalemia, metabolic alkalosis, and elevated urinary $[Cl^-]$; renal retention of Na^+ leads to **hypertension**. Primary hyperaldosteronism caused by adenoma or hyperplasia is much less common in children than in adults (see Chapters 619 and 620). **Glucocorticoid-remediable aldosteronism**, an autosomal dominant disorder that leads to high levels of aldosterone (but low renin levels), is often diagnosed in childhood, although hypokalemia is not always present. **Familial hyperaldosteronism type II**, an autosomal dominant disorder, is due to a gain-of-function variant in *CLCN2* that causes increased aldosterone synthesis. **Familial hyperaldosteronism type III**, an autosomal dominant disorder, is due to a gain-of-function variant in *KCNJ5* that causes a dramatic increase in aldosterone synthesis and severe hypertension and hypokalemia. **Familial hyperaldosteronism type IV**, an autosomal dominant disorder, is due to a gain-of-function variant in *CACNA1H* that causes increased aldosterone synthesis.

Increased aldosterone levels may also be *secondary* to increased renin production. Renal artery stenosis leads to hypertension from increased renin and secondary hyperaldosteronism. The increased aldosterone can cause hypokalemia and metabolic alkalosis, although most patients have normal electrolyte levels. Renin-producing tumors, which are extremely rare, can cause hypokalemia.

A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels. Some are a result of increased levels of mineralocorticoids other than aldosterone. Such increases occur in two forms of **congenital adrenal hyperplasia** (see Chapter 616). In **11β-hydroxylase deficiency**, which is associated with virilization, 11-deoxycorticosterone is elevated, causing variable hypertension and hypokalemia. A similar mechanism, increased 11-deoxycorticosterone, occurs in **17α-hydroxylase deficiency**, but patients with this disorder are more uniformly hypertensive and hypokalemic, and they have a defect in sex hormone production. **Cushing syndrome**, frequently associated with hypertension, less frequently causes metabolic alkalosis and hypokalemia, secondary to the mineralocorticoid activity of cortisol. In **11β-hydroxysteroid dehydrogenase deficiency**, an autosomal recessive disorder, the enzymatic defect prevents the conversion of cortisol to cortisone in the kidney. Because cortisol binds to and activates the aldosterone receptor, children with this deficiency have all the features of excessive mineralocorticoids, including hypertension, hypokalemia, and metabolic alkalosis, but low levels of aldosterone and renin. Patients with this disorder, which is also called **apparent mineralocorticoid excess**, respond to spironolactone therapy, which blocks the mineralocorticoid receptor. An acquired form of 11β-hydroxysteroid dehydrogenase deficiency occurs from the ingestion of substances that inhibit this enzyme. A classic example is glycyrrhizic acid, which is found in natural licorice. **Liddle syndrome** is an autosomal dominant disorder that results from activating pathogenic variants of the distal nephron sodium channel that is normally upregulated by aldosterone. Patients have the characteristics of hyperaldosteronism—hypertension, hypokalemia, and alkalosis—but low serum renin and aldosterone levels. These patients respond to the potassium-sparing diuretics (triamterene and amiloride) that inhibit this sodium channel (see Chapter 571.3). A pathogenic variant in the mineralocorticoid receptor causes **early-onset autosomal dominant hypertension with exacerbation in pregnancy**. Hypokalemia is usually mild but worsens during pregnancy; renin and aldosterone levels are low.

Clinical Manifestations

The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave (Fig. 73.5). Ventricular fibrillation and torsades de pointes may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block (see Chapter 484).

The clinical consequences of hypokalemia in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication, generally only at $[K^+]$ <2.5 mEq/L. It usually starts in the legs and moves to the arms. Respiratory paralysis may require mechanical ventilation. Some patients have rhabdomyolysis; the risk increases with exercise. Hypokalemia slows GI motility. This effect manifests as constipation; with K^+ levels <2.5 mEq/L, an ileus may occur. Hypokalemia impairs bladder function, potentially leading to urinary retention.

Hypokalemia causes **polyuria** and **polydipsia** by impairing urinary concentrating ability, which produces nephrogenic diabetes insipidus. Hypokalemia stimulates renal ammonia production, an effect that is clinically significant if hepatic failure is present, because the liver cannot metabolize the ammonia. Consequently, hypokalemia may worsen hepatic encephalopathy. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts.

Diagnosis

Most causes of hypokalemia are readily apparent from the history. It is important to review the child's diet, GI losses, and medications. Both emesis and diuretic use can be surreptitious. The presence of **hypertension** suggests excess mineralocorticoid effects or levels. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea and distal and proximal RTA. A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, use of diuretics, and

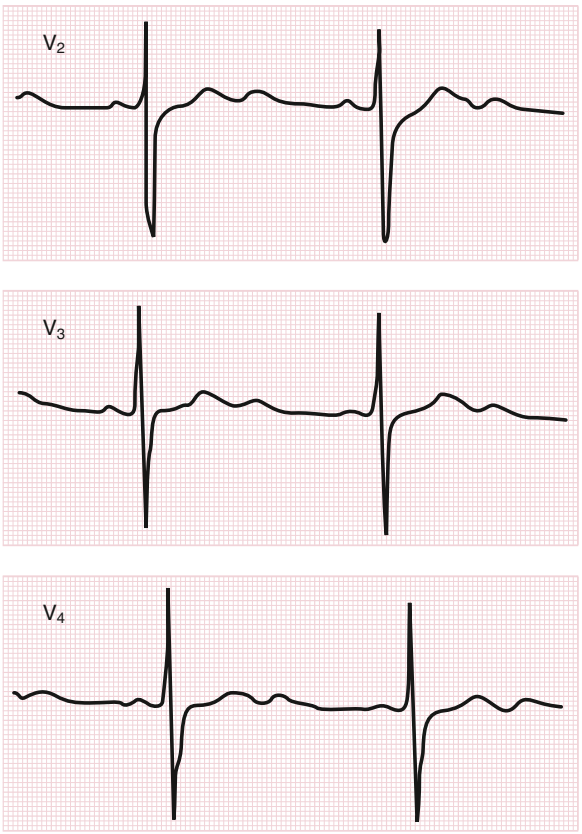

Fig. 73.5 The ECG manifestations of hypokalemia. The serum potassium concentration was 2.2 mEq/L. The ST segment is prolonged, primarily because of a U wave following the T wave, and the T wave is flattened. *(From Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Elsevier; 2020. Fig. 109.1, p 727.)*

Bartter and Gitelman syndromes. Figure 73.6 shows an approach to persistent hypokalemia.

If a clear etiology is not apparent, the measurement of urinary K^+ distinguishes between renal and extrarenal losses. The kidneys should conserve K^+ in the presence of extrarenal losses. Urinary K^+ losses can be assessed with a 24-hour urine collection, spot K^+:creatinine ratio, fractional excretion of K^+, or calculation of the *transtubular K^+ gradient* (TTKG), which is the most widely used approach in children:

$$\text{TTKG} = [K]_{\text{urine}} / [K]_{\text{plasma}} \times (\text{plasma osmolality} / \text{urine osmolality})$$

where $[K]_{\text{urine}}$ = urine potassium concentration and $[K]_{\text{plasma}}$ = plasma potassium concentration.

The urine osmolality must be greater than the serum osmolality for the result of this calculation to be valid. A TTKG >4 in the presence of hypokalemia suggests excessive urinary losses of K^+. The urinary K^+ excretion value can be misleading if the stimulus for renal loss, such as a diuretic, is no longer present.

Treatment

Factors that influence the treatment of hypokalemia include the K^+ level, clinical symptoms, kidney function, the presence of transcellular shifts of K^+, ongoing losses, and the patient's ability to tolerate oral K^+. Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive K^+. The plasma potassium level does not always provide an accurate estimation of the total body K^+ deficit because there may be shifts of K^+ from the ICS to the plasma. Clinically, such shifts occur most often with metabolic acidosis and the insulin deficiency of DKA; the plasma $[K^+]$ measurement underestimates the degree of total body K^+ depletion. When these problems are corrected, K^+ moves into the ICS, so more K^+ supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of K^+ into the cells indicates that the total body K^+ depletion is less severe. In an isolated transcellular shift, as in hypokalemic periodic paralysis, K^+ supplementation should be used cautiously, given the risk of hyperkalemia when the transcellular shift resolves. This caution is especially required in thyrotoxic periodic paralysis, which responds dramatically to propranolol, with correction of weakness and hypokalemia. Patients who have ongoing losses of K^+ need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, IV K^+ should be used very cautiously. Oral K^+ is safer, but not as rapid in urgent situations. Liquid preparations are bitter tasting; microencapsulated or wax matrix formulations are less irritating than tablets to the gastric mucosa. Oral dosing is variable depending on the clinical situation. A typical starting dose is 1-2 mEq/kg/day, with a maximum of 60 mEq/day in divided doses. The dose of IV potassium is 0.5-1.0 mEq/kg, usually given over 1 hour. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. Potassium chloride is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities may dictate other options. Patients with acidosis and hypokalemia can receive potassium acetate or potassium citrate. If hypophosphatemia is present, some of the potassium deficit can be replaced with potassium phosphate. It is sometimes possible to decrease ongoing K^+ losses. For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with decreased kidney function. If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), restoration of intravascular volume with adequate NaCl will decrease urinary K^+ losses. Correction of concurrent hypomagnesemia is important because it may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

73.5 Magnesium

Larry A. Greenbaum

MAGNESIUM METABOLISM

Body Content and Physiologic Function

Magnesium is the fourth most common cation in the body and the third most common intracellular cation (see Fig. 73.3). From 50–60% of body magnesium is in bone, where it serves as a reservoir because 30% is exchangeable, allowing movement to the ECS. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable. Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver.

The normal plasma magnesium concentration is 1.5-2.3 mg/dL (1.2-1.9 mEq/L; 0.62-0.94 mmol/L), with some variation among clinical laboratories. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only 1% of body magnesium is extracellular (60% ionized, 15% complexed, 25% protein bound). In the United States, serum magnesium is reported as mg/dL (Table 73.6). Values in the left-column unit are converted into the right-column unit by multiplying the conversion factor (e.g., calcium of 10 mg/dL × 0.25 = 2.5 mmol/L). Dividing the right-column unit by the conversion factor converts to the units of the left-column unit.

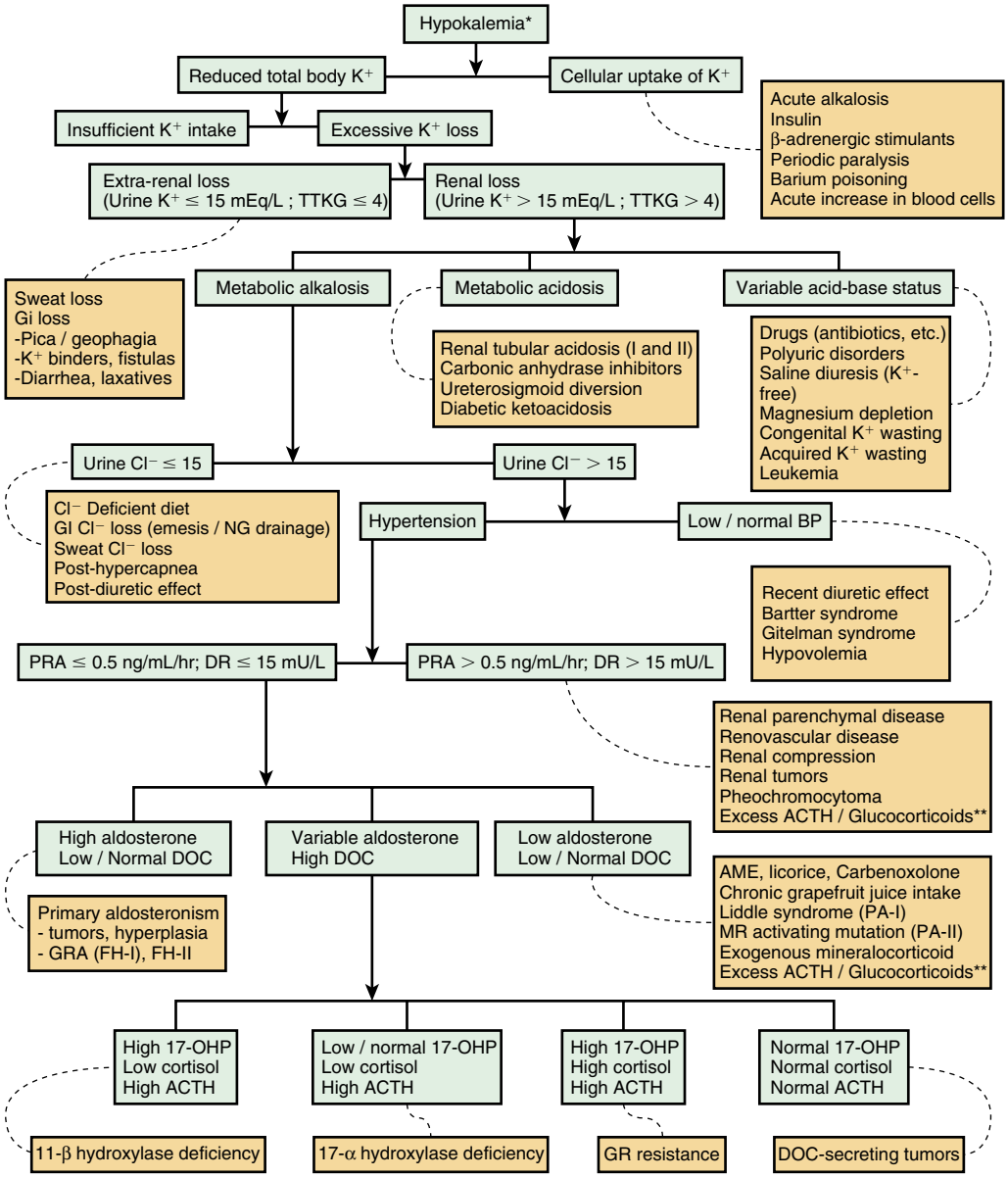

Fig. 73.6 Diagnostic algorithm to evaluate persistent hypokalemia. *Spurious hypokalemia must be excluded. **Hypokalemia is uncommon in uncomplicated edematous disorders and in conditions associated with excessive glucocorticosteroids. Conditions associated with high circulating levels of glucocorticosteroids often have normal renin activity. 17-OHP, 17-Hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; Cl^-, chloride; DOC, 11-deoxycorticosterone; DR, direct renin assay; GI, gastrointestinal; FH-II, familial hyperaldosteronism type II; GR, glucocorticoid receptor; GRA (FH-I), glucocorticoid remediable aldosteronism (familial hyperaldosteronism type I); K^+, potassium; MR, mineralocorticoid receptor; PA-I, pseudohyperaldosteronism type I; PA-II, pseudohyperaldosteronism type II; PRA, plasma renin activity; TTKG, transtubular potassium gradient. *(From Shoemaker LR, Eaton BV, Buchino JJ. A three-year-old with persistent hypokalemia. J Pediatr. 2007;151[6]:696–699.)*

Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by ATPases, cyclases, and kinases.

Magnesium Intake

Between 30% and 50% of dietary magnesium is absorbed. Good dietary sources include green vegetables, cereals, nuts, meats, and hard water, although many foods contain magnesium. Human milk contains approximately 35 mg/L of magnesium; formula contains 40-70 mg/L. The small intestine is the major site of magnesium absorption, but the regulation of magnesium absorption is poorly understood. There is passive absorption, which permits high absorption in the presence of excessive intake. It probably occurs by a paracellular mechanism. Absorption is diminished in the presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and parathyroid hormone (PTH) may enhance absorption, although this effect is limited. Intestinal absorption does increase when intake is decreased, possibly by a saturable, active transport system. If there is no oral intake of magnesium, obligatory secretory losses prevent the complete elimination of intestinal losses.

Magnesium Excretion

Renal excretion is the principal regulator of magnesium balance. There is no defined hormonal regulatory system, although PTH may increase

tubular resorption. Approximately 15% of resorption occurs in the proximal tubule and 70% in the thick ascending limb (TAL) of the loop of Henle. Proximal resorption may be higher in neonates. High serum magnesium levels inhibit resorption in the TAL, suggesting that active transport is involved. Approximately 5–10% of filtered magnesium is resorbed in the distal tubule. Hypomagnesemia increases absorption in the TAL and the distal tubule.

HYPOMAGNESEMIA

Hypomagnesemia is relatively common in hospitalized patients, although most cases are asymptomatic. Detection requires a high index of suspicion because magnesium is not measured in most basic metabolic panels.

Table 73.6 Conversion Factors for Calcium, Magnesium, and Phosphorus

	UNIT	CONVERSION FACTOR	UNIT
Calcium	mg/dL	0.25	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.5	mEq/L
Magnesium	mg/dL	0.411	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.822	mEq/L
Phosphorus	mg/dL	0.32	mmol/L

Etiology and Pathophysiology

GI and renal losses are the major causes of hypomagnesemia (Table 73.7). Diarrheal fluid contains up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss because of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses. The potassium-lowering agent patiromer binds magnesium and may cause hypomagnesemia.

Hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder, is caused by decreased intestinal absorption of magnesium and renal magnesium wasting. Patients with this disorder have pathogenic variants in a gene expressed in intestine and kidney; *TRPM6* codes for a transient receptor potential cation channel. The patients have seizures, tetany, tremor, or restlessness at 2-8 weeks of life because of severe hypomagnesemia (0.2-0.8 mg/dL) and secondary hypocalcemia.

Renal losses may occur because of medications that are direct tubular toxins. Amphotericin frequently causes significant magnesium wasting and is typically associated with other tubular defects (especially potassium wasting). Cisplatin produces dramatic renal magnesium losses. Diuretics affect tubular handling of magnesium. Loop diuretics cause a mild increase in magnesium excretion, and thiazide diuretics have even less effect. Chronic use of proton pump inhibitors (PPIs) may cause hypomagnesemia. Potassium-sparing diuretics reduce magnesium losses. Osmotic agents, such as mannitol, glucose in diabetes mellitus, and urea in the recovery phase of acute tubular necrosis, increase urinary magnesium losses. Epidermal growth factor (EGF) receptor inhibitors cause renal magnesium wasting. IV fluid, by expanding the intravascular volume, decreases renal resorption of

Table 73.7 Causes of Hypomagnesemia

GASTROINTESTINAL LOSSES
- Diarrhea
- Nasogastric suction or emesis
- Inflammatory bowel disease
- Celiac disease
- Cystic fibrosis
- Intestinal lymphangiectasia
- Small bowel resection or bypass
- Pancreatitis
- Protein-calorie malnutrition
- Patiromer
- Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*

RENAL DISORDERS
- Medications
  - Amphotericin
  - Cisplatin
  - Cyclosporine, tacrolimus
  - Loop and thiazide diuretics
  - Mannitol
  - Pentamidine
  - Proton pump inhibitors
  - Aminoglycosides
  - Thiazide diuretics
  - Epidermal growth factor receptor inhibitors
- Diabetes
- Acute tubular necrosis (recovery phase)
- Postobstructive nephropathy
- Chronic kidney diseases
  - Interstitial nephritis
  - Glomerulonephritis
  - Post–renal transplantation
- Hypercalcemia
- Intravenous fluids
- Primary aldosteronism
- Genetic diseases
  - Gitelman syndrome (OMIM 263800)
  - Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
  - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
  - Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
  - Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)
  - Renal cysts and diabetes syndrome due to *HNF1β* variants (OMIM 137920)
  - Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
  - EAST syndrome (OMIM 612780)
  - Autosomal dominant hypoparathyroidism (OMIM 146200)
  - Mitochondrial disorders (OMIM 500005)
- Hyperuricemia, pulmonary hypertension, renal failure in infancy and alkalosis, HUPRA syndrome (OMIM 613845)
- Transient neonatal hyperphenylalaninemia followed by hypomagnesemia and maturity onset diabetes of the young (OMIM 264070)
- Hypomagnesemia, seizures and mental retardation due to *CNNM2* pathogenic variants (OMIM 616418)
- Autosomal dominant kidney hypomagnesemia due to *RRAGD* pathogenic variants (OMIM not assigned)

MISCELLANEOUS CAUSES
- Poor intake
- Hungry bone syndrome
- Insulin administration
- Pancreatitis
- Intrauterine growth restriction
- Infants of diabetic mothers
- Exchange transfusion

*This disorder is also associated with renal magnesium wasting.
EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

sodium and water, thereby impairing magnesium resorption. Hypercalcemia inhibits magnesium resorption in the loop of Henle, although this inhibition does not occur in hypercalcemia caused by familial hypercalcemic hypocalciuria or lithium.

A number of rare genetic diseases cause renal magnesium loss. Gitelman and Bartter syndromes, both autosomal recessive disorders, are the most common entities (see Chapter 571). **Gitelman syndrome**, caused by a defect in the thiazide-sensitive Na^+-Cl^- cotransporter in the distal tubule, is usually associated with hypomagnesemia. Hypomagnesemia occurs in a minority of patients with **Bartter syndrome**, which can be caused by pathogenic variants in multiple genes necessary for Na^+ and Cl^- reabsorption in the loop of Henle. In both disorders, there is hypokalemic metabolic alkalosis. Typically, hypomagnesemia is not severe and is asymptomatic, although tetany as a result of hypomagnesemia occasionally occurs.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (Michelis-Castrillo syndrome), an autosomal recessive disorder, is caused by pathogenic variants in the gene for claudin 16 (paracellin-1), located in the tight junctions of the TAL of the loop of Henle. Patients with the disease have severe renal wasting of magnesium and calcium with secondary hypomagnesemia and nephrocalcinosis; serum calcium levels are normal. Chronic kidney failure frequently occurs during childhood. Other features include kidney stones, urinary tract infections, hematuria, increased PTH levels, tetany, seizures, incomplete distal RTA, hyperuricemia, polyuria, and polydipsia. Patients with **familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement** have pathogenic variants in the gene for claudin 19.

Autosomal recessive renal magnesium wasting with normocalciuria is caused by pathogenic variants in the EGF gene. Clinical manifestations include seizures, mild to moderate psychomotor retardation, and brisk tendon reflexes.

Autosomal dominant renal magnesium wasting is caused by pathogenic variants in a number of different genes. A dominant-negative pathogenic variant in the gene encoding the Na^+,K^+-ATPase γ subunit is associated with hypomagnesemia, increased urinary magnesium losses, hypocalciuria, and normocalcemia. Patients may present with seizures; most are asymptomatic, despite serum magnesium levels of 0.8-1.5 mg/dL. Pathogenic variants in *CNNM2*, which encodes a protein that mediates magnesium-sensitive sodium currents, cause isolated hypomagnesemia. A pathogenic variant in *KCNA1*, a gene that encodes a K^+ channel, also causes an autosomal dominant form of hypomagnesemia; symptoms may be severe.

Renal cysts and diabetes syndrome, which is caused by pathogenic variants in the gene for hepatocyte nuclear factor-1β, is associated with hypomagnesemia, despite the frequent presence of decreased kidney function. The hypomagnesemia is usually mild but may cause symptomatic hypocalcemia. **EAST syndrome** is caused by pathogenic variants in a potassium channel, and patients with this autosomal recessive disorder have hypokalemia, metabolic alkalosis, and hypomagnesemia. Pathogenic variants of *RRAGD* cause **autosomal dominant kidney hypomagnesemia,** and affected patients may have hypokalemia, hypomagnesemia, metabolic alkalosis, hypercalciuria, nephrocalcinosis, and a severe cardiomyopathy. **Autosomal dominant hypoparathyroidism** is caused by an activating pathogenic variant in the calcium-sensing receptor, which also senses magnesium levels in the kidney (see Chapter 611). The abnormal receptor inappropriately perceives that magnesium and calcium levels are elevated, leading to urinary wasting of both cations. Hypomagnesemia, if present, is usually mild. A pathogenic variant in a mitochondrially encoded transfer RNA is associated with hypomagnesemia, hypertension, and hypercholesterolemia. Hypomagnesemia is occasionally present in children with other mitochondrial disorders.

Poor intake is an unusual cause of hypomagnesemia, although it can be seen in children who are hospitalized and receive only IV fluids without magnesium. In **hungry bone syndrome**, which most frequently occurs after parathyroidectomy in patients with hyperparathyroidism, magnesium moves into bone as a result of accelerated bone formation. These patients usually have hypocalcemia and hypophosphatemia through the same mechanism. A similar mechanism can occur during the **refeeding phase of protein-calorie malnutrition** in children, with high magnesium use during cell growth depleting the patient's limited reserves. Insulin therapy stimulates uptake of magnesium by cells, and in DKA, in which total body magnesium is low because of osmotic losses, hypomagnesemia frequently occurs. In **pancreatitis** there is saponification of magnesium and calcium in necrotic fat, causing both hypomagnesemia and hypocalcemia.

Transient hypomagnesemia in newborns, which is sometimes idiopathic, is more common in infants of diabetic mothers, presumably as a result of maternal depletion from osmotic losses. Other maternal diseases that cause magnesium losses predispose infants to hypomagnesemia. Hypomagnesemia is more common in infants with intrauterine growth restriction. Hypomagnesemia may develop in newborn infants who require exchange transfusions because of magnesium removal by the citrate in banked blood.

Clinical Manifestations

Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH. Thus hypomagnesemia is part of the differential diagnosis of hypocalcemia. It usually occurs only at magnesium levels <0.7 mg/dL. The dominant manifestations of hypomagnesemia are caused by hypocalcemia: tetany, presence of Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Persistent hypocalcemia caused by hypomagnesemia is a rare cause of rickets.

Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Diagnosis

The etiology of hypomagnesemia is often readily apparent from the clinical situation. The child should be assessed for GI disease, adequate intake, and kidney disease, with close attention paid to medications that may cause renal magnesium wasting. When the diagnosis is uncertain, an evaluation of urinary magnesium losses distinguishes between renal and nonrenal causes. The *fractional excretion of magnesium* (FE_{Mg}) is calculated via the following formula:

$$FE_{Mg} = (U_{Mg} \times P_{Cr}) \,/\, ([0.7 \times P_{Mg}] \times U_{Cr}) \times 100$$

where U_{Mg} = urinary magnesium concentration, P_{Cr} = plasma creatinine concentration, P_{Mg} = plasma magnesium concentration, and U_{Cr} = urinary magnesium concentration. The plasma magnesium concentration is multiplied by 0.7 because approximately 30% is bound to albumin and not filtered at the glomerulus.

The FE_{Mg} does not vary with age, but it does change according to the serum magnesium concentration. The FE_{Mg} ranges from 1–8% in children with normal magnesium levels. In the patient with hypomagnesemia as a result of extrarenal causes, FE_{Mg} should be low because of renal conservation, typically <2%. The FE_{Mg} is inappropriately elevated in the setting of renal magnesium wasting; values are usually >4% and frequently >10%. The measurement should not be made during a magnesium infusion, because the acute increase in serum magnesium increases urinary magnesium. Other approaches for evaluating urinary magnesium losses include calculation of 24-hour urinary magnesium losses and the urine magnesium/creatinine ratio, both of which vary with age.

The genetic causes of renal magnesium loss are distinguished based on the measurement of other serum and urinary electrolytes. *Children with Gitelman or Bartter syndrome have hypokalemia and metabolic alkalosis.*

Treatment

Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate is given at a dose of 25-50 mg/kg (0.05-0.1 mL/kg of a 50% solution; 2.5-5.0 mg/kg of elemental magnesium). It is administered as a slow IV infusion, although it may be given intramuscularly in neonates. The rate of IV infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hours (every 8-12 hours in neonates), for a total of 2-3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with decreased kidney function.

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). Sustained-release preparations include Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatives to oral magnesium are intramuscular injections and nighttime nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

HYPERMAGNESEMIA

Clinically significant hypermagnesemia is almost always secondary to excessive intake. It is unusual, except in neonates born to mothers who are receiving IV magnesium for preeclampsia or eclampsia (see Chapter 121.5).

Etiology and Pathophysiology

There is no feedback mechanism to prevent magnesium absorption from the GI tract. Magnesium is present in high amounts in certain laxatives, enemas, cathartics used to treat drug overdoses, and antacids. It is also usually present in total parenteral nutrition (TPN), and neonates may receive high amounts transplacentally if maternal levels are elevated. Usually the kidneys excrete excessive magnesium, but this ability is diminished in patients with chronic kidney disease. In addition, neonates and young infants are vulnerable to excessive magnesium ingestion because of their reduced GFR. Most pediatric cases not related to maternal hypermagnesemia occur in infants because of excessive use of antacids or laxatives. Mild hypermagnesemia may occur in chronic kidney disease, familial hypocalciuric hypercalcemia, DKA, lithium ingestion, milk-alkali syndrome, and tumor lysis syndrome. The hypermagnesemia in DKA occurs despite significant intracellular magnesium depletion because of urinary losses; hypomagnesemia often occurs after insulin treatment.

Clinical Manifestations

Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dL. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction, producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by aminoglycoside antibiotics. Direct CNS depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium values are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations from a direct effect on cardiac function. ECG changes include prolonged PR interval, QRS complex, and QT interval. Severe hypermagnesemia (>15 mg/dL) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.

Diagnosis

Except for the case of the neonate with transplacental exposure, a high index of suspicion and a good history are necessary to determine the etiology of hypermagnesemia. Prevention is essential; magnesium-containing compounds should be used judiciously in children with decreased kidney function.

Treatment

Most patients with normal kidney function rapidly clear excess magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially in patients with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and the use of pressors for hypotension. In acute emergencies, especially in the context of severe neurologic or cardiac manifestations, 100 mg/kg of IV calcium gluconate is transiently effective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

73.6 Phosphorus

Larry A. Greenbaum

Approximately 65% of plasma phosphorus is in phospholipids, but these compounds are insoluble in acid and are not measured by clinical laboratories. It is the phosphorus content of *plasma phosphate* that is determined. The result is reported as either phosphate or phosphorus, although even when the term *phosphate* is used, it is actually the *phosphorus* concentration that is measured and reported. The result is that the terms phosphate and phosphorus are often used interchangeably. The term *phosphorus* is preferred when referring to the plasma concentration. Conversion from the units used in the United States (mg/dL) to mmol/L is straightforward (see Table 73.6).

PHOSPHORUS METABOLISM

Body Content and Physiologic Function

Most phosphorus is in bone or is intracellular, with <1% in plasma. At a physiologic pH, there are monovalent and divalent forms of phosphate because the pK_a (ionization constant of acid) of these forms is 6.8. Approximately 80% is divalent, and the remainder is monovalent at a pH of 7.4. A small percentage of plasma phosphate, approximately 15%, is protein bound. The remainder can be filtered by the glomerulus, with most existing as free phosphate and a small percentage complexed with calcium, magnesium, or sodium. Phosphate is the most plentiful intracellular anion, although the majority is part of a larger compound (ATP).

More than that of any other electrolyte, the phosphorus concentration varies with age (Table 73.8). The teleologic explanation for the high concentration during childhood is the need for phosphorus to facilitate growth. There is diurnal variation in the plasma phosphorus concentration, with the peak during sleep.

Table 73.8 Serum Phosphorus Levels During Childhood

AGE	PHOSPHORUS LEVEL (mg/dL)
0-5 day	4.8-8.2
1-3 yr	3.8-6.5
4-11 yr	3.7-5.6
12-15 yr	2.9-5.4
16-19 yr	2.7-4.7

Phosphorus, as a component of adenosine triphosphate (ATP) and other trinucleotides, is critical for cellular energy metabolism. It is necessary for cell signaling and nucleic acid synthesis, and it is a component of cell membranes and other structures. Along with calcium, phosphorus is necessary for skeletal mineralization. A net positive phosphorus balance is required during growth, with the growing skeleton especially vulnerable to deficiency.

Phosphorus Intake

Phosphorus is readily available in food. Milk and milk products are the best sources of phosphorus; high concentrations are present in meat and fish. Vegetables have more phosphorus than fruits and grains. GI absorption of phosphorus is proportional to intake, with approximately 65% of intake being absorbed, including a small amount that is secreted. Absorption, almost exclusively in the small intestine, occurs via a paracellular diffusive process and a vitamin D–regulated transcellular pathway. However, the impact of the change in phosphorus absorption caused by vitamin D is relatively small compared with the effect of variations in phosphorus intake.

Phosphorus Excretion

Despite the wide variation in phosphorus absorption dictated by oral intake, excretion matches intake, except for the needs for growth. The kidney regulates phosphorus balance, which is determined by intrarenal mechanisms and hormonal actions on the nephron.

Approximately 90% of plasma phosphate is filtered at the glomerulus, although there is some variation based on plasma phosphate and calcium concentrations. There is no significant secretion of phosphate along the nephron. Resorption of phosphate occurs mostly in the proximal tubule, although a small amount can be resorbed in the distal tubule. Normally, approximately 85% of the filtered load is resorbed. Sodium-phosphate co-transporters mediate the uptake of phosphate into the cells of the proximal tubule.

Dietary phosphorus determines the amount of phosphate resorbed by the nephron. There are both acute and chronic changes in phosphate resorption that are based on intake. Many of these changes appear to be mediated by intrarenal mechanisms that are independent of regulatory hormones. **Fibroblast growth factor-23** (**FGF-23**) inhibits renal resorption of phosphorus in the proximal tubule, and its level increases in the setting of hyperphosphatemia. FGF-23 also inhibits synthesis of 1,25-vitamin D in the kidney by decreasing 1α-hydroxylase activity.

Secreted in response to a low plasma calcium level, PTH decreases resorption of phosphate, increasing the urinary phosphate level. This process appears to have a minimal effect during normal physiologic variation in PTH levels. However, it does affect urinary phosphate in the setting of pathologic changes in PTH synthesis.

Low plasma phosphorus stimulates the 1α-hydroxylase in the kidney that converts 25-hydroxyvitamin D (25-D) to 1,25-dihydroxyvitamin D (1,25-D; calcitriol). Calcitriol increases intestinal absorption of phosphorus and is necessary for maximal renal resorption of phosphate. The effect of a change in calcitriol on urinary phosphate is significant only when the level of calcitriol was initially low, arguing against a role for calcitriol in nonpathologic conditions.

HYPOPHOSPHATEMIA

Because of the wide variation in normal plasma phosphorus levels, the definition of hypophosphatemia is age dependent (see Table 73.8). The normal range reported by a laboratory may be based on adult normal values and therefore may be misleading in children. A serum phosphorus level of 3 mg/dL, a normal value in an adult, indicates clinically significant hypophosphatemia in an infant.

The plasma phosphorus level does not always reflect the total body stores because only 1% of phosphorus is extracellular. Thus a child may have significant phosphorus deficiency despite a normal plasma phosphorus concentration when there is a shift of phosphorus from the ICS.

Etiology and Pathophysiology

A variety of mechanisms cause hypophosphatemia (Table 73.9). A transcellular shift of phosphorus into cells occurs with processes that stimulate cellular usage of phosphorus (glycolysis). Usually, this shift causes only a minor, transient decrease in plasma phosphorus, but if intracellular phosphorus deficiency is present, the plasma phosphorus level can decrease significantly, producing symptoms of acute hypophosphatemia. Glucose infusion stimulates insulin release, leading to entry of glucose and phosphorus into the cells. Phosphorus is then used during glycolysis and other metabolic processes. A similar phenomenon can occur during the treatment of DKA, and patients with DKA are typically phosphorus depleted because of urinary phosphorus losses.

Table 73.9 Causes of Hypophosphatemia

TRANSCELLULAR SHIFTS
Glucose infusion
Insulin
Refeeding
Total parenteral nutrition
Respiratory alkalosis
Tumor growth
Bone marrow transplantation
Hungry bone syndrome
DECREASED INTAKE
Nutritional
Premature infants
Low phosphorus formula
Antacids and other phosphate binders
RENAL LOSSES
Hyperparathyroidism
Parathyroid hormone–related peptide
X-linked hypophosphatemic rickets (OMIM 307800)
Overproduction of fibroblast growth factor-23
Tumor-induced rickets
McCune-Albright syndrome (OMIM 174800)
Epidermal nevus syndrome
Neurofibromatosis
Autosomal dominant hypophosphatemic rickets (OMIM 193100)
Autosomal recessive hypophosphatemic rickets, types 1, 2, and 3 (OMIM 241520/613312)
Ferric carboxymaltose
Dent disease (OMIM 300009/300555)
Fanconi syndrome (OMIM 134600/613388/615605/616026/618913/612392)*
Hypophosphatemic rickets with hypercalciuria (OMIM 241530)
Hypophosphatemic rickets with nephrolithiasis and osteoporosis types 1 and 2 (OMIM 612286/612287)
Volume expansion and intravenous fluids
Metabolic acidosis
Diuretics
Glycosuria
Glucocorticoids
Chemotherapy (cisplatin, ifosfamide)
Kidney transplantation
MULTIFACTORIAL
Vitamin D deficiency
Vitamin D–dependent rickets type 1 (OMIM 264700)
Vitamin D–dependent rickets type 2 (OMIM 277440)
Alcoholism
Sepsis
Dialysis

*These are primary genetic causes of Fanconi syndrome. Fanconi syndrome may also be secondary to medications, genetic disorders (cystinosis) or systemic disease (Sjögren syndrome).

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Refeeding of patients with protein-calorie malnutrition causes anabolism, which leads to significant cellular demand for phosphorus (see Chapter 63). The increased phosphorus uptake for incorporation into newly synthesized compounds containing phosphorus leads to hypophosphatemia, which can be severe and symptomatic. **Refeeding hypophosphatemia** occurs frequently during treatment of severe anorexia nervosa. It can occur during treatment of children with malnutrition from any cause, such as cystic fibrosis, Crohn disease, burns, neglect, chronic infection, or famine. Hypophosphatemia usually occurs within the first 5 days of refeeding and is prevented by a gradual increase in nutrition with appropriate phosphorus supplementation. TPN without adequate phosphorus can cause hypophosphatemia.

Phosphorus moves into the ICS during a respiratory alkalosis and during recovery from a respiratory acidosis. An acute decrease in the carbon dioxide concentration, by raising the intracellular pH, stimulates glycolysis, leading to intracellular use of phosphorus and hypophosphatemia. Because a metabolic alkalosis has less effect on the intracellular pH (CO_2 diffuses across cell membranes much faster than bicarbonate), transcellular phosphorus movement is minimal with a metabolic alkalosis.

Tumors that grow rapidly, such as those associated with leukemia and lymphoma, may use large amounts of phosphorus, leading to hypophosphatemia. A similar phenomenon may occur during the hematopoietic reconstitution that follows bone marrow transplantation. In **hungry bone syndrome**, there is avid bone uptake of phosphorus, along with calcium and magnesium, which can produce plasma deficiency of all three ions. Hungry bone syndrome is most common after parathyroidectomy for hyperparathyroidism because the stimulus for bone dissolution is acutely removed, but bone synthesis continues.

Nutritional phosphorus deficiency is unusual because most foods contain phosphorus. However, infants are especially susceptible because of their high demand for phosphorus to support growth, especially of the skeleton. Very low birthweight infants have particularly rapid skeletal growth, and phosphorus deficiency and rickets may develop if they are fed human milk or formula for term infants. There is also a relative deficiency of calcium. The provision of additional calcium and phosphorus, using breast milk fortifier or special premature infant formula, prevents this complication. Phosphorus deficiency, sometimes with concomitant calcium and vitamin D deficiencies, occurs in infants who are not given enough milk or who receive a milk substitute that is nutritionally inadequate.

Antacids containing aluminum hydroxide (e.g., Maalox, Mylanta) bind dietary phosphorus and secreted phosphorus, preventing absorption. This process can cause phosphorus deficiency and rickets in growing children. A similar mechanism causes hypophosphatemia in patients who are overtreated for hyperphosphatemia with phosphorus binders. In children with kidney failure, the addition of dialysis to phosphorus binders increases the risk of iatrogenic hypophosphatemia in these normally hyperphosphatemic patients. This complication, which is more common in infants, can worsen kidney osteodystrophy.

Excessive renal losses of phosphorus occur in a variety of inherited and acquired disorders. Because PTH inhibits the resorption of phosphorus in the proximal tubule, **hyperparathyroidism** causes hypophosphatemia (see Chapter 613). The dominant clinical manifestation, however, is hypercalcemia, and the hypophosphatemia is usually asymptomatic. The phosphorus level in hyperparathyroidism is not extremely low, and there is no continued loss of phosphorus because a new steady state is achieved at the lower plasma phosphorus level. Renal excretion therefore does not exceed intake over the long term. Occasional malignancies produce PTH-related peptide, which has the same actions as PTH and causes hypophosphatemia and hypercalcemia.

A variety of diseases cause renal phosphate wasting, hypophosphatemia, and rickets resulting from excess FGF-23 (see Chapter 69). These disorders include X-linked hypophosphatemic rickets, tumor-induced osteomalacia, autosomal dominant hypophosphatemic rickets, and autosomal recessive hypophosphatemic rickets types 1-3. Ferric carboxymaltose, an IV iron preparation for correcting iron deficiency, causes hypophosphatemia via increased levels of FGF-23.

Fanconi syndrome is a generalized defect in the proximal tubule leading to urinary wasting of bicarbonate, phosphorus, amino acids, uric acid, and glucose (see Chapter 569.1). The clinical sequelae result from the metabolic acidosis and hypophosphatemia. In children, an underlying genetic disease, usually cystinosis, often causes Fanconi syndrome, but it can be secondary to a variety of toxins and acquired diseases. Some patients have incomplete Fanconi syndrome, and phosphorus wasting may be one of the manifestations.

Dent disease, an X-linked disorder, can cause renal phosphorus wasting and hypophosphatemia, although the latter is not present in most cases. Other possible manifestations of Dent disease include tubular proteinuria, hypercalciuria, nephrolithiasis, rickets, and decreased kidney function. Dent disease may be secondary to pathologic variants in a gene that encodes a chloride channel or the *OCRL1* gene, which may also cause Lowe syndrome (see Chapter 569.1). **Hypophosphatemic rickets with hypercalciuria** is a rare autosomal recessive disorder, principally described in kindreds from the Middle East (see Chapter 69). Pathologic variants in a sodium-phosphate co-transporter cause hypophosphatemia in this disorder, and complications may include nephrolithiasis and osteoporosis. Similar findings are seen in hypophosphatemic rickets with nephrolithiasis and osteoporosis types 1 and 2 (see Chapter 69).

Metabolic acidosis inhibits resorption of phosphorus in the proximal tubule. In addition, metabolic acidosis causes a transcellular shift of phosphorus out of cells because of intracellular catabolism. This released phosphorus is subsequently lost in the urine, leading to significant phosphorus depletion, even though the plasma phosphorus level may be normal. This classically occurs in DKA, in which renal phosphorus loss is further increased by the osmotic diuresis. With correction of the metabolic acidosis and the administration of insulin, both of which cause a transcellular movement of phosphorus into the cells, there is a marked decrease in the plasma phosphorus level.

Volume expansion from any cause, such as hyperaldosteronism or SIADH, inhibits resorption of phosphorus in the proximal tubule. This effect also occurs with high rates of IV fluids. Thiazide and loop diuretics can increase renal phosphorus excretion, but the increase is seldom clinically significant. Glycosuria and glucocorticoids inhibit renal conservation of phosphorus. Hypophosphatemia is common after kidney transplantation because of urinary phosphorus losses. Possible explanations include preexisting secondary hyperparathyroidism from chronic kidney disease, glucocorticoid therapy, and upregulation of FGF-23 before transplantation. The hypophosphatemia usually resolves in a few months.

Both acquired and genetic causes of **vitamin D deficiency** are associated with hypophosphatemia (see Chapter 69). The pathogenesis is multifactorial. By impairing intestinal calcium absorption, vitamin D deficiency causes secondary hyperparathyroidism that leads to increased urinary phosphorus wasting. An absence of vitamin D decreases intestinal absorption of phosphorus and directly decreases renal resorption of phosphorus. The dominant clinical manifestation is rickets, although some patients have muscle weakness that may be related to phosphorus deficiency.

Alcoholism is the most common cause of severe hypophosphatemia in adults. Fortunately, many of the risk factors that predispose alcoholic adults to hypophosphatemia are not usually present in adolescents (malnutrition, antacid abuse, recurrent DKA episodes). Hypophosphatemia often occurs in sepsis, but the mechanism is not clear. Aggressive, protracted hemodialysis, as might be used for

the treatment of methanol or ethylene glycol ingestion, can cause hypophosphatemia.

Clinical Manifestations

There are acute and chronic manifestations of hypophosphatemia. **Rickets** occurs in children with long-term phosphorus deficiency. The clinical features of rickets are described in Chapter 69.

Severe hypophosphatemia, typically at levels <1.0-1.5 mg/dL, may affect every organ in the body because phosphorus has a critical role in maintaining adequate cellular energy. Phosphorus is a component of ATP and is necessary for glycolysis. With inadequate phosphorus, 2,3-diphosphoglycerate levels in RBCs decrease, impairing release of oxygen to the tissues. Severe hypophosphatemia can cause hemolysis and dysfunction of WBCs. Chronic hypophosphatemia causes proximal muscle weakness and atrophy. In the intensive care unit, phosphorus deficiency may slow weaning from mechanical ventilation or cause acute respiratory failure. **Rhabdomyolysis** is the most common complication of acute hypophosphatemia, usually in the setting of an acute transcellular shift of phosphorus into cells in a child with chronic phosphorus depletion (anorexia nervosa). The rhabdomyolysis is actually somewhat protective, in that cellular release of phosphorus occurs. Other manifestations of severe hypophosphatemia include cardiac dysfunction and neurologic symptoms, such as tremor, paresthesia, ataxia, seizures, delirium, and coma.

Diagnosis

The history and basic laboratory evaluation often suggest the etiology of hypophosphatemia. The history should investigate nutrition, medications, and familial disease. Hypophosphatemia and rickets in an otherwise healthy young child suggest a genetic defect in renal phosphorus conservation, Fanconi syndrome, inappropriate use of antacids, poor nutrition, vitamin D deficiency, or a genetic defect in vitamin D metabolism. The patient with Fanconi syndrome usually has metabolic acidosis, glycosuria, aminoaciduria, and a low plasma uric acid level. Measurement of 25-D and 1,25-D, calcium, and PTH differentiates among the various vitamin D deficiency disorders and primary renal phosphate wasting (see Chapter 69). Hyperparathyroidism is easily distinguished by the presence of elevated plasma PTH and calcium values.

Treatment

The plasma phosphorus level, the presence of symptoms, the likelihood of chronic depletion, and the presence of ongoing losses dictate the approach to therapy. Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that losses are ongoing. Oral phosphorus can cause diarrhea, so the doses should be divided. IV therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. IV phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08-0.16 mmol/kg over 6 hours. The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome and malnutrition. Oral maintenance dosages are 2-3 mmol/kg/day in divided doses, although the maintenance dose varies considerably between patients.

Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually from dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy (see Chapter 69). Specifically, X-linked hypophosphatemia responds to burosumab, a monoclonal antibody targeting FGF-23.

Table 73.10 Causes of Hyperphosphatemia

TRANSCELLULAR SHIFTS
Tumor lysis syndrome
Rhabdomyolysis
Acute hemolysis
Diabetic ketoacidosis and lactic acidosis
INCREASED INTAKE
Enemas and laxatives
Cow's milk in infants
Treatment of hypophosphatemia
Vitamin D intoxication
DECREASED EXCRETION
Kidney failure
Hypoparathyroidism or pseudohypoparathyroidism (OMIM 146200/603233/103580/241410/203330)
Acromegaly
Hyperthyroidism
Tumoral calcinosis with hyperphosphatemia: genetic (OMIM 211900/617993/617994) or autoimmune

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

HYPERPHOSPHATEMIA

Etiology and Pathophysiology

Renal insufficiency is the most common cause of hyperphosphatemia, with the severity proportional to the degree of kidney impairment (see Chapter 572). This occurs because GI absorption of the large dietary intake of phosphorus is unregulated, and the kidneys normally excrete this phosphorus. As kidney function deteriorates, increased excretion of phosphorus is able to compensate. When kidney function is <30% of normal, hyperphosphatemia usually develops, although this varies considerably depending on dietary intake. Many of the other causes of hyperphosphatemia are more likely to develop in the setting of decreased kidney function (Table 73.10).

Cellular content of phosphorus is high relative to plasma phosphorus, and cell lysis can release substantial phosphorus. This is the etiology of hyperphosphatemia in **tumor lysis syndrome**, **rhabdomyolysis**, and **acute hemolysis**. These disorders cause concomitant potassium release and the risk of hyperkalemia. Additional features of tumor lysis and rhabdomyolysis are hyperuricemia and hypocalcemia, whereas indirect hyperbilirubinemia and elevated lactate dehydrogenase (LDH) values are often present with hemolysis. An elevated CPK level is suggestive of rhabdomyolysis. During lactic acidosis or DKA, use of phosphorus by cells decreases, and phosphorus shifts into the ECS. This problem reverses when the underlying problem is corrected, and especially with DKA, patients subsequently become hypophosphatemic because of previous renal phosphorus loss.

Excessive intake of phosphorus is especially dangerous in children with decreased kidney function. Neonates are at risk because kidney function is normally reduced during the first few months of life. In addition, they may erroneously be given doses of phosphorus that are meant for an older child or adult. In infants fed cow's milk, which has higher phosphorus content than breast milk or formula, hyperphosphatemia may develop. **Fleet Enema** has a high amount of phosphorus that can be absorbed, especially in the patient with an ileus; infants and children with Hirschsprung disease are especially vulnerable. There is often associated hypernatremia from sodium absorption and water loss from diarrhea. Sodium phosphorus laxatives may cause hyperphosphatemia if the dose is excessive or if renal insufficiency is present. Hyperphosphatemia occurs in children who receive overaggressive treatment for hypophosphatemia. **Vitamin D intoxication** causes excessive GI absorption of both calcium and phosphorus, and the suppression of PTH by hypercalcemia decreases renal phosphorus excretion.

The absence of PTH in **hypoparathyroidism** or PTH responsiveness in **pseudohypoparathyroidism** causes hyperphosphatemia because of increased resorption of phosphorus in the proximal tubule of the kidney (see Chapters 611 and 612). The associated hypocalcemia is responsible for the clinical symptoms. The hyperphosphatemia in hyperthyroidism or acromegaly is usually mild. It is secondary to increased resorption of phosphorus in the proximal tubule from the actions of thyroxine or growth hormone. Excessive thyroxine can also cause bone resorption, which may contribute to the hyperphosphatemia and cause hypercalcemia. Patients with **familial tumoral calcinosis** (three types), a rare autosomal recessive disorder, have hyperphosphatemia because of decreased renal phosphate excretion and heterotopic calcifications. The disease may be secondary to pathologic variants in the genes for a glycosyltransferase (most common etiology), FGF-23, or klotho, which encodes the co-receptor for FGF-23. Autoimmune hyperphosphatemic tumoral calcinosis occurs with antibodies producing FGF-23 resistance.

Clinical Manifestations

The principal clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. The hypocalcemia is probably caused by tissue deposition of calcium-phosphorus salt, inhibition of 1,25-D production, and decreased bone resorption. Symptomatic hypocalcemia is most likely to occur when the phosphorus level increases rapidly or when diseases predisposing to hypocalcemia are present (chronic kidney disease, rhabdomyolysis). Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. Clinically, this condition is often apparent in the conjunctiva, where it manifests as a foreign body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and kidney failure from nephrocalcinosis.

Diagnosis

Plasma creatinine and BUN levels should be assessed in any patient with hyperphosphatemia. The history should focus on intake of phosphorus and the presence of chronic diseases that may cause hyperphosphatemia. Measurement of K^+, uric acid, calcium, LDH, bilirubin, hemoglobin, and CPK may be indicated if rhabdomyolysis, tumor lysis, or hemolysis is suspected. With mild hyperphosphatemia and significant hypocalcemia, measurement of the serum PTH level distinguishes between hypoparathyroidism and pseudohypoparathyroidism.

Treatment

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; the resolution can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, IV fluids can enhance renal phosphorus excretion. For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the GI tract. Phosphorus binders are most effective when given with food. Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective alternative and may be preferred if there is a need to treat concomitant hypocalcemia. Preservation of renal function, as with high urine flow in rhabdomyolysis or tumor lysis, is an important adjunct because it will permit continued excretion of phosphorus. If the hyperphosphatemia is not responding to conservative management, especially if acute kidney injury is supervening, dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism and mild chronic kidney disease. For more problematic hyperphosphatemia, such as with moderate chronic kidney disease and end-stage kidney disease, phosphorus binders are usually necessary. They include calcium carbonate, calcium acetate, sevelamer, ferric citrate, sucroferric oxyhydroxide, and lanthanum. Aluminum-containing phosphorus binders are no longer used in patients with **chronic kidney disease** because of the risk of aluminum toxicity. Dialysis directly removes phosphorus from the blood in patients with end-stage kidney disease, but it is only an adjunct to dietary restriction and phosphorus binders; removal by dialysis does not keep up with normal dietary intake.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

73.7 Acid-Base Balance

Larry A. Greenbaum

ACID-BASE PHYSIOLOGY

Terminology

Chronic, mild derangements in acid-base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid-base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

A normal pH is 7.35-7.45. There is an inverse relationship between the pH and the hydrogen ion concentration([H^+]). At a pH of 7.40, [H^+] is 40 nmol/L. A normal serum sodium concentration, 140 mEq/L, is 1 million times higher. Maintaining a normal pH is necessary because hydrogen ions are highly reactive and are especially likely to combine with proteins, altering their function.

An **acid** is a substance that releases ("donates") a hydrogen ion (H^+). A **base** is a substance that accepts a hydrogen ion. An acid (HA) can dissociate into a hydrogen ion and a conjugate base (A^-), as follows:

$$HA \leftrightarrow H^+ + A^-$$

A strong acid is highly dissociated, so in this reaction, there is little HA. A weak acid is poorly dissociated; not all the hydrogen ions are released from HA. A^- acts as a base when the reaction moves to the left. These reactions are in equilibrium. When HA is added to the system, there is dissociation of some HA until the concentrations of H^+ and A^- increase enough that a new equilibrium is reached. Addition of hydrogen ions causes a decrease in A^- and an increase in HA. Addition of A^- causes a decrease in hydrogen ions and an increase in HA.

Buffers are substances that attenuate the change in pH that occurs when acids or bases are added to the body. Given the extremely low [H^+] in the body at physiologic pH, without buffers a small amount of hydrogen ions could cause a dramatic decline in the pH. Buffers prevent the decrease in pH by binding the added hydrogen ions, as follows:

$$A^- + H^+ \rightarrow HA$$

The increase in [H^+] drives this reaction to the right. Similarly, when base is added to the body, buffers prevent the pH from increasing by releasing hydrogen ions, as follows:

$$HA \rightarrow A^- + H^+$$

The best buffers are weak acids and bases. This is because a buffer works best when it is 50% dissociated (half HA and half A^-). The pH at which a buffer is 50% dissociated is its pK_a (ionization constant

of acid). The best physiologic buffers have a pK_a close to 7.40. The concentration of a buffer and its pK_a determine the buffer's effectiveness (buffering capacity). When the pH is lower than the pK_a of a buffer, there is more HA than A^-. When the pH is higher than the pK_a, there is more A^- than HA.

Physiologic Buffers

The bicarbonate and nonbicarbonate buffers protect the body against major changes in pH. The **bicarbonate buffer system** is routinely monitored clinically and is based on the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-):

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

CO_2 acts as an acid in that, after combining with water, it releases an H^+; bicarbonate acts as its conjugate base in that it accepts an H^+. The pK_a of this reaction is 6.1. The **Henderson-Hasselbalch equation** expresses the relationship among pH, pK_a, and the concentrations of an acid and its conjugate base. This relationship is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and CO_2 is as follows:

$$pH = 6.1 + \log [HCO_3^-] \; / \; [CO_2]$$

The **Henderson-Hasselbalch equation** for the bicarbonate buffer system has three variables: pH, bicarbonate concentration ($[HCO_3^-]$), and carbon dioxide concentration ($[CO_2]$). Thus, if any two of these variables are known, it is possible to calculate the third. When one is using the Henderson-Hasselbalch equation, it is important that CO_2 and bicarbonate have the same units. CO_2 is reported clinically as mm Hg and must be multiplied by its solubility constant, 0.03 mmol/L/mm Hg, before the equation can be used. Mathematical manipulation of the Henderson-Hasselbalch equation produces the following relationship:

$$\left[H^+\right] = 24 \times PCO_2 / \left[HCO_3^-\right]$$

At a normal $[H^+]$ of 40 nmol (pH 7.40), the partial pressure of carbon dioxide (P_{CO_2}), which is expressed as mm Hg in this equation, is 40 when the $[HCO_3^-]$ is 24 mEq/L. This equation emphasizes that $[H^+]$, and thus pH, can be determined by the ratio of P_{CO_2} and $[HCO_3^-]$.

The bicarbonate buffer system is very effective because of the high concentration of bicarbonate in the body (24 mEq/L) and because it is an open system. The remaining body buffers are in a closed system. The bicarbonate buffer system is an open system because the lungs increase CO_2 excretion when the blood CO_2 concentration increases. When acid is added to the body, the following reaction occurs:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

In a closed system, the CO_2 would increase. The higher CO_2 concentration would lead to an increase in the reverse reaction:

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

This would increase $[H^+]$, limiting the buffering capacity of bicarbonate. However, because the lungs excrete the excess CO_2, the reverse reaction does not increase; this fact enhances the buffering capacity of bicarbonate. The same principle holds with the addition of base, because the lungs decrease CO_2 excretion and prevent the CO_2 level from falling. The lack of change in $[CO_2]$ dramatically increases the buffering capacity of bicarbonate.

The **nonbicarbonate buffers** include proteins, phosphate, and bone. Protein buffers consist of extracellular proteins, mostly albumin and intracellular proteins, including hemoglobin. Proteins are effective buffers, largely because of the presence of the amino acid *histidine,* which has a side chain that can bind or release H^+. The pK_a of histidine varies slightly, depending on its position in the protein molecule, but its average pK_a is approximately 6.5. This is close enough to a normal pH (7.4) to make histidine an effective buffer. Hemoglobin and albumin have 34 and 16 histidine molecules, respectively.

Phosphate can bind up to three hydrogen molecules, so it can exist as PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^{1-}$, or H_3PO_4. However, at a physiologic pH, most phosphate exists as either HPO_4^{2-} or $H_2PO_4^{1-}$. $H_2PO_4^{1-}$ is an acid, and HPO_4^{2-} is its conjugate base:

$$H_2PO_4^{1-} \leftrightarrow H^+ + HPO_4^{2-}$$

The pK_a of this reaction is 6.8, making phosphate an effective buffer. The concentration of phosphate in the ECS is relatively low, limiting the overall buffering capacity of phosphate; it is less important than albumin. However, phosphate is found at a much higher concentration in the urine, where it is an important buffer. In the ICS, most phosphate is covalently bound to organic molecules (ATP), but it still serves as an effective buffer.

Bone is an important buffer. Bone is *basic*—it is composed of compounds such as sodium bicarbonate and calcium carbonate—and thus dissolution of bone releases base. This release can buffer an acid load, although at the expense of bone density, if it occurs over an extended period. In contrast, bone formation, by consuming base, helps buffer excess base.

Clinically, we measure the extracellular pH, but it is the intracellular pH that affects cell function. Measurement of the intracellular pH is unnecessary because changes in the intracellular pH parallel the changes in the extracellular pH. However, the change in the intracellular pH tends to be less than the change in the extracellular pH because of the greater buffering capacity in the ICS.

NORMAL ACID-BASE BALANCE

The lungs and kidneys maintain a normal acid-base balance. Carbon dioxide generated during normal metabolism is a weak acid. The lungs prevent an increase in the P_{CO_2} in the blood by excreting the CO_2 that the body produces. CO_2 production varies according to the body's metabolic needs, increasing with physical activity. The rapid pulmonary response to changes in the CO_2 concentration occurs via central sensing of the P_{CO_2} and a subsequent increase or decrease in ventilation to maintain a normal P_{CO_2} (35-45 mm Hg). An increase in ventilation decreases the P_{CO_2}, and a decrease in ventilation increases the P_{CO_2}.

The kidneys excrete endogenous acid. An adult normally produces approximately 1-2 mEq/kg/24 hr of H^+. Children normally produce 2-3 mEq/kg/24 hr of H^+. The three principal sources of H^+ are dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. Because metabolism of protein generates H^+, endogenous acid production varies with protein intake. The complete oxidation of carbohydrates or fats to CO_2 and water does not generate H^+; the lungs remove the CO_2. However, incomplete metabolism of carbohydrates or fats produces H^+. Incomplete glucose metabolism can produce lactic acid, and incomplete triglyceride metabolism can produce ketoacids, such as β-hydroxybutyric acid and acetoacetic acid. There is always some baseline incomplete metabolism that contributes to endogenous acid production. This factor increases in pathologic conditions, such as **lactic acidosis** and diabetic ketoacidosis (DKA). Stool loss of bicarbonate is the third major source of endogenous acid production. The stomach secretes H^+, but most of the remainder of the GI tract secretes bicarbonate, and the net effect is a loss of bicarbonate from the body. To secrete bicarbonate, the cells of the intestine produce hydrogen ions that are released into the bloodstream. For each bicarbonate molecule lost in the stool, the body gains one H^+. This source of endogenous acid production is normally minimal but may increase dramatically in a patient with diarrhea.

The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to decrease. The kidneys regenerate this bicarbonate by secreting H^+. The lungs cannot regenerate bicarbonate, even though loss of CO_2 lowers the $[H^+]$, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

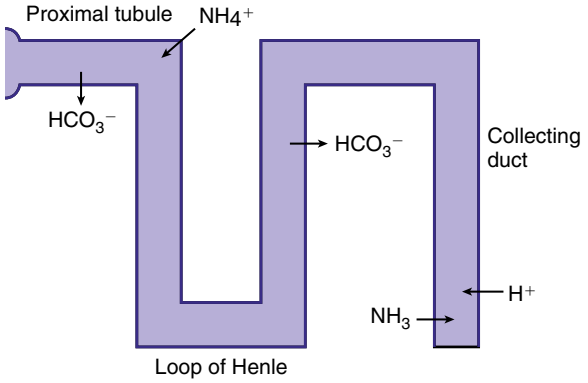

Fig. 73.7 Tubular sites involved in acid-base balance. The proximal tubule is the site where most filtered bicarbonate is reclaimed, even though other sites along the nephron, especially the thick ascending limb of the loop of Henle, resorb some of the filtered bicarbonate. The collecting duct is the principal location for the hydrogen ion secretion that acidifies the urine. The proximal tubule generates the ammonia that serves as a urinary buffer in the collecting duct.

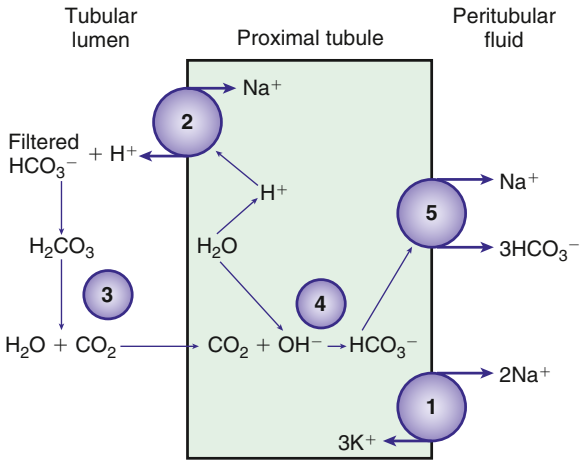

Fig. 73.8 Resorption of filtered bicarbonate in the proximal tubule. The Na^+,K^+-ATPase *(1)* excretes sodium across the basolateral cell membrane, maintaining a low intracellular sodium concentration. The low intracellular sodium concentration provides the energy for the Na^+,H^+ antiporter *(2)*, which exchanges sodium from the tubular lumen for intracellular hydrogen ions. The hydrogen ions that are secreted into the tubular lumen then combine with filtered bicarbonate to generate carbonic acid. CO_2 and water are produced from carbonic acid (H_2CO_3). This reaction is catalyzed by luminal carbonic anhydrase *(3)*. CO_2 diffuses into the cell and combines with OH^- ions to generate bicarbonate. This reaction is catalyzed by an intracellular carbonic anhydrase *(4)*. The dissociation of water generates an OH^- ion and an H^+ ion. The Na^+,H^+ antiporter *(2)* secretes the hydrogen ions. Bicarbonate ions cross the basolateral membrane and enter the blood via the $3HCO_3^-/1Na^+$ co-transporter *(5)*. The energy for the $3HCO_3^-/1Na^+$ co-transporter comes from the negatively charged cell interior, which makes it electrically favorable to transport a net negative charge (i.e., 3 bicarbonates and only 1 sodium) out of the cell.

A decrease in $[CO_2]$ causes the reaction to move to the right, which decreases $[H^+]$, but it also lowers $[HCO_3^-]$. During a metabolic acidosis, hyperventilation can lower $[CO_2]$, decrease $[H^+]$, and thus increase pH. The underlying metabolic acidosis is still present. Similarly, the kidneys cannot correct an abnormally high $[CO_2]$, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

An increase in $[HCO_3^-]$ also causes the reaction to move to the right, which increases $[CO_2]$ while simultaneously decreasing $[H^+]$. During a respiratory acidosis, increased renal generation of bicarbonate can decrease $[H^+]$ and increase pH but cannot repair the respiratory acidosis. Both the lungs and the kidneys can affect $[H^+]$ and thus pH. However, only the lungs can regulate $[CO_2]$, and only the kidneys can regulate $[HCO_3^-]$.

Renal Mechanisms

The kidneys regulate the serum bicarbonate concentration by modifying acid excretion in the urine. This requires a two-step process. First, the renal tubules resorb the bicarbonate that is filtered at the glomerulus. Second, there is tubular secretion of H^+. The urinary excretion of H^+ generates bicarbonate that neutralizes endogenous acid production. The tubular actions necessary for renal acid excretion occur throughout the nephron (Fig. 73.7).

The resorption of filtered bicarbonate is a necessary first step in renal regulation of the acid-base balance. A normal adult has a GFR of approximately 180 L/24 hr. This fluid enters Bowman's space with $[HCO_3^-]$ that is essentially identical to the plasma concentration, normally 24 mEq/L. Multiplying 180 L by 24 mEq/L indicates that >4,000 mEq of bicarbonate enters Bowman's space each day. This bicarbonate, if not reclaimed along the nephron, would be lost in the urine and would cause a profound metabolic acidosis.

The proximal tubule reclaims approximately 85% of the filtered bicarbonate (Fig. 73.8). The final 15% is reclaimed beyond the proximal tubule, mostly in the ascending limb of the loop of Henle. Bicarbonate molecules are not transported from the tubular fluid into the cells of the proximal tubule. Rather, hydrogen ions are secreted into the tubular fluid, leading to conversion of filtered bicarbonate into CO_2 and water. The secretion of H^+ by the cells of the proximal tubule is coupled to generation of intracellular bicarbonate, which is transported across the basolateral membrane of the proximal tubule cell and enters the capillaries. The bicarbonate produced in the cell replaces the bicarbonate filtered at the glomerulus.

Increased bicarbonate resorption by the cells of the proximal tubule—the result of increased H^+ secretion—occurs in a variety of clinical situations. Volume depletion increases bicarbonate resorption. This is partially mediated by activation of the renin-angiotensin system; angiotensin II increases bicarbonate resorption. Increased bicarbonate resorption in the proximal tubule is one of the mechanisms that accounts for the metabolic alkalosis that may occur in some patients with volume depletion. Other stimuli that increase bicarbonate resorption include hypokalemia and an increased P_{CO_2}. This partially explains the observations that hypokalemia causes a metabolic alkalosis, and that a respiratory acidosis leads to a compensatory increase in serum $[HCO_3^-]$.

Stimuli that decrease bicarbonate resorption in the proximal tubule may cause a decrease in the serum $[HCO_3^-]$. A decrease in the P_{CO_2} (respiratory alkalosis) decreases proximal tubule bicarbonate resorption, partially mediating the decrease in serum $[HCO_3^-]$ that compensates for a respiratory alkalosis. PTH decreases proximal tubule bicarbonate resorption; hyperparathyroidism may cause a mild metabolic acidosis. A variety of medications and diseases cause a metabolic acidosis by impairing bicarbonate resorption in the proximal tubule. Examples are the medication acetazolamide, which directly inhibits carbonic anhydrase, and the many disorders that cause proximal RTA (see Chapter 569.1).

After reclaiming filtered bicarbonate, the kidneys perform the second step in renal acid-base handling, the excretion of the acid created by endogenous acid production. Excretion of acid occurs mostly in the collecting duct, with a small role for the distal tubule.

Along with secretion of H^+ by the tubular cells lining the collecting duct, adequate excretion of endogenous acid requires the presence of urinary buffers. The hydrogen pumps in the collecting duct cannot lower the urine pH below 4.5. The $[H^+]$ at pH 4.5 is <0.04 mEq/L; it would require >25 L of water with a pH of 4.5 to excrete one mEq of H^+. A 10-kg child, with an endogenous acid production of 20 mEq H^+ each day, would need to have a daily urinary output of >500 L without the presence of urinary buffers. As in the blood, buffers in the urine attenuate the decrease in pH that occurs with the addition of H^+. The two principal urinary buffers are phosphate and ammonia.

Urinary **phosphate** is proportional to dietary intake. Whereas most of the phosphate filtered at the glomerulus is resorbed in the proximal tubule, the urinary phosphate concentration is usually much greater than the serum phosphate concentration. This arrangement allows phosphate to serve as an effective buffer through the following reaction:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^{1-}$$

The pK_a of this reaction is 6.8, making phosphate an effective buffer as the urinary pH decreases from 7.0 to 5.0 within the collecting duct. Although phosphate is an effective buffer, its buffering capacity is limited by its concentration; there is no mechanism for increasing urinary phosphate excretion in response to changes in acid-base status.

In contrast, **ammonia** production can be modified, allowing for regulation of acid excretion. The buffering capacity of ammonia (NH_3) is based on the reaction of ammonia with hydrogen ions to form ammonium:

$$NH_3 + H^+ \rightarrow NH_4^+$$

The cells of the proximal tubule are the source of the excreted ammonia, mostly through metabolism of glutamine through the following reactions:

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate}^-$$

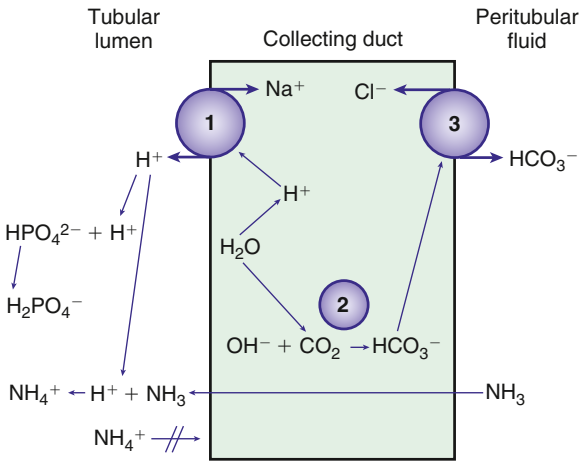

Fig. 73.9 Secretion of hydrogen ions in the collecting duct. The dissociation of water generates an OH^- ion and an H^+ ion. The H^+-ATPase *(1)* secretes hydrogen ions into the tubular lumen. Bicarbonate is formed when an OH^- ion combines with CO_2 in a reaction mediated by carbonic anhydrase *(2)*. Bicarbonate ions cross the basolateral membrane and enter the blood via the HCO_3^-/Cl^- exchanger *(3)*. The hydrogen ions in the tubular lumen are buffered by phosphate and ammonia (NH_3). NH_3 can diffuse from the peritubular fluid into the tubular lumen, but ammonium (NH_4^+) cannot pass through the cells of the collecting duct.

$$\text{Glutamate}^- \rightarrow NH_4^+ + \alpha - \text{ketoglutarate}^{3-}$$

The metabolism of glutamine generates two ammonium ions. In addition, the metabolism of α-ketoglutarate generates two bicarbonate molecules. The ammonium ions are secreted into the lumen of the proximal tubule, whereas the bicarbonate molecules exit the proximal tubule cells via the basolateral $Na^+,3HCO_3^-$ co-transporter (see Fig. 73.8). This arrangement would seem to accomplish the goal of excreting H^+ (as NH_4^+) and regenerating bicarbonate molecules. However, the ammonium ions secreted in the proximal tubule do not remain within the tubular lumen. Cells of the TAL of the loop of Henle resorb the ammonium ions. The result is that there is a high medullary interstitial concentration of ammonia, but the tubular fluid entering the collecting duct does not have significant amounts of ammonium ions. Moreover, the hydrogen ions that were secreted with ammonia (as ammonium ions) in the proximal tubule enter the bloodstream, canceling the effect of the bicarbonate generated in the proximal tubule. The excretion of ammonium ions, and thus of hydrogen ions, depends on the cells of the collecting duct.

The cells of the collecting duct secrete H^+ and regenerate bicarbonate, which is returned to the bloodstream (Fig. 73.9). This bicarbonate neutralizes endogenous acid production. Phosphate and ammonia buffer the H^+ secreted by the collecting duct. Ammonia is an effective buffer because of the high concentrations in the medullary interstitium and because the cells of the collecting duct are permeable to ammonia but not to ammonium. As ammonia diffuses into the lumen of the collecting duct, the low urine pH causes almost all the ammonia to be converted into ammonium. This process maintains a low luminal ammonia concentration. Because the luminal pH is lower than the pH in the medullary interstitium, there is a higher concentration of ammonia within the medullary interstitium than in the tubular lumen, favoring movement of ammonia into the tubular lumen. Even though the concentration of ammonium in the tubular lumen is higher than in the interstitium, the cells of the collecting duct are impermeable to ammonium, preventing back-diffusion of ammonium out of the tubular lumen and permitting ammonia to be an effective buffer.

The kidneys adjust H^+ excretion according to physiologic needs. There is variation in endogenous acid production, largely a result of diet and pathophysiologic stresses, such as diarrheal losses of bicarbonate, which increase the need for acid excretion. H^+ excretion is increased by upregulation of H^+ secretion in the collecting duct, causing the pH of the urine to decrease. This response is prompt, occurring within hours of an acid load, but it is limited by the buffering capacity of the urine; the hydrogen pumps in the collecting duct cannot lower the pH to <4.5. A more significant increase in acid excretion requires upregulation of ammonia production by the proximal tubule so that more ammonia is available to serve as a buffer in the tubular lumen of the collecting duct. This response to a low serum pH reaches its maximum within 5-6 days; ammonia excretion can increase approximately 10-fold over the baseline value.

Acid excretion by the collecting duct increases in a number of different clinical situations. The extracellular pH is the most important regulator of renal acid excretion. A decrease in the extracellular pH from either a respiratory or a metabolic acidosis causes an increase in renal acid excretion. Aldosterone stimulates H^+ excretion in the collecting duct, causing an increase in the serum bicarbonate concentration. This explains the metabolic alkalosis that occurs with primary hyperaldosteronism or secondary hyperaldosteronism caused by volume depletion. Hypokalemia increases acid secretion, by both stimulating ammonia production in the proximal tubule and increasing H^+ secretion in the collecting duct. Hypokalemia therefore tends to produce a metabolic alkalosis. Hyperkalemia has the opposite effects, which may cause a metabolic acidosis.

In patients with an increased pH, the kidney has two principal mechanisms for correcting the problem. First, less bicarbonate is resorbed in the proximal tubule, leading to an increase in urinary bicarbonate losses. Second, in a limited number of specialized cells, the process for

secretion of H^+ by the collecting duct can be reversed (see Fig. 73.9), leading to secretion of bicarbonate into the tubular lumen and secretion of hydrogen ions into the peritubular fluid, where they enter the bloodstream.

CLINICAL ASSESSMENT OF ACID-BASE DISORDERS

The following rearrangement of the Henderson-Hasselbalch equation emphasizes the relationship among P_{CO_2}, bicarbonate concentration, and hydrogen ion concentration:

$$[H^+] = 24 \times PCO_2 [HCO_3^-]$$

An increase in the P_{CO_2} or a decrease in $[HCO_3^-]$ increases $[H^+]$; the pH decreases. A decrease in the P_{CO_2} or an increase in $[HCO_3^-]$ decreases $[H^+]$; the pH increases.

Terminology

Acidemia is a pH below normal (<7.35), and **alkalemia** is a pH above normal (>7.45). An **acidosis** is a pathologic process that causes an increase in $[H^+]$, and an **alkalosis** is a pathologic process that causes a decrease in $[H^+]$. Whereas acidemia is always accompanied by an acidosis, a patient can have an acidosis and a low, normal, or high pH. For example, a patient may have a mild metabolic acidosis but a simultaneous, severe respiratory alkalosis; the net result may be alkalemia. Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

A **simple acid-base disorder** is a single primary disturbance. During a simple metabolic disorder, there is respiratory compensation. With a metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in P_{CO_2}. The decrease in the $[CO_2]$ leads to an increase in the pH. This appropriate respiratory compensation is expected with a primary metabolic acidosis. Despite the decrease in $[CO_2]$, appropriate respiratory compensation is not a respiratory alkalosis, even though it is sometimes erroneously called a "compensatory" respiratory alkalosis. A low P_{CO_2} can result either from a primary respiratory alkalosis or from appropriate respiratory compensation for a metabolic acidosis. Appropriate respiratory compensation also occurs with a primary metabolic alkalosis, although in this case $[CO_2]$ increases to attenuate the increase in the pH. The respiratory compensation for a metabolic process happens quickly and is complete within 12-24 hours; it cannot overcompensate for or normalize the pH.

During a primary respiratory process, there is metabolic compensation, mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing H^+ excretion, thereby increasing bicarbonate generation and raising the serum $[HCO_3^-]$. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; $[HCO_3^-]$ decreases. Unlike respiratory compensation, which occurs rapidly, it takes 3-4 days for the kidneys to complete appropriate metabolic compensation. There is, however, a small and rapid compensatory change in $[HCO_3^-]$ during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A **mixed acid-base disorder** is present when there is more than one primary acid-base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic alkalosis from the furosemide used to treat the chronic lung disease. More dramatically, a child with pneumonia and sepsis may have severe acidemia because of a combined metabolic acidosis caused by lactic acid and respiratory acidosis caused by ventilatory failure.

There are formulas for calculating the appropriate metabolic or respiratory compensation for the six primary simple acid-base disorders (Table 73.11). The appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have the appropriate compensation, a mixed acid-base disorder is present. For example, if a patient has a primary metabolic acidosis with a serum $[HCO_3^-]$ of 10 mEq/L, the expected respiratory compensation is $[CO_2]$ of 23 mm Hg ± 2 ($1.5 \times 10 + 8 \pm 2 = 23 \pm 2$; see Table 73.11). If the patient's $[CO_2]$ is >25 mm Hg, a concurrent respiratory acidosis is present; $[CO_2]$ is higher than expected. A patient may have a respiratory acidosis despite a CO_2 level below the "normal" value of 35-45 mm Hg. In this example, $[CO_2]$ <21 mm Hg indicates a concurrent respiratory alkalosis; $[CO_2]$ is lower than exp ected.

Table 73.11 Appropriate Compensation During Simple Acid-Base Disorders

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in serum $[HCO_3^-]$
Respiratory Acidosis	
Acute	$[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in P_{CO_2}
Chronic	$[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in P_{CO_2}
Respiratory Alkalosis	
Acute	$[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in P_{CO_2}
Chronic	$[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in P_{CO_2}

Table 73.12 Normal Values of Arterial Blood Gases

pH	7.35-7.45
$[HCO_3^-]$	20-28 mEq/L
P_{CO_2}	35-45 mm Hg

Diagnosis

A systematic evaluation of an arterial blood gas (ABG) sample, combined with the clinical history, can usually explain the patient's acid-base disturbance. Assessment of an ABG sample requires knowledge of normal values (Table 73.12). In most cases, this is accomplished through a three-step process (Fig. 73.10):

1. Determine whether acidemia or alkalemia is present.
2. Determine a cause of the acidemia or alkalemia.
3. Determine whether a mixed disorder is present.

Most patients with an acid-base disturbance have an abnormal pH, although there are two exceptions. One exception is in the patient with a mixed disorder in which the two processes have opposite effects on pH (a metabolic acidosis and a respiratory alkalosis) and cause changes in $[H^+]$ that are comparable in magnitude, although opposite. The other exception is in the patient with a simple chronic respiratory alkalosis; in some cases, the appropriate metabolic compensation is enough to normalize the pH. In both situations, the presence of an acid-base disturbance is deduced because of the abnormal CO_2 and bicarbonate levels. Determining the acid-base disturbance in these patients requires proceeding to the third step of the process.

The second step requires inspection of the serum $[HCO_3^-]$ and P_{CO_2} to determine a cause of the abnormal pH (see Fig. 73.10). In most cases, there is only one obvious explanation for the abnormal pH. In some mixed disorders, however, there may be two possibilities (e.g., a high P_{CO_2} and a low $[HCO_3^-]$ in a patient with acidemia). In such cases, the patient has two causes for abnormal pH—a metabolic acidosis and a respiratory acidosis, in this instance—and it is unnecessary to proceed to the third step.

The third step requires determining whether the patient's compensation is appropriate. It is assumed that the primary disorder was

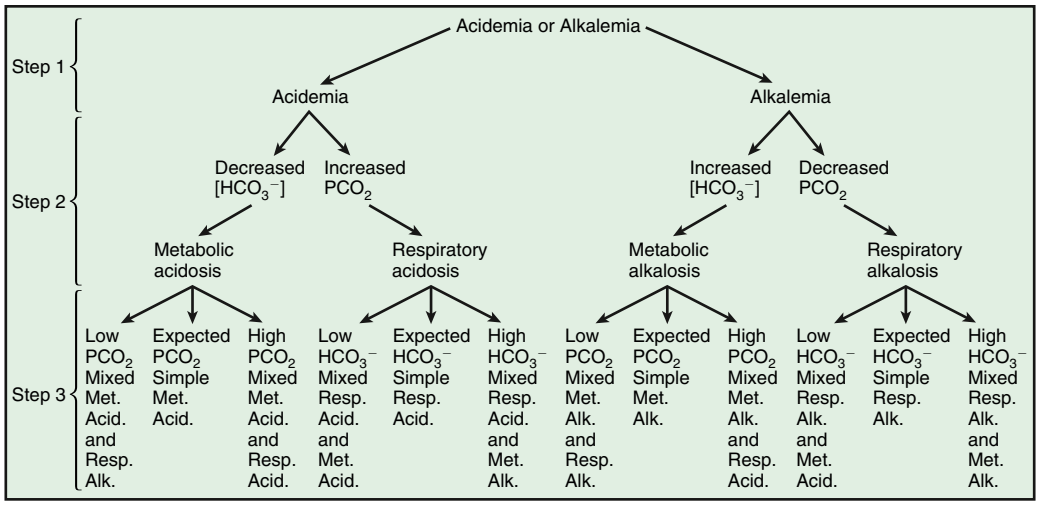

Fig. 73.10 Three-step process for interpreting acid-base disturbances. In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 73.11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.

diagnosed in the second step, and the expected compensation is calculated (see Table 73.11). If the compensation is appropriate, a simple acid-base disorder is present. If the compensation is not appropriate, a mixed disorder is present. The identity of the second disorder is determined by deciding whether the compensation is too little or too much compared with what was expected (see Fig. 73.10).

The history is always useful in evaluating and diagnosing patients with acid-base disturbances. It is especially helpful in a respiratory process. The expected metabolic compensation for a respiratory process changes according to whether the process is **acute** or **chronic**, which can be deduced only from the history. The metabolic compensation for an acute respiratory acidosis is less than that for a chronic respiratory acidosis. In a patient with a respiratory acidosis, a small increase in $[HCO_3^-]$ would be consistent with a simple acute respiratory acidosis or a mixed disorder (a chronic respiratory acidosis and a metabolic acidosis). Only the history can differentiate among the possibilities. Knowledge of the length of the respiratory process and the presence or absence of a risk factor for a metabolic acidosis (diarrhea) allows the correct conclusion to be reached.

An alternative to the **physiologic** approach just described (which includes calculation of the anion gap; see later) is the **physiochemical** approach, often called the **Stewart method**. Some view this approach as superior to the physiologic approach, but it requires multiple calculations and additional laboratory values and is thus more challenging to use in the clinical setting. The physiochemical approach requires measurement of the blood pH and P_{CO_2} and calculation of the apparent strong ion difference (SIDa), the effective strong ion difference (SIDe), the strong ion gap (SIG), and the total concentration of weak acids (A_{TOT}).

METABOLIC ACIDOSIS

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common etiology. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically, because it suggests a relatively narrow differential diagnosis.

Patients with a metabolic acidosis have a low serum $[HCO_3^-]$, although not every patient with a low serum $[HCO_3^-]$ has a metabolic acidosis. The exception is the patient with a respiratory alkalosis, which causes a decrease in the serum $[HCO_3^-]$ as part of appropriate renal compensation. In a patient with an isolated metabolic acidosis, there is a predictable decrease in the blood $[CO_2]$, as follows:

$$PCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$$

A mixed acid-base disturbance is present if the respiratory compensation is not appropriate. If the P_{CO_2} is greater than predicted, the patient has a concurrent respiratory acidosis. A lower P_{CO_2} than predicted indicates a concurrent respiratory alkalosis or, less frequently, an isolated respiratory alkalosis. Because the appropriate respiratory compensation for a metabolic acidosis never normalizes the patient's pH, the presence of a normal pH and a low $[HCO_3^-]$ occurs only if some degree of respiratory alkalosis is present. In this situation, distinguishing an isolated chronic respiratory alkalosis from a mixed metabolic acidosis and acute respiratory alkalosis may be possible only clinically. In contrast, the combination of a low serum pH and a low $[HCO_3^-]$ occurs only if a metabolic acidosis is present.

Etiology and Pathophysiology

There are many causes of a metabolic acidosis (Table 73.13), resulting from three basic mechanisms:

1. Loss of bicarbonate from the body
2. Impaired ability to excrete acid by the kidney
3. Addition of acid to the body (exogenous or endogenous)

Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and $[HCO_3^-]$ of the stool, which tends to increase with more severe diarrhea. The kidneys attempt to balance the losses by increasing acid secretion, but metabolic acidosis occurs when this compensation is inadequate. Diarrhea often causes volume depletion because of losses of sodium and water, potentially exacerbating the acidosis by causing shock and a lactic acidosis. In addition, diarrheal losses of potassium lead to hypokalemia. Moreover, the volume depletion causes increased production of aldosterone. This increase stimulates renal retention of sodium, helping to maintain intravascular volume, but also leads to increased urinary losses of potassium, exacerbating the hypokalemia.

There are four forms of renal tubular acidosis (RTA): distal (type I), proximal (type II), mixed (type III), and hyperkalemic (type IV) (see Chapter 569). In **distal** RTA, children may have accompanying hypokalemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis. Failure

Table 73.13 Causes of Metabolic Acidosis

NORMAL ANION GAP
Diarrhea
RTA
Distal (type I) RTA (OMIM 179800/602722/267300/611590)*
Proximal (type II) RTA (OMIM 604278)†
Mixed (type III) RTA (OMIM 259730)
Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)‡
Urinary tract diversions
Posthypocapnia
Ammonium chloride intake
INCREASED ANION GAP
Lactic Acidosis
Tissue hypoxia
Shock
Hypoxemia
Severe anemia
Liver failure
Malignancy
Intestinal bacterial overgrowth
Inborn errors of metabolism
Medications
Nucleoside reverse transcriptase inhibitors
Metformin
Propofol
Linezolid
Ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Kidney Failure
Poisoning
Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.
†Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.
‡Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.
OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim); RTA, renal tubular acidosis.

to thrive because of chronic metabolic acidosis is the most common presenting complaint. Patients with distal RTA cannot acidify their urine and thus have a urine pH >5.5 despite a metabolic acidosis.

Proximal RTA is rarely present in isolation. In most patients, proximal RTA is part of **Fanconi syndrome**, a generalized dysfunction of the proximal tubule. The dysfunction leads to glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically. Chronic hypophosphatemia leads to rickets in children (see Chapter 69). Rickets and/or failure to thrive may be the presenting complaint. The ability to acidify the urine is intact in proximal RTA; thus untreated patients have a urine pH <5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases. A mixed RTA (combined distal and proximal) occurs in patients with autosomal recessive osteopetrosis caused by pathologic variants in the gene for carbonic anhydrase II.

In **hyperkalemic** RTA, renal excretion of acid and potassium is impaired. Hyperkalemic RTA is the result of hyperkalemia, absence of aldosterone, or inability of the kidney to respond to aldosterone. In severe **aldosterone deficiency**, as occurs with congenital adrenal hyperplasia because of 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia. Patients may have aldosterone deficiency caused by decreased renin production by the kidney; renin normally stimulates aldosterone synthesis. Children with hyporeninemic hypoaldosteronism usually have either isolated hyperkalemia or hyperkalemic RTA. The manifestations of aldosterone resistance depend on the severity of the resistance. In the autosomal recessive form of **pseudohypoaldosteronism** type I, which is the result of an absence of the sodium channel that normally responds to aldosterone, there is often severe salt wasting and hyponatremia. In contrast, the aldosterone resistance in kidney transplant recipients usually produces either isolated hyperkalemia or hyperkalemic RTA; hyponatremia is unusual. Similarly, the medications that cause hyperkalemic RTA do not cause hyponatremia. Pseudohypoaldosteronism type II, an autosomal dominant disorder also known as **Gordon syndrome**, is a unique cause of hyperkalemic RTA because the genetic defect causes volume expansion and hypertension.

Children with abnormal urinary tracts, usually secondary to congenital malformations, may require diversion of urine through intestinal segments. Ureterosigmoidostomy, anastomosis of a ureter to the sigmoid colon, almost always produces a metabolic acidosis and hypokalemia. Consequently, ileal conduits are the more commonly used procedure, although there is still a risk of a metabolic acidosis.

The appropriate metabolic compensation for a chronic respiratory alkalosis is a decrease in renal acid excretion. The resultant decrease in the serum [HCO_3^-] lessens the alkalemia caused by the respiratory alkalosis. If the respiratory alkalosis resolves quickly, the patient continues to have a decreased serum [HCO_3^-], causing acidemia as the result of a metabolic acidosis. This resolves over 1-2 days through increased acid excretion by the kidneys.

Lactic acidosis (L-lactic) typically occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. When the underlying cause of the lactic acidosis is alleviated, the liver is able to metabolize the accumulated lactate into bicarbonate, correcting the metabolic acidosis. There is normally some tissue production of lactate metabolized by the liver. In children with severe liver dysfunction, impairment of lactate metabolism may produce a lactic acidosis. Rarely, a metabolically active malignancy grows so fast that its blood supply becomes inadequate, with resultant anaerobic metabolism and lactic acidosis. Patients who have **short bowel syndrome** resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive intestinal bacterial metabolism of glucose into *D-lactic acid* can cause a lactic acidosis. Lactic acidosis occurs in a variety of **inborn errors of metabolism**, especially those affecting mitochondrial oxidation (see Chapters 107.4 and 108). **Medications** also can cause lactic acidosis. Nucleoside reverse transcriptase inhibitors that are used to treat HIV infection inhibit mitochondrial replication; lactic acidosis is a rare complication, although elevated serum lactate concentrations without acidosis are quite common. Metformin, used to treat type 2 diabetes mellitus, is most likely to cause a lactic acidosis in patients with chronic kidney disease. High dosages and prolonged use of propofol can cause lactic acidosis. Propylene glycol is a diluent in a variety of oral and IV medications; excessive intake causes a lactic acidosis, principally from accumulation of D-lactic acid. Linezolid is another medication that may cause a lactic acidosis

In **insulin-dependent diabetes mellitus**, inadequate insulin leads to hyperglycemia and DKA (see Chapter 629). Production of acetoacetic acid and β-hydroxybutyric acid causes the metabolic acidosis. Administration of insulin corrects the underlying metabolic problem and permits conversion of acetoacetate and β-hydroxybutyrate into bicarbonate, which helps correct the metabolic acidosis. However, in some patients, urinary losses of acetoacetate and β-hydroxybutyrate may be substantial, preventing rapid regeneration of bicarbonate. In these patients, full correction of the metabolic acidosis requires renal regeneration of bicarbonate, a slower process. The hyperglycemia causes an osmotic diuresis, usually producing volume depletion, along with substantial losses of potassium, sodium, and phosphate.

In **starvation ketoacidosis** the lack of glucose leads to ketoacid production, which in turn can produce a metabolic acidosis, although it is usually mild as a result of increased acid secretion by the kidney. In **alcoholic ketoacidosis**, which is much less common in children than in adults, the acidosis usually follows a combination of an alcoholic binge with vomiting and poor intake of food. The acidosis is potentially more severe than with isolated starvation, and the blood glucose level may be low, normal, or high. Hypoglycemia and acidosis also suggest an inborn error of metabolism.

Kidney failure causes a metabolic acidosis because of the need for the kidneys to excrete the acid produced by normal metabolism. With mild or moderate chronic kidney disease, the remaining nephrons are usually able to compensate by increasing acid excretion. When the GFR is <20–30% of normal, the compensation is inadequate, and a metabolic acidosis develops. In some children, especially those with chronic kidney disease because of tubular damage, the acidosis develops at a higher GFR because of a concurrent defect in acid secretion by the distal tubule (distal RTA).

A variety of **toxic ingestions** can cause a metabolic acidosis (see Chapter 94). **Salicylate** intoxication is now much less common because aspirin is no longer recommended for fever control in children. Acute salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible with gradual buildup of the drug. Especially in adults, respiratory alkalosis may be the dominant acid-base disturbance. In children, the metabolic acidosis is usually the more significant finding. Other symptoms of salicylate intoxication are fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication.

Ethylene glycol, a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause kidney failure. The toxicity of **methanol** ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and CNS. Symptoms may include nausea, emesis, visual impairment, and altered mental status. **Toluene** inhalation and **paraldehyde** ingestion are other potential causes of a metabolic acidosis.

Many **inborn errors of metabolism** cause a metabolic acidosis (see Chapters 104-107). The metabolic acidosis may be the result of excessive production of ketoacids, lactic acid, and other organic anions. Some patients have accompanying hypoglycemia or hyperammonemia. In most patients, the acidosis occurs episodically during acute decompensations, which may be precipitated by ingestion of specific dietary substrates, the stress of a mild illness, or poor compliance with dietary or medical therapy. In a few inborn errors of metabolism, patients have a chronic metabolic acidosis.

Clinical Manifestations

The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than those with a concomitant respiratory acidosis. At a serum pH <7.2, there may be impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in newborn infants with **persistent pulmonary hypertension** (see Chapter 130).

The normal respiratory response to metabolic acidosis—compensatory hyperventilation— may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. The acute metabolic effects of acidemia include insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis causes failure to thrive in children. Acidemia causes potassium to move from the ICS to the ECS, thereby increasing the serum [K^+]. Severe acidemia impairs brain metabolism, eventually resulting in lethargy and coma.

Diagnosis

The etiology of a metabolic acidosis is often apparent from the history and physical examination. Acutely, diarrhea and shock are common causes of a metabolic acidosis. Shock, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, sepsis, or heart disease. Failure to thrive suggests a chronic metabolic acidosis, as with renal insufficiency or RTA. New onset of polyuria occurs in children with undiagnosed diabetes mellitus and DKA. Metabolic acidosis with seizures and/or a depressed sensorium, especially in an infant, warrants consideration of an inborn error of metabolism. Meningitis and sepsis with lactic acidosis are more common explanations for metabolic acidosis with neurologic signs and symptoms. Identification of a toxic ingestion (e.g., ethylene glycol, methanol) is especially important because of the potentially excellent response to specific therapy. A variety of medications can cause a metabolic acidosis, whether prescribed or accidentally ingested. Hepatomegaly and metabolic acidosis may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.

Basic laboratory tests in a child with a metabolic acidosis should include measurements of BUN, serum creatinine, serum glucose, urinalysis, and serum electrolytes. Metabolic acidosis, hyperglycemia, glycosuria, and ketonuria support a diagnosis of DKA. Starvation causes ketosis, but the metabolic acidosis, if present, is usually mild (HCO_3^- >18 mEq/L). Most children with ketosis from poor intake and metabolic acidosis have a concomitant disorder, such as gastroenteritis with diarrhea, that explains the metabolic acidosis. Alternatively, metabolic acidosis with or without ketosis occurs in inborn errors of metabolism; patients with these disorders may have hyperglycemia, normoglycemia, or hypoglycemia. Adrenal insufficiency may cause metabolic acidosis and hypoglycemia. Metabolic acidosis with hypoglycemia also occurs with liver failure. Metabolic acidosis, normoglycemia, and glycosuria occur in children when type II RTA is part of Fanconi syndrome; the defect in resorption of glucose by the proximal tubule of the kidney causes the glycosuria.

The serum [K^+] is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the ICS to the ECS, many patients with a metabolic acidosis have a low serum [K^+] because of excessive body losses of K^+. With diarrhea, there are high stool losses of K^+ and, often, secondary renal losses of K^+, whereas in type I or type II RTA, there are increased urinary losses of K^+. In DKA, urinary losses of K^+ are high, but the shift of K^+ out of cells because of a lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum [K^+] can be low, normal, or high, even though total body K^+ is almost always decreased. The serum [K^+] is usually increased in patients with acidosis caused

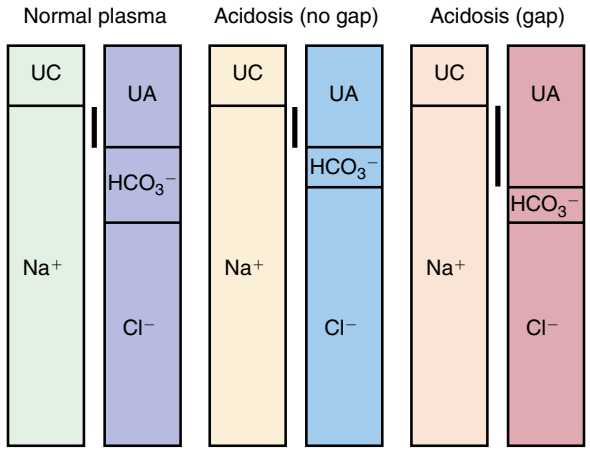

Fig. 73.11 Anion gap. The anion gap is the difference between the sodium concentration and the combined concentrations of chloride and bicarbonate *(vertical black bars)*. In both a gap and a nongap metabolic acidosis, there is a decrease in the bicarbonate concentration. There is an increase in unmeasured anions (UA) in patients with a gap metabolic acidosis. In a nongap metabolic acidosis, there is an increase in the serum chloride concentration. UC, Unmeasured cations.

by renal insufficiency; urinary K^+ excretion is impaired. The combination of metabolic acidosis, hyperkalemia, and hyponatremia occurs in patients with severe aldosterone deficiency (adrenogenital syndrome) or aldosterone resistance. Patients with less severe, type IV RTA often have only hyperkalemia and metabolic acidosis. Very ill children with metabolic acidosis may have an elevated serum K^+ because of a combination of renal insufficiency, tissue breakdown, and a shift of K^+ from the ICS to the ECS secondary to the metabolic acidosis.

The **plasma anion gap** is useful for evaluating patients with a metabolic acidosis. It divides patients into two diagnostic groups, those with normal anion gap and those with increased anion gap. The following formula determines the anion gap:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

A normal anion gap is 4-11, although there is variation among laboratories. Approximately 11 mEq of the anion gap is normally secondary to albumin. A 1 g/dL decrease in the albumin concentration decreases the anion gap by approximately 2.5 mEq/L. Thus, if the albumin is not close to 4 g/dL, the anion gap should be corrected for the albumin concentration:

$$\text{Anion gap (corrected for albumin)} = [Na^+] - ([Cl^-] + [HCO_3^-]) + [2.5 \times (4 - \text{observed albumin})]$$

The number of serum anions must equal the number of serum cations to maintain electrical neutrality (Fig. 73.11). The anion gap is the difference between the measured cation (Na^+) and the measured anions (Cl^- + bicarbonate). The anion gap is also the difference between the unmeasured cations (K^+, magnesium, calcium) and the unmeasured anions (albumin, phosphate, urate, sulfate). An increased anion gap occurs when there is an increase in unmeasured anions. With a lactic acidosis, there is endogenous production of lactic acid, which is composed of positively charged hydrogen ions and negatively charged lactate anions. The hydrogen ions are largely buffered by serum bicarbonate, resulting in a decrease in $[HCO_3^-]$. The hydrogen ions that are not buffered by bicarbonate cause the serum pH to decrease. The lactate anions remain, causing the increase in the anion gap.

An increase in unmeasured anions, along with H^+ generation, is present in all causes of an increased gap metabolic acidosis (see Table 73.13). In DKA, the ketoacids β-hydroxybutyrate and acetoacetate are the unmeasured anions. In kidney failure there is retention of unmeasured anions, including phosphate, urate, and sulfate. The increase in unmeasured anions in kidney failure is usually less than the decrease in $[HCO_3^-]$. Kidney failure is thus a mix of an increased-gap and a normal-gap metabolic acidosis. The normal-gap metabolic acidosis is especially prominent in children with kidney failure because of tubular damage, as occurs with renal dysplasia or obstructive uropathy, because these patients have a concurrent RTA. The unmeasured anions in toxic ingestions vary: formate in methanol intoxication, glycolate in ethylene glycol intoxication, and lactate and ketoacids in salicylate intoxication. In inborn errors of metabolism, the unmeasured anions depend on the specific etiology and may include ketoacids, lactate, and other organic anions. In a few inborn errors of metabolism, the acidosis occurs without generation of unmeasured anions; thus the anion gap is normal.

A **normal–anion gap metabolic acidosis** occurs when there is a decrease in $[HCO_3^-]$ without an increase in the unmeasured anions. With diarrhea, there is a loss of bicarbonate in the stool, causing a decrease in the serum pH and $[HCO_3^-]$; the serum $[Cl^-]$ increases to maintain electrical neutrality (see Fig. 73.11). **Hyperchloremic metabolic acidosis** is an alternative term for a normal–anion gap metabolic acidosis. Calculation of the anion gap is more precise than using $[Cl^-]$ to differentiate between a normal-gap and an increased-gap metabolic acidosis, in that the anion gap directly determines the presence of unmeasured anions. Electrical neutrality dictates that the $[Cl^-]$ increases or decreases according to the serum $[Na^+]$, making $[Cl^-]$ a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap.

An increase in unmeasured cations, such as calcium, potassium, and magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other variables, the presence of a normal or an increased anion gap is not always reliable in differentiating among the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. In some patients, there is more than one explanation for the metabolic acidosis, such as the child with diarrhea and lactic acidosis as a result of poor perfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

Treatment

The most effective therapeutic approach for patients with a metabolic acidosis is repair of the underlying disorder, if possible. The administration of insulin in DKA and the restoration of adequate perfusion with IV fluids in lactic acidosis because of hypovolemia or shock eventually result in normalization of the acid-base balance. In other diseases, the use of bicarbonate therapy is indicated because the underlying disorder is irreparable. Children with metabolic acidosis caused by RTA or chronic kidney disease require long-term base therapy. Patients with acute kidney injury and metabolic acidosis may need base therapy until their kidneys' ability to excrete hydrogen normalizes. In other disorders the cause of the metabolic acidosis eventually resolves, but base therapy may be necessary during the acute illness. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings (ethylene glycol, methanol) and inborn errors of metabolism (pyruvate carboxylase deficiency, propionic acidemia). Some inborn errors of metabolism require long-term base therapy.

The use of base therapy in DKA with lactic acidosis is controversial; *there is little evidence that it improves patient outcome, and it has a variety of potential side effects.* The risks of giving sodium bicarbonate

include the possibility of causing hypernatremia or volume overload. Furthermore, the patient may have overcorrection of the metabolic acidosis once the underlying disorder resolves, because metabolism of lactate or ketoacids generates bicarbonate. The rapid change from acidemia to alkalemia can cause a variety of problems, including hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO_2, which can accumulate in patients with respiratory failure. Because CO_2 readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe DKA.

Oral base therapy is given to children with chronic metabolic acidosis. Sodium bicarbonate tablets are available for older children. Younger children generally take citrate solutions; the liver generates bicarbonate from citrate. Citrate solutions are available as sodium citrate, potassium citrate, and a 1:1 mix of sodium citrate and potassium citrate. The patient's potassium needs dictate the choice. Children with type I or type II RTA may have hypokalemia and benefit from potassium supplements, but most children with chronic kidney failure cannot tolerate additional potassium.

Oral or IV base can be used in acute metabolic acidosis; IV therapy is generally used when a rapid response is necessary. Sodium bicarbonate may be given as a bolus, usually at a dose of 1 mEq/kg, in an emergency situation. Another approach is to add sodium bicarbonate or sodium acetate to the patient's IV fluids, remembering to remove an equal amount of sodium chloride from the solution to avoid giving an excessive sodium load. Careful monitoring is mandatory so that the dose of base can be titrated appropriately. Tris(hydroxymethyl) aminomethane (**tromethamine, THAM**) is an option in patients with a metabolic acidosis and a respiratory acidosis, because it neutralizes acids without releasing CO_2. THAM also diffuses into cells and therefore provides intracellular buffering.

Hemodialysis is another option for correcting a metabolic acidosis, and it is an appropriate choice in patients with renal insufficiency, especially if significant uremia or hyperkalemia is also present. Hemodialysis is advantageous for correcting the metabolic acidosis caused by methanol or ethylene glycol intoxication, because hemodialysis efficiently removes the offending toxin. In addition, these patients often have a severe metabolic acidosis that does not respond easily to IV bicarbonate therapy. Peritoneal dialysis is another option for correcting the metabolic acidosis due to chronic kidney disease.

Many causes of metabolic acidosis require specific therapy. Administration of a glucocorticoid and a mineralocorticoid is necessary in patients with adrenal insufficiency. Patients with DKA require insulin therapy, whereas patients with lactic acidosis respond to measures that alleviate tissue hypoxia. Along with correction of acidosis, patients with methanol or ethylene glycol ingestion should receive an agent that prevents the breakdown of the toxic substance to its toxic metabolites. Fomepizole has supplanted ethanol as the treatment of choice. These agents work by inhibiting alcohol dehydrogenase, the enzyme that performs the first step in the metabolism of ethylene glycol or methanol. There are a variety of disease-specific therapies for patients with a metabolic acidosis resulting from an inborn error of metabolism.

METABOLIC ALKALOSIS

Metabolic alkalosis in children is most often secondary to emesis or diuretic use. The serum bicarbonate concentration is increased with a metabolic alkalosis, although a respiratory acidosis also leads to a compensatory elevation of the serum [HCO_3^-]. With a simple metabolic alkalosis, however, the pH is elevated; alkalemia is present. Patients with a respiratory acidosis are acidemic. Decreasing ventilation causes appropriate respiratory compensation for a metabolic alkalosis. P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in the serum [HCO_3^-]. Appropriate respiratory compensation never exceeds a P_{CO_2} of 55-60 mm Hg. The patient has a concurrent respiratory alkalosis if the P_{CO_2} is lower than the expected compensation. A greater than expected P_{CO_2} occurs with a concurrent respiratory acidosis.

Table 73.14 Causes of Metabolic Alkalosis

CHLORIDE-RESPONSIVE (URINARY CHLORIDE <15 MEQ/L)
Gastric losses
Emesis
Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Low chloride formula
Cystic fibrosis (OMIM 219700)
Posthypercapnia
CHLORIDE-RESISTANT (URINARY CHLORIDE >20 MEQ/L)
High Blood Pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism/Familial hyperaldosteronism type I (OMIM 103900)
Familial hyperaldosteronism type II (OMIM 605635)
Familial hyperaldosteronism type III (OMIM 613677)
Familial hyperaldosteronism type IV (OMIM 617027)
Renovascular disease
Renin-secreting tumor
17α-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)
Normal Blood Pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Hyperuricemia, Pulmonary Hypertension, Renal Failure in Infancy and Alkalosis, HUPRA Syndrome (OMIM 613845)
Autosomal dominant kidney hypomagnesemia due to *RRAGD* variant (OMIM not assigned)
Base administration

EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Etiology and Pathophysiology

The kidneys normally respond promptly to a metabolic alkalosis by increasing base excretion. Two processes are therefore usually present to produce a metabolic alkalosis: (1) the generation of the metabolic alkalosis, which requires the addition of base to the body, and (2) the maintenance of the metabolic alkalosis, which requires impairment in the kidney's ability to excrete base.

The etiologies of a metabolic alkalosis are divided into two categories based on the urinary chloride level (Table 73.14). The alkalosis in patients with a low urinary [Cl^-] is maintained by **volume depletion**; thus volume repletion is necessary for correction of the alkalosis. The volume depletion in these patients is caused by losses of Na^+ and K^+, but the loss of Cl^- is usually greater than the losses of Na^+ and K^+ combined. Because Cl^- losses are the dominant cause of the volume depletion, these patients require Cl^- to correct the volume depletion and metabolic alkalosis; they are said to have **Cl^--responsive metabolic alkalosis.** In contrast, the alkalosis in a patient with an elevated urinary [Cl^-] does not respond to volume repletion and so is termed **Cl^--resistant metabolic alkalosis.**

Emesis or nasogastric suction results in **loss of gastric fluid**, which has a high content of HCl. Generation of H^+ by the gastric mucosa causes simultaneous release of bicarbonate into the bloodstream. Normally, the hydrogen ions in gastric fluid are reclaimed in the small intestine (by neutralizing secreted bicarbonate); thus there is no net loss of acid. With loss of gastric fluid, this does not occur, and a metabolic alkalosis develops. This period is the *generation phase* of the metabolic alkalosis.

The *maintenance phase* of the metabolic alkalosis from gastric losses is caused by the volume depletion ("chloride depletion" from gastric loss of HCl). Volume depletion interferes with urinary loss of bicarbonate, the normal renal response to a metabolic alkalosis. During volume depletion, several mechanisms prevent renal bicarbonate loss. First, there is a reduction in the GFR, so less bicarbonate is filtered. Second, volume depletion increases resorption of sodium and bicarbonate in the proximal tubule, limiting the amount of bicarbonate that can be excreted in the urine. This effect is mediated by angiotensin II and adrenergic stimulation of the kidney, both of which are increased in response to volume depletion. Third, the increase in aldosterone during volume depletion increases bicarbonate resorption and H^+ secretion in the collecting duct.

In addition to volume depletion, gastric losses are usually associated with hypokalemia as a result of both gastric loss of K^+ and, most importantly, increased urinary K^+ losses. The increased urinary losses of K^+ are mediated by aldosterone, through volume depletion, and by the increase in intracellular K^+ secondary to the metabolic alkalosis, which causes K^+ to move into the cells of the kidney, causing increased K^+ excretion. Hypokalemia contributes to the maintenance of the metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia increases H^+ secretion in the distal nephron and stimulates ammonia production in the proximal tubule. Ammonia production enhances renal excretion of H^+.

A metabolic alkalosis can develop in patients receiving **loop** or **thiazide diuretics.** Diuretic use leads to volume depletion, which increases angiotensin II, aldosterone, and adrenergic stimulation of the kidney. Diuretics increase the delivery of sodium to the distal nephron, further enhancing acid excretion. Moreover, these diuretics cause hypokalemia, which increases acid excretion by the kidney. The increase in renal acid excretion generates the metabolic alkalosis, and the decrease in bicarbonate loss maintains it. In addition, patients who are receiving diuretics have a "contraction alkalosis." Diuretic use causes fluid loss without bicarbonate; thus the remaining body bicarbonate is contained in a smaller total body fluid compartment. The $[HCO_3^-]$ increases, helping to generate the metabolic alkalosis.

Diuretics are often used in patients with edema, such as those with nephrotic syndrome, heart failure, or liver failure. In many of these patients, metabolic alkalosis resulting from diuretic use develops despite the continued presence of edema. This is because the effective intravascular volume is low, and it is the effective intravascular volume that stimulates the compensatory mechanisms that cause and maintain a metabolic alkalosis. Many of these patients have a decreased effective intravascular volume before they begin diuretic therapy, increasing the likelihood of diuretic-induced metabolic alkalosis.

Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urine $[Cl^-]$ is typically high (>20 mEq/L). After the diuretic effect has worn off, the urinary $[Cl^-]$ is low (<15 mEq/L) because of appropriate renal Cl^- retention in response to volume depletion. Thus categorization of diuretics because of urinary $[Cl^-]$ depends on the timing of the measurement. However, the metabolic alkalosis from diuretics is Cl^- responsive; it is corrected after adequate volume repletion. This is the rationale for including this process among the chloride-responsive causes of a metabolic alkalosis.

Most patients with diarrhea have a metabolic acidosis because of stool losses of bicarbonate. In **chloride-losing diarrhea**, an autosomal recessive disorder, there is a defect in the normal intestinal exchange of bicarbonate for chloride, causing excessive stool losses of chloride (see Chapter 385). In addition, stool losses of H^+ and K^+ cause metabolic alkalosis and hypokalemia, both of which are exacerbated by increased renal H^+ and K^+ losses from volume depletion. Treatment is with oral supplements of K^+ and NaCl. Use of a gastric proton pump inhibitor (PPI), by decreasing gastric HCl production, reduces both the volume of diarrhea and the need for electrolyte supplementation.

Formulas with extremely low Cl^- content have led to Cl^- deficiency and volume depletion. There is secondary metabolic alkalosis and hypokalemia. **Cystic fibrosis** can rarely cause metabolic alkalosis, hypokalemia, and hyponatremia because of excessive NaCl losses in sweat (see Chapter 454). The volume depletion causes the metabolic alkalosis and hypokalemia through increased urinary losses, whereas the hyponatremia, a less common finding, is secondary to Na^+ loss combined with renal water conservation in an effort to protect the intravascular volume ("appropriate" ADH production).

A **posthypercapnic metabolic alkalosis** occurs after the correction of a chronic respiratory acidosis. This is typically seen in patients with chronic lung disease who are started on mechanical ventilation. During chronic respiratory acidosis, appropriate renal compensation leads to an increase in the serum $[HCO_3^-]$. Because it is still present after acute correction of the respiratory acidosis, the elevated $[HCO_3^-]$ causes a metabolic alkalosis. The metabolic alkalosis persists because the patient with a chronic respiratory acidosis is intravascularly depleted because of the Cl^- loss that occurred during the initial metabolic compensation for the primary respiratory acidosis. In addition, many children with a chronic respiratory acidosis receive diuretics, which further decrease the intravascular volume. The metabolic alkalosis responds to correction of the intravascular volume deficit.

The **chloride-resistant** causes of metabolic alkalosis can be subdivided according to blood pressure status. Patients with **hypertension** either have increased aldosterone levels or act as if they do. Aldosterone levels are elevated in children with adrenal adenomas or hyperplasia. Aldosterone causes renal retention of sodium, with resultant hypertension. Metabolic alkalosis and hypokalemia result from aldosterone-mediated renal excretion of H^+ and K^+. The urinary Cl^- level is not low because these patients are volume overloaded, not volume depleted. The volume expansion and hypertension allow normal excretion of Na^+ and Cl^- despite the presence of aldosterone. This is known as the *mineralocorticoid escape phenomenon.*

In **glucocorticoid-remediable aldosteronism**, an autosomal dominant disorder, excess production of aldosterone results from the presence of an aldosterone synthase gene regulated by adrenocorticotropic hormone (ACTH) (see Chapter 616.8). Glucocorticoids effectively treat this disorder by inhibiting ACTH production by the pituitary, downregulating the inappropriate aldosterone production. Familial hyperaldosteronism type II, which causes elevated aldosterone levels, responds to spironolactone. Familial hyperaldosteronism type III typically requires bilateral adrenalectomy due to the severity of the hyperaldosteronism. Renovascular disease and renin-secreting tumors both cause excessive renin, leading to an increase in aldosterone, although hypokalemia and metabolic alkalosis are less common findings than hypertension. In two forms of **congenital adrenal hyperplasia**, 11β-hydroxylase deficiency and 17α-hydroxylase deficiency, there is excessive production of the mineralocorticoid 11-deoxycorticosterone (see Chapters 616.2 and 616.4). Hypertension, hypokalemia, and metabolic alkalosis are more likely in 17α-hydroxylase deficiency than in 11β-hydroxylase deficiency. These disorders respond to glucocorticoids because the excess production of 11-deoxycorticosterone is under the control of ACTH.

Cushing syndrome frequently causes hypertension. Cortisol has *some* mineralocorticoid activity, and high levels can produce hypokalemia and metabolic alkalosis in patients with Cushing syndrome.

Cortisol can bind to the mineralocorticoid receptors in the kidney and function as a mineralocorticoid. This binding normally does not occur because 11β-hydroxysteroid dehydrogenase in the kidney converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. In the autosomal recessive disorder 11β-hydroxysteroid dehydrogenase deficiency, also called **apparent mineralocorticoid excess**, cortisol is not converted in the kidney to cortisone. Cortisol is therefore available to bind to the mineralocorticoid receptor in the kidney and act as a mineralocorticoid. Patients with this deficiency, despite low levels of aldosterone, are hypertensive and hypokalemic, and they have a metabolic alkalosis. The same phenomenon can occur with excessive intake of natural licorice, a component of which, glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase. The autosomal dominant disorder **Liddle syndrome** is secondary to an activating variant in the gene for the sodium channel in the distal nephron (see Chapter 571.3). Upregulation of this sodium channel is one of the principal actions of aldosterone. Because this Na^+ channel is continuously open, children with Liddle syndrome have the features of hyperaldosteronism, including hypertension, hypokalemia, and metabolic alkalosis, but low serum levels of aldosterone.

Bartter and Gitelman syndromes are autosomal recessive disorders associated with normal blood pressure, elevated urinary Cl^-, metabolic alkalosis, and hypokalemia (see Chapter 571). In **Bartter syndrome**, patients have a defect in Na^+ and Cl^- resorption in the loop of Henle. This leads to excessive urinary losses of Na^+ and Cl^-, and as in patients receiving loop diuretics, volume depletion and secondary hyperaldosteronism occur, causing hypokalemia and metabolic alkalosis. **Gitelman syndrome** is usually milder than Bartter syndrome. Patients have renal Na^+ and Cl^- wasting with volume depletion caused by variants in the gene encoding the thiazide-sensitive Na^+-Cl^- transporter in the distal tubule. As in patients receiving a thiazide diuretic, affected patients have volume depletion and secondary hyperaldosteronism with hypokalemia and metabolic alkalosis. Children with Gitelman syndrome have hypocalciuria and hypomagnesemia. Some patients with autosomal dominant hypoparathyroidism have hypokalemia and metabolic alkalosis from impaired Na^+ and Cl^- resorption in the loop of Henle. **EAST syndrome** causes hypokalemia, metabolic alkalosis, and hypomagnesemia.

Excessive base intake can cause a metabolic alkalosis. Affected patients do not have low urine $[Cl^-]$, unless there is associated volume depletion. In the absence of volume depletion, excess base is rapidly corrected via renal excretion of bicarbonate. Rarely, massive base intake can cause a metabolic alkalosis by overwhelming the kidney's ability to excrete bicarbonate. This may occur in infants who are given baking soda as a "home remedy" for colic or stomach upset. Each teaspoon of baking soda has 42 mEq of sodium bicarbonate. Infants have increased vulnerability because of a lower GFR, limiting the rate of compensatory renal bicarbonate excretion. A metabolic alkalosis may also occur in patients who receive a large amount of sodium bicarbonate during cardiopulmonary resuscitation. Blood products are anticoagulated with citrate, which is converted into bicarbonate by the liver. Patients who receive large amounts of blood products may have a metabolic alkalosis. Iatrogenic metabolic alkalosis can occur because of acetate in TPN. Aggressive use of bicarbonate therapy in a child with a lactic acidosis or DKA may cause a metabolic alkalosis. This is especially likely in a patient in whom the underlying cause of the lactic acidosis is successfully corrected (restoration of intravascular volume in a patient with severe dehydration). Once the cause of the lactic acidosis resolves, lactate can be converted by the liver into bicarbonate, which when combined with infused bicarbonate can create a metabolic alkalosis. A similar phenomenon can occur in a child with DKA because the administration of insulin allows ketoacids to be metabolized, producing bicarbonate. However, this phenomenon rarely occurs because of judicious use of bicarbonate therapy in DKA and because there are usually significant pretreatment losses of ketoacids in the urine, preventing massive regeneration of bicarbonate. Base administration is most likely to cause a metabolic alkalosis in patients who have an impaired ability to excrete bicarbonate in the urine. This impairment occurs in patients with concurrent volume depletion or renal insufficiency.

Clinical Manifestations

The symptoms in patients with a metabolic alkalosis are often related to the underlying disease and associated electrolyte disturbances. Children with Cl^--responsive causes of metabolic alkalosis often have symptoms related to volume depletion, such as thirst and lethargy. In contrast, children with Cl^--unresponsive causes may have symptoms related to hypertension.

Alkalemia causes potassium to shift into the ICS, producing a decrease in the extracellular $[K^+]$. Alkalemia leads to increased urinary losses of K^+. Increased K^+ losses are present in many of the conditions that cause a metabolic alkalosis. Therefore most patients with a metabolic alkalosis have hypokalemia, and their symptoms may be related to the hypokalemia (see Chapter 73.4).

The symptoms of a metabolic alkalosis are caused by the associated alkalemia. The magnitude of the alkalemia is related to the severity of the metabolic alkalosis and the presence of concurrent respiratory acid-base disturbances. During alkalemia, the ionized calcium concentration decreases because of increased binding of calcium to albumin. The decrease in the ionized calcium concentration may cause symptoms of **tetany** (**carpopedal spasm**).

Arrhythmias are a potential complication of a metabolic alkalosis, and the risk for arrhythmia increases if there is concomitant hypokalemia. Alkalemia increases the risk of digoxin toxicity, and antiarrhythmic medications are less effective in the presence of alkalemia. In addition, alkalemia may decrease cardiac output. A metabolic alkalosis causes a compensatory increase in the P_{CO_2} by decreasing ventilation. The decrease in ventilatory drive can cause hypoxia.

Diagnosis

Measurement of the urine $[Cl^-]$ is the most helpful test in differentiating among the causes of a metabolic alkalosis. The urine $[Cl^-]$ is low in patients with a metabolic alkalosis resulting from volume depletion, unless there is a defect in renal handling of Cl^-. The urine $[Cl^-]$ is superior to the urine $[Na^+]$ in assessment of volume status in patients with a metabolic alkalosis because the normal renal response to a metabolic alkalosis is to excrete bicarbonate. Because bicarbonate is negatively charged, it can only be excreted with cations, usually Na^+ and K^+. Therefore a patient with a metabolic alkalosis may excrete Na^+ in the urine despite the presence of volume depletion, which normally causes avid Na^+ retention. The urine $[Cl^-]$ is usually a good indicator of volume status, and it differentiates Cl^--resistant and Cl^--responsive causes of a metabolic alkalosis.

Diuretics and gastric losses are the most common causes of metabolic alkalosis and are usually apparent from the patient history. Occasionally, metabolic alkalosis, usually with hypokalemia, may be a clue to the presence of bulimia or surreptitious diuretic use (see Chapter 41). Patients with bulimia have a low urine Cl^- level, indicating that they have volume depletion because of an extrarenal etiology, but there is no alternative explanation for their volume depletion. Surreptitious diuretic use may be diagnosed by obtaining a urine toxicology screen for diuretics. The urine $[Cl^-]$ is increased while a patient is using diuretics but is low when the patient stops taking them. *Rarely, children with mild Bartter or Gitelman syndrome are misdiagnosed as having bulimia or abusing diuretics.* The

urine [Cl^-] is always elevated in Bartter and Gitelman syndromes, and the urine toxicology screen for diuretics has a negative result. Metabolic alkalosis with hypokalemia is occasionally the initial manifestation of cystic fibrosis. An elevated sweat Cl^- finding is diagnostic.

Patients with a metabolic alkalosis and a high urinary [Cl^-] are subdivided according to blood pressure status. Children with normal blood pressure may have Bartter or Gitelman syndrome. Excess base administration is another diagnostic possibility, but it is usually apparent from the history. In patients with sodium bicarbonate ingestion (baking soda), which may be unreported by the parent, the metabolic alkalosis usually occurs with significant hypernatremia. In addition, unless volume depletion is superimposed, the metabolic alkalosis from base ingestion resolves itself once the source of base is eliminated.

Measuring serum concentrations of renin and aldosterone differentiates children with a metabolic alkalosis, a high urinary [Cl^-], and elevated blood pressure. Both renin and aldosterone are elevated in children with either renovascular disease or a renin-secreting tumor. Aldosterone is high and renin is low in patients with adrenal adenomas or hyperplasia and glucocorticoid-remediable aldosteronism. Renin and aldosterone are low in children with Cushing syndrome, Liddle syndrome, licorice ingestion, and 17α-hydroxylase, 11β-hydroxylase, and 11β-hydroxysteroid dehydrogenase deficiencies. An elevated 24-hour urine cortisol value is diagnostic of Cushing syndrome, which is suspected from the presence of the other classic features of this disease (see Chapter 619). Elevations of 11-deoxycorticosterone values are seen in 17α-hydroxylase and 11β-hydroxylase deficiency.

Treatment

The approach to treatment of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ([HCO_3^-] <32 mEq/L), intervention is often unnecessary, although this depends on the specific circumstances. In a child with congenital heart disease who is receiving a stable dose of a loop diuretic, a mild alkalosis does not require treatment. In contrast, intervention may be appropriate in a child with a worsening mild metabolic alkalosis because of nasogastric suction. The presence of a concurrent respiratory acid-base disturbance also influences therapeutic decision-making. A patient with a concurrent respiratory acidosis should have some increase in bicarbonate from metabolic compensation; thus the severity of the pH elevation is more important than [HCO_3^-]. In contrast, a patient with respiratory alkalosis and a metabolic alkalosis is at risk for severe alkalemia; treatment may be indicated, even if the increase in bicarbonate value is only mild.

Intervention is usually necessary in children with moderate or severe metabolic alkalosis. The most effective approach is to address the underlying etiology. In some children, nasogastric suction may be decreased or discontinued. Alternatively, the addition of a gastric PPI reduces gastric secretion and losses of HCl. Diuretics are an important cause of metabolic alkalosis, and if a change is tolerated, they should be eliminated or the dose reduced. Adequate potassium supplementation or the addition of a potassium-sparing diuretic is also helpful in a child with a metabolic alkalosis from diuretics. Potassium-sparing diuretics not only decrease renal K^+ losses but, by blocking the action of aldosterone, also decrease H^+ secretion in the distal nephron, increasing urinary bicarbonate excretion. Many children cannot tolerate discontinuation of diuretic therapy; hence, potassium supplementation and potassium-sparing diuretics are the principal therapeutic approach. Arginine HCl may also be used to treat chloride-responsive metabolic acidosis if sodium or potassium salts are not appropriate. Arginine HCl may raise the serum K^+ levels during administration. Rarely, in cases of severe metabolic alkalosis, acetazolamide is an option. A carbonic anhydrase inhibitor, acetazolamide decreases resorption of bicarbonate in the proximal tubule, causing significant bicarbonate loss in the urine. The patient receiving this drug must be monitored closely, because acetazolamide produces major losses of potassium in the urine and increases fluid losses, potentially necessitating a reduction in dosage of other diuretics.

Most children with a metabolic alkalosis have one of the **chloride-responsive** etiologies. In these situations, administration of sufficient sodium chloride and potassium chloride to correct the volume deficit and the potassium deficit is necessary to correct the metabolic alkalosis. This approach may not be an option in the child who has volume depletion due to diuretics, because volume repletion may be contraindicated. Adequate replacement of gastric losses of sodium and potassium in a child with a nasogastric tube can minimize or prevent the development of the metabolic alkalosis. With adequate intravascular volume and a normal serum [K^+], the kidney excretes the excess bicarbonate within 2 days.

In children with the **chloride-resistant** causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it would exacerbate the hypertension and would not repair the metabolic alkalosis. Ideally, treatment focuses on eliminating the excess aldosterone effect. Adrenal adenomas can be resected, licorice intake can be eliminated, and renovascular disease can be repaired. Glucocorticoid-remediable aldosteronism, 17α-hydroxylase deficiency, and 11β-hydroxylase deficiency respond to the administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β-hydroxysteroid dehydrogenase deficiency can be decreased with the use of spironolactone, which blocks the mineralocorticoid receptor. In contrast, the metabolic alkalosis in children with Liddle syndrome does not respond to spironolactone; however, either triamterene or amiloride is effective therapy because both agents block the sodium channel that is constitutively active in Liddle syndrome.

In children with Bartter or Gitelman syndrome, therapy includes oral potassium and sodium supplementation; potassium-sparing diuretics may be helpful in select cases. Children with Gitelman syndrome often require magnesium supplementation, whereas children with severe Bartter syndrome often benefit from indomethacin.

RESPIRATORY ACIDOSIS

A respiratory acidosis is an inappropriate increase in blood carbon dioxide tension (P_{CO_2}). CO_2 is a by-product of metabolism and is removed from the body by the lungs. During a respiratory acidosis, the effectiveness of CO_2 removal by the lungs is decreased. A respiratory acidosis is secondary to either pulmonary disease, such as severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose (see Chapter 86). Even though body production of CO_2 can vary, normal lungs are able to accommodate this variation; excess production of CO_2 is not an isolated cause of a respiratory acidosis. With impairment of alveolar ventilation, the rate of body production of CO_2 may affect the severity of the respiratory acidosis, but this is usually not a significant factor.

A respiratory acidosis causes a decrease in the blood pH, but there is normally a metabolic response that partially compensates, minimizing the severity of the acidemia. The acute metabolic response to a respiratory alkalosis occurs within minutes. The metabolic compensation for an *acute* respiratory acidosis is secondary to titration of acid by nonbicarbonate buffers. This buffering of H^+ causes a predictable increase in the serum [HCO_3^-]: Plasma bicarbonate increases by 1 for each 10 mm Hg increase in the P_{CO_2} (acute compensation).

With a *chronic* respiratory acidosis, there is more significant metabolic compensation and thus less severe acidemia than in an acute respiratory acidosis with the same increase in P_{CO_2}. During a chronic respiratory acidosis, the kidneys increase acid excretion. This response occurs over 3-4 days and causes a predictable increase in the serum [HCO_3^-]: Plasma bicarbonate increases by 3.5 for each 10 mm Hg increase in the P_{CO_2} (chronic compensation).

The increase of serum [HCO_3^-] during a chronic respiratory acidosis is associated with a decrease in body chloride. After acute correction of a chronic respiratory acidosis, the plasma bicarbonate continues to

Table 73.15 Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION
- Encephalitis
- Head trauma
- Brain tumor
- Central sleep apnea
- Primary pulmonary hypoventilation (Ondine curse)
- Stroke
- Hypoxic brain damage
- Obesity-hypoventilation (Pickwickian) syndrome
- Increased intracranial pressure
- Medications
  - Narcotics
  - Barbiturates
  - Anesthesia
  - Benzodiazepines
  - Propofol
  - Alcohols

DISORDERS OF SPINAL CORD, PERIPHERAL NERVES, OR NEUROMUSCULAR JUNCTION
- Diaphragmatic paralysis
- Guillain-Barré syndrome
- Poliomyelitis
- Acute flaccid myelitis
- Spinal muscular atrophies
- Tick paralysis
- Botulism
- Myasthenia
- Multiple sclerosis
- Spinal cord injury
- Medications
  - Vecuronium
  - Aminoglycosides
  - Organophosphates (pesticides)

RESPIRATORY MUSCLE WEAKNESS
- Muscular dystrophy
- Hypothyroidism
- Malnutrition
- Hypokalemia
- Hypophosphatemia
- Medications
  - Succinylcholine
  - Corticosteroids

PULMONARY DISEASE
- Pneumonia
- Pneumothorax
- Asthma
- Bronchiolitis
- Pulmonary edema
- Pulmonary hemorrhage
- Acute respiratory distress syndrome
- Neonatal respiratory distress syndrome
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Hypoplastic lungs
- Meconium aspiration
- Pulmonary thromboembolus
- Interstitial fibrosis

UPPER AIRWAY DISEASE
- Aspiration
- Laryngospasm
- Angioedema
- Obstructive sleep apnea
- Tonsillar hypertrophy
- Vocal cord paralysis
- Extrinsic tumor
- Extrinsic or intrinsic hemangioma

MISCELLANEOUS
- Flail chest
- Cardiac arrest
- Kyphoscoliosis
- Decreased diaphragmatic movement due to ascites or peritoneal dialysis

be increased, and the patient has a metabolic alkalosis. Because of the Cl^- deficit, this is a chloride-responsive metabolic alkalosis; it corrects once the patient's Cl^- deficit is replaced.

A **mixed disorder** is present if the metabolic compensation is inappropriate. A higher than expected bicarbonate value occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected bicarbonate value occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory acidosis requires clinical knowledge of the acuity of the process, because the expected compensation is different, depending on whether the process is acute or chronic.

The P_{CO_2} cannot be interpreted in isolation to determine whether a patient has a respiratory acidosis. A respiratory acidosis is always present if a patient has acidemia and an elevated P_{CO_2}. However, an elevated P_{CO_2} also occurs as appropriate respiratory compensation for a simple metabolic alkalosis. The patient is *alkalemic*; this is not a respiratory acidosis. During a mixed disturbance, a patient can have a respiratory acidosis and a normal or even low P_{CO_2}. This condition may occur in a patient with a metabolic acidosis. A respiratory acidosis is present if the patient does not have appropriate respiratory compensation (the P_{CO_2} is higher than expected from the severity of the metabolic acidosis).

Etiology and Pathophysiology

The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 73.15). CNS disorders can decrease the activity of the central respiratory center, reducing ventilatory drive. A variety of medications and illicit drugs suppress the respiratory center. The signals from the respiratory center need to be transmitted to the respiratory muscles via the nervous system. Respiratory muscle failure can be secondary to disruption of the signal from the CNS in the spinal cord, the phrenic nerve, or the neuromuscular junction. Disorders directly affecting the muscles of respiration can prevent adequate ventilation, causing a respiratory acidosis.

Mild or moderate lung disease often causes a respiratory alkalosis as a result of hyperventilation secondary to hypoxia or stimulation of lung mechanoreceptors or chemoreceptors. Only more severe lung disease causes a respiratory acidosis. Upper airway diseases, by impairing air entry into the lungs, may decrease ventilation, producing a respiratory acidosis.

Increased production of CO_2 is never the sole cause of a respiratory acidosis, but it can increase the severity of the disease in a patient with decreased ventilation of CO_2. Increased production of CO_2 occurs in patients with fever, hyperthyroidism, excess caloric intake, and high levels of physical activity. Increased respiratory muscle work also increases CO_2 production.

Clinical Manifestations

Patients with a respiratory acidosis are often tachypneic in an effort to correct the inadequate ventilation. Exceptions include patients with a respiratory acidosis resulting from CNS depression and patients who are on the verge of complete respiratory failure secondary to fatigue of the respiratory muscles.

The symptoms of respiratory acidosis are related to the severity of the **hypercarbia**. Acute respiratory acidosis is usually more symptomatic than chronic respiratory acidosis. Symptoms are also increased by concurrent hypoxia or metabolic acidosis. In a patient breathing room air, hypoxia is always present if a respiratory acidosis is present. The potential CNS manifestations of respiratory acidosis include anxiety, dizziness, headache, confusion, asterixis, myoclonic jerks, hallucinations, psychosis, coma, and seizures.

Acidemia, no matter the etiology, affects the cardiovascular system. An arterial pH <7.2 impairs cardiac contractility and the normal response to catecholamines in both the heart and the peripheral vasculature. Hypercapnia causes vasodilation, most dramatically in the cerebral vasculature, but hypercapnia produces vasoconstriction of the pulmonary circulation. Respiratory acidosis increases the risk of cardiac **arrhythmias**, especially in a child with underlying cardiac disease.

Diagnosis

The history and physical findings often point to a clear etiology. For the obtunded patient with poor respiratory effort, evaluation of the CNS is often indicated. This may include imaging studies (CT or MRI) and, potentially, a lumbar puncture for cerebrospinal fluid analysis. A toxicology screen for illicit drugs may also be appropriate. A response to naloxone is both diagnostic and therapeutic. In many of the diseases affecting the respiratory muscles, there is evidence of weakness in other muscles. Stridor is a clue that the child may have upper airway disease. Along with a physical examination, a chest radiograph is often helpful in diagnosing pulmonary disease.

In many patients, respiratory acidosis may be multifactorial. A child with bronchopulmonary dysplasia, an intrinsic lung disease, may worsen because of respiratory muscle dysfunction caused by severe hypokalemia resulting from long-term diuretic therapy. Conversely, a child with muscular dystrophy, a muscle disease, may worsen because of aspiration pneumonia.

For a patient with respiratory acidosis, calculation of the gradient between the alveolar oxygen concentration and the arterial oxygen concentration, the A-a O_2 gradient, is useful for distinguishing between poor respiratory effort and intrinsic lung disease. The A-a O_2 gradient is increased if the hypoxemia is caused by intrinsic lung disease (see Chapter 421).

Treatment

Respiratory acidosis is best managed by treatment of the underlying etiology. In some patients, the response is very rapid, such as after the administration of naloxone to a patient with a narcotic overdose. In contrast, in the child with pneumonia, a number of days of antibiotic therapy may be required before the respiratory status improves. In many children with a chronic respiratory acidosis, there is no curative therapy, although an acute respiratory illness superimposed on a chronic respiratory condition is usually reversible.

All patients with an *acute* respiratory acidosis are hypoxic and therefore need to receive supplemental oxygen. Mechanical ventilation is necessary in some children with respiratory acidosis. Children with significant respiratory acidosis caused by CNS disease usually require mechanical ventilation because such a disorder is unlikely to respond quickly to therapy. In addition, hypercarbia causes cerebral vasodilation, and the increase in ICP can be dangerous in a child with an underlying CNS disease. Readily reversible CNS depression, as from a narcotic overdose, may not require mechanical ventilation. Decisions on mechanical ventilation for other patients depend on a number of factors. Patients with severe hypercarbia (P_{CO_2} >75 mm Hg) usually require mechanical ventilation (see Chapter 86.1). The threshold for intubation is lower if there is concomitant metabolic acidosis, a slowly responsive underlying disease, or hypoxia that responds poorly to oxygen, or if the patient appears to be tiring and respiratory arrest seems likely.

In patients with a *chronic* respiratory acidosis, the respiratory drive is often less responsive to hypercarbia and more responsive to hypoxia. Thus, with chronic respiratory acidosis, excessive use of oxygen can blunt the respiratory drive and therefore increase the P_{CO_2}. In these patients, oxygen must be used cautiously.

When possible, it is best to avoid mechanical ventilation in a patient with chronic respiratory acidosis because extubation is often difficult. However, an acute illness may necessitate mechanical ventilation in a child with a chronic respiratory acidosis. When intubation is necessary, the P_{CO_2} should be lowered only to the patient's normal baseline, and this should be done gradually. These patients normally have an elevated serum [HCO_3^-] as a result of metabolic compensation for their respiratory acidosis. A rapid lowering of the P_{CO_2} can cause a severe metabolic alkalosis, potentially leading to complications, including cardiac arrhythmias, decreased cardiac output, and decreased cerebral blood flow. In addition, prolonged mechanical ventilation at a normal P_{CO_2} causes the metabolic compensation to resolve. When the patient is subsequently extubated, the patient will no longer benefit from metabolic compensation, causing a more severe acidemia because of the respiratory acidosis.

RESPIRATORY ALKALOSIS

A respiratory alkalosis is an inappropriate reduction in the blood CO_2 concentration. This is usually secondary to hyperventilation, initially causing removal of CO_2 to surpass production. Eventually, a new steady state is achieved, with removal equaling production, although at a lower CO_2 tension (P_{CO_2}). A respiratory alkalosis that is not the result of hyperventilation may occur in children receiving extracorporeal membrane oxygenation, with CO_2 lost directly from the blood in the extracorporeal circuit.

With a simple respiratory alkalosis, the pH increases, but there is a normal metabolic response that attenuates some of the change in the blood pH. A metabolic response to an acute respiratory alkalosis occurs within minutes, mediated by hydrogen ion release from nonbicarbonate buffers. The metabolic response to an acute respiratory alkalosis is predictable: Plasma bicarbonate falls by 2 for each 10 mm Hg decrease in the P_{CO_2} (acute compensation).

A chronic respiratory alkalosis leads to more significant metabolic compensation because of the actions of the kidneys, which decrease acid secretion, producing a decrease in the serum [HCO_3^-]. Both the proximal and distal tubules decrease acid secretion. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days to produce the full effect: Plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the P_{CO_2} (chronic compensation).

A chronic respiratory alkalosis is the only acid-base disturbance in which appropriate compensation may *normalize the pH,* although >7.4.

A **mixed disorder** is present if the metabolic compensation is inappropriate. A higher than expected HCO_3^- level occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected HCO_3^- level occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory alkalosis requires clinical knowledge of the acuity of the process, because the expected compensation differs according to whether the process is acute or chronic.

A low P_{CO_2} value does not always indicate a respiratory alkalosis. The P_{CO_2} also decreases as part of the appropriate respiratory compensation for a metabolic acidosis; this is not a respiratory alkalosis.

Table 73.16 Causes of Respiratory Alkalosis

HYPOXEMIA OR TISSUE HYPOXIA
Pneumonia
Pulmonary edema
Cyanotic heart disease
Congestive heart failure
Asthma
Severe anemia
High altitude
Laryngospasm
Aspiration
Carbon monoxide poisoning
Pulmonary embolism
Interstitial lung disease
Hypotension
LUNG RECEPTOR STIMULATION
Pneumonia
Pulmonary edema
Asthma
Pulmonary embolism
Hemothorax
Pneumothorax
Respiratory distress syndrome (adult or infant)
CENTRAL STIMULATION
Central nervous system disease
Subarachnoid hemorrhage
Encephalitis or meningitis
Trauma
Brain tumor
Stroke
Fever
Pain
Anxiety (panic attack)
Psychogenic hyperventilation or anxiety
Liver failure
Sepsis
Pregnancy
Mechanical ventilation
Hyperammonemia
Extracorporeal membrane oxygenation or hemodialysis
Medications
Salicylate intoxication
Theophylline
Progesterone
Exogenous catecholamines
Caffeine

A metabolic acidosis is the dominant acid-base disturbance in a patient with acidemia and a low P_{CO_2}, even though there could still be a concurrent respiratory alkalosis. In contrast, a respiratory alkalosis is always present in a patient with alkalemia and a low P_{CO_2}. Even a normal P_{CO_2} value may be consistent with a respiratory alkalosis in a patient with a metabolic alkalosis, because an elevated P_{CO_2} is expected as part of appropriate respiratory compensation for the metabolic alkalosis.

Etiology and Pathophysiology

A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 73.16). Arterial hypoxemia or tissue **hypoxia** stimulates peripheral chemoreceptors to signal the central respiratory center in the medulla to increase ventilation. The resultant greater respiratory effort increases the oxygen content of the blood (P_{O_2}) but depresses the P_{CO_2}. The effect of hypoxemia on ventilation begins when the arterial oxygen saturation (Sa_{O_2}) decreases to approximately 90% (P_{O_2} = 60 mm Hg), and hyperventilation increases as hypoxemia worsens. Acute hypoxia is a more potent stimulus for hyperventilation than chronic hypoxia; thus chronic hypoxia, as occurs in cyanotic heart disease, causes a much less severe respiratory alkalosis than an equivalent degree of acute hypoxia. The many causes of hypoxemia or tissue hypoxia include primary lung disease, severe anemia, and carbon monoxide (CO) poisoning.

The lungs contain chemoreceptors and mechanoreceptors that respond to irritants and stretching and send signals to the respiratory center to increase ventilation. Aspiration or pneumonia may stimulate the chemoreceptors, whereas pulmonary edema may stimulate the mechanoreceptors. Most of the diseases that activate these receptors may also cause hypoxemia and can therefore potentially lead to hyperventilation by two mechanisms. Patients with primary lung disease may initially have a respiratory alkalosis, but worsening of the disease, combined with respiratory muscle fatigue, often causes respiratory failure and the development of a respiratory acidosis.

Hyperventilation in the absence of lung disease occurs with direct stimulation of the central respiratory center. This occurs with CNS diseases such as meningitis, hemorrhage, and trauma. Central hyperventilation caused by lesions, such as infarcts or tumors near the central respiratory center in the midbrain, increases the rate and depth of the respiratory effort. This respiratory pattern portends a poor prognosis because these midbrain lesions are frequently fatal. Systemic processes may cause centrally mediated hyperventilation. Although the exact mechanisms are not clear, liver disease causes a respiratory alkalosis that is usually proportional to the degree of liver failure. **Pregnancy** causes a chronic respiratory alkalosis, probably mediated by progesterone acting on the respiratory centers. **Salicylates**, although often causing a concurrent metabolic acidosis, directly stimulate the respiratory center to produce a respiratory alkalosis. The respiratory alkalosis during sepsis is probably caused by cytokine release.

Hyperventilation may be secondary to an underlying disease that causes pain, stress, or anxiety. In psychogenic hyperventilation or in **panic attacks**, there is no disease process accounting for the hyperventilation. This disorder may occur in a child who has had an emotionally stressful experience. Alternatively, it may be part of a panic disorder, especially if there are repeated episodes of hyperventilation. In such a patient, the symptoms of acute alkalemia increase anxiety, potentially perpetuating the hyperventilation.

A respiratory alkalosis is quite common in children receiving mechanical ventilation because the respiratory center is not controlling ventilation. In addition, these children may have a decreased metabolic rate and thus less CO_2 production because of sedation and paralytic medications. Normally, decreased CO_2 production and the resultant hypocapnia decrease ventilation, but this physiologic response cannot occur in a child who cannot reduce ventilatory effort.

Clinical Manifestations

The disease process causing the respiratory alkalosis is usually more concerning than the clinical manifestations. Chronic respiratory alkalosis is usually asymptomatic because metabolic compensation decreases the magnitude of the alkalemia.

Acute respiratory alkalosis may cause chest tightness, palpitations, lightheadedness, circumoral numbness, and paresthesias of the extremities. Less common manifestations include tetany, seizures, muscle cramps, and syncope. The lightheadedness and syncope probably result from the reduction in cerebral blood flow caused by hypocapnia. The reduction in cerebral blood flow is the rationale for using hyperventilation to treat children with increased intracranial pressure (ICP). The paresthesias, tetany, and seizures may be partially related to the reduction in ionized calcium that occurs because alkalemia causes more calcium to bind to albumin. A respiratory alkalosis also causes a mild reduction in the serum potassium level. Patients with psychogenic hyperventilation tend to be symptomatic because of the respiratory alkalosis, and these symptoms, along with a sensation of breathlessness, exacerbate the hyperventilation.

Diagnosis

In many patients, hyperventilation producing a respiratory alkalosis is not clinically detectable, even with careful observation of the patient's

respiratory effort. Metabolic compensation for a respiratory alkalosis causes a low serum [HCO_3^-]. When hyperventilation is not appreciated and only serum electrolytes are evaluated, there is often a presumptive diagnosis of a metabolic acidosis. If a respiratory alkalosis is suspected, only ABG determination can make the diagnosis.

Hyperventilation does not always indicate a primary respiratory disorder. In some patients, the hyperventilation is appropriate respiratory compensation for a metabolic acidosis. With a primary metabolic acidosis, acidemia is present, and the serum HCO_3^- level is usually quite low if there is clinically detectable hyperventilation. In contrast, the serum HCO_3^- level never goes below 17 mEq/L as part of the metabolic compensation for acute respiratory alkalosis, and simple acute respiratory alkalosis causes alkalemia.

The etiology of a respiratory alkalosis is often apparent from the physical examination or history, and it may consist of lung disease, neurologic disease, or cyanotic heart disease. **Hypoxemia** is a common cause of hyperventilation, and it is important to diagnose because it suggests a significant underlying disease that requires expeditious treatment. Hypoxemia may be detected on physical examination (cyanosis) or by pulse oximetry. However, normal pulse oximetry values do not eliminate hypoxemia as the etiology of the hyperventilation. There are two reasons why pulse oximetry is not adequate for eliminating hypoxemia as a cause of a respiratory alkalosis. First, pulse oximetry is not very sensitive at detecting a mildly low arterial P_{O_2} (Pa_{O_2}). Second, the hyperventilation during a respiratory alkalosis causes Pa_{O_2} to increase, possibly to a level that is not identified as abnormal by pulse oximetry. Only ABG measurement can eliminate hypoxia as an explanation for a respiratory alkalosis. Along with hypoxemia, it is important to consider processes that cause **tissue hypoxia without necessarily causing hypoxemia**. Examples are CO or cyanide poisoning, severe anemia, and heart failure.

Lung disease without hypoxemia may cause hyperventilation. Although lung disease is often apparent by history or physical examination, a chest radiograph may detect more subtle disease. The patient with a pulmonary embolism may have benign chest radiograph findings, normal Pa_{O_2}, and isolated respiratory alkalosis, although hypoxia may eventually occur. Diagnosis of a pulmonary embolism requires a high index of suspicion and should be considered in children without another explanation for respiratory alkalosis, especially if risk factors are present, such as prolonged bed rest and a hypercoagulable state (e.g., nephrotic syndrome, lupus anticoagulant).

Treatment

There is seldom a need for specific treatment of respiratory alkalosis. Rather, treatment focuses on the underlying disease. Mechanical ventilator settings are adjusted to correct **iatrogenic** respiratory alkalosis, unless the hyperventilation has a therapeutic purpose (e.g., treatment of increased ICP).

For the patient with hyperventilation secondary to anxiety, efforts should be undertaken to reassure the child, usually enlisting the parents. Along with reassurance, patients with **psychogenic hyperventilation** may benefit from benzodiazepines. During an acute episode of psychogenic hyperventilation, rebreathing into a paper bag increases the patient's P_{CO_2}. Using a paper bag instead of a plastic bag allows adequate oxygenation but permits [CO_2] in the bag to increase. The resultant increase in the patient's P_{CO_2} decreases the symptoms of the respiratory alkalosis that tend to perpetuate the hyperventilation. Rebreathing should be performed only when other causes of hyperventilation have been eliminated; pulse oximetry during the rebreathing is prudent.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 74

Maintenance and Replacement Therapy

Larry A. Greenbaum

Maintenance intravenous (IV) fluids are used in a child who cannot be fed enterally. Along with maintenance fluids, children may require concurrent **replacement fluids** if they have continued excessive losses, as may occur with drainage from a nasogastric (NG) tube or with high urine output because of nephrogenic diabetes insipidus. If dehydration is present, the patient also needs to receive **deficit** replacement (see Chapter 75). A child awaiting surgery may need only maintenance fluids, whereas a child with diarrheal dehydration needs maintenance and deficit therapy and also may require replacement fluids if significant diarrhea continues.

MAINTENANCE THERAPY

Children normally have large variations in their daily intake of water and electrolytes. The only exceptions are patients who receive fixed dietary regimens orally, via a gastric tube, or as IV total parenteral nutrition (TPN). Healthy children can tolerate significant variations in intake because of the many homeostatic mechanisms that can adjust absorption and excretion of water and electrolytes (see Chapter 73). The calculated water and electrolyte need that form the basis of maintenance therapy are not absolute requirements. Rather, these calculations provide reasonable guidelines for a *starting point to estimate IV therapy*. Children do not need to be started on IV fluids simply because their intake is being monitored in a hospital and they are not taking "maintenance fluids" orally, unless there is a pathologic process present that necessitates high fluid intake.

Maintenance fluids are most often necessary in preoperative and postoperative surgical patients; many nonsurgical patients also require maintenance fluids. It is important to recognize when it is necessary to begin maintenance fluids. A normal teenager who is given nothing by mouth (NPO) overnight for a morning procedure does not require maintenance fluids because a healthy adolescent can easily tolerate 12-18 hours without oral intake. In contrast, a 6-month-old child waiting for surgery should begin receiving IV fluids within 8 hours of the last feeding. Infants become dehydrated more quickly than older patients. A child with obligatory high urine output from nephrogenic diabetes insipidus should begin receiving IV fluids soon after being classified as NPO.

Maintenance fluids are composed of a solution of water, glucose, sodium (Na^+), and potassium (K^+). This solution has the advantages of simplicity, long shelf life, low cost, and compatibility with peripheral IV administration. Such a solution accomplishes the major objectives of maintenance fluids (Table 74.1). Patients lose water, Na^+, and K^+ in their urine and stool; water is also lost from the skin and lungs. Maintenance fluids replace these losses, thereby avoiding the development of dehydration and Na^+ or K^+ deficiency.

Table 74.1 Goals of Maintenance Fluids

- Prevent dehydration
- Prevent electrolyte disorders
- Prevent ketoacidosis
- Prevent protein degradation

The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient, prevents the development of starvation ketoacidosis, and diminishes the protein degradation that would occur if the patient received no calories. Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. This fact is typically not problematic for a patient receiving IV fluids for a few days. A patient receiving maintenance IV fluids is receiving inadequate calories and will lose 0.5–1% of weight each day. It is imperative that patients not remain on maintenance therapy indefinitely; TPN should be used for children who cannot be fed enterally for more than a few days, especially patients with underlying malnutrition.

Prototypical maintenance fluid therapy does not provide electrolytes such as calcium, phosphorus, magnesium, and bicarbonate. For most patients, this lack is not problematic for a few days, although there are patients who will not tolerate this omission, usually because of excessive losses. A child with proximal renal tubular acidosis wastes bicarbonate in urine. Such a patient will rapidly become acidemic unless bicarbonate (or another base) is added to the maintenance fluids. It is important to remember the limitations of maintenance fluid therapy.

MAINTENANCE WATER

Water is a crucial component of maintenance fluid therapy because of the obligatory daily water losses. These losses are both measurable (urine, stool) and not measurable (**insensible losses** from the skin and lungs). Failure to replace these losses leads to a child who is thirsty, uncomfortable, and ultimately dehydrated.

The goal of maintenance water is to provide enough water to replace these losses. Although urinary losses are approximately 60% of the total, the normal kidney can greatly modify water losses, with daily urine volume potentially varying by more than a factor of 20. Maintenance water is designed to provide enough water so that the kidney does not need to significantly dilute or concentrate the urine. It also provides a margin of safety so that normal homeostatic mechanisms can adjust urinary water losses to prevent overhydration and dehydration. This adaptability obviates the need for absolute precision in determining water requirements. This fact is important, given the absence of absolute accuracy in the formulas for calculation of water needs.

Table 74.2 provides a system for calculating maintenance water on the basis of the patient's weight and emphasizes the high water needs of smaller, less mature patients. This approach is reliable, although calculations based on weight do overestimate the water needs of an overweight child, in whom it is better to base the calculations on the lean body weight, which can be estimated by using the 50th percentile of body weight for the child's height. It is also important to remember that there is an upper limit of 2.4 L/24 hr in adult-sized patients. IV fluids are written as an hourly rate. The formulas in Table 74.3 enable rapid calculation of the rate of maintenance fluids.

Table 74.2 Body Weight Method for Calculating Daily Maintenance Fluid Volume

BODY WEIGHT	FLUID PER DAY
0-10 kg	100 mL/kg
11-20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg*

*The maximum total fluid per day is normally 2,400 mL.

Table 74.3 Hourly Maintenance Water Rate

For body weight 0-10 kg: 4 mL/kg/hr
For body weight 10-20 kg: 40 mL/hr + 2 mL/kg/hr × (wt − 10 kg)
For body weight >20 kg: 60 mL/hr + 1 mL/kg/hr × (wt − 20 kg)*

*The maximum fluid rate is normally 100 mL/hr.

INTRAVENOUS SOLUTIONS

The components of available solutions are shown in Table 74.4. These solutions are available with 5% dextrose (D5), 10% dextrose (D10), or without dextrose. Except for Ringer lactate (lactated Ringer, LR), they are also available with added potassium (10 or 20 mEq/L). A *balanced IV fluid* contains a base (lactate or acetate), a more physiologic chloride concentration than normal saline (NS), and additional physiologic concentrations of electrolytes such as potassium, calcium, and magnesium. Examples include LR and Plasma-Lyte, and there is evidence suggesting benefit versus NS in some but not all clinical situations. A hospital pharmacy can also prepare custom-made solutions with different concentrations of sodium or potassium. In addition, other electrolytes, such as calcium, magnesium, phosphate, acetate, and bicarbonate, can be added to IV solutions. Custom-made solutions take time to prepare and are much more expensive than commercial solutions. The use of custom-made solutions is necessary only for patients who have underlying disorders that cause significant electrolyte imbalances. The use of commercial solutions saves time and expense.

A normal plasma osmolality is 285-295 mOsm/kg. Infusing an IV solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus IV fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Thus 0.2NS (osmolality = 68) should not be administered peripherally, but D5 0.2NS (osmolality = 346) or D5 1/2NS + 20 mEq/L potassium chloride (KCl) with an osmolality of 472 can be administered.

Hypotonic fluids seem more physiologic given the low Na^+ content of breast milk and formula (~7 mEq/L). However, hospitalized children often have impaired water excretion because of volume depletion or nonosmotic stimuli for antidiuretic hormone (ADH) production, such as respiratory disease, central nervous system disease, stress, pain, nausea, and medications (e.g., narcotics). Hypotonic fluids increase the risk of hyponatremia, which may have serious sequelae; *hence, isotonic fluids with D5 are recommended as standard maintenance fluid except in neonates <28 days of age.*

GLUCOSE

Maintenance fluids usually contain D5, which provides 17 calories/100 mL and nearly 20% of the daily caloric needs. This level is enough to prevent ketone production and helps minimize protein degradation, but the child will lose weight on this regimen. Maintenance fluids are also lacking in such crucial nutrients as protein, fat, vitamins, and minerals. Hence, a patient needs to be started on TPN after a few days of maintenance fluids if enteral feedings are still not possible.

SELECTION OF MAINTENANCE FLUIDS

An isotonic fluid (NS, LR, Plasma-Lyte) with D5 and KCl (10-20 mEq/L is usually added to NS) is recommended for maintenance IV fluids. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hours postoperatively; the rate is typically approximately two thirds the calculated maintenance rate, with dextrose added if clinically indicated. Subsequent maintenance fluids have the addition of D5 and 10-20 mEq/L KCl based on the serum K^+ and the clinical setting. Electrolytes should be measured at least daily in all children receiving >50% of maintenance fluids intravenously unless the child is receiving prolonged IV fluids (TPN).

These guidelines assume that no disease process is present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Neonates, and especially premature infants, are outside the scope of these guidelines given their unique physiology. Children with renal insufficiency may be hyperkalemic or unable to excrete K^+ and may not tolerate 10 or 20 mEq/L of potassium. Patients with persistent ADH production because of an underlying disease process (syndrome of inappropriate ADH secretion, congestive heart failure, nephrotic syndrome, liver disease) should receive less

Table 74.4 Composition of Intravenous Solutions*

FLUID	[NA^+]	[CL^-]	[K^+]	[CA^{2+}]	[LACTATE$^-$]
Normal saline (0.9% NaCl)	154	154	—	—	—
Half-normal saline (0.45% NaCl)	77	77	—	—	—
0.2 normal saline (0.2% NaCl)	34	34	—	—	—
Ringer lactate	130	109	4	3	28

*Electrolyte concentrations in mEq/L.

than maintenance fluids. Children with meningitis are fluid restricted unless intravascular volume depletion is present (see Chapter 643.1). Treatment is individualized, and careful monitoring is critical.

In children with complicated pathophysiologic derangements, it may be necessary to adjust empirically the electrolyte composition and rate of maintenance fluids on the basis of electrolyte measurements and assessment of fluid balance. In all children it is critical to monitor weight, urine output, and electrolytes carefully to identify overhydration or underhydration, hyponatremia, and other electrolyte disturbances, and then adjust the rate or composition of the IV solution accordingly.

VARIATIONS IN MAINTENANCE WATER AND ELECTROLYTES

The calculation of maintenance water is based on standard assumptions regarding water losses. In some patients, however, these assumptions are incorrect. To identify such situations, it is helpful to understand the source and magnitude of normal water losses. Table 74.5 lists the three sources of normal water loss.

Urine is the most important contributor to normal water loss. Insensible losses represent approximately one third of total maintenance water (40% in infants; 25% in adolescents and adults). Insensible losses are composed of evaporative losses from the skin and lungs that cannot be quantitated. The evaporative losses from the skin *do not* include sweat, which would be considered an additional (sensible) source of water loss. Stool normally represents a minor source of water loss.

Maintenance water and electrolyte needs may be increased or decreased, depending on the clinical situation. This may be obvious, as in the infant with profuse diarrhea, or subtle, as in the patient who has decreased insensible losses while receiving mechanical ventilation. It is helpful to consider the sources of normal water and electrolyte losses and to determine whether any of these sources is being modified in a specific patient. It is then necessary to adjust maintenance water and electrolyte calculations.

Table 74.6 lists a variety of clinical situations that modify normal water and electrolyte losses. The skin can be a source of very significant water loss, particularly in neonates, especially premature infants, who are under radiant warmers or are receiving phototherapy. Very low birthweight infants can have insensible losses of 100-200 mL/kg/24 hr. Burns can result in massive losses of water and electrolytes, and there are specific guidelines for fluid management in children with burns (see Chapter 89). Sweat losses of water and electrolytes, especially in a warm climate, can also be significant. Children with cystic fibrosis and some children with pseudohypoaldosteronism have increased sodium losses from the skin.

Fever increases evaporative losses from the skin. These losses are somewhat predictable, leading to a 10–15% increase in maintenance water needs for each 1°C (1.8°F) increase in temperature above 38°C (100.4°F). These guidelines are for a patient with a persistent fever; a 1-hour fever spike does not cause an appreciable increase in water needs.

Tachypnea or a tracheostomy increases evaporative losses from the lungs. A humidified system (nasal cannula, mask, ventilator) causes a decrease in insensible losses from the lungs and can even lead to water absorption via the lungs; a ventilated patient has a decrease in maintenance water requirements. It may be difficult to quantify the changes that take place in the individual patient in these situations.

Table 74.5 Sources of Water Loss

- Urine: 60%
- Insensible losses: ≈35% (skin and lungs)
- Stool: 5%

REPLACEMENT FLUIDS

The gastrointestinal (GI) tract is potentially a source of considerable water loss. GI water losses are accompanied by electrolytes and thus may cause disturbances in intravascular volume and electrolyte concentrations. GI losses are often associated with loss of potassium, leading to hypokalemia. Because of the high bicarbonate concentration in stool, children with diarrhea usually have a **metabolic acidosis**, which may be accentuated if volume depletion causes hypoperfusion and a concurrent lactic acidosis. Emesis or losses from an NG tube can cause a **metabolic alkalosis** (see Chapter 73).

In the absence of vomiting, diarrhea, or NG drainage, GI losses of water and electrolytes are usually quite small. All GI losses are considered excessive, and the increase in the water requirement is equal to the volume of fluid losses. Because GI water and electrolyte losses can be precisely measured, an appropriate replacement solution can be used.

It is impossible to predict the losses for the next 24 hours; it is better to replace excessive GI losses as they occur. The child should receive an appropriate maintenance fluid that does not consider the GI losses. The losses should then be replaced after they occur, with use of a solution with a similar electrolyte concentration as the GI fluid. The losses are usually replaced every 1-6 hours, depending on the rate of loss, with very rapid losses being replaced more frequently.

Diarrhea is a common cause of fluid loss in children and can result in dehydration and electrolyte disorders. In the unusual patient with significant diarrhea and a limited ability to take oral fluid, it is important to have a plan for replacing excessive stool losses. The volume of stool should be measured, and an equal volume of replacement solution should be given. Data are available on the average electrolyte composition of diarrhea in children (see Table 74.7). With this information, an appropriate replacement solution can be designed. The solution shown in Table 74.7 replaces stool losses of Na^+, K^+, chloride (Cl^-), and bicarbonate. Each 1 mL of stool should be replaced by 1 mL of this solution. The average electrolyte composition of diarrhea is just an average, and there may be considerable variation. It is therefore advisable to consider measuring the electrolyte composition of a patient's diarrhea if the amount is especially excessive or if the patient's serum electrolyte levels are problematic.

Loss of gastric fluid, through emesis or NG suction, is also likely to cause dehydration, in that most patients with either condition have impaired oral intake of fluids. Electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, are also common. These complications can be avoided by judicious use of a replacement solution. The composition of gastric fluid shown in Table 74.8 is the basis for designing a replacement solution.

Table 74.6 Adjustments in Maintenance Water

SOURCE	CAUSES OF INCREASED WATER NEEDS	CAUSES OF DECREASED WATER NEEDS
Skin	Radiant warmer	Incubator (premature infant)
	Phototherapy	
	Fever	
	Sweat	
	Burns	
Lungs	Tachypnea	Humidified system (nasal cannula, mask, ventilator)
	Tracheostomy	
Gastrointestinal tract	Diarrhea	—
	Emesis	
	Nasogastric suction	
Renal	Polyuria	Oliguria/anuria
Miscellaneous	Surgical drain	—
	Third spacing	

Table 74.7 Replacement Fluid for Diarrhea

AVERAGE COMPOSITION OF DIARRHEA
Sodium: 55 mEq/L
Potassium: 25 mEq/L
Bicarbonate: 15 mEq/L
APPROACH TO REPLACEMENT OF ONGOING LOSSES
Solution: D5 1/2NS + 30 mEq/L sodium bicarbonate + 20 mEq/L KCl
Replace stool mL/mL every 1-6 hr

D5, 5% dextrose; NS, normal saline.

Table 74.8 Replacement Fluid for Emesis or Nasogastric Losses

AVERAGE COMPOSITION OF GASTRIC FLUID
Sodium: 60 mEq/L
Potassium: 10 mEq/L
Chloride: 90 mEq/L
APPROACH TO REPLACEMENT OF ONGOING LOSSES
Solution: normal saline + 10 mEq/L KCl
Replace output mL/mL every 1-6 hr

Patients with gastric losses frequently have hypokalemia, although the K^+ concentration of gastric fluid is relatively low. The associated urinary K^+ loss is an important cause of hypokalemia in this situation (see Chapter 73). These patients may need additional potassium either in their maintenance fluids or in their replacement fluids to compensate for prior or ongoing urinary losses. Restoration of the patient's intravascular volume, by decreasing aldosterone synthesis, lessens the urinary K^+ losses.

Urine output is normally the largest cause of water loss. Diseases such as renal failure and syndrome of inappropriate ADH secretion can lead to a decrease in urine volume. The patient with oliguria or anuria has a decreased need for water and electrolytes; continuation of maintenance fluids produces fluid overload. In contrast, postobstructive diuresis, the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus increase urine production. To prevent dehydration, the patient must receive more than standard maintenance fluids when urine output is excessive. The electrolyte losses in patients with polyuria are variable. In diabetes insipidus, the urine electrolyte concentration is usually low, whereas children with diseases such as juvenile nephronophthisis and obstructive uropathy usually have increased losses of both water and sodium.

Table 74.9 Adjusting Fluid Therapy for Altered Renal Output

OLIGURIA/ANURIA
Replacement of insensible fluid losses (25–40% of maintenance) with D5 1/2NS
Replace urine output mL/mL with D5 1/2NS ± KCl
POLYURIA
Replacement of insensible fluid losses (25–40% of maintenance) with D5 1/2NS ± KCl
Measure urine electrolytes
Replace urine output mL/mL with solution based on measured urine electrolytes

D5, 5% dextrose; NS, normal saline.

The approach to decreased or increased urine output is similar (Table 74.9). The patient receives fluids at a rate to replace insensible losses. This is accomplished by a rate of fluid administration that is 25–40% of the normal maintenance rate, depending on the patient's age. Replacing insensible losses in the anuric child will theoretically maintain an even fluid balance, with the caveat that 25–40% of the normal maintenance rate is only an estimate of insensible losses. In the individual patient, this rate is adjusted on the basis of monitoring of the patient's weight and volume status. Most children with renal insufficiency receive little or no potassium because the kidney is the principal site of K^+ excretion.

For the **oliguric** child, it is important to add a urine replacement solution to prevent dehydration. This issue is especially important in the patient with acute kidney injury, in whom output may increase, potentially leading to volume depletion and worsening of kidney injury if the patient remains on only insensible fluids. A replacement solution of D5 1/2NS is usually appropriate initially, although its composition may have to be adjusted if urine output increases significantly.

Most children with **polyuria** (except in diabetes mellitus; see Chapter 629) should be started on replacement of insensible fluid plus urine losses. This approach avoids the need to attempt to calculate the volume of urine output that is "normal" so that the patient can be given

replacement fluid for the excess. In these patients, urine output is, by definition, excessive, and it is often helpful to measure Na^+ and K^+ concentrations of the urine to help in formulating the urine replacement solution.

Surgical drains and chest tubes can produce measurable fluid output. These fluid losses should be replaced when they are significant. They can be measured and replaced with an appropriate solution. **Third space losses**, which manifest as edema and ascites, are caused by a shift of fluid from the intravascular space into the interstitial space. Although these losses cannot be quantitated easily, third space losses can be large and may lead to intravascular volume depletion, despite the patient's weight gain. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic, so they usually require replacement with an isotonic fluid, such as NS or LR. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient's intravascular volume status. Protein losses from chest tube drainage can be significant, occasionally necessitating that 5% albumin be used as a replacement solution.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 75

Deficit Therapy

Larry A. Greenbaum

Dehydration, most often caused by gastroenteritis, is a common problem in children. Most cases can be managed with oral rehydration (see Chapter 387). *Even children with mild to moderate hyponatremic or hypernatremic dehydration can be managed with oral rehydration.*

CLINICAL MANIFESTATIONS

The first step in caring for the child with dehydration is to assess the degree of dehydration (Table 75.1), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. The infant with mild dehydration (3–5% of body weight dehydrated) has few clinical signs or symptoms. The infant may be thirsty; the alert parent may notice a decline in urine output. The history is most helpful. The infant with moderate dehydration has clear physical signs and symptoms. Intravascular volume depletion is evident from an increased heart rate and reduced urine output. This patient needs fairly prompt intervention. The infant with severe dehydration is gravely ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion. Immediate and aggressive intervention is necessary. If possible, the child with severe dehydration should initially receive intravenous (IV) therapy. For older children and adults, mild, moderate, or severe dehydration represents a lower percentage of body weight lost. This difference occurs because water accounts for a higher percentage of body weight in infants (see Chapter 73).

Table 75.1 Clinical Evaluation of Dehydration

Mild dehydration (<5% in an infant; <3% in an older child or adult): Normal or increased pulse; decreased urine output; thirsty; normal physical findings
Moderate dehydration (5–10% in an infant; 3–6% in an older child or adult): Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (>1.5 sec); cool and pale
Severe dehydration (>10% in an infant; >6% in an older child or adult): Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (>3 sec); cold and mottled; limp, depressed consciousness

Clinical assessment of dehydration is only an estimate; thus the patient must be continually reevaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the movement of water from the intracellular space (ICS) to the extracellular space (ECS) helps preserve the intravascular volume.

The history usually suggests the etiology of the dehydration and may predict whether the patient will have a normal sodium concentration (isotonic dehydration), hyponatremic dehydration, or hypernatremic dehydration. The neonate with dehydration caused by poor intake of breast milk often has hypernatremic dehydration. **Hypernatremic dehydration** is likely in any child with losses of hypotonic fluid and poor water intake, as may occur with diarrhea, and poor oral intake because of anorexia or emesis. **Hyponatremic dehydration** occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula.

Some children with dehydration are appropriately thirsty, but in others the lack of intake is part of the pathophysiology of the dehydration. Even though decreased urine output is present in most children with dehydration, good urine output may be deceptively present if a child has an underlying renal defect, such as diabetes insipidus or a salt-wasting nephropathy, or in infants with hypernatremic dehydration.

Physical examination findings are usually proportional to the degree of dehydration. Parents may be helpful in assessment of the child for the presence of sunken eyes, because this finding may be subtle. Pinching and gently twisting the skin of the abdominal or thoracic wall detects tenting of the skin (turgor, elasticity). Tented skin remains in a pinched position rather than springing quickly back to normal. It is difficult to properly assess tenting of the skin in premature infants or severely malnourished children. Activation of the sympathetic nervous system causes **tachycardia** in children with intravascular volume depletion; diaphoresis may also be present. Postural changes in blood pressure are often helpful for evaluating and assessing the response to therapy in children with dehydration. **Tachypnea** in children with dehydration may be present secondary to a metabolic acidosis from stool losses of bicarbonate or lactic acidosis from shock (see Chapter 85).

LABORATORY FINDINGS

Several laboratory findings are useful for evaluating the child with dehydration. The serum sodium concentration determines the type of dehydration. **Metabolic acidosis** may be a result of stool bicarbonate losses in children with diarrhea, secondary **acute kidney injury** (see Chapter 572.1), or lactic acidosis from shock. The anion gap is useful for differentiating among the various causes of a metabolic acidosis (see Chapter 73). Emesis or nasogastric losses usually cause a **metabolic alkalosis**. The serum potassium (K^+) concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric K^+ losses, metabolic alkalosis, and urinary K^+ losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of K^+ out of cells, and acute kidney injury may lead to hyperkalemia. A combination of mechanisms may be present; thus it may be difficult to predict the child's acid-base status or serum K^+ level from the history alone.

The blood urea nitrogen (BUN) value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal kidney injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or

with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests acute kidney injury, although a small, transient increase can occur with dehydration. Decreased kidney perfusion is the most common etiology of acute kidney injury in a child with volume depletion, but occasionally the child may have previously undetected chronic kidney disease or an alternative explanation for the acute kidney injury. **Renal vein thrombosis** is a well-described sequela of severe dehydration in infants; findings may include thrombocytopenia and hematuria (see Chapter 562.2).

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak. An acute or chronic protein-losing enteropathy may also cause a low serum albumin concentration.

CALCULATION OF THE FLUID DEFICIT

Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L.

APPROACH TO SEVERE DEHYDRATION

The child with dehydration needs acute intervention to ensure that there is adequate tissue perfusion. This resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of **shock** with an isotonic solution, such as normal saline (NS), Ringer lactate (lactated Ringer solution, LR), or Plasma-Lyte (see Chapter 85). The child is given a fluid bolus, usually 20 mL/kg of the isotonic fluid, over approximately 20 minutes. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as fast as possible. In a child with a known or probable *metabolic alkalosis* (e.g., child with isolated vomiting), LR or Plasma-Lyte should not be used because the lactate or acetate would worsen the alkalosis. However, LR or Plasma-Lyte may be preferable to NS in shock since it is a balanced solution (see Chapters 74 and 85); NS may cause a hyperchloremic metabolic acidosis.

Colloids, such as blood, 5% albumin, and plasma, are rarely needed for fluid boluses. A crystalloid solution (NS or LR) is satisfactory, with both lower risk of infection and lower cost. Blood is obviously indicated in the child with significant anemia or acute blood loss. Plasma is useful for children with a coagulopathy. The child with hypoalbuminemia may benefit from 5% albumin, although there is evidence that albumin infusions increase mortality in adults. The volume and the infusion rate for colloids are generally modified compared with crystalloids (see Chapter 522).

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume. Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

With adequate intravascular volume, it is appropriate to plan the fluid therapy for the next 24 hours. A general approach is outlined in Table 75.2, with the caveat that there are many different approaches to correcting dehydration. A balanced solution can be substituted for NS. In isonatremic or hyponatremic dehydration, the entire fluid deficit is corrected over 24 hours; a slower approach is used for hypernatremic dehydration (discussed later). The volume of isotonic fluids that the patient has received is subtracted from this total. The remaining fluid volume is then administered over 24 hours. The potassium concentration may need to be decreased or, less frequently, increased, depending on the clinical situation. Potassium is not usually included in the IV fluids until the patient voids and normal renal function is documented by measurement of BUN and creatinine. Children with significant ongoing losses need to receive an appropriate replacement solution (see Chapter 74).

MONITORING AND ADJUSTING THERAPY

The formulation of a plan for correcting a child's dehydration is only the beginning of management. *All calculations in fluid therapy are only approximations.* This statement is especially true for the assessment of percentage dehydration. It is equally important to monitor the patient during treatment and to modify therapy on the basis of the clinical situation. Table 75.3 lists the cornerstones of patient monitoring. The patient's vital signs are useful indicators of intravascular volume status. The child with decreased blood pressure and an increased heart rate will probably benefit from a fluid bolus.

The patient's intake and output are critically important in the dehydrated child. The child who, after 8 hours of therapy, has more output than input because of continuing diarrhea needs to be started on a replacement solution. See the guidelines in Chapter 74 for selecting an appropriate replacement solution. Urine output is useful for evaluating the success of therapy. Good urine output indicates that rehydration has been successful.

Signs of dehydration on physical examination suggest the need for continued rehydration. Signs of fluid overload, such as edema and pulmonary congestion, are present in the child who is overhydrated. An accurate daily weight measurement is critical for the management of the dehydrated child. There should be a gain in weight during successful therapy.

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving IV rehydration. Such a child is at risk for sodium, potassium, and acid-base disorders. It is always important to look at trends. For example, a sodium concentration ($[Na^+]$) of 144 mEq/L is normal; but if the $[Na^+]$ was 136 mEq/L 12 hours earlier, there is a distinct risk that the child will be hypernatremic in 12 or 24 hours. It is advisable to be proactive in adjusting fluid therapy.

Both hypokalemia and hyperkalemia are potentially serious (see Chapter 73). Because dehydration can be associated with acute kidney injury and hyperkalemia, potassium is withheld from IV fluids until the patient has voided. The potassium concentration in the patient's IV fluids is not rigidly prescribed. Rather, the patient's serum K^+ level and underlying kidney function are used to modify potassium delivery. The patient with an elevated creatinine value and K^+ level of 5 mEq/L does not receive any potassium until the serum K^+ level decreases.

Table 75.2 Fluid Management of Dehydration

1. Restore intravascular volume
   Isotonic fluid (NS or LR): 20 mL/kg over 20 min
   Repeat as needed
2. Calculate 24 hr fluid needs: maintenance + deficit volume
3. Subtract isotonic fluid already administered from 24 hr fluid needs
4. Administer remaining volume over 24 hr using 5% dextrose NS + 20 mEq/L KCl
5. Replace ongoing losses as they occur

LR, Ringer lactate; NS, normal saline.

Table 75.3 Monitoring Therapy

- Vital signs
  - Pulse
  - Blood pressure
- Intake and output
  - Fluid balance
  - Urine output
- Physical examination
  - Weight
  - Clinical signs of depletion or overload
- Electrolytes

Conversely, the patient with a K^+ level of 2.5 mEq/L may require additional potassium.

Metabolic acidosis can be quite severe in dehydrated children. Although normal kidneys eventually correct this problem, a child with renal dysfunction may be unable to correct a metabolic acidosis, and a portion of the patient's IV sodium chloride may have to be replaced with sodium bicarbonate, sodium lactate (as in LR), or sodium acetate.

The serum K^+ level is modified by the patient's acid-base status. Acidosis increases serum K^+ by causing intracellular K^+ to move into the ECS. Thus, as acidosis is corrected, the serum potassium concentration ($[K^+]$) decreases. Again, it is best to anticipate this problem and to monitor the serum $[K^+]$ and adjust potassium administration appropriately.

HYPONATREMIC DEHYDRATION

The pathogenesis of hyponatremic dehydration usually involves a combination of sodium and water loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and the lost fluid contains sodium. Most fluid that is lost has a lower sodium concentration, so patients with only fluid loss would have hypernatremia. Diarrhea has, on average, a sodium concentration of 50 mEq/L. Replacing diarrheal fluid with water, which has almost no sodium, causes a reduction in the serum $[Na^+]$ (see Chapter 74). The volume depletion stimulates synthesis of antidiuretic hormone, resulting in reduced renal water excretion. Therefore the body's usual mechanism for preventing hyponatremia, renal water excretion, is blocked. The risk of hyponatremia is further increased if the volume depletion is a result of loss of fluid with a higher sodium concentration, as may occur with renal salt wasting, third space losses, or diarrhea with high sodium content (cholera).

The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid. An overly rapid (>8-10 mEq/L over the first 24 hours) or overcorrection in the serum $[Na^+]$ (>135 mEq/L) is associated with an increased risk of **osmotic demyelination syndrome** (formerly *central pontine myelinolysis*) (see Chapter 73). Most patients with hyponatremic dehydration do well with the same basic strategy outlined in Table 75.2. Again, K^+ delivery is adjusted according to the initial serum K^+ level and the patient's renal function. Potassium is not given until the patient voids.

The patient's $[Na^+]$ is monitored closely to ensure appropriate correction, and the sodium concentration of the fluid is adjusted accordingly. Patients with ongoing losses require an appropriate replacement solution (see Chapter 74). Patients with neurologic symptoms (seizures) as a result of hyponatremia need to receive an acute infusion of hypertonic (3%) saline to increase the serum $[Na^+]$ rapidly (see Chapter 73).

HYPERNATREMIC DEHYDRATION

Hypernatremic dehydration is the most dangerous form of dehydration because of complications of hypernatremia itself and of its therapy. Hypernatremia can cause serious neurologic damage, including central nervous system hemorrhages and thrombosis. This damage appears to be secondary to the movement of water from the brain cells into the hypertonic extracellular fluid (ECF), causing brain cell shrinkage and tearing blood vessels within the brain (see Chapter 73).

The movement of water from the ICS to the ECS during hypernatremic dehydration partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention with more profound dehydration.

Children with hypernatremic dehydration are often lethargic, and they may be irritable when touched. Hypernatremia may cause fever, hypertonicity, and hyperreflexia. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. **Idiogenic osmoles** are generated within the brain during the development of hypernatremia; they increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage caused by movement of water out of the cells and into the hypertonic ECF. Idiogenic osmoles dissipate slowly during the correction of hypernatremia. With overly rapid lowering of the extracellular osmolality during the correction of hypernatremia, an osmotic gradient may be created that causes water movement from the ECS into the cells of the brain, producing cerebral edema. Symptoms of the resultant cerebral edema can range from seizures to brain herniation and death.

To minimize the risk of **cerebral edema** during the correction of hypernatremic dehydration, *the serum sodium concentration should not decrease by >10 mEq/L every 24 hours.* The deficits in severe hypernatremic dehydration may need to be corrected over 2-4 days (Fig. 75.1).

The initial resuscitation of hypernatremic dehydration requires restoration of the intravascular volume with NS. LR should not be used because it is more hypotonic than NS and may cause too rapid a decrease in the serum $[Na^+]$, especially if multiple fluid boluses are necessary.

To avoid cerebral edema during correction of hypernatremic dehydration, the fluid deficit is corrected slowly. The rate of correction depends on the initial sodium concentration (see Fig. 75.1). There is no general agreement on the choice or the rate of fluid administration for correcting hypernatremic dehydration; these factors are not nearly as important as vigilant monitoring of the serum $[Na^+]$ and adjustment of the therapy according to the result. The rate of decrease of the serum $[Na^+]$ is roughly related to the "free water" delivery, although there is considerable variation between patients. Free water is water without sodium. NS contains no free water, half-normal saline (½ NS) is 50% free water, and water is 100% free water. Smaller patients, to achieve the same decrease in the sodium concentration, tend to need higher amounts of free water delivery per kilogram because of **higher insensible fluid losses**. Five percent dextrose (D5) with ½ NS is usually an appropriate starting solution for correction of a patient with hypernatremic dehydration. Some patients, especially infants with ongoing high insensible water losses, may rarely need to receive D5 0.2NS, which should be used with great caution and constant monitoring. Others require D5 NS. A child with dehydration as a result of pure free water loss, as usually occurs with diabetes insipidus, usually needs a more hypotonic fluid than a child with depletion of both sodium and water from diarrhea.

Adjustment in the sodium concentration of the IV fluid is the most common approach to modify the rate of decrease in the serum concentration (see Fig. 75.1). For difficult-to-manage patients with severe hypernatremia, having two IV solutions (e.g., D5 ½ NS and D5 NS, both with the same concentration of potassium) at the bedside can facilitate this approach by allowing for rapid adjustments of the rates of the two fluids. If the serum $[Na^+]$ decreases too rapidly, the rate of D5 NS can be increased and the rate of D5 ½ NS can be decreased by the same amount. Adjustment in the total rate of fluid delivery is another approach to modifying free water delivery. For example, if the serum $[Na^+]$ is decreasing too slowly, the rate of a hypotonic IV fluid can be increased, thereby increasing the delivery of free water. There is limited flexibility in modifying the rate of the IV fluid because patients generally should receive 1.25-1.5 times the normal maintenance fluid rate. Nevertheless, in some situations, it can be a helpful adjustment.

Because increasing the rate of the IV fluid increases the rate of decline of the sodium concentration, signs of volume depletion are treated with additional isotonic fluid boluses. The serum $[K^+]$ and the level of renal function dictate the potassium concentration of the IV fluid; potassium is withheld until the patient voids. Patients with hypernatremic dehydration need an appropriate replacement solution if they have ongoing, excessive losses (see Chapter 74).

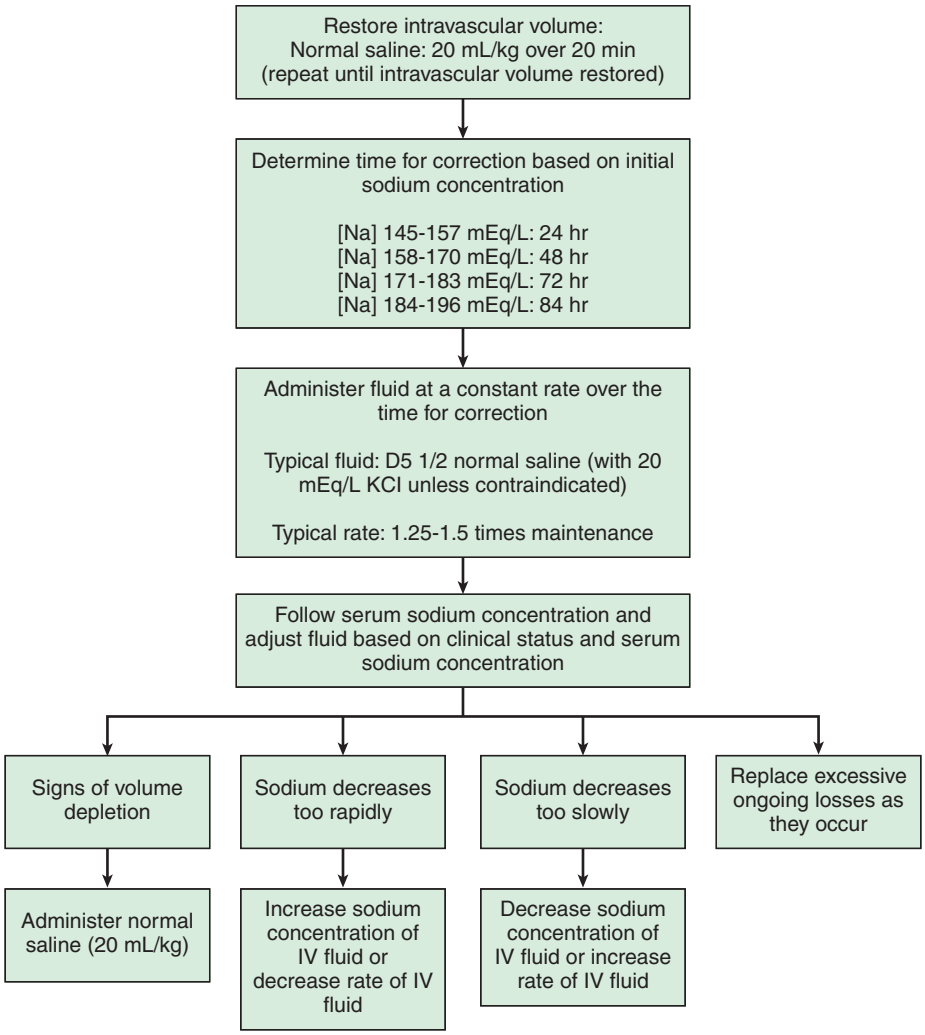

Fig. 75.1 Algorithm for the treatment of hypernatremic dehydration. *(From Londeree JT, Greenbaum LA. Dehydration and replacement therapy. In: Marcdante KJ, Kliegman RM, Schuh AM, eds. Nelson Essentials of Pediatrics, 9th ed. Philadelphia: Elsevier, 2023. Fig 33.1.)*

Seizures and a depressed level of consciousness are the most common manifestations of **cerebral edema** from an overly rapid decrease of the serum [Na^+] during correction of hypernatremic dehydration. Signs of increased intracranial pressure or impending herniation may develop quite rapidly (see Chapter 82). Acutely, increasing the serum [Na^+] through an infusion of 3% sodium chloride can reverse the cerebral edema. Each 1 mL/kg of 3% NaCl increases the serum [Na^+] by approximately 1 mEq/L. An infusion of 4 mL/kg often results in resolution of the symptoms. This strategy is similar to that used for treating symptomatic hyponatremia (see Chapter 73).

Many patients with mild to moderate hypernatremic dehydration as a result of gastroenteritis can be managed with oral rehydration (see Chapter 387). In patients with severe hypernatremia, oral fluids must be used cautiously. Infant formula, because of its low sodium concentration, has a high free water content, and especially if added to IV therapy, it may contribute to a rapid decrease in the serum [Na^+]. Less hypotonic fluid, such as an oral rehydration solution, may be more appropriate initially. If oral intake is allowed, its contribution to free water delivery must be taken into account, and adjustment in the IV fluid is usually appropriate. Judicious monitoring of the serum [Na^+] is critical.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 76

Fluid and Electrolyte Treatment of Specific Disorders

ACUTE DIARRHEA

See Chapter 387.

PYLORIC STENOSIS

See Chapter 375.1.

PERIOPERATIVE FLUIDS

See Chapter 91.

Emergency Medicine, Critical Care, and Anesthesia

PART VII

Chapter 77

Emergency Medical Services for Children

Charles G. Macias, Katherine E. Remick, and Steven E. Krug

The overwhelming majority of the 27 million children who present annually for emergency care in the United States are seen at community-based general emergency departments (EDs). Visits to children's hospital EDs account for just 10% of initial ED encounters. Additionally, across emergency medical services, children account for approximately 10% of all transports. This distribution suggests that the greatest opportunity to optimize care for acutely ill or injured pediatric patients, on a population basis, occurs broadly as part of a systems-based approach to emergency services, an approach that incorporates the unique needs of children at every level. Conceptually, emergency medical services for children are characterized by an integrated, continuum-of-care model (Fig. 77.1). The model is designed such that patient care flows seamlessly from the primary care medical home through transport and on to hospital-based definitive care. It includes the following five principal domains of activity:

1. Prevention, both primary and secondary
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: ED and inpatient, including critical care
4. Interfacility transport, as necessary, for definitive or pediatric medical and surgical subspecialty care (see Chapter 77.1)
5. Rehabilitation



Fig. 77.1 The emergency medical services for children (EMSC) continuum of care. Seriously ill and injured children interface with a large number of healthcare personnel as they move through the EMSC system.

The federal **Emergency Medical Services for Children (EMSC)** program of the Health Resources and Services Administration Maternal and Child Health Bureau has stewarded improvements in the care of children in the context of the continuum-of-care model. The programmatic mission of the EMSC program is as follows:

- To ensure U.S. emergency care systems across the continuum of care are pediatric-ready, meaning pediatric-specific needs are incorporated into every aspect of patient care, including patient safety practices, equipment and supplies, competency requirements, policies and procedures, quality improvement efforts, and administrative oversight and coordination of care.
- To ensure access to high-quality emergency medical care for ill or injured children and adolescents of all ages regardless of geographic location.
- To ensure that pediatric services are well integrated into an emergency medical services (EMS) system and backed by optimal resources.
- To ensure that the entire spectrum of emergency services—including primary prevention of illness and injury, acute care, and rehabilitation—is provided to infants, children, and adolescents at a level equal to that of adults.

PRIMARY CARE PHYSICIAN AND OFFICE PREPAREDNESS

The primary care physician (PCP) has multiple important roles in the EMS system. Through anticipatory guidance, the PCP can help shape the attitudes, knowledge, and behaviors of parent and child, with the primary goal of preventing acute medical events, such as injury and exacerbations of illness. The point-of-care initiation for many acute problems is often the PCP office. From the standpoint of personnel, equipment, training, and protocols, the PCP office setting must be adequately prepared to initially manage acute and emergency exacerbations of common pediatric conditions, such as respiratory distress and seizures. Furthermore, on rare occasion, the PCP office environment may be confronted with a child in clinical extremis who requires resuscitation and stabilization. It is therefore incumbent on the PCP not only to ensure access to EMS, that is, 911 system activation, but also to ensure that there is adequate equipment and supplies and on-site cognitive and psychomotor skill preparation to deal with such an emergency. **Office preparedness** requires training and continuing education for staff members, protocols for emergency interventions, ready availability of appropriate resuscitation drugs and equipment, and knowledge of local EMS resources and ED capabilities. PCPs can also play a pivotal role in informing and advocating for pediatric emergency and disaster readiness for families (especially those of children and youth with special healthcare needs) and in local EMS agencies, schools and childcare programs, and community hospitals. In all communities, the medical home plays a vital role in promoting family readiness for emergencies and disasters.

Staff Training and Continuing Education

It is a reasonable expectation that all office staff, including receptionists and medical assistants, be trained in cardiopulmonary resuscitation (CPR) with recertification maintained every 2 years. Nurses and physicians should also have training in a systematic approach to pediatric resuscitation that optimizes performance of high-quality CPR. Core knowledge may be obtained through standardized courses in **advanced life support (ALS)** offered by national medical associations and professional organizations. Frequent practice and timely

recertification are important for knowledge retention and skill maintenance. Examples include the Pediatric Advanced Life Support (PALS) and Pediatric Emergency Assessment, Recognition and Stabilization (PEARS) courses sponsored by the American Heart Association (AHA), the Advanced Pediatric Life Support (APLS) course sponsored by the American Academy of Pediatrics (AAP) and American College of Emergency Physicians (ACEP), and the Emergency Nurses Pediatric Course (ENPC) sponsored by the Emergency Nurses Association (ENA).

Protocols

Standardized protocols for telephone triage of seriously ill or injured children are essential. When a child's clinical status is guarded and prehospital care is available, ambulance transport in the care of trained personnel is always preferable to transport by other means (e.g., private vehicle). This obviates the potentially serious medical consequences of relying on distraught, often untrained, parents who lack essential equipment and supplies to provide even **basic life support (BLS)** measures to an unstable child during transport. Practitioners can work with their regional pediatric emergency care resource center (e.g., children's hospital, academic medical center, trauma center) to develop and maintain written protocols for office-based management of a range of conditions, including anaphylaxis, cardiopulmonary arrest, head trauma, ingestions, shock, status asthmaticus, status epilepticus, extremity injuries, and upper airway obstruction. Regular practice using mock code scenarios improves office-based practitioner and staff performance and self-efficacy in managing these problems.

Resuscitation Equipment

Availability of necessary equipment is a vital part of an emergency response. Every physician's office should have essential resuscitation equipment and medications packaged in a weight-based pediatric resuscitation cart or kit (Table 77.1). This cart or kit should be checked on a regular basis and kept in an accessible location known to all office staff. Outdated medication, a laryngoscope with a failed light source, or an empty oxygen tank represents a potential catastrophe in a resuscitation scenario. Such an incident can be easily avoided if an equipment checklist and regular maintenance schedule are implemented. A pediatric kit that includes posters to reinforce clinical management and procedures, a drug-dosing formulary, and a color-coded length-based resuscitation tape specifying weight and emergency equipment size are invaluable in avoiding critical therapeutic errors during resuscitation.

To facilitate emergency response when a child needs rapid intervention in the office, all personnel should have designated roles. Organizing a "rapid response team" within the office ensures that necessary equipment is made available to the physician in charge, an appropriate medical record detailing all interventions and the child's response is generated, and the 911 call for EMS response or a critical care transport team is made in a timely fashion. Regular practice for these infrequent events will promote timely response when needed.

Transport

Once efforts to stabilize the child have begun, a decision must be made on how best to transport a child to a facility capable of providing definitive care. If a child requires airway or cardiovascular support, has an altered mental state or unstable vital signs, or has significant potential to deteriorate en route, it is not appropriate to send the child via privately owned vehicle, regardless of proximity to a hospital. Even when an ambulance is called, it is the PCP's responsibility to initiate essential life support measures and to attempt to stabilize the child before transport.

In metropolitan centers with numerous public and private ambulance agencies, the PCP must be knowledgeable about the scope of service provided by each. The availability of BLS vs ALS services, the configuration of the transport team, and pediatric expertise vary greatly among agencies and across jurisdictions. BLS services provide basic support of airway, breathing, and circulation, whereas ALS units are capable of providing resuscitation drugs and procedural interventions as well. Some communities may have only BLS services available, whereas others may have a two-tiered system, providing both BLS and ALS. It may be appropriate to consider medical air transport when definitive or specialized care is not available within the community or when ground transport times are prolonged. In that case, initial transport via ground to an appropriate helicopter landing zone or a local hospital for interval stabilization may be undertaken, pending arrival

Table 77.1 Recommended Drugs and Equipment for Pediatric Office Emergencies

DRUGS/EQUIPMENT	PRIORITY
DRUGS	
Oxygen	E
Albuterol for inhalation	E
Epinephrine (1:1,000 [1 mg/mL])	E
Activated charcoal	S
Antibiotics	S
Anticonvulsants (diazepam/lorazepam)	S
Corticosteroids (parenteral/oral)	S
Dextrose (25%)	S
Diphenhydramine (parenteral, 50 mg/mL)	S
Epinephrine (1:10,000 [0.1 mg/mL])	S
Atropine sulfate (0.1 mg/mL)	S
Naloxone (0.4 mg/mL)	S
Sodium bicarbonate (4.2%)	S
INTRAVENOUS FLUIDS	
Normal saline (0.9 NS) *or* lactated Ringer solution (500-mL bags)	S
5% dextrose, 0.45 NS (500-mL bags)	S
EQUIPMENT FOR AIRWAY MANAGEMENT	
Oxygen and delivery system	E
Bag-valve-mask (450 mL and 1,000 mL)	E
Clear oxygen masks, breather and non-rebreather, with reservoirs (infant, child, adult)	E
Suction device, tonsil tip, bulb syringe	E
Nebulizer (or metered-dose inhaler with spacer/mask)	E
Oropharyngeal airways (sizes 00-5)	E
Pulse oximeter	E
Nasopharyngeal airways (sizes 12-30F)	S
Magill forceps (pediatric, adult)	S
Suction catheters (sizes 5-16F and Yankauer suction tip)	S
Nasogastric tubes (sizes 6-14F)	S
Laryngoscope handle (pediatric, adult) with extra batteries, bulbs	S
Laryngoscope blades (straight 0-2; curved 2-3)	S
Endotracheal tubes (uncuffed 2.5-5.5; cuffed 6.0-8.0)	S
Stylets (pediatric, adult)	S
Esophageal intubation detector or end-tidal carbon dioxide detector	S
EQUIPMENT FOR VASCULAR ACCESS AND FLUID MANAGEMENT	
Butterfly needles (19-25 gauge)	S
Catheter-over-needle device (14-24 gauge)	S
Arm boards, tape, tourniquet	S
Intraosseous needles (16 and 18 gauge)	S
Intravenous tubing, micro-drip	S
MISCELLANEOUS EQUIPMENT AND SUPPLIES	
Color-coded tape or preprinted drug doses	E
Cardiac arrest board/backboard	E
Sphygmomanometer (infant, child, adult, thigh cuffs)	E
Splints, sterile dressings	E
Automated external defibrillator with pediatric capabilities	S
Spot glucose test	S
Stiff neck collars (small/large)	S
Heating source (overhead warmer/infrared lamp)	S

E, essential; S, strongly suggested.
From Frush K, American Academy of Pediatrics, Committee on Pediatric Emergency Medicine. Policy statement-preparation for emergencies in the offices of pediatricians and pediatric primary care providers. *Pediatrics*. 2007;120:200-212. Reaffirmed in *Pediatrics*. 2011;128:e748.

of the air transport team. Independent of whether a child is to be transported by air or ground, copies of the pertinent medical records and any imaging or laboratory studies should be sent with the patient and a call made to the physician at the receiving facility to alert them to the referral and any treatments administered. Such notification is not merely a courtesy; direct physician-to-physician communication is essential for optimal care quality and to ensure adequate transmission of patient care information, to allow mobilization of necessary resources in the ED, and to redirect the transport if the emergency physician believes that the child would be more optimally treated at an alternative facility.

PEDIATRIC PREHOSPITAL CARE

Prehospital care refers to emergency assistance rendered by trained emergency medical personnel before a child reaches a treating medical facility. The goals of prehospital care are to further minimize systemic insult or injury through a series of well-defined and appropriate interventions and serve as the first link in high-quality emergency care. Prehospital emergency care services embrace patient safety, family-centered care, and timely and effective interventions as core tenets. Most U.S. communities have a formalized EMS system; the organizational structure and nature of emergency medical response depend greatly on local demographics and population base. EMS may be provided by volunteers or career professionals working in a fire department–based or independent third-service response system. All EMS and fire-based agencies have an identified medical director who defines provider competencies and scope of practice. Key points to recognize in negotiation of the juncture between the community physician and the local EMS system include access to the system, provider capability, and destination determination.

Access to the EMS System

Virtually all Americans have access to the 911 telephone service that provides direct access to a dispatcher who coordinates police, fire, and EMS responses. Many communities have a next-generation 911 system, in which the location of the caller is automatically provided to the call taker and/or dispatcher regardless of landline or mobile device use, permitting emergency response even if the caller, such as a young child, cannot give an address. Next-generation 911 also provides text-messaging capabilities. The extent of medical training for call takers and dispatchers varies among communities, as do the protocols by which they assign an emergency response level (BLS vs ALS). Many dispatch centers have adopted the Medical Priority Dispatch System (MPDS) to use standardized protocols and prearrival/postdispatch instructions. MPDS requires emergency medical dispatchers to ask a series of questions that determine the appropriate level of priority and EMS response. In some smaller communities, no coordinated dispatch exists, and emergency medical calls are handled by the local law enforcement agency or fire department. When activating the 911 system, the physician must make clear to the dispatcher the nature of the medical emergency and the condition of the child.

Provider Capability

There are many levels of training for prehospital EMS providers, ranging from individuals capable of providing only first aid to those trained and licensed to provide ALS. All EMS personnel, whether basic **emergency medical technicians (EMTs)** or paramedics, receive some initial training in pediatric emergencies; however, in most programs the dedicated time allotted to pediatric emergencies is minimal. Furthermore, state requirements vary for pediatric continuing education, and exposure to critically ill or injured children in the prehospital setting is infrequent, even in urban settings. PCPs should recognize that prehospital providers may need additional consultation or support, especially when managing children with uncommon medical conditions. PCPs can support maintenance of pediatric knowledge by EMS providers by serving as or working closely with an identified pediatric emergency care coordinator (PECC) within the EMS agency to fully integrate the needs of children into every aspect of system-based care: policies, protocols, quality improvement, patient safety, family-centered care, staff competencies, and equipment and supplies. Although children represent a minority population in the prehospital setting, the joint policy statement, *Pediatric Readiness in Emergency Medical Services Systems,* provides a comprehensive overview of how EMS systems can address the needs of children throughout all aspects of care. The identification of a PECC and physical demonstration of pediatric-specific skills represent two of the reference standards that the federal EMSC program has adopted as performance measures for state-level operational readiness to care for children in an EMS system.

First responders may be law enforcement officers or firefighters, who are dispatched to provide emergency medical assistance, or bystanders. Public safety personnel have a minimum of 40 hours of training in first aid and CPR. Their role is to provide rapid response and stabilization pending the arrival of more highly trained personnel. In some smaller communities, this may be the only prehospital emergency medical response available.

In the United States the bulk of emergency medical response is provided by EMTs, who may be volunteers or paid professionals. Basic EMTs may staff an ambulance after undergoing a training program of approximately 100 hours. They are licensed to provide BLS services but may receive further training in some jurisdictions to expand their scope of practice to include intravenous catheter placement and fluid administration, management of airway adjuncts, and use of an automated external defibrillator (AED).

Paramedics, or EMT-Ps, represent the highest level of EMT response, with medical training and supervised field experience of at least 1,000 hours. Paramedic skills include advanced airway management, including endotracheal intubation; placement of peripheral vascular or intraosseous lines; intravenous administration of drugs and blood products; administration of nebulized aerosols; needle and finger thoracostomy; and cardioversion, cardiac pacing, and manual defibrillation. These professionals provide ALS services, functioning out of an ambulance equipped as a mobile intensive care unit (ICU). The joint position statement *Recommended Essential Equipment for Basic Life Support and Advanced Life Support Ground Ambulances 2020* published by the AAP, ACEP, American College of Surgeons Committee on Trauma, EMSC Innovation and Improvement Center, ENA, National Association of EMS Physicians, and National Association of EMS Officials outlines national standards for essential equipment, medications, and supplies necessary to provide BLS and ALS care across the age spectrum.

Both basic EMTs and paramedics function under the delegated licensing authority of a supervisory EMS medical director. This physician oversight of prehospital practice is broadly characterized under the umbrella term *medical control.* **Direct**, or **online**, **medical control** refers to medical direction either at the scene or in real time via voice or video transmission. **Indirect**, or **offline**, **medical control** refers to the administration of medical direction before and after the provision of care (i.e., clinical protocols). Offline activities, such as provider education and training, protocol development, and medical leadership of quality assurance/quality improvement programs, represent areas in need of greater pediatric input. Whether in the presence or absence of a PECC, a pediatric advisory committee may provide additional pediatric knowledge and expertise. Evaluation and tracking of pediatric performance is critical to ensuring high-quality care for children in a community. The National EMS Information System (NEMSIS) serves as a registry for standardized EMS data collection. EMS agency participation in NEMSIS-compliant data submission is one of the federal EMSC performance measures. The National EMS Quality Alliance (NEMQA) and the National EMS Model Clinical Guidelines complement the NEMSIS program by providing evidence-derived pediatric quality measures for adoption in any EMS agency. As a measure of the degree to which EMSC permanence is being established in state EMS systems, the federal EMSC program has required demonstration of the presence of an EMSC advisory committee at the state level. These advisory bodies are well positioned to support EMS agencies in their pediatric readiness and provide a forum for the active engagement of pediatric care experts at a system level.

Destination Determination

The destination to which a pediatric patient is transported may be defined by parental preference, provider preference, or jurisdictional protocol, which is typically predicated on field assessment and, in the case of trauma, mechanism of injury. The 2021 National Guidelines for the Field Triage of Injured Patients relies on injury patterns, physiologic criteria, mechanism of injury, and other special considerations (e.g., suspicion for child maltreatment). Based on these criteria, EMS providers determine the optimal trauma center destination in the setting of injury. In communities served by an organized trauma system that incorporates pediatric designation based on objectively verified hospital capabilities (i.e., pediatric readiness), seriously injured children may be triaged by protocol to the highest-level pediatric-capable trauma center reachable within a reasonable amount of time. Other communities have established state or regional emergency care systems that use pediatric readiness criteria to recognize EDs appropriate for pediatric patients. A high level of pediatric readiness in both medical and trauma centers is linked to decreased mortality in critically ill and injured children. The mantra is to deliver the child to the *right care in the right time,* even if it requires bypassing closer hospitals.

Regionalization in the context of EMS is defined as a geographically organized system of services that ensures access to care at a level appropriate to patient needs while maintaining efficient use of available resources. This system concept is especially germane in the care of children, given the relative scarcity of facilities and their associated providers that are capable of managing the full range and scope of pediatric conditions (Fig. 77.2). Regionalized systems of care coordinated with emergency medical dispatch, field triage, and EMS transport have demonstrated efficacy in improving outcomes for pediatric medical and trauma patients. The existence of statewide or regional standardized systems that formally recognize hospitals able to stabilize and/or manage pediatric medical and traumatic emergencies is a federal EMSC performance measure against which operational capacity to provide optimal pediatric emergency care in the United States is currently being evaluated. Over 15 states now offer pediatric medical facility recognition programs. For the majority, hospital participation in these programs is voluntary. EMSC state partnership programs in the respective jurisdiction can provide further guidance on the application process and requirements for participation. Similarly, several state trauma systems now integrate elements of pediatric readiness into trauma center designation. Moreover, beginning in 2023, the American College of Surgeons (ACS) Committee on Trauma requires all ACS-verified trauma centers to adhere to specific pediatric readiness criteria.

In communities that do not have a hospital with the equipment and personnel resources to provide definitive pediatric inpatient care, **interfacility transport** of a child to a regional pediatric center should be undertaken after initial stabilization (see Chapter 77.1). In the end, all emergency care facilities must stand ready to provide care to ill and injured children of all ages.

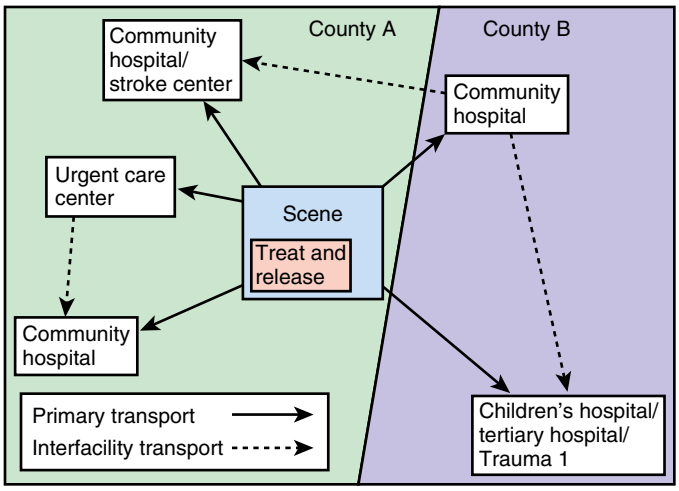

Fig. 77.2 Transport options within a coordinated, regionalized emergency medical services system model. The objective is to ensure access to definitive care at a level appropriate to meet patient needs. *Solid arrows,* Primary transport; *dashed arrows,* interfacility transport. *(Adapted from Institute of Medicine, Committee on the Future of Emergency Care in the U.S. Health System.* Hospital-Based Emergency Care: At the Breaking Point. *Washington, DC: National Academies Press; 2006.)*

THE EMERGENCY DEPARTMENT

The ability of EDs to respond to critically ill and injured children depends on all aspects of pediatric readiness: administrative oversight, staff competencies, pediatric-specific policies and procedures, patient and medication safety, quality improvement, and equipment and supplies. Training, awareness, and experience of the staff as well as access to support services, pediatricians, and medical and surgical subspecialists also play a key role. The majority of children who require emergency care are evaluated in community EDs. Emergency care staff, including physicians, nurses, and advanced practice providers, may have variable degrees of pediatric training and experience. Although children account for approximately 25% of all ED visits, only a fraction of these encounters represents true emergencies. Because the volume of critical pediatric cases is low, emergency physicians and nurses working in lower-volume EDs often have limited opportunity to reinforce and sustain their knowledge and skills in the assessment and stabilization of severely ill or injured children. Indeed, nearly 70% of U.S. EDs provide care for <15 children per day. General pediatricians from the community or pediatric hospitalists may be consulted when a seriously ill or injured child presents to the ED, and they should have a structured approach to the initial evaluation and treatment of an unstable child of any age, regardless of the underlying diagnosis. Telemedicine and e-health may serve as a mechanism to provide better connectivity between patients, primary care, EDs, and tertiary/quaternary institutions. *Early recognition of life-threatening abnormalities in oxygenation, ventilation, perfusion, and central nervous system function and rapid intervention to correct those abnormalities are key to successful resuscitation and stabilization of the pediatric patient.*

The **National Pediatric Readiness Project (NPRP)** is a national quality improvement initiative started by the federal EMSC program, AAP, ACEP, and ENA to ensure high-quality emergency care for all children. The effort began in 2013 with a national assessment of pediatric readiness in U.S. EDs (as measured by compliance with published guidelines). Initial results demonstrated a high level of engagement in pediatric readiness but notable gaps in the ability of U.S. EDs to meet the needs of children: 48% of EDs had a physician PECC; 59% of EDs had a nurse PECC; 46% of EDs included pediatric-specific needs in quality improvement efforts; and 47% had a disaster plan that addressed the needs of children. Higher readiness levels are seen in larger-volume EDs and in EDs with physician and nurse PECCs and/or quality improvement plans that included children. Since then, numerous efforts, including national quality improvement collaboratives, have targeted key areas of readiness. A second NPRP assessment was completed in 2021, and national efforts continue to promote widespread adoption of pediatric readiness within U.S. EDs. In 2019, the National Prehospital Pediatric Readiness Project launched with similar efforts focused on ensuring high-quality prehospital emergency care for children. Table 77.2 lists essential policies, procedures, and protocols specifically addressing the needs of children in the ED. ED staff and other stakeholders can access pediatric readiness checklists and toolkits and identify opportunities to participate in pediatric readiness efforts on the website of the EMSC Innovation and Improvement Center, https://emscimprovement.center/. Given the link between pediatric readiness and increased survival for critically ill and injured children, baseline readiness standards must be met by all EDs and EMS agencies to ensure that children receive the best emergency care possible.

The way the family supports the child during a crisis, and consequently how the family is supported by the local EMS agency and in the ED when caring for the child, are critical to patient recovery,

Table 77.2 Guidelines for Pediatric-Specific Policies, Procedures, and Protocols for the Emergency Department (ED)

- Illness and injury triage
- Pediatric patient assessment and reassessment
- Documentation of pediatric vital signs, abnormal vital signs, and actions to be taken for abnormal vital signs
- Identification and notification of the responsible provider of abnormal vital signs (age or weight based)
- Immunization assessment and management of the underimmunized patient
- Sedation and analgesia for procedures, including medical imaging
- Consent (including situations in which a parent is not immediately available)
- Social and mental health issues
- Physical or chemical restraint of patients
- Child maltreatment (physical and sexual abuse, sexual assault, and neglect) mandated reporting criteria, requirements, and processes
- Death of the child in the ED
- Do-not-resuscitate orders
- Lack of a medical home
- Children with special healthcare needs
- Family-centered care, including:
  1. Involving families in patient care decision-making and in medication safety processes
  2. Family and guardian presence during all aspects of emergency care, including resuscitation
  3. Education of the patient, family, and regular caregivers
  4. Discharge planning and instruction
  5. Bereavement counseling
- Communication with patient's medical home or primary healthcare provider
- Telehealth and telecommunications
- Medical imaging policies that address age- or weight-appropriate dosing for children receiving studies that impart ionizing radiation, consistent with ALARA (as low as reasonably achievable) principles
- All-hazard disaster preparedness plan that addresses the following pediatric issues:
  1. Availability of medications, vaccines, equipment, and appropriately trained providers for children in disasters
  2. Pediatric surge capacity for both injured and noninjured children
  3. Decontamination, isolation, and quarantine of families and children of all ages
  4. Minimization of parent-child separation and includes system tracking of pediatric patients, allowing for the timely reunification of separated children with their families
  5. Access to specific medical and mental health therapies, as well as social services, for children in the event of a disaster
  6. Disaster drills, which should include a pediatric mass casualty incident at least every 2 years
  7. Care of children with special healthcare needs
  8. A plan that includes evacuation of pediatric units and pediatric critical care and specialty units
- Evidence-based clinical pathways, order sets, or decision support tools
- Written interfacility transfer procedure and agreements that include the following components:
  1. Defined process for initiation of transfer, including the roles and responsibilities of the referring facility and referral center (including responsibilities for requesting transfer, method of transport, and communication)
  2. Transport plan to deliver children safely (including the use of child passenger restraint devices) and in a timely manner to the appropriate facility capable of providing definitive care
  3. Process for selecting the appropriate care facility for pediatric specialty services not available at the hospital
  4. Process for selecting the appropriately staffed transport service to match the patient's acuity level (i.e., level of care required and equipment needed for transport) and appropriate for children with special healthcare needs
  5. Process for patient transfer (including obtaining informed consent)
  6. Plan for transfer of critical patient information (i.e., medical record, imaging, copy of signed transport consent), as well as personal belongings and provision of directions and referral institution information to family
  7. Process for return transfer of the pediatric patient to the referring facility as appropriate
  8. Integration with telehealth/telecommunications processes and mobile integrated health/community paramedicine as appropriate

Adapted from Remick K, Gausche-Hill M, Joseph MM, Brown K, Snow SK, Wright JL; American Academy of Pediatrics Committee on Pediatric Emergency Medicine and Section on Surgery; American College of Emergency Physicians Pediatric Emergency Medicine Committee; Emergency Nurses Association Pediatric Committee. Pediatric readiness in the emergency department. *Pediatrics*. 2018;142(5):e20182459.

family satisfaction, and mitigation of behavioral and mental health impact. Commitment to patient- and family-centered care in the ED ensures that the patient and family experience guides the practice of culturally sensitive care and promotes patient dignity, comfort, and autonomy. In both the ED and EMS settings, particular issues, such as family presence, deserve specific attention. Surveys of parents have indicated that most want to be with their child during invasive procedures and even during resuscitation. Allowing their presence has been shown to reduce parental and patient anxiety and does not interfere with procedure performance. Patient- and family-centered care practices are also strongly associated with improved care quality and patient safety.

Disaster Preparedness

Throughout a public health emergency or catastrophic event, natural or human-made, several unique factors place children at disproportionate, increased risk. Combined with other factors, global climate change has promoted increased frequency and severity of weather-related disasters. During an average workday, an estimated 69 million U.S. children are separated from their families in schools and childcare centers, where mass casualty events can easily occur. This separation adds the further challenge of safe and timely reunification of children with family during or after an incident. Furthermore, in the event of a biologic, chemical, or radio-nuclear attack, unique anatomic, developmental, and physiologic features make children especially vulnerable to absorption, ingestion, or inhalation of toxic agents and related morbidity and mortality (see Chapter 763).

Pediatric planning considerations include training of first responders and other care providers, patient triage, decontamination, surge capacity and capabilities, medical countermeasures (medications, vaccines, equipment, supplies), evacuation, transport, sheltering, and family reunification. The community plays a significant role in preparedness and is inclusive of schools, school nurses, faith-based organizations, and other community entities.

All levels of the healthcare system must be prepared for disaster-driven surges in patient care needs. Surge capacity refers to the ability to evaluate and care for a markedly increased volume of patients—one that challenges or exceeds normal variations in operating capacity. Surge capability refers to the ability to provide specialized medical services for unique patient populations, such as children, that may not be routinely available under normal operating conditions. Surges may require alternative care processes and additional resources to meet the demand for services. Critical surges may require consideration of contingency plans that typically require activation of alternative care standards. Surges that exceed the additional capacity of contingency plans may require implementation of crisis care standards as a means to increase capacity beyond levels that exceed normal daily operations. During a public health emergency, surge requirements may extend beyond direct patient care to include tasks such as laboratory screening or epidemiologic investigations. All levels of the healthcare system may be challenged to increase their capabilities, providing medical services for patient populations, such as children, that may not be routinely available. As an example, the community hospital that routinely transfers higher-acuity ill or injured children or children with medical

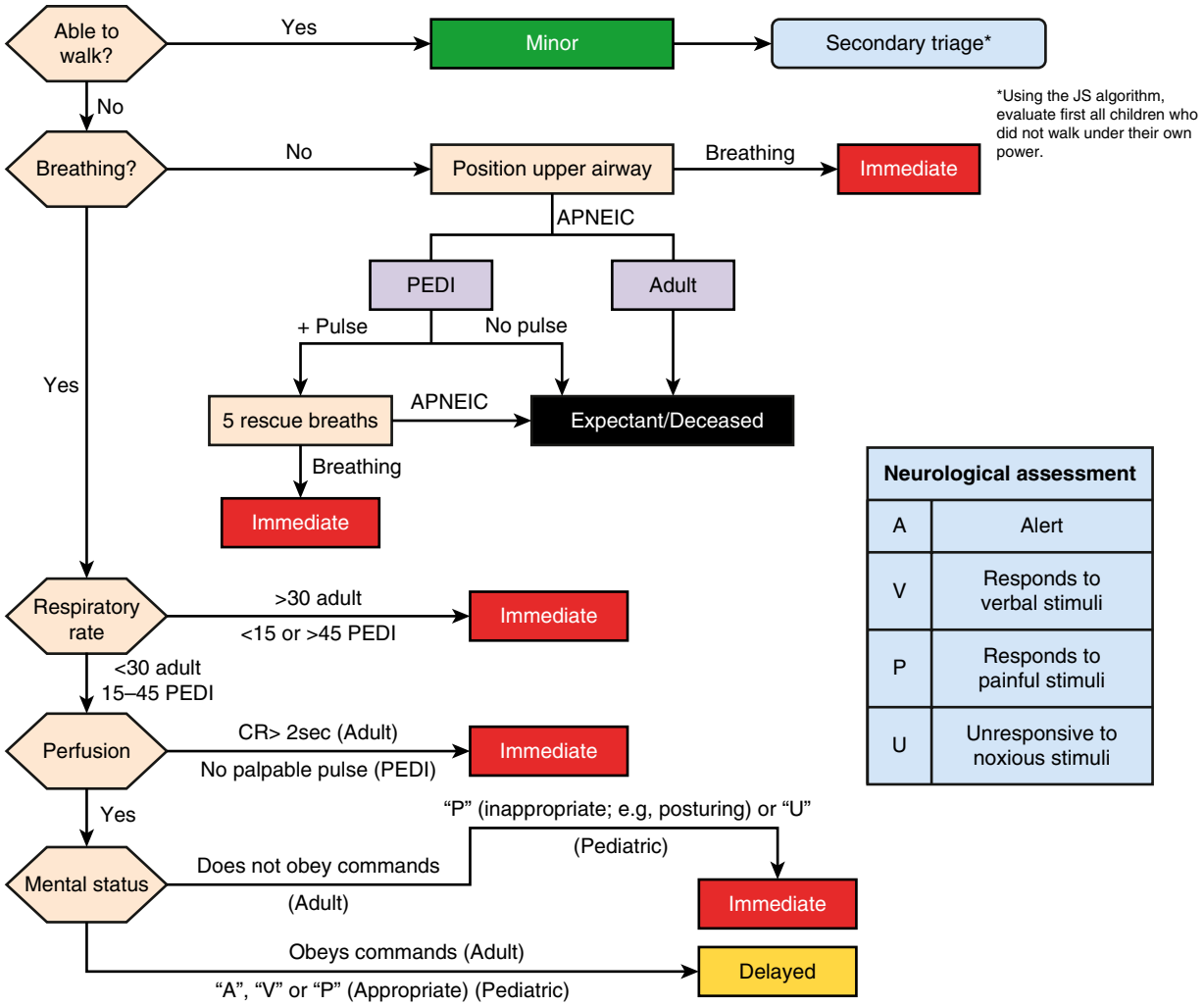

Fig. 77.3 Combined START/Jump START triage algorithm. (*Copyright 2002, Lou Romig, MD.*)

complexity to a pediatric tertiary center may be unable to do so during a disaster. Mechanisms for remote consultation and support of pediatric care, leveraging community pediatricians and tertiary pediatric subspecialists via telemedicine, should be considered.

Beyond acute medical treatment needs, pediatric planning must also consider the typically broad mental and behavioral health impact disasters have on children and families. Mental and behavioral health concerns commonly represent the largest impact of disasters on children and adolescents. Pediatric plans must also be in place for locations where children congregate, such as schools and childcare; these plans must be aligned with local jurisdiction planning and communicated to families.

Community practice and healthcare system readiness and resiliency begin with *personal and family readiness planning* engaged by healthcare providers and support staff; these efforts should also include attention to provider wellness.

The AAP's Children and Disasters website* (https://www.aap.org/en/community/aap-councils/council-on-disaster-preparedness-and-recovery-codpr/) contains toolkits, checklists, and other resources pertinent to pediatric readiness within the community, schools, the medical home, and hospitals; educational materials are also available for families. Reliable information and excellent disaster readiness resources are also located on the websites of the EMSC Innovation and Improvement Center and U.S. Department of Health and Human Services (HHS) and Assistant Secretary for Preparedness and Response (ASPR) Eastern Great Lakes Pediatric Disaster Center of Excellence (https://emscimprovement.center), U.S. Centers for Disease Control and Prevention (https://emergency.cdc.gov), U.S. Department of Health and Human Services (https://www.phe.gov/preparedness/Pages/default.aspx), U.S. HHS ASPR Technical Resources, Assistance Center, and Information Exchange (TRACIE) (https://asprtracie.hhs.gov/), U.S. Federal Emergency Management Agency (https://www.fema.gov), HHS ASPR Western Regional Alliance for Pediatric Emergency Management (WRAPEM) (https://www.wrap-em.org/index.php/resources-edocman-public), and HHS HRS Pediatric Network (PPN) (https://pedspandemicnetwork.org/).

Triage in Disaster Pediatric Medical Care

Mass causality events (hurricanes, bombings, gas leaks, bus or plane crashes, earthquakes, mass shootings, fires, others) require *scene-based* assessment, assignment, and tagging (Figs. 77.3 and 77.4). Assessment must be rapid (~30 seconds) and includes breathing, circulation, and mental status. These parameters are incorporated in the **START** (simple triage and rapid treatment) triage tool for adolescent and adults and the **Jump START** assessment for 0- to 14-year-old children. The combined algorithm is noted in Figure 77.3. The "jump" in Jump START relates to one difference between pediatric and adult approaches wherein children are given a rescue breath if they remain apneic with a pulse after positioning the airway (see Fig. 77.3). Triage categories are color coded (see Fig. 77.4) at the site of the disaster based on risk. **Red** – immediate life-threatening injury; **Yellow** – potentially stable for a short period; **Green** – minor injury, walking wounded; **Black** – dead or not expected to survive.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

* https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/default.aspx.

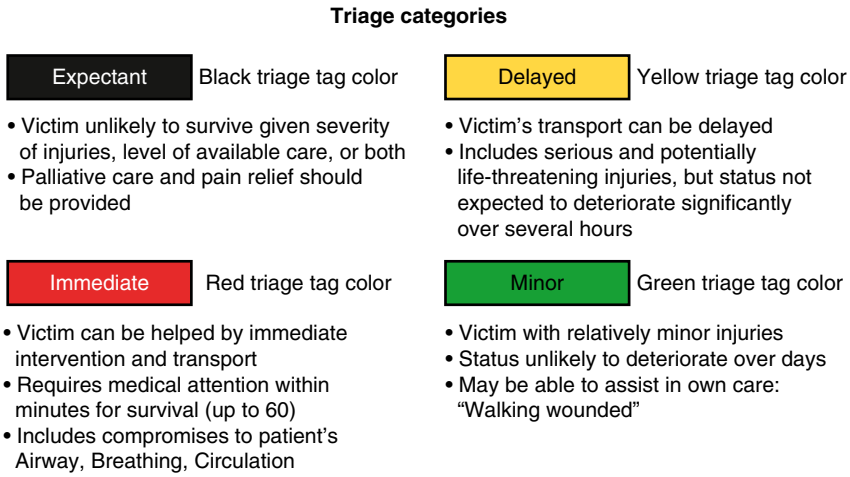

Fig. 77.4 Triage categories. (*From US Department of Health and Human Services: https://chemm.hhs.gov/startpediatric.htm.*)

77.1 Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

*Corina Noje, Mary Beth Howard, and Bruce L. Klein**

Patients often seek treatment at facilities that lack sufficient expertise to treat their conditions, necessitating transfer to more appropriate specialty centers. This is especially pronounced in pediatrics. Emergency medical services (EMS) providers or parents usually take children to local emergency departments (EDs) first, where their conditions and physiologic stabilities are assessed. Although bringing a child directly to the local ED may be proper logistically, community-based local EDs can be less than ideal for pediatric emergencies. Children have been reported to account for about 20% of all ED visits, but not all EDs have the necessary supplies for pediatric emergencies. Also, general EDs are less likely to have pediatric expertise or policies in place for the care of children. Outcomes for critically ill children treated in pediatric intensive care units (PICUs) are better than for those treated in adult ICUs. When pediatric critical care is required, transport to a regional PICU is indicated. In addition, often the type of subspecialty care needed (e.g., pediatric orthopedics) is available only at the pediatric center.

Pediatric transport medicine consists of the interfacility transfer of infants, children, and adolescents from community facilities to pediatric centers that can provide the needed level of expertise. Transport is performed by professionals proficient in pediatric transport using age-equipped ground, rotorcraft, or fixed-wing ambulances. Pediatric transport medicine is a multidisciplinary field comprising pediatric critical care and pediatric emergency medicine (PEM) physicians (and, sometimes for newborn infants, neonatologists); nurses, respiratory therapists, and paramedics with advanced training for pediatric transport; and communications specialists. The goal is to deliver quality pediatric care to the region's children, while optimizing the use of regional resources. For the individual child, the aim is to stabilize and, when appropriate, begin treating as soon as possible—that is, at the local ED and during transport, well before arrival at the referral center.

Models for pediatric transport services vary depending on the needs and available resources in a geographic region, but all should have certain basic components: a network of community hospitals and regional pediatric centers; an established communications and dispatch system that easily facilitates transfer to the pediatric center; ground and/or air ambulances; medical and nursing leadership from pediatric critical care or PEM (or neonatology); experienced pediatric **medical control physicians (MCPs)**; a multidisciplinary team of pediatric transport professionals specially trained and equipped to provide the appropriate level of care required during transport; operational and clinical policies and procedures that guarantee safe, state-of-the-art, and timely pediatric critical care transport; and a database for quality and performance assessment.

COMMUNICATIONS AND DISPATCH CENTER

Communications are one of the most vital components of a regional transport system. Treating a critically ill or injured child is generally an uncommon event for most community physicians. Therefore they need to know *whom, how,* and *when* to call for assistance in the stabilization and transfer of a pediatric patient. The communications and dispatch center provides a single telephone number for such calls.

The communications and dispatch center coordinates communications among the outlying facility, receiving unit, MCP, transport team, and other consultants. This center may be part of a hospital unit (e.g., ED, PICU), self-contained in a single institution (e.g., emergency communications and information center), or based off-site as a freestanding center coordinating communications and dispatch for multiple transport programs.

Staffing varies depending on the type of center. On-duty nurses or physicians may receive calls at unit-based models with low volumes. In contrast, dedicated communications specialists usually staff self-contained or freestanding centers, which tend to be busier. The communications specialist has numerous responsibilities, including answering the referring physician's call promptly; documenting essential patient demographic information; arranging for immediate consultation with the MCP; dispatching the transport team to the referring facility expeditiously; updating the referring facility with any changes in the arrival time; and coordinating medical control and other necessary transport-related calls. The transport team must be able to contact the receiving and referring facilities immediately, when necessary. Furthermore, with advances in technology and wireless communication systems, **telemedicine**—either *interactive* (synchronous) or *store and forward* (asynchronous)—is being used during pediatric transport, and certain programs have incorporated it into their routine transport operations.

MEDICAL CONTROL PHYSICIAN

The MCP is involved in the clinical care and safe transport of the patient from the time of referral through arrival at the receiving hospital unit. The MCP's oversight increases once the transport team arrives at the referring facility. The MCP should have expertise in pediatric critical care or PEM (or sometimes neonatology). Besides having the knowledge required to stabilize a critically ill or injured child, the MCP must be familiar with the transport environment; the transport team members' resources and capabilities; the program's policies and procedures; and the region's geography, medical resources, and regulations regarding interhospital transport. The MCP must possess good interpersonal and communication skills and must be able to maintain

* Adapted initially from Dr. Lorry R. Frankel's chapter in the 18th edition of this book. We also want to thank Dr. Beth Edgerton, who co-authored a prior version of this chapter.

collegiality with the referring hospital's staff during a potentially difficult and stressful situation.

Once a transport call is received, the MCP must be immediately available to confer with the referring physician. Although the MCP may have other responsibilities, these transport responsibilities take priority in order to avoid undue delays when transferring a critically ill child. Often the MCP recommends further testing or therapeutic interventions that can be delivered by the referring hospital before the transport team arrives. The MCP may seek additional guidance from other specialists, as necessary. Because the child's condition may change rapidly, the MCP must remain ready to give additional advice. All conversations and recommendations regarding the care of the patient should be documented. Some centers record these conversations.

After discussion with the referring physician—and when warranted, with the transport staff—the MCP determines the best team composition and vehicle for transport. The MCP usually does not accompany the team but remains available to supervise care. With advances in video conferencing capabilities, there has been increased use of telemedicine in the pediatric transport medical direction process. For some acutely ill patients or those requiring visual diagnoses, telemedicine has been reported to improve disposition at the receiving hospital, potentially leading to improved clinical outcomes.

TRANSPORT TEAM

Transport team composition varies greatly among programs—and sometimes within an individual program. The team's composition is based on a variety of factors, including the child's age; the severity of the illness or injury; the distance to the referring facility; the transport vehicle used; the team members' advanced practice scope and abilities; the referrer's insistence that a physician be present; the program's historical professional makeup; and the region's staffing regulations. The pediatric transport workforce may include physicians, advanced practice providers, nurses, respiratory therapists, and paramedics who have expertise in pediatric critical care, PEM, or neonatology (in some cases), as well as advanced education and training in those cognitive and procedural areas important for pediatric critical care transport. Physician trainees—usually fellows and, less often, residents—may also participate in transport in some capacity. There is a lower incidence of transport-related morbidity for critically ill and injured children transported by pediatric specialty teams than for those transported by generalist teams. Nevertheless, in-transit critical events occur in ~10% of pediatric critical care transports.

Various scoring systems that can help guide team composition and/or mode of transport have been developed to aid in transport planning. A team member's training, experience, and skill in treating critically ill patients are more important considerations than that team member's professional degree. Team members must understand basic pediatric pathophysiology and collectively must be able to assess and monitor a critically ill or injured child; manage the airway and provide respiratory support; obtain vascular access; perform point-of-care testing; and administer fluids and medications (including infusions) typically used in pediatric critical care transport. They must be familiar with the physiologic alterations and practical difficulties of the transport environment and, importantly, must be comfortable working in an out-of-hospital setting. Physicians are less often deployed on transport teams in part because of the advanced training that other healthcare professionals on the transport team receive.

The transport team should have a designated team leader who, in addition to the team leader's many other responsibilities, interacts with the MCP during the transport. Once the team arrives at the referring facility, the team should reassess the child's condition, review all the pertinent diagnostic studies and therapies, and discuss the situation with the referring staff and parents. If the patient's condition has changed significantly, the team leader may need to contact the MCP for additional advice. Otherwise, the team leader should generally notify the MCP before starting to bring the child to the receiving facility. Any care delivered by the team during transport should be documented, and copies of all medical records—including laboratory data, radiographs, and scans—should accompany the child to the pediatric center. The receiving unit must be updated before arrival so it can finalize preparations for the patient.

GROUND VS AIR AMBULANCE

Transport vehicle options include ground, rotorcraft, and fixed-wing ambulances. Vehicle selection depends on the child's emergency needs, transport team's capabilities, any out-of-ordinary staffing or equipment requirements (e.g., extracorporeal membrane oxygenation, inhaled nitric oxide, heliox), referring facility's abilities, distance, terrain, traffic patterns, ground or air ambulance availability, helicopter landing pad or airport access, weather conditions, and expense.

The transport vehicle must be equipped with electrical power, oxygen, and suction and must have sufficient space for the equipment and supplies that the team brings along—stretcher or isolette, monitor, ventilator, oxygen tank(s), medication pack(s), infusion pumps, and more. Compared with helicopters, ambulances typically are more spacious and able to carry more weight, so they can accommodate larger teams and more equipment. Another advantage of ground ambulance transport is the ability to stop en route if the patient's condition deteriorates; this may facilitate the performance of certain interventions or procedures, such as intubation.

An airplane may be able to fly to an area when distance (>150 miles), altitude, or weather precludes helicopter use. However, the use of an airplane necessitates several ambulance transfers, with their attendant delays and additional risks. There also are delays when the plane must fly from a remote base to the program's jurisdiction.

TRANSPORT PHYSIOLOGY

When possible, the transport team tries to provide the same care during transport as the patient would receive in the specialty center. This can be difficult, however, because of limitations in personnel, equipment, and space, as well as other environmental challenges.

The team and child are subjected to variable intensities of background noise and vibration while traveling in the vehicle cabin. **Noise** can impair the team's ability to auscultate breath sounds and heart sounds or accurately measure the blood pressure manually—another reason for monitoring vital signs mechanically and relying on other assessment modalities, such as the level of mentation, skin color, and capillary refill. For rotor transports in particular, the crew and patient should wear helmets or headphones (or another wearable noise attenuator) to mitigate noise. **Motion** and **vibration** are additional transport hazards and can lead to increased metabolic rate, shortness of breath, and fatigue in the patient, as well as motion sickness in the patient and staff.

On fixed-wing or certain rotary-wing transports, the patient may suffer adverse physiologic effects from **altitude**. With increasing altitude, the barometric (atmospheric) pressure decreases, and gas expands to occupy a greater volume due to the decreased pressure exerted on it. Therefore, as barometric pressure drops with altitude, the partial pressures of inspired oxygen (Pio_2) and, consequently, arterial oxygen (Pao_2) decrease, as does the arterial oxygen-hemoglobin saturation (Spo_2). For example, at 8,000 feet—an elevation at which unpressurized airplanes may fly, as well as the effective cabin altitude for many pressurized airplanes flying at 35,000-40,000 feet—the barometric pressure, Pio_2, Pao_2, and Spo_2 fall to 565 mm Hg, 118 mm Hg, 61 mm Hg, and 93%, respectively. In comparison, the barometric pressure, Pio_2, Pao_2, and Spo_2 are 760 mm Hg, 159 mm Hg, 95 mm Hg, and 100% at sea level. Although healthy individuals usually tolerate these changes well, patients with respiratory insufficiency, pulmonary hypertension, significant blood loss, or shock may decompensate and should receive supplemental oxygen and/or have the cabin pressurized at sea level.

Gases expand up to 10% at the few thousand feet where helicopters typically fly, and approximately 30–40% at 8,000 feet. Gases within the body itself also expand as the altitude increases. The degree of gas expansion must be considered during transport via air of any patient with pneumocephalus, pneumothorax, bowel obstruction, or another condition involving entrapped gas. Before transport, a pneumothorax should generally be decompressed and a nasogastric tube inserted for ileus.

SAFETY

Safety is of paramount importance and mandates constant vigilance by everyone involved. Accident rates for pediatric air and ground transport have been estimated at approximately 1 in 1,000 transports. The team should routinely attend pilot briefs and perform safety inspections of the vehicles and equipment, aided by checklists. When in doubt, the MCP should solicit input from the staff about whether to transport via air or ground ambulance or to employ lights and sirens, decisions that cannot be taken lightly. The pilot's or driver's judgment as to the safety of proceeding during inclement weather or with a mechanical problem must not be overruled.

Organizations such as the Federal Aviation Administration (FAA) and the National Transportation Safety Board (NTSB) play a role in ensuring safe interfacility transport. The **Commission on Accreditation of Medical Transport Systems (CAMTS)** is an independent, peer-review organization established in 1990 in response to the number of air medical accidents in the 1980s. CAMTS, through voluntary participation, audits and accredits fixed-wing, rotary-wing, and ground interfacility medical transport services.

FAMILY-CENTERED CARE

Family-centered care represents a philosophy that respects the important role that family members play in a child's care. It recognizes family members and healthcare providers as partners in caring for the child. Family presence during transport is beneficial because it provides support to both children and parents in stressful situations and assists healthcare providers in delivering care to patients with complex and chronic medical problems.

As care is transitioned from the referring hospital, it is the transport team's responsibility to maintain culturally sensitive, family-centered care. The team meets with family members to explain the transport process, help obtain consent, and discuss anticipated management. When possible, the transport team should attempt to accommodate a family member's presence onboard. However, the family member and child may need to be separated when the child is critically ill and rapid transport is essential, or in case of space or weight limitations in the air or ground ambulance. In these situations, it is important that family members have a clear understanding of how the child will be cared for during the separation.

REFERRING HOSPITAL RESPONSIBILITIES

Transfer of a child to another facility requires written documentation by the referring physician of the need and reasons for transfer, including a statement that the risks and benefits, as well as any alternatives, have been discussed with the parents. Informed consent should be obtained from the parent/legal guardian before transfer.

Federal law under the Emergency Medical Treatment and Active Labor Act (EMTALA), part of the Consolidated Omnibus Budget Reconciliation Act (COBRA), imposes specific requirements that a patient presenting to an ED be given a medical screening examination without regard for ability to pay. If on examination an emergency medical condition is found, the hospital is required to stabilize the patient or to transfer the patient to another facility if unable to stabilize the patient (or if requested by the patient in writing after being informed of the risks). The primary requirement is that the referring physician must certify that the medical risks of transfer are outweighed by its potential benefits. The receiving hospital must agree to accept the patient if it has the space and staff to provide the necessary level of care. The transferring hospital is responsible for arranging for the transfer and ensuring that it is performed by qualified medical personnel with appropriate equipment. The transferring hospital must also send copies of the patient's medical records and test results, even those that become available after the transfer is complete.

Some referring hospitals have entered into transfer agreements with specialty centers to facilitate the smooth and safe transfer of pediatric patients. Having prepared forms for all the purposes noted earlier also aids in the transfer process.

Each hospital needs to review its facility's guidelines; if established guidelines do not exist, the Emergency Medical Services for Children National Resource Center in partnership with the Emergency Nurses Association and the Society of Trauma Nurses has developed the "Interfacility Transfer Tool Kit for the Pediatric Patient" (available at: https://emscimprovement.center/education-and-resources/toolkits/interfacility-transfer-toolbox/). This tool kit includes the essentials for comprehensively and safely transferring the pediatric patient to the most appropriate level of care in a timely manner.

EDUCATIONAL OUTREACH

Besides safe and rapid transport, regional pediatric transport programs (and their specialty centers) have an obligation to provide educational opportunities to community healthcare providers so that these providers can acquire the necessary skills to evaluate and stabilize a critically ill or injured child until the transport team arrives. These learning activities may include transport case reviews; lectures on pediatric acute care topics; resuscitation and related programs such as the Pediatric Advanced Life Support (PALS) course, Advanced Pediatric Life Support (APLS) course, Pediatric Education for Prehospital Professionals (PEPP) course, and S.T.A.B.L.E. (sugar and safe care, temperature, airway, blood pressure, lab work, emotional support) program; and rotations through the specialty center's pediatric ED and PICU. These activities also help cement relationships with the referring facility's staff.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

77.2 Risk Adjustment and Outcomes Measurement of Pediatric Emergency Medical Services

Anna K. Weiss

Health services research has demonstrated wide variation in implementation of equitable, evidence-based care for pediatric patients in U.S. hospitals, a reality that can negatively affect the health of children and youth (see Chapter 2). The complexities of delivering high-quality, evidence-based care are magnified in the emergency department (ED), where patients are often in crisis, patient-physician interactions are brief, and the variety and volume of complaints and diagnoses are immense. In the context of this frenetic environment, practitioners can only assess their local system relative to recognized benchmarks and standards of care if there are clear guidelines for measurement of performance. However, no two places of practice are the same, and a single ED may differ significantly from a theoretical "best practice" standard. To reflect this, practitioners seeking to make local improvements must assess not only raw outcomes (e.g., throughput times, mortality, patient satisfaction) but must also adjust for severity of illness, case mix, and risk of morbidity.

OUTCOME MEASURES IN EMERGENCY MEDICAL SERVICES FOR CHILDREN

To ensure delivery of equitable, evidence-based care in the ED, pediatric emergency medical systems must support the use of national standards for emergency care performance measurement. The *Donabedian structure-process-outcome model* provides a framework for most contemporary quality measurement and improvement activities. In this framework, **structural** elements provide indirect quality-of-care measures related to a physical setting and resources (e.g., available staff, equipment, and supplies). **Process** indicators provide a measure of the quality of care and services by evaluating the method or process by which care is delivered, including both technical and interpersonal components. **Outcome** elements describe valued results related to lengthening life, relieving pain, reducing disabilities, and satisfying the consumer.

A true *outcome-based* approach to **performance improvement** describes observable measures such as mortality, risk of organ system failure, and disability. An alternative approach is a *resource-based* outcome measure with a definition that is relative to the level of care required. Children who are more ill generally require more resources; therefore resource use across groups of patients reflects relative **severity of illness** within the groups, provided clinicians have a similar approach to practice. Examples of resource-based outcomes include need for hospital admission (ED disposition), ED length of stay, costs, and diagnostic and therapeutic interventions performed in the ED. Although this approach provides a measurement of clinical activity, when used in a vacuum it does not indicate whether the patient receiving the therapeutic interventions or resources actually needed them (i.e., data may also reflect physician behavior and/or [lack of] experience). Therefore some other assessment is needed that incorporates information on *how sick* the patient is or their specific diagnosis.

Table 77.3 provides a list of performance measures for pediatric ED care developed by the **Emergency Medical Services for Children Innovation and Improvement Center** supported by the Health Resources and Services Administration of the U.S. Department of Health and Human Services.

RISK ADJUSTMENT

The purpose of measuring outcomes in the ED is to evaluate **performance**—offering EDs and other components of the healthcare system the opportunity to make meaningful improvements over time using benchmarks within and between units. When making comparisons over time, one must ensure that patient-related attributes (e.g., age, preexisting conditions, severity of illness) have not changed; otherwise, one may be looking at changes in demography and case mix rather than at true change in performance. To ensure fair and meaningful measurement across time, **risk adjustment** is necessary to *level the playing field*. As an example, illness severity typifies the concept of *risk*—the higher the severity, the higher the risk of a given outcome. Without risk adjustment, EDs with sicker patients may appear to have poorer outcomes.

Risk Adjustment Tools in the ED

Although other risk adjustment scoring systems—such as the PRISM score for pediatric critical care—use mortality and morbidity as primary outcomes, this approach is not appropriate for the ED setting. Across U.S. EDs, pediatric mortality is low, and a patient's presenting physiology may reflect interventions performed in the prehospital setting. Similarly, eventual morbidity and/or mortality may reflect what happens in the PICU or during hospital ward care.

Table 77.3 Stakeholder-Endorsed Performance Measures for Pediatric Emergency Care

- Measuring weight in kilograms for patients <18 years of age
- Presence of a method to identify age-based abnormal pediatric vital signs
- Pediatric equipment in the ED
- Presence of on-site pediatric coordinator(s)
- Parent/caregiver understanding of discharge instructions
- Door to provider time
- Total length of stay
- Reducing pain in children with acute fractures
- Children with minor head trauma receiving a head CT scan
- Protocol for suspected child abuse in place
- Systemic corticosteroids in asthma patients with acute exacerbation
- Evidence-based guideline for bronchiolitis
- Reducing antibiotic use in children with viral illnesses
- Return visits within 48 hours resulting in admission
- Medication error rates

ACEP, American College of Emergency Physicians; AAP, American Academy of Pediatrics; ENA, Emergency Nurses' Association; GCS, Glasgow Coma Score; CT, computed tomography.

In the ED, the choice of a risk adjustment tool depends on ED-specific outcomes of interest. Two general risk adjustment tools have been developed specifically for PEM, the second-generation Pediatric Risk of Admission (PRISA II) score and the Revised Pediatric Emergency Assessment Tool (RePEAT).

Pediatric Risk of Admission II

PRISA II uses components of acute and chronic medical history as well as acute physiology to determine the probability of hospitalization. The outcome measure of interest is *mandatory hospital admission* (admissions using therapies that are best delivered in the inpatient setting). Table 77.4 lists the patient-related attributes contributing to the PRISA II risk adjustment score. Analytic models, including the PRISA II score, have good **calibration** (how well the probabilities predicted from the model correlated with the observed outcomes in the population) and **discrimination** (the ability to categorize subjects correctly into the categories of interest) with respect to mandatory hospital admission. Construct validity of the PRISA II score has been demonstrated by measuring rates of the secondary outcomes: mandatory admission, PICU admission, and mortality. As the probability of hospital admission rises, the proportion of patients with these increasing care requirements also increases. This finding supports the use of the PRISA II score as a measure of illness severity. PRISA II has also been used to demonstrate racial/ethnic differences in severity-adjusted hospitalization rates, as well as variation in hospitalization rates between teaching and nonteaching hospitals.

Revised Pediatric Emergency Assessment Tool

RePEAT uses a limited set of data collected at the time of ED triage to model severity of illness as reflected by the level of care provided in the ED—for example, routine assessment (clinical examination only ± nonprescription medicine) vs specific ED care (ED diagnostics and/or therapeutics) vs hospital admission. In this model, it is assumed that patients needing a higher level of care have a higher severity of illness. Table 77.5 lists the patient-related attributes contributing to

Table 77.4 Elements of the PRISA II Score

- Age
- Injury severity
- Temperature
- Referral status (e.g., self-referral vs referral from physician's office or from another ED)
- Presence of:
  - Abdominal pain in an adolescent
  - Immunodeficiency
  - Indwelling medical device
  - Controller asthma medication
  - Decreased mental status
  - Low systolic blood pressure (<70 neonates and infants; <83 children; <100 adolescents)
  - High diastolic blood pressure (>59 neonates and infants; >70 children; >90 adolescents)
  - Low serum bicarbonate value (<20 mEq/L)
  - High potassium value (>4.9 mEq/L)
  - High blood urea nitrogen value (>80 mg/dL)
  - High white blood cell count (>20,000/mm^3)
  - Oxygen therapy other than during inhaled bronchodilator treatments
  - Low bicarbonate and high potassium values

Table 77.5 Elements of the RePEAT Score

- Age
- Chief complaint
- Triage category
- Current use of prescription medications
- Arrival via EMS (ground/air)
- Heart rate (relative to age-based norms)
- Respiratory rate (relative to age-based norms)
- Temperature

the RePEAT risk adjustment score. Analytic models such as RePEAT have good calibration and discrimination with respect to predicting ED care and hospital admission. Furthermore, analytic models that compare costs and length of stay between EDs are improved by adjusting for severity of illness using the RePEAT score. RePEAT is a reasonable objective marker of severity of illness that could be used in the administrative process comparing outcomes between EDs. With implementation of scoring systems such as PRISA II and RePEAT, U.S. EDs can benchmark the care that they provide to children and make meaningful improvements to ensure that this care is equitable and evidence-based.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

77.3 Principles Applicable to the Developing World

David M. Walker and Victorio R. Tolentino Jr.

The maturity of pediatric emergency medicine (PEM) in any given area depends on the healthcare priorities and resources of that geographic or physical setting. The places in which emergency care takes place range from the community (especially for those with no access to organized medical care) to state-of-the-art pediatric emergency departments (EDs), typically in larger population centers. The scope ranges from the care of the individual patient to the management of populations of children involved in large-scale disasters. Barriers to quality care vary in each situation and in each part of the world, with the implication for the PEM practitioner that the care provided must be relevant to the local context of healthcare.

CONTINUUM-OF-CARE MODEL

This Emergency Medical Services for Children (EMSC) framework can also be applied to discussion of emergency care for children on a global level (see Chapter 77). Although medical infrastructure in some parts of the developing world may not be consistent or well organized, or has been weakened by civil strife, natural disasters, or economic loss, the EMSC framework can still apply generally to individual healthcare systems.

Prevention

Infectious Diseases

International child health has focused mainly on reducing the incidence of preventable childhood illnesses, primarily through immunization initiatives. Enormous advances have been realized in measles, neonatal tetanus, and polio; wild-type smallpox was eradicated in 1978. Although there are advocates for providing primary care interventions (e.g., vaccinations) in the ED, the role of the PEM practitioner in this area of prevention has been limited.

Injuries

Injuries are a leading cause of childhood morbidity and mortality. Unintentional injuries constitute 90% of injury mortality to children 5-19 years old and are the cause of 9% of the world's mortality (see Chapter 14). Intentional injuries, which remain underrecognized and underreported, make a smaller but significant contribution. Unintentional injuries cause more than 2,000 childhood deaths daily, or 950,000 annually worldwide. The burden of these deaths is borne disproportionately by children in middle- and lower-income countries, where >95% of all injury-related deaths occur. For each of these deaths, many more children are permanently disabled, and an even larger number are treated and released without permanent sequelae.

Traffic-related injuries, burns, and drowning are the main causes of injury-related mortality in children. The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) have outlined several proven injury prevention strategies of which child health practitioners in the global community must be aware. Although these strategies have proved effective, the data are based on U.S. research and may not be generalizable to other countries.

Out-of-Hospital Care

Out-of-hospital care comprises access to emergency services, prehospital care, and interfacility transport of patients. Morbidity and mortality arise from delayed or limited access to emergency care, lack of prehospital care, transport without proper monitoring or trained personnel, or delayed transport to a higher level of care. Safe transport of seriously ill children is a neglected global health issue. An emergency response system must address the following links in the patient's care: a communication system with prompt activation of emergency medical services (EMS), the correct assessment and initial treatment of the patient, and the rapid transport to definitive care.

Access to Care

When a child is injured or ill, a parent or caretaker must be able to access help and activate EMS. In the majority of low- and middle-income countries, no universal emergency numbers have been established, requiring access by direct dialing to an ambulance, if such private services exist. In countries that have a universal emergency number, barriers remain related to absence of phones in some households, unclear addresses in rural areas, and insufficient reach of the emergency system.

In most low- and middle-income countries, the family must bring the ill or injured child to the health facility for stabilization and treatment. For this to occur, families must also overcome financial and geographic barriers, which can result in delayed presentation for care. This delay predictably increases the likelihood of associated complications and decreases the likelihood of full recovery and survival.

Prehospital Care

In regions with maturing EMS systems, there must be adequately trained personnel to stabilize and transport the child to a medical facility. The quality and level of training of such prehospital personnel vary among countries and within regions of the same country. In urban areas, there is a greater concentration of medical care and therefore a greater opportunity to have strong prehospital training. In most of Asia and sub-Saharan Africa, trained personnel are used primarily to transfer patients between health facilities, not from the initial site of illness or injury. In most high-income countries, medical services are dispatched to the patient.

Around the world, the effort to establish standardized approaches to prehospital care exists primarily in the form of courses to educate EMS and hospital personnel in the emergency management of patients. The WHO manuals *Prehospital Trauma Care Systems* and *Guidelines for Essential Trauma Care* focus on guidelines for prehospital and trauma care systems that are affordable and sustainable. The American Academy of Pediatrics (AAP) course "Pediatric Education for Prehospital Professionals" is a dynamic, modularized teaching tool designed to provide specific pediatric prehospital education that can be adapted to any EMS system. Table 77.6 describes additional prehospital resources.

Although most middle- and high-income countries have a system of trained EMS workers, lower-income countries lack this advanced tier of emergency care. In these countries, commercial drivers, volunteers, and willing bystanders provide the first line of care. Training a cadre of first responders can rely on existing networks of aid or can be drawn from specific populations, such as students, soldiers, or public servants. Training needs to emphasize basic lifesaving and limb-saving interventions, including how to stop bleeding and support breathing, access advanced care, and splint broken limbs. In Ghana, for example, taxi drivers participated in a first-aid course that relied heavily on demonstration and practice rather than knowledge transfer through didactic sessions. Taxi drivers were selected because they already provided much of the transport for injured patients. Two years after the course, external evaluators favorably rated the quality

Table 77.6 Pediatric Emergency Care Resources

PREHOSPITAL CARE

Emergency Pediatric Care
Course developed by the National Association of Emergency Medical Technicians (NAEMT) focused on field treatment of sick and injured children. Course is open to physicians, nurses, EMTs, and paramedics.
Website: https://www.naemt.org/education/epc

Pediatric Trauma Life Support for Prehospital Care Providers
An 8-hour pediatric prehospital course sponsored by the global organization International Trauma Life Support (ITLS)
Website: https://www.itrauma.org/education/itls-pediatric/

Pediatric Education for Prehospital Professionals (PEPP)
Curriculum designed specifically to teach prehospital professionals how to assess and manage ill or injured children.
Website: https://www.peppsite.com/

HOSPITAL CARE

Pocket Book of Hospital Care for Children: Second Edition
WHO publication providing guidelines for the management of common illnesses in resource-limited settings; incorporates both the Emergency Triage Assessment and Treatment (ETAT) and Integrated Management of Childhood Illness (IMCI) guidelines.
Website: https://www.who.int/publications/i/item/978-92-4-154837-3

African Federation of Emergency Medicine (AFEM) Handbook of Acute and Emergency Care
Management strategies organized according to low-, moderate-, and full-resource settings.
Website: https://afem.africa/project/afem-handbook-of-acute-and-emergency-care/

African Federation of Emergency Medicine (AFEM) Rapid Approach Protocols for Children
Open-access clinical protocols for common presenting problems in children. Includes differential diagnoses and recommendations on initial investigations.
Website: https://www.dropbox.com/sh/cwhcl3eu8vrvwqu/AAA-MSDs9u3Y0SIgwU1R3hFxa?dl=0

African Federation of Emergency Medicine (AFEM) Tier 1 Paediatric Emergency Medicine Curriculum
Open-access curriculum targeted to nurses, EMS personnel, pharmacists, and other providers who care for acutely ill and injured children. Organized into modules by clinical presentation or disease processes.
Website: https://www.dropbox.com/sh/pgv8zd5y6z1elvo/AAA_df2fUj1bSzABbjZFjSgfa?dl=0

Standards of Care for Children in Emergency Departments, Version 3.0
Open-access document from the International Federation of Emergency Medicine that proposes worldwide standards for pediatric emergency care.
Website: https://www.ifem.cc/standards_of_care_for_children_in_emergency_departments_v3_2019

African Emergency Nursing Curriculum
Open-access educational framework for emergency nursing practice in resource-limited settings. Developed by the African Federation of Emergency Nurses.
Website: http://afem.co.za/wp-content/uploads/2017/10/AFEM-African-Emergency-Nursing-Curriculum.pdf

HUMANITARIAN EMERGENCIES

Manual for the Health Care of Children in Humanitarian Emergencies
WHO publication that provides comprehensive guidance on childcare in emergencies; includes information on care of traumatic injuries and mental health emergencies.
Website: https://www.who.int/publications/i/item/9789241596879

Pediatric Disaster Care Centers of Excellence (United States)
Coalition of medical centers and government agencies established to guide the delivery of pediatric healthcare services in a disaster.
Website: https://emscimprovement.center/domains/preparedness/asprcoe/

MENTAL HEALTH EMERGENCIES

The Mental Health & Psychosocial Support Network
A hosted online practice network organized around crowdsourcing of mental health and psychosocial support resources for use in emergencies and ongoing humanitarian crises in the developing world.
Website: https://mhpss.net/

Save the Children Psychological First Aid Training
Practitioner training manual dedicated to the provision of psychological first aid to children exposed to trauma.
Website: https://resourcecentre.savethechildren.net/document-collections/save-children-psychological-first-aid-training

Psychological First Aid: Guide for Field Workers
Open-access training manual from the WHO for those who may respond to large-scale crises.
Website: https://www.who.int/publications/i/item/9789241548205

ACCESS TO ACADEMIC PUBLICATIONS RELEVANT TO PEM

PEMdatabase.org
A website devoted to pediatric emergency medicine (PEM). Contains links to conferences, evidence-based medicine reviews, research networks, and professional organizations.
Website: www.pemdatabase.org

HINARI Access to Research for Health Programme
Program established by WHO and others to enable developing countries to gain access to one of the world's largest collections of biomedical and health literature.
Website: https://partnership.who.int/hinari

ORGANIZATIONS INVOLVED IN GLOBAL PEM ACTIVITIES

American College of Emergency Physicians (ACEP) Ambassador Program
Provides the names of U.S.-boarded emergency medicine physicians who can provide advice and information on issues pertaining to the progress and status of emergency medicine in their assigned countries.
Website: https://www.acep.org/intl/ambassador-program/

U.S. Agency for International Development (USAID)
Government agency providing U.S. economic and humanitarian assistance worldwide.
Website: https://www.usaid.gov/global-health/health-areas/maternal-and-child-health/technical-areas/child-health

Child Health and Development Unit, World Health Organization (WHO)
United Nations agency dedicated to child health.
Website: https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/child-health

United Nations Children's Fund (UNICEF)
Organization dedicated to providing lifesaving assistance to children affected by disasters and to protecting their rights in any circumstances; formerly United Nations International Children's Emergency Fund.
Website: www.unicef.org

Safe Kids Worldwide
International nonprofit organization dedicated to preventing unintentional childhood injury.
Website: www.safekids.org

of their care compared with untrained drivers. In rural areas, such first responders become vital in providing emergency interventions when more definitive care is distant. Thus a system of trained first responders forms the foundation of an effective prehospital system.

In the French model, a physician, often an emergency medicine specialist, will review calls for acuity and can dispatch a physician-led team by ambulance to go to the patient's home to assess, stabilize, and initiate treatment. This Franco-German system is used in other countries, including many in Latin America and Europe. There are no clear data on the cost-effectiveness and patient outcomes associated with delivery of patients to the nearest facility vs bringing hospital resources to the patient.

Methods of Transport

In many low-income countries, there is no reliable means of transport. Health centers may only have one vehicle for transport to a

higher-level facility. This vehicle may also be used for outreach primary care services, such as offering immunizations and collecting drugs and equipment from a central supply location, and sometimes, improperly for personal reasons by local officials or politicians. In large cities, taxis and auto rickshaws are frequently used because they are rapidly available, well disseminated, and able to pass around traffic jams. Where organized prehospital systems exist, different types of vehicles are adapted for emergency transportation. The WHO recommends identifying transport vehicles in advance, choosing vehicles that can be repaired and maintained locally, and equipping the vehicles according to recognized standards. The provision of available and appropriately staffed and equipped transport vehicles is crucial to the realization of recommended emergency care plans.

Hospital-Based Care

Once a child has reached a medical facility for the care of an injury or illness, adequate emergency services should be available. In many countries the ED serves only as a triage area where patients are distinguished by their likely disease process and directed for admission to the corresponding unit within the hospital. Strengthening emergency services includes seeing the ED as a unit where definitive treatment can be provided to the ill and injured child. Critically ill children must receive not only prompt care but also correct care. Such expedience and accuracy are ensured by implementation of an effective triage system, moving the sickest patients to immediate care and standardizing the initial care of emergency conditions.

Triage

Too often, children presenting to EDs are treated on a first-come first-served basis in an approach that creates long waiting times for critically ill children, a contributor to unnecessary mortality. Medical facilities should adopt an efficient and effective triage system to respond rapidly to the needs of patients and to assign the appropriate amount of resources. The WHO has developed a course entitled **Emergency Triage Assessment and Treatment (ETAT)**. This course teaches emergency, priority, or nonurgent signs and how to provide emergency treatment for life-threatening conditions. ETAT emphasizes the evaluation of a patient's ABCD status to identify emergency situations—the patency of the airway (A), the quality of breathing (B), the quality of circulation and presence of coma or convulsions (C), and the presence of severe dehydration (D).

One of the benefits of the ETAT guidelines is that they can be adapted to centers with limited resources and are applicable to areas with high morbidity and mortality from meningitis, dehydration, malaria, respiratory illness, and malnutrition. Another benefit is that the care algorithms are based on limited diagnostic studies, that is, hemoglobin measurement, blood smear for malaria, and bedside blood glucose testing. Widely accepted triage assessment guidelines are teachable to emergency care staff, and their adoption can provide better organization within a healthcare center. At the Queen Elizabeth Central Hospital in Blantyre, Malawi, for example, the institution of triage and rapid treatment in its emergency care center led to a 50% decrease in the mortality of children within 24 hours of presentation to the hospital, with a further 50% decrease as implementation and practice of triaging patients have continued.

Beyond triage, education on overall emergency center organization is a low-resource intervention that can reduce some of the obstacles to quality care delivery. Additionally, the arrangement of short-stay areas (hydration and infusion rooms) within or near the ED can lessen the burden on inpatient units.

Pediatric-Specific Emergency Centers

Anecdotally, most countries have developed at least one pediatric-capable center, usually as part of an academic medical center. The emergency services in these centers are variable, but certainly can be a starting point from which to build overall improvement in pediatric emergency care.

Practitioners

Throughout the world, nurses, paramedics, nonphysician clinicians, and nonspecialist physicians deliver most of the care to acutely ill or injured children. The majority of sick children attend local clinics or district or central hospitals, where financial and human resources are not always matched to the potential acuity of presenting patient complaints. Nominal supervision is provided to staff attending these patients. Pediatric EDs located in tertiary hospitals are often staffed by training physicians with little or no supervision from faculty, who themselves may have limited exposure to or training in pediatric emergencies. General hospitals lack dedicated pediatric staff; guidelines as to which patients should be moved to a higher level of care are often not standardized and depend on local influences and/or cultural beliefs about health and illness.

Clinical Guidelines

The **Integrated Management of Childhood Illnesses (IMCI)** guidelines were developed by the WHO and UNICEF to provide assistance in the initial triage and management of the presenting signs and symptoms of the major killers of children <5 years old in first-level health facilities (e.g., clinics, health centers, outpatient departments of hospitals). The flow charts within each chapter of the IMCI manuals allow easy accessibility to materials that can enhance education and outreach to less experienced health workers.

Evaluations in various countries of the implementation of IMCI guidelines have shown improvements in health worker performance and quality of care, as well as decreases in delay in treatment and mortality of the under-5 population. These guidelines also dramatically reduce the cost of healthcare. The WHO website provides all the necessary implementation tools, including course manuals and evaluation tools.

The International Federation of Emergency Medicine developed Standards of Care for Children in Emergency Departments to improve emergency care globally. These standards are not just aimed at dedicated EDs, but at any setting where emergency care takes place, regardless of the providers or the resources available. At the same time, however, the existence of the standards allows sites to advocate for improved resources dedicated to expertise in the various aspects of providing quality emergency care for children. The standards address design of care spaces, child- and family-centered care, assessment of ill and injured children, staff training and competencies, quality and safety, and disaster response.

Trauma

Morbidity and mortality from trauma are among the most prevalent problems for children worldwide. Trauma care presents the challenge of sequential, often simple, interventions that must be performed in a timely manner to limit the severity of the outcome. However, with lack of specific training, signs and symptoms of pediatric trauma may go unrecognized or may be underappreciated. Trauma courses such as Advanced Trauma Life Support (ATLS) are educational tools that can be disseminated to improve the quality of care at emergency centers worldwide. For low-resource settings, the WHO has developed the Integrated Management for Emergency and Essential Surgical Care toolkit, which provides clear directions and reasoning for the initial care of injured patients. Not expressly addressed in the ATLS course is specific concern about child abuse as the cause of trauma. This is an area of pediatric care that many countries do not yet address comprehensively in their medical training, their law enforcement, or their judicial systems. The epidemiologic need for reliable trauma registries is great, as is the need to identify personnel with trauma management skill sets and dedicated trauma centers to serve as higher-level referral sites.

Equipment

Pediatric emergency equipment guidelines are available for a variety of settings where acutely ill and injured children would present. Although these equipment guidelines may represent minimum supplies to treat

the widest variety of pediatric emergencies, the roles of substitution and improvisation often provide for the equivalent function of recommended supplies.

Inpatient Services

After the initial stabilization, children requiring ongoing care are admitted to the hospital. The quality of inpatient services varies greatly depending on institutional and provider experience, comfort with pediatric conditions, and the resources available to treat them. The WHO has produced the *Pocket Book of Hospital Care for Children,* which is based on IMCI guidelines and focuses on inpatient management of high-morbidity/high-mortality illnesses common in developing countries.

Mental Health Emergencies

The recognition of mental health conditions among the pediatric population is continuing to evolve. It is estimated that about 15% of children globally suffer from anxiety, depression, or other mental health challenges. The prevalence of mental health problems is likely higher, as much of the existing data comes from Europe and North America, whereas a majority of children live in middle- and lower-income regions of the world.

Mental health capacity varies by country and is reflective of cultural beliefs about mental health and the priority and funding that local governments have allocated to address these concerns. It is widely accepted that the current global mental health infrastructure fails to meet the existing demands of the world's population. These concerns are amplified in the developing world and disproportionately affect children whose lives are often touched by emotional and social trauma (e.g., poverty, natural disasters, armed conflict).

Increasingly, children are presenting to emergency settings in crisis. In many developing countries, mental health services are concentrated in urban settings and lacking in rural areas. Where there is no shortage of medical personnel, expertise in child psychiatry corresponds with the local development of this specialty. In areas with no formal mental health system, care is provided by an informal network of family members, faith healers, or community leaders who do not have formal medical training. It is essential that children presenting for mental health evaluation receive a comprehensive examination, as certain psychiatric presentations can be rooted in infectious diseases conditions or inadequate nutrition, which are prevalent in some developing world contexts.

The WHO has provided examples of best practice in the acute treatment of mental health conditions in *Hospital-Based Mental Health Services: Promoting Person-Centered and Rights-Based Approaches*. This document is available as a section of the *Guidance and Technical Packages on Community Mental Health Services* available on the WHO website. Although the publication does not include examples of pediatric-specific care, the document is meant to be tailored to the local context and can be adapted to the needs of children.

Telemedicine

Telemedicine technology is one way to overcome provider shortages or geographic challenges that can affect the care of acutely ill and injured children. Patients and families can potentially access basic emergency care through video-based platforms. The responding provider can use established triage techniques to help determine the severity of illness and the need for consultation at a healthcare center; they can also recommend basic first aid as needed.

Access to real-time lectures, case discussions, and conferences, led by experts in PEM, can increase the capacity of those in limited-resource settings to provide care for pediatric emergency patients. These educational offerings can also provide a forum for a bilateral exchange of ideas and perspectives. Expert consultations via real-time telemedicine programs or a store-and-forward process, in which the request for consultation is recorded and sent to an expert who can reply typically over email, can be used. Additionally, within a given region, telemedicine can link the referring hospital to the receiving hospital in order to collaborate on decisions about management and the need for transfer.

The success of telemedicine collaborations depends on a variety of factors, including availability of easy-to-use technology and reliable internet access.

HUMANITARIAN DISASTERS

Children are a vulnerable population who experience disproportionate suffering during humanitarian emergencies, either natural (earthquakes, tsunamis, hurricanes, floods, droughts) or manmade (armed conflicts, terrorist attacks). The under-5 population is especially susceptible to infectious diseases, malnutrition, and trauma after disasters.

The WHO *Manual for the Health Care of Children in Humanitarian Emergencies* is based on IMCI guidelines and addresses the emergency care of children in disaster situations where hospital facilities and resources are not immediately available. It goes beyond the IMCI guidelines by discussing initial assessment and management of trauma, burns, poisonings, neonatal illness, and psychosocial problems, which are considered high priority in acute care settings.

Exchange and Dissemination of Information

The WHO established the internet-based **HINARI** Access to Research for Health Programme in 2002 to provide institutions in low-resource countries free or reduced-cost access to medical literature. Registration for the program is required. Eligibility is based on national economic or development criteria.

Another valuable tool is the website pemdatabase.org. This nonproprietary site was started as an online resource for PEM practitioners. It contains links to PEM abstracts and articles, evidence-based reviews, pediatric resuscitation websites, and relevant journals, as well as PEM conferences and professional organizations.

In countries where internet access continues to be a barrier, resources for education and research may be limited to out-of-date textbooks and journals.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 78

Triage of the Acutely Ill Child

Anna K. Weiss and Frances B. Balamuth

Identifying the acutely ill child in the ambulatory setting is a challenge. Children presenting to pediatricians' offices, urgent care practices, and emergency departments (EDs) may have a range of illnesses from simple viral infections to life-threatening emergencies. Although most children in this setting will have a benign course of illness, it is incumbent on the pediatric practitioner to discern quickly and accurately which children are likely to deteriorate from potentially serious or life-threatening disease. When assessing an acutely ill child, practitioners must remember that the early signs of severe illness may be subtle. There are about five pediatric triage system tools that assess the severity of illness and thus the degree of needed interventions. One example is presented in Table 78.1.

ASSESSMENT OF VITAL SIGNS

Assessment of vital signs is critical in all pediatric visits for acute illness, including temperature, heart rate, respiratory rate, and blood pressure. Normal vital signs vary with age. Although there have been increasing efforts to build evidence-based vital sign cutoffs for different age-groups, most institutions use nonempirically derived cutoffs such as those in Pediatric Advanced Life Support (PALS). **Tachycardia** is common in children presenting for acute care and can result from benign (fever, pain, dehydration) to life-threatening (septic shock, hemorrhage, multisystem inflammatory system in children [MIS-C], dysrhythmia, heart failure, hyperthyroidism) conditions. An abnormal heart rate should prompt a full history and physical examination, as described later, and careful *reassessment* (often multiple times) after the presumed cause is identified and treated. Most children will improve after initiation of simple interventions such as antipyretics or analgesia. Tachycardia that persists after fever, pain, and dehydration have been treated *must* be evaluated further, particularly if the child appears ill or has a deficit in perfusion or altered mental state.

Tachypnea is also common among ill children and has many causes, including fever, respiratory conditions (bronchiolitis, asthma, pneumonia), cardiac disease (heart failure), and metabolic acidosis (shock, poisoning, diabetic ketoacidosis). Like tachycardia, tachypnea often resolves with antipyretics in febrile children and should be reassessed to ensure resolution once fever has been managed. In cases where bronchiolitis and asthma have been ruled out, persistent tachypnea and fever can be a sign of pneumonia, even in the absence of focal lung findings on examination. Consider evaluation for metabolic acidosis in cases of significant tachypnea without apparent pulmonary or cardiac causes. **Apnea** is a sign of respiratory failure and should be *treated emergently with bag-valve-mask ventilation and immediate ED evaluation.*

Hypotension is rare in children and, when present, it is a sign of critical illness. Children with hypotension should be evaluated in an ED. Hypotension is evidence of decompensated circulatory shock and can result from severe dehydration, sepsis, hemorrhage, neurogenic spinal shock, anaphylaxis, or cardiogenic shock.

Pulse oximetry (oxygen-hemoglobin saturation, Spo_2) should be assessed in children with respiratory or cardiac illness/compromise and in children with underlying abnormalities of oxygenation. Healthy children have Spo_2 >95%. The practitioner should consider evaluating for any underlying respiratory or cardiac causes in children with Spo_2 <93–95%. For children with underlying abnormalities, the child's baseline Spo_2 should be assessed and alterations from that baseline should be investigated further.

The combination of bradycardia, hypertension, and altered breathing known as **Cushing triad** can be a sign of life-threatening increased intracranial pressure (ICP) and should be evaluated in an ED. Anisocoria and a sixth cranial nerve palsy are other signs of increased ICP. **Toxidromes** should also be considered in children with abnormal combinations of vital signs (see Chapter 94).

HISTORY

A thorough history is paramount to identifying patients whose condition will require prompt intervention. Obtaining an accurate history from young patients is challenging, particularly with preverbal or anxious children who are unable or unwilling to localize the source of their discomfort. In such instances, parents or caretakers often provide the most important information, and their perceptions of the child's course of illness must be carefully considered. Pediatricians should be guided by the patient's chief complaint to ask *open-ended questions* that help distinguish between benign and potentially life-threatening disease entities. The most common complaints leading to acute care visits among children include fever, headache and altered mental status, trauma, abdominal pain and vomiting, respiratory distress, and chest pain. Table 78.2 describes signs and symptoms and risk factors that should prompt immediate transfer to an ED or, if already in the ED, initiation of rapid intervention.

Fever is the most common reason for a sick-child visit. Most cases of fever are the result of self-limited viral infection. However, pediatricians need to be aware of the age-dependent potential for serious bacterial or viral infections, such as urinary tract infection (UTI), sepsis, meningitis, pneumonia, acute abdominal infection, and osteoarticular infection.

During the first 2 months of life, the neonate is at risk for sepsis caused by pathogens that are uncommon in older children. These organisms include group B streptococcus, *Escherichia coli, Listeria monocytogenes,* and herpes simplex virus (HSV). In neonates, the history must include maternal obstetric information and the patient's birth history. Risk factors for sepsis include untreated maternal group B streptococcus colonization, prematurity, chorioamnionitis, and prolonged rupture of membranes. If there is a maternal history of sexually transmitted infections (STIs) during the pregnancy, the differential diagnosis must be expanded to include infection with those pathogens. Septic infants can present with lethargy, poor feeding, grunting respirations, and cool or mottled extremities in addition to fever (or hypothermia). Febrile infants in the first 1 to 2 months of life should be evaluated broadly for infection, including sampling blood, urine, and, in some cases, cerebrospinal fluid (CSF) (see Chapter 220).

When the infant matures beyond 2 months of age and receives their first set of vaccinations, serious bacterial infections become less common. Evaluation to rule out serious infection is an important part of treating the febrile older child. Children with fever should have a full set of vital signs, history, and physical examination to ensure that critical illness is absent and to identify any focal source. Red flags for **septic shock** include hypotension, poor perfusion, altered mental status, or the presence of purpuric or erythrodermic rash. Red flags for **meningitis** include severe headache, meningismus, and altered mental state. The presence of any of these signs should prompt emergency evaluation in the ED or rapid treatment if the patient is already in the ED.

Additional focal findings to consider include evaluation for acute otitis media, pharyngitis, pneumonia, abdominal infections (bacterial enteritis, appendicitis), skin and soft tissue infections, septic arthritis, and osteomyelitis. Occult UTI should be considered if three of the following risk factors are present: age <1 year, fever >39°C, fever >48 hours, and no focal source of fever. Pneumonia should be considered in the presence of tachypnea, hypoxia, or focal findings on chest examination. Bacteremia is rare in the post–pneumococcal and *Haemophilus influenzae* vaccine era but should be considered if staphylococcal infection or meningococcemia is suspected and in unvaccinated children or children with signs of septic shock. In addition to infection, inflammatory conditions to consider include juvenile idiopathic arthritis (JIA), macrophage activating syndrome (MAS), Kawasaki disease (KD), and MIS-C. The diagnosis of KD, MIS-C, or MAS should be considered if

Table 78.1 Definition of Emergency Severity Index for Children

LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 5
Cardiac arrest Respiratory arrest Severe respiratory distress SpO_2 <90 Critically injured and unresponsive trauma patient Severe respiratory distress with agonal or Gasping-type respirations Severe bradycardia or tachycardia with signs of Hypoperfusion Hypotension with signs of hypoperfusion Trauma patient who needs resuscitation Anaphylactic reaction Baby who is flaccid Hypoglycemia with a change in mental status	Seizures Sepsis, severe dehydration Diabetic ketoacidosis Child abuse, burns Head trauma Vitamins/iron or other overdoses/ingestions Infant less than 28 days of age with a fever of 38°C (100.4°F) or greater 1-3 mo of age with a fever of 38°C (100.4°F) or greater may be considered up to II Vital signs not stable	Multiple resources needed 3 mo to 3 yr of age T >39°C (102.2°F)	Single resource needed	Only history, physical exam required

From Wang L, Zhou H, Zhu JF. Application of emergency severity index in pediatric emergency department. *World J Emerg Med.* 2011;2(4):279-282, Table 1, p. 280.

the patient meets the diagnostic criteria for that illness, although some patients may have an atypical or incomplete presentation (see Chapters 207 and 208).

For patients presenting in an **altered mental state**, the pediatrician should inquire about symptoms such as fever or headache. Screening questions should explore feeding changes, medications in the household, ill contacts, and the possibility of trauma. Parents will often describe a febrile child as lethargic, but further questioning will reveal a tired-appearing child who interacts appropriately when no longer febrile. The child who appears ill only when febrile must be differentiated from the lethargic patient who presents with suspected sepsis or meningitis and from the child whose altered behavior is secondary to an intracranial emergency or seizure. Infants with meningitis, sepsis, or cardiac defects may have a history of irritability, inconsolability, poor feeding, grunting breathing, seizures, poor urine output, and/or color changes such as pallor, mottling, or cyanosis. Patients with poisoning or inborn error of metabolism can also present with lethargy, poor feeding, unusual odors, seizures, and vomiting. **Nonaccidental trauma** should always be considered in a lethargic infant, particularly in the absence of additional signs or symptoms. In infants and young toddlers, rapidly growing head circumference or bulging anterior fontanel may signal increased ICP. Older children may present with altered mental state as a result of meningitis/encephalitis, trauma, or ingestions. School-age children and adolescents with meningitis may have a history of fever and neck pain; other associated symptoms may include rash, headache, photophobia, or vomiting. Children with ingestions can present with other abnormal neurologic symptoms, such as ataxia, slurred speech, and seizures, or with characteristic constellations of vital sign changes and other physical findings consistent with certain toxidromes.

In patients with **headache**, ask questions about the chronicity of the headache and any accompanying symptoms. Headaches that occur upon arising in the morning, that are worse when lying flat, or that are accompanied by vomiting are concerning for increased ICP. Similarly, headache accompanied by focal neurologic deficit(s) should be referred to an ED for urgent head imaging. Although migraine headaches in teenagers are similar in presentation to those in adults (unilateral, throbbing, accompanied by an aura), pediatric practitioners should be aware that migraines in prepubertal children may have a nonclassic presentation; may be bilateral; and may not be accompanied by aura, photophobia, or phonophobia.

Parents may interpret a variety of symptoms as **respiratory distress**, and care must be taken to distinguish normal and benign respiratory patterns from true respiratory distress. Tachypnea secondary to fever is a common source of parental anxiety, and parents of newborn infants are sometimes alarmed by the presence of periodic breathing. Parents should be questioned about their child's other symptoms, such as fever, limitation of neck movement, drooling, choking, and the presence of stridor or wheezing. A history of apnea or cyanosis warrants further investigation. Practitioners should also remember that tachypnea in a child without evidence of true respiratory distress may be evidence of compensation for shock or metabolic acidosis, both of which will require rapid treatment. Although wheezing is often secondary to bronchospasm, it can also be caused by cardiac disease or congenital airway anomalies such as vascular rings. Parents may interpret **stridor** as noisy breathing or wheezing. Stridor is most frequently caused by upper airway obstruction such as croup. However, anatomic abnormalities such as laryngeal webs, laryngomalacia, subglottic stenosis, and paralyzed vocal cords also cause stridor. Toddlers who present with breathing difficulty after a coughing or choking episode should be evaluated for **foreign body aspiration**. In these cases, practitioners must ask about the possibility of button-battery ingestion, as this constitutes a true medical emergency that warrants immediate endoscopic removal or transfer to a facility that can perform the procedure. In toxic-appearing children with stridor, the pediatrician should consider epiglottitis, bacterial tracheitis, or a rapidly expanding retropharyngeal abscess. The incidence of epiglottitis has greatly declined with the advent of the *H. influenzae* type b (Hib) vaccine, but it remains a possibility in the unimmunized or partially immunized patient. Children with retropharyngeal abscesses may also present with drooling and limitation of neck movement (especially hyperextension) after a recent upper respiratory infection or penetrating mouth injury.

Abdominal pain is a common complaint in the ambulatory setting and can herald either acute intraabdominal or pelvic pathology, or it can be a subtler sign of systemic illness. Both relatively benign (e.g., streptococcal infection, UTI, pneumonia) and severe abdominal (e.g., appendicitis) or systemic (e.g., diabetic ketoacidosis, MIS-C) illness can present with abdominal pain, and questions to the patient and parent should include whether there is an extraabdominal source of discomfort. Questions should include details about pain onset and location; presence of accompanying symptoms, such

Table 78.2 History and Examination Findings that Should Prompt Immediate Intervention and/or Transfer to Emergency Department

HISTORY AND EXAM FINDINGS	RISK FACTORS
RED FLAGS FOR RESPIRATORY FAILURE	
Tachycardia	Tracheostomy
Tachypnea	Ventilator dependence
Cyanosis	History of critical airway
Apnea	
Brief resolved unexplained event (BRUE) with cyanosis or change in tone	
Suspected button-battery ingestion	
Foreign body aspiration with respiratory distress	
Sitting up, leaning forward, drooling	
Respiratory distress with hypoxemia	
Altered mental status	
RED FLAGS FOR CIRCULATORY FAILURE	
Tachycardia	Oncology (or other immunosuppressed) patients
Tachypnea	Bone marrow or solid organ transplants
Cyanosis	Sickle cell (or otherwise asplenic) patients
Cold extremities, poor pulses	Infants <60 days old
Apnea	Unrepaired or repaired congenital heart disease with change from baseline pulse oximetry
Petechial or purpuric rashes	Bleeding disorder with trauma
Erythroderma	
Peritonitis	
Bilious emesis	
Post-tonsillectomy or post-adenoidectomy with bleeding	
Extremity trauma with neurovascular deficits	
RED FLAGS FOR NEUROLOGIC FAILURE	
Tachycardia	Ventriculoperitoneal shunt
Bradycardia-hypertension	Diabetes or metabolic disease with altered mental status
Double vision	Hypoxic-ischemic encephalopathy
Ptosis	Clotting disorder with neurologic change(s)
Unequal pupils	Drug ingestion
Apnea	
Frequent or prolonged seizure(s)	
Focal neurologic deficit(s)	
Acute onset of severe headache	
Suicidal or homicidal ideation	
Psychosis	

Adapted from Farah MM, Tay Y, Lavelle J. A general approach to ill and injured children. In: Shaw KN, Bachur RG, eds. *Fleischer and Ludwig's Textbook of Pediatric Emergency Medicine*, 8th ed. Philadelphia: Lippincott, Williams & Wilkins; 2020.

as fever and abdominal distention; and changes in feeding, urination, and stooling patterns. Care should be taken to elicit a history of peritonitis or obstruction, including worsening pain with abrupt movements and persistent or bilious vomiting.

In neonates, a tender abdomen with or without bilious emesis should raise concern for the presence of a small bowel obstruction (e.g., volvulus). These infants appear ill and may have a history of decreased stooling. Pediatricians should be wary of neonates with abdominal tenderness and bloody stools, as 10% of cases of necrotizing enterocolitis occur in term infants. Infants with milk protein intolerance can also present with bloody stools, but these infants appear well and do not have abdominal tenderness. In older patients the differential diagnosis for emergency causes of abdominal pain expands to include intussusception and appendicitis. Patients with intussusception present in a variety of ways, ranging from colicky abdominal pain but otherwise well between episodes to being lethargic or in shock. The diagnosis of appendicitis in the child younger than 3 years is extremely difficult because children in this age-group cannot localize pain well. In adolescent females with abdominal pain, practitioners must obtain a menstrual and sexual history, as acute lower abdominal pain may be caused by adnexal pathology, including ovarian torsion or ectopic pregnancy.

For patients with **vomiting**, pediatricians should ask if they have experienced bilious or blood-stained emesis, abdominal distention or constipation, weight changes, and diarrhea or bloody stools. An infant with bilious emesis and abdominal distention may have intestinal obstruction (as with midgut volvulus or Hirschsprung disease), whereas an infant who appears immediately hungry after nonbilious projectile vomiting may have pyloric stenosis. In an older child, vomiting may be caused by peritonitis or obstruction and by systemic illnesses, including diabetic ketoacidosis, ingestion, or trauma. Patients with headache and vomiting raise the concern for increased ICP and should be questioned about neurologic changes, meningismus, and fever.

Practitioners should also obtain a thorough account of the child's **past medical history**. It is important to be aware of any underlying chronic problems that might predispose the child to recurring infections or a serious acute illness. Children with sickle cell anemia, indwelling central venous access devices, or immune compromise are at increased risk for bacteremia and sepsis. Similarly, children with prior surgery, including ventriculoperitoneal shunt placement or intraabdominal procedures, can develop complications from their previous surgeries.

PHYSICAL EXAMINATION

Observation is important when evaluating the acutely ill child. Most observational data that the pediatrician gathers should focus on assessing the child's response to stimuli. Does the child awaken easily? Does the child smile and interact with the parent or with the examiner? Evaluating these responses requires knowledge of normal child development and an understanding of the manner in which normal responses are elicited, depending on the child's age.

During the physical examination, the pediatric practitioner seeks evidence of illness. The portions of the exam that require the child to be most cooperative are completed first. Initially, it is best to seat the child on the parent's lap; the older child may be seated on the examination table. It is also important to assess the child's willingness to move, as well as ease of movement. It is reassuring to see the child moving about on the parent's lap with ease and without discomfort. *Vital signs are often overlooked but are invaluable in assessing ill children.* The presence of tachycardia out of proportion to fever and the presence of tachypnea and blood pressure abnormalities raise the suspicion for more serious illness. The respiratory evaluation includes determining respiratory rate; noting the presence or absence of hypoxia by Spo_2; and noting any evidence of inspiratory stridor, expiratory wheezing, grunting, coughing, or increased work of breathing (e.g., retractions, nasal flaring, accessory muscle use). The **skin** should be carefully examined for rashes. Frequently, viral infections cause an exanthem, and many of these eruptions are diagnostic, such as the reticulated rash and slapped-cheek appearance of parvovirus infections and the stereotypical appearance of hand-foot-and-mouth disease caused by coxsackieviruses, as well as measles, chickenpox, and roseola. The skin examination may also yield evidence of more serious infections, including petechiae and purpura associated with bacteremia and erythroderma associated with a toxin-producing systemic infection. Cutaneous perfusion should be assessed by warmth and capillary refill time. The extremities may then be evaluated not only for ease of movement but also for the presence of swelling, warmth, tenderness, or alterations in perfusion. Such abnormalities may indicate focal infections (e.g., cellulitis, bone/joint infection) or vascular changes (e.g., arterial or venous thromboembolus).

When an infant is seated and least perturbed, the examiner should assess the anterior fontanel to determine whether it is depressed, flat, or bulging. While the child is calm and cooperative, the **eyes** should be examined to identify features that might indicate an infectious or neurologic process. Often, viral infections result in watery discharge or redness of the bulbar conjunctivae. Bacterial infection, if superficial,

results in purulent drainage; if the infection is more deep-seated, tenderness, swelling, and redness of the tissues surrounding the eye may be present, as well as proptosis, altered visual acuity, and impaired extraocular movements. Abnormalities in pupillary response, extraocular movements, or ptosis may also be indicators of cranial nerve abnormalities and, if new, are indications for head imaging.

During this initial portion of the physical examination, when the child is most comfortable (and therefore most likely to be quiet), the **heart and lungs** are auscultated. It is important to assess the adequacy of air entry into the lungs; the equality of breath sounds; and any evidence of adventitial breath sounds, especially wheezes, rales, or rhonchi. The coarse sound of air moving through a congested nasal passage is frequently transmitted to the lungs. The examiner can become attuned to these coarse sounds by placing the stethoscope near the child's nose and then compensating for this sound as the chest is auscultated. The cardiac examination is next; findings such as pericardial friction rubs, loud murmurs, irregular rhythms, gallop rhythm, and distant heart sounds may indicate cardiac inflammation or infection. In the neonate, murmurs may herald congenital heart disease, especially in the presence of cyanosis, unequal extremity pulses, or a differential in upper- vs lower-extremity blood pressures. A complete cardiac exam should also look for displacement of the point of maximal impulse (PMI) and the presence of jugular venous distention or facial plethora.

The components of the physical examination that are more bothersome to the child are completed last. This is best done with the patient on the examination table. Initially, the **neck** is examined to assess for areas of swelling, redness, or tenderness, as may be seen in cervical adenitis. Resistance to neck movement should prompt evaluation for signs of meningeal irritation or retropharyngeal abscess. During examination of the **abdomen**, the diaper—if present—is removed. The abdomen is inspected for distention. Auscultation is performed to assess adequacy of bowel sounds, followed by palpation. Every attempt should be made to quiet a fussing child during this part of the exam; if this is not possible, practitioners should note that increased crying as the abdomen is palpated may indicate tenderness, especially if this finding is focally reproducible. In addition to focal tenderness, palpation may elicit involuntary guarding or rebound tenderness (including tenderness to percussion); these findings indicate peritoneal irritation, as may be seen in appendicitis. During palpation of the abdomen, practitioners should look for signs of hepatomegaly or splenomegaly. When palpating the bottom-most edge of the liver or spleen, examiners should begin in the pelvis and work upward toward the ribs, because severe organomegaly can be missed if the examiner begins palpating in the mid-abdomen. The **inguinal area and genitals** are then examined. One should assess the inguinal area for hernias. Care should be taken to examine the testicles of males with abdominal pain; testicular trauma, testicular torsion, and epididymitis all may present with abdominal discomfort. A unilateral swollen or painful testicle with an absent cremasteric reflex on the affected side is concerning for testicular torsion and should be referred for emergent ultrasound and urologic consultation. After the genital exam, the child is then placed in the prone position, and abnormalities of the **back** are sought. The spine and costovertebral angle areas are percussed to elicit any tenderness; such findings may be indicative of vertebral osteomyelitis or diskitis and pyelonephritis, respectively.

Examining the **ears and throat** completes the physical examination. These are usually the most bothersome parts of the examination for the child, and parents frequently can be helpful in minimizing head movement. During the oropharyngeal examination, it is important to document the presence of enanthems; these may be seen in many infectious processes, such as stomatitis caused by herpes or enteroviruses. This portion of the examination is also important in documenting inflammation or exudates on the tonsils, which may indicate viral or bacterial infection. Findings such as trismus or unilateral tonsillar swelling are concerning for peritonsillar abscess and for infections in the parapharyngeal and retropharyngeal spaces; such cases should be referred for specialist ear, nose, and throat evaluation and potential imaging of the neck.

Repeating portions of the assessment may be indicated. If the child cried continuously during the initial clinical evaluation, the examiner may not be certain whether the crying was caused by the high fever, stranger anxiety, or pain or is indicative of a serious or localizing illness. Constant crying also makes portions of the physical examination, such as auscultation of the chest, more difficult. Before a repeat assessment is performed, efforts to make the child as comfortable as possible are indicated. In young infants, **persistent irritability**, even when the examiner is absent from the room, is concerning for meningitis, encephalitis, or other causes of meningeal irritation (e.g., intracranial injury from nonaccidental trauma). When faced with a truly inconsolable infant, practitioners should have a low threshold to obtain head imaging and/or perform lumbar puncture, as the clinical scenario dictates.

MANAGEMENT

Most patients who present to the pediatrician's office with an acute illness will not require acute stabilization. However, the pediatrician needs to be prepared to evaluate and begin resuscitation for the seriously ill or unstable child. Outpatient pediatric offices and urgent care facilities should be stocked with appropriate equipment necessary to stabilize an acutely ill child. Maintenance of that equipment and ongoing training of the office staff in its use are required, and every effort should be made to ensure that pediatric clinicians are PALS certified (see Chapter 79).

The evaluation of the potentially unstable child must begin with assessment of the ABCs—airway, breathing, and circulation. When assessing the **airway**, chest rise should be evaluated and evidence of increased work of breathing sought. The examiner should ensure that the trachea is midline and should listen carefully for evidence of air exchange at the level of the extrathoracic airway. If the airway is patent and no signs of obstruction are present, the patient is allowed to assume a position of comfort. If the child shows signs of airway obstruction, repositioning of the head with the chin-lift maneuver may alleviate the obstruction. An oral or nasal airway may be necessary in patients in whom airway patency cannot be maintained. These devices are not well tolerated in conscious patients because they may induce gagging or vomiting; instead, they are most often used to facilitate effective bag-valve-mask ventilation in semiconscious or unconscious children. Once airway patency has been established, the adequacy of **breathing** should be evaluated. Slow respiratory rates or cyanosis may signal impending respiratory failure. If the airway is patent but the child's respiratory effort is inadequate, positive pressure ventilation via bag-valve-mask support should be initiated. Oxygen should be administered to all seriously ill or hypoxic children via nasal cannula or face mask. Auscultation of the lung fields should assess for air entry, symmetry of breath sounds, and presence of adventitious breath sounds such as crackles or wheezes. Bronchodilator therapy can be initiated to alleviate bronchospasm. Racemic epinephrine is indicated for stridor at rest in a patient with upper airway obstruction (e.g., croup). Once airway and breathing have been addressed, **circulation** must be evaluated. Symptoms of *shock* include tachycardia, cool extremities, delayed capillary refill time, mottled or pale skin, and effortless tachypnea. In children, hypotension is a late finding in shock and indicates that significant decompensation has already taken place. Vascular access is necessary for volume resuscitation in patients with impaired circulation, and an intraosseous line should be considered early if there is any difficulty in obtaining vascular access for a patient requiring resuscitation. Each time an intervention is performed, the clinician should **reassess the patient** to determine whether interventions have been successful and whether additional care is needed.

DISPOSITION

Most children evaluated for acute illness in the office or urgent care setting can be managed on an **outpatient** basis. These patients should have a reassuring physical examination, stable vital signs, and an adequate follow-up plan before being sent home. A mildly dehydrated

patient can be discharged home for a trial of oral rehydration. Patients with respiratory illness who exhibit signs of mild respiratory distress may be monitored at home, with a repeat examination scheduled the next day. Depending on the child's condition, the comfort of the parents, and the relationship of the family with the physician, telephone follow-up may be all that is necessary. When no specific diagnosis has been established at the first outpatient visit, a follow-up examination may yield the diagnosis and can provide reassurance for both the caregiver and the practitioner that a child's severity of illness has not progressed.

However, if it is deemed that the child needs a higher level of care, it is the pediatrician's responsibility to decide what method of transfer is appropriate. Physicians may be reluctant to call for help because of a misperception that emergency 911 services should be activated only for ongoing resuscitation. Emergency medical services (EMS) transport should be initiated for any child who is physiologically unstable (e.g., with severe respiratory distress, hypoxia, signs of shock, or altered mental state). If the family's ability to adhere promptly to a recommendation for ED evaluation is in question, this patient also should be transported by EMS. Some physicians and families may defer calling EMS because of the perception that a parent can reach the hospital faster by private motor vehicle. Although rapidity of transport should be considered, the need for further interventions during transport and the risk of clinical decompensation are other important factors in the decision to activate EMS. Ultimately, the legal responsibility for choosing an appropriate level of transport for a patient lies with the referring physician until responsibility of care is officially transferred to another medical provider.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 79

Pediatric Cardiorespiratory Emergencies and Resuscitation

Ryan W. Morgan and Alexis A. Topjian

Children in the community and those in the hospital are at risk for a variety of injuries and life-threatening disease processes that lead to cardiac or respiratory compromise, which require prompt evaluation and intervention.

ASSESSMENT AND EVALUATION OF CHILDREN WITH CARDIORESPIRATORY EMERGENCIES

The first response to a pediatric emergency of any cause is a rapid and systematic **general assessment** of the scene and the child to identify immediate threats to the child, care providers, and others. If an emergency is identified, the emergency response system (emergency medical services [EMS]) should be activated immediately. Care providers should then proceed through **primary**, **secondary**, and **tertiary** assessments as allowed by the child's condition, safety of the scene, and resources available. This standardized approach organizes what might otherwise be a confusing or chaotic situation and ensures that key elements of assessment and treatment are not omitted. If at any point during these assessments the provider identifies a life-threatening problem, progression through the systematic assessment is paused and targeted lifesaving interventions are prioritized. Further assessments and interventions should be delayed until other providers arrive to assist or until the life-threatening condition is successfully treated or stabilized.

General Assessment

Upon arrival at the scene of a critically ill or injured child or upon the child's presentation for medical care, a provider's first task is a quick survey of the scene itself. Is the rescuer or child in imminent danger because of circumstances at the scene (e.g., fire, high-voltage electricity)? If so, can the child be safely extricated to a safe location for assessment and treatment? Can the child be safely moved with the appropriate precautions (e.g., cervical spine protection) if indicated? A rescuer is expected to proceed only if these important safety conditions have been met so that they do not jeopardize their own safety.

Once the provider's and child's safety have been ensured, the provider performs a rapid **visual survey** of the child, assessing the child's **general appearance** and **cardiopulmonary function**. This action should only take a few seconds and includes assessment of (1) general appearance, determining color, tone, alertness, and responsiveness; (2) adequacy of breathing, distinguishing between normal, comfortable respirations versus respiratory distress or apnea; and (3) adequacy of circulation, identifying cyanosis, pallor, or mottling. If a child is found unresponsive or becomes unresponsive during the provider's assessment, the provider should stimulate the patient and assess the patient's response to voice. If there is no response, the provider should assess for breathing. If the child is breathing but ineffectively, rescue breathing should be started. If the child is not breathing or has agonal respirations, the provider should initiate cardiopulmonary resuscitation (CPR) and follow Basic Life Support (BLS) pediatric cardiac arrest algorithms for one rescuer or two or more rescuers (Figs. 79.1 and 79.2).

Primary Assessment

Once the emergency response system has been activated and the child is determined not to require CPR, the provider should proceed with a primary assessment that includes a brief, hands-on evaluation of cardiopulmonary and neurologic function. This assessment includes a limited physical examination, evaluation of vital signs, and measurement of pulse oximetry if available. The American Heart Association (AHA), in its Pediatric Advanced Life Support (PALS) curriculum, supports the structured format of **airway, breathing, circulation, disability, exposure (ABCDE)**. *The goal of the primary assessment is to obtain a focused, systems-based assessment of the child's injuries or abnormalities so that resuscitative efforts can be rapidly targeted to these areas;* if the provider identifies a life-threatening abnormality, further evaluation is postponed until appropriate corrective action has been taken.

The exam and vital sign data can be interpreted only if the provider has a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Table 79.1). These ranges can be difficult to remember, especially if used infrequently, and providers should therefore maintain ready access to these normal ranges. Hypotension is defined as blood pressure less than the fifth percentile for age. This is considered a systolic blood pressure of <60 mm Hg for neonates up to 28 days, <70 mm Hg for infants from 1 month to 1 year, <70+ (age in years ×2) mm Hg for children 1-10 years, and <90 mm Hg for children older than 10 years of age.

Airway and Breathing

The most common precipitating event for cardiac instability in infants and children is respiratory failure (the inability to adequately oxygenate or ventilate). Therefore *rapid assessment for respiratory failure and immediate restoration of adequate ventilation and oxygenation remain the first priorities in the resuscitation of a child.* Using a systematic approach, the provider should first assess whether the child's airway is patent and maintainable. A **patent** airway is unobstructed, allowing normal respiration without noise or effort. A **maintainable** airway is one that is either already patent or can be made patent with a simple maneuver. To assess airway patency, the provider should look for breathing movements in the child's chest and abdomen, listen for breath sounds, and feel for the movement of air at the child's mouth and nose. Abnormal breathing sounds (e.g., snoring or stridor), increased work of breathing,

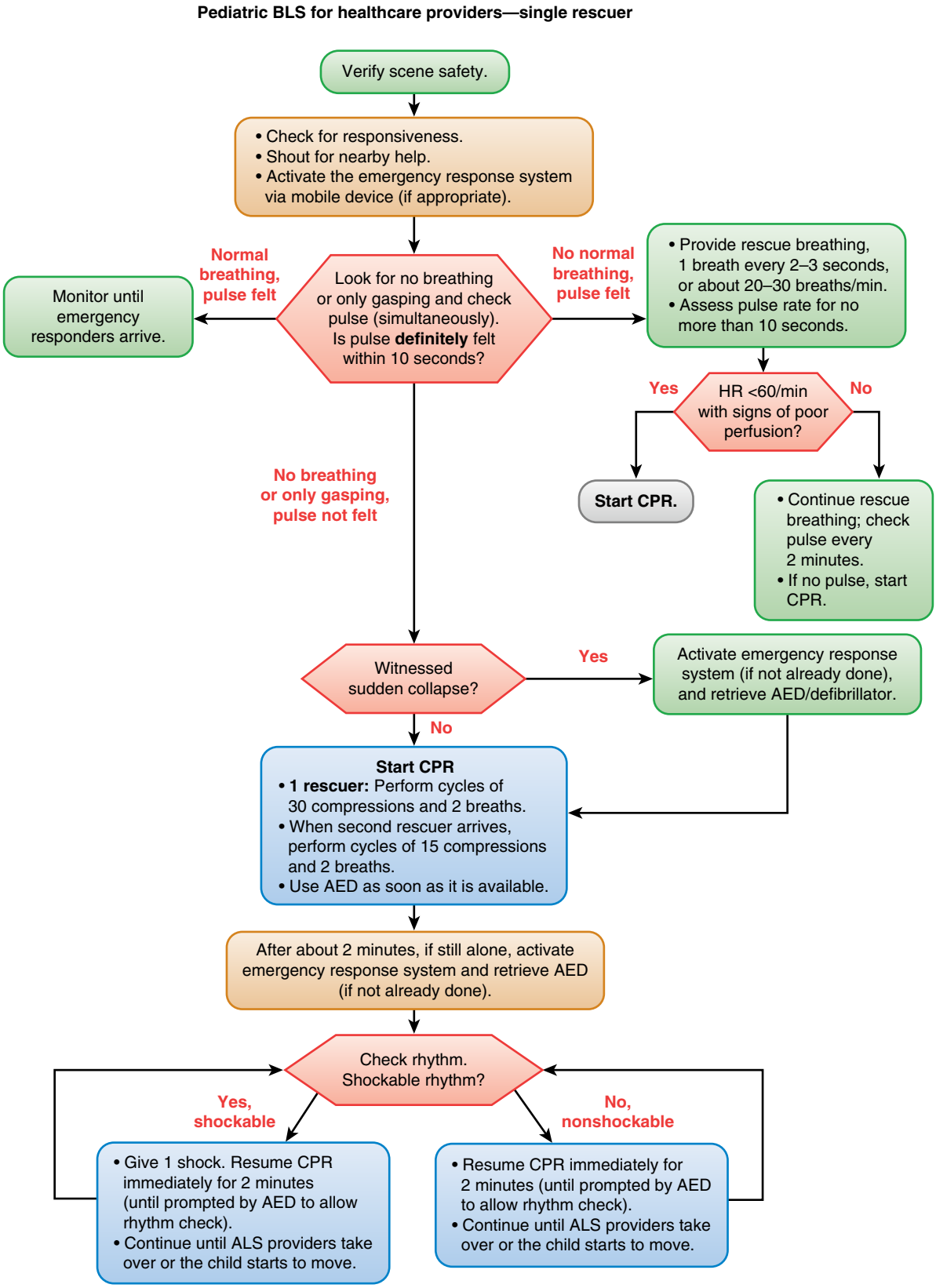

Fig. 79.1 Basic Life Support (BLS) algorithm for healthcare providers: Pediatric cardiac arrest algorithm for the single rescuer—2020 update. AED, Automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. (*From Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142[16 Suppl 2]:S469-S523.*)

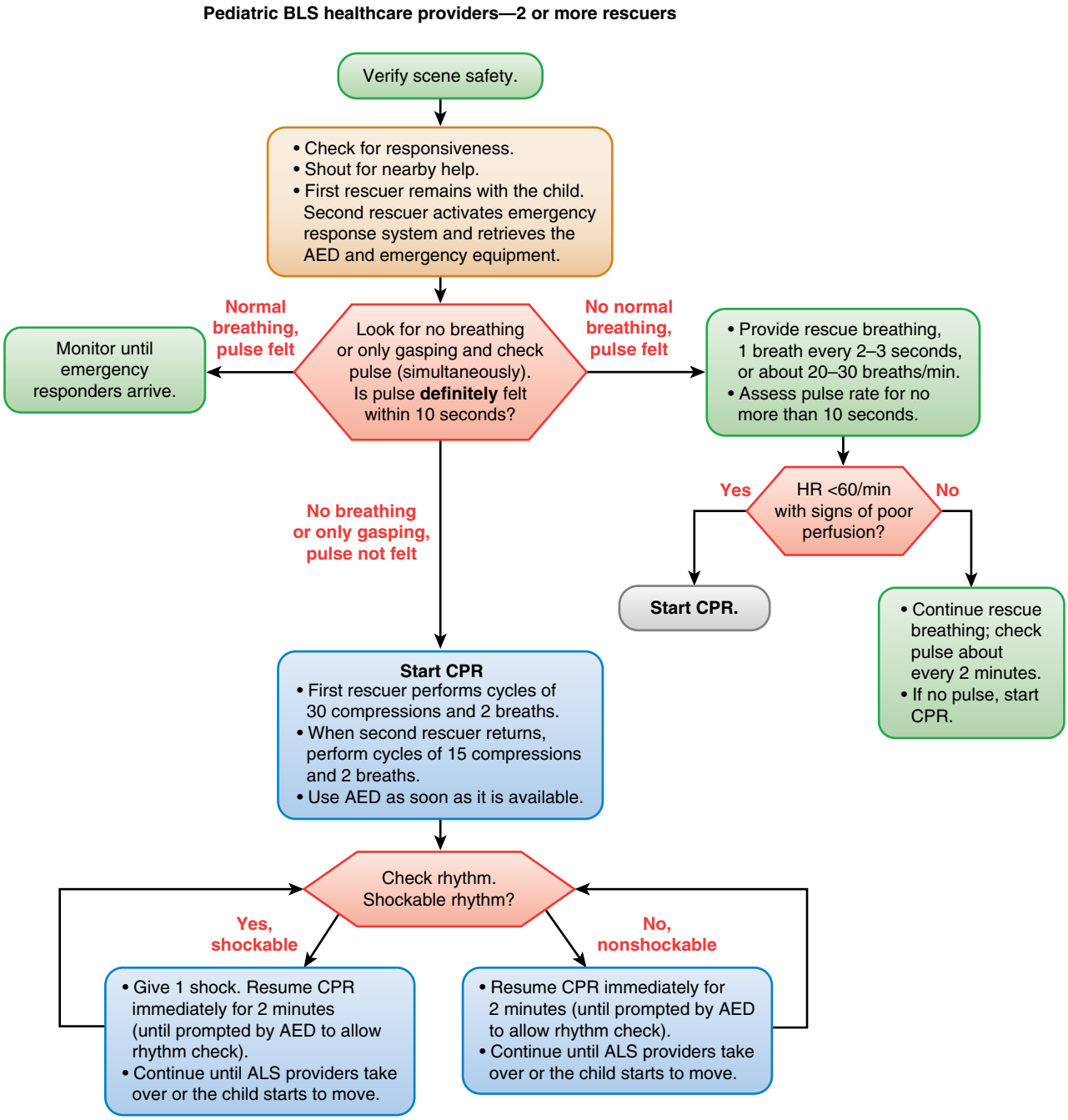

Fig. 79.2 Basic Life Support (BLS) algorithm for healthcare providers: Pediatric cardiac arrest algorithm for two or more rescuers—2020 update. AED, Automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. (*From Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142[16 Suppl 2]:S469-S523.*)

and apnea are all findings potentially consistent with airway obstruction. If there is evidence of obstruction, the provider should start with repositioning and "head-tilt, chin-lift" if neck injury is not suspected or a jaw thrust if neck injury is a concern (Fig. 79.3). Suctioning of the airway or placement of adjunct airway devices such as a nasopharyngeal airway should be considered based on the exam findings and the likely etiologies of airway obstruction. Maneuvers to relieve the obstruction should be instituted before the provider proceeds to evaluate the child's breathing.

Assessment of breathing includes evaluation of the child's respiratory rate, respiratory effort, breath sounds, and peripheral oxygen saturation via pulse oximetry. Normal breathing appears comfortable, is quiet, and occurs at an age-appropriate rate. Abnormal respiratory rates include apnea and rates that are either abnormally slow (bradypnea) or fast (tachypnea). *Bradypnea and irregular respiratory patterns (such as gasping or agonal respirations) require urgent attention because they are often signs of impending respiratory failure, apnea, or cardiorespiratory arrest.* Signs of increased respiratory effort include nasal flaring, grunting, chest or neck muscle retractions, head bobbing, and seesaw respirations. Hypoxemia, measured by pulse oximetry, often accompanies parenchymal lung disease, apnea, or airway obstruction. However, providers should keep in mind that adequate perfusion is required to produce a reliable peripheral oxygen saturation measurement. Central cyanosis is a sign of severe hypoxemia and indicates an emergent need for oxygen supplementation and respiratory support.

Table 79.1 Normal Vital Signs According to Age

AGE	HEART RATE (beats/min)	BLOOD PRESSURE† (mm Hg)	RESPIRATORY RATE+ (breaths/min)
Premature	120-205*	60-76/31-45	40-70
Neonate	100-205*	67-84/35-53	35-55
Infant	100-180	72-104/37-56	30-53
Toddler	98-140	86-106/42-63	22-37
Preschooler	80-120	89-112/46-72	20-29
School-age child	75-118	97-120/57-80	18-25
Adolescent	60-100	110-131/64-83	12-20

*In sleep, heart rates may be significantly lower, but if perfusion is maintained, no intervention is required.
†A blood pressure cuff should cover approximately two-thirds of the arm; too small a cuff yields spuriously high pressure readings, and too large a cuff yields spuriously low pressure readings. Values are systolic/diastolic and assume 50th percentile for height for children 1 year and older.
+The respiratory rate is expected to increase in the presence of fever and stress.
‡Approximately equal to postconception age in weeks (may add 5 mm Hg).
Modified from Hazinski MF. Children are different. In Hazinski MF, ed. *Nursing Care of the Critically Ill Child,* 3rd ed. Philadelphia: Mosby; 2013:1-18.

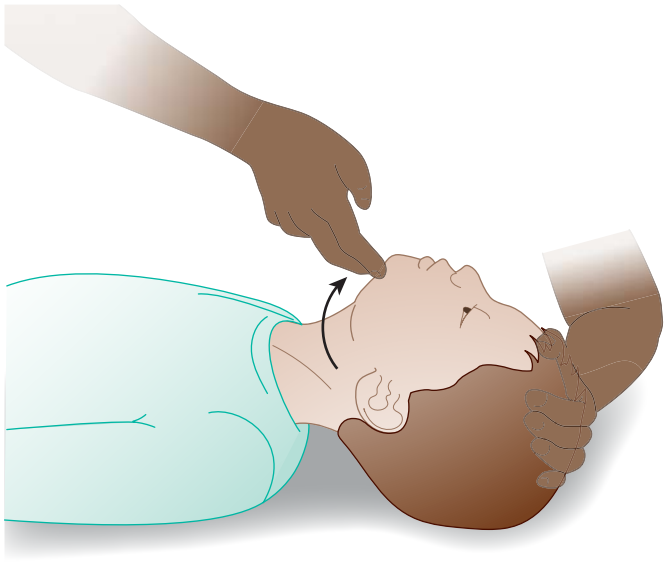

Fig. 79.3 Opening the airway with the head-tilt/chin-lift maneuver. One hand is used to tilt the head, extending the neck. The index finger of the rescuer's other hand lifts the mandible outward by lifting the chin.

Table 79.2 AVPU Neurologic Assessment

A	The child is awake, alert, and appropriately responsive to caregivers and stimuli.
V	The child responds only to voice such as calling the child's name or speaking loudly.
P	The child responds only to painful stimuli, such as sternal rub or pinching the trapezius.
U	The child is unresponsive to all stimuli.

A, Alert; V, verbal; P, pain; U, unresponsive.
From Ralston M, Hazinski MF, Zaritsky AL, et al., eds. *Pediatric Advanced Life Support Course Guide and PALS Provider Manual*. Dallas: American Heart Association; 2007.

Table 79.3 Modified Pediatric Glasgow Coma Scale

≥2 YEARS		<2 YEARS	
EYE OPENING			
Spontaneous	4	Spontaneous	4
To sound	3	To sound	3
To pressure	2	To pressure	2
None	1	None	1
VERBAL RESPONSE			
Oriented; words/phrases normal for chronological age	5	Babbles, coos; words/phrases normal for chronological age	5
Confused; some words/phrases not normal for chronological age	4	Some words/phrases not normal for chronological age	4
Words	3	Inconsolable crying	3
Sounds	2	Sounds	2
None	1	None	1
MOTOR RESPONSE			
Obeys commands	6	Normal spontaneous movement	6
Localizes pain	5	Rapidly withdraws extremity to stimulation	5
Normal flexion	4	Normal flexion	4
Abnormal flexion	3	Abnormal flexion	3
Extension	2	Extension	2
None	1	None	1

Adapted from Kirschen MP, Snyder M, Smith K, et al. Inter-rater reliability between critical care nurses performing a pediatric modification to the Glasgow Coma Scale. *Pediatr Crit Care Med.* 2019;20(7):660-666.

Circulation

Cardiovascular function is assessed by evaluation of skin color and temperature, heart rate, heart rhythm, presence and quality of pulses, capillary refill time, and blood pressure. In nonhospital settings, much of this important information can be obtained without measuring the blood pressure; lack of blood pressure data should not prevent the provider from determining adequacy of circulation or implementing lifesaving support. Mottling, pallor, delayed capillary refill, cyanosis, weak pulses, and cool extremities are all signs of diminished perfusion and compromised cardiac output. **Tachycardia** is the earliest and most common sign of shock but lacks both sensitivity and specificity and should be correlated with other components of the exam, such as weakness, threadiness, or absence of pulses. An age-specific approach to heart rate assessment will yield the most reliable interpretation. **Bradycardia** can be normal in athletic children but should be assessed in the context of the child's perfusion, blood pressure, mental status, and oxygen saturation, as it can be a sign of impending cardiac arrest.

Disability

In the setting of a pediatric emergency, *disability* refers to a child's neurologic function in terms of the level of consciousness and cortical function. Standard evaluation of a child's neurologic condition can be done quickly with an assessment of pupillary response to light (if one is available) and use of either of the standard scores used in children: the Alert, Verbal, Pain, Unresponsive (AVPU) Pediatric Response Scale and the Glasgow Coma Scale (GCS) (Tables 79.2 and 79.3). The

Table 79.4 Pupillary Responses

DILATED (MYDRIASIS)	PINPOINT (MIOSIS)
Bilateral Anticholinergic agents (systemic, topical) Sympathomimetic agents Serotonin syndrome Botulism Brain death (fixed, nonreactive usually midposition)	Bilateral Opiates Organophosphates Barbiturates Pontine lesions
Unilateral Third nerve compression with uncal herniation	Unilateral Horner syndrome

causes of decreased level of consciousness in children are numerous and include conditions as diverse as respiratory failure with hypoxia or hypercarbia, hypoglycemia, poisonings or drug overdose, trauma, seizures, infection, and shock. *Most often, an acutely ill or injured child has an altered level of consciousness because of respiratory compromise, circulatory compromise, or both.* Any child with a depressed level of consciousness should be immediately assessed for abnormalities in cardiorespiratory status.

Alert, Verbal, Pain, Unresponsive (AVPU) Pediatric Response Scale: The AVPU scoring system is used to determine a child's level of consciousness and cerebral cortex function (see Table 79.2). Unlike the GCS, the AVPU scale is not developmentally dependent—a child does not have to understand spoken language or follow commands, merely respond to a stimulus. The child is scored according to the amount of stimulus required to obtain a response, from *alert* (no stimulus; the child is already awake and interactive) to *unresponsive* (child does not respond to any stimulus).

Glasgow Coma Scale (GCS): Although it has not been systematically validated as a prognostic scoring system for infants and young children, the GCS is frequently employed to describe level of consciousness and neurologic status. It has value as a way to communicate mental status to other providers and when used serially to detect improvement or deterioration. The GCS has three components: eyes, verbal, and motor. Individual scores for eye opening, verbal response, and motor response are added together, with a maximum of 15 points (see Table 79.3). There are numerous versions of the pediatric GCS, but most importantly, the pediatric GCS accounts for differences in development and the inability for children <2 years of age to follow commands and talk. Patients who have severe head injury with a GCS score ≤8 require aggressive management, generally including securement of the airway with endotracheal intubation and breathing with mechanical ventilation and, if indicated, placement of an intracranial pressure monitoring device.

The Full Outline of Unresponsiveness (FOUR) score is a neurologic assessment that incorporates brainstem reflex components and is associated with outcomes; it is commonly used in the intensive care unit setting (Table 82.1).

The pupillary response can give insight to causes of altered mental status. Pinpoint pupils can be due to many conditions, including narcotic ingestion, and dilated *asymmetric* pupils (anisocoria) can be caused by uncal herniation (Table 79.4 and Fig. 79.4). If a patient has a normal mental status, other causes of pupillary dilation and asymmetry should be considered.

Lesion/process associated with coma	Pupils	Comment
Metabolic		Normal
Bilateral hypothalamic		Small but reactive
Uncal herniation		Ipsilateral "blown," unreactive pupil, ptosis
Tectal		Midposition and unreactive to light
Midbrain		Dilated and unreactive
Pontine		Pinpoint but reactive
Brain death		Midposition to large, unreactive

Fig. 79.4 Pupils in comatose patients. (*From Balcer LJ: Pupillary disorders. In Liu G, Volpe L, Galetta S (eds): Liu, Volpe, and Galetta's Neuro-Ophthalmology: Diagnosis and Management, 3rd ed. Philadelphia: Elsevier, 2018. Fig 13.32.*)

Exposure

Exposure is the final component of the pediatric primary assessment. This component of the exam is reached only after the child's airway, breathing, circulation, and disability have been assessed and reasonably stabilized. In this setting, *exposure* stands for the dual responsibility of the provider both to expose the child to assess for previously unidentified injures and to consider prolonged exposure in a cold environment as a possible cause of hypothermia and cardiopulmonary instability. The provider should undress the child (as is feasible and reasonable) to perform a physical exam, assessing for burns, bruising, bleeding, joint laxity, and fractures. If possible, the provider should assess the child's temperature. All maneuvers should be performed with careful maintenance of cervical spine precautions when indicated.

Secondary and Tertiary Assessment

Secondary Assessment

For healthcare providers in community or outpatient settings, transfer of care of a child to emergency or hospital personnel may occur before a full secondary assessment is possible. However, before the child is removed from the scene and separated from witnesses or family, a brief history should be obtained for medical providers at the accepting facility. The components of a secondary assessment include a **focused history** and **focused physical examination**.

The history should be targeted to information that could explain cardiorespiratory or neurologic dysfunction and should take the form of a **SAMPLE history**: signs/symptoms; allergies; medications; past medical history; timing of last meal; and events leading to this situation. Medical personnel not engaged in resuscitative efforts can be dispatched to elicit history from witnesses or relatives. The physical examination during the secondary assessment is a thorough head-to-toe exam, although the severity of the child's illness or injury could necessitate curtailing portions of the exam or postponing nonessential elements until a later time.

Tertiary Assessment

The tertiary assessment occurs in a hospital setting, where ancillary laboratory and radiographic assessments contribute to a thorough understanding of the child's condition. A basic blood chemistry profile, complete blood count, liver function tests, coagulation studies, and arterial blood gas analyses provide estimates of renal function, acid-base balance, cardiorespiratory function, and presence or absence of shock. Chest radiographs can be useful to evaluate both the heart and

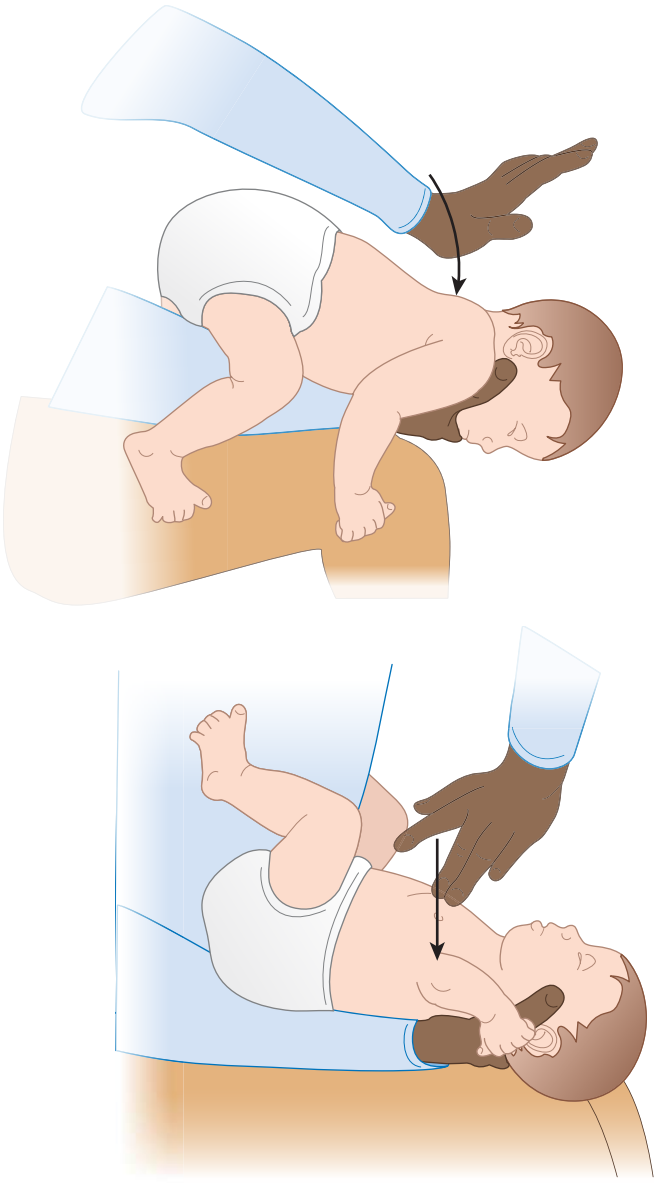

Fig. 79.5 Back blows *(top)* and chest thrusts *(bottom)* to relieve foreign body airway obstruction in the infant.



Fig. 79.6 Abdominal thrusts with the conscious victim standing or sitting.

lungs, although more detailed assessment of cardiac function can be performed with echocardiography.

RECOGNITION AND TREATMENT OF RESPIRATORY DISTRESS AND FAILURE

The goals of initial management of respiratory distress or failure are to rapidly stabilize the child's airway and breathing and to identify the cause of the problem so that further therapeutic efforts can be appropriately directed.

Airway Obstruction Due to Foreign Body

Children under 5 years of age are particularly susceptible to foreign body aspiration and choking. Liquids are the most common cause of choking in infants, whereas small objects and food (e.g., grapes, nuts, hot dogs, candy) are the most common source of foreign bodies in the airways of toddlers and older children. A history consistent with foreign body aspiration is considered diagnostic. Any child in the proper setting with the sudden onset of choking, stridor, or wheezing should be considered to have a foreign body aspiration until proven otherwise. Unfortunately, this classic history is not always present in all cases of foreign body aspiration.

Airway obstruction is treated with a sequential approach starting with the head-tilt/chin-lift maneuver to open and support the airway, followed by inspection for a foreign body, and finger-sweep clearance or suctioning if one is visualized. *Blind suctioning or finger sweeps of the mouth are not recommended.* A conscious child suspected of having a partial foreign body obstruction should be permitted to cough spontaneously until coughing is no longer effective, respiratory distress and stridor increase, or the child becomes unconscious. They can be allowed to find a comfortable position to facilitate air entry.

For *conscious infants,* providers should administer five back blows and then five chest thrusts (Fig. 79.5). After each cycle of back blows and chest thrusts, the child's mouth should be visually inspected for the presence of the foreign body. If identified within finger's reach, it should be removed with a gentle finger sweep. If no foreign body is visualized and the child is conscious, repeat back blows and chest thrusts. Do not blindly sweep for objects if they are not visible, as this can push the object farther into the airway.

For *conscious children* older than 1 year, providers should give a series of five abdominal thrusts **(Heimlich maneuver)** with the child standing or sitting (Fig. 79.6). After the abdominal thrusts, the airway is examined for a foreign body, which should be removed if visualized. If no foreign body is seen, abdominal thrusts should be repeated. For both infants and children, the sequence is repeated until the object is expelled or the patient loses consciousness, at which time CPR with ventilations should be initiated.

If the child becomes *unconscious,* the child should be gently placed on the ground in a supine position and ventilations should be initiated; compressions should also be started if the child is pulseless. The airway should be inspected for a foreign body at the time of ventilations.

Airway Obstruction or Narrowing from Other Causes

Airway obstruction can also be caused by airway narrowing in both the upper and lower airways. Upper airway obstruction refers to narrowing of the extrathoracic portion of the airway, including the oropharynx, larynx, epiglottitis, and trachea. In the upper airways, narrowing is most often caused by airway edema (e.g., croup or anaphylaxis) or epiglottic edema (e.g., epiglottitis) and often manifests with stridor. Stridor, in cases of extrathoracic airway obstruction, is a high-pitched sound heard on inspiration. When airway obstruction is intrathoracic, stridor can be biphasic, heard during both inspiration and expiration. Lower airway obstruction affects all intrathoracic airways, notably the bronchi and bronchioles. **Bronchiolitis** and acute **asthma** exacerbations are the major causes of intrathoracic airway obstruction in children, causing lower airway narrowing through a combination of airway swelling, mucus production, and circumferential smooth muscle constriction of smaller airways.

The approach to upper airway obstruction is dictated by both the underlying condition and the clinical severity of the problem. In cases of mild upper airway obstruction, the child has minimally increased work of breathing (evidenced by tachypnea and absent to mild retractions). Stridor, if present at all, should be audible with only coughing or activity. Children with these findings can often be supported with supplemental oxygen as needed. In cases with moderate obstruction, in which the child has more significant work of breathing or more pronounced stridor, nebulized **racemic epinephrine** and oral or intravenous (IV) **dexamethasone** can be added, particularly for **croup** (i.e., laryngotracheobronchitis) (see Chapter 434). **Heliox** (combined helium-oxygen therapy) administration may also be considered. Children with severe upper airway obstruction have marked intercostal retractions, prominent stridor, and decreased air entry on auscultation of the lung fields. They can also be hypoxemic, dyspneic, and either agitated or somnolent. A child in severe distress that does not rapidly respond to therapies may require endotracheal intubation to overcome the area of obstruction. Clinicians need to carefully observe patients, as impending respiratory failure may be initially confused with improvement. Stridor becomes quieter and retractions less prominent when a child's respiratory effort begins to diminish. This can either be the result of improvement or progressive respiratory failure with less air entry. The child in respiratory failure may have poor air movement on auscultation and decreased level of consciousness from hypercarbia, hypoxia, or both. When **anaphylaxis** is suspected as the cause for upper airway edema, providers should administer an intramuscular dose of epinephrine as needed (see Chapter 190). Racemic epinephrine can also help decrease localized airway edema. **Epiglottitis** often presents with a muffled voice, drooling, and difficulty swallowing. Epiglottitis is a medical emergency for which the initial focus should be on alerting otolaryngology and/or anesthesiology experts to be immediately present while keeping the patient calm. These patients usually need to have their airway secured in an operating room with contingency planning for emergency surgical airway placement. No matter the cause, any child with upper airway obstruction and impending respiratory failure should be prepared to undergo endotracheal intubation and respiratory support. Prompt notification of providers trained in advanced airway management is essential.

In cases of lower airway obstruction, therapies are targeted to both relieve the obstruction and reduce the child's work of breathing. For asthma, **inhaled bronchodilators**, such as albuterol, augmented by oral or IV **corticosteroids**, remain the mainstay of therapy in mild to moderate acute distress. Children with more significant obstruction appear dyspneic, with tachypnea, retractions, forced expiration, and audible wheezing or reduced breath sounds. In these cases, the addition of an anticholinergic agent, such as nebulized ipratropium bromide, or a smooth muscle relaxant, such as magnesium sulfate, may provide further relief, although the evidence for these measures remains controversial (see Chapter 185). Supplemental oxygen and IV fluid hydration can be useful adjuncts. Infants and young children with bronchiolitis often present with tachypnea. Patients with moderate to severe disease may have retractions, nasal flaring, or grunting and can be hypoxemic. These patients often do not respond to bronchodilators. Supportive care with chest physiotherapy to support mucous clearance and noninvasive positive pressure ventilation support can be used as these patients recover from this lower airway viral disease process.



Fig. 79.7 Rescue breathing in an infant. The rescuer's mouth covers the infant's nose and mouth, creating a seal. One hand performs the head-tilt while the other hand lifts the infant's jaw.

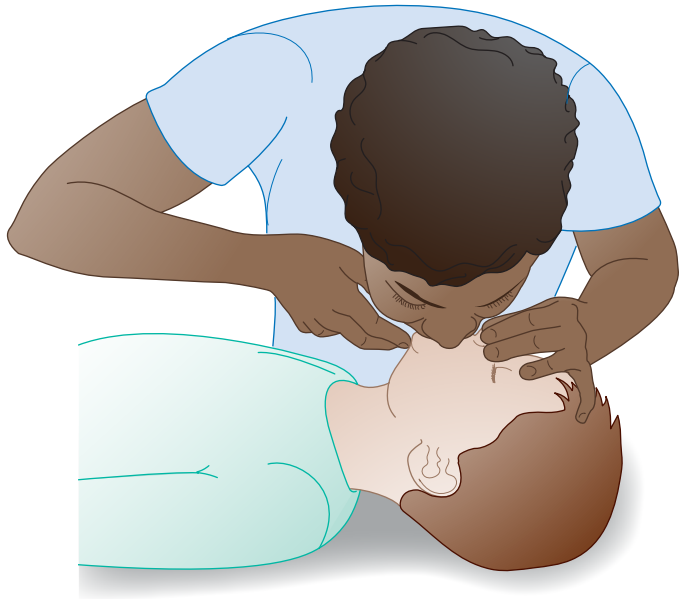

Fig. 79.8 Rescue breathing in a child. The rescuer's mouth covers the child's mouth, creating a mouth-to-mouth seal. One hand maintains the head-tilt; the thumb and forefinger of the same hand are used to pinch the child's nose. The other hand lifts the child's jaw.

Impending respiratory failure in children with lower airway obstruction can be insidious. When diagnosed early in a school-age child who is cooperative, respiratory failure can potentially be averted through judicious use of noninvasive support, including heated, high-flow nasal cannula (HFNC) therapy, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP). Endotracheal intubation should be performed only by skilled providers, preferably in a hospital setting, because there is a high risk of cardiorespiratory compromise in patients with lower airway obstruction during the procedure.

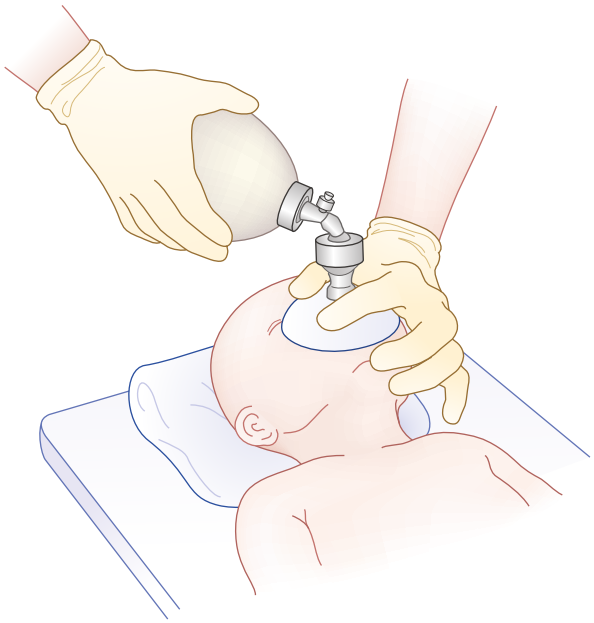

Fig. 79.9 "C-E" grip to secure a mask to a child's face with appropriate seal.

Parenchymal Lung Disease

Parenchymal lung disease includes a heterogeneous list of conditions, such as pneumonia, pediatric acute respiratory distress syndrome (PARDS), pneumonitis, bronchiolitis, bronchopulmonary dysplasia, cystic fibrosis, and pulmonary edema. The commonalities of these conditions are their effects on the small airways and alveoli, including inflammation and exudation leading to consolidation of lung tissue, decreased gas exchange, and increased work of breathing. Clinical management of these conditions includes specific treatment as indicated (e.g., antibiotics for bacterial pneumonia) and supportive care with oxygen, noninvasive respiratory support (e.g., HFNC, CPAP, or BiPAP), or invasive mechanical ventilation. The severity of work of breathing and degree of oxygenation or ventilation failure determine the degree of respiratory support needed and should be expected to evolve with time.

Airway and Breathing Management

Rescue Breathing

If a child is unconscious and not breathing effectively or apneic, **rescue breathing** should be provided. The provider should open the airway with the head-tilt/chin-lift maneuver and attempt mouth-to-mouth ventilation (Figs. 79.7 and 79.8). In trauma patients with suspected cervical spine injuries, a jaw thrust should be performed without the head-tilt maneuver. If ventilation is unsuccessful, the airway is repositioned, and ventilation should be attempted again.

Bag-Mask Ventilation

Ventilation with a bag-mask apparatus can be as effective as endotracheal intubation and safer when the provider is inexperienced with intubation. Bag-mask ventilation (BMV) requires training to ensure that the provider is competent to select the correct mask size, open the child's airway, form a tight seal between the mask and the child's face, deliver effective ventilation, and assess the effectiveness of ventilations. An appropriately sized mask is one that fits over the child's mouth and nose but does not extend below the chin or over the eyes. An adequate seal is best achieved through a combination "C-E" grip on the mask, in which the thumb and index finger form the letter "C" on top of the mask, holding the mask onto the child's face, and the remaining three fingers form an "E" grip under the child's mandible, holding the jaw forward without pressing on the soft tissues and extending the head up toward the mask. Using this method, the care provider can secure the mask to the child's face with one hand and use the other hand to compress the ventilation bag (Fig. 79.9).

The provider may have to move the head and neck through a range of positions to find the one that best maintains airway patency with adequate chest rise. In infants and young children, optimal ventilation is often provided when the child's head is in the neutral sniffing position without hyperextension of the head. Poor chest rise or persistent hypoxemia indicate inadequate ventilation. In this setting, the care provider should recheck the mask's seal on the child's face, reposition the child's head, and consider suctioning the airway. If these maneuvers do not restore ventilation, the provider should consider placement of a nasopharyngeal or oral airway. The inability to ventilate a patient with positive pressure after the previous measures is an emergency requiring expert consultation while preparing for endotracheal intubation.

Endotracheal Intubation

A child generally requires intubation when at least one of these conditions exists: (1) the child is unable to maintain airway patency or protect against aspiration (as occurs in settings of neurologic compromise such as seizures or traumatic brain injury); (2) the child is failing to maintain adequate oxygenation despite supplemental oxygen or noninvasive therapies; (3) the child cannot be adequately ventilated with evidence of elevated blood carbon dioxide levels and an unsafe acid-base balance; (4) sedation and/or paralysis is required for a procedure; (5) the need to decrease metabolic demand by sedating the patient to support extrapulmonary organs (e.g., septic shock or heart failure) is present; and (6) providers anticipate a deteriorating course that will eventually lead to any of the first five conditions. It should be noted that in centers experienced in noninvasive respiratory support, a trial of HFNC, CPAP, or BiPAP may be indicated based on the specific clinical scenario.

There are few *absolute contraindications* to tracheal intubation, but experts generally agree that in settings of known complete airway obstruction (e.g., severe subglottic stenosis), endotracheal intubation should be avoided, and emergency cricothyroidotomy or tracheostomy performed instead. It is important to assess a patient's airway before initiating endotracheal intubation. Any history of a difficult airway (difficult to intubate) or critical airway (unable to bag-mask ventilate) should prompt further investigation and expert consultation. Both history and physical exam features such as limited mouth opening, limited neck mobility, or micrognathia should raise concern for further assessment. Another important consideration is to ensure that providers maintain appropriate cervical spine (C-spine) protection during the intubation procedure when neck or spinal cord injury is suspected.

A critical phase of the intubation procedure is the preprocedural preparation, when the provider ensures all the equipment and staff needed for safe intubation are present and functioning. An easy pneumonic for this is **SOAP MM**: *suction* (Yankauer suction catheter attached to wall suction); *oxygen* (both preoxygenation of the patient and devices needed to deliver oxygen, such as a bag-mask); *airway* (appropriately sized endotracheal tube and laryngoscope as well as adjunct airway devices); *people* (all those needed during and immediately after the procedure, including respiratory therapists and nurses); *monitor* (pulse oximetry, ECG, blood pressure, capnography); and *medications* (sedation and often neuromuscular blockade to facilitate intubation). A simple formula for selecting the appropriately sized endotracheal tube (ETT) is:

$$\text{Uncuffed ETT size (in mm)} = \left(\frac{\text{age in years}}{4}\right) + 4$$

Cuffed ETTs should generally be 0.5 mm smaller. Providers should always have a range of ETTs available, given the heterogeneity of patients and airway size. The use of cuffed ETTs is recommended in most pediatric populations, as it may decrease the need for ETT changes caused by difficulty ventilating and may decrease the risk of aspiration.

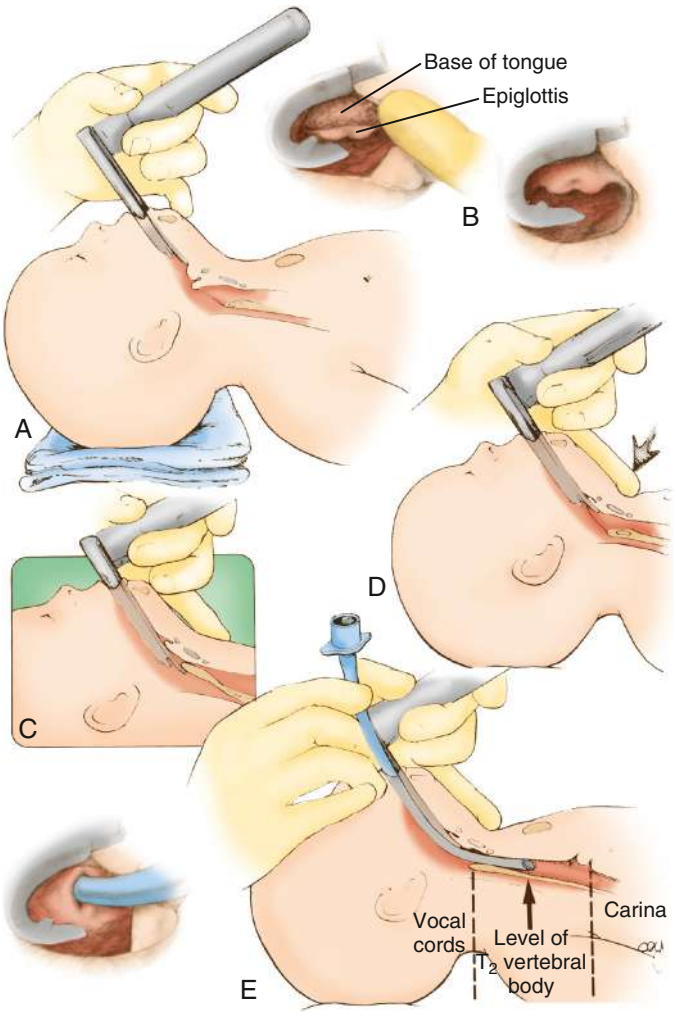

Fig. 79.10 A-E, Tracheal intubation technique. (*From Fleisher G, Ludwig S. Textbook of Pediatric Emergency Medicine, Baltimore: Williams & Wilkins;1983:1250.*)

Analgesia is recommended to reduce metabolic stress, discomfort, and anxiety during intubation. Pretreatment with a sedative, an analgesic, or an anesthetic or dissociative medication and potentially a neuromuscular relaxing agent (paralytic agent) is recommended unless the situation is emergent (e.g., cardiac arrest) and the administration of drugs would cause an unacceptable delay. Neuromuscular blocking agents should generally be avoided in patients who cannot be bag-mask ventilated because if the patient cannot be successfully intubated and cannot be bag-mask ventilated, they may progress to cardiopulmonary arrest.

Because many intubations in critically ill children are emergency procedures, providers should be prepared to rapidly intubate (Fig. 79.10). Rapid sequence intubation (RSI)—the process of intubating with a sedative (etomidate, ketamine, propofol) and neuromuscular blockade (rocuronium, succinylcholine) preintubation medications (order of administration not important)—is not always feasible in critically patients because BMV is necessary to maintain oxygenation and ventilation due to severe lung disease or intracranial hypertension. The routine use of cricoid pressure is not recommended because it does not decrease the risk of regurgitation of stomach contents, and it can impede effective BMV and airway visualization. Although there is a risk of regurgitation and aspiration, supporting the patient during induction and supporting rapid intubation is critical to minimize the risk to the patient.

Once the patient is intubated, proper ETT placement should be assessed by auscultation of breath sounds, observation of symmetric chest rise, and analysis of exhaled carbon dioxide (CO_2) by a colorimetric device or a capnographic device that quantifies CO_2 elimination. Chest radiography should be obtained to confirm appropriate tube position. Clinicians should assess ETT cuff pressures to minimize the risk of airway trauma.

RECOGNITION AND MANAGEMENT OF SHOCK

Shock occurs when oxygen and nutrient delivery to the tissues is inadequate to meet metabolic demands (see Chapter 85). A diagnosis of shock does not require the presence of hypotension. It is important for providers to recognize that **shock can occur with hypertension, normotension, or hypotension**. In early *compensated* shock, blood pressure is maintained, and oxygen delivery is mostly preserved through compensatory mechanisms such as tachycardia, increased systemic vascular resistance, or increased cardiac contractility. When compensatory mechanisms fail or are inadequate, the patient progresses to *decompensated* shock, which is defined by hypotension and organ dysfunction. If shock is not rapidly identified and treated, it can progress to multisystem organ dysfunction, cardiac arrest, and death.

Shock is also often described according to the underlying pathophysiology, which dictates the appropriate therapeutic response. **Hypovolemic shock** is the most common type of shock in children worldwide, usually related to fluid losses from severe diarrhea. Hemorrhagic shock is a specific type of hypovolemic shock after trauma or other causes of bleeding. **Distributive shock** occurs because of pathogenic dilation of the body's blood vessels and is often accompanied by relative intravascular hypovolemia due to capillary leak and "third-spacing" of intravascular fluids into the extravascular compartment. The most common causes of distributive shock are sepsis, anaphylaxis, and burn injuries, in which release of inflammatory cytokines causes massive capillary leak of fluid and proteins, leading to low oncotic pressure and intravascular volume. In the setting of myocardial dysfunction, a child has tissue hypoperfusion from **cardiogenic shock**. Common causes of cardiogenic shock are myocarditis, cardiomyopathy, and congenital heart disease, often in the postoperative setting. Severe sepsis and septic shock are often accompanied by myocardial dysfunction, and children with septic shock thus frequently manifest components of hypovolemic, distributive, and cardiogenic shock. **Obstructive shock** occurs when cardiac output is lowered by obstruction of blood flow to the body, as occurs with pericardial tamponade, tension pneumothorax, or massive pulmonary embolism. **Dissociative shock** manifests with normal cardiac and volume status but poor oxygen delivery due to severe anemia and carbon monoxide or cyanide poisoning.

The evaluation of a child in shock should proceed based on the primary, secondary, and tertiary assessments. Initial resuscitation should include the administration of crystalloid fluids in 10-20 mL/kg aliquots up to 60 mL/kg in the first hour if hypotension is present while paying close attention for signs of volume overload. If shock persists, volume overload is evident, or myocardial dysfunction is suspected, vasoactive infusions (e.g., epinephrine, norepinephrine) should be initiated. In hospital settings, catecholamine-dependent shock should trigger providers to consider placing a central venous catheter for stable venous access and an arterial line for continuous blood pressure monitoring. Laboratory assessment should include studies of renal and liver function; acid-base balance, including the presence of lactic acidosis, hypoxemia, and/or hypercapnia; and evidence of coagulopathy or disseminated intravascular coagulation to assess for signs of end-organ dysfunction and response to treatment. Assessment of peripheral perfusion, mental status, and urine output are also important to monitor. Treatment of the various etiologies of shock is noted in Chapter 85.

RECOGNITION AND TREATMENT OF ARRHYTHMIAS

In the advanced life support setting, arrhythmias are most usefully classified according to the observed heart rate (i.e., bradycardia or tachycardia) and the presence of cardiopulmonary compromise (e.g., altered mental status, hypotension, signs of shock). If the primary survey identifies a child with an abnormal heart rate and altered mental

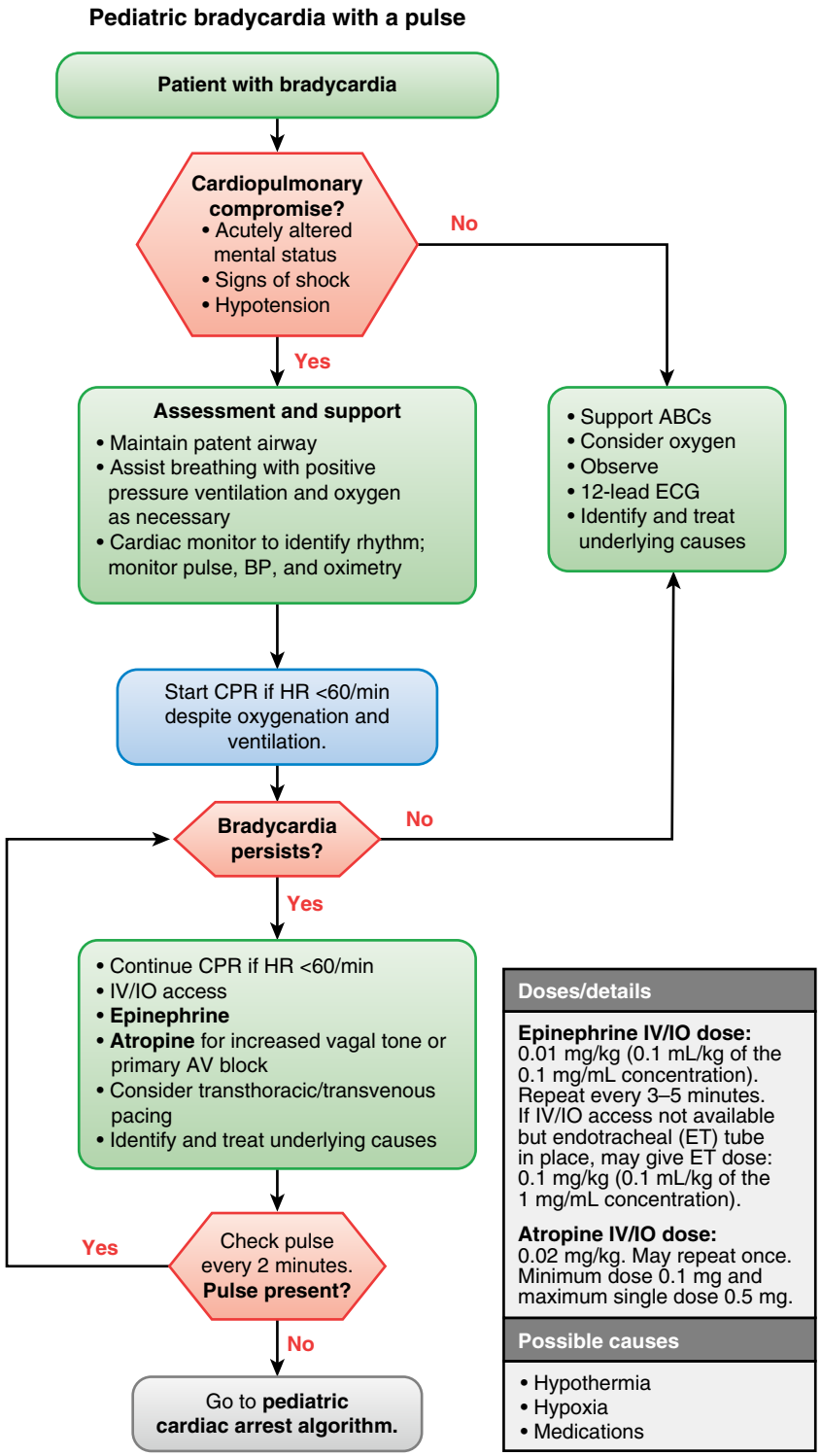

Fig. 79.11 Pediatric advanced life support: Bradycardia with a pulse algorithm. ABCs, Airway, breathing, and circulation; AV, atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate; IO/IV, intraosseous/intravenous. (*From Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142[16 Suppl 2]:S469-S523.*)

status or other signs of shock or hypotension, the rhythm is inadequate no matter its rate.

Bradyarrhythmias

By definition, a child is *bradycardic* when the heart rate is slower than the normal range for age (see Table 79.1). Sinus bradycardia can be a harmless incidental finding in an otherwise healthy person and is not usually associated with cardiac compromise. A clinically significant bradycardia occurs when the heart rate is slow and there are signs of systemic hypoperfusion (i.e., pallor, altered mental status, hypotension, acidosis). Symptomatic bradycardia occurs most often in the setting of hypoxemia but can also be caused by hypoglycemia, hypocalcemia, other electrolyte abnormalities, hypothermia, heart block, and intracranial hypertension. Bradyarrhythmias are often the most common *prearrest* rhythms in young children.

Initial management of symptomatic bradycardia includes support or opening of the airway and confirming or establishing adequate oxygenation and ventilation (Fig. 79.11). After adequate oxygenation and ventilation have been confirmed, the child should be reassessed for continued bradycardia and poor perfusion. If cardiac

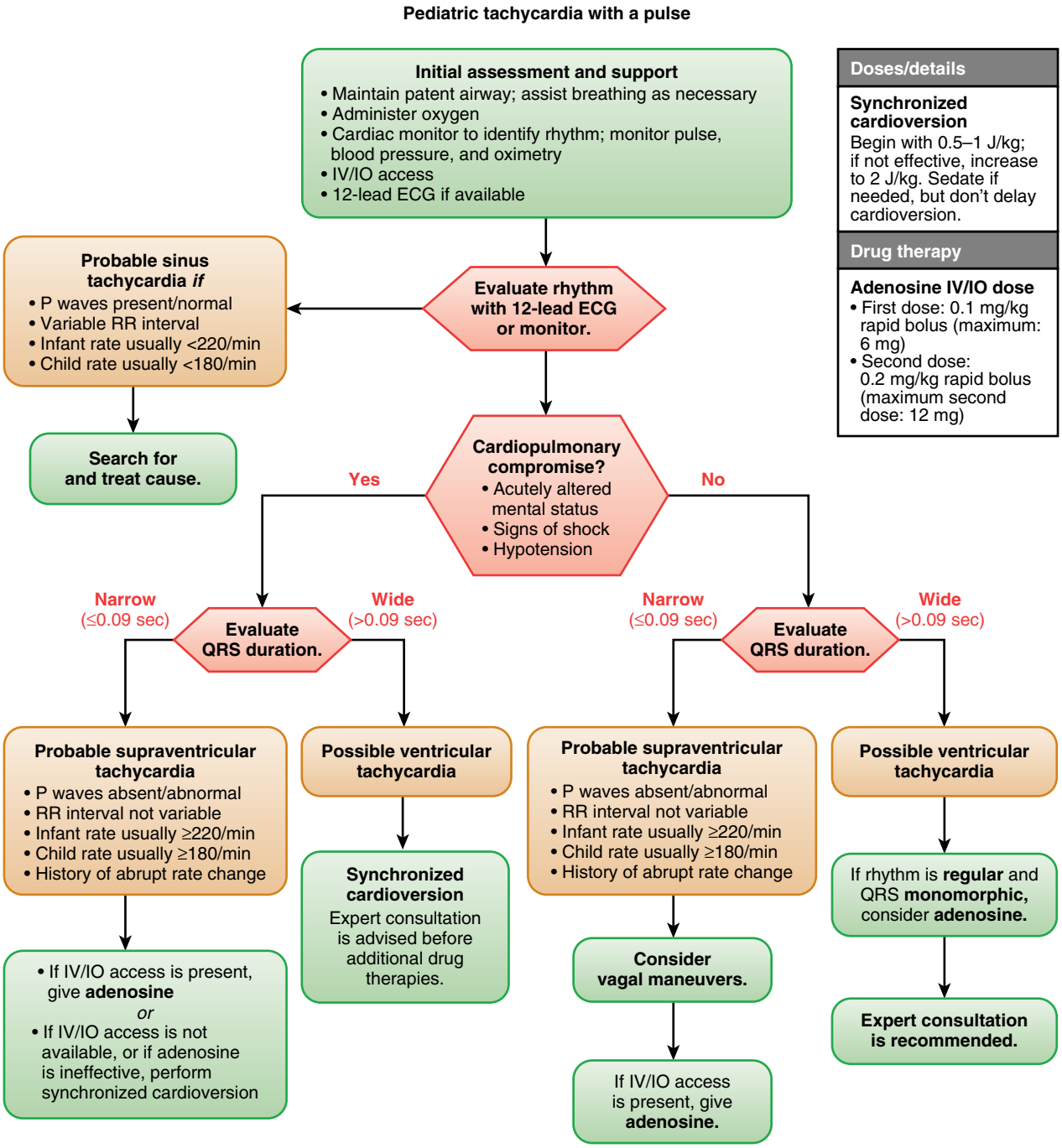

Fig. 79.12 Pediatric advanced life support: Tachycardia with a pulse algorithm. AV, Atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate; IO/IV, intraosseous/intravenous. (*From Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142[16 Suppl 2]:S469-S523.*)

compromise was solely the result of respiratory insufficiency, support of the child's airway and breathing may have been sufficient to restore normal hemodynamics. If respiratory support does not quickly correct the perfusion abnormalities, further care is based on the quality of perfusion and degree of bradycardia. *A heart rate <60 beats/min with cardiopulmonary compromise is an indication to begin CPR,* including the administration of epinephrine. If increased vagal tone or primary atrioventricular block is suspected, atropine can be administered. For cases of refractory bradycardia, cardiac pacing should be considered (see Fig. 79.11).

Tachyarrhythmias

Tachyarrhythmias represent a wide variety of rhythm disturbances of atrial and ventricular origin (see Chapter 484). Sinus tachycardia is a normal physiologic response to the body's need for increased cardiac output or oxygen delivery, as occurs with fever, exercise, or stress. It can also occur in more pathologic states, such as hypovolemia, anemia, pain, anxiety, thyrotoxicosis, and shock. Non–sinus tachyarrhythmias that do not originate in the sinus node are often categorized as either *narrow complex rhythms* (i.e., originating in the atrium, such as supraventricular tachycardia or atrial flutter) or *wide*

Table 79.5 Medications for Pediatric Resuscitation and Arrhythmias

MEDICATION	DOSE	REMARKS
Adenosine	0.1 mg/kg (max dose: 6 mg) Repeat: 0.2 mg/kg (max dose: 12 mg)	Monitor ECG Rapid IV/IO bolus with flush
Amiodarone	5 mg/kg IV/IO; repeat 5 mg/kg doses up to 15 mg/kg Max dose: 300 mg	Monitor ECG and blood pressure, as it can cause hypotension Give over 20-60 min (can give via IV push for patients in cardiac arrest) Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Atropine	IV/IO: 0.02 mg/kg Minimum dose: 0.1 mg for bradycardia treatment Max dose: • Child: 0.5 mg • Adolescent: 1 mg Repeat once if needed ETT* 0.04-0.06 mg/kg Max dose: 2 mg	Higher doses may be used with organophosphate poisoning ETT dosing only if no IV/IO access
Calcium chloride (10%) Calcium gluconate	20 mg/kg IV/IO 50-100 mg/kg Max dose: 2 g	Administer slowly; fast push can cause heart block/asystole Use only with documented hypocalcemia
Dextrose	0.5-1 g/kg IV/IO • D10W: 5-10 mL/kg • D25W: 2-4 mL/kg • D50W: 1-2 mL/kg	Recheck serial blood sugars after administration, as hypoglycemia can recur
Epinephrine	IV/IO: 0.01 mg/kg (0.1 mL/kg of the 0.1 mg/mL concentration) Max dose: 1 mg ETT*: 0.1 mg/kg (0.1 mL/kg of the 1 mg/mL concentration) Max dose: 2.5 mg	May repeat every 3-5 min as needed Only give via ETT if no IV/IO access
Lidocaine	IV/IO: 1 mg/kg bolus Max dose: 100 mg Infusion: 20-50 µg/kg/min ETT*: 2-3 mg/kg	Repeat bolus dose if infusion is initiated >15 min after initial bolus
Magnesium sulfate	25-50 mg/kg IV/IO Max dose: 2 g	Can cause hypotension Administer over 10-20 min; faster in torsades de pointes
Naloxone	IV/IO/IM/SQ: 0.1 mg/kg for full reversal Max dose 2 mg IN: 4 mg spray; may repeat q2-3min ETT*: 2-3 times IV dose	Use lower doses in patients with opioid-induced respiratory depression from therapeutic opioid dosing (0.001-0.005 mg/kg) May need to redose every 2-3 minutes, as half-life is shorter than most narcotics ETT if IV/IO routine not available
Sodium bicarbonate	1 mEq/kg IV/IO	Administer slowly; ensure adequate ventilation

*Flush with 5 mL of normal saline and follow with 5 ventilations.
D5W, 5% Dextrose in water; IO, intraosseous; IV, intravenous; ETT, endotracheal tube; IM, intramuscular; IN, intranasal.

complex rhythms (i.e., rhythms of ventricular origin, such as ventricular tachycardia).

The initial management of tachycardia should include assessment for cardiopulmonary compromise (Fig. 79.12). If the patient has evidence of cardiopulmonary compromise (i.e., hypotension, altered mental status, or other signs of shock), further treatment is based on whether the QRS complex of the ECG is narrow (≤0.09 sec) or wide (>0.09 sec). For narrow complex tachycardia, providers must distinguish between sinus tachycardia and supraventricular tachycardia (SVT). In **sinus tachycardia**, the history and onset are consistent with a known cause of tachycardia, such as fever or dehydration. Sinus tachycardia usually has some degree of rate variability, and p-waves are consistently present on the ECG and are of normal morphology and axis. Treatment is then geared toward identifying and treating the cause of sinus tachycardia. In **SVT**, onset is often abrupt without prodrome, and p-waves are absent or have a nonsinus ECG axis. When SVT is associated with cardiopulmonary compromise, providers should rapidly move to convert the child's heart rhythm back to sinus rhythm. If the child already has IV access, adenosine should be administered (Table 79.5). Adenosine has an extremely short half-life, so administration through an IV close to the heart (e.g., upper extremity) is best. Adenosine should be administered with a three-way stopcock inline so that it can be given and immediately flushed into the circulation. If the child does not have IV access or adenosine does not successfully convert the heart rhythm back to sinus rhythm, then **synchronized cardioversion** (0.5-1.0 joule [J]/kg) should be performed. For wide-complex tachycardia (i.e., **ventricular tachycardia [VT]**) with a pulse and evidence of cardiopulmonary compromise, synchronized cardioversion should be performed.

For patients with tachycardia without cardiopulmonary compromise, the rhythm assessment proceeds in the same fashion, but treatment potentially differs. Vagal maneuvers can be considered for SVT in the stable patient, followed by administration of adenosine and obtaining expert consultation. Wide-complex tachyarrhythmias without cardiovascular compromise should also trigger expert consultation before administration of antiarrhythmic medications. If the rhythm is monomorphic, adenosine can be given, as some stable wide-complex tachycardias are SVT with aberrant conduction and thus have a wide QRS complex. Patients should be continually reassessed for development of cardiovascular compromise.

CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION

Overview

Cardiac arrest occurs when the heart fails as an effective pump and blood flow ceases. Outwardly, the patient in cardiac arrest presents as unresponsive and apneic with no palpable pulse. Internally, the cessation of cardiac output and oxygen delivery causes progressive tissue ischemia and organ failure. If not rapidly reversed, cardiac arrest leads to progressive deterioration in brain, heart, and other organ function, such that resuscitation and recovery are no longer possible. Cardiac arrest outcomes in children have improved as a result of improvements in the recognition of deteriorating patients and delivery of high-quality CPR. Prehospital and hospital providers should understand that pediatric cardiac arrest is an intervenable process for which favorable outcomes are common. Early recognition and rapid treatment with high-quality CPR can be lifesaving.

Prevention of Cardiac Arrest

Out-of-hospital cardiac arrest (OHCA) occurs due to a variety of causes, including sudden infant death syndrome (SIDS), drowning, foreign body aspiration, poisoning or drug overdose, and trauma. Sudden cardiac arrest due to arrhythmias or cardiac disease do occur (usually in adolescents and those with preexisting congenital heart disease) and should be recognized and promptly treated, but most pediatric OHCAs have an underlying respiratory etiology. Preventive measures such as "back to sleep" for infants to lower the risk of SIDS (see Chapter 423), child supervision around bodies of water, and minimizing access to high-risk choking foods substantially decrease the incidence of cardiac arrest. Recognition of the child with respiratory distress or impending respiratory failure and delivery of appropriate care, as outlined earlier, is the most common and practical means of preventing pediatric OHCA.

In hospitalized children, cardiac arrest is most often the result of the progression or worsening of an underlying respiratory, cardiac, or neuromuscular disease process. Most pediatric in-hospital cardiac arrests (IHCAs) occur in the setting of progressive respiratory failure or shock. Recognition of deteriorating patients, transfer to monitored settings (i.e., intensive care units), and institution of appropriate directed and supportive therapies are effective means of preventing IHCA or ensuring that if it does occur, care is delivered in a well-equipped and prepared setting.

Recognition of Cardiac Arrest

Cardiac arrest is recognized from general assessment and primary survey findings consistent with a pale or cyanotic child who is unresponsive, apneic, and pulseless. Even experienced providers have a relatively high error rate when asked to determine presence or absence of pulse in a child. Therefore lay rescuers should begin CPR immediately for any patient without signs of life. Healthcare providers can palpate for a pulse for up to 10 seconds but should provide CPR unless a pulse is definitively felt.

Although initial responders should focus on signs of lifelessness when determining if a patient requires CPR, recognition and understanding of cardiac arrest rhythms is also important for providers. Most pediatric cardiac arrest rhythms are "nonshockable" (i.e., asystole, pulseless electrical activity [PEA], or bradycardia with cardiopulmonary compromise). It is important pediatric providers recognize that bradycardia with cardiopulmonary compromise that does not swiftly resolve with ventilation and oxygenation should be treated with CPR. "Shockable" rhythms (ventricular fibrillation [VF] and pulseless VT) account for a relatively small proportion of pediatric OHCAs or IHCAs. However, these rhythms can occur as a secondary rhythm later in arrest. Because these rhythms require prompt defibrillation in addition to high-quality CPR, it is important to recognize and be prepared to treat VF or pulseless VT when present.

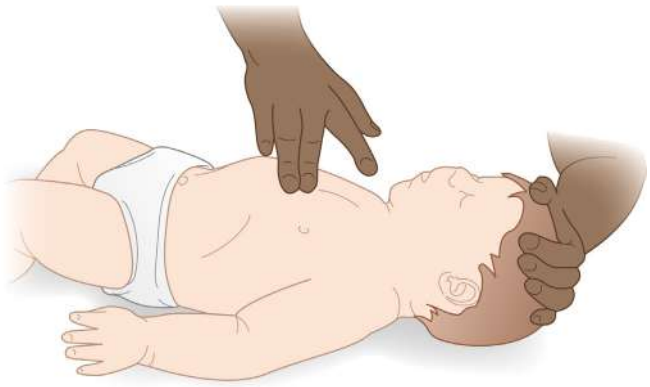

Fig. 79.13 Hand position for infant CPR for the single provider. The two-finger technique.

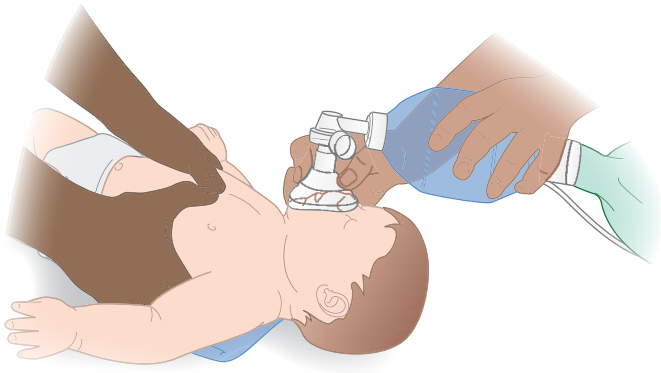

Fig. 79.14 Hand position for infant CPR for two providers. The 2-thumb-encircling hands technique.

Basic Life Support

The AHA Pediatric BLS algorithms for both single- and two-rescuer scenarios are depicted in Figures 79.1 and 79.2. Upon recognition of cardiac arrest, rescuers should begin CPR with both chest compressions and rescue breaths. Single rescuers who witness a sudden collapse should activate the emergency response system and retrieve an automated electronic defibrillator (AED) or defibrillator, if immediately available, before starting compressions, as many of these children have shockable rhythms. For single rescuers treating children in cardiac arrest without a witnessed sudden collapse, CPR should begin immediately with cycles of 30 compressions followed by two rescuer breaths for at least 2 minutes. An AED should be applied, and automated directions followed as soon as it is available. When two or more rescuers are present, one rescuer should be responsible for activating the emergency response system and retrieving an AED while the other rescuer(s) begins CPR. When both rescuers are providing CPR for an infant or prepubescent child, cycles of 15 compressions followed by two ventilations should be provided. Adolescents should receive cycles of 30 compressions and two ventilations regardless of the number of rescuers.

Components of High-Quality Cardiopulmonary Resuscitation

The goal of CPR is to provide temporary blood flow and oxygen delivery to the body during cardiac arrest. High-quality CPR that meets established goals and metrics optimizes this blood flow and is associated with improved outcomes from cardiac arrest. **Components of high-quality CPR include optimal hand positioning, appropriate chest compression rate, adequate chest compression depth, allowing for full chest recoil, minimization of interruptions, and appropriate ventilation rate.**

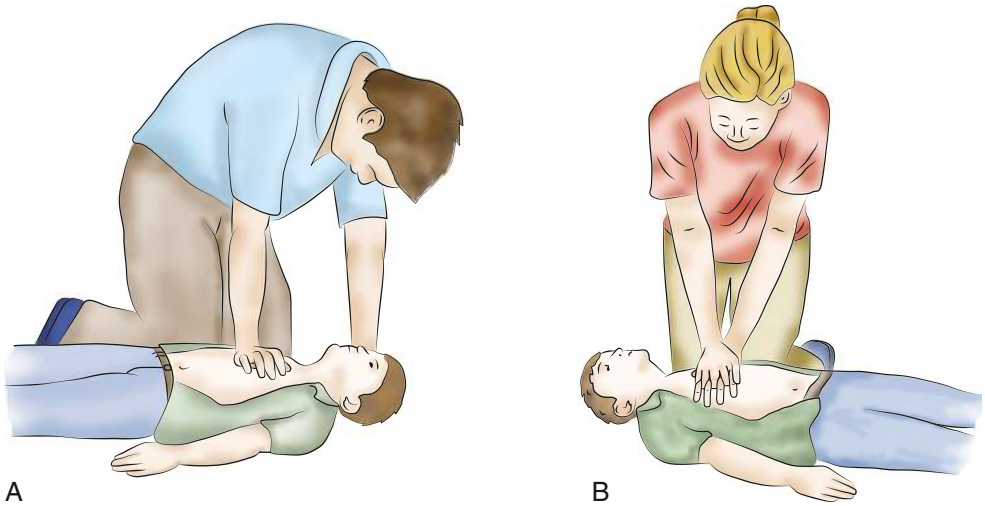

Fig. 79.15 Hand position for child CPR. A, One-handed chest compressions in a child. B, Two-handed chest compressions in a child or adult.

Hand positioning and CPR technique: Chest compressions in infants <1 year old performed by a single provider may be performed by placing two fingers or two thumbs just below the intramammary line (Fig. 79.13). When two providers are present, the two-thumb-encircling hands technique (Fig. 79.14) is recommended unless the rescuer cannot physically encircle the victim's chest, in which case two fingers can be used. If goal depths cannot be reached with these techniques, it is reasonable to use the heel of one hand for chest compressions. For children >1 year old, the care provider should perform chest compressions over the lower half of the sternum with the heel of one hand, or with two hands as used for adult resuscitation (Fig. 79.15). In all cases, care should be taken to avoid compression of the xiphoid and the ribs. When feasible, a backboard should be placed under the child's back and the hospital bed should be placed into "CPR mode" when applicable to maximize the effectiveness of compressions.

Chest compression mechanics: Chest compressions should be provided at a rate of **100-120 compressions per minute**. The goal chest compression depth for infants and children is at least **one-third the anterior-posterior diameter of the chest**, which is approximately 4 cm (1.5 inches) in infants and 5 cm (2 inches) in children. For children who have reached puberty, the adult depth of 5-6 cm can be used. Rescuers should avoid leaning and **allow the chest to fully recoil** after each compression in order to facilitate venous return to the heart. Resuscitation teams should seek to **minimize the duration and frequency of chest compression interruptions** during CPR. These chest compression mechanics can be measured during CPR through CPR quality-monitoring defibrillators, which are now widely used.

Advanced Life Support

The AHA PALS algorithm for cardiac arrest is depicted in Figure 79.16. Chest compressions should be delivered as detailed earlier. Ventilation is a key component of pediatric CPR because most patients have concomitant respiratory failure. For children without an advanced airway in place, chest compressions are paused to allow for the delivery of ventilations via mask with the compression-to-ventilation ratios discussed previously. For children with an advanced airway at the time of arrest, ventilations should be provided asynchronously (i.e., without interrupting chest compressions) at a rate of 20-30 breaths/minute. Providers should avoid overventilation during CPR, as this may increase intrathoracic pressure and decrease venous return to the heart.

Epinephrine is administered during CPR to increase systemic vascular resistance and coronary perfusion pressure in order to restore spontaneous circulation. Epinephrine should be administered intravenously or intraosseously (IO), though it can be administered via ETT if IV or IO access is not available (see Table 79.5). **The first dose of epinephrine should be given within 5 minutes of the onset of cardiac arrest and repeated every 3-5 minutes** until return of spontaneous circulation (ROSC) is achieved. Pulse and rhythm checks should be performed approximately every 2 minutes but should not last more than 10 seconds.

CPR quality can also be gauged by monitoring the patient's physiologic response to resuscitation. End-tidal carbon dioxide, which reflects pulmonary blood flow, can be an indicator of the adequacy of chest compressions. Diastolic blood pressure, measured via an arterial line, is used as a surrogate of coronary perfusion pressure, and values are therefore correlated with the likelihood of ROSC. Either of these tools can be used during CPR by practitioners appropriately trained in the nuances of their interpretation.

Defibrillation and Antiarrhythmic Medications

For those children with VF or pulseless VT, emergency defibrillation is indicated (see Fig. 79.16). Defibrillator pads should be applied to the bare chest during CPR regardless of initial rhythm, as these rhythms can develop later during cardiac arrest. Lay providers should follow the verbal instructions given by the AED. Ideally, the AED used for children <8 years of age should deliver an attenuated adult dose or should be designed for children; if neither of these options is available, a standard adult AED should be used. Healthcare providers should use either an AED or a manual defibrillator. An **initial defibrillation should be provided at a dose of 2 J/kg** with subsequent dosing per the PALS algorithm. CPR should be promptly resumed after each defibrillation attempt, with additional rhythm assessments and defibrillation attempts every 2 minutes while a shockable rhythm persists. Either amiodarone or lidocaine can be given as an antiarrhythmic for shock-refractory VF or VT (see Table 79.5).

Identification and Treatment of Underlying Causes of Cardiac Arrest

Pediatric cardiac arrest can occur because of a discrete and clear event (e.g., drowning), due to the progression of underlying disease processes (e.g., refractory hypoxemic respiratory failure), or for reasons that are unclear to the resuscitation team at the time of the arrest. In addition to providing high-quality CPR, reversing the underlying cause of cardiac arrest is critical in order to restore and maintain spontaneous circulation. Focused evaluation of likely etiologies based on the patient's history, risk factors, physical exam, and other findings often reveals addressable cause. Additionally, providers should systematically address common and correctable causes of cardiac arrest (e.g., the "Hs and Ts"; Table 79.6).

Duration of CPR

Unsurprisingly, children who receive prolonged CPR have worse outcomes than those who require brief CPR. However, previous assertions

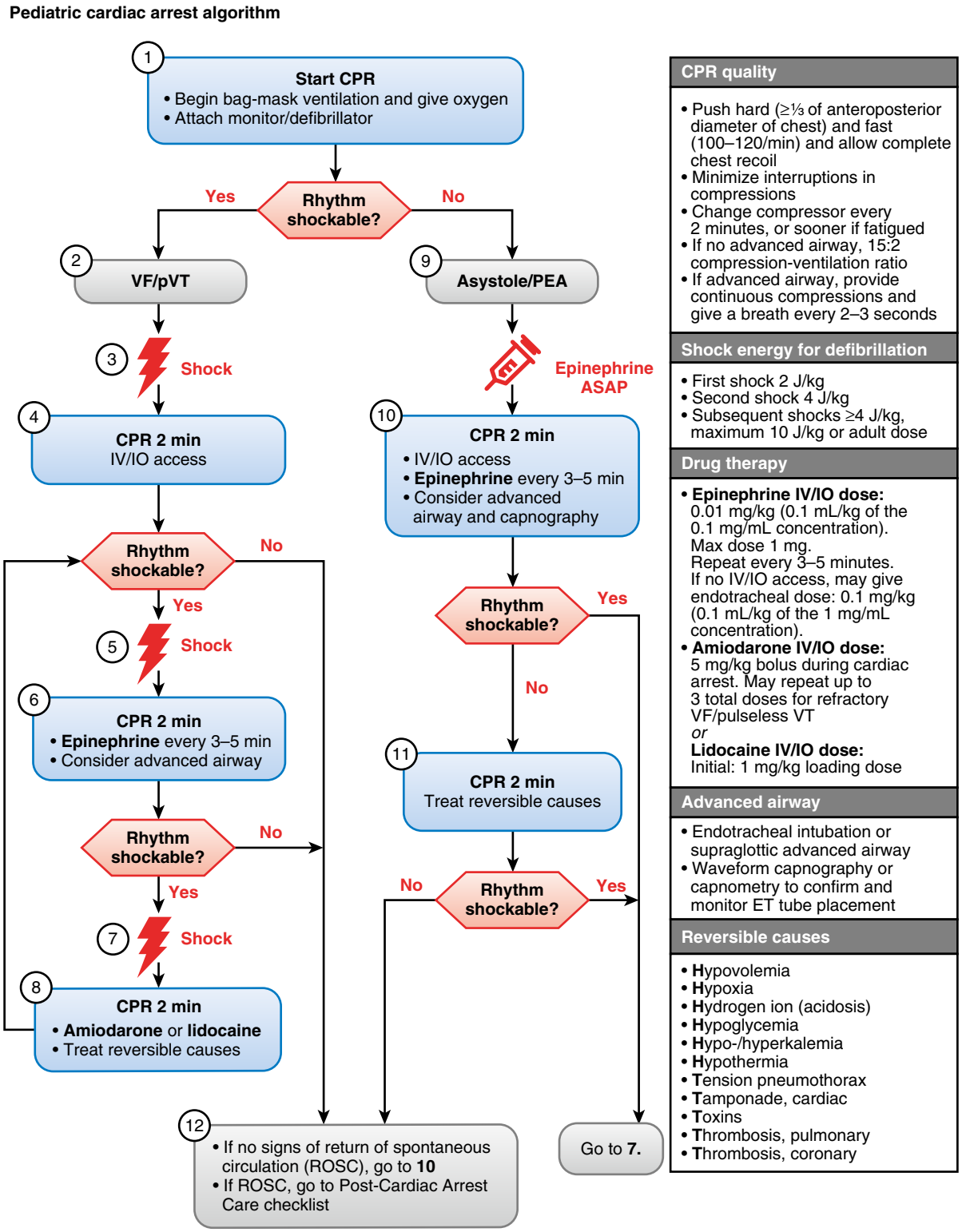

Fig. 79.16 Pediatric advanced life support cardiac arrest algorithm. CPR, Cardiopulmonary resuscitation; IO/IV, intraosseous/intravenous; PEA, pulseless electrical activity; VF/VT, ventricular fibrillation/tachycardia. (*From Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142[16 Suppl 2]:S469-S523.*)

that CPR >20 minutes in duration was futile have been disproven. More than 15% of children who received >35 minutes of CPR for IHCA survived to hospital discharge in one large registry study. Therefore decisions regarding futility and when to cease resuscitation efforts should take into account patient factors, goals of care, arrest etiology and characteristics, and a host of other factors, rather than CPR duration alone.

Extracorporeal Membrane Oxygenation and Extracorporeal Cardiopulmonary Resuscitation

Extracorporeal membrane oxygenation (ECMO) is a modified form of cardiopulmonary bypass that can be employed in children with severe cardiac or respiratory failure. Blood is removed from a large central vein, carried through tubing to an oxygenator for gas

Table 79.6 Potentially Reversible Causes of Cardiac Arrest

CONDITION	COMMON CLINICAL SETTINGS	TREATMENT
THE H'S		
Hypovolemia	Dehydration, hemorrhage, major burns, diabetes, gastrointestinal losses, shock, and trauma	Administer fluids For hemorrhage, administer packed red blood cells and other blood products
Hypoxemia	Upper airway obstruction (croup, anaphylaxis, foreign body) Lower airway obstruction (asthma, bronchiolitis) Parenchymal lung disease (pneumonia) Restrictive lung disease (pleural effusion)	Provide supplemental oxygen Confirm endotracheal tube placement and chest rise
Hydrogen ion (acidosis)	Preexisting acidosis, diabetes, diarrhea, drugs and toxins, prolonged resuscitation, renal disease, and shock	Reassess the adequacy of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement Ensure adequate ventilation and avoid concomitant respiratory acidosis Administer IV fluids May consider bicarbonate administration with documented severe acidosis
Hypoglycemia	Starvation, toxin, diabetes medications, metabolic disease	Administer dextrose (glucagon if dextrose not available) Discontinue causative medications
Hyperkalemia	Metabolic acidosis, excessive administration of potassium, renal failure, drugs and toxins, vigorous exercise, hemolysis, rhabdomyolysis, tumor lysis syndrome, and clinically significant tissue injury	Stop potassium-containing fluids Stabilize cardiac membrane: calcium Treat acidosis: sodium bicarbonate Shift potassium intracellularly: sodium bicarbonate, insulin (with glucose to prevent hypoglycemia), and albuterol Promote potassium excretion: loop diuretics, Kayexalate Removal of potassium: dialysis
Hypokalemia	Diabetes, diuretic use, drugs and toxins, profound gastrointestinal losses	If profound hypokalemia is accompanied by cardiac arrest, initiate urgent IV potassium replacement
Hypothermia	Alcohol abuse, burns, central nervous system disease, debilitated patient, drowning, drugs and toxins, endocrine disease, history of exposure, homelessness, extensive skin disease, spinal cord disease, and trauma	If hypothermia is severe (temperature <30°C [86°F]), defibrillation may be ineffective; initiate active internal rewarming with cardiopulmonary support; can consider extracorporeal rewarming If hypothermia is moderate (temperature 30-34°C [86-93.2°F]), actively rewarm during CPR
THE T'S		
Tension pneumothorax	Procedural complication, mechanical ventilation complication, pulmonary disease with "air leak" (including asthma, chronic obstructive pulmonary disease, and necrotizing pneumonia), thoracentesis, and trauma	Needle decompression followed by chest tube insertion or primary chest tube insertion
Cardiac tamponade	Hemorrhage, malignancy, pericarditis, trauma, cardiac surgery, post–myocardial infarction	Administer fluids to increase cardiac preload (temporizing only); obtain bedside echocardiogram, if available Perform pericardiocentesis; immediate surgical intervention is appropriate if pericardiocentesis is unhelpful but cardiac tamponade is known or highly suspected
Toxins	Alcohol abuse, behavioral or metabolic presentation, classic toxicologic syndrome, psychiatric disease, depressed mental status of unclear etiology, medications in the home, history of depression/suicidality	Supportive care and toxin-directed therapies in consultation with a toxicologist
Thrombosis, pulmonary	Hospitalized patient, recent surgical procedure, peripartum, known risk factors for venous thromboembolism, history of venous thromboembolism, or prearrest presentation consistent with a diagnosis of acute pulmonary embolism, recent immobility or fractures	Administer fluids; augment with vasoactive medications as necessary Consider pulmonary vasodilators (e.g., inhaled nitric oxide) Consider systemic or site-directed thrombolytic therapy Consider mechanical thrombectomy Consider ECMO
Thrombosis, coronary	Known risk factors for myocardial infarction (congenital heart disease, family history of sudden cardiac death)	Consider fibrinolytic therapy Consider percutaneous coronary intervention

Adapted from Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 Suppl 3):S876-S908.

exchange, and then returned to the body via either a vein (venovenous or VV-ECMO) or an artery (venoarterial or VA-ECMO). VV-ECMO is typically used in patients with refractory respiratory failure who require ECMO for gas exchange but continue to rely on their native cardiac function for cardiac output. VA-ECMO is used for patients with shock or cardiac failure, with or without concomitant respiratory failure, with the ECMO pump and circuit augmenting or replacing native cardiac output. The processes of determining ECMO candidacy, performing ECMO cannulation, maintaining ECMO circuit integrity, and caring for critically ill children on ECMO are

Table 79.7 Medications to Maintain Cardiac Output and for Postarrest Stabilization*

MEDICATION	DOSE RANGE	COMMENT
Dobutamine	2-20 µg/kg/min IV/IO	Inotrope, chronotrope, vasodilator
Dopamine	2-20 µg/kg/min IV/IO	Inotrope, chronotrope, vasodilator at low doses, vasoconstrictor at high doses
Epinephrine	0.01-1 µg/kg/min IV/IO	Inotrope, chronotrope, vasodilator at low doses, vasoconstrictor at medium and high doses
Milrinone	50 µg/kg IV/IO over 10-60 min then 0.25-0.75 µg/kg/min	Inodilator, lusitrope, vasodilator
Norepinephrine	0.01-1 µg/kg/min	Vasopressor; weak inotrope

*Alternative formula for calculating an infusion: Infusion rate (mL/hr) = [weight (kg) × dose (µg/kg/min) × 60 (min/hr)]/concentration µg/mL).
Data from Kleinman ME, Brennan EE, Goldberger ZD, et al. Part 5: Adult Basic Life Support and Cardiopulmonary Resuscitation Quality: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 Suppl 2):S414-S435.

complex; ECMO is thus performed only at centers with appropriate expertise and equipment.

Extracorporeal support can be employed as a rescue therapy for refractory cardiac arrest. Extracorporeal CPR (ECPR), which involves cannulating and placing a patient on VA-ECMO while CPR is in progress, has been successfully used in children. Its efficacy has been best demonstrated in hospitalized children with underlying cardiac disease; AHA guidelines therefore state that it can be considered for children "with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment." In addition, ECPR has been employed in patients with noncardiac etiologies of cardiopulmonary arrest who are not responding to standard resuscitation protocols.

Post–Cardiac Arrest Care

After resuscitation from cardiac arrest, patients are at risk for developing **post-cardiac arrest syndrome (PCAS)**. PCAS is composed of post–cardiac arrest brain injury, myocardial dysfunction, systemic ischemia-reperfusion response, and persistence of preexisting pathophysiology and can last for days to weeks after the cardiac arrest. Primary brain injury occurs due to hypoxia and ischemia during the no-flow (pre-CPR) and low-flow (during CPR) periods. Secondary brain injury occurs during the postarrest period. Signs and symptoms of brain injury are encephalopathy, seizures, cerebral edema, and autonomic dysfunction. Myocardial dysfunction can present as hypotension, depressed left or right ventricular systolic or diastolic function, arrhythmias, or pulmonary edema. The systemic ischemia-reperfusion response is a "sepsis-like" syndrome and has clinical findings of hyperglycemia, coagulopathy, hypovolemia, fever, and multisystem organ dysfunction. These three components combined with the precipitant that caused the arrest (e.g., septic shock or PARDS) result in varied severity of PCAS ranging from minimal symptoms, with patients returning quickly to their neurologic baseline, to severe multisystem organ failure with high risk of repeat cardiac arrest.

To address this clinical spectrum, it is important to be deliberate and vigilant in caring for the postarrest patient. Thus close postarrest observation in an intensive care unit, where the child can receive ongoing multiorgan system assessments and support, is critical. To prevent secondary brain injury, which occurs during the postarrest period, clinicians should monitor for, prevent, and treat PCAS. Hypotension is common and can lead to organ hypoperfusion. Clinicians should frequently monitor blood pressure and should do so continuously with an arterial catheter if appropriate resources are available. IV fluids and vasoactive agents such as epinephrine or norepinephrine should be used to maintain a blood pressure greater than the fifth percentile for age. Clinicians should be proactive and not wait for hypotension to occur. Rather, they should be prepared with fluids, vasoactive infusions, and clearly defined postarrest blood pressure targets. Continuous arterial blood pressure monitoring can help the provider determine the need for, and response to, inotropic and chronotropic medications (Table 79.7).

Hyperoxia (Pao_2 >300) and hypoxemia after cardiac arrest should be prevented because both can worsen secondary brain injury. Clinicians should wean supplemental oxygen after ROSC, targeting a saturation of 94–99%. In most cases, weaning supplemental oxygen when patients are saturating 100% is not harmful. For patients with hypoxemia, clinicians may need to try alternative ventilator strategies if supplemental oxygen is insufficient to achieve a saturation above 94% or higher.

Fever is common after cardiac arrest and may worsen secondary brain injury. **Targeted temperature management (TTM)** is performed with an active temperature control device and should be used for children postarrest who do not return to their neurologic baseline. Because there is no difference in survival or neurologic outcomes between patients who receive TTM 33°C (32-34°C [89.6-91.4°F]) and patients who receive TTM 36.8°C (98.2°F) (36-37.5°C [96.8-99.5°F]), either can be selected. Patients should have continuous core temperature monitoring and receive sedation and analgesics to prevent discomfort. If shivering occurs, patients should be treated with a sedative or neuromuscular blockade. Hyperthermia must be avoided.

Seizures are common after cardiac arrest and often are nonconvulsive and therefore can only be detected on an EEG. It is unclear if treatment improves outcomes; however, antiseizure medications can be administered for convulsive and nonconvulsive seizures.

Most care is supportive, but close monitoring for organ injury that can be treated (e.g., coagulopathy or adrenal insufficiency) or that may require modification of therapies (e.g., medication dose adjusting in patients with acute kidney injury) should be considered. Survivors of cardiac arrest can have long-standing neurologic, cognitive, physical, and quality-of-life deficits. Clinicians should refer children for ongoing evaluation and assessments.

Communication with the patient's family is an essential element of postarrest care, as it is for the care of any acutely ill or injured child. The family should be thoroughly briefed on the elements of the resuscitation performed, the child's condition, and ongoing medical concerns, uncertainties, or issues. The provider should be available to answer the family's questions, clarify information, and provide comfort. Other support staff, including social workers and chaplains, should be contacted, as the family wishes, to provide additional support and comfort. For situations in which the resuscitation is ongoing, it is recommended that the provider make every effort possible to have the family present at the bedside, if they wish. Family presence during CPR or other emergency resuscitative efforts, even if the child dies, is associated with a more positive medical experience than if they are excluded. In situations where the child is critically ill but stable, the family should be brought to the bedside as soon as the healthcare team deems it safe and appropriate (see Chapter 8).

PROCEDURES

Vascular Access

Venous Access

Veins suitable for cannulation are numerous, but there is considerable anatomic variation from patient to patient. In the upper extremities, the *median antecubital vein,* located in the antecubital fossa, is often the largest and easiest to access. Many veins on the dorsum of the hand are also suitable for cannulation because they are often large and easily located, and their cannulation is generally well tolerated. The *cephalic vein* is usually cannulated at the wrist, along the forearm, or at the elbow. The *median vein* of the forearm is also suitable as it lies along a flat surface of the forearm. In the lower extremity, the *great saphenous vein,* located just anterior to the medial malleolus, is accessible in most patients. The dorsum of the foot usually has a large vein in the midline, passing across the ankle joint, but catheters are difficult to maintain in

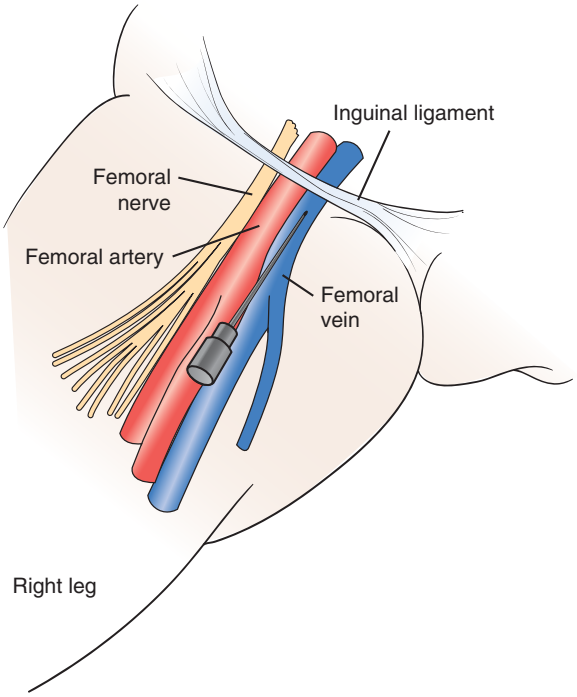

Fig. 79.17 Approach to the femoral vein. The patient is flat and supine, with the thigh slightly abducted and externally rotated. The introducer needle enters the skin 1-2 cm distal to the inguinal ligament and 0.5-1 cm medial to the pulse of the femoral artery. Remember the lateral to medial mnemonic NAVEL for nerve, artery, vein, empty space, and lymphatics. (*From Edwards LR, Malone MP, Prodham P, Schexnayder SM. Pediatric vascular access and centeses. In: Zimmerman JJ, Rotta AT, eds. Fuhrman & Zimmerman's Pediatric Critical Care, 6th ed. Philadelphia: Elsevier; 2022: Fig. 14.6, p. 102.*)

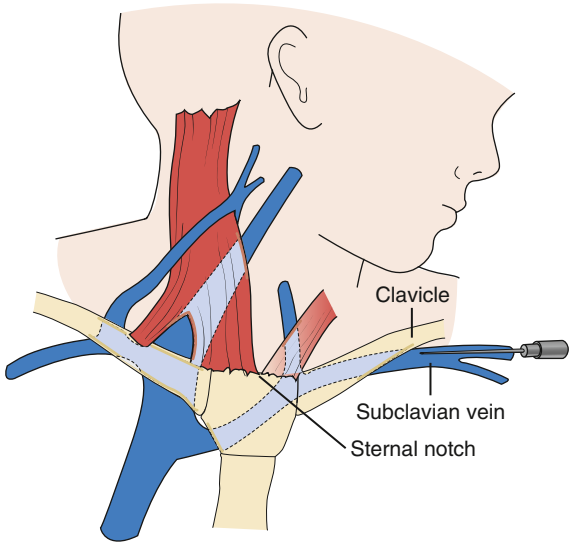

Fig. 79.19 Approach to the subclavian vein. The patient is supine, in slight Trendelenburg position, with a small roll along the spine between the shoulders. The needle enters the skin at the junction of the lateral and middle thirds of the inferior clavicle and is directed toward the suprasternal notch, passing along the inferior edge of the clavicle. (*From Edwards LR, Malone MP, Prodham P, Schexnayder SM. Pediatric vascular access and centeses. In: Zimmerman JJ, Rotta AT, eds. Fuhrman & Zimmerman's Pediatric Critical Care, 6th ed. Philadelphia: Elsevier: 2022: Fig. 14.5, p. 102.*)

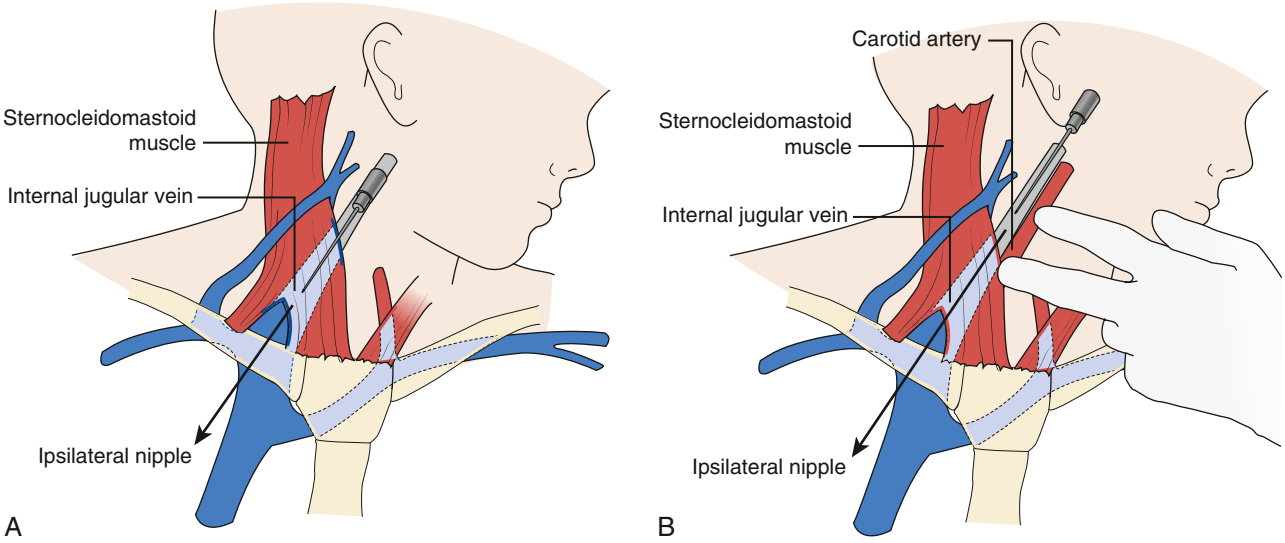

Fig. 79.18 Approaches to the internal jugular vein. The patient is supine, in slight Trendelenburg position, with the neck extended over a shoulder roll and the head rotated to the contralateral side. **A,** Middle approach: The introducer needle enters the skin at a 30-degree angle at the apex of the triangle formed by the heads of the sternocleidomastoid muscle and clavicle, directing it toward the ipsilateral nipple. **B,** Anterior approach: The carotid pulse is palpated and may be slightly retracted medially. The introducer needle enters along the anterior margin of the sternocleidomastoid, about halfway between the suprasternal notch and mastoid process, while being directed toward the ipsilateral nipple. (*Modified from Edwards LR, Malone MP, Prodham P, Schexnayder SM. Pediatric vascular access and centeses. In: Zimmerman JJ, Rotta AT, eds. Fuhrman & Zimmerman's Pediatric Critical Care, 6th ed. Philadelphia: Elsevier; 2022: Fig. 14.4, p. 101.*)

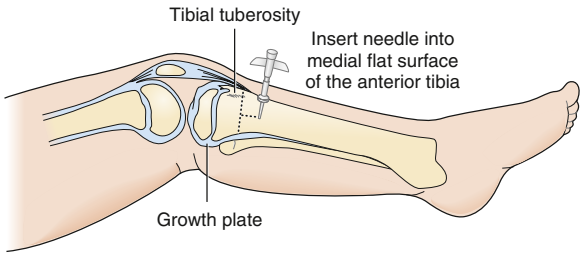

Fig 79.20 Insertion of the intraosseous needle into the anterior tibia. *(From Edwards LR, Malone MP, Prodham P, Schexnayder SM. Pediatric vascular access and centeses. In: Zimmerman JJ, Rotta AT, eds. Fuhrman & Zimmerman's Pediatric Critical Care, 6th ed. Philadelphia: Elsevier; 2022: Fig. 14.2, p. 95.)*

this vein because dorsiflexion tends to dislodge them. A second large vein on the lateral side of the foot, running in the horizontal plane, usually 1-2 cm dorsal to the lower margin of the foot, is preferable. The most notable scalp veins are the *superficial temporal* (just anterior to the ear) and *posterior auricular* (just behind the ear).

Deeper and larger central veins can provide more reliable access for medications, nutritive solutions, and blood sampling than peripheral venous lines. Placement of central access should be considered in the patient with difficult peripheral access where IVs may be challenging to obtain or may last for brief periods with increased risk of infiltration; when a patient is critically ill requiring numerous medications and needs stable access; when a patient requires IV vasoactive medications for more than a brief period; if long-term medications need to be administered in the hospital or at home; or if administered agents are vascular irritants (IV nutrition, electrolyte infusions, certain antibiotics). Central veins may be reached by percutaneous cannulation or surgical exposure. In infants and young children, the *femoral vein* or *internal jugular vein* are often the easiest to access and cannulate, but the subclavian veins may also be used (Figs. 79.17, 79.18, and 79.19). Peripherally inserted central catheters (PICCs) can be placed for longer-term access through the upper or lower extremity to administer medications or IV nutrition and can be used at home. With the expansion of bedside ultrasound availability and expertise, central venous catheters should be placed under ultrasound guidance to improve first-pass success and minimize the risk of complications.

Intraosseous Access

IO needles (for intramedullary venous plexus access) are specialized, rigid, large-bore needles. IO cannulation is recommended for patients in whom IV access proves difficult or unattainable in an emergent setting, even in older children. If venous access is not available within approximately 1 minute in a child with cardiopulmonary arrest, an IO needle should be placed in the anterior proximal tibia (with care taken to avoid traversing the epiphyseal plate) or other approved site. The needle should penetrate the anterior layer of compact bone, and its tip is advanced into the spongy interior of the bone (Fig. 79.20). Commercially available IO kits frequently include drills that mitigate the complications of needle placement associated with manual placement. All medications, blood products, and fluids may be administered through the IO route, including medications required for emergency resuscitation. Laboratory values can be sampled, although a complete blood count will be unreliable. Complications are uncommon but may include osteomyelitis with prolonged infusions, tibial fracture, and infiltration of fluids with dislodgement.

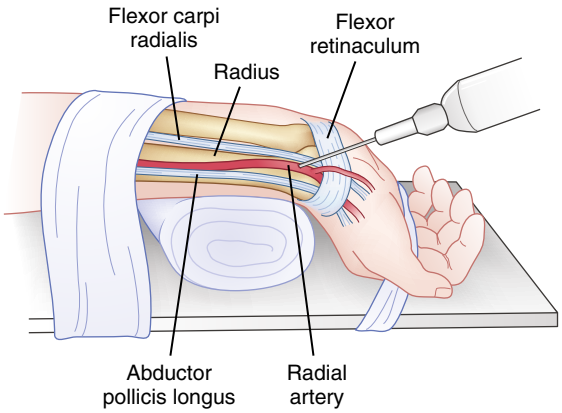

Fig. 79.21 Radial artery anatomy and cannulation.

Arterial Access

Arterial access is indicated when care providers need frequent blood sampling, particularly to assess adequacy of oxygenation, ventilation, or acid-base balance, or continuous blood pressure monitoring. The *radial artery,* the most commonly cannulated artery, lies on the lateral side of the anterior wrist, just medial to the styloid process of the radius (Fig. 79.21). The *ulnar artery,* just lateral to the tendon of the flexor carpi ulnaris, is used less often because of its proximity to the ulnar nerve. Useful sites in the lower extremity, particularly in neonates and infants, are the *dorsalis pedis artery,* on the dorsum of the foot between the tendons of the tibialis anterior and the extensor hallucis longus, and the *posterior tibial artery,* posterior to the medial malleolus. Arterial catheters require special care for insertion and subsequent management. Clinicians should monitor for signs of decreased perfusion distal to catheter placement.

NONVASCULAR EMERGENCY PROCEDURES

Thoracentesis and Chest Tube Placement

Thoracentesis is the placement of a needle or catheter into the pleural space to evacuate fluid, blood, or air. Most insertions are performed in one of the intercostal spaces between the fourth and sixth ribs in the plane of the midaxillary line. After appropriate systemic and local anesthesia/sedation, a needle (and later the chest tube) that enters the pleural space should penetrate the intercostal space by passing over the superior edge of the lower rib, because there are larger vessels along the inferior edge of the rib. Ideally, the chest tube should lie *anterior* in the pleural space for air accumulation and *posterior* for fluid accumulation. A radiograph must be obtained to verify chest tube placement and evacuation of the pleural space.

Pericardiocentesis

When fluid, blood, or gas accumulates in the pericardial sac, the heart may become compressed and may be unable to fill/empty with normal volumes of blood, leading to diminished cardiac output (i.e., pericardial tamponade with obstructive shock). The cardinal signs of such a restrictive pericardial effusion are tachycardia and hypotension, generally with a narrowed pulse pressure. Pericardiocentesis includes needle aspiration of the pericardial sac, often followed by the placement of a catheter for continuous drainage. As with thoracentesis, chest radiography should be done to confirm catheter location and to evaluate for any complications, such as pneumothorax or hemothorax. Pericardiocentesis may be performed with echocardiography.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 80

Acute Care of Multiple Trauma

Courtney W. Mangus, Howard I. Pryor II, and Bruce L. Klein

EPIDEMIOLOGY

Injury is a leading cause of death and disability in children throughout the world (see Chapter 14). Deaths represent only a small fraction of the total trauma burden. Approximately 140,000 children were treated in U.S. trauma centers in 2016 for serious injury. Many survivors of trauma have permanent or temporary functional limitations. Motor vehicle–related injuries and falls rank among the top 15 causes of disability-adjusted life years in children worldwide. In childhood, blunt trauma predominates, accounting for the majority of injuries. In adolescence, penetrating trauma increases in frequency, accounting for approximately 13% of injuries, and penetrating trauma secondary to a firearm is associated with a high case fatality rate of 11%.

REGIONALIZATION AND TRAUMA TEAMS

Morbidity and mortality rates have decreased in geographic regions with comprehensive, coordinated trauma systems. Treatment at designated trauma centers is associated with decreased mortality. At the scene of injury, paramedics should administer necessary advanced life support and perform **triage** (Fig. 80.1). It is usually preferable to bypass local hospitals and rapidly transport a seriously injured child directly to a pediatric trauma center (or a trauma center with pediatric commitment). *Children have lower mortality rates, lower complication rates, and fewer operative interventions after severe blunt trauma when they are treated in designated pediatric trauma centers or in hospitals with pediatric intensive care units.*

When the receiving emergency department (ED) is notified before the child's arrival, the trauma team should be mobilized in advance. Each member has defined tasks. A senior surgeon (surgical coordinator) or an emergency physician leads the team. Team compositions vary somewhat from hospital to hospital; Figure 80.2 shows the model used at the Johns Hopkins Hospital Bloomberg Children's Center (Baltimore, MD). Consultants, especially neurosurgeons and orthopedic surgeons, must be promptly available, and the operating room staff should be alerted.

Physiologic status and mechanism of injury are used for field triage and to determine whether to activate the trauma team. More importance should be placed on physiologic compromise and less on mechanism of injury. Scoring scales such as the Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), Pediatric Trauma Score (Table 80.1), and Revised Trauma Score use these parameters to predict patient outcome. The AIS and ISS are used together. First, the AIS is used to numerically score injuries—as 1 minor, 2 moderate, 3 serious, 4 severe, 5 critical, or 6 probably lethal—in each of six ISS body regions: head/neck, face, thorax, abdomen and pelvic contents, extremities/bony pelvis, and external. The ISS is the sum of the squares of the highest three AIS region scores.

ATLS: SYSTEMATIC EVALUATION OF THE INJURED PATIENT

The American College of Surgeons (ACS) endorses a systematic approach to trauma patients known as **Advanced Trauma Life Support** (ATLS). ATLS is accepted as the standard of care for the initial assessment of injured patients and is used internationally. The approach is centered on a standardized patient evaluation that prioritizes identification and management of injuries in a specific order that addresses their immediate risk to life. ATLS principles are detailed here and include performance of the primary survey with initial adjuncts followed by the secondary survey.

PRIMARY SURVEY

During the primary survey, the trauma team quickly assesses and treats life-threatening injuries (see also Chapter 79). The principal causes of death shortly after trauma are airway obstruction, respiratory insufficiency, shock from hemorrhage, and central nervous system (CNS) injury. The primary survey addresses the **ABCDEs**: Airway, Breathing, Circulation, Disability/Neurologic Deficit, and Exposure of the patient and control of the Environment.

Airway

Optimizing oxygenation and ventilation, while protecting the cervical spine (C-spine) from potential further injury, is of paramount importance. Airway obstruction manifests as snoring, gurgling, hoarseness, stridor, and/or diminished breath sounds even with apparently good respiratory effort. Children are more likely than adults to have airway obstruction because of their smaller oral and nasal cavities, proportionately larger tongues, more tonsillar and adenoidal tissue, higher and more anterior glottic opening, and narrower larynx and trachea. Obstruction is common in patients with severe head injuries, partly because of decreased muscle tone, which allows the tongue to fall posteriorly and occlude the airway. With trauma, obstruction can also result from fractures of the mandible or facial bones, secretions such as blood or vomit, crush injuries of the larynx or trachea, and foreign body aspiration.

If it is necessary to open the airway, a jaw thrust without head tilt is recommended. This procedure minimizes cervical spine motion. In an unconscious child, an oropharyngeal airway may be inserted to prevent posterior displacement of the mandibular tissues. A semiconscious child will gag with an oropharyngeal airway but may tolerate a nasopharyngeal airway. A nasopharyngeal airway is contraindicated when there is significant nasal trauma or possibility of cribriform plate fracture. If these maneuvers plus suctioning do not clear the airway, oral endotracheal intubation is indicated. When endotracheal intubation proves difficult, a laryngeal mask airway can be used as a temporary alternative. A laryngeal mask airway consists of a tube with an inflatable cuff that rests above the larynx and thus does not require placement of the tube into the trachea. Other extraglottic devices that can be blindly inserted in a difficult airway scenario include the Combitube and King laryngeal airway tube; these devices are considered temporary and should be exchanged for a definitive airway as soon as possible. Video-assisted laryngoscopy or the use of a bougie can also be particularly helpful in the management of a difficult airway. Emergency cricothyrotomy is needed in <1% of trauma victims.

Breathing

The physician assesses breathing by counting the respiratory rate; visualizing chest wall motion for symmetry, expansion, and accessory muscle use; and auscultating breath sounds in both axillae. Pulse oximetry and continuous waveform capnography monitoring should also be used; however, they may be less reliable in patients with shock. If ventilation is inadequate, bag-valve-mask ventilation with 100% oxygen must be initiated immediately, followed by endotracheal intubation. End-expiratory carbon dioxide (CO_2) detectors or capnography help verify accurate tube placement.

Head trauma is the most common cause of respiratory insufficiency. An unconscious child with severe head injury may have a variety of breathing abnormalities, including Cheyne-Stokes respiration, slow irregular breaths, and apnea. A child with significant neurologic impairment will require endotracheal intubation and mechanical ventilation.

Although less common than a pulmonary contusion, tension pneumothorax and massive hemothorax are immediately life threatening (Tables 80.2 and 80.3). A **tension pneumothorax** occurs when air accumulates under pressure in the pleural space. The adjacent lung is compacted; the mediastinum is pushed toward the opposite hemithorax; and the heart, great vessels, and contralateral lung are compressed

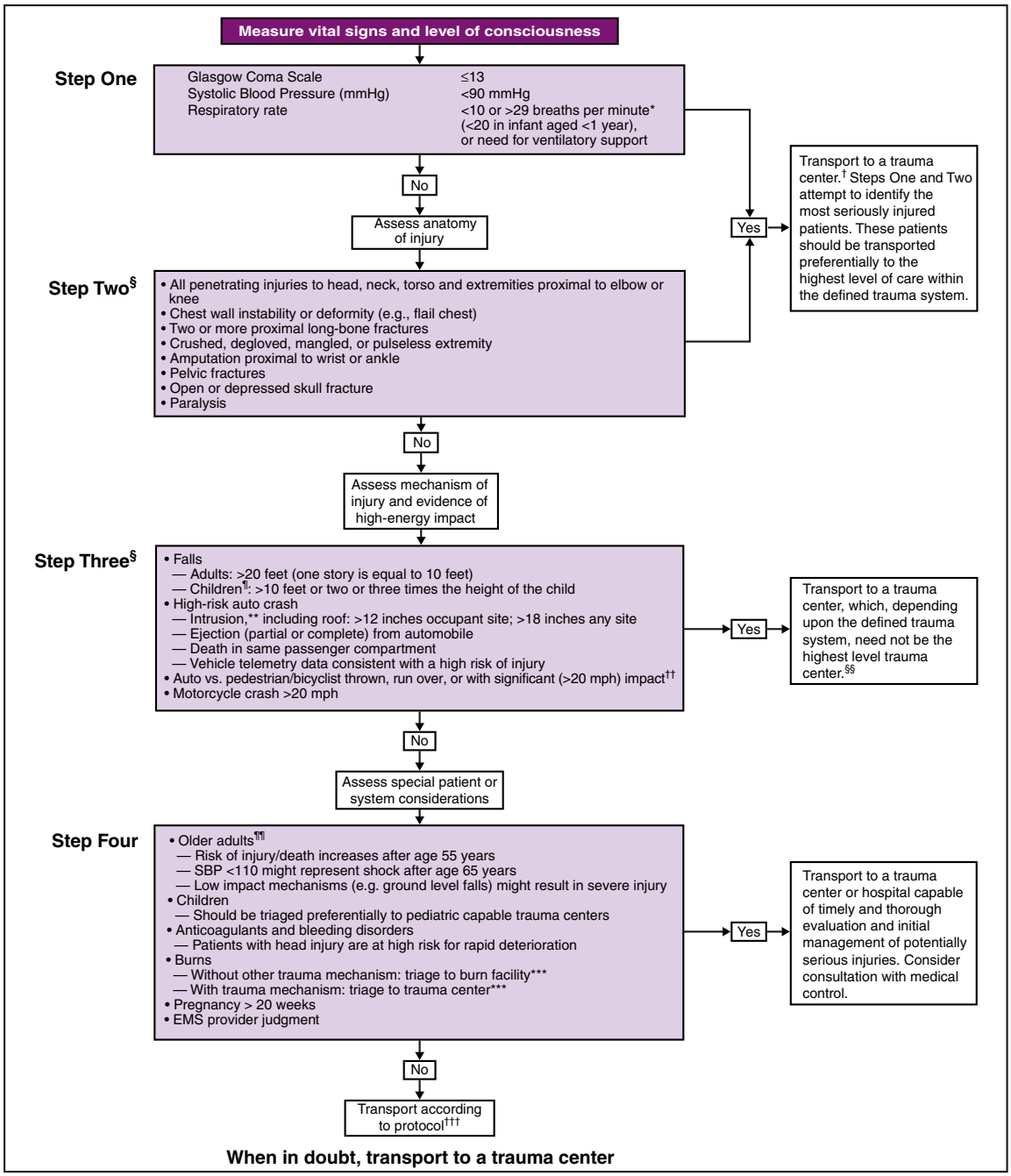

* The upper limit of respiratory rate in infants is >29 breaths per minute to maintain a higher level of overtriage for infants.
† Trauma centers are designated Level I-IV. A Level I center has the greatest amount of resources and personnel for care of the injured patient and provides regional leadership in education, research, and prevention programs. A Level II facility offers similar resources to a Level I facility, possibly differing only in continuous availability of certain subspecialties or sufficient prevention, education, and research activities for Level I designation; Level II facilities are not required to be resident or fellow education centers. A Level III center is capable of assessment, resuscitation, and emergency surgery, with severely injured patients being transferred to a Level I or II facility. A Level IV trauma center is capable of providing 24-hour physician coverage, resuscitation, and stabilization to injured patients before transfer to a facility that provides a higher level of trauma care.
§ Any injury noted in Step Two or mechanism identified in Step Three triggers a "yes" response.
¶ Age <15 years.
** Intrusion refers to interior compartment intrusion, as opposed to deformation which refers to exterior damage.
†† Includes pedestrians or bicyclists thrown or run over by a motor vehicle or those with estimated impact >20 mph with a motor vehicle.
§§ Local or regional protocols should be used to determine the most appropriate level of trauma center within the defined trauma system; need not be the highest-level trauma center.
¶¶ Age >55 years.
*** Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma presents a greater immediate risk, the patient may be stabilized in a trauma center and then transferred to a burn center.
††† Patients who do not meet any of the triage criteria in Steps One through Four should be transported to the most appropriate medical facility as outlined in local EMS protocols.

Fig. 80.1 Algorithm showing guidelines for field triage of injured patients—United States, 2011. (*From Guidelines for Field Triage of Injured Patients: Recommendations of the National Expert Panel on Field Triage. MMWR. 2012;61:6.*)

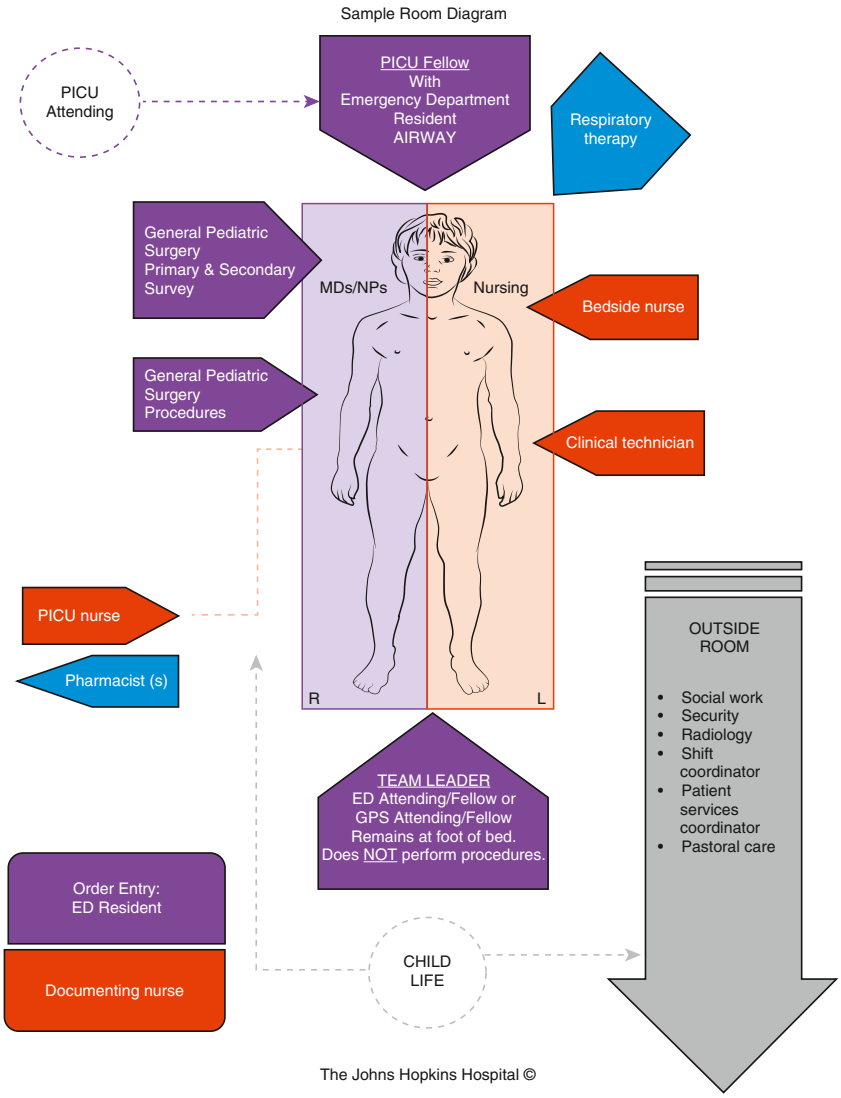

Fig. 80.2 Staff in the ED trauma bay at Johns Hopkins Hospital Bloomberg Children's Center. ED, Emergency department; NP, nurse practitioner; GPS, general pediatric surgery; PICU, pediatric intensive care unit. (*Courtesy The Johns Hopkins Hospital, Baltimore, Maryland.*)

Table 80.1 Pediatric Trauma Score*

COMPONENT	+2	+1	−1
Size	≥20 kg	10-20 kg	<10 kg
Airway	Normal	Maintainable	Unmaintainable
Systolic BP	≥90 mm Hg	50-90 mm Hg	<50 mm Hg
CNS	Awake	Obtunded/ LOC	Coma/ decerebrate
Open wound	None	Minor	Major/penetrating
Skeletal	None	Closed fracture	Open/multiple fractures
Sum total points			

*Children with a Pediatric Trauma Score ≤6 are at increased risk of mortality and morbidity.
BP, Blood pressure; CNS, central nervous system; LOC, loss of consciousness.
From Tepas JJ 3rd, Mollitt DL, Talbert JL, et al. The Pediatric Trauma Score as a predictor of injury severity in the injured child. *J Pediatr Surg.* 1987;22:14-18, Table 1, p. 15.

(see Chapter 461). Both ventilation and cardiac output are impaired. Characteristic findings include cyanosis, tachypnea, retractions, asymmetric chest rise, contralateral tracheal deviation, diminished breath sounds on the ipsilateral (more than contralateral) side, and signs of shock. When suspected, a tension pneumothorax should be treated before obtaining chest radiographs. Needle thoracentesis, followed by thoracostomy tube insertion, is diagnostic and lifesaving. **Hemothorax** results from injury to the intercostal vessels, lungs, heart, or great vessels. When ventilation is adequate, volume resuscitation should begin before evacuation, because a large volume of blood may drain through the chest tube, resulting in shock.

Circulation

Signs of **shock** include tachycardia; weak pulse; delayed capillary refill; altered mental status; and cool, mottled, or pale skin (see Chapter 85). The most common type of shock in trauma is *hypovolemic shock* caused by hemorrhage. Cardiac tamponade, which is a form of *obstructive shock,* occurs when blood or fluid accumulates in the pericardium. It may be suspected clinically with the classic findings of jugular venous distension, muffled heart sounds, and low blood pressure—collectively known as **Beck's triad**. Cardiac tamponade may be definitively diagnosed by ultrasound during a **focused assessment with sonography in**

Table 80.2 Differential Diagnosis of Immediately Life-Threatening Cardiopulmonary Injuries

	TENSION PNEUMOTHORAX	MASSIVE HEMOTHORAX	CARDIAC TAMPONADE
Breath sounds	Ipsilaterally decreased more than contralaterally	Ipsilaterally decreased	Normal
Percussion note	Hyperresonant	Dull	Normal
Tracheal location	Contralaterally shifted	Midline or shifted	Midline
Neck veins	Distended	Flat	Distended
Heart tones	Normal	Normal	Muffled

Modified from Cooper A, Foltin GL. Thoracic trauma. In: Barkin RM, ed. *Pediatric Emergency Medicine*, 2nd ed. St Louis: Mosby; 1997:325.

Table 80.3 Life-Threatening Chest Injuries

TENSION PNEUMOTHORAX
One-way valve leak from the lung parenchyma or tracheobronchial tree
Lung collapse with mediastinal and tracheal shift to the side opposite the leak
Compromises venous return and decreases ventilation of the other lung
Clinically, manifests as respiratory distress, unilateral absence of breath sounds, tracheal deviation, distended neck veins, tympany to percussion of the involved side, and cyanosis
Relieve first with needle aspiration, then with chest tube drainage

OPEN PNEUMOTHORAX (SUCKING CHEST WOUND)
Effect on ventilation depends on size

MAJOR FLAIL CHEST
Usually caused by blunt injury resulting in multiple rib fractures
Loss of bone stability of the thoracic cage
Major disruption of synchronous chest wall motion
Mechanical ventilation and positive end-expiratory pressure required

MASSIVE HEMOTHORAX
Must be drained with a large-bore tube
Initiate drainage only with concurrent vascular volume replacement

CARDIAC TAMPONADE
Beck's triad:
1. Decreased or muffled heart sounds
2. Jugular venous distention
3. Hypotension (with narrow pulse pressure)

Must be drained

Modified from Krug SE. The acutely ill or injured child. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*, 4th ed. Philadelphia: Saunders; 2002:97.

trauma (FAST) examination or echocardiography. Cardiac tamponade is best managed by thoracotomy or pericardial window, although pericardiocentesis may be a necessary temporizing maneuver (see Table 80.3).

Early in shock, blood pressure remains normal because of compensatory increases in heart rate and peripheral vascular resistance (Table 80.4). Some individuals can lose up to 30% of blood volume before blood pressure declines. Notably, 25% of blood volume equals 20 mL/kg, which is only 200 mL in a 10-kg child. Loss of >40% of blood volume causes severe hypotension that, if prolonged, may be irreversible. Direct pressure should be applied to control external hemorrhage. When direct pressure does not control hemorrhage, a tourniquet should be applied to a proximal pressure point. Blind clamping of bleeding vessels, which risks damaging adjacent structures, is not advisable.

Cannulating a larger vein, such as an antecubital vein, is usually the quickest way to achieve intravenous (IV) access (see Chapter 79). A short, large-bore catheter offers less resistance to flow, allowing for more rapid fluid administration. Ideally, a second catheter should be placed within the first few minutes of resuscitation in a severely injured child. If IV access is not rapidly obtainable, an intraosseous (IO) needle should be inserted; all medications and fluids can be administered intraosseously (see Chapter 79). Other alternatives are central venous access using the Seldinger technique (e.g., in the femoral vein) and, rarely, surgical cutdown (e.g., in the saphenous vein). Ultrasonography may be employed to safely facilitate both peripheral IV placement and central venous catheter placement.

Traditionally, fluids are administered aggressively early in hemorrhagic shock to reverse and prevent further clinical deterioration. Isotonic crystalloid solution, such as lactated Ringer's or normal saline (20 mL/kg), should be infused rapidly. When necessary, repeated crystalloid boluses may be given. Most children are stabilized with administration of crystalloid solution alone; however, if the patient remains in shock after boluses totaling 40 mL/kg of crystalloid, packed red blood cells should be transfused. Massive transfusion protocols (including fresh-frozen plasma) should be initiated early to prevent coagulopathy, and tranexamic acid (TXA) should be considered. When shock persists despite these measures, exploratory surgery to stop internal hemorrhage is usually indicated. Emerging literature suggests modern trauma techniques for adults, including permissive hypotension, hemostatic resuscitation, and damage control surgery, confer similar benefits in children.

Disability/Neurologic Deficit

Neurologic status is briefly assessed by determining the level of consciousness and evaluating pupil size and reactivity. The level of consciousness can be classified using the mnemonic **AVPU**: Alert, responsive to Verbal commands, responsive to Painful stimuli, or Unresponsive. A **Glasgow Coma Scale** (GCS) or Pediatric GCS score (see Chapters 79 and 82) should be assigned to every child with significant head trauma or neurologic impairment. This scale assesses eye opening and motor and verbal responses. In the Pediatric GCS, the verbal score is modified for age. The GCS helps categorize neurologic disability, and serial measurements identify improvement or deterioration over time. Patients with GCS ≤8 should undergo endotracheal intubation and supportive mechanical ventilation. Importantly, the patient's pupil size/reactivity and ability to move extremities should be quickly assessed before administration of anticholinergics, sedatives, and paralytics in preparation for intubation.

The majority of pediatric blunt trauma deaths are accounted for by head injuries. Primary direct cerebral injury occurs within seconds of the event and is irreversible. Secondary injury is caused by subsequent anoxia or ischemia. *The goal is to minimize secondary injury by ensuring adequate oxygenation, ventilation, and perfusion and by maintaining normal cerebral perfusion pressure.* Focal hemorrhagic lesions (e.g., epidural or subdural hematomas) are less common but may require immediate neurosurgical intervention (Fig. 80.3).

Signs of increased intracranial pressure (ICP), including progressive neurologic deterioration and evidence of transtentorial herniation, must be treated immediately (see Chapter 82). Hyperventilation lowers the arterial partial pressure of carbon dioxide ($Paco_2$), resulting in cerebral vasoconstriction, reduced cerebral blood flow, and decreased

Table 80.4 Systemic Responses to Blood Loss in Pediatric Patients

SYSTEM	MILD BLOOD LOSS (<30%)	MODERATE BLOOD LOSS (30–45%)	SEVERE BLOOD LOSS (>45%)
Cardiovascular	Increased heart rate; weak, thready peripheral pulses; normal systolic blood pressure; normal pulse pressure	Markedly increased heart rate; weak, thready central pulses; peripheral pulses absent; low normal systolic blood pressure; narrowed pulse pressure	Tachycardia followed by bradycardia; central pulses very weak or absent; peripheral pulses absent; hypotension; narrowed pulse pressure (or undetectable diastolic blood pressure)
Central nervous	Anxiety; irritability; confusion	Lethargy; dulled response to pain	Coma
Skin	Cool, mottled; capillary refill prolonged	Cyanotic; capillary refill markedly prolonged	Pale and cold
Urine output	Low to very low	Minimal	None

Adapted from American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support: Student Course Manual,* 10th ed. Chicago: American College of Surgeons; 2018:196.

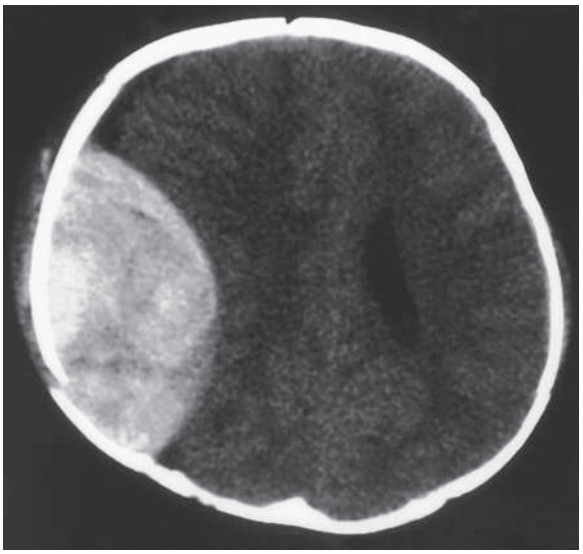

Fig. 80.3 Epidural hematoma. CT head scan from 7-mo-old female who, according to the history provided, did not wake up for her nightly feeding and began vomiting in the morning. The mother's friend reported that the infant had fallen from a chair the previous day. The CT scan shows a large epidural hematoma on the right and marked shift of the midline from right to left. The right lateral ventricle is compressed as a result of the mass effect, and the left lateral ventricle is slightly prominent. The infant underwent emergency surgical evacuation of the epidural hematoma and recovered uneventfully. (*From O'Neill JA Jr. Principles of Pediatric Surgery, 2nd ed. St Louis: Mosby; 2003:191.*)

ICP. Brief hyperventilation, targeting an end-tidal CO_2 goal of 30-35 mm Hg, remains an immediate option for patients with acute increases in ICP. Prophylactic hyperventilation, or vigorous or prolonged hyperventilation, is not recommended, because the consequent vasoconstriction may excessively decrease cerebral perfusion and oxygenation. Mannitol and hypertonic saline lower ICP and may improve survival. Because mannitol induces an osmotic diuresis, it can exacerbate hypovolemia and must be used cautiously. Hypertonic saline may be a more useful agent for control of increased ICP in patients with severe head injury. Neurosurgical consultation is mandatory and will dictate further management, including ICP monitoring and emergent neurosurgical interventions.

Exposure and Environmental Control

Full exposure of the patient occurs during the primary survey. Using trauma shears, all clothing should be removed to reveal any injuries. Cutting clothing is fastest and minimizes unnecessary patient movement. Children often arrive in the ED mildly hypothermic because of their higher body surface area–to–mass ratios. They can be warmed with use of radiant heat and heated IV fluids, as necessary. After a thorough physical exam, the patient should be covered with warmed blankets with close monitoring of body temperature.

Initial Adjuncts

While the primary survey is being performed, the patient will simultaneously be placed on a cardiac monitor, vitals obtained, and vascular access established. Fluid resuscitation can be initiated as soon as access is established. Initial laboratory work generally includes a complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function tests, lipase, lactate, blood gas, coagulation studies, type and cross match, and urinalysis. Per ATLS, portable (single, anterior-posterior view) radiographs of the chest and pelvis should be obtained to screen for life-threatening injury and identify potential causes of hemorrhage (e.g., pelvic fracture, hemothorax, great vessel injury as suggested by a widened mediastinum). Finally, a FAST exam should be performed at the bedside to assess for the presence of free fluid (blood) and guide resuscitation.

FAST Exam

The FAST exam and extended FAST (eFAST) are other adjuncts to the initial trauma survey. This bedside ultrasound can be performed by any trained member of the trauma team to assess for the presence of blood or free fluid in the intraperitoneal, pericardial, or pleural space. The exam assesses four windows: the right upper quadrant abdominal view, the left upper quadrant abdominal view, the suprapubic view, and the subxiphoid cardiac view. The eFAST adds additional views of bilateral lungs to assess for the absence of lung sliding, which is indicative of a pneumothorax. In addition to detection of hemoperitoneum, the eFAST can identify findings that may require emergent management in an unstable patient—such as a pneumothorax requiring needle decompression or a large pericardial effusion requiring pericardiocentesis.

Although the FAST examination helps detect hemoperitoneum, the variably low sensitivity of this test in children suggests that it should not be used alone to exclude intraabdominal injury in patients with a moderate to high pretest probability for injury (e.g., a patient with elevated serum lipase or transaminases). A positive FAST exam for hemoperitoneum requires further investigation. The FAST exam is most clinically useful in patients who have blunt trauma and are hemodynamically unstable or in patients who require immediate operative intervention for nonabdominal injuries, because in these cases the performance of a CT scan will delay emergency surgery.

SECONDARY SURVEY

During the secondary survey, the trauma team completes a thorough, head-to-toe physical examination to assess for additional injuries. In critically ill or hemodynamically unstable patients, emergent interventions may delay the secondary survey until the patient has been stabilized.

Head Trauma

Initial management of traumatic brain injuries is discussed earlier. The secondary survey of the head should identify and document injuries,

including scalp hematomas and lacerations. The skull and face should be carefully palpated to assess for possible fractures. Findings suggestive of basilar skull fractures include bruising around the eyes ("raccoon eyes"), bruising over the mastoid process (Battle sign), and blood behind the tympanic membrane (hemotympanum). The eyes should be assessed for conjunctival hemorrhages, hyphemas, and corneal injuries. Limitation in extraocular movements may suggest orbital fractures with muscle entrapment. The nares should be inspected for bleeding and presence of a nasal septal hematoma, which must be evacuated urgently to prevent permanent disfigurement. The mouth should be assessed for injuries to the tongue, teeth, gums, palate, and oropharynx; normal jaw mobility should be ensured. Patients with suspected head or facial injuries will typically undergo CT of the head, orbits, and/or maxillofacial region.

Spinal Trauma

Spinal Immobilization

Initially, spinal injury should be suspected in any child sustaining multiple blunt trauma. To prevent further spinal injury, paramedics have traditionally been taught to immobilize the C-spine in neutral position with a stiff collar, head blocks, and tape or cloth placed across the forehead. To immobilize the rest of the spine, the child is typically placed on a rigid backboard, and straps or tape are placed across the torso and thighs to restrain them. Care should be taken to continue spinal immobilization during initial evaluation and resuscitation until spinal injury can be excluded (see Chapter 81).

C-Spine Trauma

Cervical spine injuries occur in <3% of children with blunt trauma—with the risk being substantially higher in those with GCS scores ≤8—but they are associated with significant mortality and morbidity (see Chapter 81). Bony injuries occur mainly from C1 to C4 in children younger than 8 years. In older children, they occur equally in the upper and lower cervical spine. The mortality rate is significantly higher in patients with upper C-spine injuries, and ~30% of all patients with C-spine injuries have permanent neurologic deficits.

Evaluation

Evaluation begins with a detailed history and neurologic examination. Identifying the mechanism of injury helps in estimating the likelihood of a spinal injury. Both the patient and the paramedic should be asked whether any neurologic symptoms or signs, such as weakness or abnormal sensation, were present before arrival in the ED. The spine should then be examined while maintaining immobilization. If no other distracting injuries are present (e.g., a displaced femur fracture), the collar can be carefully removed by one provider while a second provider manually stabilizes the neck. The C-spine should be palpated to assess for tenderness or step-offs. If the patient has neck pain, has neurologic symptoms, or is unable to participate in the exam, the collar should be replaced immediately. To assess the thoracic and lumbar spine, multiple providers are required to log-roll the patient and maintain spinal immobilization. A third provider will palpate the spine, assess for cutaneous injuries, and evaluate rectal tone. Before rolling the patient back to the supine position, the backboard must be removed to prevent further injury or patient discomfort.

Whenever the history, physical examination, or mechanism of injury suggests a spinal injury, imaging must be obtained after initial resuscitation. Depending on clinical suspicion, mechanism of injury, and the patient's symptoms and physiologic status, the provider may elect either radiography, CT, or MRI as the initial imaging modality.

The **National Emergency X-Radiography Utilization Study (NEXUS)** cervical spine rule helps identify low-risk patients who may not require radiographs (Table 80.5). The standard series of plain radiographs includes lateral, anteroposterior (AP), and odontoid views. Some centers use C-spine CT as the primary diagnostic tool, particularly in patients with abnormal GCS scores or significant injury mechanisms, recognizing that CT is more sensitive in detecting bony injury than plain radiographs. CT is also helpful if an odontoid fracture is suspected, because young children typically do not cooperate enough to obtain an open-mouth (odontoid) radiographic view. Use of cervical spine CT scan must be balanced with the knowledge that CT exposes thyroid tissue to 90-200 times the amount of radiation from plain films.

Table 80.5 National Emergency X-Radiography Utilization Study (NEXUS) to Rule Out Cervical Spine Injury After Blunt Trauma

*If **NONE** of the following is present, the patient is at very low risk for clinically significant cervical spine injury:*

- Midline cervical tenderness
- Evidence of intoxication
- Altered level of alertness
- Focal neurologic deficit
- Distracting painful injury

Data from Hoffman JR, Mower WR, Wolfson AB, et al. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. *N Engl J Med.* 2000;343:94-99; and Viccellio P, Simon H, Pressman BD, et al. A prospective multicenter study of cervical spine injury in children. *Pediatrics.* 2001;108:e20.

SCIWORA

In a child with neurologic symptoms and normal findings on C-spine plain radiographs and CT scan, **spinal cord injury without radiographic abnormalities (SCIWORA)** must be considered. MRI of the spine is indicated in a child with suspected SCIWORA and in the evaluation of children who remain obtunded.

Thoracic Trauma

Pulmonary contusions occur frequently in young children with blunt chest trauma. A child's chest wall is relatively pliable; therefore less force is absorbed by the rib cage and more is transmitted to the lungs. Respiratory distress may be noted initially or may develop during the first 24 hours after injury.

Rib fractures result from significant external force. They are noted in patients with more severe injuries and are associated with a higher mortality rate. Flail chest, which is caused by multiple rib fractures, is rare in children. Table 80.6 lists indications for operative management in thoracic trauma. (See Table 80.2 for the differential diagnosis of immediately life-threatening cardiopulmonary injuries.) Thoracic trauma can be investigated via chest radiograph or CT, depending on the patient's symptoms, physical exam findings, mechanism of injury, and index of suspicion for injury.

Abdominal Trauma

Liver and spleen contusions, hematomas, and lacerations account for the majority of intraabdominal injuries from blunt trauma. The kidneys, pancreas, and duodenum are relatively spared because of their retroperitoneal location. Pancreatic and duodenal injuries are more common after a bicycle handlebar impact or a direct blow to the abdomen.

Although a thorough examination for intraabdominal injuries is essential, achieving it often proves difficult. Misleading findings can result from gastric distention after crying or in an uncooperative toddler. Calm reassurance, distraction, and gentle, persistent palpation help with the examination. Important findings include distention, bruises, and tenderness. Specific symptoms and signs give insight into the mechanism of injury and the potential for particular injuries. Pain in the left shoulder may signify splenic trauma. A lap belt mark across the abdomen raises concern for bowel or mesentery injury. The presence of certain other injuries, such as lumbar spinal fractures and femur fractures, increases the likelihood of intraabdominal injury.

An abdominal (and pelvic) CT scan with IV contrast medium enhancement rapidly identifies structural abnormalities and is the preferred study in a stable child. A negative abdominal CT scan has been shown to have a negative predictive value (NPV) of 99.6%. It has excellent sensitivity and specificity for splenic (Fig. 80.4), hepatic (Fig. 80.5), and renal injuries, but is less sensitive for diaphragmatic, pancreatic, or intestinal injuries. Small amounts of free fluid or air or a mesenteric

Table 80.6 Indications for Operation in Thoracic Trauma

THORACOTOMY IMMEDIATELY OR SHORTLY AFTER INJURY
Massive continuing pneumothorax or large air leak from tracheobronchial injury (cannot expand lung and ventilate)
Cardiac tamponade
Open pneumothorax
Esophageal injury
Aortic or other vascular injury
Acute rupture of the diaphragm
DELAYED THORACOTOMY OR THORACOSCOPY
Chronic rupture of the diaphragm
Clotted hemothorax
Persistent chylothorax
Traumatic intracardiac defects
Evacuation of large foreign bodies
Chronic atelectasis from traumatic bronchial stenosis

Modified from O'Neill JA Jr. *Principles of Pediatric Surgery,* 2nd ed. St Louis: Mosby; 2003:157.

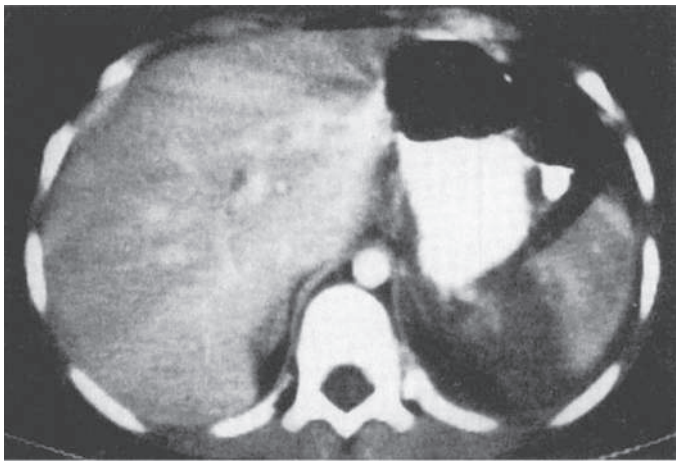

Fig. 80.4 Splenic rupture. CT scan with intravenous and gastrointestinal contrast enhancement shows an isolated splenic rupture that resulted from blunt trauma. This injury responded to nonoperative management, as do most splenic injuries. (*From O'Neill JA Jr. Principles of Pediatric Surgery, 2nd ed. St Louis: Mosby; 2003:166.*)

hematoma may be the only sign of an intestinal injury. Administration of an oral contrast agent is not routinely recommended for all abdominal CT scans, but it sometimes aids in identifying an intestinal, especially a duodenal, injury.

Nonoperative treatment has become standard for hemodynamically stable children with splenic, hepatic, and renal injuries from blunt trauma. The majority of such children can be treated nonsurgically. In addition to avoiding perioperative complications, nonoperative treatment decreases the need for blood transfusions and shortens hospital stay. When laparotomy is indicated, splenic repair is preferable to splenectomy.

Pelvic Trauma

Pelvic fractures in children are much less common than in adults, occurring in approximately 4% of children with more severe blunt trauma. Pelvic fractures are typically caused by high forces (e.g., high-speed motor vehicle crashes or pedestrian impacts) and are often associated with intraabdominal and/or vascular injuries. The pelvis itself

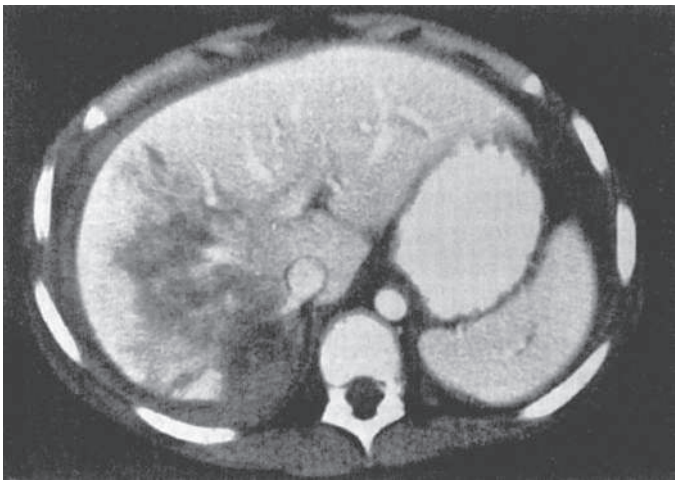

Fig. 80.5 Liver injury. CT scan performed after severe blunt injury of the abdomen shows a bursting injury of the liver. The patient was stable, and no operative intervention was required. The decision to perform surgery should be based on the patient's physiologic stability. (*From O'Neill JA Jr. Principles of Pediatric Surgery, 2nd ed. St Louis: Mosby; 2003:168.*)

forms a ring, and high-force impacts can lead to disruption of this ring. When the ring is disrupted in more than one location, such as the symphysis pubis and the sacroiliac joint, the ring can become unstable and displaced, potentially injuring large pelvic vessels and leading to massive blood loss. Catheter-directed embolization to control bleeding, performed by an interventional radiologist, may be required.

The pelvis should be assessed for stability by means of compression-distraction maneuvers. If instability is noted, immediate external fixation with a pelvis-stabilizing device or a sheet should be applied and orthopedic consultation sought. A trauma patient with a potential pelvic fracture should receive an AP pelvic radiograph in the trauma bay followed by a CT scan if there is still suspicion of injury. Children *without* a high-risk clinical finding (e.g., GCS <14; abdominal pain or tenderness; pelvic tenderness, laceration, ecchymosis, or abrasion; gross hematuria or >20 red blood cells/high-power field on urinalysis; or femur fracture) or a high-risk mechanism of injury (e.g., unrestrained motor vehicle collision, motor vehicle collision with ejection, motor vehicle collision rollover, auto vs pedestrian, or auto vs bicycle), however, are unlikely to have pelvic fractures.

Genitourinary Trauma

The perineum should be inspected and the stability of the bones of the pelvis assessed. Urethral injuries are more common in males. Findings suggestive of urethral injury include scrotal or labial ecchymosis, blood at the urethral meatus, gross hematuria, and a superiorly positioned prostate on rectal examination (in an adolescent male). Certain pelvic fractures also increase the risk for potential genitourinary injury. Any of these findings is a contraindication to urethral catheter insertion and warrants consultation with a urologist. Retrograde urethrocystogram and CT scan of the pelvis and abdomen are used to determine the extent of injury.

Extremity Trauma

Thorough examination of the extremities is essential because extremity fractures are among the most frequently overlooked injuries in children with multiple traumas. All limbs should be inspected for deformity, swelling, and bruises; palpated for tenderness; and assessed for active and passive range of motion, sensory function, and perfusion.

Before radiographs are obtained, suspected fractures and dislocations should be immobilized and an analgesic administered. Splinting a femur fracture helps alleviate pain and may decrease blood loss. An orthopedic surgeon should be consulted immediately to evaluate children with compartment syndrome, neurovascular compromise, open fracture, or traumatic amputations.

An acute extremity compartment syndrome is a surgical emergency usually associated with extremity fractures (e.g., tibia, supracondylar humerus, distal radius) but has also been noted after thermal and electric injuries, rhabdomyolysis, coagulopathies, or nephrotic syndrome. Manifestations include pain out of proportion to the injury, pain with passive stretching of the muscles, poor distal pulses, pallor, paresthesia, and weakness. In children, escalating pain not relieved by pain medications, anxiety, and agitation are additional features. If needed, compartmental pressure should be measured (normal is 8 mm Hg in adults, 10-15 mm Hg in children). Absolute pressure ≥30 mm Hg is one indication for fasciotomy. Another indication for fasciotomy is a diastolic blood pressure minus compartment pressure <30 mm Hg.

Advanced Imaging

After completion of the primary survey, diagnostic adjuncts, and secondary survey, most stable trauma patients will require advanced imaging with CT or additional plain radiographs. As detailed earlier, injury mechanism, patient history, and clinical exam findings will help determine the specific imaging to be obtained. Additionally, clinical prediction rules have been developed to identify those at low risk of injury for whom specific imaging studies may not be necessary. The NEXUS C-spine rule is a sensitive, easily applicable rule that was validated for adults and children, although there were fewer young patients studied (see Table 80.5). Several clinical prediction rules have been developed to identify children at low risk of traumatic brain injury in whom head CT can be safely avoided (Table 80.7). Another clinical prediction rule has been developed to identify children at very low risk of clinically important intraabdominal injuries after blunt trauma (Table 80.8). Although this rule has an NPV of 99.9%, it needs to be externally validated before widespread implementation. One benefit of standardizing the evaluation of patients with major trauma is that fewer decisions need to be made on an individual basis, possibly expediting ED management.

DISPOSITION

Disposition from the ED trauma bay is determined by several factors. Patients who are critically unstable with suspected internal hemorrhage are emergently transferred to the operating room (OR) for exploratory surgery before advanced imaging. Up to 30% of children evaluated for trauma require hospitalization. Of the children admitted for trauma, 30% have operative injuries identified on the physical exam or advanced imaging and undergo surgery during that hospitalization. Of those requiring surgery, 25% will require surgery within 24 hours of admission, and of that group, 57% require emergent intervention. Nonoperative patients who are critically injured will ultimately benefit from continued management in an ICU capable of caring for children and in a facility with the necessary surgical subspecialists.

PSYCHOLOGIC AND SOCIAL SUPPORT

Serious multisystem trauma may result in significant long-term psychologic and social difficulties for the child and family, particularly when there is a major head injury. Like adults, children are at risk for depressive symptoms and posttraumatic stress disorder. Caregivers face persistent stress and have been noted to have more psychologic symptoms. Psychologic and social support, during the resuscitation period and afterward, is extremely important. Parents often prefer to be offered the choice to be present during resuscitations. A member of the resuscitation team should be made responsible for answering the family's questions and supporting them in the trauma room.

Table 80.7 Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Brain Injuries After Head Trauma

*Children <2 yr old are at very low risk of clinically important traumatic brain injury if they have **NONE** of the following:*
Severe mechanism of injury
History of LOC >5 sec
GCS ≤14 or other signs of altered mental status
Not acting normally per parent
Palpable skull fracture
Occipital/parietal/temporal scalp hematoma
*Children 2-18 yr old are at very low risk of clinically important traumatic brain injury if they have **NONE** of the following:*
Severe mechanism of injury
History of LOC
History of vomiting
GCS ≤14 or other signs of altered mental status
Severe headache in the ED
Signs of basilar skull fracture

LOC, Loss of consciousness; GCS, Glasgow Coma Scale score; ED, emergency department.

Modified from Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: A prospective cohort study. *Lancet.* 2009;374:1160-1170.

Table 80.8 Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Intraabdominal Injuries After Blunt Trauma

*If **NONE** of the following is present, the patient is at very low risk for clinically significant intraabdominal injury:*
Glasgow Coma Scale score <14
Vomiting
Evidence of thoracic wall trauma
Decreased breath sounds
Evidence of abdominal wall trauma or seatbelt sign
Abdominal pain
Abdominal tenderness

Modified from Holmes JF, Lillis K, Monroe D, et al. Identifying children at very low risk of clinically important blunt abdominal injuries. *Ann Emerg Med.* 2013;62:107-116, e2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 81

Spinal Cord Injuries in Children

Katie P. Fehnel and Mark R. Proctor

See also Chapter 751.

Compared with adults, spine and spinal cord injuries are rare in children, particularly young children, because of both anatomic differences and etiologies of injury. The main mechanisms of injury to the spine are motor vehicle crashes, falls, sports, and violence, which affect young children less often (see Chapter 80).

Several anatomic differences affect the pediatric spine. The head of a young child is larger relative to body mass than in adults, and the neck muscles are still underdeveloped, which places the fulcrum of movement higher in the spine. Therefore children <9 years old have a higher percentage of injuries in the upper cervical spine (C-spine) than do older children and adults. The spine of a small child also is very mobile, with pliable bones and ligaments, so fractures of the spine are exceedingly rare. However, this increased mobility is not always a positive feature. Transfer of energy leading to spinal distortion may not affect the structural integrity of the bones and ligaments of the spine but can still lead to significant injuries of the spinal cord. This phenomenon of **spinal cord injury without radiographic abnormalities (SCIWORA)** is more common in children than in adults (see Chapter 80). The term is relatively outdated, because almost all injuries are detectable by MRI, but is still clinically useful when referring to spinal cord injuries evaluated by plain radiographs or CT. There seem to be two distinct forms of SCIWORA. The **infantile** form involves severe injury of the cervical or thoracic spinal cord; these patients have a poor chance of complete recovery. In older children and adolescents, SCIWORA is more likely to be a less severe injury, with a high likelihood of complete recovery over time. The **adolescent** form, also called *transient neurapraxia,* is assumed to be a spinal cord concussion or mild contusion, as opposed to the severe spinal cord injury related to the mobility of the spine in small children.

Although the mechanisms of spinal cord injury in children include birth trauma, falls, and child abuse, the major cause of morbidity and mortality across all ages remains **motor vehicle injuries**. Adolescents incur spinal cord injuries with epidemiology similar to that of adults, including significant male predominance and a high likelihood of fracture dislocations of the lower cervical spine or thoracolumbar region. In infants and children <5 years old, fractures and mechanical disruption of spinal elements are more likely to occur in the upper cervical spine between the occiput and C3. Certain conditions predispose to C-spine injury (Table 81.1).

Table 81.1 Conditions that Predispose Patients to a Cervical Spine Injury

CATEGORY	CONDITIONS
Abnormal development of the cervical spine	Trisomy 21 Larsen syndrome Mucopolysaccharidosis IV/Morquio syndrome Klippel-Feil syndrome Achondroplasia Chiari malformation Syringomyelia
Abnormal bone and soft tissue	Marfan syndrome Ehlers-Danlos syndrome Osteogenesis imperfecta
Arthritis	Ankylosing spondylitis Rheumatoid arthritis
History of cervical spine injury or surgery	

Modified from McCollum M, Guse S. Neck trauma: Cervical spine, seatbelt sign and penetrating palate injuries. *Emerg Med Clin N Am.* 2021;39:573-588, Table 1, p. 574.

CLINICAL MANIFESTATIONS

One in three patients with significant trauma to the spine and spinal cord will have a concomitant severe head injury, which makes early diagnosis challenging. For these patients, clinical evaluation may be difficult. Patients with a potential spine injury need to be maintained in a protective environment, such as a collar, until the spine can be cleared by clinical and/or radiographic means. A careful neurologic examination is necessary for infants with suspected spinal cord injuries. Complete spinal cord injury will lead to **spinal shock** with early areflexia (see Chapter 751). Severe C-spine injuries will usually lead to paradoxical respiration in patients who are breathing spontaneously. **Paradoxical respiration** occurs when the diaphragm, which is innervated by the phrenic nerves with contributions from C3, C4, and C5, is functioning normally, but the intercostal musculature innervated by the thoracic spinal cord is paralyzed. In this situation, inspiration fails to expand the chest wall but distends the abdomen. Other complications during the acute (2-48 hours) phase include autonomic dysfunction (bradyarrhythmias and tachyarrhythmias, orthostatic hypotension, hypertension), temperature instability, thromboembolism, dysphagia, and bowel/bladder dysfunction.

The *mildest* injury to the spinal cord is **transient quadriparesis** evident for seconds or minutes with complete recovery in 24 hours. This injury follows a concussion of the cord and is most frequently seen in adolescent athletes. If their imaging is normal, these children can generally return to normal activities after a period of rest from days to weeks, depending on the initial severity, similar to cerebral concussion management.

Significant spinal cord injury in the cervical region is characterized by flaccid quadriparesis, loss of sphincter function, and a sensory level corresponding to the level of injury. An injury at the high cervical level (C1-C2) can cause respiratory arrest and death in the absence of ventilatory support. Injuries in the thoracic region are generally the result of fracture dislocations. They may produce paraplegia when at T10 or above or the **conus medullaris syndrome** if at the T12-L1 level. This includes a loss of urinary and rectal sphincter control, flaccid weakness, and sensory disturbances of the legs. A **central cord lesion** may result from contusion and hemorrhage in the center of the spinal cord (Fig. 81.1). It typically involves the upper extremities to a greater degree than the legs because the motor fibers to the cervical and thoracic region are more centrally located in the spinal cord. There are lower motor neuron signs in the upper extremities and upper motor neuron signs in the legs, bladder dysfunction, and loss of sensation caudal to the lesion. There may be considerable recovery, particularly in the lower extremities, although sequelae are common (see Chapter 751).

CLEARING THE CERVICAL SPINE IN CHILDREN

The management of children after major trauma is challenging. For older children, the clearance is similar to a lucid adult, and the National Emergency X-Radiography Utilization Study (NEXUS) criteria are appropriate (see Chapter 80, Table 80.5). Clearing the cervical spine in younger and uncooperative children involves similar issues as in adults with an altered level of consciousness

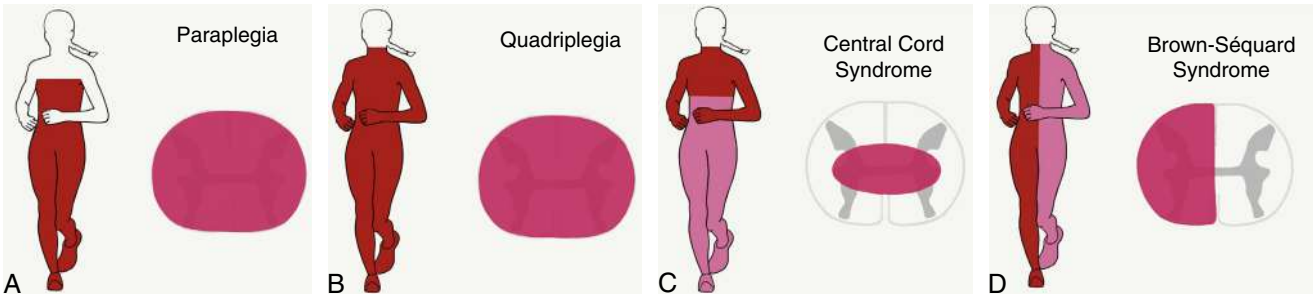

Fig 81.1 Patterns of spinal cord injury. Note the contrast between these syndromes and peripheral nerve/radicular injuries based on the distribution of motor and/or sensory loss beyond the affected extremity. *Paraplegia* (A) and *quadriplegia* (B): Complete loss of motor and sensory function below the level of injury resulting in loss of function of the legs only or arms and legs, respectively. *Central cord syndrome* (C): Injury of the central spinal cord resulting in functional greater impact of arm motor function than legs. Sensory deficits in this injury are variable. *Brown-Séquard syndrome* (D): Injury to one-half of the spinal cord resulting in ipsilateral motor weakness with contralateral sensory loss below the level of the lesion. (*From Jea A, Belal A, Zaazoue MA, Martin J. Cervical spine injury in children and adolescents. Pediatr Clin N Am. 2021;68:875-894: Fig. 11, p. 886.*)

Table 81.2 Risk Factors that Preclude Clinical Clearance of the C-Spine

HISTORY	PHYSICAL EXAMINATION
Child or parent reports persistent neck pain, abnormal head posture, or difficulty with neck movement	Visible known substantial injury to chest, abdomen, or pelvis (injury that is life-threatening, warrants surgical intervention or inpatient admission)
History of focal sensory abnormality or motor deficit	GCS of <14
High-risk injury*	Torticollis/abnormal head position
	Posterior midline neck tenderness
	Limited cervical range of motion
	Inability to maintain focus due to other injuries

*Diving, high speed motor vehicle crash, bike crash, motorized all-terrain vehicle.
GCS, Glasgow Coma Scale.
Modified from McCollum M, Guse S. Neck trauma: Cervical spine, seatbelt sign and penetrating palate injuries. *Emerg Med Clin N Am.* 2021;39:573-588, Table 2, p. 575.

(Table 81.2). Small children generally have a difficult-to-assess physical examination, and it is difficult to determine if they have cervical pain. Plain radiography remains a mainstay for assessing the spine because it is easy to obtain. There has been increasing emphasis on MRI for evaluation of potential C-spine instability, but in small children MRI requires sedation and in most centers the presence of an anesthesiologist (Fig. 81.2). CT scan is another important study with high sensitivity and specificity, but the risk of radiation exposure must be considered.

In addition to C-spine injury, neck trauma may also produce a radiculopathy or neuropathy (Table 81.3).

TREATMENT

The cervical spine should be immobilized in the field by the emergency medical technicians. In cases of acute spinal cord injury, weak data suggest acute infusion of a bolus of high-dose (30 mg/kg) methylprednisolone, followed by a 23-hour infusion (5.4 mg/kg/hr). The data for this treatment are controversial; the current neurosurgical guidelines for management of adult spine trauma do not recommend methylprednisolone; corticosteroids have not been specifically tested in children. *As such, many centers no longer use them routinely.*



Fig. 81.2 T2-weighted MRI performed the day after the accident showed cervical spinal cord swelling combined with high signal intensity (C1-C3) *(arrow)* and dislocation of C5-C6 *(arrowhead)*. (*From Inoue K, Kumada T, Fujii T, Kimura N. Progressive cervical spinal cord atrophy after a traffic accident. J Pediatr. 2017;180:287: Fig. 1, p. 287.*)

Maintenance of euvolemia and normotension is important, and vasopressors might be needed if the sympathetic nervous system has been compromised.

Surgical management of spinal injuries must be tailored to the patient's age but can be a crucial step in management. Any compression of the spinal cord must be surgically relieved to afford the best chance of a favorable outcome. In addition, spinal cord injury can be worsened by instability, so surgical stabilization can prevent further injury (Fig. 81.3). In general, younger children have a higher healing capacity for bones and ligaments, and external immobilization might be considered for injuries that require surgery in older children and adults. However, some injuries are highly unstable and always require surgery. **Occipitocervical dislocation** is one such highly unstable injury, and early surgery with fusion from the occiput to C2 or C3 should be performed, even in very young children. Fixation of the subaxial spine must be tailored to the size of the pedicles and other osseous structures of the developing axial skeleton.

Table 81.3 History and Examination Features Allowing for Discrimination of Myelopathy, Radiculopathy, and Peripheral Neuropathy

FINDING	PERIPHERAL NEUROPATHY	RADICULOPATHY	MYELOPATHY
Pain • Quality • Location	"Electric" Radiates either proximally or distally from injury site	Sharp, aching Radiates distally from the neck	Typically painless
Weakness	Variable, usually present	Variable, usually present	Variable, may be present
Sensory loss	Sharply demarcated borders	Indistinct borders	Indistinct borders, typically extends beyond single extremity
Tone/reflexes	Decreased	Decreased	Increased

From Jea A, Belal A, Zaazoue MA, Martin J. Cervical spine injury in children and adolescents. *Pediatr Clin N Am.* 2021;68:875-894, Table 4, p. 883.

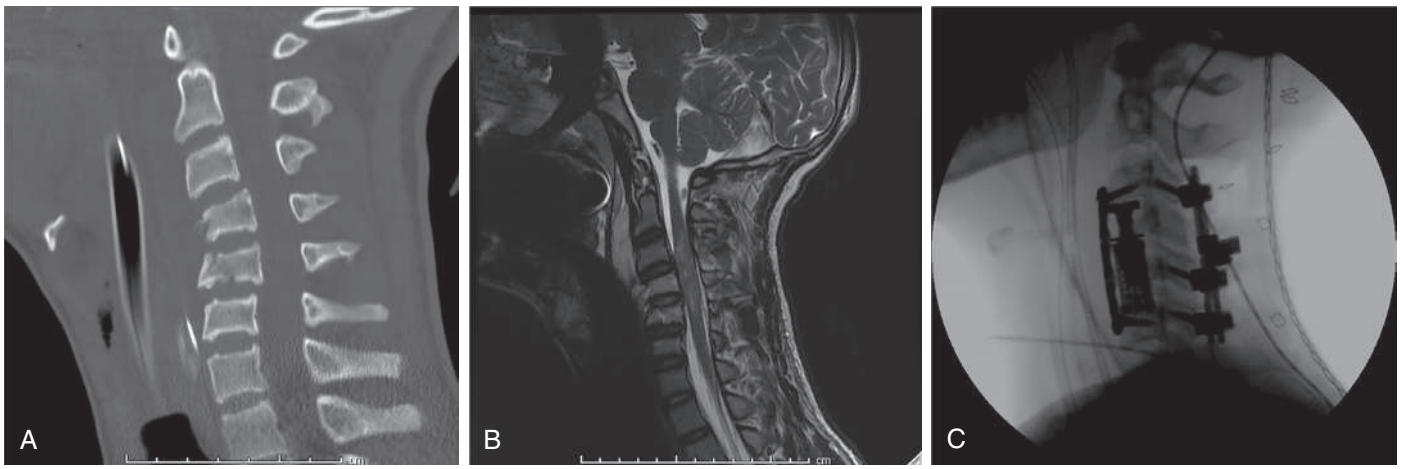

Fig. 81.3 A 15-year-old hockey player suffered acute paraplegia after his head struck the boards during a hockey game. **A,** CT scan shows compression fractures of C4 and C5. **B,** MRI shows severe spinal cord contusion. **C,** Because of the need to decompress the spinal cord and stabilize the spine, anterior and posterior surgery was performed. No meaningful recovery was obtained.

PREVENTION

The most important aspect of the care of spinal cord injuries in children is injury prevention. Use of appropriate child restraints in automobiles is the most important precaution. In older children and adolescents, rules against "spear tackling" in American football and the *Feet First, First Time* aimed at adolescents diving into swimming pools and natural water areas are important ways to help prevent severe cervical spinal cord injuries. Safe driving practices, such as using safety belts, avoiding distracted driving, and following the speed limit, can have substantial beneficial effects on injury rates.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 82

Neurologic Emergencies and Stabilization

Patrick M. Kochanek and Michael J. Bell

NEUROCRITICAL CARE PRINCIPLES

The brain has high metabolic demands, which are further increased during growth and development. Preservation of nutrient supply to the brain is the mainstay of care for children with evolving brain injuries. *Intracranial dynamics* describes the physics of the interactions of the contents—brain parenchyma, blood (arterial, venous, capillary), and cerebrospinal fluid (CSF)—within the cranium. Normally, brain parenchyma accounts for up to 85% of the contents of the cranial vault, and the remaining portion is divided between CSF and blood. The brain resides in a relatively rigid cranial vault, and cranial compliance decreases with age as the skull ossification centers gradually replace cartilage with bone. The **intracranial pressure (ICP)** is derived from the volume of its components and the bony compliance. The **perfusion pressure** of the brain (cerebral perfusion pressure [CPP]) is equal to the pressure of blood entering the cranium (mean arterial pressure [MAP]) minus the ICP, in most cases.

Increases in intracranial volume can result from swelling, masses, or increases in blood and CSF volumes. As these volumes increase, compensatory mechanisms prevent increases in ICP by (1) decreasing CSF volume (CSF is displaced into the spinal canal or absorbed by arachnoid villi), (2) decreasing cerebral blood volume (venous blood return to the thorax is augmented), and/or (3) increasing cranial volume (sutures pathologically expand or bone is remodeled). Once compensatory mechanisms are exhausted (the increase in cranial volume is too large), small increases in volume lead to clinically meaningful increases in ICP or intracranial hypertension (Fig. 82.1). As ICP continues to increase, brain ischemia can occur as CPP falls. Further increases in ICP can ultimately displace the brain downward into the foramen magnum—a process called **cerebral herniation**, which can become irreversible in minutes and may lead to severe disability or death; Figure 82.2 notes other sites of brain herniation.

Oxygen and glucose are required by brain cells for normal functioning, and these nutrients must be constantly supplied by cerebral blood flow (CBF). Normally, CBF is constant over a wide range of blood pressures (blood pressure autoregulation of CBF) via actions mainly within

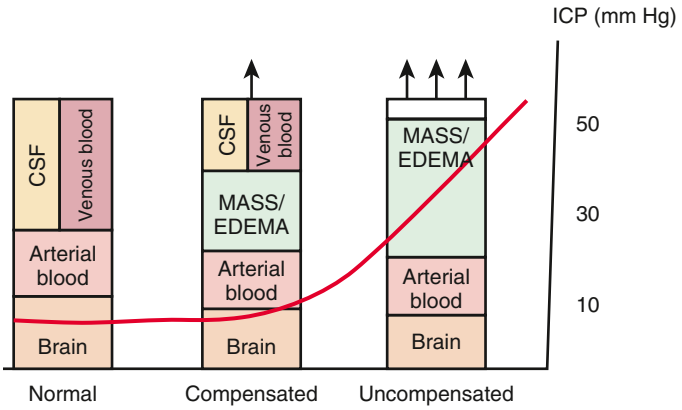

Fig. 82.1 The Munro-Kellie doctrine describes intracranial dynamics in the setting of an expanding mass lesion (i.e., hemorrhage, tumor) or brain edema. In the normal state, the brain parenchyma, arterial blood, CSF, and venous blood occupy the cranial vault at a low pressure, generally <10 mm Hg. With an expanding mass lesion or brain edema, initially there is a compensated state as a result of reduced CSF and venous blood volumes, and ICP remains low. Further expansion of the lesion, however, leads to an uncompensated state when compensatory mechanisms are exhausted and intracranial hypertension results.

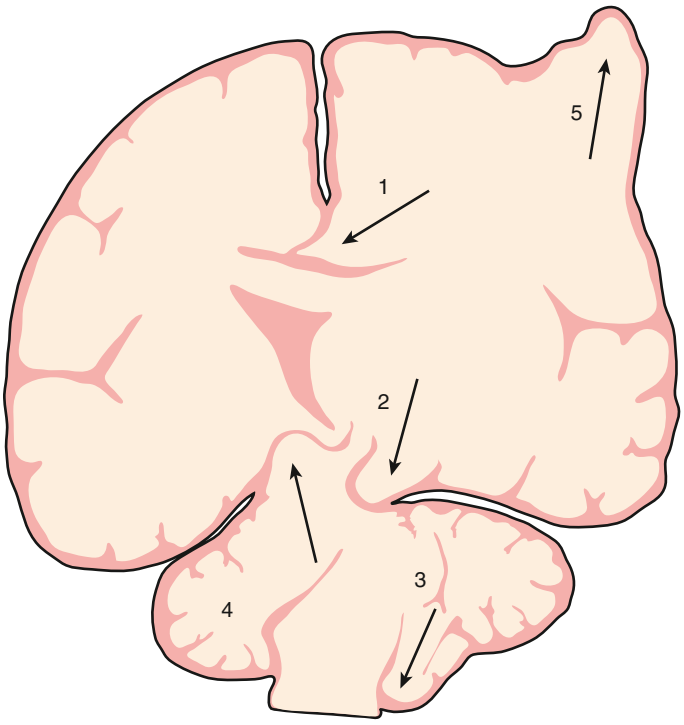

Fig. 82.2 Different forms of brain herniation. *1*, Cingulate. *2*, Uncal. *3*, Cerebellar tonsillar. *4*, Upward cerebellar. *5*, Transcalvarial. *(From Fishman RA. Cerebrospinal Fluid in Diseases of the Nervous System. Philadelphia: Saunders; 1980.)*

the cerebral arterioles. Cerebral arterioles are maximally dilated at lower blood pressures and maximally constricted at higher pressures so that CBF does not vary during normal fluctuations (Fig. 82.3). Above the upper limit of autoregulation, breakthrough dilation occurs that, if severe, can produce hypertensive encephalopathy. Acid-base balance of the CSF (often reflected by acute changes in arterial partial pressure of carbon dioxide [$Paco_2$]), body/brain temperature, glucose utilization,

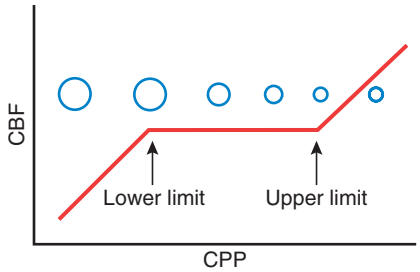

Fig. 82.3 Schematic of the relationship between CBF and CPP. The diameter of a representative cerebral arteriole is also shown across the center of the *y* axis to facilitate understanding of the vascular response across CPP that underlies blood pressure autoregulation of CBF. CPP is generally defined as the mean arterial pressure (MAP) minus the ICP. At normal values for ICP, this generally represents MAP. Thus, normally, CBF is kept constant between the lower limit and upper limit of autoregulation; in normal adults, these values are ≈50 mm Hg and 150 mm Hg, respectively. In children, the upper limit of autoregulation is likely proportionally lower than the adult value relative to normal MAP for age. However, according to the work of Vavilala et al. (2003), lower limit values are surprisingly similar in infants and older children. Thus infants and young children may have less reserve for adequate CPP. See text for details.

blood viscosity, and other vasoactive mediators (i.e., adenosine, nitric oxide, prostanoids) can also affect the cerebral vasculature.

Knowledge of these concepts is instrumental to preventing secondary brain injury. Increases in CSF pH that occur because of inadvertent hyperventilation (decreased $Paco_2$) can produce cerebral ischemia. Hyperthermia-mediated increases in cerebral metabolic demands may damage vulnerable brain regions after injury. Hypoglycemia can produce neuronal death when CBF fails to compensate. Prolonged seizures can lead to permanent injuries if hypoxemia occurs from loss of airway control.

Attention to detail and constant reassessment are paramount in managing children with critical neurologic insults. Among the most valuable tools for serial, objective assessments of neurologic condition is the **Glasgow Coma Scale (GCS)** (Table 82.1 and see Table 79.3). Originally developed to assess level of consciousness after traumatic brain injury (TBI) in adults, the GCS is also valuable in pediatrics. Modifications to the GCS have been made for nonverbal children and are available for infants and toddlers (see Table 79.3 in Chapter 79). Serial assessments of the GCS score along with a focused neurologic examination are invaluable to detect injuries before permanent damage occurs in the vulnerable brain. The **FOUR (full outline of unresponsiveness) score** (see Table 82.1) is a modification of the GCS, which eliminates the patient's verbal response but adds functional assessments of the brainstem (pupil, corneal, and cough reflexes) and respiratory pattern.

The most-studied monitoring device in clinical practice is the **ICP monitor**. Monitoring is accomplished by a catheter inserted either into the cerebral ventricle (externalized ventricular drain) or into brain parenchyma (parenchymal transducer). ICP-directed therapies are standard of care in TBI and are used in other conditions, such as intracranial hemorrhage, Reye syndrome, and some cases of encephalopathy, meningitis, and encephalitis. Other devices being used include catheters that measure brain tissue oxygen concentration, external probes that noninvasively assess brain oxygenation by absorbance of near-infrared light (near-infrared spectroscopy [NIRS]), monitors of brain electrical activity (continuous electroencephalography [EEG] or somatosensory, visual, or auditory evoked potentials), and CBF monitors (transcranial Doppler, xenon CT, perfusion MRI, or tissue probes). In the severe TBI guidelines, brain tissue oxygen concentration monitoring received level III support and thus may be considered as an adjunct to ICP-directed therapy.

Table 82.1 Commonly Used Coma Scores

GLASGOW COMA SCALE

Eye Opening
1 = does not open eyes
2 = opens eyes in response to noxious stimuli
3 = opens eyes in response to voice
4 = opens eyes spontaneously

Verbal Output
1 = makes no sounds
2 = makes incomprehensible sounds
3 = utters inappropriate words
4 = confused and disoriented
5 = speaks normally and oriented

Motor Response (Best)
1 = makes no movements
2 = extension to painful stimuli
3 = abnormal flexion to painful stimuli
4 = flexion/withdrawal to painful stimuli
5 = localized to painful stimuli
6 = obeys commands

FULL OUTLINE OF UNRESPONSIVENESS (FOUR) SCORE

Eye Response
4 = eyelids open or opened, tracking, or blinking to command
3 = eyelids open but not tracking
2 = eyelids closed but open to loud voice
1 = eyelids closed but open to pain
0 = eyelids remain closed with pain

Motor Response
4 = thumbs-up, fist, or peace sign
3 = localizing to pain
2 = flexion response to pain
1 = extension response to pain
0 = no response to pain or generalized myoclonus status

Brainstem Reflexes
4 = pupil and corneal reflexes present
3 = one pupil wide and fixed
2 = pupil or corneal reflexes absent
1 = pupil and corneal reflexes absent
0 = absent pupil, corneal, and cough reflex

Respiration
4 = not intubated, regular breathing pattern
3 = not intubated, Cheyne-Stokes breathing pattern
2 = not intubated, irregular breathing
1 = breathes above ventilatory rate
0 = breathes at ventilator rate or apnea

From Edlow JA, Rabinstein A, Traub SJ, Wijdicks EFM. Diagnosis of reversible causes of coma. *Lancet.* 2014;384:2064-2076.

TRAUMATIC BRAIN INJURY

Etiology

Mechanisms of TBI include motor vehicle crashes, falls, assaults, and abusive head trauma. Most TBIs in children are from closed-head injuries.

Epidemiology

TBI is an important pediatric public health problem, with over 800,000 emergency department visits, 23,000 hospitalizations, and over 2,500 deaths in children annually in the United States. It is also 1 of the top 10 causes of years lost to disability throughout infancy, childhood, and adolescence.

Pathology

Epidural, subdural, and parenchymal intracranial hemorrhages can result. Injury to gray or white matter is also commonly seen and includes focal cerebral contusions, diffuse cerebral swelling, axonal injury, and injury to the cerebellum or brainstem. Patients with severe TBI often have multiple findings; diffuse and potentially delayed cerebral swelling is common.

Pathogenesis

TBI results in primary and secondary injury. Primary injury from the impact produces irreversible tissue disruption. In contrast, two types of secondary injury are targets of neurointensive care. First, some of the ultimate damage seen in the injured brain evolves over hours or days, and the underlying mechanisms involved (including edema, apoptosis, programmed necrosis, and secondary axotomy) are therapeutic targets. Second, the injured brain is vulnerable to additional insults because injury disrupts normal autoregulatory defense mechanisms; disruption of autoregulation of CBF can lead to ischemia from hypotension that would otherwise be tolerated by the uninjured brain.

Clinical Manifestations

The hallmark of **severe TBI** is coma **(GCS score 3-8)**. Coma is often seen immediately after the injury and is sustained. In some cases, such as with an epidural hematoma, a child may be initially alert on presentation but may deteriorate after a period of hours. A similar picture can be seen in children with diffuse swelling in whom a *talk-and-die* scenario has been described. Clinicians should also not be lulled into underappreciating the potential for deterioration of a child with **moderate TBI (GCS score 9-12)** with a significant contusion, because progressive swelling can potentially lead to devastating complications. In the comatose child with severe TBI, the second key clinical manifestation is the development of *intracranial hypertension*. The development of increased ICP with impending herniation may be heralded by new-onset or worsening headache, depressed level of consciousness, vital sign changes (hypertension, bradycardia, irregular respirations), and signs of sixth (lateral rectus palsy) or third (anisocoria [dilated pupil], ptosis, down-and-out position of globe as a result of rectus muscle palsies) cranial nerve compression. Increased ICP is managed with continuous ICP monitoring, as well as monitoring for clinical signs of increased ICP or impending herniation. The development of brain swelling is progressive. Significantly raised ICP (>20 mm Hg) can occur early after severe TBI, but peak ICP generally is seen at 48-72 hours. Need for ICP-directed therapy may persist for longer than a week. A few children have coma without increased ICP resulting from axonal injury or brainstem injury. *In addition to head trauma, it is critical to identify potential cervical spine injury* (see Chapter 81).

Laboratory Findings

Cranial CT should be obtained immediately after resuscitation and cardiopulmonary stabilization (Figs. 82.4-82.10). In some cases, MRI can be diagnostic (Fig. 82.11). An approach to CT scanning is noted in Figure 82.12. Generally, other laboratory findings are normal in isolated TBI, although occasionally coagulopathy or the development of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion or cerebral salt wasting (CSW) is seen. In the setting of TBI with polytrauma, other injuries can result in laboratory and/or radiographic abnormalities, and a **full trauma survey** is important in all patients with severe TBI (see Chapter 80).

Diagnosis and Differential Diagnosis

In severe TBI, the diagnosis is generally obvious from the history and clinical presentation. Occasionally, TBI severity can be overestimated because of concurrent alcohol or drug intoxication. The diagnosis of TBI can be problematic in cases of abusive head trauma or after an anoxic event such as drowning or smoke inhalation.

Treatment

Infants and children with severe or moderate TBI (GCS score 3-8 or 9-12, respectively) receive intensive care unit (ICU) monitoring. Evidence-based guidelines for the management of severe TBI have been published (Fig. 82.13 and Fig. 82.14). This approach to ICP-directed therapy is also reasonable for other conditions in which ICP is monitored. Care involves a multidisciplinary team comprising pediatric caregivers from neurologic surgery, critical care medicine, surgery, and rehabilitation, among other services, and is directed at

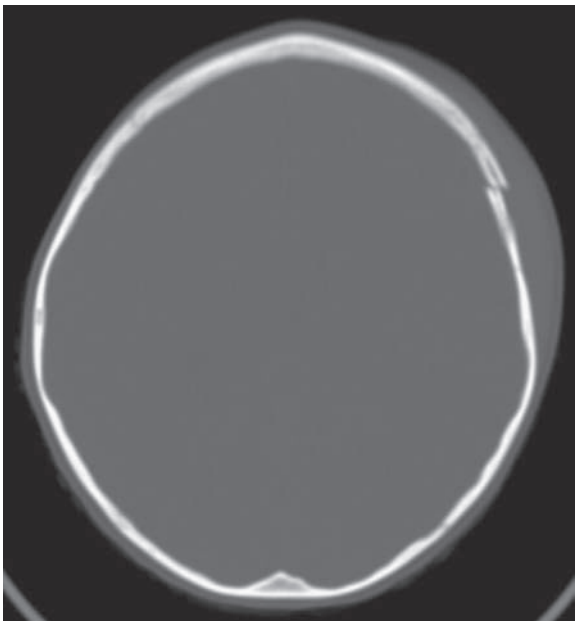

Fig. 82.4 Skull fracture. Mildly displaced skull fracture seen on CT imaging (bone window view) in a 4-year-old who fell and hit her head on a curb.

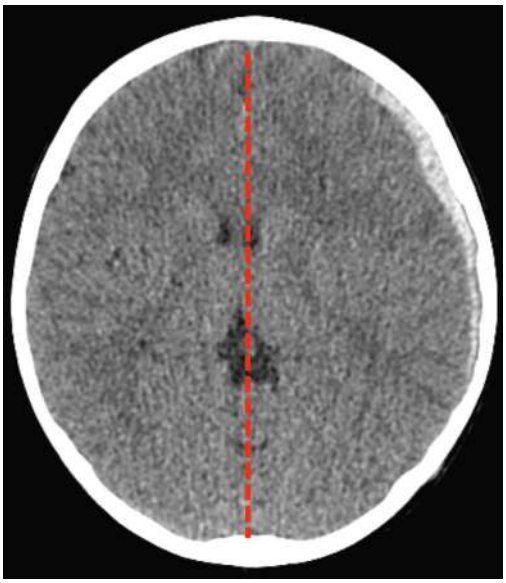

Fig. 82.6 Subdural hematoma. Left subdural hematoma observed on CT imaging in a 10-year-old child after a motor vehicle accident. Note effacement of the left lateral ventricle and midline shift (see *dashed line* for midline reference).

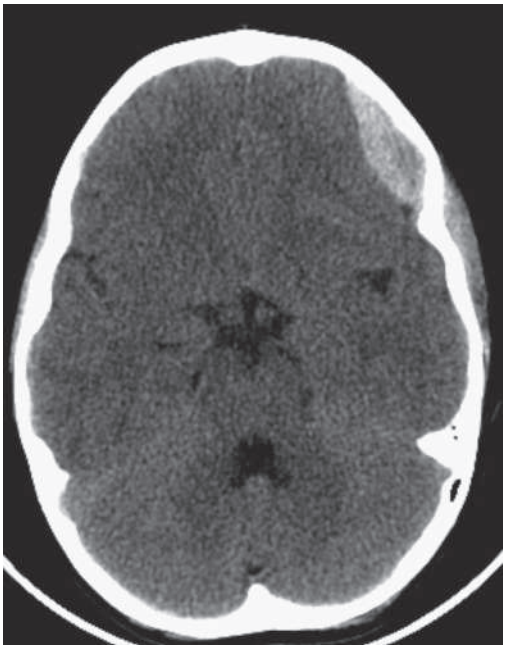

Fig. 82.5 Epidural hematoma. Left frontal epidural hematoma observed on CT imaging in a 12-year-old child who fell off his bike onto a concrete surface.

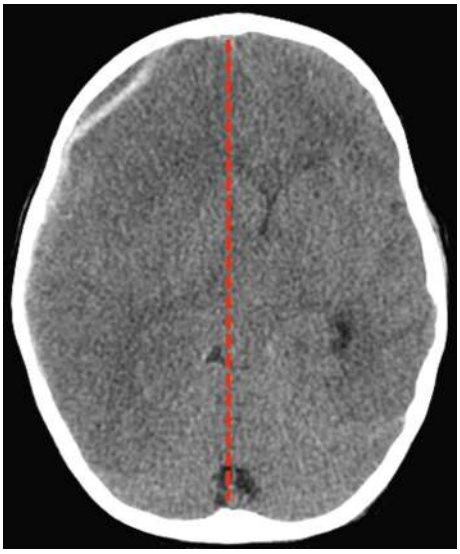

Fig. 82.7 Subdural hematoma. Hyperacute right frontal subdural hematoma observed on CT imaging in a 5-year-old after a motor vehicle accident. Note that the hyperacute aspect of the subdural hematoma is dark on CT imaging in the early stage after injury. Also, note that there is marked midline shift of intracranial contents, as both lateral ventricles are displaced into the left side of the skull.

preventing secondary insults and managing raised ICP. Initial stabilization of infants and children with severe TBI includes rapid sequence tracheal intubation with spine precautions along with maintenance of normal extracerebral hemodynamics, including blood gas values (Pao_2 and $Paco_2$), MAP, and temperature. Intravenous fluid boluses may be required to treat hypotension. Euvolemia is the target, and hypotonic fluids must be rigorously avoided; *normal saline is the fluid of choice*. Pressors may be needed as guided by monitoring of central venous pressure, with avoidance of both fluid overload and exacerbation of brain edema. A trauma survey should be performed. Once stabilized, the patient should be taken for CT scanning to rule out the need for emergency neurosurgical intervention. If surgery is not required, an ICP monitor should be inserted to guide the treatment of intracranial hypertension. Repeat CT scan may help determine whether a new lesion requiring surgical intervention has developed; this should be obtained if there is a change in examination or for refractory intracranial hypertension.

During stabilization or at any time during the treatment course, patients can present with signs and symptoms of *cerebral herniation* (pupillary dilation, systemic hypertension, bradycardia, extensor posturing). Because herniation and its devastating consequences can sometimes be reversed if promptly addressed, it should be treated as a medical emergency, with use of hyperventilation with a fraction of inspired oxygen of 1.0 titrated to reversal of pupillary dilation and

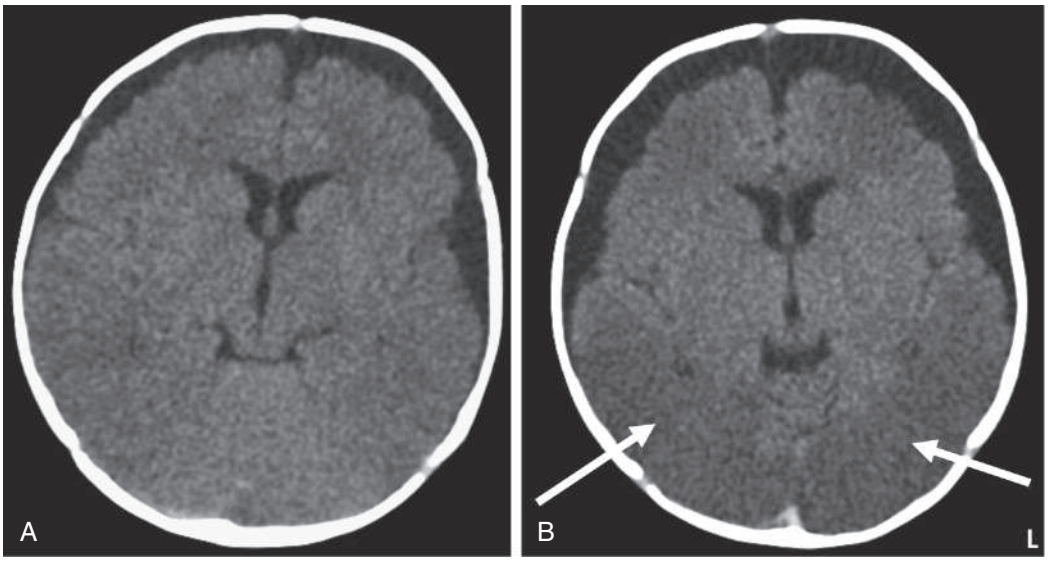

Fig. 82.8 Subdural hematoma. In a 3-month-old child who suffered from abusive head trauma, initial CT imaging (A) demonstrates chronic subdural hematoma bilaterally. Three days after hospitalization (B), the subdural hematomas are slightly larger but infarctions are noted in the posterior areas of brain parenchyma (*arrows*).

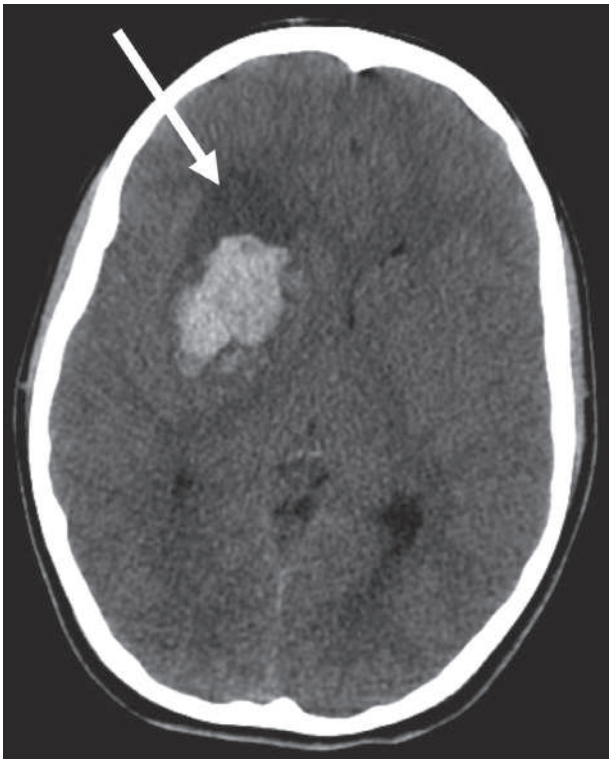

Fig. 82.9 Hemorrhage and edema. In a 16-year-old who fell from his dirt bike, CT imaging demonstrates intraparenchymal hemorrhage and significant surrounding edema *(arrow).*

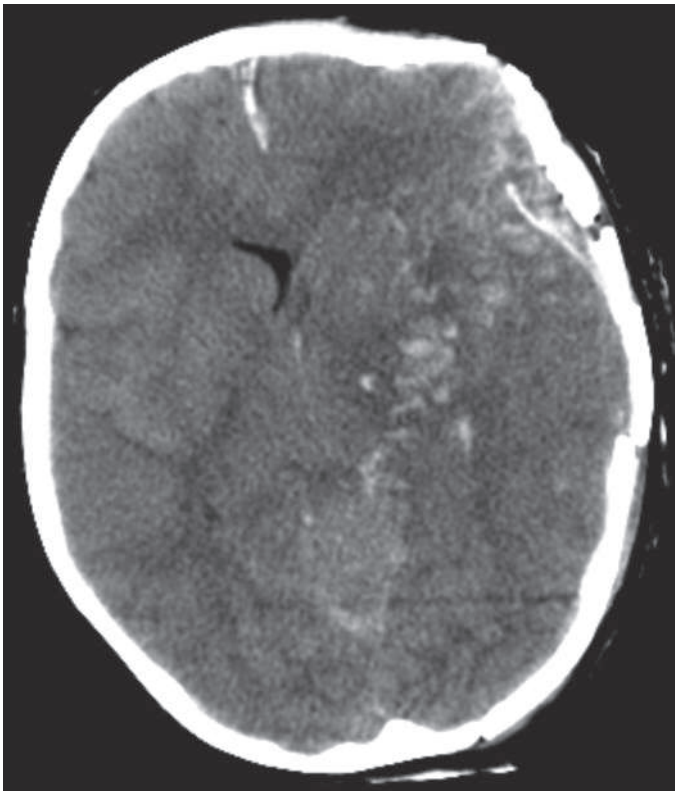

Fig. 82.10 Skull fractures and hemorrhage. An 11-year-old child was hit in the head by a horse, and CT imaging demonstrates multiple comminuted skull fractures with fragments of bone within the brain parenchyma, multifocal areas of intraparenchymal hemorrhage, and obliteration of the left lateral ventricle.

administration of either hypertonic saline (3% solution, 5-10 mL/kg IV) or mannitol (0.25-1.0 g/kg IV). If an external ventricular drain is in place, it should be opened to continuous drainage. Pentobarbital administration can also be considered if a prompt clinical response has not been observed.

ICP should be maintained at <20 mm Hg; age-dependent CPP targets are approximately 50 mm Hg for children 2-6 years of age, 55 mm Hg for those 7-10 years of age, and 65 mm Hg for those 11-16 years of age. **First-tier** therapy includes elevation of the head of the bed, ensuring midline positioning of the head, controlled mechanical ventilation, and analgesia and sedation (i.e., narcotics and benzodiazepines). If neuromuscular blockade is needed, it may be desirable to monitor EEG continuously because *status epilepticus* can occur; this complication will not be recognized in a paralyzed patient and is associated with raised ICP and unfavorable outcome. If a ventricular rather than parenchymal catheter is used to monitor ICP, therapeutic CSF drainage is available and can be provided either continuously (often targeting an ICP >5 mm Hg) or intermittently in response to ICP spikes, generally >20

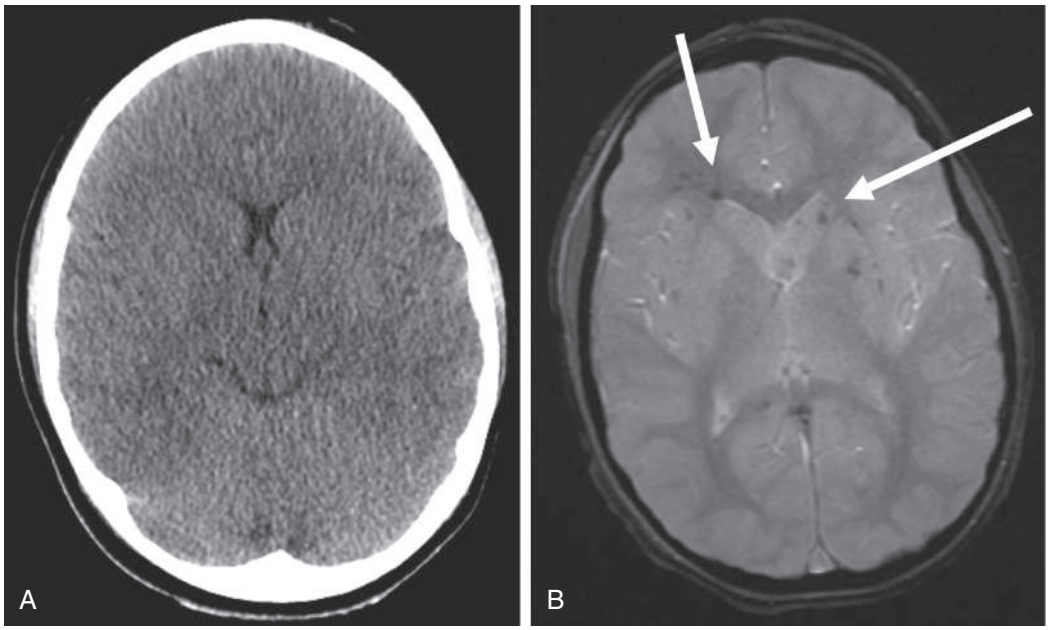

Fig. 82.11 Hemorrhages and axonal injury. In a 6-year-old child who was hit by a car while riding his bike, initial CT imaging demonstrates no obvious abnormality (**A**). However, immediate MRI demonstrates multiple areas of punctate hemorrhages (lucencies) consistent with diffuse axonal injury (**B**, *arrows*).

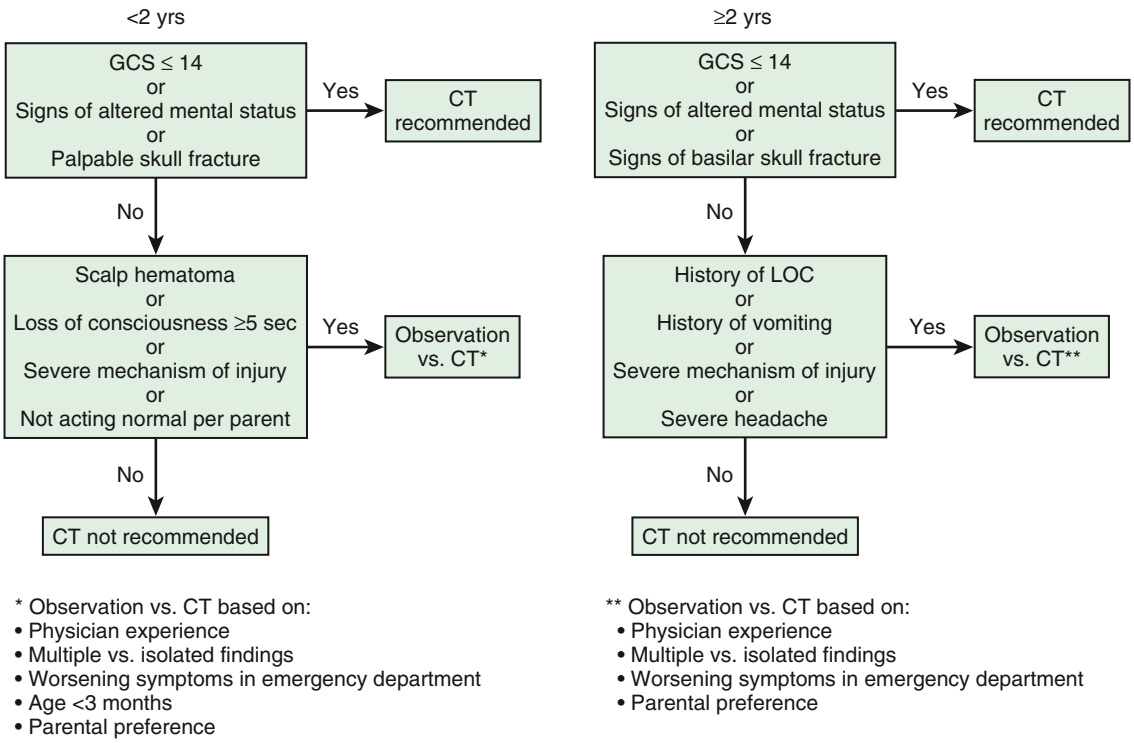

Fig. 82.12 Algorithm for head computed tomography (CT) scan using predictive rules. GCS, Glasgow Coma Scale; LOC, level of consciousness. *(Modified from Kupperman N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically important brain injuries after head trauma: A prospective cohort study.* Lancet. *2009;374:1160-1170.)*

mm Hg. Other first-tier therapies include the osmolar agents hypertonic saline or mannitol. Bolus administration of 3% **hypertonic saline** (between 2 and 5 mL/kg over 10-20 minutes) has guideline-based level II evidence supporting its use to treat ICP spikes >20 mm Hg or using a fixed (q4-q6h) dosing interval. It can also be given as a continuous infusion of 3% saline at 0.1-1.0 mL/kg/hr. **Mannitol** (0.25-1.0 g/kg IV over 20 minutes) represents an alternative. These agents can be used concurrently. It is recommended to avoid serum osmolality >320 mOsm/L. A Foley urinary catheter should be placed to monitor urine output.

If increased ICP remains refractory to treatment, careful reassessment of the patient is needed to rule out unrecognized hypercarbia, hypoxemia, fever, hypotension, hypoglycemia, pain, and seizures. Repeat imaging should be considered to rule out a surgical lesion. Guideline-based **second-tier** therapies for refractory raised ICP are available, but evidence favoring a given second-tier therapy is limited.

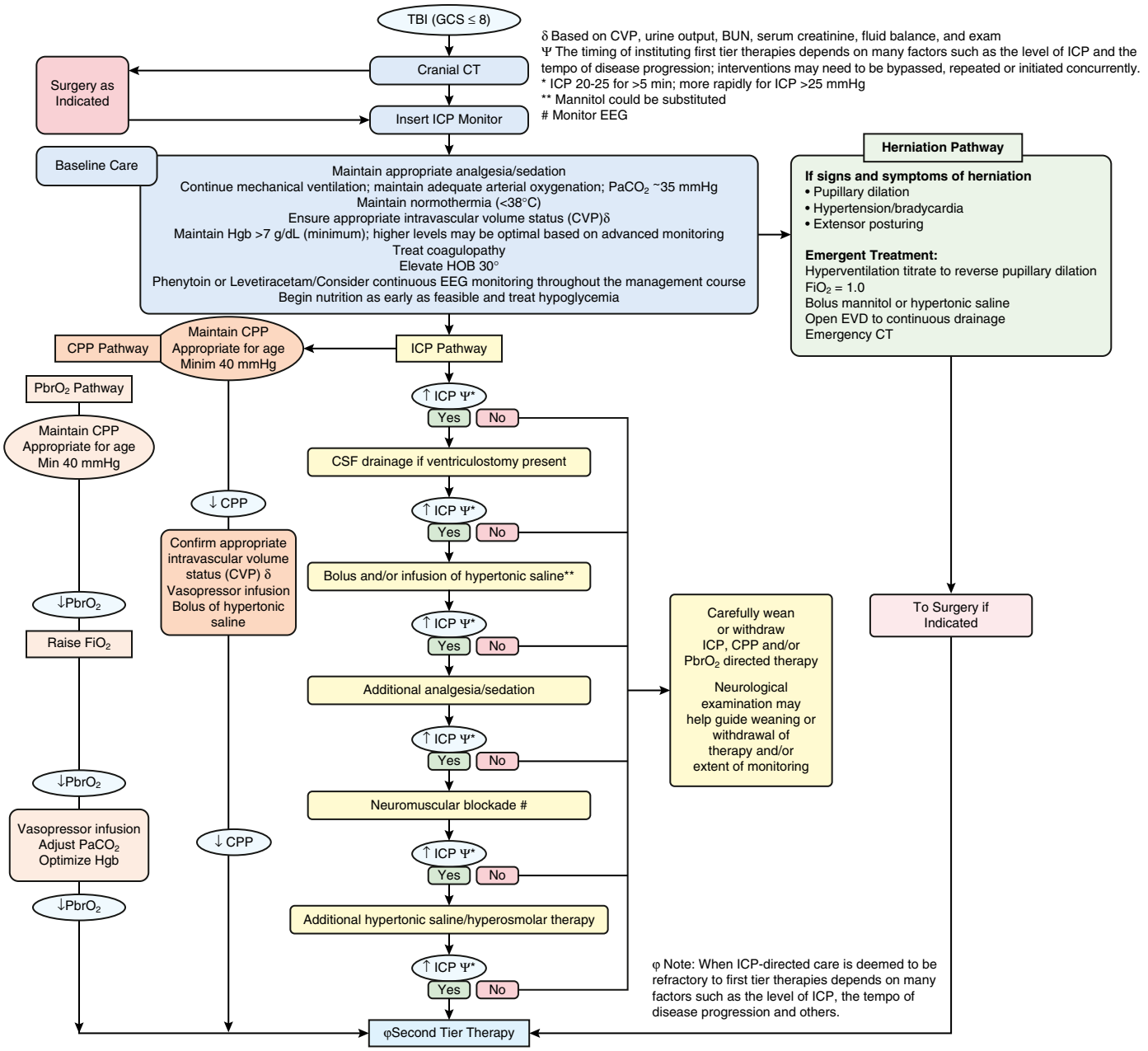

Fig. 82.13 Algorithm for use at the bedside to guide first-tier therapies to treat severe pediatric traumatic brain injury (TBI). This evidence- and consensus-based document that accompanied the third edition of the guidelines includes baseline care *(gray)*, an intracranial pressure (ICP) pathway *(yellow)*, a herniation pathway *(green)*, a cerebral perfusion pressure (CPP) pathway *(orange)*, a brain tissue partial pressure of oxygen ($PbrO_2$) pathway (purple), and surgical intervention (red). The caregiver should integrate all the available information and implement the evidence in the guidelines in the context of each patient's unique response to therapies to craft the most optimal treatment regimen. Although a linear approach in each pathway is provided, variations in tempo and timing during which therapies are implemented will vary from case to case. In some cases, a single intervention for raised ICP may suffice, whereas in others, multiple simultaneous interventions may be required. The *blue box* indicates the need for second-tier therapy (see Fig. 82.14). BUN, Blood urea nitrogen; CSF, cerebrospinal fluid; CT, computed tomography; CVP, central venous pressure; EEG, electroencephalogram; EVD, external ventricular drain; FiO_2, fraction of inspired oxygen concentration; GCS, Glasgow Coma Scale; Hgb, hemoglobin; HOB, head of bed; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen. *(From Kochanek PM, Bell MJ, Simon DW, et al. Traumatic brain injury. In: Zimmerman JJ, Totta AT, eds. Fuhrman & Zimmerman's Pediatric Critical Care, 6th ed. Philadelphia: Elsevier; 2022: Fig. 118.11, p. 1391.)*

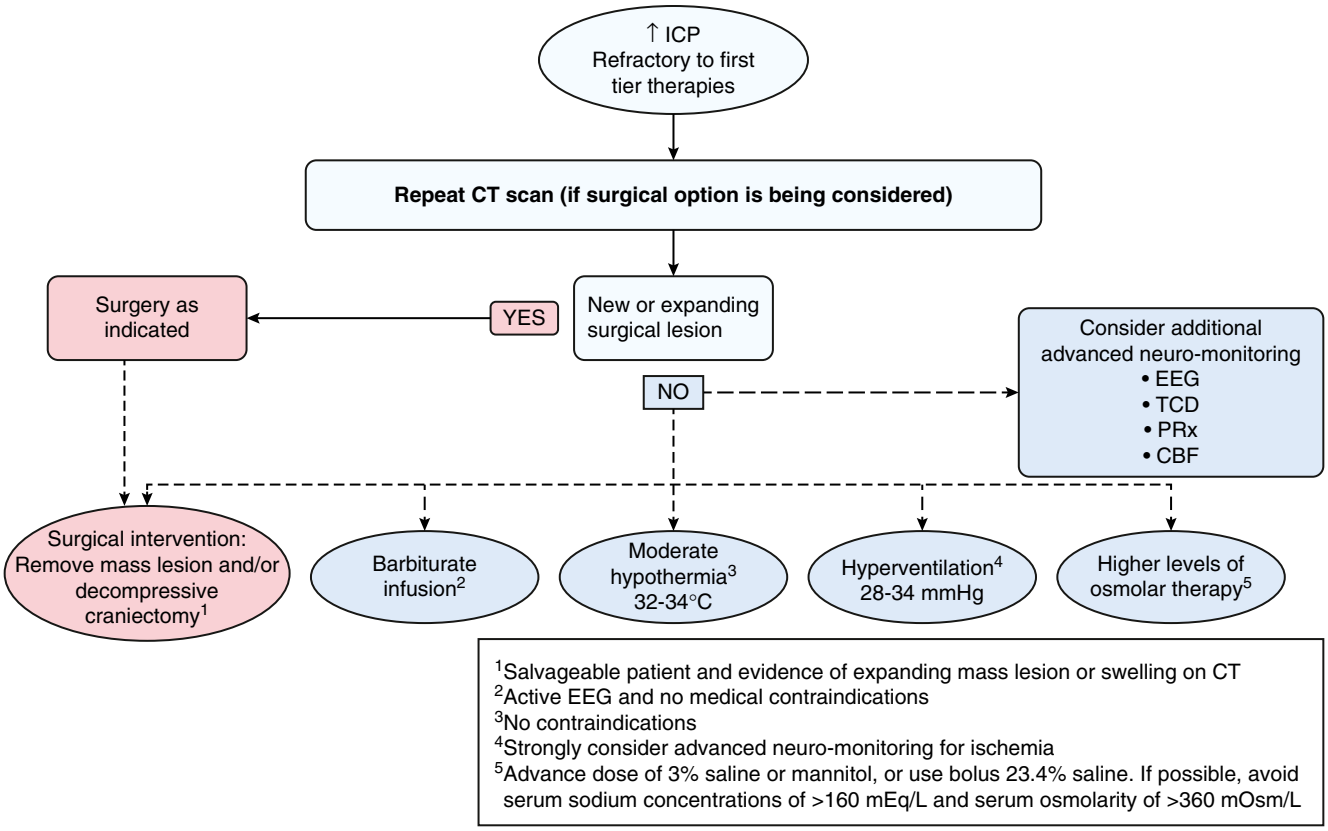

Fig. 82.14 Bedside algorithm to guide second-tier therapies to treat refractory intracranial hypertension in severe pediatric traumatic brain injury (TBI). This evidence- and consensus-based document that accompanied the third edition of the guidelines represents the treatment options when tier 1 approaches are inadequate. These therapies may be applied singly, serially, or in combination. In addition, as shown, management of refractory intracranial hypertension in the second-tier phase may be aided by advanced monitoring. CBF, Cerebral blood flow; CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; PRx, pressure reactivity index; TCD, transcranial Doppler ultrasonography. (*From Kochanek PM, Bell MJ, Simon DW, et al. Traumatic brain injury. In: Zimmerman JJ, Totta AT, eds.* Fuhrman & Zimmerman's Pediatric Critical Care, *6th ed. Philadelphia: Elsevier; 2022: Fig. 118.12, p. 1394.*)

In some centers, decompressive **craniectomy** is used. Others use a **pentobarbital infusion**, with a loading dose of 5-10 mg/kg over 30 minutes followed by 5 mg/kg every hour for 3 doses and then maintenance with an infusion of 1 mg/kg/hr. Careful blood pressure monitoring is required because of the possibility of drug-induced hypotension and the frequent need for support with fluids and/or pressors. Mild hypothermia (32–34°C [89.6–93.2°F]) to control refractory ICP is controversial but can be induced and maintained by means of surface cooling. Sedation and neuromuscular blockade are used to prevent shivering, and rewarming should be slow. Hypotension should be prevented during rewarming. Refractory raised ICP can also be treated with hyperventilation ($Paco_2$ = 25-30 mm Hg). Combinations of these second-tier therapies are often required.

Supportive Care

Euvolemia should be maintained, and isotonic fluids are recommended throughout the ICU stay. Either SIADH or CSW can develop and are important to differentiate, because management of SIADH is fluid restriction and that of CSW is sodium replacement. Severe hyperglycemia (blood glucose level >200 mg/dL) should be avoided and treated. The blood glucose level should be monitored frequently. Early nutrition with enteral feedings is advocated. Corticosteroids should generally not be used unless adrenal insufficiency is documented. Tracheal suctioning can exacerbate raised ICP. Timing of the use of analgesics or sedatives around suctioning events and/or use of tracheal or IV lidocaine can be helpful. Seizures are common after severe acute TBI. Early posttraumatic seizures (within 1 week) will complicate management of TBI and are often difficult to treat. Anticonvulsant prophylaxis with fosphenytoin or levetiracetam is recommended. Late posttraumatic seizures (≥7 days after TBI) and, if recurrent, late posttraumatic epilepsy are not prevented by prophylactic anticonvulsants, whereas early posttraumatic seizures are prevented by initiating anticonvulsants soon after TBI. Antifibrinolytic agents (tranexamic acid) reduce hemorrhage size, as well as the development of new focal ischemic cerebral lesions and improve survival in adults with severe TBI.

Prognosis

Mortality rates for children with severe TBI who reach the pediatric ICU range between 10% and 30%. Ability to control ICP is related to patient survival, and the extent of cranial and systemic injuries correlates with quality of life. Motor and cognitive sequelae resulting from severe TBI generally benefit from rehabilitation to minimize long-term disabilities. Recovery from TBI may take months or years to achieve. Physical therapy, and in some centers methylphenidate or amantadine, helps with motor and behavioral recovery. Pituitary insufficiency may be an uncommon but significant complication of severe TBI.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 83

Brain Death: Death by Neurologic Criteria

Matthew P. Kirschen and Wynne Morrison

Brain death, also known as **death by neurologic criteria**, is legally and culturally accepted as death in most of the world. In the United States, the **Uniform Determination of Death Act (UDDA)** defines brain death as the irreversible (some use "permanent") cessation of all functions of the entire brain, including the brainstem. The UDDA or a similar statute has been adopted in all states. Guidelines for the declaration of brain death in infants and children were published jointly by the Society of Critical Care Medicine (SCCM), American Academy of Pediatrics (AAP), and Child Neurology Society (CNS) in 2011. In 2020, the World Brain Death Project published a consensus statement with recommendations for the minimum clinical standards for determination of brain death in adults and children.

EPIDEMIOLOGY

Brain death by definition must occur as a result of catastrophic permanent global brain injury. Approximately 20% of children who die in pediatric intensive care units (PICUs) are declared brain dead. The most common etiologies of brain injury leading to brain death are hypoxic-ischemic injury from cardiac arrest, shock and/or respiratory failure without cardiac arrest, traumatic brain injury, intracranial infections, toxic ingestions, and causes of malignant cerebral edema. Mimics of brain death include botulism, Guillain-Barré syndrome, and high cervical cord injuries.

CLINICAL EVALUATION AND DIAGNOSIS

Brain death is determined by a careful, thorough clinical evaluation. The fundamental components of brain death are **coma**, **absence of brainstem reflexes**, and **apnea**. The first step in the brain death evaluation is to confirm that the catastrophic brain injury occurred because of an etiology known to lead to brain death. The next step is to ensure that there are no confounding conditions that could mimic or falsely suggest brain death. This is done by meticulously ensuring the patient is not hypotensive or hypothermic; does not have severe metabolic abnormalities like hypoglycemia, hyponatremia, or acidosis; and that sufficient time has passed to allow for clearance of all sedating medication or other toxins that could confound the examination. This involves review of the medical history, neuroimaging, electroencephalography (EEG), and laboratory data to rule out reversible causes of coma. Additionally, the patient should be observed for a sufficient amount of time (typically at least 24 hours after CPR or from their severe acute brain injury) to ensure there is no recovery of neurologic function. Checklists are very helpful in ensuring no prerequisites are missed (Fig. 83.1). Confounding factors must be corrected, if feasible, before initiation of the brain death evaluation. If all confounders are unable to be adequately corrected, ancillary testing is required to diagnose brain death. Brain death evaluation should not be performed in infants <37 weeks corrected gestational age.

Brain Death Neurologic Examination

The clinical examination evaluates for coma; absence of motor responses of the head, neck, and extremities; and brainstem areflexia including apnea in a setting of an adequate respiratory stimulus. The patient must be unresponsive to tactile, auditory, and visual stimulation other than spinally mediated reflexes. If it is unclear if motor movements are spinally mediated, ancillary testing may be necessary before brain death can be diagnosed. Brainstem reflexes must be absent. Table 83.1 lists the components of the neurologic examination, including brainstem reflexes to be tested, the brainstem location of each reflex, and the exam finding that is consistent with brain death. Several injuries and conditions can preclude completion or interpretation of the clinical examination. These include spinal cord injury, orbital/facial trauma, and severe neuromuscular disorders. In these situations, an ancillary test must be performed before declaring brain death. It is still necessary to perform all examination components that can be completed, and every component assessed must be consistent with brain death to allow declaration.

Apnea Test

Apnea is the absence of respiratory effort. The purpose of the required apnea test is to evaluate whether the chemoreceptors in the brainstem's medulla, which stimulate respiration when exposed to hypercarbia and acidosis, are functional. The patient should be euvolemic, normotensive, and euthermic before beginning the apnea test. The apnea test can result in cardiopulmonary decompensation and should only be performed in a PICU by clinicians with skills to stabilize or resuscitate the patient if needed. Before the apnea test, the patient is preoxygenated with 100% oxygen for approximately 10 minutes, and ventilation is adjusted to achieve a $Paco_2$ of approximately 40 mm Hg. A baseline arterial blood gas (ABG) documents the starting $Paco_2$ value. The patient is then removed from intermittent mechanical ventilation and provided apneic oxygenation by delivering 100% oxygen via continuous positive airway pressure (CPAP) on the ventilator or via flow-inflating resuscitation bag with a functioning peak end-expiratory pressure (PEEP) valve. The patient's hemodynamics and pulse oximetry oxygen-hemoglobin saturation (Spo_2) are monitored continuously while the physician observes for respiratory effort. An ABG sample is obtained approximately 5-10 minutes into the test and every 2 minutes thereafter until the target $Paco_2$ is surpassed; ventilatory support is resumed at that time. Absence of respiratory effort with a $Paco_2$ ≥60 mm Hg *and* >20 mm Hg above baseline is consistent with brain death. If at any point during the test the patient becomes hypoxic (Spo_2 <85%) or hypotensive, the test is aborted and ventilatory support resumed.

OBSERVATION PERIODS

To determine brain death in the United States, current guidelines recommend the neurologic examination and apnea test be performed by different attending physicians separated by an observation period. The examination determines that the child has met criteria for brain death. An observation period before the examination is based on the patient's age: For infants (≥37 weeks corrected gestational age) and children <24 months, observe for at least 48 hours. For patients >2 years, observe for at least 24 hours. Before testing, core body temperature should be maintained ≥36° C. In addition in adults, systolic blood pressure (SBP) should be ≥100 mm Hg and mean arterial blood pressure (MAP) should be ≥75 mm Hg; in children SBP and MAP should be ≥5th percentile for age.

Similar MAPs are recommended for patients on venoarterial ECMO. Furthermore, before treating metabolic disorders, intoxication and effects of therapeutic medications that depress the CNS and peripheral nervous system (paralytics) must be excluded. In children, two different clinicians must perform independent neurological and apnea examinations separated by a minimal interval of 12 hours.

ANCILLARY STUDIES

Ancillary studies are not required for the diagnosis of brain death and should only be used to assist the clinician in declaring brain death (1) when components of the neurologic examination or apnea test cannot be completed safely because of the underlying medical condition of the patient; (2) if there is uncertainty about the results of the neurologic examination; (3) if a medication effect may be present; or (4) to reduce the observation period between examinations. If an ancillary test is used to shorten the observation period, the physician is still required to complete two clinical examinations and apnea tests, along with the ancillary study.

The most common ancillary tests are EEG and radionuclide perfusion scintigraphy (or cerebral blood flow) studies. Other tests are available (Table 83.2); however, these have not been incorporated into clinical practice in the United States, although they are used outside of the United States in some practice settings. A valid **electroencephalogram** to support a diagnosis of brain death must be performed according to the American EEG Society standards and technical requirements. Confounders should be excluded, and the EEG must demonstrate

Checklist for Documentation of Brain Death

Brain Death Examination for Infants and Children[a]

Age of Patient	Timing of First Examination	Interexamination Interval
Term newborn 37 weeks gestational age and up to 30 days old	☐ First examination may be performed 24 hours after birth OR following cardiopulmonary resuscitation or other severe brain injury	☐ At least 24 hours ☐ Interval shortened because ancillary study (Section 4) is consistent with brain death
31 days to 18 years old	☐ First examination may be performed 24 hours following cardiopulmonary resuscitation or other severe brain injury	☐ At least 12 hours OR ☐ Interval shortened because ancillary study (Section 4) is consistent with brain death

Section 1. Prerequisites for Brain Death Examination and Apnea Test

A. Irreversible and Identifiable Cause of Coma (please check)

☐ Traumatic brain injury ☐ Anoxic brain injury ☐ Known metabolic disorder ☐ Other (specify) _____

B. Correction of Contributing Factors That Can Interfere with the Neurologic Examination

	Examination 1		Examination 2	
a. Core body temperature is >95°F (35°C)	☐ Yes	☐ No	☐ Yes	☐ No
b. Systolic blood pressure or MAP in acceptable range (Systolic BP not less than 2 standard deviations below age-appropriate norm) based on age	☐ Yes	☐ No	☐ Yes	☐ No
c. Sedative/analgesic drug effect excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
d. Metabolic intoxication excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
e. Neuromuscular blockade excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No

☐ If ALL prerequisites are marked YES, then proceed to section 2, OR

☐ _____ confounding variable was present. Ancillary study was therefore performed to document brain death (Section 4).

Section 2. Physical Examination (please check); Note: Spinal Cord Reflexes Are Acceptable

	Examination 1, Date/Time: _____		Examination 2, Date/Time: _____	
a. Flaccid tone, patient unresponsive to deep painful stimuli	☐ Yes	☐ No	☐ Yes	☐ No
b. Pupils are midposition or fully dilated and light reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
c. Corneal, cough, gag reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
d. Sucking and rooting reflexes are absent (in neonates and infants)	☐ Yes	☐ No	☐ Yes	☐ No
e. Oculovestibular reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
f. Spontaneous respiratory effort while on mechanical ventilation is absent	☐ Yes	☐ No	☐ Yes	☐ No

☐ The _____ (specify) element of the examination could not be performed because _____.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death (Section 4).

Section 3. Apnea Test

	Examination 1, Date/Time: _____	Examination 2, Date/Time: _____
No spontaneous respiratory efforts were observed despite final $PaCO_2$ ≥60mmHg and a ≥20mmHg increase above baseline (Examination 1). No spontaneous respiratory efforts were observed despite final $PaCO_2$ ≥60mmHg and a ≥20mmHg increase above baseline (Examination 2).	Pretest $PaCO_2$: _____ Apnea duration: _____ min Post-test $PaCO_2$: _____	Pretest $PaCO_2$: _____ Apnea duration: _____ min Post-test $PaCO_2$: _____

Apnea test is contraindicated or could not be performed to completion because _____.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death (Section 4).

Section 4. Ancillary Testing

Ancillary testing is required (1) when any components of the examination or apnea testing cannot be completed; (2) if there is uncertainty about the results of the neurologic examination; or (3) if a medication effect may be present. Ancillary testing can be performed to reduce the interexamination period; however, a second neurologic examination is required. Components of the neurologic examination that can be performed safely should be completed in close proximity to the ancillary test.

Date/Time:_____

☐ EEG report documents electrocerebral silence OR ☐ Yes ☐ No

☐ CBF study report documents no cerebral perfusion ☐ Yes ☐ No

Section 5. Signatures

Examiner 1
I certify that my examination is consistent with cessation of function of the brain and brainstem. Confirmatory examination to follow.
Printed name _____
Signature _____
Specialty _____
Pager #/license # _____
Date mm/dd/yyyy _____
Time _____

Examiner 2
I certify that my examination ☐ and/or ancillary test report ☐ confirms unchanged and irreversible cessation of function of the brain and brainstem. The patient is declared brain dead at this time.
Date/time of death _____
Printed name _____
Signature _____
Specialty _____
Pager #/license # _____
Date mm/dd/yyyy _____
Time _____

[a]Two physicians must perform independent examinations separated by specified intervals.
BP = blood pressure; CBF = cerebral blood flow; EEG = electroencephalography; MAP = mean arterial pressure.

Fig. 83.1 Checklist for documentation of brain death. *(From Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: An update of the 1987 Task Force recommendations—executive summary.* Ann Neurol. *2012;71:573-585, Table 2.)*

Table 83.1 Neurologic Examination to Evaluate a Patient for Brain Death

EXAM COMPONENT	HOW TO PERFORM	RESPONSE CONSISTENT WITH BRAIN DEATH
Coma	Visual response: blink to visual threat Auditory response: clapping and yelling the child's name loudly Tactile response: apply deep pressure to the condyles at the level of the temporomandibular joints, the supraorbital notch bilaterally, the sternum, and all four extremities proximally and distally	No response to visual or auditory stimuli; noxious stimuli do not produce grimacing, facial or body muscle movement, or any motor response other than spinally mediated reflexes
Pupillary light reflex (CNs II and III)	Shine a bright light into each eye while closely observing pupillary size and reactivity	Absence of ipsilateral and contralateral pupillary response, with pupils fixed in a midsize or dilated position (4-6 mm) in both eyes
Corneal reflex (CNs III, V, VII)	Touch the cornea of each eye with a cotton swab at the external border of the iris, applying light pressure and observing for any eyelid movement	Absence of eyelid movement
Oculocephalic reflex (CNs III, VI, and VIII)	Confirm integrity of the cervical spine. Secure the endotracheal tube to prevent dislodgement; briskly rotate the head horizontally to both sides and observe for movement of the eyes	Absence of movement of the eyes relative to head movement; eyes follow the head movement, staying in mid-position
Oculovestibular reflex (CNs III, IV, VI, and VIII)	Irrigate the ear canal with 50-60 mL of ice water for at least 60 sec while observing for eye movement; test each side separately and with a 5-min interval in between	Absence of eye movement
Gag and cough reflex (CNs IX and X)	Touch the posterior pharynx with a tongue depressor or a rigid suction catheter to stimulate a gag; touch the tracheobronchial wall at the level of the carina with placement of a suction catheter through the endotracheal tube to stimulate a cough	Absence of both cough and gag
Sucking and rooting reflexes	Place a gloved finger inside the baby's mouth to stimulate sucking; stroke the external surface of both cheeks and corners of the mouth to stimulate rooting	Absence of sucking and rooting

CN, Cranial nerve.

Table 83.2 Ancillary Tests for Determining Brain Death

TEST	CONFOUNDER/LIMITATION*	SENSITIVITY/ SPECIFICITY
BRAIN BLOOD FLOW		
Computed tomography angiography	Requires transport to the scanner Image variability based on injection technique Potential to miss a slow flow state Risk of nephrotoxicity Not recommended by AAN 2023 Guidelines[#]	52–97% / 100%
Digital subtraction angiography[†]	Requires transport to angiography suite Risk of nephrotoxicity Image variability based on injection technique	100% / 100%
Magnetic resonance angiography	Requires transport to the scanner Image variability based on injection technique	93–100% / 100%
Radionuclide angiography[†]	Limited evaluation of brainstem	99% / 56%
Radionuclide scintigraphy[†]	Requires transport to the scanner Planar imaging may have limited evaluation of brainstem	Planar: 78% / 100% SPECT: 88% / 100%
Transcranial Doppler ultrasonography[†]	Potential for technical difficulties in performance Potential for lack of windows	90% / 98%
ELECTROPHYSIOLOGIC FUNCTION		
Electroencephalography	Risk of environmental artifact Confounded by sedation, hypothermia and toxic-metabolic derangements Predominantly provides information about cortical function	53–80% / 97%
Evoked potentials-auditory	Can be absent in comatose patients with other intact brainstem reflexes Confounded by sedation, hypothermia, isolated eighth nerve and brainstem lesions Only evaluates auditory pathways Performance/interpretation may be limited by experience	NA / NA
Evoked potentials-somatosensory	Can be absent in comatose patients with ongoing brain function Confounded by cervical spine injury, isolated brainstem lesions, sedation, and hypothermia Only evaluates somatosensory pathways Performance/interpretation may be limited by experience	100% / 78%
Evoked potentials-visual	Can be absent in comatose patients with ongoing brain function Confounded by sedation, retinal or optic nerve lesions Only evaluates visual pathways Performance/interpretation may be limited by experience	NA / NA

*Performance/interpretation of all ancillary tests may be limited by experience
[†]Accepted by the World Brain Death Project (WBDP).
[#]Report of the AAN Guidelines Subcommittee, AAP, CNS, SCCM. Pediatric and adult brain death/death by neurologic criteria consensus guideline. *Neurology* 2023;101:1-21.
NA, Not available.
From Lewis A, Kirschen MP, Badenes R. Quality improvement in the determination of death by neurologic criteria around the world. *Crit Care.* 2023;27(1):96.

electrocerebral silence. A **radionuclide cerebral blood flow study** consists of intravenous injection of a radiopharmaceutical agent followed by imaging of the brain by planar or single-photon emission computed tomography (SPECT) imaging. A study that demonstrates absence of intracranial blood flow and cerebral perfusion is supportive of brain death. CT and MR angiography are not recommended.

Interpretation of both EEG and cerebral blood flow studies should only be performed by trained and qualified individuals. If the study shows any evidence of electrical activity or cerebral blood flow, brain death cannot be declared. A 24-hour waiting period is recommended before repeating the brain death evaluation.

DOCUMENTATION

Documentation is an important aspect of the brain death evaluation and determination and should follow a checklist, including the following points:

1. Etiology of brain injury
2. Absence of confounding factors, including hypothermia, hypotension, metabolic abnormalities, and recent doses of sedative or neuromuscular blocking agents
3. Absence of motor response to tactile, auditory, and visual stimuli
4. Absence of brainstem reflexes, including pupillary light reflex, oculocephalic/oculovestibular reflex, corneal reflex, cough reflex, and gag reflex
5. ABG values during the apnea test and statement about respiratory effort
6. Results of ancillary testing (if indicated)

AFTER DECLARATION OF BRAIN DEATH

After brain death has been declared, the child is legally dead. The time of death is the time the final required component of the evaluation is completed: either ABG results or ancillary test. Families may be approached by representatives of organ procurement organizations to discuss options for organ donation after brain death. For families that choose not to donate organs, the next appropriate step in the care of the child is removal of technologic supports, including mechanical ventilation, after which the child's heart will become asystolic. It is important for care providers to be supportive of the family dealing with this difficult situation. Child life and palliative care specialists can be helpful in guiding families during this time. Technologic support is typically stopped within a few hours of declaring brain death, although in some situations it can be delayed at the discretion of the physician and in accordance with hospital protocols.

OBJECTIONS TO THE CONCEPT OF BRAIN DEATH

The concept of brain death may not be accepted by families for personal, religious, or cultural reasons. Some families have difficulty comprehending the fact that their child meets criteria for legal death despite having a heartbeat, blood pressure, and being warm to the touch. Other families maintain hope for recovery, and some have religious views that death can only be declared after cessation of cardiorespiratory function. Some individuals have challenged the brain death guidelines claiming that they do not sufficiently evaluate "all functions of the entire brain, including the brainstem," as mandated by the UDDA, particularly as some patients who meet brain death criteria continue to show evidence of *integrative functioning,* such as control over free water homeostasis (absence of diabetes insipidus), control of temperature regulation, and capacity for growth and wound healing. Others argue that the intent of the UDDA is met by the current clinical evaluation. Objections to performing the brain death evaluation or declaration of death should be handled by a multidisciplinary team with experience in these situations. These teams often include physicians, social workers, ethicists, chaplains, hospital administrators, and lawyers as appropriate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 84

Syncope

Aarti S. Dalal and George F. Van Hare

Syncope is defined as a sudden transient loss of consciousness with inability to maintain postural tone. The most common cause of syncope in the normal pediatric population is **neurocardiogenic syncope** (vasovagal syncope, fainting). **Vasovagal syncope** is classically associated with a prodrome that includes diaphoresis, warmth, pallor, or feeling lightheaded and is often triggered by acute position changes or by a specific situation or event such as pain, medical procedures, or emotional distress (Table 84.1). This type of syncope is characterized by hypotension and bradycardia. Approximately 30–50% of children will have had a **fainting** episode before 18 years of age. The symptoms of vasovagal syncope can overlap with those of postural orthostatic tachycardia syndrome (POTS), a constellation of symptoms characterized by symptoms of rapid heart rate and supported by a positional increase in heart rate by 40 beats per minute with normal blood pressure (see Chapter 84.1).

Most patients with a vasovagal syncope episode will have prodromal features followed by loss of motor tone. Once in a horizontal position, consciousness returns rapidly, usually in 1-2 minutes; some patients may have a brief period of stiffening or jerking, which should not be confused with a **seizure** (Table 84.2). Syncope must also be distinguished from **vertigo** and **ataxia** (Table 84.3).

Although this type of syncope is very common in adolescence and has an excellent prognosis, other causes for loss of consciousness are more dangerous; thus syncope may be the first sign of more serious conditions (Table 84.4). Indeed, the occurrence of syncope may well be the pediatrician's best opportunity to diagnose a life-threatening condition before the patient subsequently succumbs. The task of the clinician therefore is not only to counsel the family and the patient concerning the common form but also to rule out a number of important life-threatening cardiac problems.

MECHANISMS

Syncope by whatever mechanism is caused by a lack of adequate cerebral blood flow with loss of consciousness and inability to remain upright.

Primary **cardiac causes** of syncope (see Table 84.4) include conditions that predispose a patient to arrhythmias or conditions such as congenital or acquired structural heart disease. Arrhythmic causes of syncope include Wolff-Parkinson-White syndrome (particularly with atrial fibrillation), ventricular tachycardia (VT), and occasionally supraventricular tachycardia (see Chapter 484). VT may be associated with hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy, repaired congenital heart disease, or an inherited arrhythmia syndrome such as catecholaminergic polymorphous ventricular tachycardia (CPVT) or long QT syndrome (LQTS) (Table 84.5). Other arrhythmias that may lead to syncope are bradyarrhythmias such as sinus node dysfunction and high-grade second- or third-degree atrioventricular (AV) block. Syncope may also be caused by cardiac obstructive lesions, such as critical aortic stenosis, or coronary artery anomalies, such as an aberrant left coronary artery arising from the right sinus of Valsalva. Patients with primary pulmonary hypertension or Eisenmenger syndrome may also experience syncope. In all the obstructive forms of syncope, exercise increases the likelihood of an episode because the obstruction interferes with the ability of the heart to increase cardiac output in response to exercise.

Noncardiac causes of loss of consciousness include epilepsy, basilar artery migraine, hysterical syncope, and psychogenic nonepileptic seizures (see Table 84.1). Occasionally, patients with narcolepsy may present with syncope. Hypoglycemia and hyperventilation may also present as syncope.

Table 84.1 Noncardiac Causes of Syncope

REFLEX VASODEPRESSOR SYNCOPE
Neurocardiogenic (vasovagal)
Emotion (seeing blood)
Pain (needle phobia)
Reflex asystolic syncope (pallid breath-holding)

MISCELLANEOUS SITUATIONAL REFLEX
Tussive
Sneeze
Exercise, after exercise
Swallowing
Stretching
Defecation
Micturition
Hair grooming
Valsalva (increased intrathoracic pressure)
Trumpet playing
Weightlifting
Breath-holding spells (cyanotic)

SYSTEMIC ILLNESS
Hypoglycemia
Anemia
Infection
Hypovolemia, dehydration
Adrenal insufficiency
Narcolepsy, cataplexy
Pulmonary embolism
Pheochromocytoma
Mastocytosis
Ruptured ectopic pregnancy

CENTRAL NERVOUS SYSTEM
Seizure (atonic, absence, myoclonic-astatic)
Hyperekplexia
Stroke, transient ischemic attack
Friedreich ataxia
Subarachnoid hemorrhage

OTHER NEUROLOGIC
Dysautonomia
Myotonic dystrophy
Kearns-Sayre syndrome
Congenital myasthenia gravis
Basilar artery migraine
Arnold Chiari malformation

DRUG EFFECTS
β-Blocking agents
Vasodilating agents
Opiates
Sedatives
Diuretics
Anticonvulsant agents
Antihistamines
Antidepressant agents
Anxiolytic agents
Drugs of abuse
Insulin, oral hypoglycemic agents
Carbon monoxide

OTHER ETIOLOGIES
Carotid sinus sensitivity
Subclavian steal
Panic attack, anxiety
Conversion disorder

Table 84.2 Comparison of Clinical Features of Syncope and Seizures

FEATURES	SYNCOPE	SEIZURES
Relation to posture	Common	No
Time of day	Diurnal	Diurnal or nocturnal
Precipitating factors	Emotion, injury, pain, crowds, heat, exercise, fear, dehydration, coughing, micturition, venipuncture, prolonged standing	Sleep loss, drug/alcohol withdrawal, illness, medication nonadherence
Skin color	Pallor	Cyanosis or normal
Diaphoresis	Common	Rare
Aura or premonitory symptoms	Often minutes or longer, but can be very brief	Brief
Convulsion	Rare	Common
Other abnormal movements	Minor irregular twitching	Rhythmic jerks
Injury	Rare	Common (with convulsive seizures)
Urinary incontinence	Rare	Common
Tongue biting	No	Common with convulsive seizures
Postictal confusion	Rare	Common
Postictal headache	No	Common
Focal neurologic signs	No	Occasional
Cardiovascular signs	Common to have low blood pressure and heart rate during event; cardiovascular exam may be completely normal after event unless there is an underlying cardiac disorder	Rare
Abnormal findings on EEG	Rare (generalized slowing may occur during the event)	Common

From Winkel D, Cassimatis D. Episodic impairment of consciousness. In: Jankovic JM, Mazziotta JC, Pomeroy SL, Newman NJ, eds. *Bradley and Daroff's Neurology in Clinical Practice*, 8th ed. Philadelphia: Elsevier; 2021.

Table 84.3 Syncope and Dizziness

	VERTIGO	PRESYNCOPE	DISEQUILIBRIUM	LIGHTHEADEDNESS
Patient complaint	"My head is spinning." "The room is whirling."	"I feel I might pass out." "I feel faint." "I feel like blacking out."	"I feel unsteady." "My balance is off."	"I feel dizzy." "I feel disconnected, drugged."
Associated features	Motion, swaying, spinning, nystagmus	Syncope: loss of postural tone, brief loss of consciousness Situational	Poor balance No vertigo or ataxia	Anxiety, hyperventilation, paresthesias, respiratory alkalosis, panic attacks
Usual cause	Vestibular disorders	Impaired cerebral perfusion	Sensory and/or central neurologic dysfunction	Decreased venous return
Key differential diagnoses	Peripheral (labyrinthine-cochlear) vs central neurologic disorder	Neurocardiogenic (vagal) vs cardiac syncope vs neuropsychiatric syncope	Sensory deficit vs central neurologic disease	Anxiety/depression vs hyperventilation vs medication effects

Adapted from Cohen G. Syncope and dizziness. In: Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*; 2018: Table 6.1, p. 84.

Table 84.4 Causes of Cardiovascular Syncope: Potentially Fatal If Unrecognized

ARRHYTHMIAS

Bradyarrhythmias

1. Sinus node dysfunction (especially in patients with congenital heart defects)
2. Atrioventricular block (congenital or acquired; Lyme, Fabry, Chagas diseases)
3. Kearns-Sayre syndrome
4. Pacemaker malfunction

Tachyarrhythmias

1. Supraventricular
   a. Wolff-Parkinson-White syndrome
   b. Supraventricular tachycardia/atrial arrhythmias (especially in patients with congenital heart defects)
2. Ventricular: ventricular tachycardia/torsades/ventricular fibrillation
   a. Channelopathies
      - Long QT syndromes
      - Catecholaminergic polymorphic ventricular tachycardia
      - Brugada syndrome
      - Short QT syndrome
   b. Drug induced
   c. Idiopathic
      - Ventricular fibrillation
      - Ventricular tachycardia from outflow tract

STRUCTURAL/FUNCTIONAL HEART DISEASE

Cardiomyopathy

1. Hypertrophic cardiomyopathy
2. Dilated cardiomyopathy
3. Arrhythmogenic right ventricular dysplasia
4. Left ventricular noncompaction

Coronary Anomalies

1. Anomalous origin
2. Kawasaki disease
3. Multisystemic inflammatory syndrome in children (MIS-C) secondary to SARS-CoV-2

Valvar Aortic Mitral or Pulmonary Stenosis

Takotsubo Disease

Acute Myocarditis

Congenital Heart Disease (Repaired and Unrepaired)

Pulmonary Hypertension, Pulmonary Embolus

Aortic Dissection (Marfan Syndrome)

Cardiac Masses (Myxoma, Rhabdomyoma, Thrombus)

Eisenmenger Syndrome

From MacNeill E, Vashist S. Approach to syncope and altered mental status. *Pediatr Clin N Am.* 2013;60:1083-1106.

EVALUATION

The most important goal in the evaluation of the new patient with syncope is to diagnose life-threatening causes of syncope so that these causes can be managed and more severe outcomes avoided. Many patients presenting with sudden cardiac arrest caused by conditions such as LQTS will have previously experienced an episode of syncope, so the presentation with syncope is an opportunity to prevent sudden death.

The most important tool in evaluation of syncope is a careful **personal** and **family history**. The characteristics of cardiac syncope differ significantly from benign causes of syncope such as neurocardiogenic syncope (Table 84.6). Several red flags can be identified that should lead the clinician to suspect that the mechanism is a life-threatening cardiac cause rather than simple fainting (Table 84.7). The occurrence *during* exercise suggests an arrhythmia or an outflow tract or coronary artery obstruction. Noncardiac (postexercise) syncope is seen in athletes *after* a strenuous workout or competition and has no associated cardiac features. The occurrence of syncope resulting in injury also suggests an arrhythmia, as it indicates a sudden onset with a lack of adequate prodromal symptoms. The occurrence of syncope while recumbent would be quite unusual in a patient with neurocardiogenic syncope and therefore suggests a cardiac or neurologic cause. Occasionally, a patient with syncope caused by a tachyarrhythmia will report the sensation of a racing heart before the event, but this is often not present.

A careful family history is essential in evaluation of syncope. Specifically, if there are first-degree relatives with inherited syndromes, such as LQTS, CPVT, or HCM, this should lead to more specific evaluation of the patient. If relatives died suddenly at a young age without a clear and convincing cause, inherited cardiac arrhythmias or cardiomyopathies should also be suspected. Other questions that may increase suspicion for an inherited arrhythmia include family history of congenital deafness, unexplained recurrent syncope, poorly controlled seizures, single-vehicle car accidents, or drowning events.

Patients with a history of heart disease requiring surgical repair may have causes of syncope that are specific to their repair. Sinus node dysfunction is common after the Senning or Mustard procedure for transposition of the great vessels or after the Fontan procedure for single-ventricle palliation. VT may be seen after repair of tetralogy of Fallot. A patient with a history of repair of a ventricular septal defect or an AV canal defect should be evaluated for the late occurrence of AV block. Patients with an implanted pacemaker should be evaluated for pacemaker lead failure.

The **physical examination** may also offer clues (see Table 84.7) that point toward cardiac syncope. Patients with HCM or aortic stenosis may have a prominent cardiac impulse and/or an ejection murmur. A patient with primary pulmonary hypertension will have a displaced apical impulse, with a loud and single second

Table 84.5 Primary Electrical Abnormalities: Features, ECG, and Treatment

PRIMARY ELECTRICAL ABNORMALITIES	FEATURES	ECG	TREATMENT
LQTS: Romano-Ward, Jervell–Lange-Nielsen, acquired	• Familial genetic or acquired disorders • Ion channel pathologic gene variant (~17 genes)* • Presents in torsades de pointes • Romano-Ward is most common inherited • LQTS Jervell–Lange-Nielsen has congenital deafness	• Prolonged QT measured from the onset of the Q wave to the end of the T wave in lead II • Varies with HR but >0.44 in men, >0.46 in children and women for HR 50-90 beats/min is prolonged • Torsades de pointes can occur • Can deteriorate from polymorphic ventricular tachycardia to ventricular fibrillation	• β-Blocker therapy • Recommendations on exercise intensity by a cardiologist • ICD if β blockers fail
Brugada syndrome	• Inherited autosomal dominant arrhythmogenic syndrome characterized by life-threatening ventricular arrhythmias • Pathologic gene variant in *SCN5A* and 13 other genes	• ECG abnormalities are from repolarization and depolarization abnormalities • Coved-type ST-segment elevations in the right precordial leads • J wave amplitude ≥2 mm followed by a negative T wave	• Placement of ICD
Wolff-Parkinson-White	• Owing to one or more reentrant pathways inducing SVT or atrial fibrillation • Up to 14% associated with malignant tachycardias • Malignant arrhythmias from short reentrant pathway repolarization or multiple pathways	• Short PR interval • Delta waves present	• Undergo EPS and ablation
Dilated cardiomyopathy: ventricular tachycardia/ fibrillation	• Cardiac dilation and systolic dysfunction • Inherited or acquired • Lamin AC pathologic gene variant a common cause of DCM and SCD	• Marked LVH • Poor R-wave progression • Left atrial enlargement • Right axis deviation	• Permanent pacemaker and ICD placement
Catecholamine-exercise: ventricular tachycardia	• Ventricular ectopy induced by exercise or emotional stress • Variant in gene that encodes Ca-mediated sarcoplasmic fibers • Lethal in 30–50% if left untreated	• Preexercise ECG is usually normal, stress testing recommended • ECG with exercise • Nonsustained wide ventricular tachycardia	• β-Blocker therapy • Recommendations on exercise intensity by a cardiologist • ICD if β blockers fail

DCM, Dilated cardiomyopathy; EPS, electrophysiology study; HR, heart rate; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; SVT, supraventricular tachycardia.
*Major genes: *KCNQ1, KCNH2, SCN5A* in ~75% cases.
Modified from Ellison S. Sudden cardiac death in adolescents. *Prim Care Clin Office Pract.* 2015;42:57-76.

Table 84.6 Differentiating Features for Causes of Syncope

NEUROCARDIOGENIC
Symptoms after prolonged motionless standing, sudden unexpected pain, fear, or unpleasant sight, sound, or smell; pallor
Syncope in a well-trained athlete *after* exertion (without heart disease)
Situational syncope during or immediately after micturition, cough, swallowing, or defecation
Syncope with throat or facial pain (glossopharyngeal or trigeminal neuralgia)
ORGANIC HEART DISEASE (PRIMARY ARRHYTHMIA, OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY, PULMONARY HYPERTENSION)
Brief sudden loss of consciousness, no prodrome, history of heart disease
Syncope while sitting or supine
Syncope with exertion
History of palpitations
Family history of sudden death
NEUROLOGIC
Seizures: preceding aura, postevent symptoms lasting >5 min (includes postictal state of decreased level of consciousness, confusion, headache, or paralysis)
Migraine: syncope associated with antecedent headaches with or without aura
OTHER VASCULAR
Carotid sinus: syncope with head rotation or pressure on the carotid sinus (as in tumors, shaving, tight collars)
Orthostatic hypotension: syncope immediately on standing, especially after prolonged bed rest
DRUG INDUCED
Patient is taking a medication that may lead to long QT syndrome, orthostasis, or bradycardia
PSYCHIATRIC ILLNESS
Frequent syncope, somatic complaints, no heart disease

From Cohen G. Syncope and dizziness. In: Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis.* Philadelphia: Elsevier; 2018: Table 6.4.

Table 84.7 Red Flags in Evaluation of Patients with Syncope

Syncope with activity or exercise or supine
Syncope not associated with prolonged standing
Syncope precipitated by loud noise or extreme emotion
Absence of presyncope or lightheadedness
Family history of syncope, drowning, sudden death, familial ventricular arrhythmia syndromes,* cardiomyopathy
Syncope requiring CPR
Injury with syncope
Anemia
Other cardiac symptoms
Chest pain
Dyspnea
Palpitations
History of cardiac surgery
History of Kawasaki disease
Implanted pacemaker
Abnormal physical examination
Murmur
Gallop rhythm
Loud and single second heart sound
Systolic click
Increased apical impulse (tachycardia)
Irregular rhythm
Hypotension or hypertension
Digital clubbing
Cyanosis

*Long QT syndrome, Brugada syndrome, catecholamine polymorphic ventricular tachycardia, arrhythmogenic cardiomyopathy.

heart sound, with an ejection click or murmur of pulmonary insufficiency. Patients with repaired congenital heart disease will have obvious scars on their chest and abdomen from prior cardiac surgery or device implantation.

All patients presenting with syncope *should* have an **electrocardiogram**, looking primarily for QT interval prolongation, preexcitation, ventricular hypertrophy, T-wave abnormalities, and conduction abnormalities. Additional tests that may be needed include echocardiography, exercise testing, cardiac MRI, or 24-hour Holter monitoring. In patients for whom there is a strong suspicion of a paroxysmal arrhythmia, an insertable cardiac monitor (loop recorder) may offer the most effective means of diagnosis. Additional tests may be useful to look for anemia, hypoglycemia, drugs of abuse, and other etiologies noted in Table 84.1 as determined by the history and physical examination.

TREATMENT

Therapy for vasovagal syncope includes avoiding triggering events (if possible), fluid and salt supplementation, and if needed, specific therapies targeting the orthostatic hypotension (i.e., midodrine) (Table 84.8). Immediately after the event, the patient should remain supine until symptoms abate to avoid recurrence.

Treatment for cardiac causes of syncope will be determined by the diagnosis. If supraventricular tachycardia (SVT) is found, then a catheter ablation may be indicated. If bradycardia from sinus node dysfunction or AV block is the cause of the syncope, a pacemaker may be warranted. Patients with syncope from medically refractory malignant arrhythmias, as may be seen in HCM, LQTS, arrhythmogenic cardiomyopathy, or CPVT, require an implantable cardioverter-defibrillator. Patients with structural heart disease (valvular disease or coronary artery anomalies) should be referred for surgery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 84.8 Treatment of Neurocardiogenic Syncope/Vasovagal Syncope (V-VS)

Patient education on the diagnosis and prognosis of V-VS is recommended. In all patents with the common faint or V-VS, an explanation of the diagnosis, education targeting awareness of and possible avoidance of triggers (prolonged standing, warm environments, coping with dental and medical settings), and reassurance about the benign nature of the condition should be provided.
Physical counterpressure maneuvers can be useful in patients with V-VS who have a sufficiently long prodromal period. Patients with a syncope prodrome should be instructed to assume a supine position to prevent a faint and minimize possible injury. In patients with a sufficiently long prodrome, physical counter-maneuvers (leg crossing, limb and/or abdominal contraction, squatting, isometric handgrip, arm tensing) are a core management strategy.
Midodrine is reasonable in patients with recurrent V-VS with no history of hypertension, heart failure, or urinary retention. Midodrine is a prodrug that is metabolized to desglymidodrine, which is a peripherally active α-agonist used to ameliorate the reduction in peripheral sympathetic neural outflow responsible for venous pooling and vasodepression in V-VS.
The usefulness of orthostatic training is uncertain in patients with frequent V-VS. There are 2 main methods of orthostatic training. Patients undergo repetitive tilt-table tests in a monitored setting until a negative tilt-table test occurs and then are encouraged to stand quietly against a wall for 30-60 min daily, or patients simply stand quietly against a wall at home for a prolonged period daily.
Fludrocortisone might be reasonable for patients with recurrent V-VS and inadequate response to salt and fluid intake, unless contraindicated. Fludrocortisone has mineralocorticoid activity resulting in sodium and water retention and potassium excretion, which results in increased blood volume. Serum potassium level should be monitored because of potential drug-induced hypokalemia. POST II (Prevention of Syncope Trial II) reported a marginally insignificant 31% risk of reduction in adults with moderately frequent V-VS, which was significant in patients after a 2-wk dose stabilization period.
Encouraging increases in salt and fluid intake may be reasonable in selected patients with V-VS, unless contraindicated. Evidence for the effectiveness of salt and fluid intake for patients with V-VS is limited. Nonetheless, in patients with recurrent V-VS and no clear contraindication, such as a history of hypertension, renal disease, heart failure, or cardiac dysfunction, it may be reasonable to encourage ingestion of 2-3 L of fluid per day and a total of 6-9 g (100-150 mmol) of salt per day, or about 1-2 heaping teaspoonfuls. The long-term balance of risks and benefits of a strategy of increasing salt and water intake is unknown.
In selected patients with V-VS, it may be reasonable to reduce or withdraw medications that cause hypotension when appropriate. A careful examination of the patient's history for medications that may lower blood pressure (hypotensive agents) should be performed. Care should be taken to withdraw or reduce medications only when safe to do so and in conjunction with the prescribing healthcare provider.
In patients with recurrent V-VS, a selective serotonin reuptake inhibitor might be considered. Serotonin has central neurophysiologic effects on blood pressure and heart rate and acutely induces syncope during tilt-table testing.

Modified from Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in *Circulation*. 2017 Oct 17;136(16):e271-e272]. *Circulation*. 2017;136(5):e60-e122.

84.1 Postural Tachycardia Syndrome

Gisela G. Chelimsky and Thomas Chelimsky

Several complex and interrelated mechanisms allow humans to stand despite the pull of gravity on the cerebral circulation. In the supine posture, most blood sits in the thoracic cavity, with 25–30% of total volume in the splanchnic vasculature. When an adult stands up, about 500 mL of blood shifts to the lower extremities and to the splanchnic vasculature. The decrease in hydrostatic pressure in the carotid sinuses produces vasoconstriction in the peripheral vessels mediated by sympathetic outflow and in the splanchnic vasculature. This action is mediated by norepinephrine, adenosine triphosphate (ATP), and neuropeptide Y. The muscles in the legs and gluteal area work as a pump when the individual is upright and during exercise to help return the blood to the heart.

Understanding postural tachycardia syndrome, or postural orthostatic tachycardia syndrome **(POTS)**, requires an understanding of other orthostatic conditions. Many adolescents have lightheadedness or tunnel vision in the first few seconds of assuming the upright posture. This phenomenon, termed **initial orthostatic hypotension (IOH)**, can lead to *syncope,* but usually is very short, perhaps 30-60 seconds, and occurs primarily with active standing. Blood pressure (BP) may drop 30% of baseline at 10-20 seconds of standing and may be associated with tachycardia. BP returns to baseline in 30-60 seconds, whereas heart rate (HR) typically returns to a new, higher value above the baseline when supine. Because of its transient rapidity, IOH escapes detection with standard BP machines and requires beat-to-beat monitoring of BP and HR. The clinical diagnosis requires a careful history. The symptoms usually happen after prolonged recumbence and when the individual stands. The person complains of lightheadedness and "blacking out" or tunnel vision 5-10 seconds after standing.

In contrast to IOH, **orthostatic hypotension (OH)** is defined as a *sustained* decrease in the systolic BP of >20 mm Hg or diastolic BP >10 mm Hg in the first 3 minutes of upright tilt. OH rarely occurs in children. The patient often has no orthostatic symptoms while upright despite very low pressures (Fig. 84.1). This distinguishes OH from POTS, which *requires* symptoms while upright. A third orthostatic disorder, **reflex syncope** (i.e., vasovagal or neurally mediated), is defined as relatively sudden change in autonomic nervous system activity that leads to a sudden decrease in BP, HR, and cerebral perfusion (Fig. 84.2).

In children, POTS is defined as a syndrome characterized by HR increase of >40 beats/min during the first 10 minutes of upright tilt test without associated hypotension, (>30 beats/min if >19 years old) while replicating orthostatic symptoms that occur when upright (Fig. 84.3). Improvement of symptoms in the supine position is expected. The diagnosis of POTS also requires *daily* orthostatic symptoms. In patients with POTS, the larger decline in cardiac stroke volume appears to be the primary trigger for the tachycardia, which may result from various pathophysiologic mechanisms, such as the following:

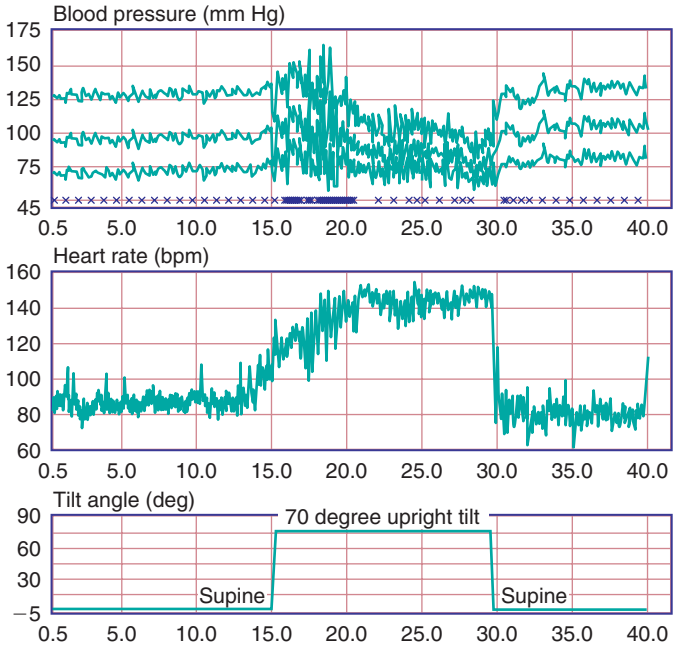

Fig. 84.1 Example of orthostatic hypotension.

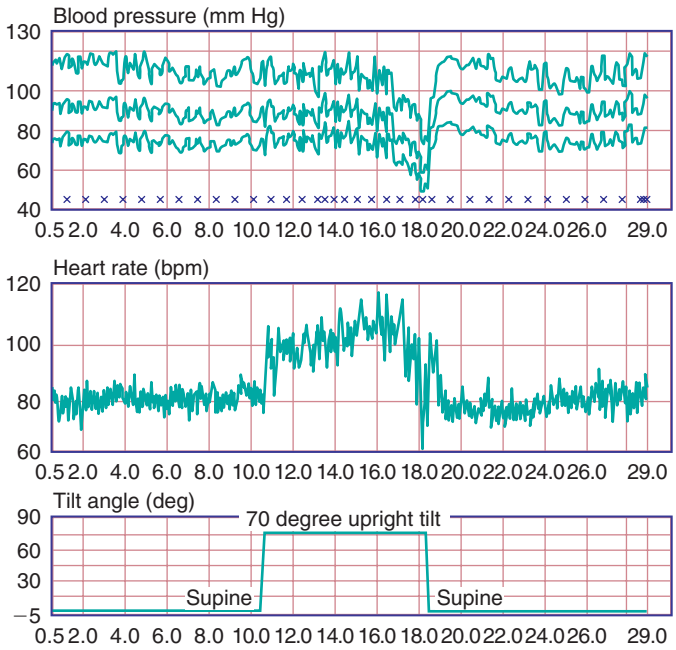

Fig. 84.2 Example of neurally mediated syncope.

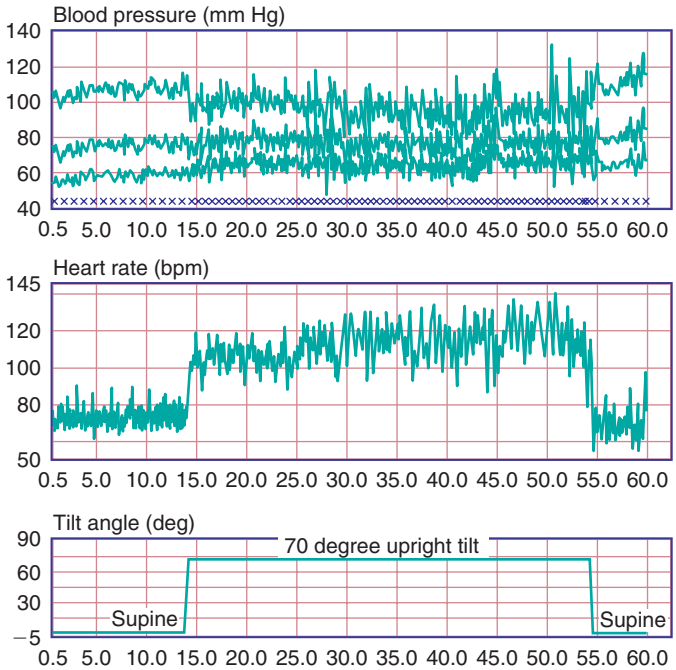

Fig. 84.3 Example of postural tachycardia syndrome.

- **Neuropathic** POTS, an autonomic neuropathy impairing sympathetic venoconstriction in the lower extremities or splanchnic circulation, decreasing stroke volume and consequently resulting in tachycardia.
- **Hypovolemic** POTS, a common contributor, often related to decreased aldosterone with reduced renin activity, resulting in tachycardia caused by decreased blood volume.
- **Hyperadrenergic** POTS, with norepinephrine levels rising threefold to fourfold in the standing position (norepinephrine normally doubles on standing), which may occur in norepinephrine transporter deficiency or strong stimulation of central baroreflex responses.
- **Autoimmune** POTS, typically assumed based on a postviral chronology, but seldom proven; such a form may or may not exist. The antiganglionic antibody is almost never elevated in these patients. Nonetheless, a group of patients report that intravenous immunoglobulin (IVIG) is helpful to them. Whether they benefit from the increase in intravascular volume or an actual immune effect is unknown.

Some patients have orthostatic symptoms while upright but do not meet criteria for syncope, OH, or POTS. This group has **orthostatic intolerance not otherwise specified (OI-NOS)**.

CLINICAL PRESENTATION

The symptoms that intrinsically relate to POTS are those that are replicated during upright tilt testing or standing. Many other symptoms also occur in patients with POTS, fitting the description of comorbid conditions, but not reproduced while upright. A patient may have nausea while upright associated with lightheadedness and have a diagnosis of POTS. Another patient may complain of nausea on awakening and have POTS, but have no nausea while upright. In the former patient the nausea is a symptom of POTS itself, whereas in the latter nausea is an associated condition. The symptoms that often directly relate to POTS include lightheadedness, orthostatic nausea, orthostatic headaches, fatigue, tunnel vision, and brain fog. About 20–30% of pediatric patients with POTS will also have syncope (Fig. 84.4). Other comorbid conditions frequently occur in these patients but are not caused by POTS (i.e., not an orthostatic phenomenon). These comorbidities include (1) sleep issues, usually delayed onset of sleep, frequent awakening, and not feeling refreshed in the morning; (2) joint hypermobility and aches in different parts of the body; (3) abdominal pain; (4) headaches and migraines; (5) nausea and vomiting; (6) depression and anxiety; and (7) Raynaud-like symptoms and other, less frequent problems (e.g., urinary symptoms).

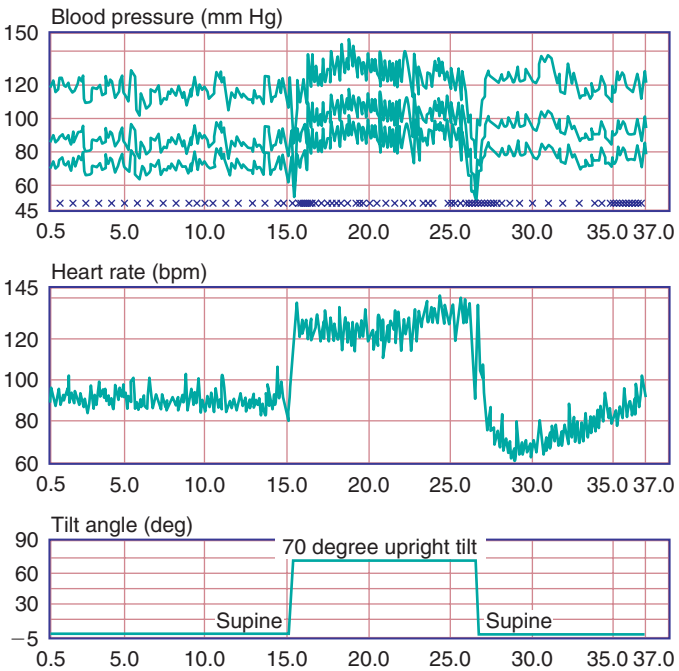

Fig. 84.4 Example of postural tachycardia syndrome (POTS) followed by a neurally mediated syncope.

The association between upper gastrointestinal (GI) symptoms and POTS is well described. Nausea, early satiety, and bloating are described in association with POTS. Such GI symptoms relate mechanistically to POTS only when they occur in the upright position. Many patients with POTS have comorbid GI symptoms that are not a consequence of the orthostatic challenge. Therefore only the GI symptoms replicated during tilt testing will improve with treatment aimed at orthostasis. Patients with POTS have changes in the electrical activity of the stomach while upright, which may explain the upright GI symptoms; they usually do not have delayed gastric emptying. The emptying is either normal or accelerated, implying that the cause of nausea is not gastroparesis.

Patients with **hypermobility Ehlers-Danlos syndrome** (h-EDS) may have POTS. Typically, such individuals have more migraines and syncope. Joint hypermobility itself in *adults* is associated with more autonomic complaints such as syncope, presyncope, palpitations, chest discomfort, fatigue, and heat intolerance. Those with hypermobility have more frequent positive tilt tests than healthy controls. Interestingly, in children, joint hypermobility does not influence the number of comorbidities or autonomic disorders. Similarly, those with pediatric chronic overlapping pain conditions with or without POTS have the same comorbidities, suggesting that neither POTS nor hypermobility are drivers of the comorbidities or the chronic overlapping pain condition, but rather another associated disorder (see Chapter 212).

DIAGNOSIS

Orthostatic intolerance is clinically diagnosed by detailed history attending specifically to symptoms as they relate to body position. Dizziness that begins in the supine position cannot be a manifestation of orthostatic intolerance. Furthermore, those symptoms that do develop while upright should improve or resolve when supine. Importantly, the history should include a detailed description of current physical exercise habits, with frequency, type, and endurance. One should also assess sleep, diet (mainly evaluating intake of salt), fluid intake, and other comorbidities. The physical examination is also important and should include a cardiac and neurologic evaluation with supine and standing BP and HR. Examination of the extremities may provide information about venous pooling, such as mild edema or reddish-purple discoloration when sitting or standing. Cold, clammy hands can signify excess sympathetic activity.

To diagnose POTS the patient needs to undergo a *head-up tilt test for at least 10 minutes*. It is important to have the patient supine for at least 20 minutes before the tilt test. POTS can also be assessed by a standing test, measuring BP and HR at 1, 3, 5, and 10 minutes standing, but to have a reliable test similar to the tilt test, the patient needs to be supine for 1 hour before standing. The HR increase with active standing is typically less than with tilt, because the lower-extremity muscle pump is less active in tilt. The diagnosis of POTS requires replication of the day-to-day symptoms while upright, not just the increased HR while upright. A small but significant proportion of healthy teenagers in school will have an increased HR that may be diagnosed as POTS but will not have associated symptoms.

Other tests may include electrocardiogram, echocardiogram, and Holter monitor when there is concern of a primary cardiac cause of tachycardia or if there is a need to determine if symptoms correlate with tachycardia (see Chapter 84). Supine and standing plasma catecholamines help confirm the diagnosis of POTS, as one expects to see either the normal doubling of norepinephrine levels from supine to standing or a tripling with hyperadrenergic POTS. Beyond tilt table testing, autonomic testing will also include cardiac response to deep breathing (checking cardiac parasympathetic function), Valsalva maneuver (checking cardiac sympathetic and parasympathetic functions and vasomotor sympathetic function), and quantitative axon reflex sudomotor test (to assess for an autonomic neuropathy and vasomotor sympathetic dysfunction).

Table 84.9 First-Line Medications in Treatment of Postural Tachycardia Syndrome (POTS)

DRUG	MECHANISM OF ACTION	SIDE EFFECTS	TREATMENT GUIDELINES
Fludrocortisone	Low dose: sensitizes α-receptors Higher doses: mineralocorticoid effect	Peripheral edema, headache, irritability, hypokalemia, hypomagnesemia, acne	Monitor basic metabolic panel and magnesium
Midodrine	α_1-Agonist; produces vasoconstriction	Scalp tingling, urinary retention, goosebumps, headache, supine hypertension	Monitor supine blood pressure 30-60 min after dose
Metoprolol succinate/ tartrate	β Blocker	Worsening of asthma, dizziness, fatigue	Use with caution in asthma If fatigue is severe, use at bedtime
Propranolol	Nonselective β blocker	Bradycardia, gastrointestinal symptoms, lightheadedness, sleepiness, hypotension, syncope	Use with caution in diabetes and asthma
Pyridostigmine	Peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine in autonomic ganglia and at peripheral muscarinic receptors	Symptoms of excessive cholinergic activity (diarrhea, urinary incontinence, salivation)	Very useful if patient has POTS and constipation Use with caution in asthma Contraindicated in urinary or bowel obstruction

Additional studies depend on the clinical symptoms and include morning cortisol (to rule out Addison disease) and thyroid studies if the patient has unusually severe fatigue or is not responsive to usual treatment. Serum tryptase and urine methylhistamine are tested if mast cell activation disorder is suspected, based on a history of flushing during the spells. If an autoimmune cause for the POTS is a concern, antibodies such as voltage-gated potassium channel and acetylcholine receptor antibodies could be checked, but this etiology for POTS is being questioned. Patients rarely (<5 in 1,000) benefit from IVIG; if this mechanism is really causing POTS, such patients should experience peak benefit at about 10 days after the infusion rather than immediately (which may simply reflect increasing intravascular volume). If the patient has hypertension, plasma and urine metanephrines should be measured to test for a pheochromocytoma. In addition, if symptoms are associated with perimenstrual timing, an assessment of sex hormone axis is helpful, with occult polycystic ovarian syndrome or low testosterone levels sometimes present.

MANAGEMENT

The core of POTS management is **nonpharmacologic**. Medications will be of little benefit without these measures being undertaken first. The best measure for treating POTS is a regular **aerobic exercise** program. Given the combination of orthostatic symptoms and severe deconditioning found in most patients, the exercise program must be introduced in a slow, progressive manner. Patients with POTS typically have moderate to severe exercise intolerance, and compared with sedentary healthy controls, have decreased peak oxygen uptake. After 3 months of exercise, POTS patients have an increase in cardiac mass and size, blood volume, and peak oxygen uptake, as reflected in a better exercise performance. The tachycardia in POTS is caused by a decrease in stroke volume and not an intrinsic circulatory problem. An exercise program should start with water exercises combined with recumbent aerobic activities (recumbent bike or rowing machine), slowly increasing the exercise time to 45 minutes at least 5 times per week. When tolerance increases, patients can advance to more upright aerobic activities. These aerobic activities need to be combined with light core- and limb-strengthening exercises.

Exercise usually cannot be performed without simultaneous expansion of the intravascular volume. To this end, encourage teenagers to drink >80 oz of fluids daily and to add 2 g of salt to their usual diet in both the morning and the early afternoon. **Salt supplementation** increases plasma and blood volume, improves orthostatic tolerance, and decreases baroreflex sensitivity. Salt also reduces nitric oxide production, resulting in less vasodilation. Trial and error of different salt formulations can help to identify the best method for each individual patient. Salt tablets are simple and inexpensive but may make some people nauseous. An alternative is simply to obtain empty capsules on the internet and fill them with table salt. A "0" size capsule contains about 400 mg of salt.

The content of sodium in the body determines the extracellular fluid volume that in turn dictates orthostatic tolerance. Patients with POTS who have lower urinary sodium excretion have more symptoms than those with higher urinary sodium (>123 mmol/24 hours), and they often respond less well to salt supplementation. Those with severe orthostatic symptoms either in the morning or before sports should drink 16 oz of plain water, which is known to increase sympathetic response mainly in individuals with baroreflex dysregulation. The effect starts soon after drinking the water and lasts for about 1 hour. Compression garments may also be useful. These can be thigh or waist high; the waist-high compression garments may not be tolerated.

Medications can be added when the nonpharmacologic interventions are not sufficient. Different centers use different strategies, and there is no single correct evidence-based approach. Table 84.9 addresses first-line medications that primary care physicians could use; only the most common side effects are included.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 85

Shock

Scott L. Weiss, Pierre Tissières, and Mark J. Peters

Shock is an acute, life-threatening process of cardiovascular insufficiency characterized by inadequate delivery of oxygen and nutrients (e.g., glucose) by the circulatory system to meet the metabolic demands of vital organs that results in cellular dysfunction and injury. The initial imbalance between oxygen/nutrient delivery through the circulation and oxygen/nutrient consumption within organ systems can be compensated for by increasing tissue oxygen extraction. However, with further limitations in delivery of oxygen and nutrients as the shock state progresses, energy production gradually shifts from aerobic metabolism to less efficient anaerobic metabolic pathways, and a cellular bioenergetic crisis can ensue. If this process is not corrected, numerous adverse vascular, inflammatory, metabolic, cellular, and endocrine responses contribute to a state of **multiple organ dysfunction syndrome (MODS)**, cardiovascular collapse, and death.

It is important to recognize that the shock state can be present *before* the onset of hypotension, especially in children, and that inadequate cellular metabolism of oxygen and nutrients (not just impaired delivery) contributes to the clinical manifestations and outcomes observed in patients with shock. Therefore it is necessary to recognize early symptoms and signs of impaired circulation, including tachycardia, altered mental status (e.g., irritability, confusion, lethargy), tachypnea (often secondary to acidemia), abnormal capillary refill time, diminished peripheral pulses, and oliguria, in combination with metabolic markers such as acidemia, hyperlactatemia, and low central venous oxygen saturation. Hypotension, when present, is also important to recognize, but children—especially infants and preschool-age children—with *compensated* shock may be able to maintain a normal blood pressure (BP) for age until the later phases of shock. When hypotension is present, the child has reached a state of *uncompensated shock* and is at risk of irreversible organ damage and death without immediate treatment.

EPIDEMIOLOGY

Shock occurs in approximately 2% of all hospitalized infants, children, and adults in developed countries, and the mortality rate varies substantially depending on the etiology and clinical circumstances. Of patients who do not survive, many do not die in the initial acute phase of shock, but rather because of associated complications and MODS. MODS is defined as dysfunction in two or more organ systems; the presence of MODS in patients with shock substantially increases the probability of death. In 2017, there were an estimated 20.3 million cases of sepsis, with 2.9 million deaths, worldwide among children younger than 5 years and 4.9 million cases of sepsis, with 454,000 deaths, among older children and adolescents. In the United States, over 70,000 children are hospitalized with sepsis each year at an annual healthcare cost of $7.31 billion. In pediatrics, educational efforts and the use of standardized management guidelines that emphasize early recognition and intervention, along with the rapid transfer of critically ill patients to a pediatric intensive care unit (PICU), have decreased mortality from shock.

TYPES OF SHOCK

Shock classification systems generally define five major types of shock: hypovolemic, cardiogenic, obstructive, distributive, and dissociative (Table 85.1 and Fig. 85.1). **Hypovolemic shock**, the most common cause of shock in children worldwide, is most frequently caused by acute fluid losses resulting from diarrhea, vomiting, or hemorrhage. A special cause of hypovolemic shock is hemorrhagic shock, which may be caused by traumatic injury or gastrointestinal (GI), peritoneal, vaginal, soft tissue, or other sources of severe bleeding. **Cardiogenic shock** is seen in patients with congenital heart disease (before or after surgery, including heart transplantation) or those with congenital or acquired cardiomyopathies, including acute myocarditis and multisystem inflammatory syndrome in children (MIS-C). **Obstructive shock** stems from any lesion that creates a mechanical impediment to ventricular blood outflow, which includes pericardial tamponade, tension pneumothorax, pulmonary embolism, and ductal-dependent left-sided heart lesions (hypertrophic left heart syndrome, aortic coarctation, interrupted aortic arch, and critical aortic valve stenosis). **Distributive shock** is caused by inappropriate vasodilation, pooling of blood in the peripheral vasculature, leakage of blood plasma into the interstitium through a compromised endothelial barrier, and microvascular shunting. Common causes of distributive shock in children include sepsis, anaphylaxis, and accidental or intentional drug overdose (e.g., calcium channel blockers, atypical antipsychotics). Neurogenic shock is a type of distributive shock caused by a sudden disruption of sympathetic nerve stimulation to the vascular smooth muscle leading to a profound decrease in vasomotor tone, typically with severe traumatic brain or cervical spine injury. Unlike other types of shock, the unopposed vagal activity classically results in bradycardia, or at least absence of the usual tachycardic response to hypotension. **Dissociative shock** is a special category of shock in which cellular oxygen delivery or utilization is severely impaired despite sustained or supranormal tissue perfusion and is typically caused by exposure to a toxic metabolite or drug, such as severe anemia, methemoglobinemia, carbon monoxide poisoning, or thiamine deficiency (beriberi).

Septic shock is life-threatening cardiovascular dysfunction in patients with suspected or confirmed infection and confers a high risk for mortality in children compared to those with uncomplicated infections or sepsis without shock. Sepsis in children is operationalized as a Phoenix Sepsis Score of at least 2 points from a composite four-organ system model that includes criteria for respiratory, neurologic, coagulation, and cardiovascular dysfunction, with septic shock requiring at least 1 point in the cardiovascular subscore (Table 85.2). Many children with septic shock also have MODS, including respiratory, kidney, hematologic (disseminated intravascular coagulation [DIC]), hepatobiliary, and neurologic dysfunction. Septic shock classically presents as a type of distributive shock with high cardiac output and low systemic vascular resistance (SVR). However, most children with sepsis also have features of hypovolemic shock from poor oral intake, GI fluid losses, and vascular leak as well as cardiogenic shock due to decreased myocardial contractility. In younger children, septic shock often presents with low cardiac output and high SVR in which features of cardiogenic and hypovolemic shock predominate.

PATHOPHYSIOLOGY

An initial insult triggers shock, leading to a decrease in effective cardiac output with inadequate oxygen delivery to organs and tissues. Compensatory mechanisms attempt to maintain BP by increasing cardiac output and SVR. The body also attempts to optimize oxygen delivery to the tissues by increasing oxygen extraction and redistributing blood flow to the brain, heart, and kidneys at the expense of the skin, skeletal muscles, and GI tract. These responses lead to an initial state of **compensated shock** in which BP is often maintained near normal levels for age. If resuscitative treatment is not initiated or is inadequate during this period, **uncompensated shock** develops, with hypotension and tissue damage that may lead to irreversible organ damage, MODS, and, ultimately, death.

In the early phases of shock, multiple compensatory physiologic mechanisms act to maintain BP and preserve tissue perfusion and oxygen delivery. Cardiovascular effects include increases in heart rate (HR), stroke volume, and vascular smooth muscle tone, which are regulated through sympathetic nervous system activation and neurohormonal responses. Respiratory compensation involves greater carbon dioxide (CO_2) elimination in response to the metabolic acidosis and increased CO_2 production from poor tissue perfusion. Renal excretion of hydrogen ions (H^+) and retention of bicarbonate (HCO_3^-) also increase in an effort to maintain normal body pH (see Chapter 73.7). Maintenance of intravascular volume is facilitated via renal sodium retention mediated by activation of the renin-angiotensin-aldosterone and atrial natriuretic factor axes, cortisol and catecholamine synthesis

Table 85.1 Types of Shock

TYPES OF SHOCK	PATHOPHYSIOLOGY	APPEARANCE	EXAMPLES	TREATMENTS
Hypovolemic*	Decreased cardiac output due to volume depletion → decreased preload	Tachycardia and vasoconstriction maintain adequate circulation up to 30% of circulating volume Narrowed pulse pressure, delayed capillary refill, orthostatic changes, late hypotension, AMS, and decreased UOP	Nonhemorrhagic (vomiting and diarrhea) Hemorrhagic (trauma)	IV fluid bolus Vasopressors Blood replacement
Cardiogenic	Decreased cardiac output due to myocardial dysfunction, increased afterload, and/or lack of ventricular filling	Tachycardia, vasoconstriction, cool extremities, narrow pulse pressure, delayed capillary refill, respiratory distress, rales or gallop rhythm, enlarged liver, JVD, cardiomegaly on chest radiograph Significant gradient between upper and lower extremity blood pressures	Cardiomyopathies, infectious myocarditis, and systemic inflammatory process, autoimmune disease, impaired coronary perfusion, cardiopulmonary bypass, acidosis, HIE, and dysrhythmias Infants: ductal-dependent lesions, tachydysrhythmias	Judicious IV fluid resuscitation, ionotropic agents to improve contractility, vasodilators to reduce afterload, and management of tachyarrhythmias PGE for infants <2 mo
Distributive	Decreased cardiac output and systemic vascular resistance due to peripheral vasodilation → decreased afterload and preload, redistribution of blood flow away from vital organs, and loss of sympathetic outflow	Tachycardic, vasodilated, flushed, warm extremities, wide pulse pressure, bounding pulses, flash capillary refill Anaphylaxis: rash; facial swelling; lip, tongue, or airway swelling; bronchospasm; hypotension Spinal shock: unable to raise HR, hypotension Neurogenic: Control ↑ ICP	Septic shock Toxic ingestions Anaphylaxis Spinal cord injuries	IV fluids, vasopressors, antibiotics Specific antidotes Remove triggers, IV fluids, IM epinephrine, antihistamines, vasopressors IV fluids, vasoconstrictors
Obstructive	Decreased cardiac output due to increased afterload of the right ventricle from an obstructive process	Tachycardia, delayed capillary refill, cool extremities, narrow pulse pressure, distended neck veins, distant heart tones, asymmetric breath sounds	Tension pneumothorax Pulmonary embolism Cardiac tamponade	Anticoagulants Drain pericardial effusion Evacuate pneumothorax
Dissociative	High cardiac output failure due to inadequate oxygen-releasing capacity	Tachycardia ± delayed capillary refill, cool extremities, weakened pulse, pallor or flushed cheeks	Anemia Carbon monoxide Methemoglobinemia Cyanide	Gradual fluid replacement and blood replacement 5 mL/dL Oxygen, hyperbaric chamber Methylene blue Hydroxocobalamin and cyanide antidote kit (sodium thiosulfate, sodium nitrate, amyl nitrite) plus oxygen

*Most common.
AMS, Altered mental status; HIE, hypoxic ischemic encephalopathies; HR, heart rate; IM, intramuscular; ICP, intracranial pressure; IV, intravenous; JVD, jugular venous distention; PGE, prostaglandin; UOP, urine output.
Modified from Baumer-Mouradian SH, Drendel AL. Shock. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier;2023: Table 10.4.

and release, and antidiuretic hormone secretion. Despite these compensatory mechanisms, the underlying shock and host response lead to vascular endothelial cell injury and loss of endothelial adhesion proteins that allow significant leakage of intravascular fluid into the interstitial extracellular space.

Another important aspect of the initial pathophysiology of shock is the impact on cardiac output. All forms of shock affect cardiac output through several mechanisms, with changes in HR, preload, afterload, and myocardial contractility occurring separately or in combination (see Fig. 85.1). **Hypovolemic shock** is characterized primarily by fluid loss and decreased preload. Tachycardia and an increase in SVR are the initial compensatory responses that seek to maintain cardiac output, systemic BP, and tissue perfusion. Without adequate volume replacement, hypotension inevitably develops, followed by tissue ischemia and further clinical deterioration. When there is preexisting low plasma oncotic pressure (caused by nephrotic syndrome, malnutrition, hepatic dysfunction, acute severe burns, etc.), further volume loss and exacerbation of shock may result from worsening vascular leak.

In contrast, the underlying pathophysiologic mechanism leading to **distributive shock** is a state of abnormal vasodilation and decreased SVR. In sepsis, loss of normal regulation of vasomotor tone is due to a combination of factors, including excessive nitric oxide (NO) produced from an increase in inducible NO synthase, altered sympathetic and parasympathetic tone, and diminished circulating levels and/or reduced responsiveness to vasopressin, endogenous catecholamines, and cortisol. In anaphylaxis, vasodilation is caused by an acute release of histamine and other mediators from mast cells. Irrespective of the inciting event, the sudden fall in SVR is accompanied initially by a maldistribution of blood flow away from vital organs and a compensatory increase in cardiac output caused by an increase in HR and, potentially, left ventricular stroke volume. This process leads to significant decreases in both preload and afterload. Therapies for distributive shock must address both these problems simultaneously.

Cardiogenic shock may be seen in patients with myocarditis, cardiomyopathy, arrhythmias, and congenital heart disease (generally after cardiac surgery) (see Chapter 483). In these patients, myocardial contractility is directly impaired, leading to systolic and/or diastolic dysfunction. The later phases of all forms of shock frequently have a negative impact on the myocardium, leading to development of a cardiogenic component to the initial shock state.

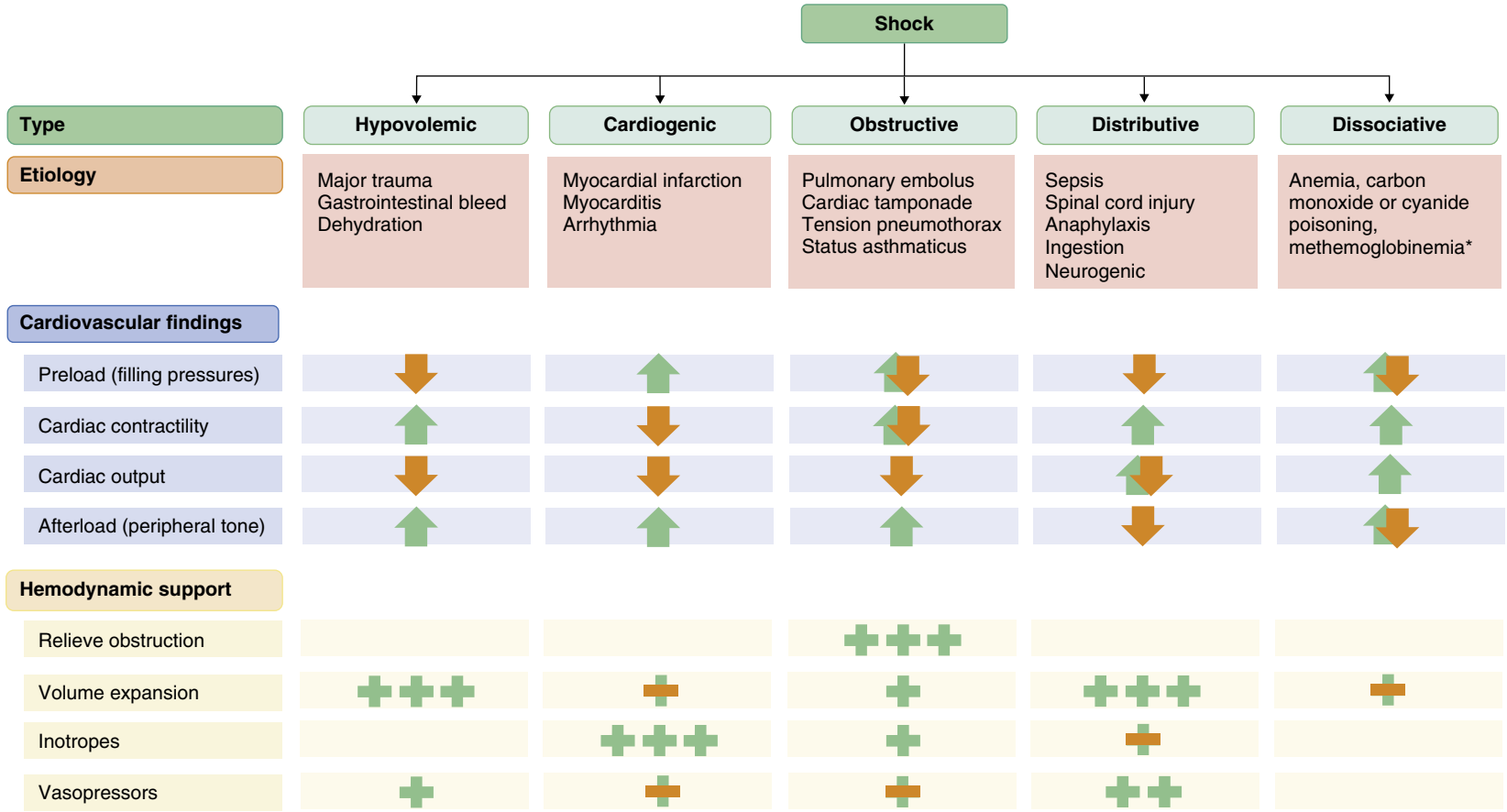

Fig. 85.1 The causes, cardiovascular findings, and hemodynamic support for different types of shock. Under cardiovascular findings, *bidirectional arrows* indicate variation in findings among patients with the particular type. Under hemodynamic support, the number of *+ signs* indicates the importance of therapy. A combined *+ and −* indicates that the intervention could help some patients but must be used with caution. *Treat specific etiology transfusion or specific antidotes. *(Modified from Angus DC. Approach to the patient with shock. In: Goldman L, Schafer AI, eds.* Goldman-Cecil Medicine, *26th ed. Philadelphia: Elsevier; 2020:642, Fig. 98-1.)*

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 85.2 The Phoenix Sepsis Score[a]

VARIABLES	0 POINTS	1 POINT	2 POINTS	3 POINTS
RESPIRATORY, 0–3 POINTS				
	PaO_2:FIO_2 ≥400 or SpO_2:FIO_2 ≥292[b]	PaO_2:FIO_2 <400 on any respiratory support or SpO_2:FIO_2 <292 on any respiratory support[b,c]	PaO_2:FIO_2 100–200 and IMV or SpO_2:FIO_2 148–220 and IMV[b]	PaO_2:FIO_2<100 and IMV or SpO_2:FIO_2 <148 and IMV[b]
CARDIOVASCULAR, 0–6 POINTS		1 point each (up to 3)	2 points each (up to 6)	
	No vasoactive medications[d]	1 Vasoactive medication[d]	≥2 Vasoactive medications[d]	
	Lactate <5 mmol/L[e]	Lactate 5–10.9 mmol/L[e]	Lactate ≥11 mmol/L[e]	
AGE BASED[f]	Mean Arterial Pressure, mm Hg[g]			
<1 mo	>30	17–30	<17	
1 to 11 mo	>38	25–38	<25	
1 to <2 yr	>43	31–43	<31	
2 to <5 yr	>44	32–44	<32	
5 to <12 yr	>48	36–48	<36	
12 to 17 yr	>51	38–51	<38	
COAGULATION, 0–2 POINTS[H]		1 point each (maximum 2 points)		
	Platelets ≥100 × 10^3/μL	Platelets <100 × 10^3/μL		
	International normalized ratio ≤1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
NEUROLOGIC, 0–2 POINTS[i]				
	Glasgow Coma Scale score >10; pupils reactive[j]	Glasgow Coma Scale score ≤10[j]	Fixed pupils bilaterally	
PHOENIX SEPSIS CRITERIA				
Sepsis	Suspected infection and Phoenix Sepsis Score ≥2 points			
Septic shock	Sepsis with ≥1 cardiovascular point(s)			

[a]The score may be calculated in the absence of some variables (eg, even if lactate level is not measured and vasoactive medications are not used, a cardiovascular score can still be ascertained using blood pressure). It is expected that laboratory tests and other measurements will be obtained at the discretion of the medical team based on clinical judgment. Unmeasured variables contribute no points to the score. Ages are not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, neonates whose postconceptional age is younger than 37 weeks, or those 18 years of age or older.

[b]SpO_2:FIO_2 ratio is only calculated if SpO_2 is 97% or less.

[c]The respiratory dysfunction of 1 point can be assessed in any patient receiving oxygen, high-flow, noninvasive positive pressure, or IMV respiratory support, and includes a PaO_2:FIO_2 ratio of less than 200 and a SpO_2:FIO_2 ratio of less than 220 in children who are not receiving IMV. For children receiving IMV with a PaO_2:FIO_2 less than 200 and SpO_2:FIO_2 less than 220, see criteria for 2 and 3 points.

[d]Vasoactive medications include any dose of epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and/or vasopressin (for shock).

[e]Lactate reference range is 0.5 to 2.2 mmol/L. Lactate can be arterial or venous.

[f]Age is not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, children whose postconceptional age is younger than 37 weeks, or those 18 years or older.

[g]Use measured MAP preferentially (invasive arterial if available or noninvasive oscillometric), and if measured MAP is not available, a calculated MAP (1/3 × systolic + 2/3 × diastolic) may be used as an alternative.

[h]Coagulation variable reference ranges: platelets, 150 to 450 × 103/μL; D-dimer, <0.5mg/L FEU; fibrinogen, 180 to 410mg/dL. The INR reference range is based on the local reference prothrombin time.

[i]The neurological dysfunction subscore was pragmatically validated in both sedated and nonsedated patients, and those receiving or not receiving IMV support.

[j]The Glasgow Coma Scale score measures level of consciousness based on verbal, eye, and motor response (range, 3–15, with a higher score indicating better neurological function).

FEU, fibrinogen equivalent units; IMV, invasive mechanical ventilation; INR, international normalized ratio of prothrombin time; MAP, mean arterial pressure; PaO_2:FIO_2, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; SpO_2, oxygen saturation measured by pulse oximetry (only SpO_2 of ≤97%).

SI conversion factor: To convert lactate from mmol/L tomg/dL, divide by 0.111.

From Schlapbach LJ, Watson RS, Sorce LR, et al. International Consensus Criteria for Pediatric Sepsis and Septic Shock. *JAMA*. Published online January 21, 2024. https://doi.org/10.1001/jama.2024.0179.

Obstructive shock manifests as an acute increase in SVR typically in response to a sudden decrease in cardiac output that resembles a state of functional hypovolemia. A compensatory increase in HR and afterload provides temporary support, but compensation will soon fail without relief of the mechanical obstruction.

Dissociative shock is caused by the inability to deliver oxygen due to severe anemia or a congenital or acquired hemoglobinopathy, such as carbon monoxide intoxication. Alternatively, oxygen delivery may be preserved, but consumption can be impaired by a metabolic disorder or acquired state of mitochondrial dysfunction, such as cyanide

Table 85.3 Differential Diagnosis of Systemic Inflammatory Response Syndrome (SIRS)

INFECTION
Bacteremia or meningitis (*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*, group A *Streptococcus*, *Staphylococcus aureus*)
Viral illness (influenza, enteroviruses, hemorrhagic fever group, herpes simplex virus, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus, COVID-19)
Encephalitis (arboviruses, enteroviruses, herpes simplex virus)
Rickettsiae (Rocky Mountain spotted fever, Ehrlichia, Q fever)
Syphilis
Vaccine reaction (pertussis, influenza, measles)
Toxin-mediated reaction (toxic shock, staphylococcal scalded skin syndrome)

CARDIOPULMONARY
Pneumonia (bacteria, virus, mycobacteria, fungi, allergic reaction)
Pulmonary emboli
Heart failure
Arrhythmia
Pericarditis
Myocarditis

METABOLIC-ENDOCRINE
Adrenal insufficiency (adrenogenital syndrome, Addison disease, corticosteroid withdrawal)
Electrolyte disturbances (hyponatremia or hypernatremia, hypocalcemia or hypercalcemia)
Diabetes insipidus
Diabetes mellitus
Inborn errors of metabolism (organic acidosis, urea cycle, carnitine deficiency, mitochondrial disorders)
Hypoglycemia

GASTROINTESTINAL
Gastroenteritis with dehydration
Volvulus
Intussusception
Appendicitis
Peritonitis (spontaneous, associated with perforation or peritoneal dialysis)
Necrotizing enterocolitis
Hepatitis
Hemorrhage
Pancreatitis

HEMATOLOGIC/IMMUNE
Anemia (sickle cell disease, blood loss, nutritional)
Methemoglobinemia
Splenic sequestration crisis
Leukemia or lymphoma
Hemophagocytic syndromes
Cytokine release syndrome s/p CAR-T therapy
Immune reconstitution syndrome
Graft-versus-host disease

NEUROLOGIC
Intoxication (drugs, carbon monoxide, intentional or unintentional overdose)
Intracranial hemorrhage
Infant botulism
Trauma (child abuse, accidental)
Guillain-Barre syndrome
Myasthenia gravis

OTHER
Anaphylaxis (food, drug, insect sting, idiopathic)
Hemolytic-uremic syndrome
Kawasaki disease
Erythema multiforme, toxic epidermal necrolysis
MIS-C
Poisoning, iron, cyanide
Toxic envenomation
Systemic JIA
Macrophage activation syndrome
Idiopathic systemic capillary leak (Clarkson) syndrome

CAR-T, Chimeric antigen receptor T-cell; JIA, juvenile idiopathic arthritis; MIS-C, multisystem inflammatory syndrome in children; S/P, status post.
From Baumer-Mouradian SH, Drendel AL. Shock. In: Kliegman RM, Bordini BJ, Toth H, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Elsevier: Philadelphia; 2022: Table 10.6.

toxicity. Notably, varying degrees of dissociative shock may also be present in other shock types, especially sepsis, in which acquired pyruvate dehydrogenase deficiency or mitochondrial dysfunction have been increasingly recognized.

Septic shock is generally a unique combination of distributive, hypovolemic, and cardiogenic shock, as well as dissociative shock. Hypovolemia from insufficient fluid intake, GI losses, and/or vascular leak is common. Cardiogenic shock results from the myocardial-depressant effects of sepsis, and distributive shock is the result of decreased SVR. The degree to which a patient exhibits each of these responses varies, but there are frequently alterations in preload, afterload, and myocardial contractility.

In septic shock, it is important to distinguish between the inciting infection and the host inflammatory response. Normally, host immunity prevents the development of sepsis through activation of the reticular endothelial system along with the cellular and humoral immune systems. This host immune response produces an *inflammatory cascade* mediated by hormones, cytokines, and chemokines. If this inflammatory cascade is uncontrolled, derangement of the microcirculatory system leads to subsequent organ and cellular dysfunction.

Systemic inflammatory response syndrome (SIRS) is an inflammatory cascade that is initiated by the host response to an infectious or noninfectious trigger (Table 85.3). This inflammatory cascade is triggered when the host defense system does not adequately recognize and/or eliminate the triggering event. The inflammatory cascade initiated by shock can lead to hypovolemia, cardiac and vascular failure, acute respiratory distress syndrome (ARDS), insulin resistance, decreased cytochrome P450 activity (decreased steroid synthesis), coagulopathy, and unresolved or secondary infection. Tumor necrosis factor (TNF) and other inflammatory mediators increase vascular permeability, causing diffuse vascular leak, decreased vascular tone, and an imbalance between perfusion and metabolic demands of the tissues. Early increases in TNF, interleukin (IL)-1, and IL-6 stimulate the release of both proinflammatory and antiinflammatory mediators, causing fever, vasodilation, and myocardial dysfunction. Simultaneous upregulation of antiinflammatory mediators (such as circulating levels of IL-4, IL-10, and transforming growth factor-β), downregulation of hematopoietic growth factors (such as IL-7), and increased expression of immune cell surface checkpoint proteins (such as programmed death [PD]-1 and its PD ligand [PD-L1/2]), as well as production of immature immune cells through emergency myelopoiesis contribute to a state of immune dysregulation that can impair pathogen clearance and allow for secondary infections.

The inflammatory cascade is initiated by toxins or superantigens through macrophage binding or lymphocyte activation. The vascular endothelium is both a target of tissue injury and a source of mediators that may cause further injury. Biochemical responses include the production of arachidonic acid metabolites, release of myocardial-depressant factors and endogenous opiates, activation of the complement system, and production and release of other mediators, which

Table 85.4 Signs of Decreased Perfusion

ORGAN SYSTEM	↓ PERFUSION	↓↓ PERFUSION	↓↓↓ PERFUSION
Central nervous system	—	Restless, apathetic, anxious	Agitated/confused, stuporous, coma
Respiratory	—	↑ Ventilation	↑↑ Ventilation
Metabolic	—	Compensated metabolic acidemia	Uncompensated metabolic acidemia
Gastrointestinal	—	↓ Motility	Ileus
Kidney	↓ Urine volume ↑ Urinary specific gravity	Oliguria (<0.5 mL/kg/hr)	Oliguria/anuria
Skin	Delayed capillary refill	Cool extremities	Mottled, cyanotic, cold extremities
Cardiovascular system	↑ Heart rate	↑↑ Heart rate ↓ Peripheral pulses	↑↑ Heart rate ↓ Blood pressure, central pulses only

may be proinflammatory or antiinflammatory. The balance among these mediator groups for an individual patient contributes to the progression (and resolution) of disease and affects the prognosis.

CLINICAL MANIFESTATIONS

Table 85.1 and Figure 85.1 show a classification system for shock. Categorization is important, but there may be significant overlap among these groups, especially in septic shock. The clinical presentation of shock depends in part on the underlying etiology, but if unrecognized and untreated, all forms of shock follow a common progression of clinical signs and pathophysiologic changes that may ultimately lead to irreversible organ injury and death. Among the first physiologic responses is sympathetic adrenergic system activation and its related signs and symptoms.

Shock may initially manifest as only tachycardia, with or without tachypnea. Progression leads to decreased urine output, poor peripheral perfusion, respiratory distress or failure, alteration of mental status, and low BP (Table 85.4). A significant misconception is that shock occurs only with low BP. Hypotension is often a late finding, especially in infants and young children, and is not a criterion for the diagnosis of shock because of a complex set of compensatory mechanisms that attempt to preserve BP and peripheral perfusion. Hypotension reflects an advanced state of uncompensated shock and is associated with increased morbidity and mortality.

Hypovolemic shock often manifests initially as tachycardia and orthostatic hypotension and is associated with dry mucous membranes, dry axillae, poor skin turgor, and decreased urine output. Depending on the degree of dehydration, the patient with hypovolemic shock may present with either normal or slightly cool distal extremities, and peripheral pulses may be normal, decreased, or absent depending on disease severity.

The presenting signs of **cardiogenic shock** are often tachypnea, cool extremities, delayed capillary filling time, poor peripheral and/or central pulses, reduced pulse pressure, declining mental status, and decreased urine output caused by the combination of decreased cardiac output and compensatory peripheral vasoconstriction (see Chapter 491.1).

Obstructive shock often also manifests as inadequate cardiac output because of a physical restriction of forward blood flow with tachycardia, delayed capillary refill, cool extremities, diminished peripheral pulses, and decreased pulse pressure (difference between systolic and diastolic BP) or presence of pulsus paradoxus. The acute presentation may quickly progress to cardiac arrest. Obstructive shock due to tension pneumothorax typically includes signs of respiratory distress, hypoxia, and diminished breath sounds. Pericardial tamponade includes Beck's triad of hypotension, jugular vein distention, and muffled heart sounds. A saddle pulmonary embolism often presents with a sudden cardiac arrest. Left-heart obstructive lesions may present in newborns with discrepant perfusion of the upper and lower extremities.

Distributive shock includes signs of vasodilation, including tachycardia, flash capillary refill, warm extremities, bounding peripheral pulses, and increased pulse pressure, often with diastolic hypotension. In neurogenic shock, tachycardia may be absent or frank bradycardia may be present. Similar to distributive shock, signs of vasodilation may be present, although in the immediate phase, the patient can feel cool peripherally with delayed capillary refill.

Septic shock can be difficult to diagnose because of the wide spectrum of presenting signs and symptoms. A key historical clue is the presence of fever (or hypothermia) along with evidence for either a *systemic* (e.g., bacteremia, rickettsial disease, fungemia, viremia) or *localized* (e.g., meningitis, pneumonia, pyelonephritis, peritonitis, necrotizing fasciitis) infection. Infants and young children most commonly present with "cold shock," with features of hypovolemic and cardiogenic shock predominating, including tachycardia, delayed capillary refill, cool extremities, diminished peripheral pulses, and decreased pulse pressure. Older children and adolescents, especially those with sepsis from indwelling central venous catheters, more commonly present with "warm shock" that resembles distributive shock, including tachycardia, flash capillary refill, warm extremities, bounding peripheral pulses, and increased pulse pressure. However, the pathobiology of sepsis can evolve over time and with treatment in children, such that "warm shock" may shift to "cold shock" or vice versa.

In addition to the traditional description of septic shock, a subgroup immunophenotype presents with **hyperferritinemia**. Ferritin levels >3,000 mg/mL often predict a poor prognosis and the need for intensive care unit (ICU) admission. Hyperferritinemic septic shock may be due to familial primary genetic hemophagocytic lymphohistiocytosis (HLH) (usually age <2 years; see Chapter 556.2) or, more often, secondary HLH initiated by an infectious agent or macrophage activation syndrome (MAS) (see Chapter 207) associated with autoimmune diseases (Table 85.6).

Regardless of etiology, uncompensated shock, with hypotension, high SVR, decreased cardiac output, respiratory failure, obtundation, and oliguria, occurs late in the progression of disease. Table 85.1 lists the hemodynamic findings in various shock states. Additional clinical findings in shock include cutaneous lesions such as petechiae, diffuse erythema, ecchymoses, ecthyma gangrenosum, and peripheral gangrene. Jaundice can be present either as a sign of infection or as a result of MODS.

DIAGNOSIS

Shock is a clinical diagnosis that should be primarily based on a thorough history and physical examination (see Tables 85.1, 85.4, and 85.6). Important clues to consider in the history are recent trauma or bleeding, exposure to new medications or substances, preceding or concurrent symptoms of infection or fluid losses, the patient's comorbid conditions, and a brief review of systems. The physical examination should include rapid assessment of vital signs (including pulse oximetry), mental status/level of consciousness, extremity temperature, peripheral and central pulses, capillary refill, and presence of rashes or skin changes.

Increasingly, point-of-care ultrasound (POCUS) is being incorporated into the initial assessment of children with shock to assess intravascular volume status, likelihood of a positive hemodynamic response to fluid

Table 85.5 Considerations in Management of Hyperferritinemic Sepsis Beyond Usual Diagnostic and Therapeutic Measures Used in Sepsis Patients Without Hyperferritinemia

WHAT OCCULT INFECTION IS PRIMING AND WHAT CO-INFECTION IS PRESENT FOR THE HYPERFERRITINEMIC PROCESS?
Perform diagnostic workup for **viruses** (e.g., herpes simplex virus 1, HHV-6, HHV-8, Epstein-Barr virus, adenovirus, cytomegalovirus, parvovirus, Ebola, COVID-19, Dengue, hepatitis A, HIV, severe fever with thrombocytopenia syndrome virus, influenza, hemorrhagic fevers), **parasites** (e.g., toxoplasmosis, leishmaniasis, malaria, scrub typhus, babesiosis), **intracellular bacteria** (e.g., tuberculosis, atypical mycobacteria, mycoplasma, fusobacteria, babesiosis, ehrlichiosis), rickettsia, and **fungi** (e.g., histoplasmosis).
Begin empiric therapy and specific therapies according to context.
Give IVIG if no specific therapy is available to neutralize infection.
IS HEMOLYSIS AND FREE HEMOGLOBIN DRIVING THE HYPERFERRITINEMIC PROCESS?
Measure free hemoglobin and ferritin sequentially.
Minimize blood transfusions.
If unable to reverse hemolysis or hyperferritinemia, consider 5 days of plasma exchange to remove free hemoglobin and ferritin and to resolve inflammation.
IS AN ANTIINFLAMMATORY STRATEGY NEEDED TO SAFELY CONTROL INFLAMMASOME ACTIVATION?
If ferritin is >3,000 ng/mL in the high-resource PICU setting, or >500 ng/mL in the resource-poor PICU setting, then mortality risk is increased.
Methylprednisone, IVIG, and interleukin 1 receptor antagonist (anakinra) can be safely given to reduce mortality risk in these children.

HHV, human herpes virus; PICU; pediatric intensive care unit; IVIG, IV immunoglobulin. Modified from Carcillo JA, Kernan KK, Horvat CM, et al. Why and how is hyperferritinemic sepsis different from sepsis without hyperferritinemia? *Pediatr Crit Care Med.* 21(5):509-512, Table 1, p. 511.

therapy, and myocardial function. Cardiac and lung POCUS may also provide important diagnostic information about the etiology of shock, such as the presence of pericardial fluid to support tamponade, pneumothorax, or dilated right ventricle to support pulmonary embolus. The focused assessment with sonography for trauma (FAST) is commonly performed to screen for pericardial effusion and hemoperitoneum.

LABORATORY FINDINGS

Although the initial diagnosis of shock can and should be based on clinical data from the history and physical examination, the overall evaluation of shock should also include early laboratory testing to screen for hyperlactatemia (as a sign of increased anaerobic metabolism), acidemia, and electrolyte disturbances, including hypoglycemia and hypocalcemia. In children with septic shock, elevations in both venous and arterial blood lactate levels in the emergency department (ED) are associated with risk of organ dysfunction when measured in the ED and are associated with higher risk of death if elevated at the time of PICU admission. Although the optimal cutoff remains to be defined, arterial lactate ≥2 mmol/L is worrisome and associated with worse outcome. Laboratory evidence of concurrent MODS should also be sought, including a complete blood count, renal function tests, liver function tests, and coagulation profile (including fibrinogen and D-dimer or fibrin split products). Elevated neutrophil counts with increased immature forms (i.e., bands, myelocytes, promyelocytes) and elevated CRP and procalcitonin levels may be seen with infection. A blood gas analysis may be helpful to assess the degree of respiratory dysfunction, and an elevated venous to arterial Pco_2 gap ≥5 mm Hg (≥0.67 KPa) may signify an early shock state. For septic shock, at least one blood culture should be collected along with other cultures as supported by the history and physical. Ferritin levels should be determined in all patients with septic shock. In the presence of hyperferritinemia, laboratory studies for HLH and MAS should be obtained, including fibrinogen, triglycerides, CBC, soluble IL-2 receptor, natural killer (NK) cells, and specific genetic testing.

The hallmark of *uncompensated* shock is an imbalance between oxygen delivery (Do_2) and oxygen consumption (Vo_2). Oxygen delivery normally exceeds oxygen consumption by threefold. The oxygen extraction ratio is approximately 25%, thus producing a normal central venous oxygen saturation (Svo_2) of approximately 75%, most commonly measured from a catheter at the junction of the superior vena cava and right atrium. Svo_2 values <70% reflect an increased oxygen extraction ratio and document a decrease in oxygen delivery relative to consumption. This increase in tissue oxygen extraction is an attempt to maintain adequate oxygen delivery at the cellular level. This state is manifested clinically by increased lactic acid production (e.g., high anion gap, metabolic acidemia) caused by anaerobic metabolism and a compensatory increase in tissue oxygen extraction. Notably, in dissociative shock, hyperlactatemia is often accompanied by an elevated Svo_2 >80–85%, which reflects a state of impaired oxygen use despite adequate tissue perfusion. *Elevated blood lactate levels reflect poor tissue oxygen delivery noted in all forms of shock.*

TREATMENT

Almost all healthcare professionals that care for ill children will be faced with managing the clinical syndrome of shock, given that many childhood illnesses, such as gastroenteritis, infection, trauma, and toxic ingestions, can precipitate shock. Without timely medical intervention, the child in shock will inevitably follow a common pathway to MODS and death. Early recognition and resuscitation are therefore critical to limit morbidity and mortality associated with shock.

General Principles of Shock Management

Initial management begins with early recognition of the compensated or uncompensated shock state based on the history, physical examination, and laboratory assessments outlined earlier. Once recognized, immediate efforts to restore oxygen (and other nutrient) delivery by supporting the circulation and identifying and reversing the underlying etiology of shock are necessary (Fig. 85.2). Restoration of oxygen delivery includes ensuring airway patency and adequacy of breathing, providing supplemental oxygen if hypoxemia (Spo_2 <92–94%) is present, establishing vascular access, expanding the circulating blood volume, supporting the cardiac and vascular system with appropriate vasoactive agents when necessary, and frequently reassessing the patient's response to initial therapy. The management strategies discussed in the following sections apply to all shock types, with additional discussion at the end of the section for type-specific management recommendations.

Vascular access should be established within the first few minutes of shock recognition, ideally with at least two large-bore peripheral intravenous (IV) catheters. If peripheral IV access is not successful within 5 minutes, intraosseous (IO) access should be established until more definitive access is secured. Central venous access should be considered for patients with unstable peripheral IV access, persistence of shock despite 40-60 mL/kg fluid bolus therapy *(fluid-refractory shock),* or need for vasoactive medications or concentrated dextrose/electrolyte administration. In addition to optimizing safe administration of certain medications, central venous access will also enable measurement of Svo_2. Placement of an arterial catheter should be considered for patients with fluid-refractory shock who require active titration of vasoactive medications and/or those who may need serial laboratory tests, including frequent reassessment of blood lactate or electrolyte derangements. Notably, placement of a central venous or arterial catheter requires specialized skills that may not be immediately available, in which case continued resuscitation through peripheral IV or IO access, including initiation of vasoactive medications, is safe and appropriate.

Volume resuscitation with fluid bolus therapy in aliquots of 10-20 mL/kg pushed over 5-10 minutes is currently recommended for most types of shock and in most settings in children (see special considerations in septic shock later and Fig. 85.3). Several observational studies have demonstrated improved outcomes in children with shock with initial volume resuscitation titrated to improvements in hemodynamic targets, including decrease in HR; increase in BP; normalization of capillary refill, peripheral pulse strength, and extremity temperature;

Table 85.6 Physical Examination and Selected Laboratory Signs in Shock

Central nervous system	Acute delirium, restlessness, disorientation, confusion, and coma, which may be secondary to decreased cerebral perfusion pressure (mean arterial pressure minus intracranial pressure). Patients with chronic hypertension or increased intracranial pressure may be symptomatic at normal blood pressures. Cheyne-Stokes respirations may be seen with severe decompensated heart failure. Blindness can be a presenting complaint or complication.
Temperature	Hyperthermia results in excess tissue respiration and greater systemic oxygen delivery requirements. Hypothermia can occur when decreased systemic oxygen delivery or impaired cellular respiration decreases heat generation.
Skin	Cool distal extremities (combined low serum bicarbonate and high arterial lactate levels) aid in identifying patients with hypoperfusion. Pallor, cyanosis, sweating, and decreased capillary refill and pale, dusky, clammy, or mottled extremities indicate systemic hypoperfusion. Dry mucous membranes and decreased skin turgor indicate low vascular volume. Low toe temperature correlates with the severity of shock.
General cardiovascular	Neck vein distention (e.g., heart failure, pulmonary embolus, pericardial tamponade) or flattening (e.g., hypovolemia), tachycardia, and arrhythmias. Decreased coronary perfusion pressures can lead to ischemia, decreased ventricular compliance, and increased left ventricular diastolic pressure. A "mill wheel" heart murmur may be heard with an air embolus.
Heart rate	Usually elevated. However, paradoxical bradycardia can be seen in patients with preexisting cardiac disease and severe hemorrhage. Heart rate variability is associated with poor outcomes.
Systolic blood pressure	May actually increase slightly when cardiac contractility increases in early shock and then fall as shock advances.
Diastolic blood pressure	Correlates with arteriolar vasoconstriction and may rise early in shock and then fall when cardiovascular compensation fails.
Pulse pressure	Defined as systolic minus diastolic pressure and related to stroke volume and the rigidity of the aorta. Increases early in shock and decreases before systolic pressure decreases.
Pulsus paradoxus	An exaggerated change in systolic blood pressure with respiration (systolic blood pressure declines >10 mm Hg with inspiration) seen in asthma, cardiac tamponade, and air embolus.
Mean arterial blood pressure	Diastolic blood pressure + [pulse pressure/3]
Shock index	Heart rate/systolic blood pressure. Normal = 0.5-0.7. A persistent elevation of the shock index (>1.0) indicates impaired left ventricular function (as a result of blood loss or cardiac depression) and is associated with increased mortality.
Respiratory	Tachypnea, increased minute ventilation, increased dead space, bronchospasm, hypocapnia with progression to respiratory failure, acute lung injury, and adult respiratory distress syndrome.
Abdomen	Low-flow states may result in abdominal pain, ileus, gastrointestinal bleeding, pancreatitis, acalculous cholecystitis, mesenteric ischemia, and shock liver.
Renal	Because the kidney receives 20% of cardiac output, low cardiac output reduces the glomerular filtration rate and redistributes renal blood flow from the renal cortex toward the renal medulla, thereby leading to oliguria. Paradoxical polyuria in early sepsis may be confused with adequate hydration.
Metabolic	Respiratory alkalosis is the first acid-base abnormality, but metabolic acidosis rapidly occurs as shock progresses. Hyperglycemia, hypoglycemia, and hyperkalemia may develop. Hyperferritinemia suggests a poor prognosis.

From Angus DC. Approach to the patient with shock. In Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:643, Table 98-1.

improved urine output; and fall in blood lactate by ≥10–20%. Fluid boluses totaling up to 60 mL/kg may be needed in the first hour of resuscitation, with volumes exceeding 200 mL/kg over several hours. Fluid should be administered via IV push or a rapid infuser system. IV push delivery may be facilitated by attaching a large syringe with a three-way stopcock to the IV tubing from the fluid bag, creating a "push-pull system" that allows the user to rapidly draw up fluid into the syringe and then administer to the patient without repeatedly disconnecting and reconnecting the syringe to the patient's IV. In patients >50 kg, a pressure bag or rapid infuser may be used to rapidly administer fluid through a large-gauge peripheral IV. Notably, in neonates, additional caution should be paid to fluid resuscitation, as tolerance may be limited by reduced myocardial ventricular compliance at baseline.

Importantly, not all children with shock will continue to improve with repeated volume resuscitation, particularly those with cardiogenic and dissociative shock, severe anemia, or malnutrition. Before repeating a fluid bolus, the clinician should determine if the patient responded in a hemodynamically desirable way after the prior fluid bolus and ensure that signs of fluid overload, such as rales, gallop rhythm, or hepatomegaly, have not developed. POCUS may also be helpful to identify ongoing hypovolemia and predict response to ongoing volume resuscitation. For children with evidence of fluid overload, adequate intravascular volume, or lack of hemodynamic improvement with prior fluid boluses, resuscitation should shift from volume resuscitation to vasoactive medications. Trials of earlier initiation of vasoactive support are ongoing to further clarify the optimal role of volume resuscitation in pediatric shock.

The optimal fluid type for initial shock resuscitation remains a matter of debate. Most studies have not demonstrated a clear benefit for use of colloids, such as 4–5% albumin, over crystalloids, though there may be a small clinical benefit for resuscitation with colloids in septic shock. There is also evidence supporting a risk of kidney injury and coagulopathy with the use of synthetic colloids, such as hydroxyethyl starch and gelatin, and their use is currently not recommended. Because crystalloids are inexpensive, easy to administer, and readily available, current guidelines generally recommend initial resuscitation begin with these fluids. Exceptions include children with hemorrhagic shock and dissociative shock resulting from severe anemia for whom early blood product transfusion is preferred.

Crystalloid volume resuscitation may include 0.9% normal saline or balanced/buffered fluids, such as lactated Ringer solution, Hartmann solution, and Plasma-Lyte. Saline consists of only sodium and chloride in a 1:1 ratio with a supraphysiologic chloride concentration, whereas balanced fluids have an anion buffer and electrolyte composition closer to human blood plasma, though formulations vary. As a result, high-volume resuscitation with 0.9% saline often induces a hyperchloremic metabolic acidemia. Although 0.9% remains the most commonly used crystalloid

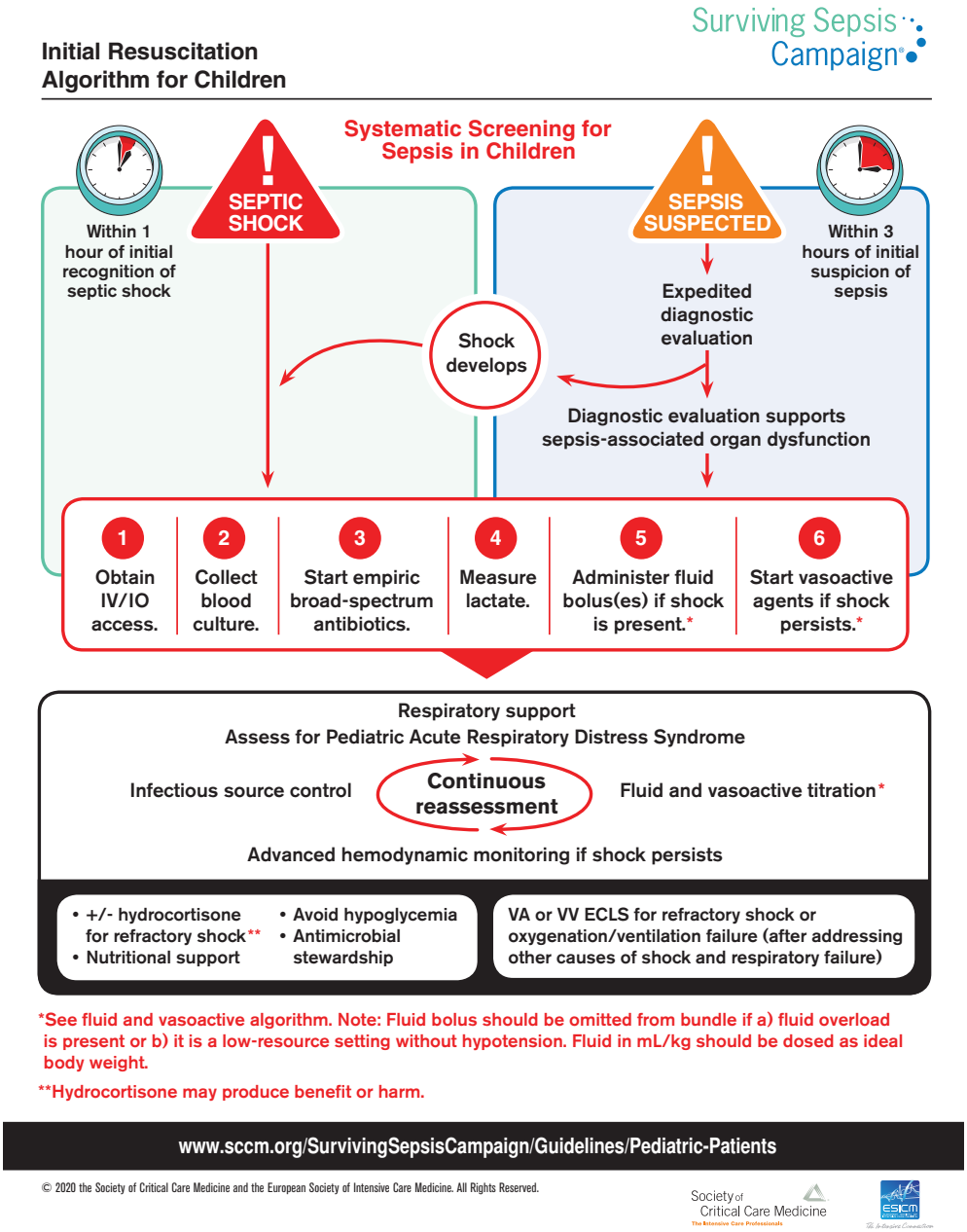

Fig. 85.2 Surviving Sepsis Campaign 2020 Initial Resuscitation Algorithm for Children. For children with clinical signs of shock, the following six key management steps should be completed within 1 hour of initial recognition of shock: (1) obtain intravenous/intraosseous access, (2) collect blood culture, (3) start empiric broad-spectrum antibiotics, (4) measure blood lactate, (5) administer crystalloid fluid therapy with volume and rate reflecting healthcare setting and titrated to patient response, and (6) initiate vasoactive medications if shock persists despite fluid and other therapy. VA, venoarterial; VV, venovenous; ECLS, extracorporeal life support. *(© 2020 the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. All Rights Reserved. https://www.sccm.org/getattachment/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients/Initial-Resuscitation-Algorithm-for-Children.pdf.aspx?lang=en-US.)*

for pediatric volume resuscitation, increasing data suggest that balanced/buffered fluids are associated with less acute kidney injury, inflammation, coagulopathy, endotheliopathy, and death. However, pediatric studies comparing balanced/buffered fluids with 0.9% saline have reported conflicting results, and adult interventional trials have not shown a consistent benefit for either crystalloid fluid type. Consequently, pending further data from ongoing studies, either 0.9% saline or balanced/buffered crystalloids are appropriate for initial volume resuscitation.

Resuscitation with blood products should be prioritized for children with hemorrhagic shock. The *Advanced Trauma Life Support* guidelines recommend resuscitation with red blood cells, plasma, and platelets in a ratio of 1:1:1 to limit coagulopathy and other risks associated with large-scale transfusion. For children with other forms of shock, the criteria to transfuse red blood cells are not clear, though it is reasonable to target hemoglobin levels >9 g/dL for children who remain hemodynamically unstable with low Svo_2 and/or high blood lactate despite other interventions. Notably, transfusion of plasma or platelets should be reserved to treat active bleeding or reduce risk of bleeding before an invasive procedure rather than used solely to correct laboratory abnormalities or as volume expanders.

Vasoactive medications should be initiated for children with fluid-refractory shock, with early consideration for inotropes, such as epinephrine, when myocardial dysfunction is present and vasopressors, such as norepinephrine, when vasoplegia is present (Table 85.7). For children with septic shock, two randomized trials have demonstrated that epinephrine as first-line vasoactive therapy is more effective at reducing mortality than dopamine. As such, epinephrine is the preferred first-line vasoactive therapy for fluid-refractory septic shock.

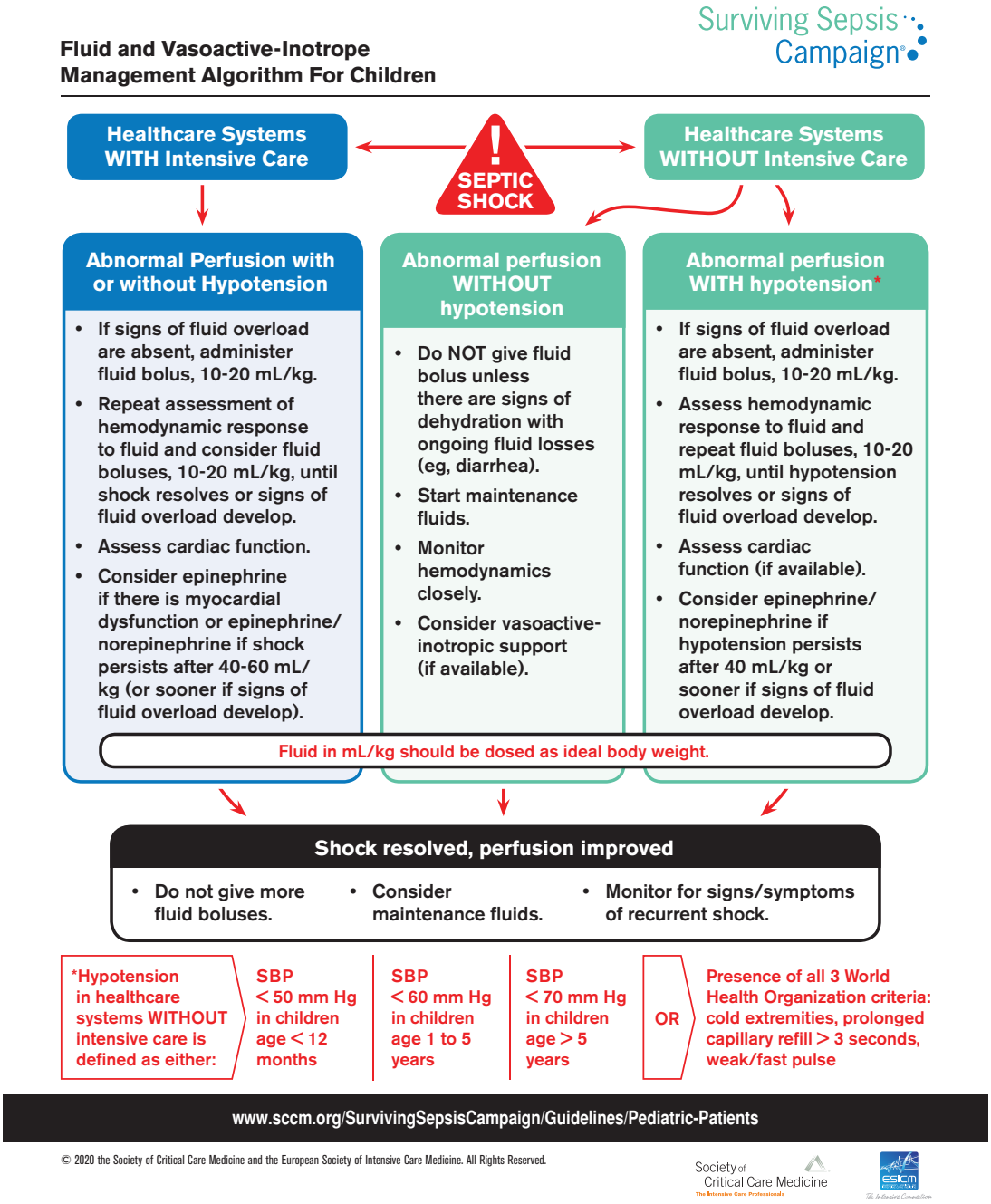

Fig. 85.3 Surviving Sepsis Campaign 2020 Fluid and Vasoactive-Inotrope Management Algorithm for Children. For children with septic shock treated in healthcare systems in which intensive care is accessible (either locally or via transport), fluid bolus therapy up to 40-60 mL/kg is recommended in the first hour of therapy until shock resolves or signs of fluid overload develop. For children with septic shock treated in healthcare systems in which intensive care is not available locally or via transport, fluid bolus therapy is not recommended unless hypotension is present. For all children, early assessment of cardiac function is recommended with consideration for initiation of epinephrine (or alternative inotrope) if myocardial dysfunction is evident. SBP, systolic blood pressure. (*© 2020 the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. All Rights Reserved.* https://www.sccm.org/getattachment/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients/Initial-Resuscitation-Algorithm-for-Children.pdf.aspx?lang=en-US.)

Epinephrine is also a potent inotrope and is the recommended initial vasoactive agent in children with cardiogenic shock. However, in children with a low-SVR state, as may be seen with distributive, septic, or neurogenic shock, norepinephrine should be preferentially prescribed as the first-line vasoactive therapy. Although vasoactive agents are ideally administered through a central venous line, these medications can be safely initiated through a peripheral IV or an IO in dilute concentrations while central venous access is obtained.

Electrolyte abnormalities, such as hypoglycemia and hypocalcemia, may precipitate or worsen shock. Blood glucose and ionized calcium can both be measured rapidly via bedside point-of-care testing, and if present, hypoglycemia and hypocalcemia should be corrected during the initial resuscitation. Other patterns of electrolyte abnormalities may indicate the presence of an underlying inborn error of metabolism, particularly in a neonate with shock. Any provider treating a patient with known or suspected inborn error of metabolism should consult immediately with a specialty center while resuscitating with volume and dextrose.

Airway management is an essential component of the initial management of shock. Early intervention to maintain an unobstructed

Table 85.7 Vasoactive Medications to Treat Shock

DRUG	EFFECT(S)	DOSING RANGE	COMMENT(S)
Epinephrine	↑ Heart rate and ↑ cardiac contractility Vasodilator at low doses, but potent vasoconstrictor at doses >0.1 mcg/kg/min	0.05-2.0 µg/kg/min	May ↓ renal perfusion at high doses ↑ Myocardial O_2 consumption Risk of arrhythmia at high doses
Norepinephrine	Potent vasoconstriction ↑ Cardiac contractility (but may be blunted by increased afterload)	0.05-2.0 µg/kg/min	↑ Blood pressure secondary to ↑ systemic vascular resistance ↑ Left ventricular afterload
Dopamine	↑ Cardiac contractility Significant peripheral vasoconstriction at >10 µg/kg/min	3-20 µg/kg/min	↑ Risk of arrhythmias at high doses
Dobutamine	↑ Cardiac contractility Peripheral vasodilator	3-10 µg/kg/min	—
Phenylephrine	Potent vasoconstriction No effect on cardiac contractility	0.25-2.0 µg/kg/min	Can cause sudden hypertension
Vasopressin	Potent vasoconstriction	0.5-20 milliunits/kg/min	Can cause sudden hypertension
Angiotensin II	Potent vasoconstrictor	Stepwise increase 5-10-25-40-80 ng/kg/min over 3 hr with titration down to 1.25-40 ng/kg/min after 3 hr	Can cause sudden hypertension, arterial ischemia
Methylene blue	Reduce responsiveness to cGMP-dependent (e.g., ischemia-reperfusion, NO mediated) vasodilators	Bolus 1-2 mg/kg, then consider continuous infusion 0.5-.01 mg/kg/hr	Causes blue/green discoloration of skin and urine
Milrinone	Increased cardiac contractility Improves cardiac diastolic function Peripheral vasodilation	0.25-1.0 µg/kg/min	Phosphodiesterase inhibitor—slows cyclic adenosine monophosphate breakdown
Prostaglandin E_1	Vasodilator Maintains an open ductus arteriosus in the newborn with ductal-dependent congenital heart disease	0.01-0.2 µg/kg/min	Can lead to hypotension Risk of apnea

airway may be needed in patients who are obtunded or have suffered a traumatic neck or chest injury. Supplemental oxygen should be provided to correct hypoxemia if Spo_2 is <92–94%. Although universal supplemental oxygen administration can, in theory, augment tissue oxygen delivery by increasing oxygen content of the blood, this approach is of little benefit if the oxyhemoglobin saturation is >92–94%, and some studies suggest harm from hyperoxia. However, universal administration of high fraction of inspired oxygen is likely to be beneficial for patients with severe anemia or dissociative shock. When oxygen is required, use of a 100% non-rebreather mask provides the highest amount of noninvasive supplemental oxygen delivery.

Indications for intubation and mechanical ventilation include acute hypoxemic or hypercarbic respiratory failure or persistence of circulatory failure, in which case a reduction in metabolic demand facilitated by sedation and ventilatory support can be helpful. Sedation and endotracheal intubation reduce the work of breathing, which can divert cardiac output away from the muscles of respiration and improve perfusion to other organs. However, extra caution needs to be taken during intubation and the transition from negative pressure to positive pressure ventilation. Positive pressure ventilation will decrease venous return in a patient who is already hypovolemic, which could precipitate cardiovascular collapse. It is therefore prudent to have fluid boluses readily available and vasoactive agents started or immediately ready to administer during this transition. Of the sedative agents available for intubation, ketamine is generally preferred because of its favorable hemodynamic effects that typically augment cardiac output and BP. As several studies have reported adverse outcomes after intubation with etomidate, pediatric septic shock guidelines recommend against using etomidate in these patients.

Specific Management Considerations by Shock Type

For children with **cardiogenic shock** due to congenital heart disease, cardiomyopathies, myocarditis, MIS-C, or other causes, decreased myocardial contractility must be reversed by early treatment with inotropes, such as epinephrine, dopamine, dobutamine, or milrinone. Gentle volume resuscitation to optimize preload may also be helpful, but excessive fluid administration can worsen volume overload and further compromise heart function. Despite adequate cardiac output with the support of inotropic agents, a high SVR with poor peripheral perfusion and acidosis may persist in cardiogenic shock. Therefore, if not already started, inodilators such as milrinone may improve systolic function and decrease SVR without causing a significant increase in HR. Furthermore, this agent has the added benefit of enhancing diastolic relaxation. Dobutamine or other vasodilating agents, such as nitroprusside, may also be considered in this setting (see Table 85.7).

In **obstructive shock**, action is often needed to relieve the point of mechanical obstruction. Examples include thoracentesis for tension pneumothorax, pericardiocentesis for cardiac tamponade, and administration of systemic fibrinolytic medications for pulmonary embolism. For neonates or young infants (typically <2-3 weeks of age) with shock caused by ductal-dependent congenital heart disease, a prostaglandin infusion should be started to maintain systemic cardiac output while preparing to transfer to a pediatric specialty center.

The management of **septic shock** should follow the recommendations of the 2020 Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children (see Fig. 85.2 and Fig. 85.3). These guidelines recommend six initial management steps in the first hour after shock

recognition, including obtaining IV/IO access, collecting a blood culture, administering empiric broad-spectrum antibiotics, measuring lactate, providing volume resuscitation, and initiating vasoactive medication if shock persists despite fluid therapy. Early administration of antibiotics targeted to the most likely pathogens for each patient has been associated with reduced mortality and more rapid resolution of organ dysfunction.

Notably, the Surviving Sepsis Campaign suggests volume resuscitation with up to 40-60 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for children with septic shock treated in geographic regions that have access to intensive care (either locally or via transport) or in any setting when hypotension is present. However, in healthcare systems with no availability to access intensive care, fluid bolus therapy was associated with increased risk of mortality in the FEAST clinical trial when hypotension was not present, and thus fluid management should focus on starting maintenance fluids only in these settings (see Fig. 85.3).

Fluid-Refractory and Catecholamine-Resistant Shock

If shock persists despite volume resuscitation and vasoactive support with an initial catecholaminergic agent, such as epinephrine, the child has **fluid-refractory and catecholamine-resistant shock**. Such children have an increased risk for MODS and death, especially if requirement for vasoactive support is high, blood lactate exceeds 8 mmol/L (or is rising after 6 hours of resuscitation), and/or myocardial dysfunction is present. Several additional management considerations must be taken into account in this scenario, including evaluation for atypical and/or reversible etiologies, second-line vasoactive medications, stress-dose corticosteroids, and extracorporeal membrane oxygenation (ECMO).

Atypical and reversible etiologies that may contribute to refractory shock include hypothyroidism and intraabdominal hypertension/abdominal compartment syndrome. In addition, one must consider the presence of obstructive shock (tamponade, pneumothorax), an unrecognized closing ductus arteriosus, uncontrolled hemorrhage (which often requires surgical intervention), anaphylaxis, and need for removal of an infectious source (e.g., infected catheter, empyema, abdominal abscess).

Stress-dose corticosteroids are indicated for patients with septic shock who have absolute adrenal insufficiency, such as that caused by congenital adrenal hyperplasia, septic shock with purpura, prior steroid therapy for chronic illness, or hypopituitarism. Some children with septic shock may also develop *critical illness–related corticosteroid insufficiency* with an inadequate adrenal response to a severe stress. Stress doses of hydrocortisone (50-100 mg per m^2 per day) are recommended for those with risk factors for absolute adrenal insufficiency (e.g., septic shock with purpura, prior steroid therapy for chronic illness, known pituitary or adrenal abnormalities) and can be considered for children with fluid-refractory, catecholamine-resistant shock without a reversible etiology pending further data from ongoing clinical trials.

Second-line vasoactive therapy should be considered for patients in whom shock persists despite titration of the initial vasoactive agent. For patients with "warm" shock or evidence of low SVR initially treated with norepinephrine, the addition of vasopressin or epinephrine may be considered. Case reports, case series, and one trial indicate that administration of vasopressin is associated with an increase in mean arterial BP and urine output in children with fluid-refractory, catecholamine-resistant septic shock. However, in a multicenter trial of 65 children with vasodilatory shock, low-dose vasopressin did not decrease the time to hemodynamic stability off of vasoactive agents versus placebo (49.7 vs 47.1 hours), and there was a concerning trend toward increased mortality in the vasopressin group (30% vs 16%, $p = 0.24$). For patients with "cold" shock or evidence of myocardial dysfunction, priority should be given to improving cardiac contractility with inotropes. First-line therapy with epinephrine is recommended, with addition of dopamine, dobutamine, or norepinephrine as second-line agents, but these agents should be carefully titrated, as they may contribute to arrhythmias and increase myocardial oxygen demand. Initiation of inodilators, such as milrinone, can help to augment contractility, improve lusitropy (diastolic relaxation), and lower SVR but are generally longer-acting and should be carefully titrated to avoid worsening hypotension. Notably, it may be difficult to accurately differentiate between "warm" (low SVR) from "cold" (high SVR) shock using only clinical signs, such as extremity temperature, strength of peripheral pulses, and capillary refill time. Frequent reassessment and response to therapy are therefore paramount to ensure optimal titration of vasoactive therapies.

ECMO is a rescue option for patients suffering refractory septic shock, with reported survival rates of ~70% for newborns and ~50% for older children. One study suggests that central cannulation via sternotomy may achieve survival rates of 74% for refractory septic shock. In cardiogenic shock due to myocarditis treated with ECMO, survival rates of 70% have been reported. Although counterintuitive because of the need for systemic anticoagulation, ECMO has also been used successfully in hemorrhagic shock in a small series. In most cases of refractory shock, venoarterial ECMO is preferred over the venovenous route due to the presence of hemodynamic instability. A ventricular assist device may be considered as an alternative to ECMO in some children with cardiogenic shock.

Targets for Shock Reversal

Clinical signs of successful resuscitation include a decrease in HR and respiratory rate, increase in BP, improved urine output to >0.5 mL/kg/hr, normalization of mental status, decreased capillary refill time, warmth of distal extremities, and improved peripheral pulses. Serial laboratory measurements should aim for a rise in Svo_2 to >70% and a decreasing trend in blood lactate levels as evidence for increased tissue oxygen extraction and adequate oxygen delivery to meet cellular metabolic demand. In one observational study of septic shock in children, normalization of blood lactate to <2 mmol/L within 4 hours was associated with reduced organ dysfunction. Blood pH and base deficit may also be used as laboratory surrogates for improved tissue perfusion, but these may be affected by the degree of hyperchloremia after fluid resuscitation or by changes in ventilation.

Other parameters to monitor for improvement in shock include serial POCUS to assess volume status, cardiac output, and tissue perfusion; cutaneous near-infrared spectroscopy (NIRS) to measure regional tissue perfusion; and other devices that can estimate cardiac output based on the relationship among BP, stroke volume, arterial compliance, and SVR (e.g., pulse contour waveform analysis). If cardiac output is measured, aiming for a cardiac index between 3.3 and 6.0 L/min/m^2 is appropriate.

Though children can have isolated cardiovascular dysfunction with shock, many have additional associated organ dysfunctions or MODS. Ongoing support of noncardiovascular organ dysfunction is often required even after improvement or resolution of shock.

PROGNOSIS

In septic shock, mortality rates are as low as 3% in previously healthy children and 6–9% in children with chronic illness (compared with 25–30% in adults). With early recognition and therapy, the mortality rate for pediatric shock continues to improve, but shock and MODS remain one of the leading causes of nonaccidental death in infants and children. The risk of death involves a complex interaction of factors, including the underlying etiology, presence of chronic illness, host immune response, and timing of recognition and therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 86

Acute Care of Respiratory Distress and Failure

Alexandre T. Rotta, Martin C.J. Kneyber, and Ashok P. Sarnaik

The term *respiratory distress* is used to denote signs and symptoms of an abnormal respiratory pattern. A child with nasal flaring, tachypnea, chest wall retractions, stridor, grunting, dyspnea, or wheezing has respiratory distress. Taken together, the magnitude of these findings is used to judge clinical severity. Nasal flaring is nonspecific, but the other signs are useful in localizing the site of pathology (see Chapter 421). *Respiratory failure* is defined as the inability of the lungs to provide sufficient oxygen (hypoxic respiratory failure) or remove carbon dioxide (ventilatory failure) to meet metabolic demands. Therefore, whereas respiratory distress is determined by a clinical impression, respiratory failure is diagnosed when inadequate oxygenation or ventilation (or both) are present. Respiratory distress can occur in patients without respiratory disease, and respiratory failure can occur in patients without respiratory distress.

RESPIRATORY DISTRESS

A careful physical examination must be performed when evaluating a child in respiratory distress. **Nasal flaring**, although nonspecific, is an extremely important sign of distress in infants. It may indicate discomfort, pain, fatigue, acidosis, or breathing difficulty. The state of **responsiveness** is another crucial sign. Lethargy, disinterest in surroundings, and weak cry are suggestive of exhaustion, hypercarbia, and impending respiratory failure. Abnormalities of the rate and depth of **breathing** can occur with both pulmonary and nonpulmonary causes of respiratory distress. In diseases of decreased lung compliance, such as pneumonia and pulmonary edema, breathing is characteristically rapid and shallow (decreased tidal volume). In obstructive airway diseases, such as asthma and laryngotracheitis, breathing generally is deep with increased tidal volume, but less rapid. Rapid and deep breathing (tachypnea and hyperpnea) without other respiratory signs should raise suspicion of possible nonpulmonary or nonthoracic causes of respiratory distress, such as response to metabolic acidosis (e.g., diabetic ketoacidosis, renal tubular acidosis) or stimulation of the respiratory center (e.g., encephalitis, ingestion of central nervous system stimulants). Suprasternal, intercostal, and subcostal **retractions** are manifestations of increased inspiratory effort, weak chest wall, or both. Inspiratory **stridor** indicates airway obstruction above the thoracic inlet, whereas expiratory **wheezing** results from airway obstruction below the thoracic inlet. **Grunting** is most commonly heard in diseases with decreased functional residual capacity (e.g., pneumonia, pulmonary edema) or peripheral airway obstruction (e.g., bronchiolitis).

Respiratory Disease Manifesting as Respiratory Distress

Clinical examination is paramount in localizing the site of pathology and creating a differential diagnosis. Extrathoracic airway obstruction occurs anywhere above the thoracic inlet and is marked by inspiratory stridor, retractions, and prolongation of inspiration. In contrast, features of intrathoracic airway obstruction are prolongation of expiration and expiratory wheezing. Typical manifestations of alveolar interstitial pathology are rapid, shallow respirations, chest wall retractions, and grunting (Tables 86.1 and 86.2).

Respiratory Distress Without Respiratory Disease

Although respiratory distress most frequently results from diseases of lungs, airways, and chest wall, pathology in other organ systems can manifest as respiratory distress and lead to misdiagnosis and inappropriate management (Table 86.3). Respiratory distress resulting from heart failure or diabetic ketoacidosis may be misdiagnosed as asthma and improperly treated with albuterol, resulting in worsened hemodynamic state or ketoacidosis. Careful history and physical examination provide essential clues in avoiding misdiagnosis.

Cardiovascular Disease Manifesting as Respiratory Distress

A child with cardiovascular pathology may present with respiratory distress caused by either *decreased lung compliance* or *cardiogenic shock* (Table 86.4). Diseases that result in increased pulmonary arterial blood flow (e.g., left-to-right shunts) or increased pulmonary venous pressure (e.g., left ventricular dysfunction from hypertension or myocarditis, obstructed total anomalous pulmonary venous return) cause an increase in pulmonary capillary pressure and transudation of fluid into the pulmonary interstitium and alveoli. The increased pulmonary blood and water content lead to decreased lung compliance and result in rapid shallow breathing.

It is important to recognize that interstitial lung edema may not only manifest as alveolar fluid but as small airway obstruction as well. **Wheezing** as a sign of congestive cardiac disease is common in infants and young children and should be recognized. Patients with cardiac lesions that result in low cardiac output often present in shock. For example, obstructive lesions of the left side of the heart (e.g., critical coarctation of the aorta) and acquired or congenital cardiomyopathy result in decreased perfusion and metabolic acidosis, as well as respiratory distress because of chemoreceptor and baroreceptor stimulation. The likelihood of a particular cardiovascular illness manifesting as respiratory distress depends on age at presentation (Table 86.5).

Neurologic Disease Manifesting as Respiratory Distress

Central nervous system (CNS) dysfunction can lead to alterations in respiratory patterns and manifest as respiratory distress. Increased intracranial pressure (ICP) may manifest as respiratory distress. Early rise in ICP results in stimulation of respiratory centers, leading to increases in the rate **(tachypnea)** and depth **(hyperpnea)** of respiration. The resultant decrease in arterial blood partial pressure of carbon dioxide ($Paco_2$) and elevation of cerebrospinal fluid (CSF) pH leads to cerebral vasoconstriction and temporary amelioration of intracranial hypertension. Stereotypical respiratory patterns are associated

Table 86.1 Typical Localizing Signs for Pulmonary Pathology

SITE OF PATHOLOGY	RESPIRATORY RATE	RETRACTIONS	AUDIBLE MANIFESTATION
Extrathoracic airway	↑	↑↑↑↑	Stridor
Intrathoracic extrapulmonary	↑	↑↑	Wheezing
Intrathoracic intrapulmonary	↑↑	↑↑	Wheezing
Alveolar or interstitial	↑↑↑	↑↑↑	Grunting, crackles

Table 86.2 Examples of Anatomic Sites of Lesions Causing Respiratory Failure

LUNG	RESPIRATORY PUMP
CENTRAL AIRWAY OBSTRUCTION	**THORACIC CAGE**
Choanal atresia Tonsilloadenoidal hypertrophy Retropharyngeal/peritonsillar abscess Laryngomalacia Epiglottitis Vocal cord paralysis Laryngotracheitis Subglottic stenosis Vascular ring/pulmonary sling Mediastinal mass Foreign body	Kyphoscoliosis Diaphragmatic hernia Flail chest Eventration of diaphragm Asphyxiating thoracic dystrophy Prune-belly syndrome Dermatomyositis Abdominal distention
PERIPHERAL AIRWAY OBSTRUCTION	**BRAINSTEM**
Asthma Bronchiolitis Foreign body Aspiration of gastric contents Cystic fibrosis α_1-Antitrypsin deficiency	Arnold-Chiari malformation Central hypoventilation syndrome CNS depressants, including drug overdose Trauma Increased intracranial pressure CNS infections
ALVEOLAR OR INTERSTITIAL DISEASE	**SPINAL CORD**
Lobar pneumonia* ARDS Surfactant deficiency Interstitial pneumonia Hydrocarbon pneumonitis Pulmonary hemorrhage/hemosiderosis Vaping lung injury Smoke inhalation Drowning	Trauma Transverse myelitis Spinal muscular atrophy Poliomyelitis Compression (tumor, abscess, bleed) Acute flaccid myelitis
	NEUROMUSCULAR
	Phrenic nerve injury Birth trauma Infant botulism Guillain-Barré syndrome Muscular dystrophy Myasthenia gravis Organophosphate poisoning

*Including bacteria and viral; fungal or parasitic less common.
ARDS, Acute respiratory distress syndrome; CNS, central nervous system.

Table 86.3 Nonpulmonary Causes of Respiratory Distress

DOMAIN	EXAMPLE(S)	MECHANISM(S)
Cardiovascular	Left-to-right shunt Congestive heart failure Cardiogenic shock	↑ Pulmonary blood/water content Metabolic acidosis Baroreceptor stimulation
CNS	Increased intracranial pressure Encephalitis Neurogenic pulmonary edema Toxic encephalopathy	Stimulation of brainstem respiratory centers
Metabolic	Diabetic ketoacidosis Organic acidemia Hyperammonemia	Stimulation of central and peripheral chemoreceptors
Renal	Renal tubular acidosis	Stimulation of central and peripheral chemoreceptors
	Hypertension	Left ventricular dysfunction → increased pulmonary blood/water content
Infection	Toxic shock syndrome Septic shock Meningococcemia	Cytokine stimulation of respiratory centers Baroreceptor stimulation from shock Metabolic acidosis

CNS, Central nervous system.
Courtesy Dr. Ashok Sarnaik.

with dysfunction at various levels of the brain. Cerebral hemisphere and midbrain lesions result in hyperpnea and tachypnea. In such situations, arterial blood gas (ABG) measurements typically show respiratory alkalosis without hypoxemia. Pathology affecting the pons and medulla manifests as irregular breathing patterns such as **apneustic breathing** (prolonged inspiration with brief expiratory periods), **Cheyne-Stokes breathing** (alternate periods of rapid and slow breathing), and irregular, ineffective breathing or apnea (Table 86.6). Along with respiratory changes, other manifestations of CNS dysfunction and increased ICP generally are present, such as focal neurologic signs, pupillary abnormalities, hypertension, and bradycardia (see Chapter 82). Occasionally, severe CNS dysfunction can result in **neurogenic pulmonary edema** and respiratory distress, which may follow excessive sympathetic discharge resulting in increased pulmonary venous hydrostatic pressure and increased pulmonary capillary permeability. **Central neurogenic hyperventilation** is characteristically observed in illnesses such as urea cycle defects and encephalitis. **Bradycardia** and **apnea** may be caused by CNS-depressant medications, poisoning, prolonged hypoxia, trauma, or infection (see Table 86.2).

Toxic Metabolic States Manifesting as Respiratory Distress

Direct stimulation of respiratory centers resulting in respiratory alkalosis is encountered in intoxication involving agents such as salicylates and theophylline. Similarly, intoxication with general CNS stimulants, such as cocaine and amphetamines, may result in increased respiration. Presence of endogenous (e.g., organic acids) or exogenous (e.g., methanol, ethylene glycol, salicylates) toxins causes metabolic acidosis and compensatory hyperventilation, which can manifest as respiratory distress. ABG measurements show decreased pH and compensatory hypocarbia with normal oxygenation. Conversely, metabolic disorders with hyperammonemia cause respiratory alkalosis (decreased $Paco_2$ with increased pH) as ammonia directly stimulates the respiratory centers. Cyanide poisoning and methemoglobinemia may also produce respiratory distress.

Other Nonpulmonary Entities Manifesting as Respiratory Distress

Sepsis and **septic shock** may cause respiratory distress from hypovolemic stimulation of baroreceptors, cytokine stimulation of respiratory centers, and lactic acidosis; they can also lead to **acute respiratory distress syndrome** (ARDS). Other indirect causes of ARDS include systemic inflammatory conditions, trauma, transfusion-related acute lung injury, and pancreatitis. Similarly, renal disease may manifest as respiratory distress by causing metabolic acidosis (e.g., renal tubular acidosis or renal failure) or hypertensive left ventricular failure and fluid overload.

RESPIRATORY FAILURE

Respiratory failure occurs when oxygenation and ventilation are insufficient to meet the metabolic demands of the body. Respiratory failure may result from an abnormality in (1) lung and airways, (2) chest wall and muscles of breathing, or (3) central and peripheral chemoreceptors. Clinical manifestations depend largely on the site of pathology. Although respiratory failure is traditionally defined as respiratory

Table 86.4 Cardiovascular Pathology Manifesting as Respiratory Distress

I. DECREASED LUNG COMPLIANCE

A. Left-to-right shunts

1. Ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular canal, truncus arteriosus
2. Cerebral or hepatic arteriovenous fistula

B. Ventricular failure

1. Left heart obstructive lesions
   a. Aortic stenosis
   b. Coarctation of the aorta
   c. Interrupted aortic arch
   d. Mitral stenosis
   e. Hypoplastic left heart syndrome
2. Myocardial infarction
   a. Anomalous left coronary artery from the pulmonary artery (ALCAPA)
   b. Ventriculocoronary arterial connections (coronary sinusoids)
3. Hypertension
   a. Acute glomerulonephritis
4. Inflammatory/infectious
   a. Myocarditis
   b. Pericardial effusion
5. Idiopathic/genetic
   a. Dilated cardiomyopathy
   b. Hypertrophic obstructive cardiomyopathy
   c. Takotsubo syndrome

C. Pulmonary venous obstruction

1. Total anomalous pulmonary venous connection with obstruction
2. Cor triatriatum

II. SHOCK RESULTING IN METABOLIC ACIDOSIS

A. Left heart obstructive lesions

B. Acute ventricular failure

1. Myocarditis, myocardial infarction

Table 86.5 Typical Chronology of Heart Disease Presentation in Children

AGE	MECHANISM	DISEASE
Newborn (1-10 days)	↑ Arteriovenous pressure difference	Arteriovenous malformation (brain, liver)
	Ductal closure	Single ventricle lesions or severe ventricular outflow obstruction
	Independent pulmonary and systemic blood flow	Transposition of the great arteries
	Pulmonary venous obstruction	Total anomalous pulmonary venous return (TAPVR)
Young infant (1-6 mo)	↓ Pulmonary vascular resistance	Left-to-right shunt lesions
	↓ Pulmonary artery pressure	Anomalous left coronary artery from the pulmonary artery (ALCAPA)
Any age	Heart rate disturbance	Tachyarrhythmias or bradyarrhythmias
	Infection	Myocarditis, endocarditis, pericarditis
	Abnormal cardiac myocytes	Cardiomyopathy
	Excess afterload	Hypertension

dysfunction resulting in arterial partial pressure of oxygen (Pa_{O_2}) <60 mm Hg when breathing ambient air and Pa_{CO_2} >50 mm Hg resulting in acidemia, the patient's general state, respiratory effort, and potential for impending exhaustion are more important indicators than ABG values.

Pathophysiology

Respiratory failure can be classified into *hypoxic* respiratory failure (failure of oxygenation) and *hypercarbic* respiratory failure (failure of ventilation). Systemic venous (pulmonary arterial) blood is arterialized through equilibration with alveolar gas in the pulmonary capillaries and is carried back to the heart by pulmonary veins. Arterial blood oxygen and carbon dioxide content are influenced by the composition of the inspired gas, effectiveness of alveolar ventilation, pulmonary capillary perfusion, and diffusion capacity of the alveolar capillary membrane. An abnormality in any of these steps can result in respiratory failure. **Hypoxic respiratory failure** results from intrapulmonary shunting and venous admixture or insufficient diffusion of oxygen from alveoli into pulmonary capillaries. This physiology can be caused by small airways obstruction, increased barriers to diffusion (e.g., interstitial edema, fibrosis), and conditions in which alveoli are collapsed or filled with fluid (e.g., pneumonia, atelectasis, pulmonary edema). In most cases, hypoxic respiratory failure is associated with decreased functional residual capacity and can be managed by lung volume recruitment with positive pressure ventilation. **Hypercarbic respiratory failure** is caused by decreased minute ventilation (i.e., tidal volume multiplied by respiratory rate). This can result from centrally mediated disorders of respiratory drive, increased dead space ventilation, or obstructive airway disease. *Hypoxic and hypercarbic respiratory failure may coexist as a combined failure of oxygenation and ventilation.*

Ventilation-Perfusion Mismatch

For exchange of O_2 and CO_2 to occur, alveolar gas must be exposed to blood transiting in close proximity through the pulmonary capillaries. Both ventilation and perfusion are lower in nondependent areas (upper lobes in upright position) of the lung and higher in dependent areas (lower lobes in upright position). The difference in perfusion ($\dot{Q}$) is greater than the difference in ventilation ($\dot{V}$). Perfusion in excess of ventilation results in incomplete arterialization of systemic venous (pulmonary arterial) blood and is referred to as **venous admixture**. Perfusion of unventilated areas is referred to as **intrapulmonary shunting**. Conversely, ventilation that is in excess of perfusion is wasted; that is, it does not contribute to gas exchange and is referred to as **dead space ventilation**. Dead space ventilation results in return of greater amounts of atmospheric gas (which has not participated in gas exchange and has negligible CO_2) back to the atmosphere during exhalation. The respiratory dead space is divided into the **anatomic dead space** and the **alveolar dead space**. The *anatomic dead space* includes the conducting airways from the nasopharynx to the terminal bronchioles, ends at the alveoli, and has no contact with the pulmonary capillary bed. The *alveolar dead space* refers to areas of the lung where alveoli are ventilated but not perfused. Under normal conditions, this usually occurs in West zone I, where alveolar pressure is greater than pulmonary capillary pressure, thus restricting blood flow. Under clinical conditions, this alveolar dead space may result from dynamic hyperinflation, high levels of positive end-expiratory pressure (PEEP), or large tidal volume in mechanically ventilated patients. Additionally, conditions that cause decreased pulmonary artery perfusion (e.g., pulmonary embolism, decreased cardiac output, hypovolemia) can result in alveolar dead space. The result is a decrease in mixed expired CO_2 (P_{ECO_2}) and an increase in the $Pa_{CO_2} - P_{ECO_2}$ gradient. Dead space as a fraction of tidal volume (V_D/V_T) is calculated as:

$$(Pa_{CO_2} - P_{ECO_2}) \div Pa_{CO_2}$$

Normal V_D/V_T is approximately 0.33. Venous admixture and intrapulmonary shunting predominantly affect oxygenation, resulting in an alveolar partial pressure of oxygen (P_{AO_2}) to Pa_{O_2} ($A\text{-}a_{O_2}$) gradient without elevation in Pa_{CO_2}. This occurs due to greater ventilation of perfused areas, which is sufficient to normalize Pa_{CO_2} but not Pa_{O_2} because of their respective dissociation curves. The relative straight-line

Table 86.6 Respiratory Patterns in Neurologic Disease

INJURY SITE	PATTERN*	COMMENTS
Normal	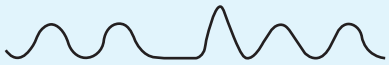	Variable V_T with normal respiratory pauses and sighs
Cortex		Hyperpnea and tachypnea
Midbrain	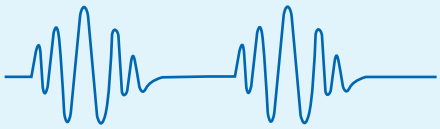	*Cheyne-Stokes breathing:* Gradually increasing and decreasing V_T
Pons		*Apneustic breathing:* Prolonged inspiration followed by prolonged expiration
Medulla and pons		*Biot breathing:* Rapid and irregular respirations with pauses

*Pattern tracings represent lung volume over time.
V_T, Tidal volume.

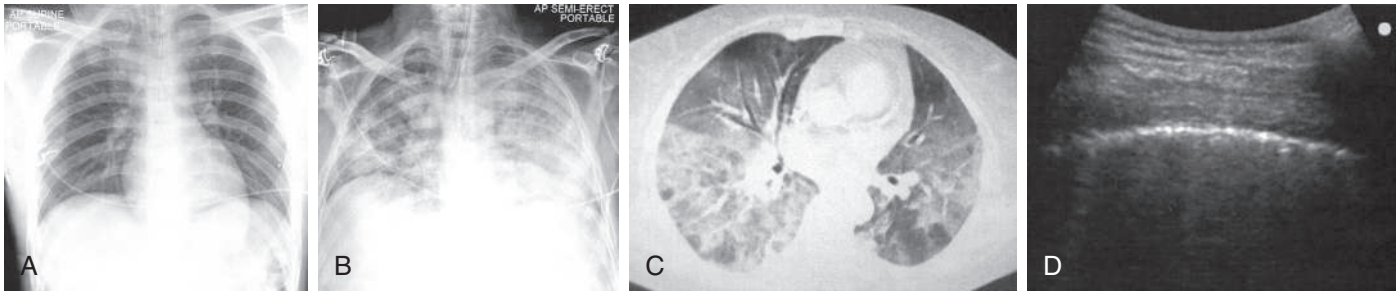

Fig. 86.1 Acute respiratory distress syndrome (ARDS). **A,** Normal chest radiograph. **B,** Chest radiograph demonstrating bilateral alveolar infiltrates consistent with ARDS. **C,** Chest CT showing bilateral pneumonitis and consolidation with air bronchograms consistent with ARDS. **D,** Lung ultrasonogram illustrating smooth pleural line, absence of horizontal A lines, and presence of vertical B lines suggestive of ARDS. *(Modified from MacSweeney R, McAuley DF. Acute respiratory distress syndrome.* Lancet. *2016;388:2416-2430, Fig. 3.)*

relationship of the hemoglobin-CO_2 dissociation allows for averaging of capillary P_{CO_2} (P_{cCO_2}) from hyperventilated and hypoventilated areas. Because the association between oxygen tension and hemoglobin saturation plateaus with increasing Pa_{O_2} (i.e., "S-shaped" curve), the decreased hemoglobin-O_2 saturation in poorly ventilated areas cannot be compensated for by well-ventilated areas where hemoglobin-O_2 saturation has already reached near-maximum. This results in decreased arterial oxyhemoglobin saturation (Sa_{O_2}) and Pa_{O_2}. Elevation of Pa_{CO_2} in such situations is indicative of coincident alveolar hypoventilation. Examples of diseases leading to venous admixture include asthma and aspiration pneumonia and pulmonary embolism, and those of intrapulmonary shunt include lobar pneumonia and ARDS.

Diffusion

Even if ventilation and perfusion are matched, gas exchange requires diffusion across the interstitial space between the alveoli and pulmonary capillaries. Under normal conditions, there is sufficient time for the pulmonary capillary blood to equilibrate with alveolar gas across the interstitial space. When the interstitial space is thickened by extravasated fluid or inflammatory cells, diffusion is impaired. Because the diffusion capacity of CO_2 is 20 times greater than that of O_2, diffusion defects manifest as hypoxemia rather than hypercarbia. Even with the administration of 100% oxygen, P_{AO_2} increases to approximately 660 mm Hg from 100 mm Hg at sea level, and the concentration gradient for diffusion of O_2 is increased by only 6.6 times. Therefore, with diffusion defects, lethal hypoxemia will set in before clinically significant CO_2 retention results. In fact, in such situations, Pa_{CO_2} is often decreased because of the hyperventilation that accompanies hypoxemia. The presence of hypercarbia in diseases that impair diffusion is indicative of alveolar hypoventilation from coexisting airway obstruction, CNS depression, or exhaustion. Examples of disease that impair diffusion are interstitial pneumonia, scleroderma, pulmonary lymphangiectasia, and ARDS.

Acute Respiratory Distress Syndrome

Some patients with respiratory failure meet criteria for ARDS, a pulmonary condition of myriad etiologies characterized by hypoxemia of acute onset and chest radiograph findings consistent with acute pulmonary parenchymal disease (Fig. 86.1). ARDS affects both children and adults and can be the result of pulmonary (direct) or extrapulmonary (indirect) insults. Causes of direct ARDS include pneumonia, aspiration of gastric contents or toxic chemicals, lung contusion, and smoke inhalation. Causes of indirect ARDS include sepsis, transfusion-related lung injury, and pancreatitis, to name a few. The diagnostic criteria for pediatric acute respiratory distress syndrome (PARDS) are outlined in Table 86.7.

Table 86.7 Pediatric Acute Respiratory Distress Syndrome (PARDS 2.0) Definition

Age	Excludes patients with perinatal-related lung disease		
Timing	Within 7 days of a known clinical insult		
Origin of edema	Not fully explained by cardiac failure or fluid overload		
Chest imaging	New opacities (unilateral or bilateral) consistent with acute pulmonary parenchymal disease and which are not due primarily to atelectasis or pleural effusion[a]		
Oxygenation[b]	IMV: OI ≥ 4 or OSI ≥ 5 NIV[c]: $Pao_2/ Fio_2 \leq 300$ or $SPo_2/ Fio_2 \leq 250$		
	Stratification of PARDS severity: Apply ≥ 4 after initial diagnosis of PARDS		
	IMV PARDS	Mild/moderate: OI <16 or OSI <12	Severe: OI ≥16 or OSI ≥12
	NIV PARDS[c]	Mild/moderate: $Pao_2/ Fio_2 > 100$ or $SPo_2/ Fio_2 > 150$	Severe: $Pao_2/ Fio_2 \leq 100$ or $SPo_2/ Fio_2 \leq 150$
Special Populations[d]			
Cyanotic heart disease	Above criteria, with acute deterioration in oxygenation not explained by cardiac disease		
Chronic lung disease	Above criteria, with acute deterioration in oxygenation from baseline		

[a]Children in resource-limited settings where imaging is not available who otherwise meet PARDS criteria are considered to have possible PARDS.
[b]Oxygenation should be measured at steady state and not during transient desaturation episodes. When S_{PO_2} is used, ensure that S_{PO_2} is ≤ 97%.
[c]Diagnosis of PARDS on NIV (NIV PARDS) requires full facemask interface with continuous airway positive pressure/positive end-expiratory pressure ≥ 5cm H_2O.
[d]Stratification of PARDS severity does not apply to these populations.
IMV, invasive mechanical ventilation; NIV noninvasive ventilation; OI, oxygenation index; OSI, oxygen saturation index; PARDS, pediatric acute respiratory distress syndrome; S_{PO_2}, pulse oximeter oxygen saturation; Pao_2, partial pressure of arterial oxygen; Fio_2, fraction of inspired oxygen.
OI = mean airway pressure (MAP) (cm H2O) × Fio_2 /Pao_2 (mm Hg).
OSI = MAP (cm H2O) × Fio_2 /S_{PO_2}.
Adapted from Executive Summary of the Second International Guidelines for the Diagnosis and Management of Pediatric Acute Respiratory Distress Syndrome (PALICC-2): *Pediatr Crit Care Med* 2023;24:143–168.

MONITORING A CHILD IN RESPIRATORY DISTRESS AND RESPIRATORY FAILURE

Clinical Examination

Clinical observation is the most important component of monitoring. The presence and magnitude of abnormal clinical findings, their progression with time, and their temporal relation to therapeutic interventions serve as guides to diagnosis and management (see Chapter 421). As much as possible, the child with respiratory distress or failure should be observed in the position of greatest comfort and in the least threatening environment.

Pulse oximetry is the most commonly used technique to monitor oxygenation. Noninvasive and safe, it is the standard of care in bedside monitoring of children during transport, procedural sedation, surgery, and critical illness. It indirectly measures arterial hemoglobin-O_2 saturation by differentiating oxyhemoglobin from deoxygenated hemoglobin through their respective light absorption at wavelengths of 660 nm (red) and 940 nm (infrared). A pulsatile circulation is required to enable detection of arterialized blood entering the capillary bed. Percentage of arterial oxyhemoglobin is reported as Sao_2; however, the correct description is *oxyhemoglobin saturation as measured by pulse oximetry* (Spo_2). Such precision is needed because Spo_2 may not always reflect Sao_2. It is important to be familiar with the hemoglobin-O_2 dissociation curve (see Chapter 421) to estimate Pao_2 at a given oxyhemoglobin saturation. Because of the shape of the hemoglobin-O_2 dissociation curve, changes in Pao_2 above 70 mm Hg are not readily identified by pulse oximetry. Also, at the same Pao_2, there may be significant change in Spo_2 at a different blood pH value. In most situations, Spo_2 >95% is a reasonable goal, especially in emergency care. In patients receiving supplemental oxygen, a target saturation range of 94–96% should be considered in order to decrease unnecessary exposure that could result in oxygen toxicity. There are exceptions, such as in patients with large left-to-right shunts (e.g., ventricular septal defect, patent ductus arteriosus) or with single-ventricle cardiac lesions in whom the pulmonary and systemic circulations are receiving blood flow from the same ventricle (e.g., after stage I palliation for hypoplastic left heart syndrome). In the latter, a lower Spo_2 (75–85%) is desired to avoid excessive blood flow to the lungs and reduced blood flow to the systemic circulation that can lead to morbidity and death. Because most commercially available pulse oximeters recognize all types of hemoglobin as either oxyhemoglobin or deoxygenated hemoglobin, they provide inaccurate information in the presence of carboxyhemoglobin and methemoglobin. In carbon monoxide poisoning, **carboxyhemoglobin** absorbs light in the same (red) wavelength as oxyhemoglobin, leading to overestimation of oxygen saturation. **Methemoglobin** absorbs light in both the oxygenated and deoxygenated wavelengths, which can cause either an overestimation or underestimation of oxygen saturation. Data suggest that increasing methemoglobin concentrations tend to drive Spo_2 toward 85%, no matter the actual percent of oxyhemoglobin. At lower methemoglobin levels, the pulse oximetry reading is falsely low, whereas high levels lead to a falsely high pulse oximetry reading. Newer specialized pulse oximeters can distinguish dyshemoglobinemias and prevent false readings, but their use is not widespread. It should be recognized that dangerous levels of hypercarbia may exist in patients with ventilatory failure, who have satisfactory Spo_2 if they are receiving supplemental oxygen. Pulse oximetry should not be the only monitoring method in patients with primary ventilatory failure, such as neuromuscular weakness and CNS depression. It is also unreliable in patients with poor perfusion and poor pulsatile flow to the extremities. Pulse oximetry may underestimate the degree of hypoxia in Black patients. Despite these limitations, pulse oximetry is a noninvasive, easily applicable, and effective means of assessing oxygenation in most patients.

Volumetric capnography (end-tidal CO_2 [$Petco_2$] measurement) is helpful to noninvasively assess the effectiveness of ventilation and pulmonary circulation. The $Petco_2$ can be used to determine the alveolar dead space fraction (V_D/V_T) and is calculated as follows:

$$V_D/V_T = (Paco_2 - Petco_2) \div Paco_2$$

Changes in the alveolar dead space fraction usually correlate well with changes in the gradient of $Paco_2$ and $Petco_2$ ($Paco_2 - Petco_2$). Thus a change in $Paco_2 - Petco_2$ can be used as an index of changes in alveolar dead space. Diseases resulting in increased alveolar dead space (e.g., asthma with dynamic hyperinflation) or decreased pulmonary blood flow (e.g., pulmonary embolism, low cardiac output) lead to decreases in $Petco_2$ and an increase in $Paco_2 - Petco_2$. $Petco_2$ alone may overestimate adequacy of ventilation.

Blood Gas Abnormalities

Arterial blood gas analysis offers valuable assistance in diagnosis, monitoring, and management of a child in respiratory distress and failure. Because arterial blood sampling in children can be impractical without an indwelling catheter, a *capillary blood gas* (CBG) sample often is obtained, especially in emergency situations. A properly arterialized CBG sample obtained by warming the digit or heel that yields free-flowing blood is an acceptable surrogate. The blood sample needs to be processed without delay. CBG provides a good estimate of $Paco_2$ and arterial pH, but less so for Pao_2. In patients who mainly require monitoring of ventilation (especially those whose oxygenation is being monitored with pulse oximetry), a *venous blood gas* sample provides a reasonable estimate of arterial pH and $Paco_2$ values, provided tissue perfusion is adequate. Venous Pco_2 ($Pvco_2$) is approximately 6 mm Hg higher and pH approximately 0.03 lower than the arterial values. Pvo_2 has a poor correlation with Pao_2. Mixed venous O_2 saturation obtained from a central venous catheter in the right atrium is a useful marker of the balance between oxygen delivery and oxygen consumption. In patients with a constant arterial O_2 content and O_2 consumption, mixed venous O_2 saturation offers valuable information about cardiac output.

Blood gas analysis is important not only for determining the adequacy of oxygenation and ventilation but also for determining the site of respiratory pathology and planning treatment (see Chapter 421). Briefly, in the presence of pure alveolar hypoventilation (e.g., airway obstruction above carina, decreased CO_2 responsiveness, neuromuscular weakness), the blood gas will show respiratory acidosis with an elevated $Paco_2$ but a relative sparing of oxygenation. $\dot{V}/\dot{Q}$ mismatch (peripheral airway obstruction, bronchopneumonia) will be reflected in increasing hypoxemia and variable levels of $Paco_2$ (low, normal, high) depending on severity of disease. Intrapulmonary right-to-left shunting and diffusion defects (alveolar-interstitial diseases such as pulmonary edema, ARDS) will be associated with a large A-ao_2 gradient and hypoxemia with relative sparing of CO_2 elimination, unless there is coincident fatigue or CNS depression.

Acid-Base Abnormalities

It is crucial to analyze the magnitude and appropriateness of changes in pH, $Paco_2$, and bicarbonate concentration ($[HCO_3^-]$) because they provide useful clues to the underlying pathophysiology and presence of more than one disorder. To do so, it is useful to assume baseline values of pH 7.40, $Paco_2$ 40 mm Hg, and $[HCO_3^-]$ 24 mEq/L. Newborns have a lower renal threshold for bicarbonate and therefore have slightly different baseline values of pH 7.38, $Paco_2$ 35 mm Hg, and $[HCO_3^-]$ 20 mEq/L.

Metabolic Acidosis with Respiratory Compensation

Patients with metabolic acidosis have decreased pH resulting from decreased serum $[HCO_3^-]$. Chemoreceptor stimulation results in hyperventilation and respiratory compensation that may clinically manifest as respiratory distress. Normal compensation does not completely correct the pH, but rather minimizes a change in pH that would otherwise occur without compensation. The adequacy of respiratory compensation is judged by the extent of the decline in $Paco_2$ in response to the decline in $[HCO_3^-]$ or pH. A normal compensation for metabolic acidosis results in a fall in $Paco_2$ by 1.2 mm Hg for every 1 mEq/L fall in $[HCO_3^-]$. The most commonly used method to analyze the adequacy of respiratory compensation is Winter's formula:

$$Paco_2 \text{ mm Hg} = (HCO_3^- \times 1.5) + 8 \pm 2$$

A quick method is to look at the last two digits of pH (provided it is not <7.10), which should be within 2 mm Hg of $Paco_2$. For example, pH 7.27, $Paco_2$ 26 mm Hg, and $[HCO_3^-]$ 12 mEq/L represent metabolic acidosis with a normal respiratory compensation response. On the other hand, pH 7.15, $Paco_2$ 30 mm Hg, and $[HCO_3^-]$ 10 mEq/L constitutes metabolic acidosis with inadequate respiratory compensation. The reasons for inadequate compensation include decreased CO_2 responsiveness (e.g., narcotic poisoning, cerebral edema), abnormalities of lungs and airways, or neuromuscular weakness. A decrease in $Paco_2$ that is greater than what could be expected as a normal compensatory response to metabolic acidosis is indicative of a mixed disorder. A pH 7.20, $Paco_2$ 15 mm Hg, and $[HCO_3^-]$ 7.5 mEq/L represent metabolic acidosis with a concomitant respiratory alkalosis because the decline in $Paco_2$ is greater than what can be expected as normal compensation. A combination of metabolic acidosis and respiratory alkalosis is often encountered in serious conditions such as cardiogenic shock (e.g., stimulation of baroreceptors), sepsis, or toxic-metabolic states (e.g., salicylates, organic acidemia).

Respiratory Acidosis with Metabolic Compensation

Patients with respiratory acidosis have decreased pH as a result of elevated $Paco_2$. An acute increase in $Paco_2$ of 10 mm Hg results in a decrease in pH by 0.08. Thus a child with severe critical asthma and a $Paco_2$ of 60 mm Hg will have a blood pH of approximately 7.24. Chronically elevated (>3-5 days) $Paco_2$ is accompanied by renal compensation and increase in serum $[HCO_3^-]$, limiting the fall in pH to 0.03 for every 10 mm Hg rise in $Paco_2$. Thus an infant with bronchopulmonary dysplasia who has a basal $Paco_2$ of 60 mm Hg will have a blood pH of approximately 7.34. These findings are helpful in distinguishing acute from chronic changes in $Paco_2$. Also, for a given level of CO_2 accumulation, a decrease in pH that is greater than expected is indicative of concomitant metabolic acidosis, and a decline in pH that is less than expected is caused by accompanying metabolic alkalosis.

Assessment of Oxygenation and Ventilation Deficits

For standardizing management, following clinical progress, and determining prognosis for patients with defects in oxygenation or ventilation, the following indicators have been proposed, each with its strengths and limitations:

- **A-ao_2 gradient** is calculated by the subtraction, $Pao_2 - Pao_2$. For the comparison to be valid, both values must be taken at the same time and with the same fraction of oxygen in the inspired gas (Fio_2).
- **Pao_2/Fio_2 ratio** (P/F ratio) is calculated by dividing Pao_2 by Fio_2. The P/F ratio is the measure of oxygenation adequacy employed in the Berlin definition of ARDS in adults (Table 86.8). According to the Berlin definition, a P/F ≤300 mm Hg is consistent with mild ARDS, a P/F ratio between 100 and 200 mm Hg is consistent with moderate ARDS, and a P/F ratio ≤100 mm Hg is consistent with severe ARDS. Although the intent is to gauge the degree of $\dot{V}/\dot{Q}$ mismatch, intrapulmonary shunt, and diffusion defect, the status of alveolar hypoventilation could have a significant impact on P/F ratio.
- **Spo_2/Fio_2 ratio** may be used as a surrogate measure of oxygenation adequacy when Pao_2 is not available. It is calculated by dividing the pulse oximeter saturation by the Fio_2. P/F ratios of 200 mm

Table 86.8 The Berlin Definition of ARDS

- Acute onset (within 7 days of new or worsening respiratory symptoms)
- Bilateral radiographic opacities that are not fully explained by effusion, atelectasis, or masses
- Arterial hypoxemia defined by thresholds:
  - *Mild:* 200 <Pao_2/Fio_2 ratio ≤300 mm Hg, on CPAP* or PEEP† ≥5 cm H_2O (observed mortality 27%)
  - *Moderate:* 100 <Pao_2/Fio_2 ratio ≤200 mm Hg, on PEEP ≥5 cm H_2O (observed mortality 32%)
  - *Severe:* Pao_2/Fio_2 ratio ≤100 mm Hg, on PEEP ≥5 cm H_2O (observed mortality 45%)
- Identified risk factor for ARDS (if no clear risk factor, exclude heart failure as a cause)
- Not exclusively the result of cardiac causes

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure.

*Delivered by noninvasive or invasive ventilation.

†Delivered by invasive mechanical ventilation.

From Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet.* 2021;398:622-637, Panel 1, p. 622.

Hg and 300 mm Hg correlate approximately with S/F ratios of 235 and 315, respectively. This relationship is most valid for Spo_2 values between 80% and 97%.

Pao_2/P_{AO_2} ratio is determined by dividing Pao_2 by P_{AO_2}. The level of alveolar ventilation is accounted for in the calculation of Pao_2. Therefore Pao_2/P_{AO_2} is more indicative of $\dot{V}/\dot{Q}$ mismatch and alveolar capillary integrity.

Oxygenation index (OI) is aimed at standardizing oxygenation to the level of concomitant therapeutic interventions (e.g., mean airway pressure [MAP] and Fio_2) that influence oxygenation. None of the indicators of oxygenation mentioned earlier take into account the degree of positive pressure respiratory support. The OI is calculated as follows:

$$OI = (MAP \times Fio_2 \times 100) / Pao_2$$

Oxygenation saturation index (OSI) is analogous to OI and useful when Pao_2 measurements are not available. It substitutes Spo_2 for Pao_2 in the formula as follows:

$$OSI = (MAP \times Fio_2 \times 100) / Spo_2$$

Both the OI and OSI are used in the Pediatric Acute Lung Injury Consensus Conference (PALICC) definition of PARDS. The main limitation of OI and OSI is that level of ventilation is not accounted for in the assessment.

MANAGEMENT

The goal of management for respiratory distress and respiratory failure is to ensure a patent airway and provide necessary support for adequate oxygenation of the blood and removal of CO_2. Compared with hypercapnia, **hypoxemia** is a life-threatening condition; therefore initial therapy for respiratory failure should be aimed at ensuring adequate oxygenation.

Oxygen Administration

Supplemental oxygen administration is the least invasive and most easily tolerated therapy for hypoxemic respiratory failure. **Nasal cannula** oxygen provides low levels of oxygen supplementation and is easy to administer. Oxygen is humidified in a bubble humidifier and delivered via nasal prongs inserted into the nares. In children, a flow rate <5 L/min is most often used because of increasing nasal irritation with higher flow rates. A common formula for an estimation of the Fio_2 during use of a nasal cannula in older children and adults follows:

$$Fio_2 \text{ (as a percentage)} = 21\% + (\text{Nasal cannula flow [L/min]} \times 3)$$

The typical Fio_2 value (expressed as a percentage rather than a fraction of 1) using this method is between 23% and 40%, although the Fio_2 varies according to the size of the child, the respiratory rate, and the volume of air moved with each breath. In a young child, because typical nasal cannula flow rates are a greater percentage of total minute ventilation, significantly higher Fio_2 may be provided. Alternatively, a **simple mask** may be used, which consists of a mask with open side ports and a valveless oxygen source. Variable amounts of room air are entrained through the ports and around the side of the mask, depending on the fit, size, and minute volume of the child. Oxygen flow rates administered through a simple mask generally vary from 5 to 10 L/min, yielding typical Fio_2 values (expressed as a percentage rather than a fraction of 1) between 30% and 65%. If more precise delivery of oxygen is desired, other mask devices should be used.

A **Venturi mask** provides preset Fio_2 through a mask and reservoir system by entraining precise flow rates of room air into the reservoir along with high-flow oxygen. The adapter at the end of each mask reservoir determines the flow rate of entrained room air and the subsequent Fio_2 adapters provide Fio_2 of 0.30-0.50. Oxygen flow rates of 5-10 L/min are recommended to achieve the desired Fio_2 and to prevent rebreathing. Partial rebreather and non-rebreather masks use a reservoir bag attached to a mask to provide higher Fio_2. **Partial rebreather masks** have two open exhalation ports and contain a valveless oxygen reservoir bag. Some exhaled gas can mix with reservoir gas, although most exhaled gas exits the mask via the exhalation ports. Through these same ports, room air is entrained, and the partial rebreather mask can provide Fio_2 up to 0.60 for as long as oxygen flow is adequate to keep the bag from collapsing (typically 10-15 L/min). As with nasal cannulas, smaller children with smaller tidal volumes entrain less room air, and their delivered Fio_2 will be higher. **Non-rebreather masks** include two one-way valves, one between the oxygen reservoir bag and the mask and the other on one of the two exhalation ports. This arrangement minimizes mixing of exhaled and fresh gas and entrainment of room air during inspiration. The second exhalation port has no valve, a safeguard to allow some room air to enter the mask in the event of disconnection from the oxygen source. A non-rebreather mask can provide Fio_2 up to 0.95. The use of a non-rebreather mask in conjunction with an oxygen blender allows delivery of Fio_2 between 0.50 and 0.95 (Table 86.9). When supplemental oxygen alone is inadequate to improve oxygenation, or when ventilation impairments coexist, additional therapies may be necessary.

Airway Adjuncts

Maintenance of a patent airway is a critical step in establishing adequate oxygenation and ventilation. Artificial pharyngeal airways may be useful in patients with oropharyngeal or nasopharyngeal airway obstruction and in those with neuromuscular weakness in whom inherent extrathoracic airway resistance contributes to respiratory compromise. An **oropharyngeal airway** is a stiff plastic spacer with grooves along each side that is placed in the mouth to run from the teeth along the tongue to its base just above the vallecula. The spacer prevents the tongue from opposing the posterior pharynx and occluding the airway. Because the tip sits at the base of the tongue, it is usually not tolerated by patients who are awake or whose gag reflex is strong. The **nasopharyngeal airway**, or *nasal trumpet,* is a flexible tube that can be inserted into the nose to run from the nostril along the top of the hard and soft palate with the tip ending in the hypopharynx. It is useful in bypassing obstruction from enlarged adenoids or from contact of the soft palate with the posterior pharynx. Because it is inserted past the adenoids, a nasopharyngeal airway should be used with caution in patients with bleeding tendencies.

Inhaled Gases

Helium-oxygen mixture (heliox) is useful in overcoming airway obstruction and improving ventilation. Helium is much less dense and slightly more viscous than nitrogen. When substituted for nitrogen in the inspired gas, helium helps maintain laminar flow across an obstructed airway, decreases airway resistance, and improves ventilation. It is especially helpful in diseases of large airways obstruction in which turbulent airflow is more common, such as acute laryngotracheobronchitis, subglottic stenosis, and vascular ring. To be effective, helium should be administered in concentrations of at least 60%, so associated hypoxemia may limit its use in patients requiring >40% oxygen.

Table 86.9 Approximate Oxygen Delivery According to Device and Flow Rates in Infants and Older Children*

DEVICE	FLOW (L/min)	Fio_2 DELIVERED
Nasal cannula	0.1-6	0.21-0.4
Simple face mask	5-10	0.4-0.6
Partial rebreather	6-15	0.55-0.7
Non-rebreather	6-15	0.7-0.95
Venturi mask	5-10	0.25-0.5
Hood/tent	7-12	0.21-1.0
High-flow systems	1-60	0.21-1.0

*Individual delivery varies and depends on the patient's size, respiratory rate, and gas volume moved with every breath.

Inhaled nitric oxide (iNO) is a powerful pulmonary vasodilator. Its use may improve pulmonary blood flow and $\dot{V}/\dot{Q}$ matching in patients with diseases that elevate pulmonary vascular resistance, such as persistent pulmonary hypertension of the newborn, primary pulmonary hypertension, and secondary pulmonary hypertension from chronic excess pulmonary blood flow (e.g., ventriculoseptal defect) or collagen vascular diseases. iNO is administered in doses ranging generally from 5 to 20 parts per million of inspired gas. Although administration of iNO to unintubated patients is possible, it is most commonly used in patients undergoing mechanical ventilation via an endotracheal tube.

Positive Pressure Respiratory Support

Noninvasive positive pressure respiratory support is useful in treating both hypoxemic and hypoventilatory respiratory failure. Positive airway pressure helps with aeration of partially atelectatic or fluid-filled alveoli, prevention of alveolar collapse at end exhalation, and increase in functional residual capacity (FRC). These actions improve pulmonary compliance and hypoxemia, and decrease intrapulmonary shunt. In addition, positive pressure ventilation is useful in preventing collapse of extrathoracic airways by maintaining positive airway pressure during inspiration. Improving compliance and overcoming airway resistance also improves tidal volume and, therefore, ventilation.

A **high-flow nasal cannula (HFNC)** delivers conditioned (heated and humidified) gas at flows generally ranging from 0.5 to 2 L/kg/min up to a maximum of 60 L/min. The F_{IO_2} can be adjusted by provision of gas flow through an oxygen blender, or directly, when a dedicated commercial high-flow system is employed. A properly sized cannula for HFNC support should have prongs that occupy no more than 50% of the cross-sectional area of the nostrils, thus allowing for ample leakage of gas (open system). Therefore although elevated pressures may be generated in areas of the nasopharynx, very low levels of positive expiratory pressure (<1 cm H_2O) thought to be clinically insignificant are transmitted to the intrathoracic airway. The principal mechanisms of action of HFNC are washout of CO_2 from the pharyngeal anatomic dead space and facilitation of gas movement across the nasopharyngeal airway resistor. This is in contrast to **continuous positive airway pressure (CPAP)**, a clinically equivalent support modality predicated on the use of a tight-fitting interface (closed system) in the form of nasal prongs, masks, or helmet. CPAP creates a stable level of operator-selected airway pressure that is transmitted to the intrathoracic airway. CPAP levels of 6-7 cm H_2O have been shown to unload the diaphragm and decrease work of breathing in infants with bronchiolitis. CPAP is most useful in diseases of mildly decreased lung compliance and low FRC, such as bronchiolitis with atelectasis and pneumonia. Patients with diseases of extrathoracic airway obstruction, in which extrathoracic negative airway pressures during inspiration result in airway narrowing (e.g., laryngotracheitis, laryngomalacia, obstructive sleep apnea, postextubation airway edema), may also benefit from CPAP. Potential risks include nasal irritation, pressure injury, hyperinflation from excessive CPAP in smaller patients, and abdominal distention from swallowed air.

Noninvasive positive airway pressure ventilation (NIPPV) provides positive airway pressure during exhalation and a higher pressure that supports inspiration, also termed *bilevel noninvasive ventilation* (see Chapter 86.1).

Endotracheal Intubation and Mechanical Ventilation

When hypoxemia or significant hypoventilation persists despite the interventions already described, endotracheal intubation and mechanical ventilation are indicated. Additional indications for intubation include maintaining airway patency in patients who have the potential for airway compromise, such as those with actual or potential neurologic deterioration, and in patients with hemodynamic instability.

Proper monitoring is essential to ensuring a safe and successful endotracheal intubation. Pulse oximetry, heart rate, and blood pressure monitoring are mandatory and should be forgone only in situations calling for emergency intubation. All necessary equipment, including bag-mask ventilation device, laryngoscope, endotracheal tube (ETT) with stylet, and suction equipment, must be available and working properly before intubation. The proper internal diameter (ID) for the ETT can be estimated using the following formula:

$$ID = (Age\ [yr]/4)+4$$

Table 86.10 provides average values for age, size, and depth of insertion for tracheal tubes. Preoxygenation of the patient with high F_{IO_2} is essential and will allow maximum procedure time before the onset of hypoxemia. Although intubation can be accomplished without sedation and pharmacologic paralysis in selected patients, the physiologic benefits of these measures to the patient and to the facilitation of the intubation usually far outweigh the risks. Administration of a sedative and analgesic followed by a neuromuscular-blocking agent is a common pharmacologic regimen for facilitating intubation. In fact, sedation and paralysis with neuromuscular blocking agents should be considered standard unless contraindicated. The particular type and dose of each agent often depends on the underlying disease and clinician preference. Table 86.11 lists commonly used agents. *Dexmedetomidine* has been a standard sedating agent for maintenance during mechanical ventilation. An alternative to this pharmacologic approach is **rapid sequence intubation**, used when endotracheal intubation is urgent or the patient is suspected of having a full stomach and at increased risk of aspiration (see Chapter 79).

Once adequate sedation and/or paralysis has been achieved, ventilation should be assisted with a **bag-mask device**. After optimal preoxygenation, intubation can be performed. The clinician uses the dominant hand to open the patient's mouth and insert the laryngoscope blade gently along the tongue to its base. The airway opening can be visualized by lifting up and away from the clinician, along the axis of the laryngoscope handle. When a *straight* (Miller) laryngoscope blade is used to visualize the glottis, the tip of the blade lifts the epiglottis anteriorly. When a *curved* (Macintosh) blade is used to visualize the glottis, the tip of the blade should be advanced into the vallecula and then lifted. Secretions often obscure visualization at this step and should be suctioned clear. Once clear visualization of the vocal cords is accomplished, the ETT can be placed through the vocal cords. Rapid confirmation of ETT placement is essential and should be assessed by as many of the following steps as possible: (1) presence of exhaled CO_2 determined by a colorimetric device, capnometry, or, preferably, capnography, attached in-line with the ETT; (2) auscultation of both lung fields for equal breath sounds and the epigastrium; (3) bilateral chest wall expansion; and (4) condensation (misting) inside the ETT. An increasing heart rate, if heart rate had decreased before or during

Table 86.10 Average Size and Depth Dimensions for Tracheal Tubes

PATIENT AGE	INTERNAL DIAMETER (mm)	OROTRACHEAL DEPTH (cm)	NASOTRACHEAL DEPTH (cm)
Premature	2.0-3.0	8-9	9-10
Full-term neonate	3.0-3.5	10	11
6 mo	4.0	11	13
12-24 mo	4.5	13-14	16-17
4 yr	5.0	15	17-18
6 yr	5.5	17	19-20
8 yr	6.0	19	21-22
10 yr	6.5	20	22-23
12 yr	7.0	21	23-24
14 yr	7.5	22	24-25
Adult	8.0-9.0	23-25	25-28

Courtesy Dr. Ashok Sarnaik.

Table 86.11 Medications Commonly Used for Intubation

DRUG	DOSE	ONSET (min)	DURATION (min)	COMMENTS
SEDATIVES/ANESTHETICS				
Midazolam	0.1 mg/kg IV	3-5	60-120	Amnesia Respiratory depression
Lorazepam	0.1 mg/kg IV	3-5	120-240	Amnesia Respiratory depression
Ketamine	1-2 mg/kg IV 4-6 mg/kg IM	2-3	10-15	↑ HR, BP, and ICP Bronchodilation, sialorrhea
Propofol	1-3 mg/kg IV	0.5-2	10-15	↓ BP Apnea
Thiopental	4-7 mg/kg IV	0.5-1	5-10	↓ BP Apnea
ANALGESICS				
Fentanyl	2-5 µg/kg IV	3-5	30-90	Respiratory depression Chest wall rigidity
Morphine	0.1 mg/kg IV	5-15	120-240	↓ BP Respiratory depression
NEUROMUSCULAR BLOCKING AGENTS				
Vecuronium	0.1 mg/kg IV	1.5-2	30-75	↑ HR Renal elimination
Rocuronium	0.6-1.2 mg/kg IV 1 mg/kg IM	1-1.5	15-60	↑ HR Renal elimination
Cisatracurium	0.1 mg/kg IV	3-5	25-30	Histamine release Nonrenal elimination

BP, Blood pressure; HR, heart rate; ICP, intracranial pressure; IM, intramuscularly; IV, intravenously.

the attempt, and a rising or normal Spo_2 reading are suggestive of successful tube placement. Preoxygenation may significantly delay any drop in Spo_2 with improper tube placement, leading to a delay in its recognition. A properly placed ETT should be well secured to avoid displacement or dislodgement. As soon as feasible, a chest radiograph should also be obtained to confirm proper position of the ETT, which should lie with the tip about halfway between the thoracic inlet and the carina (see Chapter 79).

Transient Manual Ventilation in Immediate Preintubation and Postintubation Periods

Establishment of supportive ventilation via bag-mask or bag-ETT is required before transport of the patient to a setting of continued critical care. The technique of manual ventilation should take into account the underlying pathology. Mechanical ventilation of patients with diseases characterized by low FRC (e.g., pneumonia, pulmonary edema, ARDS) should include the application of PEEP to prevent alveolar derecruitment. Lung volume recruitment can be accomplished with a PEEP valve on a self-inflating ventilation bag or by careful manipulation of exhaust gas using an anesthesia bag. Such diseases are also characterized by a short time constant for lung deflation and therefore are best managed with relatively small tidal volumes and high ventilation rates.

In contrast, diseases characterized by airway obstruction, such as critical asthma, have prolonged deflation time constants and are therefore best managed with relatively slow rates and high tidal volumes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

86.1 Mechanical Ventilation

Martin C.J. Kneyber, Ashok P. Sarnaik, and Alexandre T. Rotta

The decision to institute mechanical ventilation is based mainly on the need to assist native pulmonary function in patients with acute respiratory failure; supporting performance of the left ventricle (LV), decreasing metabolic demand, and modulating of cerebral blood flow in intracranial hypertension are additional indications. Respiratory distress leading to fatigue and impending exhaustion are also indications for respiratory support, even in the presence of adequate gas exchange. Although there are no absolute criteria for derangement of gas exchange, Pao_2 <60 mm Hg while breathing >60% oxygen, $Paco_2$ >60 mm Hg, and pH <7.25 are often used in the decision-making to institute respiratory support. Positive pressure ventilation is a powerful means of decreasing LV afterload, and it is used for this purpose in patients with cardiogenic shock resulting from LV dysfunction. Mechanical ventilation is also used in patients whose breathing is unreliable (e.g., unconscious patients, those with neuromuscular dysfunction) and when deliberate hyperventilation is desired, such as in patients with intracranial hypertension.

Mechanical ventilation is not intended to normalize gas exchange. The goals are to maintain sufficient oxygenation and ventilation to ensure tissue viability until the disease process that has compromised the patient's lung function has resolved, while minimizing excessive work of breathing and complications. When precisely employed, mechanical ventilation is a lifesaving intervention, yet care must be taken to avoid ventilator-induced lung injury (VILI). Several factors have been identified as contributors to VILI. These include lung strain from the delivery of excessive tidal volume **(volutrauma)**, injury from the repetitive opening and closing of alveoli **(atelectrauma)**, injury from excessive pressure delivery **(barotrauma)**, local and systemic cytokine release **(biotrauma)**, and damage caused by oxygen toxicity (Figs. 86.2 and 86.3).

BASIC CONCEPTS OF VENTILATOR MANAGEMENT

Equation of Motion

A pressure gradient is required for air to move from one place to another. During natural spontaneous ventilation, inspiration results from generation of negative intrapleural pressure from contraction of the diaphragm and intercostal muscles, drawing air from the atmosphere across the airways into the alveoli. During mechanical ventilation, inspiration results from positive pressure created by compressed gases through the ventilator, which pushes air across the airways into alveoli. In both spontaneous and mechanical ventilation, exhalation results from alveolar pressure generated by the elastic recoil of the lung

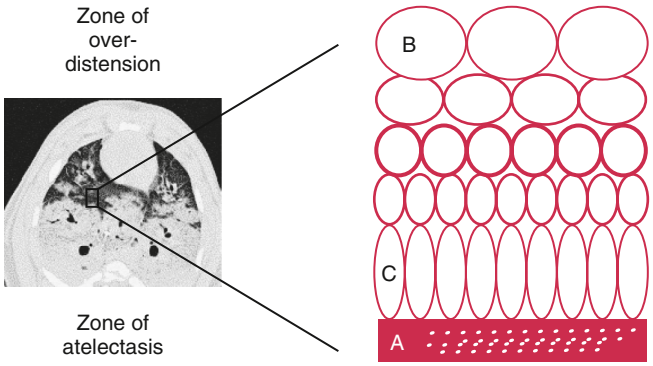

Fig. 86.2 Atelectrauma. The interface between collapsed and consolidated lung *(A)* and overdistended lung units *(B)* is heterogeneous and unstable. Depending on ambient conditions, this region is prone to cyclic recruitment and derecruitment and localized asymmetric stretch of lung units *(C)* immediately apposed to regions of collapsed lung. *(From Pinhu L, Whitehead T, Evans T, et al. Ventilator-associated lung injury.* Lancet. *2003;361:332-340.)*

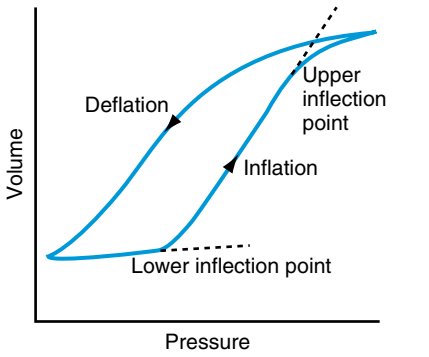

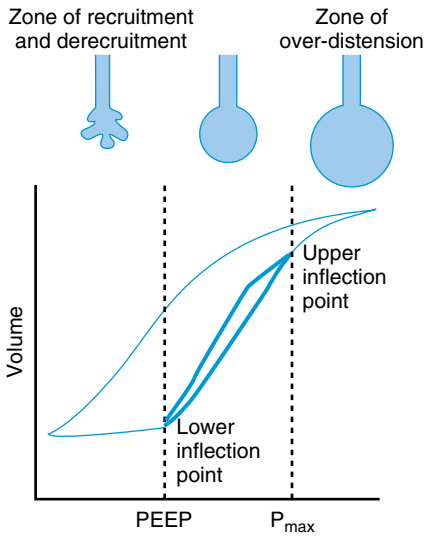

Fig. 86.3 Pulmonary pressure-volume relation in a patient with acute lung injury. *Top,* The lower inflection point is typically 12-18 cm H_2O and the upper inflection point 26-32 cm H_2O. *Bottom,* Specific protective ventilation strategies require that positive end-expiratory pressure (PEEP) is set just above the lower inflection point and the pressure limit (P_{max}) just below the upper inflection point. Thus the lung is ventilated in the safe zone between the zone of recruitment and derecruitment and the zone of overdistention, and both high-volume and low-volume injuries are avoided. This zone is located on the deflation limb of the pressure-volume curve, making use of the pulmonary hysteresis. *(From Pinhu L, Whitehead T, Evans T, et al. Ventilator-associated lung injury.* Lancet. *2003;361:332-340.)*

1. Pressure gradient is required to move air from one place to another
2. Movement of air is opposed by flow-resistive and elastic properties of the system

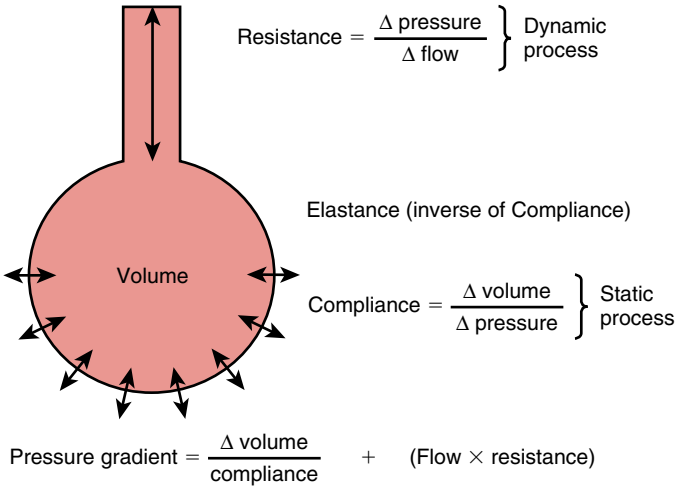

Fig. 86.4 Equation of motion. A pressure gradient is required to move air from one place to another. In the lungs, the required pressure gradient must overcome the lung and chest wall elastance (static component) and the flow-resistive properties (dynamic component). The static component is increased in alveolar interstitial diseases and stiff chest wall, whereas the dynamic component is increased with airway obstruction.

and the chest wall. Pressure necessary to move a given amount of air into the lung is determined by two factors: lung and chest wall elastance and airway resistance. Figure 86.4 describes the relationship in pressure gradient, compliance, and resistance. *Elastance*—defined as the change in pressure (ΔP) divided by the change in volume (ΔV)—refers to the property of a substance to oppose deformation. It is opposite of *compliance* (ΔV ÷ ΔP), the property of a substance to allow distention or lengthening when subjected to pressure. Compliance (C) is therefore expressed as 1/elastance.

The pressure needed to overcome tissue elastance is measured in conditions in which there is no flow (at end inspiration and end expiration) and is therefore a reflection of static conditions in the lung. It is influenced by tidal volume (Vᴛ) and compliance (P = ΔV ÷ C). It is increased with high Vᴛ and low compliance. This pressure gradient is used to calculate the static compliance of the respiratory system (C_{STAT}).

Resistance (R) refers to the opposition to generation of flow. It is measured as the amount of pressure needed to generate a unit of flow (ΔP ÷ ΔFlow). Pressure needed to overcome airway resistance is calculated as flow multiplied by resistance. Because this pressure is needed only when the flow is occurring through the airways, it is referred to as the *dynamic component*. Pressure to overcome flow-resistive properties is measured when there is maximum flow and is therefore under dynamic conditions. It is increased in conditions with greater airway resistance and flow rate. Flow rate depends on the time allowed for inspiration and expiration. At higher respiratory rates, there is less time available for each inspiration and expiration, necessitating higher flows; therefore higher pressure is required to overcome flow-resistive properties. The pressure gradient necessary to move air from one place to another is the sum of pressure needed to overcome the elastic and flow-resistive properties of the lung. This pressure gradient is taken into account to calculate the dynamic compliance of the respiratory system (C_{DYN}). The difference in change in pressure between static conditions and dynamic conditions is attributable to airway resistance.

Functional Residual Capacity

During inspiration, oxygen-enriched gas enters alveoli. During exhalation, oxygen continues to be removed by the pulmonary capillary

circulation. Functional residual capacity (FRC) is the volume of gas left in the alveoli at end expiration; in mechanically ventilated patients, it is generally referred to as *end-expiratory lung volume* (EELV). It is the only source of gas available for gas exchange during exhalation. In diseases with decreased FRC (e.g., pediatric acute respiratory distress syndrome [PARDS], pulmonary edema), P_{AO_2} declines sharply throughout expiration, resulting in hypoxemia. Two ventilator strategies used to improve oxygenation in such situations are the application of PEEP and increasing the *inspiratory time* (TI) (Fig. 86.5). Positive end-expiratory pressure (PEEP) increases EELV by stabilizing recruited alveoli, whereas a longer TI allows longer exposure of pulmonary capillary blood to a higher concentration of O_2 during inspiration (see also Chapter 421).

Time Constant

At the beginning of inspiration, the atmospheric pressure is higher than the pressure in the alveoli, resulting in movement of air into the alveoli. During mechanical ventilation, the ventilator circuit serves as the patient's atmosphere. As alveoli expand with air, the alveolar pressure rises throughout inspiration until it equilibrates with the ventilator pressure, at which time airflow ceases. Expiration starts when the ventilator pressure falls below the alveolar pressure. Alveolar pressure decreases throughout expiration until it reaches the ventilator pressure, at which time no further egress of air from the alveoli occurs. If inspiration or expiration is terminated before pressure equilibration between alveoli and the ventilator is allowed to occur, alveolar expansion during inspiration or alveolar emptying during expiration is incomplete. Incomplete inspiration results in delivery of decreased VT, whereas incomplete expiration is associated with air trapping and the presence of residual PEEP in the alveoli that is greater than the PEEP set at the ventilator, referred to as **auto-PEEP**. Some time is required for pressure equilibration to occur between alveoli and the atmosphere, which is reflected in the *time constant* (TC). It takes 3 TCs for 95% (and 5 TCs for 99%) of pressure equilibration to occur. The TC depends on compliance (C) and resistance (R), and their relationship is depicted in Figure 86.6. TC is calculated as compliance multiplied by resistance (C × R) and is measured in seconds.

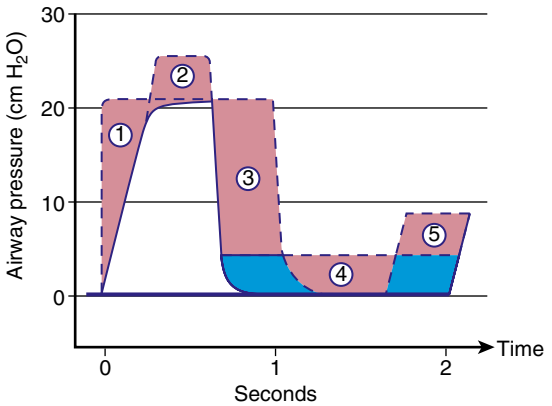

Fig. 86.5 Five different ways to increase mean airway pressure. *(1)* Increase the respiratory flow rate, producing a square wave inspiratory pattern; *(2)* increase the peak inspiratory pressure; *(3)* reverse the inspiratory-expiratory ratio or prolong the inspiratory time without changing the rate; *(4)* increase positive end-expiratory pressure; and *(5)* increase the ventilatory rate by reducing the expiratory time without changing the inspiratory time. *(From Harris TR, Wood BR. Physiologic principles. In Goldsmith JP, Karotkin EH, eds.* Assisted Ventilation of the Neonate, *3rd ed. Philadelphia: Saunders;1996.)*

Diseases with decreased compliance (increased elastance) are characterized by high elastic recoil pressure, which results in more rapid equilibration of alveolar and ventilator pressures, thereby decreasing TC. Diseases with increased airway resistance are associated with slower flow rates, require longer time for movement of air from one place to another, and therefore have increased TC. Airways expand during inspiration and narrow during expiration. Therefore expiratory time constant (TCE) is longer than inspiratory time constant (TCI). In intrathoracic airway obstruction (e.g., asthma, bronchiolitis, aspirated foreign body), airway narrowing is much more pronounced during expiration. Therefore although both TCE and TCI are prolonged in such diseases, TCE is much more prolonged than TCI. Patients with such diseases therefore are best ventilated with slower rates, larger VT, and longer expiratory time than inspiratory time. In diseases characterized by decreased compliance, both TCE and TCI are short; however, the TCE is closer to TCI than in normal lungs because the stiffer alveoli recoil with greater force. Patients with these diseases are best ventilated with smaller VT to prevent VILI, increased respiratory rate, and a relatively longer inspiratory time in each breath to improve oxygenation.

Critical Opening Pressure

Collapsed or atelectatic alveoli require a considerable amount of pressure to open. Once open, the alveoli require relatively less pressure for continued expansion. The process of opening atelectatic alveoli is called **recruitment**. In a normal lung, alveoli remain open at end expiration, and therefore the lung requires relatively less pressure to receive its VT. In a disease process in which alveoli collapse at end expiration (e.g., PARDS), a substantial amount of pressure is required to open the alveoli during inspiration. This pressure causes VILI by two mechanisms: *barotrauma* at the terminal airway-alveolar junction and *volutrauma* as a result of overdistention of alveoli that are already open (see Figs. 86.2 and 86.3). Although pulmonary parenchymal disease is rarely uniform and each of the millions of alveoli may have its own mechanical characteristics, a composite volume-pressure relationship could be conceptualized for the whole lung (Fig. 86.7).

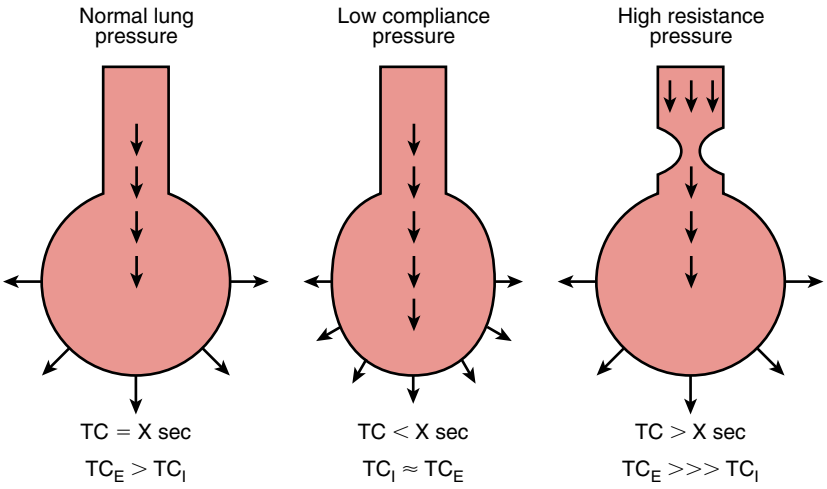

Fig. 86.6 Time constant (TC). A certain amount of time is necessary for pressure equilibration (and therefore completion of delivery of gas) to occur between the proximal airway and alveoli. TC, a reflection of time required for pressure equilibration, is a product of compliance and resistance. In diseases of decreased lung compliance, less time is needed for pressure equilibration to occur, whereas in diseases of increased airway resistance, more time is required. Expiratory TC (TC_E) is increased much more than inspiratory TC (TC_I) in obstructive airway diseases because airway narrowing is exaggerated during expiration.

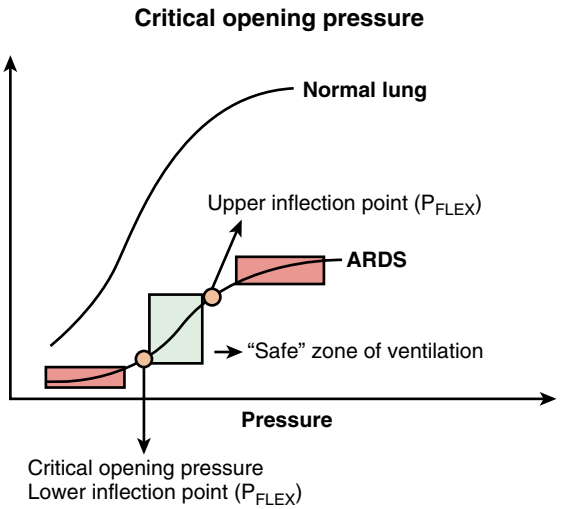

Fig. 86.7 Volume-pressure relationship in normal lung and in acute respiratory distress syndrome (ARDS). In ARDS, atelectatic alveoli require a considerable amount of pressure to open. Critical opening pressure, also referred to as lower P_{FLEX}, is the airway pressure above which further alveolar expansion occurs with relatively less pressure. Upper P_{FLEX} is the airway pressure above which further increase in pressure results in less alveolar expansion; this is the area of alveolar overdistention. Keeping tidal volume between upper and lower P_{FLEX} values is considered less injurious to the lung.

In these situations, the lower and upper portions of the curve are relatively horizontal and the middle portion is more vertical. At the beginning of inspiration, atelectatic alveoli are being recruited, requiring high pressure for a relatively small increase in volume. Once they are recruited, further increase in volume requires relatively less pressure. The pressure at which most alveoli are open is called *critical opening pressure;* this point is also referred to as the *lower inflection point* (lower P_{FLEX}). After the lower P_{FLEX}, greater volume can be delivered for relatively less pressure until the upper P_{FLEX} is reached, at which point the volume-pressure curve again becomes relatively horizontal. The goal of mechanical ventilation in alveolar interstitial pathology is to deliver a V_T between the lower and upper inflection points, the so-called *safe zone of ventilation.* If V_T is delivered with a change in inflation pressure that includes the lower P_{FLEX}, alveoli are likely to open *and* close during every breath, a process termed **tidal recruitment** that is injurious to the lung (atelectrauma), especially at the terminal airway-alveolar junction. If V_T is delivered with a change of pressure that includes the upper P_{FLEX}, overdistention of alveoli is likely to occur, resulting in volutrauma and barotrauma. Keeping tidal ventilation between the upper and lower P_{FLEX} values is accomplished by maintaining a level of PEEP to produce baseline alveolar recruitment and delivering a relatively small V_T. This lung-protective ventilation is also known as "open lung" strategy and is the preferred approach in diffuse alveolar interstitial diseases such as PARDS.

Mechanical ventilation may be delivered either noninvasively with a patient-machine interface other than an ETT or invasively after endotracheal intubation.

NONINVASIVE MECHANICAL VENTILATION

Delivering positive pressure mechanical respiratory support without the use of endotracheal intubation is called noninvasive positive pressure ventilation **(NIPPV)**. This type of respiratory support has been increasingly used in the pediatric intensive care setting.

The most common techniques applied are continuous positive airway pressure **(CPAP)** or biphasic (inspiratory and expiratory) positive airway pressure **(BiPAP)**. Of note, CPAP is only the delivery of a continuous airway pressure; therefore by definition, it is not a true form of noninvasive ventilation because a minute volume is generated exclusively by the patient, not by the device. A variety of devices with increasing sophistication has been developed in recent years, and different interfaces are available, such as nasal prongs, nasal and full-face masks, and helmets. Especially in the pediatric population, an age-appropriate, properly sized, and comfortable interface that minimizes air leak is critical for the successful application of NIPPV. NIPPV has been successfully used in acute and chronic hypoxic and/or hypercarbic respiratory failure. Indications range from acute lower airway obstruction, such as asthma, or acute upper airway obstruction, including postextubation airway swelling, to parenchymal lung diseases such as pneumonia and mild to moderate PARDS. Acute and chronic respiratory failure from neuromuscular weakness or chest wall deformities have been the classic indication for its use. NIPPV can also be used to help prevent reintubation after prolonged mechanical ventilation.

BiPAP provides positive airway pressure during exhalation and additional positive pressure during inspiration. These pressures can be adjusted independently to suit individual needs and comfort, and a respiratory rate can be delivered. The additional positive pressure during inspiration helps improve alveolar ventilation in low compliance and obstructive lung disease. During exhalation, expiratory positive airway pressure can decrease the effects of airway closure by raising intraluminal pressure and ameliorating intrathoracic airway collapse. During inspiration, inspiratory positive airway pressure unloads inspiratory muscle work.

These mechanics may explain many of the physiologic benefits of NIPPV, including an increase in lung compliance and FRC, a decrease of dynamic airway narrowing, augmentation of V_T and alveolar ventilation, and decreased work of breathing. Physiologic benefits of NIPPV in obstructive (e.g., asthma) and restrictive (e.g., PARDS) lung disease are schematically presented in Figures 86.8 and 86.9. Additional benefits result from improving cardiopulmonary interactions, especially LV afterload reduction, thereby improving cardiac output in patients with acute or chronic LV dysfunction.

NIPPV is often well tolerated and may be associated with fewer complications compared to invasive mechanical ventilation; airway trauma from endotracheal intubation can be avoided, and less sedation is required. Breaks can be given for the administration of oral medications and clearance of respiratory secretions, and selected stable patients can be fed by mouth. The rate of nosocomial infections, ventilator-associated pneumonia, and VILI is expected to decrease as well. In addition, aerosol therapy delivered by NIPPV appears to be more effective.

Complications of NIPPV include pressure injury, upper airway mucosal irritation, abdominal distention, aspiration, feeding intolerance, and pulmonary hyperinflation with resulting interstitial emphysema, pneumomediastinum, and pneumothorax. Patients initiated on NIPPV need close cardiorespiratory monitoring because the respiratory failure may progress, leading to the need for endotracheal intubation. Patients with more severe respiratory distress and those who do not show improvement of respiratory indices (i.e., respiratory rate, SpO_2/FIO_2 ratio, reduction in FIO_2) within 2 hours of initiation are more likely to require invasive ventilation. Patients with underlying severe systemic diseases such as sepsis, multiorgan dysfunction, and malignancies are less likely to respond favorably to NIPPV. Absolute contraindications include loss of airway reflexes, acute severe neurologic insults, cardiorespiratory arrest, and severe hemodynamic instability. Patients with midface abnormalities or facial trauma and burns should not be considered candidates for NIPPV. Other contraindications include the immediate postoperative period after facial and upper airway surgery, recent gastrointestinal surgery, or patients with bowel obstruction and vomiting. Patients who are severely agitated and confused should not be initiated on NIPPV. NIPPV has been shown to decrease intubation rates and reintubation rates after liberation from invasive mechanical ventilation, and has been increasingly used to treat acute or chronic respiratory failure in pediatric patients.

INVASIVE MECHANICAL VENTILATION

Mechanical ventilation involves considering the four phases of the respiratory cycle: (1) initiation of respiration and a variable that is controlled, often referred to as *mode;* (2) inspiratory phase characteristics, which determine the duration of inspiration and how the pressure or

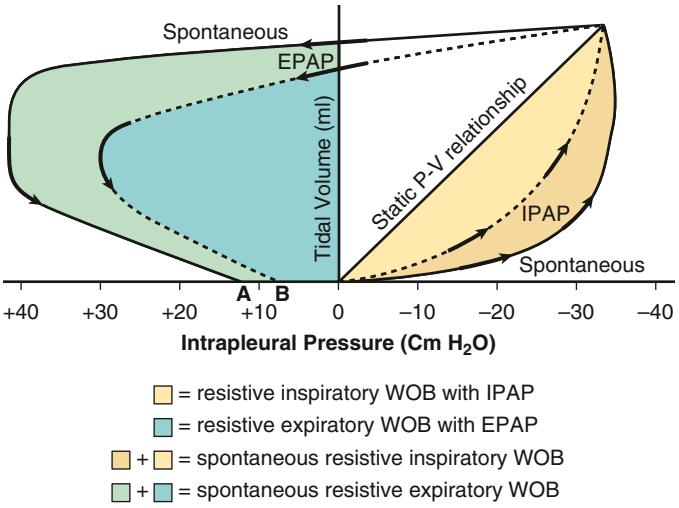

Fig. 86.8 Work of breathing (WOB) in status asthmaticus with and without noninvasive positive pressure ventilation. In the expiratory limb of the respiratory cycle, the equal pressure point is displaced distally, causing airways to begin to close at a higher lung volume (increased closing capacity), leading to dynamic hyperinflation, and auto–positive end-expiratory pressure (auto-PEEP). *(A),* Application of expiratory positive airway pressure (EPAP) stents the airways, reducing intrathoracic airway collapse, dynamic hyperinflation, auto-PEEP *(B),* and WOB. In the inspiratory limb, the patient needs to generate less negative pressure to initiate inspiration because of lower auto-PEEP. Inspiratory muscles are further unloaded by inspiratory positive airway pressure (IPAP) throughout inspiration for the given tidal volume. Both expiratory and inspiratory WOB are thus reduced by application of noninvasive positive pressure ventilation. P-V, Pressure-volume. *(From Sarnaik AA, Sarnaik AP. Noninvasive ventilation in pediatric status asthmaticus: Sound physiologic rationale but is it really safe, effective, and cost-efficient?* Pediatr Crit Care Med. *2012;13:484-485.)*

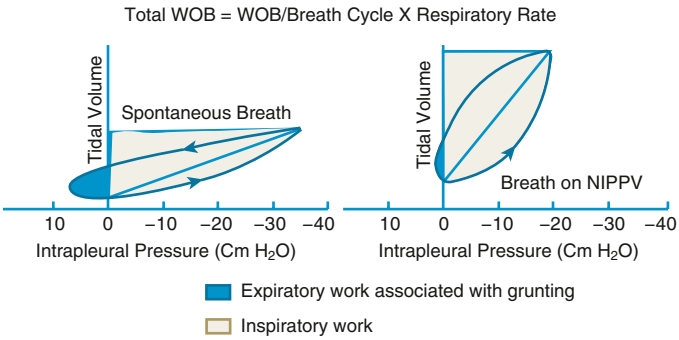

Fig. 86.9 Beneficial physiologic pulmonary effects of noninvasive positive pressure ventilation (NIPPV) in restrictive lung disease (e.g., ARDS). *Left,* Without NIPPV, the slope of pressure-volume relationship is flatter, resulting in lower tidal volume for a given inflation pressure and necessitating an increased respiratory rate to maintain required minute alveolar ventilation. Start of inspiration is at a lower lung volume, indicating decreased functional residual capacity (FRC). Expiration is active toward the end as a result of grunting aimed at increasing FRC. *Right,* On institution of NIPPV, the slope of the pressure-volume relationship is increased, resulting in greater tidal volume for a given inflation pressure, with a subsequent decrease in respiratory rate and inspiratory work of breathing (WOB). FRC is increased because of expiratory positive airway pressure (EPAP), resulting in improved oxygenation and decreased expiratory work associated with grunting.

volume is delivered; (3) termination of inspiration, often referred to as *cycle;* and (4) expiratory phase characteristics. Ventilation should not completely take over the work of breathing unless indicated in specific clinical conditions, such as in severe traumatic brain injury or pulmonary hypertensive crisis, but rather should assist the patient's own respiratory effort, if present.

Initiation of Inspiration and the Control Variable (Mode)

The initiation of inspiration may be set to occur at a predetermined rate and interval regardless of patient effort, or it could be timed in response to patient effort. Once inspiration is initiated, the ventilator breath either is controlled entirely by the ventilator *(control mode)* or supports the patient's inspiratory effort to a predetermined inspiratory volume or pressure target *(support mode).* Advances in technology allow for greater patient-ventilator synchrony to occur. The ventilator may be set to be *triggered* by the signal it receives as a result of patient effort. This feature may be in the form of lowering of either pressure *(pressure trigger)* or airflow *(flow trigger)* in the ventilator circuit generated by the patient's inspiratory effort. If no such signal is received because of lack of patient effort, the ventilator delivers a breath at an interval selected by the operator. Most ventilators make use of flow triggering.

Control Modes

Intermittent Mandatory Ventilation Mode. In intermittent mandatory ventilation **(IMV)**, inspiration is initiated at a set frequency with a timing mechanism independent of patient effort. In between machine-delivered breaths, the patient can breathe spontaneously from a fresh source of gas. IMV allows for adjustment of ventilator support according to the patient's needs, making it useful in the weaning process. Lack of synchrony between machine-delivered breaths and patient efforts may result in ineffective ventilation and patient discomfort, especially when IMV is delivered at a high rate. In such cases the patient may require sedation and pharmacologic neuromuscular blockade for efficient delivery of VT. To obviate this problem, **synchronized IMV (SIMV)** is preferred, whereby the machine-delivered breaths are triggered by the patient's inspiratory efforts (Fig. 86.10). In between the machine-delivered breaths, a fresh source of gas is available for spontaneous patient breaths. In the absence of patient effort, the patient receives a predetermined backup rate. Even with SIMV, ventilator-patient asynchrony can occur because VT, inflation pressure, and inspiratory time are determined by the ventilator alone.

Assist-Control Mode. In assist-control (AC) mode, every patient breath is triggered by pressure or flow generated by patient inspiratory effort and "assisted" with either preselected inspiratory pressure or volume. The rate of delivered breaths is therefore determined by the patient's inherent respiratory rate. A backup total (patient and ventilator) obligatory rate is set to deliver a minimum number of breaths. For illustration, on AC mode with a backup rate of 20 breaths/min and a patient's inherent rate of 15 breaths/min, the ventilator will assist all the patient's breaths and the patient will receive 5 additional breaths/min. On the other hand, a patient with an inherent rate of 25 breaths/min will receive all 25 breaths assisted. Although useful in some patients, the AC mode cannot be used in the weaning process, which involves gradual decrease in ventilator support.

Control Variable

Once initiated, either the VT or the pressure delivered by the machine can be controlled. The machine-delivered breath is thus referred to as either volume controlled or pressure controlled (Table 86.12). With **volume-controlled ventilation (VCV)**, machine-delivered volume is the primary control, and the inflation pressure generated depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance are therefore easily detected from changes observed in inflation pressure. In **pressure-controlled ventilation (PCV)**, the pressure change above the baseline is the primary control, and the VT delivered to the lungs depends on the respiratory system's C and R. Changes in respiratory system C and R do not affect inflation pressure and may therefore go undetected unless the exhaled VT is closely monitored. VCV and PCV have their own advantages and disadvantages (see Table 86.12). Favoring one mode over the other is largely driven by institutional preference and personal beliefs. VCV is characterized by a constant inspiratory flow with

a constant, preset VT, whereas PCV makes use of a decelerative flow pattern, with a variable delivered VT. A potential benefit of PCV is that the inspiratory pressures are limited, making it a more attractive mode in disease conditions where there is airway obstruction, preventing the normally compliant alveolus from being exposed to large VT. Generally speaking, PCV is more efficient than VCV in terms of amount of VT delivered for a given inflation pressure during ventilation of a lung that has nonuniform TC, as in asthma. In VCV, relatively less-obstructed airways are likely to receive more of the machine-delivered volume throughout inspiration than relatively more obstructed airways with longer TC (Fig. 86.11A). This situation would result in uneven ventilation, higher peak inspiratory pressure (PIP), and a decrease in C_{DYN}. In PCV, because of a constant inflation pressure that is held throughout inspiration, relatively less obstructed lung units with shorter TC would achieve pressure equilibration earlier during inspiration than the relatively more obstructed areas. Thus units with shorter TCs would attain their final volume earlier in inspiration, and those with longer TCs would continue to receive additional volume later in inspiration (see Fig. 86.11B). This situation would result in more uniform distribution of inspired gas, delivery of more VT for the same inflation pressure, and improved C_{DYN} compared with VCV.

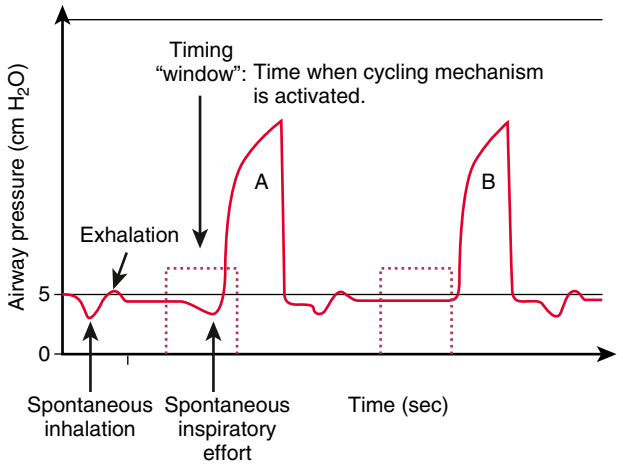

Fig. 86.10 Synchronized intermittent mandatory ventilation. At set intervals, the ventilator's timing circuit becomes activated and a timing "window" appears *(dashed line area)*. If the patient initiates a breath in the timing window, the ventilator delivers a mandatory breath *(A)*. If no spontaneous effort occurs, the ventilator delivers a mandatory breath at a fixed time after the timing window *(B)*. *(From Banner MJ, Gallagher TJ. Respiratory failure in the adult: Ventilatory support. In: Kirby RR, Smith RA, Desautels DA, eds.* Mechanical Ventilation. *New York: Churchill Livingstone;1985.)*

Pressure-regulated volume control (PRVC) combines the characteristics of VCV and PCV. In this mode, VT and TI are controlled as primary variables, but the ventilator determines the lowest amount of pressure needed to deliver the desired VT. Inflation pressure is thus continuously adjusted to deliver the prescribed VT over the TI, depending on the patient's respiratory C and R.

Support Modes

Pressure-support ventilation (PSV) and **volume-support ventilation (VSV)** are designed to support the patient's spontaneous respirations. With PSV, initiation of inspiration is triggered by the patient's spontaneous breath, which is then "supported" by a rapid rise in ventilator pressure to a preselected level. The inspiration is continued until the inspiratory flow rate falls to a set level (generally 25% of peak flow rate) as the patient's lungs inflate. Each inspiration is initiated and terminated by the patient, thus TI is controlled by the patient's own efforts. PSV has no backup rate, so a ventilator breath will not be delivered to the apneic patient. PSV can be combined with SIMV so that any breath above the SIMV rate is supported by PSV. Allowing the patient to control as much of the rate, VT, and inspiratory time as possible is considered to be a more comfortable form of mechanical ventilation than those in which the VT (or inflation pressure) and TI are preset. PSV as the sole source of mechanical ventilator support is often inadequate for patients with severe lung disease and those with a depressed respiratory drive, but may be especially useful in patients being weaned and in those who require mechanical ventilation for relatively minor lung disease or for neuromuscular weakness.

VSV is similar to PSV, in that all the spontaneous breaths are supported. In VSV, inspiratory pressure to support spontaneous breaths is adjusted to guarantee a preset VT goal. If there is a change in respiratory mechanics or patient effort, the inspiratory pressure to support the breath initiated by patient effort is automatically adjusted to achieve the set VT.

Inspiratory Phase Characteristics

Inspiratory flow waveform, TI, and pressure rise time can be adjusted in the inspiratory phase to suit the patient's respiratory mechanics.

In PCV the duration of TI is directly set in seconds. In VCV the TI can be adjusted by adjusting the inspiratory flow (volume/time) and/or setting an inspiratory pause before exhalation starts. Irrespective of ventilator mode, the choice of TI value depends on the respiratory rate, which determines the total duration of each breath, and on the estimation of inspiratory and expiratory TCs. Decreasing the flow rate delivery increases TI, and vice versa. With an increase in TI, the pulmonary capillary blood is exposed to a higher level of P_{AO_2} for a longer time. This feature is beneficial in diseases with decreased EELV, such as PARDS and pulmonary edema. An increase

Table 86.12 Characteristics of Pressure-Controlled and Volume-Controlled Methods of Ventilation

	PRESSURE-CONTROLLED VENTILATION	VOLUME-CONTROLLED VENTILATION
Control setting(s)	Inflation pressure Inspiratory time Rise time	Tidal volume Flow rate Inspiratory flow pattern (constant vs decelerating)
Machine-delivered volume	Depends on respiratory system compliance and resistance	Constant
Inflation pressure	Constant	Depends on respiratory system compliance and resistance
Endotracheal tube leak	Somewhat compensated	Leaked volume part of tidal volume
Distribution of ventilation	More uniform in lungs with varying time constant units	Less uniform in lungs with varying time constant units
Patient comfort	Possibly compromised	Possibly enhanced
Weaning	Inflation pressure adjustment required to deliver desired tidal volume	Tidal volume remains constant; inflation pressure automatically weaned

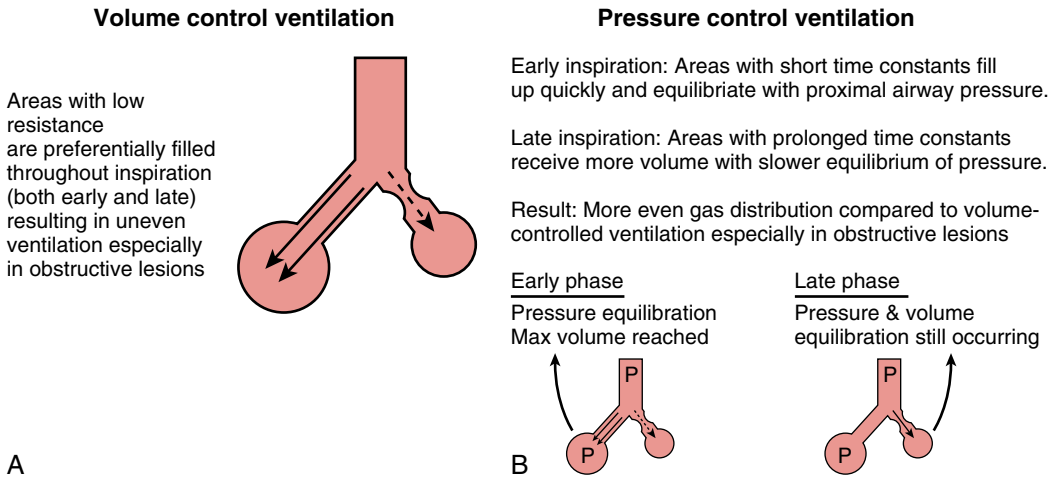

Fig. 86.11 A, In volume-controlled ventilation (VCV), tidal volume (V_T) is delivered to the less obstructed areas throughout inspiration. Obstructed areas of the lung therefore receive a lower proportion of V_T, resulting in uneven ventilation. B, In pressure-controlled ventilation (PCV), less obstructed areas equilibrate with inflation pressure and therefore receive most of their V_T early during inspiration. More obstructed areas, with prolonged time constants, require longer time for pressure equilibration and therefore continue to receive a portion of their V_T later during inspiration. The entire V_T is more evenly distributed than with volume-cycled ventilation.

in T_I also increases V_T without increasing inflation pressure in PCV if inspiratory flow is still occurring at end expiration. It must be recognized that at a given ventilator rate, an increase in T_I decreases expiratory time (T_E). Therefore any strategy that employs an increase in the inspiratory component of the respiratory cycle should ensure that the decreased T_E is still sufficient for complete exhalation.

Inspiratory flow waveform can be adjusted in VCV mode as either a constant flow (square waveform) or a decelerating flow (descending ramp waveform). With a square waveform, flow is held constant throughout inspiration. In a descending ramp waveform, flow is maximal at the start of inspiration and declines throughout its duration. It is debatable which flow pattern is better for a given disease.

In PCV and PSV, the prescribed PIP is reached through delivery of airflow. *Pressure rise time* reflects the time required for the ventilator to reach PIP and can be adjusted by control of flow at the beginning of the inspiratory phase. The inspiratory flow rise time may be adjusted to prevent too rapid a rise in inspiratory pressure, which can be uncomfortable for a patient who is awake and lead to dyssynchrony.

Termination of Inspiration (Cycle)

The two most commonly used inspiratory terminating mechanisms in control modes are time-cycled and volume-cycled. With a **time-cycled** mechanical breath, inspiration is terminated after a preselected T_I has elapsed, whereas with **volume-cycled** breath, the inspiration ends after a preselected volume has been delivered by the machine into the ventilator circuit. A time-cycled breath is almost always pressure-limited, with the PIP held constant for the duration of inspiration. A volume-cycled breath can be pressure-limited as a safety mechanism to avoid barotrauma. The inspiration-terminating mechanism is set somewhat differently in support modes. In PSV the inspiration is set to end after the inspiratory flow decreases below a certain percentage (usually 25%) of peak inspiratory flow. This happens when the patient no longer desires to receive additional V_T. Such a breath is termed **flow-cycled**. In VSV the inspiration is terminated when the patient has received the selected V_T.

Expiratory Phase Maneuvers

The most useful expiratory phase maneuver is the application of PEEP, which is applied to both the control breath and the assisted breath. The most important clinical benefits of PEEP are to stabilize recruited alveoli to increase EELV in patients with alveolar-interstitial diseases and thereby improve oxygenation. Any situation where there is zero end-expiratory pressure (ZEEP), as is the case when the patient is disconnected from the ventilator circuit (even if briefly), will result in alveolar **derecruitment** and decline in oxygenation. In patients with obstructive lesions in which insufficient exhalation results in air trapping and auto-PEEP, extrinsic PEEP (applied through a mechanical device) can prevent airway closure during expiration and improve ventilation. Other salutary effects of PEEP include redistribution of extravascular lung water away from gas-exchanging areas, improved $\dot{V}/\dot{Q}$ relationship, stabilization of the chest wall, and reduction in work of breathing in patients with intrinsic PEEP. The effect of PEEP on lung C is variable, depending on the level of PEEP provided and the patient's pulmonary mechanics. By shifting tidal ventilation to a more favorable part of the pressure-volume curve, PEEP may maintain more recruited alveoli, delay airway closure, and improve lung C. Excessive PEEP, on the other hand, may lead to overdistention of alveoli and reduced C. The effect of PEEP in individual patients can be ascertained by measuring exhaled V_T and calculating C_{DYN}. Other potentially deleterious effects of PEEP include decreased venous return, increased pulmonary vascular resistance, and decreased cardiac output.

ADDITIONAL VENTILATORY MODALITIES

Airway Pressure Release Ventilation

Airway pressure release ventilation (**APRV**) aims to improve oxygenation in patients with preserved respiratory drive suffering from severe hypoxemic respiratory failure due to alveolar-interstitial disease. This modality applies a CPAP, designated $CPAP_{HIGH}$, to recruit and maintain EELV with brief intermittent release phases of $CPAP_{LOW}$ to allow alveolar gas to escape. $CPAP_{HIGH}$ is analogous to PIP, and $CPAP_{LOW}$ is similar to setting PEEP. In contrast to the patient receiving conventional mechanical ventilation, a patient receiving APRV spends the majority of time in the $CPAP_{HIGH}$ phase, which may last as long as 3-5 seconds with a brief (0.3-0.5 seconds) time in the $CPAP_{LOW}$ phase. These atypically long T_Is are tolerated because of a floating expiratory valve in the ventilator circuit that permits spontaneous breathing during $CPAP_{HIGH}$ phase. Therefore even if the $CPAP_{HIGH}$ phase can be considered "inspiratory" and the $CPAP_{LOW}$ phase "expiratory" in regard to the ventilator, the patient is able to breathe spontaneously during both these phases. The longer ventilator T_I recruits lung units, and the ability to breathe spontaneously during this phase allows distribution of gas flow to atelectatic lung regions. The outcome benefit of APRV in pediatric hypoxemic respiratory failure has not been proven.

High-Frequency Ventilation

Mechanical ventilation at supraphysiologic rates and low V_T, known as high-frequency ventilation (**HFV**), improves gas exchange in a select group of patients who show no response to more traditional ventilatory modalities. The mechanism of alveolar ventilation in HFV is very different from that in conventional ventilation, in that HFV is less dependent

on VT and more dependent on asymmetric velocities and convective dispersion of inspired gas. Patients with severe persistent hypoxic failure are most likely to benefit from HFV. HFV is also helpful in patients with bronchopleural fistula and persistent air leaks. The main tenet of HFV is to recruit lung volume with a high mean airway pressure (MAP) and produce smaller fluctuations in alveolar pressure during inspiration and expiration, thus maintaining a satisfactory EELV and reducing alveolar stretch. The two most investigated techniques of HFV are HFOV and HFJV.

The most commonly used HFV modality is **high-frequency oscillatory ventilation (HFOV)**, which employs a mechanism to generate to-and-fro air movement. Additional air is drawn in (entrained) through a parallel circuit via a Venturi effect. Air is pushed in during inspiration and actively pulled out during expiration. The main determinants of oxygenation are F_{IO_2} and MAP, whereas ventilation is determined by changes in pressure (amplitude) around the MAP and frequency. The optimal frequency varies for the individual patient and disease process and depends on the so-called *corner frequency,* where the pressure cost of ventilation is the lowest. In PARDS this usually means frequency >8 Hz, irrespective of age.

In **high-frequency jet ventilation (HFJV)**, a high-frequency interrupter is interposed between a high-pressure gas source and a small cannula that is incorporated in the ETT. The cannula propels tiny amounts of gas (jets) at high velocity and high frequency through the ETT. An additional amount of gas is entrained from a parallel circuit. Unlike in HFOV, expiration occurs passively in HFJV as a result of elastic recoil of the lung and the chest wall. PEEP is set through the parallel circuit by a conventional ventilator in-line. Respiratory rate is generally set at 420 breaths/min. Major determinants of oxygenation are F_{IO_2} and PEEP, and the major determinant of ventilation is PIP.

CONVENTIONAL VENTILATOR SETTINGS

Fraction of Inspired Oxygen

The shape of the hemoglobin-O_2 dissociation curve dictates that oxygen content in the blood is not linearly related to P_{AO_2}. A P_{AO_2} value that results in an oxyhemoglobin saturation of ≤97% is reasonable in most situations, because a higher P_{AO_2} would cause minimal increase in arterial oxygen content, and a modest (10 mm Hg) drop in P_{AO_2} would result in minimal decrease in oxyhemoglobin saturation. In most cases, a P_{AO_2} value of >60 mm Hg is a reasonable goal. F_{IO_2} values that are higher than those necessary to attain oxyhemoglobin saturations of approximately 95% expose the patient to unnecessary oxygen toxicity. Whenever possible, F_{IO_2} values should be decreased to a level ≤0.40 as long as oxyhemoglobin saturation remains ≥92%. In patients with severe lung disease, oxyhemoglobin saturation of 88–92% may be acceptable.

Mode

The choice of mode of ventilation depends on the disease entity that is being treated and how much ventilator-patient interaction is desired. SIMV or AC is chosen as the control mode; PCV, VCV, or PRVC as the variable that is to be controlled; and pressure support and volume support are the choices for support modes. SIMV pressure-controlled modes are most commonly used in children.

Tidal Volume and Rate

As previously discussed, alveolar ventilation, the chief determinant of P_{ACO_2}, is calculated using VT, respiratory rate, and VD. A change in VT results in a corresponding change in alveolar ventilation without affecting VD-ventilation. A change in respiratory rate will affect alveolar ventilation and the VD-ventilation. Choice of VT and rate depends on the TC. In a patient with relatively normal lung compliance, an age-appropriate ventilator rate and a VT of 5-8 mL/kg would be appropriate initial settings. Diseases associated with decreased TC (decreased static compliance; e.g., PARDS, pneumonia, pulmonary edema) are best treated with small (4-6 mL/kg) VT and relatively rapid rates (e.g., 25-40 breaths/min). Diseases associated with prolonged TCs (increased airway resistance; e.g., asthma, bronchiolitis) are best treated with relatively slow rates and higher (10-12 mL/kg) VT. In PCV the delivered VT depends on the C and R of the patient's respiratory system and needs to be monitored to ensure the appropriate amount for a given situation. The operator titrates the inflation pressure, depending on the volume of exhaled VT. It should be emphasized that achieving a *normal* P_{ACO_2} value is not a goal of mechanical ventilation. Some degree of hypercapnia (permissive hypercapnia) should be accepted, especially when one is attempting to limit injurious inflation pressures or VT.

Inspiratory Time and Expiratory Time

TI and TE are adjusted by setting inspiratory flow rate and/or inspiratory pause in VCV and by setting the precise TI in PCV. Increasing the TI results in increased MAP, improved oxygenation in diseases with decreased EELV, and potentially a better distribution of VT in obstructive lung disease. Sufficient expiratory time must be provided to ensure adequate emptying of the alveoli.

Positive End-Expiratory Pressure

The best level of PEEP depends on the disease entity that is being treated, and it may change in the same patient from time to time. Decisions are often based on the P_{AO_2}/F_{IO_2} ratio and the measurement of C_{DYN}. For patients with PARDS, the adult-based $PEEP/F_{IO_2}$ grid may be useful.

PATIENT-VENTILATOR ASYNCHRONY

Patient-ventilator asynchrony occurs when the patient's respiratory pattern does not match that of the ventilator. This can occur during all phases of respiration. Adverse effects of patient-ventilator asynchrony include wasted effort, ineffective delivery of desired VT, excessive generation of intrathoracic pressure resulting in injury and adverse effects on cardiac output, increased work of breathing, and patient discomfort. Although several mechanisms exist to facilitate patient-ventilator synchrony, a certain amount of asynchrony is inevitable unless the patient is pharmacologically sedated and paralyzed.

Triggering the Ventilator

The patient must be able to trigger the ventilator without excessive effort. Ventilators can be pressure-triggered or flow-triggered. With **pressure triggering**, the inspiratory valve opens and flow is delivered when a set negative pressure is generated within the patient-ventilator circuit during inspiration. The amount of pressure required to trigger an inspiration depends on the pressure trigger sensitivity. In **flow triggering**, the ventilator provides a base flow of gas through the ventilator-patient circuit. When a flow sensor on the expiratory limb of the patient-ventilator circuit detects a decrease in flow as a result of the patient's inspiratory effort, the inspiratory valve opens and a ventilator breath is delivered. The degree of change in flow required to trigger an inspiration depends on the flow trigger sensitivity. Flow triggering is considered to be more comfortable, primarily because the patient receives some flow before triggering the ventilator, in contrast to pressure triggering, in which no flow is provided until the ventilator breath is triggered through generation of negative pressure. Increasing the trigger sensitivity by decreasing the change in either pressure or flow needed to trigger an inspiration decreases the work of breathing and may improve comfort. However, reducing the required pressure or flow excessively could result in accidental triggering and unwanted breaths by turbulence, caused by condensation in the ventilator circuit, endotracheal tube (ETT) air leaks, or cardiac oscillations.

Selection of Appropriate Inspiratory Time

The duration of TI should match the patient's own inspiratory phase. If TI is too long, the patient's drive to exhale may begin before the ventilator breath has cycled off. When this occurs, exhalation occurs against inspiratory flow and a closed exhalation valve, resulting in increased work of breathing, excessive rise in intrathoracic pressure, and discomfort. If TI is too short, the patient may be still inhaling without respirator support. In general terms, TI is usually initiated at 0.5-0.7 second for neonates, 0.8-1 second in older children, and 1-1.2 second for adolescents and adults, but should really be driven by the inspiratory TC. Adjustments need to be made through individual patient observations and according to the type of lung disease present. In patients with severe lung disease (both obstructive and restrictive), unnatural TI and TE values may have to be selected, as discussed earlier. In such situations, adequate analgesia, sedation, and, in extreme cases, neuromuscular blockade may be needed.

Selection of Inspiratory Flow Pattern

In VCV, inappropriate flow may be another source of patient-ventilator dyssynchrony. After initiation of inspiration, if the set amount of flow is

inadequate to meet patient demand, a state of **flow starvation** occurs, resulting in excessive work of breathing and discomfort. Such patients may require a decelerating inspiratory flow pattern, in which a higher flow is provided in the beginning of inspiration and less toward the end as the lungs fill up. On the other hand, such a pattern may be uncomfortable for a patient who desires more gradual alveolar filling. The selection of inspiratory flow pattern should be based on the individual patient's respiratory mechanics. In PCV and PSV, the inspiratory rise time determines the manner in which the airway pressure is raised and VT delivered. Considerations for choosing the appropriate rise time in PCV and PSV are similar to those for choosing the inspiratory flow pattern in VCV.

Use of Support Modes

A conscious patient should be allowed to have spontaneous breaths that are supported by either PSV or VSV. This approach minimizes the mandatory breaths generated by the ventilator that are beyond the patient's control to modulate. Therefore continued assessments should be made to determine whether the patient is able to maintain ventilatory requirements more in support modes and less in control modes.

Use of Sedation and Neuromuscular Blockade

Having a conscious yet comfortable patient is a desirable goal during mechanical ventilation. Spontaneous breaths with good muscle tone and presence of cough are important for adequate clearance of tracheobronchial secretions. The patient's ability to indicate distress is also important in identifying and preventing potential injurious factors. In certain situations, management of patient-ventilator asynchrony assumes much greater importance when the asynchrony is causing unacceptable derangement of gas exchange and VILI. Both alveolar interstitial lung pathology and obstructive airway diseases may necessitate unnatural and uncomfortable settings for respiratory rate, TI, and inflation pressures. In such patients, deep sedation is often necessary; dexmedetomidine, benzodiazepines, and opiates are the agents most commonly used for this purpose. In extreme situations, pharmacologic neuromuscular blockade is required to abolish any patient effort and respiratory muscle tone. When such pharmacologic paralysis is used, deep sedation must be ensured so that the patient does not sense pain and discomfort. Pharmacologic sedation and paralysis can ensure total control of the patient's ventilation by mechanical means and may result in lifesaving improvement in gas exchange with reduction in inflation pressures. However, long-term use of such agents may be associated with undesirable consequences and higher morbidity. The risk of inadequate clearance of tracheobronchial secretions and atelectasis is potentially greater. Long-term use of pharmacologic sedation may be associated with chemical dependency and withdrawal manifestations, and prolonged neuromuscular blockade is associated with neuromyopathy in critically ill patients. The benefits of sedation and pharmacologic paralysis therefore should be carefully balanced with the risks, and periodic assessments should be made to determine the need for their continuation.

Cardiopulmonary Interactions

Mechanical ventilation can have salutary and adverse effects on cardiac performance. By decreasing oxygen consumption necessary for work of breathing, oxygen supply to vital organs is improved. Positive pressure breathing decreases LV afterload, thus enhancing stroke volume and cardiac output in patients with a failing myocardium (e.g., myocarditis). On the other hand, the decreased systemic venous return may further compromise stroke volume in hypovolemic (preload-dependent) patients. Such patients will require intravascular fluid loading when subjected to positive pressure ventilation. Also, an increase in pulmonary vascular resistance (PVR) caused by positive intrathoracic pressure may result in further decompensation of a poorly performing right ventricle. PVR is at its lowest value at an optimum FRC. When FRC is too low or too high, PVR (and therefore the right ventricular afterload) is increased. Both desirable and undesirable effects of cardiopulmonary interactions may coexist and require ongoing assessment and necessary interventions (Table 86.13).

Table 86.13 Suggested Mechanical Ventilation Strategies in Various Clinical Situations

SITUATION	DISEASE	STRATEGY
Low compliance, normal resistance	ARDS	PCV, APRV, HFOV
Normal compliance, high resistance	Asthma	PCV, PRVC
Normal compliance, normal resistance, for weaning	Head trauma, drug overdose, subglottic stenosis	VCV

APRV, Airway pressure release ventilation; ARDS, acute respiratory distress syndrome; HFOV, high-frequency oscillatory ventilation; PCV, pressure-controlled ventilation; PRVC, pressure-regulated volume control; VCV, volume-controlled ventilation.

MONITORING RESPIRATORY MECHANICS

Exhaled Tidal Volume

Exhaled tidal volume (VTE) is measured by a pneumotachometer in the ventilator circuit during exhalation; in small children, it is preferably measured near the connection of the ETT. Measurement of VTE more accurately describes the VT that is contributing to the patient's alveolar ventilation. In PCV the VTE depends on the patient's respiratory system compliance and resistance and therefore offers valuable diagnostic clues. A decrease in VTE during PCV is indicative of either decrease in compliance or increase in resistance and is helpful in directing the clinician to appropriate investigation and management. An increase in VTE is indicative of improvement and may require weaning of inflation pressures to adjust the VTE.

Peak Inspiratory Pressure

In VCV and PRVC, the PIP is the secondary variable determined by the patient's respiratory system compliance and resistance. An increase in PIP in these modes is indicative of decreased C (e.g., atelectasis, pulmonary edema, pneumothorax) or increased R (e.g., bronchospasm, obstructed ETT). During VCV and PRVC, decreasing the respiratory rate or prolonging the TI will result in a lower PIP in patients with prolonged TCs because more time will be available for alveoli to fill. In such patients, a decrease in PIP (or plateau pressure when an inspiratory pause is set during VCV) suggests increased C or decreased R of the respiratory system.

Respiratory System Dynamic Compliance and Static Compliance

The changes in PIP (or plateau pressure) during VCV and PRVC, and in VTE during PCV, are determined by C_{DYN} of the respiratory system (lung and chest wall). C_{DYN} is calculated as follows

$$C_{DYN} = V_{TE} \div (PIP - PEEP)$$

C_{DYN} takes into account both the flow-resistive and the elastic properties of the respiratory system. Changes in C_{DYN} can be used to assess effects of different levels of PEEP as tidal ventilation is shifted along the slope of the volume-pressure curve (see Fig. 86.7). An increase in PEEP in alveolar-interstitial diseases (increased elastance), resulting in an increase in C_{DYN}, suggests alveolar recruitment, whereas a decrease in C_{DYN} may indicate overdistention. Similarly, in obstructive diseases (increased R), adjustment in PEEP levels to ameliorate airway collapse during exhalation can be guided by monitoring C_{DYN}. To assess only the elastic recoil of the lung, measurement of C_{STAT} when there is no airflow is required. This measurement is performed by using an inspiratory hold maneuver with the patient under neuromuscular blockade and observing pressure-time and flow-time waveforms (Fig. 86.12). During this maneuver, inspiratory flow ceases while the expiratory valve continues to remain closed, thus allowing pressure to equilibrate throughout the ventilator circuit and the patient's lungs. This pressure, referred to as the *plateau pressure* (P_{plat}), reflects alveolar pressure. C_{STAT} is calculated as follows:

$$C_{STAT} = V_{TE} \div (P_{plat} - PEEP)$$

The difference between C_{DYN} and C_{STAT} is attributable to airway resistance. This difference is minimal in alveolar-interstitial diseases but substantial in airway obstruction.

Assessment of Auto-PEEP

Auto-PEEP is assessed with the use of an expiratory pause maneuver in which inspiration is delayed and alveolar pressure is allowed to

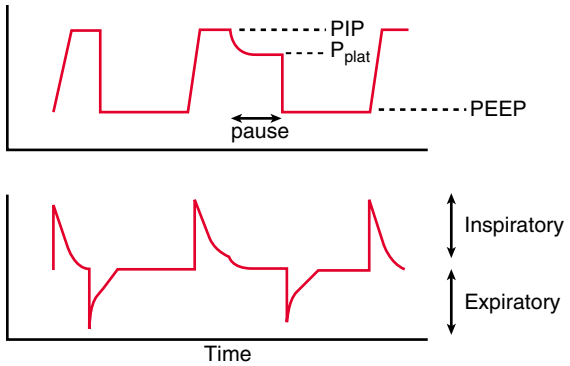

Fig. 86.12 Alveolar pressure is best determined by measurement of plateau pressure (P_{plat}). Inspiration is paused for an extended period, and alveolar gas pressure is allowed to equilibrate with the ventilator circuit pressure. Airway pressure at the end of the inspiratory pause is P_{plat}. The difference between peak inspiratory pressure (PIP) and P_{plat} is meant to overcome flow-resistive properties of the lung, whereas P_{plat} reflects the pressure needed to overcome elastic properties of the lung and chest wall. PEEP, Positive end-expiratory pressure.

equilibrate with the airway. In diseases with airway obstruction, insufficient alveolar emptying may occur if exhalation time is not adequate. The alveolar pressure in excess of the set PEEP at the completion of the expiratory pause is measured as auto-PEEP or intrinsic PEEP. Auto-PEEP can have adverse effects on ventilation and hemodynamic status. It can be managed by decreasing the respiratory rate or TI and thus allowing longer time for exhalation. Auto-PEEP may also be managed by increasing the set PEEP (*extrinsic* PEEP), thereby delaying airway closure during exhalation and improving alveolar emptying.

Assessment of Dead Space Ventilation

Positive pressure ventilation and application of PEEP may result in a decrease in venous return, cardiac output, and therefore pulmonary perfusion. Ventilation of poorly perfused alveoli results in dead space ventilation, which does not contribute to gas exchange. The VD/VT fraction can be calculated (see Chapter 86). Normal VD/VT is 0.33. Increased VD/VT is indicative of poorly perfused alveoli. Patients with increased VD/VT may require intravascular volume infusion or other means of augmenting the cardiac output to improve pulmonary perfusion. The VD/VT fraction is calculated and displayed by commercially available capnographs, which measure endotracheal $PetCO_2$ continuously.

VENTILATOR-INDUCED LUNG INJURY (VILI)

As with most medical therapies, mechanical ventilation can be harmful. Pathophysiology of VILI can be multifactorial. Large tidal volumes and high inspiratory pressures delivered with increased frequency cause cyclic strain, which may lead to disruption of the tight junctions between the alveolar epithelial and capillary endothelial cells, with intracapillary blebs resulting in alveolar and interstitial edema. This may cause the release of proinflammatory mediators (**biotrauma**) that further injure the lung and travel in the blood outside the lung, contributing to the development of multiorgan failure. Evidence shows that in patients with ARDS, avoidance of VT ≥10 mL/kg and P_{plat} ≥30 cm H_2O limits diffuse alveolar damage.

Atelectrauma is shear stress on the alveolar walls caused by cyclic opening and closing of the alveoli. PEEP can be used to prevent collapse and keep alveoli open. It is important that alveolar units are neither overdistended nor collapsed. Careful adjustments of PEEP may also permit the clinician to wean a patient from a high FIO_2, another potential source of lung injury, through exposure to reactive oxygen species (**oxytrauma**). Although most patients receive an FIO_2 of 1.0 at the time of endotracheal intubation and at the beginning of mechanical ventilation, increasing PEEP to recruit alveoli without overdistention should be quickly instituted to improve oxygenation and permit weaning of the FIO_2. Although the FIO_2 value below which there is no risk of oxygen toxicity is unknown, most clinicians aim for a value <0.6. Regional mechanics may play a role in lung injury.

Ventilator-Associated Pneumonia

The pathophysiology of ventilator-associated pneumonia (VAP) is multifactorial. Aspiration of oral and/or gastric secretions, colonization of the ETT, and suppression of cough reflexes from sedation all play a role. New-onset fever and leukocytosis accompanied by demonstration of an infiltrative process on chest radiography are consistent with a diagnosis of VAP. This complication can lead to worsened gas exchange, increased duration of ventilation, and even death. Elevation of the head of the bed to 30 degrees after initiation of mechanical ventilation and use of a protocol for oral decontamination during mechanical ventilation are common means of reducing the risk for VAP. The most effective strategy to minimize any of the aforementioned complications is regular assessment of extubation readiness and liberation from mechanical ventilation as soon as clinically possible.

Weaning

Weaning from mechanical ventilation should be considered as a patient's respiratory insufficiency begins to improve. Most pediatricians favor gradual weaning from ventilator support. With SIMV, the ventilator rate is slowly reduced, allowing the patient's spontaneous breaths (typically assisted with pressure or volume support) to assume a larger proportion of the minute ventilation. When the ventilator rate is low (<5 breaths/min) such that its contribution to minute ventilation is minimal, assessment of extubation readiness is performed. An alternative method of gradual weaning is transition to PSV. In this mode, no ventilator rate is set, allowing all triggered breaths to be assisted with pressure support. The clinician reduces the pressure support slowly to a low value (<5-10 cm H_2O), at which point assessment of extubation readiness is performed. During either technique, weaning should be halted if tachypnea, increased work of breathing, hypoxemia, hypercapnia, acidosis, diaphoresis, tachycardia, or hypotension occurs.

The most objective means of assessing extubation readiness is a **spontaneous breathing trial (SBT)**. Before performance of an SBT, a patient should be awake with intact airway reflexes, capable of handling oropharyngeal secretions, and with stable hemodynamic status. In addition, gas exchange should be adequate, defined as PaO_2 >60 mm Hg while receiving FIO_2 <0.4 and PEEP ≤5 cm H_2O. If these criteria are present, a patient should be started on CPAP with minimal (≤5 cm H_2O) or no pressure support. If this SBT is tolerated with no episodes of respiratory or cardiovascular decompensation, successful extubation is likely.

Some neonates and small children cannot be calmed or consoled long enough to complete the SBT. In this situation, extubation readiness must be assessed on a low level of ventilator support. Data suggest a low risk of extubation failure if the patient is comfortable and has stable hemodynamic status, with adequate gas exchange and spontaneous VT >6.5 mL/kg while receiving <20% of total minute ventilation from the ventilator. Certain patient populations are at increased risk for extubation failure, such as young infants, children mechanically ventilated for longer than 7 days, and patients with chronic respiratory or neurologic conditions. These children often benefit from transition to a noninvasive form of respiratory support (e.g., high-flow nasal cannula, CPAP, or BiPAP) upon liberation from mechanical ventilation to increase the odds of successful extubation.

The likelihood of **postextubation upper airway obstruction**, the most common cause of extubation failure in children, cannot be predicted by the results of an SBT or bedside measurements of physiologic variables. Traumatic endotracheal intubation and subglottic swelling from ETT irritation, especially in patients who exhibit agitation while receiving mechanical ventilation, are common causes of airway narrowing after extubation. Administration of intravenous corticosteroids (dexamethasone 0.5 mg/kg every 6 hr for four doses before extubation) has been shown to decrease the incidence of postextubation airway obstruction. In patients in whom postextubation airway obstruction develops, the need for reintubation may be obviated by administration of nebulized racemic epinephrine and helium-oxygen mixtures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

blood cells, which begin to appear in the circulation in 4 or 5 days. Hypoxemia also increases 2,3-DPG, resulting in a rightward shift of the oxyhemoglobin dissociation curve and favoring release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, raising Sao_2. Climbers at extreme altitude respond with marked hyperventilation, alkalosis, and leftward shift. This leftward shift favors oxygen loading in a hypoxic environment and increases Sao_2.

ACUTE MOUNTAIN SICKNESS

Epidemiology and Risk Factors

The incidence of high-altitude illness depends on several variables, including the rate of ascent, previous altitude exposure, and individual genetic susceptibility. Sleeping altitude, final altitude reached, and duration of stay at altitude are also risk factors for AMS development. Individual susceptibility for the development of AMS plays a significant role in risk assessment. Most individuals with previous histories of AMS after acute ascent are likely to experience similar symptoms with repeated visits to altitude. Gender and age do not affect the incidence of AMS.

AMS is very common with **rapid ascent**. Climbers around the world who ascend quickly (1 or 2 days) from sea level to altitudes of 4,000-6,000 m (~13,000-20,000 ft) have a very high incidence of AMS (27–83%). The rapid ascent profile associated with air travel to high altitude locations also results in high AMS rates. Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%). Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively moderate altitudes: 2,000-3,000 m (~6,500-9,800 ft). Among this population, AMS occurs in approximately 25%.

Pathophysiology

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally require several days of altitude exposure. Because hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness, but rather the initiating factor for a cascade of events that lead to the development of the altitude clinical syndromes.

The clinical manifestations of AMS/HACE are primarily the result of central nervous system (CNS) dysfunction caused by hemodynamic mechanical factors and biochemical mediators of permeability. The CNS vasodilatory response to hypoxemia causes an increase in cerebral blood flow and volume. Significant elevation of brain volume is observed in moderate to severe AMS and HACE but has not been demonstrated in mild AMS. Hypoxic alteration of CNS vascular autoregulation and hypertension from exercise may increase pressure transmission to the brain's capillary beds, resulting in transcapillary leakage and vasogenic edema. Inflammatory mediators also contribute to vascular permeability and edema formation. HIF-mediated vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation can increase permeability. Both mechanical and biochemical activation of the trigeminovascular system have been proposed as the cause of *high-altitude headache*, the primary symptom of AMS. Although vasogenic edema has been implicated in severe AMS and HACE, MRI reveals signal changes in subjects with and without clinical AMS.

Many of these responses to hypoxia and altitude exposure occur both in individuals who develop symptoms and those who remain free of AMS. To address the discrepancy in symptomatic illness, the "tight fit" hypothesis was proposed. This theory suggests that the development of AMS/HACE is due to a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude. The adequacy of the intracranial and intraspinal space to buffer changes in brain and cerebrospinal fluid (CSF) volume is the central concept. Buffering occurs as the intracranial CSF is displaced via the foramen magnum into the space available in the spinal canal, followed by increased CSF absorption and decreased CSF production. Individuals with less CSF buffering capacity have less compliance and are hypothesized to become more symptomatic (develop AMS).

Diagnosis

The diagnosis of AMS in older children and adults requires the history of a recent gain in altitude, presence at the new altitude for at least several hours, and the report of a headache plus one or more of the following symptoms: gastrointestinal (GI) upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness, or lightheadedness. The **2018 Lake Louise Acute Mountain Sickness Score** is based on self-report of symptoms and aids clinicians in making the diagnosis and quantifying AMS severity in older children and adolescents (Table 87.1). Symptoms develop within a few hours after ascent and generally reach maximum severity between 24 and 48 hours, followed by gradual resolution. Sleep disturbance caused by periodic breathing is common in all visitors to high altitudes and is not part of the adult diagnostic criteria; sleep disturbance is likely the result of hypoxia rather than AMS. There are no diagnostic physical signs in cases of mild AMS. Any evidence of CNS dysfunction, such as mild ataxia or altered mentation, is early evidence of HACE. Similarly, whereas shortness of breath on exertion is common at high altitudes, dyspnea at rest is an early indicator of HAPE.

Table 87.1 2018 Lake Louise Acute Mountain Sickness Score

HEADACHE
0 – None at all
1 – Mild headache
2 – Moderate headache
3 – Severe headache, incapacitating
GASTROINTESTINAL SYMPTOMS
0 – Good appetite
1 – Poor appetite or nausea
2 – Moderate nausea or vomiting
3 – Severe nausea and vomiting, incapacitating
FATIGUE AND/OR WEAKNESS
0 – Not tired or weak
1 – Mild fatigue/weakness
2 – Moderate fatigue/weakness
3 – Severe fatigue/weakness, incapacitating
DIZZINESS/LIGHTHEADEDNESS
0 – No dizziness/lightheadedness
1 – Mild dizziness/lightheadedness
2 – Moderate dizziness/lightheadedness
3 – Severe dizziness/lightheadedness, incapacitating
AMS CLINICAL FUNCTIONAL SCORE
Overall, if you had AMS symptoms, how did they affect your activities?
0 – Not at all
1 – Symptoms present, but did not force any change in activity or itinerary
2 – My symptoms forced me to stop the ascent or to go down on my own power
3 – Had to be evacuated to a lower altitude
To obtain the AMS score, add number from each category earlier. Although no official severity rankings exist, many consider mild AMS to be 3-5 points, moderate AMS 6-9 points, and severe AMS 10-12 points.

From Roach RC, Hackett PH, Oelz O, et al. The 2018 Lake Louise Acute Mountain Sickness Score. *High Alt Med Biol.* 2018;19(1):4–6, Table 1.

The diagnosis of AMS in children with early language skills (age 4-11 years) may be made with cautious use of the 2018 Lake Louise criteria (see Table 87.1). The language used in this adult questionnaire may be too complex and may underestimate AMS if not understood by the child. This is particularly true for questions regarding headache (the key symptom of AMS) and GI symptoms.

In preverbal young children and infants, recognition of AMS relies on observable signs and exclusion of other causes. In this age range, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance. In most cases of AMS in very young children, all these symptoms are present. Fussiness is defined as a state of irritability that is not easily explained by another cause, such as tiredness, wet diaper, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Decreased playfulness may be profound. Alterations of appetite may progress to frank vomiting. Sleep disturbance can manifest with either increased or decreased sleep when compared with normal patterns. Most often, decreased sleep and the inability to nap are noted.

The Children's Lake Louise Score (CLLS) has been successfully tested in preverbal children <4 years old by parents briefed on the use of the scoring system. The CLLS combines a score for the amount and intensity of unexplained fussiness with a symptom score of how well the child has eaten, played, and slept in the past 24 hours. Evaluating for the presence of headache can be accomplished by asking if the "head hurts" or by using a visual "faces" pain scale. GI symptoms are evaluated by asking children if they are "hungry" rather than trying to evaluate their appetite. A combined score of ≥7 is indicative of AMS (Fig. 87.1). Many of the symptoms manifested by AMS in children may also result from the disruption of the normal routine with travel. A change in environment, sleeping accommodation, or eating options can result in a fussy child. The threshold scores for AMS diagnostic criteria are modified to account for these baseline variations. Educating parents to recognize the symptoms of AMS in themselves is also important, as an ill parent can indirectly compromise a child's safety.

Other acute illnesses can mimic AMS in young children. *It must be emphasized that altered mental status, neurologic abnormalities, breathing difficulty, and cyanosis are not part of uncomplicated AMS.* **Any of these signs warrant immediate medical attention.** If serious bacterial illness, a surgical condition, or another problem meriting specific intervention is suspected in a child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

Periodic Breathing

Periodic breathing at altitude is common at all ages during sleep, resulting in brief repeated episodes of oxyhemoglobin desaturation. Prepubertal children (9-12 years old) have similar nighttime oxygen desaturations as their parents; however, they have somewhat more stable breathing patterns with less periodicity. Although periodic breathing is not a sign of AMS, the exacerbation of hypoxia during sleep plays a role in AMS development. Newborn infants normally have periodicity in their respiratory pattern, and this periodicity is increased by high-altitude exposure and sleep. Oxygen saturations of awake neonates born at 3,100 m (~10,100 ft) in Colorado range from 88% to 91%. During sleep with increased periodic breathing, oxygen saturation may drop to 81% during the first week of life. The amount and magnitude of respiratory periodicity decrease as the child matures, and saturation during sleep increases to 86% after 2 months. A stable mature pattern is usually reached by 6 months of age. Preterm babies may demonstrate marked periodicity with prolonged desaturation because of their immaturity. Acute ascent with a child born preterm is best delayed until maturity, when normal pulmonary function and respiratory drive can be demonstrated. Parents of normal young babies may become distressed as they note marked periodic breathing patterns in their child after ascent to moderate altitude. Clinicians can reassure parents that this is generally not a precursor of true apnea; desaturation can occur with periodic breathing in sleep, especially at higher altitudes.

Management

The management of AMS must include strict adherence to the principle that further ascent to a higher sleeping altitude is contraindicated after the symptoms of altitude illness occur. Halting ascent or activity to allow further acclimatization may reverse the symptoms; however, continuing the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. Stopping further ascent and waiting for acclimatization treats most AMS in 1-4 days. Mild cases of AMS may be treated without descent if monitoring by a reliable caregiver is available. Conservative treatment may be provided, including rest, analgesics for headache, and antiemetics for nausea. When conservative measures are inadequate, acetazolamide and/or oxygen titrated to maintain Sao_2 >94% are generally effective. Although no studies have formally assessed its use in pediatric patients, anecdotal reports have demonstrated efficacy of acetazolamide in treating mild AMS in this population. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention mandates descent. Descent (500-1,000 m, ~1,600-3,300 ft) is effective treatment for all forms of altitude illness and should be tailored to the individual response. The presence of neurologic abnormalities (e.g., ataxia or altered mentation) mandates descent because these signs indicate a progression of AMS to severe altitude illness (HACE).

Supplemental oxygen administration relieves AMS symptoms, including small amounts (1-2 L/min) given during sleep. In the wilderness, oxygen tanks are impractically heavy and are usually unavailable in adequate amounts; therefore oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. Hyperbaric therapy that simulates descent is also effective.

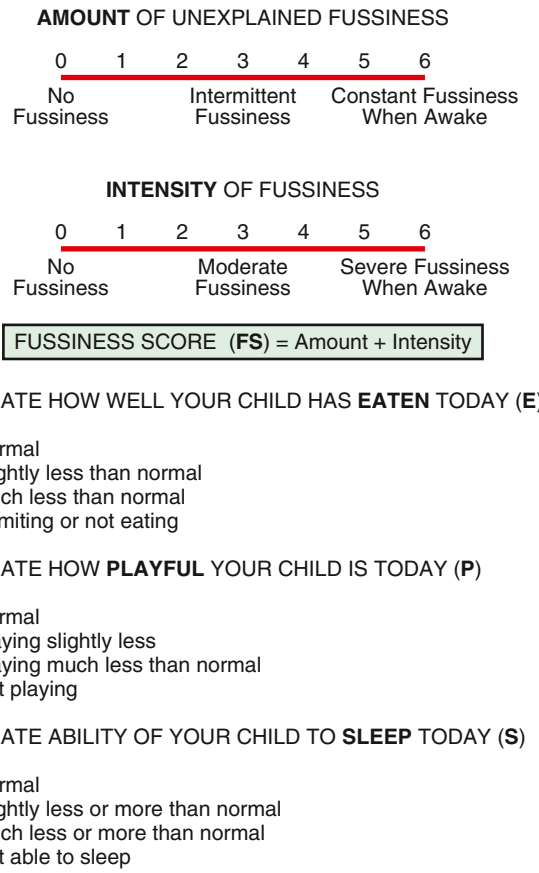

Fig. 87.1 Children's Lake Louise Score (CLLS). Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Please rate your child's typical fussy behavior *during the last 24 hours* without the benefit of your intervention.

Treatment of headache and nausea can be beneficial for mild AMS, and in many cases this may be all that is necessary. Evidence supports the use of ibuprofen and acetaminophen for the treatment of high-altitude headache in children; aspirin and combination products containing aspirin should be avoided in children because of possible association with Reye syndrome. For nausea and vomiting, ondansetron may be used.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. Acetazolamide accelerates acclimatization and, if given early in the development of AMS, rapidly resolves symptoms. Anecdotal experience supports the use of acetazolamide in children, particularly when conservative measures have been insufficient (Table 87.2). Treatment for 48 hours is usually adequate for resolution of symptoms. Acetazolamide may be prepared as a solution by a compounding pharmacy.

Adverse reactions to acetazolamide in adults include paresthesias, polyuria, and taste alterations for carbonated beverages. Less common reactions include nausea, drowsiness, tinnitus, transient myopia, and rarely, rash. Acetazolamide is a nonantibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics. A history of anaphylaxis or severe skin reactions to any sulfa-containing medication contraindicates the use of acetazolamide. Acetazolamide should be avoided in breastfeeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment for AMS in adults. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization, and symptoms may recur when the treatment is withdrawn. Adverse reactions to dexamethasone of concern in the pediatric population are pancreatitis, pseudotumor cerebri, and interference with normal growth. Although these reactions are generally seen with prolonged use, dexamethasone should be used for treatment in children only in extreme situations where alternatives such as descent or oxygen therapy are unavailable.

Prevention

Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical may consider prophylactic medication. *Acetazolamide remains the compound of choice for AMS prophylaxis.* Numerous studies have demonstrated its effectiveness in adults starting 24 hours before ascent and continuing for the first 2 days at high altitude. Controlled studies for prophylaxis with acetazolamide in children are unavailable; however, anecdotal evidence supports its use (see Table 87.2). Ibuprofen, when compared with acetazolamide, has been found to be equally efficacious in preventing headache in adults. Dexamethasone also prevents AMS; however, the potential adverse effects in children preclude its use for prophylaxis in this age group. Recommendations for hyperhydration are frequently given in the lay literature, yet no evidence supports this advice. Drinking excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

HIGH-ALTITUDE CEREBRAL EDEMA

Epidemiology and Risk Factors

HACE is rare and may occur in children. Prompt recognition and treatment are necessary, because if unrecognized, it is rapidly fatal. HACE is generally seen in adults with prolonged stays above 4,000 m (~13,000 ft), but in rare cases has been reported as low as 2,100 m (~6,900 ft). HACE is usually associated with concurrent AMS or HAPE, but can occur on its own.

Pathophysiology

HACE is regarded as the extreme expression of the same pathophysiology underlying AMS. The edema and increased intracranial pressure are believed to be primarily caused by a vasogenic process where fluid moves from the vascular to the interstitial space due to a combination of increased hydrostatic pressure and increased vascular permeability. In the later stages of HACE, a cytotoxic component may contribute to the edema. These proposed mechanisms are supported by MRI studies revealing white matter changes consistent with vasogenic and cytotoxic edema.

Diagnosis

HACE is differentiated from severe AMS by the presence of **neurologic signs**. Most common are ataxia and altered mental status, including confusion, progressive decrease in responsiveness, and eventually coma. Less common are focal cranial nerve palsies, motor and sensory deficits, and seizures. CT imaging is consistent with edema and increased intracranial pressure. MRI shows a high T2 signal in the white matter, specifically in the splenium of the corpus callosum, with diffusion-weighted technique.

Management

Descent remains the most effective treatment for HACE. Supplemental oxygen, if available, is useful, especially if descent is not possible or

Table 87.2 Medications for Treatment of Altitude-Associated Illness in Children*

MEDICATION	CLASSIFICATION	INDICATION	DOSE AND ROUTE	ADVERSE EFFECTS
Acetazolamide	Carbonic anhydrase inhibitor	AMS treatment	2.5 mg/kg PO every 12 hours; maximum 250 mg/dose	Collateral effects include paresthesias, altered taste and visual acuity, electrolyte disturbance
		AMS or re-entry HAPE prevention[1]	1.25 mg/kg PO every 12 hours; maximum dose 125 mg/dose	Collateral effects reduced at lower doses
Dexamethasone	Steroid	AMS or HACE treatment[2,3]	0.15 mg/kg PO/IM/IV every 6 hours; maximum 4 mg/dose	Hypertension, GI hemorrhage, pancreatitis, growth inhibition
Nifedipine	Calcium-channel blocker	HAPE treatment or prevention[4]	If > 50 kg use adult dosing of 30 mg extended-release PO every 12 hours	Flushing, gastrointestinal distress, hypotension
Amlodipine	Calcium-channel blocker	HAPE treatment or prevention[4,5]	*1-5 years:* 0.1-0.6 mg/kg/dose PO daily; maximum 5 mg/day *6-17 years:* 2.5-5.0 mg PO daily (tablet or liquid suspension)	Flushing, abdominal pain, dizziness, hypotension

*No studies in children for high-altitude indications.

[1]AMS prophylaxis is not routinely recommended in children but indicated when rapid ascent profile is unavoidable or previous altitude illness occurred in a child about to undergo similar ascent profile. AMS and re-entry HAPE prophylaxis should be started 24 hours before ascent and continued for 2 days at altitude.

[2]Oxygen and descent are the treatment of choice for severe AMS. If acetazolamide is not tolerated, dexamethasone may be used. Oxygen, descent and dexamethasone should be used in HACE.

[3]Prophylactic use of dexamethasone for AMS is not warranted because of potential adverse effects. Use slow graded ascent or acetazolamide.

[4]In emergency settings where oxygen and descent are not an option, amlodipine or nifedipine may be used for treatment. Extended-release (ER) nifedipine formulations cannot be broken to obtain smaller doses. If ≥ 50 kg, 30 mg extended-release nifedipine is preferred.

[5]Amlodipine offers advantages over nifedipine for small children because of once daily dosing and availability as liquid or appropriately sized tablet.

Adapted from Luks AM, Beidleman BA, Freer L et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention, Diagnosis and Treatment of Acute Altitude Illness: 2024 Update. *Wilderness Environ Med.* 2023;Oct 11:S1080-6032(23)00167-9.

delayed. Portable hyperbaric treatment is beneficial, but its use should not delay descent. Dexamethasone should be administered at a dose of 0.15 mg/kg per dose given orally every 6 hours to a maximum of 4 mg per dose (see Table 87.2). The few mild cases of HACE reported in children have recovered with dexamethasone *and* descent.

HIGH-ALTITUDE PULMONARY EDEMA

Epidemiology and Risk Factors

HAPE is a noncardiogenic pulmonary edema caused by intense pulmonary vasoconstriction and subsequent high capillary pressure, secondary to hypoxia, resulting in altered permeability of the alveolocapillary membrane and the extravasation of intravascular fluid into the extravascular space of the lung. The development of HAPE depends on factors affecting pulmonary vasoreactivity, rate of ascent, altitude achieved, and time spent at that altitude. HAPE generally occurs in the setting of recent ascent, most often at altitudes above 3,000 m (~9,800 ft), but in some cases at altitudes as low as 1,740 m (~5,700 ft). Among children HAPE occurs in 2 distinct settings. Most commonly, HAPE occurs in a child who resides at low altitude who travels to high altitude. Reentry HAPE affects children who reside at high altitude but become ill on their return home after descent to lower altitudes (see Special Considerations). HAPE may also occur with or without ascent in children who develop acute respiratory illnesses that exacerbate hypoxia at high altitude. Fatal outcomes of HAPE in children have been reported. Most mild and moderate cases resolve without difficulty; however, if unrecognized and untreated, rapid progression to death can occur, especially when infection or cardiac conditions complicate the illness.

HAPE affects male and female children more equally than adults, among whom the observed male predominance appears due to strenuous sport activities and military assignments. The occurrence, and even the pathophysiology, of HAPE may vary by population and genetic background. Several conditions may predispose a child to HAPE (Table 87.3). Preexisting viral respiratory infections have been linked to HAPE, especially in children. Cardiorespiratory conditions associated with pulmonary hypertension, such as atrial and ventricular septal defects, pulmonary vein stenosis, congenital absence of a pulmonary artery, and obstructive sleep apnea, also predispose to HAPE. Down syndrome is a risk factor for HAPE development, as are previously repaired congenital heart defects and the presence of hypoplastic lungs. Undiagnosed structural cardiopulmonary abnormalities may result in severe hypoxia and/or altitude illness once ascent occurs; for this reason, a new diagnosis of HAPE in a child warrants active investigation of underlying causes.

Table 87.3 Conditions Associated with Increased Risk of HAPE

ENVIRONMENTAL
Ascent above 2,500 m (~8,200 ft)
Rapid rate of ascent (generally >1,000 m [~3,300 ft] per day)
Cold exposure
CARDIAC
Anomalies causing increased pulmonary blood flow or increased pulmonary arterial pressure
• Ventricular septal defect, atrial septal defect, patent foramen ovale, patent ductus arteriosus
• Anomalous pulmonary venous return or pulmonary vein stenosis
• Unilateral absent pulmonary artery or isolated pulmonary artery of ductal origin
Coarctation of the aorta
Congestive heart failure
PULMONARY
Chronic lung disease
Bronchopulmonary dysplasia
Cystic fibrosis (FEV-1 <30% predicted)
Pulmonary hypoplasia
Supplemental oxygen requirement at sea level
Pulmonary hypertension
Perinatal respiratory distress
Persistent pulmonary hypertension of the newborn
Perinatal asphyxia or depression
Sleep apnea
INFECTIOUS
Upper respiratory tract infection
Bronchitis/bronchiolitis
Pneumonitis
Otitis media
PHARMACOLOGIC
Any medication causing central nervous system and respiratory depression
Alcohol
Sympathomimetics
SYSTEMIC
Down syndrome (trisomy 21)
History of premature birth or low birthweight

Physiology

Alveolar hypoxia results in vasoconstriction of the pulmonary arterioles just proximal to the alveolar capillary bed. Hypoxic pulmonary vasoconstriction is a normal physiologic response to optimize ventilation/perfusion ($\dot{V}/\dot{Q}$) matching by redistributing regional pulmonary blood flow to areas of highest ventilation, thereby optimizing arterial oxygenation. However, under conditions that result in widespread alveolar hypoxia, extensive pulmonary vasoconstriction will lead to significant elevations in pulmonary arterial pressure, and uneven pulmonary vasoconstriction can result in localized overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels. This explains the patchy and heterogeneous edema that is classically observed in HAPE. The combination of pulmonary hypertension and uneven pulmonary vasoconstriction appears to be necessary in the pathogenesis of HAPE. Children and adolescents acutely exposed to high-altitude hypoxia demonstrate pulmonary hypertension, with increases in pulmonary artery pressure inversely related to age. Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE.

The conditions that predispose to HAPE are often directly referable to elements in the cascade of pathophysiology. Viral infections result in inflammation that may predispose the pulmonary endothelium to mechanical injury and increase susceptibility to alveolar fluid accumulation and HAPE during ascent. Exercise and cold stress at altitude may increase hypoxemia and exacerbate pulmonary hypertension. Overperfusion of a restricted vascular bed is illustrated by cases of congenital unilateral absence of a pulmonary artery in which the entire cardiac output is delivered to one lung, predisposing to pulmonary hypertension and overperfusion injury. Although data from mechanistic studies of children are lacking, adult HAPE-susceptible subjects have been characterized as having significantly elevated pulmonary artery pressure during altitude exposure and illness, altered vascular permeability, augmented hypoxic pulmonary vasoreactivity during hypoxia and normoxic exercise, blunted hypoxic ventilatory responsiveness, smaller lung volumes, and impaired alveolar fluid clearance.

Diagnosis

The diagnosis of HAPE is based on clinical findings and their evolution in the context of recent ascent from lower elevation. There is no single diagnostic test or constellation of laboratory findings. Symptoms commonly develop within 24-96 hours, and onset of symptoms often occurs during the first or second night at altitude, when hypoxia may be exacerbated during sleep. HAPE is rarely observed beyond 5 days after ascent to altitude (unless additional ascent occurs) because pulmonary vascular remodeling and acclimatization have taken place. The diagnosis of HAPE is made by observing the combination of symptoms, including dyspnea at rest, cough, weakness, or decreased exercise performance, and signs including crackles or wheezing in at least one lung field, central cyanosis, tachypnea, or tachycardia. Determining the onset and timing of the illness relative to ascent and radiographic evidence of alveolar infiltrates may help confirm the diagnosis.

The symptoms of AMS and HAPE show considerable overlap, and AMS may precede the development of HAPE in approximately half of patients. Frequently patients with HAPE first exhibit general malaise, which may progress to more specific signs of cardiopulmonary distress. Young children may show agitation and general debility. Older children may complain of headache, and children of all ages frequently experience nausea and vomiting. Cough is a common pulmonary sign. Dyspnea at rest, orthopnea, cyanosis, tachycardia, and chest pain herald worsening compromise, which may advance within hours to production of pink-tinged sputum.

Findings on physical exam frequently are less severe than a patient's chest radiograph and the hypoxemia on pulse oximetry would predict. Children often appear pale, with or without visible cyanosis. Low-grade fever (<38.5°C) is common, and respiratory rate is generally increased. Auscultation typically reveals rales, usually greater in the right lung than the left, on presentation. The radiographic pattern of pulmonary edema can be highly variable, from patchy and peripheral to more homogeneous in severe cases. Often, the right lung shows more radiographic changes of edema than the left (Fig. 87.2). Cardiomegaly is an uncommon finding, but peribronchial and perivascular cuffing are frequent, as is enlargement of the pulmonary artery silhouette and dilation of more peripheral pulmonary arteries. Portable ultrasound has been shown useful to diagnose HAPE through the finding of "comet tails," artifacts created by microreflections of the ultrasound beam within interlobular septae thickened by interstitial and/or alveolar edema. Significant arterial oxygen desaturation, as measured by pulse oximetry, is a consistent finding, with saturations frequently below 75%. A complete blood count often reveals a leukocytosis with a left shift of the granulocyte series.

The differential diagnosis of HAPE includes viral and bacterial pneumonia, bronchitis/bronchiolitis, asthma, vaping-associated lung disease, and other forms of cardiogenic and noncardiogenic pulmonary edema as well as pulmonary embolism. HAPE is most frequently misdiagnosed as pneumonia or a viral respiratory illness, especially when suspicion of altitude-associated pathology is not appropriately high. The presenting signs of cough, dyspnea, and orthopnea, followed by sputum production, can easily be misinterpreted as pneumonia, an impression that is reinforced by the frequent accompaniment of low-grade fever. Respiratory viral infections increase the risk of developing HAPE, which may lead to further confusion in diagnosis.

Complications of HAPE in children often relate to underlying, sometimes undiagnosed, cardiopulmonary pathology or coexisting viral infections, which potentiate the severity of pulmonary edema and pulmonary hypertension. Acute altitude exposure in such circumstances may lead to severe presentations that progress rapidly to extreme hypoxemia or cardiac failure and death. Children with Down syndrome, with or without structural cardiac anomalies, show increased susceptibility to HAPE and rapid symptom progression. Neonatal respiratory distress with pulmonary hypertension has been linked to exaggerated hypoxic pulmonary vasoreactivity in early adulthood and thereby a theoretical predisposition to HAPE. Other conditions related to pulmonary overcirculation (atrial and ventricular septal defects, patent foramen ovale, patent ductus arteriosus), small cross-sectional area of the pulmonary vascular bed (unilateral absent pulmonary artery, pulmonary hypoplasia), obstruction to pulmonary venous return (total anomalous pulmonary venous return, pulmonary vein stenosis), or left-sided obstruction (coarctation of the aorta) potentiate HAPE. Recent inflammatory processes, such as viral infection, predispose to HAPE and may worsen hypoxemia. Infection with respiratory syncytial virus in particular may trigger severe pulmonary hypertension.

Management

Descent with supplemental oxygen is the treatment of choice for HAPE in children. When feasible, or in the absence of medical care, rapid descent of at least 500-1,000 m (~1,500-3,300 ft) usually results in rapid recovery. As with all altitude illness, the magnitude of the descent is tailored to the resolution of symptoms. Oxygen and bed rest without descent can be safe and effective treatment for mild HAPE in children where careful medical observation is available.

Supplemental oxygen at altitude is administered at 2-6 L/min by nasal cannula for 48-72 hours to maintain an arterial oxygen saturation of at least 90%. Increasing oxygen saturation above 90% does not result in further reduction in pulmonary artery pressure and does not accelerate edema resolution in adults. Oxygen flow can be weaned with improvement in symptoms and saturations; at flow rates below 2-4 L/min, children may be sufficiently stable and comfortable to continue treatment at home under the monitoring of family. Instructions to avoid physical exertion and exposure to cold should be given to reduce exposure to factors known to elevate pulmonary artery pressure. Most children experience complete resolution of mild HAPE within 24-72 hours of oxygen therapy when treated at the altitude of symptom onset.

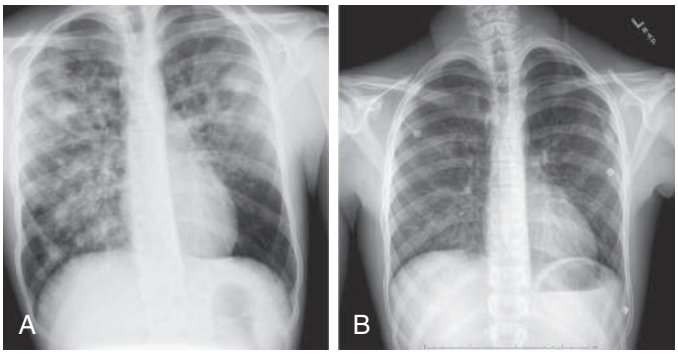

Fig. 87.2 High-altitude pulmonary edema (HAPE). A healthy teenager who resides at low altitude flew to Denver, Colorado, with a school group and immediately drove to a ski resort at 9,300 feet. The following day he felt dizzy and complained of headache. Symptoms progressed over the next 2 days to include emesis, dyspnea, cough, and fatigue. He was taken to an emergency department, where pulse oximetry showed an arterial saturation of 51%. Chest x-ray was obtained. **A,** This diagnostic image of HAPE was obtained at the altitude of presentation. The chest x-ray shows patchy, nodular infiltrates generalized through the right lung and the left upper lobe. The patient was started on supplemental oxygen and transported to Denver. Saturations improved with descent and were 94% on room air at time of arrival. **B,** Repeat radiograph obtained at lower altitude 2 days after presentation with HAPE. This diagnostic image shows substantial resolution of patchy pulmonary edema. *(Courtesy Children's Hospital Colorado, Department of Radiology.)*

Pharmacotherapy for pediatric HAPE is rarely needed because oxygen and descent are so effective. In emergency situations without the options of supplemental oxygen or descent, pharmacotherapy aimed at reducing pulmonary hypertension is indicated (see Table 87.2). Although not systematically studied in children, nifedipine is indicated for the treatment of adult HAPE. Amlodipine offers advantages over nifedipine in children because of daily dosing and availability of a liquid suspension. Patients should be monitored for hypotension during calcium channel blocker administration.

SPECIAL CONSIDERATIONS

Reentry HAPE and HAPE in High-Altitude Residents Without Travel

Children residing at high altitude may experience reentry HAPE upon reascent to the altitude of residence after a sojourn to low altitude. Although stays at low altitude as short as 24 hours may be sufficient to trigger reentry HAPE, most cases occur after several days at lower altitude. Several case series have demonstrated that children between 4 and 18 years of age are much more likely to develop reentry HAPE than adults. Observations from Colorado and Peru suggest that reentry HAPE may occur in 6–17% of children 2-19 years of age compared with <1–3% of adult residents. Various explanations have been proposed for the greater incidence and severity of reentry HAPE among children, including general lack of moderated behavior on ascent, increased likelihood of preexisting inflammatory processes, developmental differences in endothelial cell tight junctions, occult chronic pulmonary artery hypertension, and retained pulmonary arteriolar muscularity with potential for elevated pulmonary arterial pressure and potentially uneven pulmonary arterial vasoconstriction.

Reentry HAPE has a significant probability of recurrence and may justify pharmacologic prophylaxis to prevent the accumulated burden

of morbidity. There are no controlled trials of prophylaxis for reentry HAPE in children; however, acetazolamide has been used empirically (see Table 87.2), based on its blunting of hypoxic pulmonary vasoconstriction in adults and the potential risk of hypotension and reflex tachycardia with calcium channel blockers.

HAPE can also occur in children residing at high altitude without travel, and it should be considered in the differential diagnosis of children who present with hypoxemia at high altitude. The chest radiograph may be consistent with HAPE or viral pneumonia. When rapid improvement with oxygen and little to no response to bronchodilators suggest HAPE, the use of antibiotics and other treatments can be minimized.

Symptomatic High-Altitude Pulmonary Hypertension

Infants and young children residing at high altitude may experience symptomatic high-altitude pulmonary hypertension (SHAPH). All infants, regardless of altitude of gestation and birth, have thickened and muscularized interlobular and intralobular pulmonary arteries and pulmonary artery pressures that are initially near systemic. Although muscular regression and fall in pulmonary artery pressure occur rapidly at sea level, infants permanently residing at high altitude demonstrate slowed regression of these characteristics through infancy and even childhood. Similar changes may occur in infants who experience pulmonary complications at birth (respiratory distress syndrome of prematurity, persistent pulmonary hypertension of the newborn). Infants with SHAPH become symptomatic with exaggerated hypoxemia and signs of subacute pulmonary hypertension; these signs correlate with pathologic findings of right ventricular hypertrophy and dilation, increased muscularization of the pulmonary arterial bed, and eventual right-sided congestive heart failure. Although supplemental oxygen and medications may be used, definitive treatment is relocation to a lower altitude.

Cognitive Dysfunction

It is known that adults may have reversible changes in cognitive function with acute exposure to high altitude. A small study evaluating cognitive function in healthy 10- to 17-year-old children found impairment in verbal short-term memory, episodic memory, and executive functions 24 hours after ascent to 3,450 m (~11,400 ft). These findings were no longer present upon reassessment 3 months after returning to sea level. Similar results were found in children with permanent residence at high altitude; however, additional study is needed to assess the long-term implications of these findings.

Travel with Young Infants

Newborn infants retain some of the circulatory characteristics of recent fetal life, and these can pose a unique risk for altitude exposure. The fetal circulation has high pulmonary resistance, low pulmonary blood flow, and both intracardiac and extracardiac shunts that optimize oxygenation via the placenta instead of the fetal lungs. After birth, a transition begins that closes fetal shunts and establishes normal pulmonary circulation and oxygen transport. Exposure to marked hypoxia can result in reversion to fetal shunting patterns despite the absence of a placenta. Normal infants at sea level complete these changes in 4-6 weeks, though for infants born at moderate or high altitude, changes may last 3 months or longer. Travel to high altitude with young infants is generally safe after 4-6 weeks, when circulatory changes have occurred, breastfeeding is established, and congenital abnormalities may have been detected.

Air travel with young infants frequently raises questions about the effects of exposure to hypobaric hypoxia, as the pressurization of aircraft cabins may vary up to an altitude equivalent of 8,500 ft (~2,600 m). Even transoceanic flights are generally not long enough to trigger AMS or HAPE. However, infants may experience transient desaturation with feedings during flight and likely experience discomfort due to dry air and stress resulting from noise and vibration, much as adults do. Former preterm infants without chronic lung disease who have attained 3 months corrected gestational age do not appear to experience greater hypoxia during air travel than term infants; infants with more significant lung disease merit hypoxic challenge or provision of supplemental oxygen in flight.

Sickle Cell Disease/Trait

Children with sickle cell disease or sickle cell trait should avoid travel to altitude, as hypoxemia may trigger intravascular sickling, leading to acute vasoocclusive pain crises or splenic infarction or sequestration. Up to 20% of pediatric patients with sickle cell disease and sickle-thalassemia disease may experience a vasoocclusive crisis at moderate altitude or in pressurized aircraft. Oxygen is advised for air travelers with known sickle cell disease. Although many children with sickle cell trait remain asymptomatic, children can experience splenic ischemia or infarction with severe left upper quadrant pain.

Recommendations for High-Altitude Travel with Children

A comprehensive approach to travel to high altitude with children should focus on 3 phases: planning the ascent and assessment of risk, recognition and management of altitude-associated illness, and follow-up of any illness relative to future travel or diagnostic testing necessary. Planning for travel to high altitude with children should consider rate of ascent, formulation of an emergency plan for communication and evacuation, and availability of medical care at the high-altitude destination. Slow ascent with time for acclimatization is the best prevention for all forms of altitude illness. Ideally, the first night should not be spent at an altitude higher than 2,800 m (9,000 ft), and then 2-3 nights should be spent at 2,500-3,000 m (~8,200-9,800 ft), with a subsequent increase (to a new sleeping altitude) of not more than 500 m (1,600 ft) each night. One extra night of acclimatization (at the same sleeping altitude) should be taken for every 1,000 m (~3,300 ft) gained. Rapid ascent by air may be avoidable through alternative routes or means of transportation. Difficult descent situations (where further ascent may be necessary before descent is possible) should be avoided with children. Widespread coverage by cellular and satellite phone service may give a false sense of security in remote regions where both terrain and weather can limit the arrival of definitive help.

Prompt recognition of altitude-associated illness requires awareness of the context in which illness occurs and familiarity with the signs and symptoms. Parents are generally adept at recognizing deviation from baseline behavior of their children. Scales such as the Lake Louise Acute Mountain Sickness Score and CLLS may aid parents in modifying activity and/or seeking treatment. Clinicians should emphasize to parents that breathing difficulty, cyanosis, cough productive of pink-tinged sputum, altered mental status, and neurologic abnormalities are *not* part of uncomplicated AMS, but instead are serious signs of potential HAPE or HACE that deserve immediate medical attention.

Descent is the mainstay of therapy for all forms of altitude-associated illness in children. When descent is not feasible or illness is mild, other therapeutic options may be considered. Severe altitude illness or death can be avoided in children by adherence to three general principles:

1. Recognition of the early signs of altitude illness and willingness by adult caregivers to acknowledge them
2. No further ascent, especially to sleep at a higher altitude, when experiencing even minor symptoms/signs of altitude illness
3. Immediate descent if signs/symptoms worsen while resting/receiving treatment at the altitude of onset

Altitude-associated illness in children merits follow-up with the primary care physician. Uncomplicated AMS with full resolution of symptoms upon descent or treatment does not require diagnostic workup, but may prompt discussion of slower ascent, specific plans for treatment, or even prophylaxis for future travel. Signs of HAPE or severe hypoxemia in a child out of proportion to the altitude reached should prompt further diagnostic evaluation, including consideration of echocardiography. Underlying cardiac conditions may not be apparent on physical examination at low altitude; therefore cardiac catheterization or echocardiography under conditions of controlled hypoxia or hypoxic exercise may be necessary. Families of HAPE-susceptible children should be advised to avoid travel during or shortly after viral infections.

ACKNOWLEDGMENTS

The authors thank Dr. Dunbar Ivy and Dr. Deborah Liptzin for their careful review of the manuscript.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 88

Drowning and Submersion Injury

William Benjamin Prince

Drowning is the second most frequent cause of unintentional injury death among children in the United States after traffic accidents. Prevention is the most important step to reducing the impact of drowning injury, followed by early initiation of cardiopulmonary resuscitation (CPR) at the scene.

ETIOLOGY

Children are at risk of drowning when they are exposed to a water hazard in their environment. The World Congress on Drowning and the World Health Organization (WHO) definition of drowning is "the process of experiencing respiratory impairment from submersion/immersion in liquid." Drowning outcomes are classified as death, no morbidity, or morbidity further divided into moderately or severely disabled, vegetative state/coma, and brain death. Use of confusing descriptive terms such as "near," "wet," "dry," "secondary," "silent," "passive," and "active" should not be used.

EPIDEMIOLOGY

From 2010 to 2020, an average of 4012 people per year were victims of **fatal drowning**, and an estimated 8061 persons per year were treated in U.S. hospital emergency departments (EDs) for **nonfatal drowning**. Compared with other types of injuries, drowning has one of the highest case fatality rates and is in the top 10 causes of death related to unintentional injuries for all pediatric age-groups. In 2019, the highest drowning death rates were seen in children age 1-4 years (crude rate of 2.4 per 100,000); in children age 1-4 years, drowning was the number-one cause of death from *unintentional injury* in the United States in 2019 (Fig. 88.1). Rates of fatal drowning hospitalization declined by ~25% during the same period (Fig. 88.2).

The risk of drowning and the circumstances leading to it vary by age. Drowning risk also relates to other host factors, including male sex, alcohol or drug use, a history of seizures, autism, or cardiac arrhythmia, and swimming lessons. Environmental risk factors include exposure to water and varying supervision. These factors are embedded in the context of geography, climate, socioeconomic status, and culture.

Children <1 Year Old

Most (75%) drowning deaths in children younger than 1 year occur in the **bathtub**, when an infant is left alone or with an older sibling. Infant tub seats or rings may exacerbate the risk by giving caregivers a false sense of security that the child is safe in the tub. The next major risk to children <1 year is the large (5-gallon) household bucket. These buckets are approximately 30 cm (1 ft) tall and designed not to tip over when half-full. The average 9-month-old child tends to be top-heavy and thus can easily fall headfirst into a half-full bucket, become stuck, and quickly drown.

Children 1-4 Years Old

Drowning rates are consistently highest in 1- to 4-year-old children, likely because of their curious but unaware nature, coupled with the rapid progression of their physical capabilities. A common factor in many of these deaths is a lapse in adult supervision, often reportedly <5 minutes. Most U.S. drownings occur in residential **swimming pools**. Usually, the child is in their own home, and the caregiver does not expect the child to be near the pool.

In rural areas, children 1-4 years old often drown in irrigation ditches or nearby ponds and rivers. The circumstances are like those noted previously, in a body of water that is near the house. Drowning is one of the leading causes of *farm injury–related deaths* in children.

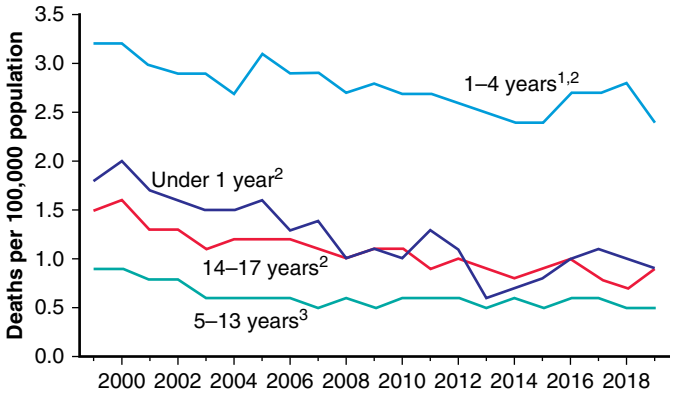

Fig. 88.1 Unintentional drowning death rates among children age 0-17 years, by age group: United States, 1999–2019. [1]Rates significantly higher than those for other age groups over the study period, $p < 0.05$. [2]Significant decreasing trend from 1999 through 2019, $p < 0.05$. [3]Significant decreasing trend from 1999 through 2005 $p < 0.05$; stable trend from 2005 through 2019.Notes: Unintentional drowning deaths are identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes W65–W74 Accidental drowning and submersion. Rates shown are crude rates (deaths per 100,000). Source: National Center for Health Statistics, National Vital Statistics System, Mortality. *(From Spencer MR, Hedegaard H, Warner M. Unintentional drowning deaths among children aged 0-17 years: United States, 1999-2019. NCHS Data Brief. 2021;413. Fig. 2.)*

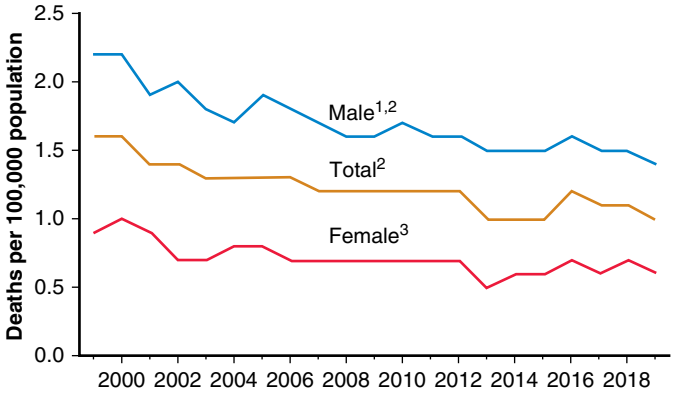

Fig 88.2 Unintentional drowning death rates among children age 0-17 years, by sex: United States, 1999–2019. [1]Rates significantly higher than those for females over the study period, $p < 0.05$. [2]Significant decreasing trend from 1999 through 2019, with different rates of change over time, $p < 0.05$. [3]Significant decreasing trend from 1999 through 2014; stable trend from 2014 through 2019, $p < 0.05$. Notes: Unintentional drowning deaths are identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes W65–W74 Accidental drowning and submersion. Drowning deaths totaled 756 in 2019 among children age 0-17 years. Rates shown are crude rates (deaths per 100,000). Source: National Center for Health Statistics, National Vital Statistics System, Mortality. *(From Spencer MR, Hedegaard H, Warner M. Unintentional drowning deaths among children aged 0-17 years: United States, 1999-2019. NCHS Data Brief. 2021;413, Fig. 1.)*

School-Age Children

School-age children are at increased risk of drowning in natural bodies of water such as lakes, ponds, rivers, and canals. Hazards such as unknown depths, undefined areas, and presence of currents and waves increase this risk. Although swimming pools account for most nonfatal drownings across all ages, **natural waterways** account for a higher death rate in children 10-19 years old. Unlike for preschool children,

swimming or boating activities are important factors in drowning injuries in school-age children.

Adolescents

The second peak incidence in drowning death rates occurs in older adolescents, age 15-19 years. Almost 90% drown in open water. In this age-group particularly, striking disparities in drowning deaths exist in gender and ethnicity. Drowning death is roughly twice as common for males when compared with females, but among adolescents, the rate is almost 10 times higher among males. The gender disparity may likely be related to males' greater exposure to aquatic environments, overestimation of swimming ability, underestimation of dangerous situations, increased risk-taking behavior, and greater alcohol use.

Dangerous underwater breath-holding behaviors (DUBBs) are often performed by experienced healthy swimmers or fitness enthusiasts (hypoxic training) or when teenagers hold breath-holding contests during horseplay. DUBBs have been primarily reported in regulated swimming facilities. Behaviors include intentional hyperventilation before submersion, static apnea, and extended periods of underwater distance swimming or breath-hold intervals.

Ethnic Disparities

There is significant ethnic disparity seen across drowning rates and causes. Among children age 0-19 years, the drowning rates from 2014 to 2018 are highest among Black (1.79 per 100,000) and Indigenous Nations people and Alaska Native (1.49 per 100,000) individuals. Rates are lower among White (1.06 per 100,000), Asian American and Pacific Islander (0.85 per 100,000), and Hispanic (0.82 per 100,000) individuals. Age dramatically influences drowning disparities. Black children drown at significantly higher rates than those for White and Hispanic children at every age from 5 to 18 years. Black children are more likely to drown in unguarded public pools, apartment pools, or hotel pools; White children are more likely to drown in private residential pools. Reasons for disparities in drowning rates may include cultural attitudes toward swimming, prohibitive cost and location of swimming lessons, fears about swimming, and lack of lifeguards at pools in many communities.

Underlying Conditions

Several underlying medical conditions are associated with drowning at all ages. **Epilepsy** is a known risk factor in drowning, with a relative risk for fatal and nonfatal drowning 7.5- to 10-fold higher than children without seizures. Drowning is the most common cause of death from unintentional injury for people with epilepsy. **Cardiac etiologies**, including arrhythmias, myocarditis, and prolonged QT or catecholaminergic polymorphic ventricular tachycardia syndromes, have been found in some children who die suddenly in the water, particularly in those with a family history of syncope, cardiac arrest, prior drowning, or QT prolongation. Exertion and fright while swimming can trigger arrhythmia among individuals with long QT and should be considered a possible cause for unexplained submersion injuries, particularly among proficient swimmers in low-risk settings (see Chapter 484.5).

Children with autism spectrum disorder (ASD) are at a significantly higher risk of drowning when compared with the general population; wandering was the most reported behavior leading to drowning in children with ASD. Children with muscle disease or peripheral neuropathies have an increased risk for drowning because of the degree of fatigability.

Drowning may also be an **intentional injury**. A history of the event that changes or is inconsistent with the child's developmental stage is the key to recognition of intentional drowning. Physical examination and other physical injuries rarely provide clues. **Child abuse** is more often recognized in bathtub-related drownings. **Suicide** usually occurs in lone swimmers in open water.

Alcohol Use

The use of alcohol and drugs greatly increases the risk of drowning. A meta-analysis found that 30–70% of swimming and boating fatal drowning victims have a measurable blood alcohol concentration. Alcohol can impair judgment, leading to riskier behavior, decreased balance and coordination, hypothermia, and blunted ability to self-rescue. Alcohol use while boating is also associated with low life jacket use. Furthermore, an intoxicated adult may provide less effective supervision of children around water.

Sports and Recreation

Most U.S. drowning deaths occur during recreational activities. Drowning is the leading cause of *noncardiac sports-related deaths*. Surveys confirm that not using a personal flotation device (PFD) is common during boating activities. In 2021 the U.S. Coast Guard reported that 83% of those who drowned in boating accidents were not wearing a PFD.

Global Impact of Drowning

Drowning injury is the third leading cause of unintentional death worldwide, with the majority (90%) of fatalities occurring in low- and middle-income countries. More than half of the global drowning occurs in the WHO Western Pacific and Southeast Asia regions. Global drowning rates are vastly underestimated, because many drowning deaths in this region go unreported, and many immediate fatalities are unrecognized. In addition, these data exclude any cases of drowning as the result of intentional harm or assault, accidents of watercraft or water transport, and drowning related to forces of nature or cataclysmic storms, which usually claim large numbers of lives per incident; thus true numbers of fatal drowning are likely much higher.

Some patterns of pediatric drowning are similar in all countries. By most accounts, the highest rates are seen in males and in children 1-4 years old. The predominant locations are near or around the home, involving bodies of water used for activities of daily living. These include water-collecting systems, ponds, ditches, creeks, and watering holes. In tropical areas, death rates increase during monsoon season, when ditches and holes rapidly fill with rain, and are highest during daylight hours, when caregivers are busy with daily chores.

Drowning during natural disasters such as **storms** and **floods** is important in all areas of the world. The largest numbers of reported flood-related deaths occur in developing nations; most are drownings that occur during the storm surge. In the United States and much of Europe, advances in weather monitoring and warning systems have reduced such deaths. U.S. flooding incidents, including hurricanes Katrina and Sandy, showed that drowning caused the most deaths, particularly when people became trapped in their vehicles, were unable or refused to evacuate homes, or attempted to rescue others.

PATHOPHYSIOLOGY

Drowning victims drown quickly and quietly and do not signal distress or call for help. Vocalization is precluded by efforts to achieve maximal lung volume to keep the head above the water or by aspiration leading to laryngospasm (Fig. 88.3). Young children can struggle for only 10-20 seconds and adolescents for 30-60 seconds before final submersion. The *instinctive drowning response* is a phenomenon where actual or perceived suffocation in water triggers autonomic nervous system responses resulting in unlearned, instinctive drowning movements. A swimmer in distress is vertical in the water, with arms extended to the side to lift the body up and bring the mouth above water to breathe. This splashing or efforts to breathe are often misconstrued by nearby persons as merely playing in the water, until the victim sinks.

Anoxic-Ischemic Injury

During drowning there is a period of voluntary breath-holding, typically less than 1 minute, before small amounts of water enter the hypopharynx, triggering laryngospasm as a protective reflex. There is a progressive decrease in arterial blood oxyhemoglobin saturation (Sao_2), and the person soon loses consciousness from hypoxia. Profound hypoxia and medullary depression lead to terminal apnea. Laryngospasm resolves, allowing additional fluid (water, stomach contents) into the lungs. At the same time, the cardiovascular response progresses to decreasing cardiac output and oxygen delivery to other organs. By 3-4 minutes, myocardial hypoxia leads to peripheral vasoconstriction, decreased cardiac output, and abrupt circulatory

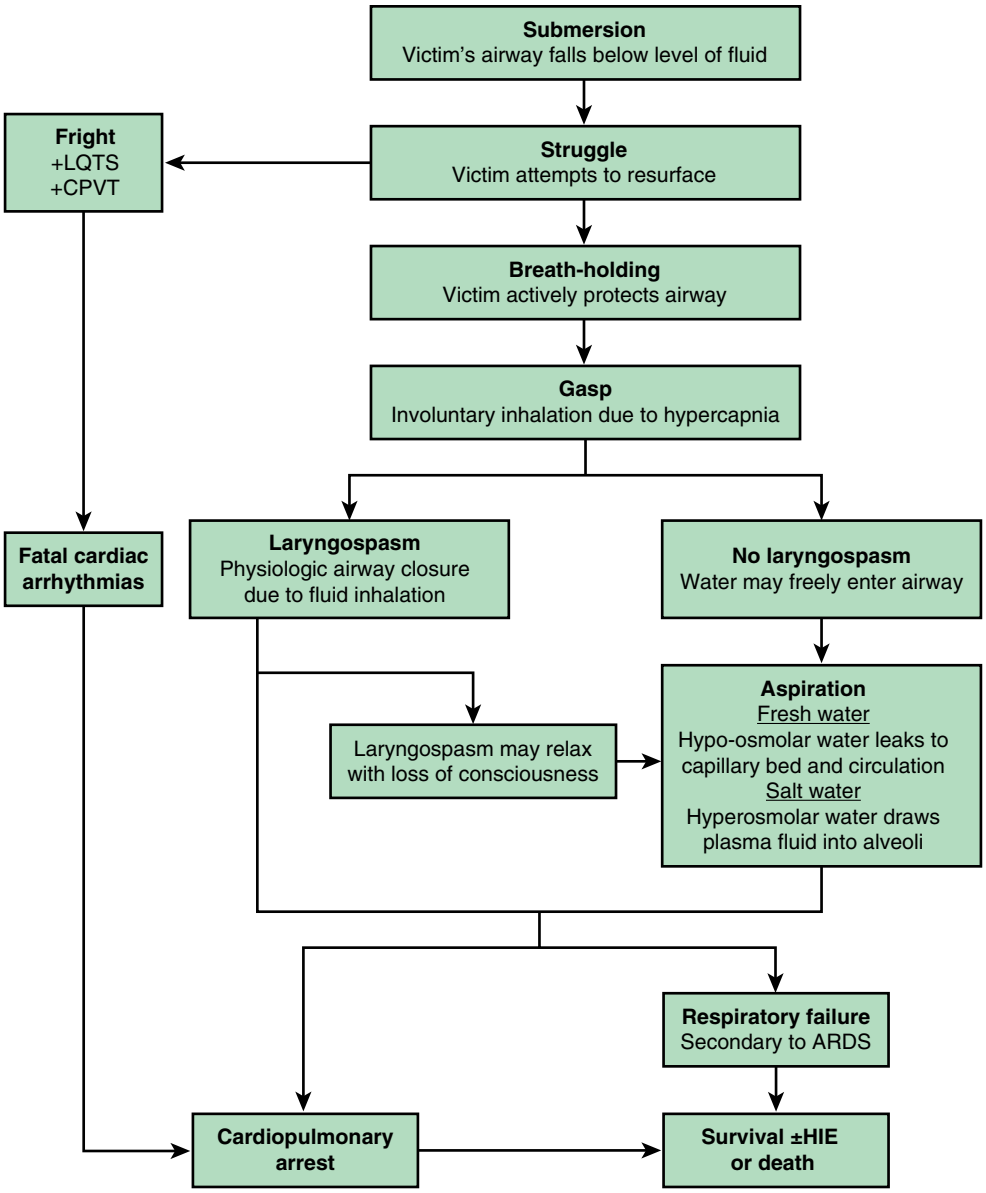

Fig. 88.3 Pathophysiologic events of the drowning process. LQTS, Long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; HIE, hypoxic-ischemic encephalopathy; ARDS, acute respiratory distress syndrome. *(Courtesy Andrew Schmidt, DO, MPH.)*

failure. Cardiac arrhythmias progress from tachycardia, to bradycardia, followed by ineffective cardiac contractions with electrical activity **(pulseless electrical activity)**. With early initiation of CPR, spontaneous circulation may initially be successfully restored. The extent of the global **hypoxic-ischemic injury** determines the outcome and becomes more evident over subsequent hours.

With modern intensive care, the cardiorespiratory effects of resuscitated drowning victims are usually manageable and are less often the cause of death than irreversible hypoxic-ischemic central nervous system (CNS) injury (see Chapter 82). CNS injury is the most common cause of mortality and long-term morbidity. Although the duration of anoxia before irreversible CNS injury begins is uncertain, it is probably on the order of 3-5 minutes. Submersion <5 minutes is associated with a favorable prognosis, whereas those >25 minutes are generally fatal.

Several hours after cardiopulmonary arrest, **cerebral edema** may occur, although the mechanism is not entirely clear. Severe cerebral edema can elevate intracranial pressure (ICP), contributing to further ischemia; intracranial hypertension is an ominous sign of profound CNS damage.

All other organs and tissues may exhibit signs of hypoxic-ischemic injury. In the lung, damage to the pulmonary vascular endothelium can lead to **acute respiratory distress syndrome** (ARDS; see Chapter 86). Aspiration may also compound pulmonary injury. Myocardial dysfunction, arterial hypotension, decreased cardiac output, arrhythmias, and cardiac infarction may also occur. Acute kidney injury, cortical necrosis, and renal failure are common complications of major hypoxic-ischemic events (see Chapter 572.1). Vascular endothelial injury may initiate disseminated intravascular coagulation, hemolysis, and thrombocytopenia. Many factors contribute to gastrointestinal damage; bloody diarrhea with mucosal sloughing may be seen and often portends a fatal injury. Serum levels of hepatic transaminases and pancreatic enzymes are often acutely increased. Violation of normal mucosal protective barriers predisposes the victim to bacteremia and sepsis.

Pulmonary Injury

Pulmonary aspiration occurs in many drowning victims, but the amount of aspirated fluid is usually small (see Chapter 446). Aspirated water does not obstruct airways and is readily moved into the

pulmonary circulation with positive pressure ventilation. More importantly, it can wash out surfactant and cause alveolar instability, ventilation-perfusion mismatch, and intrapulmonary shunting. The disruption of the alveolar capillary membrane leads to alveolar edema resulting in local ARDS-like syndrome.

In humans, aspiration of small amounts (1-3 mL/kg) can lead to marked hypoxemia and a 10–40% reduction in lung compliance. The composition of aspirated material can also affect the patient's clinical course: gastric contents, oropharyngeal flora, pathogenic organisms, toxic chemicals, and other foreign matter can injure the lung or cause airway obstruction. Aspiration is typically considered the source of pneumonia in cases of drowning, and antibiotics should be initiated based on radiographic evidence and clinical suspicion; no mortality benefit has been shown in those patients who received empiric or prophylactic antimicrobial therapy. Clinical management is not significantly different in saltwater and freshwater aspirations, because most victims do not aspirate enough fluid volume to make a clinical difference.

Cold Water Injury

Drowning should be differentiated from cold water **immersion** injuries, in which the victim remains afloat, keeping the head above water without respiratory impairment in cold waters. The definition of cold water varies from <15–20°C (<59–68°F).

Heat loss through conduction and convection is more efficient in water than in air. Children are at increased risk for **hypothermia** because of their relatively high ratio of body surface area (BSA) to mass, decreased subcutaneous fat, and limited thermogenic capacity. Body temperature may also continue to fall after removal from the water because of cold air, wet clothes, hypoxia, and hospital transport time. Hypothermia in pediatric drowning victims may be observed even after drowning in relatively warm water and in warm climates (see Chapter 90).

Immersion in cold water has immediate respiratory and cardiovascular effects. Victims experience **cold water shock**, a dynamic series of cardiorespiratory physiologic responses that can cause drowning. In adults, immersion in icy water results in intense involuntary reflex hyperventilation and a decrease in breath-holding ability to <10 seconds, which leads to fluid aspiration. Severe bradycardia, the *diving reflex*, occurs in adults but is transient and rapidly followed by supraventricular and ectopic tachycardia and hypertension. There is *no evidence* that the diving reflex has any protective effect.

Even after surviving the chaotic minutes of cold-water shock, after an additional 5-10 minutes of cold-water immersion, the victim can become incapacitated. Cooling of large and small muscles disables the victim's ability to grab hold, swim, or perform other self-rescue maneuvers. Severe hypothermia with body temperatures below 28°C (82.4°F) can lead to cardiac arrhythmia and asystole.

Depending on water and air temperature, insulation, BSA, thermogenic capacity, physical condition, swimming efforts, or high-water flow rates, heat loss with continued immersion can significantly decrease core temperature to hypothermic levels within 30-60 minutes.

The symptoms and severity of hypothermia are categorized based on body temperature. The victim with mild hypothermia has a core body temperature of 32–35°C (90–95°F) with intact thermogenic mechanisms (shivering and nonshivering thermogenesis, vasoconstriction) and active movements. Compensatory mechanisms usually attempt to restore normothermia at body temperatures >32°C (89.6°F). Lower core temperatures lead to impaired cognition, coordination, and muscle strength and, with it, less ability to self-rescue. Thermoregulation may fail, and spontaneous rewarming will not occur. With moderate hypothermia (28 to <32°C [82 to <90°F]), loss of consciousness leads to water aspiration. Progressive bradycardia, impaired myocardial contractility, and loss of vasomotor tone contribute to inadequate perfusion, hypotension, and possible shock. At body temperatures <28°C (82.4°F), extreme bradycardia is usually present with decreases in cardiac output, and the propensity for spontaneous ventricular fibrillation or asystole is high. Central respiratory center depression with moderate to severe hypothermia results in hypoventilation and eventual apnea. A deep coma, with fixed and dilated pupils and absence of reflexes at very low body temperatures (<25–29°C [77–84.2°F]), may give the false appearance of death.

If the cooling process is quick—and cardiac output lasts long enough for sufficient heat loss to occur before the onset of severe hypoxia—the brain can cool to a level that may be considered in the *neuroprotective* range, approximately 33°C (91.4°F) in controlled, experimental conditions. However, if submersion leading to drowning occurs before development of a neuroprotective level of hypothermia, severe anoxia devastates tissue organs. The theoretical benefits, implications, and consequences of hypothermia in drowning victims are areas of controversy. Known adverse effects are associated with hypothermia, and these must be balanced against the potential benefits observed in experimental data. One should clearly differentiate among **controlled hypothermia**, such as that used in the operating room before the onset of hypoxia or ischemia; **accidental hypothermia**, such as occurs in drowning, which is uncontrolled and variable, with onset during or shortly after hypoxia-ischemia; and **therapeutic hypothermia**, involving the purposeful and controlled lowering and maintenance of body (or brain) temperature after a hypoxic-ischemic event.

In drowning victims with uncontrolled accidental hypothermia associated with icy water submersion, there are isolated and rare reports of good neurologic recovery after prolonged (10-150 minutes) cardiopulmonary arrest. Almost all these rare survivors have been in freezing water (<5°C [41°F]) and had core body temperatures <30°C (86°F), often much lower. Presumably, very rapid and sufficiently deep hypothermia developed in these fortunate survivors before irreversible hypoxic-ischemic injury occurred. Intact neurologic functioning after sustaining a severe hypothermic submersion is likely associated with a combination of variables, including submersion times (most important), water temperature, immediate resuscitation, quality and duration of resuscitation, idioventricular bradycardia, and rewarming speed.

Most often, hypothermia is a poor prognostic sign, and a neuroprotective effect has not universally been demonstrated. A 2014 study from Washington State found that submersion duration <6 minutes is most strongly related to good outcome, not water temperature. In another study of comatose drowning patients admitted to the pediatric intensive care unit (PICU), 65% of hypothermic patients (body temperature <35°C [95°F]) died, compared with a 27% observed mortality rate in nonhypothermic victims. Thus a beneficial effect of drowning-associated hypothermia has not been seen in most pediatric submersion victims.

MANAGEMENT

Duration of submersion, speed of the rescue, effectiveness of resuscitative efforts, and clinical course determine the outcome in submersion victims (Fig. 88.4). Two groups may be identified based on responsiveness at the scene. The first group consists of children who require minimal resuscitation at the scene and quickly regain spontaneous respiration and consciousness. They have good outcomes and minimal complications. In awake, alert victims with hypoxemia, the first line of therapy is supplemental oxygen. These victims should be transported from the scene to the ED for further evaluation and observation. The second group comprises children in cardiac arrest who require aggressive or prolonged resuscitation and have a high risk of multiple organ system complications, major neurologic morbidity, or death. Compared with cardiac arrest from other causes, cardiac arrest from drowning has a higher survival rate.

Initial management of drowning victims requires coordinated and experienced prehospital care following the ABCs (airway, breathing, circulation) of emergency resuscitation. CPR of drowning victims must include providing adequate ventilation as the initial phase of respiratory arrest, as these children may still have intact circulation. However, this phase will progress to cardiac arrest if hypoxia persists. Children with severe hypoxic injury and symptoms often remain comatose and lack brainstem reflexes despite the restoration of oxygenation and circulation. Subsequent ED and PICU care often involve advanced life support (ALS) strategies and management of multiorgan dysfunction with discussions about end-of-life care.

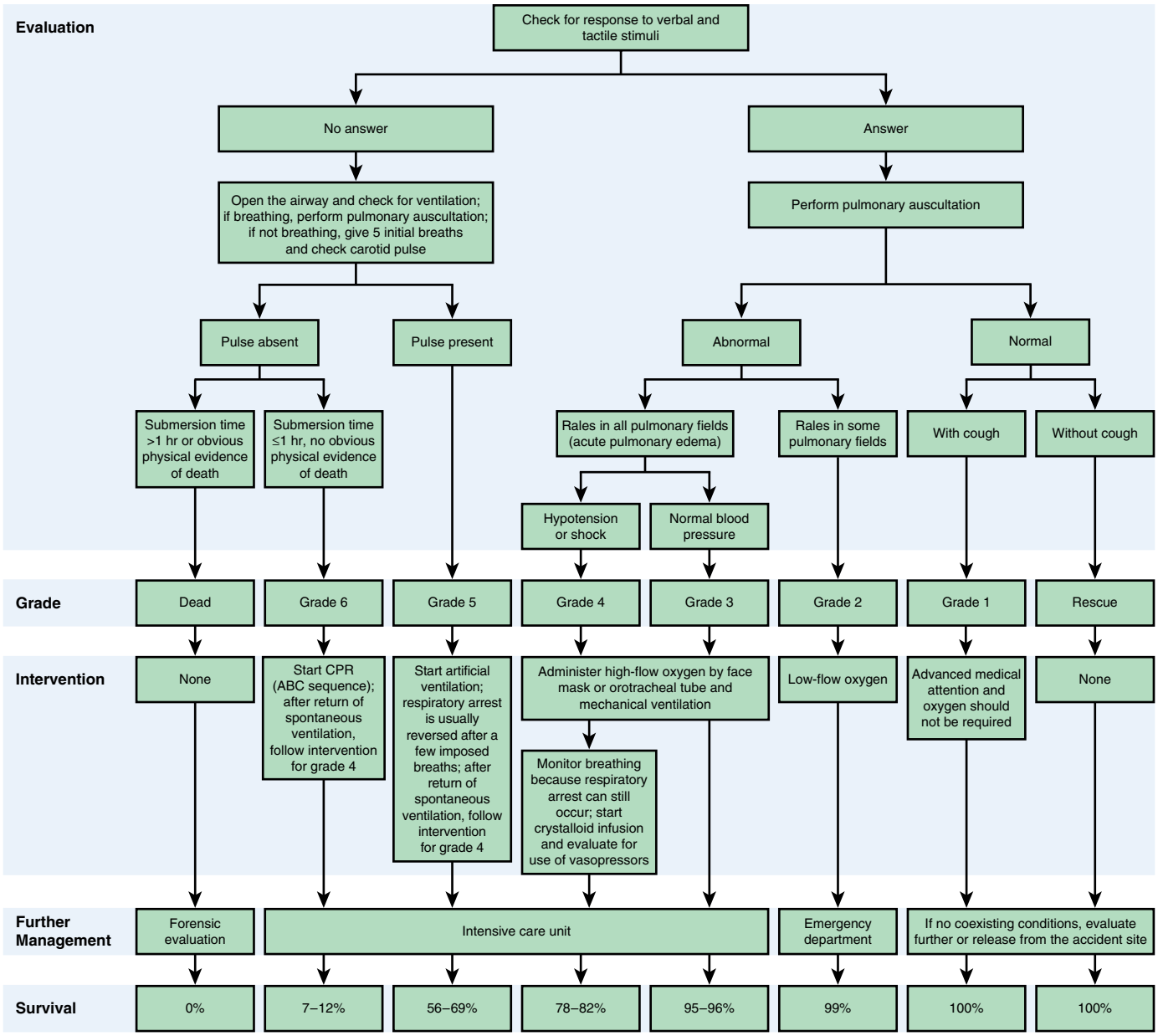

Fig. 88.4 Treatment of persons who have drowned, with classification system. *(From Szpilman D, Bierens J, Handley A, Orloweski J. Drowning. N Engl J Med 2012;366:2102–2110. Fig. 1.)*

Initial Evaluation and Resuscitation

See Chapter 79.

Immediate resuscitation at the submersion site, even before arrival of emergency medical services (EMS) personnel, is the most effective method to improve outcomes after drowning. Neurologic prognosis is significantly improved by prompt bystander CPR and activation of prehospital ALS. The goal is to reverse the anoxia from submersion and limit secondary hypoxic injury after submersion. Every minute that passes without the reestablishment of adequate breathing and circulation dramatically decreases the possibility of a good outcome. When safe for the victim and the rescuer, institution of in-water resuscitation for nonbreathing victims by trained personnel may improve the likelihood of survival. In-water resuscitation protocols recommend performing up to 1 minute of ventilation before attempting to bring the unconscious and apneic patient to shore. For patients in deep water, in-water resuscitation requires rescue flotation equipment or at least 2 rescuers. Practically, victims usually need to be extricated from the water as quickly as possible so that effective CPR can be provided.

Initial resuscitation must focus on rapidly restoring oxygenation, ventilation, and adequate circulation. The airway should be clear of vomitus and foreign material, which may cause obstruction or aspiration. Abdominal thrusts *should not* be used for fluid removal, because many victims have a distended abdomen from swallowed water; abdominal thrusts may increase the risk of regurgitation and aspiration. In cases of suspected airway foreign body, chest compressions or back blows are preferable maneuvers.

The cervical spine (C-spine) should be protected in anyone with potential traumatic neck injury (see Chapters 80 and 81). Cervical spine injury is a rare concomitant injury in drowning; approximately 0.5% of submersion victims have C-spine injuries, and history of the event and victim's age should guide suspicion of C-spine injury. Drowning victims with C-spine injury are usually preteens or teenagers whose drowning event involved diving, a motor vehicle crash, a fall from a height, a water sport accident, child abuse, or other clinical signs of serious traumatic injury. In such cases, the neck should be maintained in a neutral position and protected with a well-fitting cervical collar. Patients

rescued from unknown circumstances may also warrant C-spine precautions. In low-impact submersions, spinal injuries are exceedingly rare, and routine spinal immobilization is not warranted.

If the victim has ineffective respirations or apnea, ventilatory support must be initiated immediately. Mouth-to-mouth or mouth-to-nose breathing by trained bystanders often restores spontaneous ventilation. As soon as it is available, supplemental oxygen should be administered to all victims. Positive pressure bag-mask ventilation with 100% inspired oxygen should be instituted in patients with respiratory insufficiency. If apnea, cyanosis, hypoventilation, or labored respiration persists, trained personnel should perform endotracheal intubation as soon as possible. Intubation is also indicated to protect the airway in patients with depressed mental status or hemodynamic instability. Hypoxia must be corrected rapidly to optimize the chance of recovery.

Concurrent with securing of airway control, oxygenation, and ventilation, the child's cardiovascular status must be evaluated and treated according to the usual resuscitation guidelines and protocols. Heart rate and rhythm, blood pressure, temperature, and end-organ perfusion require urgent assessment. CPR should be instituted immediately in pulseless, bradycardic, or severely hypotensive victims, as studies have shown receiving bystander CPR is associated with neurologically favorable survival in all age groups. Continuous monitoring of the electrocardiogram (ECG) allows appropriate diagnosis and treatment of arrhythmias. Slow capillary refill, cool extremities, and altered mental status are potential indicators of shock (see Chapter 85).

Recognition and treatment of hypothermia are unique aspects of cardiac resuscitation in the drowning victim. Core temperature must be evaluated, especially in children, because moderate to severe hypothermia can depress myocardial function and cause arrhythmias. Wet clothing should be removed to prevent ongoing heat losses, although in the hemodynamically stable patient, rewarming should be initiated in the controlled environment of the receiving ED or PICU. Unstable patients (i.e., arrhythmias) should be warmed to 34°C (93.2°F), taking care not to overheat (see Chapter 90, Fig. 90.2).

Often, intravenous (IV) fluids and vasoactive medications are required to improve circulation and perfusion. Vascular access should be established as quickly as possible for the administration of fluids or pressors. Intraosseous catheter placement is a potentially lifesaving vascular access technique that avoids the delay usually associated with multiple attempts to establish IV access in critically ill children. Epinephrine is the initial drug of choice in victims with brady-asystolic cardiopulmonary arrest (IV dose is 0.01 mg/kg using the 1:10,000 [0.1 mg/mL] solution given every 3-5 minutes, as needed). Epinephrine can be given intratracheally (endotracheal tube dose is 0.1-0.2 mg/kg of 1:1,000 [1 mg/mL] solution) if no IV access is available. An intravascular bolus of lactated Ringer solution or 0.9% normal saline (10-20 mL/kg) is often used to augment preload; repeated doses may be necessary.

Hospital-Based Evaluation and Treatment

Most pediatric drowning victims should be observed for at least 4-6 hours, even if they are asymptomatic on presentation to the ED. Serial monitoring of vital signs and oxygenation by pulse oximetry, repeated pulmonary examination, and neurologic assessment should be performed in all drowning victims. Additional studies may also be warranted, depending on the specific circumstances (possible abuse or neglect, traumatic injuries, or suspected intoxication). Almost half of asymptomatic or minimally symptomatic alert children (who did not require ALS in the prehospital setting or who have an initial ED Glasgow Coma Scale [GCS] score of ≥13) experience some level of respiratory distress or hypoxemia progressing to pulmonary edema during the initial 4-6 hours after submersion. Most alert children with early respiratory symptoms respond to oxygen and, despite abnormal initial radiographs, become asymptomatic with a return of normal room-air pulse oximetry oxyhemoglobin saturation (Spo_2) and pulmonary examination by 4-6 hours. Subsequent delayed respiratory deterioration is extremely unlikely in such children. Low-risk patients who present with normal mental status and normal respiratory function may be considered for discharge after 4-6 hours of observation if there is no deterioration of respiratory symptoms and appropriate follow-up can be ensured.

Initial ED management of symptomatic patients with respiratory distress or lethargy may require further testing depending on clinical severity. Initial studies may include blood gas monitoring, a complete metabolic panel, a complete blood count, and chest radiography. Toxicology tests, including drug and alcohol levels, should be considered when appropriate.

There has been much misinformation about **dry drowning** and **secondary drowning**. These are misnomers and not accepted medical terms. Dry drowning has been described historically as cases in which no water was found in the lungs at autopsy. Secondary drowning has been used interchangeably to describe patients who clinically worsen due to pulmonary edema after aspiration of water. These terms cause harm by misdiagnosing cases of sudden death as drowning when there is an alternative diagnosis. They also cause confusion when describing and monitoring drowning events. Drowning victims with no or minimal clinical signs of distress will either improve or worsen within 4–6 hours, and patients will not unexpectedly die of drowning days or weeks later without preceding signs.

Cardiorespiratory Management

For children who are not in cardiac arrest, the level of respiratory support should be appropriate to the patient's condition and is a continuation of prehospital management. Frequent assessments are required to ensure that adequate oxygenation, ventilation, and airway control are maintained (see Chapter 86). Hypercapnia should generally be avoided in potentially brain-injured children. Patients with altered mental status, actual or potential hypoventilation, or markedly elevated work of breathing should receive mechanical ventilation to avoid hypercapnia and decrease the energy expenditures of labored respiration. Noninvasive ventilation (NIV) strategies such as bilevel positive airway pressure (BiPAP) and high-flow nasal canula (HFNC) have been associated with rapid improvement in the early phase of oxygenation in patients without altered mental status to reduce mortality.

Measures to stabilize cardiovascular status should also continue. Conditions contributing to myocardial insufficiency include hypoxic-ischemic injury, hypoxia, hypothermia, acidosis, high airway pressures during mechanical ventilation, alterations of intravascular volume, and electrolyte disorders. Heart failure, shock, arrhythmias, or cardiac arrest may occur. Continuous ECG monitoring is mandatory for recognition and treatment of arrhythmias (see Chapter 484).

The provision of adequate oxygenation and ventilation is a prerequisite to improving myocardial function. Patients should be given 100% inspired oxygen until oxygen saturation can be reasonably measured. Fluid resuscitation and inotropic agents are often necessary to improve heart function and restore tissue perfusion (see Chapter 79). Increasing preload with IV fluids may be beneficial through improvements in stroke volume and cardiac output. Overzealous fluid administration, however, especially in the presence of poor myocardial function, can worsen pulmonary edema.

For patients with persistent cardiopulmonary arrest on arrival in the ED after *non–icy water* drowning, the decision to withhold or stop resuscitative efforts can be addressed by review of the history and the response to treatment. Because there are reports of good outcome after ongoing CPR in the ED, most drowning victims should be treated aggressively on presentation. However, for children who do not show ready response to aggressive resuscitative efforts, the need for prolonged ongoing CPR after non–icy water submersion almost invariably predicts death or persistent vegetative state. Consequently, in most cases, discontinuation of CPR in the ED is probably warranted for victims of non–icy water submersion who do not respond to resuscitation within 25-30 minutes. Final decisions regarding whether and when to discontinue resuscitative efforts must be individualized, with the understanding that the possibility of good outcome is generally very low with protracted resuscitation efforts. In circumstances of severe ARDS or cardiac insufficiency, extracorporeal life support has been successfully employed.

Neurologic Management

Drowning victims who present to the hospital awake and alert usually have normal neurologic outcomes. In comatose victims, irreversible

CNS injury is highly likely. The most critical and effective neurologic intensive care measures after drowning are rapid restoration and maintenance of adequate oxygenation, ventilation, and perfusion. Core body temperature and glucose management are important modulators of neurologic injury after hypoxia-ischemia.

Comatose drowning patients are at risk for intracranial hypertension. There is little evidence that ICP monitoring and therapy to reduce intracranial hypertension improve outcomes for drowning victims. Patients with elevated ICP usually have poor outcomes—either death or persistent vegetative state. Children with normal ICP can also have poor outcomes, although less frequently. Conventional neurologic intensive care therapies, such as fluid restriction; hyperventilation; and administration of muscle relaxants, osmotic agents, diuretics, barbiturates, and corticosteroids, have not been shown to benefit the drowning victim, either individually or in combination. There is some evidence that these therapies may reduce overall mortality but increase the number of survivors with severe neurologic morbidity.

Seizures after hypoxic brain injury are common, although detection is often difficult in the ICU because these patients are frequently sedated. Continuous electroencephalographic (EEG) monitoring in critically ill patients revealed a 13% incidence of seizures, 92% of which were exclusively nonconvulsive. However, EEG monitoring has only limited value in the management of drowning victims, except to detect seizures or as an adjunct in the clinical evaluation of brain death (see Chapter 83). Seizures should be treated, if possible, to stabilize cerebral oxygen use, although benefits are inconclusive. Fosphenytoin or phenytoin (loading dose of 10-20 mg of phenytoin equivalents/kg, followed by maintenance dosing with 5-8 mg of phenytoin equivalents/kg/day in two or three divided doses; levels should be monitored) may be considered as an anticonvulsant; it may have some neuroprotective effects and may mitigate neurogenic pulmonary edema. Benzodiazepines, barbiturates, and other anticonvulsants may also have some role in seizure therapy, although no conclusive studies have shown improved neurologic outcome.

With optimal management, many initially comatose children can have impressive neurologic improvement, but usually do so within the first 24-72 hours. Unfortunately, half of deeply comatose drowning victims admitted to the PICU die of their hypoxic brain injury or survive with severe neurologic damage. Deeply comatose drowning victims who do not show substantial improvement on neurologic examination after 24-72 hours and whose coma cannot be otherwise explained should be seriously considered for limitation or withdrawal of support.

Additional Management Issues

Many drowning victims may have traumatic injury (see Chapter 80), especially if their drowning event involved participation in high-energy water sports such as personal watercraft, boating, diving, or surfing. A high index of suspicion for such injury is required. *Spinal precautions should be maintained in victims with altered mental status and suspected traumatic injury.*

Hypoxic-ischemic injury can have multiple systemic effects, although protracted organ dysfunction is uncommon in the absence of severe CNS injury. Hyperglycemia is associated with a poor outcome in critically ill pediatric drowning victims. Glucose control in patients after drowning should be focused on avoiding hypoglycemia, hyperglycemia, and wide or rapid fluctuations in serum glucose to prevent further harm.

Manifestations of acute kidney injury may be seen after hypoxic-ischemic injury (see Chapter 572). Diuretics, fluid restriction, and dialysis are occasionally needed to treat fluid overload or electrolyte disturbances; renal function usually normalizes in survivors. Rhabdomyolysis after drowning has been reported.

Profuse bloody diarrhea and mucosal sloughing usually portend a grim prognosis; conservative management includes bowel rest, nasogastric suction, and gastric pH neutralization. Nutritional support for most drowning victims is usually not difficult, because most children either die or recover quickly and resume a normal diet within a few days. Enteral tube feeding or parenteral nutrition is occasionally indicated in children who do not recover quickly.

Hyperthermia after drowning or other types of brain injury may increase the risk of mortality and exacerbate hypoxic-ischemic CNS damage. Almost half of drowning victims have a fever during the first 48 hours after submersion. Hyperthermia is usually not caused by infection and resolves without antibiotics in approximately 80% of patients. Generally, prophylactic antibiotics are not recommended. However, there is general consensus that fever or hyperthermia (core body temperature >37.5°C [99.5°F]) in comatose drowning victims resuscitated from cardiac arrest should be prevented at all times in the acute recovery period (at least the first 24-48 hours).

Psychiatric and psychosocial sequelae in the family of a pediatric drowning victim are common. Grief, guilt, and anger are typical among family members, including siblings. Divorce rates increase within a few years of the injury, and parents often report difficulties with employment or substance abuse. Friends and family may blame the parents for the event. Professional counseling, pastoral care, or social work referral should be initiated for drowning victims and their families.

Hypothermia Management

Attention to core body temperature starts in the field and continues during transport and in the hospital. The goal is to prevent or treat moderate or severe hypothermia. Damp clothing should be removed from all drowning victims. Rewarming measures are generally categorized as passive, active external, or active internal (see Chapter 90). **Passive rewarming measures** can be applied in the prehospital or hospital setting and include the provision of dry blankets, a warm environment, and protection from further heat loss. These should be instituted as soon as possible for hypothermic drowning victims who have not had a cardiac arrest.

Full CPR with chest compressions is indicated for hypothermic victims if no pulse can be found or if narrow complex QRS activity is absent on ECG (see Chapters 79 and 90). When core body temperature is <30°C (86°F), resuscitative efforts should proceed according to the American Heart Association guidelines for CPR, but IV medications may be given at a lower frequency in moderate hypothermia because of decreased drug clearance. When ventricular fibrillation is present in severely hypothermic victims (core temperature <30°C [86°F]), defibrillation should be initiated, but may not be effective until the core temperature is ≥30°C (86°F), at which time successful defibrillation may be more likely.

Significant controversy surrounds the discontinuation of prolonged resuscitative efforts in hypothermic drowning victims. Body temperature should be considered before resuscitative efforts are terminated. Other considerations include whether the victim may have been immersed before submerged, whether water was icy, or the cooling was very rapid with fast-flowing cold water. Victims with profound hypothermia may appear clinically dead, but full neurologic recovery is possible, although rare. Attempts at lifesaving resuscitation should not be withheld based on initial clinical presentation unless the victim is obviously dead (dependent lividity or rigor mortis). Rewarming efforts should usually be continued until the temperature is 32–34°C (89.6–93.2°F); if the victim continues to have no effective cardiac rhythm and remains unresponsive to aggressive CPR, resuscitative efforts can be discontinued.

Complete rewarming is not indicated for all arrest victims before resuscitative efforts are abandoned. Discontinuing resuscitation in victims of non–icy water submersion who remain asystolic despite 30 minutes of CPR is probably warranted. Physicians must use their individual clinical judgment about deciding to stop resuscitative efforts, taking into account the unique circumstances of each incident.

Once a drowning victim has undergone successful CPR after a cardiac arrest, temperature management should be carefully considered and body temperature continuously monitored. In victims in whom resuscitation duration was brief and who are awake soon after resuscitation, attempts to restore and maintain normothermia are warranted. Careful monitoring is necessary to prevent unrecognized worsening hypothermia, which can have untoward consequences.

For drowning victims who remain comatose after successful CPR, more contentious issues include rewarming of hypothermic patients and controlled application of therapeutic hypothermia. Although there is no evidence basis or opinion consensus, many investigators

cautiously recommend that hypothermic drowning victims who remain unresponsive because of hypoxic-ischemic encephalopathy after restoration of adequate spontaneous circulation should not be actively rewarmed to normal body temperatures. Active rewarming should be limited to victims with core body temperatures <32°C (89.6°F), but temperatures 32–37.5°C (89.6–99.5°F) should be allowed without further rewarming efforts.

More controversial is the **induction of therapeutic hypothermia** in drowning victims who remain comatose because of hypoxic-ischemic encephalopathy after CPR for cardiac arrest. *A specific recommendation for therapeutic hypothermia, especially in children, is not yet generally accepted.* The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (2002) did not recommend therapeutic hypothermia in drowned children resuscitated after cardiopulmonary arrest, citing insufficient evidence and older studies demonstrating a potential deleterious effect in pediatric drowning victims. Several subsequent studies evaluating extracorporeal membrane circulation, rewarming, and therapeutic hypothermia in pediatric and adult drowning patients have shown no significant improvement in neurologic outcome or mortality.

The Therapeutic Hypothermia After Out-of-Hospital Pediatric Cardiac Arrest (THAPCA) randomized controlled trial (RCT) investigators analyzed post hoc the findings of *targeted temperature management* (TTM) in pediatric comatose survivors of out-of-hospital cardiac arrest caused by drowning. Drowning comprised 28% of the landmark pediatric TTM (33°C vs 36.8°C) RCT, and the authors' principal observation is that targeting hypothermia, compared with targeting normothermia, did not result in better survival.

PROGNOSIS

The outcomes for drowning victims are remarkably bimodal: The great majority of victims either have a good outcome (intact or mild neurologic sequelae) or a poor outcome (severe neurologic sequelae, persistent vegetative state, or death), with very few exhibiting intermediate neurologic injury at hospital discharge. Subsequent evaluation of good-outcome survivors may identify significant persistent cognitive deficits. Of hospitalized pediatric drowning victims, 15% die and as many as 20% survive with severe permanent neurologic damage.

Strong predictors of outcome are based on the incident and response to treatment at the scene. Intact survival or mild neurologic impairment has been seen in 91% of children with submersion duration <5 minutes and in 87% with resuscitation duration <10 minutes. Children with normal sinus rhythm, reactive pupils, or neurologic responsiveness at the scene virtually always had good outcomes (99%). Poor outcome is highly likely in patients with deep coma, apnea, absence of pupil responses (fixed dilated pupils), and hyperglycemia in the ED; with submersion durations >10 minutes; and with failure of response to CPR given for 25 minutes. In one comprehensive case series, all children with resuscitation durations >25 minutes either died or had severe neurologic morbidity, and all victims with submersion durations >25 minutes died. Long-term health-related quality of life and school performance in those who had received either bystander- or emergency medical service personnel–initiated CPR were high if their submersion duration was <5 minutes. Higher morbidity, higher mortality, and lower quality of life were reported in patients with >10 minutes submersion duration. In several studies of pediatric drowning, submersion duration was the best predictor of outcome and water temperature was not. However, there are rare case reports of intact recovery after non–icy water drowning with longer submersion or resuscitation duration.

The GCS score has some limited utility in predicting recovery. Children with a score ≥6 on hospital admission generally have a good outcome, whereas those with a score ≤5 have a much higher probability of poor neurologic outcome. Improvement in the GCS score during the first several hours of hospitalization may indicate a better prognosis. Overall, early GCS assessments fail to adequately distinguish children who will survive intact from those with major neurologic injury.

Neurologic examination and progression during the first 24-72 hours are the best prognosticators of long-term CNS outcome. Children who regain consciousness within 48-72 hours, even after prolonged resuscitation, are unlikely to have serious neurologic sequelae. Laboratory and technologic methods to improve prognostication have not yet proved superior to neurologic examination. Serial neurologic evaluations after CPR should be performed over the ensuing 48-72 hours, with consideration given to limitation or withdrawal of support in patients who do not have significant neurologic recovery, even though this may occur before absolute prognostic certainty is achieved. Patients with minimal improvement during this initial period rarely show significant subsequent neurologic recovery despite aggressive resuscitation efforts and remain in a persistent vegetative state or die. Survivors with severe neurologic limitations necessitate neurorehabilitation to restore function and facilitate psychomotor development and prevent long-term damage caused by contractures, deformities, or scoliosis.

PREVENTION

The most effective way to decrease the injury burden of drowning is prevention. Drowning is a multifaceted problem, but several evidence-based preventive strategies are effective. The pediatrician has a prime opportunity to identify and inform families at risk of these strategies through anticipatory guidance. Advocacy should focus on anticipatory guidance regarding the appropriate supervision of children, access to swim lessons, presence of lifeguards, barriers to swimming pools, and use of PFDs. A family-centered approach to anticipatory guidance for water safety helps explore and identify the water hazards that each family is exposed to in their environment. The practitioner can then discuss the best tools and strategies for prevention that are relevant for the family. It is important to identify the risk both in and around the home and in other locations they may frequent, often when vacationing, such as vacation or relatives' homes. If the family recreates near or on open water, they also need to learn about safety around boats and open water. In a rural environment, water collection systems and natural bodies of water may pose great risk.

Parents must build layers of water protection around their children. Table 88.1 provides an approach to the hazards and preventive strategies relevant to the most common sources of water involved in childhood drowning. A common preventive strategy for exposure to all water types and all ages is ensuring **appropriate supervision**. Pediatricians should define for parents what constitutes appropriate supervision at the various developmental levels of childhood. Many parents either underestimate the importance of adequate supervision or are simply unaware of the risks associated with water. Even parents who say that constant supervision is necessary will often admit to brief lapses while their child is alone near water. Parents also overestimate the supervisory abilities of older siblings; many bathtub drownings occur when an infant or toddler is left with a child <5 years old.

Drowning most often occurs quickly and quietly during periods of inadequate supervision. Supervisory behavior is composed of three components: proximity, attention, and continuity. The caregiver must be alert, must not be consuming alcohol or other drugs or socializing, and must be attentive and focused entirely on watching the child. If the child cannot swim independently, *touch supervision* is required, meaning that the caregiver should always be within arm's reach. Adolescents require active adult supervision and avoidance of alcohol or drug use during water activities.

Learning to swim offers another layer of protection. Children may start swim lessons at an early age that are developmentally appropriate and aimed at the individual child's readiness and skill level. Swim lessons are beneficial and provide some level of protection to young children. A study from Bangladesh, where drowning accounts for 20% of all deaths in children age 1-4 years, showed that swim lessons and water safety curricula are cost-effective and led to a decrease in mortality from drowning. As with any other water safety intervention, parents need to know that swimming lessons and acquisition of swim skills cannot be solely relied on to prevent drowning. *No child can be drown-proof.* A supervising caretaker should be aware of where and how to get help and know how to safely rescue a child in trouble. Because only those trained in water rescue can safely attempt it, families should be encouraged to swim in designated areas only when and where a lifeguard is on duty.

Table 88.1 Approach to Prevention Strategies for Drowning

	HOME	RECREATION	NEIGHBORHOOD
Water hazards	• Swimming pools • Ponds • Bathtubs • Large buckets • Drain entrapment	• Playing in water (swimming, wading) • Playing near water • Being on water (boating)	• Irrigation ditches • Watering holes • Water drainage

Common risks	• Lapse in supervision
	• Unexpected toddler exposure
	• Delayed discovery of child
	• Reliance on water wings or pool toys
	• Reliance on sibling or bath seat for bathing supervision
	• Epilepsy
	• Autism
	• ADHD
	• LQTS
		• Lapse in supervision
		• Change in weather
		• Unfamiliarity with or change(s) in water conditions:
		  • Steep drop-off
		  • Current/tide
		  • Low temperature
		• Alcohol and other drug use
		• Peer pressure
			• Lapse in supervision, particularly when caregiver is socializing
			• Risky behavior when with peers

Prevention strategies	• Recognize hazards and risks • Provide constant adult supervision around water • Install 4-sided, isolation locked fencing of pools • Install rescue equipment and phone at poolside • Learn swimming and water survival skills • Avoid unsupervised baths in older child/teen with seizure disorder; instead, shower • Learn first aid and CPR	• Provide constant adult supervision • Swim in lifeguarded areas • Know when and how to wear US Coast Guard–approved PFDs • Avoid alcohol and other drugs • Learn swimming and water survival skills • Teach children about water safety • Be aware of current weather and water conditions • Buddy system • Learn first aid and CPR	• Identify hazardous bodies of water • Prevent access to water with barriers • Provide fenced-in "safe area" for water recreation • Provide lifeguarded swim sites • Provide access to low-cost swim/water survival lessons

ADHD, attention deficit hyperactivity disorder; CPR, cardiopulmonary resuscitation; LQTS, long QT syndrome; PFDs, personal floatation devices.

Children and adolescents should never swim alone regardless of their swimming abilities. Even as they become more independent and participate in recreational activities without their parents, they should be encouraged to seek areas that are watched by **lifeguards**. The United States Lifesaving Association (USLA) reports that more than 75% of drownings at USLA sites occurred at times when the beaches were unguarded. It is important to emphasize that even if the child is considered a strong swimmer, the ability to swim in a pool does not translate to being safe in open water, where water temperature, currents, and underwater obstacles can present additional and unfamiliar challenges. For swimmers, supervision by lifeguards reduces drowning risk, because lifeguards monitor risk behaviors and are trained in the difficult and potentially dangerous task of rescuing drowning victims.

Two of the preventive strategies listed in Table 88.1 deserve special mention. The most vigorously evaluated and effective drowning intervention applies to swimming pools. Compared with no fencing, installation of four-sided **isolation fencing** surrounding in-ground and aboveground pools with a secure, self-locking gate decreases the number of pool immersion injuries among young children by more than 50%. Guidelines for appropriate fencing, provided by the U.S. Consumer Product Safety Commission (CPSC), are very specific; they were developed through testing of active toddlers in a gymnastics program on their ability to climb barriers of different materials and heights, and recent studies show them to be effective in preventing drowning in young children. In families who have a pool on their property, caregivers often erroneously believe that if a child falls into the water, there will be a loud noise or splash to alert them. Unfortunately, these events are usually silent, delaying timely rescue. This finding highlights the need for a fence that separates the pool from the house, not just surrounds the entire property. The CPSC recommends power safety covers be installed on pools, as well as door alarms if the pool is not completely separated from the house and the yard by a fence. Entrapment and hair entanglement in open drains or pipes are other risks commonly associated with drowning in the pediatric population; special drain covers, safety vacuum release systems, and filter pumps with multiple drains can help prevent this.

The use of U.S. Coast Guard–approved **lifejackets or PFDs** should be advised with all families spending time around open water, not just those who consider themselves boaters. A PFD should be chosen with respect to the weight of the child and the proposed activity. Young children should wear PFDs that will float their head up. Parents should be urged to wear PFDs as well, because their use of PFDs is associated with greater use by their children. Toys such as water wings and "floaties" should not be relied on as drowning prevention measures. The use of life jackets decreases boat-related drowning morbidity and mortality by 50%; unfortunately, their use remains low.

Effective preventive efforts must also consider **cultural practices**. Different ethnic groups may have certain attitudes, beliefs, dress, or other customs that may affect their water safety. The higher drowning risk of minority children needs to be addressed by community-based prevention programs.

In addition to anticipatory guidance, pediatricians can play an active role in drowning prevention by participating in advocacy efforts to improve legislation for pool fencing, PFD use, and alcohol consumption in various water activities. Several counties in the United States, Australia, and New Zealand have laws requiring isolation fencing for pools. Their effectiveness has been limited by a lack of enforcement. Similarly, all states have boating-under-the-influence laws but, similarly, rarely enforce them. Furthermore, efforts at the community level may be needed to ensure the availability of swimming lessons for underserved populations and lifeguarded swim areas.

The Drowning Chain of Survival refers to a series of steps that, when followed, attempt to reduce mortality associated with drowning. The steps of the chain include prevent drowning, recognize distress, provide flotation, remove from water, and provide care as needed. These interventions may be used by the drowning victim for self-rescue or via bystanders who recognize child distress, initiate rescue, and provide resuscitation. The timeline shows that rescue and resuscitation must occur within minutes to save lives, and care should be taken by rescuers to not become victims themselves.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 89

Burn Injuries

Tina L. Palmieri

Burns are among the top five leading causes of *unintentional injury* in children, after motor vehicle crashes, suffocation, drowning, and poisoning. There has been a decline in the incidence of burn injury requiring medical care that has coincided with a stronger focus on burn treatment and prevention, increased fire and burn prevention education, greater availability of regional treatment centers, widespread use of smoke detectors, greater regulation of consumer products and occupational safety, and societal changes such as reductions in smoking and alcohol abuse.

EPIDEMIOLOGY

Approximately 1.1 million people in the United States require medical care for burn injuries each year, with over 100,000 children admitted to a hospital or treated in the emergency department (ED). **Fires** remain a major cause of mortality in children, but children <14 years old have a lower relative risk of dying in a fire than the general population.

Thermal burns are caused when an external heat source comes in contact with the skin and tissues causing injury; thermal burns may occur from contact with hot surfaces, hot liquids, steam, or flame. **Scald burns** are most prevalent in children ≤4 years old and account for 65% of burn-related admissions in this age-group. Although the incidence of hot water scalding has been reduced by legislation requiring water heaters to be preset at 48.9°C (120°F), scald injury remains the leading cause of hospitalization for burns in this age-group. **Steam** inhalation used as a home remedy to treat respiratory infections is a rare potential cause of burns. **Flame burns** are the most common cause of burn injury in all age-groups ≥5 years old. Electrical and chemical burns are also more common in older children and adults than in young children. **Clothing ignition** events have declined since passage of the Federal Flammable Fabric Act requiring sleepwear to be flame-retardant. Polyester is the fabric most resistant to ignition by a small flame source. Polyester burns deeply as it melts, but it self-extinguishes when the flame source is removed. Cotton, on the other hand, continues to burn after the flame source has been removed, resulting in large, deep burns. Polyester melts downward, sparing the face and respiratory tract; cotton burns upward toward the face. Pellet stoves, glass front stoves, and flat top stoves are frequent sources of hand burns in children, as is contact with hot hair appliances, such as curling irons and hair straighteners. Approximately 18% of burns are the result of **child abuse** (usually scalds), making it important to assess the pattern and site of injury and their consistency with the patient's history (see Chapter 17). **Friction burns** from treadmills are also a problem. Hands are the most commonly injured sites, with burns ranging from deep second-degree to fourth-degree with tendon disruption and fractures from the friction injury. *Anoxia,* not the actual burn, is a major cause of morbidity and mortality in house fires.

Review of the history usually shows a common pattern: a v-shaped distribution of the scald burns to the chest and abdomen if liquid is pulled from a table or stove, burns in the pant leg area if clothing ignites, burns in a splash pattern from a hot liquid spill, and burns on the palm of the hand from contact with a hot stove or curling iron. However, **glove or stocking burns** of the hands and feet; single-area deep burns on the trunk, buttocks, or back; and small, full-thickness burns (e.g., cigarette burns) in young children should raise the suspicion of child abuse.

Burn care involves a range of activities: prevention, acute care and resuscitation, wound management, pain relief, reconstruction, rehabilitation, and psychosocial adjustment. Children with massive burns require early and appropriate psychologic and social support as well as resuscitation. Surgical debridement, wound closure, and rehabilitative efforts should be instituted concurrently to promote optimal outcomes. To maximize survival, the clinical approach includes aggressive surgical removal of devitalized tissue with timely skin closure via grafting, infection control, and judicious use of antibiotics; life support with endotracheal intubation and mechanical ventilation; and use of early enteral nutrition. Children who have sustained burn injuries differ in appearance from their peers, necessitating supportive efforts for reentry to school and social and sporting activities.

PREVENTION

The aim of burn prevention is a continuing reduction in the number of serious burn injuries (Table 89.1). Effective first aid and triage can decrease both the extent (area) and the severity (depth) of injuries. The use of flame-retardant clothing and smoke detectors, control of hot water temperature (thermostat settings) to 48.9°C (120°F) within buildings, and prohibition of cigarette smoking have been partially successful in reducing the incidence of burn injuries. Treatment of children with significant burn injuries in dedicated burn centers facilitates medically effective care, improves survival, and leads to greater cost efficiency. Survival of at least 80% of patients with burns of 90% of the total body surface area (TBSA) is possible for children and young adults. Death is more likely in children with irreversible anoxic brain injury sustained at the time of the burn. Some burns occur on a seasonal basis, including:

Winter:
- Glass-front fireplaces/pellet stoves and radiators increase hand burns
- Treadmill injuries as more people exercise inside—child imitates adults or young child touches belt
- Soup scald burns from spilling liquid while removing bowl from microwave

Summer:
- Fireworks, sparklers—temperatures reach 537.8°C (1,000°F)
- Burn contact with hot grill; hand/feet burn from hot embers
- Burns from children walking or falling into a campfire
- Lawnmowers

Spring/Fall:
- Burning leaves
- Gasoline burns
- Tap water scalds
- House fires from propane heater explosion

Pediatricians can play a major role in preventing the most common burns by educating parents and healthcare providers. Simple, effective, efficient, and cost-effective preventive measures include the use of appropriate clothing and smoke detectors and the planning of routes for emergency exit from the home. The National Fire Protection Association (NFPA) recommends replacing smoke detector batteries

Table 89.1 Burn Prophylaxis

PREVENT FIRES
Install and use smoke detectors.
Control the hot water thermostat; maximum water temperature should be 48.9°C (120°F).
Keep fire, matches, and lighters out of the reach of children.
Avoid cigarette smoking, especially in bed.
Do not leave lit candles unattended.
Keep hair appliances such as curling irons and straighteners out of the reach of children.
Use caution when cooking, especially with oil.
Keep cloth items off heaters.
PREVENT INJURY
Stop, drop, and roll (do not run) if clothing catches fire; wrap in a blanket.
Practice escape procedures.
Crawl beneath smoke if a fire occurs indoors.
Use educational materials.*

*National Fire Protection Association pamphlets and videos.

Table 89.2 Indications for Referral to a Burn Center

Partial-thickness burns affecting >10% TBSA
Full-thickness burn affecting >5% TBSA
Third-degree burns
Electrical burns caused by high-tension wires or lightning
Chemical burns
Inhalation injury, regardless of the amount of TBSA burned
Inadequate home or social environment
Suspected child abuse or neglect
Burns to the face, hands, feet, perineum, genitals, or major joints
Burns in patients with preexisting medical conditions that may complicate the acute recovery phase
Associated injuries (fractures)

TBSA, Total body surface area.
Adapted from American Burn Association/American College of Surgeons. Guidelines for the operation of burn centers. *J Burn Care Res.* 2007;28(1):134–141 and Bettencourt AP, Romanowski KS, Joe V, et al. Updating the Burn Center Referral Criteria: Results from the 2018 eDelphi Consensus Study. *J Burn Care Res.* 2020;41(5):1052–1062.

Table 89.3 Acute Treatment of Burns

First aid, including washing of wounds and removal of devitalized tissue
Fluid resuscitation
Provision of energy requirements
Control of pain
Prevention of infection
Early excision and grafting
Prevention of excessive metabolic expenditures
Control of bacterial wound flora
Early mobility, range of motion, and strength exercises

annually and the smoke detector alarm every 10 years (or earlier, if indicated on the device).

ACUTE CARE, RESUSCITATION, AND ASSESSMENT

Indications for Admission

Burns covering >10% TBSA, burns associated with smoke inhalation, burns resulting from high-tension (voltage) electrical injuries, and burns associated with suspected child abuse or neglect should be treated emergently and referred to a burn center for definitive care (Table 89.2). Small first- and second-degree burns of the hands, feet, face, perineum, and joint surfaces may require admission if close follow-up care is difficult to provide. Children who have been in enclosed-space fires and those who have significant face and neck burns should be evaluated carefully for airway or neurologic compromise, including monitoring for 24 hours in the hospital for potential central nervous system (CNS) effects of anoxia from carbon monoxide (CO) poisoning or pulmonary effects from smoke inhalation.

First Aid Measures

Acute care should include the following measures:

1. Extinguish flames by rolling the child on the ground; cover the child with a blanket, coat, or carpet.
2. Remove smoldering clothing or clothing saturated with hot liquid. Jewelry, particularly rings and bracelets, should be removed or cut away to prevent constriction and vascular compromise during the edema phase in the first 24-72 hours after burn injury.
3. In cases of **chemical injury**, brush off any remaining chemical, if powdered or solid; then use copious irrigation or wash the affected area with water. Call the local poison control center for the neutralizing agent to treat a chemical ingestion.
4. Wash the burned area with soap and cool running water. For burns on less than 10% of the body, irrigate with cool tap water for 10-20 minutes. Significant large-burn injury (>15% TBSA) decreases body temperature control so the use of cold water is contraindicated.
5. Cover the burned area with clean, dry sheeting or dressing. Avoid using tape.
6. If the burn is caused by *hot tar,* cool the burn and then use mineral oil to remove the tar.
7. Administer analgesic medications.

Emergency Care

Supportive measures are as follows (Table 89.3 and Table 89.4):

1. Rapidly review the cardiovascular and pulmonary status and document preexisting or physiologic lesions (asthma, congenital heart disease, renal or hepatic disease).
2. Ensure and maintain an adequate airway (Fig. 89.1). For any child with a facial burn or suspected inhalation of smoke, the following actions are indicated:
   a. Start 100% oxygen and measure carboxyhemoglobin (CO) levels as well as a blood gas, because cutaneous oxygen saturations are not accurate in CO poisoning (see Chapters 79 and 86).
   b. Assess for laryngeal edema (examine mouth; assess for stridor, retractions) and intubate for evidence of significant airway compromise.
   c. Assess oxygenation to evaluate for lung damage from smoke inhalation. Bronchoscopy may be helpful in the intubated child to further delineate the extent of smoke inhalation injury. Use a humidified ventilator circuit to prevent dry secretions that can obstruct an airway.
3. Children with burns >15% TBSA require intravenous (IV) fluid resuscitation to maintain adequate perfusion. IV access is preferably obtained in a nonburned area, but if none is readily available, placing the initial line through a burn may be necessary. Monitor peripheral IV sites closely for infiltration, as extremities will become edematous after burn injury. In an emergency situation in which IV access is unattainable, an intraosseous (IO) line may be placed. The IO line should be replaced in a timely fashion with a central line, as IO needles may be unable to sustain the large fluid volume needed for major burn resuscitation. Patients with inhalation injury, regardless of the extent of TBSA burn, require large volumes of fluid for resuscitation due to insensible losses from the injured airway epithelium. Significant high-tension and electrical injuries require venous access to ensure sufficient fluid resuscitation volumes, as forced alkaline diuresis may be needed in fluid-refractory myoglobinuria to avoid renal damage. Lactated Ringer solution, 10-20 mL/kg/hr (normal saline may be used if lactated Ringer solution is not available), is initially infused until proper fluid replacement can be calculated. Consultation with a specialized burn unit should be made to coordinate fluid therapy, including the type of fluid, the preferred formula for calculation, and preferences for the use of colloid agents, particularly if transfer to a burn center is anticipated.
4. For patients with circumferential burns of the extremities, elevate the extremities and monitor perfusion (capillary refill, pulses), as compartment syndrome (see Chapter 80) may develop and require escharotomy.
5. Evaluate the child for associated injuries. Children with burns may have associated accidental traumatic injuries (fall) or nonaccidental injuries (child abuse). In cases of high-voltage electrical burn (>1,000 volts), especially if there has also been a fall from a height, injuries to the spine, bones, and thoracic or intraabdominal organs may occur (see Chapter 80). Cervical spine precautions should be observed until this injury is ruled out. If ventricular fibrillation occurs at the scene of an electrocution, cardiopulmonary resuscitation (CPR) should be instituted promptly, and cardiac monitoring started on the patient's arrival at the ED (see Chapter 79).
6. Children with burns of >15% TBSA should not initially receive oral fluids because gastric distention may develop. These children may require insertion of a nasogastric tube in the ED to prevent aspiration.
7. A Foley catheter should be inserted into the bladder to monitor urine output in children who require IV fluid resuscitation.

Table 89.4 Phases of Burn Care

PHASE AND TIMING	PHYSIOLOGIC CHANGES	OBJECTIVES
1: Resuscitation, 0-72 hours	Massive capillary leak, edema, and burn shock	Airway, breathing, and circulation optimization via accurate fluid resuscitation and thorough evaluation
2: Acute treatment phase, day 3 through discharge	Hyperdynamic and catabolic state, immunosuppression, risk of infection	Enteral nutrition to optimize wound healing; excision and biologic wound closure of full-thickness wounds with excision and grafting within 7 days of injury
3: Rehabilitation, day 1 through discharge	Gradual waning of initial catabolic state, wounds heal, scars form, and strength recovers	Maintain and restore range of motion; reduce edema; strengthen muscles; facilitate return to home, work, and school

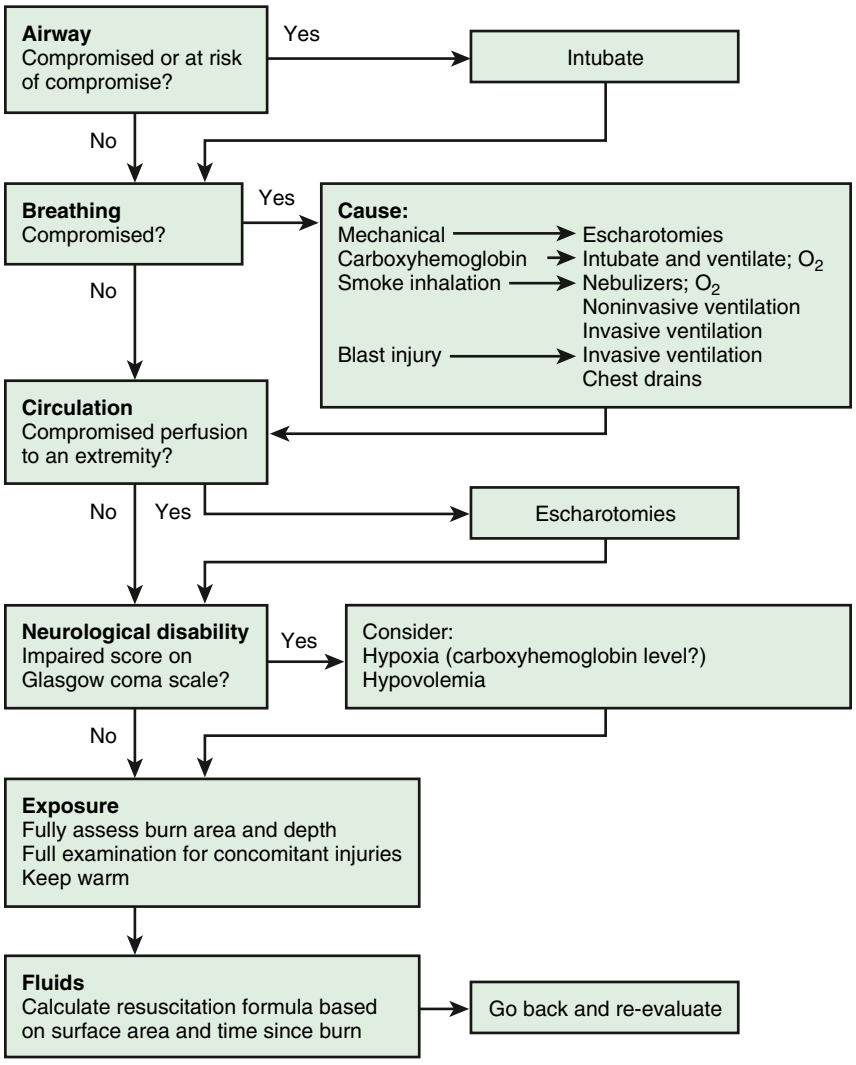

Fig. 89.1 Algorithm for primary survey of a major burn injury. (*From Hettiaratchy S, Papini R. Initial management of a major burn. I. Overview. BMJ. 2004;328:1555–1557.*)

8. In general, wounds should be wrapped with a clean sheet or dressing until it is decided whether to treat the patient on an outpatient basis or refer to an appropriate facility.
9. For children trapped in a fire, a CO measurement (carboxyhemoglobin [HbCO]) should be obtained and 100% oxygen administered until the result is known. Pulse oximetry is unreliable in CO poisoning.
10. Review child immunizations, including tetanus immunization. Use diphtheria, tetanus toxoids, and acellular pertussis (DTaP) for tetanus prophylaxis for children <7 years old, and use tetanus, diphtheria, and pertussis (TdaP) for children ≥7 years old (see Chapter 257).

Classification of Burns

Proper triage and treatment of burn injury require assessment of the extent and depth of the injury (Table 89.5 and Fig. 89.2). **First-degree burns** involve only the epidermis and are characterized by swelling, erythema, and pain (similar to mild sunburn). Tissue damage is usually minimal, and there is no blistering. Pain resolves in 48-72 hours; in a small percentage of patients, the damaged epithelium peels off, leaving no residual scars.

A **second-degree burn** involves injury to the entire epidermis and a variable portion of the dermal layer (vesicle and blister formation are characteristic). A *superficial* second-degree burn is extremely painful because many remaining viable nerve endings are exposed. Superficial

Table 89.5 Categories of Burn Depth

	FIRST-DEGREE BURN	SECOND-DEGREE BURN (PARTIAL THICKNESS)	THIRD-DEGREE BURN (FULL-THICKNESS)
Surface appearance	Dry, no blisters Minimal or no edema Erythematous Blanches, bleeds	Moist blebs, blisters Underlying tissue is mottled pink and white, with fair capillary refill Bleeds	Dry, leathery eschar Mixed white, waxy, khaki, mahogany, soot-stained No blanching or bleeding
Pain	Very painful	Very painful	Insensate centrally, edges (usually less deep) may still have sensation
Histologic depth	Epidermal layers only	Epidermis, papillary, and reticular layers of dermis May include domes of subcutaneous layers	Through all layers of the skin to subcutaneous tissue (loss of muscle, bone is fourth-degree burn)
Healing time	2-5 days with no scarring	Superficial: 5-21 days with no grafting Deep partial: 21-35 days with no infection, but scar is expected; if infected, converts to full-thickness burn	Large areas require grafting, but small areas may heal from the edges after weeks

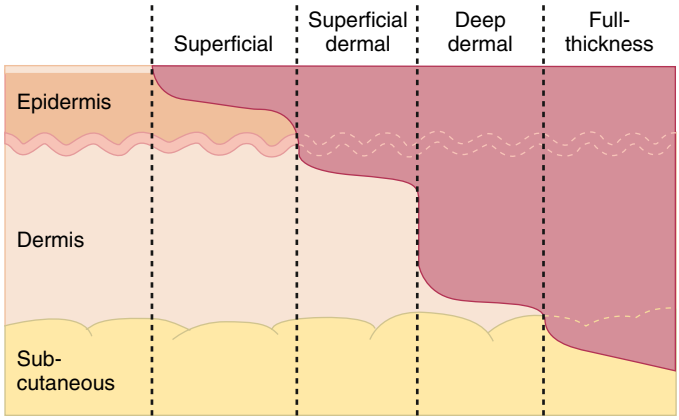

Fig. 89.2 Diagram of different burn depths. (*From Hettiaratchy S, Papini R. Initial management of a major burn. II. Assessment and resuscitation. BMJ. 2004;329:101–103.*)

second-degree burns heal in 7-14 days as the epithelium regenerates in the absence of infection. *Mid-level to deep* second-degree burns will generally heal in 14-21 days, but often result in significant scarring. Deep second-degree burns tend to be dry, pale, and white (flame) or red (scald); they are often grafted to mitigate scarring (Fig. 89.3). Pain may be less with these burns than in more superficial burns because fewer nerve endings remain viable; however, the edge of the burn, which will be less deep, will still cause pain. Fluid losses and metabolic effects of deep dermal (second-degree) burns are essentially the same as those of third-degree burns. If a blister is intact in a burned area, the burn is at least second-degree but may be deeper. Definitive diagnosis of burn depth is not possible because the blister blocks visualization of the burned tissue under the blister.

Full-thickness, or **third-degree burns**, involve destruction of the entire epidermis and dermis, leaving no residual epidermal cells to repopulate the damaged area. The wound heals by wound contraction or skin grafting. Wounds are either white or leathery (flame burn) or mottled, nonblanching, and cherry red (scald) (Fig. 89.4). The absence of painful sensation and capillary filling demonstrates the loss of nerve and capillary elements. Pain exists at the edges of the burn. Hence, using pain to determine burn depth is not accurate.

Technologies can help accurately determine the depth of burns. Laser *Doppler imaging* can be used from 25 days after the burn. It produces a color map of the affected tissue; *yellow* indicates second-degree burns, reflecting the presence of capillaries, arterioles, and venules, and *blue* reflects very low or absence of blood flow, which indicates third-degree burns. Although early reports are promising, the clinical utility of laser Doppler imaging for burn depth determination is not clearly established.

Estimation of Total Body Surface Area for a Burn

Appropriate burn charts for different childhood age-groups should be used to accurately estimate the extent of TBSA burned. The extent and depth of the burn are the largest determinants of fluid resuscitation requirements. Mortality and morbidity also depend on the extent and depth of the burn. Children have a larger surface area to mass ratio than adults, and the variable growth rate of the child's head and extremities makes it necessary to use body surface area (BSA) charts, such as that modified by Lund and Brower, to accurately calculate burn size (Fig. 89.5). Another method of estimating burn size is to employ the palm rule. The palm of the child's hand (from base of palm to fingertip) is 1% of the child's TBSA. A quick method of estimating burn size is to hold your hand up to the child's hand to gauge the area and use that to determine burn size. The **rule of nines** used in adults should only be used in children >14 years old or >20 kg as a rough estimate to institute therapy before transfer to a burn center. The rule of nines divides body regions by 9% BSA: head and neck, chest and upper back, each arm, abdomen, lower back, upper leg, and lower leg; hand or genitals (1%).

TREATMENT

Outpatient Management of Minor Burns

A patient with first- and second-degree burns <10% TBSA may be treated on an outpatient basis unless pain is uncontrolled on oral agents, the family cannot successfully complete wound care, or there are issues of child neglect or abuse. These outpatients do not require prophylactic antibiotics. Blisters should be left intact and dressed with a nonstick dressing such as Telfa or Xeroform. Topical creams do not penetrate the blister and are not indicated unless the blister ruptures. Dressings should be changed once daily, after the wound is washed with lukewarm water. Very small wounds, especially those on the face, may be treated with bacitracin ointment and left open. **Debridement** (i.e., removal) of the devitalized skin is indicated when the blisters rupture. A variety of wound dressings are available for application to second-degree burns; the affected area should be subsequently wrapped with a dry, clean dressing. Silver dressings are popular because they provide pain relief, prevent wound desiccation, reduce wound colonization, and can be left in place for 5-7 days (Table 89.6). Although silver dressings are antimicrobial, wound infections can occur beneath these dressings. Patients should be instructed to seek immediate medical care for signs and symptoms of infection (elevated temperature, malaise, pain) and should be reevaluated at least weekly by the medical team. The great majority of superficial burns heal in 7-10 days, with deep second-degree burns taking longer to heal. Burns that have not healed within 2 weeks (or clearly will not be healed in 2 weeks) have a >97% chance of developing a significant scar and should be referred to a burn center.

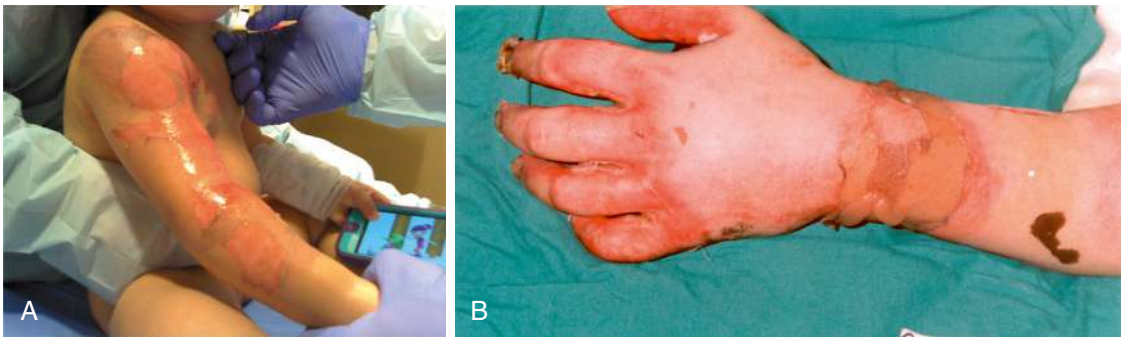

Fig. 89.3 Second-degree burns. **A**, Superficial partial-thickness (second-degree) burn, which is pink and glistening. **B**, Deep partial-thickness (second-degree) burn. The white-appearing area over the dorsum of the hand is a deep partial-thickness burn. (*From Singer AJ, Lee CC. Thermal burns. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. Rosen's Emergency Medicine, 9th ed. Philadelphia: Elsevier; 2018: Figs. 56.1 and 56.2, p. 717.*)



Fig. 89.4 Full-thickness (third-degree) burn over both feet. The central area is depressed and has a yellowish color indicating it is full thickness. (*Modified from Singer AJ, Lee CC. Thermal burns. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. Rosen's Emergency Medicine, 9th ed. Philadelphia: Elsevier; 2018: Fig. 56.3, p. 717.*)

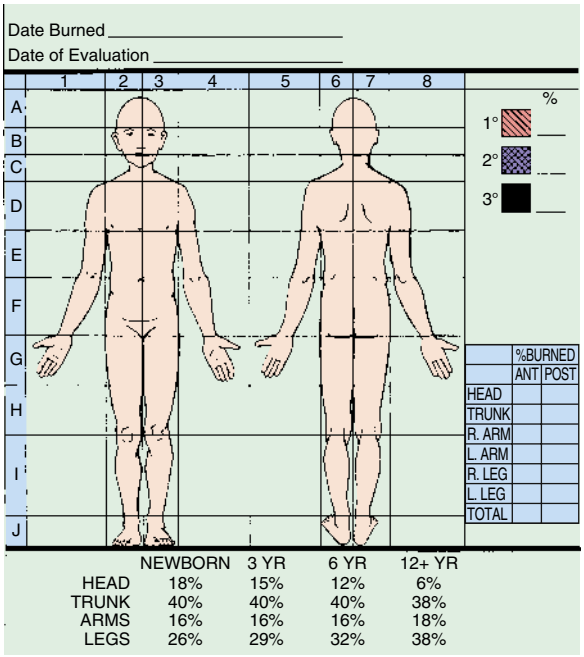

Fig. 89.5 Chart to determine developmentally related percentage of body surface area affected by burn injury. ANT, Anterior; POST, posterior; R., right; L., left. (*Courtesy Shriners Hospital, Burn Institute, Boston Unit.*)

Table 89.6 Select Silver Antimicrobial Dressings for Burns

DRESSING	CHARACTERISTIC(S)
Mepitel Ag	Silicone mesh dressing
Mepilex Ag	Foam dressing
ACTICOAT	Polyethylene nonadherent net dressing
AQUACEL Ag	Absorptive Hydrofiber
Silverlon	Knitted nylon nonadherent dressing

The palm of the hand is one of the most frequently burned areas in children, particularly toddlers. Because the skin on the palm of the hand is thicker than other parts of the body, burns to the palm often heal. Generally, blisters of the palm can be left intact unless they are already open, or they are so large that they will likely rupture (usually about 1-2 cm in height), or purulence is draining from the blister. If leaving a blister intact, inform the family to either return to the office if the blister ruptures or instruct them on how to remove the blister and apply bacitracin to the wound. If a palm burn has not healed in 2 weeks (or it is clear that it will not be healed), referral to a burn center is needed.

The depth of scald injuries is difficult to assess early, as the wounds are often reddish in color. Nonoperative treatment is appropriate initially. Generally, third-degree scald burns will become increasingly pale and white by 4-5 days post injury, whereas those that heal will be a lighter pink color. A wound that has not healed in 2 weeks will likely need grafting (Fig. 89.6). This conservative approach obviates the risk of anesthesia and unnecessary grafting.

Fluid Resuscitation

Fluid resuscitation, if required, should begin as soon as possible (at the scene, in the ED, or before transfer) after the injury has occurred because delays of as little as 30 minutes affect outcomes. Numerous formulas exist to help guide practitioners in calculating fluid resuscitation needs in patients with burns. For most children, the *Parkland formula* is an appropriate *guideline* to determine starting IV fluid resuscitation rate; however, fluids should be adjusted hourly based on the patient's response. The steps in calculating the starting rate are as follows:

1. Calculate the 24-hour fluid requirement: 4 mL lactated Ringer solution per (times) weight in kg per (times) % TBSA burned. The TBSA burned is a whole number, NOT a percentage.
2. Determine the volume of fluid to be given in the first 8 hours: for the Parkland formula, that is half of the 24-hour requirement.
3. Calculate the starting hourly infusion rate: divide the volume to be given in the first 8 hours by 8 to determine the starting rate. The

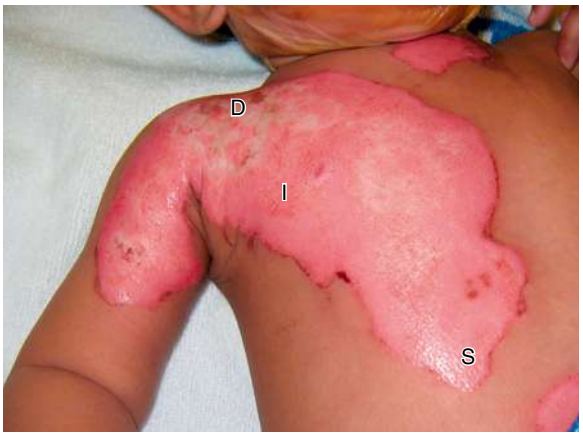

Fig. 89.6 Tea scald over the chest and shoulder of a child showing heterogeneity of burn depth. D, Deep; I, intermediate; S, superficial. (*From Enoch S, Roshan A, Shah M. Emergency and early management of burns and scalds. BMJ. 2009;338:937–941.*)

infusion rate is adjusted hourly based on urine output goals of 0.8-1 mL/hour in children <20 kg or <12 years of age and 0.4-0.5 mL/kg/hr (maximum of 30 mL/hr) in children >12 years or >20 kg.

Providers should increase the fluid rate by 10% if urine output is below the hourly target and decrease the fluids by 10% if over the target. Because major burns have a hypermetabolic response, tachycardia is NOT an accurate measure of resuscitation in a child with a major burn. Acid-base balance, mental status, serum lactate, and noninvasive monitoring are useful adjuncts to evaluate the adequacy of resuscitation. Because of interstitial edema and sequestration of fluid in muscle cells, patients may gain up to 20% over baseline (preburn) body weight. Patients with burns of >20% TBSA often require a large venous access (central venous line) to deliver the fluid required over the critical first 24 hours; these patients are best cared for in a specialized pediatric burn unit. In addition to fluid resuscitation, children <20 kg should receive standard maintenance fluids (see Chapter 74).

During the second 24 hours after the burn, patients begin to reabsorb edema fluid and to experience diuresis. IV fluid requirements after resuscitation will consist of isotonic crystalloid infusion for insensible losses (see Chapter 73) plus the fluid losses from the burn wound. Controversy surrounds whether *colloid* should be provided in the early period of burn resuscitation. One preference is to administer albumin if a patient is not responding to crystalloid resuscitation. In children <12 months old, sodium tolerance is limited; the volume and sodium concentration of the resuscitation solution should be decreased if the urinary sodium level is rising. The adequacy of resuscitation should be constantly reassessed by integrating vital signs with urine output, blood gas, serum lactate, base deficit, hematocrit, and serum protein measurements. Some patients require arterial and central venous lines, particularly those undergoing multiple excision and grafting procedures, for monitoring and fluid replacement purposes. Central venous pressure monitoring may be indicated to assess circulation in patients with hemodynamic or cardiopulmonary instability. Femoral vein cannulation is a safe access for fluid resuscitation, especially in infants and children. Burn patients who require frequent blood gas monitoring benefit from radial or femoral arterial catheterization.

Oral supplementation may start as soon as enteral access is obtained. Early nutrition helps to minimize effects of the hypermetabolic response. Milk formula, artificial feedings, homogenized milk, or soy-based products can be given by bolus or constant infusion through a nasogastric or small bowel feeding tube. These feedings are not part of the initial 24-hour fluid resuscitation, as absorption may be variable. When oral fluids are tolerated after several days, IV fluids are decreased proportionately to keep the total fluid intake constant, particularly if pulmonary dysfunction is present.

Colloids such as albumin are lost through the burn wound. To maintain oncotic pressure and protein binding, a **5% or 25% albumin infusion** may be used to maintain the serum albumin levels at a desired 2 g/dL. Infusion of **packed red blood cells** is recommended if the hematocrit falls to <20% (hemoglobin = 7 g/dL). Most patients are hemoconcentrated during resuscitation; thus transfusion in the first 24-48 hours is rare unless there is accompanying trauma. **Fresh-frozen plasma** (FFP) is indicated if clinical and laboratory assessment shows a deficiency of clotting factors, a prothrombin level >1.5 times control, or a partial thromboplastin time >1.2 times control in children who are bleeding or are scheduled for an invasive procedure or a grafting procedure that could result in an estimated blood loss of more than half of blood volume. Although FFP use for volume resuscitation during the first 24 hours of injury is advocated by some, this strategy has not yet undergone rigorous evaluation through randomized prospective trials.

Sodium supplementation may be required for children with burns of >20% TBSA, particularly if 0.5% silver nitrate solution is used as the topical antibacterial burn dressing. Sodium losses with silver nitrate therapy are regularly as high as 350 mEq/m^2 burn surface area. The aim is to maintain serum sodium levels >130 mEq/L and urinary sodium concentration >30 mEq/L. Young children <5 years are especially susceptible to hyponatremia and cerebral edema. IV **potassium supplementation** is supplied to maintain a serum potassium level >3 mEq/dL. Potassium losses may be significantly increased when 0.5% silver nitrate solution is used as the topical antibacterial agent or when aminoglycoside, diuretic, or amphotericin therapy is required. Magnesium and ionized calcium can also become rapidly depleted and should be assessed at least daily for the first week and weekly thereafter in major burns.

Prevention of Infection and Surgical Management of the Burn Wound

In general, prophylactic antibiotic administration is not indicated for burn injuries because it predisposes patients to development of resistant pathogens. Topical antimicrobial creams or silver agents reduce wound colonization; systemic antibiotics do not reach the nonviable tissue in the burn wound. There is conflicting evidence as to whether relocation of the IV catheter every 48-72 hours decreases or increases the incidence of catheter-related sepsis in burn injury. Central venous catheters should be monitored closely for infection. Many burn units replace or relocate central lines every 5-7 days, even if the site is not inflamed and there is no suspicion of catheter-related sepsis, particularly if the line is near a burn wound. The incidence of central line–associated bloodstream infection is directly related to the distance between the catheter and the burn wound. The fragile tissue and frequency of patient turning and movement, combined with the moisture of the burn wound, make it imperative to securely attach central venous catheters with sutures placed securely in at least three locations to prevent catheter movement, kinking, or accidental removal.

Mortality related to burn injury is associated not with the toxic effect of thermally injured skin, but with the metabolic and bacterial consequences of a large open wound, reduction of the patient's immune response, and malnutrition. These abnormalities set the stage for life-threatening bacterial infection originating from the burn wound. Thorough early wound cleaning, application of topical antimicrobial creams, and early wound excision and grafting promote wound healing and improve aesthetic and functional outcomes. Topical antimicrobial agents for burn wound treatment include bacitracin (second-degree burns or burns that will heal in a week), silver sulfadiazine cream (third-degree burns), mafenide acetate (Sulfamylon) cream (third-degree burns on ears, cartilage), or 0.5% silver nitrate solution (third-degree burns with sulfa allergy) (Table 89.7). Regardless of the choice of topical antimicrobial agent, it is essential that all third-degree burn tissue be fully excised and grafted before bacterial colonization progresses to systemic infection. Children with a burn of >20% TBSA should be housed in reverse isolation with all personnel required to wear gown, gloves, mask, and hat to prevent cross-contamination and to provide a temperature- and humidity-controlled environment that minimizes hypermetabolism.

Deep third-degree burns of >10% TBSA benefit from early excision and grafting. To improve outcome, sequential excision and grafting of

Table 89.7 Topical Agents Used for Burns

AGENT	EFFECTIVENESS	SIDE EFFECTS	EASE OF USE
Bacitracin	Gram-positive organisms; good for wounds that will heal in 7-10 days	May cause yeast overgrowth rash or pustules if on intact skin; resolves with discontinuation	Clear ointment, 1-2 times daily, easy to clean off
Silver sulfadiazine cream (Silvadene)	Broad spectrum including gram-positive and -negative organisms, some fungus; may cause leukopenia	Leukopenia, self-limited; may be painful Leaves adherent residue	Changed twice daily Residue *must* be washed off with each dressing change
Mafenide acetate cream* (Sulfamylon)	Targets resistant gram-negative organisms, particularly *Pseudomonas*, some gram-positive coverage Rapid and deep wound penetration; used on cartilage (ears) and deep wound infection	Carbonic anhydrase inhibitor, may cause metabolic acidosis	Changed twice daily; application may be painful Residue *must* be washed off with each dressing change
0.5% Silver nitrate solution	Bacteriostatic Broad spectrum, including some fungi Superficial penetration	Permanent staining of surfaces from silver oxidation; electrolyte disturbances from hypotonic solution, potential methemoglobinemia	Closed bulky dressing soaked every 2 hr and changed 1-2 times daily

*Mafenide acetate solution at concentrations of 2.5% or 5% for use on heavily colonized, multidrug-resistant organisms to be used for 5 days only.

third-degree and deep second-degree burns may be required in children with large burns. Prompt excision with immediate wound closure is achieved with **autografts**, skin obtained from another part of the patient's body, which may be meshed to increase the efficiency of coverings. Alternatives for wound closure, such as allografts, dermal substitutes, and other biologic dressings, may be important for wound coverage in patients with extensive injury to limit fluid, electrolyte, and protein losses and to reduce pain and minimize temperature loss. Cultured epidermal cells (autologous keratinocytes), grown from a skin biopsy from the patient, are a costly alternative and are not always successful. Another approach employs an autologous cell spray (theoretically containing stem cells) as an adjunct to meshed skin for wound closure. An experienced burn team can safely perform early stage or total excision while burn fluid resuscitation continues. Important keys to success are (1) accurate preoperative and intraoperative determination of burn depth, (2) the choice of excision area and appropriate timing, (3) control of intraoperative blood loss, (4) specific instrumentation, and (5) the type of wound coverage chosen.

Nutritional Support

Supporting the increased energy requirements of a patient with a burn is a high priority. The burn injury produces a hypermetabolic response characterized by both protein and fat catabolism. Depending on the time lapse since the burn, children with a burn of 40% TBSA require basal energy expenditure (oxygen consumption) approximately 50–100% higher than predicted for their age. Early excision and grafting can decrease the energy requirement. Pain, anxiety, and immobilization increase the physiologic demands. Additional energy expenditure is caused by cold stress if environmental humidity and temperature are not controlled; this is especially true in young infants, in whom the large BSA:mass ratio allows proportionately greater heat loss than in adolescents and adults. Providing environmental temperatures of 28–33°C (82.4–91.4°F), adequate covering during transport, and liberal use of analgesics and anxiolytics can decrease caloric demands. Appropriate sleep intervals are necessary and should be part of the regimen. Early enteral nutrition, initially with high-carbohydrate, high-protein caloric content (1,800 kcal/m^2/24-hr maintenance plus 2,200 kcal/m^2 of burn/24 hr) reduces metabolic stress.

The objective of nutrition supplementation programs is to maintain body weight and minimize weight loss by meeting metabolic demands. This reduces the loss of lean body mass. Calories are provided at approximately 1.5 times the basal metabolic rate, with 3-4 g/kg of protein/day. The focus of nutritional therapy is to support and compensate for the metabolic needs. Multivitamins, particularly the B vitamin group, vitamin C, vitamin A, vitamin D, vitamin E, copper, selenium, and zinc, are also necessary.

Alimentation should be started as soon as is practical, preferably enterally, to meet all caloric needs and maintain gastrointestinal (GI) tract function throughout treatment. Patients with burns of >40% of TBSA need a flexible nasogastric or small bowel feeding tube to facilitate continuous delivery of calories without the risk of aspiration at the time of admission. To decrease the risk of infectious complications, parenteral nutrition should be avoided or discontinued as soon as is practical after delivery of sufficient enteral calories is established. Continuous GI feeding is essential, even if feeding is interrupted for frequent visits to the operating room, until full grafting takes place. In third-degree burns >20% the use of anabolic agents such as *oxandrolone* to improve wound healing and promote protein synthesis or anticatabolic agents (propranolol) to reduce metabolic stress is common practice. It is vital to continue enteral feeding while using these agents to obtain maximal response. Liver function studies should be monitored weekly when giving oxandrolone, and oxandrolone should be discontinued if liver function deteriorates.

Topical Therapy

Topical therapy is widely used to decrease wound colonization from a wide variety of wound pathogens (see Table 89.7). Preferences vary among burn units. Each topical agent has advantages and disadvantages in application, comfort, and bacteriostatic spectrum. However, all agents impair wound healing. The type of organism on a wound varies with the age of the wound. In the first week, gram-positive organisms predominate. During weeks 2-4, gram-negative organisms are frequently found in burn wounds. Prolonged open burn wounds eventually tend to develop resistant gram-negative organisms, fungus, or mold. The choice of topical antimicrobial depends on wound age and depth. *Bacitracin* is a clear ointment effective against gram-positive organisms and is often used in wounds that will heal within a week. If placed on nonburned skin, it may cause a yeast rash or pimples that resolve with discontinuation. *Silver sulfadiazine* is a white cream containing silver with a broad spectrum of coverage, including

gram-positive and gram-negative organisms and some fungi. It is used commonly in deep third-degree burns that require grafting and may cause transient self-limiting leukopenia if applied over large areas. *Mafenide acetate* is a white cream with the ability to diffuse through the burn eschar; it is the treatment of choice for injury to cartilaginous surfaces, such as the ear. Mafenide acetate solution at a concentration of 5% is useful for the treatment of burn wounds that are heavily colonized with multidrug-resistant gram-negative bacteria and is often used postoperatively to keep grafts moist. The carbonic anhydrase inhibition activity of mafenide acetate may cause metabolic acidosis if large surface areas are treated in a small child. No sulfa-containing agent should be used if the child has a history of sulfa allergies. Silver nitrate solution may be used in children with sulfa allergy because of its broad spectrum of coverage. However, it causes gray staining of the environment and wound from silver oxidation as well as electrolyte disturbances because of the hypotonic nature of the solution.

Inhalation Injury

Inhalation injury is serious in the infant and child, particularly if preexisting pulmonary conditions are present (see Chapter 86). Inhalation injury should be suspected based on history of sustained exposure to smoke in association with the burn injury, such as being confined in a closed space or from an indoor explosion, with decreased level of consciousness or with evidence of carbon deposits in the oropharynx or nose, singed facial hair, or carbonaceous sputum. Mortality estimates vary, depending on the type of inhalation injury and the extent of exposure. Each of the three types of inhalation injury (toxic gases, upper airway edema, and lower airway injury) has a different treatment.

Toxic Gases

Carbon monoxide poisoning from the burning of organic materials is caused by displacement of oxygen from the hemoglobin molecule by CO, leading to tissue hypoxia (see Chapter 94). CO poisoning should be treated with 100% oxygen until carboxyhemoglobin levels drop below 10%. Toxic fumes, including cyanides from combustible plastics as well as sulfur and nitrogen oxides and alkalis formed during the combustion of synthetic fabrics, produce corrosive chemicals that may erode the mucosa and cause significant tissue sloughing. Exposure to smoke may cause degradation of surfactant and decrease its production, resulting in atelectasis. Inhalation injury and burn injury are synergistic, and the combined effect can increase morbidity and mortality.

Injury from gases generally manifests early in the course of treatment. Acute asphyxia is the leading cause of death at the fire scene and can cause anoxic brain injury, particularly in children. Signs of CNS injury from hypoxemia caused by asphyxia or CO poisoning vary from irritability to depression. CO poisoning may be *mild,* with slight dyspnea, headache, nausea, and decreased visual acuity and higher cerebral functions; *moderate,* with irritability, agitation, nausea, dimness of vision, impaired judgment, and rapid fatigue; or *severe,* producing confusion, hallucination, ataxia, cardiovascular collapse, acidosis, and coma. Measurement of HbCO is important for diagnosis and treatment. Pulse oximetry is NOT a reliable marker of oxygenation in CO poisoning. If significant CO exposure is suspected, a blood gas with co-oximetry and a HbCO level should be obtained to determine Pao_2 and CO toxicity extent. CO poisoning and hypoxia are assumed to be present until the tests are performed, and patients should receive 100% oxygen until the HbCO level is <10% and adequate oxygenation is confirmed. Significant CO poisoning (level >25%) may require hyperbaric oxygen therapy; the risk of transporting a burn patient to the hyperbaric chamber needs to be carefully considered. **Cyanide poisoning** should be suspected if a metabolic acidosis persists despite adequate fluid resuscitation and in environments containing synthetic polymers (see Chapter 94). Unless specifically suspected, most burn centers do not routinely screen for cyanide poisoning.

Upper Airway Edema

The treatment priority for edema of the upper airway caused by inhalation injury focuses on establishing and maintaining a patent airway. If airway obstruction is apparent, prompt and early nasotracheal or orotracheal intubation is indicated to maintain airway patency and assure adequate ventilation and oxygenation. The most experienced provider should perform the intubation, as edema may allow only one attempt. The endotracheal tube size should be chosen carefully, as replacement during the first 1-3 days is often not possible. Endotracheal tubes should *not be secured* with tape if a facial burn is present, as the tape will not adhere to the moist surface. The endotracheal tube can be secured to a tooth, to the maxilla, or tied in two planes. Monitoring the security of the endotracheal tube and assuring it remains in the same location at the level of the teeth is essential, as edema may alter tube position.

Parenchymal Injury

Intubation and mechanical ventilation may be required in patients who have significant hypoxia, hypercarbia, or mental status changes caused by smoke inhalation. Wheezing and bronchospasm are common, and use of inhaled bronchodilators is often helpful. Smoke inhalation injury is gauged via clinical progression and bronchoscopy. Aggressive pulmonary toilet and chest physiotherapy are necessary, as casts and airway obstruction from debris are common. Extubation should be delayed until the patient has adequate oxygenation and ventilation, is able to sustain the increased minute ventilation and work of breathing that accompanies burn injury, and edema has resolved. A spontaneous breathing trial and a cuff leak test are often used to gauge readiness for extubation. Children with an anticipated need for mechanical ventilation >2 weeks may benefit from tracheostomy, as it provides a secure, comfortable airway with decreased sedation requirements. Tracheostomy should only be performed under general anesthesia by experienced surgeons using optimal positioning, proper tracheostomy tube size, and hemostatic conditions. In children with deep burns of the face, tracheostomy provides a secure airway that facilitates excision and grafting yet allows for oral movement, including a pacifier.

Patients with severe inhalation injury or with other causes of respiratory deterioration that lead to pediatric acute respiratory distress syndrome who do not improve with conventional pressure-controlled ventilation (progressive oxygenation failure, as manifested by oxygen saturation <90% while receiving Fio_2 of 0.9-1.0 and positive end-expiratory pressure of at least 12 cm H_2O) may benefit from high-frequency ventilation or nitric oxide inhalation treatment. Nitric oxide usually is administered through the ventilator at 5 parts per million (ppm) and increased to 30 ppm. This method of therapy reduces the need for extracorporeal membrane oxygenation (ECMO; see Chapter 86). ECMO may be indicated for failure of these conventional techniques.

Pain Relief and Psychologic Adjustment

See Chapter 93.

It is important to provide adequate analgesia, anxiolysis, sedation, and psychologic support to reduce early metabolic stress, decrease the potential for posttraumatic stress disorder (PTSD), and allow future stabilization as well as physical and psychologic rehabilitation. Patients and family members require team support to work through the grieving process and accept long-term changes in appearance.

Children with burn injury have frequent and wide fluctuations in pain intensity. Appreciation of pain depends on the depth of the burn; the stage of healing; the patient's age, stage of emotional development, and cognition; the experience and efficiency of the treating team; the use of analgesics and other drugs; the patient's pain threshold; and interpersonal and cultural factors. From the onset of treatment, **preemptive pain control** during dressing changes is crucial. The use of a variety of nonpharmacologic interventions and pharmacologic agents must be reviewed throughout the treatment period. Opioid analgesia, prescribed in an adequate dose and timed to cover dressing changes, is essential to comfort management. A supportive person who is consistently present and knows the patient profile can integrate and encourage patient participation in burn care. The problem of *undermedication* is most prevalent in adolescents, in whom fear of drug dependence may inappropriately influence treatment. A related problem is that the child's specific pain experience may be misinterpreted;

for anxious patients, those who are confused and alone, or those with preexisting emotional disorders, even small wounds may illicit intense pain. Anxiolytic medication added to the analgesic is usually helpful and has more than a synergistic effect. Equal attention is necessary to decrease stress in the intubated patient. Other modalities of pain and anxiety relief **(relaxation techniques)** can decrease the physiologic stress response.

A multimodal pain strategy is recommended for burns, as burn pain is a combination of background, acute, procedural, neuropathic, and inflammatory pain. The specific agents used will vary by institution and provider training. *Background pain,* which exists primarily in burns >20%, should be addressed with long-acting oral agents administered twice daily, such as methadone or long-acting morphine. This helps to maintain a steady state of pain relief. *Acute pain* from the injury (all burn sizes) is generally treated initially with oral acetaminophen, escalating to a short-acting opioid such as morphine, hydromorphone, oxycodone, or similar agents orally. If oral administration is not sufficient (a common scenario in major burn injury), intermittent IV opioids are used. The use of *codeine* is not recommended because of the possibility of ultrarapid metabolism of codeine. *Procedural pain,* such as for dressing changes, is short-lived but severe. Potent IV opioids such as fentanyl, morphine, or hydromorphone are effective but require appropriate monitoring. Naloxone is rarely needed but should be immediately available to reverse the effect of IV narcotics. Ketamine 1-4 mg/kg IV can be employed for children with high opioid requirements; however, continuous cardiovascular monitoring is mandatory, and ketamine should be administered by a provider trained in advanced airway techniques. *Neuropathic pain* (pins and needles sensation) should be addressed with scheduled oral gabapentin given 4 times daily. *Inflammatory pain* can be effectively treated with nonsteroidal antiinflammatory agents unless the patient has upcoming surgery, as this may increase surgical complications. *Midazolam* is very useful for conscious sedation at a dose of 0.01-0.02 mg/kg for nonintubated patients and 0.05-0.1 mg/kg for intubated patients as an IV bolus and may be repeated in 10 minutes; if used with an opioid, continuous cardiovascular monitoring is warranted. Oral midazolam for premedication before a dressing change at 0.5 mg/kg can be highly effective in reducing anxiety surrounding dressings. Dexmedetomidine infusion may be required for children with high levels of anxiety or who are refractory to benzodiazepine therapy, but this requires monitoring in an intensive care unit (ICU) setting. Postoperative pain after burn surgery, which is severe because of the combination of donor sites and the wound itself, is often treated with a multimodal continuous infusion of an opioid (hydromorphone or morphine) and sedative (dexmedetomidine and/or ketamine). This combination decreases opioid requirements and improves pain but requires monitoring in an ICU. Regional blocks by a trained anesthesiologist can mitigate donor site pain.

During the process of weaning from IV analgesics, the dose of opiates is reduced by 25% over 1-3 days, sometimes with the addition of oral opioids and then acetaminophen as opioids are tapered. When weaning off antianxiety medications, the approach involves reducing the dose of benzodiazepines, at 25–50% per dose, daily over 1-3 days.

Regular evaluation of burned children during hospitalization by a trained psychologist or psychiatrist is necessary, as PTSD, anxiety, depression, acute stress disorder, and other psychiatric issues are common after burn injury. Early recognition and treatment of the patient and family improve psychosocial outcomes. As a result, there is a growing use of *psychotropic medication* in the care of children with burns, including prescription of selective serotonin reuptake inhibitors as antidepressants, the use of neuroleptic agents in the critical care setting, and the treatment of PTSD with prazosin.

Reconstruction and Rehabilitation

To ensure maximum cosmetic and functional outcome, occupational and physical therapy must begin on the day of admission, continue throughout hospitalization, and for many patients, continue after discharge. Physical rehabilitation involves body and limb positioning, splinting, exercises (active and passive movement), assistance with activities of daily living, and gradual ambulation. These measures maintain adequate joint and muscle activity with as normal a range of movement as possible after healing or reconstruction. **Pressure therapy** is necessary to reduce hypertrophic scar formation; a variety of prefabricated and custom-made garments are available for use in different body areas. These custom-made garments deliver consistent pressure on scarred areas; shorten the time of scar maturation; and decrease scar thickness, redness, and associated itching. Continued adjustments to scarred areas (scar release, grafting, rearrangement) and multiple minor cosmetic surgical procedures are necessary to optimize long-term function and improve appearance. Replacement of areas of alopecia and scarring has been achieved with the use of tissue-expander techniques. The use of ultrapulse laser for reduction of scarring is an adjunct in scar management. Pruritis can be a severe issue in the rehabilitative phase. Commonly used oral agents include antihistamines such as loratadine, hydroxyzine, and diphenhydramine, as well as gabapentin or H2 blockers. Topical agents include moisturizers, topical steroid creams, or colloidal oatmeal baths. Refractory itching may be treated with desensitization therapy or laser treatment, although literature supporting these therapies is scarce.

School Reentry and Long-Term Outcome

Optimally the child will return to school immediately after discharge. Occasionally, a child may need to attend on an altered schedule because of rehabilitation needs. It is important for the child to return to the normal routine of attending school and being with peers to begin the resocialization process. Planning for a return to home and school often requires a **school reentry program** that is individualized to each child's needs. For a school-age child, planning for the return to school occurs simultaneously with planning for discharge. The hospital schoolteacher contacts the local school and plans the program with the school faculty, nurses, social workers, recreational/child-life therapists, and rehabilitation therapists. This team should work with students and staff to ease anxiety, answer questions, and provide information. Burns and scars evoke fears in those who are not familiar with this type of injury and can result in a tendency to withdraw from or reject the burned child. A school reentry program designed based on the child's developmental and educational needs can alleviate these fears and facilitate the child's reintegration into the school environment.

Major medical advances have made it possible to save the lives of children with massive burns. Although some children have lingering physical difficulties, most have a satisfactory quality of life. The comprehensive burn care that includes experienced multidisciplinary aftercare plays an important role in recovery. Table 89.8 lists the long-term disabilities and complications of burns.

ELECTRICAL BURNS

Three types of burns are caused by electricity: electrical burns, caused by electricity passing through the body; arc burns, caused by the heat released from high-amperage currents discharging through the air; and thermal contact burns, from touching a hot electrical device. Electrical burns are divided into high voltage (>1,000 volts) and low voltage (<1,000 volts). Electricity is delivered via alternating current (AC), which is generally used in households, or direct current (DC), often used in industry or car batteries. The majority of pediatric electrical burns involve 110 volts AC electricity and occur in the household. **Minor electrical burns** in children usually occur as a result of biting on an extension cord or inserting an object in an electrical outlet. These injuries produce localized burns to the mouth or finger. Children who chew electrical cords usually sustain burns to portions of the upper and lower lips that come in contact with the extension cord, particularly the corners of the mouth. Because these are *nonconductive* injuries (do not extend beyond the site of injury), hospital admission is not necessary. Care is focused on the area of the injury visible in the mouth, ensuring it is low voltage and does not cause entry or exit wounds or cardiac issues. Treatment with topical antibiotic creams is sufficient until the patient is seen in a burn unit outpatient department or by a plastic surgeon for potential reconstruction or excision of the burn site.

A more serious category of electrical burn is the **high-voltage electrical burn**, for which children must be admitted for observation,

Table 89.8 Common Long-Term Complications and Disabilities in Patients with Burn Injuries

COMPLICATIONS AFFECTING THE SKIN AND SOFT TISSUE	**PSYCHIATRIC AND NEUROLOGIC DISABILITIES**
Hypertrophic scars	Sleep disorders
Susceptibility to minor trauma	Adjustment disorders
Dry skin	Posttraumatic stress disorder
Contractures	Depression
Itching and neuropathic pain	Body image issues
Alopecia	Neuropathy and neuropathic pain
Chronic open wounds	Long-term neurologic effects of carbon monoxide poisoning
Skin cancers	Anoxic brain injury
Epidermal inclusion cysts	**LONG-TERM COMPLICATIONS OF CRITICAL CARE**
Cutaneous abscesses	Deep vein thrombosis, venous insufficiency, or varicose veins
ORTHOPEDIC DISABILITIES	Tracheal stenosis, vocal cord disorders, or swallowing disorders
Amputations	Renal or adrenal dysfunction
Contractures	Hepatobiliary or pancreatic disease
Heterotopic ossification	Cardiovascular disease
Temporary reduction in bone density	Reactive airway disease or bronchial polyposis
Decreased endurance and weakness	**PREEXISTING DISABILITIES THAT CONTRIBUTED TO THE INJURIES**
METABOLIC DISABILITIES	Risk-taking behavior
Heat sensitivity	Untreated or poorly treated psychiatric disorder
Obesity	
Glucose intolerance	
Hypertension	

Modified from Sheridan RL, Schultz JT, Ryan CM, et al. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 6-2004: A 35-year-old woman with extensive, deep burns from a nightclub fire. *N Engl J Med.* 2004;350:810–821.

regardless of the extent of the surface area burn. Deep muscle injury is typical and cannot be readily assessed initially. These injuries occur in high-voltage installations, such as electric power stations or railroads; children climb an electric pole and touch an electric box out of curiosity or accidentally touch a high-tension electrical wire. Such injuries have a mortality rate of 3–15% for children who arrive at the hospital for treatment. Survivors have a high rate of morbidity, including major limb amputations. Points of entry of current through the skin and the exit site show characteristic features consistent with current density and heat. The majority of entrance wounds involve the upper extremity, with small exit wounds in the lower extremity. The current is conducted throughout the body, regardless of entry and exit points. Virtually any structure in the body is at risk (Table 89.9). Damage to the abdominal viscera, thoracic structures, and nervous system (confusion, coma, paralysis) in areas remote from obvious extremity injury occurs and must be sought, particularly in injuries with multiple current pathways or those in which the victim falls from a high pole. *Cardiac abnormalities,* manifested as ventricular fibrillation or cardiac arrest, are common; patients with high-tension electrical injury need an initial electrocardiogram (ECG) and cardiac monitoring until they are stable and have been fully assessed. Higher-risk patients have abnormal ECG findings and a history of loss of consciousness. Renal damage from *deep muscle necrosis* and subsequent myoglobinuria is another complication; such patients need forced alkaline diuresis to minimize renal damage. Soft tissue (muscle) injury of an extremity may produce a **compartment syndrome** (see Chapter 80). Aggressive removal of all dead and devitalized tissue, even with the risk of functional loss, remains the key to effective management of the electrically damaged extremity. Early debridement facilitates early closure of the wound. Damaged major vessels must be isolated and buried in a viable muscle to prevent exposure. Survival depends on immediate intensive care; functional result depends on long-term care and delayed reconstructive surgery. The incidence of cataract formation is also increased in patients who have sustained electrical injuries; patients should be referred to an ophthalmologist for regular examinations.

Arc burns generally are caused by clothing *ignition* from the superheated arc that can be emitted from high-amperage current discharge. The hallmark of this injury is a large cutaneous burn following clothing lines and covered in thick soot. Discreet entrance and exit points are not generally seen. Muscle injury is rare, as current does not actually traverse the skin. Treatment should follow the principles for major flame burn injury treatment.

Contact burns, in which tissue destruction is localized to a small area of contact with an electrical box with no evidence of electricity conducted through the body, are generally treated as any other burn injury. Careful history and physical examination should be performed to assure that there was no transmission of electricity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

89.1 Lightning Burns

Tina L. Palmieri

Worldwide, lightning occurs approximately 50 times per second, primarily via ground strikes involving 30,000-100,000 amperes at 30,000 Kelvin temperature. Fortunately, the incidence of lightning burns is low, with 400 injuries and 40 deaths per year attributed to lightning. Lightning injury occurs via (1) direct strike (electrical current), (2) thermal burns from conversion of electrical energy to heat, or (3) mechanical trauma from the acoustic shock wave, flying debris, fall, or muscle contraction. The most common form of lightning burn, accounting for approximately half of lightning injuries, is **ground current**, in which lightning strikes the ground or an object near an individual and travels through the ground to the individual. **Side splash** injuries constitute ~30% of lightning injuries and occurs when current jumps from a nearby object, then follows the path of least resistance to an individual. Direct strikes account for 5% of lightning injuries. Sudden death after a direct strike is due to simultaneous cardiac and respiratory arrest from depolarization of cardiac muscle cells and paralysis of the medullary respiratory center.

Lightning cutaneous burns depend on the current path, the type of clothing worn, the presence of metal, and cutaneous moisture. Entry, exit, and path lesions are possible; the prognosis is poorest for lesions of the head or legs. Internal organ injury along the path is common

Table 89.9 Electrical Injury: Clinical Considerations

SYSTEM	CLINICAL MANIFESTATIONS	MANAGEMENT
General	—	• Extricate the patient • Perform ABCs of resuscitation; immobilize the spine • Obtain history: voltage, type of current • Obtain complete blood count with platelets, electrolytes, BUN, creatinine, and glucose
Cardiac	Dysrhythmias: asystole, ventricular fibrillation, sinus tachycardia, sinus bradycardia, premature atrial contractions, premature ventricular contractions, conduction defects, atrial fibrillation, ST- and T-wave changes	• Treat dysrhythmias • Provide cardiac monitor, electrocardiogram, and radiographs with suspected thoracic injury • Perform creatinine phosphokinase with isoenzyme measurements if indicated
Pulmonary	Respiratory arrest, acute respiratory distress, aspiration syndrome	• Protect and maintain the airway • Provide mechanical ventilation if indicated, chest radiograph, and arterial blood gas levels
Renal	Acute kidney injury, myoglobinuria	• Provide aggressive fluid management unless central nervous system injury is present • Maintain adequate urine output, >1 mL/kg/hr if myoglobinuria; addition of HCO_3^-, mannitol may be needed to alkalinize urine and stimulate diuresis, respectively • Consider central venous or pulmonary artery pressure monitoring • Measure urine myoglobin; perform urinalysis; measure BUN, creatinine
Neurologic	Immediate: loss of consciousness, motor paralysis, visual disturbances, amnesia, agitation; intracranial hematoma	• Treat seizures • Provide fluid restriction if indicated
	Secondary: pain, paraplegia, brachial plexus injury, syndrome of inappropriate antidiuretic hormone secretion, autonomic disturbances, cerebral edema	• Consider spine radiographs and MRI, especially cervical
	Delayed: paralysis, seizures, headache, peripheral neuropathy	• Perform CT or MRI scan of the brain if indicated
Cutaneous/oral	Oral commissure burns, tongue and dental injuries; skin burns resulting from ignition of clothes, entrance and exit burns, and arc burns	• Document entrance and exit wounds • Treat cutaneous burns; determine patient's tetanus status • Obtain consultation for plastic surgery of ear, nose, and throat, if indicated
	Electrical burns to mouth could include oral commissures and lips; low-voltage electrical burns secondary to high conductivity of saliva	• Ensure no entry or exit wounds and no cardiac involvement • Confirm all injuries are localized • Management is observation until eschar sloughs off and granulation tissue fills in • If bleeding at corner of mouth from labial artery, pinch lower lip to stop bleeding and consult surgeon • High risk for scarring; refer to burn center for long-term management
Abdominal	Viscus perforation and solid-organ damage; ileus; abdominal injury rare without visible abdominal burns	• Place nasogastric tube if patient has airway compromise or ileus • Obtain serum ALT, AST, amylase, BUN, and creatinine measurements and CT scans as indicated
Musculoskeletal	Compartment syndrome from subcutaneous necrosis limb edema and deep burns	• Monitor patient for possible compartment syndrome
	Long-bone fractures, spine injuries	• Obtain radiographs and orthopedic/general surgery consultations as indicated
Ocular	Visual changes, optic neuritis, cataracts, extraocular muscle paresis	• Obtain an ophthalmology consultation to document and follow for cataract formation

AST, Aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen.
Adapted from Hall ML, Sills RM. Electrical and lightning injuries. In: Barkin RM, ed. *Pediatric Emergency Medicine*. St Louis: Mosby; 1997: p. 484.

and *does not* relate to the severity of the cutaneous burn. Linear burns, usually first- or second-degree, are in the locations where sweat is present. **Feathering**, also called *Lichtenberg figures,* is an arborescent pattern appearing on the skin and is pathognomonic for lightning injury (Fig. 89.7). The feathering skin appearance, thought to be caused by changes in cutaneous blood flow, is transient and disappears within several hours. Lightning may ignite clothing or produce serious cutaneous burns from heated metal in the clothing. Internal complications of lightning burns include cardiac arrest caused by asystole, transient hypertension, premature ventricular contractions, ventricular fibrillation, and myocardial ischemia. Most severe cardiac complications resolve if the patient is supported with CPR (see Chapter 79). CNS complications include cerebral edema, hemorrhage, seizures, mood changes, depression, and paralysis of the lower extremities. Rhabdomyolysis and myoglobinuria (with possible renal failure) also occur but are rare. Ocular manifestations include vitreous hemorrhage, iridocyclitis, retinal tearing, or retinal detachment. Rupture of the tympanic membrane occurs in 50–80% of those sustaining a direct strike.

Treatment of lightning injury generally follows traditional trauma management with one exception: In the event of multiple lighting injuries (mass casualty), a "reverse triage" system is employed, in which initial treatment is focused on those who appear to be in cardiac arrest,



Fig. 89.7 Lightning burn: Lichtenberg feathering. (*Courtesy Dr. Mary Ann Cooper.*)

which is often reversible. Early attention to ventilation after restoration of cardiac rhythm in lightning-injured patients is crucial to prevent recurrent cardiovascular collapse and hypoxic brain injury. This triage algorithm is employed because those who have cardiorespiratory function immediately after the strike rarely succumb to their injury before hospital arrival. Ultimate outcomes depend on injury severity, mental status, organ involvement, cardiac arrest presence, and arrhythmias. Lightning survivors who have a normal ECG and normal vital signs and no obvious injury can be discharged home if they *do not* have history of a direct strike, loss of consciousness, focal neurologic complaint, major trauma, significant burns, or chest pain or dyspnea. However, they should be referred for ophthalmologic evaluation and audio-vestibular evaluation should there be ocular or otic injury. Neurologic effects of lightning injury may be significant. CNS dysfunction can be immediate or delayed and includes spinal cord injury, ischemic stroke, or *keraunoparalysis* (temporary condition that mimics spinal cord injury) as well as trauma-related injuries such as skull fractures or spinal cord injury. Personality alterations and sleep disorders may develop over time post injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 90

Cold Injuries

Jennifer Dow

Children and youth are exposed to cold environments through outdoor recreation, occupational activities, or housing crises. Although cold injuries are commonly attributed to subfreezing temperatures, it is a misnomer that it must be below 0°C (32°F) for systemic injury or local tissue damage to occur. Injury from cold occurs when the body's ability to generate heat is overwhelmed by environmental loss.

MECHANISMS OF HEAT TRANSFER

Environmental heat or cold injury occurs when the metabolic capacity for thermoregulation cannot maintain core body temperature in the setting of extreme environmental temperatures. The hypothalamus controls the production and conservation of heat, responding to central and peripheral receptors. Local skin temperature is partially responsible for the regulation of peripheral blood flow. Heat production is a product of cellular metabolism and by both voluntary (exercise) and involuntary (shivering) muscle use, while vasoconstriction and behavioral action influence conservation. Heat is transferred to the environment by five mechanisms: radiation, conduction, convection, respiration, and evaporation.

Radiation is the transfer of heat from one object to another without physical contact. This type of heat loss is moderated by vasoconstriction, diminishing warm blood flow to the periphery, and behavioral adaptation of wearing insulating layers. Medications or conditions that prohibit the vasoconstrictive response contribute to heat loss by radiation. Children may not have the knowledge or experience to recognize when additional clothing is necessary; adults are obliged to ensure that appropriate clothing is available. In a dry environment, radiation is the predominant method of heat transfer. **Conduction** is the direct transfer of heat to another object and is the primary mechanism of heat loss when a body is immersed, as water has up to 30 times more thermal conductivity than air. Heat is also conducted when an individual touches a cold object (e.g., a cold rock, snow, metal chair). Behavioral adaptations include avoidance and placement of insulation between the individual and the surface. **Convective** loss of body heat to cooler circulating air or water can be mitigated by clothing and vasoconstriction. Convection is a method of rewarming, using hot air as a delivery method. **Evaporative** heat loss results from the conversion of water (sweat) to vapor; like *respiratory* loss, it is a small but obligate contribution to thermal balance.

HYPOTHERMIA

Accidental hypothermia is the unintentional drop in core temperature below 35°C (95°F), occurring when the combination of physiologic and behavioral mechanisms to maintain core temperature are overwhelmed by environmental losses. Although cold and wet environments pose the most significant risk, accidental hypothermia can occur in any season and in most climates. The predominant clinical manifestations are reflective of disruptions of the cardiopulmonary and central nervous systems (Table 90.1). Cerebral function begins to diminish at a core temperature of 33–34°C (91.4–93.2°F), with early manifestations being irritability, confusion, and poor decision-making, progressing to lethargy, somnolence, and coma. Cerebral oxygen requirements are decreased by cooling, affording transient protection in cardiac standstill or cold-water drowning events. The initial cardiopulmonary response to cold is an increase in cardiac output and ventilation to support the metabolic demand of shivering. Further cardiac cooling manifests as bradycardia and abnormalities of cardiac conduction (atrial and ventricular dysrhythmias, including fibrillation) (Fig. 90.1). The crucial factors for reducing morbidity and mortality due to hypothermia are prevention, prompt recognition, and rapid treatment.

Risk Factors and Prevention of Hypothermia

The risk factors associated with hypothermia are extensive. Illnesses, medications, and substance use can disrupt the normal physiologic responses to cold. Vasoconstriction is disrupted by ethanol, vasodilatory medications, and infections. Central nervous system (CNS) trauma, stroke, medications (antidepressants, mood stabilizers, anxiolytics), and endocrine disorders (hypothyroid, adrenal insufficiency, diabetes, hypoglycemia, hypopituitarism) disrupt the hypothalamic response to cold. Mental illness, intoxication (opiates, organophosphates, barbiturates, carbon monoxide), and lack of awareness, as seen in the extremes of age, may impair the ability to recognize cold. General conditions of malnutrition and inability to move make it such that the patient does not have the caloric reserves to shiver or cannot move safely out of the cold. Autonomic dysfunction may produce hypothermia. Knowledge of these conditions ideally results in a heightened attentiveness to the potential for hypothermia. Active prevention includes awareness of the weather conditions and the utilization of appropriate clothing. Insulation

Table 90.1 Physiologic Characteristics of the Four Zones of Hypothermia

STATE	CORE TEMPERATURE °C (°F)	CHARACTERISTICS
Mild	35 (95)	Urine temperature, 34.8°C (94.6°F); increased shivering thermogenesis; increase in metabolic rate
	34 (93.2)	Amnesia and dysarthria develop; normal blood pressure; maximum respiratory stimulation
	33 (91.4)	Ataxia, apathy develop
Moderate	32 (89.6)	Stupor; 25% decrease in oxygen consumption
	31 (87.8)	Decreased shivering thermogenesis
	30 (86)	Atrial fibrillation and other dysrhythmias; poikilothermia; pulse and cardiac output two-thirds normal; insulin ineffective
	29 (85.2)	Progressive decrease in level of consciousness, pulse, and respiration; pupils dilated
Severe	28 (82.4)	Ventricular fibrillation susceptibility; 50% decrease in oxygen consumption and pulse
	27 (80.6)	Losing reflexes and voluntary motion
	26 (78.8)	Major acid-base disturbances; no reflexes or response to pain
	25 (77)	Cerebral blood flow one-third normal; cardiac output 45% normal; pulmonary edema may develop
	24 (75.2)	Significant hypotension
	23 (73.4)	No corneal or oculocephalic reflexes
	22 (71.6)	Maximum risk of ventricular fibrillation; 75% decrease in oxygen consumption
Profound	20 (68)	Lowest resumption of cardiac electromechanical activity; pulse 20% of normal
	19 (66.2)	Flat electroencephalogram
	18 (64.4)	Asystole develops
	14.2 (57.6)	Lowest accidental hypothermia survival in an infant
	13.7 (56.7)	Lowest accidental hypothermia survival in an adult
	9 (48.2)	Lowest therapeutic hypothermia survival

From Zafren K, Danzl DF. Accidental hypothermia. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. *Rosen's Emergency Medicine*, 9th ed. Philadelphia: Elsevier; 2018, Table 132.1, p. 1744.

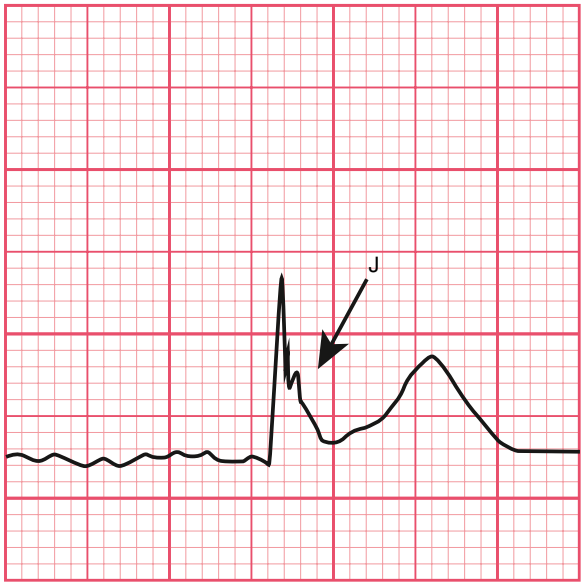

Fig. 90.1 Characteristic J or Osborne wave of hypothermia (temp <32°C) closely follows QRS. It may be mistaken for a T wave with narrow QT interval if the true T wave is not appreciated. The slightly rounded peak distinguishes it from R′ of bundle branch block. (*From Gunnarsson B, Heard CMB. Accidental hypothermia. In: Zimmerman JJ, Clark RSB, Fuhrman BP, et al., eds. Fuhrman & Zimmerman's Pediatric Critical Care, 6th ed. Elsevier: Philadelphia; 2022: Fig. 114.1, p. 1333.*)

and ease of layering are factors to be considered when choosing clothing. Removing a layer while engaging in aerobic activity helps prevent sweating and subsequent evaporative heat loss; replacing it when activity slows prevents loss by radiation through the inadequate insulation. Socks and gloves should fit properly, without circulatory impingement, and be constructed of materials other than cotton. Covering the head and face prevents losses through these exposed areas. Infants and young children will lose more heat by radiation through the head than adults because of its relatively increased surface area. The utilization of wind-blocking materials mitigates loss due to convection, and waterproofing keeps clothing dry and minimizes losses resulting from convection and radiation. Additional preventative measures are ensuring adequate nutrition for the activity, recognizing an increased metabolic demand in the cold, and having access to shelter for warmth.

Clinical Presentation of Hypothermia

Hypothermia is a cold injury syndrome with progressive signs and symptoms (see Table 90.1 and Fig. 90.2). The differential diagnosis is broad, and the clinician must be aware of the environment from which the patient presents. It is also essential that the clinician recognize that each patient is unique and presents with subtle differences. A patient may continue to shiver below the 30°C (86°F) "cut-off" but manifest all other signs of moderate to severe hypothermia. Standard classification is based on measured core temperature, whereas field classification is based on signs and symptoms (see Fig. 90.2). Treatment of all stages includes preventing further heat loss and initiating rewarming (Fig. 90.3).

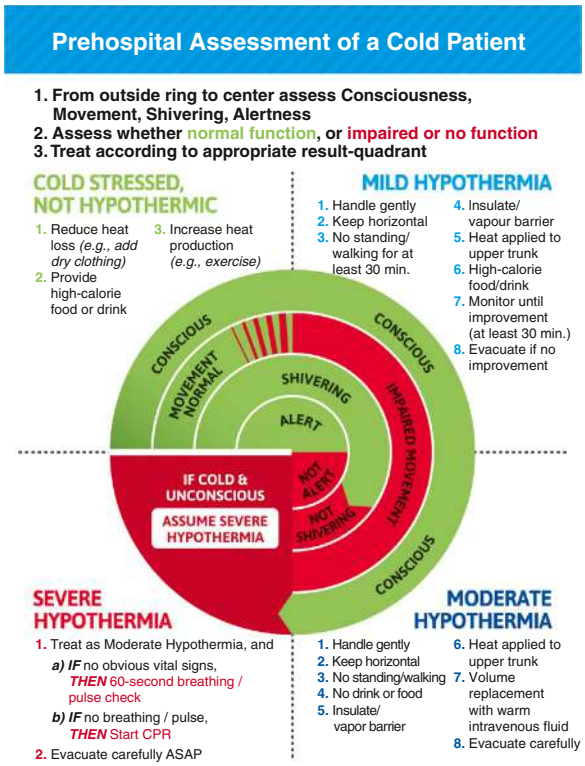

Fig. 90.2 Algorithm for field assessment and treatment of a cold patient. (*Sources: BICOrescue.com; Zafren K, Giesbrecht GG, Danzl DF, et al. Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2014 update. Wilderness Environ Med. 2014;25(4 Suppl):S66-S85.*)

Cold Stress

Cold stress is marked by shivering and a core temperature >35°C (95°F). Measures to prevent further heat loss and increase heat production are all that are necessary for reversal. This may entail increasing physical activity to generate warmth, relocating to a warm environment, or adding clothing layers.

Mild Hypothermia

Patients with mild hypothermia are conscious and alert with measured core temperatures of 32–35°C (89.6–95°F). Most will shiver, even violently, if there are enough energy reserves. As the core temperature drops, the patient may begin to demonstrate discoordination or loss of fine motor control. Hemodynamic parameters are generally stable, with tachycardia and tachypnea observed due, in part, to the increased catecholamine response and support of the metabolic demands of shivering. Protection from further heat loss, removal and replacement of wet clothing, and calorie replacement should be initiated simultaneously. Application of insulation (e.g., sleeping bag) and a vapor barrier will optimize passive rewarming. Active external rewarming can be initiated using hot water bottles or rewarming heat packs applied to the neck, chest, upper torso, axilla, and groin. Try to avoid burns to exposed skin. Patients with mild hypothermia retain consciousness but may demonstrate diminished alertness. Transport for further evaluation and observation is recommended if they do not return to full alertness and function in the field.

Moderate Hypothermia

Moderate hypothermia, with core temperatures of 28–32°C (82.4–89.6°F), is the slowing phase of symptom progression. Patients present with bradycardia, respiratory depression, and altered mental status, manifesting as depressed level of consciousness, often stuporous, and hyporeflexia. Shivering generally stops at 30°C (86°F), but there is variation among patients. Active external rewarming should be initiated with heat applied to the upper torso, chest, axilla, and back. Fluid replacement is initiated with intravenous fluids, ideally containing glucose, warmed to 40–42°C (104–107.6°F). Cardiac monitoring is indicated, as a cold heart and hypothermia-associated acidosis increases the risk of unstable arrhythmias. Hemodynamically stable patients may be transported to any hospital; however, if unstable, a hospital with extracorporeal membrane oxygenation (ECMO) is recommended.

Severe/Profound Hypothermia

Core temperatures <28°C (82.4°F) are characterized by stupor, leading to coma with loss of cerebrovascular autoregulation. Further cardiovascular instability manifests as bradycardia, hypotension, and a significant risk for unstable tachycardias, often beginning as atrial fibrillation with progression to ventricular dysrhythmias. There is no coordinated musculoskeletal activity. Patients with severe hypothermia may appear dead. Cardiopulmonary resuscitation (CPR) should be initiated if there is no cardiac activity, as determined by a pulse check of at least 1 minute duration or the absence of organized electrical activity on a monitor. Bedside echocardiography may also be used to identify cardiac activity. Vasoactive medications should be held until the core temperature is >30°C (86°F) and then administered at twice the dosing interval until 35°C (95°F). Defibrillation or cardioversion, if indicated, is attempted once, at maximum power, then held until the core temperature is above 30°C (86°F).

In hypothermic cardiac arrest, rescuers should initiate CPR regardless of the patient's temperature. Contraindications to initiation of CPR include if there is obvious fatal injury, ice or snow is visualized in the airway, chest wall compression is impossible, or rescuers are at risk. The usual signs of death—rigor, pupillary dilation, and lividity—are unreliable in the hypothermic patient.

Complications of hypothermia include compartment syndrome, rhabdomyolysis, hyperkalemia or hypokalemia, hemoconcentration, hypercoagulability, disseminated intravascular coagulation (DIC), confusion (paradoxical undressing), Takotsubo cardiomyopathy, and mydriasis. Core temperature **afterdrop** is a decrease in core temperature after removal from the cold and/or when external rewarming begins; external rewarming extremities with frostbite is another risk factor.

Hypothermia is fatal if not treated. Prevention and risk mitigation through awareness of weather conditions, appropriate clothing and layering systems, and breaks for rewarming during outdoor activities will limit its incidence. Adults supervising children and adolescents participating in outdoor activities must be aware that behavior changes and apparent clumsiness might signal the onset of hypothermia.

SOFT TISSUE COLD INJURY

Soft tissue injuries caused by cold are divided into freezing and nonfreezing injuries. Frostbite is a freezing injury, whereas frostnip, chilblains (pernio), cold immersion, and cold-induced fat necrosis are nonfreezing injuries.

FROSTBITE

Frostbite is an injury occurring at or below freezing temperatures. It can have devastating effects with tissue loss leading to functional debility. It is preventable. Frostbite, like hypothermia, is a condition occurring when tissue heat loss is greater than the warmth delivered by peripheral perfusion. Minimizing exposure to cold, either by avoidance, use of appropriate clothing, and responding to changing conditions appropriately, are keys to frostbite prevention. Clothing, especially hand and footwear, should insulate well and not be constricting. Vasoconstriction inhibits peripheral cutaneous warming. Inhibitors of peripheral perfusion, such as vasoconstricting medications, circulatory disorders (e.g., Raynaud syndrome), and chronic skin conditions (e.g., psoriasis), increase frostbite risk. Emollients applied to the skin do not protect from the cold. Any complaints of numbness are to be taken seriously, and the child should be assessed for signs of cold injury in a protected environment. Frostnip, although not a freezing injury, does indicate that the temperature and exposure conditions may promote frostbite.

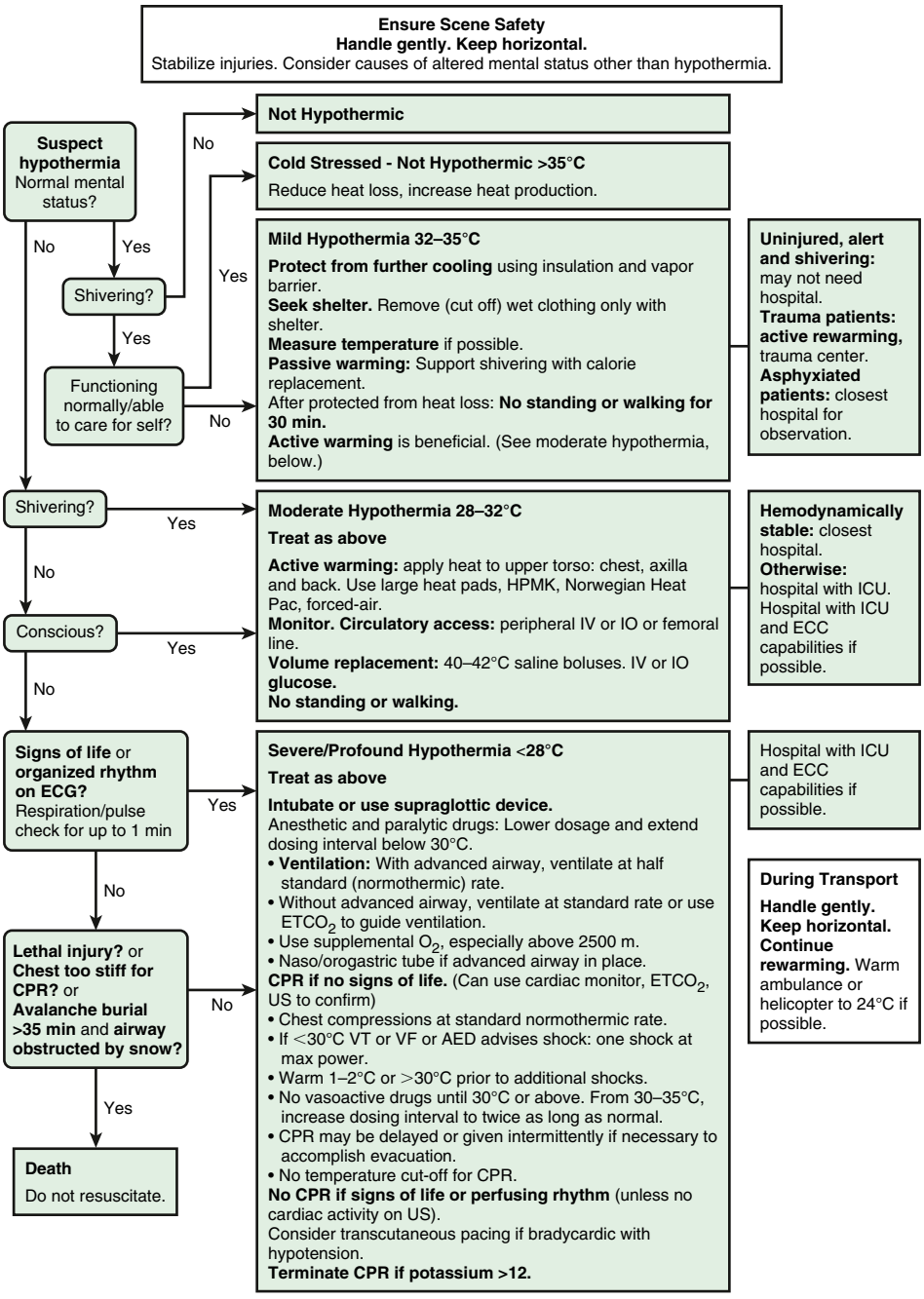

Fig. 90.3 Recommendations for out-of-hospital evaluation and treatment of accidental hypothermia. AED, Automatic external defibrillator; CPR, cardiopulmonary resuscitation; ECC, extracorporeal circulation; ECG, electrocardiogram; $ETCO_2$, end-tidal carbon dioxide; HPMK, Hypothermia Prevention Management Kit; ICU, intensive care unit; IO, intraosseous; IV, intravenous; US, ultrasound; VF, ventricular fibrillation; VT, ventricular tachycardia. (*From Zafren K, Giesbrecht GG, Danzl DF, et al. Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2014 update. Wilderness Environ Med. 2014;25:S66–S85, Fig. 2.*)

Table 90.2 Different Degrees of Frostbite and Their Physiologic Characteristics

GRADE I INJURY	GRADE II INJURY	GRADE III INJURY	GRADE IV INJURY
• Superficial • Edema and redness without tissue necrosis in the affected area • Numbness, firm white-yellow plaque • No blisters or necrosis • Occasional skin desquamation (5-10 days later)	• Blister formation • Erythema, substantial edema • Vesicles with clear or milky fluid • Blisters • Desquamation and black eschar formed	• Tissue necrosis • Hemorrhagic deeper blisters • Skin necrosis • Blue-gray discoloration	• Development of gangrene, requiring amputation • Full-thickness skin, subcutaneous tissue, muscle, tendon, and bone freezing • Little edema • Initially mottled, deep red or eventually dry, black, and mummified

Modified from Joshi K, Goyary D, Mazumder B, et al. Frostbite: Current status and advancements in therapeutics. *J Therm Biol*. 2020;93:102716, Table 1.

Pathophysiology of Frostbite

Frostbite is a freezing injury with four phases: prefreeze, freeze-thaw, vascular stasis, and late ischemic. The degree of cold, duration of exposure, and physiologic compromise caused by medications and underlying illness determine how severe the injury will be. The tissue cooling of **prefreeze** is marked by local vasoconstriction and ischemia without the formation of ice crystals. Intracellular and extracellular ice crystal development causes cellular damage during the **freeze-thaw phase**. Reperfusion leads to ischemic-reperfusion injury and initiation of the inflammatory cascade. **Vascular stasis** is characterized by both blood leaking from vessels and the formation of thrombi. Progressive tissue ischemia from micro-emboli, local thrombosis, and persistent



Fig. 90.4 Frostbite with clear vesiculations. (*Courtesy Dr. Bill Mills.*)



Fig. 90.5 Early appearance of severe frostbite of the hand after thawing. A purple color and absence of blisters are very unfavorable prognostic signs. (*Courtesy Dr. Ken Zafren.*)

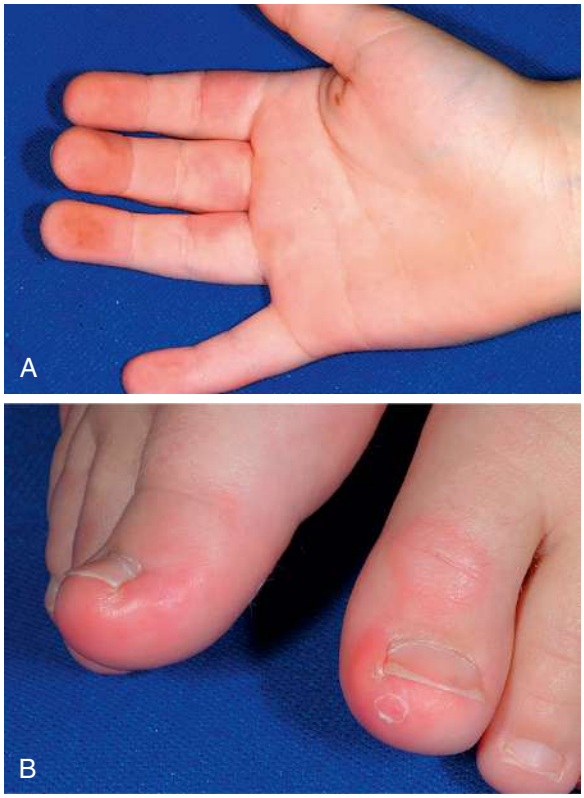

Fig. 90.7 A, Perniosis (chilblains). Edematous, red, painful nodules appeared on the fingers after exposure to cold. B, Perniosis (chilblains). Note the inflamed nodules on the toes of this adolescent girl. Although nodules resolved, painful nodules continued to develop on an annual basis beginning in January and lasting until April. She was otherwise healthy. (*From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Elsevier: Philadelphia; 2022, Figs. 20.48 and 20.49, p. 566.*)

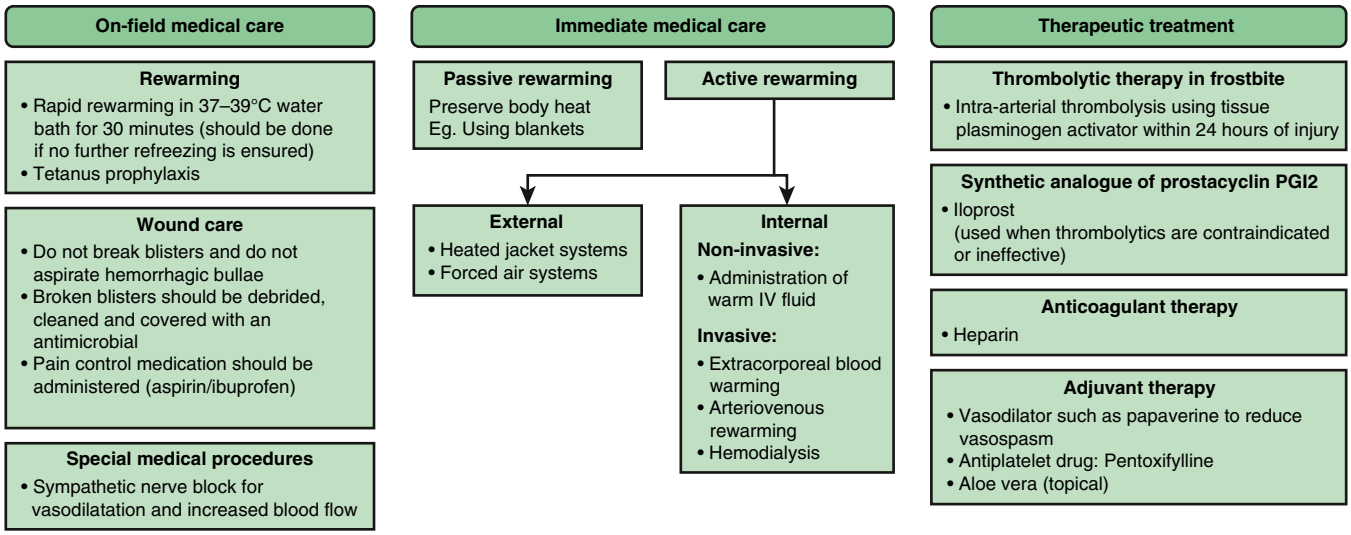

Fig. 90.6 Treatment protocol for the management of frostbite. (*Modified from Joshi K, Goyary D, Mazumder B, et al. Frostbite: Current status and advancements in therapeutics. J Therm Biol. 2020;93:102716, Fig. 2.*)

reperfusion injury marks the **late-ischemic phase**. Compromise of microcirculation and cellular destruction from crystal formation are the main factors contributing to cellular death.

Clinical Presentation of Frostbite

The depth of injury is the basis for the classification of frostbite injury. In the field, frostbite is classified as superficial or deep. Upon arrival to a healthcare facility, a degree or grade of injury is assigned after the tissue has thawed and any advanced imaging is performed (Table 90.2).

First-degree frostbite is marked by numbness and local erythema with a pale raised plaque in the area of injury. Only mild tissue sloughing occurs, and there is no infarction. **Second-degree** injury presents with clear, fluid-filled blisters and surrounding erythema (Fig. 90.4). Local edema may be present. First- and second-degree frostbite injury results in minimal tissue loss and is considered superficial in the field. **Third-degree** frostbite extends into the dermis and dermal vascular plexus. The resulting blisters are hemorrhagic. **Fourth-degree** injury involves the dermis and underlying tissues, extending into muscle and bone (Fig. 90.5). Third- and fourth-degree frostbite has anticipated tissue loss and is field classified as deep.

Treatment of Frostbite

Prevention is preferred for any environmental injury, but rapid recognition and treatment will mitigate the long-term impact. Once frostbite is suspected, the patient should be assessed for concomitant hypothermia. The injury must be protected from the cold and prevented from refreezing if spontaneous thawing has begun. Any constricting items, such as jewelry, are removed. Thawing should be initiated with a circulating water bath at 37–39°C (98.6–102.2°F). Pain medication should be administered. There are numerous combined therapies for frostbite, including anticoagulants, thrombolytics, and vasodilators (Fig. 90.6). The indications for each therapy depend on the extent of injury, length of time since tissue thaw, local availability, and individual national regulatory decisions. It is recommended that the clinician be aware of their local resources and protocols. Regardless, treatment with these agents must be initiated within 12-72 hours of tissue thaw.

NONFREEZING COLD INJURY

Nonfreezing cold injuries include but are not limited to frostnip, chilblains (pernio), cold-immersion foot, and cold-induced fat necrosis.

Frostnip is associated with vasoconstriction of skin exposed to the cold with ice crystals, or frost, forming on the skin surface. The tissue may be numb, and local pallor is present. There is no cellular damage, and the condition resolves rapidly upon warming. Frostnip does indicate that conditions are appropriate for frostbite, and preventative measures should be taken.

Chilblains, also called **pernio**, is an idiopathic condition suspected to be a vasculopathy. Typically occurring in cold, damp conditions, vasculitic-appearing lesions develop on the fingers and toes, ears, and exposed areas of the legs after environmental exposure (Fig. 90.7). It is suspected that vasoconstriction and inflammatory reaction are responsible for the lesions. Recognition and prevention of further cold exposure is key to treatment. The lesions are self-limiting, and symptoms may be addressed with nonsteroidal antiinflammatory drugs (NSAIDs) and topical soothing creams. Continued exposure to cold can cause persistent lesions. Lesions similar to chilblains have been noted in children with COVID-19 infection. **Familial chilblain lupus**, an autosomal dominant variant of lupus, is caused by variants in the *TREX1* and *SAMHD1* genes (see Chapter 90.1). Patients develop cold-induced erythematous peripheral skin lesions and manifest systemic disease typical of lupus. In addition, fever and arthralgias may be present.

Immersion foot or **trench foot** occurs with continuous immersion in warm or cold water. The injury occurs more rapidly in cold water. Continuous exposure to the wet environment, whether through actual immersion in water or saturated footwear, causes hyperemia, edema, and ultimately blister formation with skin sloughing. The condition can progress to ischemia and gangrene. Awareness of wet footwear and subsequent changing, or drying, of shoes and socks is the method of prevention. Vapor barrier socks or boots do not prevent sweat from accumulating and creating a wet environment. Like other cold injuries, treatment consists of thoroughly drying and warming the tissue. Antibiotics are not necessary unless signs of infection are present.

Cold-induced fat necrosis is secondary to local cold injury to the superficial adipose tissue. It presents with raised, erythematous nodules or plaques, evolving over 12-72 hours after exposure to cold. Distribution in children is predominantly on the face, specifically the cheeks and forehead. Obese children and adolescents may have lesions on areas poorly protected from the cold, including the buttocks, thighs, abdominal pannus, and under the chin. Lesions are self-limiting and typically resolve in 10-20 days. Treatment consists of rewarming, avoidance of the cold, and NSAIDs as necessary for discomfort.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

90.1 Cold-Induced Autoinflammatory and Other Genetic Disorders

James J. Nocton and James W. Verbsky

A number of **autoinflammatory** and other genetic disorders have been identified that are characterized by an *exacerbation of symptoms upon exposure to cold temperatures*. These disorders differ from **cold injury**, **cold urticaria**, and problems related primarily to vasoconstriction because they typically manifest very early in life and are associated with a wider spectrum of signs and symptoms, reflecting either underlying systemic inflammation or the protean effects of specific genetic variants. A relatively lower ambient temperature or rapid cooling and evaporation from the skin are often sufficient to produce the signs and symptoms of these disorders; therefore the relationship to cold temperature is not always obvious. The genetic variants associated with most of these disorders impact cellular signaling pathways that lead to the expression of proinflammatory cytokines in the absence of an extrinsic trigger; therefore most of these diseases are classified as autoinflammatory.

These conditions should be suspected primarily in infants or very young children who develop persistent, recurrent, or periodic fevers associated with rashes or arthralgias that cannot be explained by an infectious disease or another chronic inflammatory or rheumatic disease. Signs and symptoms associated with these diseases may begin as early as the first week of life. The very early onset distinguishes these genetic diseases from acquired conditions such as Raynaud phenomenon, pernio, cryoglobulinemia, cold urticaria, and other cold-induced problems potentially related to acquired autoimmunity. The rashes are most often evanescent and appear similar to urticaria; however, they are usually not pruritic and are histologically different from urticaria. Laboratory evidence of chronic inflammation is often present, including elevations of the erythrocyte sedimentation rate and C-reactive protein. The association with cold exposure may be subtle and not initially apparent.

The diagnostic algorithm for these disorders should begin with a thorough history and a careful examination, paying particular attention to potential additional signs of conjunctivitis, a frequent accompanying feature, decreased limb movement that might indicate arthralgia or arthritis, the morphology of any cutaneous lesions, and the association of symptoms and signs with cooling or colder temperatures. Unlike cold urticaria, the hivelike lesions often associated with these disorders cannot be precipitated by a cold stimulation test using the application of an ice cube to the skin. Measurement of serum inflammatory markers may help distinguish autoinflammatory disease from more benign conditions; infectious diseases may need to be excluded with appropriate testing. A skin biopsy may provide information that will help narrow the differential diagnosis by identifying either a neutrophilic dermatosis, granulomatous inflammation, or vasculitis characteristic of one of these diseases. Ultimately, focused genetic sequencing can

be performed, searching for specific genetic variants that will confirm a diagnosis.

Familial cold autoinflammatory syndrome (FCAS), along with neonatal-onset multisystem inflammatory disorder (NOMID) and Muckle-Wells syndrome (MWS), constitute the **cryopyrin-associated periodic syndromes (CAPS)** (see Chapter 204). These diseases are all the result of pathogenic variants in *NLRP3* which encodes the protein **cryopyrin**, a component of the inflammasome complex, which is critical in the production of the proinflammatory cytokines interleukin (IL)-1β and IL-18. Although each of these diseases may be exacerbated by cold exposure or cooling, the association with cold is most consistent in those with **FCAS**. **FCAS** should be considered in infants who develop episodes of a hivelike rash, often beginning in the neonatal period, accompanied by fever, conjunctivitis, joint pain, neutrophilia, thrombocytosis, and elevated inflammatory markers, and triggered by exposure to cold or low ambient temperatures. The rash is typically not pruritic and histologically consists of a neutrophilic perivascular and perieccrine inflammatory infiltrate. Episodes are short and generally last less than 24 hours. **MWS** is more severe than FCAS, causing more frequent hivelike rashes and fevers, along with arthralgias, conjunctivitis, and aseptic meningitis, and with potential eventual progression to hearing loss. Like FCAS, the onset of symptoms is most often in infancy, and the histology of skin lesions in these two disorders is similar. **NOMID** is the most severe form of CAPS and is associated with a nonpruritic urticarial rash often present at birth and more profound neurologic and bone disease. CAPS are inherited in an autosomal dominant manner, and the diagnosis is made based on clinical features and the identification of a variant in the NLRP3 gene. Variants in *NLRP12* and in *NLRC4* have also been associated with similar clinical syndromes sometimes referred to as **FCAS2** and **FCAS4**, respectively. Treatment with the IL-1 inhibitors anakinra and canakinumab has been effective in most individuals with CAPS.

PLCG2-associated antibody deficiency and immune dysregulation (PLAID) (sometimes referred to as **FCAS3**) is an autosomal dominant disease resulting from a pathogenic variant of *PLCG2*, which encodes a transmembrane enzyme expressed primarily in myeloid and lymphoid cells that regulates inflammasome activity and proinflammatory cytokine production. PLAID causes pruritic urticaria from birth induced by ambient cold temperatures or cooling and lasting for minutes to hours. In some individuals, acral blistering lesions resembling a burn may also be present during infancy on the ears, nose, and fingers. Histology of urticarial lesions reveals increased mast cells. Because PLCG2 is expressed in mast cells and affects mast cell degranulation, these subjects can have more classic hives as compared with other FCAS syndromes. Other lesions reveal noncaseating granulomas. Older individuals may develop syncope induced by cold exposure and a burning sensation in the throat when eating cold foods. Hypogammaglobulinemia may lead to frequent sinopulmonary and other infections. The diagnosis is made based on clinical features and the identification of variants in the PLCG2 gene. Treatment of PLAID includes avoiding evaporative cooling and minimizing cold exposure, antihistamines, and for those with evidence of immunodeficiency, intravenous immunoglobulin infusions to prevent frequent infections.

STING-associated vasculopathy with onset in infancy (SAVI) is an autosomal dominant disease resulting from a pathogenic variant in *TMEM173*, which encodes **stimulator of interferon genes (STING)**, an activator of interferon gene transcription (see Chapter 205). Signs and symptoms usually appear in infancy but may also appear later and include fever and a variety of cutaneous lesions. Violaceous nodules and plaques on the cheeks, ears, and nose and telangiectasias, pustules, or blisters, often most noticeable on the extremities, may occur. The skin lesions are exacerbated by cold temperatures, and some develop ulcerative or gangrenous lesions. In time, interstitial lung disease progressing to fibrosis has been described. Histology reveals vasculitis of medium and small vessels. The diagnosis is made based on clinical features and the identification of the variant in the TMEM173 gene. Responses to treatment with corticosteroids and immunomodulators, including cyclophosphamide and mycophenolate mofetil, have been variable and inconsistent. Janus kinase inhibitors, which inhibit interferon receptor signaling, have shown promise in treatment of these disorders.

Familial chilblain lupus is a rare condition triggered by cold exposure that presents with painful, bluish-red, papular or nodular lesions of the skin in acral locations. Ulceration can occur, but deep ulceration and necrosis are infrequent, and the lesions tend to heal without scarring. This is an autosomal dominant disorder caused by heterozygous variants in *TREX1* or *SAMHD1*, the same genes containing variants associated with Aicardi-Goutières syndrome (AGS). AGS is a syndrome characterized by developmental delay, abnormal neurologic signs, microcephaly with brain calcifications, and CNS pleocytosis, as well as skin lesions resembling chilblains. Both *TREX1* and *SAMHD1* are involved in DNA degradation, and their deficiencies result in intracellular nucleic acid that stimulates interferon production. AGS and familial chilblain lupus can be considered a spectrum of severity of the same genetic defect.

Factor XII–associated cold autoinflammatory syndrome is an autosomal dominant disease resulting from a pathogenic variant in *F12* encoding the coagulation factor XII. The variant leads to spontaneous activation of factor XII, which in turn increases bradykinin and IL-1 levels. Individuals with this mutation develop an urticarial-like rash that begins in the first few weeks of life precipitated by cold. The rash is nonpruritic and evanescent, and as individuals age it is accompanied by more severe systemic symptoms of chills, headaches, arthralgias, and fatigue. Serum inflammatory markers are elevated, and skin histology reveals perivascular macrophage and neutrophilic infiltrates. The diagnosis is made by identifying a variant in *F12*. Treatment with the IL-1 receptor antagonist anakinra or the bradykinin B2 receptor antagonist icatibant has shown promise in a small number of individuals.

Crisponi syndrome/cold-induced sweating syndrome (CS/CISS) is an autosomal recessive disease resulting from variants in *CRLF1* or *CLCF1*. These genes encode proteins involved in neurologic development, including facial motor neurons and the sympathetic nervous system; therefore this syndrome is not classified as an autoinflammatory syndrome. Symptoms and signs are typically apparent in the neonatal period and include fever, camptodactyly, and involuntary episodic contractions of facial and pharyngeal muscles resulting in breathing and feeding difficulties. There is high neonatal mortality, and those that survive develop cold-induced profuse sweating in childhood. Scoliosis and other dysmorphic features (depressed nasal bridge, high arched palate) are also common. The diagnosis is made by identifying a variant most commonly in *CRLF1*. Treatment of the neonatal symptoms is supportive. The cold-induced sweating is managed with clonidine, amitriptyline, or moxonidine.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 91

Anesthesia and Perioperative Care

John P. Scott

The continuum of anesthesia includes varying degrees of sedation (i.e., mild, moderate, or deep) and general anesthesia. All forms of **sedation** are characterized by some preservation of purposeful movement (see Chapter 92), whereas **general anesthesia** is defined by the complete loss of consciousness. Potent pharmacologic agents are required to suppress the perception and physiologic response to noxious stimuli. Perioperatively, the anesthesiologist is responsible for providing hypnosis and analgesia while preserving physiologic homeostasis (Table 91.1). This begins with the performance of a comprehensive preanesthesia history (Table 91.2). Although anesthetic risk has greatly decreased with advancements in pharmacology and monitoring technology, the persistent risk of perioperative morbidity and mortality demands vigilance. The risk is elevated in certain disease states (Table 91.3).

PREANESTHETIC EVALUATION

All children presenting for surgery should undergo a preanesthetic history and multiorgan system assessment with assignment of **American Society of Anesthesiologists Physical Status (ASA-PS)** (Table 91.4). Children of ASA-PS I-II generally require a brief focused history and physical examination with no additional testing. Patients with a complex medical history of ASA-PS ≥III require a more comprehensive preanesthetic assessment, often with ancillary preoperative testing. Every patient should be screened for anesthetic risks, including drug allergies, previous reactions to anesthetics, and family history of problems with anesthesia (e.g., sudden perioperative death, hyperthermia after surgery), which may indicate risk of malignant hyperthermia.

Respiratory System

Recent respiratory tract infections should be noted. *Clear rhinorrhea without fever or evidence of lower respiratory disease is not associated with increased anesthetic risk.* Respiratory illnesses associated with fever, mucopurulent nasal discharge, productive cough, or lower respiratory symptoms (wheezing, rales) are associated with increased airway reactivity and anesthetic complications (laryngospasm, bronchospasm, reduced mucociliary clearance, atelectasis, and hypoxemia) for up to 6 weeks thereafter. Thus elective procedures requiring general anesthesia should be postponed 4-6 weeks in this setting.

Children with reactive airway disease require a thorough preanesthetic assessment. Acute, potentially fatal bronchospasm can occur during induction of anesthesia and endotracheal intubation for routine, minor surgery in children with asthma. Risk factors for anesthetic complications include previous asthma exacerbations requiring (1) hospital admission within the previous year, (2) emergency department (ED) care within the last 6 months, (3) previous intensive care unit (ICU) admission, or (4) previous parenteral systemic corticosteroids. Ideally, children should be free of wheezing for least several days before surgery, even if this necessitates increased controller medication administration (β-adrenergic agonist and corticosteroids). Active wheezing may be an indication to delay elective surgery. Chronic respiratory conditions such as bronchopulmonary dysplasia and cystic fibrosis are also associated with significant intraoperative risks. Every effort should be made to ensure that children with such disorders achieve optimal respiratory status before surgery.

Table 91.1 Goals of Anesthesia

Analgesia
Amnesia
Hypnosis
Akinesia
Maintenance of physiologic homeostasis
Vigilance

Airway Evaluation

Induction of general anesthesia is associated with reduced spontaneous ventilation and airway reflexes. Prediction of difficult bag-mask ventilation and/or intubation before anesthesia is critical. Congenital anomalies associated with airway compromise include micrognathia, macroglossia, and thoracic anomalies (Table 91.5). Conditions that impair mouth opening (e.g., temporomandibular joint disease) should be noted. A history of wheezing or stridor may indicate postoperative airway complications and difficult intraoperative airway management. It is imperative to ask about a history of sleep-disordered breathing, including obstructive and central sleep apnea, as this may lead to increased risk of perianesthetic respiratory complications in children. Polysomnography is the gold standard for diagnosis and grading of sleep disordered breathing. The **STBUR** (snoring, trouble breathing, unrefreshed) questionnaire is used to identify patients with sleep-disordered breathing who may be at risk for perioperative respiratory complications. Postoperative admission for monitoring may be indicated for patients with moderate and severe forms of sleep-disordered breathing.

Cardiovascular System

Most anesthetic agents possess myocardial depressant properties. All patients should be screened for the presence of heart disease. Important cardiovascular considerations include history of congenital heart disease (CHD), cyanosis, arrhythmias, or cardiomyopathy. Room-air pulse oximetry should be performed as part of the preanesthetic evaluation. Accurate diagnosis of cardiac murmurs in neonates is essential. A history of cardiac dysrhythmias should be investigated because inhalational anesthetics may be arrhythmogenic. A pediatric cardiologist should evaluate children with known CHD undergoing surgery. Preoperative ancillary studies may include chest x-ray, electrocardiogram (ECG), echocardiogram, or cardiac catheterization. Lesions associated with increased anesthetic risk include single-ventricle heart disease, fixed obstructive outflow tract lesions (aortic valve and pulmonary valve stenosis), and cardiomyopathy. Children with these conditions should be cared for by a **cardiac anesthesia service**. Antibiotic prophylaxis for the prevention of bacterial endocarditis should be administered when appropriate in accordance with the American Heart Association (AHA) guidelines.

Hematologic System

Evidence of coagulopathy should be sought. Easy bruising, familial bleeding disorders, and anticoagulant (e.g., aspirin, heparin, direct oral anticoagulant [DOAC], warfarin) use should be discussed. Preoperative adequacy of hemostatic function (e.g., platelet count, fibrinogen, prothrombin time, partial thromboplastin time) and correction of coagulopathic disorders may be indicated for complex procedures associated with significant risk of perioperative hemorrhage. In neonates, assurance of vitamin K prophylaxis and adequate coagulation status is critical before any major surgery. Although anemia may be well tolerated in healthy children, anesthesia and surgery increase oxygen consumption. Preoperative anemia should be corrected when oxygen delivery is limited or blood loss is expected. In the patient with life-threatening hemorrhage (trauma), massive transfusion protocols of 1:1:1 replacement of packed red blood cells:fresh-frozen plasma:platelets should be used. Initiation of early antifibrinolytic therapy in the setting of life-threatening hemorrhage has been linked to reduced early morality.

Neurologic System

A history of neurologic and neuromuscular disorders should be sought. Preoperative developmental assessments may be helpful in interpreting age-dependent variation in the response to pain. Maintenance of appropriate perioperative anticonvulsant therapy is essential

Table 91.2 The Preanesthetic History

Child's Previous Anesthetic and Surgical Procedures
- Review previous anesthetic records:
  - Ease of mask ventilation
  - Grade of laryngoscopy; type and size of laryngoscope; endotracheal tube size
  - Issues during emergence (awakening) from anesthesia (postoperative vomiting, emergence delirium)
  - History of hyperthermia or acidosis in the child or family members

Perinatal Problems (Especially for Infants)
- Prematurity
- Need for supplemental oxygen or intubation and ventilation
- History of apnea and bradycardia
- History of cardiovascular compromise
- Other major illnesses and hospitalizations
- Family history of anesthetic complications, malignant hyperthermia, or pseudocholinesterase deficiency

Respiratory Problems
- Long-term exposure to environmental tobacco smoke
- Obstructive breathing score
- STBUR (snoring, trouble breathing, unrefreshed)
- Cyanosis (especially in infants <6 mo of age)
- Recurrent respiratory infections
- Recent lower respiratory tract infection
- Previous laryngotracheitis (croup) or laryngomalacia
- Reactive airway disease
- Airway abnormalities, facial anomalies, mucopolysaccharidosis

Cardiac Problems
- Murmur or history of congenital heart disease
- Dysrhythmia
- Exercise intolerance
- Syncope
- Cyanosis

Gastrointestinal Problems
- Reflux and vomiting
- Feeding difficulties
- Failure to thrive
- Liver disease
- Exposure to infectious pathogens

Neuromuscular Problems
- Neuromuscular diseases
- Developmental delay
- Myopathy
- Seizure disorder

Hematologic Problems
- Anemia
- Bleeding diathesis
- Tumor
- Immunocompromise
- Prior blood transfusions and reactions

Renal Problems
- Renal insufficiency, oliguria, anuria
- Fluid and electrolyte abnormalities

Psychosocial Considerations
- Drug abuse, use of cigarettes or alcohol
- Physical or sexual abuse
- Family dysfunction
- Previous traumatic medical or surgical experience
- Psychosis, anxiety, depression

Gynecologic Considerations
- Sexual history (sexually transmitted infections)
- Possibility of pregnancy

Current Medications
- Prior administration of corticosteroids

Allergies
- Drugs
- Iodine
- Latex products
- Surgical tape
- Food (especially soy and egg albumin)

Other
- Dental condition (loose or cracked teeth)
- When and what the child last ate (especially in emergency procedures)

in children with seizure disorders because the seizure threshold may be lowered perioperatively. Children with obstructive hydrocephalus typically require ventriculoperitoneal (VP) shunt insertion to divert cerebrospinal fluid (CSF) and to prevent intracranial hypertension (ICH). Repeated shunt malfunction is common, and these children may present for shunt revision with signs of ICH (vomiting, altered mentation, sundowning). Similarly, shunt patency and function should be ensured preoperatively in children with VP shunts presenting for non-neurosurgical procedures.

Psychologic Assessment

Surgery and painful medical procedures are psychologically traumatic events for children and families. Children who require anesthesia may experience fear and anxiety. They may also sense stressful signals from parents and caregivers. Children undergoing surgery may exhibit negative behavioral changes postoperatively. These maladaptive behavioral responses may include enuresis, separation anxiety, temper tantrums, and nighttime crying, as well as fear of strangers, medical providers, and hospitals. Sleep quality may be altered postoperatively, resulting in further behavioral compromise. Preoperative psychologic preparation programs have been developed to reduce the incidence of perioperative behavioral changes. **Parental presence during induction (PPI)** has not been shown to improve postoperative behavior. Oral preoperative midazolam (0.5 mg/kg) produces rapid-onset anxiolysis and amnesia and may decrease negative behavioral changes.

Genetic Evaluation

Children with genetic conditions may have syndrome-specific anesthetic considerations. For example, children with trisomy 21 may have cardiac anomalies, macroglossia, upper airway obstruction, and hypothyroidism (see Chapter 99.2). Atlantoaxial instability, common in trisomy 21, has been linked to cervical dislocation and spinal cord trauma with neck extension during intubation. Some anesthesiologists recommend extension and flexion lateral neck films to detect instability before surgery. For children with other known genetic disorders, it is essential to review specific anesthetic considerations.

PREOPERATIVE PREPARATION

Preoperative Fasting

Preoperative fasting guidelines have been developed to reduce the incidence of aspiration of gastric contents during anesthesia. Aspiration may lead to laryngospasm, bronchospasm, and postoperative pneumonitis. Aspiration of gastric contents may be a potentially lethal complication in children with chronic lung disease or critical illness. Table 91.6 lists preoperative fasting guidelines (e.g., nothing by mouth, or nil per os [NPO] status). Clear, sweet liquids (e.g., Pedialyte, 5% dextrose

Table 91.3 Specific Pediatric Diseases and Their Anesthetic Implications

DISEASE	IMPLICATIONS
RESPIRATORY SYSTEM	
Asthma	Intraoperative bronchospasm that may be life threatening
	Pneumothorax or atelectasis
	Optimal preoperative medical management is essential
Difficult airway	Special equipment and personnel may be required
	Should be anticipated with dysmorphic features or storage diseases
	Patients with trisomy 21 may require atlantooccipital joint evaluation
	Increased risk with acute airway obstruction, epiglottitis, laryngotracheobronchitis, or airway foreign body
Bronchopulmonary dysplasia	Barotrauma with positive pressure ventilation
	Oxygen toxicity, pneumothorax a risk
Cystic fibrosis	Airway reactivity, bronchorrhea, increased intraoperative pulmonary shunt and hypoxia
	Risk of pneumothorax, pulmonary hemorrhage
	Atelectasis, risk of prolonged postoperative ventilation
	Patient should be assessed for cor pulmonale
Sleep apnea	Pulmonary hypertension and cor pulmonale must be excluded
	Careful postoperative observation for obstruction required
CARDIAC	
	Bacterial endocarditis prophylaxis as indicated
	Use of air filters; careful purging of air from the intravenous equipment
	Physician must understand the effects of various anesthetics on the hemodynamics of specific lesions
	Possible need for preoperative evaluation of myocardial function and pulmonary vascular resistance
	Provide information about pacemaker function and ventricular device function
HEMATOLOGIC	
Sickle cell disease	Possible need for simple or exchange transfusion based on preoperative hemoglobin concentration and percentage of hemoglobin S
	Avoid hypoxemia, hypothermia, dehydration, and hyperviscosity states
Oncology	Pulmonary evaluation of patients who have received bleomycin, *bis*-chloroethyl-nitrosourea, chloroethyl-cyclohexyl-nitrosourea, methotrexate, or radiation to the chest
	Avoidance of high oxygen concentration
	Cardiac evaluation of patients who have received anthracyclines; risk of severe myocardial depression with volatile agents
	Potential for coagulopathy
RHEUMATOLOGIC	
	Limited mobility of the temporomandibular joint, cervical spine, arytenoid cartilages
	Careful preoperative evaluation required
	Possible difficult airway
GASTROINTESTINAL	
Esophageal, gastric	Potential for reflux and aspiration
Liver	Altered metabolism of many anesthetic drugs
	Potential for coagulopathy and uncontrollable intraoperative bleeding
RENAL	
	Altered electrolyte and acid-base status
	Altered clearance of many anesthetic drugs
	Need for preoperative dialysis in selected cases
	Succinylcholine to be used with extreme caution and only when the serum potassium level has recently been shown to be normal
NEUROLOGIC	
Seizure disorder	Avoidance of anesthetics that may lower the seizure threshold
	Optimal control ascertained preoperatively
	Preoperative serum anticonvulsant measurements
Increased intracranial pressure	Avoidance of agents that increase cerebral blood flow
	Maintain cerebral perfusion pressure.
Neuromuscular disease	Avoidance of depolarizing relaxants; at risk for hyperkalemia
	Patient may be at risk for malignant hyperthermia; avoid volatile anesthetics in myopathies
Developmental delay	Patient may be uncooperative during induction and emergence
Psychiatric	Monoamine oxidase inhibitor (or cocaine) may interact with meperidine, resulting in hyperthermia and seizures
	Selective serotonin reuptake inhibitors may induce or inhibit various hepatic enzymes that may alter anesthetic drug clearance
	Illicit drugs may have adverse effects on cardiorespiratory homeostasis and may potentiate the action of anesthetics
ENDOCRINE	
Diabetes	Greatest risk is unrecognized intraoperative hypoglycemia; intraoperative blood glucose level monitoring needed especially when insulin is administered
SKIN	
Burns	Difficult airway
	Fluid shifts
	Bleeding
	Risk of rhabdomyolysis and hyperkalemia from succinylcholine after burns for many months
IMMUNOLOGIC	
	Retroviral drugs may inhibit benzodiazepine clearance
	Immunodeficiency requires careful infection control practices
	Cytomegalovirus-negative blood products, irradiation, or leukofiltration may be required
METABOLIC	
	Careful assessment of glucose homeostasis in infants

in water [D5W]) facilitate gastric emptying, prevent hypoglycemia, and may be given up to 2 hours before anesthesia. Breast milk may be given to infants up to 4 hours before surgery. Solids should be avoided for 6-8 hours before surgery. Conditions associated with delayed gastric emptying may require prolonged periods of fasting. The optimal duration of preoperative fasting in otherwise well patients without risk factors for delayed gastric emptying remains a source of controversy. Many efforts have sought to shorten NPO duration for clear liquids from 2 hours to 1 hour in order to preserve fluid and glycemic balance in children presenting for surgery.

Table 91.4 American Society of Anesthesiology Physical Status Classification

Class 1: Healthy patient, no systemic disease
Class 2: Mild systemic disease with no functional limitations (mild chronic renal failure, iron-deficiency anemia, mild asthma)
Class 3: Severe systemic disease with functional limitations (hypertension, poorly controlled asthma or diabetes, congenital heart disease, cystic fibrosis)
Class 4: Severe systemic disease that is a constant threat to life (critically and/or acutely ill patients with major systemic disease)
Class 5: Moribund patients not expected to survive 24 hr, with or without surgery
Additional classification: "E"—emergency surgery

Copyright American Society of Anesthesiology, http://www.asahq.org.

Table 91.5 Common Difficult Airway Syndromes

Achondroplasia
Airway tumors, hemangiomas
Apert syndrome
Beckwith-Wiedemann syndrome
Choanal atresia
Cornelia de Lange syndrome
Cystic hygroma/teratoma
DiGeorge syndrome
Fractured mandible
Goldenhar syndrome
Juvenile rheumatoid arthritis
Mucopolysaccharidosis
Pierre Robin syndrome
Smith-Lemli-Opitz syndrome
Treacher-Collins syndrome
Trisomy 21
Turner syndrome

The Full Stomach

Gastric emptying may be delayed for up to 96 hours after an acute episode of trauma or surgical illness. To mitigate risk of aspiration, it is desirable to secure the airway as rapidly as possible during induction of anesthesia in patients at risk for having a full stomach. Under these circumstances, rapid sequence induction of anesthesia is indicated (**rapid sequence induction**; see Chapter 86).

Parental Presence During Induction of Anesthesia

Parents or guardians may expect to be with their child during the induction of anesthesia. Removing a fearful child from a parent is stressful for the child and caregivers. Premedication with an oral benzodiazepine (e.g., midazolam) frequently provides calm, smooth parental separation conditions. When parental separation cannot be achieved comfortably with premedication and behavioral modification (patient education and desensitization to the operative environment), PPI may be indicated. Although PPI in the hands of a confident, competent anesthesia practitioner may replace the need for preoperative medication, it does not reliably predict smooth induction. PPI has not been shown to decrease emergence delirium or postoperative behavioral changes, and it does not appear to be superior to premedication with oral midazolam.

GENERAL ANESTHESIA

Analgesia

Pediatric anesthesiologists are responsible for providing analgesia to children for procedures within operating room (OR) and non-OR settings (Table 91.7). Multimodal techniques exist to provide pain relief during operative procedures for children of all ages, including critically ill infants. Effective analgesia is essential to blunt physiologic responses to painful stimuli (surgery) and modulate the deleterious physiologic and metabolic consequences. The response to painful and stressful stimuli may provoke **systemic inflammatory response syndrome (SIRS)**, which has been linked to increased catabolism, physiologic instability, and mortality (see Chapter 85).

Table 91.6 Guidelines for Preoperative Fasting ("2-4-6-8 Rule")*

TIME BEFORE SURGERY (hr)	ORAL INTAKE
2	Clear, sweet liquids
4	Breast milk
6	Infant formula, fruit juices, gelatin
8	Solid food

*These are general guidelines and may differ among hospitals.

Hypnosis and Amnesia

The attenuation of both consciousness **(hypnosis)** and conscious recall **(amnesia)** is critical during pediatric anesthesia care. Awareness during procedures may be as physically and psychologically deleterious as the experience of pain. A primary goal of anesthetic management is to minimize fear and anxiety during both painful and nonpainful procedures. Many drugs provide anxiolysis and amnesia for such events (Table 91.8). However, it is important to remember that sedative-hypnotic agents may alter consciousness without producing analgesia; *analgesia* and *hypnosis* are not synonymous. It is also possible to provide analgesia (local, spinal, or epidural) without altering consciousness.

Sedation describes a medically induced state in the continuum between wakefulness and general anesthesia in which patients maintain the ability to respond purposefully to varying degrees of stimulation (see Table 91.7). *Light (minimal) sedation* is defined as anxiolysis with minimally reduced reflexes or airway patency with normal response to verbal commands. In *moderate sedation,* the patient continues to respond purposefully to verbal commands, either alone or with light touch. *Deep sedation* is defined by preservation of purposeful movement with repeated or painful stimulation. **General anesthesia** is characterized by unconsciousness, amnesia, and reduced physiologic reflexes, including cardiorespiratory reflexes (**airway-protective** and **vasomotor reflexes**). It is common to transition between states of sedation and general anesthesia with loss of consciousness, airway patency, and airway-protective reflexes; in this scenario, loss of cardiovascular stability may occur. Individuals providing sedation and anesthesia for children must be able to identify the anesthetic state of the patient and support cardiorespiratory insufficiency.

Akinesia (Immobility or Muscular Relaxation)

Akinesia, the absence of movement, is commonly indicated to ensure safe and adequate operative conditions. Neuromuscular blocking agents (NMBAs) may be used to produce akinesia (see Table 91.8). However, the absence of movement is not indicative of hypnosis, amnesia, or analgesia. Whenever NMBAs are used, *sedation and analgesia must be provided.*

Monitoring

Administration of anesthesia increases the need to monitor and support physiologic integrity and homeostasis because of potentially life-threatening physiologic consequences (see Tables 91.7 and 91.8). Consequently, the ASA mandates routine monitoring of oxygenation, ventilation, and circulation during the provision of anesthesia. This includes assessment of continuous pulse oximetry, capnography, electrocardiography, intermittent blood pressure measurements (every 5 minutes), and temperature when temperature instability is anticipated. The use of advanced invasive (arterial and central venous pressure) or noninvasive (near-infrared spectroscopy) monitoring varies based on procedural complexity and ASA-PS.

Table 91.7 Definitions of Anesthesia Care

MONITORED ANESTHESIA CARE

A designated anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure.

Monitored anesthesia care includes all aspects of anesthesia care: a preprocedure assessment, intraprocedure care, and postprocedure anesthesia management.

During monitored anesthesia care, the anesthesiologist or a member of the anesthesia care team provides a number of specific services, which may include but are not limited to the following:

- Discussing anesthesia care with the family and child, obtaining consent for anesthesia, allaying anxiety and answering questions—family-centered anesthesia care.
- Monitoring of vital signs, maintenance of the patient's airway, and continual evaluation of vital functions.
- Diagnosing and treating clinical problems that occur during the procedure.
- Administering sedatives, analgesics, hypnotics, anesthetic agents, or other medications as necessary to ensure patient safety and comfort.
- Providing other medical services as needed to accomplish the safe completion of the procedure.

Anesthesia care often includes the administration of medications for which the loss of normal protective reflexes or loss of consciousness is likely.

Monitored anesthesia care refers to those clinical situations in which the patient remains able to protect the airway for the majority of the procedure.

If the patient is rendered unconscious and/or loses normal protective reflexes for an extended period, this is considered a general anesthetic.

LIGHT SEDATION

Administration of anxiolysis or analgesia that obtunds consciousness but does not obtund normal protective reflexes (cough, gag, swallow, hemodynamic) or spontaneous ventilation; patient responds normally to verbal commands.

MODERATE SEDATION

No interventions are required to maintain a patent airway or spontaneous ventilation; patient responds purposefully to verbal commands either on their own or with light touch.

DEEP SEDATION

Sedation that obtunds consciousness and normal protective reflexes or possesses a significant risk of blunting normal protective reflexes (cough, gag, swallow, hemodynamic); hemodynamic and respiratory insufficiency may occur.

GENERAL ANESTHESIA

Administration of hypnosis, sedation, and analgesia that results in the loss of normal protective reflexes.

REGIONAL ANESTHESIA

Induction of neural blockade (either central, neuraxial, epidural, or spinal; or peripheral nerve block, e.g., digital nerve block, brachial plexus block), which provides analgesia and is associated with regional motor blockade.

Consciousness is not obtunded.

Special expertise is required.

Frequently, in children, anxiolysis and sedation are also necessary for this technique to be successful.

Regional anesthesia (e.g., caudal epidural blockade) is used to supplement general anesthesia and provide postoperative analgesia.

LOCAL ANESTHESIA

Provision of analgesia by local infiltration of an appropriate anesthetic agent.

Does not require the presence or involvement of an anesthesiologist, although an anesthesiologist may provide local anesthesia services.

Specific Medications

Inhalational Anesthetics

Inhalational anesthetics are frequently used for the induction and maintenance of general anesthesia in children. Pediatric inhalational anesthetics include sevoflurane, isoflurane, and desflurane. Although halothane is the prototypical pediatric inhalational anesthetic and may be used in other parts of the world, it has been replaced by sevoflurane and is no longer used in the United States and Europe.

The **minimum alveolar concentration (MAC)** of an inhalational anesthetic is the alveolar concentration (expressed as percent at 1 atmosphere) that provides sufficient depth of anesthesia for surgery in 50% of patients. For potent inhalational agents, the alveolar concentration of an anesthetic reflects the arterial concentration of anesthetic in the blood perfusing the brain. MAC is a measure of anesthetic potency analogous to the $\mathbf{ED_{50}}$ (effective dose in 50% of recipients) of a drug. MAC is age dependent; it is lower in premature than in full-term infants and decreases from term through infancy to preadolescence. In adolescence, MAC again increases, falling thereafter.

Respiratory Effects. The advantages of inhalational anesthesia are rapid onset and offset with the convenient route of delivery and respiratory excretion. These agents provide profound analgesia and amnesia. Inhalational volatile anesthetic agents are poorly soluble in blood but rapidly equilibrate between alveolar gas and blood. They may irritate the airway and provoke laryngospasm. All inhalational anesthetics depress ventilation in a dose-dependent manner. Thus expired carbon dioxide (CO_2) and $Paco_2$ (arterial partial pressure of CO_2) will increase in spontaneously breathing children. Volatile anesthetics shift the CO_2 response curve to the right, thus decreasing the normal increase in minute ventilation with increasing $Paco_2$. Inhalational anesthesia decreases end-expiratory lung volume (functional residual capacity). Small lung volumes are associated with reduced lung compliance, increased pulmonary vascular resistance, and restrictive lung defects. Volatile agents depress normal hypoxic pulmonary vasoconstriction, increasing intrapulmonary arteriovenous shunting and hypoxemia.

Cardiovascular Effects. All volatile anesthetics reduce cardiac output and peripheral vascular resistance; hypotension is common. This is accentuated in hypovolemic patients and more pronounced in neonates. Inhalational anesthetics also depress baroreceptor and heart rate responses. The administration of inhalational anesthesia may result in decreased tissue oxygen delivery. Perioperatively, cellular metabolism increases, creating a potential imbalance between oxygen demand and oxygen delivery. Development of intraoperative dysoxia is a sign of this imbalance. All volatile inhalational anesthetic agents cause **cerebrovasodilation** and uncouple cerebral blow flow with cerebral metabolic rate. Although inhalational anesthetics decrease cerebral oxygen consumption, they may disproportionately increase cerebral oxygen blood flow. Thus inhalational anesthetics should be used with caution in children who have elevated intracranial pressure (ICP) or impaired cerebral perfusion (i.e., traumatic brain injury).

Sevoflurane

Sevoflurane is the most commonly used inhalational agent for induction and maintenance of general anesthesia in children. Sevoflurane possesses minimal airway irritant properties and is a useful induction agent when co-administered with nitrous oxide. Emergence from sevoflurane anesthesia is rapid; however, there is a significant incidence of **emergence delirium**, especially with inadequate pain control. This effect may be attenuated with adequate analgesia and supplemental hypnotic agents (e.g., midazolam, dexmedetomidine, propofol). Metabolism of sevoflurane by cytochrome P450 (CYP) yields free fluoride, which may be nephrotoxic. Sevoflurane degradation by desiccated CO_2 absorbents at low fresh gas flows (<2 L/min) may produce

Table 91.8 Selected Drugs Used in Anesthesia

DRUG	USES AND IMPLICATIONS
MUSCLE RELAXANTS	
Succinylcholine	A depolarizing neuromuscular blocking agent with rapid onset and offset properties Used to facilitate endotracheal intubation and maintain muscle relaxation in emergency situations; rarely used Associated with the development of malignant hyperthermia in susceptible patients Degraded by plasma cholinesterase, which may be deficient in some individuals; such a deficiency may result in prolonged effect Fasciculations may be associated with immediate increases in intracranial and intraocular pressures and postoperative muscle pain
Vecuronium, rocuronium, cisatracurium, all aminosteroids	Nondepolarizing neuromuscular blockers Have less rapid onset than succinylcholine but are longer acting Prolonged ICU use may lead to profound muscle weakness Vecuronium and rocuronium are metabolized by the liver and excreted in bile; they are the most commonly used neuromuscular blocking agents Cisatracurium is metabolized by plasma cholinesterase and therefore may be of benefit in patients with hepatic or renal disease
HYPNOTICS	
Propofol	Rapid-acting hypnotic amnestic agent No analgesic properties Respiratory depressant Increases seizure threshold Antiemetic Propofol infusion syndrome may occur with prolonged intravenous infusion (>24 hr)
Etomidate	Cardiovascular stability on induction Inhibits corticosteroid synthesis Increases ICU mortality after use Associated with myoclonus and pain on injection
Ketamine	Hypnotic analgesic Causes sialorrhea and may be co-administered with an antisialagogue, such as atropine or glycopyrrolate Induces endogenous catecholamine release and tachycardia Bronchodilator Increases intracranial and intraocular pressures Decreases the seizure threshold
SEDATIVE-ANXIOLYTICS	
Benzodiazepines	Produce sedation, anxiolysis, amnesia, and hypnosis All agents raise the seizure threshold, are metabolized by the liver, and depress respiration, especially when administered with opioids Effective as premedication Diazepam may be painful on injection and has active metabolites Midazolam can be administered by various routes Lorazepam has no active metabolites Reversed with flumazenil
Dexmedetomidine	Produces anxiolysis, sedation, and sympatholysis by α_2-receptor stimulation centrally; has mild analgesic properties Side effects include hypertension, hypotension, and bradycardia Commonly used for procedural sedation; IV, IN, and IM dosing available Continuous infusion useful for ICU sedation
ANALGESIC-SEDATIVES	
Opioids	Gold standard for providing analgesia All cause respiratory depression Morphine and, to a lesser extent, hydromorphone may cause histamine release The synthetic opioids fentanyl, sufentanil, and short-acting alfentanil may have a greater propensity to cause chest wall rigidity when administered rapidly or in high doses and are also associated with the rapid development of tolerance; these drugs have particular utility in cardiac surgery because of the hemodynamic stability associated with their use Remifentanil is an ultrashort-acting synthetic opioid that is metabolized by plasma cholinesterase; it may have particular utility when deep sedation and analgesia are required along with the ability to assess neurologic status intermittently
INHALATIONAL AGENTS	
Nitrous oxide	Produces amnesia and analgesia at low concentrations Danger of hypoxic gas mixture if the oxygen concentration is not monitored and preventive safety mechanisms are not in place
Potent vapors, sevoflurane, desflurane, isoflurane	"Complete anesthetics"—induce hypnosis, analgesia, and amnesia All are myocardial depressants, and some are vasodilators May trigger malignant hyperthermia in susceptible individuals Sevoflurane is used for induction of anesthesia in children All bronchodilate at equipotent concentrations Isoflurane and desflurane are associated with laryngospasm and should not be used for anesthesia induction

IV, Intravenous; IN, intranasal; IM, intramuscular.

the nephrotoxin Compound A. Large-scale studies of sevoflurane-associated renal injury in humans are lacking. However, the U.S. Food and Drug Administration (FDA) has recommended maintenance of fresh gas flow rates >2 L/min for surgical cases lasting more than 2 hours of monitored anesthesia care.

Isoflurane

Isoflurane is a pungent volatile anesthetic and airway irritant and is not suitable for induction because of the high incidence of complications, such as laryngospasm. However, maintenance of anesthesia with isoflurane is common after induction with sevoflurane or an intravenous (IV) hypnotic. Emergence from anesthesia with isoflurane is slower than for sevoflurane. Isoflurane administration in the setting of desiccated CO_2 absorbents may yield the production of carbon monoxide.

Desflurane

Desflurane is a potent airway irritant associated with coughing, breath holding, and laryngospasm and is *not* useful for induction. Desflurane has the lowest solubility and potency of all commonly used volatile agents. It is frequently administered for maintenance of anesthesia. Emergence from desflurane anesthesia is rapid because of its low tissue solubility.

Nitrous Oxide

Nitrous oxide (N_2O) is a tasteless, colorless, odorless gas with potent analgesic properties. It produces a state of euphoria (thus its nickname, "laughing gas"). The MAC of N_2O is >100; consequently, it may not be used as a sole agent to maintain anesthesia. N_2O produces little hemodynamic or respiratory depression. It is typically used in combination with volatile and IV anesthetic agents during maintenance of general anesthesia. The deleterious effects of N_2O include postoperative nausea and vomiting (PONV) and, with long-term use (i.e., days), bone marrow suppression. N_2O diffuses out of blood rapidly and is contraindicated in patients with closed gas-filled body cavities (pneumothorax, lung cysts, bowel injury).

Intravenous Anesthetic Agents

IV anesthetics may be administered for induction and maintenance of anesthesia in bolus form or as continuous infusions. Common IV agents include propofol, opioids, benzodiazepines, ketamine, dexmedetomidine, and barbiturates. For children with vascular access, IV induction should be routine. All IV agents affect cardiorespiratory function.

Propofol

Propofol is the most commonly administered IV induction agent. Administered in doses of 2-5 mg/kg, propofol rapidly produces unconsciousness. Propofol may burn and itch on injection. After induction of anesthesia, propofol is a useful agent for maintaining hypnosis and amnesia and may be used as a sole anesthetic agent for nonpainful procedures (e.g., radiation therapy) and imaging studies. When combined with opioids, propofol provides excellent anesthesia for brief painful procedures, such as lumbar puncture and bone marrow aspiration. Although hemodynamic stability, and even spontaneous respirations, may be maintained during propofol administration, it remains a potent anesthetic that can obtund airway reflexes, respiration, and hemodynamic function. As such, some hospitals have limited its use to anesthesia professionals. Propofol may produce both respiratory depression and hypotension. Extrapyramidal symptoms are a rarer complication. Prolonged use may cause hemodynamic collapse, bradycardia, metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidemia, profound shock, and death (**propofol infusion syndrome**). Prolonged propofol administration (>24-48 hours) in the ICU in children is not recommended. Propofol is formulated in 10% soy emulsion with egg emulsifiers and was once thought to be contraindicated in patients with soy or egg allergy. According to the American Academy of Allergy, Asthma, and Immunology, patients with soy and egg allergies may safely receive propofol for anesthesia.

Etomidate

Etomidate is an imidazole derivative used for the induction of anesthesia, frequently in emergent situations. Its onset of action is slower than propofol. Etomidate lacks significant cardiovascular depressant effects, making it a popular induction agent in patients with hemodynamic compromise and cardiac disease. However, etomidate inhibits 11β-hydroxylase, thereby suppressing mineralocorticoid and glucocorticoid synthesis for up to 72 hours after a single induction dose. Etomidate is associated with increased mortality when used as a sedative in the ICU (for which it is contraindicated); the effect of a single induction dose on mortality remains controversial. Any decision to use etomidate must weigh the short-term benefits of hemodynamic stability with the serious risks of adrenal suppression.

Ketamine

Ketamine (1-3 mg/kg IV) produces rapid induction of general anesthesia that lasts for 15-30 minutes. Ketamine is effective when given intramuscularly (IM), subcutaneously (SC), intranasally (IN), or orally (PO). However, the dose must be increased for alternative routes. Ketamine dissociates connections between the cerebral cortex and limbic system *(dissociative anesthesia)* through inhibition of *N*-methyl-D-aspartate receptors. Ketamine is also an analgesic and may be used as a sole IV agent to provide general anesthesia. It has few side effects and generally preserves blood pressure and cardiac output. However, ketamine increases myocardial oxygen demand and should be used cautiously in patients with impaired myocardial oxygen delivery or ventricular outflow tract obstruction. With low-dose (1-2 mg/kg) ketamine, airway reflexes and spontaneous ventilation may be maintained; at higher doses (3-5 mg/kg), loss of airway reflexes, apnea, and respiratory depression occur. Aspiration of gastric contents remains a risk during deep sedation with ketamine. IV ketamine is a useful general anesthetic agent for short procedures.

Ketamine has been linked to disturbing postanesthetic dreams and hallucinations after emergence from anesthesia. In adults the incidence of this effect is 30–50%; in prepubertal children it may be 5–10%. Benzodiazepines (e.g., midazolam) reduce these sequelae and may be given to children receiving ketamine. Ketamine is also a potent secretagogue, enhancing oral and bronchial secretions. An antisialagogue, such as atropine or glycopyrrolate, should also be considered before the administration of ketamine. Ketamine is a bronchodilator and is a useful agent for sedating patients with asthma in the ICU. Ketamine has been reported to increase ICP and therefore is contraindicated in patients with elevated ICP.

Opioids

Opioids are superb analgesics for painful procedures and postprocedural pain (see Chapters 92 and 93). Opioids are respiratory depressants that suppress CO_2 responsiveness and can produce apnea. Importantly, in equianalgesic doses, all opioids are equally potent respiratory depressants. Other inhalational or IV anesthetics generally potentiate opioid-induced respiratory depression.

Morphine is a long-acting opioid analgesic with important age-dependent pharmacokinetics. Equivalent doses of morphine per kilogram are associated with higher blood levels in neonates than in older children, with plasma concentrations approximating three times those of adults. Morphine exhibits a longer elimination half-life (14 hours) in young children than in adults (2 hours). The immature blood-brain barrier of neonates is more permeable to morphine. Morphine is often associated with hypotension and bronchospasm from histamine release and should be used with caution in children with asthma. Morphine has renally excreted active metabolites and is relatively contraindicated in renal failure. Because of morphine's prolonged duration of action and cardiorespiratory side effects, the fentanyl class of synthetic opioids has increased in popularity for perioperative analgesia.

Fentanyl is a potent synthetic opioid with a shorter duration of action and a more stable hemodynamic profile than morphine. Fentanyl attenuates the hemodynamic response to surgery and provides stable operating conditions. Effective analgesia and anesthesia may be provided with IV fentanyl administered as a 2-3 μg/kg bolus followed

by a 1-3 μg/kg/hr continuous infusion. Nitrous-narcotic anesthetic techniques that incorporate fentanyl are effective for maintenance of stable hemodynamics while still providing adequate hypnosis and analgesia. Fentanyl is the most commonly used *synthetic* opioid, but other formulations of varying potency are available (alfentanil < fentanyl < sufentanil). *Sufentanil* is ten times more potent than fentanyl and is frequently used during pediatric cardiac anesthesia. *Alfentanil* is approximately 25% as potent as fentanyl. *Remifentanil* has very rapid onset and offset of action. In doses of 0.25 μg/kg/min, surgical anesthesia can be maintained with this agent. Remifentanil is metabolized through nonspecific ester hydrolysis and has a short elimination half-life (<10 minutes), advantageous for rapid emergence from anesthesia. Unfortunately, this short duration of action has been linked to inadequate postprocedural analgesia and increased need for postprocedural opioid analgesic supplementation, limiting remifentanil's use.

Benzodiazepines

Benzodiazepines induce hypnosis, anxiolysis, sedation, and amnesia and have anticonvulsant properties. In high doses, benzodiazepines cause respiratory depression and are synergistic with opioids and barbiturates in their respiratory depressant effects. Benzodiazepines are γ-aminobutyric acid (GABA) agonists.

Midazolam is the most commonly used benzodiazepine in pediatric anesthesia. Short acting and water soluble, it can be injected without pain. It is a potent hypnotic-anxiolytic-anticonvulsant and is approximately four times more potent than diazepam. Midazolam may be administered orally, nasally, rectally, intravenously, or intramuscularly. Midazolam (0.10-0.15 mg/kg IV) has minimal effect on respiratory rate, heart rate, or blood pressure and provides excellent preoperative anxiolysis and amnesia. Premedication with oral midazolam (0.5-1.0 mg/kg) mixed in sweet-flavored syrup induces anxiolysis in approximately 90% of children without hemodynamic or respiratory depressant effects. However, children may experience loss of coordination (head control), blurred vision, and rarely, dysphoria. A child sedated with midazolam should not be left unattended. Most children readily accept an inhalational anesthetic by face mask after oral midazolam premedication. The widespread use of preoperative oral midazolam has decreased the practice of PPI.

Dexmedetomidine

Dexmedetomidine is a central α_2 adrenergic receptor agonist similar to clonidine. Dexmedetomidine lacks respiratory depressant effects and produces anxiolysis, sedation, mild analgesia, and sympatholysis. Rapid administration may produce hypertension and bradycardia, whereas continuous infusions may produce hypotension and bradycardia. Dexmedetomidine is frequently used for sedation in ICU patients and for procedures. Dexmedetomidine has become a popular adjuvant for general anesthesia during pediatric cardiac surgery.

Barbiturates

Sodium thiopental is the classic barbiturate IV induction agent, although it is now rarely used. Side effects of thiopental include respiratory depression, apnea, and hypotension. Induction with 3-5 mg/kg of thiopental produces unconsciousness within seconds, lasting 5-10 minutes. Thiopental is not useful for maintenance of anesthesia, which requires other IV or inhalational anesthetics. Pentobarbital is a barbiturate traditionally administered IV for sedation in children during imaging procedures of intermediate duration (e.g., diagnostic studies) that require akinesia. **Pentobarbital** is a potent respiratory depressant, particularly when combined with opioids and benzodiazepines. Pentobarbital has a prolonged duration of action. Pentobarbital sedation for nonpainful procedures generally results in delayed emergence. **Sodium methohexital** (Brevital) is another IV induction agent, similar to sodium thiopental in respiratory depressant effects. Barbiturates lack analgesic properties, and painful procedures require supplemental analgesia.

Neuromuscular Blocking Agents

Neuromuscular blockade is performed to facilitate endotracheal intubation and akinesia during surgery. NMBAs may be *depolarizing* (e.g., succinylcholine) or *nondepolarizing* (e.g., vecuronium, rocuronium, cisatracurium). **Succinylcholine** has a high-risk profile in children. Its use is associated with postoperative pain from muscle spasms; hyperkalemia; elevated intracranial, intraocular, and intragastric pressures; malignant hyperthermia; myoglobinuria; and renal damage. Consequently, succinylcholine is rarely used, except to provide rapid relief of laryngospasm. Endotracheal intubation is most often facilitated with nondepolarizing NMBAs. **Rocuronium** is most commonly used for intubation because of its rapid onset of action. For procedures that last >40 minutes, **vecuronium** and **cisatracurium** are also suitable to induce muscle relaxation for intubation. After intubation, repeat administration of NMBAs may be indicated to maintain muscle relaxation to facilitate surgery. Prolonged use of nondepolarizing NMBAs in critical illness may contribute to myopathy, especially when combined with high-dose corticosteroids.

INDUCTION OF GENERAL ANESTHESIA

The goal of induction of general anesthesia is the safe transition to a state of unconsciousness. Induction in children is typically achieved with inhalational anesthetics, although IV agents are indicated when patients have IV access. Many children will not tolerate the establishment of vascular access before induction of anesthesia, and it is routine to induce anesthesia by face mask with inhaled anesthetics. Before the induction of anesthesia, monitors applied may include pulse oximetry, ECG, and noninvasive blood pressure cuff. The child is then cautiously introduced to the face mask, which contains a high gas flow (5-7 L/min O_2), frequently mixed with N_2O. Inhalation of N_2O and O_2 for 60-90 seconds induces a state of euphoria. Nitrous oxide blunts the airway responses to potent volatile inhalational agents, and sevoflurane may then be safely introduced into the inhaled gas mixture. This leads to unconsciousness within 30-60 seconds while the child continues to breathe spontaneously.

After induction, IV access is obtained and standard intraoperative monitoring initiated. Thereafter, definitive airway management is performed. Airway management for short procedures (i.e., myringotomy tubes) frequently includes a mask airway and spontaneous ventilation; this is safe when the airway is secure and patent and aspiration risk is low. Longer procedures (>30-60 minutes) are not usually performed with mask airways. Definitive artificial airways include laryngeal mask airways and endotracheal tubes (ETTs). The **laryngeal mask** is a supraglottic airway generally reserved for procedures in spontaneously ventilating patients and does not effectively prevent the aspiration of gastric contents.

For complex surgical procedures, **endotracheal intubation** is generally required (e.g., intraabdominal, intrathoracic, airway procedures). Although endotracheal intubation may be performed under deep inhalational anesthesia, the depth of anesthesia required to attenuate airway reflexes may produce hemodynamic instability. Therefore NMBAs are frequently administered to facilitate intubation. The depolarizing NMBA succinylcholine is rarely used, and nondepolarizing NMBAs such as rocuronium and vecuronium are most frequently used (see earlier). After muscle relaxation, direct laryngoscopy and endotracheal intubation can be performed. Correct ETT placement is confirmed by direct laryngoscopy, end-tidal CO_2 measurement, and assessment of bilaterally equal breath sounds. Additional confirmatory tests include chest radiograph and fiberoptic bronchoscopy. After endotracheal intubation, controlled mechanical ventilation is required in the setting of neuromuscular blockade (see Chapter 86).

Children with full stomach precautions may require **rapid sequence induction**. Before performing a rapid sequence induction, preoxygenation with 100% oxygen for 2-5 minutes increases alveolar oxygen content and delays hypoxemia if intubation is difficult. Rapid sequence induction involves concurrent administration of hypnotic agents and NMBAs. Assisted ventilation before or after drug administration is avoided because of the risk of gastric distention, regurgitation, and aspiration. Traditionally, after administering a sedative and NMBA, the Sellick maneuver (cricoid pressure) was performed by applying firm pressure in a posterior direction against the cricoid cartilage. This displaces the cricoid cartilage into the esophagus and was thought to form an artificial sphincter to prevent reflux of the gastroesophageal contents. However, evidence suggests that cricoid pressure may be counterproductive, as it does not appear to prevent pulmonary aspiration

and may increase time to intubation. Because of this controversy, the clinician must consider the risks and benefits of cricoid pressure in each case.

The major risk of rapid sequence induction is intubation failure. In this situation the child is paralyzed without a protected airway, and ventilation may be hazardous or impossible. Only experienced airway specialists should undertake rapid sequence induction. It should be avoided in patients with a history of failed endotracheal intubation or features (micrognathia) associated with difficult intubation. Under these circumstances, bronchoscopic awake intubation may be indicated.

Complications During Induction

During induction of anesthesia, the transition between full wakefulness to unconsciousness is fraught with potential complications, including laryngospasm, bronchospasm, vomiting, and aspiration. Concerns for vomiting and aspiration dictate adherence to preanesthetic fasting guidelines and may be an indication for rapid sequence anesthetic induction.

During induction of anesthesia, especially with inhalational anesthetics, a period of excitement may occur. This period is associated with heightened airway reflexes, which can lead to coughing, gagging, laryngospasm, and bronchospasm. **Laryngospasm** is the reflex closure of the larynx, which prevents spontaneous or assisted ventilation. The child may make violent inspiratory efforts against a closed glottis, generating significantly negative intrathoracic pressure and resulting in postobstructive pulmonary edema. Laryngospasm can be prolonged, and hypoxia may ensue. Laryngospasm occurs in up to 2% of all anesthetic inductions in children <9 years old and is much less common in older patients. Laryngospasm occurs twice as frequently in children with active or recent upper respiratory tract infection. A history of tobacco exposure increases the likelihood of laryngospasm significantly.

Laryngospasm can be relieved by increasing the depth of anesthesia, either intravenously or through inhalation (although with the glottis closed, further administration of inhalational anesthesia is not possible). Neuromuscular blockade relieves laryngospasm, and an acute situation may be an indication for succinylcholine administration. Continuous positive airway pressure administration may be beneficial in alleviating laryngospasm. Laryngospasm may also occur during emergence from anesthesia because airway tone is increased during the transition to wakefulness.

Bronchospasm may result from increased airway reactivity during the hyperexcitable stage of induction or secondary to histamine release induced by anesthetic agents. Endotracheal intubation may provoke bronchospasm, especially in patients with asthma, which may be associated with life-threatening hypoxemia and inability to ventilate. Alternative airway management strategies such as laryngeal mask should be considered when appropriate in children with severe reactive airway disease. The use of histamine-releasing anesthetic agents has been associated with severe bronchospasm and, in rare instances, cardiorespiratory failure. Environmental tobacco smoke is another risk factor.

Hypoxemia during induction may be secondary to reduced functional residual capacity, atelectasis, and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. Volatile anesthetics blunt hypoxic pulmonary vasoconstriction, further contributing to $\dot{V}/\dot{Q}$ abnormalities. **Hypersecretion** may result in airway obstruction and should managed with antisialagogues, such as glycopyrrolate and atropine. The newer inhalation agents are less potent secretagogues, and the routine use of atropine premedication is much less common but often indicated when ketamine is used.

Hemodynamic complications may also develop during induction of anesthesia. **Hypotension** is common and may be exaggerated in the setting of hypervolemia, decreased myocardial function, or congenital heart disease. Inhalational anesthetics sensitize the myocardium to circulating catecholamines, and induction and excitement are associated with a hypercatecholaminergic state.

MAINTENANCE OF ANESTHESIA

Maintenance of anesthesia is the period between induction and emergence. The child should be unaware of pain, unresponsive to painful stimuli, and physiologically supported. Anesthesia is typically maintained with a volatile anesthetic (e.g., isoflurane, sevoflurane) supplemented with opioid-based analgesia. IV hypnotic agents (e.g., dexmedetomidine, benzodiazepines) may be administered to augment hypnosis and amnesia. Choice of ventilatory strategy (spontaneous, assisted, or controlled) varies according to procedure type and patient condition (see Chapter 86). Surgical trauma may result in hypothermia and hypovolemia caused by blood loss and significant fluid shifts (third spacing). Management of these physiologic disturbances is the responsibility of the anesthesiologist during maintenance.

Temperature Management

Thermoregulation is critical during anesthesia. The absence of movement and inhibition of shivering reduce thermogenesis. Although temperature sensing may remain normal, the autonomic response to hypothermia is reduced. Anesthetic agents cause vasoparesis, which further impairs thermoregulation and increases heat loss. In newborns, inhalational anesthetics inhibit nonshivering thermogenesis from brown fat, increasing the risk for hypothermia. Mechanisms of heat loss during anesthesia include radiation, convection, evaporation, and conduction. Radiant and convective heat loss are most common and may be minimized by preheating the operating room and by use of radiant heat lamps and forced-air warming blankets. Humidification and warming of inspired gases may also be useful.

Fluid Management

Most anesthetics produce vasodilation and increase venous capacitance, effectively reducing myocardial preload. Surgical bleeding and insensible/third space fluid losses further contribute to intravascular volume depletion. Volume expansion with isotonic salt-containing solutions (normal saline, lactated Ringer, Plasma-Lyte) may be required to maintain cardiac output and organ perfusion. Increased renin-angiotensin-aldosterone axis activation and antidiuretic hormone (ADH) secretion further complicate fluid regulation.

Intraoperative fluid management must account for (1) deficits acquired during preoperative fasting, (2) maintenance fluid requirements, (3) surgical blood loss, and (4) insensible fluid loss. Infants should receive glucose-containing isotonic fluid to prevent perioperative hypoglycemia. Table 91.9 is a guideline for determining fluid deficits and maintenance requirements in the OR. For longer procedures, fluid deficits should be replaced with isotonic fluid over the first 3 hours of intraoperative management. Deficits are generally calculated as the number of hours of fasting status multiplied by the hourly maintenance rate for the child. Half the deficit is replaced during the first hour and half during the subsequent 2 hours. If hypotension or tachycardia persists in the early stages of anesthesia, more rapid replacement of the fluid deficit may be indicated.

Third space interstitial fluid losses should be replaced with isotonic salt solutions. For smaller operations, such as herniorrhaphy, pyloromyotomy, and minor procedures, fluid replacement at 3-5 mL/kg/hr is indicated for insensible losses. Complex abdominal or thoracic procedures with large insensible losses may require an additional 8-10 mL/kg/hr of IV fluid replacement. Crystalloid solution is indicated for blood loss as a 3:1 ratio. Allogenic blood products should be replaced as a 1:1 ratio. Colloid (albumin) administration also may decrease the amount of crystalloid replacement needed for blood loss. During large-volume transfusions, active fluid warming should be performed to prevent hypothermia. With major surgery and resultant SIRS, capillary

Table 91.9 Intraoperative Pediatric Fluid Replacement

INFUSION RATE	PATIENT WEIGHT
4 mL/kg/hr	1-10 kg
2 mL/kg/hr	10-20 kg
1 mL/kg/hr	per kg >20 kg
Example: 22 kg child requires (4 × 10) + (2 × 10) + (1 × 2) = 62 mL/hr	

integrity is lost, and third space losses are common. Failure to replace fluid loss and restore intravascular volume may lead to shock.

Perioperative **hypoglycemia** may result from preoperative fasting, most often in neonates or in children with metabolic disorders. In neonates, perioperative glucose monitoring is indicated, and glucose replacement is frequently required. In older children with normal nutritional status, isotonic salt solutions without glucose are adequate. In patients receiving total parenteral alimentation containing high glucose concentrations (>10%), continuous glucose administration should be ensured to avoid rebound hypoglycemia.

Postprocedural care includes supervision of emergence and recovery from anesthesia and surgery. **Emergence** describes the transition period between the anesthetized state and consciousness. During emergence, patients experience decreased anesthetic effect and increased physiologic and psychologic responses to painful stimuli (e.g., reactive autonomic tone, excitement, anxiety). Inhalational anesthetic agents are rapidly excreted during ventilation, and muscle relaxants can be reversed; however, the effects of opioids, benzodiazepines, and IV hypnotics may be prolonged. Normal physiologic functions such as spontaneous ventilation resume, and hemodynamic function improves. Before leaving the OR after routine elective procedures, the child should be conscious with intact airway reflexes and a patent airway. The effects of muscle relaxants should be reversed. Ideally, emergence should be as brief as possible, with maintenance of analgesia and anxiolysis and restoration of cardiorespiratory function. However, critically ill patients scheduled for ICU admission may require postoperative endotracheal intubation and mechanical ventilation. In these patients, deeper levels of sedation and analgesia should be maintained after the procedure.

During emergence, it is essential to assess whether **residual neuromuscular blockade** (NMB) exists. If weakness or respiratory depression is observed in the postoperative phase, prolonged NMB should be considered. *Reversal of residual NMB is standard anesthetic practice.* With the virtual abandonment of succinylcholine, only nondepolarizing NMBAs are routinely used for intubation. The termination of NMB depends on metabolism and elution away from the neuromuscular junction. Classically, nondepolarizing muscle relaxants are reversed by increasing the acetylcholine concentration at the neuromuscular junction with acetylcholine esterase inhibitors (neostigmine, edrophonium), which work through competitive antagonism. Vagolytic agents (e.g., atropine, glycopyrrolate) must be co-administered to prevent bradycardia. This process, even for the shortest-acting muscle relaxant, rocuronium, can take several minutes. An intubating dose of rocuronium to rapidly induce paralysis in emergency situations may not spontaneously reverse for 20 minutes or longer (compared with about 3 minutes for succinylcholine). The effects of long-acting, nondepolarizing NMBAs (vecuronium, pancuronium) are invariably reversed. Acetylcholine esterase inhibitor efficacy is dependent on the degree of NMB at the time of administration, and residual NMB is common despite reversal with these agents. **Sugammadex** is an alternative reversal agent that has a very low rate of residual NMB induced by the aminosteroids rocuronium and vecuronium. Its mechanism of action involves noncompetitive antagonism through encapsulation of neuromuscular agents.

POSTANESTHESIA CARE UNIT

In the postanesthesia care unit (PACU), the child is observed until there is adequate recovery from anesthesia. Achievement of spontaneous breathing, adequate pulse oximetry saturation (>95%), and hemodynamic stability are key recovery end-points. The child should be arousable, responsive, and oriented before discharge from the PACU. The amount of time spent in the PACU varies based on disposition (transfer to acute care or ICU, transfer to day surgery postrecovery unit, or discharge to home). Parents should be permitted to comfort their children in the PACU. Discharge from the PACU depends on the child's overall functional status, which includes physiologic endpoints, adequate analgesia, and control of PONV. Various scoring systems have been used for determining readiness for discharge from the PACU (Table 91.10).

Postanesthetic Complications

Respiratory insufficiency after general anesthesia is common. Prolonged emergence from anesthesia and respiratory depression may be caused by the residual effects of opioids, hypnotic agents, or NMBAs. Pain may also cause significant hypoventilation, especially after thoracic or abdominal surgery. Delayed emergence from anesthesia may result from retention of inhaled anesthetics worsened by hypoventilation. Hypothermia, especially in neonates, delays metabolism and excretion of anesthetics and prolongs neuromuscular blockade. Hypoventilation after surgery is associated with the development of **atelectasis**. Microatelectasis may lead to postoperative infections. When airway obstruction is present, maintenance of airway patency may necessitate oropharyngeal or nasopharyngeal airway placement. In the setting of profound respiratory depression, endotracheal intubation and mechanical ventilation may be indicated.

Opioid reversal with naloxone may be indicated in rare instances when excessive **opioid effect** is suspected. However, naloxone reverses both the respiratory depressant and the analgesic properties. After naloxone administration, a somnolent child with respiratory depression may experience increased pain. Opioid reversal requires bedside attention by the physician to monitor the child's behavioral, hemodynamic, and respiratory status. Importantly, naloxone is shorter acting than most opioid analgesics, which may result in renarcotization.

Postoperative stridor occurs in up to 2% of all pediatric patients. The use of appropriately sized ETTs and assurance of an air leak <30 cm H_2O

Table 91.10 Postanesthesia Recovery Scores

ALDRETE RECOVERY SCORE	≥9 REQUIRED FOR DISCHARGE
ACTIVITY—VOLUNTARILY OR ON COMMAND	
Moves four extremities	2
Moves two extremities	1
No motion	0
BREATHING	
Deep breath, cough, cry	2
Dyspnea or shallow breathing	1
Apnea	0
BLOOD PRESSURE	
Within 20% of preanesthetic value	2
Within 20–50% of preanesthetic value	1
>50% outside preanesthetic value	0
COLOR	
Pink	2
Pale, blotchy, dusky	1
Cyanotic	0
CONSCIOUSNESS	
Fully aware, responds	2
Arouses to stimulus	1
Unresponsive	0
STEWARD RECOVERY SCORE	**6 REQUIRED FOR DISCHARGE**
ACTIVITY	
Moves limbs purposefully	2
Nonpurposeful movement	1
Still	0
CONSCIOUSNESS	
Awake	2
Responsive	1
Unresponsive	0
AIRWAY	
Coughing on command or crying	2
Maintaining patent airway	1
Requires airway maintenance	0

pressure decreases the risk of airway trauma or edema. A history of stridor increases the likelihood of postoperative complications. Stridor may be severe enough after extubation to require reintubation. Racemic epinephrine aerosols and dexamethasone are commonly employed therapies; their use requires prolonged observation because of the potential for rebound stridor. Stridor in infants may be an indication for overnight observation.

Cardiovascular complications are less frequently encountered in the PACU. Fluid administration may be required to augment cardiac output, perfusion, and urine output. Large-volume fluid resuscitation (>30 mL/kg) in the postoperative period may be an indication of evolving shock physiology, and sources of hypovolemia (e.g., occult bleeding) or myocardial dysfunction (e.g., tamponade, pneumothorax) should be considered.

Emergence delirium immediately after anesthesia is noted in 5–10% of children and is more common in those 3-9 years old. Manifestations include restlessness, combativeness, disorientation, and inconsolability. Almost all anesthetic agents have been linked to the development of delirium, especially newer volatile anesthetic agents (e.g., sevoflurane, desflurane). Potential postoperative complications, such as hypoglycemia and hypoxemia, should also be ruled out. Occasionally, it is necessary to provide additional sedation (e.g., propofol, dexmedetomidine, benzodiazepines), although these agents prolong postanesthesia recovery time and may not effectively reduce delirium.

Awareness During Anesthesia

A fundamental aim of anesthesia is to prevent recall by inducing hypnosis and amnesia. In adults, certain anesthetic techniques and surgical procedures have been associated with increased incidence of recall. The long-term sequelae of recall in children are unknown. Continuous cerebral bispectral index (BIS) electroencephalographic monitoring has been used to assess consciousness and aid in the prevention of intraoperative awareness. Unfortunately, pediatric studies have not confirmed the usefulness of BIS monitoring as a means of determining anesthetic depth. Existing data do not support the routine use of BIS monitoring during pediatric anesthesia. Volatile anesthetic agents reliably produce dose-dependent hypnotic and amnestic effects and remain a mainstay of general anesthesia.

Postoperative Nausea and Vomiting

After general anesthesia, 40–50% of children may experience PONV that generally lasts for several hours. This complication prolongs recovery room times and requires significant nursing attention. The etiology is not completely understood but is likely multifactorial and related to the emetic effects of anesthetics, pain, and surgical stress. Opioid analgesics may also provoke nausea and vomiting. Other risk factors for PONV include surgery lasting greater than 30 minutes, age ≥3 years, strabismus surgery, and a history of PONV in the patient or their relatives. Importantly, preoperative fasting does not decrease the incidence of PONV. Indeed, hydration and glucose supplementation appear to be important factors in decreasing PONV. Multimodal analgesia with nonopioid agents (e.g., acetaminophen, ibuprofen, ketorolac) and regional or local anesthesia may be associated with reduced PONV. The serotonin antagonist ondansetron is an effective treatment of PONV. Ondansetron prophylaxis is recommended for patients at increased risk of PONV. Serotonin antagonists are contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. Dexamethasone may also be used for the treatment of PONV.

Thermoregulation and Malignant Hyperthermia

After anesthesia, thermoregulation remains abnormal for several hours. **Hypothermia**, especially in neonates, may be associated with cardiorespiratory depression and prolongation of the effect of opioids and NMBAs. Although hypothermia has deleterious effects, active rewarming should be performed cautiously to avoid hyperthermia and cutaneous burns. Postoperative shivering is common and may occur in the absence of hypothermia. **Hyperthermia**, with temperatures in excess of 39°C (102.2°F), is of concern in the postoperative period. When high fevers occur within hours of the use of an inhalational anesthetic, especially if succinylcholine was used, malignant hyperthermia (MH) must be ruled out.

Malignant hyperthermia is a hypermetabolic syndrome triggered by volatile anesthetic agents and succinylcholine. The onset of MH may be acute, fulminant, and lethal without appropriate interventions. The disease is genetically heterogeneous, with >10 genes contributing to susceptibility, but typically displays an autosomal dominant inheritance pattern. A family history of death or febrile reactions during anesthesia should alert the anesthesiologist to its potential. Pathogenic variants within the gene encoding for the ryanodine receptor (the calcium channel of the sarcoplasmic reticulum) predispose to MH susceptibility and have been identified in 20–40% of humans with MH. Certain **myopathies** are associated with the risk of MH, including Duchenne muscular dystrophy, central core disease, and King Denborough syndrome.

The pathophysiology of MH involves uncontrolled intracellular calcium release from skeletal muscle sarcolemma, resulting in prolonged muscle contraction, adenosine triphosphate (ATP) depletion, and muscle cell death. Rhabdomyolysis results in the release of myoglobin, creatine phosphokinase (CPK), and potassium into the blood. The clinical course of MH is characterized by rapid onset of high fever (>38.5°C [101.3°F]), muscle rigidity, acidosis (metabolic and respiratory), high end-tidal CO_2, and multiorgan dysfunction. Death may ensue secondary to hemodynamic collapse from shock and cardiac dysrhythmias. Signs of MH generally occur within the first 2 hours of anesthesia but (rarely) can occur up to 24 hours later.

When MH is suspected, treatment involves discontinuation of all inhalational anesthetics, correction of the metabolic acidosis, and administration of the muscle relaxant dantrolene. The initial dose of dantrolene is 2.5 mg/kg, and repeat doses, up to a maximum of 10 mg/kg, are indicated for persistent fever, muscle rigidity, acidosis, and tachycardia. Once symptoms are controlled, the patient should be observed for at least 24 hours, because recrudescence may occur. The MH mortality rate was once >70% and is now <5% with standardized treatment algorithms. An MH cart with sufficient supplies of dantrolene should be present at every site where pediatric anesthesia is provided.

Certain phenomena suggest an increased risk of MH. Masseter spasm during induction, with rigid clenching of the masseter muscles and an inability to open the mouth, may signal MH susceptibility. Acute myoglobinuria associated with an MH-triggering agent is another clue. The child may not be hypermetabolic or febrile but may have dark urine, high CPK levels, and risk of myoglobin-induced renal tubular damage. The finding of dark urine after administration of an anesthetic requires further investigation, including measurement of electrolytes and CPK. Prevention of MH in susceptible patients requires the avoidance of triggering agents, which include inhalational anesthetics and succinylcholine. IV anesthesia and nitrous-opioid techniques are safe. MH-safe anesthesia machines devoid of trace concentrations of volatile anesthetic vapors should be used. Dantrolene prophylaxis is not recommended because MH is rapidly treatable, and the drug causes respiratory depression and muscle weakness. For a child in whom MH is suspected, the MH hotline, 1-800-MHHYPER (1-800-644-9737), should be used to notify the Malignant Hyperthermia Association of the United States (MHAUS). MHAUS registers susceptible patients and provides diagnostic and therapeutic information. Preanesthesia susceptibility testing includes genetic analysis of the ryanodine receptor gene, muscle biopsies, in vitro contraction studies, and possibly measurement of muscle CO_2 production in response to intramuscular caffeine.

Mediastinal Masses

Children with anterior mediastinal masses such as lymphomas, teratomas, and other primary mediastinal tumors are at serious risk for cardiorespiratory failure during anesthesia secondary to airway compromise, difficult ventilation, cardiac tamponade, vascular obstruction, and circulatory collapse. These patients generally require surgical tissue diagnosis before treatment is initiated. Significant compression of vital structures can occur with seemingly mild symptoms. Tachypnea, orthopnea, wheezing, and avoidance of prone or supine positions are significant indications of serious risk. Echocardiographic or CT evidence of pericardial tamponade, right ventricular compression, or compression of the pulmonary artery suggests severe risk. Biopsy with light sedation under local anesthesia may be indicated. When anesthesia is required, preservation of spontaneous ventilation is critical during

induction of anesthesia. Rigid bronchoscopy may be used to assist with ventilation in the setting of external airway compression. Provisions to provide mechanical circulatory support (cardiopulmonary bypass) should also be available. In high-risk children, consideration should be given to initiating treatment with corticosteroids, radiation therapy, and chemotherapy before obtaining a tissue diagnosis.

Postoperative Apnea

Neonates and infants are at increased risk for the development of postoperative apnea after exposure to potent hypnotic and analgesic medications. Both central and obstructive apnea may occur. Postanesthetic apnea is most common within the first 12 hours, although apnea has been reported in premature infants up to 48 hours later. Risk factors for postoperative apnea include history of apnea, caffeine treatment, chronic hypoventilation, and anemia. The risk of apnea is inversely proportional to postconceptual age (PCA) at surgery and is highest in premature neonates less than 36 weeks estimated gestational age. This risk is minimal by the time premature infants have reached 60 weeks PCA. When surgery is required in early infancy, overnight observation and monitoring may be indicated. In term infants >44 weeks PCA without risk factors, management should include observation and monitoring for 6 hours with at least one sleep-wake-feed cycle without hypoxia, bradycardia, or supplemental oxygen. Premature infants with risk factors <52 weeks PCA require admission for observation for 12 hours after anesthesia.

POSTOPERATIVE PAIN MANAGEMENT

Postprocedural pain management should ensure adequate analgesia and anxiolysis (see Chapter 93). Preoperative education focusing on pain management through development of skills designed to decrease anticipatory anxiety and participation in treatment planning can be helpful for children and families. Pediatric pain management relies on multimodal therapy, including opioid and nonopioid analgesics. Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, acetaminophen, opioids, and regional analgesia all have roles in postoperative pain management. Repeated evaluation is critical to effective pain management. Adjunctive therapy, such as pet therapy, may also decrease the need for potent analgesics postoperatively.

Patient-controlled analgesia (PCA) and **parent/nurse-controlled analgesia (PNCA)** are widely accepted postoperative pain regimens. PCA/PNCA may be used to administer a low-dose continuous (basal) infusion of opioid with intermittent (bolus) supplements as needed. The practitioner must determine the basal rate, bolus dose, lockout interval, and acceptable number of bolus doses per hour. PCA/PNCA safety requires appropriate medication dosing and assumes that patients are unlikely to overdose because somnolence will limit repeated self-administration. In young children, proper PCA/PNCA use may be more difficult to ensure, although children as young as 5 years have been able to use PNCA successfully. In older children and adolescents, PCA is a standard modality of postoperative pain management.

Regional Anesthesia

Regional anesthesia is the use of anesthetics to block the conduction of afferent neural impulses to the central nervous system. Forms of regional anesthesia include local anesthesia, peripheral nerve blocks, nerve plexus blocks, and neuraxial (epidural and subarachnoid/spinal) blocks. Anesthetics may be administered as a single injection or as a continuous infusion. Regional anesthesia may be used for both intraoperative and postoperative analgesia and has been linked to shortened recovery times and hospital stays in children. A major benefit of regional anesthesia is lesser central cardiorespiratory depressant effects. Injection of local anesthetics (e.g., lidocaine, bupivacaine) into the affected area may provide procedural analgesia lasting for hours to days. Wound infiltration with local anesthetics at the conclusion of surgery may also decrease early postoperative pain.

Neuraxial (epidural, spinal) analgesia is common in pediatric practice. The epidural space lies between the dura and the pia and arachnoid membranes, an area through which all nerve roots pass. Caudal epidural analgesia is placed through the sacral hiatus, inferior to the distal end of the spinal cord. This site is often used for pelvic and lower-limb anesthesia during urologic and orthopedic surgery in infants and toddlers. A single dose of caudal epidural anesthesia may provide hours of pain relief, and a continuous infusion may provide effective pain relief for hours to days. The epidural injection of opioids can provide analgesia for 12-24 hours and is a potential supplement to postoperative analgesia. Longer-acting local anesthetics (e.g., bupivacaine, ropivacaine) combined with an opioid (e.g., fentanyl, preservative-free morphine) are typically used in single-injection and continuous epidural therapy. It is also possible to provide epidural PCA with a continuous infusion pump and the patient's ability to self-administer analgesia as needed. Epidural analgesia can also provide pain relief in patients with chronic pain or pain caused by advanced malignant conditions.

Complications of neuraxial anesthesia include cephalad spread of blockade with respiratory depression, paralysis of respiratory muscles, and brainstem depression. Common complications of neuraxial analgesia are paresthesias and, if opioids are used, pruritus, nausea, and vomiting. Neuraxial opioid use necessitates antipruritic and antiemetic therapy. Infection and epidural hematoma are extremely rare. Neuraxial opioids, especially when administered intrathecally, may cause respiratory depression and require postoperative monitoring.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

91.1 Anesthetic Neurotoxicity

John P. Scott

Laboratory animal studies have suggested a link between anesthetic exposure at an early age and neurotoxicity in developing brains. Existing nonclinical data implicate *N*-methyl-D-aspartate and γ-aminobutyric acid (GABA) pathways in apoptosis and neuronal cell death. Histopathologic changes and adverse neurodevelopmental outcomes have been associated with exposure to both inhalational and IV anesthetics, including isoflurane, sevoflurane, ketamine, benzodiazepines, and propofol. Animal studies were initially performed in nonprimates (rodents), and controversy remains concerning experimental design (dose, duration of treatment, species differences). However, work in nonhuman primates has also shown an increased incidence of adverse neurodevelopmental outcomes after prolonged and/or multiple exposures to volatile anesthetics.

Human studies of anesthesia-induced neurotoxicity have yielded conflicting results. Further complicating the situation are other potential triggers for adverse neurodevelopmental outcomes, including comorbidities, surgical trauma, and perioperative cardiorespiratory status. Multiple population-based epidemiologic studies have suggested a potential association between anesthetic exposure and adverse neurodevelopmental outcomes after multiple or prolonged anesthetic exposures. Large-scale European and Canadian cohort studies using national registries have revealed subtle differences in standardized psychometric testing of early school-age children after exposure to general anesthesia. Interestingly, other studies in children have failed to yield similar results. The Pediatric Anesthesia and Neurodevelopmental Assessment (PANDA), a multicenter matched-sibling control study, revealed no association between brief anesthetic exposure for inguinal hernia repair and aptitude on psychometric testing. Similarly, the General Anaesthesia and Awake-Regional Anaesthesia in Infancy (GAS) study, a prospective multicenter randomized controlled trial comparing general and neuraxial spinal anesthesia in infants for hernia repair, *did not* demonstrate any significant differences in neurodevelopment at 2 years of age between groups. A follow-up study at 5 years of age similarly showed no difference in neurodevelopment between groups receiving general and spinal anesthesia. Importantly, studies have not shown an association between adverse neurodevelopmental outcomes and anesthetic exposure <3 hours.

Alternatives to general anesthesia for many procedures in young children do not exist. Regional anesthetic techniques and narcotic-based anesthetics may gain popularity. Dexmedetomidine may also have some neuroprotective properties. Currently, there are insufficient data to make conclusions regarding the safety of one anesthetic approach over another. Ultimately, the potential for neurotoxicity must be balanced against the necessity of providing adequate anesthesia for children presenting for surgery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 92

Procedural Sedation

John P. Scott

See also Chapters 91 and 93.

Sedation describes the continuum between wakefulness and general anesthesia (see Table 91.7). Many of the same medications used to induce general anesthesia may be used to provide sedation (see Table 91.8). Analogous to the provision of anesthesia, performance of procedural sedation requires a comprehensive presedation evaluation, intraprocedural monitoring, and postsedation recovery care. The term **conscious sedation** refers to a condition in which a patient is sleepy, comfortable, and cooperative but maintains airway-protective and ventilatory reflexes. Depending on the choice of pharmacotherapy, sedation may not provide analgesia. Sedation that is sufficient to obtund painful responses describes deep sedation. **Deep sedation** is a state of unarousability to voice and may be accompanied by suppression of reflex responses, with preservation of ability to respond purposefully to repeated or painful stimulation.

Pediatric procedural sedation requires vigilance and knowledge to ensure safety and is governed by the same guidelines as anesthesia care (Table 92.1). Adherence to guidelines for appropriate monitoring and management of sedation in children is imperative. Sedative doses that cause minimal sedation in one patient may produce complete unconsciousness and apnea in another. Anxiolysis or light sedation with chloral hydrate, benzodiazepines, and dexmedetomidine is often sufficient for nonpainful procedures. The use of dexmedetomidine for procedural sedation is safe, but recovery time can be prolonged and success variable. For painful procedures (e.g., bone marrow aspiration), the combination of hypnosis and analgesia is required. The addition of opioids to sedation regimens increases the risk of respiratory insufficiency. Short-acting anesthetics (e.g., propofol, methohexital, remifentanil) provide effective procedural sedation, but their use carries a higher likelihood of inadvertent induction of general anesthesia. Use of these medications requires the presence of an anesthesiologist and/or specially trained, experienced, credentialed, and qualified physicians.

Many pediatric subspecialists provide sedation and anesthesia care for children. The use of anesthetic agents is not limited to anesthesiologists, but anesthesiology departments are obligated to help develop, manage, and oversee sedation services. Together, hospitals and providers, including anesthesiologists, share responsibility for the oversight and credentialing of individuals administering sedation and anesthesia.

The elements of a safe pediatric procedural sedation system include the following:

- Clearly defined knowledge and skill sets
- Adequate prerequisite training
- Credentialing of providers
- Maintenance of certification
- Ensuring that sedation sites meet recognized standards
- Continuous quality improvement

Table 92.2 provides an approach to proper language to help the child cope with procedural pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 92.1 Systematic Approach to Sedation in Children

Comprehensive medical history and organ system assessment, anticipating underlying medical problems that predispose the patient to anesthetic complications
Careful physical examination focused on the cardiorespiratory system and airway
Appropriate fasting
Informed consent
Pediatric drug dosing (mg/kg)
Appropriately sized equipment
Documentation of vital signs and condition on a time-based record
Rapid response ("code") team to respond to emergencies with "crash cart"
Fully equipped and staffed recovery area
Discharge criteria documenting recovery from sedation

Table 92.2 Suggested Language for Parents and Healthcare Providers

LANGUAGE TO AVOID	LANGUAGE TO USE
You will be fine; there is nothing to worry about. (reassurance)	What did you do in school today? (distraction)
This is going to hurt/this will not hurt. (vague; negative focus)	It might feel like a pinch. (sensory information)
The nurse is going to take some blood. (vague information)	First, the nurse will clean your arm, you will feel the cold alcohol pad, and next . . . (sensory and procedural information)
You are acting like a baby. (criticism)	Let's get your mind off of it; tell me about that film . . . (distraction)
It will feel like a bee sting. (negative focus)	Tell me how it feels. (information)
The procedure will last as long as . . . (negative focus)	The procedure will be shorter than . . . (television program or other familiar time for child) (procedural information; positive focus)
The medicine will burn. (negative focus)	Some children say they feel a warm feeling. (sensory information; positive focus)
Tell me when you are ready. (too much control)	When I count to 3, blow the feeling away from your body. (coaching to cope; distraction-limited control)
I am sorry. (apologizing)	You are being very brave. (praise; encouragement)
Do not cry. (negative focus)	That was hard; I am proud of you. (praise)
It is over. (negative focus)	You did a great job doing the deep breathing, holding still . . . (labeled praise)

Adapted from Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet.* 2016;387:83–92.

Chapter 93

Pediatric Pain Management

Stacy J.B. Peterson and Steven J. Weisman

Pain is both a sensory and an emotional experience. Infants, children, and adolescents experience a wide range of acute and chronic pain etiologies. When unrecognized and undertreated, pain extracts a significant physiologic, biochemical, and psychologic toll on both the child and the family. Many disease processes and most interventional diagnostic or treatment procedures in pediatrics are associated with pain. Similarly, traumatic, developmental, cognitive, psychologic, and social experiences can also trigger and maintain chronic pain.

DEFINITION AND CATEGORIES OF PAIN

The International Association for the Study of Pain (IASP) defines **pain** as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Furthermore, the IASP expanded the definition to include the following six key notes:

1. Pain is always a personal experience that is influenced to varying degrees by biologic, psychologic, and social factors.
2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
3. Through their life experiences, individuals learn the concept of pain.
4. A person's report of an experience as pain should be respected.
5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychologic well-being.
6. Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human experiences pain.

Important elements to emphasize in this definition are (1) pain encompasses both peripheral physiologic and central neural components and (2) pain may or may not be associated with ongoing tissue damage. The experience of pain lies primarily in the strength and patterning of central neural connectivity (Fig. 93.1). Although immediate upstream neural activation can originate from inflammatory, structural, or biochemical events, processes not only in the periphery but also in the spinal cord and the brain influence the intensity and duration of pain. Similarly, central neural processes in the brain are associated with the location, intensity, and distress associated with pain. Chronic pain can develop when the upstream neural signaling continues to activate central neural circuits, such as with continued peripheral inflammatory or structural pain-associated processes. Sometimes, this signaling does not regress and the individual experiences ongoing chronic pain after the resolution of the original process.

Often, however, pediatricians face the most difficult problems when either acute pain becomes chronic or chronic pain develops and is maintained without a definable infectious, inflammatory, metabolic, or structural cause. When no "cause" can be found, patients are often referred to mental health specialists, or the cause for the pain is labeled as "stress." Children read this message as, "The doctor thinks I am faking pain, or I am crazy." Parents see their child suffering and often seek care from additional providers, with the child undergoing numerous tests, procedures, medication trials, and visits and many physicians looking for the cause of the pain so it can be "fixed" or to "get an answer." Meanwhile, the child is often missing school, social, and physical activities. In addition, they often develop poor sleep habits, nonrestorative sleep, and exhibit increasing fatigue.

It is recognized that chronic pain, in the absence of a specific identified structural, biochemical, or inflammatory cause, develops through the initiation, maintenance, and strength of central neural connectivity patterns (see Chapter 212). *Centrally mediated pain* derives from neural connectivity patterns in the brain that include centers involved in autonomic nervous system control, memory, and other cognitive centers, as well as emotional centers of the brain. In pediatrics, birth history and child development overlay these central patterns that contribute to the development of chronic pain. Parents may understand the concept of a "sticky nervous system" as the perpetuator of the continued pain in such a child. This model of brain connectivity patterns, or "top-down" mediators of chronic pain, is important, because it explains how psychologic and other nonpharmacologic interventions work to reduce chronic pain and suffering.

Table 93.1 specifies important pain categories typically treated (somatic, visceral, and neuropathic) and defines the elements and characteristics of **nociception**, the peripheral physiologic aspect of pain perception. Nociception refers to how specialized fibers (largely, but not exclusively, the small, unmyelinated A-delta and C fibers) in the peripheral nervous system transmit nerve impulses (usually transmitting signals originating from peripheral mechanoreceptors and chemoreceptors) through synapses in the spinal cord's dorsal horn through (but not exclusively through) the spinothalamic tracts to the brain's higher centers, where the development of neural connectivity patterns creates the experience of pain.

ASSESSMENT AND MEASUREMENT OF PAIN IN CHILDREN

Assessing pain entails much more than merely quantifying it. Whenever feasible, the physician should ask the patient about the character, location, quality, duration, frequency, and intensity of the pain. Depending on their age, children may be able to answer some or all the questions independently or with assistance from their parents. Severity can also be assessed via utilization of various scales, which will be discussed later. Some children may not report pain because of fears of talking to strangers, disappointing, or bothering others, receiving an injection if they report pain, returning to the hospital if they admit to pain, and other negative reactions. For infants and nonverbal children, their parents, pediatricians, nurses, and other caregivers are constantly challenged to interpret whether the child's distressed behaviors represent pain, fear, hunger, or a range of other perceptions or emotions. Similarly, lack of normal interest in play without behavioral distress signals can be manifestations of pain. Therapeutic trials of comfort measures (cuddling, feeding) and analgesic medication may be helpful in clarifying the triggers of the behaviors.

Behavior and physiologic signs are useful but can be misleading. A toddler may scream and grimace during an ear examination because of fear rather than pain. Conversely, children with inadequately relieved persistent pain from cancer, sickle cell disease, trauma, or surgery may withdraw from their surroundings and appear very quiet, leading observers to conclude falsely that these children are comfortable or sedated. In adolescents, increased reports of pain may be misinterpreted as "drug seeking" behaviors. In these situations, it is important to assess pain appropriately and determine how to best improve pain and function. Although this may be best accomplished by adjustment to analgesic medications, it may also involve the optimization of other nonpharmacologic techniques. This approach, although increasing the number or amount of interventions, may make the child become more, not less, interactive and alert as pain control improves. Similarly, neonates and young infants may close their eyes, furrow their brows, and clench their fists in response to pain. Adequate analgesia is often associated with eye opening and increased involvement in surroundings. A child who is experiencing significant chronic pain may play normally to distract attention away from pain. These coping behaviors are sometimes misinterpreted as evidence of the child's "faking" or exaggerating pain.

Age-Specific and Developmentally Specific Measures

Because infants, young children, and nonverbal children cannot express the quantity of pain they experience, several pain scales have been devised attempting to quantify pain in these populations (Fig. 93.2 and Table 93.2).

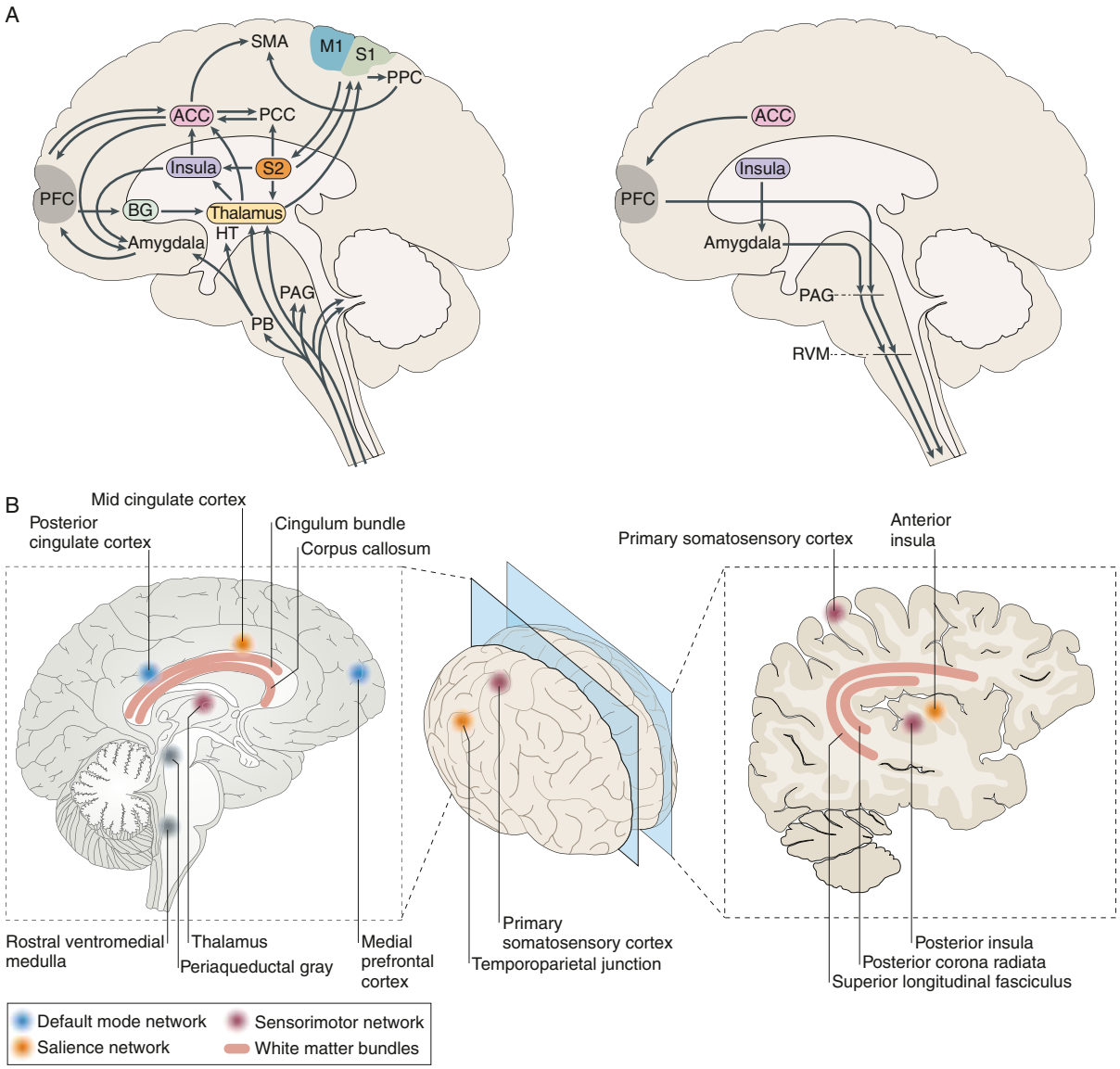

Fig. 93.1 Brain pathways, regions, and networks involved in acute and chronic pain. ACC, Anterior cingulate cortex; PCC, posterior cingulate cortex; BG, basal ganglia; HT, hypothalamus; PAG, periaqueductal gray; PB, parabrachial nuclei; PFC, prefrontal cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; RVM, rostral ventromedial medulla. (**A**, *left panel from Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9:463–484;* **A**, *right panel from Schweinhardt P, Bushnell MC. Pain imaging in health and disease—how far have we come? J Clin Invest. 2010;120:3788–3797;* **B** *from Davis KD, Flor H, Greely HT, et al. Brain imaging tests for chronic pain: Medical, legal and ethical issues and recommendations. Nat Rev Neurol. 2017;13:624–638.)*

Table 93.1 Pain Categories and Characteristics

PAIN CATEGORY	DEFINITION	EXAMPLES	CHARACTERISTICS
Somatic	Pain resulting from injury to or inflammation of tissues (e.g., skin, muscle, tendons, bone, joints, fascia, vasculature)	Burns, lacerations, fractures, infections, inflammatory conditions	*In skin and superficial structures:* sharp, pulsatile, well localized *In deep somatic structures:* dull, aching, pulsatile, not well localized
Visceral	Pain resulting from injury to or inflammation of viscera	Angina, hepatic distention, bowel distention or hypermobility, pancreatitis	Aching and cramping; nonpulsatile; poorly localized (e.g., appendiceal pain perceived around umbilicus) or referred to distant locations (e.g., angina perceived in shoulder)
Neuropathic	Pain resulting from injury to, inflammation of, or dysfunction of the peripheral or central nervous system	Complex regional pain syndrome (CRPS), phantom limb pain, Guillain-Barré syndrome, sciatica	Spontaneous; burning; lancinating or shooting; dysesthesias (pins and needles, electrical sensations); **hyperalgesia** (amplification of noxious stimuli); **hyperpathia** (widespread pain in response to a discrete noxious stimulus); **allodynia** (pain in response to nonpainful stimulation); pain may be perceived distal or proximal to site of injury, often corresponding to innervation pathways (e.g., sciatica)

Behavioral Indicators

Facial grimacing: The Neonatal Facial Coding System uses several facial actions that may be indicators of pain. Pain is characterized by a bulging brow with tight creases in between; tightly closed eyelids; a deeply furrowed nasolabial groove; a horizontal, wide opened mouth; and a taut tongue that may be quivering along with the chin.

Crying: May be an indicator of pain.

Activity: Withdrawal or immobilization of a limb may be an indicator of pain.

Response to comfort measures: Feeding, swaddling, holding, and ensuring that the infant is neither wet nor cold may help to discriminate between pain and other conditions.

Physiologic indicators: Alterations in heart rate, blood pressure, SpO_2, respiratory rate, or alterations in pattern of respiration may be nonspecific indicators of pain.

Self-Report of Pain

Categorical description: Toddlers or young children are asked to say if they are having "a little bit," a "middle amount," or "a lot" of pain.

Faces Scales: Children who do not have an appreciation of ordinal numbering are asked to rate their pain based upon cartoons depicting facial indicators of distress.

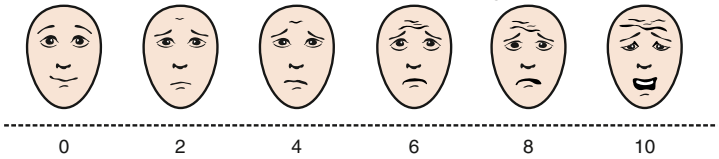

Numerical Rating Scale (NRS): Older children and teenagers are asked to rate their pain on a scale of "0" (no pain) to "10" (worst pain).

Visual Analog Scale (VAS): Children or teenagers are asked to move an indicator along a mechanical slide to depict the level of pain; the clinician reads a number along a 10-cm indicator on the back to determine the numeric score.

Fig. 93.2 Clinically useful pain assessment tools. *(Adapted from Burg FD, Ingelfinger JR, Polin RA, et al., eds. Current Pediatric Therapy, 18th ed. Philadelphia: Saunders; 2006:16; and Hicks CL, von Baeyer CL, Spafford P, et al. The Faces Pain Scale—revised: Toward a common metric in pediatric pain measurement. Pain. 2001;93:173–183.)*

Table 93.2 Pain Measurement Tools

NAME	FEATURES	AGE RANGE	ADVANTAGES	VALIDATION AND USES	LIMITATIONS
Visual Analog Scale (VAS)	Horizontal 10-cm line; subject marks a spot on the line between anchors of "no pain" and "most pain imaginable"	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Cannot be used in younger children or in those with cognitive limitations Requires language skills and numerical processing; upper anchor of "most pain" requires an experiential reference point that is lacking in many children
Numerical Rating Scale (NRS)	Integers from 0 to 10, inclusive, corresponding to a range from no pain to most pain	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Same as for VAS
Faces Scales (e.g., FACES-R, Wong-Baker, Oucher, Bieri, McGrath scales)	Subjects rate their pain by identifying with line drawings of faces or photos of children	3 yr and older	Can be used at younger ages than VAS and NRS	Acute pain Surgical pain	Choice of "no pain" face affects responses (neutral vs smiling); not culturally universal
Behavioral or combined behavioral-physiologic scales (e.g., FLACC, N-PASS, CHEOPS, OPS, FACS, NIPS)	Scoring of observed behaviors (e.g., facial expression, limb movement) ± heart rate and blood pressure	Some work for any ages; some work for specific age-groups, including preterm infants	May be used in both infants and nonverbal children	FLACC, N-PASS: Acute pain Surgical pain	Nonspecific; overrates pain in toddlers and preschool children; underrates persistent pain; some measures are convenient, but others require videotaping and complex processing; vital sign changes unrelated to pain can occur and may affect total score
Autonomic measures (e.g., heart rate, blood pressure, heart rate spectral analyses)	Scores changes in heart rate, blood pressure, or measures of heart rate variability (e.g., "vagal tone")	All ages	Can be used at all ages; useful for patients receiving mechanical ventilation		Nonspecific; vital sign changes unrelated to pain may occur and may artifactually increase or decrease score
Hormonal-metabolic measures	Plasma or salivary sampling of "stress" hormones (e.g., cortisol, epinephrine)	All ages	Can be used at all ages		Nonspecific; changes unrelated to pain can occur; inconvenient; cannot provide "real-time" information; standard normal values not available for every age bracket

VAS, visual analog scale; NRS, numerical rating scale; FLACC, face, legs activity, cry, and consolability pain scale for preverbal/nonverbal patients; N-PASS, neonatal pain agitation and sedation scale.

The Newborn and Infant

There are several behavioral distress scales for the infant and young child, mostly emphasizing the patient's facial expressions, crying, and body movement. Facial expression measures appear most useful and specific in neonates. Autonomic and vital signs can indicate pain, but because they are nonspecific, they may reflect other processes, including fever, hypoxemia, and cardiac or renal dysfunction (Tables 93.3 and 93.4).

Table 93.3 Signs and Symptoms of Pain in Infants and Young Children

PHYSIOLOGIC CHANGES	BEHAVIORAL CHANGES
• Increase in heart rate, respiratory rate, blood pressure, muscle tone • Oxygen desaturation • Sweating • Flushing • Pallor	• Change in facial expression (grimacing, furrowing of the brow, nasal flaring, deep nasolabial groove, curving of the tongue, quivering of the chin) • Finger clenching • Thrashing of limbs • Writhing • Back arching • Head banging • Poor feeding • Sleep disturbance • Pseudoparalysis

From Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet.* 2016;387:83–92.

Table 93.4 CRIES Neonatal Pain Assessment Scale

	0	1	2
Crying	No	High pitched but consolable	Inconsolable
Requires oxygen for saturation >95%	No	FiO_2 <30%	FiO_2 >30%
Increased vital signs	No	HR or BP <20%	HR or BP >20%
Expression	No	Grimace	Grimace and grunt
Sleepless	No	Wakes often	Constantly awake

Score <4 initiate nonpharmacologic measures
Score >4 initiate pharmacologic and nonpharmacologic measures
BP, Blood pressure; HR, heart rate.
From Davis PJ, Cladis FP, eds. *Smith's Anesthesia for Infants and Children,* 10th ed. Philadelphia: Elsevier; 2022, Table 23.2, p. 487.

The Older Child

Children age 3-7 years old become increasingly articulate in describing the intensity, location, and quality of pain. Pain is occasionally referred to adjacent areas; referral of hip pain to the thigh or area above the knee is common in this age range. Self-report measures for children this age include using drawings, pictures of faces, or graded color intensities. Children ≥8 years old can usually use verbal numerical rating scales (NRS) or visual analog pain scales (VAS) accurately (see Fig. 93.2). Verbal numerical ratings are preferred and considered the gold standard: valid and reliable ratings can be obtained from children ≥8 years of age. The NRS consists of numbers from 0 to 10, in which 0 represents no pain and 10 represents very severe pain. There is debate about the label for the highest pain rating, but the current agreement is *not* to use the phrase "worst pain possible," because children can always imagine a greater pain. In the United States, regularly documented pain assessments are required for hospitalized children and children attending outpatient hospital clinics and emergency departments. Pain scores do not always correlate with changes in heart rate or blood pressure.

The Cognitively Impaired Child

Measuring pain in cognitively impaired children remains a challenge. Understanding pain expression and experience in this population is important because behaviors may be misinterpreted as indicating that cognitively impaired children are more insensitive to pain than neurotypical children. Children with trisomy 21 may express pain less precisely and more slowly than the general population. Pain in children with autism spectrum disorder (ASD) may be difficult to assess because these children may be both *hyposensitive* and *hypersensitive* to many different types of sensory stimuli, and they may have limited communication abilities. Although self-reports of pain can be elicited from some children who are cognitively impaired, observational measures have better validation among these children. The **Noncommunicating Child's Pain Checklist—Postoperative Version** is recommended for children up to 18 years old. In addition, the FLACC pain scale has been validated in nonverbal and cognitively impaired children (Table 93.5). Maladaptive behaviors and reduction in function may also indicate pain. Children with severe cognitive impairments experience pain frequently, and children with the fewest abilities experience the most pain. For this reason, providers must be able to recognize subtle signs and symptoms of pain (see Table 93.3)

Table 93.5 Revised FLACC for Pain Assessment in the Cognitively Impaired*

	0	1	2
Face	No particular expression or smile	Occasional grimace/frown; withdrawn or disinterested (appears sad or worried)	Consistent grimace or frown; frequent/constant quivering chin, clenched jaw (distressed-looking face; expression of fright or panic)
Legs	Normal position or relaxed	Uneasy, restless, tense (occasional tremors)	Kicking or legs drawn up (marked increase in spasticity, constant tremors, or jerking)
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense (mildly agitated [e.g., head back and forth, aggression]; shallow, splinting respirations, intermittent sighs)	Arched, rigid, or jerking (severe agitation, head banging; shivering [not rigors]; breath-holding, gasping or sharp intake of breath; severe splinting)
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint (occasional verbal outburst or grunt)	Crying steadily, screams or sobs, frequent complaints (repeated outbursts, constant grunting)
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or talking; distractible	Difficult to console or comfort (pushing away caregiver, resisting care or comfort measures)

*Revised descriptors for children with disabilities shown in brackets.
0= Relaxed/comfortable
1–3 = Mild discomfort
4–6 = Moderate pain
7–10 = Severe pain
FLACC Scoring System: May be used in preverbal, mechanically ventilated, or cognitively impaired patients; it is an acronym that includes 5 indicators, each scored as a 0, 1, or 2, that form a 10-point composite scale with a range from 0 (no pain) to 10 (worst pain). FLACC: Score each category between 0 and 2. The total score may be any number from 0 to 10.
From Davis PJ, Cladis FP, eds. *Smith's Anesthesia for Infants and Children,* 10th ed. Philadelphia: Elsevier; 2022, Table 23.3, p. 488.

CONCEPTUAL FRAMEWORK FOR TREATMENT OF PEDIATRIC PAIN

Many models of pain focus on factors that explain the interindividual variability in pain perception and the chronicity and impairment experienced with pain. Central to these models are interrelationships among biologic, cognitive, affective, and social factors that influence children's pain and disability, commonly referred to as *biopsychosocial models* of pain. **Biologic** factors include the child's physical health, central nervous system (CNS) factors (pain processing), gender, pubertal status, and genetic factors. Individual child **cognitive and affective** factors related to perception of pain include anxiety, fear, negative affect, pain behaviors, and functional disability, whereas **social** factors include such areas as culture, socioeconomic status, school environment, social and peer interactions, adverse childhood events, and parental and family factors. For children, **developmental** factors need to be considered, such as cognitive and motor development, birth history, and epigenetic factors (the interaction in development between genetic and environmental factors).

A framework that considers the interplay of biologic, psychologic, and social factors is useful for understanding pediatric pain and to guide pain assessment and the delivery of pain prevention and management. Many simple interventions designed to promote relaxation and patient control can work either alone or synergistically with pain medications for relief of pain and related distress. Moreover, psychologic interventions are often coupled with physical therapy interventions to assist in the management of disabling chronic pain.

Pharmacologic Treatment of Pain

The pharmacokinetics and pharmacodynamics of analgesics vary with age. This results in drug responses in infants and young children that differ from those in older children and adults. The elimination half-life of most analgesics is prolonged in neonates and young infants because of their immature hepatic enzyme systems and reduced glomerular filtration. Clearance of analgesics may also be variable in young infants and children. Renal blood flow, glomerular filtration, and tubular secretion increase dramatically in the first few weeks after birth, approaching adult values by 3-5 months of age. Renal clearance of analgesics is often greater in toddlers and preschool-age children than in adults, whereas in premature infants, clearance is reduced. Age-related differences in body composition and protein binding also exist. Total body water as a fraction of body weight is greater in neonates than in children or adults. Tissues with high perfusion, such as the brain and heart, account for a larger proportion of body mass in neonates than do other tissues, such as muscle and fat. Because of decreased serum concentrations of albumin and α_1-acid glycoprotein, neonates have reduced protein binding of some drugs, resulting in higher amounts of free, unbound, pharmacologically active drugs.

Acetaminophen, Aspirin, and Nonsteroidal Antiinflammatory Drugs

Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) have replaced aspirin as the most used antipyretics and oral, nonopioid analgesics (Table 93.6). This is because of the association of Reye syndrome with the use of aspirin in children with a viral infection, such as influenza or chickenpox.

Acetaminophen, a generally safe, nonopioid analgesic and antipyretic, has the advantage of intravenous (IV), rectal, and oral routes of administration. Acetaminophen is not associated with the gastrointestinal (GI) or antiplatelet effects of aspirin and NSAIDs, making it a particularly useful drug in patients with cancer. Unlike aspirin and NSAIDs, acetaminophen has only mild antiinflammatory action. Although acetaminophen alone may not adequately treat various types of pain, in conjunction with other agents, it can lead to improved pain control and decreased opioid use. One effective management strategy can be to schedule acetaminophen and/or NSAIDs to decrease the need for opioids, while still maintaining good pain control.

Acetaminophen toxicity can result from a large single dose or cumulative excessive dosing over days or weeks (see Chapter 94). Toxicity manifests as fulminant hepatic necrosis and liver failure in infants, children, and adults. Drug biotransformation processes are immature in neonates, very active in young children, and somewhat less active in adults. Young children are more resistant to acetaminophen-induced hepatotoxicity than are adults as a result of metabolic differences. Sulfation predominates over glucuronidation in young children, leading to a reduction in NAPQI production.

Aspirin is indicated for certain rheumatologic conditions and for inhibition of platelet adhesiveness, as in the treatment of Kawasaki disease. Concerns about Reye syndrome have resulted in a substantial decline in pediatric aspirin use. In general, aspirin should not be used for routine pain control in children. It is important to be aware of

Table 93.6 Commonly Used Nonopioid Medications (Antiinflammatory Medications)

MEDICATION	DOSAGE	COMMENT(S)
Acetaminophen	10-15 mg/kg PO q4h 10 mg/kg IV q4h 15 mg/kg IV q6h 10 mg/kg IV q6h (<2 yr) 20-30 mg/kg/PR q4h 40 mg/kg/PR q6-8h *Maximum daily dosing:* 75 mg/kg/24 hr (children) 60 mg/kg/24 hr (<2 yr) 30-45 mg/kg/24 hr (neonates)	Minimal antiinflammatory action; no antiplatelet or adverse gastric effects; overdosing can produce fulminant hepatic failure.
Ibuprofen	8-10 mg/kg PO q6h 10 mg/kg IV q4-6h to maximum of 400 mg *Maximum daily dose:* 2,400 mg	Antiinflammatory; transient antiplatelet effects; may cause gastritis; extensive pediatric safety experience.
Naproxen	5-7 mg/kg PO q8-12h *Maximum daily dose:* 1,000 mg	Antiinflammatory; transient antiplatelet effects; may cause gastritis; more prolonged duration than that of ibuprofen.
Ketorolac	Loading dose 0.3 mg/kg, then 0.25-0.3 mg/kg IV q6h to a maximum of 5 days; maximum single dose 15 mg for those < 50 kg and 30 mg for those ≥ 50 kg	Antiinflammatory; reversible antiplatelet effects; may cause gastritis; useful for short-term situations in which oral dosing is not feasible.
Diclofenac sodium	2-3 mg/kg/day divided in 2 or 3 doses *Maximum daily dose:* 150 mg	Antiinflammatory; reversible antiplatelet effects; lower risk of gastritis and ulceration compared with other NSAIDs.
Celecoxib	Only approved for children ≥2 yr; ≥10 kg to ≤25 kg: 50 mg PO bid >25 kg: 100 mg PO bid	Antiinflammatory; no or minimal antiplatelet or gastric effects; cross-reactivity with sulfa allergies.

aspirin-containing medications that may be available over the counter when treating patients.

NSAIDs are used widely to treat pain and fever in children. Most currently available NSAIDs are nonselective cyclooxygenase (COX) inhibitors, that is, drugs that nonselectively block the activity of both COX-1 (found in gastric mucosa and platelets) and COX-2 (active in inflammatory pathways and cortical renal blood flow regulation) enzymes that synthesize prostaglandins. In children with juvenile idiopathic arthritis, ibuprofen and aspirin are equally effective, but ibuprofen is associated with fewer side effects and better drug adherence. NSAIDs, used adjunctively in surgical patients, reduce opioid requirements (and therefore opioid side effects) by as much as 35–40%. Although NSAIDs can be useful postoperatively, they should be used as an adjunct to, not as a substitute for, opioids in patients with acute moderate to severe pain.

Ketorolac is useful in treating moderate to severe acute pain in patients who are unable or unwilling to take oral NSAIDs. Intravenous diclofenac is also available in other countries. U.S. Food and Drug Administration (FDA) recommendations limit ketorolac to five consecutive days of administration. IV ibuprofen (Caldolor) is FDA approved for the management of pain and fever in infants and children >6 months of age, but is not widely available.

Adverse effects of NSAIDs are uncommon but may be serious when they occur, including gastritis with pain and bleeding; decreased renal blood flow that may reduce glomerular filtration and enhance sodium reabsorption, in some cases leading to tubular necrosis; hepatic dysfunction and liver failure; inhibition of platelet function; and an increased incidence of cardiovascular events in patients predisposed to stroke and myocardial infarction. Although the overall incidence of bleeding is very low, gastric bleeding is the most common cause of serious morbidity related to this class of analgesics. NSAIDs should not be used in the child with a bleeding diathesis or at risk for bleeding and should be used with caution postsurgically. Use after surgeries such as tonsillectomy has been debated, but current postoperative guidelines do include the use of NSAIDs. Renal injury from short-term use of ibuprofen in euvolemic children is quite rare; the risk is increased by hypovolemia or cardiac dysfunction. The safety of both ibuprofen and acetaminophen for short-term use is well established (see Table 93.6).

The only **COX-2 specific NSAID** currently available in the United States is oral celecoxib, whereas in other countries parenteral parecoxib and oral rofecoxib are also available. The coxib drugs are selective COX-2 enzyme inhibitors. Therefore they are effective antiinflammatory and analgesic molecules that generally do not result in platelet inhibition with enhanced bleeding or in gastric inflammation or ulceration, findings that may be seen with the nonselective COX inhibitors in the NSAID class. COX-2 selective NSAIDs do inhibit regulation of cortical renal blood flow and therefore carry the same risk of renal toxicity and acute tubular necrosis, particularly in the setting of low cardiac output states or dehydration. Celecoxib is therefore an appropriate primary or adjunctive analgesic to use in children after surgery, in children with gastric mucosal pathology, or in oncology patients in whom concern for hemostasis contraindicates conventional NSAIDs.

Use of NSAIDs for pain management in children less than 6 months is not generally recommended due to immature glomerular filtration. However, limited use between 3 and 6 months may be appropriate.

Opioids

Opioids are analgesic substances either derived from the opium poppy **(opiates)** or synthesized to have a similar chemical structure and mechanism of action **(opioids)**. The term "narcotics" (narcotic analgesics) should be avoided for these agents, as it connotes criminality and lacks pharmacologic descriptive specificity. Opioids are administered for moderate and severe pain, such as acute postoperative pain, pain from trauma, sickle cell crisis pain, and cancer pain. Opioids can be administered by the oral, rectal, oral transmucosal, transdermal, intranasal, epidural, intrathecal, IV, subcutaneous (SC), or intramuscular (IM) route. Regardless of route of administration, the site of action is at mu (μ) opioid receptors in the peripheral nervous system, spinal cord, brainstem, and higher CNS centers. Infants and young children are sometimes underdosed with opioids because of concern about significant respiratory side effects. Opioids' respiratory depressant effects result from infants' lower metabolic clearance of opioids and higher blood levels with frequent dosing. With proper understanding of the pharmacokinetic and pharmacodynamics of opioids, children can receive effective relief of pain and suffering with a good margin of safety, regardless of pharmacokinetic maturity, age, or size (Tables 93.7-93.9).

Opioids act by mimicking the actions of endogenous opioid peptides, binding to receptors in the brain, brainstem, spinal cord, and to a lesser extent in the peripheral nervous system, thus leading to inhibition of nociception. Opioids also bind to μ receptors in the pleasure centers of the midbrain, particularly in genetically susceptible individuals, a factor responsible for the euphoric effect in some individuals and the predilection to psychologic dependence and addictive behavior. Opioids also have dose-dependent respiratory depressant effects when interacting with the μ-opioid receptors in the respiratory centers of the brainstem, depressing ventilatory drive and blunting ventilatory responses to both hypoxia and hypercarbia. These respiratory depressant effects are increased with co-administration of other sedating drugs, particularly benzodiazepines or barbiturates.

Optimal use of opioids requires proactive and anticipatory management of side effects (see Table 93.8) as well as dose adjustments for renal or hepatic disease (Table 93.10). Common side effects include sedation, constipation, nausea, vomiting, urinary retention, and pruritus. Tolerance usually develops to the side effect of **nausea**, which typically subsides with long-term dosing, but nausea may require treatment with antiemetics, such as a phenothiazine, butyrophenones, antihistamines, or a serotonin receptor antagonist such as ondansetron or granisetron. Pruritus and other complications during patient-controlled analgesia with opioids may be effectively managed by low-dose IV naloxone.

The most common troubling, but treatable, side effect is **constipation**. Patients who take opioids for chronic pain for long periods predictably develop tolerance to the sedative and analgesic effects of opioids over time, but tolerance to constipation does not occur, and constipation remains a troublesome and distressing problem in almost all patients with long-term opioid administration. Stool softeners and stimulant laxatives should be administered to most patients receiving opioids for more than a few days. Osmotic and bulk laxatives are less effective, usually producing more distention and discomfort. A peripherally acting opiate μ-receptor antagonist, **methylnaltrexone**, promptly and effectively reverses opioid-induced constipation in patients with chronic pain who are receiving opioids daily. Methylnaltrexone is approved for use as either an injectable or oral formulation, but only the SC injection is commercially available, which most children will object to receiving. Naldemedine and naloxegol are other agents with actions similar to methylnaltrexone. **Lubiprostone** is a colonic chloride channel inhibitor that impairs water reabsorption in the colon and is very effective for opioid-induced constipation.

Media and government attention to the "opioid epidemic" has reasonably led to scrutiny of the prescription of opioids to children, and FDA approval of opioid formulations for children has raised alarm and criticism by some vocal critics of the use of opioids for medical purposes. Thus one of the potent barriers to effective management of pain with opioids is the fear of addiction held by many prescribing pediatricians and parents alike. Pediatricians should understand the phenomena of tolerance, dependence, withdrawal, and addiction (Table 93.11). **Opioid addiction** is the result of the complex interplay of genetic predisposition, psychiatric pathology, and social forces, including poverty, joblessness, hopelessness, and despair. The dramatic increase in the amount of opioid abuse and overdoses and opioid-related deaths, although highest in the adult non-Hispanic American Indian or Alaska Native population age 35–44 years old, has also significantly risen in children and adolescents. Among persons 14–18 years, overdose deaths increased 114% from 2019 to 2021 with 2,037 (91.3%) of adolescent overdose deaths in 2021 involving at least one opioid. Despite this rise in abuse of opioids, a longitudinal study of children and adolescents treated for medical reasons with opioids found that there was no increased risk of the development of substance abuse, at least until their

Table 93.7 Pediatric Dosage Guidelines for Opioid Analgesics

DRUG	EQUI-ANALGESIC DOSES		PARENTERAL DOSING		IV:PO DOSE RATIO	ORAL DOSING		COMMENTS
	IV	ORAL	<50 kg	≥50 kg		<50 kg	≥50 kg	
Fentanyl	10 µg	100 µg	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	Oral transmucosal: 1:10 Transdermal: 1:1	Oral transmucosal: 10 µg/kg Transdermal: 12.5-50 µg/hr	Transdermal patches available; patch reaches steady state at 24 hr and should be changed q72h	70-100 times as potent as morphine with rapid onset and shorter duration. With high doses and rapid administration, can cause chest wall rigidity. Useful for short procedures; transdermal form should be used only in opioid-tolerant patients with chronic pain.
Hydrocodone	N/A	1.5 mg	N/A	N/A	N/A	0.15 mg/kg	10 mg	Weak opioid; only available in form with acetaminophen.
Hydromorphone	0.2 mg	0.6 mg	0.01 mg q2-4h 0.002 mg/kg/hr	0.01 mg q2-4h 0.002 mg/kg/hr	1:3	0.04-0.08 mg/kg q3-4h	2-4 mg q3-4h	Five times the potency of morphine; no histamine release and fewer adverse events than morphine.
Methadone	1 mg	2 mg	0.1 mg/kg q8-24h	0.1 mg/kg q8-24h	1:2	0.2 mg/kg q8-12h PO; available as liquid or tablet	2.5 mg TID	Duration 12-24 hr; useful in certain types of chronic pain; requires additional vigilance because it will accumulate over 72 hr and produce delayed sedation. When patients tolerant of opioids are switched to methadone, they show incomplete cross-tolerance and improved efficacy. Because methadone is associated with prolonged QTc, monitoring is needed for children receiving high and extended dosing.
Morphine	1 mg	3 mg	0.05 mg/kg q2-4h 0.01-0.03 mg/kg/hr	0.1 mg/kg q2-4h 0.01-0.03 mg/kg/hr	1:3	Immediate release: 0.3 mg/kg q3-4h Sustained release: 20-35 kg: 10-15 mg q8-12h 35-50 kg: 15-30 mg q8-12h	Immediate release: 15-20 mg q3-4h Sustained release: 30-90 mg q8-12h	Potent opioid for moderate/severe pain; may cause histamine release. Sustained-release form must be swallowed whole; if crushed, becomes immediate acting, leading to acute overdose.
Oxycodone	N/A	3 mg	N/A	N/A	N/A	0.1-0.2 mg q3-4h; available in liquid (1 mg/mL)	Immediate release: 5-10 mg q4h Sustained release: 10-120 mg q8-12h	Strong opioid only available as an oral agent in North America; more potent than and preferable to hydrocodone. Sustained-release form must be swallowed whole; if crushed, becomes immediate acting, leading to acute overdose.

N/A, not available.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 93.8 Management of Opioid-Induced Adverse Effects

Respiratory depression	*Naloxone:* 0.01-0.02 mg/kg up to a full reversal dose of 0.1 mg/kg. May be given IV, IM, IN, SC, or via ETT. The full reversal dose should initially be used for apnea in opioid-naive patients. In opioid-tolerant patients, a reduced dose should be given and titrated up slowly to treat symptoms but prevent acute withdrawal. Ventilation may need to be supported during this process. Dose may be repeated every 2 min to a total of 10 mg. Adult maximum dose is 2 mg/dose. Give with caution to patients who are receiving long-term opioid therapy, as it may precipitate acute withdrawal. Duration of effect is 1-4 hr; therefore close observation for recurrent symptoms is essential.
Excessive sedation without evidence of respiratory depression	Change opioid or decrease the dose. In palliative patients or other special circumstances, can consider treating with stimulants. *Methylphenidate**:* 0.3 mg/kg per dose PO (typically 10-20 mg/dose to a teenager) before breakfast and lunch. Do not administer to patients receiving clonidine, because dysrhythmias may develop. *Dextroamphetamine*: 2.5-10 mg on awakening and at noon. Not for use in young children or in patients with cardiovascular disease or hypertension. *Modafinil:* Pediatric dose not established. May be useful in selected patients. Typical adult dose: 50-200 mg/day.
Nausea and vomiting	*Metoclopramide*†*:* 0.15 mg/kg IV up to 10 mg/dose q6-12h for 24 hr. *Trimethobenzamide:* if weight <15 kg, 100 mg PO or PR q6h; if >15 kg, 200 mg PO or PR q6h. (*Note:* Suppository contains benzocaine 2%.) Not for use in newborn infants or premature infants. 5-HT_3 receptor blockers: *Ondansetron:* 0.15 mg/kg up to 8 mg IV q6-8h not to exceed 32 mg/day (also available as a sublingual tablet). *Granisetron:* 10 to 20 µg/kg IV q12-24h. *Prochlorperazine**‡ (Compazine): >2 yr or >20 kg, 0.1 mg/kg per dose q8h IM or PO up to 10 mg/dose. Change opioid.
Pruritus	*Hydroxyzine*: 0.5 mg/kg PO q6h. *Nalbuphine:* 0.1 mg/kg IV q6h for pruritus caused by intraaxial opioids, especially fentanyl. Administer slowly over 15-20 min. May cause acute reversal of systemic µ-receptor effects and leave κ-agonism intact. *Naloxone:* 0.5-2 mcg/kg/hr IV infusion (titrate up to decrease pruritus and reduce infusion if pain increases). *Ondansetron:* 0.05-0.1 mg/kg IV or PO q8h. *Cyproheptadine*†*:* 0.1-0.2 mg/kg PO q8-12h. Maximum dose 12 mg. Change opioid.
Constipation	Encourage water consumption, high-fiber diet, and vegetable fiber. *Bulk laxatives:* Metamucil, Maltsupex. *Lubricants:* Mineral oil 15-30 mL PO daily as needed (not for use in infants because of aspiration risk). *Surfactants:* Sodium docusate (Colace): <3 yr: 10 mg PO q8h 3-6 yr: 15 mg PO q8h 6-12 yr: 50 mg PO q8h >12 yr: 100 mg PO q8h *Stimulants:* Bisacodyl suppository (Dulcolax): <2 yr: 5 mg PR qhs >2 yr: 10 mg PR qhs *Senna syrup* (218 mg/5 mL): >3 yr: 5 mL qhs *Enema:* Fleet hypertonic phosphate enema (older children; risk of hyperphosphatemia). *Electrolytic/osmotic:* Milk of magnesia; for severe impaction: polyethylene glycol (GoLYTELY, MiraLAX). Methylnaltrexone is an opioid antagonist that works in the colon and does not cross the blood-brain barrier to reverse analgesia; given as subcutaneous injection every day or every other day (0.15 mg/kg) and is effective in producing stool in 30-60 min in most patients.
Urinary retention	Straight catheterization, indwelling catheter. Decrease opioids, use naloxone drip.

*Avoid in patients taking monoamine oxidase inhibitors.
†May be associated with extrapyramidal side effects, which may be more often seen in children than in adults.
‡Consider pretreatment with diphenydramine to decrease risk of anti-dopaminergic adverse events (e.g., dystonia).
ETT, Endotracheal tube; IV, intravenously; IM, intramuscularly; IN, intranasally; PO, orally; PR, rectally; SC, subcutaneously.
Modified from Burg FD, Ingelfinger JR, Polin RA, et al., eds. *Current Pediatric Therapy,* 18th ed. Philadelphia: Saunders; 2006, p 16.

mid-20s. Thus the rational short- or even long-term use of opioids in children does not lead to a predilection for or risk of addiction in a child not otherwise at risk because of genetic background, economic factors, or social milieu.

It is equally important for pediatricians to realize that even patients with recognized substance abuse diagnoses are entitled to effective analgesic management, which often includes the use of opioids. If legitimate concerns exist about addiction in a patient, safe, effective opioid pain management is often best provided by specialists in pain management and addiction medicine. Table 93.12 outlines the U.S. Centers for Disease Control and Prevention (CDC) opioid recommendations for **chronic pain** (primarily in adults).

There is no longer a reason to administer opioids by IM injection. Continuous IV infusion of opioids is an effective option that permits more constant plasma concentrations and clinical effects than intermittent IV bolus dosing without the pain associated with IM injection. The most common approach in pediatric centers is to administer a low-dose basal opioid infusion while permitting patients to use a **patient-controlled analgesia (PCA)** device to titrate the dosage above the infusion (Fig. 93.3) (see Chapter 91). Compared with children given intermittent IM morphine, children using PCA reported better pain scores. PCA has several other advantages: (1) dosing can be adjusted to account for individual pharmacokinetic and pharmacodynamic variation and for changing pain intensity during the day; (2) psychologically the patient is more in control, actively coping with the pain; (3) overall opioid consumption tends to be lower; (4) fewer opioid side effects occur; and (5) patient satisfaction is generally much higher. Children as young as 5-6 years old can effectively use PCA. The device can also

be activated by parents or nurses, known as **PCA-by-proxy (PCA-P) or parent-nurse controlled analgesia (PNCA)**, which produces analgesia in a safe, effective manner for children who cannot activate the PCA demand button themselves because they are too young or intellectually or physically impaired. PCA overdoses have occurred when well-meaning, inadequately instructed parents pushed the PCA button in medically complicated situations, with or without the use of PCA-P, highlighting the need for patient and family education, use of protocols, physiologic monitoring, and adequate nursing supervision.

Because of the high risk of adverse side effects (respiratory depression), the FDA has issued **contraindications** for the pediatric use of codeine and tramadol (Table 93.13).

Table 93.9 Equianalgesic Doses and Half-Life ($T_{1/2\beta}$) of Some Commonly Used Opioids

OPIOID	IM/IV DOSE (mg)	ORAL DOSE (mg)	$T_{1/2\beta}$ (hr)
Morphine	10	30	2-3
Oxycodone	15	20-30	2-3
Fentanyl	0.15-0.2	—	3-5
Alfentanil	0.75-1.5	—	1-2
Sufentanil	0.02	—	2-3
Methadone	10	10-15	15-40
Hydromorphone	1.5	7.5	3-4
Tramadol†	100	100	5-7
Buprenorphine	0.4	0.8 (sublingual)	3-5
Pentazocine	60	150	3-5
Nalbuphine	10-20	—	2-4
Butorphanol	2	—	2-3

†Only part of its analgesic action results from action on μ-opioid receptors.
NOTES:
- Published reports vary in the suggested doses considered to be equianalgesic to morphine. Therefore titration to clinical response in each patient is necessary.
- Suggested doses are the results of single-dose studies only. Therefore use of the data to calculate total daily dose requirements and repeated or continuous doses may not be appropriate.
- There may be incomplete cross-tolerance between these drugs. In patients who have been receiving one opioid for a prolonged period, it is usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid and to titrate to effect.

Modified from Macintyre PE, Ready LB. *Acute Pain Management: A Practical Guide*, 2nd ed. Philadelphia: Saunders; 2001, p 19.

Local Anesthetics

Local anesthetics are widely used in children for topical application, cutaneous infiltration, peripheral nerve block, neuraxial blocks (intrathecal or epidural infusions), and IV infusions (see Chapter 91). Local anesthetics can be used with excellent safety and effectiveness. Local anesthetics interfere with neural transmission by blocking neuronal sodium channels. Excessive systemic dosing can cause seizures, CNS depression, and (by cardiac and arteriolar sodium channel blockade) hypotension, arrhythmias, cardiac depression, and cardiovascular collapse. Local anesthetics therefore require a strict maximum dosing schedule. Pediatricians should be aware of the need to calculate these doses and adhere to guidelines.

Topical local anesthetic preparations do not generally result in measurable systemic blood levels and can reduce pain in diverse circumstances: suturing of lacerations, placement of peripheral IV catheters, lumbar punctures, and accessing indwelling central venous ports (Table 93.14). The application of tetracaine, epinephrine (adrenaline), and cocaine (TAC) results in good anesthesia for suturing wounds but should not be used on mucous membranes or the hypervascular faces of young children. An alternative combination of lidocaine, epinephrine, and tetracaine (LET) is preferred to avoid the psychomimetic properties of cocaine. EMLA, a topical eutectic mixture of lidocaine and prilocaine used to anesthetize intact skin, is frequently applied for venipuncture, lumbar puncture, and other needle procedures. A 5% liposomal lidocaine cream (LMX4) is also effective as a topical anesthetic. Another unique device is the needle-free J-tip, which uses a CO_2 cartridge to deliver lidocaine into the subcutaneous tissue via a micro-atomizing tip. This can be used to

Table 93.10 Opioid Use Guidelines in Hepatic and Renal Dysfunction

DRUG	PKA	PROTEIN BINDING (%)	PHASE 1 METABOLISM	PHASE 2 METABOLISM	ACTIVE METABOLITE	BILIARY EXCRETION[1] (%)	RENAL EXCRETION[2]	USE IN RENAL FAILURE
Morphine	8.0	30	None	Glucuronidation	M6G	10	Metabolites	Use with caution[a,c]
Fentanyl	8.4	80	CYP3A4	None	None		Norfentanyl	Preferred[b,e]
Hydromorphone	8.2	20	None	Glucuronidation	H6G		H3G & H6G	Use with caution[a,d]
Methadone	8.3	90	CYP2B6 CYP3A4, CYP2D6	None	None	20-40	Metabolites	Use with caution[b,e]
Codeine	8.2	25	CYP2D6	None	Morphine, Hydrocodone M6G		M6G	No[b,d]
Oxycodone	8.5	45	CYP3A4, CYP2D6	None	Oxymorphone		Noroxycodone	Use with caution[f]
Oxymorphone	8.2	10	CYP3A4	Glucuronidation	None		Noroxymorphone	Use with caution[a,c]
Remifentanil	7.1	70	Esterase	None	None		Metabolite	

[1]In the setting of hepatic dysfunction, all opioids should be used cautiously ("go low, go slow"). Meperidine (inactive metabolite associated with seizures) and codeine (cannot be metabolized into active metabolite, morphine) should not be used. Fentanyl may be the best opioid to use (in severe liver dysfunction, plasma cholinesterase may not be available to metabolize remifentanil).
[2]In the setting of renal failure, metabolites of morphine, codeine, hydromorphone, hydrocodone, and meperidine can accumulate, producing increased therapeutic and adverse effects.
[a]Parent drug removed by dialysis; [b]Parent drug not/poorly dialyzed; [c]Metabolites removed by dialysis; [d]Metabolites not/poorly dialyzed; [e]Metabolites inactive;
From Davis PJ, Cladis FP, eds. *Smith's Anesthesia for Infants and Children*, 10th ed. Philadelphia: Elsevier; 2022, Table 23.6, p. 496.

Table 93.11 Practical Aspects of Prescribing Opioids

- Morphine, hydromorphone, or fentanyl is regarded as first choice for severe pain.
- Dosing should be titrated and individualized. There is no "right" dose for everyone.
- The right dose is the dose that relieves pain with a good margin of safety.
- Dosing should be more cautious in infants, in patients with coexisting diseases that increase risk or impair drug clearance, and with concomitant administration of sedatives.
- Hydromorphone is metabolized by CYP2D6 and fentanyl by CYP3A4 and to some extent 2D6; drugs that compete for 2D6 enzyme will raise blood levels and increase risk of respiratory depression.
- Morphine is metabolized by glucuronidation to an active metabolite, morphine-6-glucuronide, which accumulates and causes CNS toxicity in renal impairment.
- Anticipate and treat peripheral side effects, including constipation, nausea, and itching.
- Give doses at sufficient frequency to prevent the return of severe pain before the next dose.
- Use a drug delivery method, such as patient-controlled anesthesia or continuous infusions, that avoids the need for "prn" decision-making.
- With opioid dosing for >1 wk, taper gradually to avoid abstinence syndrome.
- When converting between parenteral and oral opioid doses, use appropriate potency ratios (see Table 93.9).
- *Tolerance* refers to decreasing drug effect with continued administration of a drug. Over time a patient will need higher dosing to achieve the same clinical effect; however, tolerance to sedation and respiratory depression develop more rapidly than tolerance to analgesia. Thus with higher doses, patients do not experience oversedation or respiratory depression.
- *Dependence* refers to the need for continued drug dosing to prevent abstinence syndrome when a drug is abruptly discontinued or its dose reduced. Abstinence syndrome is characterized by irritability, agitation, autonomic arousal, nasal congestion, piloerection, diarrhea, jitteriness, and yawning; it is produced by administration of potent opioids for >5-7 days.
- *Addiction*, a psychiatric pathology, refers to psychologic craving, compulsive drug-seeking behavior, and drug use despite medical harm. Addiction has strong genetic and environmental determinants. Opioid therapy will not lead to addiction in nonsusceptible individuals, and opioid underdosing does not prevent addiction; it may in fact increase drug-seeking behavior for relief of pain (e.g., watching the clock), referred to as "pseudoaddiction."

start IVs or provide superficial analgesia before a procedure (e.g., lumbar puncture).

Lidocaine is the most commonly used local anesthetic for cutaneous infiltration. Maximum safe doses of lidocaine are 5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Although concentrated solutions (2%) are commonly available from hospital pharmacies, more dilute solutions (0.25% and 0.5%) are equally as effective as 1–2% solutions. The diluted solutions cause less burning discomfort on injection and permit use of larger volumes without achieving toxic doses. In the surgical setting, cutaneous infiltration is more often performed with bupivacaine 0.25% or ropivacaine 0.2% because of the much longer duration of effect; maximum dosage of these long-acting amide anesthetics is 2-3 mg/kg and 3-4 mg/kg, respectively. Liposomal bupivacaine injectable suspension (Exparel) is approved for children age 6 years old and above. It is an excellent choice for surgical wound infiltration. The maximum dose for children is 4 mg/kg.

Neuropathic pain may respond well to the local application of a 5% lidocaine topical patch (Lidoderm) for 12 hours/day (see Table 93.14), although access to lidocaine topical patches may be limited by insurance coverage. Over-the-counter 4% lidocaine patches are available without prescription. Peripheral and central neuropathic pain also may respond to IV lidocaine infusions, which may be used in hospital settings for refractory pain, complex regional pain syndromes, and pain associated with malignancies or the therapy of malignancies, such as oral mucositis after bone marrow transplantation. In these patients, 1-2 mg/kg/hr should be administered and the infusion titrated to achieve a blood lidocaine level in the 2-5 μg/mL range, with use of twice-daily therapeutic blood monitoring.

UNCONVENTIONAL MEDICATIONS IN PEDIATRIC PAIN

Unconventional analgesic medication refers to a wide number of drugs developed for other indications but found to have analgesic properties. These drugs have been used for acute and chronic pain and include antidepressants, antiepileptic drugs, and neurotropic drugs (Tables 93.15 and 93.16).

The unconventional analgesics are generally used to manage neuropathic pain conditions, migraine disorders, fibromyalgia syndrome, and some forms of functional chronic abdominal pain syndromes. These agents also are used as components of multimodal analgesia in the management of surgical, somatic, and musculoskeletal pain. Figure 93.4 presents a decision-making tree to help the physician select the appropriate analgesic category for various types of pain.

Although several unconventional pain medications are FDA approved for analgesic use, most are not approved for use in youth with acute or chronic pain. Thus these drugs should be used with caution, with a focus on mitigating pain to allow a child to participate effectively in therapies and return to normal activity as soon as possible. The use of psychotropic medications should be guided by the principles applied to pharmacologic treatment of any symptom or disease. Target symptoms should be identified and medication side effects monitored. To determine dosing regimens, the physician should consider the child's weight and the effects that the medical condition and other medications, such as psychotropic drugs, may have on the child's metabolism. Therapeutic blood level monitoring can be considered. Side effects should be addressed in detail with both parent and child and specific instructions given for responding to possible adverse events. Directly addressing concerns about addiction, dependence, and tolerance may be necessary to decrease treatment-related anxiety and improve medication adherence.

Antidepressant Medications

Antidepressants are useful in adults with chronic pain, including neuropathic pain, headaches, and rheumatoid arthritis, independent of their effects on depressive disorders. Antidepressants' analgesic mechanism of action is inhibition of norepinephrine reuptake in the CNS. In children, because clinical trials have been limited, the practitioner should use antidepressants cautiously to treat chronic pain or associated depressive or anxiety symptoms. The FDA has issued a "black box warning" to inform the public of a small but significant increase in suicidal thoughts and attempts in children and adolescents receiving antidepressants. A meta-analysis of studies involving children and adolescents receiving antidepressants for pain indicated that no suicides had been completed. The pediatrician should address this issue with parents of patients being treated with antidepressants and should develop monitoring plans consistent with current FDA recommendations (see Table 93.16).

Tricyclic antidepressants (TCAs) have been studied in children with chronic pain and found to be effective in pain relief for symptoms that include neuropathic pain, functional abdominal pain, and migraine. TCA efficacy may be based on inhibition of the neurochemical pathways involved in norepinephrine and serotonin reuptake and interference with other neurochemicals involved in the perception or neural conduction of pain. Because sedation is a common side effect, TCAs may also be effective in treating the sleep disorders that frequently accompany pediatric pain. Biotransformation of TCAs is extensive in healthy children. Typically, TCAs are administered only at bedtime, especially the more sedating tricyclic medications such as amitriptyline. Alternatively, the patient can be started on a bedtime dose of a TCA, which may be able to then be titrated to a daily divided dose, with the larger dose given at bedtime. It should be noted that pain symptoms usually remit at lower doses than those recommended

Table 93.12 CDC Practice Guideline for Prescribing Opioids for Pain (2022) Excluding Sickle Cell Anemia, Cancer, Palliative Care and End of Life Care

DETERMINING WHETHER OR NOT TO INITIATE OPIOIDS FOR PAIN

All patients with pain should receive treatment that provides the greatest benefits relative to risks. (See *Recommendation 1* for determining whether or not to initiate opioids for acute pain [i.e., pain lasting <1 month] and *Recommendation 2* for determining whether or not to initiate opioids for subacute pain [i.e., pain lasting 1–3 months] or chronic pain [i.e., pain lasting >3 months].)

Recommendation 1

Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy.

Recommendation 2

Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks.

SELECTING OPIOIDS AND DETERMINING OPIOIDS DOSAGES

Recommendation 3

When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids.

Recommendation 4

When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients.

Recommendation 5

For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh the risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue such as warning signs of impending overdose (e.g., confusion, sedation, or slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages.

DECIDING DURATION OF INITIAL OPIOID PRESCRIPTION AND CONDUCTING FOLLOW-UP

Recommendation 6

When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.

Recommendation 7

Clinicians should evaluate benefits and risks with patients within 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients.

ASSESSING RISK AND ADDRESSING POTENTIAL HARMS OF OPIOID USE

Recommendation 8

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone.

Recommendation 9

When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.

Recommendation 10

When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.

Recommendation 11

Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants.

Recommendation 12

Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death.

From Dowell D, Ragan KR, Jones CM, et al: CDC clinical practice guidelines for prescribing opioids for pain – United States, 2022. *MMWR* 2022;71(3):1-95.

or required for the treatment of mood disorders. Most children and adolescents do not require more than 0.25-1 mg/kg of amitriptyline or nortriptyline once daily at bedtime.

Attention should also be paid to hepatic microsomal enzyme metabolism, because CYP2D6 inhibitors, such as cimetidine and quinidine, can increase levels of TCAs. Anticholinergic side effects, which are less common in children than in adults, may remit over time. Constipation, orthostatic hypotension, and dental caries from dry mouth should be addressed by emphasizing the importance of hydration, good oral hygiene, and regular dental visits. Other side effects include weight gain, mild bone marrow suppression, and liver dysfunction. Some practitioners recommend monitoring CBC and liver function values at baseline and periodically during therapy. TCA blood levels can be obtained as well, but the need for therapeutic blood monitoring should be assessed on an individual basis. Reasons for blood level monitoring include concerns for altered metabolism, adherence, overdose, or sudden change in mental status.

All TCAs inhibit cardiac conduction pathways and prolong the QT interval. Sudden cardiac death has been reported in children taking TCAs, principally desipramine, probably related to QTc prolongation. There is no general agreement for monitoring the electrophysiologic effects of these drugs, but it is prudent to obtain a careful personal and family history focusing on cardiac arrhythmias, heart disease, and syncope before the initiation of treatment. A baseline electrocardiogram (ECG) should be obtained, with care taken to ensure that

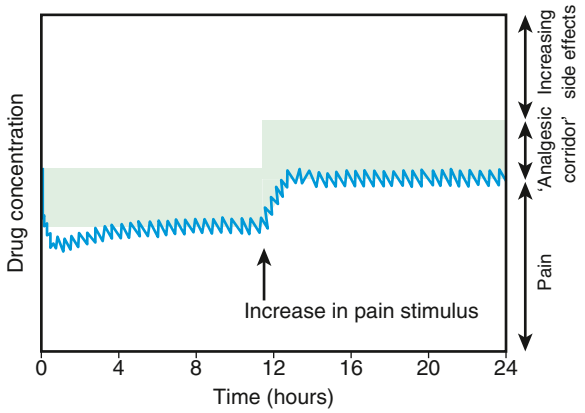

Fig. 93.3 Patient-controlled analgesia is more likely to keep blood concentrations of opioid within the "analgesic corridor" and allows rapid titration if there is an increase in pain stimulus requiring higher blood levels of opioid to maintain the analgesia. *(From Burg FD, Ingelfinger JR, Polin RA, et al., eds. Current Pediatric Therapy,18th ed. Philadelphia: Saunders; 2006:16.)*

Table 93.13 Summary of FDA Recommendations

- Use of codeine to treat pain or cough in children <12 yr old is contraindicated.
- Use of tramadol to treat pain in children <12 yr old is contraindicated.
- Use of tramadol for treatment of pain after tonsillectomy or adenoidectomy in patients <18 yr old is contraindicated. (Codeine was already contraindicated in such patients.)
- Use of codeine or tramadol in children 12-18 yr old who are obese or who have an increased risk of serious breathing problems, such as those with obstructive sleep apnea or severe lung disease, is not recommended.
- Use of codeine or tramadol in breastfeeding women should be avoided.

From FDA warns against use of codeine and tramadol in children and breastfeeding women. *Med Lett.* 2017;59(1521):86–88.

the QTc is <450 msec. If the dose of amitriptyline or nortriptyline is increased beyond 0.5 mg/kg/day, an ECG should be performed for each dosing increase. With TCAs, as with other antidepressants, physical dependence and a known discontinuation syndrome can occur. The **discontinuation syndrome** includes agitation, sleep disturbances, appetite changes, and GI symptoms. These medications should be tapered slowly to assist in distinguishing among symptoms that indicate rebound, withdrawal, or the need for continuing the medication.

Selective serotonin reuptake inhibitors (SSRIs) have minimal efficacy in the treatment of a variety of pain syndromes in adults. SSRIs are very useful when symptoms of depression or anxiety are present and cannot be addressed adequately by nonpharmacologic means. Escitalopram (Lexapro), fluoxetine (Prozac), and sertraline (Zoloft) have been approved by the FDA for use in children and adolescents. SSRIs have a significantly milder side effect profile than TCAs (most side effects are transient), and they have no anticholinergic side effects. Chief side effects include GI symptoms, headaches, agitation, insomnia, sexual dysfunction, and anxiety. Rarely, hyponatremia, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH), may occur. Interactions with other medications that have serotonergic effects may also occur. When multiple medications with serotonergic activity are used in combination, there may be increased likelihood that a life-threatening **serotonin syndrome** may occur, with associated symptoms of myoclonus, hyperreflexia, autonomic instability, muscle rigidity, and delirium (see Chapter 94). It is important to note that although triptans have serotonergic effects, it is unlikely that the combination will lead to serotonin syndrome. This is because it is hypothesized that serotonin receptors 2A and 1A are the receptors involved in serotonin syndrome, whereas triptans are selective for serotonin antagonists 1B and 1D. There is also a **discontinuation syndrome** associated with shorter-acting SSRIs (e.g., paroxetine), which includes dizziness, lethargy, paresthesias, irritability, and vivid dreams. To avoid this, dosages of medications should be tapered slowly over several weeks.

The **selective serotonin-norepinephrine reuptake inhibitors (SNRIs)** duloxetine and venlafaxine have demonstrated significant efficacy with chronic neuropathic and other pain syndromes because they inhibit both serotonin and norepinephrine reuptake, and they may directly block associated pain receptors as well. Venlafaxine has no pain indication labeling. Duloxetine is FDA approved for managing neuropathic pain (specifically, diabetic neuropathy) and fibromyalgia

Table 93.14 Topical Pharmacologic Management of Acute Pain in Children

DRUG	DOSE	NOTES
INTACT SKIN		
Lidocaine 2.5% and prilocaine 2.5% (EMLA cream)	<3 mo old or <5 kg: 1 g 3-12 mo and >5 kg: 2 g 1-6 yr and >10 kg: 10 g 7-12 yr and >20 kg: 20 g	60 min is needed to achieve maximum effect; cover cream with an occlusive dressing (Tegaderm)
Lidocaine, liposomal 5% (LMX4)	1-20 g as noted earlier	30-60 min needed to achieve maximum effect; cover with an occlusive dressing (Tegaderm)
Lidocaine 70 mg and tetracaine 70 mg (Synera patch)	Age ≥3 yr: apply patch	20-30 min needed to achieve maximum effect
Tetracaine 4% (Ametop)	>1 mo and <5 yr: apply 1 tube of gel (1 g) >5 yr: apply up to 5 tubes of gel (5 g)	30 min before venipuncture 45 min before intravenous cannulation
WOUNDS		
Lidocaine, epinephrine, tetracaine (LET) solution or gel*	Age ≥1 yr: apply to wound	20 min needed for maximum effect

*Also referred to as ALA on the basis of alternative names for the constituents: adrenaline, lignocaine, amethocaine. These mixtures are locally made by hospital formularies, with a common formula being lidocaine 4% plus epinephrine 0.1% plus tetracaine 0.5%. The cocaine-based formulation was historically avoided on wounds of digits, ears, penis, nose, mucous membranes, close to the eye, or deep wounds involving bone, cartilage, tendon, or vessels. The lidocaine-based formulation can be used in such settings.

Adapted from Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet.* 20166;387:83–92.

Table 93.15 Commonly Used Adjunctive Analgesics

DRUG NAME (TRADE NAME)	SUGGESTED STARTING DOSE AND DOSING INTERVAL MAXIMUM DOSE PER DAY	ADVANTAGES (INDICATION FOR USE)	DISADVANTAGES (SIDE EFFECTS)
Gabapentin (Neurontin)	10-15 mg/kg per day divided bid or tid Max dose: 50 mg/kg per day (3 g/day)	Adjunct for the management of pediatric neuropathic pain, epilepsy	Drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylaxis, somnolence, dizziness, peripheral edema, emotional lability, respiratory depression when combined with opioids
Pregabalin (Lyrica)	2.5 mg/kg per day divided bid or tid Max dose: 600 mg per day	Adjunct for the management of neuropathic pain associated with spinal cord injury, fibromyalgia, and epilepsy	Ataxia, blurred vision, visual field loss, constipation, drowsiness, headaches, peripheral edema, weight gain, tremor
Clonidine (Catapres)	5-25 mcg/kg per day divided every 4-8 hours if PO dosing Max dose: 2.4 mg/day	Used to treat hypertension and mitigate drug withdrawal symptoms; also used as a pain or peripheral nerve block additive	Drowsiness, dizziness, fatigue, headache, dry mouth, hypotension
Dexmedetomidine (Precedex)	Loading dose: 0.5-1 mcg/kg Infusion rate: 0.2-0.7 mcg/kg per hour titrated to effect Suggested max dose: 2.5 mcg/kg per hour	Sedative and analgesic properties; intraoperative bolus dose of 1 mcg/kg decreases postoperative morphine consumption and 2 mg/kg decreases emergence delirium	Bradycardia, hypotension
Tizanidine (Zanaflex)	Patients >18 yr: starting dose 2 mg q6-8h Max single dose: 16 mg Max daily dose: 36 mg	Antispasmodic agent	Dizziness, drowsiness, bradycardia, hypotension, fatigue, hallucinations, xerostomia
Diazepam (Valium)	PO: 0.1-0.8 mg/kg/day IV: 0.05-0.3 mg/kg/dose every 4-8 hr Max dose: 10 mg Use lowest needed dose; use lower dose when combined with opioids or other sedating medications	Antispasmodic, anxiolytic, sedative, seizure prophylaxis, promotes sleep	Somnolence, unsteady gait
Cyclobenzaprine (Flexeril)	Patients >15 yr: 5 mg PO bid-tid Max dose: 10 mg PO tid	Antispasmodic	Blurry vision, dizziness, drowsiness, lightheadedness, xerostomia
Ketamine	Loading dose: 0.25-0.5 mg/kg IV before incision Infusion rate: 0.1-1 mg/kg per hr intraoperatively 0.05-0.1 mg/kg per hr postoperatively Max parenteral dose 3,600 mg/day	Sedation, analgesic adjunct, especially beneficial for opioid-tolerant or chronic pain patients	Hallucinations, double/blurry vision, jerky muscle movements, drowsiness, loss of appetite, nausea
Lidocaine	Loading dose: 1-1.5 mg/kg IV Infusion rate: 1-2 mg/kg per hr intraoperatively Max dose: 4.5 mg/kg (not to exceed 300 mg in 2 hr)	Used during intraabdominal procedures to prevent severe postoperative pain	Cardiac arrhythmia, epilepsy/seizures, renal failure

Modified from Davis PJ, Cladis FP, eds. *Smith's Anesthesia for Infants and Children,* 10th ed. Philadelphia: Elsevier; 2022, Table 23.12, p. 510.

syndrome. It is approved for the treatment of pediatric fibromyalgia in adolescents 13-17 years of age and for the treatment of generalized anxiety disorder in children 7-17. A significant advantage of SNRIs over TCAs when used for headache prophylaxis or neuropathic pain is that they have therapeutic effects on mood and anxiety at dosages effective for pain control.

Because both SSRIs and SNRIs have fewer anticholinergic side effects than TCAs, adherence to them is better than in psychiatric populations taking TCAs. Side effects of both types of drugs include GI symptoms, hyperhidrosis, dizziness, and agitation, but these effects generally wane over time. Hypertension and orthostatic hypotension may occur; in addition, the patient's blood pressure should be closely followed, and appropriate hydration should be stressed. Note that whereas appetite stimulation and weight gain are associated with all TCAs, duloxetine is often associated with weight loss, frequently a desirable side effect, especially in overweight adolescents.

All antidepressants, including the TCAs, SSRIs, and SNRIs, are thought to have the potential to increase the risk of suicidal ideation and the risk of suicide in patients, as noted earlier. The FDA states, "All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases." However, the FDA also notes, "Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases."

Table 93.16 Medications for Pediatric Chronic Pain

MEDICATION	DOSING	COMMENTS
TRICYCLIC ANTIDEPRESSANTS		
Amitriptyline, nortriptyline	For patients ≥50 kg: Initial dose 5-10 mg PO qhs; titrate over 2-3 weeks to 25-50 mg PO qhs For patients 25-50 kg: Initial dose 0.1 mg/kg PO qhs. Titrate over 2-3 weeks to max dose of 0.5 mg/kg	Obtain 12-lead ECG for prolonged QT interval Side effects are related to anticholinergic effects, including tachycardia, dry mouth, urinary retention, and sedation Use with caution with other antidepressants because of risk of serotonin syndrome Concomitant use with CYP2D6 inhibitors may lead to increased serum concentration
SELECTIVE SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS		
Duloxetine (Cymbalta)	For patients > 13 yr: Dose 30-60 mg PO daily; max 600 mg/day	Review risk of suicidality
ANTICONVULSANTS		
Gabapentin (Neurontin)	For patients ≥50 kg: Initial dose 100-300 mg PO 1-2 times daily; titrate slowly to max dose of 1,800 mg/day divided tid; higher dosing possible in select patients For patients <50 kg: Initial dose 2-5 mg/kg PO daily; titrate slowly to max dose of 35 mg/day divided tid; higher dosing possible in select patients	Side effects include drowsiness, concentration and memory impairments, and peripheral edema (rare) Dose adjustment necessary with renal impairment
Pregabalin (Lyrica)	Patients >12 yr of age: Initial dose 25-75 mg PO 1-2 times daily; titrate up to max of 300 mg/day divided bid or tid	Side effects include drowsiness, headaches, peripheral edema (rare), and thrombocytopenia (rare)
Titrate all medications according to clinical benefit and side effects; use lowest effective dose. Antidepressants and anticonvulsants may increase the risk of suicidal thinking and behavior in children, adolescents, and young adults. Monitor closely for changes in mood or behavior.		

Modified from Davis PJ, Cladis FP, eds. *Smith's Anesthesia for Infants and Children,* 10th ed. Philadelphia: Elsevier; 2022, Table 25.2, p. 580.

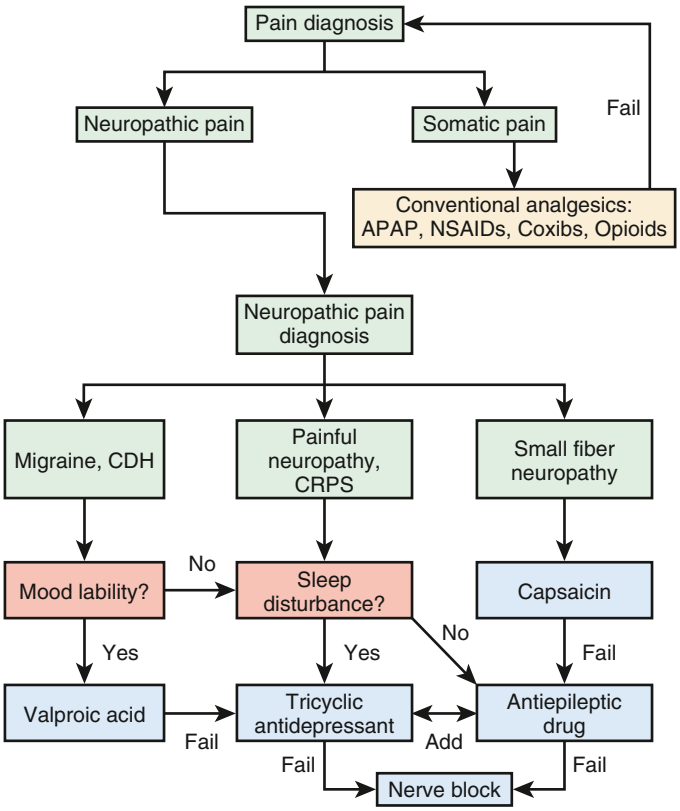

Fig. 93.4 Algorithm for selection of conventional and nonconventional analgesics. APAP, Acetaminophen; CDH, chronic daily headaches; CRPS, complex regional pain syndrome; NSAIDs, nonsteroidal antiinflammatory drugs.

Antiepileptic Drugs

Antiepileptic drugs (AEDs), such as gabapentin, pregabalin, carbamazepine, and valproic acid, are believed to relieve chronic pain by blocking sodium (valproate and the gabapentinoids) or calcium (carbamazepine and oxcarbazepine) channels at the cellular neuronal level, thereby suppressing spontaneous electrical activity and restoring the normal threshold to depolarization of hypersensitive nociceptive neurons, without affecting normal nerve conduction. These medications are particularly useful in patients with mood disorders who have neuropathic pain. In adults, the FDA has approved carbamazepine for trigeminal neuralgia; valproate for migraine prophylaxis; and pregabalin for neuropathic pain complicating diabetes, herpes zoster, and for management of fibromyalgia. AEDs generally have GI side effects in addition to sedation, anemia, ataxia, rash, and hepatotoxicity. The majority are also associated with weight gain. Carbamazepine and oxcarbazepine are also associated with Stevens-Johnson syndrome.

Liver function and CBC should be monitored at the start of therapy and periodically with AEDs. Carbamazepine and valproic acid have narrow therapeutic windows and variability in therapeutic blood medication levels, in addition to many drug-drug interactions, and may cause liver disease and renal impairment. Drug levels should be measured with each dose increase and periodically thereafter. Carbamazepine, in particular, causes autoinduction of hepatic microsomal enzymes, which can further complicate obtaining a therapeutic medication level. Female patients should have pregnancy testing before taking valproate, and those who are sexually active must be cautioned to use effective contraception, because neural tube defects are associated with carbamazepine.

Less toxic AEDs (gabapentin and pregabalin) have supplanted the use of valproate and carbamazepine in patients with pain. These agents have their own side effect profiles, but they are much less toxic than their predecessors and do not require monitoring of liver or bone marrow function or blood levels. Furthermore, they are also far less lethal in accidental or deliberate overdose.

Gabapentin is approved for treatment of postherpetic neuralgia and is also widely prescribed for other pain disorders. It has demonstrated some efficacy in treating children with chronic pain, particularly neuropathic pain, and is used in treatment of chronic headache disorders, complex regional pain syndromes, chemotherapy-induced neuropathy, and diabetic neuropathy in both children and adults. Gabapentin has a relatively benign side effect profile and no drug interactions. Side effects include somnolence, dizziness, and ataxia; children occasionally demonstrate side effects not reported in adults, such as impulsive

or oppositional behavior, agitation, and occasionally depression. These side effects do not seem to be dose related.

Pregabalin works by similar mechanisms as gabapentin and may have a lower side effect profile. It is most often dosed twice a day rather than three times a day, which may lead to increased adherence. Both gabapentin and pregabalin undergo virtually no hepatic metabolism, with no significant drug-drug interactions, a common concern in patients with chronic pain, who frequently take multiple medications—for both the pain and the underlying medical condition associated with the pain. However, because both AEDs depend on renal function for clearance, doses must be adjusted in the presence of renal dysfunction.

Topiramate also demonstrates greater success than traditional AEDs in treating trigeminal neuralgia in adults and in migraine prophylaxis. Topiramate is approved for migraine prophylaxis in children and adolescents from the age of 12-17. Topiramate therapy results more frequently in cognitive dysfunction and short-term memory loss than gabapentin or pregabalin, and although these neurocognitive effects are often well tolerated, they should be monitored. The pediatrician should also be aware that topiramate is associated with weight loss, whereas other AEDs are typically associated with significant weight gain. This side effect is particularly valuable in weight-conscious adolescents, whereas in the anorexic cancer patient, a TCA would be preferable to induce appetite and weight gain. In at-risk populations, routine weight checks are recommended.

Benzodiazepines

Children and adolescents with chronic pain may have comorbid psychologic conditions, such as depressed mood, sleep disturbances, and anxiety disorders, including generalized anxiety disorder, separation anxiety, posttraumatic stress disorder (PTSD), and panic attacks. Psychologic factors affect a youth's perception of pain and mechanisms of coping with a pain disorder. A *conditioned response* to pain may be to feel out of control and increase anxiety and pain, and conversely, *anticipatory anxiety* related to pain will inhibit activities and recovery. Feelings of helplessness sensitize the child to increasing amounts of pain, leading the child to perseverate on pain, think catastrophically, and feel hopeless. Changes in children's normal routines, with a negative impact on participation in valued activities, may further promote hopelessness, resulting in increased pain experiences and development of a depressive disorder.

Benzodiazepines are anxiolytic medications that also have muscle relaxant effects. They have a role in the treatment of acute pain in the hospital, where they are useful adjuncts because they inhibit painful muscle spasms in postsurgical patients. They also can suppress the anxiety that often occurs in hospitalized children, anxiety that interferes with restorative sleep and amplifies the child's perception of pain. Benzodiazepines are useful to calm children with anxiety and anticipatory anxiety about planned painful procedures. They are frequently used as a part of procedural sedation or preoperatively before surgical procedures.

Because dependence, tolerance, and withdrawal may occur with prolonged use, benzodiazepines are generally not recommended for the routine management of *chronic pain* or anxiety in children. Further, the risk of respiratory depression when benzodiazepines are combined with opioid therapy has contributed to the increasing number of opioid-related deaths in the United States. In concert with psychotherapy, benzodiazepines may help control anxiety symptoms that amplify the perception of pain, but we recommend the appropriate use of benzodiazepines in the chronic setting occur under the direction of a psychiatrist. In addition, other alternatives such as hydroxyzine may provide similar benefit without the negative aspects encountered with chronic benzodiazepine use.

Infrequently, benzodiazepines may cause behavioral disinhibition, psychosis-like behaviors, or, in large doses, respiratory depression. When dosing these medications, the pediatrician should consider that many benzodiazepines are metabolized by the cytochrome P450 microsomal enzyme system. This issue may be less significant with lorazepam and oxazepam, which undergo first-pass hepatic conjugation. Side effects common to benzodiazepines include sedation, ataxia, anemia, increased bronchial secretions, and depressed mood. If a benzodiazepine is administered for more than 5 consecutive days, the dosage should be slowly tapered. Abrupt discontinuation of therapy can lead to autonomic instability, delirium, agitation, seizures, and profound insomnia. The routine use of benzodiazepines to treat anxiety during hospitalization is not recommended and should only be used under expert guidance.

Antipsychotics and Major Sedatives

Low doses of antipsychotic medications are often used to address the more severe anxiety, agitation, and behavioral decompensation sometimes associated with severe pain. The use of these medications is controversial because associated adverse events may be severe and irreversible. Typical antipsychotics used in the past, including thioridazine (Mellaril), haloperidol (Haldol), and chlorpromazine (Thorazine), are associated with a decreased seizure threshold, dystonia, agranulocytosis, weight gain, cardiac conduction disturbances, tardive dyskinesia, orthostatic hypotension, hepatic dysfunction, and life-threatening laryngeal dystonia and have little role in the routine treatment of pain in children. Chlorpromazine is approved in adults for intractable hiccups, and its use may be appropriate in select settings such as the palliative setting, although this is not considered a first-line medication. Side effects are generally less severe with atypical antipsychotics. Because these effects may still occur, however, the pediatrician should obtain a baseline ECG, liver function values, and CBC and, if possible, obtain a child psychiatry consultation. If the pediatrician is using typical antipsychotics, an inventory of movement disturbances, such as the Abnormal Involuntary Movement Scale (AIMS) test, should be performed at baseline and at every follow-up visit, because movement disorders can worsen with abrupt withdrawal of medications or can become irreversible.

Atypical antipsychotics are generally associated with less severe side effect profiles, particularly dyskinesias and dystonias. Use of olanzapine (Zyprexa), which is particularly helpful with insomnia and severe anxiety, requires assessing and monitoring blood levels of glucose, cholesterol, and triglyceride; olanzapine's side effects may include diabetes, hypercholesterolemia, or significant weight gain. The anticholinergic side effects associated with quetiapine (Seroquel) warrant frequent monitoring of blood pressure. Risperidone at doses >6 mg may cause side effects similar to those of typical antipsychotics. Aripiprazole (Abilify) has been used for severe anxiety and/or for treatment-resistant depression. All antipsychotics are associated with the rare but potentially lethal **neuroleptic malignant syndrome**, which includes severe autonomic instability, muscular rigidity, hyperthermia, catatonia, and altered mental status (see Chapter 33).

Other Pain Control Medications

Alpha-adrenergic receptor agonists such as clonidine are typically used as antihypertensive agents. However, they are often helpful as both anxiolytics and sleep-onset agents in the anxious hospitalized child. The α-agonists also have central effects on pain reduction. **Clonidine** can be given orally or transdermally if the child's blood pressure permits. In certain settings, IV **dexmedetomidine**, an α-agonist sedating agent, can be used preoperatively for anxiety, in the intensive care unit (ICU) for sedation, and may be used for pain in certain circumstances. Weaning off dexmedetomidine can often be accomplished with a transition to clonidine. **Propranolol** and metoprolol are both β-blocking agents typically used for the child with autonomic instability and for thalamic storm. They may also be used in migraine prophylaxis. There are reports that β blockers can enhance depression in a child who already has a major depressive disorder, and discussion with a child psychiatrist may be helpful in decisions about using propranolol if needed. Both clonidine and propranolol have been found useful for the agitated child with ASD. Another α-agonist, **guanfacine**, is more likely to be used during the day for the child with ASD because it is less sedating than clonidine. Despite research on the impact of clonidine on chronic pain, no data are available to determine if guanfacine is as effective in reducing pain. **Ketamine**, a blocker of *N*-methyl-D-aspartate (NMDA) receptors, has been used for intractable pain in hospitalized children

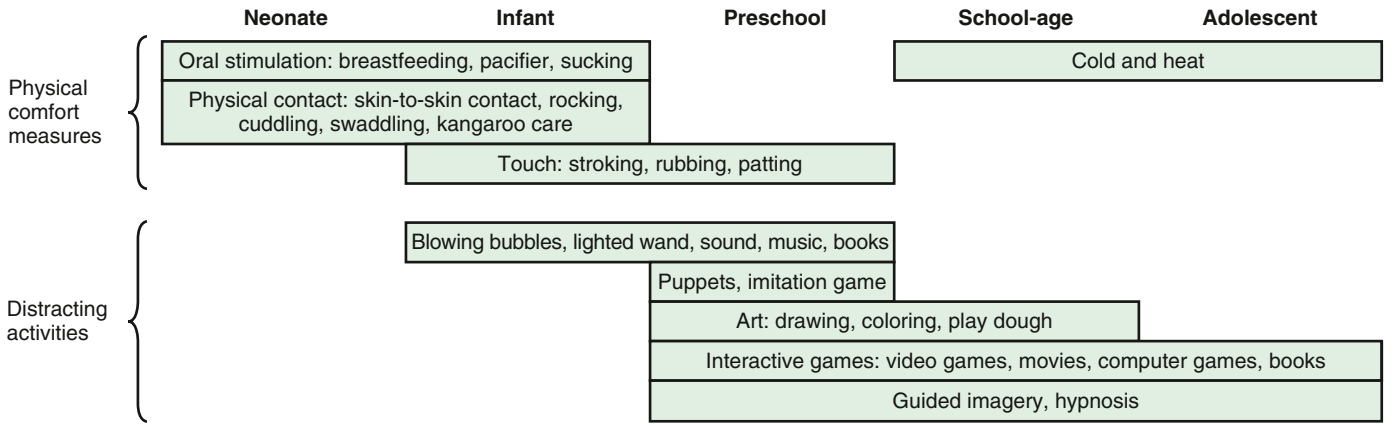

Fig. 93.5 Nonpharmacologic interventions for pediatric pain. *(From Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. Lancet. 2016;387:83–92.)*

and in outpatients with severe sickle cell disease–related chronic pain, as well as others in palliative care for whom opioids are not sufficient to reduce pain. Recommended doses for pain management in non-ICU settings are between 0.1 and 0.3 mg/kg/hr. Higher doses may result in increased side effects, sedation with little benefit, and possible ICU admission. Because ketamine can have central hallucinatory effects, such children should be monitored closely.

NONPHARMACOLOGIC TREATMENT OF PAIN

Numerous psychologic and physical treatments for relieving pain, fear, and anxiety as well as enhancing functioning have excellent safety profiles and proven effectiveness and should always be considered for incorporation into pediatric pain treatment (Fig. 93.5). In acute and procedural pain, nonpharmacologic strategies have long been used to help reduce distress in children undergoing medical procedures and surgery. Many of these methods aim to help children shift attention from pain and alter pain perception (e.g., distraction, hypnosis, imagery). Similarly, in the treatment of chronic pain, several strategies, often falling under the umbrella category of **cognitive-behavioral therapies (CBTs)**, have been shown to reduce pain and improve functioning and quality of life. CBT was developed with the goal of modifying social/environmental and behavioral factors that may exacerbate the child's experience of pain and pain-related disability. Meta-analyses of randomized controlled trials (RCTs) of CBT interventions have found large positive effects of psychologic intervention on reductions in pain and/or its deleterious effects in children with headache, abdominal pain, and fibromyalgia, with relative or comparative effectiveness of different interventions examined in areas such as headache and abdominal pain in children. **Biofeedback** and **relaxation therapies** have been found to have superior effects to pharmacologic treatments in reducing headache pain in children and adolescents. Similarly, for recurrent abdominal pain, positive effects for CBT were found relative to attention-control conditions and pharmaceutical, botanical, and dietary interventions (which had very weak evidence). Positive results have even resulted from very brief (three sessions) and remotely delivered (telephone or internet) therapies, with outcomes lasting up to 12 months after intervention.

When deciding how to incorporate nonpharmacologic techniques to treat pain, the practitioner should (1) conduct a thorough assessment of individual, social, and environmental factors that may be contributing to the patient's pain and functioning limitations; (2) based on this assessment, decide whether nonpharmacologic techniques alone may be sufficient as a beginning to treatment or if these treatments should be integrated with appropriate analgesics; (3) give children (and family members) developmentally and situationally appropriate information as to the rationale for treatment selection and what to expect, given the child's medical condition, procedures, and treatments; (4) include patients and their families in decision-making to ensure an appropriate treatment choice and to optimize adherence to treatment protocols; and (5) above all, develop a communication plan among the different care providers, typically with the pediatrician as the case manager, so that the messages to the child and parent are consistent and the modes of therapy are organized into an integrative team approach. Finally, it is important to recognize that in addition to pain, other psychologic disorders (e.g., anxiety disorders, major depression) may affect the presenting pain complaint and may need to be identified and addressed as part of, or separate from, the pain management plan. Individual psychotherapy or psychiatric intervention may be warranted to adequately treat a comorbid disorder.

CBT strategies refer to a range of techniques that teach children (and their caregivers) how to manage pain by learning new ways to think about the pain and how to change behaviors associated with it. Strategies focusing on **cognitions** are typically aimed at enhancing parents' and children's confidence and self-efficacy to handle pain and decrease fear of pain. In addition, pain coping skills may shift the child's attentional focus away from pain and painful stimuli.

The goals of those strategies focusing on **behavior change** are to modify (1) contingencies in the child's environment, such as teaching parents how to respond to pain behaviors in ways that encourage wellness, rather than illness behaviors; (2) the ways parents model reactions to pain or discomfort; (3) child and parent coping techniques when psychosocial distress or problems in social relations exist; and (4) the child's behavioral reactions to situations, such as relaxation and exposure to previously avoided activities. Common examples of these strategies are discussed in the next several paragraphs. Whereas comprehensive CBTs are typically conducted by trained mental health specialists over several sessions, some basic CBT strategies can be briefly and easily introduced by practitioners into most medical settings. If more in-depth CBT treatment is needed, a referral to a qualified mental health specialist with CBT skills is warranted.

Parent and family education and/or **psychotherapy**, particularly within cognitive-behavioral family approaches, is one treatment modality through which these goals are accomplished and has been shown to be effective for treating chronic pain. Parents can learn to cope with their own distress and to understand pain mechanisms and appropriate treatment of pain. Key components include teaching parents to alter family patterns that may inadvertently exacerbate pain through developing behavior plans. Parents are taught to create plans for the child to manage the child's own symptoms and increase independent functioning. Often, adult caregivers (e.g., parents, teachers) need only guidance on developing a behavioral incentive plan to help the child return to school, gradually increase attendance, and receive tutoring after a prolonged, pain-related absence. *Suggested sample brief strategy:* Ask caregivers how they react to the child's pain complaints; assess whether they encourage wellness activities or give attention and "rewards" primarily when the child says he or she does not feel well; and suggest that caregivers respond to the child in ways that encourage wellness, both when complaining and not complaining.

Relaxation training is often employed to promote muscle relaxation and reduction of anxiety, which often accompanies and increases pain. Relaxation training, along with distraction and biofeedback, are treatments often included in CBT, but also are discussed in the literature without mention of CBT.

Controlled breathing and **progressive muscle relaxation** are commonly used relaxation techniques taught to preschool-age and older children. *Suggested sample brief strategy:* Ask the child (or instruct the caregiver to do so) to practice the following and use if pain is coming on: focus on the breath and pretend to be blowing up a big balloon while pursing the lips and exhaling slowly. This is one way to help induce controlled breathing.

Distraction can be used to help a child of any age shift attention away from pain and onto other activities. Common attention sustainers in the environment include bubbles, music, video games, television, the telephone, conversation, school, and play. Asking children to tell stories, asking parents to read to the child, and even mutual storytelling can be helpful distracters. Being involved with social, school, physical, or other activities helps the child in chronic pain to regain function. *Suggested sample brief strategy:* Encourage the child (or instruct the caregiver to do so) to shift attention away from the pain by continuing to engage in other activities and/or think of something else.

Biofeedback involves controlled breathing, relaxation, or hypnotic techniques with a computer synchronized device that provides visual or auditory feedback to the child when the desired action is approximated. Common targets of actions include muscle tension, peripheral skin temperature through peripheral vasodilation, and anal control through rectal muscle contraction and relaxation. Biofeedback also enhances the child's sense of mastery and control, especially for the child who needs more "proof" of change than that generated through hypnotherapy alone.

Hypnotherapy has also been used in the treatment of chronic pain in children, although the evidence for its effectiveness has not been as extensively studied as CBT. Hypnotherapy helps a child focus on an imaginative experience that is comforting, safe, fun, or intriguing. Hypnotherapy captures the child's attention, alters his or her sensory experiences, reduces distress, reframes pain experiences, creates time distortions, helps the child dissociate from the pain, and enhances feelings of mastery and self-control. Children with chronic pain can use *metaphor,* for example, imagining they have overcome something feared because of pain in real life. As the child increases mastery of imagined experiences, the enhanced sense of control can be used during actual pain rehabilitation. Hypnotherapy is best for children of school age or older.

Nonpharmacologic treatments of pain may also be applied to other treatment needs. A child who learns relaxation to reduce distress from lumbar punctures in cancer treatment may also apply this skill to other stressful medical and nonmedical situations, such as stressors caused by school.

Yoga is intended to achieve balance in mind, body, and spirit. **Therapeutic yoga** can be helpful in treating chronic pain; improving mood, energy, and sleep; and reducing anxiety. Yoga involves a series of *asanas* (body poses) oriented to the specific medical condition or symptoms. Some forms of yoga use poses within a movement flow and format. *Iyengar* yoga is an alignment-based system that uses props, such as blankets, bolsters, blocks, and belts, to support the body while the practitioner assumes more healing poses. Yoga promotes a sense of energy, relaxation, strength, balance, and flexibility and, over time, enhances a sense of mastery and control. Within a yoga practice, the child may learn certain types of breathing *(pranayama)* for added benefit. With a focus on body postures or in types of flow yoga, the child learns mindfulness or being present in the moment. By focusing on body and breath, the child can develop strategies to avoid ruminating about the past or worrying about the future.

Mindfulness meditation involves a focus on the present, "in-the-moment" experience using a variety of strategies. Many studies in adults report the value of meditation for chronic pain states and for anxiety and depression. These strategies help children learn how to be mindful and in the present with enhanced parasympathetic control. Many mindfulness smartphone applications are geared to children of different ages, as well as books for parents on how to help their children achieve a mindful state to enhance relaxation. Although there are different schools of mindfulness, such as *Vipassana* (insight-oriented meditation, often using a focus on the breath) and *transcendental* meditation (in which the child learns the use of a silent mantra to facilitate acquiring a deeper inner calmness), the goal is to help the child learn strategies that enhance self-competence in reducing stress and enhancing a state of well-being.

Massage therapy involves the therapist's touching and applying varied degrees of pressure on the child's muscles. Massage is very useful for children with chronic pain and especially helpful for those with myofascial pain. There are several types of massage, including craniosacral therapy. For young children, it can be helpful to have parents learn and perform brief massage on their children before bedtime. Massage therapy likely will not be helpful to or tolerated by the child with sensory sensitivity and sensory aversion.

Physical therapy can be especially useful for children with chronic musculoskeletal pain and for those deconditioned from inactivity. Exercise appears specifically to benefit muscle functioning, circulation, and posture while also improving body image, body mechanics, sleep, and mood. The physical therapist and the child can develop a graded exercise plan for enhancing the child's overall function for the child to continue at home. Research indicates that physical therapy affects central neurobiologic mechanisms that enhance "top-down" pain control.

Acupuncture/acupressure involves the placement of needles or pressure at specific points along a *meridian,* or energy field, after the acupuncturist has made a diagnosis of excess or deficient energy in that meridian as the primary cause of the pain. Acupuncture/acupressure is a feasible, popular part of a pain management plan for children with chronic pain. Acupuncture/acupressure alleviates chronic nausea, fatigue, and several chronic pain states, including migraine and chronic daily headaches, abdominal pain, and myofascial pain. Acupuncture/acupressure also has efficacy in adults with myofascial pain, primary dysmenorrhea, sickle cell crisis pain, and sore throat pain. The acupuncturist must relate well to children so that the experience is not traumatic, because added stress would undo the benefits gained.

Transcutaneous electrical nerve stimulation (TENS) is the use of a battery-operated tool worn on the body to send electrical impulses into the body at certain frequencies set by the machine. TENS is believed to be safe and can be tried for many forms of localized pain. Children often find TENS helpful and effective.

Music therapy and **art therapy** can be especially helpful for young and nonverbal children who would otherwise have trouble with traditional talk psychotherapies. Also, many creative children can more easily express fears and negative emotions through creative expression and, with the therapist's help, learn about themselves in the process. There is also increasing research on the impact of art and music therapy on altering central neural circuits that maintain and enhance pain.

Dance, movement, pet therapies, and **aromatherapy** have also been used and may be helpful, but these have not been as well studied in children for pain control as have other complementary therapies. Often, clinical experience helps guide the pediatrician in the benefits of these therapies with individual patients. For example, pet therapy is gaining favor in hospitals and in stress reduction for sick children. Pets often can become self-regulators for the child with ASD, although the neurobiologic mechanisms are not yet understood.

INVASIVE INTERVENTIONS FOR TREATING PAIN

Various interventional neuraxial and peripheral nerve blocks may have a role in the treatment of pain acutely (e.g., long-bone fracture), perioperatively, and for the patient with chronic pain (e.g., headache, abdominal pain, complex regional pain syndrome [CRPS], or cancer pain). Interventions also provide intraoperative anesthesia and postoperative analgesia (see Chapter 91). Use of interventional procedures varies greatly across institutions; they may be frequently used at some hospitals, whereas other institutions focus mainly on noninterventional treatment plans. Interventional procedures may be useful in some children who have specific types of chronic pain, but their use in children (as widely practiced in adult pain clinics) generally is not

recommended because the pediatric research is insufficient. Therefore the data are largely extrapolated from the adult population. Use of such procedures in children should generally not be considered or undertaken by an adult chronic pain provider who is willing to perform such a procedure on a child or adolescent. Rather, the potential procedure or block should be undertaken only at the direction or guidance of a pediatric pain specialist. Complications and lack of benefit can occur in children, as may occur in adults; however, more harm may be done in the pediatric populations. This is especially true as children and families may "pin their hopes" on a particular intervention "curing their child," when in reality chronic pain is a complex phenomenon that responds best to multidisciplinary management. This does not mean that no block should be recommended in children, but that procedural interventions should be used judiciously, appropriately, and in conjunction with other biopsychosocial treatments by or under the guidance of a pediatric pain expert.

Regional anesthesia provides several benefits, particularly in the acute perioperative setting. As an alternative to or in augmentation of opioid-based pain control, regional anesthesia minimizes opioid requirements and therefore opioid side effects, including nausea, vomiting, somnolence, respiratory depression, pruritus, constipation, and physical dependence. It can provide equal or improved analgesia, as it interrupts nociceptive pathways and may profoundly inhibit endocrine stress responses. Regional anesthesia also results in earlier ambulation in recovering surgical patients, helps prevent atelectasis in the patient with chest pain, and usually results in earlier discharge from the hospital. Theoretically, the interruption of nociceptive pathways in the periphery by regional anesthetics will prevent or reverse the process of amplification of pain signals induced by nociception (e.g., CNS windup, glial cell activation). For postoperative pain, effective regional anesthesia reduces the risks of acute pain evolving to chronic pain. Regional anesthesia is considered safe and effective if performed by trained staff with the proper instruments and equipment. Most frequently, nerve blocks are performed by an anesthesiologist or pain management physician; a few are easily performed by a nonanesthesiologist with appropriate training. The benefits of regional anesthesia are dependent on adequate coverage of the surgical area, the patient and family's expectation of the block, and the expertise of the provider performing the block. When procedures fail to provide adequate analgesia, it can lead to the need to "catch up" with pain control after surgery.

Head and Neck Blocks

Primary pain syndromes of the head, such as trigeminal neuralgia, are distinctly unusual in the pediatric population, and few surgical procedures in the head and neck are amenable to regional anesthesia. Headache disorders, very common in the pediatric age-group, may respond well to regional anesthesia of the greater occipital nerve. However, this is not generally considered a first-line treatment of pediatric headache. The greater occipital nerve (second cervical, C2) provides sensation to much of the cranial structures, from the upper cervical region, the occiput to the apex of the head, or even to the hairline. The greater occipital nerve can be blocked medial to the occipital artery, which can usually be identified at the occipital ridge midway between the occipital prominence and the mastoid process by palpation, Doppler sound amplification, or visualization by ultrasound. The short-term and especially long-lasting effects of nerve blocks for chronic headaches in children have not been documented by research. Studies are needed to determine which children with which types of headaches will benefit most from occipital nerve blocks. Sphenopalatine blocks are increasingly used in the treatment of multiple types of headaches in adults, including migraine and postdural puncture headache (PDPH). There is some evidence to support the benefit of this procedure in children and adolescents. The sphenopalatine ganglion (SPG) is a collection of cells closely related to the trigeminal nerve that plays a role in headache pathology. This block can be performed in a minimally invasive fashion through the nasal cavity. The procedure may be performed either with the use of marketed devices or with the use of cotton-tipped applicators. SPG blocks may be performed with or without fluoroscopic guidance.

Onabotulinum toxin A (Botox) may also be used for the treatment of chronic migraine in children and adolescents. As with many interventions, the available data for benefit of this treatment for pediatric migraine are lacking compared with the adult data. However, many children or adolescents, who may have experienced treatment failure with medical management of headache, may be considered as candidates for the use of Botox.

Upper Extremity Blocks

The brachial plexus block controls pain of the upper extremity. These blocks also protect the extremity from movement, reduce arterial spasm, and block sympathetic tone of the upper extremity. The brachial plexus, responsible for cutaneous and motor innervation of the upper extremity, is an arrangement of nerve fibers originating from spinal nerves C5 through T1, extending from the neck into the axilla, arm, and hand. The brachial plexus innervates the entire upper limb, except for the trapezius muscle and an area of skin near the axilla. If pain is located proximal to the elbow, the brachial plexus may be blocked above the clavicle (roots and trunks); if the pain is located distal to the elbow, the brachial plexus may be blocked at the axilla (cords and nerves). The block may be given as a single injection with a long-acting anesthetic such as bupivacaine or ropivacaine. This may provide up to 12-16 hours of analgesia. Use of a catheter and infusion pump may increase duration and provide continuous analgesia for several days.

Trunk and Abdominal Visceral Blocks

Trunk blocks provide somatic and visceral analgesia and anesthesia for pain or surgery of the thorax and abdominal area. Sympathetic, motor, and sensory blockade may be obtained. These blocks are often used in combination to provide optimal relief. Intercostal and paravertebral blocks may be beneficial in patients for whom a thoracic epidural injection or catheter is contraindicated (e.g., patient with coagulopathy). Respiratory function is maintained, and the side effects of opioid therapy are eliminated.

The intercostal, paravertebral, erector spinae, rectus sheath, and transverse abdominal plane blocks are most useful for pediatric chest and somatic abdominal pain. The celiac plexus and splanchnic nerve block can be useful for abdominal visceral pain, such as that caused by malignancy or pancreatitis. These blocks are best performed by an experienced anesthesiologist, pain physician, or interventional radiologist using ultrasound or CT imaging guidance.

The **intercostal block** is used to block the intercostal nerves, the anterior rami of the thoracic nerves from T1 to T11. These nerves lie inferior to each rib, between the inner and innermost intercostal muscles with their corresponding vein and artery, where they can be blocked, generally posterior to the posterior axillary line. Guidance with either fluoroscopy or ultrasound is often employed to decrease risks associated with this block. With use of ultrasound imaging, the intercostal nerves and the pleura can be identified, which can decrease risks such as pneumothorax or hemothorax that are associated with this procedure. The **erector spinae plane** block has also shown to be effective for blocking several levels of intercostal nerves while avoiding the attendant risks of multilevel intercostal nerve blocks.

The **paravertebral block**, another alternative to intercostal nerve block or epidural analgesia, is useful for pain associated with thoracotomy or with unilateral abdominal surgery, such as nephrectomy or splenectomy. Essentially this block results in multiple intercostal blocks with a single injection. The thoracic paravertebral space, lateral to the vertebral column, contains the sympathetic chain, rami communicantes, dorsal and ventral roots of the spinal nerves, and dorsal root ganglion. Because it is a continuous space, local anesthetic injection will provide sensory, motor, and sympathetic blockade to several dermatomes. The paravertebral block may be performed as a single injection or, for a very prolonged effect, as a continuous infusion over several days or weeks via a catheter. This block is best performed by an anesthesiologist or interventional pain physician under ultrasound guidance.

Ilioinguinal and iliohypogastric nerve blocks are indicated with surgery for inguinal hernia repair, hydrocele, or orchidopexy repair and for chronic pain subsequent to these procedures. The first lumbar (L1) nerve divides into the iliohypogastric and ilioinguinal nerves, which emerge from the lateral border of the psoas major muscle. The iliohypogastric nerve supplies the suprapubic area as it pierces the transversus abdominis muscle and runs deep to the internal oblique muscle. The ilioinguinal nerve supplies the upper medial thigh and superior inguinal region, as it also pierces the transversus abdominis muscle and runs across the inguinal canal. Ultrasound guidance helps ensure success for this nerve block.

The **celiac plexus block** is indicated for surgery or pain of the pancreas and upper abdominal viscera. The celiac plexus, located on each side of the L1 vertebral body, contains one to five ganglia. The aorta lies posterior, the pancreas anterior, and the inferior vena cava lateral to these nerves. The celiac plexus receives sympathetic fibers from the greater, lesser, and least splanchnic nerves, as well as from parasympathetic fibers from the vagus nerve. Autonomic fibers from the liver, gallbladder, pancreas, stomach, spleen, kidneys, intestines, and adrenal glands originate from the celiac plexus. This block is best performed with CT guidance to provide direct visualization of the appropriate landmarks, avoid vascular and visceral structures, and confirm correct needle placement. The close proximity of structures such as the aorta and vena cava make this a technical procedure best performed by an anesthesiologist, interventional pain physician, or interventional radiologist. The evidence for use of this block for chronic pediatric pain is lacking; as such, this block should not be routinely employed in the treatment of chronic noncancer pain.

Nerve blocks have been used for the treatment of *anterior cutaneous nerve entrapment syndrome (ACNES)*. ACNES is characterized by pain associated with use of abdominal muscles. On exam, this can be identified via Carnett sign. Pathology and causation in the pediatric population are not well understood. Treatment may include identification of a specific pain source under ultrasound guidance with infiltration of a local anesthetic or local anesthetic and steroid mixture. Evidence for use of this procedure is limited.

Lower Extremity Blocks

Lumbar plexus and sciatic nerve blocks provide pain control for painful conditions or surgical procedures of the lower extremities, with the benefit of providing analgesia to only one extremity while preserving motor and sensory function of the other. The lumbosacral plexus is an arrangement of nerve fibers originating from spinal nerves L2-L4 and S1-S3. The lumbar plexus arises from L2-L4 and forms the lateral femoral cutaneous, femoral, and obturator nerves. These nerves supply the muscles and sensation of the upper leg, with a sensory branch of the femoral nerve (saphenous nerve) extending below the knee to innervate the medial aspect of the foreleg, ankle, and foot. The sacral plexus arises from L4-S3 and divides into the major branches of the sciatic, tibial, and common peroneal nerves. These nerves in turn supply the posterior thigh, lower leg, and foot. Unlike the brachial plexus block, blockade of the entire lower extremity requires more than one injection because the lumbosacral sheath is not accessible. Separate injections are necessary for the posterior (sciatic) and anterior (lumbar plexus) branches, and the injections can be performed at any of several levels during the course of the nerve, as is clinically expedient. The lumbar plexus can be blocked in the back, resulting in analgesia of the femoral, lateral femoral cutaneous, and obturator nerves. Alternatively, any of these three nerves can be individually anesthetized, depending on the location of the pain. Similarly, the sciatic nerve can be anesthetized proximally as it emerges from the pelvis or, more distally, in the posterior thigh, or its major branches (tibial and peroneal nerves) can be individually anesthetized. These nerve blocks are generally best performed by an anesthesiologist, pain physician, or radiologist.

Sympathetic Blocks

Sympathetic blocks were once thought to be useful in the diagnosis and treatment of sympathetically mediated pain, CRPS (Table 93.17), and other neuropathic pain conditions (Table 93.18), but large meta-analyses have shown their utility to be minimal. When blocks of the sympathetic plexuses are performed, sympathectomy is obtained

Table 93.17 Budapest Criteria for Clinical Diagnosis of CRPS

1. **Pain** (ongoing and disproportionate to any inciting event)
2. **Symptoms (reported):** At least one symptom in three out of four of the following categories:
   - *Sensory* – Hyperesthesia and/or allodynia
   - *Vasomotor* – Temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - *Sudomotor/Edema* – Edema and/or sweating changes and/or sweating asymmetry
   - *Motor/Trophic* – Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. **Signs (examined):** At least one sign in two out of four of the following categories:
   - *Sensory* – Hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - *Vasomotor* – Temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
   - *Sudomotor/Edema* – Edema and/or sweating changes and/or sweating asymmetry
   - *Motor/Trophic* – Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. **Diagnosis of exclusion:** No other diagnosis better explains the signs and symptoms.

CRPS, Complex regional pain syndrome
From Davis PJ, Cladis FP, eds. *Smith's Anesthesia for Infants and Children*, 10th ed. Philadelphia: Elsevier; 2022, Box 25.1, p. 583.

Table 93.18 Examples of Neuropathic Pain Syndromes

PERIPHERAL NERVOUS SYSTEM FOCAL AND MULTIFOCAL LESIONS
Postherpetic neuralgia
Cranial neuralgias (e.g., trigeminal neuralgia, glossopharyngeal neuralgia)
Diabetic mononeuropathy
Nerve entrapment syndromes
Plexopathy from malignancy or irradiation
Phantom limb pain
Posttraumatic neuralgia (e.g., nerve root compression, after thoracotomy)
Ischemic neuropathy
Complex regional pain syndrome types 1 and 2
Erythromelalgia
PERIPHERAL NERVOUS SYSTEM GENERALIZED POLYNEUROPATHIES
Metabolic/nutritional: Diabetes mellitus, pellagra, beriberi, multiple nutritional deficiency, hypothyroidism
Toxic: Alcohol-, platinum-, or taxane-based chemotherapy; isoniazid; antiretroviral drugs
Infective/autoimmune: HIV, acute inflammatory polyneuropathy (Guillain-Barré syndrome), neuroborreliosis (Bannwarth syndrome)
Hereditary: Fabry disease
Malignancy: Carcinomatosis
Others: Idiopathic small fiber neuropathy, erythromelalgia
CENTRAL NERVOUS SYSTEM LESIONS
Spinal cord injury
Prolapsed disc
Stroke (brain infarction, spinal infarction)
Multiple sclerosis
Surgical lesions (e.g., rhizotomy, cordotomy)
Complex neuropathic disorders
Complex regional pain syndrome types 1 and 2

Adapted from Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. *BMJ*. 2009;339:b3002.

without attendant motor or sensory anesthesia. Their use for pain management was grounded in the notion that many types of chronic pain were mediated via the sympathetic nerves. This mechanistic model has been proven to be false.

The **stellate ganglion block** was indicated for pain in the face or upper extremity and for CRPS, phantom limb pain, amputation stump pain, or circulatory insufficiency of the upper extremities. The lumbar sympathetic block addressed pain in the lower extremity, CRPS, phantom limb pain, amputation stump pain, and pain from circulatory insufficiency.

The analgesia produced by peripheral sympathetic blocks usually outlives the duration of the local anesthetic, often persisting for weeks or indefinitely. If analgesia is transient, the blocks may be performed with catheter insertion for continuous local anesthesia of the sympathetic chain over days or weeks. Because precise, radiographically guided placement of the needle and/or catheter is required for safety and success, sympathetic blocks are generally best performed by an anesthesiologist, interventional pain physician, or interventional radiologist.

While all these procedures can be considered for the treatment of certain chronic pediatric pain conditions, there is overall a lack of evidence to support routine use in children and adolescents. This information should be used for learning and awareness rather than as a guide map for specific treatment of these conditions. When needed, a dedicated pediatric pain provider should be consulted and these blocks used judiciously when appropriate.

In addition, any time these procedures are considered for the treatment of chronic pain, special consideration should be given to potential risks and complications.

Epidural Anesthesia (Thoracic, Lumbar, and Caudal)

Epidural anesthesia and analgesia are indicated for pain below the clavicles, management of regional pain syndromes, cancer pain unresponsive to systemic opioids, and pain limited by opioid side effects.

The three layers of the spinal meninges—dura mater (outer), arachnoid mater (middle), and pia mater (inner)—envelop the spinal neural tissue. The subarachnoid space contains cerebrospinal fluid between the arachnoid mater and pia mater. The epidural space extends from the foramen magnum to the sacral hiatus and contains fat, lymphatics, blood vessels, and the spinal nerves as they leave the spinal cord. The epidural space separates the dura mater from the periosteum of the surrounding vertebral bodies. In children, the fat in the epidural space is not as dense as in adults, predisposing to greater spread of the local anesthetic from the site of injection.

Epidural local anesthetics block both sensory and sympathetic fibers, and if the local anesthetic is of sufficient concentration, they also block motor fibers. Mild hypotension may occur, although it is unusual in children <6 years of age. Epidural local anesthetics high in the thoracic spine may also anesthetize the sympathetic nerves to the heart (the cardiac accelerator fibers), producing bradycardia. In addition to using local anesthetics, it is routine to use opioids and sometimes α-agonists as adjunctive medications in the epidural space. Clonidine and opioids have been well studied and shown not to be neurotoxic. Side effects of epidural opioid administration include delayed respiratory depression, particularly when hydrophilic opioids such as morphine are used. The risk of this effect requires that children receiving epidural opioids by intermittent injection or continuous infusion be monitored by continuous pulse oximetry and nursing observation, particularly during the first 24 hours of therapy or after significant dose escalations. Respiratory depression occurring after the first 24 hours of epidural opioid administration is distinctly unusual.

Epidural clonidine (an α_2-agonist with μ-opioid analgesic properties) is associated with minimal risk and side effects. Although product labeling indicates use only in children with severe cancer pain, clonidine may be used for treatment of routine postoperative pain as well as pain syndromes such as CRPS. Mild sedation is the most common side effect of epidural clonidine, and it is not associated with respiratory depression.

Because performing epidural blockade is technical and may result in spinal cord injury, it is best done by an anesthesiologist or pain physician skilled in the technique. Caution is advised in the use of epidural anesthesia/analgesia for CRPS in children because no published RCTs have shown these procedures superior to a combination of less invasive physical and psychologic therapy, with or without neuropathic pain-focused medications.

INTRATHECAL ANALGESIA

Intrathecal catheters infused with opioids, clonidine, ziconotide (derived from a marine neurotoxin produced by the cone snail), and local anesthetics are occasionally applicable in pediatric patients with intractable pain from cancer or other life-threatening conditions. Typically, intrathecal catheters are attached to an implanted electronic pump containing a drug reservoir sufficient for several months of dosing. The technique is technical and best performed by an experienced pain management physician or neurosurgeon.

NERVE ABLATION AND DESTRUCTION

In some cases, pain remains refractory despite maximal reliance on oral and IV medications and nerve blockade. In these patients, temporary (pulsed radiofrequency ablation) or permanent neurolytic destruction (phenol or alcohol) of one or more nerves may be performed. The techniques should be carefully weighed against the consideration of permanent nerve destruction in a growing child with decades of life ahead. On the other hand, when pain is severe in life-limiting disease processes, the long-term considerations are less concerning, and these techniques should be discussed with a skilled pain management specialist.

CONSIDERATIONS FOR SPECIAL PEDIATRIC POPULATIONS

Pain Perception and Effects of Pain on Newborns and Infants

Pain may result from a number of circumstances in the newborn period, including acute pain (diagnostic and therapeutic procedures, minor surgery, monitoring), continuous pain (pain from thermal/chemical burns, postsurgical and inflammatory pain), and chronic or disease-related pain (necrotizing enterocolitis, nerve injury, chronic conditions, thrombophlebitis). The most common sources of pain in healthy infants are acute procedures, such as heel lances, surgical procedures, and in males, circumcision.

Many procedures are performed for premature infants in the neonatal intensive care unit (NICU). In the first week of life, approximately 94% of preterm infants <28 weeks gestational age are mechanically ventilated; in these situations, heelsticks and airway suctioning are frequent, yet few of these procedures are preceded by any type of analgesia. Repeated handling and acute pain episodes sensitize the neonate to increased reactivity and stress responses to subsequent procedures. Typical stress responses include increases in heart rate, respiratory rate, blood pressure, and intracranial pressure. Cardiac vagal tone, transcutaneous oxygen saturation, carbon dioxide levels, and peripheral blood flow are decreased. Autonomic signs include changes in skin color, vomiting, gagging, hiccupping, diaphoresis, dilated pupils, and palmar and forehead sweating (see Table 93.4).

Untreated pain in the newborn has serious short- and long-term consequences. There has been a shift in most NICUs to more liberal use of opioids. Nonetheless, **morphine**, the traditional gold standard of analgesia for acute pain, may not be effective and may have adverse long-term consequences. No differences have been found in the incidence of severe intraventricular hemorrhage or in the mortality rate when infants receiving morphine are compared with a placebo group, and there are no changes in assessed pain from tracheal suctioning in ventilated infants receiving morphine compared with those receiving a placebo infusion. Morphine may not alleviate acute pain in ventilated preterm neonates, although there are few data on the effects of morphine and fentanyl in nonventilated newborns. The lack of opioid effects for acute pain in neonates may result from immaturity of opioid receptors; acute pain may cause the uncoupling of μ-opioid receptors in the forebrain. Repetitive acute pain may create central neural changes in the newborn that may have long-term consequences for later pain vulnerability, cognitive effects, and opioid tolerance. Most

Table 93.19 World Health Organization Analgesic Ladder for Cancer Pain

STEP 1
Patients who present with mild to moderate pain should be treated with a nonopioid.

STEP 2
Patients who present with moderate to severe pain or for whom the step 1 regimen fails should be treated with an oral opioid for moderate pain combined with a nonopioid analgesic.

STEP 3
Patients who present with very severe pain or for whom the step 2 regimen fails should be treated with an opioid used for severe pain, with or without a nonopioid analgesic.

neonatologists use opioids in painful situations. Sucrose and pacifiers are also being used in the NICU. The effects of 24% **sucrose** (Sweetease) are believed to be opioid mediated because the effect can be reversed with naloxone. Sucrose, with or without a pacifier, may be effective for acute pain and stress control. Other nonpharmacologic strategies for stress and pain control include infant care by an individual primary nurse, tactile-kinesthetic stimuli (massage), "kangaroo care," and soothing sensorial saturation.

Children With Cancer Pain

The World Health Organization (WHO) proposed an analgesic therapy model for cancer pain known as the *analgesic ladder* (Table 93.19). Designed to guide therapy in care systems with limited access to analgesic experts, this ladder consists of a hierarchy of oral pharmacologic interventions intended to treat pain of increasing magnitude. The hierarchy ignores modalities such as the use of nonconventional analgesics and interventional pain procedures, which physicians in developed countries are often able to prescribe. Nevertheless, because oral medications are simple and efficacious, especially for home use, the ladder presents a framework for rationally using them, before applying other drugs and techniques of drug administration.

Oral medications are the first line of analgesic treatment. Because NSAIDs affect platelet adhesiveness, they are typically not used. As noted earlier, celecoxib may be the exception to this rule. Opioid therapy is the preferred approach for moderate or severe pain. Nonopioid analgesics are used for mild pain, a weak opioid is added for moderate pain, and strong opioids are administered for more severe pain. Adjuvant analgesics can be added, and side effects and comorbid symptoms are actively managed. Determining the type and sources of the pain will help develop an effective analgesic plan. Certain treatments, such as the chemotherapeutic agent vincristine, are associated with neuropathic pain. Such pain might require anticonvulsants or TCAs. Stretching pain from tumor growth within an organ might require strong opioids and/or radiation therapy if the tumor is radiosensitive. Organ obstruction, such as intestinal obstruction, should be diagnosed to relieve or bypass the obstruction.

It is important to consider both pharmacologic and nonpharmacologic strategies (e.g., CBT, family/parent support) to treat pain in children with cancer.

Children with Pain Associated with Advanced Disease

Patients with advanced diseases, including cancer, acquired immunodeficiency syndrome (AIDS), neurodegenerative disorders, and cystic fibrosis, need palliative care approaches that focus on optimal quality of life. Nonpharmacologic and pharmacologic management of pain and other distressing symptoms is a key component. *Palliative care* should be offered to all children with serious diseases, whether or not the diseases are potentially curable or long life expectancy is predicted (see Chapter 8). Examples include young children diagnosed with acute lymphoblastic leukemia (>90% posttreatment life expectancy) and children undergoing organ transplantation. Palliative care in pediatrics connotes treatment that focuses on symptom reduction, quality of life, and good family and clinical team communication. It is not only for patients in hospice care or those at the end of life. Differences in the progression of underlying illness, associated distressing symptoms, and common emotional responses in these conditions should shape individual treatment plans. For end-of-life care, >90% of children and adolescents with cancer can be made comfortable by standard escalation of opioids according to the WHO protocol. A small subgroup (5%) requires enormous opioid dose escalation to >100 times the standard morphine or other opiate infusion rate. Most of these patients have spread of solid tumors to the spinal cord, roots, or plexus, and signs of neuropathic pain are evident. **Methadone** given orally is often used in palliative care, not only end-of-life care, because of its long half-life and its targets at both opioid and NMDA receptors.

The type of pain experienced by the patient (neuropathic, myofascial) should determine the need for adjunctive agents. Complementary measures, such as massage, hypnotherapy, and spiritual care, must also be offered in palliative care. Although the oral route of opioid administration should be encouraged, especially to facilitate care at home, if possible, some children are unable to take oral opioids. Transdermal and sublingual routes, as well as IV infusion with PCA, are likely next choices. Small, portable infusion pumps are convenient for home use. If venous access is limited, a useful alternative is to administer opioids (especially morphine or hydromorphone, but not methadone or meperidine) through continuous SC infusion, with or without a bolus option. A small (e.g., 22-gauge) cannula is placed under the skin and secured on the thorax, abdomen, or thigh. Sites may be changed every 3-7 days, as needed. As noted, alternative routes for opioids include the transdermal and oral transmucosal routes. These latter routes are preferred over IV and SC drug delivery when the patient is being treated at home.

CHRONIC AND RECURRENT PAIN SYNDROMES

Chronic pain is defined as recurrent or persistent pain lasting longer than the normal tissue healing time (3-6 months). Children may experience pain related to injury (e.g., burns) or to a chronic or underlying disease process (e.g., cancer, arthritis), or pain can also be the chronic condition itself (e.g., CRPS, fibromyalgia, functional abdominal pain) (see Chapter 212). During childhood, abdominal, musculoskeletal, and headache pain are the most frequently occurring conditions. However, definitions of chronic pain do not take into account standard criteria for assessing particular pain symptoms or for evaluating the intensity or impact of pain and therefore include individuals with varying symptoms and experiences. Consequently, in epidemiologic surveys, prevalence estimates vary widely. Overall prevalence rates for different childhood pains range from 4% to 88%. An average of 13.5–31.8% of adolescents in a community sample reported having weekly abdominal, headache, or musculoskeletal pains. Most epidemiologic studies report prevalence and do not report the *severity* or impact of the pain. Research indicates that only a subset of children and adolescents with chronic pain (approximately 5%) experience moderate to severe disability, and this likely better represents the estimated population for whom help is needed to treat pain and associated problems.

Neuropathic Pain Syndromes

Neuropathic pain is caused by abnormal excitability in the peripheral or central nervous system that may persist after an injury heals or inflammation subsides. The pain, which can be acute or chronic, is typically described as burning or stabbing and may be associated with cutaneous hypersensitivity **(allodynia)**, distortion of sensation **(dysesthesia)**, and amplification of noxious sensations **(hyperalgesia** and **hyperpathia)**. Neuropathic pain conditions may be responsible for >35% of referrals to chronic pain clinics, conditions that typically include posttraumatic and postsurgical peripheral nerve injuries, phantom pain after amputation, pain after spinal cord injury, and pain caused by metabolic neuropathies (see Table 93.18). Patients with neuropathic pain typically respond poorly to opioids. Evidence supports

the efficacy of antidepressants (nortriptyline, amitriptyline, venlafaxine, duloxetine) and anticonvulsants (gabapentin, pregabalin, oxcarbazepine) for treatment of neuropathic pain (see Table 93.16).

Complex regional pain syndrome is well described in the pediatric population (see Chapter 211 and Table 93.17). **CRPS type 1** is a syndrome of neuropathic pain that typically follows an antecedent and usually minor injury or surgery to an extremity without identifiable nerve injury. It is seen after injury such as sprain or fracture or even in instances as minimal as an IV start. The syndrome of CRPS type 1 includes severe spontaneous neuropathic pain, hyperpathia, hyperalgesia, severe cutaneous allodynia to touch and cold, changes in blood flow (typically extremity cyanosis), and increased sweating. In more advanced cases, symptoms include dystrophic changes of the hair, nails, and skin; immobility of the extremity (dystonia); and muscle atrophy. In the most advanced cases, symptoms include ankylosis of the joints of the extremity. Specific causal factors in CRPS type 1 in both children and adults remain elusive, although coincidental events may be noted. **CRPS type 2** clinically appears the same with respect to symptoms but is associated with a known nerve injury.

Treatment of CRPS in children has been extrapolated from that in adults, with some evidence for efficacy of physical therapy, CBT, nerve blocks, antidepressants, AEDs, and other related drugs. All experts in pediatric pain management agree on the value of aggressive physical therapy, including desensitization. Some centers provide aggressive therapy without the use of pharmacologic agents or interventional nerve blocks. Unfortunately, recurrent episodes of CRPS may be seen in up to 25–50% of patients, particularly adolescent females. Physical therapy can be extraordinarily painful for children to endure; it is tolerated only by the most stoic and motivated patients. If children have difficulty enduring the pain, there is a well-established role for pharmacologic agents, with or without peripheral or central neuraxial nerve blocks, to render the affected limb sufficiently analgesic so that physical therapy can be tolerated. Pharmacologic interventions include the use of AEDs such as gabapentin and/or TCAs such as amitriptyline (see Fig. 93.4). Although there is clear evidence of a peripheral inflammatory component of CRPS, with release of cytokines and other inflammatory mediators from the peripheral nervous system in the affected limb, the use of antiinflammatory agents has been disappointing. Common nerve block techniques include IV regional anesthetics, epidural analgesia, and peripheral nerve blocks. In extreme and refractory cases, more invasive strategies have been reported, including surgical sympathectomy and spinal cord stimulation, although these are not generally recommended in the pediatric population

Although an array of treatments has some benefit, the mainstay of treatment remains **physical therapy** emphasizing desensitization, strengthening, and functional improvement. Additionally, pharmacologic agents and psychologic and complementary therapies are important components of a treatment plan. Invasive techniques, although not curative, can be helpful if they permit the performance of frequent and aggressive physical therapy that cannot be carried out otherwise. A good biopsychosocial evaluation will help determine the orientation of the treatment components. There are insufficient data to indicate the superior value of interventional blocks, such as epidural anesthesia, in children with CRPS over physical and psychologic interventions, with or without pharmacologic support.

Myofascial Pain Disorders and Fibromyalgia

Myofascial pain disorders are associated with tender points in the affected muscles and with muscle spasms (tight muscles). Treatment is targeted at relaxing the affected muscles through physical therapy, Iyengar yoga, massage, and acupuncture. Rarely are pharmacologic muscle relaxants helpful other than for creating tiredness at night for sleep. Dry needling or injections of local anesthetic into the tender points has been advocated, but the data do not support this as a standard treatment. Similarly, although botulinum toxin injections may be used, no data support this practice in children. Often, poor body postures, repetitive use of a body part not accustomed to that movement, or carrying heavy backpacks initiates pain. When it becomes widespread, a diagnosis may be made of **juvenile fibromyalgia**, which may or may not continue to subsequently become adult fibromyalgia. Newer guidelines do not use "tender points" in the diagnosis of fibromyalgia. Instead, diagnosis relies on a model that assesses for widespread pain and symptom severity (see Chapter 211). Likely there are different subtypes of widespread pain syndromes, and physical therapy is a key component of treatment. Psychologic interventions may play an important role to assist the child in resuming normal activities and to manage any psychologic comorbidities. Any pain rehabilitation plan should enhance return to full function. Because there is a high incidence of chronic pain in parents of children presenting with a chronic pain condition, especially fibromyalgia, attention to parent and family

Table 93.20 Clinical Features of Human Disorders Caused by Pathologic Variants in Ion-Channel Genes That Lead to Altered Pain Perception and Are Inherited in a Mendelian Manner

	AFFECTED GENE (PROTEIN)	TYPE AND EFFECT OF MUTATION	MAIN PHENOTYPE	ADDITIONAL FEATURES
Inherited erythromelalgia	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset by age 20 yr; episodic pain triggered by warmth; feet affected more frequently than hands	Erythema of feet
Paroxysmal extreme pain disorder	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset at birth; episodic pain; sacral region is affected most frequently, face is affected more often than the limbs; physical triggers include defecation	Erythema of the sacrum; tonic attacks
Small fiber neuropathy	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset at any age but more common in early adulthood; persistent burning pain; feet affected more frequently than hands	Could be autonomic features
Small fiber neuropathy	*SCN10A* ($Na_v1.8$)	Heterozygous, activating	Persistent burning pain	Could be autonomic features
Familial episodic pain syndrome type I	*TRPA1* (TRPA1)	Heterozygous, activating	Onset at birth or in infancy; episodic chest or arm pain; triggers are hunger and cold	—
Familial episodic pain syndrome type III	*SCN11A* ($Na_v1.9$)	Heterozygous, activating	Onset in first decade; episodic hand and foot pain; triggers are intercurrent illness or exercise	—

Na_v, Sodium ion channel.
Modified from Bennett DLH, Woods CG. Painful and painless channelopathies. *Lancet Neurol*. 2014;13:587–599, Table 1, p. 590.

factors is important. Parent training may entail teaching the parent to model more appropriate pain coping behaviors and to recognize the child's independent attempts to manage pain and function adaptively. Parents may also need referrals to obtain appropriate pain management for their own pain condition.

Pregabalin and duloxetine are FDA approved for management of fibromyalgia in adults; duloxetine is also approved for adolescents ages 13-17. However, the best evidence for the treatment of adolescents with fibromyalgia remains a multimodal approach including CBT and physical therapy. This is generally considered superior to solitary use of pharmacologic agents.

Erythromelalgia

Erythromelalgia in children is generally primary, whereas in adults it may be either primary or secondary to malignancy or other hematologic disorders, such as polycythemia vera (see Chapter 211.5). Patients with erythromelalgia exhibit red, warm, hyperperfused distal limbs. The disorder is usually bilateral and may involve either or both the hands and feet. Patients perceive burning pain and typically seek relief by immersing the affected extremities in ice water, sometimes so often and for so long so that skin pathology results. **Primary erythromelalgia** is caused by a gain of function pathogenic variant (autosomal dominant) in the gene for the NaV1.7 neuronal sodium channel on peripheral C nociceptive fibers, resulting in their spontaneous depolarization, and thus continuous burning pain. The most common pathogenic variant identified is in the *SCN9A* gene, although there are several variants that affect the NaV1.7 channel (Table 93.20). Other ion channel pathologic gene variants are associated with rare pain syndromes (see Table 93.20). Another pathogenic variant (loss of function) in the NaV1.7 channel results in a rare but serious genetic condition, the congenital indifference to pain.

Although some similarities to CRPS may be present in erythromelalgia, there are differences to distinguish the two conditions. CRPS in general is a unilateral phenomenon rather than bilateral. CRPS often presents with a cold, cyanotic limb (although "hot" CRPS with a warm, erythematous limb may occur as well). In addition, erythromelalgia is associated with intermittent pain compared with the more continuous nature and symptoms seen in CRPS. In erythromelalgia, ice water immersion is analgesic, the condition is bilateral and symmetric, and it is associated with hyperperfusion of the distal extremity.

The evaluation of hyperperfused limbs with burning pain should include genetic testing for **Fabry disease (alpha-galactosidase deficiency)** and screening for hematologic malignancies, with diagnosis of primary erythromelalgia being one of exclusion. The definitive treatment of Fabry disease includes enzyme replacement (as disease-modifying treatment) and administration of neuropathic pain medications such as gabapentin, although the success of antineuropathic pain drugs in small fiber neuropathies has not been impressive. The treatment of erythromelalgia is much more difficult. Antineuropathic pain medications (AEDs, TCAs) are typically prescribed but rarely helpful (see Fig. 93.4). Although one might predict that sodium channel–blocking AEDs might be effective in this sodium channelopathy, oxcarbazepine has not proved to be a particularly effective modality. The pain responds well to regional anesthetic nerve blocks, but it returns immediately when the effects of the nerve block resolve. In contrast, in other neuropathic syndromes, the analgesia usually (and inexplicably) persists well after the resolution of the pharmacologic nerve block. Aspirin and even nitroprusside infusions have been anecdotally reported to be of benefit with secondary erythromelalgia but have not been reported to be helpful in children with primary erythromelalgia. Case reports in adults and clinical experience in children suggest that periodic treatment with high-dose **capsaicin cream (8%)** may be effective in alleviating the burning pain and disability of erythromelalgia. Capsaicin (essence of chili pepper) cream is a vanilloid receptor (TRPV1) agonist that depletes small fiber peripheral nerve endings of the neurotransmitter substance P, an important neurotransmitter in the generation and transmission of nociceptive impulses. Once depleted, these nerve endings are no longer capable of generating spontaneous pain until the receptors regenerate, a process that takes many months.

Other Chronic Pain Conditions in Children

A variety of genetic and other medical/surgical conditions are often associated with chronic pain. Examples include Fabry disease, Chiari malformation/syringomyelia, epidermolysis bullosa, juvenile idiopathic arthritis, porphyria, mitochondrial disorders, degenerative neurologic diseases, cerebral palsy, ASD, intestinal pseudoobstruction, inflammatory bowel disease, chronic migraine/daily headaches, and irritable bowel disease. In many cases, treating the underlying disease, such as with enzyme replacement in Fabry disease and in other lysosomal disorders, will reduce what otherwise might be progression of symptoms but may not totally reduce pain and suffering, and other modalities will be needed. Pain that persists and is not well treated can lead to central sensitization and widespread pain, such as seen in children with one pain source who then develop fibromyalgia.

MANAGING COMPLEX CHRONIC PAIN PROBLEMS

Some patients with chronic pain have a prolonged course of evaluation in attempts to find what is expected as the singular "cause" of the pain and thus also undergo many failed treatments (see Chapter 212). Parents worry that the doctors have not yet discovered the cause that may be serious and life threatening, and children often feel not believed, that others perceive they are faking their pain or are "crazy." There may be no identifiable or diagnosable condition, and families may seek opinions from multiple treatment facilities to find help for their suffering child. For some children, what may have begun as an acute injury or infectious event may result in a chronic pain syndrome, with changes in the neurobiology of the pain-signaling system.

In the context of disabling chronic pain, it is very important for the pediatrician to avoid overmedication, because this can exacerbate associated disability. In addition, it is important to maintain an open mind and reassess the diagnosis if the clinical presentation changes. It is essential to communicate to the family that pain has a biologic basis (likely related to neural signaling and neurotransmitter dysregulation) and that the pain is naturally distressing to the child and family. All patients and families should receive a simple explanation of pain physiology that helps them understand the importance of (1) functional rehabilitation to normalize pain signaling, (2) the low risk of causing further injury with systematic increases in normal functioning, and (3) the likely failure of treatment if pain is managed as if it were acute. Because it is counterintuitive for most people to move a part of the body that hurts, many patients with chronic pain have atrophy or contractures of a painful extremity from disuse. Associated increases in worry and anxiety may exacerbate pain and leave the body even more vulnerable to further illness, injury, and disability.

Pain can have a significant impact on many areas of normal functioning and routines for children, and school absenteeism and related consequences of missed schooling are often significant problems. Appropriate assessment and evaluation of the child with chronic pain and the family is the critical first step in developing a treatment plan. For example, a high–academically functioning child might have an acute injury that leads to chronic pain and significant school absenteeism. Although many downstream contributors to pain and disability maintenance can accumulate the more school that is missed, often previously unrecognized focal learning disabilities may become the increasing trigger for a downhill cascade of pain, disability, and school absenteeism. Even for the child with outstanding grades, it may be helpful to learn about the amount of time spent on each subject. As certain subjects become more complicated, such as math, the child with a previously unrecognized math learning disability may be spending hours on math homework each night, even with good grades in math. In this case, the acute illness or injury becomes the "final straw" that breaks down the child's coping and turns the acute pain into a chronic problem.

Interdisciplinary pediatric pain programs have become the standard of care for treating complex chronic pain problems in youth. Although available in many parts of the United States, Canada, Europe, Australia, and New Zealand, the overall number of programs is still small. Therefore many children and adolescents with chronic pain will

be unable to receive specialized pain treatment in their local communities. In recognition of the severity and complexity of pain and disability for some children, different settings and treatment delivery models for providing pain care have been explored. One option is inpatient and day hospital treatment programs, which often address barriers to access to outpatient treatment and coordination of care. In addition, these programs provide an intensive treatment option for children who do not make adequate progress in outpatient treatment or who are severely disabled by pain. Early programs developed in the 1990s focused on CRPS treatment through intensive inpatient rehabilitation and exercise-based programs. Later programs expanded to other clinical populations and broadened the treatment focus to incorporate a range of rehabilitation and psychologic therapies delivered both individually and in groups. The typical length of inpatient admissions for children with chronic pain in such programs is 3-4 weeks, and emerging evidence suggests benefit from these programs. A major problem that limits such care for children with complex chronic disabling pain is the long waiting list for entry into these programs, as well as obtaining financial coverage for the treatment. Additional, more widespread models of care are needed.

Another intervention delivery option is *remote management,* referring to pain interventions used outside the clinic/hospital setting to reach children in their homes or communities. Interventions are typically delivered using some form of technology, such as the internet, or may rely on other media, such as telephone counseling or written self-help materials. Typically, remote management of pain includes monitoring, counseling, and delivery of behavioral and CBT interventions. Internet interventions have received the most research attention to date, with published examples of several different pediatric chronic pain conditions with promising findings for pain reduction. *Telemedicine* may offer additional ways to connect experts in pediatric pain with patients in remote communities. Within any community, the pediatrician will need to locate appropriate referral sources for patients with complex chronic pain. However, although psychologic interventions can be delivered through these telemedicine strategies, the pediatrician is still relied on to obtain the needed biopsychosocial history, complete a thorough physical examination, and provide the pharmacologic management as needed. The pediatrician also communicates with the family to help the child and family understand the pain and how the different pharmacologic and nonpharmacologic treatments will enhance function and alter the long-term neural processes underlying pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography

Chapter 94

Poisoning

Jillian L. Theobald and Justin N. Corcoran

Poisoning is the leading cause of injury-related death in the United States, surpassing that from motor vehicle crashes. Most of these deaths are unintentional (i.e., not suicide). In adolescents, poisoning is the second leading cause of injury-related death. Of the more than 2 million human poisoning exposures reported annually to the National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC), approximately 50% occur in children <6 years old, with the highest number of exposures occurring in 1- and 2-year-olds. Almost all these exposures are unintentional and reflect the propensity for young children to put virtually anything in their mouth. Fortunately, children <6 years old account for <2% of all poisoning fatalities reported to NPDS.

More than 90% of toxic exposures in children occur in the home, and most involve a single substance. Ingestion accounts for the majority of exposures, with a minority occurring by the dermal, inhalational, and ophthalmic routes. Approximately 40% of cases involve nondrug substances, such as cosmetics, personal care items, cleaning solutions, plants, and foreign bodies. Pharmaceutical preparations account for the remainder of exposures, and analgesics, topical preparations, vitamins, and antihistamines are most commonly reported.

The majority of poisoning exposures in children <6 years old can be managed without direct medical intervention beyond a call to the regional **poison control center (PCC)**. This is because the product involved is not inherently toxic or the quantity of the material is not sufficient to produce clinically relevant toxic effects. However, a number of substances can be highly toxic to toddlers in small doses (Table 94.1). In 2019, carbon monoxide (CO), batteries, and analgesics (mainly opioids) were the leading identifiable causes of poison-related fatalities in young children (<6 years). In addition, anesthetics, antihistamines, chemicals, cough and cold preparations, tobacco/nicotine/e-cigarette products, and hydrocarbons were significant causes of mortality.

Poison prevention education should be an integral part of all well-child visits, starting at the 6-month visit. Counseling parents and other caregivers about potential poisoning risks, poison-proofing a child's environment, and actions in the event of an ingestion diminish the likelihood of serious morbidity or mortality. Poison prevention education materials are available from the American Academy of Pediatrics (AAP) and regional PCCs. Through a U.S. network of PCCs, anyone at any time can contact a regional poison center by calling the toll-free number **1-800-222-1222**. Parents should be encouraged to share this number with grandparents, relatives, babysitters, and any other caregivers.

Product safety measures, poison prevention education, early recognition of exposures, and around-the-clock access to regionally based PCCs all contribute to the favorable exposure outcomes in young children. Poisoning exposures in children 6-12 years are much less common, involving only approximately 10% of all reported pediatric exposures. A second peak in pediatric exposures occurs in adolescence. Exposures in the adolescent age-group are primarily intentional (suicide or abuse or misuse of substances) and thus often result in more severe toxicity (see Chapter 157). Families should be informed and given anticipatory guidance that nonprescription and prescription medications, and even household products (e.g., inhalants), are common sources of adolescent exposures. Although adolescents (age 13-19 years) account for only about 16% of pediatric exposures, they constitute a larger proportion of deaths. Of the 159 poison-related pediatric deaths in 2021 reported to NPDS, 86 were adolescents (2% of all fatalities called in to poison centers). Pediatricians should be aware of the signs of drug abuse or suicidal ideation in adolescents and should aggressively intervene (see Chapter 40).

PREVENTION

Deaths caused by unintentional poisoning among younger children have decreased dramatically over the past 2 decades, particularly among children <5 years old. In 1970, when the U.S. Poison Packaging Prevention Act was passed, 226 poisoning deaths of children <5 years old occurred, compared with only 25 in 2021. Poisoning prevention demonstrates the effectiveness of passive strategies, including the use of child-resistant packaging and limited doses per container. Difficulty using child-resistant containers by adults is an important cause of poisoning in young children today. In 18.5% of households in which poisoning occurred in children <5 years old, the child-resistant closure was replaced, and 65% of the packaging used did not work properly. Almost 20% of ingestions occur from drugs belonging to grandparents, who have difficulty using traditional child-resistant containers and often put their medications in pill organizers that are not childproof.

Even though there has been success in preventing poisoning in young children, there has been a remarkable rise in adolescent poison-related death over the past 20 years. This has mirrored the increasing rate of antidepressant prescriptions written by healthcare providers and the epidemic increase in opioid-related fatalities.

Table 94.1 Common Agents Potentially Toxic to Young Children (<6 yr) in Small Doses*

SUBSTANCE	TOXICITY
Aliphatic hydrocarbons (e.g., gasoline, kerosene, lamp oil)	Acute lung injury
Antimalarials (chloroquine, quinine)	Seizures, dysrhythmias
Benzocaine	Methemoglobinemia
β-Adrenergic receptor blockers†	Bradycardia, hypotension
Calcium channel blockers	Bradycardia, hypotension, hyperglycemia
Camphor	Seizures
Caustics (pH <2 or >12)	Airway, esophageal and gastric burns
Clonidine	Lethargy, bradycardia, hypotension
Diphenoxylate and atropine (Lomotil)	CNS depression, respiratory depression
Ethylene glycol	Altered mental status, seizures
Hypoglycemics, oral (sulfonylureas and meglitinides)	Hypoglycemia, seizures
Imidazolines (oxymetazoline, tetrahydrozoline)	CNS depression, respiratory depression
Laundry detergent packets (pods)	Airway issues, respiratory distress, altered mental status
Lindane	Seizures
Marijuana (cannabis, THC)	Lethargy, seizures, coma
Monoamine oxidase inhibitors	Hypertension followed by delayed cardiovascular collapse
Methyl salicylate	Tachypnea, metabolic acidosis, seizures
Opioids (especially methadone, buprenorphine)	CNS depression, respiratory depression
Organophosphate pesticides	Cholinergic crisis
Phenothiazines (especially chlorpromazine, thioridazine)	Seizures, dysrhythmias
Sulfonylureas (glipizide, glyburide)	Hypoglycemia
Theophylline	Seizures, dysrhythmias
Tricyclic antidepressants	CNS depression, seizures, dysrhythmias, hypotension

*"Small dose" typically implies one to two pills or 5 mL.
†Lipid-soluble β blockers (e.g., propranolol) are more toxic than water-soluble β blockers (e.g., atenolol).
CNS, Central nervous system.

APPROACH TO THE POISONED PATIENT

The initial approach to the patient with a witnessed or suspected poisoning should be no different than that in any other sick child, starting with stabilization and rapid assessment of the airway, breathing, circulation (pulse, blood pressure), and mental state. In any patient with altered mental status, a serum glucose concentration should be obtained early, and naloxone administration should be considered if there is coma or respiratory depression. A targeted history and physical examination serve as the foundation for a thoughtful differential diagnosis, which can then be further refined through laboratory testing and other diagnostic studies.

History

Obtaining an accurate problem-oriented history is of paramount importance. *Intentional* poisonings (suicide attempts, drug abuse/misuse) are typically more severe than unintentional, exploratory ingestions. In patients without a witnessed exposure, historical features such as age of the child (toddler or adolescent), acute onset of symptoms without prodrome, multisystem organ dysfunction, or high levels of household stress should suggest a possible diagnosis of poisoning. In patients with a witnessed exposure, determining exactly what the child was exposed to and the circumstances surrounding the exposure is crucial to initiating directed therapy quickly. For household and workplace products, names (brand, generic, chemical) and specific ingredients, along with their concentrations, can often be obtained from the labels. PCC specialists can also help to identify possible ingredients and review the potential toxicities of each component. Poison center specialists can also help identify pills based on markings, shape, and color. If referred to the hospital for evaluation, parents should be instructed to bring the products, pills, and/or containers with them to assist with identifying and quantifying the exposure. If a child is found with an unknown pill, a list of all medications in the child's environment, including medications that grandparents, parents, siblings, caregivers, or other visitors might have brought into the house, must be obtained. In the case of an unknown exposure, clarifying where the child was found (e.g., garage, kitchen, laundry room, bathroom, backyard, workplace) can help to generate a list of potential toxins.

Next, it is important to clarify the *timing* of the ingestion and to obtain some estimate of how much of the substance may have been ingested. It is better to overestimate the amount ingested to prepare for the worst-case scenario. Counting pills or measuring the remaining volume of a liquid ingested can sometimes be useful in generating estimates. For inhalational, ocular, or dermal exposures, the concentration of the agent and the length of contact time with the material should be determined, if possible.

Symptoms

Obtaining a description of symptoms experienced after ingestion, including their timing of onset relative to the time of ingestion and their progression, can generate a list of potential toxins and help anticipate the severity of the ingestion. Coupled with physical exam findings, reported symptoms assist practitioners in identifying **toxidromes**, or recognized poisoning syndromes, suggestive of toxicity from specific substances or classes of substances (Tables 94.2 to 94.5).

Past Medical and Developmental History

Underlying diseases can make a child more susceptible to the effects of a toxin. Concurrent drug therapy can also increase toxicity because certain drugs may interact with the toxin. A history of psychiatric illness can make patients more prone to substance abuse, misuse, intentional ingestions, and polypharmacy complications. Pregnancy is a common precipitating factor in adolescent suicide attempts and can influence both evaluation of the patient and subsequent treatment. A developmental history is important to ensure that the exposure history provided is appropriate for the child's developmental stage (e.g., report of 6-month-old picking up a large container of laundry detergent and drinking it should indicate a "red flag").

Social History

Understanding the child's social environment helps to identify potential sources of exposure (caregivers, visitors, grandparents, recent parties or social gatherings) and social circumstances (new baby, parent's illness, financial stress) that might have contributed to the ingestion (suicide or unintentional). Unfortunately, some poisonings occur in the setting of serious neglect or intentional abuse.

Table 94.2 Selected Historical and Physical Findings in Poisoning

SIGN	TOXIN
ODOR	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Rotten eggs	Hydrogen sulfide, sulfur dioxide, methyl mercaptans (additive to natural gas)
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
Mothballs	Camphor, naphthalene
Freshly mowed hay	Phosgene
Carrots	Water hemlock
Gasoline	Petroleum distillates
OCULAR SIGNS	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines (typical antipsychotics), sedative-hypnotics, olanzapine
Mydriasis	Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (cocaine, amphetamines, PCP), post–anoxic encephalopathy, opiate withdrawal, cathinones, MDMA
Nystagmus	Anticonvulsants, sedative-hypnotics, alcohols, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
CUTANEOUS SIGNS	
Diaphoresis	Cholinergics (organophosphates), sympathomimetics, salicylates, phencyclidine (PCP), withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
Bullae/blisters	Barbiturates, mustard gas, xylazine, snake, spiders
ORAL SIGNS	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine
Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
GASTROINTESTINAL SIGNS	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Constipation	Lead
CARDIAC SIGNS	
Tachycardia	Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthines (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonidine, opioids), serotonin syndrome, neuroleptic malignant syndrome, MDMA, cathinones
Bradycardia	β Blockers, calcium channel blockers, digoxin, clonidine, organophosphates, opioids, sedative-hypnotics xylazine
Hypertension	Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, nicotine, caffeine, neuroleptic malignant syndrome, clonidine withdrawal
Hypotension	β Blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonidine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation, xylazine
RESPIRATORY SIGNS	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, marijuana, barbiturates, xylazine
Tachypnea	Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration
CENTRAL NERVOUS SYSTEM SIGNS	
Ataxia	Alcohols, anticonvulsants, sedative-hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative-hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates, hypoglycemics, lead, arsenic, rohypnol, carbon monoxide
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal (especially ethanol), strychnine, cocaine
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal, MDMA, cathinones
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates, nicotine
Hypothermia	Carbon monoxide, opioids, oral hypoglycemics, liquor, sedative-hypnotics
Hyperthermia	Antihistamines, amphetamines, salicylates, antidepressants (TCAs), antipsychotics, serotonin syndrome, neuroleptic malignant syndrome, withdrawal (alcohol, baclofen)

GHB, γ-Hydroxybutyrate; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); NSAIDs, nonsteroidal antiinflammatory drugs; PCP, phencyclidine; TCAs, tricyclic antidepressants.

Table 94.3 Recognizable Poison Syndromes ("Toxidromes")

	SIGNS						
TOXIDROME	**VITAL SIGNS**	**MENTAL STATUS**	**PUPILS**	**SKIN**	**BOWEL SOUNDS**	**OTHER**	**POSSIBLE TOXINS**
Sympathomimetic	Hypertension, tachycardia, hyperthermia	Agitation, psychosis, delirium, violence	Dilated	Diaphoretic, flushed	Normal to increased		Amphetamines, cocaine, PCP, bath salts (cathinones), ADHD medication
Anticholinergic	Hypertension, tachycardia, hyperthermia	Agitated, delirium, coma, seizures	Dilated	Dry, hot, flushed	Diminished	Ileus, urinary retention	Antihistamines, TCAs, atropine, jimsonweed
Cholinergic	Bradycardia, BP and temp typically normal	Confusion, coma, fasciculations	Small	Diaphoretic	Hyperactive	Diarrhea, urination, bronchorrhea, bronchospasm, emesis, lacrimation, salivation	Organophosphates (insecticides, nerve agents), carbamates (physostigmine, neostigmine, pyridostigmine) Alzheimer medications, myasthenia treatments
Opioids	Respiratory depression, bradycardia, hypotension, hypothermia	Depression, coma, euphoria	Pinpoint	Normal	Normal to decreased		Methadone, buprenorphine, morphine, oxycodone, heroin, etc.
Sedative-hypnotics	Respiratory depression, HR normal to decreased, BP normal to decreased, temp normal to decreased	Somnolence, coma	Small or normal	Normal	Normal		Barbiturates, benzodiazepines, ethanol xylazine
Serotonin syndrome (similar findings with neuroleptic malignant syndrome)	Hyperthermia, tachycardia, hypertension or hypotension (autonomic instability)	Agitation, confusion, coma	Dilated	Diaphoretic	Increased	Neuromuscular hyperexcitability: clonus, hyperreflexia (lower > upper extremities)	SSRIs, lithium, MAOIs, linezolid, tramadol, meperidine, dextromethorphan
Salicylates	Tachypnea, hyperpnea, tachycardia, hyperthermia	Agitation, confusion, coma	Normal	Diaphoretic	Normal	Nausea, vomiting, tinnitus, ABGs with primary respiratory alkalosis and primary metabolic acidosis; tinnitus or difficulty hearing	Aspirin and aspirin-containing products, methyl salicylate
Withdrawal (sedative-hypnotic)	Tachycardia, tachypnea, hyperthermia	Agitation, tremor, seizure, hallucinosis, delirium tremens	Dilated	Diaphoretic	Increased		Lack of access to ethanol, benzodiazepines, barbiturates, GHB, or excessive use of flumazenil
Withdrawal (opioid)	Tachycardia	Restlessness, anxiety	Dilated	Diaphoretic	Hyperactive	Nausea, vomiting, diarrhea	Lack of access to opioids or excessive use of naloxone

ABGs, Arterial blood gases; ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; GHB, γ-hydroxybutyrate; HR, heart rate; MAOIs, monoamine oxidase inhibitors; PCP, phencyclidine; SSRIs, selective serotonin reuptake inhibitors; temp, temperature; TCAs, tricyclic antidepressants.

Table 94.4 Mini-Toxidromes

TOXIDROME	SYMPTOMS AND SIGNS	EXAMPLES
α_1-Adrenergic receptor antagonists	CNS depression, tachycardia, miosis	Chlorpromazine, quetiapine, clozapine, olanzapine, risperidone
α_2-Adrenergic receptor agonist	CNS depression, bradycardia, hypertension (early), hypotension (late), miosis	Clonidine, oxymetazoline, tetrahydrozoline, tizanidine, dexmedetomidine
Clonus/myoclonus	CNS depression, myoclonic jerks, clonus, hyperreflexia	Carisoprodol, lithium, serotonergic agents, bismuth, organic lead, organic mercury, serotonin or neuroleptic malignant syndrome
Sodium channel blockers	CNS toxicity, wide QRS	Cyclic antidepressants and structurally related agents, propoxyphene, quinidine/quinine, amantadine, antihistamines, bupropion, cocaine
Potassium channel blockers	CNS toxicity, long QT interval	Antipsychotics, methadone, phenothiazines
Cathinones, synthetic cannabinoids	Hyperthermia, tachycardia, delirium, agitation, mydriases	See Chapter 157.

CNS, Central nervous system.
From Ruha AM, Levine M. Central nervous system toxicity. *Emerg Med Clin North Am.* 2015;32(1):205–221, p. 208.

Table 94.5 Predicting Toxicity from Vital Signs

BRADYCARDIA (PACED)
Propranolol (β blockers), poppies (opioids), propoxyphene, physostigmine
Anticholinesterase drugs, antiarrhythmics
Clonidine, calcium channel blockers
Ethanol or other alcohols
Digoxin, digitalis

TACHYCARDIA (FAST)
Free base or other forms of cocaine, Freon
Anticholinergics, antihistamines, antipsychotics amphetamines, alcohol withdrawal
Sympathomimetics (cocaine, caffeine, amphetamines, phencyclidine [PCP]), solvent abuse, strychnine
Theophylline, tricyclic antidepressants (TCAs), thyroid hormones

HYPOTHERMIA (COOLS)
Carbon monoxide
Opioids
Oral hypoglycemics, insulin
Liquor (alcohols)
Sedative-hypnotics

HYPERTHERMIA (NASA)
Neuroleptic malignant syndrome (NMS), nicotine
Antihistamines, alcohol withdrawal
Salicylates, sympathomimetics, serotonin syndrome
Anticholinergics, antidepressants, antipsychotics

HYPOTENSION (CRASH)
Clonidine, calcium channel blockers
Rodenticides (containing arsenic, cyanide)
Antidepressants, aminophylline, antihypertensives
Sedative-hypnotics (xylazine)
Heroin or other opioids

HYPERTENSION (CT SCAN)
Cocaine
Thyroid supplements
Sympathomimetics
Caffeine
Anticholinergics, amphetamines
Nicotine

RAPID RESPIRATION (PANT)
PCP, paraquat, pneumonitis, phosgene
Acetylsalicylic acid (ASA) and other salicylates
Noncardiogenic pulmonary edema, nerve agents
Toxin-induced metabolic acidosis

SLOW RESPIRATION (SLOW)
Sedative-hypnotics (barbiturates, benzodiazepines, xylazine)
Liquor (alcohols)
Opioids
Weed (marijuana)

From Meehan TJ. Approach to the poisoned patient. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. *Rosen's Emergency Medicine*, 9th ed. Philadelphia: Elsevier; 2018, Box 139.6, p. 1816.

Physical Examination

A targeted physical examination is important to identifying the potential toxin and assessing the severity of the exposure. Initial efforts should be directed toward assessing and stabilizing the airway, breathing, circulation, and mental status. Once the airway is secure and the patient is stable from a cardiopulmonary standpoint, a more extensive physical exam can help to identify characteristic findings of specific toxins or classes of toxins.

In the poisoned patient, key features of the physical exam are vital signs, mental status, pupils (size, reactivity), nystagmus, skin, bowel sounds, and muscle tone. These findings might suggest a toxidrome, which can then guide the differential diagnosis and management.

Laboratory Evaluation

A basic chemistry panel (electrolytes, renal function, glucose) is necessary for all poisoned or potentially poisoned patients. Any patient with acidosis (low serum bicarbonate level on serum chemistry panel) must have an anion gap calculated because of the more specific differential diagnoses associated with an elevated **anion gap metabolic acidosis** (Table 94.6). Patients with a known overdose of acetaminophen should have liver transaminases (alanine transaminase [ALT], aspartate transaminase [AST]) and international normalized ratio (INR) assessed. A serum creatinine kinase level is indicated on any patient with a prolonged "down time" to evaluate for **rhabdomyolysis**. A urine pregnancy test is mandatory for all postpubertal female patients. Based

Table 94.6 Laboratory Clues in Toxicologic Diagnosis

ANION GAP METABOLIC ACIDOSIS (MNEMONIC = MUDPILES CAT)
Methanol, metformin
Uremia
Diabetic ketoacidosis
Propylene glycol
Isoniazid, iron, massive ibuprofen
Lactic acidosis
Ethylene glycol
Salicylates
Cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide)
Alcoholic ketoacidosis
Tylenol (clinical significance depends upon presence or absence of liver injury), toluene

ELEVATED OSMOLAR GAP
Alcohols: ethanol, isopropyl, methanol, ethylene glycol

HYPOGLYCEMIA (MNEMONIC = HOBBIES)
Hypoglycemics, oral: sulfonylureas, meglitinides
Other: quinine, unripe ackee fruit
Beta Blockers
Insulin
Ethanol
Salicylates (late)

HYPERGLYCEMIA
Salicylates (early)
Calcium channel blockers
Caffeine

HYPOCALCEMIA
Ethylene glycol
Fluoride

RHABDOMYOLYSIS
Neuroleptic malignant syndrome, serotonin syndrome
Statins
Mushrooms (Tricholoma equestre)
Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics) or excessive muscle activity or seizures (e.g., sympathomimetics)

RADIOPAQUE SUBSTANCE ON KUB (MNEMONIC = CHIPPED)
Chloral hydrate, calcium carbonate
Heavy metals (lead, zinc, barium, arsenic, lithium, bismuth)
Iron
Phenothiazines
Play-Doh, potassium chloride
Enteric-coated pills
Dental amalgam, drug packets

KUB, Kidney-ureter-bladder radiograph.

on the clinical presentation and the presumed poison, additional laboratory tests may also be helpful. Acetaminophen is a widely available medication and a commonly detected co-ingestant with the potential for severe toxicity. There is an effective antidote to acetaminophen poisoning that is time dependent. Given that patients might initially be asymptomatic and might not report or be aware of acetaminophen ingestion, an acetaminophen level should be checked in all patients who present after an intentional exposure or ingestion.

For select intoxications (e.g., salicylates, some anticonvulsants, acetaminophen, iron, digoxin, methanol, ethanol, lithium, ethylene glycol, theophylline, CO, lead), **quantitative blood concentrations** are integral to confirming the diagnosis and formulating a treatment plan. However, for most other exposures, quantitative measurement is not readily available and is not likely to alter management. All intoxicant levels must be interpreted in conjunction with the history. For example, a methanol level of 20 mg/dL 1 hour after ingestion may be nontoxic, whereas a similar level 24 hours after ingestion implies a significant poisoning. In general, patients with multiple or chronic exposures to a drug or other chemical will be more symptomatic at lower drug levels than those with a single acute exposure.

Both the rapid urine drug-of-abuse screens and the more comprehensive drug screens vary widely in their ability to detect toxins and generally add little information to the clinical assessment. This is particularly true if the agent is known and the patient's symptoms are consistent with that agent. If a drug screen is ordered, it is important to know that the components screened for, and the lower limits of detection, vary from laboratory to laboratory. In addition, the interpretation of most drug screens is hampered by many false-positive and false-negative results. Many opiate toxicology screens poorly detect hydrocodone and do not detect the fully synthetic opioids at all (e.g., meperidine, methadone, buprenorphine, fentanyl, carfentanil, furanylfentanyl, tramadol). Several common benzodiazepines (e.g., alprazolam and clonazepam) may not be detected; synthetic cannabinoids or "bath salts" may also be missed. The amphetamine screen, on the other hand, is typically overly sensitive and often is triggered by prescription amphetamines and some over-the-counter cold preparations. As such, the urine drug-of-abuse screen is typically of limited utility for the poisoned patient but may serve a useful function for other providers, including psychiatrists, in their evaluation of the adolescent patient. Urine drug-of-abuse screens are potentially helpful in patients with altered mental status of unknown etiology, persistent unexplained tachycardia, and acute myocardial ischemia or stroke at a young age. These screens can also be useful in the assessment of a neglected or abused child. Consultation with a medical toxicologist can be helpful in interpreting drug screens and directing which specific drug levels or other laboratory analyses might aid in patient management.

In the case of a neglected or allegedly abused child, a positive toxicology screen can add substantial weight to a claim of abuse or neglect. In these cases, and any case with medicolegal implications, any positive screen *must* be followed by confirmatory testing (most commonly via gas chromatography/mass spectroscopy), which is considered the gold-standard measurement for legal purposes.

Additional Diagnostic Testing

An electrocardiogram (ECG) is a quick and noninvasive bedside test that can yield important clues to diagnosis and prognosis. Particular attention should be paid to the ECG intervals (Table 94.7). A widened QRS interval, putting the patient at risk for monomorphic ventricular tachycardia, suggests blockade of fast sodium channels. A widened QTc interval suggests effects at the potassium rectifier channels and portends a risk of torsades de pointes (polymorphic ventricular tachycardia).

Further diagnostic testing is based on the differential diagnosis and pattern of presentation. For example, adjunctive chest radiography may reveal signs of pneumonitis (e.g., hydrocarbon aspiration), noncardiogenic pulmonary edema (e.g., salicylate toxicity), or a foreign body. Abdominal radiography is most helpful in screening for the presence of lead paint chips or other foreign bodies. It may detect a *bezoar* (concretion), demonstrate radiopaque tablets, or reveal drug packets in a "body packer."

Table 94.7 Electrocardiographic Findings in Poisoning

PR INTERVAL PROLONGATION
Digoxin
Lithium
Calcium channel antagonists
β-Antagonists
QRS PROLONGATION
Tricyclic antidepressants
Diphenhydramine
Carbamazepine
Cardiac glycosides
Chloroquine, hydroxychloroquine
Cocaine
Lamotrigine
Quinidine, quinine, procainamide, disopyramide
Phenothiazines
Propoxyphene
Propranolol
Bupropion, venlafaxine (rare)
QTc PROLONGATION*
Amiodarone
Antipsychotics (typical and atypical)
Arsenic
Cisapride
Citalopram
Clarithromycin, erythromycin
Disopyramide, dofetilide, ibutilide
Fluconazole, ketoconazole, itraconazole
Methadone
Pentamidine
Phenothiazines
Sotalol

*This is a select list of important toxins; other medications are also associated with QTc prolongation.

PRINCIPLES OF MANAGEMENT

The principles of management of the poisoned patient are supportive care, decontamination, directed therapy, and enhanced elimination. Few patients meet criteria for all these interventions, although clinicians should consider each option in every poisoned patient so as not to miss a potentially lifesaving intervention. Antidotes are available for relatively few poisons (Tables 94.8 and 94.9), thus emphasizing the importance of meticulous supportive care and close clinical monitoring.

Poison control center personnel are specifically trained to provide expertise in the management of poisoning exposures. Parents should be instructed to call the poison control center **(1-800-222-1222)** for any concerning exposure. PCC specialists can assist parents in assessing the potential toxicity and severity of the exposure. They can further determine which children can be safely monitored at home and which children should be referred to the emergency department for further evaluation and care. Although up to one third of calls to PCCs involve hospitalized patients, 86% of PCC calls for exposures in children <6 years old are managed at home. The AAPCC has generated consensus statements for out-of-hospital management of common ingestions (e.g., acetaminophen, iron, calcium channel blockers [CCBs]) that serve to guide poison center recommendations.

Supportive Care

Careful attention is paid first to the "ABCs" of airway, breathing, and circulation; there should be a low threshold to aggressively manage the airway of a poisoned patient because of the patient's propensity to quickly become comatose. Endotracheal intubation is often the only significant intervention needed in many poisoned patients. An important caveat is the tachypneic patient with a clear lung examination and normal oxygen saturation. This should alert the clinician to the likelihood that the patient is compensating for an acidemia. Paralyzing such a patient and underventilating might prove fatal. If intubation is necessary for airway protection or a tiring patient, a good rule of thumb is to match the ventilatory settings to the patient's preintubation minute ventilation.

Hypotensive poisoned patients often are not hypovolemic, and aggressive fluid resuscitation may lead to fluid overload. If hypotension persists after one to two standard boluses of crystalloid, infusion of a direct-acting vasopressor, such as norepinephrine or epinephrine, is preferred. Dysrhythmias are typically managed in the standard manner. The exceptions are for dysrhythmias caused by agents that block fast sodium channels of the heart, for which boluses of sodium bicarbonate are given; dysrhythmias caused by hydrocarbons, which should be treated with β blockers; and an overall avoidance of amiodarone for toxicologic-induced arrythmias.

Seizures should primarily be managed with agents that potentiate the γ-aminobutyric acid (GABA) complex, such as benzodiazepines or barbiturates. Using sodium channel blockers such as phenytoin is likely to be ineffective and potentially harmful. The goal of supportive therapy is to support the patient's vital functions until the patient can eliminate the toxin. Patients with an elevated creatine phosphokinase (CPK) should be aggressively hydrated with crystalloid, with a goal urine output of 1-2 mL/kg/hr and close monitoring of CPK trend.

Decontamination

Most poisonings in children are from ingestion, although exposures can also occur by inhalational, dermal, and ocular routes (Table 94.10). The goal of decontamination is to minimize absorption of the toxic substance. The specific method employed depends on the properties of the toxin itself and the route of exposure. Regardless of the decontamination method used, the efficacy of the intervention decreases with increasing time since exposure. *Decontamination should not be routinely employed for every poisoned patient.* Instead, careful decisions regarding the utility of decontamination should be made for each patient and should include consideration of the toxicity and pharmacologic properties of the exposure, route of the exposure, time since the exposure, and risks vs benefits of the decontamination method.

Dermal and ocular decontamination begins with removal of any contaminated clothing and particulate matter, followed by flushing of the affected area with tepid water or normal saline (NS). Treating clinicians should wear proper protective gear when performing irrigation. Flushing for a minimum of 10-20 minutes is recommended for most exposures, although some chemicals (e.g., alkaline corrosives) require much longer periods of flushing. Dermal decontamination, especially after exposure to adherent or lipophilic (e.g., organophosphates) agents, should include thorough cleansing with soap and water. Water should *not* be used for decontamination after exposure to highly reactive agents, such as elemental sodium, phosphorus, calcium oxide, and titanium tetrachloride. After an inhalational exposure, decontamination involves moving the patient to fresh air and administering supplemental oxygen if indicated.

Gastrointestinal (GI) decontamination strategies are most likely to be effective in the 1-2 hours after an acute ingestion. GI absorption may be delayed after ingestion of agents that slow GI motility (anticholinergic medications, opioids), massive amounts of pills, sustained-release (SR) preparations, and agents that can form pharmacologic bezoars (e.g., enteric-coated salicylates). GI decontamination more than 2 hours after ingestion may be considered in patients who ingest toxic substances with these properties. However, even rapid institution of GI decontamination with activated charcoal will bind only approximately 30% of the ingested substance. GI decontamination should never supplant excellent supportive care and should not be employed in an unstable or persistently vomiting patient. Methods of GI decontamination include induced emesis with ipecac, gastric lavage, cathartics, activated charcoal, and whole-bowel irrigation (WBI). *Of these, only activated charcoal and WBI are of potential benefit.*

Table 94.8 Common Antidotes for Poisoning

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Acetaminophen	*N*-Acetylcysteine (Mucomyst)	140 mg/kg loading, followed by 70 mg/kg q4h for 17 additional doses (total of 72 hr)	PO	Vomiting (patient-tailored regimens are the norm)
	N-Acetylcysteine (Acetadote)	150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by 100 mg/kg over 16 hr	IV	Anaphylactoid reactions (most commonly seen with loading dose) Higher doses of the infusion are often recommended depending on acetaminophen level or degree of injury
Anticholinergics	Physostigmine	0.02 mg/kg over 5 min; may repeat q5-10 min to 2 mg max	IV/IM	Bradycardia, seizures, bronchospasm *Note:* Relatively contraindicated if conduction delays on ECG.
Benzodiazepines	Flumazenil	0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max	IV	Agitation, seizures from precipitated withdrawal (doses over 1 mg) **Relatively contraindicated for unknown or polypharmacy ingestions**
β Blockers	Glucagon	0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr	IV	Vomiting, relative lack of efficacy
Calcium channel blockers	Insulin	1 unit/kg bolus followed by infusion of 1-10 units/kg/hr	IV	Hypoglycemia Follow serum potassium and glucose closely.
	Calcium salts	Dose depends on the specific calcium salt	IV	
Carbon monoxide	Oxygen	100% FIO_2 by non-rebreather mask (or ETT if intubated)	Inhalation	Some patients may benefit from hyperbaric oxygen (see text).
Cyanide	Hydroxocobalamin (Cyanokit)	70 mg/kg (adults: 5 g) given over 15 min	IV	Flushing/erythema, nausea, rash, chromaturia, hypertension, headache
Digitalis	Digoxin-specific Fab antibodies (Digibind, DigiFab)	1 vial binds 0.6 mg of digitalis glycoside; #vials = digitalis level × weight in kg/100	IV	Allergic reactions (rare), return of condition being treated with digitalis glycoside
Ethylene glycol, methanol	Fomepizole	15 mg/kg load; 10 mg/kg q12h × 4 doses; 15 mg/kg q12h until ethylene glycol level is <20 mg/dL	IV	Infuse slowly over 30 min If fomepizole is not available, can treat with oral ethanol (80 proof)
Iron	Deferoxamine	Infusion of 15 mg/kg/hr (max: 6 g/24 hr)	IV	Hypotension (minimized by titrating dose up slowly)
Isoniazid (INH)	Pyridoxine	Empirical dosing: 70 mg/kg (max dose = 5 g) If ingested dose is known: 1 g per gram of INH	IV	May also be used for *Gyromitra* mushroom ingestions
Lead and other heavy metals (e.g., arsenic, inorganic mercury)	BAL (dimercaprol)	3-5 mg/kg/dose q4h, for the first day; subsequent dosing depends on the toxin	Deep IM	Local injection site pain and sterile abscess, vomiting, fever, salivation, nephrotoxicity *Caution:* Prepared in peanut oil; contraindicated in patients with peanut allergy
	Calcium disodium EDTA	35-50 mg/kg/day × 5 days; may be given as a continuous infusion or 2 divided doses/day	IV	Vomiting, fever, hypertension, arthralgias, allergic reactions, local inflammation, nephrotoxicity (maintain adequate hydration; follow UA and renal function)
	Dimercaptosuccinic acid (succimer, DMSA, Chemet)	10 mg/kg/dose q8h × 5 days, then 10 mg/kg q12h × 14 days	PO	Vomiting, hepatic transaminase elevation, rash
Methemoglobinemia	Methylene blue, 1% solution	0.1-0.2 mL/kg (1-2 mg/kg) over 5-10 min; may be repeated q30-60 min	IV	Vomiting, headache, dizziness, blue discoloration of urine
Opioids	Naloxone	1 mg if patient not likely to be addicted 0.04-0.4 mg if possibly addicted; repeated as needed; may need continuous infusion; higher and prolonged dosing is required for novel potent opioid overdose	IV, intranasal, IO, IM, nebulized	Acute withdrawal symptoms if given to addicted patients May also be useful for clonidine ingestions (typically at higher doses)

Table 94.8 Common Antidotes for Poisoning—cont'd

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Organophosphates	Atropine	0.05-0.1 mg/kg repeated q5-10 min as needed	IV/ET	Tachycardia, dry mouth, blurred vision, urinary retention
	Pralidoxime (2-PAM)	25-50 mg/kg over 5-10 min (max: 200 mg/min); can be repeated after 1-2 hr, then q10-12h as needed	IV/IM	Nausea, dizziness, headache, tachycardia, muscle rigidity, bronchospasm (rapid administration)
Salicylates	Sodium bicarbonate	Bolus 1-2 mEq/kg followed by continuous infusion	IV	Follow potassium closely and replace as necessary. Goal urine pH: 7.5-8.0
Sulfonylureas	Octreotide and dextrose	1-2 µg/kg/dose (adults 50-100 µg) q6-8h	IV/SC	
Tricyclic antidepressants	Sodium bicarbonate	Bolus 1-2 mEq/kg; repeated bolus dosing as needed to keep QRS <110 msec	IV	Indications: QRS widening (≥110 msec), hemodynamic instability; follow potassium.

BAL, British antilewisite; DMSA, dimercaptosuccinic acid; ECG, electrocardiogram; F_{IO_2}, fraction of inspired oxygen; EDTA, ethylenediaminetetraacetic acid; ET, endotracheal tube; IO, intraosseous; max, maximum; UA, urinalysis.

Table 94.9 Other Antidotes

ANTIDOTES	TOXIN OR POISON
Latrodectus antivenin	Black widow spider
Botulinum antitoxin	Botulinum toxin
Diphenhydramine and/or benztropine	Dystonic reactions
Calcium salts	Fluoride, calcium channel blockers
Intravenous lipid emulsion (ILE)	Local anesthetics; consider for bupropion, calcium channel blockers, β blockers, and type I antidysrhythmics
Protamine	Heparin
Folinic acid	Methotrexate, trimethoprim, pyrimethamine, methanol
Crotalidae-specific Fab antibodies	Rattlesnake envenomation
Sodium bicarbonate	Sodium channel blockade (tricyclic antidepressants, type 1 antiarrhythmics)

Table 94.10 Toxins Associated with Systemic Toxicity After Dermal Absorption

Aniline dyes
Camphor
Dinitrophenol
Hexachlorophene
Hydrofluoric acid
Lindane (γ-benzene hydrochloride)
Organophosphate insecticide
Nerve agents
Nitrobenzene
Organic mercury
Phenol
Thallium

From Shannon MW. Emergency management of poisoning. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: Saunders; 2007, Box 2A-12, p. 28.

Syrup of Ipecac

Syrup of ipecac contains two emetic alkaloids that work in both the central nervous system (CNS) and locally in the GI tract to produce vomiting. Many studies have failed to document a significant clinical impact from the use of ipecac and have documented multiple adverse events from its use. The AAP, the American Academy of Clinical Toxicology (AACT), and the AAPCC have all published statements in favor of *abandoning the use of ipecac.*

Gastric Lavage

Gastric lavage involves placing a large tube orally into the stomach to aspirate contents, followed by flushing with aliquots of fluid, usually water or NS. Although gastric lavage was used routinely for many years, objective data do not document or support clinically relevant efficacy. This is particularly true in children, in whom only small-bore tubes can be used. Lavage is time-consuming and painful and can induce bradycardia through a vagal response to tube placement. It can delay administration of more definitive treatment (activated charcoal) and under the best circumstances, only removes a fraction of gastric contents. *Thus, in most clinical scenarios, the use of gastric lavage is no longer recommended.*

Single-Dose Activated Charcoal

Activated charcoal is a potentially useful method of GI decontamination. Charcoal is "activated" by heating to extreme temperatures, creating an extensive network of pores that provides a very large adsorptive surface area that many (but not all) toxins will bind to, preventing absorption from the GI tract. Charged molecules (i.e., heavy metals, lithium, iron) and liquids do not bind well to activated charcoal (Table 94.11). Administration should also be avoided after ingestion of a caustic substance, as it can impede subsequent endoscopic evaluation. *Charcoal is most likely to be effective when given within 1 hour of ingestion.* A repeat dose of activated charcoal may be warranted in the cases of ingestion of an extended-release product or, more frequently, with significant salicylate poisoning as a result of its delayed and erratic absorption pattern.

The dose of activated charcoal, with or without sorbitol, is 1g/kg in children or 50-100 g in adolescents and adults. Before administering charcoal, one *must* ensure that the patient's airway is intact or protected and that the patient has a benign abdominal examination. In the awake, uncooperative adolescent or child who refuses to drink the activated charcoal, there is little utility and potential morbidity associated

Table 94.11	Substances Poorly Adsorbed by Activated Charcoal

Alcohols
Caustics: alkalis and acids
Cyanide
Heavy metals (e.g., lead)
Hydrocarbons
Iron
Lithium

with forcing activated charcoal down a nasogastric (NG) tube, and such practice should be avoided. In young children, practitioners can attempt to improve palatability by adding flavorings (chocolate or cherry syrup) or giving the mixture over ice cream. Approximately 20% of children vomit after receiving a dose of charcoal, emphasizing the importance of an intact airway and avoiding administration of charcoal after ingestion of substances that are particularly toxic when aspirated (e.g., hydrocarbons). If charcoal is given through a gastric tube in an intubated patient, placement of the tube should be confirmed before activated charcoal is given. Instillation of charcoal directly into the lungs can have disastrous effects. Constipation is another common side effect of activated charcoal, and in rare cases, bowel perforation has been reported.

Cathartics (sorbitol, magnesium sulfate, magnesium citrate) have been used in conjunction with activated charcoal to prevent constipation and accelerate evacuation of the charcoal-toxin complex. There are no data demonstrating their value and numerous reports of adverse effects from cathartics, such as dehydration and electrolyte imbalance.

Whole-Bowel Irrigation

WBI involves instilling large volumes (25 mL/kg/hr in children or 1-2 L/hr in adolescents) of a polyethylene glycol electrolyte solution (e.g., GoLYTELY) to "wash out" the entire GI tract. This technique may have some success for the ingestion of SR preparations, substances not well adsorbed by charcoal (e.g., lithium, iron), transdermal patches, foreign bodies, and drug packets. WBI is most frequently administered to decontaminate the gut of a child whose abdominal radiograph demonstrates multiple lead paint chips. Careful attention should be paid to assessment of the airway and abdominal exam before initiating WBI. WBI should never be given to a patient with signs of obstruction or ileus or with a compromised airway. Given the rate of administration and volume needed to flush the system, WBI is typically administered by NG tube. WBI is continued until the rectal effluent is clear. If the WBI is for a child with ingested paint chips, the end-point will be clearing of the chips from the bowel based on repeat radiographs. Complications of WBI include vomiting, abdominal pain, and abdominal distention. Bezoar formation might respond to WBI but may also require endoscopy or surgery.

Directed Therapy

Antidotal Therapy

Antidotes are available for relatively few toxins (see Tables 94.8 and 94.9), but early and appropriate use of an antidote is a key element in managing the poisoned patient.

Intravenous Lipid Emulsion Therapy

Intravenous lipid emulsion (ILE) therapy is a potentially lifesaving intervention. ILE therapy sequesters fat-soluble drugs, decreasing their impact at target organs; this is known as a "lipid sink." It also enhances cardiac function by supplying an alternative energy source to a depressed myocardium and acting on calcium channels in the heart, increasing myocardial calcium and thus cardiac function. ILE is most effective as a reversal agent for toxicity from inadvertent intravenous (IV) injection of bupivacaine. Using the same 20% lipid solution used for total parenteral nutrition (TPN), a bolus dose of 1.5 mL/kg is given over 3 minutes, followed by an infusion of 0.25 mL/kg/min until recovery or until a total of 10 mL/kg has been infused. *Lipophilic drugs,* those in which the logarithm of the coefficient describing the partition between two solvents (hydrophobic phase and hydrophilic phase) is >2, have the most potential to be bound by ILE. These include but are not limited to CCBs (verapamil, diltiazem), bupropion, tricyclic antidepressants, and refractory β-blocker overdose. Complications associated with ILE include significant lipemia that interferes with serum laboratory tests, pancreatitis, and acute respiratory distress syndrome (ARDS).

Enhanced Elimination

Enhancing elimination results in increased clearance of a poison that has already been absorbed. It is only useful for a few toxins and in these cases is a potentially lifesaving intervention. Methods of enhanced elimination include urinary alkalinization, hemodialysis, and multidose activated charcoal.

Urinary Alkalinization

Urinary alkalinization enhances the elimination of drugs that are weak acids by forming charged molecules, which then become trapped in the renal tubules. Charged molecules, being polar and hydrophilic, do not easily cross cellular membranes; thus they remain in the renal tubules and are excreted. Urinary alkalinization is accomplished by a continuous infusion of sodium bicarbonate–containing IV fluids, with a goal urine pH of 7.5-8. Alkalinization of the urine is most useful in managing salicylate and methotrexate toxicity. Complications of urinary alkalinization include electrolyte derangements (e.g., hypokalemia, hypocalcemia), fluid overload, and excessive serum alkalinization. Serum pH should be closely monitored and not exceed a pH >7.55. Patients typically unable to tolerate the volumes required for alkalinization are those with heart failure, kidney failure, pulmonary edema, or cerebral edema.

Hemodialysis

Few drugs or toxins are removed by dialysis in amounts sufficient to justify the risks and difficulty of dialysis. Toxins amenable to dialysis have the following properties: low volume of distribution (<1 L/kg) with a high degree of water solubility, low molecular weight, and low degree of protein binding. Hemodialysis may be useful for toxicity from methanol, ethylene glycol, salicylates, theophylline, bromide, lithium, and valproic acid. Hemodialysis is also used to correct severe electrolyte disturbances and acid-base derangements resulting from the ingestion (e.g., severe metformin-associated lactic acidosis).

Multidose Activated Charcoal

Whereas single-dose activated charcoal is used as a method of decontamination, multidose activated charcoal (**MDAC**) can help to enhance the elimination of certain toxins. MDAC is typically given as 0.5 g/kg every 4-6 hr (for four doses). MDAC enhances elimination by two proposed mechanisms: interruption of enterohepatic recirculation and "GI dialysis." The concept of GI dialysis involves using the intestinal mucosa as a dialysis membrane and pulling toxins from the bloodstream back into the intraluminal space, where they are adsorbed to the charcoal. The AACT/European Association of Poisons Centres and Clinical Toxicologists position statement recommends MDAC in managing significant ingestions of carbamazepine, dapsone, phenobarbital, quinine, and theophylline. As with single-dose activated charcoal, contraindications to the use of MDAC include an unprotected airway and a concerning abdominal examination (e.g., ileus, distention, peritoneal signs). Thus the airway and abdominal exam *should be assessed before each dose.* A cathartic (e.g., sorbitol) may be given with the first dose, but it should not be used with subsequent doses because of the risk of dehydration and electrolyte derangements. Although MDAC reduces the serum level of an intoxicant quicker than without MDAC, it has not been shown to have a significant impact on outcome.

SELECT COMPOUNDS IN PEDIATRIC POISONING

See other chapters for drug use (Chapter 157) and environmental health hazards (Chapters 757-763).

Pharmaceuticals

Analgesics

Acetaminophen. Acetaminophen (APAP) is the most widely used analgesic and antipyretic in pediatrics, available in multiple formulations, strengths, and combinations. Consequently, APAP is commonly available in the home, where it can be unintentionally ingested by young children, taken in an intentional overdose by adolescents and adults, or inappropriately dosed in all ages. In the United States, APAP toxicity remains the most common cause of acute liver failure and one of the leading causes of death from oral poisonings.

Pathophysiology. APAP toxicity results from the formation of a highly reactive intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). In therapeutic use, only a small percentage of a dose (approximately 5%) is metabolized by the hepatic cytochrome P450 enzyme CYP2E1 to NAPQI, which is then immediately conjugated with glutathione to form a nontoxic mercapturic acid conjugate. In overdose, glutathione stores are overwhelmed, and free NAPQI is able to combine with hepatic macromolecules to produce hepatocellular necrosis. The single acute toxic dose of APAP is generally considered to be >200 mg/kg in children and >7.5-10 g in adolescents and adults. Repeated administration of APAP at supratherapeutic doses (>90 mg/kg/day for consecutive days) can lead to hepatic injury or failure in some children, especially in the setting of fever, dehydration, poor nutrition, and other conditions that serve to reduce glutathione stores.

Any child with a history of acute ingestion of >200 mg/kg (unusual in children <6 years) or with an acute intentional ingestion of any amount should be referred to a healthcare facility for clinical assessment and measurement of a serum APAP level.

Clinical and Laboratory Manifestations. Classically, four general stages of APAP toxicity have been described (Table 94.12). In the first 24 hours after ingestion, patients are most frequently asymptomatic, although they may have nonspecific symptoms such as nausea/vomiting. Thus the diagnosis of APAP toxicity cannot be based on clinical symptoms alone, but instead requires consideration of the combination of the patient's history, symptoms, and laboratory findings.

If a toxic ingestion is suspected, a serum APAP level should be measured 4 hours after the reported time of ingestion. For patients who present to medical care more than 4 hours after ingestion, a stat APAP level should be obtained. *APAP levels obtained <4 hours after ingestion, unless "nondetectable," are difficult to interpret and cannot be used to estimate the potential for toxicity.* Other important baseline laboratory tests include hepatic transaminases, bilirubin, renal function tests, and coagulation parameters.

Table 94.12 Classic Stages in Clinical Course of Acetaminophen Toxicity

STAGE	TIME AFTER INGESTION	CHARACTERISTICS
I	0-24 hr	Anorexia, vomiting, malaise Laboratory tests typically normal, except for acetaminophen level
II	24-48 hr	Resolution of earlier symptoms; right upper quadrant abdominal pain and tenderness; elevated hepatic transaminases (aspartate > alanine), INR
III	3-5 days	Peak transaminase elevations; development of liver failure, multiorgan system failure, death *or* recovery begins
IV	4 days to 2 wk	Resolution of liver function abnormalities Clinical recovery precedes histologic recovery

Treatment. When considering the treatment of a patient poisoned or potentially poisoned with APAP, and after assessment of the ABCs, it is helpful to place the patient into one of the following four categories:

1. Prophylactic. These patients have a normal AST. If the APAP level is known and the ingestion is within 24 hours of the level being drawn, treatment decisions are based on where the level falls on the Rumack-Matthew nomogram (Fig. 94.1). Any patient with a serum APAP level in the possible or probable hepatotoxicity range per the nomogram should be treated with *N*-acetylcysteine (NAC). This nomogram is only intended for use in patients who present within 24 hours of a single *acute* APAP ingestion with a known time of ingestion. If treatment is recommended, they should receive NAC. Food and Drug Administration (FDA)–approved treatment regimens include a 21-hour protocol for IV administration and a 72-hour protocol for oral administration. Several shorter dosing regimens have been described and may be considered in consultation with a toxicologist. Regardless of treatment duration, serial transaminases and APAP level should be monitored. If the AST becomes elevated while receiving NAC, the patient moves into the next category of treatment (hepatic injury, see later). If AST remains normal but APAP is still present, NAC should be continued until the level is nondetectable. In the case of a patient with a documented APAP level, normal AST, and an unknown time of ingestion, treatment should ensue until the level is undetectable, with normal transaminases.

The importance of instituting therapy with either IV or oral NAC *no later than 8 hours from the time of ingestion* cannot be overemphasized.

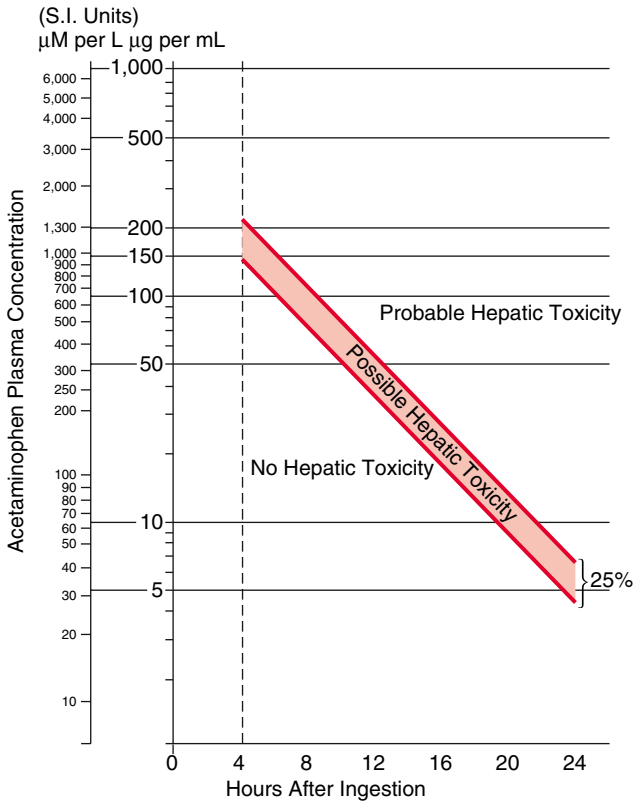

Fig. 94.1 Rumack-Matthew nomogram for acetaminophen poisoning, a semilogarithmic plot of plasma acetaminophen concentrations vs time. *Cautions for the use of this chart:* The time coordinates refer to time after ingestion; serum concentrations obtained before 4 hours are not interpretable, and the graph should be used only in relation to a single acute ingestion with a known time of ingestion. This nomogram is not useful for chronic exposures or unknown time of ingestion and should be used with caution in the setting of co-ingestants that slow gastrointestinal motility. The *lower solid line* is typically used in the United States to define toxicity and direct treatment, whereas the *upper line* is generally used in Europe. *(From Rumack BH, Hess AJ, eds.* Poisindex, *Denver: Micromedix; 1995. Adapted from Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics.1975;55:871–876.)*

No patient, regardless of the size of the ingestion, who receives NAC within 8 hours of overdose should die from liver failure. The longer from the 8 hour-mark that the initiation of therapy is delayed, the greater the risk of acute liver failure. Any patient presenting close to or beyond the 8-hour mark after an APAP overdose should be empirically started on NAC pending laboratory results.

2. Hepatic Injury. These patients exhibit evidence of hepatocellular necrosis, manifested first as elevated liver transaminases (usually AST first, then ALT), followed by a rise in the INR. Any patient in this category requires therapy with NAC (IV or oral). When to discontinue therapy in the clinically well-appearing patient remains controversial, but in general NAC can be discontinued when the transaminases and INR have peaked and are declining significantly (they do not need to be normal). Most patients' liver enzymes will peak 3-4 days after their ingestion.

3. Acute Liver Failure. The King's College criteria are used to determine which patients should be referred for consideration of liver transplant. These criteria are met when a patient exhibits either acidemia (serum pH <7.3) after adequate fluid resuscitation or all three of the following: coagulopathy (INR >6.5), renal dysfunction (creatinine >3.4 mg/dL), and grade III or IV hepatic encephalopathy (see Chapter 412). A serum lactic acid >3 mmol/L (after IV fluids) adds to both sensitivity and specificity of the criteria to predict death without liver transplant. The degree of transaminase elevation does not factor into this decision-making process.

4. Repeated Supratherapeutic Ingestion. APAP is particularly prone to unintentional overdose through the ingestion of multiple medications containing the drug or simply because people assume it to be safe at any dose. Ingestion of amounts significantly greater than the recommended daily dose for several days or more puts one at risk for liver injury. Because the Rumack-Matthew nomogram is not helpful in this scenario, a conservative approach is taken. In the asymptomatic patient, if the AST is normal and the APAP is <10 μg/mL, no therapy is indicated. A normal AST and an elevated APAP warrant NAC dosing for at least long enough for the drug to metabolize while the AST remains normal. An elevated AST puts the patient in the "hepatic injury" category previously described. A patient presenting with symptoms (i.e., right upper quadrant pain, vomiting, jaundice) should be empirically started on NAC pending laboratory results.

NAC is available in oral and IV forms, and both are considered equally efficacious (see Table 94.8 for the dosing regimens of the oral and IV form). The IV form is used in patients with intractable vomiting, those with evidence of hepatic failure, and pregnant patients. Oral NAC has an unpleasant taste and smell and can be mixed in a soft drink or fruit juice or given by NG tube to improve tolerability of the oral regimen. Administration of IV NAC (as a standard 3% solution to avoid administering excess free water, typically in 5% dextrose), especially the initial loading dose, is associated in some patients with the development of anaphylactoid reactions (non–immunoglobulin E mediated). These reactions are typically managed by stopping the infusion; treating with diphenhydramine, albuterol, and/or epinephrine as indicated; and restarting the infusion at a slower rate once symptoms have resolved. IV NAC is also associated with mild elevation in measured INR (range: 1.2-1.5) because of laboratory interference. IV dosing, however, delivers less medication to the liver compared with the oral regimen. As a result, many toxicologists now recommend higher doses of the IV formulation in patients with large overdoses. Transaminases, synthetic function, and renal function should be followed at least daily while the patient is being treated with NAC. Patients with worsening hepatic function or clinical status might benefit from more frequent laboratory monitoring. A patient-tailored approach is now the norm for when to stop NAC therapy, for deciding whom to refer for transplantation evaluation, and often for the dose of IV NAC in patients with either very high APAP levels or signs of injury. Consultation with the regional PCC and medical toxicologist can help streamline the care of these patients, ultimately shortening their length of stay with potentially improved outcomes.

Adjunctive Therapies

Although activated charcoal binds acetaminophen, risks of vomiting associated with large APAP overdoses as well as the likelihood of co-ingestion that may affect mental status must be considered. Activated charcoal may be considered in the first 1-2 hours after ingestion in an alert patient, but its use should not have bearing on the need for NAC. Similarly, hemodialysis is not routinely used in APAP overdose but may be indicated in massive ingestions in consultation with a toxicologist.

Salicylates. The incidence of salicylate poisoning in young children has declined dramatically since APAP and ibuprofen replaced aspirin as commonly used analgesics and antipyretics in pediatrics. However, salicylates remain widely available not only in aspirin-containing products but also in antidiarrheal medications, topical agents (e.g., keratolytics, sports creams), oil of wintergreen, and some herbal products. Oil of wintergreen contains 5 g of salicylate in 5 mL, meaning ingestion of very small volumes of this product has the potential to cause severe toxicity.

Pathophysiology. Salicylates lead to toxicity by interacting with a wide array of physiologic processes, including direct stimulation of the respiratory center, uncoupling of oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, and stimulation of glycolysis and gluconeogenesis. The acute toxic dose of salicylates is generally considered to be >150 mg/kg. More significant toxicity is seen after ingestions of >300 mg/kg, and severe, potentially fatal, toxicity is described after ingestions of >500 mg/kg.

Clinical and Laboratory Manifestations. Salicylate ingestions are classified as acute or chronic, and acute toxicity is much more common in pediatric patients. Early signs of **acute salicylism** include nausea, vomiting, diaphoresis, and tinnitus. Moderate salicylate toxicity can manifest as tachypnea and hyperpnea, tachycardia, and altered mental status. The tachycardia largely results from marked insensible losses from vomiting, tachypnea, diaphoresis, and uncoupling of oxidative phosphorylation. Thus careful attention should be paid to volume status and early volume resuscitation in the significantly poisoned patient. Signs of severe salicylate toxicity include mild hyperthermia, coma, and seizures. **Chronic salicylism** can have a more insidious presentation, and patients can show marked toxicity (e.g., altered mental status, noncardiogenic pulmonary edema, acidemia) at significantly lower salicylate levels than in acute toxicity.

Classically, laboratory values from a patient poisoned with salicylates reveal a primary respiratory alkalosis and a primary, elevated anion gap metabolic acidosis. Early in the course of acute salicylism, respiratory alkalosis dominates and the patient is alkalemic. As the respiratory stimulation diminishes, the patient will move toward acidemia. Hyperglycemia (early) and hypoglycemia (late) have been described. Abnormal coagulation studies and acute kidney injury may be seen but are not common.

Serial serum salicylate levels should be closely monitored (every 2-4 hours initially) until they are consistently downtrending (three consecutive levels <30 mg/dL and decreasing by at least 10–20% on each subsequent measurement). Salicylate absorption in overdose is unpredictable and erratic, especially with an enteric-coated product, and levels can rapidly increase into the highly toxic range, even many hours after the ingestion. The Done nomogram is of poor value and should not be used. Serum and urine pH and electrolytes should be followed closely. An APAP level should be checked in any patient who intentionally overdoses on salicylates, because APAP is a common co-ingestant, and people often confuse or combine their nonprescription analgesic medications. Salicylate toxicity can cause a noncardiogenic pulmonary edema, especially in chronic overdose; consequently, a chest radiograph is recommended in any patient in respiratory distress.

Treatment. For the patient who presents soon after an acute ingestion, initial treatment should include gastric decontamination with activated charcoal. Salicylate pills occasionally form bezoars, which should be suspected if serum salicylate concentrations continue to rise many hours after ingestion or are persistently elevated despite appropriate management. Gastric decontamination is typically not useful after chronic exposure.

Initial therapy focuses on aggressive volume resuscitation and prompt initiation of sodium bicarbonate therapy in the symptomatic patient, even before obtaining serum salicylate levels. Therapeutic salicylate levels are 10-20 mg/dL, and levels >30 mg/dL warrant treatment.

The primary mode of therapy for salicylate toxicity is **urinary alkalinization**. Urinary alkalinization enhances the elimination of salicylates by converting salicylate to its ionized form, "trapping" it in the renal tubules. In addition, maintaining an alkalemic serum pH decreases CNS penetration of salicylates because charged particles are less able to cross the blood-brain barrier. Alkalinization is achieved by administration of a sodium bicarbonate infusion at approximately two times maintenance fluid rates. *The goals of therapy include a urine pH of 7.5-8, a serum pH of 7.45-7.55, and decreasing serum salicylate levels.* In general, the lower the patient's serum pH, the greater the relative amount of salicylate in the uncharged, nonpolar form and the greater amount of salicylate penetration of the blood-brain barrier. Salicylate penetration of the brain leads to severe consequences such as cerebral edema; therefore maintaining alkalemia is imperative. Careful attention should also be paid to serial potassium levels in any patient on a bicarbonate infusion, because potassium will be driven intracellularly, and hypokalemia impairs alkalinization of the urine. For these reasons, potassium is often added to the bicarbonate drip. Repeat doses of charcoal may be beneficial because of the often delayed and erratic absorption of aspirin. Parenteral glucose should be provided to any salicylate-poisoned patients with altered mental status because they may have CNS hypoglycemia (i.e., neuroglycopenia) not seen in a peripheral serum glucose test.

In patients with severe toxicity, hemodialysis may be required. Indications for dialysis include severe acid-base abnormalities (specifically severe acidosis and acidemia), a rising salicylate level (despite adequate decontamination and properly alkalinized urine), pulmonary edema or respiratory failure, cerebral edema, seizures, hepatic failure, and renal failure. Serum salicylate concentrations alone are not a clear indicator of the need for dialysis and should always be interpreted along with the clinical status of the patient.

Ibuprofen and Other Nonsteroidal Antiinflammatory Drugs (NSAIDs). Ibuprofen and other NSAIDs are often involved in unintentional and intentional overdoses because of their widespread availability and common use as analgesics and antipyretics. Fortunately, serious effects after acute NSAID overdose are rare because of their wide therapeutic index.

Pathophysiology. NSAIDs inhibit prostaglandin synthesis by reversibly inhibiting the activity of cyclooxygenase (COX), the primary enzyme responsible for the biosynthesis of prostaglandins. In therapeutic use, side effects include GI irritation, reduced renal blood flow, and platelet dysfunction. To minimize these side effects, NSAID analogs have been developed that are more specific for the inducible form of COX (the COX-2 isoform) than the constitutive form (COX-1). However, overdose of the more selective COX-2 inhibitors (e.g., celecoxib [Celebrex]) is treated the same as overdose of nonspecific COX inhibitors (e.g., ibuprofen) because at higher doses, COX-2–selective agents lose their COX inhibitory selectivity.

Ibuprofen, the primary NSAID used in pediatrics, is well tolerated, even in overdose. In children, acute doses of <200 mg/kg rarely cause toxicity, but ingestions of >400 mg/kg can produce more serious effects, including altered mental status and metabolic acidosis.

Clinical and Laboratory Manifestations. Symptoms usually develop within 4-6 hours of ingestion and resolve within 24 hours. If toxicity does develop, it is typically manifested as nausea, vomiting, and abdominal pain. Although GI bleeding and ulcers have been described with chronic use, they are rare in the setting of acute ingestion. After massive ingestions, patients can develop marked CNS depression, anion gap metabolic acidosis, renal insufficiency, and (rarely) respiratory depression. Seizures have also been described, especially after overdose of mefenamic acid. Specific drug levels are not readily available, nor do they inform management decisions. Renal function studies, acid-base balance, complete blood count (CBC), and coagulation parameters should be monitored after very large ingestions. Co-ingestants, especially APAP, should be ruled out after any intentional ingestion.

Treatment. Supportive care, including use of antiemetics and acid blockade as indicated, is the primary therapy for NSAID toxicity. Decontamination with activated charcoal should be considered if a patient presents within 1-2 hours of a potentially toxic ingestion. There is no specific antidote for this class of drugs. Given the high degree of protein binding and excretion pattern of NSAIDs, none of the modalities used to enhance elimination is particularly useful in managing these overdoses. Unlike in patients with salicylate toxicity, urinary alkalinization is not helpful for NSAID toxicity. Patients who develop significant clinical signs of toxicity should be admitted to the hospital for ongoing supportive care and monitoring. Patients who remain asymptomatic for 4-6 hours after ingestion do not require further medical care but may need psychiatric assessment if their ingestion was intentional.

Prescription Opioids. Opioids are a frequently abused class of medications in both IV and oral forms. The opioid epidemic gripping the United States and other countries is discussed in Chapter 157. Two specific oral opioids, buprenorphine and methadone, merit mention because of potential life-threatening toxicity in toddlers with ingestion of even one pill. Both agents are used in managing opioid use disorder, although **buprenorphine** is the drug of choice. **Methadone** is also widely used in the treatment of chronic pain, meaning multiday prescriptions can be filled. Other agents commonly available in the home include morphine, oxycodone, and hydrocodone, as they are frequently prescribed to patients after injuries or surgical procedures. All of these drugs are also readily available for illicit purchase and potential abuse. Opioids are of great potential toxicity to small children if not dosed appropriately, especially buprenorphine because of its long half-life and high potency.

Pathophysiology. Opioids are well absorbed via multiple routes, including the GI tract, which is the most common route of accidental overdose in young children. At therapeutic dosing, opioids are typically absorbed within a few hours, but absorption may be slowed and symptoms prolonged in overdose. Individual opioids cross the blood-brain barrier to varying degrees. Opioids all undergo hepatic metabolism with renal excretion.

Methadone is a lipophilic synthetic opioid with potent agonist effects at μ-opioid receptors, leading to both its desired analgesic effects and undesired side effects, including sedation, respiratory depression, and impaired GI motility. Methadone is thought to cause QTc interval prolongation through interactions with the human ether-a-go-go–related gene (hERG)–encoded potassium rectifier channel. Its duration of effect for pain control averages only about 8 hours, whereas the dangerous side effects can occur up to 24 hours from the last dose and longer after overdose. Methadone has an average half-life >25 hours, which may be extended to >50 hours in overdose.

Suboxone is a combination of buprenorphine, a potent opioid with partial agonism at μ-opioid receptors and weak antagonism at κ-opioid receptors, and naloxone. Naloxone has poor oral bioavailability but is included in the formulation to discourage diversion for IV use, during which it can precipitate withdrawal. Suboxone is formulated for buccal or sublingual administration; consequently, toddlers can absorb significant amounts of drug even by sucking on a tablet. Buprenorphine has an average half-life of 37 hours.

Clinical and Laboratory Manifestations. In children, opioid ingestions can manifest with the classic toxidrome of respiratory depression, sedation, and miosis. Signs of more severe toxicity can include bradycardia, hypotension, and hypothermia. Many opioids have clinical features that are unique to their chemical structure (Table 94.13). Even in therapeutic use, methadone is associated with a prolonged QTc interval and risk of torsades de pointes. Accordingly, an ECG should be part of the initial evaluation after ingestion of methadone or any unknown opioid. Many prescription opioids, including methadone and buprenorphine, are not detected on routine urine opiate screens, although some centers have added a separate urine methadone screen. Levels of many drugs can be measured, although this is rarely done clinically and is seldom helpful in the acute setting. An exception may be in the cases involving concerns about neglect or abuse, at which point urine for gas chromatography/mass spectroscopy, the legal gold standard, should be sent to confirm and document the presence of the drug.

Treatment. Patients with significant respiratory depression or CNS depression should be treated with the opioid antidote **naloxone**

Table 94.13 Clinical Properties of Select Prescription Opioids

CLINICAL EFFECT	OPIOID
QRS widening, sodium channel blockade	Propoxyphene
QT widening, potassium channel blockade	Methadone
Seizures	Propoxyphene, meperidine
Serotonin syndrome	Meperidine, methadone, tramadol
Hearing loss, ototoxicity	Methadone, hydrocodone

Modified from Nikolaides JK, Thompson TM. Opioids. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. *Rosen's Emergency Medicine*, 9th ed. Philadelphia: Elsevier; 2018, Table 156.2, p. 1944.

(see Table 94.8). In pediatric patients who are not chronically taking opioids, the full reversal dose of 1-2 mg should be used. In contrast, opioid-dependent patients should be treated with smaller initial doses (0.04-0.4 mg), which can then be repeated as needed to achieve the desired clinical response, avoiding abrupt induction of withdrawal. Because the half-life of many opioids is much longer than that of naloxone, patients can require multiple doses of naloxone. These patients may benefit from a continuous infusion of naloxone, typically started at two thirds of the reversal dose per hour and titrated to maintain an adequate respiratory rate and level of consciousness. Patients who have ingested methadone should be placed on a cardiac monitor and have serial ECGs to monitor for the development of a prolonged QTc interval. If a patient does develop a prolonged QTc, management includes close cardiac monitoring, repletion of electrolytes (potassium, calcium, and magnesium), and having a defibrillator readily available should the patient develop torsades de pointes.

Given the potential for clinically significant and prolonged toxicity, any toddler who has ingested methadone, even if asymptomatic, should be admitted to the hospital for at least 24 hours of monitoring. Duration of observation after ingestion of other opioids depends on the half-life and dose of the agent ingested. All such cases should be discussed with a PCC or medical toxicologist before determining disposition.

Cardiovascular Medications

β-Adrenergic Receptor Blockers. β Blockers competitively inhibit the action of catecholamines at the β-adrenergic receptor. Therapeutically, β blockers are used for a variety of conditions, including hypertension, coronary artery disease, tachydysrhythmias, anxiety disorders, migraines, essential tremor, and hyperthyroidism. Because of its lipophilicity and blockade of fast sodium channels, **propranolol** is considered to be the most toxic member of the β-blocker class. Overdoses of water-soluble β blockers (e.g., atenolol) are associated with milder symptoms.

Pathophysiology. In overdose, β blockers decrease chronotropy and inotropy in addition to slowing conduction through atrioventricular (AV) nodal tissue. Clinically, these effects are manifested as bradycardia, hypotension, and heart block. Patients with reactive airway disease can experience bronchospasm as a result of blockade of β_2-mediated bronchodilation. β_2 Blockers interfere with glycogenolysis and gluconeogenesis, which can sometimes lead to hypoglycemia, especially in patients with poor glycogen stores (e.g., toddlers).

Clinical and Laboratory Manifestations. Toxicity typically develops within 6 hours of ingestion, although it may be delayed after ingestion of sotalol or SR preparations. The most common features of severe poisoning are bradycardia and hypotension. Lipophilic agents, including propranolol, can enter the CNS and cause altered mental status, coma, and seizures. Overdose of β blockers with sodium channel–blocking properties (e.g., propranolol) can cause QRS interval widening and ventricular dysrhythmias.

Evaluation after β-blocker overdose should include an ECG, frequent reassessments of hemodynamic status, and blood glucose. Serum levels of β blockers are not readily available for routine clinical use and are not useful in management of the poisoned patient.

Treatment. In addition to supportive care and GI decontamination as indicated, **glucagon** is theoretically the preferred antidote of choice for β-blocker toxicity (see Table 94.8). Glucagon stimulates adenylate cyclase and increases levels of cyclic adenosine monophosphate (cAMP) independent of the β-receptor. Glucagon is typically given as a bolus and, if this is effective, followed by a continuous infusion. In practice, glucagon is often only marginally effective, limited by its proemetic effects, especially at the high doses typically required. Other useful interventions include calcium, vasopressors, and high-dose insulin. Seizures are managed with benzodiazepines, and QRS widening should be treated with sodium bicarbonate. Lipid emulsion therapy (discussed earlier) may be considered in patients with signs of shock who do not respond to conventional treatments. Children who ingest one or two water-soluble β blockers are unlikely to develop toxicity and can typically be discharged to home if they remain asymptomatic over a 6-hour observation period. Children who ingest SR products, highly lipid-soluble agents, and sotalol require longer periods of observation before safe discharge. Any symptomatic child should be admitted for ongoing monitoring and directed therapy.

Calcium Channel Blockers. CCBs are used for a variety of therapeutic indications and have the potential to cause severe toxicity, even after exploratory ingestions. Specific agents include verapamil, diltiazem, and the dihydropyridines (e.g., amlodipine, nifedipine). Of these, diltiazem and verapamil are the most dangerous in overdose because of their higher lipophilicity and direct cardiac suppressant effects.

Pathophysiology. CCBs antagonize L-type calcium channels, inhibiting calcium influx into myocardial and vascular smooth muscle cells. Verapamil works primarily by slowing inotropy and chronotropy and in therapeutic dosing has no effect on systemic vascular resistance (SVR). Diltiazem has effects both on the heart and the peripheral vasculature. The dihydropyridines exclusively diminish SVR. Verapamil and diltiazem can significantly diminish myocardial contractility and conduction, with diltiazem also lowering SVR. By contrast, dihydropyridines will decrease the SVR, leading to vasodilation and reflex tachycardia, although this receptor selectivity may be lost after a large overdose. Because the same L-type calcium channels blocked by CCBs are also on the pancreatic islet cells, any patient significantly poisoned with a CCB may develop hyperglycemia.

Clinical and Laboratory Manifestations. Overdoses of CCBs lead to hypotension, accompanied by bradycardia, normal heart rate, or even tachycardia, depending on the agent. Other rhythm disturbances, including AV block, bundle branch blocks, QT prolongation, and junctional rhythms, may also be seen. A common feature of CCB overdose is the patient exhibiting profound hypotension with preserved consciousness.

Initial evaluation should include an ECG, continuous and careful hemodynamic monitoring, and rapid measurement of serum glucose levels. Both the absolute degree of hyperglycemia and the percentage increase in serum glucose have been correlated with the severity of CCB toxicity in adults. The development of hyperglycemia can even precede the development of hemodynamic instability. Blood levels of CCBs are not readily available and are not useful in guiding therapy.

Treatment. Once initial supportive care has been instituted, GI decontamination should begin with activated charcoal as appropriate. WBI may be beneficial in a stable patient after ingestion of an SR product. Calcium channel blockade in the smooth muscles of the GI tract can lead to greatly diminished motility; thus any form of GI decontamination should be undertaken with careful attention to serial abdominal exams.

Calcium salts, administered through a peripheral IV line as calcium gluconate or a central line as calcium chloride, help to overcome blocked calcium channels. **High-dose insulin euglycemia therapy** is considered the antidote of choice for CCB toxicity. An initial bolus of 1 unit/kg of regular insulin is followed by an infusion at 1-10 units/kg/hr (see Table 94.8). The main mechanism of high-dose insulin euglycemia

is to improve the metabolic efficiency of a poisoned heart that needs carbohydrates for energy (instead of the usual free fatty acids) but has minimal circulating insulin. Blood glucose and serum potassium levels should be closely monitored, and supplemental dextrose may be necessary to maintain euglycemia. Mild hypokalemia may be tolerated, as this reflects intracellular shifting of potassium rather than whole-body potassium depletion; severe hypokalemia (e.g., K <2.8 mEq/L) is treated with IV potassium supplementation.

Additional therapies include judicious IV fluid boluses and vasopressors (often in very high doses). Cardiac pacing is rarely of value. Lipid emulsion therapy (discussed earlier) is a potentially lifesaving intervention, especially for patients poisoned with the more lipid-soluble CCBs, verapamil and diltiazem. In extreme cases an intraaortic balloon pump or extracorporeal membrane oxygenation (ECMO) are potential treatments. Given the potential for profound and sometimes delayed toxicity in toddlers after ingestion of one or two CCB tablets, hospital admission and 12-24 hours of monitoring for all of these patients is strongly recommended.

α_2-Adrenergic Agonists. Although originally intended for use as antihypertensives, the number of **clonidine** and **guanfacine** prescriptions in the pediatric population has greatly increased because of its reported efficacy in the management of attention-deficit/hyperactivity disorder (ADHD), tic disorders, and other behavioral disorders. With this increased use has come a significant rise in pediatric ingestions and therapeutic misadventures. Clonidine is available in pill and transdermal patch forms, while guanfacine is available in pill form.

Pathophysiology. Clonidine, along with the closely related agent guanfacine, is a centrally acting α_2-adrenergic receptor agonist with a very narrow therapeutic index. Agonism at central α_2 receptors decreases sympathetic outflow, producing lethargy, bradycardia, hypotension, and apnea. Toxicity can develop after ingestion of only one pill or after sucking on or swallowing a discarded transdermal patch. Even a "used" transdermal patch might contain as much as one third to one half the original amount of drug.

Clinical and Laboratory Manifestations. The most common clinical manifestations of toxicity are lethargy, miosis, and bradycardia. Hypotension, respiratory depression, and apnea may be seen in severe cases. Very early after ingestion, patients may be hypertensive in the setting of agonism at peripheral α-receptors and resulting vasoconstriction. Symptoms develop relatively soon after ingestion and typically resolve within 24 hours. Serum clonidine concentrations are not readily available and are of no clinical value in the acute setting. Although signs of clinical toxicity are common after clonidine or guanfacine overdose, death is extremely unusual.

Treatment. Given the potential for significant toxicity, most young children warrant referral to a healthcare facility for evaluation after unintentional ingestions of α_2-adrenergic agonists. Gastric decontamination is of minimal value because of the small quantities ingested and the rapid onset of serious symptoms. Aggressive supportive care is imperative and is the cornerstone of management. Naloxone, often in high doses (i.e., 10 mg IV), has shown variable efficacy in treating clonidine toxicity. Other potentially useful therapies include atropine, IV fluid boluses, and vasopressors. Symptomatic children should be admitted to the hospital for close cardiovascular and neurologic monitoring. Also, in a patient receiving chronic clonidine or guanfacine therapy, rapid discontinuation of the drug, or even missing one or two doses, could lead to potentially dangerous elevations in blood pressure.

Digoxin. Digoxin is a cardiac glycoside extracted from the leaves of *Digitalis lanata*. Other natural sources of cardiac glycosides include *Digitalis purpura* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), Siberian ginseng, and the *Bufo marinus* toad. Therapeutically, digoxin is used in the management of heart failure and some supraventricular tachydysrhythmias. Acute overdose can occur in the setting of dosing errors (especially in younger children), unintentional or intentional medication ingestion, or exposure to plant material containing digitalis glycosides. Regarding exposure to such plants, toxicity is unusual unless the poison is concentrated in the form of a tea. Chronic toxicity can result from alteration of the digoxin dose, alteration in digoxin clearance as a result of renal impairment, or drug interactions.

Pathophysiology. Digoxin blocks the sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) pump, leading to intracellular loss of K^+ and gain of Na^+ and calcium (Ca^{2+}). This resulting rise in Ca^{2+} available to the contractile myocardium improves inotropy. An increase in myocardial automaticity leads to subsequent atrial, nodal, and ventricular ectopy. Digoxin also affects nodal conduction, leading to a prolonged refractory period, decreased sinus node firing, and slowed conduction through the AV node. Impaired Na^+/K^+ exchange can lead to elevated serum K^+. Overall, digoxin overdose manifests as a combination of slowed or blocked conduction and increased ectopy.

Clinical and Laboratory Manifestations. Nausea and vomiting are common initial symptoms of acute digoxin toxicity, manifesting within 6 hours of overdose. Cardiovascular manifestations include bradycardia, heart block, and a wide variety of dysrhythmias. CNS manifestations consist of lethargy, confusion, and weakness. Chronic toxicity (which is rare in children) is more insidious and may also manifest as altered mental status and visual disturbances.

Initial assessment should include an ECG, serum digoxin level, serum potassium, and kidney function tests. The serum digoxin level should be assessed at least 6 hours after ingestion and carefully interpreted in the setting of clinical symptoms, because the digoxin level alone does not entirely reflect the severity of intoxication. In acute ingestions, serum potassium is an independent marker of morbidity and mortality, with levels >5 mEq/L predicting poor outcomes. In chronic toxicity, serum K^+ concentration is less useful as a prognostic marker and may be altered from concomitant use of diuretics or renal dysfunction.

Digoxin has a very narrow therapeutic index. Therapeutic plasma digoxin concentrations are 0.5-2 ng/mL; a level >2 ng/mL is considered toxic, and >6 ng/mL is considered potentially fatal (in chronic poisonings). As with all serum levels of intoxicants, one must be careful to interpret the number in the context of the scenario of the poisoning and the status of the patient. An acutely poisoned patient may have a very high serum level and minimal to no symptoms, whereas a patient with a chronic or acute-on-chronic poisoning will usually be sicker with a lower serum level.

Numerous drug interactions affect plasma digoxin concentrations. Medications known to increase serum digoxin concentrations include the macrolides, erythromycin and clarithromycin, spironolactone, verapamil, amiodarone, and itraconazole.

Treatment. Initial treatment includes good general supportive care and gastric decontamination with activated charcoal if the ingestion was recent. An antidote for digoxin, digoxin-specific antibody fragments (Fab: Digibind or DigiFab) is available (see Table 94.8). Fab fragments bind free digoxin in both the intravascular and the interstitial spaces to form a pharmacologically inactive complex that is subsequently eliminated renally. Indications for administration of Fab fragments in children are listed in Table 94.14. Atropine is potentially useful in managing symptomatic bradycardia. Although dogma states that patients on digoxin with severe hyperkalemia and QRS widening on the ECG should not receive calcium salts, this has not been supported in the literature. Once stabilized, consultation with a cardiologist is recommended in the management of patients receiving chronic digoxin therapy, because administration of Fab fragments can lead to recurrence of the patient's underlying dysrhythmias or dysfunction.

Iron. Historically, iron was a common cause of childhood poisoning deaths. However, preventive measures such as childproof packaging have significantly decreased the rates of serious iron toxicity in young children. Iron-containing products remain widely available, with the most potentially toxic being adult iron preparations and prenatal vitamins. The severity of an exposure is related to the amount of *elemental iron* ingested. Ferrous sulfate contains 20% elemental iron, ferrous gluconate 12%, and ferrous fumarate 33%. Multivitamin preparations and children's vitamins rarely contain enough elemental iron to cause significant toxicity. Furthermore, nonionic forms of iron, carbonyl iron and iron polysaccharide, also do not cause significant toxicity.

Pathophysiology. Iron is directly corrosive to the GI mucosa, leading to hematemesis, melena, ulceration, and potential perforation.

Table. 94.14 Indications for Administration of Digoxin Antibody Fragments in Children

Ingestion of >0.1-0.3 mg/kg *or* steady-state digoxin concentration >5 ng/mL *PLUS* one of the following: • Rapidly progressive symptoms • Signs of cardioactive steroid intoxication • Potentially life-threatening dysrhythmias or conduction blocks • Serum potassium concentration >5 mEq/L
Co-ingestion of other cardiotoxic drugs with additive or synergistic toxicity
Ingestion of plant known to contain cardioactive steroids *plus* severe dysrhythmias

Modified from Cole JB. Cardiovascular drugs. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. *Rosen's Emergency Medicine*, 9th ed. Philadelphia: Elsevier; 2018, Box 147.4, p. 1879.

Table 94.15 Clinical Manifestations of Iron Toxicity After Acute Overdose

PHASE	CLINICAL FEATURES
1. Gastrointestinal (6 hr)	Vomiting Diarrhea Hematemesis Hematochezia
2. Latent (6-24 hr)	Resolution of GI symptoms Tachycardia Acidosis Depressed mental status
3. Systemic (12-24 hr)	Return of GI symptoms Acidosis Leukocytosis Coagulopathy Renal failure Lethargy or coma Cardiovascular collapse
4. Hepatic (2-5 days)	Fulminant liver failure Coagulopathy
5. Obstructive (3-6 wk)	Pyloric or bowel scarring Obstruction

GI, Gastrointestinal.
Modified from Theobald JL, Mycyk MB. Iron and heavy metals. In: Walls RM, Hockberger RS, Gausche-Hill M, et al., eds. *Rosen's Emergency Medicine*, 9th ed. Philadelphia: Elsevier; 2018, Table 151.2, p. 1913.

Early iron-induced hypotension is caused by massive volume losses, increased permeability of capillary membranes, and vasodilation mediated by free iron. Iron accumulates in tissues, including the Kupffer cells of the liver and myocardial cells, leading to hepatotoxicity, coagulopathy, and cardiac dysfunction. Metabolic acidosis develops in the setting of hypotension, hypovolemia, and iron's direct interference with oxidative phosphorylation and the Krebs cycle. Pediatric patients who ingest >40 mg/kg of elemental iron should be referred to medical care for evaluation, although moderate to severe toxicity is typically seen with ingestions >60 mg/kg.

Clinical and Laboratory Manifestations. Iron toxicity is described in five often-overlapping stages (Table 94.15). Patients who do not develop GI symptoms within 6 hours of ingestion are unlikely to develop serious toxicity. Symptomatic patients and patients with a large exposure by history should have serum iron levels drawn 4-6 hours after ingestion. Serum iron concentrations of <350 µg/dL 4-8 hours after ingestion suggest a low risk of significant toxicity, concentrations of 350-500 µg/dL suggest moderate toxicity, and concentrations of >500 µg/dL indicate that significant toxicity is likely. Additional laboratory evaluation in the ill patient should include arterial or venous blood gas, lactate, CBC, serum glucose level, liver transaminases, and coagulation parameters. Careful attention should be paid to the patient's hemodynamic status. An abdominal radiograph may reveal the presence of iron tablets, although not all formulations of iron are radiopaque.

Treatment. Close clinical monitoring, combined with aggressive supportive and symptomatic care, is essential to the management of iron poisoning. Activated charcoal does not adsorb iron, and WBI remains the decontamination strategy of choice. **Deferoxamine**, a specific chelator of iron, is the antidote for moderate to severe iron intoxication (see Table 94.8). Indications for deferoxamine treatment include a serum iron concentration >500 µg/dL or moderate to severe symptoms of toxicity (e.g., acidosis), regardless of serum iron concentration. Deferoxamine is preferably given by continuous IV infusion at 15 mg/kg/hr. Hypotension is a common side effect of deferoxamine infusion and is managed by slowing the rate of the infusion and administering fluids and vasopressors as needed. Prolonged deferoxamine infusion (>24 hours) has been associated with pulmonary toxicity (ARDS) and *Yersinia* sepsis. The deferoxamine-iron complex can color the urine reddish ("vin rosé"), although the degree of this coloration should not guide therapy. Deferoxamine is typically continued until clinical symptoms and acidosis resolve. Consultation with a PCC or medical toxicologist can yield guidelines for discontinuing deferoxamine.

Oral Hypoglycemics

Oral medications used in the management of type 2 diabetes include sulfonylureas, biguanides (e.g., metformin), thiazolidinediones, and meglitinides. Of these, only the sulfonylureas and meglitinides have the potential to cause profound hypoglycemia in both diabetic and nondiabetic patients. These classes of medications are widely prescribed and thus readily available. In toddlers, unintentional ingestion of a single sulfonylurea tablet can lead to significant toxicity.

Pathophysiology. Sulfonylureas work primarily by enhancing endogenous insulin secretion. In binding to the sulfonylurea receptor, these drugs induce closure of K^+ channels, leading to membrane depolarization, opening of Ca^{2+} channels, and stimulation of Ca^{2+}-mediated insulin release. Even in therapeutic use, the duration of hypoglycemic action can last up to 24 hours.

Clinical and Laboratory Manifestations. Hypoglycemia and symptoms associated with hypoglycemia are the primary clinical manifestations of sulfonylurea toxicity. These signs and symptoms can include diaphoresis, tachycardia, lethargy, irritability, coma, seizures, and even focal neurologic findings. As with other hyperinsulinemic states, sulfonylurea overdoses are associated with a nonketotic hypoglycemia. In the majority of patients, hypoglycemia develops within 6 hours of ingestion but can be delayed up to 16-18 hours after ingestion. Toddlers are particularly susceptible to hypoglycemia during an overnight fast.

Treatment. Patients with symptomatic hypoglycemia should be promptly treated with dextrose. In patients with mild symptoms, oral dextrose may be sufficient. However, patients with severe symptoms or profound hypoglycemia should be treated with a bolus of IV dextrose. Continuous dextrose infusions and repeated IV dextrose boluses should be avoided, if possible, because this can stimulate further insulin release and lead to recurrent and prolonged hypoglycemia. Instead, the preferred antidote for persistent (i.e., requiring ≥2 doses of IV dextrose) sulfonylurea toxicity is **octreotide** (see Table 94.8). Octreotide is a somatostatin analog that inhibits insulin release. Octreotide is given IV or subcutaneously (SC), typically in doses of 1-2 µg/kg (50-100 µg in teens or adults) every 6-8 hours.

Given the potential for significant hypoglycemia, toddlers with witnessed or suspected sulfonylurea ingestions should be admitted to the hospital for serial glucose measurements for at least 12 hours, including an overnight fast. Patients of any age who develop hypoglycemia are also candidates for admission, given the prolonged duration of hypoglycemic activity with these medications. Prophylactic IV dextrose infusions are not recommended because they can mask the symptoms of toxicity and stimulate further insulin secretion. Patients who require IV dextrose and/or octreotide should be monitored until they can demonstrate euglycemia for at least 8 hours off all therapy.

With the increasing numbers of adolescents with type 2 diabetes, pediatricians should be familiar with the toxic effects of **metformin** as well. Although metformin does not cause hypoglycemia, its association with lactic acidosis is well documented (metformin-associated lactic acidosis [MALA]). This state typically arises after a large overdose in which the agent interferes with the liver's ability to clear lactic acid. Dangerously high serum lactate levels can result, leading to hemodynamic instability. Hemodialysis is usually the best option for patients with severe MALA.

Psychiatric Medications: Antidepressants

Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, paroxetine, citalopram) are the most commonly prescribed class of antidepressants. This trend largely results from their wide therapeutic index and more favorable side effect profile compared with older agents such as tricyclic antidepressants (TCAs; amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, imipramine) and monoamine oxidase inhibitors (MAOIs). Other agents include the serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine) and atypical antidepressants (e.g., bupropion).

Tricyclic Antidepressants. Although now prescribed less often for depression, TCAs remain in use for a variety of other conditions, including chronic pain syndromes, enuresis, ADHD, and obsessive-compulsive disorder. TCAs can cause significant toxicity in children, even with ingestion of one or two pills (10-20 mg/kg).

Pathophysiology. TCAs achieve their desired antidepressant effects primarily through blockade of norepinephrine and serotonin reuptake. TCAs have complex interactions with other receptor types. Antagonism at muscarinic acetylcholine receptors leads to clinical features of the anticholinergic toxidrome. Antagonism at peripheral α-receptors leads to hypotension and syncope. Key to the toxicity of TCAs is their ability to block fast sodium channels, leading to impaired cardiac conduction and arrhythmias.

Clinical and Laboratory Manifestations. Cardiovascular and CNS symptoms dominate the clinical presentation of TCA toxicity. Symptoms typically develop within 1-2 hours of ingestion, and serious toxicity usually manifests within 6 hours of ingestion. Patients can have an extremely rapid progression from mild symptoms to life-threatening dysrhythmias. Patients often develop features of **anticholinergic toxidrome**, including delirium, mydriasis, dry mucous membranes, tachycardia, hyperthermia, urinary retention, and slow GI motility. CNS toxicity can include lethargy, coma, myoclonic jerks, and seizures. Sinus tachycardia is the most common cardiovascular manifestation of toxicity; however, patients can also develop widening of the QRS complex, premature ventricular contractions, and ventricular dysrhythmias. Refractory hypotension is a poor prognostic indicator and is the most common cause of death in TCA overdose.

An ECG can help determine the diagnosis and prognosis of the TCA-poisoned patient (Fig. 94.2; see Table 94.7). A QRS duration >100 msec identifies patients who are at risk for seizures and cardiac arrhythmias. An R wave in lead aVR of ≥3 mm is also an independent predictor of toxicity. Both ECG parameters are superior to measured serum TCA concentrations for identifying patients at risk for serious toxicity, and obtaining levels is rarely helpful in management of the acutely ill patient.

Treatment. Initial attention should be directed to supporting vital functions, including airway and ventilation as needed. Gastric decontamination can be accomplished with activated charcoal in patients who are alert and cooperative without clinical signs of toxicity. Treating clinicians should obtain an ECG as soon as possible and follow serial ECGs to monitor for progression of toxicity. The four primary effects described next may be seen at the bedside.

1. Altered Mental State. TCA-poisoned patients can become deeply comatose relatively quickly, so careful and prompt attention to the airway and placement of an endotracheal tube is of paramount importance.

2. Widened QRS on ECG. TCAs, as well as other agents (e.g., diphenhydramine, cocaine), block the fast Na^+ channels on the myocardial cells, slowing the upstroke of the QRS complex. Because the effect on Na^+ channels is greatest within the first 6 hours, frequent ECGs (i.e., every 20-30 minutes) during this period are important. As the QRS approaches 160 msec, the risk of the patient developing monomorphic ventricular tachycardia rises to 30%. Sodium, usually in the form of sodium bicarbonate, is the antidote of choice. *Indications for sodium bicarbonate include a QRS duration ≥100 msec, ventricular dysrhythmias, and hypotension.* Multiple bolus doses of sodium bicarbonate, 1-2 mEq/kg each, may be needed to narrow the QRS to <100 msec. Some prefer then to place the patient on an infusion of sodium bicarbonate, but this may not be necessary if the QRS is carefully monitored after the initial doses and repeat bolus dosing is provided as needed during the first 6-12 hours. Hypertonic (3%) saline and/or lipid emulsion therapy may be beneficial in refractory cases.

3. Hypotension. A direct-acting vasopressor such as norepinephrine or epinephrine is the agent of choice. Boluses of IV crystalloid fluids should be used with caution to prevent fluid overload.

4. Seizures. Seizures are relatively common and likely the result of multiple factors, including increased synaptic monoamines, sodium channel inhibition, and GABA receptor antagonism. Seizures are typically brief and should be treated with agents targeting the GABA-receptor complex in the brain. Benzodiazepines are the agent of choice.

Asymptomatic children should receive appropriate decontamination and have continuous cardiac monitoring and serial ECGs for at least 6 hours after exposure. If any manifestations of toxicity develop, the child should be admitted to a monitored setting. Children who remain

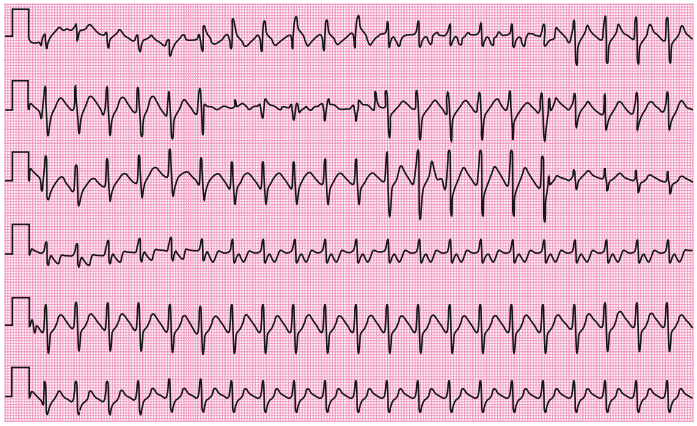

Fig. 94.2 Electrocardiographic findings in tricyclic antidepressant toxicity. Note the tachycardia, widened QRS interval (144 msec), and prominent R wave in lead aVR. These findings are consistent with blockade of fast sodium channels.

completely asymptomatic with normal serial ECGs may be candidates for discharge after that monitoring period.

Selective Serotonin Reuptake Inhibitors. In overdose, SSRIs are considerably less toxic than TCAs. SSRIs are unlikely to cause significant toxicity in exploratory ingestions. Some data suggest that initiating SSRI therapy is associated with an increased risk of suicidal ideation and behavior (see Chapter 40).

Pathophysiology. SSRIs selectively block the reuptake of serotonin in the CNS. In contrast to TCAs and atypical antidepressants, SSRIs do not directly interact with other receptors.

Clinical and Laboratory Manifestations. Although seen more often after therapeutic use or overdose of several serotonergic agents in combination, **serotonin syndrome** has also been described in ingestion of SSRIs alone (Table 94.16). Clinically, serotonin syndrome describes a spectrum of altered mental status, autonomic instability, fever, and neuromuscular hyperactivity (hyperreflexia, tremors, clonus in lower extremities > upper extremities) (Table 94.17). One or all of these signs may be present to varying degrees.

In overdose, the principal clinical manifestations of toxicity are sedation and tachycardia. Cardiac conduction abnormalities (primarily QTc prolongation) and seizures have been described in significant overdoses, especially after ingestions of citalopram. An ECG should be part of the initial assessment after SSRI ingestion. Serum creatine kinase (CK) levels are almost always elevated in a patient with clinically significant serotonin syndrome. The differential diagnosis includes neuroleptic malignant syndrome and malignant hyperthermia (Table 94.18).

Table 94.16 Drugs Associated with Serotonin Syndrome

DRUG TYPE	DRUGS
Selective serotonin reuptake inhibitors	Sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram
Antidepressant drugs	Trazodone, nefazodone, buspirone, clomipramine, venlafaxine, amitriptyline, nortriptyline
Monoamine oxidase inhibitors	Phenelzine, moclobemide, clorgyline, isocarboxazid
Anticonvulsants	Valproate
Analgesics	Meperidine, fentanyl, tramadol, pentazocine
Antiemetic agents	Ondansetron, granisetron, metoclopramide
Antimigraine drugs	Sumatriptan
Bariatric medications	Sibutramine
Antibiotics	Linezolid (a monoamine oxidase inhibitor), ritonavir (through inhibition of cytochrome P450 enzyme isoform 3A4)
Nonprescription cough and cold remedies	Dextromethorphan
Drugs of abuse	Methylenedioxymethamphetamine (MDMA, "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products	Tryptophan, *Hypericum perforatum* (St. John's wort), *Panax ginseng* (ginseng)
Other	Lithium

From Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112–1120.

Treatment. Initial management includes a careful assessment for signs and symptoms of serotonin syndrome and an ECG. Most patients simply require supportive care and observation until their mental status improves and tachycardia, if present, resolves. Management of serotonin syndrome is directed by the severity of symptoms; possible therapeutic interventions include benzodiazepines in mild cases and intubation, sedation, and paralysis in patients with severe manifestations (e.g., significant hyperthermia). Because agonism at the 5-HT_{2A} serotonin receptor is thought to be primarily responsible for the development of serotonin syndrome, use of the 5-HT_{2A} receptor antagonist cyproheptadine has been considered a possible antidote; the efficacy of cyproheptadine in managing serotonin syndrome is not well-supported by the available literature. Furthermore, cyproheptadine should be used with caution when the diagnosis is unclear, as it can worsen anticholinergic toxicity.

Atypical Antidepressants. The atypical antidepressant class includes agents such as venlafaxine and duloxetine (SNRIs), bupropion (dopamine, norepinephrine, and some serotonin reuptake blockade), and trazodone (serotonin reuptake blockade and peripheral α-receptor antagonism). The variable receptor affinities of these agents lead to some distinctions in their clinical manifestations and management.

Clinical and Laboratory Manifestations. In overdose, **venlafaxine** and other SNRIs have been associated with cardiac conduction defects, including QRS and QTc prolongation, and seizures (typically within a few hours of ingestion). **Bupropion** warrants special consideration because it is one of the most common etiologies of toxicant-induced seizures in the United States. After ingestion of SR or extended-release (ER) preparations of bupropion, seizures can occur as late as 18-20 hours after ingestion. In addition, bupropion can cause tachycardia, agitation, and QRS and QTc prolongation. These cardiac effects are thought to result from a reduction in cardiac intracellular coupling caused by inhibition at gap junctions in the heart. Mortality results from not only status epilepticus but also the cardiac conduction disturbances causing ventricular tachycardia and dysrhythmias. In addition to sedation and signs of serotonin excess, trazodone overdose may be associated with hypotension from blockade of peripheral α-receptors.

Treatment. Management is directed at clinical signs and symptoms. QRS and QTc interval prolongation after bupropion poisoning is typically resistant to the standard treatments of sodium bicarbonate and magnesium. Seizures are often brief and self-limited but can be treated with benzodiazepines if necessary. A patient poisoned with bupropion who shows unstable hemodynamics with prolonged ECG intervals or persistent seizure activity after the appropriate therapies should be discussed with a toxicologist for possible lipid emulsion therapy. Because of the potential for delayed seizures, asymptomatic patients who have ingested an SR preparation of bupropion should be admitted to a monitored setting for at least 20-24 hours. Trazodone-associated hypotension typically responds to fluids, though it can require vasopressors in extreme cases.

Monoamine Oxidase Inhibitors. Although now rarely used therapeutically, MAOIs remain important agents given their potential for serious and delayed toxicity. Ingestions of only one or two pills (6 mg/kg) are associated with toxicity in children. Clinical manifestations initially include hypertension, hyperthermia, tachycardia, muscle rigidity, and seizures, followed up to 24 hours later by hemodynamic instability and cardiovascular collapse. *Any child who ingests a MAOI should be admitted to a monitored setting for at least 24 hours, regardless of symptoms.* Management includes blood pressure control, cooling and benzodiazepines for hyperthermia, serial monitoring of CK and renal function, and fluid and vasopressor therapy for hemodynamic instability.

Psychiatric Medications: Antipsychotics

Clinicians are increasingly prescribing antipsychotic medications in the pediatric population. Antipsychotics are usually classified as either typical or atypical. In general, typical agents are associated with more side effects and toxicity than the atypical agents.

Table 94.17 Spectrum of Symptoms of Serotonergic Toxicity

SEVERITY	NEUROMUSCULAR EXCITATION	ALTERED MENTAL STATUS	AUTONOMIC DYSFUNCTION
Mild	Hyperreflexia Tremor Myoclonus	Anxiety Restlessness Insomnia	Diaphoresis Mydriasis Tachycardia
Moderate	Opsoclonus Spontaneous or inducible clonus	Agitation	Hypertension Hyperthermia (<40°C [<104°F]) Hyperactive bowel sounds Diarrhea, nausea, vomiting
Severe	Rigidity Respiratory failure Tonic-clonic seizure	Coma Delirium Confusion	Severe hyperthermia (≥40°C [≥104°F]) Dynamic blood pressure

Adapted from Wang RZ, Vashistha V, Kaur S, Houchens NW. Serotonin syndrome: Preventing, recognizing, and treating it. *Clev Clinic J Med*. 2016;83(11):810–817, Table 2, p. 812.

Table 94.18 Signs and Symptoms of Neuroleptic Malignant Syndrome (NMS)/Serotonin Syndrome/Malignant Hyperthermia

CLINICAL FEATURES	NMS	SEROTONIN SYNDROME	MALIGNANT HYPERTHERMIA
Triggering agent	Neuroleptic	Proserotonergic agent	Succinylcholine or inhaled anesthetic
Onset	Slow (hours to days)	Fast (minutes to hours)	Very fast to fast (minutes to hours)
Duration	Long (days to weeks)	Short (1-2 days)	Short (1-3 days)
Agitation	Sometimes	Yes	No
Confusion	Yes	Sometimes	Unusual
Hyperactivity	No	Yes	No
Bradykinesia/stupor	Yes	No	Unusual
Myoclonus	No	Yes	No
Shivering	No	Yes/sometimes	No
Tremor	Sometimes	Yes	No
Pupils	Mid-sized	Large	Not specific
Hyperreflexia	No	Yes (especially lower extremities)	No
Rigidity	Severe	Sometimes	Severe
Rigidity type	Extrapyramidal (lead pipe)	Pyramidal (clasp-knife)	Generalized
Hyperpyrexia	Yes	Yes	Severe
Tachypnea	Yes	Yes	Yes
Tachycardia	Yes	Yes	Yes (severe)
Hypertension	Sometimes	Yes	Sometimes
Leukocytosis	Yes	Uncommon	Not typical
Elevated creatine phosphokinase	Severe	Mild	Severe

Adapted from Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol* 1999;13:100–109; Gillman K; Serotonin toxicity www.psychotropical.com/serotonin-toxicity; and Wappler F, Fiege M, Schulte am Esch J. Pathophysiological role of the serotonin system in malignant hyperthermia. *Br J Anaesth*. 2001;87(5):794–798.

Pathophysiology. *Typical,* or "traditional," antipsychotics (haloperidol, droperidol, thioridazine, chlorpromazine, fluphenazine) are characterized by their antagonism at D_2 dopamine receptors. In therapeutic use, these agents are associated with extrapyramidal symptoms, tardive dyskinesia, and, rarely, development of **neuroleptic malignant syndrome (NMS)** (see Table 94.18). The *atypical* agents (aripiprazole, clozapine, quetiapine, risperidone, ziprasidone) were developed with relatively less dopamine (D_2-receptor) antagonism in the nigrostriatum to avoid these side effects and improve their efficacy in managing the "negative" symptoms of schizophrenia. Instead, these agents have complex and varied interactions with multiple receptor types, including α-receptors, serotonin receptors, muscarinic acetylcholine receptors, and histamine receptors.

Clinical and Laboratory Manifestations. Typical antipsychotic toxicity usually includes sedation, tachycardia, and QTc prolongation. Patients can present with acute dystonia, akathisia, and NMS, although these are seen less frequently in acute overdoses than in therapeutic use. The phenothiazines (e.g., thioridazine) can cause widening of the QRS interval from blockade of fast sodium channels. Clinically, NMS can be difficult to distinguish from serotonin syndrome.

Although the presentation of atypical antipsychotic toxicity can vary based on the receptor affinities of the specific agent, sedation, tachycardia, and QTc prolongation are common. Peripheral α-receptor blockade (e.g., with quetiapine) is associated with hypotension. In therapeutic use, clozapine is associated with agranulocytosis. Atypical antipsychotics that antagonize muscarinic acetylcholine receptors (e.g., olanzapine, quetiapine) may cause symptoms of anticholinergic toxidrome.

Diagnostic testing should include an ECG. Patients with hyperthermia or muscle rigidity should have a serum CK level sent to monitor

for possible rhabdomyolysis. CBC is indicated in patients with fever to evaluate for neutropenia. Antipsychotic levels are not readily available and are not helpful in managing acute poisoning.

Management. Initial management involves assessing and supporting vital functions. In some patients, CNS depression may be so profound as to require intubation for airway control. Acute dystonia is treated with diphenhydramine and benztropine. Management of NMS includes aggressive supportive care, IV fluids, active cooling, benzodiazepines, and bromocriptine or dantrolene in severe cases. QTc prolongation is managed with repletion of electrolytes (especially calcium, magnesium, and potassium), continuous cardiac monitoring, prevention of bradycardia (overdrive pacing, isoproterenol, atropine), and defibrillation if the patient develops torsades de pointes. Delirium associated with anticholinergic toxicity may be managed with benzodiazepines, and a specific antidote (physostigmine) can be considered in consultation with a medical toxicologist (see Table 94.8). Seizures typically are well controlled with benzodiazepines. Hypotension usually responds to boluses of IV fluids, although vasopressor therapy is necessary in some patients.

Household Products

Caustics

Caustics include acids and alkalis as well as a few common oxidizing agents (see Chapter 373). Strong acids and alkalis can produce severe injury even in small-volume ingestions.

Pathophysiology. **Alkalis** produce a *liquefaction necrosis,* allowing further tissue penetration of the toxin and setting the stage for possible perforation. **Acids** produce a *coagulative necrosis,* which limits further tissue penetration, although perforation can still occur. The severity of the corrosive injury depends on the pH and concentration of the product and the length of contact time with the product. Agents with a pH of <2 or >12 are most likely to produce significant injury.

Clinical Manifestations. Ingestion of caustic materials can produce injury to the oral mucosa, posterior pharynx, vocal cords, esophagus, and stomach. Patients can have significant esophageal injury even in the absence of visible oral burns. Symptoms include pain, drooling, vomiting, abdominal pain, and difficulty swallowing or refusal to swallow. Laryngeal injury can manifest as stridor and respiratory distress, necessitating intubation. In the most severe cases, patients can present in shock after perforation of a hollow viscus. Circumferential burns of the esophagus are likely to cause strictures when they heal, which can require repeated dilation or surgical correction and long-term follow-up for neoplastic changes in adulthood. Caustic exposures on the skin or in the eye can cause significant tissue damage.

Treatment. Initial treatment of caustic exposures includes thorough removal of the product from the skin or eye by flushing with water. *Emesis and lavage are contraindicated.* Activated charcoal should not be used because it does not bind these agents, interferes with endoscopy, and can predispose the patient to vomiting and subsequent aspiration. Stridor or other signs of respiratory distress should alert the provider to the need for a thorough evaluation of the airway for potential intubation or surgical airway management. Endoscopy can be performed within 12-24 hours of ingestion in *symptomatic* patients or those with suspected injury based on history and known characteristics of the ingested product. The role of endoscopy is purely diagnostic and is contraindicated in patients with severe oropharyngeal injury with edema and necrosis, evidence of perforation, respiratory distress, or hemodynamic instability, as these patients instead require immediate surgical consultation. Expectant management with a period of nothing by mouth (NPO) and proton pump inhibitor therapy is likely appropriate for most *asymptomatic* patients. Corticosteroids or prophylactic antibiotics are not beneficial.

Pesticides

Cholinesterase-Inhibiting Insecticides. The most commonly used insecticides in agriculture are **organophosphates** and **carbamates**; both are inhibitors of cholinesterase enzymes: acetylcholinesterase (AChE), pseudocholinesterase, and erythrocyte AChE. Most pediatric poisonings occur as the result of unintentional exposure to insecticides in and around the home or farm. The chemical warfare weapons known as "nerve agents" are also organophosphate compounds with a similar mechanism of action but much greater potency.

Pathophysiology. Organophosphates and carbamates produce toxicity by binding to and inhibiting AChE, preventing the degradation of acetylcholine (ACh) and resulting in its accumulation at nerve synapses. If left untreated, organophosphates form an irreversible bond to AChE, permanently inactivating the enzyme. This process, called *aging,* occurs over a variable period, depending on the characteristics of the specific organophosphate. A period of weeks to months is required to regenerate inactivated enzymes. In contrast, carbamates form a temporary bond with the enzymes, typically allowing reactivation of AChE within 24 hours.

Clinical and Laboratory Manifestations. Clinical manifestations of organophosphate and carbamate toxicity relate to ACh accumulation at peripheral nicotinic and muscarinic synapses and in the CNS. Symptoms of carbamate toxicity are usually less severe than those seen with organophosphates. A commonly used mnemonic for the symptoms of cholinergic excess at muscarinic receptors is **DUMBBELS**: diarrhea/defecation, urination, miosis, bronchorrhea/bronchospasm, bradycardia, emesis, lacrimation, and salivation. Nicotinic signs and symptoms include muscle weakness, fasciculation, tremors, hypoventilation (diaphragm weakness), hypertension, tachycardia, and dysrhythmias. Severe manifestations include coma, seizures, shock, arrhythmias, and respiratory failure.

Diagnosis of poisoning is based primarily on history and physical exam findings. Red blood cell cholinesterase and pseudocholinesterase activity levels can be measured in the laboratory. These are only helpful when compared with the patient's known baseline. As such, these assessments are typically limited to farmworkers undergoing ongoing occupational surveillance.

Treatment. Basic decontamination should be performed, including washing all exposed skin with soap and water and immediately removing all clothing. Activated charcoal is unlikely to be of benefit because these are liquids that are rapidly absorbed. Basic supportive care should be provided, including fluid and electrolyte replacement, intubation, and ventilation if necessary. The use of succinylcholine for rapid sequence intubation should be avoided because the same cholinesterase enzymes that are poisoned metabolize this neuromuscular blocking agent, leading to prolonged paralysis.

Two antidotes are useful in treating cholinesterase inhibitor poisoning: atropine and pralidoxime (see Table 94.8). **Atropine**, which antagonizes the muscarinic ACh receptor, is useful for both organophosphate and carbamate intoxication. Often, large doses of atropine must be administered by intermittent bolus or continuous infusion to control symptoms. Atropine dosing is primarily targeted to drying the respiratory secretions. **Pralidoxime** breaks the bond between the organophosphate and the enzyme, reactivating AChE. Pralidoxime is only effective if it is used before the bond ages and becomes permanent. Pralidoxime is not necessary for carbamate poisonings because the bond between the insecticide and the enzyme degrades spontaneously.

Without treatment, symptoms of organophosphate poisoning can persist for weeks, requiring continuous supportive care. Even with treatment, some patients develop a delayed polyneuropathy and a range of chronic neuropsychiatric symptoms.

Pyrethrins and Pyrethroids. Pyrethrins are derived from the chrysanthemum flower and, along with synthetic derivatives, pyrethroids, are the most used pesticides in the home. Although >1,000 pyrethrins and pyrethroids exist, <20 are available in the United States, with **permethrin** being the most common. Exposure to these compounds occurs by inhalation, dermal absorption, or ingestion. Ingestion is the predominant route and typically occurs by eating contaminated foods. Permethrin is also a prescribed medication for the treatment of scabies and lice.

Pathophysiology. Pyrethrins and pyrethroids prolong the open state of the voltage-gated Na^+ channel conduction, which is the main mechanism resulting in its pesticide activity. Pyrethrins have minimal toxicity in mammals because of rapid metabolism, higher affinity for the insect Na^+ channel, and decreased activity at higher temperatures

seen in warm-blooded animals. Because pyrethroids were specifically manufactured to be more stable in the environment, they have a higher likelihood of toxicity.

Clinical and Laboratory Manifestations. Pyrethrin exposures can lead to allergic reactions ranging from dermatitis to urticaria to anaphylaxis. Acute pyrethroid exposure can result in headache, nausea, dizziness, tremors, ataxia, choreoathetosis, loss of consciousness, and seizures. The severity of the symptoms depends on the magnitude of the exposure. Reports of acute lung injury have also occurred after pyrethroid exposures, although this is likely from the other components of the insecticide, such as surfactants and solvents. Paresthesias limited to the cutaneous exposure area can also occur after a dermal exposure. Chronic exposures have not been shown to result in any clinical manifestations. Although one can test for urinary pyrethroid metabolites, this is only useful for monitoring occupational exposure and has no role in the acute exposure.

Treatment. Initial treatment should focus on decontamination, which involves removing all clothing and irrigation of exposed areas. Allergic reactions are treated with oral antihistamines and topical corticosteroids. Systemic toxicity should be treated with excellent supportive care, using benzodiazepines for tremors and seizures.

Hydrocarbons

Hydrocarbons include a wide array of chemical substances found in thousands of commercial products. Specific characteristics of each product determine whether exposure will produce systemic toxicity, local toxicity, both, or neither. Nevertheless, aspiration of even small amounts of certain hydrocarbons can lead to serious, potentially life-threatening toxicity.

Pathophysiology. The most important manifestation of hydrocarbon toxicity is *aspiration pneumonitis* through inactivation of the type II pneumocytes and resulting in surfactant deficiency (see Chapter 446). Aspiration usually occurs during coughing and gagging at the time of ingestion or vomiting after the attempted ingestion of an aliphatic hydrocarbon. The propensity of a hydrocarbon to cause aspiration pneumonitis is inversely proportional to its viscosity and directly proportional to its volatility. Compounds with low viscosity and high volatility, such as mineral spirits, naphtha, kerosene, gasoline, and lamp oil, spread rapidly across surfaces and cover large areas of the lungs when aspirated. Only small quantities (<1 mL) of such chemicals need be aspirated to produce significant injury. Pneumonitis does not result from dermal absorption of hydrocarbons or from ingestion in the absence of aspiration. Gasoline and kerosene are poorly absorbed, but they often cause considerable irritation of the GI mucosa as they pass through the intestines.

Certain hydrocarbons have unique toxicities and can cause symptoms after ingestion, inhalation, or dermal exposures. Several chlorinated solvents, most notably carbon tetrachloride, can produce hepatic toxicity. **Methylene chloride**, found in some paint removers, is metabolized to carbon monoxide. **Benzene** is known to cause cancer, most often acute myelogenous leukemia, after long-term exposure. Nitrobenzene, aniline, and related compounds can produce methemoglobinemia. A number of **volatile** hydrocarbons, including toluene, propellants, refrigerants, and volatile nitrites, are frequently abused by inhalation. Some of these substances, principally the **halogenated** hydrocarbons (which contain a chlorine, bromine, or fluorine), can sensitize the myocardium to the effects of endogenous catecholamines. This can result in dysrhythmias and "sudden sniffing death." Chronic abuse of these agents can lead to cerebral atrophy, neuropsychologic changes, peripheral neuropathy, and kidney disease (see Chapter 157).

Clinical and Laboratory Manifestations. Transient, mild CNS depression is common after hydrocarbon ingestion or inhalation. Aspiration is characterized by coughing, which usually is the first clinical finding. Chest radiographs may initially be normal, but they often show abnormalities within 6 hours of exposure in patients who have aspirated. Respiratory symptoms can remain mild or progress rapidly to ARDS and respiratory failure. Fever and leukocytosis are common accompanying signs in patients with pneumonitis and do not necessarily imply bacterial superinfection. Chest radiographs can remain abnormal long after the patient returns to their clinical baseline. Pneumatoceles can appear on the chest radiograph 2-3 weeks after exposure.

After inhalational exposures to halogenated hydrocarbons, patients can present with ventricular dysrhythmias, often refractory to conventional management. Recurrent inhalation of the aromatic hydrocarbon **toluene** can lead to a type IV renal tubular acidosis.

Treatment. *Emesis and lavage are contraindicated given the risk of aspiration*. Activated charcoal is not useful because it does not bind the common hydrocarbons and can also induce vomiting. If hydrocarbon-induced pneumonitis develops, respiratory treatment is supportive (see Chapter 446). Neither corticosteroids nor prophylactic antibiotics have shown any clear benefit. Standard mechanical ventilation, high-frequency ventilation, and ECMO have all been used to manage the respiratory failure and ARDS associated with severe hydrocarbon-induced pneumonitis.

Patients with dysrhythmias in the setting of halogenated hydrocarbon inhalation should be treated with β blockers (usually esmolol) to block the effects of endogenous catecholamines on the sensitized myocardium.

Toxic Alcohols

Methanol is found in windshield washer fluids, deicers, paint removers, fuel additives, liquid fuel canisters, and industrial solvents. **Ethylene glycol** is found in antifreeze. Unintentional ingestion is the most common exposure in children, and small-volume ingestions of concentrated products can theoretically cause toxicity. The pathophysiology, acid-base derangements, and treatment of both chemicals are similar, although they differ in their primary end-organ toxicity. In both cases the metabolites of the parent compounds are responsible for the serious clinical effects that can follow exposure.

Isopropyl alcohol (rubbing alcohol), found in hand sanitizers, causes intoxication similar to that associated with ethanol but can also cause a hemorrhagic gastritis and myocardial depression in massive ingestions. Unlike ethylene glycol and methanol, isopropyl alcohol is metabolized to a ketone and does not cause a metabolic acidosis. Management is similar to that of ethanol ingestions (see Chapter 157) and is not further discussed here.

Methanol

Pathophysiology. Methanol is oxidized in the liver by alcohol dehydrogenase to formaldehyde, which is further oxidized to formic acid by aldehyde dehydrogenase. Toxicity is caused primarily by formic acid, which inhibits mitochondrial respiration.

Clinical and Laboratory Manifestations. Drowsiness, mild inebriation, nausea, and vomiting develop early after methanol ingestion. The onset of serious effects, including profound metabolic acidosis and visual disturbances, is often delayed up to 12-24 hours as methanol undergoes metabolism to its toxic metabolites. This metabolism is further slowed if *ethanol* has also been ingested, because the liver will preferentially metabolize ethanol. Visual disturbances include blurred or cloudy vision, constricted visual fields, decreased acuity, and the "feeling of being in a snowstorm" and appear only after acidosis is well established. These visual defects may be reversible if treated early, but untreated can lead to permanent blindness. On examination, dilated pupils, retinal edema, and optic disc hyperemia may be noted. Initially, patients have an elevated osmolar gap, then develop an anion gap metabolic acidosis as the parent compound is metabolized to formic acid.

In young children, determining if a significant exposure has occurred is usually difficult based on history. Methanol blood levels are available at some laboratories and should be sent after a concerning exposure. If methanol blood levels are not readily available, estimation of an osmolar gap may be used as a surrogate marker, but a normal osmolar gap does not rule out ingestion of any alcohol. Serum osmolality is measured by the freezing-point depression method and compared with a calculated serum osmolarity.

Treatment. Treatment is as discussed for ethylene glycol toxicity.

Ethylene Glycol

Pathophysiology. Ethylene glycol is oxidized by alcohol dehydrogenase in the liver to glycolaldehyde, which is further converted to

glycolic acid by aldehyde dehydrogenase. Glycolic acid is responsible for the metabolic acidosis and is further metabolized to glyoxylic and then to oxalic acid. Oxalic acid combines with serum and tissue calcium, forming calcium oxalate crystals that deposit throughout the body, especially in the renal parenchyma, leading to acute tubular necrosis.

Clinical and Laboratory Manifestations. Early symptoms include nausea, vomiting, CNS depression, and inebriation. Delayed manifestations include an anion gap metabolic acidosis, hypocalcemia, and acute kidney injury. Even later, patients can develop cranial nerve palsies.

Both ethylene glycol and methanol can produce profound, life-threatening metabolic acidosis and acidemia, with measured serum bicarbonates that may even be nondetectable. The onset of the acidosis is delayed up to 4-12 hours after ethylene glycol ingestion and may be delayed further with any concomitant ingestion of ethanol. Ethylene glycol blood concentrations are technically difficult to perform and are available only at some larger reference laboratories. In the absence of readily available ethylene glycol concentrations, calculation of the osmolar gap may be helpful as a surrogate marker.

Examination of the urine with a Wood lamp is neither sensitive nor specific for ethylene glycol ingestion. The earliest sign on a urinalysis of ethylene glycol poisoning is usually hematuria. Calcium oxalate crystals can be seen on urine microscopy but might not be evident early after exposure. Electrolytes (including calcium), acid-base status, kidney function, and ECG should be closely monitored in poisoned patients.

Treatment. Because methanol and ethylene glycol are rapidly absorbed, gastric decontamination is generally not of value. The classic antidote for methanol and ethylene glycol poisoning was ethanol, a preferential substrate for alcohol dehydrogenase, thus preventing the metabolism of parent compounds to toxic metabolites. **Fomepizole**, a potent competitive inhibitor of alcohol dehydrogenase, has almost entirely replaced ethanol because of its ease of administration, lack of CNS and metabolic effects, and overall excellent patient tolerability profile (see Table 94.8). A serum concentration must be interpreted along with the time removed from exposure. A patient with a methanol level of 20 mg/dL 24 hours after exposure had a much larger dose than a patient with the same level only 1 hour after ingestion. Indications for fomepizole include ethylene glycol or methanol level >20 mg/dL (assuming no ethanol is present), history of potentially toxic ingestion (e.g., any intentional overdose), or history of ingestion with evidence of acidosis. There are few disadvantages to giving the initial dose of fomepizole to patients with a concerning history of ingestion or laboratory findings. Given the dosing schedule of fomepizole (every 12 hours), this strategy buys the clinician time to confirm or exclude the diagnosis before giving a second dose. Adjunctive therapy includes folate (methanol toxicity), pyridoxine (ethylene glycol toxicity), and sodium bicarbonate infusion (if acidemic). If a child has had an unintentional exposure and the toxic alcohol level cannot be obtained, a reasonable approach is to follow serum chemistries every 4 hours until 12 hours after the exposure. If the bicarbonate level on the chemistry panel does not fall in that period, a toxic exposure is unlikely (assuming no ethanol is present).

Hemodialysis effectively removes ethylene glycol, methanol, and their metabolites (except calcium oxalate) and corrects acid-base and electrolyte disturbances. Fomepizole should be given both before and immediately after dialysis. Indications for dialysis include a methanol or ethylene glycol level >50 mg/dL, acidosis, severe electrolyte disturbances, renal failure, and hemodynamic instability. However, in the absence of acidosis and kidney failure, even massive ethylene glycol ingestions have been managed without dialysis. Methanol, however, because its elimination in the setting of alcohol dehydrogenase inhibition is prolonged, often warrants dialysis to remove the parent compound. Therapy (fomepizole and/or dialysis) should be continued until ethylene glycol and methanol levels are <20 mg/dL. Although the visual effects from methanol poisoning are usually permanent, the kidney injury from ethylene glycol injury is not. Patients requiring hemodialysis after ethylene glycol poisoning will almost always recover complete renal function within 2-6 weeks. Consultation with a PCC, medical toxicologist, and nephrologist may be helpful in managing toxic alcohol ingestions.

Plants

Exposure to plants, both inside the home and outside in backyards and fields, is one of the most common causes of unintentional poisoning in children. Fortunately, most ingestions of plant parts (leaves, seeds, flowers) result in either no toxicity or mild, self-limiting effects. However, ingestion of certain plants can lead to serious toxicity (Table 94.19).

The potential toxicity of a particular plant is highly variable, depending on the part of the plant involved (flowers are generally less toxic than the root or seed), the time of year, growing conditions, and the route of exposure. Assessment of the potential severity after an exposure is also complicated by the difficulty in properly identifying the plant. Many plants are known by several common names, which can vary among communities. PCCs have access to professionals who can assist in properly identifying plants. They also are well versed in the common poisonous plants in their service area and the seasons when they are more abundant. For these reasons, consultation with the local PCC may be very helpful in the management of these ingestions.

For potentially toxic plant ingestions, consider decontamination with activated charcoal in patients who present within 1-2 hours of ingestion; otherwise, treatment is primarily supportive and based on symptoms. The most common manifestation of toxicity after plant ingestion is GI upset, which can be managed with antiemetics and fluid and electrolyte support. Table 94.19 outlines management strategies for a few specific toxicities.

Herbal Remedies

Herbal remedies represent a relatively common exposure in children; despite this, reports of life-threatening toxicity are rare.

There are several mechanisms by which herbal remedies may be poisonous. Many herbal remedies are inherently toxic; it is either the dose used or specific processing of the remedy that renders them safe for use. For example, oil of wintergreen used as a liniment contains a high concentration of methyl salicylate, a concerning source of salicylate poisoning in small children. A remedy intended to contain one compound may accidentally contain another; reports exist of contamination of skin creams with mercury, herbal remedies contaminated with lead, and weight loss supplements contaminated with cardioactive steroids. Herbal remedies may interfere with the metabolism of pharmaceuticals; an example is St. John's wort, which by induction of the cytochrome oxidase system (specifically, CYP3A4) may render certain medications less effective.

Management of toxicity associated with herbal remedies remains largely the same as for other organic compounds. Decontamination with activated charcoal should be considered for patients arriving within 1-2 hours of an ingestion. Signs and symptoms should be treated as outlined previously in this chapter, with excellent supportive care and therapy directed toward the suspected toxin. In the rare case of concern for contamination with a heavy metal, specific assays may be obtained for confirmation of exposure. A list of herbal remedies and their associated toxicities are provided in Table 94.20.

In limited cases, specific antidotes are suggested based on the pathophysiologic mechanism. Several plant and animal species contain cardioactive steroids with digoxin-like toxicity. Although digoxin-specific immune fragments are only evidence based for the management of yellow oleander *(Thevetia peruviana)* toxicity, it is reasonable to use this therapy in a critically ill patient who has developed cardiac toxicity or hyperkalemia after ingestion of lily of the valley, squill, or oleander. Several essential oils (pennyroyal oil, clove oil) deplete glutathione as part of their toxic mechanism, and thus treatment with NAC may be of benefit. Gingko causes a depletion of active pyridoxine stores, and thus pyridoxine administration may be helpful in the setting of benzodiazepine-refractory seizures.

Table 94.19 Commonly Ingested Plants with Significant Toxic Potential

PLANT	SYMPTOMS	MANAGEMENT
Autumn crocus (Colchicum autumnale)	Vomiting Diarrhea Initial leukocytosis followed by bone marrow failure Multisystem organ failure	Activated charcoal decontamination Aggressive fluid resuscitation and supportive care
Belladonna alkaloids: jimsonweed (Datura stramonium) Belladonna ("deadly nightshade"; Atropa belladonna)	Anticholinergic toxidrome Seizures	Supportive care, benzodiazepines Consider physostigmine; only use if no conduction delays on ECG
Cardiac glycoside–containing plants (e.g., foxglove, lily of the valley, oleander, yellow oleander)	Nausea Vomiting Bradycardia Dysrhythmias (AV block, ventricular ectopy) Hyperkalemia	Digoxin-specific Fab fragments
Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)	Oral pain Vomiting Diarrhea Shock Hemolysis Renal failure	Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities
Monkshood (Aconitum species)	Numbness and tingling of lips/tongue Vomiting Bradycardia	Atropine for bradycardia Supportive care
Oxalate-containing plants: Philodendron, Dieffenbachia, Colocasia ("elephant ear")	Local tissue injury Oral pain Vomiting	Supportive care, pain control
Poison hemlock (Conium maculatum)	Vomiting Agitation followed by CNS depression Paralysis Respiratory failure	Supportive care
Pokeweed	Hemorrhagic gastroenteritis Burning of mouth and throat	Supportive care
Rhododendron	Vomiting Diarrhea Bradycardia	Atropine for symptomatic bradycardia Supportive care
Tobacco	Vomiting Agitation Diaphoresis Fasciculations Seizures	Supportive care
Water hemlock (Cicuta species)	Abdominal pain Vomiting Delirium Seizures	Supportive care, including benzodiazepines for seizures
Yew (Taxus species)	GI symptoms QRS widening Hypotension CV collapse	Supportive care Atropine for bradycardia Sodium bicarbonate does not appear to be effective

AV, Atrioventricular; CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; Fab, fragment, antigen binding; GI, gastrointestinal.

Toxic Gases

Carbon Monoxide

Although many industrial and naturally occurring gases pose a health risk by inhalation, the most common gas involved in pediatric exposures is CO. CO is a colorless, odorless gas produced during the combustion of any carbon-containing fuel; the less efficient the combustion, the greater the amount of CO produced. Wood-burning stoves, kerosene heaters, old furnaces, hot-water heaters, closed-space fires, and automobiles are a few of the potential sources of CO.

Pathophysiology. CO binds to hemoglobin with an affinity >200 times that of oxygen, forming carboxyhemoglobin (HbCO). In doing so, CO displaces oxygen and creates a conformational change in hemoglobin that impairs the delivery of oxygen to the tissues, leading to tissue hypoxia. HbCO levels are not well correlated with clinical signs of toxicity, likely because CO interacts with multiple proteins in addition to hemoglobin. CO binds to cytochrome oxidase, disrupting cellular respiration. CO displaces nitric oxide (NO) from proteins, allowing NO to bind with free radicals to form the toxic metabolite peroxynitrite, leading to lipid peroxidation and cellular damage. NO is also a potent vasodilator, in part responsible for clinical symptoms such as headache, syncope, and hypotension.

Table 94.20 Clinical Toxicity of Selected Herbs

COMMON NAME	BOTANICAL NAME	THERAPEUTIC USES	POTENTIAL TOXICITY
Aconite (monkshood, wolfsbane)	*Aconitum* spp.	Sedative, analgesic, antihypertensive	Cardiac arrhythmias
Aloe	*Aloe* spp.	Burns, skin diseases	Nephritis, GI upset
Betel nut	*Areca catechu*	Mood elevation	Bronchoconstriction, oral cancers
Bloodroot	*Sanguinaria canadensis*	Emetic, cathartic, eczema	GI upset, vertigo, visual disturbances
Chaparral (greasewood)	*Larrea tridentata*	Aging, free radical scavenging	Hepatitis
Compound Q	*Trichosanthes kirilowii*	Anthelmintic, cathartic	Diarrhea, hypoglycemia, CNS toxicity
Dandelion	*Taraxacum officinale*	Diuretic, heartburn remedy	Anaphylaxis
Figwort (xuan shen)	*Scrophularia* spp.	Antiinflammatory, antibacterial	Cardiac stimulation
Ginseng	*Panax quinquefolium*	Antihypertensive, aphrodisiac, stimulant, mood elevation, digestive aid	Ginseng abuse syndrome
Goldenseal	*Hydrastis canadensis*	Digestive aid, mucolytic, antiinfective	Uterine, cardiac stimulation; GI upset, leukopenia
Hellebore	*Veratrum* spp.	Antihypertensive	Vomiting, bradycardia, hypotension
Hyssop	*Hyssopus officinalis*	Asthma, mucolytic	Seizures
Juniper	*Juniperus communis*	Hallucinogen	GI upset, seizures, renal injury, hypotension, bradycardia
Kava	*Piper methysticum*	Sedative	Inebriation
Kombucha		Stimulant	Metabolic acidosis, hepatotoxicity, death
Licorice	*Glycyrrhiza* spp.	Indigestion	Mineralocorticoid effects
Lily of the valley	*Convallaria* spp.	Cardiotonic	GI (nausea, vomiting), cardiac arrhythmias
Linn (willow)	*Salix caprea*	Purgative	Hemolysis with glucose-6-phosphate dehydrogenase deficiency
Lobelia (Indian tobacco)	*Lobelia* spp.	Stimulant	Nicotine intoxication
Ma Huang	*Ephedra sinica*	Stimulant	Sympathetic crisis, especially with monoamine oxidase inhibitors
Mandrake	*Mandragora officinarum*	Hallucinogen	Anticholinergic syndrome
Mormon tea	*Ephedra nevadensis*	Stimulant, asthma, antipyretic	Hypertension, sympathomimetic
Nutmeg	*Myristica fragrans*	Hallucinogen, abortifacient	Hallucinations, GI upset
Oleander	*Nerium oleander*	Cardiac stimulant	Cardiac arrhythmias
Passionflower	*Passiflora caeruliea*	Hallucinogen	Hallucinations, seizures, hypotension
Periwinkle	*Vinca* spp.	Antiinflammatory, diabetes	Alopecia, seizures, hepatotoxicity
Pokeweed	*Phytolacca* spp.	Arthritis, chronic pain	GI upset, seizures, death
Sabah	*Sauropus androgynus*	Weight loss, vision	Pulmonary injury
Sage	*Salvia* spp.	CNS stimulant	Seizures
Snakeroot	*Rauwolfia serpentina*	Sedative, antihypertensive	Bradycardia, coma
Squill	*Urginea maritima*	Arthritis, cardiac stimulant	Seizures, arrhythmias, death
Thorn apple (jimsonweed)	*Datura stramonium*	Hallucinations	Anticholinergic
Tonka bean	*Dipteryx odorata*	Anticoagulant	Bleeding diathesis
Valerian root	*Valeriana* spp.	Sedative	Sedation, obtundation
Wild (squirting) cucumber	*Ecballium elaterium*	Constipation, antiinflammatory, rheumatic disease	Airway obstruction
Wormwood (mugwort)	*Artemisia* spp.	Stimulant, hallucinogen	Hallucinations, seizures, uterine stimulation
Yohimbine	*Corynanthe yohimbe*	Aphrodisiac, stimulant	Hypertension, sympathetic crisis

CNS, Central nervous system; GI, gastrointestinal.

From Kingston RL, Foley C. Herbal, traditional, and alternative medicines. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: Saunders; 2007, Table 68.1, p. 1081.

Clinical and Laboratory Manifestations. Early symptoms are nonspecific and include headache, malaise, nausea, and vomiting. These symptoms are often misdiagnosed as indicating flu or food poisoning. At higher exposure levels, patients can develop mental status changes, confusion, ataxia, syncope, tachycardia, and tachypnea. Severe poisoning is manifested by coma, seizures, myocardial ischemia, acidosis, cardiovascular collapse, and potentially death. Physical examination should focus on the cardiovascular and neurologic systems because these are the most detrimentally affected by CO. Emergency department evaluation should include arterial or venous blood gas analysis with HbCO determined by CO-oximetry, CK level in severely poisoned patients, pregnancy test, and ECG and troponin in any patient with cardiac symptoms.

Treatment. Prevention of CO poisoning is paramount and should involve educational initiatives and the use of home CO detectors. Treatment of CO poisoning focuses on the administration of 100% oxygen to enhance elimination of CO. In ambient air the average half-life of HbCO is 4-6 hours. This is dramatically reduced to 60-90 minutes by providing 100% oxygen at normal atmospheric pressures by non-rebreather face mask. Severely poisoned patients might benefit from **hyperbaric oxygen (HBO)**, which decreases the half-life of HbCO to 20-30 minutes and is thought also to decrease the risk of delayed neurologic sequelae. Although the clinical benefits and referral guidelines for HBO therapy remain controversial, frequently cited indications include syncope, coma, seizure, altered mental status, evidence of myocardial ischemia, HbCO level >25% (or >15% in pregnancy), and abnormal cerebellar examination. Consultation with a PCC, medical toxicologist, or HBO facility can assist clinicians in determining which patients could benefit from HBO therapy. Sequelae of CO poisoning include persistent and delayed cognitive and cerebellar effects. HBO advocates believe that the risk of such sequelae is minimized through the delivery of 100% oxygen at 3 atm of pressure. Patients typically receive oxygen, by non-rebreather mask or hyperbaric chamber, for 6 hours.

Hydrogen Cyanide

Pathophysiology. Cyanide inhibits cytochrome-*c* oxidase, part of the electron transport chain, interrupting cellular respiration and leading to profound tissue hypoxia. Patients may be exposed to hydrogen cyanide (HCN) gas in the workplace (manufacturing of synthetic fibers, nitriles, and plastics) by smoke inhalation in a closed-space fire or by ingestion of cassava flour.

Clinical and Laboratory Manifestations. Onset of symptoms is rapid after significant exposure. Clinical manifestations of toxicity include headache, agitation/confusion, sudden loss of consciousness, tachycardia, cardiac dysrhythmias, and metabolic acidosis. Cyanide levels can be measured in whole blood but are not readily available at most institutions. A severe lactic acidosis (lactate >10 mmol/L) in fire victims suggests cyanide toxicity. Impaired oxygen extraction by tissues is implied by elevated mixed-venous oxyhemoglobin saturation, another laboratory finding suggesting cyanide toxicity.

Treatment. Treatment includes removal from the source of exposure, rapid administration of high concentrations of oxygen, and antidotal therapy.

Hydroxocobalamin is the preferred agent for use in known or suspected cyanide poisoning (see Table 94.8). This antidote reacts with cyanide to form the nontoxic cyanocobalamin (vitamin B_{12}), which is then excreted in urine. Side effects of hydroxocobalamin include red discoloration of the skin and urine, transient hypertension, and interference with colorimetric laboratory assays. Other FDA-approved treatments for cyanide poisoning include sodium nitrite and sodium thiosulfate, either alone or in combination. Sodium nitrite induces methemoglobinemia, which may exacerbate symptoms of carboxyhemoglobinemia and thus should be avoided in patients with smoke inhalation.

Miscellaneous Toxic Agents Found in the Home

Nicotine-Containing Products

Nicotine poisoning has become increasingly common with the recent advent of vaporizer ("vaping") and e-cigarette devices (see Chapter 157). Although there are many nicotine-containing products (patches, gums, snuff, chewing tobacco, sprays, lozenges), tobacco cigarettes remain the main source of exposure. Prescription medications (varenicline and cytisine) are available that are partial nicotine receptor agonists. For children, some of the most concerning exposures are from the bottles of liquid nicotine used to refill vaping and e-cigarette devices. These bottles typically do not have childproof caps and contain a large amount of concentrated nicotine.

Pathophysiology. Nicotine acts on nicotinic ACh receptors in the nervous system, neuromuscular junctions, and adrenal medulla, stimulating neurotransmitter release. Nicotine's effects on the dopaminergic reward pathway play a significant role in its addictive properties. The effects of nicotine are dose dependent; at lower doses it primarily acts on the brain, causing stimulation. At higher doses, nicotine overstimulates receptors, leading to inhibition and resulting in neuromuscular and nervous system blockade.

Clinical and Laboratory Manifestations. Clinical effects of nicotine also depend on the dose. At low doses typically achieved through smoking, nicotine results in cognitive and mood enhancement, increased energy, and appetite suppression. Shortness of breath, cough, and fever may be seen with e-cigarette use–associated lung injury (EVALI), an inflammatory response in the lungs triggered by vaping. At higher doses, significant toxicity follows a biphasic pattern, where cholinergic stimulation symptoms predominate and are later followed by inhibition. The first signs of nicotine poisoning are nausea, vomiting, diarrhea, and often muscle fasciculations. Tachycardia and hypertension occur initially, although in severe poisoning these progress to bradycardia, hypotension, coma, and respiratory muscle failure, which typically leads to death if not treated. Serum and urinary levels of nicotine and its metabolite cotinine can be obtained, but these rarely are available in real time and therefore have little effect on diagnosis and management.

Treatment. Treatment of nicotine poisoning focuses on maximizing symptomatic and supportive care. Aggressive airway management should be the priority, especially in severe poisonings, because death usually occurs from respiratory muscle paralysis. IV fluids with escalation to vasopressors should be used for hypotension. Seizures should be managed with benzodiazepines, barbiturates, or propofol.

Single-Use Detergent Sacs

Commonly known as laundry "pods" for clothing, these products resemble candy to many children. When bitten into, a relatively large dose of concentrated detergent is expelled under pressure onto the posterior pharynx and vocal cords. This can lead to stridor and other signs of respiratory distress. Occasionally, and for unknown reasons, these children may also develop altered mental status. Supportive care with attention to any airway and breathing issues is warranted. Admission to the hospital is often indicated. Importantly, these are not considered caustic ingestions; the pH of these products is in the neutral zone. Upper GI endoscopy is rarely indicated. Curiously, laundry detergent ingested from a bottle is rarely of significant concern.

Electric Dishwasher Detergent

Especially when in the form of crystals, these products are highly alkaline (pH >13), and exposure by ingestion can cause significant burns to the vocal cords and GI tract. Admission for expectant management or upper GI endoscopy is usually indicated.

Magnets

Most foreign body ingestions pass through the GI tract once known to have passed into the stomach. However, ingestion of ≥2 magnets (unless very weak refrigerator-style magnets) cause concern for bowel obstruction and perforation (see Chapter 380). Admission for attempted retrieval by endoscopy or clearance by WBI should be considered.

Batteries

Any disk or button-style battery lodged in the esophagus or airway should be considered a true emergency warranting immediate referral

to an endoscopist for removal (see Chapter 373). These batteries can cause necrosis of the tissues in which they are lodged by continued electrical discharge and leaking of their contents (the former is likely the primary method of injury). Mucosal contact for even 2 hours might induce necrosis. Once past the lower esophageal sphincter, button or even larger batteries (e.g., AA, AAA) can usually be allowed to pass through the GI tract with close follow-up.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Human Genetics

PART VIII

Chapter 95

Genetics in Pediatric Medicine

Daryl A. Scott and Brendan Lee

Since the completion of the Human Genome Project, there has been an unprecedented expansion in the understanding of how human health is impacted by variations in genomic sequence and epigenetic, non-sequence-based changes that affect gene expression. There has also been the development and implementation of accurate clinical tests that makes it easier for physicians to detect pathogenic variant changes. In addition, there has been a dramatic increase in the availability of information about the genetic aspects of pediatric diseases, particularly on the internet (Table 95.1).

THE BURDEN OF GENETIC DISORDERS IN CHILDHOOD

Medical problems associated with genetic disorders can appear at any age, with the most obvious and serious problems typically manifesting in childhood. It has been estimated that 53/1,000 children and young adults can be expected to have diseases with an important genetic component. If congenital anomalies are included, the rate increases to 79/1,000. In 1978 just over half of admissions to pediatric hospitals were for a genetic condition. By 1996, because of changes in healthcare delivery and a greater understanding of the genetic basis of many disorders, that percentage increased to 71% in one large pediatric hospital in the United States, with 96% of chronic disorders leading to admission having an obvious genetic component or influenced by genetic susceptibility.

Major categories of genetic disorders include single-gene, genomic, chromosomal, and multifactorial conditions.

Individually, each **single-gene disorder** is rare, but collectively they represent an important contribution to childhood disease. The hallmark of a single-gene disorder is that the phenotype is overwhelmingly determined by changes that affect an individual gene. The character and severity of a phenotype associated with some single-gene disorders can vary from one patient to another. In some cases, this may be due to differences in the severity of the change affecting the gene. In other cases, variability is seen in individuals who carry the same pathogenic variant or variants. This is termed **variable expressivity**; the same pathogenic variants in *GJB2* can cause mild, moderate, severe, or profound sensorineural hearing loss in different individuals. This variability may be due to differences in other genetic, epigenetic, environmental, and/or stochastic factors. If this variability results in some individuals being completely unaffected, we say that the disorder shows **incomplete penetrance**. Some single-gene disorders are associated with phenotypes that affect different organ systems or biologic functions that may appear unrelated. Pendred syndrome is caused by pathogenic variants in *SLC26A4* and is characterized by both hearing loss and thyroid enlargement (goiter). This feature of some genetic diseases is referred to as **pleiotropy**.

Common single-gene disorders include sickle cell anemia and cystic fibrosis. Some identifiable syndromes and diseases can be caused by more than one gene. Noonan syndrome can be caused by pathogenic variants in at least 12 different genes. In addition, pathogenic variants

Table 95.1 Useful Internet Genetic Reference Sites

RESOURCE	WEB ADDRESS
National Center for Biotechnology Information A general reference maintained by the National Library of Medicine	www.ncbi.nlm.nih.gov
Online Mendelian Inheritance in Man A useful resource for clinicians containing information on all known mendelian disorders and >12,000 genes. Information focuses on the relationship between phenotype and genotype.	www.ncbi.nlm.nih.gov/omim
Genetic Testing Registry A resource that provides information on individual genes, genetic tests, clinical laboratories, and medical conditions. This resource also provides access to GeneReviews, a collection of expert-authored reviews on a variety of genetic disorders.	www.ncbi.nlm.nih.gov/gtr/
Genetics — MedlinePlus A resource that provides consumer-friendly information about the effects of genetic variations on human health	http://medlineplus.gov/genetics/
National Human Genome Research Institute A resource for information about human genetics and ethical issues	www.genome.gov
Human Gene Mutation Database A searchable index of all described pathogenic variants in human genes with phenotypes and references	www.hgmd.cf.ac.uk
DECIPHER A database designed to aid physicians in determining the potential consequences of chromosomal deletions and duplications	http://decipher.sanger.ac.uk
Database of Genomic Variants A database of chromosomal alterations seen in normal controls	http://dgv.tcag.ca/dgv/app/home
American Society of Human Genetics	www.ashg.org
American College of Medical Genetics and Genomics	www.acmg.net

affecting a single gene may cause more than one disorder. Variants in *SCN5A* can cause Brugada syndrome type 1, long QT syndrome type 3, dilated cardiomyopathy type 1E, familial atrial fibrillation type 10, familial ventricular fibrillation type 1, progressive heart block type 1A, nonprogressive heart block, and sick sinus syndrome type 1.

Single-gene disorders tend to occur when changes in a gene have a profound effect on the *quantity* of the gene product produced, either too much or too little, or the *function* of the gene product, either a loss of function or a harmful gain of function. Single-gene disorders can be caused by de novo sequence changes that are not found in the unaffected parents of the affected individual, or they may be caused by inheriting the affected gene. When a single-gene disorder is known to be caused by changes in only one gene, or a small number of individual genes, searching for deleterious changes is classically performed by directly sequencing that gene and, in some cases, looking for small deletions and/or duplications in that gene. When multiple genes can cause a particular disorder, it is sometimes more efficient and cost-effective to screen large numbers of disease-causing genes using a disease-specific panel, which takes advantage of massively parallel or next-generation sequencing technology, rather than screening genes individually. When such panels are not available, or when the diagnosis is in question, physicians may consider screening the protein-coding regions of all genes by **exome sequencing (ES),** also termed whole exome sequencing (WES), on a clinical basis. In many circumstances, ES is less expensive than sequencing multiple individual genes. **Whole genome sequencing (WGS)**, in which an individual's entire genome is sequenced, is another clinical option (see Chapter 98; Table 95.2).

The risk of having a child with a particular single-gene disorder can vary from one population to another. This may be the result of a **founder effect**, in which a specific change affecting a disease-causing gene becomes relatively common in a population derived from a small number of founder individuals. This high frequency is maintained when there is relatively little interbreeding with persons outside that population because of social, religious, or physical barriers. This is the case for Tay-Sachs disease in Ashkenazi Jews and French Canadians. Other changes may be subject to **positive selection** when found in the heterozygous carrier state. In this case, individuals who carry a single copy of a genetic change **(heterozygotes)** have a survival advantage over noncarriers. This can occur even when individuals who inherit two copies of the change **(homozygotes)** have severe medical problems. This type of positive selection is evident among individuals in sub-Saharan Africa who carry a single copy of a hemoglobin pathogenic variant that confers relative resistance to malaria but causes sickle cell anemia in homozygotes.

Genomic disorders are a group of diseases caused by alterations in the genome, including **deletions** (copy number loss), **duplications** (copy number gain), **inversions** (altered orientation of a genomic region), and **chromosomal rearrangements** (altered location of a genomic region). **Contiguous gene disorders** are caused by changes that affect two or more genes that contribute to the clinical phenotype and are located near one an other on a chromosome. DiGeorge syndrome, which is caused by deletions of genes located on chromosome 22q11, is a common example. Some genomic disorders are associated with distinctive phenotypes whose patterns can be recognized clinically. Other genomic disorders do not have a distinctive pattern of anomalies but can cause developmental delay, cognitive impairment, structural birth defects, abnormal growth patterns, and changes in physical appearance.

Fluorescent in situ hybridization (FISH) can provide information about the copy number and location of a specific genomic region. **Array-based copy number detection assays**, sometimes referred to as chromosomal microarray analyses, can be used to screen for chromosomal deletions and duplications (large and small) across the genome but do not provide information about the orientation or location of genomic regions. A **chromosome analysis (karyotype)** can detect relatively large chromosomal deletions and duplications and can also be useful in identifying inversions and chromosomal rearrangements even when they are **copy number neutral** changes that do not result in a deletion or duplication of genomic material (e.g., balanced translocations).

Table 95.2 Indications for Single Gene, Gene Panel, Exome, and Genome Sequencing

INDICATIONS	EXAMPLES
SINGLE GENE	
Minimal locus heterogeneity (only one or a small number of genes known to cause the condition)	*CFTR* for cystic fibrosis
Distinctive clinical findings that clearly point to specific gene	*PAH* for phenylketonuria
GENE PANEL	
Locus heterogeneity (multiple genes are known to cause the same or similar conditions)	Muscular dystrophy panel
Disorders with overlapping phenotypes	Cardiomyopathy panel
Disorders that share one manifestation but can have very different presentations	Epilepsy panel
Disorders associated with genes from a common pathway or structure	*RAS*opathy panel
EXOME	
Extreme heterogeneity and de novo mutations common	Autism, intellectual disability
Two or more unrelated phenotypes in one patient	Oculocutaneous albinism and neutropenia
No distinctive phenotypic feature present	Kabuki syndrome
Phenotype indistinct and underlying cause not clear	Congenital diarrhea, Zellweger syndrome
GENOME	
As above for Exome, plus:	
Noncoding variation is suspected as a cause	Hypertrophic cardiomyopathy
Structural variation is suspected as a cause	DiGeorge syndrome
Exome sequencing already performed and was nondiagnostic	Undiagnosed Diseases Network
Rapid generation of sequencing data needed for patients who are critically ill	Neonates and children in intensive care
Suspected mitochondrial disorder: multisystem (heart, brain, muscle, liver) disorder	Whole genome and/or mitochondrial DNA (tissue) sequencing

From Manolio TA, Rowley R, Williams MS, et al. Opportunities, resources, and techniques for implementing genomics in clinical care. *Lancet*. 2019;394:511–520. Table 2.

Deletions, duplications, and chromosomal rearrangements that affect whole chromosomes, or large portions of a chromosome, are typically referred to as **chromosomal disorders**. One of the most common chromosomal disorders is Down syndrome, which is most often associated with the presence of an extra copy, or **trisomy**, of an entire chromosome 21. When all or part of a chromosome is missing, the disorder is referred to as **monosomy**. **Translocations** are a type of chromosomal rearrangement in which a genomic region from one chromosome is transferred to a different location on the same chromosome or on a different (nonhomologous) chromosome. Translocations can be *balanced*, meaning that no genetic material has been lost or gained, or they can be *unbalanced*, in which some genetic material has been deleted or duplicated.

In some cases, only a portion of cells that make up a person's body are affected by a single-gene defect, a genomic disorder, or a chromosomal defect. This is referred to as **mosaicism** and indicates that the individual's body is made up of two or more distinct cell populations. Through use of technologies with high sensitivity, it has become

evident that there can be significant low-level mosaicism in *somatic* tissues.

Polygenic disorders are caused by the cumulative effects of variations in more than one gene. **Multifactorial** disorders are caused by the cumulative effects of variations in multiple genes or the combined effects of genetic, epigenetic, and/or environmental factors. Spina bifida and isolated cleft lip or palate are common birth defects that display multifactorial inheritance patterns. Multifactorial inheritance is seen in many common pediatric disorders, such as asthma and diabetes mellitus. These traits can cluster in families but do not have a mendelian pattern of inheritance (see Chapter 97). In these cases, the genetic changes or variations that are contributing to a particular disorder are often unknown, and genetic counseling is based on empirical data and estimates.

THE CHANGING PARADIGM OF GENETICS IN MEDICINE

Genetic testing is increasingly available for a wide variety of both rare and relatively common genetic disorders. Genetic testing is typically used in pediatric medicine to resolve uncertainty regarding the underlying etiology of a child's medical problems. Identifying a molecular cause often provides the basis for improved genetic counseling, may alter medical management, and may suggest that a specific therapy should be employed. Even in cases where a specific treatment is not available, identifying a genetic cause can aid physicians in providing individuals and families with accurate prognostic and recurrence risk information, can often help to relieve unfounded feelings of guilt, and may stem the tide of misdirected blame.

Genetic tests are influencing an increasing number of medical decisions and are becoming a seamless part of routine medical care. Although most genetic testing is presently aimed at identifying or confirming a diagnosis, in the future genetic testing may find wider application as a means of determining whether an individual is predisposed to develop a particular disease. Another area in which genetic testing could make a significant impact is on individualized drug treatment (pharmacogenetics). It has long been known that genetic variation in the enzymes involved in drug metabolism underlies differences in the therapeutic effect and toxicity of some drugs. When the genetic changes that underlie these variations are identified, new genetic tests can be developed that allow physicians to tailor treatments based on individual variations in drug metabolism, responsiveness, and susceptibility to toxicity. It is likely that the expansion of such testing will depend, at least in part, on the extent to which such tests can be linked to strategies to prevent disease or improve outcome (see Chapter 98).

Long-standing and highly successful carrier screening programs have existed for disorders such as Tay-Sachs disease and many other rare, single-gene disorders that are prevalent in specific populations. Couples are usually offered screening for a variety of conditions based, in part, on ancestry (Tay-Sachs disease, hemoglobinopathies, cystic fibrosis). Couples found to be at increased risk for such disorders can be offered preconception or prenatal testing aimed at detecting specific disease-causing variants.

Prenatal screening is routinely offered for chromosomal disorders such as trisomy 13, trisomy 18, and Down syndrome. Pregnancies affected by these, and possibly other genetic disorders, are being recognized by noninvasive screening tests targeting **fetal cell-free DNA** in maternal blood and by fetal ultrasound. When genetic disorders are suspected, chorionic villus sampling at 10-12 weeks of gestation or amniocentesis at 16-18 weeks of gestation can provide material for genetic testing. When a couple are at risk for a specific genetic defect, **preimplantation genetic diagnosis** can sometimes be used to select unaffected early embryos, which are then implanted as part of an in vitro fertilization procedure.

Although prenatally obtained genetic material can be used to identify single-gene disorders, genomic disorders, and chromosomal anomalies, the information obtained on any pregnancy depends on the tests that are ordered. It is important that physicians select the most appropriate prenatal tests and that couples understand the limitations of these tests. No amount of genetic testing can guarantee the birth of a healthy child.

Specific treatments are not available for most genetic disorders, although some important exceptions exist (see Chapter 98). **Inborn errors of metabolism** were the first genetic disorders to be recognized, and many are amenable to treatment by dietary manipulation (see Chapter 104). These conditions result from genetically determined deficiency of specific enzymes, leading to the buildup of toxic substrates and/or deficiency of critical end products.

Individual metabolic disorders tend to be very rare, but their combined impact on the pediatric population is significant. Tandem mass spectrometry has made it relatively inexpensive to screen for a large number of these disorders in the newborn period. Use of this technology not only dramatically increases the number of metabolic disorders identified within a population but also allows treatment to be initiated at a much earlier stage in development. Broader screening in the postnatal period, in the form of metabolomic screening, has increased the potential for identifying an increasing list of rare inborn errors of metabolism, especially when combined with exome or genome sequencing.

Progress in genetic therapies has improved the treatment of some **lysosomal storage disorders** (see Chapter 106.4). These metabolic diseases are caused by defects in lysosomal function. Lysosomes are cellular organelles that contain specific digestive enzymes. Some of these disorders that were characterized by early lethal or intractable chronic illness can now be treated using specially modified enzymes administered by intravenous infusion. These enzymes are taken up by cells and incorporated into lysosomes. Conditions such as Gaucher disease and Fabry disease are routinely treated using **enzyme replacement**; similar therapies are being developed for other lysosomal disorders.

Therapeutic advances are also being made in the treatment of nonmetabolic genetic disorders. Improvements in surgical techniques and intensive care medicine are extending the survival of children with life-threatening birth defects such as congenital diaphragmatic hernia and severe cardiac defects. In many cases, the life expectancy of children with debilitating genetic disorders is also increasing. Improvements in nutrition and the management of chronic pulmonary disease in patients with cystic fibrosis allow an increasing percentage of affected patients to survive into adulthood, creating a need to transition care from pediatric to adult providers.

Gene replacement therapies are being used in the treatment of a variety of genetic disorders (see Chapter 98). Stem cell–based therapies have also been employed as a potential treatment for a number of intractable disorders.

DIRECT-TO-CONSUMER GENETIC TESTING

In most cases, healthcare providers order genetic tests, interpret the results, communicate these results to their patients, and then document these finding in the medical record. The costs of these tests are often covered completely or in part by a health insurance company. In contrast, some companies are offering direct-to-consumer genetic tests in which individuals order their own tests and receive test results directly from the company. The individual usually pays for these tests, and the results are not recorded in their medical record unless the individual chooses to share this information with their healthcare providers. Some direct-to-consumer genetic tests only provide information about common traits or information about an individual's ancestry or relationship to others **(ancestry testing)**. Other direct-to-consumer tests are designed to make predictions about health and/or to identify pathogenic variants associated with specific genetic disorders. In some cases, individuals ordering these tests may have the option of reviewing their results with a healthcare provider employed by the company performing the test.

One of the main benefits of direct-to-consumer testing is that it allows individuals to privately access their genetic information without having to involve a healthcare provider or their insurance company. Although this could be seen as a means of empowering individuals with regards to their healthcare, the benefits derived from such testing depend heavily on the appropriateness of the test ordered, the quality of

the testing/reporting services, the capacity of the individual to understand the test results, and their ability to make informed choices based on those results.

ETHICS ISSUES

Genetic testing, diagnosis, and treatment should be performed *confidentially*. Nothing is as personal as one's genetic information, and all efforts should be made to avoid any stigma for the patient. Many people worry that results of genetic testing will put them, or their child, at risk for genetic discrimination. **Genetic discrimination** occurs when people are treated unfairly because of a difference in their DNA that suggests they have a genetic disorder or they are at an increased risk of developing a certain disease. In the United States the Genetic Information Nondiscrimination Act of 2008 protects individuals from genetic discrimination at the hands of health insurers and employers but does not extend protection against discrimination from providers of life, disability, or long-term care insurance.

The decisions about genetic testing should be based on a careful evaluation of the potential benefits and risks. In the pediatric setting, these decisions may be more difficult because physicians and parents are often called on to make decisions for a child who cannot directly participate in discussions about testing. Molecular diagnostic tests are often used to diagnose malformation syndromes, cognitive delay, or other disabilities in which there is a clear benefit to the child. In other cases, such as genetic testing for susceptibility to adult-onset diseases, it is appropriate to wait until the child or adolescent is mature enough to weigh the potential risks and benefits and make their own decisions about genetic testing.

Policies regarding genetic testing of children have been developed collaboratively by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG; *Pediatrics* 131[3]:620–622, 2013). These recommendations are outlined in the following list.

General Recommendations

1. Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child.
2. Genetic testing is best offered in the context of genetic counseling. Genetic counseling can be performed by clinical geneticists, genetic counselors, or any other healthcare provider with appropriate training and expertise. AAP and ACMG support the expansion of educational opportunities in human genomics and genetics for medical students, residents, and practicing pediatric primary care providers.

Diagnostic Testing

3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally, and when appropriate, the assent of the child should be obtained.
4. When performed for therapeutic purposes, pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent. If a pharmacogenetic test result carries implications beyond drug targeting or dose responsiveness, the broader implications should be discussed before testing.

Newborn Screening

5. AAP and ACMG support the mandatory offering of newborn screening for all children. After education and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected.

Carrier Testing

6. AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The AAP and ACMG advise against school-based testing or screening programs, because the school environment is unlikely to be conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or appropriate counseling about test results.
7. For pregnant adolescents or for adolescents considering reproduction, genetic testing and screening should be offered as clinically indicated, and the risks and benefits should be explained clearly.

Predictive Genetic Testing

8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.
9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and the parents concur in their interest in predictive testing.
10. For ethical and legal reasons, healthcare providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychologic, and social implications, not only for the minor but also for other family members.

Histocompatibility Testing

11. Tissue compatibility testing of minors of all ages is permissible to benefit immediate family members but should be conducted only after thorough exploration of the psychosocial, emotional, and physical implications of the minor serving as a potential stem cell donor. A donor advocate or similar mechanism should be in place from the outset to avert coercion and safeguard the interests of the child.

Adoption

12. The rationale for genetic testing of children in biological families should apply for adopted children and children awaiting placement for adoption. If a child has a known genetic risk, prospective adoptive parents must be made aware of this possibility. In rare cases, it may be in a child's best interest to undergo predictive genetic testing for a known risk before adoption to ensure the child's placement with a family capable of and willing to accept the child's potential medical and developmental challenges. In the absence of such indications, genetic testing should not be performed as a condition of adoption.

Disclosure

13. At the time of genetic testing, parents or guardians should be encouraged to inform their child of the test results at an appropriate age. Parents or guardians should be advised that, under most circumstances, a request by a mature adolescent for test results should be honored.
14. Results from genetic testing of a child may have implications for the parents and other family members. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications. Healthcare providers should encourage patients and families to share this information and offer to help explain the results to the extended family or refer them for genetic counseling.
15. Misattributed paternity, use of donor gametes, adoption, or other questions about family relationships may be uncovered "incidentally" whenever genetic testing is performed, particularly when testing multiple family members. This risk should be discussed, and a plan about disclosure or nondisclosure should be in place before testing.

Direct-to-Consumer Testing

16. AAP and ACMG strongly discourage the use of direct-to-consumer and home-kit genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 96

Principles of Human Genetics

Daryl A. Scott and Brendan Lee

THE HUMAN GENOME

The human genome has approximately 20,000 genes that encode the wide variety of proteins found in the human body. Reproductive or germline cells contain one copy (N) of this genetic complement and are **haploid**, whereas somatic (nongermline) cells contain two complete copies (2N) and are **diploid**. Genes are organized into long segments of deoxyribonucleic acid (**DNA**), which, during cell division, are compacted into intricate structures together with proteins to form chromosomes. Each somatic cell has 46 chromosomes: 22 pairs of **autosomes**, or nonsex chromosomes, and one pair of **sex chromosomes** (XY in a male, XX in a female). Germ cells (ova or sperm) contain 22 autosomes and one sex chromosome, for a total of 23. At fertilization, the full diploid chromosome complement of 46 is again realized in the embryo.

Most of the genetic material is contained in the cell's nucleus. The mitochondria (the cell's energy-producing organelles) contain their own unique genome. The **mitochondrial chromosome** consists of a double-stranded circular piece of DNA, which contains 16,568 base pairs (bp) of DNA and is present in multiple copies per cell. The proteins that occupy the mitochondria are produced either in the mitochondria, using information contained in the mitochondrial genome, or are produced outside of the mitochondria, using information contained in the nuclear genome, and then transported into the organelle. Sperm do not usually contribute mitochondria to the developing embryo, so all mitochondria are maternally derived, and a child's mitochondrial genetic makeup derives exclusively from the child's biologic mother (see Chapter 108).

FUNDAMENTALS OF MOLECULAR GENETICS

DNA consists of a pair of chains of a sugar-phosphate backbone linked by pyrimidine and purine bases to form a **double helix** (Fig. 96.1). The sugar in DNA is deoxyribose. The pyrimidines are cytosine (C) and thymine (T), and the purines are guanine (G) and adenine (A). The bases are linked by hydrogen bonds such that A always pairs with T and G with C. Each strand of the double helix has polarity, with a free phosphate at one end (5′) and an unbonded hydroxyl on the sugar at the other end (3′). The two strands are oriented in opposite polarity in the double helix.

The replication of DNA follows the pairing of bases in the parent DNA strand. The original two strands unwind by breaking the hydrogen bonds between base pairs. Free nucleotides, consisting of a base attached to a sugar-phosphate chain, form new hydrogen bonds with their complementary bases on the parent strand; new phosphodiester bonds are created by enzymes called **DNA polymerases.** Replication of chromosomes begins simultaneously at multiple sites, forming replication bubbles that expand bidirectionally until the entire DNA molecule (chromosome) is replicated. Errors in DNA replication, or pathogenic variants induced by environmental mutagens such as irradiation or chemicals, are detected and potentially corrected by DNA repair systems.

Information encoded in DNA, predominantly located in the cell's nucleus, is transcribed into **messenger** ribonucleic acid **(mRNA)**, which is then transported to the cytoplasm, where it is translated into protein. A prototypical gene consists of a regulatory region, segments called **exons** that encode the amino acid sequence of a protein, and intervening segments called **introns** (Fig. 96.2).

Transcription is initiated by attachment of ribonucleic acid (RNA) polymerase to the promoter site upstream of the beginning of the coding sequence. Specific proteins bind to the region to repress or activate transcription by compacting or opening chromatin, which is a complex of DNA and histone proteins. It is the action of these regulatory proteins **(transcription factors)** that determines, in large part, when a gene is turned on or off. Some genes are also turned on and off by methylation of cytosine bases that are adjacent to guanine bases **(cytosine-phosphate-guanine bases** [**CpGs**]). Methylation is an example of an **epigenetic** change, meaning a change that can affect gene expression, and possibly the characteristics of a cell or organism, but that *does not* involve a change in the underlying genetic sequence. Gene regulation is flexible and responsive, with genes being turned on or off during development and in response to internal and external environmental conditions and stimuli. Another epigenetic mechanism that controls gene expression is the biochemical modification of histone proteins around which DNA is wound. These modifications can affect the relative accessibility of chromatin by enzymes for transcription.

Transcription proceeds through the entire length of the gene in a 5′ to 3′ direction to form an mRNA transcript whose sequence is complementary to that of one of the DNA strands. RNA is a sugar-phosphate chain with pyrimidines and purines. In RNA the sugar is ribose, and uracil replaces the thymine found in DNA. A "cap" consisting of 7-methylguanosine is added to the 5′ end of the RNA in a 5′-5′ bond and, for most transcripts, several hundred adenine bases are enzymatically added to the 3′ end after transcription.

mRNA processing occurs in the nucleus and consists of excision of the introns and splicing together of the exons. Specific sequences at the start and end of introns mark the sites where the splicing machinery will act on the transcript. In some cases, there may be tissue-specific patterns to splicing, so that the same primary transcript can produce multiple distinct proteins.

The processed transcript is next exported to the cytoplasm, where it binds to ribosomes, which are complexes of protein and **ribosomal** RNA **(rRNA)**. The genetic code is then read in triplets of bases, each triplet corresponding with a specific amino acid or providing a signal that terminates **translation**. The triplet codons are recognized by **transfer** RNAs **(tRNAs)** that include complementary anticodons and bind the corresponding amino acid, delivering it to the growing peptide. New amino acids are enzymatically, sequentially attached to the growing peptide. Each time an amino acid is added, the ribosome moves one triplet codon step along the mRNA. Eventually a **stop codon** is reached, at which point translation ends and the peptide is released. In some proteins, there are **posttranslational modifications**, such as attachment of sugars **(glycosylation)**. The protein is then delivered to its destination within or outside the cell by trafficking mechanisms that recognize portions of the peptide.

Another mechanism of gene regulation is **noncoding** RNAs, which are RNAs transcribed from DNA but not translated into proteins. Noncoding RNAs function in many contexts, including mediating splicing, the processing of coding RNAs in the nucleus, and the translation of coding mRNAs in ribosomes. The roles of *long* noncoding RNAs (>200 bp) and *short* noncoding RNAs (<200 bp) extend beyond these processes to impact a diverse set of biologic functions, including the regulation of gene expression. **MicroRNAs (miRNAs)** are a class of small RNAs that control gene expression in the cell by directly targeting specific sets of coding RNAs by direct RNA–RNA binding. This RNA–RNA interaction can lead to degradation of the target-coding RNA or inhibition of translation of the protein specified by that coding RNA. miRNAs often target and regulate several hundred mRNAs.

GENETIC VARIATION

The process of producing protein from a gene is subject to disruption at multiple levels because of alterations in the DNA sequence (Fig. 96.3). Changes in the regulatory region can lead to altered gene expression, including increased or decreased rates of transcription, failure of gene activation, or activation of the gene at inappropriate times or in inappropriate cells. Changes in the coding sequence can lead to **substitution** of one amino acid for another (**missense variant** or **nonsynonymous variant**) or creation of a stop codon in the place of an amino acid codon (**nonsense** or **stop-gain variant**).

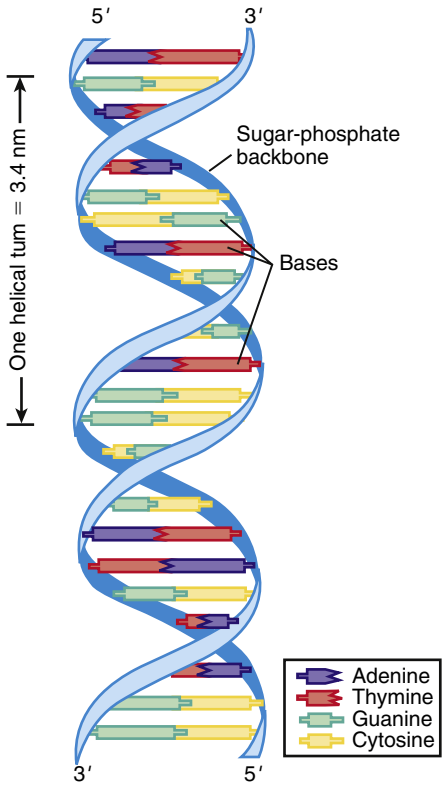

Fig. 96.1 DNA double helix, with sugar-phosphate backbone and nitrogenous bases. (*From Jorde LB, Carey JC, Bamshad MJ, et al., eds. Medical Genetics, 2nd ed. St Louis: Mosby; 1999: p. 8.*)

Overall, missense and nonsense variants are the most common (56% of variants); small deletions or insertions represent approximately 24% of variants (Table 96.1). Some single-base changes do not affect the amino acid (**silent**, **wobble**, or **synonymous variants**) because there may be several triplet codons that correspond to the same single amino acid. Amino acid substitutions can have a profound effect on protein function if the chemical properties of the substituted amino acid are markedly different. Other substitutions can have a subtle or no effect on protein function, particularly if the substituted amino acid is chemically similar to the original. Single nucleotide changes, whether silent or missense, are termed **single nucleotide variants (SNV)**.

Genetic changes can also include **insertions** or **deletions** ("**indels**"). Insertions or deletions of a nonintegral multiple of three bases into the coding sequence leads to a **frameshift,** altering the grouping of bases into triplets. This leads to translation of an incorrect amino acid sequence and often a premature stop to translation. Insertion or deletion of an integral multiple of three bases into the coding sequence will insert or delete a corresponding number of amino acids from the protein, leading to **in-frame** alterations that maintain the amino acid sequence outside the deleted or duplicated amino acids. Larger scale insertions or deletions can disrupt a coding sequence or result in complete deletion of an entire gene or group of genes.

Pathogenic variants usually can be classified as causing a loss of function or a gain of function. **Loss-of-function variants** lead to a reduction in the level of protein function as a result of decreased expression or production of a protein that does not work as efficiently. In some cases, loss of protein function from one of two alleles is sufficient to cause disease. **Haploinsufficiency** describes the situation in which maintenance of a normal phenotype requires the proteins produced by both alleles of a gene, and a 50% decrease in gene function results in an abnormal phenotype. *Haploinsufficient phenotypes are dominantly inherited.* Loss-of-function variants can also have a **dominant**

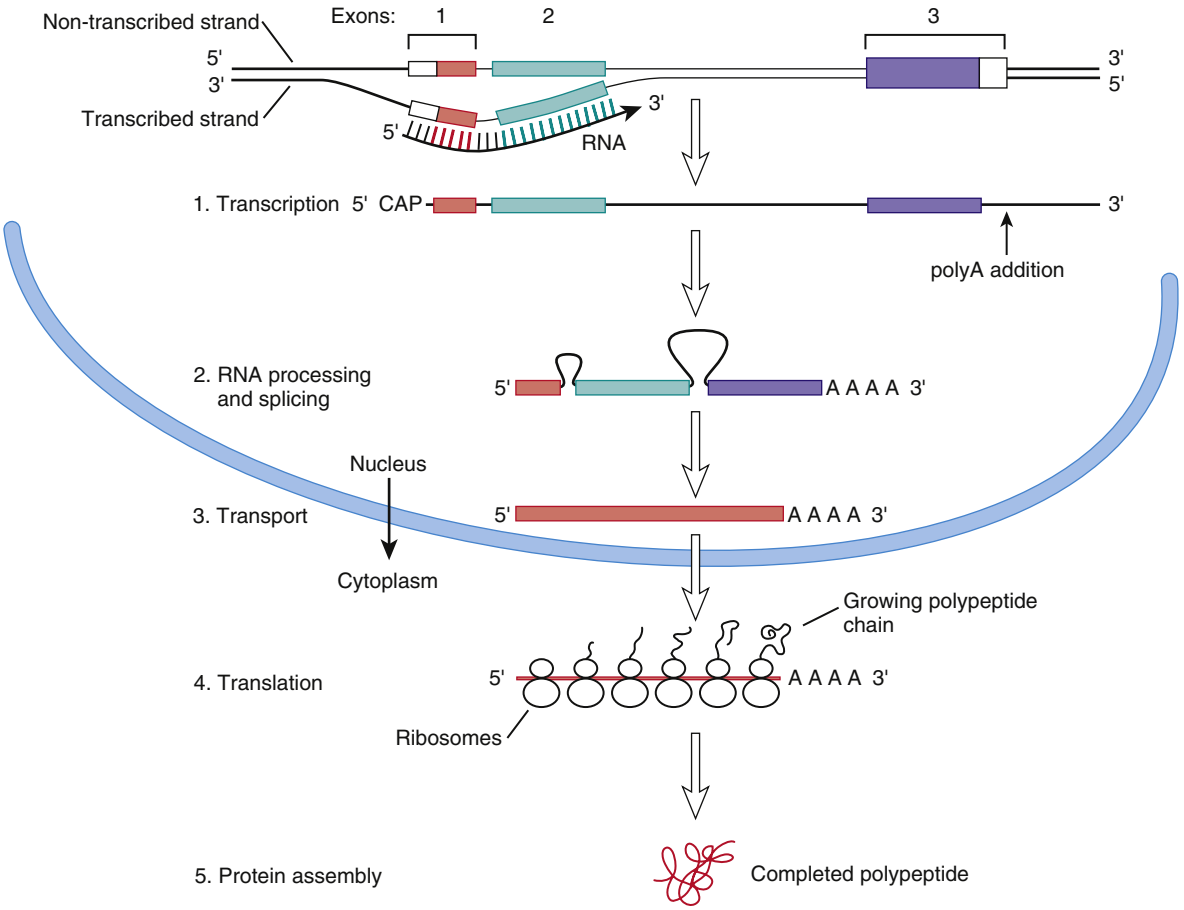

Fig. 96.2 Flow of information from DNA to RNA to protein for a hypothetical gene with three exons and two introns. Within the exons, *colored regions* indicate coding sequences. Steps include transcription, RNA processing and splicing, RNA transport from the nucleus to the cytoplasm, translation, and protein assembly. (*From Nussbaum RL, McInnis RR, Willard HF, Hamosh A, eds. Thompson & Thompson Genetics in Medicine, 7th ed. Philadelphia: Saunders; 2007: p. 31.*)

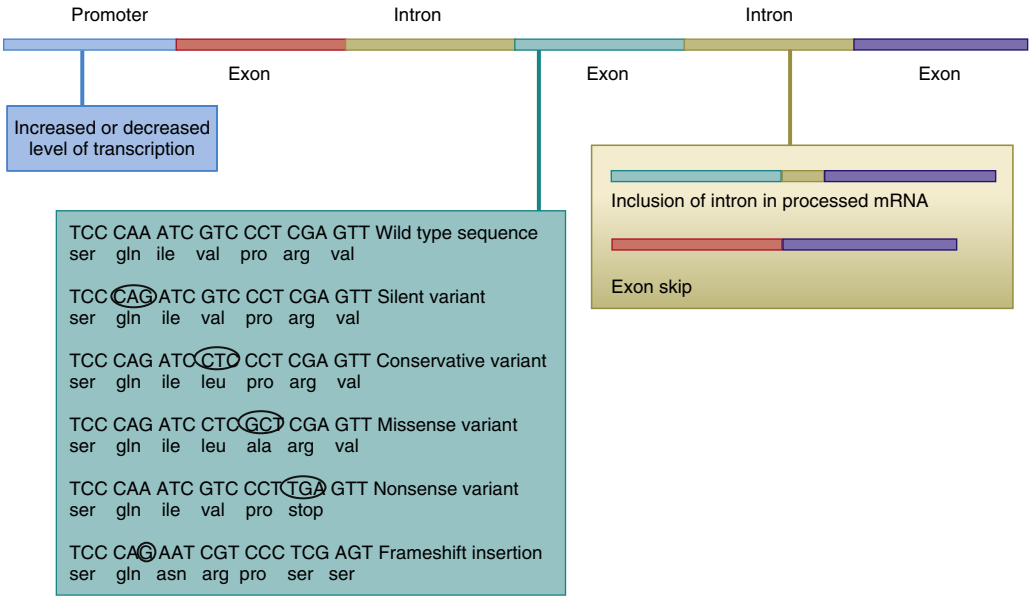

Fig. 96.3 Various types of intragenic sequence variants. Promoter variants alter rate of transcription or disrupt gene regulation. Base changes within exons can have various effects, as shown. Variants within introns can lead to inclusion of some intronic sequence in the final processed mRNA, or it can lead to exon skipping.

Table 96.1 Main Classes, Groups, and Types of Sequence Variants and Their Effects on Protein Products

CLASS	GROUP	TYPE	EFFECT ON PROTEIN PRODUCT
Substitution	Synonymous	Silent*	Same amino acid
	Nonsynonymous	Missense*	Altered amino acid—may affect protein function or stability
		Nonsense or stop-gain*	Stop codon—loss of function or expression from degradation of mRNA
		Splice site	Aberrant splicing—exon skipping or intron retention
		Promoter	Altered gene expression
Deletion	Multiple of three (codon)		In-frame deletion of one or more amino acid(s)—may affect protein function or stability
	Not multiple of three	Frameshift	Likely to result in premature termination with loss of function or expression
	Large deletion	Partial gene deletion	May result in premature termination with loss of function or expression
		Whole gene deletion	Loss of expression
Insertion	Multiple of three (codon)		In-frame insertion of one or more amino acid(s)—may affect protein function or stability
	Not multiple of three	Frameshift	Likely to result in premature termination with loss of function or expression
	Large insertion	Partial gene duplication	May result in premature termination with loss of function or expression
		Whole gene duplication	May have an effect because of increased gene dosage
	Expansion of trinucleotide repeat	Dynamic pathogenic variant	Altered gene expression or altered protein stability or function

*Some have been shown to cause aberrant splicing.
From Turnpenny P, Ellard S, eds. *Emery's Elements of Medical Genetics*, 14th ed. Philadelphia: Churchill Livingstone; 2012: p. 23.

negative effect when the abnormal protein product actively interferes with the function of the normal protein product. Both situations lead to diseases inherited in a dominant fashion. Haploinsufficiency of type I collagen can cause relatively mild osteogenesis imperfecta (OI) type I. In contrast, heterozygous, missense glycine substitutions in type I collagen can act in a dominant negative fashion to cause severe OI type II, III, and IV. In other cases, loss-of-function variants must be present in both copies of a gene before an abnormal phenotype results. This situation typically results in diseases inherited in a **recessive** fashion (see Chapter 97). Some conditions are **semidominant** where one affected copy (heterozygous pathogenic variant) causes a milder phenotype than when both copies are affected (compound heterozygous or homozygous pathogenic variants). This is seen in classical achondroplasia vs homozygous achondroplasia

Gain-of-function variants typically cause dominantly inherited diseases. These variants can result in production of a protein molecule with an increased ability to perform a normal function or can confer a novel property on the protein. The gain-of-function variant

in **achondroplasia**, the most common of the disproportionate, short-limbed short stature disorders, exemplifies the enhanced function of a normal protein. Achondroplasia results from a pathogenic variant in the fibroblast growth factor (FGF) receptor three gene *(FGFR3)*, which leads to activation of the receptor, even in the absence of FGF. In **sickle cell disease**, an amino acid is substituted into the hemoglobin molecule and has little effect on the ability of the protein to transport oxygen. However, sickle hemoglobin chains have a novel property. Unlike normal hemoglobin, sickle hemoglobin chains aggregate under conditions of deoxygenation, forming fibers that deform the red cells.

Other gain-of-function variants result in overexpression or inappropriate expression of a gene product. Many cancer-causing genes **(oncogenes)** are normal regulators of cellular proliferation during development. However, expression of these genes in adult life and/or in cells in which they usually are not expressed can result in neoplasia.

In some cases, changes in gene expression are caused by changes in the number of copies of a gene that are present in the genome (Fig. 96.4). Although some **copy number variations** are common and do not appear to cause or predispose to disease, others are clearly disease causing. **Charcot-Marie-Tooth disease type 1A**, the most common inherited form of chronic peripheral neuropathy of childhood, is caused by duplications of the gene for peripheral myelin protein 22, resulting in overexpression due to the existence of three active copies of this gene (see Chapter 653.1). Deletions of this same gene, leaving only one active copy, are responsible for a different disorder, **hereditary neuropathy with liability to pressure palsies**.

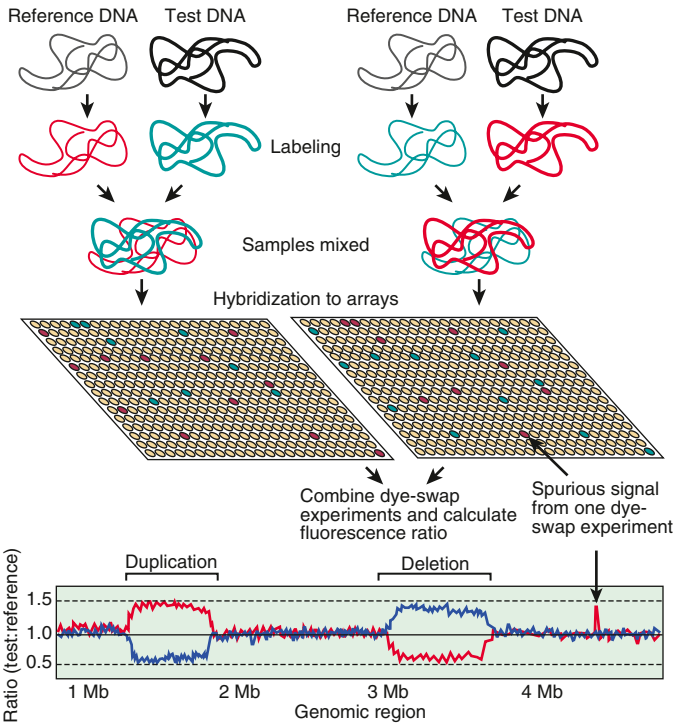

Fig. 96.4 Array comparative genomic hybridization. Test and reference DNA samples are differentially labeled, mixed, and passed over a target array of probes (e.g., bacterial artificial chromosome clones or oligonucleotides) containing DNA fragments from across the whole human genome. The experiment is often repeated with reversal of the test and reference dyes to detect dye effects or identify spurious signals. DNA samples hybridize with their corresponding probe, and the ratio of fluorescence from each probe *(test:reference)* is used to detect regions that vary in copy number between the test and the reference sample (*red line*, original hybridization; *blue line*, dye-swapped hybridization). Equal copy number for both the test and the reference DNA is identified by equal binding, resulting in a ratio of 1:1. Duplication in a genomic region of the test sample is identified by an increased ratio, and a deletion is identified by a decreased ratio, but a deletion in the test sample is indistinguishable from a duplication in the reference sample. These ratios are usually converted to log2 scale for further analysis. *Mb*, megabase. (*Adapted from Feuk L, Carson AR, Scherer SW. Structural variation in the human genome. Nat Rev Genet 2006;7:85–97.*)

Deletions and duplications can vary in their extent and can involve several genes, even when they are not detectable using a traditional chromosome analysis. Such changes are commonly called **microdeletions** and **microduplications**. When deletion or duplication of two or more genes in the same chromosomal region each play a role in the resulting clinical features, the condition can also be referred to as a **contiguous gene disorder**.

In some cases, the recognition of a specific constellation of features leads clinicians to suspect a specific microdeletion or microduplication syndrome. Examples of such disorders include Smith-Magenis, DiGeorge, and Williams syndromes. In other cases, the clinician may be alerted to this possibility by an unusually diverse array of clinical features in one patient or the presence of unusual features in a person with a known condition. Because of the close physical proximity of a series of genes, different deletions involving the short arm of the X chromosome can produce individuals with various combinations of ichthyosis, Kallmann syndrome, ocular albinism, intellectual disability, chondrodysplasia punctata, and short stature.

DNA rearrangements can also take place in **somatic cells** (cells that do not go on to produce ova or sperm). Rearrangements that occur in **lymphoid** cells are required for the normal formation of functional immunoglobulin in B cells and antigen-recognizing receptors on T cells. Large segments of DNA, which code for the variable and the constant regions of either immunoglobulin or the T-cell receptor (TCR), are physically joined at a specific stage in the development of an immunocompetent lymphocyte. These rearrangements take place during development of the lymphoid cell lineage in humans and result in the extensive diversity of immunoglobulin and TCR molecules. Because of this postgermline DNA rearrangement, no two individuals, not even identical twins, are fully identical, because mature lymphocytes from each will have undergone random DNA rearrangements at these loci.

The human genome demonstrates that any two individuals will differ in about one base in 1,000. Some of these differences are silent; some result in changes that explain phenotypic differences (hair or eye color, physical appearance); and some have medical significance, causing single-gene disorders such as sickle cell anemia or explaining susceptibility to common pediatric disorders such as asthma. Genetic variants in a single gene that occur at a frequency of >1% in a population are often referred to as **polymorphisms**. These variations may be silent or subtle or may have significant phenotypic effects.

GENOTYPE-PHENOTYPE CORRELATIONS IN GENETIC DISEASE

The term **genotype** is used to signify the internally coded, heritable information of an individual and can also be used to refer to which particular alternative version **(allele)** of a gene is present at a specific location **(locus)** on a chromosome. A **phenotype** is the observed structural, biochemical, and physiologic characteristics of an individual, determined by the genotype, and can also refer to the observed structural and functional effects of a variant allele at a specific locus. Many sequence variants result in predictable phenotypes; physicians can predict clinical outcomes and plan appropriate treatment strategies based on a patient's genotype. There is also phenotypic expansion where multiple alleles (variants) within a gene can be associated with often diverse and distinct clinical presentations.

Long QT syndrome exemplifies a disorder with predictable associations between a patient's genotype and his or her phenotype (see Chapter 484.5). Long QT syndrome is genetically heterogeneous, meaning that pathogenic variants in *several different genes* can cause the same disorder. The risk for cardiac events (syncope, aborted cardiac arrest, or sudden death) is higher in patients with long QT syndrome involving *KCNQ1* (63%) or *KCNH2* (46%) than in those with pathogenic variants in *SCN5A* (18%). In addition, individuals with *KCNQ1* variants experience most of their episodes during exercise and rarely during rest or sleep. In contrast, individuals with pathogenic variants in *KCNH2* and *SCN5A* are more likely to have episodes during sleep or rest and rarely during exercise. Therefore variants in specific genes

(genotype) are correlated with specific manifestations (phenotype) of long QT syndrome. These types of relationships are commonly referred to as *genotype-phenotype correlations.*

Pathogenic variants in the fibrillin-1 gene associated with **Marfan syndrome** represent another example of predictable genotype-phenotype correlations (see Chapter 743). Marfan syndrome is characterized by the combination of skeletal, ocular, and aortic manifestations, with the most devastating outcome being aortic root dissection and sudden death. The fibrillin-1 gene consists of 65 exons, and pathogenic variants have been found in almost all these. The location of the variant within the gene (genotype) might play a significant role in determining the severity of the condition (phenotype). Neonatal Marfan syndrome is often caused by variants in exons 24-27 and in exons 31 and 32, whereas milder forms are caused by variants in exons 59-65 and in exons 37 and 41.

Genotype-phenotype correlations have also been observed in some complications of **cystic fibrosis** (CF; see Chapter 454). Although pulmonary disease is the major cause of morbidity and mortality, CF is a multisystem disorder that affects not only the epithelia of the respiratory tract but also the exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands. CF is caused by pathogenic variants in the CF transmembrane conductance regulator *(CFTR)* gene. More than 1,600 different pathogenic *CFTR* variants have been identified. The most common is a deletion of three nucleotides that removes the amino acid phenylalanine (F) at the 508th position on the protein (ΔF508 variant), which accounts for approximately 70% of all pathogenic CF variants and is associated with severe disease. The best genotype-phenotype correlations in CF are seen in the context of pancreatic function, with common pathogenic variants being classified as either *pancreatic sufficient* or *pancreatic insufficient.* Persons with pancreatic sufficiency usually have either one or two pancreatic-sufficient alleles, indicating that pancreatic-sufficient alleles are dominant. In contrast, the genotype-phenotype correlation in pulmonary disease is much weaker, and persons with identical genotypes have wide variations in the severity of their pulmonary disease. This finding may be accounted for, in part, by genetic modifiers or environmental factors.

In many disorders, the effects of variants on phenotype can be modified by changes in the other allele of the same gene, by changes in specific **modifier genes**, and/or by variations in a number of unspecified genes **(genetic background)**. When sickle cell anemia is co-inherited with the gene for hereditary persistence of fetal hemoglobin, the sickle cell phenotypic expression is less severe. Modifier genes in CF can influence the development of congenital meconium ileus, or colonization with *Pseudomonas aeruginosa.* Modifier genes can also affect the manifestations of Hirschsprung disease, neurofibromatosis type 2, craniosynostosis, and congenital adrenal hyperplasia. The combination of genetic variants producing glucose-6-phosphate dehydrogenase deficiency and longer versions of the TATAA element in the uridine diphosphate–glucuronosyltransferase gene promoter exacerbates neonatal physiologic hyperbilirubinemia.

HUMAN GENOME PROJECT

A rudimentary genetic map can be made using genetic linkage, which is based on the principle that alleles at two genetic loci that are located near each other segregate together in a family unless they are separated by genetic **recombination**. In contrast to linkage maps, physical maps rely on overlapping DNA fragments to determine the location of loci with respect to one another. Overlapping segments of the genomic regions can be identified and used to piece together a map composed of overlapping DNA fragments to obtain the DNA sequence of the entire region. An alternative strategy involves breaking the entire genome into random fragments, sequencing the fragments, and then computationally assembling them into overlapping segments. This whole genome approach in combination with next-generation sequencing technologies has resulted in a dramatic reduction in the cost of sequencing an individual's entire genome.

Analysis of the human genome has produced some surprising results. The number of genes appears to be ~20,000. *However, the number of protein products encoded by the genome is far greater than the number of genes.* This is a result of the presence of alternative promoter regions, alternative splicing, and posttranslational modifications, which can allow a single gene to encode a number of protein products.

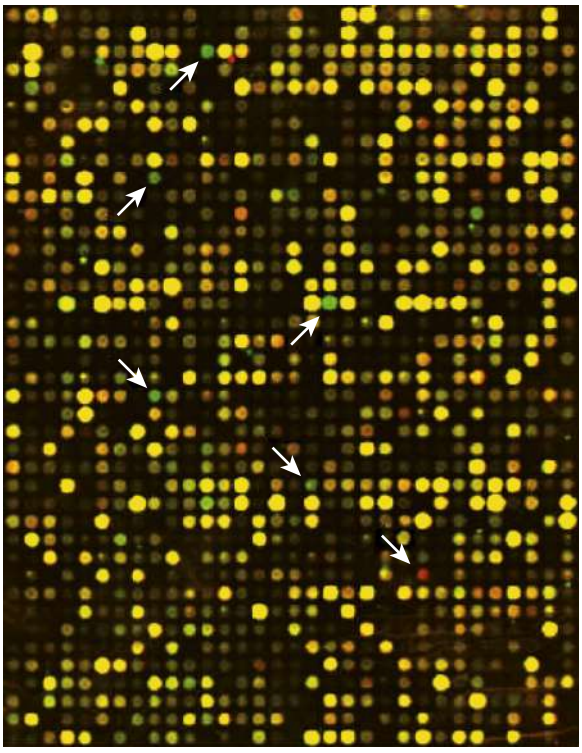

Fig. 96.5 Microarray containing 36,000 oligonucleotides. The microarray was exposed to RNA from normal fibroblasts (labeled in *red*; see *arrows*) and fibroblasts from a patient with Niemann-Pick disease, type C (labeled *green*). *Arrows* point to regions in which there was a strong hybridization signal with either normal or disease RNA. This microarray was used to search for genes that are highly expressed in the fibroblasts of patients. (*From Jorde LB, Carey JC, Bamshad MJ, White RL. Medical Genetics, 3rd ed. St Louis: Mosby; 2006: p. 116.*)

It is also apparent that most of the human genome *does not* encode protein, with <5% being transcribed and translated, although a much larger percentage may be transcribed without translation. Many transcribed sequences are not translated but represent genes that encode RNAs that serve *regulatory* roles. A large fraction of the genome consists of repeated sequences that are interspersed among the genes. Some of these are transposable genetic elements that can move from place to place in the genome. Others are static elements that were expanded and dispersed in the past during human evolution. Other repeated sequences might play a structural role. There are also regions of *genomic duplications.* Such duplications are substrate for evolution, allowing genetic motifs to be copied and modified to serve new roles in the cell. Duplications can also play a role in chromosomal rearrangement, permitting nonhomologous chromosome segments to pair during meiosis and exchange material. This is another source of evolutionary change and a potential source of chromosomal instability leading to congenital anomalies or cancer. Low copy repeats also play an important role in causing genomic disorders. When low copy repeats flank unique genomic segments, these regions can be duplicated or deleted through a process known as *nonallelic homologous recombination.*

Availability of the entire human genomic sequence permits the study of large groups of genes, looking for patterns of gene expression or genome alteration. Studies of gene expression are performed using next-generation sequencing techniques to obtain information about all RNA transcripts in a tissue or single cell. The patterns of gene expression may provide signatures for particular disease states, such as cancer, or change in response to therapy (Fig. 96.5).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 97

Patterns of Genetic Transmission

Daryl A. Scott and Brendan Lee

FAMILY HISTORY AND PEDIGREE NOTATION

The family history remains the most important screening tool for pediatricians in identifying a patient's risk for developing a wide range of diseases, from multifactorial conditions such as diabetes and attention-deficit/hyperactivity disorder, to single-gene disorders such as sickle cell anemia and cystic fibrosis. Through a detailed family history, the physician can often ascertain the mode of genetic transmission and the risks to family members. Because not all familial clustering of disease is caused by genetic factors, a family history can also identify common environmental and behavioral factors that influence the occurrence of disease. The main goal of the family history is to identify genetic susceptibility, and the cornerstone of the family history is a systematic and standardized pedigree.

A **pedigree** provides a graphic depiction of a family's structure and medical history. It is important when taking a pedigree to be systematic and use standard symbols and configurations so that anyone can read and understand the information (Figs. 97.1-97.4). In the pediatric setting, the **proband** is typically the child or adolescent who is being evaluated. The proband is designated in the pedigree by an arrow.

A three- to four-generation pedigree should be obtained for every new patient as an initial screen for genetic disorders segregating within the family. The pedigree can provide clues to the inheritance pattern of these disorders and can aid the clinician in determining the risk to the proband and other family members. The closer the relationship of the proband to the person in the family with the genetic disorder, the greater is the shared genetic complement. **First-degree** relatives, such as a parent, full sibling, or child, share one half their genetic information on average; first cousins share one eighth. Sometimes the person providing the family history may mention a distant relative who is affected with a genetic disorder. In such cases a more extensive pedigree may be needed to identify the risk to other family members. For example, a history of a distant maternally related cousin with intellectual disability caused by fragile X syndrome can still place a male proband at an elevated risk for this disorder.

MENDELIAN INHERITANCE

There are three classic forms of genetic inheritance: **autosomal dominant, autosomal recessive,** and **X-linked**; these are referred to as **mendelian inheritance** forms.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is determined by the presence of one abnormal gene on one of the **autosomes** (chromosomes 1-22). Autosomal genes exist in pairs, with each parent contributing one copy. In an autosomal dominant trait, a change in one of the paired genes affects the phenotype of an individual, even though the other copy of the gene is functioning correctly. A **phenotype** can refer to a physical manifestation, a behavioral characteristic, or a difference detectable only through laboratory tests.

The pedigree for autosomal dominant disorders demonstrates certain characteristics. These disorders show a **vertical transmission** (parent-to-child) pattern and can appear in multiple generations (Fig. 97.5). An affected individual has a 50% chance of passing on the deleterious gene in *each* pregnancy and, therefore, of having a child affected by the disorder. This is referred to as the **recurrence risk** for the disorder. Unaffected individuals (family members who do not manifest the trait and do not harbor a copy of the deleterious gene) do not pass the disorder to their children. Males and females are equally affected.

Although not a characteristic per se, the finding of male-to-male transmission essentially confirms autosomal dominant inheritance. Vertical transmission can also be seen with X-linked traits. However, because a father passes on his Y chromosome to a son, male-to-male transmission cannot be seen with an X-linked trait. Therefore male-to-male transmission eliminates X-linked inheritance as a possible explanation. Although male-to-male transmission can occur with Y-linked genes as well, there are very few Y-linked disorders, compared with thousands having the autosomal dominant inheritance pattern.

Although parent-to-child transmission is a characteristic of autosomal dominant inheritance, many patients with an autosomal dominant disorder have no history of an affected family member, for several possible reasons. First, the patient may have the disorder due to a **de novo** (new) pathogenic variant that occurred in the DNA of the egg or sperm that formed that individual. Second, many autosomal dominant conditions demonstrate **incomplete penetrance**, meaning that not all individuals who carry the pathogenic variant have phenotypic manifestations. In a pedigree, this can appear as a **skipped generation**, in which an unaffected individual links two affected persons (Fig. 97.6). There are many potential reasons that a disorder might exhibit incomplete penetrance including the effect of modifier genes, environmental factors, gender, and age. Third, individuals with the same autosomal dominant variant can manifest the disorder to different degrees. This is termed **variable expression** and is a characteristic of many autosomal dominant disorders.

Fourth, some spontaneous genetic pathogenic variants occur not in the egg or sperm that forms a child, but rather in a *cell* in the developing embryo or in a tissue after birth. Such events are referred to as **somatic pathogenic variants**. Because only a subset of cells in the body are affected, the change is said to be **mosaic**. The phenotypes caused by a somatic pathogenic variant can vary but are usually milder than if all cells were affected by the pathogenic variant. Some cancers typically arise from cells that have been affected by multiple somatic pathogenic variants. In **germline mosaicism,** the pathogenic variant occurs in a subset of cells that ultimately produce ova or sperm. An individual who is germline mosaic for a pathogenic variant might not have any manifestations of the associated disorder but may pass that change on to his or her offspring by producing ova or sperm that carry the pathogenic variant. Children whose bodies derive from those ova or sperm will carry the pathogenic variant in all of their cells unless the change undergoes a rare reversion of the somatic pathogenic variant. Recurrence of a dominantly inherited condition to apparently unaffected parents can sometimes be explained by germline mosaicism for the dominantly transmitted variant in one of the parents.

Autosomal Recessive Inheritance

Autosomal recessive inheritance requires deleterious variants in both copies of a gene to cause disease. Examples include cystic fibrosis and sickle cell disease. Autosomal recessive disorders are characterized by **horizontal transmission**, the observation of multiple affected members of a kindred in the same generation, but no affected family members in other generations (Fig. 97.7). They are associated with a recurrence risk of 25% for carrier parents who have had a previous affected child. Male and female offspring are equally likely to be affected, although some traits exhibit differential expression between sexes. The offspring of consanguineous parents are at increased risk for rare, autosomal recessive traits due to the increased chance that both parents may carry a gene affected by a deleterious variant that they inherited from a common ancestor. **Consanguinity** between parents of a child with a suspected genetic disorder implies, but certainly does not prove, autosomal recessive inheritance. Although consanguineous unions are uncommon in Europe and the Americas, in other parts of the world (southern India, Japan, and the Middle East) as high as 50% of all children may be conceived in consanguineous unions. The risk of a genetic disorder in the offspring of a first-cousin union (6–8%) is about double the risk in the general population (3–4%).

Instructions:
—Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
—For clinical (non-published) pedigrees include:
a) name of proband/consultand
b) family names/initials of relatives for identification, as appropriate
c) name and title of person recording pedigree
d) historian (person relaying family history information)
e) date of intake/update
f) reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
g) ancestry of both sides of family
—Recommended order of information placed below symbol (or to lower right)
a) age; can note year of birth (e.g., b.1978) and/or death (e.g., d. 2007)
b) evaluation (see Fig. 97.4)
c) pedigree number (e.g., I-1, I-2, I-3)
—Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual	b.1925	30 y	4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
			With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.	
3. Multiple individuals, number known	5	5	5	Number of siblings written inside symbol. (Affected individuals should not be grouped.)
4. Multiple individuals, number unknown or unstated	n	n	n	"n" used in place of "?".
5. Deceased individual	d. 35	d. 4 mo	d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/testing.
7. Proband	P	P		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	SB 28 wk	SB 30 wk	SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	P LMP: 7/1/2007 47,XY,+21	P 20 wk 46, XX	P	Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)	17 wks female cystic hygroma	<10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)	18 wks 47, XY,+18		Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)	ECT		Write ECT below symbol.

Fig. 97.1 Common pedigree symbols, definitions, and abbreviations. (*From Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17:424–433.*)

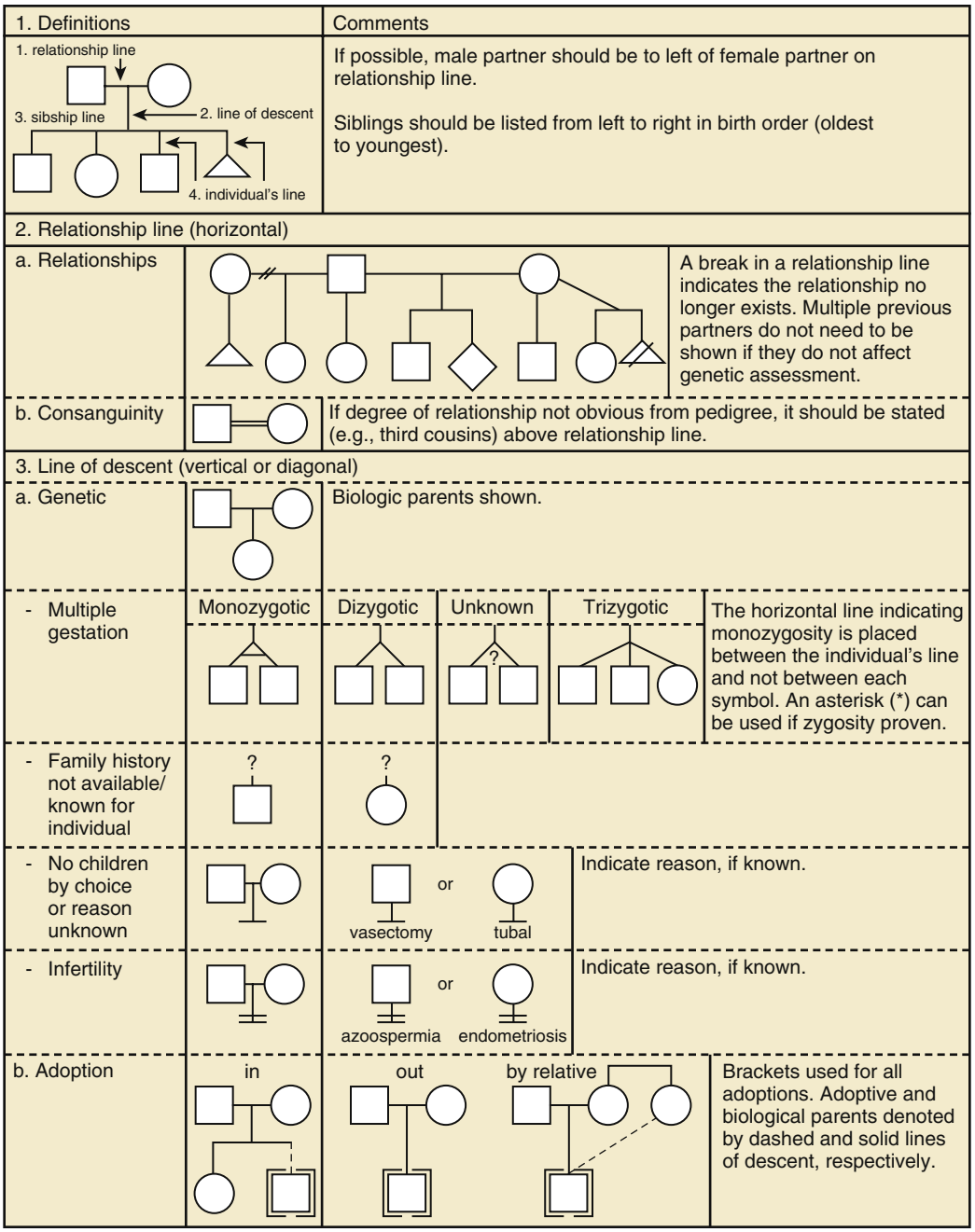

Fig. 97.2 Pedigree line definitions. (*From Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17:424–433.*)

Every individual probably carries several rare, deleterious recessive pathogenic sequence variants. Because most pathogenic variants carried in the general population occur at a very low frequency, it does not make economic sense to screen the entire population to identify the small number of persons who carry these variants. These variants typically remain undetected unless an affected child is born to a couple who both carry pathogenic variants affecting the same gene.

However, in some **genetic isolates** (small populations isolated by geography, religion, culture, or language), certain rare recessive pathogenic variants are much more common than in the general population. Even though there may be no known consanguinity, couples from these genetic isolates have a greater chance of sharing pathogenic alleles inherited from a common ancestor. Screening programs have been developed among some such groups to detect persons who carry common disease-causing variants and, therefore, are at increased risk for having affected children.

A variety of autosomal recessive conditions are more common among Ashkenazi Jews than in the general population. Couples of Ashkenazi Jewish ancestry should be offered prenatal or preconception screening for Gaucher disease type one (carrier rate 1:14), cystic fibrosis (1:25), Tay-Sachs disease (1:25), familial dysautonomia (1:30), Canavan disease (1:40), glycogen storage disease type 1A (1:71), maple syrup urine disease (1:81), Fanconi anemia type C (1:89), Niemann-Pick disease type A (1:90), Bloom syndrome (1:100), mucolipidosis IV (1:120), and possibly neonatal familial hyperinsulinemic hypoglycemia.

The prevalence of carriers of certain autosomal recessive variants in some larger populations is unusually high. In such cases, **heterozygote advantage** is postulated. The carrier frequencies of sickle cell disease in the African population and of cystic fibrosis in the northern European population are much higher than would be expected from the rate of new pathogenic variants. In these populations,

Instructions:
— D represents egg or sperm donor
— S represents surrogate (gestational carrier)
— If the woman is both the ovum donor and a surrogate, in the interest of genetic assessment, she will only be referred to as a donor (e.g., 4 and 5); the pregnancy symbol and its line of descent are positioned below the woman who is carrying the pregnancy
— Available family history should be noted on the gamete donor and/or gestational carrier

Possible Reproductive Scenarios		Comments
1. Sperm donor	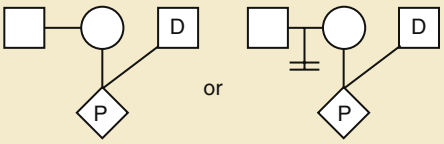	Couple in which woman is carrying pregnancy using donor sperm. No relationship line is shown between the woman carrying the pregnancy and the sperm donor.
2. Ovum donor	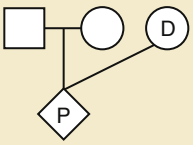	Couple in which woman is carrying pregnancy using a donor egg and partner's sperm. The line of descent from the birth mother is solid because there is a biologic relationship that may affect the fetus (e.g., teratogens).
3. Surrogate only	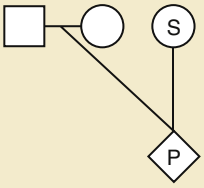	Couple whose gametes are used to impregnate a woman (surrogate) who carries the pregnancy. The line of descent from the surrogate is solid because there is a biological relationship that may affect the fetus (e.g., teratogens).
4. Surrogate ovum donor	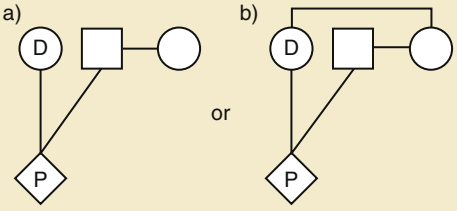	Couple in which male partner's sperm is used to inseminate (a) an unrelated woman or (b) a sister who is carrying the pregnancy for the couple.
5. Planned adoption	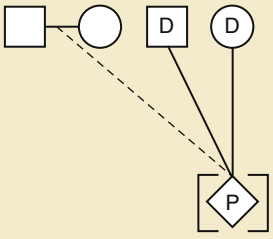	Couple contracts with a woman to carry a pregnancy using ovum of the woman carrying the pregnancy and donor sperm.

Fig. 97.3 Assisted reproductive technology symbols and definitions. (*From Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17:424–433.*)

heterozygous carriers may have had an advantage in terms of survival and reproduction over noncarriers. In sickle cell disease, the carrier state is thought to confer some resistance to malaria. In cystic fibrosis, the carrier state has been postulated to confer resistance to cholera or enteropathogenic *Escherichia coli* infections. Population-based **carrier screening** for cystic fibrosis is recommended for persons of northern European and Ashkenazi Jewish ancestry, and population-based screening for sickle cell disease is recommended for persons of African ancestry.

If the frequency of an autosomal recessive disease is known, the frequency of the heterozygote or carrier state can be calculated from the **Hardy-Weinberg formula:**

$$p^2 + 2pq + q^2 = 1$$

where p is the frequency of one of a pair of alleles and q is the frequency of the other. For example, if the frequency of cystic fibrosis among White Americans is one in 2,500 (p^2), then the frequency of the heterozygote ($2pq$) can be calculated: If $p^2 = 1/2{,}500$, then $p = 1/50$ and $q = 49/50$; $2pq = 2 \times (1/50) \times (49/50) = 98/2{,}500$, or 3.92%.

Pseudodominant Inheritance

Pseudodominant inheritance refers to the observation of apparent dominant (parent to child) transmission of a known autosomal recessive disorder (Fig. 97.8). This occurs when a homozygous affected individual has a partner who is a heterozygous carrier. This is most likely to occur for relatively common recessive traits within a population, such as sickle cell anemia or nonsyndromic autosomal recessive hearing loss caused by deleterious variants in *GJB2*, the gene that encodes connexin 26.

X-Linked Inheritance

X-linked inheritance describes the inheritance pattern of most disorders caused by deleterious changes in genes located on the X chromosome (Fig. 97.9). In X-liked disorders, males are more commonly

Instructions:
- E is used for evaluation to represent clinical and/or test information on the pedigree
  a. E is to be defined in key/legend
  b. If more than one evaluation, use subscript (E_1, E_2, E_3) and define in key
  c. Test results should be put in parentheses or defined in key/legend
- A symbol is shaded only when an individual is clinically symptomatic
- For linkage studies, haplotype information is written below the individual. The haplotype of interest should be on left and appropriately highlighted
- Repetitive sequences, trinucleotides, and expansion numbers are written with affected allele first and placed in parentheses
- If variant known, identify in parentheses

Definition	Symbol	Scenario
1. Documented evaluation (*) Use only if examined/evaluated by you or your research/clinical team or if the outside evaluation has been reviewed and verified.	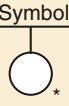	Woman with negative echocardiogram. 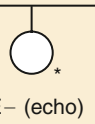
2. Carrier—not likely to manifest disease regardless of inheritance pattern		Male carrier of Tay-Sachs disease by patient report (* not used because results not verified). 
3. Asymptomatic/presymptomatic carrier—clinically unaffected at this time but could later exhibit symptoms		Woman age 25 with negative mammogram and positive BRCA1 DNA test. 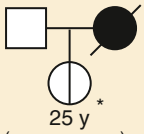
4. Uninformative study (u)		Man age 25 with normal physical exam and uninformative DNA test for Huntington disease (E_2). 
5. Affected individual with positive evaluation (E+)		Individual with cystic fibrosis and positive variant study; only one variant has currently been identified. 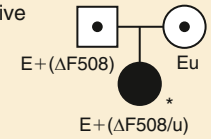
		10 week male fetus with a trisomy 18 karyotype. 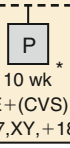

Fig. 97.4 Pedigree symbols of genetic evaluation and testing information. (*From Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17:424–433.*)

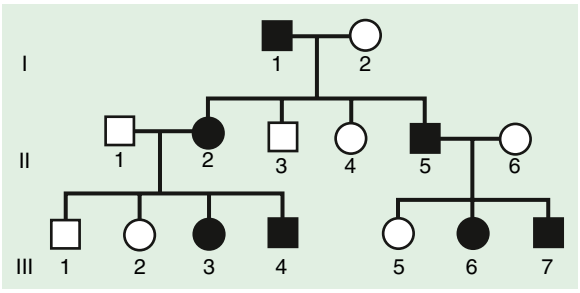

Fig. 97.5 Autosomal dominant pedigree. Pedigree showing typical inheritance of a form of achondroplasia *(FGFR3)* inherited as an autosomal dominant trait. *Black,* Affected patients.

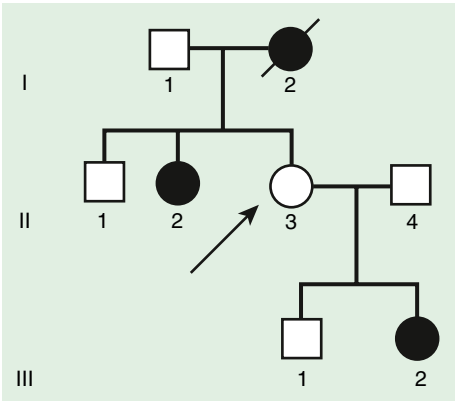

Fig. 97.6 Incomplete penetrance. This family segregates a familial cancer syndrome, familial adenomatous polyposis. Individual II.3 is an obligate carrier *(arrow),* but there are no findings to suggest the disorder. This disorder is nonpenetrant in this individual. *Black,* Affected patients.

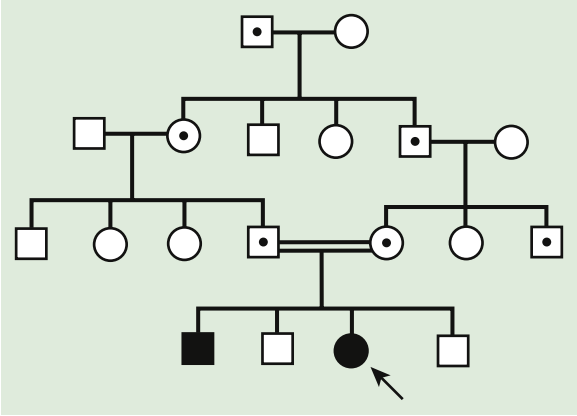

Fig. 97.7 Autosomal recessive pedigree with parental consanguinity. *Central dot,* Carriers; *Black,* affected patients.

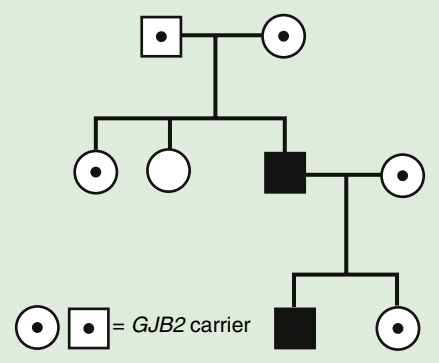

Fig. 97.8 Pseudodominant inheritance. *Black,* Affected (deaf); *central dot* shows carrier who is asymptomatic (unaffected).

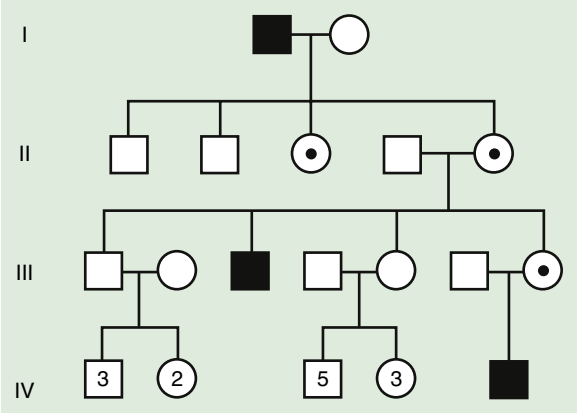

Fig. 97.9 Pedigree demonstrating X-linked recessive inheritance. *Central dot,* Carriers; *black,* affected patients.

affected than females. Female carriers of these disorders are generally unaffected, or if affected, they are affected more mildly than males. In each pregnancy, female carriers have a 25% chance of having an affected son, a 25% chance of having a carrier daughter, and a 50% chance of having a child that does not inherit the mutated X-linked gene. Because affected males pass their X chromosome to all their daughters and their Y chromosome to all their sons, they have a 50% chance of having a daughter who is a carrier. Male-to-male transmission excludes X-linked inheritance but is seen with autosomal dominant and Y-linked inheritance.

A female occasionally exhibits signs of an X-linked trait similar to a male. This occurs rarely from homozygosity for an X-linked trait or the presence of a sex chromosome abnormality (45,X or 46,XY female) but more commonly from skewed or nonrandom X-inactivation. **X chromosome inactivation** occurs early in development and involves the random and irreversible inactivation of most genes on one X chromosome in female cells (Fig. 97.10). In some cases, a preponderance of cells inactivates the same X chromosome, resulting in phenotypic expression of an X-linked pathogenic variant if it resides on the active chromosome. This can occur because of chance, selection against cells that have inactivated the X chromosome carrying the normal gene, or an X chromosome abnormality that results in inactivation of the X chromosome carrying the normal gene.

In some X-linked disorders, both **hemizygous** males and **heterozygous** females who carry an affected X-linked gene have similar phenotypic manifestations. In these cases, an affected male will have a 50% chance of having an affected daughter and a 50% chance of having an unaffected son in each pregnancy, whereas half the male and female offspring of an affected mother will be affected (Fig. 97.11). Some X-linked conditions are lethal in a high percentage of males, such as **incontinentia pigmenti**. In such cases the pedigree typically shows only affected females and an overall female/male ratio of 2:1, with an increased number of miscarriages (Fig. 97.12).

Y-LINKED INHERITANCE

There are few Y-linked traits. These demonstrate *only* male-to-male transmission, and only males are affected (Fig. 97.13). Most Y-linked genes are related to male sex determination and reproduction and are associated with infertility. Therefore it is rare to see familial transmission of a Y-linked disorder. However, advances in assisted reproductive technologies might make it possible to have familial transmission of male infertility.

INHERITANCE ASSOCIATED WITH PSEUDOAUTOSOMAL REGIONS

There are pseudoautosomal regions on the X and Y chromosomes. Because these regions are made up of homologous sequences of nucleotides, genes that are located in these regions are present in equal numbers among both males and females. *SHOX* is one of the best-characterized disease genes located in these regions. Heterozygous *SHOX* pathogenic variants cause **Leri-Weil dyschondrosteosis**, a rare skeletal dysplasia that involves bilateral bowing of the forearms with dislocations of the ulna at the wrist and generalized short stature. Homozygous *SHOX* pathogenic variants cause the much more severe **Langer mesomelic dwarfism**.

DIGENIC INHERITANCE

Digenic inheritance explains the occasional occurrence of **retinitis pigmentosa (RP)** in children of parents who each carry a pathogenic variant in a different RP-associated gene (Fig. 97.14). Both parents have normal vision, as would be expected, but their offspring who are **double heterozygotes**—having inherited both variants—develop RP. Digenic pedigrees can exhibit characteristics of both autosomal dominant (vertical transmission) and autosomal recessive inheritance (one in four recurrence risk). A couple in which the two unaffected partners are carriers for variants in two different RP-associated genes that show digenic inheritance have a one in four risk of having an affected child, similar to what is seen in autosomal recessive inheritance. However, their affected children, and affected children in subsequent generations, have a one in four risk of transmitting both variants to their offspring, who would be affected (vertical transmission).

PSEUDOGENETIC INHERITANCE AND FAMILIAL CLUSTERING

Sometimes nongenetic causes of a particular disease in multiple family members can produce a pattern that mimics genetic transmission. These nongenetic factors can include identifiable environmental factors, teratogenic exposures, or undetermined or undefined factors.

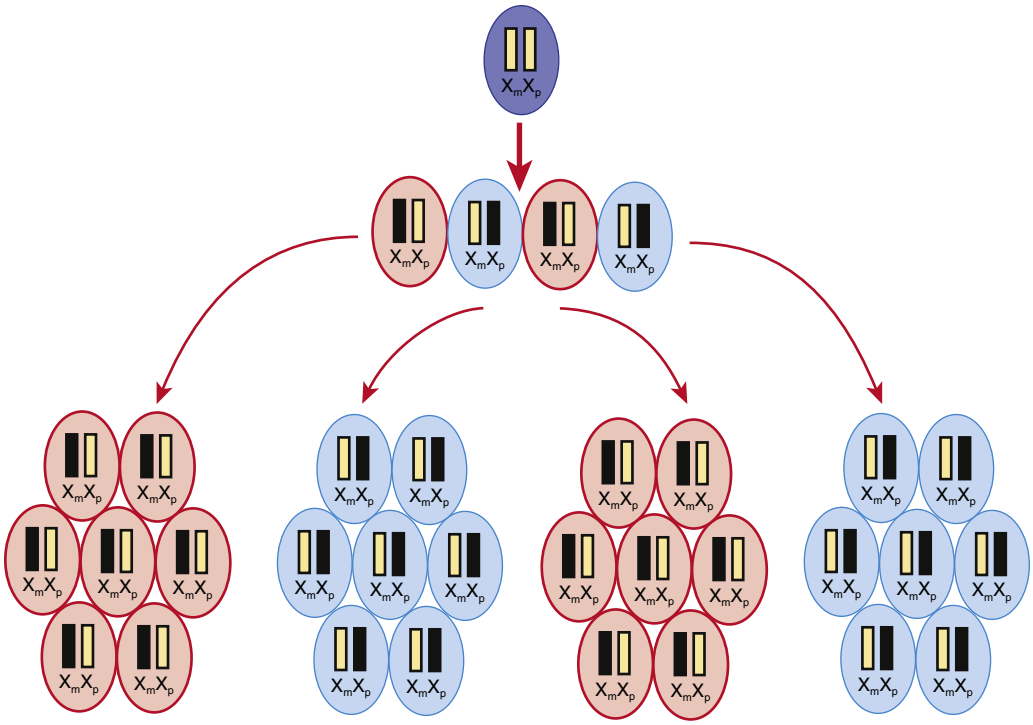

Fig. 97.10 X-inactivation. *Black* marks the active X chromosome. Color of the cell represents its active X chromosome is paternally (X_p, *blue*) or maternally (X_m, *pink*) derived.

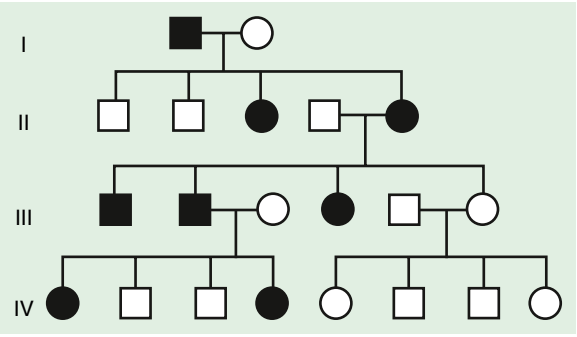

Fig. 97.11 Pedigree pattern demonstrating X-linked dominant inheritance. *Black,* Affected patients. Note there is no father-to-son transmission in this situation, and hemizygosity (i.e., X-linked gene in a male) is not lethal. In some X-linked dominant conditions, X-linked males have a more severe phenotype and might not survive. In that case, only females manifest the disease (see Fig. 97.12).

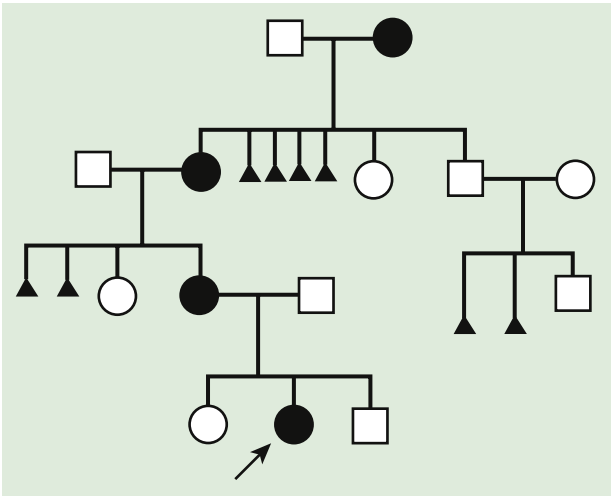

Fig. 97.12 Pedigree of an X-linked dominant disorder with male lethality, such as incontinentia pigmenti. *Black,* Affected patients.

Examples of identifiable factors might include multiple siblings in a family having asthma because of exposure to cigarette smoke from their parents or having failure to thrive, developmental delay, and unusual facial appearance caused by exposure to alcohol during pregnancy.

In some cases, the disease is sufficiently common in the general population that some familial clustering occurs simply by chance. Breast cancer affects 11% of all women, and it is possible that several women in a family will develop breast cancer even in the absence of a specific genetic predisposition. However, hereditary breast cancer associated with pathogenic variants in *BRCA1* and *BRCA2* should be suspected in any individual who has a personal history of breast cancer with onset before age 50, early-onset breast and ovarian cancer at any age, bilateral or multifocal breast cancer, a family history of breast cancer or breast and ovarian cancer consistent with autosomal dominant inheritance, or a personal or family history of male breast

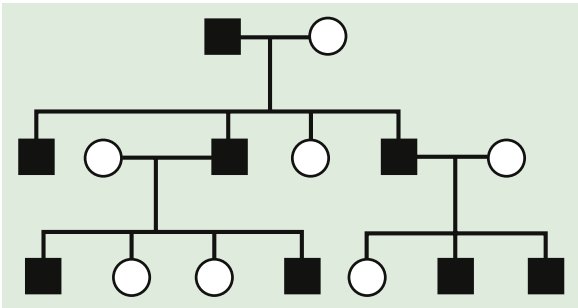

Fig. 97.13 Y-linked inheritance. *Black,* Affected patients.

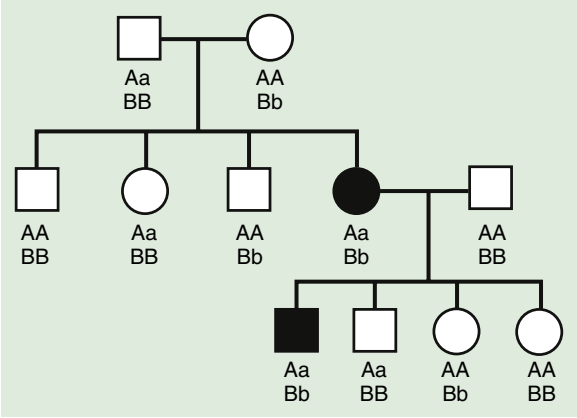

Fig. 97.14 Digenic pedigree. Here, the disease alleles are *a* and *b* and they reside on distinct genetic loci or genes. For a person to have the disease, heterozygosity for variant alleles in both genes (A/a; B/b) is required. *Black,* Affected patients.

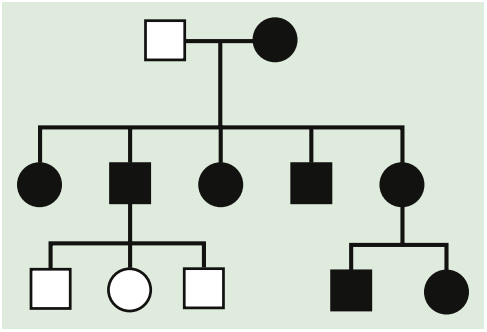

Fig. 97.15 Pedigree of a mitochondrial disorder, exhibiting maternal inheritance. *Black,* Affected patients.

cancer. In other cases, clustering within a family may be caused by undefined genetic factors or unidentified pathogenic sequence variants (nuclear or mitochondrial).

NONTRADITIONAL INHERITANCE

Some genetic disorders are inherited in a manner that does not follow classical mendelian patterns. Nontraditional inheritance is seen in mitochondrial disorders, triplet repeat expansion diseases, and imprinting defects.

Mitochondrial Inheritance

An individual's mitochondrial genome is entirely derived from the mother because sperm contain relatively few mitochondria, which are degraded after fertilization. It follows that **mitochondrial inheritance** is, essentially, **maternal inheritance**. A female with a mitochondrially inherited genetic disorder can have affected offspring of either sex, but an affected father cannot pass on the disease to his offspring (Fig. 97.15). Mitochondrial DNA pathogenic variants are often deletions or point pathogenic variants. Overall, one person in 400 has a maternally inherited pathogenic mitochondrial DNA pathogenic variant (see Chapter 108). In individual families, mitochondrial inheritance may be difficult to distinguish from autosomal dominant or X-linked inheritance, but in many cases, the sex of the transmitting and nontransmitting parents can suggest a mitochondrial basis (Table 97.1).

Mitochondria are the cell's suppliers of energy; the organs that are most affected by the presence of abnormal mitochondria are those that have the greatest energy requirements, such as the brain, muscle, heart, and liver (see Chapters 107.4, 409, 638.2, and 651.4; Fig. 97.16). Common manifestations include developmental delay, seizures, cardiac dysfunction, decreased muscle strength and tone, and hearing and vision problems.

Mitochondrial diseases can be highly variable in their clinical manifestations. This is partly because cells can contain multiple mitochondria, each bearing several copies of the mitochondrial genome. Thus a cell can have a mixture of normal and abnormal mitochondrial genomes, which is referred to as **heteroplasmy**. In contrast, **homoplasmy** refers to a state in which all copies of the mitochondrial genome carry the same sequence variant. Unequal segregation of mitochondria carrying normal and abnormal genomes and replicative advantage can result in varying degrees of heteroplasmy in the cells of an affected individual, including the individual ova of an affected female. Because of this, a mother may be asymptomatic and yet have children who are severely affected. The level of heteroplasmy at which disease symptoms typically appear can also vary based on the type of mitochondrial variant.

Detection of variants in the mitochondrial genome may require sampling of the affected tissue for DNA analysis. In some tissues, such as blood, testing for mitochondrial DNA variants may be inadequate because the variant may be found primarily in affected tissues such as muscle (Fig. 97.17). Growth and differentiation factor 15 (GDF-15) and blood lactate levels are screening tests for mitochondrial disorders. GDF-15 is only accurate in children ≥1 year of age and in the absence of heart, liver, or renal disease.

Triplet Repeat Expansion Disorders

Triplet repeat expansion disorders are distinguished by the special dynamic nature of the disease-causing variant. Triplet repeat expansion disorders include fragile X syndrome, myotonic dystrophy, Huntington disease, and spinocerebellar ataxias (Table 97.2 and Fig. 97.18). These disorders are caused by expansion in the number of 3-bp repeats. The fragile X gene, *FMR1,* normally has 5-40 CGG triplets. An error in replication can result in expansion of that number to a level in the gray zone between 41 and 58 repeats or to a level referred to as a **prepathogenic variant**, which comprises 59-200 repeats. Some prepathogenic variant carriers, more often males, develop fragile X–associated tremor/ataxia syndrome (FXTAS) as adults. Female prepathogenic variant carriers are at risk for fragile X–associated primary ovarian insufficiency (FXPOI). Persons, especially females, with a prepathogenic variant are also at risk for having the repeat expand further in subsequent meiosis, thus crossing into the range of a **full pathogenic variant** (>200 repeats) in offspring. With this number of repeats, the *FMR1* gene becomes hypermethylated, and protein production is lost.

Some triplet expansions associated with other genes can cause disease through a mechanism other than decreased protein production. In Huntington disease, the expansion causes the gene product to have a new, toxic effect on the neurons of the basal ganglia. For most triplet repeat disorders, there is a clinical correlation to the size of the expansion, with a greater expansion causing more severe symptoms and having an earlier age of disease onset. The observation of increasing severity of disease and early age at onset in subsequent generations is termed **genetic anticipation** and is a defining characteristic of many triplet repeat expansion disorders (Fig. 97.19).

Genetic Imprinting

The two copies of most autosomal genes are functionally equivalent. However, in some cases, only one copy of a gene is transcribed, and the second copy is silenced. This gene silencing is typically associated with methylation of DNA, which is an **epigenetic** modification; it does not change the nucleotide sequence of the DNA (Fig. 97.20). In **imprinting**, gene expression depends on the *parent of origin* of the chromosome (see Chapter 99.7). Imprinting disorders result from an imbalance of active copies of a given gene, which can occur for several reasons. Prader-Willi and Angelman syndromes,

Table 97.1 Representative Examples of Disorders Caused by Pathogenic Variants in Mitochondrial DNA and Their Inheritance

DISEASE	PHENOTYPE	MOST FREQUENT PATHOGENIC VARIANT IN mtDNA MOLECULE	HOMOPLASMY vs HETEROPLASMY	INHERITANCE
Leber hereditary optic neuropathy	Rapid optic nerve atrophy, leading to blindness in young adult life; sex bias approximately 50% males with visual loss, only 10% females	Substitution p.Arg340His in *ND1* gene of complex I of electron transport chain; other complex I missense pathogenic variants	Homoplasmic (usually)	Maternal
NARP, Leigh disease	*N*europathy, *a*taxia, *r*etinitis *p*igmentosa, developmental delay, intellectual disability lactic academia	Point pathogenic variants in ATPase subunit six gene	Heteroplasmic	Maternal
MELAS	*M*itochondrial encephalomyopathy, *l*actic *a*cidosis, and *s*trokelike episodes; may manifest only as diabetes mellitus or deafness	Point pathogenic variant in $tRNA^{Leu}$	Heteroplasmic	Maternal
MERRF	*M*yoclonic *e*pilepsy, *r*agged *r*ed *f*ibers in muscle, ataxia, sensorineural deafness	Point pathogenic variant in $tRNA^{Lys}$	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	m.1555A>G pathogenic variant in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	m.7445A>G pathogenic variant in 12S rRNA	Homoplasmic	Maternal
Chronic progressive external ophthalmoplegia (CPEO)	Progressive weakness of extraocular muscles, cardiomyopathy, ptosis, heart block, ataxia, retinal pigmentation, diabetes	The common MELAS point pathogenic variant in $tRNA^{Lys}$; large deletions similar to KSS	Heteroplasmic	Maternal if point pathogenic variants
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletions	Heteroplasmic	Sporadic, somatic pathogenic variants
Kearns-Sayre syndrome (KSS)	PEO of early onset with heart block, retinal pigmentation	5-kb large deletion	Heteroplasmic	Sporadic, somatic pathogenic variants

mtDNA, Mitochondrial DNA; rRNA, ribosomal RNA; tRNA, transfer RNA.
From Nussbaum RL, McInnes RR, Willard HF, eds. *Thompson & Thompson Genetics in Medicine*, 6th ed. Philadelphia: Saunders; 2001: p. 246.

two distinct disorders associated with developmental impairment, are caused by microdeletions of chromosome 15q11-12. The microdeletion in **Prader-Willi syndrome** is always on the *paternally* derived chromosome 15, whereas in **Angelman syndrome** it is on the *maternal* copy. *UBE3A* is the gene responsible for Angelman syndrome. The paternal copy of *UBE3A* is transcriptionally silenced in the brain, but the maternal copy continues to be transcribed. If an individual has a maternally derived deletion, an insufficient amount of UBE3A protein is produced in the brain, resulting in the neurologic deficits seen in Angelman syndrome.

Uniparental disomy (UPD), the rare occurrence of a child inheriting both copies of a chromosome from the *same parent*, is another genetic mechanism that can cause Prader-Willi and Angelman syndromes. Inheriting both chromosomes 15 from the mother is functionally the same as deletion of the paternal 15q12 region and results in Prader-Willi syndrome. Approximately 30% of cases of Prader-Willi syndrome are caused by maternal UPD15, whereas paternal UPD15 accounts for only 3% of Angelman syndrome (see Chapter 99.7). Pathogenic variants in *UBE3A* account for ~11% of patients with Angelman syndrome and result in familial transmission. The least common cause is a pathogenic variant affecting the imprinting center, which results in an inability to correctly imprint *UBE3A*. In a mother, inability to reset the imprinting on her paternally inherited chromosome 15 imprint results in a 50% risk of passing on an incorrectly methylated copy of *UBE3A* to a child, who would then develop Angelman syndrome.

Other imprinted regions of clinical interest include the short arm of chromosome 11, where the genes for Beckwith-Wiedemann syndrome and nesidioblastosis map, and the long arm of chromosome seven with maternal UPD of 7q being associated with some cases of idiopathic short stature and Russell-Silver syndrome.

Imprinting of a gene can occur during gametogenesis or early embryonic development **(reprogramming)**. Genes can become inactive or active by various mechanisms including DNA methylation or demethylation or histone acetylation or deacetylation, with different patterns of (de)methylation noted on paternal or maternal imprintable chromosome regions. Some genes demonstrate tissue-specific imprinting (see Fig. 97.20). There is a small but increased incidence of imprinting disorders, specifically Beckwith-Wiedemann and Angelman syndrome, following assisted reproductive technologies such as in vitro fertilization and intracytoplasmic sperm injection. The overall incidence of these disorders in children conceived using assisted reproductive technologies is likely to be <1%.

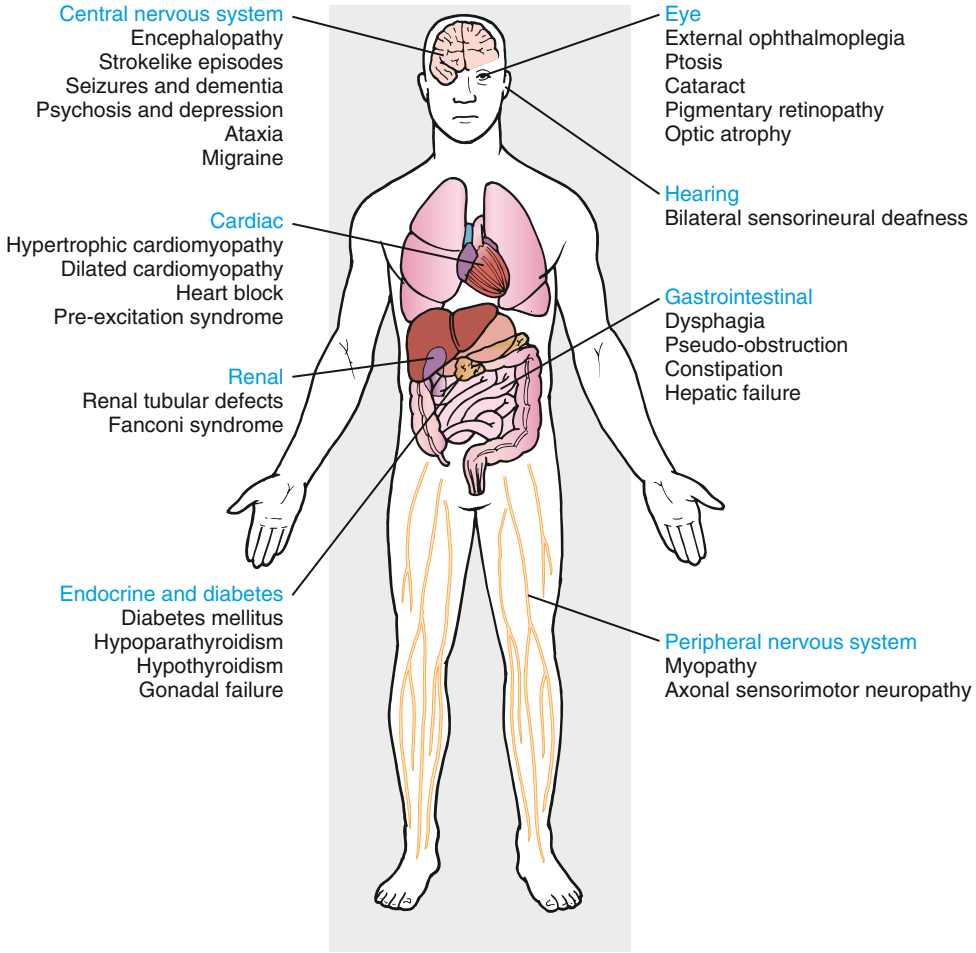

Fig. 97.16 The range of affected tissues and clinical phenotypes associated with pathogenic variants in mitochondrial DNA (mtDNA). (*Modified from Chinnery PF, Turnbull DM. Mitochondrial DNA and disease. Lancet. 1999;345:SI17–SI21.*)

MULTIFACTORIAL AND POLYGENIC INHERITANCE

Multifactorial inheritance refers to traits that are caused by a combination of inherited, environmental, and stochastic factors (Fig. 97.21). Multifactorial traits differ from polygenic inheritance, which refers to traits that result from the additive effects of multiple genes. Multifactorial traits segregate within families but do not exhibit a consistent or recognizable inheritance pattern. Characteristics include the following:

- There is a similar rate of recurrence among all first-degree relatives (parents, siblings, offspring of affected child). It is unusual to find a substantial increase in risk for relatives related more distantly than second degree to the index case.
- The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection, as indicated by an unequal male:female incidence. Pyloric stenosis, for example, is more common in males, whereas congenital dislocation of the hips is more common in females. With an altered sex ratio, the risk is higher for the relatives of an index case whose gender is less often affected than relatives of an index case of the more frequently affected gender. The risk to the son of an affected female with infantile pyloric stenosis is 18%, compared with the 5% risk for the son of an affected male. An affected female presumably has a greater genetic susceptibility, which can be passed on to offspring.
- The likelihood that both identical twins will be affected with the same malformation is <100% but much greater than the chance that both members of a nonidentical twin pair will be affected. This contrasts with the pattern seen in mendelian inheritance, in which identical twins almost always share fully penetrant genetic disorders.
- The risk of recurrence is increased when multiple family members are affected. A simple example is that the risk of recurrence for unilateral cleft lip and palate is 4% for a couple with one affected child and increases to 9% with two affected children. It is sometimes difficult to distinguish between a multifactorial and mendelian etiology in families with multiple affected individuals.
- The risk of recurrence may be greater when the disorder is more severe. For example, an infant who has long-segment Hirschsprung disease has a greater chance of having an affected sibling than the infant who has short-segment Hirschsprung disease.

There are two types of multifactorial traits. One exhibits **continuous variation**, with "normal" individuals falling within a statistical range—often defined as having a value two standard deviations (SDs) above and/or below the mean—and "abnormals" falling outside that range. Examples include such traits as intelligence, blood pressure, height, and head circumference. For many of these traits, offspring values can be estimated based on a modified average of their parental values, with nutritional and environmental factors playing an important role.

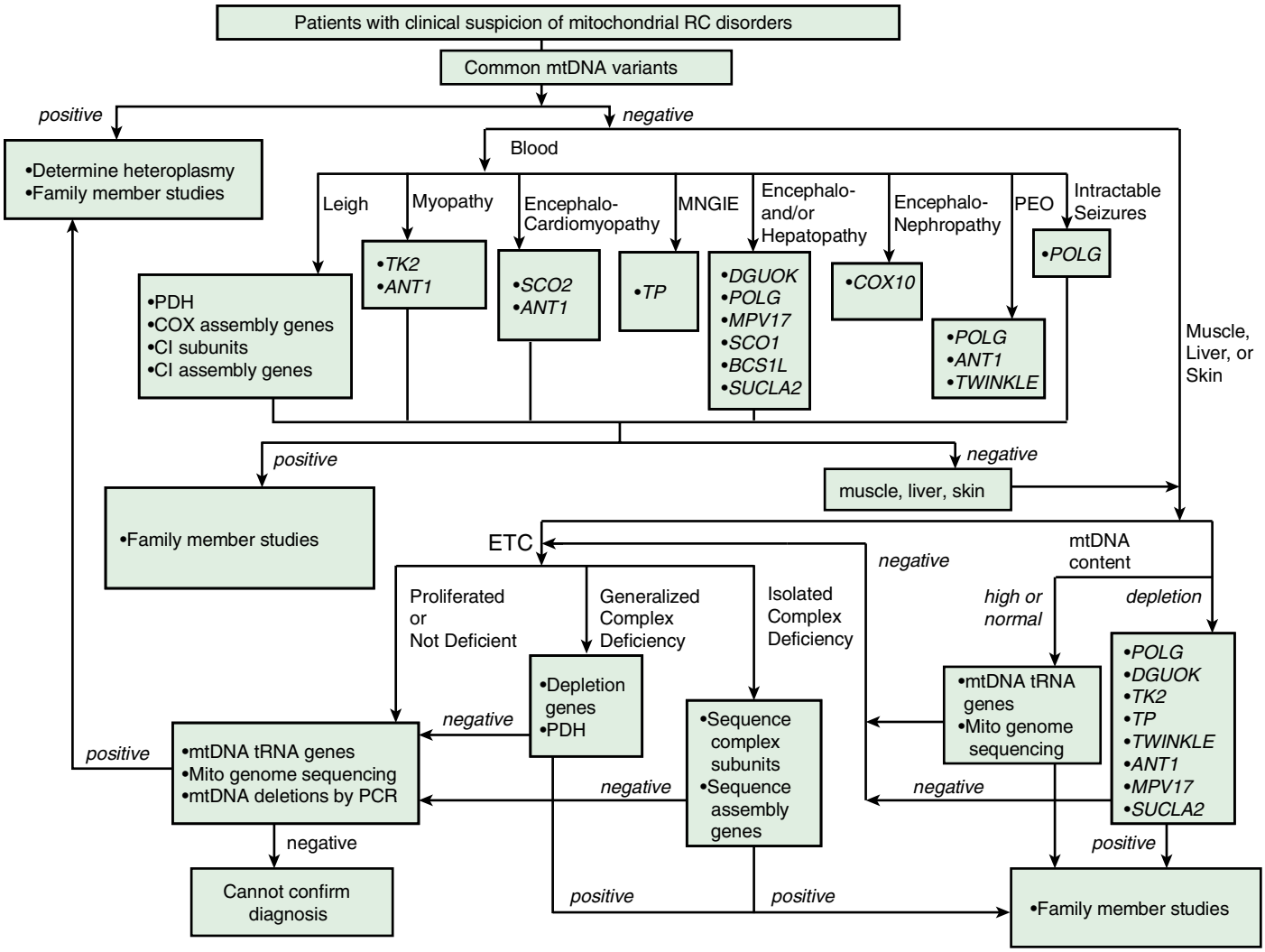

Fig. 97.17 Clinical algorithm for genetic diagnostic testing of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) genes in patients suspected of mitochondrial disorders (Baylor College of Medicine, Mitochondrial Diagnostics Laboratory). RC, Respiratory chain; MNGIE, mitochondrial neurogastrointestinal encephalopathy; PEO, progressive external ophthalmoplegia; PDH, pyruvate dehydrogenase; CI, respiratory complex I; ETC, electron transport chain; PCR, polymerase chain reaction. (*From Haas RH, Parikh S, Falk MJ, et al. The in-depth evaluation of suspected mitochondrial disease. Mol Genet Metab. 2008;94:16–37.*)

Table 97.2 Diseases Associated with Polynucleotide Repeat Expansions

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATION OF EXPANSION
CATEGORY 1						
Huntington disease	Loss of motor control, dementia, affective disorder	CAG	6-34	36-100 or more	More often through father	Exon
Spinal and bulbar muscular atrophy	Adult-onset motor-neuron disease associated with androgen insensitivity	CAG	11-34	40-62	More often through father	Exon
Spinocerebellar ataxia type 1	Progressive ataxia, dysarthria, dysmetria	CAG	6-39	41-81	More often through father	Exon
Spinocerebellar ataxia type 2	Progressive ataxia, dysarthria	CAG	15-29	35-59	—	Exon
Spinocerebellar ataxia type three (Machado-Joseph disease)	Dystonia, distal muscular atrophy, ataxia, external ophthalmoplegia	CAG	13-36	68-79	More often through father	Exon

Continued

Table 97.2 Diseases Associated with Polynucleotide Repeat Expansions—cont'd

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATION OF EXPANSION
CATEGORY 1						
Spinocerebellar ataxia type 6	Progressive ataxia, dysarthria, nystagmus	CAG	4-16	21-27	—	Exon
Spinocerebellar ataxia type 7	Progressive ataxia, dysarthria, retinal degeneration	CAG	7-35	38-200	More often through father	—
Spinocerebellar ataxia type 17	Progressive ataxia, dementia, bradykinesia, dysmetria	CAG	29-42	47-55	—	Exon
Dentatorubral-pallidoluysian atrophy/Haw River syndrome	Cerebellar atrophy, ataxia, myoclonic epilepsy, choreoathetosis, dementia	CAG	7-25	49-88	More often through father	Exon
CATEGORY 2						
Pseudoachondroplasia, multiple epiphyseal dysplasia	Short stature, joint laxity, degenerative joint disease	GAC	5	6-7	—	Exon
Oculopharyngeal muscular dystrophy	Proximal limb weakness, dysphagia, ptosis	GCG	6	7-13	—	Exon
Cleidocranial dysplasia	Short stature, open skull sutures with bulging calvaria, clavicular hypoplasia, shortened fingers, dental anomalies	GCG, GCT, GCA	17	27 (expansion observed in one family)	—	Exon
Synpolydactyly	Polydactyly and syndactyly	GCG, GCT, GCA	15	22-25	—	Exon
CATEGORY 3						
Myotonic dystrophy (DM1; chromosome 19)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CTG	5-37	100 to several thousand	Either parent, but expansion to congenital form through mother	3′ untranslated region
Myotonic dystrophy (DM2; chromosome 3)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CCTG	<75	75-11,000	—	3′ untranslated region
Friedreich ataxia	Progressive limb ataxia, dysarthria, hypertrophic cardiomyopathy, pyramidal weakness in legs	GAA	7-2	200-900 or more	Autosomal recessive inheritance, so disease alleles are inherited from both parents	Intron
Fragile X syndrome (FRAXA)	Intellectual impairment, large ears and jaws, macroorchidism in males	CGG	6-52	200-2,000 or more	Exclusively through mother	5′ untranslated region
Fragile site (FRAXE)	Mild intellectual impairment	GCC	6-35	>200	More often through mother	5′ untranslated region
Spinocerebellar ataxia type 8	Adult-onset ataxia, dysarthria, nystagmus	CTG	16-37	107-127	More often through mother	3′ untranslated region
Spinocerebellar ataxia type 10	Ataxia and seizures	ATTCT	12-16	800-4,500	More often through father	Intron
Spinocerebellar ataxia type 12	Ataxia, eye movement disorders; variable age at onset	CAG	7-28	66-78	—	5′ untranslated region
Progressive myoclonic epilepsy type 1	Juvenile-onset seizures, myoclonus, dementia	12-bp repeat motif	2-3	30-75	Autosomal recessive inheritance, so transmitted by both parents	5′ untranslated region

From Jorde LB, Carey JC, Bamshad MJ, White, RL. *Medical Genetics*, 3rd ed. St Louis: Mosby; 2006: p. 82.

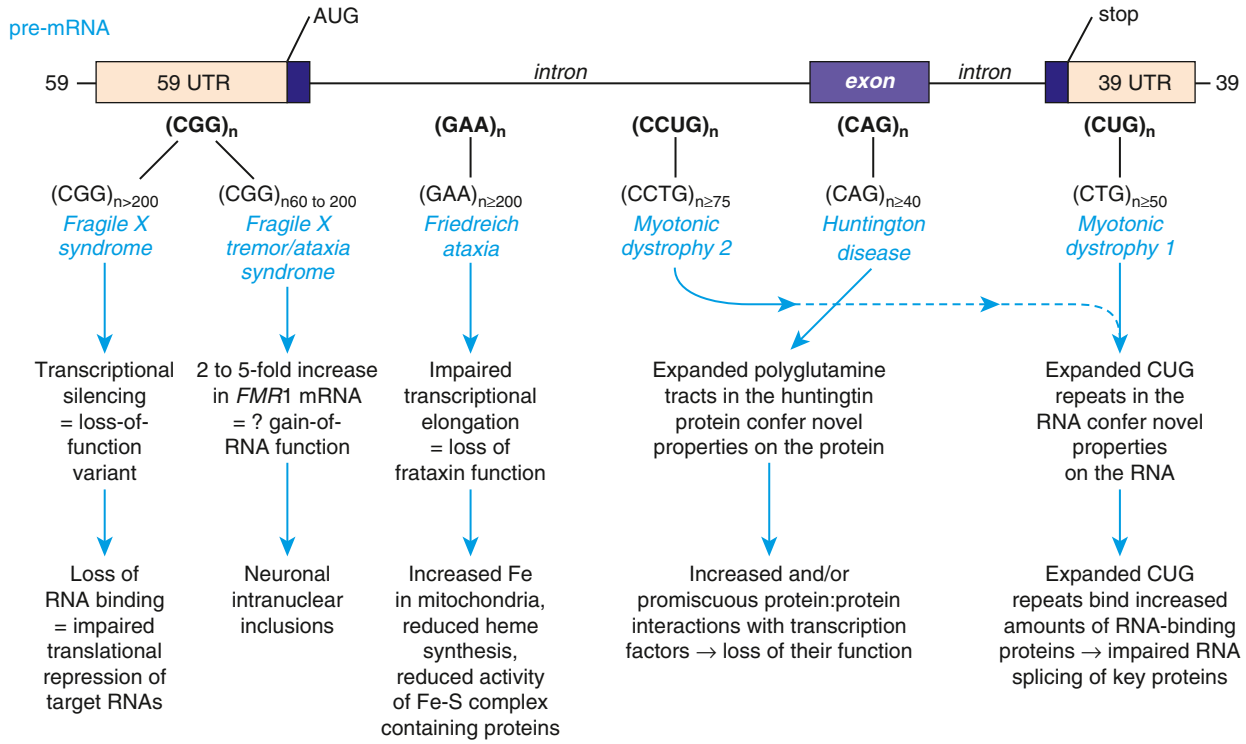

Fig. 97.18 The locations of the trinucleotide repeat expansions and the sequence of each trinucleotide in five representative trinucleotide repeat diseases, shown on a schematic of a generic pre–messenger RNA (mRNA). The minimal number of repeats in the DNA sequence of the affected gene associated with the disease is also indicated, as well as the effect of the expansion on the mutant RNA or protein. (*From Nussbaum RL, McInnes RR, Willard HF, eds. Thompson & Thompson Genetics in Medicine, 8th ed. Philadelphia: Elsevier; 2016; based partly on an unpublished figure from John A. Phillips III, Vanderbilt University.*)

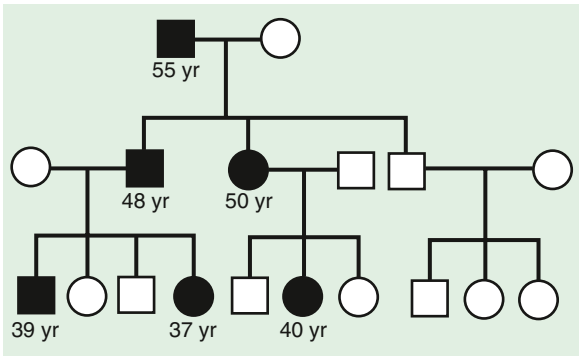

Fig. 97.19 Myotonic dystrophy pedigree illustrating genetic anticipation. In this case the age at onset for family members affected with an autosomal dominant disease is lower in more recent generations. *Black,* Affected patients.

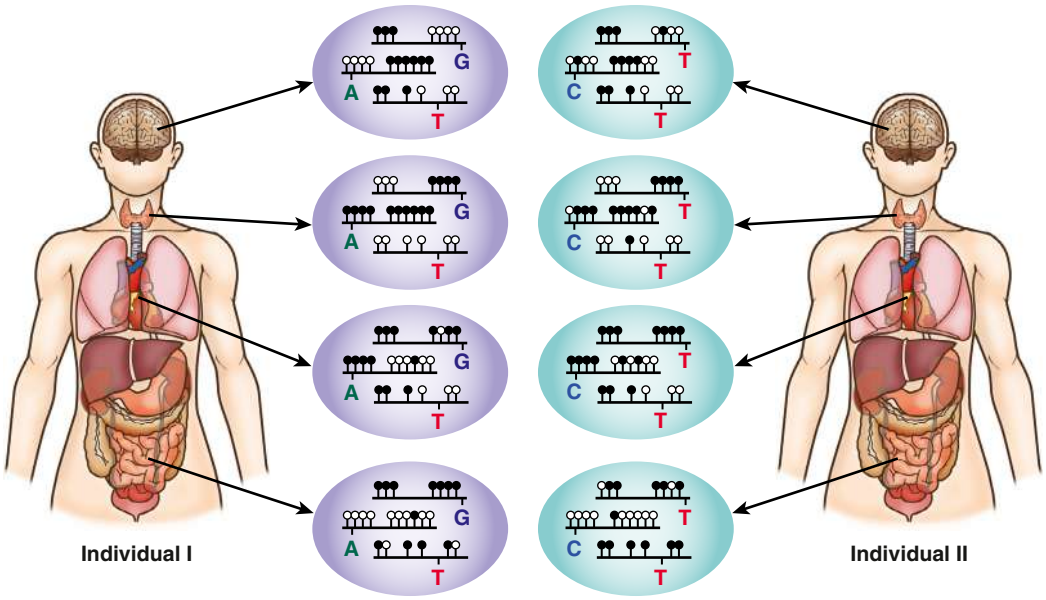

Fig. 97.20 Tissue-specific DNA methylation and epigenetic heterogeneity among individuals. A subset of the DNA methylation patterns within a cell is characteristic of that cell type. Cell type–specific and tissue-specific DNA methylation patterns are illustrated by organ-to-organ variations in the clusters of methylated cytosine-phosphate-guanine bases (CpGs) within the same individual. Despite overall consistency in tissue-specific DNA methylation patterns, variations in these patterns exist among different individuals. Methylated CpGs are indicated by a *filled circle* and unmethylated CpGs by an *open circle*. Single nucleotide polymorphisms (SNPs) are indicated by the corresponding base. (*Redrawn from Brena RM, Huang THM, Plass C. Toward a human epigenome. Nat Genet. 2006;38:1359–1360.*)

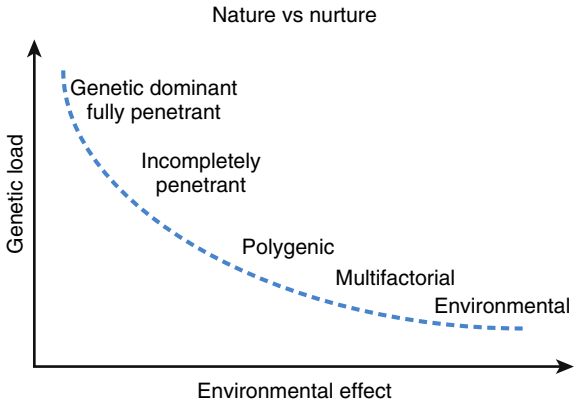

Fig. 97.21 The progressive decrease in the genetic load contributing to the development of a disease creates a smooth transition in the distribution of illnesses on an etiologic diagram. In theory, no diseases are completely free from the influence of both genetic and environmental factors. (*From Bomprezzi R, Kovanen PE, Martin R. New approaches to investigating heterogeneity in complex traits. J Med Genet. 2003;40:553–559.*)

With other multifactorial traits, the distinction between normal and abnormal is based on the **qualitative** presence or absence of a particular trait. Examples include pyloric stenosis, neural tube defects, congenital heart defects, and cleft lip and cleft palate. Such traits follow a **threshold model** (see Fig. 97.15). A distribution of liability because of genetic and nongenetic factors is postulated in the population. Individuals who exceed a threshold liability develop the trait, and those below the threshold do not.

The balance between genetic and environmental factors is demonstrated by neural tube defects. Genetic factors are implicated by the increased recurrence risk for parents of an affected child compared with the general population, yet the recurrence risk is about 3%, less than what would be expected if the trait was caused by a single, fully penetrant pathogenic variant. The role of nongenetic environmental factors is shown by the recurrence risk decreasing up to 87% if the mother-to-be takes 4 mg of folic acid daily starting 3 months before conception.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 98

Integration of Genetics into Pediatric Practice

Brendan Lee and Nicola Brunetti-Pierri

Genetic testing involves analyzing genetic material to obtain information related to a person's health status using chromosomal (cytogenetic) analysis (see Chapter 99) and nucleic acid (primarily DNA but also RNA)-based testing.

DIAGNOSTIC TESTING

Diagnostic genetic testing helps to aggregate a set of signs and symptoms (phenotype) for disease diagnosis. The list of disorders for which specific genetic tests are available is extensive and growing. The website http://www.ncbi.nlm.nih.gov/gtr/ provides one database of reported available tests.

Single-gene disorders can be tested by at least three different approaches: linkage analysis (a classical approach now rarely used), chromosome microarray (CMA), and direct pathogenic variant analysis, usually by DNA sequencing (Table 98.1). Linkage analysis is used if the responsible gene is mapped but not yet identified, or if it is impractical to find specific pathogenic variants, usually because of the large size and large number of different pathogenic variants in some genes. CMA can be used to detect large, multigene deletions or duplications **(copy number variations, or CNVs)**. In addition, with increasing resolution, single-gene or smaller intragenic deletions or duplications can be detected by CMA, although it is important to note that coverage of each gene varies by array type used. *Direct DNA pathogenic variant identification is readily available with the advent of the complete human genome sequence next-generation sequencing (NGS) tools.* We also recognize the relatively frequent co-occurrence of multiple disorders, each caused by distinct pathogenic variants, in patients with complex or "blended" features. This may include partial to minimal clinical manifestations in a substantial percentage of individuals harboring pathogenic variants in known disease genes that remain undiagnosed. The ability to simultaneously sequence hundreds to thousands of genes (via NGS approaches) has provided insight into this complexity of disease pathogenesis.

Linkage testing involves tracking a genetic trait through a family using closely linked polymorphic markers as a surrogate for the trait (Fig. 98.1). It requires testing an extended family and is vulnerable to several pitfalls, such as genetic recombination, genetic heterogeneity, and incorrect diagnosis in the proband or family member. **Genetic recombination** occurs between any pair of loci, with the frequency being proportional to the distance between them. This problem is minimized using very closely linked markers and, if possible, using markers that flank the specific gene. **Genetic heterogeneity** can be problematic for a linkage-based test if there are multiple distinct genomic loci that can cause the same phenotype, resulting in the risk that the locus tested for is not the one responsible for disease in the family. **Incorrect diagnosis** in the proband also leads to tracking the wrong gene. Linkage testing remains useful for several genetic conditions, but it has been superseded by the availability of DNA sequencing of either single gene, panel, or exome sequencing.

CMAs can detect CNVs in a patient's DNA (see Chapter 99). CMA provides a level of genetic resolution between that available with DNA sequencing (single nucleotide) and that available with chromosome analysis (~5 million base pairs). CMA can resolve deletions or duplications of several kilobases within one gene. In theory, this approach can detect deletion and duplication pathogenic variants that would be missed by either chromosome analysis or direct pathogenic variant testing by DNA sequencing. However, because the specific resolution and coverage of different CMA platforms can vary tremendously for different gene regions, the sensitivity for detecting deletions and duplications can vary for different diseases and laboratories. The highest resolution used is detection of a deletion or duplication at the single exon level.

Direct DNA-based pathogenic variant testing avoids the pitfalls of linkage testing by detecting the specific gene pathogenic variant (i.e., sequence change). The specific approach used is customized to the biology of the gene being tested. In some disorders, one or a few distinct pathogenic variants occur in all affected individuals and a specific assay for that variant could be used. This is the case in sickle cell anemia, in which the same single-base substitution occurs in everyone with the disorder. In other conditions, many possible pathogenic variants may account for the disorder in different individuals. In cystic fibrosis, for example, >1,000 distinct pathogenic variants have been found in the *CFTR* gene. Pathogenic variant analysis is challenging because no single technique can detect all possible pathogenic variants (e.g., single nucleotide variation [SNV]), small (several nucleotide) insertion-deletions ("indels"), CNV (larger deletion or duplications), complex structural variations (e.g., translocations, inversions, etc.), DNA repeat expansions (e.g., variable repeat expansions), and epigenetic alterations (e.g., changes in DNA methylation without changing the underlying DNA sequence). However, with high-throughput DNA sequencing technology, the most frequently used approach is to

Table 98.1 Approaches for Genetic Testing

TYPE OF TESTING	RESOLUTION	ADVANTAGES	DISADVANTAGES	SAMPLE REQUIREMENTS
Linkage analysis	Depends on location of polymorphic markers near putative disease gene	Possible when specific disease-causing genetic pathogenic variant is not identifiable or found	Can give only diagnostic probability based on likelihood of genetic recombination between presumed DNA pathogenic variant and polymorphic markers	Requires multiple family members with documented Mendelian pattern of inheritance within family
Chromosome microarray (CMA)	Several hundred base pairs to several hundreds of kilobases	Able to detect small deletion or duplications within one or more genes	Can miss small deletions or insertions depending on the resolution of the array used	Single patient sample sufficient, but having sample from biological parents can help with interpretation
Direct DNA-based testing (e.g., DNA sequencing)	Single–base-pair changes	High specificity if previously described deleterious pathogenic variant is found	Can miss deletion or duplication of a segment of gene	Single patient sample sufficient, but having sample from biological parents and siblings (affected or unaffected) can help with interpretation

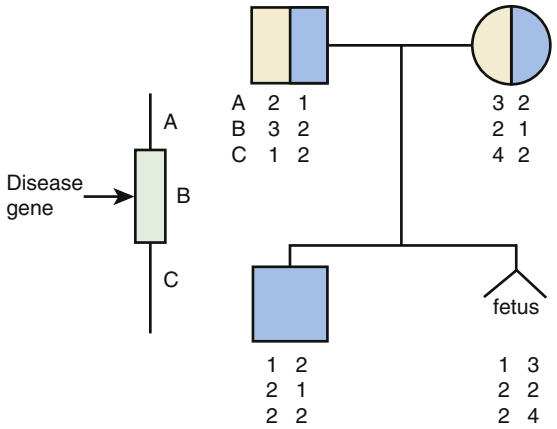

Fig. 98.1 Use of linkage analysis in prenatal diagnosis of an autosomal recessive disorder. Both parents are carriers, and they have one affected son. The numbers below the symbols indicate alleles at three polymorphic loci: A, B, and C. Locus B resides within the disease gene. The affected son inherited the 1-2-2 chromosome from his father and the 2-1-2 chromosome from his mother. The fetus has inherited the same chromosome from the father but the 3-2-4 chromosome from the mother and therefore is most likely to be a carrier.

directly sequence DNA segments "captured" and amplified from DNA isolated from peripheral blood white blood cells. The limitation of this approach is that only amplified DNA segments are sequenced and are usually restricted to the *coding exonic* regions of a gene. Because pathogenic variants sometimes occur in the *noncoding* and *intronic* regions, failure to detect a pathogenic variant does not fully exclude the diagnosis. In addition, deleted genes or regions may not be detected.

NGS tests panels of genes that target disease symptoms (e.g., epilepsy, brain malformations, sensorineural deafness, or skeletal dysplasias) or the majority of the exome **(exome sequencing)**. **Genome sequencing**, where both *coding* and *noncoding* sequences are sequenced, can provide even more information. However, clinical interpretation is limited predominantly to the coding sequences of the approximately 20,000 human genes, the "digital exome," as it is extracted electronically from genome data. Genome sequencing, compared with exome sequencing, also has the advantage of providing improved detection of CNV, structural variation, and repeat expansions, although this is highly dependent on the bioinformatics algorithms used in interpretation.

With NGS, the challenge is the interpretation of enormous genetic variation within a single individual. Direct sequencing of tens to hundreds of genes in NGS panels offers a potentially higher sensitivity because the "depth" of read is higher without complicating high discovery rate of **variants of unknown sequences (VUS)** (Fig. 98.2). Exome and genome sequencing also offer the potential for identifying new disease-gene associations as well as the ability to detect clinical presentations caused by more than one altered gene (i.e., oligogenic phenotypes).

An important ethical consideration is the reporting of *incidental findings,* whether medically actionable or not medically actionable in a patient. For example, exome and genome sequencing may identify pathogenic variants that cause aminoglycoside-sensitive hearing loss, which would be medically actionable but unrelated to the primary indication for which the test was ordered. At the same time, the discovery of apolipoprotein E variants in a child that increase Alzheimer disease risk susceptibility would not typically be medically actionable. Therefore counseling for patients undergoing these tests is important so that only requested results are reported back to the patient. Guidelines continue to evolve for reporting of incidental findings from exome and genome sequencing by the American College of Medical Genetics and Genomics (www.acmg.net). Practice and recommendations continue to vary among international genetic organizations revealing incidental findings to patients, and many strongly advocate the engagement of the patient and family in the decision. Some groups require revealing to the patient and/or family significant diseases (actionable) with a specific and successful treatment or prevention strategy (Table 98.2).

Genetic testing is interpreted by three factors: analytic validity, clinical validity, and clinical utility. **Analytical validity** is test accuracy: Does the test correctly detect the presence or absence of pathogenic variant? Most genetic tests have a very high analytical validity assuming human error has not occurred. Human errors are possible, and unlike most medical tests, a genetic test is unlikely to be repeated because it is assumed that the result will not change over time. Therefore human errors can go undetected for long periods of time. *In addition, variants may be reinterpreted over time as our knowledge base of disease-causing pathogenic variants and genes increases.*

Clinical validity is the degree to which the test correctly predicts presence or absence of disease. False-positive and false-negative test results can occur. **False-positive results** are more likely for predictive tests than for diagnostic tests. An important contributing factor is **nonpenetrance**, where an individual with an at-risk genotype might not clinically express the condition. Another factor is the finding of a **VUS**. Detection of a base sequence variation in an affected patient does not prove that it is the cause of the patient's disorder. Exome sequencing of an individual may identify more than 30,000 VUS and more than 3,000,000 VUS for genome sequencing. Various lines of evidence are used to establish pathogenicity. These include the absence of the variant in large populations of control individuals, finding the variant in affected individuals, demonstration or inference that the variant alters the function of the gene product, noting that the amino acid altered by the pathogenic variant is conserved in evolution, and segregation of the variant with disease in a family. For many variants, it is possible to be certain whether the variant is pathogenic or benign, but for others it might be impossible to definitively assign causality or noncontribution with 100% confidence. For these reasons, they are noted as **VUS.** *Notably, interpretation of pathogenicity for a specific VUS may change over time as our knowledge base increases, underscoring the importance of counseling and reinterpretation.*

False-negative results reflect an inability to detect a pathogenic variant in an affected patient. This occurs principally in disorders with genetic heterogeneity—**allelic** (different pathogenic variants occur in one causative gene) or **locus** (>1 gene can cause a disease) heterogeneity. It is often difficult to detect all possible pathogenic variants within a gene because pathogenic variants vary, both in location within the gene and in the type of variant. Direct sequencing can miss gene deletions or rearrangements (i.e., structural variants), and pathogenic variants may be found within noncoding sequences such as introns or promoter. Therefore a negative DNA test does not necessarily exclude a diagnosis.

Clinical utility is the degree to which the results of a test guide clinical management. For genetic testing, clinical utility includes establishing a diagnosis that obviates the need for additional workup or guiding surveillance or treatment. Test results may also be used as a basis for genetic counseling. For some disorders, genetic testing is possible, but the test results do not add to the clinical assessment. If the diagnosis and genetic implications are already clear, it might not be necessary to pursue genetic testing.

Predictive genetic testing involves performing a test in a person at risk for developing a genetic disorder **(presymptomatic)**, usually on the basis of family history, yet who does not manifest signs or symptoms. This is usually done for disorders that display age-dependent penetrance (e.g., the likelihood of manifesting signs and symptoms increases with age, as in cancer genetic syndromes or Huntington disease).

A major caution with predictive testing is that the presence of a gene pathogenic variant does not necessarily mean that the disease will develop. Many of the disorders with age-dependent penetrance display *incomplete penetrance*. A person who inherits a pathogenic variant may never develop signs of the disorder. There is concern that a positive DNA test could result in stigmatization of the person and might not provide information that will guide medical management. Stigmatization might include psychologic stress, but it could also include

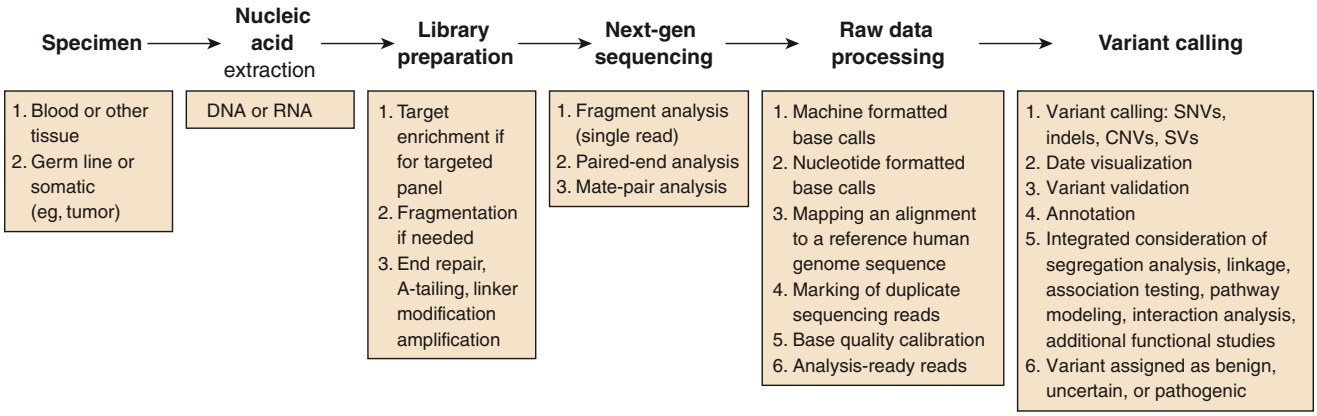

Fig. 98.2 Overview of the next-generation DNA sequencing workflow. CNV, Copy number variant; Indels, insertions and deletions; SNV, single nucleotide variant; SV, structural variant. (*Adapted from Casey G, Conti D, Haile R, et al. Next generation sequencing and a new era of medicine. Gut. 2013;62[6]:920–932.*)

Table 98.2 Variants That Are Incidental Findings Are Assigned to One of Four Categories

Childhood onset	Medically actionable*
Childhood onset	Not medically actionable†
Adult onset	Medically actionable*
Adult onset	Not medically actionable†

*"Medically actionable" refers to a variant in a gene in which knowledge of the particular variant will affect medical decision-making, such as initiation of a treatment or family planning.

†"Not medically actionable" refers to variants that increase the individual's risk for a disease in which no treatment is proven to significantly change the disease natural history.

From Bick D, Dimmock D. Whole exome and whole genome sequencing. *Curr Opin Pediatr.* 2011;23:594–600.

discrimination, including denial of health, life, or disability insurance, or employment (see Chapter 95).

It is generally agreed that predictive genetic tests should be performed for children only if the results of the test will benefit the medical management during childhood; otherwise, the test should be deferred until the individual understands the risks and benefits of testing and can provide their own informed consent. Individual states offer varying degrees of protection from discrimination on the basis of genetic testing. A major milestone in the prevention of genetic discrimination was the passage of the **Genetic Information Nondiscrimination Act** (GINA) in 2008, which is a U.S. federal law that prohibits discrimination in health coverage or employment based on genetic information. *Of note, it does not* protect against refusal of life insurance.

Predispositional genetic testing is available with the goal of predicting risk of disease. The rationale for predispositional testing is that the results would lead to strategies aimed at risk reduction as part of a *personalized approach* to healthcare maintenance. This might include avoidance of environmental exposures that would increase risk of disease (cigarette smoking and α_1-antitrypsin deficiency), medical surveillance (familial breast cancer and mammography), or in some cases, pharmacologic treatment (statins and hypercholesterolemia).

Common disorders are multifactorial in etiology, and many different genes may contribute to risk of any specific condition (see Chapter 103). Most genetic variants found to correlate with risk of a common disease add small increments of relative risk and, in most cases, too little to guide management based on a single variant.

Statistical models for predicting risk based on a collection of DNA variants has been integrated into approaches such as *polygenic risk scores*. By combining the relative risk conferred by a group of DNA variants, the goal is to quantify a larger proportion of risk for a specific disease. These predictions are confounded by the source of data from which they are generated, and current population genetic data have limitations including lack of ethnic diversity and population stratification.

PHARMACOGENETICS

Polymorphisms in drug metabolism genes can result in distinctive patterns of drug absorption, metabolism, excretion, or effectiveness. Knowledge of individual genotypes can guide pharmacologic therapy, allowing customization drug choice and dosage to avoid toxicity and provide a therapeutic response. Well-known examples include testing for polymorphisms within the methylenetetrahydrofolate reductase *(MTHFR)* gene for susceptibility of potentially increased toxicity to methotrexate antimetabolite therapy and thiopurine *S*-methyltransferase (*TPMT)* to avoid adverse effects with 6-mercaptopurine therapy (Fig. 98.3).

Pediatric Pharmacogenomics

Pharmacogenomics is the study of how variants contribute to interindividual variability in drug response. The finding that drug responses can be influenced by the patient's genetic profile offers great hope for realizing *individualized* pharmacotherapy, in which the relationship between genotype and phenotype (either disease and/or drug response) is predictive of drug response. In addition to genetic differences, environmental factors (e.g., diet, concomitant drug or toxic exposure), physiologic variables (age, sex, pregnancy), and patient adherence all contribute to variations in drug metabolism and response. Interindividual differences in children are further complicated by the changing patterns of gene expression occurring during the developmental processes from birth through adolescence. Combining these genetic and nongenetic individual-specific variables, it is expected that children will benefit from the promise of precision medicine, e.g., identifying the right drug for the right patient at the right time and dosing (Fig. 98.4).

Examples of pharmacogenomic traits include specific adverse drug reactions, such as prolonged respiratory muscle paralysis due to succinylcholine, hemolysis associated with antimalarial therapy, carbamazepine-induced Stevens-Johnson syndrome, isoniazid-induced neurotoxicity, and others (Table 98.3). The pharmacokinetic properties of a drug are determined by genes that control drug absorption, distribution, metabolism, and excretion. Drug-metabolizing enzymes and drug transporters play a particularly important role in this process. One of the better recognized clinical manifestations of pharmacogenomic variability in drug biotransformation is an increased risk of concentration-dependent toxicity caused by reduced clearance and consequent tissue drug accumulation. Equally important is the lack of efficacy caused by variations in metabolism of prodrugs that require biotransformation to be converted into a pharmacologically active form. The pharmacogenomics of drug receptors and other target proteins involved in signal transduction or disease pathogenesis are also expected to contribute to interindividual variability in drug disposition and response.

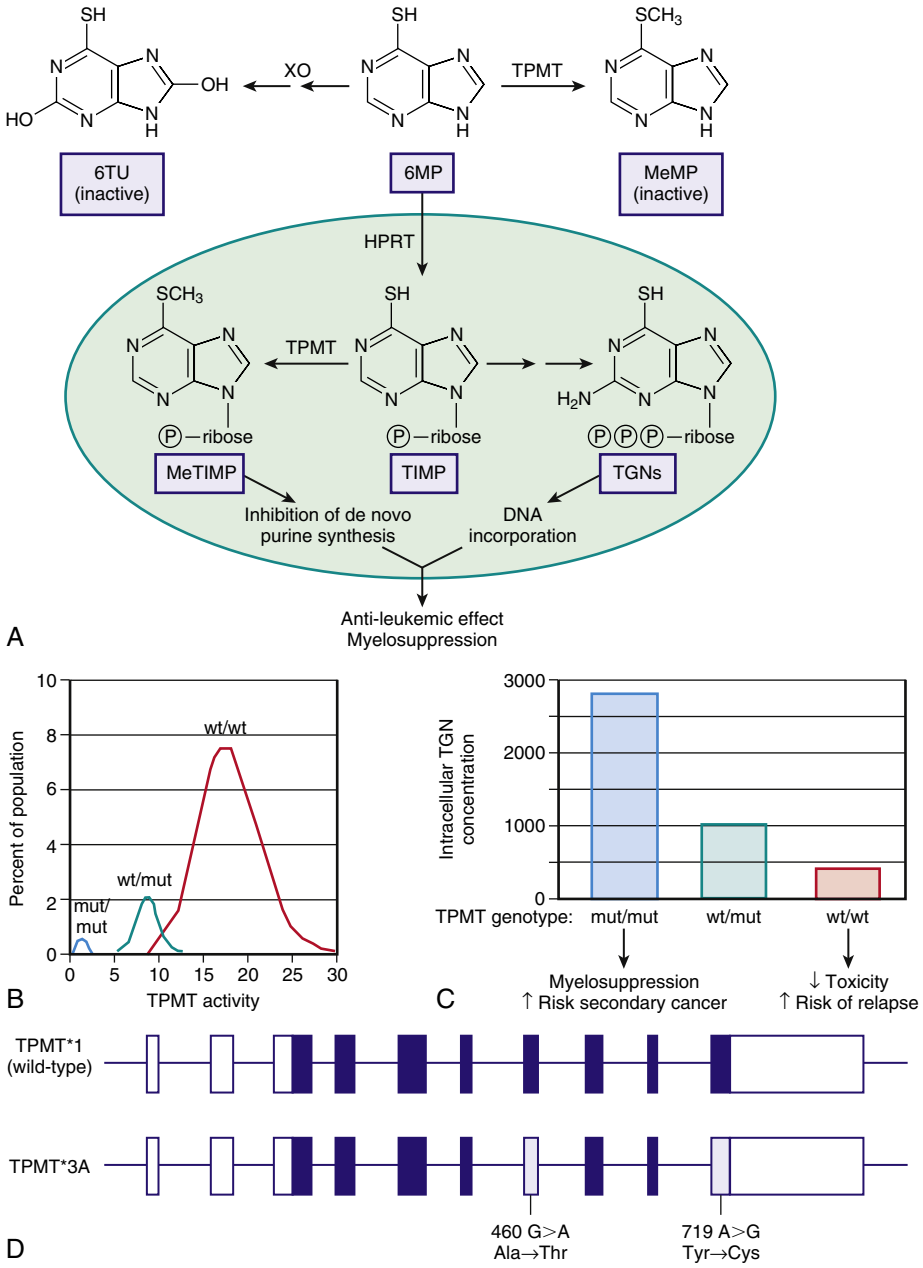

Fig. 98.3 Thiopurine *S*-methyltransferase (TPMT) polymorphism. **A,** 6-Mercaptopurine (6MP) undergoes metabolism to thioguanine nucleotides (TGNs) to exert its cytotoxic effects. TPMT and xanthine oxidase reduce the amount of 6MP available for the bioactivation pathway to TGNs. TPMT can also methylate 6-thioinosine 5′-monophosphate (TIMP) to generate a methylated compound capable of inhibiting de novo purine synthesis. **B,** Distribution of TPMT activity in humans. Of the population, 89% has high activity, whereas 11% has intermediate activity. Approximately 1 in 300 individuals homozygous for two loss-of-function alleles has very low activity. **C,** Correlation between the TPMT genotype and intracellular TGN concentrations. In TPMT-poor metabolizers, more 6MP is available to go down the bioactivation pathway to form TGNs; this situation is associated with an increased risk of myelosuppression. **D,** The most common variant TPMT allele is the result of two pathogenic variants that give rise to an unstable protein product that undergoes proteolytic degradation. Each box represents an exon. Non-coding sequences are shown as white boxes and colored boxes indicate coding sequences. 6TU, 6-Thiouric acid; MeMP, 6-methylmercaptopurine; HPRT, 6-thiomethylinosine 5-monophosphate; MeTIMP, hypoxanthine-guanine phosphoribosyl transferase; wt, wild type; mut, mutant; Ala, alanine; Thr, threonine; Tyr, tyrosine; Cys, cysteine. (*Modified from Relling MV, Dervieux T. Pharmacogenetics and cancer therapy. Nat Rev Cancer. 2001;11:99–108.*)

Individuals are classified as "fast," "rapid," or "extensive" metabolizers at one end and "slow" or "poor" metabolizers at the other end of the continuum. For biotransformation, fetuses and newborns may be phenotypically "slow" or "poor" metabolizers for certain drug-metabolizing pathways because of their stage of development, and they may acquire a phenotype consistent with their genotype at some point later in the developmental process. Moreover, not all infants acquire drug metabolism activity at the same rate, and there is interindividual variability in the trajectory (i.e., rate and extent) of drug biotransformation capacity (Fig. 98.5). The primary organ responsible for drug metabolism is the liver, although the kidney, intestine, lung, adrenals, blood (phosphatases, esterases), and skin can also biotransform certain compounds. Drug biotransformation is characterized by three important features: (1) broad substrate specificity, in which a single isozyme may metabolize a large variety of chemically diverse compounds; (2) many different enzymes may be involved in the biotransformation of a single drug (enzyme multiplicity); and (3) a given drug may undergo several different types of reactions. Drug biotransformation reactions are classified into phase I reactions that introduce or reveal (through oxidation, reduction, or hydrolysis) a functional group within the substrate drug molecule that serves as a site for phase II reactions. These reactions involve conjugation with endogenous substrates (such as acetate, glucuronic acid, glutathione, glycine, and sulfate), making the compound more water soluble to be excreted in urine. A supergene family with at least 16 primary cytochrome P450 (CYP) enzymes are quantitatively the most important phase I enzymes and catalyze the metabolism of many lipophilic endogenous (steroids, fatty acids, fat-soluble vitamins, prostaglandins, leukotrienes, thromboxanes) and exogenous compounds, including a multitude of drugs and environment toxins. The specific CYP isoforms responsible for the majority of human drug metabolism are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These enzymes are the products of genes that in some cases are polymorphically expressed, with allelic variants producing enzymes generally resulting in either no or reduced catalytic activity. At birth the activities of drug-oxidizing enzymes in the liver are reduced, which results in slow clearance (and prolonged elimination) of several substrate drugs (e.g., phenytoin, caffeine, diazepam). Phase

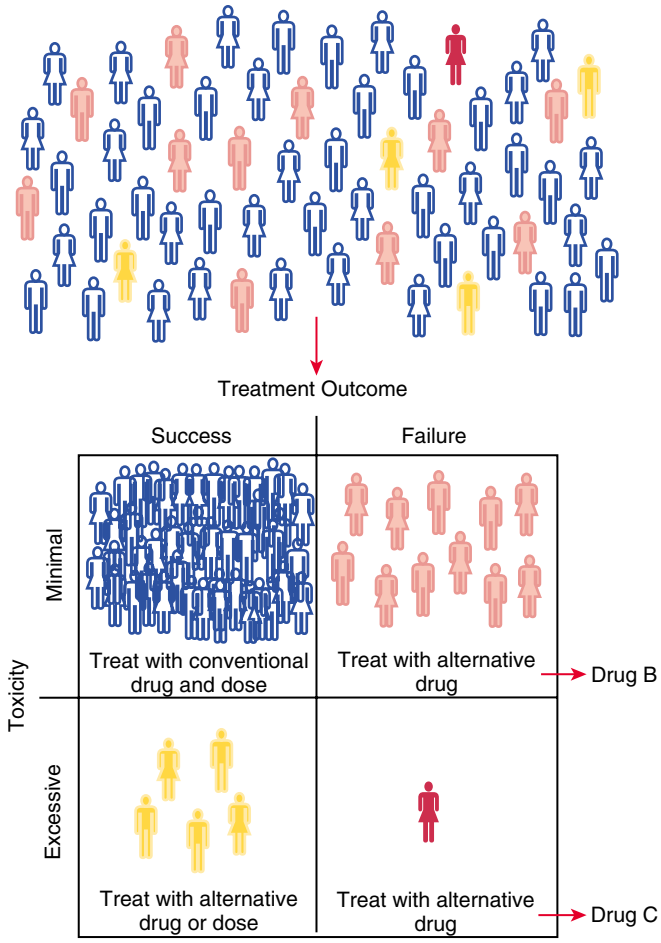

Fig. 98.4 The promise of genomic medicine to human health and disease. The goal of personalized medicine is to identify subgroups of patients who will respond favorably to a given drug with minimum side effects, as well as those who will not respond or who will show toxicity with standard doses. A further benefit of pharmacogenomics is to select the most appropriate alternative drug for patients who cannot be treated successfully with conventional drugs and doses. (*Adapted from Yaffe SJ, Aranda JV. Neonatal and Pediatric Pharmacology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.*)

II enzymes include arylamine *N*-acetyltransferases (NAT1, NAT2), uridine diphospho-glucuronosyltransferases (UGTs), epoxide hydrolase, glutathione *S*-transferases (GSTs), sulfotransferases (SULTs), and methyltransferases (catechol *O*-methyltransferase, thiopurine *S*-methyltransferase, several *N*-methyltransferases). Phase II enzyme activity is decreased in the newborn and increases into childhood. Conjugation of compounds metabolized by isoforms of UGT (e.g., morphine, bilirubin, chloramphenicol) is reduced at birth but can exceed adult values by 3-4 years of age.

Membrane transporters are involved in drug disposition and actively transport substrate drugs between organs and tissues. They include organic anion transporters (OATs), organic anion–transporting polypeptides (OATPs), organic cation transporters (OCTs), and the adenosine triphosphate–binding cassette (ABC) transporters, such as P-glycoprotein and the multidrug-resistant proteins. Drug transporters are expressed at numerous barriers, such as intestinal epithelial cells, hepatocytes, renal tubular cells, and the blood-brain barrier (Fig. 98.6). Transporters are often determinants of drug resistance, and many drugs work by affecting the function of transporters. Polymorphisms in the genes encoding these transporters might affect drug absorption, distribution, metabolism, and excretion.

98.1 Genetic Counseling

Brendan Lee and Pilar L. Magoulas

Genetic counseling is a communication process in which the genetic contribution to health, specific risks of transmission of a trait, and options to manage the condition are explained to individuals and their family members (Table 98.4). Genetic counselors are specialized healthcare providers trained in the psychosocial aspects of counseling and the science of medical genetics who may serve as members of medical teams in many different specialties. The genetic counselor is expected to present information in a neutral, nondirective manner while providing resources and psychosocial support to the individual and family to cope with decisions that are made (see Table 98.4).

In the prenatal setting, a common indication for genetic counseling is to assess risk of occurrence or recurrence of having a child with a genetic condition and to discuss management or treatment options that might be available before, during, or after the pregnancy, such as preimplantation genetic testing, noninvasive prenatal screening, prenatal diagnosis or fetal intervention, and perinatal management. In pediatric and adult genetics practices, the goals of genetic counseling are to help establish a diagnosis in an individual, provide longitudinal care and psychosocial support to the family, and discuss the genetic basis and inheritance of the condition as it relates to immediate and distant family members.

The genetic counseling role has expanded, particularly with advances in understanding the genetics of adult-onset or common and rare disease therapeutics. In the former context, genetic counseling has a major role in risk assessment for cancer, especially breast, ovarian, or colon cancer, for which well-defined risk models and genetic tests are available to assess risk to an individual. In the latter, the genetic counselor may discuss developments in rare disease therapeutics and make appropriate referral for medical therapies.

There are several situations in which genetic counseling plays a particularly important role. The first situation is the **prenatal diagnosis** of a congenital anomaly or genetic disease. The need for information is urgent because a family must often make time-sensitive decisions about treatment and management options, such as fetal intervention or continuation of a pregnancy in the context of fetal anomalies. Risks to the mother must also be considered. The second type of situation occurs when a child is born with a life-threatening **congenital anomaly** or suspected **genetic disease**. Decisions must be made immediately on how much support should be provided to the child and whether certain types of therapy should be attempted. The third situation arises when there are concerns about a **genetic condition** affecting one later in life. This may occur in an adolescent or young adult with a family history of an adult-onset genetic disorder (e.g., Huntington disease, hereditary breast/ovarian cancer), in an individual with a suspected yet undiagnosed genetic condition, or if a couple with a personal or family history of a genetic condition (or a carrier) is planning a family. In these situations, it is often necessary to have several meetings with a family to discuss possible testing, screening, and management options. Urgency is not as much of an issue as being sure that they have as much information and as many options as are available. Last, with the advent of genomic testing in all areas of clinical care, **pretest genetic counseling** before testing is essential to provide individuals with accurate information regarding the types of results they may receive. During this process, individuals are also given the option of what type of results they want reported back to them, such as medically actionable results unrelated to the primary indication for testing and incidental findings.

GENETIC COUNSELING ELEMENTS

Components of a genetic counseling session and providing accurate information to families requires the following:

- Taking a targeted family history and constructing a pedigree that diagrams the patient's relatives (including miscarriages, abortions, stillbirths, deceased persons) with their sex, age, ethnicity, and state of health, up to and including third-degree relatives.

Table 98.3 Examples of Effects of Gene Polymorphisms on Drug Response

GENE	ENZYME/TARGET	DRUG	CLINICAL RESPONSE
BCHE	Butyrylcholinesterase	Succinylcholine	Prolonged paralysis
CYP2C9	Cytochrome P450 2C9	Warfarin	Individuals having ≥1 reduced function alleles require lower doses of warfarin for optimal anticoagulation, especially initial anticoagulant control.
CYP2C19	Cytochrome P450 2C19	Clopidogrel	Individuals having ≥1 loss-of-function alleles have reduced capacity to form pharmacologically active metabolite of clopidogrel and reduced antiplatelet effect.
CYP2D6	Cytochrome P450 2D6	Codeine	Poor metabolizers (individuals with two loss-of-function alleles) do not metabolize codeine to morphine and thus experience no analgesic effect. Ultrarapid metabolizers (individuals with ≥3 functional alleles) may experience morphine toxicity.
G6PD	Glucose-6-phosphate dehydrogenase	Primaquine (others)	Hemolysis
*HLA-A*3101*	Human leukocyte antigen A31	Carbamazepine	Carriers of *HLA-A*3101* allele have increased risk of SJS and TEN from carbamazepine.
*HLA-B*1502*	Human leukocyte antigen B15	Allopurinol	Han Chinese carriers of *HLA-B*1502* allele have increased risk of SJS and TEN from carbamazepine.
*HLA-B*5701*	Human leukocyte antigen B57	Abacavir Flucloxacillin	Carriers of *HLA-B*5701* allele have increased risk of hypersensitivity reactions to abacavir- and flucloxacillin-induced liver injury.
*HLA-B*5801*	Human leukocyte antigen B58	Allopurinol	Carriers of *HLA-B*5801* allele have increased risk of severe cutaneous adverse reactions to allopurinol, including hypersensitivity reactions, SJS, and TEN.
NAT2	*N*-Acetyltransferase 2	Isoniazid, hydralazine	Individuals homozygous for "slow acetylation" polymorphisms are more susceptible to isoniazid toxicity, or hydralazine-induced systemic lupus erythematosus.
SLCO1B1	Organic anion–transporting protein (OATP) 1B1	Simvastatin	Carriers of the *SLCO1B1*5* allele are at increased risk for musculoskeletal side effects from simvastatin.
TPMT	Thiopurine *S*-methyltransferase	Azathioprine 6-Mercaptopurine	Individuals homozygous for an inactivating pathogenic variant have severe toxicity if treated with standard doses of azathioprine or 6-mercaptopurine; rapid metabolism causes undertreatment.
UGT1A1	Uridine diphospho-glucuronosyltransferase 1A1	Irinotecan	*UGT1A1*28* allele is associated with decreased glucuronidation of SN-38, the active metabolite of irinotecan, and increased risk of neutropenia.
VKORC1	Vitamin K oxidoreductase complex 1	Warfarin	Individuals with a haplotype associated with reduced expression of VKORC1 protein (therapeutic target of warfarin) require lower doses of the drug for stable anticoagulation.

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

- Gathering information from hospital records about the affected individual and, in some cases, about other family members.
- Documenting prenatal, pregnancy, and delivery histories.
- Reviewing the latest available medical, laboratory, and genetic information concerning the disorder.
- Reviewing a careful physical examination of the affected individual (photographs, measurements) and of apparently unaffected individuals in the family (typically performed by a physician rather than a genetic counselor).
- Reviewing genetic testing and screening options.
- Establishing or confirming the diagnosis by the diagnostic tests available.
- Providing psychosocial support to the individual and family throughout the diagnostic process.
- Giving the family information about support groups and local and national resources.
- Providing new information to the family as it becomes available (a mechanism for updating needs to be established).

Genetic counseling sessions often include anticipatory guidance regarding the occurrence or risk of occurrence of a specific condition, knowledge of the diagnosis of the particular condition, natural history of the condition, genetic aspects of the condition, risk of recurrence, prenatal diagnosis and reproductive options, therapies and referrals, and provision of support resources.

The Diagnostic Process

If a specific diagnosis is made and confirmed, this should be discussed with the family and information provided in writing. Often, however, the disorder fits into a spectrum (e.g., one of many types of arthrogryposis) or the diagnosis is clinical rather than confirmed with molecular testing. In these situations, the family needs to understand the limits of the diagnostic process and present knowledge, and that additional research will probably lead to better information in the future.

Although it is not always possible to make an exact diagnosis, having a diagnosis *as accurate as possible* is important. Estimates of recurrence risk for various family members depend on an accurate diagnosis that

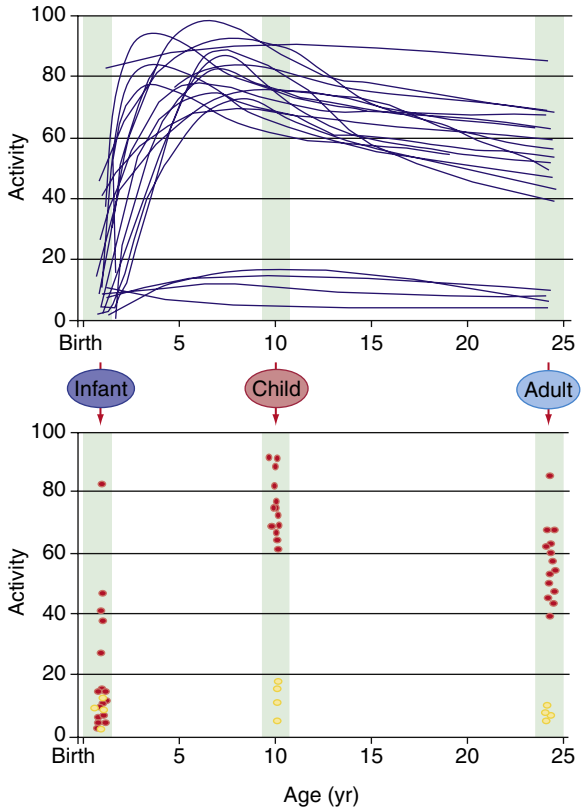

Fig. 98.5 "Developmental" phenotypes. Variability in developmental changes in gene expression and functional enzyme activity are superimposed on pharmacogenetic determinants. **Top,** Developmental profile of a theoretical drug-metabolizing enzyme over a 25-year span in 20 individuals. **Bottom,** At maturity (adults), allelic variation within the coding region of the gene gives rise to two distinct phenotypes: high activity in 92% of the population ("extensive metabolizers"; *red circles*) and low activity in 8% of the population ("poor metabolizers"; *yellow circles*). However, there is also interindividual variability in the rate at which functional activity is acquired after birth. For example, the two phenotypes may not be readily distinguishable in newborn infants. Furthermore, there may be discrete periods during childhood in which the genotype-phenotype relationship may differ from that observed in adults (e.g., developmental stages at which enzyme activity appears to be greater in children than in adults). (*Adapted from Leeder JS. Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatric and beyond. Drug Discov Today. 2004;9:567–573.*)

considers the likelihood that a particular finding is isolated, associated with a syndrome, or nonsyndromic (e.g., isolated cleft lip and palate). When a specific diagnosis cannot be made (as in many cases of multiple congenital anomalies), the various possibilities in the differential diagnosis should be discussed with the family and empirical information provided. If available, specific diagnostic tests should be discussed. Often, empirical recurrence risks can be given even without a specific laboratory-based diagnosis. At the same time, even negative laboratory testing can further modify this risk.

Natural History of the Condition

It is important to discuss the natural history of the specific genetic disorder in the family. Affected persons and their families have questions regarding the prognosis and potential management or therapy that can be answered only with knowledge of the natural history. If there are other possible diagnoses, their natural history may also be discussed. If the disorder is associated with a spectrum of clinical outcomes or complications, the range of possible outcomes and variability of the condition, as well as treatment and referral to the appropriate specialist, should be addressed.

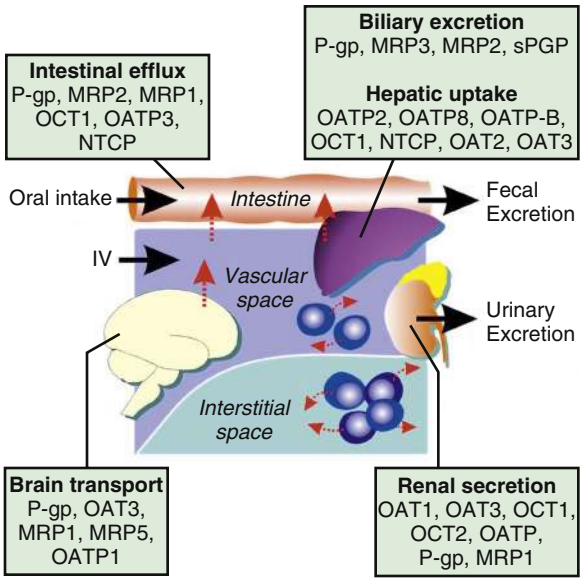

Fig. 98.6 Schematic diagram of important transport proteins and their known locations in humans. *Spheres* correspond to drug molecules. (*From American Pharmacists Association. Ritschel WA, Kearns GL, eds. Handbook of Basic Pharmacokinetics Including Clinical Applications, 7th ed. Washington, DC: American Pharmacists Association, 2009. p 45.*)

Genetic Aspects of the Condition and Recurrence Risk

The genetic aspects and risk of recurrence are important because all family members should be informed of their reproductive choices. The genetic basis of the disorder can be explained with visual aids (e.g., diagrams of chromosomes and inheritance patterns). It is important to provide accurate occurrence and recurrence risks for various members of the family, including unaffected individuals. If a definite diagnosis cannot be made, it is necessary to use empirical recurrence risks. Genetic counseling gives patients the necessary information to understand the various options and to make their own informed decisions regarding pregnancy, adoption, assistive reproductive technologies, prenatal diagnosis, screening, carrier detection, or termination of pregnancy. It may be necessary to have more than one counseling session. Even if a specific molecular diagnosis has been made and a well-defined inheritance pattern has been described for the condition, it is important to recognize that the principles of incomplete penetrance, variable expressivity, and germline/somatic mosaicism can contribute uncertainty to the recurrence risk and severity of a potentially affected pregnancy conception or child.

Prenatal Diagnosis and Prevention

Many different methods of prenatal screening and diagnosis are available, depending on the specific genetic disorder (see Chapter 117). The use of ultrasonography allows prenatal screening of anatomic abnormalities such as congenital heart defects. Amniocentesis and chorionic villus sampling are used to obtain fetal tissue for analysis of chromosomal abnormalities, biochemical disorders, and DNA studies. Maternal blood or serum sampling is used for some types of screening, including noninvasive prenatal screening by direct analysis of cell-free fetal DNA found in maternal blood, which is used for screening of conditions such as trisomy 21 and other aneuploidies. In addition, this source of cell-free fetal DNA has also been used clinically for DNA sequencing for selected dominant de novo conditions in the fetus that may occur with increased frequency with increasing paternal age. Current tests of fetal DNA from maternal blood should be considered screening tests, and invasive testing like amniocentesis or chorionic villus sampling should be considered for confirmatory diagnostic testing.

Table 98.4 Indications for Genetic Counseling

Advanced parental age
• Maternal age ≥35 years
• Paternal age ≥40 years
Previous child with or family history of:
• Congenital abnormality
• Dysmorphology
• Intellectual disability
• Isolated birth defect
• Metabolic disorder
• Chromosome abnormality
• Single-gene disorder
Adult-onset genetic disease (presymptomatic testing)
• Cancer
• Huntington disease
Pharmacogenomics
Consanguinity
Teratogen exposure (occupational, abuse)
Repeated pregnancy loss or infertility
Pregnancy screening abnormality
• Maternal serum α-fetoprotein
Maternal first-trimester screen
• Maternal triple or quad screen or variant of this test
• Fetal ultrasonography
Noninvasive prenatal testing (NIPT)
• Fetal karyotype
Heterozygote screening based on ethnic risk
• Sickle cell anemia
• Tay-Sachs, Canavan, and Gaucher diseases
• Thalassemias
Universal carrier screening panels
Follow-up to abnormal neonatal genetic testing
Prior to whole genome or exome sequencing
Prior to preimplantation genetic testing

Therapies and Referral

Some genetic disorders require the care of multiple specialists. Many genetic conditions have diagnosis and management guidelines to aid in the treatment and management of these complex patients. Prevention of known complications is a priority, so close follow-up with the necessary specialists involved in the child's care is essential to identify any potentially concerning issues early. The psychologic adjustment of the family might also require specific intervention. Some challenges may involve when to discuss the diagnosis of a chronic disease with the patient, siblings, and other family members or friends. The decision to do so should always involve the parents and an assessment of the maturity and capacity of the child or adolescent.

Alternative medicines or nontraditional therapies are often brought to attention by parents after exhaustive internet searches. Such treatments should not necessarily be dismissed since the physician and genetic counselor should serve as an important resource for helping parents navigate the maze of nonstandard treatments. Instead, the relative merits of treatments should be framed in the context of cost and benefit, scientific rationale, evidence from controlled and observational studies, the placebo effect, safety of the treatment, and the gaps in our own scientific knowledge base.

Support Groups

A large number of community and online lay disease–specific support groups have been formed to provide information and to fund research on specific genetic and nongenetic conditions. An important part of genetic counseling is to give information about these groups to patients and to suggest a contact person for the families. Many groups have established websites and social media platforms with very helpful information. With the rise of social media and its ability to connect families with rare syndromes from around the world, it is important to stress to families that their individual disease course will be unique and significant biases of reporting occur on such platforms. This should be balanced by the benefit of sharing potential important natural history elements of the underlying rare disease.

Follow-Up

Families should be encouraged to continue to ask questions and keep up with new information about the specific disorder. New developments often influence the diagnosis and therapy of specific genetic disorders.

Nondirective Counseling

Genetic counseling is usually nondirective; choices about reproduction are left to the family to decide what is right for them. The role of the counselor (physician, genetic counselor, nurse, medical geneticist) is to provide information in understandable terms and outline the range of options available.

98.2 Principles of Management and Treatment of Genetic Disorders

Brendan Lee and Nicola Brunetti-Pierri

TREATMENT OF GENETIC DISEASES

Genetic conditions are often chronic disorders. Some are amenable to curative therapies, although there has been a rapid increase in the number of treatable disorders. Based on ongoing preclinical and clinical investigations, new therapies for a growing number of diseases are expected to become available in the near future. Surgical management is available for many conditions that are associated with congenital anomalies or predisposition to tumors. All patients and families should be provided information about the disorder, genetic counseling, anticipatory guidance, and appropriate medical surveillance.

Resources for patients include the National Organization of Rare Disorders (www.rarediseases.org), the Genetic Alliance (www.geneticalliance.org), the National Library of Medicine (www.nlm.nih.gov/medlineplus/geneticdisorders.html), and a large number of disease-specific websites. A current listing of federally and privately funded clinical trials, including many for genetic diseases, is available at www.ClinicalTrials.gov.

Specific medical therapies for genetic disorders can be classified into **physiologic** and **replacement** therapies. Another approach to *correct protein misfolding* induced by missense pathogenic variants is through use of small molecules that specifically bind to mutant proteins, stabilizing their conformation, thereby preventing early degradation, and allowing proper cellular trafficking and localization. This strategy has found successful applications for therapy of cystic fibrosis caused by specific *CFTR* pathogenic variants, including the F508del (see Chapter 454).

PHYSIOLOGIC THERAPIES

Physiologic therapies attempt to ameliorate the phenotype of a genetic disorder by modifying the physiology of the affected individual. The underlying defect itself is not altered by treatment. Physiologic therapies are used in the treatment of **inborn errors of metabolism** (see Chapter 104). These include dietary manipulations, such as reducing phenylalanine intake by persons with phenylketonuria, coenzyme supplementation for some patients with methylmalonic acidemia and mitochondrial diseases, stimulation of alternative pathways to excrete ammonia for those with urea cycle disorders, phototherapy to increase excretion of neurotoxic unconjugated bilirubin in Crigler-Najjar syndrome, bisphosphonate treatment for those with osteogenesis imperfecta to reduce bone fractures, and avoiding cigarette smoking by persons with α_1-antitrypsin deficiency or specific foods and drugs by persons with glucose-6-phosphate dehydrogenase deficiency or acute intermittent porphyria. Physiologic treatments can be highly effective, but they usually need to be maintained for a lifetime because they do not affect the underlying genetic disorder. Many of these treatments are most effective early in life

before irreversible damage has occurred. This is the rationale for comprehensive newborn screening for inborn errors of metabolism.

Many physiologic therapies use small-molecule pharmaceuticals (e.g., to remove ammonia in those with urea cycle disorders). **Pharmacologic treatments** directly target a defective cellular pathway that is altered by an abnormal or a missing gene product. One approach is the inhibition of an enzyme reaction that is upstream of the deficient enzyme to prevent accumulation of the toxic metabolites, such as the nitisinone (NTBC) for therapy of tyrosinemia type I. A similar approach focuses on partially reducing the synthesis of the substrate of the abnormal enzyme or its precursors in lysosomal storage disorders (see Chapter 106.4). Other examples include targeting the FGFR3 signaling pathway by the C-type natriuretic peptide in achondroplasia, FGF23 by the monoclonal antibody burosumab in X-linked hypophosphatemia, or the angiopoietin-like protein 3 (ANGPTL3) by the monoclonal antibody evinacumab in homozygous familial hypercholesterolemia.

REPLACEMENT THERAPIES

Replacement therapies include replacement of a missing metabolite, an enzyme, an organ, or even a specific gene.

Enzyme Replacement

Enzyme replacement therapy is a component of the treatment of cystic fibrosis to manage intestinal malabsorption. Pancreatic enzymes are easily administered orally, because they must be delivered to the gastrointestinal tract. Recombinant alkaline phosphatase coupled to a bone-targeting motif is available for intravenous therapy of hypophosphatasia, a skeletal disorder caused by alkaline-phosphatase deficiency.

Enzyme replacement strategies are effective for several lysosomal storage disorders. Enzymes are targeted for the lysosome by modification with mannose-6-phosphate, which binds to a specific receptor. This receptor is also present on the cell surface, so lysosomal enzymes with exposed mannose-6-phosphate residues can be infused into the blood and are taken into cells and delivered to lysosomes. Enzyme replacement therapies are available for Gaucher disease and Fabry disease, most of the mucopolysaccharidoses (MPS I, II, IVA, VI, VII), acid lipase deficiency, α-mannosidosis, neuronal ceroid lipofuscinosis late infantile (CLN2), and Pompe disease, and are being tested for MPS IIIA and IIIB, metachromatic leukodystrophy, and Niemann-Pick disease type B. Other examples include enzyme replacement therapy with pegylated recombinant phenylalanine ammonia lyase for phenylketonuria that is effective at reducing blood phenylalanine concentrations in most patients, such that most of them can come off a phenylalanine-restricted diet.

One complication of enzyme replacement therapy is antibody response to the infused recombinant enzyme. The magnitude of this response is not always predictable and varies depending on the enzyme preparation and the disease. In most cases, the patient's antibody response does not affect the treatment's efficacy (e.g., Gaucher disease), but in other situations it may be a significant hurdle (e.g., Pompe disease and phenylketonuria).

Transplantation

Cell transplantation and organ transplantation are potentially effective approaches to replacement of a defective gene. Aside from transplantation to replace damaged tissues, transplantation of stem cells, liver, or bone marrow is also used for several diseases, mainly inborn errors of metabolism, and hematologic or immunologic disorders. A successful transplant can be essentially curative, although there may be significant risks and side effects (see Chapters 177-181). Cell and tissue transplantation is effective in many clinical scenarios, but there is always short-term morbidity, often associated with either surgical (liver) or preparative (bone marrow) regimens, and long-term morbidity related to chronic immunosuppression and graft failure. Bone marrow transplantation is the best example of stem cell therapy, but much effort also is focused on identifying, characterizing, expanding, and using other tissue stem cells for regenerative therapies. In contrast to transplantation from a healthy donor, the infused cells are the patient's own cells in ex vivo gene therapy of hematopoietic stem cells. Therefore, although it requires preparative myeloablation akin to regular bone marrow transplantation from healthy donors, engraftment of genetically modified hematopoietic stem cells is devoid of risks of rejection or graft-versus-host disease. Increasingly, this approach is combined with gene therapy after genetic correction of autologous stem cells.

Gene Therapy

Another approach focuses on replacing or correcting a defective gene **(gene therapy)**. In theory, if one can target the specific tissue that has a deficiency in the gene or gene product, this can offer a less invasive means of achieving a cure for a genetic disorder compared to transplantations. Ultimately, gene therapy depends on the unique interaction of the disease pathophysiology, which is specific to the patient, and the gene delivery vehicle.

Gene-transfer vehicles include viral and nonviral vectors administered through ex vivo or in vivo approaches. In ex vivo approaches the patient's cells are removed and after gene correction or replacement are infused into the patient. An example of this is the US Food and Drug Administration (FDA)-approved chimeric antigen receptor (CAR) T-cell therapy for lymphomas and leukemias. In the in vivo approaches the gene therapy vector is directly injected into the body by either systemic (e.g., intravenous) or localized (e.g., intracerebral, intraocular) injections. Most human clinical trials have used viral vectors because of their efficiency of gene delivery to tissues. In some diseases, such as X-linked and adenosine deaminase–deficient severe combined immunodeficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome, clinical gene therapy is a viable and effective option. Ex vivo gene transfer of hematopoietic stem cells can be considered at least as effective to allogenic hematopoietic stem cell transplantation in presymptomatic patients with X-linked adrenoleukodystrophy, metachromatic leukodystrophy and Hurler syndrome.

In vivo gene therapy is also promising for Leber congenital amaurosis by intraocular delivery, and hemophilias and several inborn errors of liver metabolism by systemic intravenous injection. In vivo gene therapy is FDA approved for treatment of a specific RPE65-deficient form of retinitis pigmentosa using adeno-associated virus (AAV)-mediated expression of the normal RPE65 gene via subretinal injections. In vivo AAV-mediated gene therapy is also an approved treatment that has significantly changed the early course of the disease and improved motor function in children with spinal muscular atrophy (SMA) (see Chapter 652.2). Although patients with SMA typically present with muscle atrophy, respiratory failure, and die before 2 years of age, treated patients have remained healthy and attained motor milestones that are typically not achieved in any of the untreated patients. Similar efficacy has also been achieved by intrathecal delivery of antisense oligonucleotides (ASOs) correcting *SMN2* splicing. Brain-directed gene therapy is available for aromatic L-amino acid decarboxylase (AADC) deficiency by intracerebral injections of an AAV-based vector. Systemic intravenous AAV-based gene therapy vectors have been approved for both hemophilia A and B.

Gene editing with *direct correction* of a disease-causing pathogenic variant is another possible approach to genetic therapy. Various nucleases with specific DNA-recognition sequences are available for genome editing; they include zinc finger nucleases (ZFNs), transcription activator–like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated nine (Cas9). They all permit permanent gene modification of genes in cells. This is achieved by DNA site-specific double-strand breaks (DSBs) induced by the endonuclease and a template encompassing the wild-type sequence to be used as a substrate for repair by **homology-directed repair (HDR)**. Following site-specific DSB, DNA repair is mediated by either nonhomologous end joining (NHEJ) or HDR that repairs DNA in the presence of a donor sequence (Fig. 98.7A and B). NHEJ repairs the DSB by joining the two ends of the DSB, often introducing small insertions or deletions (indels) at the DSB site that generally inactivate gene function (see Fig. 98.7A). Compared with NHEJ, HDR is less efficient and requires a donor DNA template (see Fig. 98.7C). The wild-type copy of the mutated gene can be integrated into the endogenous locus or into "safe harbors" that allow high expression levels of the therapeutic gene (see Fig. 98.7A). Based on

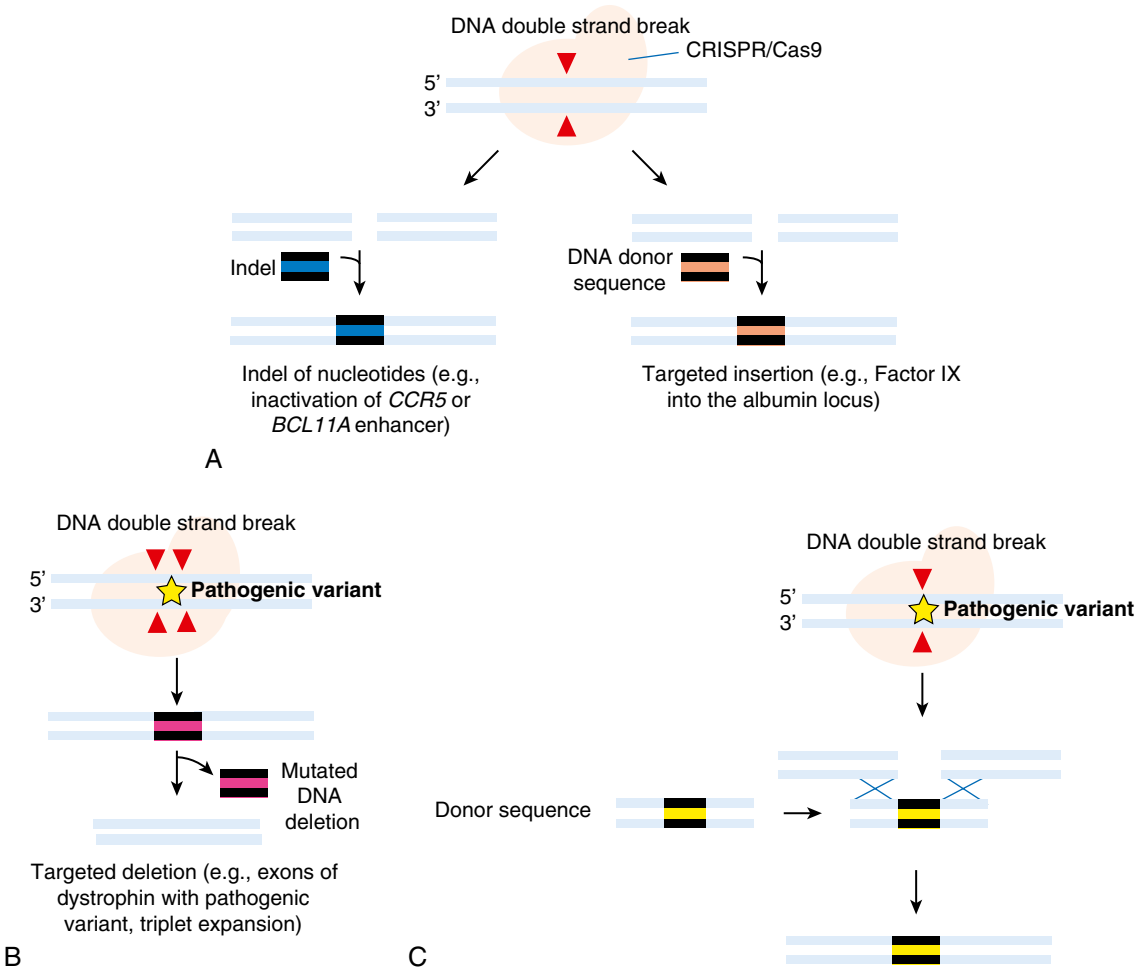

Fig. 98.7 A, Double-strand breaks can be repaired by nonhomologous end-joining (NHEJ) repair mechanisms, giving rise to small insertions and deletions (Indel) that can disrupt gene expression *(blue)*. B, Two double-strand breaks can also be corrected by NHEJ and can eliminate the DNA carrying the pathogenic variant *(pink)* located between the two breaks. C, Double-strand breaks can be repaired by homology-directed repair mechanisms in the presence of a donor template allowing the incorporation of a donor sequence *(yellow)* that correct the mutated gene. CRISPR/Cas9, Clustered regularly interspaced short palindromic repeat/CRISPR-associated nine (Cas9).

these features, genome editing has the potential to overcome several limitations of gene replacement therapy. First, genotoxicity due to ectopic activation of nearby protooncogenes or knockout of tumor suppressor genes does not occur with on-target editing. Second, genome editing allows physiologic regulation of the expression of the corrected gene in contrast to gene replacement therapy. Third, gene editing is maintained in proliferating cells, and it overcomes the dilution effect due to cell division that is observed with gene replacement therapy by nonintegrating vectors such as AAV vectors.

Genome editing tools have corrected the gene defect in several preclinical murine models and are in clinical trials. ZFNs have been used ex vivo to disrupt CCR5 expression in human T cells to induce resistance to HIV infection. ZFNs and CRISPR/Cas9 are being used to boost fetal hemoglobin in β-thalassemia and sickle cell disease by disrupting the enhancer of the *BCL11A* gene, which suppresses fetal hemoglobin production. Moreover, ZFN-mediated targeted introduction of therapeutic genes downstream of the highly active albumin promoter in hepatocytes is currently under clinical investigation for several diseases.

RNA-Targeted Therapy

Antisense oligonucleotides (ASOs) are short synthetic nucleic acids that hybridize with cellular RNA using classic base pairing to modulate gene expression. To ensure specificity, their sequences are complementary to their target sequences (Fig. 98.8). Through binding to pre-mRNA or mRNA, ASOs can posttranscriptionally regulate protein synthesis by mechanisms including modification of pre-mRNA processing and splicing, competitive inhibition, steric blockade of translational machinery, and degradation of the target RNA. Clinical ASOs have been developed for treatment of Duchenne muscular dystrophy and SMA, respectively (Table 98.5). In SMA, *SMN1* and *SMN2* genes are identical (99% homology), except for an 11-nucleotide sequence in exon seven that alters splicing (see Chapter 652.2). Splicing of the *SMN2* pre-mRNA leads to the exclusion of exon seven, generating a truncated, unstable protein that is rapidly degraded. Therefore *SMN2* cannot compensate for *SMN1* loss in SMA. The ASO designed to correct *SMN2* splicing by promoting the inclusion of exon seven allows SMN2 to compensate for the loss of expression caused by the *SMN1* pathogenic variant. ASOs are also effective for treatment of homozygous familial hypercholesterolemia and have been also designed to inhibit HTT mRNA to reduce concentrations of mutant huntingtin in Huntington disease.

Conjugation of siRNA with GalNAc to target the asialoglycoprotein receptor is an efficient strategy to facilitate cell uptake and to increase siRNA liver accumulation (see Fig. 98.8). A GalNAc-siRNA targeting the mRNA for aminolevulinate synthase 1 (ALAS1), the first enzyme in the heme synthesis pathway, has been developed for treatment of acute hepatic porphyria, and a similar strategy targeting glycolate oxidase is effective at reducing oxalate levels for treatment of primary hyperoxaluria type 1.

Lipid nanoparticles (LNPs) are spherical structures with a composition very similar to cell membranes and are suitable carriers for

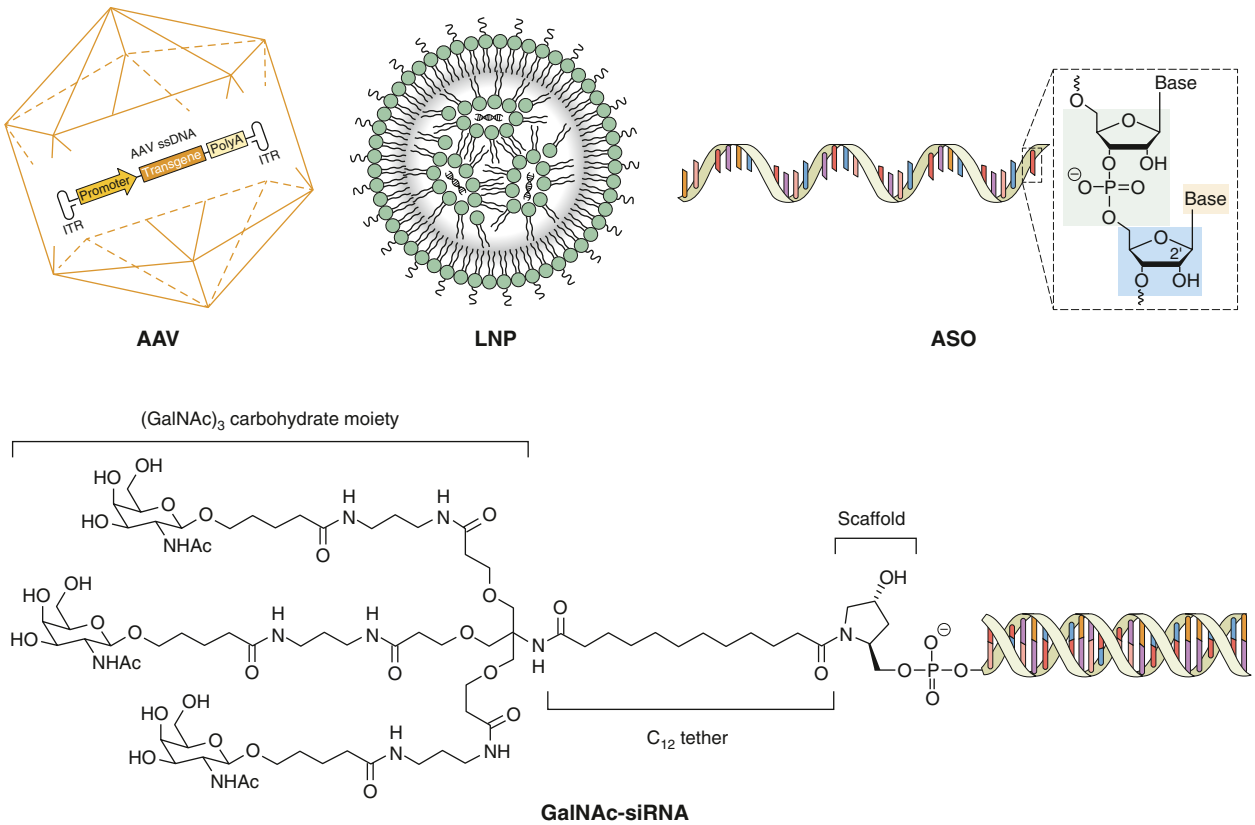

Fig. 98.8 Approved delivery technologies for in vivo gene therapy. Four platform technologies have been clinically approved for gene-based therapies of genetic diseases: adeno-associated virus (AAV) vector containing a 4.7-kb single-stranded DNA with inverted terminal repeats (ITRs), antisense oligonucleotides (ASO) therapeutics, lipid nanoparticle (LNP) containing siRNA or mRNA including key lipid components, and N-acetyl-galactosamine-short-interfering RNA (GALNAc-siRNA) therapeutics made of a trivalent ligand with terminal GalNAc moieties covalently linked to siRNA at the 3′-end of the sense strand.

Table 98.5 Approved In Vivo Gene-Based (DNA and RNA) Therapies for Genetic Disorders

PRODUCT	GENE TARGET	DISEASE	ROUTE OF ADMINISTRATION
ASO			
Eteplirsen	Dystrophin (exon 51)	Duchenne muscular dystrophy	Intrathecal
Golodirsen	Dystrophin (exon 53)	Duchenne muscular dystrophy	Subcutaneous
Casimersen	Dystrophin (exon 45)	Duchenne muscular dystrophy	Subcutaneous
Inotersen	Transthyretin (TTR)	TTR-mediated amyloidosis	Subcutaneous
Nusinersen	Survival of motor neuron two (SMN2)	Spinal muscular atrophy	Intrathecal
Mipomersen	Apolipoprotein B-100	Hypercholesterolemia	Subcutaneous
Volanesorsen	Apolipoprotein CIII	Familial chylomicronemia	Subcutaneous
GALNAc-sIRNA CONJUGATES			
Givosiran	ALAS1	Acute hepatic porphyrias	Subcutaneous
Inclisiran	PCSK9	Hypercholesterolemia	Subcutaneous
Lumasiran	Glycolate oxidase	Primary hyperoxaluria type 1	Subcutaneous
LNP-RNA			
Patisiran	TTR siRNA	TTR-mediated amyloidosis	Intravenous
AAV VECTORS			
Voretigene neparvovec-rzyl	RPE65 (AAV2)	Leber congenital amaurosis	Subretinal
Onasemnogene abeparvovec	SMN1 (AAV9)	Spinal muscular atrophy	Intravenous
Eladocagene exuparvovec	DDC (AAV2)	AADC deficiency	Bilateral intraputaminal infusions
Valoctocogene roxaparvovec	Factor VIII (AAV5)	Hemophilia A	Intravenous
Etranacogene dezaparvovec	Factor IX (AAV5)	Hemophilia B	Intravenous

AAV, Adeno-associated virus; AADC, aromatic L-amino acid decarboxylase; ASO, antisense oligonucleotides; LNP, lipid nanoparticle.

nucleic acid delivery, such as siRNA and mRNAs (see Fig. 98.8). A liver targeting LNP carrying an siRNA targeting transthyretin has been effective for treatment of hereditary transthyretin amyloidosis that has been recently approved. In various preclinical models, LNPs have been shown to deliver mRNA molecules to hepatocytes with high efficiency. LNPs are being used for the delivery of gene editing molecules such as ZFNs and Cas9 mRNA together with a single guide (sg)RNA. In addition, LNPs have been used for delivery of genome editing tools such as ZFNs and CRISPR/Cas9 together with a viral vector carrying a promoterless DNA sequence capable of homologous recombination that can result in high levels of the integrated sequence and short-term expression of the endonucleases.

Correction of Genetic Diseases in the Human Germline

Prevention of genetic diseases has been accomplished by **preimplantation genetic diagnosis (PGD)**. This procedure requires in vitro fertilization and single–embryo cell genetic testing of the known families' pathogenic variant and is performed with polymerase chain reaction (PCR) amplification of the affected gene. To avoid disease recurrence, only the unaffected embryos are implanted. With the advent of efficient genome editing by CRISPR/Cas9, editing human embryos is technically possible. The announcement of the birth of "CRISPR babies" has led to calls for a moratorium on human germline genome editing, and currently, germline and/or embryonic gene editing studies in humans have not been approved. Given the limited understanding of the consequences of CRISPR/Cas9-mediated DSBs on the germline human genome, it is unlikely that these approaches will become available any time soon.

In contrast, **mitochondrial replacement therapies** to avoid mitochondrial DNA pathogenic variants are available. In one technique, the pathogenic variant carrier mother's nuclear DNA is removed from the unfertilized oocyte and transferred to an unaffected mitochondrial donor oocyte (minus that cell's nuclear DNA). In another approach, the pronucleus from the pathogenic variant-carrier mother's fertilized oocyte is transferred to the unaffected mitochondrial donor's fertilized oocyte (minus the pronucleus).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 99.1 Incidence of Chromosomal Abnormalities in Newborn Surveys

TYPE OF ABNORMALITY	NUMBER	APPROXIMATE INCIDENCE
SEX CHROMOSOME ANEUPLOIDY		
Males *(43,612 newborns)*		
47,XXY	45	1/1,000*
47,XYY	45	1/1,000
Other X or Y aneuploidy	32	1/1,350
Total	**122**	**1/360 male births**
Females *(24,547 newborns)*		
45,X	6	1/4,000
47,XXX	27	1/900
Other X aneuploidy	9	1/2,700
Total	**42**	**1/580 female births**
AUTOSOMAL ANEUPLOIDY (68,159 NEWBORNS)		
Trisomy 21	82	1/830
Trisomy 18	9	1/7,500
Trisomy 13	3	1/22,700
Other aneuploidy	2	1/34,000
Total	**96**	**1/700 live births**
STRUCTURAL ABNORMALITIES (68,159 NEWBORNS)		
Balanced Rearrangements		
Robertsonian	62	1/1,100
Other	77	1/885
Unbalanced Rearrangements		
Robertsonian	5	1/13,600
Other	38	1/1,800
Total	**182**	**1/375 live births**
All chromosome abnormalities	**442**	**1/154 live births**

*Recent studies show the prevalence is currently 1:580 (Morris JK, Alberman E, Scott C, Jacobs P. Is the prevalence of Klinefelter syndrome increasing? *Eur J Hum Genet.* 2008;16(2):163–170.)

Data from Hsu LYF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Milunsky A, ed, *Genetic Disorders and the Fetus*, 4th ed. Baltimore: Johns Hopkins University Press; 1998: pp. 179–248.

Chapter 99

Chromosome Disorders

Carlos A. Bacino and Brendan Lee

99.1 Methods of Chromosome Analysis

Carlos A. Bacino and Brendan Lee

Clinical cytogenetics is the study of chromosomes, including their structure, function, inheritance, and abnormalities. Chromosome abnormalities are very common and occur in approximately 1–2% of live births, 5% of stillbirths, and 50% of early fetal losses in the first trimester of pregnancy (Table 99.1). Chromosome abnormalities are more common among individuals with intellectual disability and play a significant role in the development of some neoplasias.

Chromosome analyses are indicated in persons presenting with multiple congenital anomalies, dysmorphic features, and/or intellectual disability. The specific indications for studies include prenatal testing in conceptuses of women with advanced maternal age (>35 years), multiple abnormalities on fetal ultrasound, multiple congenital anomalies, unexplained growth restriction in the fetus, postnatal problems in growth and development, ambiguous genitalia, unexplained intellectual disability with or without associated anatomic abnormalities, primary amenorrhea or infertility, recurrent miscarriages (≥3) or prior history of stillbirths and neonatal deaths, a first-degree relative with a known or suspected structural chromosome abnormality, clinical findings consistent with a known anomaly, some malignancies, and chromosome breakage syndromes (e.g., Bloom syndrome, Fanconi anemia).

Cytogenetic studies are usually performed on peripheral blood lymphocytes, although cultured fibroblasts obtained from a skin biopsy may also be used. Prenatal (fetal) chromosome studies are performed with cells obtained from the amniotic fluid (amniocytes), chorionic villus tissue, and fetal blood or, in the case of preimplantation diagnosis, by analysis of a *blastomere* (cleavage stage) biopsy, polar body biopsy, or blastocyst biopsy. Cytogenetic studies of bone marrow have an important role in tumor surveillance, particularly among patients with leukemia. These are useful to determine induction of remission and success of therapy, or in some cases the occurrence of relapses.

Chromosome anomalies include abnormalities of number and structure and are the result of errors during cell division. There are two types of cell division: mitosis, which occurs in most somatic cells, and meiosis, which is limited to the germ cells. In **mitosis,** two genetically identical daughter cells are produced from a single parent cell. DNA replication (duplication of DNA material) has already occurred during **interphase** in the S phase of the cell cycle (DNA synthesis). Therefore, at the beginning of mitosis, the chromosomes consist of two double DNA strands joined together at the centromere, known as *sister chromatids*. Mitosis can be divided into four stages: prophase, metaphase, anaphase, and telophase. **Prophase** is characterized by condensation of the DNA. Also during prophase, the nuclear membrane and the nucleolus disappear and the mitotic spindle forms. In **metaphase** the chromosomes are maximally compacted and are clearly visible as distinct structures. The chromosomes align at the center of the cell, and spindle fibers connect to the centromere of each chromosome and extend to centrioles at the two poles of the mitotic figure. In **anaphase** the chromosomes divide along their longitudinal axes to form two separate daughter chromatids, which then migrate to opposite poles of the cell. **Telophase** is characterized by formation of two new nuclear membranes and nucleoli, duplication of the centrioles, and cytoplasmic cleavage to form the two daughter cells.

Meiosis begins in the female oocyte during fetal life and is completed years to decades later. In males it begins in a spermatogonial cell sometime between adolescence and adult life and is completed in a few days. Meiosis is preceded by DNA replication so that at the outset, each of the 46 chromosomes consists of two chromatids. In meiosis, a **diploid cell** (2n = 46 chromosomes) divides to form four **haploid cells** (n = 23 chromosomes). Meiosis consists of two major rounds of cell division. In **meiosis I**, each of the homologous chromosomes pair precisely so that **genetic recombination**, involving exchange between two DNA strands **(crossing over)**, can occur. This results in reshuffling of the genetic information for the recombined chromosomes and allows further genetic diversity. Each daughter cell then receives one of each of the 23 homologous chromosomes. In oogenesis, one of the daughter cells receives most of the cytoplasm and becomes the egg, whereas the other smaller cell becomes the first polar body. **Meiosis II** is similar to a mitotic division but without a preceding round of DNA replication. Each of the 23 chromosomes divides longitudinally, and the homologous chromatids migrate to opposite poles of the cell. This produces four spermatogonia in males, or an egg cell and a second polar body in females, each with a haploid (n = 23) set of chromosomes. Consequently, meiosis fulfills two crucial roles: It enables genetic recombination, and it reduces the chromosome number from diploid (46) to haploid (23) so that on fertilization a diploid number is restored.

Two common errors of cell division may occur during meiosis or mitosis, and either can result in an abnormal number of chromosomes. The first error is **nondisjunction**, in which two chromosomes fail to separate during meiosis and thus migrate together into one of the new cells, producing one cell with two copies of the chromosome and another with no copy. The second error is **anaphase lag**, in which a chromatid or chromosome is lost during mitosis because it fails to move quickly enough during anaphase to become incorporated into one of the new daughter cells (Fig. 99.1).

For chromosome analysis, cells are cultured (for varying periods depending on cell type), with or without stimulation, and then artificially arrested in mitosis during metaphase (or prometaphase), later subjected to a hypotonic solution to allow disruption of the nuclear cell membrane and proper dispersion of the chromosomes for analysis, fixed, banded, and finally stained. The most commonly used banding and staining method is the **GTG banding** (G bands by trypsin using Giemsa), also known as **G banding**, which produces a unique combination of dark (G-positive) and light (G-negative) bands that permits recognition of all individual 23 chromosome pairs for analysis.

Metaphase chromosome spreads are first evaluated microscopically, and then their images are photographed or captured by a video camera and stored on a computer for later analysis. Humans have 46 chromosomes or 23 pairs, which are classified as *autosomes* for chromosomes

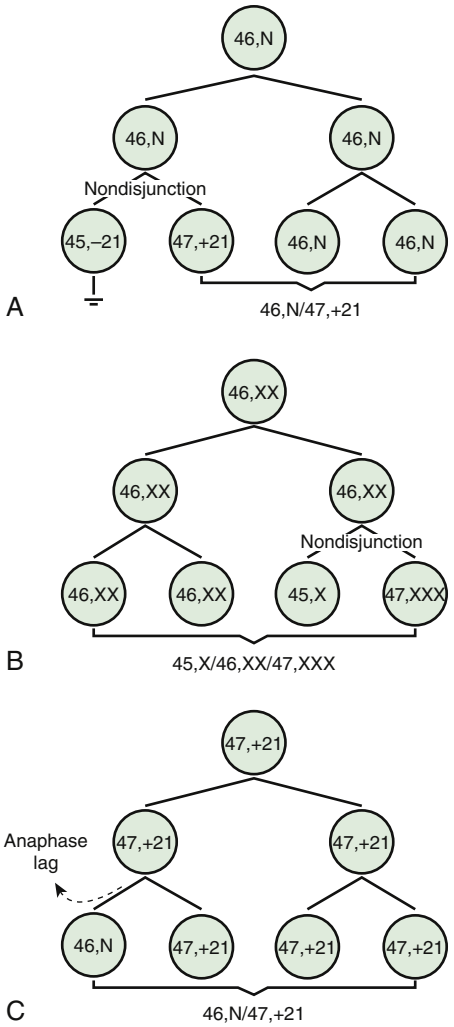

Fig. 99.1 Generation of mosaicism. A, Postzygotic nondisjunction in an initially normal conceptus. In this example, one cell line (monosomic 21) is subsequently lost, with the final karyotype 46,N/47,+21. B, Postzygotic nondisjunction in an initially 46,XX conceptus, resulting in 45,X/46,XX/47,XXX mosaicism. C, Postzygotic anaphase lag in an initially 47,+21 conceptus. *(From Gardner RJM, Sutherland GR. Chromosome Abnormalities and Genetic Counseling, 3rd ed. New York: Oxford University Press; 2003: Fig. 43.1, p. 33.)*

1-22, and the *sex chromosomes*, often referred as *sex complement*: XX for females and XY for males. The homologous chromosomes from a metaphase spread can then be paired and arranged systematically to assemble a karyotype according to well-defined standard conventions such as those established by International System for Human Cytogenetic Nomenclature (ISCN), with chromosome 1 being the largest and 22 the smallest. According to nomenclature, the description of the karyotype includes the total number of chromosomes followed by the sex chromosome constitution. A normal karyotype is 46,XX for females and 46,XY for males (Fig. 99.2). Abnormalities are noted after the sex chromosome complement.

Although the internationally accepted system for human chromosome classification relies largely on the length and banding pattern of each chromosome, the position of the centromere relative to the ends of the chromosome also is a useful distinguishing feature (Fig. 99.3). The centromere divides the chromosome in two, with the short arm designated the **p arm** and the long arm designated the **q arm**. A plus or minus sign before the number of a chromosome indicates that there is an extra or missing chromosome, respectively. Table 99.2 lists some of the abbreviations used for the descriptions of chromosomes and their abnormalities. A metaphase chromosome spread usually

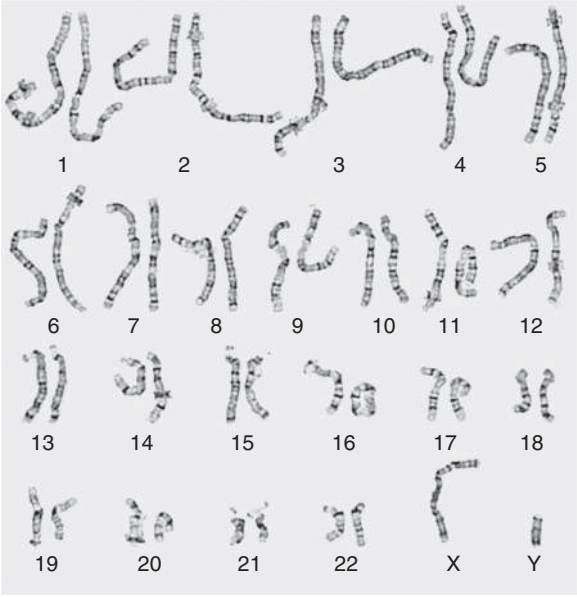

Fig. 99.2 Karyotype of a normal male at the 550-600 band level. The longer the chromosomes are captured at metaphase or sometimes prometaphase, the more bands can be visualized.

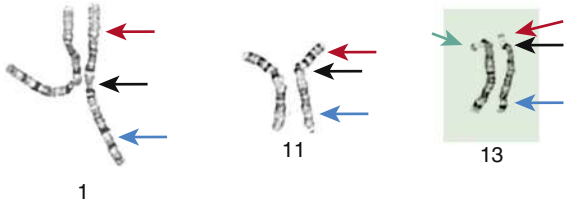

Fig. 99.3 Example of different chromosome types according to the position of the centromere. On the *left* is a chromosome one pair with the centromere equidistant from the short and long arm (also known as *metacentric*). In the *center* is a chromosome 11 pair that is submetacentric. On the *right* is a chromosome 13 pair that is an example of an acrocentric chromosome. Acrocentric chromosomes contain a very small short arm, stalks, and satellite DNA. The *black arrow* indicates the position of the centromere. The *blue arrow* shows the long arm of a chromosome. The *red arrow* shows the short arm of a chromosome. The *green arrow* highlights the satellite region, which is made of DNA repeats. The *light area* between the short arm and the satellite is known as the *stalk*.

shows 450-550 bands. Prophase and prometaphase chromosomes are longer, are less condensed, and often show 550-850 bands. High-resolution analysis may detect small chromosome abnormalities, although this has been mostly replaced by chromosome **microarray analysis (CMA)**, also called array comparative genomic hybridization (aCGH).

Molecular techniques (e.g., fluorescence in situ hybridization [FISH], CMA) identify subtle abnormalities that are often below the resolution of standard cytogenetic studies. **FISH** is used to identify the presence, absence, or rearrangement of *specific* DNA segments and is performed with gene- or region-specific DNA probes. Several FISH probes are used in the clinical setting: unique sequence or single-copy probes, repetitive-sequence probes (alpha satellites in the pericentromeric regions), and multiple-copy probes (chromosome specific or painting) (Fig. 99.4A,B). FISH involves using a unique, known DNA sequence or probe labeled with a fluorescent dye that is complementary to the studied region of disease interest. The labeled probe is exposed to the DNA on a microscope slide, typically metaphase or interphase chromosomal DNA. When the probe pairs with its complementary DNA sequence, it can then be visualized by fluorescence microscopy (Fig. 99.5). In metaphase chromosome spreads, the exact chromosomal location of each probe copy can be documented, and often the *number of copies* (deletions, duplications) of the DNA sequence as well. When the interrogated segments (as in genomic duplications) are close together, interphase cells can accurately determine the presence of two or more copies or signals, because in chromosome-condensed metaphase cells some duplications might falsely appear as a single signal.

Chromosome rearrangements <5 million bp (5 Mbp) cannot be detected by conventional cytogenetic techniques. FISH has facilitated the clinical characterization of several **microdeletion syndromes** (50-200 kb of DNA). Some FISH probes hybridize to repetitive sequences located in the pericentromeric regions. Pericentromeric probes are still used for rapid identification of certain trisomies in interphase cells of blood smears, or even in the rapid analysis of prenatal samples from cells obtained through amniocentesis. Such probes are available for chromosomes 13, 18, and 21 and for the sex pair X and Y (see Fig. 99.4C and D). FISH is *no longer* the first line of testing, and its role has also mostly changed to the confirmation of chromosome microarray findings. FISH is reserved for (1) confirmation studies of abnormalities detected by CMA, (2) rapid prenatal screening on interphase amniotic fluid cells, and (3) interphase blood smear for sex assignment of newborns who present with ambiguous genitalia.

Array comparative genomic hybridization (aCGH) is a type of **chromosomal microarray (CMA)** that uses a molecular-based technique that differentially labels the patient's DNA with a fluorescent dye (green fluorophore) and a normal reference DNA with a red fluorophore (Figs. 99.6 and 99.7). Oligonucleotides (short DNA segments) encompassing the entire genome are spotted onto a slide or **microarray** grid. Equal amounts of the two-labeled DNA samples are mixed, and the green:red fluorescence ratio is measured along each tested area. Regions of amplification of the patient's DNA display an excess of green fluorescence, and regions of loss show excess red fluorescence. If the patient's and the control DNA are equally represented, the green:red ratio is 1:1, and the tested regions are represented as yellow (see Chapter 96 and Fig. 96.5).

Another frequently used chromosome microarray type in the clinical setting is the **single nucleotide polymorphism (SNP) array**. SNPs are polymorphic variations between two nucleotides and, when analyzed in massive parallel fashion, they can provide valuable clinical information. Several million SNPs normally occur in the human genome. SNP arrays can help with the detection of **uniparental disomies** (i.e., genetic information derived from only one parent), as well as consanguinity in the family. Many arrays used in clinical practice combine the use of oligonucleotides for the detection of copy number variations (CNVs) in conjunction with SNPs.

The detection of abnormalities by CMA is possible at the single-exon resolution level, depending on the configuration of the array used. The many advantages of CMA include its ability to test for duplications or deletions in critical disease-causing regions of the genome at once, including single-gene and contiguous gene deletion syndromes. In addition, CMA does not require cell cultures to generate sufficient DNA, which may be important in the context of prenatal testing because of timing. However, CMA cannot detect balanced translocations or inversions and may not detect low levels of chromosomal mosaicism. **Targeted CMAs** can detect clinically known cryptic chromosomal aberrations associated with known disease phenotypes. CNV detection can also be diagnosed by next-generation sequencing in the context of whole *genome* sequencing.

There are large numbers of deletion and duplication CNVs in the human genome. Thus many detected genetic abnormalities, unless associated with well-known clinical phenotypes, may require *parental investigations* because a detected CNV that is inherited could be benign or an incidental polymorphic variant often described as variants of uncertain significance (VUS). A **de novo** abnormality (i.e., one found only in the child and not the parents) is often significant if it is associated with an abnormal phenotype found only in the child and if it involves genes with important functions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 99.2 Some Abbreviations Used for Description of Chromosomes and Their Abnormalities

ABBREVIATION	MEANING	EXAMPLE	CONDITION
XX	Female	46,XX	Normal female karyotype
XY	Male	46,XY	Normal male karyotype
[##]	Number [#] of cells	46,XY[12]/47,XXY[10]	Number of cells in each clone, typically inside brackets Mosaicism in Klinefelter syndrome with 12 normal cells and 10 cells with an extra X chromosome
cen	Centromere		
del	Deletion	46,XY,del(5p)	Male with deletion of chromosome 5 short arm
der	Derivative	46,XX,der(2),t(2p12;7q13)	Female with a structurally rearranged chromosome 2 that resulted from a translocation between chromosomes 2 (short arm) and 7 (long arm)
dup	Duplication	46,XY,dup(15)(q11-q13)	Male with interstitial duplication in the long arm of chromosome 15 in the Prader-Willi/Angelman syndrome region
ins	Insertion	46,XY,ins(3)(p13q21q26)	Male with an insertion within chromosome 3 A piece between q21 and q26 has reinserted on p13
inv	Inversion	46,XY,inv(2)(p21q31)	Male with pericentric inversion of chromosome 2 with breakpoints at bands p21 and q31
ish	Metaphase FISH	46,XX.ish del(7)(q11.23q11.23)	Female with deletion in the Williams syndrome region detected by in situ hybridization
nuc ish	Interphase FISH	nuc ish(DXZ1 × 3)	Interphase in situ hybridization showing three signals for the X chromosome centromeric region
mar	Marker	47,XY,+mar	Male with extra, unidentified chromosome material
mos	Mosaic	mos 45,X[14]/46,XX[16]	Turner syndrome mosaicism (analysis of 30 cells showed that 14 cells were 45,X and 16 cells were 46,XX)
p	Short arm	46,XY,del(5)(p12)	Male with a deletion on the short arm of chromosome 5, band p12 (short nomenclature)
q	Long arm	46,XY,del(5)(q14)	Male with a deletion on the long arm of chromosome 5, band 14
r	Ring chromosome	46,X,r(X)(p21q27)	Female with one normal X chromosome and a ring X chromosome
t	Translocation	t(2;8)(q33;q24.1)	Interchange of material between chromosomes 2 and 8 with breakpoints at bands 2q33 and 8q24.1
ter	Terminal	46,XY,del(5)(p12-pter)	Male with a deletion of chromosome 5 between p12 and the end of the short arm (long nomenclature)
/	Slash	45,X/46,XY	Separate lines or clones Mosaicism for monosomy X and a male cell line
+	Gain of	47,XX,+21	Female with trisomy 21
−	Loss of	45,XY,−21	Male with monosomy 21

FISH, Fluorescence in situ hybridization.

99.2 Abnormalities of Chromosome Number

Carlos A. Bacino and Brendan Lee

ANEUPLOIDY AND POLYPLOIDY

Typical human cells contain 46 chromosomes, which is a multiple of 23 chromosomes. Haploid cells contain 23 chromosomes (n=23, typically in the ovum or sperm). If a cell's chromosomes are an exact multiple of 23 (46, 69, 92 in humans), those cells are referred to as **euploid**. **Polyploid** cells are euploid cells with more than the normal **diploid** number of 46 (2n) chromosomes, such as 3n, 4n. Polyploid conceptions are usually not viable, but the presence of mosaicism with a karyotypically normal cell line can allow survival. **Mosaicism** is an abnormality defined as the presence of two or more different cell lines in a single individual. **Polyploidy** is a common abnormality seen in first-trimester pregnancy losses.

Triploid cells are those with three haploid sets of chromosomes (3n) and are only viable in a mosaic form. Nonmosaic triploid infants can be liveborn but typically die shortly after birth. **Triploidy** is often the result of fertilization of an egg by two sperm (dispermy). Failure of one of the meiotic divisions, resulting in a diploid egg or sperm, can also result in triploidy. The phenotype of a triploid conception depends on the origin of the extra chromosome set. If the extra set is of **paternal** origin, it results in a partial *hydatidiform mole* (excessive placental growth) with poor embryonic development, but triploid conceptions that have an extra set of **maternal** chromosomes result in severe embryonic restriction with a small, fibrotic placenta (insufficient placental development) that is typically spontaneously aborted.

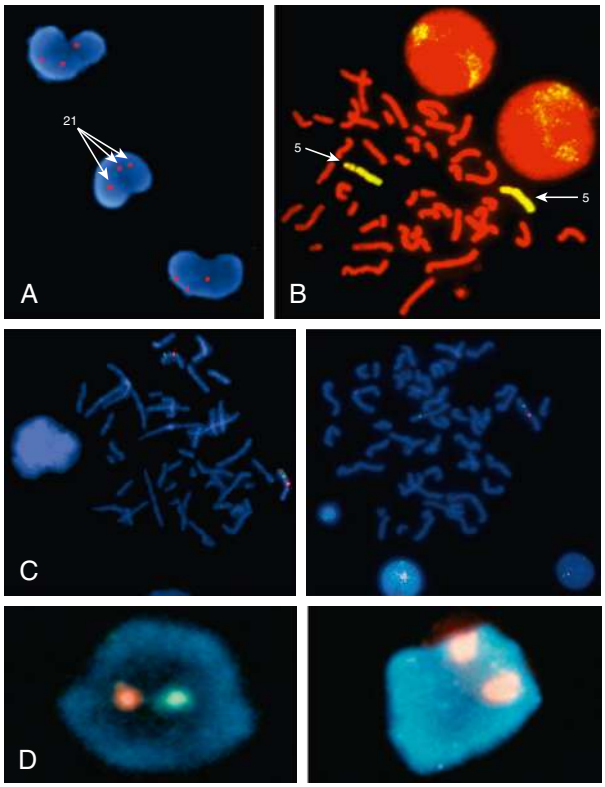

Fig. 99.4 A, Fluorescence in situ hybridization (FISH) analysis of interphase peripheral blood cells from a patient with Down syndrome using a chromosome 21–specific probe. The three *red signals* mark the presence of three chromosomes 21. B, FISH analysis of a metaphase chromosome spread from a clinically normal individual using a whole chromosome paint specific for chromosome 5. Both chromosome 5s are completely labeled *(yellow)* along their entire length. C, FISH on metaphase cells using a unique sequence probe that hybridizes to the elastin gene on chromosome 7q11.23, inside the Williams syndrome critical region. The elastin probe is labeled in *red*, and a control probe on chromosome 7 is labeled in *green*. The *left* image shows normal hybridization to chromosome 7, with two signals for the elastin region and two for the control probe. The *right* image shows a normal chromosome on the right with control and elastin signals and a deleted chromosome 7 on the left, evidenced by a single signal for the control probe. This image corresponds to a patient with a Williams syndrome region deletion. D, FISH in interphase cells using DNA probes that hybridize to repetitive α-satellite sequences in the pericentromeric region for the sex chromosomes. *Left,* interphase cells with two signals, one labeled in *red* for the X chromosome and *green* for the Y chromosome, consistent with a normal male chromosome complement. *Right,* interphase cell showing two *red* signals for the X chromosome, compatible with a normal female chromosome complement.

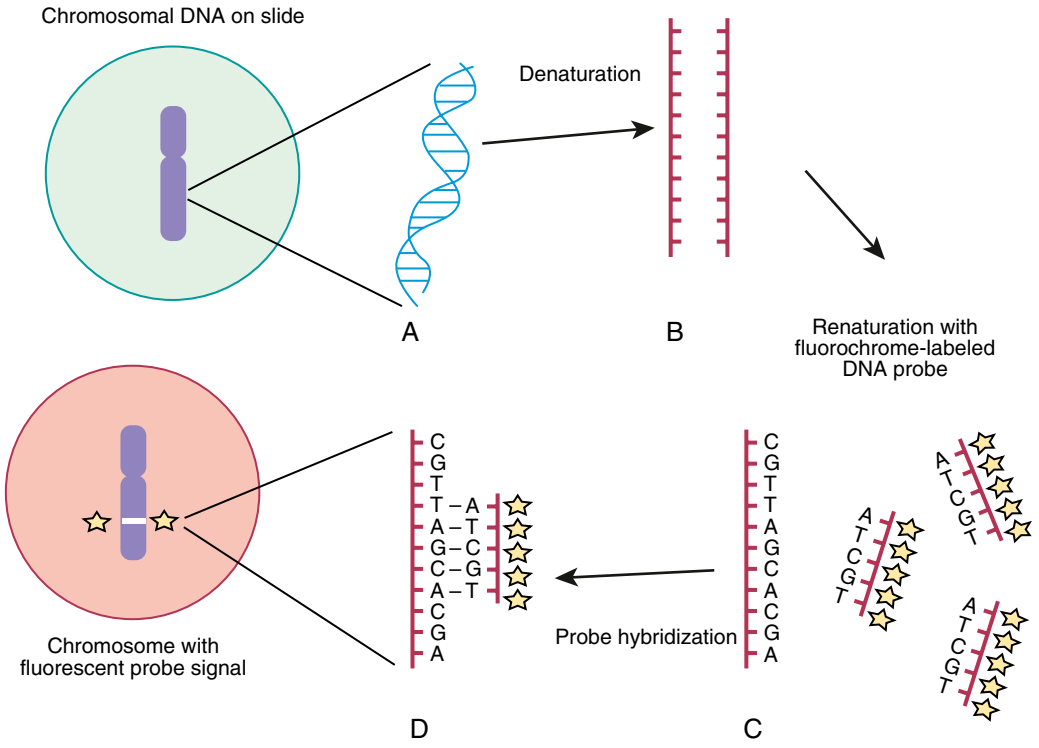

Fig. 99.5 FISH involves denaturation of double-stranded DNA as present in metaphase chromosomes or interphase nuclei on cytogenetic slide preparations (A) into single-stranded DNA (B). The slide-bound (in situ) DNA is then renatured or reannealed in the presence of excess copies of a single-stranded, fluorochrome-labeled DNA base-pair sequence or probe (C). The probe anneals or "hybridizes" to sites of complementary DNA sequence (D) within the chromosomal genome. Probe signal is visualized and imaged on the chromosome by fluorescent microscopy. *(From Lin RL, Cherry AM, Bangs CD, et al. FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In: Hyme HE, Greydanus D, eds, Genetic Disorders in Adolescents: State of the art reviews. Adolescent medicine. Philadelphia: Hanley and Belfus; 2002: pp. 305–313.)*

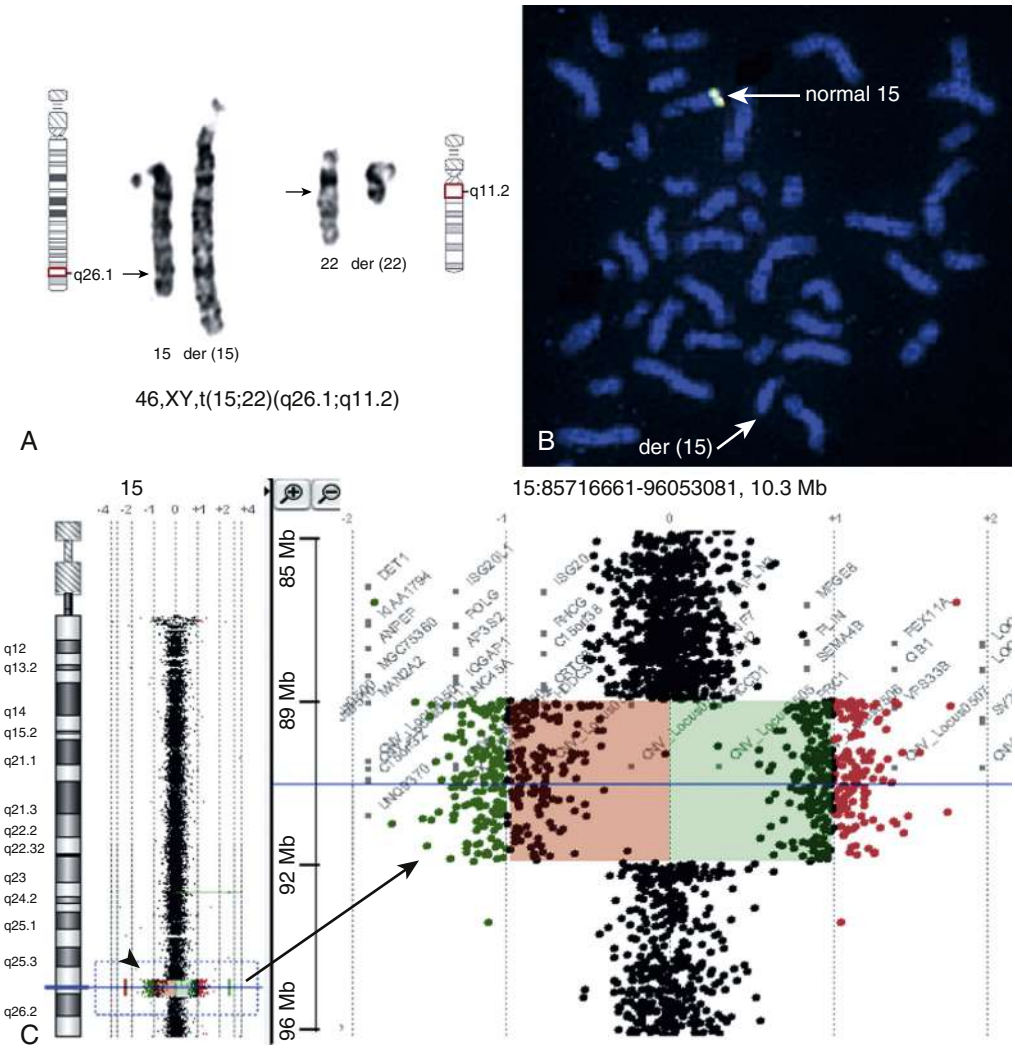

Fig. 99.6 Example of a cryptic microdeletion at a translocation breakpoint of an apparently balanced translocation in a patient with developmental delay (dd) and growth defect. **A,** Partial karyotype shows t(15;22)(q26.1;q11.2). **B,** Fluorescence in situ hybridization (FISH) with clones 2O19 *(top arrow)* and 354M14 *(bottom arrow)* at 15q26.1; *arrows* indicate signals only present on the normal chromosome 15, suggesting a deletion on the der(15). **C,** Two-color array comparative genomic hybridization (aCGH) with dye swap with 244 K oligo probes; *arrowhead* indicates a 3.3-Mbp deletion at chromosome 15q26.1-q26.2; *arrow* points to the close-up view of the deletion. *(From Li MM, Andersson HC. Clinical application of microarray-based molecular cytogenetics: an emerging new era of genomic medicine. J Pediatr. 2009;155:311–317, with permission of the authors and publisher.)*

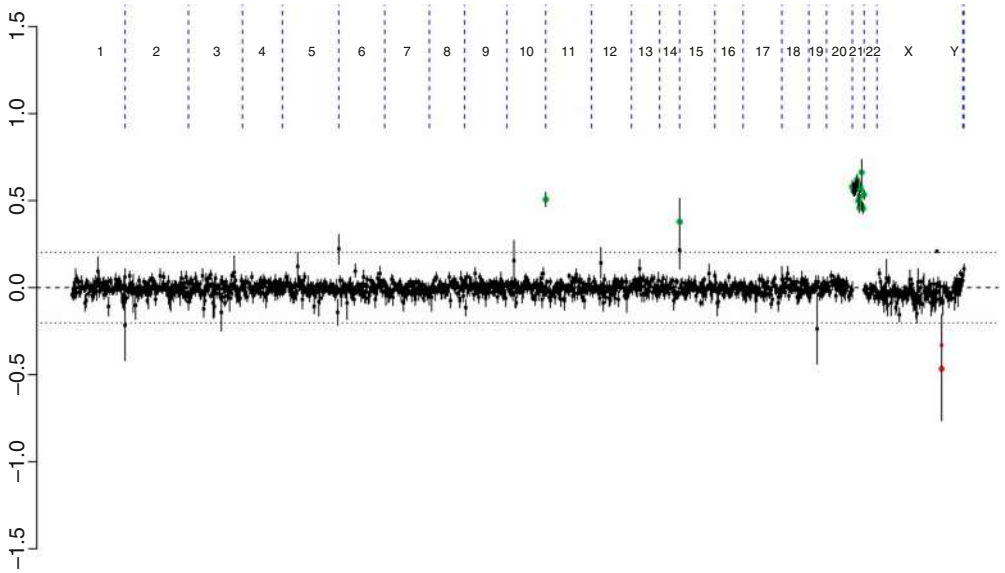

Fig. 99.7 Array comparative genomichybridization (aCGH) in a female patient with Down syndrome. Each *black dot* represents a piece of DNA segment specific for different chromosome location. Most of the dots displayed between the 0.0 and 0.2 axis are considered within normal range. Exceptions are often a result of polymorphic variations. A group of dots colored in *green* clusters on chromosome 21 and above 0.5. These represent a *gain* in copy number of DNA segments for chromosome 21, as seen in Down syndrome and consistent with trisomy 21.

Table 99.3 Chromosomal Trisomies and Their Clinical Findings*

SYNDROME	INCIDENCE	CLINICAL MANIFESTATIONS
Trisomy 13, Patau syndrome	1/10,000 births	Cleft lip often midline; flexed fingers with postaxial polydactyly; ocular hypotelorism, bulbous nose; low-set, malformed ears; microcephaly; cerebral malformation, especially holoprosencephaly; microphthalmia, cardiac malformations; scalp defects; hypoplastic or absent ribs; visceral and genital anomalies Early lethality in most cases, with a median survival of 12 days; ~80% die by 1 year; 10-year survival ~13%; survivors have significant neurodevelopmental delay
Trisomy 18, Edwards syndrome	1/6,000 births	Low birthweight, closed fists with index finger overlapping the third digit and the fifth digit overlapping the fourth, narrow hips with limited abduction, short sternum, rocker-bottom feet, microcephaly, prominent occiput, micrognathia, cardiac and renal malformations, intellectual disability ~88% of children die in the first year; 10-year survival ~10%; survivors have significant neurodevelopmental delay
Trisomy 8, mosaicism	1/20,000 births	Long face; high, prominent forehead; wide, upturned nose; thick, everted lower lip; microretrognathia; low-set ears; high-arched, sometimes cleft, palate; osteoarticular anomalies common (camptodactyly of second through fifth digits, small patella); deep plantar and palmar creases; moderate intellectual disability

*For trisomy 21, see Chapter 57.

Abnormal cells that do not contain a multiple of haploid number of chromosomes are termed **aneuploid** cells. **Aneuploidy** is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3–4% of all clinically recognized pregnancies. **Monosomies** occur when only one, instead of the normal pair (two), of a given chromosome is present in an otherwise diploid cell. In humans, most autosomal monosomies appear to be lethal early in development, and survival is possible in **mosaic forms** or by means of chromosome rescue (restoration of the normal number by duplication of single monosomic chromosome, also known as monosomy rescue). An exception to this rule is monosomy for the X chromosome (45,X), seen in Turner syndrome; nonetheless, the majority of 45,X conceptuses are believed to be lost early in pregnancy for as yet unexplained reasons.

The most common cause of aneuploidy is **nondisjunction**, the failure of chromosomes to disjoin normally during meiosis (see Fig. 99.1). Nondisjunction can occur during meiosis I or II or during mitosis, although maternal meiosis I is the most common nondisjunction in aneuploidies (e.g., Down syndrome, trisomy 18). After meiotic nondisjunction, the resulting gamete either lacks a chromosome or has two copies instead of one normal copy, resulting in a monosomic or trisomic zygote, respectively.

Trisomy is characterized by the presence of three chromosomes, instead of the normal pair (two), of any particular chromosome. Trisomy is the most common form of aneuploidy. Trisomy can occur in all cells, or it may be mosaic. Most individuals with a trisomy exhibit a consistent and specific phenotype depending on the chromosome involved.

FISH is a technique that can be used for rapid diagnosis in the prenatal detection of common fetal aneuploidies, including chromosomes 13, 18, and 21, as well as sex chromosomes (see Fig. 99.4C and D). Direct detection of cell-free fetal DNA (trophoblastic or placental origin) in maternal plasma for fetal trisomy detection is a safe and highly effective screening test for fetal aneuploidy. The most common numerical abnormalities in liveborn children include trisomy 21 (Down syndrome) (see Chapter 57); trisomy 18 (Edwards syndrome); trisomy 13 (Patau syndrome); and sex chromosomal aneuploidies, such as Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XXX, and 47,XYY. By far the most common type of trisomy in liveborn infants is trisomy 21 (47,XX,+21 or 47,XY,+21) (see Table 99.1). Trisomy 18 and trisomy 13 are relatively less common and are associated with a characteristic set of congenital anomalies and severe intellectual disability (Table 99.3). The occurrence of trisomy 21 and other trisomies increases with advanced maternal age (≥35 years). Because of this increased risk, women who are ≥35 years old at delivery should be offered genetic counseling and prenatal diagnosis (including serum screening, ultrasonography, and cell-free DNA detection, amniocentesis, or chorionic villus sampling; see Chapter 117).

99.3 Abnormalities of Chromosome Structure

Carlos A. Bacino and Brendan Lee

TRANSLOCATIONS

Translocations, which involve the transfer of material from one chromosome to another, occur with a frequency of 1 in 500 liveborn human infants. They may be inherited from a carrier parent or appear de novo, with no other affected family member. Translocations are usually reciprocal or Robertsonian, involving two chromosomes (Fig. 99.8).

Reciprocal translocations are the result of breaks in nonhomologous chromosomes, with reciprocal exchange of the broken segments. Carriers of a reciprocal translocation are usually phenotypically normal but are at an increased risk for miscarriage caused by transmission of unbalanced reciprocal translocations and for bearing chromosomally abnormal offspring. Unbalanced translocations are the result of abnormalities in the segregation or crossover of the translocation carrier chromosomes in the germ cells.

Robertsonian translocations involve two acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22) that fuse near the centromeric region with a subsequent loss of the short arms. Because the short arms of all five pairs of acrocentric chromosomes have multiple copies of genes encoding for ribosomal RNA, loss of the short arms of acrocentric chromosomes has no deleterious effect. The resulting karyotype has only 45 chromosomes, including the translocated chromosome, which consists of the long arms of the two fused chromosomes. Carriers of Robertsonian translocations are usually phenotypically normal. However, they are at increased risk for miscarriage and unbalanced translocations in phenotypically abnormal offspring.

In some rare instances, translocations can involve three or more chromosomes, as seen in complex rearrangements. Another less

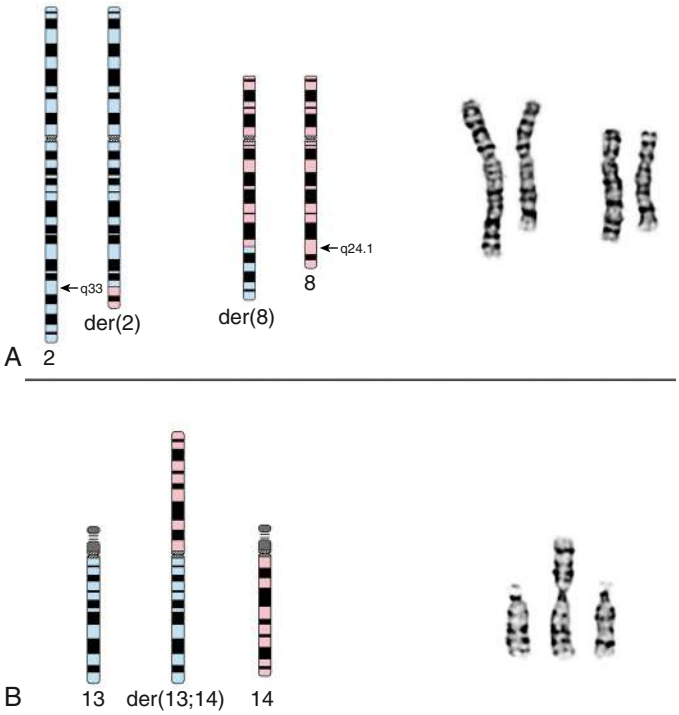

Fig. 99.8 A, Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a reciprocal translocation between chromosome two *(blue)* and chromosome eight *(pink)*. The breakpoints are on the long *(q)* arm of both chromosomes at bands 2q33 and 8q24.1, with the reciprocal exchange of material between the derivative *(der)* chromosomes 2 and 8. This translocation is balanced, with no net gain or loss of material. The nomenclature for this exchange is t(2;8)(q33:q24.1). B, Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a Robertsonian translocation between chromosomes 13 *(blue)* and 14 *(pink)*. The breakpoints are at the centromere (band q10) of both chromosomes, with fusion of the long arms into a single derivative chromosome and loss of the short *(p)* arm material. The nomenclature for this exchange is der(13;14)(q10;q10).

common type is the insertional translocation. **Insertional translocations** result from a piece of chromosome material that breaks away and later is reinserted within the same chromosome at a different site or inserted into another chromosome.

INVERSIONS

An inversion requires that a single chromosome breaks at two points; the broken piece is then inverted and joined into the same chromosome. Inversions occur in 1 in 100 live births. There are two types of inversions, pericentric and paracentric. In **pericentric inversions** the breaks are in the two opposite arms of the chromosome and include the centromere. They are usually discovered because they change the position of the centromere. The breaks in **paracentric inversions** occur in only one arm. Carriers of inversions are usually phenotypically normal, but they are at increased risk for miscarriages, typically in paracentric inversions, and chromosomally abnormal offspring in pericentric inversions.

DELETIONS AND DUPLICATIONS

Deletions involve loss of chromosome material and, depending on their location, can be classified as **terminal** (at the end of chromosomes) or **interstitial** (within the arm of a chromosome). They may be isolated or may occur along with a duplication of another chromosome segment. The latter typically occurs in unbalanced reciprocal chromosomal translocation secondary to abnormal crossover or segregation in a translocation or inversion carrier.

A carrier of a deletion is monosomic for the genetic information of the missing segment. Deletions are usually associated with intellectual disability and malformations. The most commonly observed deletions in routine chromosome preparations include 1p–, 4p–, 5p–, 9p–, 11p–, 13q–, 18p–, 18q–, and 21q– (Table 99.4 and Fig. 99.9), all distal or terminal deletions of the short or the long arms of chromosomes. Deletions may be observed in routine chromosome preparations, and deletions and translocations larger than 5-10 Mbp are usually visible microscopically.

High-resolution banding techniques, FISH, and molecular studies such as CMA can reveal deletions that are too small to be seen in ordinary or routine chromosome spreads (see Fig. 99.7). **Microdeletions** involve loss of small chromosome regions, the largest of which are detectable only with prophase chromosome studies and molecular methods. For submicroscopic deletions, the missing piece can only be detected using molecular methodologies such as DNA-based studies (e.g., CMA, FISH). The presence of extra genetic material from the same chromosome is referred to as **duplication**. Duplications can also

Table 99.4 Common Deletions and Their Clinical Manifestations

DELETION	CLINICAL ABNORMALITIES
4p–	Wolf-Hirschhorn syndrome. The main features are a typical "Greek helmet" facies secondary to ocular hypertelorism, prominent glabella, frontal bossing, microcephaly, dolichocephaly, hypoplasia of the orbits, ptosis, strabismus, nystagmus, bilateral epicanthic folds, cleft lip and palate, beaked nose with prominent bridge, hypospadias, cardiac malformations, and intellectual disability.
5p–	Cri du chat syndrome. The main features are hypotonia, short stature, characteristic shrill cry in the first few weeks of life (also called cat's cry syndrome), microcephaly with protruding metopic suture, hypertelorism, bilateral epicanthic folds, high arched palate, wide and flat nasal bridge, and intellectual disability.
9p–	The main features are craniofacial dysmorphic features with trigonocephaly, slanted palpebral fissures, discrete exophthalmos secondary to supraorbital hypoplasia, arched eyebrows, flat and wide nasal bridge, short neck with low hairline, genital anomalies, long fingers and toes with extra flexion creases, cardiac malformations, and intellectual disability.
13q–	The main features are low birthweight, failure to thrive, microcephaly, and severe intellectual disability. Facial features include high, wide nasal bridge; hypertelorism; ptosis; and micrognathia. Ocular malformations are common (retinoblastoma). The hands have hypoplastic or absent thumbs and syndactyly.
18p–	A few patients (15%) are severely affected and have cephalic and ocular malformations: holoprosencephaly, cleft lip and palate, ptosis, epicanthal folds, and varying degrees of intellectual disability. Most (80%) have only minor malformations and mild intellectual disability.
18q–	The main features are growth deficiency and hypotonia with a "froglike" position with the legs flexed, externally rotated, and in hyperabduction. The face is characteristic, with depressed midface and apparent protrusion of the mandible, deep-set eyes, short upper lip, and everted lower lip ("carplike" mouth); antihelix of the ears is very prominent. Varying degrees of intellectual disability and belligerent personality are present. Myelination abnormalities occur in the central nervous system.

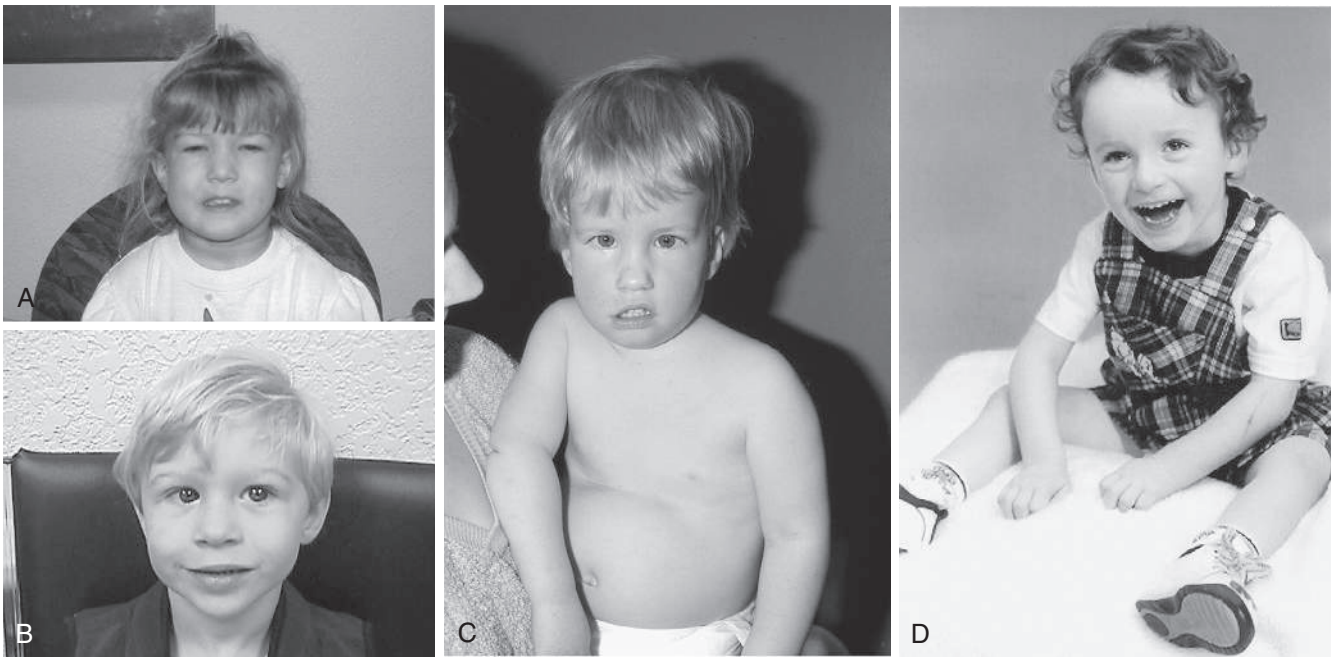

Fig. 99.9 **A,** Child with velocardiofacial syndrome (deletion 22q11.2). **B,** Child with Williams syndrome (deletion 7q11.23). **C,** Child with Prader-Willi syndrome (deletion 15q11-13). **D,** Child with Angelman syndrome (deletion 15q11-13). *(From Lin RL, Cherry AM, Bangs CD, et al. FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In: Hyme HE, Greydanus D, eds, Genetic Disorders in Adolescents: state of the art reviews. Adolescent medicine. Philadelphia: Hanley and Belfus; 2002: pp. 305–313.)*

Table 99.5 Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
1p36	1p deletion	Growth restriction, dysmorphic features with midface hypoplasia, straight thin eyebrows, pointy chin, sensorineural hearing loss, progressive cardiomyopathy, hypothyroidism, seizures, intellectual disability
5q35	Sotos (50% are deletions of *NSD1* gene in Asians but only 6% in Whites)	Overgrowth, macrocephaly, prominent forehead, prominence of extraaxial fluid spaces on brain imaging, large hands and feet, hypotonia, clumsiness, mental disabilities
6p25	Axenfeld-Rieger	Axenfeld-Rieger malformation, hearing loss, congenital heart defects, dental anomalies, developmental delays, facial dysmorphism
7q11.23	Williams	Round face with full cheeks and lips, long philtrum, stellate pattern in iris, strabismus, supravalvular aortic stenosis and other cardiac malformations, varying degrees of intellectual disability, friendly personality
8p11	8p11	Kallmann syndrome type 2 (hypogonadotropic hypogonadism and anosmia), spherocytosis (deletions of ankyrin 1), multiple congenital anomalies, intellectual disability
8q24.1-q24.13	Langer-Giedion or trichorhinophalangeal type II	Sparse hair, multiple cone-shaped epiphyses, multiple cartilaginous exostoses, bulbous nasal tip, thickened alar cartilage, upturned nares, prominent philtrum, large protruding ears, mild intellectual disability
9q22	Gorlin	Multiple basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, calcification falx cerebri
9q34	9q34 deletion	Distinct face with synophrys, anteverted nares, tented upper lip, protruding tongue, midface hypoplasia, conotruncal heart defects, intellectual disability
10p12-p13	DiGeorge type 2	Many of the DiGeorge type 1 and velocardiofacial type 1 features (conotruncal defects, immunodeficiency, hypoparathyroidism, dysmorphic features)
11p11.2	Potocki-Shaffer	Multiple exostoses, parietal foramina, craniosynostosis, facial dysmorphism, syndactyly, intellectual disability
11p13	WAGR	Hypernephroma (Wilms tumor), aniridia, male genital hypoplasia of varying degrees, gonadoblastoma, long face, upward-slanting palpebral fissures, ptosis, beaked nose, low-set poorly formed auricles, intellectual disability (retardation)
11q24.1-11qter	Jacobsen	Growth restriction, intellectual disability, cardiac and digit anomalies, thrombocytopenia
15q11-q13 (paternal)	Prader-Willi	Severe hypotonia and feeding difficulties at birth, voracious appetite and obesity in infancy, short stature (responsive to growth hormone), small hands and feet, hypogonadism, intellectual disability

Continued

Table 99.5 Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations—cont'd

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
15q11-q13 (maternal)	Angelman	Hypotonia, feeding difficulties, gastroesophageal reflux, fair hair and skin, midface hypoplasia, prognathism, seizures, tremors, ataxia, sleep disturbances, inappropriate laughter, poor or absent speech, severe intellectual disability
16p13.3	Rubinstein-Taybi	Microcephaly, ptosis, beaked nose with low-lying philtrum, broad thumbs and large toes, intellectual disability
17p11.2	Smith-Magenis	Brachycephaly, midfacial hypoplasia, prognathism, myopia, cleft palate, short stature, severe behavioral problems, intellectual disability
17p13.3	Miller-Dieker	Microcephaly, lissencephaly, pachygyria, narrow forehead, hypoplastic male external genitals, growth restriction, seizures, profound intellectual disability
20p12	Alagille	Bile duct paucity with cholestasis; heart defects, particularly pulmonary artery stenosis; ocular abnormalities (posterior embryotoxon); skeletal defects such as butterfly vertebrae; long nose
22q11.2	Velocardiofacial-DiGeorge	Conotruncal cardiac anomalies, cleft palate, velopharyngeal incompetence, hypoplasia or agenesis of thymus and parathyroid glands, hypocalcemia, hypoplasia of auricle, learning disabilities, psychiatric disorders
22q13.3 deletion		Hypotonia, developmental delay, normal or accelerated growth, severe expressive language deficits, autistic behavior
Xp21.2-p21.3		Duchenne muscular dystrophy, retinitis pigmentosa, adrenal hypoplasia, intellectual disability, glycerol kinase deficiency
Xp22.2-p22.3		Ichthyosis, Kallmann syndrome, intellectual disability, chondrodysplasia punctata
Xp22.3	MLS	*M*icrophthalmia, *l*inear skin defects, poikiloderma, congenital heart defects, seizures, intellectual disability

Table 99.6 Microduplications and Their Clinical Manifestations

DUPLICATION CHROMOSOME REGION	DISEASE REGION	CLINICAL FEATURES
1q21.1		Macrocephaly, DD, learning disabilities
3q29		Mild to moderate DD, ID, microcephaly
7q11.23	Williams syndrome	DD and severe expressive language disorder, autistic features, subtle dysmorphisms
15q13.3	Prader-Willi/Angelman syndrome	DD, ID, autistic features in duplications of maternal origin
15q24		Growth restriction, DD, microcephaly, digital anomalies, hypospadias, connective tissue abnormalities
16p11.2		FTT, severe DD, short stature, GH deficiency, dysmorphic features
17p11.2	Potocki-Lupski syndrome	Hypotonia, cardiovascular anomalies, FTT, DD, verbal apraxia, autism, anxiety
17q21.31		Severe DD, microcephaly, short and broad digits, dysmorphic features
22q11.2	Velocardiofacial-DiGeorge syndrome	Cardiovascular defects, velopharyngeal insufficiency
Xq28	*MECP2* gene (Rett syndrome)	In males: infantile hypotonia, immune deficiency, dysmorphic features, DD, speech delay, autistic behavior, regression in childhood

DD, Developmental delay; FTT, failure to thrive; GH, growth hormone; ID, intellectual disability.

be sporadic or result from abnormal segregation in translocation or inversion carriers.

Microdeletions and microduplications usually involve regions that include several genes, so the affected individuals can have a distinctive phenotype depending on the number of genes involved. When such a deletion involves more than a single gene, the condition is referred to as a **contiguous gene deletion syndrome** (Table 99.5). With the advent of chromosome microarray, a large number of microduplications, have been uncovered. Many of those **microduplication syndromes** are the reciprocal duplications of the known deletions or microdeletion counterparts and have distinctive clinical features (Table 99.6).

Subtelomeric regions are often involved in chromosome rearrangements that cannot be visualized using routine cytogenetics. *Telomeres,* which are the distal ends of the chromosomes, are gene-rich regions. The distal repetitive sequence structure of telomeres is essentially common to all chromosomes, but proximal to these are unique regions known as *subtelomeres,* which typically are involved in deletions and other chromosome rearrangements. Small subtelomeric deletions, duplications, or rearrangements (translocations, inversions) may be relatively common in children with nonspecific intellectual disability and minor anomalies. Subtelomeric rearrangements have been found in 3–7% of children with moderate to severe intellectual disability and 0.5% of those with mild intellectual disability and can be detected by CMA studies.

Pathogenic variants affecting telomere function and length have been associated with dyskeratosis congenita and other aplastic anemia syndromes, as well as pulmonary or hepatic fibrosis. Both the subtelomeric rearrangements and the microdeletion and microduplication syndromes are typically diagnosed by molecular techniques like CMA and multiple ligation-dependent probe amplification (MLPA) studies. CMA can detect 14–18% of abnormalities in patients who previously had normal cytogenetic studies.

INSERTIONS

Insertions occur when a piece of a chromosome broken at two points is incorporated into a break of a chromosome in another location. A total of three breakpoints are then required, and they can occur between two or within one chromosome. A form of nonreciprocal translocation, insertions are rare. Insertion carriers are at risk of having offspring with deletions or duplications of the inserted segment.

ISOCHROMOSOMES

Isochromosomes consist of two copies of the same chromosome arm joined through a single centromere and forming mirror images of one another. The most commonly reported autosomal isochromosomes tend to involve chromosomes with small arms. Some of the more common chromosome arms involved in this formation include 5p, 8p, 9p, 12p, 18p, and 18q. There is also a common isochromosome abnormality seen in long arm of the X chromosome and associated with Turner syndrome. Individuals who have one isochromosome X within 46 chromosomes are monosomic for genes in the lost short arm and trisomic for the genes present in the long arm of the X chromosome.

MARKER AND RING CHROMOSOMES

Marker chromosomes are rare and are usually chromosome fragments that are too small to be identified by conventional cytogenetics; they usually occur in addition to the normal complement of 46 chromosomes. Most are sporadic (70%); mosaicism is often (50%) noted because of the mitotic instability of the marker chromosomes. The incidence in newborn infants is 1 in 3,300, and the incidence in persons with intellectual disability is 1 in 300. The associated phenotype ranges from normal to severely abnormal, depending on the amount of chromosome material and number of genes included in the fragment.

Ring chromosomes, which are found for all human chromosomes, are rare. A ring chromosome is formed when both ends of a chromosome are deleted and the ends are then joined to form a ring. Depending on the amount of chromosome material that is lacking or in excess (if the ring has duplicated chromosomal material), a patient with a ring chromosome can appear normal or can have different degrees of intellectual disability and/or multiple congenital anomalies.

Marker and ring chromosomes can be found in the cells of solid tumors of children. Some of these markers can be the result of tumor-specific rearrangements, such as translocations, deletions, and duplications, ultimately leading to gene fusions and tumor gene amplifications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

99.4 Sex Chromosome Aneuploidy

Carlos A. Bacino and Brendan Lee

About 1 in 400 males and 1 in 650 females have some form of sex chromosome abnormality. Considered together, sex chromosome abnormalities are the most common chromosome abnormalities seen in liveborn infants, children, and adults. Sex chromosome abnormalities can be either structural or numerical and can be present in all cells or in a mosaic form. Those affected with these abnormalities might have few or no physical or developmental problems (Table 99.7).

TURNER SYNDROME

Turner syndrome is a condition characterized by complete or partial monosomy of the X chromosome and defined by a combination of phenotypic features (see Table 99.7 and Table 99.8). Half the patients with Turner syndrome have a 45,X chromosome complement. The other half exhibit mosaicism and varied structural abnormalities of the X or Y chromosome. Maternal age is not a predisposing factor for children with 45,X. Turner syndrome occurs in approximately 1

Table 99.7 Sex Chromosome Abnormalities

DISORDER	KARYOTYPE	APPROXIMATE INCIDENCE
Klinefelter syndrome	47,XXY	1/580 males
	48,XXXY	1/50,000-1/80,000 male births
	Other (48,XXYY; 49,XXXYY; mosaics)	
XYY syndrome	47,XYY	1/800-1,000 males
Other X or Y chromosome abnormalities		1/1,500 males
XX males	46,XX	1/20,000 males
Turner syndrome	45,X	1/2,500-1/5,000 females
	Variants and mosaics	
Trisomy X	47,XXX	1/1,000 females
	48,XXXX and 49,XXXXX	Rare
Other X chromosome abnormalities		1/3,000 females
XY females	46,XY	1/20,000 females

Table 99.8 Signs Associated with Turner Syndrome

Short stature
Congenital lymphedema
Horseshoe kidneys
Patella dislocation
Increased carrying angle of elbow (cubitus valgus)
Madelung deformity (chondrodysplasia of distal radial epiphysis)
Congenital hip dislocation
Scoliosis
Widespread nipples
Shield chest
Redundant nuchal skin (in utero cystic hygroma)
Low posterior hairline
Coarctation of aorta
Bicuspid aortic valve
Cardiac conduction abnormalities
Hypoplastic left heart syndrome and other left-sided heart abnormalities
Gonadal dysgenesis (infertility, primary amenorrhea)
Gonadoblastoma (increased risk if Y chromosome material is present)
Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
Developmental delay (in 10%)
Social awkwardness
Hypothyroidism (acquired in 15–30%)
Type 2 diabetes mellitus (insulin resistance)
Strabismus
Cataracts
Red-green color blindness (as in males)
Recurrent otitis media
Sensorineural hearing loss
Inflammatory bowel disease
Celiac disease (increased incidence)

in 5,000 female live births. In 75% of patients, the lost sex chromosome is of paternal origin (whether an X or a Y). 45,X is one of the chromosome abnormalities most often associated with spontaneous pregnancy losses. It has been estimated that 95–99% of 45,X conceptions are miscarried.

Clinical findings in the newborns can include small size for gestational age, webbing of the neck, protruding ears, and lymphedema of the hands and feet, although many newborns are phenotypically normal (Fig. 99.10). Older children and adults have short stature and exhibit variable dysmorphic features. Congenital heart defects (40%) and structural renal anomalies (60%) are common. The most common heart defects are bicuspid aortic valves, coarctation of the aorta, aortic stenosis, and mitral valve prolapse. The gonads are generally streaks of fibrous tissue **(gonadal dysgenesis)** (see Chapter 626). There is primary amenorrhea and lack of secondary sex characteristics. These children should receive regular endocrinologic testing.

Patients with **45,X/46,XY mosaicism** can have Turner syndrome, although this form of mosaicism can also be associated with male pseudohermaphroditism, male or female genitalia in association with mixed gonadal dysgenesis, or a normal male phenotype. This variant is estimated to represent approximately 6% of patients with mosaic Turner syndrome. Some of the patients with Turner syndrome phenotype and a Y cell line exhibit masculinization. Phenotypic females with 45,X/46,XY mosaicism have a 15–30% risk of developing **gonadoblastoma**. The risk for the patients with a male phenotype and external testes is not so high, but tumor surveillance is nevertheless recommended. The American Academy of Pediatrics (AAP) has recommended the use of FISH analysis to look for Y chromosome mosaicism in all 45,X patients. If Y chromosome material is identified, laparoscopic gonadectomy is recommended.

Noonan syndrome (see Chapter 101.1) shares many clinical features with Turner syndrome and was formerly called *pseudo-Turner syndrome*, although it is an autosomal dominant disorder resulting from pathogenic variants in several genes involved in the RAS-MAPK pathway. In contrast to Turner syndrome, Noonan syndrome affects both sexes and has a different pattern of congenital heart disease, typically involving right-sided heart lesions.

KLINEFELTER SYNDROME

Persons with Klinefelter syndrome are phenotypically male. This syndrome is the most common cause of hypogonadism and infertility in males and the most common sex chromosome aneuploidy in humans (see Chapter 623). Eighty percent of children with Klinefelter syndrome have a male karyotype with an extra chromosome X-47,XXY. The remaining 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46,XY/47,XXY), or structurally abnormal X chromosomes; the greater the aneuploidy, the more severe the mental impairment and dysmorphism. The prevalence of 47,XXY is 1 in 580 liveborn males. Errors in paternal nondisjunction in meiosis I account for ~50% of the cases.

47,XYY

The incidence of 47,XYY is approximately 1 in 800-1,000 males, with many cases remaining undiagnosed, because most affected individuals have a normal appearance and normal fertility. The extra Y is the result of nondisjunction at paternal meiosis II. Those with this abnormality have normal intelligence but are at risk for learning disabilities. Behavioral abnormalities, including hyperactive behavior, pervasive developmental disorder, and aggressive behavior, have been reported. Early reports that assigned stigmata of criminality to this disorder have long been disproved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

99.5 Mosaicism

Carlos A. Bacino and Brendan Lee

Mosaicism describes an individual or tissue that contains ≥2 genetically different cell lines typically derived from a single zygote. Genetic differences can result from mitotic nondisjunction (see Fig. 99.1; Table 99.9) or sporadic variant. Study of placental tissue from chorionic villus samples collected at or before the 10th week of gestation has shown that ≥2% of all conceptions are mosaic for a chromosome abnormality. With the exception of chromosomes 13, 18, and 21, complete autosomal trisomies are usually nonviable, and the contribution of a normal cell line might allow these other trisomic conceptions to survive to term. Depending on the point at which the new cell line arises during early embryogenesis, mosaicism may be present in some tissues but not in others. **Germline mosaicism**, which refers to the presence of mosaicism in the germ cells of the gonad, may be associated with an increased risk for recurrence of an affected child if the germ cells are affected with a chromosomal abnormality or with a specific gene pathogenic variant.

PALLISTER-KILLIAN SYNDROME

Pallister-Killian syndrome is characterized by coarse facies (prominent full cheeks), abnormal ear lobes, localized alopecia (sparse hair



Fig. 99.10 Physical manifestations associated with Turner syndrome. **A,** This newborn shows a webbed neck with low hairline, shield chest with widespread nipples, abnormal ears, and micrognathia. **B,** The low-set posterior hairline can be better appreciated in this older child, who also has protruding ears. **C,** In this frontal view, mild webbing of the neck and small, widely spaced nipples are evident, along with a midline scar from prior cardiac surgery. The ears are low-set and prominent, protruding forward. **D** and **E,** The newborn shown in **A** also has prominent lymphedema of the hands and feet. *(From Madan-Khetarpal S, Arnold G. Genetic disorders and dysmorphic conditions. In: Zitelli BJ, McIntire SC, Nowalk AJ, eds, Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th ed. Philadelphia: Elsevier; 2012: Fig. 1.25.)*

in the temporal regions), pigmentary skin anomalies, diaphragmatic hernia, cardiovascular anomalies, supernumerary nipples, seizures, and profound intellectual disability. The syndrome is caused by mosaicism for an isochromosome of the short chromosome of 12 (12p). The presence of the isochromosome 12p in cells gives four functional copies for the short arm of chromosome 12 in the affected cells. The isochromosome 12p is preferentially cultured from fibroblasts that can be readily obtained from a skin punch biopsy and is seldom present in lymphocytes. A CMA obtained from a buccal swab can be another tool to detect this disorder. The abnormalities seen in affected persons probably reflect the presence of abnormal cells during early embryogenesis.

HYPOMELANOSIS OF ITO

Hypomelanosis of Ito is characterized by unilateral or bilateral macular hypo- or hyperpigmented whorls, streaks, and patches (see Chapter 694). Sometimes these pigmentary defects follow the lines of Blaschko that represent areas of early epidermal cell migration. Hair and tooth anomalies are common. Abnormalities of the eyes, musculoskeletal system (growth asymmetry, syndactyly, polydactyly, clinodactyly), and central nervous system (microcephaly, seizures, intellectual disability) may also be present. Patients with hypomelanosis of Ito might have two genetically distinct cell lines. The mosaic chromosome anomalies that have been observed involve both autosomes and sex chromosomes and have been demonstrated in about

Table 99.9 Other Rare Mosaic Aneuploidy Syndromes

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Variable growth and intellectual deficiency The majority of patients are mosaic Deep palmar and plantar furrows Joint contractures
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaic Craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) Skeletal (joint contractures) Heart defects (60%)
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion Recurrence risk negligible
Tetrasomy 12p	46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)	Pallister-Killian syndrome Sparse anterior scalp hair (more so temporal region), eyebrows, and eyelashes; prominent forehead; full cheeks; long philtrum with thin upper lip and cupid-bow configuration; polydactyly; streaks of hyper- and hypopigmentation

50% of clinically affected patients. The mosaicism might not be visible in lymphocyte-derived chromosome studies; it is more likely to be found when chromosomes are analyzed from skin fibroblasts. The distinct cell lines might not always be caused by observable chromosomal anomalies but might result from single-gene pathogenic variants or other mechanisms.

99.6 Chromosome Instability Syndromes

Carlos A. Bacino and Brendan Lee

Chromosome instability syndromes, formerly known as *chromosome breakage syndromes,* are characterized by an increased risk of malignancy and specific phenotypes. They display autosomal recessive inheritance and have an increased frequency of chromosome breakage and/or rearrangement, either spontaneous or induced. Chromosome instability syndromes result from specific defects in DNA repair, cell cycle control, and apoptosis. The resulting chromosomal instability leads to the increased risk of developing neoplasms. The classic chromosome instability syndromes are Fanconi anemia, ataxia telangiectasia, Nijmegen syndrome, ICF (immunodeficiency, centromere instability, facial anomalies) syndrome, Roberts syndrome, and Bloom syndrome (Table 99.10).

99.7 Uniparental Disomy and Imprinting

Carlos A. Bacino and Brendan Lee

UNIPARENTAL DISOMY

Uniparental disomy **(UPD)** occurs when both chromosomes of a pair or areas from one chromosome in any individual have been inherited from a single parent. UPD can be of two types, uniparental *iso*disomy or uniparental *hetero*disomy. **Uniparental isodisomy** means that both chromosomes or chromosomal regions are identical (typically the result of monosomy rescue by duplication). **Uniparental heterodisomy** means that the two chromosomes are different members of a pair, both of which were still inherited from one parent. This results from a trisomy that is later reduced to disomy, leaving two copies from one parent. The phenotypic result of UPD varies according to the chromosome involved, the parent who contributed the chromosomes, and whether it is isodisomy or heterodisomy. Three types of phenotypic effects are seen in UPD: those related to imprinted genes (i.e., the absence of a gene that is normally expressed only when inherited from a parent of a specific sex), those related to the uncovering of autosomal recessive disorders, and those related to a vestigial aneuploidy producing mosaicism (see Chapter 97).

In **uniparental isodisomy**, both chromosomes or regions (and thus the genes) in the pair are identical. This is particularly important when the parent is a carrier of an autosomal recessive disorder. If the offspring of a carrier parent has UPD with isodisomy for a chromosome that carries an abnormal gene, the abnormal gene will be present in two copies, and the phenotype will be that of the autosomal recessive disorder; the child has an autosomal recessive disorder even though only one parent is a carrier of that recessive disorder. It is estimated that all humans carry approximately 20 abnormal autosomal recessive genes. Some autosomal recessive disorders, such as spinal muscular atrophy, cystic fibrosis, cartilage-hair hypoplasia, α- and β-thalassemias, and Bloom syndrome, have been reported in cases of UPD. The possibility of uniparental isodisomy should also be considered when a person is affected with >1 recessive disorder because the abnormal genes for both disorders could be carried on the same isodisomic chromosome. Uniparental isodisomy is a *rare* cause of recessively inherited disorders. Uniparental isodisomies can also be detected by SNP microarrays.

Maternal UPD involving chromosomes 2, 7, 14, and 15 and **paternal UPD** involving chromosomes 6, 11, 15, and 20 are associated with phenotypic abnormalities of growth and behavior. UPD of maternal chromosome 7 is associated with Russell-Silver syndrome with intrauterine growth restriction. These phenotypic effects may be related to imprinting (see later) (Fig. 99.11).

Although microdeletions cause the majority of cases, UPD for chromosome 15 is seen in some instances of Prader-Willi syndrome and Angelman syndrome. In **Prader-Willi syndrome**, approximately 25–29% of cases have maternal UPD (missing the paternal chromosome 15) (Fig. 99.12). In **Angelman syndrome**, paternal UPD of chromosome 15 is only observed in approximately 5% of the cases (missing the maternal chromosome 15). The phenotype for Prader-Willi syndrome and Angelman syndrome in cases of UPD is thought to result from the lack of specific parental contributions from chromosome 15. In Prader-Willi syndrome the paternal contribution is missing, and the maternal contribution is missing in Angelman syndrome. Prader-Willi syndrome may be caused by paternal deficiency of a cluster of small nucleolar RNAs (snoRNAs).

Table 99.10 Chromosome Instability Syndromes

SYNDROME	LABORATORY FINDINGS AND GENES INVOLVED	CLINICAL FINDINGS
Fanconi anemia (FA)	Chromosome breakage induced by diepoxybutane and mitomycin C There are least 21 FA genes, most are autosomal recessive, only one is X linked	Short stature, microcephaly in 1/3 of cases, radial ray defects including thumb anomalies, pancytopenia, skeletal anomalies, renal anomalies, café-au-lait macules, ear abnormalities and hearing loss
Ataxia telangiectasia	Chromosome instability with rearrangements between chromosomes 7 and 14 in lymphocytes often involving the T-cell receptors in those chromosomes Decreased IgA levels Pathogenic variants in the *ATM* gene. Autosomal recessive	Progressive cerebellar ataxia with later development of conjunctival telangiectasias, choreoathetosis, and dystonia Sinopulmonary infections Predisposition to malignancies like B-cell lymphomas, T-cell leukemias and solid tumors
Nijmegen syndrome	Translocations involving chromosomes 7 and 14 in up to 50% of cells Pathogenic variants in the *NBN* gene (autosomal recessive)	IUGR, short stature, progressive microcephaly, and intellectual disability, recurrent sinopulmonary infections Susceptibility to malignancies before age 20 years like T- and B-cell lymphomas, medulloblastomas, gliomas, rhabdomyosarcoma
ICF (immunodeficiency, centromere instability, facial anomalies) syndrome, types I and II	Pericentromeric chromosomal instability on PHA-stimulated metaphases in chromosomes 1, 9, and 16 Decrease of IgG and IgE in type I, IgM and IgE in type II Low T cells, like NK cells. Pathogenic variants in *DNMT3B* and ZBTB24 genes in types I and II, respectively Autosomal recessive	Immunodeficiency, recurrent infections, intellectual disability, facial dysmorphic features
Roberts-SC phocomelia syndrome	Premature chromosome separation with chromatid/centromere repulsion in prophase or early metaphase easily detected using C-banding Pathogenic variants in *ESCO2* gene Autosomal recessive	Prenatal growth deficiency, absent or hypoplastic arms typically symmetric with reduction of digits' length including thumbs that are usually more affected than lower extremities, bilateral cleft lip and palate, dysmorphic features, cardiac anomalies, renal anomalies, and intellectual disability
Bloom syndrome	Marked chromosomal increase of sister chromatid exchange in the presence of BrdU and increased spontaneous chromosome breakage Decreased IgG, IgA, IgM Pathogenic variants in the *RECQL3* gene. Autosomal recessive	Severe prenatal and postnatal growth deficiency, microcephaly (average intelligence), sensitivity to sunlight (butterfly distribution over the face), cafe-au-lait macules, insulin resistance, predisposition to malignancies: lymphomas, leukemias, squamous cell carcinoma and solid tumors Hypersensitivity to chemotherapy
Werner syndrome	"Variegated translocation mosaicism": chromosomal aberrations, including translocations, inversions, and deletions Telomere loss Pathogenic variants in *RECQL2* Autosomal recessive	Short stature, premature aging appearance, and predisposition to malignancies Loss and graying of hair, hoarseness, scleroderma-like changes in the 20s Cataracts, type II diabetes, osteoporosis, hypogonadism in the 30s Neoplasms in >40% of cases including sarcomas, melanomas, and thyroid cancer Myocardial infarction and malignancies are cause of early death

IUGR, Intrauterine growth restriction; PHA, phytohemagglutinin; NK, natural killer.

These findings suggest that there are differences in function of certain regions of chromosome 15, depending on whether it is inherited from the mother or from the father. Angelman syndrome is caused by absent function of the maternal gene *UBE3A* and can be the result of maternal deletion, maternal *UBE3A* pathogenic variant, paternal UPD, and abnormalities in the maternal imprinting center on chromosome 15q11-13 region.

UPD most frequently arises when a pregnancy starts off as a **trisomic conception** followed by **trisomy rescue.** Because most trisomies are lethal, the fetus can only survive if a cell line loses one of the extra chromosomes to revert to the disomic state. One third of the time, the disomic cell line is uniparental. This is the typical mechanism for Prader-Willi syndrome, and it is often associated with advanced maternal age. The embryo starts off as trisomy 15 secondary to maternal meiosis I nondisjunction, followed by random loss of the paternal chromosome. In this case the disomic cell line becomes the more viable one and outgrows the trisomic cell line. When mosaic trisomy is found at prenatal diagnosis, care should be taken to determine whether UPD has resulted and whether the chromosome involved is one of the disomies known to be associated with phenotypic abnormalities (i.e., chromosome involved in UPD containing imprinted genes). There must always be concern that some residual cells that are trisomic are present in some tissues, leading to malformations or dysfunction. The

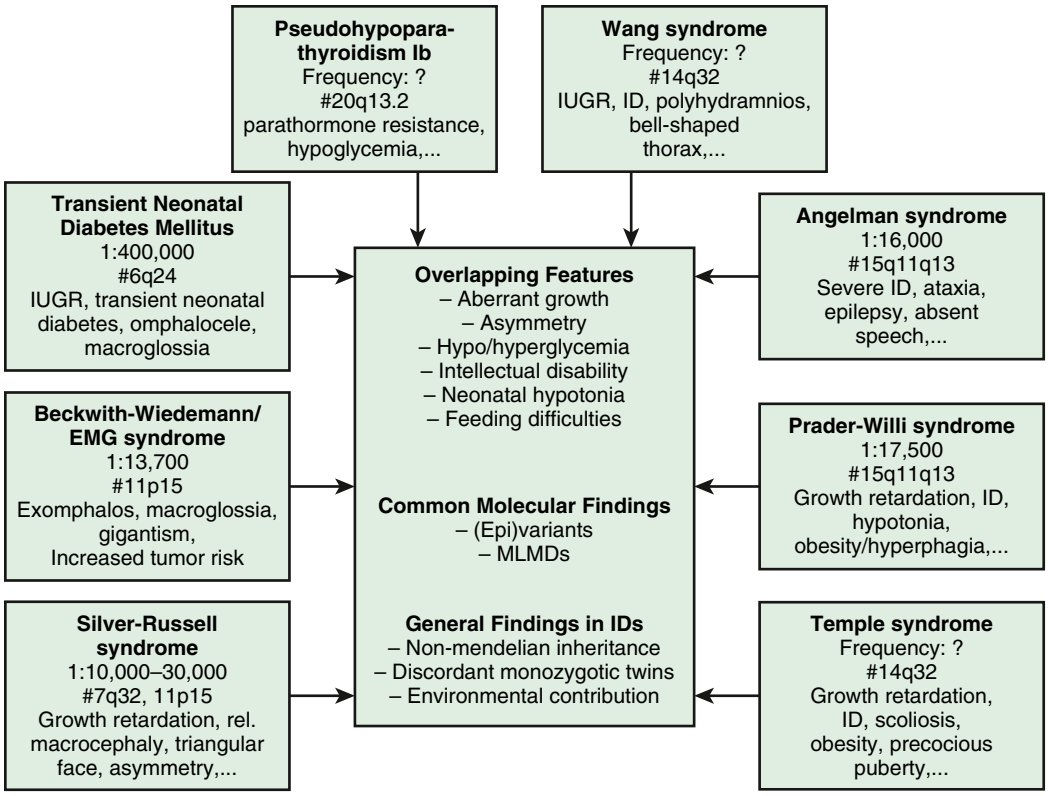

Fig. 99.11 Overview of the common clinical and molecular findings in the eight known imprinting disorders, including specific features, frequencies, and major chromosomal localization. #6q24, Chromosome 6q24; EMG, exomphalos-macroglossia-gigantism; IUGR, intrauterine growth restriction; ID, intellectual disability; MLMDs, multilocus methylation defects. *(From Eggermann T, Elbracht M, Schröder C, et al. Congenital imprinting disorders: a novel mechanism linking seemingly unrelated disorders. J Pediatr. 2013;163:1204.)*

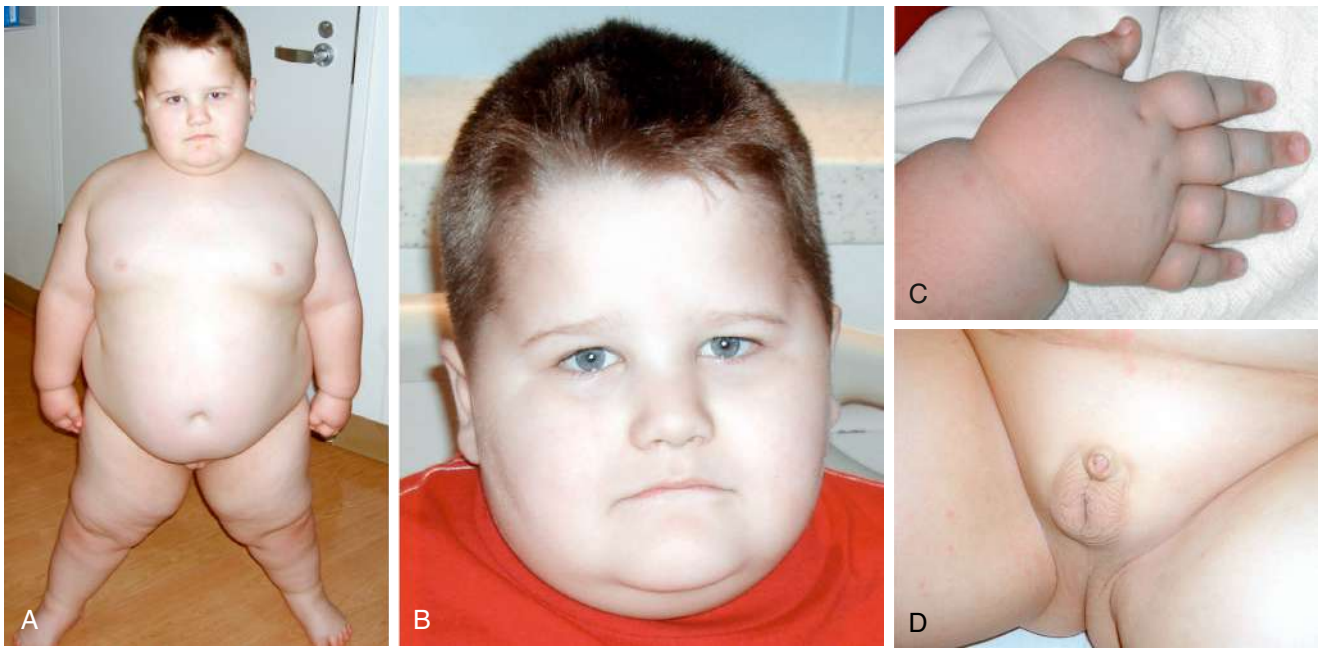

Fig. 99.12 Prader-Willi phenotype. A and B, Individual showing morbid obesity with facial features as shown. C, Upper extremities are notable for small hands relative to body size. D, External genitalia after laparoscopic orchiopexy at 13 months. Parental informed consent, as approved by the Baylor College of Medicine Institutional Review Board, was obtained to publish the photographs. *(From Sahoo T, del Gaudio D, German JR, et al. Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. Nat Genet. 2008;40:719–721.)*

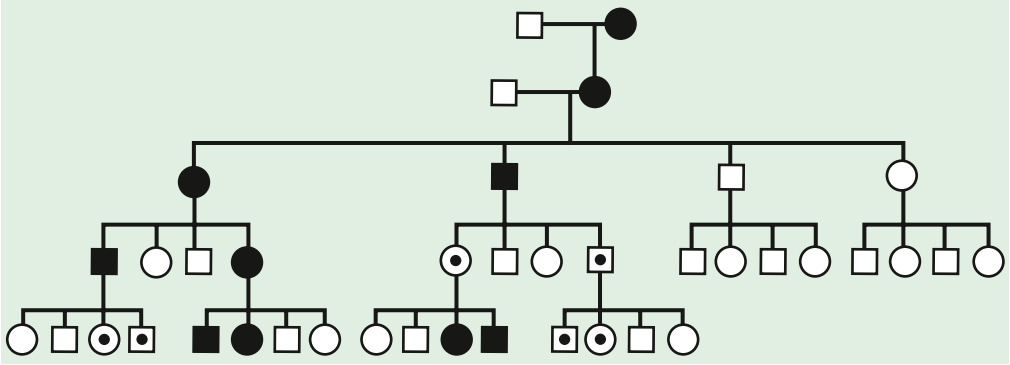

Fig. 99.13 In this hypothetical pedigree suggestive of imprinting, phenotypic effects occur only when the mutated gene is transmitted from the mother, but not when it is transmitted from the father, that is, maternal deficiency. Equal numbers of males and females can be affected and not affected phenotypically in each generation. A nonmanifesting transmitter gives a clue to the sex of the parent who passes the expressed genetic information; that is, in maternal deficiency disorders (also termed *paternal imprinting*), there are "skipped" nonmanifesting females. This is theoretical, because in most clinical scenarios of maternal deficiency, such as Angelman syndrome, affected persons do not reproduce.

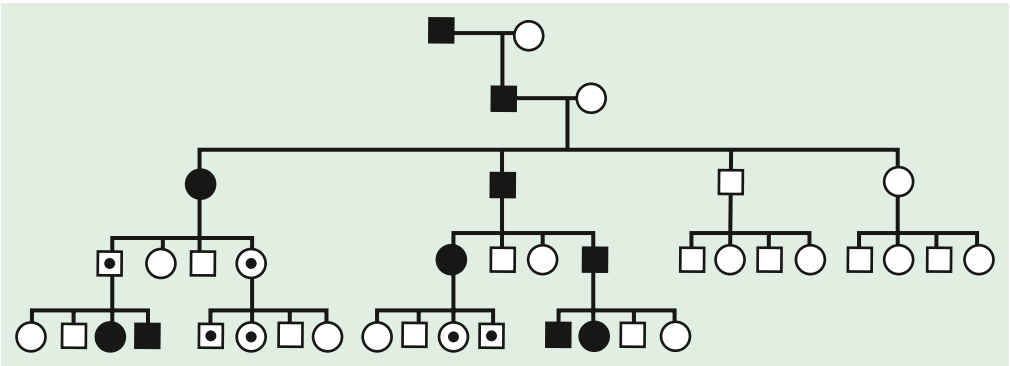

Fig. 99.14 In theoretical pedigrees suggestive of paternal deficiency (maternal imprinting), phenotypic effects occur only when the mutated gene is transmitted from the father but not when transmitted from the mother. Equal numbers of males and females can be affected and not affected phenotypically in each generation. In a theoretical situation, a nonmanifesting transmitter gives a clue to the sex of the parent who passes on the expressed genetic information; that is, in paternal deficiency (also known as *maternal imprinting*), there are "skipped" nonmanifesting males. In real-life clinical cases of Prader-Willi syndrome, affected persons do not reproduce.

Table 99.11 Consensus Diagnostic Criteria for Prader-Willi Syndrome

	MAJOR CRITERIA (1 POINT EACH)	MINOR CRITERIA (1/2 POINT EACH)
1	Neonatal/infantile hypotonia	Decreased fetal movement and infantile lethargy
2	Feeding problems and failure to thrive as an infant	Typical behavior problems
3	Weight gain at 1-6 years; obesity; hyperphagia	Sleep apnea
4	Characteristic dysmorphic facial features	Short stature for family by 15 years
5	Small genitalia; pubertal delay and insufficiency	Hypopigmentation for the family
6	Developmental delay/intellectual disability	Small hands and feet for height
7		Narrow hands, straight ulnar border
8		Esotropia, myopia
9		Thick, viscous saliva
10		Speech articulation defects
11		Skin picking

From Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med.* 2012;14(1):15. Table 2.

Table 99.12 Nutritional Phases in Prader-Willi Syndrome

PHASE	MEDIAN AGES	CLINICAL CHARACTERISTICS
0	Prenatal to birth	Decreased fetal movements and lower birthweight than siblings
1a	0-9 mo	Hypotonia with difficulty feeding and decreased appetite
1b	9-25 mo	Improved feeding and appetite and growing appropriately
2a	2.1-4.5 yr	Weight increasing without appetite increase or excess calories
2b	4.5-8 yr	Increased appetite and calories, but can feel full
3	8 yr to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

Modified from Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. *Am J Med Genet A.* 2011;155A:1040–1049.

Table 99.13 Molecular Mechanisms Causing Prader-Willi and Angelman Syndromes

	PRADER-WILLI SYNDROME	ANGELMAN SYNDROME
15q11-q13 deletion	~70% (paternal)	~70% (maternal)
Uniparental disomy	~30% (maternal)	~5% (paternal)
Single-gene pathogenic variants	None detected	*UBE3A* gene encoding the E6-AP ubiquitin-protein ligase (11% of total but mostly in familial cases)
Imprinting center pathogenic variants	5%	1%
Unidentified	<1%	10–15%

Data from Nicholls RD, Knepper JL. Genome organization, function and imprinting in Prader-Willi and Angelman syndromes. *Annu Rev Genomics Hum Genet.* 2001;2:153–175; and Horsthemke B, Buiting K. Imprinting defects on human chromosome 15. *Cytogenet Genome Res.* 2006;113:292–299.

presence of aggregates of trisomic cells might account for the spectrum of abnormalities seen in persons with some UPDs.

IMPRINTING

Genomic imprinting occurs when the phenotypic expression of a gene depends on the *parent of origin* for certain genes or chromosome regions. Whether the genetic material is expressed or not depends on the sex of the parent from whom it was derived. Genomic imprinting can be suspected in some cases on the basis of a pedigree. In these pedigrees the disease is always transmitted from the same sex and could be passed on silently for several generations by the opposite sex (Figs. 99.13 and 99.14). Imprinting probably occurs in many different parts of the human genome and is thought to be particularly important in gene expression related to development, growth, cancer, and behavior; >60 genes have been classified as imprintable. Imprinting disorders may arise from UPD, deletions or duplications, epigenetic aberrant methylation patterns, or single nucleotide pathogenic variants in a specific gene.

A classic example of imprinting disorder is seen in **Prader-Willi syndrome** and **Angelman syndrome**, two very different clinical conditions. These syndromes are both commonly caused by a deletion of the same region in the proximal long arm of chromosome 15. A deletion of the paternally derived chromosome causes Prader-Willi syndrome, in which the maternally derived copy is still intact, for which some of the imprinted genes within this region normally remain silent. Prader-Willi syndrome can be diagnosed clinically (Table 99.11) and confirmed with genetic testing. Additional clinical features and issues of weight gain are noted in Table 99.12. The weight gain is difficult to control, but treatment with growth hormone has resulted in improvements in height, lean body mass, decreased adipose tissue, and improvement in cognitive function.

A maternal deletion of the same region as in Prader-Willi syndrome causes Angelman syndrome, leaving intact the paternal copy that in this case has genes that are also normally silent. In other situations, UPD can lead to the same diagnosis (Table 99.13). Many other disorders are associated with this type of parent-of-origin effect, as in some cases of Beckwith-Wiedemann syndrome (see Chapter 598.1), Russell-Silver syndrome, and neonatal diabetes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 100

Dysmorphology, Phenotyping, and Sequences

Anne M. Slavotinek

Dysmorphology is the study of differences in human form and the mechanisms that cause them. It has been estimated that 1 in 40 newborns, or 2.5%, have a recognizable birth defect or pattern of malformations at birth; ~50% of these newborns have a single, isolated malformation, whereas in the other half, multiple malformations are present. About 20–30% of infant deaths and 30–50% of deaths after the neonatal period are caused by congenital abnormalities (http://www.marchofdimes.com/peristats/). In 2021, birth defects accounted for ~1 in 5 infant deaths in the United States, with a rate of 108.2 deaths per 100,000 live births, which was higher than other causes of mortality, such as preterm/low birthweight (80.4/100,000), sudden infant death syndrome (39.8/100,000), maternal complications of pregnancy (33.4/100,000), and unintentional injury (33.5/100,000).

CLASSIFICATION OF BIRTH DEFECTS

Birth defects can be subdivided into isolated (single) defects or multiple defects, typically described as multiple congenital anomalies (MCAs). An isolated primary defect can be classified, according to the presumed cause of the defect, as a malformation, dysplasia, deformation, or disruption (Table 100.1 and Fig. 100.1). Most birth defects are malformations, a term used interchangeably with anomalies. A malformation is a structural defect arising from a *localized* error in morphogenesis that results in the abnormal formation of a tissue or organ. Dysplasia refers to the *abnormal organization of cells* into tissues. Malformations and dysplasias can both affect the intrinsic structure of tissues and organs. In contrast, a deformation is an *alteration* in the shape or form of a structure or organ that has previously developed or differentiated normally. A disruption is a defect resulting from the *destruction* of a structure that had formed normally before the insult.

Most human disorders with altered morphogenesis display multiple anomalies or malformations rather than an isolated birth defect. When several malformations coexist in a single individual, they can be classified as a syndrome, sequence, or an association. A **syndrome** is defined as a pattern comprising multiple anomalies that are related by pathophysiology, resulting from a single, defined etiology. **Sequences** consist of multiple anomalies that are caused by a single event, although the sequence itself can have different etiologies. An **association** refers to a nonrandom grouping of anomalies in which there is an unclear, or unknown, relationship among the anomalies, such that they do not fit the criteria for a syndrome or sequence.

Malformations and Dysplasias

Human anomalies and dysplasias can be caused by pathogenic gene variants, chromosome aberrations and copy number variants, environmental factors, or interactions between genetic and environmental factors (Table 100.2). Some malformations are caused by deleterious sequence variants in single genes, whereas other anomalies arise because of deleterious sequence variants in multiple genes acting in combination, termed *digenic* or *oligogenic* inheritance. In the past, it was thought that malformations were caused by monogenic pathogenic variants in 7.5% of patients; chromosomal anomalies in 6%; multigenic pathogenic variants in 20%; and known environmental factors, such as maternal diseases, infections, and teratogens, in 6–7% (Table 100.3). In the remaining 60–70% of patients, malformations were classified as having an unknown etiology. Currently, the percentages have increased for all of the possible genetic etiologies of malformations due to improved cytogenetic and molecular genetic methods, including microarrays and single nucleotide polymorphism (SNP) arrays for detecting copy number variants, and next-generation sequencing (NGS) technologies, such as exome or genome sequencing, for identifying novel genes and pathogenic sequence variants.

Many developmental abnormalities caused by *pathogenic sequence variants* in a single gene display characteristic of mendelian patterns of inheritance such as autosomal dominant, autosomal recessive, and X-linked inheritance. Genes that cause birth defects or MCA syndromes are often transcription factors, part of evolutionarily conserved signal transduction pathways, or regulatory proteins required for key developmental events (see Chapters 101 and 102 and Table 100.2).

In addition, syndromes with MCA can be caused by chromosomal aberrations or copy number variants and teratogens (see Tables 100.2 and 100.3). **Down syndrome** typically results from an extra copy of an entire chromosome 21 or, less frequently, an extra copy of the Down syndrome critical region on chromosome 21. Chromosome 21 is a small chromosome that contains an estimated 250 genes, and thus individuals with Down syndrome typically have an increased dosage

Table 100.1 Mechanisms, Terminology, and Definitions of Dysmorphology

TERMINOLOGY	DEFINITION	EXAMPLE
Sequence	Single error in morphogenesis that results in a series of subsequent defects	Pierre-Robin sequence, in which a small jaw results in glossoptosis and cleft palate 22q11 deletion sequence of primary fourth brachial arch and third and fourth pharyngeal pouch defects, leading to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
22q11 deletion	Mechanical (uterine) force that alters structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (e.g., dislocated hips, equinovarus foot deformity), crumpled ears, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and tissue bands
Dysplasia sequence	Atypical organization of cells into tissues or organs	Neurocutaneous melanosis sequence, with atypical migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartomas of skin and meninges
Malformation syndrome	Appearance of multiple malformations in unrelated tissues that have a known, unifying cause	Trisomy 21 Teratogens Numerous multiple congenital anomaly syndromes as described above

From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004.



Fig. 100.1 Four major types of problems in morphogenesis: malformation, deformation, disruption, and dysplasia. **A,** Infant with campomelic dysplasia syndrome, which results in multiple anomalies caused by a pathogenic variant in *SOX9*. **B,** Infant with oligohydramnios deformation sequence caused by premature rupture of membranes from 17 weeks' gestation until birth at 36 weeks; the infant was delivered from a persistent transverse lie. **C,** Fetus with early amnion rupture sequence with attachment of the placenta to the head and resultant disruption of craniofacial structures with distal limb contractures. **D,** Infant with diastrophic dysplasia caused by biallelic pathogenic variants in a sulfate transporter protein. *(From Graham Jr JM. Smith's Recognizable Patterns of Human Deformation, 3rd ed. Philadelphia: Saunders; 2007, Fig. 1-1, p. 4.)*

for the genes encoded by this chromosome that causes their physical differences (see Chapter 57).

Neural tube defects (NTDs) are an example of a birth defect that typically displays multifactorial inheritance. NTDs and other birth defects, such as cleft lip and palate, can recur in families, but inheritance for the majority of affected individuals does not follow a straightforward, mendelian inheritance pattern, and multiple genes and environmental factors acting together likely contribute to the pathogenesis (see Table 100.2). Many of the genes involved in NTDs are unknown, so one cannot predict with certainty the mode of inheritance or a precise recurrence risk for an individual case. Empirical recurrence risks can be provided on the basis of population studies and the presence of single or multiple family members with the same malformation. However, one important gene/environment interaction has been identified for NTDs (see Chapter 631.1). **Folic acid deficiency** is associated with NTDs and can result from a combination of dietary factors and increased utilization during pregnancy. A common variant in the gene for an enzyme in the folate recycling pathway, 5,10-methylene-tetrahydrofolate reductase *(MTHFR)*, that makes this enzyme less stable, may also be important in folic acid status. Several teratogenic causes of birth defects have been described (see Tables 100.2 and 100.3). **Ethanol** causes a recognizable pattern of anomalies that is variably called fetal alcohol syndrome (FAS), fetal alcohol spectrum disorder (FASD), or fetal alcohol effects (FAE) (see Chapter 146). Children who were exposed to ethanol during the pregnancy can display microcephaly, developmental delays, hyperactivity, and facial anomalies. Ethanol, which is toxic to the developing central nervous system (CNS), causes cell death in developing neurons.

Deformations

Many deformations involve the musculoskeletal system (Fig. 100.2). Fetal movement is required for the proper development of the musculoskeletal system, and restriction of fetal movement can result in musculoskeletal deformations, such as clubfoot, or talipes. Two major intrinsic etiologies of deformations are **primary neuromuscular disorders** and **oligohydramnios**, or decreased amniotic fluid, which can be caused by fetal renal defects. Both primary neuromuscular disorders and oligohydramnios can compromise fetal movements. The major extrinsic causes of deformations are those that result in fetal crowding and restriction of fetal movement. Examples of extrinsic causes include oligohydramnios resulting from chronic leakage of amniotic fluid, and abnormal shape of the amniotic cavity. When a fetus is in the breech position (Fig. 100.3), the incidence of deformations is increased 10-fold. The shape of the amniotic cavity also has a profound effect on the shape of the fetus and is influenced by many factors, including uterine shape and the volume of amniotic fluid (Fig. 100.4).

It is important to determine whether deformations result from intrinsic or extrinsic causes. Most children with deformations from *extrinsic* causes are otherwise completely normal, and their prognosis is usually excellent. Correction typically occurs spontaneously. Deformations caused by *intrinsic* factors, such as multiple joint contractures resulting from CNS or peripheral nervous system defects, have a different prognosis and may be much more significant for the child (Fig. 100.5).

Disruptions

Disruptions are caused by destruction of a previously normally formed organ or body part. At least two mechanisms are known to produce disruptions. One involves entanglement followed by tearing apart, or amputation, of a normally developed structure, usually a digit or limb, by strands of amnion floating within amniotic fluid that are termed amniotic bands (Fig. 100.6). The other mechanism involves interruption to the blood supply to a developing body part, which can lead to infarction, necrosis, and resorption of structures distal to the insult. If interruption to the blood supply occurs early in gestation, the disruptive defect typically involves **atresia,** or absence of a body part. Genetic factors have been considered to play a minor role in the pathogenesis of disruptions, as most occur as sporadic events in otherwise healthy individuals, but little is known regarding etiology. The prognosis for a disruptive defect is determined entirely by the extent and location of the tissue loss.

Multiple Anomalies: Sequences, Associations, and Syndromes

The pattern of multiple anomalies that occurs when a single primary defect in early development produces multiple anomalies because of a cascade of secondary and tertiary developmental effects is called a *sequence* (Fig. 100.7). When evaluating a child with MCAs, the physician must differentiate between multiple anomalies that are caused by a single localized error in morphogenesis (a sequence) from syndromes with multiple anomalies. In the former, recurrence risk counseling for the multiple anomalies depends entirely on the risk of recurrence for the single, localized malformation. **Pierre-Robin sequence** is a pattern of multiple anomalies produced by mandibular hypoplasia. Because the tongue is relatively large for the oral cavity, it drops back (glossoptosis), blocking closure of the posterior palatal shelves and causing a U-shaped cleft palate. There are numerous causes of mandibular hypoplasia, all of which can result in the characteristic features of Pierre-Robin sequence.

VATER association was first defined as the nonrandom occurrence of a combination of congenital anomalies comprising vertebral defects,

Table 100.2 Examples of Malformations with Distinct Causes, Clinical Features, and Pathogenesis

DISORDER	CAUSE/INHERITANCE	SELECTED CLINICAL FEATURES	PATHOGENESIS
Spondylocostal dysostosis syndrome	Mendelian; autosomal recessive	Abnormal vertebral and rib segmentation	Deleterious sequence variants in *DLL3* and other genes
Rubinstein-Taybi syndrome	Autosomal dominant	Intellectual disability Broad thumbs and halluces; valgus deviation of these digits Hypoplastic maxillae Prominent nose and columella Congenital heart disease	Deleterious sequence variants in *CBP* and *EP300*
X-linked lissencephaly	X-linked	Male: severe intellectual disability, seizures Female: variable	Deleterious sequence variants in *DCX*
Aniridia	Autosomal dominant	Absent iris or iris/foveal hypoplasia	Deleterious sequence variants in *PAX6*
Waardenburg syndrome, type I	Autosomal dominant	Deafness White forelock Wide-spaced eyes Iris heterochromia and/or pale skin pigmentation	Deleterious sequence variants in *PAX3*
Holoprosencephaly	Loss of function or haploinsufficiency for multiple genes	Microcephaly Cyclopia Single central incisor	*SHH,* multiple other genes
Velocardiofacial syndrome	Microdeletion 22q11.2	Congenital heart disease, including conotruncal defects Cleft palate T-cell defects Facial anomalies	*TBX1* haploinsufficiency/ pathogenic variants; haploinsufficiency for other genes in the deleted interval also contributes to the phenotype
Down syndrome	Additional copy of chromosome 21 (trisomy 21)	Intellectual disability Characteristic facial anomalies Congenital heart disease Increased risk of leukemia Alzheimer disease	Increase in dosage of an estimated 250 genes on chromosome 21
Neural tube defects	Multifactorial	Meningomyelocele	Defects in folate sensitive enzymes or folic acid uptake
Fetal alcohol syndrome	Teratogenic	Microcephaly Developmental delay Facial anomalies Behavioral abnormalities	Ethanol toxicity to developing brain
Retinoic acid embryopathy	Teratogenic	Microtia Congenital heart disease	Isotretinoin effects on neural crest and branchial arch development

anal atresia, tracheoesophageal fistula (TEF) with esophageal atresia, radial anomalies, and renal dysplasia. The association was expanded to include cardiac anomalies (C) and limb anomalies (L), leading to the longer acronym, **VACTERL**. Although there are still no definitively established diagnostic criteria, most clinicians consider that a minimum of three of the seven component features must be present for the diagnosis. In addition, the designation of VATER/VACTERL association is typically one of exclusion; *growth and developmental delays as well as facial anomalies are atypical and should prompt the consideration of alternative diagnoses.* Anorectal defects and TEF are considered more characteristic of VATER/VACTERL association than some of the other components, such as cardiac anomalies. A single umbilical artery is a common finding. The estimated incidence of VATER/VACTERL has ranged from 1 in 10,000 to 1 in 40,000 infants. VACTERL with hydrocephalus, also known as VACTERL-H, is a separate condition.

VATER/VACTERL association has so far defied the identification of a simple mendelian etiology. Many cases are sporadic, although there are rare reports of familial inheritance and first-degree relatives with clinical findings in the component systems of VATER/VACTERL association. Hedgehog signaling has been postulated to be important, as mouse models with defective Hedgehog and/or ciliary signaling manifest the clinical findings observed in VATER/VACTERL. However, cytogenetic studies have not demonstrated chromosome aberrations or copy number variants. Exome sequencing (ES) has not identified a single causative gene or gene family, although nonrecurrent variants have been described in mendelian disease genes, most typically in patients with renal involvement. Clinical overlap has led to the identification of pathogenic variants in the *SALL1*, *SALL4,* and *MID1* genes in patients with anorectal malformations.

Pathogenic variants in several autosomal recessive genes in the **kynurenine pathway**, including *KYNU*, *HAAO,* and *NADSYN1*, have been associated with a spectrum of anomalies that overlap with VATER/VACTERL association, including vertebral defects, cardiac anomalies, renal malformations, and limb defects of variable severity. Biallelic variants in these genes perturb the synthesis of nicotinamide adenine dinucleotide (NAD) synthesis; these conditions have been grouped together as **congenital NAD deficiency disorders.** The overall contribution of these genes to the pathogenesis of VATER/VACTERL association appears to be small in terms of the entire group of patients but remains an important diagnostic consideration. Interestingly, studies in mice with biallelic

Table 100.3 Causes of Congenital Malformations

MONOGENIC
X-linked hydrocephalus
Achondroplasia
Ectodermal dysplasia
Apert syndrome
Treacher Collins syndrome
CHROMOSOMAL ABERRATIONS AND COPY NUMBER VARIANTS
Trisomy 21, 18, 13
XO, XXY
Deletions 4p−, 5p−, 7q−, 13q−, 18p−, 18q−, 22q−
Prader-Willi syndrome (70% of affected patients have deletion of chromosome 15q11.2-q13)
MATERNAL INFECTION
Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, Zika virus, toxoplasmosis)
MATERNAL ILLNESS
Diabetes mellitus
Phenylketonuria
Hyperthermia
UTERINE ENVIRONMENT
Deformation
Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, seventh nerve palsy
Disruption
Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia
Twinning
ENVIRONMENTAL AGENTS
Polychlorinated biphenyls
Herbicides
Mercury
Alcohol
MEDICATIONS
Thalidomide
Diethylstilbestrol
Phenytoin
Warfarin
Cytotoxic drugs
Paroxetine
Angiotensin-converting enzyme inhibitors
Isotretinoin (vitamin A)
D-Penicillamine
Valproic acid
Mycophenolate mofetil
UNKNOWN ETIOLOGIES
Neural tube defects, such as anencephaly and spina bifida
Cleft lip/palate
Pyloric stenosis
SPORADIC SEQUENCE COMPLEXES
VATER/VACTERL sequence (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with esophageal atresia, radial and renal anomalies)
Pierre-Robin sequence
NUTRITIONAL
Neural tube defects due to low folic acid

From Behrman RE, Kliegman RM, eds. *Nelson's Essentials of Pediatrics*, 4th ed. Philadelphia: Saunders; 2002.

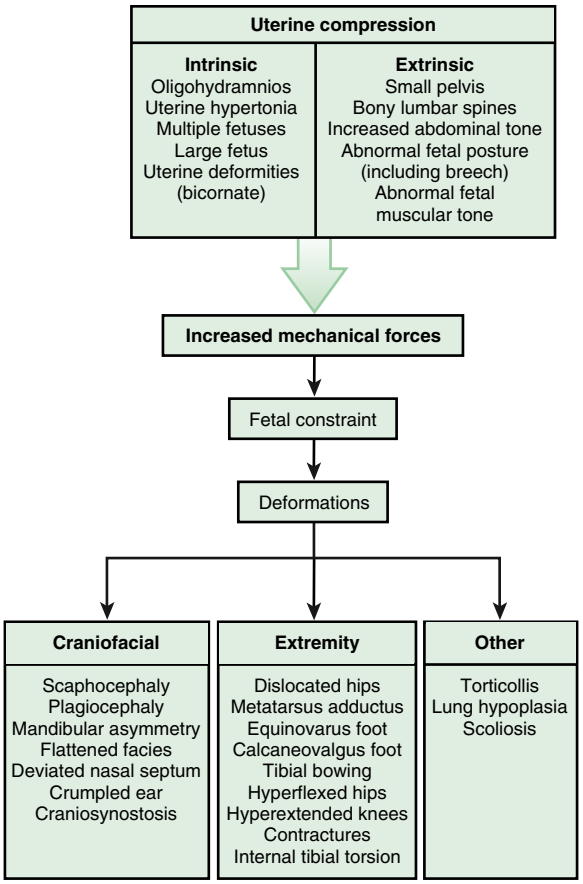

Fig. 100.2 Deformation abnormalities resulting from uterine compression. *(From Kliegman RM, Jenson HB, Marcdante KJ, et al., eds.* Nelson Essentials of Pediatrics, *5th ed. Philadelphia: Saunders; 2005.)*



Fig. 100.3 Breech deformation sequence.

loss-of-function variants in *Haao* and *Kynu* that were provided with niacin in their diet showed that the vitamin can overcome the metabolic block associated with loss-of-function for these genes. Niacin enters the NAD biosynthesis pathway downstream to *Haao* and *Kynu*, and this finding implies that the availability of niacin and other components of the kynurenine pathway can influence NAD levels during pregnancy and consequently the clinical severity resulting from the variants affecting some of the genes involved in NAD synthesis. These conditions outline the importance of considering the influence of environmental factors on the phenotype caused by genetic variation.

MOLECULAR MECHANISMS OF MALFORMATIONS

Inborn Errors of Development

Genes that cause malformation syndromes, as well as genes whose expression is disrupted by environmental agents or teratogens, can participate in numerous cellular processes, including signal transduction, transcription, or the regulation of genes and proteins required for key developmental events. When anomalies are viewed as alterations resulting from disturbances to important developmental pathways, this provides a molecular framework for understanding the birth defects (see Chapter 101).

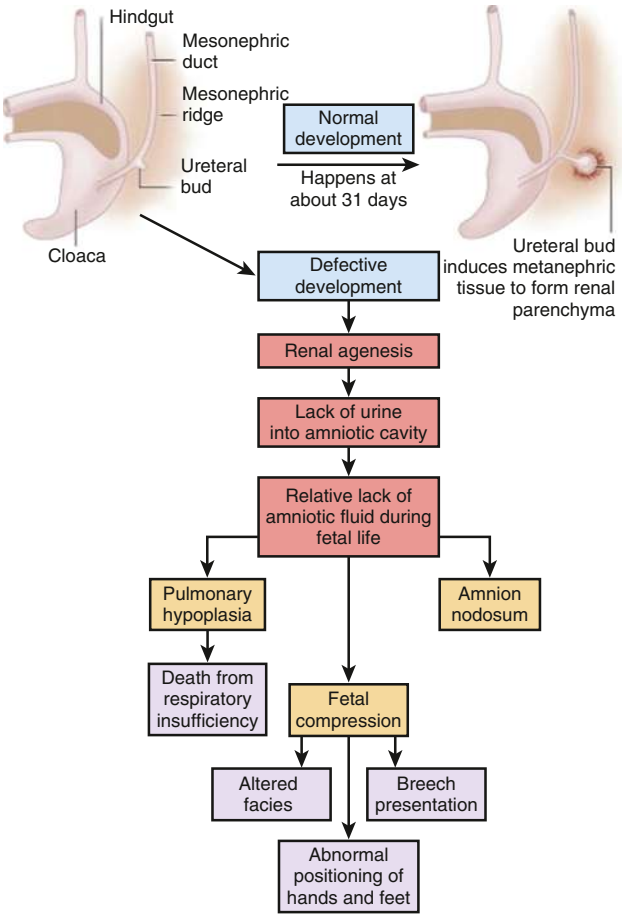



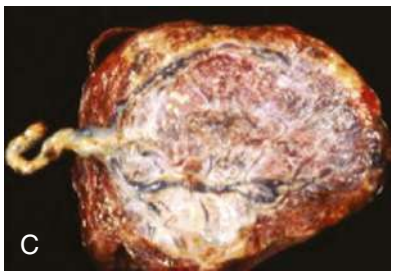

Fig. 100.4 A, Consequences of renal agenesis. B, Multiple deformational defects. C, Defects in amnion nodosum; brown-yellow granules from vernix have been ribbed into defects of the amniotic surface. *(From Jones KL, Jones MC, Del Campo M, eds. Smith's Recognizable Patterns of Human Malformation, 7th ed. Philadelphia: Elsevier; 2013: p. 821.)*

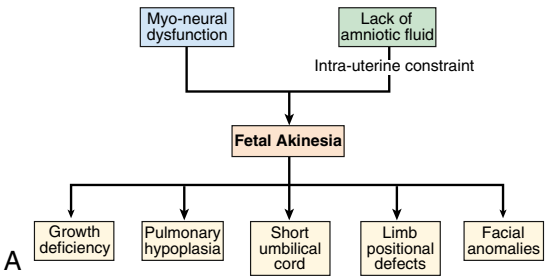



Fig. 100.5 A, Diagram demonstrating the etiologically heterogeneous phenotype that results from fetal akinesia. B, Infant born with myotonic dystrophy to a mother with the same condition. He had multiple joint contractures with thin bones and respiratory insufficiency. C, Infant immobilized in a transverse lie after amnion rupture at 26 weeks. D, Fetus with bilateral renal agenesis resulting in oligohydramnios. *(From Graham JL. Smith's Recognizable Patterns of Human Malformation, 3rd ed. Philadelphia: Elsevier; 2007: Fig. 47-2.)*

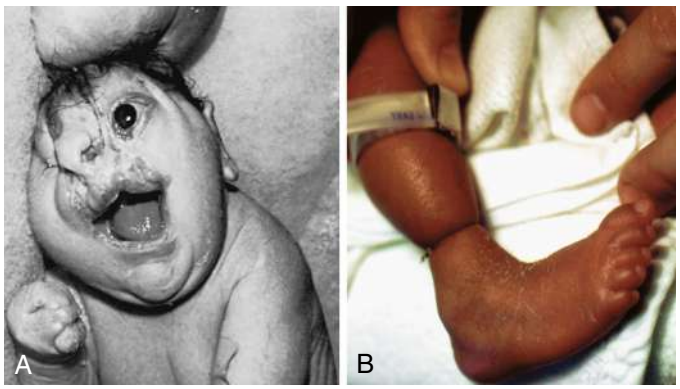

Fig. 100.6 A, Amniotic band disruption sequence. B, Bands constricting the ankle leading to deformational defects and amputations. *(From Jones KJ. Smith's Recognizable Patterns of Human Malformation, 6th ed. Philadelphia: Saunders; 2006.)*

It is important to consider MCA syndromes as members of a group based on shared or overlapping clinical findings and related causative genes that act in the same developmental or metabolic pathway. See Chapter 101 for the Sonic Hedgehog disorders, RASopathies, craniosynostoses, and chromatin regulatory disorders as examples; disruption of specific steps in this pathway result in a variety of related developmental disorders and anomalies (see Fig. 100.2).

Cytogenetic Aberrations and Chromosomal Imbalance

Cytogenetic imbalances resulting from an additional copy of a whole human chromosome can result in characteristic and recognizable

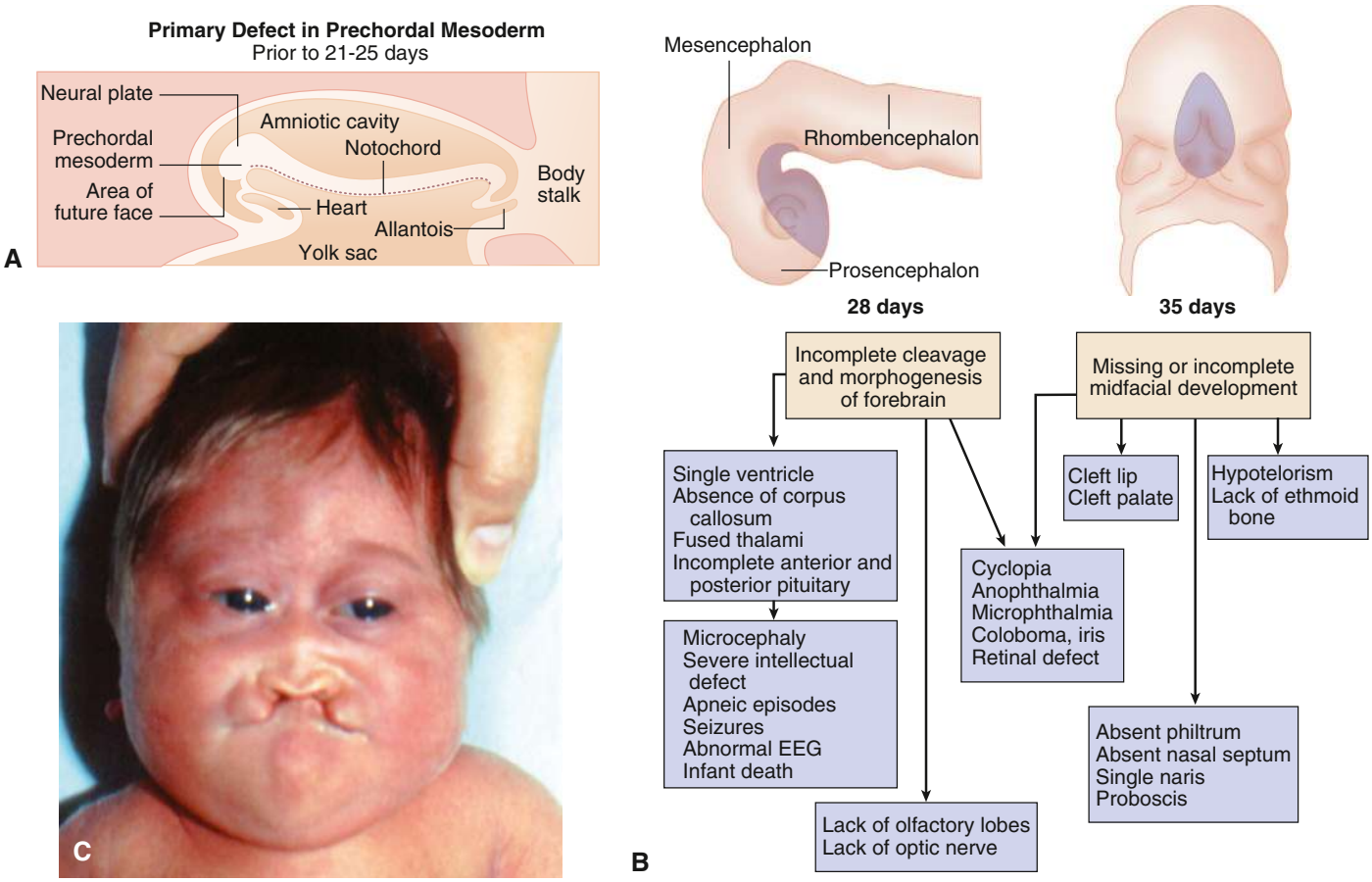

Fig. 100.7 Holoprosencephaly sequence. **A**, Schematic longitudinal section of 21-day embryo. **B**, Developmental pathogenesis of the sequence. **C**, Affected individual. *(From Jones KL, Jones MC, Del Campo M, eds.* Smith's Recognizable Patterns of Human Malformation*, 7th ed. Philadelphia: Elsevier; 2013: pp. 802–803.)*

syndromes. An additional copy of chromosome 21 results in **Down syndrome** (see Chapter 57); loss of one of the X chromosomes results in **Turner syndrome** (see Chapter 99.2 for discussion of syndromes with whole chromosomal imbalances). With the advent of high-resolution cytogenetic techniques, such as fluorescence in situ hybridization (FISH), array comparative genomic hybridization (array CGH), and SNP arrays, it has become straightforward to identify **submicroscopic chromosome deletions and duplications**. Several recurrent chromosome deletions and duplications have been identified as the cause of characteristic and recognizable syndromes (see Table 100.6 and Chapter 99), including **Williams syndrome** (deletion of chromosome 7q11.23), **Miller-Dieker syndrome** (deletion of chromosome 17p13.3), **Smith-Magenis syndrome** (deletion of chromosome 17p11.2), and 22q11 deletion syndrome (deletion of chromosome 22q11.2, also known as **velocardiofacial syndrome**). Collectively, chromosome microarrays (CMAs) and genetic sequencing have made it possible to uncover rare microdeletions, microduplications, and single nucleotide pathogenic variants associated with birth defects, intellectual disability, and neuropsychiatric disorders. The sensitivity and specificity of microarrays made them a standard starting point for the evaluation of a child with MCAs and intellectual disabilities, but exome, genome, and gene panel testing have been preferred due to higher diagnostic yield. It is important to note that unaffected individuals may carry small microdeletions and microduplications as part of familial variation. Therefore it is important to compare copy number variants that are identified in children with birth defects or developmental delays with their parents' chromosome analyses and with databases of normal variants detected in individuals without such birth defects.

APPROACH TO THE CHILD WITH FACIAL ANOMALIES

One approach to the child with facial anomalies is the *pattern recognition* approach, which compares the physical differences in the patient against a broad and memorized (or computerized) knowledge of human disorders. This approach can be appropriate for experienced dysmorphologists and clinical geneticists. In conjunction, a systematic *genetic mechanism* approach can also be effective for clinicians who are not dysmorphology experts. By gathering and analyzing the clinical data, the general pediatrician can diagnose the patient in a straightforward case or initiate a referral to an appropriate specialist.

Medical History

The history for a patient with birth defects includes elements related to etiologic factors. The family history, or *pedigree*, is necessary to assess the inheritance pattern, or lack thereof, for a disorder. For disorders that have a simple mendelian inheritance pattern, recognition of the mode of inheritance can be critical for narrowing the differential diagnosis, then prioritizing common genes with the appropriate inheritance pattern that could cause the patient's clinical features. Many common birth defects have a complex, or multifactorial, genetic etiology, such as isolated cleft palate and spina bifida or NTDs. The recognition of a close relative affected with a birth defect similar to the proband's findings can be useful. Typically, a three-generation pedigree is sufficient for this purpose (see Chapter 97).

The perinatal history is also an essential component of the history. It includes the pregnancy history of the mother, which can be useful for recognition of recurrent miscarriages that may be indicative of a chromosomal disorder, factors that may relate to deformations or disruptions such as oligohydramnios, and maternal exposures to teratogenic drugs or chemicals, including isotretinoin and ethanol, that are potential causes of microcephaly.

Another component of the history that is often useful is the natural history of the **phenotype**. MCA syndromes caused by chromosomal aberrations and single-gene disorders are frequently *static*, meaning that, although the patients can experience new complications over

Table 100.4 Definitions of Common Clinical Signs of Syndromes with Facial Anomalies

SIGN	DEFINITION
Brachycephaly	A condition in which head shape is shortened from front to back along the sagittal plane; typically the back of the skull (occiput) and face are flatter than normal.
Brachydactyly	Short digits.
Brushfield spots	Speckled white spots or rings about two-thirds of the distance to the periphery of the iris of the eye.
Camptodactyly	Permanent flexion of one or more fingers that can be associated with missing interphalangeal creases.
Clinodactyly	A medial or lateral curving of the fingers or toes; usually refers to incurving of the fifth finger.
Hypoplastic or small nail	A small nail on a digit.
Low-set ears	This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi.
Melia	A suffix meaning "limb" (e.g., amelia, missing limb; brachymelia, short limb).
Wide-set eyes	Increased distance between the center of the pupils of the two eyes; can be measured as an *increased interpupillary distance* (IPD).
Plagiocephaly	A condition in which head shape is asymmetric in the sagittal or coronal plane; can result from asymmetry in cranial suture closure, asymmetry of brain growth, or deformation of the skull.
Posterior hair whorl	A single hair whorl occurs to the right or left of midline and is within 2 cm anterior to the posterior fontanel in 95% of cases.
Postaxial polydactyly	Extra finger or toe present on the lateral side of the hand or foot.
Preaxial polydactyly	Extra finger or toe present on the medial side of the hand or foot.
Prominent lateral palatine ridges	Relative overgrowth of the lateral palatine ridges that can be caused by a deficit of tongue thrust into the hard palate.
Scaphocephaly	A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic; also termed *dolichocephaly*.
Shawl scrotum	The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds.
Short palpebral fissures	Decreased horizontal distance of the eyelid folds based on measurements from the inner canthus to the outer canthus.
Syndactyly	Incomplete separation of the fingers or toes. It most commonly occurs between the third and fourth fingers and between the second and third toes.
Synophrys	Eyebrows that meet in the midline.
Telecanthus	Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the IPD is normal.
Widow's peak	V-shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periocular hair growth suppression. A widow's peak can occur together with wide-spaced eyes.

time, the phenotype is typically not progressive. In contrast, disorders that cause facial anomalies because of metabolic perturbations, for example, Hunter syndrome or Sanfilippo syndrome, can be mild or may not be apparent at birth, but can progress, causing deterioration of patient status over time.

Physical Examination

The physical examination is very important for identifying anomalies that can aid a genetic diagnosis. The essential element of the physical evaluation is an assessment of the patient's clinical findings, with the clinician performing an organized evaluation of the size and formation of various body structures. Familiarity with the terminology typically used to describe anomalies is helpful (Table 100.4). The size and shape of the head is relevant; for example, many children with Down syndrome have mild microcephaly and a shortened anteroposterior dimension of skull, termed brachycephaly. Eye position, shape, and the slant of the palpebral fissures are useful signs for many disorders. Reference standards are available with which physical measurements (e.g., interpupillary distance) can be compared. It can be useful to categorize anomalies as "major" or "minor" birth defects. Major defects either cause significant dysfunction or require surgical correction (see Table 100.5), and minor defects neither cause significant dysfunction nor require surgical correction (e.g., clinodactyly) (Table 100.6 and Fig. 100.8). By cataloging physical parameters, the clinician may be able to identify a characteristic pattern of anomalies and recognize the diagnosis. Facial recognition software has been helpful in identifying the etiology of patients with facial dysmorphology (Fig. 100.9).

Imaging Studies

Imaging studies can be critical in diagnosing an underlying genetic etiology. If short stature or disproportionate stature (e.g., long trunk and short limbs) is noted, a full skeletal survey with radiographs should be performed. The skeletal survey can detect anomalies in bone number, structure, and formation that can be used to narrow the differential diagnosis. When there are abnormal neurologic signs or symptoms, such as hypotonia, and an abnormal head size, such as microcephaly, brain imaging can be indicated. Other studies and examinations, such as echocardiography, renal ultrasonography, and hearing and ophthalmology evaluation, can also be useful to identify additional major or minor anomalies that may serve as diagnostic clues.

Table 100.5 Major Malformations*

NEUROLOGIC
Severe hydrocephalus
Lissencephaly
Schizencephaly
Megalencephaly
Neural tube defect
Meningomyelocele
Encephalocele

CARDIOVASCULAR
Various congenital heart malformations
Cardiomyopathy
Genetic arrhythmia syndromes

GENITOURINARY
Ambiguous genitalia
Kidney malformations
Urachal defects

RESPIRATORY
Congenital pulmonary airway malformation
Tracheoesophageal fistula

ABDOMINAL WALL
Gastroschisis
Omphalocele

CRANIOFACIAL
Craniosynostosis
Facial cleft
Cleft lip and palate
Structural eye defect
Coloboma
Aniridia
Structural ear defects
Microtia
Aplasia of the auditory canal

LIMB
Amelia
Split/hand foot malformation

*Not an inclusive list.
From Basel D. Dysmorphology in a genomic era. *Clin Perinatol.* 2020;47:15–23. Table 1.

Table 100.6 Minor Malformations*

CRANIOFACIAL
Large fontanel
Flat or low nasal bridge
Saddle nose, upturned nose
Micrognathia
Cutis aplasia of the scalp

EYE
Palpebral fissures
Telecanthus or epicanthus
Up or down slanting
Hypertelorism
Brushfield spots

EAR
Posteriorly rotated pinna
Lack of helical fold
Preauricular with or without auricular skin tags
Small pinna
Auricular (preauricular) pit or sinus
Folding of helix
Darwinian tubercle
Crushed (crinkled) ear
Asymmetric ear sizes
Low-set ears

SKIN
Dimpling over the bones
Capillary hemangioma (face/posterior neck)
Dermal melanosis (African, Asian)
Sacral dimple
Pigmented nevi
Redundant skin folds
Cutis marmorata
Café-au-lait macules

HAND
Simian crease
Bridged upper palmar creases
Fifth finger clinodactyly
Joint hypermobility (hyperextension of thumb)
Cutaneous syndactyly
Polydactyly
Short, broad thumb
Narrow or hyperconvex nails
Hypoplastic nails
Camptodactyly
Short fourth metacarpal

FOOT
Syndactyly of second/third toe
Asymmetric toe length
Clinodactyly of second toe
Overlapping toes
Nail hypoplasia
Wide gap between hallux and second toe
Deep plantar crease between hallux and second toe

OTHER
Mild calcaneovalgus
Hydrocele
Shawl scrotum
Hypospadias
Hypoplasia of labia majora
Supernumerary nipples
Undescended testes
Tongue tie

*Not an inclusive list.
From Basel D. Dysmorphology in a genomic era. *Clin Perinatol.* 2020;47:15–23. Table 2.

Diagnosis

The examining physician should gather data on the patient's pedigree and perinatal and pediatric history and should have an appreciation for the natural history of the clinical findings. At this point, the physician has examined the child, identified atypical physical features, and obtained appropriate imaging studies.

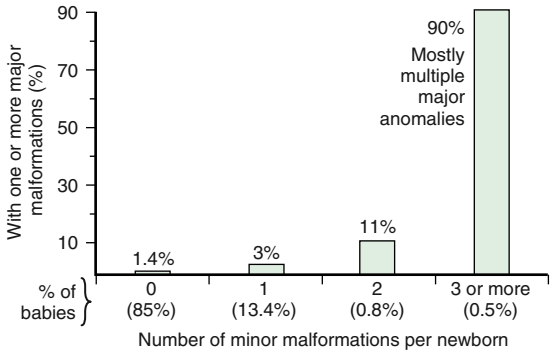

Fig. 100.8 Frequency of major malformations in relation to the number of minor anomalies detected in a given newborn baby. *(From Jones KJ. Smith's Recognizable Patterns of Human Malformation, 6th ed. Philadelphia: Saunders; 2006.)*

The clinician should now attempt to organize the findings to elucidate potential developmental processes. An assessment based on **specificity** can be helpful for this process. If a child has multiple findings, such as a patent ductus arteriosus (PDA), mild growth restriction, mild microcephaly, and holoprosencephaly, micropenis, and ptosis, a selection of the rarer or pathognomonic findings may be prioritized. The PDA, ptosis, mild growth restriction, and mild microcephaly are considered *nonspecific findings*, as they are present in many disorders or often present as isolated features that are not part of a syndrome. However, holoprosencephaly and micropenis are present in fewer syndromes and are not considered part of normal variation. The clinician can therefore search for disorders that include both holoprosencephaly and micropenis. The search can be performed manually using the features index of a textbook such as *Smith's Recognizable Patterns of Human Malformation* or a computerized database such as Online Mendelian Inheritance in Man (OMIM). Searching for both holoprosencephaly and micropenis returns a list of diagnostic possibilities, and the physician can then return to the patient to examine for additional features of the leading possible candidate disorders. Appropriate genetic testing can then be undertaken to confirm the clinician's hypothesis and verify the diagnosis. Alternatively, broad genetic testing can be undertaken if the patient's clinical findings are nonspecific.

Laboratory Studies and Genetic Testing

The laboratory evaluation of a child with anomalies can be critical to reach or confirm the correct diagnosis, particularly for metabolic conditions. Array CGH and SNP arrays enable the detection of chromosome abnormalities and copy number variants and, in the case of SNP arrays, evaluation for loss of heterozygosity. Chromosome deletion syndromes may also be identified with specific and sensitive FISH analysis, although this technology has been largely replaced by chromosome arrays and NGS sequencing. Cytogenetic studies with Giemsa-banded (G-banded) chromosome analysis are still useful for the diagnosis of Down syndrome and balanced translocations (Table 100.7). These tests are sensitive methods for the detection of cytogenetic alterations associated with birth defects and MCAs. Cytogenetic alterations can also be detected by whole genome sequencing that is becoming increasingly utilized.

Molecular testing for deleterious sequence variants that cause pleiotropic malformation syndromes is also available for many disorders as clinical testing. In most cases, however, such testing should not be performed indiscriminately; instead, it should be ordered thoughtfully after a differential diagnosis has been considered. *NGS with ES and whole genome sequencing has led to the identification of innumerable novel genes and revolutionized the testing that is available for patients and families with intellectual disability, birth defects, and other genetic diseases.* A strong suspicion of a genetic diagnosis warrants consideration of testing to confirm the diagnosis, facilitate patient treatment and anticipatory guidance, clarify recurrence risks, and enable carrier testing for additional family members. Single genes can still be tested by *Sanger sequencing* that targets single or multiple exons. However,

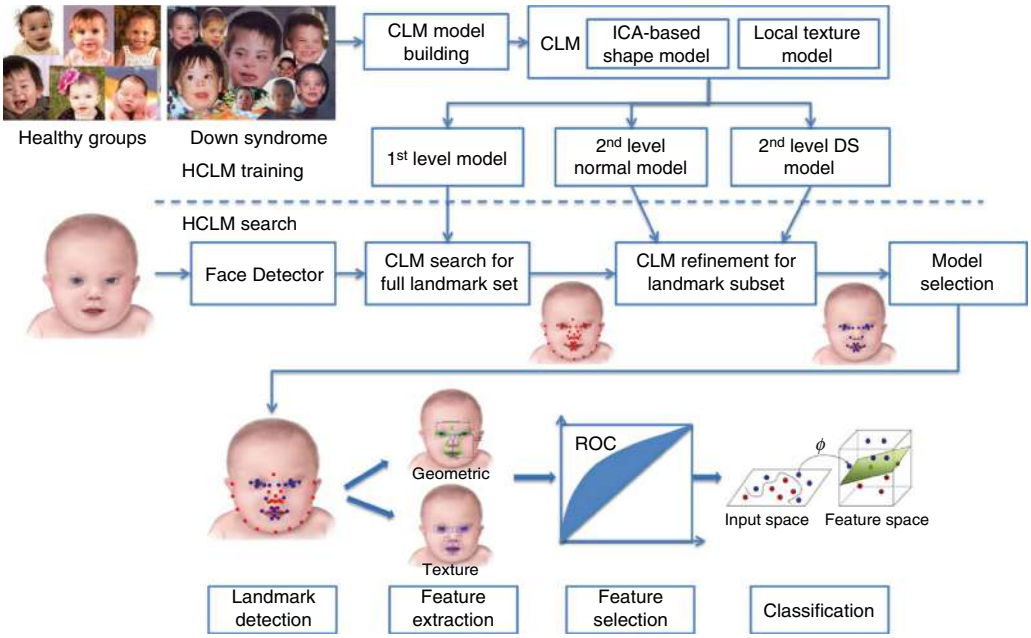

Fig. 100.9 The Framework of Facial Recognition for Genetic Syndrome Detection. ICA, Independent component analysis; CLM, constrained local model; HCLM, hierarchical CLM; DS, Down syndrome; ROC, receiver operating characterstics. *(From Zhao Q, Okada K, Rosenbaum K, et al. Digital facial dysmorphology for genetic screening: hierarchical constrained local model using ICA.* Med Image Anal. *2014;18:699–710. Fig. 2.)*

Table 100.7 Chromosomal Deletion Syndromes

CONDITION	BRIEF DESCRIPTION	PROBE
Williams syndrome	Proportionate short stature, mild-moderate to severe intellectual disability, friendly personality, stellate pattern of iris pigmentation, supravalvular aortic stenosis, wide mouth with full lips	7q11
WAGR syndrome	Wilms tumor, aniridia, growth delay, intellectual disability, and genitourinary anomalies	11p13
Prader-Willi syndrome Angelman syndrome	Distinct syndromes with common or overlapping areas of deletion; phenotype depends on gender of the parent of origin of the deletion Prader-Willi syndrome: hypotonia in infancy, short stature, obesity, mild-moderate and occasionally severe intellectual disability, small hands and feet (caused by paternal deletion of 15q11-13 or maternal uniparental disomy for chromosome 15) Angelman syndrome: severe intellectual disability, absence of speech, ataxia, tremulous movements, large mouth, frequent drooling (caused by maternal deletion of chromosome 15q11-13 or paternal uniparental disomy)	15q11
Smith-Magenis syndrome	Brachycephaly, prognathism, self-destructive behavior, wrist biting, pulling out nails, head banging, indifference to pain, intellectual disability, hyperactivity	17p11.2
Miller-Dieker syndrome	Microcephaly, narrow temples, hypotonia/hypertonia, abnormal posturing, seizures, severe to profound intellectual disability, poor growth, lissencephaly and other brain abnormalities on CT or MRI	17p13
22q11 deletion syndrome	Cleft palate, congenital heart disease, learning/behavior problems, long face, prominent nose, limb hypotonia, slender hands with tapering fingers, T-cell deficiency, immunoglobulin deficiency	22q11

WAGR, Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.
From Kliegman RM, Lye PS, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, Philadelphia: Elsevier; 2018: Table 25-10.

for diagnoses that have substantial genetic heterogeneity (e.g., hearing loss), *panel testing* often using NGS, in which multiple relevant genes can be interrogated for single nucleotide variants and gene deletions and duplications, is more expeditious than single-gene testing. Panel tests also frequently have the advantage of providing high coverage for the genes on the panel compared with the coverage for the same genes that can be obtained by ES. However, in situations with diagnostic uncertainty, such as the investigation of a child with intellectual disability and facial anomalies for which there is no clearly recognizable pattern, **exome** or **genome sequencing (GS)** may be most useful as a broad testing approach. ES examines approximately 200,000 exons, or the 1–2% of the DNA that comprises the coding regions of the genome. ES is typically performed with a *trio* approach, in which the patient and both biological parents are tested simultaneously, so that the inheritance pattern, or segregation, of deleterious sequence variants can be determined, thus simplifying analysis. Trio sequencing has resulted in higher diagnostic yields than proband-only sequencing and can approach 30–40% for indications such as intellectual disability. In contrast, GS examines the entire DNA content, including noncoding regions, and increasingly enables analysis for cytogenetic rearrangements in addition to copy number loss or gain. ES and GS are applicable to a wide range of birth defects and genetic diseases and can discover causative variants in known or novel genes associated with a particular condition.

Management and Counseling

Management and genetic counseling are essential aspects of the approach to a patient with a genetic disorder. For example, children with Down syndrome have a high incidence of hypothyroidism, and children with achondroplasia have a high incidence of cervicomedullary

junction abnormalities and monitoring for both is appropriate. One of the many benefits of an early and accurate diagnosis is that **anticipatory guidance and medical monitoring** of patients for syndrome-specific medical risks can improve their quality of life and prolong it. When a diagnosis is made, the treating physicians can access published information on the natural history and management of the disorder through the medical literature, genetics reference texts, and databases. Providing access to disorder-specific patient support groups can also provide immense benefit to patients and families.

The second major benefit of an accurate diagnosis is that it provides data for **recurrence risk** estimates. Genetic disorders may have direct effects on only one member of the family, but the diagnosis of the condition can have implications for the entire family. One or both parents may be carriers, and siblings may be carriers or may want to know their genetic status when they reach their reproductive years. Recurrence risk provision is an important component of genetic counseling and should be included in all evaluations for families affected with birth defects or other inherited disorders (see Chapter 98).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

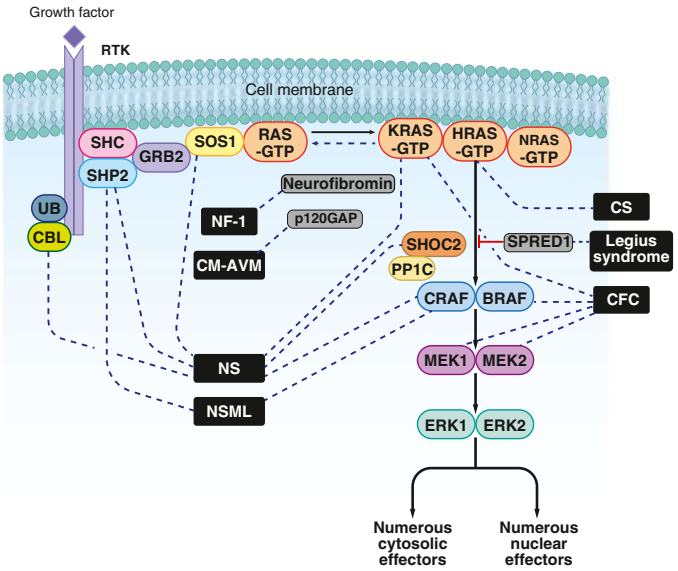

Fig. 101.1 The RAS/MAPK signal transduction pathway. The MAPK signaling pathway of protein kinases is critically involved in cellular proliferation, differentiation, motility, apoptosis, and senescence. The RASopathies are patterns of anomalies caused by pathogenic variants in genes that encode components or regulators of the RAS/MAPK pathway (indicated by *dashed lines*). These disorders include neurofibromatosis type one (NF1), Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), capillary malformation–arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardiofaciocutaneous syndrome (CFC), and Legius syndrome. RAS/MAPK, RAS protein family/mitogen-activated protein kinase. (*From Rauen KA. The RASopathies. Annu Rev Genom Hum Genet. 2013;14:355–369.*)

Chapter 101

Signaling Pathway Disorders

Chad R. Haldeman-Englert and Anne M. Slavotinek

An increasing number of defined molecular genetic etiologies explain many multiple congenital anomaly (MCA) syndromes. Several themes have emerged: (1) many clinical disorders that were believed to represent a single entity have multiple genetic etiologies, often within genes that are functionally related; (2) many disorders believed to be distinct have common underlying genetic bases; and (3) teratogens and genetic disorders with similar clinical features can often be understood in the context of shared underlying pathology.

It is useful to consider MCA syndromes as members of a group of disorders based on shared or overlapping clinical findings and related causative genes that act in the same developmental or metabolic pathway.

101.1 RAS/MAPK Pathway

Chad R. Haldeman-Englert and Anne M. Slavotinek

The RASopathies comprise a clinically defined group of conditions caused by germline pathogenic variants in genes encoding the components or regulators of the renin-angiotensin system (RAS)/mitogen-activated protein kinase (MAPK) pathway. This pathway is one of the most important signaling pathways in human development (Fig. 101.1). Signaling is initiated when one of several growth factors or cytokines binds extracellularly to a transmembrane receptor tyrosine kinase (RTK), which transmits the signal to activate of one of several intracellular RAS proteins, such as HRAS, KRAS, or NRAS. Phosphorylation then occurs in a stepwise manner to one or more RAF proteins (ARAF, BRAF, and/or CRAF), and subsequently to MEK1 and/or MEK2, and then ERK1 and/or ERK2. Activation of ERK1/2 has downstream targets including transcription factors, membrane proteins, and other protein kinases that direct cellular growth and differentiation.

More than 20 genes implicated in RAS/MAPK signaling have been implicated in human disorders, most with some degree of clinical overlap. Common RASopathies include **Noonan syndrome (NS),** NS with multiple lentigines, Costello syndrome, cardiofaciocutaneous (CFC) syndrome, neurofibromatosis type one (NF1), Legius syndrome, and capillary malformation–arteriovenous malformation syndrome (Table 101.1).

NS represents the canonical RASopathy and is an autosomal dominant disorder resulting from pathogenic variants in several genes in the RAS/MAPK pathway. NS occurs in an estimated 1 in 1,000-2,500 live births. Approximately 30–75% of the cases are familial, and the condition typically exhibits autosomal dominant inheritance, although the *LZTR1* gene can be associated with autosomal dominant or autosomal recessive inheritance. Pathogenic variants in RAS/MAPK genes are found in ~70% of individuals with NS, with missense variants activating the *PTPN11* gene that encodes the nonreceptor protein tyrosine phosphatase SHP-2; this is observed in 50% of affected individuals. Pathogenic variants involving *SOS1* occur in 10–13% of affected individuals; variants in *RAF1* and *RIT1* each occur in 5% of patients, and variants in *KRAS*, *BRAF*, *MAP2K1*, *LZTR1*, and *NRAS* and duplications of the 12q24 region containing the *PTPN11* gene are rare. The strong clinical overlap between NS and other RASopathies, such as CFC syndrome, is due to the involvement of the same pathway and often identical genes in pathogenesis.

Common features in NS comprise short stature, a characteristic pattern of facial anomalies including ptosis, wide-spaced eyes with down-slanting palpebral fissures, epicanthal folds, anomalous and low-set ears and micrognathia, congenital heart disease, chest deformities with pectus excavatum and/or pectus carinatum, a short or wide neck with a low posterior hairline, and cryptorchidism

Table 101.1 Genes and Features of the RAS/MAPK Pathway

SYNDROME	RAS/MAPK PATHWAY GENE	PROTEIN	PROTEIN FUNCTION	CLINICAL PHENOTYPE
Noonan syndrome	*PTPN11* *SOS1* *RAF1* *KRAS* *NRAS* *SHOC2* *CBL* *RIT1*	SHP2 SOS1 CRAF KRAS NRAS SHOC2 CBL RIT1	Phosphatase RasGEF Kinase GTPase GTPase Scaffolding E3 ubiquitin ligase GTPase	Craniofacial dysmorphic features, including a broad forehead, hypertelorism, down-slanting palpebral fissures, ptosis, a high-arched palate, and low-set, posteriorly rotated ears; congenital heart defects; short stature; undescended testicles; ophthalmologic abnormalities; bleeding disorders; normal neurocognitive function or mild impairment; predisposition to cancer
Noonan syndrome with multiple lentigines	*PTPN11* *RAF1*	SHP2 RAF1/CRAF	Phosphatase Kinase	Same as Noonan syndrome, but with possible development of multiple skin lentigines as individuals age; unclear predisposition to cancer
Capillary malformation–arteriovenous malformation	*RASA1*	p120-RasGAP	RasGAP	Multifocal capillary malformations, which may be associated with arteriovenous malformations and fistulae; unclear predisposition to cancer
Costello syndrome	*HRAS*	HRAS	GTPase	Craniofacial features similar to those of Noonan syndrome but potentially more coarse; congenital heart defects; failure to thrive; short stature; ophthalmologic abnormalities; multiple skin manifestations, including papilloma; normal neurocognitive function or mild impairment; hypotonia; predisposition to cancer
Cardiofaciocutaneous syndrome	*BRAF* *MAP2K1* *MAP2K2* *KRAS*	BRAF MEK1 MEK2 KRAS	Kinase Kinase Kinase GTPase	Craniofacial features similar to those of Noonan syndrome; congenital heart defects; failure to thrive; short stature; ophthalmologic abnormalities; multiple skin manifestations, including progressive formation of nevi; normal neurocognitive function or mild impairment; hypotonia; unclear predisposition to cancer
Neurofibromatosis type 1	*NF1*	Neurofibromin	RasGAP	Café-au-lait maculae; intertriginous freckling; neurofibromas and plexiform neurofibromas; iris Lisch nodules; osseous dysplasia; optic pathway glioma; normal neurocognitive function or mild impairment; predisposition to other cancers
Legius syndrome	*SPRED1*	SPRED1	SPROUTY-related, EVH1 domain–containing protein 1	Café-au-lait maculae; intertriginous freckling; macrocephaly; normal neurocognitive function or mild impairment; no apparent predisposition to cancer

Modified from Rauen KA. The RASopathies. *Annu Rev Genom Hum Genet*. 2013;14:355–369. Table 3.

(Table 101.2 and Fig. 101.2). The pattern of congenital heart disease typically involves right-sided lesions, most frequently presenting with pulmonary valvular stenosis and hypertrophic cardiomyopathy, but atrial and ventricular septal defects, branch pulmonary artery stenosis, tetralogy of Fallot, and coarctation of the aorta have all been described. Children with NS can manifest developmental delays in association with hypotonia and may have challenges with articulation and coordination. High-frequency sensorineural hearing loss is common and should be considered in patients with language delays. Hepatosplenomegaly, low levels of clotting factors XI and XII, and primary lymphatic anomalies have also been noted; patients may rarely develop acute lymphoblastic leukemia or juvenile myelomonocytic leukemia (JMML). Puberty may be delayed, and an adult height that reaches the lower limit of the typical range can be achieved by the end of the second decade. Other distinctive phenotypes include NS-like disorder with loose anagen hair caused by *SHOC2* variants and NS-like disorder with or without JMML caused by *CBL* variants.

DIAGNOSIS

Initial suspicion of a RASopathy generally depends on recognition of one or more characteristic features associated with the various conditions. Genetic testing includes a panel of genes including those in the RAS/MAPK pathway. Multigene panel testing is preferred over single-gene analysis due to the many overlapping symptoms seen in RASopathy disorders. Genetic testing can often be performed on blood, saliva, or a buccal swab. If a gene in the RAS/MAPK pathway is found to have a pathogenic or likely pathogenic variant, this would provide molecular confirmation of the clinical diagnosis.

TREATMENT

Management of NS is noted in Table 101.3. Human growth hormone will improve growth velocity in many individuals with NS and short stature; it is recommended for those who fall below the third percentile for height. MEK inhibitors, such as trametinib, have been used to treat refractory lymphedema or chylous effusions and possibly severe cardiac hypertrophy.

Table 101.2	Clinical Findings Associated with Noonan Syndrome
Short stature	
Failure to thrive (use of specific Noonan syndrome growth curves is recommended)	
Tall forehead	
Epicanthal folds	
Ptosis	
Blue-green irides	
Wide-spaced eyes	
Low nasal bridge, upturned nose	
Down-slanting palpebral fissures	
Low-set and posteriorly rotated ears	
Dental malocclusion	
Low posterior hairline	
Pectus excavatum	
Pectus carinatum superiorly	
Scoliosis	
Pigmented villonodular synovitis (polyarticular)	
Cubitus valgus	
Pulmonary valve stenosis (dysplastic valve)	
Hypertrophic cardiomyopathy	
Atrial septal defect, ventricular septal defect	
Lymphedema	
Nevi, lentigines, café-au-lait spots	
Cryptorchidism	
Small penis	
Delayed puberty	
Bleeding disorders, including thrombocytopenia and coagulation factor deficiencies	
Leukemia, myeloproliferative disorders, other malignancies	
Cognitive delay	

NEUROFIBROMATOSIS

NF1 is a multisystem disorder that primarily abstractly involves the skin and peripheral nervous system (see Chapter 636.1). NF1 is associated with marked clinical variability. NF1 is inherited in an autosomal dominant manner. The disorder is caused by pathogenic variants in the *NF1* gene, which encodes neurofibromin and functions as a regulator of RAS signaling (see Table 101.1 and Fig. 101.1).

LEGIUS SYNDROME

Legius syndrome is a RASopathy caused by pathogenic variants in *SPRED1,* which encodes an HRAS regulator. Individuals with Legius syndrome present with typical multiple café-au-lait macules inherited as an autosomal dominant trait but do not develop the serious medical complications of NF1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

101.2 Sonic Hedgehog Pathway

Chad R. Haldeman-Englert

The Hedgehog signaling pathway plays numerous tissue-specific critical roles during embryogenesis and postnatal life. Disruption of specific steps in this pathway result in a variety of related developmental disorders and anomalies (Fig. 101.3). Activation of this pathway in the child or adult may lead to abnormal cellular proliferation and cancer. Three genes, Sonic (SHH), Indian (IHH), and Desert (DHH), comprise the hedgehog family, with SHH being the most widely expressed. These

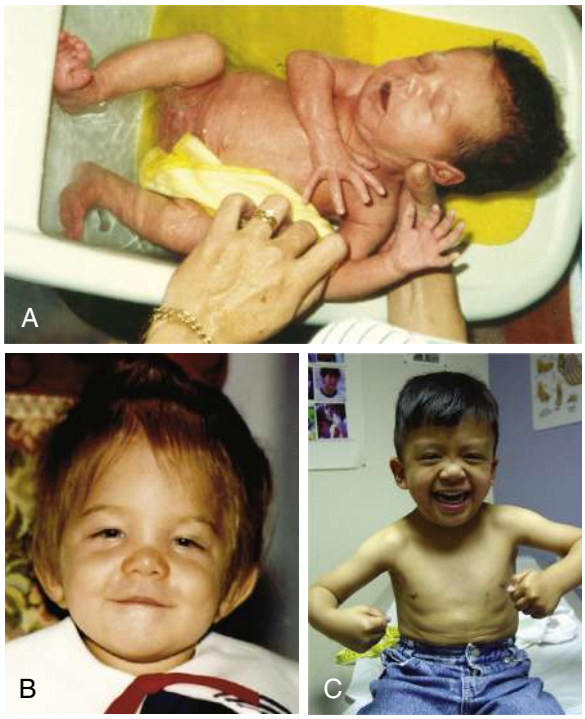

Fig. 101.2 Noonan syndrome. **A,** Newborn. **B,** Toddler. **C,** Affected male. Note the down-slanting palpebral fissures, low-set ears, elevated left shoulder secondary to scoliosis, and wide-spaced nipples. (*From Jones KL, Jones MC, Del Campo M, eds. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 1AC, p. 150 and Fig. 2A, p. 151; **A** and **B** courtesy Dr. Jacqueline Noonan, University of Kentucky, Lexington, Kentucky.*)

genes encode secreted signaling molecules important in cellular differentiation, proliferation, and survival. Secreted SHH acts as a *ligand* for specific cellular receptors to have a signal transduced by other components of the pathway to regulate downstream gene transcription. The SHH ligand is expressed in the embryo in regions important for development of the brain, face, limbs, and the gut.

Deleterious sequence variants in *SHH* can cause **holoprosencephaly** (see Fig. 100.7), a variably severe, midline defect associated with clinical effects ranging from cyclopia to a single maxillary incisor with close spacing of the ocular orbits. The SHH protein is processed by proteolytic cleavage to an active N-terminal form, which is then further modified by the addition of cholesterol. The steroidal alkaloid cyclopamine exerts a teratogenic effect by inhibiting cholesterol modification of SHH and can result in holoprosencephaly in sheep. In humans, a defect in cholesterol biosynthesis involving the recessive delta-7-dehydrocholesterol reductase gene *(DHCR7)* results in **Smith-Lemli-Opitz syndrome** (SLOS) (see Chapter 106).

In addition to microcephaly and holoprosencephaly, patients with SLOS (see Fig. 101.3) display syndactyly, classically of the second and third toes, postaxial polydactyly of the hands and feet, an upturned or anteverted nose, ptosis, and cryptorchidism.

The cholesterol-modified active form of SHH binds to its transmembrane receptor Patched (PTCH1). This SHH-PTCH1 complex then inhibits the activity of the transmembrane protein Smoothened (SMO). Because SMO normally acts to suppress downstream targets, the GLI family of transcription factors, inhibition of SMO by PTCH1 results in activation of GLI1, GLI2, and GLI3. Pathogenic variants resulting in activation of *SMO* can be oncogenic, particularly in basal cell carcinomas and medulloblastomas. In addition, *PTCH1* and its orthologue, *PTCH2*, act as tumor suppressors, and somatic, inactivating sequence variants can be associated with loss of tumor suppressor function. Relatedly, germline inactivating variants in *PTCH1* result in **Gorlin syndrome** (see Fig. 101.3), an autosomal dominant disorder characterized by a broad face, dental anomalies, rib defects and shortened

Table 101.3 Management of Noonan Syndrome

	AT DIAGNOSIS	AFTER DIAGNOSIS	IF SYMPTOMATIC
General	Complete physical and neurologic examination; medical genetics consultation to confirm diagnosis, consider molecular genetic testing and genetic counseling	Yearly complete physical and neurologic examination; return to geneticist if genotype negative or for multisystem assessment; genetic counseling at adolescence or when a young adult	Orchiopexy by age 1 year for cryptorchidism; if lymphoedema, refer to specialty clinic; brain and cervical spine MRI if intracranial pressure increases; electroencephalogram and referral to neurologist if seizures suspected
Developmental	Multidisciplinary developmental assessment	Developmental screening yearly for children age 5-18 years	Neuropsychologist testing if screening abnormal; referral to early intervention if delays detected before age 3 years; individual education plan for children age 5-18 years with delays
Dental	First dental assessment between age 1 year and 2 years	Yearly dental assessment	—
Growth and feeding	Plot growth on curves for Noonan syndrome	Plot growth on curves for Noonan syndrome 3 times per year until age 3 years, then yearly	Refer to gastroenterologist for feeding problems or recurrent vomiting, or if evidence of growth failure without comorbid cause exists; thyroid function tests if signs or symptoms of hypothyroidism
Cardiovascular	Cardiac examination, electrocardiogram, echocardiogram	Follow up on the basis of initial findings. If initial assessment normal, repeat every 5 years	—
Ophthalmologic	Baseline eye examination Baseline audiology examination	Repeat every 2 years, sooner if indicated	—
Audiologic	Baseline audiology examination	Repeat if recurrent otitis media or speech delay	Refer to ear, nose, and throat specialist for recurrent otitis media or serous otitis; hearing aids or classroom interventions for hearing loss
Hematologic	Complete blood cell count with differential, and prothrombin time or activated partial thromboplastin time	Repeat complete blood cell count with differential and prothrombin time or activated partial thromboplastin time if age 6-12 months at initial screen Preoperatively: complete blood cell count with differential and prothrombin time or activated partial thromboplastin time, second tier (in consultation with hematologist) factor IX, XI, and XII concentrations, von Willebrand factor, platelet aggregation	Prothrombin time or activated partial thromboplastin time if bleeding abnormal or persistent, refer to hematologist; complete blood cell count with differential for splenomegaly; complete blood cell count with differential and liver function studies for hepatosplenomegaly
Renal	Kidney ultrasound	—	—
Skeletal	Clinical assessment of spine with radiology if indicated by examination	Repeat spinal examination yearly through adolescence; radiology and referral to orthopaedic specialist if abnormal	—

From Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet*. 2013;381:333–342.

metacarpals; basal cell nevi that can undergo malignant transformation; and an increased risk of cancers, including medulloblastomas and rhabdomyosarcomas. *GLI1* amplification has been found in several human tumors, including glioblastoma, osteosarcoma, rhabdomyosarcoma, and B-cell lymphomas. Likewise, pathogenic variants in *GLI3* can cause **Greig cephalopolysyndactyly syndrome** (GCPS), **Pallister-Hall syndrome** (PHS), postaxial polydactyly type A (and A/B), and preaxial polydactyly type IV (see Fig. 101.3). GCPS consists of wide-spaced eyes, syndactyly, additional digits on the radial border of the hand or inner aspect of the foot, termed preaxial polydactyly, and broad thumbs and halluces. PHS is an autosomal dominant disorder characterized by postaxial polydactyly, syndactyly, hypothalamic hamartomas, imperforate anus, and occasionally holoprosencephaly. GLI3 binds to CBP, the protein that is haploinsufficient in **Rubinstein-Taybi syndrome**.

Disorders that are caused by pathogenic variants in genes that function together in a developmental pathway typically have overlapping clinical manifestations. The overlapping features result from the embryonic tissues in which SHH is important for development, including the brain, face, limbs, and gut as previously noted. Brain defects are present in holoprosencephaly (see Fig. 100.7), SLOS, and PHS. Facial anomalies are found in holoprosencephaly, SLOS, Gorlin syndrome, GCPS, and PHS. Limb defects occur in SLOS, Gorlin syndrome, GCPS, PHS, and the polydactyly syndromes. Overexpression, or activating sequence variants, affecting the SHH pathway results in cancer,

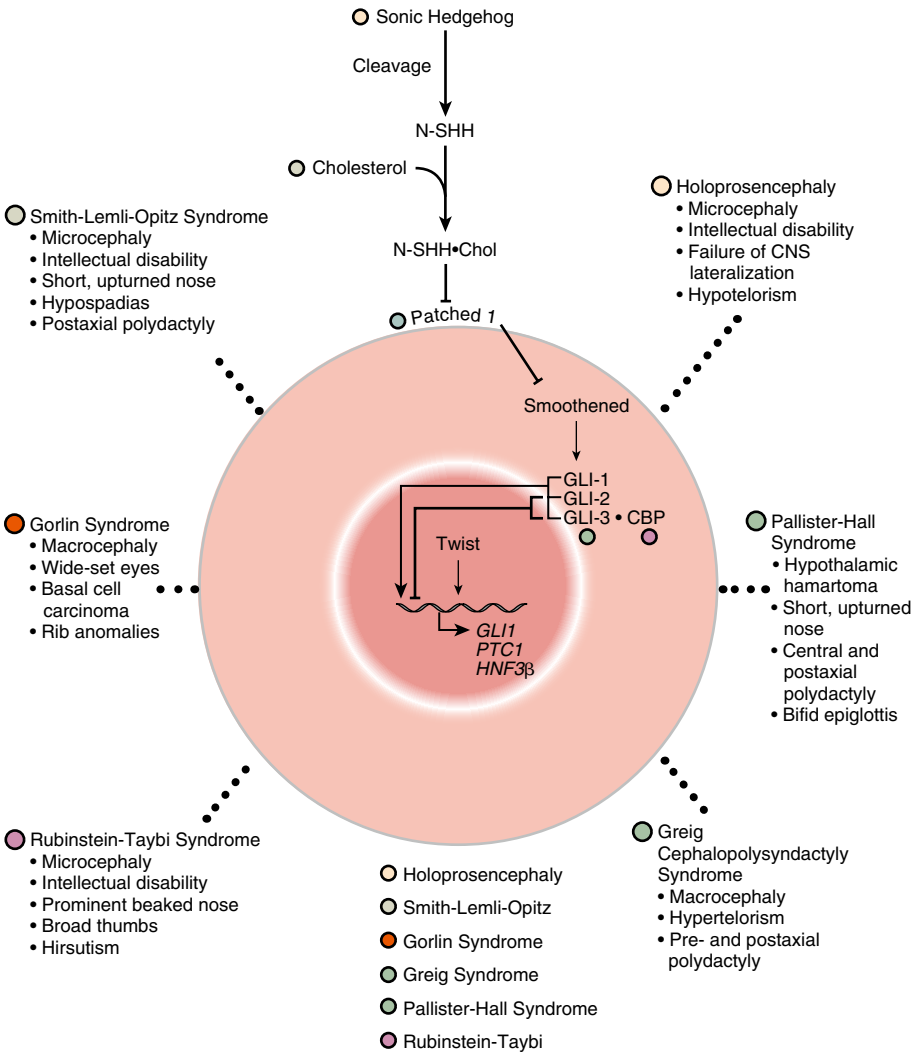

Fig. 101.3 Signaling components and clinical features of the sonic hedgehog (SHH) signaling pathway. Deleterious sequence variants in genes that function together in a developmental pathway typically have overlapping clinical manifestations. Several components of the SHH pathway have been identified and their relationships elucidated. Pathogenic variants in several members of this pathway result in phenotypes with facial anomalies, as seen in holoprosencephaly, Smith-Lemli-Opitz syndrome, Gorlin syndrome, Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, and Rubinstein-Taybi syndrome. CNS, Central nervous system.

including basal cell carcinomas, medulloblastomas, glioblastomas, and rhabdomyosarcomas.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

101.3 Ciliopathies

Chad R. Haldeman-Englert

Cilia are microtubule-containing organelles that project from the surface of most human cells. Three types of cilia exist in humans: motile cilia, nodal cilia, and primary cilia. Motile cilia typically contain a sweeping motion and play important roles in the respiratory epithelium (see Chapter 455 for discussion of structure of cilia and their role in primary ciliary dyskinesia and respiratory disorders). Nodal cilia play a very brief role during embryonic development, and their whirling flow in the Henson's node during gastrulation is central in determining the left-right body axis. Defects in this process manifest as alterations in body orientation, including situs inversus and heterotaxy (see Chapter 480.11).

Primary cilia are nonmotile and are present in nearly all cells. The membrane of each cilium is continuous with the plasma membrane. There are unique differences in its membrane that allow cilia to detect changes in the extracellular environment to function as mechanoreceptors, osmosensors, and chemosensors and convey this information via various intracellular signaling pathways to regulate diverse cellular processes (proliferation, polarity, nerve growth, differentiation, and tissue maintenance). These pathways may include Hedgehog (HH), G-protein–coupled receptors (GPCRs), Wingless and Int-1 (WNT), RTKs, and transforming growth factor β (TGF-β).

Pathogenic changes to genes that control the function and signaling within the cilia give rise to conditions called *ciliopathies*. Given the extent of cilia located throughout the human body, symptoms associated with ciliopathies can be variable and extensive. Defects can occur to many different organs during fetal development through adulthood. Organ systems generally affected in ciliopathies include the brain, eyes, liver, kidneys, and skeleton (Fig. 101.4). There are many well-described ciliopathy effects, including retinitis pigmentosa, hearing loss, infertility, primary ciliary dyskinesia, polycystic kidney disease, and nephronophthisis, as well as a number of syndromes including Joubert, Bardet-Biedl, Meckel-Gruber, and orofaciodigital syndromes (Table 101.4).

The diagnosis of a ciliopathy is generally based on recognition of the clinical features followed by either targeted gene testing, a multigene panel, or exome/genome sequencing. If a diagnosis is established with molecular testing, additional studies may be indicated to evaluate for additional medical and developmental concerns. Surveillance for potential changes to the kidneys, liver, and eyes should be routinely performed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

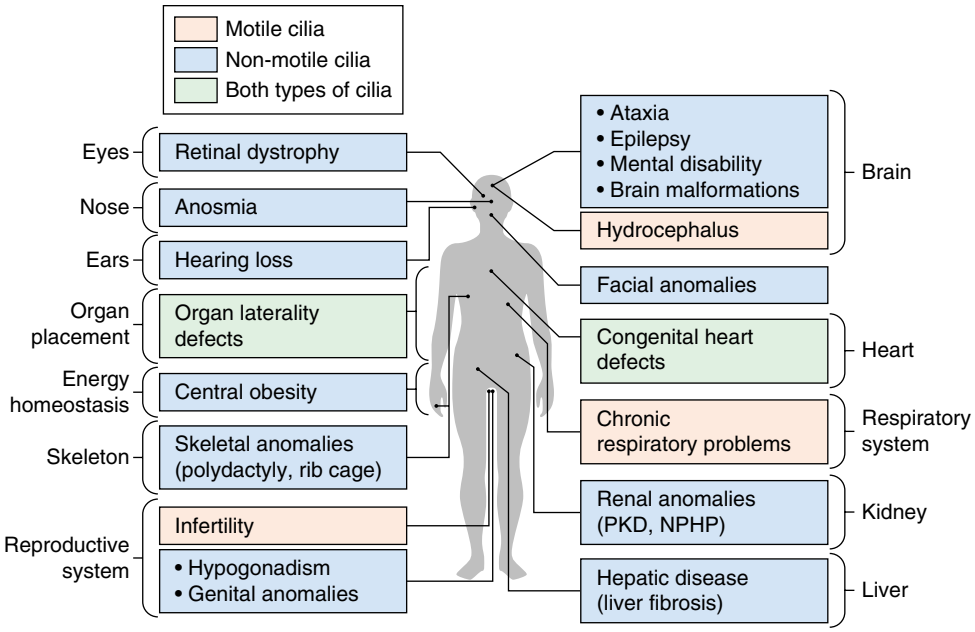

Fig. 101.4 Ciliopathies of motile and/or nonmotile cilia encompass most human organ systems. Different organ systems or tissues are affected in diverse ciliopathies, with the most common phenotypic manifestations for each organ. Ciliopathies caused primarily by defects in motile cilia are in *orange,* those in nonmotile (primary) cilia are in *blue,* and those associated with defects in nodal cilia are in *green.* NPHP, Nephronophthisis; PKD, polycystic kidney disease. (*Modified from Reiter JF, Leroux MR. Genes and molecular pathways underpinning ciliopathies. Nat Rev Molec Cell. 2017;18:533–547. Fig. 2.*)

Table 101.4 Childhood Diseases and Syndromes Associated with Motile and Primary/Sensory Ciliopathies

PEDIATRIC CILIOPATHY	CLINICAL MANIFESTATIONS	SELECTED GENE(S)
MOTOR		
Primary ciliary dyskinesia	Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD	*DNAI1, DNAH5, DNAH11, DNAI2, KTU, TXNDC3, LRRC50, RSPH9, RSPH4A, CCDC40, CCDC39*
PRIMARY/SENSORY		
Autosomal recessive polycystic kidney disease	RFD, CHF	*PKHD1*
Nephronophthisis	RFD, interstitial nephritis, CHF, RP	*NPHP1-8, ALMS1, CEP290*
Bardet-Biedl syndrome	Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD	*BBS1-12, MKS1, MKS3, CEP290*
Meckel-Gruber syndrome	RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft palate	*MKS1-6, CC2D2A, CEP290, TMEM216*
Joubert syndrome	CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft palate	*NPHP1, JBTS1, JBTS3, JBTS4, CORS2, AHI1, CEP290, TMEM216*
Alström syndrome	Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	*ALMS1*
Orofaciodigital syndrome type I	Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, ID, RFD	*OFD1*
Ellis van Creveld syndrome	Chondrodystrophy, polydactyly, ectodermal dysplasia, CHD	*EVC, EVC2*
Jeune asphyxiating thoracic dystrophy	Narrow thorax, RFD, RP, dwarfism, polydactyly	*IFT80*
Sensenbrenner syndrome	Dolichocephaly, ectodermal dysplasia, dental dysplasia, narrow thorax, RFD, CHD	*IFT122, IFT43, WDR35*
Short rib–polydactyly syndromes	Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia	*WDR35, DYNC2H1, NEK1*

CHD, Congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.

From Ferkol TW, Leigh MW. Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. *J Pediatr.* 2012;160:366–371.

101.4 Craniosynostoses

Chad R. Haldeman-Englert

To permit appropriate brain growth, the cranial sutures do not completely fuse until adulthood. Growth of the skull occurs perpendicular to the direction of each suture. Craniosynostosis arises when one or more cranial sutures prematurely ossify, which usually becomes apparent between the third trimester of pregnancy and the first year of life (see Chapter 631.10). The shape of the skull is often the clue to the affected suture (Fig. 101.5). Most patients with craniosynostosis do not have additional syndromic features; this may depend on the sutures involved. Patients with bicoronal or multisuture craniosynostosis often have an associated genetic syndrome, whereas patients with isolated sagittal craniosynostosis do not have features of an identifiable genetic cause.

Craniosynostosis can result from reduced intrinsic factors (poor brain growth), increased extrinsic forces (primiparity, multiple pregnancy, fetal position, high birth weight), or genetic abnormalities leading to uncontrolled cranial bone growth. Genes commonly associated with syndromic craniosynostosis include three fibroblast growth factor receptor genes *(FGFR1*, *FGFR2*, *FGFR3)*, *TWIST1*, and *EFNB1*. *FGFR1*, *FGFR2*, and *FGFR3* are associated with recognizable conditions such as Crouzon, Pfeiffer, Apert, and Muenke syndromes; *TWIST1* with Saethre-Chotzen syndrome; and *EFNB1* with craniofrontonasal syndrome. Distinguishing between the FGFR-related craniosynostosis syndromes can often be made based on additional features, particularly of the hands and feet (see Chapter 631.10).

Other pathogenic gene variants have been identified in patients with syndromic and nonsyndromic craniosynostosis (Table 101.5). Given the overlap of clinical features of many of the craniosynostosis conditions, appropriate genetic testing for patients with craniosynostosis could include either a multigene panel or exome/genome sequencing. The diagnosis is made based on the genetic abnormality and clinical features.

Management of patients with craniosynostosis is often complex and performed with a multidisciplinary team of various specialists, including audiology, dentistry, genetics, neurosurgery, ophthalmology, orthodontics, otolaryngology, pediatrics, plastic surgery, and speech therapy (see Chapter 631.10).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

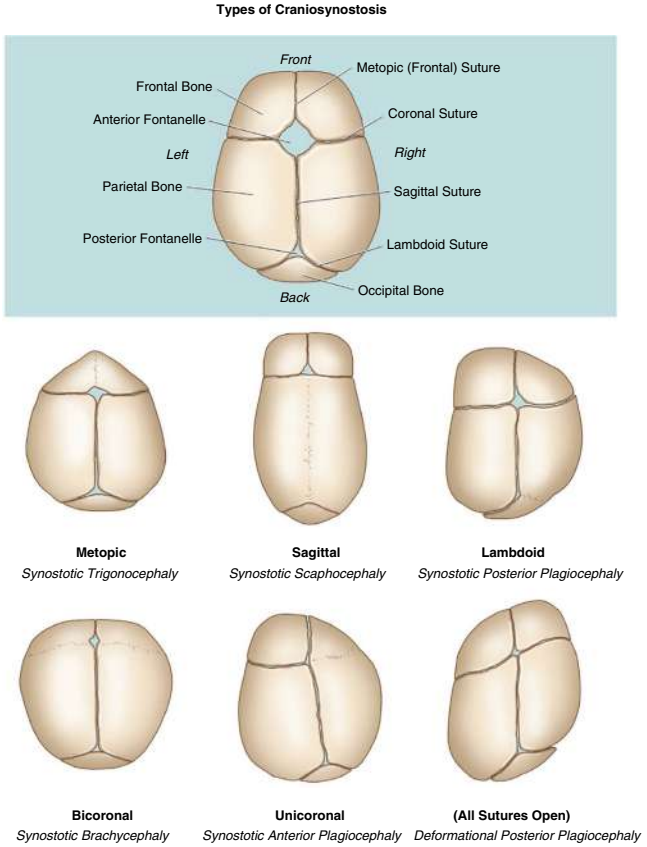

Fig. 101.5 Types of craniosynostosis. (*From Buchanan EP, Xue Y, Xue AS, Olshinka A, Lam S. Multidisciplinary care of craniosynostosis. J Multidiscip Healthcare. 2017;10:263–270. Fig. 1.* Dove Medical Press Ltd.)

Table 101.5 Core Genes For Which Specific Types of Variants Are Associated with Craniosynostosis in More Than Half of Affected Individuals

GENE (MIM#)	INHERITANCE PATTERN	CLINICAL DISORDER (MIM#)	PREVALENCE (%)	TYPICAL SUTURE FUSION	MAJOR PHENOTYPIC FEATURES
ASXL1 (612990)	AD (n)	Bohring-Opitz syndrome (605039)	—	Metopic	Forehead nevus flammeus, ulnar deviation and flexion of wrists and metacarpophalangeal joints, severe intellectual disability
CDC45 (603465)	AR	—	—	Coronal	Thin eyebrows, small ears, variable short stature
COLEC11 (612502)	AR	3MC syndrome 2 (265050)	—	Metopic	Hypertelorism, blepharoptosis, arched eyebrows, cleft lip/palate, hearing loss, radioulnar synostosis, genital and vesicorenal anomalies
EFNB1 (300035)	XLD (male sparing)	Craniofrontonasal syndrome (304110)	0.8	Coronal	Hypertelorism, notched nasal tip, chest anomalies, longitudinal splitting of nails; heterozygous females more severely affected than hemizygous males
ERF (611888)	AD	ERF-related craniosynostosis (600775)	1.1	Multisuture	Exorbitism, midface hypoplasia, Chiari type I malformation, postnatal onset of craniosynostosis
FGFR1 (136350)	AD	Pfeiffer syndrome (101600)	—	Coronal	Mild craniofacial features, broad medially deviated thumbs and halluces, cutaneous syndactyly, specific amino acid substitution p.Pro252Arg
FGFR1	AD (n)	Osteoglophonic dysplasia (166250)	—	Multisuture	Prominent brow ridges, depressed nasal bridge, rhizomelic dwarfism, localized lytic lesions of metaphyses
FGFR2 (176943)	AD (n)	Apert syndrome (101200)	3.6	Coronal, multisuture	Midface hypoplasia, dilated cerebral ventricles, complex syndactyly of the hands and feet
FGFR2	AD (n)	Beare-Stevenson syndrome (123790)	*	Multisuture	Choanal atresia, prominent umbilical stump, furrowed scalp/neck skin, acanthosis nigricans in survivors
FGFR2	AD	Crouzon syndrome (123500)	2.4	Multisuture, coronal, sagittal	Exorbitism, midface hypoplasia, beaked nose ("crouzonoid" facies), clinically normal hands and feet
FGFR2	AD (n)	Pfeiffer syndrome (101600)	0.8	Multisuture	Broad thumbs and halluces; in severe cases, cloverleaf skull, brain anomalies, tracheal sleeve, fused elbows
FGFR2	AD (n)	Bent bone dysplasia (614592)	*	Coronal	Osteopenia, reduced mineralization of the calvaria, bent long bones; perinatal lethal
FGFR3 (134934)	AD	Muenke syndrome (602849)	4.0	Coronal	Defined by specific amino acid substitution p.Pro250Arg; may include sensorineural hearing loss, mild brachydactyly, cone-shaped epiphyses
	AD (n)	Crouzon/acanthosis nigricans (612247)	0.4	Multisuture	Crouzonoid facies, choanal stenosis, hydrocephalus, acanthosis nigricans; specific amino acid substitution p.Ala391Glu
	AD (n)	Thanatophoric dysplasia II (187601)	*	Multisuture	Lethal skeletal dysplasia, micromelic limb shortening, straight femora; specific amino acid substitution p.Lys650Glu
IHH (600726)	AD	Philadelphia craniosynostosis (185900)	—	Sagittal	Cutaneous and osseous syndactyly

Table 101.5 Core Genes For Which Specific Types of Variants Are Associated with Craniosynostosis in More Than Half of Affected Individuals—cont'd

GENE (MIM#)	INHERITANCE PATTERN	CLINICAL DISORDER (MIM#)	PREVALENCE (%)	TYPICAL SUTURE FUSION	MAJOR PHENOTYPIC FEATURES
IL11RA(600939)	AR	Craniosynostosis and dental anomalies (614188)	—	Multisuture	Maxillary hypoplasia, delayed tooth eruption, supernumerary teeth, minor digit abnormalities, conductive hearing loss
MEGF8(604267)	AR	Carpenter syndrome 2 (614796)	—	Metopic	Hypertelorism, arched eyebrows, lateralization defects, brachydactyly, syndactyly, preaxial polydactyly
MSX2(123101)	AD	Boston craniosynostosis (604757)	—	Sagittal, coronal, multisuture	None diagnostic; syndrome defined by specific amino acid substitutions p.Pro148His, p.Pro148Leu
POR(124015)	AR	Antley-Bixler syndrome (201750)	—	Bicoronal, multisuture	Choanal stenosis, radiohumeral synostosis, bowed femora, multiple joint contractures, genital abnormalities; abnormal steroidogenesis
RAB23(606144)	AR	Carpenter syndrome 1 (201000)	—	Multisuture	Obesity, cardiac defects, polysyndactyly, brachydactyly, genu valgum, hypogenitalism, umbilical hernia, learning disability
RUNX2(600211)	AD (n)	—	—	Multisuture	None diagnostic; syndrome defined by specific gene duplication
SKI(164780)	AD (n)	Shprintzen-Goldberg syndrome (182212)	—	Sagittal, multisuture	Hypertelorism, micrognathia, high-arched palate, arachnodactyly, joint contractures, pectus deformity, aortic root aneurysm, mitral valve prolapse, learning disability
TCF12(600480)	AD	TCF12-related craniosynostosis (615314)	1.3	Coronal	Resembles mild Saethre-Chotzen syndrome; diagnosis defined by presence of mutations in the gene, ~50% nonpenetrance
TWIST1(601622)	AD	Saethre-Chotzen syndrome (101400)	3.6	Coronal	Low frontal hairline, hypertelorism, eyelid ptosis, down-slanting palpebral fissures, blocked tear ducts, small ears with prominent crus helicis
WDR35(613602)	AR	Cranioectodermal dysplasia 2 (613610)	—	Sagittal	Facial dysmorphism, narrow thorax, short long bones, brachydactyly, sparse hair, hypoplastic teeth, cystic kidneys, hepatic fibrosis
ZIC1(600470)	AD (n)	ZIC1-related craniosynostosis	0.2	Coronal	Severe learning disability

The prevalence figures are for percent total craniosynostosis cases with specified mutation, from the cohort attending the Craniofacial Unit, Oxford, born between 1998 and 2008 (n = 531) and surgically treated before end of 2013.
*Usually lethal at birth.
AD, Autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant; (n), usually arises by new mutation.
From Twigg SRF, Wilkie AOM. A genetic-pathophysiological framework for craniosynostosis. *Am J Hum Genetics*. 2015;97:359–377. Table 1.

Chapter 102

Chromatin Regulatory Disorders

Kosuke Izumi

Pathogenic variants in genes that encode chromatin proteins that orchestrate gene expression in a range of human tissues frequently cause pediatric developmental disorders that include developmental delay/intellectual disability and facial dysmorphisms.

KABUKI SYNDROME

Kabuki syndrome (MIM: 147920 and 300867) is a genetic disorder characterized by facial features, mild to moderate intellectual disability, growth deficiency, and skeletal anomalies. Kabuki syndrome was originally named "Kabuki make-up syndrome" due to patients' facial features, suggestive of those of Kabuki actors (Fig. 102.1). Approximately 1:32,000 to 1:86,000 individuals are estimated to have Kabuki syndrome.

Molecular Etiology

Heterozygous *KMT2D* pathogenic variants (~90%), and hemizygous (in males) or heterozygous (in females) *KDM6A* pathogenic variants (~10%) cause classic Kabuki syndrome; *KMT2D* encodes a histone methyltransferase and *KDM6A* encodes a histone demethylase. Both of these histone modification enzymes regulate histone codes to orchestrate global gene expression. Most genetic changes causing Kabuki syndrome are due to de novo changes. However, because *KDM6A* locates on the X chromosome, its inheritance pattern can be complex, with most *KDM6A* pathogenic variants being de novo, but maternal transmission of pathogenic *KDM6A* variants has been seen. Kabuki-like syndromes share many clinical features but do not have pathogenic variants in *KMT2D* or *KDM6A*.

Clinical Features of Kabuki Syndrome (Table 102.1)

Physical features: Common features of Kabuki syndrome include long palpebral fissures with eversion of the lateral third of the lower eyelid, arched broad eyebrows, a short columella, depressed nasal tip, large, prominent or cupped ears, and persistent fingertip pads (see Fig. 102.1). Dental anomalies such as widely spaced teeth and hypodontia are commonly seen.

Growth and feeding: Individuals with Kabuki syndrome often have short stature and feeding difficulties. The degree of difficulty with feeding and growth varies, but it is not uncommon for infants or children with Kabuki syndrome to require feeding tubes.

Development and behavior: Global developmental delay is commonly seen in children with Kabuki syndrome, and individuals with Kabuki syndrome typically have mild to moderate intellectual disability. Most individuals speak and ambulate independently. Although infrequent, autism is seen in Kabuki syndrome.

Neurology: Hypotonia is a common feature. Structural brain differences are typically not seen, but individuals with Kabuki syndrome have an ~30% risk for seizures.

Congenital heart disease: Approximately 70% of children with Kabuki syndrome have a structural heart defect. The most common types include coarctation of the aorta and septal defects, although complex congenital heart disease is also seen.

Gastrointestinal: In addition to feeding difficulties, structural anomalies such as anal atresia, congenital diaphragmatic hernia (CDH), and cholestasis can be seen.

Endocrinology: Hypoglycemia or hyperinsulinemia can be seen, and some females with Kabuki syndrome have early premature thelarche.

Ophthalmology: The common everted lower eyelid seen in Kabuki can lead to excessive tearing. Other eye differences can include ptosis, cataracts, corneal differences, blue sclerae, or strabismus.

Ear, nose, and throat: Hearing loss, mainly conductive hearing loss, and more rarely sensorineural hearing loss, is seen in up to 50% of individuals with Kabuki syndrome. Chronic otitis media is a major cause of conductive hearing loss. Individuals with Kabuki syndrome can also have cleft lip and/or palate.

Genitourinary: Kidney and urinary tract disorders occur in more than 25% and can include abnormal renal location, duplicated collecting system, hypospadias and cryptorchidism in males, and hypoplastic labia in females.

Musculoskeletal: Many individuals have joint hypermobility that can manifest with scoliosis. Spinal abnormalities such as sagittal clefts and hemivertebrae can be seen in individuals with Kabuki syndrome.

Immunology and hematology: Frequent and recurrent infections including sinopulmonary infections and otitis media are common in children with Kabuki syndrome. Some can have hypogammaglobulinemia and immune dysfunction, with some needing regular intravenous immunoglobulin injection. Autoimmune disorders such as vitiligo, immune thrombocytopenia, hemolytic anemia, and coagulopathy are also common.

Molecular diagnosis of Kabuki syndrome: This is often made using sequencing and deletion/duplication analyses of *KMT2D* and *KDM6A* following clinical suspicion or by exome sequencing. Often, parental testing is performed to determine whether the identified variant is de novo. In addition, a DNA methylation profile has been identified for Kabuki syndrome caused by *KMT2D* and *KDM6A* variants, and a matching profile can support the diagnosis in the context of uncertain pathogenicity of identified *KMT2D* or *KDM6A* variants.



Fig. 102.1 Physical features of Kabuki syndrome. A, Patient with *KMT2D* c.10201C>T, p.Gln3401* pathogenic variant. Dysmorphic features include long and up-slanted palpebral fissures and large prominent ears. B, Patient with *KDM6A* c.3717G>A; p.Trp1239* pathogenic variant. Dysmorphic features include long and up-slanted palpebral fissures.

RUBINSTEIN-TAYBI SYNDROME

Rubinstein-Taybi syndrome (RSTS; MIM 180849 and 613684) is characterized by down-slanted palpebral fissures, broad thumb and first toe, developmental delay/intellectual disability, and short stature (Fig. 102.2). It occurs in ~1 in 125,000 births.

Molecular Etiology

RSTS is caused by heterozygous pathogenic variants in *CREBBP* and *EP300* genes. These genes encode transcriptional co-activators as histone lysine acetyltransferases. RSTS is caused by pathogenic variants, typically de novo in *CREBBP* in 55% and in *EP300* in ~8%. *CREBBP* pathogenic variants tend to result in more typical RSTS features, with *EP300* alterations resulting in a wider, often milder, phenotypic spectrum.

Table 102.1 Kabuki Phenotype Scoring List

CLINICAL FEATURES	POSSIBLE SCORE	FEATURES
Facial features	0-5 points (0-3 features = 1 point; 4-6 = 2 point; 7-9 = 3 point; 10-12 = 4 point; 13-15 = 5 point)	Long palpebral fissures; everted lower eyelids; large dysplastic ears; arched eyebrows, sparse lateral one third; flat nasal tip; abnormal dentition; high/cleft palate; strabismus; blue sclera; micrognathia; ptosis; broad nasal root; oligodontia; thin upper and full lower lip; lip nodules
Limb/extremity features	Up to 1 point (0-1 features = 0 point; 2-4 = 1 point)	Persistent fetal pads; brachy- or clinodactyly; lax joints; hip dislocation
Microcephaly	1 point	
Short stature	1 point	
Heart	1 point	
Kidney	1 point	
Sum	0-10	

From Wang YR, Xu NX, Wang J, Wang XM. Kabuki syndrome: review of the clinical features, diagnosis and epigenetic mechanisms. *World J Pediatr*. 2019;15:528–535. Table 1.



Fig. 102.2 Rubinstein-Taybi syndrome. A, A 21-month-old child. Note the hirsutism, down-slanting palpebral fissures, maxillary hypoplasia, prominent nose with nasal septum extending below alae nasi, and low, posteriorly rotated ears. B, Broad thumbs with radial angulation and persistent fingertip pads. *(A courtesy Dr. Marilyn C. Jones, Children's Hospital, San Diego, California; from Jones KL, Jones MC, Del Campo M, eds.* Smith's Recognizable Patterns of Human Malformation, *8th ed. Philadelphia: Elsevier; 2022, Fig. 1C, p. 108 and Fig. 2C, p. 109.)*

Clinical Features of RSTS

Physical features: Characteristic facial features include arched eyebrows, down-slanting palpebral fissures, low-hanging columella, and grimacing smile. Individuals often have broad thumbs and/or halluces.

Growth: Prenatal growth is usually normal, but most individuals have short stature caused by slow postnatal growth. Obesity may be seen during childhood or adolescence.

Development: Global developmental delay is typical with milder features often seen in individuals with *EP300* pathogenic variants. The average age of walking is 30 months and first words 25 months. Speech delay occurs in 90% of children and some remain nonverbal. Features of autism spectrum disorder, as well as impulsivity, distractibility, mood instability, and stereotypies can be seen.

Intellectual disability: This is in the moderate to severe range is typical for individuals with RSTS, with an IQ range of 25-79. Verbal ability is typically poorer than other skills.

Neurologic: Craniospinal and posterior fossa abnormalities, such as Chiari malformation or cervical cord compression, can be seen as well as seizures or abnormal electroencephalogram (EEG).

Eye findings: These can include refractory errors, ptosis, cataracts, coloboma, nystagmus, strabismus, and glaucoma.

Congenital heart defects: These are seen in ~30% of individuals with RSTS. Common defects include atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, pulmonary stenosis, aortic stenosis, and vascular ring.

Respiratory: Obstructive sleep apnea is common.

Genitourinary: Kidney anomalies include hydronephrosis and duplications. Many males have cryptorchidism.

Gastrointestinal: Feeding problems due to gastroesophageal reflux and constipation are common.

Musculoskeletal: Joint laxity, scoliosis, and vertebral abnormalities can be seen. Hypotonia is common.

Molecular diagnosis: This can be made using a gene panel (sequencing and deletion/duplication analyses of *CREBBP* and *EP300*). For individuals with clinical features with atypical RSTS features, exome sequencing is recommended.

CORNELIA DE LANGE SYNDROME

Cornelia de Lange syndrome (CdLS; MIM 122470) is characterized by craniofacial features including synophrys, high-arched eyebrows and thin downturned upper lip, hirsutism, intellectual disability, microcephaly, growth retardation, limb anomalies, such as micromelia, phocomelia, and oligodactyly, and several other systemic abnormalities. Its population incidence is approximately 1 in 50,000.

Molecular Mechanism of CdLS

CdLS is caused by pathogenic variants in genes encoding the structural and regulatory components of the cohesin complex. Variants have been found in *NIPBL*, *HDAC8*, *RAD21*, *SMC1A,* and *SMC3* in CdLS. The cohesin complex is composed of SMC1A, SMC3, RAD21, and other subunits that comprise a ringlike structure that "embraces" chromatin. *NIPBL* encodes a protein that controls cohesin complex genome loading. The SMC3 component of the cohesin complex becomes acetylated once loaded onto the genome and is subsequently deacetylated by HDAC8 for cohesin protein recycling. Pathogenic variants in *BRD4* are an infrequent cause of CdLS. Cohesin has shown to play a key role in transcriptional regulation, and global transcriptional alterations due to cohesin dysfunction are thought to lead to the pathogenesis of CdLS.

NIPBL pathogenic variants are found in approximately 60% of the individuals with CdLS and are more likely to be identified in more severely (or "classically") affected individuals, with loss-of-function variants resulting in a more severe phenotype. Pathogenic variants in *SMC1A*, *SMC3, RAD21*, *HDAC8,* and *BRD4* can be found in 1–5% of the individuals with CdLS. Pathogenic variants in all related genes are typically acquired de novo, although instances of inherited variants from minimally affected mothers have been noted for the X-linked *HDAC8* and *SMC1A* genes.



Fig. 102.3 Physical features of Cornelia de Lange syndrome. **A**, Patient with *NIPBL* c.3100_3106del; p.K1034QfsX7 pathogenic variant. Dysmorphic features include synophrys, long eyelashes, upturned nasal tip with anteverted nares, long philtrum, and micrognathia. Severe reduction defects of upper extremities are also depicted. **B**, Patient with *SMC1A* c.2077C>G; p.R693G mutation. Dysmorphic features include mild synophrys.

Clinical Manifestations of CdLS

Facial features: Include synophrys with highly arched and/or thick eyebrows, long/thick eyelashes, short nasal bridge, upturned nasal tip with anteverted nares, long and/or smooth philtrum, thin vermilion of the upper lip, downturned corners of the mouth, highly arched palate with or without cleft palate, small widely spaced teeth, and micrognathia (Fig. 102.3).

Growth failure: Prenatal-onset growth failure and microcephaly are common.

Ophthalmologic: Common manifestations include ptosis, myopia, and nystagmus.

Otolaryngologic: Sensorineural hearing impairment is common, but conductive hearing loss can be seen.

Cardiovascular: Approximately 50% of individuals with CdLS have congenital heart disease. The most common abnormalities include pulmonic or peripheral pulmonic stenosis, ventricular septal defects, atrial septal defects, coarctation or hypoplastic aortic arch, aortic valve anomaly, tetralogy of Fallot, double-outlet right ventricle, and atrioventricular canal.

Gastrointestinal: Gastroesophageal reflux disease is present in nearly all instances, and some require a feeding tube during infancy/childhood. Other rare gastrointestinal abnormalities include pyloric stenosis (4%), intestinal malrotation (2%), and CDH (1%).

Genitourinary. Renal abnormalities such as vesicoureteral reflux and cryptorchidism are common.

Skeletal: Severe abnormalities of the upper extremities are seen in 25% of individuals with classical CdLS. Upper extremity deficiencies range from severe reduction defects such as complete absence of the forearms to mild fifth finger clinodactyly (see Fig. 102.3). Radioulnar synostosis is also common.

Skin: Hypertrichosis is common, and scalp hair, typically thick, can extend onto the temporal regions.

Developmental delay/intellectual disability: Most individuals with classical CdLS demonstrate global developmental delay. The overall range of IQ levels is broad, from below 30 to 85, with an average IQ of 53. Those affected individuals with classic features are more likely to have severe to profound intellectual disability. Fifty percent of children with CdLS walk by 24 months and 95% by 10 years old. A range of behavioral issues have been reported, and behavior problems are often directly related to frustration from an inability to communicate.

Neurologic: Approximately 25% of individuals with CdLS experience seizures.

Molecular Diagnosis of CdLS: Due to a relatively high frequency of mosaic variants not detected in blood, a next-generation sequencing panel of CdLS genes (*NIPBL, SMC1A, HDAC8, SMC3, RAD21,* and *BRD4*) performed on DNA extracted from buccal cells has been recommended as the most effective way of detecting causal variants. For individuals with atypical CdLS features, exome sequencing is recommended.



Fig. 102.4 Coffin-Siris syndrome. Note the coarse face and wide mouth with full lips (**A**), and hypoplastic fifth fingernails (**B**). *(From Jones KL, Jones MC, Del Campo M, eds.* Smith's Recognizable Patterns of Human Malformation, *8th ed. Philadelphia: Elsevier; 2022, Fig. 1A and 1D, p. 819.)*

COFFIN-SIRIS SYNDROME

Coffin-Siris syndrome (CSS) is characterized by thick eyebrows, periorbital fullness, wide mouth with full lips, and coarse facial features; fifth fingernail hypoplasia; absence of terminal phalanges; hypertrichosis; developmental delay/intellectual disability; and short stature (Fig. 102.4).

Molecular Mechanism of CSS

CSS is typically caused by de novo heterozygous germline pathogenic variants in genes encoding a component of BAF (BRG1/hBRM-associated factors) complex, which belongs to the SWI/SNF chromatin remodeler complex family. Pathogenic variants have been found in *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, *SMARCE1,* and *SOX11*. Variants in one of these genes can be found in ~60–70% of the patients with CSS.

Clinical Features of CSS

Facial features: Characteristic facial features of CSS include wide mouth with thick, everted upper and lower lips, broad nasal bridge with broad nasal tip, thick eyebrows, and long eyelashes. Facial features typically coarsen over time.

Growth: Prenatal growth profile tends to be normal, but postnatal weight and height measurements are usually below the 50th percentile.

Development: Global developmental delay is common and variable; children sit around 12 months, walk at around 30 months, and say their first words at 24 months. Most individuals have intellectual disability, typically moderate to severe (IQ range: 40-69). Some individuals with CSS have behavioral concerns, aggression, or autistic features.

Neurologic: The majority of children with CSS have hypotonia. Structural brain malformations such as Dandy-Walker variant, and

agenesis of the corpus callosum may be seen. Seizures occur in up to 50% of individuals. Hearing impairment can occur.

Ophthalmology: Visual impairment is common, and ocular abnormalities include ptosis, strabismus and myopia.

Gastrointestinal: Feeding issues and slow growth are common.

Genitourinary: Renal malformation such as horseshoe kidney, and genitourinary malformation such as cryptorchidism and hypospadias have been noted.

Musculoskeletal: Fifth digit nail and distal phalanx hypoplasia or aplasia, a diagnostic criterion in the pre-exome era, is commonly seen. Brachydactyly of the fifth finger, joint laxity, and scoliosis are also frequent.

Cardiac: Congenital heart defects can be seen and include ventricular septal defects, atrial septal defects, and tetralogy of Fallot.

Skin: Hirsutism and hypertrichosis are typical.

Molecular Diagnosis of CSS

For those whom clinical diagnosis of CSS is strongly suspected, CSS gene sequencing and deletion/duplication panel is recommended. For those with atypical clinical features, comprehensive genetic testing such as exome sequencing is warranted.

OTHER CHROMATIN DISORDERS

An increasing number of genetic disorders, due to mutations in genes encoding chromatin transcriptional regulatory proteins, have been identified. These disorders include CHARGE syndrome due to *CHD7* pathogenic variants, Wiedemann-Steiner syndrome due to *KMT2A* pathogenic variants, Arboleda-Tham syndrome due to *KAT6A* pathogenic variants, and Say-Barber-Biesecker/Young-Simpson syndrome due to *KAT6B* pathogenic variants. CHD7 is a chromatin remodeler protein with a chromodomain histone-modification recognition motif. *KAT6A* and *KAT6B* encode histone modification enzymes. Common manifestations of genetic diagnoses due to these chromatin remodelers and histone modification enzyme defects include developmental delay, hypotonia, and facial dysmorphisms. Some of the clinical features enable astute clinicians to distinguish between typical cases of these syndromes. However, in their atypical presentations, a clinical diagnosis may not be feasible. Exome sequencing is recommended in any children with facial dysmorphisms as well as developmental delay to detect possible chromatin disorders.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 103
Genetics of Common Disorders

Neil A. Hanchard and Brendan Lee

Common pediatric diseases, like many common adult-onset diseases, are usually multifactorial. The combination of many genes and environmental factors contribute to a complex sequence of events leading to disease. The complexity of the combination of contributing factors increases the challenge of finding genetic variants that cause disease. Genetic tools include public databases of genetic variants and the human haplotype map. Genotyping has permitted very large numbers of common genetic variants (those with population frequencies >5%) to be efficiently tested in large numbers of patients. Genetic sequencing technologies are being used to investigate the role of rare coding sequence variants in common diseases. The incorporation of these tools into large, well-designed population studies has developed into the field of **genetic epidemiology**.

103.1 Major Genetic Approaches to the Study of Common Pediatric Disorders

Neil A. Hanchard and Brendan Lee

Millions of genetic variants are present in every person. Many of these variants have no known impact on health, while others have a measurable influence. Sometimes, sequence changes in a single gene consistently cause a disease, as seen with cystic fibrosis and sickle cell anemia; more often, specific genetic changes are insufficient to determine the manifestation of a specific medical condition by themselves. Rather, these changes can contribute indirectly or partially to the development of disease, and these are best conceptualized as *modifiers* of disease risk. Figure 103.1 demonstrates the relationship between variant frequency and the relative medical impact of the allele. The spectrum of variant impact ranges widely from a slightly increased risk of illness to predetermined, fully expressed disease. Studies aimed at discovering *rare* variants with strong health effects require only small sample populations to achieve statistical significance, whereas those studying *common* variants that contribute partially to the overall effect often require much larger sample sizes because of the small impact of multiple variants.

In many cases, genetic susceptibility is the result of the cumulative risk of many common variants. For common conditions, the genetic predisposition alone is not sufficient to cause disease. Everyone inherits a different degree of disease vulnerability, which is then augmented by exposure to certain environmental or other factors. Figure 103.2 is a model for the contribution of common genetic variants to individual health. One goal of medical genetics is to identify the genes that contribute to initial genetic susceptibility and help prevent the occurrence of disease, either by avoiding inciting environmental factors or by instituting interventions that reduce risk. For persons who cross the threshold of disease, the goal is to better understand the pathogenesis in the hope that this will suggest better approaches to treatment. Common genetic variation can also influence responses to medications and the risk of adverse drug reactions, as well as augments the impact of environmental exposures.

Complex traits may be inherently difficult to study if the precision of diagnosis **(phenotype)** is low, as often occurs with neurobehavioral traits. A starting point in the genetic analysis of a complex trait, therefore, is to obtain evidence in support of a genetic contribution and to estimate the relative strength of genetic and environmental factors. Complex traits typically exhibit familial clustering but are not transmitted in a distinct pattern as seen with classical mendelian autosomal dominant or recessive inheritance. Complex traits often show variation between groups of different ancestries, possibly reflecting the differences in frequency and/or effect of genetic variants within these groups.

Assessing the potential genetic contribution begins by determining whether the trait is seen among related individuals more often than in the general population. A common measure of **familiality** is the first-degree relative risk (usually designated by the symbol λ_s), which is equal to the ratio of the prevalence rate in siblings and/or parents to the prevalence rate in the general population. The λ_s for type 1 diabetes is about 15. The relative strength of genetic and nongenetic risk factors can be estimated by variance components analysis. The **heritability** of a trait is the estimate of the fraction of the total variance contributed by genetic factors (Fig. 103.3).

A minority of cases of common diseases such as diabetes may be caused by single-gene pathogenic variants (mendelian inheritance), chromosomal disorders, and other genomic disorders (see Chapter 629.4). However, these *unique* causes of the disease can provide important insight into the molecular pathways involved. Chromosomal regions with genes that might contribute to disease susceptibility have historically been located with **linkage mapping**, which locates regions

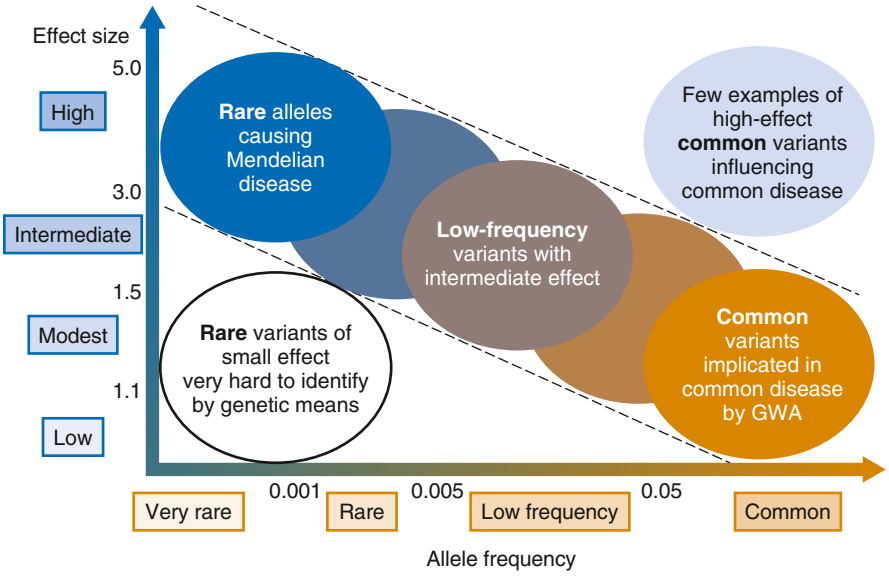

Fig. 103.1 Relationship between allele frequency and relative strength of genetic effect. Alleles with large effect tend to be very rare but can be studied with a small sample size because of the relative ease of allele detection when medical impact is high. Common variants tend to have a modest or low effect on health, requiring large datasets to visualize statistically small effects. The vast majority of disease-associated alleles identified to date have the characteristics shown within the *diagonal dotted lines*. GWA, Genome-wide association. *(Adapted from McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet. 2008;9:356–369.)*

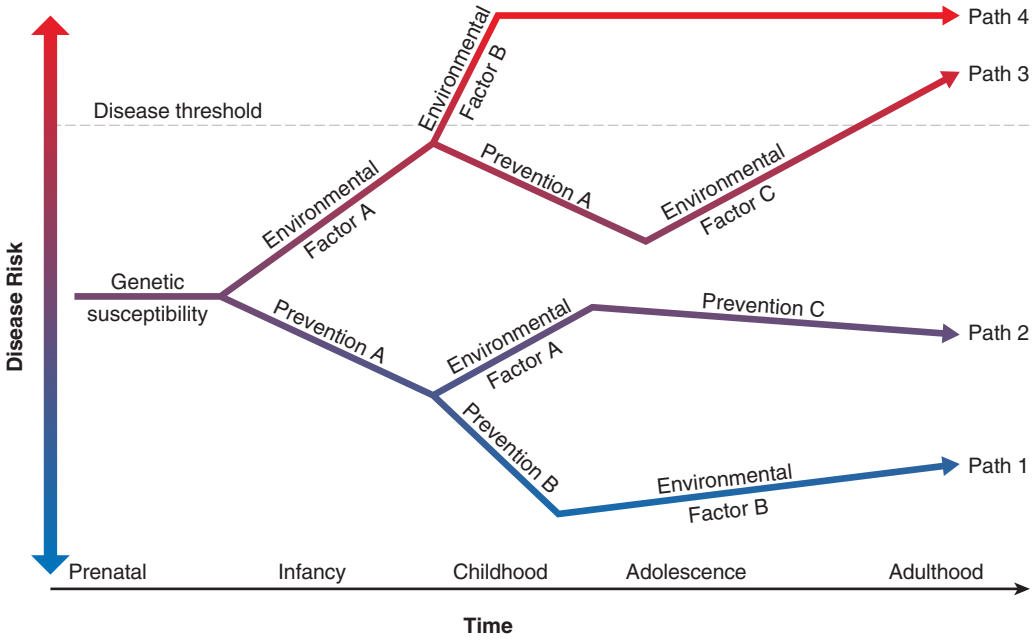

Fig. 103.2 Model for the influence of gene-environment interaction on genetic susceptibility to common diseases. Everyone inherits common variants that determine initial genetic liability for disease risk. For multifactorial disorders, the initial genetic susceptibility is insufficient to produce disease on its own. Over time, exposure to environmental factors increases the likelihood of a disease state. Identifying the gene variants responsible for risk can lead to prevention strategies or treatments.

Phenotypic variance		Genetic variance		Environmental variance		Measurement variance
V_P	=	V_G	+	V_E	+	V_M

$$h^2 = V_G / V_P$$

Heritability

Fig. 103.3 Heritability concept. The phenotypic variance of a particular trait can be partitioned between the contributions of the genetic variance, environmental variance, and measurement variance. This is usually empirically determined. Heritability is defined by the proportion of the phenotypic variance that is accounted for by the genetic variance. One can estimate the heritability from correlation of a quantitative trait between relatives.

of DNA that are inherited in families with the specific disease. In practical terms, however, this has become quite difficult for most complex traits either because of a dearth of families or because the effects of individual genetic loci are weak; thus linkage mapping is seldom used anymore.

Genetic **association studies** are a powerful way of identifying common gene variants (>5% in the population) that each have an effect on the risk of disease. Detection of the usually small to moderate effect of each variant alongside interactions with environmental factors requires well-powered studies that often include thousands of individuals. A number of parallel approaches for analyzing the aggregate effects of rare variants in genes have also been developed. Such rare variant association methods also require large sample sizes because the gene effects also appear to be relatively weak.

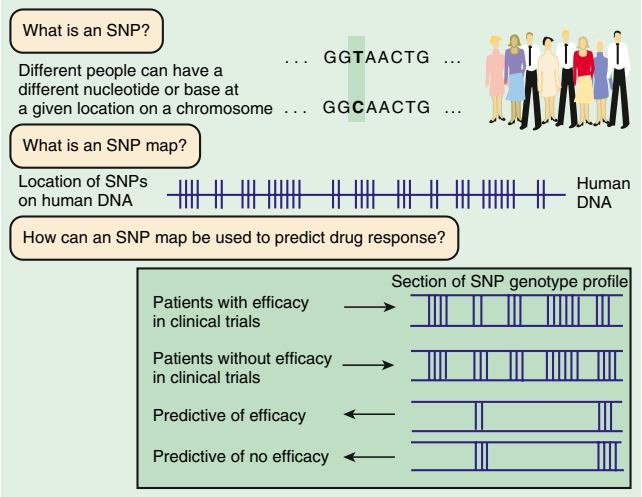

Fig. 103.4 Different combinations of single nucleotide polymorphisms (SNPs) are found in different individuals. The locations of these SNPs can be pinpointed on maps of human genes. Subsequently, they can be used to create profiles that are associated with difference in response to a drug, such as efficacy and nonefficacy. *(Adapted from Roses A. Pharmacogenetics and the practice of medicine. Nature. 2000;405:857–865.)*

Association studies require markers along the DNA that can be **genotyped** (ascertaining the combination of alleles at a locus in a diploid organism), typically with large-scale, high-throughput laboratory techniques. Markers that are typically used are **single nucleotide polymorphisms** (**SNPs**; Fig. 103.4). A sample of the same region of genome from 50 people will reveal that approximately 1 in every 200 bases varies between individuals. Catalogues of SNPs identified in thousands of individuals from multiple populations consist of tens of millions of SNPs across the genome (dbSNP; https://www.ncbi.nlm.nih.gov/snp/). Although most SNPs lack an obvious function, some will alter the amino acid sequence of the protein, and many have been shown to regulate the expression of nearby or distant genes (https://gtexportal.org/home/) or indirectly impact expression by altering the level of surrounding DNA methylation or the ability of proteins to act *(The ENCODE Project Consortium)*. Some of these functional alterations can directly affect susceptibility to disease.

A complex clinical **phenotype** can be defined by the presence or absence of a disease as a **dichotomous trait**, or by selection of a clinically meaningful continuous or **quantitative trait**, such as serum glucose in type 2 diabetes. Although it might not be possible to define subgroups of patients in advance based on disease mechanisms, the more uniform the phenotype, the more likely that a genetic study will be informative. **Locus heterogeneity** refers to the situation in which a similar trait results from alteration of different genes. **Allelic heterogeneity** is when more than one variant in a particular gene can contribute to different diseases. The development of a trait or disease from a nongenetic mechanism results in a **phenocopy**. These three factors often contribute to the difficulty in identifying individual disease susceptibility genes, because they reduce the effective size of the study population and thus require even larger sample sizes.

For genetic variants that directly lead to disease, a person bearing any variant or **allele** (inherited unit, DNA segment, or chromosome) in a gene has a given probability of being affected with a specific gene variant–associated disease. This is called the **penetrance**. Some diseases manifest signs only later in life **(age-related penetrance)**, which could lead to misclassifying children with the disease-producing variant to be classified as unaffected. Single-gene disorders are typically caused by pathogenic variants with relatively high penetrance. In contrast, most common variants have low penetrance because their overall contribution to the disease is small. Many such common variants can contribute to disease risk for a complex trait; for example, human height is influenced by >400 genes.

Ideally, important environmental exposures should be measured and accounted for in a population because there may be a dependent interaction between the environmental factor and specific genetic variant. An example is the likely requirement for a viral infection preceding onset of type 1 diabetes. Although **gene-environment interactions** are strongly suspected to play an important role in common diseases, it is difficult to identify and measure them. Very large studies with uniform collection of information about environmental exposures are rare, but are becoming more common with the expansion of large biorepositories that are integrated with electronic health records. Methods, such as genome-wide analyses of DNA methylation, sometimes referred to as epigenome-wide association studies, have been used to assess evidence for early environmental exposures that influence common diseases in later life. This apparent relationship between the environment and DNA methylation (and related genetic features) is being used to discover and validate other possible gene-environment interactions.

GENOME-WIDE APPROACHES TO ASSOCIATION

For multifactorial common diseases, association analyses have been used to identify disease-related genes. There are two types of association study: **direct association**, in which the risk-altering variant itself is tested to see whether its presence correlates with disease, and **indirect association**, in which markers that are physically close to the biologically important variant are used as proxies. The correlation of markers with other genetic variants in a small region of the genome is called **linkage disequilibrium**. Indirect association is enabled by the construction of linkage disequilibrium maps in continental reference populations (e.g., Europeans, Asians, West Africans) (International HapMap Project). SNPs that proxy most genetic variation have been identified across most of the genome and can be genotyped at low cost using specially designed microarrays that typically include 2-5 million genetic markers. This resolution provides a good proxy of genetic variation in relatively homogenous populations where linkage disequilibrium is generally high (such as Europeans), thus facilitating "genome-wide" testing of variants in those populations.

Three basic study designs are used for association testing:

1. **Case-control design:** the frequency of an allele in an affected group is compared with an unaffected group. This is the mostly commonly used framework for association testing, as it aligns with many more traditional epidemiologic study designs.
2. **Cohort design:** large numbers of people are ascertained and then followed for the onset of any number of diseases. Cohort analysis is very expensive, and there are few true cohort studies. However, investments in genomics of large-scale population-based cohorts in Iceland *(https://www.decode.com/)*, the United Kingdom *(https://www.ukbiobank.ac.uk/)*, and the United States *(https://allofus.nih.gov/)* include hundreds of thousands of individuals all tied to electronic health records and have begun to show unique insights to disease risk and pathogenesis.
3. **Family-based control design:** parents or siblings of an affected individual are used as the controls. Family-based control study designs are somewhat attractive for pediatric diseases because it is usually possible to enroll parents. These studies also solve a major problem in testing for association because the parents are perfectly matched for genetic background; however, family-based study designs are inherently less efficient to recruit than case-control studies and are used less commonly.

The success of any association analysis depends on the design of a well-powered study and an accurately measured trait to avoid phenotypic misclassification. In large, population-based studies, confounding by ethnicity or **population stratification,** could distort results. Variants more common in people from a particular ancestry group could cause an apparent association of a variant with a disease. This association would not be a true association between an allele and a disease, because the association would be confounded by genetic background. Methods for measuring subtle mismatching between cases and controls using many thousands of markers routinely genotyped

in genome-wide association studies allow researchers to account for this effect. The implementation of stringent thresholds for statistical significance replicate associations in other groups have helped make genome-wide association studies robust and reproducible.

Association studies are a powerful tool to find genetic variation that confers risk to an individual; however, the effect of any single genetic variant will be a small contribution to the overall risk and pathogenesis of disease. Hundreds of thousands of genetic associations between a variant or gene and disease, such as the *APOE*ε4 allele with an increased risk of Alzheimer disease, have now been observed for thousands of complex diseases and traits, including autoimmune disease, asthma, and bone density/fractures. Genetic variants that implicate a novel gene in a process drive research into systems and pathways that can alter disease outcome. With increasingly large datasets and advances in statistical analyses, all the genetic variants that impact common disease risk can also be combined to derive a composite genetic risk score. This score can then be integrated with known environmental risk factors to identify individuals at particularly high risk of disease who might require more urgent intervention or monitoring. In adults, this approach is being developed to identify individuals at high risk for coronary heart disease, although concerns about how well genetic risk scores work in different population groups are yet to be overcome.

Low-cost methods for sequencing the complete coding (exomes) *and* full DNA sequence (genomes) of individuals have facilitated comprehensive evaluation of a wider range of genetic variants involved in common diseases. Rare genetic variants, including small insertions or deletions, are important in pediatric diseases such as neurodevelopmental disorders, cardiovascular malformations, and other birth defects. Common traits such as height, obesity, diabetes, and autoimmune diseases are also affected by rare variants. In common severe disorders such as intellectual disability and complex heart malformations, de novo pathogenic variants (i.e., pathogenic variants not present in either parent) play an important role.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Metabolic Disorders

PART IX

Chapter 104

An Approach to Inborn Errors of Metabolism

Oleg A. Shchelochkov and Charles P. Venditti

Many childhood conditions are caused by single-gene pathogenic variants that encode specific proteins. These pathogenic variants can change the primary protein structure or the amount of protein synthesized. The function of a protein, whether it is an enzyme, receptor, transport vehicle, membrane component, transcriptional coregulator, or structural element, may be compromised or abolished. Hereditary diseases that disrupt normal biochemical processes are termed **inborn errors of metabolism** or **inherited metabolic diseases** (Fig. 104.1).

Most genetic changes are clinically inconsequential and represent *benign* variants. However, pathogenic variants produce diseases that range in severity of presentation and the time of onset. Severe metabolic disorders usually become clinically apparent in the newborn period or shortly thereafter, whereas milder forms may present later in childhood and even in adulthood. With some exceptions, the presenting symptoms of most metabolic conditions lack the specificity to enable a definitive diagnosis without further evaluation. The combination of *low specificity* of presenting symptoms and *low prevalence* of metabolic disorders makes specific diagnosis difficult. Progressive symptoms, the absence of a plausible nongenetic diagnosis after detailed evaluation, history of overlapping symptoms in a patient's relatives, or consanguinity should alert a pediatrician to seek a consultation with a geneticist and prompt metabolic testing early in the evaluation.

Correct diagnosis is often only the beginning of a long medical journey for most families affected by metabolic conditions (see Chapter 95). Although each inherited metabolic disorder is individually rare, improved diagnosis and increasing survival of patients with metabolic conditions virtually ensure that a pediatrician will encounter and provide care to affected patients. Pediatricians can play a critical role in establishing the continuity of care; managing some aspects of treatment; fostering adherence; and delivering routine pediatric interventions such as immunizations, referrals to specialists, and elements of genetic counseling (see Chapter 98.1).

The greater awareness of metabolic conditions, wider availability of biochemical laboratories, global metabolomic analysis, and routine application of exome and genome sequencing dramatically increased the detection rate of the known disorders and contributed to the discovery of new metabolic disorders. Nonetheless, collection and analysis of family history remain critical screening tests that a healthcare provider can use to identify an infant or child at risk for a metabolic disorder. The identification of consanguinity or a particular ethnic background with an unusually high incidence of inborn errors of metabolism can be important to direct further studies. For example, tyrosinemia type 1 is more common among French Canadians of Quebec, maple syrup urine disease is seen with higher frequency in the U.S. Amish population, and Canavan disease is more common in patients of the Ashkenazi Jewish ancestry.

NEWBORN SCREENING

The individual rarity of inborn errors of metabolism, the importance of early diagnosis, and the ensuing genetic counseling ramifications make a strong argument for the universal screening of all newborn infants. **Tandem mass spectrometry** of metabolites and **enzyme assays** form the foundation of first-tier newborn screening. Worldwide, newborn screening programs have begun incorporating reflex second-tier testing using **molecular analysis** of target genes. These methods require only a few drops of blood to be placed on a filter paper and delivered to a central laboratory for assay. Many genetic conditions can be identified by these methods, and the list of disorders continues to grow (Tables 104.1 and 104.2). Pediatricians need to be aware of the general screening procedure and limitations of screening. As a screening method, a positive result may require a repeat newborn screen or confirmatory testing to secure the diagnosis. The time required to return the results varies from country to country and even within states in the same country. Some metabolic conditions can be severe enough to cause clinical manifestations before the results of the newborn screening become available. Conversely, diagnostic metabolites in milder forms of screened disorders may not reach a set threshold to trigger secondary studies, thus leading to negative newborn screen results and delayed diagnosis. *Therefore negative newborn screening in a patient with symptoms suggestive of a metabolic disorder warrants a referral to a genetics specialist for further evaluation.*

Universal newborn screening may also identify mild forms of inherited metabolic conditions, some of which may never cause clinical manifestations in the lifetime of the individual. For example, short-chain acyl-CoA dehydrogenase deficiency has been identified with unexpectedly high frequency in screening programs using tandem mass spectrometry, but most of these children have remained asymptomatic. This highlights the need for an ongoing evaluation of metabolite cutoff values and approaches to confirmatory testing to maximize the diagnostic yield and minimize potential psychosocial and economic implications of such findings. Premature infants represent a special population in whom the incidence of false-positive or false-negative test results can be especially high.

With the advent of genetic therapy for spinal muscular atrophy (SMA) and enzyme replacement therapy for some lysosomal storage diseases (e.g., Pompe disease, Fabry disease, Gaucher disease, and mucopolysaccharidosis type 1), most state newborn screening programs include screening for SMA and lysosomal storage disorders.

CLINICAL MANIFESTATIONS OF GENETIC METABOLIC DISEASES

Physicians and other healthcare providers who care for children should familiarize themselves with early manifestations of inborn errors of metabolism, because (1) severe forms of some of these conditions may cause symptoms before the results of screening studies become available and (2) the current screening methods, although quite extensive, identify a small number of all inherited metabolic conditions. In the newborn period, the clinical findings are usually nonspecific and similar to those seen in infants with sepsis. An inborn error of metabolism should be considered in the differential diagnosis of a severely ill newborn infant, and special studies should be undertaken if the index of suspicion is high (see Fig. 104.1).

Signs and symptoms such as lethargy, hypotonia, hypothermia, convulsions (Table 104.3), poor feeding, and vomiting may develop as early as a few hours after birth. Occasionally, vomiting may be severe enough to suggest the diagnosis of pyloric stenosis, which is usually not present, although it may occur simultaneously in some infants.



Fig. 104.1 Sunburst chart depicting the hierarchical nature of the International Classification of Inherited Metabolic Disorders. The size of each section of the chart is directly proportional to the number of disorders in that group. *Including phosphatidylinositol (with lesser numbers for ether lipids and lesser still for phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine) (*From Ferreira CR, Rahman S, Keller M, et al. An international classification of inherited metabolic disorders [ICIMD]. J Inherit Metab Dis. 2021;44:164–177, Fig. 1.*)

Table 104.1 Core Conditions on the Recommended Uniform Screening Panel by the Advisory Committee on Heritable Disorders in Newborns and Children of the U.S. Health Resources & Services Administration*

DISORDERS OF ORGANIC ACID METABOLISM
Propionic acidemia
Methylmalonic acidemia (methylmalonyl-CoA mutase)
Methylmalonic acidemia (cobalamin disorders)
Isovaleric acidemia
3-Methylcrotonyl-CoA carboxylase deficiency
3-Hydroxy-3-methyglutaric aciduria
Holocarboxylase synthase deficiency
β-Ketothiolase deficiency
Glutaric acidemia type I

DISORDERS OF FATTY ACID METABOLISM
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Systemic primary carnitine deficiency

DISORDERS OF AMINO ACID METABOLISM
Classic phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia type 1
Argininosuccinic acidemia
Tyrosinemia type I

HEMOGLOBINOPATHIES
Sickle cell anemia (hemoglobin SS disease)
Hemoglobin S/β-thalassemia
Hemoglobin S/C disease

ENDOCRINE DISORDERS
Primary congenital hypothyroidism
Congenital adrenal hyperplasia

OTHER DISORDERS
Classic galactosemia
Biotinidase deficiency
Glycogen storage disease type II (Pompe disease)
Mucopolysaccharidosis type 1
X-linked adrenoleukodystrophy
Cystic fibrosis
Hearing loss
Severe combined immunodeficiency (SCID)
Critical congenital heart disease
Spinal muscular atrophy (SMA) due to homozygous deletion of exon 7 in *SMN1*

*Adopted from https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html, last revised in February 2020.

Table 104.2 Secondary Conditions on the Recommended Uniform Screening Panel by the Advisory Committee on Heritable Disorders in Newborns and Children of the U.S. Health Resources & Services Administration

ORGANIC ACID METABOLISM DISORDERS
Methylmalonic acidemia with homocystinuria
Malonic acidemia
2-Methyl-3-hydroxybutyric aciduria
Isobutyryl-CoA dehydrogenase deficiency
2-Methylbutyryl-CoA dehydrogenase deficiency
3-Methylglutaconic aciduria

FATTY ACID OXIDATION DISORDERS
Short-chain acyl-CoA dehydrogenase deficiency
Glutaric acidemia type 2
Medium-/short-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency
Medium-chain ketoacyl-CoA thiolase deficiency
Carnitine palmitoyltransferase IA deficiency
Carnitine palmitoyltransferase II deficiency
Carnitine-acylcarnitine translocase deficiency
2,4-Dienoyl-CoA reductase deficiency

AMINO ACID METABOLISM DISORDERS
Hyperphenylalaninemia, benign (not classic phenylketonuria)
Tyrosinemia type II
Tyrosinemia type III
Defects of biopterin cofactor biosynthesis
Defects of biopterin cofactor regeneration
Argininemia
Hypermethioninemia
Citrullinemia type II (citrin deficiency)

HEMOGLOBINOPATHIES
Hemoglobin variants (including hemoglobin E)

OTHERS
Galactose epimerase deficiency
Galactokinase deficiency
T-cell–related lymphocyte deficiencies

Table 104.3 Select Inborn Errors of Metabolism Associated with Neurologic and Laboratory Manifestations in Neonates

DETERIORATION IN CONSCIOUSNESS
Metabolic Acidosis
Organic acidemias
Disorders of pyruvate metabolism
Fatty acid oxidation defects
Fructose-1,6-bisphosphatase deficiency
Glycogen storage diseases
Mitochondrial respiratory chain defects
Disorders of ketone metabolism

HYPOGLYCEMIA*
Fatty acid oxidation defects
Disorders of gluconeogenesis
Disorders of fructose and galactose metabolism
Glycogen storage diseases
Disorders of ketogenesis
Organic acidemias
Hyperinsulinemic hypoglycemias
Mitochondrial respiratory chain defects
Neonatal intrahepatic cholestasis caused by citrin deficiency
Disorders of pyruvate metabolism
Carbonic anhydrase VA deficiency

Continued

Table 104.3 Select Inborn Errors of Metabolism Associated with Neurologic and Laboratory Manifestations in Neonates—cont'd

HYPERAMMONEMIA**
Urea cycle disorders
Organic acidemias
Fatty acid oxidation disorders
Disorders of pyruvate metabolism
GLUD1-related hyperinsulinemic hypoglycemia
Carbonic anhydrase VA deficiency

SEIZURES AND HYPOTONIA
Antiquitin deficiency (pyridoxine-dependent epilepsy)
Pyridoxamine 5′-phosphate oxidase (PNPO) deficiency (pyridoxal phosphate-responsive epilepsy)
Folate metabolism disorders
Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency)
Urea cycle disorders
Organic acidemias
Fatty acid oxidation disorders
Disorders of creatine biosynthesis and transport
Disorders of neurotransmitter metabolism
Molybdenum cofactor deficiency and sulfite oxidase deficiency
Serine deficiency disorders
Glycine encephalopathy
Asparagine synthetase deficiency
Mitochondrial respiratory chain defects
Zellweger spectrum disorders
Congenital disorders of glycosylation
Purine and pyrimidine metabolism defects

NEONATAL APNEA
Glycine encephalopathy
Asparagine synthetase deficiency
Urea cycle disorders
Organic acidemias
Disorders of pyruvate metabolism
Fatty acid oxidation defects
Mitochondrial respiratory chain defects

*Refer to Table 104.4 for more details on the metabolic disorders associated with neonatal hypoglycemia.
**Refer to Table 104.5 for more details on the differential diagnosis of neonatal and infantile hyperammonemia.
Modified from El-Hattab AW. Inborn errors of metabolism. *Clin Perinatol.* 2015;42:413–439, Box 1.

Table 104.4 Select Inborn Errors of Metabolism Associated with Neonatal Hypoglycemia

CATEGORY OF DISORDERS	DISORDERS
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase Ia deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency Medium-chain acyl-CoA dehydrogenase deficiency Very-long-chain acyl-CoA dehydrogenase deficiency Multiple acyl-CoA dehydrogenase deficiency
Disorders of gluconeogenesis	Fructose-1,6-diphosphatase deficiency Phosphoenolpyruvate carboxykinase deficiency
Disorders of fructose and galactose metabolism	Hereditary fructose intolerance Classic galactosemia
Glycogen storage diseases (GSD)	GSD type Ia (glucose-6-phosphatase deficiency) GSD type Ib (impaired glucose-6-phosphate exchanger) GSD type III (glycogen debrancher enzyme deficiency) GSD type VI (liver glycogen phosphorylase deficiency) GSD type IX (phosphorylase kinase deficiencies)
Disorders of ketone metabolism	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency Succinyl-CoA:3-oxoacid-CoA transferase (SCOT) deficiency β-Ketothiolase deficiency
Disorders of amino acid metabolism	Maple syrup urine disease
Organic acidemias	Propionic acidemia Methylmalonic acidemia Isovaleric acidemia Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency)
Hyperinsulinemic hypoglycemia	*HADH*-related disorder (3-alpha-hydroxyacyl-CoA dehydrogenase deficiency) *GLUD1*-related disorder (hyperammonemia-hyperinsulinism syndrome [HIHA])
Other	Mitochondrial respiratory chain defects Neonatal intrahepatic cholestasis caused by citrin deficiency Pyruvate carboxylase deficiency Carbonic anhydrase VA deficiency

Modified from Zinn AB. Inborn errors of metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant,* 10th ed. Philadelphia: Elsevier; 2015: Table 99.17, p. 1605.

Lethargy, poor feeding, seizures, and coma may also be seen in infants with hypoglycemia (Table 104.4) (see Chapters 113 and 147), hypocalcemia (Chapters 69 and 611), and hyperammonemia (Table 104.5) (Chapter 105). Measurements of blood concentrations of glucose and calcium and prompt response to intravenous injection of glucose or calcium help guide the diagnostic decisions.

Every organ can be affected by metabolic disorders. However, *physical examination* usually reveals nonspecific findings; most signs are related to the central nervous system such as lethargy, coma, seizures, hyperventilation, or opisthotonus. Hepatomegaly is a common finding in a variety of inborn errors of metabolism (Table 104.6). Cardiomyopathy (Table 104.7), dysmorphic features (Table 104.8),

Table 104.5 Differential Diagnosis of Hyperammonemia

INBORN ERRORS OF METABOLISM
Urea Cycle Enzyme Defects
N-acetylglutamate synthase (NAGS) deficiency
Carbamoyl phosphate synthetase one (CPS1) deficiency
Ornithine transcarbamylase (OTC) deficiency
Argininosuccinate synthetase (ASS) deficiency (citrullinemia type 1)
Argininosuccinate lyase (ASL) deficiency (argininosuccinic aciduria)
Arginase 1 deficiency
Transport and Synthesis Defects of Urea Cycle Intermediates
Hyperornithinemia-hyperammonemia-homocitrullinemia (HHH syndrome)
Citrullinemia type 2 caused by citrin deficiency
Lysinuric protein intolerance
Ornithine aminotransferase deficiency
Carbonic anhydrase VA deficiency
Organic Acidemias
Propionic acidemia
MMUT-related methylmalonic acidemia and cobalamin metabolism disorders
Isovaleric acidemia
Fatty Acid Oxidation Disorders
Long-chain fatty acid oxidation defects
Systemic primary carnitine deficiency
Other
Pyruvate carboxylase deficiency
GLUD1-related hyperinsulinemic hypoglycemia
Neonatal iron overload disorders (e.g., hereditary hemochromatoses)

ACQUIRED DISORDERS
Transient Hyperammonemia of the Newborn
Diseases of the Liver and Biliary Tract
Liver failure
Biliary atresia
Severe Systemic Neonatal Illness
Neonates sepsis
Heart failure
Medications
Valproic acid
Cyclophosphamide
5-Pentanoic acid
Asparaginase
Other
Reye syndrome

ANATOMIC VARIANTS
Vascular bypass of the liver (e.g., a portosystemic anastomosis)

TECHNICAL
Inappropriate sample collection (e.g., capillary blood or prolonged placement of a tourniquet)
Sample not immediately analyzed

Modified from El-Hattab AW. Inborn errors of metabolism. *Clin Perinatol*. 2015;42:413–439, Box 8.

and fetal hydrops (Table 104.9) are additional potential manifestations of a metabolic disorder (Table 104.10). Occasionally, a peculiar odor may offer an invaluable clue leading to the right diagnosis (Table 104.11).

In an increasing number of patients, a metabolic condition may be recognized months or years after birth. This is more typical in patients carrying milder autosomal recessive pathogenic variants, in mitochondrial disorders, in females affected by X-linked recessive conditions, and specific metabolic conditions that usually present later in life. There may be an episodic or intermittent pattern, with episodes of acute clinical manifestations separated by periods of seemingly disease-free states. The episodes are usually triggered by stress or nonspecific catabolic stress such as an infection, overfeeding, prolonged fasting, or physical exertion. Thus an inborn error of metabolism should be considered in any child with one or more of the following unexplained clinical manifestations: failure to thrive; coarse facial features and reduced range of motion in the joints; developmental delay; intellectual disability; developmental regression; motor deficits or adventitious movements (e.g., dystonia, choreoathetosis, ataxia); seizures; catatonia; myopathy; intermittent episodes of unexplained vomiting, acidosis, mental deterioration, psychosis, or coma; hepatomegaly; renal stones; renal dysfunction, especially Fanconi syndrome or renal tubular acidosis; cardiomyopathy; persistent leukopenia; megaloblastic anemia; and unusual odor (particularly during an acute illness) (Table 104.12).

Diagnosis usually requires a variety of specific laboratory studies. Plasma amino acid analysis, total plasma homocysteine, plasma acylcarnitine profile, total and free carnitine levels, and urine organic acid assay, although not exhaustive in their diagnostic scope, are useful as initial screening tests to evaluate for a suspected inborn error of metabolism. Measurements of plasma ammonia, glucose, lactate, bicarbonate, and pH are readily available in hospitals and very helpful *initially* in differentiating major causes of genetic metabolic disorders (Table 104.13 and Fig. 104.2). Elevation of blood ammonia is usually caused by defects of urea cycle enzymes, organic acidemias, and disorders of fatty acid oxidation. Infants with elevated blood ammonia levels from urea cycle defects tend to have normal serum pH and bicarbonate values; without measurement of blood ammonia, they may remain undiagnosed and succumb to their disease. In organic acidemias, elevated plasma ammonia is accompanied by severe acidosis caused by accumulation of organic acids, ketone bodies, and lactate in body fluids.

When blood ammonia, pH, and bicarbonate values are normal, other aminoacidopathies (e.g., hyperglycinemia) or galactosemia should be considered. Galactosemic infants may also manifest cataracts, hepatomegaly, ascites, and jaundice.

Currently, more targeted assays, such as those used with newborn screening, have the highest sensitivity in the diagnosis or monitoring of specific disorders in question. However, some success has been shown in the context of undiagnosed individuals where metabolomic (assays for entire small molecule metabolites) data can be correlated with genomic information to provide supporting evidence for a pathogenic variant in a suspected causal gene.

TREATMENT

Most patients with genetic disorders of metabolism respond to one or more of the following treatments:

1. Special diets play an important role in the treatment of affected children. Dietary changes should be tailored to the pathophysiology of the condition and vary greatly among disorders.
2. Hemodialysis for expeditious removal of accumulated noxious compounds. This is a very effective modality for treatment of the acute phase of the condition.
3. Catabolic states in patients at risk for metabolic crisis can be treated with fluids containing dextrose and electrolytes.
4. Administration of the deficient metabolite.
5. Administration of the cofactor or coenzyme to maximize the residual enzyme activity.
6. Activation of alternative pathways to reduce the noxious compounds accumulated because of the genetic abnormality.
7. Administration of the deficient enzyme.
8. Bone marrow transplantation.
9. Liver and kidney transplantation.

Table 104.6 Select Metabolic Disorders Associated with Hepatic Dysfunction

CATEGORY OF DISORDERS	DISORDERS
Disorders of amino acid metabolism	Tyrosinemia type I Citrullinemia type II caused by citrin deficiency Disorders of methionine metabolism Urea cycle disorders
Biliary tract disorders and disorder of bile acid synthesis	See Chapter 383
Disorders of fructose and galactose metabolism	Hereditary fructose intolerance Classic galactosemia Epimerase deficiency galactosemia
Congenital disorders of glycosylation	Multiple types
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase Ia deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency Very-long-chain acyl-CoA dehydrogenase deficiency Multiple acyl-CoA dehydrogenase deficiency
Glycogen storage disorders (GSD)	GSD type 1a (deficiency of glucose-6-phosphatase catalytic activity) GSD type 1b (a defect in glucose-6-phosphate exchanger encoded by *SLC37A4*) GSD type III (glycogen debrancher enzyme deficiency) GSD type IV (glycogen branching enzyme deficiency) GSD type VI (liver glycogen phosphorylase deficiency)
Peroxisomal disorders	Zellweger spectrum disorders Disorders of peroxisomal β-oxidation
Mitochondrial respiratory chain (RC) defects	Mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) defects: Specific single-nucleotide pathogenic variants in mtDNA Large-scale mtDNA re-arrangements (Pearson syndrome) Disorders of mitochondrial translation (e.g., $tRNA^{Glu}$) Disorder of protein synthesis of RC complexes Disorders affected the assembly or stabilization of RC complexes (e.g., *BCS1L*) Disorders of cofactor biosynthesis (e.g., coenzyme Q10) Disorders of mitochondrial transport and dynamics mtDNA depletion syndromes (e.g., *DGUOK, MPV17, POLG, SUCLG1*)
Lysosomal storage disorders	Niemann-Pick disease type C
Other	α_1-Antitrypsin deficiency

Modified from Zinn AB. Inborn errors of metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant,* 10th ed. Philadelphia: Elsevier; 2015: Table 99.5, p. 1579.

Table 104.7 Select Metabolic Disorders Associated with Cardiomyopathy

CATEGORY OF DISORDERS	DISORDERS
Organic acidemias	Propionic acidemia Cobalamin C deficiency 3-methylglutaconic acidurias (e.g., Barth syndrome and DCMA syndrome)
Lysosomal storage disorders	Sphingolipidoses (e.g., Fabry disease) Oligosaccharidoses and mucolipidoses (e.g., I-cell disease) Mucopolysaccharidoses
Glycogen storage disorders (GSD)	GSD type II (Pompe disease) GSD type III (glycogen debrancher enzyme deficiency) *PRKAG2*-related disorders (includes lethal congenital glycogen storage disease of heart)
Congenital disorders of glycosylation	Multiple types
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency *ACAD9*-related disorder (mitochondrial acyl-CoA dehydrogenase deficiency) Multiple acyl-CoA dehydrogenase deficiency (includes glutaric aciduria type 2) Very-long-chain acyl-CoA dehydrogenase deficiency Systemic primary carnitine deficiency
Mitochondrial respiratory chain (RC) defects	Mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) defects: Specific single-nucleotide pathogenic variants in mtDNA Large-scale mtDNA deletions Disorders of mitochondrial translation (e.g., $tRNA^{Leu}$) Disorders of protein synthesis of RC complexes (e.g., *MT-ATP6, MT-ATP8, NDUFS2, NDUFV2, SDHA, SCO2, COX10, COX15*) Disorders affecting the assembly or stabilization of RC complexes (e.g., *TMEM70*) Disorders of cofactor biosynthesis (e.g., coenzyme Q10) Disorders of mitochondrial transport and dynamics (e.g., *SLC25A3*) mtDNA depletion syndromes (e.g., *SUCLG1*)
Other	Danon disease

DCMA, dilated cardiomyopathy with ataxia.
Modified from Zinn AB. Inborn errors of metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant,* 10th ed. Philadelphia: Elsevier; 2015: Table 99.4, p. 1576.

Table 104.8 Select Inborn Errors of Metabolism Associated with Dysmorphic Features

CATEGORY OF DISORDERS	DISORDERS
Congenital disorders of glycosylation	N-Glycosylation disorders (e.g., PMM2-CDG and ALG3-CDG) O-Glycosylation disorders (e.g., Walker-Warburg syndrome)
Disorders of cholesterol biosynthesis	Smith-Lemli-Opitz syndrome Desmosterolosis Lathosterolosis *EBP*-related disorder (includes Conradi-Hunermann syndrome)
Lysosomal storage disorders	Sphingolipidoses Oligosaccharidoses and mucolipidoses Mucopolysaccharidoses
Organic acidurias	Multiple acyl-CoA dehydrogenase deficiency (includes glutaric aciduria type 2) Mevalonic aciduria*
Peroxisomal disorders	Zellweger spectrum disorders Disorders of peroxisomal β-oxidation
Other	Pyruvate dehydrogenase complex deficiency

*Mevalonic aciduria has been classified as an organic acidemia based on the method used for its diagnosis, but it can also be classified as a peroxisomal single-enzyme disorder or as a defect in cholesterol biosynthesis because of its intracellular location or function.

Modified from Zinn AB. Inborn errors of metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant,* 10th ed. Philadelphia: Elsevier; 2015: Table 99.8, p. 1583.

Table 104.9 Select Inborn Errors of Metabolism Associated with Hydrops Fetalis

LYSOSOMAL STORAGE DISORDERS	ZELLWEGER SPECTRUM DISORDERS
Mucopolysaccharidoses types I, IVA, and VII	Glycogen storage disease type IV
Sphingolipidoses (e.g., Gaucher disease, Farber disease, Niemann-Pick disease A, GM_1 gangliosidosis, multiple sulfatase deficiency)	Congenital disorders of glycosylation
Lipid storage diseases (Wolman and Niemann-Pick disease C)	Mitochondrial respiratory chain defects
Oligosaccharidases (e.g., sialidosis type I)	Transaldolase deficiency
Mucolipidoses (e.g., I-cell disease)	

Modified and adapted from El-Hattab AW. Inborn errors of metabolism. *Clin Perinatol.* 2015;42:413–439, Box 6.

Table 104.10 Physical Examination Findings Associated with Inborn Errors of Metabolism (Select Examples)

FINDINGS	DISORDERS
Hepatomegaly	Disorders of fructose and galactose metabolism (e.g., classic galactosemia and hereditary fructose intolerance) Glycogen storage diseases Disorders of gluconeogenesis Disorders of fatty acid oxidation and transport Mitochondrial respiratory chain defects Tyrosinemia type 1 Urea cycle disorders Zellweger spectrum disorders Niemann-Pick disease type C Congenital disorders of glycosylation
Hepatosplenomegaly	Mucopolysaccharidoses Niemann-Pick disease types A, B, and C Sphingolipidoses (e.g., GM_1 gangliosidosis or Gaucher disease) Wolman disease Farber disease (acid ceramidase deficiency)
Macrocephaly	Glutaric acidemia type 1 Canavan disease
Microcephaly	Mitochondrial respiratory chain defects Disorders of intracellular cobalamin metabolism (e.g., *cblC* deficiency) Cholesterol metabolism disorders (e.g., Smith-Lemli-Opitz syndrome) Serine synthesis disorders
Coarse facial features	Mucopolysaccharidoses Oligosaccharidoses and mucolipidoses (e.g., α-mannosidosis) Sphingolipidoses (e.g., GM_1 gangliosidosis) Galactosialidosis
Macroglossia	Glycogen storage disease type II (Pompe disease) Mucopolysaccharidoses Oligosaccharidoses and mucolipidoses Sphingolipidoses Galactosialidosis
Dystonia or extrapyramidal signs	Gaucher disease type 2 Glutaric acidemia type 1 Methylmalonic acidemia Propionic acidemia Krabbe disease Crigler-Najjar syndrome Disorders of neurotransmitter metabolism Pyruvate dehydrogenase complex deficiency
Macular "cherry-red spot"	GM_1 gangliosidosis Tay-Sachs disease (GM_2 gangliosidosis) Farber disease (acid ceramidase deficiency) Galactosialidosis Niemann-Pick disease type A Sialidosis Multiple sulfatase deficiency
"Bull eye" maculopathy	*cblC* and *cblD* deficiency (combined methylmalonic acidemia and homocystinuria, type C)
Retinitis pigmentosa	Mitochondrial respiratory chain defects Peroxisomal disorders Abetalipoproteinemia
Optic nerve atrophy or hypoplasia	Pyruvate dehydrogenase complex deficiency Mitochondrial respiratory chain defects Peroxisomal disorders Propionic acidemia *MMUT*-related methylmalonic acidemia and cobalamin metabolism disorders

Continued

Table 104.10 Physical Examination Findings Associated with Inborn Errors of Metabolism (Select Examples)—cont'd

FINDINGS	DISORDERS
Corneal clouding or opacities	Mucolipidoses Mucopolysaccharidoses Steroid sulfatase deficiency Tyrosinemia type II Cystinosis
Cataracts	Disorders of galactose metabolism (e.g., classic galactosemia) Congenital disorders of glycosylation Mitochondrial respiratory chain (RC) defects Peroxisomal disorders Lowe oculocerebrorenal syndrome
Dislocated lens	Cystathionine β-synthase deficiency Molybdenum cofactor deficiency and sulfite oxidase deficiency
Skeletal dysplasias and dysostosis multiplex	Oligosaccharidoses and mucolipidoses Mucopolysaccharidoses Sphingolipidoses Galactosialidosis Peroxisomal disorders Disorders of cholesterol biosynthesis Congenital disorders of glycosylation
Thick skin	Oligosaccharidoses and mucolipidoses Mucopolysaccharidoses Sphingolipidoses
Desquamating, eczematous, or vesiculobullous skin lesions	Acrodermatitis enteropathica Essential amino acid deficiencies in organic acidemias Hartnup disorder Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency) Porphyrias
Ichthyosis	Gaucher disease type 2 Steroid sulfatase deficiency Refsum disease *ELOVL4*-related disorder Serine deficiency disorders
Alopecia	Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency)
Steely or kinky hair	Menkes disease
Trichorrhexis nodosa	Argininosuccinic aciduria (ASL deficiency)
Megaloblastic anemia	Cobalamin metabolism disorders Folate metabolism disorders Mevalonic aciduria Orotic aciduria Pearson syndrome
Leukopenia	Folate metabolism disorders Organic acidemias Pearson syndrome
Persistent diarrhea	Glucose-galactose malabsorption Congenital lactase deficiency Congenital chloride diarrhea Sucrase-isomaltase deficiency Acrodermatitis enteropathica Abetalipoproteinemia Congenital folate malabsorption Wolman disease Lysinuric protein intolerance Classic galactosemia

Modified from Cederbaum S. Introduction to metabolic and biochemical genetic diseases. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*, 10th ed. Philadelphia: Elsevier; 2018: Table 21.1, p. 227.

Table 104.11 Inborn Errors of Amino Acid Metabolism Associated with Peculiar Odor

INBORN ERROR OF METABOLISM	URINE ODOR
Isovaleric acidemia Glutaric acidemia (type II)	"Sweaty feet," acrid
Maple syrup urine disease	Maple syrup, burnt sugar
Multiple carboxylase deficiency 3-Methylcrotonyl-CoA carboxylase deficiency 3-Hydroxy-3-methylglutaric aciduria	Cat urine
Phenylketonuria	Mousey or musty
Trimethylaminuria Dimethylglycine dehydrogenase deficiency	Rotten fish
Tyrosinemia type 1	Boiled cabbage, rancid butter
Hypermethioninemia	Boiled cabbage
Cystinuria Tyrosinemia type I	Sulfur
Hawkinsinuria	"Swimming pool"
Oasthouse urine disease	Hopslike

In select inborn errors of metabolism, organ transplantation modalities may offer the best treatment modality to stabilize a metabolic patient and improve quality of life. To date, replacement of the affected gene with a normal copy using gene therapy has been successful in only a few diseases.

Treatment of genetic disorders of metabolism is complex and requires medical and technical expertise. Effective treatment is best achieved by a team of specialists—metabolic genetics specialist, nutritionist, neurologist, and psychologist—in a major medical center. The therapeutic regimen often needs to be tailored to the individual patient because of large phenotypic variations in the severity of the disease, even within a single family. Providing genetic counseling, education, and ongoing social services support for the family is the key to successful long-term therapy. Even in patients with poor prognoses, every effort should be made to establish correct diagnoses premortem.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 104.12 Clinical Findings That Should Prompt a Metabolic Workup

Family history	Sibling(s) who died from unexplained causes or exhibit overlapping symptoms Ethnic groups with a high prevalence of metabolic disorders Consanguinity
Perinatal history	Intrauterine growth restriction, sepsis-like presentation in the neonatal period, nonimmune fetal hydrops
Growth	Postnatal failure to thrive, microcephaly, macrocephaly, short stature
Central and peripheral nervous systems	Progressive encephalopathy, lethargy, coma, intractable seizures, developmental delay, developmental regression, intellectual disability, autism spectrum disorder, hypotonia, spasticity, dystonia, strokes, ataxia, psychosis, intracranial calcifications, white matter disease, peripheral neuropathy
Respiratory system	Hyperventilation, apnea
Cardiovascular system	Cardiac failure with or without cardiomyopathy, arrhythmia
Musculoskeletal system	Rhabdomyolysis, myopathy Osteopenia, early-onset osteoporosis, skeletal dysplasia, epiphyseal abnormalities, bone crises
Eye	Retinitis pigmentosa, macular dystrophy, cataracts, corneal opacities, nystagmus, cherry-red spot
Hearing	Sensorineural hearing loss
Gastrointestinal system	Hepatomegaly, hepatic adenoma, splenomegaly, liver failure, Reye syndrome, cholestasis, cirrhosis, chronic diarrhea, vomiting, acute pancreatitis
Kidney	Renal dysfunction, renal Fanconi syndrome, renal stones
Hematologic system	Anemia, leukopenia, thrombocytopenia, pancytopenia, hemolytic-uremic syndrome
Skin	Hair abnormality, alopecia, lipodystrophy, recalcitrant eczema

Table 104.13 Laboratory Findings That Should Prompt a Metabolic Workup

Hyperammonemia	Hypoglycemia
Metabolic acidosis	Liver dysfunction
Lactic acidosis	Pancytopenia
Ketosis	

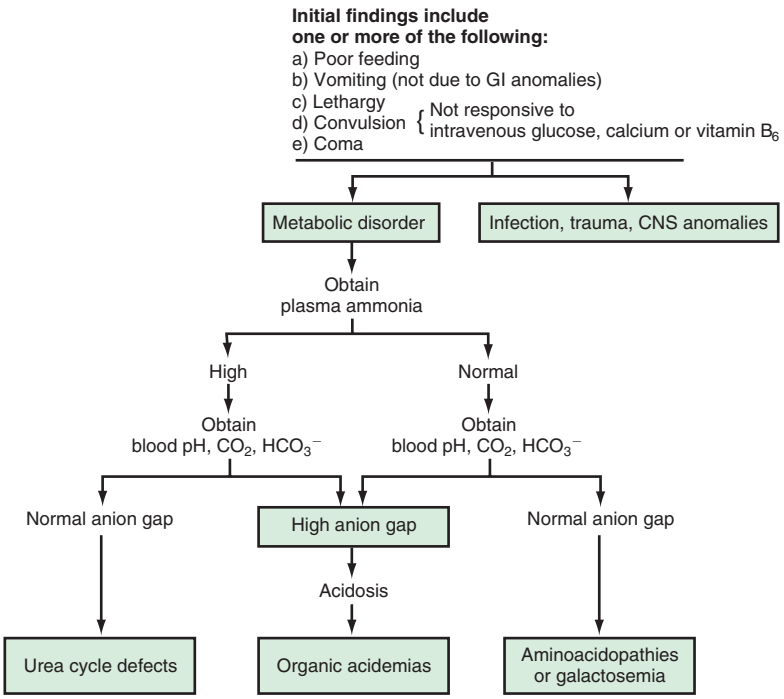

Fig. 104.2 Algorithm showing the initial clinical approach to a full-term newborn infant with a suspected genetic metabolic disorder. This schema is a guide to elucidate some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases affected by disorders or intermediate metabolism. CNS, Central nervous system; GI, gastrointestinal; HCO_3^-, bicarbonate.

Chapter 105

Defects in Metabolism of Amino Acids

105.1 Phenylalanine

Oleg A. Shchelochkov and Charles P. Venditti

Phenylalanine is an essential amino acid. Dietary phenylalanine that is not used for protein synthesis is normally degraded by way of the tyrosine pathway (Fig. 105.1). Deficiency of the enzyme **phenylalanine hydroxylase (PAH)** or one of its cofactors **tetrahydrobiopterin (BH_4)** causes accumulation of phenylalanine and its metabolites in body fluids and in the brain.

Elevations of phenylalanine in the plasma reflect the degree of enzyme deficiency, presenting as a spectrum of biochemical and clinical findings. In patients with **severe PAH deficiency** (also referred to as *classical phenylketonuria*), plasma phenylalanine levels on an unrestricted diet usually exceed 20 mg/dL (>1,200 µmol/L). Patients with milder PAH pathogenic variants have plasma phenylalanine levels between 10 mg/dL (600 µmol/L) and 20 mg/dL (1,200 µmol/L). Levels between 2 and 10 mg/dL (120 and 600 µmol/L) on an unrestricted diet are observed in patients with **mild hyperphenylalaninemia**. In affected infants with plasma concentrations >20 mg/dL, excess phenylalanine is metabolized to phenylketones (phenylpyruvate and phenylacetate; see Fig. 105.1) that are excreted in the urine, giving rise to the term *phenylketonuria* (PKU). These metabolites have no known role in the mechanisms of central nervous system (CNS) damage in PKU patients, but their presence in body fluids can signify the severity of the condition. The **brain** is most vulnerable to the damage incurred by PKU, but the exact mechanism of injury remains elusive. Both toxic elevations of phenylalanine and insufficient tyrosine may play roles. Phenylalanine hydroxylase converts phenylalanine to **tyrosine**, which is necessary for the production of neurotransmitters such as epinephrine, norepinephrine, and dopamine (Fig. 105.2). If the degree of enzymatic block is severe, tyrosine becomes an essential amino acid and may be deficient if its intake is not adequate. On the other hand, observations that lower concentrations of phenylalanine in plasma and brain tissue are associated with improved neurobehavioral outcomes support the view that toxic levels of phenylalanine are key to PKU pathogenesis. High blood levels of phenylalanine can saturate the transport system across the blood-brain barrier (BBB) and inhibit the cerebral uptake of other large neutral amino acids such as the branched-chain amino acids tyrosine and tryptophan, impairing brain protein synthesis.

SEVERE PHENYLALANINE HYDROXYLASE DEFICIENCY (CLASSIC PHENYLKETONURIA)

Elevations of plasma phenylalanine >20 mg/dL (>1,200 µmol/L), if untreated, invariably result in the development of signs and symptoms of classic PKU, except in uncommon and unpredictable cases.

Clinical Manifestations

The affected infant appears normal at birth. Profound intellectual disability gradually develops if the infant remains untreated. Cognitive delay may not be evident for the first few months. In untreated patients, 50–70% will have an IQ below 35, and 88–90% will have an IQ below 65. Less than 5% of untreated patients attain IQ scores in the average range. Vomiting, sometimes severe enough to be misdiagnosed as pyloric stenosis, may be an early symptom. Older untreated children become hyperactive and show autistic behaviors, including stereotypic hand movements and rhythmic rocking.

Untreated and undertreated infants are lighter in their complexion than unaffected siblings. Some may have a seborrheic or eczematoid rash, which is usually mild and disappears with age. Affected children have an odor of phenylacetic acid, which has been described as musty or "mousey." Neurologic signs include seizures (approximately 25%), spasticity, hyperreflexia, tremors, and athetosis; >50% have electroencephalographic (EEG) abnormalities. Microcephaly, prominent maxillae with widely spaced teeth, enamel hypoplasia, and growth retardation are other common findings in untreated children. Low bone mineral density and osteopenia have been reported in affected individuals of all ages. Although inadequate intake of natural proteins seems to be the major culprit, the exact pathogenesis of this sequela remains unclear.

Long-term care of patients with PKU is best achieved by a team of experienced professionals (metabolic specialist, nutritionist, and psychologist), typically in a regional treatment center. The clinical manifestations of classical PKU are rarely seen in countries where neonatal screening programs for the detection of PKU are in effect.

Non-PKU Hyperphenylalaninemia

Implementation of universal screening for PKU led to identification of a group of infants in whom initial plasma concentrations of phenylalanine are above normal (i.e., >2 mg/dL, or 120 µmol/L) but <20 mg/dL (1,200 µmol/L). These infants typically do not excrete phenylketones. Patients with non-PKU hyperphenylalaninemia may still require dietary therapy, depending on their untreated plasma phenylalanine level. Attempts have been made to classify these patients into different subgroups depending on the degree of hyperphenylalaninemia, but the effects of this classification on PKU management and outcomes remain to be clarified. The possibility of deficiency of tetrahydrobiopterin (BH_4) should be investigated in all infants, especially those with milder forms of hyperphenylalaninemia.

Diagnosis

Because of the gradual and nonspecific nature of early clinical symptoms such as vomiting, developmental delay, or eczematoid rash, hyperphenylalaninemia is usually diagnosed through newborn screening in all developed countries. In infants with positive screening results, the diagnosis should be confirmed by quantitative measurement of plasma phenylalanine concentration and molecularly by identifying pathogenic variants in *PAH*. Identification and measurement of phenylketones in the urine have no place in any screening program. In countries and places where such programs are not in effect, identification of phenylketones in the urine by ferric chloride may offer a simple test for the diagnosis of infants with developmental and neurologic abnormalities. All patients with a biochemical diagnosis of hyperphenylalaninemia should undergo pterin measurements in blood or urine to evaluate for defects in BH_4 synthesis or recycling.

Neonatal Screening for Hyperphenylalaninemia

Effective and relatively inexpensive methods for mass screening of newborn infants are used in the United States and many other countries. A few drops of blood, which are placed on a filter paper and mailed to a central laboratory, are used for assay. The screening method of choice uses **tandem mass spectrometry**, which can identify all forms of hyperphenylalaninemia with a low false-positive rate and excellent accuracy and precision. The addition of the phenylalanine:tyrosine molar ratio can improve test specificity and reduce the number of false-positive results. Diagnosis must be confirmed by measurement of plasma phenylalanine concentration and, ultimately by identifying pathogenic variants in *PAH*. Blood phenylalanine in affected infants with PKU may rise to diagnostic levels as early as 4 hours after birth, even in the absence of protein feeding. However, to reduce the number of false-negative results, especially in the milder forms of the condition, it is recommended that the blood for screening be obtained in the first 24-48 hours of life after feeding protein.

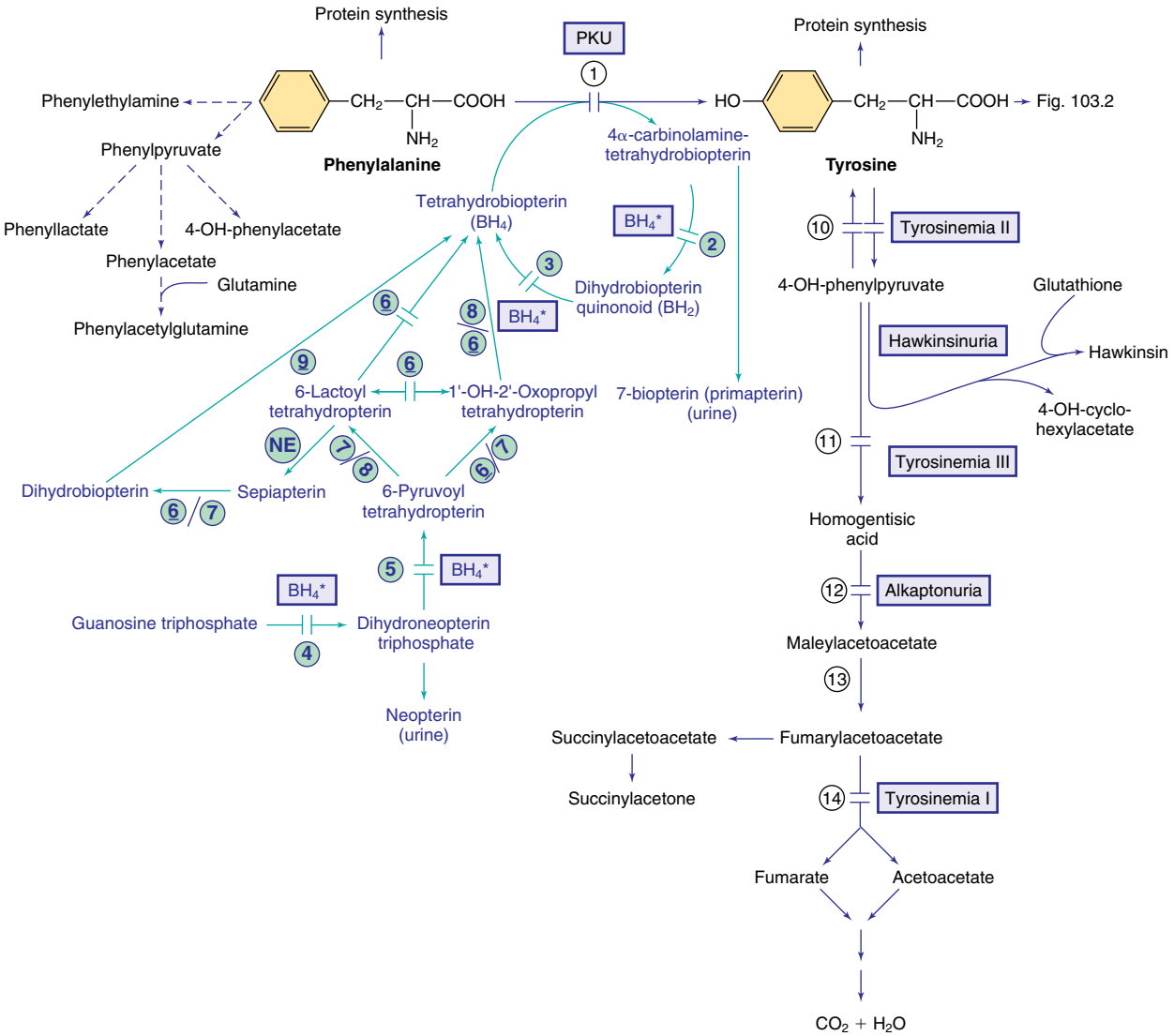

Fig. 105.1 Pathways of phenylalanine and tyrosine metabolism. Enzyme defects causing genetic conditions are depicted as *horizontal bars* crossing the reaction arrow(s). Pathways for synthesis of cofactor BH_4 are shown in *purple*. BH_4* refers to defects of BH_4 metabolism that affect the phenylalanine, tyrosine, and tryptophan hydroxylases (see Figs. 105.2 and 105.5). PKU, Phenylketonuria; NE, nonenzymatic. **Enzymes:** *(1)* Phenylalanine hydroxylase, *(2)* pterin-carbinolamine dehydratase, *(3)* dihydrobiopterin reductase, *(4)* guanosine triphosphate (GTP) cyclohydrolase, *(5)* 6-pyruvoyltetrahydropterin synthase, *(6)* sepiapterin reductase, *(7)* carbonyl reductase, *(8)* aldolase reductase, *(9)* dihydrofolate reductase, *(10)* tyrosine aminotransferase, *(11)* 4-hydroxyphenylpyruvate dioxygenase, *(12)* homogentisic acid dioxygenase, *(13)* maleylacetoacetate isomerase, *(14)* fumarylacetoacetate hydrolase.

Treatment

The mainstay of treatment of PKU is a *low-phenylalanine diet*. The general consensus is to start diet treatment immediately in patients with blood phenylalanine levels >10 mg/dL (600 µmol/L). It is recommended that infants with persistent (more than a few days) plasma levels of phenylalanine ≥6 mg/dL (360 µmol/L) should also be treated with a phenylalanine-restricted diet similar to that in classic PKU. The goal of therapy is to reduce phenylalanine levels in the plasma and brain. Formulas free of or low in phenylalanine are commercially available. The diet should be started as soon as the diagnosis is established. Because phenylalanine is not synthesized endogenously, the diet should provide phenylalanine to prevent phenylalanine deficiency. Dietary phenylalanine tolerance is determined based on age and severity of the PAH deficiency. **Phenylalanine deficiency** is manifested by lethargy, failure to thrive, anorexia, anemia, rashes, diarrhea, and even death. Furthermore, tyrosine can become an essential amino acid in this disorder, and its adequate intake must be ensured. Special food items low in phenylalanine are commercially available for dietary treatment of affected children and adults.

There is no firm consensus concerning optimal levels of blood phenylalanine in affected patients either across different countries or among treatment centers in the United States. The current recommendation is to maintain blood phenylalanine levels between 2 and 6 mg/dL (120 and 360 µmol/L) throughout life. Discontinuation of therapy, even in adulthood, may cause deterioration of neurocognitive performance.

Lifelong adherence to a low-phenylalanine diet is extremely difficult. Patients who maintain good control as children but discontinue the phenylalanine-restricted diet as teenagers or adults may experience significant difficulties with executive function, concentration, emotional liability, and depression. Executive dysfunction may also occur in early-treated children despite diet treatment.

Given the difficulty of maintaining a strict low-phenylalanine diet, there are continuing attempts to find other modalities for treatment of these patients. Administration of **large neutral amino acids** (LNAAs) is one approach to dietary therapy. LNAAs (tyrosine, tryptophan, leucine, isoleucine, valine, methionine, histidine, and phenylalanine) use the same transporter protein (LNAA type 1 or LAT-1) for transit

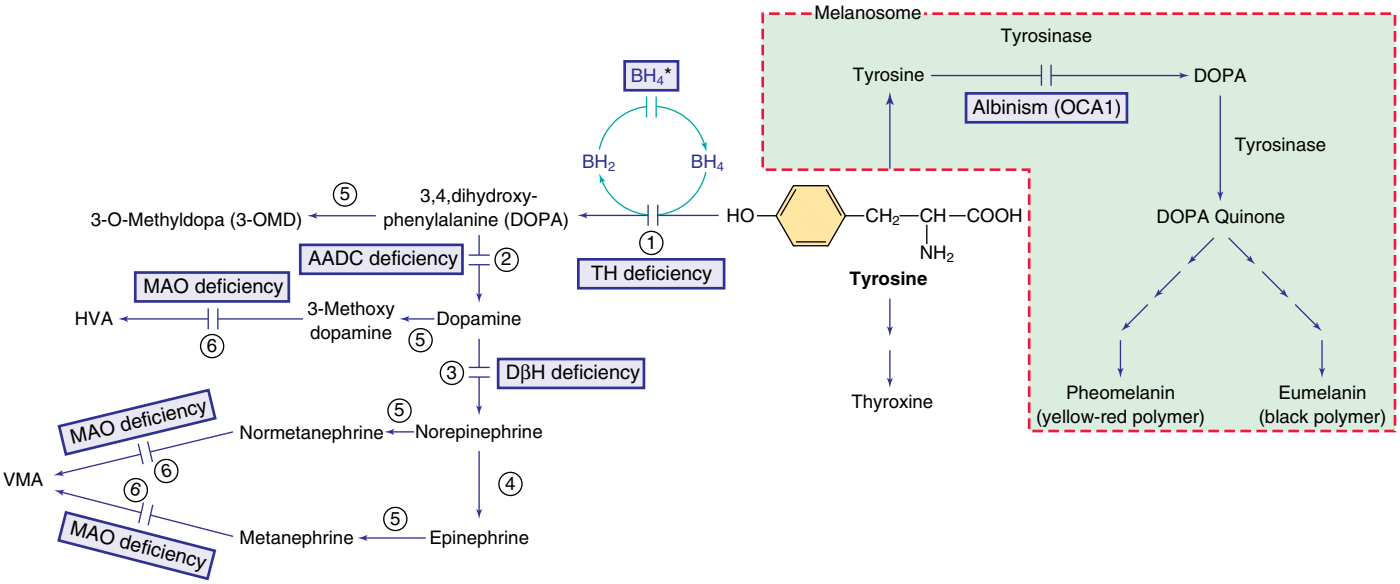

Fig. 105.2 Other pathways involving tyrosine metabolism. BH_4* indicates hyperphenylalaninemia caused by tetrahydrobiopterin (BH_4) deficiency (see Fig. 105.1). HVA, Homovanillic acid; VMA, vanillylmandelic acid. **Enzymes:** *(1)* Tyrosine hydroxylase (TH), *(2)* aromatic L-amino acid decarboxylase (AADC), *(3)* dopamine β-hydroxylase (DβH), *(4)* phenylethanolamine-*N*-methyltransferase (PNMT), *(5)* catechol *O*-methyltransferase (COMT), *(6)* monoamine oxidase (MAO).

through the intestinal cell membrane and BBB. Binding of LNAAs to the transporter is a competitive process. Therefore when LNAAs compete with phenylalanine at the transport level, their large concentrations in the intestinal lumen and blood can reduce the uptake of phenylalanine into the bloodstream and the brain, respectively. Large, controlled clinical trials are necessary to establish the efficacy of this treatment.

Oral administration of BH_4, the cofactor for PAH, may result in the reduction of plasma phenylalanine in some patients with PAH deficiency. Plasma phenylalanine in these patients may decrease enough to allow for considerable modification of their dietary restriction. In very rare cases the diet may be discontinued because the phenylalanine remains under 6 mg/dL (360 µmol/L). The response to BH_4 cannot be predicted consistently based on the genotype alone, especially in compound heterozygous patients. **Sapropterin dihydrochloride**, a synthetic form of BH_4, which acts as a cofactor in patients with residual PAH activity, is approved by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) to reduce phenylalanine levels in PKU. A sustained decrease of plasma phenylalanine by at least 30% is consistent with sapropterin responsiveness. Injectable PEGylated recombinant phenylalanine ammonia–lyase has been approved by the FDA and EMA for adult PKU patients with uncontrolled blood phenylalanine levels greater than 600 µmol/L despite prior management.

Pregnancy in Women with PAH Deficiency (Maternal Phenylketonuria)

Pregnant women with PAH deficiency who are not on a phenylalanine-restricted diet have a very high risk of having offspring with intellectual disability, microcephaly, growth retardation, congenital malformations, and congenital heart disease. These complications are directly correlated with elevated maternal blood phenylalanine levels during pregnancy. Prospective mothers who have been treated for PAH deficiency should be maintained on a phenylalanine-restricted diet before and during pregnancy. The best observed outcomes occur when strict control of maternal blood phenylalanine concentration is instituted before pregnancy. Plasma phenylalanine levels >6 mg/dL (360 µmol/L) after conception are associated with increased incidence of intrauterine growth restriction and congenital malformations, as well as lower performance on neurocognitive testing. However, there is strong evidence that phenylalanine control instituted after conception can also result in improved outcomes. The recommended phenylalanine concentration is 2-6 mg/dL (120-360 µmol/L) throughout the pregnancy, although some expert groups advocate plasma phenylalanine levels <4 mg/dL (<240 µmol/L). All women with PAH deficiency who are of childbearing age should be counseled properly regarding the risk of congenital anomalies in their offspring.

HYPERPHENYLALANINEMIA CAUSED BY DEFICIENCY OF THE COFACTOR TETRAHYDROBIOPTERIN

In 1–3% of infants with hyperphenylalaninemia, the defect resides in one of the enzymes necessary for production or recycling of the cofactor BH_4 (see Fig. 105.1). If these infants are misdiagnosed as having PKU, they may deteriorate neurologically despite adequate control of plasma phenylalanine. BH_4 is synthesized from guanosine triphosphate (GTP) through several enzymatic reactions (see Fig. 105.1). In addition to acting as a cofactor for PAH, BH_4 is also a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are involved in the biosynthesis of dopamine (see Fig. 105.2) and serotonin (see Fig. 105.5), respectively. Therefore patients with hyperphenylalaninemia resulting from BH_4 deficiency also manifest neurologic findings related to deficiencies of these neurotransmitters. Four enzyme deficiencies leading to defective BH_4 formation cause hyperphenylalaninemia with concomitant deficiencies of dopamine and serotonin: autosomal recessive GTP cyclohydrolase I deficiency (encoded by *GCH1*), 6-pyruvoyl-tetrahydropterin synthase deficiency (encoded by *PTS*), dihydropteridine reductase deficiency (encoded by *QDPR*), and pterin-4-α-carbinolamine dehydratase deficiency (encoded by *PCBD1*). 6-Pyruvoyl-tetrahydropterin synthase is the most frequent cause of hyperphenylalaninemia-associated BH_4 deficiency. Autosomal dominant forms of GTP cyclohydrolase I deficiency and sepiapterin reductase deficiency result in deficiencies of neurotransmitters without hyperphenylalaninemia (see Chapter 105.11).

Clinical Manifestations

Infants with cofactor BH_4 deficiency are identified during screening programs for PKU because of hyperphenylalaninemia. Plasma phenylalanine levels may be as high as those in classic PKU or may be in the milder range. However, clinical manifestations of the neurotransmitter disorders differ greatly from those of PKU. Neurologic symptoms of the neurotransmitter disorders often manifest in the first few months of life and include extrapyramidal signs (choreoathetotic or dystonic limb movements, axial and truncal hypotonia, hypokinesia), feeding

difficulties, and autonomic abnormalities. Intellectual disability, seizures, hypersalivation, and swallowing difficulties can also be seen. The symptoms are usually progressive and often have a marked diurnal fluctuation. Prognosis and outcome strongly depend on the age of diagnosis, treatment, and the underlying enzyme defect.

Diagnosis

Despite the low incidence of BH_4 synthesis and recycling defects, all newborns with hyperphenylalaninemia detected through newborn screening *must* be screened for BH_4 synthesis defects. BH_4 deficiency and the responsible enzyme defect may be diagnosed by several studies.

Measurement of Neopterin and Biopterin

Neopterin (an oxidative product of dihydroneopterin triphosphate) and biopterin (an oxidative product of dihydrobiopterin and BH_4) are measured in body fluids, especially urine (see Fig. 105.1). In patients with the autosomal recessive form of GTP cyclohydrolase I deficiency, urinary excretion of both neopterin and biopterin is reduced and is often very low. In patients with 6-pyruvoyl-tetrahydropterin synthase deficiency, there is a marked elevation of neopterin excretion and a concomitant decrease in biopterin excretion. Patients with pterin-4-α-carbinolamine dehydratase deficiency can be identified by detecting urinary primapterin (an isomer of biopterin). In dihydropteridine reductase deficiency, no consistent pattern in the excretion of neopterin and biopterin has been observed, thus necessitating enzymatic studies of DHPR in erythrocytes and/or molecular confirmation through *QDPR* gene analysis.

Cerebrospinal Fluid Studies

Examination of cerebrospinal fluid (CSF) may reveal decreased levels of dopamine and serotonin metabolites (see Chapter 105.11).

BH_4 Loading Test

An oral dose of BH_4 (20 mg/kg) normalizes plasma phenylalanine and the phenylalanine:tyrosine ratio in patients with BH_4-responsive deficiency within 4-12 hours. The baseline blood phenylalanine should be elevated (>400 μmol/L) to enable interpretation of the results. This may be achieved by discontinuing diet therapy for 2 days before the test. In BH_4-responsive PAH deficiency, blood phenylalanine levels may decrease during the BH_4 loading test but increase later, even with BH_4 supplementation. Patients who demonstrate phenylalanine levels within the normal range over at least 1 week without a phenylalanine-restricted diet can continue BH_4 supplementation as the sole treatment for the hyperphenylalaninemia. However, it is imperative that plasma phenylalanine levels be monitored prospectively to ensure that phenylalanine levels remain within the normal range.

Molecular Testing

Sequencing and deletion/duplication analysis are clinically available and have an important role in confirming the biochemical diagnosis of PAH deficiency and of the BH_4 synthesis and recycling disorders.

Enzyme Assay

The activity of dihydropteridine reductase can be measured in the dry blood spots on the filter paper used for screening purposes or in erythrocytes. 6-Pyruvoyl-tetrahydropterin synthase activity can be measured in liver tissue, fibroblasts, and erythrocytes. Pterin-4-α-carbinolamine dehydratase activity can be measured in liver tissue and fibroblasts. GTP cyclohydrolase I activity can be measured in the liver and in cytokine (interferon-γ)–stimulated mononuclear cells or fibroblasts (the enzyme activity is normally very low in unstimulated cells). Molecular testing offers a more convenient method to secure the diagnosis in this group of disorders.

Treatment

The goals of therapy are to correct hyperphenylalaninemia and to restore neurotransmitter deficiencies in the CNS. Control of hyperphenylalaninemia is important in patients with cofactor deficiency because high levels of phenylalanine cause intellectual disability and interfere with the transport of neurotransmitter precursors (tyrosine and tryptophan) into the brain. Plasma phenylalanine should be maintained as close to normal as possible (<6 mg/dL or <360 μmol/L). This can be achieved by oral supplementation of BH_4 (5-20 mg/kg/day). Sapropterin dihydrochloride, the synthetic form of BH_4, is commercially available but expensive. In patients receiving dietary interventions, phenylalanine and tyrosine deficiencies should be avoided.

Lifelong supplementation with neurotransmitter precursors such as L-dopa and 5-hydroxytryptophan, along with carbidopa to inhibit degradation of L-dopa before it enters the CNS, is necessary in most of these patients even when treatment with BH_4 normalizes plasma levels of phenylalanine. BH_4 does not readily enter the brain to restore neurotransmitter production. To minimize untoward side effects (especially L-dopa–induced dyskinesia), the treatment should be started with low doses of L-dopa/carbidopa and 5-hydroxytryptophan. The treatment should be gradually adjusted based on response to therapy and clinical improvement for each individual patient. Supplementation with folinic acid is also recommended in patients with dihydropteridine reductase deficiency. Unfortunately, attempting to normalize neurotransmitter levels using neurotransmitter precursors usually does not fully resolve the neurologic symptoms because of the inability to attain normal levels of BH_4 in the brain. Patients often demonstrate intellectual disability, fluctuating abnormalities of tone, eye movement abnormalities, poor balance and coordination, decreased ability to ambulate, and seizures despite supplementation with neurotransmitter precursors.

Hyperprolactinemia occurs in patients with BH_4 deficiency and may be the result of hypothalamic dopamine deficiency. Measurement of serum prolactin levels may be a convenient method for monitoring adequacy of neurotransmitter replacement in affected patients.

Some drugs, such as trimethoprim/sulfamethoxazole, methotrexate, and other antileukemic agents, are known to inhibit dihydropteridine reductase enzyme activity and should be used with great caution in patients with BH_4 deficiency.

Genetics and Prevalence

All defects causing hyperphenylalaninemia are inherited as autosomal recessive traits. Autosomal dominant forms of GTP cyclohydrolase I deficiency and sepiapterin reductase deficiency result in neurotransmitter disorders without hyperphenylalaninemia (see Chapter 105.11). The prevalence of PKU in the United States is estimated at 1 in 14,000 to 1 in 20,000 live births. The prevalence of non-PKU hyperphenylalaninemia is estimated at 1 in 50,000 live births. Most patients are compound heterozygotes for two different pathogenic variants.

TETRAHYDROBIOPTERIN DEFECTS WITHOUT HYPERPHENYLALANINEMIA

See Chapter 105.11.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.2 Tyrosine

Oleg A. Shchelochkov and Charles P. Venditti

Tyrosine is derived from ingested proteins or is synthesized endogenously from phenylalanine. It is used for protein synthesis and as a precursor of dopamine, norepinephrine, epinephrine, melanin, thyroxine, and quinoproteins. Excess tyrosine is metabolized to carbon dioxide and water through the tyrosine degradation pathway (see Fig. 105.1). Hereditary causes of hypertyrosinemia include deficiencies of the enzymes fumarylacetoacetate hydrolase **(FAH)**, tyrosine aminotransferase **(TAT)**, and 4-hydroxyphenylpyruvate dioxygenase **(4-HPPD)**. **Acquired hypertyrosinemia** may occur in severe hepatocellular dysfunction (liver failure), scurvy (vitamin C is a cofactor for 4-HPPD), and hyperthyroidism. Hypertyrosinemia is common in blood samples obtained soon after eating and in premature infants.

TYROSINEMIA TYPE I (FUMARYLACETOACETATE HYDROLASE DEFICIENCY, HEPATORENAL TYROSINEMIA)

Tyrosinemia type I is a severe multisystemic disease caused by FAH deficiency. Liver, kidney, and nerve damage is likely caused by metabolites of tyrosine degradation, especially fumarylacetoacetate and succinylacetone.

Clinical Manifestations and Natural History

Affected infants may appear healthy at birth but develop symptoms in the first year of life. Most patients present between 2 and 6 months of age but rarely may become symptomatic in the first month or appear unaffected beyond the first year of life. Earlier presentation confers poorer prognosis. In untreated children, a 1-year mortality can approach 60% if infants develop symptoms before 2 months of age and decrease to 4% in infants who become symptomatic after 6 months.

An acute **hepatic crisis** typically heralds the disease onset and is usually precipitated by an intercurrent illness leading to a catabolic state. Fever, irritability, vomiting, hemorrhage, hepatomegaly, jaundice, elevated levels of serum transaminases, hypoglycemia, and neuropathy are common. An odor resembling boiled cabbage resulting from increased methionine metabolites may be present. Without treatment, hepatic crises may progress to liver failure and death. Between the crises, varying degrees of failure to thrive, hepatomegaly, and coagulation abnormalities often persist. Cirrhosis and eventually hepatocellular carcinoma occur with increasing age.

Episodes of acute **peripheral neuropathy** resembling acute porphyria occur in approximately 40% of affected children. These crises, often triggered by a minor infection, are characterized by severe pain, often in the legs, associated with extensor hypertonia of the neck and trunk, vomiting, paralytic ileus, and occasionally self-induced injuries of the tongue or buccal mucosa. Marked weakness occurs in about 30% of episodes, which may lead to respiratory failure requiring mechanical ventilation. Crises typically last 1-7 days, but recuperation from paralytic crises can take weeks to months.

Renal involvement manifests as a Fanconi renal syndrome with hyperphosphaturia, hypophosphatemia, normal–anion gap metabolic acidosis, and vitamin D–resistant rickets. Nephromegaly and nephrocalcinosis may be present on ultrasound examination. Glomerular abnormalities can be observed in adolescents and older patients.

Hypertrophic cardiomyopathy and hyperinsulinism are seen in some infants.

Laboratory Findings

Elevated levels of succinylacetone in serum and urine are diagnostic for tyrosinemia type I (see Fig. 105.1). Succinylacetone levels may fall below the diagnostic threshold in patients treated with nitisinone. In untreated patients, serum α-fetoprotein is increased, often greatly, and liver-synthesized coagulation factors are decreased in most patients. Increased levels of α-fetoprotein are present in the cord blood of affected infants, indicating liver damage beginning prenatally. Serum transaminase levels are often increased, with marked increases during acute hepatic episodes. Serum concentration of bilirubin is usually normal but can be increased in severe liver failure. Plasma tyrosine levels are usually elevated at diagnosis, but this is a nonspecific finding and can vary depending on dietary intake. Plasma levels of other amino acids, particularly methionine, may also be elevated in patients with liver damage. Hyperphosphaturia, hypophosphatemia, and generalized aminoaciduria may occur. Urinary 5-aminolevulinic acid (also known as *delta-aminolevulinic acid*) is elevated due to the inhibition of 5-aminolevulinate dehydratase by succinylacetone (see Fig. 112.1).

Diagnosis is usually established by demonstration of elevated succinylacetone in urine or blood. Neonatal screening for hypertyrosinemia using tyrosine alone detects only a fraction of patients with tyrosinemia type I. Succinylacetone assayed by many neonatal screening programs has higher sensitivity and specificity than tyrosine and is the preferred metabolite for screening. Tyrosinemia type I should be differentiated from other causes of hepatitis and hepatic failure in infants, including galactosemia, hereditary fructose intolerance, neonatal iron storage disease, giant cell hepatitis, citrullinemia type II, citrin deficiency, and hemophagocytic lymphohistiocytosis (see Chapter 105.12).

Treatment and Outcome

A diet low in phenylalanine and tyrosine can slow, but not halt, the progression of the condition. The treatment of choice is **nitisinone** (NTBC), which inhibits 4-HPPD, reduces the flux of tyrosine metabolites to FAH, and decreases the production of the offending compounds fumarylacetoacetate and succinylacetone (see Fig. 105.1). The dose of nitisinone is titrated to the lowest, most effective dose (usually targeting the blood range of 20-40 μmol/L), aiming to suppress succinylacetone production while maintaining a plasma tyrosine level <400 μmol/L (7.2 mg/dL). This treatment with nitisinone can prevent acute hepatic and neurologic crises. Although nitisinone greatly slows disease progression, pretreatment liver damage cannot be completely reversed. Therefore patients must be followed for the development of cirrhosis or hepatocellular carcinoma. On imaging, the presence of even a single liver nodule usually indicates underlying cirrhosis. Most liver nodules in FAH-deficient patients are benign, but current imaging techniques cannot accurately distinguish all malignant nodules. For patients with severe liver failure not responding to nitisinone, liver transplantation is an effective therapy, which can also alleviate the risk of hepatocellular carcinoma. The impact of nitisinone treatment on liver transplantation is under study, but the greatest positive effect is seen in patients treated early, such as children detected by neonatal screening, before developing clinical symptoms. In early-treated patients, nitisinone has greatly reduced the need for liver transplantation. Because nitisinone treatment can increase plasma tyrosine, a low-tyrosine, low-phenylalanine diet is recommended. Rarely, nitisinone-treated patients develop corneal crystals, presumably composed of tyrosine, but these tend to be reversible with strict dietary compliance. This finding, combined with observations of developmental delay in some patients with tyrosinemia type II who chronically have elevated tyrosine levels, suggest that a diet low in phenylalanine and tyrosine should be continued in patients treated with nitisinone. The dietary treatment of patients with tyrosine and phenylalanine restriction necessitates surveillance of growth and development by ensuring adequate intake of amino acids and other nutrients.

Genetics and Prevalence

Tyrosinemia type I is inherited as an autosomal recessive trait and is caused by biallelic pathogenic variants in *FAH*. DNA analysis is useful for carrier testing in groups at risk for specific pathogenic variants, such as French Canadians from the Saguenay-Lac Saint-Jean region of Quebec. The prevalence of tyrosinemia type I is estimated to be 1 in 1,846 live births in the Saguenay-Lac Saint-Jean region and approximately 1 in 100,000 live births worldwide. Prenatal screening can be performed by measurement of succinylacetone in amniotic fluid.

TYROSINEMIA TYPE II (TYROSINE AMINOTRANSFERASE DEFICIENCY, RICHNER-HANHART SYNDROME, OCULOCUTANEOUS TYROSINEMIA)

Tyrosinemia type II is a rare autosomal recessive disorder caused by deficiency of cytosolic tyrosine aminotransferase that results in palmar and plantar hyperkeratosis, herpetiform corneal ulcers, and intellectual disability (see Fig. 105.1). *Ocular manifestations,* which may occur as early as 6 months of age, include excessive tearing, redness, pain, and photophobia. Corneal lesions are presumed to be caused by tyrosine crystals deposition. In contrast to herpetic ulcers, corneal lesions in tyrosinemia type II stain poorly with fluorescein and often are bilateral. *Skin lesions,* which may develop later in life, include painful, nonpruritic hyperkeratotic plaques on the soles, palms, and fingertips. Intellectual disability, which occurs in approximately 50% of patients, is usually mild to moderate. The contribution of consanguinity in this rare disorder is incompletely understood.

The principal **laboratory finding** in untreated patients is marked hypertyrosinemia, >500 μmol/L, and it may reach 1,100-2,750 μmol/L. Surprisingly, in some patients urinary 4-hydroxyphenylpyruvic acid and its metabolites can be elevated despite them being downstream

from the metabolic block (see Fig. 105.1). It is hypothesized that other transaminases in the presence of high tyrosine concentrations can produce 4-hydroxyphenylpyruvic acid in mitochondria, where it cannot be further degraded. In contrast to tyrosinemia type I, liver and kidney function tend to be normal, as are serum concentrations of other amino acids and succinylacetone. Tyrosinemia type II is caused by tyrosine aminotransferase *(TAT)* gene pathogenic variants, causing a deficiency of cytosolic TAT activity in the liver.

Diagnosis of type II tyrosinemia is established by an assay of plasma tyrosine concentration in patients with suggestive findings and can be confirmed molecularly. An assay of hepatic TAT requires a liver biopsy and is rarely indicated.

Treatment with a diet low in tyrosine and phenylalanine, aiming to achieve plasma tyrosine levels <500 μmol/L, helps improve skin and eye manifestations. Early dietary intervention can lead to improved intellectual outcomes.

TYROSINEMIA TYPE III (PRIMARY DEFICIENCY OF 4-HYDROXYPHENYLPYRUVATE DIOXYGENASE)

Tyrosinemia type III is an autosomal recessive condition caused by biallelic pathogenic variants in *HPD* encoding the enzyme 4-HPPD. Only a few patients with tyrosinemia type III have been reported. Most were detected by amino acid chromatography performed for various neurologic findings. Therefore ascertainment bias likely confounds current understanding of this disorder. Some asymptomatic infants with 4-HPPD deficiency have been identified by neonatal screening for hypertyrosinemia. Age at presentation varied between 1 and 17 months. In symptomatic patients, developmental delay, seizures, intermittent ataxia, and self-injurious behavior have been reported. Liver and renal abnormalities tend to be absent.

The role of 4-HPPD deficiency in the disease needs further study. The **diagnosis** is suspected in children with sustained moderate increases in plasma levels of tyrosine (typically 350-700 μmol/L on a normal diet) and the presence of 4-hydroxyphenylpyruvic acid and its metabolites, urinary 4-hydroxyphenyllactate and 4-hydroxyphenylacetate. The diagnosis should be confirmed by demonstrating biallelic pathogenic variants in *HPD* or, rarely, by demonstrating a low activity of the 4-HPPD enzyme. The latter requires a liver biopsy and is not usually indicated.

Given a possible association with neurologic abnormalities and corneal deposition of tyrosine crystals, dietary control of plasma tyrosine levels is recommended. One could also consider a trial with vitamin C, the cofactor for 4-HPPD, which can help lower plasma tyrosine in some patients.

HAWKINSINURIA

Hawkinsinuria is a condition allelic to tyrosinemia type III (4-HPPD deficiency). Some specific missense variants (e.g., p.Ala33Thr or p.Asn241Ser) in *HPD* that encode 4-HPPD can result in uncoupling of typical oxidization of 4-hydroxyphenylpyruvate to homogentisic acid and lead to premature release of quinolacetic acid. The abnormal enzyme, incapable of normally oxidizing 4-hydroxyphenylpyruvate to homogentisic acid, forms an intermediate that reacts with glutathione to form the unusual organic acid **hawkinsin** ([2-L-cystein-*S*-yl-1,4-dihydroxycyclohex-5-en-1-yl]acetic acid, see Fig. 105.1). As a result, secondary glutathione deficiency may ensue. Hawkinsinuria is inherited as an autosomal dominant trait. In one patient, compound heterozygosity for alleles associated with hawkinsinuria and tyrosinemia type III produced biochemical features of hawkinsinuria.

The clinical course of this rare disorder is incompletely understood. Individuals with hawkinsinuria may present with symptoms only during infancy. The symptoms usually appear in the first few months of life, typically after weaning from breastfeeding and with the introduction of a high-protein diet. Severe metabolic acidosis, ketosis, failure to thrive, anemia, mild hepatomegaly, renal tubular acidosis, and an unusual odor are reported manifestations of this disorder. Neurocognitive development is usually normal.

Symptomatic infants and asymptomatic affected children and adults excrete hawkinsin, 4-hydroxyphenylpyruvate, and its metabolites (4-hydroxyphenyllactate and 4-hydroxyphenylacetate) as well as 4-hydroxycyclohexylacetate and 5-oxoproline (due to secondary glutathione deficiency) in their urine. Plasma tyrosine is moderately elevated in symptomatic infants and may normalize in asymptomatic older patients.

Treatment consists of a low-protein diet during infancy. Breastfeeding is encouraged. Successful long-term use of *N*-acetyl-L-cysteine to treat secondary glutathione deficiency has been reported. A trial with vitamin C is recommended. Although the affected enzyme is susceptible to inhibition by nitisinone, clinical studies showing its efficacy in symptomatic infants are lacking, and the indications for its use are not known.

TRANSIENT TYROSINEMIA OF THE NEWBORN

In a small number of newborn infants, plasma tyrosine may be as high as 3,300 μmol/L during the first 2 weeks of life. Most affected infants are premature and are on a high-protein diet. Transient tyrosinemia is thought to result from delayed maturation of 4-HPPD (see Fig. 105.1). Lethargy, poor feeding, and decreased motor activity are noted in some patients. Most are asymptomatic and are identified by a high blood phenylalanine or tyrosine level on routine newborn screening. Laboratory findings include marked elevation of plasma tyrosine with a moderate increase in plasma phenylalanine. The finding of hypertyrosinemia differentiates this condition from PKU. 4-Hydroxyphenylpyruvic acid and its metabolites are present in the urine. Hypertyrosinemia tends to resolve spontaneously in the first 2 months of life and can be improved by reducing dietary protein to below 2 g/kg/day and by administering vitamin C. Mild intellectual deficits have been reported in some infants who had this condition, but the causal relationship to hypertyrosinemia has not been conclusively established.

ALKAPTONURIA

Alkaptonuria is a rare (approximately 1 in 250,000 live births) autosomal recessive disorder caused by a deficiency of homogentisate 1,2-dioxigenase encoded by *HGD*. Large amounts of homogentisic acid are formed (see Fig. 105.1) and excreted in urine or deposited in tissues. Alkaptonuria has a worldwide distribution, with a higher disease prevalence in the Dominican Republic and Slovakia.

The main **clinical manifestations** of alkaptonuria consist of ochronosis and arthritis in adulthood. The only sign in children is blackening of the urine on standing, caused by oxidation and polymerization of homogentisic acid. A history of gray- or black-stained diapers should suggest the diagnosis. This sign may never be noted, thus delaying the diagnosis until adulthood. *Ochronosis,* seen clinically as dark spots on the sclera or ear cartilage, results from the accumulation of the black polymer of homogentisic acid. *Arthritis* is another result of this deposition and can be disabling with advancing age. It can involve the spine and large joints (shoulders, hips, and knees) and is usually more severe in males. As with rheumatoid arthritis, the alkaptonuric arthritis has acute exacerbations, but its radiologic findings are more typical of osteoarthritis, with characteristic narrowing of the joint spaces and calcification of the intervertebral disks. A high incidence of heart disease (mitral and aortic valvulitis, calcification of heart valves, myocardial infarction) has been reported.

The **diagnosis** is confirmed by finding massive excretion of homogentisic acid on urine organic acid testing. Tyrosine levels are normal. The enzyme is expressed in high levels only in the liver and kidneys.

Treatment of the arthritis is symptomatic. In clinical trials, nitisinone, an inhibitor of 4-HPPD, has been shown to reduce urinary homogentisic acid. Additional studies are needed to establish its clinical efficacy and safety profile.

TYROSINE HYDROXYLASE DEFICIENCY

See Chapter 105.11.

ALBINISM

See also Chapters 662 and 694.

Albinism is caused by impaired synthesis and distribution of **melanin**, the main pigment of the skin and eye (Table 105.1). Melanin is synthesized by melanocytes from tyrosine in a membrane-bound intracellular organelle, the melanosome. Melanocytes

Table 105.1 Classification of Major Causes of Albinism

TYPE	GENE	DISTINGUISHING MOLECULAR AND CLINICAL FEATURES
OCULOCUTANEOUS ALBINISM (OCA)		
OCA1A (severe deficiency)	*TYR*	OCA1A (no melanin synthesis) vs OCA1B (minimal amounts of melanin present). OCA1A results in poorer visual outcomes.
OCA2 (tyrosinase positive)	*OCA2*	Newborns typically have light pigment, and hair color can darken with age.
OCA3 (Rufous, red OCA)	*TYRP1*	TYRP1 is required for maturation of eumelanin, but not reddish pheomelanin.
OCA4	*SLC45A2*	Newborns typically have light pigment, and hair color can darken with age. Clinically, it tends to overlap with OCA2.
OCA6	*SLC24A5*	*SLC24A5* encodes the protein NCKX5 involved in the maturation of melanosomes.
OCA7	*LRMDA*	Tends to be associated with poorer visual outcomes.
OCA8	*DCT*	*DCT* encodes dopachrome tautomerase involved in the melanin synthesis upstream of TYRP1. Likely results in milder forms of OCA.
Hermansky-Pudlak syndrome	Multiple genes	A multisystemic, genetically heterogenous disorder characterized by OCA, bleeding tendency, interstitial pneumonia, and granulomatous colitis, among other complications.
Chédiak-Higashi syndrome	*LYST*	Results in partial OCA, bleeding tendency, immunodeficiency, and hemophagocytic lymphohistiocytosis.
OCULAR ALBINISM (OA)		
OA1 (Nettleship-Falls ocular albinism)	*GPR143*	X-linked inheritance. Affected males present with significant ocular manifestations with minor skin involvement.
LOCALIZED ALBINISM		
Piebaldism	*KIT* and *SNAI2*	Pathogenic variants in *KIT* have been associated with a number of phenotypes, including piebaldism, mastocytosis, familial, and sporadic cancers.
Waardenburg syndrome (WS1-WS4)	See text.	See text.

originate from the embryonic neural crest and migrate to the skin, eyes (choroid and iris), hair follicles, and inner ear. The melanin in the eye is confined to the iris stromal and retinal pigment epithelia, whereas in skin and hair follicles, it is secreted into the epidermis and hair shaft. Albinism can be caused by deficiencies of melanin synthesis, by some hereditary defects of melanosomes, or by disorders of melanocyte migration. Neither the biosynthetic pathway of melanin nor many facets of melanocyte cell biology are completely elucidated (see Fig. 105.2). The end products are two pigments: *pheomelanin,* which is a yellow-red pigment, and *eumelanin,* a brown-black pigment.

Clinically, primary albinism can be *generalized* or *localized.* Primary generalized albinism can be *ocular* or *oculocutaneous.* Some syndromes feature albinism in association with platelet, immunologic, or neurologic dysfunction. In generalized oculocutaneous albinism, hypopigmentation can be either complete or partial. Individuals with complete albinism do not develop either generalized (tanning) or localized (pigmented nevi) skin pigmentation.

The **diagnosis** of albinism is usually evident, but for some children whose families are particularly light-skinned, normal variation may be a diagnostic consideration. Unlike patients with albinism, unaffected fair-skinned children progressively develop pigmentation with age, do not exhibit the eye manifestations of albinism, and have pigmentary development similar to other family members. The clinical diagnosis of oculocutaneous albinism, as opposed to other types of cutaneous hypopigmentation, requires the presence of characteristic eye findings.

The **ocular manifestations** of albinism include hypopigmentation of the iris and retina, often with foveal hypoplasia, along with reduced visual acuity, refractive errors, nystagmus, alternating strabismus, and iris transillumination (diffuse reddish hue of the iris produced during ophthalmoscopic or slit-lamp examination of the eye).

Albinism is also associated with an abnormality in routing optic fibers at the chiasm. Unlike in pigmented individuals, in patients with albinism, the majority of nerve fibers from the temporal side of the retina cross to the contralateral hemisphere of the brain. This results in impaired depth perception, alternating strabismus, and a characteristic pattern of visual evoked potentials. These findings are highly specific for albinism. Regular ophthalmologic follow-up is recommended for patients with oculocutaneous albinism. Correction of refractive errors can maximize visual function. Usually, the alternating strabismus does not result in amblyopia and does not require surgery.

Patients with albinism should be counseled to avoid ultraviolet (UV) radiation by wearing protective long-sleeved clothing and by using sunscreens with a sun protection factor (SPF) rating >30. Melanin is also present in the cochlea; therefore albino individuals may be more susceptible to ototoxic agents such as gentamicin.

Genetics of Albinism

Oculocutaneous albinism is inherited as an autosomal recessive trait. Many clinical forms of albinism have been identified. Some of the seemingly distinct clinical forms are caused by different pathogenic variants of the same gene. Implicated genes are involved in different stages of melanogenesis and melanosome maturation (see Table 105.1). The classification outlined next is based on the distribution of albinism in the body and the affected genes. Genetic analysis is clinically available for most forms of albinism (see Table 105.1). Molecular diagnosis is of little use therapeutically in isolated albinism but can be helpful for precise genetic counseling of families.

Oculocutaneous (Generalized) Albinism

Lack of pigment is generalized, affecting skin, hair, and eyes. At least eight genetically distinct forms of oculocutaneous albinism **(OCA)** have been identified of which seven have pathogenic variants in

associated genes (OCA1, OCA2, OCA3, OCA4, OCA6, OCA7, and OCA8). Many forms of OCA may not be clinically distinguishable from one another. All affected individuals have ocular manifestations of albinism. All known forms of OCA are inherited as autosomal recessive traits.

OCA1

The defect in patients with OCA1 resides in the tyrosinase gene, *TYR*. Many pathogenic variants have been identified. Most affected individuals are compound heterozygotes. A clinical clue to the diagnosis of OCA1 is complete lack of pigment at birth. The condition can be subdivided into OCA1A and OCA1B, based on enzyme activity and difference in clinical manifestations as a function of age. In patients with OCA1A, the most severe form of OCA, both *TYR* alleles have pathogenic variants that completely inactivate tyrosinase. Clinically, lack of pigment in the skin (milky white), hair (white hair), and eyes (red-gray irides) is evident at birth and remains unchanged throughout life. They do not tan and do not develop pigmented nevi or freckles.

Patients with OCA1B have *TYR* gene pathogenic variants that preserve some residual activity. Clinically, they completely lack pigment at birth but with age become light blond with light-blue or hazel eyes. They develop pigmented nevi and freckles, and they may tan.

OCA2

OCA2 is the *most common form of generalized OCA,* particularly in patients of African ancestry. Clinically, the phenotype is highly variable; most patients demonstrate some pigmentation of the skin and eyes at birth and continue to accumulate pigment throughout life. The hair is yellow at birth and may darken with age. They have pigmented nevi and freckles, and some may tan. They may be clinically indistinguishable from OCA1B patients. Individuals with OCA2, however, have normal tyrosinase activity in hair bulbs. The defect is in the *OCA2* gene, which is an orthologue of the *p* (pink-eyed dilution) gene in the mouse. This gene produces the P protein, a melanosome membrane–bound protein. Patients with **Prader-Willi** and **Angelman** syndromes caused by microdeletion of chromosome 15q12 that includes the *OCA2* gene have mild pigmentary deficiency (see Chapter 98.8).

OCA3

This form has been identified predominantly in patients of African and Asian ancestry. Patients with OCA3 can make pheomelanin but not eumelanin. Patients have reddish hair and reddish-brown skin as adults. The skin color is peculiar to this form. In young persons the coloration may resemble that of OCA2. The altered gene *TYRP1* encodes the tyrosinase-related protein 1, the function of which is not well-understood.

OCA4

Similar manifestations to OCA2 (both in the skin and the eyes) have been observed in OCA4 patients (mostly from Japan) with pathogenic variants in the *SLC45A2* gene.

Ocular Albinism

Patients with ocular albinism **(OA)** present in the first months of life with nystagmus, hypopigmentation of the iris and fundus, foveal hypoplasia, and decreased visual acuity. Electron microscopy demonstrates characteristic macromelanosomes in skin biopsies or hair root specimens. Most patients affected by OA have ocular albinism type 1 **(OA1)**, an X-linked disorder caused by pathogenic variants in the *GPR143* gene. A rare form of OA with late-onset sensorineural deafness and apparent autosomal dominant inheritance has also been reported.

Ocular Albinism Type 1 (Nettleship-Falls Ocular Albinism)

OA1 is an X-linked disorder characterized by congenital nystagmus, reduced pigmentation of ocular structures, and visual impairment in affected males. Heterozygous females may present with segments of abnormal retinal pigmentations. Infrequently, depending on the pattern of X chromosome inactivation, heterozygous females may also present with severe manifestations, including nystagmus, iris and foveal hypopigmentation, foveal hypoplasia, and reduced visual acuity. In families with darker skin complexion, mild skin hypopigmentation can be seen. The diagnosis of OA1 is suspected in males with features of albinism in the eye, normal to mildly reduced skin pigmentation, and a family history suggestive of an X-linked transmission. It is a nonprogressive disorder, and the eye findings often improve with age. In patients who are the first of their families to be affected, genetic analysis of *GPR143* helps confirm the diagnosis.

Syndromic Forms of Generalized Albinism

Hermansky-Pudlak Syndrome

This group of autosomal recessive disorders is caused by biallelic pathogenic variants in one of ten genes *(HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S6, AP3D1)*. Hermansky-Pudlak syndrome **(HPS)** can be suspected in patients with albinism associated with a bleeding diathesis, inflammatory bowel disease (IBD), and/or pulmonary fibrosis. Disease subtype can be established with molecular studies (see Chapter 533). Genes associated with HPS are required for normal structure and function of lysosome-derived organelles, including melanosomes and platelet-dense bodies. Patients have a tyrosinase-positive OCA of variable severity associated with platelet dysfunction (caused by the absence of platelet-dense bodies). A ceroid-like material accumulates in tissues. HPS is pan-ethnic. Patient ancestry can help develop a cost-effective testing strategy. HPS is prevalent in two regions of Puerto Rico (**type 1** in the northwest and **type 3** in the central regions because of different founder effects). The cutaneous and ocular symptoms of albinism are present. Patients can develop epistaxis, postsurgical bleeding, or abundant menses. Bleeding time is prolonged, but platelet count is normal. Major complications include progressive pulmonary fibrosis in young adults and Crohn's-like IBD in adolescents and young adults. Kidney failure and cardiomyopathy have been reported. Neutropenia has been described in HPS **type 2**. Treatment is symptomatic.

Chédiak-Higashi Syndrome

Patients with this rare autosomal recessive condition have OCA of variable severity and susceptibility to infection (see Chapter 156). Bacterial infections of the skin and the upper respiratory tract are common. Giant peroxidase-positive lysosomal granules can be seen in granulocytes in a blood smear. Patients have a reduced number of melanosomes, which are abnormally large (macromelanosomes) and can have silvery-gray hair. The bleeding tendency is typically mild. If treatment is not successful, children can reach a stage of the disease known as the **accelerated phase**, which is a major, life-threatening complication of Chédiak-Higashi syndrome. It is caused by macrophage activation resulting in hemophagocytic lymphohistiocytosis with manifestations that include fever, lymphadenopathy, hepatosplenomegaly, cytopenia, and an elevated plasma ferritin level. Patients surviving childhood may develop cerebellar atrophy, peripheral neuropathy, and cognitive delay. Pathogenic variants in *LYST* are the only known cause for this syndrome. Hematopoietic stem cell transplantation offers an effective approach to control immunodeficiency and hematologic abnormalities and to prevent development of the accelerated phase.

Other Disorders Featuring Generalized Albinism

Hypopigmentation can be a feature in other syndromes, some with abnormalities of lysosomal biogenesis or melanosome biology. **Griscelli syndrome** patients have silver-gray hair, pigmentary dilution of skin, and melanosomal clumping in hair shafts and the center of melanocytes, with intellectual disability or macrophage activation with hemophagocytosis in different subtypes. All forms are autosomal recessive caused by pathogenic variants in *MLPH, MYO5A,* or *RAB27A*. **Vici syndrome** patients have combined immunodeficiency, intellectual disability, agenesis of the corpus callosum, cataracts, and cleft lip/palate. It is autosomal recessive, caused by pathogenic variants in *EPG5*. Patients with **MAPBP-interacting protein deficiency** have a short stature, recurrent infections, and neutropenia, and inheritance occurs in an autosomal recessive manner due to pathogenic variants in the gene *LAMTOR2*.

Localized Albinism

Localized albinism refers to localized patches of hypopigmentation of skin and hair, which may be evident at birth or develop with time. These conditions are caused by abnormal migration of melanocytes during embryonic development.

Piebaldism

Piebaldism is an autosomal dominant inherited condition in which the individual is usually born with a white forelock. The underlying skin is depigmented and devoid of melanocytes. In addition, there are usually white macules on the face, trunk, and extremities. Pathogenic variants in the *KIT* and *SNAI2* genes have been identified in affected patients.

Waardenburg Syndrome

In Waardenburg syndrome, a white forelock is often associated with lateral displacement of the inner canthi of the eyes, a broad nasal bridge, heterochromia of irides, and sensorineural deafness. This condition is inherited as an autosomal dominant trait with four main subtypes known. Patients with Waardenburg syndrome type 1 (**WS1**, the *most common form*) have all the previous clinical findings, including lateral displacement of the inner canthi. The condition is typically caused by pathogenic variants (>90%) in the *PAX3* gene. Patients with Waardenburg syndrome type 2 **(WS2)** have the clinical findings of WS1 except for the lateral displacement of the inner canthi. Genetically, this is a heterogeneous condition caused by pathogenic variants in several genes, including *MITF, SOX10,* and *SNAI2*. Patients with Waardenburg syndrome type 3 **(WS3)** have all the findings seen in individuals with WS1 plus hypoplasia and contractures of the upper limbs. It is caused by heterozygous or homozygous pathogenic variants of the *PAX3* gene. Finally, Waardenburg syndrome type 4 **(WS4)**, associated with **Hirschsprung disease**, is genetically heterogeneous, with pathogenic variants in different genes (*EDN3, EDNRB,* or *SOX10*) identified.

Other causes of **localized hypopigmentation** include vitiligo and hypomelanosis of Ito (see Chapter 694).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.3 Methionine

Oleg A. Shchelochkov and Charles P. Venditti

The usual pathway for catabolism of methionine, an essential amino acid, produces S-*adenosylmethionine,* which serves as a methyl group donor for methylation reactions for a variety of compounds, and *cysteine,* which is formed through a series of reactions collectively called *trans-sulfuration* (Fig. 105.3).

HOMOCYSTINURIA (HOMOCYSTINEMIA)

Normally, most *homocysteine,* an intermediate compound of methionine degradation, is remethylated to methionine. This methionine-sparing reaction is catalyzed by the enzyme methionine synthase, which requires a metabolite of folic acid (5-methyltetrahydrofolate) as a methyl donor and a metabolite of vitamin B_{12} (methylcobalamin) as a cofactor (see Fig. 105.3). In healthy individuals, most plasma homocysteine is either protein-bound or exists as disulfides. Three major forms of homocystinemia and homocystinuria have been identified.

Homocystinuria Caused by Cystathionine β-Synthase Deficiency (Classic Homocystinuria)

Classic homocystinuria is the most common inborn error of methionine metabolism. It is an autosomal recessive condition caused by biallelic pathogenic variants in *CBS* encoding cystathionine β-synthase. Clinical presentation in the first years of life is nonspecific. Universal newborn screening to detect elevated methionine in dried blood spot samples can identify most affected infants. Second-tier testing after a positive newborn screen result should include plasma methionine and total plasma homocysteine and followed up by confirmatory testing using *CBS* molecular gene analysis. Most affected patients are compound heterozygotes for two different alleles. Heterozygous carriers are asymptomatic.

Infants with classic homocystinuria appear healthy at birth. **Clinical manifestations** during infancy are nonspecific and may include failure to thrive and developmental delay. Without newborn screening, the diagnosis can be delayed and is usually made after 3 years of age, when subluxation of the ocular lens *(ectopia lentis)* occurs. This causes severe myopia and iridodonesis (quivering of the iris). Astigmatism, glaucoma, staphyloma, cataracts, retinal detachment, and optic atrophy may develop later in life. Progressive intellectual disability is common. Neurocognitive scores in the average range have been reported; IQ scores range from 10 to 135. Higher IQ scores are seen in vitamin B_6–responsive patients. Psychiatric and behavioral disorders have been observed in more than 50% of affected patients. Seizures are seen in approximately 20% of untreated patients. Affected individuals with homocystinuria manifest skeletal abnormalities resembling those of Marfan syndrome (see Chapter 743): tall with elongated limbs and arachnodactyly. Scoliosis, pectus excavatum or pectus carinatum, genu valgum, pes cavus, high-arched palate, and crowding of the teeth have been reported. These children usually have a fair complexion, blue eyes, and a peculiar malar flush. Generalized osteoporosis, especially of the spine, is the main x-ray finding. Thromboembolic episodes involving both large and small vessels, especially those of the brain, are common and may occur at any age. Optic atrophy, paralysis, cor pulmonale, and severe hypertension (from renal infarcts) are among the serious consequences of thromboembolism, which is likely caused by elevated homocysteine levels leading to abnormal angiogenesis and inhibition of fibrinolytic activity. The risk of thromboembolism increases after surgical procedures or dehydration. Spontaneous pneumothorax and acute pancreatitis are rare complications.

Elevations of both total plasma homocysteine and methionine in body fluids are the diagnostic laboratory findings. Cysteine is low or absent in plasma. Total plasma homocysteine is the preferred analyte for screening and management of classic homocystinuria. Free plasma homocysteine may normalize or remain normal when total plasma homocysteine is lowered. If urinary homocystine is used for diagnostic purposes, a freshly voided urine sample is preferred because this compound is unstable and may disappear after prolonged storage. The diagnosis may be established by molecular analysis of *CBS.* Prenatal diagnosis is feasible by DNA analysis or by performing an enzyme assay of cultured amniotic cells.

Treatment with high doses of vitamin B_6 (100-200 mg/day) can produce significant improvement in patients who are responsive to this therapy. Approximately 40% of affected patients respond to high doses of vitamin B_6 and usually have milder clinical manifestations than those who are unresponsive to vitamin B_6 therapy. The degree of response to vitamin B_6 treatment may vary across families. Some patients may not respond because of folate depletion; a patient should not be considered unresponsive to vitamin B_6 until folic acid (1-5 mg/day) has been added to the treatment regimen. For patients who are unresponsive to vitamin B_6, lifelong restriction of methionine intake in conjunction with cysteine supplementation is also recommended. The need for dietary restriction and its extent remains controversial in patients with the vitamin B_6–responsive form. In some patients with this form, addition of betaine may obviate the need for any dietary restriction. *Betaine* (trimethylglycine, 6 g/day for adults or 100-200 mg/kg/day for children) lowers homocysteine levels in body fluids by remethylating homocysteine to methionine (see Fig. 105.3), which may result in elevation of plasma methionine levels. This treatment has produced clinical improvement (preventing vascular events) in patients who are unresponsive to vitamin B_6 therapy. Cerebral edema has occurred in a patient with vitamin B_6–nonresponsive homocystinuria and dietary noncompliance during betaine therapy.

More than 100 pregnancies in women with classic homocystinuria have been reported with favorable outcomes for both mothers and infants. The majority of infants were full-term and healthy at birth. Postpartum thromboembolic events occurred in a few mothers.

The screening of newborn infants for classic homocystinuria has been performed worldwide, with an estimated prevalence of 1 in

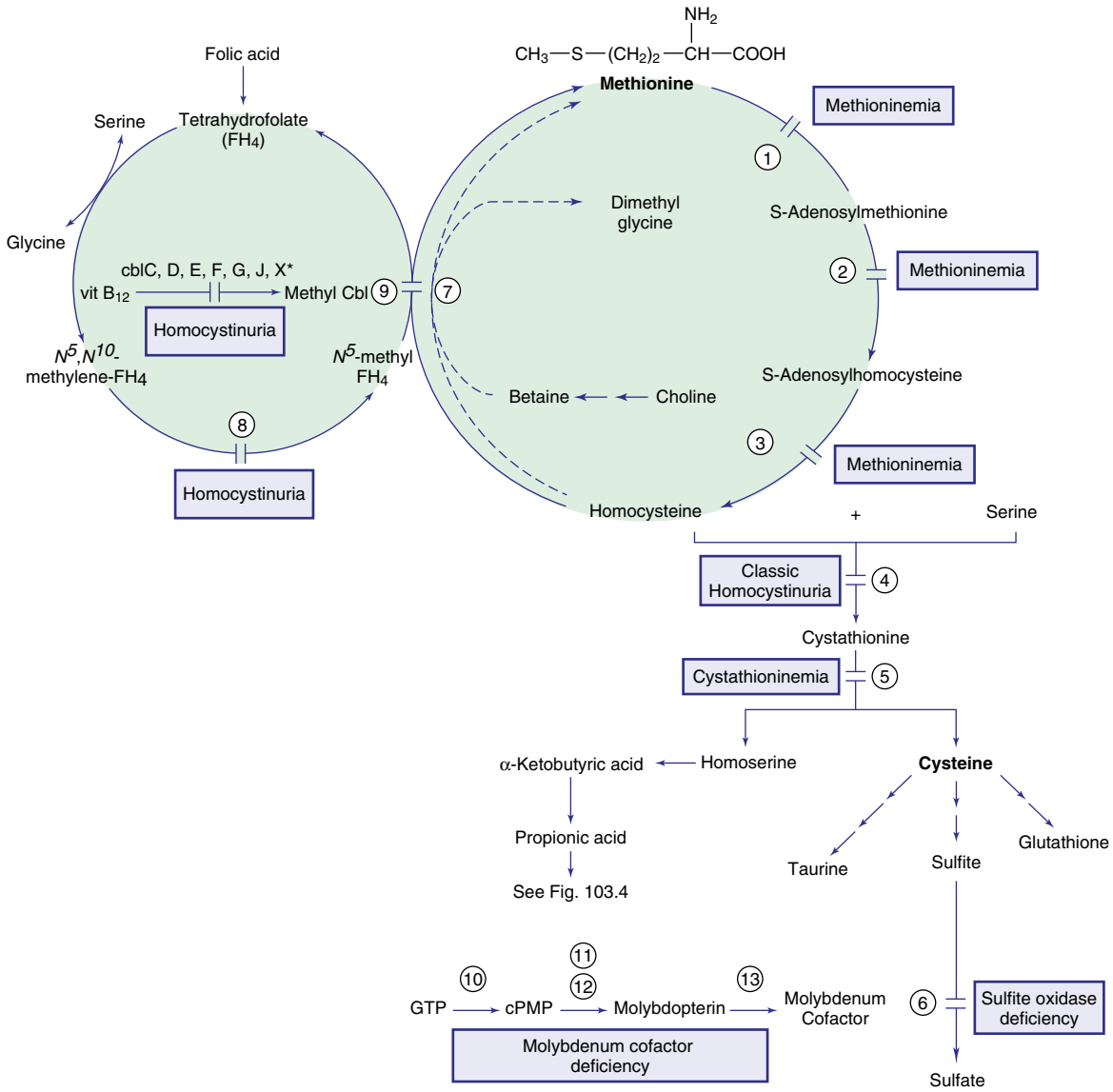

Fig. 105.3 Pathways in the metabolism of sulfur-containing amino acids. **Enzymes:** *(1)* Methionine adenosyltransferase (MAT I/III), *(2)* glycine *N*-methyltransferase, *(3)* *S*-adenosylhomocysteine hydrolase, *(4)* cystathionine synthase, *(5)* cystathionase, *(6)* sulfite oxidase, *(7)* betaine homocysteine methyltransferase, *(8)* methylene tetrahydrofolate reductase, *(9)* methionine synthase (cblG), *(10)* molybdenum cofactor biosynthesis protein 1, *(11)* molybdopterin synthase, *(12)* adenylyltransferase and sulfurtransferase (*MOCS3*), *(13)* gephyrin. GTP, Guanosine triphosphate; cPMP, cyclic pyranopterin monophosphate. *Defects in cblC, D, F, J, and X result in methylmalonic acidemia and homocystinuria.

200,000 to 1 in 350,000 live births, although it can be more common in some parts of the world (e.g., 1 in 1,800 in Qatar). Early treatment of patients identified by screening has produced favorable results. The mean IQ of patients with the vitamin B_6–unresponsive form treated in early infancy was in the normal range. Dislocation of the lens appeared to be preventable in some patients.

Homocystinuria Caused by Defects in Methylcobalamin Formation

Methylcobalamin is the cofactor for methionine synthase, which catalyzes remethylation of homocysteine to methionine. At least seven distinct defects in the intracellular metabolism of cobalamin may interfere with the formation of methylcobalamin (for a more detailed discussion on cobalamin metabolism, see Chapter 105.6 and Figs. 105.3 and 105.4). The seven defects are designated as *cbl*C, *cbl*D (including *cbl*D variant 1), *cbl*E (methionine synthase reductase), *cbl*G (methionine synthase), *cbl*F, *cbl*J, and *cbl*X. Patients with *cbl*C, *cbl*D, *cbl*F, *cbl*J, and *cbl*X defects have **methylmalonic acidemia** *in addition* to homocystinuria, because the formation of both adenosylcobalamin and methylcobalamin is impaired.

Patients with *cbl*E, *cbl*G, and *cbl*D variant one defects are unable to form methylcobalamin and develop homocystinuria without methylmalonic acidemia (Fig. 105.4). The clinical manifestations are similar in patients with these three defects. Nonspecific symptoms such as vomiting, poor feeding, failure to thrive, lethargy, hypotonia, seizures, and developmental delay may occur in the first few months of life. Late-onset forms of these disorders may present with neurocognitive defects, psychosis, and peripheral neuropathy. **Laboratory findings** include megaloblastic anemia, hyperhomocysteinemia, homocystinuria, and hypomethioninemia. The absence of hypermethioninemia differentiates these conditions from cystathionine β-synthase deficiency. Renal artery thrombosis, hemolytic uremic syndrome, pulmonary hypertension, and optic nerve atrophy have been reported in some patients with these defects.

Diagnosis is established by DNA testing or using complementation studies performed in cultured fibroblasts. Prenatal diagnosis can be accomplished by studies in amniotic cell cultures. *cbl*E, *cbl*G, and *cbl*D variant one deficiencies are inherited as autosomal recessive traits. The gene for *cbl*E is *MTRR*, encoding methionine synthase reductase.

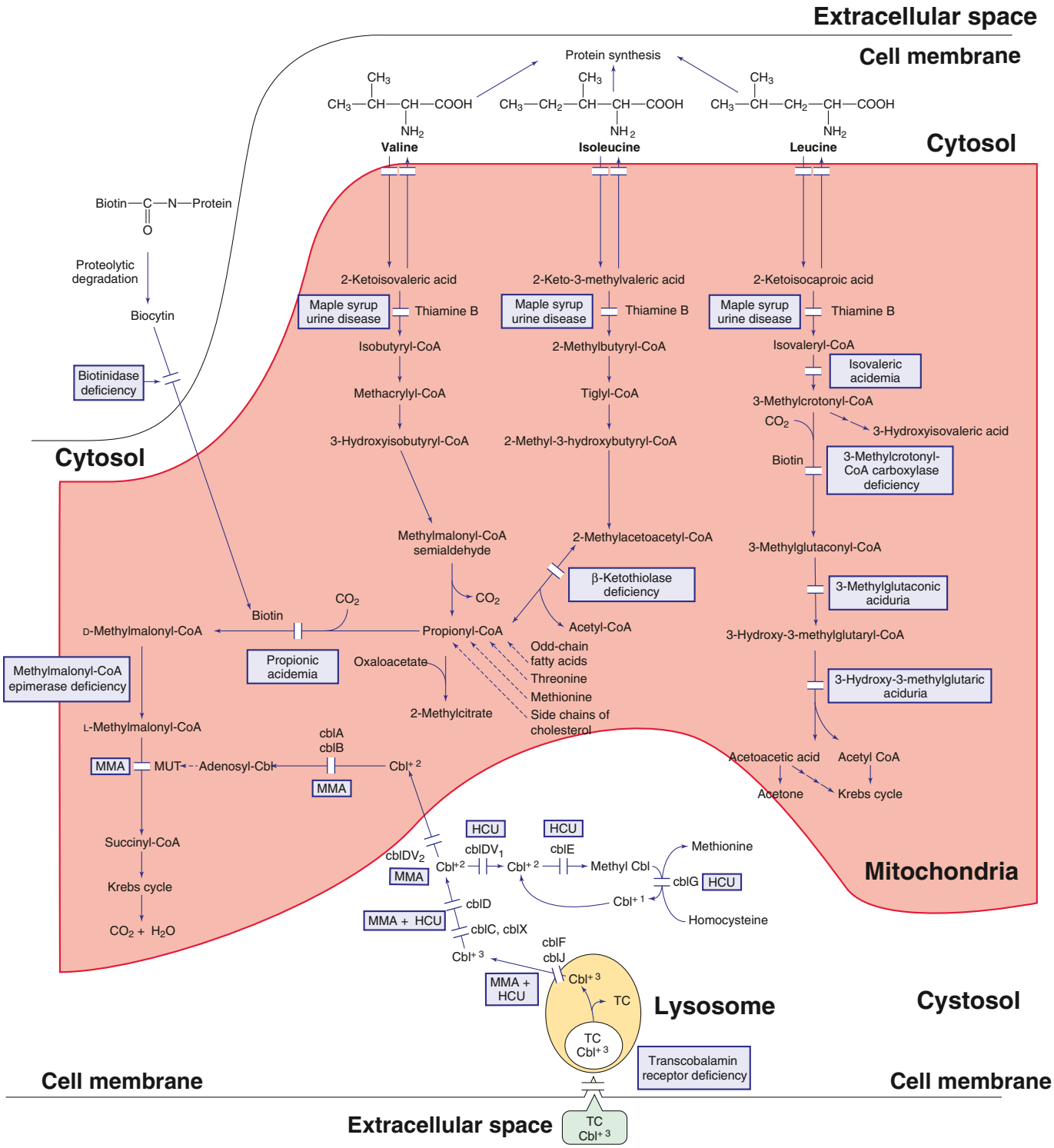

Fig. 105.4 Pathways in the metabolism of the branched-chain amino acids, biotin, and vitamin B_{12} (cobalamin). Adenosyl Cbl, Adenosylcobalamin; Cbl, cobalamin; *cbl*, defect in metabolism of cobalamin; *cbl*DV1, *cbl*D variant 1; *cbl*DV2, *cbl*D variant 2; HCU, homocystinuria; methyl Cbl, methylcobalamin; MMA, methylmalonic acidemia; MUT, mutase; OHCbl, hydroxycobalamin; TC, transcobalamin; TCR, transcobalamin receptor. See text for the name of the enzymes.

The gene for *cbl*G is *MTR*, encoding methionine synthase. The *cbl*D variant one deficiency is caused by pathogenic variants affecting the C-terminal of the *MMADHC* gene.

Treatment with vitamin B_{12} in the form of high-dose parenteral hydroxycobalamin (0.3 mg/kg/day) helps improve the clinical and biochemical findings. Results vary among both diseases and sibships.

Homocystinuria Caused by Deficiency of Methylenetetrahydrofolate Reductase (MTHFR Deficiency)

This enzyme reduces 5,10-methylenetetrahydrofolate to form 5-methyltetrahydrofolate, which provides the methyl group needed for remethylation of homocysteine to methionine (see Fig. 105.3). The severity of the enzyme defect and the clinical manifestations vary considerably

in different families. **Clinical findings** vary from apnea, seizure, microcephaly, coma, and death to developmental delay, ataxia, motor abnormalities, peripheral neuropathy, and psychiatric manifestations. Thromboembolism has also been observed. Exposure to the anesthetic nitrous oxide (which inhibits methionine synthase) in patients with MTHFR deficiency may result in neurologic deterioration and death.

Laboratory findings include moderate hyperhomocysteinemia and homocystinuria. The methionine concentration is low or low-normal. This finding helps differentiate MTHFR deficiency from classic homocystinuria caused by cystathionine β-synthase deficiency. The diagnosis can be confirmed by molecular analysis of *MTHFR* or by the enzyme assay in cultured fibroblasts or leukocytes.

MTHFR deficiency should be differentiated from **mild hyperhomocysteinemia** due to two common variants in the *MTHFR* gene. Two "thermolabile" polymorphisms have been extensively studied: c.665C>T (p.Ala222Val, previously referred to as c.677C>T) and c.1286A>C (p.Glu429Ala, formerly referred to as c.1298A>C). These variants may minimally affect levels of plasma total homocysteine in some patients and are often confounded by dietary folate deficiency. Population-based studies revealed a surprisingly high prevalence of homozygosity for these polymorphisms in the general population: up to 10–15% of North American Whites and >25% in some Hispanics. The best data support a role for the c.665C>T polymorphic variant (formerly c. 677C>T) as a risk factor for neural tube defects. Although clinical tests for this polymorphic variant are widely available, meta-analyses have not supported the association between the *MTHFR* polymorphic variants and risk for venous thromboembolism or between mild hyperhomocysteinemia and an increased risk for coronary heart disease. It is hypothesized that fortification of flour with folate may have decreased the strength of associations observed in the past.

Homocystinuria caused by the loss of function in MTHFR (MTHFR deficiency) is an autosomal recessive disorder. The **diagnosis** can be confirmed by *MTHFR* gene analysis. Prenatal diagnosis can be achieved by molecular analysis of *MTHFR* of known familial pathogenic variants or by measuring MTHFR enzyme activity in cultured chorionic villus cells or amniocytes.

Treatment of MTHFR deficiency with a combination of folic acid, vitamin B_6, vitamin B_{12}, methionine supplementation, and betaine has been tried. Of these, early treatment with betaine appears to have the most beneficial effect.

HYPERMETHIONINEMIA

Primary (Genetic) Hypermethioninemia

Elevation of plasma level of methionine occurs in several genetic conditions. These should be differentiated from acquired (nongenetic) forms of hypermethioninemia, which can occur under various conditions of physiologic stress, especially when involving liver dysfunction.

Classic Homocystinuria

See earlier discussion.

Hepatic Methionine Adenosyltransferase (MAT I/MAT III) Deficiency (Mudd Disease). This hepatic enzyme, which has two isoforms, MAT I (tetrameric) and MAT III (dimeric), is encoded by a single gene, *MAT1A,* and is involved in the first step of methionine catabolism (see Fig. 105.3). Another structurally similar enzyme, MAT II, is encoded by a different gene, *MAT2A,* and is expressed predominantly in nonhepatic tissues (e.g., kidney, brain, lymphocytes). Deficiency of MAT I/MAT III causes hypermethioninemia. In severe deficiency, total plasma homocysteine can also be elevated. The majority of these patients have been diagnosed in the neonatal period through screening for classic homocystinuria. Most affected individuals have residual enzyme activity and remain asymptomatic throughout life despite persistent hypermethioninemia. Some complain of an unusual odor to their breath, likely caused by accumulation of dimethylsulfide. A few patients with complete enzyme deficiency have had neurologic abnormalities related to demyelination (intellectual disability, dystonia, dyspraxia).

Laboratory studies reveal markedly elevated levels of plasma methionine with a normal or low level of *S*-adenosylmethionine, normal concentrations of *S*-adenosylhomocysteine, and normal or slightly elevated total plasma homocysteine. These findings help differentiate MAT I/MAT III deficiency from other causes of hypermethioninemia.

No uniformly accepted therapeutic regimen has yet emerged. Long-term follow-up to monitor for neurologic and liver abnormalities should be considered. Diets low in methionine result in lowering of plasma methionine, but the advisability of such diets has been questioned because lowering plasma methionine, an essential amino acid, causes further lowering of *S*-adenosylmethionine, thus interfering with reactions of remethylation. Supplementation with *S*-adenosylmethionine in conjunction with a low-methionine diet seems prudent, but no large clinical experience is yet available. Normal pregnancies producing normal offspring have been reported in mothers with MAT I/MAT III *(MAT1A)* deficiency. The condition is inherited as an autosomal recessive trait, although the pathogenic variant p.Arg264His in *MAT1A* appears to disrupt protein dimerization and may result in mild hypermethioninemia even in heterozygous patients.

Glycine *N*-Methyltransferase Deficiency. Glycine *N*-methyltransferase *(GNMT)* mediates catabolism of *S*-adenosylmethionine to *S*-adenosylhomocysteine (see Fig. 105.3). A few patients with deficiency of this enzyme have been reported to date. Clinically, patients were asymptomatic except for mild hepatomegaly and elevated serum levels of aminotransferases. Other laboratory findings included hypermethioninemia and very high levels of serum *S*-adenosylmethionine. No specific treatment has yet been identified. The condition is inherited as an autosomal recessive trait.

S-Adenosylhomocysteine Hydrolase (SAHH) Deficiency. SAHH deficiency (see Fig. 105.3) has been described infrequently. Intellectual disability, severe hypotonia, and progressive liver dysfunction were common clinical findings. Laboratory studies included elevated levels of serum creatine kinase, hypoalbuminemia (associated with fetal hydrops in one family), hypoprothrombinemia, and greatly elevated levels of serum *S*-adenosylhomocysteine with moderate elevations of plasma methionine and *S*-adenosylmethionine. Marked elevation in *S*-adenosylhomocysteine has been thought to cause inhibition of methyltransferases, including those involved in the synthesis of creatine (see Fig. 105.10) and choline, resulting in their deficiencies. Brain MRIs often reveal delayed myelination of the white matter. The diagnosis can be achieved by *AHCY* gene analysis or, if needed, by biochemical assay of red blood cells, cultured skin fibroblasts, or liver biopsy. Treatment with a low-methionine diet has been used, but its long-term effectiveness has not been established.

Tyrosinemia Type I. See Chapter 105.2.

Citrin Deficiency. See Chapter 105.12.

Acquired (Nongenetic) Hypermethioninemia

Hypermethioninemia occurs in premature and some full-term infants receiving high-protein diets, in whom it may represent delayed maturation of the enzyme MAT. Adjusting protein intake under the control of plasma methionine usually resolves the abnormality. Hypermethioninemia is also commonly found in patients with various forms of liver disease.

PRIMARY CYSTATHIONINEMIA (CYSTATHIONINURIA)

Cystathionase (cystathionine γ-lyase encoded by *CTH*) deficiency results in massive cystathioninuria and mild to moderate cystathioninemia. Cystathionase deficiency of this enzyme is inherited as an autosomal recessive trait, with an estimated prevalence of 1 in 14,000 live births. A wide variety of clinical manifestations have been reported. Lack of a consistent clinical picture and the presence of cystathioninuria in some individuals *without* apparent clinical findings suggest that cystathionase deficiency may be of no clinical significance. Many reported cases are responsive to oral administration of large doses of vitamin B_6 (~100 mg/day). When cystathioninuria is discovered in a patient, vitamin B_6 treatment can be tried, but its beneficial effect has not been established.

Primary cystathioninuria needs to be differentiated from secondary cystathioninuria, which can occur in patients with vitamin B_6 and/or

B_{12} deficiency, liver disease (particularly damage caused by galactosemia), thyrotoxicosis, hepatoblastoma, neuroblastoma, ganglioblastoma, or defects in remethylation of homocysteine.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.4 Cysteine and Cystine

Oleg A. Shchelochkov and Charles P. Venditti

Cysteine is a sulfur-containing amino acid synthesized from methionine (see Fig. 105.3). Oxidation of cysteine forms *cystine,* a poorly soluble dimer. The most common genetic disorders of cysteine and cystine metabolism are cystinuria (see Chapter 584) and cystinosis (see Chapter 569.3).

SULFITE OXIDASE DEFICIENCY AND MOLYBDENUM COFACTOR DEFICIENCY

In the last step in cysteine metabolism, sulfite is oxidized to sulfate by sulfite oxidase, and the sulfate is excreted in the urine (see Fig. 105.3). Sulfite oxidase is encoded by *SUOX* and requires a molybdenum-pterin complex called *molybdenum cofactor.* This cofactor is also necessary for the function of two other enzymes in humans: xanthine dehydrogenase (oxidizes xanthine and hypoxanthine to uric acid) and aldehyde oxidase (involved in oxidizing a number of natural compounds and drugs). Three enzymes, encoded by three different genes (*MOCS1, MOCS2,* and *GPHN*), are involved in the synthesis of the cofactor. Deficiency of any of the three enzymes causes cofactor deficiency with similar phenotypes. Most patients, who were originally diagnosed as having **sulfite oxidase deficiency**, have been shown to have **molybdenum cofactor deficiency**. Sulfite oxidase deficiency and molybdenum cofactor deficiency are autosomal recessive disorders.

The enzyme and cofactor deficiencies present with overlapping and often nonspecific **clinical manifestations**. Refusal to feed, vomiting, an exaggerated startle reaction, severe intractable seizures (tonic, clonic, myoclonic), cortical atrophy with subcortical multicystic lesions, and severe developmental delay may develop within a few weeks after birth. The biochemical diagnosis should be considered in infants presenting with neonatal seizures and neonates with symptoms reminiscent of hypoxic-ischemic encephalopathy. Bilateral dislocation of ocular lenses is a common finding in patients who survive the neonatal period. The intractable seizures seen in this condition are in part a consequence of secondary vitamin B_6 dependency. The accumulation of sulfites in body fluids in this condition causes the inhibition of the *antiquitin* enzyme, which is necessary for the conversion of α-amino adipic semialdehyde to α-aminoadipic acid; the resultant accumulation of α-aminoadipic semialdehyde and its cyclic form, P6C, causes the inactivation of pyridoxal-5-phosphate (the active form of vitamin B_6), leading to **vitamin B_6–dependent** epilepsy (see also Chapter 105.14).

Affected children excrete large amounts of sulfite, thiosulfate, *S*-sulfocysteine, xanthine, and hypoxanthine in the urine. Serum uric acid and urinary excretion of sulfate and uric acid are diminished. Fresh urine should be used for screening purposes and for quantitative measurements of sulfite, because oxidation of sulfite to sulfate at room temperature may produce false-negative results. Increased concentrations of α-aminoadipic semialdehyde and P6C can be found in the CSF, plasma, and urine.

Diagnosis is confirmed by analysis of affected genes (often using a multigene panel). Infrequently, measurement of sulfite oxidase and molybdenum cofactor in fibroblasts and liver biopsies is required. Prenatal diagnosis is possible by DNA studies or by performing an assay of sulfite oxidase activity in cultured amniotic cells, in samples of chorionic villi. The prevalence of these deficiencies in the general population is not known but likely is very low.

Patients with *MOCS1*-related molybdenum cofactor deficiency may benefit from daily intravenous **cyclic pyranopterin monophosphate** (a cPMP analogue), a compound under investigation in a multicenter clinical trial. Large doses of vitamin B_6 may alleviate the frequency and severity of seizures but do not seem to alter the devastating neurologic outcome. A cysteine-restricted diet under control of plasma amino acids to avoid essential amino acid deficiencies can be attempted in some patients, but the long-term efficacy of this approach is unknown.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.5 Tryptophan

Oleg A. Shchelochkov and Charles P. Venditti

Tryptophan is an essential amino acid and a precursor for nicotinic acid (niacin) and serotonin (Fig. 105.5). The genetic disorders of metabolism of serotonin, one of the major neurotransmitters, are discussed in Chapter 105.11.

HARTNUP DISEASE

Hartnup disease is an autosomal recessive condition caused by biallelic pathogenic variants in *SLC6A19*. This gene encodes a monoamino-monocarboxylic amino acid transporter (B^0AT1), which facilitates transport of neutral amino acids, including tryptophan, across the intestinal mucosa and renal tubules. Patients show significant variability in presentation, likely related to nutritional factors, environment, and genetic heterogeneity of modifier genes (e.g., two proteins, TMEM27 and ACE2, that interact with B^0AT1). The prevalence of Hartnup disorder is estimated to be 1 in 20,000 to 1 in 55,000 live births. Most children with Hartnup disease remain asymptomatic. Decreased intestinal absorption of tryptophan in conjunction with its increased renal loss can lead to reduced availability of tryptophan for niacin synthesis. **Tryptophan deficiency** can be accentuated by malabsorption such as celiac disease. One of the more noticeable clinical manifestations in the rare symptomatic patient is **cutaneous photosensitivity**. The skin becomes rough and red after moderate exposure to the sun, and with greater exposure, a pellagra-like rash may develop. The rash may be pruritic, and a chronic eczema may develop. The skin changes have been reported in affected infants as young as 10 days of age. Some patients may have intermittent ataxia manifested as an unsteady, wide-based gait. The ataxia may last a few days and can respond to niacin supplementation. Cognitive development is usually normal. Episodic psychiatric manifestations such as irritability, emotional instability, depression, and suicidal tendencies, have been observed; these changes are usually associated with bouts of ataxia. Short stature and atrophic glossitis are seen in some patients.

Most children diagnosed with Hartnup disorder by neonatal screening have remained asymptomatic. This indicates that other factors are also involved in the pathogenesis of the clinical condition.

The main laboratory finding is **aminoaciduria**, which is restricted to neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine). Urinary excretion of proline, hydroxyproline, and arginine remains normal. This finding helps differentiate Hartnup disorder from other causes of generalized aminoaciduria, such as renal Fanconi syndrome. Plasma concentrations of neutral amino acids are normal or mildly decreased. This seemingly unexpected finding reflects compensatory mechanisms that maintain normal transport and utilization of amino acids. The indole derivatives (especially indican) may be found in large amounts in some patients, resulting from bacterial breakdown of unabsorbed tryptophan in the intestines.

Diagnosis of Hartnup disorder is established by the intermittent nature of symptoms and characteristic findings on the urine amino acid analysis. When necessary, the diagnosis can be confirmed molecularly by *SLC6A19* gene analysis.

Treatment with nicotinic acid or nicotinamide (50-300 mg/day) and a high-protein diet results in a favorable response in symptomatic patients with Hartnup disorder. Because of the intermittent nature of the clinical manifestations, the efficacy of these treatments is difficult to establish. Normal outcome for both the mother and fetus has been reported in several affected women.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

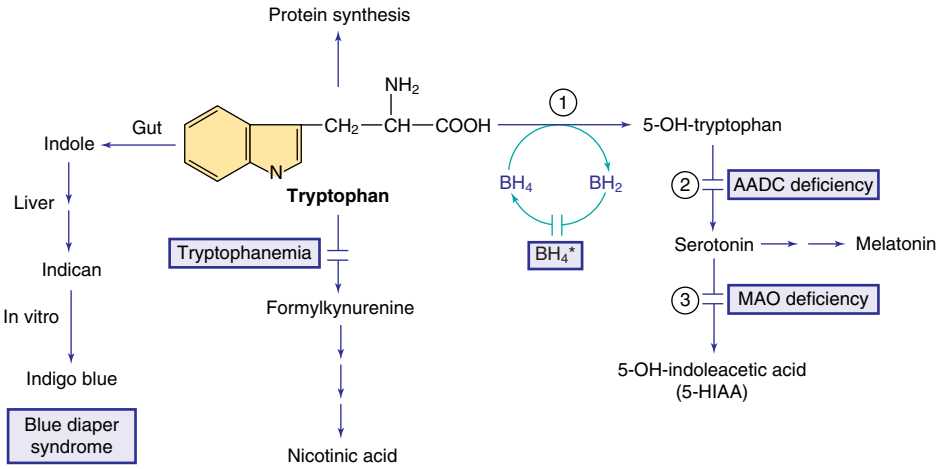

Fig. 105.5 Pathways in the metabolism of tryptophan. BH_4* indicates hyperphenylalaninemia caused by tetrahydrobiopterin deficiency (see Fig. 105.1). **Enzymes:** *(1)* Tryptophan hydroxylase, *(2)* aromatic L-amino acid decarboxylase (AADC), *(3)* monoamine oxidase (MAO).

105.6 Isoleucine, Leucine, Valine, and Related Organic Acidemias

Oleg A. Shchelochkov, Irini Manoli, and Charles P. Venditti

The early steps in the degradation of the branched-chain amino acids (BCAAs)—isoleucine, leucine, and valine—are similar (see Fig. 105.4). Under catabolic conditions, BCAAs in the muscle tissue undergo a reversible reaction of transamination catalyzed by BCAA transaminase. α-Ketoacids formed by this reaction then undergo an oxidative decarboxylation step mediated by a branched-chain α-ketoacid dehydrogenase **(BCKDH)** complex. The deficiency of BCKDH results in **maple syrup urine disease**, whereas the deficiency of enzymes mediating more distal reactions results in accumulation of enzyme-specific levels of organic acids excreted in the urine, thus giving those inborn errors of metabolism the eponyms **organic acidemias** and **organic acidurias**. These disorders typically cause metabolic acidosis, which usually occurs in the first few days of life. Although most of the clinical findings are nonspecific, some manifestations may provide important clues to the nature of the enzyme deficiency. Figure 105.6 presents an approach to infants suspected of having an organic acidemia. The diagnosis is usually established by identifying and measuring specific organic acids in body fluids (blood, urine), amino acid analysis (blood), and identifying pathogenic variants in the respective gene.

Organic acidemias *are not limited* to defects in the catabolic pathways of BCAAs. Disorders causing accumulation of other organic acids include those derived from lysine (see Chapter 105.14), disorders of the γ-glutamyl cycle (see Chapter 105.11), those associated with lactic acid (see Chapter 107), and dicarboxylic acidemias associated with defective fatty acid degradation (see Chapter 106).

MAPLE SYRUP URINE DISEASE

Decarboxylation of leucine, isoleucine, and valine is accomplished by a complex enzyme system (BCKDH) using thiamine (vitamin B_1) pyrophosphate as a coenzyme. This mitochondrial enzyme consists of four subunits: $E_{1\alpha}$, $E_{1\beta}$, E_2, and E_3. The E_3 subunit is shared with two other dehydrogenases: pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Deficiency of any of these subunits causes maple syrup urine disease **(MSUD)** (see Fig. 105.4), a disorder named after the sweet odor of maple syrup discerned from body fluids, especially cerumen, sweat, and urine. Clinical conditions caused by defects in $E_{1\alpha}$, $E_{1\beta}$, E_2 and E_3 are designated as MSUD type 1A, type 1B, type 2, and type 3, respectively. This classification, however, is not very helpful clinically because the severity of clinical manifestations does not correlate with, or correspond specifically to, any single enzyme subunit. An affected infant with a type 1A defect can have clinical manifestations ranging from relatively mild to very severe. A more useful classification, based on clinical findings and response to thiamine administration, delineates five phenotypes of MSUD.

Classic Maple Syrup Urine Disease

Classic MSUD has the most severe clinical manifestations. The BCKDH complex activity in this group varies between 0% and 2% of controls. Patients with uncontrolled or poorly controlled disease develop signs of acute encephalopathy. The mechanisms underlying this life-threatening complication are complex, but leucine and its derivative, α-ketoisocaproic acid, appear to be the key factors underlying acute encephalopathy. Elevated leucine competitively inhibits the uptake of other amino acids by the LNAA transporter. Once taken up by the brain tissue, leucine is metabolized by BCAA aminotransferase to α-ketoisocaproic acid, which disrupts metabolism of neurotransmitters and amino acids (glutamate, γ-aminobutyric acid [GABA], glutamine, alanine, and aspartate). α-Ketoisocaproic acid can reversibly inhibit oxidative phosphorylation and result in cerebral lactic acidosis. Collectively, these processes are detrimental to the normal function of neurons and glia, clinically manifesting as *encephalopathy* and *brain edema,* referred to as **leucinosis**. Affected infants who appear healthy at birth develop poor feeding and vomiting in the first days of life. Lethargy and coma may ensue within a few days. Physical examination reveals hypertonicity and muscular rigidity with severe opisthotonos. Periods of hypertonicity may alternate with bouts of flaccidity manifested as repetitive movements of the extremities ("boxing" and "bicycling"). Neurologic findings are often mistakenly thought to be caused by generalized sepsis and meningitis. Cerebral edema may be present; seizures occur in most infants, and hypoglycemia is common. In contrast to most hypoglycemic states, correction of the blood glucose concentration *does not* improve the clinical condition. Aside from the blood glucose and varying degrees of ketoacidosis, routine laboratory findings are usually unremarkable. If left untreated, death can occur in the first few weeks or months of life.

Diagnosis was classically suspected because of the peculiar odor of maple syrup in urine, sweat, and cerumen. It is usually confirmed by amino acid analysis showing marked elevations in plasma levels of leucine, isoleucine, valine, and alloisoleucine and a depressed level of alanine. Alloisoleucine is a stereoisomer of isoleucine not normally found in blood and is the most sensitive and specific diagnostic marker for all forms of MSUD. Leucine levels are usually higher than those of isoleucine and valine. Urine contains high levels of leucine, isoleucine, and valine and their respective ketoacids. These ketoacids may be detected qualitatively by adding a few drops of 2,4-dinitrophenylhydrazine reagent (0.1% in 0.1N HCl) to the urine; a yellow precipitate of 2,4-dinitrophenylhydrazone is formed in a positive test. Neuroimaging during the acute state may show cerebral edema, which is most

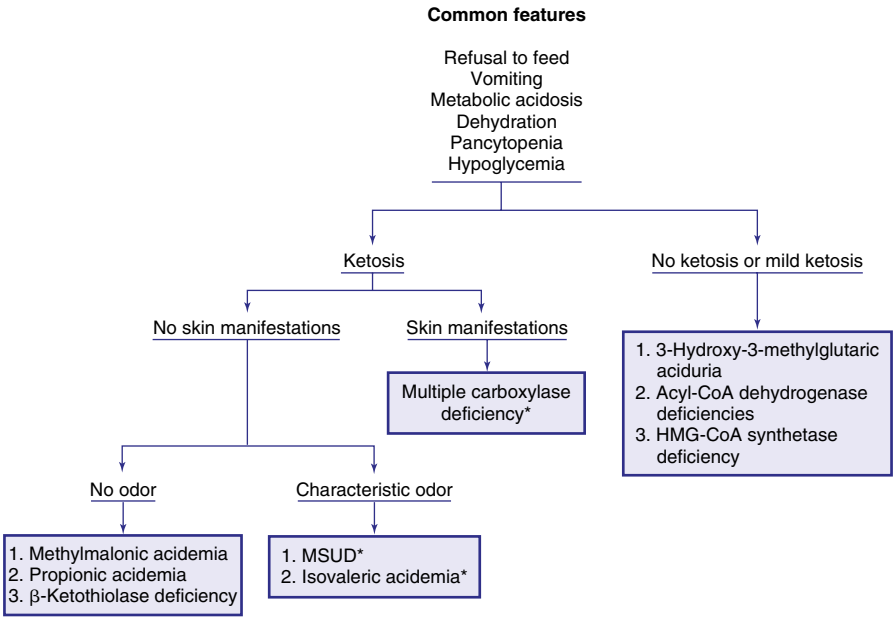

Fig. 105.6 Clinical algorithmic approach to infants with organic acidemia. *Asterisks* indicate disorders in which patients have a characteristic odor (see text and Table 105.2). MSUD, Maple syrup urine disease.

prominent in the cerebellum, dorsal brainstem, cerebral peduncle, and internal capsule. After recovery from the acute state and with advancing age, hypomyelination and cerebral atrophy may be seen in neuroimaging of the brain.

Treatment of the acute state is aimed at hydration and rapid removal of the BCAAs and their metabolites from the tissues and body fluids. Uptake of leucine by the brain and accumulation of the downstream metabolite, α-ketoisocaproic acid, appear to be the key metabolic events underlying the MSUD encephalopathy. Therefore MSUD management strategies focus on decreasing plasma leucine to control acute and chronic manifestations of the disease.

Because renal clearance of leucine is low, hydration alone may not produce a rapid improvement. *Hemodialysis* is the most effective mode of therapy in critically ill infants and should be instituted promptly; significant decreases in plasma levels of leucine, isoleucine, and valine are usually seen within 24 hours. Sufficient calories and nutrients should be provided intravenously or orally as soon as possible to reverse the patient's catabolic state. Cerebral edema, if present, may require treatment with mannitol, diuretics (e.g., furosemide), or hypertonic saline. Counterintuitively, supplementation with isoleucine and valine is also needed to achieve adequate control of the plasma leucine level in MSUD patients and to sustain the net protein synthesis in tissues. Judiciously administered isoleucine and valine will compete with leucine for the LNAA transporter at the BBB, decrease leucine entry into the CNS, and help in the prevention and treatment of leucine encephalopathy. Phenylbutyrate, a nitrogen scavenger used to treat hyperammonemia in urea cycle disorders, has been shown to activate the BCKDH complex and lower BCAA levels, with promising results in a subset of MSUD patients.

Treatment after recovery from the acute state requires a diet low in BCAAs. Synthetic formulas devoid of leucine, isoleucine, and valine are available commercially. Because these amino acids cannot be synthesized endogenously, age-appropriate amounts of BCAAs should be provided in the diet in the form of complete protein. To avoid essential amino acid deficiencies, the amount should be titrated carefully by performing frequent analyses of plasma amino acids, with close attention to plasma isoleucine, leucine, and valine levels. A clinical condition resembling **acrodermatitis enteropathica** (see Chapter 691) occurs in affected infants whose plasma isoleucine or valine had been *overrestricted*; the addition of isoleucine or valine, respectively, to the diet will hasten the recovery of the skin rash. Patients with MSUD need to remain on the diet for life. Liver transplantation is offered to patients with classic MSUD, allowing some patients to lift protein restrictions and improve metabolic control during intercurrent illnesses.

The long-term prognosis of affected children remains guarded. Severe ketoacidosis, cerebral edema, and death may occur during any stressful situation such as infection or surgery, especially in mid-childhood. Cognitive and other neurologic deficits are common sequelae.

Intermediate (Mild) Maple Syrup Urine Disease

Children with intermediate MSUD develop milder disease after the neonatal period. Clinical manifestations are insidious and limited to the CNS. Patients have mild to moderate intellectual disability with or without seizures. They have the odor of maple syrup and excrete moderate amounts of the BCAAs and their ketoacid derivatives in the urine. Plasma concentrations of leucine, isoleucine, and valine are moderately increased, whereas those of lactate and pyruvate tend to be normal. These children are commonly diagnosed during an intercurrent illness, when signs and symptoms of classic MSUD may occur. The dehydrogenase activity is 3–40% of the reference population. Because patients with thiamine-responsive MSUD usually have manifestations similar to the mild form, a trial of thiamine therapy is recommended. Diet therapy, similar to that of classic MSUD, is needed.

Intermittent Maple Syrup Urine Disease

In intermittent MSUD, seemingly normal children develop vomiting, odor of maple syrup, ataxia, lethargy, and coma during any stress or catabolic state such as infection or surgery. During these attacks, laboratory findings are indistinguishable from those of the classic form, and death may occur. Treatment of the acute attack of intermittent MSUD is similar to that of the classic form. After recovery, although a normal diet can be tolerated, a low-BCAA diet is recommended. The BCKDH activity in patients with the intermittent form is higher than in the classic form and may reach 40% of the control activity.

Thiamine-Responsive Maple Syrup Urine Disease

Some children with mild or intermediate forms of MSUD who are treated with high doses of thiamine show dramatic clinical and biochemical improvement. Although some respond to treatment with thiamine at 10 mg/day, others may require as much as 100 mg/day for at least 3 weeks before a favorable response is observed. These patients also require a BCAA-restricted diet. The enzymatic activity in these patients can be up to 40% of the reference population.

Maple Syrup Urine Disease Caused by Deficiency of E_3 Subunit (MSUD Type 3)

Although sometimes referred to as "maple syrup urine disease type 3," this very rare disorder leads to clinical and biochemical abnormalities that encompass a wide range of mitochondrial reactions. The E_3 subunit, dihydrolipoamide dehydrogenase, is a component of the BCKDH complex, pyruvate dehydrogenase complex, and α-ketoglutarate dehydrogenase complex. Causative biallelic pathogenic variants in *DLD* that encode the E_3 dihydrolipoamide dehydrogenase cause lactic acidosis, elevated pyruvate, and signs and symptoms similar to intermediate MSUD. Progressive neurologic impairment manifested by hypotonia and developmental delay occurs after 2 months of age. Abnormal movements can progress to ataxia or Leigh syndrome. Death may occur in early childhood.

Laboratory findings include persistent lactic acidosis with high levels of plasma pyruvate and alanine. Plasma BCAA concentrations are moderately increased. Patients excrete large amounts of lactate, pyruvate, α-ketoglutarate, and the three branched-chain ketoacids in their urine.

No effective treatment is available. BCAA-restricted diets and treatment with high doses of thiamine, biotin, and lipoic acid have been ineffective.

Genetics and the Prevalence of Maple Syrup Urine Disease

Biallelic pathogenic variants in any of the following genes may result in the clinical and biochemical manifestations of MSUD: *BCKDHA* (encodes subunit $E_{1\alpha}$), *BCKDHB* (encodes subunit $E_{1\beta}$), *DBT* (encodes subunit E_2), and *DLD* (encodes subunit E_3). Genotype-phenotype correlations are difficult to establish and are usually imprecise. The exception is thiamine-responsive MSUD, shown to be caused by pathogenic variants in *DBT*. Most patients are compound heterozygotes inheriting two different pathogenic alleles. Pathogenic variants in *BCKDHA* (45%) and *BCKDHB* (35%) account for approximately 80% of cases. Pathogenic variants in *DBT* are responsible for 20% of MSUD cases.

The prevalence is estimated at 1 in 185,000 live births. Classic MSUD is more prevalent in the Old Order Mennonites in the United States, at an estimated 1 in 380 live births. Affected patients in this population are homozygous for a specific pathogenic variant (c.1312T>A) in the *BCKDHA*-encoding $E_{1\alpha}$ subunit.

Early detection of MSUD is possible by universal newborn screening. In many cases, however, especially those with classic MSUD, the infant may be very ill by the time screening results become available (see Chapter 104). Prenatal diagnosis has been accomplished by enzyme assay of the cultured amniocytes, cultured chorionic villus tissue, or direct assay of samples of the chorionic villi and by identification of the known pathogenic variants in the affected gene.

Successful pregnancies have occurred in women with different forms of MSUD. The teratogenic potential of leucine during pregnancy is unknown. Tight control of isoleucine, leucine, and valine before and during the pregnancy is important to minimize the risk of metabolic decompensation and to optimize fetal nutrition. Mothers affected by MSUD require close monitoring and meticulous management of nutrition, electrolytes, and fluids in the postpartum period.

BRANCHED-CHAIN α-KETOACID DEHYDROGENASE KINASE DEFICIENCY

A defect in the regulation of BCKDH by BCKDH kinase (BCKDK), the enzyme responsible for phosphorylation-mediated inactivation of the BCKDH complex, causes the *reverse* biochemical phenotype of MSUD. Pathogenic variants in *BCKDK* decrease the negative regulation by the kinase, resulting in uncontrolled degradation and depletion of isoleucine, leucine, and valine in plasma and the brain. Patients with BCKDK deficiency present with low plasma concentrations of isoleucine, leucine, and valine associated with autism, intellectual impairment, fine motor coordination problems, and seizures.

BRANCHED-CHAIN AMINO ACID TRANSPORTER DEFICIENCY

Isoleucine, leucine, and valine are transported across the BBB mainly by the heterodimeric LNAA transporter LAT1 encoded by *SLC7A5*. A defect in LAT1 caused by pathogenic variants in *SLC7A5* results in low brain concentrations of isoleucine, leucine, and valine. Patients with this defect may present similarly to BCKDK-deficient patients, with autism, microcephaly, gross motor delays, and in some cases, seizures.

ISOVALERIC ACIDEMIA

Isovaleric acidemia **(IVA)** is an autosomal recessive condition caused by biallelic pathogenic variants in *IVD* resulting in the deficient activity of isovaleryl–coenzyme A (CoA) dehydrogenase (see Fig. 105.4). The prevalence of IVA is estimated to range between 1 in 62,500 (in parts of Germany) and 1 in 250,000 live births (in the United States). Decreased or absent activity of isovaleryl-CoA dehydrogenase results in impaired leucine degradation. Accumulating derivatives of isovaleric acid, isovalerylcarnitine, isovalerylglycine, and 3-hydroxyisovaleric acid can be detected in body fluids and thus enable the biochemical diagnosis and screening. Clinically, the course of IVA can be highly variable, ranging from essentially asymptomatic to severe. Introduction of newborn screening and proactive management of IVA has changed the prognosis and clinical course. Older siblings of symptomatic newborn infants have been reported with identical genotype and biochemical abnormalities but without clinical manifestations, suggesting that presymptomatic detection of affected patients on the newborn screen can improve clinical outcomes.

Patients with severe IVA can present with vomiting, severe acidosis, hyperammonemia, hypoglycemia, hypocalcemia, and bone marrow suppression in infancy. Lethargy, convulsions, and coma may ensue, and death may occur if proper therapy is not initiated. Vomiting may be severe enough to suggest pyloric stenosis. The characteristic odor of "sweaty feet" or "rancid cheese" may be present. Infants who survive this acute episode are at risk of developing episodes of metabolic decompensation later in life. In the mild form without treatment, typical clinical manifestations of severe IVA (vomiting, lethargy, acidosis, or coma) may not appear until the child is a few months or years old. Acute episodes of metabolic decompensation may occur during a catabolic state, such as infection, dehydration, surgery, or high-protein intake. Acute episodes may be mistaken for diabetic ketoacidosis. Some patients may experience acute and recurrent episodes of pancreatitis.

Laboratory findings during the acute attacks include ketoacidosis, neutropenia, thrombocytopenia, and occasionally pancytopenia. Hypocalcemia, hypoglycemia, and moderate to severe hyperammonemia may be present in some patients. Increases in plasma ammonia may suggest a defect in the urea cycle (see Chapter 105.12). In urea cycle defects, the infant usually shows no significant ketoacidosis (see Fig. 105.6).

Diagnosis is established by demonstrating marked elevations of isovaleric acid metabolites (isovalerylglycine, 3-hydroxyisovaleric acid) in body fluids, especially urine. The main compound in plasma is isovalerylcarnitine (C5-carnitine). C5-carnitine can be measured in dried blood spots, enabling universal newborn screening using tandem mass spectrometry. The diagnosis can be confirmed by molecular analysis of the *IVD* gene. In some patients with equivocal results, measurement of the enzyme activity in cultured skin fibroblasts may be necessary.

Treatment of the acute attack is aimed at rehydration, reversal of the catabolic state (by providing adequate calories orally or intravenously), correction of metabolic acidosis, and facilitation of the isovaleric acid excretion. L-Carnitine (100 mg/kg/day orally) also increases removal of isovaleric acid by forming isovalerylcarnitine, which is excreted in the urine. Because isovalerylglycine has a high urinary clearance, some centers recommend glycine supplementation (250 mg/kg/day) to enhance the formation of isovalerylglycine. Temporary restriction of protein intake (<24 hours) may be beneficial in some cases. In patients with significant hyperammonemia (blood ammonia >200 μmol/L), measures that reduce blood ammonia should be employed (see Chapter 105.12). Renal replacement therapy may be needed if the previously described measures fail to produce significant clinical and biochemical improvement. Long-term management of IVA patients requires restriction of protein according to age-appropriate intake (recommended dietary allowance of protein). Patients benefit from carnitine supplementation with or without glycine. Normal development can be achieved with early and proper treatment.

Prenatal diagnosis can be accomplished using *IVD* gene analysis if causative pathogenic variants are known or, less frequently, by using an enzyme assay of cultured amniocytes. Successful pregnancies with favorable outcomes have been reported. Universal newborn screening of IVA is used in the United States and other countries (see Chapter 104).

MULTIPLE CARBOXYLASE DEFICIENCIES (DEFECTS OF THE BIOTIN CYCLE)

Biotin is a water-soluble vitamin that serves as a cofactor for four carboxylase enzymes in humans: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase. The latter two are involved in the catabolic pathways of leucine, isoleucine, and valine (see Fig. 105.4).

Most dietary biotin is bound to proteins. Free biotin is generated in the intestine by the action of digestive enzymes, by intestinal bacteria, and perhaps by biotinidase. **Biotinidase**, found in serum and most tissues, is also essential for the recycling of biotin in the body by releasing it from the apoenzymes (carboxylases; see Fig. 105.4). Free biotin must form a covalent bond with the apocarboxylases to produce the activated enzyme (holocarboxylase). This binding is catalyzed by holocarboxylase synthetase. Deficiencies either in holocarboxylase synthetase or in biotinidase result in the impaired catalytic activity of carboxylases and organic acidemias.

Holocarboxylase Synthetase Deficiency

Infants with this rare autosomal recessive disorder become symptomatic in the first few weeks of life. Symptoms may appear as early as a few hours after birth to as late as 8 years of age. Clinically, shortly after birth, affected infants develop breathing difficulties (tachypnea and apnea). Feeding problems, vomiting, and hypotonia are also usually present. If the condition remains untreated, *generalized erythematous rash with exfoliation and alopecia,* failure to thrive, irritability, seizures, lethargy, and even coma may occur. Developmental delay is common. Immune deficiency manifests with susceptibility to infection. Urine may have a peculiar odor, which has been described "tomcat urine." The rash, when present, helps to differentiate this condition from other organic acidemias (see Fig. 105.6).

Laboratory findings include metabolic acidosis, ketosis, hyperammonemia, and the presence of a variety of organic acids and their conjugates (lactic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, tiglylglycine, 3-OH-propionic acid, methylcitric acid, and 3-hydroxyisovaleric acid) in body fluids. **Diagnosis** is confirmed by identification of pathogenic variants in *HLCS* or by the enzyme assay in lymphocytes or cultured fibroblasts. Most pathogenic variants cause the enzyme to have an increased K_m (Michaelis-Menten dissociation constant) for biotin; the enzyme activity in such patients can be restored by the administration of large doses of biotin. Newborn screening can identify holocarboxylase synthetase–deficient infants by detecting elevated C5-OH-carnitine on tandem mass spectrometry. In these infants, biotinidase enzymatic assay would be normal.

Treatment with biotin (10-20 mg/day orally) usually results in an improvement in clinical manifestations and biochemical abnormalities. Early diagnosis and treatment are critical to prevent irreversible neurologic damage. In some patients, complete resolution may not be achieved even with large doses (up to 60 mg/day) of biotin.

Prenatal diagnosis can be accomplished by prenatal molecular analysis of known pathogenic variants in *HLCS* or by assaying enzyme activity in cultured amniotic cells. Pregnant mothers who had previous offspring with holocarboxylase synthetase deficiency have been treated with biotin late in pregnancy. Affected infants were normal at birth, but the efficacy of prenatal treatment remains unclear.

Biotinidase Deficiency

Impaired biotinidase activity results in biotin deficiency. Affected infants may develop clinical manifestations similar to those seen in infants with holocarboxylase synthetase deficiency. Unlike the latter, however, symptoms tend to appear later, when the child is several months or years old. The delay in onset of symptoms presumably results from the availability of free biotin derived from the mother or the diet. Clinical manifestations are mostly confined to the skin and the nervous system. Without treatment, atopic or seborrheic dermatitis, candidiasis, alopecia, ataxia, seizures (usually myoclonic), hypotonia, developmental delay, optic nerve atrophy, sensorineural hearing loss, and immunodeficiency resulting from impaired T-cell function may occur. A small number of children with *intractable seborrheic dermatitis* and *partial* (15–30% activity) biotinidase deficiency, in whom the dermatitis resolved with biotin therapy, have been reported; these children were otherwise asymptomatic. Asymptomatic children and adults with this enzyme deficiency have been identified in screening programs. Most of these individuals have been shown to have partial biotinidase deficiency. With universal newborn screening leading to early identification and treatment of the affected patients, the clinical disease should become extinct.

Laboratory findings and the pattern of organic acids in body fluids resemble those associated with holocarboxylase synthetase deficiency. **Diagnosis** can be established by measurement of the enzyme activity in the serum and confirmed by identifying biallelic pathogenic variants in *BTD*. **Treatment** with free biotin (5-20 mg/day) results in a dramatic clinical and biochemical improvement. Treatment with biotin is also suggested for individuals with partial biotinidase deficiency. The prevalence of this autosomal recessive disorder is estimated to be 1 in 60,000 live births. **Prenatal diagnosis** is possible by identification of known pathogenic variants in *BTD* or, less frequently, by the measurement of the enzyme activity in the amniotic cells, although in practice, a prenatal approach is rarely used.

Multiple Carboxylase Deficiency Caused by Acquired Biotin Deficiency

Acquired deficiency of biotin may occur in infants receiving total parenteral nutrition without added biotin, in patients with prolonged use of antiepileptic drugs (phenobarbital, phenytoin, primidone, carbamazepine), and in children with short bowel syndrome or chronic diarrhea who are receiving formulas low in biotin. Excessive ingestion of raw eggs may also cause biotin deficiency because the protein avidin in egg white binds biotin, decreasing its absorption. Infants with acquired biotin deficiency may develop dermatitis, alopecia, and candidal skin infections. This condition readily responds to treatment with oral biotin.

3-METHYLCROTONYL-COA CARBOXYLASE DEFICIENCY

This enzyme is one of the four carboxylases requiring biotin as a cofactor (see Fig. 105.4). An isolated deficiency of this enzyme must be differentiated from disorders of biotin metabolism (multiple carboxylase deficiency), which causes diminished activity of all four carboxylases (see earlier). 3-Methylcrotonyl-CoA carboxylase (3-MCC) is a heteromeric enzyme consisting of α (biotin containing) and β subunits, encoded by the genes *MCCC1* and *MCCC2,* respectively. 3-MCC deficiency can be detected in the newborn period by identifying elevated 3-hydroxyisovalerylcarnitine (C5-OH) in dried blood spots. Universal newborn screening using tandem mass spectrometry has identified an unexpectedly high number of infants with 3-MCC deficiency, with its prevalence ranging between 1 in 2,400 and 1 in 68,000.

Clinical manifestations are highly variable, ranging from completely asymptomatic adults (including mothers of affected newborn infants), to children presenting with developmental delay without episodes of metabolic decompensation, to patients with seizures, hyperammonemia, and metabolic acidosis. Rarely, infants who are affected by severe 3-MCC deficiency may appear healthy at birth but later develop acute episodes of vomiting, hypotonia, lethargy, and convulsions after a minor infection, in some cases progressing to life-threatening complications (e.g., Reye syndrome, coma). In patients prone to developing these symptoms, the onset is usually between 3 weeks and 3 years of age. Among infants identified through newborn screening, 85–90% of children remain apparently asymptomatic. The reason for differences in outcomes is unknown. None of the symptoms reported so far could be clearly attributed to the degree of enzyme deficiency.

Laboratory findings during acute episodes include mild to moderate metabolic acidosis, ketosis, hypoglycemia, hyperammonemia, and elevated serum transaminase levels. Large amounts of 3-hydroxyisovalerate and 3-methylcrotonylglycine are found in the urine. Urinary excretion of 3-methylcrotonate is usually not detected in this condition because the accumulated 3-methylcrotonyl-CoA is converted to 3-hydroxyisovalerate. The plasma acylcarnitine profile shows elevated 3-hydroxyisovalerylcarnitine (C5-OH). Severe secondary carnitine deficiency is common. 3-MCC deficiency should be differentiated biochemically from multiple carboxylase deficiency (see earlier), in which, in addition to 3-hydroxyisovalerate, lactate and metabolites of propionic acid are also present. **Diagnosis** may be confirmed by molecular analysis of *MCCC1* and *MCCC2* or by measurement of the enzyme activity in cultured fibroblasts. Documentation of normal activities of other carboxylases is necessary to rule out multiple carboxylase deficiency.

Treatment of acute episodes is similar to that of isovaleric acidemia (see earlier). Hydration and measures to correct both hypoglycemia and severe metabolic acidosis by infusing glucose and sodium bicarbonate should be instituted promptly. Secondary carnitine deficiency, seen in up to 50% of patients, can be corrected with L-carnitine supplementation. For symptomatic patients, some centers recommend keeping protein intake at the recommended dietary allowance in conjunction with the oral administration of L-carnitine and the proactive management of catabolic states. Normal physiologic growth and development are expected in most patients.

3-MCC deficiency is an autosomal recessive condition. Biallelic pathogenic variants in either *MCCC1* or *MCCC2* result in the enzyme deficiency with overlapping clinical features.

3-METHYLGLUTACONIC ACIDURIAS

The 3-methylglutaconic acidurias comprise a heterogeneous group of metabolic disorders characterized by excessive excretion of 3-methylglutaconic acid in the urine (Table 105.2). Other metabolites found in 3-methylglutaconic aciduria patients may include 3-methylglutaric acid and 3-hydroxyisovaleric acid. The current classification distinguishes between primary and secondary forms. **Primary** 3-methylglutaconic aciduria is caused by the deficiency of mitochondrial 3-methylglutaconyl-CoA hydratase (see Fig. 105.4), formerly *3-methylglutaconic aciduria type I*. **Secondary** 3-methylglutaconic aciduria can be further classified based on the underlying mechanism (e.g., defective phospholipid remodeling versus dysfunction of mitochondrial membrane) or now the more preferred classification based on the underlying molecular cause. Known causes of secondary 3-methylglutaconic aciduria include the X-linked *TAZ*-related syndrome **(Barth syndrome)**, *OPA3*-related 3-methylglutaconic aciduria **(Costeff syndrome)**, *SERAC1*-related syndrome **(MEGDEL syndrome)**, *TMEM70*-related syndrome, and *DNAJC19*-related syndrome **(DCMA syndrome)**.

Significant and persistent 3-methylglutaconic aciduria with negative molecular evaluation for known genetic causes represents a heterogeneous group called 3-methylglutaconic aciduria **not otherwise specified** awaiting further molecular characterization. Primary and secondary 3-methylglutaconic aciduria should be distinguished from mild and transient urinary elevations of 3-methylglutaconic acid seen in patients affected by other metabolic disorders or liver dysfunction, such as mitochondrial disorders of diverse etiology.

3-Methylglutaconyl-CoA Hydratase Deficiency

Two main clinical presentations have been described for 3-methylglutaconyl-CoA hydratase deficiency, an autosomal recessive disorder (see Fig. 105.4). In the **childhood** form, nonspecific neurodevelopmental findings such as speech delay or regression, choreoathetoid movements, optic nerve atrophy, and mild psychomotor delay may be present. Metabolic acidosis may occur during a catabolic state. In the **adulthood** form, affected individuals may remain asymptomatic until the second or third decade of life, when a clinical picture of *slowly progressing leukoencephalopathy* with optic nerve atrophy, dysarthria, ataxia, spasticity, and dementia occurs. Brain MRI typically shows white matter abnormalities, which may precede the appearance of clinical symptoms by years. Asymptomatic pediatric and adult patients have also been reported. Patients excrete large amounts of 3-methylglutaconic acid and moderate amounts of 3-hydroxyisovaleric and 3-methylglutaric acids in urine. **Treatment** with L-carnitine may help some patients. The effectiveness of a low-leucine diet has not been established. The condition is caused by biallelic pathogenic variants in *AUH* and is inherited in an autosomal recessive manner.

Barth Syndrome (*Tafazzin*-Related Disorder)

This X-linked condition is caused by a deficiency of *tafazzin,* a mitochondrial protein, encoded by the *TAFAZZIN* gene. This enzyme is necessary for remodeling of immature cardiolipin into its mature form. *Cardiolipin,* a mitochondrial phospholipid, is critical for the integrity of the inner mitochondrial membrane. **Clinical manifestations** of Barth syndrome usually begin in the first year of life in a male infant and include cardiomyopathy, hypotonia, growth restriction, hypoglycemia, and mild to severe neutropenia. The onset of clinical manifestations may be as late as adulthood, but most affected individuals become symptomatic by adolescence. If patients survive infancy, relative improvement may occur with advancing age. Cognitive development is usually normal, although delayed motor function and learning disabilities occur.

Laboratory findings include mild to moderate increases in urinary excretion of 3-methylglutaconic, 3-methylglutaric, and 2-ethylhydracrylic acids. Unlike primary 3-methylglutaconic aciduria (type I), urinary excretion of 3-hydroxyisovaleric acid is not elevated. The activity of the enzyme 3-methylglutaconyl-CoA hydratase is normal. *Neutropenia is a common finding.* Lactic acidosis, hypoglycemia, low serum cholesterol, low prealbumin, and abnormal mitochondrial ultrastructure are also common. Total cardiolipin and subclasses of cardiolipin are very low in skin fibroblast cultures from these patients. The monolysocardiolipin/cardiolipin ratio in cultured fibroblast is useful for establishing the diagnosis in patients with negative or equivocal molecular results. Because of its nonspecific presentation, the condition is likely underdiagnosed and underreported.

The condition is inherited in an *X-linked* recessive manner. The gene *(TAFAZZIN)* has been mapped to chromosome Xq28. The modest 3-methylglutaconic aciduria seen in Barth syndrome is thought to be related to the defect in the mitochondrial membrane, causing the leakage of this organic acid. Gene-specific treatment is not available. Patients with an unsatisfactory response to medical management of cardiomyopathy may benefit from cardiac transplantation. Daily aspirin to reduce the risk of strokes has been described. Regular use of granulocyte colony stimulating factor (G-CSF) can help limit recurrent infections in patients with neutropenia.

OPA3-Related 3-Methylglutaconic Aciduria (Costeff Syndrome)

Clinical manifestations in patients with Costeff syndrome include early-onset optic nerve atrophy and later development of choreoathetoid movements, spasticity, ataxia, dysarthria, and cognitive impairment. Patients excrete moderate amounts of 3-methylglutaconic and 3-methylglutaric acids. Activity of the enzyme 3-methylglutaconyl-CoA hydratase is normal. The condition is inherited in an autosomal recessive manner. Pathogenic variants in *OPA3* are thought to cause electron transport chain dysfunction. Treatment is supportive.

Disorders Formerly Described as 3-Methylglutaconic Aciduria Type IV

3-Methylglutaconic aciduria type IV represents a group of disorders with a diverse genetic etiology. Two disorders in this group have been linked to specific molecular etiology, whereas other conditions are still awaiting the discovery of underlying molecular defects.

MEGDEL syndrome (3-*me*thylglutaconic aciduria with *d*eafness, *e*ncephalopathy, and *L*eigh-like) is an autosomal recessive disorder caused by pathogenic variants in *SERAC1*. Affected patients experience optic nerve atrophy, progressive deafness, dystonia, feeding difficulty with dysphagia, spasticity, and basal ganglia injury similar to patients

Table 105.2 Primary and Select Secondary 3-Methylglutaconic Acidurias

GROUP	DISORDER	GENE (CHROMOSOME)	PREVIOUS CLASSIFICATION	DISEASE MECHANISM	CLINICAL DESCRIPTION
Primary 3-methylglutaconic aciduria	3-Methylglutaconyl-CoA hydratase deficiency	*AUH* (9q22.31)	Type I	Enzyme deficiency in the leucine degradation pathway	Depending on age, variable presentation is seen ranging from younger asymptomatic patients to older patients with progressive leukoencephalopathy
Secondary 3-methylglutaconic acidurias	Barth syndrome	*TAZ* (Xq28)	Type II	Defective phospholipid remodeling	X-linked inheritance, cardiomyopathy, endocardial fibroelastosis, proximal myopathy, failure to thrive, neutropenia, dysmorphic findings
	Costeff syndrome	*OPA3* (19q13.32)	Type III	Mitochondrial membrane dysfunction	Progressive optic nerve atrophy, chorea, spastic paraparesis, cognitive impairment
	MEGDEL syndrome	*SERAC1* (6q25.3)	Type IV	Defective phospholipid remodeling	Progressive deafness, dystonia, spasticity, basal ganglia changes
	TMEM70-related disorder	*TMEM70* (8q21.11)	Type IV	Mitochondrial membrane dysfunction	Developmental delay, failure to thrive, metabolic decompensations, microcephaly, cardiomyopathy, dysmorphic findings
	3-Methylglutaconic aciduria, not otherwise specified	Unknown	Type IV	Unknown	Variable presentation
	DCMA syndrome	*DNAJC19* (3q26.33)	Type V	Mitochondrial membrane dysfunction	Cardiomyopathy, ataxia, optic nerve atrophy, failure to thrive

DCMA, Dilated cardiomyopathy ataxia syndrome; MEGDEL, 3-methylglutaconic aciduria deafness, encephalopathy, Leigh-like syndrome.

with Leigh syndrome. Laboratory evaluation reveals elevated urinary 3-methylglutaconic, high plasma lactate and alanine. Treatment is symptomatic.

***TMEM70*-related disorder** is also inherited in an autosomal recessive manner. Biallelic pathogenic variants in *TMEM70* result in a mitochondrial complex V deficiency, although the exact molecular mechanism of disease is unknown. Clinical manifestations include developmental delay, developmental regression, Reye syndrome–like episodes, intellectual disability, failure to thrive, microcephaly, cardiomyopathy, and dysmorphic findings. Patients are prone to metabolic decompensation, characterized by hyperammonemia (up to 900 µmol/L) and lactic acidosis, which are more common in the first year of life. **Acute hyperammonemic** episodes are treated with intravenous glucose, lipid emulsion, ammonia-scavenging drugs, and occasionally hemodialysis. Long-term therapy that has been described includes L-carnitine, coenzyme Q_{10}, and bicarbonate substitution (e.g., citric acid/sodium citrate). Patients require interval echocardiographic and electrocardiographic (ECG) monitoring to enable early diagnosis and management of cardiomyopathy.

DCMA Syndrome (*DNAJC19*-Related Syndrome, 3-Methylglutaconic Aciduria Type V)

DCMA syndrome (*d*ilated *c*ardio*m*yopathy with *a*taxia) is an autosomal recessive disorder identified in patients of Canadian Dariusleut Hutterite ancestry in the Great Plains of North America. As the disorder's abbreviated name suggests, affected individuals present with dilated cardiomyopathy, long QTc interval, and CNS involvement. Neurologic symptoms include intellectual disability, cerebellar involvement, and optic atrophy. Growth is affected in all patients. Intrauterine growth restriction is seen in up to 50% of patients. Cryptorchidism and hypospadias are frequent findings in affected boys. Urine organic acid assay reveals increased 3-methylglutaconic acid and 3-methylglutaric acid. Biallelic pathogenic variants in *DNAJC19* are the underlying cause of DCMA syndrome. Treatment is symptomatic. Interval echocardiography and ECG can prospectively identify patients requiring treatment for cardiomyopathy and long QTc interval.

β-KETOTHIOLASE (3-OXOTHIOLASE) DEFICIENCY (MITOCHONDRIAL ACETOACETYL-COA THIOLASE [T_2] DEFICIENCY)

The bidirectional reaction catalyzed by mitochondrial β-ketothiolase is involved in the final steps of both isoleucine catabolism and ketolysis. In the isoleucine catabolic pathway, the enzyme cleaves 2-methylacetoacetyl-CoA into propionyl-CoA and acetyl-CoA (see Fig. 105.4). In the fatty acid oxidation pathway, the enzyme generates two moles of acetyl-CoA from one mole of acetoacetyl-CoA (Fig. 105.7). The same enzyme can synthesize 2-methylacetoacetate-CoA and acetoacetyl-CoA in the reverse direction. The hallmark of this disorder is **ketoacidosis**, often triggered by infections, prolonged fasting, and large protein load. The mechanism of ketosis in this condition is incompletely understood, because in this enzyme deficiency one would expect impaired ketone formation (see Fig. 105.7). It is postulated that excess acetoacetyl-CoA produced from other sources can be used as a substrate for 3-hydroxy-3-methylglutaryl-CoA synthesis in the liver.

Clinical manifestations are quite variable, ranging from mild cases showing normal development to severe episodes of acidosis starting in the first year of life causing severe cognitive impairment. Unless identified on the newborn screening, affected children present with intermittent episodes of unexplained ketoacidosis. These episodes usually occur after an intercurrent infection and respond promptly to

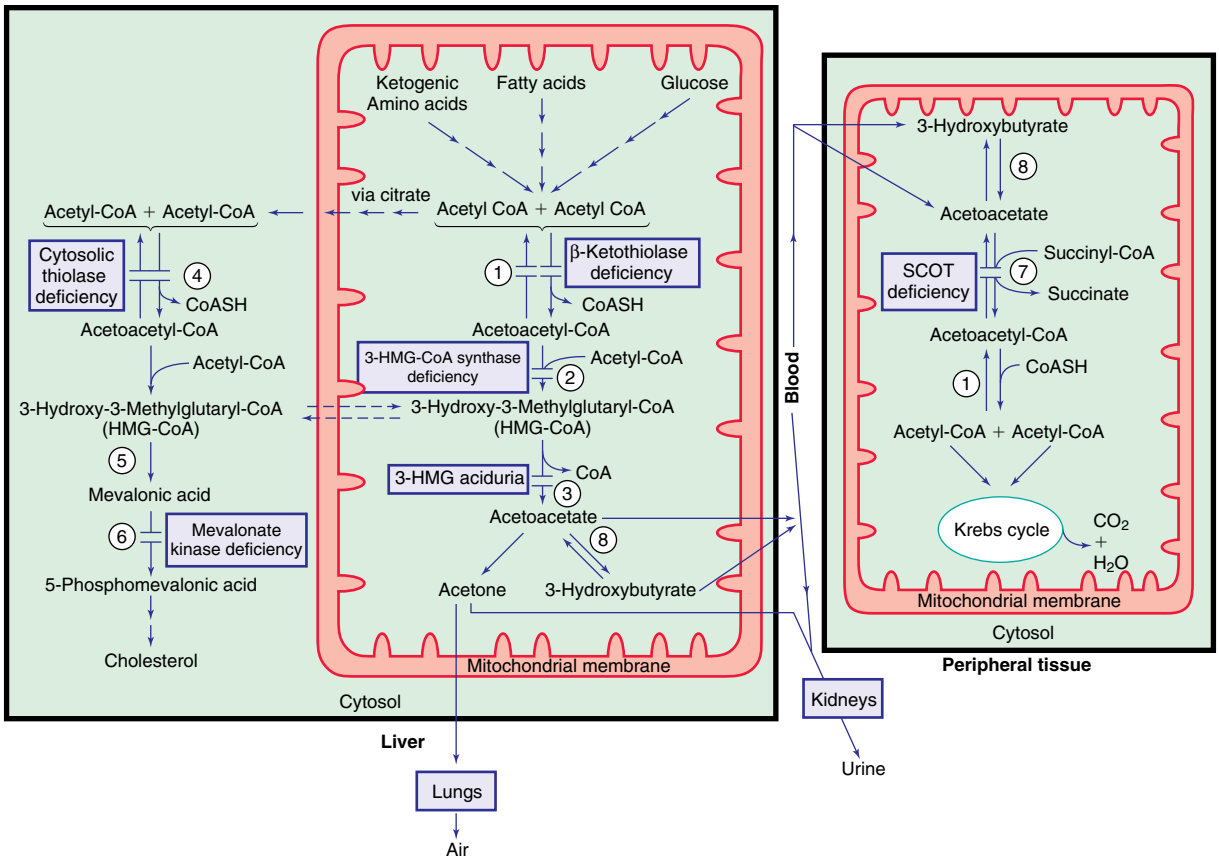

Fig. 105.7 Formation (liver) and metabolism (peripheral tissues) of ketone bodies and cholesterol synthesis. **Enzymes:** *(1)* Mitochondrial acetoacetyl CoA thiolase, *(2)* HMG-CoA synthase, *(3)* HMG-CoA lyase, *(4)* cytosolic acetoacetyl-CoA thiolase, *(5)* HMG-CoA reductase, *(6)* mevalonic kinase, *(7)* succinyl CoA:3-ketoacid CoA transferase (SCOT), *(8)* 3-hydroxybutyrate dehydrogenase.

intravenous fluids and bicarbonate therapy. Mild to moderate hyperammonemia may also be present during attacks. Both hypoglycemia and hyperglycemia have been reported in isolated cases. The child may be completely asymptomatic between episodes and may tolerate a normal protein diet. Cognitive development is normal in most children. The episodes may be misdiagnosed as salicylate poisoning because of the similarity of the clinical findings and the interference of elevated blood levels of acetoacetate with the colorimetric assay for salicylate.

Laboratory findings during the acute attack include ketoacidosis and hyperammonemia. Findings of ketones in the urine and hyperglycemia may be interpreted as diabetic ketoacidosis, and a high index of suspicion is needed to suspect this metabolic disorder. Urine organic acid assay can provide clues leading to a correct diagnosis. Urine contains large amounts of 2-methylacetoacetate and its decarboxylated products butanone, 2-methyl-3-hydroxybutyrate, and tiglylglycine. Lower concentrations of urinary metabolites can be seen when patients are stable. Mild hyperglycinemia may also be present. The plasma acylcarnitine profile shows elevations of C5:1 and C5-OH carnitines, although these metabolites can normalize between catabolic episodes. Absent or minimal elevations of C5:1 and C5-OH carnitines can result in false-negative results on the newborn screening of affected infants who were clinically well at the time of blood collection. The clinical and biochemical findings should be differentiated from those seen with propionic and methylmalonic acidemias (see later).

Treatment of acute episodes includes hydration. Recalcitrant metabolic acidosis can be severe enough to require infusion of bicarbonate. A 10% glucose solution with the appropriate electrolytes is used to suppress protein catabolism, lipolysis, and ketogenesis. Restriction of protein intake to age-appropriate physiologic requirements is recommended for long-term therapy. Oral L-carnitine (50-100 mg/kg/day) is also recommended to prevent possible secondary carnitine deficiency. The long-term prognosis for achieving a normal quality of life seems very favorable. Successful pregnancy with a normal outcome has been reported.

β-Ketothiolase deficiency is inherited in an autosomal recessive manner and may be more prevalent than appreciated. **Diagnosis** may be confirmed by molecular analysis of the *ACAT1* gene or using an enzyme assay of leukocytes or cultured fibroblasts.

CYTOSOLIC ACETOACETYL-COA THIOLASE DEFICIENCY

This enzyme catalyzes the cytosolic production of acetoacetyl-CoA from two moles of acetyl-CoA (see Fig. 105.7). Cytosolic acetoacetyl-CoA is the precursor of hepatic cholesterol synthesis. Cytosolic acetoacetyl-CoA thiolase (encoded by *ACAT2*) should be differentiated from the mitochondrial thiolase (see earlier and Fig. 105.4). Clinical manifestations in patients with this very rare enzyme deficiency have been incompletely characterized. Patients may present with severe progressive developmental delay, hypotonia, and choreoathetoid movements in the first few months of life. Laboratory findings are nonspecific; elevated levels of lactate, pyruvate, acetoacetate, and 3-hydroxybutyrate may be found in blood and urine. One patient had normal levels of acetoacetate and 3-hydroxybutyrate. Diagnosis can be aided by demonstrating a deficiency in cytosolic thiolase activity in liver biopsy or in cultured fibroblasts or by DNA analysis of *ACAT2*. No effective treatment has been described, although a low-fat diet helped to diminish ketosis in one patient.

MITOCHONDRIAL 3-HYDROXY-3-METHYLGLUTARYL-COA SYNTHASE DEFICIENCY

3-Hydroxy-3-methylglutaryl (HMG)-CoA synthase (mitochondrial or type 2) catalyzes synthesis of 3-HMG-CoA from acetoacetyl-CoA and acetyl-CoA in the mitochondria. This is a critical step in ketone body synthesis in the liver (see Fig. 105.7). Only a few patients with

deficiency of this enzyme have been reported. The principal clinical syndrome is *hypoketotic hypoglycemia* triggered by physiologic stress, such as infections or fasting. Age at presentation has ranged from infancy to 6 years. Children tend to be asymptomatic before these episodes and with appropriate management can remain stable after the recovery (except for mild hepatomegaly with fatty infiltration). Future episodes can be prevented by avoiding prolonged fasting during ensuing intercurrent illnesses. Hepatomegaly is the most consistent physical finding in these patients. **Laboratory findings** include hypoglycemia, acidosis with mild or no ketosis, elevated levels in liver function tests, and massive dicarboxylic aciduria. The clinical and laboratory findings may be confused with fatty acid metabolism defects (see Chapter 104). In contrast to the latter, in patients with HMG-CoA synthase deficiency, the blood concentrations of acylcarnitine conjugates are negative for acylcarnitine findings characteristic of fatty acid oxidation disorders. Treatment of the secondary carnitine deficiency with L-carnitine supplementation can result in elevated plasma acetylcarnitine (C2-carnitine), likely reflecting intracellular accumulation of acetyl-CoA.

Treatment consists of provision of adequate calories and avoidance of prolonged periods of fasting. No dietary protein restriction was needed.

The condition is inherited in an autosomal recessive manner and is caused by biallelic pathogenic variants in *HMGCS2*. The condition should be considered in any child with fasting hypoketotic hypoglycemia and may be more common than appreciated.

3-HYDROXY-3-METHYLGLUTARYL-COA LYASE DEFICIENCY (3-HYDROXY-3-METHYLGLUTARIC ACIDURIA)

3-HMG-CoA lyase (encoded by *HMGCL*) catalyzes the cleavage of 3-HMG-CoA to acetoacetate, a rate-limiting enzyme for ketogenesis (see Fig. 105.4 and Fig. 105.7). The deficiency of this enzyme is a rare disorder seen with increased frequency in Saudi Arabia, the Iberian Peninsula, and in Brazil in patients of Portuguese ancestry. Clinically, approximately 30% develop symptoms in the first few days of life, and >60% of patients become symptomatic between 3 and 11 months of age. Infrequently, patients may remain asymptomatic until adolescence. With the addition of 3-HMG-CoA lyase deficiency to the newborn screening using C5-OH-carnitine, many infants are identified presymptomatically in the newborn period. Similar to 3-HMG-CoA synthase deficiency, patients affected by 3-HMG-CoA lyase deficiency may present with acute hypoketotic hypoglycemia. Episodes of vomiting, severe hypoglycemia, hypotonia, acidosis with mild or no ketosis, and dehydration may rapidly lead to lethargy, ataxia, and coma. These episodes often occur during a catabolic state such as prolonged fasting or an intercurrent infection. Hepatomegaly is common. These manifestations may be mistaken for Reye syndrome or fatty acid oxidation defects such as medium-chain acyl-CoA dehydrogenase deficiency. Long-term complications can include dilated cardiomyopathy, hepatic steatosis, and pancreatitis. Development can be normal, but intellectual disability and seizures with abnormalities in the white matter seen on brain MRI have been observed in patients after prolonged episodes of hypoglycemia.

Laboratory findings include hypoglycemia, moderate to severe hyperammonemia, and acidosis. There is mild or no ketosis (see Fig. 105.7). Urinary excretion of 3-hydroxy-3-methylglutaric acid and other proximal intermediate metabolites of leucine catabolism (3-methylglutaric acid, 3-methylglutaconic acid, and 3-hydroxyisovaleric acid) is markedly increased, causing the urine to smell like "cat's urine." Glutaric and dicarboxylic acids may also be increased in urine during acute attacks. Secondary carnitine deficiency is common. The condition is inherited in an autosomal recessive manner. 3-HMG-CoA lyase is encoded by the gene *HMGCL*. **Diagnosis** may be confirmed by molecular analysis of *HMGCL* or by enzyme assay in cultured fibroblasts, leukocytes, or liver specimens. Prenatal diagnosis is possible by molecular DNA analysis if the familial pathogenic variants are known or by enzymatic assay of the cultured amniocytes or a chorionic villi biopsy.

Treatment of acute episodes includes hydration, infusion of glucose to control hypoglycemia, provision of adequate calories, and administration of bicarbonate to correct acidosis. Hyperammonemia should be treated promptly (see Chapter 105.12). Dialysis may be required in patients with severe recalcitrant hyperammonemia. Restriction of protein and fat intake can be considered for long-term management. Oral administration of L-carnitine (50-100 mg/kg/day) prevents secondary carnitine deficiency. Prolonged fasting should be avoided.

SUCCINYL-COA:3-OXOACID-COA TRANSFERASE DEFICIENCY

Succinyl-CoA:3-oxoacid-CoA transferase **(SCOT)** deficiency and β-ketothiolase deficiency collectively are referred to as **ketone utilization disorders**. SCOT participates in the conversion of ketone bodies (acetoacetate and 3-hydroxybutyrate) generated in liver mitochondria into *acetoacetyl-CoA in the nonhepatic tissues* (see Fig. 105.7). A deficiency of this enzyme results in the accumulation of ketone bodies, ketoacidosis, increased use of glucose, and hypoglycemia. During fasting, patients tend to have a proportional elevation of plasma free fatty acids. The condition may be more common than recognized because many cases tend to be mild and remain undiagnosed. SCOT deficiency can be distinguished from β-ketothiolase deficiency by the absence of 2-methylacetoacetate, 2-methyl-3-hydroxybutyrate, and tiglylglycine, characteristic of the latter disorder. Plasma acylcarnitine profile tends to show no specific abnormalities.

A common clinical presentation is an acute episode of severe ketoacidosis in an infant who had been growing and developing normally. About half the patients become symptomatic in the first weeks of life, and practically all become symptomatic before 2 years of age. The acute episode is often precipitated by a catabolic state triggered by an infection or prolonged fasting. Without treatment, the ketoacidotic episode can result in death. A chronic subclinical ketosis may persist between the attacks. Development is usually normal, although severe and recurrent episodes of ketoacidosis and hypoglycemia can predispose patients to neurocognitive impairment.

Laboratory findings during the acute episode are nonspecific and include metabolic acidosis and ketonuria with high levels of acetoacetate and 3-hydroxybutyrate in blood and urine. No other organic acids are found in the blood or in the urine. Blood glucose levels are usually normal, but hypoglycemia has been reported in some affected newborn infants with severe ketoacidosis. Plasma amino acids and the plasma acylcarnitine profile are usually normal. Severe SCOT deficiency can be accompanied by ketosis even when patients are clinically stable. This condition should be considered in any infant with unexplained bouts of ketoacidosis. SCOT deficiency is an autosomal recessive disorder. **Diagnosis** can be established by molecular analysis of *OXCT1* or by demonstrating a deficiency of enzyme activity in cultured fibroblasts.

Treatment of acute episodes consists of rehydration with solutions containing dextrose, correction of acidosis, and the provision of a diet adequate in calories. Long-term treatment should include a high-carbohydrate diet and avoidance of prolonged fasting and administration of dextrose before anticipated or during established catabolic states.

MEVALONATE KINASE DEFICIENCY

Mevalonic acid, an intermediate metabolite of cholesterol synthesis, is converted to 5-phosphomevalonic acid by the action of the enzyme mevalonate kinase (MVK) (see Fig. 105.7). MVK deficiency presents with a range of symptoms. Mevalonic aciduria occupies the more severe end of the spectrum, whereas hyperimmunoglobulinemia D syndrome represents the milder form of the underlying enzyme defect. Both disorders are accompanied by recurrent fever, gastrointestinal symptoms, mucocutaneous manifestations, and lymphadenopathy. Patients with mevalonic aciduria also show growth retardation and nervous system involvement.

Mevalonic Aciduria

Clinical manifestations include failure to thrive, growth restriction, intellectual disability, hypotonia, ataxia, myopathy, hepatosplenomegaly,

cataracts, and facial dysmorphisms (dolichocephaly, frontal bossing, low-set ears, downward slanting of eyes, long eyelashes). Most patients experience recurrent crises characterized by fever, vomiting, diarrhea, hepatosplenomegaly, arthralgia, lymphadenopathy, edema, and morbilliform rash. These episodes typically last 2-7 days and recur up to 25 times a year. Death may occur during these crises.

Laboratory findings include marked elevation of mevalonic acid in urine; the concentration of urinary mevalonic acid ranges between 500 and 56,000 mmol/mol of creatinine (normal: <0.3 mmol/mol of creatinine). Plasma levels of mevalonic acid are also greatly increased (as high as 540 μmol/L; normal: <0.04 μmol/L). Mevalonic acid levels tend to correlate with the severity of the condition and increase during crises. Serum cholesterol concentration is normal or mildly decreased. Serum concentration of creatine kinase can be greatly increased. Inflammatory markers are elevated during the crises. Brain MRI may reveal progressive atrophy of the cerebellum.

Diagnosis may be confirmed by molecular analysis of *MVK* or by assaying the MVK activity in lymphocytes or cultured fibroblasts. The enzyme activity in this form of the condition is below the detection level. **Treatment** with high doses of prednisone helps in the acute crises, but because of side effects, it is not routinely used long term. TNF-α inhibitors and interleukin-1 receptor antagonists have shown to be effective in bringing significant clinical improvement, especially in patients with chronic inflammation and frequent attacks. The condition is inherited in an autosomal recessive manner. **Prenatal diagnosis** is possible by identifying known familial pathogenic variants in *MVK,* by measurement of mevalonic acid in the amniotic fluid, or by assaying the enzyme activity in cultured amniocytes or chorionic villi samples.

Hyperimmunoglobulinemia D Syndrome (Hyperimmunoglobulinemia D and Periodic Fever Syndrome)

Some pathogenic variants of the *MVK* gene cause milder enzyme deficiency and produce the clinical picture of **periodic fever with hyperimmunoglobulinemia D**. These patients have periodic bouts of fever associated with abdominal pain, vomiting, diarrhea, arthralgia, arthritis, hepatosplenomegaly, lymphadenopathy, and morbilliform rash (even petechiae and purpura), which usually start before 1 year of age. The attacks can be triggered by vaccination, minor trauma, or stress and can occur every 1-2 months, lasting 2-7 days. Patients are free of symptoms between acute attacks. The diagnostic laboratory finding is elevation of serum immunoglobulin D (IgD). IgA is also elevated in 80% of patients. During acute attacks, leukocytosis, increased C-reactive protein, and mild mevalonic aciduria may be present. High concentrations of serum IgD help differentiate this condition from familial Mediterranean fever. See Chapter 204 for treatment recommendations.

PROPIONIC ACIDEMIA (PROPIONYL-COA CARBOXYLASE DEFICIENCY)

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids, and side chains of cholesterol. Normally, propionic acid in the form of propionyl-CoA undergoes carboxylation to D-methylmalonyl-CoA, catalyzed by the mitochondrial enzyme propionyl-CoA carboxylase. This enzyme requires biotin as a cofactor; thus the disorders of biotin metabolism, among other findings, can also result in elevation of propionic acid metabolites (see Fig. 105.4). Propionyl-CoA carboxylase is a multimeric enzyme composed of two nonidentical subunits, α and β, encoded by two genes, *PCCA* and *PCCB,* respectively. Biallelic pathogenic variants in propionyl-CoA carboxylase result in an autosomal recessive disorder called *propionic acidemia.*

Clinical findings of propionic acidemia are not specific to this disorder only. In the severe form, patients develop symptoms in the first few days of life. Poor feeding, vomiting, hypotonia, lethargy, dehydration, a sepsis-like picture, and clinical signs of severe ketoacidosis progress rapidly to coma and death. Seizures occur in approximately 30% of affected infants. If an infant survives the first attack, similar episodes of metabolic decompensation may occur during an intercurrent infection, trauma, surgery, prolonged fasting, severe constipation, or after ingestion of a high-protein diet. Moderate to severe intellectual disability and neurologic manifestations reflective of extrapyramidal (dystonia, choreoathetosis, tremor) and pyramidal (paraplegia) dysfunction are common sequelae in survivors. Neuroimaging shows that these abnormalities, which often occur after an episode of metabolic decompensation, are the result of damage to the basal ganglia, especially to the globus pallidus. This phenomenon has been referred to as **metabolic stroke**. This is the main cause of neurologic sequelae seen in the surviving affected children. Additional long-term complications include failure to thrive, optic nerve atrophy, pancreatitis, cardiomyopathy, and osteopenia.

In the *milder* form, episodes of metabolic decompensation are less frequent, but these children are still at risk of developing intellectual disability, seizures, long QTc interval, and severe cardiomyopathy. Universal newborn screening can identify propionic acidemia by detecting elevated propionylcarnitine (C3-carnitine) with an abnormal C3/C2 ratio in dried blood spots. However, in patients with the mild form of propionic acidemia, propionylcarnitine may remain below the cutoff value set by the screening laboratory, resulting in a false-negative result. Therefore physicians should maintain a high index of suspicion for this disorder and follow up with a biochemical evaluation of infants and children presenting with unexplained ketosis or metabolic acidosis.

Laboratory findings during the acute attack include various degrees of metabolic acidosis, often with a large anion gap, ketosis, ketonuria, hypoglycemia, anemia, neutropenia, and thrombocytopenia. Moderate to severe hyperammonemia is common; plasma ammonia concentrations usually correlate with the severity of the disease. In contrast to other causes of hyperammonemia, plasma concentration of glutamine tends to be within normal limits or decreased. The presence of severe metabolic acidosis and normal to reduced plasma glutamine help differentiate propionic academia from hyperammonemia caused by urea cycle defects. Measurement of plasma ammonia is especially helpful in planning therapeutic strategies during episodes of exacerbation in a patient whose diagnosis has been established. Mechanisms of hyperammonemia in propionic acidemia are not well understood but are likely related to the perturbed biochemical and pH environment of the mitochondrial matrix, where the proximal part of the urea cycle resides.

Glycine concentration can be elevated in all body fluids (blood, urine, CSF) and possibly is the result of the inhibited glycine cleavage system in the hepatic mitochondria (Fig. 105.8). Glycine elevation has also been observed in patients with methylmalonic acidemia. These disorders were collectively referred to as *ketotic hyperglycinemia* in the past before the specific enzyme deficiencies were elucidated. Mild to moderate increase in blood lactate and lysine may also be present in these patients. Concentrations of propionylcarnitine, 3-hydroxypropionic acid, and methylcitric acid (presumably formed through condensation of propionyl-CoA with oxaloacetic acid) are greatly elevated in the plasma and urine of infants with propionic acidemia. Propionylglycine and other intermediate metabolites of BCAA catabolism, such as tiglylglycine, can also be found in urine. Moderate elevations in blood levels of glycine and previously mentioned organic acids can persist between the acute attacks. Brain imaging may reveal cerebral atrophy, delayed myelination, and abnormalities in the globus pallidus and other parts of the basal ganglia.

The **diagnosis** of propionic acidemia should be differentiated from multiple carboxylase deficiencies (see earlier and Fig. 105.6). In addition to propionic acid metabolites, infants with the latter condition excrete large amounts of lactic acid, 3-methylcrotonylglycine, and 3-hydroxyisovaleric acid. The presence of hyperammonemia may suggest a genetic defect in the urea cycle enzymes. Infants with defects in the urea cycle are usually *not* acidotic (see Fig. 105.1) and have elevated levels of plasma glutamine. The definitive diagnosis of propionic acidemia can be established through molecular analysis of *PCCA* and *PCCB* or by measuring the enzyme activity in leukocytes or cultured fibroblasts.

Treatment of acute episodes of metabolic decompensation includes hydration with solutions containing glucose, correction of acidosis, and amelioration of the catabolic state by provision of adequate calories through enteral or parenteral hyperalimentation. A brief restriction of

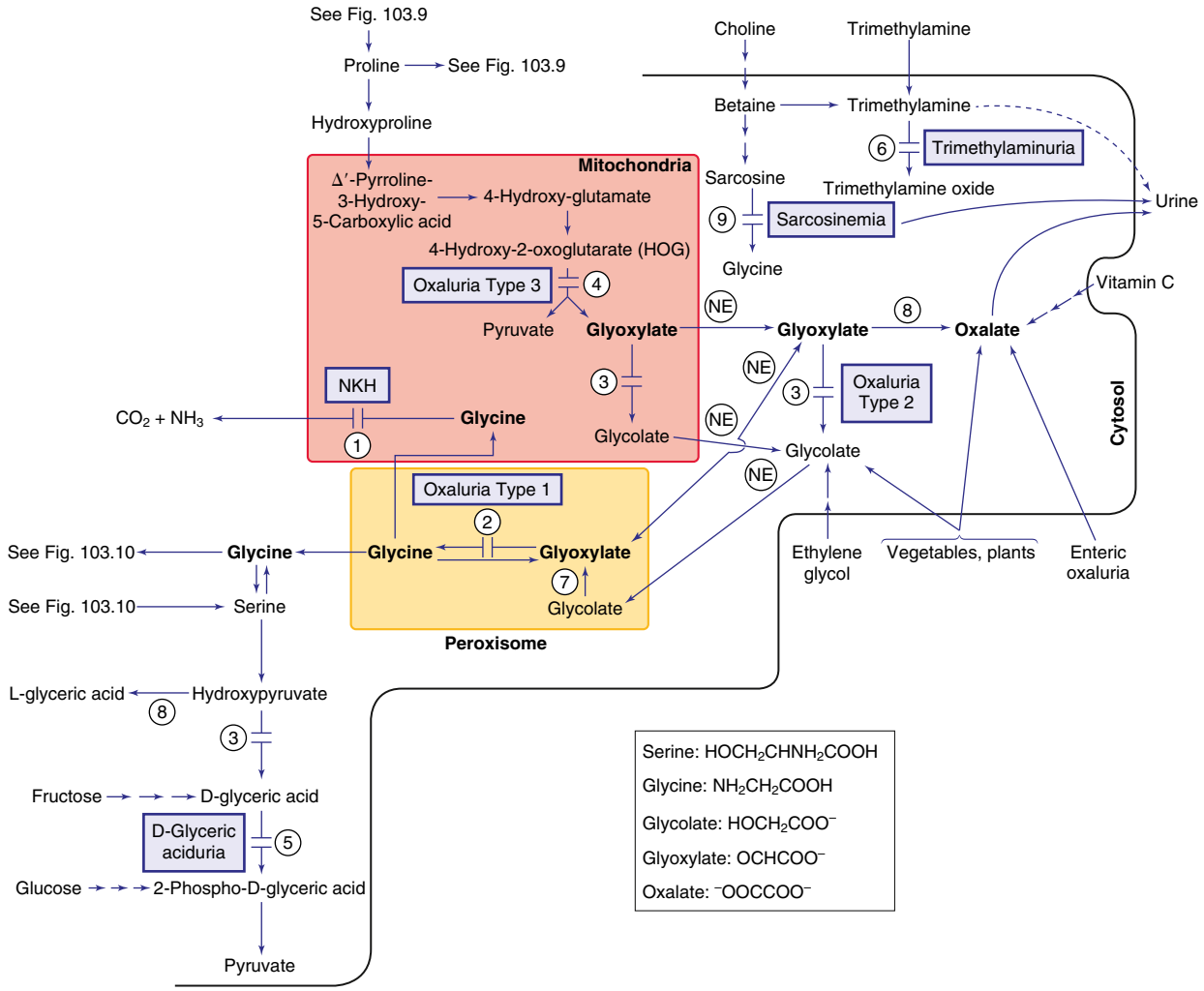

Fig. 105.8 Pathways in the metabolism of glycine and glyoxylic acid. **Enzymes:** *(1)* Glycine cleavage system, *(2)* alanine:glyoxylate aminotransferase, *(3)* glyoxylic reductase/hydroxypyruvate reductase (GR/HRP), *(4)* hydroxyoxoglutarate aldolase one (HOGA1), *(5)* glycerate kinase, *(6)* trimethylamine oxidase, *(7)* glycolate oxidase (D-amino acid oxidase), *(8)* lactate dehydrogenase, *(9)* sarcosine dehydrogenase. NE, Nonenzymatic; NKH, nonketotic hyperglycinemia.

protein intake, no more than 24 hours, is often necessary. Depending on the clinical status, gradual reintroduction of protein is recommended. If enteral feedings cannot be tolerated after 48 hours of protein restriction, parenteral nutrition should be instituted to achieve the age-specific recommended protein intake. Patients unable to tolerate the recommended dietary allowance of protein can receive specialized medical foods free of isoleucine, valine, threonine, and methionine. The composition and amount of protein typically vary among patients. The metabolic diet composition can be adjusted by monitoring growth and plasma amino acids drawn 3-4 hours after the typical feeding. Some patients may benefit from the suppression of propionogenic gut microflora. This can be achieved by oral antibiotics such as oral neomycin or metronidazole. Prolonged use of metronidazole should be avoided because it has been associated with reversible peripheral neuropathy and increased QTc interval. The risk of QTc prolongation can be problematic in propionic acidemia patients, who are at risk for cardiomyopathy and long QT interval. Baseline and interval ECGs are recommended before and after initiation of metronidazole therapy. Patients may benefit from management of constipation.

Patients with propionic acidemia often develop *secondary carnitine deficiency,* presumably as a result of the urinary loss of propionylcarnitine. Administration of L-carnitine (50-100 mg/kg/day orally or intravenously) helps restore free carnitine in blood. In patients with concomitant hyperammonemia, measures to reduce blood ammonia should be employed (see Chapter 105.12). Very ill patients with severe acidosis and hyperammonemia require hemodialysis to remove ammonia and other toxic compounds rapidly and efficiently. Carglumic acid and nitrogen scavengers (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate) can aid in the treatment of acute hyperammonemia. Although no infant with propionic acidemia has been found to be responsive to biotin, this compound should be administered (10 mg/day orally) to all infants during the first attack and until the diagnosis is established and multiple carboxylase deficiency ruled out.

Long-term treatment consists of a low-protein diet meeting age-specific recommended dietary allowance and administration of L-carnitine (50-100 mg/kg/day orally). Some centers manage mild cases of propionic acidemia without medical foods, opting for only restricting the protein intake to the recommended dietary allowance. Patients unable to tolerate the recommended dietary intake of protein may require medical foods free of propionate precursors (isoleucine, valine, methionine, and threonine). Excessive use of medical foods while restricting natural-source protein may cause a deficiency of the essential amino acids, especially isoleucine and valine, which may cause a condition resembling **acrodermatitis enteropathica** (see Chapter 712). Over-restriction of methionine, especially in the first years of life, may contribute to the reduced brain growth and microcephaly. To avoid this problem, natural proteins should comprise most of the dietary protein. Some patients may require bicarbonate substitution (e.g., citric acid/sodium citrate) to correct chronic acidosis. The concentration of plasma ammonia usually normalizes between attacks, although

some patients may experience mild chronic hyperammonemia. Acute attacks triggered by infections, fasting, trauma, stress, constipation, or dietary indiscretions should be treated promptly and aggressively. Close monitoring of plasma ammonia, plasma amino acids obtained 3-4 hours after the last typical meal (especially isoleucine, leucine, valine, threonine, and methionine), and growth parameters is necessary to ensure the diet is appropriate. Orthotopic liver transplantation is used in clinically unstable patients experiencing recurrent hyperammonemia, frequent metabolic decompensations, and poor growth. Liver transplantation does not cure propionic acidemia, and lifelong dietary management and proactive management during periods of significant metabolic stress are recommended.

The long-term **prognosis** is poor. Death may occur during an acute attack. Normal psychomotor development is possible in a mild form identified through newborn screening. Children identified clinically may manifest some degree of permanent neurodevelopmental deficit, such as tremor, dystonia, chorea, and spasticity despite adequate therapy. These neurologic findings may be the sequelae of a metabolic stroke occurring during an acute decompensation. A long QTc interval and cardiomyopathy with potential progression to heart failure, fatal arrhythmias, and death may develop in older affected children despite adequate metabolic control. Acute pancreatitis is a common and severe complication in propionic acidemia. Osteoporosis can predispose to fractures, which can occur with minimal mechanical stress.

Prenatal diagnosis can be achieved by identification of known familial pathogenic variants in *PCCA* or *PCCB* or by measuring the enzyme activity in cultured amniotic cells or in samples of uncultured chorionic villi.

Propionic acidemia is inherited in an autosomal recessive manner. It has a worldwide prevalence of 1 in 105,000 to 1 in 250,000 live births. It is more prevalent in Greenlandic Inuits (1 in 1,000) and in some Saudi Arabian tribes (1 in 2,000 to 1 in 5,000 live births). Biallelic pathogenic variants in either gene result in similar clinical and biochemical manifestations. Although pregnancies with normal outcomes have been reported, the perinatal period poses special risks to females with propionic acidemia because of hyperemesis gravidarum, worsening cardiomyopathy, changing protein requirements, and risk of metabolic decompensation.

ISOLATED METHYLMALONIC ACIDEMIAS

Methylmalonic acidemias are a group of metabolic disorders of diverse etiology characterized by impaired conversion of methylmalonyl-CoA into succinyl-CoA. Propionyl-CoA derived from catabolism of isoleucine, valine, threonine, methionine, side chain of cholesterol, and odd-chain fatty acids is catalyzed by propionyl-CoA carboxylase to form D-methylmalonyl-CoA. Methylmalonyl-CoA epimerase then converts D-methylmalonyl-CoA to its enantiomer L-methylmalonyl-CoA. **Methylmalonyl-CoA epimerase deficiency** is a rare disorder associated with persistent elevations of propionate-related metabolites and methylmalonic acid. It may present with metabolic acidosis, ketosis, but patients appear more clinically stable than those with severe forms of methylmalonic acidemia.

In the next biochemical step, L-methylmalonyl-CoA is converted to succinyl-CoA by methylmalonyl-CoA mutase (see Fig. 105.4). The latter enzyme requires 5-deoxyadenosylcobalamin, a metabolite of vitamin B_{12}, as a coenzyme. Deficiency of either the mutase or its coenzyme results in the accumulation of methylmalonic acid and its precursors in body fluids. Two biochemical forms of methylmalonyl-CoA mutase deficiencies have been identified. These are designated *mut*^{0}, referring to no detectable enzyme activity, and *mut*$^-$, indicating residual, although insufficient, mutase activity. Patients with methylmalonic acidemia due to deficiency of the mutase apoenzyme (*mut*^{0}) are not responsive to hydroxocobalamin therapy.

In the remaining methylmalonic acidemia patients, the defect resides in the formation of adenosylcobalamin from dietary vitamin B_{12}. The absorption of dietary vitamin B_{12} in the terminal ileum requires *intrinsic factor,* a glycoprotein secreted by the gastric parietal cells. It is transported in the blood by haptocorrin and transcobalamin II. The transcobalamin II–cobalamin complex (TCII-Cbl) is recognized by a specific receptor on the cell membrane (a transcobalamin receptor encoded by *CD320*) and enters the cell by endocytosis. In the lysosome, TCII-Cbl is hydrolyzed, and, with the participation of LMBRD1 (*cbl*F) and ABCD4 (*cbl*J), free cobalamin is released into the cytosol (see Fig. 105.4). Biallelic pathogenic variants in either *LMBRD1* or *ABCD4* genes result in impaired release of cobalamin from lysosomes. In the cytoplasm, cobalamin binds to the MMACHC protein (see *cbl*C later), which removes a moiety attached to cobalt in the cobalamin molecule and reduces the cobalt from oxidation state +3 (cob[III]alamin) to +2 (cob[II]alamin). It then enters the mitochondria, where it is catalyzed by MMAB (*cbl*B) and MMAA (*cbl*A) to form adenosylcobalamin, a coenzyme for methylmalonyl-CoA mutase. The other arm of the pathway directs cytosolic cobalamin toward methionine synthase reductase (*cbl*E), which forms methylcobalamin, acting as a coenzyme for methionine synthase (*cbl*G, see Fig. 105.3). The MMADHC protein (see *cbl*D) appears to play a role in determining whether cobalamin enters the mitochondria or remains in the cytoplasm.

The uptake of TCII-Cbl by cells is impaired in individuals with pathogenic variants affecting the transcobalamin receptor *(CD320),* which is located on the cell surface. Individuals homozygous for pathogenic variants in the *CD320* gene encoding the transcobalamin receptor may have mild elevations of methylmalonic acid in the blood and urine. These patients can be identified by the newborn screen based on the elevated propionylcarnitine (C3-carnitine). In **transcobalamin receptor deficiency**, methylmalonic acid levels and plasma propionylcarnitine tend to normalize in the first year of life. It is not clear whether a long-term clinical phenotype is associated with this defect.

Nine different defects in the intracellular metabolism of cobalamin have been identified. These are designated *cbl*A through *cbl*G, *cbl*J, and *cbl*X, where *cbl* stands for a defect in any step of cobalamin metabolism. The *cbl*A, *cbl*B, and *cbl*D-MMA defects cause methylmalonic acidemia *alone*. In patients with *cbl*C, *cbl*D-combined methylmalonic acidemia and homocystinuria, *cbl*F, *cbl*J, and *cbl*X defects, synthesis of both adenosylcobalamin and methylcobalamin is impaired, resulting in *combined* methylmalonic acidemia and homocystinuria. The *cbl*D-homocystinuria, *cbl*E, and *cbl*G defects affect only the synthesis of methylcobalamin, resulting in homocystinuria without methylmalonic aciduria (see Chapter 105.3).

Biochemical manifestations of patients with isolated methylmalonic acidemia caused by *mut*^{0}, *mut*$^-$, *cbl*A, *cbl*B, and *cbl*D-MMA overlap. The wide variations in the severity of the clinical course range from very sick newborn infants to apparently asymptomatic adults. In **severe** forms, lethargy, feeding problems, vomiting, a sepsis-like picture, tachypnea (from metabolic ketoacidosis), and hypotonia may develop in the first few days of life and may progress to hyperammonemic encephalopathy, coma, and death if left untreated. Infants who survive the first attack may go on to develop similar acute metabolic episodes during a catabolic state such as infection or prolonged fasting or after ingestion of a high-protein diet. In certain situations, such acute events can cause a sudden injury of the basal ganglia, a metabolic stroke, resulting in a debilitating movement disorder. Between the acute attacks, the patient usually continues to exhibit hypotonia and feeding problems with failure to thrive, while other complications of the disease occur with age, including recurrent episodes of pancreatitis, bone marrow suppression, osteopenia, and optic nerve atrophy. Chronic renal failure and tubulointerstitial nephritis necessitating renal transplant have been reported in older patients. Renal complications are more severe in patients with the *mut*^{0} and severe *cbl*B forms of methylmalonic acidemia. In milder forms, patients may present later in life with hypotonia, failure to thrive, and developmental delay. Neurocognitive development of patients with mild methylmalonic acidemia may remain within the normal range.

The episodic nature of the condition and its biochemical abnormalities in some patients may be confused with those of *ethylene glycol (antifreeze) ingestion*. Furthermore, the peak of propionate in a blood sample from an infant with methylmalonic acidemia has been mistaken for ethylene glycol when the sample was assayed by gas chromatography without mass spectrometry.

Laboratory findings include ketosis, metabolic acidosis, hyperglycinemia, hyperammonemia, hypoglycemia, anemia, neutropenia, thrombocytopenia, and the presence of large quantities of methylmalonic acid in body fluids (see Fig. 105.6). Metabolites of propionic acid (3-hydroxypropionate and methylcitrate) are also found in the urine. The plasma acylcarnitine profile reveals elevated propionylcarnitine (C3-carnitine) and methylmalonylcarnitine (C4DC-carnitine). Hyperammonemia in methylmalonic acidemia may be confused with a urea cycle disorder. However, patients with defects in urea cycle enzymes are typically *not* acidotic and tend to have high plasma glutamine (see Fig. 105.12). The reason for hyperammonemia is not well understood, but it is likely related to the inhibition of the proximal urea cycle in the mitochondrial matrix.

The diagnosis can be confirmed by identifying pathogenic variants in the causal gene, by measuring propionate incorporation with complementation analysis in cultured fibroblasts, and by measuring the specific activity of the mutase enzyme in biopsies or cell extracts.

Treatment of acute attacks is similar to propionic acidemia. Long-term treatment consists of administration of a low-protein diet limited to the recommended dietary allowance and L-carnitine (50-100 mg/kg/day orally). Patients with severe forms of methylmalonic acidemia may require protein diet modifications similar to those prescribed for patients with propionic acidemia. Patients with isolated methylmalonic acidemia caused by defects in the intracellular metabolism of cobalamin (*cbl*A, *cblD*-MMA, and some patients with *cbl*B) respond to parenteral hydroxocobalamin. Chronic bicarbonate replacement therapy is usually required to correct chronic acidosis. Carglumic acid is used to improve ureagenic function by stimulating its first step catalyzed by the carbamoyl-phosphate synthetase 1 (CPS1) and to facilitate ammonia detoxification during acute hyperammonemia. Ammonia scavengers (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate) should be used cautiously. Plasma ammonia tends to normalize between attacks, and chronic treatment of hyperammonemia is rarely needed. Stressful situations that may trigger acute attacks (infection, prolonged fasting, trauma, surgeries, high-protein meals) should be treated promptly.

Inadequate oral intake secondary to poor appetite, protein overrestriction, or essential amino acid deficiencies is a common complication in the long-term management of these patients. Consequently, enteral feeding through gastrostomy is often recommended early in the course of treatment. Close monitoring of blood pH, essential amino acid levels, blood and urinary concentrations of methylmalonate, and growth parameters is required to ensure that the nutritional prescription meets the patient's metabolic demands. In addition, frequent monitoring of kidney function, vision, hearing, and bone mineral density are necessary for early recognition and management of chronic complications. Glutathione deficiency responsive to treatment with ascorbate has been described.

Liver, kidney, and combined liver-kidney transplantations have been attempted in an increasing number of affected patients. Liver and liver-kidney transplantation can alleviate, but not eliminate, the metabolic abnormalities. Furthermore, liver and liver-kidney transplants do not provide complete protection against the occurrence of metabolic stroke. Kidney transplantation alone can restore the renal function but results in only minor improvement of the clinical stability of patients.

Prognosis depends on the severity of symptoms and the occurrence of complications. In general, patients with complete deficiency of mutase apoenzyme (mut^0) and severe forms of *cbl*B deficiency have the least favorable prognosis, and those with mut^- and *cbl*A defects have a better outcome.

Methylmalonic acidemia can be identified on the universal newborn screening by measuring propionylcarnitine (C3) using tandem mass spectrometry. The prevalence of all forms of methylmalonic aciduria is estimated at 1 in 50,000 to 1 in 100,000 live births. All defects causing isolated methylmalonic acidemia are inherited in an autosomal recessive manner. Pathogenic variants in the genes for *cbl*A *(MMAA)*, *cbl*B *(MMAB)*, and all forms of *cbl*D *(MMADHC)* have been identified in affected patients. The previously described *cbl*H group is identical to the *cbl*D-MMA defect.

COMBINED METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA (*cblC, epi-cblC, cblD, cblF, cblJ,* AND *cblX* DEFECTS)

Combined methylmalonic acidemia and homocystinuria caused by *cbl*C deficiency is the most common type of intracellular cobalamin (vitamin B_{12}) biosynthesis defect. Deficiency of *cbl*C is as common as methylmalonyl-CoA mutase deficiency. The other disorders (*cbl*D, *cbl*F, *cbl*J, *cbl*X) are much rarer (see Figs. 105.3 and 105.4). Neurologic findings are prominent in patients with *cbl*C, *epi-cblC*, *cbl*D-combined, and *cbl*X defects. Most patients with the *cbl*C defect present in the first month of life because of failure to thrive, lethargy, poor feeding, developmental delay, nystagmus, and seizures. Hyperammonemia may be seen infrequently, whereas hyperglycinemia is not present, unlike in isolated *mut*-type methylmalonic acidemia. Intrauterine growth restriction and microcephaly suggest that *cbl*C can manifest prenatally in some affected infants. Late-onset patients with sudden development of dementia and myelopathy have been reported, even with presentation in adulthood. Megaloblastic anemia is a common finding in patients with *cbl*C defect. Mild to moderate increases in concentrations of methylmalonic acid and significant elevations in total plasma homocysteine are found in blood. Unlike classic homocystinuria, in untreated *cbl*C, patients' plasma methionine is low to normal. Retinal abnormalities (e.g., bull's eye maculopathy) resulting in severe progressive vision loss are common and can be seen as early as 3 months of age, even in prospectively identified and well-treated patients. **Thrombotic microangiopathy** can present as hemolytic uremic syndrome, pulmonary hypertension, and cor pulmonale. Hydrocephalus and noncompaction cardiomyopathy have been reported as complications in patients with *cbl*C defect.

Similar to *cblC* patients, males with *cbl*X have elevations of both total plasma homocysteine and methylmalonic acid, but they tend to have milder elevations of these metabolites. Unlike *cbl*C-deficient patients, who tend to respond to treatment, *cbl*X-deficient patients experience failure to thrive, severe developmental delay, and intractable epilepsy despite aggressive treatment.

Clinical findings in *cbl*F deficiency are quite variable. Patients may present with poor feeding, growth and developmental delay, and persistent stomatitis manifesting in the first months of life. Delay in diagnosis and treatment can be accompanied by hyperpigmentation of skin, developmental delay, intellectual disability, and short stature. Vitamin B_{12} malabsorption and low plasma vitamin B_{12} has been noted in patients with *cbl*F defect. Clinical manifestations of *cblJ* defect show significant overlap with those of the *cbl*F deficiency. Dysmorphic features and congenital heart disease have been reported in some patients with *cbl*F and *cbl*J defects.

Experience with **treatment** of patients with *cbl*C, *cbl*D, *cbl*F, *cbl*J, and *cbl*X defects is limited. Large doses of hydroxocobalamin (up to 0.3 mg/kg/day) in conjunction with betaine (up to 250 mg/kg/day) produce biochemical improvement with variable clinical effect. Patients with *cbl*F and *cblJ* deficiency typically show a favorable biochemical and clinical response to smaller hydroxocobalamin doses (1 mg once weekly to 1 mg daily parenterally). Folic or folinic acid supplementation is recommended. Dietary methionine deficiency should be avoided.

The *cbl*C disorder is caused by pathogenic variants in the *MMACHC* gene. A frameshift variant (c.271dupA) is seen in up to 40% of *MMACHC* alleles and is associated with a less favorable clinical outcome. Epi-*cbl*C, with a similar phenotype, is caused by compound heterozygous variants in *MMACHC* and *PRDX1,* a neighboring gene. Pathogenic variants in *PRDX1* cause hypermethylation and silencing of the promoter/exon 1 of *MMACHC,* resulting in repressed gene expression. The *cbl*D disorder is caused by pathogenic variants in the *MMADHC* gene. Pathogenic variants resulting in *cbl*D-homocystinuria affect the C-terminal domain of the gene product; those resulting in *cbl*D-MMA (e.g., causing only methylmalonic aciduria) affect the N-terminus. Patients with classic *cbl*D, with both homocystinuria and methylmalonic acidemia, have pathogenic variants resulting in decreased protein expression. The *cbl*F disorder is caused by pathogenic variants in the *LMBRD1* gene encoding a lysosomal membrane protein. The *cblJ* disorder is associated with pathogenic variants in the *ABCD4*

gene, encoding an adenosine triphosphate–binding cassette protein localized to the lysosomal membrane. The *cbl*X disorder is caused by pathogenic variants in the *HCFC1* gene on the X chromosome (Xq28), which encodes a transcription factor that appears to be essential for expression of the *MMACHC* gene. This is the only X-linked disorder in the B_{12} intracellular metabolism pathway. Rare defects resulting in a phenotype overlapping with *cbl*X deficiency have been associated with biallelic pathogenic variants in the genes *THAP11* or *ZNF143*.

ISOLATED HOMOCYSTINURIA

Patients with *cbl*D variant one, *cbl*E, and *cbl*G deficiency present with isolated homocystinuria without methylmalonic acidemia (see Chapter 105.3).

COMBINED MALONIC AND METHYLMALONIC ACIDURIA (*ACSF3*-RELATED DISORDER)

Combined *m*alonic and *m*ethyl*m*alonic *a*ciduria **(CMAMMA)** is a rare autosomal recessive disorder resulting from pathogenic variants in *ACSF3*. ACSF3 is a putative acyl-CoA synthetase required for the conversion of malonic and methylmalonic acids to their CoA derivatives in the mitochondrial matrix. The disorder can be suspected based on the presence of elevated malonic and methylmalonic acids in urine and plasma. It is distinguished from malonyl-CoA decarboxylase because methylmalonic acid is about fivefold greater than malonic acid in the urine. Plasma propionylcarnitine (C3-carnitine) in CMAMMA patients is normal, so universal newborn screening programs using C3-carnitine in blood spots to screen for methylmalonic acidemia would not detect this condition. The clinical phenotype is incompletely understood. Young patients identified prospectively in infancy through urine-based newborn screening were reported to be asymptomatic, but the long-term outcome in this cohort awaits further characterization. Older patients ascertained clinically have highly variable presentations, including metabolic crises, failure to thrive, seizures, memory problems, optic nerve or spinal cord atrophy, and progressive neurodegeneration. Treatment of CMAMMA is supportive and includes avoidance of an excessively high-protein diet. Vitamin B_{12} supplementation does not appear to lower malonic and methylmalonic metabolites in body fluids.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.7 Glycine

Oleg A. Shchelochkov and Charles P. Venditti

Glycine is a nonessential amino acid synthesized by multiple endogenous sources, including serine, choline, and threonine. Structurally, it is the simplest amino acid. Glycine is involved in many reactions in the body, especially in the nervous system, where it functions as a neurotransmitter (excitatory in the cortex, inhibitory in the brainstem and the spinal cord; see Chapter 105.11). Its main catabolic pathway requires the *glycine cleavage system,* a pyridoxal phosphate–dependent, mitochondrial enzyme complex that converts glycine to carbon dioxide and ammonia and transfers α-carbon to tetrahydrofolate (see Fig. 105.8). The glycine cleavage system is composed of four proteins: P protein (glycine decarboxylase), H protein, T protein, and L protein, which are encoded by four different genes.

HYPOGLYCINEMIA

Defects in the biosynthetic pathway of serine (see Chapter 105.8) cause a deficiency of glycine in addition to that of serine in body fluids, especially in the CSF. Isolated primary deficiency of glycine has not been reported.

HYPERGLYCINEMIA

Elevated levels of glycine in body fluids occur in propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and β-ketothiolase deficiency, which are collectively referred to as **ketotic hyperglycinemia** because of the coexistence of acidosis and ketosis. The pathogenesis of hyperglycinemia in these disorders is not understood. Inhibition of the glycine cleavage enzyme system by the various organic acids and post-translational modification has been shown to occur in some of these biochemical disorders. The term **nonketotic hyperglycinemia (NKH)** is reserved for the clinical condition caused by the genetic deficiency of the *glycine cleavage enzyme system* (GCS, see Fig. 105.8). In this condition, hyperglycinemia is present without ketosis.

NONKETOTIC HYPERGLYCINEMIA (GLYCINE ENCEPHALOPATHY)

Four forms of NKH have been identified: neonatal, infantile, late onset, and transient. NKH is an autosomal recessive disorder caused by biallelic pathogenic variants in either of three genes, *GLDC* (encodes P protein), *AMT* (encodes T protein), and *GCSH* (encodes H protein). The L-protein gene *(DLD)* encodes dihydrolipoamide dehydrogenase, the E3 component of α-ketoacid dehydrogenase complexes, and is discussed in Chapter 105.6. Birth prevalence of NKH is ~1:75,000, but a high frequency of the disorder has been noted in Northern Finland (1:12,000 live births), suggesting that this disorder is likely underdiagnosed in some regions of the world.

NKH should be differentiated from the GCS cofactor deficiency caused by the deficiency of lipoate resulting from biallelic pathogenic variants in genes involved in lipoate synthesis (*LIAS, LIPT2, BOLA3, GLRX5, IBA57,* and *NFU1*).

Neonatal Nonketotic Hyperglycinemia

This is the most common form of NKH. Clinical manifestations become apparent in the first few days of life (between 6 hours and 8 days after birth). Poor feeding, failure to suck, lethargy, and profound hypotonia may progress rapidly to a deep coma, apnea, and death. Convulsions, especially myoclonic seizures, and hiccups are common.

Laboratory findings reveal moderate to severe hyperglycinemia (as high as eight times the upper reference range) and hyperglycinuria. The unequivocal elevation of glycine concentration in CSF (15-30 times the upper reference range) and the high ratio of glycine concentration in CSF to that in plasma (a value >0.08, reference value <0.02) are diagnostic of NKH. Affected patients' blood pH is usually normal. The plasma acylcarnitine profile and urine organic acid assay reveal no abnormalities. CSF serine levels can be low.

Approximately 30% of NKH infants die despite supportive therapy. Those who survive develop profound intellectual disability and intractable seizure disorders (myoclonic and/or grand mal seizures). Hydrocephalus, requiring shunting, and pulmonary hypertension have been noted in survivors. Transient hyperglycemia may prompt evaluation for biochemical phenocopies of NKH (e.g., organic acidemias), brain imaging studies to evaluate for intracerebral hemorrhage or hypoxic-ischemic injury, and ultimately may require molecular studies of *AMT, GLDC,* and *GCSH*.

Transient Nonketotic Hyperglycinemia

Most clinical and laboratory manifestations of transient NKH are indistinguishable from those of the neonatal form. By 2-8 weeks of age, however, a complete clinical recovery may occur, and the elevated glycine levels in plasma and CSF normalize after the patient stops a glycine-lowering medication. Some of these patients develop normally with no neurologic sequelae, but intellectual disability has been noted in others. The etiology of this condition is not known, but it is thought to be a consequence of immaturity of the enzyme system; genetic testing is normal. Transient hyperglycemia should prompt consideration of additional biochemical studies; brain imaging; and molecular studies to evaluate for pathogenic variants in *AMT, GLDC,* and *GCSH*.

Infantile Nonketotic Hyperglycinemia

In infantile NKH, previously healthy-appearing infants develop signs and symptoms of neonatal NKH after 6 months of age. Seizures and hypotonia are common presenting signs. Infantile NKH appears to be a milder form of neonatal NKH; infants usually survive, and intellectual

disability is not as profound as in the neonatal form. Laboratory findings in patients with infantile NKH are identical to those seen in neonatal NKH.

Late-Onset Nonketotic Hyperglycinemia

Clinical manifestations of this atypical form of NKH include progressive spastic diplegia, optic nerve atrophy, and choreoathetotic movements. Age of onset has been between 2 and 33 years. Symptoms of delirium, chorea, and vertical gaze palsy may occur episodically in some patients during an intercurrent infection. Mental development is usually normal, but mild cognitive impairment and infrequent seizures have been reported in some patients.

Laboratory findings in late-onset NKH are similar but not as pronounced as in neonatal NKH.

All forms of NKH should be differentiated from *ketotic* hyperglycinemia, pyridox(am)ine phosphate oxidase (PNPO) deficiency, ingestion of valproic acid, and transient glycine encephalopathy. Valproic acid can moderately increase blood, CSF, and urinary concentrations of glycine. Repeat assays after discontinuation of the drug will help establish the diagnosis.

Diagnosis and Treatment

A diagnosis of NKH can be suspected based on the findings of elevated glycine in plasma or CSF and the abnormal CSF/plasma ratio of glycine. The diagnosis is confirmed using molecular analysis of the NKH-related genes (*AMT, GLDC,* and *GCSH*). Rarely, enzymatic assay on liver specimens is necessary to establish the diagnosis. Enzyme activity in the neonatal form is close to zero, whereas in the other forms, some residual activity is present. In most patients with neonatal NKH, the enzyme defect resides in the P protein (75%). Defects in the T protein account for approximately 20% of cases, whereas <1% are caused by pathogenic variants in the H protein.

Prenatal diagnosis can be accomplished by identifying known familial pathogenic variants in the affected gene or by performing an assay of the enzyme activity in chorionic villus biopsy specimens.

No effective treatment is currently available. Exchange transfusion, dietary restriction of glycine, and administration of sodium benzoate or folate have not altered the neurologic outcome in severe forms of NKH. Patients with attenuated NKH may experience clinical improvement from enteral sodium benzoate. Drugs that counteract the effect of glycine on neuronal cells, such as dextromethorphan and felbamate, have shown some beneficial effects in patients with the mild forms of the condition.

SARCOSINEMIA

Increased concentrations of sarcosine (*N*-methylglycine) are observed in both blood and urine of probands affected by sarcosine dehydrogenase complex deficiency. This autosomal recessive metabolic condition is caused by a defect in sarcosine dehydrogenase, the enzyme that converts sarcosine to glycine (see Fig. 105.8) and is encoded by *SARDH*. No consistent clinical picture has been attributed to sarcosinemia.

PRIMARY TRIMETHYLAMINURIA

Trimethylamine is normally produced by intestinal bacteria from the breakdown of dietary choline and trimethylamine oxide by bacteria. Egg yolk and liver are the main sources of choline, and fish is the major source of trimethylamine oxide. Trimethylamine is absorbed and oxidized in the liver by trimethylamine oxidase (a flavin-containing monooxygenase encoded by *FMO3*) to trimethylamine oxide, which is odorless and excreted in the urine (see Fig. 105.8). Deficiency of this enzyme results in massive excretion of trimethylamine in urine. There is a body odor that resembles that of rotting fish, which may have significant psychosocial ramifications. Transient symptomatic trimethylaminuria can occur in normal individuals after ingestion of large quantities of the previously mentioned foods.

Treatment with oral activated charcoal and short courses of oral metronidazole, neomycin, or lactulose cause temporary reduction in body odor. Restriction of fish, eggs, liver, and other sources of choline (e.g., nuts, grains) in the diet significantly reduces the odor. Topical use of acidic soaps (pH 5.5) can also help control the odor.

HYPEROXALURIA AND OXALOSIS

Normally, oxalic acid is derived mostly from oxidation of glyoxylic acid and, to a lesser degree, from oxidation of ascorbic acid (see Fig. 105.8). Glyoxylic acid is formed from oxidation of glycolic acid and glycine in the peroxisomes and catabolism of **hydroxyproline** in the mitochondria mediated by 4-hydroxy-2-oxoglutarate aldolase 1 (encoded by *HOGA1*), the underlying cause of **primary hyperoxaluria type 3** (Fig. 105.9). Vegetables and foods containing oxalic acid, such as spinach, rhubarb, and almond milk, are the main *exogenous* sources of glycolic and oxalic acids; most of glyoxylic and oxalic acids are produced endogenously. Normally, a major portion of glyoxylate produced in the body is shuttled to peroxisomes, where it is converted to glycine by the action of the enzyme alanine:glyoxylate transaminase (AGT encoded by *AGXT*). Deficiency of this enzyme causes **primary hyperoxaluria** type 1. Most of the remaining glyoxylate in the cytosol is reduced to glycolate by the action of the enzyme glyoxylate reductase/

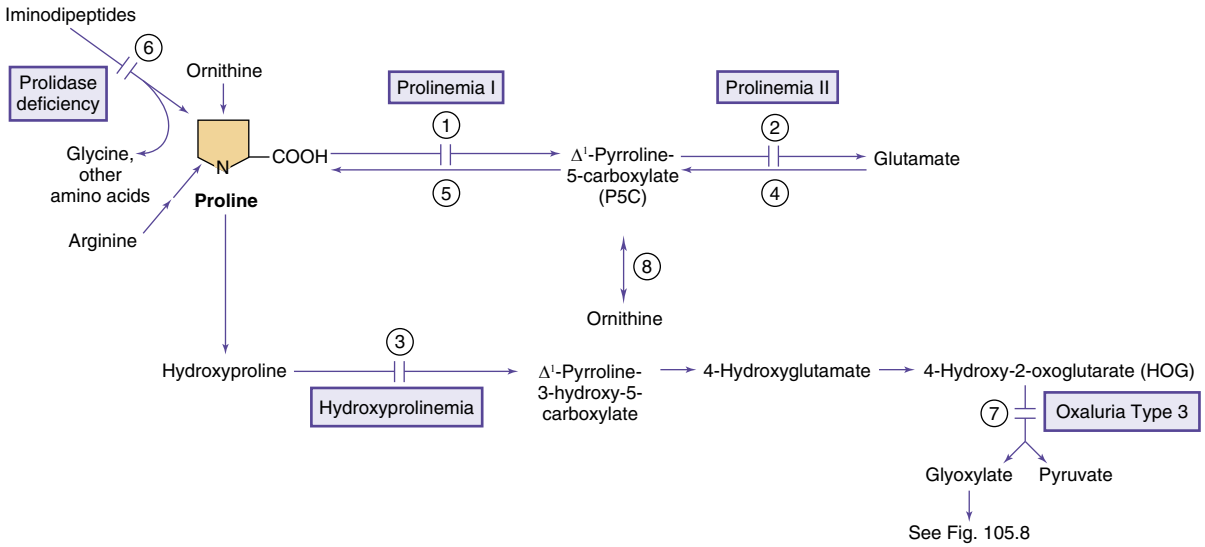

Fig. 105.9 Pathways in the metabolism of proline. **Enzymes:** *(1)* Proline oxidase (dehydrogenase), *(2)* Δ^1-pyrroline-5-carboxylic acid (P5C) dehydrogenase, *(3)* hydroxyproline oxidase, *(4)* Δ^1-pyrroline-5-carboxylic acid (P5C) synthase, *(5)* Δ^1-pyrroline-5-carboxylic acid (P5C) reductase, *(6)* prolidase, *(7)* 4-hydroxyoxoglutarate aldolase one (HOGA1), *(8)* ornithine aminotransferase.

hydroxypyruvate reductase (GR/HPR encoded by *GRHPR*). Deficiency of this enzyme causes **primary hyperoxaluria type 2**. These pathways protect the body from excessive production of oxalic acid (see Fig. 105.8). Any glyoxylate that cannot be disposed of through these pathways is readily converted to oxalic acid by the action of the enzyme lactate dehydrogenase (LDH). Oxalic acid cannot be further metabolized in humans and is excreted in the urine as oxalates. Calcium oxalate is relatively insoluble in water and precipitates in tissues (kidneys and joints) if its concentration increases in the body.

Secondary hyperoxaluria has been observed in pyridoxine deficiency (cofactor for alanine:glyoxylate transaminase), in patients with IBD, extensive resection of the small bowel or jejunoileal bypass *(enteric hyperoxaluria)*, after ingestion of ethylene glycol or high doses of vitamin C, and after administration of the anesthetic agent methoxyflurane (which can be catabolized to oxalic acid as one of its by-products). Acute, fatal hyperoxaluria may develop after ingestion of plants with high oxalic acid content (e.g., sorrel) or intentional ingestion of oxalic acid. Precipitation of calcium oxalate in tissues causes hypocalcemia, liver necrosis, renal failure, cardiac arrhythmia, and death. The lethal dose of oxalic acid is estimated at 5-30 g.

Primary hyperoxaluria is a group of disorders in which large amounts of oxalates accumulate in the body. Three types of primary hyperoxaluria have been identified to date. The term **oxalosis** refers to deposition of calcium oxalate in parenchymal tissues.

Primary Hyperoxaluria Type 1

This rare autosomal recessive condition (prevalence of 1 in 120,000 live births in Europe) is the most common form of primary hyperoxaluria and can be seen in in ~1% of children diagnosed with end-stage renal disease. Primary hyperoxaluria type 1 is caused by deficiency of the peroxisomal enzyme alanine:glyoxylate transaminase *(AGXT)*, which is expressed almost exclusively in the liver peroxisomes and requires pyridoxine (vitamin B_6) as a cofactor. In the absence of this enzyme, glyoxylic acid cannot be converted to glycine and is transferred to the cytosol, where it is oxidized to oxalic acid (see earlier and Fig. 105.8).

The age of presentation varies widely, from the neonatal period to late adulthood. The majority of patients become symptomatic in late childhood or early adolescence. In about 20% of cases, symptoms develop before the infant's first birthday. The initial clinical manifestations are related to renal stones and nephrocalcinosis. Renal colic and asymptomatic hematuria lead to a gradual deterioration of renal function, manifested by growth retardation and uremia. If the disorder is left untreated, most patients die before 20 years of age from renal failure. Other frequent manifestations of the disease include failure to thrive, short stature, arterial calcifications, arrhythmia, heart failure, hypothyroidism, and skin nodules. Acute arthritis is a rare manifestation and can be misdiagnosed as gout because uric acid is often elevated in patients with type 1 hyperoxaluria, driven in part by the worsening renal function. Crystalline retinopathy and optic neuropathy causing visual loss have been reported.

A marked increase in urinary excretion of oxalate (typical excretion: 10-50 mg/day) is the most important laboratory finding. The presence of oxalate crystals in urinary sediment is rarely helpful for diagnosis because such crystals can also be seen in otherwise healthy individuals. Urinary excretion of glycolic acid and glyoxylic acid is increased in most, but not all, patients. Diagnosis can be confirmed by identification of biallelic pathogenic variants in the *AGXT* gene or by performing an enzymatic assay in liver specimens.

The **diagnosis** of primary hyperoxaluria type 1 can be suspected in patients presenting with recurrent renal stones, nephrocalcinosis, and oxalate crystals in the urine after ruling out possible secondary causes (e.g., gastrointestinal disorders or dietary causes). Laboratory studies will reveal elevated urinary oxalate excretion, high urinary glycolate, and elevated plasma oxalate. Confirmatory testing of *AGXT* as a single gene or part of a multigene panel will secure the ultimate diagnosis. The most common pathogenic variant in patients with high residual enzyme activity (c.508G>A, p.Gly170Arg) results in mislocalization of the enzyme to mitochondria instead of peroxisomes, thus leading to the loss of in vivo function. **Prenatal diagnosis** has been achieved by DNA analysis of chorionic villus samples when biallelic pathogenic variants are known.

Treatment focuses on the reduction of oxalic acid production and on improving calcium oxalate disposal. Patients with primary hyperoxaluria type 1 should receive a 3-month trial of pyridoxine treatment to establish pyridoxine responsiveness. In up to 30% of patients (e.g., those homozygous for the *AGXT* pathogenic variant c.508G>A), administration of large doses of pyridoxine can reduce the plasma level and urinary excretion of oxalate. To increase calcium oxalate disposal and prevent nephrolithiasis, high oral fluid intake (2-3 L/m^2/day while controlling for fluid balance), urine alkalinization, phosphate supplementation, monitoring of vitamin C and vitamin D intake, and avoidance of drugs that can increase urinary calcium excretion (e.g., loop diuretics) are recommended. Urinary stones should be managed by experienced urologists, as excessive surgical trauma may contribute to renal dysfunction. Renal function replacement strategies (e.g., hemodialysis) are used in some patients (e.g., to bridge patients to transplant or when transplant is not a viable option).

Organ **transplantation** has emerged as the most definitive treatment. The decision to undergo kidney, liver, or liver-kidney transplant is complex, and referral rates may vary from one medical center to another. Except for older patients with the pyridoxine-responsive form of disease, renal transplantation alone in patients with renal failure may not improve the outcome, because oxalosis can recur in the transplanted kidney. Combined liver-kidney transplants have resulted in a significant decrease in plasma and urinary oxalate and thus may be the most effective treatment strategy, particularly in children.

Primary Hyperoxaluria type 2 (L-Glyceric Aciduria)

This rare autosomal recessive condition is caused by a deficiency of the glyoxylate reductase–hydroxypyruvate reductase enzyme complex encoded by *GRHPR* (see Fig. 105.8). A deficiency in the activity of this complex results in accumulation of two intermediate metabolites: hydroxypyruvate (the ketoacid derivative of serine) and glyoxylic acid. Both these compounds are further metabolized by LDH to L-glycerate and oxalate, respectively. A high prevalence of this disorder is reported in the Saulteaux-Ojibway Indians of Manitoba.

Primary hyperoxaluria type 2 results in the deposition of calcium oxalate in the renal parenchyma and urinary tract. Renal stones presenting with renal colic and hematuria may develop before age 2 years. Renal failure is less common in this condition than in primary hyperoxaluria type 1.

Urinary testing reveals large amounts of L-glyceric acid in addition to high levels of oxalate. Urinary L-glyceric acid is considered a pathognomonic finding in primary hyperoxaluria type 2. Urinary excretion of glycolic acid and glyoxylic acid is not increased. The presence of L-glyceric acid without increased levels of glycolic and glyoxylic acids in urine differentiates this type from type 1 hyperoxaluria. The diagnosis can be confirmed by molecular analysis of *GRHPR* or by the enzyme assay in liver biopsy.

The principles of therapy are similar to those in primary hyperoxaluria type 1. Renal transplant is used in some patients; experience with kidney-liver transplantation is limited at this time.

Primary Hyperoxaluria Type 3

Approximately 10% of patients with primary hyperoxaluria have deficiency of 4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1), the underlying cause of hyperoxaluria type 3. The enzyme is encoded by *HOGA1*. This mitochondrial enzyme catalyzes a step in the metabolic pathway of hydroxyproline that generates pyruvate and glyoxylate from 4-hydroxy-2-oxoglutarate (HOG; see Figs. 105.8 and 105.9). In vitro studies show inhibition of glyoxylate reductase–hydroxypyruvate reductase enzyme activity by a high concentration of HOG that accumulates in patients with hyperoxaluria type 3. HOGA1 deficiency results in a biochemical phenotype similar to primary hyperoxaluria type 2 (see Fig. 105.8).

Patients with primary hyperoxaluria type 3 usually present with calcium oxalate kidney stones in early childhood, but asymptomatic older siblings have also been identified. Gradually, renal function may

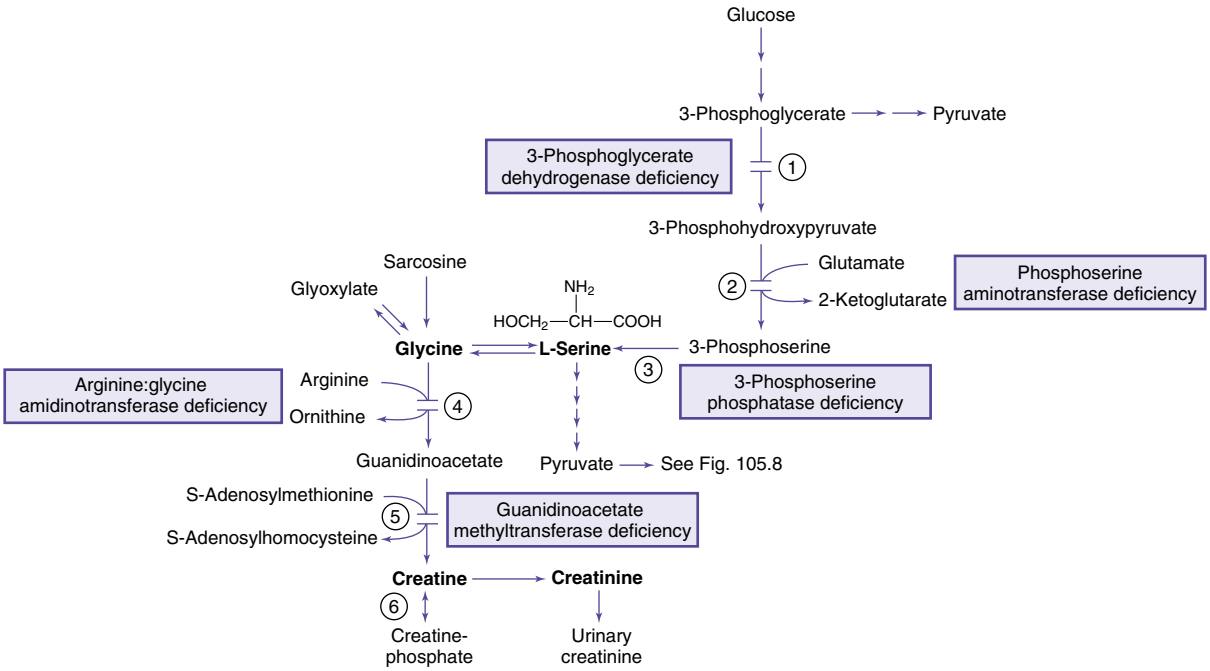

Fig. 105.10 Biosynthesis of serine and creatine. **Enzymes:** *(1)* 3-Phosphoglycerate dehydrogenase, *(2)* 3-phosphoserine aminotransferase, *(3)* 3-phosphoserine phosphatase, *(4)* arginine:glycine amidinotransferase (AGAT), *(5)* guanidinoacetate methyltransferase (GAMT), *(6)* creatine kinase.

decline, infrequently resulting in end-stage renal disease. Increased levels of HOG in urine, serum, and liver biopsy samples of these patients are the distinguishing feature of this disorder. **Treatment** involves high oral fluid intake, management of oral citrate or phosphate intake to prevent calcium oxalate renal stone formation, and avoidance of dehydration to prevent acute kidney injury. In severe forms of this disorder, dialysis and transplantation may be required to address the end-stage renal disease.

Creatine Deficiency Disorders

Creatine is synthesized mainly in the liver, pancreas, and kidneys and to a lesser degree in the brain from arginine and glycine and is transported to muscles and the brain, where there is high activity of the enzyme creatine kinase (Fig. 105.10). Phosphorylation and dephosphorylation of creatine in conjunction with adenosine triphosphate and diphosphate provide high-energy phosphate transfer reactions in these organs. Creatine is nonenzymatically metabolized to creatinine at a relatively constant daily rate and is excreted in the urine. Three genetic conditions are known to cause creatine deficiency in the brain and other tissues. Two enzymes, arginine:glycine amidinotransferase (see Fig. 105.10; **AGAT**, encoded by *GATM*) and guanidinoacetate methyltransferase (**GAMT**, encoded by *GAMT*), are involved in the biosynthesis of creatine. Both conditions may respond to creatine supplementation, especially when the treatment is started at an early age. The third condition, an X-linked inherited defect, is caused by a deficiency of the **creatinine transporter** (CRTR, encoded by *SLC6A8*) mediating uptake of creatine by the brain and muscle. A CRTR defect is the most common cause of creatine deficiency, accounting for up to 1–2% of males with intellectual disability of unknown cause.

Clinical manifestations of the three defects overlap, relate to the brain and muscle, and may appear in the first few weeks or months of life. Developmental delay, intellectual disability, speech delay, psychiatric symptoms (autism and psychosis), hypotonia, ataxia, and seizures are common findings. Dystonic movements have been documented in GAMT and CRTR deficiency.

Laboratory findings include decreased creatine in plasma in patients with AGAT and GAMT defects. Plasma creatinine level alone is insufficient to diagnose these disorders. Secondary to impaired reabsorption of creatine in kidneys, the urinary ratio of creatine to creatinine is increased in male patients with a CRTR defect but can also be mildly elevated in female carriers. Marked elevations of guanidinoacetate in the blood, urine, and especially in CSF are diagnostic of GAMT defects. In contrast, low levels of guanidinoacetate can be found in body fluids in the AGAT defect. Evidence of creatine and creatine phosphate deficiency (in all three defects) and high levels of guanidinoacetate (in the GAMT defect) in the brain can be demonstrated by magnetic resonance spectroscopy (MRS). Brain MRI may show signal hyperintensity in the globus pallidus. Diagnosis of AGAT deficiency or GAMT deficiency may be confirmed by DNA analysis or by measuring enzymatic activity in cultured fibroblasts (GAMT) or lymphoblasts (AGAT). The diagnosis of CRTR deficiency can be confirmed by DNA analysis or a creatine uptake assay in fibroblasts.

The outcomes of **treatment** are age-dependent, and the best outcomes are seen when treatment is started in the neonatal period or presymptomatically. In AGAT-deficient patients, oral creatine monohydrate (up to 400-800 mg/kg/day) can improve muscle weakness, seizures, and neurocognitive outcomes in some patients. In GAMT-deficient patients, supplementation with oral creatine monohydrate (up to 400-800 mg/kg/day), ornithine (up to 400-800 mg/kg/day), and dietary arginine restriction may result in improved muscle tone and neurocognitive development and may alleviate seizures. In CRTR-deficient patients, administration of creatine monohydrate and its precursors (arginine and glycine) may improve seizures and neurocognitive outcomes in some patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.8 Serine Deficiency Disorders (Serine Biosynthesis and Transport Defects)

Oleg A. Shchelochkov and Charles P. Venditti

Serine is a nonessential amino acid supplied through dietary sources and through endogenous synthesis, mainly from glucose and glycine. The endogenous production of serine comprises an important portion of the daily requirement of this amino acid, especially in the synaptic junctions, where it contributes to phospholipid metabolism of D-serine and glycine, both of which are involved in neurotransmission (see Chapter 105.11). Consequently, deficiency of any of the enzymes

involved in the biosynthesis of serine or its transport causes neurologic manifestations. The clinical spectrum of serine deficiency disorders ranges widely and varies from **Neu-Laxova syndrome** on the severe end of spectrum to epilepsy and developmental delay on the milder end. Affected patients respond favorably to oral supplementation with serine and glycine when treatment is initiated very early in life. Figures 105.8 and 105.10 show the metabolic pathway for the synthesis and catabolism of serine.

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

3-Phosphoglycerate dehydrogenase (**PHGDH** encoded by *PHGDH*) deficiency has a broad range of symptoms and ages of presentation. **Neu-Laxova syndrome type 1**, an autosomal recessive condition, is on the most severe end of the spectrum, presenting prenatally with intrauterine growth restriction and congenital anomalies, including dysmorphic facial features, microcephaly, CNS malformations, limb deformities, and ichthyosis. Most patients with this form are stillborn or have early neonatal mortality. The infantile form of PHGDH deficiency can present with feeding problems, failure to thrive, vomiting, irritability, seizures, severe developmental delay, and hypertonia progressing to spastic quadriplegia. Nystagmus, cataracts, hypogonadism, and megaloblastic anemia have been observed in some affected infants. Patients with a milder form of this disorder experience cognitive impairment, behavioral problems, sensorineural polyneuropathy, and childhood-onset seizures.

Laboratory findings include low fasting levels of serine and glycine in plasma and very low levels of serine and glycine in CSF. No abnormal organic acid metabolite is found in the urine. MRI of the brain shows cerebral atrophy with enlarged ventricles, significant attenuation of white matter, and impaired myelination. **Diagnosis** can be confirmed by DNA analysis or by measurement of the enzyme activity in cultured fibroblasts. **Treatment** with high doses of serine (200-700 mg/kg/day orally) and glycine (200-300 mg/kg/day) normalizes the serine levels in the blood and CSF. When started postnatally, this treatment may improve seizures, spasticity, and brain myelination. One case report suggests that developmental delay may be prevented if the treatment commences in the first days of life or prenatally.

If familial pathogenic variants are known, molecular **prenatal diagnosis** is possible. Administration of serine to a mother carrying an affected fetus was associated with stabilization of the fetal head circumference, as evidenced by ultrasound. Treatment with supplemental serine continued postnatally, and the patient remained normal neurologically at 4 years of age. The favorable response of this condition to a relatively straightforward treatment makes this diagnosis an important consideration in any child with microcephaly and neurologic defects such as psychomotor delay or a seizure disorder. Measurements of serine and glycine in the CSF are critical for diagnosis because mild decreases of these amino acids in the plasma can be easily overlooked.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

Phosphoserine aminotransferase 1 (**PSAT1** encoded by *PSAT1*) catalyzes conversion of 3-phosphohydroxypyruvate to 3-phosphoserine (see Fig. 105.10). Deficiency of this enzyme, an autosomal recessive disorder, may present in the neonatal period with poor feeding, cyanotic episodes, and irritability and may progress to intractable, multifocal seizures and microcephaly. Brain imaging may reveal generalized cerebral and cerebellar atrophy. Laboratory studies done on postprandial plasma samples may reveal normal or mildly decreased levels of serine and glycine. Serine and glycine levels are usually more depressed on the CSF amino acid analysis. **Treatment** with serine and glycine as outlined earlier may result in clinical improvement.

3-PHOSPHOSERINE PHOSPHATASE DEFICIENCY

3-Phosphoserine phosphatase catalyzes the final step in the L-serine synthesis, converting 3-phosphoserine to L-serine. Deficiency of this enzyme results in an autosomal recessive disorder with clinical and biochemical findings indistinguishable from the PHGDH and PSAT1 deficiencies. The disorder is caused by biallelic pathogenic variants in *PSPH*.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.9 Proline

Oleg A. Shchelochkov and Charles P. Venditti

Proline is a nonessential amino acid synthesized endogenously from glutamic acid, ornithine, and arginine (see Fig. 105.9). Proline and hydroxyproline are found in high concentrations in collagen. Normally, neither of these amino acids is found in large quantities in urine. Excretion of proline and hydroxyproline as *iminopeptides* (dipeptides and tripeptides containing proline or hydroxyproline) is increased in disorders of accelerated collagen turnover, such as rickets or hyperparathyroidism. Proline is also found in synapses, where it can interact with glycine and glutamate receptors (see Chapter 105.11). The catabolic pathway of proline and hydroxyproline produces glyoxylic acid, which can be further metabolized to glycine or oxalic acid (see Fig. 105.8).

Accumulation of proline in tissues is associated with disorders of hyperprolinemia type 1 and hyperprolinemia type 2. Two types of primary hyperprolinemia have been described. Reduced de novo synthesis of proline may manifest with **cutis laxa** (see Fig. 700.8) with **progeroid features** or **spastic paraplegia**.

HYPERPROLINEMIA TYPE I

This rare autosomal recessive condition is caused by a deficiency of proline oxidase (proline dehydrogenase; see Fig. 105.9). Most patients with hyperprolinemia type 1 appear asymptomatic, although some may present with intellectual disability, seizures, and behavioral problems. Hyperprolinemia may also be a risk factor for autism spectrum disorders and schizophrenia. The nature of such a wide phenotypic range in this biochemical condition is incompletely understood. The gene encoding proline oxidase *(PRODH)* is mapped to 22q11.2 within the critical region for velocardiofacial syndrome. Laboratory studies reveal high concentrations of proline in plasma, urine, and CSF. Increased urinary excretion of hydroxyproline and glycine is also present, which could be related to saturation of the shared tubular reabsorption mechanism due to massive prolinuria.

No effective treatment has yet emerged. Restriction of dietary proline causes a modest improvement in plasma proline but with no proven clinical benefit.

HYPERPROLINEMIA TYPE II

This is a rare autosomal recessive condition caused by the deficiency of Δ^1-pyrroline-5-carboxylate dehydrogenase (aldehyde dehydrogenase 4, *ALDH4A1*; see Fig. 105.9). Intellectual disability and seizures (usually precipitated by an intercurrent infection) have been reported in affected children, but asymptomatic patients have also been described. The cause for such disparate clinical outcomes is incompletely understood.

Laboratory studies reveal increased concentrations of proline and Δ^1-pyrroline-5-carboxylate (P5C) in blood, urine, and CSF. The presence of P5C differentiates this condition from hyperprolinemia type I. An increased level of P5C in body fluids, especially in the CNS, appears to antagonize vitamin B_6 and leads to vitamin B_6 dependency (see Chapter 105.14). Vitamin B_6 dependency may be the main cause of seizures and neurologic findings in this condition and can explain the variability in clinical manifestations in different patients. **Treatment** with high doses of vitamin B_6 is recommended.

PROLIDASE DEFICIENCY

During collagen degradation, imidodipeptides are formed and are normally cleaved by tissue prolidase. Prolidase deficiency, an autosomal recessive condition caused by biallelic pathogenic variants in *PEPD,* results in the accumulation of imidodipeptides in body fluids. The age at onset varies from 6 months to the third decade of life.

Clinical manifestations vary and include recurrent, severe, and painful skin ulcers typically found on the hands and legs. Other skin lesions may precede ulcers by several years and may include a scaly erythematous maculopapular rash, purpura, and telangiectasia. Most ulcers become infected. Healing of the ulcers may take months. Other findings include developmental delays, intellectual disability, organomegaly, anemia, thrombocytopenia, and immune dysfunction resulting in increased susceptibility to infections (recurrent otitis media, sinusitis, respiratory infection, splenomegaly). Some patients have craniofacial abnormalities such as ptosis, ocular proptosis, hypertelorism, small beaked nose, and prominent cranial sutures. Asymptomatic cases have also been reported. Increased incidence of systemic lupus erythematosus has been noted in children. High levels of urinary excretion of imidodipeptides are diagnostic. The diagnosis can be confirmed using DNA analysis. Enzyme assay may be performed in erythrocytes or cultured skin fibroblasts.

Treatment of prolidase deficiency is supportive. Infectious complications can be fatal and warrant close and proactive antibiotic management. Oral supplementation with proline, ascorbic acid, and manganese and topical proline and glycine have not been found to be consistently effective in all patients.

DISORDERS OF DE NOVO PROLINE SYNTHESIS

De novo synthesis of proline and ornithine from glutamate appears to be critical in the normal biology of connective tissue and to maintain the urea cycle in a repleted state. Correspondingly, clinical manifestations of these disorders encompass connective tissue abnormalities, nervous system abnormalities, and variable biochemical abnormalities reflecting urea cycle dysfunction. Clinical and laboratory findings associated with the deficient function of Δ^1-P5C synthase (see Fig. 105.9), encoded by *ALDH18A1,* and P5C, reductase encoded by *PYCR1,* are discussed.

Deficient activity of P5C synthase has been associated with several phenotypes, including **de Barsy syndrome**, characterized by cataracts, growth restriction, intellectual disability, a prematurely aged appearance (progeroid features), and cutis laxa. Some patients may show pyramidal signs. Skin biopsy may reveal decreased size of elastic fibers and collagen abnormalities. Brain imaging studies show cortical atrophy, ventriculomegaly, and reduced creatine. Laboratory findings include reduced levels of proline, ornithine, citrulline, and arginine as well as mild fasting hyperammonemia. Patients may show only intermittent abnormalities on the plasma amino acid profile, likely related to the time of blood sampling in relation to the last meal. Interestingly, both autosomal recessive and autosomal dominant forms of inheritance have been described. The diagnosis can be suspected in a patient presenting with cutis laxa, developmental delay, mild hyperammonemia, and characteristic amino acid abnormalities. The diagnosis can be confirmed using molecular DNA analysis or the glutamine loading test on skin fibroblasts. Treatment is supportive, although supplementation with citrulline or arginine to address hyperammonemia and cerebral creatine depletion have been proposed.

Biallelic pathogenic variants in *PYCR1* result in the abnormal function of the mitochondrial Δ^1-pyrroline-5-carboxylate reductase, which catalyzes the last step in the synthesis of proline from P5C. The most consistent finding in patients carrying proven pathogenic variants in *PYCR1* include triangular facies, cutis laxa **(de Barsy–like syndrome)**, joint hypermobility, wrinkled skin, gerodermia osteodysplastica, and progeroid features. Skin biopsy reveals reduction of the elastic fibers and infiltration with inflammatory cells. Some patients may have epilepsy, developmental delays, intellectual disability, cataracts, osteopenia, and failure to thrive. However, many of the affected families are consanguineous, thus complicating interpretation of the phenotype. Of note, plasma amino acid analysis reveals no specific abnormalities. The diagnosis depends on the recognition of the skin findings and can be confirmed using molecular DNA analysis. Available pedigrees of families affected by *PYCR1*-related disorder supports the autosomal recessive mode of inheritance.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.10 Glutamic Acid

Oleg A. Shchelochkov and Charles P. Venditti

Glutamic acid and its amide derivative glutamine have a wide range of functions in the body. *Glutamate* plays numerous biologic roles, functioning as a neurotransmitter, an intermediate compound in many fundamental biochemical reactions, and a precursor of an inhibitory neurotransmitter, γ-aminobutyric acid (GABA) (see Chapter 105.11). Another major product of glutamate is *glutathione* (γ-glutamylcysteinylglycine). This ubiquitous tripeptide, with its function as the major antioxidant in the body, is synthesized and degraded through a complex cycle called the γ-glutamyl cycle (Fig. 105.11). Because of its free sulfhydryl (−SH) group and its abundance in the cell, glutathione protects other sulfhydryl-containing compounds (e.g., enzymes, coenzyme A) from oxidation. It is also involved in the detoxification of peroxides, including hydrogen peroxide, and in keeping the intracellular milieu in a reduced state. In addition, glutathione participates in amino acid transport across the cell membrane through the γ-glutamyl cycle.

One of the biochemical manifestations of γ-glutamyl cycle deficiency is increased urinary excretion of 5-oxoproline, which could be the result of both genetic and nongenetic causes. 5-Oxoprolinemia should be routinely considered in the differential diagnosis of **high–anion gap metabolic acidosis** (HAGMA). Two metabolic disorders can present with massive 5-oxoprolinuria: **glutathione synthetase deficiency** and **5-oxoprolinase deficiency** (see Fig. 105.11). However, a more common clinical scenario is a transient and mild urinary elevation of 5-oxoproline that can be seen in a variety of metabolic and acquired conditions, such as exposure to acetaminophen and some hydrolyzed-protein formulas, severe burns, Stevens-Johnson syndrome, homocystinuria, urea cycle defects, and tyrosinemia type I.

GLUTATHIONE SYNTHETASE DEFICIENCY

Three forms of this rare autosomal recessive condition have been reported. In the **mild form**, glutathione synthetase deficiency causes glutathione deficiency in erythrocytes. These patients present with hemolytic anemia without chronic metabolic acidosis and demonstrate high residual activity of glutathione synthetase on enzymatic testing. A **moderate form** has also been observed in which the hemolytic anemia is associated with variable degrees of metabolic acidosis and 5-oxoprolinuria. Its **severe form** is distinguished by the presence of hemolytic anemia accompanied by severe acidosis, massive 5-oxoprolinuria, and neurologic manifestations.

Glutathione Synthetase Deficiency, Moderate and Severe Forms

Affected newborn infants with severe and moderate forms of glutathione synthetase deficiency usually develop acute symptoms of metabolic acidosis, jaundice, and mild to moderate hemolytic anemia in the first days of life. Chronic acidosis continues after recovery. Similar episodes of life-threatening acidosis may occur during an infection (e.g., gastroenteritis) or after a surgical procedure. Progressive neurologic damage develops with age, manifested by intellectual disability, spastic tetraparesis, ataxia, tremor, dysarthria, and seizures. Susceptibility to infections, presumably because of granulocyte dysfunction, is observed in some patients. Patients with the moderate form of glutathione synthetase deficiency have milder acidosis and less 5-oxoprolinuria than is seen in the severe form, with few neurologic manifestations.

Laboratory findings include metabolic acidosis, mild to moderate degrees of hemolytic anemia, and 5-oxoprolinuria. High concentrations of 5-oxoproline are also found in the blood. The urinary and blood levels of 5-oxoproline are less pronounced in patients with the moderate form of the condition. The glutathione content of erythrocytes is markedly decreased. Increased synthesis of 5-oxoproline in this disorder is thought to be the result of the conversion of γ-glutamylcysteine to 5-oxoproline by the enzyme γ-glutamyl cyclotransferase (see Fig. 105.11). γ-Glutamylcysteine production increases greatly because the normal inhibitory effect of glutathione on the γ-glutamylcysteine synthetase enzyme is removed.

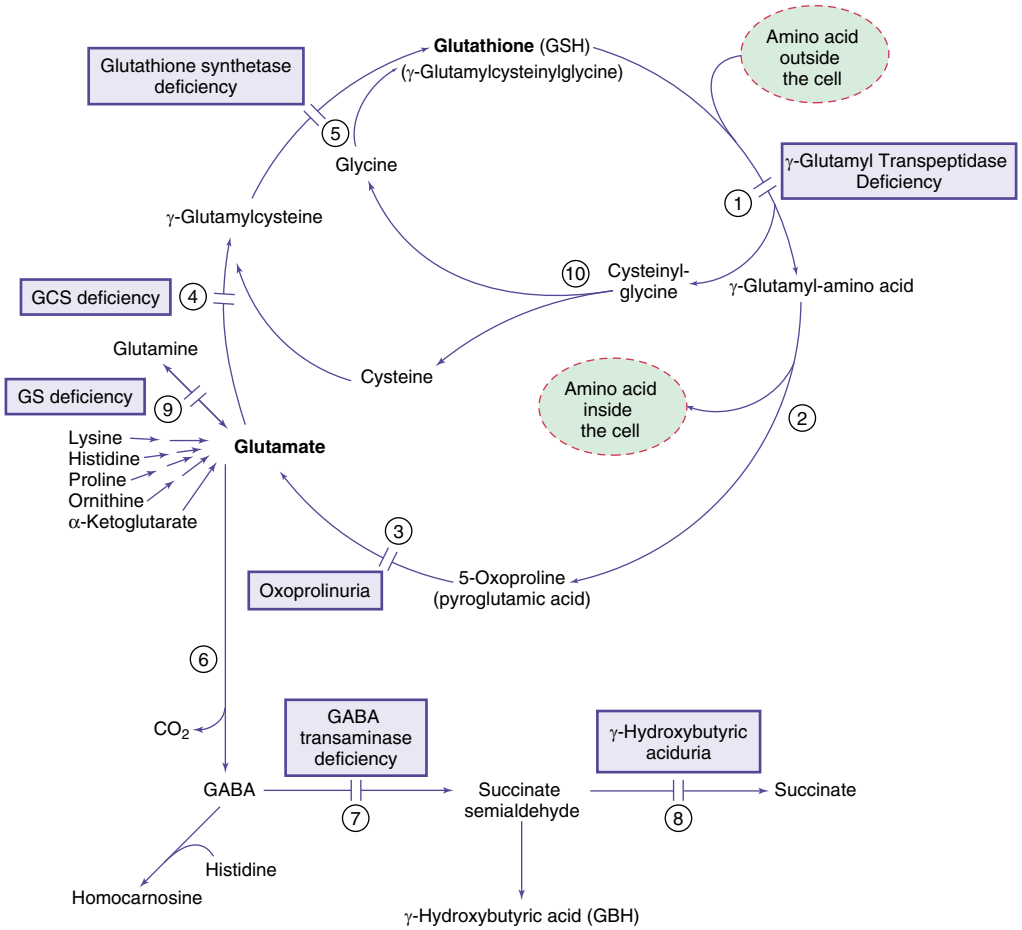

Fig. 105.11 The γ-glutamyl cycle and related pathways. Defects of the glutathione (GSH) synthesis and degradation are noted. **Enzymes:** *(1)* γ-Glutamyl transpeptidase (GGT), *(2)* γ-glutamyl cyclotransferase, *(3)* 5-oxoprolinase, *(4)* γ-glutamyl-cysteine synthetase, *(5)* glutathione synthetase, *(6)* glutamate decarboxylase, *(7)* γ-aminobutyric acid (GABA) transaminase, *(8)* succinate-semialdehyde dehydrogenase, *(9)* glutamine synthetase, *(10)* dipeptidase.

Treatment of acute attack includes hydration, correction of acidosis (by infusion of sodium bicarbonate), and measures to correct anemia and hyperbilirubinemia. Chronic administration of alkali is usually needed indefinitely. Supplementation with vitamin C, vitamin E, and selenium is recommended. Drugs and oxidants known to cause hemolysis and stressful catabolic states should be avoided. Oral administration of glutathione analogs has been tried with variable success.

Prenatal diagnosis can be achieved by the measurement of 5-oxoproline in amniotic fluid, by enzyme analysis in cultured amniocytes or chronic villus samples, or by *GSS* gene analysis. Successful pregnancy in an affected female (moderate form) has been reported, with favorable outcomes for both mother and infant.

Glutathione Synthetase Deficiency, Mild Form

The mild form has been reported in only a few patients. Mild to moderate hemolytic anemia has been the only clinical finding. Splenomegaly has been reported in some patients. Cognitive development is normal. Chronic metabolic acidosis typically is not seen. Some patients can have increased concentrations of 5-oxoproline in the urine. Biallelic pathogenic variants in *GSS*, the gene encoding the enzyme, appear to decrease the half-life of the enzyme, causing an increased rate of protein turnover without affecting its catalytic function. The expedited rate of enzyme turnover caused by these pathogenic variants is of little or no consequence for tissues with protein synthetic capability. However, inability of mature erythrocytes to synthesize protein results in glutathione deficiency in the erythrocytes. **Treatment** is that of hemolytic anemia and avoidance of drugs and oxidants that can trigger the hemolytic process.

All forms of glutathione synthetase deficiency are inherited as an autosomal recessive trait. **Diagnosis** can be confirmed by *GSS* gene analysis or enzyme activity in erythrocytes or skin fibroblasts.

5-Oxoprolinase Deficiency

More than 20 patients with 5-oxoprolinuria (4-10 g/day) caused by 5-oxoprolinase (see Fig. 105.11) deficiency *(OPLAH)* have been described. No specific clinical picture has yet emerged; completely asymptomatic affected individuals have also been identified. It is therefore not clear whether 5-oxoprolinase deficiency is of any clinical consequence. No treatment is currently recommended.

γ-Glutamylcysteine Synthetase Deficiency (Glutamate-Cysteine Ligase Deficiency)

γ-Glutamylcysteine synthetase deficiency is an autosomal recessive disorder caused by biallelic pathogenic variants in *GCLC*. Only a few patients with this enzyme deficiency have been reported. The most consistent clinical manifestation has been mild chronic hemolytic anemia. Acute attacks of hemolysis have occurred after exposure to sulfonamides. Peripheral neuropathy and progressive spinocerebellar degeneration have been noted in two siblings in adulthood. Laboratory findings of chronic hemolytic anemia were present in all patients. Generalized aminoaciduria is also found because the γ-glutamyl cycle is involved in amino acid transport in cells (see Fig. 105.11). **Treatment** focuses on the management of hemolytic anemia and avoidance of drugs and oxidants that may trigger the hemolytic process.

γ-GLUTAMYL TRANSPEPTIDASE DEFICIENCY (GLUTATHIONEMIA)

γ-Glutamyl transpeptidase (GGT) is expressed in any cell that has secretory or absorptive functions. It is especially abundant in the kidneys, pancreas, intestines, and liver. The enzyme is also present in the bile. Measurement of GGT in the blood is frequently performed to evaluate for liver and bile duct diseases.

GGT deficiency causes elevation in glutathione concentrations in body fluids, but the cellular levels remain normal (see Fig. 105.11). Because only a few patients with GGT deficiency have been reported, the scope of clinical manifestations has not yet been defined. Mild to moderate intellectual disability and severe behavioral problems were observed in three patients. However, one of two sisters with this condition had normal intelligence as an adult, and the other had Prader-Willi syndrome.

Laboratory findings include marked elevations in urinary glutathione (up to 1 g/day), γ-glutamylcysteine, and cysteine. None of the reported patients have had generalized aminoaciduria, a finding that would have been expected to occur in this enzyme deficiency (see Fig. 105.11).

Diagnosis can be confirmed by measurement of the enzyme activity in leukocytes or cultured skin fibroblasts. *No effective treatment has been proposed.* The condition is inherited as an apparent autosomal recessive trait. The γ-glutamyl transpeptidases represent a large family of enzymes encoded by at least seven genes.

GENETIC DISORDERS OF METABOLISM OF γ-AMINOBUTYRIC ACID

See Chapter 105.11.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.11 Disorders of Neurotransmitter Metabolism

Oleg A. Shchelochkov and Charles P. Venditti

Neurotransmitters are chemical substances released from the axonal end of excited neurons at the synaptic junctions; they mediate initiation, amplification, or inhibition of neural impulses. Several amino acids and their metabolites act as neurotransmitters in the central and peripheral nervous system. Pathogenic variants in genes responsible for the synthesis, transport, or degradation of these substances may cause conditions that manifest neurologic and/or psychiatric abnormalities (Table 105.3). Previously, children affected by disorders of neurotransmitters have been given syndromic diagnoses such as cerebral palsy, epilepsy, parkinsonism, dystonia, or autism. Diagnosis, in most cases, requires specialized laboratory studies of the CSF, because some of the neurotransmitters generated in the CNS, dopamine and serotonin, do not cross the BBB, and their abnormal concentrations are not detected in the serum or urine.

TYROSINE HYDROXYLASE DEFICIENCY (INFANTILE PARKINSONISM, AUTOSOMAL RECESSIVE DOPA-RESPONSIVE DYSTONIA, AUTOSOMAL RECESSIVE SEGAWA SYNDROME)

Tyrosine hydroxylase catalyzes the formation of L-dopa from tyrosine. Deficiency of this enzyme results in deficiencies of dopamine and norepinephrine (see Fig. 105.2 and Fig. 105.12). The differential diagnosis includes a wide range of inherited dystonias, including autosomal dominant dystonia caused by GTP cyclohydrolase 1 deficiency.

Clinical manifestations range from mild to very severe. In general, two phenotypes have been recognized. In the **mild** form (dopa-responsive dystonia, or **type A**), symptoms of unilateral limb dystonia causing gait incoordination and postural tremor occur in childhood and worsen with age when the condition remains untreated. Diurnal variation of symptoms (worse at the end of the day) may be present. Cognitive development is usually normal.

In the **severe** form of tyrosine hydroxylase deficiency (infantile parkinsonism, infantile encephalopathy, or **type B**), the clinical manifestations occur at birth or shortly thereafter and include microcephaly, developmental delay, involuntary movements of the limbs with spasticity, dystonia, ptosis, expressionless face, oculogyric crises (upward eye-rolling movements), and autonomic dysfunction (temperature instability, excessive sweating, hypoglycemia, salivation, tremor, gastrointestinal reflux, constipation). Brisk reflexes, myoclonus, athetosis, and distal chorea may be present. The patient with the severe form usually shows incomplete response to treatment with L-dopa and is prone to developing L-dopa–induced dyskinesia as a side effect.

Laboratory findings include reduced levels of dopamine and its metabolite homovanillic acid (HVA) and normal concentrations of tetrahydrobiopterin (BH_4), neopterin, and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) in the CSF. Serum prolactin levels are usually elevated. These findings are not diagnostic of the condition; diagnosis should be established by molecular gene analysis.

Treatment with L-dopa/carbidopa results in significant clinical improvement in most patients, but the severe forms are invariably associated with L-dopa–induced dyskinesias. To minimize the side effects of therapy, treatment should be started with a low dose and, if needed, increased very slowly. Other therapeutic interventions include anticholinergics, serotonergic agents, and monoamine oxidase (MAO) B inhibitors, including amantadine, biperiden, and selegiline. Bilateral subthalamic nucleus deep brain stimulation has shown clinical efficacy in one case. Tyrosine hydroxylase deficiency is inherited as an autosomal recessive trait. Molecular testing for pathogenic variants in the *TH* gene is available clinically.

AROMATIC L-AMINO ACID DECARBOXYLASE DEFICIENCY

Aromatic L-amino acid decarboxylase (AADC encoded by *DDC*) is a vitamin B_6–dependent enzyme that catalyzes the decarboxylation of both 5-hydroxytryptophan to form serotonin (see Fig. 105.5 and Fig. 105.12) and L-dopa to generate dopamine (see Fig. 105.2 and Fig. 105.12). **Clinical manifestations** of this autosomal recessive disorder reflect the reduced availability of dopamine and serotonin. Poor feeding, lethargy, hypotension, hypothermia, oculogyric crises, and ptosis have been observed in affected neonates. Clinical findings in infants and older children include developmental delay, truncal hypotonia with hypertonia of limbs, oculogyric crises, extrapyramidal movements (choreoathetosis, dystonia, myoclonus), and autonomic abnormalities (sweating, salivation, irritability, temperature instability, hypotension). Symptoms may have a diurnal variation, becoming worse by the end of the day.

Laboratory findings include decreased concentrations of dopamine and serotonin and their metabolites (HVA, 5-HIAA, norepinephrine, vanillylmandelic acid [VMA]) and increased levels of 5-hydroxytryptophan, L-dopa, and its metabolite (3-*O*-methyldopa) in body fluids, especially in CSF. Elevated serum concentrations of prolactin (the result of dopamine deficiency) have also been observed. Brain MRI reveals cerebral atrophy with degenerative changes in the white matter. A urine screening program, focused on 3-*O*-methyl-dopa and VMA, has demonstrated diagnostic promise in high-disease-prevalence populations.

Treatment with neurotransmitter precursors has produced limited clinical improvement. Dopamine and serotonin have no therapeutic value because of their inability to cross the BBB. Nonergot dopamine agonists, MAO inhibitors (tranylcypromine), serotonergic agents, and high doses of pyridoxine/pyridoxal phosphate, a cofactor for the AADC enzyme, are preferred. The demonstration of putamen-directed gene therapy with an adeno-associated viral vector has shown some benefit in patients. Preimplantation genetic diagnosis after in vitro fertilization has been achieved in the high-prevalence Taiwanese population.

TETRAHYDROBIOPTERIN DEFICIENCY

See Chapter 105.1.

Tetrahydrobiopterin (BH_4) is the enzymatic cofactor for phenylalanine hydroxylase (see Fig. 105.1 and Fig. 105.12), tyrosine hydroxylase

Table 105.3 Neurotransmitter Disorders Affecting Biogenic Amines and GABA Metabolism and Transport: Biomarker Assessment in Biologic Fluids

CSF MARKER	DISEASE OMIM[A]/GENE	BIOCHEMICAL PATTERN
Biogenic amines	TH deficiency 191290/*TH*	*CSF*:↓ HVA, MHPG, and HVA/5-HIAA ratio
	AADC deficiency 107930/*DDC*	*CSF*: ↓↓ HVA and 5-HIAA; ↑↑ 3OMD and 5HTP *Urine*: ↑ vanillactate; *blood*: ↑ 3OMD
	MAOA deficiency 309850/*MAO-A*	*CSF*: ↓↓ 5-HIAA and HVA *Plasma/urine*: ↑ catecholamines and serotonin
	DBH deficiency 609312/*DBH*	*CSF*: ↑ HVA, HVA/5-HIAA ratio, ↓ MHPG[a] *Urine/plasma*: ↓↓ norepinephrine and epinephrine; ↑ dopamine and DOPAC
	DAT1 deficiency 126455/*SLC6A3*	*CSF*: ↑ HVA and HVA/5-HIAA ratio
	VMAT2 deficiency 193001/SLC18A2	*Urine*: ↑ HVA and 5-HIAA ↓ Norepinephrine and dopamine
Pterins	Dominant GTPCH-I deficiency 600225/*GCH*	*CSF*: ↓ NP, BP, BH_4, HVA, and 5-HIAA
	SR deficiency 182125/*SRD*	*CSF*: ↑ BP and SP; normal NP; ↓ BH_4, HVA, and 5-HIAA *Urine*: ↑ SP
GABA	SSADH deficiency 610045/*ALDH5A1*	*CSF*: ↑ GABA *Plasma and urine*: ↑↑ GHB

[a]Expected values.

↑: Increased values compared with reference aged values; ↓: decreased values compared with reference aged values.

5-HIAA, 5-Hydroxyindoleacetic acid; AADC, aromatic L-amino acid decarboxylase; BP, biopterin; CSF, cerebrospinal fluid; DBH, dopamine β-hydroxylase; DOPAC, dihydroxyphenylacetic acid; GHB, γ-hydroxybutyrate; GTPCH-I, guanosine triphosphate cyclohydrolase-I; HVA, homovanillic acid; MAOA, monoamine oxidase A; MHPG, 3-methoxy-4-hydroxyphenylethyleneglycol; NP, neopterin; SP, sepiapterin; SR, sepiapterin reductase; SSADH, succinic semialdehyde dehydrogenase; TH, tyrosine hydroxylase.

From García-Cazorla À, Artuch R. Neurotransmitter disorders. In Rosenberg RN, Pascual JM, eds. *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease*, 6th ed. Vol. 1. London: Elsevier; 2020: Table. 67.1.

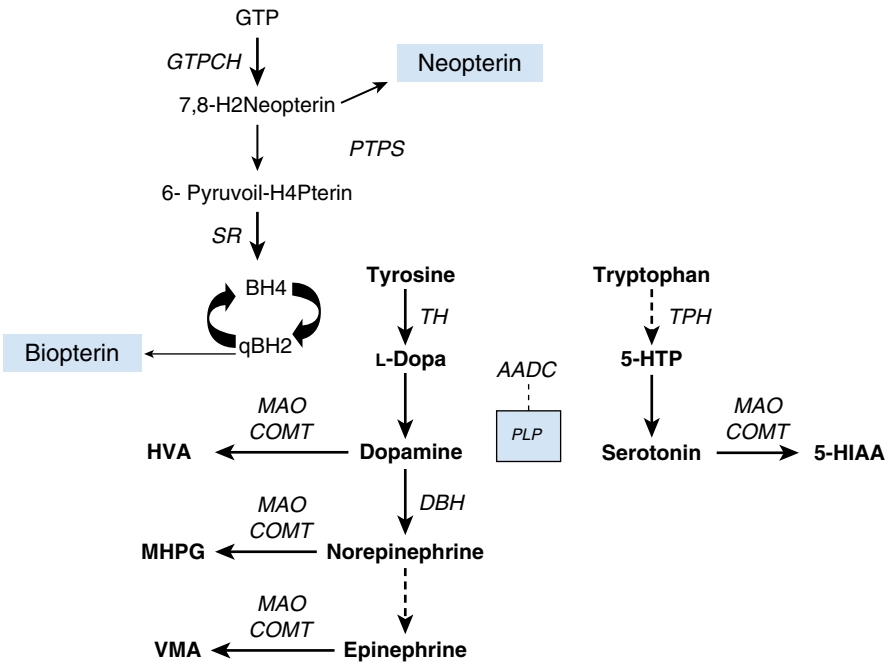

Fig. 105.12 Metabolic pathways of monoamines. The first step in their formation is catalyzed by amino acid–specific hydroxylases, which require tetrahydrobiopterin (BH_4) as a cofactor. The synthesis of BH_4 comes from GTP, and it is initiated by the enzyme GTPCH-I, which forms dihydroneopterin triphosphate. Levodopa and 5-HTP are metabolized by a common B_6-dependent AADC into dopamine and serotonin. MAOA catabolizes adrenaline and noradrenaline to VMA and MHPG. This enzyme is also involved in the catabolism of both dopamine into HVA and serotonin into 5-HIAA. 5-HIAA, 5-Hydroxyindoleacetic acid; 5-HTP, 5-hydroxytryptophan; AADC, aromatic l-amino acid decarboxylase; GTP, guanosine triphosphate; GTPCH-I, GTP cyclohydrolase-1; HVA, homovanillic acid; MAOA, monoamine oxidase A; MHPG, 3-methoxy-4-hydroxyphenylethyleneglycol; VMA, vanillylmandelic acid. (*From García-Cazorla À, Artuch R. Neurotransmitter disorders. In: Rosenberg RN, Pascual JM, eds. Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 6th ed. Vol. 1. London: Elsevier; 2020: Fig. 67.1.*)

(see Fig. 105.2 and 105.12), tryptophan hydroxylase (see Fig. 105.5 and 105.12), and nitric oxide synthase. It is synthesized from GTP in many tissues (see Fig. 105.1). Deficiencies of enzymes involved in the biosynthesis of BH_4 result in inadequate production of this cofactor, which causes deficiencies of monoamine neurotransmitters with or without concomitant hyperphenylalaninemia.

Tetrahydrobiopterin Deficiency with Hyperphenylalaninemia

See Chapter 105.1.

Tetrahydrobiopterin Deficiency Without Hyperphenylalaninemia

GTP Cyclohydrolase 1 Deficiency (Hereditary Progressive Dystonia, Autosomal Dominant Dopa-Responsive Dystonia, Autosomal Dominant Segawa Syndrome)

Guanosine triphosphate (GTP) cyclohydrolase 1 catalyzes the first and rate-limiting step in the biopterin biosynthesis pathway (see Fig. 105.1). This form of dystonia, caused by GTP cyclohydrolase 1 deficiency *(GCH1)*, has an autosomal dominant mode of inheritance and is more common in females than in males (4:1 ratio) (see Chapter 637.4). **Clinical manifestations** usually start in early childhood with tremor and dystonia of the lower limbs **(toe gait)**, which may spread to all extremities within a few years. Torticollis, dystonia of the arms, and poor coordination may precede dystonia of the lower limbs. Early development is generally normal. Symptoms have an impressive diurnal variation, becoming worse by the end of the day and improving with sleep. Autonomic instability is common. Parkinsonism may also be present or develop with advancing age. Late presentation in adult life has also been reported, associated with **action dystonia** ("writer's cramp"), torticollis, or generalized rigid hypertonia with tremor but without postural dystonia. Additionally, limited data on adults suggest symptoms related to serotonin deficiency (sleep disturbance, cognitive impairment, impulsivity).

Laboratory findings show reduced levels of BH_4 and neopterin in the CSF without hyperphenylalaninemia (not to be confused with the autosomal recessive form of BH_4-deficient hyperphenylalaninemia, see Chapter 105.1). Dopamine and its metabolite (HVA) may also be reduced in CSF. The serotonergic pathway is less affected by this enzyme deficiency; thus concentrations of serotonin and its metabolites are usually normal. Plasma phenylalanine is normal, but an oral phenylalanine loading test (100 mg/kg) produces an abnormally high plasma phenylalanine level with an elevated phenylalanine/tyrosine ratio. The ratio, obtained 2-3 hours after the load, in combination with urine neopterin level, has optimal diagnostic specificity and sensitivity. The existence of asymptomatic carriers indicates that other factors or genes may play a role in pathogenesis. Asymptomatic carriers may be identified using molecular testing or by the phenylalanine loading test. **Diagnosis** is confirmed by demonstrating reduced levels of BH_4 and neopterin in CSF, measurement of the enzyme activity, and molecular genetic analysis of *GCH1* (see Chapter 105.1). Clinically, the condition should be differentiated from other causes of dystonias and childhood parkinsonism, especially tyrosine hydroxylase, sepiapterin reductase, and aromatic amino acid decarboxylase deficiencies.

Treatment with L-dopa/carbidopa usually produces dramatic clinical improvement. Oral administration of BH_4 is also effective but is rarely used.

Sepiapterin Reductase Deficiency

Sepiapterin reductase (encoded by *SPR*) is involved in the conversion of 6-pyruvoyl-tetrahydropterin to BH_4. It also participates in the salvage pathway of BH_4 synthesis (see Fig. 105.1 and Fig. 105.12). Sepiapterin reductase deficiency, an autosomal recessive condition, results in accumulation of 6-lactoyl-tetrahydropterin, which can be converted to sepiapterin nonenzymatically. The majority of sepiapterin is metabolized to BH_4 through the salvage pathway in peripheral tissues (see Fig. 105.1 and Fig. 105.12), but because of the low activity of dihydrofolate reductase in the brain, the amount of BH_4 remains insufficient for proper synthesis of dopamine and serotonin. This explains the absence of hyperphenylalaninemia and the often-delayed diagnosis.

Clinical manifestations in severely affected patients usually appear within a few months of life. Cardinal manifestations include paroxysmal stiffening, oculogyric crises, and hypotonia. Additional findings include motor and language delays, weakness, limb hypertonia, dystonia, hyperreflexia, and early-onset parkinsonism. The symptoms usually have a diurnal variation. Misdiagnosis as cerebral palsy is common, and a wide variability of symptoms has been reported. **Diagnosis** is established by measurement of CSF neurotransmitters and pterin metabolites, which reveal decreased dopamine, HVA, norepinephrine, and 5-HIAA and marked elevations of sepiapterin and dihydrobiopterin. The serum concentration of prolactin may be elevated. The phenylalanine loading test may have diagnostic utility, but it is being replaced by molecular genetic analysis, which can confirm the diagnosis. **Treatment** with slowly increasing doses of L-dopa/carbidopa and 5-hydroxytryptophan usually produces dramatic clinical improvement.

DOPAMINE β-HYDROXYLASE DEFICIENCY

Dopamine β-hydroxylase catalyzes the conversion of dopamine to norepinephrine (see Fig. 105.2 and Fig. 105.12). The deficiency of this enzyme results in reduced or absent synthesis of norepinephrine, leading to dysregulation of the sympathetic function. Infants and children may present with difficulty opening the eyes, ptosis, hypotension, hypothermia, hypoglycemia, and nasal stuffiness. Adult patients may present with profound deficits of autonomic regulation, resulting in severe orthostatic hypotension, and sexual dysfunction in males. Presyncopal symptomatology includes dizziness, blurred vision, dyspnea, nuchal discomfort, and chest pain; olfactory function remains relatively intact. The **diagnosis** can be aided by performing autonomic function testing (measurement of the sinus arrhythmia ratio, blood pressure studies during controlled hyperventilation, Valsalva maneuver, cold pressor, handgrip exercise). **Laboratory findings** include decreased or absent norepinephrine and epinephrine and their metabolites, with elevated levels of dopamine and its metabolite (HVA), in plasma, CSF, and urine. Elevated plasma dopamine may be pathognomonic for this disease. MRI of the brain shows decreased brain volume, consistent with the neurotrophic role of norepinephrine. **Treatment** with L-dihydroxyphenylserine, which is converted to norepinephrine directly in vivo by the action of AADC, leads to significant improvement in orthostatic hypotension and normalizes noradrenaline and its metabolites. The condition is inherited as an autosomal recessive trait. Dopamine β-hydroxylase is encoded by *DBH*.

MONOAMINE OXIDASE A DEFICIENCY

The human genome encodes two MAO isoenzymes: MAO A and MAO B. Both enzymes catalyze oxidative deamination of most biogenic amines in the body, including serotonin (see Fig. 105.5 and Fig. 105.12), norepinephrine, epinephrine, and dopamine (see Fig. 105.2 and Fig. 105.12). The genes for both isoenzymes are on the X chromosome (Xp11.3). A deletion of both genes can also encompass a neighboring gene, *NDP,* resulting in a contiguous deletion syndrome, which can present as an atypical **Norrie disease** (see Chapter 640). Male patients with MAO A deficiency manifest borderline intellectual deficiency and impaired impulse control. The consequences of the isolated MAO B deficiency are incompletely understood. Combined MAO A and B deficiency causes severe intellectual disability and behavioral problems and can be associated with pronounced laboratory abnormalities (e.g., fourfold to sixfold serotonin elevation in physiologic fluids, elevated *O*-methylated amine metabolites, and reduced deamination products [VMA, HVA]). Dietary intervention (low tyramine, phenylethylamine, and L-dopa/dopamine intake) did not improve patients' blood serotonin levels. Inheritance of MAO deficiency is X-linked. **Treatment** of MAO A deficiency is supportive.

DISORDERS OF GABA METABOLISM

GABA is the main inhibitory neurotransmitter synthesized in the synapses through decarboxylation of glutamic acid by glutamate decarboxylase (GAD). The same pathway is responsible for production of GABA in other organs, especially the kidneys and the β cells of the pancreas. The GAD enzyme requires pyridoxine (vitamin B_6) as a cofactor.

Two GAD enzymes, GAD1 (GAD_{67}) and GAD2 (GAD_{65}), have been identified. **GAD1** is the main enzyme in the brain, and **GAD2** is the major enzyme in the β cells. Antibodies against GAD_{65} and GAD_{67} have been implicated in the development of type 1 diabetes and **stiff-person syndrome**, respectively. GABA is catabolized to succinic acid by two enzymes: GABA transaminase and succinic semialdehyde dehydrogenase (SSADH) (see Figs. 105.11 and 105.12).

GABA Transaminase Deficiency

Clinical manifestations in the two index infant siblings included severe developmental delay and intellectual disability, hypotonia, hyperreflexia, lethargy, refractory seizures, and increased linear growth likely related to GABA-mediated increased secretion of growth hormone. Increased concentrations of GABA and β-alanine were found in the CSF (see Fig. 105.11 and Fig. 105.12). Evidence of leukodystrophy was noted in the postmortem examination of the brain. A third patient showed severe psychomotor retardation, recurrent episodic lethargy, and intractable seizures with comparable CSF metabolite abnormalities to those of the index probands. GABA transaminase deficiency is demonstrated in the brain and lymphocytes. **Treatment** is symptomatic. Intervention with vitamin B_6, the cofactor for the enzyme, was without therapeutic benefit. The condition is inherited in the autosomal recessive manner and caused by biallelic pathogenic variants in *ABAT*.

Succinic Semialdehyde Dehydrogenase Deficiency (β-Hydroxybutyric Aciduria)

Clinical manifestations of SSADH deficiency, an autosomal recessive disorder, usually begin in infancy with developmental delays with a disproportionate deficit in expressive language, hypotonia, and ataxia; seizures occur in approximately 50% of patients (see Fig. 105.11 and Fig. 105.12). Many patients also carry the diagnosis of **autism spectrum disorder**. Neuropsychiatric comorbidity (especially oppositional defiance, obsession-compulsion, and hyperactivity) can be disabling, particularly in adolescents and adults. Abnormal EEG findings include background slowing and generalized spike-wave paroxysms, with variable lateralization in hemispheric onset and voltage predominance. Photosensitivity and electrographic status epilepticus of sleep have been reported in combination with difficulties in sleep maintenance and excessive daytime somnolence. Brain MRI shows an increased T2-weighted hyperintensity involving the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei, usually in a bilaterally symmetric distribution.

The biochemical hallmark, γ-hydroxybutyric acid (GHB), is elevated in physiologic fluids (CSF, plasma, urine) in all patients. Increased concentrations of GABA are also found in the CSF. Heightened diagnostic suspicion evolves through documentation of elevated urinary GHB, and confirmation is achieved by molecular genetic testing.

Effective **treatment** is lacking. Vigabatrin (a GABA-transaminase inhibitor) has been employed empirically, with mixed outcomes, and there is concern with its use, as it further elevates CNS GABA in an already hyper-GABAergic disorder. Additionally, vigabatrin can cause constriction of the visual field, and long-term use is contraindicated.

SSADH is encoded by *ALDH5A1,* and inheritance follows an autosomal recessive pattern. **Prenatal diagnosis** has been achieved by measurement of GHB in the amniotic fluid, assay of the enzyme activity in the amniocytes, chorionic villus sampling, or DNA analysis.

DEFECTS IN NEUROTRANSMITTER TRANSPORTER PROTEINS

More than 20 different proteins are involved in transporting neurotransmitters across the neuronal membranes. The main function of most of these transporters is to remove excess neurotransmitters from the synaptic junction into the presynaptic neurons (reuptake). This recycling process not only regulates the precise effect of neurotransmitters at the synaptic junction but also resupplies the presynaptic neurons with neurotransmitters for future use. A few transporter proteins are involved in shuttling neurotransmitters from the neuronal cytoplasm across the membrane of synaptic vesicles for storage (vesicular transporters). On neuronal stimulation, these vesicles release a bolus of neurotransmitters through exocytosis. As expected, pathogenic variants in transporter proteins interfere with the proper reuptake and storage of neurotransmitters and may result in clinical manifestations similar to those seen in deficiencies of neurotransmitter metabolism. Several conditions caused by pathogenic variants of neurotransmitter protein transporters have been described, including dopamine transporter protein deficiency and dopamine-serotonin vesicular transporter disease.

SLC6A3-Related Dopamine Transporter Protein Deficiency

This transporter protein is involved in the reuptake of dopamine by the presynaptic neurons, and its deficiency causes depletion of dopamine and thus a dopamine-deficient state. The dopamine transporter protein (DAT) is encoded by *SLC6A3*. Children with biallelic pathogenic variants in *SLC6A3* present with symptoms of infantile **parkinsonism-dystonia syndrome**. Irritability and feeding difficulties start shortly after birth and progress to hypotonia, lack of head control, parkinsonism, dystonia, and global developmental delay by early infancy. Brain MRI usually shows no abnormalities.

CSF examination reveals elevation of HVA and a normal level of 5-HIAAs. The urinary level of HVA and serum concentration of prolactin are increased. Diagnosis can be established by demonstrating loss-of-function pathogenic variants in the *SLC6A3* gene.

Dopamine-Serotonin Vesicular Transporter Disease (Vesicular Monoamine Transporter Deficiency)

This autosomal recessive condition is caused by pathogenic variants in the *SLC18A2* gene. This gene encodes the vesicular monoamine transporter 2 (VMAT2) involved in transporting dopamine and serotonin from the cytoplasm into the synaptic storage vesicles located in the axonal terminals of the presynaptic neurons. Most affected children presented in the first year of life with symptoms consistent with deficiencies of dopamine (hypotonia progressing into dystonia, parkinsonism, oculogyric crises), serotonin (sleep and psychiatric disturbances), and norepinephrine-epinephrine (excessive sweating, tremors, temperature instability, postural hypotension, ptosis). Neurocognitive delays become apparent in the first year of life. No diurnal variation of the symptoms was noted. Brain imaging studies were within normal limits. Changes in the levels of CNS neurotransmitters and their metabolites have been inconsistent.

The phenotype resembles that seen in AADC and BH_4 deficiencies. Diagnosis requires demonstration of biallelic pathogenic variants in *SLC18A2*. **Treatment** with L-dopa/carbidopa caused exacerbation of symptoms, whereas pramipexole, a dopamine receptor agonist, has resulted in a promising clinical response.

HISTIDINE DECARBOXYLASE DEFICIENCY

Decarboxylation of histidine by histidine decarboxylase produces histamine, which functions as a neurotransmitter in the brain. Deficiency of this enzyme (expressed mainly in the posterior hypothalamus) results in deficiency of histamine in the CNS and in one family has been reported as an autosomal dominant form of Tourette syndrome (see Chapter 105.13).

HYPERPROLINEMIA

Intellectual disability and seizures are common findings in most patients with hyperprolinemia types I and II. Patients with **type I** hyperprolinemia typically show a benign clinical course but could have an increased risk of developing schizophrenia. The contribution of increased concentrations of proline to the mechanisms of schizophrenia, however, remains unclear. The neurologic abnormalities observed in hyperprolinemia **type II** are mainly caused by development of vitamin B_6 dependency in this condition (see Chapter 105.9). Dietary intervention in hyperprolinemia type I and II is neither feasible nor recommended.

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

See Chapter 105.8.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

See Chapter 105.8.

NONKETOTIC HYPERGLYCINEMIA

See Chapter 105.7.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.12 Urea Cycle and Hyperammonemia (Arginine, Citrulline, Ornithine)

Oleg A. Shchelochkov and Charles P. Venditti

Catabolism of amino acids results in the production of free ammonia, which in high concentrations is toxic to the CNS. Mammals detoxify ammonia to urea through a series of reactions known as the **urea cycle** (Fig. 105.13). It is composed of five enzymes: carbamoyl phosphate synthetase 1 **(CPS1)**, ornithine transcarbamylase **(OTC)**, argininosuccinate synthetase **(ASS)**, argininosuccinate lyase **(ASL)**, and arginase 1 **(ARG1)**. A sixth enzyme, *N*-acetylglutamate (NAG) synthetase **(NAGS)**, catalyzes synthesis of NAG, an obligatory activator (effector) of the CPS1 enzyme. Individual deficiencies of these enzymes have been observed and, with an overall estimated prevalence of 1 in 35,000 live births, they are the most common genetic causes of hyperammonemia in infants (Table 105.4).

GENETIC CAUSES OF HYPERAMMONEMIA

Hyperammonemia, sometimes severe, occurs in inborn errors of metabolism other than the urea cycle defects (Table 105.5; see also Table 104.5). The mechanisms of hyperammonemia in some of these conditions are diverse and include accumulation of toxic metabolites (e.g., organic acids), impaired transport of urea cycle intermediates (e.g., HHH syndrome), or depletion of urea cycle intermediates (e.g., lysinuric protein intolerance), leading to compromised function of the urea cycle.

CLINICAL MANIFESTATIONS OF HYPERAMMONEMIA

In the **neonatal period**, symptoms and signs are mostly related to brain dysfunction and are similar regardless of the cause of the hyperammonemia. The affected infant appears healthy at birth but becomes symptomatic in the first days of life, often following the introduction of dietary protein. Refusal to eat, vomiting, tachypnea, and lethargy can quickly progress to a deep coma. Seizures are common. Physical examination may reveal hepatomegaly in addition to obtundation. Hyperammonemia can trigger increased intracranial pressure that may be manifested by a bulging fontanelle and dilated pupils.

In **infants and older children**, acute hyperammonemia is manifested by vomiting and neurologic abnormalities such as ataxia, confusion, agitation, irritability, combativeness, and psychosis. These manifestations may alternate with periods of lethargy and somnolence that may progress to coma.

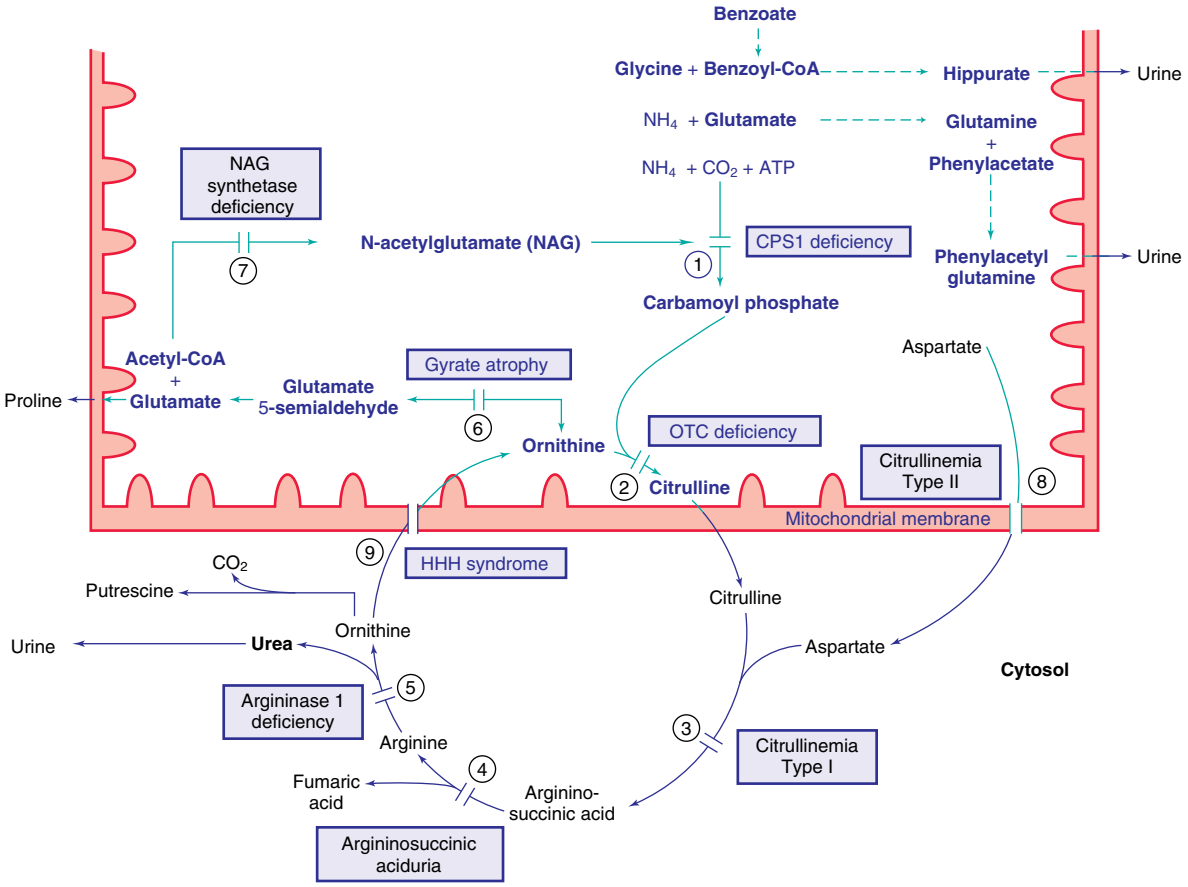

Fig. 105.13 Urea cycle: Pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in *purple*. Reactions shown with *interrupted arrows* are the alternative pathways for the disposal of ammonia. **Enzymes:** *(1)* Carbamoyl phosphate synthetase type 1 (CPS1), *(2)* ornithine transcarbamylase (OTC), *(3)* argininosuccinate synthetase (ASS), *(4)* argininosuccinate lyase (ASL), *(5)* arginase 1, *(6)* ornithine aminotransferase, *(7)* *N*-acetylglutamate (NAG) synthetase, *(8)* citrin, *(9)* ornithine transporter (ORNT1). HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia.

Table 105.4 The Urea Cycle Disorders

ENZYME OR TRANSPORTER DEFICIENCY	GENE (INHERITANCE)	INCIDENCE	CLINICAL MANIFESTATIONS	AMINO ACIDS (PLASMA, UNLESS OTHERWISE INDICATED)	URINE ORGANIC ACIDS
N-Acetylglutamate synthetase MIM 237310	*NAGS* (AR)	<1:2,000,000	Acute episodic hyperammonemia Late-onset presentations	↓ Citrulline ↓ Arginine ↑ Glutamine	Unremarkable
Carbamyl phosphate synthetase I MIM 237300	*CPS1* (AR)	1:1,300,000	Acute episodic hyperammonemia Late-onset presentations	↓ Citrulline ↓ Arginine ↑ Glutamine	Unremarkable
Ornithine transcarbamylase MIM 311250	*OTC* (XL)	1:56,500	Acute episodic hyperammonemia Late-onset presentations	↓ Citrulline ↓ Arginine ↑ Glutamine	↑↑ Orotic acid
Argininosuccinate synthetase MIM 215700	*ASS1* (AR)	1:250,000	Acute episodic hyperammonemia Late-onset presentations	↑↑ Citrulline ↑ Glutamine ↓ Arginine	*N*-to-↑ orotic acid
Argininosuccinate lyase MIM 207900	*ASL* (AR)	1:218,750	Acute episodic hyperammonemia Late-onset presentations ↑ Neurodevelopmental issues Chronic liver disease Trichorrhexis nodosa	↑ Argininosuccinate and anhydrides ↑ Glutamine ↑ Citrulline ↓ Arginine	*N*-to-↑ orotic acid
Arginase MIM 207800	*ARG1* (AR)	1:950,000	Progressive spasticity (LL > UL) Usually mild ID Hyperammonemia (rare)	↑ Arginine	*N*-to-↑ orotic acid
Citrin MIM 605814, 603471	*SLC25A13* (AR)	<1:2,000,000	*NICCD* Intrahepatic cholestasis Poor growth Spontaneous improvement by 1 yr of age *FTTDCD* Failure to thrive Dyslipidemia Chronic liver disease *Citrullinemia type II* Acute episodic hyperammonemia Neuropsychologic manifestations	↑ Citrulline ↑ Arginine ↑ Methionine ↑ Threonine	Unremarkable
Ornithine transporter MIM 238970	*SLC25A15* (AR)	<1:2,000,000	Acute episodic hyperammonemia Liver failure (with or without hyperammonemia) Recurrent vomiting Neurologic presentation (e.g., DD, spasticity) Recurrent	↑ Ornithine ↑ Glutamine ↔-to-↓ citrulline ↑ Urine homocitrulline	*N*-to-↑ orotic acid

AR, Autosomal recessive; DD, developmental delay; FTTDCD, failure to thrive and dyslipidemia caused by citrin deficiency; IV, intravenous; LL, lower limb; NICCD, neonatal intrahepatic cholestasis caused by citrin deficiency; UL, upper limb; XL, X-linked.
From Rossignol F, Ah Mew N, Meltzer MR, Gropman AL. Urea cycle disorders. In: Rosenberg RN, Pascual JM, eds. *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease,* 6th ed. Vol. 1. London: Elsevier; 2020: Table 61.1.

Routine laboratory studies show no specific findings when hyperammonemia is caused by defects of the urea cycle enzymes. Blood urea nitrogen is usually low-normal or low in these patients. Some patients may initially present with unexplained elevated serum alanine transaminase (ALT) and aspartate transaminase (AST) and even meet the criteria for acute liver failure. In infants with organic acidemias, hyperammonemia is commonly associated with severe *acidosis* and *ketonuria*. Newborn infants with hyperammonemia are often misdiagnosed as having sepsis; they may succumb without a correct diagnosis. Neuroimaging may reveal cerebral edema. Autopsy may reveal microvesicular steatosis, mild cholestasis, and fibrosis of the liver. Thus because of the nonspecific presentation or urea cycle disorders, it is imperative to measure plasma ammonia levels in any ill infant with severe sepsis, unexplained liver dysfunction, recurrent emesis, or progressive encephalopathy.

DIAGNOSIS

The main criterion for diagnosis is hyperammonemia. Each clinical laboratory should establish its own normal values for blood ammonia. Normal newborn values are higher than those of the older child or adult. Occasionally, levels as high as 100 μmol/L can occur in healthy term infants. An ill infant usually manifests a blood ammonia level >150 μmol/L. Figure 105.14 illustrates an approach to the differential diagnosis of hyperammonemia in the newborn infant. Careful inspection of individual plasma amino acid profiles usually reveals abnormalities that assist in diagnosis. In patients with deficiencies of CPS1, OTC, or NAGS, frequent findings include elevations in plasma glutamine and alanine with concurrent decrements in citrulline and arginine. These disorders cannot be differentiated from one another by plasma amino acid levels alone. A marked increase in urinary orotic acid in patients with OTC deficiency helps differentiate this defect from CPS1 deficiency (see Table 105.4). Differentiation between the CPS1 deficiency and the NAGS deficiency may require molecular analysis of the relevant genes or, infrequently, an assay of the respective enzyme. Significant clinical improvement occurring after oral administration of carbamylglutamate, however, supports the diagnosis of NAGS deficiency. Patients with a deficiency of ASS, ASL, or arginase 1 have marked increases in the plasma levels of citrulline, argininosuccinic

Table 105.5 Inborn Errors of Metabolism Causing Hyperammonemia

DEFICIENCIES OF THE UREA CYCLIC ENZYMES
Carbamyl phosphate synthetase 1
Ornithine transcarbamylase
Argininosuccinate synthetase
Argininosuccinate lyase
Arginase 1
N-acetylglutamate synthetase
ORGANIC ACIDEMIA
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
β-Ketothiolase deficiency
Multiple carboxylase deficiencies
Medium-chain fatty acid acyl-CoA dehydrogenase deficiency
Glutaric acidemia type I
3-Hydroxy-3-methylglutaric aciduria
OTHERS
Lysinuric protein intolerance
Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome
Transient hyperammonemia of the newborn
Congenital hyperinsulinism with hyperammonemia
Carbonic anhydrase VA deficiency

Table 105.6 Treatment of Acute Hyperammonemia in an Infant

1. Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, NaCl* and intravenous lipids 1 g/kg/day). Add minimal amounts of protein, preferably as a mixture of essential amino acids (0.25 g/kg/day) during the first 24 hr of therapy.
2. Give priming doses of the following compounds (to be added to 20 mL/kg of 10% glucose and infused within 1-2 hr):
   - Sodium benzoate 250 mg/kg†
   - Sodium phenylacetate 250 mg/kg†
   - Arginine hydrochloride 200-600 mg/kg as a 10% solution
3. Continue infusion of sodium benzoate† (250-500 mg/kg/day), sodium phenylacetate† (250-500 mg/kg/day), and arginine (200-600 mg/kg/day‡) following the above priming doses. These compounds should be added to the daily intravenous fluid.
4. Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

*The concentration of sodium chloride should be calculated to be 0.45–0.9%, including the amount of the sodium in the drugs.
†Sodium from these drugs should be included as part of the daily sodium requirement.
‡The higher dose of the range is recommended in the treatment of patients with citrullinemia and argininosuccinic aciduria. Arginine is not recommended in patients with arginase deficiency and in those whose hyperammonemia is secondary to organic acidemia. Sodium benzoate and sodium phenylacetate should be used with caution in patients with organic acidemias.

acid, or arginine, respectively. The combination of hyperammonemia and marked hypercitrullinemia or argininosuccinic acidemia is virtually pathognomonic for these disorders. Additional clinical clues may come from the past medical history. Children with urea cycle defects often self-select a low-protein, high-carbohydrate diet, especially those with late-onset disease or symptomatic females with partial OTC deficiency.

Because of the nonspecific clinical and laboratory findings, mass screening of newborn infants has been implemented in many countries, which can identify patients with ASS, ASL, and arginase 1 deficiencies.

TREATMENT OF ACUTE HYPERAMMONEMIA

The clinical outcome depends mainly on the severity and the duration of hyperammonemia. Serious neurologic sequelae are likely in newborns with severe elevations in blood ammonia (>300 μmol/L) lasting more than 12 hours. Thus acute hyperammonemia should be treated promptly and vigorously. The goal of therapy is to lower the concentration of ammonia. This is accomplished by (1) temporarily restricting dietary sources of ammonia (protein), (2) minimizing endogenous protein breakdown and favoring endogenous protein synthesis by providing adequate calories and essential amino acids, and (3) removal of ammonia from the body in a form other than urea (Table 105.6). Fluid, electrolytes, glucose (10–15%), and lipids (1-2 g/kg/day) should be infused intravenously, together with minimal amounts of protein (0.25 g/kg/day), preferably including essential amino acids. Oral feeding with a low-protein formula (0.5-1.0 g/kg/day) through a nasogastric tube should be started as soon as sufficient improvement is seen.

Because the kidneys clear ammonia poorly, its removal from the body must be expedited by formation of compounds with a high renal clearance. An important advance in the treatment of hyperammonemia has been the introduction of **nitrogen scavenging therapy** by using an exogenous organic acid that conjugates to endogenous nonessential amino acids (glycine and glutamine) to form nontoxic compounds with high renal clearance. The main organic acids used for this purpose are sodium salts of benzoic acid and phenylacetic acid. **Benzoate** forms hippurate through enzymatic conjugation with endogenous glycine in the liver (see Fig. 105.13). Each mole of benzoate removes one mole of ammonia as glycine. **Phenylacetate** enzymatically conjugates with glutamine to form phenylacetylglutamine readily excreted in the urine. One mole of phenylacetate can remove two moles of ammonia as glutamine from the body (see Fig. 105.13). Sodium phenylbutyrate, metabolized to phenylacetate, is the primary oral formulation. For intravenous (IV) use, a combined formulation of benzoate and phenylacetate (Ammonul) is commercially available.

Another valuable therapeutic adjunct is IV infusion of **arginine**, which is effective in all patients except those with arginase deficiency. Arginine administration supplies the urea cycle with ornithine (see Fig. 105.13). In patients with citrullinemia, one mole of arginine reacts with one mole of ammonia as carbamoyl phosphate to form citrulline. In patients with argininosuccinic acidemia, two moles of ammonia (as carbamoyl phosphate and aspartate) react with arginine to form argininosuccinic acid. Citrulline and arginosuccinate are less toxic than ammonia and more readily excreted by the kidneys. In patients with CPS1 or OTC deficiencies, arginine administration is indicated because this amino acid is not produced in sufficient amounts to enable endogenous protein synthesis. For enteral therapy, patients with OTC deficiency benefit from supplementation with *citrulline* (200 mg/kg/day) because one mole of citrulline reacts with one mole of ammonia (through aspartic acid) to form arginine. Administration of arginine or citrulline is contraindicated in patients with **arginase deficiency**, a rare condition in which the spastic diplegia is a much more common presenting feature rather than hyperammonemia. Arginine therapy is of no benefit if hyperammonemia is secondary to an organic acidemia. In a newborn infant with an initial episode of hyperammonemia, arginine should be used until the diagnosis is established (see Table 105.6).

Benzoate, phenylacetate, and arginine may be administered together for maximal therapeutic effect. A priming dose of these compounds is followed by continuous infusion until recovery from the acute state occurs. Both benzoate and phenylacetate are usually supplied as concentrated solutions and should be properly diluted (1–2% solution) for IV use. The recommended therapeutic doses of both compounds deliver a substantial amount of sodium to the patient; this amount should be included in the calculation of the daily sodium requirement. Benzoate and phenylacetate (or the combined formulation) should be used with caution in newborn infants with hyperbilirubinemia because they may displace bilirubin from albumin; however, there are no documented cases of kernicterus (see Chapter 123.4) reported in neonates with hyperammonemia who have received such therapies. In infants at risk, it is advisable to monitor and manage bilirubin levels while considering IV administration of benzoate or phenylacetate.

If the initial ammonia level is <500 μmol/L and if the foregoing therapies fail within 4-6 hours to produce any appreciable change in the blood ammonia level, **hemodialysis** should be considered. For patients

presenting with an ammonia level >500 μmol/L, extracorporeal detoxification is the initial method of ammonia removal. Exchange transfusion has little effect on reducing total body ammonia. It should be used only if dialysis cannot be employed promptly or when the patient is a newborn infant with significant hyperbilirubinemia (see earlier). Hemodialysis dramatically lowers blood ammonia within a few hours, but if it is unavailable or technically unfeasible, peritoneal dialysis may be used as a temporary solution. When hyperammonemia is caused by an organic acidemia and hemodialysis is not available, peritoneal dialysis can be used to remove both the offending organic acid and ammonia.

Oral administration of **neomycin** limits the growth of intestinal bacteria that can produce ammonia. However, this modality is of limited use in urea cycle patients (e.g., affected neonates) in whom reduction of hyperammonemia is an urgent priority. Oral **lactulose** acidifies the intestinal lumen, thereby reducing the diffusion of ammonia across the intestinal epithelium. This agent is of limited applicability in newborns, who have a high risk of acidemia and dehydration.

There may be considerable lag between the normalization of ammonia level and an improvement in the patient's neurologic status. Several days may be needed before the infant becomes fully alert.

There has been interest in the use of **cooling** as a therapeutic adjunct in newborn infants with metabolic encephalopathy such as that caused by hyperammonemia. Clinical studies are in progress to evaluate the efficacy of this approach.

Long-Term Therapy

Once the acute hyperammonemic episode is under control, maintenance therapy should be tailored to address the underlying cause of the hyperammonemia. All patients, regardless of the enzymatic defect, require protein restriction limited to the age-adjusted recommended dietary allowance (RDA). In pediatric patients with urea cycle defects, chronic administration of sodium benzoate (250 mg/kg/day), sodium phenylbutyrate (250-500 mg/kg/day), and arginine (200-400 mg/kg/day) or citrulline (in patients with OTC deficiency, 200-400 mg/kg/day) is effective in maintaining blood ammonia levels within the normal range (doses above are for patients who weigh <20 kg). Arginine and citrulline are contraindicated in patients with argininemia. Patients who have difficulty taking sodium phenylbutyrate can be trialed on glycerol phenylbutyrate. This compound conceals the offensive odor of sodium phenylbutyrate and may help with patient adherence. Benzoate and phenylacetate may lower carnitine levels, but clinical signs of carnitine deficiency or benefit from carnitine supplementation have not yet been demonstrated. These compounds have been used during pregnancy without obvious teratogenic effect. However, experience is still limited, and appropriate caution should be exercised.

Growth parameters, especially head circumference, and nutritional indices (blood albumin, prealbumin, pH, electrolytes, amino acids, zinc, selenium) should be followed closely. Long-term care of these patients is best achieved by a team of experienced professionals (pediatrician, nutritionist, child neurologist, metabolic geneticist). Skin lesions resembling **acrodermatitis enteropathica** (see Chapter 691) have been noted in a few patients with different types of urea cycle defects, presumably resulting from the deficiency of essential amino acids, caused by overzealous dietary protein restriction. Catabolic states (infections, fasting) that may trigger hyperammonemia should be avoided. They must be treated vigorously when they occur. It is important that all children with urea cycle defects avoid valproic acid because this drug can elevate blood ammonia even in some healthy individuals. In patients with CPS1, OTC, or ASS deficiency, acute hyperammonemic attacks may be precipitated by valproate administration.

CARBAMOYL PHOSPHATE SYNTHETASE 1 AND *N*-ACETYLGLUTAMATE SYNTHASE DEFICIENCIES

Without treatment, deficiencies of these two enzymes produce similar clinical and biochemical manifestations (see Figs. 105.13 and 105.14). There is a wide variation in the severity of symptoms and in the age at presentation. In near-complete enzymatic deficiency, symptoms appear during the first few days or even hours of life with signs and symptoms of hyperammonemia (refusal to eat, vomiting, lethargy, convulsion, coma). Increased intracranial pressure is frequent. Late forms (as late as the fourth decade of life) may present as an acute bout of hyperammonemia (lethargy, headache, seizures, psychosis) in a seemingly healthy individual. Coma and death may occur during these episodes. Diagnostic confusion with migraine is common. Intermediate forms with intellectual disability and chronic subclinical hyperammonemia interspersed with bouts of acute hyperammonemia have also been observed.

Laboratory findings include hyperammonemia. The plasma amino acid analysis typically shows a marked increase of glutamine and alanine with relatively low levels of citrulline and arginine. These are nondiagnostic changes that occur in hyperammonemia of diverse causes. Urinary orotic acid is usually low or may be absent (see Fig. 105.14).

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier (see Table 105.6). Treatment with oral carbamylglutamate of patients with NAGS deficiency can produce successful rescue of biochemical findings and symptoms. It is therefore important to differentiate between CPS1 and NAGS deficiencies by gene analysis of *CPS1* and *NAGS,* respectively.

CPS1 and NAGS deficiencies are both autosomal recessive conditions; the CPS1 enzyme is normally present in the liver and intestine. Neither of these conditions can be reliably identified by the mass screening of the newborn infants using current approaches.

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

In this X-linked disorder, the hemizygous males are more severely affected than heterozygous females (see Figs. 105.13 and 105.14). The heterozygous females may have a mild form of the disease, but the majority (approximately 75%) remain asymptomatic, although investigations indicate subtle neurologic defects even in females without a discernable history of hyperammonemia. OTC deficiency is the most common form of all the urea cycle disorders, comprising approximately 40% of cases.

Clinical manifestations in a male newborn are usually those of **severe** hyperammonemia (see earlier) occurring in the first few days of life. **Mild forms**, such as in some heterozygous females, characteristically have episodic manifestations, which may occur at any age (usually after infancy). Episodes of hyperammonemia, manifested by vomiting and neurologic abnormalities (e.g., ataxia, mental confusion, agitation, combativeness, frank psychosis), are separated by periods of wellness. These episodes usually occur after ingestion of a high-protein diet or as a result of a catabolic state such as infection. Hyperammonemic coma, cerebral edema, and death may occur during one of these attacks. Cognitive development may proceed normally. Mild to moderate intellectual disability, however, is common. Gallstones have been seen in the survivors, although the mechanism remains unclear.

The major **laboratory finding** during the acute attack is hyperammonemia accompanied by marked elevations of plasma concentrations of glutamine and alanine with low levels of citrulline and arginine. The blood level of urea is usually low. A marked increase in the urinary excretion of orotic acid differentiates this condition from CPS1 deficiency (see Fig. 105.14). Orotate may precipitate in urine as pink-colored crystals. In the **mild form**, these laboratory abnormalities may revert to normal between attacks. This form should be differentiated from all the episodic conditions of childhood. Patients with lysinuric protein intolerance (see Chapter 105.14) may demonstrate some features of OTC deficiency, but the former can be differentiated by increased urinary excretion of lysine, ornithine, and arginine and elevated blood concentrations of citrulline.

The prevalence of OTC deficiency is 1 in 56,000 to 1 in 77,000 live births. This condition is not identifiable by the mass screening of newborn infants using current approaches. The **diagnosis** is most conveniently confirmed by *OTC* gene analysis. Many *OTC* pathogenic variants (>300) have been identified. Genotype and degree of enzyme deficiency determine the severity of the phenotype in most cases. Mothers of affected infants are expected to be carriers of the mutant gene unless a de novo pathogenic variant has occurred. A mother who gave birth to two affected male offspring was found to have a normal

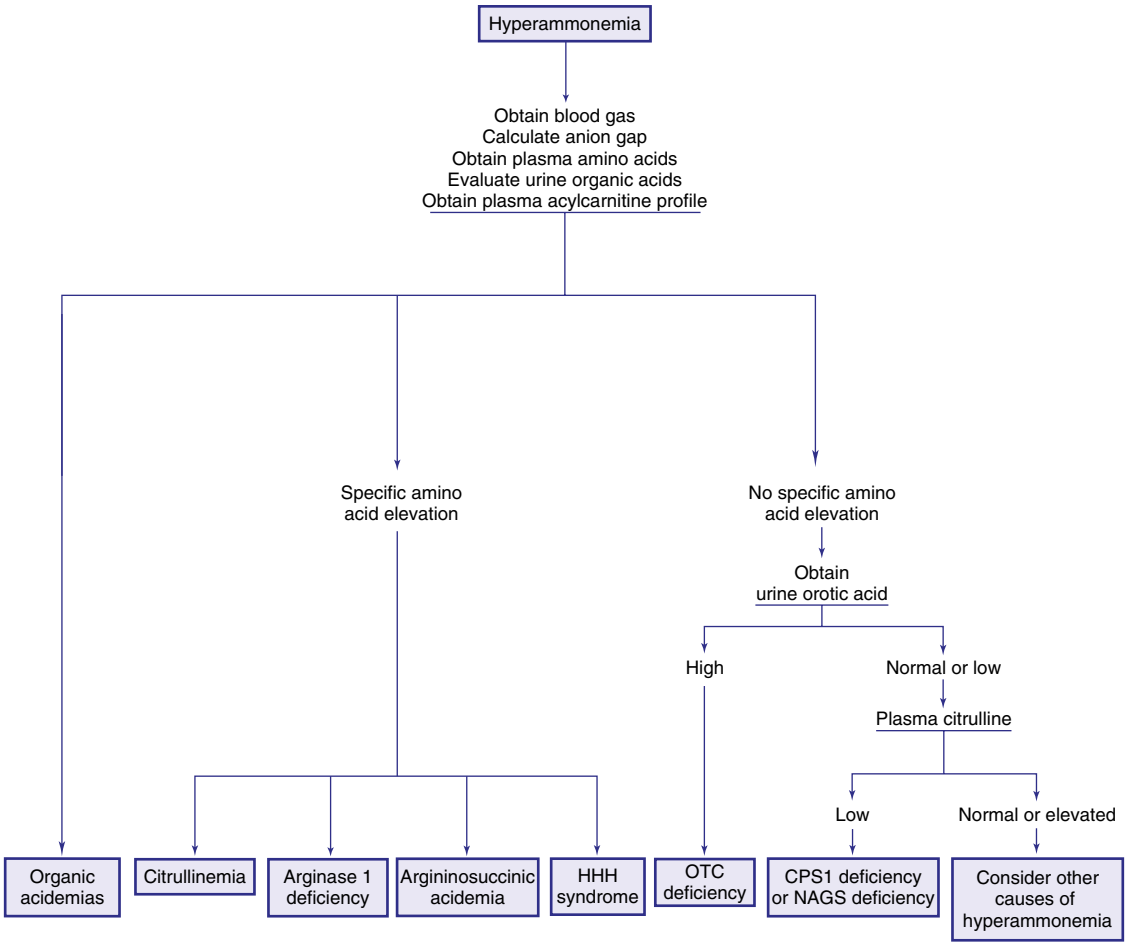

Fig. 105.14 Clinical algorithmic approach to a newborn infant with symptomatic hyperammonemia. CPS1, Carbamoyl phosphate synthetase 1; HHH syndrome, hyperornithinemia-hyperammonemia-homocitrullinemia; NAGS, *N*-acetylglutamate synthetase; OTC, ornithine carbamoyltransferase.

genotype, suggesting that gonadal mosaicism can be seen. As many as 20% of affected patients demonstrate normal results by Sanger sequencing, perhaps because the pathogenic variant involves copy number variants, deep intronic regions, or a promoter sequence. Copy number variants can be evaluated using a chromosomal microarray, and if positive, a contiguous gene deletion should be considered. If the molecular diagnostic approach is negative, a liver biopsy may be indicated. Prenatal diagnosis is feasible by analysis of DNA in amniocytes or chorionic villus samples. Increase in urinary excretion of orotidine after an allopurinol loading test can identify female carriers. Mild cerebral dysfunction may be present in asymptomatic female carriers. The importance of a detailed family history cannot be overemphasized. A history of migraine or protein aversion is common in maternal female relatives of the proband. Indeed, careful scrutiny of the family history may reveal a pattern of unexplained deaths in male newborns in the maternal lineage.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are as outlined earlier. For enteral use, citrulline is used in place of arginine for patients with OTC deficiency. Liver transplantation is a surgical treatment option for patients with severe OTC deficiency.

CITRULLINEMIA

Two clinically and genetically distinct forms of citrullinemia have been described. The classic form (**type I**) is caused by the deficiency of the ASS enzyme. Citrullinemia **type II** is caused by the deficiency of a mitochondrial transport protein called *citrin*. (See Figs. 105.13 and 105.14.)

Citrullinemia Type I (Argininosuccinate Synthetase Deficiency, Classic Citrullinemia)

This condition is caused by the deficiency of ASS (see Fig. 105.13) and has variable clinical manifestations depending on the degree of the enzyme deficiency. Two major forms of the condition have been identified. The **severe** or **neonatal form**, which is most common, appears in the first few days of life with signs and symptoms of hyperammonemia (see earlier). In the **subacute or mild form**, clinical findings such as failure to thrive, frequent vomiting, developmental delay, and dry, brittle hair appear gradually after 1 year of age. Acute hyperammonemia, triggered by an intercurrent catabolic state, may bring the diagnosis to light.

Laboratory findings are similar to those found in patients with OTC deficiency, except that the plasma citrulline concentration is greatly elevated (50-100 times the reference range) (see Fig. 105.14). Urinary excretion of orotic acid is moderately increased; crystalluria may also occur as a result of precipitation of orotates. The diagnosis is confirmed by DNA analysis of *ASS1* or, less frequently, by an assay of enzyme activity in cultured fibroblasts. Prenatal diagnosis is feasible with an enzyme assay in cultured amniotic cells or by DNA analysis of cells obtained from chorionic villus biopsy.

Treatment of acute hyperammonemic attacks and long-term therapy are outlined earlier (see Table 105.6). Plasma concentration of citrulline remains elevated at all times and may increase further after administration of arginine. Patients can do well on a protein-restricted diet in conjunction with sodium benzoate, phenylbutyrate, and arginine therapy. Mild to moderate cognitive impairment is a common sequela, even in a well-treated patient.

Citrullinemia is an autosomal recessive condition caused by biallelic pathogenic variants in *ASS1*. The majority of patients are compound heterozygotes for two different alleles. The prevalence of the condition is 1 in 250,000 live births. The recent introduction of neonatal screening for urea cycle defects has shown that some affected patients are ostensibly asymptomatic even on a regular diet. Long-term follow-up is needed to be certain that these individuals do not sustain neurologic sequelae.

Citrin Deficiency (Citrullinemia Type II)

Citrin (aspartate-glutamate carrier protein) is a mitochondrial transporter encoded by *SLC25A13*. One of this protein's functions is to transport aspartate from mitochondria into cytoplasm and replenish the cytosolic aspartate pool required for converting citrulline to argininosuccinic acid (see Fig. 105.13). If aspartate is unavailable to the cytoplasmic component of the urea cycle, urea will not be formed at a normal rate, and citrulline will accumulate. ASS activity is diminished in the liver of these patients, but no pathogenic variant in the *ASS1* gene has been found. It is postulated that citrin deficiency interferes with translation of the messenger RNA for the ASS enzyme in the liver. The condition initially was reported in Japan (regional prevalence ~1 in 20,000), but many non-Japanese patients have been since identified (worldwide prevalence between 1 in 100,000 and 1 in 230,000). Biallelic pathogenic variants in *SLC25A13* have been associated with three clinical forms of citrin deficiency.

Neonatal Intrahepatic Cholestasis (Citrullinemia Type II, Neonatal Form)

Clinical and laboratory manifestations, which usually start before the infant's first birthday, include cholestatic jaundice with mild to moderate direct (conjugated) hyperbilirubinemia, marked hypoproteinemia, and clotting dysfunction (increased prothrombin time and partial thromboplastin time); increased serum γ-glutamyltransferase and alkaline phosphatase activities; and liver transaminases are usually normal. Plasma concentrations of ammonia and citrulline are usually normal, but moderate elevations have been reported. There may be increases in plasma concentrations of methionine, tyrosine, alanine, and threonine. Elevated levels of serum galactose have been found, even though the enzymes of galactose metabolism are normal. The reason for hypergalactosemia is not clear. Marked elevation in the serum level of α-fetoprotein is also present. These findings resemble those of tyrosinemia type I, but unlike the latter condition, urinary excretion of succinylacetone is not elevated (see Chapter 105.2). Liver biopsy shows fatty infiltration, cholestasis with dilated canaliculi, and a moderate degree of fibrosis. The condition is usually self-limiting, and the majority of infants recover spontaneously by 1 year of age with supportive and symptomatic treatment. Hepatic failure requiring liver transplantation has occurred in a few cases. Although the condition is commonly seen in Japan, the diagnosis should be considered in any case of unexplained neonatal hepatitis with cholestasis. Data on the long-term prognosis and the natural history of the condition are limited; development into the adult form of the condition after several years of a seemingly asymptomatic hiatus has been observed.

Failure to Thrive and Dyslipidemia Due to Citrin Deficiency

Some patients can present between 1 and 10 years of age with peculiar dietary habits favoring high-protein and high-lipid foods. It is accompanied by poor appetite, hypoglycemic episodes, and failure to thrive. Laboratory evaluation may reveal mild hyperammonemia, hypertriglyceridemia, elevated low-density lipoprotein (LDL) cholesterol, and low high-density lipoprotein (HDL) cholesterol levels. This presentation of citrin deficiency in children is often considered a prodromal form of the adult form of citrullinemia type II.

Citrullinemia Type II, Adult Form (Adult-Onset Citrullinemia; Citrullinemia Type II, Mild Form)

Without prior molecular diagnosis or family history, individuals affected by this form of citrullinemia type II (CTLN2) are often identified acutely. A previously healthy individual may present with nonspecific neuropsychiatric symptoms such as disorientation, delirium, delusion, aberrant behavior, tremors, and psychosis. Moderate degrees of hyperammonemia and hypercitrullinemia are present. The age at onset is usually between 20 and 40 years but can happen at any point after age 11 years. Patients who recover from the first episode may have recurrent attacks. Pancreatitis, hyperlipidemia, and hepatoma are major complications among the survivors. Medical **treatment** of CTLN2 has been mostly ineffective to prevent future attacks. A diet enriched in protein and lipids helps restore cytosolic aspartate and stimulate ureagenesis. In confirmed citrin deficiency, a low-protein/high-carbohydrate diet should be avoided. Although liver transplantation appears to be effective in preventing future episodes of hyperammonemia, enteral supplementation with pyruvate, arginine, and medium-chain triglycerides can be tried first to help prevent hyperammonemic episodes and improve growth.

ARGININOSUCCINATE LYASE DEFICIENCY (ARGININOSUCCINIC ACIDURIA)

The severity of the clinical and biochemical manifestations varies considerably (see Figs. 105.13 and 105.14). In the severe form of ASL deficiency, severe hyperammonemia (see earlier) can develop in the first few days of life, and without treatment affected infants can perish. The clinical course of ASL deficiency in patients who survive the initial acute episode is often characterized by intellectual disability, failure to thrive, hypertension, gallstones, liver fibrosis, and hepatomegaly. A common finding in untreated patients is dry and brittle hair (**trichorrhexis nodosa**), although this finding is relatively nonspecific. Acute attacks of severe hyperammonemia may occur during a catabolic state triggered by infections, trauma, or dietary indiscretion. Laboratory findings include hyperammonemia, moderate elevations in liver enzymes, nonspecific increases in plasma levels of glutamine and alanine, a moderate increase in plasma levels of citrulline (less than in citrullinemia), and a marked increase in the concentration of argininosuccinic acid in plasma, urine, and CSF. The CSF levels are usually higher than those in plasma. The enzyme is present in erythrocytes, the liver, and cultured fibroblasts. **Prenatal diagnosis** is possible by identification of biallelic pathogenic variants in the *ASL* gene or, rarely, by measurement of the enzyme activity in cultured amniotic cells. Argininosuccinic acid is also elevated in the amniotic fluid of affected fetuses.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter. Intellectual disability, persistent hepatomegaly with mild increases in liver enzymes, and bleeding tendencies as a result of abnormal clotting factors are common sequelae. ASL deficiency is an autosomal recessive disorder with a prevalence of about 1 in 220,000 live births. Early detection is achieved through mass screening of newborn infants.

ARGINASE 1 DEFICIENCY (HYPERARGININEMIA)

Arginase 1 deficiency is an autosomal recessive condition caused by biallelic pathogenic variants in *ARG1* (see Figs. 105.13 and 105.14). Two genetically distinct arginases are present in humans. Arginase 1 (ARG1) is a cytosolic enzyme and is expressed in the liver and can be found in erythrocytes. Arginase 2 (ARG2) is expressed in renal and brain mitochondria. The role of ARG2 is not well understood; its activity in patients with argininemia appears to have no protective effect.

Clinical manifestations of arginase 1 deficiency are somewhat different from other urea cycle enzyme defects, although acute neonatal hyperammonemia presenting with intractable seizures, cerebral edema, and death has also been reported. Outside of the neonatal period, the onset of arginase 1 deficiency often is insidious. The infant can remain asymptomatic in the first few months or years of life. A **progressive spastic diplegia** with scissoring of the lower extremities, choreoathetotic movements, loss of developmental milestones, and failure to thrive in a previously normal infant may suggest the diagnosis. Some children were treated for cerebral palsy before arginase 1 deficiency was confirmed. Intellectual disability is progressive; seizures are common, but episodes of severe hyperammonemia are not as frequent as in the more proximal urea cycle defects. Hepatomegaly may be present.

Laboratory evaluation reveals marked elevations of arginine in plasma and CSF (see Fig. 105.14). Urinary orotic acid can be increased. Determination of amino acids in plasma is a critical step in the diagnosis of argininemia. Guanidino compounds (α-keto-guanidinovaleric acid and α-keto-argininic acid) can be markedly increased in urine. The diagnosis is secured by identification of biallelic pathogenic variants in *ARG1* or, rarely, by assaying arginase activity in erythrocytes.

Treatment consists of a low-protein diet at the age-appropriate RDA. The dietary composition and daily intake of protein should be monitored by frequent plasma amino acid determinations. Supplementation with arginine in ARG1-deficient patients is contraindicated. Sodium benzoate or sodium phenylbutyrate is also effective in controlling hyperammonemia and lowering plasma arginine levels. Liver transplantation has produced promising results, but experience with long-term outcome is limited. Early detection is feasible through mass screening of newborn infants.

TRANSIENT HYPERAMMONEMIA OF THE NEWBORN

The blood concentration of ammonia in a full-term infant can be as high as 100 μmol/L, or two to three times greater than that of the older child or adult. Blood levels approach the adult normal values after a few weeks of life (see Fig. 105.14). Plasma ammonia levels greater than 100 μmol/L should prompt additional diagnostic steps to evaluate for possible genetic causes of hyperammonemia. Infrequently, **severe transient hyperammonemia** can be observed in infants whose diagnostic workup reveals no biochemical abnormalities implicating genes encoding components of the urea cycle. The majority of affected infants are premature and have mild respiratory distress syndrome. Hyperammonemic coma can develop within 2-3 days of life, and the infant may succumb to the disease if treatment is not started immediately. Laboratory studies reveal marked hyperammonemia (plasma ammonia as high as 4,000 μmol/L) with moderate increases in plasma levels of glutamine and alanine. Plasma concentrations of urea cycle intermediate amino acids are usually normal except for citrulline, which may be moderately elevated. The cause of the disorder is unknown. Urea cycle enzyme activities are normal. **Treatment** of hyperammonemia should be initiated promptly and continued vigorously. Recovery without sequelae has been reported, and hyperammonemia does not recur even with a normal-protein diet.

DISORDERS OF ORNITHINE METABOLISM

Ornithine, a key intermediate of the urea cycle, is not incorporated into natural proteins. Rather, it is generated in the cytosol from arginine and must be transported into mitochondria, where it becomes a substrate in reactions catalyzed by OTC forming citrulline. Excess ornithine is catabolized by two enzymes: ornithine aminotransferase, a mitochondrial enzyme converting ornithine to a proline precursor, and ornithine decarboxylase, which resides in the cytosol and converts ornithine to putrescine (see Fig. 105.13). Two genetic disorders feature **hyperornithinemia**: gyrate atrophy of the retina and hyperammonemia-hyperornithinemia-homocitrullinemia (HHH) syndrome.

Gyrate Atrophy of the Retina and Choroid

This rare, autosomal recessive disorder is caused by biallelic pathogenic variants in *OAT* leading to the deficient activity of ornithine aminotransferase (see Fig. 105.13). Approximately 30% of the reported cases are from Finland. Clinical manifestations may include hyperammonemia in the first months of life in some patients. Findings that define the phenotype of ornithine aminotransferase deficiency include night blindness, myopia, loss of peripheral vision, and posterior subcapsular cataracts. These eye changes start between 5 and 10 years of age and progress to complete blindness by the fourth decade of life. Atrophic lesions in the retina resemble cerebral gyri. These patients usually have normal intelligence. Besides the characteristic 10- to 20-fold increase in plasma levels of ornithine (400-1,400 μmol/L), plasma levels of glutamate, glutamine, lysine, creatine, and creatinine can be moderately decreased. Some patients show partial improvement with high doses of pyridoxine. An arginine-restricted diet in conjunction with supplemental lysine, proline, and creatine has been successful in reducing plasma ornithine concentration and has produced some clinical improvement.

Hyperammonemia-Hyperornithinemia-Homocitrullinemia Syndrome

Biallelic pathogenic variants in *SLC25A15* result in an autosomal recessive disorder, HHH syndrome. This defect of the ornithine transport system leads to accumulation of ornithine in the cytosol and a depletion of this amino acid in mitochondria. The former causes hyperornithinemia, and the latter results in disruption of the urea cycle and hyperammonemia (see Fig. 105.13). Homocitrulline is presumably formed through condensation of mitochondrial carbamoyl phosphate with lysine. Clinical manifestations of hyperammonemia can develop shortly after birth or may be delayed until adulthood. Acute episodes of hyperammonemia manifest as refusal to feed, vomiting, and lethargy; coma may occur during infancy. Progressive neurologic signs, such as lower limb weakness, increased deep tendon reflexes, spasticity, clonus, seizures, and varying degrees of psychomotor retardation may develop if the condition remains undiagnosed. No ocular findings have been observed in these patients. Laboratory findings reveal marked increases in plasma levels of ornithine and homocitrulline in addition to hyperammonemia (see Fig. 105.14). Acute episodes of hyperammonemia should be treated promptly (see earlier). Restriction of protein intake improves hyperammonemia. Oral supplementation with arginine (or citrulline) has produced clinical improvement in some patients.

CONGENITAL GLUTAMINE DEFICIENCY

Glutamine is synthesized endogenously from glutamate and ammonia by a ubiquitously expressed enzyme, glutamine synthetase (see Fig. 105.11). Glutamine is known to be involved in several important functions, including detoxification of ammonia. Deficiency of this enzyme, resulting in glutamine deficiency, has been reported in three infants from three unrelated families. All affected infants manifested multiorgan involvement, including brain malformations (abnormal gyrations, hypomyelination), facial abnormalities (broad nasal root, low-set ears), hypotonia, and seizures at birth. Two of the patients died from multiorgan failure (respiratory and heart failure) in the neonatal period. One child was alive at 3 years of age with severe developmental delay. Glutamine was absent in plasma, urine, and CSF, but plasma levels of glutamic acid were normal. Congenital glutamine deficiency is an autosomal recessive condition caused by biallelic pathogenic variants in *GLUL*.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.13 Histidine

Oleg A. Shchelochkov and Charles P. Venditti

Histidine is degraded through the urocanic acid pathway to glutamic acid. Several genetic biochemical aberrations involving the degradative pathway of histidine have been reported, but the clinical significance of elevated histidine levels has not been established.

Decarboxylation of histidine by histidine decarboxylase produces histamine. Deficiency of this enzyme has been implicated in the familial form of **Tourette syndrome** (see Chapter 105.11).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.14 Lysine

Oleg A. Shchelochkov and Charles P. Venditti

Lysine is catabolized through two pathways. In the first pathway, lysine is condensed with α-ketoglutaric acid to form saccharopine. Saccharopine is then catabolized to α-aminoadipic semialdehyde and glutamic acid. These first two steps are catalyzed by α-aminoadipic semialdehyde synthase, which has two activities: lysine-ketoglutarate reductase and saccharopine dehydrogenase (Fig. 105.15). In the second pathway, lysine is first transaminated and then condensed to its cyclic forms: pipecolic acid and piperideine-6-carboxylic acid **(P6C)**. P6C and its linear form, α-aminoadipic semialdehyde, are oxidized to α-aminoadipic acid by the enzyme **antiquitin**. This is the major pathway for D-lysine in the body and for L-lysine in the brain.

Hyperlysinemia-saccharopinuria, α-aminoadipic, and α-ketoadipic acidemia are biochemical conditions caused by inborn errors of lysine degradation. Individuals with these conditions are usually asymptomatic.

PYRIDOXINE–DEPENDENT EPILEPSY (PDE)

Pyridoxal 5′-phosphate **(P5P)**, the active form of pyridoxine (vitamin B_6), is the cofactor for many enzymes, including those involved in the metabolism of neurotransmitters. Intracellular P5P deficiency in the brain may result in a seizure disorder that is refractory to common anticonvulsant agents but is responsive to high doses of pyridoxine. These pyridoxine-responsive phenotypes are seen in the following genetic metabolic conditions.

Antiquitin (α-Aminoadipic Semialdehyde Dehydrogenase) Deficiency

This is the most common cause of PDE. A deficiency of antiquitin (encoded by *ALDH7A1*) results in accumulation of P6C in brain tissue (see Fig. 105.15). P6C reacts with P5P and renders it inactive. Large doses of pyridoxine are therefore needed to overcome this inactivation. The condition is inherited as an autosomal recessive trait.

Pyridox(am)ine 5′-Phosphate Oxidase (PNPO) Deficiency

PNPO deficiency clinically overlaps with antiquitin deficiency. PNPO-deficient patients often present with neonatal-onset seizures, developmental delays, spastic tetraplegia, and nonspecific findings on brain imaging (delayed myelination, cerebral atrophy, and abnormal signals in the basal ganglia). Developmental regression, optic disc pallor, and retinopathy have been reported infrequently. Plasma and CSF amino acid analysis may reveal elevated glycine, prompting evaluation for NKH (see Chapter 105.7), leading to a delay in initiating treatment with P5P. A CSF neurotransmitter assay revealed inconsistent changes in the levels of 3-*O*-methyldopa, homovanillic acid, and 5-hydroxyindoleacetic acid. A normal CSF level of P5P was reported in one patient, suggesting that a therapeutic trial with P5P and molecular analysis may be a prudent strategy in some patients irrespective of the CSF studies. The lowest effective dose of P5P should be used to avoid toxicity. The disorder is caused by biallelic pathogenic variants in *PNPO*.

Sulfite Oxidase Deficiency and Molybdenum Cofactor Deficiency

In this rare condition (see Chapter 105.4), accumulation of sulfites causes inhibition of enzymatic activity of antiquitin and accumulation of P6C, which in turn causes inactivation of P5P and vitamin B_6 dependency.

Hyperprolinemia Type II

In this condition, accumulation of P5C in brain tissue can also cause inactivation of P5P, leading to pyridoxine dependency (see Chapter 105.9 and Fig. 105.9).

Hypophosphatasia

P5P is the main circulating form of pyridoxine. Alkaline phosphatase (ALP) is required for dephosphorylation of P5P to generate free pyridoxine, which is the only form of vitamin B_6 that can cross the BBB and enter the brain cells. Pyridoxine is rephosphorylated

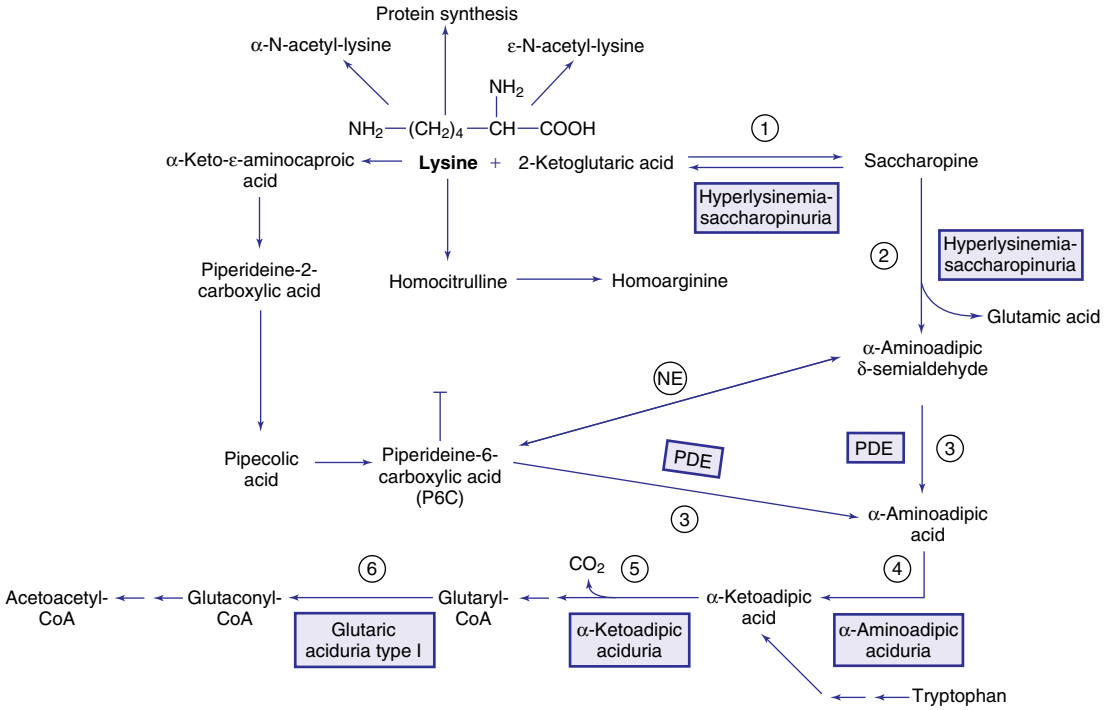

Fig. 105.15 Pathways in the metabolism of lysine. **Enzymes:** *(1)* Lysine ketoglutarate reductase, *(2)* saccharopine dehydrogenase, *(3)* α-aminoadipic semialdehyde/piperidine-6-carboxylic acid (P6C) dehydrogenase (antiquitin), *(4)* α-aminoadipic acid transferase, *(5)* α-ketoadipic acid dehydrogenase, *(6)* glutaryl-CoA-dehydrogenase. NE, Nonenzymatic; PDE, pyridoxine-dependent epilepsy.

intracellularly to form P5P. In the infantile form of hypophosphatasia, P5P cannot be dephosphorylated to free pyridoxine because of the marked deficiency of tissue-nonspecific ALP. This results in deficiency of pyridoxine in the brain and PDE (see Chapters 611 and 724).

The main **clinical manifestation** of PDE caused by antiquitin deficiency is generalized seizures, which usually occur in the first days of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report abnormal intrauterine fluttering movements. The seizures are usually tonic-clonic in nature but can be almost any type. Other manifestations such as dystonia, respiratory distress, and abdominal distention with vomiting, hepatomegaly, hypoglycemia, and hypothermia may be present. Learning problems and speech delay are common sequelae. Late-onset forms of the condition (as late as 5 years of age) have been reported. Consequently, a trial with vitamin B_6 is recommended in any infant with intractable convulsions (see Chapters 611.04 and 611.06).

Laboratory findings show increased concentrations of α-aminoadipic semialdehyde and pipecolic acid in the CSF, plasma, and urine. EEG abnormalities may normalize after treatment. Neuroimaging may be normal, but cerebellar and cerebral atrophy, periventricular hyperintensity, intracerebral hemorrhage, and hydrocephalus have been reported.

Treatment with vitamin B_6 (50-100 mg/day) usually results in a dramatic improvement of both seizures and the EEG abnormalities. High doses of pyridoxine can result in peripheral neuropathy, and doses >500 mg/day should be avoided. The pyridoxine dependency, and thus the therapy, are lifelong. The therapeutic benefit of a lysine-restricted, L-arginine-enriched diet is being evaluated.

Glutaric Aciduria Type 1 (Glutaryl-CoA Dehydrogenase Deficiency)

Glutaric acid is an intermediate in the degradation of lysine (see Fig. 105.15), hydroxylysine, and tryptophan. Glutaric aciduria type 1, a disorder caused by a deficiency of glutaryl-CoA dehydrogenase, should be differentiated from glutaric aciduria type 2, a distinct clinical and biochemical disorder caused by defects in the mitochondrial electron transport chain (see Chapter 106.1).

Glutaric aciduria type 1 is an autosomal recessive disorder caused by biallelic loss-of-function variants in *GCDH*. Its prevalence is estimated at 1 in 100,000 live births worldwide. The condition is more prevalent in some ethnic populations (e.g., Canadian Oji-Cree Indians, Irish Travelers, Black South Africans, Swedes, and the Old Order Amish population in the United States). A high prevalence of known pathogenic variants in specific ethnic populations can enable a cost-effective molecular evaluation and counseling. **Prenatal diagnosis** can be accomplished by demonstrating increased concentrations of glutaric acid in amniotic fluid, by assay of the enzyme activity in amniocytes or chorionic villus samples, or by identification of the known pathogenic variants in *GCDH*.

Clinical Manifestations

Macrocephaly is a common, but nonspecific, finding in patients with glutaric aciduria type 1. It develops in the first year of life but can also be present at birth and precede the onset of neurologic manifestations. Some affected infants may also show subtle neurologic symptoms, such as delayed onset of motor milestones, irritability, and feeding problems, during this seemingly asymptomatic period. The onset of the condition is usually heralded by **acute encephalopathic findings**, such as loss of normal developmental milestones (head control, rolling over, or sitting), seizures, generalized rigidity, opisthotonos, choreoathetosis, and dystonia caused by acute striatal injury. These symptoms may occur suddenly in an apparently normal infant after a minor infection. Brain imaging reveals increased extraaxial (particularly frontal) fluid with stretched bridging veins, striatal lesions, dilated lateral ventricles, cortical atrophy (mainly in the frontotemporal region), and fibrosis. Recovery from the first attack usually occurs slowly, and some residual neurologic abnormalities may persist, especially dystonia and choreoathetosis. Without treatment, additional acute attacks resembling the first can occur during subsequent episodes of intercurrent infections or catabolic states. In some patients, these signs and symptoms may develop gradually in the first few years of life. Hypotonia and choreoathetosis may gradually progress into rigidity and dystonia **(insidious form)**. Acute episodes of metabolic decompensation with vomiting, ketosis, seizures, and coma also occur in this form after infection or other catabolic states. Without treatment, death may occur in the first decade of life during one of these episodes. Affected infants are prone to development of subdural hematoma and retinal hemorrhage after minor falls and head traumas. This can be misdiagnosed as child abuse. The intellectual abilities usually remain relatively normal in most patients.

Laboratory Findings

During acute episodes, mild to moderate metabolic acidosis and ketosis may occur. Hypoglycemia, hyperammonemia, and elevations of serum transaminases are seen in some patients. High concentrations of glutaric acid are usually found in the urine, blood, and CSF. 3-Hydroxyglutaric acid may also be present in the body fluids. The acylcarnitine profile shows elevated glutarylcarnitine (C5DC) in blood and urine. Plasma concentrations of amino acids are usually within normal limits. Laboratory findings may be unremarkable between attacks. Glutaric aciduria type 1 can be identified on the newborn screen by measuring glutarylcarnitine (C5DC) levels in blood spots. The sensitivity of this screening method depends on the cutoff value used by a newborn screen program, and some patients may not be detected. For example, a subset of patients with glutaric aciduria type 1 can present with normal plasma and urinary levels of glutaric acid and variably elevated plasma glutarylcarnitine. This type of glutaric aciduria type 1, referred to as a "low-excretor" phenotype, carries the same risk of developing brain injury as in a "high-excretor" phenotype. In some low-excreting patients, glutaric acid is elevated only in the CSF. Urinary glutarylcarnitine appears to be a more sensitive screening method to identify affected low-excreting patients. Molecular analysis of *GCDH* can aid in identifying patients with a low-excretor phenotype associated with specific pathogenic variants (e.g., p.M405V, p.V400M, p.R227P). We recommend performing molecular analysis of *GCDH* or glutaryl-CoA dehydrogenase enzyme activity in any child presenting with unexplained progressive dystonia and dyskinesia.

Treatment

Patients require a lysine- and tryptophan-restricted diet while meeting physiologic requirements for protein, micronutrients, and vitamins. Increased dietary arginine may decrease cellular uptake of lysine and decrease the endogenous formation of glutaryl-CoA. Patients should be routinely evaluated for lysine and tryptophan deficiency by monitoring plasma amino acids and growth. L-Carnitine supplementation (50-100 mg/kg/day orally) is recommended in all cases. Emergency treatment during acute illness, including temporary cessation of protein intake for 24 hours, replacement of lost calories using carbohydrates or lipids, IV L-carnitine, IV dextrose, prompt treatment of infection, and control of fever is critical to decreasing the risk of striatal injury. All patients should be provided with an emergency letter describing the underlying diagnosis, recommended evaluation, and treatment. Early diagnosis through newborn screening with prevention and aggressive treatment of intercurrent catabolic states (infections) can help minimize striatal injury and ensure a more favorable prognosis. Patients with movement disorder and spasticity may require treatment with baclofen, diazepam, trihexyphenidyl, and injectable botulinum toxin A.

LYSINURIC PROTEIN INTOLERANCE (LPI)

This rare autosomal recessive disorder is caused by pathogenic variants in *SLC7A7* leading to impaired function of a protein transporting the cationic amino acids lysine, ornithine, and arginine in the intestine and kidneys. A deficiency of the transporter protein (Y+L amino acid transporter 1) in this condition causes multisystem manifestations, which often start with gastrointestinal symptoms. The transport defect in this condition resides in the basolateral (antiluminal) membrane of enterocytes and renal tubular epithelia. This explains the observation that cationic amino acids are unable to cross these cells even when administered as dipeptides. Lysine in the form of dipeptide crosses the luminal membrane of the enterocytes but hydrolyzes to free lysine in the cytoplasm. Free lysine, unable to cross the basolateral membrane of the cells, can diffuse back into the lumen leading to gastrointestinal symptoms.

Refusal to feed, nausea, aversion to protein, vomiting, and mild diarrhea, which may result in failure to thrive, wasting, and hypotonia, can be seen shortly after birth. Breastfed infants usually remain asymptomatic until soon after weaning, possibly because of the switch to a higher-protein solid foods. Episodes of hyperammonemia caused by the depletion of ornithine and arginine in the urea cycle may occur after ingestion of a high-protein meal. Mild to moderate hepatosplenomegaly, osteoporosis, sparse brittle hair, thin extremities with moderate centripetal adiposity, and growth retardation are common physical findings in patients whose condition has remained undiagnosed. Neurocognitive status is usually normal, but moderate intellectual disability has been observed in some patients.

Progressive interstitial pneumonitis with bouts of acute exacerbation often occurs and often progresses to severe alveolar proteinosis. Clinical manifestations include progressive exertional dyspnea, fatigue, cough, diminished breath sound, and inspiratory rales; cyanosis may develop in older patients. Some LPI patients have remained undiagnosed until the appearance of pulmonary manifestations. Radiographic evidence of pulmonary fibrosis has been observed in up to 65% of patients without clinical manifestations of pulmonary involvement.

Renal involvement is manifested initially by proteinuria, hematuria, and elevation of serum creatinine, which may progress to end-stage renal failure. Renal tubular involvement with laboratory findings of renal Fanconi syndrome may also be present. Renal biopsy reveals pathologic findings consistent with glomerulonephritis and tubulointerstitial nephritis. Hematologic findings of anemia, leukopenia, thrombocytopenia, and elevated ferritin may also be present.

Other organs are frequently involved. A condition resembling **hemophagocytic lymphohistiocytosis/macrophage activation syndrome** has been reported. Immunologic abnormalities (impaired lymphocyte function, abnormalities in immune globulins, hypocomplementemia) and acute pancreatitis are frequent features of LPI.

Pregnancies in affected mothers have been complicated by anemia, thrombocytopenia, toxemia, and bleeding, but offspring appear healthy at birth.

Laboratory findings may reveal hyperammonemia and an elevated concentration of urinary orotic acid, which develop after high-protein feeding. Plasma concentrations of lysine, arginine, and ornithine are usually mildly decreased, but urinary levels of these amino acids, especially lysine, are greatly increased. The pathogenesis of hyperammonemia is likely related to the depletion of urea cycle intermediates caused by poor absorption and the increased renal loss of ornithine and arginine. Plasma concentrations of alanine, glutamine, serine, glycine, and proline are usually increased. Anemia, increased serum levels of ferritin, LDH, thyroxine-binding globulin, hypercholesterolemia, and hypertriglyceridemia are common findings often leading to the workup for hemophagocytic lymphohistiocytosis. This condition should be differentiated from hyperammonemia caused by urea cycle defects (see Chapter 105.12), especially in heterozygous females with OTC deficiency, in whom increased urinary excretion of lysine, ornithine, and arginine is not seen.

Treatment with a low-protein diet providing the RDA of protein and supplemented with oral citrulline (50-100 mg/kg/day) can produce biochemical and clinical improvements. Episodes of hyperammonemia should be treated promptly (see Chapter 105.12). Supplementation with lysine (10-30 mg/kg/day) given in small and frequent doses helps improve plasma levels. The dose of lysine should be titrated down if patients develop abdominal pain and diarrhea. Treatment with high doses of prednisone has been effective in the management of acute pulmonary complications in some patients. **Bronchopulmonary lavage** is the treatment of choice for patients with alveolar proteinosis. The condition is more prevalent in Finland and Japan, where the prevalence is 1 in 60,000 and 1 in 57,000 live births, respectively.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

105.15 *N*-Acetylaspartic Acid (Canavan Disease)

Reuben K. Matalon[†] and Dena R. Matalon

N-Acetylaspartic acid **(NAA)**, a derivative of aspartic acid, is synthesized in the brain and is found in a high concentration similar to glutamic acid. NAA has multiple functions, such as serving as an acetate reservoir for myelin synthesis, as well as being an organic osmolyte that helps regulate cerebral osmolality. However, the complete function of NAA is not yet fully understood. **Aspartoacylase** (ASPA) cleaves the *N*-acetyl group from NAA. A deficiency of aspartoacylase leads to **Canavan disease**, a severe **leukodystrophy** characterized by excessive excretion of NAA and spongy degeneration of the white matter of the brain. Canavan disease is an autosomal recessive disorder and is more prevalent in individuals of Ashkenazi Jewish descent than in other ethnic groups. The defective gene for Canavan disease *(ASPA)* can be tested in patients, family members, and at-risk populations.

ETIOLOGY AND PATHOLOGY

Deficiency of the enzyme aspartoacylase due to pathogenic variants in the *ASPA* gene leads to NAA accumulation in the brain, especially in the white matter, and massive urinary excretion. Excessive amounts of NAA are also present in the blood and CSF. Brain biopsies of patients with Canavan disease show spongy degeneration of the myelin fibers, astrocytic swelling, and elongated mitochondria. There is striking vacuolization and astrocytic swelling in the white matter. Electron microscopy reveals distorted mitochondria. As the disease progresses, the ventricles enlarge because of cerebral atrophy.

CLINICAL MANIFESTATIONS

The severity of Canavan disease covers a wide spectrum. Infants usually appear normal at birth and may not manifest symptoms of the disease until 3-6 months of age, when they develop **progressive macrocephaly**, severe hypotonia, persistent head lag, and delayed milestones. As the disease progresses, there is spasticity, joint stiffness, and contractures. Optic atrophy and seizures subsequently develop. Feeding difficulties, poor weight gain, and gastroesophageal reflux may occur in the first year of life followed by swallowing deterioration that may require nasogastric feeding or permanent gastrostomy. In the past, most individuals died in the first decade of life, but with the advances in medical technology and improved supportive care, survival now extends to the second or third decade.

[†]Deceased

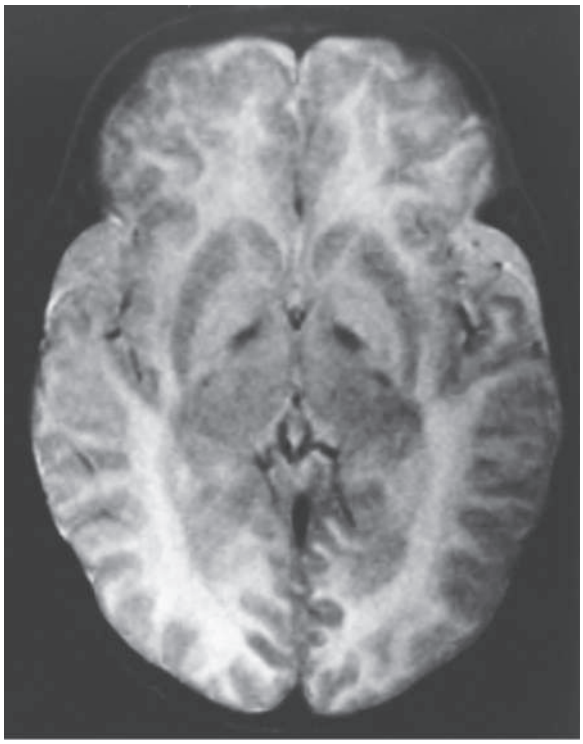

Fig. 105.16 Axial T2-weighted MRI of a 2-yr-old patient with Canavan disease. Extensive thickening of the white matter radiation is seen.

ATYPICAL CANAVAN DISEASE

Juvenile or **mild** Canavan disease is less common than **infantile** Canavan disease and is most prevalent in non-Ashkenazi Jews. Affected individuals with juvenile Canavan disease usually present with mild speech and motor delay and may have **retinitis pigmentosa**. The other typical features of Canavan disease are usually not present. These children have moderately increased urinary excretion of NAA to suggest Canavan disease. Brain MRI demonstrates increased signal intensity in the basal ganglia rather than global white matter disease, sometimes leading to confusion with mitochondrial disease.

DIAGNOSIS

In a typical individual with Canavan disease, brain MRI shows diffuse white matter degeneration, primarily in the cerebral hemispheres, with less involvement of the cerebellum and brainstem (Fig. 105.16). Repeated evaluations may be required. Magnetic resonance spectroscopy (MRS) can be done to show the high peak of NAA, which strongly suggests Canavan disease. The diagnosis can also be established by finding elevated amounts of NAA in the urine or blood. NAA is found in only trace amounts (24 ± 16 μmol/mmol creatinine) in the urine of unaffected individuals, whereas its concentration is in the range of 1,440 ± 873 μmol/mmol creatinine in individuals with Canavan disease. High levels of NAA can also be detected in plasma, CSF, and brain tissue. Aspartoacylase enzyme analysis from fibroblasts is often used to confirm the diagnosis but is not necessary. The activity of aspartoacylase in the fibroblasts of obligate carriers is half or less the activity found in normal individuals. Molecular analysis for variants in the *ASPA* gene is now recommended for all individuals in which Canavan disease is suspected.

The differential diagnosis of Canavan disease should include Alexander disease, another leukodystrophy associated with macrocephaly. Alexander disease is caused by a defect in the synthesis of glial fibrillary acidic protein, and the diagnosis can be ruled out by genetic testing of variants in the *GFAP* gene.

There are two predominant pathogenic variants leading to Canavan disease in the Ashkenazi Jewish population. The first is an amino acid substitution (p.Glu285Ala) in which glutamic acid is substituted for alanine. This pathogenic variant is the most frequent and encompasses 83% of mutant alleles in Ashkenazi Jewish individuals with Canavan disease. The second most common pathogenic variant is a change from tyrosine to a nonsense pathogenic variant, leading to a stop in the coding sequence (p.Tyr231*). This accounts for 13% of mutant Ashkenazi alleles. In the non-Jewish population, more diverse pathogenic variants have been observed, with the two variants common in the Ashkenazi Jewish population being rare. A different variant (p.Ala305Glu), the substitution of alanine for glutamic acid, accounts for 40% of mutant alleles in non-Jewish individuals. Over 70 pathogenic variants have been reported in the non-Jewish population. With Canavan disease, it is important to obtain a molecular diagnosis because this will lead to accurate counseling and prenatal guidance for the family. If the specific variants are not known, prenatal diagnosis relies on the NAA level in the amniotic fluid. In Ashkenazi Jewish individuals, the carrier frequency may be as high as 1:40, nearing that of Tay-Sachs disease. Carrier screening for Canavan disease is available. Genotype-phenotype studies and aspartoacylase expression and enzymatic activity help to prognosticate the severity of disease. Patients with juvenile or mild forms of Canavan disease have been compound heterozygotes with a mild pathogenic variant on one allele and a severe variant on the other allele. Mild variants include p.Tyr288Cys and p.Arg71His.

TREATMENT AND PREVENTION

Treatment for Canavan disease is supportive. After diagnosis, individuals should be monitored closely in terms of feeding and nutritional status, development, and risk for seizures. Medical intervention may be necessary such as antiepileptics, acetazolamide for increased intracranial pressures, and botulinum toxin injections for spasticity. Individuals benefit from early therapy interventions and special education programs to maximize developmental potential and communication. Genetic counseling, carrier testing, and prenatal diagnosis are the only current methods of prevention.

Studies of gene therapy using recombinant adeno-associated viruses (rAAVs) have shown some positive results in knockout mice models. Gene therapy attempts in children with Canavan disease have shown a lack of adverse events, some decrease in the brain elevation of *N*-acetylaspartic acid, improved seizure frequency, and slowing of the progression of brain atrophy. However, there was no improvement in long-term clinical status. Novel rAAV serotypes have been shown to better cross the **blood-brain barrier** and improved longevity of Canavan disease knockout mice, giving promise for further use of gene therapy in individuals with Canavan disease. **Enzyme-replacement therapy** with ASPA and pegylated ASPA is being studied in mice and has shown a decrease of NAA in the brain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 106

Defects in Metabolism of Lipids

106.1 Disorders of Mitochondrial Fatty Acid β-Oxidation

Jerry Vockley

Mitochondrial β-oxidation of fatty acids is an essential energy-producing pathway. It is particularly important during prolonged periods of reduced caloric intake such as fasting or gastrointestinal illness or increased energy expenditure during physiologic stress such as febrile illness. Under these conditions, the body switches from using predominantly *carbohydrate* to predominantly *fat* as its major fuel. Fatty acids are also important fuels for exercising skeletal muscle and are the preferred substrate for normal cardiac metabolism. In these tissues, fatty acids are completely oxidized to carbon dioxide and water. The end products of hepatic fatty acid oxidation are the ketone bodies 3-*hydroxybutyrate* and *acetoacetate*. These compounds cannot be oxidized by the liver but are exported to serve as important fuels in peripheral tissues, particularly the brain, where ketone bodies can partially substitute for glucose during periods of fasting.

Genetic defects have been identified in almost all the known steps in the fatty acid oxidation pathway; all are recessively inherited (Table 106.1).

Clinical manifestations characteristically involve tissues with a high β-oxidation flux, including liver, skeletal, and cardiac muscle, and are age dependent. The most common early presentation is an acute episode of life-threatening coma, hepatic encephalopathy, and hypoglycemia with or without hyperammonemia induced by a period of fasting or illness in the first 2-4 years of life. After about age 6 years, muscle symptoms predominate in the disorders of long-chain fatty acid oxidation, including myopathy, fatiguability, and recurrent rhabdomyolysis. The latter is often brought on by excess activity or exercise. Cardiomyopathy can occur at any age in individuals with long-chain defects and may be exacerbated with acute episodes of illness. Patients with fatty acid oxidation defects are often asymptomatic when well. Acutely presenting disease may be misdiagnosed as **Reye syndrome** or, if fatal, as **sudden unexpected infant death**. In some circumstances, clinical manifestations appear to arise from toxic effects of fatty acid metabolites rather than inadequate energy production. These circumstances include certain long chain fatty acid oxidation disorders (deficiencies of long chain 3-hydroxyacyl dehydrogenase **[LCHAD]**, carnitine palmitoyltransferase-IA **[CPT-IA]**, or mitochondrial trifunctional protein [**MTP**; also known as *TFP*]) in which the presence of a homozygous affected fetus increases the risk of a life-threatening illness in the heterozygote mother, resulting in **acute fatty liver of pregnancy** (AFLP) or **preeclampsia with HELLP** (hemolysis, elevated liver enzymes, low platelets) syndrome. The mechanism of these obstetric complications is likely accumulation of toxic intermediates. Malformations of the brain and kidneys have been described in severe deficiencies of electron transfer flavoprotein **(ETF)**, ETF dehydrogenase **(ETF-DH)**, and carnitine palmitoyltransferase-II **(CPT-II)**, which might reflect in utero toxicity of fatty acid metabolites or a developmental role for these enzymes. Progressive retinal degeneration, peripheral neuropathy, and chronic progressive liver disease have been identified in LCHAD and MTP deficiency.

Fatty acid oxidation disorders are easily overlooked because the only specific clue to the diagnosis may be the finding of inappropriately *low* concentrations of plasma or urinary ketones in an infant who has hypoglycemia unless specialized metabolic testing is performed. Genetic defects in ketone body utilization may also be overlooked because ketonemia is an expected finding with fasting hypoglycemia. Newborn screening programs using tandem mass spectrometry detect characteristic plasma acylcarnitine profiles in most of these disorders, allowing early and presymptomatic diagnosis. Screening programs have demonstrated that all the fatty acid oxidation disorders combined are among the most common inborn errors of metabolism, at least in predominantly White populations.

Figures 106.1 and 106.2 outline the steps involved in the oxidation of a typical long chain fatty acid. In the *carnitine cycle,* long chain fatty acids are transported across the barrier of the inner mitochondrial membrane as acylcarnitine esters. Medium-chain fatty acids, which are commonly provided as medium-chain triglyceride supplementation in infants who are failing to thrive, can bypass the carnitine cycle and enter the mitochondrial β-oxidation cycle directly. Within the mitochondria, successive rounds of the four-step *β-oxidation cycle* convert the **coenzyme A (CoA)**–activated fatty acids to acetyl-CoA units. Two or three different chain-length-specific isoenzymes are needed for each of these β-oxidation steps to accommodate the different chain-length fatty acyl-CoA species. The electrons generated in the first β-oxidation step (acyl-CoA dehydrogenase) are carried by the *electron transfer pathway* to the *electron transport chain* at the level of coenzyme Q for adenosine triphosphate production, whereas electrons generated from the third step (3-hydroxyacyl-CoA dehydrogenase) enter the *electron transport chain* at the level of complex 1. Most of the acetyl-CoA generated from fatty acid β-oxidation in the liver flows through the *pathway of ketogenesis* to form 3-hydroxybutyrate and acetoacetate, whereas in muscle and heart, the fatty acids are completely oxidized to CO_2 and water through oxidative phosphorylation. It has been demonstrated that the enzymes of fatty acid oxidation physically and functionally interact with each other and those of the mitochondrial electron transport chain.

DEFECTS IN THE β-OXIDATION CYCLE

Medium-Chain Acyl-CoA Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase **(MCAD)** deficiency is the most common fatty acid oxidation disorder. The disorder shows a strong founder effect; most patients have a northwestern European ancestry, and the majority of these patients have at least one copy of a common MCAD missense pathogenic variant, an A-G transition at cDNA position 985 (c.985A>G) that changes a lysine to glutamic acid at residue 329 (p.Lys329Glu).

Clinical Manifestations

Previously undiagnosed affected patients usually present in the first 3 months to 5 years of life with episodes of acute illness triggered by prolonged fasting (>12-16 hours). Signs and symptoms include vomiting and lethargy, which rapidly progress to coma or seizures and cardiorespiratory collapse. Sudden unexpected infant death may occur. The liver may be slightly enlarged with fat deposition. Episodes are rare until the infant is beyond the first few months of life, presumably because of more frequent feedings at a younger age. Affected older infants are at higher risk of symptoms as they begin to fast through the night or are exposed to fasting stress during an intercurrent childhood illness. Presentation in the first days of life with neonatal hypoglycemia has been reported in newborns who were fasted inadvertently or were being breastfed exclusively and thus are at higher risk because of early reduced caloric intake. A diagnosis of MCAD has occasionally been documented in previously healthy teenage and adult individuals, indicating that even patients who have been asymptomatic in infancy are still at risk for metabolic decompensation if exposed to sufficient periods of fasting. An unknown number of patients may remain asymptomatic. Prior to routine newborn screening testing, as many as 25% of MCAD-deficient patients died or suffered severe brain injury from their first episode. Most patients are diagnosed in the newborn period by **blood spot acylcarnitine screening** (part of newborn screening), allowing the initiation of early intervention and prevention of most signs and symptoms.

Laboratory Findings

During acute episodes, hypoglycemia is usually present. Plasma and urinary ketone concentrations are inappropriately low **(hypoketotic**

Table 106.1 Mitochondrial Fatty Acid Oxidation Disorders: Clinical and Biochemical Features

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
Carnitine transporter	*SLC22A5*	Cardiomyopathy, skeletal myopathy, liver disease, sudden death, endocardial fibroelastosis, cardiac arrhythmia	↓ Total and free carnitine; normal acylcarnitines, acylglycine, and organic acids; prenatal and newborn possible diagnosis reported
Long chain fatty acid transporter	*FATP1-6*	Rare, acute liver failure in childhood requiring liver transplantation	↓ Intracellular C_{14}-C_{18} fatty acids; ↓ fatty acid oxidation; disease-causing pathogenic variants have not been identified in patients
Carnitine palmitoyl transferase-IA	*CPTIA*	Liver failure, renal tubulopathy, and sudden death reported; maternal preeclampsia; HELLP syndrome association described in a few patients	Normal or ↑ free carnitine; normal acylcarnitines, acylglycine, and organic acids; newborn screening diagnosis reported
Carnitine acylcarnitine translocase	*SLC25A20*	Chronic progressive liver failure, persistent ↑ NH_3, hypertrophic cardiomyopathy	Normal or ↓ free carnitine, abnormal acylcarnitine profile; newborn screening diagnosis reported
Carnitine palmitoyl transferase-II	*CPT2*	Early and late onset types; liver failure, encephalopathy, skeletal myopathy, cardiomyopathy, renal cystic changes; adult form with acute rhabdomyolysis, myoglobinuria	Normal or ↓ free carnitine; abnormal acylcarnitine profile; newborn screening diagnosis possible
Short chain acyl-CoA dehydrogenase	*ACADS*	Biochemical phenotype only; no consistent clinical phenotype	Normal or ↓ free carnitine; elevated urine ethylmalonic acid; inconsistently abnormal acylcarnitine profile
Medium-chain acyl-CoA dehydrogenase	*ACADM*	Hypoglycemia, hepatic encephalopathy, sudden death; maternal preeclampsia, HELLP syndrome association described rarely, possible long QT interval	Normal or ↓ free carnitine, ↑ urine acylglycine, plasma C_6-C_{10} free fatty acids, ↑ C_8-C_{10} acyl-carnitine; newborn screening diagnosis possible
Very long chain acyl-CoA dehydrogenase (VLCAD)	*ACADVL*	Dilated cardiomyopathy, arrhythmias, hypoglycemia, and hepatic steatosis; late-onset, stress-induced rhabdomyolysis, episodic myopathy	Normal or ↓ free carnitine; ↑ plasma $C_{14:1}$, C_{14} acylcarnitine; ↑ plasma C_{10}-C_{16} free fatty acids; prenatal and newborn screening diagnosis possible
ETF dehydrogenase*	*ETFDH*	Nonketotic fasting hypoglycemia, congenital anomalies, milder forms of liver disease, cardiomyopathy, and skeletal myopathy	Normal or ↓ free carnitine; increased ratio of acyl:free carnitine, ↑ blood acylcarnitines; characteristic urine organic acids and acylglycines; newborn screening diagnosis possible
ETF-α*	*ETFA*	Nonketotic fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy; skeletal myopathy also described	Normal or ↓ free carnitine; increased ratio of acyl:free carnitine; ↑ acylcarnitines; urine organic acid and acylglycines; newborn screening diagnosis possible
ETF-β*	*ETFB*	Fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy; skeletal myopathy also described	Normal or ↓ free carnitine; increased ratio of acyl:free carnitine, ↑ blood acylcarnitines; urine organic acid and acylglycines; newborn screening diagnosis possible
Short chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD)	*HAD1*	Hyperinsulinemic hypoglycemia, cardiomyopathy, myopathy	Normal or ↓ free carnitine, elevated free fatty acids, inconsistently abnormal urine organic acid, ↑ 3-OH glutarate, ↑ plasma C_4-OH acylcarnitine; newborn screening diagnosis possible
Long chain L-3-hydroxyacyl-CoA dehydrogenase (LCHAD)	*HADHA*	Maternal preeclampsia, HELLP syndrome, and AFLP association described frequently; see MTP later for clinical manifestations	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines; newborn screening diagnosis possible
MTP	*HADHA, HADHB*	Severe cardiac and skeletal myopathy, hypoglycemia, acidosis, hyper NH_3, sudden death, elevated liver enzymes, retinopathy; maternal preeclampsia, HELLP syndrome, and AFLP association described frequently	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines; newborn screening diagnosis possible
Long chain 3-ketoacyl-CoA thiolase	*HADHB*	Severe neonatal presentation, hypoglycemia, acidosis, ↑ creatine kinase, cardiomyopathy, neuropathy, and early death	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ 2-*trans*, 4-*cis*-decadienoylcarnitine; newborn screening diagnosis possible
Short chain 2,3-enoyl-CoA hydratase	*ECHS1*	Leigh disease, lactic acidosis, seizures, cystic degeneration of white matter, microcephaly, metabolic acidosis, extrapyramidal dystonia, dilated cardiomyopathy	Abnormal organic acids, 2-methacrylglycine, 2-methyl-2,3 dihydroxybutyrate, also S-(2-carboxypropyl)cysteine, S-(2-carboxyethyl) cysteamine; acylcarnitine shows ↑ C4OH (inconsistently)

Table 106.1 Mitochondrial Fatty Acid Oxidation Disorders: Clinical and Biochemical Features—cont'd

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
2,4-Dienoyl-CoA reductase	*DECR1*	Only one patient described, hypotonia in the newborn, mainly severe skeletal myopathy and respiratory failure; hypoglycemia is rare	Normal or ↓ free carnitine, ↑ acyl:free carnitine ratio, normal urine organic acids and acylglycines
HMG CoA synthetase	*HMGCS2*	Hypoketosis and hypoglycemia, rarely myopathy	↑ Total plasma fatty acids; enzyme studies in biopsied liver may be diagnostic; genetic testing preferred
HMG CoA lyase	*HMGCL*	Hypoketosis and hypoglycemia, rarely myopathy	Normal free carnitine, ↑ C_5-OH, and methylglutaryl-carnitine; enzymes studies in fibroblasts may be diagnostic
Monocarboxylate transporter 1 (MCT1)	*SLC16A1*	Severe fasting-induced ketoacidosis, rarely hypoglycemia	Profound ketoacidosis; no specific biomarkers yet identified

*Also known as glutaric acidemia type II or multiple acyl-CoA dehydrogenase defect (MADD).
AFLP, Acute fatty liver of pregnancy; CoA, coenzyme A; ETF, electron transport flavoprotein; HELLP, hemolysis, elevated liver enzymes, low platelets; MTP, mitochondrial trifunctional protein; NH_3, ammonia.
From Shekhawat PS, Matern D, Strauss AW. Fetal fatty oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management. *Pediatr Res.* 2005;57:78R–84R.

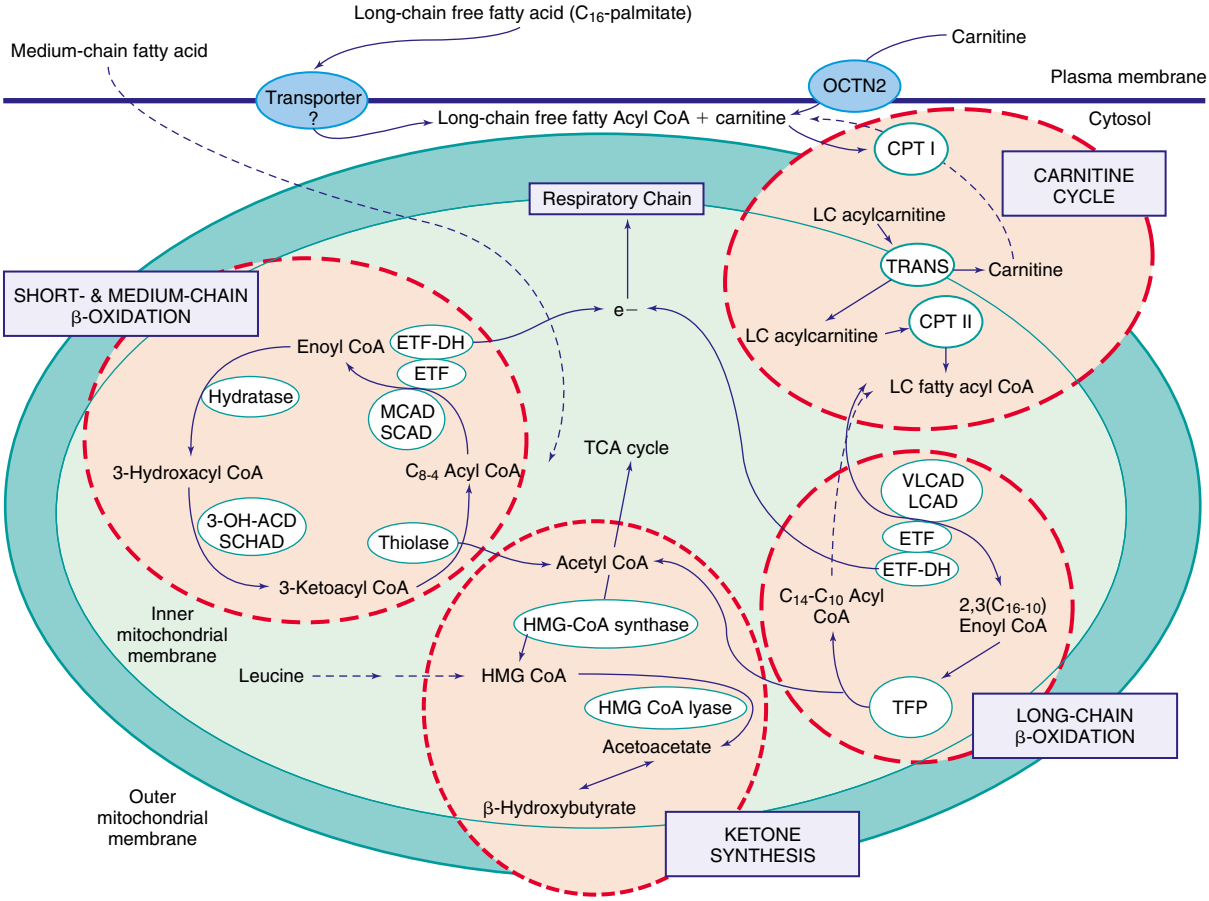

Fig. 106.1 Mitochondrial fatty acid oxidation. Carnitine enters the cell through the action of the organic cation/carnitine transporter (OCTN2). Palmitate, a typical 16-carbon long chain (LC) fatty acid, is transported across the plasma membrane and can be activated to form an LC fatty acyl coenzyme A (CoA). It then enters into the carnitine cycle, where it is transesterified by carnitine palmitoyltransferase-I (CPT-I), translocated across the inner mitochondrial membrane by carnitine/acylcarnitine translocase (TRANS), and then reconverted into an LC fatty acyl-CoA by carnitine palmitoyltransferase-II (CPT-II) to undergo β-oxidation. Very LC acyl-CoA dehydrogenase (VLCAD/LCAD) leads to the production of (C_{16}-C_{10}) 2,3-enoyl CoA. Mitochondrial trifunctional protein (MTP) contains the activities of enoyl CoA hydratase (hydratase), 3-OH-hydroxyacyl-CoA dehydrogenase (3-OH-ACD), and β-ketothiolase (thiolase). Acetyl-CoA, a reduced form of flavin adenine dinucleotide (FADH), and a reduced form of nicotinamide adenine dinucleotide (NADH) are produced. Medium- and short chain fatty acids (C8-4) can enter the mitochondrial matrix independent of the carnitine cycle. Medium-chain acyl-CoA dehydrogenase (MCAD), short chain acyl-CoA dehydrogenase (SCAD), and short chain hydroxy acyl-CoA dehydrogenase (SCHAD) are required. Acetyl-CoA can then enter the Krebs (TCA) cycle. Electrons are transported from FADH to the respiratory chain via the electron transfer flavoprotein (ETF) and the electron transfer flavoprotein dehydrogenase (ETF-DH). NADH enters the electron transport chain through complex I. In the liver, acetyl-CoA can be converted into hydroxymethylglutaryl (HMG) CoA by β-hydroxy-β-methylglutaryl-CoA synthase (HMG CoA synthase) and then the ketone body acetoacetate by the action of β-hydroxy-β-methylglutaryl-CoA lyase (HMG-CoA lyase).

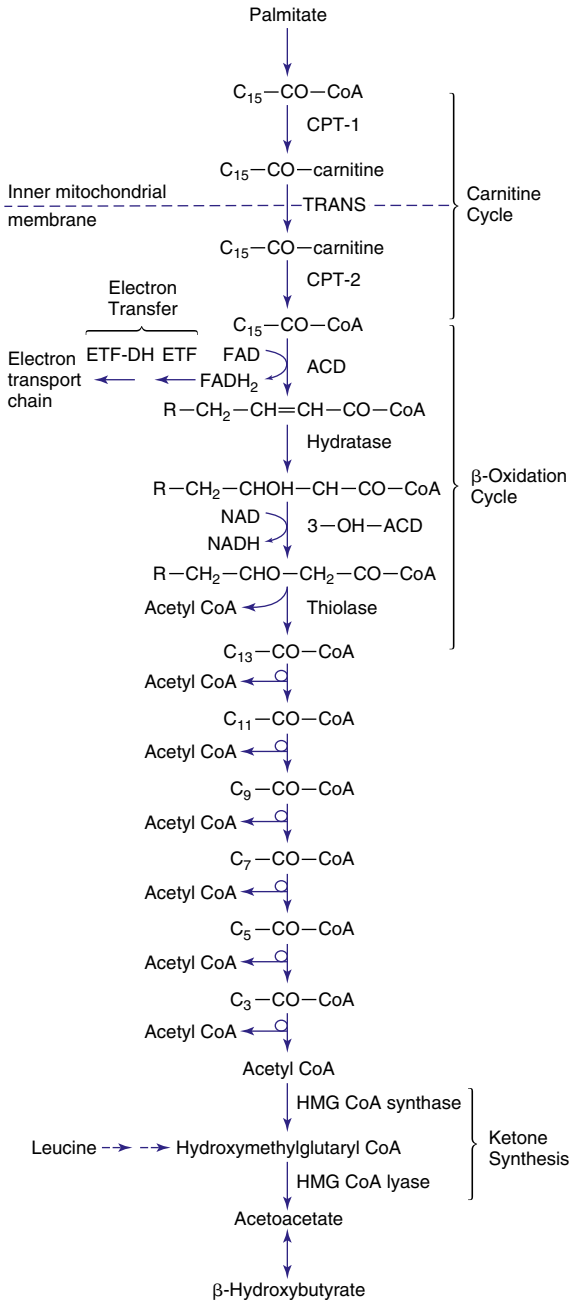

Fig. 106.2 Pathway of mitochondrial oxidation of palmitate, a typical 16-carbon long chain fatty acid. Enzyme steps include carnitine palmitoyltransferase (CPT) 1 and 2, carnitine/acylcarnitine translocase (TRANS), electron transfer flavoprotein (ETF), ETF dehydrogenase (ETF-DH), acyl-CoA dehydrogenase (ACD), enoyl CoA hydratase (hydratase), 3-hydroxy-acyl-CoA dehydrogenase (3-OH-ACD), β-ketothiolase (thiolase), β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase, and lyase.

hypoglycemia). Because of the hypoketonemia, there is little or no metabolic acidosis, which is typically present in children with hypoglycemia not caused by fatty acid oxidation disorders. Liver function tests (LFTs) are abnormal, with elevations of liver enzymes (alanine transaminase, aspartate transaminase), elevated blood ammonia, and prolonged prothrombin and partial thromboplastin times. Liver biopsy at times of acute illness shows microvesicular or macrovesicular steatosis from triglyceride accumulation. During fasting stress or acute illness, urinary organic acid profiles by gas chromatography/mass spectrometry show inappropriately low concentrations of ketones and elevated levels of medium-chain dicarboxylic acids (adipic, suberic, and sebacic acids) that derive from microsomal and peroxisomal omega oxidation of accumulated medium-chain fatty acids. Plasma and tissue concentrations of total carnitine are reduced to 25–50% of normal, and the fraction of total esterified carnitine is increased. This pattern of **secondary carnitine deficiency** is seen in most fatty acid oxidation defects and reflects competition between increased acylcarnitine levels and free carnitine for transport at the renal tubular plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA, and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase deficiencies, which do not manifest secondary carnitine deficiency.

Diagnostic metabolite patterns for MCAD deficiency include increased plasma $C_{6:0}$, $C_{8:0}$, $C_{10:0}$, and $C_{10:1}$ acylcarnitine species and increased urinary acylglycines, including hexanoylglycine, suberylglycine, and 3-phenylpropionylglycine. Newborn screening, performed in all states in the United States and in many other countries, can detect presymptomatic MCAD deficiency based on these abnormal acylcarnitines in filter paper blood spots. The diagnosis can be confirmed by demonstrating the common Ala985Gly pathogenic variant or sequencing the MCAD gene. A second common variant, Thr199Cys, has been detected in infants identified by newborn screening. Interestingly, this allele has not been seen to date in symptomatic MCAD patients, likely because of the significant residual activity of this milder pathogenic variant.

Treatment

Acute illnesses should be promptly treated with intravenous (IV) fluids containing 10% dextrose to correct or prevent hypoglycemia and to suppress lipolysis as rapidly as possible (see Chapter 113). Chronic therapy consists of avoiding fasting. This usually requires simply adjusting the diet to ensure that overnight fasting periods are limited to <6 hours in infants under 6 months of age, <8 hours for infants 6-24 months of age, and <12 hours for older children. Restricting dietary fat or treatment with carnitine is unnecessary. There is likely no need for active therapeutic intervention for individuals with the Thr199Cys variant.

Prognosis

Up to 25% of previously undiagnosed patients may die during their first attack of illness. There is often a history of a previous sibling death that is presumed to be from an unrecognized MCAD deficiency. Some patients may sustain permanent brain injury during an attack of profound hypoglycemia. For survivors without brain damage and essentially all babies identified by newborn screening, the prognosis is excellent because progressive cognitive impairment or cardiomyopathy does not occur in MCAD deficiency. Fasting tolerance improves with age, and the risk of decompensation decreases. Because as many as 35% of affected patients have never had an episode, testing of siblings of affected patients is important to detect asymptomatic family members who did not receive newborn screening.

Very Long Chain Acyl-CoA Dehydrogenase Deficiency

Very long chain acyl-CoA dehydrogenase **(VLCAD)** deficiency is the second most common diagnosed disorder of fatty acid oxidation. It was originally termed "long chain acyl-CoA dehydrogenase deficiency" before the existence of the inner mitochondrial membrane-bound VLCAD was known. *All patients previously diagnosed as having long chain acyl-CoA dehydrogenase deficiency have* VLCAD *gene defects.* Patients with VLCAD deficiency have no ability to oxidize physiologic long chain fatty acids and are usually more severely affected than those with MCAD deficiency, who have a milder oxidative defect. VLCAD deficiency presents earlier in infancy and has more chronic problems with muscle weakness or episodes of muscle pain and rhabdomyolysis. Cardiomyopathy may be present during acute attacks provoked by fasting. The left ventricle may be hypertrophic or dilated and may show poor contractility on echocardiography. Sudden unexpected death has occurred in several patients, but most who survive the initial episode show improvement, including normalization of cardiac function.

Other physical and routine laboratory features are similar to those of MCAD deficiency, including secondary carnitine deficiency. The urinary organic acid profile shows a nonketotic dicarboxylic aciduria with increased levels of $C_{6\text{-}12}$ dicarboxylic acids. Diagnosis may be suggested by an abnormal acylcarnitine profile with plasma or blood spot $C_{14:0,\ 14:1,\ 14:2}$ acylcarnitine species. However, the specific diagnosis requires pathogenic variant analysis of the *VLCAD* gene. Newborn screening by tandem mass spectrometry of dried blood spots is effective in identifying early/severe disease, though it can miss milder, later-onset cases. A common mild variant is identified by a newborn screen that typically predicts later-onset disease. Treatment has traditionally been based primarily on avoidance of fasting for >8-12 hours depending on age, along with supplementation with medium-chain triglycerides. Triheptanoin (Dojolvi) has been approved as a treatment for VLCAD deficiency and for all other disorders of long-chain fatty acid oxidation. The odd-chain fat heptanoate (C7) released from this triglycerol provides acetyl-CoA for the tricarboxylic acid cycle *and* propionyl-CoA, which is metabolized through methylmalonyl-CoA to succinyl-CoA and succinate. This anaplerotic effect essentially eliminates hypoglycemia in long-chain fatty acid oxidation disorder patients and significantly improves heart function in patients with cardiomyopathy. However, although heptanoin does reduce the incidence, rhabdomyolysis remains a major problem in treated patients. This finding led to the recognition of previously unrecognized inflammation as a component of these disorders, likely caused by the accumulation of a high level of proinflammatory long-chain complex lipids. Patients can develop a secondary carnitine deficiency; however, the need for replacement therapy remains unclear. If the free carnitine level in blood is <10 μM, supplementation with 25-50 mg/kg of oral carnitine (with a maximum of 1,000 mg/day) may be helpful, especially in the face of cardiomyopathy or significant muscular symptoms.

Short Chain Acyl-CoA Dehydrogenase Deficiency

A small number of patients with two null pathogenic variants in the short chain acyl-CoA dehydrogenase (SCAD) gene have been described with a variable phenotype. Most individuals classified as being SCAD deficient actually have polymorphic DNA changes in the *SCAD* gene; two common polymorphisms are Gly185Ser and Arg-147Trp, present in biallelic fashion in 7% of the population. Although SCAD deficiency was originally reported with a wide range of symptoms, it was likely a result of the frequency of the common polymorphisms in unrelated disease rather than a true causal relationship. Long-term follow-up of infants identified by newborn screening has failed to demonstrate a convincing, consistent phenotype, and thus SCAD deficiency is best described as a biochemical phenotype rather than a disease. The diagnosis is indicated by elevated levels of butyrylcarnitine (C4-carnitine) on newborn blood spots or plasma and increased excretion of urinary ethylmalonic acid and butyrylglycine. These metabolic abnormalities are most pronounced in patients with null pathogenic variants and are variably present in patients who are homozygous for the common polymorphisms. In the context of metabolic abnormalities consistent with SCAD deficiency in patients with significant clinical problems, a thorough evaluation for *another* unrelated diagnosis is indicated. There is no need for treatment of individuals with SCAD deficiency.

Long Chain 3-Hydroxyacyl-CoA Dehydrogenase/ Mitochondrial Trifunctional Protein Deficiency

The LCHAD enzyme is part of the MTP, which also contains two other steps in β-oxidation: long chain 2,3-enoyl CoA hydratase and long chain β-ketothiolase. MTP is a heterotetrameric protein composed of two α and two β chains derived from distinct contiguous genes, *HADHA* and *HADHB,* that share a common promoter. In some patients, only the LCHAD activity of the MTP is affected **(LCHAD deficiency)**, whereas others have deficiencies of all three activities **(MTP deficiency)**.

Clinical manifestations include attacks of acute hypoketotic hypoglycemia similar to VLCAD deficiency; however, patients often show evidence of more severe disease, including cardiomyopathy, muscle cramps and weakness, and abnormal liver function (cholestasis). Pigmented retinopathy leading to blindness, progressive liver failure, peripheral neuropathy, and rhabdomyolysis are also present, with retinopathy being more severe in isolated LCHAD deficiency and neuropathy worse in combined MTP defects. Life-threatening obstetric complications (AFLP, HELLP syndrome) have been observed in heterozygous mothers carrying homozygous fetuses affected with LCHAD/MTP deficiency. Sudden unexpected infant death may occur, especially in populations where tandem mass spectrometry newborn screening is not routine. The **diagnosis** is indicated by elevated levels of blood spot or plasma 3-hydroxy acylcarnitines of chain lengths C_{16}-C_{18}. The urinary organic acid profile in patients may show increased levels of 3-hydroxydicarboxylic acids of chain lengths C_6-C_{14}. Secondary carnitine deficiency is common. A common pathogenic variant in the α subunit, E474Q, is seen in more than 60% of isolated LCHAD-deficient patients. This pathogenic variant in the fetus is especially associated with the obstetric complications, but other pathogenic variants in either subunit may also be linked to maternal illness.

Treatment is similar to that for VLCAD deficiency; that is, avoiding fasting stress, triheptanoin, and potentially carnitine. Docosahexaenoic acid may slow the retinal changes but does not prevent them. None of these therapeutic measures likely affect the development or progression of peripheral neuropathy. Liver transplantation has been attempted in patients with severe liver failure but does not ameliorate the metabolic abnormalities or prevent the myopathic or retinal complications.

Short Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency

Very few patients with proven pathogenic variants of short chain 3-hydroxyacyl-CoA dehydrogenase **(SCHAD)** have been reported. Most cases with recessive pathogenic variants of the SCHAD gene have presented with episodes of hypoketotic hypoglycemia that was caused by *hyperinsulinism*. In contrast to those with other forms of fatty acid oxidation disorders, these patients required specific therapy with diazoxide for hyperinsulinism to avoid recurrent hypoglycemia. A single patient with compound heterozygous pathogenic variants presented with fulminant hepatic failure at age 10 months. The SCHAD protein has a nonenzymatic function in which it directly interacts with glutamate dehydrogenase (GDH) to inhibit its activity. In the absence of SCHAD protein, this inhibition is removed, leading to upregulation of GDH enzyme activity, a recognized cause of *hyperinsulinism,* usually from activating pathogenic variants of the *GDH* gene. Severe deficiency of SCHAD protein often presents predominantly as **protein-sensitive hypoglycemia** rather than as fasting hypoglycemia. It appears that if SCHAD protein is present, inhibition of GDH is maintained even when there is no SCHAD enzyme activity; these patients may present with a more traditional fatty acid oxidation defect. Specific metabolic markers for SCHAD deficiency include elevated plasma C4-hydroxy acylcarnitine and urine 3-hydroxyglutaric acid. Successful newborn screening for SCHAD deficiency has been recorded, but the sensitivity of the process has not yet been established.

Treatment of SCHAD-deficient patients with hyperinsulinism is with diazoxide. There is insufficient experience with the non-hyperinsulinemic form of SCHAD deficiency at present to recommend treatment modalities, but prevention of fasting seems advisable.

Short Chain 2,3-Enoyl-CoA Hydratase Deficiency

This rare disorder, resulting from pathogenic variants in the *ECHS1* gene, was identified through exome sequencing. The disorder affects a shared pathway of short chain fatty acid and valine metabolism. The clinical phenotypes are more characteristic of mitochondrial disorders of pyruvate metabolism with predominantly a **Leigh-like disease** (see Chapters 108 and 638.2) with profound and often-fatal lactic acidosis. No treatment modalities or specific biomarkers have been established. Several patients were found to excrete increased levels of methacrylylglycine, a highly reactive and potentially toxic intermediate; 2-methyl-2.3 dihydroxybutyrate; *S*-(2-carboxypropyl) cysteine; and *S*-(2-carboxpropyl) cysteamine.

DEFECTS IN THE CARNITINE CYCLE

Plasma Membrane Carnitine Transport Defect (Primary Carnitine Deficiency)

Primary carnitine deficiency is the only genetic defect in which carnitine deficiency is the *cause,* rather than the consequence, of impaired fatty acid oxidation. The most common presentation is progressive **cardiomyopathy** with or without **skeletal muscle weakness** beginning at age 1-4 years. A smaller number of patients may present with fasting hypoketotic hypoglycemia in the first year of life, before the cardiomyopathy becomes evident. Cardiac arrythmias are often seen. A common pathogenic variant causes late-onset disease in the Faroe Islands with sudden death caused by cardiomyopathy and/or arrhythmia. The underlying defect involves the high-affinity plasma membrane sodium gradient–dependent carnitine transporter encoded by the *SLC22A5* gene that is expressed at high levels in heart, muscle, and kidney. This transporter is responsible both for maintaining intracellular carnitine concentrations 20- to 50-fold higher than plasma concentrations and for renal conservation of carnitine.

Diagnosis of the carnitine transporter defect is aided by patients having extremely reduced carnitine levels in plasma and muscle (1–2% of normal). Heterozygote parents have plasma carnitine levels approximately 50% of normal. Fasting ketogenesis may be normal because liver carnitine transport is normal, but it may become impaired if dietary carnitine intake is interrupted. The fasting urinary organic acid profile may show a hypoketotic dicarboxylic aciduria pattern if hepatic fatty acid oxidation is impaired but is otherwise unremarkable. The defect in carnitine transport can be demonstrated clinically by the severe reduction in renal carnitine threshold or by in vitro assay of carnitine uptake using cultured fibroblasts or lymphoblasts. *SLC22A5* sequencing is the most common method to confirm the diagnosis. A common relatively severe pathogenic variant has been described in the Chinese population in Taiwan. **Treatment** with pharmacologic doses of oral carnitine (100-300 mg/kg/day) is highly effective in correcting the cardiomyopathy and muscle weakness, as well as any impairment in fasting ketogenesis. Muscle total carnitine concentrations remain <5% of normal on treatment.

Carnitine Palmitoyltransferase-IA Deficiency

Several dozen infants and children have been described with a deficiency of the liver and kidney CPT-I isozyme (CPT-IA). **Clinical manifestations** include fasting-induced hypoketotic hypoglycemia, occasionally with extremely abnormal LFTs and, rarely, with renal tubular acidosis. The heart and skeletal muscles are not involved because the muscle isozyme is unaffected. Fasting urinary organic acid profiles sometimes show a hypoketotic C_6-C_{12} dicarboxylic aciduria but may be normal. Plasma acylcarnitine analysis demonstrates mostly free carnitine with very little acylated carnitine. This observation has been used to identify CPT-IA deficiency on newborn screening by tandem mass spectrometry. CPT-IA deficiency is the only fatty acid oxidation disorder in which plasma total carnitine levels may be elevated, often to 150–200% of normal. This phenomenon is explained by the absence of inhibitory effects of long chain acylcarnitines on the renal tubular carnitine transporter in CPT-IA deficiency. The enzyme defect can be demonstrated in cultured fibroblasts or lymphoblasts. CPT-IA deficiency in the fetus has been associated in a single case report with AFLP in the mother. A common variant in the *CPTIA* gene (c.1436C>t, p.Pro479Leu) has been identified in individuals of Inuit background in the United States, Canada, and Greenland. This variant is associated with an increased risk for sudden infant death syndrome (SIDS) in the Inuit population. The variant can be detected by newborn screening; enzyme activity is reduced by 80%, and regulation by malonyl-CoA is lost. It has not been established whether this variant is a pathologic enzyme variant or an adaptation to ancient Inuit high-fat diets. Another pathogenic variant is common in the Ashkenazi Jewish population and leads to infantile symptoms. **Treatment** for the severe form of CPT-IA deficiency that is found in non-Inuit populations is similar to that for VLCAD deficiency, with avoidance of situations where fasting ketogenesis is necessary and use of triheptanoin to provide an anaplerotic fuel source. The need for treatment of the Inuit variant has not yet been determined.

Carnitine:Acylcarnitine Translocase Deficiency

This defect of the inner mitochondrial membrane carrier protein for long chain acylcarnitines blocks the entry of long chain fatty acids into the mitochondria for oxidation. The clinical phenotype of this disorder is driven by a typically severe and generalized impairment of fatty acid oxidation. Most newborn patients present with attacks of fasting-induced hypoglycemia, hyperammonemia, and cardiorespiratory collapse. All symptomatic newborns have had evidence of cardiomyopathy and muscle weakness. Several patients with a partial translocase deficiency and milder disease without cardiac involvement have also been identified. No distinctive urinary or plasma organic acids are noted, although increased levels of plasma long chain acylcarnitines of chain lengths C_{16}-C_{18} are reported, not distinguishable from the pattern seen in CPT-II deficiency (see later). **Diagnosis** can be confirmed using genetic analysis. Functional carnitine:acylcarnitine translocase activity can be measured in cultured fibroblasts or lymphoblasts. **Treatment** is similar to that of VLCAD deficiency and is particularly effective in reducing the hyperammonemia that is often otherwise persistent in severe patients.

Carnitine Palmitoyltransferase-II Deficiency

Three forms of CPT-II deficiency have been described. A **severe neonatal lethal** presentation associated with a profound enzyme deficiency, and early death has been reported in newborns with hypoglycemia and hyperammonemia in association with dysplastic kidneys, cerebral malformations, and mild facial anomalies. A milder defect is associated with an **adult presentation** of episodic rhabdomyolysis. The first episode usually does not occur until late childhood or early adulthood. Attacks are frequently precipitated by prolonged exercise. There is aching muscle pain and myoglobinuria that may be severe enough to cause renal failure. Hypoglycemia has not been described, but fasting may contribute to attacks of myoglobinuria. Muscle biopsy shows increased deposition of neutral fat. This adult myopathic presentation of CPT-II deficiency is associated with a common *CPT2* pathogenic variant, c.338C>T, p.Ser113Leu, seen as a recurrent pathogenic variant in the Ashkenazi Jewish population. This pathogenic variant produces a heat-labile protein that is unstable to increased muscle temperature during exercise that may contribute to the myopathic presentation. A third **intermediate form** of CPT-II deficiency presents in infancy or early childhood with fasting-induced hepatic failure, cardiomyopathy, and skeletal myopathy with hypoketotic hypoglycemia but is not associated with the severe developmental changes seen in the neonatal lethal presentation. This pattern of illness is similar to VLCAD deficiency, and management is identical. It is often caused by the presence of one severe pathogenic variant in combination with the mild c.338C>T variant.

Diagnosis of all forms of CPT-II deficiency can be made by a combination of molecular genetic analysis and demonstrating deficient enzyme activity in muscle or other tissues and in cultured fibroblasts. Severe and intermediate disease can be identified through newborn screening, but patients homozygous for the common mild variant typically have normal newborn screens.

DEFECTS IN THE ELECTRON TRANSFER PATHWAY

Electron Transfer Flavoprotein and Electron Transfer Flavoprotein Dehydrogenase Deficiencies (Glutaric Acidemia Type 2, Multiple Acyl-CoA Dehydrogenation Defects)

Electron transfer flavoprotein (ETF) and electron transfer flavoprotein dehydrogenase (ETF-DH) function to transfer electrons into the mitochondrial electron transport chain from dehydrogenation reactions catalyzed by VLCAD, MCAD, SCAD, and glutaryl-CoA dehydrogenase, four enzymes involved in branched-chain amino acid (BCAA) oxidation and sarcosine and dimethylglycine dehydrogenases. Deficiencies of ETF or ETF-DH produce illness that combines the features of impaired fatty acid oxidation and impaired oxidation of several amino acids. Complete deficiencies of either protein are associated with severe illness in the newborn period, characterized by acidosis, hypoketotic hypoglycemia, coma, hypotonia, cardiomyopathy, and

an unusual odor of sweaty feet caused by isovaleryl-CoA dehydrogenase inhibition. Some affected neonates have had congenital facial dysmorphism and polycystic kidneys similar to those in severe CPT-II deficiency, which suggests that toxic effects of accumulated metabolites may occur in utero. Most severely affected infants do not survive the neonatal period. Disorders of cellular or mitochondrial riboflavin transport or flavin adenine dinucleotide (FAD, an essential cofactor for the acyl-CoA dehydrogenases) have been identified with similar biochemical profiles to ETF and ETF-DH deficiency but with more variable features.

Diagnosis can be made from the newborn blood spot acylcarnitine profile and urinary organic acids; both tests show abnormalities corresponding to disruptions in the oxidation of fatty acids (ethylmalonate and C_6-C_{10} dicarboxylic acids), lysine (glutarate), and BCAAs (isovaleryl-, isobutyryl-, and 2-methylbutyrylglycine). The diagnosis can be confirmed by genetic testing of *ETFA, ETFB,* and *ETFDH*. If no pathogenic variants in these genes are identified, additional testing for the riboflavin transport and FAD synthesis genes should be pursued.

Partial deficiencies of ETF and ETF-DH produce a disorder that may mimic MCAD deficiency or other milder long-chain fatty acid oxidation defects with attacks of fasting hypoketotic coma. The urinary organic acid profile reveals primarily elevations of dicarboxylic acids and ethylmalonate, derived from short chain fatty acid intermediates. Secondary carnitine deficiency is present. Some patients with mild forms of ETF/ETF-DH deficiency may benefit from treatment with high doses of *riboflavin,* a precursor of the various flavoproteins involved in electron transfer.

DEFECTS IN THE KETONE SYNTHESIS PATHWAY

The final steps in production of ketones from mitochondrial fatty acid β-oxidation convert acetyl-CoA to acetoacetate through two enzymes of the HMG-CoA pathway (see Fig. 106.2).

β-Hydroxy-β-Methylglutaryl-CoA (HMG-CoA) Synthase Deficiency

See Chapter 103.6.

HMG-CoA synthase is the rate-limiting step in the conversion of acetyl-CoA derived from fatty acid β-oxidation in the liver to ketones. The presentation of deficiency is one of fasting hypoketotic hypoglycemia without evidence of impaired cardiac or skeletal muscle function. The urinary organic acid profile shows only a nonspecific hypoketotic dicarboxylic aciduria. Plasma and tissue carnitine levels are normal, in contrast to all the other disorders of fatty acid oxidation. A separate synthase enzyme, present in cytosol for cholesterol biosynthesis, is not affected. The HMG-CoA synthase defect is expressed only in the liver and kidney and cannot be demonstrated in cultured fibroblasts. The **diagnosis** can be made by genetic testing. *Avoiding fasting is usually a successful treatment.*

β-Hydroxy-β-Methylglutaryl-CoA Lyase Deficiency (3 Hydroxy-3-Methylgutaric Aciduria)

See Chapter 105.6.

DEFECTS IN KETONE BODY UTILIZATION

The ketone bodies β-hydroxybutyrate and acetoacetate are the end products of hepatic fatty acid oxidation and are important metabolic fuels for the brain during fasting. Three defects in utilization of ketones in brain and other peripheral tissues present as episodes of **hyperketotic coma**, with or without hypoglycemia.

Monocarboxylate Transporter-1 Deficiency

About 10 patients have been described with recurrent episodes of potentially lethal ketoacidosis, with or without hypoglycemia, caused by a deficiency of monocarboxylate transporter 1 (MCT1), a plasma membrane carrier encoded by *SLC16A1* that is required to transport ketones into tissues from plasma. Although the first cases identified were homozygous for inactivating pathogenic variants of *SLC16A1,* heterozygous carriers can also be affected. Affected patients develop severe ketoacidosis provoked by fasting or infections in their first years of life; hypoglycemia is not always present. The differential includes ketotic hypoglycemia associated with milder forms of glycogen storage disease, such as phosphorylase or phosphorylase kinase deficiency (see Chapter 107). **Treatment** for acute episodes includes IV dextrose to suppress lipolysis and inhibit ongoing ketogenesis. Long-term treatment includes avoidance of prolonged fasting stress. The **diagnosis** should be suspected by unusually severe ketosis and delayed suppression of ketones after starting treatment with dextrose. There are no specific metabolic markers or newborn screening methods. The diagnosis can be established by genetic sequencing of *SLC16A1*.

Succinyl-CoA:3-Ketoacid-CoA Transferase Deficiency

See Chapter 103.6.

The characteristic presentation of succinyl-CoA:3-ketoacid-CoA transferase **(SCOT)** deficiency is an infant with recurrent episodes of severe ketoacidosis induced by fasting. Plasma acylcarnitine and urine organic acid abnormalities do not distinguish SCOT deficiency from other causes of ketoacidosis. **Treatment** of episodes requires infusion of glucose and large amounts of bicarbonate until metabolic stability is reestablished. Patients usually exhibit inappropriate, persistent hyperketonemia even between episodes of illness. SCOT is responsible for activating acetoacetate in peripheral tissues, using succinyl CoA as a donor to form acetoacetyl-CoA. Deficient enzyme activity can be demonstrated in the brain, muscle, and fibroblasts from affected patients. The gene has been cloned, and numerous pathogenic variants have been characterized. The diagnosis is usually established by sequencing analysis of the *OXCT1* gene that encodes the SCOT enzyme.

β-Ketothiolase Deficiency

See Chapter 105.6.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

106.2 Disorders of Very Long Chain Fatty Acids and Other Peroxisomal Functions

Michael F. Wangler

PEROXISOMAL DISORDERS

Disorders of very long chain fatty acids (VLCFAs) fall within the broader group of peroxisomal diseases. The peroxisomal diseases are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is localized to the peroxisome. These disorders cause serious disability in childhood and occur more frequently and present a wider range of phenotypes than recognized in the past. Many, but not all, peroxisomal disorders are associated with elevations of VLCFAs.

Etiology

Peroxisomal disorders are subdivided into two major categories (Table 106.2). In the **peroxisomal biogenesis disorders (PBDs)**, the basic defect is the failure to import one or more proteins into the organelle. In the other group, defects affect a single peroxisomal protein (**single-enzyme defects**). The *peroxisome* is present in all cells except mature erythrocytes and is a subcellular organelle surrounded by a single membrane; there are >50 peroxisomal enzymes. Some enzymes are involved in the production and decomposition of hydrogen peroxide and others in lipid and amino acid metabolism. Peroxisomal enzymes have a unique system to ship them to the peroxisome that uses specific **peroxisome targeting sequences** (PTSs). These enzymes are first synthesized in their mature form on free polyribosomes and float free in the cytoplasm until their specific PTS is recognized. Most peroxisomal matrix proteins contain a **PTS1**, a short amino acid sequence at the carboxyl terminus. In addition, the amino-terminal–located **PTS2** is critical for the import of enzymes involved in plasmalogen

Table 106.2 Peroxisomal Disorder Classification, Disorders, and Genes

PEROXISOMAL BIOGENESIS DISORDERS	GENES
Peroxisome biogenesis disorder–Zellweger spectrum disorders (PBD-ZSD) Zellweger syndrome (severe PBD-ZSD) Neonatal adrenoleukodystrophy (intermediate PBD-ZSD) Infantile Refsum disease (mild PBD-ZSD)	*PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26*
Rhizomelic chondrodysplasia punctata, types 1 and 5 (RCDP1 and RCDP5)	*PEX7* and *PEX5*, respectively
SINGLE-ENZYME DEFECTS	
X-linked adrenoleukodystrophy	*ABCD1*
Acyl-CoA oxidase deficiency	*ACOX1*
D-Bifunctional protein deficiency	*HSD17B4*
2-Methylacyl-CoA racemase deficiency	*AMACR*
Rhizomelic chondrodysplasia punctata, types 2 and 3 (RCDP2 and RCDP3)	*AGPS, GNPAT*
Adult Refsum disease	*PHYH*

Table 106.3 Abnormal Laboratory Findings Common to Zellweger Spectrum Disorders

Defective oxidation and abnormal accumulation of very long chain fatty acids
Peroxisomes absent to reduced in number
Catalase in cytosol
Deficient synthesis and reduced tissue levels of plasmalogens
Deficient oxidation and age-dependent accumulation of phytanic acid
Defects in certain steps of bile acid formation and accumulation of bile acid intermediates
Defects in oxidation and accumulation of L-pipecolic acid
Increased urinary excretion of dicarboxylic acids

and branched-chain fatty acid metabolism. The peroxisome biogenesis machinery then recognizes, binds, and targets PTS-containing proteins to the peroxisome. This process involves a complex series of reactions mediated by at least 23 distinct proteins. These proteins, referred to as *peroxins,* are encoded by the *PEX* genes. Pathogenic genetic variants in these genes are the cause of PBDs.

Epidemiology

Except for X-linked adrenoleukodystrophy (ALD), all the peroxisomal disorders listed in Table 106.2 are inherited as *autosomal recessive diseases*. ALD is the most common peroxisomal disorder, with an estimated incidence of 1 in 17,000 live births. The combined incidence of the other peroxisomal disorders is estimated to be 1 in 50,000 live births, although with broader newborn screening, it is expected that the actual incidences of all the disorders of VLCFAs will be more accurately established.

Pathology

Absence or reduction in the number of peroxisomes is pathognomonic for disorders of peroxisome biogenesis. In most cases, a close examination of cells in these patients reveals membranous sacs that lack the normal complement of matrix proteins; these are peroxisome "ghosts," and they indicate the inability of the cell to properly localize peroxisomal proteins. Pathologic changes are observed in most organs and include profound and characteristic defects in neuronal migration, micronodular cirrhosis of the liver, renal cysts, chondrodysplasia punctata, sensorineural hearing loss, retinopathy, congenital heart disease, and dysmorphic features.

Pathogenesis

Clinical pathologic changes of the PBDs are secondary to the underlying peroxisome biogenesis defect. As a result, multiple peroxisomal enzymes fail to function in the PBDs (Table 106.3). PBDs include the Zellweger spectrum disorders **(PBD-ZSD)** and one form of rhizomelic chondrodysplasia punctata **(PBD-RCDP)**, which are distinguished by clinical phenotype and differences in the extent of biogenesis abnormality. In PBDs, enzymes that are synthesized cannot be properly located to the peroxisome and are thus degraded abnormally quickly because they are unprotected outside the peroxisome. However, it has yet to be clarified as to how specific peroxisome defects lead to each of the pathologic manifestations.

Pathogenic variants in 14 different *PEX* genes have been identified in PBDs. For PBD-RCDP, *PEX7* pathogenic variants are the most common, but rarer *PEX5* pathogenic variants are seen. The pattern and severity of pathologic features vary with the nature of the import defects and the degree of import impairment leading to the severity spectrum of PBD-ZSD. These gene defects lead to disorders named prior to recognizing their relationship to the peroxisome, namely, Zellweger syndrome, neonatal ALD, infantile Refsum disease, and RCDP. The first three disorders are considered to be a form of *clinical continuum,* with Zellweger syndrome the most severe **(severe PBD-ZSD)**, infantile Refsum disease the least severe **(mild PBD-ZSD)**, and neonatal ALD being intermediate **(intermediate PBD-ZSD)**. For PBD-ZSD, 13 genes can be affected to result in autosomal recessive disease *(PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26)*. Specific gene defects cannot be distinguished by clinical features. Clinical severity varies with the degree to which protein import is impaired. Pathogenic variants that completely abolish import are often associated with the severe PBD-ZSD or Zellweger phenotype, whereas a missense variant, in which some degree of import function is retained, leads to the somewhat milder presentations. A defect in *PEX7* or, very rarely, *PEX5*, which depend on peroxisomal import that use PTS2, is associated with RCDP. *PEX7* defects that leave the import partially intact are associated with milder phenotypes, some of which resemble classic (adult) Refsum disease.

The genetic disorders that involve single peroxisomal enzymes usually have clinical manifestations that are more restricted and relate to the single biochemical defect. The primary adrenal insufficiency of ALD is caused by an accumulation of VLCFAs in the adrenal cortex, and the peripheral neuropathy in adult Refsum disease is caused by the accumulation of phytanic acid in Schwann cells and myelin.

PBD-ZSD

Newborn infants with *severe* PBD-ZSD, previously described as **Zellweger syndrome**, show striking and consistent recognizable abnormalities. Of central diagnostic importance are the typical facial appearance (large anterior fontanelle, wide sutures, high forehead, hypoplastic supraorbital ridges, flat face, and broad nasal bridge; Fig. 106.3), severe weakness and hypotonia, neonatal seizures, and eye abnormalities. Because of the hypotonia and craniofacial appearance, Down syndrome may be suspected in neonates. Infants with severe PBD-ZSD rarely live more than a few months. More than 90% show postnatal growth failure. Table 106.4 lists the main clinical abnormalities.

Patients with *intermediate* PBD-ZSD, previously described as **neonatal ALD**, show fewer, less prominent craniofacial features. Neonatal seizures occur frequently. Psychomotor developmental delay is present; function remains in the range of severe intellectual disability, and development may regress after 3-5 years of age, likely from progressive leukodystrophy. Hepatomegaly, impaired liver function, pigmentary degeneration of the retina, and severely impaired hearing are invariably present. Adrenocortical function is usually impaired and may require adrenal hormone replacement. Chondrodysplasia punctata and renal cysts are absent.

Patients with *mild* PBD-ZSD, previously described as **infantile Refsum disease**, have survived to adulthood. They can walk, although gait may be ataxic and broad based. Cognitive function is generally



Fig. 106.3 Zellweger syndrome. Three affected neonates. Note the hypotonia, high forehead with shallow supraorbital ridges, anteverted nares, and mild micrognathia, as well as the talipes equinovarus and contractures at the knees. *(From Shaheen R, Al-Dirbashi OY, Al-Hassnan ZN, et al. Clinical, biochemical and molecular characterization of peroxisomal diseases in Arabs. Clin Genet. 2011;79[1]:60–70.)*

Table 106.4 Main Clinical Abnormalities in Zellweger Syndrome

	PATIENTS IN WHOM THE FEATURE WAS PRESENT	
ABNORMAL FEATURE	**NUMBER**	**%**
High forehead	58	97
Flat occiput	13	81
Large fontanelle(s), wide sutures	55	96
Shallow orbital ridges	33	100
Low/broad nasal bridge	23	100
Epicanthus	33	92
High-arched palate	35	95
External ear deformity	39	97
Micrognathia	18	100
Redundant skin fold of neck	13	100
Brushfield spots	5	83
Cataract/cloudy cornea	30	86
Glaucoma	7	58
Abnormal retinal pigmentation	6	40
Optic disc pallor	17	74
Severe hypotonia	94	99
Abnormal Moro response	26	100
Hyporeflexia or areflexia	56	98
Poor sucking	74	96
Gavage feeding	26	100
Epileptic seizures	56	92
Intellectual disability	45	100
Impaired hearing	9	40
Nystagmus	30	81

From Heymans HAS. Cerebro-hepato-renal (Zellweger) syndrome: Clinical and biochemical consequences of peroxisomal dysfunctions. Thesis, University of Amsterdam, 1984.

impaired, but accurate assessment is limited, usually by the presence of both vision and hearing impairment. Almost all have some degree of sensorineural hearing loss and pigmentary degeneration of the retina. They have moderately dysmorphic features that may include epicanthal folds, a flat nose bridge, and low-set ears. Early hypotonia and hepatomegaly with impaired function are common. Levels of plasma cholesterol and high-density and low-density lipoprotein are often moderately reduced. Chondrodysplasia punctata and renal cortical cysts are absent. Postmortem study in these mild PBD-ZSD cases reveals micronodular liver cirrhosis and small, hypoplastic adrenals. The brain shows no malformations, except for severe hypoplasia of the cerebellar granule layer and ectopic locations of the Purkinje cells in the molecular layer.

Some patients with PBD-ZSD have milder and atypical phenotypes. They may present with peripheral neuropathy or with retinopathy, impaired vision, or cataracts in childhood, adolescence, or adulthood and have been considered to have Charcot-Marie-Tooth disease or Usher syndrome. Some patients with *PEX16* variants present with cerebellar ataxia. Some patients have survived to the fifth decade.

Rhizomelic Chondrodysplasia Punctata

RCDP is characterized by the presence of stippled foci of calcification within the hyaline cartilage and is associated with short stature, cataracts (72%), and multiple malformations caused by contractures. Vertebral bodies have coronal clefting filled by cartilage that results from an embryonic arrest. Disproportionate short stature affects the proximal parts of the extremities (rhizomelia; Fig. 106.4A). Radiologic abnormalities consist of shortening of the proximal limb bones, metaphyseal cupping, and disturbed punctate ossification (Fig. 106.4B). Height, weight, and head circumference are less than the third percentile, and these children have a severe intellectual disability. Skin changes such as those observed in ichthyosiform erythroderma are present in approximately 25% of patients. RCDP can be caused by pathogenic variants in one of four genes *(PEX5, PEX7, AGPS, GNPAT)*. Defects in *PEX7*, which most frequently lead to the RCDP phenotype, may also lead to a milder phenotype with clinical manifestations similar to those of adult Refsum disease, a later-onset disorder described later.

Isolated Defects of Peroxisomal Fatty Acid Oxidation

In the group of single-enzyme defects, acyl-CoA oxidase and bifunctional enzyme deficiency involve a single enzymatic step in peroxisomal fatty acid oxidation. **Defects of bifunctional enzyme** are found in approximately 15% of patients who are initially suspected of having PBD-ZSD. Patients with isolated **acyl-CoA oxidase deficiency** have a somewhat milder phenotype that resembles mild or intermediate PBD-ZSD or Usher syndrome and typically comes to attention because of the development of an early childhood leukodystrophy.

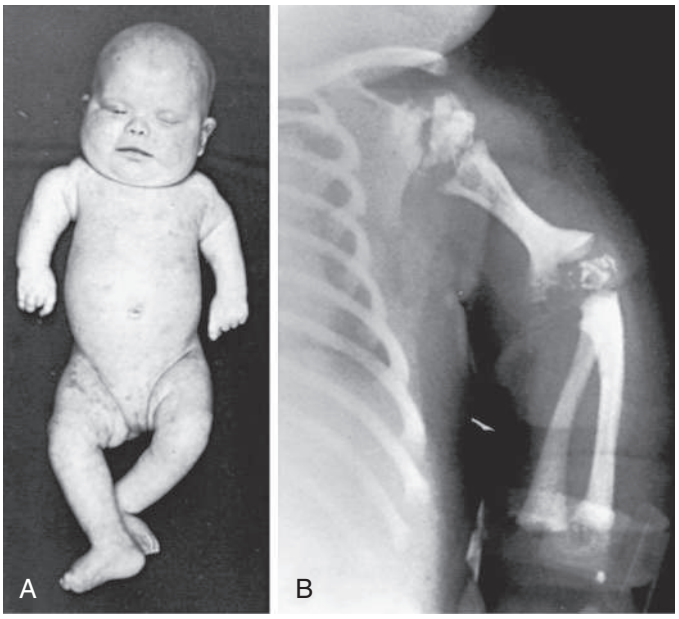

Fig. 106.4 A, Newborn infant with rhizomelic chondrodysplasia punctata. Note the severe shortening of the proximal limbs, the depressed bridge of the nose, hypertelorism, and widespread scaling skin lesions. B, Note the marked shortening of the humerus and epiphyseal stippling at the shoulder and elbow joints. *(Courtesy John P. Dorst, MD.)*

Isolated Defects of Plasmalogen Synthesis

Plasmalogens are lipids in which the first of three glycerol carbons is linked to an alcohol rather than a fatty acid. They are synthesized through a complex series of reactions, the first two steps of which are catalyzed by the peroxisomal enzymes dihydroxyacetone phosphate alkyl transferase (DHAPT, encoded by the gene *GNPAT*) and synthase (AGPS, encoded by the gene *AGPS*). Deficiency of either of these enzymes leads to RCDP types 2 and 3, respectively, phenotypes that are clinically indistinguishable from each other and from the peroxisomal import disorder RCDP1. This latter disorder is caused by a defect in *PEX7,* the receptor for PTS2 upon which DHAPT and AGPS are dependent for peroxisomal import. RCDP1 shares the severe deficiency of plasmalogens with these single-enzyme disorders but also has defects of phytanic oxidation. The fact that these single genetic disorders are associated with the full phenotype of RCDP suggests that a deficiency of plasmalogens is sufficient to produce it.

Adult (Classic) Refsum Disease

The defective enzyme (phytanoyl-CoA hydroxylase, encoded by the *PHYH* gene) is localized to the peroxisome. The manifestation of Refsum disease includes impaired vision from retinitis pigmentosa, anosmia, ichthyosis, peripheral neuropathy, ataxia, and occasionally cardiac arrhythmias. In contrast to infantile Refsum disease, cognitive function is normal, and there are no congenital malformations. Refsum disease often does not manifest until young adulthood, but visual disturbances such as night blindness, ichthyosis, and peripheral neuropathy may already be present in childhood and adolescence. Early diagnosis is important because institution of a phytanic acid–restricted diet can reverse the peripheral neuropathy and prevent the progression of the visual and central nervous system (CNS) manifestations. Adult Refsum disease may also be caused by defects in *PEX7*.

2-Methylacyl-CoA Racemase Deficiency (AMACR)

This disorder is caused by an enzyme defect that leads to the accumulation of the branched-chain fatty acids (phytanic and pristanic acid) and bile acids. Individuals present with typically an adult-onset peripheral neuropathy and may also have pigmentary degeneration of the retina.

Atypical Autosomal Dominant Disorders

Peroxisomal disorders are classically autosomal recessive in family pedigrees. X-linked adrenoleukodystrophy is a key exception. Several other exceptions of rare dominant inheritance of peroxisomal disease manifesting as neurologic disease have emerged for a few peroxisomal genes, including *ACOX1, PEX6*, and *DNM1L*.

Laboratory Findings

Clinical suspicion would be followed by specific biochemical determination of an abnormality and then confirmation through genetic testing targeted to specific genes. However, an extended gene panel and exome and genome testing have been used to identify pathogenic variants or variants of uncertain significance (VUS) in peroxisomal genes. *These patients still require biochemical testing for confirmation.* In addition, newborn screening for X-linked ALD using dried blood spots on filter paper in states across the United States and many parts of Europe also identifies other forms of peroxisomal deficiency. Early recognition of peroxisomal disorders in newborns will be a clinical reality.

Whether based on clinical suspicion, an abnormal newborn screen, or reported genetic variants, the biochemical characterization of peroxisomal disorders is a necessary step and uses the generally available testing strategy listed in Table 106.5. Measurement of plasma VLCFA levels is the most common assay. It must be emphasized that although plasma VLCFA levels are elevated in many patients with peroxisomal disorders and the same defect is the indirect basis for the newborn screen assay, this is not always the case. The most important exception is RCDP, in which VLCFA levels are normal but plasma phytanic acid levels are increased and red blood cell (RBC) plasmalogen levels are reduced. In other peroxisomal disorders, the biochemical abnormalities are still more restricted. Therefore a panel of tests is recommended and includes plasma levels of VLCFAs and phytanic, pristanic, and pipecolic acids and RBC levels of plasmalogens. Tandem mass spectrometry techniques also permit convenient quantitation of bile acids in plasma and urine. This panel of tests can be performed on very small amounts of venous blood and permits detection of most peroxisomal disorders.

Definition of the molecular defect either through gene panel testing or exome sequencing in the *proband* is essential for carrier detection and speeds prenatal diagnosis. Characterization of the pathogenic variant may be of prognostic value in patients with *PEX1* defects. This defect is present in approximately 60% of PBD patients, and about half the *PEX1* defects have the G843D allele, which is associated with a significantly milder phenotype than found in other pathogenic variants.

Diagnosis

Several noninvasive laboratory tests permit precise and early diagnosis of peroxisomal disorders (see Table 106.5). The challenge in PBDs is to differentiate them from the large variety of other conditions that can cause hypotonia, seizures, failure to thrive, or dysmorphic features. Experienced clinicians readily recognize classic Zellweger syndrome by its clinical manifestations. However, more mildly affected PBD-ZSD patients often do not show the full clinical spectrum of disease and may be identifiable only by laboratory assays. Clinical features that warrant diagnostic assessment include intellectual disability; weakness and hypotonia; dysmorphic features; neonatal seizures; retinopathy, glaucoma, or cataracts; hearing deficits; enlarged liver and impaired liver function; and chondrodysplasia punctata. The presence of one or more of these abnormalities increases the likelihood of this diagnosis. Atypical milder forms presenting as peripheral neuropathy have also been described.

Some patients with the isolated defects of peroxisomal fatty acid oxidation resemble those with ZSD and can be detected by the demonstration of abnormally high levels of VLCFAs.

Patients with RCDP must be distinguished from patients with *other* causes of chondrodysplasia punctata. RCDP is suspected clinically because of the shortness of limbs, developmental delays, and ichthyosis. The most decisive laboratory test is the demonstration of abnormally low plasmalogen levels in RBCs and an alteration in *PEX7*.

Table 106.5 Diagnostic Biochemical Abnormalities in Peroxisomal Disorders

DISORDER	VLCFA	PHYTANIC ACID	PRISTANIC ACID	PLASMALOGENS
PBD-ZSD	↑↑	↑*	↑*	↓
RCDP	Nl	↑	Nl	↓↓
ALD	↑	Nl	Nl	Nl
ACoX	↑	Nl	Nl	Nl
Bifunctional enzyme deficiency	↑	↑	↑	Nl
AMACR	Nl	↑	↑	Nl
Refsum disease	Nl	↑	↑	Nl

*Phytanic acid and pristanic acid accumulation is age dependent, and normal (Nl) levels may be seen in infants and young children.
VLCFA, Very long chain fatty acids; ZSD, Zellweger spectrum disorder; RCDP, rhizomelic chondroplasia punctata; ALD, adrenoleukodystrophy; ACoX, acyl-CoA oxidase deficiency; AMACR, 2-methylacyl-CoA racemase deficiency.

Complications
Patients with severe PBD-ZSD have multiple disabilities involving muscle tone, swallowing, cardiac abnormalities, liver disease, and seizures. These conditions are treated symptomatically, but the prognosis is poor, and most patients succumb in the first years of life. Similarly, individuals with RCDP have multiple systemic and neurologic issues. In addition, they may develop spinal cord compression at any level of the spine.

Treatment
The most effective therapy is the dietary treatment of adult Refsum disease with a phytanic acid–restricted diet. However, this only applies to this specific condition.

For patients with the somewhat milder variants of the peroxisome import disorders, success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids or cochlear implants, augmentative and alternative communication, nutrition, and support for the families. Although most patients continue to function in the impaired range, some make significant gains in self-help skills, and several are in stable condition in their teens or even early 20s.

Attempts to mitigate some of the secondary biochemical abnormalities include the oral administration of docosahexaenoic acid (DHA). The DHA level is greatly reduced in patients with disorders of peroxisome biogenesis, and this therapy normalizes DHA plasma levels. Although there were anecdotal reports of clinical improvement with DHA therapy, a randomized placebo-controlled study failed to find benefit.

Genetic Counseling
Most of these disorders can be diagnosed prenatally. Prenatal testing using chorionic villus sampling or amniocentesis enables genetic testing when the alteration is known, but biochemical measurements may be made using the same tests as described for postnatal diagnosis (see Table 106.5). Because of the 25% recurrence risk with autosomal recessive inheritance, couples with an affected child should be advised about the availability of prenatal and preconception diagnosis.

ADRENOLEUKODYSTROPHY
ALD is an X-linked disorder associated with the accumulation of saturated VLCFAs and a progressive dysfunction of the adrenal cortex and nervous system. It is the most common peroxisomal disorder.

Etiology
The key biochemical abnormality in ALD is the tissue accumulation of saturated VLCFAs, with a carbon chain length of 24 or more. Excess hexacosanoic acid ($C_{26:0}$) is the most striking and characteristic feature. This accumulation of fatty acids is caused by genetically deficient peroxisomal degradation of fatty acid. The defective gene *(ABCD1)* codes for a peroxisomal membrane protein (ALDP, the ALD protein). Many alterations in *ABCD1* have been determined to be pathogenic, with over half these being private or unique to the family. There is no genotype-phenotype correlation, as wide ranges of clinical severity can occur within a family across multiple individuals with the same pathogenic variant. A curated database of pathogenic variants is maintained (www.x-ald.nl). The mechanism by which the ALDP defect leads to VLCFA accumulation appears to be a disruption of transport of saturated fatty acids into the peroxisome, with resultant continued progressive elongation of fatty acids.

Epidemiology
The incidence of ALD in males is 1 in 21,000, and the combined incidence of ALD males and heterozygous females in the general population is estimated to be 1 in 17,000. All ethnicities are affected. The various phenotypes often occur in members of the same kindred.

Pathology
Characteristic lamellar cytoplasmic inclusions can be demonstrated on electron microscopy in adrenocortical cells, testicular Leydig cells, and nervous system macrophages. These inclusions probably consist of cholesterol esterified with VLCFA. They are most prominent in cells of the zona fasciculata of the adrenal cortex, which at first are distended with lipids and subsequently atrophy.

The nervous system displays two types of ALD lesions. In the severe cerebral form, demyelination is associated with an inflammatory response manifested by the accumulation of perivascular lymphocytes that is most intense in the involved region. In the slowly progressive adult form, **adrenomyeloneuropathy** (AMN), the main finding is a distal axonopathy that affects the long tracts in the spinal cord. In this form the inflammatory response is mild or absent.

Pathogenesis
The adrenal dysfunction is probably a direct consequence of the accumulation of VLCFAs. The cells in the adrenal zona fasciculata are distended with abnormal lipids. Cholesterol esterified to VLCFA is relatively resistant to adrenocorticotropic hormone (ACTH)–stimulated cholesterol ester hydrolases, and this limits the capacity to convert cholesterol to active steroids. In addition, $C_{26:0}$ excess increases the viscosity of the plasma membrane, which may interfere with receptor and other cellular functions.

There is no defined correlation between the neurologic phenotype and the nature of the pathogenic variant or the severity of the biochemical defect as assessed by plasma VLCFA levels or between the degree of adrenal involvement and nervous system involvement. The severity of the illness and rate of progression correlate with the intensity of the inflammatory response. The inflammatory response may be partially cytokine mediated and may involve an autoimmune response triggered in an unknown way by the excess of VLCFAs. Mitochondrial damage and oxidative stress also appear to contribute. Approximately half the patients do not experience the inflammatory response, although the basis of this difference is not understood.

Clinical Manifestations

There are five relatively distinct ALD phenotypes, three of which present in childhood with symptoms and signs. In all the phenotypes, development is usually normal in the first 3-4 years of life.

In the **childhood cerebral form** of ALD, symptoms most often are first noted between ages 4 and 8 years. The most common initial manifestations are hyperactivity, inattention, and worsening school performance in a child who had previously been a good student. *Auditory discrimination* is often impaired, although tone perception is preserved. This may be evidenced by difficulty in using the telephone and greatly impaired performance on intelligence tests in items that are presented verbally. Spatial orientation is often impaired. Other initial symptoms are disturbances of vision, ataxia, poor handwriting, seizures, and strabismus. Visual disturbances are often caused by involvement of the parietooccipital cortex rather than eye or optic tract abnormalities, which leads to variable and seemingly inconsistent visual capacity. Seizures occur in most patients and may represent the first manifestation of the disease. Some patients present with increased intracranial pressure. Impaired cortisol response to ACTH stimulation is present in 85% of patients, and mild hyperpigmentation is noted. In most patients with this phenotype, adrenal dysfunction is recognized only after the condition is diagnosed because of the cerebral symptoms. Cerebral childhood ALD tends to progress rapidly with increasing spasticity and paralysis, visual and hearing loss, and loss of ability to speak or swallow. The mean interval between the first neurologic symptom and an apparently unresponsive wakeful state is 1.9 years. Patients may continue in this apparently unresponsive wakeful state for ≥10 years.

Adolescent ALD designates patients who experience neurologic symptoms between ages 10 and 21 years. The manifestations resemble those of childhood cerebral ALD except that progression is slower. Approximately 10% of patients present acutely with status epilepticus, adrenal crisis, acute encephalopathy, or coma.

AMN first manifests in late adolescence or adulthood as a progressive paraparesis caused by long tract degeneration in the spinal cord. Approximately half the affected males also have involvement of the cerebral white matter.

The **Addison-only** phenotype is an important condition. Of male patients with Addison disease, 25% may have the biochemical defect of ALD. Many of these patients have intact neurologic systems, whereas others have subtle neurologic signs. Many acquire AMN in adulthood.

The term **asymptomatic ALD** is applied to persons who have the biochemical defect of ALD but are free of neurologic or endocrinal disturbances. Almost all persons with the gene defect eventually become neurologically symptomatic.

Approximately 50% of female heterozygotes acquire a syndrome that resembles AMN but is milder and of later onset. Adrenal insufficiency and cerebral disease are rare.

Cases of typical ALD have occurred in relatives of those with AMN. One of the most difficult problems in the management of ALD is the common observation that affected individuals in the same family may have quite different clinical courses. For example, in one family, an affected male may have severe classic ALD culminating in death by age 10 years, and another brother will have the later-onset AMN.

Laboratory and Radiographic Findings

The most specific and important laboratory finding is the demonstration of abnormally high levels of VLCFAs in plasma, RBCs, or cultured skin fibroblasts. Positive results are obtained in all male patients with ALD and in approximately 85% of female carriers of ALD. Pathogenic variant analysis is the most reliable method for the identification of carriers. Simply finding a variation in ABCD1 is not adequate for making the diagnosis of ALD. It must be shown to segregate with elevated VLCFA levels.

Neuroimaging

Patients with childhood cerebral or adolescent ALD have characteristic white matter lesions on MRI. In 80% of patients, the lesions are symmetric and involve the splenium of the corpus callosum and periventricular white matter in the posterior parietal and occipital lobes. Many will show a garland of contrast enhancement adjacent and anterior to the posterior hypodense lesions (Fig. 106.5). This zone corresponds to the zones of intense perivascular lymphocytic infiltration where the blood-brain barrier breaks down. In 10–15% of patients, the initial lesions are frontal. Unilateral lesions that produce a mass effect suggestive of a brain tumor may occur rarely. MRI provides a clearer delineation of normal and abnormal white matter than does CT and is the preferred imaging modality.

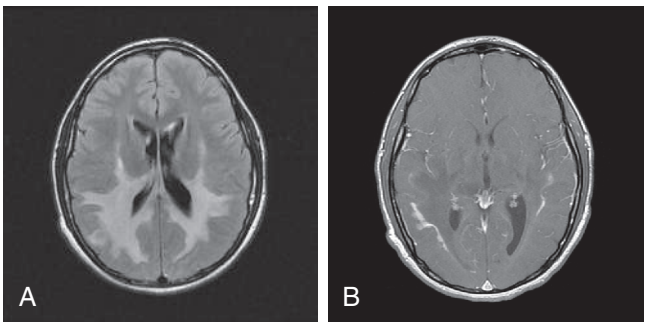

Fig. 106.5 Characteristic MRI findings in cerebral adrenoleukodystrophy. **A,** Symmetric T2-weighted MRI abnormalities involve the posterior white matter, including the corpus callosum. **B,** Contrast administration reveals a garland of enhancement.

Impaired Adrenal Function

More than 85% of patients with the childhood form of ALD have elevated levels of ACTH in plasma and a subnormal rise of cortisol levels in plasma after IV injection of ACTH.

Newborn Screening and Diagnosis

Diagnosis of asymptomatic males is available by newborn screening, which allows for early diagnosis of ALD years before the manifestations of disease. Males then enter a program of surveillance for adrenal insufficiency and early detection of potential cerebral disease. Females identified through these programs should also have confirmatory testing, genetic counseling for the family, and screening of other at-risk males. Females do not generally require any other monitoring in childhood. This early screening paradigm allows for early surveillance of ALD neurologic symptoms, which are difficult to distinguish from the more common attention-deficit disorders or learning disabilities of school-age children. Early diagnosis could lead to early cortisol treatment for adrenal problems, which could be life-threatening. Early bone marrow transplant is likely to result as a benefit of screening. For positive newborn screens or for individuals with clinical suspicion of ALD, confirmatory VLCFA testing and genetic counseling should be provided.

The Earliest Manifestations of Childhood Cerebral ALD

Rapid progression, signs of dementia, or difficulty in auditory discrimination suggest ALD. Even in early stages, neuroimaging shows abnormal changes. Other leukodystrophies or multiple sclerosis may sometimes mimic these radiographic findings, although early ALD has more of a predilection for the posterior brain than its mimics. Definitive diagnosis depends on demonstration of VLCFA excess, which occurs only in ALD and the other peroxisomal disorders.

Cerebral forms of ALD, especially if asymmetric, may be misdiagnosed as gliomas or other mass lesions. Individuals have received brain biopsy and, rarely, other therapies before the correct diagnosis was made. Measurement of VLCFAs in plasma is the most reliable differentiating test.

Adolescent or adult cerebral ALD can be confused with psychiatric disorders, dementing disorders, multiple sclerosis, or epilepsy. The first clue to the diagnosis of ALD may be the demonstration of characteristic white matter lesions by neuroimaging; VLCFA assays are confirmatory.

ALD *cannot* be distinguished clinically from other forms of Addison disease; it is recommended that assays of VLCFA levels be performed

in all male patients with Addison disease. ALD patients *do not* usually have antibodies to adrenal tissue in their plasma.

Complications

An avoidable complication is the occurrence of adrenal insufficiency. The most difficult neurologic problems are those related to bed rest, contracture, coma, and swallowing disturbances. Other complications involve behavioral disturbances and injuries associated with defects of spatial orientation, impaired vision and hearing, and seizures.

Treatment

Corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction is effective. It may be lifesaving and may increase general strength and well-being, but it does not alter the course of the neurologic disability.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) or hematopoietic stem cell therapy (HSCT) benefits patients who show early evidence of the inflammatory demyelination characteristic of the rapidly progressive neurologic disability in young males and adolescents with the cerebral ALD phenotype. BMT carries risk, and patients must be evaluated and selected with care. The mechanism of the beneficial effect is incompletely understood. Bone marrow–derived cells do express ALDP, the protein that is deficient in ALD; approximately 50% of brain microglial cells are bone marrow derived. The favorable effect may be caused by modification of the brain inflammatory response. Follow-up of young males and adolescents who had early cerebral involvement has shown stabilization. On the other hand, BMT does not arrest the course in those who already had severe brain involvement and may accelerate disease progression under these circumstances. The ALD MRI score and the use of performance measures on IQ testing have shown some predictive ability for boys likely to benefit from this procedure. Transplant is not recommended in patients with performance IQ significantly <80. Unfortunately, in more than half the patients who are diagnosed because of neurologic symptoms, the illness is so advanced at diagnosis that they are not candidates for transplant.

Consideration of BMT is most relevant in neurologically asymptomatic or mildly involved patients. Screening at-risk relatives of symptomatic patients identifies these patients most frequently. Screening by measurement of plasma VLCFA levels in patients with Addison disease may also identify candidates for BMT. Because of its risk (10–20% mortality) and because up to 50% of untreated patients with ALD do not develop inflammatory brain demyelination, transplant is not recommended in patients who are free of demonstrable brain involvement on MRI. MRI is also of key importance for the crucial decision of whether transplant should be performed. MRI abnormalities precede clinically evident neurologic or neuropsychologic abnormalities. The brain MRI should be monitored at 6-month intervals in neurologically asymptomatic young males and adolescents age 3-15 years. If the MRI is normal, BMT is not indicated. If brain MRI abnormalities develop, the young male should be evaluated by a center familiar with transplant for ALD. This should include MRI, neurologic, and neuropsychologic evaluations. It is not known whether BMT has a favorable effect on the noninflammatory spinal cord involvement in adults with the adrenomyeloneuropathy phenotype.

Autologous hematopoietic stem cell gene therapy **(elivaldogene autotemcel)** is approved for patients 4-17 years of age to slow the neurologic progression of early, active cerebral adrenoleukodystrophy.

Supportive Therapy

The progressive behavioral and neurologic disturbances associated with the childhood form of ALD are extremely difficult for the family. ALD patients require the establishment of a comprehensive management program and partnership among the family, physician, visiting nursing staff, school authorities, and counselors. In addition, parent support groups (e.g., United Leukodystrophy Foundation) are often helpful. Communication with school authorities is important because under the provisions of Public Law 94-142, children with ALD qualify for special services as "other health impaired" or "multi-handicapped." Depending on the rate of progression of the disease, special needs might range from relatively low-level resource services within a regular school program to home- and hospital-based teaching programs for children who are not mobile.

Management challenges vary with the stage of the illness. The early stages are characterized by subtle changes in affect, behavior, and attention span. Counseling and communication with school authorities are of prime importance. Changes in the sleep–wake cycle can be benefited by the judicious use of nighttime sleep medications.

As the leukodystrophy progresses, the modulation of muscle tone and support of bulbar muscular function are major concerns. Baclofen in gradually increasing doses (5 mg twice a day to 25 mg four times a day) is an effective pharmacologic agent for the treatment of acute episodic painful muscle spasms. Other agents may also be used, with care taken to monitor the occurrence of side effects and drug interactions. As the leukodystrophy progresses, bulbar muscular control is lost. Although initially this can be managed by changing the diet to soft and pureed foods, most patients eventually require a gastrostomy tube. At least 30% of patients have focal or generalized seizures that usually readily respond to standard anticonvulsant medications.

Genetic Counseling and Prevention

Genetic counseling and appropriate monitoring are of crucial importance. Extended-family screening should be offered to all at-risk relatives of symptomatic patients; one program led to the identification of >250 asymptomatic affected males and 1,200 women heterozygous for ALD. The plasma assay permits reliable identification of affected males in whom plasma VLCFA levels are increased already on the day of birth. Identification of asymptomatic males permits institution of steroid replacement therapy when appropriate and prevents adrenal crisis, which may be fatal. Monitoring of brain MRI also permits identification of patients who are candidates for BMT at a stage when this procedure has the greatest chance of success. Plasma VLCFA assay is recommended in all male patients with Addison disease. ALD has been shown to be the cause of adrenal insufficiency in >25% of boys with Addison disease of unknown cause. Identification of women heterozygous for ALD is more difficult than that of affected males. Plasma VLCFA levels are normal in 15–20% of heterozygous women, and failure to note this has led to serious errors in genetic counseling. DNA analysis permits accurate identification of carriers, provided that the pathogenic variant has been defined in a family member, and this is the procedure recommended for the identification of heterozygous women.

Prenatal diagnosis of affected male fetuses can be achieved by determination of the known pathogenic variant or by the measurement of VLCFA levels in cultured amniocytes or chorionic villus cells. Whenever a new patient with ALD is identified, a detailed pedigree should be constructed and efforts made to identify all at-risk female carriers and affected males. These investigations should be accompanied by careful and sympathetic attention to social, emotional, and ethical issues during counseling.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

106.3 Disorders of Lipoprotein Metabolism and Transport

Lee A. Pyles

EPIDEMIOLOGY OF BLOOD LIPIDS AND CARDIOVASCULAR DISEASE

There is a strong association between average intake of saturated fats, plasma cholesterol, and mortality from coronary heart disease (CHD). Of all common chronic diseases, none is so clearly influenced by both environmental *and* genetic factors as CHD. This multifactorial disorder is strongly associated with increasing age and male gender, although it is increasingly apparent that heart disease is underrecognized in women. Tobacco use confers a twofold higher lifetime risk.

Sedentary activity and high intake of processed sugars leading to adiposity increase risk through differences in the plasma levels of atherogenic lipoproteins. Family history reflects the combined influence of lifestyle and genetic predisposition to early heart disease. Risk of premature heart disease associated with positive family history is 1.7 times higher than in families with no such history.

Atherosclerosis begins during childhood. The Johns Hopkins Precursors Study demonstrated that White male medical students with blood cholesterol levels in the lowest quartile showed only a 10% incidence of CHD 3 decades later, whereas those in the highest quartile had a 40% incidence. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated a significant relationship between the weight of the abdominal fat pad and the extent of atherosclerosis found at autopsy on individuals 15-34 years of age. The Bogalusa Heart Study of more than 3,000 Black and White children and adolescents has provided the most comprehensive longitudinal data relating the presence and severity of CHD risk factors with semi-quantifiable severity of atherosclerosis. Coronary atherosclerosis was present in 8.5% of military autopsies performed after combat or unintentional injuries.

The *fetal origins hypothesis* is based on the observation that infants born with low birthweight have a higher incidence of heart disease as adults. Epidemiologic studies support the idea that prenatal and early postnatal conditions may affect adult health status. Children who are large for gestational age at birth and exposed to an intrauterine environment of either diabetes or maternal obesity are at increased risk of eventually developing **metabolic syndrome** (insulin resistance, type 2 diabetes, obesity, CHD). Breastfeeding preterm infants confers a long-term cardioprotective benefit 13-16 years later. Those adolescents who were breastfed as infants had lower C-reactive protein (CRP) concentrations and a 14% lower low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio than formula-fed infants. The impact of early nutrition and other lifestyle variables on gene expression via *epigenetics* is one mechanism by which adult metabolism and body composition may be influenced.

Secondary causes of hyperlipidemia may be the result of drugs (cyclosporine, corticosteroids, isotretinoin, protease inhibitors, alcohol, thiazide diuretics, β-blocking agents, valproate) or various diseases (nephrotic syndrome, hypothyroidism, Cushing syndrome, anorexia nervosa, obstructive jaundice). Psychotropic medications, including second-generation antipsychotics such as olanzapine, are also associated with dyslipidemia, obesity, and insulin resistance.

BLOOD LIPIDS AND ATHEROGENESIS

Numerous epidemiologic studies demonstrate the association of hypercholesterolemia, referring to elevated total, non-HDL, and LDL blood cholesterol, with atherosclerotic disease. Atherosclerosis affects primarily the coronary arteries but may also involve the aorta, arteries of the lower extremities, and carotid arteries.

The early stage of development of atherosclerosis is thought to begin with vascular endothelial dysfunction and intima-media thickness, which has been shown to occur in preadolescent children with risk factors such as obesity or familial hypercholesterolemia. The complex process of penetrating the intimal lining of the vessel may result from a variety of insults, including the presence of highly toxic oxidized LDL particles. Lymphocytes and monocytes penetrate the damaged endothelial lining, where they become macrophages laden with LDL lipids and then become foam cells. Such accumulation is counterbalanced by HDL particles capable of removing lipid deposits from the vessel wall. Fundamental to plaque formation is an inflammatory process (elevated CRP) involving macrophages and the arterial wall. The deposition of lipid within the subendothelial lining of the arterial wall appears macroscopically as fatty streaks, which may to some degree be reversible. A later stage of plaque development involves disruption of arterial smooth muscle cells stimulated by the release of tissue cytokines and growth factors. The *atheroma* is composed of a core of fatty substance separated from the lumen by collagen and smooth muscle (Fig. 106.6). Growth of the atherosclerotic plaque may result in ischemia of the tissue supplied by the artery. Chronic inflammation within the atheroma results in plaque instability and subsequent rupture. Platelet adherence leads to clot formation at the site of rupture, resulting in myocardial infarction (MI) or a cerebrovascular accident (CVA), depending on the site of thrombosis or thromboembolism.

PLASMA LIPOPROTEIN METABOLISM AND TRANSPORT

Lipoproteins are soluble complexes of lipids and proteins that effect transport of fat absorbed from the diet, or synthesis by the liver and adipose tissues, for utilization and storage. Dietary fat is transported from the small intestine as chylomicrons. Lipids synthesized by the liver as very low-density lipoproteins (VLDLs) are catabolized to intermediate-density lipoproteins (IDLs) and LDLs. HDL is fundamentally involved in VLDL and chylomicron metabolism and cholesterol transport. Nonesterified free fatty acids are metabolically active lipids derived from lipolysis of triglycerides stored in adipose tissue and bound to albumin for circulation in the plasma (Fig. 106.7).

Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins (Fig. 106.8). The density of the several classes of lipoproteins is inversely proportional to the ratio of lipid to protein, which is generally denser (Fig. 106.9).

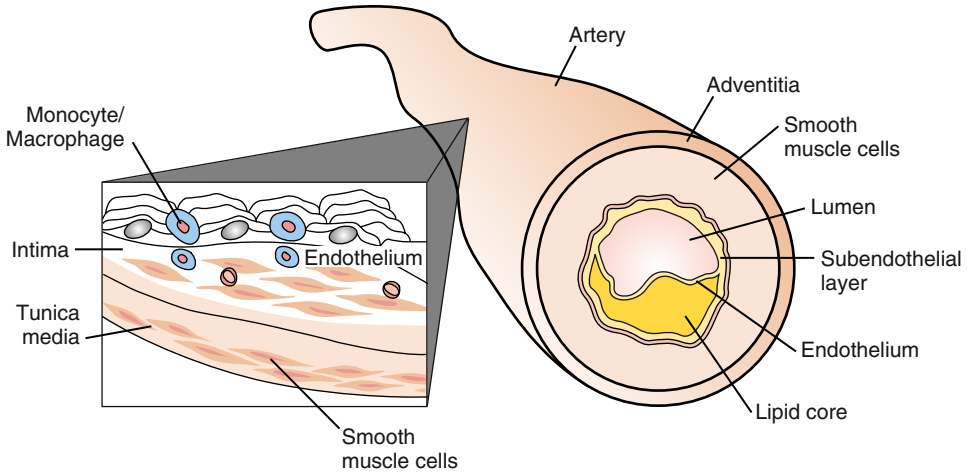

Fig. 106.6 The early stage of development of atherosclerosis begins with penetration of the intimal lining of the vessel by inflammatory cells. Deposition of lipid within the subendothelial lining of the arterial wall eventually leads to disruption of smooth muscle cells to form an atheromatous lipid core that impinges on the lumen. Chronic inflammation leads to plaque instability, setting the stage for plaque rupture and complete occlusion of the vessel lumen by clot formation.

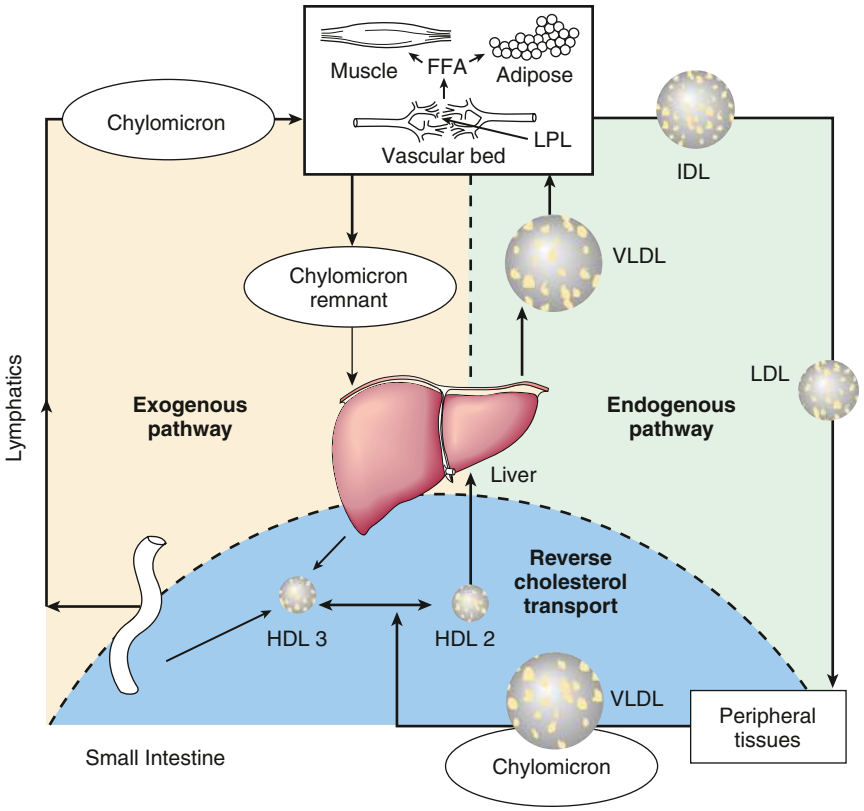

Fig. 106.7 The exogenous, endogenous, and reverse cholesterol pathways. The exogenous pathway transports dietary fat from the small intestine as chylomicrons to the periphery and the liver. The endogenous pathway denotes the secretion of very low-density lipoprotein (VLDL) from the liver and its catabolism to intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL). Triglycerides are hydrolyzed from the VLDL particle by the action of lipoprotein lipase (LPL) in the vascular bed, yielding free fatty acids (FFAs) for utilization and storage in muscle and adipose tissue. High-density lipoprotein (HDL) metabolism is responsible for the transport of excess cholesterol from the peripheral tissues back to the liver for excretion in the bile. Nascent HDL-3 particles derived from the liver and small intestine are esterified to more mature HDL-2 particles by enzyme-mediated movement of chylomicron and VLDL into the HDL core, which is removed from the circulation by endocytosis.

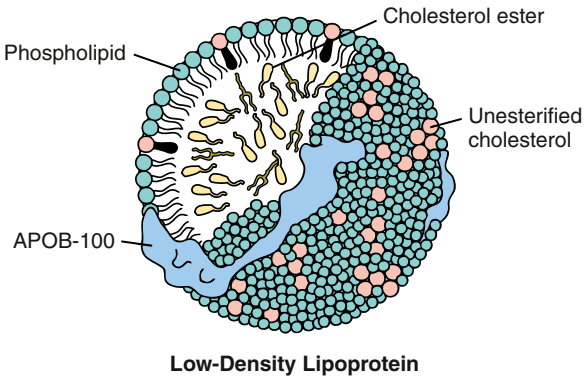

Fig. 106.8 Schematic of low-density lipoprotein. Lipoprotein consists of a central core of cholesteryl esters surrounded by phospholipids, cholesterol, and protein.

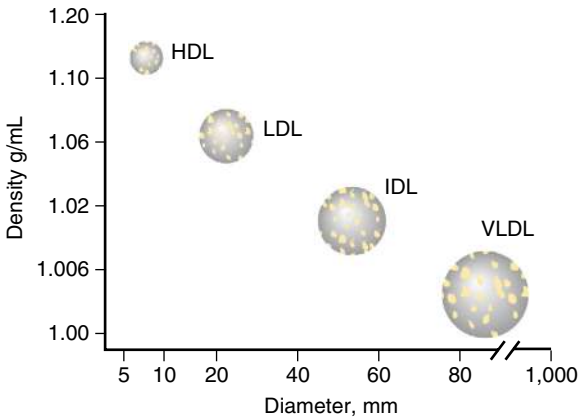

Fig. 106.9 The density of the several classes of lipoprotein is inversely proportional to the ratio of lipid to protein. As lipid is less dense than protein, the more lipid contained in the particle increases its size and decreases its density. HDL, High-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

Constituent proteins known as *apolipoproteins* are responsible for a variety of metabolic functions in addition to their structural role, including as cofactors or inhibitors of enzymatic pathways and mediators of lipoprotein binding to cell surface receptors (Table 106.6). **ApoA** is the major apolipoprotein (Apo) of HDL. **ApoB** is present in LDL, VLDL, IDL, and chylomicrons. ApoB-100 is derived from the liver, whereas apoB-48 comes from the small intestine. ApoC-I, C-II, and C-III are small peptides important in triglyceride metabolism. Loss of function and disruptive pathogenic variants of the *APOC3* gene are associated with low levels of triglycerides and a reduced risk of ischemic CHD. Likewise, **apoE**, which is present in VLDL, HDL, chylomicrons, and chylomicron remnants, plays an important role in the clearance of triglycerides.

Transport of Exogenous (Dietary) Lipids

All dietary fat except medium-chain triglycerides is efficiently carried into the circulation by way of lymphatic drainage from the intestinal mucosa. Triglyceride and cholesteryl esters combine with apoA and apoB-48 in the intestinal mucosa to form chylomicrons, which are carried into the peripheral circulation via the lymphatic system. HDL particles contribute apoC-II to the chylomicrons, required for the activation of *lipoprotein lipase* (LPL) within the capillary endothelium of adipose, heart, and skeletal muscle tissue. Free fatty acids are oxidized, esterified for storage as triglycerides, or released into the circulation bound to albumin for transport to the liver. After hydrolysis of the triglyceride core from the chylomicron, apoC particles are recirculated back to HDL. The subsequent contribution of apoE from HDL to the remnant chylomicron facilitates binding of the particle to the hepatic LDL receptor (LDL-R). Within the hepatocyte, the chylomicron remnant may be incorporated into membranes, resecreted as lipoprotein

Table 106.6 Characteristics of the Major Lipoproteins

LIPOPROTEIN	SOURCE	SIZE (nm)	DENSITY (g/mL)	COMPOSITION		
				PROTEIN (%)	LIPID (%)	APOLIPOPROTEINS
Chylomicrons	Intestine	80-1,200	<0.95	1-2	98-99	C-I, C-II, C-III, E, A-I, A-II, A-IV, B-48
Chylomicron remnants	Chylomicrons	40-150	<1.0006	6-8	92-94	B-48, E
VLDL	Liver, intestine	30-80	0.95-1.006	7-10	90-93	B-100, C-I, C-II, C-III
IDL	VLDL	25-35	1.006-1.019	11	89	B-100, E
LDL	VLDL	18-25	1.019-1.063	21	79	B-100
HDL	Liver, intestine VLDL, chylomicrons	5-20	1.125-1.210	32-57	43-68	A-I, A-II, A-IV C-I, C-II, C-III D, E

HDL, High-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins.

back into the circulation, or secreted as bile acids. Normally, all dietary fat is disposed of within 8 hours after the last meal, an exception being individuals with a disorder of chylomicron metabolism. **Postprandial hyperlipidemia** is a risk factor for atherosclerosis. Abnormal transport of chylomicrons and their remnants may result in their absorption into the blood vessel wall as *foam cells,* caused by the ingestion of cholesteryl esters by macrophages, the earliest stage in the development of fatty streaks.

Transport of Endogenous Lipids from the Liver

The formation and secretion of VLDL from the liver and its catabolism to IDL and LDL particles describe the *endogenous* lipoprotein pathway. Fatty acids used in the hepatic formation of VLDL are derived primarily by uptake from the circulation. VLDL appears to be transported from the liver as rapidly as it is synthesized, and it consists of triglycerides, cholesteryl esters, phospholipids, and apoB-100. Nascent particles of VLDL secreted into the circulation combine with apoC and apoE. The size of the VLDL particle is determined by the amount of triglyceride present, progressively shrinking in size as triglyceride is hydrolyzed by the action of LPL, yielding free fatty acids for utilization or storage in muscle and adipose tissue. Hydrolysis of approximately 80% of the triglyceride present in VLDL particles produces IDL particles containing an equal amount of cholesterol and triglyceride. The remaining remnant IDL is converted to LDL for delivery to peripheral tissues or to the liver. ApoE is attached to the remnant IDL particle to allow binding to the cell and subsequent incorporation into the lysosome. Individuals with a deficiency of either apoE2 or hepatic triglyceride lipase accumulate IDL in the plasma.

LDL particles account for approximately 70% of the plasma cholesterol in normal individuals. LDL receptors are present on the surfaces of nearly all cells. Most LDL is taken up by the liver, and the rest is transported to peripheral tissues such as the adrenal glands and gonads for steroid synthesis. Dyslipidemia is greatly influenced by LDL-R activity. The efficiency with which VLDL is converted into LDL is also important in lipid homeostasis. The normal newborn LDL level of 50 mg/dL is probably adequate for steroid synthesis throughout the life cycle.

High-Density Lipoprotein and Reverse Cholesterol Transport

Because hepatic secretion of lipid particles into the bile is the only mechanism by which cholesterol can be removed from the body, transport of excess cholesterol from the peripheral cells is a vitally important function of HDL. HDL is heavily laden with apoA-I–containing lipoproteins, which is nonatherogenic, in contrast to B lipoproteins. Cholesterol-poor nascent HDL particles secreted by the liver and small intestine are esterified to more mature HDL-2 particles by the action of the enzyme lecithin-cholesterol acyltransferase **(LCAT)**, which facilitates movement of chylomicrons and VLDL into the HDL core. HDL-2 may transfer cholesteryl esters back to apoB lipoproteins mediated by cholesteryl ester transfer protein (CETP), or the cholesterol-rich particle may be removed from the plasma by endocytosis, completing reverse cholesterol transport. Low HDL may be genetic (deficiency of apoA-I) or secondary to increased plasma triglyceride.

LCAT deficiency results in diminished maturation of HDL particles, affecting their ability to do reverse cholesterol transport. This reduces its protective effect on atherosclerosis. There are rare reports, however, of less-than-expected severity of atherosclerosis despite low HDL secondary to LCAT deficiency, suggesting that the relationship may, for unknown reasons, be variable.

HYPERLIPOPROTEINEMIAS

Hypercholesterolemia

See Table 106.7.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a monogenic autosomal dominant disorder characterized by strikingly elevated LDL cholesterol (LDL-C), premature cardiovascular disease (CVD), and tendon xanthomas. It is predominantly associated with defects of LDL-R activity but also includes defects in the genes for apoB *(APOB)* and the proprotein convertase subtilisin/kexin type 9 (PCSK-9), a protein important in LDL endocytosis. Of the almost 1,200 *LDLR* pathogenic variants described, some result in failure of synthesis of the LDL-R (receptor negative) and others cause defective binding or release at the lipoprotein-receptor interface. Receptor-negative pathogenic variants result in more severe phenotypes than receptor-defective pathogenic variants. Data from the Netherlands has confirmed the importance of LDL reduction in FH; the major adverse coronary event risk for affected siblings with statin treatment begun at age 10 years mirrored that of unaffected siblings rather than the risk profile of the affected parent.

Homozygous Familial Hypercholesterolemia

FH homozygotes inherit two abnormal LDL receptor genes, resulting in markedly elevated plasma cholesterol levels ranging between 500 and 1,200 mg/dL. Triglyceride levels are normal to mildly elevated, and HDL levels may be slightly decreased. The condition occurs in 1 in 500,000 persons. Receptor-negative patients have <2% normal LDL-R activity, whereas those who are receptor defective may have as much as 25% normal activity and consequently a better prognosis.

However, the prognosis is poor regardless of the specific LDL-R aberration. Severe atherosclerosis involving the aortic root and coronary arteries is present by early to middle childhood. These children usually present with **xanthomas**, which may cause thickening of the Achilles tendon or extensor tendons of the hands, or cutaneous lesions on the hands, elbows, knees, or buttocks (Figs. 106.10-106.12). Corneal arcus may be present. Family history is informative because premature heart disease is strongly prevalent among relatives of both parents. The diagnosis may be confirmed genetically or by measuring LDL-R

Table 106.7 Hyperlipoproteinemias

DISORDER	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETICS	ESTIMATED INCIDENCE
Familial hypercholesterolemia	LDL	Tendon xanthomas, CHD	AD	1 in 500
Familial defective ApoB-100	LDL	Tendon xanthomas, CHD	AD	1 in 1,000
Autosomal recessive hypercholesterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Sitosterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Polygenic hypercholesterolemia	LDL	CHD		1 in 30?
Familial combined hyperlipidemia	LDL, TG	CHD	AD	1 in 200
Familial dysbetalipoproteinemia	LDL, TG	Tuberoeruptive xanthomas, peripheral vascular disease	AD	1 in 10,000
Familial chylomicronemia (Frederickson type I)	TG ↑↑	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	1 in 1,000,000
Familial hypertriglyceridemia (Frederickson type IV)	TG ↑	±CHD	AD	1 in 500
Familial hypertriglyceridemia (Frederickson type V)	TG ↑↑	Xanthomas ± CHD	AD	—
Familial hepatic lipase deficiency	VLDL	CHD	AR	<1 in 1,000,000

AD, Autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; LDL, low-density lipoproteins, TG, triglycerides; VLDL, very low-density lipoproteins.



Fig. 106.10 Homozygous familial hypercholesterolemia. Tendon xanthomas in a 5-year-old boy with homozygous FH noted at the knee (**A**), wrist (**B**), and Achilles (**C**). *(Modified from Macchiaiolo M, Gagliardi MG, Toscano A, et al. Homozygous familial hypercholesterolaemia. Lancet. 2012;379:1330.)*



Fig. 106.11 Striate palmar xanthomata. *(From Durrington P. Dyslipidaemia, Lancet. 2003;362:717–731.)*



Fig. 106.12 Eruptive xanthomata on extensor surface of forearm. *(From Durrington P. Dyslipidaemia, Lancet. 2003;362:717–731.)*

activity in cultured skin fibroblasts. Phenotypic expression of the disease may also be assessed by measuring receptor activity on the surface of lymphocytes by using cell-sorting techniques.

Untreated homozygous patients rarely survive to adulthood. Symptoms of coronary insufficiency may occur early, and sudden death is common. LDL apheresis to remove LDL particles selectively from the

circulation is recommended for many children because it slows the progression of atherosclerosis. Liver transplantation is also successful in decreasing LDL-C levels, but complications related to immunosuppression are common. HMG-CoA reductase inhibitors may be modestly effective depending on the specific class of LDL-R defect present. Combination therapy with *ezetimibe,* selectively blocking cholesterol adsorption in the gut, usually results in further decline in LDL levels and has replaced the use of bile acid sequestrants. Clinical trials using microsomal triglyceride transfer protein inhibition with *lomitapide* (an oral agent) resulted in significant reduction of all apoB lipoproteins, including LDL, but hepatic fat deposition as a side effect limits this pharmacologic approach. *Mipomersen* (subcutaneous injection), an antisense oligonucleotide that binds to the apolipoprotein B mRNA, reduces the synthesis of apoB and thus also VLDL and LDL. LDL cholesterol levels may decline approximately 25% with this treatment. Adverse effects include flulike symptoms, hepatic steatosis, and cirrhosis.

Heterozygous Familial Hypercholesterolemia

Heterozygous FH is the most common single-gene disorder associated with acute coronary syndromes and atherosclerotic CHD in adults. Its prevalence is approximately 1 in 250 individuals worldwide, but the frequency may be greater in select populations, such as French Canadians, Afrikaners, Ashkenazi Jews, and Christian Lebanese, as a result of the founder effect of unique pathogenic variants. Heart disease accounts for more than half of all deaths in Western society, with the pathogenesis having both environmental and genetic influences.

Because heterozygous FH is a dominant condition with nearly full penetrance, 50% of first-degree relatives of affected individuals will have the disease, as will 25% of second-degree relatives. An estimated 20 million people have FH worldwide. Symptoms of CHD usually occur at the mean age of 45-48 years in males and a decade later in females. Genetic testing of both adult and pediatric patients who fulfill clinical diagnostic criteria for the diagnosis of heterozygous FH is variably positive dependent on the population under investigation.

One cannot overemphasize the importance of family history for suspecting the possibility of FH, especially given the low rate of cholesterol screening for children in primary care offices. Because the risk of CHD in individuals with FH can be up to 20 times greater than in the general population, guidelines have advocated for universal screening for cholesterol in childhood. There is also an interest in genetic testing for persons with suspected FH because of variability in phenotype based on genotype.

Plasma levels of LDL-C also do not allow unequivocal diagnosis of FH heterozygotes; values are generally twice normal for age because of one absent or dysfunctional allele. The U.S. MED-PED *(Make Early Diagnosis–Prevent Early Death)* Program has formulated diagnostic criteria.

Similar criteria with minor variations exist in the United Kingdom (Simon Broome criteria) and Holland (Dutch Lipid Clinic Network criteria). Within well-defined FH families, the diagnosis is reliably established according to LDL cutoff points. More stringent criteria are required to establish the diagnosis in previously undiagnosed families, requiring strong evidence of an autosomal inheritance pattern and higher LDL cutoff points. At a total cholesterol level of 310 mg/dL, only 4% of adults in the general population would have FH, whereas 95% of adults who were first-degree relatives of known cases would have the disease.

Very high cholesterol levels in children should prompt extensive screening of adult first- and second-degree relatives ("reverse cascade" cholesterol screening). In the general population, a child younger than age 18 years with total plasma cholesterol of 270 mg/dL and/or LDL-C of 200 mg/dL has an 88% chance of having FH (Table 106.8). *Formal clinical diagnosis of FH is based on the presence of two or more family members having elevated LDL-C levels* (the 95th percentile LDL-C level cutoff points for children vary with age and are lower than for adults; Table 106.9). The criteria for probable FH in a child whose first-degree relative has known FH require only modest elevation of total cholesterol to 220 mg/dL (LDL-C 160 mg/dL; see Table 106.8). The challenge of childhood FH diagnosis is heightened by the lack of clinical stigmata such as xanthomata that are employed in the Simon Broome and Dutch Lipid Clinic Network schema and highlights the needed shift toward genetic diagnosis.

Treatment of children with FH should begin with a rigorous low-fat diet. Diet alone is rarely sufficient for decreasing blood cholesterol levels to acceptable levels (LDL-C <130 mg/dL). Ezetimibe blocks cholesterol adsorption in the gastrointestinal (GI) tract and has a low risk of side effects. Data suggest that ezetimibe will lower total cholesterol by 20-30 mg/dL. *HMG-CoA reductase inhibitors (statins) are the drug of choice for treatment of FH because of their remarkable effectiveness and acceptable risk profile.* This class of drugs in children over age 10 years is as effective in children as in adults, and the risks of elevated hepatic enzymes and myositis are no greater than in adults. Another class of drugs, the proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, are monoclonal antibodies (mAbs) that block the action of PCSK-9 to downregulate the LDL-R. These agents boost LDL-R levels and result in a marked decrease in plasma LDL-C levels. PCSK-9 inhibitors have a role in adults intolerant of statins and those with subtherapeutic statin effect. *Use of evolocumab in children over age 10 is FDA approved.* In addition, tobacco avoidance and cessation of use of tobacco in the family should be stressed from the time of diagnosis.

Familial Defective ApoB-100

Familial defective apoB-100 is an autosomal dominant condition indistinguishable from heterozygous *LDLR* FH. LDL cholesterol levels are increased, triglycerides are normal, adults often develop tendon xanthomas, and premature CHD occurs. Familial defective apoB-100 is caused by a pathogenic variant in the receptor-binding region of apoB-100, the ligand of the LDL receptor, with an estimated frequency of 1 in 700 people in Western cultures. It is usually caused by missense substitution of apoB-100 (p.Arg3527Gln, previously numbered p.Arg3500Gln), which results in reduced ability of the LDL-R to bind LDL-C, thus impairing its removal from the circulation. Specialized laboratory testing can distinguish familial defective apoB-100 from FH, but this is not necessary, except in research settings, because treatment is the same.

Autosomal Recessive Hypercholesterolemia

This rare condition, caused by a defect in LDL-R–mediated endocytosis in the liver, clinically presents with severe hypercholesterolemia at levels intermediate between those found in homozygous and heterozygous FH. It is disproportionately present among Sardinians, reported in other Mediterranean populations, and is modestly responsive to treatment with HMG-CoA reductase inhibitors.

Sitosterolemia

A rare autosomal recessive condition characterized by excessive intestinal adsorption of plant sterols, sitosterolemia is caused by pathogenic variants in the adenosine triphosphate (ATP)–binding cassette transporter system (*ABCG5* or *ABCG8*), which is responsible for limiting adsorption of plant sterols in the small intestine and promotes biliary excretion of the small amounts adsorbed. Plasma cholesterol levels may be severely elevated, resulting in tendon xanthomas and premature atherosclerosis. Other features include hemolytic anemia, macrothrombocytopenia (large platelets, reduced number), and hemorrhage. Diagnosis can be confirmed by measuring elevated plasma sitosterol levels. Treatment with HMG-CoA reductase inhibitors is not effective, but cholesterol adsorption inhibitors, such as ezetimibe, and bile acid sequestrants are effective.

Polygenic Hypercholesterolemia

Primary elevation in LDL-C among children and adults is most often polygenic; the small effects of many genes are affected by environmental influences (diet). Plasma cholesterol levels are modestly elevated; triglyceride levels are normal. Polygenic hypercholesterolemia aggregates in families sharing a common lifestyle but does not follow predictable hereditary patterns found in single-gene lipoprotein defects. Treatment of children with polygenic hypercholesterolemia is directed

Table 106.8 Percentage of Youths Younger than Age 18 years Expected to Have Familial Hypercholesterolemia (FH) According to Cholesterol Levels and Closest Relative with FH

TOTAL CHOL (mg/dL)	LDL CHOL (mg/dL)	PERCENTAGE WITH FH AT THAT LEVEL			
		DEGREE OF RELATIVE			
		FIRST	SECOND	THIRD	GENERAL POPULATION
180	122	7.2	2.4	0.9	0.01
190	130	13.5	5.0	2.2	0.03
200	138	26.4	10.7	4.9	0.07
210	147	48.1	23.6	11.7	0.19
220	155	73.1	47.5	27.9	0.54
230	164	90.0	75.0	56.2	1.8
240	172	97.1	93.7	82.8	6.3
250	181	99.3	97.6	95.3	22.2
260	190	99.9	99.5	99.0	57.6
270	200	100.0	99.9	99.8	88.0
280	210	100.0	100.0	100.0	97.8
290	220	100.0	100.0	100.0	99.6
300	230	100.0	100.0	100.0	99.9
310	240	100.0	100.0	100.0	100.0

Chol, Cholesterol; LDL, low-density lipoprotein.
From Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol.* 1993;72:171–176.

toward adoption of a healthy lifestyle: reduced total and saturated fat consumption and at least 1 hour of physical activity daily. Cholesterol-lowering medication is rarely necessary.

Hypercholesterolemia with Hypertriglyceridemia

Familial Combined Hyperlipidemia

This autosomal dominant condition is characterized by moderate elevation in plasma LDL-C and triglycerides and reduced plasma HDL-C. Familial combined hyperlipidemia (FCHL) is the most common primary lipid disorder, affecting approximately 1 in 200 people. Family history of premature heart disease is typically positive; the formal diagnosis requires that at least two first-degree relatives have evidence of one of three variants of dyslipidemia: (1) >90th percentile plasma LDL-C, (2) >90th percentile LDL-C and triglycerides, and (3) >90th percentile triglycerides. Individuals can switch from one phenotype to another. Xanthomas are not a feature of FCHL. Elevated plasma apoB levels with increased small, dense LDL particles support the diagnosis.

Children and adults with FCHL have coexisting adiposity, hypertension, and hyperinsulinemia, suggesting the presence of **metabolic syndrome**. Formal diagnosis in adults, as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, identifies six major components: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without impaired glucose tolerance, evidence of vascular inflammation, and prothrombotic state. An estimated 30% of overweight adults fulfill criteria for the diagnosis of metabolic syndrome, including 65% of those with FCHL. *There is no official definition of metabolic syndrome for children.* Absolute cutoffs for diagnosis in children do not account for continuous variables in aging, sexual maturation, and race/ethnicity.

FCHL and type 2 diabetes share many features of metabolic syndrome, suggesting that they are less distinct entities than originally conceptualized. Genetic association studies reveal evidence for a common genetic background. The resultant metabolic overlap is associated with ectopic fat accumulation and insulin resistance. The mechanisms associating visceral adiposity with metabolic syndrome and type 2 diabetes are not fully understood. It is assumed that hypercholesterolemia and, with less certainty, hypertriglyceridemia confer risk for CVD in patients with FCHL. When features of metabolic syndrome are included in logistic models, shared etiologic features such as increased visceral adiposity become apparent. Visceral adiposity increases with age, and its importance in children as a risk factor for heart disease and diabetes is limited by the relative paucity of data. Body mass index (BMI) remains the surrogate for adiposity in the pediatric clinical setting.

The cornerstone of management is lifestyle modification. This includes a diet low in saturated fats, *trans* fats, and cholesterol, as well as reduced consumption of processed sugars. Increased dietary intake of fruits and vegetables is important, as is 1 hour of moderate physical activity daily. Compliance among children and their parents is often a problem, but small incremental steps are more likely to succeed than aggressive weight loss strategies. It is very important that the child's caregivers participate in the process. Plasma triglyceride levels are usually quite responsive to dietary restriction, especially reduction in the amount of sweetened drinks consumed. Blood cholesterol levels may decrease by 10–15%, but if LDL-C remains >160 mg/dL, drug therapy should be considered.

Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Familial dysbetalipoproteinemia (FDBL) is caused by pathogenic variants in *APOE,* which, when exposed to environmental influences (e.g., high-fat high-caloric diet, excessive alcohol intake), results in a mixed type of hyperlipidemia. Patients tend to have elevated plasma cholesterol and triglycerides to a relatively similar degree. HDL-C is typically normal, in contrast to other causes of hypertriglyceridemia associated with low HDL. This rare disorder affects approximately 1 in 10,000 persons. ApoE mediates removal of chylomicron and VLDL remnants from the circulation by binding to hepatic surface receptors. The polymorphic *APOE* gene expresses in three isoforms: *apoE3, apoE2,* and *apoE4. E4* is the "normal" allele present in the majority of the population. The *apoE2* isoform has lower affinity for the LDL receptor, and its frequency is approximately 7%. Approximately 1% of the population is

Table 106.9 Plasma Cholesterol and Triglyceride Levels in Childhood and Adolescence: Means and Percentiles

	TOTAL TRIGLYCERIDE (mg/dL)					TOTAL CHOLESTEROL (mg/dL)					LDL CHOLESTEROL (mg/dL)					HDL CHOLESTEROL (mg/dL)*				
	5TH	MEAN	75TH	90TH	95TH	5TH	MEAN	75TH	90TH	95TH	5TH	MEAN	75TH	90TH	95TH	5TH	10TH	25TH	MEAN	95TH
Cord	14	34	—	—	84	42	68	—	—	103	17	29	—	—	50	13	—	—	35	60
1-4 YR																				
Male	29	56	68	85	99	114	155	170	190	203	—	—	—	—	—	—	—	—	—	—
Female	34	64	74	95	112	112	156	173	188	200	—	—	—	—	—	—	—	—	—	—
5-9 YR																				
Male	28	52	58	70	85	125	155	168	183	189	63	93	103	117	129	38	42	49	56	74
Female	32	64	74	103	126	131	164	176	190	197	68	100	115	125	140	36	38	47	53	73
10-14 YR																				
Male	33	63	74	94	111	124	160	173	188	202	64	97	109	122	132	37	40	46	55	74
Female	39	72	85	104	120	125	160	171	191	205	68	97	110	126	136	37	40	45	52	70
15-19 YR																				
Male	38	78	88	125	143	118	153	168	183	191	62	94	109	123	130	30	34	39	46	63
Female	36	73	85	112	126	118	159	176	198	207	59	96	111	29	137	35	38	43	52	74

*Note that different percentiles are listed for high-density lipoprotein (HDL) cholesterol.
LDL, Low-density lipoprotein.
Data for cord blood from Strong W. Atherosclerosis: its pediatric roots. In Kaplan N, Stamler J, eds. *Prevention of Coronary Heart Disease*. Philadelphia: Saunders; 1983. Data for children 1-4 yr from Tables 6, 7, 20, and 21, and all other data from Tables 24, 25, 32, 33, 36, and 37 in *Lipid Research Clinics Population Studies Data Book*, Vol 1, "The Prevalence Study," NIH Publication No. 80-1527. Washington, DC: National Institutes of Health; 1980

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 20, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

homozygous for *apoE2/E2,* the most common pathogenic variant associated with FDBL, but only a minority expresses the disease. Expression requires precipitating illnesses such as diabetes, obesity, renal disease, or hypothyroidism. Individuals homozygous for *apoE4/E4* are at risk for late-onset Alzheimer disease and dementia from repeated sports-related head injuries.

Most patients with FDBL present in adulthood with distinctive xanthomas. Tuberoeruptive xanthomas resemble small, grapelike clusters on the knees, buttocks, and elbows. Prominent orange-yellow discoloration of the creases of the hands (palmar xanthomas) is also typically present. Atherosclerosis, often presenting with peripheral vascular disease, usually occurs in the fourth or fifth decade. Children may present with a less distinctive rash and generally have precipitating illnesses.

The diagnosis of FDBL is established by lipoprotein electrophoresis, which demonstrates a broad beta band containing remnant lipoproteins. Direct measurement of VLDL by ultracentrifugation can be performed in specialized lipid laboratories. A VLDL/total triglyceride ratio >0.30 supports the diagnosis. *APOE* genotyping for *apoE2* homozygosity can be performed, confirming the diagnosis in the presence of the distinctive physical findings. A negative result does not necessarily rule out the disease, as other pathogenic variants in *APOE* may cause even more serious manifestations.

Pharmacologic treatment of FDBL is necessary to decrease the likelihood of symptomatic atherosclerosis in adults. HMG-CoA reductase inhibitors, nicotinic acid, and fibrates are all effective. FDBL is quite responsive to recommended dietary restriction.

Hypertriglyceridemias

The familial disorders of triglyceride-rich lipoproteins include both common and rare variants of the Frederickson classification system. These include familial chylomicronemia (type I), familial hypertriglyceridemia (type IV), and the more severe combined hypertriglyceridemia and chylomicronemia (type V). Hepatic lipase deficiency also results in a similar combined hyperlipidemia.

Familial Chylomicronemia (Type I Hyperlipidemia)

This rare single-gene defect, like FH, is caused by pathogenic variants affecting clearance of apoB-containing lipoproteins. A deficiency or absence of lipoprotein lipase *(LPL)* or its cofactor apoC-II *(APOC2)*, which facilitates lipolysis by LPL, causes severe elevation of triglyceride-rich plasma chylomicrons. HDL-C levels are decreased. Clearance of these particles is greatly delayed, so the plasma is noted to have a turbid appearance even after prolonged fasting (Fig. 106.13). Chylomicronemia caused by LPL deficiency is associated with modest elevation in triglycerides, whereas this is not the case when the cause is deficient or absent apoC-II. Both are autosomal recessive conditions with a frequency of approximately 1 in 1 million. The disease usually presents during childhood with acute pancreatitis. Eruptive xanthomas on the arms, knees, and buttocks may be present, and there may be hepatosplenomegaly. The diagnosis is established by assaying triglyceride lipolytic activity. **Treatment** of chylomicronemia is by vigorous dietary fat restriction supplemented by fat-soluble vitamins. Medium-chain triglycerides that are adsorbed into the portal venous system may augment total fat intake, and administration of fish oils may also be beneficial.

Familial Hypertriglyceridemia (Type IV Hyperlipidemia)

Familial hypertriglyceridemia (FHTG) is an autosomal dominant disorder of unknown etiology that occurs in approximately 1 in 500 individuals. It is characterized by elevation of plasma triglycerides >90th percentile (250-1,000 mg/dL range), often accompanied by slight elevation in plasma cholesterol and low HDL. FHTG does not usually manifest until adulthood, although it can be detected in approximately 20% of affected children. In contrast to FCHL, FHTG is not thought to be highly atherogenic. It is most likely caused by defective breakdown of VLDL or, less often, by overproduction of this class of lipoproteins.

The diagnosis should include the presence of at least one first-degree relative with hypertriglyceridemia. FHTG should be distinguished from FCHL and FDBL, which require more vigorous treatment to prevent coronary or peripheral vascular disease. The differentiation is usually possible on clinical grounds, in that lower LDL-C levels accompany FHTG, but measurement of normal apoB levels in FHTG may be helpful in ambiguous situations.



Fig. 106.13 Milky plasma from a patient with acute abdominal pain. *(From Durrington P. Dyslipidaemia, Lancet. 2003;362:717–731.)*

A more severe hypertriglyceridemia characterized by increased levels of chylomicrons and VLDL particles (Frederickson **type V**) may occasionally be encountered. Triglyceride levels are often >1,000 mg/dL. The disease is rarely seen in children. In contrast to chylomicronemia (Frederickson **type I**), LPL or apoC-II deficiency is not present. These patients often develop eruptive xanthomas in adulthood, whereas **type IV** hypertriglyceridemia individuals do not. Acute pancreatitis may be the presenting illness. As with other hypertriglyceridemias, excessive alcohol consumption and estrogen therapy can exacerbate the disease.

Secondary causes of *transient hypertriglyceridemia* should be ruled out before making a diagnosis of FHTG. A diet high in simple sugars and carbohydrates or excessive alcohol consumption, as well as estrogen therapy, may exacerbate hypertriglyceridemia. Adolescents and adults should be questioned about excessive consumption of soda and other sweetened drinks, as it is common to encounter people who drink supersized drinks or multiple 12 oz cans of sweetened drinks daily. Cessation of this practice often results in a dramatic fall in triglyceride levels and weight among those who are obese. HDL-C levels will tend to rise as BMI stabilizes.

Pediatric diseases associated with hyperlipidemia include hypothyroidism, nephrotic syndrome, biliary atresia, glycogen storage disease, Niemann-Pick disease (NPD), Tay-Sachs disease, systemic lupus erythematosus, hepatitis, and anorexia nervosa (Table 106.10). Certain medications exacerbate hyperlipidemia, including isotretinoin (Accutane), thiazide diuretics, second-generation antipsychotic agents, oral contraceptives, corticosteroids, β blockers, immunosuppressants, and protease inhibitors used in HIV treatment.

Treatment of hypertriglyceridemia in children rarely requires medication unless levels >1,000 mg/dL persist after dietary restriction of fats,

Table 106.10 Secondary Causes of Hyperlipidemia

HYPERCHOLESTEROLEMIA
Hypothyroidism
Nephrotic syndrome
Cholestasis
Anorexia nervosa
Drugs: progesterone, thiazides, carbamazepine (Tegretol), cyclosporine
HYPERTRIGLYCERIDEMIA
Glycogen storage disease type 1
Obesity
Type 2 diabetes
Alcohol
Renal failure
Sepsis
Stress
Cushing syndrome
Pregnancy
Hepatitis
AIDS, protease inhibitors
Drugs: anabolic steroids, β blockers, estrogen, thiazides, Accutane
REDUCED HIGH-DENSITY LIPOPROTEIN
Smoking
Obesity
Type 2 diabetes
Malnutrition
Drugs: β blockers, anabolic steroids

sugars, and carbohydrates, accompanied by increased physical activity. In such patients the aim is to prevent episodes of pancreatitis. The common use of fibrates (fenofibric acid) and niacin in adults with hypertriglyceridemia is not recommended in children. HMG-CoA reductase inhibitors are variably effective in lowering triglyceride levels, and there is considerably more experience documenting the safety and efficacy of this class of lipid-lowering medications in children. In adults, the U.S. Food and Drug Administration (FDA) has approved prescription (Lovaza, Vascepa) and nonprescription fish oils as adjuncts to diet in the treatment of severe hypertriglyceridemias.

Hepatic Lipase Deficiency

Hepatic lipase deficiency is a very rare autosomal recessive condition caused by pathogenic variants in *LMF1* resulting in elevation in both plasma cholesterol and triglycerides. Hepatic lipase hydrolyzes triglycerides and phospholipids in VLDL remnants and IDL, preventing their conversion to LDL. HDL-C levels tend to be increased rather than decreased, suggesting the diagnosis. Laboratory confirmation is established by measuring hepatic lipase activity in heparinized plasma.

Disorders of High-Density Lipoprotein Metabolism

Primary Hypoalphalipoproteinemia

Isolated low HDL-C is a familial condition that often follows a pattern suggestive of autosomal dominant inheritance but may occur independent of family history. It is the most common disorder of HDL metabolism. It is defined as HDL-C <10th percentile for gender and age with normal plasma triglycerides and LDL-C. Whether it is associated with more rapid atherosclerosis is uncertain. Primary hypoalphalipoproteinemia appears to be related to a reduction in apoA-I synthesis and increased catabolism of HDL. Secondary causes of low HDL-C, such as metabolic syndrome, and rare diseases such as LCAT deficiency and Tangier disease must be ruled out.

Familial Hyperalphalipoproteinemia

This is an unusual condition conferring decreased risk for CHD among family members. Plasma levels of HDL-C exceed 80 mg/dL.

Familial Apolipoprotein A-I Deficiency

Pathogenic variants in the *APOA1* gene may result in complete absence of plasma HDL. Nascent HDL is produced in the liver and small intestine. Free cholesterol from peripheral cells is esterified by LCAT, enabling formation of mature HDL particles. ApoA-I is required for normal enzymatic functioning of LCAT. The resultant accumulation of free cholesterol in the circulation eventually leads to corneal opacities, planar xanthomas, and premature atherosclerosis. Some patients, however, may have pathogenic variants of *APOA1* that result in very rapid catabolism of the protein not associated with atherogenesis, despite HDL-C levels in the 15-30 mg/dL range.

Tangier Disease

This autosomal dominant disease is associated with HDL-C levels <5 mg/dL. It is caused by pathogenic variants in *ABCA1,* which encodes a protein that facilitates the binding of cellular cholesterol to apoA-I. This results in free cholesterol accumulation in the reticuloendothelial system, manifested by tonsillar hypertrophy of a distinctive orange color and hepatosplenomegaly. Intermittent peripheral neuropathy may occur from cholesterol accumulation in Schwann cells. Diagnosis should be suspected in children with enlarged orange tonsils and extremely low HDL-C levels.

Familial Lecithin–Cholesterol Acyltransferase Deficiency

Pathogenic variants of *LCAT* interfere with the esterification of cholesterol, thereby preventing formation of mature HDL particles. This is associated with rapid catabolism of apoA-I. Free circulating cholesterol in the plasma is greatly increased, which leads to corneal opacities and HDL-C levels <10 mg/dL. Partial LCAT deficiency is known as "fish-eye" disease because of the corneal opacities. Complete deficiency causes hemolytic anemia and progressive renal insufficiency early in adulthood. This rare disease is not thought to cause premature atherosclerosis. Laboratory confirmation is based on a demonstration of decreased cholesterol esterification in the plasma.

Cholesteryl Ester Transfer Protein Deficiency

Pathogenic variants of the *CETP* gene result in cholesteryl ester transfer protein (CETP) deficiency. CETP facilitates the transfer of lipoproteins from mature HDL to and from VLDL and chylomicron particles, thus ultimately regulating the rate of cholesterol transport to the liver for excretion in the bile. About half of mature HDL-2 particles are directly removed from the circulation by HDL receptors on the surface of the liver. The other half of cholesteryl esters in the core of HDL exchange with triglycerides in the core of apoB lipoproteins (VLDL, IDL, LDL) for transport to the liver. Homozygous deficiency of CETP has been observed in subsets of the Japanese population with extremely high HDL-C levels (>150 mg/dL).

Conditions Associated with Low Cholesterol

Disorders of apoB-containing lipoproteins and intracellular cholesterol metabolism are associated with low plasma cholesterol.

Abetalipoproteinemia

This rare autosomal recessive disease is caused by pathogenic variants in the *MTTP* gene that encodes the microsomal triglyceride transfer protein necessary for the transfer of lipids to nascent chylomicrons in the small intestine and VLDL in the liver. This results in an absence of chylomicrons, VLDL, LDL, and apoB and very low levels of plasma cholesterol and triglycerides. Fat and fat-soluble vitamin malabsorption, diarrhea, and failure to thrive present in early childhood. Spinocerebellar degeneration, secondary to vitamin E deficiency, manifests in loss of deep tendon reflexes progressing to ataxia and lower-extremity spasticity by adulthood. Patients with abetalipoproteinemia also acquire a progressive pigmented retinopathy associated with decreased night and color vision and eventual blindness. The neurologic symptoms and retinopathy may be mistaken for Friedreich ataxia. Differentiation from Friedreich ataxia is suggested by the presence of malabsorption and acanthocytosis on peripheral blood smear

in abetalipoproteinemia. Many of the clinical manifestations of the disease are a result of malabsorption of fat-soluble vitamins, such as vitamins E, A, and K. *Early treatment with supplemental vitamins, especially E, may significantly slow the development of neurologic sequelae.* Vitamin E is normally transported from the small intestine to the liver by chylomicrons, where it is dependent on the endogenous VLDL pathway for delivery into the circulation and peripheral tissues. Parents of children with abetalipoproteinemia have normal blood lipid and apoB levels.

Familial Hypobetalipoproteinemia

Familial homozygous hypobetalipoproteinemia is associated with symptoms very similar to those of abetalipoproteinemia, but the inheritance pattern is autosomal dominant caused by pathogenic variants in *APOB*. It is distinguishable from abetalipoproteinemia in that heterozygous parents of probands have plasma LDL-C and apoB levels less than half of normal. However, few symptoms or sequelae are associated with the heterozygous condition.

The selective inability to secrete apoB-48 from the small intestine results in a condition resembling abetalipoproteinemia or homozygous hypobetalipoproteinemia. Sometimes referred to as **Anderson disease** or chylomicron retention disease, caused by recessive alterations of the *SAR1B* gene, the failure of chylomicron absorption causes steatorrhea and fat-soluble vitamin deficiency. The blood level of apoB-100, derived from normal hepatocyte secretion, is normal in this condition.

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome **(SLOS)** is an autosomal recessive disorder that includes microcephaly, polydactyly, holoprosencephaly, seizures and developmental delay. Phenotypic variance ranges from microcephaly, cardiac and brain malformation, and multiorgan system failure to only subtle dysmorphic features and mild developmental delay. It is associated with low plasma cholesterol and accumulated precursors (Tables 106.11 and 106.12) (see Chapter 628.2). Pathogenic variants in the *DHCR7* (7-dehydrocholesterol-Δ7 reductase) gene result in deficiency of the microsomal enzyme DHCR7, which is necessary to complete the final step in cholesterol synthesis. Hypotheses to connect the role of cholesterol synthesis in SLOS congenital malformations have implicated the ligand sonic hedgehog (SHH), for which developmental signaling activity is dependent on cholesterol modification. The incidence of SLOS is estimated to be 1 in 20,000-60,000 births.

Spontaneous abortion of SLOS fetuses may occur. **Type II** SLOS often leads to death by the end of the neonatal period. Survival is unlikely when the plasma cholesterol level is <20 mg/dL. Laboratory measurement should be performed by gas chromatography, because standard techniques for lipoprotein assay include measurement of cholesterol precursors, which may yield a false-positive result. Milder cases may not present until late childhood. **Treatment** includes supplemental dietary cholesterol (egg yolk) and HMG-CoA reductase inhibition to prevent the synthesis of toxic precursors proximal to the enzymatic block.

Disorders of Intracellular Cholesterol Metabolism

Cerebrotendinous Xanthomatosis

This autosomal recessive disorder presents in late adolescence with tendon xanthomas, cataracts, and progressive neurodegeneration. It is caused by tissue accumulation of bile acid intermediates that are shunted into production of cholestanol that in turn result from pathogenic variants in the gene for sterol 27-hydroxylase *(CYP27A1)*. This enzyme is necessary for normal mitochondrial synthesis of bile acids in the liver. Early treatment with chenodeoxycholic acid reduces cholesterol levels and prevents the development of symptoms.

Wolman Disease and Cholesterol Ester Storage Disease

These autosomal recessive disorders are caused by pathogenic variants in *LIPA* that result in lack of lysosomal acid lipase. After LDL cholesterol is incorporated into the cell by endocytosis, it is delivered to lysosomes, where it is hydrolyzed by lysosomal lipase. Failure of hydrolysis because of complete absence of the enzyme causes accumulation of cholesteryl esters within the cells. Hepatosplenomegaly, steatorrhea, and failure to thrive occur during early infancy, leading to death by the end of the first year. In cholesterol ester storage disease, a less severe form than Wolman disease, there is low but detectable acid lipase activity (see Chapter 106.4).

Table 106.11 Major Clinical Characteristics of Smith-Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients)

CRANIOFACIAL
Microcephaly
Blepharoptosis
Anteverted nares
Retromicrognathia
Low-set, posteriorly rotated ears
Midline cleft palate
Broad maxillary alveolar ridges
Cataracts (<50%)
SKELETAL ANOMALIES
Syndactyly of toes II/III
Postaxial polydactyly (<50%)
Equinovarus deformity (<50%)
GENITAL ANOMALIES
Hypospadias
Cryptorchidism
Sexual ambiguity (<50%) or XY sex reversal
DEVELOPMENT
Prenatal and postnatal growth retardation
Feeding problems
Intellectual disability
Behavioral abnormalities

From Haas D, Kelley RI, Hoffmann GF. Inherited disorders of cholesterol biosynthesis. *Neuropediatrics.* 2001;32:113–122.

Niemann-Pick Disease Type C

This disorder of intracellular cholesterol transport is characterized by accumulation of cholesterol and sphingomyelin in the CNS and reticuloendothelial system. Death from this autosomal recessive neurologic disease usually occurs by adolescence (see Chapter 106.4).

Lipoprotein Patterns in Children and Adolescents

Derived primarily from the Lipid Research Clinics Population Studies, Table 106.9 shows the distribution of lipoprotein levels in American youth at various ages. Total plasma cholesterol rises rapidly from a mean of 68 mg/dL at birth to a level approximately twice that by the end of the neonatal period. A very gradual rise in total cholesterol level occurs until puberty, when the mean level reaches 160 mg/dL. Total cholesterol falls transiently during puberty in males because of a small decrease in HDL-C and in females secondary to a slight fall in LDL-C. Blood cholesterol levels track reasonably well as individuals age.

High blood cholesterol tends to aggregate in families, a reflection of genetic and environmental influences.

Acceptable total cholesterol among children and adolescents is <170 mg/dL; borderline is 170-199 mg/dL; and high is >200 mg/dL. Acceptable LDL-C is <110 mg/dL; borderline is 110-129 mg/dL; and high is >130 mg/dL. HDL-C should be >40 mg/dL.

Blood Cholesterol Screening

A lipid profile should be checked for all children between ages 9 and 11 years and then another between ages 17 and 21 years because cholesterol levels may vary after puberty. However, if a child would have met the selective criteria from the previous risk-based guidelines (premature coronary artery disease [CAD] in a parent or grandparent, a parent with cholesterol >240 mg/dL), screening can occur as early as age 2

Table 106.12 Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli-Opitz Patients

CENTRAL NERVOUS SYSTEM
Frontal lobe hypoplasia
Enlarged ventricles
Agenesis of corpus callosum
Cerebellar hypoplasia
Holoprosencephaly
CARDIOVASCULAR
Atrioventricular canal
Secundum atrial septal defect
Patent ductus arteriosus
Membranous ventricular septal defect
URINARY TRACT
Renal hypoplasia or aplasia
Renal cortical cysts
Hydronephrosis
Ureteral duplication
GASTROINTESTINAL
Hirschsprung disease
Pyloric stenosis
Refractory dysmotility
Cholestatic and noncholestatic progressive liver disease
PULMONARY
Pulmonary hypoplasia
Abnormal lobation
ENDOCRINE
Adrenal insufficiency

From Haas D, Kelley RI, Hoffmann GF. Inherited disorders of cholesterol biosynthesis. *Neuropediatrics.* 2001;32:113–122.

years. Data also suggest that obtaining a nonfasting lipid profile can be just as useful in detecting severe genetic dyslipidemias as a fasting lipid profile and thus can be used as first-line screening in children. Fasting lipid profiles may also be used depending on parental, child, and clinician preference, especially if there is concern for hypertriglyceridemia, because triglycerides are affected more by fasting status. Abnormal lipid panels should be repeated, and especially when the concern is the triglycerides, the second panel should be obtained ≥2 weeks later in the fasted state. Treatment other than lifestyle modification is not initiated based on a single lipid panel determination.

Risk Assessment and Treatment of Hyperlipidemia

The NCEP recommends a population-based approach toward a healthy lifestyle applicable to all children and an individualized approach directed at those children at high risk (Fig. 106.14). The important focus on maintenance of a healthy lifestyle rather than aggressive weight reduction is recommended by the American Academy of Pediatrics (AAP).

All children with dyslipidemias are stratified according to the presence of high-level or moderate-level risk factors to determine their ultimate treatment. **High-level risk factors** are defined as hypertension requiring drug therapy (blood pressure ≥99th percentile + 5 mm Hg), current cigarette smoker, BMI at the ≥97th percentile, the presence of type 1 or type 2 diabetes mellitus, chronic kidney disease, postorthoptic heart transplant, and/or Kawasaki disease with current aneurysms. **Moderate-level risk factors** are defined as hypertension that does not require drug therapy, BMI at the ≥95th percentile but <97th percentile, HDL-C <40 mg/dL, Kawasaki disease (and possibly multisystem inflammatory syndrome in children [MIS-C]) with regressed coronary aneurysms, chronic inflammatory disease, HIV infection, and/or the presence of nephrotic syndrome.

The initial treatment for dyslipidemia in a child always begins with a 6-month trial of lifestyle modification, namely, improvements in dietary and physical activity patterns. Being overweight confers a special risk of CVD because of the strong association with insulin resistance syndrome (metabolic syndrome). Although there is no standardized definition of metabolic syndrome for youth, it is likely that half of all severely obese children are insulin resistant. Data from the CARDIAC project noted that 49% of fifth-grade children with the hyperpigmented rash, acanthosis nigricans, had three or more factors for insulin resistance syndrome when using the definition classically used for adults, including evidence of insulin resistance, hypertension, HDL-C <40 mg/dL, and triglycerides >150 mg/dL, in addition to obesity.

The Cardiovascular Health Integrated Lifestyle Diet-1 **(CHILD-1)** diet is the first level of dietary change to be recommended for all children with dyslipidemias. The CHILD-1 diet is specially designed for children with risk factors for CAD and focuses on limiting dietary cholesterol to 300 mg/day, limiting sugary drink consumption, using reduced-fat/skim milk, avoiding foods high in *trans*-type fats, limiting foods high in sodium, and encouraging consumption of foods high in fiber. Specific recommendations depend on the child's age. American Heart Association (AHA) diet guidelines for all persons of all ages recommend these measures plus avoidance of highly processed foods. Specific amounts or percentages of saturated vs monosaturated or polyunsaturated fats are not addressed.

The use of the Cardiovascular Health Integrated Lifestyle Diet-2 **(CHILD-2)** diet is recommended if the CHILD-1 diet alone is unsuccessful. Although similar in many aspects to the CHILD-1 diet, the CHILD-2 diet is geared toward a specific dyslipidemia type; the **CHILD-2 LDL** diet is recommended for children with elevated LDL levels and the **CHILD-2 TG** diet for those presenting with elevated triglycerides. The basic recommendations of calorie consumption for the CHILD-2 diet are as follows: only 25–30% of calories from fat, ≤7% of calories from saturated fat, 10% of calories from monounsaturated fat, and <200 mg/day of cholesterol. If the CHILD-2 LDL diet is recommended, the use of plant sterols and water-soluble fiber is emphasized. If the CHILD-2 TG diet is recommended, increasing consumption of omega-3 fatty acids and complex rather than simple carbohydrates is emphasized.

If followed, these dietary recommendations will provide adequate calories for optimal growth and development without promoting obesity. Compliance on the part of children and their caregivers is challenging. *Children learn eating habits from their parents*. Successful adoption of a healthier lifestyle is much more likely to occur if meals and snacks in the home are applicable to the entire family rather than an individual child. A regular time for meals together as a family is desirable. Grandparents and other nonparental caregivers sometimes need to be reminded not to indulge the child who is on a restricted diet. Additionally, the rise in obesity is prompting some school districts to restrict sweetened drink availability and offer more nutritious cafeteria selections.

Changes in physical activity habits are also an important part of the initial lifestyle modification. The National Association for Sport and Physical Education recommends that children should accumulate at least 60 minutes of age-appropriate physical activity on most days of the week. Extended periods (≥2 hr) of daytime inactivity are discouraged, as is >2 hours of television and other forms of screen time.

Pharmacologic Therapy. See Tables 106.13 and 106.14.

Pharmacologic therapy with cholesterol-lowering medication is the cornerstone of treatment for children who fail to respond to 6 months of rigorous lifestyle modification. It should be considered when one of the following conditions are met (also shown in Fig. 106.14):

- LDL cholesterol remains >190 mg/dL
- LDL cholesterol remains >160 mg/dL with the presence of one high-level risk factor *and/or* at least two moderate-level risk factors
- LDL cholesterol remains >130 mg/dL with the presence of at least two high-level risk factors, one high-level risk factor, *and* at least two moderate-level risk factors, *or* evidence of CAD

HMG-CoA reductase inhibitors, also known as "statins," are remarkably effective in lowering LDL-C levels and reducing plaque

Table 106.13 Drugs Used for the Treatment of Hyperlipidemia

DRUG	MECHANISM OF ACTION	INDICATION	STARTING DOSE
HMG-CoA reductase inhibitors (statins)	↓ Cholesterol and VLDL synthesis ↑ Hepatic LDL receptors	Elevated LDL	5-80 mg every night at bedtime
Bile acid sequestrants: Cholestyramine Colestipol	↑ Bile and excretion	Elevated LDL	 4-32 g daily 5-40 g daily
Nicotinic acid	↓ Hepatic VLDL synthesis	Elevated LDL Elevated TG	100-2,000 mg three times daily
Fibric acid derivatives: Gemfibrozil	↑ LPL ↓ VLDL	Elevated TG	600 mg twice daily
Fish oils	↓ VLDL production	Elevated TG	3-10 g daily
Cholesterol absorption inhibitors:			
Ezetimibe	↓ Intestinal absorption cholesterol	Elevated LDL	10 mg daily
PCSK-9 inhibitor Evolocumab	Upregulation of hepatic LDL receptors to enhance removal of LDL from circulation	Refractory or intolerant to statin	140 mg every 2 weeks or 420 mg subcutaneous injection monthly

LDL, Low-density lipoprotein(s); LPL, lipoprotein lipase; TG, triglycerides; VLDL, very-low-density lipoprotein.

Table 106.14 Adverse Effects of Cholesterol-Lowering Drugs

STATINS
Myalgia, myositis, transaminase elevations, hepatic dysfunction, increased risk of diabetes mellitus
Rare: Rhabdomyolysis, hemorrhagic stroke

EZETIMIBE
Diarrhea, arthralgia, rhabdomyolysis, hepatitis, pancreatitis, thrombocytopenia

PCSK9 INHIBITORS
Nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions, rash, allergic skin reactions, cognitive effects, antidrug antibodies

BILE ACID SEQUESTRANTS
Constipation, heartburn, nausea, eructation, bloating
Adverse effects are more common with colestipol and cholestyramine and may diminish over time.

FIBRIC ACID DERIVATIVES
Gastrointestinal (GI) disturbances, cholelithiasis, hepatitis, myositis

NIACIN
Skin flushing, pruritus, GI disturbances, blurred vision, fatigue, glucose intolerance, hyperuricemia, hepatic toxicity, exacerbation of peptic ulcers
Adverse effects, especially flushing, occur more frequently with immediate-release products.
Rare: Dry eyes, hyperpigmentation

FISH OIL
Eructation, dyspepsia, unpleasant aftertaste

From The Medical Letter. Lipid-lowering drugs. *Med Lett.* 2016;58:133–140, Table 2, p. 136.

inflammation, thereby reducing the likelihood of a sudden coronary event in an at-risk adult within weeks of starting the medication. As a class, they work by blocking the intrahepatic biosynthesis of cholesterol, thereby stimulating the production of more LDL receptors on the cell surface and facilitating the uptake of LDL-C from the bloodstream. The NCEP Adult Treatment Panel advocates aggressive lowering of LDL to <70 mg/dL in individuals with known CAD. This information is relevant because a child who fulfills criteria for consideration of cholesterol-lowering medication will almost always have inherited the condition from one of the child's parents. Not infrequently, when providing care for the child, questions arise about screening and treatment of parents or grandparents. Statins are equally effective in children, capable of lowering LDL-C levels by 50% when necessary. They are considered first-line therapy for children who meet criteria for pharmacologic therapy. They also will effect a modest reduction in triglycerides and an inconsistent increase in HDL-C. Their side effect profile, mainly liver dysfunction and rarely rhabdomyolysis with secondary renal failure, should be taken into consideration before prescribing the drug. However, there has been no evidence that complications are any more frequent in children than in adults, and skeletal muscle discomfort seems to be somewhat less of a problem. Drug interactions may occur as well, so careful attention should be paid to a child's active prescriptions to avoid potentiation of the side effects. Children should have liver enzymes monitored regularly and creatine phosphokinase measured if muscle aches or weakness occurs. Liver (muscle) enzymes may be allowed to rise threefold before discontinuing the drug. There is a suggested link between the use of statins and increased risk of developing type 2 diabetes mellitus in adults, but these results have not been replicated in children. Sex hormones have been measured in children receiving statins and are unchanged. It should be reemphasized that children with modest elevations in cholesterol, such as that seen in polygenic hypercholesterolemia, are not, as a rule, candidates for statins because of their side effect profile and the childhood response to lifestyle modifications. Statins should be started at the lowest effective dose and allowed at least 8 weeks to achieve their peak effect. If LDL levels are not at goal, which in children who are treated is generally established to be <130 mg, the medication may be titrated upward with careful monitoring of side effects.

Other cholesterol-lowering medications, such as nicotinic acid and fibrates, have been used far less often in children than bile acid sequestrants and statins. Nicotinic acid and fibrates have been used selectively in children with marked hypertriglyceridemia (>500 mg/dL) at risk for acute pancreatitis, though dietary restriction of complex sugars (stressing elimination of sugar-sweetened beverages) and carbohydrates will usually result in significant lowering of triglyceride levels. Guidelines recommend treatment of LDL-C as the initial priority, and after LDL levels are at goal, then if triglycerides remain between 200 and 499 mg/dL and non-HDL cholesterol ≥145 mg/dL, pharmacologic treatment to reduce triglyceride levels is indicated. Omega-3 fatty acid supplementation, available in both over-the-counter and prescription form, is a safe and useful treatment thought to reduce triglyceride levels by decreasing the hepatic synthesis of triglycerides. LDL-C levels in adults

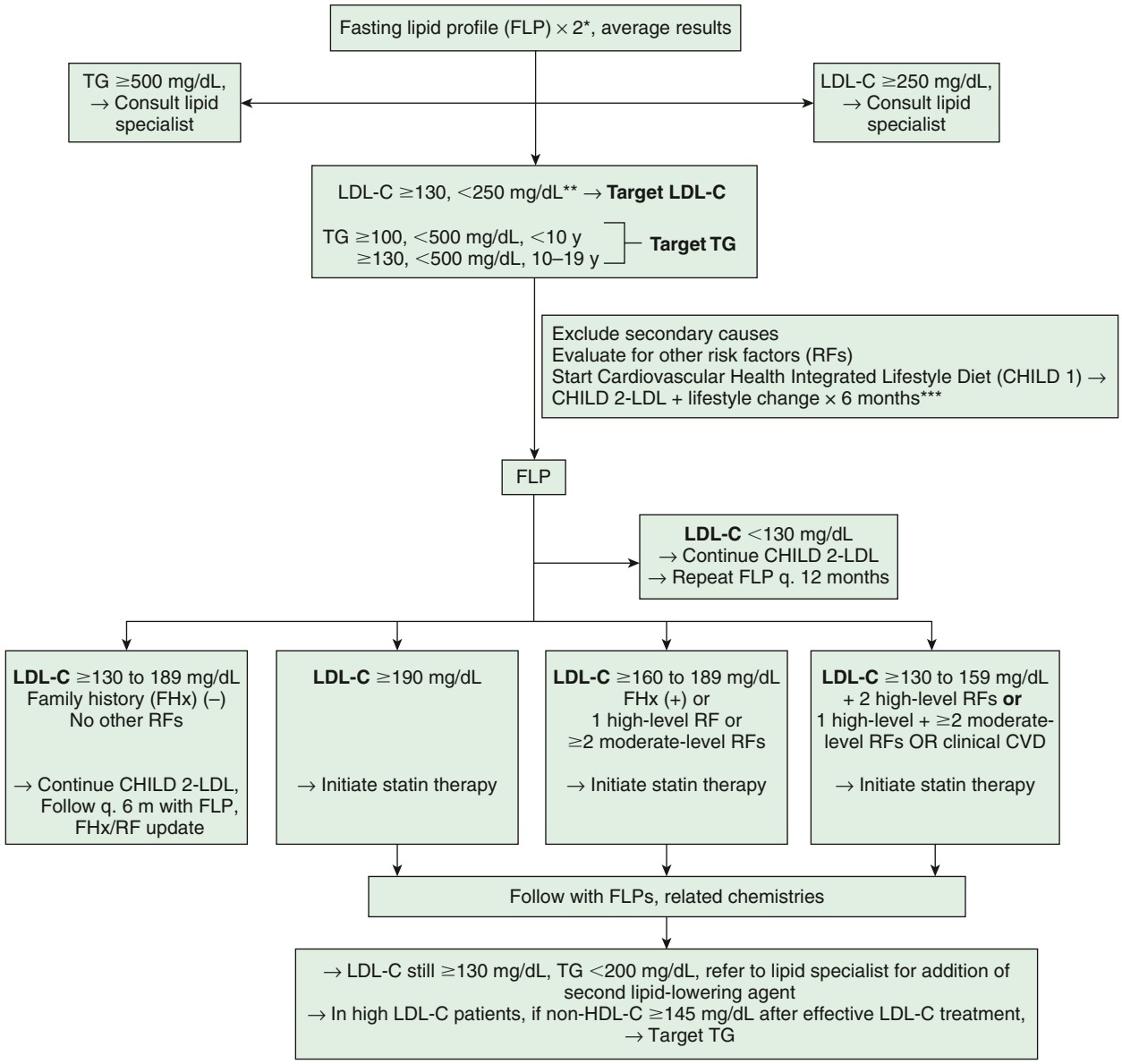

* Obtain FLPs at least 2 weeks but no more than 3 months apart.
** Use of drug therapy is limited to children ≥10 y with defined risk profiles.
*** In a child with LDL-C >190 mg/dL and other RFs, trial of CHILD 2-LDL may be abbreviated.

Fig. 106.14 Dyslipidemia treatment algorithm: Target LDL-C (low-density lipoprotein cholesterol). Note: Values given are in mg/dL. To convert to SI units, divide results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non–HDL-C by 38.6; for triglycerides (TG), divide by 88.6. *(From U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. NIH Publication No. 12-7486A, Oct. 2012, Fig 9-1.)*

of about 70 mg/dL were recently associated with coronary artery atheromatous plaque reduction and reversal of CAD. Knowledge in this area will continue to evolve.

Ezetimibe has proved to be useful in the pediatric population because of its efficacy and low side effect profile. Ezetimibe reduces plasma LDL-C by blocking sterol absorption in enterocytes. The drug is marketed as an adjunct to statins when adults are not achieving sufficient blood lipid lowering with statins alone. Sufficient reports documenting its effectiveness without side effects support recommending ezetimibe instead of a statin when moderate hypercholesterolemia is encountered or apprehension from parents makes using a statin difficult.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

106.4 Lipidoses (Lysosomal Storage Disorders)

Margaret M. McGovern and Robert J. Desnick

The lysosomal lipid storage diseases are diverse disorders each caused by an inherited deficiency of a lysosomal hydrolase leading to the intralysosomal accumulation of the enzyme's particular substrate (Tables 106.15 and 106.16). With the exceptions of Wolman disease and cholesterol ester storage disease (see Chapter 106.3), the lipid substrates share a common structure that includes a ceramide backbone (2-N-acylsphingosine) from which the various sphingolipids are derived by substitution of hexoses, phosphorylcholine, or one or more

sialic acid residues on the terminal hydroxyl group of the ceramide molecule. The pathway of sphingolipid metabolism in nervous tissue (Fig. 106.15) and in visceral organs (Fig. 106.16) is known. Each catabolic step, with the exception of the catabolism of lactosylceramide, has a genetically determined metabolic defect and a resultant disease. Because sphingolipids are essential components of all cell membranes, the inability to degrade these substances and their subsequent accumulation results in the physiologic and morphologic alterations and characteristic clinical manifestations of the lipid storage disorders (see Tables 106.15 and 106.16). Progressive lysosomal accumulation of glycosphingolipids in the CNS leads to neurodegeneration, whereas storage in visceral cells can lead to organomegaly, pulmonary infiltration, skeletal abnormalities, and other manifestations.

Diagnostic assays for the identification of affected individuals has relied on the measurement of the specific enzymatic activity in isolated leukocytes or cultured fibroblasts or lymphoblasts. An approach to differentiating these disorders is noted in Figure 106.17. In addition, next generation sequencing of lysosomal genes as well as metabolomic/protomic approaches have helped determine a specific diagnosis. For most disorders, carrier identification and prenatal diagnosis are available; a specific diagnosis is essential to permit genetic counseling. The characterization of the genes that encode the specific enzymes required for sphingolipid metabolism permit the development of therapeutic options, such as recombinant enzyme replacement therapy, as well as the potential of cell or gene therapy. Identification of specific disease-causing pathogenic variants improve diagnosis, prenatal detection, and carrier identification. For several disorders (Gaucher, Fabry, and NPD), it has been possible to make genotype-phenotype correlations that predict disease severity and allow more precise genetic counseling. Inheritance is autosomal recessive except for X-linked Fabry disease.

GM_1 GANGLIOSIDOSIS

GM_1 gangliosidosis most frequently presents in early infancy but has been described in patients with juvenile- and adult-onset subtypes (Fig. 106.18, Table 106.17). Inherited as an autosomal recessive trait, each subtype results from a different gene pathogenic variant that leads to the deficient activity of β-galactosidase, a lysosomal enzyme encoded by the gene *GLB1*. Although the disorder is characterized by the pathologic accumulation of GM_1 gangliosides in the lysosomes of both neural and visceral cells, GM_1 ganglioside accumulation is most marked in the brain. In addition, keratan sulfate, a mucopolysaccharide, accumulates in liver and is excreted in the urine of patients with GM_1 gangliosidosis.

The clinical manifestations of the infantile form of GM_1 gangliosidosis may be evident in the newborn as hepatosplenomegaly, edema, and skin eruptions (angiokeratoma). It most frequently presents in the first 6 months of life with developmental delay followed by progressive psychomotor retardation and the onset of tonic-clonic seizures. Typical facies is characterized by low-set ears, frontal bossing, a depressed nasal bridge, and an abnormally long philtrum. Up to 50% of patients have a macular cherry red spot. Hepatosplenomegaly and skeletal abnormalities similar to those of the mucopolysaccharidoses (see Chapter 109), including anterior beaking of the vertebrae, enlargement of the sella turcica, and thickening of the calvarium, are present. By the end of the first year of life, most patients are blind and deaf, with severe neurologic impairment characterized by decerebrate rigidity. Death usually occurs by 3-4 years of age. The *juvenile-onset* form of GM_1 gangliosidosis is clinically distinct, with a variable age at onset. Affected patients present primarily with neurologic symptoms including ataxia, dysarthria, intellectual disabilities, and spasticity. Deterioration is slow; patients may survive through the fourth decade of life. These patients lack the visceral involvement, facial abnormalities, and skeletal features seen in type 1 disease. *Adult-onset* patients have been described who present with gait and speech abnormalities, dystonia, and mild skeletal abnormalities. There is no specific treatment for any form of GM_1 gangliosidosis.

The diagnosis of GM_1 gangliosidosis should be suspected in infants with typical clinical features and is confirmed by the demonstration of biallelic pathogenic variants in *GLB1* and, as needed, demonstration of deficiency of β-galactosidase activity in peripheral leukocytes. Other disorders that share some of the features of the GM_1 gangliosidoses include Hurler disease (mucopolysaccharidosis type I), I-cell disease, and NPD type A, each of which can be distinguished by the demonstration of their specific genetic variants and enzymatic deficiencies. Carriers of the disorder are detected by the measurement of the enzymatic activity in peripheral leukocytes or by identifying the specific gene pathogenic variants. Prenatal diagnosis is accomplished by testing of known pathogenic variants or by determination of the enzymatic activity in cultured amniocytes or chorionic villi. Currently only supportive therapy is available for patients with GM_1 gangliosidosis.

THE GM_2 GANGLIOSIDOSES

The GM_2 gangliosidoses include the autosomal recessive Tay-Sachs disease and Sandhoff disease. Each results from the deficiency of β-hexosaminidase activity and the lysosomal accumulation of GM_2 gangliosides, particularly in the CNS. Both disorders have been classified into infantile-, juvenile-, and adult-onset forms based on the age at onset and clinical features. β-Hexosaminidase occurs as two isozymes: β-hexosaminidase A, which is composed of one α and one β subunit, and β-hexosaminidase B, which has two β subunits. β-Hexosaminidase A deficiency results from pathogenic variants in the α subunit and causes Tay-Sachs disease, whereas pathogenic variants in the β-subunit gene result in the deficiency of both β-hexosaminidases A and B and cause Sandhoff disease. Both are autosomal recessive traits, with Tay-Sachs disease having a predilection for the Ashkenazi Jewish population, where the carrier frequency is about 1/25.

More than 100 pathogenic variants in *HEXA* have been identified for Tay-Sachs disease. Most are associated with the infantile forms of disease. Three pathogenic variants account for >98% of mutant alleles among Ashkenazi Jewish carriers, including one allele associated with the adult-onset form. Pathogenic variants that cause the subacute or chronic forms result in enzyme proteins with residual enzymatic activities, the levels of which correlate with the severity of the disease.

Patients with the infantile form of Tay-Sachs disease have clinical manifestations in infancy including loss of motor skills, increased startle reaction, and macular pallor and retinal cherry red spots (see Table 106.15). Affected infants usually develop normally until 4-5 months of age, when decreased eye contact and an exaggerated startle response to noise (hyperacusis) are noted. Macrocephaly, not associated with hydrocephalus, may develop. In the second year of life, seizures develop, which may be refractory to anticonvulsant therapy. Neurodegeneration is relentless, with death occurring by the age of 4 or 5 years. The juvenile- and later-onset forms initially present with ataxia and dysarthria and may not be associated with a macular cherry red spot.

The clinical manifestations of Sandhoff disease are similar to those for Tay-Sachs disease. Infants with Sandhoff disease have hepatosplenomegaly, cardiac involvement, and mild bony abnormalities. The juvenile form of this disorder presents as ataxia, dysarthria, and intellectual deterioration, but without visceral enlargement or a macular cherry red spot. More than 50 pathogenic variants in *HEXB* have been identified for Sandhoff disease.

The diagnosis of infantile Tay-Sachs disease and Sandhoff disease is usually suspected in an infant with neurologic features and a cherry red spot. Definitive diagnosis is made by genetic testing or by determination of enzyme activities in peripheral leukocytes. The two disorders can be distinguished enzymatically, because in Tay-Sachs disease only the β-hexosaminidase A isozyme is deficient, whereas in Sandhoff disease both the β-hexosaminidase A and B isozymes are deficient. At-risk pregnancies for both disorders can be prenatally diagnosed by testing known pathogenic variants or determining enzyme levels in fetal cells obtained by amniocentesis or chorionic villus sampling. Identification of carriers in families is also possible by genetic or enzymatic determination. For Tay-Sachs disease, carrier screening of all couples in which at least one member is of Ashkenazi Jewish descent is recommended before the initiation of pregnancy to identify couples at risk. The incidence of Tay-Sachs disease has been markedly reduced since the introduction of carrier screening programs in the Ashkenazi Jewish population. Newborn screening may be possible by measuring specific glycosphingolipid markers or the relevant enzymatic activities in dried

Table 106.15 Clinical Findings in Lysosomal Storage Diseases

NATURE	ENZYME DEFECT	HYDROPS FETALIS	COARSE FACIAL FEATURES DYSOSTOSIS MULTIPLEX	HEPATOSPLENOMEGALY
MUCOLIPIDOSES				
Mucolipidoses II, I-cell disease	*N*-Acetylglucosaminylphosphotransferase	(+)	++	+
Mucolipidosis III, Pseudo-Hurler	N-Acetylglucosaminylphosphotransferase	–	+	(+)
Mucolipidosis IV	Unknown	–	–	+
SPHINGOLIPIDOSES				
Fabry disease	α-Galactosidase	–	–	–
Farber disease	Ceramidase	–	–	(+)
Galactosialidosis	β-Galactosidase and sialidase	(+)	++	++
GM1 gangliosidosis	β-Galactosidase	(+)	++	+
GM2 gangliosidosis (Tay-Sachs disease, Sandhoff disease)	β-Hexosaminidases A and B	–	–	(+)
Gaucher type I	Glucocerebrosidase	–	–	++
Gaucher type II	Glucocerebrosidase	(+)	–	++
Gaucher type III	Glucocerebrosidase	(+)	–	+
Niemann-Pick type A	Sphingomyelinase	(+)	–	++
Niemann-Pick type B	Sphingomyelinase	–	–	++
Metachromatic leukodystrophy	Arylsulfatase A	–	–	–
Krabbe disease	β-Galactocerebrosidase	–	–	–
LIPID STORAGE DISORDERS				
Niemann-Pick type C	Intracellular cholesterol transport	–	–	(+)
Wolman disease	Acid lipase	(+)	–	+
Ceroid lipofuscinosis, infantile (Santavuori-Hantia)	Palmitoyl-protein thioesterase (CLN1)	–	–	–
Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)	Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)	–	–	–
Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)	CLN3, membrane protein	–	–	–
Ceroid lipofuscinosis, adult (Kufs, Parry)	CLN4, probably heterogeneous	(+)	–	–
OLIGOSACCHARIDOSES				
Aspartylglucosaminuria	Aspartylglucosaminase	–	+	(+)
Fucosidosis	α-Fucosidase	–	++	(+)
α-Mannosidosis	α-Mannosidase	–	++	+
β-Mannosidosis	β-Mannosidase	–	+	(+)
Schindler disease	α-N-Acetylgalactosaminidase	–	–	–
Sialidosis I	Sialidase	(+)	–	–
Sialidosis II	Sialidase	(+)	++	+

++, prominent; +, often present, (+), inconstant or occurring later in the disease course; –, not present.
GAG, glycosaminoglycans.
Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al. *Storage Disorders in Inherited Metabolic Diseases.* Philadelphia: Lippincott Williams & Wilkins; 2002:346–351.

Table 106.15 Clinical Findings in Lysosomal Storage Diseases—cont'd

CARDIAC INVOLVEMENT CARDIAC FAILURE	MENTAL DETERIORATION	MYOCLONUS	SPASTICITY	PERIPHERAL NEUROPATHY	CHERRY RED SPOT	CORNEAL CLOUDING	ANGIOKERATOMATA
++	++	–	–	–	–	(+)	–
–	(+)	–	–	–	–	+	–
–	(+)	–	–	–	–	–	–
+	–	–	–	–	–	+	++
++	+	–	–	+	(+)	–	–
+	++	(+)	+	–	+	+	+
(+)	++	–	(+)	–	(+)	+	+
–	++	+	+	–	++	–	–
–	–	–	–	–	–	–	–
–	++	+	+	–	–	–	–
–	+	(+)	(+)	–	–	–	–
–	+	(+)	–	(+)	(++)	–	–
–	–	–	–	(+)	(+)	–	–
–	++	–	+	++	(+)	–	–
–	++	–	+	++	(+)	–	–
–	+	–	–	–	(+)	–	–
(+)	–	–	–	–	(+)	–	–
–	+	+	+	–	–	–	–
–	+	+	+	–	–	–	–
–	+	–	(+)	–	–	–	–
–	+	–	–	–	–	–	–
(+)	+	–	–	–	–	(+)	(+)
+	++	+	+	–	–	–	(+)
–	++	–	(+)	–	–	++	(+)
–	+	–	+	+	–	–	(+)
–	+	+	+	–	–	–	–
–	–	++	+	+	++	(+)	–
+	++	(+)	–	–	++	–	+

Table 106.16 Lysosomal Storage Disorders in the Newborn Period: Genetic and Clinical Characteristics of Neonatal Presentation

DISORDER	ONSET	FACIES	NEUROLOGIC FINDINGS	DISTINCTIVE FEATURES
Niemann-Pick A disease	Early infancy	Frontal bossing	Difficulty feeding, apathy, deafness, blindness, hypotonia	Brownish-yellow skin, xanthomas
Niemann–Pick C disease	Birth to 3 mo	Normal	Developmental delay, vertical gaze paralysis, hypotonia, later spasticity	–
Gaucher disease type 2	In utero to 6 mo	Normal	Poor suck and swallow, weak cry, squint, trismus, strabismus, opsoclonus, hypertonic, later flaccidity	Congenital ichthyosis, collodion skin
Krabbe disease	3-6 mo	Normal	Irritability, tonic spasms with light or noise stimulation, seizures, hypertonia, later flaccidity	Increased CSF protein level
GM1 gangliosidosis	Birth	Coarse	Poor suck, weak cry, lethargy, exaggerated startle, blindness, hypotonia, later spasticity	Gingival hypertrophy, edema, rashes
Farber disease type I	2 wk to 4 mo	Normal	Progressive psychomotor impairment, seizures, decreased reflexes, hypotonia	Joint swelling with nodules, hoarseness, lung disease, contractures, fever, granulomas, dysphagia, vomiting, increased CSF protein level
Farber disease types II and III	Birth to 9 mo (≤20 mo)	Normal	—	Joint swelling with nodules, hoarseness
Farber disease type IV (neonatal)	Birth	Normal	Nodules not consistent findings	Corneal opacities (1/3)
Congenital sialidosis	In utero to birth	Cognitive, edema	Intellectual impairment, hypotonia	Neonatal ascites, inguinal hernias, renal disease
Galactosialidosis	In utero to birth	Coarse	Intellectual impairment, occasional deafness, hypotonia	Ascites, edema, inguinal hernias, renal disease, telangiectasias
Wolman disease	First weeks of life	Normal	Cognitive deterioration	Vomiting, diarrhea, steatorrhea, abdominal distention, failure to thrive, anemia, adrenal calcifications
Infantile sialic acid storage disease	In utero to birth	Coarse, dysmorphic	Intellectual impairment, hypotonia	Ascites, anemia, diarrhea, failure to thrive
I-cell disease	In utero to birth	Coarse	Intellectual impairment, deafness	Gingival hyperplasia, restricted joint mobility, hernias
Mucolipidosis type IV	Birth to 3 mo	Normal	Intellectual impairment, hypotonia	—
Mucopolysaccharidosis type VII	In utero to childhood	Variable coarseness	Mild to severe intellectual impairment	Hernias

Table 106.16 Lysosomal Storage Disorders in the Newborn Period: Genetic and Clinical Characteristics of Neonatal Presentation—cont'd

EYE FINDINGS	DEFECT	GENE LOCATION/MOLECULAR FINDINGS	ETHNIC PREDILECTION
Cherry-red spot (50%)	Sphingomyelinase deficiency	*SMPD1* gene at 11p15.4; 3 of 18 variants account for approximately 92% of mutant alleles in the Ashkenazi population	1:40,000 in Ashkenazi Jews with a carrier frequency of 1:60
–	Abnormal cholesterol esterification	*NPC1* gene at 18q11 accounts for >95% of cases; *HE1* gene variants may account for remaining cases	Increased in French Canadians of Nova Scotia and Spanish Americans in the Southwest United States
–	Glucocerebrosidase deficiency	1q21; large number of variants known; five variants account for approximately 97% of mutant alleles in the Ashkenazi population but approximately 75% in the non-Jewish population	Panethnic
Optic atrophy	Galactocerebrosidase deficiency	14q 24.3-q32.1; >60 variants with some common variants in specific populations	Increased in Scandinavian countries and in a large Druze kindred in Israel
Cherry red spot (50%)	β-Galactosidase deficiency	3pter-3p21; heterogeneous variants; common variants in specific populations	Panethnic
Grayish opacification surrounding the retina in some patients, subtle cherry red spot	Lysosomal acid ceramidase	8p21.3-22; nine disease-causing variants identified	Panethnic
Normal macula, corneal opacities	—	8p21.3-p22	Panethnic
—	—	Unknown	Panethnic
Corneal clouding	Neuraminidase deficiency	*NEU 1* gene (sialidase) at 6p21	Panethnic
Cherry red spot, corneal clouding	Absence of a protective protein that safeguards neuraminidase and β-galactosidase from premature degradation	20q13.1	Panethnic
—	Lysosomal acid lipase deficiency	10q23.2-q23.3; variety of variants identified	Increased in Iranian Jews and in non-Jewish and Arab populations of Galilee
—	Defective transport of sialic acid out of the lysosome	*SLC17A5* gene at 6q	Panethnic
Corneal clouding	Lysosomal enzymes lack mannose 6-phosphate recognition marker and fail to enter the lysosome (phosphotransferase deficiency, 3-subunit complex [α2 β2 γ2])	Enzyme encoded by two genes; α and β subunits encoded by gene at 12p; γ subunit encoded by gene at 16p	Panethnic
Severe corneal clouding, retinal degeneration, blindness	Unknown; some patients with partial deficiency of ganglioside sialidase	*MCOLN1* gene at 19p13.2-13.3 encoding mucolipin 1; two founder variants accounting for 95% of mutant alleles in the Ashkenazi population	Increased in Ashkenazi Jews
Variable corneal clouding	β-Glucuronidase deficiency	*GUSB* gene at 7q21.2-q22; heterogeneous variants	Panethnic

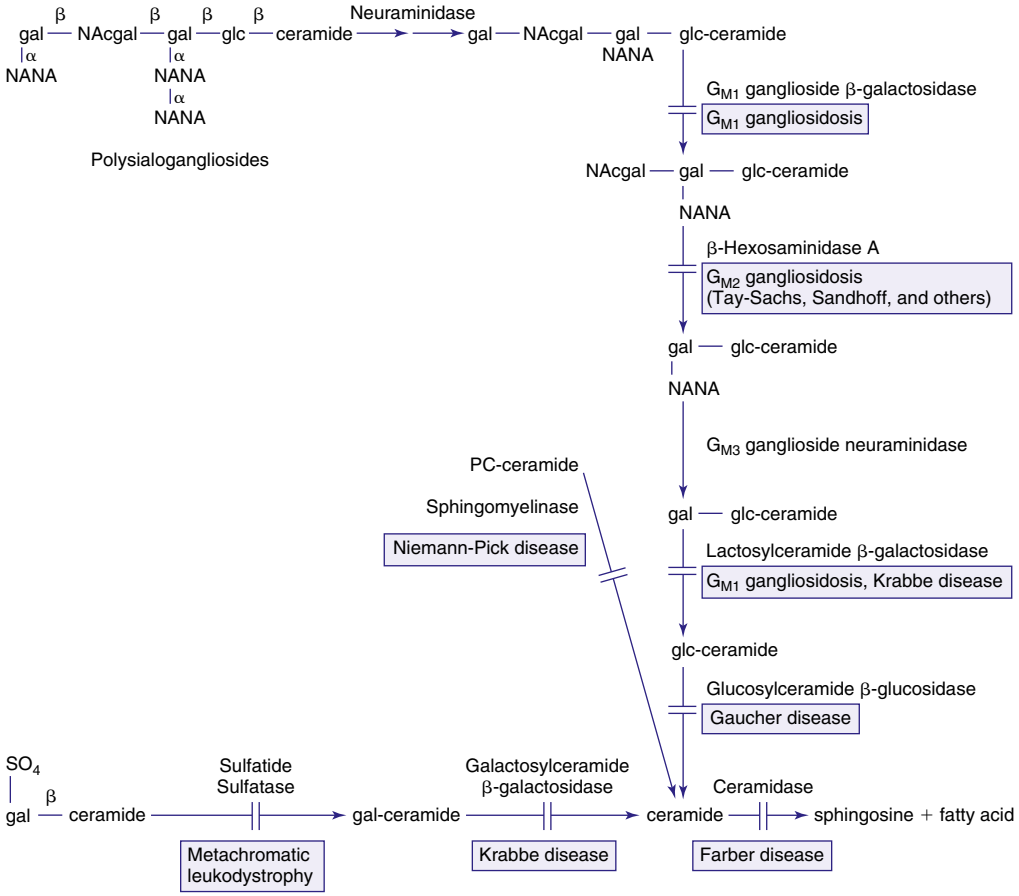

Fig. 106.15 Pathways in the metabolism of sphingolipids found in nervous tissues. The name of the enzyme catalyzing each reaction is given with the name of the substrate acted on. Inborn errors are depicted as bars crossing the reactions arrows, and the name of the associated defect or defects is given in the nearest box. The gangliosides are named according to the nomenclature of Svennerholm. Anomeric configurations are given only at the largest starting compound. Gal, galactose; glc, glucose; NAcgal, N-acetylgalactosamine; NANA, N-acetylneuraminic acid; PC, phosphorylcholine.

blood spots. There is no treatment available for Tay-Sachs disease or Sandhoff disease. The FDA has approved an investigational new drug application to initiate adeno-associated virus vector gene (beta hexosaminidase A and B) therapy for Tay-Sachs and Sandhoff disease.

GAUCHER DISEASE

This disease is a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement, the latter usually manifesting as bone pain and pathologic fractures (see Table 106.15 and 106.16). It is the most common lysosomal storage disease and the most prevalent genetic defect among Ashkenazi Jews. There are three clinical subtypes delineated by the absence or presence and progression of neurologic manifestations: type 1 or the adult, non-neuronopathic form; type 2, the infantile or acute neuronopathic form; and type 3, the juvenile or subacute neuronopathic form. All are autosomal recessive traits. Type 1, which accounts for 99% of cases, has a striking predilection for Ashkenazi Jews, with an incidence of about 1/1,000 and a carrier frequency of about 1/18.

Gaucher disease results from the deficient activity of the lysosomal hydrolase, acid β-glucosidase, which is encoded by the gene *GBA*. The enzymatic defect results in the accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in cells of the reticuloendothelial system. This progressive deposition results in infiltration of the bone marrow, progressive hepatosplenomegaly, and skeletal complications. Four pathogenic variants—p.Asn370Ser, p.Leu444Pro, c.84insG, and IVS2+1G>A—account for about 95% of mutant alleles among Ashkenazi Jewish patients, permitting screening for this disorder in this population. Genotype-phenotype correlations have been noted, providing the molecular basis for the clinical heterogeneity seen in Gaucher disease type 1. Patients who are homozygous for the p.Asn370Ser pathogenic variant tend to have a later onset, with a more indolent course than patients with one copy of p.Asn370Ser and another common allele.

Clinical manifestations of type 1 Gaucher disease have a variable age at onset, from early childhood to late adulthood, with most symptomatic patients presenting by adolescence. At presentation, patients may have bruising from thrombocytopenia, chronic fatigue secondary to anemia, hepatomegaly with or without elevated LFT results, splenomegaly, and bone pain. Occasional patients have pulmonary involvement at the time of presentation. Patients presenting in the first decade frequently are not Jewish and have growth retardation and a more malignant course. Other patients may be discovered fortuitously during evaluation for other conditions or as part of routine examinations; these patients may have a milder or even a benign course. In symptomatic patients, splenomegaly is progressive and can become massive. Most patients develop radiologic evidence of skeletal involvement, including an Erlenmeyer flask deformity of the distal femur. Clinically apparent bony involvement, which occurs in most patients, can present as bone pain, a pseudo-osteomyelitis pattern, or pathologic fractures. Lytic lesions can develop in the long bones, including the femur, ribs, and pelvis; osteosclerosis may be evident at an early age. Bone crises with severe pain and swelling can occur. Bleeding secondary to thrombocytopenia may manifest as epistaxis or bruising and is frequently overlooked until other symptoms become apparent. With the exception of the severely growth-stunted child, who may experience developmental delay secondary to the effects of chronic disease, development and intelligence are normal.

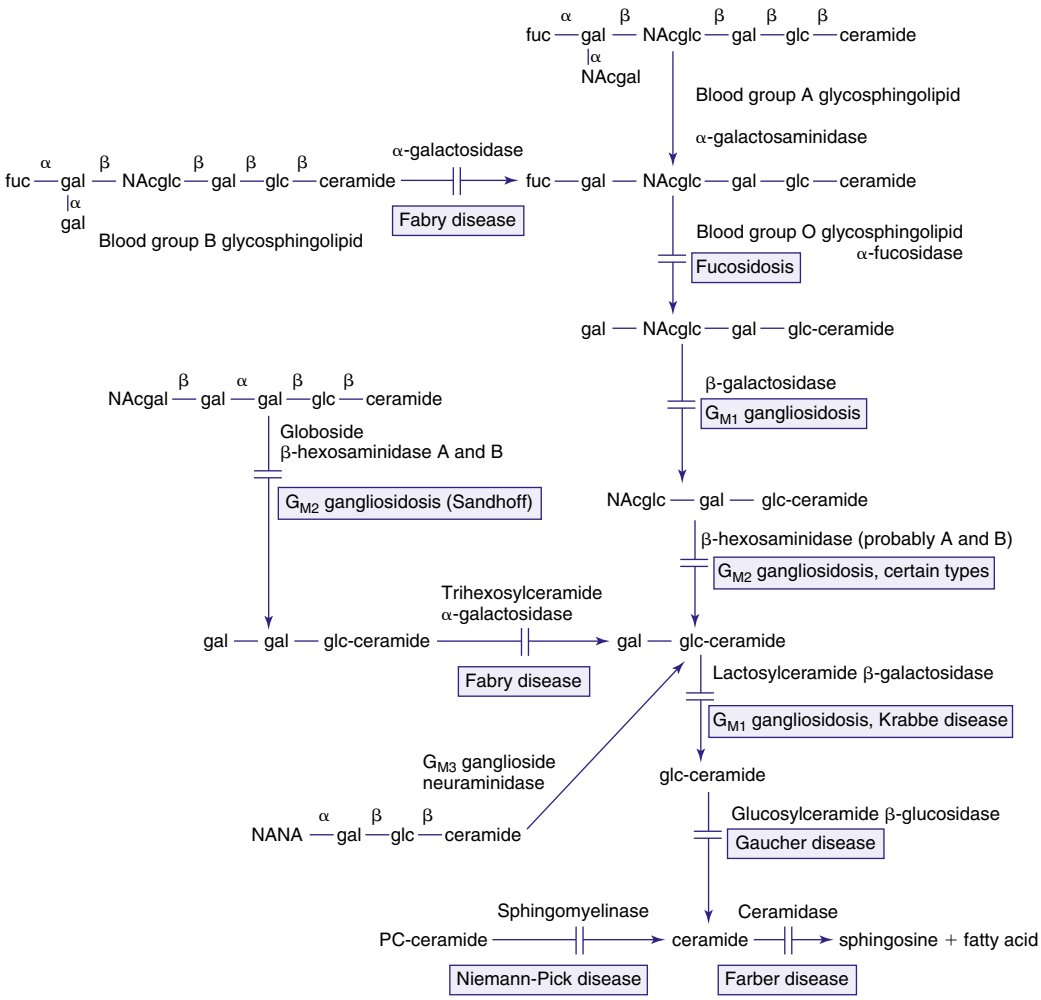

Fig. 106.16 Pathways in the degradation of sphingolipids found in visceral organs and red or white blood cells. See also the legend for Figure 106.15. Fuc, fucose; NAcglc, N-acetylglucosamine.

The pathologic hallmark of Gaucher disease is the Gaucher cell in the reticuloendothelial system, particularly in the bone marrow (Fig. 106.19). These cells, which are 20-100 μm in diameter, have a characteristic wrinkled paper appearance resulting from the presence of intracytoplasmic substrate inclusions. The cytoplasm of the Gaucher cell reacts strongly positive with the periodic acid–Schiff stain. The presence of this cell in bone marrow and tissue specimens is highly suggestive of Gaucher disease, although it also may be found in patients with granulocytic leukemia and myeloma.

Gaucher disease type 2 is much less common and does not have an ethnic predilection. It is characterized by a rapid neurodegenerative course with extensive visceral involvement and death within the first years of life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor caused by laryngospasm are typical. After a several-year period of psychomotor regression, death occurs secondary to respiratory compromise. Gaucher disease type 3 presents as clinical manifestations that are intermediate to those seen in types 1 and 2, with a presentation in childhood and death by age 10-15 years. It has a predilection for the Swedish Norrbottnian population, among which the incidence is about 1/50,000. Neurologic involvement is present. Type 3 disease is further classified as types 3a and 3b based on the extent of neurologic involvement and whether there is progressive myotonia and dementia (type 3a) or isolated supranuclear gaze palsy (type 3b).

Gaucher disease should be considered in the differential diagnosis of patients with unexplained organomegaly, who bruise easily, have bone pain, or have a combination of these conditions. Bone marrow examination usually reveals the presence of Gaucher cells. All suspected diagnoses should be confirmed by genetic testing or by determination of the acid β-glucosidase activity in isolated leukocytes or cultured fibroblasts. In Ashkenazi Jewish individuals, the identification of carriers can be achieved best by molecular testing for the common pathogenic variants. Testing should be offered to all family members, keeping in mind that heterogeneity, even among members of the same kindred, can be so great that asymptomatic affected individuals may be diagnosed. Prenatal diagnosis is available by determination of the specific family pathogenic variants and/or enzyme activity of chorionic villi or cultured amniotic fluid cells.

Treatment of patients with Gaucher disease type 1 includes enzyme replacement therapy, with recombinant acid β-glucosidase (imiglucerase). Most extraskeletal symptoms (organomegaly, hematologic indices) are reversed by enzymes (60 IU/kg) administered by intravenous infusion every other week. Monthly maintenance enzyme replacement improves bone structure, decreases bone pain, and induces compensatory growth in affected children. A small number of patients have undergone bone marrow transplantation, which can be curative but results in significant morbidity and mortality from the procedure, making the selection of appropriate candidates limited. Although enzyme replacement does not alter the neurologic progression of patients with Gaucher disease types 2 and 3, it has been used in selected patients as a palliative measure, particularly in type 3 patients with severe visceral involvement. Alternative treatments, including the use of agents designed to decrease the synthesis of glucosylceramide by chemical inhibition of glucosylceramide synthase, are available for patients who cannot be treated by enzyme replacement.

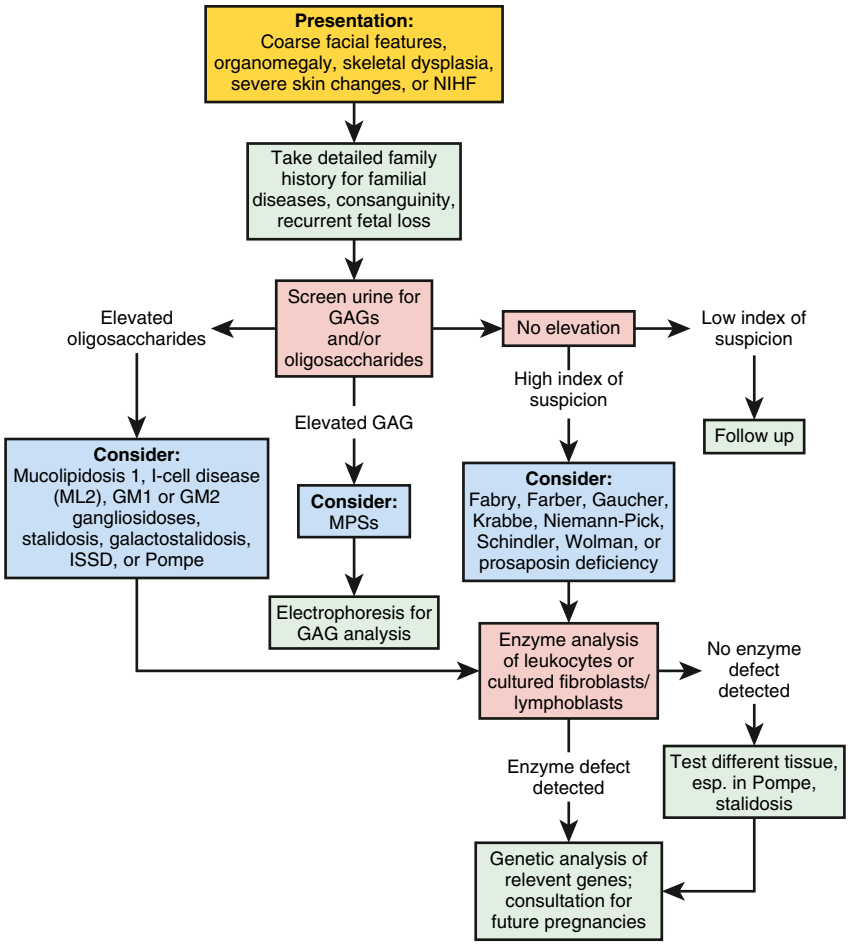

Fig. 106.17 Algorithm of the clinical evaluation recommended for an infant with a suspected lysosomal storage disease. GAGs, Glycosaminoglycans; NIHF, nonimmune hydrops fetalis. *(From Staretz-Chacham O, Lang TC, LaMarca ME, et al. Lysosomal storage disorders in the newborn. Pediatrics. 2009;123:1191–1207.)*

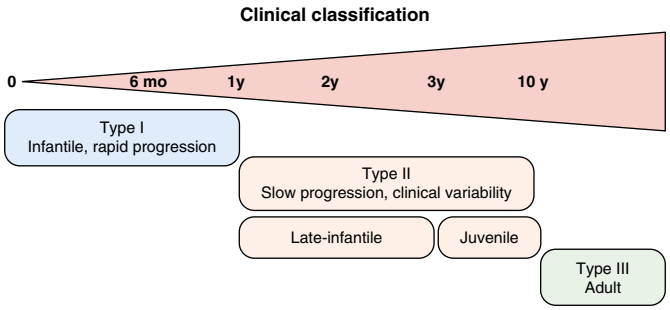

Fig. 106.18 Classification of GM1 gangliosidosis according to occurrence of the first symptom. *(From Arash-Kaps L, Komlosi K, Seegräber M, et al. The clinical and molecular spectrum of GM1 gangliosidosis. J Pediatr. 2019;215:152–157.)*

NIEMANN-PICK DISEASE

Type A NPD is a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative course that leads to death by 2-3 years of age. Type B disease is a non-neuronopathic form observed in children and adults. Type C disease is a neuronopathic form that results from defective cholesterol transport. All subtypes are inherited as autosomal recessive traits and display variable clinical features (see Tables 106.15 and 106.16).

NPD types A and B result from the deficient activity of acid sphingomyelinase, a lysosomal enzyme encoded by the gene *SMPD1*. The enzymatic defect results in the pathologic accumulation of sphingomyelin, a ceramide phospholipid, and other lipids in the monocyte-macrophage system as the primary pathologic site. The progressive deposition of sphingomyelin in the CNS results in the neurodegenerative course seen in type A and in non-neural tissue in the systemic disease manifestations of type B, including progressive lung disease in some patients. A variety of pathogenic variants in *SMPD1* that cause types A and B NPD have been identified.

The clinical manifestations and course of type A NPD is uniform and characterized by a normal appearance at birth. Hepatosplenomegaly, moderate lymphadenopathy, and psychomotor retardation are evident by 6 months of age, followed by neurodevelopmental regression and death by 3 years. With advancing age, the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating with spasticity and rigidity and in later stages. Affected infants lose contact with their environment. In contrast to the stereotyped type A phenotype, the clinical presentation and course of patients with type B disease are more variable. Most are diagnosed in infancy or childhood when enlargement of the liver or spleen, or both, is detected during a routine physical examination. At diagnosis, type B NPD patients usually have evidence of mild pulmonary involvement, usually detected as a diffuse reticular or finely nodular infiltration on the chest radiograph. Pulmonary symptoms usually present in adulthood. In most patients, hepatosple-nomegaly is particularly prominent in childhood, but with increasing linear growth, the abdominal protuberance decreases and becomes less conspicuous. In mildly affected patients, the splenomegaly may not be noted until adulthood, and there may be minimal disease manifestations.

In some type B patients, decreased pulmonary diffusion caused by alveolar infiltration becomes evident in late childhood or early

Table 106.17 Symptoms and Biochemical Signs in Three Clinical Forms of GM_1 Gangliosidosis

SYMPTOMS AND SIGNS	INFANTILE FORM	LATE-INFANTILE FORM	JUVENILE FORM
CLINICAL SYMPTOMS			
Coarse facial features	+	–	–
Cherry red macula spot	–/+	–	–
Cardiomyopathy	–/+	–/+	–
Hepatosplenomegaly	–/+	–	–
Cognitive decline	+	+	+
Dystonia	–/+	–/+	–/+
Ataxia	–/+	–/+	–/+
Pyramidal signs	+	+	–
LABORATORY SIGNS			
Increased oligosaccharides	+	–/+	–/+
Increased ASAT	–/+	–/+	–
Increased chitotriosidase activity	>1,000	>100–1,000	na

na, Not applicable.
From Arash-Kaps L, Komlosi K, Seegräber M, et al. The clinical and molecular spectrum of GM1 gangliosidosis. *J Pediatr.* 2019;215:152–157, Table II.

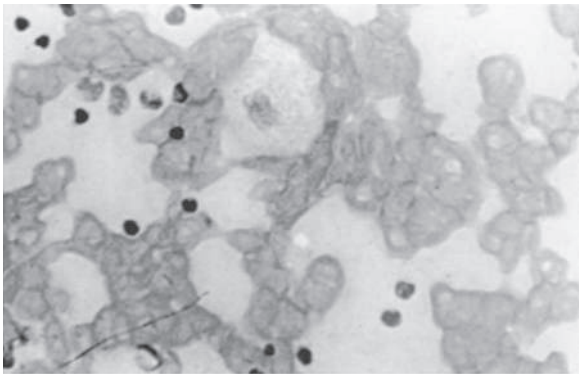

Fig. 106.19 Cells from the spleen of a patient with Gaucher disease. A characteristic spleen cell is shown engorged with glucocerebroside.

adulthood and progresses with age. Severely affected individuals may experience significant pulmonary compromise by 15-20 years of age. Such patients have low Po_2 values and dyspnea on exertion. Life-threatening bronchopneumonias may occur, and *cor pulmonale* has been described. Severely affected patients may have liver involvement leading to life-threatening cirrhosis, portal hypertension, and ascites. Clinically significant pancytopenia caused by secondary hypersplenism may require partial or complete splenectomy; this should be avoided if possible because splenectomy frequently causes progression of pulmonary disease, which can be life-threatening. In general, type B patients do not have neurologic involvement and have a normal IQ. Some patients with type B disease have cherry red maculae or haloes and subtle neurologic symptoms that can include peripheral neuropathy.

Type C NPD patients often present with prolonged neonatal jaundice, appear normal for 1-2 years, and then experience a slowly progressive and variable neurodegenerative course. Their hepato¬splenomegaly is less severe than that of patients with types A or B NPD, and they may survive into adulthood. The underlying biochemical defect in type C patients is an abnormality in cholesterol transport, leading to the accumulation of sphingomyelin and cholesterol in their lysosomes and a secondary partial reduction in acid sphingomyelinase activity (see Chapter 106.3).

In type B NPD patients, splenomegaly is usually the first manifestation detected. The splenic enlargement is noted in early childhood. In very mild disease, the enlargement may be subtle and detection may be delayed until adolescence or adulthood. The presence of the characteristic NPD cells in bone marrow aspirates supports the diagnosis of type B NPD. Patients with type C NPD, however, also have extensive infiltration of NPD cells in the bone marrow, and thus all suspected cases should be evaluated genetically or enzymatically to confirm the clinical diagnosis by measuring the acid sphingomyelinase activity level in peripheral leuko¬cytes, cultured fibroblasts, or lymphoblasts, or a combination of these cells. Patients with types A and B NPD have markedly decreased enzyme levels (1–10%), whereas patients with type C NPD have normal or mildly decreased acid sphingomyelinase activities. Without known genetic causes, the enzymatic identification of NPD carriers is problematic. In families in which the specific genetic lesion has been identified, however, family members can be accurately tested for heterozygote status by DNA analysis. Prenatal diagnosis of types A and B NPD can be made by genetic testing and reliably by the measurement of acid sphingomyelinase activity in cultured amniocytes or chorionic villi. Historically, the diagnosis of Niemann-Pick type C has relied on the demonstration of the cholesterol transport defect in cultured fibroblasts by filipin staining but is now readily accomplished by genetic testing of the *NPC1* and *NPC2* genes and the measurement of oxidative cholesterol metabolites. There is no conclusive treatment for types A and B NPD. Orthotopic liver transplantation in an infant with type A disease and amniotic cell transplantation in several type B NPD patients have been attempted with little or no success. Bone marrow transplantation in a small number of type B NPD patients has been shown to be successful in reducing the spleen and liver volumes, the sphingomyelin content of the liver, the number of Niemann-Pick cells in the marrow, and radiologically detected infiltration of the lungs. In one patient, liver biopsies taken up to 33 months after transplantation showed only a moderate reduction in stored sphingomyelin. Lung transplantation has not been performed in any severely compromised patient with type B disease, although two patients who underwent whole lung lavages with variable results have been reported. Enzyme replacement therapy (ERT) with recombinant human acid sphingomyelinase (olipudase alpha) is in clinical trials for the treatment of NPD type B. A 26-week phase 1b study in adult patients with NPD B established initial proof of concept in this patient group. In a phase 1/2 pediatric trial (ASCEND-Peds/NCT02292654) in children with chronic acid sphingomyelinase deficiency (ASMD), olipudase alfa was generally well-tolerated with improvements in disease pathology, and a phase 1/2 clinical trial in pediatric patients and a randomized phase 2/3 trial in adults (ASCEND) with ASMD documented improvement in lung function and spleen size.

Clinical trials of miglustat (Actelion, Basel, Switzerland) have been performed, and the drug has been approved in Europe for the treatment of type C disease. Treatment of type A disease with bone marrow transplantation has not been successful, presumably because of severe neurologic involvement.

FABRY DISEASE

Fabry disease is an X-linked inborn error of glycosphingolipid metabolism characterized by angiokeratomas (telangiectatic skin lesions); hypohidrosis; corneal and lenticular opacities; acroparesthesias; and vascular disease of the kidney, heart, and/or brain (see Table 106.15). The classic phenotype is caused by deficient activity of the enzyme α-galactosidase A and has an estimated prevalence of approximately 1/50,000 males. Later-onset affected males with residual α-galactosidase A activity may present with cardiac and/or renal disease, including hypertrophic cardio¬myopathy and renal failure, and is more prevalent than the classic phenotype. Heterozygous females for the classic phenotype can be either asymptomatic or as severely affected as the males—the variability is a result of random X-inactivation. The disease results from pathogenic variants in α-galactosidase A encoded by the X-linked *GLA* gene. The enzymatic defect leads to the systemic accumulation of neutral glycosphingolipids, primarily globotriaosylceramide, particularly in the plasma and lysosomes of vascular endothelial and smooth muscle cells. The progressive vascular glycosphingolipid deposition in classically affected males results in ischemia and infarction, leading to the major disease manifestations. The cDNA and genomic sequences encoding α-galactosidase A have identified more than 500 different pathogenic variants in the α-galactosidase A gene that are responsible for this lysosomal storage disease, including amino acid substitutions, gene rearrangements, and mRNA splicing defects.

Affected males with the classic phenotype have the skin lesions, acroparesthesias, hypohidrosis, and ocular changes, whereas males with the later-onset phenotypes lack these findings and present with cardiac and/or renal disease in adulthood (Table 106.18). The classic angiokeratomas usually occur in childhood and may lead to early diagnosis (Fig. 106.20). They increase in size and number with age and range from barely visible to several millimeters in diameter. The lesions are punctate, dark red to blue-black, and flat or slightly raised. They do not blanch with pressure, and the larger ones may show slight hyperkeratosis. Characteristically, the lesions are most dense between the umbilicus and knees, in the "bathing trunk area," but may occur anywhere, including the oral mucosa. The hips, thighs, buttocks, umbilicus, lower abdomen, scrotum, and glans penis are common sites, and there is a tendency toward symmetry. Variants without skin lesions have been described. Sweating is usually decreased or absent. Corneal opacities and characteristic lenticular lesions, observed under slit-lamp examination, are present in affected males and in about 90% of heterozygotes. Conjunctival and retinal vascular tortuosity is common and results from the systemic vascular involvement.

Pain is the most debilitating symptom in childhood and adolescence. Fabry crises, lasting from minutes to several days, consist of agonizing, burning pain in the hands, feet, and proximal extremities and are usually associated with exercise, fatigue, fever, or a combination of these factors. These painful acroparesthesias usually become less frequent in the third and fourth decades of life, although in some men, they may become more frequent and severe. Attacks of abdominal or flank pain may simulate appendicitis or renal colic.

The major morbid symptoms result from the progressive involvement of the vascular system. Early in the course of the disease, casts, red cells, and lipid inclusions with characteristic birefringent "Maltese crosses" appear in the urinary sediment. Proteinuria, isosthenuria, and gradual deterioration of renal function and development of azotemia occur in the second through fourth decades. Cardiovascular findings may include hypertension, left ventricular hypertrophy, anginal chest pain, myocardial ischemia or infarction, and heart failure. Mitral insufficiency is the most common valvular lesion. Abnormal electrocardiographic and echocardiographic findings are common. Cerebrovascular manifestations result from multifocal small vessel involvement. Other features may include chronic bronchitis and dyspnea, lymphedema of the legs without hypoproteinemia, episodic diarrhea, osteoporosis, retarded growth, and delayed puberty. Death most often results from uremia or vascular disease of the heart or brain. Before hemodialysis or renal transplantation, the mean age at death for affected men was 40 years. Patients with the later-onset phenotype with residual α-galactosidase A activity have cardiac and/or renal disease. The

Table 106.18 Summary of Reported Clinical Manifestations in Fabry Patients (Newborn to 4 Yr)

FABRY-RELATED SIGNS AND SYMPTOMS	EARLIEST REPORT OF SYMPTOM
Storage of globotriaosylceramide found in organs on biopsy	Prenatal
Corneal whorls/verticillata	Prenatal/newborn
Gastrointestinal problems, including nausea, vomiting, diarrhea, constipation, and abdominal pain	1.0 yr
Slow growth in boys (mean height/weight <50th percentile)	2.0 yr
Intermittent acroparesthesia/neuropathic pain triggered by stress, heat, fatigue, or exercise	2.0 yr
Hypohidrosis or anhidrosis	2.5 yr
Fabry crises of agonizing neuropathic pain typically begin in the hands and feet and may radiate proximally	2.5 yr
Heat, cold, and/or exercise intolerance	3.5 yr
Retinal vascular tortuosity	4.0 yr
Tinnitus/vertigo	4.0 yr
Low glomerular filtration rate	4.0 yr
T-wave inversion on electrocardiogram	4.0 yr
Trivial cardiac valve disease	4.0 yr
Angiokeratoma	4.4 yr

From Laney DA, Peck DS, Atherton AM, et al. Fabry disease in infancy and early childhood: A systematic literature review. *Genetics Med.* 2015;17(5):323–330, Table 2.

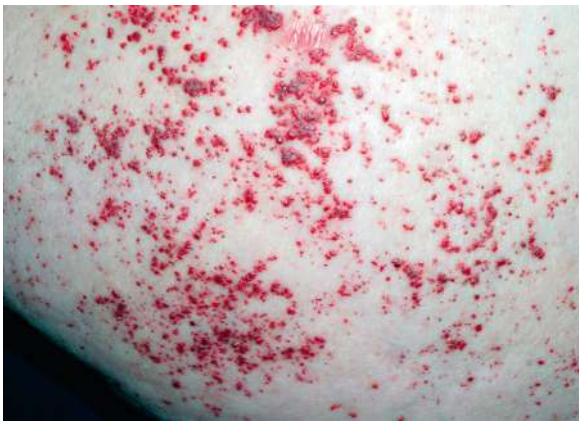

Fig. 106.20 Typical angiokeratomas. Angiokeratomas are quite large and easily recognizable, but if only a few lesions exist or they are restricted only to the genitals or umbilical regions, they can be easily missed. *(From Zarate VA, Hopkin RJ. Fabray's disease. Lancet. 2008;372:1427.)*

Table 106.19 Common Misdiagnoses for Fabry Disease

INFLAMMATORY
Systemic lupus erythematous
Rheumatic fever
Fibromyalgia
Dermatomyositis
Raynaud phenomenon
Raynaud syndrome
C1 esterase deficiency
TNF receptor–associated periodic syndrome (TRAPS)
Joint and recurrent fever syndromes (juvenile idiopathic arthritis, familial Mediterranean fever)
Erythromelalgia
NEUROLOGIC
Porphyria
Guillain-Barre syndrome
Hereditary neuropathies
Nutritional neuropathies
Uremic neuropathy
Diabetic neuropathy
Polyneuropathy
Meniere disease
Complex regional pain syndromes
Multiple sclerosis
Mitochondrial disorders
Migraine
MELAS
CADASIL
GASTROINTESTINAL/NUTRITION
Irritable bowel syndrome
Appendicitis
Metabolic bone disease (rickets, uremia, scurvy)
Crohn disease
Celiac disease
Peptic ulcer disease
OTHER
Growing pains
Chronic overlapping pain syndrome
Malingering
Coronary heart disease
Osler-Weber-Rendu disease
Cardiomyopathy
Gaucher disease

MELAS, Mitochondrial encephalopathy lactic acidosis, strokelike symptoms; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

cardiac manifestations include hypertrophy of the left ventricular wall and interventricular septum and electrocardiographic abnormalities consistent with cardiomyopathy. Others have had hypertrophic cardiomyopathy or myocardial infarction, or both.

The diagnosis in classically affected males is most readily made from the history of painful acroparesthesias, hypohidrosis, the presence of characteristic skin lesions, and the observation of the characteristic corneal opacities and lenticular lesions. The disorder is often misdiagnosed as rheumatic fever, erythromelalgia, or neurosis (Table 106.19). The skin lesions must be differentiated from the benign angiokeratomas of the scrotum (Fordyce disease) or from angiokeratoma circumscriptum. Angiokeratomas identical to those of Fabry disease have been reported in fucosidosis, aspartylglycosaminuria, late-onset GM_1 gangliosidosis, galactosialidosis, α-N-acetylgalactosaminidase deficiency, and sialidosis. Later-onset patients have been identified among patients on hemodialysis and among patients with hypertrophic cardiomyopathy or who have suffered cryptogenic strokes. Later-onset patients lack the early classic manifestations such as the angiokeratomas, acroparesthesias, hypohidrosis, and corneal opacities. The diagnosis of classic and later-onset patients is confirmed biochemically by the demonstration of markedly decreased α-galactosidase A activity in plasma, isolated leukocytes, or cultured fibroblasts or lymphoblasts.

Heterozygous females may have corneal opacities, isolated skin lesions, and intermediate activities of α-galactosidase A in plasma or cells. Rare female heterozygotes may have manifestations as severe as those in affected males. Asymptomatic at-risk females in families affected by Fabry disease, however, should be optimally diagnosed by the direct analysis of their family's specific pathogenic variant. Prenatal detection of affected males can be accomplished by the demonstration of deficient α-galactosidase A activity or the family's specific gene pathogenic variant in chorionic villi obtained in the first trimester or in cultured amniocytes obtained by amniocentesis in the second trimester of pregnancy. Fabry disease can be detected by newborn screening, and pilot studies have been conducted in Italy and Taiwan.

Treatment for Fabry disease may include the use of phenytoin and/or carbamazepine to decrease the frequency and severity of the chronic acroparesthesias and the periodic crises of excruciating pain. Renal transplantation and long-term hemodialysis are lifesaving procedures for patients with renal failure.

Recombinant α-galactosidase is a safe and effective ERT of choice for Fabry disease at a dose of 1 mg/kg every other week. It has been shown to clear microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin in patients with Fabry disease with stabilization of renal disease, regression of hypertrophic cardiomyopathy, reduction of pain, and improvement in quality of life. Migalastat, a protein-folding chaperone therapy, is an oral treatment for Fabry that can both be used as a first-line therapy in ERT-naïve patients and as an alternative to ERT in patients with a migalastat-amenable pathogenic variant.

FUCOSIDOSIS

This is a rare autosomal recessive disorder caused by the deficient activity of α-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycoproteins, and oligosaccharides in the lysosomes of the liver, brain, and other organs (see Table 106.15). α-Fucosidase is encoded by the *FUCA1* gene, and specific pathogenic variants are known. Although the disorder is panethnic, most affected patients are from Italy and the United States. There is wide variability in the clinical phenotype, with the most severely affected patients presenting in the first year of life with developmental delay and somatic features similar to those of the mucopolysaccharidoses. These features include frontal bossing, hepatosplenomegaly, facial features, and macroglossia. The CNS storage results in a relentless neurodegenerative course, with death in childhood. Patients with milder disease have angiokeratomas and longer survival. No specific therapy exists for the disorder, which can be diagnosed by the demonstration of pathogenic variants in *FUCA1* or deficient α-fucosidase activity in peripheral leukocytes or cultured fibroblasts. Carrier identification studies and prenatal diagnosis are possible by determination of the enzymatic activity or the specific family pathogenic variants.

SCHINDLER DISEASE

Schindler disease is an autosomal recessive neurodegenerative disorder that results from the deficient activity of α-N-acetylgalactosaminidase and the accumulation of sialylated and asialoglycopeptides and oligosaccharides (see Table 106.15). The enzyme is encoded by the gene *NAGA*. The disease is clinically heterogeneous, and two major phenotypes have been identified. Type I disease is an infantile-onset neuroaxonal dystrophy. Affected

infants have normal development for the first 9-15 months of life followed by a rapid neurodegenerative course that results in severe intellectual disability, cortical blindness, and frequent myoclonic seizures. Type II disease is characterized by a variable age at onset, mild retardation, and angiokeratomas. There is no specific therapy for either form of the disorder. The diagnosis is by demonstration of the enzymatic deficiency in leukocytes or cultured skin fibroblasts or specific gene pathogenic variants.

METACHROMATIC LEUKODYSTROPHY (MLD)

This is an autosomal recessive white matter disease caused by a deficiency of arylsulfatase A (ASA) encoded by the gene *ARSA,* which is required for the hydrolysis of sulfated glycosphingolipids. Another form of MLD is caused by a deficiency of a sphingolipid activator protein (SAP1) encoded by the gene *PSAP,* which is required for the formation of the substrate-enzyme complex. The deficiency of this enzymatic activity results in the white matter storage of sulfated glycosphingolipids, which leads to demyelination and a neurodegenerative course. Pathogenic variants fall into two groups that correlate with disease severity.

The clinical manifestations of the late infantile form of MLD, which is most common, usually present between 12 and 18 months of age as irritability, inability to walk, and hyperextension of the knee, causing genu recurvatum. The clinical progression of the disease relates to the pathologic involvement of both central and peripheral nervous systems, giving a mixture of upper and lower motor neuron and cognitive and psychiatric signs. Deep tendon reflexes are diminished or absent. Gradual muscle wasting, weakness, and hypotonia become evident and lead to a debilitated state. As the disease progresses, nystagmus, myoclonic seizures, optic atrophy, and quadriparesis appear, with death in the first decade of life (see Table 106.15). The juvenile form of the disorder has a more indolent course with an onset that may occur as late as 20 years of age. This form of the disease presents with gait disturbances, mental deterioration, urinary incontinence, and emotional difficulties. The adult form, which presents after the second decade, is similar to the juvenile form in its clinical manifestations, although emotional difficulties and psychosis are more prominent features. Dementia, seizures, diminished reflexes, and optic atrophy also occur in both the juvenile and adult forms. The pathologic hallmark of MLD is the deposition of metachromatic bodies, which stain strongly positive with periodic acid–Schiff and Alcian blue, in the white matter of the brain. Neuronal inclusions may be seen in the midbrain, pons, medulla, retina, and spinal cord; demyelination occurs in the peripheral nervous system. Bone marrow transplantation has resulted in normal enzymatic levels in peripheral blood but there is no clear evidence for clinical efficacy in terms of the neurologic course; supportive care remains the primary intervention. Lentiviral transduced ex vivo autologous stem and progenitor cells with human arylsulfatase cDNA treatment has resulted in sustained and clinically important benefits in children with early onset disease. Cognitive function has been preserved, as has motor development in preliminary trials.

The diagnosis of MLD should be suspected in patients with the clinical features of leukodystrophy. Decreased nerve con¬duction velocities, increased cerebrospinal fluid protein, metachromatic deposits in sampled segments of the sural nerve, and metachromatic granules in urinary sediment are all suggestive of MLD. Confirmation of the diagnosis is based on the demonstration of pathogenic variants in *ARSA* or reduced activity of ASA in leukocytes or cultured skin fibroblasts. Sphingolipid activator protein deficiency is diagnosed by genetic testing of *PSAP* or by measuring the concentration of SAP1 in cultured fibroblasts using a specific antibody to the protein. Carrier detection and prenatal diagnosis are available for all forms of the disorder.

MULTIPLE SULFATASE DEFICIENCY

This is an autosomal recessive disorder that results from the enzymatic deficiency of at least nine sulfatases including arylsulfatases A, B, and C and iduronate-2-sulfatase. The specific defect has been shown to be an enzyme in the C-α-formylglycine generating system encoded by the gene *SUMF1,* which introduces a common posttranslational modification in all of the affected sulfatases and explains the occurrence of these multiple enzyme defects. Because of the deficiency of these enzymes, sulfatides, mucopolysaccharides, steroid sulfates, and gangliosides accumulate in the cerebral cortex and visceral tissues, resulting in a clinical phenotype with features of leukodystrophy as well as those of the mucopolysaccharidoses. Severe ichthyosis may also occur. Carrier testing and prenatal diagnosis by measurement of the enzymatic activities can be performed. There is no specific treatment for multiple sulfatase deficiency other than supportive care.

KRABBE DISEASE

This condition, also called *globoid cell leukodystrophy,* is an autosomal recessive fatal disorder of infancy. It results from the deficiency of the enzymatic activity of galactocerebrosidase encoded by the *GALC* gene, leading to white matter accumulation of galactosylceramide, which is normally found almost exclusively in the myelin sheath. Both peripheral and central myelin are affected, resulting in spasticity and cognitive impairment coupled with deceptively normal or even absent deep tendon reflexes. Specific disease-causing pathogenic variants are known. The infantile form of Krabbe disease is rapidly progressive, and patients present in early infancy with irritability, seizures, and hypertonia (see Table 106.16). Optic atrophy is evident in the first years of life, and cognitive development is severely impaired. As the disease progresses, optic atrophy and severe developmental delay become apparent; affected children exhibit opisthotonos and typically die before 3 years of age. A second, late infantile form of Krabbe disease also exists, and patients present after the age of 2 years. Affected individuals, however, have a disease course similar to that of the early infantile form.

The diagnosis of Krabbe disease relies on the demonstration of the specific pathogenic variants or by enzymatic deficiency in white blood cells or cultured skin fibroblasts. Carrier identification and prenatal diagnosis are available. The development of methods to measure GALC activity on dried blood spots has led to the inclusion of Krabbe disease in the newborn screening programs of some states. Treatment of infants with Krabbe disease with umbilical cord blood cell transplantation has been reported in prenatally identified asymptomatic newborns and symptomatic infants. The long-term outcome of umbilical cord blood cell transplantation is being evaluated; transplanted infants develop neurologic manifestations at a slower rate but succumb to a neurologic demise.

FARBER DISEASE

This is a rare autosomal recessive disorder that results from the deficiency of the lysosomal enzyme acid ceramidase and the accumulation of ceramide in various tissues, especially the joints. Symptoms can begin as early as the first year of life with painful joint swelling and nodule formation (Fig. 106.21), which is sometimes diagnosed as rheumatoid arthritis. As the disease progresses, nodule or granulomatous formation on the vocal cords can lead to hoarseness and breathing difficulties; failure to thrive is common. In some patients, moderate CNS dysfunction is present (see Table 106.16). Patients may die of recurrent pneumonias in their teens; there is currently no specific therapy. The diagnosis of this disorder should be suspected in patients who have nodule formation over the joints but no other findings of rheumatoid arthritis. In such patients, ceramidase activity should be determined in cultured skin fibroblasts or peripheral leukocytes. Various disease-causing pathogenic variants have been identified in the gene encoding acid ceramidase *(ASAH1).* Carrier detection and prenatal diagnosis are



Fig. 106.21 Forearm of an 18-month old girl with Farber disease. Note the painful joint swelling and the nodule formation. The infant was suspected of having rheumatoid arthritis.

available. There is no specific treatment, but a recombinant human acid ceramidase is under development.

WOLMAN DISEASE AND CHOLESTEROL ESTER STORAGE DISEASE (CESD)

These are autosomal recessive lysosomal storage diseases that result from the deficiency of lysosomal acid lipase and the accumulation of cholesterol esters and triglycerides in histiocytic foam cells of most visceral organs. Wolman disease is the more severe clinical phenotype and is a fatal disorder of infancy. Clinical features become apparent in the first weeks of life and include failure to thrive, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly (see Table 106.15). There usually is hyperlipidemia. Hepatic dysfunction and fibrosis may occur. Calcification of the adrenal glands is pathognomonic for the disorder. Death usually occurs within 6 months.

CESD is a less severe disorder that may not be diagnosed until adulthood. Hepatomegaly can be the only detectable abnormality, but affected individuals are at significant risk for premature atherosclerosis. Adrenal calcification is not a feature.

Lysosomal acid lipase is encoded by the *LIPA* gene. Diagnosis and carrier identification can be performed by genetic testing or by measuring acid lipase activity in peripheral leukocytes or cultured skin fibroblasts. Prenatal diagnosis can use pathogenic variants or enzyme levels in cultured chorionic villi or amniocytes. Pharmacologic agents to suppress cholesterol synthesis, in combination with cholestyramine and diet modification, have been used in patients with CESD (see Chapter 106.3). Sebelipase alfa (Kanuma) is a commercially available recombinant human lysosomal acid lipase that is approved in the European Union (EU), the United States, and Japan as a long-term ERT for patients diagnosed with LAL deficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

106.5 Mucolipidoses

Margaret M. McGovern and Robert J. Desnick

I-cell disease (mucolipidosis II [ML-II]) and pseudo-Hurler polydystrophy (mucolipidosis III [ML-III]) are rare autosomal recessive disorders that share some clinical features with Hurler syndrome (see Chapter 109). These diseases result from the abnormal transport of newly synthesized lysosomal enzymes that are normally targeted to the lysosome by the presence of mannose-6-phosphate residues and recognized by specific lysosomal membrane receptors. These mannose-6-phosphate recognition markers are synthesized in a two-step reaction that occurs in the Golgi apparatus and is mediated by two enzymatic activities. The enzyme that catalyzes the first step, the UDP-N-acetylglucosamine:lysosomal enzyme *N*-acetylglucosamine-1-phosphotransferase, is defective in both ML-II and ML-III, which are allelic disorders resulting from pathogenic variants in the GlcNAc-phosphotransferase alpha/beta-subunits precursor gene *(GNPTAB)*. This enzyme deficiency results in the lack of mannose-6-phosphate tagging of lysosomal enzymes to result in disrupted targeting to the lysosome, and they are consequently secreted into the extracellular matrix. Because the lysosomal enzymes require the acidic medium of the lysosome to function, patients with this defect accumulate a variety of different substrates because of the intracellular deficiency of all lysosomal enzymes. The diagnosis of ML-II and ML-III can be made by genetic testing of the *GNPTAB* gene, determination of the serum lysosomal enzymatic activities, which are elevated, or by the demonstration of reduced enzymatic activity levels in cultured skin fibroblasts. Direct measurement of the phosphotransferase activity is possible as well. Prenatal diagnosis is available for both disorders using familial pathogenic variants or by measurement of lysosomal enzymatic activities in amniocytes or chorionic villus cells; carrier identification studies are available for both disorders using cultured skin fibroblasts. Neonatal screening by tandem mass spectroscopy may detect I-cell disease.

I-CELL DISEASE

This disorder shares many of the clinical manifestations of Hurler syndrome (see Chapter 109), although there is no mucopolysaccharidurria and the presentation is earlier (see Table 106.16). Some patients have clinical features evident at birth, including coarse facial features, craniofacial abnormalities, restricted joint movement, and hypotonia. Nonimmune hydrops may be present prenatally. The remainder of patients present in the first year with severe psychomotor retardation, coarse facial features, and skeletal manifestations that include kyphoscoliosis and a lumbar gibbus. Patients may also have congenital dislocation of the hips, inguinal hernias, and gingival hypertrophy. Progressive, severe intellectual disability leads to death in early childhood. No treatment is available.

PSEUDO-HURLER POLYDYSTROPHY

Pseudo-Hurler polydystrophy is a less severe disorder than I-cell disease, with later onset and survival to adulthood reported. Affected children may present around the age of 4 or 5 years of age with joint stiffness and short stature. Progressive destruction of the hip joints and moderate dysostosis multiplex are evident. Radiographic evidence of low iliac wings, flattening of the proximal femoral epiphyses with valgus deformity of the femoral head, and hypoplasia of the anterior third of the lumbar vertebrae are characteristic findings. Ophthalmic findings include corneal clouding, retinopathy, and astigmatism; visual complaints are uncommon (see Tables 106.15 and 106.16). Some patients have learning disabilities or mental retardation. Treatment, which should include orthopedic care, is symptomatic.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 107

Defects in Metabolism of Carbohydrates

Ghada Hijazi and Priya S. Kishnani

Carbohydrate synthesis and degradation provide the energy required for most metabolic processes. The important carbohydrates include three monosaccharides—glucose, galactose, and fructose—and a polysaccharide, glycogen. Figure 107.1 shows the relevant biochemical pathways of these carbohydrates. **Glucose** is the principal substrate of energy metabolism, continuously available through dietary intake, glycogenolysis (breakdown of glycogen), and gluconeogenesis (glucose made de novo from amino acids, primarily alanine). Metabolism of glucose generates adenosine triphosphate (ATP) via glycolysis (conversion of glucose or glycogen to pyruvate), mitochondrial oxidative phosphorylation (conversion of pyruvate to carbon dioxide and water), or both. Dietary sources of glucose come from polysaccharides, primarily starch, and the disaccharides lactose, maltose, and sucrose. However, oral intake of glucose is intermittent and unreliable. Hepatic glycogenolysis provides the rapid release of glucose and is the most significant factor in maintaining euglycemia (normal levels of glucose in the blood). **Glycogen** is also the primary stored energy source in muscle, providing glucose for muscle activity during exercise. Gluconeogenesis contributes to maintaining euglycemia but is less immediate. Galactose and fructose are monosaccharides that provide fuel for cellular metabolism, though their role is less significant than that of glucose. **Galactose** is derived from lactose (galactose + glucose), which is found in milk and milk products. Galactose is an important energy source in infants. Galactose (exogenous or endogenously synthesized from glucose) is also an important component of certain glycolipids, glycoproteins, and glycosaminoglycans. The dietary sources of **fructose** are fruits, vegetables, and honey. It is also found in the disaccharide sucrose (fructose + glucose) and the sugar alcohol sorbitol.

Defects in glycogen metabolism typically cause an accumulation of glycogen in the tissues, thus the name **glycogen storage disease** (Table 107.1). Defects in gluconeogenesis or the glycolytic pathway, including galactose and fructose metabolism, do not result in an accumulation of glycogen (see Table 107.1). The defects in pyruvate metabolism in the pathway of the conversion of pyruvate to carbon dioxide and water via mitochondrial oxidative phosphorylation are more often associated with **lactic acidosis**.

107.1 Glycogen Storage Diseases

Ghada Hijazi and Priya S. Kishnani

The disorders of glycogen metabolism, the glycogen storage diseases (GSDs), result from deficiencies of enzymes or transport proteins in the pathways of glycogen metabolism (see Fig. 107.1). Glycogen found in these disorders is abnormal in quantity, quality, or both. GSDs are categorized by numerical type in accordance with the chronological order in which these enzymatic defects were identified. This numerical classification is still widely used, at least up to number VII. The GSDs can also be classified by organ involvement into liver and muscle glycogenoses (see Table 107.1).

There are more than 15 forms of GSDs. Glucose-6-phosphatase deficiency (type I), lysosomal acid α-glucosidase deficiency (type II), debrancher deficiency (type III), branching enzyme deficiency (type IV), liver phosphorylase deficiency (type VI), and liver phosphorylase kinase deficiency (type IX) are the most common of those that typically present in early childhood. Myophosphorylase deficiency (type V, McArdle disease) is the most common in adolescents and adults. The cumulative frequency of all forms of GSD is approximately 1 in 10,000-25,000 live births.

LIVER GLYCOGENOSES

The GSDs that principally affect the liver include glucose-6-phosphatase deficiency **(type I)**, debranching enzyme deficiency **(type III)**, branching enzyme deficiency **(type IV)**, liver phosphorylase deficiency **(type VI)**, phosphorylase kinase deficiency **(type IX)**, glycogen synthase deficiency **(type 0)**, and glucose transporter-2 (GLUT2) defect (Fanconi-Bickel syndrome). Because hepatic carbohydrate metabolism is responsible for plasma glucose homeostasis, this group of disorders typically causes fasting hypoglycemia and hepatomegaly. Some GSDs (types III, IV, VI, IX) can be associated with liver fibrosis and cirrhosis. Other organs can also be involved and may manifest as renal dysfunction in type I; myopathy (skeletal and/or cardiomyopathy) in types III, IV, and some rare forms of phosphorylase kinase deficiency; and neurologic involvement in types III (peripheral nerves) and IV (diffuse central and peripheral nervous system dysfunction).

Type I Glycogen Storage Disease (Glucose-6-Phosphatase or Translocase Deficiency, von Gierke Disease)

Type I GSD is caused by the absence or deficiency of **glucose-6-phosphatase activity** in the liver, kidney, and intestinal mucosa. It has two subtypes: **type Ia**, in which the defective enzyme is glucose-6-phosphatase, and **type Ib**, in which the defective enzyme is a **translocase** that transports glucose-6-phosphate across the microsomal membrane. Deficiency of the enzymes in both types Ia and Ib lead to inadequate hepatic conversion of glucose-6-phosphate to glucose through normal glycogenolysis and gluconeogenesis, resulting in fasting hypoglycemia.

Type I GSD is an autosomal recessive disorder. The gene for subtype Ia is *G6PC*, and the gene for subtype Ib is *SLC37A4*. Common pathogenic variants have been identified in different ancestral populations. Carrier detection and prenatal diagnosis are possible with DNA-based methodologies.

Clinical Manifestations

Patients with type I GSD may present in the neonatal period with hypoglycemia and lactic acidosis, but more often present at 3-4 months of age because of increased intervals between feeds and at time of weaning. Infants can present with hepatomegaly, hypoglycemic seizures, or both. Affected children are often described as having **"doll-like" faces** with full cheeks, relatively thin extremities, short stature, and a protuberant abdomen that is a consequence of massive hepatomegaly. The kidneys are also enlarged, whereas the spleen and heart are not involved.

Intermittent diarrhea may occur in GSD I. In patients with GSD Ib, diarrhea appears to be caused by the loss of mucosal barrier function via inflammation, which is likely related to glycogen-mediated impairment of neutrophil function. Easy bruising and epistaxis are common and are associated with a **prolonged bleeding time** as a result of impaired platelet aggregation and adhesion. A von Willebrand factor–like deficiency and/or dysfunction has also been found in GSD Ia patients.

The biochemical characteristics of type I GSD are hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Hypoglycemia and lactic acidosis can develop even after short fasts. Hyperuricemia is present in young children and rarely progresses to symptomatic gout before puberty. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. The plasma may be "milky" in appearance due to strikingly elevated triglyceride levels. Cholesterol and phospholipids are also elevated, albeit less prominently. The lipid abnormality resembles type IV hyperlipidemia and is characterized by increased levels of very low-density lipoprotein, low-density lipoprotein, and a unique apolipoprotein profile consisting of increased levels of apolipoproteins B, C, and E, with relatively normal or reduced levels of apolipoproteins A and D. The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and

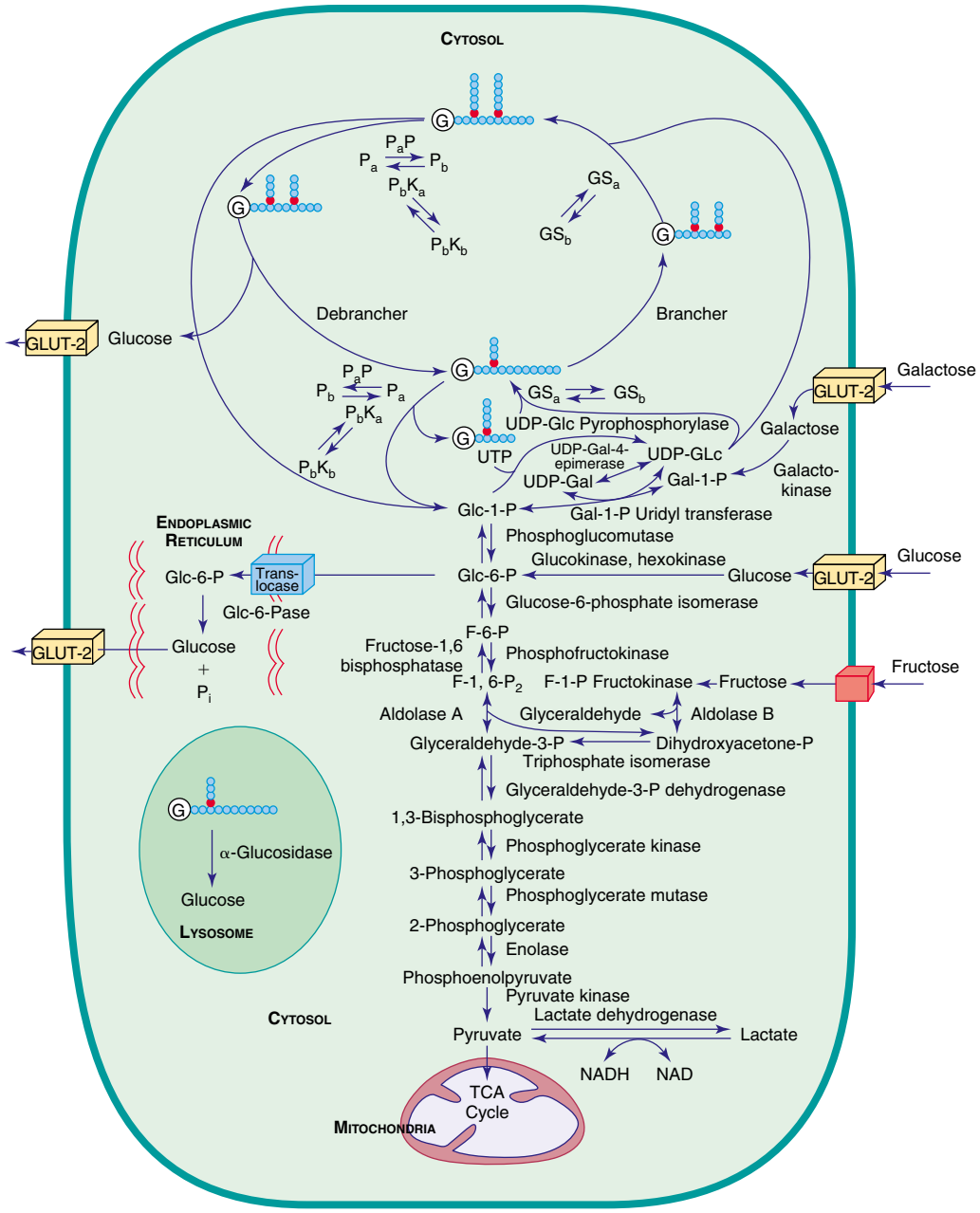

Fig. 107.1 Pathway related to glycogen storage diseases and galactose and fructose disorders. G, Glycogenin, the primer for glycogen synthesis; GLUT-2, glucose transporter 2; GSa, active glycogen synthase; GSb, inactive glycogen synthase; NAD/NADH, nicotinamide adenine dinucleotide; Pa, active phosphorylase; PaP, phosphorylase a phosphatase; Pb, inactive phosphorylase; PbKa, active phosphorylase b kinase; PbKb, inactive phosphorylase b kinase; UDP, uridine diphosphate. *(Adapted from Beaudet AR. Glycogen storage disease. In: Harrison TR, Isselbacher KJ, eds. Harrison's Principles of Internal Medicine, 13th ed. New York: McGraw-Hill; 1994.)*

fat. The lipid vacuoles are particularly large and prominent, and there is no associated liver fibrosis.

Although type I GSD affects mainly the liver, multiple organ systems are involved. **Delayed puberty** is often seen. Females can have ultrasound findings consistent with **polycystic ovaries**, even though other features of polycystic ovary syndrome (acne, hirsutism) are not seen. Nonetheless, fertility appears to be normal, as evidenced in several reports of successful pregnancy in women with GSD I. Increased bleeding during menstrual cycles, including life-threatening menorrhagia, has been reported and could be related to the impaired platelet aggregation. Symptoms of gout usually start around puberty from long-term hyperuricemia. There is an increased risk of **pancreatitis**, secondary to the lipid abnormalities. The dyslipidemia, together with elevated erythrocyte aggregation, could predispose these patients to atherosclerosis, but premature atherosclerosis has not yet been clearly documented except in rare cases. Impaired platelet aggregation and increased antioxidative defense to prevent lipid peroxidation may function as protective mechanisms to help reduce the risk of atherosclerosis. Frequent fractures and radiographic evidence of **osteopenia** are common, and bone mineral content is reduced, even in prepubertal patients.

By the second or third decade of life, some patients with type I GSD develop **hepatic adenomas** that can hemorrhage and become malignant in some cases. **Pulmonary hypertension** has been seen in some long-term survivors of the disease. Iron-refractory anemia and an increased prevalence of thyroid autoimmunity are also being recognized.

Renal disease is another late complication, and most patients with type I GSD over 20 years of age have proteinuria. Glomerular

Table 107.1 Features of the Disorders of Carbohydrate Metabolism

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
LIVER GLYCOGENOSES			
Type/Common Name			
Ia/von Gierke	Glucose-6-phosphatase complex	Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels	Common, severe hypoglycemia. Adulthood: hepatic adenomas and risk for carcinoma, osteoporosis, pulmonary hypertension, and renal failure
Ib	Glucose-6-phosphate translocase	Same as type Ia, with additional findings of neutropenia, periodontal disease, inflammatory bowel disease, and increased risk of autoimmune hypothyroidism	10% of type I
IIIa/Cori or Forbes	Liver and muscle debrancher deficiency	Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels, hepatic fibrosis, left ventricular hypertrophy. Later childhood to adulthood: muscle atrophy and weakness, liver cirrhosis and failure, risk for hepatocellular carcinoma, cardiac hypertrophy and fibrosis, life-threatening arrhythmia at any age.	Common, intermediate severity of hypoglycemia. Muscle weakness may progress to the point that ambulation assistance such as wheelchair use is required.
IIIb	Liver debrancher deficiency; normal muscle enzyme activity	Liver symptoms same as in type IIIa; no muscle or heart symptoms	15% of type III
IV/Andersen/adult polyglucosan body disease	Branching enzyme	Infancy/childhood failure to thrive, hypotonia, hepatomegaly, splenomegaly, cirrhosis progressing to liver failure (death usually before fifth year), elevated transaminase levels; a subset does not have overt progression to liver failure. Risk for extrahepatic manifestations, such as myopathy and cardiomyopathy. Perinatal: decreased fetal movements, polyhydramnios, fetal hydrops; arthrogryposis, hypotonia, muscle atrophy at birth, death in the perinatal period. Congenital: neonatal hypotonia, respiratory failure, dilated cardiomyopathy, early infantile death. Childhood: neuromuscular manifestations, cardiomyopathy. Adult form, adult polyglucosan body disease (APBD): progressive muscle weakness, neuropathic bladder, gait spasticity, central and peripheral nervous system involvement.	A continuum of disease severity, related to residual enzyme activity; multisystem involvement
VI/Hers	Liver phosphorylase	Hepatomegaly, hypoglycemia, hyperlipidemia, elevated liver enzyme levels, and ketosis	Often underdiagnosed; severe presentation also known
IX/phosphorylase kinase (PhK) deficiency			Common, X-linked GSD IX α2, typically less severe than autosomal form GSD IX γ2; clinical variability within and between subtypes; severe cases being recognized across different subtypes
IX α2 (*PHKA2* variant)	Liver PhK	Hypoglycemia, hyperketosis, hepatomegaly, chronic liver disease, liver fibrosis, hyperlipidemia, elevated liver enzymes, growth retardation	X-linked
IX β (*PHKB* variant)	Liver and muscle PhK	Hepatomegaly, growth retardation, mild or absent muscle disease.	Autosomal recessive
IX γ2 (*PHKG2* variant)	Liver PhK	More severe than IX α2; marked hepatomegaly, recurrent hypoglycemia, hyperlipidemia, markedly elevated liver enzymes, liver fibrosis/cirrhosis	Autosomal recessive
0a/Liver glycogen synthase deficiency	Liver glycogen synthase	Early morning drowsiness and fatigue, fasting hypoglycemia and ketosis, no hepatomegaly	Decreased liver glycogen stores
XI/Fanconi-Bickel syndrome	Glucose transporter 2 (GLUT-2)	Failure to thrive, rickets, hepatomegaly, renomegaly, proximal renal tubular dysfunction, impaired glucose and galactose use	GLUT-2 expressed in liver, kidney, pancreas, and intestine
MUSCLE GLYCOGENOSES			
Type/Common Name			
II/infantile Pompe	Acid α-glucosidase	Cardiomegaly, hypotonia, hepatomegaly; onset at birth to age 6 mo	Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity
II/late-onset Pompe (juvenile and adult)	Acid α-glucosidase	Myopathy (proximal limb girdle), variable cardiomyopathy, respiratory insufficiency; onset from infancy and early childhood to adulthood	Residual enzyme activity
Danon disease	Lysosome-associated membrane protein 2 (LAMP2)	Hypertrophic cardiomyopathy, heart failure, retinopathy, mild cognitive dysfunction	Rare, X-linked

Table 107.1 Features of the Disorders of Carbohydrate Metabolism—cont'd

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
PRKAG2 syndrome	Adenosine monophosphate (AMP)–activated protein kinase γ	Hypertrophic cardiomyopathy, arrhythmias, myopathy, myalgia, seizures; congenital fetal form is rapidly fatal	Autosomal dominant
0b/muscle glycogen synthase deficiency	Muscle glycogen synthase	Muscle weakness, hypertrophic cardiomyopathy, abnormal heart rate, sudden cardiac arrest	Rare, few cases reported
XV/Polyglucosan body myopathy 2	Glycogenin-1	Juvenile- or adult-onset proximal muscle weakness, nervous system involvement uncommon	Rare, autosomal recessive
V/McArdle	Myophosphorylase	Exercise intolerance, muscle cramps, myoglobinuria, "second-wind" phenomenon, muscle weakness	Common, male predominance
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, compensatory hemolytic anemia, myoglobinuria, "out-of-wind" phenomenon	Prevalent in Japanese and Ashkenazi Jewish populations
IX α1 (*PHKA1* variant)	Muscle PhK	Exercise intolerance, cramps, myalgia, increased CK, myoglobinuria in some; no hepatomegaly	X-linked
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	As with type V	Rare, X-linked
X/Phosphoglycerate mutase deficiency	M subunit of phosphoglycerate mutase	As with type V	Rare, majority of patients are Black
XI/Lactate dehydrogenase deficiency	M subunit of lactate dehydrogenase	As with type V	Rare
GALACTOSE DISORDERS			
Galactosemia with transferase deficiency	Galactose-1-phosphate uridyltransferase	Vomiting, feeding difficulties, liver failure/dysfunction/hepatomegaly, cataracts, failure to thrive, *E. coli* sepsis, generalized aminoaciduria	Black patients tend to have milder symptoms
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Generalized uridine diphosphate galactose-4-epimerase deficiency	Uridine diphosphate galactose-4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	Benign and intermediate variants also exist
Galactose mutarotase deficiency	Galactose mutarotase	Cataract	Benign
FRUCTOSE DISORDERS			
Essential fructosuria	Fructokinase	Urine-reducing substance	Benign
Hereditary fructose intolerance	Fructose-1-phosphate aldolase (aldolase-B)	Acute; vomiting, hypoglycemia, sweating, lethargy, acute liver failure/liver dysfunction Chronic; failure to thrive, hepatic failure	Prognosis good with fructose restriction
DISORDERS OF GLUCONEOGENESIS			
Fructose-1,6-bisphosphatase deficiency	Fructose-1,6-diphosphatase	Episodic hypoglycemia, lactic acidosis, liver failure/dysfunction	Good prognosis, avoid fasting
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	Hypoglycemia, hepatomegaly, hypotonia, failure to thrive	Rare
DISORDERS OF PYRUVATE METABOLISM			
Pyruvate dehydrogenase complex defect	Pyruvate dehydrogenase	Severe fatal neonatal to mild late onset, lactic acidosis, psychomotor retardation, failure to thrive, features overlapping fetal alcohol syndrome, MRI findings suggestive of Leigh syndrome, ataxia	Most commonly caused by $E_{1\alpha}$ subunit defect, X-linked
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Type B: neonatal severe lactic acidosis, hyperammonemia, hypercitrullinemia, hyperlysinemia, and hypoglycemia. Type A: late-onset mild to moderate lactic acidosis and developmental delay. Type C: recurrent episodes of lactic acidosis, ketoacidosis, and mild neurologic deficits.	Rare, autosomal recessive
Respiratory chain defects (oxidative phosphorylation disease)	Complexes I-V, many mitochondrial and nuclear DNA variants	Heterogeneous with multisystem involvement (see Table 107.3 and Table 107.5)	Mitochondrial, autosomal recessive, dominant, and X-linked inheritance
DISORDERS IN PENTOSE METABOLISM			
Pentosuria	l-Xylulose reductase	Urine-reducing substance	Benign
Transaldolase deficiency	Transaldolase	Intrauterine growth restriction, oligohydramnios, dysmorphism, cardiovascular anomalies, anemia, thrombocytopenia, hepatosplenomegaly, endocrine abnormalities, cutis laxa	Autosomal recessive, milder form exists
Ribose-5-phosphate isomerase deficiency	Ribose-5-phosphate isomerase	Progressive leukoencephalopathy and peripheral neuropathy	Four cases reported

hyperfiltration, increased renal plasma flow, and microalbuminuria are often found in the early stages of renal dysfunction and can occur before the onset of proteinuria. In younger patients, hyperfiltration and hyperperfusion may be the only signs of renal abnormalities. Many also have hypertension, renal stones, nephrocalcinosis, proteinuria, renal tubular acidosis (proximal and distal renal acidification defects), and altered creatinine clearance. With the advancement of renal disease, focal segmental glomerulosclerosis and interstitial fibrosis become evident. In some patients, renal function has deteriorated and progressed to failure, requiring dialysis and transplantation. Other renal abnormalities include amyloidosis, a Fanconi-like syndrome, hypocitraturia, hypercalciuria, and a distal renal tubular acidification defect. Patients with *GSD Ib* can have additional features of recurrent bacterial infections from **neutropenia** and impaired neutrophil function. Oral involvement, including recurrent mucosal ulceration, gingivitis, and rapidly progressive periodontal disease, may occur in type Ib. Intestinal mucosa ulceration culminating in GSD enterocolitis is also common. Type 1b is also associated with a chronic inflammatory bowel disease (IBD)–like picture involving the colon that may be associated with neutropenia and/or neutrophil dysfunction and can resemble ulcerative colitis or Crohn disease.

Diagnosis

The clinical presentation and laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia lead to a suspected diagnosis of type I GSD. Neutropenia is noted in *GSD Ib* patients, although neutrophil counts may be normal initially. Neutropenia has also been noted in some patients with GSD Ia, especially those with the p.G188A variant. Administration of glucagon or epinephrine leads to a negligible increase, if any, in blood glucose levels, but the lactate level rises significantly. Before the availability of genetic testing, a definitive diagnosis required enzyme testing via liver biopsy. Gene-based variant analysis using single-gene sequencing or multigene panel testing provides a noninvasive way to diagnose most patients with GSD types Ia and Ib and has become the primary recommended method of diagnosis.

Treatment

Treatment focuses on maintaining normal blood glucose levels and is achieved by continuous nasogastric (NG) infusion of glucose or administration of uncooked cornstarch. In infancy, overnight NG drip feeding may be needed to maintain normoglycemia. NG feedings can consist of a sucrose- and lactose-free enteral formula or only glucose or a glucose polymer to provide sufficient glucose to maintain euglycemia. During the day, frequent feedings with high-complex carbohydrate content are typically sufficient.

Uncooked cornstarch acts as a slow-release form of glucose and can be introduced at a dose of 1.6 g/kg every 4 hours for children less than 2 years of age. The response of young children is variable. For older children, the cornstarch regimen can be changed to every 4-6 hours at a dose of 1.6-2.5 g/kg body weight and can be given orally mixed with water or a sucrose-, fructose-, and lactose-free beverage. Cornstarch dosing may also be calculated based on hepatic glucose production rate and can be administered more frequently in smaller amounts to improve metabolic control. Other starch products, such as extended-release waxy maize starch with a high amylopectin content, are shown to be beneficial in extending time between overnight feedings in some individuals with hepatic GSD. Because fructose and galactose cannot be converted directly to glucose in GSD type I, these sugars should be restricted in the diet. Sucrose (table sugar, cane sugar, other ingredients), fructose (fruit, juice, high-fructose corn syrup), lactose (dairy foods), and sorbitol should be avoided or limited. As a result of these dietary restrictions, vitamins and minerals such as calcium and vitamin D may be deficient, and supplementation is required to prevent nutritional deficiencies.

Maintaining normoglycemia and avoiding hypoglycemia necessitate frequent blood glucose measurements in patients with hepatic GSDs. This can be accomplished by self-monitoring blood glucose (SMBG) using a finger prick before and after meals, before physical activity, and overnight. Continuous glucose monitoring systems (CGMSs) are a newer technique that allow for 24-hour glucose monitoring. CGMSs have been shown to be safe and effective tools for monitoring glucose levels in patients with hepatic GSDs (GSD I, GSD III, GSD VI, GSD IX) at all hours of the day. Furthermore, when accompanied with the necessary dietary changes, CGMSs aid in metabolic control, improving disease parameters, avoidance of hospitalizations, and blood glucose stability in these patients.

Dietary therapy improves hyperuricemia, hyperlipidemia, and renal function, as well as slowing the development of renal failure. Blood uric acid and lipid levels may, however, be elevated in some individuals, despite good dietary compliance, especially after puberty. The control of hyperuricemia can be further augmented by the use of allopurinol, a xanthine oxidase inhibitor. Hyperlipidemia can be reduced with lipid-lowering drugs, such as β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrate (see Chapter 106). **Microalbuminuria**, an early indicator of renal dysfunction in type I disease, is treated with angiotensin-converting enzyme (ACE) inhibitors. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and development of urinary calculi. Products containing citric acid reduce the effectiveness of cornstarch and should not be taken concurrently. Thiazide diuretics increase renal reabsorption of filtered calcium and decrease urinary calcium excretion, thereby preventing hypercalciuria and nephrocalcinosis. Growth hormone (GH) should be used with extreme caution and limited to only those with a documented GH deficiency. Even in those patients, there should be close monitoring of metabolic parameters and for the presence of adenomas. Kidney transplantation may be performed to treat end-stage renal disease (ESRD). As needed, combined liver and kidney transplantation is sometimes recommended.

In patients with **type Ib GSD**, granulocyte colony-stimulating factor is successful in correcting neutropenia, decreasing the number and severity of bacterial infections, and improving chronic IBD; the minimum effective dose should be used, given noted side effects with this agent, including splenomegaly, hypersplenism, and bone pain, with this agent. Vitamin E administration has been shown to improve neutrophil count and function and to reduce the frequency and severity of infections in GSD1b patients. The use of sodium glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin) to improve neutrophil function and reduce neutropenia and IBD symptoms in GSDIb is showing promising results. Bone marrow transplantation has been reported to correct neutropenia in type Ib GSD.

Orthotopic liver transplantation is a potential cure for type I GSD, especially for patients with liver malignancy, multiple liver adenomas, metabolic derangements refractory to medical management, and liver failure; however, because of the paucity of available organ donors, this can be challenging. Large adenomas (>2 cm) that are rapidly increasing in size and/or number may necessitate partial hepatic resection. Smaller adenomas (<2 cm) may be treated with percutaneous ethanol injection or transcatheter arterial embolization. Recurrence of liver adenomas is a challenge and may potentiate malignant transformation in these patients, ultimately requiring a liver transplant. Before any surgical procedure, the bleeding status must be evaluated and good metabolic control established. Prolonged bleeding times can be normalized with intensive intravenous (IV) glucose infusion for 24-48 hours before surgery. Treatment with DDAVP (1-deamino-8-d-arginine vasopressin) can reduce bleeding complications, but it should be used with caution because of the risk of fluid overload and hyponatremia when administered as an IV infusion. Lactated Ringer solution should be avoided because it contains lactate and no glucose. Glucose levels should be maintained in the normal range throughout surgery with the use of 10% dextrose. Overall, metabolic control is assessed by growth, improvement, and correction of the metabolic abnormalities such as elevated lactate, glucose, triglyceride, cholesterol, and uric acid levels.

GSD I is a promising target for gene therapy because it is caused by pathogenic variants in a single gene. An active phase 3 clinical trial (NCT05139316) is being conducted to determine the efficacy and safety of adeno-associated virus serotype 8 (AAV8)–mediated G6P gene replacement in patients ages 8 years and older with GSD type Ia.

Prognosis

Inadequate metabolic control during childhood can lead to long-term complications in adults. Clinical outcomes have improved dramatically with early diagnosis and effective treatment. However, serious complications such as renal disease and formation of hepatic adenomas with potential risk for malignant transformation persist. The ability to identify transformation of liver adenomas to hepatocellular carcinoma remains a challenge as α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels often remain normal in the setting of hepatocellular carcinoma.

Type III Glycogen Storage Disease (Cori Disease, Forbes Disease, Debrancher Deficiency, Limit Dextrinosis)

Type III GSD is caused by deficient activity of the **glycogen debranching enzyme**. This enzyme, together with phosphorylase and phosphorylase kinase, are responsible for complete degradation of glycogen. When debranching enzyme is defective, glycogen breakdown is incomplete, resulting in the accumulation of an abnormal glycogen with short outer-branch chains that resemble *limit dextrin*. GSD **type IIIa** is the most common type and usually involves both liver and muscle; GSD **type IIIb**, seen in approximately 15% of patients, appears to involve only the liver.

Type III GSD is an autosomal recessive disease that has been reported in many different ethnic groups. The frequency is relatively high in the Sephardic Jewish population from North Africa, inhabitants of the Faroe Islands, and the Inuit population. The gene for debranching enzyme *(AGL)* has been noted, with more than 260 different pathogenic variants. At least two pathogenic variants in exon 2, c.18_19del (p.Gln6fs) and c.16C>T (p.Gln6Ter), are specifically associated with GSD type IIIb. Carrier detection and prenatal diagnosis are possible using DNA-based testing.

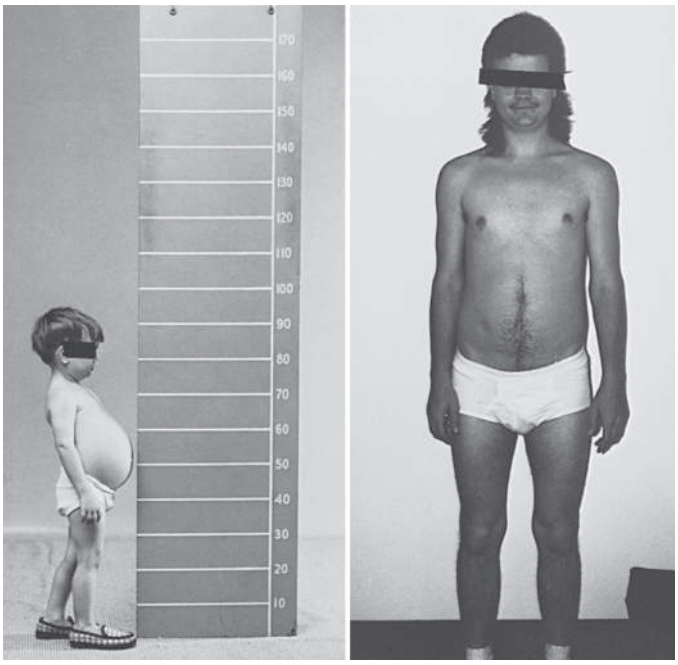

Fig. 107.2 Growth and development in a patient with type IIIb glycogen storage disease. The patient has debrancher deficiency in the liver but normal activity in muscle. As a child, he had hepatomegaly, hypoglycemia, and growth retardation. After puberty, he no longer had hepatomegaly or hypoglycemia, and his final adult height is normal. He had no muscle weakness or atrophy; this is in contrast to patients with type IIIa, in whom a progressive myopathy is seen in adulthood.

Clinical Manifestations

In infancy and childhood, type III GSD may be indistinguishable from type I because of overlapping features such as hepatomegaly, hypoglycemia, hyperlipidemia, and growth stunting (Fig. 107.2). Hepatomegaly in most patients with type III GSD decreases with age; however, liver fibrosis and/or cirrhosis progressing to liver failure are noted in many in late adulthood. Some patients develop hepatocellular carcinoma. Hepatic adenomas with transformation to carcinomas occur less frequently in individuals with GSD III than in those with GSD I. Alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels are not good predictors of malignant transformation.

In patients with GSD type IIIa, the **muscle weakness** is slowly progressive and associated with muscle wasting. The weakness can present in early childhood but can become severe after the third or fourth decade of life. Myopathy does not follow a particular pattern of involvement, and both proximal and distal muscles are involved. Electromyography (EMG) reveals a widespread myopathy, and nerve conduction studies may be abnormal.

Although overt cardiac dysfunction is rare, ventricular hypertrophy is a frequent finding. **Cardiac pathology** has shown diffuse involvement of various cardiac structures, including vacuolation of myocytes, fibrosis, glycogen accumulation in the conduction system, and hyperplasia of smooth muscles. Life-threatening arrhythmia and the need for heart transplant have been reported in some patients with GSD IIIa. Hepatic symptoms in some patients may be mild and the diagnosis is not made until adulthood, when patients show symptoms and signs of neuromuscular disease.

The initial presentation can be confused with Charcot-Marie-Tooth disease (see Chapter 653.1). Polycystic ovaries are noted; some patients can develop hirsutism, irregular menstrual cycles, and other features of polycystic ovarian syndrome. Fertility does not appear to be affected; successful pregnancies have been reported. Low bone mineral density and myopathy in patients with GSD IIIa put them at an increased risk of potential fractures.

Hypoglycemia and hyperlipidemia are common. In contrast to type I GSD, elevation of liver transaminase levels and fasting ketosis are prominent, but blood lactate and uric acid concentrations are usually normal. Glucagon administration 2 hours after a carbohydrate meal provokes a normal increase in blood glucose. However, after an overnight fast, glucagon may provoke no change in blood glucose level. Serum creatine kinase levels can be useful to identify patients with muscle involvement, although normal levels do not rule out muscle enzyme deficiency.

Diagnosis

The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and the presence of fibrous septa. The fibrosis and the paucity of fat distinguish type III glycogenosis from type I. The fibrosis, which ranges from minimal periportal fibrosis to micronodular cirrhosis, appears in most cases to be progressive. Overt cirrhosis has been seen in some patients with GSD III.

Patients with myopathy and liver symptoms have a generalized enzyme defect (type IIIa). The deficient enzyme activity can be demonstrated not only in liver and muscle but also in other tissues such as heart, erythrocytes, and cultured fibroblasts. Patients with hepatic symptoms without clinical or laboratory evidence of myopathy have debranching enzyme deficiency only in the liver, with enzyme activity retained in the muscle (type IIIb). Before the availability of genetic testing, a definitive diagnosis required enzyme assay in liver, muscle, or both. Gene sequencing allows for diagnosis and subtype assignment in the majority of patients.

Treatment

The mainstay of treatment of GSD III is dietary management, as in GSD I, although it is less demanding. Patients do not need to restrict dietary intake of fructose and galactose, although simple sugars should be avoided to prevent sudden spikes in blood glucose levels. Hypoglycemia can be prevented by small frequent meals rich in complex carbohydrates, such as cornstarch supplements or nocturnal gastric drip feedings. Additionally, a high-protein diet during the daytime as well as overnight protein enteral infusion is effective in preventing hypoglycemia. The exogenous protein can be used as a substrate for gluconeogenesis, which helps to meet energy needs and prevent endogenous

protein breakdown. Protein in the diet also reduces the overall starch requirement. Overtreatment with cornstarch should be avoided, as it can result in excessive glycogen buildup, which is detrimental and can lead to excessive weight gain. Medium-chain triglyceride (MCT) supplementation and a high-fat diet are being considered as alternative sources of energy. There is no satisfactory treatment for the progressive myopathy other than recommending a high-protein diet, physical therapy, and high-fat diet in some patients. Close monitoring with abdominal MRI is needed to detect progression of liver fibrosis to cirrhosis and hepatocellular carcinoma (HCC). Additional imaging techniques, such as hepatic elastography, are being developed. Liver transplantation has been performed in GSD III patients with progressive cirrhosis and/or HCC. There are reports of cardiac transplant in GSD III patients with end-stage cardiac disease.

Type IV Glycogen Storage Disease (Branching Enzyme Deficiency, Amylopectinosis, Polyglucosan Disease, Andersen Disease, Adult Polyglucosan Body Disease)

Type IV GSD is caused by the deficiency of **branching enzyme activity**, which results in the accumulation of an abnormal glycogen with poor solubility. The disease is also known as *amylopectinosis* because the abnormal glycogen has fewer α-1,6 branch points, more α-1,4 linked glucose units, and longer outer chains, resulting in a structure resembling amylopectin. These excessively long peripheral glucan chains form polyglucosan bodies, which are positive on periodic acid–Schiff (PAS) and resistant to diastase digestion. Polyglucosan body accumulation is seen in all affected patients but to different degrees and in different tissues.

Type IV GSD is an autosomal recessive disorder. The glycogen branching enzyme *(GBE1)* gene has been noted, with more than 128 pathogenic variants responsible for type IV GSD, and their characterization in individual patients can be useful in predicting clinical outcome. The nearly complete absence of glycogen branching enzyme (GBE) activity with null alleles has been associated with perinatal death and fatal neonatal hypotonia. Residual GBE activity results in a continuum of disease manifestations ranging from progressive hepatic cirrhosis, slowly progressive or nonprogressive liver disease, cardiomyopathy, myopathy, peripheral neuropathy, motor neuron disease, and leukodystrophy.

Clinical Manifestations

A high degree of clinical variability is associated with type IV GSD. The most common and classic form is characterized by **hepatic** involvement with progressive cirrhosis of the liver and manifests in the first 18 months of life as hepatosplenomegaly and failure to thrive. Cirrhosis may present with portal hypertension, ascites, and esophageal varices and may progress to liver failure, usually leading to death by 5 years of age. Some patients survive without progression of liver disease, and they are considered to have a milder hepatic form and do not require liver transplant. Extrahepatic involvement in some patients with GSD IV consists of musculoskeletal involvement, particularly cardiac and skeletal muscles, as well as central nervous system (CNS) and peripheral nervous system (PNS) involvement.

Neuromuscular forms of type IV GSD have been reported, with four main subtypes recognized based on age at presentation. The **perinatal** form is characterized by a *fetal akinesia deformation sequence* (FADS) and death in the perinatal period. The **congenital** form presents at birth with severe hypotonia, muscle atrophy, and neuronal involvement, with death in the neonatal period; some patients have cardiomyopathy. The **childhood** form presents primarily with myopathy or cardiomyopathy. The **adult** form, *adult polyglucosan body disease* (APBD), presents with PNS dysfunction and diffuse CNS involvement, accompanied by accumulation of polyglucosan material in the nervous system. Symptoms of neuronal involvement include progressive muscle weakness; gait spasticity; peripheral neuropathy; neuropathic bladder; and, in many cases, leukodystrophy, mood disturbances, and cognitive decline. APBD is often misdiagnosed as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), or cerebral small-vessel disease (CSVD).

Diagnosis

Deposition of amylopectin-like materials varies and can be demonstrated in the liver, heart, muscle, skin, intestine, brain, brainstem, spinal cord, and peripheral nerves (i.e., sural nerve) in type IV GSD. For patients with hepatic involvement, liver histology shows micronodular cirrhosis and faintly stained basophilic inclusions in hepatocytes. The inclusions are composed of coarsely clumped, stored material that is PAS positive and partially resistant to diastase digestion. Electron microscopy (EM) shows, in addition to the conventional α and β glycogen particles, the accumulation of fibrillar aggregations that are typical of amylopectin. Similar nonmembrane-bound cytoplasmic inclusions (PAS positive, diastase resistant) are observed in the cardiomyocytes and skeletal muscle fibers, and polyglucosan bodies may be present in the muscle biopsy from those with neuromuscular manifestations. In APBD, a peripheral nerve biopsy reveals intra-axonal polyglucosan bodies, and histologic examination of brain tissue shows polyglucosan bodies often visualized in the astrocytes and neurons. The distinct staining properties of the inclusions, as well as EM findings, could be diagnostic. However, polysaccharides with histologic features reminiscent of type IV disease but without enzymatic correlation have been observed. The diagnosis is confirmed by either identification of two pathogenic variants in *GBE1* or a reduction of GBE activity in leukocytes or fibroblasts. Prenatal diagnosis is possible by measuring enzyme activity in cultured amniocytes or chorionic villi or by DNA-based methodologies.

Treatment

There is no specific treatment for type IV GSD. Nervous system involvement, such as gait problems and bladder involvement, requires supportive, symptomatic management. Unlike patients with other liver GSDs (I, III, VI, IX), those with GSD IV do not typically have hypoglycemia. Liver transplantation has been performed for patients with progressive liver disease, but patients must be carefully selected because this is a multisystem disease and, in some patients, extrahepatic involvement may manifest or worsen after transplant. Liver transplantation corrects the hepatic phenotype of the disease but has no effects on the extrahepatic manifestations such as myopathy and cardiomyopathy. Individuals with significant diffuse reticuloendothelial involvement may have greater risk of morbidity and mortality, which may affect the success rate for liver transplant. Patients with symptomatic cardiomyopathy and skeletal myopathy may benefit from heart transplantation and physical therapy, respectively.

Type VI Glycogen Storage Disease (Liver Phosphorylase Deficiency, Hers Disease)

Type VI GSD is caused by deficiency of **liver glycogen phosphorylase**. Patients usually present with hepatomegaly and growth stunting in infancy or early childhood. Hypoglycemia, hyperlipidemia, and hyperketosis are of variable severity. Ketotic hypoglycemia may present after overnight or prolonged fasting. Lactic acid and uric acid levels are normal. Type VI GSD presents within a broad spectrum of involvement, some with a more severe clinical presentation. Patients with severe hepatomegaly, recurrent severe hypoglycemia and hyperketosis have been reported. Focal nodular hyperplasia of liver, hepatocellular adenoma with transformation into carcinoma, hepatic fibrosis, and cirrhosis have been reported in some patients.

Diagnosis

GSD VI is an autosomal recessive disease. Diagnosis can be confirmed through molecular testing of the liver phosphorylase gene *(PYGL)*. Many pathogenic variants are known in this gene, and a splice-site variant in intron 13 has been identified in the Mennonite population. A liver biopsy showing elevated glycogen content and decreased hepatic phosphorylase enzyme activity can also be used to make a diagnosis, especially in cases with inconclusive genetic results. However, with the availability of DNA analysis and next-generation sequencing (NGS) panels, liver biopsies are usually unnecessary.

Treatment

Treatment is symptomatic and aimed at preventing hypoglycemia while ensuring adequate nutrition. A low-carbohydrate (45–50% of total calories), high-protein (2–3 g protein/kg body weight or 20–25% of total calories) diet and frequent feeding are effective in preventing hypoglycemia. Blood glucose and ketones should be monitored routinely, especially during periods of increased activity/illness. Long-term follow-up of these patients is needed to monitor and manage the complications and to expand the understanding of the natural history of this disorder.

Type IX Glycogen Storage Disease (Phosphorylase Kinase Deficiency)

Type IX GSD represents a heterogeneous group of glycogenoses resulting from deficiency of the enzyme **phosphorylase kinase** (PhK), which is involved in the rate-limiting step of glycogenolysis. This enzyme has four subunits (α, β, γ, δ), each encoded by different genes differentially expressed in various tissues. Pathogenic variants in the *PHKA1* gene cause muscle PhK deficiency; pathogenic variants in the *PHKA2* and *PHKG2* genes cause liver PhK deficiency, and pathogenic variants in the *PHKB* gene cause PhK deficiency in liver and muscle. Pathogenic variants in the *PHKG1* gene have not been identified.

Clinical manifestations of liver PhK deficiency are usually recognizable within the first 2 years of life and include short stature and abdominal distention from moderate to marked hepatomegaly. The clinical severity of liver PhK deficiency varies considerably. Hyperketotic hypoglycemia, if present, can be mild but may be severe in some cases. Ketosis may occur even when glucose levels are normal. Some children may have mild delays in gross motor development and hypotonia. It is becoming increasingly clear that GSD IX is not a benign condition. Severe phenotypes are reported, with liver fibrosis progressing to cirrhosis and HCC, particularly in patients with *PHKG2* variants and also in some patients with *PHKA2* variants. Progressive splenomegaly and portal hypertension are reported secondary to cirrhosis. Interventricular septal hypertrophy has been reported in a patient with GSD IX β (*PHKB* variant). Cognitive and speech delays have been reported in a few individuals, but it is not clear whether these delays are caused by PhK deficiency or are coincidental. Renal tubular acidosis has been reported in rare cases. Unlike in GSD I, lactic acidosis, bleeding tendency, and loose bowel movements are not characteristic. Although growth is retarded during childhood, normal height and complete sexual development are eventually achieved. As with debrancher deficiency, abdominal distention and hepatomegaly usually decrease with age. Some adults with liver PhK deficiency are reportedly asymptomatic, although patients at the other end of the spectrum develop cirrhosis and liver failure. Further studies are needed to fully assess and understand the natural history of this disorder in adults.

Phenotypic variability within each subtype is being uncovered with the availability of molecular testing. The incidence of all subtypes of PhK deficiency is approximately 1:100,000 live births.

Type IX α2 Glycogen Storage Disease (X-Linked Liver Phosphorylase Kinase Deficiency, PHKA2 Variant)

Glycogen storage disease IX α2 is one of the most common forms of liver glycogenosis in males. A typical presentation for this condition includes a young male (age 1-5 years) with growth stunting, incidental finding of hepatomegaly, and mild delays in motor development. In addition to the liver, enzyme activity can also be deficient in erythrocytes, leukocytes, and fibroblasts, with normal enzyme activity in muscle. Cholesterol, triglycerides, and liver enzymes are elevated. Ketosis may occur after fasting. Lactate and uric acid levels are normal. Hypoglycemia can range from mild to severe. The response in blood glucose to glucagon is normal. Although hepatomegaly and liver enzymes might gradually reduce and normalize with age in some patients, other groups exhibit an increase in these disease parameters comparable to those observed in patients with GSD IX γ 2. Most adults achieve a normal final height. It is increasingly recognized that this disorder is not benign, as previously thought, and there are patients with severe disease and long-term hepatic sequelae. In some cases, liver fibrosis can occur and progress to cirrhosis. Liver histology shows glycogen-distended hepatocytes, steatosis, fibrosis, and/or cirrhosis. Fibrous septal formation and low-grade inflammatory changes may be seen. Adenomas have been also reported.

The gene for the common liver isoform of the PhK α subunit, *PHKA2,* is located on the X chromosome (Xp22.2). Pathogenic variants in the *PHKA2* gene account for 75% of all PhK cases. X-linked liver PhK deficiency is further subdivided into two biochemical subtypes: XLG1, with measurable deficiency of PhK activity in both blood cells and liver, and XLG2, with normal in vitro PhK activity in blood cells and variable activity in the liver. The mechanism through which XLG2 exhibits normal or increased in vitro PhK activity is unknown. Because of X-inactivation leading to variable expression of the mutant allele, some female carriers may develop symptoms ranging from mild hepatomegaly to more severe symptoms.

Type IX β Glycogen Storage Disease (Autosomal Liver and Muscle Phosphorylase Kinase Deficiency, PHKB Variant)

PhK deficiency in liver and blood cells with an autosomal recessive mode of inheritance has been reported. Similar to the X-linked form, chief symptoms in early childhood include hepatomegaly and growth retardation. Some patients also exhibit muscle hypotonia. In a few cases where enzyme activity has been measured, reduced PhK activity has been demonstrated in muscle. Pathogenic variants are found in PHKB (chromosome 16q12-q13), which encodes the β subunit, and result in liver and muscle PhK deficiency (GSD IX β). Several nonsense and missense variants, a single-base insertion, splice-site pathogenic variants, and a large intragenic pathogenic variant have been identified.

Type IX γ2 Glycogen Storage Disease (Autosomal Liver Phosphorylase Kinase Deficiency, PHKG2 Variant)

This form of PhK deficiency is caused by pathogenic variants in the testis/liver isoform (TL) of the γ2 subunit of the *PHKG2* gene. In contrast to GSD IX α2, patients with GSD IX γ2 typically have more severe phenotypes, with recurrent hypoglycemia, prominent hepatomegaly, significant liver fibrosis, and progressive cirrhosis. Hepatic adenomas have been observed in several patients. Liver involvement occasionally presents with cholestasis, bile duct proliferation, esophageal varices, and splenomegaly. The spectrum of involvement continues to evolve as more cases are recognized. Many pathogenic variants in the *PHKG2* gene have been identified.

Diagnosis

Individuals with liver PhK deficiency usually have ketotic hypoglycemia, elevated transaminases, elevated triglycerides and cholesterol, normal uric acid and lactic acid concentrations, and normal glucagon response. PhK deficiency may be diagnosed by demonstration of the enzymatic defect in affected tissues. Hepatic PhK activity can be measured in liver, leukocytes, and erythrocytes. The interpretation of PhK activity results is complicated by the possibility of both false-positive and false-negative results. False-positive findings are possible, owing to the labile nature of PhK, which is extremely sensitive to handling circumstances and temperature exposure. As a result, extreme caution is required when storing and transporting such diagnostic specimens. Because the PhK enzyme has several isozymes, the diagnosis can easily be missed without the tissue where it is deficient (liver, muscle, or cardiac studies).

Molecular genetic testing is preferable to enzyme assay for diagnosis, as liver biopsy is an invasive procedure. Gene sequencing is used for diagnostic confirmation and subtyping of GSD IX. The *PHKA2* gene encoding the α subunit is most frequently involved, followed by the *PHKB* and *PHKG2* genes encoding the β and γ subunits, respectively.

Treatment and Prognosis

The treatment for liver PhK deficiency is symptomatic and includes a high-protein (2-3 g protein/kg body weight or 20–25% of total calories) diet with complex carbohydrates (45–50% of total calories) and small, frequent feedings to prevent hypoglycemia. Cornstarch can be administered, with symptom-dependent dosage and timing (0.6-2.5 g/kg every 6 hours). Hypoglycemia should be treated with oral glucose, if tolerated; if not, IV glucose should be given.

Patients with pathogenic variants in the γ subunit typically have a more severe clinical course with progressive liver disease. In liver biopsy samples, hepatic fibrosis/cirrhosis was detected in 50% and 95% of patients with *PHKA2* and *PHKG2* pathogenic variants, respectively. Two patients with GSD IX γ2 received liver transplantation, one for liver failure secondary to cirrhosis and the other for HCC. Liver involvement needs to be monitored in all patients with GSD IX by periodic imaging (abdominal ultrasound or MRI every 6-12 months) and serial hepatic function tests.

Type 0a Glycogen Storage Disease (Liver Glycogen Synthase Deficiency)

Liver glycogen synthase deficiency type 0a **(GSD 0a)** is caused by deficiency of **hepatic glycogen synthase** activity, leading to a marked decrease of glycogen stored in the liver. It is caused by pathogenic variants in *GYS2*. The disease appears to be rare in humans and, in the true sense, is not a type of GSD because the enzyme deficiency leads to decreased glycogen stores. Patients present in infancy with early-morning (pre-breakfast) drowsiness, pallor, emesis, and fatigue, and occasional convulsions associated with hypoglycemia and hyperketonemia. Blood lactate and alanine levels are low, and there is no hyperlipidemia or hepatomegaly. **Hyperglycemia**, glycosuria, lactic acidosis, and hyperalaninemia, with normal insulin levels after administration of glucose or a meal, suggest a deficiency of glycogen synthase. ***Diagnosis*** may be through molecular testing that identifies pathogenic variants in *GYS2* or by liver biopsy to measure the enzyme activity.

Treatment consists of frequent meals rich in protein and nighttime supplementation with uncooked cornstarch to prevent hypoglycemia and hyperketonemia. Most children with GSD 0a are cognitively and developmentally age appropriate. Short stature and osteopenia are common features. The ***prognosis*** seems good for patients who survive to adulthood, with a decrease in the frequency and severity of hypoglycemia. Long-term natural history studies are required to have a better understanding of the disease's outcomes and the impact of dietary therapy.

Hepatic Glycogenosis with Renal Fanconi Syndrome (Fanconi-Bickel Syndrome)

Fanconi-Bickel syndrome is a rare autosomal recessive disorder caused by defects in the facilitative GLUT2, which transports glucose in and out of hepatocytes, pancreatic β cells, and the basolateral membranes of intestinal and renal epithelial cells. The disease is characterized by proximal renal tubular dysfunction, impaired glucose and galactose utilization, and accumulation of glycogen in the liver and kidney.

The affected child typically presents in the first year of life with failure to thrive, rickets, and a protuberant abdomen from hepatomegaly and nephromegaly. The disease may be confused with GSD I because a Fanconi-like syndrome can also develop in that patient population. Adult patients have short stature as a result of hypophosphatemic rickets. Patients are more susceptible to fractures because of early-onset generalized osteopenia. In addition, intestinal malabsorption and diarrhea may occur, and HCC has been seen. Laboratory findings include glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting, hypophosphatemia, increased serum alkaline phosphatase levels, and radiologic findings of rickets. Mild fasting hypoglycemia and hyperlipidemia may be present. Liver transaminase, plasma lactate, and uric acid levels are usually normal. Oral galactose or glucose tolerance tests show intolerance, which could be explained by the functional loss of GLUT2 preventing liver uptake of these sugars. Tissue biopsy results show marked accumulation of glycogen in hepatocytes and proximal renal tubular cells, presumably from the altered glucose transport out of these organs. Diffuse glomerular mesangial expansion, along with glomerular hyperfiltration and microalbuminuria similar to nephropathy in GSD Ia, and diabetes have been reported.

This condition is rare, and 70% of patients with Fanconi-Bickel syndrome have consanguineous parents. Most patients have homozygous pathogenic variants; some patients are compound heterozygotes. Several types of pathogenic variants in the *SLC2A2* gene have been described, including missense, nonsense, insertion/deletion, and intronic variants.

There is no specific treatment. Symptom-dependent treatment with phosphate, bicarbonate, and uncooked cornstarch can result in growth improvement. Growth may also improve with symptomatic replacement of water, electrolytes, and vitamin D and restriction of galactose intake; a diet similar to that used for diabetes mellitus, with small, frequent meals using complex carbohydrates and adequate caloric intake, is recommended.

MUSCLE GLYCOGENOSES

The role of glycogen in muscle is to provide substrates for the generation of ATP for muscle contraction. The muscle GSDs are broadly divided into two groups. The first group is characterized by hypertrophic cardiomyopathy, progressive skeletal muscle weakness and atrophy, or both and includes deficiencies of acid α-glucosidase, a lysosomal glycogen-degrading enzyme (**type II** GSD); lysosomal-associated membrane protein 2 **(LAMP2/Danon disease)**; AMP-activated protein kinase γ2 **(PRKAG2/PRKAG2 syndrome)**; and muscle glycogen synthase **(type 0b)**. Glycogenin-1 deficiency **(GYG1/polyglucosan body myopathy 2)** may manifest as muscle weakness and exercise intolerance to exercise in the absence of cardiomyopathy.

The second group comprises muscle energy disorders characterized by muscle pain, exercise intolerance, myoglobinuria, and susceptibility to fatigue. This group includes myophosphorylase deficiency (McArdle disease, **type V** GSD) and deficiencies of phosphofructokinase **(type VII)**, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase (LDH), and muscle-specific phosphorylase kinase (**type IX** α1). Some of these latter enzyme deficiencies can also be associated with *compensated hemolysis,* suggesting a more generalized defect in glucose metabolism.

Type II Glycogen Storage Disease (Lysosomal Acid α-1,4-Glucosidase Deficiency, Pompe Disease)

Pompe disease, also referred to as *GSD type II* or **acid maltase deficiency**, is caused by a deficiency of acid α-1,4-glucosidase, an enzyme responsible for the degradation of glycogen in lysosomes. This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, predominantly affecting cardiac, skeletal, and smooth muscle cells and the nervous system. In Pompe disease, glycogen typically accumulates within lysosomes, as opposed to its accumulation in cytoplasm in the other glycogenoses. However, as the disease progresses, lysosomal rupture and leakage lead to the presence of cytoplasmic glycogen as well.

Pompe disease is an autosomal recessive disorder. The incidence was previously reported to be approximately 1 in 40,000 live births in Whites and 1 in 18,000 live births in the Han Chinese population. Newborn screening for Pompe disease in the United States suggests that the prevalence is much higher than previously thought (between 1 in 10,000 and 1 in 25,000). More than 600 pathogenic variants have been identified in the gene for acid α-glucosidase *(GAA)* and are helpful in delineating the phenotypes. A splice-site variant (c.-32-13 T > G, formerly called IVS1-13 T > G) is commonly seen in White patients with late-onset disease.

Clinical Manifestations

Pompe disease is broadly classified into infantile and late-onset forms. The infantile presentation is a continuum and is further divided into two categories: classic and nonclassic. Classic **infantile Pompe disease** (IPD) is uniformly lethal *without* enzyme replacement therapy (ERT) with *alglucosidase alfa*. Affected infants present in the first days to weeks of life with hypotonia, generalized muscle weakness with a hypotonic *floppy infant* appearance, hypertrophic cardiomyopathy

with or without left ventricular outflow obstruction, feeding difficulties, macroglossia, and hepatomegaly; if untreated, the condition leads to death from cardiorespiratory failure or respiratory infection by 1 year of age. Nonclassic IPD has a slower disease course and a less severe cardiac phenotype at initial presentation.

Late-onset Pompe disease (LOPD; juvenile-, childhood-, and adult-onset disease) is characterized by proximal limb girdle muscle weakness and early involvement of respiratory muscles, especially the diaphragm. The distinguishing feature between IPD and LOPD is absence of cardiomyopathy in the first year of life in patients with LOPD. Symptoms related to progressive dysfunction of skeletal muscles can start within the first year of life to as late as the sixth decade. The clinical picture is dominated by slowly progressive proximal muscle weakness, with truncal involvement and greater involvement of the lower limbs than the upper limbs. The pelvic girdle, paraspinal muscles, and diaphragm are the muscle groups most seriously affected in patients with LOPD. Cardiac involvement can occur and ranges from cardiac rhythm disturbances to cardiomyopathy. Other symptoms may include lingual weakness, ptosis, and dilation of blood vessels (e.g., basilar artery, ascending aorta). With disease progression, patients become confined to a wheelchair and require artificial ventilation. The initial symptoms in some patients may be respiratory insufficiency manifested by somnolence, morning headache, orthopnea, and exertional dyspnea, which eventually lead to sleep-disordered breathing and respiratory failure. Respiratory failure is the cause of significant morbidity and mortality in LOPD. Basilar artery aneurysms with rupture also contribute to mortality in some cases. Small-fiber neuropathy presenting as painful paresthesia has been identified in some LOPD patients. Gastrointestinal disturbances such as postprandial bloating, dysphagia, early satiety, diarrhea, chronic constipation, and IBD have been reported. Genitourinary tract involvement is not uncommon and may present as bladder and bowel incontinence, weak urine stream, or dribbling. If untreated, the age of death varies from early childhood to late adulthood, depending on the rate of disease progression and the extent of respiratory muscle involvement. With the advent of ERT, a new natural history is emerging for survivors of both IPD and LOPD.

Laboratory Findings

Pertinent laboratory findings include elevated levels of serum creatine kinase (CK), aspartate transaminase (AST), alanine transaminase (ALT), and LDH. Urine glucose tetrasaccharide (Glc4), a glycogen breakdown metabolite, is a reliable biomarker for gauging disease severity and progression, as well as treatment response. Levels of Glc4 are extremely elevated in patients with IPD. In the infantile form, a chest x-ray film showing massive cardiomegaly is frequently the first symptom detected. **Electrocardiographic findings** include a high-voltage QRS complex, Wolff-Parkinson-White (WPW) syndrome, and a *shortened* PR interval. **Echocardiography** reveals thickening of both ventricles and/or the intraventricular septum and/or left ventricular outflow tract obstruction. Dilated cardiomyopathy and a low ejection fraction have also been reported. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen; acid phosphatase is increased, presumably from a compensatory increase of lysosomal enzymes. EM reveals glycogen accumulation within a membranous sac and with disease progression also in the cytoplasm. EMG reveals myopathic features with excessive electrical irritability of muscle fibers and pseudomyotonic discharges. Serum CK is not always elevated in adult patients. Depending on the muscle sampled or tested, the muscle histologic appearance and electromyography may not be abnormal. Some patients with infantile Pompe disease who had peripheral nerve biopsies demonstrated glycogen accumulation in the neurons and Schwann cells.

Diagnosis

A diagnosis of Pompe disease can be made by either enzyme assay in dried blood spots, leukocytes, blood mononuclear cells, muscle, or cultured skin fibroblasts demonstrating deficient acid α-glucosidase activity or gene sequencing showing two pathogenic variants in the *GAA* gene. The enzyme assay should be done in a laboratory with experience using maltose, glycogen, or 4-methylumbelliferyl-α-d-glucopyranoside (4MUG) as a substrate. In fibroblast enzyme assays, the infantile form has a more severe enzyme deficiency (less than 1% of that in normal controls) than the late-onset forms (between 1% and 30% of that in normal controls). Blood-based assays, especially dried blood spots, have the advantage of being quick and noninvasive and are increasingly being used as the first-line sample to make a diagnosis. The presence of the neutral α-glucosidase isoenzyme, which interferes with acid glucosidase, was formerly considered to be a disadvantage in blood-based assays. However, the addition of an inhibitor to this isozyme, acarbose, improves the assay's reliability by blocking isoenzyme activity. A muscle biopsy is often done with suspected muscle disease and a broad diagnostic differential, as it yields faster results and provides additional information about glycogen content and site of glycogen storage within and outside the lysosomes of muscle cells. However, a normal muscle biopsy, especially in patients with LOPD, *does not* exclude a diagnosis of Pompe disease. Late-onset patients show variability in glycogen accumulation in different muscles and within muscle fibers, and muscle histology and glycogen content can vary depending on the site of muscle biopsy. Because of the high risk of complications, anesthesia in infantile cases with significant cardiomyopathy should be reserved for situations where it is necessary. Availability of NGS panels and whole exome or genome sequencing allow for identification of additional patients with Pompe disease, especially when the diagnosis is ambiguous. *GAA* enzyme activity can be measured in chorionic villi or amniocytes for prenatal diagnosis; however, if the familial pathogenic variants are known, molecular genetic testing is the recommended approach.

Treatment

ERT with recombinant human acid α-glucosidase (alglucosidase alfa and avalgluco) is available for treatment of Pompe disease. Recombinant acid α-glucosidase can prevent deterioration or reversing abnormal cardiac and skeletal muscle functions (Fig. 107.3). ERT should be initiated as soon as possible across the disease spectrum, especially for infants with the infantile form, because the disease is rapidly progressive. Infants who are negative for cross-reacting immunologic material (CRIM) (i.e., infants that have no detectable GAA on a Western blot), develop a high-titer antibody against the infused enzyme and respond to ERT less favorably. A subset of CRIM-positive patients (presence of some protein on a Western blot) can also develop high and sustained antibody titers to ERT. Treatment using immunomodulating agents such as methotrexate, rituximab, and intravenous immunoglobulin (IVIG) have demonstrated efficacy in preventing the development of an immune response to ERT and immune tolerance. Nocturnal ventilatory support, when indicated, should be used. It has been shown to improve the quality of life and is particularly beneficial during a period of respiratory decompensation. In addition to ERT, other **adjunctive therapies** have demonstrated benefit in patients with Pompe disease. For patients with late-onset disease, a high-protein, low-carbohydrate diet may be beneficial. Respiratory muscle strength training has demonstrated improvements in respiratory parameters when combined with ERT. Submaximal aerobic exercise regimens are beneficial in improving muscle strength, pain, and fatigue.

A second-generation ERT, **avalglucosidase alfa** (NeoGAA), has been recently approved by the Food and Drug Administration (FDA) for the treatment of individuals with LOPD older than 1 year of age. Mannose-6-phosphate (M6P) is more abundant in NeoGAA than in alglucosidase alfa, which improves enzyme uptake into cells. Improvements in respiratory function (forced vital capacity [FVC]) and 6-minute walk test (6MWT) in patients with LOPD have been shown by phase 1/2 and 3 trials.

There are other therapies in development for Pompe disease, including intravenous **cipaglucosidase alfa** (a novel recombinant human GAA with high bis-M6P content; functions as substrate reduction therapy), **miglustat** (an oral chaperone; functions as enzyme stabilizer), small-molecule therapy, and gene therapy.

Early diagnosis and treatment are necessary for optimal outcomes. Newborn screening using blood-based assays in Taiwan and 28 U.S. states has resulted in early identification of Pompe cases, and thus improved disease outcomes, through the early initiation of ERT.

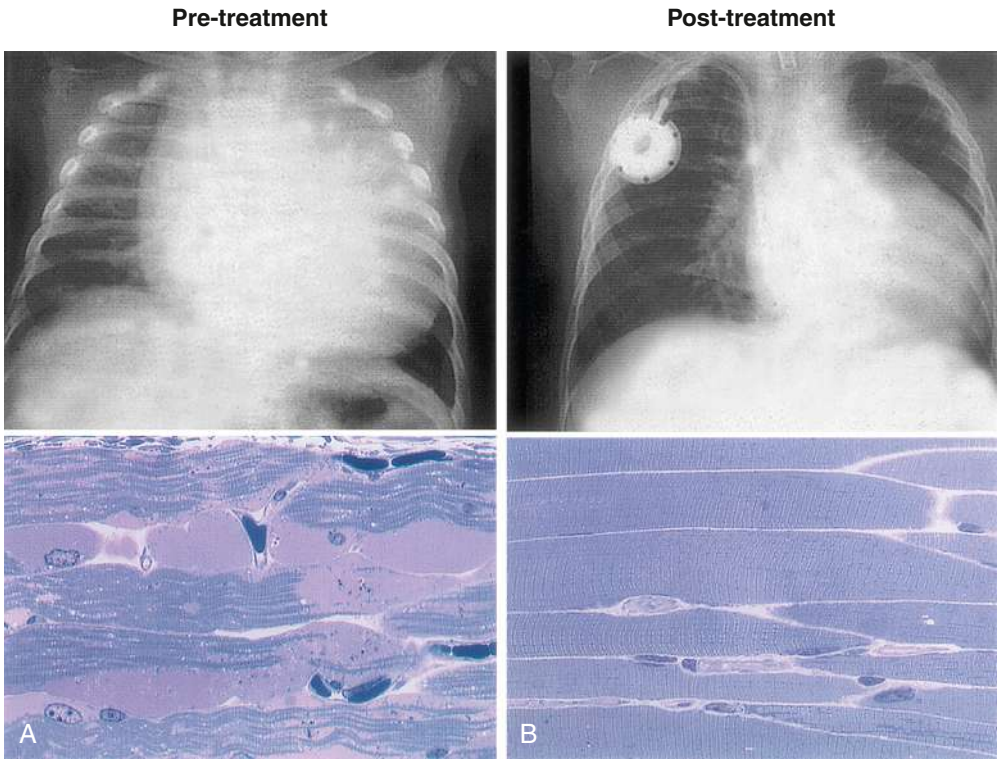

Fig. 107.3 Chest radiograph and muscle histology findings of an infantile-onset Pompe disease patient before (A) and after (B) enzyme replacement therapy. Note the decrease in heart size and muscle glycogen with therapy. *(Modified from Amalfitano A, Bengur AR, Morse RP, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. Genet Med. 2001;3:132–138.)*

Danon Disease

Danon disease is caused by pathogenic variants in the *LAMP2* gene, which leads to a deficiency of **lysosomal-associated membrane protein 2** (LAMP2). This disorder is inherited in an X-linked dominant pattern. Defects in LAMP2 lead to accumulation of glycogen in the heart and skeletal muscle, presenting primarily as hypertrophic cardiomyopathy and skeletal muscle weakness. Danon disease can be distinguished from the usual causes of hypertrophic cardiomyopathy (defects in sarcomere-protein genes) by the electrophysiologic abnormalities, particularly ventricular preexcitation and conduction defects. Patients present with cardiac symptoms, including chest pain, palpitations, syncope, and cardiac arrest, usually between ages 8 and 15 years. Other clinical manifestations include peripheral pigmentary retinopathy, lenticular changes, abnormal electroretinogram, and mild cognitive dysfunction. ***Diagnosis*** can be established by molecular testing of the *LAMP2* gene. The prognosis for LAMP2 deficiency is poor, with progressive end-stage heart failure early in adulthood. ***Treatment*** is directed toward management of symptoms in affected individuals, including management of cardiomyopathy, correction of arrhythmias, and physical therapy for muscle weakness. Cardiac transplantation has been successful in some patients. In male patients with Danon disease, a nonrandomized open-label phase 1 study (NCT03882437) is currently being conducted to assess the safety of gene therapy using recombinant adeno-associated virus serotype 9 (AAV9) containing the human lysosome-associated membrane protein 2 isoform B (LAMP2B) transgene.

PRKAG2 Syndrome (Adenosine Monophosphate [AMP]–Activated Protein Kinase γ2 Deficiency)

PRKAG2 syndrome is caused by pathogenic variants in the *PRKAG2* gene that is required for the synthesis of the enzyme AMP-activated protein kinase (AMPK), which regulates cellular pathways involved in ATP metabolism. PRKAG2 syndrome has an autosomal dominant pattern of inheritance. Common presentations include hypertrophic cardiomyopathy and electrophysiologic abnormalities such as WPW syndrome, atrial fibrillation, and progressive atrioventricular block. Cardiac involvement is variable and includes supraventricular tachycardia, sinus bradycardia, left ventricular dysfunction, and sudden cardiac death in some cases. In addition to cardiac involvement, there is a broad spectrum of phenotypic presentations including myalgia, myopathy, and seizures. Cardiomyopathy caused by *PRKAG2* variants usually allows for long-term survival, although a rare congenital form presenting in early infancy is associated with a rapidly fatal course. Cardiomyopathy in PRKAG2 syndrome often mimics that in other conditions, especially Pompe disease, and should be considered as a differential diagnosis in infants presenting with severe hypertrophic cardiomyopathy. ***Treatment*** is primarily symptomatic, including management of cardiac failure and correction of conduction defects. Patients with PRKAG2 deficiency are at risk for sudden cardiac death and require close monitoring.

Type 0b Glycogen Storage Disease (Muscle Glycogen Synthase Deficiency)

Muscle glycogen synthase deficiency (GSD 0b) results from biallelic loss-of-function pathogenic variants in the gene *GYS1*. In the true sense, this is not a type of GSD because the enzyme deficiency leads to decreased glycogen stores in skeletal and cardiac muscles. The disease is extremely rare and has only been reported in five cases. Muscle biopsies showed lack of glycogen, predominantly oxidative fibers, and mitochondrial proliferation. Glucose tolerance testing was normal. The phenotype was variable and ranged from sudden cardiac arrest, muscle fatigability, hypertrophic cardiomyopathy, abnormal heart rate, and hypotension while exercising to mildly impaired cardiac function at rest.

Type XV Glycogen Storage Disease (Glycogenin-1 Deficiency, Polyglucosan Body Myopathy 2, GYG1 Variant)

Polyglucosan body myopathy 2 is an autosomal recessive, slowly progressive skeletal myopathy caused by pathogenic variants in the *GYG1*

gene disrupting **glycogenin-1** biosynthesis. There is a reduced or complete absence of glyogenin-1, which is a precursor necessary for glycogen formation. Polyglucosan accumulation in skeletal muscles causes juvenile- or adult-onset proximal muscle weakness, prominently affecting the hip and shoulder girdles. Some patients were noted to have a cardiac phenotype. Exertion-induced chest pain, palpitations, and shortness of breath are common early symptoms. Changes in electrophysiological (ECG) parameters and impairment of left ventricular function were reported. Heart transplantation may be necessary in some cases. The missense variant c.304G>C (p. Asp102His) has been observed in homozygosity in the majority of these patients. Compared with GSD IV–APBD, nervous system involvement is uncommon, although polyglucosan deposition is seen in both disorders. Muscle biopsies show PAS-positive, diastase-resistant storage material in 30–40% of muscle fibers. EM reveals the typical polyglucosan structure, consisting of an ovoid form composed of partly filamentous material.

Type V Glycogen Storage Disease (Muscle Phosphorylase Deficiency, McArdle Disease)

GSD type V, the prototype of muscle energy disorders, is one of the most common GSDs with a prevalence of ~1 in 10,000 and is caused by deficiency of **myophosphorylase** activity. Lack of this enzyme limits muscle ATP generation from glycogenolysis, resulting in muscle glycogen accumulation. A deficiency of myophosphorylase impairs the cleavage of glucosyl molecules from the straight chain of glycogen.

Clinical Manifestations

Symptoms usually first develop in late childhood or in the second decade of life. Studies have shown that McArdle disease can manifest in individuals as old as in their seventh decade and in infancy in a fatal, early-onset form characterized by hypotonia, generalized muscle weakness, and respiratory complications. Symptoms are generally characterized by exercise intolerance with muscle cramps and pain and are precipitated by two types of activity: (1) brief, high-intensity exercise, such as sprinting or carrying heavy loads and (2) less intense but sustained activity, such as climbing stairs or walking uphill. Most patients can perform moderate exercise, such as walking on level ground, for long periods. Many patients experience a characteristic *second-wind phenomenon,* with relief of muscle pain and fatigue after a brief period of rest. An increased blood flow of glucose derived from either endogenous liver glycogenolysis or exogenous glucose and free fatty acids, which may be used as an alternative energy source by the exercising muscles, causes the second-wind phenomenon. As a result of the underlying myopathy, these patients may be at risk for **statin-induced myopathy** and rhabdomyolysis. Although patients typically experience episodic muscle pain and cramping from exercise, up to 35% of patients with McArdle disease report permanent pain that has a serious impact on sleep and other activities.

Approximately 50% of patients report burgundy-colored urine after exercise as a result of exercise-induced **myoglobinuria** secondary to **rhabdomyolysis**. Excessive myoglobinuria after intense exercise may precipitate acute renal failure.

Laboratory findings include elevated serum CK levels at rest, which further increase after exercise. Exercise also elevates the levels of blood ammonia, inosine, hypoxanthine, and uric acid, which may be attributed to accelerated recycling of muscle purine nucleotides caused by insufficient ATP production.

Diagnosis

Type V GSD is an autosomal recessive disorder. Testing of the gene for muscle phosphorylase *(PYGM)* helps confirm the diagnosis of GSD V. A common nonsense variant, c.148C>T (p.Arg50Ter) in exon 1, is found in 80% of White patients; deletion of a single codon, c.2128_2130del (p.Phe710del) in exon 17, is found in 61% of patients of Japanese origin. The c.148C>T (p.Arg50Ter) variant represents 55% of alleles in patients of Spanish descent, and the c.2392T>C (p.Trp798Arg) and c.613G>A (p.Gly205Ser) variants represent 10% and 9% of pathogenic alleles in this population. Muscle biopsy can be used to measure glycogen content and enzyme activity in cases where genetic testing results are inconclusive. Lack of an increase in blood lactate levels and exaggerated blood ammonia elevations suggest a defect in the conversion of muscle glycogen or glucose to lactate. An ischemic exercise test offers rapid diagnostic screening for patients suspected to have McArdle disease, though it should be noted that an abnormal response is *not limited* to type V GSD, as other muscle defects in glycogenolysis or glycolysis produce similar results (deficiencies of muscle phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, or LDH). Additionally, such testing was also associated with severe complications and false-positive results. A nonischemic forearm exercise test with high sensitivity that is easy to perform and is cost-effective has been deemed a more appropriate diagnostic tool; however, it also cannot differentiate abnormal exercise responses due to type V disease from other defects in glycogenolysis or glycolysis.

Treatment

To enhance patients' outcomes and physical activity capacity, a multidisciplinary team approach to care composed of a physician, physiotherapist, psychologist, clinical nurse, and dietitian is advised. Avoidance of strenuous exercise prevents symptoms; regular and moderate exercise is recommended to improve exercise capacity. Patients are advised to take advantage of the second-wind phenomenon by commencing exercise slowly and to slow down or stop if muscle weakness or discomfort, increased heart rate, or increased respiratory effort occurs. This *slow-pause-resume* pattern is intended to be maintained as needed until considerable improvement in physical activity tolerance occurs.

High-dose oral ribose, glucagon, verapamil, vitamin B_6, a high-protein diet, branched-chain amino acid supplementation, dantrolene sodium, high-dose creatine, intravenous gentamicin, and intralipid infusion treatments showed no benefit according to a revised and updated systematic review in the Cochrane Database of nutritional and pharmacologic trials for GSD V. Oral sucrose ingestion before exercise, a carbohydrate-rich diet, ramipril, and low-dose creatine were treatments that showed some promise. There is ongoing research regarding the benefits of a low-carbohydrate ketogenic diet in patients with type V GSD.

Type VII Glycogen Storage Disease (Muscle Phosphofructokinase Deficiency, Tarui Disease)

Type VII GSD is caused by pathogenic variants in the *PFKM* gene, which result in a deficiency of **muscle phosphofructokinase** enzyme. This enzyme is a key regulatory enzyme of glycolysis and is necessary for the ATP-dependent conversion of fructose-6-phosphate to fructose-1,6-diphosphate. Phosphofructokinase is composed of three isoenzyme subunits according to the tissue type, encoded by different genes: (*PFKM* [M: muscle], *PFKL* [L: liver], and *PFKP* [P: platelet]). Skeletal muscle has only the M subunit, whereas red blood cells (RBCs) express a combination of L and M forms. In type VII GSD, the M isoenzyme is defective, resulting in complete deficiency of enzyme activity in muscle and a partial deficiency in RBCs.

Type VII GSD is an autosomal recessive disorder with increased prevalence in individuals of Japanese ancestry and Ashkenazi Jewish background. A splicing defect and a nucleotide deletion in *PFKM* account for 95% of pathogenic variants in the Ashkenazi Jewish population. Diagnosis based on molecular testing for the common variants is possible in this population.

Clinical Manifestations

Although the clinical picture is similar to that of type V GSD, the following features of type VII GSD are distinctive:

- Exercise intolerance, which usually commences in childhood, is more severe than in type V disease and may be associated with nausea, vomiting, and severe muscle pain. Vigorous exercise causes severe muscle cramps and myoglobinuria.
- Compensatory hemolysis occurs, as indicated by an increased level of serum bilirubin and an elevated reticulocyte count.
- Hyperuricemia is common and exaggerated by muscle exercise to a greater degree than that observed in type V GSD.

In addition to normal glycogen, GSD VII is characterized by the accumulation of polyglucosan bodies. The accumulation of glucose-6-phosphate caused by PFKM deficiency and the inhibition of glycolysis stimulate the glycogen synthase enzyme, resulting in the formation of polyglucosan bodies.

Exercise intolerance is especially worse after carbohydrate-rich meals because the ingested glucose prevents lipolysis, thereby depriving muscle of fatty acid and ketone substrates. This is called the *out-of-wind phenomenon,* in contrast to patients with type V disease who can metabolize blood-borne glucose derived from either endogenous liver glycogenolysis or exogenous glucose. Indeed, glucose infusion improves exercise tolerance in patients with type V disease.

The *second-wind phenomenon* is absent because of the inability to break down blood glucose.

Several rare type VII presentations have been described. One form presents in infancy with hypotonia and limb weakness and proceeds to a rapidly progressive myopathy that leads to death by 4 years of age. A second type occurs in infancy and results in congenital myopathy and arthrogryposis, with a fatal outcome. A third form presents in infancy with hypotonia, mild developmental delay, and seizures. An additional presentation is *hereditary nonspherocytic hemolytic anemia;* although these patients do not experience muscle symptoms, it remains unclear whether these symptoms will develop later in life. Another group of individuals with asymptomatic partial red cell PFK deficiency has been described. One phenotype presents in adults and is characterized by a slowly progressive, fixed muscle weakness rather than cramps and myoglobinuria. It may also cause mitral valve thickening from glycogen buildup. Myopathy and hemolysis are hallmarks of the classic form.

Diagnosis

To establish a diagnosis, gene sequencing can identify pathogenic variants in the *PFKM* gene. Demonstration of the enzymatic deficiency in muscle may be required in some cases. The absence of the M isoenzyme of phosphofructokinase can also be demonstrated in muscle, blood cells, and fibroblasts.

Treatment

Strenuous exercise should be avoided to prevent acute episodes of muscle cramps, myoglobinuria, acute renal failure, and compartment syndrome. Continuous blood pressure monitoring or compressive devices, as well as the use of tourniquets, are contraindicated in these patients. Patients with GSD VII should follow the same *slow-pause-resume* routine as those with GSD V. Dietary therapy for GSD VII has not been thoroughly investigated. A ketogenic diet has been reported to show clinical improvement in a patient with GSD VII. Carbohydrate meals and glucose infusions have demonstrated worsening symptoms because of the body's inability to use glucose. The administered glucose tends to lower the levels of fatty acids in the blood—a primary source of muscle fuel. *Drugs such as statins should be avoided.* Precautionary measures should be taken to avoid hyperthermia, hypothermia, hypoglycemia, and shivering while undergoing anesthesia in both GSD V and GSD VII.

Type IX α1 Glycogen Storage Disease (Muscle-Specific Phosphorylase Kinase Deficiency, *PHKA1* Variant)

X-linked muscle PhK deficiency (IX α1 GSD) is caused by pathogenic variants in the *PHKA1* gene, which encodes a muscle-specific regulatory subunit (α subunit) of phosphorylase kinase and is located on Xq13.11. The condition is male-predominant, but affected heterozygous females have been reported. Patients generally present with mild to severe exercise intolerance in childhood or adolescence. Most patients have elevated serum CK and, in more involved cases, myoglobulinuria. There is no evidence of hepatic or cardiac disease in these patients. Blood phosphorylase kinase enzymatic activity is normal, and the enzyme activity is decreased to deficient in the muscle. Muscle biopsy reveals subsarcolemmal accumulations of glycogen, and some patients have myopathic changes on EMG. One patient has been described with comorbid muscle PhK deficiency and intellectual disability; although a connection between *PHKA1* and neurodevelopment has not yet been established, patients with the diagnosis should be monitored for developmental concerns.

The gene for the muscle γ subunit *(PHKG1)* is on chromosome 7p11.2, and no pathogenic variants in this gene have been reported to date.

Other Muscle Glycogenoses with Muscle Energy Impairment

Five additional defects in enzymes—phosphoglycerate kinase (PGK), phosphoglycerate mutase (PGAM), LDH, fructose-1,6-bisphosphate aldolase (aldolase A), and β-enolase in the pathway of the terminal glycolysis—cause symptoms and signs of muscle energy impairment similar to those in types V and VII GSD. Deficiency in PGAM, enolase, or LDH causes a myopathic phenotype marked by exercise-induced cramps and myoglobinuria. Patients with aldolase A or PGK deficiencies may present with hemolytic anemia in conjunction with myopathy. The failure of blood lactate to increase in response to exercise is a useful screening test and can be used to differentiate muscle glycogenoses from disorders of lipid metabolism, such as carnitine palmitoyltransferase II deficiency and very long-chain acyl-CoA dehydrogenase deficiency, which also cause muscle cramps and myoglobinuria. Muscle glycogen levels can be normal in the disorders affecting terminal glycolysis, and molecular testing or muscle enzyme activity assay is needed to make a definitive diagnosis. There is no specific treatment (see preceding "Treatment" section).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

107.2 Defects in Galactose Metabolism

Ghada Hijazi and Priya S. Kishnani

Milk and dairy products contain **lactose**, the major dietary source of galactose. The metabolism of galactose produces fuel for cellular metabolism through its conversion to glucose-1-phosphate (see Table 107.1). Galactose also plays an important role in the formation of galactosides, which include glycoproteins, glycolipids, and glycosaminoglycans. **Galactosemia** is a term that refers to an abnormally high quantity of galactose in the blood. It can be caused by one of four distinct inborn defects in galactose metabolism involving one of the following enzymes: galactose mutarotase (GALM), galactokinase (GALK), galactose-1-phosphate uridyl transferase (GALT), and uridine diphosphate galactose-4-epimerase (GALE). Among these, the most serious defect is severe GALT deficiency or classic galactosemia, which is frequently referred to as *galactosemia*.

GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY GALACTOSEMIA

Two forms of the deficiency exist: infants with complete or near-complete deficiency of the enzyme (classic galactosemia) and those with partial transferase deficiency. **Classic galactosemia** is a serious disease with onset of symptoms typically by the second half of the first week of life. The incidence is approximately 1 in 60,000 live births. The newborn infant receives high amounts of lactose (up to 40% in breast milk and certain formulas), which consists of equal parts of glucose and galactose. Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to the liver, kidney, and brain. This injury may begin prenatally in the affected fetus by endogenous fetal production of galactose.

Clinical Manifestations

The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features within a few days or weeks after birth: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birthweight, and aminoaciduria. Untreated children may show nuclear cataracts, vitreous hemorrhage, hepatic failure, cirrhosis, ascites, splenomegaly, or intellectual disability. Patients with galactosemia

are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia. Pseudotumor cerebri has been reported in some patients, presenting with failure to thrive and a bulging anterior fontanel. Complete withdrawal of lactose from the diet results in improvement of the acute symptoms. If untreated, death from liver failure and sepsis may follow within days. When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (intellectual disability) becomes increasingly severe and irreversible.

Partial transferase deficiency is classified into two subtypes: clinical variant galactosemia (erythrocyte GALT enzyme activity is ≥1% of controls, but not more than 10–15%) and biochemical (Duarte) variant galactosemia (erythrocyte GALT enzyme activity is ≥25% of controls). Partial transferase deficiency is more common than classic galactosemia and is diagnosed in the newborn screening setting because of moderately elevated blood galactose and/or low transferase activity. Clinical variant galactosemia should be considered in the newborn or young infant who is not thriving or who exhibits any of the classical galactosemia-related symptoms. Generally, biochemical (Duarte) variant galactosemia is asymptomatic. There is no evidence that individuals with biochemical (Duarte) variant galactosemia have an increased risk of neurodevelopmental problems or premature ovarian insufficiency. Additional research is required to properly understand and describe the natural history of this subtype.

Diagnosis

Historically, the detection of a reducing substance in several urine specimens obtained when the patient is on a diet containing human milk, cow's milk, or any other lactose-containing formula was regarded as strongly indicative of galactosemia. The clue was detecting a reducing substance in urine by Clinitest strips (e.g., glucose, galactose) that is negative by Clinistix (which is specific for glucose only). Galactose can also be identified by chromatography or an enzymatic test specific for galactose. Galactose can be detected in urine, provided the milk feeding was within the last few hours and the child is not vomiting excessively. The addition of galactosemia to the newborn screening panel resulted in a considerable reduction in the utility of Clinitest strips for galactosemia screening. Amino acids may be detected in urine (aminoaciduria) because they are excreted together with glucose as a result of proximal renal tubular dysfunction. Because galactose is injurious to persons with galactosemia, diagnostic challenge tests dependent on administering galactose orally or intravenously should not be used. Direct enzyme assay using erythrocytes establishes the diagnosis. The clinician must confirm that the patient did not receive a blood transfusion before the collection of the blood sample for enzyme assay activity in RBCs, because this may lead to a false-negative result, and the diagnosis could be missed. The activity of galactose-1-phosphate uridyl transferase in erythrocytes can be measured in a variety of ways, one of which involves the use of a nonradioactive assay using high-performance liquid chromatography (HPLC) separation and ultraviolet (UV) light detection. Patients with glucose-6-phosphate-dehydrogenase deficiency can have false-positive results. In classic galactosemia, metabolites (urinary galactitol, red cell galactose-1-phosphate, and blood galactose concentration) may be elevated and can be used to confirm the diagnosis and monitor the response to dietary changes and metabolic control.

Genetics

GALT deficiency is an autosomal recessive disorder caused by pathogenic variants in the *GALT* gene. Based on newborn screening in the United States, the frequency of the disease is approximately 1 in 47,000 live births. There are several enzymatic variants of galactosemia. More than 327 pathogenic variants have been associated with GALT deficiency. The most common pathogenic variants that result in classic galactosemia phenotype are c.563A>G (p.Gln188Arg), c.855G>T (p.Lys285Asn), and c.584T>C (p.Leu195Pro). In Whites, the p.Gln188Arg variant is linked to an increased incidence of severe disease, premature ovarian insufficiency, and speech problems in a homozygous state. In Blacks p.Ser135Leu is common, which results in a milder phenotype (clinical variant galactosemia) despite the absence of measurable GALT activity in erythrocytes. These patients retain 10% of enzyme activity in the liver and intestinal mucosa. When treated early, Blacks who are homozygous for this variant are not at risk for neonatal *E. coli* sepsis or chronic complications (i.e., premature ovarian insufficiency and language delay). Four pathogenic variants are unique to the Duarte variant (D2): a four–base pair (bp) deletion in the GALT promoter region (c.-119-116delGTCA), a c.378-27G>C, a c.508-24G>A, and a c.507+62G>A. A fifth variant is a single amino acid substitution (c.940A>G, p.Asn314Asp, also called *N314D*), which has been observed in both the Duarte variant and functionally normal GALT alleles. Individuals heterozygous for Duarte variant galactosemia typically have 25% of normal galactose activity. Symptoms are minimal or absent, metabolites range from elevated to normal, and there is no need for intervention. Carrier testing and prenatal diagnosis can be performed by molecular testing or, less commonly, direct enzyme assay on amniocytes or chorionic villi.

Treatment and Prognosis

Consensus guidelines recommend treating patients with an RBC GALT enzyme activity of ≤10% and erythrocyte galactose-1-phosphate concentration of >10 mg/dL. The decision of whether to treat those with 10–15% RBC residual GALT activity is still a matter of debate. All galactose-containing foods should be removed from the diet on initial suspicion of galactosemia. Various non–lactose-containing milk substitutes are available (casein hydrolysates, soybean-based formula). A galactose-restricted diet, along with adequate calcium and vitamin D supplementation, reverses growth failure and hepatic dysfunction. Cataracts regress, and most patients have no persistent impairment of vision. Early diagnosis and treatment have improved the prognosis of galactosemia. On long-term follow-up, patients still manifest ovarian failure with primary or secondary amenorrhea, decreased bone mineral density, developmental delay, and learning disabilities that increase in severity with age. *Hypergonadotropic hypogonadism* is reported in 80–90+% of female patients with classic galactosemia. Although most females with classic galactosemia are infertile when they reach childbearing age, a small number have given birth. Females with the Duarte variant galactosemia and who are homozygous for p.Ser135Leu do not develop premature ovarian insufficiency. Most patients manifest speech disorders, whereas a smaller number demonstrate poor growth and impaired motor function and balance (with or without overt ataxia). Strict dietary restriction and relative control of galactose-1-phosphate levels do not always correlate with long-term outcome, leading to the belief that other factors such as elevated galactitol, decreased uridine diphosphate galactose (a donor for galactolipids and proteins), and endogenous galactose production may be responsible.

GALACTOKINASE DEFICIENCY

The deficient enzyme is galactokinase, which normally catalyzes the phosphorylation of galactose. The principal metabolites accumulated are galactose and galactitol. Two genes encode enzymes with galactokinase activity, *GALK1* and *GALK2,* although pathogenic variants have been noted only in *GALK1* that cause autosomal recessive galactokinase deficiency. **Cataract** is the most common manifestation of galactokinase deficiency, and pseudotumor cerebri is a rare complication. The incidence of hypoglycemia and infection is comparable to those found in the general population. There is a higher rate of bleeding diathesis, encephalopathy, and elevated liver transaminases than in the general population during the newborn period. Some patients have intellectual impairment and motor and language delays. Heterozygous carriers may be at risk for presenile cataracts. Laboratory findings include increased concentration of blood galactose levels and urinary galactitol, provided the infant has been fed a lactose-containing formula. The diagnosis is made by demonstrating an absence of galactokinase activity in erythrocytes or fibroblasts. GALT activity is normal. Treatment is dietary restriction of galactose.

URIDINE DIPHOSPHATE GALACTOSE-4-EPIMERASE DEFICIENCY

There are three distinct forms of **epimerase** deficiency based on the level of enzyme activity in different cell types. The first is a **benign** form known as *peripheral epimerase deficiency galactosemia,* diagnosed incidentally through newborn screening programs. Affected individuals are asymptomatic because the enzyme deficiency is limited to

leukocytes and erythrocytes. This form does not require treatment. The second subtype is called **intermediate** form and is caused by epimerase deficiency in RBCs and circulating white blood cells, as well as epimerase activity below 50% of normal in all other cells. Neonates with the intermediate form are typically asymptomatic, even when fed a normal milk diet, and are diagnosed only as a result of newborn screening. The long-term consequences remain unknown. During infancy and early childhood, these individuals are treated with a galactose-/lactose-restricted diet. The third form is rarer and more **severe** as a result of generalized epimerase deficiency. Clinical manifestations resemble GALT transferase deficiency, with additional symptoms of hypotonia and nerve deafness. Clinical symptoms improve with restriction of galactose/lactose in the diet. Although this severe form of epimerase galactosemia is rare, it must be considered in a symptomatic patient with elevated RBC galactose-1-phosphate, urinary galactose, and galactitol levels but with normal GALT transferase activity. The abnormally accumulated metabolites are similar to those in transferase deficiency, with the addition of an increase in cellular uridine diphosphate (UDP) galactose. Biochemical diagnosis is confirmed by the assay of epimerase in erythrocytes demonstrating reduced activity. UDP galactose-4-epimerase is encoded by the *GALE* gene, and pathogenic biallelic variants result in autosomal recessive disease. Carrier detection is possible by measurement of epimerase activity in the erythrocytes. Prenatal diagnosis for the severe form of epimerase deficiency can be done using an enzyme assay of cultured amniotic fluid cells or testing of known familial pathogenic variants.

Patients with the severe form of epimerase deficiency cannot synthesize UDP galactose from UDP glucose and are galactose dependent. Because galactose is an essential component of many nervous system structural proteins, patients are placed on a galactose-*restricted* diet rather than a galactose-*free* diet. Galactose restriction is also indicated for infants and young children with the intermediate form. Additional outcome data are needed to optimize these approaches and develop a better understanding of long-term issues in this patient population. Infants with mild epimerase deficiency have not required treatment.

Galactose Mutarotase Deficiency

GALM catalyzes the first step in the Leloir pathway, the conversion of beta-D-galactose to alpha-D-galactose. There have been a few cases of GALM deficiency reported, with an overall estimated incidence of GALM deficiency in all populations of less than 1 in 200,000, with higher incidences in Black and Japanese populations. Apart from cataracts, individuals with GALM deficiency are often healthy. In some reported cases, elevated blood galactose-1-phosphate (Gal-1-P) and galactose levels were identified during newborn screening. There are no reports of long-term implications of this condition and no formal recommendations regarding optimal dietary intake in this population.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

107.3 Defects in Fructose Metabolism

Ghada Hijazi and Priya S. Kishnani

Two inborn errors are known in the specialized pathway of fructose metabolism: benign or essential fructosuria and hereditary fructose intolerance. Fructose-1,6-bisphosphatase deficiency, not formally a defect of the specialized fructose pathway, is discussed in Chapter 107.4.

DEFICIENCY OF FRUCTOKINASE (ESSENTIAL OR BENIGN FRUCTOSURIA)

Deficiency of fructokinase is not associated with clinical manifestations. **Fructosuria** is an incidental finding identified in asymptomatic individuals with reducing substances in urine. No treatment is necessary, and the prognosis is excellent. Inheritance of this autosomal recessive trait is caused by biallelic variants in the *KHK* gene, with an incidence of 1 in 120,000 live births.

Fructokinase catalyzes the first step of metabolism of dietary fructose—conversion of fructose to fructose-1-phosphate (see Fig. 107.1). Without this enzyme, fructose consumption results in a rise in the blood level of fructose, which is partially excreted in the urine, as there is little to no renal threshold for fructose. In adipose tissue and muscle, hexokinase converts the remainder to fructose-6-phosphate, which is considered a slower alternative process. Clinitest results reveal the urinary reducing substance, which can be identified as fructose by chromatography.

DEFICIENCY OF FRUCTOSE-1-PHOSPHATE ALDOLASE (ALDOLASE B, HEREDITARY FRUCTOSE INTOLERANCE)

In comparison to fructokinase, deficiency of fructose-1-phosphate aldolase **(aldolase-B)** is a severe condition in infants resulting from a deficiency of activity in the liver, kidney, and intestine. Fructose-1-phosphate aldolase hydrolyzes fructose-1-phosphate to glyceraldehyde and dihydroxyacetone phosphate. In the glycolytic-gluconeogenic pathway, this enzyme catalyzes the hydrolysis of fructose-1,6-bisphosphate to dihydroxyacetone phosphate and glyceraldehyde phosphate. In the absence of aldolase B activity, there is a rapid accumulation of fructose-1-phosphate and depletion of ATP, which presents with severe symptoms when fructose-containing food is ingested. Accumulation of fructose-1-phosphate also results in inhibition of gluconeogenesis (via inhibition of aldolase A) and glycogenolysis (via inhibition of glycogen phosphorylase A), resulting in decreased glucose production and a rapid decline in blood glucose. Because isozyme fructose-1,6-bisphosphate aldolase (aldolase A) metabolizes fructose-1,6-bisphosphate, glycolysis and gluconeogenesis are not affected in patients with hereditary fructose intolerance in the fasting state.

Epidemiology and Genetics

The incidence of **hereditary fructose intolerance (HFI)** is estimated to be as high as 1 in 26,000 live births. HFI is inherited in an autosomal recessive manner because of biallelic pathogenic variants in the *ALDOB* gene. At least 60 pathogenic variants causing HFI are known. The most common pathogenic variant identified in the Northern European population is p.Ala150Pro. This variant, along with two other missense variants (p.Ala175Asp and p.Asn335Lys), account for 80–85% of HFI cases in Europe and the United States. The diagnosis of HFI can be made by gene sequencing or demonstration of hepatic fructose-1-phosphate aldolase (aldolase B) activity deficiency on liver biopsy (uncommon).

Clinical Manifestations

Affected individuals remain asymptomatic until fructose, sucrose (table sugar), or sorbitol is introduced in the diet (usually from fruit, fruit juice, or sweetened cereal). Signs and symptoms typically manifest in infancy when foods or formulas containing these sugars are introduced. Certain patients are very sensitive to fructose, whereas others can tolerate moderate intake (up to 250 mg/kg/day). Early clinical manifestations resemble galactosemia and include jaundice, hepatomegaly, vomiting, lethargy, irritability, and convulsions. There may also be a higher incidence of celiac disease in patients with HFI (>10%) compared with the general population (1–3%). With age, affected individuals typically develop an aversion to fructose-containing foods because of associated symptoms of nausea, vomiting, and abdominal pain.

Characteristic laboratory findings include lactic acidosis, hypophosphatemia, hyperuricemia, and hypermagnesemia. A prolonged prothrombin time, hypoalbuminemia, elevation of bilirubin and transaminase levels, and proximal tubular dysfunction are also seen. Acute fructose ingestion produces symptomatic hypoglycemia as a result of impaired gluconeogenesis, with higher intakes causing a more severe clinical picture. Chronic ingestion results in failure to thrive and hepatic disease. If the intake of fructose persists, hypoglycemic episodes recur, leading to progressive renal and hepatic failure and eventually death.

Diagnosis

The presence of a reducing substance in urine during an acute episode raises the possibility of HFI. Oral fructose challenge is no longer considered a diagnostic approach because of the high risk to the patient,

who can become acutely ill after the test. A definitive diagnosis is made by demonstration of two pathogenic variants in *ALDOB* on molecular genetic testing. A common pathogenic variant (p.Ala150Pro) accounts for 53% of HFI alleles worldwide. An alternative approach to diagnosis is to demonstrate deficient hepatic fructose-1-phosphate aldolase (aldolase B) activity on liver biopsy. Carbohydrate-deficient transferrin (CDT) testing (see Chapter 107.7) is generally abnormal in patients with HFI and can be used to monitor fructose, sucrose, and sorbitol consumption in the diet.

Treatment

Acute episodes are managed symptomatically by correcting hypoglycemia with IV glucose (dextrose) administration, providing supportive treatment of hepatic and/or renal insufficiency, and correcting metabolic acidosis. Complete elimination of fructose usually rapidly reverses symptoms and results in normalization of related metabolic disturbances. The cornerstone of long-term treatment is the complete restriction of all sources of fructose, sucrose, and sorbitol from the diet. It may be difficult because these sugars are widely used additives, found even in many medicinal preparations. With treatment, liver and kidney dysfunction improve, and catch-up in growth is common. Intellectual development is usually unimpaired. As the patient matures, symptoms become milder even after fructose ingestion, and the long-term prognosis is good. Because of voluntary dietary avoidance of sucrose, affected patients have few dental caries. Care should be taken to avoid fructose-containing IV fluids during hospitalizations. Regular supplementation with a "sugar-free" multivitamin is required to avoid micronutrient deficiencies resulting from reduced fruit and vegetable consumption.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

107.4 Defects in Intermediary Carbohydrate Metabolism Associated with Lactic Acidosis

Ghada Hijazi and Priya S. Kishnani

Lactic acidosis **(type B3)** occurs with inborn errors of metabolism, including defects of carbohydrate metabolism, that interfere with the conversion of pyruvate to glucose via the pathway of *gluconeogenesis* or to carbon dioxide and water via the mitochondrial enzymes of the Krebs cycle. Figure 107.4 depicts the relevant metabolic pathways. Type I GSD, fructose-1,6-bis phosphatase deficiency, and phosphoenolpyruvate carboxylase deficiency are disorders of gluconeogenesis associated with lactic acidosis. Other metabolic disorders, including mitochondrial respiratory chain defects, pyruvate dehydrogenase complex deficiency, pyruvate carboxylase deficiency, defects of fatty acid oxidation, organic acidurias (see Chapters 105.6, 105.10, and 106.1), biotin synthesis, and utilization defects also can cause lactic acidosis (Table 107.2). Some of these disorders are easily distinguishable by the presence of an abnormal acylcarnitine profile, amino acids in the blood, and urine organic acids. Blood lactate, pyruvate, acylcarnitine profile, and urine organic acids should be ordered in infants and children with unexplained acidosis, especially if there is an increased anion gap.

Lactic acidosis unrelated to an enzymatic defect occurs in conditions associated with hypoxemia and/or hypoperfusion (**type A** lactic acidosis). In this case, and in defects in the respiratory chain, the serum pyruvate concentration may remain normal (<1.0 mg/dL, with increased lactate to pyruvate ratio), whereas pyruvate is usually increased when lactic acidosis results from an enzymatic defect in gluconeogenesis or pyruvate dehydrogenase complex (both lactate and pyruvate are increased, and the ratio is normal). Lactate and pyruvate should be measured in the same blood specimen and on multiple blood specimens obtained when the patient is symptomatic because lactic acidosis can be intermittent. Figure 107.5 is an algorithm for the differential diagnosis of lactic acidosis. Lactic acidosis is also noted with various underlying diseases **(type B1)** and drugs or toxins **(type B2)** (see Table 107.2).

DISORDERS OF GLUCONEOGENESIS

Deficiency of Glucose-6-Phosphatase (Type I Glycogen Storage Disease)

Type I GSD is associated with significant fasting lactic acidosis. The chronic metabolic acidosis predisposes these patients to osteopenia; acute lactic acidosis associated with hypoglycemia is a life-threatening condition in GSD I (see Chapter 107.1).

Fructose-1,6-Bisphosphatase Deficiency

Fructose-1,6-bisphosphatase (FBP) deficiency impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose. Hypoglycemia occurs when glycogen reserves are limited or exhausted. The **clinical manifestations** are characterized by life-threatening episodes of acidosis, hypoglycemia, hyperventilation,

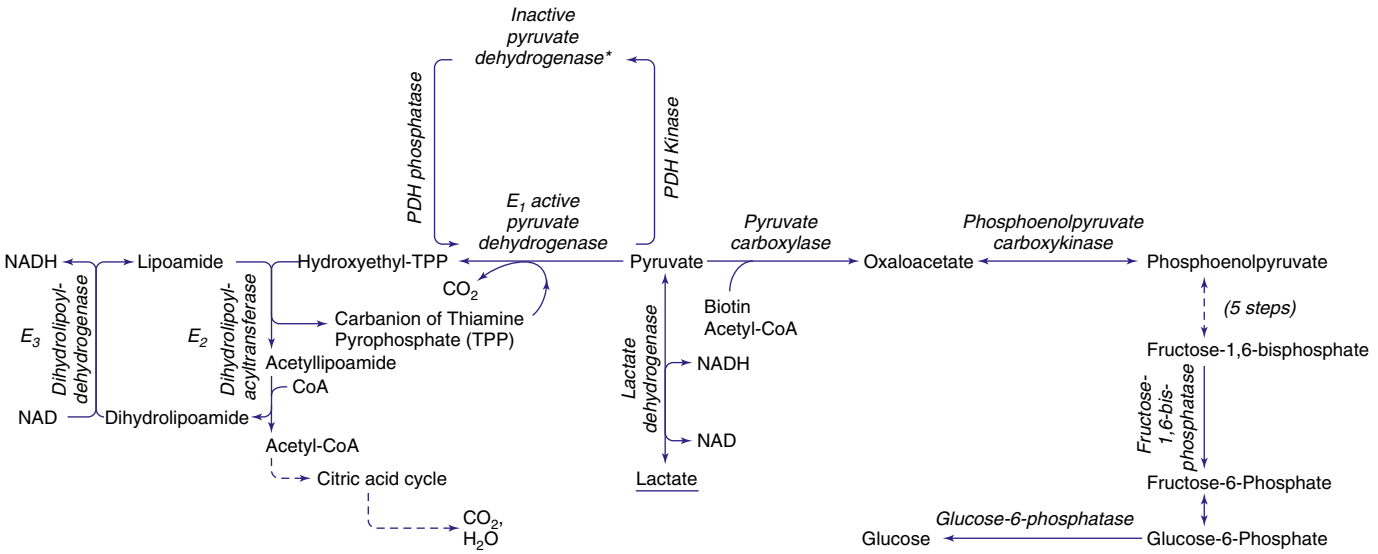

Fig. 107.4 Enzymatic reactions of carbohydrate metabolism, deficiencies of which can give rise to lactic acidosis, pyruvate elevations, or hypoglycemia. The pyruvate dehydrogenase (PDH) complex comprises, in addition to E_1, E_2, and E_3, an E_3-binding protein (not shown), previously called protein X, and PDH kinase and phosphatase. NAD/NADH, nicotinamide adenine dinucleotide.

Table 107.2 Causes of Type B Lactic Acidosis

TYPE B1—UNDERLYING DISEASES
Renal failure
Hepatic failure
Diabetes mellitus
Malignancy
Systemic inflammatory response syndrome
Human immunodeficiency virus

TYPE B2—DRUGS AND TOXINS
Acetaminophen
Alcohols: ethanol, methanol, diethylene glycol, isopropanol, and propylene glycol
Antiretroviral nucleoside analogs—zidovudine, didanosine, and lamivudine
β-Adrenergic agonists: epinephrine, ritodrine, and terbutaline
Biguanides: phenformin and metformin
Cocaine, methamphetamine
Cyanogenic compounds: cyanide, aliphatic nitriles, and nitroprusside
Diethyl ether
Fluorouracil
Halothane
Iron
Isoniazid
Linezolid
Nalidixic acid
Niacin
Propofol
Salicylates
Strychnine
Sugars and sugar alcohols: fructose, sorbitol, and xylitol
Sulfasalazine
Total parenteral nutrition
Valproic acid
Vitamin deficiencies: thiamine and biotin

TYPE B3—INBORN ERRORS OF METABOLISM
Glucose-6-phosphatase deficiency (von Gierke disease)
Fructose-1,6-diphosphatase deficiency
Phosphoenolpyruvate carboxykinase deficiency
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase complex (PDHC) deficiency
Krebs cycle defects
Methylmalonic aciduria and other organic acidemias
Kearns-Sayre syndrome
Pearson syndrome
Barth syndrome
Mitochondrial DNA depletion syndromes
Nuclear DNA respiratory chain defects
Mitochondrial DNA respiratory defects
Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)
Myoclonic epilepsy with ragged red fibers (MERRF)

Adapted from Vernon C, LeTourneau JL. Lactic acidosis: recognition, kinetics, and associated prognosis. *Crit Care Clin.* 2010;26:255–283, Box 1.

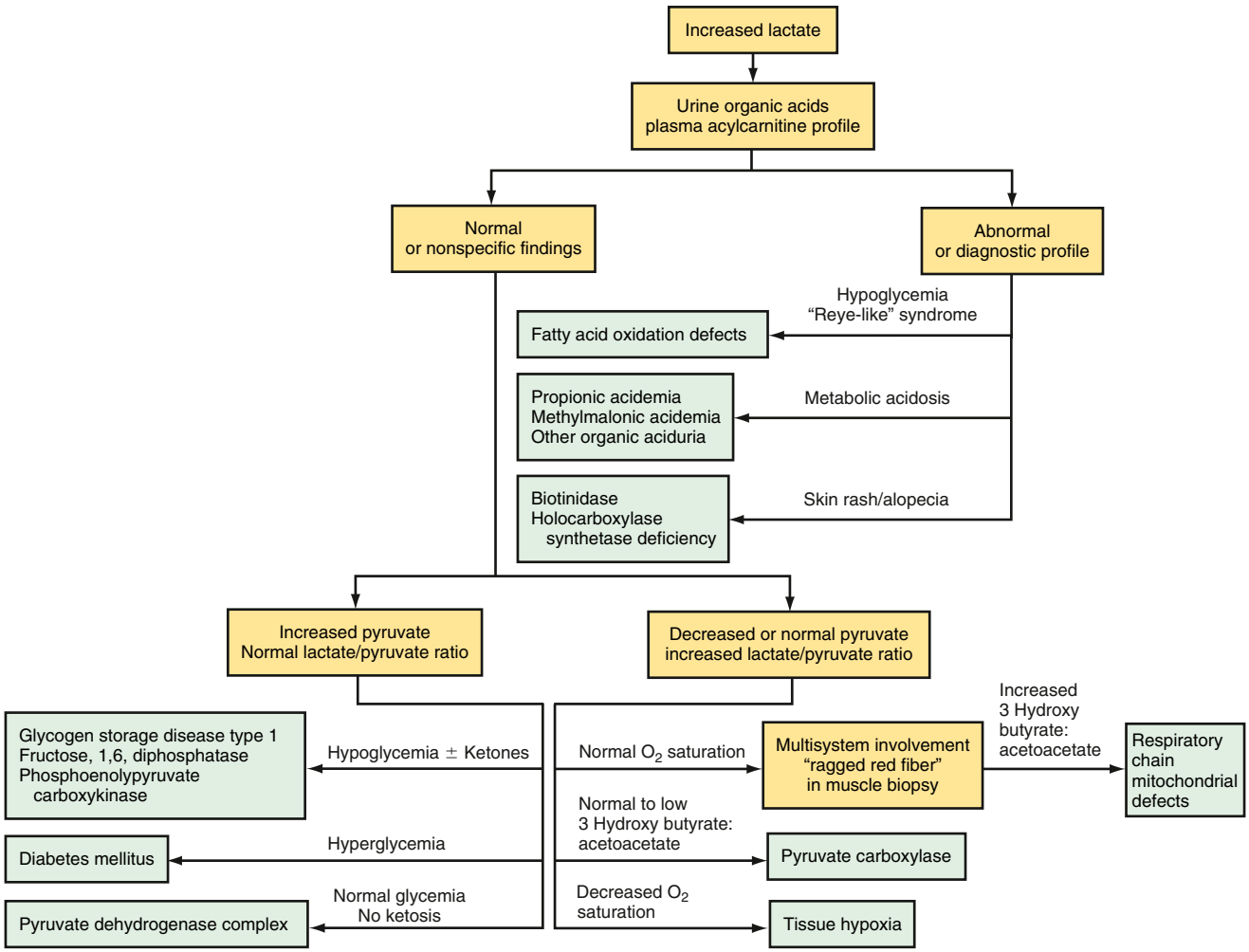

Fig. 107.5 Algorithm of the differential diagnosis of lactic acidosis.

seizures, and coma. In about half of the cases, the deficiency presents in the first week of life. In certain cases, variable degrees of liver impairment (elevated liver tests) and/or failure have been documented, requiring supportive therapy, including intravenous glucose infusion. In infants and small children, hypoglycemia and/or hepatopathy-like episodes are triggered by fasting or missing meals, febrile infections, gastroenteritis, vomiting, and/or poor oral intake. The frequency of these episodes decreases with age. Laboratory findings include low blood glucose, high lactate, glycerol, and uric acid levels and high anion gap metabolic acidosis. Because of the inability of current biochemical assays for plasma triglycerides to differentiate glycerol from triglycerides, FBP deficiency is usually associated with elevated triglyceride levels. This phenomenon is referred to as *pseudo-hypertriglyceridemia* because the plasma has a high concentration of glycerol rather than triglycerides. In contrast to HFI, there is usually no oral aversion to sweets and fruit. Between episodes, renal tubular and liver function may be normal; however, long-term studies are limited.

The **diagnosis** is established by noninvasive molecular genetic testing for pathogenic variants or demonstrating an enzyme deficiency in either liver biopsy or mononuclear white blood cells. The gene coding for fructose-1,6-bisphosphatase is *FBP1,* and pathogenic variants are known, making carrier detection and prenatal diagnosis possible. **Treatment** of acute attacks consists of correction of hypoglycemia and acidosis by IV glucose infusion, and the response is usually rapid. Avoidance of fasting, frequent feedings, aggressive management of infections, and restriction of fructose, sucrose, glycerol, and/or sorbitol from the diet can prevent further episodes. For long-term prevention of hypoglycemia, a slowly released carbohydrate such as cornstarch is useful. Children remain asymptomatic in between crises, and the majority have normal growth and psychomotor development. A few children have been documented to have suffered brain injury and/or cognitive disabilities, most likely as a result of early and untreated hypoglycemia.

Phosphoenolpyruvate Carboxykinase Deficiency

Phosphoenolpyruvate carboxykinase **(PEPCK)** is a key enzyme in gluconeogenesis. It catalyzes the conversion of oxaloacetate to phosphoenolpyruvate and carbon dioxide (see Fig. 107.4). PEPCK deficiency may occur as a cytosolic or mitochondrial enzyme deficiency, as it is encoded by two distinct genes (*PCK1* and *PCK2,* respectively).

PEPCK deficiency has been reported in only a few cases. The **clinical features** are heterogeneous, with hypoglycemia, lactic acidemia, hepatomegaly, hypotonia, developmental delay, and failure to thrive as the major manifestations. There may be multisystem involvement, with neuromuscular deficits, hepatocellular damage, renal dysfunction, and cardiomyopathy. The **diagnosis** is based on the reduced activity of PEPCK in the liver, fibroblasts, or lymphocytes. Fibroblasts and lymphocytes are not suitable for diagnosing the cytosolic form of PEPCK deficiency because these tissues possess only mitochondrial PEPCK. PEPCK deficiency can also occur as a secondary phenomenon caused by other disease, such as mitochondrial depletion disorders. As a result, molecular testing confirming the presence of two pathogenic variants in either the *PCK1* or *PCK2* gene is the recommended gold standard for diagnosis. To avoid hypoglycemia, patients should receive **treatment** with slow-release carbohydrates such as cornstarch, and fasting should be avoided.

DISORDERS OF PYRUVATE METABOLISM

Pyruvate is formed from glucose and other monosaccharides, from lactate, and from alanine. It is metabolized through four main enzyme systems: LDH, ALT, pyruvate carboxylase, and pyruvate dehydrogenase complex. Deficiency of the M subunit of LDH causes exercise intolerance and myoglobinuria (see Chapter 107.1).

Pyruvate Dehydrogenase Complex Deficiency

After entering the mitochondria, pyruvate is converted into acetyl-CoA by the pyruvate dehydrogenase complex **(PDHC)** and then enters the tricarboxylic acid cycle for ATP production. The complex comprises three functional enzymes: $\mathbf{E_1}$, an α-ketoacid decarboxylase; $\mathbf{E_2}$, a dihydrolipoyl acyltransferase; and $\mathbf{E_3}$, a dihydrolipoyl dehydrogenase. The complex also contains an E_3-binding protein (previously called **protein X**) and PDHC kinase and phosphatase, which regulate the complex's activity via phosphorylation/dephosphorylation. Additionally, it requires thiamine pyrophosphate (TPP), lipoic acid, and flavin adenine dinucleotide (FAD) as cofactors. The E_1 subunit, which is made up of two subunits, $E_{1\alpha}$ and $E_{1\beta}$, catalyzes the first and rate-limiting step in the reaction. The most common disorder is caused by a gene defect in the $E_{1\alpha}$ subunit (see Fig. 107.4).

Deficiency of the PDHC is the most common of the disorders leading to lactic acidemia and CNS anomalies and dysfunction. The CNS dysfunction occurs because the brain obtains its energy primarily from oxidation of glucose through glycolysis. Brain acetyl-CoA is synthesized almost exclusively from pyruvate.

PDHC deficiency is mostly caused by pathogenic variants in the gene coding for the $E_{1\alpha}$ subunit, which is inherited in an X-linked dominant fashion; therefore both males and females with a pathogenic variant exhibit features.

Clinical Manifestations

PDHC deficiency has a wide spectrum of presentations, from the most severe neonatal presentation to a mild late-onset form. The **neonatal onset** is associated with lethal lactic acidosis, white matter cystic lesions, agenesis of the corpus callosum, and severe enzyme deficiency. **Infantile/childhood onset** can be lethal or associated with psychomotor delay and chronic lactic acidosis, cystic lesions in the brainstem and basal ganglia, and features of **Leigh syndrome** (see later and Chapter 638.2). **Late onset** cases, including males, may have less acidosis, greater enzyme activity, and episodic ataxia upon consumption of high-carbohydrate-containing foods. Intelligence in affected males may be normal. Developmental delay, hypotonia, hypertonia, seizures, ataxia, peripheral neuropathy, dystonia, dyskinesia, and/or hemiplegia are among neurologic symptoms of PDHC deficiency. Patients of all ages may have dysmorphic facial features, resembling those seen in fetal alcohol syndrome, as a result of PDHC inhibition and reduction of energy metabolism in the latter. Typically, patients with $\mathbf{E_{1\beta}}$ deficiency are more severely affected.

The $\mathbf{E_2}$ deficiency is rare and results in a milder phenotype with varying brain MRI findings and survival into adolescence and adulthood.

The $\mathbf{E_3}$ **lipoamide dehydrogenase** deficiency leads to reduced activity not only in the PDHC but also in the α-ketoglutarate and branched-chain ketoacid dehydrogenase complexes. This deficiency is more common in the Ashkenazi Jewish population. Individuals deficient in E_3 may present with hypotonia and lactic acidosis during infancy, and affected infants typically die during the first few years of life. Surviving children have been shown to have growth delay and severe neurologic problems. Hepatic disease could be a component of this phenotype or may manifest separately. Only a small number of patients exhibit a myopathic phenotype including muscle weakness and elevated CK. In urine organic acid analysis, α-ketoglutarate and branched-chain ketoacids can be detected, and plasma amino acid analysis may reveal elevated levels of leucine, isoleucine, valine, and allo-isoleucine. These findings depend greatly on the phenotype of the disease. The $\mathbf{E_3}$ **binding protein deficiency** can present with either neonatal lactic acidosis, severe psychomotor retardation, or seizure, as well as abnormalities on brain MRI. **Pyruvate dehydrogenase phosphatase** and kinase deficiencies have also been reported. These other PDHC defects have clinical manifestations within the variable spectrum associated with PDHC deficiency caused by $E_{1\alpha}$ deficiency.

Treatment

The general prognosis is poor, except in rare patients whose variants are associated with altered affinity for thiamine pyrophosphate because they may respond to thiamine supplementation. Because carbohydrates can aggravate lactic acidosis, a ketogenic diet is recommended. The ketogenic diet has been found to decrease blood lactate levels and to reduce seizures and improve ataxia and sleep habits. Modified ketogenic diets (a 1:1 fat-to-carbohydrate and protein ratio) have also been

helpful in patients who cannot tolerate a strict ketogenic diet. Infusions of glucose, lactated Ringer, or other drugs known to increase the risk of lactic acidosis, such as metformin, are contraindicated. A potential treatment strategy is to maintain any residual PDHC in its active form by oral administration of dichloroacetate, an inhibitor of E_1 kinase. Beneficial effects of controlling postprandial lactic acidosis have been shown in some patients. Young children generally tolerate **dichloroacetate** well, but continued exposure is associated with peripheral neuropathy, a condition that could be attributable to the drug or the disease. In vitro studies have demonstrated that **phenylbutyrate** increases PDC enzyme activity, especially in those with pathogenic variants linked to residual enzyme activity. In patients with E_3 deficiency, **branched-chain amino acid** restriction and **riboflavin** supplementation are recommended.

Deficiency of Pyruvate Carboxylase

Pyruvate carboxylase is a mitochondrial, biotin-containing enzyme essential in the process of gluconeogenesis; it catalyzes the conversion of pyruvate to oxaloacetate. The enzyme is also essential for Krebs cycle function as a provider of oxaloacetate and is involved in lipogenesis and formation of nonessential amino acids. **Clinical manifestations** of this deficiency have varied from neonatal severe lactic acidosis accompanied by hyperammonemia, hypercitrullinemia, hyperlysinemia, and hypoglycemia **(type B)** to late-onset mild to moderate lactic acidosis and developmental delay **(type A)**. In both types, patients who survive usually have severe psychomotor retardation with seizures, spasticity, and microcephaly. Some patients have pathologic changes in the brainstem and basal ganglia that resemble **Leigh syndrome**. The clinical severity appears to correlate with the level of the residual enzyme activity. A "benign" form of pyruvate carboxylase deficiency has also been described, characterized by recurrent attacks of lactic acidosis and ketoacidosis, as well as mild neurologic deficits **(type C)**. Laboratory findings include elevated levels of blood lactate, pyruvate, and alanine and ketonuria. In type B, the lactate-to-pyruvate ratio is increased; this ratio is normal in types A and C. Additionally, in type B, blood ammonia, citrulline, and lysine levels are elevated with low glutamine, which might suggest a primary anaplerotic defect involving the urea cycle. The mechanism is likely the result of depletion of oxaloacetate, which leads to reduced levels of aspartate, a substrate for argininosuccinate synthase in the urea cycle (see Chapter 105.12). The gene for pyruvate carboxylase is *PC,* and many pathogenic variants have been identified.

Diagnosis of pyruvate carboxylase deficiency is made by the measurement of enzyme activity in cultured skin fibroblasts or lymphoblasts and must be differentiated from holocarboxylase synthase (HCS) or biotinidase deficiency. Molecular genetic testing is presently the preferred approach for diagnosis. **Treatment** consists of avoidance of fasting and modifying the diet to include high amounts of carbohydrate and protein. During acute episodes of lactic acidosis, patients should receive continuous IV glucose. Metabolic abnormalities have been reduced with the use of anaplerotic compounds such as citrate, aspartate, or more recently, triheptanoin, but no improvement has been shown in neurologic symptoms or increased life span. Although liver transplantation has been shown to correct biochemical abnormalities in two patients, the long-term benefits of this procedure are still unknown. Biotin is a cofactor used for this condition, but most patients do not respond to biotin. Lactated Ringer solution is contraindicated in this condition because of the theoretical risk of worsening lactic acidosis in these patients.

Deficiency of Pyruvate Carboxylase Secondary to Deficiency of Holocarboxylase Synthase or Biotinidase

Deficiency of either **HCS** or biotinidase, enzymes involved in biotin metabolism and recycling, respectively, results in multiple-carboxylase deficiency (pyruvate carboxylase, acetyl-CoA carboxylase, 3-methyl-crotonyl-CoA carboxylase, and propionyl-CoA carboxylase) and in **clinical manifestations** associated with the respective deficiencies, including rash, lactic acidosis, and alopecia (see Chapter 103.6). Both enzyme deficiencies are autosomal recessive disorders. The incidence of HCS and biotinidase deficiency is approximately 1 in 87,000 and 1 in 80,000 live births, respectively. Ancestry-specific pathogenic variants in the HCS and biotinidase (BTD) genes have been described. Two common pathogenic variants (c.98_104delinsTCC; p.Cys33PhefsTer36 and c.1612C>T; p.Arg538Cys) in the BTD account for 52% of all pathogenic alleles in symptomatic patients with biotinidase deficiency.

The course of HCS may be more protracted and less responsive to therapy than BTD deficiency. Lack of treatment may be associated with intermittent exacerbations on top of chronic lactic acidosis, failure to thrive, seizures, and hypotonia leading to spasticity, lethargy, coma, and death. Auditory and optic nerve dysfunction can lead to deafness and blindness, respectively. The course of BTD deficiency may be severe if left untreated. Late-onset milder forms have also been reported. Laboratory findings include an anion gap metabolic acidosis, lactic acidosis, and abnormal urine organic acids. Lactate, 3-methylcrotonylglycine, 3-hydroxypropionate, 3-hydroxisovalerate, and methyl citrate may accumulate in urine organic acid chromatography (OAC), though the concentrations of metabolites differ according to the severity of the enzyme deficiency. Blood and/or urine biotin levels can be used to evaluate treatment adherence, but they do not contribute to diagnosis. Biotin concentrations in plasma and urine are normal in patients with HCS deficiency and are often decreased in patients with BTD deficiency, particularly when the assay used does not detect biocytin.

Diagnosis of HCS deficiency and biotinidase deficiency can be detected through newborn screening tandem mass spectroscopy, which enables early treatment and improves outcomes. Molecular genetic testing is required to confirm the diagnosis, which involves the detection of two pathogenic variants. BTD deficiency can be diagnosed by reduced enzyme activity in the patient's serum or plasma, which helps to classify the deficiency into two categories: profound deficiency (biotinidase activity less than 10% of mean normal serum BTD activity) and partial deficiency (BTD activity between 10% and 30% of mean normal serum BTD activity). HCS activity in skin fibroblasts or lymphocytes can be assessed when HCS deficiency is suspected but genetic testing is equivocal.

Treatment

Treatment consists of biotin supplementation 5-20 mg/day and is generally effective if started early before the onset of symptoms or development of brain damage. Newborn screening has facilitated early treatment for patients with partial or profound BTD deficiency, who respond well to 5-10 mg of biotin; some patients may require higher doses during acute illness. Patients identified through newborn screening and treated with biotin have remained asymptomatic.

Mitochondrial Respiratory Chain Defects (Oxidative Phosphorylation Disease)

The mitochondrial respiratory chain catalyzes the oxidation of fuel molecules and transfers the electrons to molecular oxygen, with concomitant energy transduction into ATP **(oxidative phosphorylation)** (see Chapter 108). The respiratory chain produces ATP from adenosine diphosphate and inorganic phosphate, using the energy from electrons transferred from nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide, and includes five specific complexes (I: NADH–coenzyme Q reductase; II: succinate–coenzyme Q reductase; III: coenzyme QH2 cytochrome-c reductase; IV: cytochrome-c oxidase; V: ATP synthase). Each complex is composed of 4-35 individual proteins that are encoded by nuclear or maternally inherited mitochondrial DNA, with the exception of complex II, which is encoded solely by nuclear genes. Alterations of these complexes or assembly systems produce chronic lactic acidosis, presumably because of a change in the reduction-oxidation state with increased concentrations of NADH (Table 107.3).

In contrast to PDHC or pyruvate carboxylase deficiency, skeletal muscle and the heart are usually involved in the respiratory chain disorders. On muscle biopsy, **ragged red fibers** indicating mitochondrial proliferation are suggestive of mitochondrial involvement when present, especially when observed in young patients with symptoms (see

Table 107.3 Clinical and Genetic Heterogeneity of Disorders Related to Pathogenic Variants in Mitochondrial DNA*

SYMPTOMS, SIGNS, AND FINDINGS	LARGE DELETIONS IN MITOCHONDRIAL DNA			PATHOGENIC VARIANT IN TRANSFER RNA		PATHOGENIC VARIANT IN RIBOSOMAL RNA	PATHOGENIC VARIANT IN MESSENGER RNA		
	KSS	PEO	PS	MERRF	MELAS	AID	NARP	MILS	LHON
CENTRAL NERVOUS SYSTEM									
Seizures	−	−	±	+++	+	−	±	+	−
Ataxia	+	−	±	+	+		+	±	−
Myoclonus	−	−	−	+	±	−	−	−	−
Psychomotor retardation	−	−	±	−	±	−	−	+	−
Psychomotor regression	+	−	−	±	+	−	±	+	−
Hemiparesis and hemianopia	−	−	−	−	+++	−	−	−	−
Cortical blindness	−	−	−	−	+	−	−	−	−
Migraine-like headaches	−	−	−	±	+	−	−	−	−
Dystonia	−	−	−	−	+	−	−	+	±
PERIPHERAL NERVOUS SYSTEM									
Peripheral neuropathy	±	−	−	±	±	−	+	±	±
MUSCLE									
Weakness ± exercise intolerance	+	+++	±	+	+	−	+	+	±
Ophthalmoplegia	+	+	±	±	±	−	±	±	−
Ptosis	+	+	±	±	−	−	−	±	−
EYE									
Pigmentary retinopathy	+	−	−	±	±	−	+	±	−
Optic atrophy	−	−	−	±	±	−	±	±	+
BLOOD									
Sideroblastic anemia	-	−	+	−	−	−	−	−	−
ENDOCRINE SYSTEM									
Diabetes mellitus	±	−	±	±	±	−	−	±	−
Short stature	+	−	±	+	+	−	±	−	−
Hypoparathyroidism	±	−	±	−	±	−	−	−	−
HEART									
Conduction disorder	+	−	−	±	±	−	±	±	±
Cardiomyopathy	±	−	−	±	±	+	−	±	−
GASTROINTESTINAL SYSTEM									
Exocrine pancreatic dysfunction	±	−	±	−	−	−	−	−	−
Intestinal pseudoobstruction	−	−	−	−	±	−	−	±	−
EAR, NOSE, AND THROAT									
Sensorineural hearing loss	±	−	−	+	+	+	±	±	−
KIDNEY									
Fanconi syndrome/RTA	±	−	±	−	±	−	−	±	−
LABORATORY FINDINGS									
Lactic acidosis	+	±	+	+	+	±	±	±	−
Ragged-red fibers on muscle biopsy	+	+	±	+	+	−	−	±	−
MODE OF INHERITANCE									
Maternal	−	−	−	+	+	+	+	+	+
Sporadic	+	+	+	−	−	−	−	−	−

*Characteristic constellations of symptoms and signs are in **bold**.

+, Presence of a symptom, sign, or finding; −, absence of a symptom, sign, or finding; ±, possible presence of a symptom, sign, or finding; AID, aminoglycoside-induced deafness; KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PS, Pearson syndrome, RTA, renal tubular acidosis.

Modified from DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med.* 2003;348:2656–2668.

Fig. 107.5). Because of the ubiquitous nature of oxidative phosphorylation, a defect of the mitochondrial respiratory chain accounts for a vast array of clinical manifestations and should be considered in patients of all ages presenting with multisystem involvement. Some deficiencies resemble **Leigh syndrome** with lactic acidosis, whereas others present with strokelike episodes, myopathies, or ataxia including **MELAS** (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes), **MERRF** (myoclonic epilepsy and ragged red fibers), and **Kearns-Sayre syndrome** (external ophthalmoplegia, ptosis, metabolic acidosis, retinal degeneration, heart block, myopathy, and high cerebrospinal fluid protein) (see Table 107.3) (see Chapters 638.2 and 651.4). There is a higher incidence of neuropsychiatric disorders in adults with a primary oxidative phosphorylation disease than in the general population.

Diagnosis requires identification of pathogenic variants in mitochondrial DNA or nuclear genes encoding mitochondrial proteins or demonstrating functional abnormalities of oxidative phosphorylation enzyme complex activities in tissues (e.g., skin, muscle, or liver). In

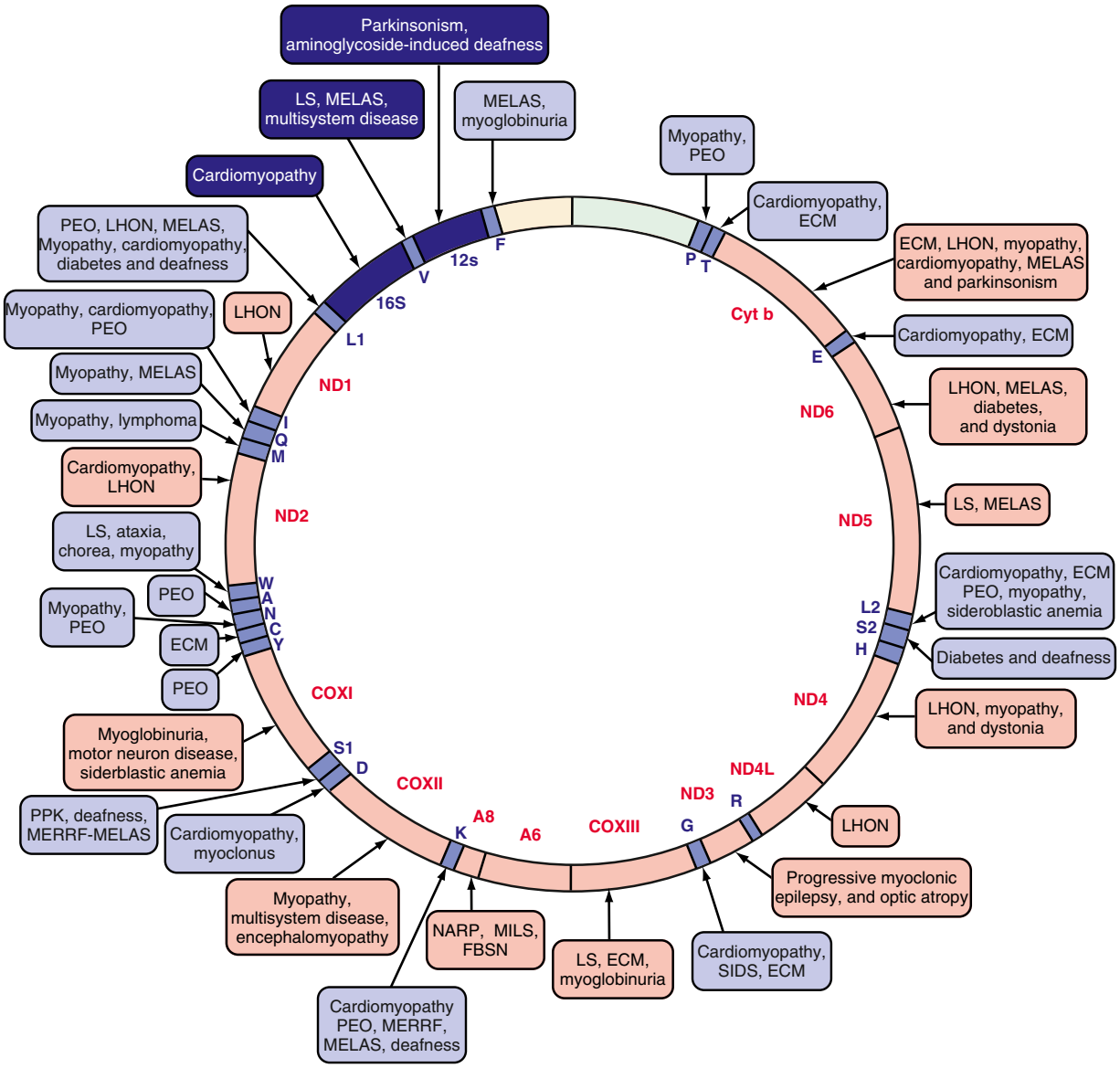

Fig. 107.6 Pathogenic variants in the human mitochondrial genome that are known to cause disease. Disorders that are frequently or prominently associated with pathogenic variants in a particular gene are shown in bold. Diseases caused by pathogenic variants that impair mitochondrial protein synthesis are shown in blue. Diseases caused by pathogenic variants in protein-coding genes are shown in red. ECM, Encephalomyopathy; FBSN, familial bilateral striatal necrosis; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PPK, palmoplantar keratoderma; SIDS, sudden infant death syndrome. *(From DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med. 2003;348:2656–2668.)*

some instances, combined molecular and functional testing may be needed (Fig. 107.6). *NGS of single or combined mitochondrial DNA and nuclear gene panels is the preferred method of testing.* Whole exome sequencing with analysis of the mitochondrial genome or whole genome sequencing may be considered if NGS panel testing is nondiagnostic. Biopsy and genetic analysis of clinically affected tissues, with or without biochemical testing, is indicated when genetic testing of blood is negative or inconclusive and there is clinical suspicion of mitochondrial disease. Muscle biopsy was considered the most reliable procedure for diagnosing mitochondrial diseases prior to the availability of molecular genetic testing. Muscle histology, including EM, can detect ragged red fibers and other abnormalities typical of mitochondrial myopathies. Analysis of oxidative phosphorylation complexes I-IV from intact mitochondria isolated from fresh skeletal muscle can be helpful for the diagnosis of mitochondrial disorders; however, electron transport chain testing of flash-frozen muscle provides an alternative approach when fresh muscle testing is not available. The presence of normal muscle biochemistry and histology does not rule out the possibility of mitochondrial disease. Several disorders, such as defects in mitochondrial maintenance, fusion/fission, translation, transcription, or abnormalities in mitochondrial membrane integrity or transport, may not manifest with substantial oxidative phosphorylation deficiency and may have normal muscle biochemistry and histology. Specific criteria may assist in making a clinical diagnosis (Table 107.4). One study conducted to reevaluate the clinical utility of mitochondrial disease criteria (MDC) determined that the criteria are still beneficial and can aid in directing the diagnostic workup and in interpreting results and deciding on muscle biopsy in certain instances. Additionally, the study demonstrated that whole exome sequencing might be used to diagnose patients with lower MDC scores as having primary mitochondrial disorders. Table 107.5 lists clues to the diagnosis of mitochondrial diseases.

Numerous nuclear genes involved in mitochondrial function and causative for the majority of mitochondrial disorders are included in

Table 107.4 Mitochondrial Disease Criteria (Simplified Version for Bedside Use)*

I. CLINICAL SIGNS AND SYMPTOMS, 1 POINT/SYMPTOM (max. 4 points)				
A. MUSCULAR PRESENTATION (max. 2 points)	**B. CNS PRESENTATION (max. 2 points)**	**C. MULTISYSTEM DISEASE (max. 3 points)**	**II. METABOLIC/IMAGING STUDIES (max. 4 points)**	**III. MORPHOLOGY (max. 4 points)**
Ophthalmoplegia†	Developmental delay	Hematology	Elevated lactate†	Ragged red/blue fibers‡
Facies myopathica	Loss of skills	GI tract	Elevated L/P ratio	COX-negative fibers‡
Exercise intolerance	Stroke-like episode	Endocrine/growth	Elevated alanine†	Reduced COX staining‡
Muscle weakness	Migraine	Heart	Elevated CSF lactate†	Reduced SDH staining
Rhabdomyolysis	Seizures	Kidney	Elevated CSF protein	SDH positive blood vessels†
Abnormal EMG	Myoclonus	Vision	Elevated CSF alanine†	Abnormal mitochondria/EM†
	Cortical blindness	Hearing	Urinary TA excretion†	
	Pyramidal signs	Neuropathy	Ethylmalonic aciduria	
	Extrapyramidal signs	Recurrent/familial	Strokelike picture/MRI	
	Brainstem involvement		Leigh syndrome/MRI†	
			Elevated lactate/MRS	

*Score 1: unlikely mitochondrial disorder; score 2-4: possible mitochondrial disorder; score 5-7: probable mitochondrial disorder; score ≥8: definite mitochondrial disorder.
†This specific symptom scores 2 points.
‡This symptom in a higher percentage scores 4 points.
GI, Gastrointestinal; L/P, lactate/pyruvate; COX, cytochrome C oxidase; SDH, succinate dehydrogenase; EM, electron microscopy; EMG, electromyography; TA, tricarbon acid.
From Morava E, van den Heuvel L, Hol F, et al. Mitochondrial disease criteria – diagnostic applications in children. *Neurology*. 2006;67:1823–1826.

clinical testing panels that are used to diagnose mitochondrial disorders. An important consideration is that many genetic and multifactorial conditions have been associated with defects in one or more of the four complexes assayed in mitochondrial oxidative phosphorylation testing; these latter conditions feature so-called secondary mitochondrial dysfunction because the conditions are not considered to be causative for primary mitochondrial dysfunction.

Treatment remains largely symptomatic and nonspecific and does not cure or significantly alter the outcome of disease. Mitochondrial drugs are mainly medicinal/nutritional supplements designed to sustain and boost the mitochondrial residual oxidative phosphorylation function, while also reducing oxidative stress. Although there is no consensus on which vitamins and cofactors should be used to treat mitochondrial disease, the main supplementations used are CoQ10, L-carnitine, creatine, alpha-lipoic acid (ALA), and B vitamins. Additional medications/supplements are indicated based on the genetic diagnosis and clinical symptoms of the patient. For example, arginine (IV, oral) can be prescribed in patients with MELAS for treatment and prevention of metabolic strokes. Citrulline and taurine have also been used with some success in ongoing clinical trials and case reports demonstrating promising results. Patients with mitochondrial disease should be encouraged to exercise regularly. Patients with mitochondrial disorders are at a greater risk of developing anesthesia-related complications. Avoiding prolonged fasting and receiving dextrose-containing IV fluids before, during, and after procedures and operations are critical for avoiding catabolism. There are an increasing number of clinical studies evaluating various therapeutic approaches, including mitochondrial augmentation therapy in pediatric children with Pearson syndrome (NCT03384420) and AAV gene therapy in individuals with Leber hereditary optic neuropathy (LHON) (NCT02161380).

Leigh Syndrome (Subacute Necrotizing Encephalomyelopathy)

Leigh syndrome is a heterogeneous neurologic disease historically diagnosed based on neuropathologic findings of demyelination, gliosis, necrosis, relative neuronal sparing, and capillary proliferation in specific brain regions (see Chapter 638.2). Leigh syndrome is characterized by decompensation (neurodevelopmental regression and lactic acidosis) initiated by viral infection or other metabolic stress. Patients frequently present with feeding and swallowing problems, failure to thrive, and developmental delay. The presentation is highly variable and may include seizures, altered consciousness, movement disorders, nystagmus, ophthalmoplegia, cerebellar ataxia, and peripheral neuropathy. Extraneurologic manifestations may include pericardial effusion, cardiomyopathy, renal tubulopathy, liver involvement, hypertrichosis, and muscle weakness. **Diagnosis** is usually confirmed by radiologic evidence of symmetric lesions affecting the basal ganglia, brainstem, and subthalamic nuclei. Patients with Leigh syndrome have defects in several enzyme complexes. Dysfunction in cytochrome-c oxidase (complex IV) is the most commonly reported defect, followed by NADH–coenzyme Q reductase (complex I), PDHC, and pyruvate carboxylase (see Chapter 108). Pathogenic variants in the nuclear *SURF1* gene, which encodes an assembly factor involved in the biogenesis of cytochrome-c oxidase, and mitochondrial DNA variants in the adenosine triphosphatase 6 (MT-ATP6) coding region have been reported in patients with Leigh syndrome in association with complex IV deficiency. The most common mitochondrial DNA variant in Leigh syndrome is the m.8993T>G variant in MT-ATP6. The **prognosis** for Leigh syndrome is poor. In a study of 14 cases, there were 7 fatalities before age 1.5 years. Pathogenic variants in *MTFMT* had a milder clinical phenotype and disease progression, according to recent research.

Lactic acidosis and encephalopathy have also been reported in patients with thiamine transporter 2 (THTR2) deficiency and with pyridoxine-dependent epilepsy. Thiamine, either alone or in combination with biotin, is required for the treatment of THTR2 deficiency, whereas pyridoxine is used to treat pyridoxine-dependent epilepsy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

107.5 Defects in Pentose Metabolism

Ghada Hijazi and Priya S. Kishnani

Approximately 90% of glucose metabolism in the body is generated via the glycolytic pathway, with the remaining 10% generated via the hexose monophosphate pathway. The hexose monophosphate shunt leads to the formation of pentose and provides NADPH. One of the metabolites of this alternative pathway is ribose-5-phosphate, which is used in the biosynthesis of ribonucleotides and deoxyribonucleotides. Through the transketolase and transaldolase reactions, pentose phosphates can be converted back to fructose-6-phosphate and glucose-6-phosphate.

ESSENTIAL PENTOSURIA

Essential pentosuria is a benign asymptomatic disorder encountered principally in the Ashkenazi Jewish population and is inherited in an

Table 107.5 Clues to the Diagnosis of Mitochondrial Disease

NEUROLOGIC
Cerebral strokelike lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy, recurrent or with low/moderate dosing of valproate
Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh syndrome
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm
CARDIOVASCULAR
Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia
OPHTHALMOLOGIC
Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy
GASTROENTEROLOGIC
Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudoobstructive episodes
OTHER
A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis
Elevated GDF-15 level

MRI, Magnetic resonance imaging, MRS, magnetic resonance spectroscopy; GDF, growth and differentiation factor.
From Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics*. 2007;120:1326–1333, Table 1.

autosomal recessive fashion. The urine contains **L-xylulose**, which is excreted in increased amounts because of a block in the conversion of L-xylulose to xylitol as a result of **xylitol dehydrogenase deficiency**. The condition is usually discovered incidentally in a urine test for reducing substances. No treatment is required.

TRANSALDOLASE DEFICIENCY

Transaldolase deficiency is a rare autosomal recessive inborn error of the pentose phosphate pathway. It is more common in Middle Eastern countries and can manifest in three distinct phenotypes. Prenatal intrauterine growth restriction (IUGR), oligohydramnios, and/or hydrops fetalis occur with the most severe phenotype. The second is a neonatal phenotype, where patients may have dysmorphic facial features (triangular-shaped face, low-set ears, wide mouth, and thin lips), cardiovascular abnormalities (ventricular and atrial septal defects), anemia, thrombocytopenia, and hepatosplenomegaly noted in the newborn period. In some cases, hepatic dysfunction was described associated with fibrosis and/or cirrhosis, and transplantation of the liver was indicated in a number of patients. Endocrine abnormalities (abnormal genitalia, vitamin D insufficiency, hypergonadotrophic hypogonadism), renal tubulopathy, and skin abnormalities (cutis laxa, wrinkled skin, capillary hemangioma) have been observed. A third, milder phenotype is described as presenting later in life. Biochemical abnormalities reveal elevated levels of the polyols arabitol, ribitol, and erythritol and the seven-carbon sugars sedoheptitol, perseitol, sedoheptulose, mannoheptulose, and sedoheptulose-7P in the urine. The **diagnosis** is established with the detection of biallelic pathogenic variants in the *TALDO1* gene. When genetic testing is inconclusive, low transaldolase activity in lymphoblasts, fibroblasts, and liver tissue can be used to confirm the diagnosis. The available **treatment** is symptomatic. Supportive management of the disease manifestations (e.g., hepatic dysfunction) is needed. Transplantation of the liver may be indicated. Regular follow-up and monitoring for complications such as anemia and thrombocytopenia is required. N-acetylcysteine (NAC) supplementation delayed the progression of disease and restored normal alpha fetoprotein levels in a research trial. Additional long-term studies are required to evaluate the broader effectiveness of NAC supplementation.

RIBOSE-5-PHOSPHATE ISOMERASE DEFICIENCY

Only four cases of ribose-5-phosphatase isomerase deficiency disorder have been reported. Affected patients may present with psychomotor delay or regression, epilepsy, peripheral neuropathy, and leukoencephalopathy. Magnetic resonance spectroscopy (MRS) and urine analysis usually reveal elevated levels of polyols arabitol and ribitol in these patients. Confirmation of diagnosis is established by identification of biallelic *RPIA* pathogenic variants or by enzyme assay in cultured fibroblasts.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

107.6 Disorders of Glycoprotein Degradation and Structure

Margaret M. McGovern and Robert J. Desnick

The disorders of glycoprotein degradation and structure include several lysosomal storage diseases that result from defects in glycoprotein degradation and the congenital disorders of glycosylation (see Chapter 107.7). *Glycoproteins* are macromolecules composed of oligosaccharide chains linked to a peptide backbone. They are synthesized by two pathways: the glycosyltransferase pathway, which synthesizes oligosaccharides linked *O*-glycosidically to serine or threonine residues, and the dolichol, lipid-linked pathway, which synthesizes oligosaccharides linked N-glycosidically to asparagine.

The **glycoprotein lysosomal storage diseases** result from the deficiency of the enzymes that normally participate in the degradation of oligosaccharides and include sialidosis, galactosialidosis, aspartylglucosaminuria, and α-mannosidosis. In some instances, the underlying abnormality that leads to glycoprotein accumulation also results in abnormal degradation of other classes of macromolecules that contain similar oligosaccharide linkages, such as certain glycolipids and proteoglycans. In these cases the underlying enzymatic deficiency results in the accumulation of both glycoproteins and *glycolipids*. The classification of these types of disorders as *lipidoses* or *glycoproteinoses* depends on the nature of the predominantly stored substance. In general, the glycoprotein disorders are characterized by autosomal recessive inheritance and a progressive disease course with clinical features that resemble those seen in the mucopolysaccharidoses.

SIALIDOSIS AND GALACTOSIALIDOSIS

Sialidosis is an autosomal recessive disorder that results from the primary deficiency of neuraminidase because of pathogenic variants in the gene *(NEU1)* that encodes this protein. In contrast, **galactosialidosis** is caused by the deficiency of two lysosomal enzymes—neuraminidase and β-galactosidase. The loss of these enzymatic activities results from pathogenic variants in a single gene, *CTSA,* that encodes the

protective protein cathepsin A, which functions to stabilize these enzymatic activities. Neuraminidase normally cleaves terminal sialyl linkages of several oligosaccharides and glycoproteins. Its deficiency results in the accumulation of oligosaccharides and the urinary excretion of sialic acid terminal oligosaccharides and sialylglycopeptides. Examination of tissues from affected individuals reveals pathologic storage of substrate in many tissues, including liver, bone marrow, and brain.

The clinical phenotype associated with neuraminidase deficiency is variable and includes **type I** sialidosis, which usually presents in the second decade of life with myoclonus and cherry-red spots in the macula. These patients typically present secondary to gait disturbances, myoclonus, or visual complaints. In contrast, **type II** sialidosis occurs at several ages of onset (congenital, infantile, and juvenile), depending on the severity of the gene pathogenic variant. The **congenital** and **infantile** forms result from isolated neuraminidase deficiency, whereas the **juvenile** form results from both neuraminidase and β-galactosidase deficiency. The congenital type II disease is characterized by hydrops fetalis, neonatal ascites, hepatosplenomegaly, stippling of the epiphyses, periosteal cloaking, and stillbirth or death in infancy. The type II infantile form presents in the first years of life with dysostosis multiplex, moderate global developmental delays, visceromegaly, corneal clouding, cherry-red maculae, and seizures. The juvenile type II form of sialidosis, which is sometimes designated *galactosialidosis,* has a variable age of onset ranging from infancy to adulthood. In infancy, the phenotype is similar to that of GM1 gangliosidosis, with edema, ascites, skeletal dysplasia, and cherry-red spots. Patients with later-onset disease have dysostosis multiplex, visceromegaly, intellectual disability, dysmorphism, corneal clouding, progressive neurologic deterioration, and cherry-red spots.

No specific therapy exists for any form of the disease, although studies in animal models have demonstrated improvement in the phenotype after bone marrow transplantation. The **diagnosis** of sialidosis and galactosialidosis is achieved by the demonstration of the specific enzymatic deficiency or by pathogenic variants in the responsible gene. **Prenatal diagnosis** using cultured amniotic cells or chorionic villi is available by demonstrating the enzyme defect and/or specific gene pathogenic variants.

ASPARTYLGLUCOSAMINURIA

This is a rare autosomal recessive lysosomal storage disorder, except in Finland, where the carrier frequency is estimated at 1 in 36 adults, the high frequency due to a *founder gene.* The disorder results from the deficient activity of **aspartylglycosaminidase** and the subsequent accumulation of aspartylglycosamine, particularly in the liver, spleen, and thyroid. The gene for the enzyme is *AGA,* and in the Finnish population, a single *AGA* pathogenic variant encoding p.Cys163Ser accounts for most mutant alleles. Outside of Finland, a large number of private pathogenic variants have been described.

Affected individuals with aspartylglucosaminuria typically present in the first year of life with recurrent infections, diarrhea, and umbilical hernias. Coarsening of the facies and short stature usually develop later. Other features include joint laxity, macroglossia, hoarse voice, crystal-like lens opacities, hypotonia, and spasticity. Psychomotor development is usually near normal until age 5 years, when a decline is noted. Behavioral abnormalities are typically seen, and IQ values in affected adults are usually <40 (severe intellectual disability). Survival to adulthood is common, with most early deaths attributable to pneumonia or other pulmonary causes. Definitive **diagnosis** requires demonstration of markedly deficient aspartylglucosaminidase in peripheral blood leukocytes and/or the specific *AGA* pathogenic variant(s). Several patients have undergone allogeneic bone marrow transplants, but this approach has not proved effective, and no specific treatment is available. **Prenatal diagnosis** is available by the determination of aspartylglucosaminidase deficiency and/or the specific *AGA* pathogenic variants in cultured amniocytes or chorionic villi.

α-MANNOSIDOSIS

This autosomal recessive disorder results from the deficient activity of **α-mannosidase** and the accumulation of mannose-rich compounds. The gene *MAN2B1* encodes the enzyme, and to date, >140 gene pathogenic variants have been reported. Affected patients display clinical heterogeneity. There is a severe infantile form, or **type I** disease, and a milder juvenile variant, **type II** disease. All patients have psychomotor retardation, facial coarsening, and dysostosis multiplex. The **infantile** form of the disorder, however, is characterized by more rapid cognitive deterioration, with death occurring between ages 3 and 10 years. Patients with the infantile form also have more severe skeletal involvement and hepatosplenomegaly. The **juvenile** disorder is characterized by onset of symptoms in early childhood or adolescence, with milder somatic features and survival to adulthood. Hearing loss, destructive synovitis, pancytopenia, and spastic paraplegia have been reported in type II patients. The **diagnosis** is made by identification of biallelic pathogenic variants in *MAN2B1* and may be supplemented by the demonstration of the marked deficiency of α-mannosidase activity in white blood cells or cultured fibroblasts. Clinical trials of ERT with recombinant human α-mannosidase are underway. **Prenatal diagnosis** can be made by demonstrating the enzyme defect and/or known pathogenic variants in cultured amniocytes or chorionic villi.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

107.7 Congenital Disorders of Glycosylation

Eva Morava and Peter Witters

Glycosylation is the complex multistep metabolic process of adding (oligo)saccharides to macromolecules such as proteins and lipids. The classification of **disorders of hypoglycosylation** is based on biochemical structures: (1) defects in protein *N*-linked glycosylation, (2) defects in protein *O*-linked glycosylation, (3) defects in glycosphingolipid and in glycosylphosphatidylinositol-anchor glycosylation, and (4) defects in multiple glycosylation pathways and in other pathways (Fig. 107.7). No disorders are known to result from abnormal *C*-linked glycosylation. Congenital disorders of glycosylation (CDGs) are labeled based on their genetic defect.

Protein glycosylation is an essential process. Most functional proteins are glycosylated, including serum proteins (e.g., transferrin, ceruloplasmin, thyroxine-binding globulin [TBG]), hormones (e.g., thyroid-stimulating hormone [TSH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], adrenocorticotropic hormone [ACTH], IGFBP3), and clotting and anticoagulation factors (e.g., factors IX and XI, antithrombin). Membrane proteins are also highly glycosylated. Important intracellular glycoproteins include enzymes such as glycosyltransferases or lysosomal enzymes.

***N*-glycans** are linked to the amide group of asparagine. They are synthetized in a complicated process throughout the cytoplasm, endoplasmic reticulum (ER), and Golgi complex, starting with sugar activation and nucleotide sugar synthesis, then oligosaccharide assembly, and finally glycan processing (see Fig. 107.7). Most of the pediatric glycosylation disorders are the result of N-glycosylation defects. ***O*-glycans** are linked to the hydroxyl group of serine or threonine. These diverse glycoproteins are mostly formed in the Golgi complex; their defects can involve xylosylation, fucosylation, mannosylation, or other modifications. An important focus is *O*-mannosylation defects because of their relevance for dystroglycanopathies.

Lipid glycosylation is an essential process for the synthesis of ceramide and ganglioside synthesis. **Glycosylphosphatidylinositols** (GPIs) are very special glycolipids that link various proteins to the plasma membrane, as complex lipid-sugar anchors (GPI anchors, see Fig. 107.7).

CDGs are predominantly multisystem diseases caused by more than 150 different genetic defects in glycoprotein and glycolipid glycan synthesis. Most patients described with CDG have N-glycosylation defects, followed by the fastest-growing groups of CDGs, involving multiple glycosylation pathways and dolicholphosphate synthesis. Smaller groups are *O*-glycosylation disorders and disorders of GPI. The "oldest" and most common CDG is PMM2-CDG, in which the

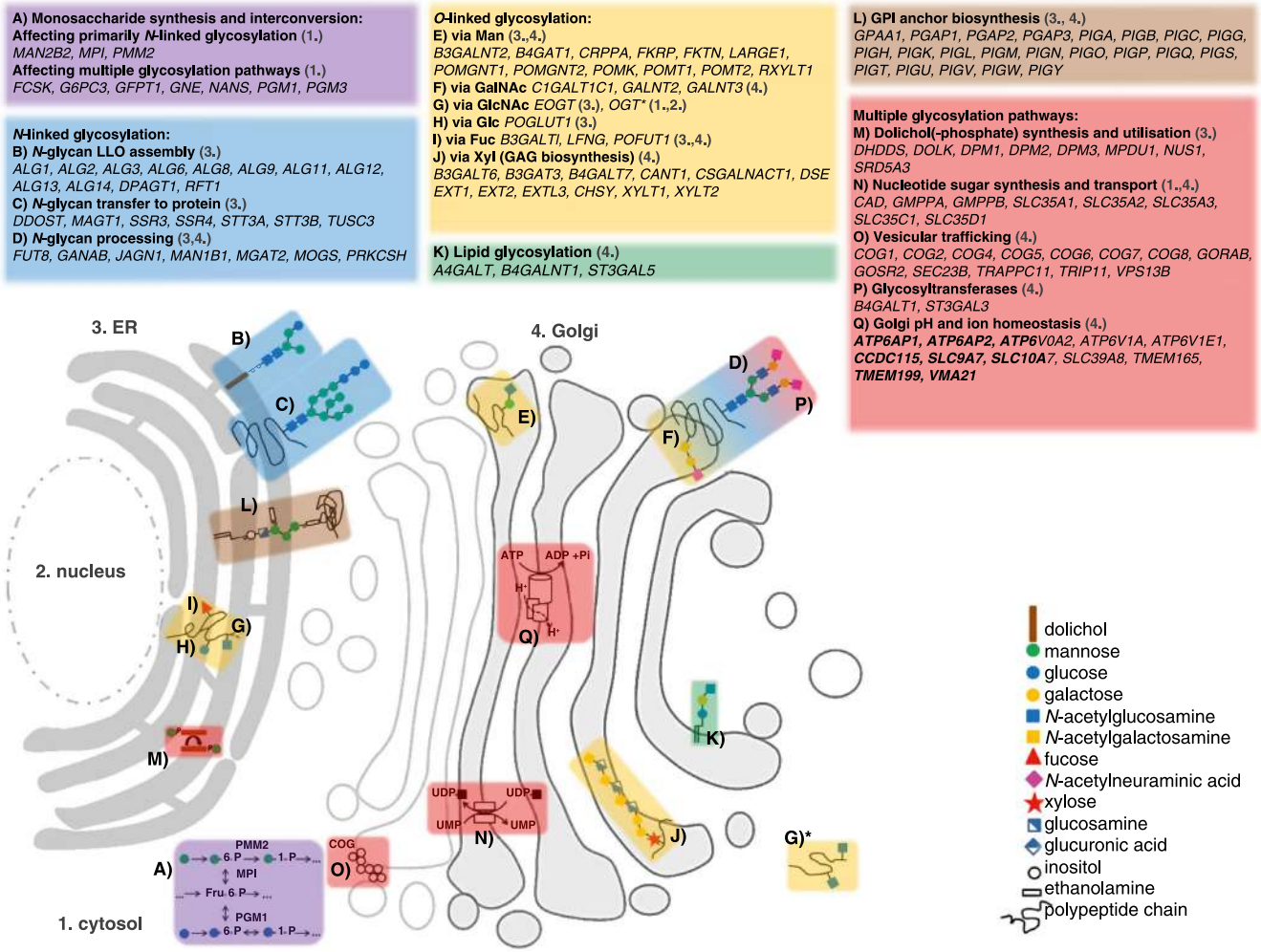

Fig. 107.7 Congenital disorders of glycosylation (CDG): an overview of the currently known subtypes. The picture shows a schematic illustration of the individual 137 CDG subtypes known to date, designated by the symbol of the affected gene, which are categorized according to the nature of the biochemical event impaired within the glycosylation pathway. Glycosylation is a complex metabolic process resulting in the attachment of an oligosaccharide chain of varying length and composition (a glycan) to proteins and lipids. It involves a set of enzyme-catalyzed reactions that take place mainly in the cytosol (1.), endoplasmic reticulum (ER; 3.) and Golgi apparatus (4.), after which the newly formed glycoconjugates are, generally, incorporated into membranes or secreted out of the cell. Depending on how a glycan is linked to the polypeptide backbone, protein glycosylation is classified into *N*-linked (a bond via the amide group of asparagine) or *O*-linked (a bond via the hydroxyl group of serine, threonine, or hydroxylysine). *N*-glycoproteins share a common core structure of the glycan, which is first assembled on a dolichol anchor and then transferred onto the protein in the ER; this is later followed by further modifications of the *N*-glycan, removing and adding different monosaccharides, in the Golgi apparatus. *O*-glycosylation consists of a stepwise addition of individual monosaccharide units in the ER and Golgi apparatus, while six subclasses can be distinguished based on which sugar (Man, GalNac, GlcNAc, Glc, Fuc, or Xyl) is the first one attached to the protein, and thus more varied *O*-glycan structures are produced. Other specific types of glycosylation involve lipid glycosylation and the modification of proteins by the glycosylphosphatidylinositol (GPI) anchor. The substrates for glycosylation in the form of nucleotide-monosaccharides are synthesized predominantly in the cytosol, and because they are used in different glycosylation reactions, their deficiency possibly influences the structure of various glycoconjugates. Similarly, several defects have been described that affect multiple glycosylation pathways, and, often, other cellular processes might be disturbed as well (e.g., because of altered ion homeostasis in the Golgi apparatus). ADP, adenosine diphosphate; ATP, adenosine triphosphate; COG, conserved oligomeric Golgi (complex); ER, endoplasmic reticulum; Fru-6-P, fructose-6-phosphate; Fuc, fucose; GalNAc, N-acetylgalactosamine; Glc, glucose; GlcNAc, N-acetylglucosamine; GPI, glycosylphosphatidylinositol; H+, protons; LLO, lipid-linked oligosaccharides; Man, mannose; MPI, mannose phosphate isomerase; PGM1, phosphoglucomutase 1; PMM2, phosphomannomutase 2; UDP, uridine diphosphate; UMP, uridine monophosphate; Xyl, xylose. *(From Ondruskova N, Cechova A, Hansikova H, et al. Congenital disorders of glycosylation: still "hot" in 2020. Biochim Biophys Acta Gen Subj. 2021;1865[1]:129751, Fig. 1.)*

genetic defect leads to the loss of **phosphomannomutase 2** (PMM2), the enzyme that catalyzes the conversion of mannose-6-phosphate into mannose-1-phosphate. The majority of CDGs have an autosomal recessive inheritance. Only two *N*-linked CDGs are autosomal dominant: GANAB-CDG and PRKCSH-CDG. The dominantly inherited *O*-linked CDGs include EXT1-CDG, H63ST-CDG, and POFUT1-CDG. Some CDGs have both an autosomal dominant and recessive phenotype such as EXT2-CDG, POGLUT1-CDG, GNE-CDG, DHDDS-CDG, NUS1-CDG, COG4-CDG, and SEC23B-CDG. X-linked CDGs include ALG13-CDG, MAGT1-CDG, SSR4-CDG, HS6ST2-CDG, OGT-CDG, PIGA-CDG, SLC35A2-CDG, TRAPPC2-CDG, VMA21-CDG, ATP6AP2-CDG, ATP6AP1-CDG, and SLC9A7-CDG.

CDGs can be lethal, with 20% of PMM2-CDG patients dying in the first 2 years of life. Some patients, however, stabilize throughout



Fig. 107.8 Patients with phosphomannomutase-2 deficiency (PMM2-CDG) and recognizable clinical features. **A,** Inverted nipples. **B** and **C,** Abnormal fat distribution. **D,** Muscle atrophy caused by peripheral neuropathy after puberty. **E,** Characteristic facial features with strabismus, short nose, anteverted nares, long philtrum, and large ears. **F,** T1-weighted sagittal MRI of the brain showing cerebellar vermis hypoplasia *(arrow)* and brain atrophy.

young adulthood. Almost any clinical phenotype can be present in a patient with CDG. It can affect any organ or organ system and most often includes the CNS. The most **common clinical features** include developmental and speech delay, seizures, ataxia, spasticity, peripheral neuropathy, hypotonia, strabismus, abnormal fat distribution, visual loss, cardiomyopathy, feeding difficulties, liver dysfunction, endocrine abnormalities, bleeding diathesis, and thrombosis (Fig. 107.8 and Table 107.6). Single-organ presentations are rare in CDGs, although some do exist, including TUSC3-CDG and ST3GAL3-CDG: brain; DHDDS-CDG: retina; ALG14-CDG: neuromuscular junction; POFUT1-CDG and POGLUT1-CDG: skin; SEC23B-CDG: red cell lineage; EXT1/EXT2-CDG: cartilage; and TMEM199-CDG: liver. Many CDGs are recognizable syndromes. *CDG should be considered in any patient with a developmental disability or an unexplained clinical condition, especially in multisystem disease with neurologic involvement.*

There are also **congenital disorders of deglycosylation**, including known lysosomal disorders and a severe neurologic condition caused by a defective *N*-glycanase function (*NGLY1* defect).

Laboratory evaluations in most *N*-linked CDGs rely on transferrin glycoform analysis in serum or plasma. A common screening method is called serum **transferrin isoelectric focusing (TIEF)**. Transferrin isoforms, which are hyposialylated (missing terminal sialic acid residues), show different cathodal shifts depending on either missing glycan chains or truncated glycans. A **type 1 pattern** suggests an early metabolic defect in the cytosolic-ER–related glycan synthesis and assembly. A **type 2 pattern** suggests Golgi-related glycan-processing defects (Fig. 107.9). **Isoelectric focusing of apolipoprotein C-III (IEF apoC-III)**, a serum mucine type *O*-glycosylated protein, can detect some *O*-glycosylation disorders (combined *N*- and *O*-linked glycosylation defects). **Mass spectrometry of intact (glycosylated) transferrin in serum** is highly sensitive for mild type 1 glycosylation abnormalities and diagnostic in most CDGs affecting N-glycosylation. Mass spectrometry of apoC-III is useful specifically in type II CDG. Glycomics by **matrix-assisted laser desorption/ionization time of flight (MALDI-TOF)** can be diagnostic in specific types of CDG (mostly Golgi related with a type 2 pattern). Dolichol-linked glycan or lipid-linked oligosaccharide (LLO) analysis is a complicated but sensitive method to detect ER-related N-glycan assembly (CDG type 1) defects in patient fibroblasts. GPI-anchor defects can be suspected based on *recurrent elevation of alkaline phosphatase levels* in blood.

Table 107.6 Clinical and Laboratory Features in Common Congenital Disorders of Glycosylation (CDGs), with Clinically Recognizable Phenotype and Abnormal Glycosylation, Detectable by Serum Transferrin Isoform Analysis (TIEF)

DEFECTIVE GENE	MOST FREQUENT CLINICAL FEATURES	SUGGESTIVE FEATURES	LABORATORY ABNORMALITIES	OTHER BIOCHEMICAL ANOMALIES
PMM2	Strabismus, nystagmus, smooth philtrum, large ears, vomiting, diarrhea, FTT, axial hypotonia, cerebellar vermis hypoplasia, ataxia, psychomotor disability, seizures, spasticity, neuropathy, pigmentary retinitis	Inverted nipples and/or abnormal fat pads, strokelike episodes	Elevated serum transaminases; hypoalbuminemia, decreased factor IX, XI, and AT activity; low serum ceruloplasmin and TBG levels	Type 1 serum TIEF, decreased PMM activity in leukocytes and fibroblasts
MPI	Cholestasis, hepatomegaly, feeding difficulties, recurrent vomiting, chronic diarrhea, ascites, recurrent thrombosis, gastrointestinal bleeding	Hyperinsulinism, protein-losing enteropathy Normal intelligence and absence of neurologic features	Elevated transaminases; hypoalbuminemia; hypoglycemia; decreased factor IX, XI, and AT-III activity	Type 1 serum TIEF, decreased PMI activity in leukocytes and fibroblasts
ALG6	Hypotonia, muscle weakness, seizures, ataxia, intellectual disability, behavioral abnormalities	Distal limb malformations	Elevated serum transaminases; hypoalbuminemia; decreased factor IX, XI, and AT activity; low serum IgG level	Type 1 serum TIEF, abnormal LLO results in fibroblasts
DPAGT1	Microcephaly, brain malformations, hypotonia, severe psychomotor disability, seizures, spasticity, proximal weakness, failure to thrive, joint contractures	Congenital myasthenia phenotype In multisystem phenotype: cataract	Decreased AT, protein C, and protein S activity; increased creatine kinase; hypoalbuminemia; normal creatine kinase in myasthenia	Type 1 serum TIEF
SRD5A3	Developmental delay, hypotonia, ataxia, cerebellar vermis hypoplasia, intellectual disability, speech delay, visual loss	Congenital cataract, retinal and iridic coloboma, glaucoma, optic nerve dysplasia, ichthyosis	Low anticoagulation factors (AT, protein C, and protein S activity), increased serum transaminases	Type 1 serum TIEF but reported false-negative TIEF
ATP6V0A2 *ATP6V1A* and *ATP6V1E1*	Generalized cutis laxa, hypotonia, strabismus, characteristic facial features, joint laxity, seizures, motor and language developmental delay, spontaneous improvement of cutis laxa by aging	Cobblestone-like brain dysgenesis Cardiovascular anomalies	Mild coagulation abnormalities, increased serum transaminase levels Mild coagulation abnormalities and increased serum transaminase levels, hypercholesterolemia	Type 2 serum TIEF but reported false-negative TIEF Abnormal apoC-III IEF, characteristic MALDI TOF profile (Note abnormal skin histology)
PGM1	Pierre Robin sequence, cholestasis, short stature, dilated cardiomyopathy	Cleft palate, hyperinsulinism, normal intelligence	Hypoglycemia, increased serum transaminase levels, decreased AT	Mixed type 1/ serum TIEF, decreased fibroblast PGM1 activity
MAN1B1	Developmental delay, speech delay, intellectual disability, muscle weakness	Obesity, autistic features, inverted nipples, characteristic face	Increased serum transaminase levels, low AT	Type 2 serum TIEF, abnormal apoC-III IEF, diagnostic MALDI TOF profile
TMEM199 *CCDC115* *ATP6AP1* and *ATP6AP2*	Cholestasis, hepatomegaly, liver steatosis, liver fibrosis, liver failure, spontaneous bleedings, motor developmental delay	Normal intelligence Hepatomegaly Immune deficiency	Decreased serum ceruloplasmin, increased serum transaminase levels, hypercholesterolemia, high AP	Type 2 serum TIEF, abnormal apoC-III IEF, characteristic MALDI TOF profile
SLC39A8	Seizures, hypsarrhythmia, hypotonia, developmental and speech delay, FTT	Dwarfism, craniosynostosis, rhizomelia, Leigh disease	Decreased serum manganese, high serum transaminases, abnormal coagulation	Type 2 serum TIEF, abnormal apoC-III, characteristic MALDI TOF profile

AP, Alkaline phosphatase; AT, antithrombin; apoC-III: apolipoprotein C-III; FTT, failure to thrive; LLO, lipid-linked oligosaccharides; MALDI-TOF, matrix-assisted laser desorption/ionization time of flight; TBG, thyroxine-binding globulin; TIEF, transferrin isoelectric focusing.

Fluorescence-activated cell sorting (FACS) analysis of the membrane-anchored markers CD16 and CD24 in leukocytes is highly suggestive for a GPI-anchor abnormality, especially when alkaline phosphatase in the blood is significantly elevated. **Enzyme analysis** in blood is only available for a few, more common CDGs (PMM2-CDG, MPI-CDG, PGM1-CDG); it is more reliable in fibroblasts. Dystroglycanopathies can be confirmed based on abnormal immunohistochemistry in a **muscle biopsy**.

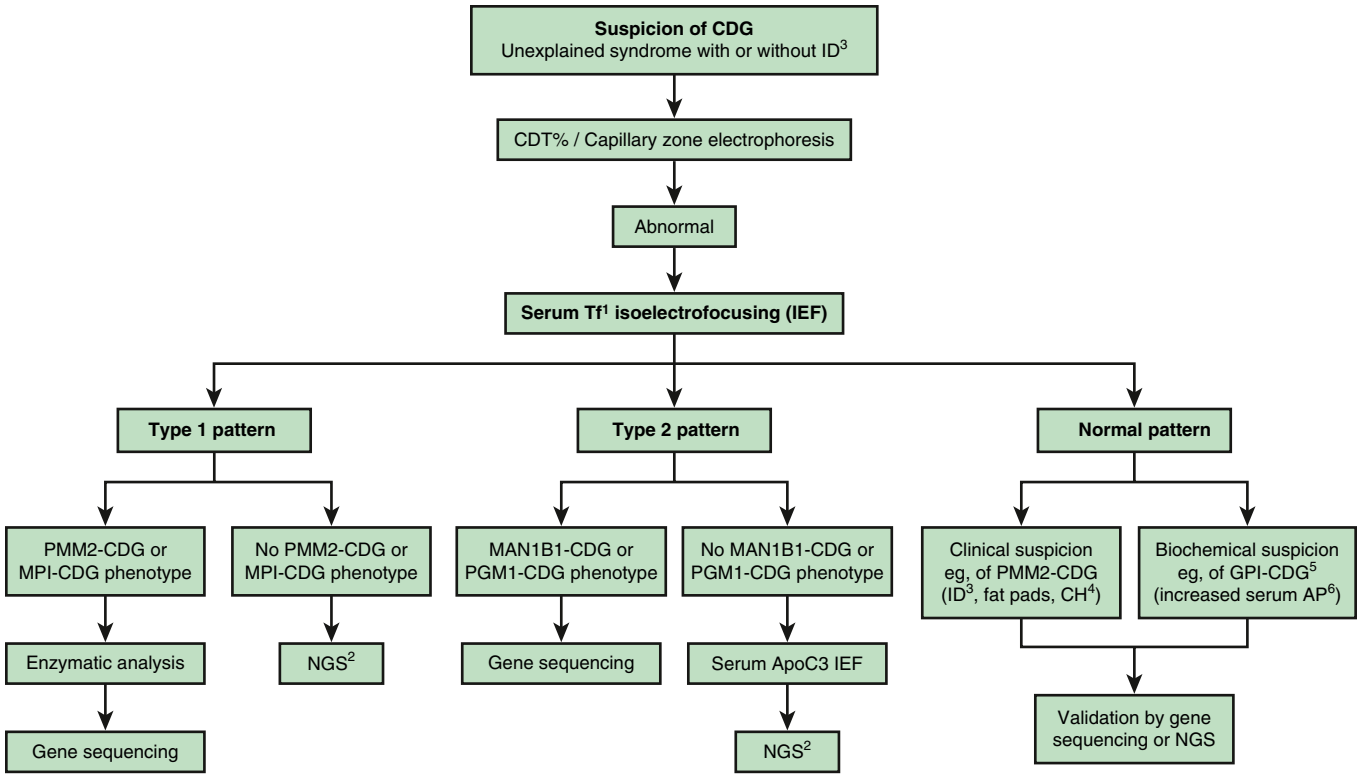

Fig. 107.9 CDG diagnosis algorithm. [1]Transferrin; [2]Next-generation sequencing (CDG panel analysis, WES, WGS); [3]Intellectual disability; [4]Cerebellar hypoplasia; [5]Glycosylphosphatidylinositol anchor synthesis defect; [6]Alkaline phosphatase. ID, intellectual disability; WES, whole exome sequencing; WGS, whole genome sequencing. *(From Quelhas D, Martins E, Azevedo L, et al. Congenital disorders of glycosylation in Portugal – two decades of experience. J Pediatr. 2021;231:148–156.)*

With an abnormal TIEF pattern result or clinical suspicion of any type of CDG, most metabolic centers use a direct **CDG gene panel analysis** or **NGS** (whole exome sequencing) (see Fig. 107.9).

CONGENITAL DISORDERS OF PROTEIN N-GLYCOSYLATION

Phosphomannomutase-2 Deficiency (PMM2-CDG)

Clinical Manifestations

PMM2-CDG is the most common and easily recognizable CDG. Over 900 patients have been identified with an estimated incidence of 1:20,000-1:80,000. Most patients have alternating strabismus, characteristic facial features (short nose, long philtrum, large ears) (see Fig. 107.8E), inverted nipples and/or abnormal fat pads (see Fig. 107.8A-C), feeding difficulties, axial hypotonia, and decreased reflexes already in the first few months of life. Nystagmus (caused by pontocerebellar and vermis hypoplasia; see Fig. 107.8F) is also common. Psychomotor disability is present in most patients, but normal intellectual development has been described in a few patients. Most patients develop a **multisystem disease**, and <25% show an isolated neurologic phenotype without other organ involvement, normal endocrine regulation, and no coagulopathy. The **neurologic involvement** is quite diverse, with ataxia, seizures, spasticity, and peripheral neuropathy (see Fig. 107.8D) the most common features. Dystonia, strokelike episodes, and proximal myopathy can also occur. PMM2-CDG is not a progressive disease, but certain features, when present, typically appear at a different age during the disease. From birth, pericardial fluid collection, cardiomyopathy, or chronic vomiting/diarrhea can occur; after the age of 7 years, retinitis pigmentosa and cataracts; and after puberty, scoliosis, neuropathy, and recurrent thrombotic events. Liver function anomalies are mild and usually improve by age, and only a few patients develop cholestasis or liver fibrosis. Most patients have a hypergonadotropic hypogonadism; no successful pregnancies have been reported. Intellectual disability can be mild to severe; speech development is frequently delayed and can even be absent. Autistic behavior is common, although most patients have a cheerful personality. The oldest patient is 72 years old.

Pathophysiology

PMM2 catalyzes the conversion of mannose-6-phosphate to mannose-1-phosphate and is essential for the formation of activated mannose units used in the synthesis of the growing glycan chain in the ER. Hypoglycosylation leads to abnormal function affecting many essential glycoproteins, such as coagulation and anticoagulation factors; endocrine regulation; transport proteins; liver function; and immune, membrane, and receptor proteins.

Diagnosis

The primary screening method for PMM2-CDG is **serum transferrin glycoform analysis**, which is most frequently performed by TIEF or mass spectrometry. Intact transferrin has four negatively charged sialic acid residues (tetrasialotransferrin). Transferrin glycoforms, missing terminal sialic acid residues, show different cathodal shifts, less abundant tetrasialotransferrin, increased disialotransferrin, and some a-sialotransferrin. This is the so-called type 1 pattern, suggestive of a defect in glycan assembly in the cytosol-ER. Transferrin isoforms are detectable by mass spectrometry, which is a more reliable diagnostic method compared with TIEF. Certain other disorders can cause a *false-positive* transferrin isoform pattern, including galactosemia, hereditary fructose intolerance, and excessive alcohol use. PMM enzyme analysis is available in leukocytes and fibroblasts.

The presence of elevated serum transaminases, hypoalbuminemia, decreased factor IX and XI and antithrombin activity, or low ceruloplasmin or TBG level is highly suggestive of CDG, including the most common type, PMM2-CDG.

PMM2-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The most frequent pathogenic variant (c.422G>A; R141H) is present in 75% of White patients. Prenatal diagnosis is only reliable by genetic testing.

Treatment

The therapy in PMM2-CDG relies on supportive treatment. Even with the best treatment, mortality is about 20% in the first 2 years of life, mostly from cardiac or kidney involvement and severe infections. Recommended therapy includes adequate nutrition, diet or tube feeding if needed, cardiac support, hormone supplements, physical and occupational therapy, speech therapy, seizure management, and strabismus surgery. Treatment with acetazolamide (7-17 mg/kg/day) resulted in improvement of ataxia and a decrease in disease severity (measured by the Nijmegen Pediatric CDG rating scale). This is likely mediated by the function of the glycosylated CaV2.1 channel. Possible dehydration, changes in plasma pH, and bicarbonate levels (renal tubular acidosis) need to be monitored throughout therapy.

Therapeutic developments include targeted (liposomal) mannose-phosphate treatment, drug repurposing, and chaperone therapy; these are only in early trial phases.

Mannosephosphoisomerase Deficiency (MPI-CDG)

Clinical Manifestations

MPI deficiency is a recognizable and treatable CDG. Approximately 35 patients have been published. Most patients show early symptoms of **liver disease** (cholestasis, elevated transaminases) and feeding difficulties, with recurrent vomiting and chronic diarrhea, most frequently with **protein-losing enteropathy**. Life-threatening episodes might appear as early as the first few months of life with recurrent thrombosis and severe gastrointestinal bleeding because of severe coagulation abnormalities. Hypoglycemia is usually caused by hyperinsulinism. Hypoalbuminemia can be severe; patients might develop visible abdominal distention from a combination of ascites and hepatomegaly. Patients with MPI-CDG have no other organ involvement, and the CNS is not affected. There are no dysmorphic features. The liver disease frequently progresses to fibrosis or cirrhosis.

Pathophysiology

Mannosephosphoisomerase (MPI) catalyzes the conversion of fructose-6-phosphate to mannose-6-phosphate, one step before PMM2, therefore blocking the formation of activated mannose units (GDP mannose) for oligosaccharide synthesis. Hypoglycosylation leads to abnormal glycoprotein function, the same as in PMM2-CDG, especially coagulation and anticoagulation factors, liver function, and hormone receptors.

Diagnosis

The primary screening method in a suspected MPI-CDG patient is **serum transferrin isoform analysis** by mass spectrometry or screening by TIEF (see Fig. 107.9). MPI deficiency leads to a type 1 pattern, as seen in PMM2 deficiency. MPI enzyme analysis is available in leukocytes and fibroblasts. The presence of elevated serum transaminases, hypoalbuminemia, decreased factor IX and XI and antithrombin activity, hyperinsulinism, and nonketotic hypoglycemia are highly suggestive for MPI-CDG.

MPI-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence of MPI-CDG is not known, but it is estimated at 1 in 800,000 in Europe. Prenatal diagnosis is only reliable by genetic testing. Although this is a rare CDG, early diagnosis is imperative because it is treatable.

Treatment

MPI-CDG is the first CDG type treatable by dietary therapy (Table 107.7). Mannose therapy is clinically effective by both IV and oral supplementation. The dose of oral mannose is 150-170 mg/kg/dose for four or five doses per day (maximum dosing 600-1200 mg/kg/day and maximum of six doses per day). IV mannose should be used only in life-threatening conditions when oral intake is not possible. The maximum dose of IV mannose is 1 g/kg/day as a continuous infusion, combined with IV glucose to prevent hypoglycemia. A known side effect is hemolysis. The treatment uses an alternative pathway: mannose can be phosphorylated by hexokinases to mannose 6-phosphate, bypassing the MPI defect. The clinical symptoms improve rapidly, but liver function may further deteriorate. Liver fibrosis and cirrhosis may necessitate liver transplantation, which will resolve the metabolic disease. The oldest patient known with MPI-CDG has survived into their late 30s.

Glucosyltransferase-1 Deficiency (ALG6-CDG)

Clinical Manifestations

ALG6-CDG is the second most common CDG. Most patients have hypotonia, muscle weakness, seizures, and ataxia. No patient with ALG6-CDG has been reported with normal intelligence. Speech delay and nystagmus are common neurologic signs. Brachydactyly, skeletal abnormalities, and transverse limb defects have been observed. Strabismus and characteristic facial dysmorphism are rare (hypertelorism, oval face, short nose). Inverted nipples and/or abnormal fat pads are exceptional in ALG6-CDG.

The most severe ALG6-CDG patients show a multisystem phenotype in the first few months of life, including severe infections, protein-losing enteropathy, hypoalbuminemia, anemia, and failure to thrive. Autistic behavior and mood changes have been observed in several patients. The oldest patient to date is almost 50 years old.

Pathophysiology

The metabolic problem is caused by defective binding of the first of three glucoses to the lipid-linked oligosaccharide in the ER. This glucose binding is essential for attachment of the oligosaccharyltransferase enzyme complex to the newly built oligosaccharide chain and the ability to transfer it to the protein. This leads to protein hypoglycosylation and abnormal glycoprotein function similar to PMM2-CDG and MPI-CDG. Laboratory abnormalities are also similar, including abnormalities in coagulation and anticoagulation factors, liver function, thyroid hormones, and immunoglobulins (IgGs).

Diagnosis

The primary screening method in a suspected ALG6-CDG patient is **serum transferrin glycoform analysis** by mass spectroscopy or TIEF analysis. ALG6 deficiency leads to a type 1 pattern (see Fig. 107.9), as seen in PMM2 and MPI deficiency. There is no available enzyme analysis, although LLOs could be evaluated in patient fibroblasts.

ALG6-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The most common pathogenic variants are p.A333V and p.I299Del. Prenatal diagnosis is only reliable by genetic testing. The exact incidence of ALG6-CDG is not known.

Treatment

The current therapy in ALG6-CDG relies on supportive treatment. Mortality is about 10% in the first years of life, mostly from protein-losing enteropathy and severe infections.

UDP-GlcNAc:Dol-P-GlcNAc-P Transferase Deficiency (DPAGT1-CDG)

Clinical Manifestations

DPAGT1 deficiency is a recognizable and potentially treatable CDG. About one third of patients show the **congenital myasthenia**

Table 107.7 Effective Therapies in CDG

CDG	TREATMENT	RECOMMENDED DOSE	CLINICAL EFFECTS	SIDE EFFECTS
MPI-CDG	Mannose	600-1200 mg/kg BW/day in 4-6 oral doses	Improvement of digestive symptoms (13/14), coagulopathy (12/12), and hypoglycemia (9/9); no long-term effect on liver symptoms	Abdominal pain and diarrhea (5/10; responding to dose adjustment)
PGM1-CDG	Galactose	1 g/kg/day (500-2500 mg/kg/day; max 50 g/day), divided in up to 6 oral doses per day	Improvement of hepatopathy (15/18), muscle symptoms (14/14), coagulopathy (10/12), hypoglycemia (10/13), and pubertal delay (2/2); minimal effect on growth (1/8), ID (0/2), and cardiologic symptoms (0/2)	Not reported
SLC35C2-CDG	Galactose	1.5 g/kg/day (up to 3 g/kg/day), divided in up to 5 oral doses per day	Improvement of psychomotor development (5/10), growth (n.s.), gastrointestinal symptoms (n.s.), and seizures (3/5)	Not reported
SLC35C1-CDG	Fucose	400 mg/kg/day (up to 1.2 g/kg/day in severe cases), divided into 2-3 oral doses per day	Normalization of neutrophil count (5/5), decreased incidence of severe infections (3/3), improvement of psychomotor development (1/5), no effect on adult form of the disease (ID, ataxia, epilepsy, autism)	Autoimmune neutropenia and hemolysis (responding to dose adjustment)
CAD-CDG	Uridine	100 mg/kg/day in 4 oral doses	Cessation of pharmacoresistant seizures (3/3), significant developmental progress (3/3), resolution of anemia (2/2), and anisopoikilocytosis (3/3)	Not reported
SLC39A8-CDG	Manganese	15-20 mg $MnSO_4$/kg BW/day in 5 oral doses	Improvement of glycosylation (2/2), motor abilities (2/2), epilepsy (1/1), ataxia (1/1), and hearing (1/1)	Not reported, risk of manganism
	Galactose	500-3750 mg/kg BW/day in 5 oral doses	Improvement of glycosylation (2/2), no clinical improvement reported	Not reported
TMEM165-CDG	Galactose	1000 mg/kg/day orally	Improvement of glycosylation (2/2), hepatopathy (2/2), coagulopathy (2/2), and IGF1 levels (2/2) (clinical improvement not mentioned)	Not reported
GFPT1-CDG	Pyridostigmine (cholinesterase inhibitors)	2.5-15 mg/kg/day in 3 oral doses	Improvement of muscle weakness (52/56)	Muscle twitching, depression, and anxiety (2/56)
ALG2-CDG	Pyridostigmine (cholinesterase inhibitors)	Oral, dose n.s.	Improvement of muscle weakness (1/1)	Not reported
ALG14-CDG	Pyridostigmine (cholinesterase inhibitors)	5-8 mg/kg/day in 2-6 oral doses	Improvement of muscle weakness (4/4, in 1 patient the effect was only temporary)	Not reported
PIGM-CDG	Sodium butyrate	60-90 mg/kg/day in 3 oral doses	Effect on seizures (3/3), developmental delay (2/2), and increase in the expression of GPI-linked blood cell surface markers (2/4)	Not reported
PMM2-CDG	Acetazolamide	7-17 mg/kg/day in 2 oral doses	Effect on cerebellar symptoms (20/23), speech (20/23), anxiety (20/23), some coagulation parameters (20/23), stereotypic movements (5/5), and SLE (1/1). No improvement of ID and non-neurologic symptoms.	Acidosis with significant decrease of serum bicarbonate (9/23), asthenia (4/23), and paresthesia (2/23) responding to dose adjustments; risk of urolithiasis, osteopenia

BW, Body weight; GPI, glycosylphosphatidylinositol; ID, intellectual disability; IGF1, insulin-like growth factor 1; n.s., not specified; SLE, strokelike episodes.
Modified from Ondruskova N, Cechova A, Hansikova H, et al. Congenital disorders of glycosylation: still "hot" in 2020. *Biochim Biophys Acta Gen Subj*. 2021;1865(1):129751, Table 2.

phenotype, indistinguishable from other genetic congenital myasthenias. CK levels are normal. These patients have a relatively good prognosis, especially with early myasthenia therapy. The other patients show a multisystem phenotype with microcephaly, brain malformations, hypotonia, severe psychomotor disability, seizures, spasticity, failure to thrive, joint contractures, and cataracts.

Pathophysiology

The DPAGT1 defect leads to very early arrest of glycan synthesis outside the ER membrane by slowing the addition of the second GlcNAc sugar to the phosphorylated dolichol arm. Abnormal receptor glycosylation in the *neuromuscular junction* leads to myasthenia. Hypoglycosylation in the multisystem type leads to

abnormal glycoprotein function similar to PMM2-CDG, especially involving the anticoagulation factors, and interestingly leading to high serum CK (in contrast to the congenital myasthenia phenotype) and hypoalbuminemia.

Diagnosis

The primary screening method is **serum transferrin glycoform analysis** by mass spectroscopy or TIEF analysis. Most patients show a type 1 pattern (see Fig. 107.9), but patients with the congenital myasthenia phenotype can show normal screening. There is no clinically available enzyme analysis.

DPAGT1-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence is not known. Prenatal diagnosis is only reliable by genetic testing. Because of the false-negative TIEF results in several patients with the myasthenic phenotype, congenital myasthenia panel testing is suggested in suspected cases, especially for determining the potential therapy.

Treatment

The congenital myasthenia phenotype is frequently treatable by high-dose pyridostigmine, eventually enhanced with salbutamol and a potassium channel blocker (amifampridine). In the multisystem phenotype of DPAGT1-CDG, treatment is supportive.

CONGENITAL DISORDERS OF PROTEIN *O*-GLYCOSYLATION

Cerebro-Ocular Dysplasia–Muscular Dystrophy and Muscle-Eye-Brain Disease Spectrum (POMT1-CDG, POMT2-CDG, POMGNT1-CDG)

From isolated muscular dystrophy to **Walker Warburg syndrome**, this group of *O*-linked glycosylation disorders presents with severe muscle weakness, congenital eye malformations, and neuronal migration defects. Pachygyria, cobblestone dysgenesis, hydrocephalus, polymicrogyria, heterotopias, and corpus callosum agenesis are variably present. Eye malformations include anophthalmia, microphthalmia, congenital cataract, or colobomas. **Congenital muscular dystrophy** is associated with significant CK elevations. There is severe psychomotor disability.

The underlying metabolic defect is the abnormal synthesis of the *O*-mannosylglycan core, which is essential for the proper glycosylation of α-dystroglycan. The α-dystroglycan is heavily *O*-glycosylated with mannose residues and is expressed in both muscle and brain. Defective mannosylation of α-dystroglycan leads to muscle degeneration and migration defects. Muscle biopsy shows abnormal α-dystroglycan staining on immunohistochemistry.

Transferrin glycoform analysis, including TIEF, is normal in patients with isolated *O*-mannosylation defects. There is also no clinically available enzyme analysis. **Diagnosis** is based on histology (muscle biopsy) and genetic analysis.

POMT1-CDG, POMT2-CDG, and POMGNT1-CDG are the most common autosomal recessive α-dystroglycanopathies. Additional gene defects occur in the pathway; *POMK, FKTN, FKRP, LARGE, B3GALNT2, B4GAT1, DAG1, TMEM5,* and *ISPD* have been described in association with human disease. The exact incidence of α-dystroglycanopathies is not known.

The treatment for α-dystroglycanopathies is supportive.

DEFECTS IN LIPID GLYCOSYLATION AND IN GLYCOSYLPHOSPHATIDYLINOSITOL ANCHOR BIOSYNTHESIS

Hyperphosphatasia–Intellectual Disability Syndromes: PIGA Deficiency (PIGA-CDG)

This clinically recognizable syndrome is an epilepsy syndrome with intellectual disability, hypotonia, dysmorphic facial features, skin anomalies, congenital brain malformations, and behavioral abnormalities, including autism. Other organ malformations, including cardiac and renal defects, have also been reported. *Somatic* pathogenic variants with a *PIGA* defect can also lead to paroxysmal nocturnal hemoglobinuria.

N-acetylglucosamine (GlcNAc) cannot be efficiently transferred to phosphatidylinositol for glycophosphatidylinositol synthesis. Abnormal anchoring of alkaline phosphatase leads to hyperphosphatasemia in the blood and loss of specific surface antigens on blood cells.

Transferrin isoform analysis is normal in GPI-anchor defects. FACS analysis demonstrating reduction of membrane-anchored markers CD16 and CD24 in leukocytes is highly suggestive for a GPI-anchor abnormality, especially in association with increased levels of serum alkaline phosphatase. Pathogenic variant analysis confirms the defect.

PIGA-CDG is X-linked. The exact incidence is not known. A similar phenotype has been described in *PIGO, PIGV, PIGY, PIG, PGAP2,* and *PGAP3* defects.

In PIGA-CDG the treatment is supportive.

DEFECTS IN MULTIPLE GLYCOSYLATION PATHWAYS AND IN OTHER PATHWAYS, INCLUDING DOLICHOLPHOSPHATE BIOSYNTHESIS DEFECTS

Steroid 5α-Reductase Deficiency (SRD5A3-CDG)

Clinical Manifestations

SRD5A3 deficiency is a clinically recognizable CDG, originally described as a **multiple-congenital malformation syndrome**. About 20 patients have been diagnosed at different ages, including one at 45 years of age. Patients have hypotonia, ataxia, and eye abnormalities, including congenital cataracts, retinal and iridic colobomas, glaucoma, optic nerve dysplasia, and visual loss. Cerebellar vermis hypoplasia can be variable. Intellectual disability has been described in all affected patients thus far. About 30% of patients have severe *congenital ichthyosis*. Hypertrichosis and dysmorphic facial features are common, including squared face, high forehead, large ears, and coarsening. Some children with SRD5A3-CDG have a severe autism spectrum disorder. Skeletal abnormalities (scoliosis) and cardiac malformations are less common.

Pathophysiology

SRD5A3 deficiency leads to abnormal dolichol synthesis affecting early glycan synthesis outside the ER membrane and affects *O*-mannosylation and GPI-anchor synthesis. Hypoglycosylation affects anticoagulation factors and leads to increased serum transaminases.

Diagnosis

The primary screening method in a suspected SRD5A3-CDG patient is **serum transferrin glycoform analysis or mass spectroscopy analysis**. Most patients show a type 1 pattern (see Fig. 107.9), but several false-negative cases have been described. There is no clinically available enzyme analysis.

SRD5A3-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence is not known. SRD5A3-CDG treatment is supportive.

Autosomal Recessive Cutis Laxa Type 2 (ARCL-2A or ATP6V0A2-CDG, ATP6V1A-CDG and ATP6V1E1-CDG)

Clinical Manifestations

ATP6V02-CDG is a multiple-malformation syndrome originally described as *cutis laxa syndrome* and recently discovered to be a combined *N*- and *O*-linked glycosylation disorder. Patients show generalized cutis laxa with inelastic, sagging skin at birth, hypotonia, strabismus, myopia, characteristic facial features, and joint laxity. The facial features include hypertelorism, short nose, long philtrum, downslanting palpebral fissures with sagging eyelids, and sagging cheeks. Cardiovascular involvement is rare, and there is variable CNS involvement. Seizures and motor and language

developmental disability are common, but normal intelligence has been described as well. Sensorineural hearing loss is sometimes observed. Some patients have vermis hypoplasia, and several children have been described with cobblestone-like dysgenesis and partial pachygyria on brain MRI. Skeletal abnormalities and short stature are common, as are late-closing fontanels and/or brachydactyly and scoliosis. There is frequently enamel dysplasia. The skin features spontaneously improve with age. **ATP6V1A-CDG** and **ATP6V1E1-CDG** show a highly overlapping phenotype with associated cardiovascular symptoms and hypercholesterolemia.

Pathophysiology

ATP6V0A2 is a membrane subunit of the proton pump of the vesicular adenosine triphosphatase (V-ATPase) complex. Abnormal function of the V-ATPase complex alters the pH gradient in the secretory pathway and affects the maturation and transport of several glycosyltransferases and elastic fibers (e.g., elastin). ATP6V1A and ATP6V1E1 are other complex subunits affecting ATP6V0A2 function and cause secondary ATPase deficiency. Both *N*- and *O*-linked glycosylation are affected. There are mild coagulation abnormalities and high serum transaminase levels in some patients.

Diagnosis

The primary screening method in a suspected ATP6V0A2-CDG patient is **serum transferrin glycoform analysis** by mass spectroscopy or TIEF analysis. Most patients show a type 2 pattern (see Fig. 107.9), but false-negative cases have been described before the age of 6 weeks. **Apolipoprotein III-C** (apoC-III) is a mucin-type secretory glycoprotein that is only *O*-glycosylated. ApoC-III TIEF shows a hypoglycosylation pattern by mass spectroscopy in patients, even when the TIEF is falsely negative. Skin biopsies in patients show classic histologic changes of cutis laxa with diminished, short, abnormal, and fuzzy elastic fibers.

ATP6V0A2-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence is not known. *ATP6V1A* and *ATP6V1E1* defects have been recently described.

Treatment

In autosomal recessive cutis laxa type 2, the treatment is supportive. Fortunately, there is continuous and spontaneous improvement of skin symptoms throughout the disease course, especially in ATP6V0A2-CDG.

Golgi-$\alpha_{1\text{-}2}$ Mannosidase-1 Deficiency (MAN1B1-CDG)

Clinical Manifestations

The *MAN1B1* defect was originally described as an intellectual disability syndrome in association with dysmorphic features. Additional patients were recognized with psychomotor disability, muscle hypotonia, and inverted nipples in association with truncal obesity. The degree of intellectual disability is quite variable. Autistic behaviors, eating disorders, and aggressive behavior are frequent features. More than 30 patients have been reported.

Pathophysiology

MAN1B1 codes for a Golgi mannosidase, which is essential for the final "trimming" of mannose units during the glycan processing in the Golgi apparatus. Hypermannosylation leads to abnormal, truncated glycans and CDG-II. The glycosylation abnormality in serum is relatively mild. Increased serum transaminases and abnormal coagulation are uncommon.

Diagnosis

Most patients show a mild type 2 pattern by TIEF, but false-negative cases have been described. MALDI-TOF analysis shows characteristic, hybrid glycans in serum. In suspected cases, direct sequence analysis is recommended, even if the TIEF is normal.

MAN1B1-CDG is autosomal recessive. The exact incidence is unknown; several adult patients are known.

Treatment

Only supportive treatment is available.

Phosphoglucomutase-1 Deficiency (PGM1-CDG)

Clinical Manifestations

PGM1-CDG is a disorder presenting with midline malformations (cleft palate, Pierre Robin sequence, bifid uvula), liver dysfunction, hypoglycemia, and short stature in almost all patients. *Hypoglycemia* is usually caused by hyperinsulinism in the first years of life. It can resolve with aging; ketotic hypoglycemia has also been observed. Cholestasis, liver fibrosis, and even cirrhosis have been described in a few patients. About one third of patients also show proximal muscle weakness and dilated cardiomyopathy; the latter led to mortality in at least seven reported cases. Other malformations, including cardiac and skeletal anomalies, have also been described. Wound healing is frequently abnormal, and there is a very high risk for bleeding during surgery. Intelligence is normal.

Pathophysiology

Phosphoglucomutase 1 (PGM1) is an essential enzyme for glycogenolysis and glycolysis. It also provides substrates for the nucleotide sugars needed for normal glycosylation. PGM1 regulates the bidirectional conversion of glucose-1-phosphate and glucose-6-phosphate. During fasting it leads to a glycogenosis-like phenotype (also called GSD XIV, MIM 614921). PGM1-CDG affects both the ER- and Golgi-related glycosylation and causes a mixed type 1/type 2 hypoglycosylation pattern. Abnormal serum proteins include coagulation and anticoagulation factors, insulin-like growth factor–binding protein 3 (IGFBP3), TBG, and TSH, in addition to serum transaminases, hypoglycemia, and elevated CK.

Diagnosis

The primary screening method in a suspected PGM1-CDG patient is **serum transferrin glycoform analysis** or mass spectroscopy analysis. Patients show a mixed type 1/type 2 pattern.

PGM1-CDG is autosomal recessive. It is among the relatively common CDGs; >40 patients have been described. Enzyme testing is possible in blood but is more reliable in fibroblasts. Direct sequencing is available for testing.

Treatment

PGM1-CDG is a treatable CDG (see Table 107.1). D-Galactose replenishes depleted levels of different nucleotide-sugars (galactose-1-phosphate, UDP-galactose, and UDP-glucose). Adding 1 g/kg/day D-galactose (500–2500 mg/kg/day, maximum 50 g/day, divided in up to six doses/day) to the diet improves glycosylation significantly after a few weeks, although the transferrin glycoform pattern does not fully normalize. This treatment improves liver transaminases and antithrombin levels and in some patients the hormonal status. The effect of D-galactose on hypoglycemic episodes, cardiomyopathy, and myopathy is not yet clear.

Disorders of Golgi Homeostasis: TMEM199-CDG, CCDC115-CDG, ATP6AP2-CDG, and ATP6AP1-CDG

Clinical Manifestations

These four disorders are clinically and biochemically indistinguishable. They have been described with liver function anomalies, cholestasis, fibrosis, and cirrhosis with liver failure, necessitating liver transplantation in a few patients. The phenotype resembles **Wilson disease**, especially because of low serum ceruloplasmin and copper levels, but there is no Kayser-Fleischer ring. In CCDC115-CDG there are frequently also neurologic features. The intellectual outcome is variable. Additional abnormalities include hypercholesterolemia

and elevated alkaline phosphatase. In ATP6AP1-CDG there is also immunologic involvement.

Pathophysiology
TMEM199-, CCDC115-, ATP6AP1-CDG, and ATP6AP2-CDG are important for Golgi homeostasis. The exact pathologic mechanism is not yet known, but it is hypothesized that the secondary Golgi dysfunction affects and delays the normal glycosylation process.

Diagnosis
The primary screening method in a patient with one of these suspected CDGs is serum transferrin glycoform analysis by mass spectroscopy or TIEF analysis. Patients show a type 2 pattern (see Fig. 107.9). ApoC-III TIEF is abnormal. Glycomics results by MALDI-TOF analysis are characteristic but cannot discriminate between the three defects. The final diagnosis requires pathogenic variant analysis. TMEM199-CDG and CCDC115-CDG are autosomal recessive, whereas ATP6AP1-CDG and ATP6AP2-CDG are X-linked.

Treatment
Treatment is supportive. Two patients successfully underwent liver transplantation.

Manganese Transporter Defect: SLC39A8-CDG
Clinical Manifestations
This intriguing disorder was originally described as a neurologic disease with hypotonia, seizures (hypsarrhythmia), and developmental disability. Some of the later-described patients had severe skeletal dysplasia with rhizomelic chondrodysplasia, craniosynostosis, and dwarfism. Mitochondrial dysfunction (Leigh disease, cerebral lactic acidemia, dystonia) may also be present.

Pathophysiology
SLC39A8 is a membrane transporter, responsible for manganese (Mn) transmembrane transport. SLC39A8 deficiency affects all Mn-dependent enzymes and therefore different parts of the metabolism. Because several glycosyltransferases (e.g., β-1,4-galactosyltransferase) are Mn dependent, a secondary Golgi glycosylation occurs with a type 2 glycosylation defect. Low serum Mn levels are suggestive but not always present in patients.

Diagnosis
The primary screening method in a suspected patient with SLC39A8-CDG is **serum transferrin glycoform analysis** by mass spectroscopy or TIEF analysis. Patients show a type 2 pattern (see Fig. 107.9). MALDI-TOF analysis is suggestive but not discriminative. Low serum Mn levels are not always present in patients. The final diagnosis requires pathogenic variant analysis. SLC39A8-CDG is an autosomal recessive disease. The exact incidence for this rare disease is unknown.

Treatment
Besides supportive treatment, a few patients have shown biochemical and clinical improvement (better seizure control) with oral D-galactose (1-3.75 g/kg/day) and manganese (II)-sulfate monohydrate (15-20 mg/kg/day) therapy (see Table 107.7).

CONGENITAL DISORDERS OF DEGLYCOSYLATION
N-Glycanase 1 Deficiency (*NGLY1* Defect)
Clinical Manifestations
Patients with NGLY1 deficiency have a glycosylation disorder, but not from the deficient synthesis; rather, it is caused by deficient breakdown of glycoproteins. The phenotype comprises severe CNS involvement, microcephaly, intellectual disability, seizures, neuropathy, movement disorders, and hypotonia. The presence of *alacrimia* or hypolacrimia is highly suggestive for the diagnosis, but not all patients have problems with tearing. Other features include failure to thrive, IUGR, and liver involvement. Some patients have a recognizable oval face with a short nose, flat profile, and hypertelorism. Masklike face also occurs, imitating the phenotype of mitochondrial disorders, especially when serum lactic acid levels are also elevated.

Pathophysiology
N-glycanase is responsible for the deglycosylation of misfolded *N*-linked glycoproteins. The enzyme is essential for cutting off the glycans before the proteins are degraded in the ER. The exact disease pathomechanism, however, is not yet clear. Serum transaminase and α-fetoprotein levels are also frequently increased.

Diagnosis
Serum transferrin isoform analysis shows a normal pattern. In some patients the excretion of a specific urine biomarker (aspartylglucosamine; Neu5Ac1Hex1GlcNAc1-Asn) is present and can be used as screening. The final diagnosis requires genetic analysis.

NGLY1-CDG is an autosomal recessive disease. The most common pathogenic variant is c.1201A>T/p.R401X. The exact incidence of the condition is unknown, but >50 patients have been reported in the few years since the discovery of the disease.

Treatment
Only supportive treatment is available for the patient with NGLY1 deficiency.

THERAPEUTIC SUMMARY (SEE TABLE 107.7)
Most CDGs are treatable only with supportive therapy. The initially discovered oral mannose treatment in MPI-CDG (1 g/kg/day) has proved to be efficient for coagulation problems and protein-losing enteropathy but cannot prevent liver fibrosis in all patients. Liver transplantation in MPI-CDG has been successful in a few patients. Oral D-galactose in PGM1-CDG (1g/kg/day) can improve serum transaminases and coagulation and have a positive effect on endocrine function but cannot restore glycosylation fully. Seizure frequency improved in patients with SLC39A8-CDG receiving oral D-galactose treatment (1 g/kg/day) and oral manganese intake. The congenital myasthenic syndrome in DPAGT1-CDG, GFPT1-CDG, and GMPPB-CDG has been successfully treated with a high dose of cholinesterase inhibitors. Several CDGs have been positively controlled by transplantation, including DOLK-CDG (DK1-CDG; heart transplantation), PGM3-CDG (hematopoietic stem cell transplantation), ATP6AP1-CDG, and CCDC155-CDG (liver transplantation).

Patients with CAD-CDG show significant clinical improvement on receiving oral uridine therapy, especially with seizure control. Two children with SLC35C1-CDG–defective immune function improved on oral fucose therapy. GNE-CDG patients showed significant improvement in muscle strength on *N*-acetylmannosamine therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 108

Mitochondrial Disease Diagnosis

Elizabeth M. McCormick and Marni J. Falk

See also Chapters 107.4, 638.2.

Mitochondrial diseases are multisystemic energy failure states with extensive clinical and genetic heterogeneity. Their common basis is best understood through recognition that mitochondria function as biologic "fuel cells" or "batteries," producing chemical energy in the form of adenosine triphosphate (ATP) by aerobic metabolism of nutrient-derived reducing equivalents, through the integrated function of the five-complex mitochondrial respiratory chain (RC) (Fig. 108.1). Mitochondria also play other essential roles that can be variably disrupted in disease states, such as regulating calcium homeostasis, diverse aspects of intermediary nutrient metabolism, nucleotide metabolism, and oxidative stress. Primary mitochondrial disease results from deficient RC function, which can be caused by pathogenic variants in genes that encode RC subunits, assembly factors or cofactors, components of mitochondrial DNA (mtDNA) metabolism and maintenance, or a host of other basic metabolic processes ongoing within mitochondria (Table 108.1). Approximately 1,500 proteins exist within the mitochondrial proteome of different tissues, with variants in more than 350 unique genes across both the nuclear and the mitochondrial genomes already implicated as causal in human mitochondrial disease.

Collectively recognized as the most common group of inherited metabolic diseases, **primary** (genetic based) mitochondrial disease has a combined minimal prevalence of 1 in 4,300 individuals across all ages. In addition, **secondary** mitochondrial dysfunction is broadly implicated in the pathogenesis of a host of complex diseases, ranging from metabolic syndrome to ischemia-reperfusion injury after stroke, to neurodegenerative diseases. Failure of high-energy-demand organs in mitochondrial diseases may clinically present as severe neurodevelopmental, cardiac, myopathic, renal, hepatic, endocrine, immune, gastrointestinal (GI), hearing, and vision disabilities, as well as global metabolic instability with lactic acidosis (Fig. 108.2) (see Tables 107.2 and 107.3). In most mitochondrial disorders, the phenotype may vary depending on the patient's age, the specific gene or genetic variant, or tissue affected. Particularly common mitochondrial disease clinical syndromes that present in children

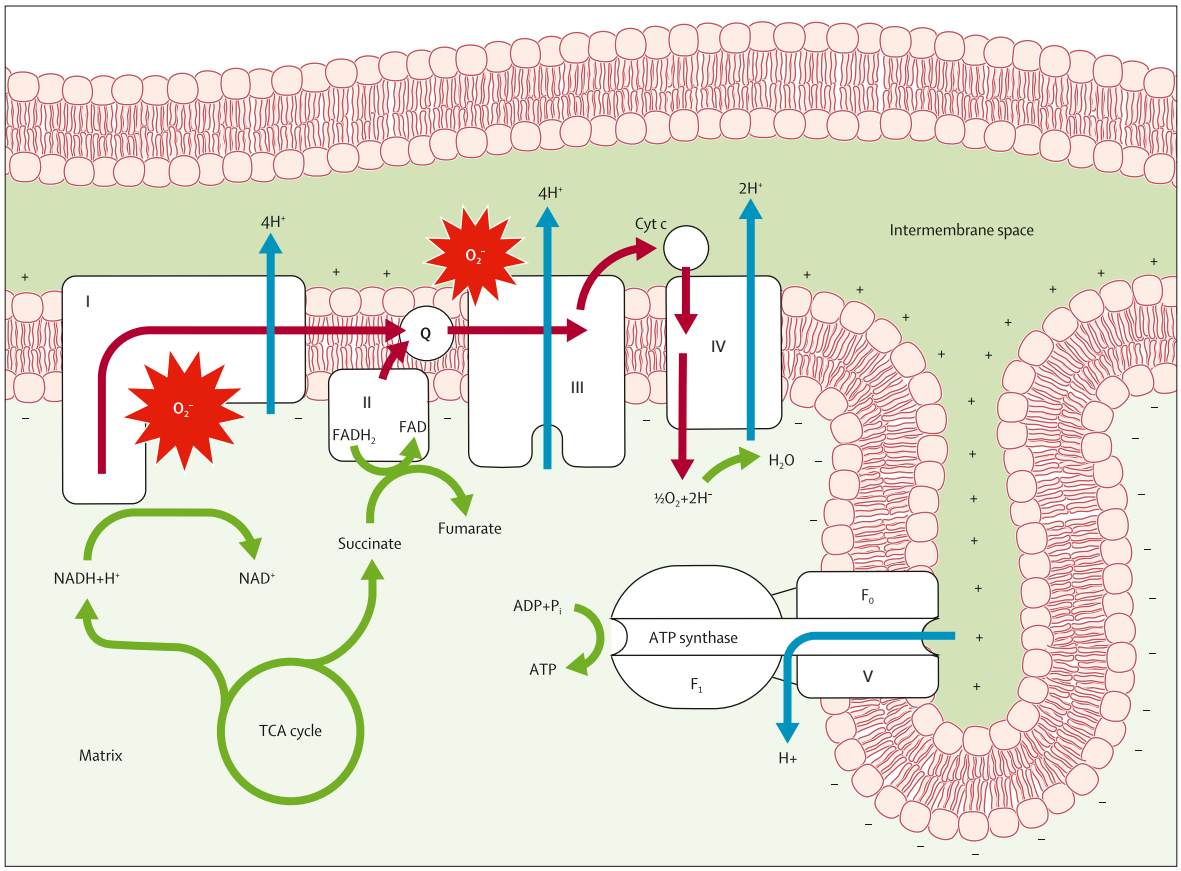

Fig. 108.1 Electron transport chain. The electron transport chain consists of four protein complexes (I-IV) coupled to a fifth (V) unlinked complex, ATP synthase. Together, these five complexes are known as the respiratory chain and are the site where oxidative phosphorylation (OXPHOS) occurs to generate energy. The transport chain accepts electrons from NADH (complex I) or $FADH_2$ (complex II) that have been produced by glycolysis, the formation of acetyl–coenzyme A, and the TCA cycle *(green arrows)*. Electrons flow from one complex to another *(red arrows)* because of the redox potential of each complex and lose a small amount of energy as they move through the chain. Three of the four complexes act as pumps, driven by electron flow, moving H^+ ions from the matrix to the intermembrane space *(blue arrows)*. This pumping builds a concentration gradient and creates an electrochemical force that is used by ATP synthase to produce ATP. Under normal conditions, this machinery provides almost all (90%) of the ATP in a cell. However, a small proportion of electrons escape the electron transport chain even under normal conditions and can react with oxygen and complexes I and III to form superoxide (O_2^-). ADP, Adenosine diphosphate; ATP, adenosine triphosphate; Cyt c, cytochrome *c*; Q, coenzyme Q; NADH, nicotinamide dinucleotide; Pi, inorganic phosphate; TCA, tricarboxylic acid cycle; FADH2, 1,5-dihydro-flavin adenine dinucleotide. (*Adapted from Hagberg H, Mallard C, Rousset CI, Thornton C. Mitochondria: hub of injury responses in the developing brain. Lancet Neurol. 2014;13[2]:217–232.*)

Table 108.1 Current Mitochondrial Gene Defects and Pathomechanisms

	GENE(S)
OXIDATIVE PHOSPHORYLATION DEFICIENCY	
Complex I subunits and assembly factors	*NDUFA1, NDUFA2, NDUFA6, NDUFA9, NDUFA10, NDUFA11, NDUFA12, NDUFA13 NDUFB3, NDUFB8, NDUFB9, NDUFB10, NDUFB11, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF7, NDUFAF8, ACAD9, ECSIT, FOXRED1, NUBPL, TIMMDC1, TMEM126B, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6*
Complex II subunits and assembly factors	*SDHA, SDHB, SDHC, SDHD, SDHAF1, SDHAF2*
Complex III subunits and assembly factors	*UQCRB, UQCRC2, UQCRFS1, UQCRQ, CYC1, BCS1L, HCCS, TTC19, LYRM7, UQCC2, UQCC3, MT-CYB*
Complex IV subunits and assembly factors	*COX4I1, COX4I2, COX5A, COX6A1, COX6B1, COX7B, COX8A, NDUFA4, SURF1, SCO1, SCO2, COX10, COX15, COA3, COA5, COA6, COA7, COX14, COX20, FASTKD2, PET100, PET117, CEP89, MT-CO1, MT-CO2, MT-CO3*
Complex V subunits and assembly factors	*ATP5A1, ATP5D, ATP5E, ATPAF2, TMEM70, USMG5, MT-ATP6, MT-ATP8*
DISORDERS OF MITOCHONDRIAL DNA MAINTENANCE	
Nucleotide pool maintenance	*ABAT, AK2, DGUOK, RRM2B, SAMHD1, SUCLA2, SUCLG1, TK2, TYMP*
Replication, maintenance, and transcription of mtDNA	*DNA2, FBXL4, MGME1, MPV17, POLG, POLG2, SSBP1, SLC25A4, TWNK*
MITOCHONDRIAL TRANSLATION DEFECTS	
Mitochondrial tRNAs	*MT-TA, MT-TC, MT-TD, MT-TD, MT-TE, MT-TF, MT-TG, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TL2, MT-TM, MT-TN, MT-TP, MT-TQ, MT-TR, MT-TS, MT-TT, MT-TV, MT-TW, MT-TY*
Mitochondrial aminoacyl-tRNA synthetases	*AARS2, CARS2, DARS, DARS2, EARS2, FARS2, GARS, HARS2, IARS, IARS2, KARS, LARS, LARS2, MARS2, NARS2, PARS2, QARS, RARS2, SARS2, TARS2, VARS2, WARS2, YARS2*
tRNA modification	*ELAC2, MTFMT, NSUN3, PDE12, QRSL1, TRIT1, TRMT5, TRMT10C, TRNT1*
Mitochondrial rRNA	*MT-RNR1, MT-RNR2*
RNA processing	*PNPT1*
Mitoribosome subunits and assembly	*ERAL1, MRPL3, MRPL12, MRPL44, MRPS2, MRPS7, MRPS16, MRPS22, MRPS23, MRPS34, MRM2, RMND1*
Protein synthesis	*C12orf65, GFM1, GFM2, GTPBP3, GUF1, LRPPRC, MTO1, MTPAP, PUS1, TACO1, TRMU, TSFM, TUFM*
MITOCHONDRIAL QUALITY CONTROL DEFECTS	
Mitochondrial membrane phospholipid and import machinery	*AGK, CHKB, DNAJC19, GFER, MIPEP, PAM16, PLA2G6, PMPCA, SERAC1, SLC25A3, SLC25A10, SLC25A12, SLC25A22, TAZ, TIMM8A, TIMM50, XPNPEP3*
Mitochondrial dynamics	*DNM1L, GDAP1, MFF, MFN2, MSTO1, OPA1, STAT2, TRAK1, YME1L1*
MICOS complex	*CHCHD10, QIL1, SLC25A46*
ER-mitochondrial tethering	*EMC1*
Mitochondrial protein quality control	*AFG3L2, ATAD3A, CLPB, CLPP, CLPX, HSPA9, HSPD1, HSPE1, LONP1, PITRM1, SACS, SPG7, TRAP1*
Toxicity	*ECHS1, ETHE1, HIBCH*
Antioxidant defense	*NNT, TXN2*
METABOLIC DEFECTS	
Tricarboxylic acid cycle enzymes	*ACO2, DHTKD1, FH, IDH3A, IDH3B, MDH2, OGDH*
Pyruvate metabolism	*DLAT, DLD, MPC1, PC, PDHA1, PDHB, PDHX, PDK3, PDP1, PDPR*
Fatty acid metabolism	*CRAT, ETFA, ETFB, ETFDH, FA2H, HSD17B10, PYCR1, SLC25A1*
CoA metabolism and transport	*COASY, PANK2, SLC25A42*
VITAMIN AND COFACTOR METABOLISM DEFECTS	
Coenzyme Q_{10} biosynthesis	*COQ2, COQ4, COQ5, COQ6, COQ7, COQ8A, COQ8B, COQ9, PDSS1, PDSS2*
Iron-sulfur cluster protein biosynthesis	*ABCB7, FDXR, FDX1L, FXN, ISCA1, ISCA2, ISCU, LYRM4, NFS1, NFU1*
Lipoic acid biosynthesis	*BOLA3, GLRX5, IBA57, LIAS, LIPT1, LIPT2, MECR*
Cytochrome *c*	*CYCS*
Biotin metabolism	*BTD, HLCS*
Thiamine metabolism and transport	*SLC19A2, SLC19A3, SLC25A19, TPK1*
Mitochondrial one-carbon metabolism	*SLC25A26, SLC25A32*
Heavy metal metabolism	*SLC25A24, SLC33A1, SLC39A8*
Selenoprotein biosynthesis	*SECISBP2, SEPSECS*
NADPH metabolism	*NADK2, NAXD, NAXE*
Riboflavin metabolism and transport	*FLAD1, SLC52A2, SLC52A3*
OTHER CELLULAR DEFECTS ASSOCIATED WITH MITOCHONDRIAL DYSFUNCTION	
Ca^{2+} homeostasis	*ANO10, C19ORF70, CISD2, CYP24A1, MICU1, MICU2, WFS1*
Heme biosynthesis	*ABCB6, ALAS2, SFXN4, SLC25A38*
Apoptosis defects	*AIFM1, APOPT1, DIABLO, HTRA2, PTRH2*
DNA repair	*APTX, XRCC4*
Miscellaneous or unknown function	*ALDH1B1, ALDH18A1, BDH1, CA5A, CTBP1, C1QBP, C19ORF12, DCC, DIAPH1, FHF1, KIF5A, OPA3, PNPLA4, PNPLA8, POP1, PPA2, ROBO3, RTN4IP1, SLC44A1, STXBP1, TANGO2, TMEM65, TMEM126A*

mtDNA, Mitochondrial DNA; MICOS, mitochondrial contact site and cristae organizing system; ER, endoplasmic reticulum.
From Rahman J, Rahman S: Mitochondrial medicine in the omics era. *Lancet.* 2018;391:2560–2574, Table 1.

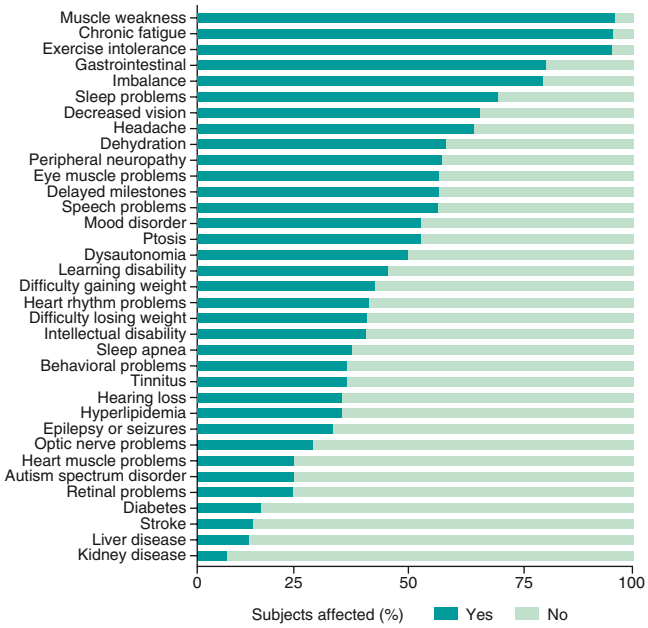

Fig. 108.2 Mitochondrial disease subject cohort experienced symptoms. Frequency of experienced symptoms as reported by the Rare Diseases Clinical Research Network (RDCRN) self-reported cohort revealed muscle weakness, chronic fatigue, exercise intolerance, imbalance, and gastrointestinal problems to be the top five common symptoms. (*Modified from Zolkipli-Cunningham Z, Xiao R, Stoddart A, et al. Mitochondrial disease patient motivations and barriers to participate in clinical trials. PLoS ONE. 2018;13[5]:e0197513. Fig. 2.*)

include **Leigh syndrome** (for which there are more than 110 causal genes; for gene listing visit https://search.clinicalgenome.org/kb/conditions/MONDO:0009723.), **mtDNA depletion syndrome** (MDS, for which there several dozen causal genes), **mtDNA deletion syndromes (Pearson**, **Kearns Sayre)**, primary lactic acidosis, and pyruvate dehydrogenase deficiency. Common clinical features in children present in at least 90% of patients include fatigue, exercise intolerance, weakness, GI and hepatic dysfunction, ataxia, and developmental delay. Thus mitochondrial diseases present to and must be considered by clinicians across every medical specialty.

Reversible infantile respiratory chain deficiency is an unusual mitochondrial disorder that presents in early (≤3 months) infancy with muscle weakness, hypotonia, poor feeding, and lactic acidosis and spontaneously resolves beginning around 1 year of age. Responsible maternal inherited genes include *mt-tRNAGlu (MT-TE)* (in 100%) and possible modifier genes *(EARS2, TRMU)*. Muscle biopsy may show ragged red fibers.

Patients with suspected mitochondrial disease often have an extensive phenotypic heterogeneity without a common biomarker, which presents a challenge to the accurate **clinical diagnosis** of mitochondrial disorders. Lactate and growth differentiation factor 15 (GDF-15) are screening tests that may be elevated in *some* mitochondrial diseases, particularly those involving mtDNA deletions or depletion. In addition, their extensive genetic heterogeneity involving known etiologies in >300 nuclear genes and all 37 mtDNA genes can make the accurate **genetic diagnosis** of an individual patient challenging. The diagnostic uncertainty can be further compounded by poor genotype-phenotype correlations and variable clinical presentations of individual gene disorders, high locus heterogeneity (i.e., multiple different causal disease genes) for similar clinical phenotypes, incomplete penetrance for some gene disorders, variable life stressors or environmental exposures that may exacerbate a given child's disease, and the unique biologic aspects of maternal inheritance for the subset of mitochondrial diseases caused by mtDNA pathogenic variants.

WHEN TO SUSPECT MITOCHONDRIAL DISEASE

Because of failure in the ability to generate cellular energy, mitochondrial diseases can involve any organ system at any age (see Fig. 108.2). Mitochondrial disease should be suspected when classic symptoms are present or if unexplained symptoms occur in three or more apparently unrelated organs. Individuals may present with a vast array of symptoms, including fatigue, muscle weakness, exercise intolerance, metabolic strokes, seizures, cardiomyopathy, arrhythmias, developmental or cognitive disabilities, autism, diabetes mellitus, and other endocrinopathies (adrenal, thyroid), dysautonomia, and autoimmune disorders, as well as impairment of hearing, vision, growth, liver, GI, or kidney function. Although individuals may have just one or a few symptoms and a fluctuating disease course in terms of symptom severity, most patients with primary mitochondrial disease tend to develop *progressive* symptoms over time. A study of patients with mitochondrial diseases showed an average of 16 different clinically significant symptoms per patient, with a range of 7-35. When considering the diagnosis, it is helpful to recognize that most symptoms of mitochondrial disease involve *functional,* rather than structural, problems.

When mitochondrial disease is considered in the differential diagnosis, it is often helpful to obtain several **laboratory screening** studies for common biochemical features of mitochondrial disease and overlapping disorders at baseline and, if unrevealing, during an acute illness or period of decompensation. Blood-based metabolic screening studies include comprehensive chemistry panel, complete blood count with differential, blood lactate and pyruvate, plasma amino acid quantitative analysis, carnitine analysis (total, free, acyl-carnitine profile), ammonia, creatine kinase, and testing for common secondary manifestations of mitochondrial disease (e.g., thyroid screen, lipoprotein profile, hemoglobin A_{1c}). Urine-based metabolic screening studies include urinalysis, urine organic acid quantitative analysis, and urine amino acid quantitative analysis. Consideration should also be given for screening for congenital disorders of glycosylation or vitamin deficiencies, which may have overlapping clinical features in some cases with mitochondrial disease. Lactic acidemia is neither highly sensitive nor specific for primary mitochondrial disease, but laboratory findings suggestive of primary mitochondrial disease include elevations of blood lactate, pyruvate, lactate:pyruvate ratio, alanine, ratios of alanine to lysine (>3) and alanine to the sum of phenylalanine and tyrosine (>4), and anion gap. Biochemical alterations further suggestive of mitochondrial disease may include secondary impairment of fatty acid oxidation with elevation of dicarboxylic acids on acyl-carnitine profile, increased branched-chain amino acids and proline on plasma amino acid analysis, increased tricarboxylic acid cycle intermediates and lactate excretion on urine organic acid analysis, and generalized aminoaciduria on urine amino acid analysis. **GDF-15** may be a useful screening test for mitochondrial depletion-based myopathies.

Similarly, when mitochondrial disease is considered in the differential diagnosis, obtaining additional **clinical evaluations** to carefully phenotype the patient for prevalent or highly morbid and potentially modifiable features of mitochondrial disease is important. Because many individuals with mitochondrial disease develop problems with their *vision* (reduced visual acuity not correctable with glasses, photophobia or nyctalopia with reduced peripheral vision associated with retinal disease or optic atrophy, ophthalmoplegia, ptosis), *hearing* (high-frequency sensorineural hearing loss), and *heart* (arrhythmia, conduction block, cardiomyopathy), carefully evaluating for involvement of these high-energy systems is indicated. **Neurologic** evaluation is essential because many mitochondrial disease patients experience a range of *central* (metabolic stroke in cortical or deep gray matter, including basal ganglia, midbrain, and/or brainstem; white matter changes; seizures; ataxia; movement disorder; migraine; cognitive changes), *peripheral* (axonal sensorimotor neuropathy), or *autonomic* nervous system dysfunction; brain imaging (MRI), spectroscopy (MRS), and, on occasion, electromyogram or nerve conduction velocity (EMG/NCV) studies can be helpful to support the diagnosis. Formal **exercise physiology** evaluation can also be useful to quantify and advise patients on their exercise capacity and safety, with some specific features (e.g., reduced Vo_2 maximal capacity) suggestive of quantifiable mitochondrial dysfunction. A **sleep** study may be useful for individuals with sleep dysfunction because sleep disorders may mimic mitochondrial disease symptoms, and sleep problems are common and potentially treatable in mitochondrial disease. **Gastrointestinal** symptoms are common and underrecognized in mitochondrial disease patients, usually involving dysmotility of any portion of the GI tract with reflux, swallowing dysfunction, delayed gastric emptying,

feeding and/or growth problems, pseudoobstruction, malabsorption, and constipation. **Endocrine** abnormalities are also common but underappreciated in many patients, including pituitary, adrenal, thyroid, and pancreatic dysfunction.

Such careful phenotyping of patients with suspected mitochondrial disease can thus provide reassurance that the common, and potentially treatable, clinical aspects of mitochondrial disease are not present although they may develop over time, or conversely if identified, increase diagnostic suspicion and direct further diagnostic evaluation. A screening tool for mitochondrial diseases is noted in Table 108.2. The differential diagnosis of mitochondrial disorders is extensive (Table 108.3).

MITOCHONDRIAL DISEASE INHERITANCE

Primary mitochondrial disease may result from variants in either nuclear genes or mtDNA genes, which may be inherited from a parent or occur de novo in an affected individual (for a list of genes curated for their association with primary mitochondrial disease, visit https://search.clinicalgenome.org/kb/affiliate/10027). Thus all *mendelian* (autosomal recessive, autosomal dominant, X-linked) or *maternal* (mtDNA) inheritance patterns can be consistent with mitochondrial diseases. Obtaining a detailed, three-generation pedigree is important to potentially highlight the specific inheritance pattern in a family. Individuals with inherited mtDNA disorders may report family members related through their **maternal** lineage (both males and females may be affected, but only affected individuals will be connected through the female germline), with a range of functional problems in different organs, such as migraines, fatigue, exercise intolerance, stroke, diabetes mellitus, thyroid dysfunction, irritable bowel syndrome, mood disorder, or vision and hearing problems (for a list of curated mtDNA variants, visit https://erepo.clinicalgenome.org). Inherited **X-linked** disorders typically present with symptoms only or, more severely, in males related through unaffected or minimally affected females. **Autosomal recessive** disorders are common in pediatric mitochondrial disease, particularly in consanguineous pedigrees, where a rare variant in the general population becomes enriched and passed down through both maternal and paternal lineages to become homozygous in the affected proband and also affect multiple individuals in a given generation without having affected individuals in earlier generations. **Autosomal dominant** variants may occur de novo or are passed on from either parent to their child, although many disorders may have reduced penetrance, which may make the genetic disorder appear to skip a generation. Identifying a likely inheritance pattern through pedigree analysis can inform accurate interpretation of large-scale genetic diagnostic evaluations, such as multigene sequencing and deletion/duplication analysis panels and exome or genome sequencing. Establishing a correct genetic diagnosis for mitochondrial disease in an affected individual is essential to enable reliable recurrence risk counseling and testing options in a given family, whether in a future pregnancy by chorionic villus sampling (CVS, typically performed at 10-12 weeks' gestation) or amniocentesis (typically performed at 16-20 weeks' gestation) or in the in vitro fertilization (IVF) setting with preimplantation genetic testing (PGT) for a specific disease-causing variant. Of note, PGT is readily available to families for known nuclear gene disorders but remains of limited availability in known pathogenic mtDNA variants.

Special mention is warranted to consider the unique aspects of *maternal inheritance* that typify mtDNA disorders. More than 300 disease-causing mtDNA variants have been identified, with extensive variation in disease manifestations and features. Most disease-causing variants are present in only a portion of an individual's mtDNA genomes, a concept known as **heteroplasmy**. For heteroplasmic mtDNA variants, the precise pathogenic variant level (percent) can vary between an individual's different tissues and can change over time, with symptom severity corresponding to different threshold pathogenic variant levels that can be difficult to define and that typically vary between organs. An individual's mtDNA genome background set of fixed sequence variants, known as a **haplogroup**, can also influence the penetrance or severity of an mtDNA disease. When a novel or rare mtDNA variant is identified in a given individual, it may be helpful to use highly sensitive sequencing methods to test the levels of that pathogenic variant (which may be accurate to detect 1% of pathogenic variant levels) in their different tissues (blood, urine, buccal, skin cells, muscle), as well as tissues from their mother or maternal relatives, to accurately determine whether it may be causal of disease in that family. Research-based functional testing may also be necessary to characterize fully the effects of a newly recognized mtDNA variant. When it is not known whether an mtDNA variant is maternally inherited or occurs de novo, the recurrence risk to future offspring of their asymptomatic parent is empirically estimated at 1 in 25 (4%), although the empirical recurrence risk rises to 1 in 2 (50%) when the mother is symptomatic.

Table 108.2 Mitochondrial Disease Criteria

	FEATURES	
Muscular	Myopathy Abnormal EMG Motor developmental delay Exercise intolerance	Maximal score for muscle is 2
Neurologic	Developmental delay or ID Speech delay Dystonia Ataxia Spasticity Neuropathy Seizures or encephalopathy	Maximal score for neurologic is 2
Multisystem	Any gastrointestinal tract disease Growth delay or failure to thrive Endocrine Immune Eye (vision) or hearing Renal tubular acidosis Cardiomyopathy	Maximal score for multisystem is 3
Total clinical		**Total maximal clinical score is 4**
Metabolic	Lactate high at least 2×: (score 2) Alanine high at least 2× Krebs cycle intermediates[a] Ethyl malonic and methyl malonic acid 3 methyl glutaconic acid CSF lactate, alanine	
Imaging/other	Leigh disease (score 2) Strokelike episodes (score 2) Lactate peak on MRS Leukoencephalopathy with brainstem and spinal cord involvement[b] Cavitating leukoencephalopathy[b] Leukoencephalopathy with thalamus involvement[b] Deep cerebral white matter involvement and corpus callosum agenesis[b]	Total metabolic and MRI maximal score is 4
Total MDC score (clinical, metabolic, imaging)		**Total maximal score is 8**

[a]Krebs cycle intermediates: alpha-ketoglutarate, succinate, fumarate.

[b]Numerous MRI patterns characteristic of mitochondrial disease have been described in addition to Leigh syndrome and basal ganglia with brainstem involvement. We include leukoencephalopathy with brainstem and spinal cord involvement *(DARS2)*, cavitating leukoencephalopathy *(LYRM7)*, leukoencephalopathy with thalamus involvement *(EARS2)*, and deep cerebral white matter involvement and corpus callosum agenesis *(NUBPL)*.

Every element scores 1 unless indicated differently. The severity of each finding is not taken into account because of the progressive nature of the disease. A total score of 1 indicates unlikely mitochondrial disorder; score 2–4, possible mitochondrial disorder; score 5–7, probable mitochondrial disorder; and score ≥8, definite mitochondrial disorder.

COX, Cytochrome c oxidase; EMG, electromyography; L/P, lactate/pyruvate; SDH, succinate dehydrogenase.

From Witters P, Saada A, Honzik T, et al. Revisiting mitochondrial diagnostic criteria in the new era of genomics. *Genetics Med.* 2018;20(4):444–451, Table 2.

Table 108.3 Differential Diagnosis of Selected Phenotypes Commonly Associated with Mitochondrial Disease

PHENOTYPE	MITOCHONDRIAL CAUSE	LIMITED DIFFERENTIAL DIAGNOSIS
Dystonia	Leigh syndrome, deafness-dystonia syndrome, other mitochondrial encephalomyopathies	Biotinidase deficiency, thiamine transporter deficiency 2, *ADAR* pathogenic variants (Aicardi-Goutières syndrome 6), organic acidemias (especially glutaric aciduria type I), NBIA, acute (viral) necrotizing encephalopathy, pathogenic variants in *NUP62, RANBP2,* and *PDE8B*, primary genetic dystonias
Epileptic encephalopathy	Alpers-Huttenlocher syndrome, many other mitochondrial disorders	Many genetic epileptic encephalopathies, including Dravet syndrome and *KCNQ2* pathogenic variants, pyridoxine-dependent epilepsies (antiquitin deficiency, PNPO deficiency), viral encephalitis
Progressive myoclonic epilepsy	MERRF	Ramsay Hunt syndrome, Unverricht-Lundborg disease, Lafora body disease, sialidosis, *PRICKLE1* pathogenic variants
Leukoencephalopathy	Complex I deficiency, complex II deficiency, SURF1 deficiency (rarely), disorders of mitochondrial translation and Fe-S cluster assembly	Vanishing white matter disease, lysosomal storage disorders, Canavan disease, Alexander disease, Pelizaeus-Merzbacher(-like), hypo/dysmyelination
Ataxia	*ADCK3* pathogenic variants, ataxia-neuropathy syndromes, for example, SCAE, MIRAS, MERRF, NARP, disorders of coenzyme Q_{10} biosynthesis	Spinocerebellar ataxias, CAPOS syndrome
Demyelination	MNGIE	ADEM, multiple sclerosis
Peripheral neuropathy	Pathogenic variants in *POLG, MPV17, KARS,* and *SURF1*; part of multisystem disease in many mitochondrial disorders, for example, MNGIE	Other nonmitochondrial genetic causes of Charcot-Marie-Tooth syndromes, riboflavin transporter deficiency, toxic neuropathies, critical illness
Ptosis and ophthalmoplegia	PEO, KSS, MNGIE, MELAS	Some congenital myopathies, pseudo-upgaze impairment in *OPMD,* horizontal gaze palsy and scoliosis (*ROBO3* pathogenic variant)
Optic neuropathy	LHON, ADOA, Leigh syndrome	Toxic optic neuropathy (e.g., methanol, cyanide, tobacco)
Hypertrophic cardiomyopathy with lactic acidosis	Complex I deficiency, *TMEM70* pathogenic variants, Sengers syndrome (AGK deficiency), disorders of mitochondrial translation	Viral infection
Dilated cardiomyopathy with lactic acidosis	Barth syndrome, disorders of mitochondrial phospholipid remodeling, other mitochondrial cardiomyopathies	Viral infection
Exocrine pancreatic insufficiency	Pearson syndrome	Cystic fibrosis
Diabetes and deafness	MIDD, other mtDNA pathogenic variants	Type 2 diabetes mellitus with incidental nonsyndromic deafness
Sideroblastic anemia	Pearson syndrome, MLASA, TRNT1 deficiency, *PUS1* or *YARS2* pathogenic variants	Blackfan-Diamond syndrome, Schwachman-Diamond syndrome, X-linked sideroblastic anemia
B-cell immune deficiency	TRNT1 deficiency	Primary immunodeficiency disorder
Liver failure	Mitochondrial DNA (mtDNA) depletion syndromes	NBAS, LARS, and IARS deficiencies, viral infection, lysosomal storage disorders, other syndromic genetic conditions
Renal tubulopathy/failure	Pearson and Kearns-Sayre syndromes, *RMND1*-related disease	Gitelman syndrome, Fanconi Bickel (*SLC2A2* pathogenic variants) syndrome, other syndromic genetic conditions
Myopathy	Part of multisystem disease in many mitochondrial disorders, especially mtDNA depletion syndromes	Congenital muscular dystrophies, myositis, many other disorders
Rhabdomyolysis	Mitochondrial myopathies (e.g., *MTCO1, MTCO2, MTCO3,* and *MTCYB* pathogenic variants)	*LPIN1* pathogenic variants, fatty acid oxidation defects (VLCAD, LCHAD), TANGO deficiency, glycolytic defects, toxic, postexercise
Low copper	Cytochrome oxidase deficiency	Menkes, *SLC33A1* pathogenic variants
Complex multisystem disorders	Many mitochondrial disorders, particularly in childhood	Congenital disorders of glycosylation, peroxisomal disorders, lysosomal storage disorders, other syndromic genetic conditions

ADEM, Acute disseminated encephalomyelitis; ADOA, autosomal dominant optic atrophy; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss; Fe-S, iron-sulfur; KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MERRF, myoclonic epilepsy with ragged red fibers; MIDD, maternally inherited diabetes and deafness; MIRAS, mitochondrial recessive ataxia syndrome; MLASA, myopathy, lactic acidosis, sideroblastic anemia; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; NBIA, neurodegeneration with brain iron accumulation; PEO, progressive external ophthalmoplegia; SCAE, spinocerebellar ataxia with epilepsy.
Modified from Parikh S, Karaa A, Goldstein A, et al. Diagnosis of "possible" mitochondrial disease: an existential crisis. *J Med Genet.* 2019;56(3):123–130, Table 1.

DIAGNOSTIC TESTING FOR MITOCHONDRIAL DISEASE

The diagnosis of mitochondrial disease relies foremost on genetic testing (genomic analysis), with biochemical screens useful in blood or urine and invasive tissue testing often seen as secondary or sometimes not required at all (Fig. 108.3).

When the clinical evaluation—medical history; detailed review of systems; careful physical, neurologic, and dysmorphic examinations; pedigree review; blood- and urine-based biochemical screening studies; and additional phenotyping clinical evaluations—is suggestive of mitochondrial disease, a range of clinical diagnostic testing options can be pursued. Without a known molecular etiology in an affected family member, first-line genetic diagnostic testing should include whole exome sequencing (WES) and mtDNA genome sequencing using methodologies that will detect both single-nucleotide variants and larger-scale gene deletions and duplications. WES is more comprehensive for genes known not only to cause mitochondrial disease but also to cause all human genetic diseases. The rationale for this diagnostic testing approach includes the following factors:

- The mtDNA genome sequence is often included at no extra cost when clinical WES is ordered in blood or buccal samples but may need to be repeated in a symptomatic tissue (e.g., muscle, liver) to detect heteroplasmic mtDNA variants that may not be present in more accessible tissues such as blood or buccal cells.
- The utility of performing concurrent proband and both parental sample sequencing *(trio-based testing)*, as usually pursued with WES but not panel-based testing, thereby allowing concurrent segregation analysis of a suspected pathogenic variants as well as ready identification of de novo dominant variants in the proband.
- The ability to use WES raw data (either on a research basis or for reanalysis at a later date by the clinical diagnostic laboratory) to highlight and/or identify "novel" gene disorders not previously recognized or associated with human disease.

Exome sequencing including mtDNA is estimated to identify the definitive genetic etiology for mitochondrial disease in at least 60% of patients in whom it is strongly suspected. Whole genome sequencing (WGS) is increasingly used when routine molecular testing such as WES with mtDNA sequencing is unrevealing of the genetic etiology. A mitochondrial disease community resource to centrally curate all mitochondrial disease, gene, and variant knowledge across both genomes is publicly accessible at https://mseqdr.org/.

Tissue-based diagnostic testing has decreased in frequency as a front-line test in all patients with suspected mitochondrial disease, although it still has clinical utility. These include (1) in the setting of rapidly deteriorating clinical status when genetic testing results may not be available in a timely fashion; (2) when a variant of uncertain significance identified on genomic testing has unclear biochemical consequences; and (3) when uninformative genomic sequencing in blood in an individual with myopathy or muscle symptoms raises concern for other disease processes that may be evident on histology, electron microscopy, immunohistochemistry, or enzymatic tissue testing. In addition, some mitochondrial diseases are only evident by tissue-based diagnostic testing. These include mtDNA deletion disorders (typically involving several thousand nucleotides) not present in blood that cause **chronic progressive external ophthalmoplegia** (CPEO) or **Kearns-Sayre syndrome** (KSS) spectrum disorder, as well as different tissue (muscle or liver)-specific mtDNA depletion disorders (e.g., reduced mtDNA tissue content) that confirm a mitochondrial pathophysiology in a given patient and highlight a likely underlying nuclear gene cause for their disease, because mtDNA maintenance requires a host of nuclear-encoded proteins. **Electron transport chain enzyme** activity analyses are the accepted gold standard to evaluate for mitochondrial dysfunction in a previously frozen tissue sample. Skin biopsies are useful to establish fibroblast cell lines in which these same studies of mitochondrial function can be clinically performed. If detected, abnormalities can be revealing of a specific type of mitochondrial disorder, although not all mitochondrial diseases may be expressed or detectable in skin analysis. Thus if fibroblast testing is unrevealing, more invasive tissue studies may subsequently need to be pursued. RNA sequencing may lead to identification of the genetic etiology in an additional 10% of individuals with mitochondrial disease in

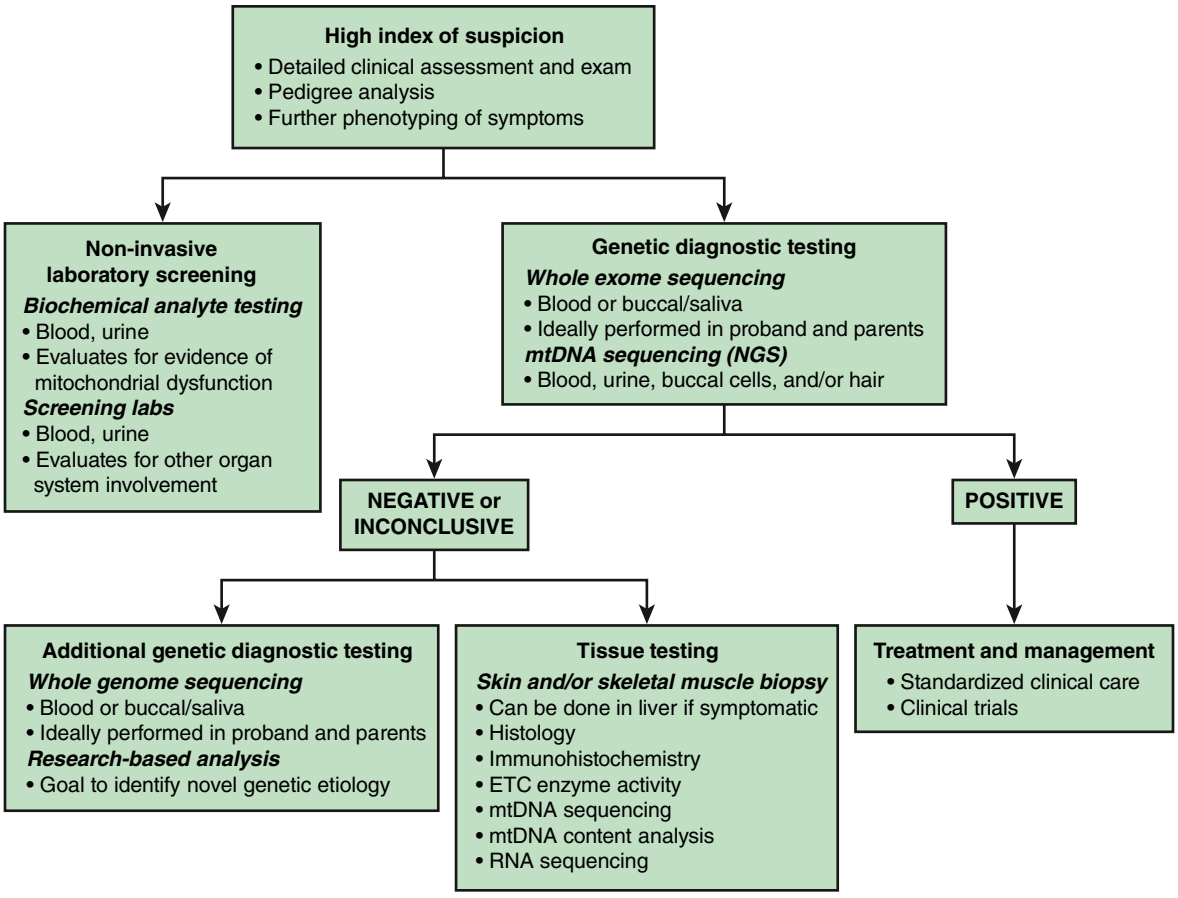

Fig. 108.3 Diagnostic algorithm for suspected mitochondrial disease. (*Modified from Murarescu CC, McCormick EM, Falk MJ. Mitochondrial disease: advances in clinical diagnosis, management, therapeutic development, and preventative strategies. Curr Genet Med Rep. 2018;6:62–72.*)

whom DNA-based sequencing did not identify the disease-causing variants. Only a small number of clinical laboratories offer this testing; this test can be performed in muscle, fibroblasts, or blood. Fibroblast cell lines, and occasionally blood-based lymphoblastoid cell lines, also provide a minimally invasive cell source to allow other clinical enzymatic analyses to be performed, as well as novel disease gene validation and research-based therapeutic modeling.

TREATMENT PRINCIPLES FOR MITOCHONDRIAL DISEASE

Effective therapies for both primary and secondary mitochondrial diseases are lacking. Clinical complexity and imprecisely defined or understood biochemical phenotypes of different mitochondrial disease subtypes have made it difficult for clinicians to effectively apply or monitor targeted therapies for RC disease. *Mitochondrial cocktails* consisting of combinatorial regimens of vitamins and supplements variably include vitamins (B_1, B_2, C), antioxidants (CoQ_{10}, lipoic acid, vitamin E, *N*-acetylcysteine), and metabolic modifiers (creatine, L-carnitine, L-arginine, folinic acid, taurine). Although the efficacy, toxicity, and optimal dose of these drugs are not known and have not been objectively assessed via clinical trials in human RC disease patients, they continue to be empirically prescribed in hopes of enhancing residual RC enzymatic function or quenching toxic metabolites theorized to accumulate in RC dysfunction and because of patient-based reports of improved well-being. However, provision of these therapies has often adopted a one-size-fits-all approach, ignoring the inherent variation in primary mitochondrial disease subtypes, the tissue-specific manifestations, and the major pathogenic factors, such as the predominant downstream metabolic and signaling alterations that occur in different disease subclasses (Fig. 108.4).

Although few mitochondrial diseases have efficacious therapies that have gained regulatory approval, improved molecular delineation has enabled selected therapies to advance from the theoretical, empirical, and largely ineffective stage to a promising horizon of rational, personalized, and effective interventions. An increasing number of mitochondrial disease diagnoses have interventions involving the initiation or *avoidance* of specific medications (corticosteroids, valproic acid, phenytoin, barbiturates, propofol for prolonged duration beyond 30-60 minutes, certain anesthetics, statins, β-blocking agents, amiodarone, nucleoside reverse transcriptase inhibitors), provision of cofactors or diets, and screening regimens for progressive clinical involvement of modifiable manifestations. General therapies for **Leigh syndrome** such as L-arginine and citrulline may prevent or reverse neurodevelopmental sequelae from a metabolic stroke. Nutritional therapies in these disorders are tailored to specific disease genes, such as thiamine and biotin for *SLC19A3* disease, ubiquinol for *PDSS2* (CoQ_{10} deficiency) disease, and thiamine and the ketogenic diet for *PDHA1* (pyruvate dehydrogenase) deficiency. Establishing the precise molecular diagnosis can further be lifesaving by avoiding fasting and mitochondrial-toxic medicines or general anesthetics in specific mitochondrial disease subsets, improving recurrence counseling for risk reduction of manifesting mitochondrial disease, enabling targeted screening for reported medical complications, and in some cases providing necessary cofactors or vitamins that may not otherwise have been considered. In addition, reproductive methodologies emerging in some countries for mitochondrial disease prevention, such as PGD and mitochondrial replacement technologies (MRTs), are only appropriate to consider in the setting of known pathogenic, inherited mtDNA variants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

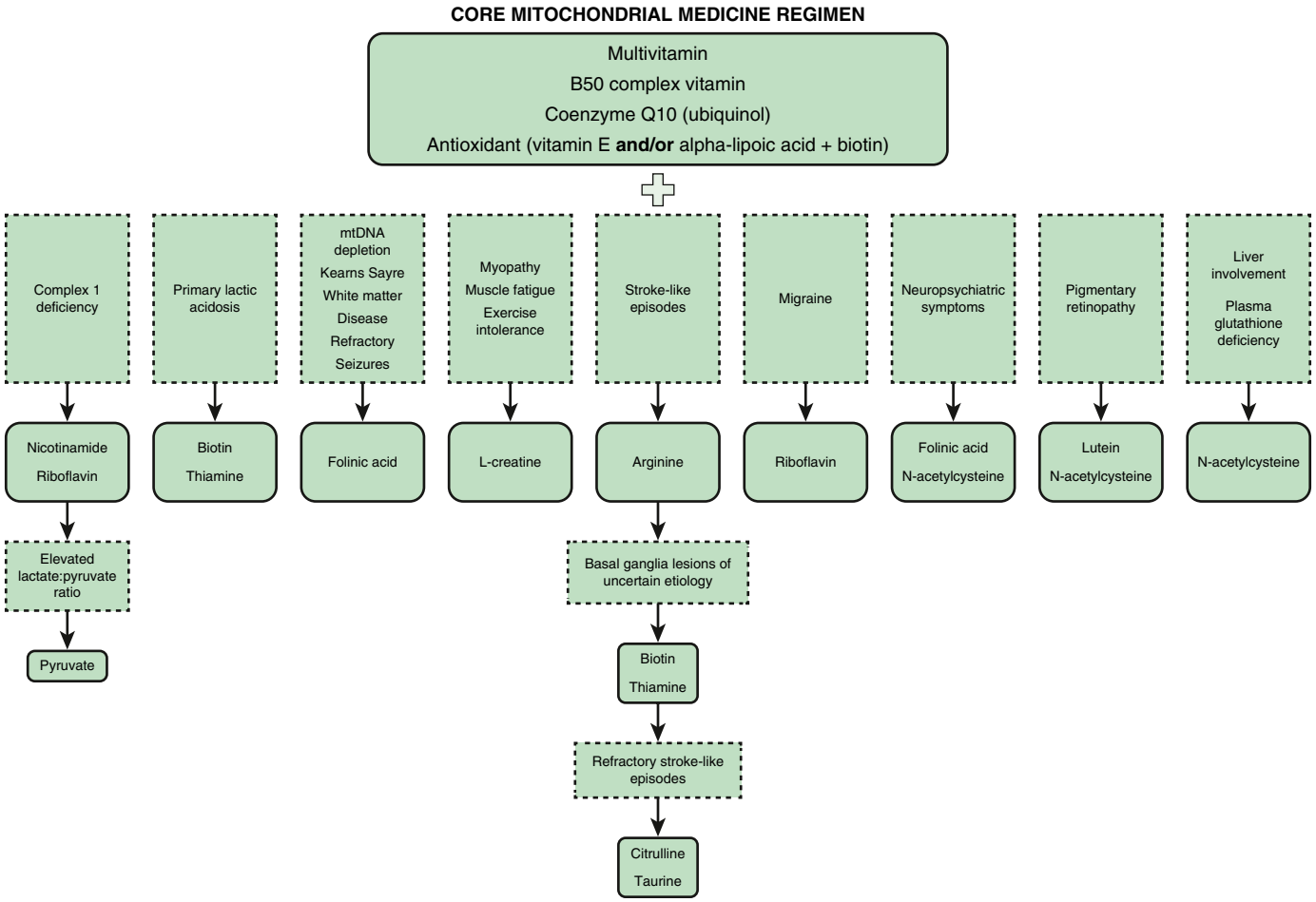

Fig. 108.4 Algorithm for the personalized prescribing of mitochondrial supplements. This figure represents the recommended approach to prescribing mitochondrial medicines. (Elevated lactate:pyruvate ratio indicates elevated NADH/NAD+ ratio.) B50, vitamins B1, B2, B3, B6, B12. (*From Barcelos I, Shadiack E, Ganetzky RD, Falk MJ. Mitochondrial medicine therapies: rationale, evidence, and dosing guidelines. Curr Opin Pediatr. 2020;32[6]:707–718.*)

Chapter 109

Mucopolysaccharidoses

Christina Lampe

Mucopolysaccharidoses are hereditary progressive diseases caused by pathogenic variants of genes coding for the lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). *Glycosaminoglycans* (GAGs) are long-chain complex carbohydrates composed of uronic acids, amino sugars, and neutral sugars. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronan. These substances are synthesized and, with the exception of hyaluronan, linked to proteins to form *proteoglycans,* major constituents of the ground substance of connective tissue and of nuclear and cell membranes. Degradation of proteoglycans starts with the proteolytic removal of the protein core, followed by the stepwise degradation of the GAG moiety. Failure of this degradation because of absent or grossly reduced activity of mutated lysosomal enzymes results in the intralysosomal accumulation of GAG fragments (Fig. 109.1). Distended lysosomes accumulate in the cell, interfere with cell function, and lead to characteristic patterns of clinical, radiologic, and biochemical abnormalities (Table 109.1 and Fig. 109.2). Within these patterns, specific diseases can be recognized that evolve from the intracellular accumulation of different degradation products (Table 109.2). As a general rule, the impaired degradation of heparan sulfate is more closely associated with **intellectual disability** and that of dermatan, chondroitin, and keratan sulfate with **mesenchymal abnormalities**. Variable expression within a given entity results from allelic pathogenic variants and varying residual activity of mutated enzymes. For instance, different allelic variants of the gene encoding L-iduronidase may result in severe **Hurler disease** (Hurler syndrome) with early death or in mild **Scheie disease** (Scheie syndrome) manifesting only with limited joint mobility, mild skeletal abnormalities, and corneal opacities. In addition, the features of an individual patient will be modified by secondary effects of lysosomal dysfunction and environmental factors.

Mucopolysaccharidoses are autosomal recessive disorders, with the exception of **Hunter disease** (Hunter syndrome), which is X-linked recessive. Their birth prevalence varies between 1.2 per 100,000 births (United States) and 16.9 per 100,000 births (Saudi Arabia). In the United States the most common subtype is MPS-III, followed by MPS-I and MPS-II.

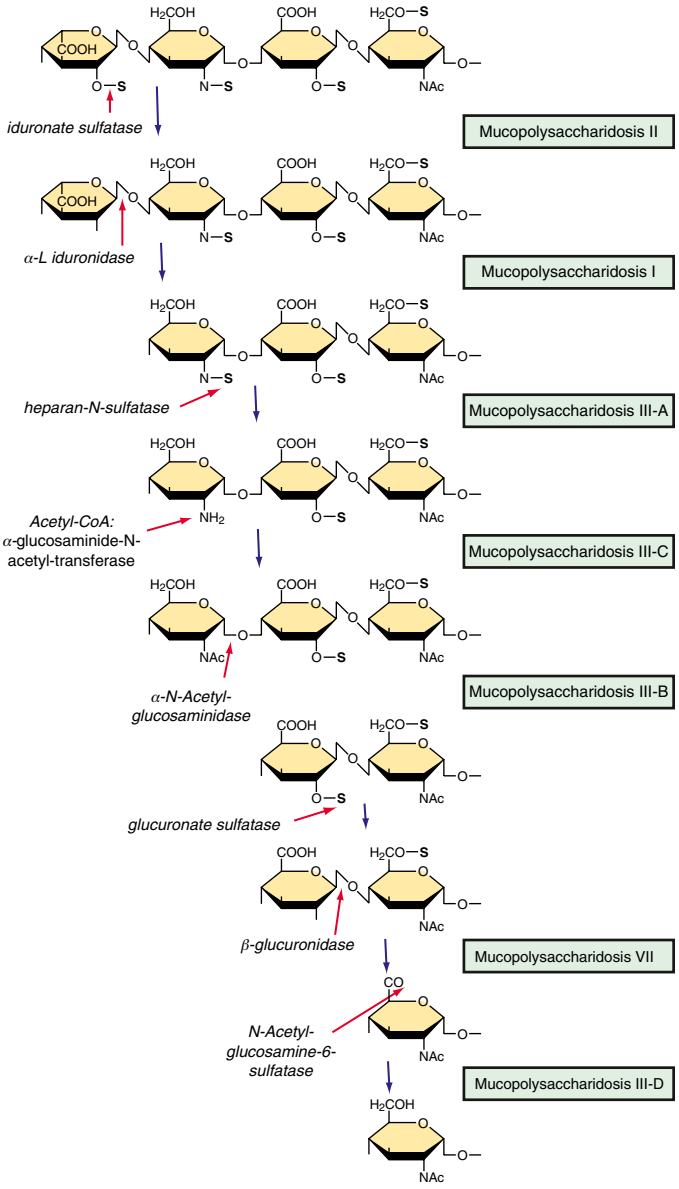

Fig. 109.1 Degradation of heparan sulfate and mucopolysaccharidoses resulting from the deficiency of individual enzymes. Some of the enzymes are also involved in the degradation of other glycosaminoglycans (not shown).

CLINICAL ENTITIES

Mucopolysaccharidosis I

Mucopolysaccharidosis I (MPS-I) is caused by pathogenic variants of the *IUA* gene on chromosome 4p16.3 encoding α-L-iduronidase. Two major alleles, W402X and Q70X, account for more than half of the MPS-I alleles in the White population. Other pathogenic variants typically occur in only one or a few individuals.

Deficiency of α-L-iduronidase results in a wide range of clinical involvement. Homozygous nonsense pathogenic variants result in the absence of enzyme and severe forms of MPS-I (Hurler syndrome). In contrast, missense pathogenic variants are more likely to preserve some residual enzyme activity and be associated with a milder form of the disease, including the milder Scheie syndrome.

Hurler Disease

The Hurler form of MPS-I **(MPS I-H)** is a severe, progressive disorder with involvement of multiple organ and tissue involvement that results in premature death, usually by 10 years of age. An infant with Hurler syndrome appears normal at birth, but inguinal hernias may be present. Diagnosis is usually made at 6-24 months, with evidence of hepatosplenomegaly, coarse facial features, corneal clouding, large tongue, enlarged head circumference, joint stiffness, short stature, and skeletal dysplasia. Acute cardiomyopathy has been found in some infants <1 year. Most patients have recurrent upper respiratory tract and ear infections, noisy breathing, and persistent copious nasal discharge. Valvular heart disease, notably with incompetence of the mitral and aortic valves, regularly develops, and narrowing of the coronary arteries occurs. Obstructive airway disease, especially during sleep, may necessitate tracheotomy. Obstructive airway disease, respiratory infection, and cardiac complications are the common causes of death.

Most children with Hurler syndrome acquire only limited language skills because of developmental delay, combined conductive and neurosensory hearing loss, and an enlarged tongue. Progressive ventricular enlargement with increased intracranial pressure caused by communicating hydrocephalus also occurs. Corneal clouding, glaucoma, and retinal degeneration are common. Radiographs show a characteristic skeletal dysplasia known as *dysostosis multiplex* (Figs. 109.3 and 109.4). The earliest radiographic signs are thick ribs and ovoid vertebral bodies. Skeletal abnormalities (in addition to those shown in the figures) include enlarged, coarsely trabeculated diaphyses of the long bones with irregular metaphyses and epiphyses. With progression of disease, macrocephaly develops with thickened calvarium, premature closure

of lambdoid and sagittal sutures, shallow orbits, enlarged J-shaped sella, and abnormal spacing of teeth with dentigerous cysts.

Hurler-Scheie Disease

The clinical phenotype of the Hurler-Scheie form of MPS-I **(MPS I-H/S)** is intermediate between Hurler and Scheie diseases and is characterized by progressive somatic involvement, including dysostosis multiplex with little or no intellectual dysfunction. The onset of symptoms is usually observed between 3 and 8 years of age, and survival to adulthood is common. Cardiac involvement and upper airway obstruction contribute to clinical morbidity. Some patients have spondylolisthesis, which may cause cord compression.

Scheie Syndrome

MPS I-S is a comparatively mild disorder characterized by joint stiffness, aortic valve disease, corneal clouding, and mild dysostosis multiplex. Onset of significant symptoms is usually after age 5 years, with diagnosis made between 10 and 20 years. Patients with Scheie syndrome have normal intelligence and stature but have significant joint and ocular involvement. A carpal tunnel syndrome often develops. Ophthalmic features include corneal clouding, glaucoma, and retinal degeneration. Obstructive airway disease, causing sleep apnea, develops in some patients, necessitating tracheotomy. Aortic valve disease is common and has required valve replacement in some patients.

Table 109.1 Recognition Pattern of Mucopolysaccharidoses

	MUCOPOLYSACCHARIDOSIS (MPS) TYPE						
MANIFESTATIONS	I-H	I-S	II	III	IV	VI	VII
Intellectual disability	+	−	±	+	−	−	±
Coarse facial features	+	(+)	+	+	−	+	±
Corneal clouding	+	+	−	−	(+)	+	±
Visceromegaly	+	(+)	+	(+)	−	+	+
Short stature	+	(+)	+	−	+	+	+
Joint contractures	+	+	+	−	−	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	−	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

I-H, Hurler syndrome; I-S, Scheie syndrome; II, Hunter syndrome; III, Sanfilippo syndrome; IV, Morquio syndrome; VI, Maroteaux-Lamy syndrome; VII, Sly syndrome, +, presence of manifestation, −, absence of manifestation; ±, possible presence of manifestation; (+), mild manifestation.

Mucopolysaccharidosis II

Hunter disease (MPS-II) is an X-linked disorder caused by the deficiency of iduronate 2-sulfatase (IDS). The gene encoding IDS is located on Xq28. Single-nucleotide variants or small deletions of *IDS* have been detected in approximately 50% of patients with MPS-II. Major deletions or rearrangements of *IDS* have been found in the rest, usually associated with a more severe and complex clinical phenotype. As an X-linked recessive disorder, Hunter syndrome manifests almost exclusively in males. However, it has been observed in females because of unfavorable skewing of inactivation of the normal X chromosome carrying the normal gene.

Marked molecular heterogeneity explains the wide clinical spectrum of Hunter disease. Patients with severe MPS-II have features similar to those of Hurler disease, except for the lack of corneal clouding and the somewhat slower progression of somatic and central nervous system (CNS) deterioration. Coarse facial features, short stature, dysostosis multiplex, joint stiffness, and intellectual disability manifest between 2 and 4 years of age. Grouped skin papules are present in some patients. Extensive congenital dermal melanocytosis (Mongolian spots) present at birth have been observed in African and Asian patients and may be an early marker of the disease. Gastrointestinal (GI) storage may produce chronic diarrhea. Communicating hydrocephalus and spastic paraplegia may develop due to thickened meninges. In severely affected patients, extensive, slowly progressive neurologic involvement precedes death, which usually occurs at age 10-15 years.

Patients with the mild form have a near-normal or normal life span, minimal CNS involvement, and slow progression of somatic deterioration with preservation of cognitive function in adult life. Survival to ages 65 and 87 years has been reported, and some patients have had children. Somatic features are Hurler-like but milder with a greatly



Fig. 109.2 Patients with various types of mucopolysaccharidoses. MPS-I: Hurler syndrome, age 3 years; MPS-II: Hunter syndrome, 12 years; MPS-III: Sanfilippo syndrome, 4 years; MPS-IV: Morquio syndrome, 10 years; MPS-VI: Maroteaux-Lamy syndrome, 15 years.

Table 109.2 Mucopolysaccharidoses: Clinical, Molecular, and Biochemical Aspects

MPS TYPE	EPONYM	INHERITANCE	GENE/ CHROMOSOME	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSAY	MIM NUMBER
I-H	(Pfaundler-) Hurler	AR	*IDUA* 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr	α-L-iduronidase	L, F, Ac, Cv	252800 607014
I-S	Scheie	AR	*IDUA* 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L-iduronidase	L, F, Ac, Cv	607016
I-HS	Hurler-Scheie	AR	*IDUA* 4p16.4	Phenotype intermediate between I-H and I-S	α-L-iduronidase	L, F, Ac, Cv	607015
II	Hunter	XLR	*IDS* Xq27.3-28	Severe course: similar to I-H but clear corneas Mild course: less pronounced features, later manifestation, survival to adulthood with mild mental deficiency or without mental deficiency	Iduronate sulfate sulfatase	S, F, Af, Ac, Cv	309900
IIIA	Sanfilippo A	AR	*SGSH* 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas Survival to adulthood possible	Heparan-S-sulfamidase	L, F, Ac, Cv	252900 605270
IIIB	Sanfilippo B	AR	*NAGLU* 17q21		*N*-Acetyl-D-glycosaminidase	S, F, Ac, Cv	252920
IIIC	Sanfilippo C	AR	*HGSNAT* 8p11.21		Acetyl-CoA-glucosaminide *N*-acetyltransferase	F, Ac	252930
IIID	Sanfilippo D	AR	*GNS* 12q14		*N*-Acetylglucosamine–6-sulfate sulfatase	F, Ac	252940 607664
IVA	Morquio A	AR	*GALNS* 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height <125 cm	*N*-Acetylgalactosamine-6-sulfate sulfatase	L, F, Ac	253000
IVB	Morquio B	AR	*GLB1* 3p21.33	Same as IVA, but milder; adult height >120 cm	β-Galactosidase	L, F, Ac, Cv	253010 230500
VI	Maroteaux-Lamy	AR	*ARSB* 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate, and severe expression in different families	*N*-Acetylgalactosamine-α-4-sulfate sulfatase (arylsulfatase B)	L, F, Ac	253200
VII	Sly	AR	*GUSB* 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β-Glucuronidase	S, F, Ac, Cv	253220
IX	Hyaluronidase deficiency	AR	*HYAL1* 3p21.3	Periarticular masses, no Hurler phenotype	Hyaluronidase 1	S	601492
MPSPS	MPS plus syndrome	AR	*VPS33A*	Mild Hurler phenotype, cognitive deficiency, organomegaly, skeletal dysplasia, pancytopenia, renal insufficiency, optic atrophy, early death	No lysosomal enzyme deficiency	L, F	617303

AR, Autosomal recessive; XLR, X-linked recessive; L, Leukocytes; S, serum; F, cultured fibroblasts; Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villus sampling; MIM, Mendelian Inheritance in Man Catalogue.

reduced rate of progression. Adult height may exceed 150 cm. Airway involvement, valvular cardiac disease, hearing impairment, carpal tunnel syndrome, and joint stiffness are common and can result in significant loss of function in both the mild and severe forms.

Mucopolysaccharidosis III

Sanfilippo disease makes up a genetically heterogeneous but clinically similar group of four recognized types. Each type is caused by a different enzyme deficiency involved in the degradation of heparan sulfate (see Fig. 109.1). Pathogenic variants have been found in all the MPS-III disorders for which genes have been isolated.

Phenotypic variation exists in MPS-III patients, but to a lesser degree than in other MPS disorders. Patients with Sanfilippo disease are characterized by slowly progressive, severe CNS involvement with mild somatic disease. Such disproportionate involvement of the CNS versus the connective tissue system is unique to MPS-III. Onset of clinical features usually occurs at age 2-6 years in a child who previously appeared normal. Presenting features include delayed development,

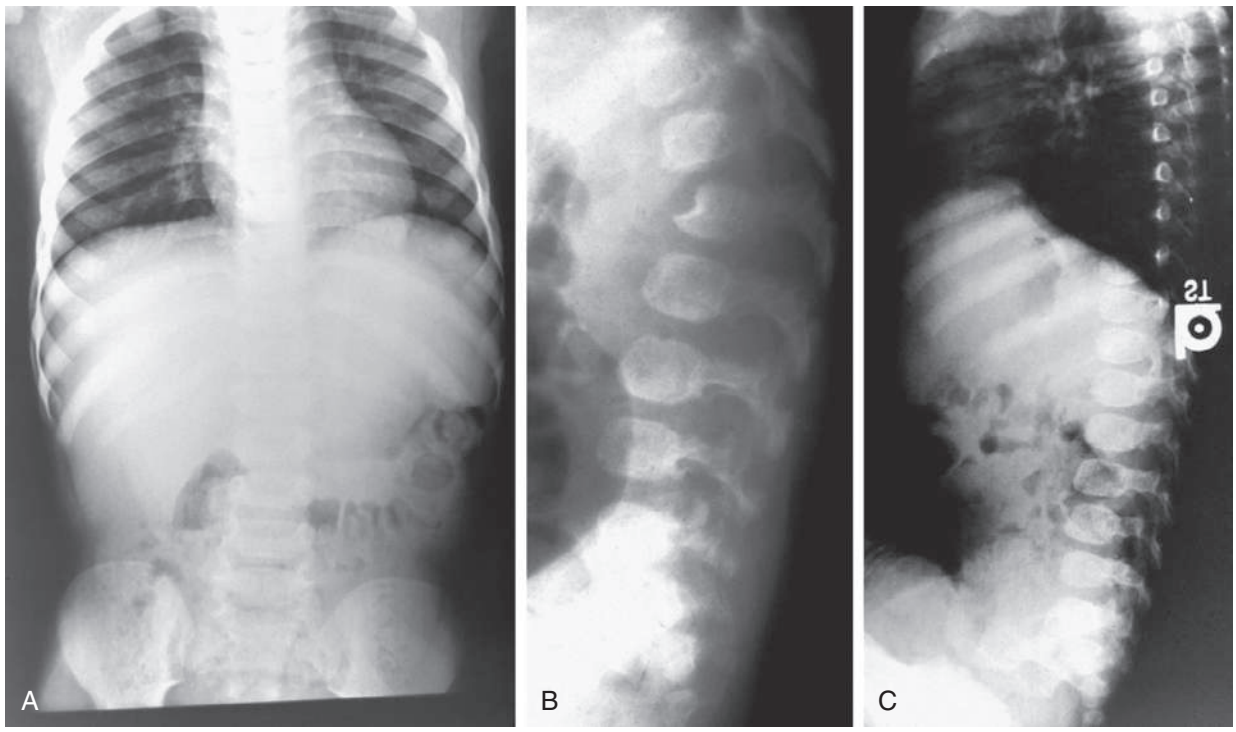

Fig. 109.3 Dysostosis multiplex. **A,** Sanfilippo syndrome, patient age 4 years; the ribs are wide. **B,** Sanfilippo syndrome, age 4 years; immature, ovoid configuration of the vertebral bodies. **C,** Hurler syndrome, age 18 months; anterosuperior hypoplasia of first lumbar vertebra (L1) resulting in hook-shaped appearance.

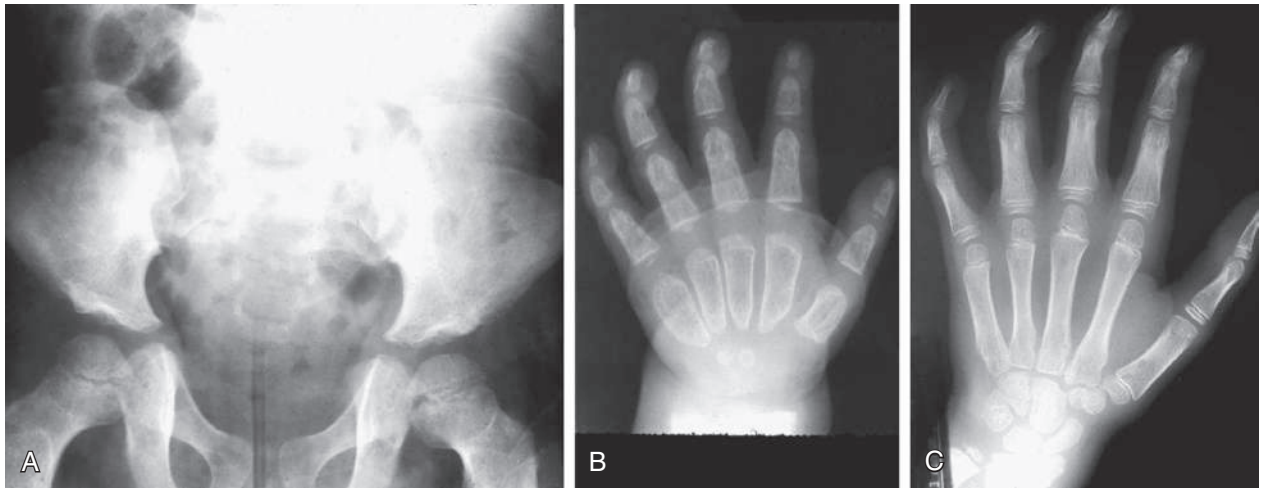

Fig. 109.4 Dysostosis multiplex. **A,** Mucopolysaccharidosis I-H, patient age 10 years. The inferior portions of the ilia are hypoplastic, with resulting iliac flare and shallow acetabular fossae. The femoral necks are in the valgus position. **B,** MPS I-H, age 4 years. Metacarpals and phalanges are abnormally short, wide, and deformed with proximal pointing of the metacarpals and bullet-shaped phalanges. Bone trabeculation is coarse, and the cortices are thin. **C,** MPS I-S, age 13 years. The carpal bones are small, leading to a V-shaped configuration of the digits. The short, tubular bones are well modeled. Flexion of the middle and distal phalanges II-V is caused by joint contractures.

hyperactivity with aggressive behavior, coarse hair, hirsutism, sleep disorders, and mild hepatosplenomegaly. Subclinical cardiac defects are common. Delays in the diagnosis of MPS-III are common because of mild physical features, hyperactivity, and slowly progressive neurologic disease. Severe neurologic deterioration occurs in most patients by age 6-10 years, accompanied by rapid deterioration of social and adaptive skills. Severe behavior problems, such as sleep disturbance, uncontrolled hyperactivity, temper tantrums, destructive behavior, and physical aggression, are common. Profound developmental regression and behavior problems often occur in patients with normal physical strength, making management particularly difficult.

Mucopolysaccharidosis IV

Morquio disease (MPS-IV) is caused by a deficiency of *N*-acetylgalactosamine-6-sulfatase (MPS-IVA) or of β-galactosidase (MPS-IVB). Both result in the defective degradation of keratan sulfate. The gene encoding *N*-acetylgalactosamine-6-sulfatase is *GALNS* on chromosome 16q24.3, and the gene encoding β-galactosidase is *GLB1* on chromosome 3p21.33. β-Galactosidase catalyzes GM_1 ganglioside in addition to endohydrolysis of keratan sulfate, and most pathogenic variants of *GLB1* result in generalized **gangliosidosis**, a spectrum of neurodegenerative disorders associated with dysostosis multiplex. A W273L pathogenic variant of the *GLB1* gene, either in the homozygous

state or as part of compound heterozygosity, commonly results in Morquio B disease.

Both types of Morquio syndrome are characterized by short-trunk dwarfism, fine corneal deposits, a skeletal dysplasia that is distinct from other mucopolysaccharidoses, and preservation of intelligence. MPS-IVA is usually more severe than MPS-IVB, with an adult height of <125 cm in the former and more than 150 cm in the latter. However, there is considerable variability of expression in both subtypes. The appearance of genu valgum, kyphosis, growth retardation with short trunk and neck, and waddling gait with a tendency to fall are early symptoms of MPS-IV. Extraskeletal manifestations include mild corneal clouding, small teeth with abnormally thin enamel, frequent caries formation, and occasionally hepatomegaly and cardiac valvular lesions. Instability of the odontoid process and ligamentous laxity is regularly present and can result in atlantoaxial instability and life-threatening dislocation. Surgery to stabilize the upper cervical spine, usually by posterior spinal fusion, before the development of cervical myelopathy, can be lifesaving.

Mucopolysaccharidosis VI

Maroteaux-Lamy disease (MPS-VI) is caused by pathogenic variants of the *ARSB* gene on chromosome 5q11-13 encoding *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B). It is characterized by severe to mild somatic involvement, as seen in MPS-I, but with preservation of intelligence. The somatic involvement of the severe form of MPS VI is characterized by corneal clouding, coarse facial features, joint stiffness, valvular heart disease, communicating hydrocephalus, and dysostosis multiplex. In the severe form, growth can be normal for the first few years of life but seems to virtually stop after age 6-8 years. The mild to intermediate forms of Maroteaux-Lamy syndrome can be easily confused with Scheie syndrome. Spinal cord compression from thickening of the dura in the upper cervical canal with resultant myelopathy is common in patients with MPS-VI.

Mucopolysaccharidosis VII

Sly disease (MPS-VII) is caused by pathogenic variants of the *GUSB* gene. Pathogenic variants result in a deficiency of β-glucuronidase, intracellular storage of glycosaminoglycan fragments, and a very wide range of clinical involvement. The most severe form presents as lethal nonimmune fetal hydrops and may be detected in utero by ultrasound. Some severely affected newborns survive for months and have, or develop, signs of lysosomal storage, including thick skin, visceromegaly, and dysostosis multiplex. Less severe forms of MPS-VII present during the first years of life with features of MPS-I but slower progression. Corneal clouding varies. Patients with manifestation after 4 years of life have coarse facial features with depressed nasal roots, malpositioned teeth with malformed roots, and skeletal abnormalities of dysostosis multiplex. Intelligence is normal, and corneae are usually clear. Patients may be found incidentally based on a blood smear that shows coarse granulocytic inclusions.

Mucopolysaccharidosis IX

MPS-IX disease is caused by pathogenic variants in *HYAL1* encoding one of three hyaluronidases. Clinical findings in the first patient, a 14-year-old girl, were bilateral nodular soft tissue periarticular masses, lysosomal storage of histiocytes, mildly dysmorphic craniofacial features, short stature, normal joint movement, and normal intelligence. Clinical findings in the only three additional patients known today were indistinguishable from those in rheumatoid arthritis.

Mucopolysaccharidosis Plus Syndrome

Coarse facial features, organomegaly, joint contractures, dysostosis multiplex, cognitive deficiency, increased mucopolysacchariduria, and massive intracellular accumulation of heparan sulfate have been found in 13 children in northeastern Siberia and two Turkish children. Additional findings include optic atrophy, intracerebral calcifications, pancytopenia, and renal insufficiency. Most patients died within the first 2 years of life from cardiorespiratory failure. Lysosomal enzyme activities were normal in children with MPS plus syndrome. This autosomal recessive multisystem disorder is caused by biallelic pathogenic variants of *VPS33A* encoding a protein involved in lysosomal fusion processes.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical suspicion of an MPS justifies a skeletal survey. Radiographs of the chest, spine, pelvis, and hands may show early signs of dysostosis multiplex. The next diagnostic step is to assay the urinary excretion of GAGs. Semiquantitative spot tests for increased urinary GAG excretion are quick, inexpensive, and useful for initial evaluation but are subject to both false-positive and false-negative results. Quantitative analysis of a single GAG in material derived from dried blood spots is preferable with few false-negative results. Using tandem mass spectrometry, type-specific profiles can be obtained. Morquio disease is often missed in urinary assays but can be reliably diagnosed in serum using monoclonal antibodies to keratan sulfate.

Newborn screening for MPS (type I, II, VI) is essential for the early detection of subclinical cases and their therapy. It is available from dried blood spots using tandem mass spectrometry of glycosaminoglycans or fluorescence-based enzyme function assays. Any individual with a suspected MPS disorder based on screening tests, clinical features, and radiographic results should have a definitive diagnosis established by enzyme assay. Serum, leukocytes, or cultured fibroblasts are used as the tissue source for measuring lysosomal enzymes (see Table 109.2).

Prenatal diagnosis is available for all MPSs and is carried out on cultured cells from amniotic fluid or chorionic villus biopsy. Molecular analysis is typically performed using appropriate gene panels. In many cases the type and location of the pathogenic variant are related to the future course of the disease and thus have a prognostic value. Carrier testing in Hunter syndrome, an X-linked disorder, requires analysis of *IDS* once the specific pathogenic variant or chromosome arrangement in the family is known. Prenatal molecular analysis should be offered in a male fetus of a proven female carrier of the *IDS* gene. His risk to be affected is 50%. In a female fetus, the risk is small, but not zero, as a result of skewed maternal X chromosome inactivation.

Mucolipidoses and oligosaccharidoses manifest with the same clinical and radiographic features as MPS. In these conditions the urinary excretion of GAGs is not elevated. Hurler-like facial features, joint contractures, dysostosis multiplex, and elevated urinary GAG excretion differentiate the MPSs from congenital disorders of glycosylation and other neurodegenerative and dwarfing conditions.

TREATMENT

Hematopoietic stem cell transplantation and enzyme replacement therapy are performed in specialized institutions.

Bone marrow transplantation from related or unrelated donors and cord blood transplantation have resulted in significant clinical improvement of somatic disease in MPSs I, II, III, and VII. Clinical effects include increased life expectancy with resolution or improvement of growth, hepatosplenomegaly, joint stiffness, facial appearance, skin changes, obstructive sleep apnea, heart disease, communicating hydrocephalus, and hearing loss. Enzyme activity in serum and urinary GAG excretion normalize. This is true for MPS I-H, II, and III. Some patients with MPS-I who have undergone transplantation before 9 months of age have been reported with normal cognitive development. Transplantation before 24 months and with a baseline mental development index >70 have improved long-term outcomes. Transplantation does not significantly improve the neuropsychologic outcome of MPS patients with impaired cognition at transplantation. Early transplantation in the MPS-II patient may have the same effect. Transplantation in the MPS-VI patient stabilizes or improves cardiac manifestations, posture, and joint mobility. Stem cell transplantation does not correct skeletal or ocular anomalies, and they should be treated with appropriate orthopedic and ophthalmologic procedures. Cord blood transplantation is the therapy of choice in children with MPS-IH, and possibly MPS-II, before the age of 2 years, but transplantation-related death or primary graft failure, which occurs in approximately one third of the patients, must be weighed against other therapeutic options.

Enzyme replacement therapy (ERT) using recombinant α-L-iduronidase has been approved for patients with MPS-I (Table 109.3). It reduces organomegaly and airway infections, improves rate of growth, improves joint mobility, pulmonary function, and endurance, and reduces the number of episodes of sleep apnea and urinary GAG excretion. The enzyme does not cross the blood-brain barrier and does not prevent deterioration of cognition and other neurologic functions. Consequently, ERT is reserved for patients with mild CNS involvement. To stabilize extraneural manifestations it is also recommended in young patients before stem cell transplantation. ERT also ameliorates somatic complications in patients with more severe CNS involvement. Recombinant iduronate-2-sulfatase ameliorates the nonneural manifestations of Hunter disease, such as respiratory dysfunction, reduced physical endurance, and daily activity. ERT with recombinant human *GALNS* improves physical endurance, respiratory function, and daily living activity of patients with MPS-IV. Similar effects produce recombinant *N*-acetylgalactosamine-4-sulfatase in patients with MPS-VI and recombinant β-glucuronidase in MPS VII.

Advanced therapies include enzyme replacement mediated via insulin receptors in MPS I and II or transferrin receptors in MPS II to assist in crossing the blood-brain barrier. A phase I/II and a phase III study using the transferrin receptor have started for MPS II. In MPS IIIA, an intravenous ERT phase 1/2 study with a chemically modified variant of recombinant human sulfamidase and a recombinant human alpha-*N*-acetylglucosaminidase for MPS IIIB were recently completed. However, the study results were not convincing. A phase I/II study for MPS III using the transferrin receptor is in planning. Gene therapies for MPS I, II, and III are under investigation. Autologous hematopoietic stem/progenitor cells transduced ex vivo with an α-L-iduronidase–encoded lentiviral vector has resulted in beneficial metabolic correction in peripheral and central nervous system tissues. A clinical trial to ameliorate the intracellular inflammation and, consequently, the CNS involvement in MPS III with anakinra (Kineret) was completed with results pending.

Symptomatic therapy focuses on respiratory and cardiovascular complications, hearing loss, carpal tunnel syndrome, spinal cord compression, hydrocephalus, and other problems (Table 109.4). The

Table 109.3 Therapies For Mucopolysaccharidoses

MPS TYPE	HEMATOPOIETIC STEM CELL TRANSPLANTATION	ENZYME REPLACEMENT THERAPY	REMARKS
I	Yes	Laronidase (Aldurazyme)	Developmental trajectory dependent on time of transplantation. Little effect on connective tissue manifestations. Enzyme replacement immediately after diagnosis. Autologous hematopoietic stem/progenitor cells transduced ex vivo with gene encoding lentiviral vector.
II	Yes	Idursulfase (Elaprase)	
III	No	No	Experimental intraventricular chimeric fusion of recombinant human N-acetyl-D-glucosaminidase and truncated insulin-like growth factor 2 in MPS IIIB
IV	Yes	Elosulfase (Vimizim)	Improved daily activities. No effect on growth or skeletal dysplasia.
VI	Yes	Galsulfase (Naglazyme)	Improved daily activities. Improved growth. No effect on skeletal dysplasia.
VII	Yes	Vestronidase alfa (MEPSEVII)	Improved daily activity. No effect on skeletal dysplasia.

Table 109.4 Symptomatic Management of Mucopolysaccharidoses

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
NEUROLOGIC		
Hydrocephalus	MPS I, II, VI, VII	Fundoscopy, CT scan
Chronic headaches	All	Ventriculoperitoneal shunting
Behavioral disturbance	MPS-III	Behavioral medication, sometimes CT scan, ventriculoperitoneal shunting
Disturbed sleep–wake cycle	MPS-III	Melatonin
Seizures	MPS I, II, III	EEG, anticonvulsants
Atlantoaxial instability	MPS IV	Cervical MRI, upper cervical fusion
Spinal cord compression	All	Laminectomy, dural excision
OPHTHALMOLOGIC		
Corneal opacity	MPS I, VI, VII	Corneal transplant
Glaucoma	MPS I, VI, VII	Medication, surgery
Retinal degeneration	MPS I, II	Nightlight
EARS, AIRWAYS		
Recurrent otitis media	MPS I, II, VI, VII	Ventilating tubes
Impaired hearing	All except MPS-IV	Audiometry, hearing aids
Obstruction	All except MPS-III	Adenectomy, tonsillectomy, bronchodilator therapy, CPAP at night, laser excision of tracheal lesions, tracheotomy
CARDIAC		
Cardiac valve disease	MPS I, II, VI, VII	Endocarditis prevention, valve replacement
Coronary insufficiency	MPS I, II, VI, VII	Medical therapy
Arrhythmias	MPS I, II, VI, VII	Antiarrhythmic medication, pacemaker

Table 109.4 Symptomatic Management of Mucopolysaccharidoses—cont'd

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
ORAL, GASTROINTESTINAL		
Hypertrophic gums, poor teeth	MPS I, II, VI, VII	Dental care
Chronic diarrhea	MPS-II	Diet modification, loperamide
MUSCULOSKELETAL		
Joint stiffness	All except MPS IV	Physical therapy
Scoliosis	All	Bracing, surgery
Weakness	All	Physical therapy, wheelchair
Gross long-bone malalignment	All	Corrective osteotomies
Carpal tunnel syndrome	MPS I, II, VI, VII	Electromyography, surgical decompression
ANESTHESIA	All except MPS III	Avoid atlantoaxial dislocation; use angulated video intubation laryngoscope and small endotracheal tubes

CT, Computed tomography; CPAP, continuous positive airway pressure; EEG, electroencephalogram; MRI, magnetic resonance imaging.

multisystem involvement and progressive nature of MPS syndromes usually require the standardized and complex care provided by medical centers.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 110

Disorders of Purine and Pyrimidine Metabolism

H. A. Jinnah

The purines and pyrimidines consist of a family of small organic molecules that are found in all cells. They are often considered together because they provide the fundamental building blocks for nucleic acids, which include DNA and RNA. The purines and pyrimidines are also involved in numerous other cellular processes. Although they share certain biochemical characteristics, the associated clinical disorders are quite varied. Historically, most were identified by characteristic abnormalities found with metabolic tests. Currently, they are increasingly being identified after discovery of a pathogenic variant in a relevant gene in tests that involve broad gene panels or exome sequencing. Most of these disorders are genetic, and most are rare. *However, they are important to recognize because specific treatments are available for some of them* (Table 110.1).

PURINES

The purines are divided into two groups. The first group involves the base adenine, its corresponding nucleoside (adenosine), and nucleotide (AMP, ADP, ATP) derivatives (Fig. 110.1). ATP serves as one of four building blocks for RNA, and its deoxy derivative (dATP) serves as one of four building blocks for DNA. ATP also provides the energy source for the majority of energy-requiring activities. ATP derivatives act as signaling factors as "second messengers" (cAMP) or cofactors (FAD, NAD, NADP) for a large number of cellular processes. Some purines such as adenosine and the adenine nucleotides serve as extracellular signaling molecules, including acting as neurotransmitters in the nervous system.

The second group of purines involves the base guanine, its corresponding nucleoside (guanosine), and nucleotide (GMP, GDP, GTP) derivatives (see Fig. 110.1). Like the adenine nucleotides, guanine nucleotide derivatives also serve as building blocks for nucleic acids (DNA and RNA). GTP also provides an energy source for some energy-requiring activities. Guanine nucleotides also play a critical role in intercellular signaling (cGMP) via membrane-bound receptors that require GTP during signal transduction (G-proteins). They also play a role in intracellular signaling via a large family of cytosolic GTPases and guanine nucleotide exchange factors.

Because purines play a critical role for so many fundamental cellular processes, their amounts are tightly regulated. The amounts of purines reflect a balance between synthesis, catabolism, and recycling (Fig. 110.2). Purines are synthesized by the de novo purine synthesis pathway. This pathway has six enzymes that carry out 10 reactions. When there is a demand for more purines, these six enzymes aggregate dynamically into giant macromolecular complexes known as *purinosomes* to accelerate synthesis. After the demand is met, these aggregates disperse and synthesis abates. In humans, purines are catabolized via several routes. The major end product of purine catabolism is uric acid, produced by the enzyme encoded by the *XDH* gene. The enzyme is known as *xanthine oxidase, xanthine reductase,* or *xanthine oxidoreductase.* Most of this uric acid is eliminated from the body in the urine, although some is also eliminated by secretion into the gastrointestinal tract. Because the synthesis of purines is energetically costly, purines are actively recycled (see Fig. 110.2). The key enzymes of purine salvage include hypoxanthine-guanine phosphoribosyl transferase (encoded by *HPRT1*) and adenine phosphoribosyl transferase (encoded by *APRT*).

The metabolism of purines differs considerably across different cells and tissues. For example, the synthetic pathway is absent in erythrocytes, because these postmitotic cells do not require large quantities of new purines to make nucleic acids for cell division. Erythrocytes rely instead predominantly on purine salvage to maintain purine levels. A similar situation is thought to occur for postmitotic neurons of the nervous system. Another example of tissue-specific differences in purine metabolism involves uric acid. The vast majority of uric acid in the human body is produced by the liver, because hepatocytes express high levels of *XDH,* whereas many other cells and tissues express little or none. In addition to tissue differences, several enzymes of purine metabolism have multiple isoforms with different tissue distributions, leading to tissue-specific consequences in disorders where one isoform is affected.

PYRIMIDINES

The pyrimidines are divided into three groups delineated by the bases cytosine, thymine, and uracil (see Fig. 110.1). Each has a corresponding nucleoside derivative (cytidine, thymidine, uridine) and nucleotide

Table 110.1 Disorders of Purines and Pyrimidines with Specific Treatments

DISORDER	GENE SYMBOL	TREATMENT	OUTCOME
APRT deficiency	*APRT*	XOR inhibitor	Prevents renal stones and renal failure
Uridine-responsive epileptic encephalopathy	*CAD*	Uridine	Suppresses seizures, reverses neurobehavioral and hematologic abnormalities
Familial juvenile hyperuricemic nephropathy	*UMOD, REN, MUC,* or *HNF-1b*	XOR inhibitor	Prevents renal stones, renal failure, and gout
Renal hypouricemia	*SLC2A9* or *SLC22A12*	XOR inhibitor	Prevents renal stones and renal failure
Hereditary orotic aciduria	*UMPS*	Uridine	Reverses neurobehavioral and hematologic deficits
Hereditary xanthinurias			
Type 1	*XOR*	XOR inhibitor	Prevents renal stones and renal failure
Type 2	*MOCOS*	XOR inhibitor	Prevents renal stones and renal failure
Molybdenum cofactor deficiencies	*MOCS1-3, GPHN*	XOR inhibitor	Prevents renal stones and renal failure
MOCS1 deficiency	*MOCS1*	cPMP	Reverses neurobehavioral deficits
HPRT1-associated disorders	*HPRT1*	XOR inhibitor	Prevents renal stones, renal failure, and gout
PRPP synthetase hyperactivity	*PRPS1*	XOR inhibitor	Prevents renal stones, renal failure, and gout
Nucleotidase-associated pervasive developmental delay	Unknown	Uridine	Reverses neurobehavioral deficits

The most common XOR inhibitors include allopurinol, febuxostat, and topiroxostat.
cPMP, Cyclic pyranopterin monophosphate; XOR, xanthine oxidoreductase.
Copyright H.A. Jinnah.

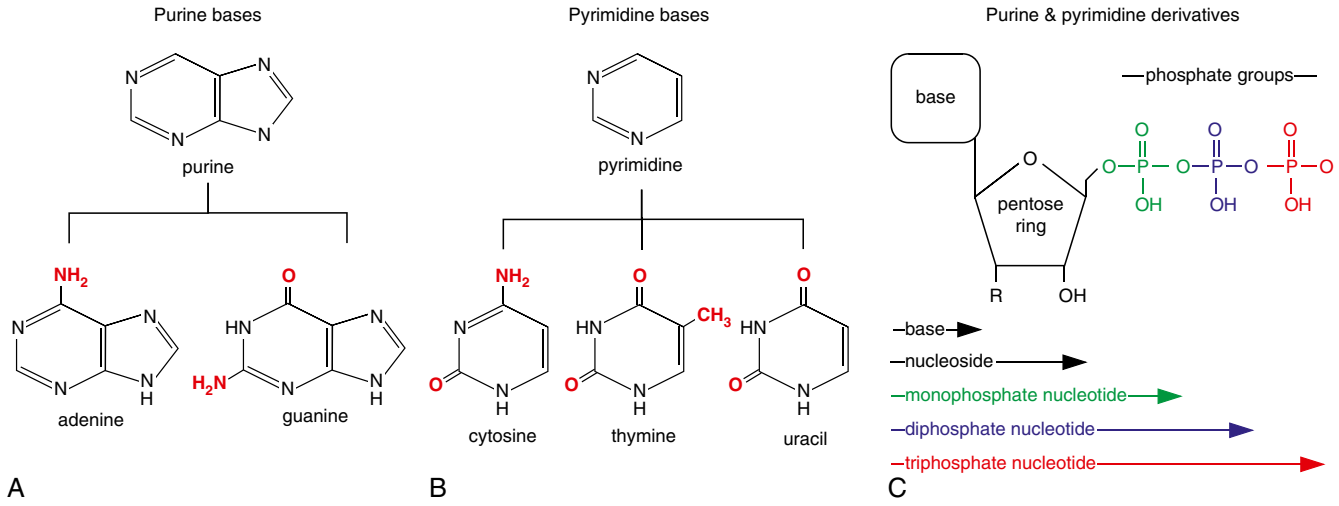

Fig. 110.1 The structure of purines and pyrimidines. A, The fundamental purine base and its variants adenine and guanine. B, The fundamental pyrimidine base and its variants cytosine, thymine, and uracil. C, The major purine and pyrimidine derivatives. Nucleosides are composed of a purine or pyrimidine base attached to a pentose ring. The R moiety in the pentose ring can be either an OH group (ribose for RNA) or a hydrogen (deoxyribose for DNA). Nucleotides are composed of a nucleoside attached to phosphate groups. (*Copyright H.A. Jinnah.*)

derivatives (see Fig. 110.1). Like the purines, the pyrimidines are key ingredients for nucleic acids. Nucleotide derivatives of cytidine are used to make DNA and RNA. Nucleotide derivatives of thymidine are used in DNA, but nucleotide derivatives of uridine replace thymidine in RNA.

The pyrimidines also have additional functions; CTP is used to make CDP-choline, an important intermediate in the production of membrane phospholipids such as phosphatidylcholine. UTP is used to make UDP-glucose, an intermediate used in the synthesis of glycogen, as well as other glycosylation reactions, to make glycolipids or glycoproteins. UTP is also used to make UDP-glucuronic acid, an intermediate used in the generation of glucuronide conjugates. Glucuronide conjugates of certain drugs and drug metabolites are excreted in the bile, and glucuronide conjugates of other endogenous biomolecules such as steroid hormones facilitate transport between tissues in the body.

The body's pyrimidine levels reflect a balance between synthesis, catabolism, and recycling. Pyrimidines are synthesized in a pathway that involves three enzymes which carry out six steps leading to the central metabolite UMP (Fig. 110.3). UMP can then be directed toward the synthesis of other pyrimidines. Pyrimidines are catabolized via several routes. Cytidine and uridine derivatives are both converted to uracil, and ultimately to β-alanine. Thymidine is converted to β-aminoisobutyrate. Both β-alanine and β-aminoisobutyrate serve as intermediates in the citric acid cycle. Free pyrimidines are also recycled at several steps by kinases that convert nucleosides to their corresponding nucleotides (see Fig. 110.3). Pyrimidine disorders are rare and clinically heterogeneous. The heterogeneity likely reflects the different functions of pyrimidines in different tissues combined with differences in the

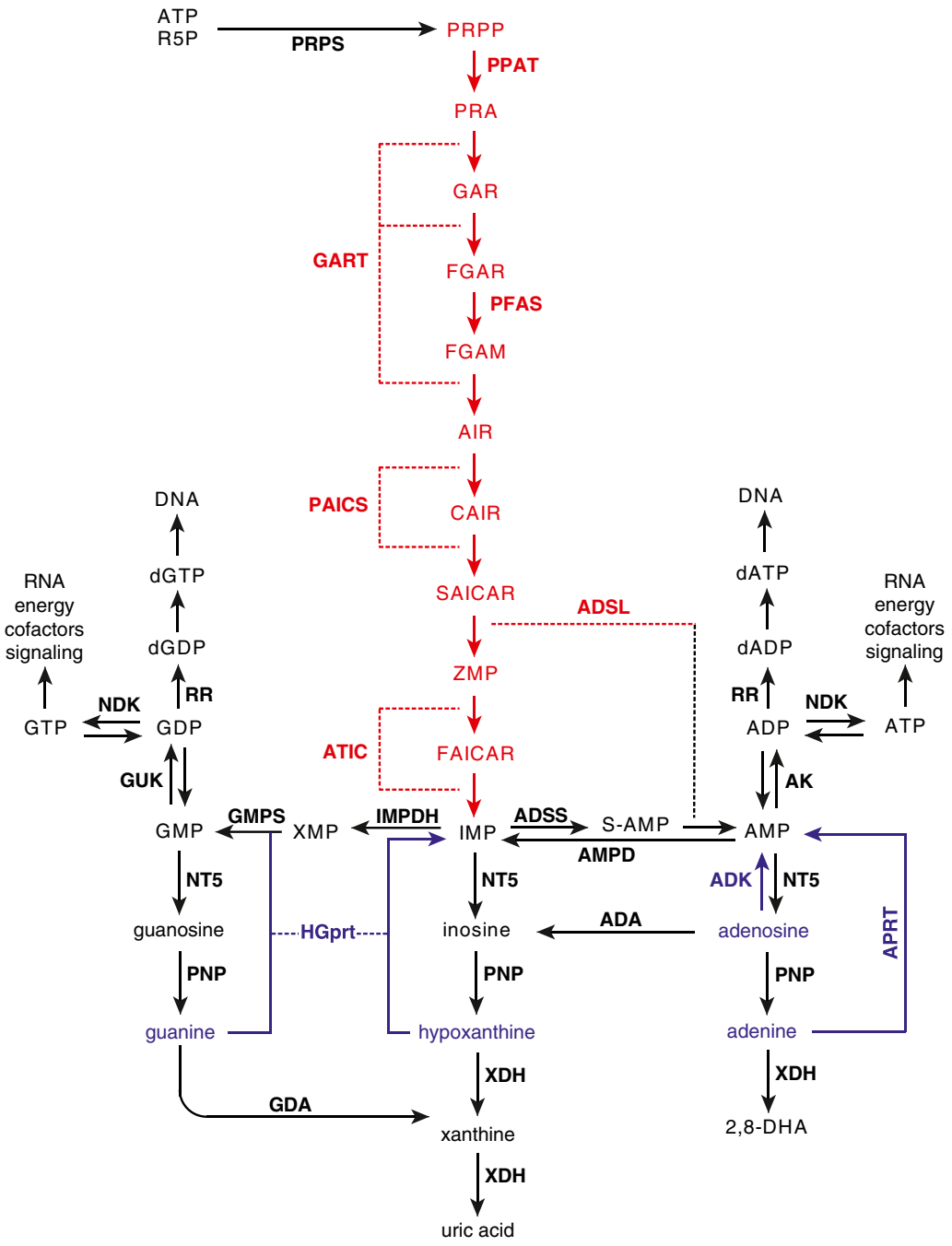

Fig. 110.2 Purine metabolism. The six enzymes and 10 reactions of de novo purine synthesis are shown in *red*. The two enzymes and three reactions of the salvage pathways are shown in *purple*. Enzyme gene names are shown in **bold font**, and metabolites are shown in regular font. For enzymes with multiple isoforms, only the core gene name is shown, without isoform numbers or letters. *Dashed lines* show enzymes with multiple functions. 2,8-DHA, Dihydroxyadenine; ADA, adenosine deaminase; ADP, adenosine diphosphate; ADK, adenosine kinase; ADSL, bifunctional adenylosuccinate lyase; ADSS, adenylosuccinate synthase; AICAR, aminoimidazole carboxamide ribotide; AMPD, adenylate deaminase; AMP, adenosine monophosphate or adenylate; APRT, adenine phosphoribosyltransferase; ATIC, bifunctional AICAR transformylase/IMP cyclohydrolase; AK, adenylate kinase; ATP adenosine triphosphate; CAIR, 5′-Phosphoribosyl-4-carboxy-5-aminoimidazole; dADP, deoxy adenosine diphosphate; dGDP, deoxy guanosine diphosphate; FAICAR, formylaminoimidazole carboxamide ribotide; GART, trifunctional phosphoribosylglycinamide formyltransferase/phosphoribosylglycinamide synthetase/phosphoribosylaminoimidazole synthetase; GDA, guanine deaminase (aka guanase or cypin); GDP, guanosine diphosphate; GMP, guanosine monophosphate or guanylate; GMPS, GMP-synthase; GTP, guanosine triphosphate; GUK, guanylate kinase; HGprt, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate or inosinate; IMPDH, IMP-dehydrogenase; NDK, nucleoside diphosphate kinase; NT5, 5′-nucleotidase; PNP, purine nucleoside phosphorylase; PAICS, bifunctional phosphoribosylaminoimidazole carboxylase; PFAS, phosphoribosyl formylglycinamide synthase; PPAT, bifunctional phosphoribosylaminoimidazole carboxylase; PRA, 5-phosphoribosylamine; PRPP, phosphoribosylpyrophosphate; PRPS, PRPP-synthase; RR, ribonucleotide reductase; S-AMP, adenylosuccinate; SAICAR, succinylaminoimidazole carboxamide ribotide; XDH, xanthine dehydrogenase, xanthine oxidase, or xanthine oxidoreductase; XMP, xanthine monophosphate or xanthylate; ZMP, 5-aminoimidazole-4-carboxamide ribonucleotide or Z-nucleotide monophosphate. (*Copyright H.A. Jinnah.*)

expression levels of different enzymes in different tissues and sometimes tissue-specific isoforms of the same enzyme.

DISORDERS OF PURINE METABOLISM

Uric Acid

Serum uric acid levels reflect a balance among production, absorption, and excretion. Most uric acid is produced in the body as a by-product of purine metabolism (see Fig. 110.2). Some also comes from the diet, when DNA and RNA of foods are metabolized by the gut and liver. About two thirds of the body's uric acid is eliminated by the kidneys, with the remainder eliminated by the gut. Normal serum uric acid levels are age dependent. Relatively low levels in young children reach adult values by puberty. After puberty, serum uric acid is lower in females than in males.

In adults, numerous epidemiologic studies have linked abnormal serum uric acid levels with a large number of disorders. High levels of uric acid have been linked with gout, kidney disease, tophi, hypertension, diabetes mellitus, obesity, metabolic syndrome, heart disease, stroke, hemolytic anemia, Down syndrome, asthma, and others. Causal links between uric acid and disease with well-defined biologic mechanisms are well established for gout, kidney disease, and tophi. Low levels of uric acid have been linked with Parkinson disease, Alzheimer disease, multiple sclerosis, and other autoimmune disorders. For these disorders, uric acid has been proposed to have antioxidant properties, so chronically low levels may contribute to cell injury during aging.

In children, low (or even absent) levels of serum uric acid do not appear to have any detrimental clinical effects, but high levels cause problems. Uric acid is normally near its limits of solubility in the body, so even small increases risk precipitation in vulnerable regions. The joints are one of these vulnerable regions, because of the low pH of synovial fluid. Such precipitates can cause an inflammatory arthritis known as **gout**. These precipitates tend to occur in cool regions of the body, such as distal joints of the toes. The typical presentation of gout is acute inflammation of one joint, often the metatarsophalangeal joint of the large toe, although any joint can be involved. Uric acid crystals also precipitate in cool regions of the skin, forming tophi at tendon insertion points over joints or the pinna of the ear. These tophi appear as visible and palpable subcutaneous masses. Excess uric acid is concentrated by the kidneys in the renal collecting system, where high levels precipitate in two different ways. Microscopic crystals may produce an inflammatory nephropathy with painless chronic renal failure. Larger stones may cause urinary obstruction with acute renal colic, dysuria, hematuria, and recurrent urinary infections. These pathologies may also overlap in some cases.

Hyperuricemia and its pathologic consequences are common in adults, especially males. These problems often reflect an inherited predisposition for high uric acid together with lifestyle related to diet and exercise. Hyperuricemia and its consequences are very uncommon in children. Their occurrence in children often signifies an underlying disorder of purine metabolism. Uric acid is a component of many routine clinical chemistry screening panels. As a result, abnormal levels of uric acid often provide an early clue to one of these disorders (Table 110.2). Kidney stones are common in adults, but they are very uncommon in children. Nephrolithiasis and renal failure also provide an important clue to disorders of uric acid and some other disorders of purine and pyrimidine metabolism (Table 110.3). Some are rare inherited disorders affecting specific biochemical pathways; others are acquired or iatrogenic.

Individual Disorders

Individuals with **renal hypouricemia** have marked reductions in serum uric acid (<2 μg/dL or <120 μM) from birth. The disorder is autosomal recessive and caused by pathogenic variants in the *SLC22A12* or *SLC2A9* genes, which code for transporters important for renal retention of uric acid. Many affected individuals remain asymptomatic for life. Some experience renal impairments after strenuous exercise because physical activity is associated with increased purine turnover and transient elevations of serum uric acid. When a sudden bolus of uric acid after exercise is concentrated quickly in the renal collecting system, there is a transient risk for stones or "sludge" with nephropathy. This sludge reflects a somewhat viscous mixture of tiny stones and partly solubilized uric acid. Gout is uncommon in renal hypouricemia.

Familial juvenile hyperuricemic nephropathy is an autosomal dominant disorder that has been linked to pathogenic variants in *UMOD* (uromodulin), *REN* (renin), *MUC* (mucin), or *HNF*-1b (hepatocyte nuclear factor 1b). All of these genes encode proteins involved in renal handling of uric acid. Affected individuals present in childhood or adolescence with hyperuricemia, renal failure, and/or gout. Individuals with pathogenic variants in the *ABCG2* gene have reduced intestinal secretion of uric acid, along with chronic hyperuricemia and gout.

Overproduction of uric acid may also occur in inherited **disorders of carbohydrate metabolism**. They include disorders associated with pathogenic variants in *ALDOB* (aldolase B deficiency, hereditary fructose intolerance, fructosemia), *SLC37A4* (glucose-6-phosphatase deficiency, glycogen storage disease type I, or von Gierke disease), *AGL* (glycogen debranching enzyme deficiency, glycogen storage disease type III, or Cori disease), *PYGM* (muscle glycogen phosphorylase deficiency, glycogen storage disease type V, or McArdle disease), and *PFKM* (muscle phosphofructokinase deficiency, or glycogen storage disease type VII, or Tarui disease). These disorders may be associated with chronic or episodic hyperuricemia, sometimes with gout or renal impairments. Hyperuricemia is often triggered by exercise because the metabolic defect impairs energy metabolism during muscle activity and leads to catabolism of adenosine triphosphate (ATP).

Some disorders of uric acid are *acquired* rather than inherited. Because uric acid is eliminated largely by the kidneys, acute or chronic renal insufficiency may lead to hyperuricemia, which may be severe. A transient but marked elevation of serum uric acid may also occur in **tumor lysis syndrome**, where the treatment of hematologic malignancies is associated with sudden death of many cells in a short period, leading to generation of large amounts of DNA and RNA that are degraded into uric acid. The sudden bolus of uric acid is rapidly concentrated by the kidneys, leading to a risk for kidney stones, sludge, and renal failure. Relatively more modest increases in serum uric acid have been associated with other childhood disorders, including obesity, metabolic syndrome, Down syndrome, asthma, cyanotic congenital heart disease, chronic hemolytic anemia, and certain medications. Medications causing hyperuricemia include thiazide diuretics, cyclosporine, and some anticonvulsants (valproate and phenobarbital).

Treatment and Prognosis

All renal purine stones, including those made of uric acid, are radiolucent. Unless they calcify, they cannot be detected with plain films or CT, so diagnosis may require ultrasound. Stones passed in the urine may be collected and chemically analyzed. Treatment of small kidney stones may require analgesics for renal colic and/or antibiotics for associated urinary tract infection until the stones are eliminated in the urine. Larger kidney stones may obstruct the urinary collecting system and may require lithotripsy or surgical removal. Because uric acid is more soluble in an alkaline environment, alkalinization of the urine with potassium-sodium citrate or sodium bicarbonate may be useful for individuals at risk for recurrent stones.

The diagnosis of gout can be made finding typical birefringent crystals in an aspirate of joint fluid. Because purine stones are radiolucent, chronic tophaceous gout may have a punched-out appearance on plain films of the joints, where the uric acid crystals have eroded normal bone. The treatment of acute painful gout usually involves nonsteroidal antiinflammatory drugs. However, for both gout and renal stones, treatments directed at uric acid levels are essential to prevent recurrences that may lead to permanent joint damage or chronic renal insufficiency. Chronic hyperuricemia can be treated with three different strategies. One strategy is to increase renal excretion of uric acid with drugs such as probenecid, sulfinpyrazone, benzbromarone, or lesinurad. Another strategy is to use drugs that inhibit uric acid production by xanthine oxidoreductase (XOR) such as allopurinol, febuxostat, and topiroxostat. The third involves administration of recombinant uricase

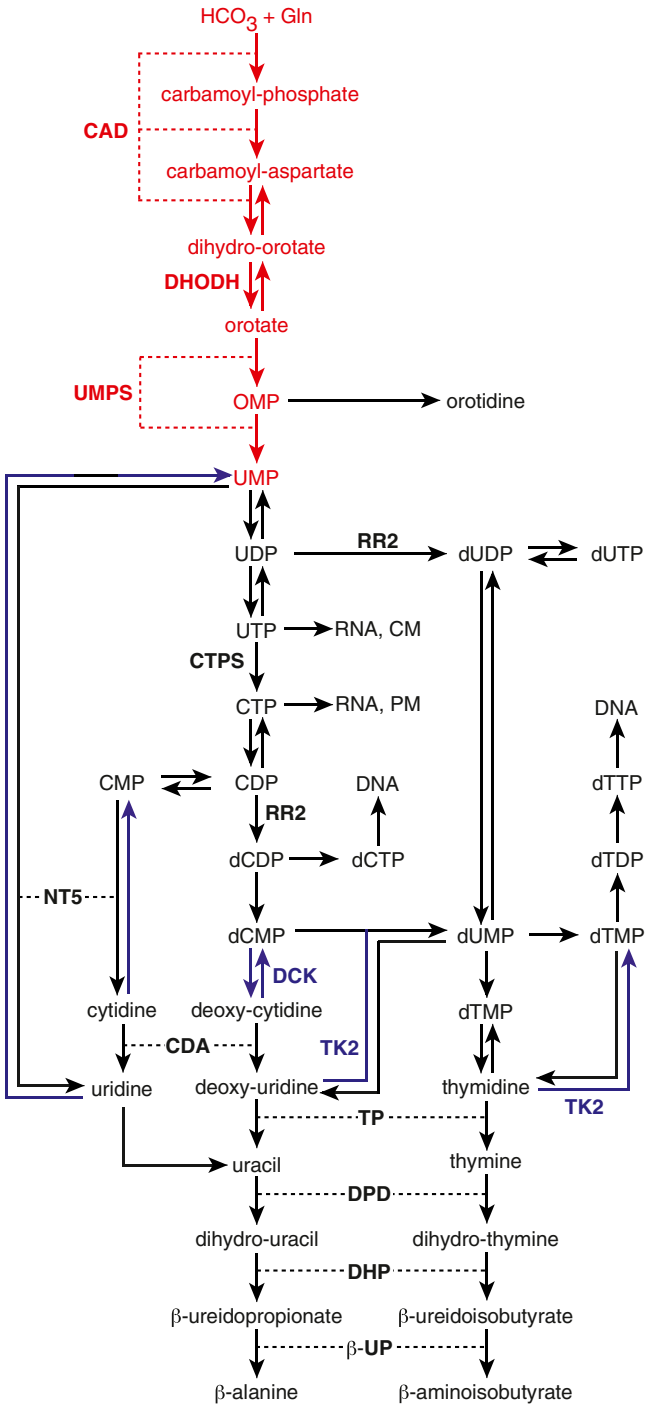

Fig. 110.3 Pyrimidine metabolism. The three enzymes and six reactions of de novo pyrimidine synthesis are shown in *red*. The enzymes of the salvage pathways are shown in *purple*. Enzyme gene names are shown in **bold font**, and metabolites are shown in regular font. For enzymes with multiple isoforms, only the core gene name is shown, without isoform numbers or letters. *Dashed lines* show enzymes with multiple functions. 5′NT, 5′-nucleotidase; β-UP, β-ureidopropionase; CAD, carbamoyl phosphate synthase; CDA, cytidine deaminase; CDP, cytidine diphosphate; CM, carbohydrate metabolism; CMP, cytidine monophosphate; CTP, cytidine triphosphate; CTPS, CTP synthase; dCDP, deoxy cytidine diphosphate; DCK; deoxycytidine kinase; dCMP, deoxycytidine monophosphate; dCTP, deoxycytidine triphosphate; DHODH, dihydro-orotate dehydrogenase; DHP, dihydropyrimidinase; DPD, dihydropyrimidine dehydrogenase; dTDP, deoxythymidine diphosphate; dTMP, deoxythymidine monophosphate; dTTP, deoxythymidine triphosphate; dUDP, deoxyuridine diphosphate; dUMP deoxyuridine monophosphate; dUTP, deoxyuridine triphosphate; gln, glutamine; OMP, orotidine monophosphate or orotic acid; PM, phospholipid metabolism; RR2, ribonucleotide reductase 2; TK2, thymidine kinase 2; TP, thymidine phosphorylase; UDP, uridine diphosphate; UMP, uridine monophosphate; UMPS, UMP synthase; UTP, uridine triphosphate. (*Copyright H.A. Jinnah.*)

(rasburicase or pegloticase), a nonhuman enzyme that can degrade uric acid.

The best choices for treatment depend on the biologic mechanisms causing excess uric acid. The many causes of hyperuricemia may be divided into two groups. The first group involves renal underexcretion, where hyperuricemia can be treated with uricosuric drugs or XOR inhibitors. The second group involves renal overload, which includes disorders where uric acid is overproduced in the body or underexcreted by the gut. Hyperuricemia associated with renal overload should be treated with XOR inhibitors, not with uricosuric drugs that further increase the burden of uric acid handled by the kidneys. Rasburicase is usually reserved for the transient marked increases in serum uric acid associated with tumor lysis syndrome. Pegloticase is usually reserved for the treatment of gout resistant to other medications.

These medications are usually combined with generous hydration to provide a constant flow of associated purine metabolites from the body. A low-purine diet is sometimes recommended as well. Some foods contain large amounts of purines, such as dried or cured meats (sardines, anchovies) and organ meats (thymus, kidney, liver). Fructose and alcohol also should be avoided because they stimulate purine turnover and result in increased uric acid production.

THE HEREDITARY XANTHINURIAS

The hereditary xanthinurias are a group of autosomal recessive disorders defined by high levels of xanthine in the urine, along with low or nondetectable serum uric acid. The estimated incidence is 0.5-1 per 100,000 live births. The metabolic abnormalities result from deficiency of XOR, the enzyme that converts hypoxanthine and xanthine into uric acid (see Fig. 110.2). XOR exists in two forms, sometimes called *xanthine oxidase* or *xanthine reductase,* both with a molybdenum-containing cofactor at the active site. These two forms are encoded by the same gene. Xanthine oxidase is derived from posttranslational modification of xanthine reductase.

Although the hereditary xanthinurias all result from XOR deficiency, distinct molecular mechanisms define three different groups. **Hereditary xanthinuria type I** is caused by pathogenic variants in the *XOR* gene. **Hereditary xanthinuria type II** is caused by pathogenic variants in the *MOCOS* gene, which encodes molybdenum cofactor sulfurase, an enzyme that sulfurates the molybdenum cofactor required for XOR as well as the enzyme aldehyde oxidase. As a result, hereditary xanthinuria type II is characterized by combined deficiency of XOR and aldehyde oxidase. The **third type of hereditary xanthinuria** is caused by defects in the synthesis of the molybdenum cofactor. Molybdenum cofactor deficiency has been linked with four genes: *MOCS1* (molybdenum cofactor synthase 1), *MOCS2* (molybdenum cofactor synthase 2), *MOCS3* (molybdenum cofactor synthase 3), and *GPHN* (gephyrin). *MOCS1* accounts for two thirds of all cases. All are required for the synthesis of the molybdenum cofactor, which is used by four enzymes including XOR, aldehyde oxidase, sulfite oxidase, and mitochondrial amidoxime reducing component. As a result, the molybdenum cofactor deficiencies are characterized by the combined defects of all four enzymes.

Clinical Features

The clinical features of hereditary xanthinuria type I caused by isolated XOR deficiency may be benign. Many individuals are asymptomatic. The increased excretion of xanthine leads to kidney stones in approximately one third of individuals. These stones may develop any time from early childhood through later adulthood. Clinical signs may be acute with dysuria, hematuria, renal colic, or a history of recurrent urinary tract infections. Alternatively, affected individuals may present with acute or chronic renal failure. Xanthine stones, like other purine stones, are radiolucent; they are detectable with ultrasound but may be missed on abdominal plain films or CT unless they calcify. Some individuals may develop myopathy after strenuous exercise with xanthine crystals in muscle because of the rapid turnover of purines associated with exercise.

The clinical features of combined deficiency of XOR and aldehyde oxidase in hereditary xanthinuria type II are similar to those of type I. There appears to be no obvious clinical impact of the added deficiency of aldehyde oxidase.

Table 110.2 Disorders Influencing Uric Acid

DISORDER	GENE SYMBOL	SERUM URIC ACID	URINARY URIC ACID
Hereditary xanthinurias			
Type I	*XOR*	↓↓	↓↓
Type II	*MOCOS*		
Molybdenum cofactor deficiencies	*MOCS1-3, GPHN*		
HPRT1-associated disorders	*HPRT1*	↑	↑↑
PRPP dysregulation disorders	*PRPS1*	↑	↑
Excretion disorders			
Renal hypouricemia	*SLC22A12, SLC2A9*	↓↓	↑↑
Reduced gut excretion	*ABCG2*	↑	↑
Carbohydrate disorders			
Fructosemia	*ALDOB*	↑ (chronic or exercise-induced)	↑ (chronic or exercise-induced)
Glucose-6-phosphatase deficiency	*SLC37AY*		
Glycogen debranching deficiency	*AGL*		
Glycogen phosphatase deficiency	*PYGM*		
Phosphofructokinase deficiency	*PFKM*		
Renal insufficiency	NA	↑	↓
Tumor lysis syndrome	NA	↑↑	↑↑

NA, not applicable. Copyright H.A. Jinnah.

Table 110.3 Renal Stones in Disorders of Purines and Pyrimidines

DISORDER	GENE SYMBOL	STONES
APRT deficiency	*APRT*	Dihydroxy-adenine
Familial juvenile hyper-uricemic nephropathy	*UMOD, REN, MUC,* or *HNF-1*b	Uric acid
Hereditary orotic aciduria	*UMPS*	Orotic acid
Hereditary xanthinurias		
Type 1	*XOR*	Xanthine
Type 2	*MOCOS*	Xanthine
Molybdenum cofactor deficiencies	*MOCS1-3, GPHN*	Xanthine
HPRT1-associated disorders	*HPRT1*	Uric acid
PRPP synthetase hyperactivity	*PRPS1*	Uric acid
Tumor lysis syndrome	Not applicable	Uric acid

Copyright H.A. Jinnah.

The clinical features of the **molybdenum cofactor deficiencies** are more severe. Individuals often present with failure to thrive during infancy, difficulties feeding, intractable seizures, psychomotor delay, and microcephaly. Brain MRI may show diffuse atrophy or cerebellar hypoplasia, multicystic encephalomalacia, and signal abnormalities of the globus pallidus. Eye findings may include ectopic lens, spherophakia, and nystagmus. Most die in early childhood.

Because uric acid is included in many routine blood chemistry screening panels, the diagnosis of the hereditary xanthinurias often starts with serendipitous identification of low or absent uric acid. Instead, urinary xanthine and hypoxanthine are elevated. However, xanthine is elevated more than hypoxanthine, because the latter can be recycled by HGprt or cleared by the kidneys. In individuals with hereditary xanthinuria type II with combined deficiency of XOR and aldehyde oxidase, urinary methyl-2-pyridone-carboxamide also is low or absent. The characteristic pattern observed among individuals with the molybdenum cofactor deficiencies includes low uric acid in serum and urine along with high urinary xanthine, hypoxanthine, sulfite, and S-sulfocysteine. Enzymatic tests for XOR are feasible but not commonly used for clinical diagnosis. They require biopsy of the liver or small bowel where the amounts of this enzyme reach high enough levels for measurement. A convenient test for aldehyde oxidase involves assessing its ability to oxidize a test dose of allopurinol to oxypurinol. Sulfite oxidase and molybdenum cofactor can be measured in liver or fibroblasts. A molecular diagnosis can be made by finding pathogenic variants in one of the relevant genes.

Treatment and Prognosis

The treatment of all hereditary xanthinurias involves generous hydration to constantly flush xanthine from the renal collecting system to avoid stone formation. Hydration is sometimes combined with a low-purine diet.

Aside from palliative care, minimal success has been achieved with numerous approaches to the treatment of the molybdenum cofactor deficiencies. However, cyclic pyranopterin monophosphate (fosdenopterin) can have a life-changing impact on the normally serious consequences of molybdenum cofactor deficiency associated with *MOCS1*. Treatment has been reported to normalize metabolic measures and allow near-normal development among individuals who start it at a very early age before there is significant brain damage. It is approved for use in individuals with *MOCS1* defects by the U.S. Food and Drug Administration (FDA).

HPRT1-ASSOCIATED DISORDERS

Disorders associated with the *HPRT1* gene are rare, with an overall prevalence of approximately three cases per million. Inheritance is X-linked and recessive, although sporadic cases are not uncommon. The gene encodes hypoxanthine-guanine phosphoribosyl transferase (HGprt), an enzyme responsible for two different reactions (see Fig. 110.2). In one reaction, the cosubstrate phosphoribosyl pyrophosphate (PRPP) is combined with the purine base hypoxanthine to produce IMP. In the other reaction, PRPP is combined with guanine to produce GMP. IMP and GMP are then recirculated into the nucleotide pools. When HGprt activity is impaired, its substrates accumulate. Accumulation of PRPP leads to excessive drive of purine synthesis, because PRPP is also used in the first and rate-limiting reaction of the de novo synthetic pathway. The substrates hypoxanthine and guanine also accumulate, and they are ultimately catabolized to uric acid. The combination of accelerated purine synthesis and increased catabolism of hypoxanthine and guanine results in a marked overproduction of uric acid. This overproduction of uric acid is responsible for several clinical features of *HPRT1*-associated disorders, including hyperuricemia, nephrolithiasis, gout, and tophi.

Overproduction of uric acid *is not* responsible for all the clinical features of HGprt deficiency. Reduced HGprt activity also leads to impaired recycling of hypoxanthine and guanine, with purine wasting. This loss of purines may lead to purine deficiency, especially in tissues where the synthetic pathway cannot compensate for purines lost due to the failure of recycling. Erythrocytes lack a fully operational synthetic pathway, so they are dependent on recycling purines taken up from the blood to maintain purines. These observations may account for *macrocytic anemia,* which is common in *HPRT1*-associated disorders.

A similar mechanism may occur in the brain, where purine recycling is important because purine synthesis is relatively low. In individuals

with HGprt deficiency, overt structural malformations are not usually found when performing routine clinical CT or MRI of the brain. Such studies are usually normal or they show only mild diffuse atrophy. However, advanced imaging methods have revealed several abnormalities. Quantitative MRI-based, voxel-based morphometry has revealed subjects with *HPRT1*-associated disorders to have volume loss in several brain regions. Similar studies, along with diffusion tensor imaging MRI, have revealed diffuse loss of white matter. The basal ganglia appear to be more affected than most other regions. In fact, PET scans have revealed a significant reduction in markers associated with basal ganglia dopamine systems.

Autopsy studies of the brains of individuals with *HPRT1*-associated disorders do not show signs of maldevelopment or neurodegeneration. Dopamine neurons are present, but they do not express normal levels of dopamine-related markers. Dysfunction of the basal ganglia is thought to be responsible for several of the neurologic features of *HPRT1*-associated disorders, including dystonia and self-injurious behavior. Dysfunction of corticospinal pathways may be responsible for cognitive impairment, spasticity, and seizures.

Clinical Features

Pathologic genetic variants in *HPRT1* are associated with a spectrum of clinical phenotypes (Fig. 110.4). Most cases are males, although rare females with defects in both *HPRT1* alleles have been described. More than 600 different gene variants are known. A complete loss of HGprt function is associated with most of these variants, such as deletions, insertions, nonsense substitutions, and some single amino acid substitutions. A partial loss of HGprt function is associated with other variants, usually conservative single amino acid substitutions and some splice variants.

The severity of the clinical phenotypes is related to the degree of associated enzyme impairment. The spectrum of clinical phenotypes is usually subdivided into three overlapping groups. *HPRT1* variants associated with a mean value of 12% of normal HGprt activity are associated with the mildest clinical phenotype. This phenotype is known as **HGprt-related hyperuricemia**. These individuals experience overproduction of uric acid, along with associated problems of hyperuricemia, nephrolithiasis, gout, and tophi. These individuals do not have overt neurologic or behavioral problems, although mild clumsiness or mild cognitive impairments may be disclosed with careful testing. The age at presentation ranges from infancy to adulthood, usually with renal problems or gout.

HPRT1 variants associated with a mean of 7% of normal HGprt activity are associated with an intermediate phenotype with overproduction of uric acid along with clinically overt neurologic impairments. This phenotype is known as **HGprt-related neurologic dysfunction**. Motor impairments vary widely and may range from minor clumsiness to a phenotype that resembles severe dyskinetic cerebral palsy. Cognitive deficits may range from attention-deficit disorder to moderate intellectual disability. These individuals typically present with delayed motor development, although some present with renal problems or gout.

HPRT1 variants associated with a mean value of 1% normal HGprt activity are associated with the most severe phenotype, known as **Lesch-Nyhan disease**. These individuals have overproduction of uric acid, disabling motor impairments, moderate intellectual disability, and an unusual behavioral syndrome. The motor problems begin with delayed development in infancy and evolve similar to severe dyskinetic cerebral palsy. Epilepsy is common. The most characteristic aspect of the behavioral syndrome is severe recurrent self-injury, with self-biting, self-hitting, recurrent scratching or poking, and others. Self-injury typically begins between 2 and 4 years of age but may be delayed until the teenage years. Other difficult behaviors are also common, such as impaired attention and impulsivity. Difficult behaviors may be also directed toward others. They include use of language that is foul, sexually inappropriate, or racially charged. Also frequent are hitting, grabbing, or spitting.

The diagnosis of any *HPRT1*-associated disorder should be suspected in a child or young adult with evidence for overproduction of uric acid such as hyperuricemia, uric acid nephrolithiasis, or gout. Uric acid (pink) crystals in diapers during infancy are frequently the first clue. Suspicion for an *HPRT1*-associated disorder increases when there is evidence for overproduction of uric acid along with a history of delayed motor development. The emergence of self-injurious behavior between 2 and 4 years of age often provides a more specific clue for Lesch-Nyhan disease. A definitive diagnosis requires demonstration of a pathogenic variant in the *HPRT1* gene and/or enzymatic evidence for reduced HGprt function.

Treatment and Prognosis

For all *HPRT1*-associated disorders, excessive production of uric acid must be treated to avoid renal complications and gouty arthritis. Treatment requires a lifelong combination of an inhibitor of XOR to reduce production of uric acid and generous hydration. The commonly used XOR inhibitor is allopurinol, although others can also be used. Doses are titrated to maintain serum uric acid within normal limits. Stones may continue to form despite treatment, and lithotripsy or surgical removal is sometimes required. High doses of XOR inhibitors that reduce serum uric acid to very low levels are discouraged, because this approach increases the risk of stones composed of the precursors xanthine and hypoxanthine. Some specialists advocate alkalinization of the urine to promote solubility of uric acid or a low-purine diet to reduce intake of purines that are metabolized to uric acid.

The motor disorder is dominated by dystonia, sometimes with spasticity. The increased muscle tone associated with these problems is most often treated with muscle relaxants such as benzodiazepines or baclofen. Anticholinergics and dopamine-related drugs are not generally successful. Several case reports describe great success with deep brain stimulation surgery, but the rate of surgical complications is unusually high, and the overall risk-benefit ratio does not favor universal recommendation of this approach.

The behavioral problems require a combination of physical protective devices, specific behavioral modification techniques, and sometimes pharmacotherapy. Most individuals with Lesch-Nyhan disease require regular restraints of the hands and arms to prevent self-hitting and biting of the fingers. Approximately half of all individuals require tooth removal to prevent biting of the lips and tongue. A custom-designed wheelchair with dangerous regions shielded is often needed. The most useful behavioral techniques involve extinction (ignoring) and redirection (distraction). Methods that use positive reinforcement are useful, but methods that use negative reinforcement amplify negative behaviors.

Individuals with the mildest clinical phenotypes may have a normal life span, provided uric acid is well-managed. Those with more severe phenotypes have a shorter life span, with death occurring in the teens through the fifth decade. Most frequent causes of death include aspiration pneumonia or complications from renal dysfunction. Cases of sudden unexplained death have also been reported.

APRT-ASSOCIATED DISORDERS

Disorders associated with the *APRT* gene are rare, with fewer than 1,000 individuals reported. More than 200 pathogenic variants have been described. Inheritance is autosomal recessive. The disorder has been reported worldwide, but there are clusters of individuals with the same genetic variants originating in Japan, France, and Iceland.

The *APRT* gene encodes adenine phosphoribosyl transferase (APRT), an enzyme that is responsible for catalyzing a reaction in which PRPP is combined with the purine base adenine to produce AMP (see Fig. 110.2). Deficiency of APRT leads to accumulation of adenine, which is metabolized by XOR into 2,8-dihydroxyadenine (DHA). DHA does not accumulate in serum because it is rapidly cleared by the kidneys. Because solubility of DHA is poor, it precipitates in the urinary collecting system as either small crystals or larger stones. Small crystals cause chronic renal insufficiency because they provoke tubulointerstitial nephritis, inflammation, and fibrosis. Larger stones may cause acute obstructive renal failure.

Clinical Features

Clinical manifestations are attributable to the kidneys, and they may develop in a wide age range from infancy through adulthood.

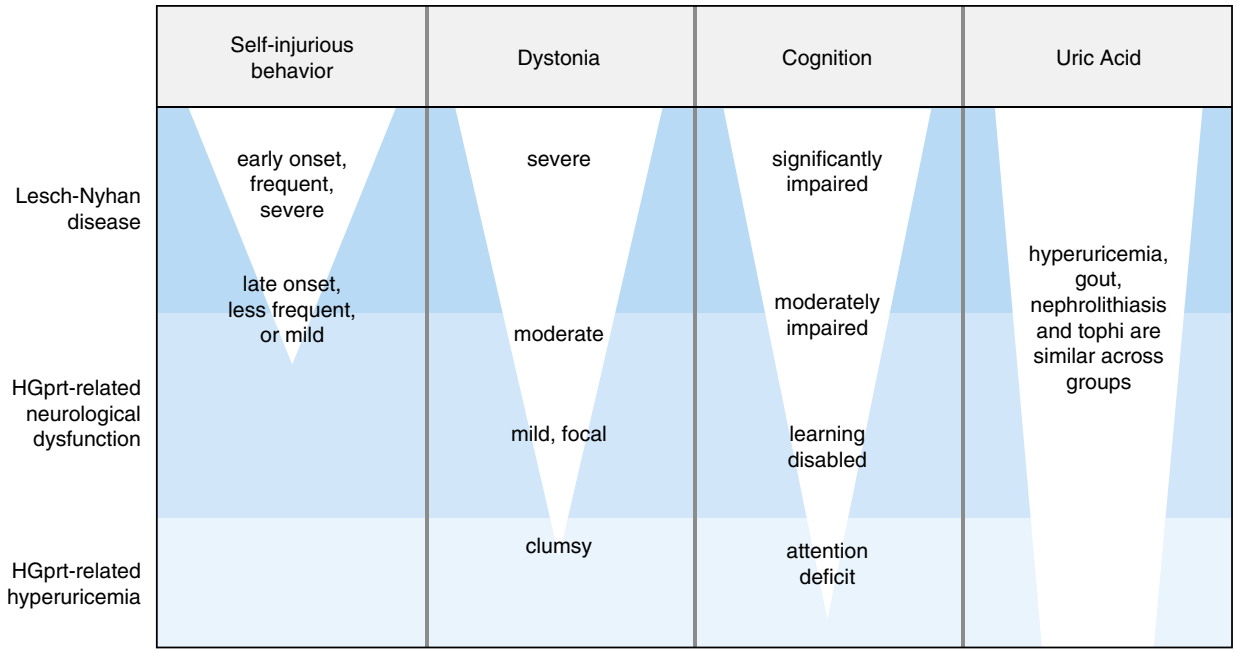

Fig. 110.4 *HPRT1*-associated disorders. This schematic provides a graphical representation of the overlapping spectrum of *HPRT1*-associated disorders. The three disorders are listed on the left side of the panel. The most common clinical features are shown in the top row. The *white triangles* depict the severity of individual clinical features for each of the disorders. For example, problems related to overproduction of uric acid occur in all phenotypes, but self-injurious behavior is limited to the most severe phenotype. Dystonia and cognition both show a wide range of severity across all groups, but severity correlates with overall phenotypic subgroup. This schematic provides only a general guide, as some exceptions may occur. (*Copyright H.A. Jinnah.*)

Approximately half of individuals with APRT deficiency have no symptoms, or symptoms may develop only in old age. The initial presentations fall into two groups which may overlap: nephrolithiasis and DHA nephropathy. Individuals with nephrolithiasis may present acutely with dysuria, hematuria, renal colic, or recurrent urinary tract infections. They may describe accompanying crystals, larger stones, or gravel in the urine. The precipitates are often reddish-brown in color and easily crushed. Alternatively, DHA nephropathy may result in a more slowly evolving renal insufficiency, with approximately 15% first presenting with end-stage renal failure.

The diagnosis should be suspected when there is evidence for crystalluria or nephrolithiasis, especially in a child. DHA stones, like other purine stones, are radiolucent. Unless they calcify, they may be detected via ultrasound but not with abdominal plain films or CT. The diagnosis may also be suspected in individuals with unexplained renal failure who undergo renal biopsy revealing a crystallopathy with tubulointerstitial nephritis, inflammation, and/or fibrosis. APRT deficiency must be distinguished from other disorders that involve nephrolithiasis and/or renal failure.

Commonly used clinical biochemical methods may not be able to distinguish DHA stones from other purine stones, but more specific methods have been developed at some specialized centers. DHA crystals in the urine can also be identified by light and polarizing microscopy, along with infrared spectrophotometry. Crystals in renal biopsy specimens can be identified by polarizing microscopy with infrared microscopy. Definitive diagnosis can also be achieved by measuring APRT enzyme activity in erythrocytes or by documenting pathogenic variants in the *APRT* gene.

Treatment and Prognosis

Treatment requires an inhibitor of XOR to reduce production of DHA. The commonly used XOR inhibitors include allopurinol or febuxostat, and they must be continued lifelong. Generous hydration is useful to flush purine metabolites through the renal collecting system. A low-purine diet is sometimes recommended. Large stones may require lithotripsy or surgical removal. Individuals who are diagnosed early in life and adhere to therapy may have a normal life span. Individuals who are diagnosed late may have chronic renal insufficiency or even renal failure that requires dialysis or kidney transplantation.

DISORDERS ASSOCIATED WITH AMP-DEAMINASE

The enzyme AMP-deaminase catalyzes the deamination of AMP to IMP with simultaneous production of NH_3. The IMP can then be recirculated either to AMP or GMP (see Fig. 110.2). The enzyme is encoded by three homologous genes. *AMPD1* is expressed predominantly in muscle, *AMPD2* is broadly expressed with high levels in the brain, and *AMPD3* is broadly expressed at high levels in bone marrow cells. Each gene has been associated with genetic variants producing null enzyme activity.

Clinical Features

For *AMPD1,* approximately 20% of White and Black individuals have a c.34C>T variant producing an early termination codon (p.Q12>X) in exon 2. In these populations, 1–2% are homozygotes with null enzyme activity in muscle. Most homozygotes have no symptoms, but **myopathic features** have been reported for some. These features include exercise intolerance with fatigue or myalgia, sometimes with muscle cramping or increased serum creatine kinase. Symptoms may begin at any age from early childhood to later adulthood. Histochemical stains for AMP-deaminase are negative in muscle biopsy specimens, but frank myopathic features are usually lacking. Because of the large numbers of nonsymptomatic individuals, the role of the genetic variant in causing symptoms is not clear. The variant may be benign, or it may combine with other genes or factors to cause symptoms. A diagnosis can be made via the forearm exercise test with measures of lactate and NH_3 production, histochemical staining of the enzyme in a muscle biopsy, or finding a variant in the *AMPD1* gene.

For *AMPD2,* pathogenic variants have been linked with **pontocerebellar hypoplasia** (PCH9). This neurologic disorder is rare, with fewer than 50 cases reported worldwide. Pontocerebellar hypoplasia is a group of disorders described by dysgenesis of the pons and cerebellum. Individuals with the PCH9 subtype also have dysgenesis of the

corpus callosum and microcephaly. Clinical symptoms include severe psychomotor delay, central visual impairment, and seizures.

ADSL-ASSOCIATED DISORDERS

Disorders associated with the *ADSL* gene are rare, with fewer than 100 individuals reported. The disorder is autosomal recessive. Pathogenic gene variants with complete loss of enzyme activity are likely incompatible with life. The pathogenic variants associated with disease produce a partial loss of enzyme function. The enzyme is bifunctional, and it mediates two distinct reactions in purine synthesis (see Fig. 110.2). Reduced enzyme function leads to accumulation of succinylpurines (succinyl-aminoimidazole carboxamide riboside and succinyl-adenosine), which are eliminated in the urine. Historically, this disorder was therefore called succinyl-purinuria. The clinical manifestations are thought to result predominantly from pathologic effects of succinyl purines in the brain. Brain MRI reveals varied findings from nearly normal to global or regional atrophy with delayed myelination.

Clinical Features

The clinical manifestations are often described in three distinct groups, but the groups overlap with a graded spectrum of severity. The most severely affected group is described as a **fatal neonatal encephalopathy**. These individuals have a severe paucity of spontaneous movement from birth, intractable seizures, and respiratory failure. They die within the first weeks of birth. Individuals in the **intermediate group** (type I) present with hypotonia and motor delay. They survive for longer periods, with moderate to severe psychomotor delay and seizures. Abnormal behaviors have been described as autistic with poor eye contact, repetitive stereotyped movements or sounds, and frequent agitation. The least severely affected group is referred to as **type II**. They present within the first years of life with evidence for psychomotor delay, sometimes with seizures and behavioral problems. The diagnosis is made by finding elevated succinyl purines in urine or cerebrospinal fluid (CSF) or by finding pathogenic variants in the *ADSL* gene.

Treatment and Prognosis

Treatment is palliative. Seizures may be refractory to conventional anticonvulsants, but some success has been reported with the ketogenic diet.

OTHER INHERITED PURINE DISORDERS

Adenosine Deaminase

Deficiency of adenosine deaminase results in **severe combined immunodeficiency syndrome (SCID)**, with defects in both humoral (B cells) and cellular (T cells) immunity. Individuals with severe SCID present shortly after birth with life-threatening infections. Individuals with milder disease may present at 2-4 years of age, or even older (see Chapter 165.1). In contrast with adenosine deaminase deficiency, superactivity of the same enzyme causes hemolytic anemia.

Adenosine kinase. Adenosine kinase is sometimes considered among the purine salvage enzymes because it recycles adenosine into adenosine monophosphate (AMP). Pathogenic variants of the associated *ADK* gene in multiple cases from independent families have been linked with hypermethioninemia, psychomotor delay, seizures, and multiple dysmorphic features. The disorder is autosomal recessive.

Adenylate kinase. There are four isoforms of adenylate kinase encoded by genes *AK1-4*. The enzyme phosphorylates AMP to ADP (see Fig. 110.2). The *AK1* gene is highly expressed in erythrocytes. Pathogenic variants in *AK1* in multiple cases from independent families have been linked with nonspherocytic hemolytic anemia, sometimes with cognitive disability.

The *AK2* gene is more broadly expressed but localizes to mitochondria. Pathogenic variants in *AK2* in multiple cases from independent families have been linked with reticular dysgenesis, a type of SCID, often with sensorineural hearing loss. Disorders associated with *AK1* and *AK2* are autosomal recessive.

Adenylosuccinate synthase. The *ADSS* gene encodes adenylosuccinate synthase, an enzyme involved in the conversion of IMP to AMP (see Fig. 110.2). There are multiple isoforms, and pathogenic variants in *ADSSL1* have been linked with a form of **myopathy**, **MPD5**. The disorder is autosomal recessive, usually begins in adolescence, and is slowly progressive. One study of affected individuals indicated that distal leg weakness was the most common feature, often with weakness of the hands. Approximately one third had weakness of the face or jaw muscles leading to difficulty with mastication. Some had left ventricular hypertrophy. Involvement of the diaphragm may lead to respiratory insufficiency in later stages of the illness.

ATIC-associated disorders. Disorders associated with the *ATIC* gene are very rare. Only four cases from three families have been reported. The disorder is autosomal recessive. The enzyme is bifunctional and mediates two distinct reactions (see Fig. 110.2). Complete loss of the enzyme is probably incompatible with life. Reduced enzyme function leads to accumulation of ZMP along with its phosphorylated derivatives. ZMP and its derivatives can be detected with the Bratton-Marshall test, a routinely used neonatal screen in some countries. All reported cases had prenatal and postnatal growth restriction, severe to profound psychomotor delay, chorioretinal atrophy with severe visual impairment, and dysmorphic facial features. Some had epilepsy. Treatment is palliative.

Deoxyguanosine kinase. The *DGK* gene encodes deoxyguanosine kinase, an enzyme that phosphorylates deoxypurine nucleosides into their respective deoxynucleotides for DNA synthesis (see Fig. 110.2). The gene is encoded by the nucleus, but the enzyme functions in mitochondria. Gene defects lead to an impairment of mitochondrial DNA synthesis, so the disorder is classified among the mitochondrial DNA depletion disorders. The disorder is rare and inherited in an autosomal recessive fashion. The clinical features reflect an early-onset multiorgan disorder, most notably liver failure, and psychomotor delay.

IMPDH-associated disorders. IMP-dehydrogenase is an enzyme that stands at a branchpoint in purine metabolism, directing the synthesis of purines toward guanine-based nucleotides rather than adenine-based nucleotides (see Fig. 110.2). This enzyme has two isoforms encoded by distinct but homologous genes. The *IMPDH1* gene is expressed primarily in the retina, whereas the *IMPDH2* gene is expressed in most other tissues. Disorders associated with these genes are rare, with only a handful of families reported.

Pathogenic variants in *IMPDH1* have been linked with **autosomal dominant retinopathy**. Affected individuals may have severe congenital retinal dysfunction with vision loss and pendular nystagmus **(Leber congenital amaurosis, LCA11)**. Others have childhood-onset retinitis pigmentosa with progressive visual impairment **(retinitis pigmentosa, RP10)**. There are no known treatments for either *IMPDH*-associated disorder.

Pathogenic variants in *IMPDH2* have been linked with an autosomal dominant neurologic disorder. Affected individuals may present with developmental delay, infantile dystonia, and seizures. Others present with a milder phenotype of dystonia that emerges in childhood or adolescence. There are no known treatments.

Phosphoribosylaminoimidazole carboxylase. The *PAICS* gene encodes a bifunctional enzyme that mediates two steps in the synthesis of purines (see Fig. 110.2). Pathogenic variants associated with *PAICS* are very rare, with only two individuals from a single family identified by exome sequencing. Both had multiple craniocervical malformations, and one had additional limb malformations. Both died within a few days of birth from respiratory failure.

Purine nucleoside phosphorylase. Deficiency of purine nucleoside phosphorylase results in selective dysfunction of T cells with susceptibility to viral illnesses. Two thirds have neurologic abnormalities, and one third have anemia. This disorder is covered in more detail in Chapter 165.2.

DISORDERS OF PYRIMIDINE METABOLISM

CAD Deficiency

The *CAD* gene encodes a trifunctional enzyme that mediates three of the initial six steps in pyrimidine synthesis (see Fig. 110.3). The disorder takes its name from the three relevant enzymatic activities, which include carbamoyl-phosphate synthetase, aspartate transcarbamylase,

and dihydroorotase. The associated clinical disorder is autosomal recessive.

Clinical Features

Fewer than 10 cases have been reported. Most presented in infancy with developmental delay, anisocytosis, and poikilocytosis. Most had medication-refractory seizures by 2 years of age, although epilepsy may start later. Many cases had global or cerebellar brain atrophy on MRI. The disorder cannot be identified by any of the metabolic tests routinely used for clinical diagnosis, but the activity of the enzyme can be measured. The disorder can also be identified by finding pathogenic variants in the *CAD* gene.

Treatment and Prognosis

Although it is quite rare, early diagnosis is important because treatment with uridine produces remarkably positive outcomes. Most of the subjects who were treated experienced a significant reduction in seizures, correction of hematologic abnormalities, and partial reversal of neurodevelopmental impairments. The disorder is therefore sometimes called **uridine-responsive epileptic encephalopathy**. It is likely that the degree of improvement depends on instituting treatments before significant brain damage occurs.

Dihydroorotate Dehydrogenase Deficiency

The *DHODH* gene encodes an enzyme that mediates the fourth of six steps in pyrimidine synthesis. The enzyme is localized in mitochondria, where electrons from the dehydrogenase are transferred to ubiquinone in the electron transport chain. A complete loss of the enzyme is not compatible with life, so all affected cases have had some residual enzyme function. The disorder is autosomal recessive.

Clinical Features

Fewer than 100 cases have been reported. Affected individuals have **Miller syndrome**, one of the acrofacial dysostosis syndromes where dysmorphic facial features are combined with abnormalities of the distal limbs. The facial anomalies include malar hypoplasia (underdeveloped cheekbones), micrognathia (small jaw), orofacial clefts (incomplete fusion of the roof of the mouth or lips), hypoplastic lower eyelids, and cup-shaped ears. The limb anomalies include abnormalities of the fifth and/or fourth fingers and toes (webbing, fusion, or hypoplasia), short forearms (ulnar hypoplasia sometimes with fusions to the radius), and hypoplasia of the fibula. Some cases also have other structural abnormalities such as pectus excavatum, rib defects, accessory nipples, or involvement of internal organs.

Treatment and Prognosis

There are no specific treatments for this disorder.

Hereditary Orotic Aciduria

The *UMPS* gene encodes a bifunctional enzyme that mediates two of the last six steps in pyrimidine synthesis (see Fig. 110.3). The relevant enzymatic activities are carried out by a single protein and include orotate phosphoribosyltransferase and orotidine 5′-monophosphate decarboxylase. These activities are sometimes combined under the term *UMP synthase,* and the disorder is sometimes known as *UMP synthase deficiency*. Affected individuals cannot convert orotic acid into UMP, so they excrete large amounts of orotic acid in the urine. Levels may be so high that orotic acid crystals may precipitate in the renal collecting system. Inheritance is autosomal recessive.

Clinical Features

The disorder is rare, with fewer than 50 reported cases. Most present in the first few weeks or months of age with failure to thrive and developmental delay. The majority have megaloblastic anemia, hypochromia, anisocytosis, and poikilocytosis. A few have had strabismus, congenital malformations, or seizures. Heterozygous carriers may excrete high levels of orotic acid without any additional symptoms.

The diagnosis is often first suspected by finding high levels of orotic acid in the urine. UMP synthase deficiency is not the only condition associated with high urinary orotic acid. Other disorders include urea cycle defects (e.g., ornithine transcarbamylase deficiency), some mitochondrial disorders, Reye syndrome, or treatment with medications (allopurinol and 6-azauridine). A definitive diagnosis of hereditary orotic aciduria comes from genetic testing that reveals pathogenic variants in the *UMPS* gene, and the enzyme can be measured in blood cells or fibroblasts.

Treatment and Prognosis

Although rare, early diagnosis is important because it is treatable with uridine. In general, supplements with uridine can reverse hematologic abnormalities and stimulate normal growth and development. Long-term treatments are associated with good results. Uridine triacetate is approved for treatment by the FDA.

Thymidine Phosphorylase Deficiency

The *TYMP* gene encodes thymidine phosphorylase, an enzyme responsible for converting thymidine to thymine (see Fig. 110.3). Deficiency of the enzyme results in marked elevations in blood thymidine. The disorder is autosomal recessive. Accumulation of phosphorylated derivatives of thymidine and deoxyuridine result in abnormal DNA replication in mitochondria and depletion of mitochondrial DNA. The enzyme has had two additional names used in the literature prior to its isolation and molecular identification. It is known as *platelet-derived endothelial cell growth factor* because of its angiogenic properties. It also is known as *gliostatin* because of a suppressive effect on the growth of glia.

Clinical Features

The disorder is rare and responsible for **mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)**. Symptoms begin in adolescents or young adults. Initial symptoms are often attributable to the gastrointestinal system and include diarrhea, vomiting, malabsorption, weight loss, and episodes of pseudoobstruction. Neurologic features include progressive external ophthalmoparesis, ptosis, myopathy, neuropathy, and hearing loss.

Treatment and Prognosis

There is no specific treatment for the early-onset severe phenotype. Treatment with 5-fluorouracil and related drugs is contraindicated.

DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY

The *DPD* gene encodes dihydropyrimidine dehydrogenase, the first enzyme involved in the catabolism of thymine and uracil (see Fig. 110.3). Genetic variants are common. Screening studies have suggested a prevalence of 3–5% for partial deficiency and 0.1–0.5% for severe deficiency. Severe enzyme deficiency is inherited in an autosomal recessive manner, and it is associated with marked elevations of thymine and uracil in urine, blood, and CSF. The associated disorder is therefore sometimes called **thiamine-uraciluria**.

Clinical Features

The clinical manifestations are quite varied, even among individuals who carry the same genetic variant. Some individuals with severe enzyme deficiency have no symptoms, and they are identified in adulthood because of severe toxicity after treatment with 5-flurouracil or related drugs. Others are identified in childhood, although fewer than 50 cases have been reported. Approximately half of these cases have had psychomotor delay, often with seizures. A few have presented with growth restriction, microcephaly, ocular abnormalities, or autistic behaviors.

Treatment and Prognosis

There is no specific treatment for the early-onset severe phenotype. For individuals with partial deficiency, treatment with 5-fluorouracil and related drugs is contraindicated.

Dihydropyrimidinase Deficiency

The *DPYS* gene encodes dihydropyrimidinase, the second enzyme involved in the catabolism of thymine and uracil (see Fig. 110.3).

Approximately 9% of individuals of European ancestry have genetic variants that substantially reduce enzyme activity, and 0.5% have almost no activity. Associated disorders are autosomal recessive. Severe enzyme deficiency is associated with marked elevations of dihydrothymine and dihydrouracil and in urine, blood, and CSF. The associated disorder is therefore sometimes called **dihydropyrimidinuria**.

Clinical Features

Genetic variants in *DPYS* are associated with very different clinical manifestations, even among individuals who carry the same genetic variant. The severe form of the disorder is rare, with fewer than 50 reported individuals. Some individuals with severe enzyme deficiency have no symptoms. Others are identified in childhood, with approximately half having psychomotor delay and a third having seizures. Gastrointestinal problems are common and include feeding difficulties with recurrent vomiting, malabsorption, and gastroesophageal reflux. A few have presented with growth restriction, microcephaly, or autistic behaviors.

Treatment and Prognosis

There is no specific treatment for the early-onset severe phenotype. Testing for common genetic variants before the use of 5-fluorouracil and related drugs has been recommended.

β-Ureidopropionase Deficiency

The *UPB1* gene encodes β-ureidopropionase, also known as *β-alanine synthase*. It is responsible for the last step of pyrimidine catabolism (see Fig. 110.3). Deficiency of the enzyme leads to accumulation of *N*-carbamoyl-β-alanine and *N*-carbamyl-β-aminoisobutyric acid in urine, blood, and CSF. As a result, the disorder is sometimes called ***N*-carbamoyl-β-amino aciduria**. The mechanism by which the enzyme defect leads to clinical disease is not well known.

Clinical Features

The disorder is autosomal recessive and rare, with fewer than 50 reported individuals. Affected individuals have psychomotor delay, seizures, microcephaly, and autistic behaviors. However, enzyme screening has revealed some individuals with no apparent symptoms. Diagnosis can be made by measuring accumulation of the associated metabolites, enzyme testing from liver biopsy, or finding pathogenic variants in the gene.

Treatment and Prognosis

There is no specific treatment for this disorder.

DISORDERS ASSOCIATED WITH THYMIDINE KINASE

Dividing cells rely on de novo synthesis of pyrimidines to make most of their nucleotides, but these pathways are downregulated in postmitotic cells, which primarily maintain pyrimidine nucleotides instead via salvage (see Fig. 110.3). Salvage enzymes include cytosolic thymidine kinase (*TK1* gene) and mitochondrial thymidine kinase (*TK2* gene). The *TK1* gene is often overexpressed in rapidly dividing cells and used as a marker for early detection or recurrence of cancer.

Pathogenic variants in the *TK2* gene impair the phosphorylation of thymidine and deoxycytosine, leading to reductions in associated nucleotides needed for DNA synthesis. The result is abnormalities in the rate and/or accuracy of mitochondrial DNA synthesis, with mitochondrial DNA depletion. Disorders associated with *TK2* are autosomal recessive, with three overlapping groups delineated by age at onset. Individuals with **infantile onset** (<1 year) have severe myopathy with proximal muscle weakness, facial diplegia, dysphagia, and respiratory compromise. Some may also have encephalopathy and seizures. Death usually occurs within 1-4 years. Individuals with the **childhood-onset** form (up to 12 years of age) have a more slowly progressive myopathy with weakness and longer survival periods. Those with **late onset** (>12 years of age) may have limited areas of weakness such as chronic progressive ophthalmoplegia, facial diplegia, or oropharyngeal weakness. There is no known treatment, but trials with relevant pyrimidine derivatives have been initiated.

COMBINED DISORDERS OF BOTH PURINES AND PYRIMIDINES

PRPS1-Associated Disorders

The *PRPS1* gene encodes the enzyme PRPP synthase type 1. Two additional isoforms of this enzyme are encoded by separate genes: *PRPS1L1* and *PRPS2*. *PRPS1* and *PRPS2* reside on opposite arms of the X chromosome, and *PRPS1L1* is on chromosome 7. *PRPS1* is ubiquitously expressed. *PRPS1L1* is expressed only in testis, and *PRPS2* is expressed in the gastrointestinal system, endocrine tissues, and reproductive organs. Only *PRPS1* has been linked with human disease. *PRPS1*-associated disorders are rare, with fewer than 1,000 individuals reported.

All three isoforms of PRPP-synthase transfer high-energy phosphate bonds from ATP to ribose-5-phosphate to generate PRPP. The PRPP can then use the high-energy phosphate bonds to drive certain energy-requiring reactions. PRPP is a cosubstrate for the first and rate-limiting reaction in purine synthesis (see Fig. 110.2). PRPP also serves as a cosubstrate for the main purine salvage enzymes HGprt and APRT. PRPP affects pyrimidine synthesis as well, because it is a cosubstrate for the first step in pyrimidine synthesis (see Fig. 110.3). PRPP is also a cosubstrate for two additional enzymes involved in the synthesis of the pyridine nucleotides: NAD and NADP (Table 110.4). PRPP-synthase plays a key role in regulating the synthesis of both purines and pyrimidines, and overexpression of *PRPS1* is common in certain cancer cells, which need large quantities of purines and pyrimidines for DNA replication during cell division.

Because of its integral involvement in many vital biochemical pathways, complete loss of PRPP-synthase is not compatible with life. Instead, clinical disease results from abnormally high enzyme activity or partial loss of enzyme activity. High levels of the enzyme produce excessive quantities of PRPP, and elevations in PRPP accelerate purine production, with resultant overproduction of uric acid. It is likely that increases in PRPP accelerate pyrimidine metabolism, but measures of this pathway are not widely used in clinical medicine. Conversely, impaired enzyme activity results in reduced metabolism of both purines and pyrimidines.

Clinical Features

The clinical phenotypes of *PRPS1*-associated disorders are remarkably diverse. Phenotypic variation is caused by varied changes in enzyme function. The phenotypes associated with *reduced enzyme activity* historically have been described as distinct entities, although clinical features overlap, and the reality is a continuous spectrum of severity (Fig. 110.5). The mildest phenotype is **X-linked nonsyndromic hearing loss (DFN2)**. Hearing impairments in males may range from a slowly progressive postlingual hearing loss to profound congenital deafness. A more severe phenotype associated with impaired enzyme activity has been called **Rosenberg-Chutorian syndrome or X-linked Charcot-Marie-Tooth disease (CMTX5)**. This phenotype in males combines prelingual hearing loss, progressive optic neuropathy, and peripheral neuropathy beginning at 5-10 years of age and sometimes gait impairments. An even more severe phenotype has been called **Arts syndrome**. It also is X-linked, and males have profound congenital deafness, early-onset optic neuropathy, peripheral neuropathy, psychomotor delay, and recurrent respiratory infections that may cause early death. In addition to these three phenotypes classically associated with reduced enzyme activity, there are reports that suggest a fourth and even more severe phenotype. Males have intrauterine growth restriction and failure to thrive after birth, congenital retinopathy and deafness, diabetes insipidus, and a more severe neurologic condition that includes severe psychomotor delay, spastic tetraparesis, seizures, and evidence for delayed white matter development on brain MRI.

The *PRPS1* gene is X-linked, so variants associated with reduced PRPP-synthase affect males, often from an early age. However, female carriers may express milder or adult-onset phenotypes. In families where males are affected only with early-onset hearing loss, female carriers may develop progressive hearing loss as young adults. In

families where males have a more severe early childhood phenotype that includes additional neurologic signs, female carriers may have progressive hearing loss, retinopathy, optic neuropathy, peripheral neuropathy, and sometimes additional signs attributable to the central nervous system. For the most severe phenotype, female carriers may also have short stature. In some families, only females are clinically affected, with evidence for embryonic lethality of males. These families suggest the existence of a fifth phenotype of embryonic lethality in males. Because hearing loss is the most consistent feature associated with reduced PRPP-synthase, the diagnosis of a *PRPS1*-associated disorder should be considered in males or females with sensorineural hearing loss, especially when combined with other neurologic signs.

There are also two different phenotypes associated with *abnormally high levels* of PRPP-synthase activity. The milder phenotype is associated with overexpression of a normal *PRPS1* mRNA transcript. Males present with signs of uric acid overproduction, including hyperuricemia and gout. Female carriers may also be affected. A more severe phenotype is associated with a point pathogenic variant in *PRPS1*, which renders the protein less durable but insensitive to feedback inhibition. The lack of feedback inhibition results in excessive PRPP production, with acceleration of purine synthesis and overproduction of uric acid. However, tissues with normally low levels of *PRPS1* may experience PRPP shortage because the enzyme is unstable. Erythrocytes lack a nucleus, so there is no ongoing mRNA transcription to provide a constant supply of new enzyme. In individuals with an unstable enzyme, erythrocyte PRPP-synthase is absent. A similar mechanism may explain the neurologic consequences, which overlap with those of PRPP-synthase deficiency syndromes. Affected individuals show signs of overproduction of uric acid combined with sensorineural hearing impairments, neuropathy, and/or psychomotor delay. The diagnosis of a disorder associated with excessive activity of PRPP-synthase should be suspected in any individual with evidence for overproduction of uric acid, especially when combined with the typical neurologic signs.

Treatment and Prognosis

The overproduction of uric acid in disorders associated with increased activity of PRPP-synthase is treated with inhibitors of XOR (allopurinol or febuxostat) combined with generous hydration. No treatments have proven effective in the treatment of disorders associated with reduced activity of the enzyme.

Disorders Associated with Nucleotidases

There are numerous enzymes that function as nucleotidases to remove phosphate groups from nucleotides (see Figs. 110.1 and 110.3). Many act nonselectively on multiple nucleotides and other small molecules, but they are often described according to their most prominent (or first discovered) enzymatic activity. At least five of these nucleotidases are cytosolic, one is bound to the plasma membrane, and another is localized to mitochondria. Early studies based on enzymatic activity did not always identify the exact isoform involved, but more recent studies have more precisely delineated the precise enzyme involved.

Nucleotidase-associated pervasive developmental delay. A marked increase in nucleotidase activity was found in cells of nine individuals with motor and cognitive delay, hyperactivity and impulsivity, delayed or absent language, seizures, awkward movements, and other abnormal behaviors. Some had immunologic impairments too. Although the exact enzyme and gene were not delineated, individuals had chronic hypouricemia, indicating reduced purine metabolism. Biochemical studies suggested the disorder was associated with depletion of pyrimidine nucleotides, and the behavioral abnormalities responded to uridine supplements.

Pyrimidine 5′-nucleotidase deficiency. The *NT5C3A* gene encodes an erythrocyte-specific 5′-nucleotidase isoform (P5N-1) with preferential activity toward the pyrimidines CMP and UMP (see Fig. 110. 3). Enzyme deficiency is inherited in an autosomal recessive manner and associated with accumulation of pyrimidine nucleotides in erythrocytes.

The clinical manifestations include chronic nonspherocytic hemolytic anemia; marked basophilic stippling and reticulocytosis; and accompanying splenomegaly, hemoglobinuria, and jaundice resulting from overproduction of bilirubin. The diagnosis is suspected when there is prominent basophilic stippling of erythrocytes, a phenomenon also associated with lead intoxication. Erythrocytes have an overabundance of pyrimidines, and the enzyme can be measured in red cells. The anemia is generally moderate and does not usually require transfusion.

Spastic paraplegia (SPG45). The *NT5C2* gene encodes a cytosolic 5′-nucleotidase with preferential activity toward IMP and other purine nucleotides. Pathogenic variants in this gene leading to reduced enzyme function have been linked with spastic paraplegia (SPG45). The disorder is rare and described for fewer than 20 individuals in a few different families. Affected individuals have early-onset gait impairment with leg weakness, spasticity, hyperreflexia, clonus, and extensor plantar reflexes. Many also have cognitive impairments. MRI may show white matter brain changes with dysgenesis of the corpus callosum.

Desbuqois dysplasia type 1 (DBQB1). The *CANT1* gene encodes a secreted calcium-dependent enzyme that functions as a triphosphatase or diphosphatase with activity toward ATP, ADP, UTP, and UDP. Pathogenic variants in this gene have been linked with a rare form of osteochondrodysplasia. Affected individuals have short stature with short limbs, joint laxity with frequent joint dislocations, pectus carinatum, osteopenia, dysmorphic facies, and intellectual disability.

Table 110.4 Enzymes Dependent on Phosphoribosylpyrophosphate

ENZYME	GENE	PATHWAY
Amido phosphoribosyl transferase	*PPAT*	Purine synthesis
Hypoxanthine-guanine phosphoribosyl transferase	*HPRT1*	Purine recycling
Adenine phosphoribosyl transferase	*APRT*	Purine recycling
Orotate phosphoribosyl transferase Uridine monophosphate synthetase	*UMPS*	Pyrimidine synthesis
Nicotinate phosphoribosyl transferase	*NAPRT*	NAD synthesis
Nicotinamide phosphoribosyl transferase	*NAMPT*	NADP synthesis

NAD, Nicotinamide adenine dinucleotide; NADP, nicotinamide-adenine dinucleotide phosphate.

Copyright H.A. Jinnah.

DISORDERS ASSOCIATED WITH RIBONUCLEOTIDE REDUCTASE

Ribonucleotide reductase is the enzyme responsible for generating the deoxynucleotides dADP, dCDP, dGDP, and dUDP (see Figs. 110.1 and 110.3). These deoxynucleotides are used to synthesize DNA, so the enzyme plays a key role in regulating DNA replication for cell division. The enzyme is the target for hydroxyurea used for sickle cell anemia and certain malignancies. The human enzyme has three subunits, but only the subunit encoded by the *RRM2B* gene has been linked with human disease.

Clinical Features

Pathogenic variants in *RRM2B* are responsible for a **mitochondrial DNA depletion syndrome** with severe encephalomyopathy. The disorder is inherited in an autosomal recessive manner. Only a handful of cases from a few families have been reported. Pathogenic variants in the same gene have also been linked with an autosomal dominant **progressive external ophthalmoplegia (PEOA5)**. Only a few cases have been reported. There is no specific treatment for either disorder.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

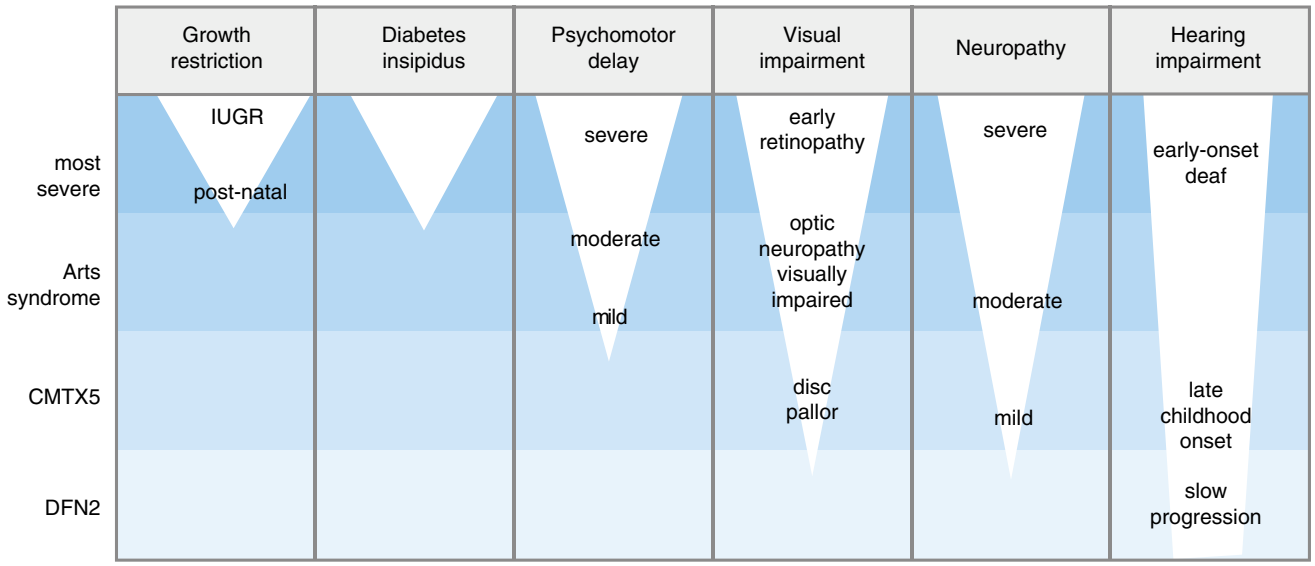

Fig. 110.5 *PRPS1*-associated disorders. This schematic provides a graphical representation of the overlapping spectrum of *PRPS1*-associated disorders. The four disorders are listed on the left side of the panel. The most common clinical features are shown in the top row. The *white triangles* depict the severity of individual clinical features for each of the disorders. For example, hearing loss may begin in adulthood with slow progression in the milder phenotypes (DFN2), whereas it may be reflected as earlier or more complete deafness in the more severe phenotypes. Conversely, growth retardation and diabetes insipidus have been reported only for the most severe phenotype. This schematic provides only a general guide, as some exceptions may occur. (*Copyright H.A. Jinnah.*)

Chapter 111

Hutchinson-Gilford Progeria Syndrome (Progeria)

Timothy R. O'Toole and Leslie B. Gordon

Hutchinson-Gilford progeria syndrome (HGPS, or progeria) is a rare, fatal, autosomal dominant segmental premature aging disease. With an estimated incidence of 1 in 4 million live births and prevalence of 1 in 20 million living individuals, there are an estimated total of 400 children living with progeria in 2023 worldwide. There is no gender, ethnic, or regional bias.

Progeria is caused by a single-base pathogenic variant in the *LMNA* gene, which results in the production of an abnormal lamin A protein called **progerin**. Lamin A is an intermediate-filament inner nuclear membrane protein found in most differentiated cells of the body. Without progerin-directed treatment, children with progeria develop **premature progressive atherosclerosis** and die of heart failure, usually between ages 5 and 20 years. Progerin is found in increased concentration in the skin and vascular wall of normal older individuals compared with younger individuals, suggesting a role in normal aging.

CLINICAL MANIFESTATIONS

Children are born looking normal and begin to develop clinical signs of disease during year one. Physical appearance and clinical findings change dramatically each year that they age (Figs. 111.1 and 111.2). Both clinical and biologic overlaps with aging are segmental, or partial. The disease features discussed next are roughly in order of clinical appearance.

Dermatologic Changes in Skin, Hair, and Nails

Skin findings are often apparent as initial signs of progeria—at birth in about 25% of cases and by age 2 months in 80% of cases. These are variable in severity and include areas of discoloration, stippled dyspigmentation, tightened areas that can restrict movement, and areas of the trunk or legs where small (1-2 cm), soft, bulging skin is present.

Although usually born with normal appearance, cranial hair is lost within the first few years. Initial hair loss occurs in the temporal and occipital areas, with preservation of hair on the mid-scalp and vertex for the longest period. Eventually total alopecia occurs, leaving soft, downy, sparse, immature hair on the scalp, no eyebrows, and scant eyelashes.

Nails on hands and feet are usually normal at birth but become dystrophic later in life.

Failure to Thrive

Children with progeria experience apparently normal fetal and early postnatal development. Between several months and 1 year of age, abnormalities in growth and body composition are readily apparent. Severe failure to thrive ensues, heralding generalized lipoatrophy, with apparent wasting of limbs, circumoral cyanosis, and prominent veins around the scalp, neck, and trunk resulting from a paucity of subcutaneous fat. The weight percentile is usually normal at birth but decreases to below the third percentile despite adequate caloric intake for normal growth and normal resting energy expenditure. A review of 35 children showed an average weight increase



Fig. 111.1 Distinguishing clinical features in Hutchinson-Gilford progeria syndrome. **A,** Alopecia, prominent scalp veins, narrowed nasal bridge, retrognathia. **B,** Generalized lipoatrophy leaves muscular prominence. **C,** Skin tightening and mottling. **D,** Skin bulging. **E,** Digital joint contractures. **F,** Nail dystrophy with spooning. **G,** Knee joint contractures, lipodystrophy. **H,** Corneal scarring secondary to exposure keratopathy. **I,** Flat umbilicus with scarred-over appearance; **J,** Calcinosis cutis in a digit. (*Photos courtesy The Progeria Research Foundation and Boston Children's Hospital.*)

of only 0.44 kg/year, beginning at 24 months of age and persisting through life. Weight gain over time is linear, which contrasts with the pulsatile acceleration in growth velocity for normal age- and gender-matched children. Children reach an average final height of approximately 1 meter and weight of approximately 15-20 kg. Head circumference is normal. The weight deficit is more pronounced than the height deficit and, associated with the loss of subcutaneous fat, results in the emaciated appearance with muscular prominence. Clinical problems caused by the lack of subcutaneous fat include sensitivity to cold temperatures and foot discomfort caused by lack of fat cushioning. Overt diabetes is unusual in progeria, but at least 75% of children eventually develop insulin resistance, usually starting at around age 8 years.

Musculoskeletal Impairments

Both upper and lower extremity range-of-motion impairments (e.g., fingers, elbows, hips, knees, ankles) may be present at birth and may progress with age. Joint contractures are caused by both bony and cartilaginous disease, along with tightened skin. Along with irregularities in the congruency of articulating joint surfaces, these changes serve to limit joint motion and affect both upper and lower extremity gross and fine motor function. *Physical therapy is recommended routinely and throughout life to maximize joint function.*

Ocular Abnormalities

Ophthalmic signs and symptoms are caused in part by shallow orbits, tight skin, and a paucity of subcutaneous fat around the eyes. Eyes are prominent and often experience ocular surface disease secondary to nocturnal lagophthalmos and exposure keratopathy, which produce photophobia, tearing, ocular irritation, corneal scarring, and corneal ulceration that can lead to vison loss. Most patients have relatively good acuity; however, advanced ophthalmic disease can be associated with reduced acuity. *Children with progeria should have an ophthalmic evaluation at diagnosis and at least yearly thereafter.* Aggressive ocular surface lubrication is recommended, including the use of tape tarsorrhaphy at night.

Craniofacial and Dental Phenotypes

Children develop craniofacial disproportion, with micrognathia and retrognathia caused by mandibular hypoplasia. Typical oral and dental manifestations include hypodontia, delayed tooth eruption, severe dental crowding caused by hypoplastic maxilla and mandible, ogival palatal arch, ankyloglossia, presence of median sagittal palatal fissure, and generalized gingival recession. Eruption may be delayed for many months, and primary teeth may persist for the duration of life. Secondary teeth are present but may or may not erupt. They sometimes erupt on the lingual and palatal surfaces of the mandibular and maxillary alveolar ridges, rather than in place of the primary incisors. In some, but not all cases, extracting primary teeth promotes movement of secondary teeth into place.

Skeletal Abnormalities

Development of bone structure and bone density represents a unique skeletal dysplasia that is not based in malnutrition. Acroosteolysis of the distal phalanges, distal clavicular resorption, and thin, tapered ribs are early signs of progeria (as early as 3 months

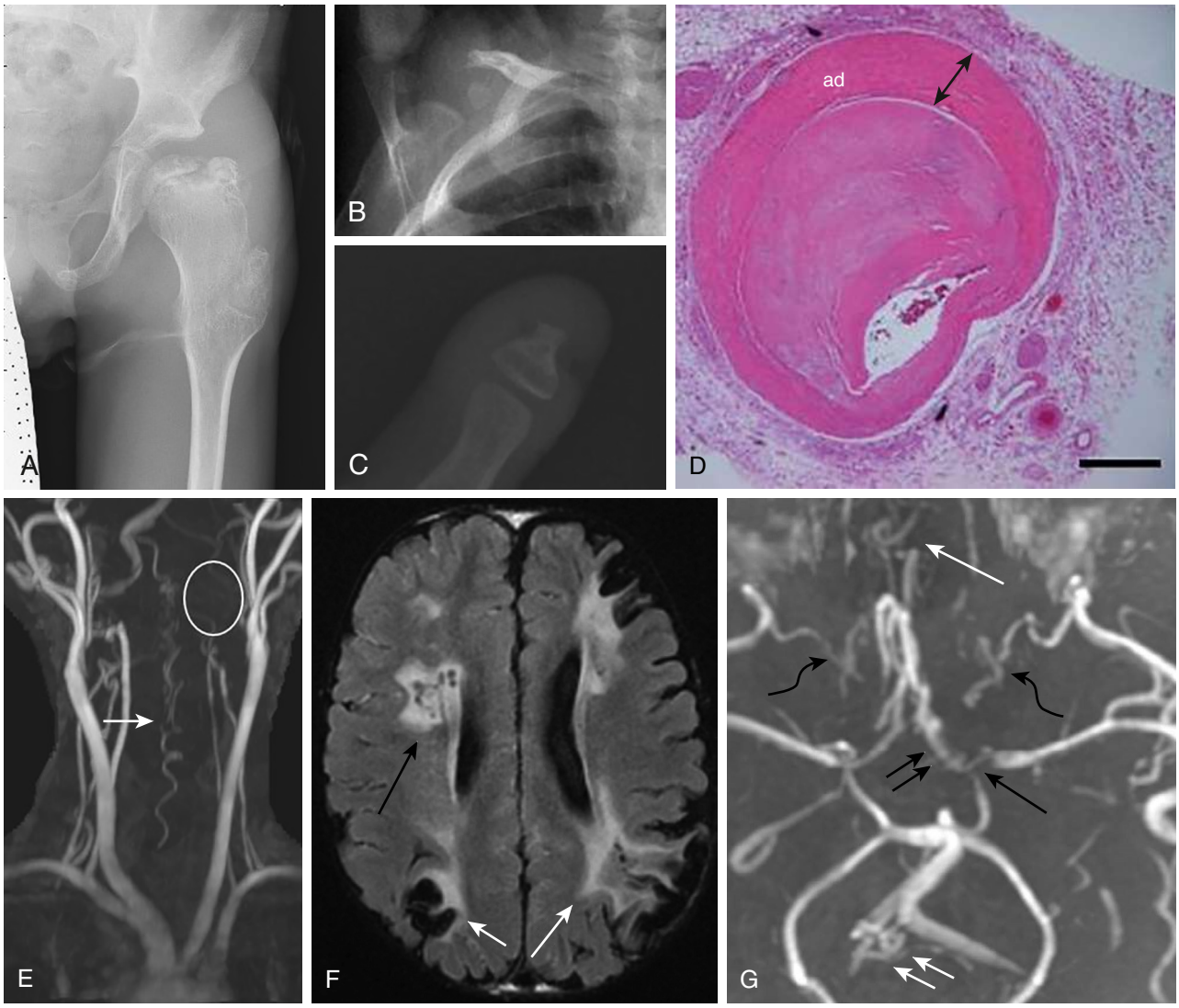

Fig. 111.2 Pathologic skeletal and cardiovascular findings in Hutchinson-Gilford progeria. **A,** Coxa valga of the hip. **B,** Clavicular osteolysis. **C,** Acroosteolysis in a thumb. **D,** H&E staining of mid-right coronary artery characterized by an enlarged and highly fibrotic adventitia *(arrow).* The media is markedly thinned in the area with adventitial fibrosis and plaque showing clinically significant stenosis (90%) and a necrotic core with calcification (staining not shown). **E,** Near-complete loss of the distal vertebral artery *(circle)* and prominent anterior spinal artery collateral *(arrow).* **F,** Acute gyral infarcts *(black arrow).* Bright signal in the sulci indicates slow cortical collateral flow *(white arrows).* **G,** M1 *(single black arrow)* and A1 stenoses *(double black arrows),* internal maxillary artery collaterals *(wavy black arrows),* subfrontal collaterals *(single white arrow),* and enlarged anterior and posterior spinal arteries *(double white arrows).*

of age). *Facial disproportion, a narrowed nasal bridge, and retrognathia make intubation extremely difficult, and fiberoptic intubation is recommended.* A pyriform chest structure and small clavicles can lead to reducible glenohumeral joint instability. Growth of the spine and bony pelvis is normal. Hip disease is pervasive and results in repeated dislocations in about 20% of cases that are not amenable to splinting. Dysplastic growth of the femoral head and neck axis results in coxa valgus (straightening of the femoral head-neck axis >125 degrees) and coxa magna, where the diameter of the femoral head is disproportionately large for the acetabulum, resulting in hip instability. The resulting hip dysplasia can be progressive and may result in osteoarthritis, avascular necrosis, hip dislocation, and inability to bear weight.

In response to repeated hip dislocations, five instances of either unilateral or bilateral surgical correction of hip dysplasia using periacetabular and femoral osteotomy have been conducted, each at different hospitals. Follow-up after 4-8 years has yielded mixed results. Other than in a single instance, hip dislocations have not recurred. In two cases, postsurgical healing occurred normally, resulting in ability to bear weight and walk short-to-long distances. In two cases, hardware failure with nonunion of femoral bone necessitated hardware removal and new hardware insertion; skin breakdown and need for additional bone grafting complicated one of these cases. These two cases yielded limited weight-bearing with no assistance when walking short distances, but the patients required wheelchair use for longer distances. Finally, one case healed well with no adverse events, but mobility was not restored because of postsurgery progression of joint contractures, resulting in inability to bear weight or walk and subsequent wheelchair use. Adequate vitamin D levels are likely important for bone healing in all cases.

Other changes to the appendicular skeleton include flaring of the humeral and femoral metaphyses and constriction of the radial neck. Growth plate morphology is generally normal but can be variable within a single radiograph. The appearance of ossification

centers used to define bone age is normal. Bone structure assessed by peripheral quantitative computed tomography (pQCT) of the radius demonstrates distinct and severe abnormalities in bone structural geometry, consistent with progeria representing a *skeletal dysplasia*. Areal bone mineral density (aBMD) *z* scores measured by dual-energy x-ray absorptiometry (DXA) adjusted for height and age and true (volumetric) BMD assessed by pQCT are normal to mildly reduced, refuting the assumption that patients with progeria are osteoporotic. Fracture rates in progeria are normal and not associated with fragility fractures observed in other pediatric metabolic bone diseases, such as osteogenesis imperfecta.

Hearing

Low-tone conductive hearing loss is pervasive in progeria and likely indicative of a stiff tympanic membrane and/or deficits in the middle ear bony and ligamentous structures. Overall, this does not affect the ability to hear the usual spoken tones, but preferential classroom seating is recommended, along with annual hearing examinations.

Cardiovascular Disease

Approximately 80% of deaths in progeria are caused by cardiovascular failure, with end-stage events sometimes precipitated by superimposed respiratory infection or stressors surrounding surgical intervention. Progeria is a **primary vasculopathy** characterized by pervasive accelerated vascular stiffening, followed by large- and medium-vessel occlusive disease from atherosclerotic plaque formation, with valvular and cardiac calcification and insufficiency at advanced stages of disease. Some evidence of vascular dysfunction is apparent in all ages tested. ECG abnormalities are generally nonspecific, but indications of left ventricular hypertrophy and nonspecific ST-T wave abnormalities can occur later in disease progression. Hypertension, angina, cardiomegaly, metabolic syndrome, and congestive heart failure are common end-stage events.

Transthoracic echocardiography reveals early-onset diastolic left ventricular dysfunction associated with age-related decline in lateral and septal early (E′) diastolic tissue Doppler velocity *z* scores and an increase in the ratio of mitral inflow (E) to lateral and septal E′ velocity *z* scores. Other echocardiographic findings include left ventricular hypertrophy, left ventricular systolic dysfunction, and mitral or aortic valve disease with calcification, which tend to appear later in life.

Vascular stiffening assessed using carotid and femoral ultrasound reveals elevated carotid-femoral pulse wave velocity (PWV_{cf}) and wall echodensity with medial and adventitial thickening. These are considered early and important indicators of cardiovascular decline. In the general population, increased PWV_{cf} is associated with increased risk of cardiac death. Intima-media thickness is normal. In addition, elevated carotid artery mean flow velocities appear early in life, and underscore the presence of arterial occlusive disease.

Routine blood pressure (BP) monitoring with special attention to proper cuff size is recommended. When normalized for patient size using height and age correction, both systolic and diastolic BP are increased in about half of patients with HGPS. These elevated BP trends would be expected in the setting of significant vascular stiffness. *Antihypertensive medications have been used in the setting of elevated BP, with special attention to maintaining adequate BP to avoid strokes.*

BP monitoring, ECG, echocardiography, carotid ultrasound for plaque evaluation, and PWV_{cf} measures for vascular stiffening are recommended.

End-stage cardiovascular disease (CVD) in progeria is often characterized by atherosclerotic plaques in large and medium-sized arteries, severe aortic stenosis, and cardiac failure. Critical aortic stenosis with heart failure is amenable to transapical transcatheter aortic valve implantation and apico-aortic conduit surgeries to alleviate severe aortic stenosis. These carry high risk of death but have yielded significant symptomatic improvement and prolongation of life in several cases (see treatment section).

Cerebrovascular Arteriopathy and Stroke

The earliest incidence of stroke occurred at age 0.4 years. More often, strokes occur in the later years. Over the life span, MRI evidence of infarction can be found in as many as 60% of patients with progeria, with half of these clinically silent. Both extracranial and intracranial occlusive disease is present in the neurovascular axis, with resulting extensive collateral vessel formation that pseudonormalizes intracranial flow. Carotid artery blockages are well documented, but infarction can occur even in their absence. Both large- and small-vessel disease is found; collateral vessel formation is extensive. A propensity for strokes and an underlying stiff vasculature make maintaining adequate blood pressure through oral hydration a priority in patients with progeria; special care should be taken when considering maintenance of consistent BP during general anesthesia, airplane trips, and hot weather. In addition, 15% of deaths in children with progeria occur from head injury or trauma, including subdural hematoma. This implies an underlying susceptibility to subdural hematoma, though known risk of stroke is much higher and frequently warrants low-dose aspirin therapy.

Sexual Development

Females with progeria can develop Tanner stage II secondary sexual characteristics, including signs of early breast development and sparse pubic hair. Progression to Tanner stage III has not been observed. Despite minimal to absent physical signs of pubertal development and markedly reduced body fat, over half of females experience spontaneous menarche at a median age of 14 years. Menarche is not preceded by gain in body mass or increase in body fat. Timing of menarche is variable; some adolescents start menstruation at Tanner stage I without progression to Tanner II, while others start at Tanner stage II. Those experiencing menarche vs nonmenstruating females have similar body mass indices, percentage body fat, and serum leptin levels, all of which are vastly below the healthy adolescent population. Menorrhagia has been observed and can result in symptomatic anemia. *In addition to iron supplementation, oral contraceptives may be indicated to regulate menses.* Progestin-only or minimal estrogen-content products are preferred because of elevated cardiovascular risks associated with estrogen-based medication in the face of HGPS-associated atherosclerosis. There are no documented cases of reproductive capacity in females or males with progeria; however, the data suggest there is potential for further sexual development and the possibility of fertility in these females. Secondary sexual characteristics in males have not been reported.

Normally Functioning Systems

Liver, kidney, thyroid, immune, gastrointestinal, and neurologic function (other than stroke related) remain intact. Intellect is normal for age, possibly in part from downregulation of progerin expression in the brain by a brain-specific micro-RNA, miR-9.

LABORATORY FINDINGS

The most consistent laboratory findings are low serum leptin below detectable levels (>90%) and insulin resistance (75%, usually starting over age 8 years). Platelet count is often moderately high. High-density lipoprotein (HDL) cholesterol and adiponectin concentrations decrease with increasing age to values significantly below normal. Otherwise, lipid panels, high-sensitivity C-reactive protein, blood chemistries, liver and kidney function tests, endocrine test, and coagulation tests are generally normal.

MOLECULAR PATHOGENESIS

Pathogenic variants in the *LMNA* gene cause progeria. The normal *LMNA/C* gene encodes the proteins lamins A and C, of which only lamin

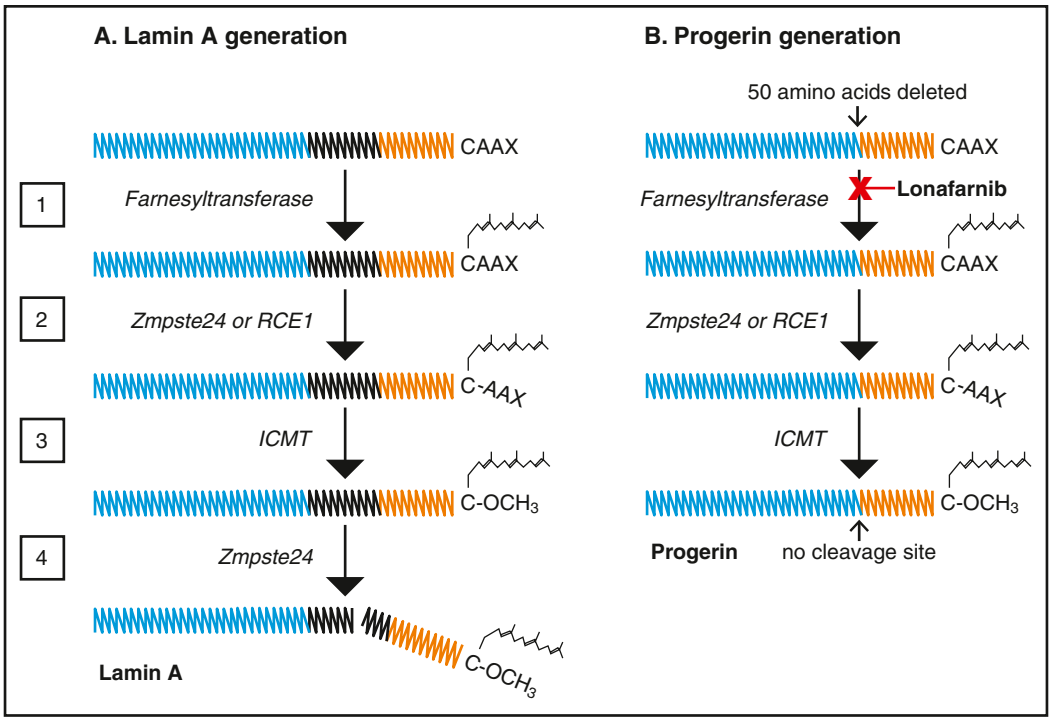

Fig. 111.3 Posttranslational processing pathways producing lamin A and progerin, including the target site for lonafarnib. **A,** Prelamin A polypeptide chain, showing its central α-helical rod domain and C-terminal–CAAX box, representing cysteine (C), aliphatic amino acids (AA), and any amino acid (X). The α-helical rod domain is divided into segments that assist in displaying the progerin defect. Posttranslational processing consists of four steps: (1) a farnesyl group is attached to the cysteine residue of the −CAAX box by farnesyltransferase; (2) the last three residues are proteolytically cleaved by the zinc metalloprotease Zmpste24 or Ras-converting enzyme (RCE1); (3) carboxy-methylation by isoprenyl-cysteine carboxyl methyltransferase (ICMT); and (4) the terminal 15 C-terminal residues, including the farnesylated and carboxymethylated cysteine, are cleaved off by Zmpste24. **B,** A 50–amino acid deletion in prelamin A (represented by the black segment of the lamin A rod) is the result of a pathogenic variant that activates a cryptic splice site within exon 11 of the *LMNA* gene. This deletion leaves progerin without an attachment site for the last processing step—cleavage of the farnesylation and carboxymethylated terminal 15 amino acid residues. Thus progerin remains farnesylated and intercalated within the inner nuclear membrane, where it causes much of its cellular damage.

A is associated with human diseases. The lamin proteins are the principal proteins of the nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and chromatin. The integrity of the lamina is central to many cellular functions, creating and maintaining structural integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, senescence, and apoptosis.

Progeria is a sporadic autosomal dominant disease in about 98% of cases. Two percent of cases presumably arise from parental mosaicism; The Progeria Research Foundation reports five identified sibling occurrences of genetically confirmed HGPS. HGPS is caused by the accelerated use of an alternative, internal splice site that results in the deletion of 150 base pairs in the 3′ portion of exon 11 of the *LMNA* gene. In about 90% of cases, this results from a single C to T transition at nucleotide 1824 that is silent (Gly608Gly) but optimizes an internal splice site within exon 11. The remaining 10% of cases possess one of several single-base pathogenic variants within the intron 11 splice donor site, thus reducing specificity for this site and altering the splicing balance in favor of the internal splice. Subsequent to all these pathogenic variants, translation followed by posttranslational processing of the altered mRNA produces progerin, a shortened abnormal lamin A protein with a 50–amino acid deletion near its C-terminal end. An understanding of the posttranslational processing pathway and how it is altered to create progerin has led to a number of treatment prospects for the disease (Fig. 111.3).

Both prelamin A and preprogerin possess a methylated farnesyl side group attached during posttranslational processing. This is a lipophilic moiety that facilitates intercalation of proteins into the inner nuclear membrane, where most of the lamin and progerin functions are performed. During posttranslational processing of normal lamin A, loss of the methylated farnesyl anchor releases prelamin from the nuclear membrane, rendering it soluble for autophagic degradation. However, preprogerin and, subsequently, progerin retain the farnesyl moiety. Progerin remains anchored to the membrane, binding other proteins, causing blebbing of the nucleus, disrupting mitosis, and altering gene expression. Progerin also retains a methyl moiety.

Disease in progeria is produced by a dominant negative mechanism; *the action of progerin,* not the diminution of lamin A, causes the disease phenotype. The severity of disease is determined in part by progerin levels, which are regulated by the particular pathogenic variant, tissue type, or other factors influencing use of the internal splice site.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Overall, the constellation of small body habitus, bone, hair, subcutaneous fat, and skin changes results in the marked physical resemblance among patients with progeria (Fig. 111.4). For this reason, if disease signs are present, clinical diagnosis can often be achieved or excluded with relative confidence even at young ages. There are rare



Fig. 111.4 Unrelated 7-yr-old female and 10-yr-old male with progeria. The appearance is remarkably similar between patients. (*Photograph courtesy The Progeria Research Foundation.*)

cases of mosaicism or relatively low-progerin-expressing patients with extremely mild clinical signs of disease. Thus lack of early disease manifestation should not be considered exclusionary. Clinical suspicion should be followed by *LMNA* genetic sequence testing. In addition, a number of premature aging disorders have features that overlap with HGPS but are not progerin-producing (Table 111.1). Patients may fall under none of these diagnoses and represent ultrarare, unnamed progeroid diseases that carry either non–progerin-producing pathogenic variants in *LMNA* or the lamin-associated enzyme (ZMPSTE24), or progeroid syndromes without lamin-associated pathogenic variants.

TREATMENT

Lonafarnib (Zokinvy) is a farnesyltransferase inhibitor that blocks the addition of a farnesyl lipid moiety onto preprogerin, thus preventing progerin from associating with the inner nuclear membrane where it effects much of its damage (see Fig. 111.3). Lonafarnib is approved by the US FDA and European Medicines Agency for use in patients with HGPS and processing-deficient progeroid laminopathies ages 12 months and older. It is the first and only approved indication for either disease. It is initiated at a dose of 115 mg/m^2 orally twice daily. After four months, the dose is increased to 150 mg/m^2 twice daily. The most common side effects are diarrhea, nausea, and loss of appetite, which can be mitigated with loperamide, ondansetron HCl, and cyproheptadine, respectively.

Overall, children with HGPS treated with long-term lonafarnib therapy demonstrated an increase in mean estimated survival of 4.3 years (30%) over untreated children. Treatment decreased plasma progerin levels by an average of 38% starting at 4-6 months and persisting for up to 10 years on therapy. In a single-arm clinical trial with lonafarnib (NCT00425607), subgroups of patients experienced increased rate of weight gain, decreased vascular stiffness measured by decreased PWV_{cf} and carotid artery echodensity, improved left ventricular diastolic function, increased radial bone structural rigidity, improved sensorineural hearing, and early evidence of decreased headache, TIA, and stroke rates. Dermatologic, dental, joint contracture, insulin resistance, lipodystrophy, BMD, and joint contractures were unaffected by drug treatment.

Dosing: In general, medications should be dosed according to weight or body surface area instead of age because of the small size and decreased weight for height.

Hydration is important for maintaining adequate blood flow in the face of generalized vascular stiffness and collateral vascular formation in the brain.

Low-dose aspirin therapy is recommended at 2 mg/kg/day, as an extension of what is known about decreasing cardiovascular risk in the general at-risk adult population. It is not known whether low-dose aspirin therapy has any effect on morbidity or mortality in HGPS.

Antihypertensive medications have been used with elevated BP, with special attention to maintaining adequate BP to avoid strokes. Due to small, thin body habitus, appropriately sized blood pressure cuff and height-age adjustments when evaluating hypertension (>95th percentile) should be employed.

Extraskeletal calcifications have been observed in patients with progeria radiographically and cutaneously, both at a baseline off therapy (around 30% of patients) and with increasing frequency during a clinical trial when the patients were treated with oral calcium carbonate supplementation, and/or zoledronic acid, pravastatin, and lonafarnib (around 45% of patients). Oral calcium carbonate supplementation may therefore aggravate calcium dysfunction in children with progeria. Given this potential concern, calcium intake via dietary means, along with vitamin D supplementation, is likely the safest intake strategy.

Physical and occupational therapy initiation are recommended as young as possible to preserve joint mobility and optimize capacity for activities of daily living.

Cardiac intervention. A primary cause of mortality in HGPS is critical aortic stenosis caused by premature atherosclerosis. At end stage, high-risk intervention has been performed using transcatheter aortic valve implantation (TAVI) for patients large enough to receive the smallest valve available, using a transapical approach because the femoral artery is small and calcified, precluding a transfemoral approach. The majority of patients' aortic valves are too small to implement TAVI. In these cases, apico-aortic conduit (aortic valve bypass) surgery has been achieved. Both procedures have resulted in postoperative symptomatic relief and lifespan extension when successful. The procedures carry high risk for perisurgical morbidity and mortality.

Clinical trials. One currently ongoing clinical trial adding *everolimus* (an FDA-approved mTOR inhibitor) to a lonafarnib regimen is aimed at accelerating autophagy of progerin, thus theoretically reducing its accumulation and cellular damage (NCT02579044). Patient treatment phase is complete and results are pending.

PROGNOSIS

Children with progeria develop a severe premature form of atherosclerosis. Before death, cardiac decline with left-sided hypertrophy, valvular insufficiency, and pulmonary edema develop; neurovascular decline with TIAs, strokes, and occasionally seizures can result in significant morbidity.

Without lonafarnib drug treatment, death occurs generally between ages 5 and 20 years, with a median life span of 14.5 years, resulting from heart failure, sometimes with superimposed respiratory infection (approximately 80%); from head injury or trauma, including subdural hematoma (approximately 15%); and, rarely, from stroke (1–3%) or complications from anesthesia during surgery (1–3%). With lonafarnib therapy, long-term use has been associated with up to 4.3 years' (30%) lifespan extension. Surgical intervention for critical aortic stenosis can decrease cardiovascular morbidity and extend lifespan by an indeterminate duration.

PATIENT RESOURCES

The Progeria Research Foundation (www.progeriaresearch.org) maintains an international progeria patient registry, provides a diagnostics program and complete patient care manual, and coordinates clinical treatment trials. It funds preclinical and clinical research to define the underpinnings of the disorder and to discover

Table 111.1 Features of Hutchinson-Gilford Progeria Syndrome and Other Premature Aging Disorders with Overlapping Features

DISEASE	CAUSATIVE GENE	ONSET	MAIN CLINICAL FEATURES
Hutchinson-Gilford progeria syndrome (HGPS)	*LMNA*: de novo dominant point pathogenic variant (c.1824C>T; p.G608G or pathogenic variants in first five intronic bases of intron 11)	Early childhood	Severe failure to thrive in infancy, progressive alopecia leading to total alopecia, skin lesions, characteristic facies, loss of subcutaneous fat, bone changes, skeletal anomalies, musculoskeletal degeneration, hearing loss, high-pitched voice, delayed and crowded dentition, atherosclerosis, cerebrovascular disease, average death in mid-teens from myocardial infarction or stroke (from cardiovascular disease).
Restrictive dermopathy (RD)	*ZMPSTE24*: recessive null pathogenic variants	Neonatal	Intrauterine growth restriction, reduced fetal movements, and preterm delivery, tight and translucent skin with erosions, facial dysmorphism, skeletal malformations, generalized arthrogryposis; lethal within the first weeks of life
Mandibuloacral dysplasia type B (MADB)	*ZMPSTE24*: recessive pathogenic variants: often compound heterozygous pathogenic variants with a null allele and one maintaining some residual activity	Early childhood	Generalized lipodystrophy, altered skin pigmentation, alopecia, severe bone and growth defects
Mandibuloacral dysplasia type A (MADA)	*LMNA*: recessive missense pathogenic variants	Early childhood	Partial lipodystrophy at torso and limbs, bone abnormalities, altered skin pigmentation, lipodystrophic signs and mildly accelerated aging
Nestor-Guillermo progeria syndrome (NGPS)	*BANF1*: recessive pathogenic variant (c.34G>A; p.Ala12Thr)	Early childhood	Failure to thrive, aged appearance, growth restriction, decreased subcutaneous fat, thin limbs, stiff joints, severe osteolysis, absence of early cardiovascular impairment
Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL)	*POLD1*: dominant pathogenic variants, including the common de novo pathogenic variant (c.1812_1814delCTC. P.Ser605del) observed in 80% of the patients	Early childhood	Mandibular hypoplasia, prominent loss of subcutaneous fat, progeroid appearance, skin abnormalities, metabolic abnormalities including insulin resistance and diabetes mellitus, sensorineural deafness, hypogonadism in males
Mandibuloacral dysplasia associated with *MTX2* (MADaM)	*MTX2*: recessive pathogenic variants	Early childhood	Small viscerocranium with mandibular underdevelopment, growth restriction, lipodystrophy, altered skin pigmentation, distal acroosteolyses, renal focal glomerulosclerosis, severe cardiovascular disease
Atypical progeroid laminopathies	*LMNA* and *ZMPSTE24*	Variable from early life to adulthood	Several *LMNA* pathogenic variants, including dominant and recessive ones, result in a spectrum of progeroid laminopathies ranging in severity from severe RD-like forms to adult-onset atypical WS; atypical (severe) MADB forms can result from recessive *ZMPSTE24* pathogenic variants
Werner syndrome (WS)	*WRN*: recessive pathogenic variants	Adulthood	Lack of the pubertal growth spurt during early teen years, graying or loss of hair, scleroderma-like skin lesions, characteristic facies, bilateral cataracts, type 2 diabetes mellitus, hypogonadism, skin ulcers, osteoporosis, arteriosclerosis, increased risk of cancer
Wiedemann-Rautenstrauch syndrome	*POLR3A*	Neonatal	Severe prenatal and postnatal growth restriction, facial dysmorphism, generalized lipodystrophy with local fatty tissue accumulations
Cockayne syndrome	CSA *(ERCC8)* CSB *(ERCC6)*	Neonatal/ infancy	Skin and dental abnormalities, subcutaneous fat loss, short stature, vasculopathy, hypogonadism, hearing loss, cataracts, intellectual disability, neurologic disorders
Rothmund-Thompson syndrome	*RECQL4*	Infancy	Diffuse hair loss, skin and dental abnormalities, short stature, osteopenia, hypogonadism, hyperkeratosis, cataracts, tumor predisposition

Adapted from Coppedè F. Mutations involved in premature-ageing syndromes. *Appl Clin Genet*. 2021;14:279–295.

treatments and a cure. Additional resources include the National Human Genome Research Institute (www.genome.gov/11007255/), National Center for Biotechnology Information Genereviews (www.ncbi.nlm.nih.gov/books/NBK1121/), National Center for Advancing Translational Sciences (www.rarediseases.info.nih.gov/diseases/7467/progeria) and NORD (rarediseases.org).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 112

The Porphyrias

Manisha Balwani, Robert J. Desnick, and Karl E. Anderson

Porphyrias are metabolic diseases resulting from altered activities of specific enzymes of the heme biosynthetic pathway. These enzymes are most active in bone marrow and liver. **Erythropoietic porphyrias**, in which overproduction of heme pathway intermediates occurs primarily in bone marrow erythroid cells, usually present at birth or in early childhood with *cutaneous photosensitivity,* or in the case of congenital erythropoietic porphyria, even in utero as *nonimmune hydrops*. Erythropoietic protoporphyria is the most common porphyria in children. Most porphyrias are hepatic, with overproduction and initial accumulation of porphyrin precursors or porphyrins in the liver. Activation of hepatic porphyrias is very rare during childhood, reflecting the distinct hepatic regulatory mechanisms for heme biosynthesis that are influenced by pubertal development. Homozygous forms of the hepatic porphyrias may manifest clinically before puberty. Children who are heterozygous for inherited hepatic porphyrias may present with nonspecific and unrelated symptoms, and parents often request advice about long-term prognosis and express concerns about drugs that may exacerbate these conditions.

THE HEME BIOSYNTHETIC PATHWAY

Heme is required for a variety of hemoproteins, such as hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes (CYPs). It is believed that the eight enzymes in the pathway for heme biosynthesis are active in all tissues. Hemoglobin synthesis in erythroid precursor cells accounts for approximately 85% of daily heme synthesis in humans. Hepatocytes account for most of the rest, primarily for synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. Pathway intermediates are the porphyrin precursors δ-**aminolevulinic acid** (ALA, also known as *5-aminolevulinic acid*) and **porphobilinogen (PBG)**, as well as porphyrins (mostly in their reduced forms, known as **porphyrinogens**) (Fig. 112.1). These intermediates do not accumulate in significant amounts or have important physiologic functions under normal conditions.

Altered activity of each enzyme in the pathway has been associated with a specific type of porphyria (Table 112.1). The first enzyme, ALA synthase (ALAS), occurs in two forms. An erythroid-specific form, ALAS2, is deficient in X-linked sideroblastic anemia as a result of pathogenic variants of the *ALAS2* gene on chromosome Xp11.2. Gain-of-function pathogenic variants of *ALAS2* caused by deletions in the last exon cause **X-linked protoporphyria (XLP)**, which is phenotypically identical to erythropoietic protoporphyria.

Regulation of heme synthesis differs in the two major heme-forming tissues. Liver heme biosynthesis is primary controlled by the ubiquitous form of ALAS (ALAS1). Synthesis of ALAS1 in liver is regulated by a "free" heme pool (see Fig. 112.1), which can be augmented by newly synthesized heme or by existing heme released from hemoproteins and destined for breakdown to biliverdin by heme oxygenase.

In comparison, in the hematopoietic system, novel regulatory mechanisms allow the production of the very large amounts of heme needed for hemoglobin synthesis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. Also, unlike the liver, heme has a stimulatory role in hemoglobin formation, and the stimulation of heme synthesis in erythroid cells is accompanied not only by increases in ALAS2 but also by sequential induction of other heme biosynthetic enzymes. Separate

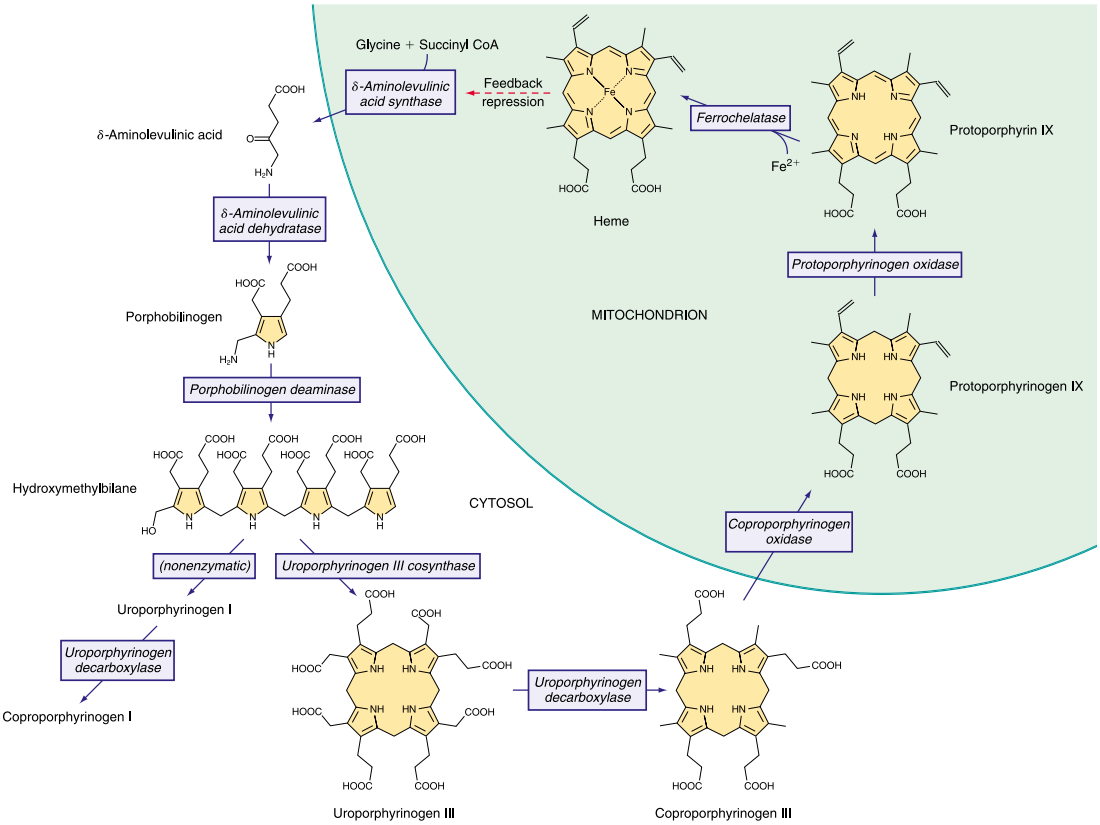

Fig. 112.1 Enzymes and intermediates of the heme biosynthetic pathway. The pathway is regulated in the liver by the end product, heme, mainly by feedback repression *(dashed red arrow)*.

Table 112.1 The Human Porphyrias: Pathogenic Variants, Time of Presentation, and Tissue- and Symptom-Based Classifications

				CLASSIFICATION*			
DISEASE	**ENZYME**	**INHERITANCE**	**PRESENTATION**	**H**	**E**	**A/N**	**C**
X-linked protoporphyria (XLP)	δ-Aminolevulinate synthase 2 (ALAS2)	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	δ-Aminolevulinic acid dehydratase (ALAD)	Autosomal recessive	Mostly postpuberty	X	X‡	X	
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase (HMBS)	Autosomal dominant	Postpuberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase (UROS)	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	Uroporphyrinogen decarboxylase (UROD)	Sporadic	Adults	X			X
PCT type 2†		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X‡		X
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase (CPOX)	Autosomal dominant	Postpuberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPOX)	Autosomal dominant	Postpuberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	Ferrochelatase (FECH)	Autosomal recessive (most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

*Classification abbreviations: H, Hepatic; E, Erythropoietic; A/N, Acute/Neurologic; C, Cutaneous.
†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT. Other genetic factors, such as HFE pathogenic variants, are sometimes found in all types of PCT.
‡ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.

erythroid-specific and nonerythroid, or "housekeeping," transcripts are known for the first four enzymes in the pathway. The separate forms of ALAS are encoded by genes on different chromosomes, but for each of the other three, erythroid and nonerythroid transcripts are transcribed by alternative promoters in the same gene. Heme also regulates the rate of its synthesis in erythroid cells by controlling the transport of iron into reticulocytes.

Intermediates of the heme biosynthetic pathway are efficiently converted to heme and, normally, only small amounts of the intermediates are excreted. Some may undergo chemical modifications before excretion. Whereas the porphyrin precursors ALA and PBG are colorless, nonfluorescent, and largely excreted unchanged in urine, PBG may degrade to colored products such as the brownish pigment called *porphobilin* or spontaneously polymerize to uroporphyrins. Porphyrins are red in color and display bright-red fluorescence when exposed to long-wavelength ultraviolet (UV) light. Porphyrinogens are the reduced form of porphyrins and are colorless and nonfluorescent, but are readily autoxidized to the corresponding porphyrins when they accumulate or are outside the cell. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are converted to heme (see Fig. 112.1).

ALA and PBG are excreted in urine. Excretion of porphyrins and porphyrinogens in urine or bile is determined by the number of carboxyl groups. Those with many carboxyl groups, such as *uroporphyrin* (octacarboxyl porphyrin) and *heptacarboxyl porphyrin,* are water soluble and readily excreted in urine. Those with fewer carboxyl groups, such as *protoporphyrin* (dicarboxyl porphyrin), are not water soluble and are excreted in bile and feces. *Coproporphyrin* (tetracarboxyl porphyrin) is excreted partly in urine and partly in bile. Because coproporphyrin I is more readily excreted in bile than coproporphyrin III, impaired hepatobiliary function may increase total urinary coproporphyrin excretion and the ratio of these isomers.

CLASSIFICATION AND DIAGNOSIS OF PORPHYRIAS

Two useful classification schemes reflect either the underlying pathophysiology or the clinical features of porphyrias (see Table 112.1). In **hepatic porphyrias** and **erythropoietic porphyrias** the source of excess production of porphyrin precursors and porphyrins is the liver and bone marrow, respectively. **Acute porphyrias** cause neurologic symptoms that are associated with increases of one or both of the porphyrin precursors, ALA and PBG. In the **cutaneous porphyrias,** photosensitivity results from transport of porphyrins in blood from the liver or bone marrow to the skin. **Dual porphyria** refers to the very rare cases of porphyria with deficiencies of two different heme pathway enzymes.

Porphyria cutanea tarda (PCT), acute intermittent porphyria (AIP), and erythropoietic protoporphyria (EPP) are the three most common porphyrias, in that order, considering all age-groups, and are very different in clinical presentation, precipitating factors, methods of diagnosis, and effective therapy (Table 112.2). Two less common acute porphyrias, **hereditary coproporphyria (HCP) and variegate porphyria (VP)**, can also cause blistering photosensitivity (see Table 112.1). **Congenital erythropoietic porphyria (CEP)** causes more severe blistering lesions, often with secondary infection and mutilation. EPP and **X-linked protoporphyria (XLP)** have the same phenotype and are distinct from the other cutaneous porphyrias in causing

Table 112.2 The Three Most Common Human Porphyrias and Major Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450 inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose, givosiran
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma or urine porphyrins	Phlebotomy, low-dose hydroxychloroquine, direct acting antivirals (if hepatitis C is present)
Erythropoietic protoporphyria	Phototoxic pain and swelling (mostly acute), childhood onset	Sunlight exposure	Total erythrocyte protoporphyrin with metal-free and zinc protoporphyrin	Sun protection

nonblistering photosensitivity that occurs acutely after sun exposure. EPP is also the most common porphyria to become manifest before puberty.

First-Line Laboratory Diagnostic Testing

A few sensitive and specific first-line laboratory tests should be obtained whenever symptoms or signs suggest the diagnosis of porphyria. If a first-line or screening test is significantly abnormal, more comprehensive testing should follow to establish the type of porphyria. Overuse of laboratory tests for screening can lead to unnecessary expense and even delay in diagnosis. In patients who present with a past diagnosis of porphyria, laboratory reports that were the basis for the original diagnosis must be reviewed, and if these were inadequate, further testing considered.

Acute porphyria should be suspected in patients with neurovisceral symptoms such as abdominal pain after puberty, when initial clinical evaluation does not suggest another cause. *Urinary PBG* should be measured. Urinary PBG is virtually always increased during acute attacks of AIP, HCP, and VP and is not substantially increased in any other medical conditions. Therefore this measurement is both sensitive and specific. Results from spot (single-void) urine specimens are highly informative because very substantial increases are expected during acute attacks of porphyria. A 24-hour collection can unnecessarily delay diagnosis. The same spot urine specimen should be saved for quantitative determination of PBG (expressed relative to creatinine) to confirm the qualitative PBG result. ALA is often measured as well, but is usually less elevated than PBG in AIP, HCP, and VP. In **ALA dehydratase porphyria (ADP)**, urinary ALA and porphyrins, but not PBG, are greatly elevated. Measurement of urinary porphyrins in addition to PBG is recommended to screen for acute porphyrias because PBG is often less elevated and returns to normal more rapidly in HCP and VP than in AIP. Porphyrin measurement *alone* should be avoided for screening, however, because it is often increased in many disorders other than porphyrias, such as liver diseases, and misdiagnoses of porphyria can result from increases in urinary porphyrins that have no diagnostic significance.

Blistering Cutaneous Porphyrias

Blistering skin lesions caused by porphyria are virtually always accompanied by increases in *total plasma* and *urinary porphyrins.* Porphyrins in plasma in VP are mostly covalently linked to plasma proteins and readily detected by a diagnostic peak in a fluorescence scanning method. The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease.

Nonblistering Cutaneous Porphyria

Measurement of total erythrocyte protoporphyrin and, if the total amount is elevated, fractionation of protoporphyrin into its metal-free and zinc-chelated forms, is essential for diagnosis of EPP and XLP. Unfortunately, this is not offered by some major commercial laboratories. Results of zinc protoporphyrin measurements are often recorded (even in the same report) as both *protoporphyrin* and *free erythrocyte protoporphyrin,* with each calculated differently, based on past practices for screening for lead poisoning (which only increases zinc protoporphyrin). Thus the obsolete term *free protoporphyrin* does not mean metal-free protoporphyrin, because it was defined as iron-free protoporphyrin and dates from before it was known that (except in protoporphyrias) protoporphyrin in erythrocytes is mostly zinc chelated. This unnecessary confusion makes diagnosis and reliable exclusion of protoporphyrias difficult. Total plasma porphyrins are elevated in most, but not all, cases of protoporphyria, so a normal level should not be relied on to exclude protoporphyria when total erythrocyte protoporphyrin is elevated.

Increases in erythrocyte total and zinc-chelated protoporphyrin occur in many other conditions, including iron deficiency, lead poisoning, hemolysis, anemia of chronic disease, and other erythrocyte disorders. Therefore the diagnosis of EPP must be confirmed by showing a predominant increase in free and metal-free protoporphyrin. In XLP, both free and zinc protoporphyrin are elevated.

Second-Line Testing

More extensive testing is well justified when a first-line test is positive. A substantial increase in PBG may be caused by AIP, HCP, or VP, and these can be distinguished by measuring urinary porphyrins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. The various porphyrias that cause blistering skin lesions are differentiated by measuring porphyrins in urine, feces, erythrocytes, and plasma. *Confirmation by genetic testing is important once the diagnosis is established by biochemical testing.*

Testing for Subclinical Porphyria

It is often difficult to diagnose or rule out porphyria in patients who had suggestive symptoms months or years in the past and in asymptomatic relatives of patients with acute porphyrias because porphyrin precursors and porphyrins may be normal. More extensive testing and consultation with a specialist laboratory and physician may be needed. Before evaluating relatives, the diagnosis of porphyria should be firmly established in an index case and the laboratory results reviewed to guide the choice of tests for the family members. Identification of a disease-causing pathogenic variant in an index case greatly facilitates detection of additional gene carriers because biochemical tests in latent carriers may be normal.

δ-AMINOLEVULINIC ACID DEHYDRATASE–DEFICIENT PORPHYRIA

ALA dehydratase–deficient porphyria (ADP) is sometimes termed *Doss porphyria* after the investigator who described the first cases. The term *plumboporphyria* emphasizes the similarity of this condition to lead poisoning, but incorrectly implies that it is caused by lead exposure.

Etiology

This porphyria results from a deficiency of ALA dehydratase (ALAD), which is inherited as an autosomal recessive trait. Only eight cases have been confirmed by pathogenic variant analysis. The prevalence of heterozygous ALAD deficiency was estimated to be <1% in Germany and approximately 2% in Sweden.

Pathology and Pathogenesis

ALAD catalyzes the condensation of two molecules of ALA to form the pyrrole PBG (see Fig. 112.1). The enzyme is subject to inhibition by a number of exogenous and endogenous chemicals. ALAD is the principal lead-binding protein in erythrocytes, and lead can displace the zinc atoms of the enzyme. Inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure.

Eleven abnormal ALAD alleles, most with point pathogenic variants, have been identified, some expressing partial activity, such that heme synthesis is partially preserved. The amount of residual enzyme activity may predict the phenotypic severity of this disease.

ADP is often classified as a hepatic porphyria, although the site of overproduction of ALA is not established. A patient with severe, early-onset disease underwent liver transplantation without significant clinical or biochemical improvement, which might suggest that the excess intermediates did not originate in the liver. Evidence suggests this disease may have an erythropoietic component. Excess urinary coproporphyrin III in ADP might originate from metabolism of ALA to porphyrinogens in a tissue other than the site of ALA overproduction. Administration of large doses of ALA to normal individuals also leads to substantial coproporphyrinuria. Increased erythrocyte zinc protoporphyrin, as in all other homozygous porphyrias, may be explained by accumulation of earlier pathway intermediates in bone marrow erythroid cells during hemoglobin synthesis, followed by their transformation to protoporphyrin after hemoglobin synthesis is complete. Neurologic symptoms are attributed to neurotoxic effects of ALA, but this is unproven.

Clinical Manifestations

In most cases, symptoms resemble other acute porphyrias, including acute attacks of abdominal pain and peripheral neuropathy. Precipitating factors, such as exposure to harmful drugs, have not been evident in most cases. Six of the reported cases were adolescent males. A Swedish infant had more severe disease, with neurologic impairment and failure to thrive. A 63-year-old man in Belgium developed an acute motor polyneuropathy concurrently with a myeloproliferative disorder. A Dutch patient with symptom onset in infancy presented in adulthood with acute symptoms and progressive asymmetric weakness of both extremities.

Laboratory Findings

Urinary ALA, coproporphyrin III, and erythrocyte zinc protoporphyrin are substantially increased. Urinary PBG is normal or slightly increased. Erythrocyte ALAD activity is markedly reduced, and both parents have approximately half-normal activity of this enzyme and normal urinary ALA.

Diagnosis and Differential Diagnosis

The other three acute porphyrias are characterized by substantial increases in both ALA and PBG. In contrast, ALA, but not PBG, is substantially increased in ADP. A marked deficiency of erythrocyte ALAD and half-normal activity in the parents support the diagnosis. Other causes of ALAD deficiency, such as **lead poisoning**, must be excluded. Succinylacetone accumulates in hereditary tyrosinemia type 1 and is structurally similar to ALA, inhibits ALAD, and can cause increased urinary excretion of ALA and clinical manifestations that resemble acute porphyria. Idiopathic acquired ALAD deficiency has been reported. Unlike lead poisoning, the deficient ALAD activity in ADP is not restored by the in vitro addition of sulfhydryl reagents such as dithiothreitol. Even if no other cause of ALAD deficiency is found, it is essential to confirm the diagnosis of ADP by molecular studies.

Treatment

Treatment experience with ADP is limited but is similar to other acute porphyrias. Glucose seems to have minimal effectiveness but may be tried for mild symptoms. **Hemin therapy** was apparently effective for acute attacks in male adolescents, and weekly infusions prevented attacks in two of these patients. Hemin was not effective either biochemically or clinically in the Swedish child with severe disease, and it produced a biochemical response but no clinical improvement in the Belgian man with a late-onset form, who had a peripheral neuropathy but no acute attacks. Hemin is also effective in treating porphyria-like symptoms associated with hereditary tyrosinemia and can significantly reduce urinary ALA and coproporphyrin in lead poisoning. Avoidance of drugs that are harmful in other acute porphyrias is advisable. Liver transplantation was not effective in the child with severe disease. In a recent report, weekly blood transfusions and hydroxycarbamide were used in addition to heme-arginate to suppress erythroid heme synthesis.

Prognosis

Recurrent attacks may occur and require repeated treatment with hemin. The course was unfavorable in the Swedish child with more severe disease and was uncertain in adults with late-onset disease associated with myeloproliferative disorders.

Prevention and Genetic Counseling

Heterozygous parents should be aware that subsequent children are at risk for ADP, as in any autosomal recessive disorder. Prenatal diagnosis is possible but has not been reported.

ACUTE INTERMITTENT PORPHYRIA

AIP is also termed *pyrroloporphyria, Swedish porphyria,* and *intermittent acute porphyria* and is the most common type of acute porphyria in most countries.

Etiology

AIP results from the deficient activity of the housekeeping form of porphobilinogen deaminase (PBGD). This enzyme is also known as **hydroxymethylbilane (HMB) synthase** (the prior term, uroporphyrinogen I synthase, is obsolete). HMB synthase catalyzes the deamination and head-to-tail condensation of four PBG molecules to form the linear tetrapyrrole, HMB (also known as *preuroporphyrinogen;* see Fig. 112.1). A unique dipyrromethane cofactor binds the pyrrole intermediates at the catalytic site until six pyrroles (including the dipyrrole cofactor) are assembled in a linear fashion, after which the tetrapyrrole HMB is released. The apo-deaminase generates the dipyrrole cofactor to form the holodeaminase, and this occurs more readily from HMB than from PBG. Indeed, high concentrations of PBG may inhibit formation of the holodeaminase. The product HMB can cyclize nonenzymatically to form nonphysiologic uroporphyrinogen I, but in the presence of the next enzyme in the pathway is more rapidly cyclized to form uroporphyrinogen III.

Erythroid and housekeeping forms of the enzyme are encoded by a single gene. The two isoenzymes are both monomeric proteins, differ only slightly in molecular weight (approximately 40 and 42 kDa), and result from alternative splicing of two distinct messenger RNA (mRNA) transcripts that arise from two different promoters. The housekeeping promoter functions in all cell types, including erythroid cells.

The pattern of inheritance of AIP is autosomal dominant, with very rare homozygous cases that present in childhood. More than 400 *HMBS* pathogenic variants, including missense, nonsense, and splicing pathogenic variants, and insertions and deletions have been identified in AIP and in many population groups. Most pathogenic variants are found in only one or a few families. Because of founder effects, some are more common in certain geographic areas, such as northern Sweden (W198X), Holland (R116W), Argentina (G116R), Nova Scotia (R173W), and Switzerland (W283X). De novo pathogenic variants may be found in approximately 3% of cases. The nature of the *HMBS* pathogenic variant does not account for the severity of the clinical presentation, which varies greatly within families. **Chester porphyria** was initially described as a variant form of acute porphyria in a large English family but was found to be caused by an *HMBS* pathogenic variant.

Most pathogenic variants lead to approximately half-normal activity of the housekeeping and erythroid isozymes and half-normal amounts of their respective enzyme proteins in all tissues of heterozygotes. In approximately 5% of unrelated AIP patients, the housekeeping isozyme is deficient, but the erythroid-specific isozyme is normal. Pathogenic

variants causing this are usually found within exon 1 or its 5′ splice donor site or initiation of translation codon.

Pathology and Pathogenesis

Induction of the rate-limiting hepatic enzyme ALAS1 is thought to underlie acute exacerbations of this and the other acute porphyrias. AIP remains latent (or asymptomatic) in the great majority of those who are heterozygous carriers of *HMBS* pathogenic variants, and this is almost always the case before puberty. In those with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic HMBS activity is sufficient unless hepatic ALAS1 activity is increased. Patients can also be asymptomatic with elevated levels of porphyrin precursors and are classified as *asymptomatic high excretors.* These patients may have a remote history of symptoms. Many factors that lead to clinical expression of AIP, including certain drugs and steroid hormones, have the capacity to induce hepatic ALAS1 and CYPs. When hepatic heme synthesis is increased, half-normal HMBS activity may become limiting, and ALA, PBG, and other heme pathway intermediates may accumulate. In addition, heme synthesis becomes impaired, and heme-mediated repression of hepatic ALAS1 is less effective.

It is not proved, however, that hepatic HMBS remains constant at approximately 50% of normal activity during exacerbations and remission of AIP, as in erythrocytes. An early report suggested that the enzyme activity is considerably less than half-normal in the liver during an acute attack. Hepatic HMBS activity might be reduced further once AIP becomes activated if, as suggested, excess PBG interferes with assembly of the dipyrromethane cofactor for this enzyme. It also seems likely that currently unknown genetic factors play a contributing role in, for example, patients who continue to have attacks even when known precipitants are avoided.

AIP is almost always latent before puberty and becomes active mostly in adult females, which suggests that endocrine factors, and especially adult levels of female steroid hormones, may be important for clinical expression. Premenstrual attacks are probably the result of endogenous progesterone. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing progestins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone.

Drugs that are unsafe in acute porphyrias (Table 112.3) include those with the capacity to induce hepatic ALAS1, which is closely associated with induction of CYPs. Some chemicals (e.g., griseofulvin) can increase heme turnover by promoting the destruction of specific CYPs to form an inhibitor (e.g., *N*-methyl protoporphyrin) of ferrochelatase (FECH, the final enzyme in the pathway). Sulfonamide antibiotics are harmful but apparently not inducers of hepatic heme synthesis. Ethanol and other alcohols are inducers of ALAS1 and some CYPs.

Nutritional factors, in particular reduced intake of calories and carbohydrates, as may occur with illness or attempts to lose weight, can increase porphyrin precursor excretion and induce attacks of porphyria. Increased carbohydrate intake may ameliorate attacks. Hepatic ALAS1 is modulated by the peroxisome proliferator-activated receptor-γ coactivator-1α, which is an important link between nutritional status and exacerbations of acute porphyria.

Other factors have been implicated. Chemicals in cigarette smoke, such as polycyclic aromatic hydrocarbons, can induce hepatic CYPs and heme synthesis. A survey of AIP patients found an association between smoking and repeated porphyric attacks. Attacks may result from metabolic stress and impaired nutrition associated with major illness, infection, or surgery. Clinical observations suggest an additive effect of multiple predisposing factors, including drugs, endogenous hormones, nutritional factors, and smoking.

Neurologic Mechanisms

The mechanism of neural damage in acute porphyrias is poorly understood. The most favored hypothesis at present is that one or more heme precursors, or perhaps a derivative, are neurotoxic. Increased ALA in AIP, HCP, VP, ADP, plumbism, and hereditary tyrosinemia type 1, which have similar neurologic manifestations, suggests that this substance or a derivative may be neuropathic. Porphyrins derived from ALA after its uptake into cells may have toxic potential. ALA can also interact with γ-aminobutyric acid (GABA) receptors. Severe AIP greatly improves after allogeneic liver transplantation. This experience and the demonstration that recipients of AIP livers develop porphyria support the hypothesis that heme precursors from the liver cause the neurologic manifestations.

Epidemiology

AIP occurs in all ethnic groups and is the most common acute porphyria, with an estimated prevalence in most countries of 5 in 100,000. In Sweden, prevalence was estimated to be 7.7 in 100,000, including latent cases with normal porphyrin precursors. A much higher prevalence of 60-100 in 100,000 in northern Sweden is the result of a founder effect. The combined prevalence of AIP and VP in Finland is approximately 3.4 in 100,000. Population screening by erythrocyte HMBS activity or DNA analysis revealed a prevalence of 200 heterozygotes per 100,000 people in Finland and 1 in approximately 1,675 (60 in 100,000) in France. Studies using exomic/genomic databases show that the estimated frequency of pathogenic variants in the *HMBS* gene is 0.00056 (56 in 100,000), suggesting that the penetrance of this disorder may be as low as 1% and that carriers of *HMBS* pathogenic variants that can cause AIP are much more common than previously believed. Higher penetrance in some families with AIP suggests a strong role of environmental factors and genetic modifiers.

Clinical Manifestations

Neurovisceral manifestations of acute porphyrias may appear any time after puberty, but rarely before it (Table 112.4). Porphyria attacks are exceedingly rare before the onset of puberty. Affected children are more often males as *opposed to affected adolescents and adults*, who are predominantly females. Reported symptomatic childhood cases often lacked adequate biochemical and molecular confirmation. The prepubertal attacks in males may be explained in part by coexisting medical conditions with the potential to upregulate ALAS1. Abdominal pain was the most common presenting symptom in such cases, but seizures, often preceding the diagnosis, were also common. Other manifestations reported in children include tachycardia, peripheral neuropathy, myalgias, hypertension, irritability, lethargy, and behavioral abnormalities. A population-based study in Sweden indicated that symptoms suggestive of porphyria may occur in heterozygotes during childhood, even, in contrast to adults, when urinary porphyria precursors are not elevated. This study did not compare the frequency of such nonspecific symptoms in a control group of children. Very rare cases of homozygous AIP present differently, with severe neurologic manifestations early in childhood.

Acute attacks in adults are characterized by a constellation of nonspecific symptoms, which may become severe and life threatening. **Abdominal pain** occurs in 85–95% of AIP patients and is usually severe, steady, and poorly localized, but is sometimes cramping, and accompanied by signs of ileus, including abdominal distention and decreased bowel sounds. Nausea, vomiting, and constipation are common, but increased bowel sounds and diarrhea may occur. Bladder dysfunction may cause hesitancy and dysuria. **Tachycardia**, the most common physical sign, occurs in up to 80% of attacks. This is often accompanied by **hypertension**, restlessness, coarse or fine tremors, and excess sweating, which are attributed to sympathetic overactivity and increased catecholamines. Other common manifestations include mental symptoms; pain in the extremities, head, neck, or chest; muscle weakness; and sensory loss. Because all these manifestations are neurologic rather than inflammatory, there is little or no abdominal tenderness, fever, or leukocytosis.

Porphyric neuropathy is primarily motor and appears to result from axonal degeneration rather than demyelinization. Sensory involvement is indicated by neuropathic pain in the extremities, which may be described as muscle or bone pain, and by numbness, paresthesias, and dysesthesias. Paresis may occur early in an attack but is more often a late manifestation in an attack that is not recognized

Table 112.3 Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	SAFE
Barbiturates (all)	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen (paracetamol)
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin
Succinimides	Atropine
Carbamazepine*	Cimetidine
Clonazepam‡	Ranitidine†
Primidone*	Acetazolamide
Valproic acid*	Allopurinol
Pyrazolones (aminopyrine, antipyrine)	Amiloride
Griseofulvin*	Bethanidine
Ergots	Bumetanide
Metoclopramide* ‡	Coumarins
Rifampin*	Fluoxetine
Pyrazinamide* ‡	Gabapentin
Diclofenac* ‡	Gentamicin
Fluconazole*	Guanethidine
Oral contraceptives	Ofloxacin
Progesterone and synthetic progestins*	Propranolol
Danazol*	Succinylcholine
Alcohol	Tetracycline
ACEIs (especially enalapril) ‡	
Spironolactone	
CCBs (especially nifedipine) ‡	
Ketoconazole	
Ketamine*	

*Porphyria has been listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. Estrogens are also listed as harmful in porphyria but have been implicated as harmful in acute porphyrias, mostly based only on experience with estrogen-progestin combinations. Although estrogens can exacerbate porphyria cutanea tarda, there is little evidence they are harmful in the acute porphyrias.
†Porphyria has been listed as a precaution in U.S. labeling for this drug. However, this drug is regarded as safe by other sources.
‡These drugs have been classified as probably safe by some sources, but this is controversial, and they should be avoided.
This partial listing does not include all available information about drug safety in acute porphyrias. Other sources should be consulted for drugs not listed here.
ACEIs, Angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

and adequately treated. Rarely, severe neuropathy develops when there is little or no abdominal pain. Motor weakness most commonly begins in the proximal muscles of the upper extremities and then progresses to the lower extremities and the periphery. It is usually symmetric, but occasionally asymmetric or focal. Initially, tendon reflexes may be little affected or hyperactive and become decreased or absent. Cranial nerves, most often X and VII, may be affected, and blindness from involvement of the optic nerves or occipital lobes has been reported. More common central nervous system (CNS) manifestations include seizures, anxiety, insomnia, depression, disorientation, hallucinations, and paranoia. Seizures may result from hyponatremia, porphyria itself, or an unrelated cause. Chronic depression and other mental symptoms occur in some patients, but attribution to porphyria is often difficult.

Hyponatremia is common during acute attacks. Inappropriate antidiuretic hormone (ADH) secretion is often the most likely mechanism, but salt depletion from excess renal sodium loss, gastrointestinal (GI) loss, and poor intake have been suggested as causes of hyponatremia in some patients. Unexplained reductions in total blood and red blood cell volumes are sometimes found, and increased ADH secretion might then be an appropriate physiologic response. Other electrolyte abnormalities may include hypomagnesemia and hypercalcemia.

The attack usually resolves within several days unless treatment is delayed. Abdominal pain may resolve within a few hours and paresis within a few days. Even severe motor neuropathy can improve over months or several years but may leave some residual weakness. Progression of neuropathy to respiratory paralysis and death seldom occurs with appropriate treatment and removal of harmful drugs. Sudden death may result from cardiac arrhythmia.

Laboratory Findings

Levels of ALA and PBG are substantially increased during acute attacks. These levels may decrease after an attack but usually remain increased unless the disease becomes asymptomatic for a prolonged period.

Porphyrins are also markedly increased, which accounts for reddish urine in AIP. These are predominantly uroporphyrins, which can form nonenzymatically from PBG. The increased urinary porphyrins in AIP are predominantly isomer III; however, their formation is likely to be largely enzymatic, which might occur if excess ALA produced in the liver enters cells in other tissues and is then converted to porphyrins by the heme biosynthetic pathway. Porphobilin, a degradation product of PBG, and dipyrrolomethanes appear to account for brownish urinary discoloration. Total fecal porphyrins and plasma porphyrins are normal or slightly increased in AIP. Erythrocyte protoporphyrin may be somewhat increased in patients with manifest AIP.

Erythrocyte HMBS activity is approximately half-normal in most patients with AIP. The normal range is wide and overlaps with the range for AIP heterozygotes. Some *HMBS* pathogenic variants cause the enzyme to be deficient only in nonerythroid tissues. HMBS activity is also highly dependent on erythrocyte age, and an increase in erythropoiesis from concurrent illness in an AIP patient may raise the activity into the normal range. Thus measurement of erythrocyte HMBS activity alone is insufficient in testing for AIP.

Diagnosis and Differential Diagnosis

An increased urinary PBG level establishes that a patient has one of the three most common acute porphyrias (see Table 112.2). Measuring PBG in serum is preferred when there is coexistent severe renal disease but is less sensitive when renal function is normal. Measurement of urinary ALA is less sensitive than PBG and also less specific, but will detect ADP, the fourth type of acute porphyria. Measurement of urinary porphyrins is also useful, because they may remain elevated after ALA and PBG return to normal and are also elevated in ADP. Decreased erythrocyte PBGD activity helps confirm the diagnosis of AIP, but is not found in all AIP patients.

Knowledge of the *HMBS* pathogenic variant in a family enables reliable identification of other pathogenic variant carriers. Prenatal diagnosis can be performed by amniocentesis or chorionic villus sampling (CVS) in a fetus with a known *HMBS* pathogenic variant in the family. Prenatal diagnosis is typically not performed because of the low penetrance of the disorder and favorable prognosis with treatment.

Complications

AIP and other acute porphyrias are typically associated with mild abnormalities in liver function tests; some patients develop chronic liver disease. The risk of hepatocellular carcinoma is also increased, perhaps 60- to 70-fold after age 50, even in asymptomatic individuals. Few patients who developed this neoplasm had increases in serum α-fetoprotein. Patients with acute porphyrias, especially >50 years old, should be screened by ultrasound or an alternative imaging method at 6-month intervals.

Table 112.4 Common Presenting Symptoms and Signs of Acute Porphyria

SYMPTOMS AND SIGNS	FREQUENCY (%)	COMMENT
GASTROINTESTINAL		
Abdominal pain	85–95	Usually unremitting (for hours or longer) and poorly localized but can be cramping.
Vomiting	43–88	Neurologic in origin and rarely accompanied by peritoneal signs, fever, or leukocytosis.
Constipation	48–84	Nausea and vomiting often accompany abdominal pain. May be accompanied by bladder paresis.
Diarrhea	5–12	
NEUROLOGIC		
Pain in extremities, back	50–70	Pain may begin in the chest or back and move to the abdomen. Extremity pain from the chest, neck, or head indicates involvement of sensory nerves; objective sensory loss reported in 10–40% of cases.
Paresis	42–68	May occur early or late during a severe attack. Muscle weakness usually begins proximally rather than distally and more often in the upper than lower extremities.
Respiratory paralysis	9–20	Preceded by progressive peripheral motor neuropathy and paresis.
Mental symptoms	40–58	May range from minor behavioral changes to agitation, confusion, hallucinations, and depression.
Convulsions	10–20	A central neurologic manifestation of porphyria or caused by hyponatremia, which often results from syndrome of inappropriate antidiuretic hormone secretion or sodium depletion.
CARDIOVASCULAR		
Tachycardia	64–85	May warrant treatment to control rate, if symptomatic.
Systemic arterial hypertension	36–55	May require treatment during acute attacks, and sometimes becomes chronic.

From Anderson KE, Bloomer JR, Bonkovsky HL, et al. Desnick recommendations for the diagnosis and treatment of the acute porphyrias, *Ann Intern Med.* 2005;142(6):439–450.

The risk of chronic hypertension and impaired renal function is increased in these patients, most often with evidence of interstitial nephritis. A nephrotoxic effect of ALA may contribute. This may progress to severe renal failure and require renal transplantation.

Patients with recurrent attacks may develop **chronic neuropathic pain**, although this has not been well characterized. Referral to a neurologist is recommended for any patient with ongoing or residual neurologic symptoms. In addition, depression and anxiety are common in these patients.

Treatment

Hemin

Intravenous (IV) hemin is the treatment of choice for most acute attacks of porphyria. There is a favorable biochemical and clinical response to early treatment with hemin, but less rapid clinical improvement if treatment is delayed. It is no longer recommended that therapy with hemin for a severe attack be started only after an unsuccessful trial of IV glucose for several days. Mild attacks without severe manifestations, such as paresis, seizures, hyponatremia, or pain requiring opioids, may be treated with IV glucose. After IV administration, hemin binds to hemopexin and albumin in plasma and is taken up primarily in hepatocytes, where it augments the regulatory heme pool in hepatocytes, represses the synthesis of hepatic ALAS1, and dramatically reduces porphyrin precursor overproduction.

Hemin* is available for IV administration in the United States as *lyophilized hematin* (Panhematin, Recordati). Degradation products begin to form as soon as the lyophilized product is reconstituted with sterile water, and these can cause infusion site phlebitis and a transient anticoagulant effect. Repeated treatment can lead to loss of venous access and iron overload. Reconstitution with 30% human albumin can enhance stability and prevent these adverse effects and is recommended especially if a peripheral vein is used for the infusion. Uncommon side effects of hemin include fever, aching, malaise, hemolysis, anaphylaxis, and circulatory collapse. Heme arginate, a more stable hemin preparation, is available in Europe and South Africa.

Hemin treatment should be instituted only after a diagnosis of acute porphyria has been initially confirmed by a marked increase in urinary PBG. When prior documentation of the diagnosis is available for review, it is not essential to confirm an increase in PBG with every recurrent attack if other causes of the symptoms are excluded clinically. The standard regimen of hemin for treatment of acute porphyric attacks is 3-4 mg/kg/day for 4 days. Lower doses have less effect on porphyrin precursor excretion and probably less clinical benefit.

Givosiran, an ALAS1-directed interfering RNA therapeutic, is effective for preventing frequent attacks in adults with acute hepatic porphyrias. Clinical trials have demonstrated rapid lowering of ALA and PBG, resulting in a reduction in attacks, chronic symptoms, and hemin utilization.

General and Supportive Measures

Drugs that may exacerbate porphyrias (see Table 112.3) should be discontinued whenever possible, and other precipitating factors identified. Hospitalization is warranted, except for mild attacks; for treatment of severe pain, nausea, and vomiting; for administration of hemin and fluids; and for monitoring vital capacity, nutritional status, neurologic function, and electrolytes. Pain usually requires an opioid; there is low risk for addiction after recovery from the acute attack. Ondansetron or promethazine is needed for nausea and vomiting and short-acting benzodiazepines for anxiety and restlessness. β-Adrenergic blocking agents may be useful to control tachycardia and hypertension but may be hazardous in patients with hypovolemia and incipient cardiac failure.

Carbohydrate Loading

The effects of carbohydrates on repressing hepatic ALAS1 and reducing porphyrin precursor excretion are weak compared with those of hemin. Therefore carbohydrate loading is recommended only for

* Hemin is the generic name for all heme preparations used for IV administration. Hemin is also a chemical term that refers to the oxidized (ferric) form of heme (iron protoporphyrin IX) and is usually isolated as hemin chloride. In alkaline solution, the chloride is replaced by the hydroxyl ion, forming hydroxyheme, or hematin.

mild attacks (e.g., without severe nausea or vomiting, hyponatremia, seizures, paresis, or pain requiring opioids). Glucose polymer solutions by mouth are sometimes tolerated. At least 300 g of IV glucose, usually given as a 10% solution, has been recommended for adults hospitalized with attacks of porphyria. Amounts up to 500 g daily may be more effective, but large volumes may favor the development of hyponatremia.

Other Therapies

Liver transplantation is effective in patients with severe AIP who are refractory to pharmacologic therapy. Patients can generally expect a complete biochemical and symptomatic resolution after transplantation. However, liver transplantation is a high-risk procedure and should be considered only as a last resort.

Seizures and Other Complications

Patients who experience seizures during an acute attack, especially if caused by hyponatremia or other electrolyte imbalances, may not require prolonged treatment with anticonvulsant drugs, most of which have at least some potential for exacerbating acute porphyrias. Gabapentin, pregabalin, levetiracetam, and vigabatrin are considered safe or probably safe, and clonazepam is probably less harmful than phenytoin, barbiturates, or valproic acid.

Control of hypertension is important and may help prevent chronic renal impairment, which can progress and require renal transplantation.

Safe and Unsafe Drugs

Patients often do well with avoidance of harmful drugs. Listings are available from the **European Porphyria Network** (www.porphyria-europe.com) and **American Porphyria Foundation** (https://porphyriafoundation.org/drugdatabase/), but some listings are controversial. Information regarding safety is lacking for many drugs, especially for those recently introduced.

Exogenous progestins can induce attacks of porphyria. Estrogens are seldom reported to be harmful when given alone. Synthetic steroids with an ethynyl substituent can cause a mechanism-based destruction of hepatic CYPs and should probably be avoided in patients with acute porphyria. Danazol is especially contraindicated.

Other Situations

Major surgery can be carried out safely in patients with acute porphyria, especially if barbiturates are avoided. Halothane has been recommended as an inhalation agent and propofol and midazolam as IV induction agents.

Pregnancy is usually well tolerated, which is surprising, because levels of progesterone, a potent inducer of hepatic ALAS1, are considerably increased during pregnancy. Some females do experience continuing attacks during pregnancy. This has sometimes been attributed to reduced caloric intake or metoclopramide, a drug sometimes used to treat hyperemesis gravidarum and considered by some to be harmful in acute porphyrias.

Diabetes mellitus and other endocrine conditions are not known to precipitate attacks of porphyria. In fact, the onset of diabetes mellitus and resulting high circulating glucose levels may decrease the frequency of attacks and lower porphyrin precursor levels in AIP.

Prognosis

In Finland, 74% of patients with AIP or VP reported that they led normal lives, and <30% had recurrent attacks during several years of follow-up. In those presenting with acute symptoms, recurrent attacks were most likely within the next 1-3 years. Moreover, only 6% of gene carriers who had never had attacks developed symptoms. The positive outlook may result from earlier detection, better treatment of acute attacks, and replacement of harmful drugs such as barbiturates and sulfonamides with safer drugs. However, some patients continue to have recurrent attacks, chronic pain, and other symptoms, even after avoiding known exacerbating factors.

Prevention

For prevention of attacks, it is important to identify multiple inciting factors and remove as many as possible. Drugs for concurrent medical conditions should be reviewed. Because dietary factors are often unapparent, consultation with a dietitian may be useful. A well-balanced diet that is somewhat high in carbohydrate (60–70% of total calories) and sufficient to maintain weight is recommended. There is little evidence that additional dietary carbohydrate helps further in preventing attacks, and it may lead to weight gain. Patients who wish to lose excess weight should do so gradually and when they are clinically stable. Rapid weight loss after bariatric surgery may exacerbate acute porphyrias. Iron deficiency, which can be detected by a low serum ferritin level, should be corrected.

Gonadotropin-releasing hormone (GnRH) analogs, which reversibly suppress ovulation, can be dramatically effective for preventing frequently recurring luteal-phase attacks, but baseline and continuing gynecologic evaluation and bone mineral density measurements are important; transdermal estrogen or a bisphosphonate may be added to prevent bone loss. Hemin administered once or twice weekly can prevent frequent attacks of porphyria in some patients. Alternatively, single-dose hemin can be administered "on demand" at an outpatient infusion center to abort an attack and prevent hospitalization, if a patient can recognize early "prodromal" symptoms.

Givosiran (Givlaari, Alnylam) an interfering RNA therapeutic that is administered subcutaneously every month, has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for prevention of acute attacks of an AHP.

Genetic Counseling

A pathogenic variant identified in the index case can be sought in offspring at any age. Counseling should emphasize that the great majority of those who inherit an *HMBS* pathogenic variant never develop symptoms, and the prognosis of those who do is favorable. Therefore a normal, healthy life is expected, especially with avoidance of harmful drugs and other factors and prompt recognition and treatment of symptoms should they occur. Given this favorable outlook, even during pregnancy, having children is not precluded for those who have inherited a pathogenic variant, and prenatal diagnosis of acute porphyrias is less important than it is for many other inherited diseases.

CONGENITAL ERYTHROPOIETIC PORPHYRIA

Also termed *Günther disease,* this rare disease usually presents with photosensitivity shortly after birth or in utero as nonimmune hydrops.

Etiology

CEP is an autosomal recessive disease caused by a marked deficiency of uroporphyrinogen III synthase (UROS). Many *UROS* pathogenic variants have been identified among CEP families. Later-onset disease in adults is often less severe and likely to be associated with myeloproliferative disorders and expansion of a clone of erythroblasts that carry a *UROS* pathogenic variant.

Pathology and Pathogenesis

UROS, which is extremely deficient in CEP, catalyzes inversion of pyrrole ring D of HMB and rapid cyclization of the linear tetrapyrrole to form uroporphyrinogen III. This enzyme is also termed *uroporphyrinogen III cosynthase.* The human enzyme is a monomer. The gene for the enzyme is found on chromosome 10q25.3→q26.3 and contains 10 exons. Erythroid and housekeeping transcripts are generated by alternative promoters but encode the same enzyme.

In CEP, HMB accumulates in erythroid cells during hemoglobin synthesis and cyclizes nonenzymatically to form uroporphyrinogen I, which is auto-oxidized to uroporphyrin I. Some of the uroporphyrinogen I that accumulates is metabolized to coproporphyrinogen I, which accumulates because it is not a substrate for coproporphyrinogen oxidase. Thus both uroporphyrin I and coproporphyrin I accumulate in the bone marrow and are then found in circulating erythrocytes, plasma, urine, and feces.

A variety of *UROS* pathogenic variants have been identified in CEP, including missense and nonsense pathogenic variants, large and small deletions and insertions, splicing defects, and intronic branch-point pathogenic variants. At least four pathogenic variants have been identified in the erythroid-specific promoter. Many patients inherited a different pathogenic variant from each parent, and most pathogenic variants have been detected in only one or a few families. An exception is a common pathogenic variant, C73R, which is at a pathogenic variant hot spot and was found in approximately 33% of alleles. One child with CEP had a *GATA1* pathogenic variant, with no *UROS* pathogenic variant. The CEP phenotype may be modulated by gain-of-function *ALAS2* pathogenic variants, which were first identified as causing XLP.

Genotype-phenotype correlations have been based on the in vitro expression of various CEP pathogenic variants and the severity of associated phenotypic manifestations. The C73R allele, which is associated with a severe phenotype in homozygotes or in patients heteroallelic for C73R and another pathogenic variant expressing little residual activity, resulted in <1% of normal enzyme activity. Patients with the C73R allele and heteroallelic for other pathogenic variants expressing more residual activity have milder disease.

Hemolysis is a common feature of CEP. Excess porphyrins in circulating erythrocytes cause cell damage, perhaps by a phototoxic mechanism, leading to both intravascular hemolysis and increased splenic clearance of erythrocytes. Also important is ineffective erythropoiesis, with intramedullary destruction of porphyrin-laden erythroid cells and breakdown of heme. Expansion of the bone marrow as a result of erythroid hyperplasia may contribute, along with vitamin D deficiency, to bone loss. Nutrient deficiencies sometimes cause erythroid hypoplasia. Despite the marked deficiency of UROS, heme production in the bone marrow is increased because of hemolysis and a compensatory increase in hemoglobin production. This occurs, however, at the expense of marked accumulation of HMB, which is converted to porphyrinogens and porphyrins.

Clinical Manifestations

In severe cases, CEP can cause fetal loss or may be recognized in utero as causing intrauterine hemolytic anemia and nonimmune hydrops fetalis. CEP may be associated with neonatal hyperbilirubinemia, and *phototherapy may unintentionally induce severe cutaneous photosensitivity and scarring.*

The most characteristic presentation is reddish urine or pink staining of diapers by urine or meconium shortly after birth (Fig. 112.2). With sun exposure, severe blistering lesions appear on exposed areas of skin on the face and hands and have been termed *hydroa estivale* because they are more severe with greater sunlight exposure during summer (Fig. 112.3). Vesicles and bullae, as well as friability, hypertrichosis, scarring, thickening, and areas of hypopigmentation and hyperpigmentation, are very similar to those seen in PCT but usually much more severe. Infection and scarring sometimes cause loss of facial features and fingers and damage to the cornea, ears, and nails. Porphyrins are deposited in dentin and bone in utero. Reddish-brown teeth in normal light, an appearance termed **erythrodontia**, display reddish fluorescence under long-wave UV light (Fig. 112.4). Unaffected children born to a mother with CEP may have erythrodontia. Hemolysis and splenomegaly are common in CEP. Bone marrow compensation may be adequate, especially in milder cases. Patients with severe phenotypes, however, are often transfusion dependent. Splenomegaly may contribute to the anemia and cause leukopenia and thrombocytopenia, which may be complicated by significant bleeding. Neuropathic symptoms are absent, and there is no sensitivity to drugs, hormones, or carbohydrate restriction. The liver may be damaged by iron overload, viral hepatitis, or other causes.

Milder cases of CEP with onset of symptoms in adult life and without erythrodontia may be misdiagnosed initially as PCT. Late-onset cases are likely to be associated with myeloproliferative disorders and expansion of a clone of erythroid cells carrying a *UROS* pathogenic variant.



Fig. 112.2 Congenital erythropoietic porphyria (CEP). The diaper of a baby with CEP demonstrates the red color of urine. (*From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006: p. 517.*)



Fig. 112.3 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. (*From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006: p. 517.*)



Fig. 112.4 Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood's lamp examination. (*From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006: p. 517.*)

Laboratory Findings

Urinary porphyrin excretion and circulating porphyrin levels in CEP are much higher than in almost all other porphyrias. Urinary porphyrin excretion can be as high as 50-100 mg daily and consists mostly of uroporphyrin I and coproporphyrin I. ALA and PBG are normal. Fecal porphyrins are greatly increased, with a predominance of coproporphyrin I.

Marked increases in erythrocyte porphyrins in CEP also consist mostly of uroporphyrin I and coproporphyrin I. These porphyrins are also increased in bone marrow, spleen, plasma, and to a lesser extent, liver. The porphyrin pattern in erythrocytes is influenced by rates of erythropoiesis and erythroid maturation. A predominance of protoporphyrin has been noted in some CEP patients, and in one such patient, uroporphyrin and coproporphyrin increased when erythropoiesis was stimulated by blood removal.

Diagnosis and Differential Diagnosis

The diagnosis of CEP should be documented by full characterization of porphyrin patterns and identification of the underlying pathogenic variants. In later-onset cases, an underlying myeloproliferative disorder and a *UROS* somatic pathogenic variant should be suspected and studied in detail.

The clinical picture in hepatoerythropoietic porphyria (HEP) may be similar, but the porphyrin patterns in urine and feces in HEP resemble PCT. A predominant increase in erythrocyte protoporphyrin is not expected in CEP, except in mild cases, but is characteristic of HEP and rare homozygous cases of AIP, HCP, and VP. EPP and XLP are also distinguished by normal urinary porphyrins and by increases in erythrocyte metal-free protoporphyrin, whereas the increased protoporphyrin in other conditions is mostly complexed with zinc.

CEP should be suspected as a cause of nonimmune hydrops or hemolytic anemia in utero. With recognition of the disease at this stage, intrauterine transfusion can be considered, and phototherapy for hyperbilirubinemia after birth, which can cause severe blistering and scarring, can be avoided. Prenatal diagnosis is feasible by finding red-brown discoloration and increased porphyrins in amniotic fluid and measuring porphyrins in fetal erythrocytes and plasma. *UROS* pathogenic variants can be identified in chorionic villi or cultured amniotic cells.

Treatment

Advising patients to avoid sunlight exposure is essential, because sunlight exposure does not cause immediate severe pain in CEP, in contrast to the protoporphyrias. Minimizing skin trauma and prompt treatment of any cutaneous infections are also essential. Sunscreen lotions and beta-carotene are of little benefit. Transfusions to achieve a level of hemoglobin sufficient to significantly suppress erythropoiesis can be quite effective in reducing porphyrin levels and photosensitivity. Concurrent deferoxamine to reduce iron overload and hydroxyurea to suppress erythropoiesis further may provide additional benefit. Splenectomy reduces hemolysis and transfusion requirements in some patients. Iron restriction by phlebotomy or iron chelators may improve photosensitivity in CEP patients by decreasing ALAS2 activity and porphyrin production.

The most effective treatment is marrow stem cell transplantation in early childhood, which has greatly reduced porphyrin levels and photosensitivity and increased long-term survival.

Prognosis

The outlook is favorable in milder cases and in patients with more severe disease, especially after successful bone marrow or stem cell transplantation. Otherwise, prognosis relates to adherence to sunlight avoidance.

Prevention and Genetic Counseling

Genetic counseling is important for affected families because CEP can be recognized before birth, and a severe phenotype can often be predicted by identifying the nature of the *UROS* pathogenic variants.

PORPHYRIA CUTANEA TARDA

Porphyria cutanea tarda is the most common and readily treated human porphyria (see Table 112.2). It occurs in mid or late adult life and is rare in children. Previous terms include *symptomatic porphyria, PCT symptomatica,* and *idiosyncratic porphyria.* The underlying cause is a liver-specific acquired deficiency of uroporphyrinogen decarboxylase (UROD) with contributions by genetic and acquired susceptibility factors, including heterozygous *UROD* pathogenic variants in familial PCT. HEP, the homozygous form of familial PCT, usually has a more severe presentation in childhood, resembling CEP clinically.

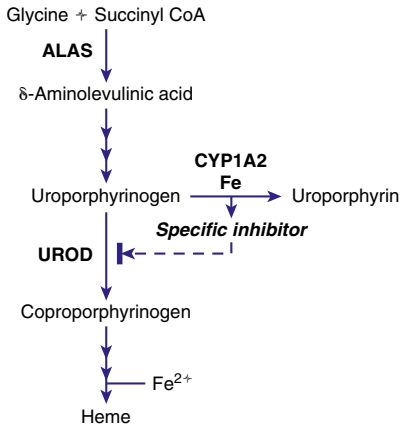

Fig. 112.5 Formation of a specific inhibitor of uroporphyrinogen decarboxylase in the liver in porphyria cutanea tarda. ALAS, δ-Aminolevulinic acid synthase; CYP1A2, cytochrome P450 1A2; UROD, uroporphyrinogen decarboxylase.

Etiology

PCT is caused by a reduction of hepatic UROD activity to ≤20% of normal activity. An inhibitor of hepatic UROD has been characterized as a *uroporphomethene,* which is derived from partial oxidation of the enzyme substrate uroporphyrinogen. CYPs, such as CYP1A2, as well as iron, are involved in its formation (Fig. 112.5). Although enzyme activity is inhibited, the amount of hepatic enzyme protein measured immunochemically remains at its genetically determined level.

UROD catalyzes the decarboxylation of the four acetic acid side chains of uroporphyrinogen (an octacarboxyl porphyrinogen) to form coproporphyrinogen (a tetracarboxyl porphyrinogen). The enzyme reaction occurs in a sequential, clockwise fashion, with the intermediate formation of hepta-, hexa-, and pentacarboxyl porphyrinogens. Uroporphyrinogen III, as compared with other uroporphyrinogen isomers, is the preferred substrate. Human UROD is a dimer with the two active site clefts juxtaposed. The *UROD* gene contains 10 exons, with only one promoter. Therefore the gene is transcribed as a single mRNA in all tissues.

The majority of PCT patients (80%) have no *UROD* pathogenic variants and have sporadic **(type 1)** disease. Some are heterozygous for *UROD* pathogenic variants and have familial **(type 2)** PCT. Described pathogenic variants include missense, nonsense, and splice-site pathogenic variants; several small and large deletions; and small insertions, with only a few identified in more than one family. A few of these pathogenic variants may be located near the active site cleft, but most appear to involve regions with important structural roles. Being heterozygous for a *UROD* pathogenic variant is insufficient to cause PCT. Individuals with type 2 PCT are born with 50% of normal UROD activity, and later in life other susceptibility factors (as in type 1) lead to production of the uroporphomethene inhibitor and further reduction on hepatic UROD activity to <20% of normal. Because penetrance of the genetic trait is low, many patients with familial PCT have no family history of the disease.

Induction of hepatic ALAS1 is not a prominent feature in PCT, although alcohol may increase this enzyme slightly. Iron and estrogens are not potent inducers of ALAS1, and drugs that are potent inducers of ALAS1 and CYPs are much less frequently implicated in PCT than in acute porphyrias.

Blistering skin lesions result from porphyrins that circulate from the liver. Sunlight exposure leads to generation of reactive oxygen species (ROS) in the skin, complement activation, and lysosomal damage.

Epidemiology

Differences in prevalence probably relate to geographic variations in susceptibility factors such as hepatitis C and ethanol use. The yearly incidence in the United Kingdom was estimated at 2-5 in 1 million in the general population, and the prevalence in the United States and Czechoslovakia was estimated at 1 in 25,000 and 1 in 5,000 in the general population, respectively. The disease was reported to be prevalent in the Bantus of South Africa in association with iron overload. PCT is more common in males, possibly because of greater alcohol intake, and in women it is usually associated with estrogen use.

A massive outbreak of PCT occurred in eastern Turkey in the 1950s. Wheat intended for planting and treated with hexachlorobenzene as a fungicide was consumed by many during a food shortage. Cases and small outbreaks of PCT after exposure to other chemicals, including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin), have been reported. The manifestations improved in most cases when the exposure was stopped. There are reported cases of delayed onset many years after chemical exposure.

Pathology and Pathogenesis

Generation of a UROD inhibitor in the liver plays an important role in all three types of PCT. Eighty percent of patients with type 1 **(sporadic)** PCT have no *UROD* pathogenic variants, and UROD activity is normal in nonhepatic tissues such as erythrocytes. In type 2 **(familial)** PCT, a heterozygous *UROD* pathogenic variant results in a partial (approximately 50%) deficiency of UROD in all tissues from birth, and the disease becomes active in some heterozygotes after further reduction of hepatic UROD activity to ≤20% of normal. **Type 3** is rare and describes PCT without a *UROD* pathogenic variant occurring in more than one family member. Another genetic basis, such as *HFE* pathogenic variants, may be identified. HEP results from inheritance of a *UROD* pathogenic variant from each parent and typically causes severe photosensitivity resembling CEP starting in early childhood. Some developed symptoms in childhood more typical of PCT.

CYPs, especially CYP1A2, can catalyze the oxidation of uroporphyrinogen to uroporphyrin. This uroporphyrinogen oxidase activity is enhanced by iron and leads to formation of a UROD inhibitor (see Fig. 112.5). CYP1a2 seems essential for development of uroporphyria in rodents, because experimental uroporphyria does not develop in *CYP1a2* knockout mice.

Susceptibility Factors

The following factors are implicated in the development of PCT, and these occur in various combinations in individual patients.

Iron

PCT is an iron-related disorder, and a normal or increased amount of iron in the liver is essential for its development. Moreover, treatment by phlebotomy to reduce hepatic iron leads to remission. Serum ferritin levels are usually in the upper part of the normal range or moderately increased, and liver histology commonly shows increased iron staining. Prevalence of the C282Y pathogenic variant of the *HFE* gene, which is the major cause of hemochromatosis in people of Northern European ancestry, is increased in both type 1 and type 2 PCT, and approximately 10% of patients are C282Y homozygotes. In Southern Europe the H63D pathogenic variant is more prevalent. PCT may develop in patients with secondary iron overload. Reduced hepatic expression of the hormone hepcidin occurs in hemochromatosis and also in PCT, regardless of *HFE* genotype, which may explain hepatic siderosis in this condition.

Hepatitis C

Hepatitis C virus (HCV) infection is highly prevalent in PCT in most geographic locations; in the United States, for example, HCV is present in 56–74% of cases, which is similar to rates in Southern Europe. Prevalence of hepatitis C in PCT is lower in Northern Europe (<20%). Steatosis and oxidative stress in HCV infection may favor iron-mediated generation of ROS and a UROD inhibitor. Dysregulation of hepcidin occurs in hepatitis C and may lead to increased iron absorption.

Human Immunodeficiency Virus

Many reports suggest that HIV infection can contribute to the development of PCT, although less frequently than HCV.

Ethanol

The long-recognized association between alcohol and PCT may be explained by the generation of ROS, which may cause oxidative damage, mitochondrial injury, depletion of reduced glutathione and other antioxidant defenses, increased production of endotoxin, and activation of Kupffer cells. Also, alcohol may contribute to iron overload by impairing hepcidin production.

Smoking and Cytochrome P450 Enzymes

Although not extensively studied as a susceptibility factor, smoking is often associated with alcohol use in PCT. It may act to induce hepatic CYPs and oxidative stress. Hepatic CYPs are thought to be important in oxidizing uroporphyrinogen and generating a UROD inhibitor (see Fig. 112.5). Genetic polymorphisms of *CYP1A2* and *CYP1A1* have been implicated in human PCT. The frequency of an inducible *CYP1A2* genotype was more common in PCT patients than in controls in several studies.

Antioxidant Status

Ascorbic acid deficiency contributes to uroporphyria in laboratory models and perhaps in human PCT. In one series, plasma ascorbate levels were substantially reduced in 84% of patients with PCT. Low levels of serum carotenoids were also described, further suggesting that oxidant stress in hepatocytes is important in PCT.

Estrogens

Use of estrogen-containing oral contraceptives (OCs) or postmenopausal estrogen replacement therapy is frequently associated with PCT (type 1 or 2) in women. PCT sometimes occurs during pregnancy, although it is not clear whether the risk is increased.

Cancer Chemotherapy

Cancer chemotherapeutic agents are commonly associated with rare childhood cases of PCT, although specific agents have not been implicated. Susceptibility factors found in adults are rare in children with PCT.

Clinical Manifestations

Cutaneous Manifestations

PCT is readily recognized by blistering and crusted skin lesions on the backs of the hands, which are the most sun-exposed areas of the body, and less often on the forearms, face, ears, neck, legs, and feet (Fig. 112.6). The fluid-filled vesicles usually rupture and become crusted or denuded areas, heal slowly, and are subject to infection. The skin is friable, and minor trauma may cause blisters or denudation of skin. Small white plaques, termed *milia,* may precede or follow vesicle formation. Facial hypertrichosis and hyperpigmentation are also common. Severe scarring and thickening of sun-exposed skin may resemble scleroderma. Skin biopsy findings include subepidermal blistering and deposition of periodic acid–Schiff-(PAS)–positive material around blood vessels and fine fibrillar material at the dermoepithelial junction, which may be related to excessive skin fragility. IgG, other immunoglobulins, and complement are also deposited at the dermoepithelial junction and around dermal blood vessels. The skin lesions and histologic changes are not specific for PCT. The same findings occur in VP and HCP and resemble those of CEP and HEP but are usually less severe. PCT usually develops in mid or late adult life. Earlier onset may be seen in those with *UROD* or *HFE* pathogenic variants and childhood onset with cancer chemotherapy and *UROD* pathogenic variants.

Liver Abnormalities

PCT is almost always associated with nonspecific liver abnormalities, especially increased serum transaminases and γ-glutamyltranspeptidase, even in the absence of heavy alcohol intake or hepatitis C. Most histologic findings, such as necrosis, inflammation,



Fig. 112.6 Porphyria cutanea tarda (PCT). A, Right hand of a patient with PCT, revealing numerous erosions and erythematous patches. B, Close-up of right hand. (*From Horner ME, Alikhan A, Tintle S, et al. Cutaneous porphyrias. Part 1. Epidemiology, pathogenesis, presentation, diagnosis, and histopathology. Int J Dermatol. 2013;52:1464–1480, Fig. 2.*)

increased iron, and increased fat, are nonspecific. Specific findings include red fluorescence of liver tissue and fluorescent, birefringent, needle-like inclusions presumably consisting of porphyrins. Electron microscopy shows these inclusions are in lysosomes, and paracrystalline inclusions are found in mitochondria. Distorted lobular architecture and cirrhosis are more common with long-standing disease.

The risk of developing hepatocellular carcinoma is increased, with reported incidences ranging from 4% to 47% in PCT. These tumors seldom contain large amounts of porphyrins.

Other Features and Associations

Mild or moderate erythrocytosis in some adult patients is not well understood, but chronic lung disease from smoking may contribute. An earlier onset of symptoms may be noted in patients with genetic predisposing factors, such as an inherited partial deficiency of UROD or the C282Y/C282Y *HFE* genotype. Iron overload secondary to conditions such as myelofibrosis and end-stage renal disease (ESRD) may be associated with PCT. The disease can be especially severe in patients with ESRD because the lack of urinary excretion leads to much higher concentrations of porphyrins in plasma, and the excess porphyrins are poorly dialyzable. PCT occurs more frequently in patients with systemic lupus erythematosus and other immunologic disorders than would be expected by chance.

Laboratory Findings

Porphyrins accumulate in the liver mostly as the oxidized porphyrins rather than porphyrinogens in PCT, as indicated by the immediate *red fluorescence* observed in liver tissue. This develops over weeks or months before porphyrins appear in plasma and are transported to the skin, causing photosensitivity. In contrast to the acute hepatic porphyrias, only a very small increase in synthesis of heme pathway intermediates and little or no increase in hepatic ALAS1 are required to account for the excess porphyrins excreted in PCT.

Hepatic UROD deficiency leads to a complex pattern of excess porphyrins, which initially accumulate as porphyrinogens and then undergo nonenzymatic oxidation to the corresponding porphyrins (uro-, hepta-, hexa-, and pentacarboxyl porphyrins, and isocoproporphyrins). Uroporphyrin and heptacarboxyl porphyrin predominate in urine, with lesser amounts of coproporphyrin and penta- and hexacarboxyl porphyrin. A normally minor pathway is accentuated by UROD deficiency, whereby pentacarboxyl porphyrinogen is oxidized by coproporphyrinogen oxidase (CPOX; the next enzyme in the pathway), forming isocoproporphyrinogen, an atypical tetracarboxyl porphyrinogen. Relative to normal values, urinary porphyrins are increased to a greater extent than fecal porphyrins. However, the total amount of porphyrins excreted in feces in PCT exceeds that in urine, and total excretion of type III isomers (including isocoproporphyrins, which are mostly derived from the type III series) exceeds that of type I isomers. Perhaps because uroporphyrinogen III is the preferred substrate for UROD, more uroporphyrinogen I than III accumulates and is excreted as uroporphyrin I in PCT. Hepta- and hexacarboxyl porphyrin are mostly isomer III, and pentacarboxyl porphyrin and coproporphyrin are approximately equal mixtures of isomers I and III.

Diagnosis and Differential Diagnosis

Plasma and urine porphyrins are always increased in clinically manifest PCT, and their measurement is useful for screening. A normal value rules out PCT and other porphyrias that produce blistering skin lesions. It is useful to determine the plasma fluorescence emission maximum at neutral pH, because a maximum near 619 nm is characteristic of PCT (as with CEP and HCP) and, importantly, excludes VP, which has a distinctly different fluorescence maximum. Increased urinary or plasma porphyrins, with a predominance of uroporphyrin and heptacarboxyl porphyrin, is characteristic, although not absolutely specific, for PCT and may occasionally be seen in other porphyrias. Nonspecific increases in urine porphyrins, especially of coproporphyrin, occur in liver disease and other medical conditions. Urinary ALA may be increased slightly in PCT, and PBG is normal. Mild cases of CEP can mimic PCT clinically, and this possibility is ruled out by finding normal or only mildly increased levels of erythrocyte porphyrins.

Familial (type 2) can be distinguished from sporadic (type 1) PCT by finding decreased erythrocyte UROD activity (in type 2) or, more reliably, by finding a disease-related *UROD* pathogenic variant. Type 3 is distinguished from type 1 only by occurrence of PCT in a relative. Biochemical findings in HEP are similar to those in PCT, but with an additional marked increase in erythrocyte zinc protoporphyrin.

Pseudoporphyria (also known as *pseudo-PCT*) presents with skin lesions that closely resemble PCT, but without significant increases in plasma or urine porphyrins. A photosensitizing agent such as a nonsteroidal antiinflammatory drug (NSAID) is sometimes implicated. Both PCT and pseudoporphyria may occur in patients with ESRD.

Complications

Cutaneous blisters may rupture and become infected, sometimes leading to cellulitis. In more severe disease in patients with ESRD, repeated infections can be mutilating, as in CEP. **Pseudoscleroderma**, with scarring, contraction, and calcification of skin and subcutaneous tissue, is a rare complication. Other complications include advanced liver disease and hepatocellular carcinoma.

Treatment

Two specific and effective forms of treatment, phlebotomy and low-dose hydroxychloroquine, are available. Susceptibility factors should be removed when possible. The diagnosis of PCT must be firmly established because conditions, including other porphyrias, that produce identical cutaneous lesions do not respond to these treatments. Treatment can usually be started after demonstrating an increase in plasma total porphyrins and excluding VP by analysis of the fluorescence spectrum at neutral pH, while urine and fecal studies are still pending. Use of alcohol, estrogens (in women), and smoking should be stopped, and patients tested for HCV, HIV, and *HFE* pathogenic variants. Susceptibility factors and degree of iron overload, as assessed by the serum ferritin concentration, can influence the choice of treatment.

Phlebotomy is considered standard therapy and is effective in both children and adults with PCT because it reduces hepatic iron content. Treatment is guided by plasma (or serum) ferritin and porphyrin levels. Hemoglobin or hematocrit levels should be followed to prevent symptomatic anemia. For adults, a unit of blood (450 mL) is removed at about 2-week intervals until a target serum ferritin near the lower limit of normal (15 ng/mL) is achieved. A total of six to eight phlebotomies is often sufficient in adults. After this, plasma porphyrin

concentrations continue to fall from pretreatment levels (generally 10-25 μg/dL) to below the upper limit of normal (1 μg/dL), usually after several more weeks. This is followed by gradual clearing of skin lesions, sometimes including pseudoscleroderma. Liver function abnormalities may improve, and hepatic siderosis, needle-like inclusions, and red fluorescence of liver tissue will disappear. Although remission usually persists even if ferritin levels later return to normal, it is advisable to follow porphyrin levels and reinstitute phlebotomies if porphyrins begin to increase. Infusions of deferoxamine, an iron chelator, may be used when phlebotomy is contraindicated.

An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of hydroxychloroquine (or chloroquine). Normal doses of these 4-aminoquinoline antimalarials in PCT increase plasma and urinary porphyrin levels and increase photosensitivity, reflecting an outpouring of porphyrins from the liver. This is accompanied by acute hepatocellular damage, with fever, malaise, nausea, and increased serum transaminases, but is followed by complete remission of the porphyria. These adverse consequences of normal doses are largely avoided by a low-dose regimen (for adults, hydroxychloroquine 100 mg or chloroquine 125 mg, i.e., half a normal tablet, twice weekly), which can be continued until plasma or urine porphyrins are normalized. In young children, half the adult dose is recommended. There is at least some risk of retinopathy, which may be lower with hydroxychloroquine. The mechanism of action of 4-aminoquinolines in PCT is not known but is quite specific, because these drugs are not useful in other porphyrias. Recent studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in adults with PCT.

Experience to date supports treatment of patients with PCT and hepatitis C with direct-acting antiviral agents to achieve cure of this viral infection within a few months as well as remission of PCT and avoiding treatment by phlebotomy or low-dose hydroxychloroquine.

PCT in patients with ESRD is often more severe and difficult to treat. However, erythropoietin administration can correct anemia, mobilize iron, and support phlebotomy in many cases. Improvement is expected after renal transplantation, related in part to resumption of endogenous erythropoietic production.

Liver imaging and a serum α-fetoprotein determination may be advisable in all PCT patients with cirrhosis or advanced fibrosis at 6-month intervals for early detection of hepatocellular carcinoma. Finding low-erythrocyte UROD activity or a *UROD* pathogenic variant identifies those with an underlying genetic predisposition, which does not alter treatment but is useful for genetic counseling.

Prognosis

Porphyria cutanea tarda is the most readily treated form of porphyria, and complete remission is expected with treatment by phlebotomy or low-dose hydroxychloroquine or by treatment of hepatitis C. There is little information on rates of recurrence and long-term outlook. Risk for cirrhosis and hepatocellular carcinoma is increased, and some susceptibility factors such as alcohol, hepatitis C, and iron overload can contribute to such risks.

Prevention and Genetic Counseling

A heritable *UROD* pathogenic variant can usually be detected or excluded by measuring erythrocyte UROD activity, although DNA studies are more sensitive. Relatives of patients with *UROD* pathogenic variants have an increased risk for developing PCT and may have increased motivation to avoid adverse behaviors such as ethanol and tobacco use and exposures to HCV and HIV (although such counseling would be given to anyone). The finding of *HFE* pathogenic variants, and especially C282Y, should prompt screening of relatives, some of whom may be C282Y homozygotes and warrant lifelong monitoring of serum ferritin.

HEPATOERYTHROPOIETIC PORPHYRIA

HEP is the homozygous form of familial (type 2) PCT; it resembles CEP clinically. Excess porphyrins originate mostly from liver, with a pattern consistent with severe UROD deficiency.

Etiology

HEP is an autosomal recessive disorder, and most patients have inherited different pathogenic variants from unrelated parents. In contrast to most pathogenic variants in familial PCT, most causing HEP are associated with expression of some residual enzyme activity. At least one genotype is associated with the predominant excretion of pentacarboxyl porphyrin.

Pathology and Pathogenesis

Excess porphyrins originate primarily from the liver in HEP, although the substantial increase in erythrocyte zinc protoporphyrin indicates that the heme biosynthetic pathway is also impaired in bone marrow erythroid cells. Apparently, porphyrinogens accumulate in the marrow while hemoglobin synthesis is most active and are metabolized to protoporphyrin after hemoglobin synthesis is complete. The cutaneous lesions are a result of photoactivation of porphyrins in skin, as in other cutaneous porphyrias.

Clinical Manifestations

This disease usually presents with blistering skin lesions, hypertrichosis, scarring, and red urine in infancy or childhood. *Sclerodermoid* skin changes are sometimes prominent. Unusually mild cases have been described. Concurrent conditions that affect liver function can alter disease severity; the disease manifested because of hepatitis A in a 2-year-old child and then improved with recovery of liver function.

Laboratory Findings

Biochemical findings resemble those in PCT, with accumulation and excretion of uroporphyrin, heptacarboxyl porphyrin, and isocoproporphyrin. In addition, erythrocyte zinc protoporphyrin is substantially increased.

Diagnosis and Differential Diagnosis

HEP is distinguished from CEP by increases in both uroporphyrin and heptacarboxyl porphyrin and isocoproporphyrins. In CEP, the excess erythrocyte porphyrins are predominantly uroporphyrin I and coproporphyrin I rather than protoporphyrin. Blistering skin lesions are unusual in EPP, the excess erythrocyte protoporphyrin in that disease is metal-free and not complexed with zinc, and urinary porphyrins are normal.

Treatment and Prognosis

Avoiding sunlight exposure is most important in managing HEP, as in CEP. Oral charcoal was helpful in a severe case associated with dyserythropoiesis. Phlebotomy has shown little or no benefit. The outlook depends on the severity of the enzyme deficiency and may be favorable if sunlight can be avoided.

Prevention and Genetic Counseling

As part of genetic counseling in affected families, it is feasible to diagnose HEP in utero, either by analysis of porphyrins in amniotic fluid or DNA studies.

HEREDITARY COPROPORPHYRIA

This autosomal dominant hepatic porphyria is caused by a deficiency of CPOX. The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity may occur, but much less often than in VP. Rare homozygous cases present in childhood, including a variant form known as *harderoporphyria*.

Etiology

A partial (50%) deficiency in CPOX activity has been found in all cells studied from patients with HCP. A much more profound deficiency is found in homozygous cases. Human CPOX is a homodimer composed of 39-kDa subunits and contains no metals or prosthetic groups. The enzyme requires molecular oxygen and is localized in the mitochondrial intermembrane space. A single active site on the enzyme catalyzes the oxidative decarboxylation of two of the four propionic acid groups of coproporphyrinogen III to form the two vinyl groups at positions

two and four, on rings A and B, respectively, of protoporphyrinogen IX. Most of the intermediate tricarboxyl porphyrinogen, termed *harderoporphyrinogen,* is not released before undergoing the second decarboxylation to protoporphyrinogen IX. Coproporphyrinogen I is not a substrate for this enzyme.

The human *CPOX* gene contains a single promoter with elements for both housekeeping and erythroid-specific expression. A variety of *CPOX* pathogenic variants have been described in HCP, with a predominance of missense pathogenic variants and no genotype-phenotype correlations. **Harderoporphyria**, an autosomal recessive biochemical variant form of HCP, is caused by *CPOX* pathogenic variants that impair substrate binding, leading to premature release of harderoporphyrinogen.

Epidemiology

HCP is less common than AIP and VP, but its prevalence has not been carefully estimated. Homozygous HCP is rare and presents during childhood. Harderoporphyria, a biochemically distinguishable variant of HCP, has been recognized in heteroallelic and homoallelic forms.

Pathology and Pathogenesis

Increased ALA and PBG during acute attacks of HCP may be explained by induction of ALAS1 and by the normally relatively low activity of PBGD in the liver. Hepatic ALAS1 is increased during acute attacks but is normal when the disease is latent and porphyrin precursor excretion is normal. Because coproporphyrinogen III concentration in the liver is probably less than the K_m for CPOX, the reaction rate is likely to be determined in part by substrate concentration. The substrate coproporphyrinogen appears to be lost more readily from the liver cell than, for example, uroporphyrinogen, especially when heme synthesis is stimulated. Coproporphyrin and coproporphyrinogen are both transported into bile and excreted in urine and do not appear to accumulate in the liver in HCP.

Clinical Manifestations

Symptoms are identical to those of AIP except that attacks are generally milder, and cutaneous lesions that resemble those in PCT develop occasionally. *Severe motor neuropathy and respiratory paralysis can occur*. HCP is almost always latent before puberty, and symptoms are most common in adult women. Attacks are precipitated by the same factors that cause attacks in AIP, including fasting, OCs, and hormone increases during the luteal phase of the menstrual cycle. Concomitant liver diseases may increase porphyrin retention and photosensitivity. The risk of hepatocellular carcinoma is increased.

The clinical features of homozygous HCP or harderoporphyria begin in early childhood and include jaundice, hemolytic anemia, hepatosplenomegaly, and skin photosensitivity. These symptoms are generally quite distinct from those seen in heterozygotes. Hematologic features are particularly characteristic in harderoporphyria.

Laboratory Findings

The porphyrin precursors ALA and PBG are increased during acute attacks in HCP but may decrease more rapidly than in AIP. Marked increases in coproporphyrin III in urine and feces are more persistent in HCP. Plasma porphyrins are usually normal or only slightly increased.

In homozygous cases, porphyrin excretion may be more increased and is accompanied by substantial increases in erythrocyte zinc protoporphyrin. Harderoporphyria is characterized by a marked increase in fecal excretion of harderoporphyrin (tricarboxyl porphyrin) and in coproporphyrin.

Diagnosis and Differential Diagnosis

The diagnosis of HCP is readily established in patients with clinically manifest disease, although urinary ALA, PBG, and uroporphyrin may revert to normal more quickly than in AIP. Urinary coproporphyrin III is increased. Urinary porphyrins, especially coproporphyrin, can be increased in many medical conditions (e.g., liver disease), and small increases that are not diagnostically significant may lead to an incorrect diagnosis of HCP. Fecal porphyrins are mostly coproporphyrin (isomer III) in HCP, whereas in VP, coproporphyrin III and protoporphyrin are often increased approximately equally. Plasma porphyrins are usually normal in HCP and increased in VP.

The ratio of fecal coproporphyrin III to coproporphyrin I is especially sensitive for detecting latent heterozygotes (especially in adults). Assays for CPOX, a mitochondrial enzyme, require cells such as lymphocytes and are not widely available. Identification of a *CPOX* pathogenic variant in an index case greatly facilitates screening family members.

Treatment and Prognosis

Acute attacks of HCP are treated as in AIP, which includes IV hemin and identifying and avoiding precipitating factors. Phlebotomy and chloroquine are not effective. GnRH analogs can be effective for prevention of cyclic attacks. The prognosis is generally better than in AIP. Givosiran, an siRNA therapeutic agent, has been approved for the prevention of acute attacks in all acute hepatic porphyrias, although experience in HCP is limited.

Prevention and genetic counseling are the same as in other acute porphyrias.

VARIEGATE PORPHYRIA

This hepatic porphyria is caused by a deficiency of protoporphyrinogen oxidase (PPOX), which is inherited as an autosomal dominant trait. The disorder is termed *variegate* because it can present with neurologic or cutaneous manifestations or both. Other terms have included *porphyria variegata, protocoproporphyria,* and *South African genetic porphyria.* Rare cases of homozygous VP are symptomatic in childhood.

Etiology

PPOX is approximately half-normal in all cells studied in patients with VP. The enzyme is more markedly deficient in rare cases of homozygous VP, with approximately half-normal enzyme activity in parents.

Human PPOX is a homodimer that contains flavin adenine dinucleotide and is localized to the cytosolic side of the inner mitochondrial membrane. Membrane-binding domains may be docked onto human FECH, the next enzyme in the pathway, which is embedded in the opposite side of the membrane. PPOX catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by the removal of six hydrogen atoms. The enzyme requires molecular oxygen. The substrate is readily oxidized nonenzymatically to protoporphyrin under aerobic conditions or if exported into the cytosol. PPOX is highly specific for protoporphyrinogen IX and is inhibited by tetrapyrroles such as heme, biliverdin, and bilirubin and by certain herbicides that cause protoporphyrin to accumulate and induce phototoxicity in plants. Inhibition by bilirubin may account for decreased PPOX activity in Gilbert disease.

The human *PPOX* gene consists of one noncoding and 12 coding exons. Many *PPOX* pathogenic variants have been reported in VP families. A missense pathogenic variant, R59W, is prevalent in South Africa. No convincing genotype-phenotype correlations have been identified. Pathogenic variants in homozygous cases of VP are more likely to encode enzyme proteins with residual activity.

Epidemiology

VP is less common than AIP in most countries. The R59W pathogenic variant is highly prevalent in South African Whites (3 in 1,000 in this population). This example of "genetic drift" or founder effect has been traced to a man or his wife who emigrated from Holland to South Africa in 1688. In Finland, prevalence is 1.3 in 100,000 people and is about as common as AIP.

Pathology and Pathogenesis

Acute attacks develop in a minority of heterozygotes for PPOX deficiency and are often attributable to drugs, steroids, and nutritional factors that play a role in other acute porphyrias. Protoporphyrinogen IX accumulates and undergoes autoxidation to protoporphyrin IX. Coproporphyrinogen III accumulates, perhaps as the result of a close functional association between PPOX in the inner mitochondrial

membrane and CPOX in the intermembrane space. Liver porphyrin content is not increased. The increased porphyrin content in plasma consists of porphyrin-peptide conjugates, which may be formed from protoporphyrinogen. Increased ALA and PBG during acute attacks may be explained, as in HCP, by induction of ALAS1 by exacerbating factors and by the normally relatively low activity of PBGD in liver. Furthermore, PBGD is inhibited by protoporphyrinogen, the substrate for PPOX.

Clinical Manifestations

Symptoms develop in some heterozygotes after puberty. Neurovisceral symptoms occurring as acute attacks are identical to AIP but are generally milder and less often fatal. Drugs, steroids, and nutritional alterations such as fasting, which are harmful in AIP, can also induce attacks of VP. Attacks occur equally in males and females, at least in South Africa. Cutaneous fragility, vesicles, bullae, hyperpigmentation, and hypertrichosis of sun-exposed areas are much more common than in HCP. They are likely to occur apart from and to be longer lasting than the neurovisceral symptoms. OCs can precipitate cutaneous manifestations. Acute attacks have become less common, and skin manifestations are more frequently the initial presentation; this may result from earlier diagnosis and counseling. The risk of hepatocellular carcinoma is increased.

Symptoms of homozygous VP begin in infancy or childhood. These children generally have severe photosensitivity, neurologic symptoms, seizures, developmental disturbances, and sometimes growth retardation, but they do not have acute attacks.

Laboratory Findings

Urinary ALA, PBG, and uroporphyrin are increased during acute attacks, but often less so than in AIP, and may be normal or only slightly increased during remission. Plasma porphyrins, urinary coproporphyrin III, and fecal coproporphyrin III and protoporphyrin are more persistently increased between attacks. The pattern of urinary porphyrins can sometime resemble that seen in PCT. Erythrocyte zinc protoporphyrin levels are greatly increased in homozygous VP and may be modestly increased in heterozygous cases.

Diagnosis and Differential Diagnosis

VP is readily distinguished biochemically from AIP and HCP, which also present with acute attacks and increases in PBG. Plasma porphyrin analysis is especially useful because the plasma porphyrins in VP are tightly protein bound, resulting in a characteristic fluorescence emission spectrum at neutral pH. Fecal porphyrins are increased, with approximately equal amounts of coproporphyrin III and protoporphyrin. Fluorometric detection of plasma porphyrins is more sensitive than stool porphyrin analysis in asymptomatic VP. PPOX assays using cells that contain mitochondria, such as lymphocytes, are sensitive for identifying asymptomatic carriers but are not widely available. Knowing the *PPOX* pathogenic variant in an index case enables the identification of relatives who carry the same pathogenic variant.

Treatment

Acute attacks are treated as in AIP. Hemin is beneficial for acute attacks but not for cutaneous symptoms. Light protection is important in patients with skin manifestations, using long-sleeved clothing, gloves, a broad-brimmed hat, and opaque sunscreen preparations. Exposure to short-wavelength UV light, which does not excite porphyrins, may increase skin pigmentation and provide some protection. Phlebotomy and chloroquine are not effective. Surprisingly, oral activated charcoal was reported to increase porphyrin levels and worsen skin manifestations.

Prognosis and Prevention

The outlook of patients with VP has improved, which may be attributed to improved treatment, earlier diagnosis, and detection of latent cases. Cyclic acute attacks in women can be prevented with a GnRH analog, as in AIP. Givosiran, an siRNA therapeutic agent, has been approved for the prevention of acute attacks in all acute hepatic porphyrias, although experience in VP is limited. A diagnosis of VP or any other acute porphyria should not lead to difficulty obtaining insurance, because the prognosis is usually good once the diagnosis is established.

Genetic counseling is the same as in other acute porphyrias.

ERYTHROPOIETIC PROTOPORPHYRIA AND X-LINKED PROTOPORPHYRIA

These forms of protoporphyria are genetically distinct but have essentially the same phenotype. In EPP, an autosomal recessive disorder, protoporphyrin accumulates as the result of a marked deficiency of FECH, the last enzyme in the heme biosynthetic pathway, because of *FECH* pathogenic variants. EPP is sometimes termed *erythrohepatic protoporphyria,* although the liver does not contribute substantially to production of excess protoporphyrin. XLP is the most recently described porphyria, in which gain-of-function *ALAS2* pathogenic variants lead to overproduction of ALA in the marrow, where it is metabolized to excess amounts of protoporphyrin.

Etiology

Ferrochelatase (FECH), the enzyme that is deficient in EPP, catalyzes the final step in heme synthesis, which is insertion of ferrous iron (Fe^{2+}) into protoporphyrin IX (see Fig. 112.1). The enzyme is also termed *heme synthetase* or *protoheme ferrolyase.* The human enzyme is a dimer, and each homodimer contains a [2Fe-2S] cluster, which may have a role in bridging homodimers. FECH is found in the mitochondrial inner membrane, where its active site faces the mitochondrial matrix. It may be associated with complex I of the mitochondrial electron transport chain, and the ferrous iron substrate may be produced on nicotinamide adenine dinucleotide oxidation. FECH is specific for the reduced form of iron but can use other metals, such as Zn^{2+} and Co^{2+}, and other dicarboxyl porphyrins. Accumulation of metal-free protoporphyrin rather than zinc protoporphyrin in EPP indicates that formation of the latter is dependent on FECH activity in vivo.

The human *FECH* gene has a single promoter sequence and contains 11 exons. Two mRNAs of 1.6 and 2.5 kb were described, which may be explained by the use of two alternative polyadenylation signals. The larger transcript is more abundant in murine erythroid cells, suggesting erythroid-specific regulation of FECH. A variety of *FECH* pathogenic variants have been reported in EPP, including missense, nonsense, and splicing pathogenic variants; small and large deletions; and an insertion.

The inheritance of two alleles associated with reduced FECH activity is required for disease expression. This is consistent with FECH activities as low as 15–25% of normal in EPP patients. In most patients, a pathogenic variant on one *FECH* allele is combined with a common variant affecting the other allele. This common-variant *FECH* allele (IVS3-48T>C) produces less-than-normal amounts of enzyme because it expresses an aberrantly spliced mRNA that is degraded by a nonsense-mediated RNA decay mechanism. The IVS3-48T>C *FECH* variant by itself does not cause disease, even when homozygous. In a few families, two severe *FECH* pathogenic variants have been found without the IVS3-48T>C allele. EPP with autosomal recessive inheritance occurs naturally in cattle and in mouse models.

XLP is associated with gain-of-function deletions in the last exon of *ALAS2*. These lesions delete the last 10-20 amino acids of the ALAS2 polypeptide and apparently make the enzyme more stable. Metal-free protoporphyrin predominates in erythrocytes in these cases, but because FECH activity is normal, the proportion of zinc protoporphyrin is greater than in EPP. XLP accounts for approximately 2% of cases with the EPP phenotype in Europe and approximately 10% of cases in North America.

EPP is sometimes associated with myelodysplastic or myeloproliferative disorders and expansion of a clone of hematopoietic cells with deletion of one *FECH* allele or with other *FECH* pathogenic variants. In such cases there is late onset of the disease.

Epidemiology

EPP is the most common porphyria to cause symptoms in children but is often not diagnosed until adult life. Overall, it is the third most

common porphyria, although its prevalence is not precisely known (see Table 112.2). An analysis from the UK biobank exome sequencing data suggests that EPP is 1.7-3.0 times more common than previously thought in the UK. It is described mostly in Whites but occurs in other ancestries. The IVS3-48T>C splice variant is common in Whites and Japanese but rare in Africans, which explains lower disease prevalence in populations of African origin.

Pathology and Pathogenesis

FECH is deficient in all tissues in EPP, but bone marrow reticulocytes are thought to be the primary source of the excess protoporphyrin, some of which enters plasma and circulates to the skin. Circulating erythrocytes are no longer synthesizing heme and hemoglobin, but they contain excess free protoporphyrin, which also contributes. In XLP caused by terminal deletions in exon 11 of *ALAS2,* all intermediates of the heme pathway are overproduced and ultimately accumulate in bone marrow erythroblasts as protoporphyrin. FECH is not deficient in XLP, so this enzyme chelates some of the excess protoporphyrin with zinc. An aberrantly spliced mitoferrin transcript, which limits iron transport into mitochondria, has also been described in EPP. The liver functions as an excretory organ rather than a major source for excess protoporphyrin. FECH deficiency in the skin and liver may be important, however, because tissue transplantation studies in mice suggest that skin photosensitivity and liver damage occur only when FECH is deficient in these tissues.

Patients with EPP and XLP are maximally sensitive to light in the 400-nm range, which corresponds to the so-called *Soret band,* the narrow peak absorption maximum that is characteristic for protoporphyrin and other porphyrins. Having absorbed light, porphyrins enter an excited energy state and release energy as fluorescence, singlet oxygen, and other ROS. Resulting tissue damage is accompanied by lipid peroxidation, oxidation of amino acids, cross linking of proteins in cell membranes, and damage to capillary endothelial cells. Such damage may be mediated by photoactivation of the complement system and release of histamine, kinins, and chemotactic factors. Repeated acute damage leads to thickening of the vessel walls and perivascular deposits from accumulation of serum components. Deposition of amorphous material containing immunoglobulin, complement components, glycoproteins, acid glycosaminoglycans, and lipids occurs around blood vessels in the upper dermis.

There is little evidence for impaired erythropoiesis or hemolysis in EPP. However, mild anemia with microcytosis, hypochromia, and reticulocytosis is common. Iron accumulation in erythroblasts and ring sideroblasts has been noted in bone marrow in some patients. Decreased transferrin saturation and low or low-normal serum ferritin suggest iron deficiency. Iron status should be carefully evaluated in EPP patients. Poor response to oral iron supplements is described in EPP and is unexplained, because iron absorption is not impaired. Some patients report increased photosensitivity when given iron supplements, but whether this is from transient increases in porphyrins when iron deficiency is corrected and erythropoiesis increases is not known. Case reports suggest that iron supplementation decreases protoporphyrin and improves anemia, especially in patients with XLP. However, recent evidence suggests that iron deficiency may reduce protoporphyrin levels in some EPP patients.

Liver damage develops in a small proportion of EPP and XLP patients and is attributed to excess protoporphyrin, which is insoluble in water and excreted only by hepatic uptake and biliary excretion. Some may be reabsorbed by the intestine and undergo enterohepatic circulation. At very high levels, protoporphyrin is cholestatic, can damage cholangiocytes, and can accumulate in hepatocytes to form crystalline structures and impair mitochondrial function.

Clinical Manifestations

Symptoms of cutaneous photosensitivity begin in childhood and consist of acute pain and itching, often occurring within minutes of sunlight exposure and followed by redness and swelling with continued exposure (Fig. 112.7). Petechiae and purpuric lesions may be seen, but blisters are rare. Swelling may resemble angioneurotic edema and *solar urticaria.* Symptoms are usually worse in the spring and summer. Chronic changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes, but changes in pigmentation and pronounced scarring are unusual. Although physical findings in EPP and XLP may not be impressive, efforts to avoid sunlight and resulting symptoms significantly impair quality of life. An association between EPP caused by pathogenic variants affecting both FECH alleles and seasonal palmar keratoderma is unexplained. Neuropathy develops only in some patients with severe hepatic decompensation. XLP males have a more severe phenotype with higher protoporphyrin levels than most EPP patients. XLP females have a variable clinical presentation—some with no symptoms or mild symptoms and others with severe symptoms similar to XLP males. This variability in females is likely the result of random X chromosome inactivation.

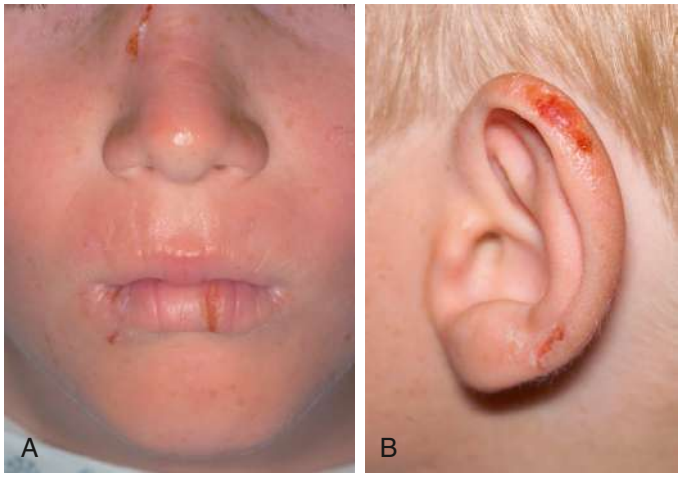

Fig. 112.7 Erythropoietic protoporphyria (EPP). **A,** Linear erosions of the lateral nasal bridge and lower lip in a patient with EPP. **B,** Erosions with crusting on the left helix of a patient with EPP. (*From Horner ME, Alikhan A, Tintle S, et al. Cutaneous porphyrias. Part 1. epidemiology, pathogenesis, presentation, diagnosis, and histopathology. Int J Dermatol. 2013;52:1464–1480, Figs. 7 and 8.*)

Unless hepatic or other complications develop, protoporphyrin levels and symptoms of photosensitivity remain remarkably stable for many years in most patients. Factors that exacerbate hepatic porphyrias play little or no role in EPP or XLP. Erythrocyte protoporphyrin levels may decrease and sunlight tolerance may improve during pregnancy, which is unexplained.

Laboratory Findings

Protoporphyrin is substantially increased in circulating erythrocytes in EPP and consists almost entirely of metal-free protoporphyrin. In XLP, both zinc protoporphyrin and metal-free protoporphyrin are increased, although the latter still predominates. Protoporphyrin is also increased in bone marrow, plasma, bile, and feces. Other porphyrins and porphyrin precursors are normal in uncomplicated EPP and XLP.

Diagnosis and Differential Diagnosis

A diagnosis of EPP is confirmed biochemically by finding a substantially elevated concentration of total erythrocyte protoporphyrin, which is predominantly (at least 85%) metal-free and not complexed with zinc. In XLP, both metal-free and zinc-complexed protoporphyrins are elevated. Erythrocyte total protoporphyrin levels are, on average, higher in XLP and more variable between individuals in EPP, possibly reflecting differences in severity of the many reported *FECH* pathogenic variants. Erythrocyte zinc protoporphyrin concentration is increased with little increase in metal-free protoporphyrin in homozygous porphyrias (except CEP), iron deficiency, lead poisoning, anemia of chronic disease, hemolytic conditions, and many other erythrocytic disorders. Measurement of FECH activity requires cells containing mitochondria and is not widely available.

Plasma total porphyrin concentration is often less increased in EPP than in other cutaneous porphyrias and may be normal. Great care must be taken to avoid light exposure during sample processing, because plasma porphyrins in EPP are particularly subject to photodegradation. Urinary porphyrin precursors and porphyrins are not increased.

DNA studies are strongly recommended for confirming *FECH* or *ALAS2* pathogenic variants and for genetic counseling.

Life-threatening **protoporphyric hepatopathy** is characterized by greater increases in erythrocyte and plasma protoporphyrin levels, increased photosensitivity, and either chronically abnormal liver function tests or rapidly progressive hepatic failure. Presumably this is heralded by increases above the patient's baseline erythrocyte and plasma porphyrin levels, but this has not been documented, because most such patients have not had sufficiently long-term determinations of porphyrin values. Increases in urinary porphyrins, especially coproporphyrin, in this setting are attributable to liver dysfunction.

Complications

There is an increased risk of biliary stones, which contain protoporphyrin and are sometimes symptomatic, requiring cholecystectomy. Protoporphyric hepatopathy occurs in <5% of protoporphyria patients, including children, and may be chronic or progress rapidly to death from liver failure. Rarely, hepatopathy is the major presenting feature of EPP or XLP. Protoporphyric hepatopathy can cause acute upper abdominal pain suggesting biliary obstruction, and unnecessary laparotomy to exclude this possibility can be detrimental. Other types of liver disease, such as viral hepatitis or alcohol- or drug-induced liver disease, must be excluded, or may contribute to the development of protoporphyric hepatopathy. Whether iron deficiency may contribute is unclear. Liver histology shows marked deposition of protoporphyrin as inclusions in liver cells and bile canaliculi. The bone marrow is probably the major source of protoporphyrin, even in EPP patients with hepatic failure.

Treatment

Exposure to sunlight should be avoided, which is aided by wearing closely woven clothing. Beta-carotene, oral cysteine, and vitamin C have no proven efficacy. One report suggested that high doses of cimetidine were effective in reducing symptoms in three children with EPP, but no objective clinical evidence of efficacy was presented.

Increasing skin melanin by narrow-band UV-B phototherapy may improve sunlight tolerance. Studies in the United States and Europe of afamelanotide, a synthetic analog of melanocyte-stimulating hormone, darkened the skin, increased pain-free sun exposure, and improved quality of life in patients with protoporphyria. This drug is approved for use in adults in Europe and the United States. Dersimelagon, an orally administered small molecule and a selective melanocortin-1 receptor (MC1R) agonist that increases skin melanin, is currently in phase 3 trials in EPP and XLP in the United States and other countries.

Drugs or hormone preparations that impair hepatic excretory function should be avoided. Iron deficiency should be corrected, particularly in XLP. Vitamin D supplementation and hepatitis A and B vaccination are recommended.

Treatment of protoporphyric hepatopathy must be individualized and exclude other causes of liver disease. Spontaneous resolution may occur, especially if another reversible cause of liver dysfunction, such as viral hepatitis or alcohol abuse, is contributing. In patients with severe hepatic decompensation, combined treatment with plasmapheresis, transfusion to correct anemia and suppress erythropoiesis, IV hemin to suppress erythroid and possibly hepatic protoporphyrin production, ursodeoxycholic acid, vitamin E, and cholestyramine may be beneficial and bridge patients to liver transplantation.

Motor neuropathy resembling that seen in acute porphyrias sometimes develops in protoporphyria patients with liver disease before or after transfusion or liver transplantation and is sometimes reversible. Artificial lights, such as operating room lights during liver transplantation or other surgery, may cause severe photosensitivity, with extensive burns of the skin and peritoneum and damage to circulating erythrocytes.

Although liver disease may recur in the transplanted liver as a result of continued bone marrow production of excess protoporphyrin, outcomes are comparable to transplantation for other types of liver disease. Bone marrow transplantation can be considered after liver transplantation if a suitable donor is available.

Prognosis

Typical EPP patients have lifelong photosensitivity but can otherwise expect normal longevity. Protoporphyric liver disease is often life-threatening; however, the incidence is low.

Prevention and Genetic Counseling

Symptoms can be prevented by avoiding sunlight. Avoiding agents that may cause liver damage may help prevent liver complications. Opinions vary on the value of iron replacement, and this is currently under study.

DNA studies to identify *FECH* pathogenic variants, the common IVS3–48T>C *FECH* hypoexpression allele, or *ALAS2* exon 11 deletions are important for genetic counseling. When EPP is caused by a severe *FECH* pathogenic variant and the common IVS3–48T>C *FECH* allele, DNA studies in the spouse to determine the presence, or more likely the absence, of the hypoexpression allele can predict whether offspring are at risk for EPP. EPP may improve during pregnancy.

DUAL PORPHYRIA

An unusual pattern of porphyrin precursors and porphyrins has led to documentation of pathogenic variants of two heme pathway enzymes. One such patient presented with acute porphyria and had heterozygous pathogenic variants of both *CPOX* and *ALAD*. Another had symptoms of AIP and PCT and was reported to have both *HMBS* and *UROD* pathogenic variants. In other reported cases, one or both enzyme deficiencies were based on enzyme measurements.

PORPHYRIA RESULTING FROM TUMORS

Erythropoietic porphyrias can develop late in life in patients with myelodysplastic or myeloproliferative diseases and clonal expansion of erythroid cells with an inherited or somatic pathogenic variant of an enzyme in the heme biosynthetic pathway.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 113

Hypoglycemia

Katherine Lord and Diva D. De León-Crutchlow

Glucose plays a central role in fuel metabolism and energy storage in the body. It provides 38 mol of adenosine triphosphate (ATP) per mole of glucose oxidized. Glucose is also essential for energy metabolism in the brain, where it is the preferred substrate. Its use accounts for nearly all the brain's oxygen consumption. Cerebral transport of glucose is a glucose transporter-1 (GLUT-1)–facilitated diffusion process that is dependent on blood glucose concentration and not regulated by insulin. *Low concentrations of blood glucose result in cerebral glucopenia, energy failure, and brain injury.* An elaborate regulatory system has evolved to maintain glucose homeostasis and prevent plasma glucose from falling precipitously to levels that impair brain function. The defense against hypoglycemia includes the autonomic nervous system and hormones that act in concert to enhance glucose production through glycogenolysis and gluconeogenesis, while simultaneously limiting peripheral glucose use, which conserves glucose for cerebral metabolism. With prolonged fasting, fat stores are mobilized via lipolysis, and fatty acid oxidation in the liver results in the generation of ketone bodies, an alternative fuel source for the brain (Fig. 113.1). Hypoglycemia results from a failure in one or several of these fasting mechanisms that normally integrate glucose homeostasis.

DEFINITION

Hypoglycemia is defined as a plasma glucose concentration low enough to cause signs and symptoms of brain dysfunction (Fig. 113.2). However, a numerical value can be difficult to define because the brain responses to hypoglycemia occur across a range of plasma glucose concentrations. In young children, signs and symptoms of hypoglycemia are suggestive but nonspecific; thus the reliance on signs and symptoms to indicate hypoglycemia in this age-group may be problematic (Table 113.1).

In older children, evidence of hypoglycemia is based on **Whipple's triad**: (1) signs and symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration, and (3) resolution of the symptoms with normalization of the plasma glucose concentration.

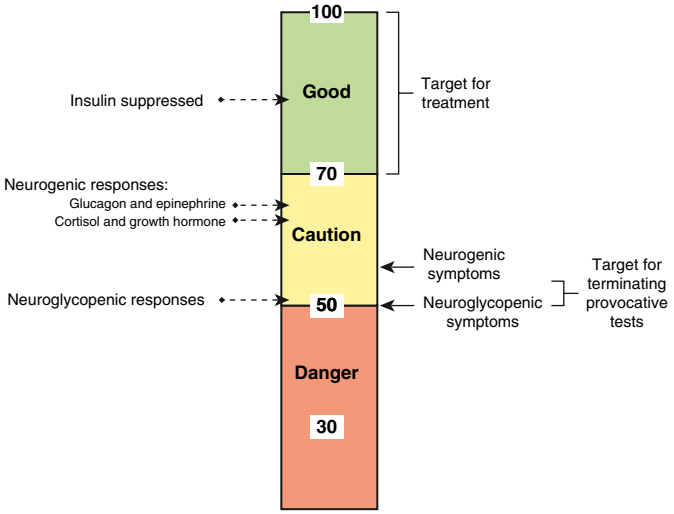

Fig. 113.2 Interpreting glucose levels and glucose treatment targets. Glucose thresholds are shown for suppression of insulin secretion, neurogenic (neuroendocrine hormone-mediated) responses, and neuroglycopenic (impaired cognition) responses. Colors show the normal range *(green)*, the range for symptoms caused by activation of sympathetic nervous system *(yellow)*, and the range for impaired neuronal function *(red)*. (*From Stanescu DL, Stanley CA. Advances in understanding the mechanism of transitional neonatal hypoglycemia and implications for management. Clin Perinatol. 2022;49:55–72, Fig. 2.*)

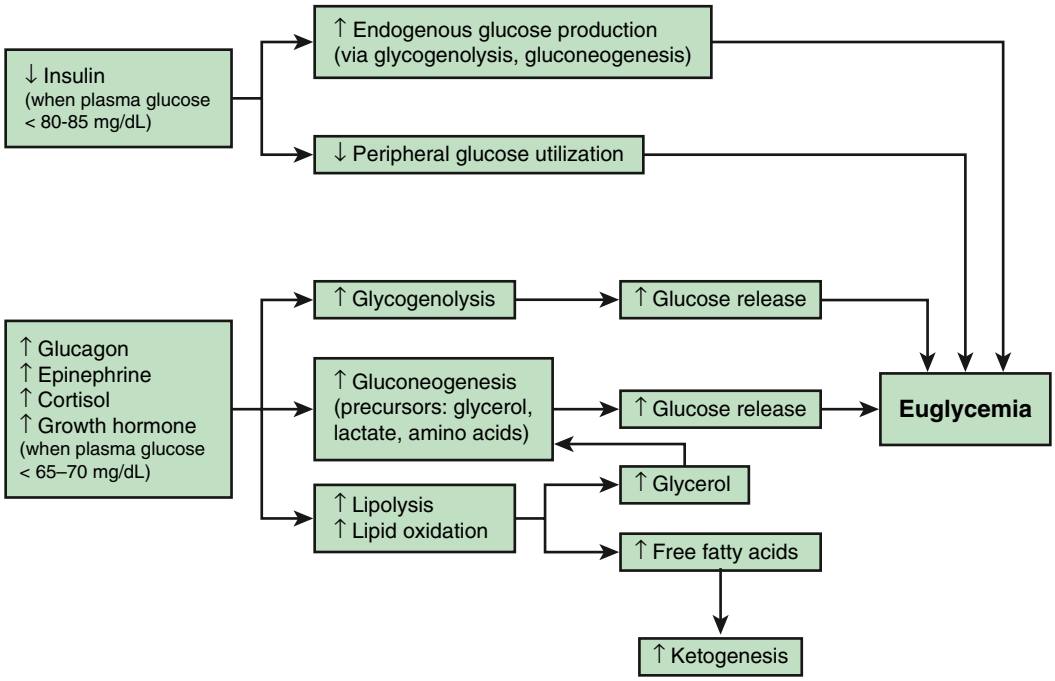

Fig. 113.1 The metabolic response to fasting. With fasting, declining glucose levels result in suppression of insulin and a rise of the counter-regulatory hormones. These changes in hormone levels lead to increased glucose output from the liver via glycogenolysis and gluconeogenesis. With prolonged fasting, counter-regulatory hormones stimulate lipolysis, which results in generation of glycerol (a key precursor in the gluconeogenic pathway) and, through ketogenesis, ketone bodies, a critical alternative fuel.

Table 113.1 Manifestations of Hypoglycemia in Childhood

FEATURES ASSOCIATED WITH ACTIVATION OF AUTONOMIC NERVOUS SYSTEM AND EPINEPHRINE RELEASE*
Anxiety
Perspiration
Palpitation (tachycardia)
Pallor
Tremulousness
Weakness
Hunger
Nausea
Emesis
FEATURES ASSOCIATED WITH CEREBRAL GLUCOPENIA
Headache
Mental confusion
Visual disturbances (↓ acuity, diplopia)
Inability to concentrate
Dysarthria
Staring
Paresthesias
Dizziness
Amnesia
Ataxia
Refusal to feed
Somnolence, lethargy
Seizures
Coma
Stroke, hemiplegia, aphasia
Decerebrate or decorticate posture

*Some of these features will be attenuated if the patient is receiving β-adrenergic blocking agents.

SIGNIFICANCE AND SEQUELAE

Brain metabolism uses the majority of endogenous hepatic glucose production in neonates, infants, and children. Because the brain grows most rapidly in the first year of life and a larger proportion of glucose turnover is used for brain metabolism, hypoglycemia in infants and children can affect brain development and function and can result in developmental delays and learning disabilities. The brain also has the capacity to absorb and oxidize ketone bodies. However, the capacity of the liver to produce ketone bodies is limited in the immediate newborn period. This is especially restricted in the presence of **hyperinsulinism (HI)**, which acutely inhibits hepatic glucose output, lipolysis, and ketogenesis, thereby depriving the brain of any alternative fuel sources. Furthermore, although the brain can metabolize ketones, these alternative fuels cannot completely replace glucose as an essential central nervous system (CNS) fuel. The deprivation of the brain's major energy source during hypoglycemic events has predictable adverse consequences on brain metabolism and growth. These arise from decreased brain oxygen consumption and increased breakdown of endogenous structural brain components, with impairment and loss of functional membrane integrity.

The major long-term sequelae of hypoglycemia are developmental delays, learning disabilities, epilepsy, and behavioral issues. A prospective cohort study of neonates at risk for hypoglycemia found that at 4 years of age, children who had experienced symptomatic hypoglycemia during the neonatal period had a two- to threefold increased risk of low executive and visual-motor function with greater impairment in children with severe or recurrent episodes. Cross-sectional studies in children with HI have found that 26–48% of children with both transient and persistent forms of HI have abnormal neurodevelopment. Children with HI have the highest risk of neurologic damage given the severity of the hypoglycemia in the condition and their inability to generate ketones as an alternative fuel for the brain. In addition, hypoglycemia associated with hypoxic-ischemic encephalopathy increases the risk of CNS sequalae. However, there are no precise data relating the duration or severity of hypoglycemia to subsequent neurologic development of children in a predictable manner. Nonetheless, early detection of hypoglycemia and effective treatment are critical to mitigating the risk of brain damage and developmental delays. Many neonates may have asymptomatic hypoglycemia identified by routine screening or laboratory testing. Although asymptomatic hypoglycemia in an otherwise healthy newborn is usually benign and transient, there remains a risk that if untreated (glucose gel, human milk, formula feedings), the hypoglycemia may become symptomatic. Hypoglycemia in older children may also produce long-term neurologic defects through neuronal death, mediated in part by cerebral excitotoxins released during hypoglycemia.

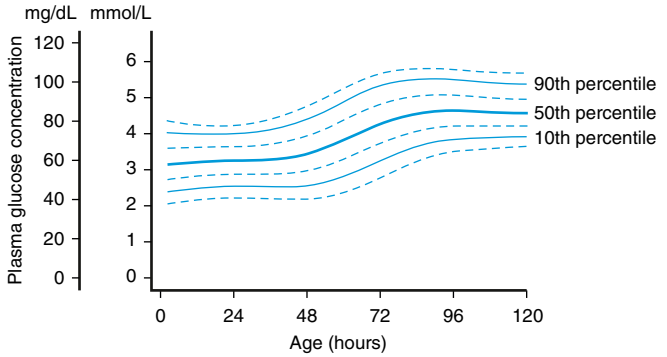

Fig. 113.3 Glucose percentiles in healthy term infants. (*Modified from Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose profiles in healthy term infants in the first 5 days: the Glucose Well Babies (GLOW) study. J Pediatr. 2020;223:34–41, Fig. 2.*)

PHYSIOLOGIC MECHANISMS OF GLUCOSE HOMEOSTASIS

Fetal glucose is derived entirely from the mother through placental-facilitated diffusion; therefore fetal glucose concentration reflects, but is slightly lower than, maternal glucose levels. After birth, plasma glucose decreases, reaching a nadir at about 2 hours of life and remaining below the normal adult range of 70-100 mg/dL for the first 3-4 days of life; this is known as *transitional hypoglycemia*. A study of healthy, full-term infants found a mean plasma glucose concentration of 59 ± 11 mg/dL during the first 48 hours of life, which then increased to 83 ± 13 mg/dL during days 4-5 of life (Fig. 113.3). Transitional asymptomatic hypoglycemia is likely caused by a persistence of fetal pancreatic β-cell fuel metabolism, which allows for the secretion of insulin at lower glucose concentrations to support insulin-mediated fetal growth. Beyond this transitional period, plasma glucose concentration and mechanisms that regulate glucose homeostasis in neonates are the same as in older children and adults.

During fasting, mechanisms responsible for the maintenance of glucose homeostasis include glycogenolysis, gluconeogenesis, lipolysis, and fatty acid oxidation, as well as the hormones that regulate the activation of these processes (see Fig. 113.1). Plasma glucose concentrations are maintained by both metabolism of the nutrients consumed in the immediate postprandial period and then by glycogenolysis and gluconeogenesis starting 2-4 hours after the meal. The liver of a 10-kg child contains 20-25 g of glycogen, which is sufficient to meet normal glucose requirements of 4-6 mg/kg/minute during an overnight fast. Glucose production during this time is augmented by gluconeogenesis (see Fig. 113.1). Defects in glycogenolysis or gluconeogenesis may not be manifested in infants until the frequent feeding pattern at 3- to 4-hour intervals ceases and infants sleep through the night, a situation usually present by 3-6 months of age.

With prolonged fasting, the glycogen stores are depleted, and energy metabolism is more dependent on fatty acid and ketone oxidation. **Lipolysis** generates fatty acids, which undergo β-oxidation in the liver to generate ketone bodies. Peripheral tissues use free fatty acids (FFAs) and ketones, whereas the CNS can use ketones for a

portion of its energy needs. Defects in β-oxidation and ketogenesis may not manifest until fasting exceeds the overnight period or, with illnesses, result in catabolism, fasting, and increased body energy requirements.

Amino acid precursors for gluconeogenesis are derived primarily from muscle protein. The muscle bulk of infants and small children is substantially smaller relative to body mass than that of adults, whereas glucose requirements per unit of body mass are greater in children. Therefore the ability to compensate for glucose deprivation by gluconeogenesis is more limited in infants and young children, as is the ability to withstand fasting for prolonged periods. The ability of muscle to generate alanine, the principal gluconeogenic amino acid, may also be limited.

The switch from glycogen synthesis during and immediately after meals to glycogen breakdown and later gluconeogenesis is governed by hormones, with insulin of central importance (see Fig. 113.1). After a meal, plasma insulin concentrations increase to peak levels of 5- to 10-fold greater than their normal baseline concentration, which serves to lower the plasma glucose through the enhancement of peripheral glucose uptake, activation of glycogen synthesis, and inhibition of gluconeogenesis. In addition, lipogenesis is stimulated, whereas lipolysis and ketogenesis are curtailed. During fasting, plasma insulin concentrations fall, and together with the rise of counter-regulatory hormones, result in maintenance of plasma glucose concentration (see Fig. 113.1).

These **counter-regulatory hormones**—glucagon, growth hormone, cortisol, and epinephrine—act synergistically and in concert to increase plasma glucose concentrations by activating glycogenolytic enzymes (glucagon, epinephrine); inducing gluconeogenic enzymes (glucagon, cortisol); inhibiting glucose uptake by muscle (epinephrine, growth hormone, cortisol); mobilizing amino acids from muscle for gluconeogenesis (cortisol); activating lipolysis and thereby providing glycerol for gluconeogenesis and fatty acids for ketogenesis (epinephrine, cortisol, growth hormone, glucagon); and inhibiting insulin release and promoting growth hormone and glucagon secretion (epinephrine).

CLINICAL MANIFESTATIONS

Clinical features of hypoglycemia fall into two categories: (1) symptoms and signs associated with the activation of the autonomic nervous system and epinephrine release **(autonomic symptoms)** and (2) symptoms and signs caused by decreased cerebral glucose use **(neuroglycopenic symptoms)** (see Table 113.1). In newborns and infants, symptoms and signs of hypoglycemia may be subtler and include cyanosis, apnea, hypothermia, hypotonia, irritability, jitteriness, poor feeding, lethargy, and seizures. *It is important to note that neonates and infants are frequently asymptomatic when hypoglycemic.*

DIAGNOSIS

Infants and children with a suspected hypoglycemia disorder require a timely and comprehensive diagnostic workup to establish the underlying cause and to initiate specific treatment, prevent hypoglycemia, and minimize the risk of brain damage and neurologic dysfunction. The Pediatric Endocrine Society provides guidelines that outline which children and adolescents should be evaluated for a hypoglycemia disorder:

- Older children and adolescents who demonstrate Whipple's triad
- Infants and younger children (who cannot communicate symptoms) with plasma glucoses <60 mg/dL on laboratory-quality assays
  - Neonates at high risk of a persistent hypoglycemic disorder
  - Glucose screening is recommended for those born large for gestational age, a history of perinatal stress, premature or postmature delivery, infants of diabetic mothers, family history of hypoglycemia disorder, or a congenital syndrome associated with hypoglycemia.
  - A persistent hypoglycemia disorder should be ruled out in those with severe hypoglycemia (symptomatic or requiring intravenous [IV] dextrose), inability to maintain plasma glucose >50 mg/dL (up to 48 hours of life) or >60 mg/dL (after 48 hours of life), family history of a genetic form of hypoglycemia, and those with a congenital syndrome associated with hypoglycemia.

Table 113.2 Clinical Features of Hypoglycemia Disorders

BIRTH HISTORY	
Large for gestational age	Congenital HI, BWS
Small for gestational age	Perinatal stress HI
Maternal gestational diabetes	Infant of diabetic mother, dominant K_{ATP} -HI
FAMILY HISTORY	
Sudden infant death	Fatty acid oxidation disorder
Diabetes*	HNF4A-HI, HNF1A-HI, dominant K_{ATP} -HI
PHYSICAL EXAM	
Hepatomegaly	Glycogen storage disease
Congenital heart disease	Perinatal stress HI, Kabuki or Turner syndrome
Midline defect	Hypopituitarism
Macroglossia	BWS
Hyperpigmentation	Primary adrenal insufficiency
Short stature	Growth hormone deficiency, glycogen storage disease

*Specifically, non–type 1 diabetes diagnosed at a younger age in lean individuals.
HI, Hyperinsulinism; BWS, Beckwith-Wiedemann syndrome; K_{ATP}, ATP-sensitive potassium channel; HNF, hepatocyte nuclear factor.

The etiology of hypoglycemia varies based on the age of the child, associated clinical and laboratory features, and more detailed diagnostic testing, including gene panels or whole exome sequencing (Tables 113.2, 113.3, 113.4, and 113.5).

A thorough history and physical exam may provide clinical clues to the underlying diagnosis (see Table 113.2). Evaluation for hypoglycemia disorders requires obtaining blood and urine at the time of hypoglycemia, ideally when the plasma glucose is <50 mg/dL. This "**critical sample**" is used to measure hormones, which regulate glucose metabolism, and metabolic fuels (Table 113.6, Fig. 113.4). The critical sample can be obtained during a spontaneous episode of hypoglycemia or during a supervised diagnostic fast. Given the likelihood of hypoglycemia, a **diagnostic fast** should be performed in a hospital setting with close supervision and placement of an IV catheter to facilitate obtaining the critical sample. Point-of-care glucose (and β-hydroxybutyrate if available) should be followed closely, so the samples can be obtained as soon as the plasma glucose falls below 50 mg/dL. The evaluation of neonates should not occur during the first 48-72 hours of life to avoid the period of transitional hypoglycemia.

After the critical sample is obtained and before the child is allowed to eat, a **glucagon stimulation test** should be performed to assess for hyperinsulinism. While the child is still hypoglycemic, 1 mg of glucagon is administered, and glucose is measured by a point-of-care meter every 10 minutes for a total of 40 minutes. A greater than 30-point rise in plasma glucose concentration is consistent with insulin excess or hyperinsulinism. If children do not have an increase in their glucose during the first 20 minutes of the test, the test should be terminated and the child should be given juice or IV dextrose as rescue therapy.

The levels of alternative fuels at the time of hypoglycemia (β-hydroxybutyrate, FFAs, and lactate) allow for the classification of the hypoglycemia disorders into four distinct groups (see Fig. 113.4). The results from the critical sample then allow for narrowing of the differential and guide additional testing. Interpretation of the critical sample results has several important caveats. Low cortisol and growth hormone levels on the critical sample are not diagnostic of a hormone deficiency, and in most cases, the appropriate (specific) stimulation testing is needed if these levels are low. Additionally, a low or undetectable insulin level does not rule out hyperinsulinism. Insulin concentrations can be affected by hemolysis, and assays have variable sensitivity for detecting insulin. Other biomarkers of insulin effect, such as β-hydroxybutyrate (to evaluate ketogenesis), FFAs (to evaluate lipolysis), and the glycemic response to glucagon (to evaluate glycogenolysis), should be used to assess for hyperinsulinism.

Table 113.3 Classification of Hypoglycemia in Infants and Children

NEONATAL TRANSITIONAL (ADAPTIVE) HYPOGLYCEMIA
Associated with inadequate substrate or immature enzyme function in otherwise normal neonates
Prematurity
Small for gestational age
Normal newborn

Transient Neonatal Hyperinsulinism
Infant of diabetic mother
Small for gestational age
Discordant twin
Birth asphyxia
Infant of toxemic mother

NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIA
Hyperinsulinism (see Tables 113.4 and 113.5)
Counter-Regulatory Hormone Deficiency
Panhypopituitarism
Isolated growth hormone deficiency
Adrenocorticotropic hormone deficiency
Addison disease (including congenital adrenal hypoplasia, adrenal leukodystrophy, triple A syndrome, ACTH receptor deficiency, and autoimmune disease complex)
Epinephrine deficiency

Glycogenolysis and Gluconeogenesis Disorders
Glucose-6-phosphatase deficiency (GSD Ia)
Glucose-6-phosphate translocase deficiency (GSD Ib)
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD III)
Liver phosphorylase deficiency (GSD VI)
Phosphorylase kinase deficiency (GSD IX)
Glycogen synthetase deficiency (GSD 0)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Galactosemia
Hereditary fructose intolerance

Lipolysis Disorders
Fatty Acid Oxidation Disorders
Carnitine transporter deficiency (primary carnitine deficiency)
Carnitine palmitoyltransferase-1deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase-2 deficiency
Secondary carnitine deficiencies
Very long-, long-, medium-, and short-chain acyl-CoA dehydrogenase deficiency

OTHER ETIOLOGIES
Substrate-Limited Causes
Ketotic hypoglycemia
Poisoning—drugs
Salicylates
Alcohol
Oral hypoglycemic agents
Insulin
Propranolol
Pentamidine
Quinine
Disopyramide
Ackee fruit (unripe)—hypoglycin
Litchi-associated toxin (toxic hypoglycemic syndrome)
Vacor (rat poison)
Trimethoprim-sulfamethoxazole (with renal failure)
L-Asparaginase and other antileukemic drugs

Liver Disease
Reye syndrome
Hepatitis
Cirrhosis
Hepatoma

AMINO ACID AND ORGANIC ACID DISORDERS
Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria

SYSTEMIC DISORDERS
Sepsis
Carcinoma/sarcoma (secreting—insulin-like growth factor II)
Heart failure
Malnutrition
Malabsorption
Antiinsulin receptor antibodies
Antiinsulin antibodies
Neonatal hyperviscosity
Renal failure
Diarrhea
Burns
Shock
Chiari malformation
Postsurgical complication
Pseudohypoglycemia (leukocytosis, polycythemia)
Excessive insulin therapy of insulin-dependent diabetes mellitus
Factitious disorder
Nissen fundoplication (dumping syndrome)
Falciparum malaria

GSD, Glycogen storage disease; HI, hyperinsulinemia; KATP, regulated potassium channel.

Table 113.4 Endocrine and Metabolic Causes of Hyperinsulinemic Hypoglycemia

TRANSIENT
Infant of diabetic mother
Perinatal asphyxia
Rhesus hemolytic disease
Intrauterine growth restriction
HNF4A / HNF1A

CONGENITAL
ABCC8 / KCNJ11 / GCK / GDH / HADH / HNF4A / HNF1A / UCP2 / SLC16A1 / PMM2 / HK1 / PGM1 / FOXA2 / CACNA1D / EIF2S3

OTHERS
Postprandial hyperinsulinemic hypoglycemia
Insulinoma
Munchausen by proxy
Exercise-induced hyperinsulinemic hypoglycemia

Modified from Güemes M, Rahman SA, Kapoor RR, et al. Hyperinsulinemic hypoglycemia in children and adolescents: recent advances in understanding of pathophysiology and management. *Rev Endo Metab Dis.* 2020;21:577–597, Table 1.

MANAGEMENT

Acute Treatment

A child presenting with hypoglycemia should be rapidly treated with oral carbohydrates or IV dextrose to normalize their plasma glucose (>70 mg/dL). If the child is asymptomatic or has mild symptoms and is capable of oral intake, the hypoglycemia can be treated with 15 grams of rapid-acting carbohydrates, such as 4 ounces of juice or two graham crackers. If a child is symptomatic or unable to tolerate oral intake (risk of aspiration, impending depressed level of consciousness), 2 mL/kg of dextrose 10% water (D10W) should be administered. After administration of the bolus, the child should be placed on an IV dextrose infusion (for infants, a glucose infusion rate of 5-6 mg/kg/minute and for older children 2-3 mg/kg/minute) to prevent recurrent hypoglycemia. Plasma glucose via point-of-care testing should be monitored every 15-20 minutes until it is >70 mg/dL, and then checks may be spaced once stable levels are demonstrated.

In an asymptomatic child with a plasma glucose <50 mg/dL, a critical sample can be obtained if the appropriate supplies and tubes are readily available. Otherwise, treatment of the hypoglycemia should not be delayed.

Table 113.5 Syndromic Forms of Hyperinsulinemic Hypoglycemia*

SYNDROME NAME	GENETIC ETIOLOGY *GENE* (LOCATION)	CLINICAL CHARACTERISTICS
PRENATAL AND POSTNATAL OVERGROWTH (MACROSOMIA)		
Beckwith-Wiedemann	(11p15)	Macroglossia, abdominal wall defects, ear lobe pits/creases, hemihypertrophy, tumor risk; IUGR if associated with placental mesenchymal dysplasia
Sotos	*NSD1* (5q35)	Macrocephaly, frontal bossing, pointed chin, developmental delay, tumor risk
Simpson-Golabi-Behmel	GPC3 (Xq26), GPC4 (Xp22)	Coarse facial features, broad feet, polydactyly, cryptorchidism, hepatomegaly, tumor risk
Perlman	*DIS3L2* (2q37)	Inverted V-shaped upper lip, prominent forehead, developmental delay, hypotonia, tumor risk
POSTNATAL GROWTH FAILURE (SHORT STATURE)		
Kabuki	*KMT2D* (12q13), *KDM6A* (Xp11.3)	Arched eyebrows, long eyelashes, developmental delay, fetal finger pads, scoliosis, heart defects, hypotonia
Costello	*HRAS* (11p15)	Deep palmar/plantar creases, developmental delay, coarse facial features, heart abnormalities, papillomas, tumor risk
CHROMOSOMAL ABNORMALITY		
Mosaic Turner	Loss of X in some cells	Milder Turner syndrome phenotype (short stature, coarctation of aorta, gonadal dysgenesis)
Patau	Trisomy 13	Developmental delay, microphthalmia, heart and neural defects
CONGENITAL DISORDERS OF GLYCOSYLATION		
Types 1a, 1b, and 1d	*PMM2* (16p13.2), *MPI* (15q24.1), *ALG3* (3q27.1)	Developmental delay, hypotonia, growth failure
CONTIGUOUS GENE DELETION AFFECTING THE *ABCC8* GENE		
Usher	11 genes	Hearing loss, visual impairment
ABNORMALITIES IN CALCIUM HOMOEOSTASIS		
Timothy	*CACNA1C* (12p13.33)	Long QT syndrome, syndactyly, developmental delay, immune deficiency
INSULIN RECEPTOR PATHOGENIC VARIANT		
Insulin resistance syndrome (leprechaunism)	*INS* (19p13)	Hypoglycemia and hyperglycemia, prenatal and postnatal growth restriction, elfin-like features, hirsutism
OTHER SYNDROMES		
Congenital central hypoventilation syndrome	*PHOX2B* (4p13)	Central hypoventilation, "box-shaped" face, neurocristopathies (Hirschsprung disease, tumor risk)

IUGR, intrauterine growth restriction.
*Various developmental syndromes have been described with the gene/s linked to the condition and the common clinical features.
Modified from Güemes M, Rahman SA, Kapoor RR, et al. Hyperinsulinemic hypoglycemia in children and adolescents: recent advances in understanding of pathophysiology and management. *Rev Endo Metab Dis.* 2020;21:577–597, Table 2.

Ongoing Management

Treatment goals of hypoglycemia disorders include maintaining euglycemia (plasma glucose >70 mg/dL), promoting normal development, and monitoring for medication side effects. Once the diagnostic evaluation identifies a specific hypoglycemia disorder, tailored treatment should be initiated promptly. Effective treatment allows the child to maintain euglycemia, both while eating an age-appropriate diet and fasting overnight. Continuous or forced feeds should not be used as treatment for hypoglycemia, as they result in long-term oral aversion and excessive weight gain. Additionally, hypoglycemia should not routinely be treated with steroids or cornstarch unless indicated as a treatment for specific disorders, such as adrenal insufficiency or glycogen storage disease. Home glucose monitoring is required for all children with hypoglycemia disorders and is particularly important during times of illnesses, as this may provoke additional hypoglycemia.

Management of individual hypoglycemia disorders is given in more detail in the following sections and in Table 113.7.

DISORDERS OF HYPOGLYCEMIA

Disorders of hypoglycemia can be classified by the metabolic fuel response to fasting (see Fig. 113.4).

Insulin-Mediated Disorders

Insulin-mediated disorders (see Table 113.4) are characterized by low plasma β-hydroxybutyrate and FFAs and a positive glycemic response to glucagon (Table 113.8).

Hyperinsulinism

HI is the most common cause of *persistent hypoglycemia* in infants and children. HI is caused by dysregulated insulin secretion by the pancreatic β-cells, resulting in severe and recurrent hypoglycemia (Fig. 113.5). HI can be categorized into three main forms: (1) perinatal stress-induced, (2) congenital or monogenic (see Table 113.4), and (3) syndromic (see Table 113.5).

Perinatal stress-induced HI (PSHI), the most common form of HI, occurs in the setting of stress on the fetus in utero or during delivery.

Table 113.6 Hypoglycemia Diagnostic Evaluation

"CRITICAL SAMPLE" TO BE OBTAINED WHEN PLASMA GLUCOSE <50 MG/DL	
LABORATORY TEST	INTERPRETATION
Comprehensive metabolic panel	Low HCO_3 suggests elevation of ketones or lactate Elevated liver function tests may indicate GSD
β-hydroxybutyrate	Low levels suggest insulin excess (most commonly HI) or FAO disorder Elevated levels suggest GSD, hormone deficiency, or ketone utilization disorder
Insulin C-peptide	Detectable levels consistent with insulin excess Detectable insulin with undetectable c-peptide is consistent with exogenous insulin
Cortisol Growth hormone	Low levels concerning for hormone deficiency; need stimulation testing to confirm
Lactate	Elevated levels concerning for disorder of gluconeogenesis
Ammonia	Elevation can be seen in forms of HI and in IEM
Acylcarnitine profile Free and total carnitine Urine organic acids	Abnormalities suggestive of FAO disorder
IGF-BP1	Low levels suggest insulin excess
GLUCAGON STIMULATION TEST	
Administer 1 mg of glucagon IV or IM when plasma glucose <50 mg/dL Check point-of-care glucose every 10 min for 40 min If glucose does not increase 20 points in 20 min, terminate test and feed child Interpretation: Increase in glucose by 30 points is consistent with insulin excess	

HCO_3, Bicarbonate; GSD, glycogen storage disorder; HI, hyperinsulinism; FAO, fatty acid oxidation; IEM, inborn errors of metabolism.

In a study of 514 neonates at risk of hypoglycemia, 19% of late-preterm and small-for-gestational-age (SGA) infants had recurrent hypoglycemia, which is concerning for PSHI. Common causes of PSHI include intrauterine growth restriction, being born SGA, maternal preeclampsia, birth asphyxia, and congenital heart disease. *Most infants with PSHI respond to diazoxide, although a subset, particularly those with liver dysfunction and hypoxic ischemic encephalopathy, may fail to respond.* PSHI typically resolves within the first 3-6 months of life.

Congenital HI is the result of genetic defects in the insulin secretory pathways of the β-cell. It is estimated to occur in 1:28,000-50,000 live births but may be as high as 1:3,000 in populations with a high frequency of consanguinity. The most common and severe type of congenital HI is caused by inactivating pathogenic variants of *ABCC8* and *KCNJ11,* which encode the ATP-sensitive potassium (K_{ATP}) channel of the β-cell. Infants born with K_{ATP}-HI are commonly large for gestation age and have high glucose requirements (glucose infusion rate [GIR] >10 mg/kg/min) (see Fig. 113.5). However, the spectrum of presentation is wide, and some infants have normal birthweights and lower glucose requirements. In addition to fasting hypoglycemia, children with this type of HI have protein-induced hypoglycemia, in which isolated protein ingestion leads to increased insulin secretion and low plasma glucose. K_{ATP}-HI is most frequently unresponsive to treatment with diazoxide, the only approved drug for HI, which acts on the K_{ATP} channel.

K_{ATP}-HI has two distinct histologic forms: a **diffuse form**, in which β-cells throughout the pancreas show evidence of hyperactivity, and a focal form, characterized by a localized area of β-cell overgrowth or adenomatosis. The diffuse form is caused by biallelic recessive pathogenic variants in *ABCC8* or *KCNJ11* or, less commonly, monoallelic dominant pathogenic variants of these genes. **Focal HI** occurs as a result of a "two-hit" mechanism: a paternally inherited recessive pathogenic variant in *ABCC8* or *KCNJ11* combined with somatic loss of the maternal 11p15 region, resulting in paternal uniparental isodisomy. Infants with the focal form are cured with resection of the focal lesion. In contrast, those with the diffuse form may require a palliative near-total pancreatectomy if intensive medical therapy fails to control the hypoglycemia (Fig. 113.6). Given the different treatment approaches and outcomes for the diffuse and focal forms of K_{ATP}-HI, distinguishing between the two is critical and is best done through genetic testing. A paternally inherited recessive pathogenic variant in *ABCC8* or *KCNJ11* has a 94% positive predictive value for focal K_{ATP}-HI.

In children with genetic testing consistent with the focal form, an 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) scan is used before surgery to localize the focal lesion (see Fig. 113.6). Frozen section evaluation of biopsies taken during surgery is used to confirm the presence of the focal lesion and guides the extent of the resection. Children with the focal form of HI should receive care at specialized centers with ^{18}F-DOPA PET access and a multidisciplinary team of endocrinologists, surgeons, pathologists, and radiologists with expertise in HI. Children with the diffuse form also benefit from care at these centers because their management and the decision to pursue intensive medical therapy or a near-total pancreatectomy are complex.

The second most common form of congenital HI is caused by **dominant activating pathogenic variants of *GLUD1***, which encodes **glutamate dehydrogenase** (GDH). This protein regulates the first step of amino acid–stimulated insulin secretion in the β-cell. Children with GDH-HI or hyperinsulinism-hyperammonemia syndrome (HI/HA) have fasting hypoglycemia, significant protein-induced hypoglycemia, and elevated plasma ammonia concentration. Seizures, attention-deficit disorder, and learning disabilities also occur in this form of HI, and these neurologic issues do not seem to correlate with the degree of hypoglycemia or ammonia elevation. *This form of HI responds well to diazoxide.*

Activating pathogenic variants of *GCK*, which encodes **glucokinase**, cause an autosomal dominant form of congenital HI. Glucokinase is the key enzyme triggering glucose-mediated insulin secretion. Children with GCK-HI have fasting hypoglycemia of variable severity and diazoxide responsiveness. Severe cases may require a near-total pancreatectomy.

Pathogenic variants in *HNF4A* and *HNF1A,* which encode the transcription factors hepatic nuclear factors 4-alpha and 1-alpha, cause a dominant form of diazoxide-responsive HI. These infants may be large for gestational age and have high GIR requirements at birth. The HI resolves within the first several years of life. However, some individuals experience progressive β-cell failure and progress to an early-onset diabetes, known as *maturity-onset diabetes of the young (MODY).*

Syndromes associated with HI are increasingly being recognized (see Table 113.5). Beckwith-Wiedemann syndrome (BWS), an imprinting disorder, is characterized by macroglossia, lateralized overgrowth, omphalocele, and a predisposition to embryonal tumors (Fig. 113.7). Hyperinsulinism occurs in approximately 50% of infants with BWS, although most cases are mild and resolve within the first several weeks of life. These cases are typically responsive to diazoxide. Children with BWS caused by paternal uniparental isodisomy of 11p can have severe and persistent HI, which does not respond to diazoxide and may

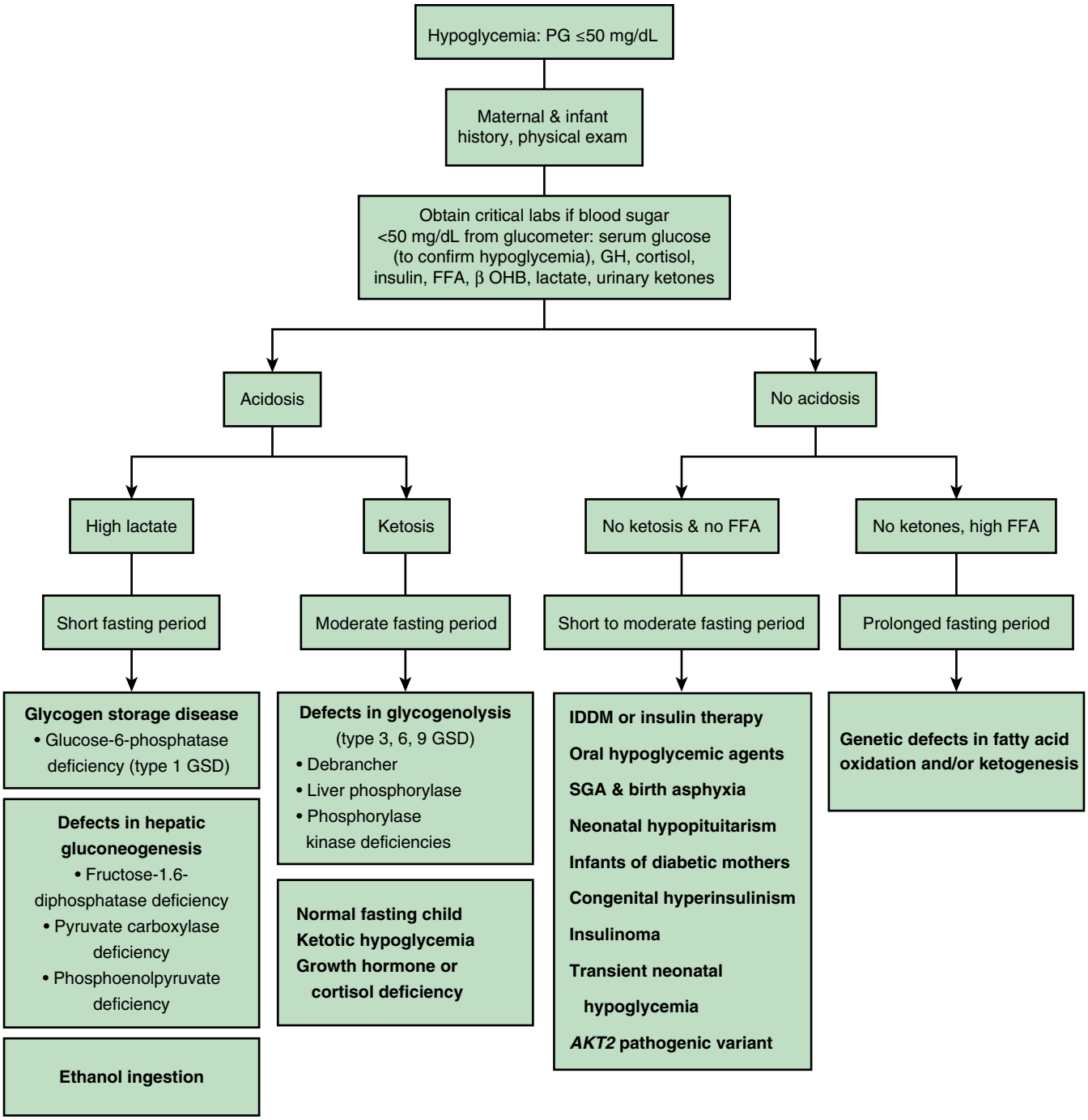

Fig. 113.4 Diagnostic algorithm for determining the etiology of hypoglycemia in children. OHB, Hydroxybutyrate; FFA, free fatty acid; GH, growth hormone, GSD, glycogen storage disease; PG, plasma glucose; IDDM, insulin-dependent diabetes mellitus. (*Modified from Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ. Williams Textbook of Endocrinology. 14th ed. Elsevier; 2020:1547, Fig. 38.14.*)

require a pancreatectomy. Other syndromes known to be associated with HI include Kabuki, Turner, and Rubinstein-Taybi. HI in these syndromes presents with variable degrees of severity and responsiveness to diazoxide.

After establishing a diagnosis of HI, a trial of diazoxide, the first-line agent for the treatment of HI, should be undertaken (Fig. 113.8). Diazoxide opens the K_{ATP} channel, inhibiting insulin secretion. Children are considered responsive to diazoxide if the cardinal feature of HI, hypoketotic hypoglycemia, is corrected. This is assessed by demonstrating that the child can maintain plasma glucose >70 mg/dL both while feeding and during an overnight fast and/or plasma β-hydroxybutyrate concentration increases to >2 mmol/L before plasma glucose decreases below 50-60 mg/dL during fasting. *Failure to respond to diazoxide strongly suggests K_{ATP}-HI, and those children require expedited genetic testing for ABCC8 and KCNJ11 to determine their risk for focal HI.* Thus the assessment of the response to diazoxide has important therapeutic and diagnostic implications.

Somatostatin analogs are used off-label as second-line agents for the treatment of diazoxide-unresponsive diffuse HI. Octreotide requires multiple daily injections, and its effectiveness is limited by

Table 113.7 Treatments for Hypoglycemia Disorders

DRUG/THERAPY	INDICATION	DOSE (ROUTE OF ADMINISTRATION)	SIDE EFFECTS/COMMENTS
Diazoxide	HI	5-15 mg/kg/day every 12 hr (PO)	Hypertrichosis, fluid overload* neutropenia, thrombocytopenia, respiratory distress, hyperglycemia
Octreotide	HI	2-20 mcg/kg/day every 6 hr (SQ)	Gallstones, transaminitis, malabsorption, suppression of thyroid and growth hormones
Lanreotide	HI	60-90 mg every 28 days (SQ)	Gallstones, transaminitis, malabsorption, suppression of thyroid and growth hormones
Enteral D20	HI	Up to 10 mg/kg/min continuously (via gastrostomy or nasogastric tube)	Vomiting, diarrhea, fluid overload
Cornstarch	GSD, rarely FAOD, IKH	1-2 g/kg per dose (PO)	Diarrhea in infants
Growth hormone	Growth hormone deficiency	0.3 mg/kg/wk daily or every 12 hr (infants) (SQ)	Pseudotumor cerebri, edema, slipped capital femoral epiphysis, hyperglycemia
Hydrocortisone	Adrenal insufficiency	8-12 mg/m^2/day (PO)	High doses: Immunosuppression, hyperglycemia, hypertension, obesity
Acarbose	Postprandial hypoglycemia	12.5-50 mg with meals	Transaminitis, diarrhea, abdominal pain
PANCREATECTOMY			
Partial	Focal HI Insulinoma		>50% pancreatectomy increases risk of diabetes and exocrine insufficiency later in life
Near-total (98%)	Severe diffuse HI		Insulin-dependent diabetes, exocrine insufficiency

*Concomitant use of diuretics is strongly recommended in neonates and infants; older children may require this as well.
HI, Hyperinsulinism; GSD, glycogen storage disease; FAOD, fatty acid oxidation disorder; IKH, idiopathic ketotic hypoglycemia.

Table 113.8 Criteria for Diagnosing Hyperinsulinism and Other Forms of Insulin Excess

DRAWN AT A TIME OF FASTING HYPOGLYCEMIA: PLASMA GLUCOSE <50 MG/DL
Detectable insulin or c-peptide (plasma insulin ≥2 μU/mL or plasma C-peptide ≥0.5 ng/mL)*
Hypofattyacidemia (plasma free fatty acids <1.7 mmol/L)
Hypoketonemia (plasma β-hydroxybutyrate <1.8 mmol/L)
Inappropriate glycemic response to glucagon (increase in glucose >30 mg/dL)

*Depends on sensitivity of insulin assay. Detectable insulin and C-peptide is not necessary to make a diagnosis of HI.

tachyphylaxis. A long-acting analog, lanreotide, is administrated monthly in children greater than 1 year old and can be an effective and more convenient alternative to octreotide. Somatostatin analogs should not be used in neonates or infants less than 2 months old because they are associated with fulminant necrotizing enterocolitis. Continuous intragastric dextrose administered via gastrostomy tube is used in combination with a somatostatin analog and allows for an age-appropriate feeding schedule.

Infants Born to Diabetic Mothers

See Chapter 147.1.

Gestational diabetes affects approximately 2% of pregnant women, and 1 in 1,000 pregnant women have insulin-dependent diabetes. Infants born to mothers with poorly controlled diabetes are born large for gestational age and with severe hypoglycemia resulting from a transient hyperinsulinemic state. Exposed to high glucose concentrations, the fetal islets compensate with increased insulin secretion that, during intrauterine life, leads to overgrowth and, after birth, results in hypoglycemia. The hypoglycemia resolves within the first 3-7 days of life. Mothers whose diabetes has been well controlled during pregnancy, labor, and delivery generally have infants near normal size who are less likely to develop hypoglycemia.

Insulinoma

Older children and adolescents presenting with insulin-mediated hypoglycemia should be evaluated for an **insulinoma**, a rare islet cell tumor. These tumors may be insidious, slow growing, and difficult to localize with conventional imaging modalities. Surgical resection is curative. Children diagnosed with an insulinoma should undergo genetic testing for the tumor predisposition syndrome, multiple endocrine neoplasia type 1 (MEN1).

Factitious Hypoglycemia

Surreptitious administration of insulin presents with abrupt onset and erratic hypoglycemia. In a younger child, a parent or guardian may provoke hypoglycemia (factitious disorder imposed on another: Munchhausen by proxy), but an adolescent may be self-administering insulin. The biochemical hallmark of exogenous insulin administration is a detectable insulin level with undetectable c-peptide. However, specialized assays may be needed to detect the analog insulins, such as aspart or glargine. Intentional or accidental ingestion of sulfonylureas also presents with hypoglycemia. In these cases, both insulin and c-peptide are detectable, and sulfonylurea blood levels are required for confirmation.

Defects of Fatty Acid Oxidation

Fatty acid oxidation disorders are characterized by low plasma β-hydroxybutyrate and high plasma FFAs. See Chapter 106.1.

Multiple enzymatic deficiencies in the mitochondria pathway of fatty acid oxidation cause defective carnitine or fatty acid metabolism. These disorders are characterized by fasting hypoglycemia, hepatomegaly, cardiomyopathy, and hypotonia, although the spectrum of severity is wide. Infants may present with a Reye-like syndrome (see

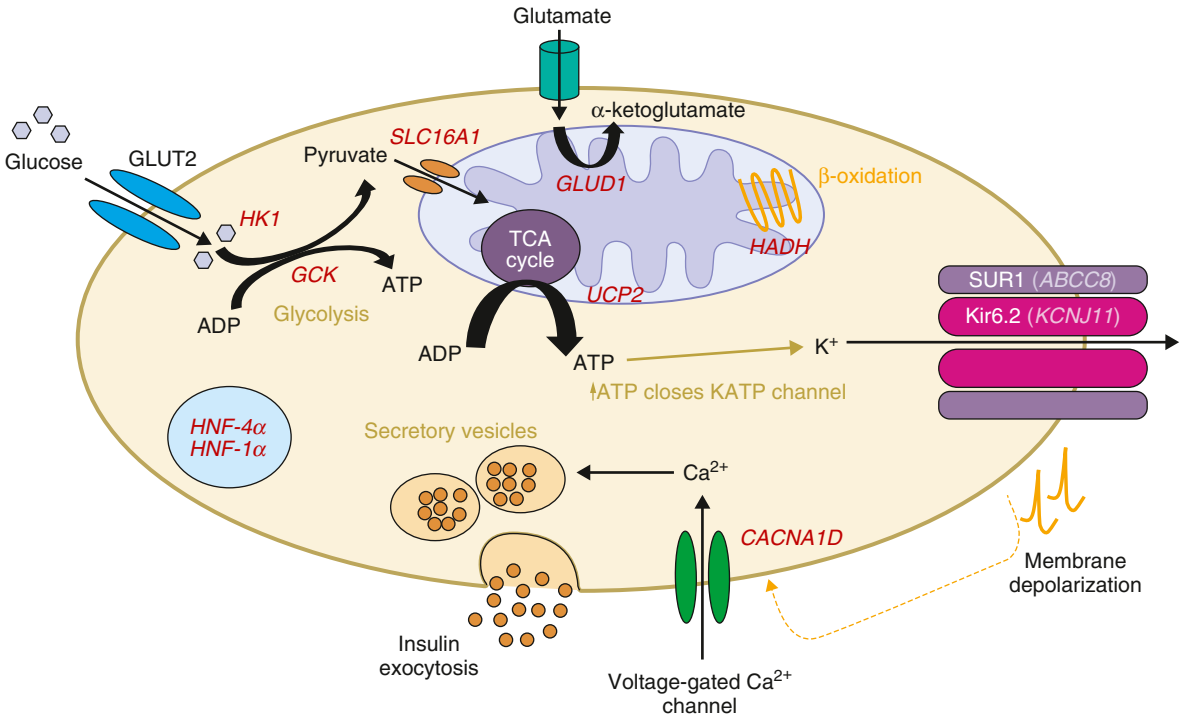

Fig. 113.5 Diagrammatic representation of β-cell function. Genetic defects associated with congenital HI are included in *red*. Postprandial glucose is taken into the β-cells via the glucose transporter 2 (GLUT-2). Glucose then enters the glycolysis pathway followed by the mitochondrial citric acid cycle (TCA), yielding the high-energy molecule, adenosine triphosphate (ATP). ATP molecules travel to and inhibit the potassium-dependent ATP channels (K_{ATP}), which prevents influx of potassium resulting in membrane depolarization. This triggers voltage-gated calcium channels to open, and influx of calcium (Ca^{2+}) occurs. The Ca^{2+} activates the enzyme phospholipase C (PLC) to produce inositol 1,3,5 triphosphate (IP3) and diacylglycerol (DAG) from phosphatidyl 1,3 bisphosphate (PIP2). The IP3 molecule binds to the protein receptor on the endoplasmic reticulum (ER) to promote a release of Ca^{2+} from the ER. This subsequent increase in cytoplasmic Ca^{2+} promotes exocytosis of the prepackaged mature insulin and active C-peptide, which are released into circulation. GLUT2: Glucose transporter 2; Glucokinase (GCK) encoded by GCK gene; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; Monocarboxylate transporter (MCT1) encoded by *SLC16A1* gene; Glutamate dehydrogenase (GDH) encoded by *GLUD1* gene; Uncoupling protein 2 (UCP2) encoded by *UCP2* gene; L-3hydroxyacyl-coenzyme A dehydrogenase (HADH) encoded by *HADH* gene; SUR1 subunit of the K_{ATP} channel encoded by the *ABCC8* gene; Kir6.2 subunit of the K_{ATP} channel encoded by *KCNJ11* gene; Hepatocyte nuclear factor 4α (HNF4α) encoded by *HNF4A* gene; Hepatocyte nuclear factor 1α (HNF1α) encoded by *HNF1A* gene; HK1: Hexokinase 1 encoded by the gene *HK1*; CACNA1D: calcium voltage-gated channel subunit alpha1 D. Gene variants in forkhead box protein A2 (FOXA2), phosphoglucomutase 1 (PGM1), and phosphomannomutase 2 (PMM2) are not included in the drawing. (*From Güemes M, Rahman SA, Kapoor RR, et al. Hyperinsulinemic hypoglycemia in children and adolescents: recent advances in understanding of pathophysiology and management. Rev Endo Metab Dis. 2020;21:577–597, Fig. 1.*)

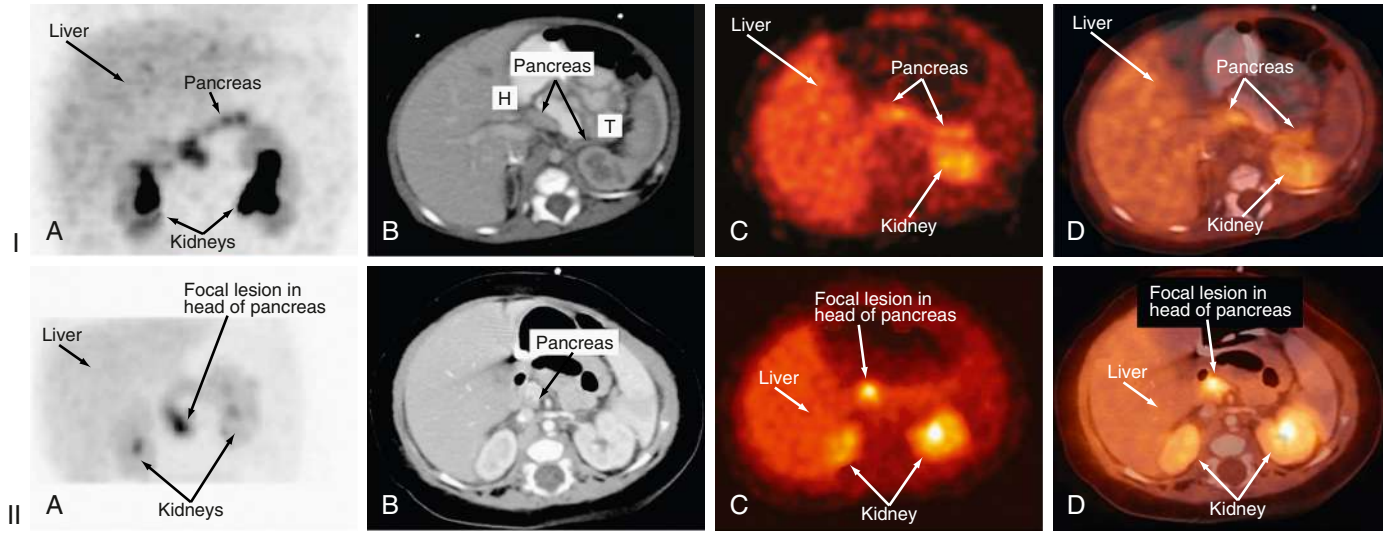

Fig. 113.6 Imaging of congenital hyperinsulinism. I Panels *(diffuse)*: 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) of a patient with a diffuse form of congenital hyperinsulinism. **A,** Diffuse uptake of ^{18}F-DOPAa is visualized throughout the pancreas. Transverse views show **(B)** normal pancreatic tissue on abdominal CT, **(C)** diffuse uptake of ^{18}F-DOPA in the pancreas, and **(D)** confirmation of pancreatic uptake of ^{18}F-DOPA with co-registration. H, Head of pancreas; T, tail of pancreas. II Panels *(focal)*: ^{18}F-DOPA PET of a patient with a focal form of congenital hyperinsulinism. **(A)** Discrete area of increased ^{18}F-DOPA uptake is visualized in the head of the pancreas. The intensity of this area is greater than that observed in the liver and neighboring normal pancreatic tissue. Transverse views show **(B)** normal pancreatic tissue on abdominal CT, **(C)** focal uptake of ^{18}F-DOPA in the pancreatic head, and **(D)** confirmation of ^{18}F-DOPA uptake in the pancreatic head with co-registration. (*Courtesy Dr. Olga Hardy, Children's Hospital of Philadelphia.*)



Fig. 113.7 Beckwith-Wiedemann syndrome. (*Courtesy Dr. Michael Cohen, Dalhousie University, Halifax, Nova Scotia. From Jones KL. Smith's recognizable patterns of human malformation, 6th ed. Philadelphia: Saunders; 2006.*)

Chapter 409) and recurrent episodes of fasting hypoglycemia, cardiorespiratory arrest, and coma, whereas older children with less severe forms may only develop symptoms with illness. Most cases are detected via newborn screening and confirmed with genetic testing. Abnormalities are seen in the acylcarnitine and urine organic acid profiles in children who are not identified through newborn screening. Treatment typically involves avoidance of fasting and administration of dextrose-containing fluids with illness.

Interference with fatty acid metabolism also underlies the fasting hypoglycemia associated with Jamaican vomiting sickness. In **Jamaican vomiting sickness**, the unripe ackee fruit contains a water-soluble toxin, hypoglycin, which produces vomiting, CNS depression, and severe hypoglycemia. The hypoglycemic activity of hypoglycin derives from its inhibition of gluconeogenesis secondary to its interference with the acyl-CoA and carnitine metabolism essential for the oxidation of long-chain fatty acids. The disease is almost totally confined to Jamaica, where ackee forms a staple of the diet. The ripe ackee fruit no longer contains this toxin. A similar illness noted in India, **acute toxic encephalopathy-hypoglycemic syndrome**, may be caused by litchi consumption. Litchi contains hypoglycin A and/or methylenecyclopropylglycine, which may inhibit fatty acid oxidation or gluconeogenesis.

KETOTIC HYPOGLYCEMIC DISORDERS

These disorders are characterized by elevated levels of plasma β-hydroxybutyrate (>2.5 mmol/L) (Table 113.9).

Glycogen Storage Disorders

See Chapter 107.1.

The **hepatic glycogen storage disorders** (GSDs; 0, I, III, VI, and IX) result from genetic defects in the enzymes that regulate the synthesis, breakdown, and release of glycogen in the liver. GSD type I also affects gluconeogenesis. GSDs are characterized by fasting ketotic hypoglycemia and various degrees of hepatomegaly, liver function abnormalities, hyperlipidemia, and

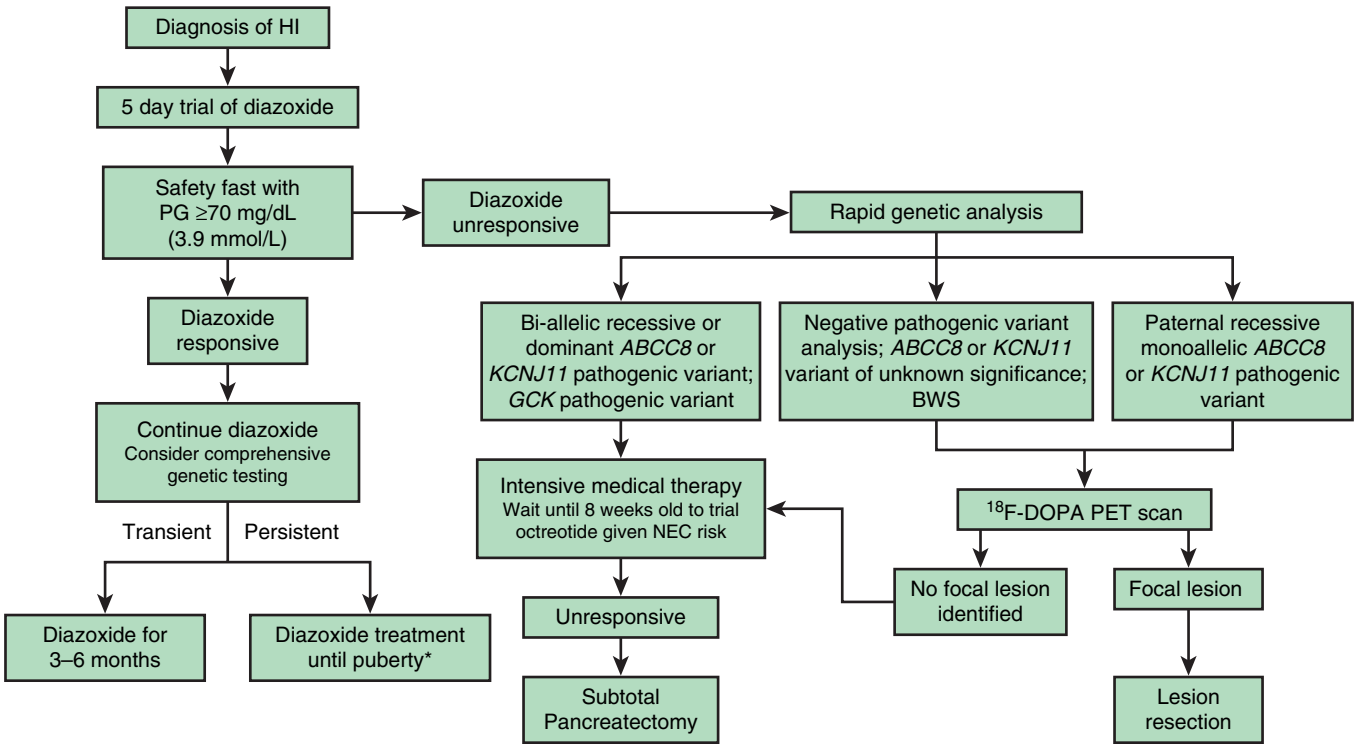

Fig. 113.8 Management algorithm for hyperinsulinism. HI, Hyperinsulinism; BWS, Beckwith-Wiedemann syndrome. *Some individuals may require diazoxide treatment into adulthood and possibly lifelong.

Table 113.9 Causes of Ketotic Hypoglycemia in Children

	GENE OR CHROMOSOME	INHERITANCE
HORMONAL		
Growth hormone deficiency or resistance	Genetic or acquired	Variable
ACTH deficiency or resistance; cortisol deficiency	Genetic or acquired	Variable
Glucagon deficiency*	*GCG, DBH*	N/D
Dopamine β-hydroxylase deficiency*	*GCG, DBH*	N/D
METABOLIC		
Glycogen storage disease (GSD)		
GSD 0; glycogen synthase deficiency	*GYS2*	AR
GSD III; glycogen debranching enzyme deficiency	*AGL*	AR
GSD VI; glycogen phosphorylase deficiency	*PYGL*	AR
GSD IX; phosphorylase kinase subunit deficiencies	*PHKA2, PHKB, PHKG2*	X-linked, AR
GLUCOSE METABOLISM AND TRANSPORT		
Phosphoglucomutase I deficiency	*PMG1*	AR
Pyruvate carboxylase deficiency	*PC*	AR
ORGANIC ACIDEMIAS		
Maple syrup urine disease, propionic aciduria, methylmalonic aciduria	Multiple genes	AR
Ketone body transport and metabolism		
Monocarboxylase transporter 1 defect	*SLC16A1 (MCT1)*	AR, AD
Ketolysis		
Succinyl CoA oxoacid transferase deficiency	*SCOT*	AR
Mitochondrial acetoacetyl-CoA thiolase (β-ketothiolase) deficiency	*ACAT1*	AR
SYNDROMES		
Silver-Russel syndrome	11p15 or 7**	Mostly sporadic
Prader-Willi syndrome	15q11-q13***	Mostly sporadic
Fanconi-Bickel syndrome	*SLC2A2 (GLUT2)*	AR
KH secondary to chronic malnutrition, severe malaria, other chronic diseases	—	—
Idiopathic ketotic hypoglycemia		
Physiologic KH in prolonged fasting or acute illness	—	—
Pathologic KH	—	—
IGF2BP1 deficiency*	*IGF2BP1*	N/D
Sodium glucose co-transporter 2 defect*	*SLC5A2*	N/D
PEP carboxykinase 1 and G-6P catalytic transcriptional induction*	*NCOR1*	N/D
Mitosis gene A-related kinase 11 defect*	*NEK11*	N/D

*Suggested, not well-established, causes of KH.
**Several mechanisms, rare other mechanisms, or unknown.
***Paternal deletion, maternal uniparental disomy, or imprinting defect.
AD, Autosomal dominant; AR, autosomal recessive; N/D, no data; PEP, phosphoenolpyruvate; G-6P, glucose 6-phosphate. The list is not fully inclusive.
From Drachmann D, Hoffman E, Carrigg A, et al. Towards enhanced understanding of idiopathic ketotic hypoglycemia: a literature review and introduction of the patient organization, Ketotic Hypoglycemia International. *Orphanet J Rare Dis*. 2021;16:173, Table 1.

failure to thrive. Muscle involvement is a feature of GSD type III, resulting in proximal muscle weakness and risk of cardiomyopathy. GSD types 0, VI, and IX present with less severe hypoglycemia compared with type I and III. The diagnosis of GSD is suspected in patients presenting with ketotic hypoglycemia, hepatomegaly, and liver enzyme abnormalities and is confirmed through genetic testing. The treatment of GSDs consists of uncooked cornstarch therapy, protein supplementation, and limited fasting.

Hormone Deficiencies

Deficiencies of cortisol or growth hormone can result in ketotic hypoglycemia, as these counter-regulatory hormones play a role in mobilizing glucose production by the liver. Hypoglycemia occurs in both primary or secondary (central) **adrenal insufficiency** and is commonly seen during an adrenal crisis. **Growth hormone deficiency** results in hypoglycemia mainly during infancy and early toddlerhood. Combined hormone deficiencies, known as hypopituitarism, can also result in hypoglycemia and are commonly caused by structural abnormalities of the pituitary gland. A clinical clue to the diagnosis of hypopituitarism is the presence of midline defects, cleft lip or palate, or in males, a microphallus. In the neonatal period, hypopituitarism presents with a hypoketotic hypoglycemia pattern that is indistinguishable from the pattern seen in neonates with HI. Thus in neonates with features suggestive of hypopituitarism, it is important to rule out hormone deficiencies before making a diagnosis of HI.

Low cortisol and growth hormone levels on a critical-sample laboratory result are suggestive of hormone deficiencies but not diagnostic. To confirm these diagnoses in a child presenting with hypoglycemia, appropriate hormone stimulation testing is recommended. A child diagnosed with central adrenal insufficiency, growth hormone deficiency, or hypopituitarism requires magnetic resonance imaging of their pituitary gland to assess for structural abnormalities or lesions. Hormone replacement with either hydrocortisone or growth hormone

resolves the hypoglycemia. Neonates and infants require twice-a-day growth hormone dosing to prevent ongoing hypoglycemia.

Idiopathic Ketotic Hypoglycemia

Idiopathic ketotic hypoglycemia (IKH) commonly occurs during the first 1-4 years of life and typically resolves by age 6-8 years old. Children present with hypoglycemia and elevated β-hydroxybutyrate (>2-3 mmol/L), frequently in the setting of illness, and demonstrate shortened fasting tolerance on a diagnostic fast. IKH is a diagnosis of exclusion, and it is important to rule out other causes of ketotic hypoglycemia, such as GSDs or hormone deficiencies, before making this diagnosis. IKH is likely the result of the lower energy stores in toddlers and young children and is not caused by an underlying metabolic defect, as evidenced by its spontaneous resolution (see Table 113.9). Treatment typically consists of limited fasting time and home glucose monitoring during times of illness. IV dextrose infusion may be required with illness if children are unable to tolerate oral feeds.

Disorders of Gluconeogenesis

Disorders of gluconeogenesis are characterized by elevated plasma lactate levels during hypoglycemia.

Glycogen Storage Disease Type I

See Chapter 107.1.

Glucose-6-phosphatase regulates the terminal step of gluconeogenesis and glycogenolysis, and deficiency of this enzyme results in GSD type I. Children with this condition experience hypoglycemia within 2-3 hours after a meal and significant elevations of lactate, uric acid, and triglycerides because of shunting of gluconeogenic precursors to alternative pathways in the liver. The diagnosis should be suspected in an infant with hypoglycemia, hepatomegaly, and the characteristic metabolic abnormalities. Sequencing of *G6PC* (type Ia) or *SLC37A4* (type Ib) confirms the diagnosis. Treatment includes frequent meals or feeds and after the first 6-12 months of life, uncooked cornstarch administered every 3-4 hours. Fasting beyond 4-6 hours can provoke life-threatening lactic acidosis.

Fructose-1,6-Bisphosphatase Deficiency

See Chapter 107.3.

A deficiency of this enzyme results in a block of gluconeogenesis from all possible precursors below the level of fructose-1,6-bisphosphate. Features are similar to GSD type I with fasting hypoglycemia, severe lactic acidosis, and elevations of uric acid and triglycerides. However, glycogenolysis remains intact, so patients do not have significant hepatomegaly or transaminitis. The diagnosis is confirmed through genetic testing of *FBP1*. Similar to GSD type I, treatment involves frequent meals, cornstarch, and avoidance of prolonged fasting.

OTHER CAUSES OF HYPOGLYCEMIA

Postprandial Hypoglycemia

Up to 30% of infants and children with **Nissen fundoplication**, a procedure used to ameliorate gastroesophageal reflux, develop **postprandial hypoglycemia**, or "late dumping syndrome." Characteristic features include hyperglycemia followed by severe hypoglycemia (average 32 mg/dL in one series) 1.5-3 hours later. The early hyperglycemia phase is associated with brisk and excessive insulin release that causes the resultant hypoglycemia. A role for exaggerated GLP-1 secretion has been proposed as being responsible for the excessive insulin release. Treatment consists of feed modifications for formula- or tube-fed children, such as the use of complex formulas or prolonged feeds. Acarbose has been successfully used in some orally fed children.

Acute Alcohol Intoxication

The generation of reducing equivalents during the oxidation of ethanol in the liver inhibits several gluconeogenic enzymes, resulting in hypoglycemia if glycogen stores are depleted by starvation or by preexisting abnormalities in glycogen metabolism. There is no correlation between blood ethanol levels and the occurrence of hypoglycemia. In toddlers who have been fasting for some time, even the consumption of small quantities of alcohol can precipitate hypoglycemia. *Alcohol-induced hypoglycemia promptly responds to IV dextrose.* However, if there is an associated alcohol toxicity, the patient may not show clinical signs of improvement despite now having a normal blood glucose level. A careful history allows the diagnosis to be made and may avoid additional workup.

β Blockers

β-Adrenergic stimulation enhances glucagon secretion and increases glycogenolysis and gluconeogenesis. β blockers impair the counterregulatory response to hypoglycemia and blunt the autonomic symptoms described earlier. Children at highest risk of hypoglycemia from β blockers include those with insulin-dependent diabetes and infants and toddlers in the setting of prolonged fasting or illness. Despite increased use of propranolol for infantile hemangiomas, the prevalence of hypoglycemia in this population appears to be low (0.9%). Propranolol has also been safely used in children with underlying hypoglycemia disorders, although close monitoring of glucose is needed during illness.

Salicylate Intoxication

See Chapter 94.

Both hyperglycemia and hypoglycemia occur in children with salicylate intoxication. Accelerated use of glucose, resulting from augmentation of insulin secretion by salicylates, and possible interference with gluconeogenesis may contribute to hypoglycemia. Infants are more susceptible than older children. Monitoring of blood glucose levels with appropriate glucose infusion in the event of hypoglycemia should form part of the therapeutic approach to salicylate intoxication in childhood. Ketosis may occur.

Systemic Disorders

Several systemic disorders are associated with hypoglycemia in infants and children. Children with acute liver failure develop hypoglycemia because of loss of gluconeogenesis. Sepsis, particularly in neonates, may result in hypoglycemia. Falciparum malaria is also associated with hypoglycemia, which is thought to be the result of increased glucose use and impaired gluconeogenesis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Aneuploidy screening is offered to pregnant persons in the first trimester or at midgestation to evaluate the risk for common aneuploidies such as Down syndrome (trisomy 21), trisomy 18, trisomy 13, and congenital malformations (e.g., abdominal wall or NTDs) known to cause elevations of various markers. A combination of these biochemical markers (including AFP, inhibin A, estriol, pregnancy-associated plasma protein A, β-human chorionic gonadotropin [β-hCG]) and US increases the positive predictive value (PPV) of these screening tests. Fetal DNA in maternal plasma and fetal cells circulating in maternal blood are potential noninvasive sources of material for prenatal genetic testing. This testing, however, is not diagnostic, and a positive test requires either amniocentesis or postnatal analysis to confirm the diagnosis. Nonetheless, fetal karyotyping by analysis of fetal DNA in maternal plasma is another screening test that is very sensitive for the detection of Down syndrome, with a higher PPV than any other prenatal screening test for Down syndrome. Currently, however, the use of this technology is only advocated in pregnancies deemed at high risk for aneuploidy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

117.7 Treatment and Prevention of Fetal Disease

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

See also Chapter 118.

Management of a fetal disease depends on coordinated advances in diagnostic accuracy and knowledge of the disease's natural history; an understanding of fetal nutrition, pharmacology, immunology, and pathophysiology; the availability of specific active drugs that cross the placenta; and therapeutic procedures. Progress in providing specific treatments for accurately diagnosed diseases has improved with the advent of real-time ultrasonography, amniocentesis, and cordocentesis (see Tables 117.1 and 117.9).

The incidence of sensitization of Rh-negative women by Rh-positive fetuses has been reduced by prophylactic administration of Rh(D) immunoglobulin to mothers early in pregnancy and after each delivery or abortion, thus reducing the frequency of hemolytic disease in their subsequent offspring. **Fetal erythroblastosis** (see Chapter 140) may be accurately detected by fetal Doppler assessment of the peak systolic velocity of the middle cerebral artery and treated with intrauterine transfusions of packed Rh-negative blood cells via the intraperitoneal or, more often, intraumbilical vein approach.

Pharmacologic approaches to fetal immaturity mostly revolve around the administration of antenatal corticosteroids to the mother to promote fetal production of surfactant with a resultant decrease in the incidence of **respiratory distress syndrome** (see Chapter 126). Tocolytic agents have been demonstrated to prolong pregnancy to allow the administration of antenatal corticosteroids (48 hours); however, there is no proven benefit beyond this time frame. Maternal administration of magnesium sulfate for fetal/neonatal neuroprotection is recommended in pregnancies deemed to be at risk of imminent delivery before 32 weeks' gestation in light of evidence demonstrating a reduction in frequency of cerebral palsy compared with those who did not receive this treatment.

Management of definitively diagnosed fetal genetic disease or congenital anomalies consists of multidisciplinary parental counseling. Rarely, high-dose **vitamin therapy** for a responsive inborn error of metabolism (e.g., biotin-dependent disorders) or fetal transfusion (with red blood cells or platelets) may be indicated. **Fetal surgery** is well-established treatment for certain conditions but remains a largely experimental approach to therapy for other conditions and is available only in a few, highly specialized perinatal centers (see Table 117.9 and Chapter 118). The nature of the defect and its consequences must be considered, as well as ethical implications for the fetus and the parents. **Termination of pregnancy** is also an option that should be discussed during the initial phases of counseling.

Folic acid supplementation decreases the incidence and recurrence of NTDs. Because the neural tube closes within the first 28 days of conception, periconceptional supplementation is needed for prevention. It is recommended that women without a prior history of a NTD ingest 400 μg/day of folic acid throughout their reproductive years. Women with a history of a prior pregnancy complicated by an NTD or a first-degree relative with an NTD should have preconceptional counseling and should ingest 4 mg/day of supplemental folic acid beginning at least 1 month before conception. Fortification of cereal-grain flour with folic acid is established policy in the United States and some other countries. The optimal concentration of folic acid in enriched grains is somewhat controversial. The incidence of NTD in the United States and other countries has decreased significantly since these public health initiatives were implemented. Use of some antiepileptic drugs (valproate, carbamazepine) during pregnancy is associated with an increased risk of NTD. Women taking these medications should ingest 1-5 mg of folic acid daily in the preconception period.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 118

Fetal Intervention and Surgery

Natalie E. Rintoul, Emily A. Partridge, and Holly L. Hedrick

Congenital anomalies have always been recognized as a therapeutic challenge. Numerous diagnoses have been evaluated for the possibility of fetal intervention (Tables 118.1 and 118.2). Some have proved beneficial to the developing infant, some have been abandoned, and some remain under investigation.

FETAL THERAPY ETHICS

With the development of advanced fetal ultrasound (US), ultrafast fetal MRI, and fetal echocardiography, the ability to accurately diagnose fetal disease has improved substantially over the past 3 decades. The first prenatal therapeutic intervention was reported in 1963 with the successful treatment of erythroblastosis fetalis by fetal intraperitoneal infusion. Other innovations, though groundbreaking, brought to light the high morbidity (fetal and maternal) and mortality associated with open fetal interventions, and it would take greater experience and techniques before open fetal surgery would be safer and therapeutic.

OBSTRUCTIVE UROPATHY

Obstructive uropathy is a diverse set of diseases affecting the bladder neck or urethra and affects between 2.2 and 3.3 per 10,000 live births. It is most frequently caused by **posterior urethral valves (PUVs)** but can be caused by a variety of other defects, including urethral atresia, persistent cloaca, caudal regression, and megacystis–microcolon–intestinal hypoperistalsis syndrome (see Chapters 577 and 578). Although male fetuses are more commonly affected, females are more commonly associated with severe pathologic variants, and 30% of survivors will require renal replacement therapy or transplantation before age 5. Congenital obstructive uropathy

Table 118.1 Fetal Diagnoses Evaluated and Treated in Fetal Centers

Amniotic band syndrome (ABS)	Gastroschisis
Anomalies in monochorionic twins	Hydrocephalus
Aortic stenosis	Hydronephrosis
Arachnoid cyst	Hypoplastic left heart syndrome (HLHS)
Bladder exstrophy	Imperforate anus
Bladder outlet obstruction	Intraabdominal cyst
Bronchopulmonary sequestration (BPS)	Lymphangioma
Cervical teratoma	Mediastinal teratoma
Cloaca	Myelomeningocele, spina bifida
Cloaca exstrophy	Neuroblastoma
Complete heart block	Obstructive uropathy
Congenital pulmonary airway malformation (CPAM)	Omphalocele
Congenital diaphragmatic hernia (CDH)	Pentalogy of Cantrell
Congenital high airway obstruction syndrome (CHAOS)	Pericardial teratoma
EXIT to airway procedure for CHAOS	Pleural effusions
Conjoined twins	Pulmonary agenesis
Dandy-Walker malformation	Pulmonary atresia with intact ventricular septum
Duodenal atresia	Sacrococcygeal teratoma (SCT)
Encephalocele	Twin reversed arterial perfusion (TRAP) sequence
Enteric duplication atresia	Twin-to-twin transfusion syndrome (TTTS)
Esophageal atresia	Vein of Galen aneurysm

EXIT, Ex utero intrapartum treatment.

Table 118.2 Indications and Rationales for In Utero Surgery on the Fetus, Placenta, Cord, or Membranes

FETAL SURGERY	PATHOPHYSIOLOGY	RATIONALE FOR IN UTERO INTERVENTION
SURGERY ON THE FETUS		
1. Congenital diaphragmatic hernia	Pulmonary hypoplasia and anatomic substrate for pulmonary hypertension	Reversal of pulmonary hypoplasia and reduced degree of pulmonary hypertension Repair of actual defect delayed until after birth
2. Lower urinary tract obstruction	Progressive renal damage due to obstructive uropathy Pulmonary hypoplasia due to oligohydramnios	Prevention of renal failure and pulmonary hypoplasia by anatomic correction or urinary deviation
3. Sacrococcygeal teratoma	High-output cardiac failure due to AV shunting and/or bleeding Direct anatomic effects of the tumoral mass Polyhydramnios-related preterm labor	Reduction of functional impact of tumor by ablation of tumor or (part of) its vasculature Reduction of anatomic effects by drainage of cysts or bladder Amnioreduction preventing obstetric complications
4. Thoracic space-occupying lesions	Pulmonary hypoplasia (space-occupying mass) Hydrops due to impaired venous return (mediastinal compression)	Creation of space for lung development Reversal of the process of cardiac failure
5. Neural tube defects	Damage to exposed neural tube Chronic CSF leak, leading to Arnold-Chiari malformation and hydrocephalus	Prevention of exposure of the spinal cord to amniotic fluid Restoration of CSF pressure correcting Arnold-Chiari malformation
6. Cardiac malformations	Critical lesions causing irreversible hypoplasia or damage to developing heart	Reversal of process by anatomic correction of restrictive pathology
SURGERY ON THE PLACENTA, CORD, OR MEMBRANES		
7. Chorioangioma	High-output cardiac failure due to AV shunting Effects of polyhydramnios	Reversal of process of cardiac failure and hydrops fetoplacentalis by ablation or reduction of flow
8. Amniotic bands	Progressive constrictions causing irreversible neurologic or vascular damage	Prevention of amniotic band syndrome leading to deformities and function loss
9. Abnormal monochorionic twinning: twin-to-twin transfusion; fetus acardius, and discordant anomalies	Twin-twin transfusion leading to oligopolyhydramnios sequence, hemodynamic changes; preterm labor, and rupture of membranes; in utero damage to brain, heart, or other organs In utero fetal death may cause damage to co-twin Cardiac failure of pump twin and consequences of polyhydramnios Serious anomaly raising the question of termination of pregnancy Selective feticide	Arrest of intertwin transfusion Prevention/reversal of cardiac failure and/or neurologic damage, including at in utero death Prolongation of gestation Selective feticide to arrest parasitic relationship, to prevent consequences of in utero fetal death, and to avoid termination of entire pregnancy

AV, Arteriovenous; CSF, cerebrospinal fluid.
From Deprest J, Hodges R, Gratacos E, Lewi L. Invasive fetal therapy. In: Creasy RK, Resnik R, Iams JD, et al., eds. *Creasy & Resnik's Maternal-Fetal Medicine*. 7th ed. Philadelphia: Elsevier; 2014. Table 35-1.

causes hydronephrosis and renal dysplasia of variable severity. Although the mechanism of renal injury is debated, hypotheses include cyst formation secondary to urinary retention and subsequent disruption of nephrogenesis versus obstruction-associated apoptosis of renal tubular cells.

Obstructive uropathy usually presents on fetal US with an enlarged bladder, bilateral hydroureteronephrosis, and oligohydramnios in the second and third trimester. Mild forms of obstructive uropathy may lead to minimal short- or long-term clinical sequelae. However, reduced fetal urine output resulting in oligohydramnios or anhydramnios in more severe forms can cause significant pulmonary hypoplasia, which is associated with death shortly after delivery in >80% of infants. Pulmonary survivors remain subject to high mortality and chronic morbidity resulting from renal dysplasia, renal failure, and the need for chronic renal replacement therapy. Workup of congenital obstructive uropathy includes genetic and structural evaluation, with additional imaging and fetal urinalysis aiding in prognostication. For example, a fetal urine sodium <100 mEq/L, chloride <90 mEq/L, and urine osmolality >210 mEq/L at a mean gestational age of 23.8 weeks predicts "good outcome," as reflected by the presence of nondysplastic kidneys at autopsy or biopsy, or normal renal and pulmonary function at birth. Fetuses with salvageable renal function should have downtrending values of urine sodium, chloride, calcium, total protein and β_2-microglobulin on repeat vesicocentesis. Fetal bladder filling time [(fetal bladder volume 48 hours post-vesicocentesis – fetal bladder volume prior to vesicocentesis)/fetal bladder volume prior to vesicocentesis)], fetal MRI, and three-dimensional fetal cystoscopy have also been shown to have utility in predicting postnatal renal function.

The primary objective of fetal intervention in fetuses with obstructive uropathy is restoration of amniotic fluid volume to prevent pulmonary hypoplasia. Although prevention of ongoing renal injury is also desired, the efficacy of fetal intervention in achieving this goal is uncertain. Therefore fetal intervention for obstructive uropathy is currently limited to fetuses in whom the obstruction is sufficient to cause oligohydramnios or anhydramnios.

For fetuses that still have adequate renal function and can produce urine, treatment options include vesicoamniotic shunting, valve ablation via cystoscopy, and vesicostomy. **Vesicoamniotic shunting** is the most common and involves percutaneous, US-guided placement of a double-pigtailed shunt from the fetal bladder to the amniotic space, allowing decompression of the obstructed bladder and restoration of the amniotic fluid volume (Figs. 118.1 and 118.2). Although simple in concept, bladder decompression may not always occur, and many catheters will become dislodged as the fetus develops; a fetus typically requires three catheter replacements before completion of pregnancy. Vesicoamniotic shunting may improve perinatal survival, but at the expense of poor long-term renal function. In a systematic review of over 250 fetuses, increased prenatal survival is present in the shunted population, but there is no difference in the 12- and 24-month survival.

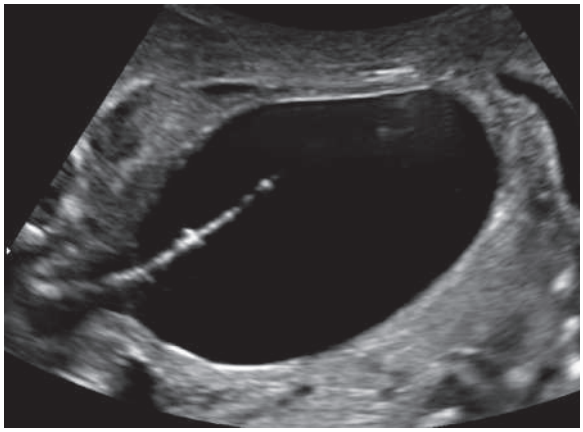

Fig. 118.1 Ultrasound image showing fetoscopic placement of a transurethral vesicoamniotic shunt in a patient with posterior urethral valves. *(Courtesy Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)*

Fetal **cystoscopy** is more technically challenging than vesicoamniotic shunt placement, more invasive, and requires more sedation, but this option holds some important advantages. Cystoscopy allows for direct visualization of the obstruction and does not require amnioinfusion. Moreover, when the obstruction is visualized and the diagnosis of PUV confirmed, the valves can be treated, restoring urine flow to the amniotic space, and eliminating the need for repeated fetal interventions in most patients. Creation of a vesicostomy (direct opening from bladder through fetal abdominal wall) by open fetal surgery has improved perinatal survival (Fig. 118.3). However, the current dataset evaluating this approach is still limited, and direct comparisons to shunting suggest no significant difference between these interventions.

NONOBSTRUCTIVE RENAL DISEASE

Nonobstructive fetal renal disease can result from renal hypoplasia/dysplasia and from genetic diseases such as autosomal recessive polycystic kidney disease. Similar to obstructive uropathy, fetal therapy is focused on restoring amniotic fluid volume in patients with oligohydramnios or anhydramnios. However, restoration of amniotic fluid volume in nonobstructive renal disease requires external sources of amniotic fluid. Current treatment options include serial percutaneous **amnioinfusion** and infusion of fluid by amnioport. Serial amnioinfusions are less invasive as a single procedure, but most pregnancies will require weekly infusions to maintain adequate amniotic fluid volume. Amnioinfusion through an amnioport involves open surgical placement of a catheter into the amniotic space that is connected to an ex utero subcutaneous port. This allows repeated fluid infusion into the amniotic space. The amnioport is more challenging and invasive as an individual procedure but provides more reliable access to the amniotic space for the duration of the pregnancy. Small studies suggest both these procedures improve pulmonary outcomes and perinatal survival in infants with renal disease, but these infants will require dialysis and then renal transplant when the infant is large enough (2-3 years of age). The Renal Anhydramnios Fetal Therapy (RAFT) is a multi-site clinical trial to determine the feasibility, safety and success rate of serial **amnioinfusions** for early pregnancy renal anhydramnios (EPRA). The trial originally included EPRA caused both by congenital bilateral **renal agenesis** (CoBRA) and by fetal renal failure

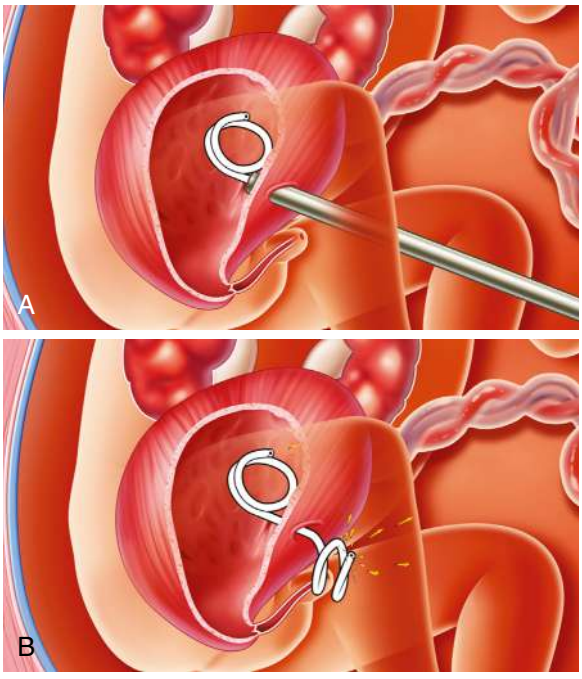

Fig. 118.2 Vesicoamniotic shunt placement. **A**, The shunt is loaded into the trocar, passed into the bladder, and recoils to a pigtail shape. **B**, The other end of the shunt recoils to a pigtail outside the abdominal wall, releasing urine into the amniotic fluid space around the fetus. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

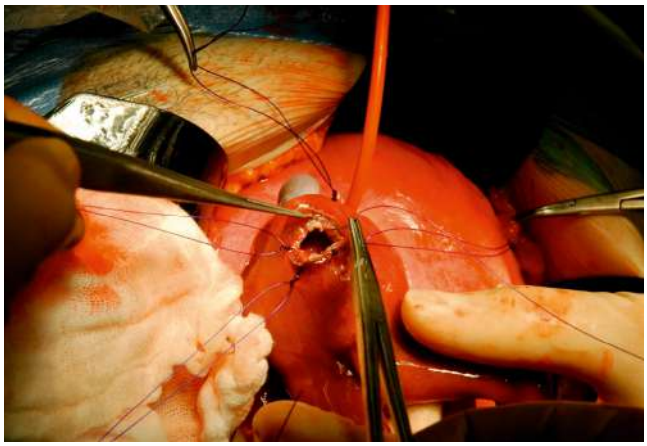

Fig. 118.3 Creation of a fetal vesicostomy. The uterine opening is stapled to prevent bleeding, and a catheter is inserted to replace amniotic fluid and maintain uterine volume. The fetus is positioned with the legs to the lower part of the field and the umbilical cord to the upper part of the field. A vesicostomy is created through the bladder and the abdominal wall to allow drainage of the obstructed bladder and restoration of amniotic fluid volume. *(Courtesy Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)*

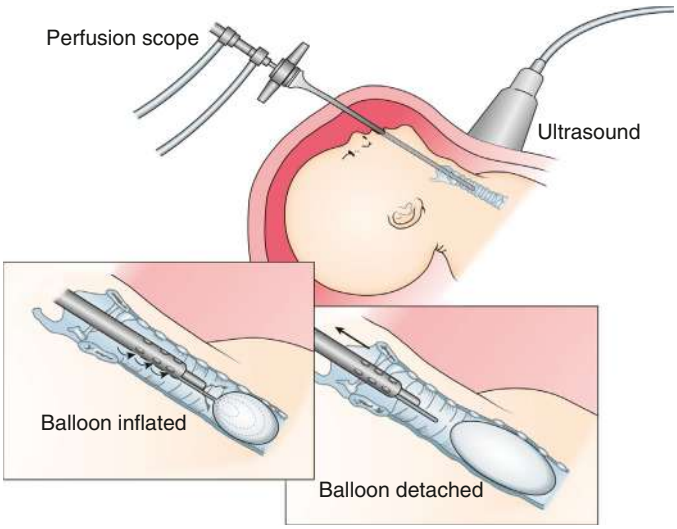

Fig. 118.4 Technique for fetoscopic tracheal occlusion using a balloon. *(Modified from Hirose S, Harrison MR. Fetal therapy. In Holcomb GW III, Murphy JP, eds. Ashcraft's Pediatric Surgery. 5th ed. St Louis: Elsevier; 2010. Fig. 10.1.)*

(FRF) with kidney tissue present. At the time of this publication, the CoBRA arm is no longer recruiting. The primary objective of this trial is to determine the proportion of neonates surviving to successful dialysis after serial amnioinfusions.

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is a structural birth defect in which the diaphragm fails to fully close during development resulting in herniation of the abdominal contents into the thorax and inhibition of fetal lung growth (see Chapter 131). CDH occurs in 1,500 live births in the United States annually and is the leading cause of in-hospital neonatal deaths as well as the costliest noncardiac birth defect. Although the pathophysiology of CDH remains unclear, most patients are affected by some degree of pulmonary hypoplasia and persistent pulmonary hypertension. A dual-hit hypothesis has been suggested to characterize lung injury in CDH, with an initial injury occurring during organogenesis resulting in bilateral pulmonary hypoplasia and a secondary insult of the ipsilateral lung due to compression by the herniated abdominal viscera. Fetal breathing and fluidic lung distension are features of normal lung development, which are mechanically compromised by the diaphragmatic defect, resulting in not only reduced parenchymal volume but also decreased vascular density. Compensatory vascular remodeling results in hypermuscularization of the arteriolar bed, increased vascular resistance, and ultimately pulmonary hypertension. It is the severity of pulmonary hypoplasia and persistent pulmonary hypertension that represents the greatest determinant of morbidity and mortality.

In mild cases of CDH, surgical repair of the diaphragm is typically performed in the first few days of life after respiratory and hemodynamic stabilization. Although these infants are affected by pulmonary hypoplasia and close monitoring is required during the first years of life, long-term outcomes are excellent in the majority of survivors of mild CDH. In cases of *severe* CDH, pulmonary hypertension leads to right ventricular dysfunction and right-to-left shunting across the patent foramen ovale and ductus arteriosus, which can result in left ventricular dysfunction and cardiac failure necessitating extracorporeal membrane oxygenation (ECMO) in the perinatal period. Mortality is high in severely affected infants, and survivors often have significant impairments in long-term respiratory, feeding, and neurodevelopmental outcomes.

More than half of all CDH cases are identified on routine second trimester anatomy US, whereas delayed diagnosis may occur secondary to small defects, technical limitations, or unavailability of prenatal care. In 50–70% of cases the lesion is isolated, whereas *syndromic* or *complex* CDH may be associated with additional anomalies warranting further imaging and genetic studies. Fetal echocardiography and ultrafast MRI should be included in comprehensive fetal diagnosis, permitting calculation of fetal lung volumes as well as ruling out major structural cardiac anomalies.

The first reports of attempted *in utero repair* of CDH noted impairment of umbilical blood flow after reduction of the liver resulting in fetal demise in a number of cases. Although the procedure proved to be technically feasible in fetuses without liver herniation, comparative analysis revealed higher rates of preterm delivery (32 vs 38 weeks' gestation) and similar rates of survival (75% fetal repair vs 86% postnatal repair), leading to abandonment of prenatal attempts at surgical repair.

Given the disappointing results after attempted open fetal surgical repair of **CDH**, researchers turned to the fetal lamb model to assess the impact of tracheal ligation on pulmonary development. By blocking the efflux of fetal lung fluid into the amniotic space, pulmonary distension results in increased lung volumes. To mitigate the risks associated with open tracheal ligation, a **fetoscopic endoluminal tracheal occlusion (FETO)** approach with balloon tracheal occlusion was developed (Fig. 118.4). In a study of 210 fetuses with *severe* hypoplasia due to isolated CDH, the use of FETO had an acceptable safety profile in the mother with improved neonatal survival but increased risk of preterm birth. In this trial the balloon was inserted at approximately 28 weeks of gestation and removal at 34 weeks, with this timing based on the hypothesis that tracheal occlusion will promote lung expansion while removal of the balloon before delivery will promote alveolar type II cell maturation. The multicenter prospective randomized Tracheal Occlusion to Accelerate Lung Growth (TOTAL) study results had inclusion criteria of gestational age less than 29 weeks 6 days at randomization, isolated left-sided CDH with no other major structural or chromosomal defects, and severe pulmonary hypoplasia defined as observed-to-expected lung-to-head ratios of less than 25%. Forty percent of infants with severe CDH in the FETO group survived to discharge compared to 15% in the expectant care group, with survival to 6 months identical to survival at discharge and increased rate of preterm rupture of membranes (47% vs 11%) and preterm birth (75% vs 29%).

CONGENITAL PULMONARY AIRWAY MALFORMATION

Congenital pulmonary airway malformations (CPAM), or fetal lung lesions, are a group of rare congenital pulmonary neoplasms including congenital cystic adenomatoid malformations (CCAMs), bronchopulmonary sequestrations (BPSs), congenital lobar emphysema, and bronchogenic cysts (Fig. 118.5). The reported incidence of CPAM is 9 per 100,000 live births, with prenatal diagnosis by fetal US most commonly coinciding with the 18–20-week anatomy scan. CCAMs are caused by abnormal branching and hamartomatous growth of the terminal respiratory structures, resulting in cystic and adenomatoid malformations (see Chapter 444), and are the most common congenital lung lesion. CCAMs

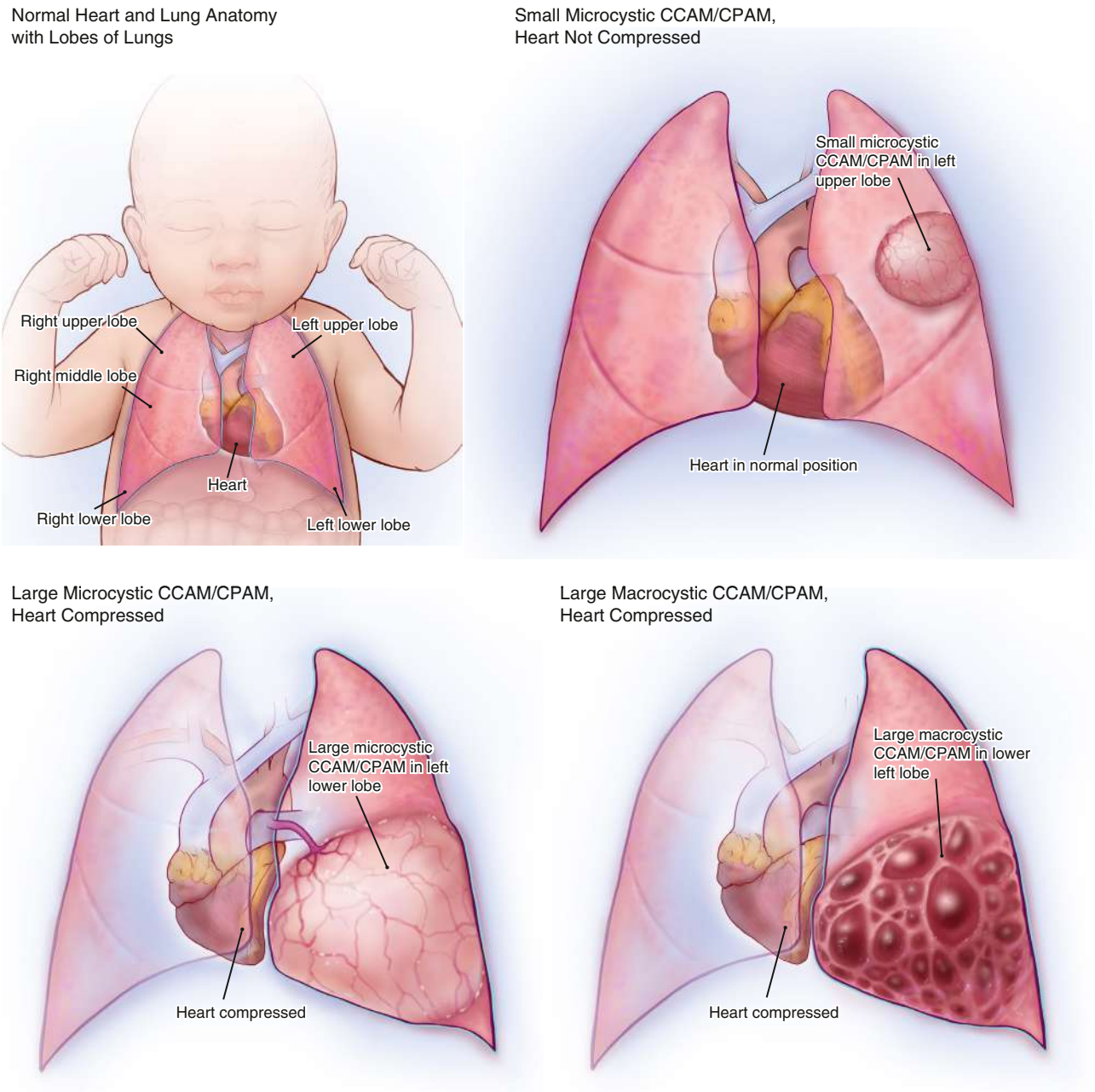

Fig. 118.5 Different types of congenital cystic adenomatoid malformation (CCAM)/congenital pulmonary airway malformation (CPAM), and how the different sizes and presentations of lung lesions can impact the heart and lungs. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

have been classified as microcystic (maximal cyst diameter <5 mm) vs macrocystic (≥5 mm), and prognosis is correlated with lesion size as well as presence of macrocysts (see Fig. 118.5). In contrast, BPSs appear as echogenic homogeneous masses on US and can be distinguished from CCAM by US evidence of systemic aortic arterial blood supply.

Large CPAMs may cause significant pulmonary hypoplasia and polyhydramnios due to decreased fetal swallowing secondary to esophageal compression. In severe cases, hydrops fetalis may result due to compression of the heart and great vessels. Hydrops with concomitant placentomegaly may result in maternal mirror syndrome, which is postulated to result from the release of vasoactive substances from the inflamed and edematous placenta. Due to the variable natural history of these lesions, a prenatal prognostic parameter, the CPAM volume ratio (CVR), is followed. The CVR is an index that compares the volume of the CPAM to the fetal head circumference. Most studies indicate >95% survival in CPAM patients with no hydrops and CVR <1.6, with greater risk for hydrops and need for closer surveillance in patients with a CVR >1.6.

Management of pregnancies complicated by prenatal diagnosis of a fetal lung lesion requires a plan for safe delivery. In the absence of mediastinal shift or flattening, small microcystic lesions will typically meet criteria for community delivery with a plan for close postnatal follow-up. Due to the risk of recurrent infection and malignant transformation, elective postnatal resection is anticipated; a CT angiogram (CTA) is performed at 4-6 weeks of age with surgical intervention following a few weeks later, when the potential for compensatory growth of the remaining lobe(s) is maximized. In the example of large macrocystic lesions with concern for respiratory compromise, delivery at an experienced center with access to ECMO and advanced emergent resection approaches is critical. For large lesions with CVR >1.6 or associated hydrops, the presence of macrocysts permits fetal thoracentesis and eventual thoracoamniotic shunt placement, which may reverse hydrops and allow continuation of the pregnancy without open fetal surgical intervention. Irrespective of the presence of drainable cysts, large lesions with threatened hydrops are treated with maternal betamethasone, which has been shown to reduce lesion size and reverse hydrops and may be given in multiple courses

to maximize therapeutic impact. Lesions not responsive to steroids or amenable to drainage may require open fetal surgery if the gestational age is less than 32 weeks; beyond 32 weeks' gestation, early delivery by C-section or ex utero intrapartum therapy (EXIT) with planned immediate resection is recommended.

CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME

Congenital high airway obstruction syndrome (CHAOS) is secondary to partial or complete intrinsic fetal upper airway obstruction. Most often due to laryngeal or tracheal atresia, CHAOS prevents lung fluid efflux resulting in dilated distal pulmonary airways and enlargement of the fetal lungs with potential for cardiac compression and the development of fetal hydrops. The diagnosis is confirmed by fetal MRI (Fig. 118.6).

In addition to CHAOS, extrinsic compression of the airway may be secondary to mass lesions (lymphangioma, teratoma, goiter) making respiratory efforts after birth difficult.

EXIT (ex utero intrapartum treatment) is a procedure to secure an airway during elective delivery (while the umbilical cord is patent and connected to the placenta), by C-section, before the onset of labor and before the fetus attempts to breathe (Fig. 118.7). The EXIT to airway procedure may be performed by direct laryngoscopy and

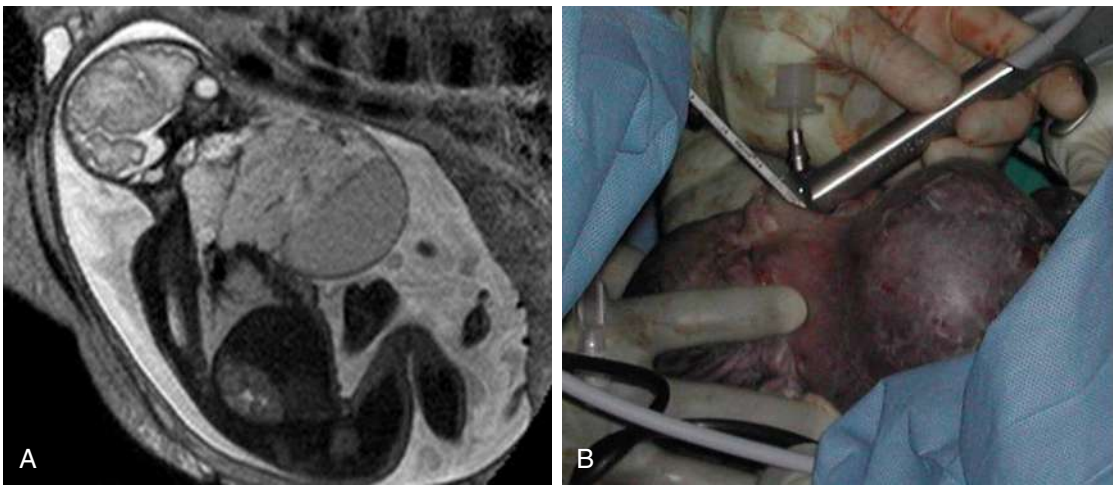

Fig. 118.6 A, Ultrafast MRI of fetus with giant cervical teratoma showing polyhydramnios and hyperextension of the neck. B, Fetus with giant cervical teratoma at the time of intubation by direct laryngoscopy and rigid bronchoscopy. *(From Lazar DA, Olutoye OO, Moise KJ, et al. Ex-utero intrapartum treatment procedure for giant neck masses – fetal and maternal outcomes. J Pediatr Surg. 2011;46:817–822, Fig. 1.)*

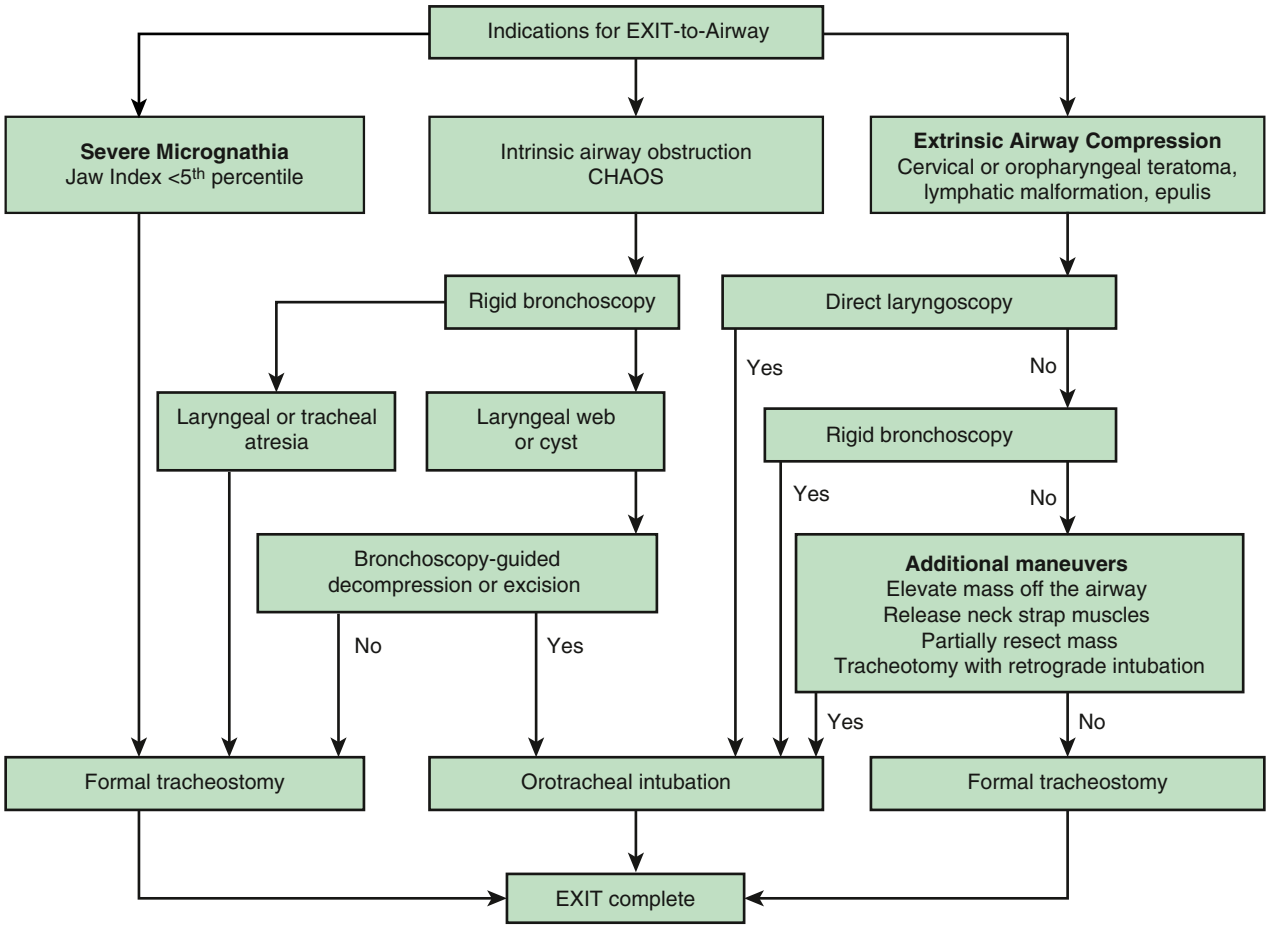

Fig. 118.7 Fetal airway management algorithm for ex utero intrapartum therapy (EXIT) procedures. Yes, Successful; No, not successful; CHAOS, congenital high airway obstruction syndrome. *(Adapted from Chatterjee D, Crombleholme TM. Airway management in EXIT procedures. In Jagannathan N, Fiadjoe JE, eds. Management of the Difficult Pediatric Airway. Cambridge, UK: Cambridge University Press; 2020.)*

endotracheal intubation or, if needed, rigid bronchoscopy, fiberoptic intubation, or tracheostomy (see Fig. 118.6).

SACROCOCCYGEAL TERATOMA

Sacrococcygeal teratoma (SCT) is one of the most common solid tumors of the newborn, with an incidence of 4.8 per 100,000 live births. This germline tumor has a female predominance (4:1) and is rarely associated with other congenital anomalies including nervous, skeletal, and cardiac abnormalities.

The high morbidity and mortality associated with SCT is multifactorial and is associated with both high rates of preterm delivery as well as hemodynamic sequelae. The mechanism of preterm delivery in SCT is believed to be a result of polyhydramnios-associated uterine irritability and premature rupture of membranes. Rupture of the tumor itself is rare but is most often fatal. The vascular composition of the tumor has hemodynamic implications for the fetus/newborn as high-output cardiac failure results from arteriovenous shunting causing vascular steal away from the placenta and the fetus to the SCT and compromised perfusion. Hydropic fetuses with placentomegaly may develop maternal mirror syndrome mandating immediate delivery. Prenatal diagnosis relies on US to identify the lesion and subsequent fetal MRI and echocardiography to assess for placental size, hydrops, and cardiac output physiology. Specific echocardiographic and Doppler US measurements of prognostic utility include cardiac output, cardiac/thoracic ratio, placental thickness, amniotic fluid index, and markers of hydrops including ascites as well as skin and scalp edema.

Given the morbidity and mortality associated with open fetal resection, prenatal intervention is limited to fetuses with mostly external masses manifesting hydrops and fetal cardiac insufficiency. The fetal approach to SCT debulking involves incision of the fetal skin circumferentially around the base of the tumor, application of a Rummel tourniquet, and debulking of the mass with a tissue stapler or energy device to interrupt the high output state (Fig. 118.8). Completion resection of the tumor and coccyx is performed postnatally. More often in the setting of early signs of evolving hydrops in the third trimester, early delivery (28-29 weeks' gestation) and debulking are considered with a similar strategy of staged debulking followed by completion resection when the neonate has stabilized. Resection of the coccyx is critical to avoid recurrence.

Reports of noninvasive interruption of blood flow with laser ablation, radiofrequency ablation, or vascular coiling are tempting but have been complicated by the inability to control the energy source leading to destructive tissue injury and injury to adjacent structures.

MYELOMENINGOCELE

Myelomeningocele (MMC) is the most common neural tube defect with an incidence of 1-2 per 1,000 live births. The disease is characterized by an abnormal outgrowth of the nerve root through the meninges with a concomitant vertebral bone and skin defect resulting in neural tissue exposure to the amniotic fluid. Associated defects include Chiari II malformation, characterized by descent of the cerebellar vermis through the foramen magnum, medullary kinking, and obliteration of the cistern magna leading to brainstem herniation. Hydrocephalus complicates up to 85% of MMC patients and is a major source of long-term morbidity, with high rates of shunting of cerebrospinal fluid required in survivors. Dermoid cysts are also common and may require intervention. Developmental and cognitive impairment is prevalent and profound, and current estimates suggest rates between 60% and 70% of pregnancies complicated by a prenatal diagnosis of MMC end in termination or demise. The etiology of MMC is likely multifactorial, with folic acid deficiency as well as use of folic acid antagonists associated with the development of neural tube defects. Screening for neural tube defects includes measurement of maternal serum α-fetoprotein (MSAFP) and US. Expectant mothers with screening concerns for MMC should be evaluated at a specialized center with further anatomic US, genetic screening, and ultrafast fetal MRI. In addition to identification of the neural tube defect, expert US can assess lower extremity function, and fetal MRI can define the extent of hindbrain herniation and ventricular size.

Before the introduction of fetal repair of MMC, fetal surgery was limited to life-threatening anomalies with high predictive mortality for the fetus or infant without intervention. However, a growing body of data suggested that the neurologic outcome in MMC was directly related to progressive injury from ongoing damage to the exposed spinal cord during pregnancy (see Chapter 631.3) (Fig. 118.9). A large multicenter National Institutes of Health–sponsored Management of Myelomeningocele Study (MOMS) comparing the safety and efficacy of prenatal repair of MMC with that of standard postnatal repair was performed and determined a clear advantage for prenatal surgery before 26 weeks' gestation. The MOMS trial demonstrated a significant reduction in the need for ventriculoperitoneal (VP) shunt at 12 months in the fetal repair group (40% vs 82% in postnatal repair group) with reduced hindbrain herniation and improved mental development and motor function at 30 months. Furthermore, the need for shunting was independent of lesion level and degree of hindbrain herniation. The 1-year neurosurgical outcomes for the complete cohort showed that prenatal surgery did not decrease the need for shunting in those fetuses with a cerebral ventricular size of ≥15 mm at initial screening. Prenatal surgery was associated with an increased risk for earlier gestational age at birth. Delivery occurred before 30 weeks of gestation in 11% of neonates that had fetal MMC repair. Adverse pulmonary sequelae were rare in the prenatal surgery group despite an increased rate of oligohydramnios. The benefits of prenatal surgery outweigh the complications of prematurity.

Open fetal repair of MMC has been a paradigm-shifting advance in fetal surgery and has led to the formation of the North American Fetal Therapy Network (NAFTNet) registry of fetal MMC patients, with follow-up studies continuing to demonstrate the benefits

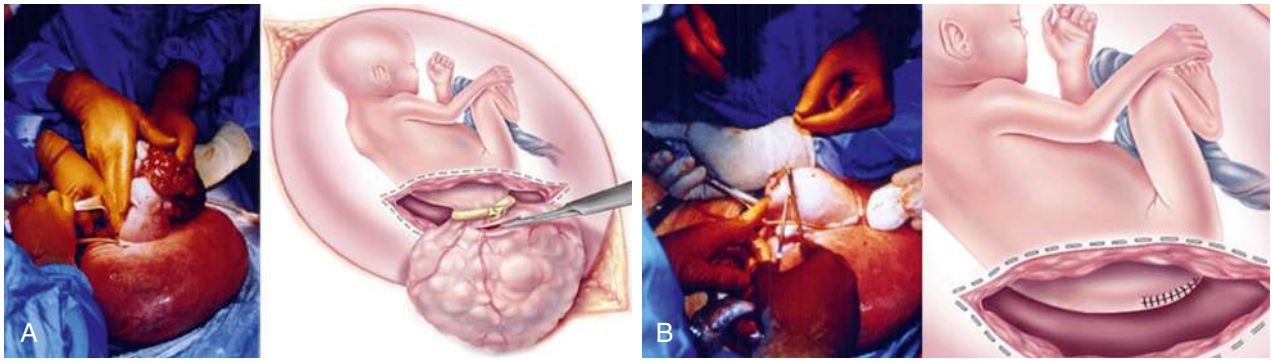

Fig. 118.8 A, Exposure of 26-week fetus through hysterotomy revealing sacrococcygeal teratoma (SCT). B, Closure of skin flaps after resection. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

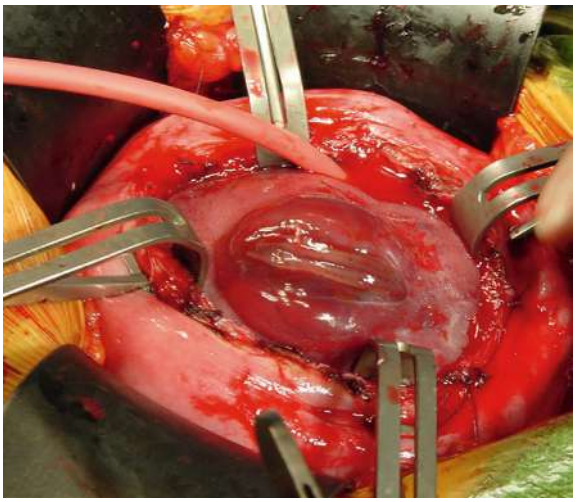

Fig. 118.9 Open fetal myelomeningocele repair. *(From Hirose S, Harrison MR. Fetal therapy. In Holcomb GW III, Murphy JP, eds. Ashcraft's Pediatric Surgery. 5th ed. St Louis: Elsevier; 2010. Fig. 10-5.)*



Fig. 118.10 In twin-to-twin transfusion syndrome (TTTS), blood flow through vascular connections on the surface of the placenta is unequal. One twin ("donor twin") pumps blood to the other twin ("recipient"). This unequal blood flow between twins results in the recipient twin *(right)* having too much amniotic fluid, and donor twin *(left)* with little or no amniotic fluid. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

observed in the MOMS trial in subsequent series. The risk of prematurity and requirement for cesarean section deliveries for all future pregnancies remain significant considerations for this procedure. The less invasive *fetoscopic* MMC repair approach, which is being developed at a limited number of centers, may reduce maternal morbidity and prematurity rates associated with open fetal MMC repair, but this remains a question of active ongoing investigation. At this time, fetoscopic fetal MMC repair is recommended in an investigational setting according to the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.

TWIN-TO-TWIN TRANSFUSION SYNDROME

Twin-to-twin transfusion syndrome (TTTS) is a condition that affects approximately 10–15% of *monochorionic diamniotic identical twin* pregnancies. In these cases, shared fetoplacental circulation can lead to unbalanced blood flow between the two fetuses which, left untreated, results in perinatal loss of one or both fetuses in approximately 80% of cases (Fig. 118.10). Unlike dichorionic twins, which do not have any vascular connections between the placentas, monochorionic twins have vascular anastomoses within the shared fetoplacental circulation. Unbalanced deep arteriovenous anastomoses without proper compensation from the superficial bidirectional vessels results in discordant blood supply, with the "donor" fetus presenting with oligohydramnios and intrauterine growth restriction while the "recipient" fetus develops polyhydramnios, heart failure, and hydrops due to hypervolemia. Neurodevelopmental delay is commonly observed in long-term survivors.

TTTS is usually a gradual process that is usually observed in the second trimester. Diagnosis is performed via US in the second trimester. The Quintero classification system is used to stratify TTTS into five stages.

- Stage I: Abnormal amniotic fluid levels (oligo- and polyhydramnios) with bladder filling in the donor twin
- Stage II: Features of stage I with collapsed bladder in the donor twin
- Stage III: New abnormal flow through the umbilical artery or ductus venosus in either the donor or recipient twin with stage II features present
- Stage IV: Hydrops in either the donor or recipient twin
- Stage V: Intrauterine demise of either the donor or recipient twin

Several therapies have been proposed for the treatment of TTTS. Amnioreduction is performed to remove excess fluid from the sac with polyhydramnios and can be done serially to help prevent preterm later. Endoscopic or fetoscopic laser ablation of the superficial vascular anastomoses is another therapeutic option. Under local or regional anesthesia, a trocar is placed under US guidance and an endoscope passed, through which superficial anastomoses are then identified and coagulated, followed by amnioreduction. The procedure is performed only once during the pregnancy, usually prior to 26 weeks. Several observational studies have noted perinatal survival approximating 60% with both amnioreduction and laser coagulation. A multicenter randomized trial demonstrated a survival and neurologic advantage after laser coagulation therapy vs amnioreduction; although after 26 weeks, amnioreduction is often still recommended for technical reasons. Other surgical therapies include septostomy (disrupting the membrane between the twins) and selective umbilical cord coagulation in severe cases. Like amnioreduction, septostomy does not alter the underlying pathophysiology. All cases should be referred to tertiary care centers with extensive experience in the treatment of TTTS.

OTHER INDICATIONS

Antenatal intervention for **cardiac defects**, such as aortic stenosis, pulmonic stenosis, and hypoplastic left heart syndrome (HLHS), have been used to dilate, with balloon valvuloplasty, stenotic valves (aortic stenosis) to prevent further development of HLHS (creating biventricular physiology) (Fig. 118.11) (see Chapter 480.10).

Laser therapy has been used to treat TTTS (Chapter 119.1) and amniotic bands (Fig. 118.12).

FETAL CENTERS

The value of fetal surgical program centers extends beyond fetal intervention itself. Often, families will present to a fetal center with a new diagnosis and little understanding of the implications for their baby and family. Prenatal counseling by the fetal team provides the opportunity to confirm the diagnosis, investigate for other anomalies and genetic susceptibilities, and provide detailed counseling to achieve understanding of both the diagnosis and

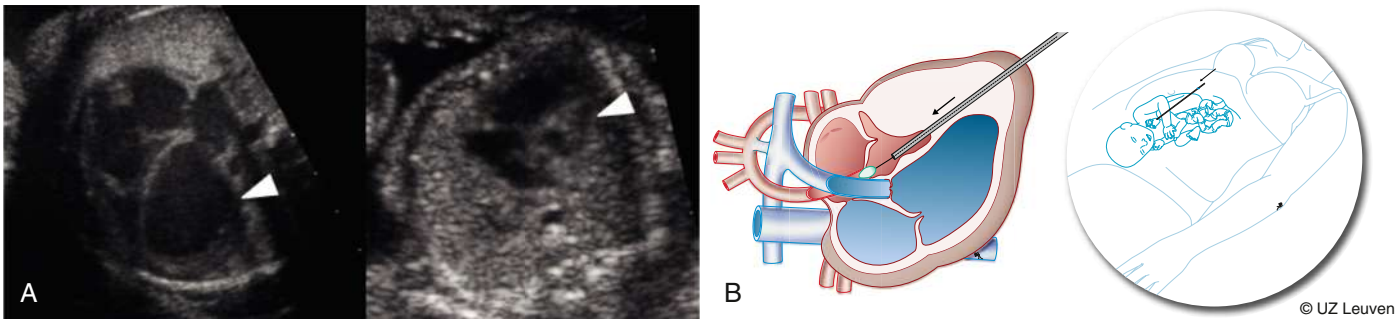

Fig. 118.11 **A,** Ultrasound image *(right panel)* is a cross section at the level of the fetal chest, demonstrating the four-chamber view in a fetus with aortic stenosis. Notice that the left ventricle *(arrowhead)* is dilated. Dilation occurs before the development of hypoplasia, which can be seen *(arrowhead)* in another fetus *(left panel)*. **B,** Schematic representation of percutaneous valvuloplasty, in this case of the left ventricular outlet tract. (***A*** *from van Mieghem T, Baud D, Devlieger R, et al. Minimally invasive fetal therapy. Best Pract Res Clin Obstet Gynaecol 2012;26:711–725;* ***B*** *copyright UZ Leuven, Leuven, Belgium.)*

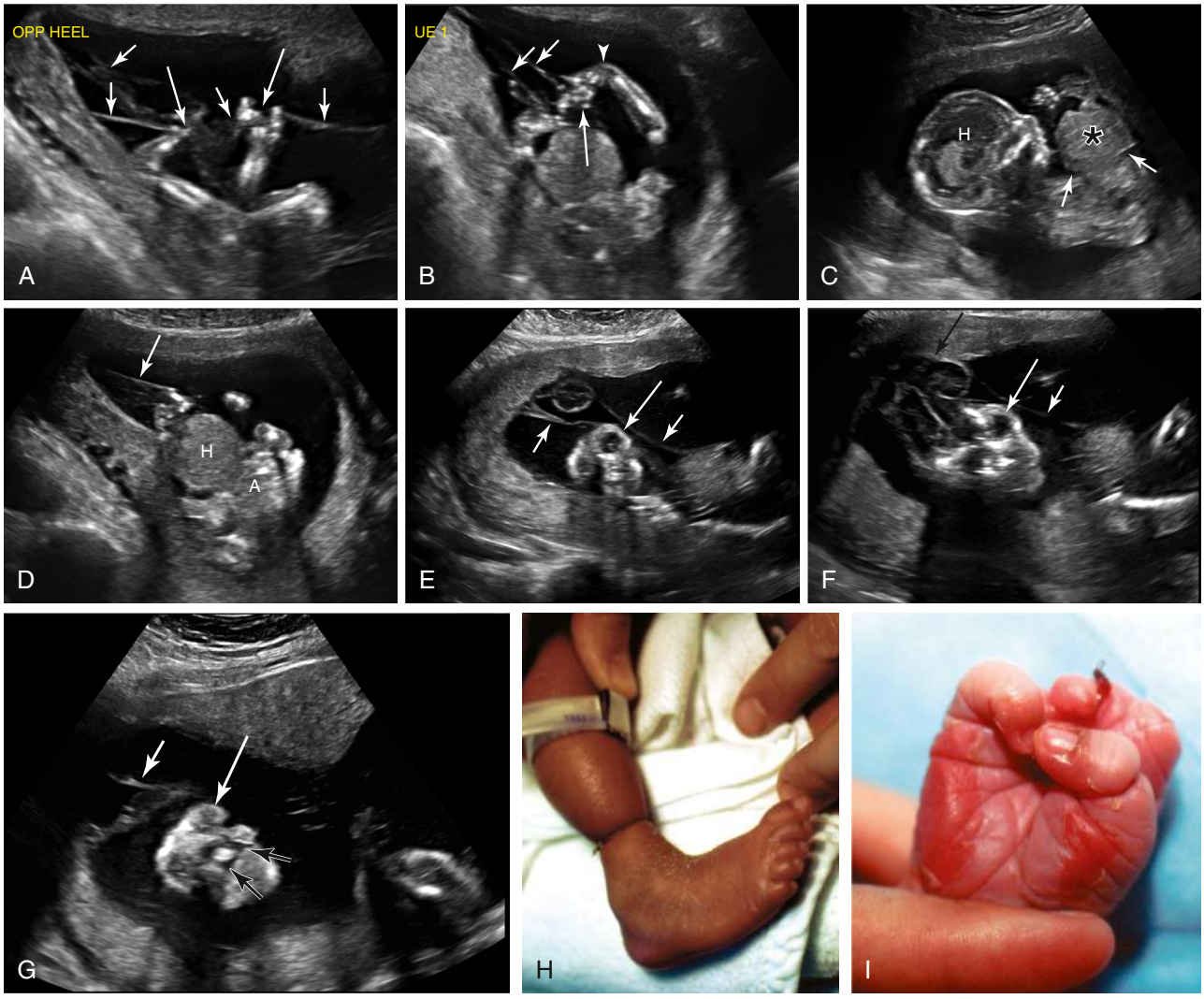

Fig. 118.12 Amniotic band sequence in two different fetuses. **A** and **B,** Effects on the extremities. Limbs of a fetus with amniotic band sequence show multiple amniotic bands (*short arrows,* **A** and **B**), amputation of fingers and toes (*long arrows,* **A** and **B**), and a fixed deformity of the hand at the wrist (*arrowhead,* **B**). **C** and **D,** Effects on the thorax and abdomen of the same fetus as in **A** and **B.** Sagittal image **(C)** shows a thoracoabdominal wall defect *(arrows)* with a large amount of herniated abdominal and thoracic contents *(asterisk)* outside the body. *White H,* Head. **D,** Axial image of the fetal abdomen **(A)** confirms the presence of a large ventral abdominal hernia *(H),* in the setting of amniotic bands *(arrow).* **E** to **G,** Effects on craniofacial structures in a different fetus. **E,** Coronal image of face shows multiple amniotic bands *(short arrows)* and nonvisualization of the calvarium. This results in a craniofacial appearance that resembles anencephaly *(long arrow).* **F,** A large encephalocele *(black arrow)* is seen above the level of the orbits *(long white arrow)* in a different scan plane. An amniotic band *(short white arrow)* is also seen. **G,** Coronal image of anterior portion of face shows facial clefts *(black arrows)* due to amniotic bands. *Short white arrow,* Amniotic band; *long white arrow,* orbits. **H,** Band constricting the ankle, leading to deformational defects. **I,** Pseudosyndactyly, amputation, and disruption of finger morphogenesis. (***A-G*** *from Hertzberg BS, Middleton WD. Ultrasound: The Requisites. 3rd ed. Philadelphia: Elsevier; 2016. Figs. 19-22;* ***H*** *and* ***I*** *from Jones KL, Smith DW, Hall BD, et al. A pattern of craniofacial and limb defects secondary to aberrant tissue bands. J Pediatr. 1974;84:90–95.)*

Table 118.3 Selection of Patients for Fetal Repair

LEVEL OF CERTAINTY	DIAGNOSIS
DIAGNOSTIC CERTAINTY/PROGNOSTIC CERTAINTY	
Genetic problems	Trisomy 13, 15, or 18 Triploidy
Central nervous system abnormalities	Anencephaly/acrania Holoprosencephaly Large encephaloceles
Heart problems	Acardia Inoperable heart anomalies
Kidney problems	Potter syndrome/renal agenesis Multicystic/dysplastic kidneys Polycystic kidney disease
DIAGNOSTIC UNCERTAINTY/PROGNOSTIC CERTAINTY	
Genetic problems	Thanatophoric dwarfism or lethal forms of osteogenesis imperfecta
Early oligo/anhydramnios and pulmonary hypoplasia	Potter syndrome with unknown etiology
Central nervous system abnormalities	Hydranencephaly
	Congenital severe hydrocephalus with absent or minimal brain growth
Prematurity	<23 weeks' gestation
PROGNOSTIC UNCERTAINTY/BEST INTEREST	
Genetic problems	Errors of metabolism that are expected to be lethal even with available therapy
Mid oligo/anhydramnios	Renal failure requiring dialysis
Central nervous system abnormalities	Complex or severe cases of meningomyelocele Neurodegenerative diseases, such as spinal muscular atrophy
Heart problems	Some cases of hypoplastic left heart syndrome Pentalogy of Cantrell (ectopia cordis)
Other structural anomalies	Some cases of giant omphalocele Severe congenital diaphragmatic hernia with hypoplastic lungs Idiopathic nonimmune hydrops Inoperable conjoined twins Multiple severe anomalies
Prematurity	23-24 weeks' gestation

From Leuthner SR. Fetal palliative care. *Clin Perinatol* 2004;31:649–665. Table 1.

all available treatment options. This collaborative and multidisciplinary family-centered approach allows for the development of a management plan that may include fetal surgery or intervention, enhanced monitoring of the fetus and mother, and coordination of complex deliveries involving multidisciplinary delivery teams and specialized equipment as required for EXIT to ECMO, EXIT to airway, EXIT to tumor resection, delivery to cardiac catheterization, and procedures on placental support.

In some highly specialized fetal centers, delivery may be facilitated with the neonatal intensivists, perinatal anesthesiologist, and pediatric surgical care teams present in the same location to permit expert stabilization and resuscitation of the neonate. The benefits range from the psychological benefits of avoiding maternal-infant separation as well as improved outcomes in diagnoses such as CDH, in which early stabilization of the neonate is critical to minimize pulmonary hypertensive crisis.

Finally, but equally importantly, not all severely affected fetuses will have available therapies in utero or after birth. In these lethal situations, fetal care planning will provide support for the family and a plan for delivery room or nursery palliative care (Table 118.3) (see Chapter 8).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 119

The High-Risk Infant

Erik Brandsma, Lori A. Christ, and Andrea F. Duncan

The term *high-risk infant* designates an infant at greater risk for neonatal morbidity and mortality; many factors can contribute to an infant being high risk (Table 119.1). There are four broad categories of high-risk infants: the preterm infant, infants with special healthcare needs or dependence on technology, infants at risk because of family issues, and infants with anticipated early death.

Table 119.1 Factors in Considering Infants as High Risk for Morbidity or Mortality in the Neonatal Period

BIRTH PARENT DEMOGRAPHIC FACTORS
Maternal age <16 yr or >40 yr
Environmental, economic, social disadvantage, racial discrimination
BIRTH PARENT MEDICAL HISTORY
Genetic disorders
Diabetes mellitus
Hypertension
Asymptomatic bacteriuria
Rheumatologic illness (systemic lupus erythematosus)
Immune-mediated diseases
Long-term medication (see Chapters 117.4 and 117.5)
PREVIOUS PREGNANCY
Intrauterine fetal demise
Neonatal death
Prematurity
Intrauterine growth restriction
Congenital malformation
Incompetent cervix
Blood group sensitization, neonatal jaundice
Neonatal thrombocytopenia
Hydrops
Inborn errors of metabolism
PRESENT PREGNANCY
Vaginal bleeding (abruptio placentae, placenta previa)
Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)
Multiple gestation
Preeclampsia
Premature rupture of membranes
Short interpregnancy time
Poly-/oligohydramnios
Acute medical or surgical illness
Familial or acquired hypercoagulable states
Abnormal fetal ultrasonographic findings
Treatment of infertility
Inadequate prenatal care
Substance use disorder
LABOR AND DELIVERY
Premature labor (<37 wk)
Postdates pregnancy (≥42 wk)
Fetal distress
Breech presentation
Meconium-stained fluid
Nuchal cord
Cesarean delivery
Forceps or vacuum assisted delivery
Apgar score <4 at 5 min
NEONATE
Birthweight <2,500 g or >4,000 g
Birth <37 wk or ≥42 wk of gestation
Small or large for gestational age
Respiratory distress, cyanosis
Congenital malformation
Pallor, plethora, petechiae

All high-risk infants require closer evaluation and/or treatment by experienced physicians and nurses. This often starts before delivery and continues in the delivery room and through a neonatal intensive care unit (NICU) stay (see Chapter 121). Regionalized care for infants is based on the acuity of care that can be provided at hospitals with different levels of care and whether transport should be undertaken (see Chapter 120). It is important to note that additional care does not stop at time of NICU discharge, and that many high-risk infants also benefit from additional resources and follow-up after discharge from the hospital (see Chapter 119.5).

Twins and higher-order multiples are at increased risk for morbidity and mortality and are discussed in Chapter 119.1, whereas other infants deemed high risk are discussed throughout this textbook. Preterm infants comprise the majority of high-risk infants. Approximately 15 million infants are born preterm (before 37 weeks' gestational age) each year worldwide, accounting for about 1 in every 10 babies born. The World Health Organization (WHO) defines infants born before 28 weeks' gestational age as *extremely preterm* infants, infants born between 28 and 31 6/7 weeks as *very preterm* (see Chapter 119.2), and infants born between 32 and 36 6/7 weeks as *moderate to late preterm* infants (see Chapter 119.3). Risk of both morbidity and mortality increases with earlier gestational age. Gestational age, birthweight, and gender are all important factors that impact neonatal mortality (Fig. 119.1). The **highest risk** of neonatal and infant mortality occurs in infants with birthweight <1,000 g and/or with gestational age <28 weeks. The **lowest risk** of neonatal mortality occurs in infants with birthweight of 3,000-4,000 g and a gestational age of 39-41 weeks. As birthweight increases

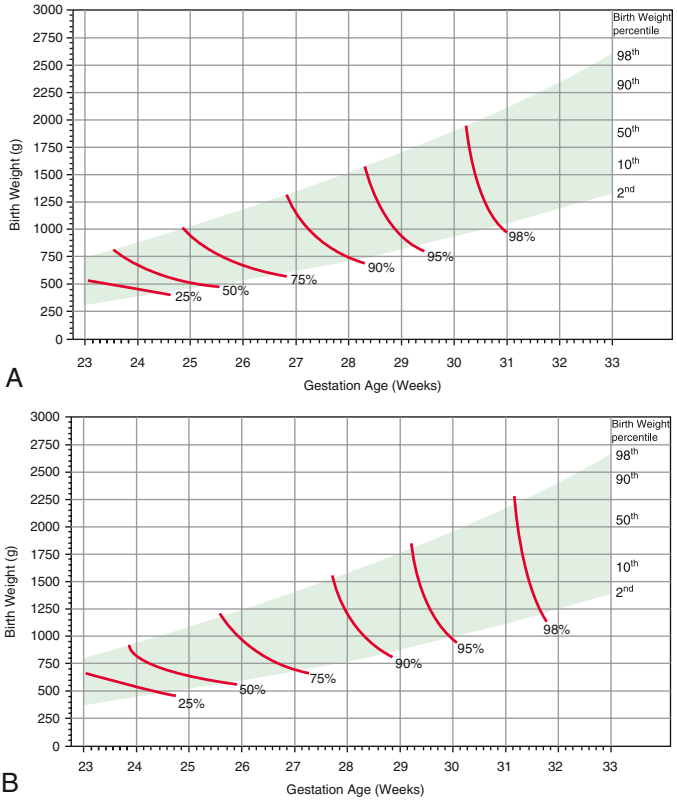

Fig. 119.1 Contour plot of predicted survival according to gestational age, birthweight, and gender. **A**, Female. **B**, Male. The contour lines join combinations of gestational age and birthweight of equal estimated probability of survival. Birthweight percentiles are shown for information. Data based on singleton infants born in the United Kingdom between January 2008 and December 2010 who survived to NICU admission. *(From Manktelow BN, Seaton SE, Fields DJ, et al. Population-based estimates of in-unit survival for very preterm infants. Pediatrics. 2013;131:e425e432. Fig. 2.)*

from 400 to 3,000 g and gestational age increases from 23 to 39 weeks, a logarithmic decrease in neonatal mortality occurs. Once birthweight exceeds 4,000 g and/or gestational age exceeds 42 weeks, the incidence of neonatal morbidities and mortality increases (see Chapter 119.4).

119.1 Multiple-Gestation Pregnancies

Lori A. Christ

CLASSIFICATION OF TWINS

Monozygotic vs Dizygotic Twins

Traditionally, twins have been classified as either **monozygotic** (originating from one ovum fertilized by one sperm in a single fertilization event that then results in postzygotic division of the conceptus into two embryos) or **dizygotic** (originating from two fertilization events each occurring when a single ovum is fertilized by a single sperm). Identifying twins as monozygotic or dizygotic is useful in determining the relative influence of heredity and environment on human development and disease. Detailed blood typing, gene analysis, or tissue (human leukocyte antigen) typing can be used for zygosity testing (an exception being blood typing in cases of **chimeric** twins, where one or both twins contain distinct cell lines from multiple zygotes). While often referred to as "identical" twins, physical and cognitive differences may still exist between monozygotic twins due to differences in the in utero environment, the mitochondrial genome, in posttranslational gene product modification, or in the epigenetic modification of nuclear genes in response to environmental factors.

Chorionicity and Amnionicity

Twins can also be classified by the number of chorions and amnions in the pregnancy. Dizygotic twins largely result in **dichorionic, diamniotic** pregnancies, although rarely may result in atypical twinning (see later). The chorionicity and amnionicity of monozygotic twins depends on the timing of fission of the zygote. One-third of monozygotic twins are dichorionic and diamniotic, and result from splitting on embryonic day 1-3. **Monochorionic**, diamniotic twins result from splitting on embryonic day 3-8, and monochorionic, **monoamniotic** twins result from splitting on day 8-13. Determination of amnionicity and chorionicity are not reliable ways of determining zygosity. An apparently single placenta may be present with either monozygotic or dizygotic twins, but inspection of a dizygotic placenta usually reveals that each twin has a separate chorion that crosses the placenta between the attachments of the cords and two amnions. Separate or fused dichorionic placentas may be disproportionate in size, resulting in growth restriction or malformation of the fetus attached to the smaller placenta or the smaller portion of the placenta.

Incidence

Differences in the incidence of twins worldwide mainly involve dizygotic twins, as monozygotic twinning appears to be independent of heritable factors. In 2019 the U.S. final natality report recorded a twin rate of 32.1 per 1,000 live births, which has continued to decline after an all-time high in 2014. Increases in monozygotic and dizygotic twinning had been associated with advanced maternal age (AMA) and the use of assisted reproductive technologies (ARTs). The rate of triplets and higher-order multiple births was 87.7 per 100,000 live births in the United States and has continued to decline since 1998. The use of single-embryo transfer in ART has decreased the numbers of triplet births and higher-order multiples.

ETIOLOGY

Dizygotic twins result from polyovulation, or the release of more than one ovum at a single ovulation. Polyovular pregnancies are more frequent after the second pregnancy, with increasing maternal age, and in families with a history of dizygotic twins. They may result from simultaneous maturation of multiple ovarian follicles, but follicles containing two ova have also been described as a genetic trait leading to twin pregnancies. Twin-prone women have higher levels of gonadotropin. Polyovular pregnancies occur in many women treated for infertility with ovarian stimulants such as clomiphene or gonadotropins.

The etiology of monozygotic twinning is unknown, but there are two prevailing theories. In the classic **fission theory**, twinning results from the splitting of a single conceptus, with the timing of splitting resulting in differing amnionicity and chorionicity (i.e., the earlier the fission occurs, the more likely the twins are to be diamniotic dichorionic) (Fig. 119.2). However, this theory fails to account for several forms of atypical twinning, including the occurrence of **diamniotic dichorionic monozygotic** twinning after single-embryo transfer in the

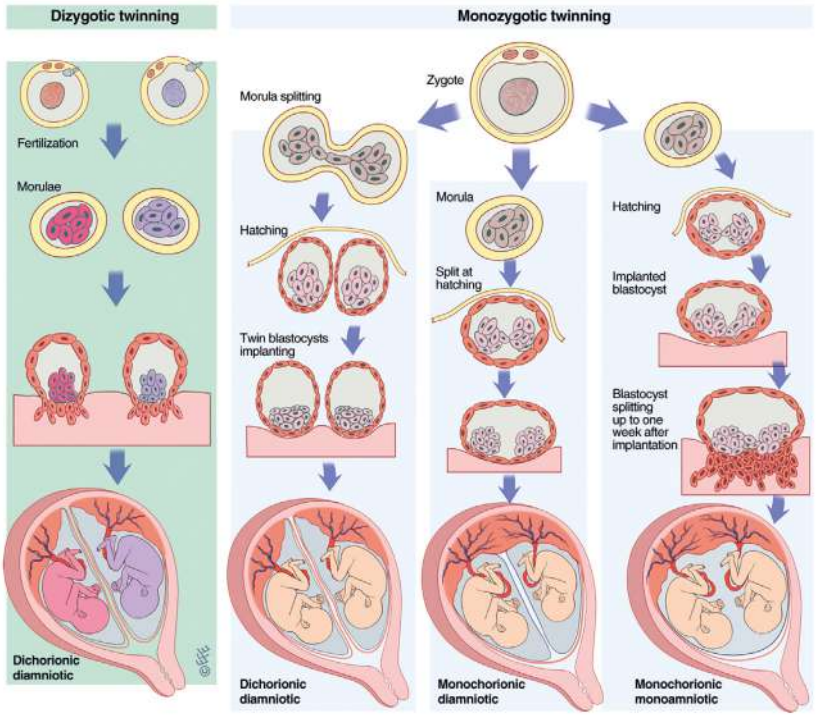

Fig. 119.2 Classical fission theory of twinning. Dizygotic twins result from two distinct fertilization events, with dichorionic diamniotic twins each developing to become a genetically distinct individual. Monozygotic twins result from postzygotic splitting of the product of a single fertilization event. Splitting on days 1-3 (up to the morula stage) results in dichorionic diamniotic twins, on days 3-8 (during which blastocyst hatching occurs) in monochorionic diamniotic twins, on days 8-13 in monochorionic monoamniotic twins. *(Illustration copyright LeventEfe, CMI. www.leventefe.com.au.)*

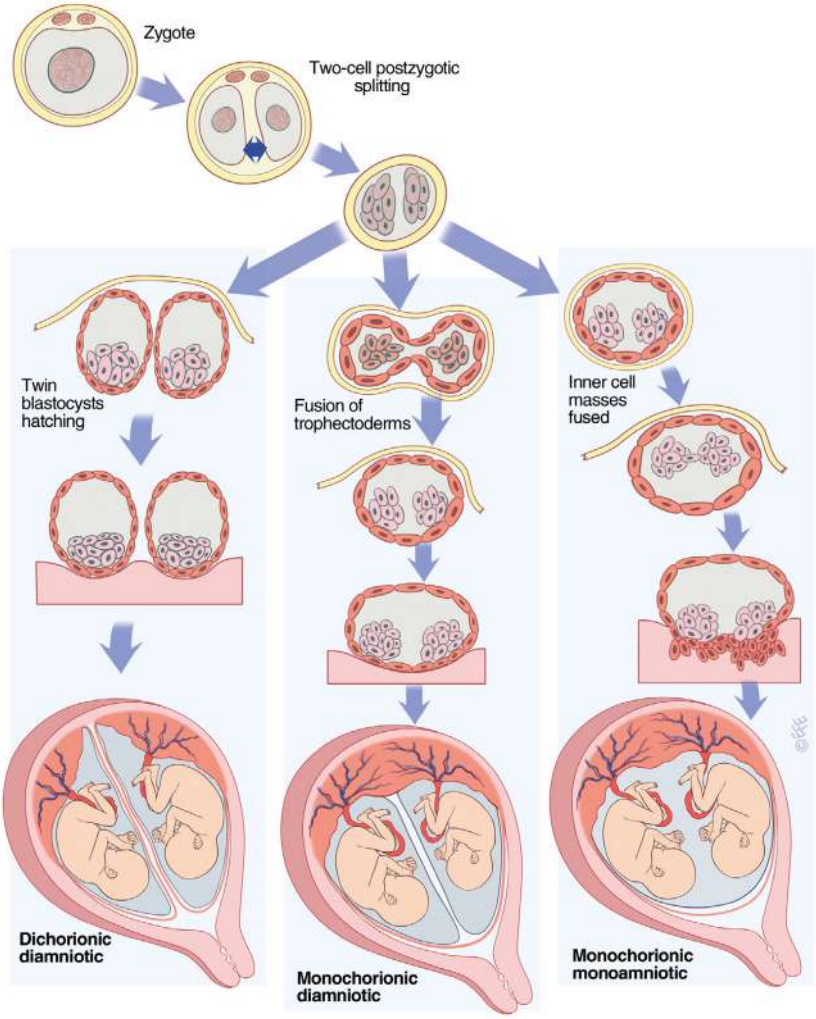

Fig. 119.3 Fusion theory of monozygotic twinning. Splitting occurs at the postzygotic two-cell stage, with each cell forming a distinct individual. If twin blastocysts hatch from the zona pellucida together, dichorionic diamniotic twins will result. If the two trophectoderms fuse before hatching and the inner cell masses are separated within the shared trophectoderm, monochorionic diamniotic twins will result. If the inner cell masses are fused and separated later, monochorionic monoamniotic twins will result. *(Illustration copyright LeventEfe, CMI. www.leventefe.com.au)*

late blastocyst state, phenotypically discordant monozygotic twins, and asymmetrically attached conjoined twins. An alternate **fusion theory** of twinning has been proposed to account for this discrepancy, in which the inner cell masses of trophectoderm fuse after the initial two-cell splitting stage (Fig. 119.3).

Atypical Twinning

Conjoined twins occur in 1 in 50,000 pregnancies and 1 in 250,000 live births. Theoretically, they result from later fission of a single zygote (10-14 days) or from fusion of two zygotes (as proposed for asymmetrically attached conjoined twins). Most conjoined twins are female. The prognosis for symmetrically conjoined twins depends on the possibility of surgical separation, which in turn depends on the extent to which vital organs are shared. The site of connections varies, as follows: thoracoomphalopagus (28% of conjoined twins), thoracopagus (18%), omphalopagus (10%), craniopagus (6%), and incomplete duplication (10%). The term *parasitic twin* has historically been used to describe the smaller and less completely developed member of a pair of conjoined twins; this twin has typically had embryonic demise but remains vascularized by the surviving *independent* twin (the **autocyte**). For asymmetrically attached conjoined twins in whom one twin is dependent on the cardiovascular system of the intact autocyte (**exoparasitic twins**, 1 in 1 million live births) survival of the autocyte depends on the feasibility of excising the *exoparasitic* twin. For **endoparasitic twins** (*fetus in fetu,* 1 in 500,000 live births) in whom one (or more) fetus exists as a benign mass in the autocyte, survival of the autocyte is unaffected. **Superfecundation,** or fertilization of an ovum by an insemination that takes place after one ovum has already been fertilized, and **superfetation**, or fertilization and subsequent development of an embryo when a fetus is already present in the uterus, have been proposed as explanations for differences in size and appearance of certain twins at birth.

Diagnosis

A prenatal diagnosis of pregnancy with twins is suggested by a uterine size that is greater than that expected for gestational age, auscultation of two fetal heartbeats, and/or elevated maternal serum α-fetoprotein (AFP) or human chorionic gonadotropin (hCG) levels. It is confirmed by ultrasonography. Physical examination of twins is necessary but not sufficient to determine zygosity of twins. In the event that congenital anomalies are present or there are transfusion or transplantation considerations, genetic testing of zygosity should be performed. Although noninvasive prenatal testing (NIPT) is becoming more common, the results should be interpreted with caution in multiple-gestation pregnancies until normative values are better established.

Complications

Twin and higher-order pregnancies are associated with poorer neonatal and perinatal outcomes compared with singleton pregnancies of the same gestation. Severe maternal morbidities and death are also

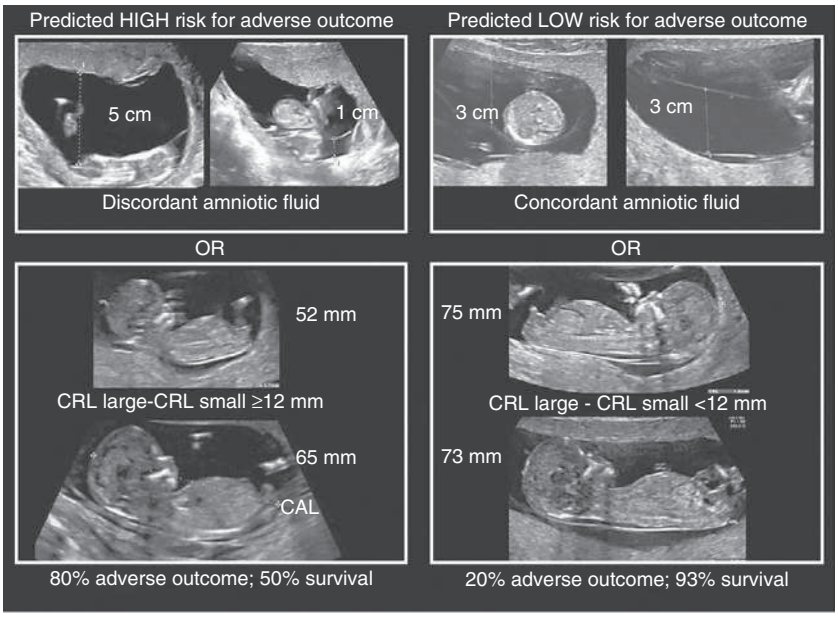

Fig. 119.4 Representation of first-trimester risk assessment for the development of discordant growth, twin-twin transfusion syndrome (TTTS), or intrauterine demise. Discordant amniotic fluid in the first trimester generally corresponded with deepest vertical pockets ≤3 cm in one sac and ≥6.5 cm in the other. Discordance in crown-rump length (CRL) was present if the difference was ≥12 mm. *(From Lewi L, Gucciardo L, Van Mieghem T, et al. Monochorionic diamniotic twin pregnancies: natural history and risk stratification. Fetal Diagn Ther. 2010;27:121–133.)*

twice as likely in twin pregnancies worldwide compared with singleton pregnancies.

Most twins are born prematurely, which contributes to additional neonatal and childhood morbidity and mortality. Spontaneous single intrauterine demise occurs at a rate of about 6% of all twin pregnancies. Twin-twin transfusion syndrome (TTTS) and early-onset discordant growth are associated with an overall worse prognosis (see Chapter 118). The perinatal mortality of twins is about four times that of singletons, with **monochorionic** twins being particularly at risk. **Monochorionic** twins have an increased risk of a demised twin in utero. The surviving twin has a greater risk for cerebral palsy and other neurodevelopmental sequelae. **Monoamniotic** twins have an increased likelihood of cord entanglement, which may lead to asphyxia. Twins are at greater risk for congenital malformations, with up to 25% of monozygotic twins being affected. Theoretically, the twin delivered second is at higher risk of anoxia than the first because the placenta may separate after birth of the first twin and before birth of the second. In addition, delivery of the second twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the first twin's birth.

Triplet or higher-order births are associated with an increased risk of death or neurodevelopmental impairment compared with extremely low birthweight (ELBW) singleton and twin infants after controlling for gestational age. The mortality for multiple gestations with ≥4 fetuses is excessively high for each fetus. Because of this poor prognosis, selective fetal reduction has been offered as a treatment option.

Twin-Twin Transfusion Syndromes

Placental vascular anastomoses occur with high frequency in **monochorionic** twins (see Chapter 118). In monochorionic placentas, the fetal vasculature is usually joined, sometimes in a very complex manner. They are usually balanced and neither twin is appreciably affected. Artery-to-artery communications cross over placental veins, and when anastomoses are present, blood can readily be stroked from one fetal vascular bed to the other. Vein-to-vein communications are similarly recognized but are less common. A combination of artery-to-artery and vein-to-vein anastomoses is associated with the condition of **acardiac fetus**. This rare lethal anomaly (1 in 35,000) is secondary to the **twin reversed arterial perfusion (TRAP) syndrome**. In utero radiofrequency or laser ablation of the anastomosis or cord occlusion can be used to treat heart failure in the surviving twin. However, death of the autocyte is reported in up to 75% of cases. In rare cases, one umbilical cord may arise from the other after leaving the placenta, and the twin attached to the secondary cord usually is malformed or dies in utero.

Table 119.2 Characteristic Changes in Monochorionic Twins with Uncompensated Placental Arteriovenous Shunts

TWIN ON:	
ARTERIAL SIDE—DONOR	**VENOUS SIDE—RECIPIENT**
Prematurity	Prematurity
Oligohydramnios	Polyhydramnios
Intrauterine growth restriction	Hydrops
Pale	Plethoric
Anemic	Polycythemic
Hypovolemic	Hypervolemic
Hypoglycemic	Cardiac hypertrophy
Microcardia	Myocardial dysfunction
Glomeruli small or normal	Glomeruli large Tricuspid valve regurgitation Right ventricular outflow obstruction
Arterioles thin walled	Arterioles thick walled

In **twin-twin transfusion syndrome (TTTS)**, an artery from one twin acutely or chronically delivers blood that is drained into the vein of the other. The latter develops polyhydramnios and polycythemia, and the former has oligohydramnios, anemia, and growth restriction (Fig. 119.4). TTTS is more common in monozygotic twins and affects up to 30% of monochorionic twins. Death of the donor twin in utero may result in generalized fibrin thrombi in the smaller arterioles of the recipient twin, possibly as the result of transfusion of thromboplastin-rich blood from the macerating donor fetus. Disseminated intravascular coagulation (DIC) may develop in the surviving twin. Table 119.2 lists the more frequent changes associated with a large shunt. Preterm birth and/or death of the surviving twin is also highly likely. **Treatment** of this highly lethal problem includes aggressive amnioreduction for polyhydramnios, selective twin termination, and most often, laser or fetoscopic ablation of anastomosis (Fig. 119.5).

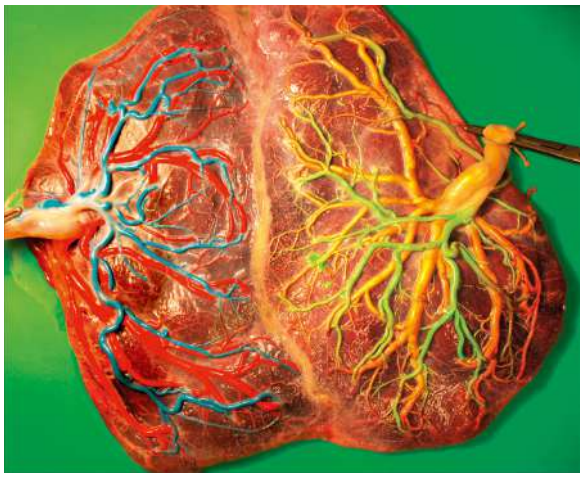

Fig. 119.5 Color-dye-stained twin-to-twin transfusion syndrome placenta that was treated using the Solomon technique. Blue and green dye are used to stain the arteries, and pink and yellow dye are used to stain the veins. After identification and coagulation of each individual anastomosis, the complete vascular equator is coagulated from one placental margin to the other. *(From Slaghekke F, Lopriore E, Lewi L, et al. Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomized controlled trial, Lancet. 2014;383:2144–2150. Fig. 3.)*

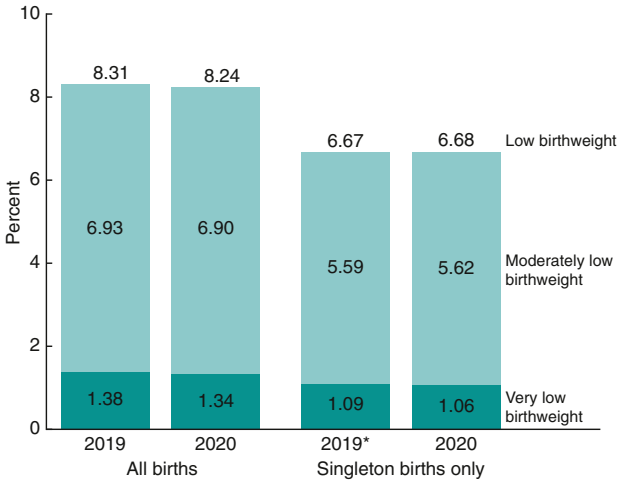

SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

Fig. 119.6 Total and singleton low birthweight rates: United States, 2019 and 2020. *Numbers do not add to total du to rounding. *(From Osterman M, Hamilton B, Martin JA, Driscoll AK, Valenzuela CP. Births: Final Data for 2020. Natl Vital Stat Rep. 2021;70[17]:1–50. Fig. 3.)*

Management

Prenatal detection of a multiple gestation pregnancy enables the obstetrician and pediatrician to anticipate complications. The risk of multiple-gestation pregnancies due to ART may be reduced by elective single-embryo transfers. Asymptomatic early cervical dilation may be managed with cerclage, which is 50% effective in preventing delivery before 28 weeks' gestation. Elective delivery of twins at 37 weeks (or earlier for **monochorionic**, **monoamniotic** twins) reduces the complication rate for the fetuses and the birth parent. Furthermore, in twin pregnancies between 32 and 39 weeks' gestation, planned vaginal delivery is preferred if the first twin is in the cephalic presentation. Close observation and attendance by a pediatric team are indicated in the immediate neonatal period so that prompt treatment of asphyxia or fetal transfusion syndrome can be initiated. The decision to perform an immediate blood transfusion in a severely anemic "donor" twin or a partial exchange transfusion of either twin due to anemia in the "donor" or polycythemia in the "recipient" twin must be based on clinical judgment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

119.2 Extremely and Very Preterm Infants

Lori A. Christ and Erik Brandsma

Traditionally, the delivery date is determined 280 days after the last menstrual period (LMP). However, only 4% of pregnant women deliver at 280 days, and only 70% deliver within 10 days of the estimated delivery date.

Infants born before 37 weeks from the first day of the LMP are termed *premature* by WHO. Infants born before 28 weeks' gestation are **extremely preterm,** also referred to as **extremely low gestational age newborns (ELGANs)**; whereas infants born between 28 and 31 weeks and 6 days' gestation are **very preterm**. Moderate and late preterm infants (born between 32 and 36 week 6 days' gestation) are discussed in Chapter 119.3.

In addition to classification by gestational age, classification is also based on birthweight. **ELBW** is used to describe infants with a birthweight <1,000 g, **very low birthweight (VLBW)** describes infants 1,000-1,500 g, and **low birthweight (LBW)** describes infants <2,500 g at birth. Birthweight, in general, is a proxy for gestational age, but in the cases of intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) infants, birthweight can sometimes be misleading for true gestational age and is an additional risk factor for comorbidities of prematurity (see Chapter 119.4).

INCIDENCE

Preterm birth, or birth before 37 weeks of gestation, occurs at a rate of approximately 11% worldwide, adding up to a total of 15 million preterm births annually. Significant variations in preterm birthrates exist between countries, with an approximate rate of 10% in the United States. The U.S. preterm birthrate declined 1% in 2020 to 10.09%. Most of this decline is due to a decrease in rate of late preterm births (7.40% of all births in 2020) and in preterm births less than 34 weeks' gestation (2.70%). These results are reflected in birthweight-specific categories (Fig. 119.6). Disparities in preterm birthrates continue to exist, ranging from a high of 14.39% of babies born to non-Hispanic black mothers to a low of 8.72% of babies born to non-Hispanic Asian mothers.

ETIOLOGY

The etiology of preterm birth is multifactorial and involves complex interactions between fetal, placental, uterine, and maternal factors. In the setting of maternal or fetal conditions that prompt early delivery, as well as placental and uterine pathology, causes of preterm birth can sometimes be identified (Table 119.3). Most preterm births are *spontaneous* without an identifiable cause. AMA, maternal health conditions, history of previous preterm delivery, short interpregnancy interval, and lower socioeconomic status (SES) have all been associated with preterm birth. Racial disparities also exist and can only be partially predicted when factoring in education and income level. Large population studies have found associations between maternal genetics and epigenetics and preterm birth. Gestational duration and actual preterm birth have been noted with genetic variants in the maternal genome. Many of these genes have roles in regulation of the estrogen receptor, uterine development, maternal nutrition, or vascular reactivity.

ASSESSMENT OF GESTATIONAL AGE

Ultrasound measurement of fetal crown-rump length at 11-14 weeks' gestation remains the most accurate method of gestational age estimation. Estimates based on ultrasound at later gestation are less accurate, but may be improved with newer methods and likely superior to postnatal assessment. With insufficient prenatal care or discrepancies between birthweight and predicted gestational age at birth, it remains helpful to be able to assess infants for an estimated gestational age. With a careful physical exam, one may be able to distinguish SGA and IUGR infants

Table 119.3 Identifiable Risk Factors for Preterm Birth

FETAL
Fetal distress
Multiple gestation
Erythroblastosis
Nonimmune hydrops
Polyhydramnios
PLACENTAL
Placental dysfunction
Placenta previa
Placental abruption
UTERINE
Bicornuate uterus
Incompetent cervix (premature dilation)
MATERNAL
Previous preterm birth
Preeclampsia
Experiencing racism
Chronic medical illness (cyanotic heart disease, renal disease, thyroid disease)
Short interpregnancy interval
Infection (*Listeria monocytogenes*, group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
Obesity
Substance use disorder
Extremes of maternal age
OTHER
Premature rupture of membranes
Polyhydramnios
Iatrogenic due to factors listed above
Assisted reproductive technology
Trauma

Physical maturity

	−1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm:−1 <40 mm: −2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola–no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (–1), tightly (–2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Fig. 119.7 Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.)*

from preterm infants. Compared with a premature infant of appropriate weight, an infant with IUGR has a reduced birthweight and may appear to have a disproportionately larger head relative to body size; infants in both groups lack subcutaneous fat. Neurologic maturity (nerve conduction velocity) in the absence of asphyxia correlates with gestational age despite reduced fetal weight. Physical signs may be useful in estimating gestational age at birth. The commonly used **Ballard scoring system** is accurate to within 2 weeks of actual gestational age (Figs. 119.7-119.9).

Neuromuscular maturity

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140-180°	110-140°	90-110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Fig. 119.8 Neuromuscular criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.)*

Maturity Rating

Score	Weeks
– 10	20
– 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Fig. 119.9 Maturity rating. The physical and neurologic scores are added to calculate gestational age. *(From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.)*

NURSERY CARE

At birth, the general measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administer vitamin K are the same for premature infants as for those of normal weight and maturity (see Chapter 123). Additional considerations are the need for (1) thermal control and monitoring of the heart rate and respiration, (2) advanced respiratory support, and (3) special attention to the details of fluid requirements and nutrition that may in turn lead to considerations of IV access. Preterm infants are at an increased risk of early and late-onset neonatal sepsis compared with their term counterparts. Routine procedures that disturb these infants may result in hypoxia and stress. The benefits of regular and active participation by the parents in the infant's care in the nursery and the question of prognosis for later growth and development require special consideration.

Thermal Control

Avoidance of hypothermia and hyperthermia decreases the risk of morbidity and mortality in ELBW and VLBW infants. Neonates in general, and ELBW and VLBW infants to an even greater extent, are at increased risk of heat loss compared with older children due to an

increased body surface/weight ratio, decreased epidermal and dermal skin thickness, minimal subcutaneous fat, and an immature nervous system.

Preterm infants should be kept in a **neutral thermal environment**. This environment comprises a set of thermal conditions, including air and radiating surface temperatures, relative humidity, and airflow, at which heat production (measured experimentally as oxygen consumption) is minimal and the infant's core temperature is within the normal range. The neutral thermal environment is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity, while minimizing heat loss through conduction, convection, radiation, and evaporation. The optimal environmental temperature for minimal heat loss and oxygen consumption for an unclothed infant is one that maintains the infant's core temperature at 36.5–37.0°C (97.7–98.6°F). The smaller and less mature the infant, the higher is the environmental temperature required. Infant warmth can be maintained by heating the air to a desired temperature or by servo-control. Continuous monitoring of the infant's temperature is required to maintain optimal body temperature. **Kangaroo care,** especially in LBW infants, with direct skin-to-skin contact between infant and parent, with a hat and blanket covering the infant, is to be encouraged (and not delayed), without untoward effects on thermoregulation.

Maintaining increased relative humidity for preterm infants in the first weeks of life aids in stabilizing body temperature by reducing heat loss at lower environmental temperatures. The ideal humidity and duration of increased humidity at a specific gestational age is not known, but typically is maintained between 60% and 80% for a week. Humidification of inspired air for infants requiring respiratory support prevents drying and irritation of the lining of respiratory passages and aids in thinning viscid secretions and reducing insensible water loss. Humidification should be gradually weaned after the first week of life to promote skin barrier formation and to reduce the risk of microbial growth associated with prolonged excessive humidity. The infant should also be weaned and then removed from the incubator or radiant warmer when the gradual change to the atmosphere of the nursery does not result in a significant change in the infant's temperature, color, activity, vital signs, or rate of weight gain.

Oxygen Administration

Administering oxygen to reduce the risk of injury from hypoxia and circulatory insufficiency (risk of cerebral palsy, death) must be balanced against the risk of hyperoxia to the eyes **(retinopathy of prematurity [ROP])** and injury to the lungs due to generation of free radicals. For ELBW infants at birth, guidelines should be followed to determine need for supplemental oxygen during resuscitation to maintain goal O_2 saturation limits (see Chapter 123).

After the initial resuscitation period, ideal target O_2 saturation limits for ELBW infants should be within the range of 90–95% for most infants.

Nutrition for the High-Risk Infant

In the absence of early parenteral and enteral nutritional support, deficits in protein, energy, and micronutrients will quickly accrue, placing the infant at risk for poor growth and neurodevelopmental outcomes. The goals of early nutritional support for extremely premature infants include approximating the rate and composition of growth for a normal fetus at the same postmenstrual age. Achieving this goal requires an understanding of the intrauterine growth rate to be targeted as well as the unique nutrient requirements of premature infants. Strategies to prevent growth failure include a combined approach of early parenteral and enteral nutrition, fortification of human milk, and the use of standardized feeding guidelines. Careful monitoring of weight gain, length, and head circumference using appropriate growth curves and timely biochemical assessment of bone health and potential nutritional deficiencies is paramount. Consultation with an experienced neonatal dietitian is important to achieve optimal outcomes.

Early Parenteral Nutrition

In the absence of IV amino acids, extremely premature infants lose 1–2% of body protein stores per day. IV amino acids and dextrose should be started immediately after birth. Many units use a *starter* or *stock* solution of amino acids and dextrose to accomplish this goal in infants weighing <1,500 g. Ideally at least 2 g/kg of amino acids should be given in the first 24 hours after birth, with a goal of at least 3 g/kg within 24-48 hours after birth. To meet total energy requirements, up to 3 g/kg of IV lipids will also be needed.

Benefits of Human Milk

Maternal milk is the preferred source of enteral nutrition for premature infants and is associated with decreased in-hospital morbidity, including lower rates of necrotizing enterocolitis (NEC), late-onset sepsis, bronchopulmonary dysplasia (BPD), and severe ROP. Maternal milk feeding is also associated with superior neurodevelopmental outcomes at 18- and 30-months corrected age compared to infants fed premature formula. Donor human milk is increasingly being used when maternal milk is not available, but it is typically lower in protein and energy content than preterm maternal milk and may result in suboptimal growth unless adequately fortified. Although donor human milk has been associated with a reduction in NEC, the impact of donor human milk on neurodevelopmental outcomes remains unclear.

Enteral Nutrition

Early enteral feedings are recommended in ELBW and VLBW infants, typically beginning between 6 and 48 hours of life with some period of trophic/minimal enteral feeding volume. Feedings are typically advanced slowly (15-30 mL/kg/day) with a target goal of delivering approximately 110-135 kcal/kg/day and 3.5-4.5 g protein/kg/day. To accomplish these goals, human milk must be fortified, or a premature formula can be given. Additional supplements such as vitamins, iron, or other micronutrients may be required and should be based on ongoing assessment and in consultation with a neonatal dietitian.

Standardized Feeding Guidelines

Standardized feeding guidelines should be developed incorporating evidence-based strategies for the provision of parenteral and enteral nutrition in ELBW and VLBW infants, including a plan to manage feeding intolerance. Regardless of the specific protocol, having a feeding guideline leads to improved outcomes (e.g., time to regain birthweight, time to reach full enteral nutrition), decreased rates of late-onset sepsis and NEC, improved growth at 36 weeks' postmenstrual age, and reduced length of hospital stay.

Transitioning to Discharge Nutrition

The earlier an infant is born before expected, the greater the likelihood that not all nutritional deficits will be resolved before hospital discharge. Regardless of weight gain during the initial hospital stay, there is strong evidence for improved bone mineralization with the use of higher concentrations of calcium and phosphorus after discharge. Fortified human milk or preterm formula with higher concentrations of protein, minerals, and trace elements is often recommended after discharge. An individualized approach to postdischarge nutrition should be developed to transition from the NICU and communicated with the outpatient pediatrician who will be caring for the infant.

Prevention of Infection

Extremely preterm infants have an increased susceptibility to infection; thus meticulous attention to infection control is required. Prevention strategies include strict compliance with handwashing and universal precautions, minimizing the risk of catheter contamination and duration, meticulous skin care, encouraging early appropriate advancement of enteral feeding, education and feedback to staff, and surveillance of nosocomial infection rates in the nursery. Although no one with an active infection should be permitted in the nursery, the risks of infection must be balanced against the disadvantages of limiting the infant's contact with the family. Early and frequent participation by parents in the nursery care of their infant does not increase the risk of infection when preventive precautions are maintained.

Preventing transmission of infection from infant to infant is difficult because often neither term nor premature newborn infants have clear clinical evidence of an infection early in their course. When epidemics occur within a nursery, cohort nursing and isolation rooms should be used. **Hand hygiene** is of upmost importance. Because premature infants have immature immune functions, some will develop nosocomial infection even when all precautions are followed.

Awareness of overutilization of antibiotics may mitigate associated complications both at the population level (cost and antibiotics resistance) and for the individual patient (alteration of the microbiome).

Routine **immunizations** should be given on the regular schedule based on chronological age at standard doses.

Transfusion Medicine

Premature infants are at increased risk of anemia due to impaired erythropoiesis and iatrogenesis due to frequent laboratory sampling. Most infants with a birthweight less than 1,000 g admitted to the NICU receive at least one blood transfusion during their stay. The need for repeated transfusion can be minimized by a thoughtful approach to laboratory sampling and establishing set hemoglobin thresholds for transfusions. A multicenter randomized controlled trial in infants 22 weeks 0 days to 28 weeks 6 days found that a lower transfusion threshold resulted in fewer transfusions per infant without an impact on neurodevelopment at 22 to 26 months' corrected gestational age. The need for transfusions depends in part on the cardiopulmonary stability of the patient, postnatal age, birthweight, and the etiology of the anemia. For severe cardiopulmonary disease, transfusions are recommended to maintain the hematocrit between 40% and 45%. For asymptomatic stable neonates with anemia of prematurity, maintaining the hematocrit at ~25% is acceptable.

Transfusion of platelets is another common practice in the NICU. Premature infants are at high risk for intraventricular hemorrhage in the first week of life, which historically prompted platelet transfusion at thresholds now considered safe. Additionally, preterm infants may also develop thrombocytopenia in the setting of severe bleeding or infection. A multicenter randomized controlled trial found that infants randomized to a higher platelet transfusion threshold ($50{,}000/m^3$) paradoxically had a higher rate of death or severe bleeding that infants randomized to a lower threshold ($25{,}000/m^3$).

IMMATURITY OF DRUG METABOLISM

Great care must be taken when prescribing and dosing medications for premature infants (Table 119.4). Renal clearance of almost all substances excreted in the urine is diminished in newborn infants, and to even a greater extent in premature infants. The glomerular filtration rate rises with increasing gestational age; therefore drug dosing recommendations vary with age. For drugs primarily excreted by the kidneys, longer intervals between dosages are often needed with increasing degree of prematurity. Drugs that are detoxified in the liver or require chemical conjugation before renal excretion should also be given with caution and in doses smaller than usual.

Many drugs apparently safe for adults on the basis of toxicity studies may be harmful to newborns, especially premature infants. Oxygen and a number of drugs have proved toxic to premature infants in amounts not harmful to term infants. Thus, administering any drug, particularly in high doses, that has not undergone pharmacologic testing in premature infants should be undertaken carefully after risks have been weighed against benefits.

Table 119.4 Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
$NaHCO_3$	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Furosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones
Heparin (*not* low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

MORBIDITY AND MORTALITY

Rates of neonatal morbidity and mortality are high in extremely preterm infants, and risks increase with decreasing gestational age and lower birthweight (Table 119.5). Data on extremely preterm infants born between 2003 and 2007 found that 42% of VLBW infants developed BPD, 12% developed ROP requiring treatment, 11% NEC, 36% late-onset sepsis, 16% grade III or IV intraventricular hemorrhage, and 3% periventricular leukomalacia (PVL). Mortality increased with lower gestational age, with a 94% mortality in infants born at 22 weeks and 8% mortality at 28 weeks. The group of extremely preterm infants had a 28% mortality rate, with 37% surviving without a significant neonatal morbidity.

Another study found that morbidity and mortality among VLBW infants decreased between 2000 and 2009. This study was limited to liveborn infants with birthweights of 500-1,500 g. For infants born in 2009, this study found a 12.4% mortality rate; 28% of infants developed BPD, 7% severe ROP, 5% NEC, 15% late-onset sepsis, 6% grade III or IV IVH, and 3% PVL; 51% survived without significant neonatal morbidity.

Outcomes are improving with time; survival among infants born at 22-24 weeks' gestation is ~50–80% in units providing active management. The percentage surviving without neurodevelopmental impairment has also increased. Factors that reduce morbidity and mortality in extremely preterm infants include higher birthweight and gestational age, receipt of antenatal corticosteroids, female sex, singleton pregnancy, and active

Table 119.5 Neonatal Morbidities Associated with Prematurity

RESPIRATORY
Respiratory distress syndrome (hyaline membrane disease)
Bronchopulmonary dysplasia*
Pneumothorax, pneumomediastinum; interstitial emphysema
Congenital pneumonia
Apnea
CARDIOVASCULAR
Patent ductus arteriosus
Hypotension
Bradycardia (with apnea)
HEMATOLOGIC
Anemia (early or late onset)
GASTROINTESTINAL
Poor gastrointestinal function—poor motility
Necrotizing enterocolitis*
Hyperbilirubinemia—indirect and direct
Spontaneous gastrointestinal isolated perforation
METABOLIC-ENDOCRINE
Hypocalcemia
Hypoglycemia
Hyperglycemia
Metabolic acidosis
Hypothermia
Euthyroid but low thyroxine status
Osteopenia
CENTRAL NERVOUS SYSTEM
Intraventricular hemorrhage*
Periventricular leukomalacia*
Seizures
Retinopathy of prematurity*
Deafness
RENAL
Hyponatremia
Hypernatremia
Hyperkalemia
Renal tubular acidosis
Renal glycosuria
Edema
OTHER
Infections* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)

*Major neonatal morbidities.

resuscitation planned at delivery. With improvement in neonatal care, a growing number of centers offer a trial of resuscitation starting at 22 0/7 weeks if that is consistent with parental goals. Outcome prediction tools such as those based on data from the United States (NICHD-VON) or UK (BAPM) and the latter organization's framework to guide management are resources for the clinician that can be used for parental counseling. The prediction tools underscore that extreme prematurity is still associated with significant risk of both mortality and major neonatal morbidities. For infants who survive to discharge, prematurity, as well as neonatal morbidities, put them at increased risk for developmental delays and impairment as they age (see Chapter 119.5). Perinatal centers should develop consensus guidelines regarding an approach to periviable birth to ensure a consistent approach to both maternal and neonatal care. Balanced and unbiased antenatal counseling that includes shared decision-making between neonatologists, obstetricians, and families is imperative.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

119.3 Moderate and Late Preterm Infants

Erik Brandsma

Whereas the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), and the WHO have precise definitions for preterm, term, and postterm births, there has been some debate on defining subcategories of preterm infants. Because outcomes vary widely within broad gestational age range groups, consensus on definitions of subcategories is important. Based on a now widely adopted recommendation from a 2005 National Institutes of Health (NIH) sponsored workshop, infants born at 34 0/7 through 36 6/7 weeks' gestation are considered late preterm. The WHO defines **moderate to late preterm** birth as infants born at 32 0/7 through 36 6/7 weeks' gestation. Therefore most define **moderate preterm** infants as those born at 32 0/7 through 33 6/7 weeks' gestation.

The initial effect of the NIH-sponsored workshop and the resulting 2007 AAP Clinical Report from the Committee on Fetus and Newborn on late preterm infants was encouraging. The report continues to be a resource for pediatricians caring for late preterm infants, listing recommended minimum criteria for their discharge. A 2019 update from the Committee on Fetus and Newborn addresses the concern of the increasing incidence of late preterm birth since 2015.

The risk of morbidity in the individual infant born moderate or late preterm is lower than infants born before 32 weeks of gestation. Because late and moderate preterm births account for approximately 75% and 11.5% of preterm births in the United States, respectively, morbidities in this group continue to be a significant burden on the healthcare system. Etiology of preterm birth is discussed elsewhere (see Chapter 117.2). The majority of moderate and late preterm births are associated with spontaneous preterm labor, preterm premature rupture of membranes (PPROM), and multiple gestation.

MODERATE PRETERM INFANT

Moderate preterm infants are at increased risk for postnatal morbidities, although to a lesser extent and severity than very preterm infants. The most common morbidities associated with preterm birth at this gestational age are temperature instability, respiratory distress, apnea, sepsis, hypoglycemia, feeding difficulties, and hyperbilirubinemia. Moderate preterm infants with birthweight >1,500 g and an unremarkable NICU course are thought to be at minimal risk for IVH and do not routinely need a head ultrasound. Similarly, the AAP does not recommend universal screening for ROP at this gestational age, unless birthweight is below 1,500 g or in select cases for infants with a history of significant cardiopulmonary compromise. Little research has examined moderate preterm infants as an isolated group; more often these infants are grouped with very preterm infants when assessing complications and outcomes. A cohort of approximately 7,000 infants born between 29 and 33 weeks' gestational age were found in a recent study to have a mean hospital stay of 33.3 days. Moderate and late preterm infants are at increased risk of mortality as well. The increased risk of mortality is modest, approximately 10-fold for moderate preterm infants and fourfold for late preterm infants compared to term infants (22 and 8.2 per 1,000 live births, respectively), but because these infants comprise close to 90% of preterm infants overall, this group as a whole contributes significantly to infant mortality.

LATE PRETERM INFANT

As described previously, the overall rate of prematurity has increased gradually since 2015. Most of the increase in overall preterm birthrate can be contributed to infants born late preterm. These infants account for approximately 7.5% of all births and almost three fourths of all preterm births in the United States. Historically, late preterm infants were referred to as *near-term infants,* and the approach to their care was similar to that of term infants. It has been increasingly recognized that late preterm infants have significantly increased morbidity, as well as mortality, compared with their term counterparts. Overall, compared to their term counterparts, late preterm infants have approximately a sevenfold risk of morbidities and fourfold risk of mortality. There is an increased incidence of congenital anomalies in preterm infants, but even when these infants are excluded, late preterm infants continue to have significantly more morbidities. Immediately after birth, there is an increased risk of requiring resuscitation, as well as increased incidence of hypoglycemia, respiratory distress due to respiratory distress syndrome (RDS) or transient tachypnea of the newborn (TTN) apnea, and

difficulty with thermoregulation. Their average birth hospital length of stay is approximately 9 days compared to 2 days for term infants. Additional concerns during this initial hospital stay include feeding difficulties and jaundice. They have a higher rehospitalization rate compared to their term peers and an increased risk of long-term morbidities and even mortality (e.g., sudden infant death syndrome [SIDS]). Some studies suggest a higher risk of lower school readiness at kindergarten and increased risk of academic difficulties in childhood when comparing late preterm infants with term peers.

In addition to universal routine newborn care, the potential morbidities associated with preterm birth need to be addressed. This starts before birth with possible interventions to prevent preterm birth or a course of betamethasone for the pregnant women at risk for preterm birth within 7 days as recommended by ACOG and continues in the delivery room, where measures should be in place to prevent and treat common preterm birth associated morbidities such as hypothermia and hypoglycemia. Whether infants are taken care of in a NICU or in a well-baby nursery, continued vigilance is required to address the potential consequences of physiologic immaturity, such as poor feeding, dehydration, and hyperbilirubinemia. Follow-up visits should occur early and additional visits may be required to ensure the infant thrives. Because of ongoing health risks that the preterm infant faces in infancy and childhood, awareness and documentation of the child's birth history is important. It is paramount that all interventions are implemented equitably, with particular attention to non-Hispanic black and Hispanic women and children, who are currently disproportionally affected by preterm birth and account for the largest increase in late preterm birth.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

119.4 Term and Postterm Infants

Andrea F. Duncan

The ACOG further divides term infants into subgroups: **early term** (37-38 6/7 weeks), **full term** (39-40 6/7 weeks), and **late term** (41-41 6/7 weeks). Many risk factors for term infants put them at higher risk for complications, such as meconium aspiration syndrome (see Chapter 129.1), hemolytic disease of the newborn (see Chapter 140), infant of a diabetic mother (see Chapter 147), and neonatal abstinence syndrome (see Chapter 145). Both SGA and large-for-gestational-age (LGA) are associated with increased morbidities.

SMALL FOR GESTATIONAL AGE AND IUGR

There is an important distinction between the terms **small for gestational age (SGA)** and **intrauterine growth restriction (IUGR)**. SGA is based on physical evaluation of an infant at birth, usually by a pediatrician or neonatologist. If the infant's weight is <10th percentile, the infant is SGA. The diagnosis of SGA does not differentiate between normal biologic growth potential and a pathologic or growth-restricted state in utero. In contrast, IUGR is a prenatal diagnosis to describe a fetus who fails to reach in utero growth potential, often diagnosed by the obstetrician using intrauterine growth curves and measures of compromise (e.g., abnormal Doppler flow measurements) (Fig. 119.10). This measure is independent of growth centile at birth. Therefore not all infants with IUGR are SGA, and, similarly, not all infants who are SGA have IUGR.

Although it is important to understand the difference between SGA and IUGR, many studies evaluate postnatal outcomes based on a diagnosis of either SGA or IUGR.



Fig. 119.10 This is a 36-week male neonate with a birthweight of 1,600 g who was born to a mother with severe preeclampsia. This baby was noted to have asymmetric intrauterine growth restriction (IUGR). Note the loss of fat over the body, visible rib cage, excessive skin folds noted over the whole body, and relatively large head compared to the body. *(From Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clin Med Insights Pediatr. 2016;10:67–83.)*

Table 119.6 Factors Often Associated with Intrauterine Growth Restriction

FETAL
Chromosomal (trisomies, microdeletions, copy number variants) and monogenetic disorders
Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis)
Congenital anomalies—syndrome complexes
Irradiation
Multiple gestation
Pancreatic hypoplasia
Insulin deficiency (production or action of insulin)
Insulin-like growth factor type I deficiency
PLACENTAL
Decreased placental weight, cellularity, or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Placental mesenchymal dysplasia
Twin transfusion syndrome
MATERNAL/PATERNAL
Preeclampsia
Hypertension or renal disease, or both
Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)
Malnutrition (micronutrient or macronutrient deficiencies)
Chronic illness
Sickle cell anemia
Drugs (opiates, alcohol, cigarettes, cocaine, prescribed medications, antimetabolites)

Table 119.7 Characteristics of Symmetric vs Asymmetric IUGR

CHARACTERISTICS	SYMMETRIC IUGR	ASYMMETRIC IUGR
Typical period of insult and presentation	Earlier gestation (often second trimester)	Later gestation (often detected in the third trimester)
Percentage of all IUGR cases	20–30%	70–80%
Etiology	Genetic disorders Congenital infections	Placental insufficiency
Antenatal scan	Proportionately decreased head circumference (HC), abdominal circumference (AC), biparietal diameter, and femur length	Only abdominal circumference decreased
Cell number	Decreased	Normal
Cell size	Normal	Decreased
Postnatal anthropometry	All parameters (HC, length, and weight) reduced	Reduced weight, HC normal, length low to normal
Features of malnutrition	Less pronounced	More pronounced

IUGR, Intrauterine growth restriction.
Adapted from Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: –part 2. *J Matern Fetal Neonatal Med.* 2016 Mar 15:1–12.

IUGR is indicative of compromise in utero and is associated with medical conditions that interfere with the circulation and efficiency of the placenta, with the development or growth of the fetus, or with the general health and nutrition of the mother (Table 119.6). Many factors are common to both prematurely born and LBW infants with IUGR. IUGR is associated with decreased insulin production or insulin-like growth factor (IGF) action at the receptor level. Infants with IGF-1 receptor defects, pancreatic hypoplasia, or transient neonatal diabetes have IUGR. Genetic mutations affecting the glucose-sensing mechanisms of the pancreatic islet cells result in decreased insulin release (loss of function of the glucose-sensing glucokinase gene) and give rise to IUGR.

IUGR may be a normal fetal response to nutritional or oxygen deprivation; therefore the issue is not the IUGR but rather the ongoing risk of fetal malnutrition or hypoxia. IUGR is often classified as *reduced growth* that is *symmetric* (head circumference, length, and weight equally affected) or *asymmetric* (with relative sparing of head growth) (Table 119.7). **Symmetric IUGR** often has an earlier onset in the first trimester of pregnancy and is associated with diseases that seriously affect fetal cell number, such as conditions with chromosomal, genetic, malformation, teratogenic, infectious, or severe maternal hypertensive etiologies. It is important to assess gestational age carefully in infants suspected to have symmetric IUGR because incorrect overestimation of gestational age may lead to the diagnosis of symmetric IUGR. It is also important to assess carefully for dysmorphic features in infants with symmetric IUGR. **Asymmetric IUGR** is often of late onset in the second half of pregnancy, demonstrates preservation of Doppler waveform velocity to the carotid vessels, and is associated with poor maternal nutrition or with late onset or exacerbation of maternal vascular disease (preeclampsia, chronic hypertension).

Table 119.8 lists common problems of infants with IUGR. In addition, in both preterm and term infants, IUGR is associated with increased risk of cardiovascular disease across the life span, and both SGA and IUGR are associated with an increased risk of neurodevelopmental impairment. To properly manage infants born IUGR and SGA, clinicians must prepare for the possible perinatal morbidities (e.g., hypoglycemia, hypothermia, pulmonary hypertension, feeding intolerance), perform any diagnostic testing needed to determine the etiology, and monitor closely for long-term deficits (e.g., growth, neurodevelopment, cardiovascular).

Table 119.8 Problems of Infants Small for Gestational Age or with Intrauterine Growth Restriction*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia-acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia-hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH†

*Other problems include pulmonary hemorrhage and those common to the gestational age–related risks of prematurity if born at <37 wk.
†TORCH, Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex infection.
↓, Decreased; ↑, increased.

LARGE-FOR-GESTATIONAL-AGE INFANTS

Infants with birthweight >90th percentile for gestational age are called **large for gestational age (LGA)**. Neonatal mortality rates decrease with increasing birthweight until approximately 4,000 g, after which they increase. These oversized infants are usually born at term, but

preterm infants with high weights for gestational age also have a significantly higher mortality than infants of the same size born at term; maternal diabetes and obesity are predisposing factors. Some infants are constitutionally large because of large parental size. LGA infants, regardless of their gestational age, have a higher incidence of shoulder dystocia and birth injuries, such as cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face. LGA infants are also at increased risk for hypoglycemia and polycythemia.

The incidence of congenital anomalies, particularly congenital heart disease, is also higher in LGA infants than in term infants of normal weight.

POSTTERM INFANTS

Postterm infants are those born after 42 weeks (294 days) of gestation, as calculated from the mother's LMP. Historically, approximately 12% of pregnancies resulted in delivery after 42 weeks. However, with current evidence demonstrating significantly increased maternal, fetal and neonatal risks after 42 weeks' gestation, obstetric interventions to induce labor often occur before 42 weeks, resulting in a decreasing rate of postterm births. The cause of true postterm birth or postmaturity is unknown, though some have been attributed to genetic influences and defects in fetal production of parturition hormones. Postterm infants are often dysmature, with normal length and head circumference but may have decreased weight, indicating impaired nutritional supply from placental insufficiency. Infants born postterm in association with presumed placental insufficiency may have various physical signs. Desquamation, long nails, abundant hair, pale skin, alert faces, and loose skin, especially around the thighs and buttocks, give them the appearance of having recently lost weight; meconium-stained nails, skin, vernix, umbilical cord, and placental membranes may also be noted. Common complications of postmaturity include perinatal depression, meconium aspiration syndrome, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia.

Perinatal mortality is 5.8% for infants born at ≥42 weeks' gestational age, compared to 0.7% for those born at term. Mortality may be due to placental insufficiency or umbilical cord compression resulting in hypoxemia and asphyxia. Mortality has been greatly reduced through improved obstetric management. Data suggest that elective delivery between the 39th and 41st week of gestation for both nulliparous and multiparous women is associated with decreased maternal and neonatal complications compared with those who were expectantly managed.

Careful obstetric monitoring, including nonstress testing (NST), biophysical profile (BPP), or Doppler velocimetry, usually provides a rational basis for choosing one of three courses: nonintervention, induction of labor, or cesarean delivery. Induction of labor or cesarean birth may be indicated in older primigravidas >2 weeks beyond term, particularly if evidence of fetal distress is present. Medical problems in the newborn are treated if they arise.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

119.5 Follow-Up of High-Risk Infants After Discharge

Andrea F. Duncan

DISCHARGE FROM THE HOSPITAL

Numerous criteria need to be met before a high-risk infant is ready for discharge from the hospital (Table 119.9). Before discharge, infants should be taking most or all nutrition by nipple, either bottle or breast. Some medically fragile infants may require discharge while receiving gavage feedings or after placement of a gastrostomy tube, after the parents have received appropriate training and education. Growth should be occurring at steady increments, with a goal weight gain of approximately 30 g/day. Temperature should be stable and normal in an open crib. Infants should have had no recent episodes of apnea or bradycardia requiring intervention for at least 5-7 days before discharge. Stable infants recovering from BPD may be discharged on a regimen of home oxygen given by nasal cannula as long as careful follow-up is arranged with home pulse oximetry monitoring and outpatient visits. Some children may require discharge on higher ventilatory support in partnership with pulmonology. All infants with birthweight <1,500 g or gestational age <30 weeks at birth should undergo an eye examination to screen for ROP. If born preterm, hemoglobin or hematocrit should be determined to evaluate for possible anemia of prematurity. Every infant should have a hearing test before discharge. Routine vaccinations should be given based on chronological age before discharge. In addition, palivizumab (Synagis) should be given to eligible infants during respiratory syncytial virus (RSV) season immediately before discharge for prophylaxis against RSV, with continued monthly doses arranged as an outpatient as appropriate.

If all major medical problems have resolved and the home setting is adequate, premature infants may then be discharged when their weight approaches 1,800-2,000 g, they are >34-35 weeks postmenstrual age (PMA), and all the above criteria are met. Parental education, close follow-up, and healthcare provider accessibility are all essential for early discharge protocols. The primary caregivers for the infant should have a chance to provide infant care in the hospital with nursing supervision and support before discharge home. All high-risk infants should follow up with their primary care provider within a few days of discharge and should

Table 119.9 Readiness for Discharge of High-Risk Infants Criteria

Resolution of acute life-threatening illnesses
Ongoing follow-up for chronic but stable problems:
Bronchopulmonary dysplasia
Intraventricular hemorrhage
Necrotizing enterocolitis after surgery or recovery
Ventricular septal defect, other cardiac lesions
Anemia
Retinopathy of prematurity
Hearing problems
Apnea
Cholestasis
Stable temperature regulation
Gain of weight with enteral feedings:
Breastfeeding
Bottle feeding
Gastric tube feeding
Free of significant apnea
Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated
Hearing screenings
Ophthalmologic examination if <30 wk of gestation or <1,500 g at birth
Parental knowledge, skill, and confidence documented in:
Administration of medications (diuretics, methylxanthines, aerosols, etc.)
Use of oxygen, apnea monitors, oximeters
Nutritional support:
Timing
Volume
Mixing concentrated formulas
Recognition of illness and deterioration
Basic cardiopulmonary resuscitation
Infant safety
Scheduling of referrals:
Primary care provider
Neonatal follow-up clinic
Occupational therapy/physical therapy
Imaging (head ultrasound)
Assessment of and solution to social risks

Data from American Academy of Pediatrics, American College of Obstetricians: *Guidelines for Perinatal Care*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2013.

Table 119.10 Sequelae of Prematurity

IMMEDIATE	LATE
Hypoxia, ischemia	Intellectual disability, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Intellectual disability, spasticity, seizures, post hemorrhagic hydrocephalus
Sensorineural injury	Hearing and visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, pulmonary hypertension, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other sequelae	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

be followed in a follow-up program that tracks medical and neurodevelopmental outcomes.

POSTDISCHARGE FOLLOW-UP

Medical Follow-Up

Even after discharge from the hospital, high-risk infants need very close medical follow-up. They continue to be at increased risk for poor weight gain and failure to thrive. In the setting of viral illness, premature infants are at increased risk for significant respiratory distress. Infants who are sent home on oxygen need very close medical follow-up with frequent visits and assessments, often with pulmonology. Table 119.10 lists common sequelae of prematurity.

Medically complex infants can go home with a multitude of subspecialty appointments to help manage existing morbidities secondary to prematurity, for example, cardiology for management of a patent ductus arteriosus or pulmonary hypertension, pulmonary for BPD, nephrology for hypertension, ophthalmology for ROP, neurosurgery for hydrocephalus, and neurology for history of seizures. The extensive follow-up requirements can be overwhelming and daunting for families. It is very important that these infants have a primary provider who serves as their "medical home" to help coordinate and assimilate the care from all these providers for families. This may be their primary care provider or subspecialty program provider.

Developmental Follow-Up

Premature infants are at much greater risk for neurodevelopmental delays than their term counterparts; the more preterm, the greater the risk of delay. In addition, certain postnatal morbidities (severe BPD, grade III or IV intraventricular hemorrhage, severe ROP, seizures) are associated with significantly increased risk of developmental delays. It is very important that these infants, particularly those born preterm, are followed and assessed for developmental delay, so that if delays are detected targeted interventions can be instituted as early as possible.

It is recommended that developmental follow-up be available for infants born <32 weeks' PMA, or at a minimum <28 weeks' PMA and/or <1 kg birthweight. Developmental follow-up in the United States is most often provided in a neonatal follow-up program for the first 2-3 years of life, and in some cases, until school age. Assessments focus on five main developmental domains: cognitive development, language development, fine and gross motor skills, social development, and emotional development. Although many assessments exist, the most widely used assessment in the United States is the *Bayley Scales of Infant and Toddler Development, 4th Edition.*

It is important to note that for at least the first 2 years of life, a child's corrected age should be used in determining whether a delay exists. Corrected age is calculated by subtracting the weeks born premature from a child's chronological age. In doing so, a corrected age accounts for a child's prematurity. There is some debate whether corrected age should continue to be used after age 2 years.

If it is determined that a delay exists, a child should be referred for appropriate therapy immediately to help minimize the delay as the child ages. Federal law under the Individuals with Disabilities Act requires states to provide *early intervention* services to children <3 years old with developmental delay. States vary greatly in how delay is defined and what services are offered. Early intervention is associated with improved cognitive outcomes in infancy and preschool age, but not lasting into school age. Motor outcomes are improved in infancy for children who receive early intervention, but this has not been shown to be a lasting effect into preschool and school age. However, these findings are difficult to interpret, given the heterogeneity of early interventions included in the reviews. With *targeted* interventions for specific delays, functional outcomes are improved.

Premature infants, especially those with a history of grade III or IV intraventricular hemorrhage or PVL seen on head imaging, are also at increased risk of motor impairments. Cerebral palsy is a *nonprogressive* but *permanent* disorder of movement and posture caused by disturbance to the developing immature brain. Historically, cerebral palsy had not been diagnosed until 18-24 months of age, but it can be diagnosed within the first 6 months of life. Early detection is critical to leveraging the neuroplasticity present in the very early years of life for improved function. International guidelines for early assessment and diagnosis of cerebral palsy and standardized assessments such as the General Movements Assessment (GMA) and the Hammersmith Infant Neurological Examination (HINE) are recommended in the guidelines to help identify children at high risk for or with cerebral palsy within the first few months to a year of life. This enables these children to access early intervention services and therapy at an earlier age, as well as undergo more frequent surveillance as needed.

Children with a history of prematurity who do not show significant developmental delays in the first few years of life are still at risk of later developing learning disabilities, attention problems, and decreased school achievement. Continued screening by their primary care provider is needed as these children age. More subtle deficits may not be recognized until school age; therefore continued surveillance is critical.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 120

Transport of the Critically Ill Newborn

David A. Munson

REGIONALIZED CARE OF NEWBORNS

The concept of regionalized care for neonates emphasizes the importance of providing regionalized care for infants in facilities with adequate personnel and equipment for an infant's severity of illness. Ideally, pregnant people should give birth to infants at a facility with the appropriate level of expertise and resources to care for the degree of prematurity and illness of the infant. Very low birthweight (VLBW) infants, or infants <1,500 g at birth, have decreased morbidity and mortality when born at **Level III** hospitals. In a meta-analysis, neonatal or predischarge death occurred in 38% of VLBW infants receiving care at a non–Level III hospital and 23% of those receiving care at a Level III hospital. A main objective of *Healthy People 2020* addresses this issue, with a goal of increasing the proportion of VLBW infants born at Level III hospitals or subspecialty perinatal centers to 83.7%. When possible it is more preferable to transport the pregnant person to meet the goals of regionalization.

LEVELS OF NEONATAL CARE

A **Level I** facility must be able to provide *basic neonatal care*. Appropriate equipment and staff must be available to perform neonatal resuscitation and care for healthy term and late preterm infants. In addition, Level I facilities must have the capacity to work to stabilize ill or preterm infants before transport to a higher level of care. A Level I nursery is the minimum requirement for a hospital providing inpatient maternity care. Providers at Level I facilities usually include pediatricians, family physicians, and nurse practitioners.

In addition to the care provided at a Level I facility, **Level II** nurseries must also be capable of providing care to moderately ill term infants with problems expected to resolve quickly. Level II centers also care for infants born ≥32 weeks' gestational age and >1,500 g at birth; therefore they must be comfortable with treating conditions common in this population, such as difficulty with oral feeds, apnea of prematurity, respiratory distress requiring continuous positive airway pressure (CPAP), and temperature regulation. These centers must also be capable of stabilizing infants born <32 weeks' gestation and <1,500 g until transfer to a higher-level facility is feasible, including the ability to intubate and provide mechanical ventilation for a brief duration if necessary. In addition to providers in Level I facilities, Level II facilities also typically have pediatric hospitalists, neonatologists, and neonatal nurse practitioners.

Level III NICUs are equipped to care for extremely preterm and critically ill neonates in addition to those infants cared for at Level I and II units. Level III units must have continuously available personnel and equipment to treat conditions commonly seen in this population, such as respiratory distress syndrome, pulmonary hypertension, and need for total parenteral nutrition. Resources should be available to obtain and interpret urgent imaging needed (e.g., CT, echocardiography). Pediatric subspecialists and pediatric surgeons should be available either on-site or through prearranged consultative agreements.

In addition to the care available at Level III neonatal intensive care units (NICUs), **Level IV** NICUs are also capable of providing continuously available pediatric subspecialty consultation and pediatric surgical intervention. Many Level IV sites are located at regional children's hospitals and also serve to provide outreach education. Level IV NICUs also have the capacity to provide extracorporeal membrane oxygenation (ECMO), an intervention that requires surgeons for catheter placement and ECMO specialists who are typically nurses or respiratory therapists with additional training in managing the ECMO circuit.

TRANSPORT OF THE CRITICALLY ILL NEONATE

In the event that a neonate requires a higher level of care, transport must be arranged to a unit with the appropriate level of care available. Additional decisions that need to be made before transport include composition of the transport team, equipment required for transport, and mode of transportation.

The composition of the **transport team** varies depending on personnel available and the needs of the infant being transported. The transport team often comprises at least two individuals, whether two registered transport trained nurses (RNs), an RN and a respiratory therapist, or an RN and a paramedic. In addition, a neonatologist, neonatology fellow, or neonatal nurse practitioner will sometimes accompany the transport team for critically ill neonates. A **medical command physician** is also available and can communicate with the transport team during the transport, as needed. The command physician is also able to communicate with the referring neonatologist to discuss the case and offer advice while the transport team is en route.

Transport staff must be competent in the treatment of common neonatal conditions and complications, as well as neonatal procedures. Many Level IV facilities have specialized teams designed only for neonatal transports. However, a Cochrane review found no evidence to support or to refute improved infant morbidity or mortality when transport occurred with a specialized neonatal team versus those that transported both neonatal as well as pediatric patients. Depending on the volume of neonatal transports and composition of the team, staff may have limited exposure to neonatal transports and procedures. **Simulation-based learning** is recommended by the American Academy of Pediatrics (AAP) Section on Transport Medicine (SOTM) as a method to help achieve and retain competency in rarely experienced procedures, as well as improve team interactions for transport teams.

The **transport vehicle** should be equipped with appropriate medicines, intravenous (IV) fluids, oxygen tanks, catheters, chest tubes, endotracheal tubes (ETTs), laryngoscopes, bag-valve-mask, and infant warming device. It should be well illuminated and have ample room for emergency procedures and monitoring equipment. Additional needs for an individual transport should be anticipated. Specifically, inhaled nitric oxide is not standard equipment for most transport teams and will need to be requested if thought necessary for safe transport. For neonates with hypoxemic ischemic encephalopathy who require hypothermia therapy, a servo-controlled cooling device is recommended as it will achieve the target temperature faster and there is less risk of overshooting the goal temperature. Prostaglandin E1 should be available for suspected ductal dependent congenital heart disease.

Common **modes of transport** include ground transport by ambulance and air transport by helicopter or fixed-wing aircraft. The stability of the infant, travel distance, traffic, and weather must all be taken into account when deciding the most appropriate mode of transportation.

Steps should be taken to stabilize the infant, as able, in a timely fashion before the transport. Securing an airway, providing oxygen, assisting with infant ventilation, providing antimicrobial therapy, maintaining the circulation, providing a warmed environment, checking a glucose level, and placing IV or arterial lines or chest tubes should be initiated, if indicated, before transport. Appropriate placement of lines and ETT should be evaluated before transport.

Some hospitals and their associated level IV NICUs offer transport of a patient on ECMO. Most commonly this is designed to transport a patient who is already cannulated onto ECMO who needs subspecialized care such as evaluation for transplant, or assessment for longer-term mechanical cardiac support. In other situations, a hospital may have the capacity to cannulate a patient onto ECMO, but do not have a program in place to support the patient for the coming days. These patients may therefore include more common patients who require ECMO such as neonates with persistent pulmonary hypertension, severe hypoxemic respiratory failure, sepsis, congenital diaphragmatic hernia, or hypoplastic left heart syndrome. In these circumstances, a transport team needs to include an ECMO specialist or perfusionist, and commonly adds a

critical care physician or surgeon. There are some programs that will bring the necessary personnel and equipment to cannulate a patient onto an ECMO circuit at the referring hospital before transport. There are considerable logistical challenges and added risks for transporting a patient on ECMO. These include inadvertent decannulation, problems with sustaining flow on the circuit, and bleeding.

Risks of transport and **consent** for transportation should be reviewed and obtained from parents before transport. Although transport teams attempt to anticipate and prepare for possible complications that could occur during transport, there is an inherent risk of complications, including death, in the event of a decompensation during transport resulting from the limited resources and personnel available. It is intrinsically more difficult to perform procedures in the physically confined space of an ambulance or helicopter. Additionally, there is the risk associated with the mode of transport itself including car and helicopter crashes. Parents should be made aware of these risks. Efforts should be made to allow parents to see their baby briefly before transport.

Communication with the transport team as well as the receiving facility is paramount throughout the transport process. Available prenatal history, information on the infant's resuscitation and hospital course, laboratory data, and radiographic images should be sent with the transport team to the receiving hospital to aid in future care. Video-assisted telecommunications can assist in giving the **medical command physician** visual as well as audio information about what is happening on-site before the patient is loaded onto the ambulance.

Reverse transport of an infant back to a lower level of care should be considered when infants are stabilized or have received and recovered from their subspecialist or surgical interventions, and no longer require the higher-level care available at the receiving hospital. Transport back to the hospital of birth aids in appropriate utilization of resources, decreases costs of care, and may further promote parent–infant bonding because of proximity to the mother's home.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 121

Clinical Manifestations of Diseases in the Newborn Period

Kathleen A. Gibbs and Eric C. Eichenwald

A variety of conditions that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders can be caused by prematurity, congenital malformations, disruption of chromosome structure, or acquired diseases and injuries.

ABNORMAL MOVEMENTS

Neonatal seizures usually suggest a central nervous system (CNS) disorder, such as hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage, stroke, cerebral anomaly, subdural effusion, or meningitis (see Chapter 633.7). In the neonate, seizures can also be secondary to hypocalcemia, hypoglycemia, benign familial seizures, or rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal.

Seizures in premature infants are often subtle and associated with abnormal eye movement (fluttering, tonic horizontal deviation, sustained eye opening with ocular fixation) or facial movement (chewing, tongue thrusting); the motor component is often that of tonic extension of the limbs, neck, and trunk. Autonomic phenomena include hypertension and tachycardia. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have subtler manifestations of seizure activity. **Apnea** may be the first manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to seizures outside the neonatal period. Electroencephalographic (EEG) evidence of seizures can occur without clinical manifestations, particularly in preterm infants. If seizures are suspected, video-EEG monitoring will improve the detection of both subtle and electrographic but clinically silent seizures. Seizures contribute to brain injury and the impact of treatment on neurodevelopmental outcomes is an active area of research, particularly in patients with HIE. Although many medications used to treat seizures have side effects, it is recommended to treat both clinical and subclinical seizures.

Seizures should be distinguished from the **jitteriness**, defined as *recurrent tremors,* that may be present in healthy newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic neonates. An examiner can suppress the tremors by holding the infant's extremity; jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures.

After severe birth asphyxia, infants may exhibit **motor automatisms** characterized by recurrent oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized EEG discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Failure to move an extremity **(pseudoparalysis)** suggests fracture, dislocation, or a paralytic brachial plexus injury, often following a traumatic delivery. It is also seen in neonatal stroke (paralytic) as well as septic arthritis, osteomyelitis, and other infections that cause pain on movement of the affected part.

ABNORMAL TONE

Hypotonia, or low tone in one or more extremities, may be due to specific genetic etiologies or as a result of pathology in the peripheral or central nervous system. Features in the history and physical examination can help narrow the differential diagnosis and guide further diagnostic evaluations (see Chapter 647). A history of decreased fetal movement in utero may be suggestive of a congenital myopathy, or spinal muscular atrophy. In a male infant with cryptorchidism, Prader-Willi syndrome can be considered. **Hypotonia** is a common finding in an infant with trisomy 21. Hypertonia is less common and should be distinguished from fixed joint contractures seen in arthrogryposis. If present in the hours after birth and associated with the need for resuscitation after birth, a case of HIE should be considered.

ALTERED MENTAL STATUS

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, an inborn error of metabolism (IEM), or, almost any severe disease. Shortly after birth, lethargy is most likely caused by maternal medications (opioids, magnesium, general anesthesia) or moderate to severe HIE. Lethargy appearing after the second day should suggest infection or an IEM manifesting with hyperammonemia, acidosis, or hypoglycemia. Lethargy with emesis may suggest increased intracranial pressure or an IEM.

critical care physician or surgeon. There are some programs that will bring the necessary personnel and equipment to cannulate a patient onto an ECMO circuit at the referring hospital before transport. There are considerable logistical challenges and added risks for transporting a patient on ECMO. These include inadvertent decannulation, problems with sustaining flow on the circuit, and bleeding.

Risks of transport and **consent** for transportation should be reviewed and obtained from parents before transport. Although transport teams attempt to anticipate and prepare for possible complications that could occur during transport, there is an inherent risk of complications, including death, in the event of a decompensation during transport resulting from the limited resources and personnel available. It is intrinsically more difficult to perform procedures in the physically confined space of an ambulance or helicopter. Additionally, there is the risk associated with the mode of transport itself including car and helicopter crashes. Parents should be made aware of these risks. Efforts should be made to allow parents to see their baby briefly before transport.

Communication with the transport team as well as the receiving facility is paramount throughout the transport process. Available prenatal history, information on the infant's resuscitation and hospital course, laboratory data, and radiographic images should be sent with the transport team to the receiving hospital to aid in future care. Video-assisted telecommunications can assist in giving the **medical command physician** visual as well as audio information about what is happening on-site before the patient is loaded onto the ambulance.

Reverse transport of an infant back to a lower level of care should be considered when infants are stabilized or have received and recovered from their subspecialist or surgical interventions, and no longer require the higher-level care available at the receiving hospital. Transport back to the hospital of birth aids in appropriate utilization of resources, decreases costs of care, and may further promote parent–infant bonding because of proximity to the mother's home.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 121

Clinical Manifestations of Diseases in the Newborn Period

Kathleen A. Gibbs and Eric C. Eichenwald

A variety of conditions that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders can be caused by prematurity, congenital malformations, disruption of chromosome structure, or acquired diseases and injuries.

ABNORMAL MOVEMENTS

Neonatal seizures usually suggest a central nervous system (CNS) disorder, such as hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage, stroke, cerebral anomaly, subdural effusion, or meningitis (see Chapter 633.7). In the neonate, seizures can also be secondary to hypocalcemia, hypoglycemia, benign familial seizures, or rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal.

Seizures in premature infants are often subtle and associated with abnormal eye movement (fluttering, tonic horizontal deviation, sustained eye opening with ocular fixation) or facial movement (chewing, tongue thrusting); the motor component is often that of tonic extension of the limbs, neck, and trunk. Autonomic phenomena include hypertension and tachycardia. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have subtler manifestations of seizure activity. **Apnea** may be the first manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to seizures outside the neonatal period. Electroencephalographic (EEG) evidence of seizures can occur without clinical manifestations, particularly in preterm infants. If seizures are suspected, video-EEG monitoring will improve the detection of both subtle and electrographic but clinically silent seizures. Seizures contribute to brain injury and the impact of treatment on neurodevelopmental outcomes is an active area of research, particularly in patients with HIE. Although many medications used to treat seizures have side effects, it is recommended to treat both clinical and subclinical seizures.

Seizures should be distinguished from the **jitteriness**, defined as *recurrent tremors,* that may be present in healthy newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic neonates. An examiner can suppress the tremors by holding the infant's extremity; jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures.

After severe birth asphyxia, infants may exhibit **motor automatisms** characterized by recurrent oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized EEG discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Failure to move an extremity **(pseudoparalysis)** suggests fracture, dislocation, or a paralytic brachial plexus injury, often following a traumatic delivery. It is also seen in neonatal stroke (paralytic) as well as septic arthritis, osteomyelitis, and other infections that cause pain on movement of the affected part.

ABNORMAL TONE

Hypotonia, or low tone in one or more extremities, may be due to specific genetic etiologies or as a result of pathology in the peripheral or central nervous system. Features in the history and physical examination can help narrow the differential diagnosis and guide further diagnostic evaluations (see Chapter 647). A history of decreased fetal movement in utero may be suggestive of a congenital myopathy, or spinal muscular atrophy. In a male infant with cryptorchidism, Prader-Willi syndrome can be considered. **Hypotonia** is a common finding in an infant with trisomy 21. Hypertonia is less common and should be distinguished from fixed joint contractures seen in arthrogryposis. If present in the hours after birth and associated with the need for resuscitation after birth, a case of HIE should be considered.

ALTERED MENTAL STATUS

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, an inborn error of metabolism (IEM), or, almost any severe disease. Shortly after birth, lethargy is most likely caused by maternal medications (opioids, magnesium, general anesthesia) or moderate to severe HIE. Lethargy appearing after the second day should suggest infection or an IEM manifesting with hyperammonemia, acidosis, or hypoglycemia. Lethargy with emesis may suggest increased intracranial pressure or an IEM.

Irritability may be a sign of discomfort accompanying intraabdominal conditions, meningeal irritation, drug withdrawal, infections, trauma (birth or nonaccidental), or any condition producing pain. It must be distinguished from normal crying behavior associated with hunger or benign environmental stimuli.

The lack of an interest to feed may indicate a sick infant and should prompt a careful search for infection, a CNS (brain or spine) or peripheral nervous system disorder, IEM, or intestinal obstruction.

APNEA

Periods of apnea, particularly in premature infants, can be attributed to many different underlying causes (see Chapter 125). When apnea occurs in a term infant, it should be considered pathologic until proven otherwise, and an immediate diagnostic evaluation for the underlying cause is imperative.

CONGENITAL ANOMALIES

Congenital anomalies are a common cause of neonatal morbidity and mortality worldwide (see Chapters 98–100). Early recognition of anomalies during fetal life is important to plan for delivery room management and subsequent neonatal care. Some malformations, including congenital heart disease, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, and intestinal obstruction, require immediate medical/surgical therapy for postnatal survival (Table 121.1). Prenatal and postnatal testing strategies, including advanced imaging techniques and genetic testing, have improved the specific diagnosis of congenital anomalies (see Chapter 103.1). Historically, genetic testing was performed by obtaining a karyotype with or without *fluorescence in situ hybridization* (FISH). A karyotype can identify a large number of chromosomal abnormalities; FISH can test for classic microdeletion syndromes such as 22q11. Chromosomal microarray is also indicated for genetic testing of infants with congenital anomalies because it can identify microdeletions or microduplications that are too small to be detected by more traditional techniques. In cases where a common aneuploidy, such as trisomy 13, 18, or 21, is suspected, obtaining a conventional karyotype and/or FISH may be the more appropriate test as those results are available in a few days. Whole exome sequencing (WES) uses next-generation sequencing to identify variants in protein coding genes that may be responsible for a disease phenotype. Rapid WES can have results available in 1-2 weeks. This can be used in a critically ill infant with a suspected genetic disorder that lacks a unifying diagnosis, and it may lead to a specific treatment and prognosis. Limitations of both microarray and WES include the identification of variants that may not be pathogenic in nature. Parents should receive genetic counseling as part of any testing strategy. It is important that healthcare providers are aware of the indication and limitations of the type of genetic test being performed.

CYANOSIS

Central cyanosis generates a broad differential diagnosis encompassing respiratory, cardiac, CNS, infectious, hematologic, and metabolic etiologies (Table 121.2). Typically, 5 g/dL of deoxyhemoglobin must be present in the blood for central cyanosis to be clinically apparent. If respiratory insufficiency is caused by pulmonary conditions, respirations tend to be rapid with increased work of breathing. If caused by CNS depression, respirations tend to be irregular and weak and are often slow. Cyanosis unaccompanied by obvious signs of respiratory difficulty suggests cyanotic congenital heart disease or methemoglobinemia. Cyanosis resulting from congenital heart disease may be difficult to distinguish clinically from cyanosis caused by respiratory disease. Episodes of cyanosis may also be the initial sign of hypoglycemia, bacteremia, meningitis, shock, or pulmonary hypertension. **Peripheral acrocyanosis** is common in neonates and thought to represent peripheral venous congestion associated with immature control of peripheral vascular tone. It does not usually warrant concern unless poor perfusion is suspected.

GASTROINTESTINAL DISTURBANCES

Vomiting during the first day of life can suggest obstruction in the upper digestive tract, metabolic disease, or may be physiologic**. Abdominal distention** with emesis**,** usually a sign of intestinal obstruction or an intraabdominal mass, may also be seen in infants with enteritis, necrotizing enterocolitis (NEC), isolated intestinal perforation, ileus accompanying sepsis, respiratory distress, ascites, or hypokalemia. Imaging studies are indicated when obstruction is suspected; proximal intestinal obstruction often occurs with a normal physical examination, whereas distal obstruction will likely be accompanied by distention. Vomiting may also be a nonspecific symptom of an illness such as sepsis with associated abdominal distention and ileus. It is a common manifestation of overfeeding, as well as gastroesophageal or physiologic reflux. Rarely, vomiting is caused by pyloric stenosis, milk protein allergy, duodenal ulcer, stress ulcer, an IEM (hyperammonemia, metabolic acidosis), or adrenal insufficiency. Vomitus containing blood is usually a sign of a serious illness, but the benign possibility of swallowed maternal blood associated with the delivery process should also be considered. Tests for maternal vs fetal hemoglobin can help

Table 121.1 Common Life-Threatening Congenital Anomalies

ANOMALY	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room; nasogastric tube cannot be passed through nares Suspect CHARGE (coloboma of eye, heart anomaly, choanal atresia, retardation, genital and ear anomalies) syndrome
Pierre Robin syndrome, Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation; nasogastric tube cannot be placed in stomach Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia) syndrome
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, or cocaine use
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephaly, meningomyelocele	Polyhydramnios, elevated α-fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

Table 121.2 Differential Diagnosis of Cyanosis in the Newborn

CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION
Birth asphyxia
Intracranial hypertension, hemorrhage
Oversedation (direct or through maternal route)
Diaphragm palsy
Neuromuscular diseases
Seizures

RESPIRATORY DISEASE
Airway
Choanal atresia/stenosis
Pierre Robin syndrome
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)

Lung
Respiratory distress syndrome
Transient tachypnea
Meconium aspiration
Pneumonia (sepsis)
Pneumothorax
Congenital diaphragmatic hernia
Pulmonary hypoplasia

CARDIAC RIGHT-TO-LEFT SHUNT
Abnormal Connections (Pulmonary Blood Flow Normal or Increased)
Transposition of great vessels
Total anomalous pulmonary venous return
Truncus arteriosus
Hypoplastic left heart syndrome
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis

OBSTRUCTED PULMONARY BLOOD FLOW (PULMONARY BLOOD FLOW DECREASED)
Pulmonic atresia with intact ventricular septum
Tetralogy of Fallot
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect
Tricuspid atresia
Single ventricle with pulmonic stenosis
Ebstein malformation of tricuspid valve
Persistent fetal circulation (persistent pulmonary hypertension of newborn)

METHEMOGLOBINEMIA
Congenital (hemoglobin M, methemoglobin reductase deficiency)
Acquired (nitrates, nitrites)

INADEQUATE DELIVERY
Inadequate ambient O2 or less O2 delivered than expected (rare)
Disconnection of O2 supply to nasal cannula, head hood
Connection of air, rather than O2, to a mechanical ventilator

SPURIOUS/ARTIFACTUAL
Oximeter artifact (poor contact between probe and skin, poor pulse searching)
Arterial blood gas artifact (contamination with venous blood)

OTHER
Hypoglycemia
Adrenogenital syndrome
Polycythemia
Blood loss

From Smith F: Cyanosis. In: Kliegman RM: *Practical Strategies in Pediatric Diagnosis and Therapy*. Philadelphia: Saunders; 1996.

discriminate between these possibilities. Bilious emesis in a term infant should be considered a surgical emergency with a presumed diagnosis of intestinal malrotation with or without volvulus until proven otherwise. This finding warrants urgent contrast radiography of the upper gastrointestinal tract (see Chapter 376.3).

Diarrhea may be a symptom of overfeeding (especially high–caloric density formula), acute gastroenteritis, congenital diarrhea syndromes, or malabsorption, or it may be a nonspecific symptom of infection. Diarrhea should be differentiated from the normal loose, seedy, yellow stool seen typically in breastfed infants. Diarrhea may occur in conditions accompanied by compromised circulation of part of the intestinal or genital tract, such as mesenteric thrombosis, NEC, strangulated hernia, intussusception, and torsion of the ovary or testis.

HYPOTENSION

Hypotension in term infants implies hypovolemic shock (hemorrhage, dehydration), a systemic inflammatory response syndrome (bacterial sepsis, intrauterine infection, NEC, cardiac dysfunction, myocarditis, asphyxia-induced myocardial stunning, anomalous coronary artery), congenital heart disease with ductal-dependent systemic blood flow (hypoplastic left heart syndrome, congenital aortic stenosis), pneumothorax, pneumopericardium, pericardial effusion, or metabolic disorders (hypoglycemia, adrenal insufficiency).

Hypotension is a common problem in sick preterm infants and may also be caused by any of the problems noted in a term infant. Some extremely low gestational age infants do not respond to fluids or inotropic agents but may improve with administration of intravenous hydrocortisone (Fig. 121.1). Sudden onset of hypotension in a very low birthweight (VLBW) infant suggests pneumothorax, intraventricular hemorrhage, or subcapsular hepatic hematoma. Strategies used to support blood pressure include volume expansion with crystalloid and/or colloid, vasopressors (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin), or corticosteroids (hydrocortisone) (see Chapter 85).

JAUNDICE

Jaundice during the first 24 hours of life warrants diagnostic evaluation and should be considered pathologic until proven otherwise. Hemolytic disease of the newborn due to rhesus blood group system (Rh) isoimmunization or blood type compatibility are the most common cause (see Chapter 140). Intrauterine infections (e.g., syphilis, cytomegalovirus, and toxoplasmosis), early-onset sepsis, or gestational alloimmune liver disease (formerly described as neonatal hemochromatosis) should be considered in infants with neonatal cholestasis, identified by an increase in *direct* bilirubin value. Immediate evaluation includes obtaining total and direct bilirubin, infant blood type and Coombs status, CBC, and reticulocyte count. There are nomograms specific to the age (in hours) of the infant to guide the initiation of therapeutic interventions depending on the levels of serum bilirubin values (see Chapter 137). Phototherapy is the standard first-line therapy. In the case of Coombs-positive hemolysis, strong consideration should be made to giving intravenous immunoglobulin (IVIG) if there is no response to intensive phototherapy. Double volume exchange transfusion is recommended in situations with rapidly rising indirect bilirubin levels, particularly in infants whose bilirubin levels rise over 20 mg/dL. In these cases, obtaining a serum albumin is also recommended.

Jaundice that is identified after the first 24 hours of age may be physiologic or pathologic. Physiologic conditions include breast-milk and breast-feeding jaundice. Pathologic conditions include bacterial sepsis, congenital hypothyroidism, galactosemia, congenital atresia of the bile ducts, or other conditions (see Chapter 137).

PAIN

Pain in neonates may be unrecognized and/or undertreated. The intensive care of neonates may involve several painful procedures, including blood sampling (heelstick, venous or arterial puncture), endotracheal intubation and suctioning, mechanical ventilation, and insertion of chest tubes and intravascular catheters. Pain in neonates results in

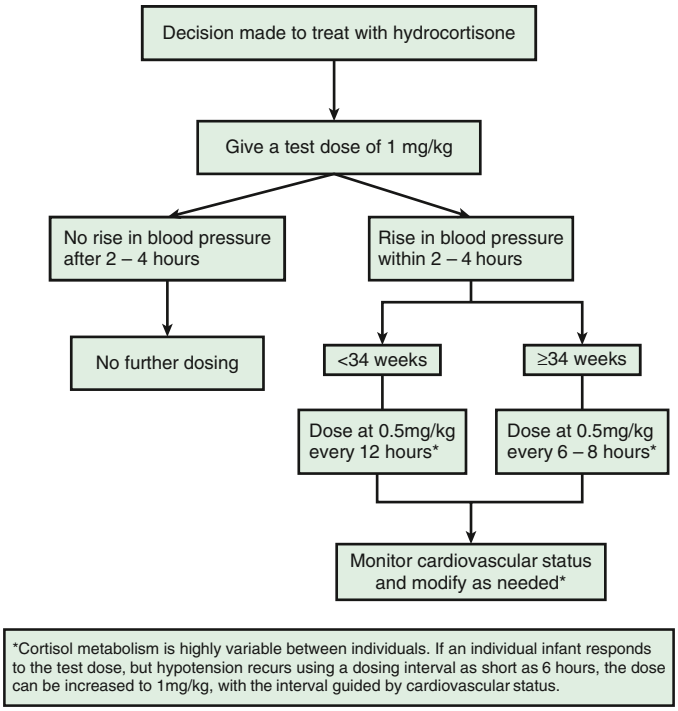

Fig. 121.1 Suggested treatment algorithm for hydrocortisone dosing in the newborn. *(From Watterberg KL. Hydrocortisone dosing for hypotension in newborn infants: less is more. J Pediatr. 2016;174:23–26.)*

obvious distress and acute physiologic stress responses, which may have developmental implications for pain in later life.

Pain and discomfort are potentially avoidable problems during the treatment of sick infants. The most common painful stimuli for healthy newborns include circumcision and phlebotomy while obtaining metabolic screening tests. There are pharmacologic and nonpharmacologic options to both prevent and treat pain. **Oral sucrose solutions** are well tolerated by most infants and have proven efficacy for procedural pain. A dorsal penile nerve block is effective to prevent procedural-related pain during a circumcision. For neonatal intensive care unit (NICU) infants, the most frequently used drugs are intermittent or continuous doses of opioids. Although the specific long-term effects of opioids and sedatives are not well established, the first concern should be the treatment and/or prevention of acute pain (Table 121.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

121.1 Hyperthermia

Kathleen A. Gibbs and Eric C. Eichenwald

Serious infection (pneumonia, bacteremia, meningitis, and viral infections, particularly herpes simplex or enteroviruses) may cause **fever** and must be considered, although such infections often occur without provoking a febrile response in newborn infants (see Chapter 220). Providers should consider evaluation for bacterial infection in infants <28 days old with a rectal temperature ≥38°C (100.5°F), including blood culture, urine culture, and lumbar puncture (LP), although stepwise approaches to identify low-risk patients and limiting LP to a subset of higher-risk infants are gaining favor. Fever immediately after birth may be caused by radiant warmers, maternal fever, or maternal epidural analgesia. Fever may also be caused by elevated environmental temperatures because of weather, overheated nurseries, incubators, or radiant warmers, or excessive clothing. It has also been attributed to dehydration, although *dehydration fever* is a diagnosis of exclusion in newborn infants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 121.3 Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Data from American Academy of Pediatrics Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery; Canadian Paediatric Society, Fetus and Newborn Committee. Prevention and Management of Pain and Stress in the Neonate: An Update. *Pediatrics* 2016;137:e20154271.

121.2 Hypothermia and Cold Stress

Kathleen A. Gibbs and Eric C. Eichenwald

Unexplained **hypothermia** may accompany infection or other serious disturbances of the circulation or CNS. A sudden servo-controlled increase in incubator ambient temperature to maintain body temperature is a sign of temperature instability and may be associated with sepsis or any of the conditions already mentioned.

Cold stress can lead to profound decompensation, including apnea, bradycardia, respiratory distress, hypoglycemia, and poor feeding. For this reason, it is paramount for the neonate to maintain normothermia in the delivery room and afterward, especially low birthweight and premature infants. For VLBW infants, a combination of occlusive plastic wrap, radiant warmers, and thermal mattresses to maintain normothermia can be used to reduce cold stress.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

121.3 Edema

Kathleen A. Gibbs and Eric C. Eichenwald

Generalized edema noted in the delivery room can be caused by hydrops fetalis secondary to several underlying causes (see Chapter 143). An infant with suspected hydrops in utero should be delivered at a specialty perinatal center with capacity for neonatal intubation, thoracentesis, paracentesis, and pericardiocentesis in the delivery room. If noted after 24 hours of age, causes are similar to those of older children and may be multifactorial and likely related to the underlying disease state. Edema may be due to interstitial fluid "third-spacing" due to a systemic inflammatory response seen in sepsis or NEC; or, in the immediate postoperative period, hypoalbuminemia may be due to low production in hepatic synthetic dysfunction or increased losses in underlying renal disease such a congenital nephrotic syndrome (see Chapter 567.3).

121.4 Hypocalcemia

Kathleen A. Gibbs and Eric C. Eichenwald

Hypocalcemia in a neonate can manifest as irritability, jitteriness, clonus, or seizures. Electrocardiography can show a prolonged QT interval. The cause may simply represent an exaggerated physiologic decrease in serum calcium levels within the first 24 hours of life or pathologic conditions such as genetic disorders (22q deletions), prematurity, growth restriction, perinatal hypoxia, hypomagnesemia, or maternal diabetes. Hypocalcemia is more common in term infants receiving formula than in those exclusively receiving breast milk. Most infants remain asymptomatic and can be managed conservatively with early nutrition and close monitoring, whereas symptomatic neonates should receive intravenous or oral calcium replacement.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

121.5 Hypermagnesemia

Kathleen A. Gibbs and Eric C. Eichenwald

Hypermagnesemia is most often caused by maternal administration of magnesium in the perinatal period for treatment of conditions such as preeclampsia and preterm labor, and as prophylaxis to mitigate brain injury associated with preterm birth. Infants are usually present with signs at birth and improve over the next 24-48 hours. Symptoms include respiratory depression, hypotonia, lethargy, and feeding intolerance. No treatment is indicated other than supportive measures.

Chapter 122
Nervous System Disorders

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Central nervous system (CNS) disorders are important causes of neonatal mortality and both short-term and long-term morbidity. The CNS can be injured as a result of asphyxia, hemorrhage, trauma, infection, hypoglycemia, or direct cytotoxicity. The etiology of CNS injury is often multifactorial and includes perinatal complications, postnatal hemodynamic instability, and developmental abnormalities that may be genetic and/or environmental. Predisposing factors for brain injury include chronic and acute maternal illness resulting in uteroplacental dysfunction, intrauterine infection, macrosomia/dystocia, malpresentation, prematurity, and intrauterine growth restriction. Acute and often unavoidable emergencies during the delivery process may result in mechanical and hypoxic-ischemic brain injury.

122.1 The Cranium

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Erythema, abrasions, ecchymoses, and subcutaneous fat necrosis of facial or scalp soft tissues may be noted after a normal delivery or after forceps or vacuum-assisted deliveries. The location depends on the area of contact with the pelvic bones or application of the forceps. Traumatic hemorrhage may involve any layer of the scalp as well as intracranial contents (Fig. 122.1).

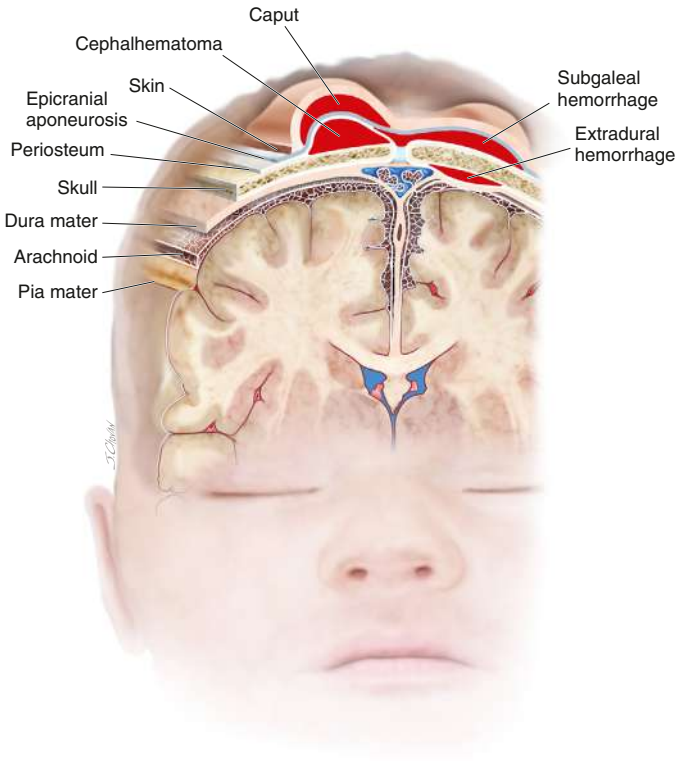

Fig. 122.1 Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. *(From Volpe JJ. Injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In: Volpe JJ, Inder TE, Darras BT, et al., eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 36-1.)*

Caput succedaneum is a diffuse, sometimes ecchymotic, edematous swelling of the soft tissues of the scalp due to the increased pressure of the vaginal and uterine walls on the fetal head during labor. The pressure causes a serosanguinous/edematous infiltration above the periosteum and below the skin or subcutaneous tissue. The edema is soft and extends across the midline of the skull, crossing suture lines and disappears within the first few days of life. Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded; they disappear during the first few weeks of life. Rarely, a hemorrhagic caput may result in shock and require blood transfusion. Analogous swelling, discoloration, and distortion of the face are seen in face presentations. No specific treatment is needed, but if extensive ecchymoses are present, hyperbilirubinemia may develop.

Cephalohematoma is a unilateral subperiosteal hemorrhage that does not cross the suture lines as it usually occurs within a single cranial plate (Fig. 122.2). Cephalohematomas occur in 1–2% of live births regardless of the mode of delivery. No discoloration of the overlying scalp occurs, and due to slow bleeding, the clinical presentation of swelling is delayed for several hours to days. The lesion becomes a firm, tense mass with a palpable rim localized over one area of the skull. Most cephalohematomas are resorbed within 3 to 4 weeks, depending on their size. They may begin to calcify by the end of the second week of life. A few remain for years as bony protuberances and are detectable on radiographs as widening of the diploic space; cystlike defects that may persist for months or years. An underlying skull fracture, usually linear and not depressed, may be associated with 10–25% of cases. A sensation of central depression suggesting but not indicative of an underlying fracture or bony defect is usually encountered on palpation of the organized rim of a cephalohematoma. Osteomyelitis of the skull is a rare complication of cephalohematoma; *Escherichia coli* and *Staphylococcus aureus* are common agents. Cephalohematomas

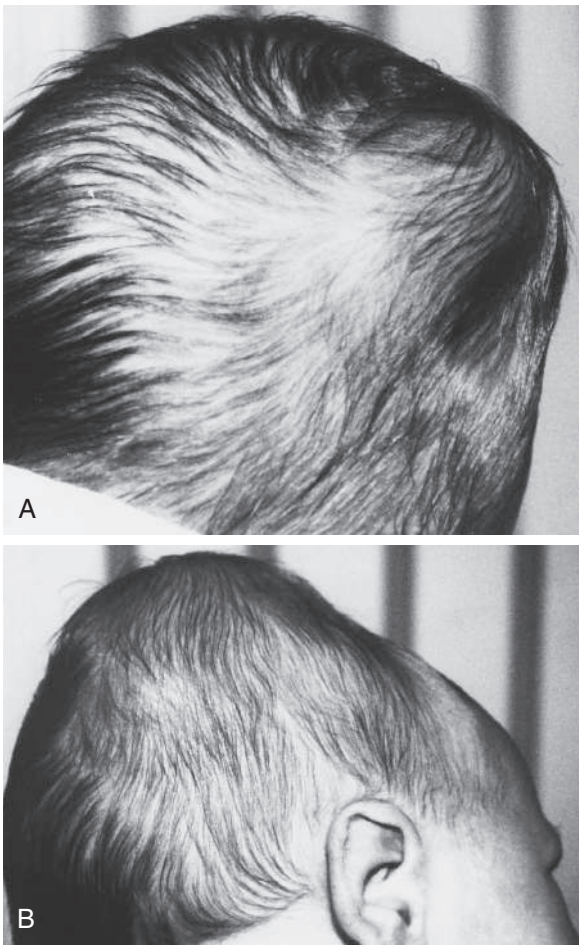

Fig. 122.2 Parietal cephalhematoma. Clinical appearance of 10-day-old infant delivered with the aid of mid-forceps. **A,** Posterior view. **B,** Right lateral view. Note prominent swelling that extends medially to the sagittal suture, posteriorly to the lambdoid suture, and laterally to the squamosal suture. *(From Volpe JJ. Injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In: Volpe JJ, Inder TE, Darras BT, et al. eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 36-3.)*

require no treatment, although phototherapy may be necessary to treat hyperbilirubinemia.

A **subgaleal hemorrhage** is a collection of blood in the loose connective tissue of the subgaleal space, located between the epicranial aponeurosis and the periosteum (see Fig. 122.1). There is often an association with vacuum-assisted delivery. A subgaleal hemorrhage manifests as a fluctuant mass that straddles cranial sutures or fontanels that increases in size after birth. The mechanism of injury is most likely secondary to rupture of emissary veins connecting the dural sinuses within the skull and the superficial veins of the scalp. Subgaleal hemorrhages are sometimes associated with skull fractures, suture diastasis, and fragmentation of the superior margin of the parietal bone. Extensive subgaleal bleeding can result in sequestration of more than 40% of the newborn's blood volume, which can potentially result in hemorrhagic shock. The mortality can be up to 14% due to hemorrhagic shock and is occasionally secondary to a hereditary coagulopathy **(hemophilia)**. In some cases, patients can develop a consumptive coagulopathy from massive blood loss. Subgaleal hemorrhages can present clinically with the triad of tachycardia, decreased hematocrit, and increasing occipital frontal circumference. When subgaleal hemorrhage is suspected, hemoglobin measurements should be performed as soon as possible and should be monitored every 4 to 8 hours, as should coagulation studies. Although it is not necessary to make the clinical diagnosis, optimal imaging for subgaleal hemorrhage is by CT or MRI. Radiographs of the skull can be done to identity accompanying fractures. These lesions typically resolve over 2 to 3 weeks.

Fractures of the skull may be caused by pressure in the setting of a forceps delivery, but they can occur rarely in uncomplicated vaginal deliveries. *Linear fractures,* the most common, cause no symptoms and require no treatment. Linear fractures should be followed up to demonstrate healing and to detect the possible complication of a leptomeningeal cyst. *Depressed fractures* often are referred to as "ping-pong" fractures because on x-ray they resemble an indented ping-pong ball. Affected infants may be asymptomatic unless they have associated intracranial injury. Surgical management of such an injury may not be necessary due to the infants' relatively thin and flexible skull bones rendering them amenable to remodeling, and intervention could be reserved for larger areas of depression. When intervention is required, the obstetric vacuum extractor is an ideal tool because it provides patent tubing unlikely to collapse during the application of suction. No traction is needed during the suction procedure, and the elevation of the depression can be ascertained by direct visualization, an audible "click" sound or a "give" sensation accompanied by an instantaneous pressure release. There is no clear recommendation for imaging in this population, but with newer techniques of low-dose CT imaging, current technology allows axial imaging to be constructed in the coronal and sagittal planes and into three-dimensional reformats, thus increasing the likelihood of detecting a fracture.

Subconjunctival and **retinal hemorrhages** are frequent; petechiae of the skin of the head and neck are also common. All are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that these hemorrhages are temporary and the result of normal events of delivery. The lesions resolve rapidly within the first 2 weeks of life.

122.2 Neonatal Traumatic Head Injuries

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Neonatal traumatic head injuries are estimated to affect ~3% of pregnancies and represent approximately 2% of neonatal deaths. Infrequently, these injuries occur during normal birth but the incidence rises in cases when the fetal head is large in proportion to the size of the mother's pelvic outlet, with prolonged labor, in breech or precipitous deliveries, or as a result of mechanical assistance with delivery. Massive **subdural hemorrhage**, often associated with tears in the tentorium cerebelli or less frequently in the falx cerebri, is rare, but is encountered more often in full-term than in premature infants. Patients with massive hemorrhage caused by tears of the tentorium or falx cerebri rapidly deteriorate and may die soon after birth. Most subdural and epidural hemorrhages resolve without intervention. Consultation with a neurosurgeon is recommended. Asymptomatic subdural hemorrhage may be noted within 48 hours of birth after vaginal or cesarean delivery. These are typically small hemorrhages, especially common in the posterior fossa, discovered incidentally in term infants imaged in the neonatal period, and usually of no clinical significance. The diagnosis of large subdural hemorrhage may be delayed until the chronic subdural fluid volume expands and produces macrocephaly, frontal bossing, a bulging fontanel, anemia, and sometimes seizures. CT scan and MRI are useful imaging techniques to confirm these diagnoses. Symptomatic subdural hemorrhage in term infants can be treated by a neurosurgical evacuation of the subdural fluid collection by a needle placed through the lateral margin of the anterior fontanel, or in severe cases an operative burr hole or craniotomy. In addition to birth trauma, **child abuse** must be suspected in all infants with subdural effusion after the immediate neonatal period. Most asymptomatic subdural hemorrhages following labor should resolve by 4 weeks of age.

Subarachnoid hemorrhage is often clinically silent in the neonate. Anastomoses between the penetrating leptomeningeal arteries or the

bridging veins are the most likely source of the bleeding. Most affected infants have no clinical symptoms, but the subarachnoid hemorrhage may be detected because of an elevated number of red blood cells in a lumbar puncture sample. Some infants experience short, benign seizures, which tend to occur on the second day of life. Rarely, an infant has a catastrophic hemorrhage and dies. There are usually no neurologic abnormalities during the acute episode or on follow-up. Significant neurologic findings should suggest an arteriovenous malformation, which can best be detected on CT or MRI.

122.3 Intracranial-Intraventricular Hemorrhage and Periventricular Leukomalacia

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Intracranial hemorrhage in preterm infants usually develops spontaneously. Less frequently, it may be caused by trauma or asphyxia, and rarely, it occurs from a primary hemorrhagic disturbance or congenital cerebrovascular anomaly. The very low birthweight infant (VLBW; birthweight <1,500 g) is at high risk for intracranial hemorrhages, with the risk for severe hemorrhage inversely related to gestational age. Intracranial hemorrhage often involves the ventricles **(intraventricular hemorrhage [IVH])** of premature infants delivered spontaneously without apparent trauma. Primary hemorrhagic disturbances and vascular malformations are rare and usually give rise to subarachnoid or intracerebral hemorrhage. In utero hemorrhage associated with maternal idiopathic or, more often, fetal alloimmune thrombocytopenia may appear as severe cerebral hemorrhage or as a porencephalic cyst after resolution of a fetal cortical hemorrhage. Intracranial bleeding may be associated with disseminated intravascular coagulation, isoimmune thrombocytopenia, and neonatal vitamin K deficiency, especially in infants born to mothers receiving phenobarbital or phenytoin.

Periventricular leukomalacia (PVL) is a disorder of the periventricular cerebral white matter that may be cystic or diffuse in nature. PVL may initially be observed during the first week of life in the VLBW infant as increased echogenicity of the periventricular white matter, sometime described as an echogenic "blush" or "flare." These areas of white matter abnormalities may become cystic on ultrasonography within 2 to 5 weeks and/or lead to ventriculomegaly from white matter volume loss, which can be visible on repeat ultrasonography at term equivalent age. Clinical risk factors for PVL include gestational age at birth and prenatal/postnatal factors including inflammation, hypoxia, postnatal steroid exposure, and metabolic disturbances.

EPIDEMIOLOGY

The overall incidence of IVH has decreased over the last few decades as a result of improved perinatal care, increased use of antenatal corticosteroids, surfactant to treat respiratory distress syndrome (RDS), and improved positive pressure mechanical ventilation strategies. The global incidence of IVH among preterm infants ranges from 14.7–44.7% with considerable variation across gestational age groups, neonatal intensive care units (NICUs), and countries. The risk for severe IVH is associated with infants with a gestational age ≤30 weeks' gestation, with the highest risk in infants born at ≤24 weeks' gestation. Infants born at >30 weeks' gestation have a low risk of severe IVH unless they have additional clinical risk factors such as low Apgar scores, metabolic acidosis, hypotension, or lack of antenatal steroids.

PVL can be described in three major pathologic forms: macroscopic cystic white matter injury, microscopic cystic white matter injury, and nonnecrotic diffuse white matter injury. Macroscopic cystic white matter injury represents the most severe form of PVL and fortunately affects <5% of very preterm infants born <32 weeks. With advances in neonatal care, there has been a shift from large cystic injury to small punctate injury. In microscopic cystic white matter injury, the necrotic areas are small and result in focal areas of gliosis, which ultrasonography is not sensitive enough to detect. The most common form of PVL in the preterm population is nonnecrotic diffuse PVL. Diffuse PVL is estimated to affect nearly a third of infants born <32 weeks and is best recognized on MRI.

PATHOGENESIS

The major neuropathologic lesions associated with VLBW infants are IVH and PVL. IVH in premature infants occurs in the gelatinous subependymal **germinal matrix**. This periventricular area is the site of origin for embryonal neurons and fetal glial cells, which migrate outwardly to the cortex. Immature and fragile blood vessels in this highly vascular region of the developing brain combined with disturbances in cerebral blood flow and coagulation predispose premature infants to hemorrhage. The germinal matrix involutes as the infant approaches 34 to 36 weeks' gestation, and the tissue's vascular integrity improves; therefore IVH is much less common in the late preterm and term infant. The cerebellum also contains a germinal matrix and is susceptible to hemorrhagic injury. **Periventricular hemorrhagic infarction (PVHI)**, previously known as **grade IV IVH**, often develops after a large IVH because of venous congestion. PVHI is not an extension of the IVH into the parenchyma. Predisposing factors for IVH include prematurity, RDS, hypoxia-ischemia, exaggerated fluctuations in cerebral blood flow (hypotensive injury, hypervolemia, hypertension), reperfusion injury of damaged vessels, reduced vascular integrity, increased venous pressure (pneumothorax, venous thrombus), or thrombocytopenia.

The pathogenesis of PVL appears to involve both intrauterine and postnatal events. A complex interaction exists between the development of the cerebral vasculature and the regulation of cerebral blood flow (both of which depend on gestational age), disturbances in the oligodendrocyte precursors required for myelination, and maternal/fetal infection and inflammation. Postnatal hypoxia or hypotension, necrotizing enterocolitis (NEC) with its resultant inflammation, and severe neonatal infection may all result in white matter injury. The risk for PVL increases in infants with severe IVH or ventriculomegaly.

CLINICAL MANIFESTATIONS

Most infants with IVH, including some with moderate to severe hemorrhages, have no initial clinical signs **(silent IVH)**. Some premature infants with severe IVH may have an acute deterioration on the second or third day of life **(catastrophic IVH)**. Hypotension, apnea, pallor, stupor or coma, seizures, decreased muscle tone, metabolic acidosis, shock, and decreased hematocrit (or failure of hematocrit to increase after transfusion) may be the first clinical indications. A *saltatory progression* may occur over several hours to days and manifest as intermittent or progressive alterations of levels of consciousness, abnormalities of tone and movement, respiratory signs, and eventually other features of the acute catastrophic IVH. Rarely, IVH may manifest at birth or even prenatally; the majority of cases of IVH in the preterm infant occur within the first 3 days of life. Of those, approximately 50% of hemorrhages occur within the first 5 hours, 70% occur within the first day of life, and by 7 days of life 95% of IVH will have occurred. A small percentage of infants have late hemorrhage, between days 14 and 30. IVH as a primary event is rare after the first month of life.

The severity of hemorrhage is defined by the location and degree of bleeding and ventricular dilation on cranial imaging. In a **grade I** hemorrhage, bleeding is isolated to the subependymal area. In **grade II** hemorrhage, there is bleeding within the ventricle *without* evidence of ventricular dilation. **Grade III** hemorrhage is IVH with ventricular dilation. In **PVHI** hemorrhage (formerly called **grade IV**, see previously), there is intraventricular and parenchymal hemorrhage (Fig. 122.3). Another grading system describes three levels of increasing severity of IVH detected on ultrasound: In **grade I,** bleeding is confined to the germinal matrix–subependymal region or to <10% of the ventricle (approximately 35% of IVH cases); **grade II** is defined as intraventricular bleeding with 10–50% filling of the ventricle (40% of IVH cases); and in **grade III**, >50% of the ventricle is involved, with dilated ventricles (see Fig. 122.3).

One of the major complications resulting from IVH is the development of **posthemorrhagic ventricular dilation (PHVD)**. Following a large IVH, multiple small clots throughout the ventricular system may obstruct

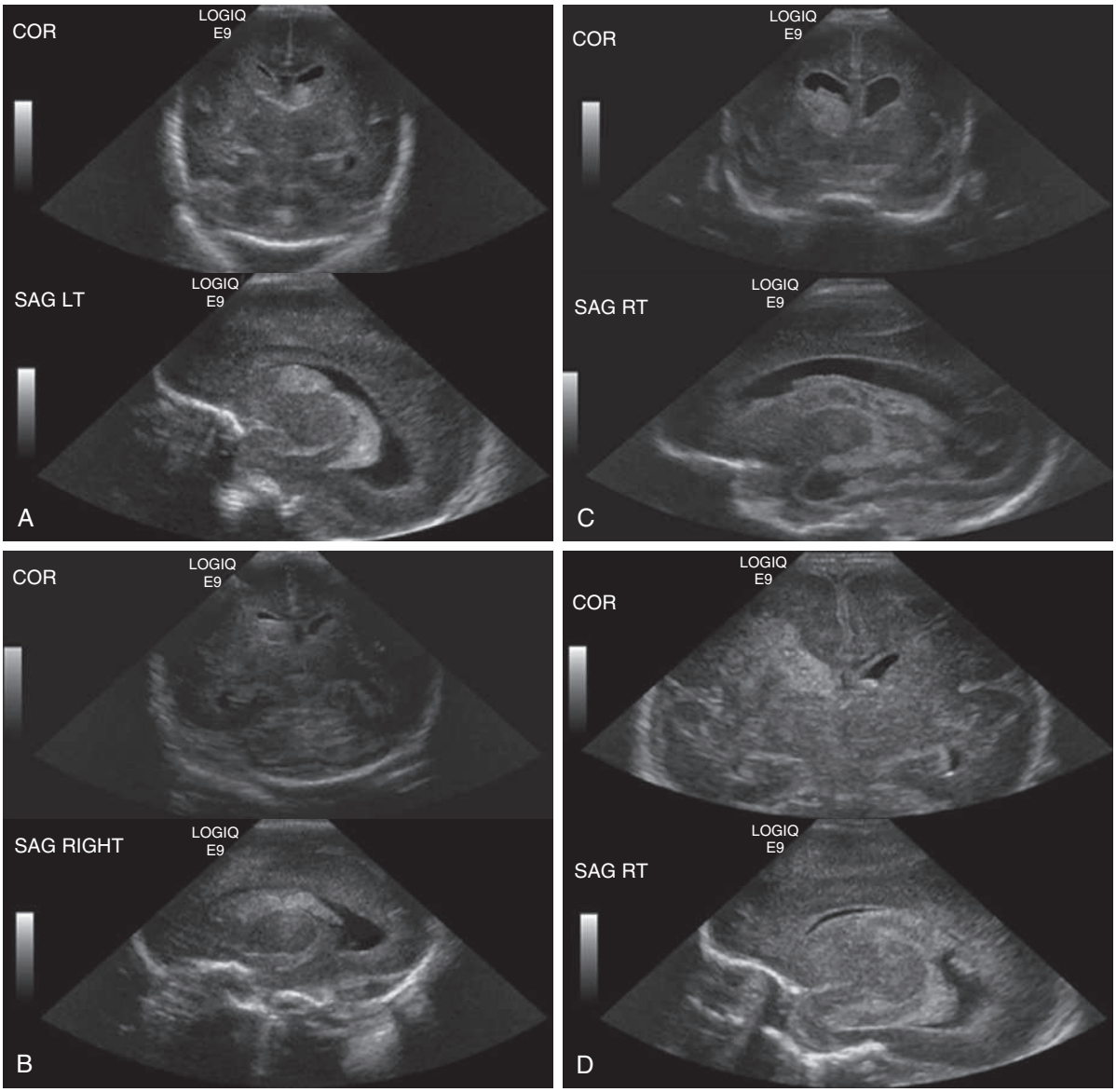

Fig. 122.3 Grading of the severity of germinal matrix–intraventricular hemorrhage (IVH): coronal (COR) and parasagittal (SAG) ultrasound scans. **A,** Germinal matrix hemorrhage, grade I. **B,** IVH (filling <50% of ventricular area), grade II. **C,** IVH with ventricular dilatation, grade III. **D,** Large IVH with associated parenchymal echogenicity (hemorrhagic infarct), grade IV. Note that the terminology has now changed for "grade IV" to periventricular hemorrhagic infarction (PVHI). (*From Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, et al., eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 24-2.*)

cerebrospinal fluid (CSF) flow and resorption, all in the face of ongoing production of CSF in the choroid plexus in the lateral ventricles and the roof of the third ventricle. The progressive accumulation of CSF changes the shape of the lateral ventricles from a slit to a balloon. The expanding ventricles distort the developing brain and intracerebral pressure (ICP) eventually starts to rise. As the preterm skull is very compliant, the ventricles can expand without pressure rising initially but eventually can result in increased ICP. PHVD develops in 30–50% of infants with severe IVH and is initially asymptomatic in most patients. *Therefore sequential cranial ultrasonography facilitates early detection*. The term ventriculomegaly is occasionally used for both infants with ventricular enlargement following IVH as well as those without hemorrhage. In infants without IVH, ventricular enlargement is more likely due to *white matter loss* rather than an accumulation of CSF. Therefore it is preferable to use the term PHVD when ventricular enlargement follows IVH.

PVL is usually clinically asymptomatic until the neurologic sequelae of white matter damage become apparent in later infancy as spasticity and/or motor deficits. PVL may be present at birth but usually occurs later, when the echodense phase is seen on ultrasound (3 to 10 days of life), followed by the typical echolucent/cystic phase (14 to 20 days).

DIAGNOSIS

Intracranial hemorrhage is suspected on the basis of history, clinical manifestations, and knowledge of the birthweight-specific risks for IVH. Associated clinical signs of IVH are typically nonspecific or absent. Neuroimaging recommendations that premature infants ≤30 weeks of gestation and selected infants with gestational age >30 weeks who are believed to be at increased risk for brain injury on the basis of identified risk factors should be screened for IVH with cranial ultrasonography. Standard ultrasonography screening includes views from the anterior and mastoid fontanelles. Additional posterior fontanelle and vascular imaging can be performed for additional information. Routine cranial ultrasonographic screening is recommended by 7 to 10 days of age, but earlier imaging may be warranted if clinical signs and symptoms are suggestive of significant injury. Repeat cranial ultrasonography screening is recommended to be performed at 4 to 6 weeks of age and at term equivalent age or before hospital discharge. CT is not considered a part of routine imaging techniques of the preterm brain. MRI for infants born ≤30 weeks gestational age is not indicated as a routine procedure, although could be offered to families of high-risk infants after a conversation about the limits of prognosticating long-term outcomes using MRI.

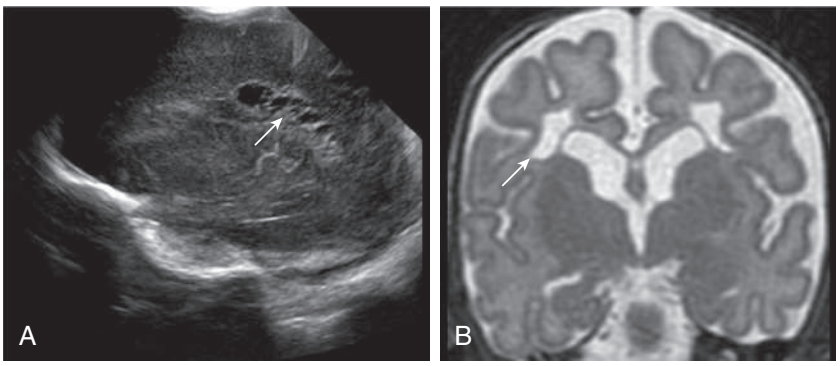

Fig. 122.4 Severe cystic periventricular leukomalacia. **A,** Parasagittal ultrasound image showing numerous large cysts superolateral to the lateral ventricle *(arrow).* **B,** Coronal T2 weighted MR image in which cysts are present superolateral to the lateral ventricles *(arrow).* (*From Neil JJ, Volpe JJ. Encephalopathy of prematurity: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 16-1.*)

Table 122.1 Short-Term Outcome of Germinal Matrix–Intraventricular Hemorrhage as a Function of Severity of Hemorrhage and Birthweight*

	DEATHS IN FIRST 14 DAYS		PVD (SURVIVORS >14 DAYS)	
SEVERITY OF HEMORRHAGE	**<750 g (n = 75)**	**751-1500 g (n = 173)**	**<750 g (n = 56)**	**751-1500 g (n = 165)**
Grade I	3/24 (12)	0/80 (0)	1/21 (5)	3/80 (4)
Grade II	5/21 (24)	1/44 (2)	1/16 (6)	6/43 (14)
Grade III	6/19 (32)	2/26 (8)	10/13 (77)	18/24 (75)
Grade III and apparent PVHI	5/11 (45)	5/23 (22)	5/6 (83)	12/18 (66)

*Values are n (%). Deaths occurring later in the neonatal period are not shown; the total mortality rates (early and late deaths) are approximately 50–100% greater for each grade of hemorrhage and birthweight than those shown in the table for early deaths alone.
PVHI, Periventricular hemorrhagic infarction; PVD, progressive ventricular dilation.
Adapted from Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn.* 6th ed. Philadelphia: Elsevier; 2018. Table 24-15; with data from Murphy BP, Inder TE, Rooks V, Taylor GA, et al. Posthemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. *Arch Dis Child Fetal Neonatal Ed.* 2002;87:F37–F41.

Table 122.2 Long-Term Outcome: Neurologic Sequelae in Survivors with Germinal Matrix–Intraventricular Hemorrhage as a Function of Severity of Hemorrhage*

SEVERITY OF HEMORRHAGE	INCIDENCE OF DEFINITE NEUROLOGIC SEQUELAE† (%)
Grade I	15
Grade II	25
Grade III	50
Grade III and apparent PVHI	75

*Data are derived from reports published since 2002 and include personal published and unpublished cases. Mean values (to nearest 5%) and considerable variability among studies was apparent, especially for the severe lesions.
†Definite neurologic sequelae included principally cerebral palsy or mental retardation, or both.
PVHI, Periventricular hemorrhagic infarction.
Adapted From Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, et al. eds. *Volpe's Neurology of the Newborn.* 6th ed. Philadelphia: Elsevier; 2018: Table 24-16.

Sequential ultrasonography appears to have the best yield for identifying lesions associated with cerebral palsy. In one study, 29% of low birthweight (LBW) infants who later experienced cerebral palsy *did not* have radiographic evidence of PVL until after 28 days of age. Ultrasound also detects the precystic and cystic symmetric lesions of PVL and the asymmetric intraparenchymal echogenic lesions of cortical hemorrhagic infarction (Fig. 122.4). Cranial ultrasonography may be useful in monitoring delayed development of cortical atrophy, porencephaly, and the severity, progression, or regression of posthemorrhagic hydrocephalus (PHH).

PHH of prematurity is a common form of pediatric hydrocephalus, accounting for 20% of shunted hydrocephalus in the United States. Under normal conditions, CSF is primarily secreted into the cerebral ventricles by the choroid plexus and moves via bulk flow through the ventricular system and subarachnoid space before being absorbed at the arachnoid villi/granulations, which are fully developed after 35 weeks. An increase in CSF production or reduction in CSF absorption may result in ventricular enlargement if the system cannot compensate for the changes. Secondary white matter injury resulting from ventricular dilation is likely exacerbated by compression and ischemia from increased ICP of symptomatic PHH. Orbitofrontal head circumference, fontanel fullness, and the splaying of sutures all show limited reliability; therefore serial neuroimaging is highly valuable for clinical decision-making for neurosurgical intervention.

PROGNOSIS

The degree of IVH and presence of PVL are strongly linked to survival and neurodevelopmental impairment (Tables 122.1 and 122.2). For infants with birthweight <1,000 g, the incidence of severe neurologic impairment (defined as Bayley Scales of Infant Development IV mental developmental index <70, psychomotor development index <70, cerebral palsy, blindness, or deafness) after IVH is highest with grade IV hemorrhage and lower birthweight. PVL, cystic PVL, and progressive hydrocephalus requiring shunt insertion are each independently associated with a poorer prognosis (Table 122.3). The risk of a poor neurodevelopmental outcome is significantly higher when severe IVH is complicated with PHVD (40–60%) and more so for infants who eventually develop PHH (75–88%). In the pre-surfactant era, up to 82% of infants with PHH who survived developed significant neurologic impairments with cerebral palsy being the most common clinical sequelae (74%). The Drainage, Irrigation, Fibrinolytic Therapy (DRIFT) trial performed neurocognitive assessments at both 2 years and 10 years after birth and demonstrated improved cognitive ability when considering birthweight, IVH grade, and sex. Infants who received DRIFT were almost twice as likely to survive without severe cognitive disability than those who received standard treatment. The

Table 122.3 Ultrasound Diagnosis of Periventricular Leukomalacia

US APPEARANCE	TEMPORAL FEATURES	NEUROPATHOLOGIC CORRELATION
Echogenic foci, bilateral, posterior > anterior	First week	Necrosis with congestion and/or hemorrhage (size >1 cm)
Echolucent foci ("cysts")	1-3 weeks	Cyst formation secondary to tissue dissolution (size >3 mm)
Ventricular enlargement, often with disappearance of "cysts"	≥2-3 months	Deficient myelin formation; gliosis, often with collapse of cyst

From Neil JJ, Volpe JJ. Encephalopathy of prematurity: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn*. 6th ed. Philadelphia: Elsevier; 2018: Table 16-6.

Table 122.4 Proposed Risk Stratification and Management of Infants with PHVD

Green Zone	Yellow Zone	Red Zone
Key criteria: Ventricular size with the following • VI ≤97th percentile and • AHW ≤6 mm And Absence of the following clinical criteria: • HC growth >2 cm per week • Separated sutures • Bulging fontanelles **Management:** • Observation in NICU • cUS twice a week until stable for 2 weeks then every 1-2 weeks until 34 weeks PMA • MRI at term equivalent	**Key criteria:** Ventricular size with the following • VI >97th percentile and • AHW >6 mm and/or TOD >25 mm And Absence of the following clinical criteria: • HC growth >2 cm per week • Separated sutures • Bulging fontanelles **Management:** • Referral to a regional center for neurosurgical review • Consider LP 2-3 times • cUS 2-3X a week until stable for 2 weeks then every 1-2 weeks until 34 weeks PMA • Neurosurgical intervention when no stabilization occurs • MRI at term equivalent	**Key criteria:** Ventricular size with the following • VI >97th percentile + 4mm and • AHW >10 mm and/or TOD >25 mm Or Any of the following clinical criteria: • HC growth >2 cm per week • Separated sutures • Bulging fontanelles **Management:** • Consider LP 2-3 times • Neurosurgical intervention including either temporizing measures or VP shunt • MRI at term equivalent

Consider alterations in NIRS (i.e., decrease cerebral oxygenation) or Doppler US (i.e., increase in Resistive Index) as additional information that may suggest impairment in cerebral perfusion and more urgent need for intervention.

VI, ventricular index; AHW, anterior horn width; cUS, cranial ultrasound; TOD, thalamo-occipital distance; LP, lumbar puncture; HC, head circumference; NIRS, near-infrared spectroscopy; NICU, neonatal intensive care unit; PMA, postmenstrual age.
From El-Dib M, Limbrick DD, Inder T, et al. Management of post-hemorrhagic ventricular dilation in the infant born preterm. *J Pediatr*. 2020;226:16–26. Fig. 5.

Early versus Late Ventricular Intervention Study (ELVIS) trial demonstrated the effectiveness of intervention at a low threshold of ventricular dilation on the outcomes of death and severe neurodevelopmental disability in preterm infants with PHVD. Post hoc analysis of this study demonstrated that infants who went on to having a shunt had better neurodevelopmental outcome scores if interventions were done at a lower threshold.

TREATMENT

No treatment is available for **IVH** once it has occurred, and the management is largely symptomatic. Seizures should be treated with anticonvulsant drugs. Anemia and coagulopathy require transfusion with packed red blood cells or fresh-frozen plasma. Shock and acidosis are treated with fluid resuscitation.

Insertion of a **ventriculoperitoneal shunt** is the preferred method to treat progressive and symptomatic **PHH**. Some infants require temporary CSF diversion before a permanent shunt can be safety inserted. Diuretics and acetazolamide are not effective. Ventricular access devices (reservoirs) and externalized ventricular drains are potential temporizing interventions, although there is an associated risk of infection and *puncture porencephaly* from injury to the surrounding parenchyma. A **ventriculosubgaleal shunt** inserted from the ventricle into a surgically created subgaleal pocket provides a closed system for constant ventricular decompression without these additional risk factors. Decompression is regulated by the pressure gradient between the ventricle and the subgaleal pocket.

One approach to therapeutic interventions is based on the severity of ultrasonographic dimensions of ventricular size (Table 122.4 and Fig. 122.5)

PREVENTION

Improved perinatal care is imperative to minimize traumatic brain injury and decrease the risk of preterm delivery. The incidence of traumatic intracranial hemorrhage may be reduced by judicious management of cephalopelvic disproportion and operative delivery. Fetal or neonatal hemorrhage caused by maternal idiopathic thrombocytopenic purpura or alloimmune thrombocytopenia may be reduced by maternal treatment with corticosteroids, intravenous immunoglobulin (IVIG), fetal platelet transfusion, or cesarean birth. Meticulous care of the VLBW infant's respiratory status and fluid-electrolyte

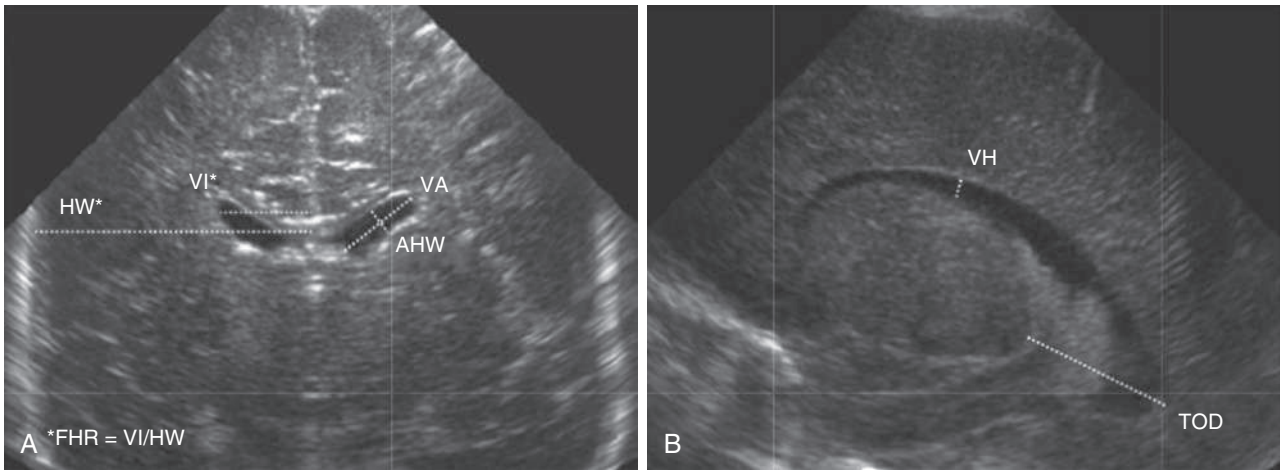

Fig. 122.5 Ventricular parameters measured in the (A) coronal and (B) sagittal planes by cranial ultrasonography. AHW, anterior horn width; FHR, frontal horn ratio; HW, hemispheric width; TOD, thalamo-occipital distance; VA, ventricular axis; VH, ventricular height; VI, ventricular index. (*From Brouwer MJ, de Vries LS, Pistorius L, et al. Ultrasound measurements of the lateral ventricles in neonates: why, how, and when? A systematic review. Acta Paediatr. 2010;99:1298–306.*)

management—avoidance of acidosis, hypocarbia, hypoxia, hypotension, wide fluctuations in neonatal blood pressure or P_{CO_2} (and secondarily fluctuation in cerebral perfusion pressure), and pneumothorax—are important factors that may affect the risk for development of IVH and PVL.

The most important protective factor against the development of IVH is antenatal administration of corticosteroids. A single course of antenatal corticosteroids is recommended for pregnant people between 24 0/7 weeks and 36 6/7 weeks of gestation who are at risk for preterm delivery within 7 days. It also may be considered for pregnant people starting at 23 weeks of gestion who are at risk for preterm delivery within 7 days, based on the family's decision regarding resuscitation. A rescue course of corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Antenatal administration of magnesium sulfate was not associated with a reduction in the incidence of IVH, although it has been associated with a reduction in the risk of cerebral palsy. Prophylactic indomethacin showed a significant reduction in the incidence of severe IVH; however, this reduction in severe IVH was not associated with a reduction in severe neurosensory impairment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

122.4 Hypoxic-Ischemic Encephalopathy

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Hypoxemia, a decreased arterial concentration of oxygen, frequently results in **hypoxia**, or decreased oxygenation to cells or organs. **Ischemia** refers to blood flow to cells or organs that is inadequate to maintain physiologic function. **Hypoxic-ischemic encephalopathy (HIE)** is a leading cause of neonatal brain injury, morbidity, and mortality globally. In the developed world, incidence is estimated at 1-8 per 1,000 live births, and in the developing world, estimates are as high as 26 per 1,000.

Approximately 20–30% of infants with HIE (depending on the severity) die in the neonatal period, and 33–50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, decreased intelligence quotient [IQ], learning/cognitive impairment). The greatest risk of adverse outcome is seen in infants with severe fetal acidosis (pH <6.7) (90% death/impairment) and a base deficit >25 mmol/L (72% mortality). Multiorgan failure and insult can occur (Table 122.5).

ETIOLOGY

Neonatal encephalopathy and seizures, in the absence of major congenital malformations or metabolic or genetic syndromes, appear to be caused by perinatal events. Brain MRI or autopsy findings in full-term neonates with encephalopathy demonstrate that 80% have acute injuries, <1% have prenatal injuries, and 3% have non–hypoxic-ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from maternal infections, exposures, diabetes, toxemia or postmaturity.

Table 122.5 Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECTS
Central nervous	Hypoxic-ischemic encephalopathy, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integumentary	Subcutaneous fat necrosis
Hematologic	Disseminated intravascular coagulation

Table 122.6 Topography of Brain Injury in Term Infants with Hypoxic-Ischemic Encephalopathy and Clinical Correlates

AREA OF INJURY	LOCATION OF INJURY	CLINICAL CORRELATES	LONG-TERM SEQUELAE
Selective neuronal necrosis	Entire neuraxis, deep cortical area, brainstem and pontosubicular	• Stupor or coma • Seizures • Hypotonia • Oculomotor abnormalities • Suck/swallow abnormalities	• Cognitive delay • Cerebral palsy • Dystonia • Seizure disorder • Ataxia • Bulbar and pseudobulbar palsy
Parasagittal injury	Cortex and subcortical white matter Parasagittal regions, especially posterior	• Proximal-limb weakness • Upper extremities affected > lower extremities	• Spastic quadriparesis • Cognitive delay • Visual and auditory processing difficulty
Focal ischemic necrosis	Cortex and subcortical white matter Vascular injury (usually middle cerebral artery distribution)	• Unilateral findings • Seizures common and typically focal	• Hemiparesis • Seizures • Cognitive delays
Periventricular injury	Injury to motor tracts, especially lower extremity	• Bilateral and symmetric weakness in lower extremities • More common in preterm infants	• Spastic diplegia

Adapted from Volpe JJ, ed. *Neurology of the Newborn*. 4th ed. Philadelphia: Saunders; 2001.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (see Chapter 117). Uterine contractions may further reduce umbilical oxygenation, depressing the fetal cardiovascular system and CNS and resulting in low Apgar scores and respiratory depression at birth.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) severe anemia (severe hemorrhage, hemolytic disease); (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage; or (4) failure to breathe after birth because of in utero CNS injury or drug-induced suppression.

PATHOPHYSIOLOGY AND PATHOLOGY

The topography of cerebral injury typically correlates with areas of decreased cerebral blood flow and areas of relatively higher metabolic demand, although regional vulnerabilities are impacted by gestational age and severity of insult (Table 122.6). After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generates increased amounts of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamatergic mechanism has a role in neurotoxicity. Whether this mechanism involves tissue accumulation of an abnormal amount of glutamate or altered sensitivity to the interaction between glutamate and its endogenous family of receptors (i.e., *N*-methyl-D-aspartate [NMDA], amino-3-hydroxy-5-methyl-4-isoxazole propionate [AMPA], and kainite) is unknown. However, receptor activation results in a cascade of events that leads to cell death by swelling (oncosis) or apoptosis. Along with these changes in the CNS, there are also potentially exacerbating bioenergetic changes as a result of the circulatory response with increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, at first trying to maintain perfusion of the brain, heart, and adrenal glands in preference to the lungs, liver, kidneys, and intestine.

The pathology of hypoxia-ischemia in tissues outside the CNS depends on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (see Chapter 130). If fetal distress produces gasping, amniotic fluid contents (i.e., meconium, desquamation products, lanugo) may be aspirated into the trachea or lungs with subsequent complications, including pulmonary hypertension and pneumothoraces.

Table 122.7 Poor Predictive Variables for Death/Disability After Hypoxic-Ischemic Encephalopathy

- Low (0-3) 10 min Apgar score
- Need for CPR in the delivery room
- Delayed onset (≥20 min) of spontaneous breathing
- Severe neurologic signs (coma, hypotonia, hypertonia)
- Seizures onset ≤12 hr or difficult to treat
- Severe, prolonged (~7 days) EEG findings including burst suppression pattern
- Prominent MRI basal ganglia/thalamic lesions
- Oliguria/anuria >24 hr
- Abnormal neurologic exam ≥14 days

CPR, Cardiopulmonary resuscitation; EEG, electroencephalogram.

CLINICAL MANIFESTATIONS

At delivery, the presence of meconium-stained amniotic fluid indicates that fetal distress may have occurred. At birth, affected infants may have neurologic impairment and may fail to breathe spontaneously. Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also nonspecific initial signs of potential HIE. During the ensuing hours, infants may be hypotonic, may change from a hypotonic to a hypertonic state, or their tone may appear normal (Tables 122.7 and 122.8). Cerebral edema may develop during the next 24 hours and result in profound brainstem depression. During this time, seizure activity may occur; seizures may be severe and refractory to standard doses of anticonvulsants. Although most often a result of the HIE, seizures in asphyxiated newborns may also be caused by vascular events (hemorrhage, arterial ischemic stroke, or sinus venous thrombosis), metabolic derangements (hypocalcemia, hypoglycemia), CNS infection, and cerebral dysgenesis or genetic disorders (nonketotic hyperglycinemia, vitamin-dependent epilepsies, channelopathies). Congenital conditions that result in neuromuscular weakness and poor respiratory effort may also result secondarily in neonatal hypoxic brain injury and seizure. Such conditions might include congenital myopathies, congenital myotonic dystrophy, or spinal muscular atrophy.

In addition to CNS dysfunction, systemic organ dysfunction is noted in up to 80% of affected neonates. Myocardial dysfunction and

Table 122.8 Hypoxic-Ischemic Encephalopathy in Term Infants

SIGNS	STAGE 1 (MILD)	STAGE 2 (MODERATE)	STAGE 3 (SEVERE)
Level of consciousness	Hyperalert, responds to minimal stimuli	Lethargic	Stuporous, coma
Spontaneous activity	Normal or decreased	Decreased	None
Posture	Mild flexion of distal joints (fingers, wrist)	Distal flexion or complete extension	Decerebrated
Tone	Normal	Hypotonia (focal or general) or hypertonia	Flaccid or rigid
PRIMITIVE REFLEXES	1	2	3
Suck	Weak or incomplete	Weak or bite	Absent
Moro reflex	Intact, low threshold	Incomplete	Absent
AUTONOMIC NERVOUS SYSTEM	1	2	3
Pupils	Mydriasis	Miosis	Variable or nonreactive
Heart rate	Tachycardia	Bradycardia	Variable heart rate
Respirations	Hyperventilation	Periodic breathing	Apnea or requiring ventilation
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Adapted from Chalak L, Latremouille S, Mir I, Sánchez PJ, Sant'Anna G. A review of the conundrum of mild hypoxic-ischemic encephalopathy: current challenges and moving forward. *Early Hum Dev.* 2018;120:88–94.

cardiogenic shock, persistent pulmonary hypertension, RDS, gastrointestinal perforation, and acute kidney and liver injury are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 122.5).

The severity of neonatal encephalopathy depends on the duration and timing of injury. The need to define severity is rooted in the need to determine eligibility for *therapeutic hypothermia*, a treatment that decreases death and disability in moderate to severe HIE. A clinical grading score first proposed by Sarnat and colleagues continues to be a useful tool. Symptoms develop over hours and days, making it important to perform serial neurologic examinations (see Tables 122.7 and 122.8). Infants with moderate to severe HIE are characterized by disturbed neurologic function, altered level of consciousness, depressed tone, abnormal reflexes, and difficulty maintaining spontaneous respirations, and seizures. An empirically validated definition of mild HIE within 6 hours uses two steps: the first step is screening for fetal acidosis and acute perinatal events, and the second step has an examiner use a modified Sarnat scoring, which is expanded to include mild in addition to moderate and severe abnormalities.

DIAGNOSIS

MRI is the most sensitive imaging modality for detecting hypoxic brain injury in the neonate. Although such injury can be detected at various times and with varying pulse sequences, diffusion-weighted sequences obtained in the first 3-5 days following a presumed sentinel event are optimal for identifying acute injury (Figs. 122.6-122.9 and Table 122.9). Severe HIE is characterized on MRI by a central pattern injury that includes the thalamus, posterior limb of the internal capsule, and hippocampus with the most severe HIE resulting in involvement of the entire cortex. Magnetic resonance spectroscopy performed within first 24 hours after birth in a full-term infant is very sensitive to the severity of HIE-related brain injury. Elevated lactate/creatine ratio on day 1 of life is a predictor of adverse neurologic outcome, whereas absence of lactate predicts a normal outcome. Where MRI is unavailable or prevented by clinical instability, brain CT scans may be helpful in ruling out focal hemorrhagic lesions or large arterial ischemic strokes. Loss of gray-white differentiation and injury to the basal ganglia in more severe HIE can be detected on CT by experienced readers, but CT often misses more subtle forms of neonatal hypoxic brain injury and results in significant radiation exposure. Ultrasound has limited utility in evaluation of hypoxic injury in the term infant, but it too can be useful for excluding hemorrhagic lesions or hydrocephalus. Because of factors of size and clinical stability, ultrasound is the initial preferred (and sometimes only feasible) modality in evaluation of the preterm infant.

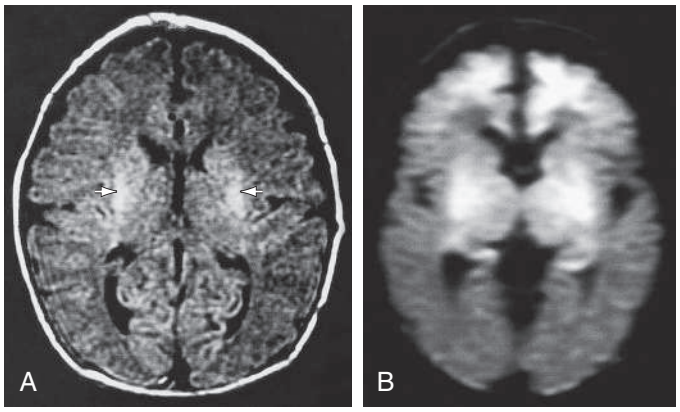

Fig. 122.6 MR images of selective neuronal injury. The infant experienced intrapartum asphyxia and had seizures on the first postnatal day. MRI was performed on the fifth postnatal day. **A,** Axial, fluid-attenuated, inversion recovery image shows increased signal in the putamen bilaterally *(arrows)* but no definite abnormality in the cerebral cortex. **B,** By contrast, a diffusion-weighted image shows striking increased signal intensity (i.e., decreased diffusion) in the frontal cortex (in addition to a more pronounced basal ganglia abnormality). (*From Volpe JJ, ed. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008. p. 420.*)

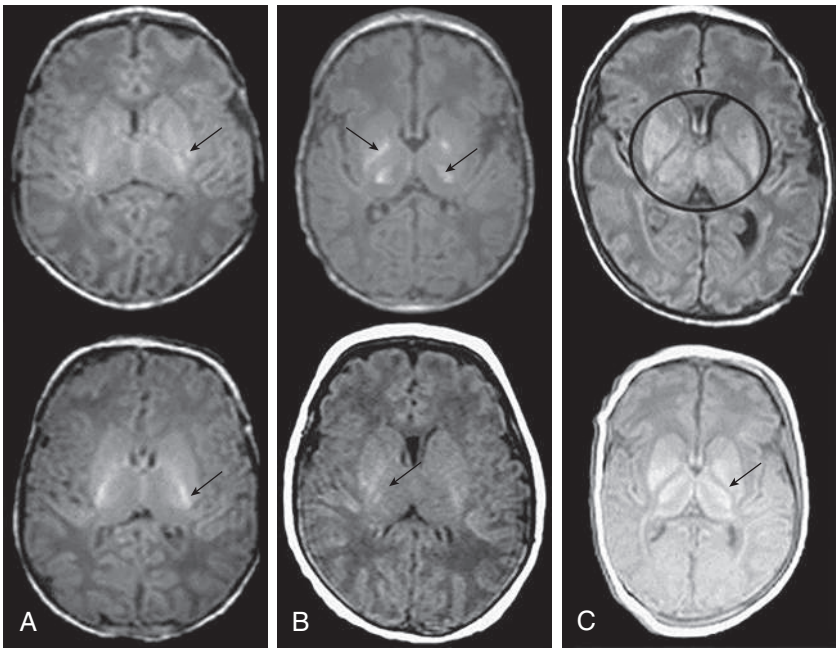

Fig. 122.7 MR images of basal ganglia/thalamic (BG/T) injury and signal intensity. *Top row,* Axial T1 weighted MR images showing mild BG/T lesions *(arrow)* **(A)**, moderate BG/T injury *(arrows)* **(B)**, and severe BG/T abnormalities *(circled)* **(C).** *Bottom row,* Axial T1 weighted MR images showing normal signal intensity (SI) in the posterior limb of the internal capsule (PLIC) *(arrow)* **(A),** equivocal, asymmetric, and slightly reduced SI in the PLIC *(arrow)* **(B),** and abnormal, absent SI in the PLIC *(arrow)* **(C).** (*From Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:675–682.*)

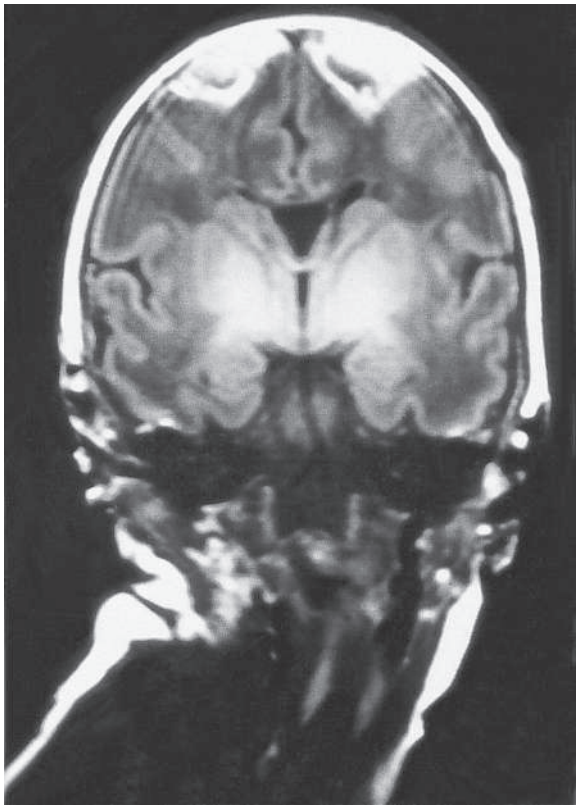

Fig. 122.8 MR image of a parasagittal cerebral injury. Coronal T1 weighted image, obtained on the fifth postnatal day in an asphyxiated term infant, shows striking triangular lesions in the parasagittal areas bilaterally; increased signal intensity is also apparent in the basal ganglia and thalamus bilaterally. (*From Volpe JJ, ed. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008. p. 421.*)

Neurophysiology Studies

Monitoring the brain of the sick newborn infant in the NICU using either multichannel electroencephalography (EEG) or limited channel amplitude integrated EEG (aEEG) may help to determine which infants are at highest risk for developmental sequelae of neonatal brain injury (Tables 122.10 and 122.11). Multichannel EEG with video is the gold standard for monitoring newborn brain function; at least 24-hour monitoring is recommended for infants at risk for seizures. The neonatal EEG contains complex spatiotemporal information and can be difficult to interpret, requiring many years in neurophysiology training. As a result, in many NICUs, EEG signal processing of a limited number of channels, with a more accessible method of data presentation, has been adopted (aEEG). Even in the absence of obvious seizures, a 24-hour multichannel EEG recording is recommended and, in infants undergoing hypothermia therapy, 72 hours is optimal to cover duration of intervention. It is known that EEG in HIE evolves following the primary HIE injury and that EEG monitoring is essential to assess this evolution and recovery. Description of EEG background grades and seizures in HIE include normal trace, which is a normal amplitude with sleep–wake cycling; mildly abnormal trace, which is a period of low amplitude and lack of sleep–wake cycling; moderately abnormal trace, which is periods of discontinuity <10 seconds; and severely abnormal trace with burst suppression pattern and discontinuity of activity for 10-60 seconds (Fig. 122.10). An aEEG is a good option if multichannel EEG is not available. The signal from biparietal electrodes is smoothed and the amplitude integrated and shows the baseline background electrical activity. A voltage classification scheme for aEEG use in HIE has been developed as follows: normal voltage (5-10 μV) and abnormal voltage (lower margin <5 μV and upper margin >10 μV).

TREATMENT

Therapeutic hypothermia, whether head cooling or systemic cooling (by servo-control to a core rectal or esophageal temperature of 33.5°C [92.3°F] within the first 6 hours after birth and maintained for 72 hours) has been shown to reduce mortality and major neurodevelopmental impairment at 18 months of age. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI, suggesting systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures than selective head cooling. The therapeutic effect of hypothermia likely results from decreased secondary neuronal injury achieved by reducing rates of apoptosis and production of mediators related to neurotoxicity. There is also benefit in seizure reduction. The therapeutic benefit of hypothermia noted at 18-22 months of age is maintained later in childhood. Once established, hypothermia may not alter the prognostic findings on MRI.

Numerous studies seeking ways to extend the benefits of therapeutic hypothermia have been attempted. The foundational clinical trials of therapeutic hypothermia had strict treatment protocols and excluded infants born before 35 or 36 weeks completed gestational weeks, those weighing <1,800 g, and infants with major congenital abnormality. Practice variation exists for offering therapeutic hypothermia to infants

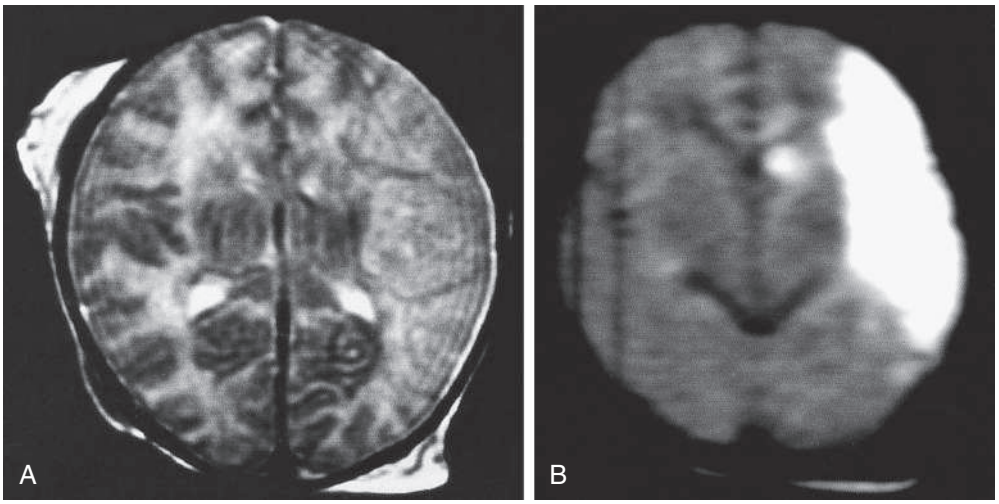

Fig. 122.9 MR images of focal ischemic cerebral injury. MRI was performed on the third postnatal day. **A,** Axial T2 weighted image shows a lesion in the distribution of the main branch of the left middle cerebral artery. **B,** Diffusion-weighted image demonstrates the lesion more strikingly. (*From Volpe JJ, ed. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008. p. 422.*)

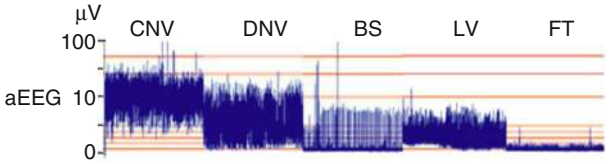

Fig. 122.10 Amplitude EEG patterns. Patterns are highlighted with pattern classification (continuous normal voltage [CNV], discontinuous normal voltage [DNV], burst suppression [BS], low voltage [LV], flat tracings [FT]). (*From Chalak L. New horizons in mild hypoxic-ischemic encephalopathy: A standardized algorithm to move past conundrum of care. Clin Perinatol. 2022;49:279–294. Fig. 3.*)

Table 122.9 Major Aspects of MRI in Diagnosis of Hypoxic-Ischemic Encephalopathy in the Term Infant

MAJOR CONVENTIONAL MR FINDINGS IN FIRST WEEK

- Cerebral cortical gray-white differentiation lost (on T1W or T2W)
- Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal peri-rolandic cortex
- Basal ganglia/thalamus, high signal (T1W and FLAIR), usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insult
- Parasagittal cerebral cortex, subcortical white matter, high signal (T1W and FLAIR)
- Periventricular white matter, decreased signal (T1W) or increased signal (T2W)
- Posterior limb of internal capsule, decreased signal (T1W or FLAIR)
- Cerebrum in a vascular distribution, decreased signal (T1W), but much better visualized as decreased diffusion (increased signal) on diffusion-weighted MRI
- **Diffusion-weighted MRI** more sensitive than conventional sequences in MRI, especially in first days after birth, when former shows decreased diffusion (increased signal) in injured areas

FLAIR, Fluid-attenuated inversion recovery; T1W and T2W, T1 weighted and T2 weighted images.
From Volpe JJ, ed. *Neurology of the Newborn.* 5th ed. Philadelphia: Elsevier; 2008: Table 9-16.

Table 122.10 Value of Electroencephalography in Assessment of Asphyxiated Term Infants

- Detection of severe abnormalities (i.e., CLV, FT, BSP) in first hours of life has a positive predictive value of an unfavorable outcome of 80–90%.
- Severe abnormalities may improve within 24 hr (~50% of BSP and 10% of CLV/FT).
- Rapid recovery of severe abnormalities is associated with a favorable outcome in 60% of cases.
- The *combination* of early neonatal neurologic examination and early aEEG enhances the positive predictive value and specificity.

aEEG, Amplitude integrated encephalography; BSP, burst suppression pattern; CLV, continuous low voltage; FT, flat trace.
From Inder TE, Volpe JJ. Hypoxic-ischemic injury in the term infant: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn.* 6th ed. Philadelphia: Elsevier; 2018: Table 20-28.

who do not meet the original study criteria, although debate for these practices also exist. A multicenter randomized clinical trial investigating the benefit of use of therapeutic hypothermia beyond 6 hours after birth reported a modest and "nonconclusive" effect. Importantly, this study extended the duration of hypothermia from 72 to 96 hours based on preclinical data suggesting that a longer period of treatment was needed at later initiation times. Assessment of deeper or longer cooling failed to show benefit in short-term outcomes, and its use is not supported by evidence nor clinically justifiable. Multicenter clinical trials are underway to assess the use of therapeutic hypothermia in preterm infants born between 33 and 35 weeks' gestation. The term "major congenital anomalies" in the original trials lead to the exclusion of numerous conditions with a favorable prognosis for survival and neurodevelopment, including trisomy 21. Unless the identified anomaly specifically imparts a medical contraindication to therapeutic hypothermia, the infant is moribund, or treatment does not align with the broader goals of care for the infant, categorical exclusion of the infant from therapeutic hypothermia solely based on the presence of one or more major congenital anomalies is likely not ethically justifiable. There have been few studies to investigate the use of therapeutic hypothermia in neonates who are beyond the perinatal period. Presently, clinical research on "targeted temperature management" in infants has been done in the pediatric intensive care setting and has little applicability to NICUs.

Complications of induced hypothermia include thrombocytopenia (usually without bleeding), reduced heart rate, and subcutaneous fat necrosis (sometimes with associated hypercalcemia) as well as the potential for overcooling and the **cold injury syndrome**. The latter is usually avoided with a servo-controlled cooling system. Therapeutic hypothermia may theoretically alter drug metabolism, prolong the QT interval, and affect the interpretation of blood gases. In clinical practice, these concerns have not been observed.

For treating seizures associated with HIE, phenobarbital continues to be used in many instances. It is typically given by intravenous loading dose (20 mg/kg). Additional doses of 5-10 mg/kg (up to 40-50 mg/kg total) may be needed. Phenobarbital levels should be monitored 24 hours after the loading dose has been given and maintenance therapy (5 mg/kg/24 hr) begun. Therapeutic phenobarbital levels are 20-40 μg/mL.

For refractory seizures, there is a high degree of variability regarding choice of a second agent. Historically, phenytoin (20 mg/kg loading dose) or lorazepam (0.1 mg/kg) have been preferred, but currently the use of levetiracetam is preferred (at times even as a first-line agent) as a second-line agent. Pharmacokinetic data suggest that due to the higher volume of distribution created by higher relative body water content in neonates, loading doses should be higher than in older children or adults. Suggested appropriate loading doses may be closer to 60 mg/kg. In addition to levetiracetam and phenytoin, other second- or third-line agents commonly used include midazolam, topiramate, and lidocaine. Pyridoxine should also be attempted, particularly in ongoing refractory seizures with highly abnormal EEG background. Status epilepticus, multifocal seizures, and need for multiple anticonvulsant medications during therapeutic hypothermia are associated with a poor prognosis.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Hyperthermia has been associated with impaired neurodevelopment and should be prevented, particularly in the interval between initial resuscitation and initiation of hypothermia. Careful attention to ventilatory status and adequate oxygenation, blood pressure, hemodynamic status, acid-base balance, and possible infection is important. Secondary hypoxia or hypotension from complications of HIE must be prevented. Aggressive treatment of seizures is critical and may necessitate continuous EEG monitoring. In addition, hyperoxia, hypocarbia, and hypoglycemia are associated with poor outcomes, so careful attention to resuscitation, ventilation, and blood glucose homeostasis is essential.

PROGNOSIS

The outcome of HIE ranges from complete recovery to death. The prognosis varies depending on the severity of the insult and the treatment. Infants with initial cord or initial (~1 hour of age) blood pH <6.7 have a 90% risk for death or severe neurodevelopmental impairment at 18 months of age. In addition, infants with Apgar scores of 0-3 at 5 minutes, high base deficit (>20-25 mmol/L), decerebrate posture, severe basal ganglia/thalamic (BG/T) lesions (Fig. 122.11; see also Fig. 122.7), persistence of severe HIE by clinical examination at 72 hours, and lack of spontaneous activity are also at increased risk for death or impairment. These predictor variables can be combined to determine a score that helps with prognosis (see Table 122.7). Infants with the highest risk are likely to die or have severe disability despite aggressive treatment, including hypothermia. Those with intermediate scores are likely to benefit from treatment. In general, severe encephalopathy, characterized by flaccid coma, apnea, absence of oculocephalic reflexes, and refractory seizures, is associated with a poor prognosis (see Table 122.8). Apgar scores alone in patients with HIE can also be associated with subsequent risk of neurodevelopmental impairment. At 10 minutes, each point decrease in Apgar score increases odds of death or disability by 45%. Death or disability occurs in 76–82% of infants with HIE with Apgar scores of 0-2 at 10 minutes. Absence of spontaneous respirations at 20 minutes of age and persistence of abnormal neurologic signs at 2 weeks of age also predict death or severe cognitive and motor deficits.

The combined use of early multichannel EEG or aEEG and MRI offers additional insight in predicting outcome in term infants with HIE (see Table 122.11). EEG or aEEG background characteristics such as pattern, voltage, reactivity, state change, and evolution after acute injury are important predictors of outcome. MRI markers include location of injury, identification of injury by certain pulse sequences, measurement of diffusivity and/or fractional anisotropy, and presence of abnormal metabolite ratios on MR spectroscopy, and all have shown

Table 122.11 Electroencephalographic Patterns of Prognostic Significance in Asphyxiated Term Infants*

ASSOCIATED WITH FAVORABLE OUTCOME
Mild depression (or less) on day 1
Normal background by day 7
ASSOCIATED WITH UNFAVORABLE OUTCOME
Predominant interburst interval >20 sec on any day
Burst suppression pattern on any day
Isoelectric tracing on any day
Mild (or greater) depression after day 12

*Associations with favorable or unfavorable outcome are generally ≥90%, but the clinical context must be considered.

From Inder TE, Volpe JJ. Hypoxic-ischemic injury in the term infant: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn*. 6th ed. Philadelphia: Elsevier; 2018: Table 20-26.

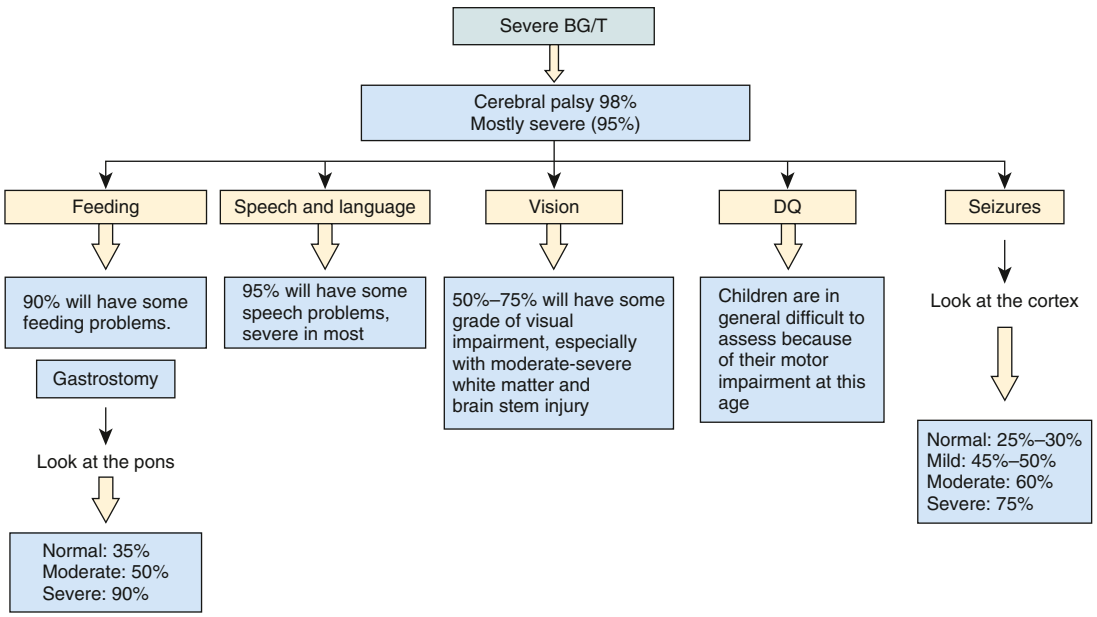

Fig. 122.11 Flow chart showing patterns of outcome with severe basal ganglia/thalamic (BG/T) injury. DQ, Developmental quotient. (*From Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:675–682.*)

correlation with outcome. Severe BG/T lesions with abnormal signal in the posterior limb of the internal capsule are highly predictive of the poorest cognitive and motor prognosis (see Fig. 122.11). Normal MRI and EEG findings are associated with a good recovery.

Microcephaly and poor head growth during the first year of life also correlate with injury to the BG/T and white matter and adverse developmental outcome at 12 months. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, and neurologic early intervention services so that the best possible outcomes can be achieved.

Brain death (death by neurologic criteria) after neonatal HIE is diagnosed from the clinical findings of coma unresponsive to pain, auditory, or visual stimulation; apnea with P_{CO_2} rising from 40 to >60 mm Hg without ventilatory support; and absence of brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, gag, sucking) (see Chapter 83). These findings must occur in the absence of hypothermia, hypotension, and elevations of depressant drugs (phenobarbital), which may take days to be metabolized and cleared completely from the blood. In the term infant, the national guideline for determination should be followed. There is no agreement on such criteria in the preterm infants. Consideration of withdrawal of life support must include discussions with the family and the healthcare team, and, if there is disagreement, an ethics committee. The best interest of the infant involves judgments about the benefits and harm of continuing therapy or avoiding ongoing futile therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

122.5 Spine and Spinal Cord

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

See also Chapter 751.

Injury to the spine/spinal cord during birth is rare but can be devastating. Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral, or forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis, especially when combined with flexion and torsion of the vertical axis, may produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury occurs most often at the level of the 4th cervical vertebra with cephalic presentations and the lower cervical–upper thoracic vertebrae with breech presentations. Transection of the cord may occur *with or without* vertebral fractures; hemorrhage and edema may produce neurologic signs that are indistinguishable from those of transection, except that they may not be permanent. Areflexia, loss of sensation, and complete paralysis of voluntary motion occur below the level of injury, although the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion.

If the injury is severe, the infant, who from birth may be in poor condition because of respiratory depression, shock, or hypothermia, may deteriorate rapidly to death within several hours before any neurologic signs are obvious. Alternatively, the course may be protracted, with symptoms and signs appearing at birth or later in the first week; Horner syndrome, immobility, flaccidity, and associated brachial plexus injuries may not be recognized for several days. Constipation may also be present. Some infants survive for prolonged periods, their initial flaccidity, immobility, and areflexia being replaced after several weeks or months by rigid flexion of the extremities, increased muscle tone, and spasms. Apnea on day 1 and poor motor recovery by 3 months are poor prognostic signs.

The **differential diagnosis** of neonatal spine/spinal cord injury includes amyotonia congenita and myelodysplasia associated with spina bifida occulta, spinal muscular atrophy (type 0), spinal vascular malformations (e.g., arteriovenous malformation causing hemorrhage or stroke), and congenital structural anomalies (syringomyelia, hemangioblastoma). Ultrasound or MRI confirms the diagnosis. Treatment of the survivors is supportive, including home ventilation; patients often remain permanently disabled. When a fracture or dislocation is causing spinal compression, the prognosis is related to the time elapsed before the compression is relieved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

122.6 Peripheral Nerve Injuries

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

See also Chapter 753.

BRACHIAL PALSY

Brachial plexus injury is a common problem, with an incidence of 0.6-4.6 per 1,000 live births. Injury to the brachial plexus may cause paralysis of the upper part of the arm with or without paralysis of the forearm or hand or, more often, paralysis of the entire arm. These injuries occur in macrosomic infants and when lateral traction is exerted on the head and neck during delivery of the shoulder in a vertex presentation, when the arms are extended over the head in a breech presentation, or when excessive traction is placed on the shoulders. The primary risk factor for brachial plexus injuries are shoulder dystocia and macrosomia (birthweight >4,000 g).

Erb-Duchenne paralysis results from injury to the nerve roots of the 5th and 6th cervical nerves, with the 7th affected in 50% of instances. The infant loses the power to abduct the arm from the shoulder, rotate the arm externally, and supinate the forearm. The characteristic position consists of adduction and internal rotation of the arm with pronation of the forearm, often described as the "waiter's tip hand." Power to extend the forearm is retained, but the biceps reflex is absent; the Moro reflex is absent on the affected side (Fig. 122.12). The outer aspect of the arm may have some sensory impairment. Power in the forearm and hand grasps is preserved unless the lower part of the plexus is also injured; the presence of hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve (in about 5% of patients), alteration in diaphragmatic excursion may be observed with ultrasound, fluoroscopy, or as asymmetric elevation of the diaphragm on chest radiograph.

Klumpke paralysis is a rare form of brachial palsy in which injury to the 7th and 8th cervical nerves and the 1st thoracic nerve produces a paralyzed hand and ipsilateral ptosis and miosis **(Horner syndrome)** if the sympathetic fibers of the first thoracic root are also injured. The incidence is as low as 0.6%, and some suggest the reason for this is modern obstetric practice and a sharp decline in the vaginal breech deliveries where there is a risk of hyperabduction of the arms. Mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury; from fracture, dislocation, or epiphyseal separation of the humerus; and from fracture of the clavicle. MRI demonstrates nerve root rupture or avulsion.

Most patients have full recovery. If the paralysis was a result of edema and hemorrhage around the nerve fibers, function should return within a few months; if it resulted from laceration, permanent damage may result. Involvement of the deltoid is usually the most serious problem and may result in **shoulder drop** secondary to muscle atrophy. In general, paralysis of the upper part of the arm has a better prognosis than paralysis of the lower part.

Treatment for **peripheral nerve injuries** consists of initial conservative management with monthly follow-up and a decision for surgical intervention by 3 months if function has not improved. Partial immobilization and appropriate positioning are used to prevent the development of contractures. In upper arm paralysis, the arm should be abducted 90 degrees with external rotation at the shoulder, full supination of the forearm, and slight extension at the wrist with the palm turned toward the face. This position may be achieved with a brace or splint during the first 1-2 weeks. Immobilization should be intermittent throughout the day while the infant is asleep and between

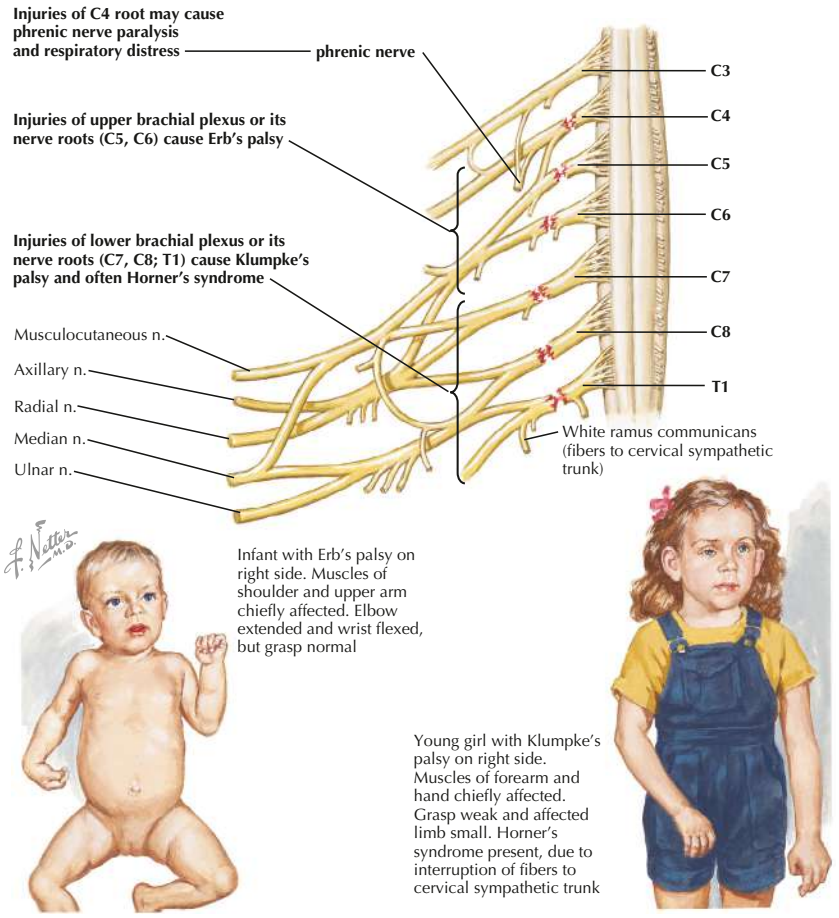

Fig. 122.12 Schematic representation of the brachial plexus with its terminal branches. The major sites of brachial plexus injury are shown. (*Courtesy Netter Images, Image ID 19943. www.netterimages.com.*)

feedings. In lower arm or hand paralysis, the wrist should be splinted in a neutral position and padding placed in the fist. When the entire arm is paralyzed, the same treatment principles should be followed. Gentle massage and range-of-motion exercises may be started by 7-10 days of age. Infants should be closely monitored with active and passive corrective exercises. If the paralysis persists without improvement for 3 months, neuroplasty, neurolysis, end-to-end anastomosis, and nerve grafting offer hope for partial recovery.

The type of treatment and the prognosis depend on the mechanism of injury and the number of nerve roots involved. The mildest injury to a peripheral nerve **(neurapraxia)** is caused by edema and heals spontaneously within a few weeks. **Axonotmesis** is more severe and is a consequence of nerve fiber disruption with an intact myelin sheath; function usually returns in a few months. Total disruption of nerves **(neurotmesis)** or root avulsion is the most severe, especially if it involves C5-T1; microsurgical repair may be indicated. Fortunately, most (75%) injuries are at the root level C5-C6, involve neurapraxia and axonotmesis, and should heal spontaneously. Botulism toxin may be used to treat biceps-triceps co-contractions.

PHRENIC NERVE PARALYSIS

Phrenic nerve injury (3rd, 4th, 5th cervical nerves) with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries, usually unilateral, are associated with ipsilateral upper brachial plexus palsies in 75% of cases. Because breathing is thoracic in type, the abdomen does not bulge with inspiration. Breath sounds are diminished on the affected side. The thrust of the diaphragm, which may often be felt just under the costal margin on the normal side, is absent on the affected side. The diagnosis is established by ultrasound or fluoroscopic examination, which reveals elevation of the diaphragm on the paralyzed side and seesaw movements of the two sides of the diaphragm during respiration. It may also be apparent on chest or abdominal radiograph.

Infants with phrenic nerve injury should be placed on the involved side and given oxygen if necessary. Some may benefit from pressure introduced by continuous positive airway pressure (CPAP) to expand the paralyzed hemidiaphragm. In extreme cases, mechanical ventilation may be needed. Initially, intravenous feedings may be needed; later, progressive gavage or oral feeding may be started, depending on the infant's condition. Pulmonary infections are a serious complication. If the infant fails to demonstrate spontaneous recovery in 1-2 months, surgical plication of the diaphragm may be indicated.

FACIAL NERVE PALSY

Facial palsy is usually a peripheral paralysis that results from pressure over the facial nerve in utero, during labor, or from forceps use during delivery. Rarely, it may result from nuclear agenesis of the facial nerve.

Peripheral facial paralysis is flaccid and, when complete, involves the entire side of the face, including the forehead. The main reported risk factors associated with traumatic facial paralysis are primigravida, birthweight >3,500 g, forceps usage, cesarean birth, and prematurity. When the infant cries, movement occurs only on the nonparalyzed side of the face, and the mouth is drawn to that side. On the affected side the forehead is smooth, the eye cannot be closed, the nasolabial fold is absent, and the corner of the mouth droops. **Central facial paralysis** spares the forehead (e.g., forehead wrinkles will still be apparent on the affected side) because the nucleus that innervates the upper face has overlapping dual innervation by corticobulbar fibers originating in bilateral cerebral hemispheres. The infant with central facial paralysis usually has other manifestations of intracranial injury, most often 6th nerve palsy from the proximity of the 6th and 7th cranial nerve nuclei in the brainstem. Prognosis depends on whether the nerve was injured by pressure or the nerve fibers were torn; improvement occurs within a few weeks in the former case. The majority of infants with traumatic facial nerve palsy will recover within the first 2 months of life. Care of the exposed eye is essential. Neuroplasty may be indicated when the paralysis is persistent. Facial palsy may be confused with absence of the depressor muscles of the mouth, which is a benign problem or with variants of Möbius syndrome.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 123

Neonatal Resuscitation and Delivery Room Emergencies

Heidi M. Herrick and Elizabeth E. Foglia

Most infants complete the transition to extrauterine life without difficulty; however, a small proportion require resuscitation after birth (Fig. 123.1). For a newborn infant, the need for resuscitation is often caused by a respiratory problem leading to inadequate ventilation. This is in contrast to an adult cardiac arrest, which is usually caused by inadequate circulation. The goals of neonatal resuscitation are to establish adequate spontaneous respirations, obtain adequate cardiac output, and prevent the morbidity and mortality associated with hypoxic-ischemic tissue (brain, heart, kidney) injury (see Chapter 122). High-risk situations should be *anticipated* from pregnancy history and labor. Improved perinatal care and prenatal diagnosis of fetal anomalies allow for appropriate maternal transports for high-risk deliveries. Infants who are born limp, cyanotic, apneic, or pulseless require immediate resuscitation before assignment of the 1 minute Apgar score. Rapid and appropriate resuscitative efforts improve the likelihood of preventing brain damage and achieving a successful outcome.

NEONATAL RESUSCITATION

See also Chapter 79.

Recommendations for the **Neonatal Resuscitation Program (NRP)** propose an *integrated* assessment/response approach for the initial evaluation of an infant, consisting of simultaneous assessment of infant general appearance and risk factors. The fundamental principles include evaluation of the airway and establishing effective respirations and adequate circulation. The guidelines also highlight the importance of the neonatal heart rate as a primary indicator of the need for and response to resuscitation.

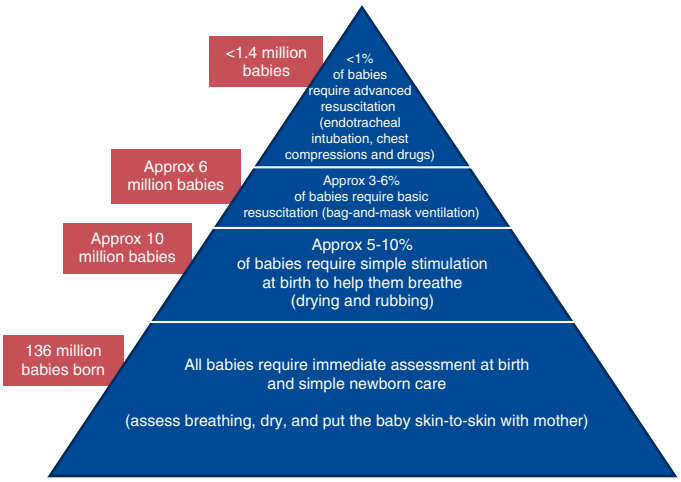

Fig. 123.1 Estimates of infants requiring resuscitation at birth. *(From Wall SN, Lee ACC, Niermeyer S, et al. Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up? Int J Gynaecol Obstet. 2009;107:S47–S64. Fig. 1.)*

Before the birth of a baby, sufficient preparation for the birth should occur. At least one individual capable of initiating neonatal resuscitation should be present at the delivery. If advanced resuscitation is anticipated, more providers should be available. Necessary equipment should be available, which routinely includes a warmer bed, blankets, infant hat, stethoscope, bulb suction, suction catheter with wall suction, bag-mask device, oxygen source with blender, pulse oximeter, laryngoscope with blade, endotracheal tubes (ETTs), laryngeal mask airway, pulse oximeter, and electrocardiogram (ECG) leads. Based on the specific details of the pregnancy, further equipment may be needed and should be readily available. The equipment should be checked to make sure it is functioning appropriately. Team members should introduce themselves, define a team leader, assign roles for the resuscitation, and discuss what actions they will take during the resuscitation. For complex resuscitations, there may be one individual whose sole job is to document the resuscitation by keeping track of time and recording interventions performed. This can help ensure the correct steps are performed in a timely manner and inform the team debriefing after resuscitation.

The umbilical cord management plan should be established before delivery. **Delayed cord clamping** after birth can be performed in both preterm and term infants. Benefits to term infants include higher hemoglobin levels at birth with improved iron stores in infancy. Benefits for preterm infants include improved hemodynamic stability, decreased need for inotropic support, and decreased red blood cell transfusions. The 2020 Neonatal Resuscitation Guidelines call for at least 30-60 seconds of delayed cord clamping after birth for vigorous term and preterm infants unless contraindications are present. It is unclear whether delayed cord clamping should be continued when an infant requires resuscitation; this is an area of active research. Umbilical cord milking should not be performed for extremely preterm infants <28 weeks' gestation because this has been associated with an increased risk of intraventricular hemorrhage.

Failure to initiate or sustain respiratory effort at birth is fairly common, with 5–10% of newborns requiring some intervention. Infants with **primary apnea** respond to stimulation by establishing normal breathing. Infants with **secondary apnea** require ventilatory assistance to establish spontaneous respiratory effort. Secondary apnea usually originates as a result of prolonged interruption of adequate oxygen delivery in the perinatal period.

Immediately after birth, all term infants should be dried, warmed, and stimulated. If the infant does not need resuscitation, these steps can occur on the mother's abdomen while delayed cord clamping is taking place. Simultaneously, the infant's tone, respiratory effort, and heart rate should be assessed (Fig. 123.2). If the infant remains apneic or bradycardic (heart rate is <100 beats/min) after stimulation, positive pressure ventilation (PPV) should be given via face mask. PPV should be initiated at peak inspiratory pressures of approximately 20 cm H_2O, positive end-expiratory pressures of 5 cm H_2O at a rate of 40-60 breaths/min.

At the same time PPV is initiated, a pulse oximeter should be placed on the right hand (preductal). Resuscitation with room air in **term infants** is effective and may reduce the risk of hyperoxia, which is associated with decreased cerebral blood flow and generation of oxygen free radicals. Room air, which is 21% fraction of inspired oxygen (F_{IO_2}), is the preferred *initial gas* for neonatal resuscitation in infants ≥35 weeks. O_2 concentration should then be titrated as needed to meet targeted peripheral oxygen saturations (>80% by 5 minutes), as defined by normal reference range by minute of life (see Fig. 123.2; see the following section on "Resuscitation of the Preterm Infant").

The most important sign of effective ventilation is a rise in heart rate. Additional signs include adequate chest rise, symmetric breath sounds, increasing O_2 saturation, spontaneous respirations, and improved tone. *If after 30 seconds of providing PPV there is no response in heart rate, corrective steps should be performed to improve ventilation.* The six

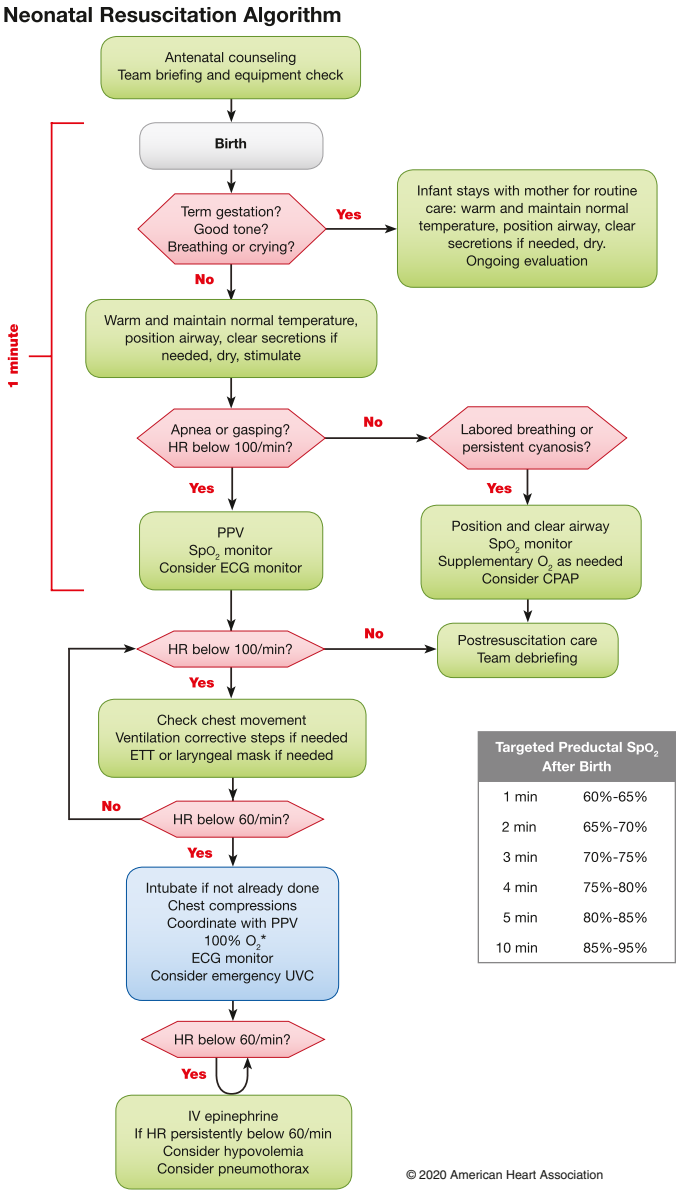

Fig. 123.2 Newborn resuscitation algorithm. CPAP, Continuous positive airway pressure; ECG, electrocardiogram; ETT, endotracheal tube; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation; UVC, umbilical venous catheter. *(From Aziz K, Lee HC, Escobedo MB, et al. Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020;142[16_suppl_2]:S524–S550. Fig. 1.)*

ventilation corrective steps can be remembered with the mnemonic **MRSOPA**: *m*ask readjustment, *r*eposition the head, *s*uction mouth and nose, *o*pen the mouth, *p*ressure increase, and *a*lternative airway.

Causes of poor response to ventilation are mask leak, airway obstruction, insufficient pressure, pleural effusions, pneumothorax, excessive air in the stomach leading to abdominal competition, hypovolemia, diaphragmatic hernia, or prolonged intrauterine asphyxia. For infants who do not respond to noninvasive PPV after corrective steps have been taken, endotracheal intubation should be performed. For infants with an otherwise normal airway weighing <1,000 g, ETT size is usually 2.5 mm; for infants 1,000-2,000 g, 3 mm; and for infants >2,000 g, 3.5 mm. A general rule for depth of insertion from upper lip in centimeters is 6 + infant's weight in kilograms. The best method to confirm accurate ETT position is exhaled CO_2 detection. A laryngeal mask airway is an alternative method to establish an airway, especially if face mask PPV is ineffective or providers skilled in intubation are unavailable.

For most infants, the underlying cause for a persistently low heart rate (<60 beats/min) is not a primary cardiac cause, but instead the result of **ineffective ventilation**. Therefore if the heart rate remains <60 beats/min after 60 seconds of PPV with corrective MRSOPA steps, the infant should be intubated (if not already done) to achieve effective ventilation. *Once the infant is intubated, if the heart rate remains <60 beats/min, chest compressions should be initiated with continued ventilation, and F_{IO_2} should be increased to 100%.* Chest compressions should be initiated over the lower third of the sternum at a rate of 90 per minute. A provider, separate from the person providing ventilation, is needed to administer chest compressions. The *thumb technique* should be used for chest compressions; the tips of both thumbs are used to depress the sternum, with the fingers on each side encircling the chest; this is the preferred method to administer chest compressions, because it has been shown to achieve a higher blood pressure, increase coronary perfusion, and result in less fatigue. In infants, regardless of whether an alternative airway has been secured, chest compressions are always coordinated with PPV. The ratio of compressions to ventilation is 3:1 (90 compressions:30 breaths). Chest compressions should continue uninterrupted for 60 seconds before reassessing heart rate to determine next steps.

Medications are rarely required, but **epinephrine** should be administered when the heart rate is <60 beats/min after 60 seconds of combined ventilation and chest compressions or during asystole. An intravenous route is recommended for epinephrine administration. The umbilical vein can generally be readily cannulated and is the preferred method for administration of medications and volume expanders during neonatal resuscitation (Fig. 123.3). An intraosseous route is another option if umbilical venous access is not obtained. Epinephrine (initial dose recommendation of 0.02 mg/kg *intravenously/intraosseously* followed by a 3-mL flush) is given for asystole or for continued heart rate <60 beats/min after 60 seconds of combined resuscitation. The dose may be repeated every 3-5 minutes. Epinephrine may also be given through the ETT (0.1 mg/kg). If adequate resuscitation continues for 20 minutes without a detectable heart rate, it is reasonable to discuss redirection of care with the team and family and to stop resuscitative efforts.

RESUSCITATION OF THE PRETERM INFANT

Resuscitation of the preterm infant should follow the same steps as a term infant, with some special considerations. Whereas resuscitation of term infants should start with room air, resuscitation of preterm infants <35 weeks' gestation should be initiated with F_{IO_2} between 21% and 30%. Pulse oximetry of the preductal (right) hand should be used to titrate O_2 concentrations for targeted saturations per the NRP algorithm (see Fig. 123.2). Most very low birthweight infants will need more than 30% once titration begins.

Special attention should be paid to *keeping the preterm infant warm in the delivery room.* Quality improvement projects have initiated bundles to improve admission temperatures of preterm infants to the neonatal intensive care unit (NICU) and have included such interventions as higher ambient temperatures in the delivery room, immediate placement of preterm infants into a plastic bag or under plastic wrap rather than drying, and exothermic mattress for resuscitation and transport of the preterm infant.

SPECIAL CIRCUMSTANCES IN THE DELIVERY ROOM

Meconium

Meconium staining of the amniotic fluid may be an indication of fetal stress. All infants born through meconium-stained amniotic fluid (regardless if the infant is vigorous or nonvigorous) should receive the same initial steps of neonatal resuscitation as infants without

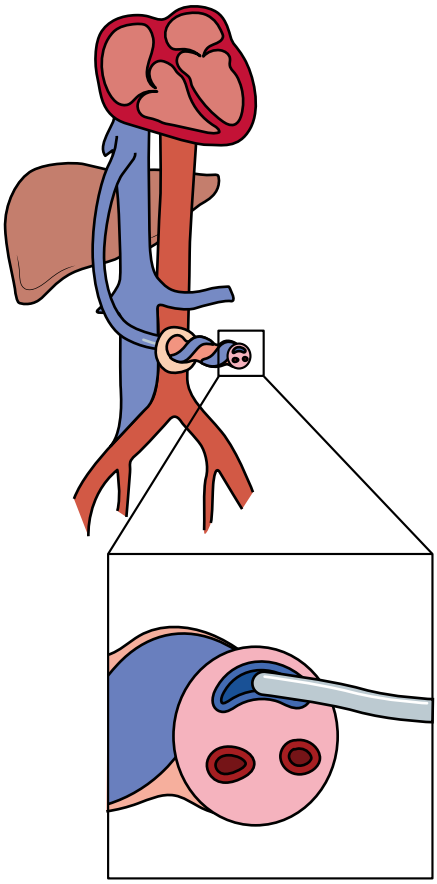

Fig. 123.3 Emergently placed umbilical venous catheter suitable for neonatal resuscitation.

meconium-stained fluid and should be assessed as any other infant. Tracheal intubation for meconium aspiration may delay the initiation of effective PPV and ultimately delay effective gas exchange and is not indicated.

Placental Abruption

Placental abruption (abruptio placentae) or uterine rupture at birth can lead to acute fetal blood loss and a hypovolemic, anemic infant at delivery. Infants can present pale and apneic with poor tone, decreased perfusion, and bradycardia. In addition to performing routine neonatal resuscitation, when an infant is suspected to be symptomatic from acute blood loss, an emergency low-lying umbilical venous catheter (UVC) or interosseous needle should be placed and emergent type O Rh-negative blood should be obtained. In acute blood loss, the blood should be administered as quickly as possible in 10 mL/kg aliquots in the delivery room. Adequate communication between obstetrics and pediatrics regarding suspected acute blood loss is crucial to early recognition and treatment of the infant.

Neonatal Encephalopathy

Infants with neonatal encephalopathy are born with abnormal neurologic function, including level of consciousness, muscle tone, apnea, and reflexes. Although there are many possible etiologies, when symptoms are accompanied by a defined perinatal event such as cord prolapse or placental abruption, hypoxic-ischemic brain injury is the presumed cause. These infants are often born with impaired respiratory drive. Immediately after initial resuscitation and stabilization, a thorough neurologic examination should be performed to assess if the infant meets formal criteria for moderate to severe encephalopathy and qualifies for therapeutic hypothermia (see Chapter 122.4).

Airway Anomalies

Hypoplasia of the mandible with posterior displacement of the tongue may result in upper airway obstruction (Pierre Robin, Stickler, DiGeorge, and other syndromes; see Chapters 118 and 357). Symptoms may sometimes be temporarily relieved by pulling the tongue or mandible forward or placing the infant in the prone position. Other rare anatomic causes of upper airway obstruction at birth include laryngeal atresia or stenosis, teratomas, hygromas, and oral tumors. Critical fetal and then neonatal airway obstruction represents an emergency in the delivery room. High-risk perinatal care has led to the more frequent prenatal diagnosis of these disorders. When diagnosed prenatally, planning can identify the location of delivery and interventions available at delivery. The **ex utero intrapartum treatment (EXIT)** procedure allows time to secure the airway in an infant known prenatally to have critical airway obstruction, before the infant is separated from the placenta (Fig. 123.4; see Chapter 118). Uteroplacental gas exchange is maintained throughout the procedure.

Pulmonary Disorders

Both congenital and acquired abnormalities can contribute to respiratory failure in the neonate. A **scaphoid abdomen** suggests a diaphragmatic hernia, as does asymmetry in contour or movement of the chest. An infant with a known diaphragmatic hernia should be immediately intubated in the delivery room and an orogastric tube placed to avoid gaseous distention of the bowel from crying or PPV. The infant should then be transferred to a tertiary referral center for surgical evaluation and treatment (see Chapter 124.1).

In infants with a prenatal diagnosis of hydrops, pleural effusions may be present at delivery, preventing adequate lung expansion and gas exchange. Similarly, infants requiring PPV in the delivery room are at risk for **pneumothorax**. Infants with pulmonary hypoplasia or meconium-stained fluid are at increased risk of this complication. Clinically, infants with a pleural effusion or pneumothorax present with respiratory distress and hypoxia, with *diminished* breath sounds on the affected side. Transillumination may be helpful to confirm the diagnosis. Emergency evacuation of a pneumothorax or pleural effusion without radiographic confirmation is indicated in an infant who is unresponsive to resuscitation efforts and has asymmetric breath sounds, bradycardia, and cyanosis. An angiocatheter attached to a stopcock and syringe should be used for evacuation. For a pleural effusion, with the infant in the supine position, the angiocatheter should be inserted in the fourth or fifth intercostal space in the anterior axillary line and directed posteriorly to evacuate the fluid. For a pneumothorax, an angiocatheter can be inserted in the fourth intercostal space in the anterior axillary line or the second intercostal space in the midclavicular line and air evacuated (see Chapter 124).

Abdominal Wall and Neural Tube Defects

Appropriate management of patients with abdominal wall defects (omphalocele, gastroschisis) in the delivery room prevents excessive fluid loss and minimizes the risk for injury to the exposed viscera. **Gastroschisis** is the more common defect, and typically the intestines are not covered by a membrane. The infant's lower body, including exposed intestines, should be gently placed in a sterile clear plastic bag after delivery. A membrane often covers an **omphalocele**, and care should be taken to prevent its rupture. The omphalocele should either be wrapped in a sterile dressing or the infant's lower body, including the omphalocele, which should be placed within a sterile bag. With both defects, a nasogastric tube should be placed, and the infant transferred to a tertiary referral center for surgical consultation and evaluation for associated anomalies (see Chapter 144).



Fig. 123.4 Ex utero intrapartum therapy (EXIT) procedure. Baby with teratoma and critical high airway obstruction syndrome (CHAOS). Trachea is displaced to the lateral neck. *(Courtesy Dr. Mark Wulkan, Pediatric Surgery, Emory University.)*

Similarly, infants born with neural tube defects such as a **myelomeningocele** need special care at delivery to protect the exposed neural tube tissue from trauma and infection; infants should be placed on their side or abdomen for resuscitation. The site of the neural tube defect should be covered with a moist sterile dressing to prevent drying and infection. The infant should then be transferred to a tertiary referral center for surgical evaluation and treatment.

INJURY DURING DELIVERY

Central Nervous System

Both extracranial and intracranial birth injuries can be seen in infants after birth. **Extracranial** lesions include cephalohematoma, caput succedaneum, and subgaleal hemorrhage. **Intracranial** birth injuries include subdural hemorrhage, subarachnoid hemorrhage, and epidural hematoma. The most common intracranial injury experienced at birth is **subdural hemorrhage**, with increasing incidence seen with instrument-assisted vaginal deliveries (see Chapters 122.1 and 122.2).

Fractures

The clavicle is the most frequently fractured bone during labor and delivery. It is particularly vulnerable to injury with difficult delivery of the shoulder in the setting of **shoulder dystocia**, as well as with extended arms in breech deliveries. In the treatment of shoulder dystocia, the obstetrician may intentionally fracture the clavicle so that delivery can proceed. Symptoms of a clavicular fracture include an infant not moving the arm freely on the affected side, palpable crepitus or bony irregularity, and asymmetric or absent Moro reflex on the affected side. The prognosis for this fracture is excellent. Often, no specific treatment is needed, although in some cases the arm and shoulder on the affected side are immobilized for comfort.

Fractures of the long bones are fairly rare. Injuries often present with absent spontaneous movement of the extremity. Associated nerve involvement may also occur. Treatment involves immobilization of the affected extremity with a splint and orthopedic follow-up.

Brachial Plexus Injuries

Brachial plexus injuries result from stretching and tearing of the brachial plexus (spinal roots C5-T1) at delivery. Although shoulder dystocia is associated with an increased risk of brachial plexus injury, it can also occur during a routine delivery (see Chapter 122.6).

ONGOING CARE AFTER RESUSCITATION

The "golden hour" after a baby's birth should emphasize effective neonatal resuscitation, postresuscitation care, prevention of hypothermia (including maternal skin-to-skin contact), immediate breastfeeding if able, prevention of hypoglycemia, and therapeutic hypothermia for cases of moderate to severe neonatal encephalopathy (birth asphyxia). After supportive measures have stabilized the infant's condition, a specific diagnosis should be established and appropriate continuing treatment instituted.

For infants who receive more intensive resuscitation, a plan for ongoing monitoring and treatment should be established. These infants may experience ongoing acidosis, electrolyte abnormalities, hypo- or hyperglycemia, impaired thermoregulation, and respiratory insufficiency. If infection is suspected, appropriate antibiotics should be started as soon as possible. Severe neonatal encephalopathy may also depress myocardial function and cause cardiogenic shock despite the recovery of heart and respiratory rates. Fluids and dopamine or epinephrine as a continuous infusion should be started after initial resuscitation efforts, to improve cardiac output in an infant with poor peripheral perfusion, weak pulses, hypotension, tachycardia, or poor urine output. Regardless of the severity of neonatal encephalopathy or the response to resuscitation, asphyxiated infants should be monitored closely for signs of multiorgan hypoxic-ischemic tissue injury (see Chapter 122.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 124

Transition to Newborn Pulmonary Respiration

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Successful establishment of adequate lung function at birth depends on airway patency, functional lung development, and maturity of respiratory control. Fetal lung fluid must be removed and replaced with gas. Functional residual capacity (FRC) must be established and maintained to develop a ventilation-perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood. Pulmonary blood flow increases dramatically, and the newborn must establish and maintain breathing patterns that are distinct from fetal breathing movements.

CLEARANCE OF FETAL LUNG FLUID

In utero, lung fluid is actively secreted by epithelial cells into air spaces. This fluid is essential for normal lung development and severe pulmonary hypoplasia results in infants who are unable to maintain appropriate fetal lung fluid. During birth, fluid must be cleared from the airways to allow for gas exchange. During birth, the lung epithelial cells must transition from fluid secreting to fluid absorbing.

Increased intrathoracic pressure from uterine squeeze and flexion of the infant during delivery likely contribute to movement of fluid out of the infant's nose and mouth at delivery. Additionally, inspiration decreases intrapleural pressure forming a pressure gradient that leads to the movement of fluid toward the smaller airways and ultimately out of the air spaces. As fluid moves out of the airways there is an increased interstitial hydrostatic pressure that contributes to fluid reentering the airway during each expiration until it is eventually cleared from the interstitial tissues over the course of hours.

ESTABLISHMENT OF A FUNCTIONAL RESIDUAL CAPACITY

FRC represents a balance point between collapsing and distending forces on the lung at end-expiration. Lung recoil comes from a combination of the intrinsic elasticity of the lung tissue and the surface tension within the lung. **Surfactant** plays an important role in reducing surface tension in the newborn. Premature infants and those infants with insufficient surfactant have an increased tendency toward lung collapse as observed in **respiratory distress syndrome** (see Chapter 126). Although the chest wall provides resistance to collapse in older children and adults, the highly compliant chest wall of the newborn and particularly the preterm newborn provides little resistance to lung recoil. Instead, resistance to lung collapse comes from a combination of lung tissue hydrostatic, osmotic, and oncotic pressures in addition to expiratory braking maneuvers. The neonate's expiratory braking maneuvers include adduction of the glottis and engagement of the diaphragm during expiration. Additional activities such as grunting and crying further support establishment of FRC.

INCREASED PULMONARY BLOOD FLOW

In utero, the placenta is the source of gas exchange, and blood is diverted away from the developing lungs by way of the foramen ovale and ductus arteriosus. Only 10% of the cardiac output passes through the fetal lung circulation. Following birth, blood flow to the pulmonary circulation increases due to decreasing **pulmonary vascular resistance** and closure of in utero shunts. The decline in pulmonary vascular resistance is driven by clearance of fetal lung fluid, oxygen-stimulated smooth muscle relaxation, and release of nitric oxide. Pulmonary vascular resistance decreases 50% over the first 24 hours and continues to decline over the first weeks of life. The foramen ovale is functionally closed after birth due to increased systemic vascular resistance and increased pressures in the left ventricle and left atrium. The ductus arteriosus is slower to close and ductal constriction is driven by a loss of prostaglandins from the placenta, increased oxygen exposure, and decreased local nitric oxide. Increasing pulmonary blood flow and decreasing mixing of oxygenated and deoxygenated blood after birth contributes to changing saturations in the newborn, which rise from 60% immediately after birth to over 90% by approximately 10 minutes of life (Fig. 124.1)

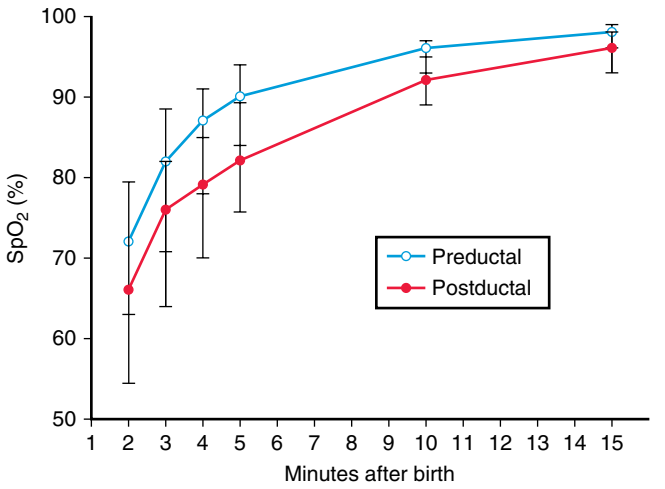

Fig. 124.1 Pre- and postductal Spo_2 levels during the first 15 minutes after birth (median; IQR). Postductal Spo_2 levels were significantly lower than preductal Spo_2 levels at 3, 4, 5, 10, and 15 minutes. *(Modified from Mariani G, Dik PB, Ezquer A, et al. Pre-ductal and post-ductal O_2 saturation in healthy term neonates after birth. J Pediatr. 2007;150:418–421.)*

BREATHING PATTERNS IN NEWBORNS

Fetal breathing movements can be observed before birth. They are generally discontinuous and generate only small tidal volumes. Following delivery, the infant must establish a regular breathing pattern with increased tidal volumes. Triggers driving this change include increased $Paco_2$, activation of chemoreceptors, and a loss of placental prostaglandins, which suppress respiratory drive. Within the fetus, low oxygen tension has an inhibitory effect on breathing. Following birth, hypoxia will eventually become a driver of respiratory effort, but in the immediate postpartum period and in the premature infant, hypoxia may depress respiratory drive.

DISORDERED TRANSITION TO PULMONARY RESPIRATION

The successful transition from placental derived oxygen delivery to pulmonary respiration requires timely completion of fetal lung fluid clearance, creation of FRC, increased pulmonary blood flow, and establishment of normal breathing patterns. Failures in any of these tasks are associated with respiratory disorders in the neonate. Failure in the timely clearance of fetal lung fluid is associated with **transient tachypnea of the newborn** (see Chapter 128). An inability to establish FRC is a feature of respiratory distress syndrome (see Chapter 126). A failure in decreasing pulmonary vascular resistance causes persistent pulmonary hypertension of the newborn (see Chapter 130) and in infants without appropriate respiratory patterns, **apnea** (see Chapter 125) is a presenting concern.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 125

Apnea

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Apnea is a prolonged cessation of respiration and must be distinguished from *periodic breathing* because apnea is often associated with serious illness. Although there is no universal agreement, apnea is usually defined as cessation of breathing for a period of ≥20 seconds, or a period <20 seconds that is associated with a change in tone, pallor, cyanosis, or bradycardia (<80-100 beats/min). Based on the absence of respiratory effort and/or airflow, apnea can be obstructive, central, or mixed. **Obstructive apnea** is characterized by absence of airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration, or it may result from incoordination of the tongue and other upper airway muscles involved in maintaining airway patency. **Central apnea** is caused by decreased central nervous system (CNS) stimuli to respiratory muscles and results in both airflow and chest wall motion being absent. Gestational age (GA) is the most important determinant of respiratory control, with the frequency of central apnea being inversely related to GA. The immaturity of the brainstem respiratory centers is manifest by an attenuated response to CO_2 and a paradoxical response to hypoxia that results in central apnea rather than hyperventilation. Mixed apnea is most often observed in apnea of prematurity with obstructive apnea preceding central apnea. Short episodes of apnea are usually central, whereas prolonged ones are often mixed.

OBSTRUCTIVE APNEA

Obstructive apnea derives from interrupted upper airway flow. Causes of obstructive apnea can largely be divided into anatomic abnormalities and neuromuscular abnormalities.

Craniofacial disorders are a common cause of obstructive apnea of the newborn. Micrognathia, retrognathia, or Pierre Robin sequence all cause upper airway obstruction due to backward dislodgement of the tongue into the airway. This obstruction may be improved by prone positioning of the neonate. Although cleft lip and palate are not always associated with obstructive apnea, infants with these conditions are at risk for apnea related to abnormal narrowing of the upper airway structures. Additional anatomic abnormalities that can contribute to obstructive apnea include narrowing or occlusion of the nasal passages (i.e., choanal atresia) or narrowing of the airways (i.e., laryngomalacia). Many causes of anatomic obstruction are syndromic and include skeletal dysplasia, VACTERL association, Joubert syndrome, CHARGE syndrome, DiGeorge syndrome, and Stickler syndrome.

Neuromuscular weakness can contribute to **obstructive apnea** via airway collapse in the setting of low tone. Additionally, respiratory muscle weakness may impede the infant from overcoming normal airway resistance.

CENTRAL APNEA

Central apnea has a wide range of etiologies and should always lead to a diagnostic evaluation as it can often be an early warning sign of clinical decompensation. Table 125.1 provides a framework for the disease processes that can contribute to apnea. Infection or metabolic derangements should always be considered as an etiology for infants with new or worsening apnea. Abnormal CNS control of breathing can be related to prematurity, but other CNS abnormalities including injury or malformation can contribute to central apnea. **Congenital central hypoventilation syndrome** is a rare permanent genetic cause of central apnea that begins in the neonatal period (see Chapter 468.2).

APNEA OF PREMATURITY

Apnea in preterm infants is defined as cessation of breathing for ≥20 seconds or for any duration if accompanied by cyanosis and bradycardia (<80-100 beats/min). The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia. Short apnea episodes (10 seconds) are rarely associated with bradycardia, whereas longer episodes (>20 seconds) have a higher incidence of bradycardia. Bradycardia follows the apnea by 1-2 seconds in >95% of cases and is most often sinus. Vagal responses and rarely heart block are causes of bradycardia *without* apnea. Short, self-resolving oxygen desaturation episodes noted with continuous monitoring are normal in neonates, and treatment is not necessary.

Apnea of prematurity results from immature respiratory control, most frequently occurs in infants <34 weeks of GA, and occurs in the absence of identifiable predisposing diseases. The incidence of apnea of prematurity varies inversely with GA. Apnea of prematurity is almost universal in infants born at <28 weeks of GA, and the incidence rapidly decreases from 85% of infants <30 weeks of GA to 20% of infants <34 weeks of GA. The onset of apnea of prematurity can be during the initial days to weeks of age but is often delayed if there is respiratory distress syndrome (RDS) or other causes of respiratory distress. In premature infants without respiratory disease, apneic episodes can occur throughout the first 7 postnatal days with equal frequency. In infants with apnea of prematurity, the events decline significantly by 34 weeks corrected GA. Resolution may be delayed in infants with **bronchopulmonary dysplasia** (see Chapter 127) because of poorer reserves and an increased incidence of subglottic stenosis, laryngomalacia, or tracheomalacia, which can contribute to **obstructive apneas**.

Table 125.1 Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), transient following general anesthesia, congenital central hypoventilation syndrome
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, paradoxical response to hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center (prematurity); sleep state; sudden unexpected postnatal collapse

Preterm infants born at <35 weeks of GA are at risk for apnea of prematurity and therefore should receive cardiorespiratory monitoring. Apnea that occurs in the absence of other clinical signs of illness in the first 2 weeks in a preterm infant is likely apnea of prematurity; therefore additional evaluation for other etiologies is often unwarranted. However, *the onset of apnea in a previously well preterm neonate after the second week of life is a critical event that may be associated with serious underlying pathology*. Prompt investigation for sepsis/meningitis, medication side effects, metabolic derangements, structural CNS anomalies, intracranial hemorrhage, or seizures is warranted.

TREATMENT

Observation is the most common treatment strategy for infants with **obstructive apnea,** and temporizing measures including prone positioning can help to minimize symptoms until sufficient patient growth alleviates the obstruction. The use of supplemental oxygen, **nasal continuous positive airway pressure (nCPAP),** or bilevel positive airway pressure may facilitate stenting of airways and limit obstructive events. Surgical interventions depend on the underlying cause and include supraglottoplasty, palatoplasty, tongue-lip adhesion, tongue base reduction, nasal stent, mandibular distraction, and in severe cases, tracheostomy to bypass areas of obstruction.

For apnea of prematurity, gentle tactile stimulation, or provision of flow and/or supplemental oxygen by nasal cannula, is often adequate therapy for mild and intermittent episodes. **nCPAP** (3-5 cm H_2O) and **high-flow nasal cannula** (**HFNC**; 1-4 L/min) are appropriate therapies for **mixed** or **obstructive apnea**. The efficacy of both nCPAP and HFNC is related to their ability to splint the upper airway to prevent airway obstruction. Additionally, the maintenance of a higher functional residual capacity can decrease the duration of **central apnea**. Both are used widely, but nCPAP may be preferred in extremely preterm infants because of its proven efficacy and safety.

Recurrent or persistent apnea of prematurity is effectively treated with methylxanthines. **Methylxanthines** increase central respiratory drive by lowering the threshold of response to hypercapnia as well as enhancing contractility of the diaphragm. **Caffeine** and **theophylline** are similarly effective methylxanthines, but caffeine is preferred because of its longer half-life and lower potential for side effects (less tachycardia and feeding intolerance). In preterm infants, caffeine reduces the incidence and severity of apnea of prematurity, facilitates successful extubation from mechanical ventilation, reduces the rate of bronchopulmonary dysplasia (see Chapter 127), and improves neurodevelopmental outcomes. Caffeine therapy can be safely administered orally (PO) or intravenously (IV). Generally, infants are given an initial loading dose of 20 mg/kg of caffeine citrate followed 24 hours later by once-daily maintenance doses of 5-10 mg/kg. Because the therapeutic window is wide and serious side effects associated with caffeine are rare, monitoring of serum drug concentrations is usually unnecessary. Monitoring is primarily through observation of vital signs (tachycardia) and clinical response. Higher doses of caffeine may be more effective without serious adverse events, but additional studies are needed to ensure safety. Studies suggest that early initiation of caffeine, in the first 3 days of life, in extremely preterm infants improves outcomes. However, it is reasonable to delay caffeine therapy until apnea occurs in older infants. Caffeine therapy is usually continued until an infant is free of clinically significant apnea or bradycardia for 5-7 days without positive pressure respiratory support, or at 34 weeks' postmenstrual age (PMA).

In an infant with significant anemia, transfusion of packed red blood cells (RBCs) increases blood O_2-carrying capacity, improves tissue oxygenation, and may be associated with a short-term reduction in apnea. However, a long-term benefit with regard to apnea appears unlikely.

Gastroesophageal reflux (GER) is common in neonates, but despite being associated with apnea anecdotally, data do not support a causal relationship between GER and apneic events. In preterm infants, medications that inhibit gastric acid production have potentially harmful side effects (increased incidence of sepsis, necrotizing enterocolitis, death) and may increase the incidence of apnea and bradycardia. Therefore the routine use of medications that inhibit gastric acid synthesis or promote gastrointestinal motility to reduce the frequency of apnea in preterm infants should be discouraged. Antireflux treatment does correlate with decreased rates of obstructive apnea; however, this does not seem to be a causal relationship. Feeding strategies including more frequent or slower/longer feedings may be considered. Thickening feedings with xanthan gum is linked to late-onset necrotizing enterocolitis and should not be attempted. Other thickeners (i.e., rice) are not nutritionally appropriate for the preterm infant. The use of elemental or extensively hydrolyzed formulas can decrease transit time and may decrease symptoms of GER and can be considered in age-appropriate populations.

PROGNOSIS

In 92% of infants by 37 weeks' PMA and in 98% of infants by 40 weeks' PMA, apnea of prematurity resolves spontaneously. However, infants born well before 28 weeks' GA may experience apnea and bradycardic events until 44 weeks' PMA. Beyond 44 weeks' PMA, extreme events (apnea >30 seconds and/or bradycardia <60 beats/min for >10 seconds) are very rare. The period that an infant should be observed to ensure resolution of apnea and bradycardia is not defined and among institutions is highly variable. However, many experts would recommend that an infant demonstrate an event-free period of 5-7 days before discharge. Although the nature and severity of events should dictate the length of observation, sufficiently large retrospective cohort studies suggest that a 1–3-day (infants born at ≥30 weeks' GA), 9–10-day (27-28 weeks' GA), or 13–14-day (<26 weeks' GA) event-free period predicts resolution of apnea in up to 95% of infants successfully. Brief, isolated bradycardic episodes associated with oral feeding are common in preterm infants and are generally not considered significant during the event-free period.

Despite its high frequency in preterm infants, the harm associated with apnea of prematurity is unknown. However, apnea of prematurity does not appear to alter an infant's prognosis unless it is severe, recurrent, and refractory to therapy. Prompt, effective therapy and careful monitoring are vital to avoid prolonged, severe hypoxia, which may increase the risk of death and neurodevelopmental impairment.

Sudden Infant Death Syndrome and Home Monitoring

Although preterm infants are at higher risk for sudden infant death syndrome (SIDS), apnea of prematurity *does not* further increase that risk. The epidemiologic evidence that placing babies supine during sleep reduces the rate of SIDS deaths by >50% suggests that positioning, and not prematurity, primarily influences the incidence of SIDS. Supine positioning on a firm sleep surface separate from the parents' bed, promotion of breastfeeding, and pacifier use during sleep reduce the incidence of SIDS. Avoidance of cigarette smoke exposure and no parental use of alcohol or illicit drugs during pregnancy and after birth are also important in the prevention of SIDS.

In-home monitoring is an area that has received significant interest in prevention of SIDS. In a large cohort study, episodes of apnea and bradycardia were not uncommon (severe events detected in 10% of infants monitored and 2.3% of healthy term infants). Preterm infants remained at risk for apnea until approximately 43 weeks' PMA; however, most SIDS deaths occurred after apnea has resolved occurring at an average of 45.8 weeks' PMA for premature infants and 52.3 weeks' PMA for term infants. There was no evidence that home monitoring impacted the incidence of SIDS. The role for home monitors is likely limited to premature infants with prolonged or extreme episodes of apnea (and should be discontinued after 44 weeks' PMA in this population), infants with specific risk factors for obstructive apnea, or requiring supplemental oxygen or mechanical ventilation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 126

Respiratory Distress Syndrome (Hyaline Membrane Disease)

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

INCIDENCE

Respiratory distress syndrome (RDS) occurs primarily in premature infants; its incidence is inversely related to gestational age (GA) and birthweight. It occurs in 60–80% of infants <28 weeks' GA, in 15–30% of those between 32 and 36 weeks' GA, and rarely in those >37 weeks' GA. The risk for development of RDS increases with maternal diabetes, multiple births, cesarean delivery, precipitous delivery, asphyxia, cold stress, and a maternal history of previously affected infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal opiate use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

ETIOLOGY AND PATHOPHYSIOLOGY

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. In the absence of pulmonary surfactant, significantly increased alveolar **surface tension** leads to atelectasis, and the ability to attain an adequate **functional residual capacity (FRC)** is impaired. Additionally, insufficient surfactant contributes to heterogenous lung expansion with atelectatic areas remaining unventilated and progressive overdistension of ventilated regions according to Laplace's law (Fig. 126.1).

Although surfactant is present in high concentrations in fetal lung by 20 weeks of gestation, it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 weeks. Mature levels of pulmonary surfactant are present usually after 35 weeks of gestation. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, SP-B, SP-C, and SP-D), and cholesterol (Fig. 126.2). With advancing GA, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells (Fig. 126.3). These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability at end-expiration. Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high O_2 concentrations and mechanical ventilation, thereby further reducing secretion of surfactant.

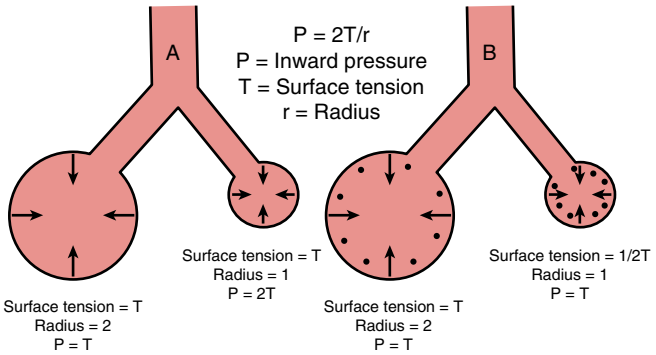

Fig. 126.1 Laplace's law as it applies to alveolar distension. Laplace's law states that the collapsing pressure in the alveolus is directly related to **surface tension** and inversely related to alveolar radius. In **A** the collapsing pressure is higher in the smaller alveoli thus the smaller alveolus further collapses, and larger alveolus distends leading to asymmetry in ventilation. In **B** with **surfactant** present, the particles become more densely spaced as the alveolus collapses, which decreases **surface tension**, and the resulting collapsing pressure is equalized between the two alveoli.

Atelectasis results in perfused but not ventilated alveoli, causing hypoxia. Decreased lung compliance, small tidal volumes, increased physiologic dead space, and insufficient alveolar ventilation eventually result in hypercapnia. The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself. Progressive injury to epithelial and endothelial cells results from atelectasis (atelectrauma), volutrauma, ischemic injury, and oxygen toxicity. This injury leads to effusion of proteinaceous material and cellular debris into the alveolar spaces (forming the classic hyaline membranes) further impairing oxygenation. RDS represents a vicious cycle of diminished surfactant production, worsening atelectasis, lung injury, and severe hypoxia (Fig. 126.4).

CLINICAL MANIFESTATIONS

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants, until rapid, shallow respirations and cyanosis become more obvious. A later onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with birthweight <1,000 g). Characteristically, tachypnea, prominent (often audible) expiratory grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis are noted. Breath sounds may be normal or diminished with a harsh tubular quality, and on deep inspiration, fine crackles may be heard. *The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated,* blood pressure may fall; *cyanosis and pallor increase, and grunting decreases or disappears, as the condition worsens. Apnea and irregular respirations are ominous signs requiring immediate intervention.* Untreated patients develop a mixed respiratory-metabolic acidosis with hypoxia and the potential to progress to respiratory failure with multisystem organ dysfunction due to inadequate oxygen delivery. In most cases, the signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired O_2 levels and/or lower ventilator support. Death can result from severe impairment of gas exchange, pulmonary air leaks (pulmonary interstitial emphysema, pneumothorax; see Chapter 132), pulmonary hemorrhage (see Chapter 133), or intraventricular hemorrhage (IVH).

DIAGNOSIS

The clinical course, chest x-ray findings, and blood gas values help establish the clinical diagnosis. On chest radiograph, the lungs may have a characteristic but not pathognomonic appearance that includes low lung volumes, a diffuse, fine reticular granularity of the parenchyma (ground-glass appearance), and air bronchograms (Fig. 126.5). The initial x-ray appearance is occasionally normal, with the typical pattern developing during the first day. Considerable variation in radiographic findings may be seen, especially in infants who have already received treatment with surfactant replacement and/or positive pressure respiratory support; this variation often results in poor correlation between radiographic findings and the clinical course. Blood gas findings are characterized initially by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

In the differential diagnosis, early-onset sepsis may be indistinguishable from RDS. In neonates with pneumonia, the chest radiograph may be identical to that for RDS. Clinical factors such as maternal group B streptococcal colonization with inadequate intrapartum antibiotic prophylaxis, maternal fever (>38.5°C) or chorioamnionitis, or prolonged

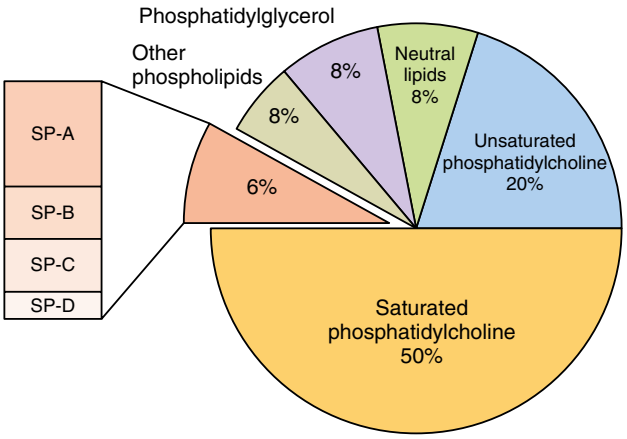

Fig. 126.2 Composition of surfactant. SP-A, Surfactant-associated protein A; SP-B, surfactant-associated protein B; SP-C, surfactant-associated protein C; SP-D, surfactant-associated protein D. *(From Jobe AH, Ikegami M. Biology of surfactant. Clin Perinatol. 2001;28:655–669.)*

rupture of membranes (>18 hours) are associated with an increased risk of early-onset sepsis. Although complete blood counts are neither sensitive nor specific in the diagnosis of early-onset sepsis, the presence of marked neutropenia has been associated with increased risk. **Transient tachypnea of the newborn** (TTN; see Chapter 128) is a common consideration that may be distinguished from RDS by its shorter and milder clinical course and is characterized by low or no need for O_2 supplementation. Cyanotic congenital heart disease (in particular, total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color-flow imaging can be performed in infants who show no response to surfactant replacement, to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance (PVR). Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions, and congenital anomalies (pulmonary congenital airway malformations, pulmonary lymphangiectasia, diaphragmatic hernia, lobar emphysema) must be considered in patients with an atypical clinical course but can generally be differentiated from RDS through radiographic and other evaluations (Fig. 126.6).

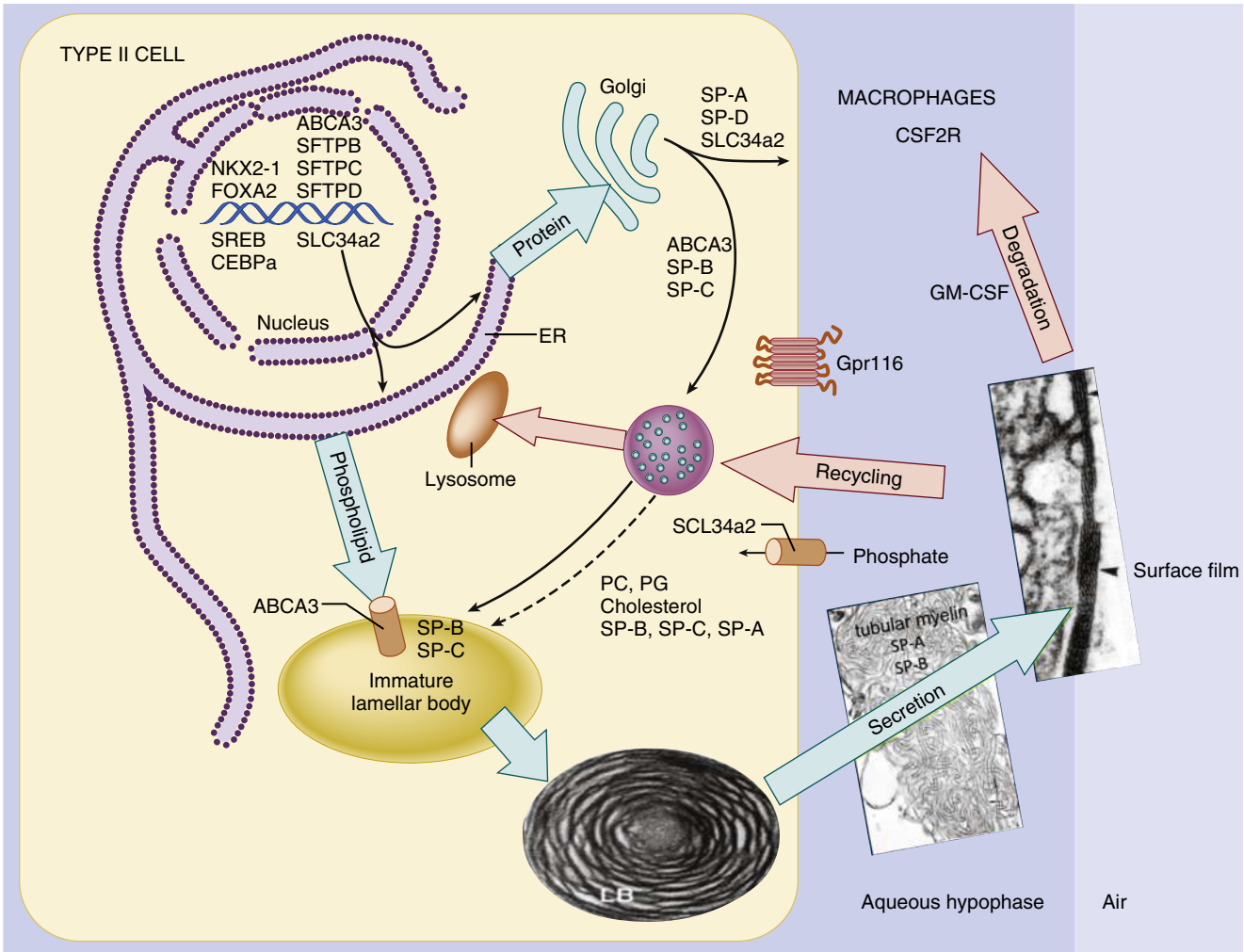

Fig. 126.3 Biosynthesis of surfactant involves distinct pathways for surfactant proteins and lipids. SP-B and SP-C are trafficked from the endoplasmic reticulum (ER) to lamellar bodies via the Golgi complex and multivesicular body (MVB); in contrast, surfactant phospholipids are likely directly transported from the ER to specific lipid importers (ABCA3) in the lamellar body–limiting membrane. Surfactant proteins and lipids are assembled into bilayer membranes that are secreted into the alveolar airspace, where they form a surface film at the air–liquid interface. Cyclical expansion and compression of the bioactive film results in the incorporation and loss of lipids and proteins from the multilayered surface film. Surfactant components removed from the film are degraded in alveolar macrophages or are taken up by type II epithelial cells for recycling or degradation in the lysosome. The MVB plays a key part in the integration of pathways for surfactant synthesis, recycling, and degradation. NKX2-1, FOXA2, SREBP, and CEBPα are transcription factors regulating surfactant protein and lipid synthesis. SLC34a2 is a phosphate transporter. Gpr116 is a membrane receptor regulating surfactant secretion. ABCA3, ATP-binding cassette transporter A3; GM-CSF, granulocyte-macrophage colony-stimulating factor; PC, phosphatidylcholine; PG, phosphatidylglycerol; SP, surfactant proteins. *(From Polin RA, Abman SH, Rowitch DH, Benits WE, eds. Fetal and Neonatal Physiology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 75.3.)*

Although rare, genetic disorders may contribute to respiratory distress. Abnormalities in **surfactant protein B and C** genes as well as a gene responsible for transporting surfactant across membranes, ABC transporter 3 *(ABCA3)*, are associated with severe and often lethal familial respiratory disease. **Congenital alveolar proteinosis** (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants (see Chapter 434). In atypical cases of RDS, a lung profile (lecithin:sphingomyelin ratio and phosphatidylglycerol determination) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency. Other familial causes of neonatal respiratory distress (not RDS) include mucopolysaccharidosis, acinar dysplasia, pulmonary lymphangiectasia, and alveolocapillary dysplasia. Evaluation for these disorders should be pursued with the assistance of pediatric pulmonologists and geneticists. Evaluation may include lung imaging, fluid sampling, tissue biopsy, and genetic testing.

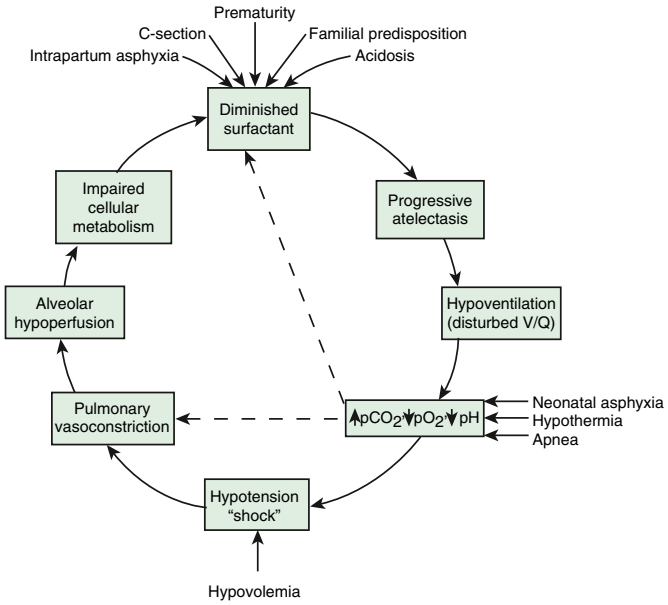

Fig. 126.4 Contributing factors in the pathogenesis of hyaline membrane disease. The potential "vicious circle" perpetuates hypoxia and pulmonary insufficiency. V/Q, Ventilation-perfusion ratio. *(From Farrell P, Zachman R. Pulmonary surfactant and the respiratory distress syndrome. In Quilligan EJ, Kretchmer N, eds. Fetal and Maternal Medicine. New York: Wiley; 1980.)*

PREVENTION

Avoidance of unnecessary or poorly timed early (<39 weeks' GA) cesarean delivery or induction of labor and appropriate management of high-risk pregnancy and labor (including administration of antenatal corticosteroids) are important preventive strategies. Strategies to prevent preterm birth include antenatal use of progesterone; measurement of cervical length and cerclage placement as indicated; and use of antibiotics, tocolytics, and magnesium for threatened preterm labor. In cases where premature delivery cannot be avoided, the transfer of the mother to an institution with appropriate neonatal care capabilities can improve early management of RDS. Antenatal and intrapartum fetal

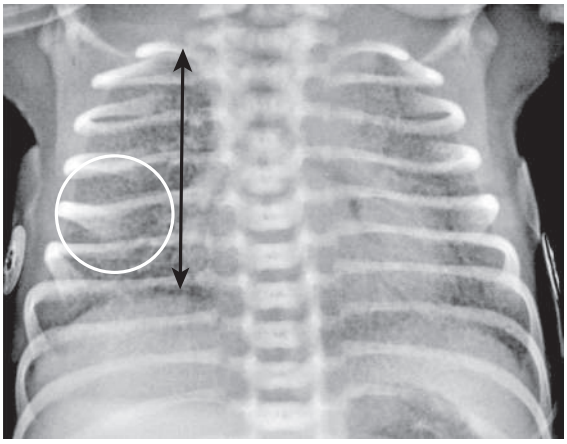

Fig. 126.5 Respiratory distress syndrome (RDS) of the newborn (hyaline membrane disease [HMD]). There is a diffuse ground-glass or finely granular appearance *(circle)* in a bilateral and symmetric distribution. Hypoaeration is seen in nonventilated lungs *(double arrow)*. *(From Herring W. Learning Radiology: recognizing the Basics, 4th ed. Philadelphia: Elsevier; 2020: Fig. 28.2.)*

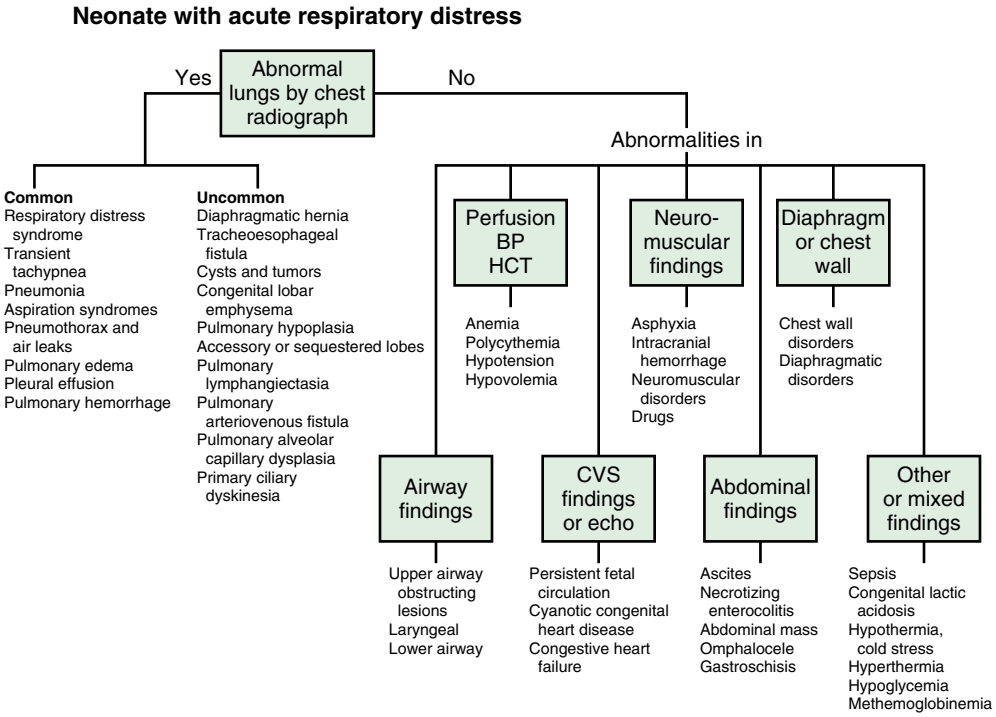

Fig. 126.6 Neonate with acute respiratory distress. BP, Blood pressure; CVS, chorionic villus sampling; HCT, hematopoietic cell transplant. *(From Battista MA, Carlo WA. Differential diagnosis of acute respiratory distress in the neonate. In Frantz ID, ed. Tufts University of School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases. Vol. 2. Issue 3. Newtown, PA: Associates in Medical Marketing Co.; 1992.)*

monitoring may decrease the risk of fetal asphyxia; asphyxia is associated with an increased incidence and severity of RDS.

Administration of **antenatal corticosteroids** to women before 37 weeks of gestation significantly reduces the incidence and mortality of RDS as well as overall neonatal mortality. Antenatal corticosteroids also reduce (1) overall mortality, (2) admission to the neonatal intensive care unit (NICU) and need for/duration of ventilatory support, and (3) incidence of severe IVH, necrotizing enterocolitis (NEC), and neurodevelopmental impairment. Betamethasone and dexamethasone have both been used antenatally. The American College of Obstetricians and Gynecologists (ACOG) recommends antenatal corticosteroids for all women presenting between 24- and 34-weeks' gestation in preterm labor. Antenatal corticosteroid use before 24 weeks' gestation for preterm labor or rupture of membranes should be driven by the family's preferences for intervention. ACOG recommends a single course of antenatal corticosteroid for mothers presenting between 34- and 36-weeks' gestation in preterm labor if no previous steroids have been given during the pregnancy. One repeat course of antenatal corticosteroids may be considered for mothers at risk of preterm delivery more than 14 days from the prior course of steroids and with a GA less than 34 weeks. Additional repeat courses of antenatal corticosteroids are not recommended due to impact on birthweight, cerebral myelination, and lung growth. Antenatal corticosteroids do not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis.

TREATMENT

The basic defect requiring treatment in RDS is inadequate pulmonary O_2-CO_2 exchange. Basic supportive care (thermoregulatory, circulatory, fluid, electrolyte, and respiratory) is essential while FRC is established and maintained. Because most cases of RDS are self-limited, the goal of treatment is to minimize abnormal physiologic variations and superimposed iatrogenic problems. Treatment of infants with RDS is best carried out in the NICU.

Continuous monitoring of vital signs, review of chest radiography, and monitoring of blood gas values guides therapy in RDS. Oxygenation (So_2) should be assessed by continuous pulse oximetry. Capillary blood samples are of limited value for determining Po_2 but may be useful for Pco_2 and pH monitoring. Arterial blood gas samples provide the most accurate assessment of oxygenation. Monitoring of blood gas parameters and mean arterial blood pressure through an umbilical or peripheral arterial catheter is useful in managing the shocklike state that may occur during the initial hours in premature infants who have been asphyxiated or have severe RDS. Because of the difficulty in distinguishing group B streptococcal or other bacterial infections from RDS, empirical antibiotic therapy should be indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested, although the choice of antibiotics should be based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated (see Chapter 129).

Nasal Continuous Positive Airway Pressure

Warm, humidified oxygen should be provided at a concentration sufficient to keep Pao_2 between 50 and 70 mm Hg (91–95% Sao_2) to maintain normal tissue oxygenation while minimizing the risk of O_2 toxicity. If there is significant respiratory distress (severe retractions and expiratory grunting) or if Sao_2 cannot be kept >90% at an Fio_2 of ≥40, applying nasal continuous positive airway pressure (nCPAP) at 5-8 cm H_2O is indicated and usually produces a rapid improvement in oxygenation. Nasal CPAP reduces collapse of surfactant-deficient alveoli and improves both FRC and ventilation-perfusion matching. Early use of nCPAP for stabilization of at-risk preterm infants beginning early (in the delivery room) reduces the need for mechanical ventilation. Alternatives to nCPAP include noninvasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC). NIPPV is generally unsynchronized, but intermittent higher pressures do appear to improve oxygenation and ventilation over several hours. Additionally, NIPPV may limit apnea as a cause of respiratory failure. **HFNC** used heated and humidified oxygen flow generally upward of 2 L/min to provide distending pressures to the airways. The distending pressure is variable, which may contribute to HFNC failure. The amount of nCPAP required usually decreases after approximately 72 hours of age, and most infants can be weaned from nCPAP shortly thereafter.

Surfactant Replacement Therapy

Surfactant deficiency is the primary pathophysiology of RDS. Immediate effects of surfactant replacement therapy include improved alveolar-arterial oxygen gradients, reduced ventilatory support, increased pulmonary compliance, and improved chest radiograph appearance. In the past, *intratracheal* surfactant replacement for symptomatic premature infants immediately after birth (prophylactic) or during the first few hours of life *(early rescue)* showed reduced air leak and mortality from RDS. However, substantial evidence supports the feasibility and efficacy of **nCPAP** as the *primary* means of respiratory support for preterm infants with RDS with addition of surfactant based on clinical indication. Nasal CPAP started at birth is as effective as prophylactic or early surfactant and is associated with a reduction in bronchopulmonary dysplasia (BPD). *Nasal CPAP is therefore the approach of choice for the delivery room management of a preterm neonate at risk for RDS.*

In neonates with RDS who fail nCPAP and require intubation and mechanical ventilation, treatment with endotracheal surfactant should be initiated immediately to avoid lung injury. *Assisted ventilation and surfactant are indicated for infants with RDS who cannot keep oxygen saturation >90% while breathing 40% oxygen and receiving nCPAP.* Delays in delivering surfactant once clinical criteria are met is associated with poorer outcomes including increased mortality, increased incidence of **pulmonary air leak,** and increased risk for **BPD**. Repeated dosing is given every 6-12 hours for a total of two to four doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management. Additional required on-site staff support includes nurses and respiratory therapists experienced in the ventilatory management of preterm infants. Bolus delivery of surfactant is generally associated with better distribution throughout the lungs and faster improvement. Lung recruitment strategies include modest increase in tidal volume or positive end-expiratory pressure (PEEP) before surfactant administration, which may improve distribution. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Complications of surfactant replacement therapy include transient hypoxia, hypercapnia, bradycardia and hypotension, blockage of endotracheal tube (ETT), and pulmonary hemorrhage.

A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. There do not appear to be significant, consistent benefits to one preparation over another. Infants requiring ventilator support after 1 week of age may experience transient episodes of surfactant dysfunction temporally associated with episodes of infection and respiratory deterioration. Surfactant treatment may be beneficial in these infants.

Recognizing the benefits of surfactant replacement therapy, in addition to the potential protective effects of prophylactic nCPAP, some experts recommend intubation for prophylactic or early rescue surfactant replacement therapy, followed by extubation back to nCPAP immediately once the infant is stable (usually within minutes). This method is commonly referred to *as intubate, surfactant, and extubate (INSURE).* A variation of the INSURE method has evolved known as *MIST (minimally invasive surfactant therapy)* or *LISA (less invasive surfactant administration),* in which a small feeding tube, rather than an ETT, is used to deliver intratracheal surfactant to a spontaneously breathing infant on nCPAP. LISA and/or MIST are increasingly being utilized as the preferred method for delivering surfactant in infants who are not anticipated to require prolonged invasive ventilation. The combination of LISA, antenatal corticosteroids, nCPAP, and limitation of positive pressure ventilation in the delivery room was associated with decreased rates of BPD when compared to INSURE. Other methods of surfactant delivery are under investigation including the use of laryngeal mask airway and the use of nebulized surfactant to avoid airway manipulation altogether. In two studies of aerosolized surfactant, the need for intubation was reduced by ~50%.

Mechanical Ventilation

Infants with respiratory failure or persistent apnea require assisted mechanical ventilation. Strict definitions for respiratory failure in extremely preterm infants with RDS are not agreed on universally, but reasonable measures of respiratory failure are (1) arterial blood pH <7.20, (2) $Paco_2$ ≥60 mm Hg, (3) Sao_2 <90% at O_2 concentration of 40% *and* nCPAP of 5-8 cm H_2O, and (4) persistent or severe apnea. The goal of mechanical ventilation is to improve oxygenation and ventilation without causing pulmonary injury or oxygen toxicity. Acceptable ranges of arterial blood gas (ABG) values vary significantly among institutions but generally range from Pao_2 50-70 mm Hg (Spo_2 >90%), $Paco_2$ 45-65 mm Hg (and higher after the first few days when risk of IVH is less), and pH 7.20-7.35. During mechanical ventilation, **oxygenation** is improved by increasing either Fio_2 or the mean airway pressure. The mean airway pressure can be increased by raising the peak inspiratory pressure (PIP), inspiratory time, ventilator rate, or PEEP. Adjustment in PEEP is usually most effective; however, excessive PEEP may impede venous return, thereby reducing cardiac output and O_2 delivery (see Chapter 89.1). PEEP levels of 4-6 cm H_2O are usually safe and effective and assist in establishing FRC. **CO_2 elimination** is determined by the minute ventilation, which is a product of the tidal volume (dependent on the inspiratory time and PIP) and ventilator rate. Ventilator settings typically include a tidal volume of 4-6 mL/kg and a starting rate of approximately 40 breaths/min. With use of high ventilatory rates, relatively short inspiratory time and sufficient expiratory time should be allowed to avoid air trapping and inadvertent PEEP.

Synchronized intermittent mechanical ventilation (SIMV) delivered by time-cycled pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. With **pressure-limited** SIMV, a set PIP is delivered in synchrony with the patient's own breaths for a specified rate per minute. For breaths above the set rate, pressure support breaths (8-10 cm H_2O above PEEP) are provided to help overcome the resistance associated with spontaneous breathing through the ETT. In pressure-limited ventilation, the delivered tidal volume is directly proportional to the respiratory compliance. Rapid changes in compliance occur with surfactant replacement therapy, requiring careful attention to tidal volumes and appropriate adjustments in PIP. In **volume-targeted** ventilation a specific tidal volume is set, and the PIP required to deliver it varies inversely with the respiratory compliance. Studies indicate that lung damage is related to recurrent lung collapse and overdistension rather than high pressures, thus volume-targeted ventilation may represent the most lung protective strategy of conventional ventilation. Evidence suggests that volume-targeted ventilation results in fewer pulmonary air leaks and may improve survival without BPD.

Neurally adjusted ventilatory assist (NAVA) is a ventilator strategy that integrates electrical signals from the diaphragm to synchronize ventilator breaths with the patient. Increased diaphragmatic electrical signal indicates the impending onset of a breath. The strength of electrical signal indicates the size of breath intended by the patient. Using this strategy, the timing and tidal volume can be customized to the patient on a breath-by-breath basis, and this is believed to decrease overall pressures required and limit lung damage. NAVA technology can also be used to synchronize noninvasive ventilation. To date there is insufficient evidence to compare the outcomes of infants with RDS initially managed on NAVA ventilation to those managed with pressure-limited or volume-limited SIMV.

High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min or 5-20 Hz). This ventilation strategy maintains sustained alveolar expansion and therefore limits injury associated with recurrent atelectasis. HFV may improve elimination of CO_2 and improve oxygenation in patients who show no response to conventional ventilators, as well as those who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) are the most frequently used methods. There is not strong evidence to favor HFOV over HFJV or vice versa. Many investigators have examined the use of HFV as a primary mode of ventilation in infants with RDS. There is some evidence that HFV may result in decreased rates of BPD and pulmonary air leak when compared to pressure-limited SIMV; however, superiority over volume-targeted SIMV has not been consistently demonstrated.

Permissive Hypercapnia and Avoidance of Hyperoxia

Permissive hypercapnia is a strategy for management of patients receiving ventilatory support in whom priority is given to limiting ventilator-associated lung injury by tolerating relatively high levels of $Paco_2$ (>60-70 mm Hg). Permissive hypercapnia can be implemented during nCPAP and mechanical ventilation but has not been shown to significantly impact outcomes. Hypocarbia is associated with poorer outcomes; therefore careful monitoring of Pco_2 should be undertaken and moderate hypercapnia (>40-50 mmHg) can be tolerated. Hyperoxia may also contribute to lung injury in preterm infants. However, a lower target range of oxygenation (85–89%) compared with a higher range (91–95%) increases mortality and does not alter rates of BPD, BPD/death, blindness, or neurodevelopmental impairment. Therefore the currently recommended range of oxygen saturation targets is 91–95%.

Discontinuation of Mechanical Ventilation

Strategies for weaning infants from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes. Extubation to nCPAP prevents postextubation atelectasis and reduces the need for reintubation. NIPPV may further decrease the need for reintubation in premature infants, particularly when combined with NAVA technology to allow synchronization. HFNC (1-8 L/min) oxygen is often used to support term and near-term infants following extubation and appears to be comparable to nCPAP in preventing postextubation failure. It is not clear whether nCPAP, NIPPV, or HFNC is more efficacious for promoting normal lung development and preventing BPD, but there is more evidence associated with nCPAP in extremely preterm infants. Preloading with methylxanthines enhances the success of extubation.

Other Pharmacologic Therapies

There are no pharmacologic therapies superior or equal to the efficacy of maintaining FRC (through noninvasive respiratory support and mechanical ventilation when necessary) and providing surfactant replacement therapy in the treatment of RDS. Systemic corticosteroids (predominantly dexamethasone), although effective in improving respiratory mechanics and reducing the incidence of BPD and death, are associated with increased risk of cerebral palsy and neurodevelopmental impairment when used indiscriminately (see Chapter 127).

Inhaled nitric oxide (iNO) has been evaluated in preterm infants following the observation of its effectiveness in term and near-term infants with hypoxemic respiratory failure. Although iNO improves oxygenation in term and near-term infants with hypoxic respiratory failure or persistent pulmonary hypertension of the neonate, trials in preterm infants have not shown significant benefit.

PROGNOSIS

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal corticosteroids, postnatal surfactant use, and improved modes of ventilation have resulted in low mortality from RDS (approximately 10%). Mortality increases with decreasing GA. Optimal results depend on the availability of experienced and skilled personnel, care in specially designed and organized regional hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irremediable congenital malformation. Premature infants with RDS may go on to develop chronic lung disease and ultimately BPD (see Chapter 127).

Pulmonary air leaks (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema) are observed in 3–9% of extremely preterm infants with RDS (see Chapter 132). PPV with excessive

inspiratory pressures (and therefore excessive tidal volumes), either during resuscitation at delivery or in the initial hours of mechanical ventilation, is a common risk factor, but air leaks can also occur in infants breathing spontaneously. Although the risk of air leak was increased in infants receiving a higher level of nCPAP (up to 8 cm H_2O) in the CPAP or Intubation at Birth (COIN) trial, subsequent trials have not demonstrated a similar effect.

Additional complications of RDS may result from intubation procedures during the treatment of this disorder. Airway injury may occur at the time of intubation and adequate training is essential. Complications of intubation including ventilator-associated pneumonias and transient obstruction of the artificial airway are possible. With prolonged or recurrent intubation local pressure injury can lead to the development of subglottic stenosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

126.1 Patent Ductus Arteriosus

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

INCIDENCE AND PATHOPHYSIOLOGY

The ductus arteriosus is a fetal vascular shunt connecting the aorta to the pulmonary artery that allows oxygenated blood to bypass the uninflated fetal lungs and enter the systemic circulation. Following term birth, the ductus arteriosus constricts and is usually closed in the first few days of life. Although ductal closure occurs by 72 hours after birth in almost all term infants, the ductus remains patent in 65% of preterm infants born at <30 weeks' GA and in 85% of infants born at 24 weeks' GA. Risk factors for delayed closure of the PDA include hypoxia, acidosis, increased pulmonary pressure secondary to pulmonary vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins (which dilate the ductus). Shunting through the patent ductus arteriosus (PDA) may initially be bidirectional or right to left. As RDS resolves, PVR decreases, and predominantly left-to-right shunting may occur, leading to left ventricular (LV) volume overload and pulmonary edema.

CLINICAL MANIFESTATIONS

Manifestations of PDA may include (1) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a machine-like continuous or systolic murmur; (2) radiographic evidence of cardiomegaly and increased pulmonary vascular markings; (3) hepatomegaly; (4) increasing oxygen dependence; (5) carbon dioxide retention; and (6) less often renal failure. Infants with a hemodynamically significant PDA often require escalation of ventilator and oxygen support. The diagnosis is confirmed by echocardiographic visualization of a PDA with Doppler flow imaging that demonstrates left-to-right shunting. A hemodynamically significant PDA by echocardiogram has a PDA ≥1.5 mm, unrestricted pulsatile transductal flow, left atrial to aortic root ratio ≥1.5, and absent (end) diastolic flow in the descending aorta (Table 126.1).

TREATMENT

Interventions to encourage ductal closure include fluid restriction, cyclooxygenase (COX) inhibitors (indomethacin or ibuprofen), acetaminophen, and surgical ligation. Short-term benefits of any therapy must be balanced against adverse effects, such as transient renal dysfunction and fluid imbalances associated with indomethacin.

By the time of discharge in the majority of extremely preterm infants (>90%), the PDA will close spontaneously. Spontaneous ductal closure may be facilitated by general supportive measures, including early (<7 days of age) avoidance of excessive fluid administration and judicious use of diuretics to manage pulmonary edema. However, within the first week of life, in 30% of infants with birthweight <1,500 g and 70% of infants <1,000 g, the PDA persists. Although many preterm infants with persistent PDA will remain clinically stable while awaiting spontaneous closure, approximately 60% of infants <1,000 g will develop significant clinical instability (hypotension, renal failure, worsening respiratory failure secondary to pulmonary edema). Pharmacologic and surgical ductal closure may be indicated in the premature infant with a moderate to large, hemodynamically significant PDA when there is a delay in clinical improvement or deterioration.

Table 126.1 Summary of Essential Parameters Used for Echocardiographic Assessment and Hemodynamic Evaluation of PDA

PDA EVALUATION CRITERIA	ESSENTIAL ECHOCARDIOGRAPHIC PARAMETERS FOR ASSESSMENT OF PDA AND HEMODYNAMIC EVALUATION
Ductal characteristics	PDA size (small 2 mm) and flow direction (left to right, right to left, or bidirectional) and Doppler assessment with maximum velocity (Vmax) in systole and end-diastole
Assessment of pulmonary over circulation	Dilated left side of the heart on visual inspection "eyeballing" and LA/Ao ratio (mild 1.6) OR LVEDD (correlate with *z* scores) OR LPA diastolic velocity, mean velocity >0.42 m/sec, end-diastolic velocity >0.2 m/sec OR reversal of mitral E/A ratio *Document presence or absence and magnitude of intraatrial shunt
Assessment of systemic hypoperfusion	Retrograde or absent blood flow during diastole in descending aorta OR celiac trunk or SMA OR anterior or middle cerebral artery

A comprehensive echocardiographic assessment should be performed to rule out any underlying congenital heart defect or pulmonary hypertension and delineate orientation of arch (left or right sidedness) before any intervention to close the PDA.
E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; LA/Ao, left atrial to aortic ratio; LPA, left pulmonary artery; LVEDD, left ventricular end-diastolic diameter; PDA, patent ductus arteriosus; SMA, superior mesenteric artery.
From Singh Y, Fraisse A, Erdeve O, Atasay B. Echocardiographic diagnosis and hemodynamic evaluation of patent ductus arteriosus in extremely low gestational age newborn (ELGAN) infants. *Front Pediatr.* 2020;8:Article 573627. Table 1.

Pharmacologic Closure

Pharmacologic closure of the PDA has been described using COX inhibitors that inhibit prostaglandin production, with equivalent efficacy and safety profiles described for ibuprofen and indomethacin. The efficacy of pharmacologic *therapy* is inversely proportional to the gestational and postnatal age, and closure is more likely when medication is administered before 21 days of age. However, successful closure has been reported up to 8 weeks of age. Whether indomethacin or ibuprofen is used, 20–40% of infants demonstrate treatment failure, and of those infants, 10–20% require eventual surgical ligation. Rates of recurrence following successful pharmacologic closure in general are low (<15%). Neither therapy significantly impacts the rate of NEC, BPD, or mortality. **General contraindications** to both indomethacin and ibuprofen include thrombocytopenia (<50,000 platelets/mm^3), active hemorrhage (including severe IVH), NEC or isolated intestinal perforation, elevated plasma creatinine (>1.8 mg/dL), or oliguria (urine output <1 mL/kg/hr). Importantly, the concomitant use of hydrocortisone and indomethacin in extremely preterm infants must be avoided because the combination is associated with a dramatic increase in spontaneous intestinal perforation. Although indomethacin reduces

mesenteric blood flow, mounting experience suggests that low-volume trophic enteral feeding during administration is safe.

Prophylactic **indomethacin** given over the first 72 hours of age to preterm infants with birthweight <1,000 g reduces the incidence of severe IVH (grade III/IV), pulmonary hemorrhage, symptomatic PDA, and need for surgical PDA ligation. Although often implicated in spontaneous intestinal perforation and NEC, randomized controlled trials (RCTs) have failed to demonstrate that indomethacin increases their risk significantly. Short-term side effects include reductions in cerebral, mesenteric, and renal blood flow. Oliguria unresponsive to diuretic therapy is observed frequently. Dosing regimens for indomethacin vary considerably, but it usually is administered as a slow IV infusion (0.1-0.2 mg/kg/dose over 30 minutes) every 12-24 hours for three doses. A repeat course can be attempted if the duct fails to close or reopens, but additional (>2) courses do not appear to be efficacious. Longer courses (5-7 days) of indomethacin are not recommended because of to an increased risk of NEC in one trial.

Ibuprofen is as effective as indomethacin in closing a PDA, but ibuprofen is associated with reduced rates of oliguria and a small but significant reduction in the length of mechanical ventilation. Although higher doses may improve closure rates in the most immature infants, the typical IV or enteral dosing regimen for ibuprofen is 10 mg/kg for one dose, followed by two doses of 5 mg/kg every 24 hours. A meta-analysis showed that a higher dose of oral ibuprofen using 20 mg/kg per dose for one dose, followed by 10 mg/kg per dose for two doses 24 hours apart is superior in closing the PDA compared to indomethacin or the traditional ibuprofen dosing. As with indomethacin, a repeat course may be considered, but additional courses of ibuprofen are not efficacious and not recommended. Risk of NEC is *not increased* with indomethacin, but in comparison, ibuprofen *reduces* the relative risk of NEC. Unlike indomethacin, ibuprofen has not been shown to reduce the risk of severe IVH. Compared to the IV route, enteral ibuprofen may be more efficacious. Whether ibuprofen used in combination with hydrocortisone results in increased risk of spontaneous intestinal perforation is unknown.

Oral acetaminophen has been shown to be an effective medication in closing the PDA, with fewer side effects than existing agents. It is given enterally at 15 mg/kg per dose q6h for 3 days. In practice, most clinicians will use a course of one of the previously mentioned medications as first-line therapy (typically ibuprofen) and follow with a second course of acetaminophen in a few days if the PDA remains patent and symptomatic.

Surgical Ligation

The infant whose *symptomatic* PDA fails to close with pharmacologic interventions or who has contraindications to COX inhibitors is a candidate for surgical closure via an open thoracotomy. Although the long-term benefits are unclear, surgical ligation in infants born at <28 weeks' GA and <1,250 g is associated with improved survival. Surgical mortality is very low even in extremely low birthweight (ELBW) infants. However, **postligation cardiac syndrome**, a significant drop in blood pressure 6-12 hours after ductal ligation, is experienced by up to 50% of low birthweight (LBW) infants. The hypotension has been attributed to increased systemic vascular resistance along with decreased pulmonary venous return, resulting in impaired preload and LV function. Fluid resuscitation, inotropic support (with dobutamine or milrinone), and hydrocortisone are usually effective. Other complications of surgery include hemorrhage, pneumothorax, chylothorax, Horner syndrome, and injury to the recurrent laryngeal nerve resulting in vocal cord dysfunction. Inadvertent ligation of the left pulmonary artery or the transverse aortic arch has rarely been reported. Increased rates of neurodevelopmental impairment have been reported following surgical ligation, although a causal relationship remains uncertain. Due to the complications associated with surgical ligation, many centers have moved away from this modality and use a less invasive, percutaneous approach to PDA closure.

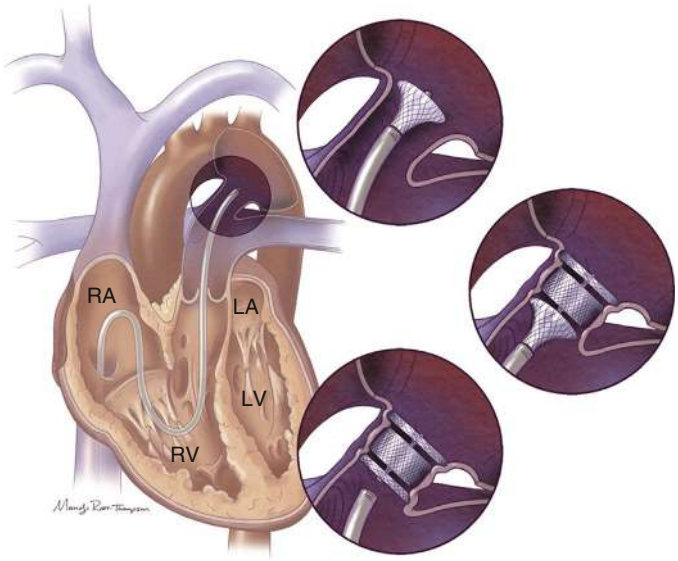

Fig. 126.7 Percutaneous device closure of a PDA using the Amplatzer Piccolo Occluder. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *(From Backes CH, Giesinger RE, Rivera BK, et al. Percutaneous closure of the patent ductus arteriosus in very low weight infants: considerations following US Food and Drug Administration approval of a novel device. J Pediatr. 2019;213:218–221.)*

Percutaneous Closure of the Patent Ductus Arteriosus

Percutaneous closure of the PDA is a safe and effective procedure for definitive PDA closure. In 2019, the U.S. Food and Drug Administration approved the Amplatzer PiccoloOccluder (Abbott Diagnostics, North Chicago, IL) for percutaneous PDA closure in preterm infants weighing 700 g or more (Fig. 126.7). A trial in 100 infants weighing <2 kg showed that this technique of PDA closure is 99% effective with a 2% risk of adverse events. Although a comparative trial has not been done against the traditional surgical approach, most US centers use percutaneous closure as the first-line approach for PDA closure when conservative treatment fails. This procedure is done under cardiac anesthesia in the catheterization laboratory. The femoral vein is accessed using modified Seldinger technique, and then, under fluoroscopic guidance, a catheter is advanced through the femoral vein all through the right ventricular and across the PDA and the Piccolo device is placed. This technique permits injection of contrast before and after device placement to ensure appropriate device selection, measure size of the PDA, and ensure that there is no occlusion of the descending aorta or left pulmonary artery after device placement. If there is evidence of narrowing, the device can be recaptured and repositioned until a satisfactory result is obtained. Rarely, appropriate device placement is not achieved, and the patient may have to undergo surgical ligation. The short-term complications are bleeding at the insertion site, embolization of the device into the descending aorta or left pulmonary artery, post-PDA ligation syndrome, and residual shunting across PDA. The long-term complications are unknown, but these patients likely need surveillance echocardiography until 2-3 years of age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 127

Bronchopulmonary Dysplasia

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

INCIDENCE

Bronchopulmonary dysplasia (BPD; also known as *chronic lung disease of prematurity*) is a clinical pulmonary syndrome that develops in the majority of extremely preterm infants and is defined by a prolonged need for respiratory support and supplemental oxygen. Almost 60% of infants born at ≤28 weeks' gestation will develop BPD, and the incidence of BPD increases inversely with gestational age. For infants born at 22-24 weeks, essentially 100% will develop BPD, the majority of whom will have moderate to severe disease. As neonatal care has improved and use of antenatal corticosteroids has become the standard of care, survival of infants born at the extreme of viability has improved, and BPD is encountered with increased prevalence. In the United States, an additional 10,000-15,000 new cases occur annually. Despite decades of experience, the incidence of BPD remains largely unchanged.

ETIOLOGY AND PATHOPHYSIOLOGY

BPD develops following preterm birth and the necessary life-supporting interventions (particularly mechanical ventilation and supplemental oxygen) that cause neonatal lung injury. As very low birthweight (VLBW) infant's survival has improved by advances in neonatal care, the clinical syndrome associated with BPD has evolved. The clinical, radiographic, and lung histology of classic BPD described in 1967 by Northway, before widespread use of antenatal corticosteroids and postnatal surfactant, was that of a disease of preterm infants who were more mature. Infants who developed BPD initially demonstrated classic respiratory distress syndrome (RDS), but the injurious mechanical ventilation and excessive supplemental oxygen required to support them resulted in a progressive, severe fibroproliferative lung disease. Improvements in respiratory care, as well as the introduction of surfactant and antenatal steroids, have allowed for less aggressive respiratory support strategies, and the need for excessive ventilator support and high percentages of inspired supplemental oxygen has decreased.

Despite a reduction in the fibroproliferative disease described previously, infants born in the modern era of neonatal care continued to require supplemental oxygen for prolonged periods. The *new* BPD is a disease primarily of infants with birthweight <1,000 g who were born at <28 weeks' gestation, some of whom have initially little or no lung disease at birth but over the first weeks of age experience progressive respiratory failure. Infants with the new BPD are born at a more immature stage of distal lung development, and lung histology demonstrates variable saccular wall fibrosis, minimal airway disease, abnormal pulmonary microvasculature development, and alveolar simplification. Although the etiology remains incompletely understood, the histopathology of BPD indicates interference with normal alveolar septation and microvascular maturation.

The pathogenesis of BPD is likely multifactorial, but pulmonary inflammation and lung injury in an immature lung are consistently observed. Alveolar collapse **(atelectrauma)** as a consequence of surfactant deficiency, together with ventilator-induced phasic overdistention of the lung **(volutrauma)**, promotes lung inflammation and injury. Supplemental oxygen produces free radicals that cannot be metabolized by the immature antioxidant systems of VLBW neonates and further contributes to the injury. Pulmonary inflammation evidenced by infiltration of neutrophils and macrophages in alveolar fluid, as well as a host of proinflammatory cytokines, contributes to the progression of lung injury. Pre- and postnatal infection, excessive pulmonary blood flow via the patent ductus arteriosus (PDA), excessive administration of intravenous fluid, and pre- and postnatal growth failure are also significantly associated with the development of BPD. In addition, pulmonary artery hypertension may complicate BPD. Although the mechanisms are unclear, all likely promote lung injury by necessitating increased or prolonged respiratory support or interfering with lung repair. Regardless, the result is an interference with normal development of the alveolar-capillary unit and interference with normal gas exchange.

CLINICAL MANIFESTATIONS

Over the first several weeks of age, infants developing BPD demonstrate persistent, often progressive respiratory distress and the need for respiratory support and supplemental oxygen. In extremely low birthweight (ELBW) infants at risk for BPD, the need for supplemental oxygen over the first 2 weeks of age follows one of three distinct patterns. Infants that follow the natural course of RDS, and by 3-4 days of age require minimal (F_{IO_2} <0.25) supplemental oxygen, have a low (<20%) risk of developing BPD. Infants who initially have a low O_2 requirement (F_{IO_2} <0.25) during the first week, but then experience early pulmonary deterioration and increased O_2 requirement (F_{IO_2} >0.25) during the second week, have a modest risk (approximately 50%) of developing BPD. Infants that have an early, persistently high (F_{IO_2} >0.25) need for supplemental oxygen have a significantly high (70%) risk of developing BPD.

Respiratory distress, commonly characterized by tachypnea and retractions, persists or worsens and is associated with hypercapnia, hypoxia, and oxygen dependence. The chest radiograph evolves from that of RDS to relative hyperinflation and fine, diffuse interstitial opacities. Wandering atelectasis is common. In the most severe cases, usually associated with prolonged mechanical ventilation and chronically high supplemental oxygen needs, frank cystic changes and/or pneumatoceles are observed (Fig. 127.1). Infants with severe BPD receiving invasive ventilation often demonstrate airway obstruction. Excessive airway mucus and edema, airway instability caused by acquired tracheobronchomalacia, and bronchospasm are proposed etiologies. Acute airway obstruction is manifest clinically by abrupt hypoxemia and bradycardia and is often referred to as *BPD spells*. Acute, intermittent right-to-left intracardiac or intrapulmonary shunting caused by abrupt elevations in pulmonary artery pressure (PAP) may also contribute and resemble BPD spells. Spells are notoriously difficult to control, but occasionally will respond to bronchodilators, increasing positive end-expiratory pressure (PEEP), and sedation acutely.

A common complication of BPD is **pulmonary hypertension**. Prospective surveillance indicates that in approximately 15% of all infants born at <1,000 g and <28 weeks' gestational age, echocardiographic signs of pulmonary hypertension will develop. Prenatal growth restriction, prolonged duration of mechanical ventilation and supplemental oxygen, and increasing severity of BPD are all associated with an increased risk. Pulmonary hypertension has been reported in as many as 40% of infants with the most severe BPD and can progress to right-sided heart failure. Pulmonary hypertension complicating BPD has been associated with increased mortality.

DIAGNOSIS

BPD is diagnosed when a preterm infant requires supplemental oxygen for the first 28 postnatal days; it is further classified at 36 weeks' postmenstrual age (PMA) according to the degree of O_2 supplementation (Table 127.1). Neonates receiving positive pressure support or ≥30% supplemental O_2 at 36 weeks' PMA or at discharge (whichever occurs first) are diagnosed as having **severe** BPD; those requiring <30% supplemental O_2 have **moderate** BPD; and those who previously required O_2 supplementation for at least 28 days but are currently breathing room air have **mild** BPD. Infants who require oxygen for <28 days of life have "no BPD." Infants receiving supplemental O_2 should undergo a stepwise reduction in supplemental O_2 to room air at 36 weeks while under continuous observation and with Spo_2 monitoring to determine whether they can be weaned off oxygen

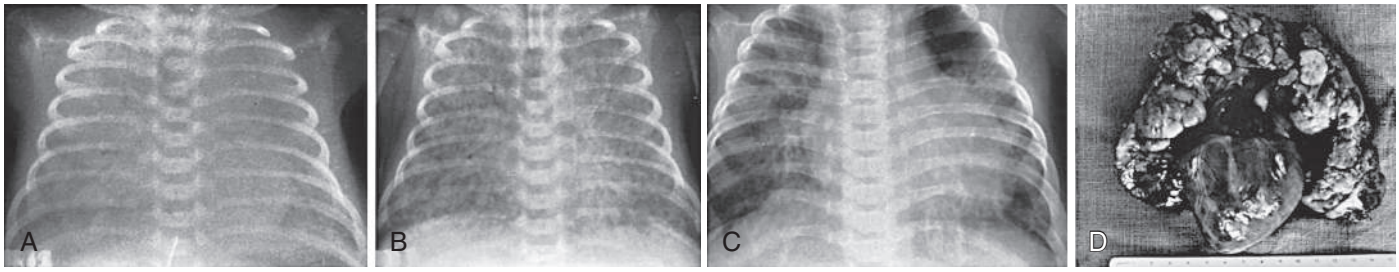

Fig. 127.1 Pulmonary changes in infants treated with prolonged, intermittent positive pressure breathing with air containing 80–100% oxygen in the immediate postnatal period for the clinical syndrome of hyaline membrane disease. **A,** A 5-day-old infant with nearly complete opacification of the lungs. **B,** A 13-day-old infant with "bubbly lungs" simulating the radiographic appearance of the Wilson-Mikity syndrome. **C,** A 7-month-old infant with irregular, dense strands in both lungs, hyperinflation, and cardiomegaly suggestive of chronic lung disease. **D,** Large right ventricle and a cobbly, irregular aerated lung of an infant who died at 11 months of age. This infant also had a patent ductus arteriosus. *(From Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. N Engl J Med. 1967;276:357–368.)*

Table 127.1 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria*

	GESTATIONAL AGE	
	<32 Wk	**≥32 Wk**
Time point of assessment	36 wk PMA or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**:	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**:
Mild BPD	Breathing room air at 36 wk PMA or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need† for <30% oxygen at 36 wk PMA or discharge home, whichever comes first	Need† for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need† for ≥30% oxygen and/or positive pressure (PPV or nCPAP) at 36 wk PMA or discharge home, whichever comes first	Need† for ≥30% oxygen and/or positive pressure (PPV or nCPAP) at 56 days postnatal age or discharge home, whichever comes first

*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most frequently respiratory distress syndrome (RDS). Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for >12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk PMA or at 56 days postnatal age or discharge should not reflect an "acute" event; rather, it should reflect the infant's usual daily therapy for several days preceding and after 36 wk PMA, 56 days postnatal age, or discharge.

†A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD, Bronchopulmonary dysplasia; nCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.

From Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163:1723–1729.

(physiologic definition of BPD). This test is highly reliable and correlated with discharge home on oxygen, length of hospital stay, and hospital readmissions in the first year of life. The risk of neurodevelopmental impairment and pulmonary morbidity and the severity of BPD are directly correlated.

Despite its simplicity, the current severity-based definition of BPD has limitations. Because of incomplete or inaccurate data related to hospital transfer or early discharge, in a significant number of infants the diagnosis of BPD is either not documented or misapplied. Additionally, those infants requiring O_2 support at relatively high flow (>2 L/min) or very low (<0.25 L/min) or those receiving other modes of noninvasive ventilation are not well characterized. Calculation of *effective oxygen* may be helpful but is cumbersome and not well validated. Clinical trials have relied on the need for supplemental O_2 at 36 weeks PMA to define BPD. Although this definition can diagnose BPD in the highest percentage of infants, it cannot discriminate between infants with milder BPD from those with most severe forms of BPD. A National Institute of Child Health and Human Development (NICHD) workshop on BPD developed a definition of BPD that would address some of the concerns mentioned earlier (Table 127.2). Specifically, it incorporates the diverse forms of respiratory support used, distinguishes infants who are receiving invasive vs noninvasive positive pressure ventilation (PPV), and introduces the term "lethal BPD" or grade III(A) severe BPD to identify infants who die from this disease before 36 weeks' PMA.

PREVENTION

In general, there remains a lack of effective interventions that prevent BPD. Avoidance of mechanical ventilation with the early use of nCPAP and early, selective surfactant replacement therapy with rapid extubation decrease the incidence of BPD modestly. The avoidance of mechanical ventilation achieved by the combination of early rescue surfactant by the INSURE, MIST, or LISA method with nasal continuous positive airway pressure (nCPAP) has been associated with a modest reduction in BPD (see Chapter 126). Gentle ventilation strategies, including volume-targeted ventilation and high-frequency oscillatory ventilation (HFOV), have also been associated with small, inconsistent reductions in BPD. Caffeine therapy for apnea of prematurity has also been associated with a decreased risk of BPD. Although the mechanisms are unknown, caffeine likely supports effective spontaneous respiration and decreases the likelihood that an infant will need invasive mechanical ventilation.

Table 127.2 New Definition of Bronchopulmonary Dysplasia Based on the 2016 NICHD Executive Workshop on Bronchopulmonary Dysplasia

For infants born <32 wk gestation, with radiographic evidence of parenchymal lung disease, who at 36 wk require one of the following F_{IO_2}/oxygen levels/oxygen concentrations for ≥3 consecutive days to maintain Sp_{O_2} in the 90–95% range

	INVASIVE IPPV	nCPAP, NIPPV, OR NASAL CANNULA ≥3 L/MIN	NASAL CANNULA 1-3 L/MIN	NASAL CANNULA <1 L/MIN
Grade I BPD	No	21% F_{IO_2}	22–29% F_{IO_2}	22–70% F_{IO_2}
Grade II BPD	21% F_{IO_2}	22–29% F_{IO_2}	≥30% F_{IO_2}	≥70% F_{IO_2}
Grade III BPD	>21% F_{IO_2}	≥30% F_{IO_2}		
Grade III(A) BPD	Infants who die between 14 days to 36 wk PMA from respiratory failure secondary to severe parenchymal lung disease not attributable to other neonatal morbidities			

NICHD, National Institute of Child Health and Human Development; BPD, bronchopulmonary dysplasia; IPPV, invasive positive pressure ventilation; nCPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation.
Adapted from Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr*. 2018;197:300–308.

Systemic corticosteroids (dexamethasone) given either early (<7 days of age to ventilated infants at risk of BPD) or late (>7 days of age to infants with progressing lung disease) prevent both mortality and BPD significantly, but because of the increased risk of cerebral palsy (CP) and neurodevelopmental impairment, their routine use is not recommended. The risk of neurodevelopmental impairment related to systemic corticosteroid use may be offset by the risk associated with BPD. A systematic review suggested that systemic corticosteroid therapy, when directed to infants with a ≥65% risk of developing BPD, may actually reduce the risk of neurodevelopmental impairment and CP. Although predictive models that use clinical characteristics have been described with promising accuracy, randomized trials using them to guide corticosteroid therapy have not been performed.

Inhaled corticosteroids administered to VLBW infants requiring mechanical ventilation at 7-14 days of age did not prevent BPD significantly. However, early, prolonged administration to mechanically ventilated extremely preterm infants until they no longer require oxygen or positive pressure support has been shown to reduce the risk of BPD, but with a concerning trend toward increased mortality. Experience with local delivery of corticosteroids by spiking surfactant with budesonide is emerging, and early data suggest that endotracheal administration of corticosteroids may reduce pulmonary inflammation and the risk of BPD and death. However, additional evidence is needed before widespread use is implemented. The routine use of antibiotics, inhaled bronchodilators, or diuretics has not been shown to *prevent* BPD.

TREATMENT

Treatment of evolving and established BPD is supportive. The basic tenets of therapy should include appropriate support of ventilation and aggressive nutritional support to optimize linear growth and encourage normal lung repair and development. Available evidence suggests short-term benefits (improved pulmonary mechanics, modest reductions in respiratory support parameters) without an indication of impact on clinically relevant outcomes (survival, need for long-term respiratory support, recurrent hospitalization). Currently, available evidence does not support the routine use of any pharmacologic agents in infants with evolving or established BPD. Treatment decisions must weigh the perceived benefit against the potential harm.

Diuretics and Fluid Restriction

Infants with BPD often have excessive pulmonary interstitial fluid that compromises lung function and increases work of breathing. Diuretic therapy (usually with furosemide or chlorothiazide) has been associated with short-term, temporary improvements in pulmonary compliance and the ability to wean respiratory support. Furosemide (1 mg/kg/dose IV or 2 mg/kg/dose orally [PO] every 12-24 hours) has been demonstrated to decrease pulmonary interstitial edema and pulmonary vascular resistance (PVR), improve pulmonary function, and facilitate weaning from mechanical ventilation and oxygen. Adverse effects of long-term furosemide therapy are common and include hyponatremia, hypokalemia, alkalosis, azotemia, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Sodium and potassium chloride supplementation is often necessary. Thiazide diuretics (e.g., chlorothiazide, 5-10 mg/kg/dose every 12 hours) have been used as an alternative to avoid hypercalciuria, limit nephrocalcinosis, and preserve bone development. Although avoidance of excessive fluid administration in the first few weeks of age is associated with a reduced risk of BPD, there is no evidence that fluid restriction (130-140 mL/kg/day) in established BPD has any impact. Whether using diuretics or fluid restriction, careful attention to maintaining appropriate electrolyte levels as well as providing adequate caloric intake (often >120-130 kcal/kg/day) is paramount to avoid negatively impacting nutrition.

Bronchodilators

Inhaled bronchodilators improve lung mechanics by decreasing airway resistance. **Albuterol** is a specific β_2-agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation but can exacerbate bronchomalacia. Changes in pulmonary mechanics may last 4-6 hours. Hypertension and tachycardia are adverse effects. Ipratropium bromide is a muscarinic antagonist related to atropine, but the bronchodilator effect is more potent. Use of ipratropium bromide in BPD has been associated with improved pulmonary mechanics. Compared with either agent used alone, combined use of albuterol and ipratropium bromide may be more effective. Few adverse effects have been noted. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD, especially if they are ventilator dependent, is unclear.

Corticosteroids

Systemic corticosteroids have been used to treat evolving and established BPD. In mechanically ventilated infants, systemic corticosteroids improve pulmonary mechanics, allow weaning of ventilator support and supplemental O_2, and facilitate extubation. When given at >7 days of age, long-term benefits include a reduced need for O_2 at 36 weeks PMA, improved survival, and decreased need for home O_2. Short-term adverse effects include hyperglycemia, hypertension, and transient hypertrophic obstructive cardiomyopathy. Long-term adverse effects include osteopenia, severe retinopathy of

prematurity (ROP), abnormal neurologic examination, poor brain growth, neurodevelopmental impairment, and CP. A strategy that utilizes a low cumulative dose (0.89 mg/kg of dexamethasone given over 10-day taper) in preterm infants who remain ventilator dependent after 7 days of age (and therefore have a high risk of developing BPD) facilitates weaning of ventilator and oxygen support and promotes successful extubation without an impact on long-term outcomes, including the incidence of BPD or neurodevelopmental impairment. The controversy concerning the appropriate use of systemic corticosteroids to prevent and/or treat BPD is ongoing, and until additional evidence is available, their use remains limited to infants with severe respiratory failure (ventilator dependent at >7-14 days of age with significant respiratory and oxygen support needs) at high risk for imminent death.

Inhaled corticosteroids (budesonide, fluticasone, and beclomethasone) have been described as an alternative therapy in evolving or established BPD. Small randomized controlled trials (RCTs) and case reports in infants with established moderate to severe BPD have not shown a significant benefit for pulmonary mechanics or reduction in the need for ventilator or oxygen support. Inhaled fluticasone propionate (corticosteroid) combined with salmeterol (long-acting β_2-agonist) may be beneficial.

Pulmonary Vasodilators

Many infants with evolving or established moderate and severe BPD demonstrate increased PVR caused by pulmonary microvascular maldevelopment and abnormal vasoreactivity. In infants *with* BPD with pulmonary hypertension, acute exposure to even modest levels of hypoxemia can cause PAP to increase abruptly. Maintaining infants with established BPD and pulmonary hypertension at higher So_2 targets (92–96%) can lower PAP effectively. For infants in whom appropriate O_2 supplementation and support of ventilation are ineffective, the use of low-dose inhaled nitric oxide (iNO) may improve oxygenation anecdotally. Despite its frequent use, there is no evidence to support the use of iNO to improve lung function, cardiac function, or oxygenation in evolving BPD. Several case series have reported on the use of the phosphodiesterase-5 inhibitor sildenafil in treating pulmonary hypertension in established moderate to severe BPD. Despite its widespread use, no RCTs are evaluating the safety and efficacy of sildenafil in preterm infants with BPD. However, many experts would recommend a trial of low-dose sildenafil (1 mg/kg/dose every 8 hours) for infants with evidence of pulmonary hypertension and persistent respiratory instability despite appropriate oxygen and ventilator support.

Chronic Respiratory Support

Experience suggests that maintaining functional residual capacity (FRC) with appropriate positive pressure support (with noninvasive support whenever possible) promotes optimal lung growth and development. Provision of nCPAP until respiratory status improves and oxygen dependence resolves, with subsequent transition directly to room air, may be beneficial. Continuation of caffeine therapy may facilitate spontaneous breathing and weaning from support. Established severe BPD with cystic, heterogeneous lung disease often requires prolonged mechanical ventilation. A long inspiratory time is required to adequately ventilate diseased lung units, and appropriate expiratory time is required to allow exhalation. The use of a low rate (<20-30 breaths/min), long inspiratory time (≥0.6 seconds) strategy is usually required. To attain appropriate minute ventilation, larger tidal volumes (10-15 mL/kg) may be necessary. Higher PEEP (often >6-8 cm H_2O) may be needed to attain adequate expansion and minimize gas-trapping caused by dynamic airway collapse. Gradual weaning of ventilator settings should be attempted as the infant grows and lung disease improves, but the incidence of death or tracheostomy placement for chronic ventilation may be as high as 20%. By 2-3 years of age, the majority of infants who undergo tracheostomy for severe BPD are successfully liberated from mechanical ventilation.

PROGNOSIS

Compared with extremely preterm infants without BPD, infants with BPD have higher rates of neurodevelopmental impairment, lung diffusion impairment, wheezing and airflow obstruction, rehospitalization, and mortality. The risk of these complications increases with BPD severity. Infants with grade III BPD are most likely to either die or have long-term respiratory morbidity. Prolonged mechanical ventilation, intraventricular hemorrhage (IVH), pulmonary hypertension, cor pulmonale, and oxygen dependence beyond 1 year of life are poor prognostic signs. Mortality in infants with BPD ranges from 10–25% and is highest in infants who remain ventilator dependent for >6 months. Cardiorespiratory failure associated with cor pulmonale and acquired infection (respiratory syncytial virus [RSV]) are common causes of death. Infants are at risk for severe RSV infections and must receive prophylactic therapy (see Chapter 307).

Pulmonary function slowly improves in most survivors because of ongoing lung repair and the natural period of lung growth and alveolarization. *Rehospitalization* for impaired pulmonary function is most common during the first 3 years of life and is much more common in infants requiring respiratory support at discharge. The incidence of physician-diagnosed asthma, use of bronchodilators, and wheezing is elevated. Despite a gradual decrease in symptom frequency, persistence of respiratory symptoms and abnormal pulmonary function test results are measurable in children, adolescence, and young adults. Although not always clinically apparent, pulmonary function testing consistently reveals impaired exercise capacity, reduced pulmonary diffusing capacity, and persistent expiratory flow obstruction. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality. The ultimate long-term pulmonary health of survivors of BPD is unknown. As trajectories of developing lung function remain abnormal in survivors of BPD, concerns have been raised highlighting the potential for pulmonary emphysema, chronic obstructive pulmonary disease, and pulmonary vascular disease resulting in early debilitating lung dysfunction.

Other complications of BPD include growth failure, neurodevelopmental impairment, and parental stress, as well as sequelae of therapy, such as nephrolithiasis, osteopenia, and electrolyte imbalance. Airway problems such as vocal cord paralysis, subglottic stenosis, and tracheomalacia are common and may aggravate or cause pulmonary hypertension. Subglottic stenosis may require tracheotomy or an anterior cricoid split procedure to relieve upper airway obstruction. Cardiac complications of BPD include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and development of aortopulmonary collateral vessels, which, if large, may cause heart failure.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 128

Transient Tachypnea of the Newborn

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

INCIDENCE

Transient tachypnea of the newborn (TTN) is a clinical syndrome of self-limited tachypnea associated with delayed clearance of fetal lung fluid. Although the actual incidence is likely underreported, it is estimated at 3-6 per 1,000 term infant births, making TTN the most common etiology of tachypnea in the newborn. Twin gestation, maternal asthma, maternal hypertension, late prematurity, precipitous delivery, perinatal depression, gestational diabetes, macrosomia, and cesarean delivery, particularly without labor, are common risk factors.

ETIOLOGY AND PATHOPHYSIOLOGY

TTN is believed to result from ineffective clearance of fetal lung fluid. Retained fetal lung fluid decreases pulmonary compliance and impedes gas exchange. Clearance of fetal lung fluid occurs through increased expression of epithelial sodium channels (ENaCs) and sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) that drive active sodium (and thereby fluid) reabsorption. There is evidence that the channels involved in fluid clearance differ for infants with TTN. Additional lung fluid is cleared via compressive forces at the time of delivery and hydrostatic forces with the infant's first breaths (see Chapter 124.1). Decreased respiratory effort can delay fluid clearance and increase the risk for TTN.

CLINICAL MANIFESTATIONS

TTN is characterized by the early onset of tachypnea (>60 breaths/min), sometimes with retractions or expiratory grunting and occasionally with cyanosis that is relieved by minimal O_2 supplementation (<40%). The chest generally sounds clear without crackles or wheeze, and the chest radiograph shows prominent perihilar pulmonary vascular markings, fluid in the intralobar fissures, and rarely small pleural effusions (Fig. 128.1). Hypercapnia and acidosis are uncommon. Respiratory failure requiring positive pressure support (either with nasal continuous positive airway pressure [nCPAP] or mechanical ventilation) also is uncommon, but when it occurs usually resolves rapidly (<12-24 hours). Most infants recover with supportive care alone, and over the first 24-72 hours the tachypnea and O_2 requirements slowly resolve.

DIAGNOSIS

Distinguishing TTN from respiratory distress syndrome (RDS) and other respiratory disorders (e.g., pneumonia) may be difficult, and transient tachypnea is frequently a diagnosis of exclusion. The distinctive features of TTN are rapid recovery of the infant and the absence of radiographic findings for RDS (low lung volumes, diffuse reticulogranular pattern, air bronchograms) and other lung disorders. Other respiratory disorders to consider include meconium aspiration syndrome (see Chapter 129), persistent pulmonary hypertension of the newborn (see Chapter 130), congenital lung anomalies, and spontaneous air leak (see Chapter 132). **Primary ciliary dyskinesia (PCD)** often presents in the newborn period and may resemble TTN or RDS. PCD in the newborn often lasts longer than TTN and requires a longer duration of oxygen therapy (Chapter 455).

PREVENTION

Prevention of TTN generally focuses on avoidance of modifiable risk factors. As prematurity increases the risk of TTN, the American College of Obstetrics and Gynecology recommends against nonmedically indicated deliveries, either vaginal or cesarean, before 39 weeks. They further state that documentation of fetal lung maturity, previously accomplished via amniocentesis with amniotic fluid testing, should not be used to guide early delivery as this does not ensure appropriate maturation of physiologic processes. When late-preterm delivery is medically indicated or threatened, the use of a single course of antenatal steroids is associated with a decreased risk of TTN and may be considered. Use of antenatal steroids at increasing gestational ages must be balanced against an increased risk of hypoglycemia in the neonate postpartum.

TREATMENT

Treatment for TTN is supportive. Based on the degree of symptoms and progression of those symptoms over the first 2 hours after birth, transfer to a facility with appropriate neonatal intensive care unit (NICU) care may be required. Supplemental oxygen should be provided to maintain saturations over 90%. nCPAP can be used to support infants with more significant work of breathing or oxygen requirements. Further evaluation with chest radiograph or blood gas analysis can be undertaken when distress is more significant, or the diagnosis is in question. Infants with significant tachypnea may be unable or unsafe to feed orally and can be supported with intravenous fluids or nasogastric feedings. Generally, TTN is unrelated to an underlying infection; however, antibiotic coverage may be initiated in patients with additional risk factors. Further evaluation for an alternate diagnosis should be undertaken if symptoms are not resolving by 72 hours of age.

Inhaled β_2-agonists such as albuterol (salbutamol) increase expression and activation of ENaC and Na^+,K^+-ATPase and facilitate fluid clearance. Emerging evidence suggests that when given early in the course of TTN, albuterol may improve oxygenation, shorten the duration of supplemental O_2 therapy, and expedite recovery; however, more data are needed before employing this method.

PROGNOSIS

Infants with a history of TTN do have an increased risk of developing a wheezing diagnosis during childhood. This association persists even after stratifying for the underlying risk factor of maternal asthma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

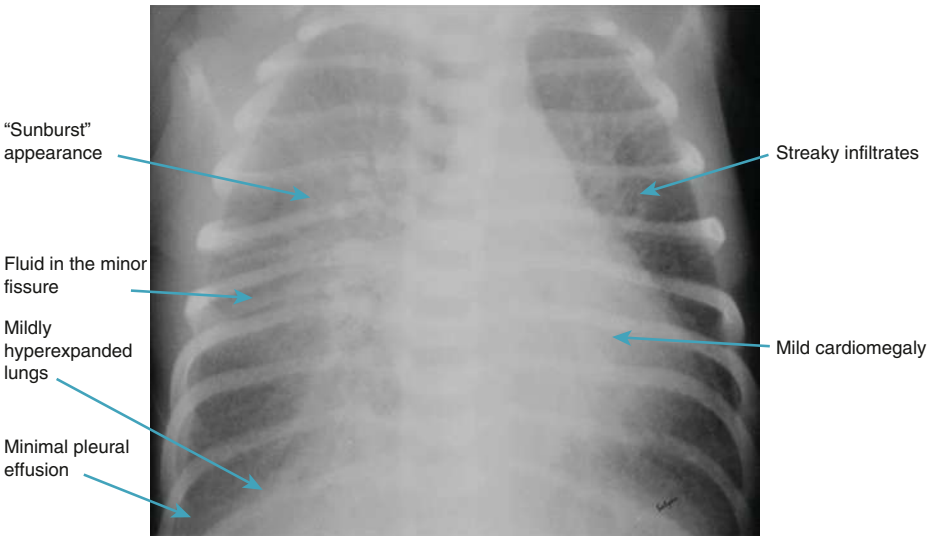

Fig. 128.1 Chest radiograph of an infant with transient tachypnea of the newborn. Notable features include increased pulmonary markings particularly in the perihilar region and fluid in the fissure. This contrasts with the radiograph of an infant with respiratory distress syndrome, which generally includes a homogenous ground glass appearance and hypoinflation. *(From Alhassen Z, Vali P, Guglani L, Lakshminrusimha S, Ryan RM. Recent advances in pathophysiology and management of transient tachypnea of newborn. J Perinatol. 2021;41:6–16. Fig. 5.)*

Chapter 129

Aspiration of Foreign Material (Meconium Aspiration Syndrome, Aspiration Pneumonia)

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Aspiration in the neonate can occur intrapartum often as a result of fetal distress or aspiration may occur postpartum, which can be related to a number of conditions including cardiopulmonary dysfunction, gastroesophageal reflux, aerodigestive tract anomalies, neurodevelopmental impairment, and craniofacial abnormalities.

INTRAPARTUM ASPIRATION

With fetal distress, the fetus often initiates vigorous respiratory movements in utero because of interference with the supply of oxygen through the placenta. Under such circumstances, the infant may aspirate amniotic fluid containing vernix caseosa, epithelial cells, meconium, blood, or material from the birth canal, which may block the smallest airways and interfere with alveolar exchange of O_2 and CO_2. Pathogenic bacteria may accompany the aspirated material, and pneumonia may ensue, but even in noninfected cases, respiratory distress accompanied by radiographic evidence of aspiration is seen (Fig. 129.1). The most relevant consequences of intrapartum aspiration are pneumonia and meconium aspiration syndrome (MAS).

Early-Onset Sepsis and Neonatal Pneumonia

Pneumonia as a presentation of early-onset sepsis typically arises following aspiration of infected amniotic fluid (see Chapter 149). The incidence of early-onset sepsis is 0.5 per 1,000 among term infants and increases to 1 per 1,000 among late preterm infants. The mortality rate is 2–3%. The most common causative agent is group B streptococcus (GBS; 40–45% of cases). Other causative agents include *Escherichia coli* and other gram-negative rods (10–15% of cases), *Enterococcus faecalis*, *Staphylococcus aureus*, and *Listeria monocytogenes*.

Bacteria within the airways causes direct mucosa injury, surfactant dysfunction, pulmonary edema, mechanical airway obstruction due to inflammation and debris, and can trigger vasoconstriction and pulmonary hypertension. Infants are particularly susceptible to infection due to immaturity of their innate and adaptive immune systems, a risk factor that is more pronounced in premature or growth-restricted infants. Additional risk factors for infection include being male, known maternal colonization with GBS, maternal fever, and prolonged rupture of membranes (>18 hours).

Diagnosis of neonatal pneumonia includes radiographic evidence of infiltrate, and consolidation, and less often cavitation or pneumatocele. Infants will display hypoxic and hypercarbic respiratory failure with frequent need for invasive ventilation; hypotension is common. Temperature instability, particularly hypothermia, is also common. White blood cell counts and single values of inflammatory markers have limited predictive potential. Blood cultures are indicated, and cerebrospinal fluid should be obtained if the blood culture is positive.

Treatment of neonatal pneumonia includes the prompt initiation of empiric broad-spectrum antibiotics. Commonly, ampicillin and an aminoglycoside (gentamicin) are used as first-line therapy with the substitution of a cephalosporin or meropenem in place of the aminoglycoside when meningitis is a concern or in cases of suspected antibiotic resistance. Therapy is typically 7-14 days in duration and should be completed parenterally.

Prevention of early-onset sepsis has largely involved the targeted intrapartum antibiotic prophylaxis of mothers known to be colonized with GBS. GBS prophylaxis, generally penicillin, is indicated for women who screen positive for colonization via vaginal-rectal culture at 36-37 weeks' gestation, have a history of an infant affected by GBS disease, or for preterm labor when GBS status is unknown. Additional broad-spectrum antibiotic therapy is indicated for women with intrapartum fever to decrease risk of ascending infection.

For more information on early-onset sepsis see Chapter 149.

Meconium Aspiration Syndrome

Meconium-stained amniotic fluid is found in 10–15% of births and usually occurs in term or postterm infants. MAS develops in 5% of such infants; 30% require mechanical ventilation, and 3–5% die. Usually, but



Fig. 129.1 Anteroposterior chest radiograph of a term infant with meconium aspiration syndrome shows the typical pattern of mixed atelectasis and local emphysema. An endotracheal tube is seen in good position. Two chest tubes are present in the right chest without persistent pneumothorax. *(From Rodriguez NE. Assessment of the neonatal and pediatric patient. In Heuer AJ, ed. Wilkins' Clinical Assessment in Respiratory Care, 9th ed. Philadelphia: Elsevier; 2022: Fig. 12.17)*

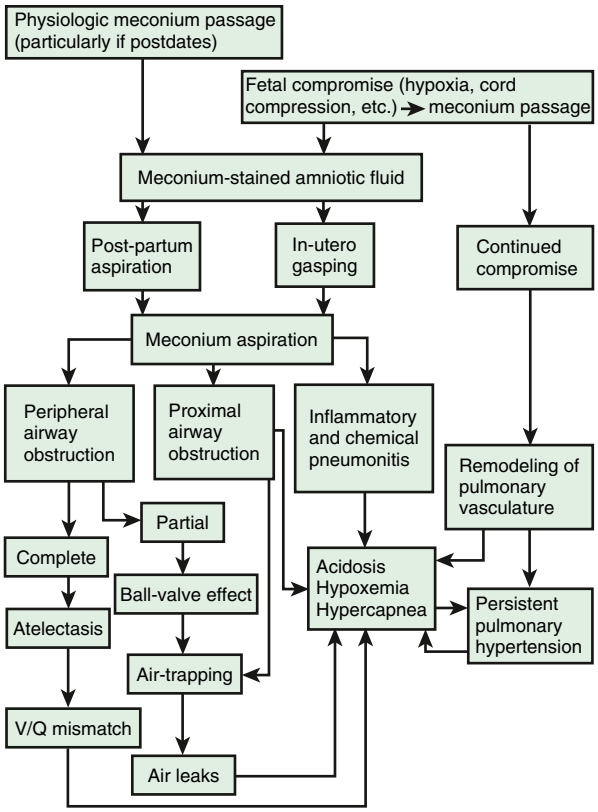

Fig. 129.2 Pathophysiology of meconium passage and the meconium aspiration syndrome. V/Q, ventilation-perfusion ratio. *(From Wiswell TE, Bent RC. Meconium staining and the meconium aspiration syndrome: unresolved issues. Pediatr Clin North Am. 1993;40:955–981.)*

not invariably, fetal distress and hypoxia occur before the passage of meconium into amniotic fluid. The infants are meconium stained and may be depressed and require resuscitation at birth. Either in utero or with the first breath, thick, particulate meconium is aspirated into the lungs. Partial obstruction of some airways may lead to pneumomediastinum, pneumothorax, or both. Overdistention of the chest may be prominent. Meconium within the lungs causes a chemical pneumonitis leading to surfactant dysfunction and inflammation (Fig. 129.1). The combination of airway obstruction and chemical injury can contribute to the development of persistent pulmonary hypertension of the newborn (PPHN; see Chapter 130). The pathophysiology of MAS is further described in Figure 129.2.

The clinical presentation of MAS is that of respiratory distress and cyanosis. In cases where in utero hypoxia was present, the presentation of MAS may be compounded by hypoxic ischemic encephalopathy and multiorgan dysfunction (including myocardial injury). The condition usually improves within 72 hours, but when its course requires assisted ventilation, it may be severe, prolonged, and with a risk for mortality. Tachypnea may persist for many days or even several weeks. The typical chest radiograph is characterized by patchy infiltrates, coarse streaking of both lung fields, increased anteroposterior diameter, and flattening of the diaphragm with possible pneumothorax (see Fig. 129.1).

The risk of meconium aspiration may be decreased by rapid identification of fetal distress and initiation of prompt delivery. Intrapartum nasopharyngeal suctioning in infants with meconium-stained amniotic fluid does not reduce the risk for MAS. Routine intubation and aspiration of depressed infants (those with hypotonia, bradycardia, or decreased respiratory effort) born through meconium-stained fluid is not effective in reducing the MAS or other major adverse outcomes and is not recommended for neonatal resuscitation. The risk of meconium-stained amniotic fluids increases with increasing gestational age. Additionally, among those infants with meconium-stained fluids, the risk for MAS increases with increasing gestational age (4.8% at >42 weeks vs 2.6% at 40 weeks) therefore limiting significantly postterm deliveries (>42 weeks) decreases the incidence of MAS.

Treatment of MAS includes supportive care and standard management for respiratory distress. The beneficial effect of mean airway pressure on oxygenation must be weighed against the risk of pneumothorax. Administration of exogenous surfactant and/or inhaled nitric oxide (iNO) to infants with MAS and hypoxemic respiratory failure, or pulmonary hypertension requiring mechanical ventilation, decreases the need for extracorporeal membrane oxygenation (ECMO), which is required by the most severely affected infants who show no response to therapy. In infants with MAS who demonstrate no other signs of sepsis, there is no role for continued antibiotic therapy. Severe meconium aspiration may be complicated by persistent pulmonary hypertension. Patients with MAS refractory to conventional mechanical ventilation may benefit from high-frequency ventilation (HFV) or ECMO (see Chapter 130). Management may also include concurrent treatment for hypoxic injury as discussed in Chapter 120.

The mortality rate of meconium-stained infants is considerably higher than that of nonstained infants. The decline in neonatal deaths caused by MAS is related to improvements in obstetric and neonatal care. Residual lung problems are rare but include symptomatic cough, wheezing, and persistent hyperinflation for up to 5-10 years. The ultimate prognosis depends on the extent of central nervous system injury from asphyxia and the presence of associated problems such as pulmonary hypertension.

POSTPARTUM ASPIRATION

Aspiration in the newborn after birth can be globally divided into categories of anatomic abnormalities and swallowing dysfunction. Regardless of the cause, the consequences of aspiration include pneumonia, chemical pneumonitis, and airway swelling.

Anatomic Causes of Postpartum Aspiration

Abnormalities of the aerodigestive tract can contribute to the passage of oral secretions and milk into the lungs. Obstruction or narrowing of the nasal cavity or nasopharynx can interrupt the normal

suck-swallow-breath cycle of the infant and increase the risk of aspiration. These conditions include genetic disorders associated with midface hypoplasia, choanal atresia, and congenital nasal masses or tumors. Infants with nasal obstruction will present with stertor, cyanosis improved with crying, and an inability to pass a nasal feeding tube. Oral sources of aspiration include micrognathia/retrognathia and oral masses that compromise airway protection. Cleft lip and palate can impair velopharyngeal closure and increase nasal regurgitation of milk with subsequent aspiration. Anatomic causes of aspiration at the level of the larynx include laryngomalacia due to increased work of breathing with poorer airway protective mechanisms, laryngotracheoesophageal clefts, and vocal fold paralysis or paresis where aspiration occurs as the vocal folds are unable to adduct and protect the airway. Tracheoesophageal fistula (TEF) contributes to aspiration via a direct connection between the esophagus and the airway. TEF can be divided into five types based on the location of the fistula and presence of esophageal atresia. Prenatal diagnosis may occur after the recognition of polyhydramnios and a small fetal stomach. Postnatal symptoms include excessive salivation that worsen with feeding attempts, choking, cough, cyanosis, respiratory distress, and an inability to pass an orogastric (OG) tube. TEF should prompt an evaluation for other anomalies.

When an anatomic abnormality is believed to be contributing to aspiration, initial management should include cessation of feeding pending an evaluation. Some conditions including vocal fold paresis and laryngomalacia may resolve spontaneously, and modified feeding strategies, often under the direction of a speech language pathologist, can allow delivery of nutrition until the condition improves with time and growth. Cleft palate can often be managed with feeding modification until surgical repair in infancy. Other conditions including choanal atresia and TEF require surgical intervention in the newborn period. In some cases, tracheostomy is required for infants unable to adequately protect their airway. Although reflux alone is not the cause of aspiration in these cases, decreasing the acidity of the aspirate may decrease airway swelling, and antireflux medications can be considered in select populations.

Swallowing Dysfunction

Swallowing dysfunction is another cause of aspiration in the newborn. Swallowing is a complex process and must be coordinated with respirations. Infants with neurologic injury may display abnormalities in the swallowing reflex or in the recognition and prevention of aspiration. Infants with pulmonary or cardiovascular disease leading to tachypnea will have more trouble coordinating a suck-swallow-breath cycle. Premature infants are more likely to have swallowing dysfunction because of prematurity-related pulmonary insufficiency and because of immaturity of the swallow mechanism, which begins to mature between 32 and 34 weeks. Hypotonic infants due to neuromuscular diseases or as a sequalae of hypoxic-ischemic encephalopathy are at increased risk of aspiration.

Evaluation of the swallow in at-risk infants often occurs with the assistance of a speech language pathologist and may include video fluoroscopic swallow studies to evaluate swallowing pattern and document aspiration. A fiberoptic endoscopic evaluation of the swallow (FEES) is another strategy whereby a speech language pathologist and ear, nose, and throat doctor observe a small-volume swallow via direct endoscopic visualization. Neurologic imaging may be indicated to assess for the underlying etiology of an ineffective or uncoordinated swallow.

Treatment strategies include feeding modifications such as pacing (tilting the bottle down every three to five sucks to allow recovery time), modified feeding position, or using a slower flow nipple. In cases where feeding modification does not adequately improve swallow safety, a percutaneous gastric tube for feeding may be indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 130

Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Persistent pulmonary hypertension of the newborn (PPHN) predominantly occurs in term and postterm infants. Predisposing factors include birth asphyxia, meconium aspiration syndrome (MAS), early-onset sepsis, respiratory distress syndrome (RDS), hypoglycemia, polycythemia, maternal use of nonsteroidal antiinflammatory drugs with in utero constriction of the ductus arteriosus, maternal late trimester use of selective serotonin reuptake inhibitors, and pulmonary hypoplasia caused by diaphragmatic hernia (Table 130.1). PPHN is often idiopathic. Some patients with PPHN have low plasma arginine and nitric oxide (NO) metabolite concentrations and polymorphisms of the carbamoyl phosphate synthase gene, findings suggestive of a possible subtle defect in NO production. The incidence is 1 in 500-1,500 live births, with a wide variation among clinical centers. Regardless of etiology of PPHN, profound hypoxemia from right-to-left shunting and normal or elevated $Paco_2$ are present (Fig. 130.1).

PATHOPHYSIOLOGY

Persistence of the fetal circulatory pattern of right-to-left shunting through the patent ductus arteriosus (PDA) and foramen ovale after birth is a result of excessively high pulmonary vascular resistance (PVR). Fetal PVR is usually elevated relative to fetal systemic or postnatal pulmonary pressure. This fetal state normally permits shunting of oxygenated umbilical venous blood to the left atrium (and brain) through the foramen ovale, from which it bypasses the lungs through the ductus arteriosus and passes to the descending aorta. After birth, PVR normally declines rapidly as a consequence of vasodilation secondary to lung inflation, a rise in postnatal Pao_2, a reduction in $Paco_2$, increased pH, and release of vasoactive substances. Increased neonatal PVR may be (1) **maladaptive** from an acute injury (not demonstrating normal vasodilation in response to increased O_2 and other changes after birth); (2) the result of increased pulmonary artery medial muscle thickness and extension of smooth muscle layers into the usually nonmuscular, more peripheral pulmonary arterioles in response to chronic fetal hypoxia; (3) a consequence of **pulmonary hypoplasia** (diaphragmatic hernia, Potter syndrome); or (4) **obstructive** as a result of polycythemia, total anomalous pulmonary venous return (TAPVR), or congenital diffuse development disorders of acinar lung development.

CLINICAL MANIFESTATIONS

PPHN usually manifests in the delivery room or within the first 12 hours after birth. Idiopathic PPHN or PPHN related to polycythemia, hypoglycemia, hypothermia, or asphyxia may result in severe cyanosis and respiratory distress. In some cases, however, initial signs of respiratory distress may be minimal. Infants who have PPHN associated with meconium aspiration, group B streptococcal pneumonia, diaphragmatic hernia, or pulmonary hypoplasia usually exhibit cyanosis, grunting, flaring, retractions, tachycardia, and shock. Multiorgan involvement may be present. Myocardial ischemia, papillary muscle dysfunction with mitral and tricuspid regurgitation, and biventricular dysfunction produce cardiogenic shock with decreases in pulmonary blood flow, tissue perfusion, and O_2 delivery.

Table 130.1 Etiology of Persistent Pulmonary Hypertension of the Newborn in Neonates

Maladaptation of pulmonary vasculature (abnormal, "reactive" pulmonary vasoconstriction)
- Parenchymal lung diseases, such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), and pneumonia
- In response to systemic disorders, such as hypothermia, sepsis, fetal hypoxia/distress, hypercapnia, acidosis, and hyperviscosity
- Toxic/pharmacologic exposure in utero (maternal selective serotonin reuptake inhibitor (SSRI) use)

Maldevelopment of pulmonary vasculature (remodeling of pulmonary vasculature)
- In utero closure of ductus arteriosus (maternal cyclooxygenase inhibitor use)
- Sustained pulmonary over circulation in congenital heart disease with large left-to-right shunts
- Intrauterine growth restriction
- Genetic/chromosomal anomalies (trisomy 21, alveolar-capillary dysplasia, surfactant protein deficiency)

Underdevelopment of pulmonary vasculature (hypoplastic pulmonary vessels; ↓ cross-sectional area)
- Congenital diaphragmatic hernia
- Pulmonary hypoplasia (premature prolonged rupture of membranes, oligohydramnios and anhydramnios, space-occupying lesions in the chest).

From Sharma M, Callan E, Konduri GG. Pulmonary vasodilator therapy in persistent pulmonary hypertension of the newborn. *Clin Perinatol*. 2022;49:103–105. Box 1.

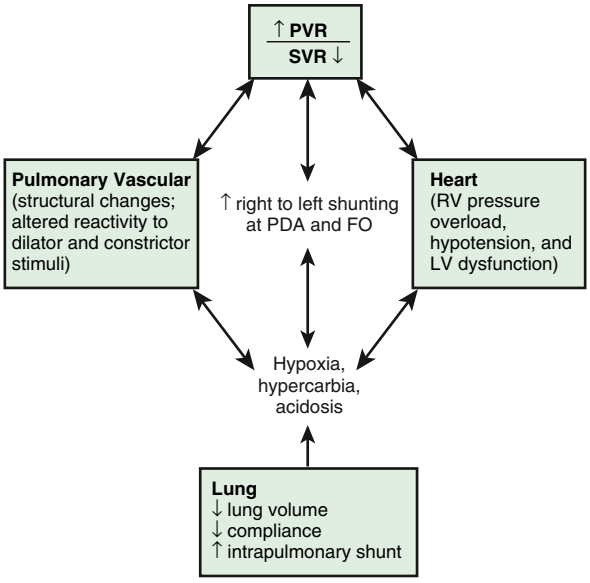

Fig. 130.1 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn (PPHN). FO, Foramen ovale; LV, left ventricle; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance. *(From Kinsella JP, Abman SH. Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. J Pediatr. 1995;126:853–864.)*

Hypoxemia is often labile and out of proportion to the findings on chest radiographs. In PPHN due to asphyxia and idiopathic PPHN, chest x-ray findings are often normal, whereas in PPHN associated with pneumonia and diaphragmatic hernia, parenchymal opacification and bowel/liver in the chest, respectively, are seen.

DIAGNOSIS

Independent of the prenatal history, PPHN should be suspected in all term infants who have cyanosis. Hypoxemia is universal and intermittently unresponsive to 100% O_2 given by oxygen hood or nasal

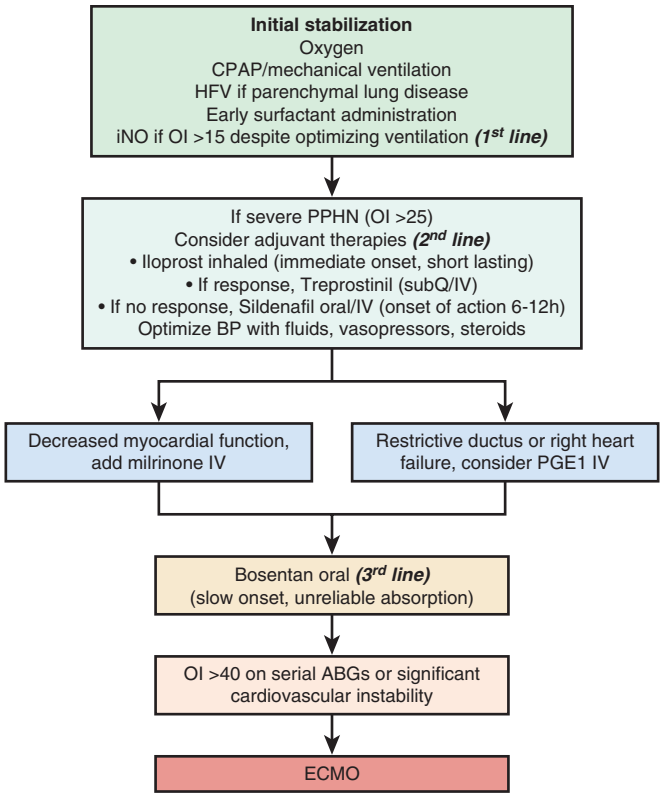

Fig. 130.2 Algorithm for the suggested approach and timing of interventions for the management of hypoxic respiratory failure (HRF)/persistent pulmonary hypertension of the newborn (PPHN). It is important to consider cardiopulmonary system to be one fully integrated unit and optimize lung recruitment, pulmonary vasodilation, and cardiac function to facilitate successful transition. The algorithm focuses on vasodilator agents and is not meant to be inclusive of all therapies used in the management of PPHN. ABG, Arterial blood gas; BP, blood pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HFV, high-frequency ventilation; iNO, inhaled nitric oxide; IV, intravenous; OI, oxygenation index; PGE1, prostaglandin E1; subQ, subcutaneous. *(From Sharma M, Callan E, Konduri GG. Pulmonary vasodilator therapy in persistent pulmonary hypertension of the newborn. Clin Perinatol. 2022;49:103–105, Fig. 3.)*

cannula. A Pao_2 or Sao_2 gradient between a preductal (right radial artery) and a postductal (umbilical artery) site of blood sampling suggests right-to-left shunting through the ductus arteriosus. Intracardiac shunting through the patent foramen ovale does not lead to a Pao_2 or Sao_2 gradient.

Real-time echocardiography combined with Doppler flow imaging is very helpful in evaluating PPHN. Systolic flattening of the interventricular septum as the right ventricular systolic pressure approaches the left ventricular systolic pressure can be used to estimate the degree of pulmonary hypertension. The peak velocity of the tricuspid valve regurgitation jet, when present, yields a quantitative estimate of the right ventricular systolic pressure. Likewise, the direction and velocity of a shunt across the PDA provides a quantitative comparison between the aortic and pulmonary artery pressures. In advanced cases, right-to-left or bidirectional shunting across a PDA and a patent foramen ovale can be observed.

The differential diagnosis of PPHN includes cyanotic heart disease (especially obstructed TAPVR), idiopathic pulmonary vein stenosis, congenital surfactant (protein) deficiency syndromes, pulmonary artery thrombosis, and congenital diffuse development disorders of acinar lung development (acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins).

Alveolocapillary dysplasia (ACD) is a rare, lethal autosomal recessive disorder of distal lung development characterized by immature lobular development and reduced capillary density. Infants with ACD

present with idiopathic PPHN, demonstrating little or no parenchymal lung disease and profound hypoxemia. Over 60% of infants with ACD manifest hypoxemia and respiratory failure within 48 hours of birth, while some with milder disease present beyond 6 months of age. The diagnosis is made on autopsy in 90% of cases, and the constellation of findings include thickened alveolar septa, increased muscularization of the pulmonary arterioles, a reduced number of capillaries, with the remaining capillaries demonstrating abnormal apposition to the air interface, and misalignment of the intrapulmonary veins. In up to 80% of cases, extrapulmonary malformations of the genitourinary, gastrointestinal, or cardiovascular system are present. Pathogenic variants in the transcription factor gene *FOXFI* have been identified in up to 40% of cases, but the diagnosis continues to rest on clinical and histopathologic features. There also may be associated gastrointestinal (malrotation), genitourinary, and cardiac (hypoplastic left heart syndrome) malformations. ACD is uniformly lethal and should be suspected in infants with idiopathic PPHN who fail to respond to maximal medical therapy, or when symptoms recur after successful weaning from extracorporeal membrane oxygenation (ECMO). In a UK ECMO report, up to 14% of infants who failed ECMO ultimately were diagnosed with ACD. Regardless of the timing of presentation, ACD is uniformly fatal, and lung transplantation remains the sole, experimental therapy.

TREATMENT

Therapy for PPHN is directed toward correcting any predisposing condition (e.g., hypoglycemia, polycythemia) and improving poor tissue oxygenation by addressing the underlying pathology (Fig. 130.2). Initial management includes O_2 administration and correction of acidosis, hypotension, and hypercapnia. Persistent hypoxemia should be managed with intubation and mechanical ventilation.

Infants with PPHN are usually managed *without* hyperventilation or alkalization. Gentle ventilation with normocarbia or permissive hypercarbia and avoidance of hypoxemia result in excellent outcomes and a low incidence of chronic lung disease and ECMO use.

Because of their instability and ability to fight the ventilator, newborns with PPHN usually require sedation. Nonpharmacologic measures such as minimal noise, light, and tactile stimulation are also employed. The use of paralytic agents is controversial and reserved for the newborn who cannot be treated with sedatives alone. Muscle relaxants may promote atelectasis of dependent lung regions and ventilation-perfusion mismatch and may be associated with an increased risk of death.

Inotropic therapy is frequently needed to support blood pressure and perfusion. Whereas epinephrine is frequently used as a first-line agent, other agents, such as dobutamine and milrinone, may be helpful when myocardial contractility is poor. Many centers use echo-guided assessment of cardiac function to choose appropriate inotropic therapy. Dopamine is typically avoided due to its ability to increase PVR. Some of the sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamines by overwhelming illness and relative adrenal insufficiency. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency.

Inhaled nitric oxide (iNO) is an endothelium-derived signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by inhalation. *Use of iNO reduces the need for ECMO support by approximately 40%.* The optimal starting dose is 20 ppm. Higher doses have not been shown to be more effective and are associated with side effects, including methemoglobinemia and increased levels of nitrogen dioxide, a pulmonary irritant. Most newborns require iNO for <5 days. Although iNO has been used as long-term therapy in children and adults with primary pulmonary hypertension, prolonged dependency is rare in neonates and suggests the presence of lung hypoplasia, congenital heart disease, or ACD. The maximal safe duration of iNO therapy is unknown. The infant can be weaned to 5 ppm after 6-24 hours of therapy. The dose can then be reduced slowly and discontinued when F_{IO_2} is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided because it may cause rebound pulmonary hypertension. iNO should be used only at institutions that offer ECMO support or have the capability of transporting an infant on iNO therapy if a referral for ECMO is necessary. Some infants with PPHN do not respond adequately to iNO. Therapy with continuous inhaled or intravenous (IV) prostacyclin (prostaglandin I_2) can improve oxygenation in infants with PPHN. The safety and efficacy of sildenafil (type 5 phosphodiesterase inhibitor) in newborns with PPHN is under investigation; initial results are promising.

In 5–10% of patients with PPHN, the response to 100% O_2, mechanical ventilation, and drugs is poor, and many of these infants benefit from ECMO. In such patients, two parameters have been used to predict mortality: the alveolar-arterial oxygen gradient ($P_A\text{-}aO_2$), and the oxygenation index (OI), calculated as F_{IO_2} (as %) × MAP/P_{aO_2}. A $P_A\text{-}aO_2$ >600 for 8-12 hours and an OI >40 unresponsive to iNO predict a high mortality rate (>80%) and are indications for ECMO. In carefully selected, severely ill infants with hypoxemic respiratory failure caused by RDS, meconium aspiration pneumonia, congenital diaphragmatic hernia, PPHN, or sepsis, ECMO significantly improves survival.

ECMO is a form of cardiopulmonary bypass that augments systemic perfusion and provides gas exchange. Most experience has been with *venoarterial bypass,* which requires carotid artery ligation and the placement of large catheters in the right internal jugular vein and carotid artery. *Venovenous bypass* avoids carotid artery ligation and provides gas exchange, but it does not support cardiac output. Blood is initially pumped through the ECMO circuit at a rate that approximates 80% of the estimated cardiac output (150-200 mL/kg/min). Venous return passes through a membrane oxygenator, is rewarmed, and returns to the aortic arch in venoarterial ECMO and to the right atrium in venovenous ECMO. Venous O_2 saturation values are used to monitor tissue O_2 delivery and subsequent extraction for infants undergoing venoarterial ECMO, whereas arterial O_2 saturation values are used to monitor oxygenation for infants receiving venovenous ECMO.

Because ECMO requires complete heparinization to prevent clotting in the circuit, its use is generally avoided in patients with existing intracranial hemorrhage or who are at high risk of developing intraventricular hemorrhage (weight <2 kg, gestational age <34 weeks). In addition, infants being considered for ECMO should have reversible lung disease, no signs of systemic bleeding, and no severe asphyxia or lethal malformations, and they should have been ventilated for <10 days. Complications of ECMO include thromboembolism, air embolization, bleeding, stroke, seizures, atelectasis, cholestatic jaundice, thrombocytopenia, neutropenia, hemolysis, infectious complications of blood transfusions, edema formation, and systemic hypertension.

PROGNOSIS

Survival in patients with PPHN varies with the underlying diagnosis but is generally ~90%. Long-term, survivors of PPHN are at risk for neurodevelopmental impairment and sensorineural deafness, which can occur in about 25% of patients. The outcome for infants with PPHN who are treated with ECMO is also favorable; >80–90% survive, and 60–75% of survivors appear normal at 1-3.5 years of age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 131

Diaphragmatic Hernia

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax (Fig. 131.1). The etiology is rarely traumatic and usually congenital. The symptoms and prognosis depend on the location of the defect and associated anomalies. The defect may be at the esophageal hiatus **(hiatal hernia)**; paraesophageal, adjacent to the hiatus (**paraesophageal hernia**; see Chapter 131.2); retrosternal (**foramen of Morgagni hernia**; see Chapter 131.1); or at the posterolateral portion of the diaphragm **(Bochdalek hernia)**. In **congenital diaphragmatic hernia (CDH),** the Bochdalek hernia accounts for up to 90% of the hernias seen, with 80–90% occurring on the left side. The Morgagni hernia accounts for 2–6% of CDH. The size of the defect is highly variable, ranging from a small hole to complete agenesis of this area of the diaphragm. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity.

CONGENITAL DIAPHRAGMATIC HERNIA (BOCHDALEK)

Pathology and Etiology

Although CDH is characterized by a structural diaphragmatic defect, a major limiting factor for survival is the association with other anomalies, syndromes, and primarily with pulmonary hypoplasia. Lung hypoplasia was initially thought to be solely caused by the compression of the lung from the herniated abdominal contents, which impaired lung growth. However, evidence indicates that pulmonary hypoplasia, at least in some cases, may precede the development of the diaphragmatic defect.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles, and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal saccules, thickened alveoli, and thickened pulmonary arterioles. Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli, and decreased levels of phosphatidylcholine, total DNA, and total lung protein, all of which contribute to limited gas exchange.

Epidemiology

The incidence of CDH is between 1 in 2,000 and 1 in 3,000 live births, with males affected more often than females. Defects are more common on the left (85%) and are occasionally bilateral (<5%). Pulmonary hypoplasia and malrotation of the intestine are part of the lesion, not associated anomalies. Most cases of CDH are nonsyndromic (sporadic; 60%), but familial and syndromic cases have been reported. Associated anomalies in nonsyndromic patients have been reported in up to 30% of cases, including hypoplastic left heart syndrome and accessory spleens. CDH is recognized as part of several aneuploidy syndromes: trisomies 21, 13, and 18 and those with copy number variation: del 15q26.1-q26.2, del 8p23.1, del 1q41-q42, and del 4p16.3 as well as definable single gene syndromes including Cornelia de Lange, Donnai-Barrow, Cutis Laxa, cardiac-urogenital, and Matthew-Wood syndromes.

Diagnosis and Clinical Presentation

In >50% of cases, CDH can be diagnosed on prenatal ultrasonography (US) between 16 and 24 weeks of gestation. High-speed fetal MRI can further define the lesion. US findings may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity, and fetal hydrops. Certain imaging features may predict outcome including liver position in the chest, observed-to-expected total lung volume (O/E TLV), and observed-to-expected lung-to-head ratio (O/E LHR). Nonetheless, no definitive characteristic reliably predicts outcome. After delivery, a chest radiograph is needed to confirm the diagnosis (Fig. 131.2). In some infants with an echogenic chest mass, further imaging is required. The differential diagnosis may include other diaphragm disorders, such as eventration or a cystic lung lesion (pulmonary sequestration, cystic adenomatoid malformation).

Arriving at the diagnosis early in pregnancy allows for prenatal counseling, possible fetal interventions (see Chapter 118), and planning for postnatal care. A referral to a center providing high-risk obstetrics, pediatric surgery, and tertiary care neonatology is advised. Careful evaluation for other anomalies should include echocardiography and amniocentesis. To avoid unnecessary pregnancy termination and unrealistic expectations, an experienced multidisciplinary group must carefully counsel the parents of a child diagnosed with a diaphragmatic hernia.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth, or there may be a period of up to 48 hours during which the baby is relatively stable. Respiratory distress

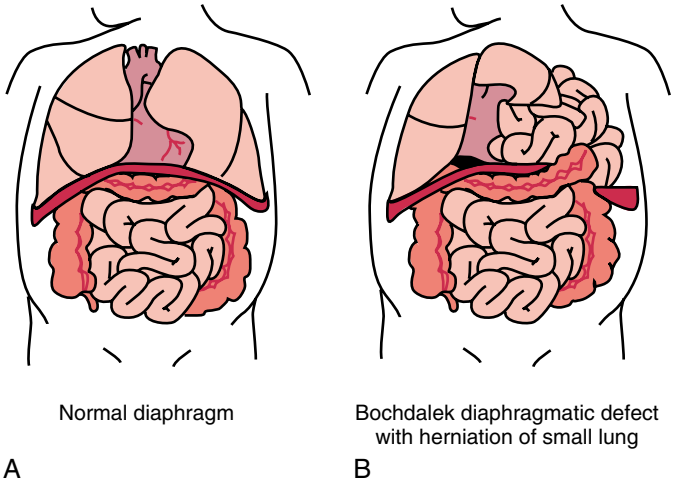

Fig. 131.1 A, Normal diaphragm separating the abdominal and thoracic cavity. B, Diaphragmatic hernia with a small lung and abdominal contents in the thoracic cavity.

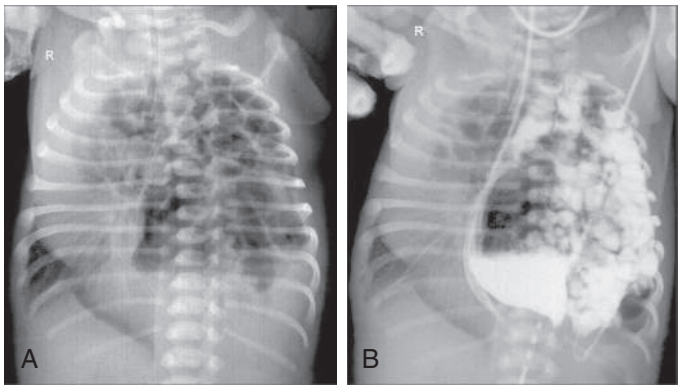

Fig. 131.2 Bochdalek hernia. A, Chest radiograph showing herniated bowel loops in the left hemithorax, displacement of the mediastinum to the contralateral side, severely reduced lung space, and unclear lung fields bilaterally. B, Upper gastrointestinal tract radiograph showing the stomach and bowel loops stained with contrast in the left hemithorax. *(From Hu X, Liu B. Bochdalek hernia. Lancet. 2018;392:60.)*

is characterized clinically by tachypnea, grunting, use of accessory muscles, and cyanosis. Children with CDH may also have a scaphoid abdomen and increased chest wall diameter. Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest radiograph and passage of a gastric tube are usually sufficient to confirm the diagnosis.

A small group of infants with CDH present beyond the neonatal period. Patients with a delayed presentation may experience vomiting as a result of intestinal obstruction or mild respiratory symptoms. Occasionally, incarceration of the intestine proceeds to ischemia with sepsis and shock. Unrecognized diaphragmatic hernia is a rare cause of sudden death in infants and toddlers. Group B streptococcal sepsis has been associated with delayed onset of symptoms and a CDH (often right side).

Treatment

Initial Management

Delivery at a tertiary center with experience in the management of CDH is required to provide early, appropriate respiratory support. In the delivery room, infants with respiratory distress should be rapidly stabilized with endotracheal intubation. *Prolonged mask ventilation in the delivery room, which enlarges the stomach and small bowel and thus makes oxygenation more difficult, must be avoided and a nasogastric or orogastric tube placed immediately for decompression.* Once in the neonatal intensive care unit (NICU), central arterial and venous (umbilical) lines are placed, pre- and postductal saturations monitored, and gastric contents intermittently decompressed to prevent enlargement. A preductal arterial oxygen saturation (Spo_2) value ≥85% should be the minimum goal. An initial arterial Pco_2 >80 mm Hg is predictive of mortality in infants with CDH. Volutrauma is a significant problem. *Gentle ventilation with permissive hypercapnia* reduces lung injury, need for extracorporeal membrane oxygen (ECMO), and mortality. Factors that contribute to persistent pulmonary hypertension of the newborn (PPHN; hypoxia, acidosis, hypothermia) should be avoided (see Chapter 130). Echocardiography is important to guide therapeutic decisions by measuring pulmonary and system vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Neonates with CDH may be surfactant deficient. Although surfactant is frequently used, no study has proved that it is beneficial in treatment of CDH, and it may precipitate decompensation. In infants with severe respiratory failure and hypoxemia, sedation and paralysis may be required.

Ventilation Strategies

Conventional mechanical ventilation, high-frequency oscillatory ventilation (HFOV), and ECMO are the three main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and CO_2 elimination without inducing volutrauma. Conventional ventilation using a gentle, lung protective strategy (peak inspiratory pressure [PIP] <25, positive end-expiratory pressure [PEEP] 3-5 cm H_2O) that allows for permissive hypercapnia ($Paco_2$ <65 mm Hg) is recommended. Permissive hypercapnia (as opposed to hyperventilation with high PIP) has reduced lung injury and improved survival. HFOV as a rescue therapy is indicated if a PIP >25 is required to maintain appropriate ventilation or if hypoxemia persists.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator. Its use reduces ductal shunting and pulmonary pressures and results in improved oxygenation. Although iNO has been helpful in PPHN, randomized trials have not demonstrated improved survival or reduced need for ECMO when iNO is used in newborns with CDH. Nonetheless, iNO is used in patients with CDH as a bridge to ECMO.

Extracorporeal Membrane Oxygenation

The availability of ECMO and the utility of preoperative stabilization has improved survival of babies with CDH. ECMO is the therapeutic option for children in whom conventional ventilation or HFOV fails. ECMO is most often used before repair of the defect. Several objective criteria for ECMO have been developed. Birthweight and the 5-minute Apgar score may be the best predictors of outcome in patients treated with ECMO. There is no strict lower weight limit for ECMO, but generally, vessels in infants <1,800 g are too small to cannulate.

The duration of ECMO for neonates with diaphragmatic hernia is longer (than for those with isolated PPHN or meconium aspiration and may last up to 2-4 weeks). Timing of repair of the diaphragm while the infant receives ECMO is controversial; some experts prefer early repair to allow a greater duration of ECMO after the repair, whereas many defer repair until the infant has demonstrated the ability to tolerate weaning from ECMO. The recurrence of pulmonary hypertension is associated with high mortality and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, redirection of care toward comfort is usually offered to families.

Prenatal Markers of Severity and Fetal Treatment

The most studied prenatal predictor of outcome in children with CDH studied is fetal US. A prospective study of US at 24-26 weeks compared fetal LHR with mortality. There were no survivors with LHR <1, but all babies with LHR >1.4 survived. A second important consideration is the presence of liver in the thoracic cavity, which is a poor prognostic feature. Because LHR measurements increase with gestation, an O/E LHR is considered a more reliable predictor of severity irrespective of GA. O/E LHR of ≥45% is considered a good prognostic sign, whereas <25% is considered a poor prognostic sign. Fetal MRI is used at many fetal centers at 28-32 weeks for prognostication. The advantages of fetal MRI are that they are operator independent, allow measurement of both lungs, and allow better tissue contrast and better images. Normal reference values for fetal lung volumes on MRI have been published and TLV can be compared with the referent fetus. O/E TLV ≥45% is a good prognostic sign, whereas <25% is considered a poor prognostic sign.

Based on the observation that hydrostatic pressure exerted by fetal lung fluid plays a critical role in lung growth and maturity, a promising fetal therapy is in utero tracheal occlusion **(fetoscopic endoluminal tracheal occlusion [FETO])**. FETO therapy at 27–29 weeks' gestation improves survival from 15% to 40% in fetuses with severe left CDH with O/E LHR of <25%; preterm birth is a risk factor. FETO therapy is only offered at a select few centers across the United States (see Chapter 118).

Surgical Repair

Most experts plan surgery at least 48 hours after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low PIP, and Fio_2 <50%. If the newborn is receiving ECMO, an ability to be weaned from this support should be a consideration before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers the cannulas are removed. A subcostal approach is most frequently used (Fig. 131.3). This allows for good visualization of the defect, and if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (Silastic) patch can be placed, commonly known as a silo. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

The defect size and amount of native diaphragm present are variable. Whenever possible, a primary repair using native tissue is performed. If the defect is too large, a porous polytetrafluoroethylene (Gore-Tex) patch is used.

Following surgical repair, the infant must be carefully monitored for worsening pulmonary hypertension. In some patients, a postoperative course of ECMO is needed. Other recognized complications include bleeding, chylothorax, and bowel obstruction. CDH recurrence can occur in about 10% of cases, usually during the first year of life, but can occur up to the first 5 years of life. There is a higher recurrence rate of CDH in children with patches (the patch does not grow as the child grows) than in those with native tissue repairs, those with larger defects, and those with liver in the defect. A loosely fitted patch may reduce the recurrence rates.

Outcome and Long-Term Survival

Overall survival of liveborn infants with CDH is 75%. Relative predictors of a poor prognosis include an associated major anomaly and syndromes,

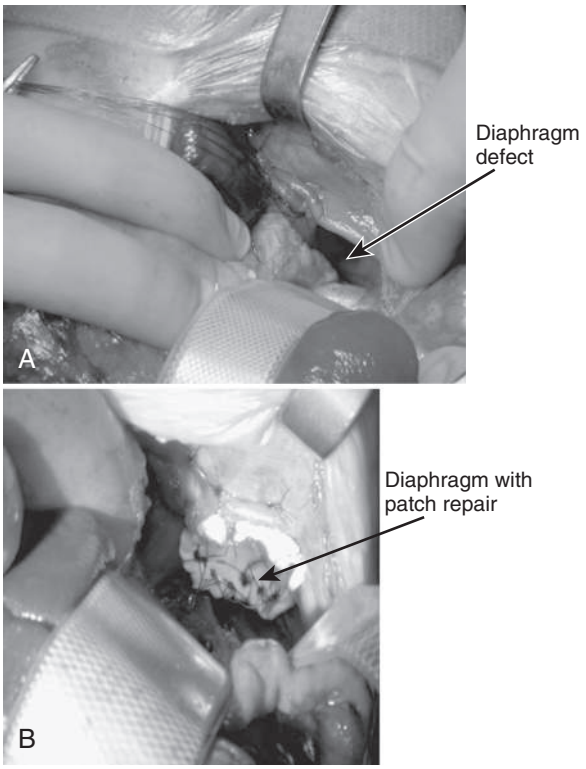

Fig. 131.3 A, Intraoperative photo of congenital diaphragmatic hernia (CDH) before repair. B, Intraoperative photo of patch repair of CDH.

severe pulmonary hypoplasia, herniation to the contralateral lung, and the need for ECMO. The size of the defect appears to be the strongest predictor of morbidity.

Pulmonary problems continue to be a source of morbidity for long-term survivors of CDH. Children receiving CDH repair who were studied at 6-11 years of age demonstrated significant decreases in forced expiratory flow at 50% of vital capacity and decreased peak expiratory flow. Chronic lung disease can occur in about 15% of patients. Both obstructive and restrictive patterns can occur. Those without severe pulmonary hypertension and volutrauma do the best. Those at highest risk include children who required ECMO and patch repair, but the data clearly show that CDH survivors who did not require ECMO also need frequent attention to pulmonary issues. At discharge, up to 20% of infants require oxygen, but only 1–2% require oxygen past 1 year of age.

Gastroesophageal reflux disease (GERD) is reported in >50% of children with CDH. GERD is more common in children whose diaphragmatic defect involves the esophageal hiatus. **Intestinal obstruction** is reported in up to 20% of children and may result from a midgut volvulus, adhesions, or a recurrent hernia that became incarcerated.

Children with CDH typically have delayed growth in the first 2 years of life. Contributing factors include poor intake, GERD, and a caloric requirement that may be higher because of the energy required to breathe. Many children normalize and "catch up" in growth by the time they are 2 years old.

Neurocognitive defects are common and may result from the disease or the interventions. The incidence of neurologic abnormalities is higher in infants who require ECMO (67% vs 24% of those who do not). The abnormalities are similar to those seen in neonates treated with ECMO for other diagnoses and include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in up to 28% of children who underwent ECMO. The majority of neurologic abnormalities are classified as mild to moderate.

Other long-term problems include pectus excavatum and scoliosis. Survivors of CDH repair, particularly those requiring ECMO support, have a variety of long-term abnormalities that appear to improve with time but require close monitoring and multidisciplinary support.

Health-related quality of life (HRQoL) of school-age children born with CDH is overall good and comparable to healthy children, although some children report lower quality of life. The burden of the child's diagnosis on families long-term is also reportedly low. ECMO use is associated with a lower HRQoL in certain domains, as is the need for special education services in school, and chronic respiratory problems.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

131.1 Foramen of Morgagni Hernia

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

Failure of the sternal and crural portions of the diaphragm to meet and fuse produces the foramen of Morgagni hernia. These defects are usually small, with a greater transverse than anteroposterior diameter, and are more often right sided (90%) but may be bilateral. The transverse colon, small intestine, or liver is usually contained in the hernial sac. Most children with these defects are asymptomatic and are diagnosed beyond the neonatal period, often by chest radiograph performed for evaluation of another condition. The anterolateral radiograph shows a structure behind the heart, and a lateral film localizes the mass to the retrosternal area. Chest CT or MRI confirms the diagnosis. When symptoms occur, they can include recurrent respiratory infections, cough, vomiting, or reflux; in rare cases, incarceration may occur. Repair is recommended for all patients, in view of the risk of bowel strangulation, and can be accomplished laparoscopically. Prosthetic material is rarely required.

131.2 Paraesophageal Hernia

Shawn K. Ahlfeld

Paraesophageal hernia is differentiated from the hiatal hernia in that the gastroesophageal junction is in the normal location. The herniation of the stomach alongside or adjacent to the gastroesophageal junction is prone to incarceration with strangulation and perforation. A previous Nissen fundoplication and other diaphragmatic procedures are risk factors. This unusual diaphragmatic hernia should be repaired promptly after identification.

131.3 Eventration

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

Eventration of the diaphragm is an abnormal elevation consisting of a thinned diaphragmatic muscle that causes elevation of the entire hemidiaphragm or more often the anterior aspect of the hemidiaphragm. This elevation produces a paradoxical motion of the affected hemidiaphragm. Most eventrations are asymptomatic and do not require repair. A congenital form is the result of either incomplete development of the muscular portion or central tendon or abnormal development of the phrenic nerves. Congenital eventration may affect lung development, but it has not been associated with pulmonary hypoplasia. The differential diagnosis includes diaphragmatic paralysis, diaphragmatic hernia, traction injury, and iatrogenic injury after heart surgery. Eventration is also associated with pulmonary sequestration, congenital heart disease, spinal muscular atrophy with respiratory distress, and chromosomal trisomies. Most eventrations are asymptomatic and do not require repair. The indications for surgery include continued need for mechanical ventilation, recurrent infections, and failure to thrive. Large or symptomatic eventrations can be repaired by plication through an abdominal or thoracic approach that is minimally invasive.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 132

Pulmonary Air Leaks: Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Pulmonary air leaks represent air breaching the alveolus and entering potential cavities within the chest. *Asymptomatic* pneumothorax, usually unilateral, is estimated to occur in 1–2% of all newborn infants; *symptomatic* pneumothorax and pneumomediastinum are less common. The incidence of pneumothorax is increased in infants with lung diseases such as meconium aspiration and respiratory distress syndrome (RDS); in those who receive assisted ventilation, especially if high-frequency ventilation (HFV) support is necessary; and in infants with pulmonary hypoplasia.

ETIOLOGY AND PATHOPHYSIOLOGY

The most common cause of pneumothorax is overdistention resulting in alveolar rupture. Alveolar overdistention can occur with positive pressure ventilation during neonatal resuscitation, or it may occur in association with the "ball-valve" phenomenon that results from aspiration (classically meconium) and bronchial/bronchiolar obstruction. Although spontaneous rupture of an underlying pulmonary malformation (e.g., lobar emphysema, congenital lung cyst, pneumatocele) occurs, pneumothorax usually occurs in an otherwise normal lung, and no underlying etiology is identified.

Pneumothorax associated with **pulmonary hypoplasia** is common, tends to occur during the first few hours after birth, and is caused by reduced alveolar surface area and poorly compliant lungs. It is associated with disorders of decreased amniotic fluid volume (Potter syndrome, renal agenesis, renal dysplasia, chronic amniotic fluid leak), decreased fetal breathing movement (oligohydramnios, neuromuscular disease, fetal akinesia syndrome), pulmonary space-occupying lesions (diaphragmatic hernia, pleural effusion, chylothorax), and thoracic abnormalities (thoracic dystrophies).

Gas from a ruptured alveolus escapes into the interstitial spaces of the lung, where it tracks along small conducting airways and dissects along the peribronchial and perivascular connective tissue sheaths to the hilum of the lung **(pulmonary interstitial emphysema, PIE)**. If the volume of escaped air is great enough, it may collect in the mediastinal space (pneumomediastinum) or rupture into the pleural space (pneumothorax), subcutaneous tissue **(subcutaneous emphysema)**, and/or pericardial sac **(pneumopericardium)**.

Tension pneumothorax occurs if an accumulation of air within the pleural space is sufficient to elevate intrapleural pressure above atmospheric pressure. Unilateral **tension pneumothorax** results in impaired ventilation not only in the ipsilateral lung but also in the contralateral lung because of a shift in the mediastinum toward the contralateral side. Compression of the vena cava and torsion of the great vessels may interfere with venous return.

CLINICAL MANIFESTATIONS

The physical findings of a clinically asymptomatic pneumothorax are hyperresonance and diminished ipsilateral breath sounds with or without tachypnea. Symptomatic pneumothorax is characterized by respiratory distress, which varies from merely high respiratory rate to severe dyspnea, tachypnea, and cyanosis. Irritability and restlessness or apnea may be the earliest signs. The onset is usually sudden but may be gradual; an infant may rapidly become critically ill. Physical exam findings include chest asymmetry with an increased anteroposterior diameter, hyperresonance, and diminished or absent breath sounds. The heart is displaced toward the contralateral side, resulting in displacement of the cardiac apex and point of maximal impulse. The diaphragm is displaced downward, as is the liver with right-sided pneumothorax, and may result in abdominal distention. Because pneumothorax may be bilateral in approximately 10% of patients, symmetry of findings does not rule it out. In tension pneumothorax, signs of shock are typical.

Pneumomediastinum can occur with or without a pneumothorax and itself is usually asymptomatic. The degree of respiratory distress depends on the amount of trapped gas; if great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last two findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, **subcutaneous emphysema** in newborn infants is almost pathognomonic of pneumomediastinum. Rarely, air may embolize into the circulation (pulmonary air embolism) and cause cutaneous blanching, air in intravascular catheters, an air-filled heart and vessels on chest radiographs, and death.

PIE may precede the development of a pneumothorax or may occur independently and lead to increasing respiratory distress as a result of decreased compliance, hypercapnia, and hypoxemia. Hypoxemia is caused by an increased $P_A\text{-}aO_2$ gradient and intrapulmonary shunting. Progressive enlargement of blebs of gas may result in cystic dilation and respiratory deterioration resembling pneumothorax. In severe cases, PIE precedes the development of bronchopulmonary dysplasia (BPD). Avoidance of high inspiratory or mean airway pressures may prevent the development of PIE.

Pneumopericardium is generally associated with pneumothorax with air moving into the pericardium via areas of weakness in the pericardiac sac or via embryonic connections between the pleura and pericardium. Pneumopericardium may be asymptomatic, requiring only general supportive treatment, but it usually manifests as sudden shock with tachycardia, muffled heart sounds, and poor pulses suggesting tamponade. Air pressure within the pericardium can cause cardiac tamponade.

Preterm infants whose course is complicated by pulmonary air leaks are at increased risk for mortality, BPD (see Chapter 127), severe intracranial hemorrhage, and prolonged NICU stays.

DIAGNOSIS

Pneumothorax and other air leaks should be suspected in newborn infants who show signs of respiratory distress, are restless or irritable, or have a sudden change in condition. The diagnosis of pneumothorax is established by chest radiography, with the edge of the collapsed lung standing out in relief against the pneumothorax (Fig. 132.1). Pneumomediastinum is signified by hyperlucency around the heart border and between the sternum and the heart border and the displacement of the thymus by air, typically referred to as the "spinnaker sail" sign (Fig. 132.2). *Transillumination* of the thorax is often helpful in the emergency diagnosis of pneumothorax; the affected side transmits excessive light. In pneumopericardium, chest radiography demonstrates a halo of air around the cardiac silhouette. PIE appears as small cystic

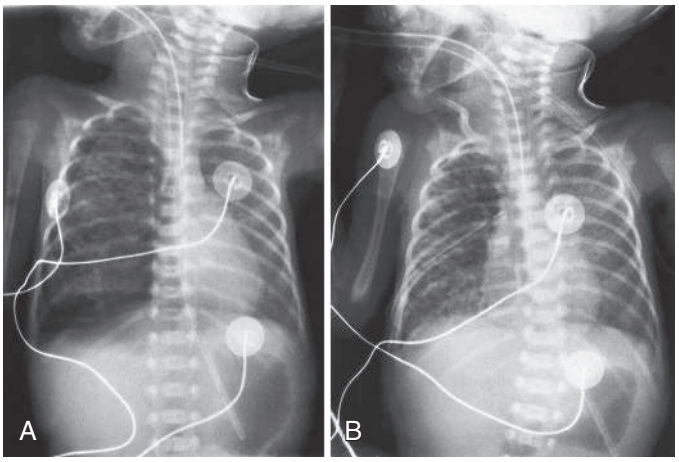

Fig. 132.1 A, Right-sided tension pneumothorax and widespread right lung pulmonary interstitial emphysema (PIE) in a preterm infant receiving intensive care. B, Resolution of pneumothorax with a chest tube in place; PIE persists. *(From Meerstadt PWD, Gyll C. Manual of Neonatal Emergency X-Ray Interpretation. Philadelphia: Saunders; 1994. p. 73.)*

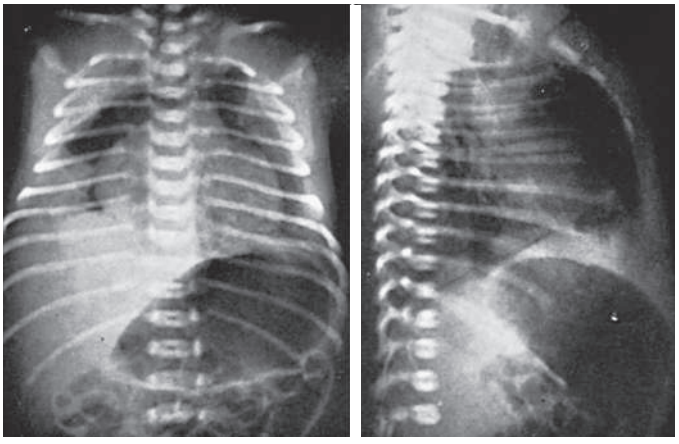

Fig. 132.2 Pneumomediastinum in newborn infant. Anteroposterior view *(left)* demonstrates compression of the lungs, and lateral view *(right)* shows bulging of the sternum, each resulting from distention of the mediastinum by trapped air.

radiolucencies along the interstitium often with hyperexpansion and is typically only seen in premature infants with preexisting lung disease.

PREVENTION

Early recognition of patients at risk for air leak is essential. Infants with oligohydramnios, extreme prematurity, or congenital pulmonary malformations are at increased risk. Surfactant therapy for RDS (see Chapter 126) reduces the incidence of **pneumothorax**. Avoidance of high inspiratory or mean airway pressures may prevent the development of air leaks.

TREATMENT

Without a continued air leak, small asymptomatic and mildly symptomatic pneumothorax, pneumomediastinum, and pneumopericardium require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring ventilatory support. Frequent small feedings may prevent gastric dilation and minimize crying, which can further compromise ventilation and worsen the pneumothorax. Breathing 100% oxygen in term infants may accelerate the resorption of free pleural air into blood by reducing the nitrogen tension in blood and producing a resultant nitrogen pressure gradient from the trapped gas in the blood; however, this is no longer practiced given the risks of oxygen toxicity.

When a pneumothorax is large, expanding, or with severe respiratory or circulatory embarrassment, emergency decompression by needle thoracentesis and/or chest tube placement is indicated. Needle thoracentesis is typically accomplished with the use of an angiocath or a 23-gauge butterfly needle attached to a stopcock and syringe to withdraw air. It can be inserted into the second intercostal space of the anterior chest. After the needle thoracentesis a chest radiograph should be obtained to evaluate and monitor for reaccumulation.

Chest tube placement should be undertaken in cases of recurrent pneumothorax after needle decompression or as a primary intervention in select patients at risk for ongoing air leak (i.e., on high-pressure invasive ventilation). In studies comparing needle decompression with primary chest tube placement there are no differences in mortality; however, approximately 30% of patients receiving a needle thoracentesis eventually required chest tube placement. **Chest tube placement** should occur under sterile conditions whenever possible and be preceded by appropriate analgesia. Pigtail catheters are the preferred type of chest tube in infants because of higher success rates and low complication rates. These catheters are placed using the Seldinger technique by introducing a needle, aspirating free air, and subsequently introducing a guidewire over which a pigtail catheter is advanced. Ideally the chest tube should be introduced into the fourth intercostal space (generally at the level of the nipple) in the anterior axillary line. Following placement, the chest tube should be attached to underwater seal drainage or continuous suction (−5 to −20 cm H_2O). Serial chest radiographs should be obtained for all infants with a chest tube in place.

Pneumopericardium with clinical symptoms (tamponade) requires prompt evacuation of entrapped air via pericardiocentesis. **Pericardiocentesis** should be performed using sterile technique and analgesia whenever possible. Ideally an echocardiogram should be completed before undertaking the procedure and cardiology or cardiothoracic surgery involvement is encouraged. Continuous cardiopulmonary monitoring is essential during the procedure. A 20–23-gauge butterfly needle is introduced into the chest to the left of the subxiphoid process at a 30–45-degree angle pointing toward the right shoulder. The needle is advanced until air returns and the pericardium is subsequently evacuated of air. The provider should stop aspirating once air no longer returns, if there is blood return, or if ectopy is observed. Following the procedure an echocardiogram should be obtained.

Treatment of PIE may include bronchoscopy in patients with evidence of mucous plugging, selective intubation and ventilation of the uninvolved bronchus, oxygen, general respiratory care, and use of HFV.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 133

Pulmonary Hemorrhage

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the first 2 weeks of life. The reported incidence at autopsy varies from 1-4 per 1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight (ELBW) infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of respiratory distress syndrome (RDS). The onset may occur at birth or may be delayed several days. **Hemorrhagic pulmonary edema** is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The risk of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, patent ductus arteriosus (PDA), congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication in which the rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1–5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting an additional bleeding diathesis, such as disseminated intravascular coagulation. In preterm infants, often intraventricular hemorrhage can occur at the same time. Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 458).

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and tamponade with increased mean airway pressure (often requiring high-frequency ventilation [HFV]). Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intraalveolar blood and protein can inactivate surfactant.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 134

Digestive System Disorders

Robert M. Kliegman

Signs and symptoms suggestive of gastrointestinal (GI) tract pathology in the newborn may reflect immaturity, disorders specific to the GI tract, or systemic diseases affecting the GI tract as part of a multisystem disorder (Table 134.1; see Chapter 121).

Feeding intolerance in the very low birthweight neonate may be due to immaturity of GI motility but also to anatomic lesions from the esophagus to the anus, as well as systemic, metabolic (galactosemia, etc.), or inflammatory processes (sepsis, hemophagocytic lymphohistiocytosis). Recognizing other organ system abnormalities and abnormal laboratory findings (anemia, thrombocytopenia, leukocytosis, neutropenia, elevated inflammatory markers, acidosis, hypoglycemia) may help identify the specific disease.

Table 134.1 Differential Diagnosis of Gastrointestinal Symptoms

SYMPTOM	GI DISORDERS	SYSTEMIC DISORDERS
Emesis	Reflux Volvulus Pyloric stenosis Hirschsprung disease Imperforate anus NEC Meconium plug	Sepsis Inborn error of metabolism Congenital adrenal hyperplasia Increased intracranial pressure
Jaundice	Hepatitis Biliary atresia GALD PFIC Alagille syndrome	Physiologic Hemolysis HLH Sepsis HSV Inborn error of metabolism
Abdominal distention	Feeding intolerance GI obstruction Meconium plug Ileus Meconium ileus NEC Pseudoobstruction Inguinal hernia	Sepsis Hypokalemia Hydronephrosis Ascites Hypermagnesemia

GALD, Gestational alloimmune liver disease; PFIC, progressive familial intrahepatic cholestasis; GI, gastrointestinal; NEC, necrotizing enterocolitis; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus.

Chapter 133

Pulmonary Hemorrhage

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the first 2 weeks of life. The reported incidence at autopsy varies from 1-4 per 1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight (ELBW) infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of respiratory distress syndrome (RDS). The onset may occur at birth or may be delayed several days. **Hemorrhagic pulmonary edema** is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The risk of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, patent ductus arteriosus (PDA), congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication in which the rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1–5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting an additional bleeding diathesis, such as disseminated intravascular coagulation. In preterm infants, often intraventricular hemorrhage can occur at the same time. Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 458).

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and tamponade with increased mean airway pressure (often requiring high-frequency ventilation [HFV]). Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intraalveolar blood and protein can inactivate surfactant.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 134

Digestive System Disorders

Robert M. Kliegman

Signs and symptoms suggestive of gastrointestinal (GI) tract pathology in the newborn may reflect immaturity, disorders specific to the GI tract, or systemic diseases affecting the GI tract as part of a multisystem disorder (Table 134.1; see Chapter 121).

Feeding intolerance in the very low birthweight neonate may be due to immaturity of GI motility but also to anatomic lesions from the esophagus to the anus, as well as systemic, metabolic (galactosemia, etc.), or inflammatory processes (sepsis, hemophagocytic lymphohistiocytosis). Recognizing other organ system abnormalities and abnormal laboratory findings (anemia, thrombocytopenia, leukocytosis, neutropenia, elevated inflammatory markers, acidosis, hypoglycemia) may help identify the specific disease.

Table 134.1 Differential Diagnosis of Gastrointestinal Symptoms

SYMPTOM	GI DISORDERS	SYSTEMIC DISORDERS
Emesis	Reflux Volvulus Pyloric stenosis Hirschsprung disease Imperforate anus NEC Meconium plug	Sepsis Inborn error of metabolism Congenital adrenal hyperplasia Increased intracranial pressure
Jaundice	Hepatitis Biliary atresia GALD PFIC Alagille syndrome	Physiologic Hemolysis HLH Sepsis HSV Inborn error of metabolism
Abdominal distention	Feeding intolerance GI obstruction Meconium plug Ileus Meconium ileus NEC Pseudoobstruction Inguinal hernia	Sepsis Hypokalemia Hydronephrosis Ascites Hypermagnesemia

GALD, Gestational alloimmune liver disease; PFIC, progressive familial intrahepatic cholestasis; GI, gastrointestinal; NEC, necrotizing enterocolitis; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus.

Chapter 135

Meconium Ileus, Peritonitis, Intestinal Obstruction, and Gastroschisis

Eric C. Eichenwald

Meconium consists of bile salts, bile acids, and debris shed from the intestinal mucosa in the intrauterine period. More than 90% of full-term newborn infants and 80% of very low birthweight (VLBW) infants pass meconium within the first 24 hours. The possibility of intestinal obstruction should be considered in any infant who does not pass meconium by 24-36 hours.

MECONIUM PLUGS

Meconium plugs syndrome refers to intestinal obstruction, usually in the distal colon, rectum, and anal canal, caused by meconium plugs (Fig. 135.1). Resulting from a disproportionately low amount of water in the intestinal lumen, meconium plugs are a rare cause of intrauterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis (CF). **Anorectal plugs** may also cause mucosal ulceration from bowel wall erosion and subsequent intestinal perforation. **Meconium plugs** are associated with small left colon syndrome in infants of diabetic mothers, infants with CF (40%) and Hirschsprung disease (40%), maternal opiate use, and magnesium sulfate therapy for preeclampsia and tocolysis. Up to 30% of patients can have spontaneous resolution. Initial treatment may include administration of a glycerin suppository or rectal irrigation with isotonic saline. In up to 95% of patients, a Gastrografin enema (meglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 [Tween 80] and 37% organically bound iodine) will be both diagnostic and therapeutic, inducing passage of the plug, presumably because the high osmolarity (1,900 mOsm/L) of the solution draws fluid rapidly into the intestinal lumen and loosens the inspissated material. Such rapid loss of fluid into the bowel may result in acute fluid shifts with dehydration and shock, so it is advisable to dilute the contrast material with an equal amount of water and provide intravenous (IV) fluids, during and for several hours after the procedure, sufficient to maintain normal vital signs, urine output, and electrolytes. After removal of a meconium plug, the infant should be observed closely, and consideration given to performing diagnostic testing to identify **Hirschsprung disease** (congenital aganglionic megacolon; see Chapter 378.4) and CF (see Chapter 454).

MECONIUM ILEUS

Meconium ileus, or impaction of inspissated meconium in the distal small bowel, accounts for up to 30% of cases of neonatal intestinal obstruction. It is common in patients with CF in whom the lack of fetal pancreatic enzymes inhibits digestive mechanisms, and meconium becomes viscid and mucilaginous. Clinically, neonates present with intestinal obstruction with or without perforation. Abdominal distention is prominent, and vomiting, often bilious, becomes persistent, although occasionally inspissated meconium stools may be passed shortly after birth. Meconium ileus can present as early as in utero, in which the fetus develops acute intestinal obstruction resulting in volvulus or perforation, peritoneal ascites, meconium peritonitis, and hydrops; if untreated, fetal loss may occur.

Meconium ileus is primarily associated with cystic fibrosis transmembrane regulator (CFTR) pathologic variants F508del, G542X, W1282X, R553X, and G551D. Patients with two copies of the F508del variant have a 25% chance of presenting with meconium ileus. F508del plus any other CF mutation confers 17% risk, and two other CF variants confer a 12% risk of meconium ileus. In addition, non-CFTR genetic modifier genes influence meconium ileus. In families who already have at least one child with CF complicated by meconium ileus, there is a 39% risk for meconium ileus in subsequent children, which is more than the rates expected with autosomal recessive inheritance. In a twin study, 82% of monozygotic twins showed concordance for meconium ileus, whereas only 22% of dizygotic and 24% of two affected siblings showed concordance. Positive newborn screening for CF should prompt sweat testing when the infant weighs >2 kg and is at least 36 weeks of corrected gestational age. Genetic testing confirms the diagnosis of CF (see Chapter 454). In ~20% of patients with meconium ileus, there is no evidence of CF; in some of these patients, pathogenic variants in *GUCY2C* are identified.

The differential diagnosis involves other causes of intestinal obstruction, including intestinal pseudoobstruction, and other causes of pancreatic insufficiency (see Chapter 398). Prenatal diagnosis is readily achieved by ultrasound with identification of enlarged bowel loops or a mass with distention of the proximal small bowel. Clinically the diagnosis can be made with a history of CF in

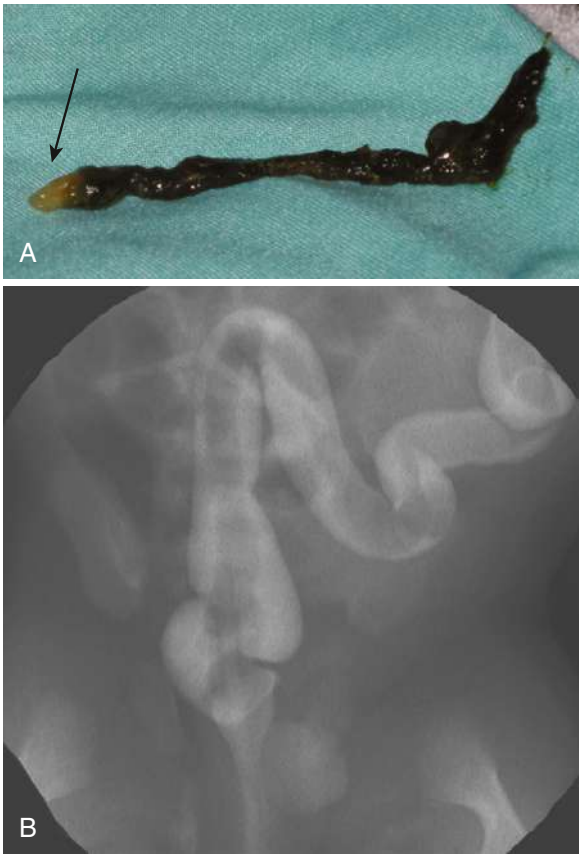

Fig. 135.1 Meconium plug. **A,** Meconium plug evacuated after a diagnostic contrast enema demonstrated the distinctive white tip *(arrow)*. **B,** Image from a contrast enema in a term neonate with vomiting and bowel distension demonstrates the long filling defect characteristic of meconium plug syndrome. The child was relieved of the obstruction after evacuation of the plug, without recurrence of symptoms. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging. 12th ed. Philadelphia: Elsevier; 2013: Fig. 106-14.)*

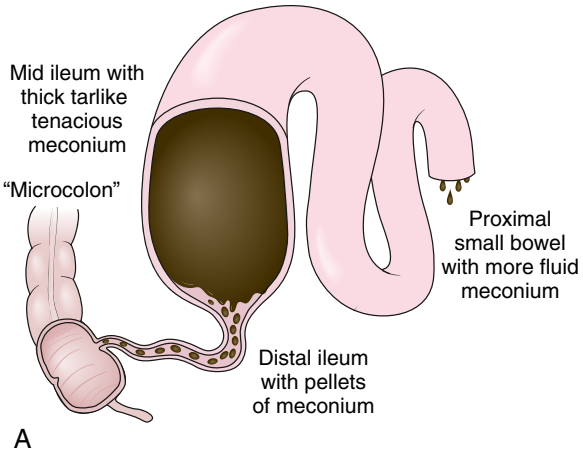

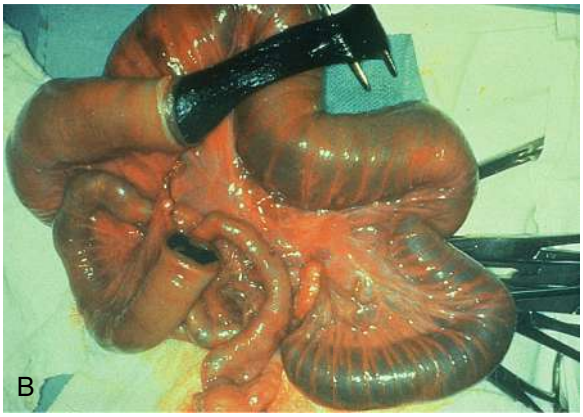

Fig. 135.2 Meconium ileus. **A,** Schematic drawing of uncomplicated meconium ileus. Pellets of inspissated meconium fill the terminal ileum proximal to a microcolon. Several loops of more proximal ileum contain thick, tenacious meconium. **B,** Enterotomy of proximal bowel and the nature of the thick and tenacious meconium. Note the dilated proximal loops of bowel filled with meconium and the progressively small caliber of the distal bowel leading to the microcolon. *(A from Leonidas JC, Berdon WE, et al. Meconium ileus and its complications: a reappraisal of plain film roentgen diagnostic criteria. Am J Roentgenol Radium Ther Nucl Med. 970;108[3]:598–609; B courtesy Dr. Wallace W. Neblett III, Nashville, TN.)*

a sibling, by palpation of doughy or cordlike masses of intestines through the abdominal wall, and from the radiographic appearance. Plain radiographs reveal small bowel obstruction. Air-fluid levels may not be apparent because of the thickened meconium.

In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and are not as evenly filled with gas. At points of heaviest meconium concentration, the infiltrated gas may create a bubbly, granular appearance (Figs. 135.2 and 135.3).

Treatment for simple meconium ileus is a high-osmolarity Gastrografin enema, as described for meconium plugs. If the procedure is unsuccessful or perforation of the bowel wall is suspected, a laparotomy is performed and the ileum opened at the point of largest diameter of the impaction. Approximately 50% of these infants have associated intestinal atresia, stenosis, or volvulus that requires surgery. The inspissated meconium is removed by gentle and patient irrigation with warm isotonic sodium chloride or *N*-acetylcysteine (Mucomyst) solution through a catheter passed between the impaction and

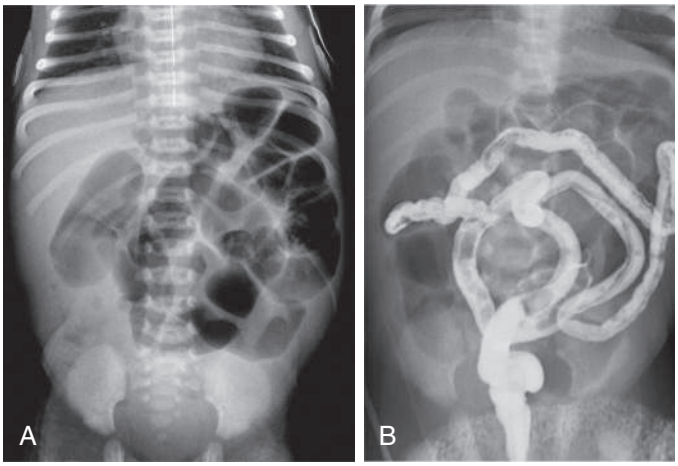

Fig. 135.3 Uncomplicated meconium ileus. **A,** Abdominal radiograph in 3-day-old infant with abdominal distention and bilious aspirates shows dilation of multiple loops of bowel. No calcifications are seen on the radiograph to suggest complicated meconium ileus. Orogastric tube near the gastroesophageal junction was subsequently advanced. **B,** Contrast enema demonstrates a microcolon, with multiple meconium plugs, consistent with the diagnosis of meconium ileus. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging. 13th ed. Philadelphia: Elsevier; 2019: Fig. 102-36)*

the bowel wall. Some patients will require bowel resection with a temporary double-barrel enterostomy followed by serial irrigations and distal refeeding, or primary anastomosis at the initial operation. Most infants with meconium ileus survive the neonatal period. If meconium ileus is associated with CF, the long-term prognosis depends on the severity of the underlying disease (see Chapter 454). In ~20% of patients with meconium ileus, there is no evidence of CF; in some of these patients pathogenic variants in *GUCY2C* are identified.

MECONIUM PERITONITIS

Perforation of the intestine may occur in utero or shortly after birth. Frequently, the intestinal perforation seals naturally with relatively little meconium leakage into the peritoneal cavity. Perforations occur most often as a complication of meconium ileus in infants with CF but occasionally result from a meconium plug or in utero intestinal obstruction of another cause.

Cases at the most severe end of the spectrum may be diagnosed on prenatal ultrasound with fetal ascites, polyhydramnios, bowel dilation, intraabdominal speckled calcifications, and hydrops fetalis (Fig. 135.4). At the other end are cases in which an intestinal perforation may seal spontaneously and patients remain asymptomatic, except when meconium becomes calcified and is later discovered on radiographs. Alternatively, the clinical picture may be dominated by signs of intestinal obstruction (as in meconium ileus) with abdominal distention, vomiting, and absence of stools or chemical peritonitis presenting with sepsis. Treatment consists primarily of elimination of the intestinal obstruction and drainage of the peritoneal cavity with a timely surgical intervention proved to result in high survival rate and favorable outcome even in complicated meconium peritonitis.

GASTROSCHISIS

Gastroschisis is the herniation of abdominal contents (usually small intestine) through a defect in the anterior abdominal wall lateral to the umbilical cord (Fig. 135.5). The etiology is unknown, but it has been

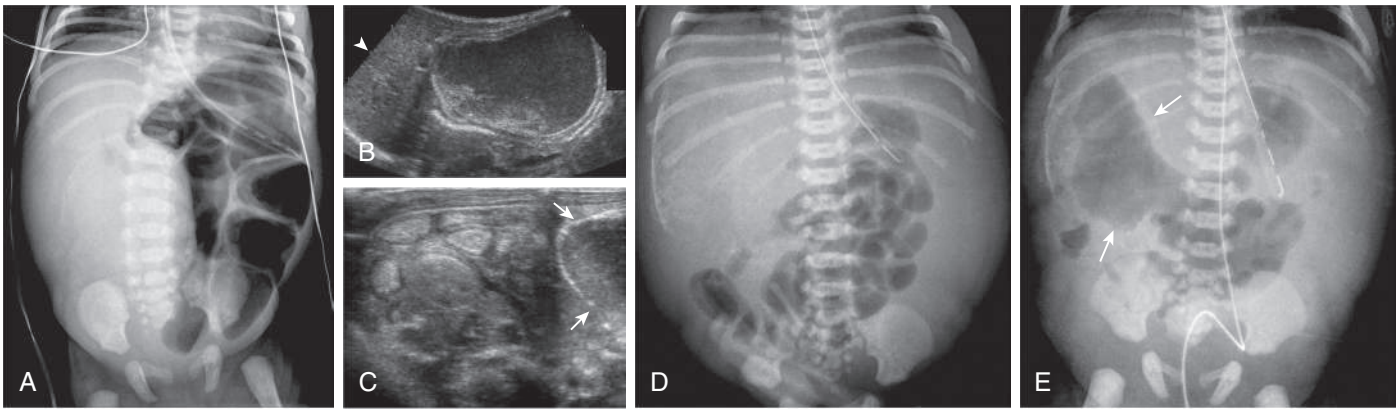

Fig. 135.4 Complicated meconium ileus. **A,** Abdominal radiograph in 2-day-old girl with abdominal distention and bilious aspirates shows absence of bowel gas in the right abdomen with a partly calcified mass displacing gas-filled dilated loops of bowel to the left. **B,** Ultrasound image demonstrates the subhepatic, partly calcified mass with internal debris and fluid-fluid level *(arrowhead)*. **C,** Additional ultrasound image shows a portion of the cyst wall *(arrows)* and multiple, abnormal, hyperechoic loops of bowel. **D,** Abdominal radiograph in different 1-day-old infant shows a calcified mass in right upper quadrant, shown at sonography to represent a loculated complex meconium collection. **E,** Radiograph a few hours later of the same infant shown in **D** shows a persistent perforation with gas entering into the right upper quadrant collection *(arrows)*. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging. 13th ed. Philadelphia: Elsevier; 2019: Fig. 102-37)*

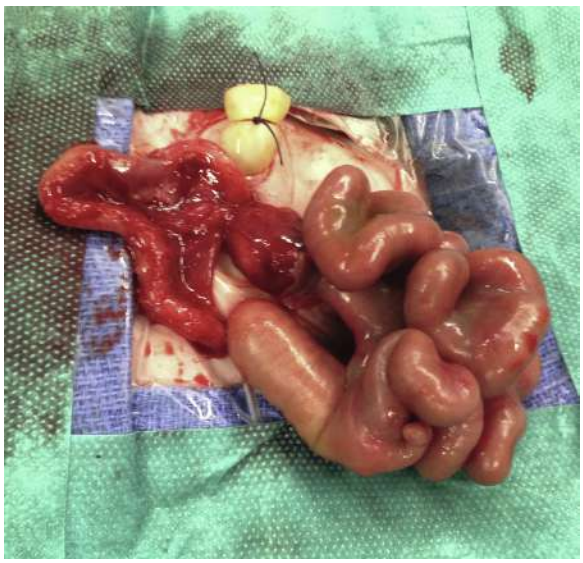

Fig. 135.5 Intraoperative view of a complex gastroschisis with intestinal atresia. Note the severe bowel matting in the complex gastroschisis. *(Modified from Vinit N, Talbotec C, De Tristan MA, et al. Predicting factors of protracted intestinal failure in children with gastroschisis. J Pediatr. 2022;243:122–129. Fig. 1B.)*

associated with young maternal age and possible opioid use; the incidence is ~2-5 infants in 10,000 births.

Gastroschisis is usually an isolated anomaly but has a high morbidity and mortality especially in complex lesions associated with intestinal atresias and necrosis resulting in short bowel syndrome and intestinal failure (see Chapter 385.6). Treatment requires resection of atretic or necrotic tissue and long-term parenteral alimentation until enteral nutrition can be established.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 136

Necrotizing Enterocolitis

Sagori Mukhopadhyay and Misty Good

Necrotizing enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal (GI) tract in the newborn period. The disease is characterized by various degrees of mucosal or transmural necrosis of the intestine followed by local and systemic inflammation. The cause of NEC remains unclear but is most likely multifactorial.

DEFINITION

NEC is clinically identified using a combination of clinical and radiographic signs and staged by categorizing NEC into suspected (stage I), definite (stage II, clinical signs of abdominal pathology with an abnormal abdominal radiograph showing pneumatosis intestinalis, portal venous gas, or ileus), and advanced (stage III, signs of stage II plus severe systemic signs of inflammation and acidosis with or without signs of intestinal perforation). In addition, NEC is also categorized into *medical and surgical NEC* defined by the type of acute intervention required. These criteria have been criticized for categorizing conditions with heterogeneous origins as the same disease. For example, conditions such as spontaneous intestinal perforation, septic ileus, and allergic enterocolitis can present with signs similar to NEC, but they arise from differing pathogenesis and may have differing outcomes. Similarly, term infants often present with NEC attributable to coexisting conditions such as congenital heart disease or gastroschisis, and likely do not share identical pathogenesis with NEC occurring in preterm infants. To minimize the heterogeneity of presentations that get diagnosed as NEC, a definition of "preterm NEC" has been proposed for use in clinical research. **Preterm NEC** in clinical research is defined by the presence of (1) clinical sign of abdominal distention and/or hematochezia; (2) onset between 10 days after birth to 36 weeks' postmenstrual age with the highest risk period being 30-32 weeks'

postmenstrual age; and (3) one of the following—pneumatosis intestinalis or portal venous gas by radiograph or ultrasound, histopathologic evidence of intestinal necrosis, or evidence of vasculitis, coagulopathy, or inflammation in the absence of infection.

EPIDEMIOLOGY

Epidemiologic studies have reported changes in NEC incidence in the past decade. Among 473,895 very low birthweight infants (VLBW, birthweight <1,500 g) admitted to one of 820 centers in the United States (2006-2017), the overall rate of NEC was 7.6%. From 2006–2017, there was a significant reduction in the prevalence of medical but not surgical NEC; mortality with NEC also decreased from 20.7% to16.8% among infants with medical NEC, and 36.6% to 31.6% for neonates with surgical NEC.

PATHOLOGY AND PATHOGENESIS

Many factors contribute to the development of the pathologic findings of NEC, including mucosal ischemia and subsequent necrosis; gas accumulation in the submucosa of the bowel wall **(pneumatosis intestinalis)**; and progression of the necrosis to perforation, peritonitis, sepsis, and death. An overview of common hypothesized pathogenic mechanisms, related clinical presentation, and management is shown in Figure 136.1. The distal part of the ileum and the proximal segment of the colon are involved most frequently; in fatal cases, transmural necrosis may extend from the stomach to the rectum **(NEC totalis)**. The pathogenesis of NEC is not fully understood, but three major risk factors have been implicated: prematurity, bacterial colonization of the gut, and enteral feeding. NEC develops primarily in premature infants with exposure to a nutritional substrate in the context of immature intestinal motility, and immunity, microbial dysbiosis, and mucosal ischemia. An underlying genetic predisposition is recognized with variants in genes regulating immunomodulation and inflammation (e.g., toll-like receptor-4, interleukin [IL]-4 receptor α chain, IL-6), apoptosis and cellular repair (e.g., platelet-activating factor), and oxidant stress (e.g., vascular endothelial growth factor, arginine, nitric oxide). *The greatest risk factor for NEC is prematurity, with a mean onset between 30 and 32 weeks' postmenstrual age.* Other risk factors include small for gestational age, polycythemia, and conditions resulting in in utero hypoxia. NEC rarely occurs before the initiation of enteral feeding and is much less common in infants fed human milk.

CLINICAL MANIFESTATIONS

Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset (Table 136.1). Age of onset is inversely related to gestational age. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to GI pathology, such as abdominal tenderness and distention, feeding intolerance, and bloody stools. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Laboratory findings may include neutropenia, anemia, thrombocytopenia, coagulopathy, and metabolic acidosis. Hypotension and respiratory failure are common. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hours.

DIAGNOSIS

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of pneumatosis intestinalis confirms the clinical suspicion of NEC and is diagnostic; 50–75% of patients have pneumatosis when treatment is started (Fig. 136.2). Portal venous gas is a sign of severe disease, and pneumoperitoneum indicates a perforation (Figs. 136.3 and 136.4). Ultrasound may be useful to evaluate for free fluid, abscess, pneumatosis intestinalis, and bowel wall thickness, peristalsis, and perfusion (Fig. 136.5). Doppler flowmetry studies can be used to assess flow in superior mesenteric artery and portal vein.

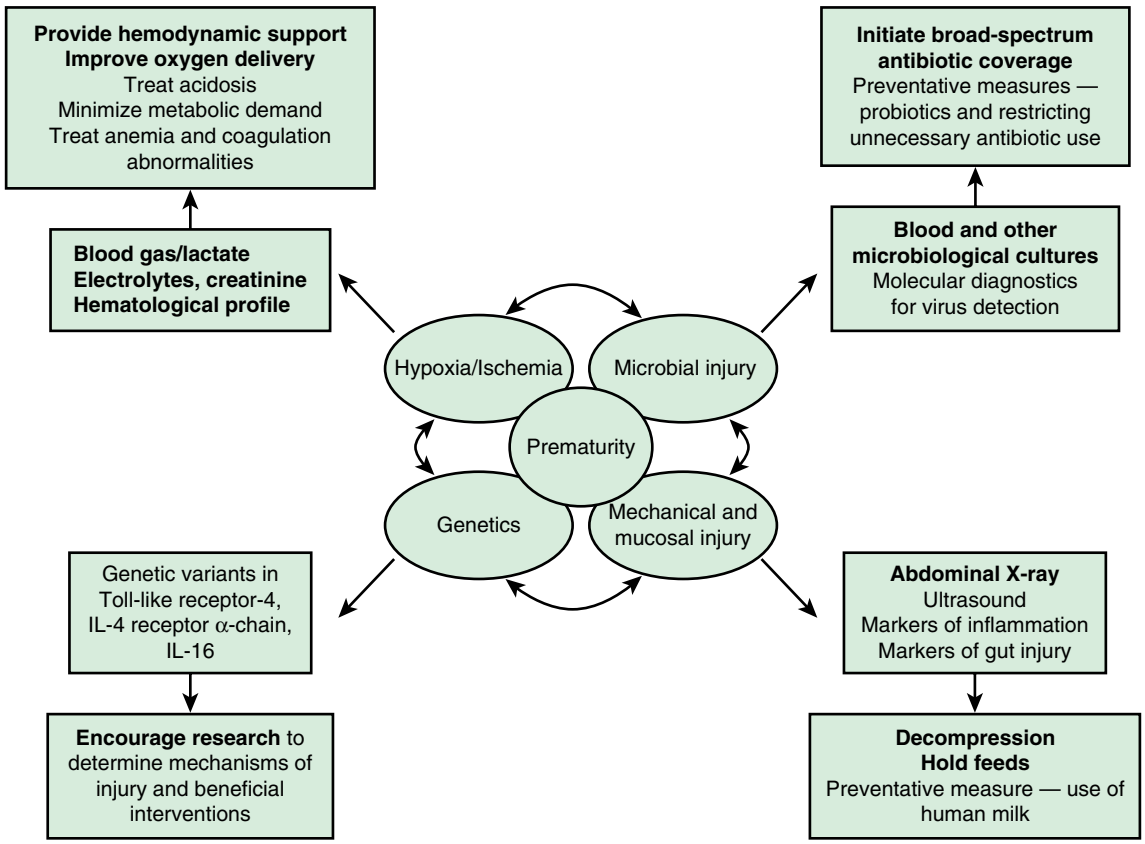

Fig. 136.1 Overview of risk factors and mechanisms of injury in necrotizing enterocolitis–associated presentation and management approaches. **Bold** indicates interventions that are common first-line interventions for NEC. IL, Interleukin. (*Figure created by authors using BioRender.com.*)

Table 136.1 Signs and Symptoms Associated with Necrotizing Enterocolitis

GASTROINTESTINAL	SYSTEMIC
Abdominal distention	Lethargy
Abdominal tenderness	Apnea/respiratory distress
Feeding intolerance	Temperature instability
Delayed gastric emptying	Acidosis (metabolic and/or respiratory)
Emesis	Glucose instability
Occult/gross blood in stool	Poor perfusion/shock
Change in stool pattern/diarrhea	Thrombocytopenia
Abdominal mass	Disseminated intravascular coagulopathy
Erythema of abdominal wall	

From Kanto WP Jr, Hunter JE, Stoll BJ. Recognition and medical management of necrotizing enterocolitis. *Clin Perinatol.* 1994;21:335–346.

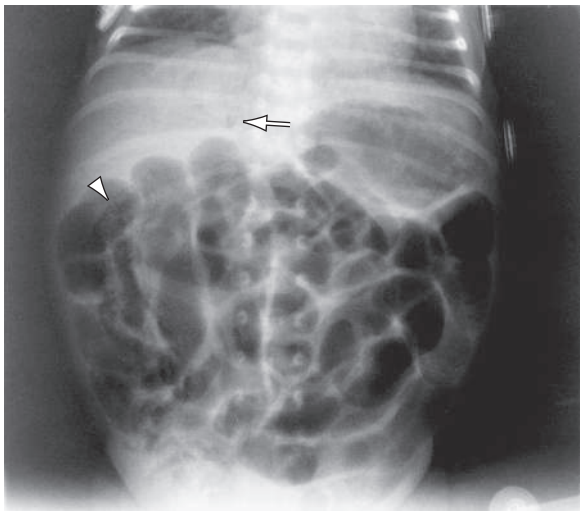

Fig. 136.2 Necrotizing enterocolitis (NEC). Kidney-ureter-bladder film demonstrates abdominal distention, hepatic portal venous gas *(arrow),* and a bubbly appearance of pneumatosis intestinalis (*arrowhead;* right lower quadrant). The latter two signs are thought to be pathognomonic for neonatal NEC.

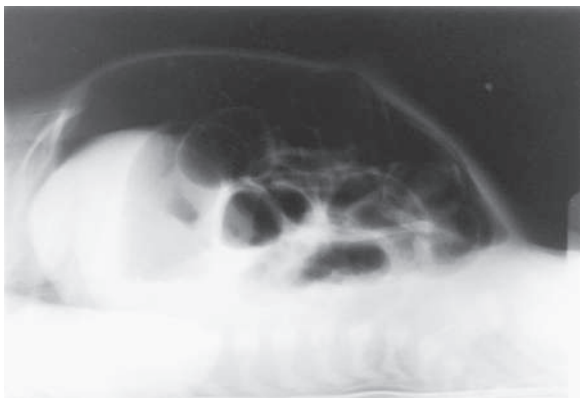

Fig. 136.3 Intestinal perforation. Cross-table abdominal radiograph in patient with neonatal necrotizing enterocolitis demonstrates marked distention and massive pneumoperitoneum, as evidenced by the free air below the anterior abdominal wall.

The differential diagnosis of NEC includes septic ileus, GI obstruction, volvulus, and isolated intestinal perforation. **Idiopathic focal intestinal perforation** can occur spontaneously or can be associated with the early use of postnatal corticosteroids and indomethacin. Pneumoperitoneum develops in such patients, but they are usually less ill than those with NEC. Occasional clusters of NEC cases have been attributed to viral infections, specifically norovirus, enterovirus, and rotavirus. Stool viral testing and infectious disease consultation should be considered when multiple cases occur together.

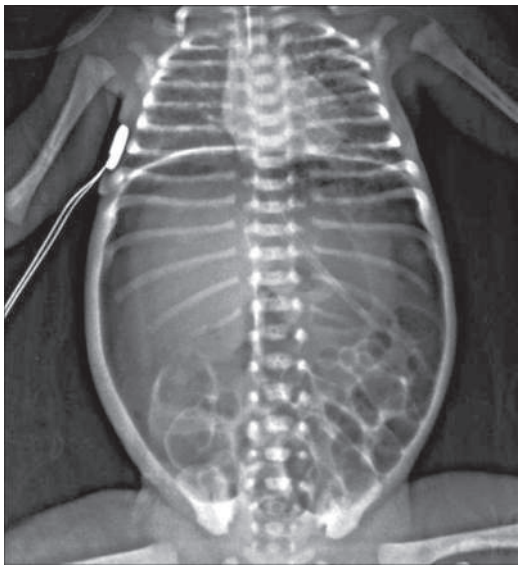

Fig. 136.4 Necrotizing enterocolitis (NEC). Plain abdominal x-ray film of an infant with perforated NEC showing pneumoperitoneum. *(From Tam PKH, Chung PHY, St Peter SD, et al. Advances in paediatric gastroenterology. Lancet. 2017;390:1072–1082. Fig. 4)*

TREATMENT

Rapid initiation of therapy is required for infants with suspected, as well as proven NEC. There is no specific treatment for established NEC, so therapy is directed at providing supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids and antibiotics (see Fig. 136.1). Careful attention to the respiratory status, coagulation profile, and acid-base and electrolyte balances are important. Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC. Umbilical arterial catheters are reported to reduce blood flow in the mesenteric blood vessels and should be removed if they remain in place after a diagnosis of NEC. Maintaining reliable intravenous access for ongoing hemodynamic support and medication administration is critical.

Approximately 16% of definite NEC cases may be associated with bacteremia detected within 72 hours of its diagnosis, most frequently with a gram-negative organism. NEC with associated bacteremia has a higher risk for requiring surgical intervention and mortality. Once blood has been drawn for culture, systemic antibiotics (with broad coverage based on the antibiotic sensitivity patterns in the particular neonatal ICU) should be started immediately. The addition of anaerobic coverage with antibiotics such as metronidazole or clindamycin is variably practiced. Management of NEC with anaerobic coverage is

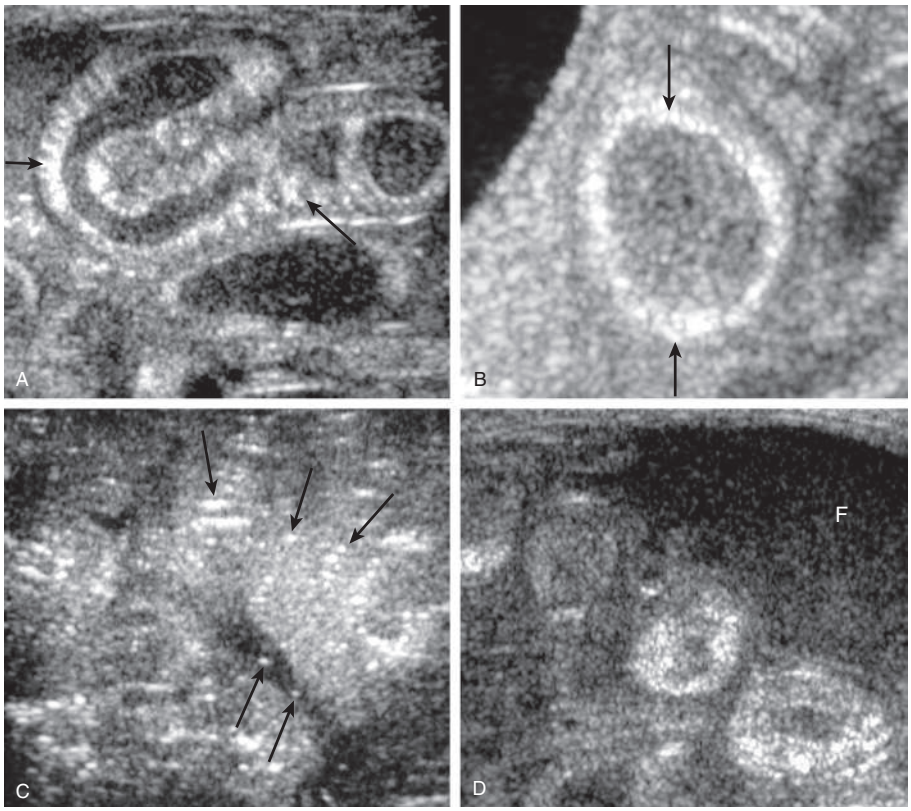

Fig. 136.5 Necrotizing enterocolitis. **A,** Mucosal and submucosal thickening *(arrows)*. **B,** Intramural gas (pneumatosis intestinalis) creates an echogenic ring *(arrows)*. **C,** Widespread echogenic bubbles of gas in the portal veins *(arrows)*. **D,** Fluid with echogenic debris (F) lies adjacent to thick loops. *(From John SD, Hollingsworth C: The pediatric gastrointestinal tract. In Levine D, Rumack CM, Wilson SR, Charboneau JW, eds. Diagnostic Ultrasound, 4th ed. Philadelphia: Elsevier, 2014. Fig 55.29.)*

associated with slightly lower risk of mortality and higher risk of subsequent strictures.

The patient's course should be monitored closely by means of frequent physical assessments in the NICU; sequential anteroposterior and cross-table lateral or lateral decubitus abdominal radiographs to detect intestinal perforation; and serial determinations of hematologic, electrolyte, and acid-base status. A surgeon should be consulted early in the course of treatment. The only *absolute* indication for surgery is evidence of perforation on an abdominal radiograph (pneumoperitoneum). However, this is present in less than half of infants with perforation or necrosis at operative exploration. Progressive clinical deterioration despite maximum medical management, a single fixed bowel loop on serial radiographs, and abdominal wall erythema are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur. The optimal surgical approach, however, remains controversial. The options for surgical treatment include primary peritoneal drainage (PPD) or exploratory laparotomy with resection of the necrotic intestine and usually stoma creation. Laparotomy is usually the initial therapy in the majority of VLBW infants with surgical NEC, even in those <1,000 g. Randomized clinical trials comparing these approaches failed to demonstrate significant differences in survival, nutritional outcomes, or length of stay. However, among those with a diagnosis of NEC *(as opposed to intestinal perforation)*, 69% died or had neurodevelopmental impairment (NDI) when managed with initial laparotomy versus 85% when managed with PPD. In contrast, among infants with a diagnosis of *intestinal perforation*, death or NDI occurred 69% and 63% after initial management with laparotomy or PPD, respectively. When the diagnosis is confirmed NEC, initial management with laparotomy is more likely to reduce risk of death or NDI compared to PPD. However, the ultimate surgical approach for an individual case also depends on the surgeon's assessment and physiologic status of the patient.

PROGNOSIS

In patients with pneumatosis intestinalis at NEC diagnosis, disease progression is nonresponsive to medical management alone in approximately 20–40%; of these that require surgery, 20–50% die. Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include intestinal strictures, which occur in approximately 25–35% of surgically or medically managed patients. After massive intestinal resection, complications from postoperative NEC include short bowel syndrome (malabsorption, growth failure, malnutrition), complications related to central venous catheters (sepsis, thrombosis), and cholestatic jaundice. Preterm infants with NEC who require surgical intervention are at increased risk for adverse growth and neurodevelopmental outcomes.

PREVENTION

The most effective preventive strategy for NEC is the use of human milk (maternal or donor); newborns exclusively fed breast milk have a reduced risk of NEC. However, because human milk does not provide complete nutritional support for very preterm infants, nutritional fortification is usual practice. Some studies have suggested that an "exclusive human milk diet" using human rather than bovine fortifiers may further reduce the risk of NEC. An optimal feeding protocol (rapid vs slow volume increments) has not been discovered; it is important to note that strict adherence to a NICU-specific feeding protocol reduces the risk of NEC. Additionally, while extensive data and meta-analyses would support the use of probiotics to prevent NEC, there is no clear consensus on the safest, most effective formulation, timing of administration, or length of therapy. Other preventive strategies using prebiotics and synbiotics have also been studied, with variable outcomes. Inhibitors of gastric acid secretion (H_2-receptor blockers, proton pump inhibitors), high osmolality enteral fluids, or prolonged empirical antibiotics in the early neonatal period have been associated with increased risk of NEC and should be avoided.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 137

Jaundice and Hyperbilirubinemia in the Newborn

Kelsey S. Ryan and Robert M. Kliegman

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. **Jaundice** is observed during the first week after birth in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated **indirect-acting** by nature of the van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin **(direct-reacting).** Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates potentially serious hepatic disorders or a systemic illness.

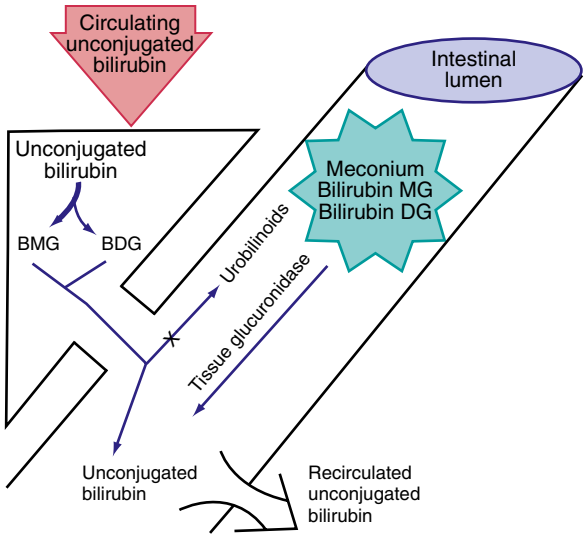

Fig. 137.1 Metabolism of bilirubin in the neonatal period. Neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione *S*-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

ETIOLOGY

During the neonatal period, metabolism of bilirubin is in transition from the *fetal stage,* during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the *adult stage,* during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. **Unconjugated hyperbilirubinemia** may be caused or increased by any factor that (1) increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened RBC life as a result of immaturity or transfusion of cells, increased enterohepatic circulation, infection), (2) damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency), (3) competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation), or (4) leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, prematurity). Gene polymorphisms in the hepatic uridine diphosphate glucuronosyltransferase isoenzyme 1A1 *(UGT1A1)* and the solute carrier organic anion transporter 1B1 *(SLCO1B1)*, alone or in combination, influence the incidence of neonatal hyperbilirubinemia.

The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood-brain barrier (BBB) and nerve cell membranes but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas suboptimal feedings and dehydration increases serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 137.1). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia.

CLINICAL MANIFESTATIONS

Jaundice usually appears during the early neonatal period, depending on etiology. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, approximately 5 mg/dL; mid-abdomen, 15 mg/dL; soles, 20 mg/dL), *but clinical examination cannot reliably estimate serum levels*. Noninvasive techniques for transcutaneous measurement of bilirubin that correlate with serum levels may be used to *screen* infants, but determination of the serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for hemolysis or sepsis. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without treatment, can progress to acute bilirubin encephalopathy (kernicterus) (see Chapter 137.1).

DIFFERENTIAL DIAGNOSIS

The distinction between *physiologic* and *pathologic* jaundice relates to the timing, rate of rise, and extent of hyperbilirubinemia, because some of the same causes of physiologic jaundice (e.g., large RBC mass, decreased capacity for bilirubin conjugation, increased enterohepatic circulation) can also result in pathologic jaundice. Evaluation should be determined on risk factors, clinical appearance, and severity of the hyperbilirubinemia (Tables 137.1-137.3). Jaundice that is present at birth or appears within the first 24 hours after birth should be considered **pathologic** and requires immediate attention. Potential diagnoses would include erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital

Table 137.1 Risk Factors for Severe Neonatal Hyperbilirubinemia

GENETIC FACTORS
- Gilbert syndrome
- Crigler-Najjar syndrome
- Alagille syndrome
- β thalassemia
- Glucose-6-phosphate dehydrogenase deficiency
- Bilirubin glucuronosyltransferase polymorphism
- Pyruvate kinase deficiency
- Erythrocyte structural defects (including hereditary spherocytosis and elliptocytosis)
- Galactosemia

MATERNAL FACTORS
- Family history of severe jaundice, splenectomy, or cholecystectomy
- Primiparity
- Teenage pregnancy
- Diabetes
- Rhesus incompatibility
- ABO incompatibility
- Other blood group isoimmunization
- Use of drugs during labor (including oxytocin, promethazine, and bupivacaine)
- Exclusive breastfeeding

PERINATAL FACTORS
- Mode of deliver (breech vs vertex, instrumentation)
- Birth trauma (cephalohematoma or substantial bruising, extravasation)
- Birth asphyxia
- Congenital infections (including cytomegalovirus and syphilis)
- Sepsis

NEONATAL FACTORS
- Male sex
- Prematurity or low birthweight and small-for-gestational age
- Hypothyroidism
- Polycythemia
- Hypoglycemia
- Low intake of breast milk, dehydration, or weight loss
- Breast milk jaundice
- Jaundice in the first day of life
- Trisomy 21
- Infant of diabetic mother
- Cephalohematoma, other bruising

OTHER RISK FACTORS AND MARKERS
- Previous sibling received phototherapy or exchange transfusion
- Predischarge total serum bilirubin or transcutaneous bilirubin concentration in the high zone
- Use of hemolytic agents (e.g., naphthalene or menthol-based products) in glucose-6-phosphate dehydrogenase deficient population groups
- Folate deficiency
- Aflatoxins
- Hypothermia
- Birth outside of a healthcare facility

Modified from Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. *Lancet Child Adolesc.* 2018;2:610–618. Panel 2, p. 612.

Table 137.2 Evaluation of the Neonate with Significant Jaundice

CONCERN	POSSIBLE DIAGNOSIS	INITIAL LABORATORY TESTS
Jaundice on day 1	Hemolysis* TORCH/sepsis Hepatic failure syndromes† Internal hemorrhage	CBC, smear Total and direct bilirubin Blood type and Coombs test
Jaundice requiring phototherapy	Hemolysis* TORCH/sepsis	As above
Direct/conjugated hyperbilirubinemia	TORCH/sepsis Biliary atresia Other causes of cholestasis‡ Hepatic failure syndromes†	Hepatic enzymes, INR, check newborn screen for metabolic disease, blood glucose, blood ammonia and lactate, urine and blood cultures, CMV and HSV PCR

*Hemolysis may be immune or nonimmune (RBC membrane or enzyme defects).
†Hepatic failure syndromes: HSV, CMV, gestational alloimmune liver disease, mitochondrial liver disease, familial hemophagocytic syndrome.
‡See Chapter 404.
CMV, Cytomegalovirus; CBC, complete blood count; HSV, herpes simplex virus; PCR, polymerase chain reaction; INR, international normalized ratio; TORCH, toxoplasmosis, other, rubella, CMV, herpes.

infections, including syphilis, cytomegalovirus (CMV), rubella, and toxoplasmosis. Significant hemolysis is suggested by a rapid rise in serum bilirubin concentration (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history. An unusually high proportion of direct-reacting bilirubin may characterize jaundice in infants who have received intrauterine transfusions for erythroblastosis fetalis. Jaundice that first appears on the second or third day is usually **physiologic** but may represent a more severe form. Familial nonhemolytic icterus **(Crigler-Najjar syndrome)** and early-onset breastfeeding (suboptimal intake) jaundice are seen initially on the second or third day. Jaundice *appearing* after the third day and within the first week suggests bacterial sepsis or urinary tract infection; it may also be caused by other infections, notably syphilis, toxoplasmosis, CMV, herpes simplex virus (HSV), and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the first day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

There is a long differential diagnosis for jaundice first recognized *after* the first week of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, cystic fibrosis (CF), pyloric stenosis, and congenital hemolytic anemia crises related to RBC morphology and enzyme deficiencies (Fig. 137.2). The differential diagnosis for persistent jaundice during the first month of life includes hyperalimentation-associated cholestasis, hepatitis, CMV, syphilis, toxoplasmosis, familial nonhemolytic icterus, biliary atresia, galactosemia and other inborn errors of metabolism, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

Regardless of gestation or time of appearance of jaundice, patients with *significant* hyperbilirubinemia *and* those with symptoms or signs require a complete diagnostic evaluation, which includes review of risks (Table 137.1), determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, direct antiglobulin/antibody test (DAT) (Coombs test), and examination of a peripheral blood smear. Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of RBC destruction suggest hemolysis (see Table 137.2). In the absence of blood group incompatibility, non–immunologically-induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 137.2). If direct hyperbilirubinemia is present, diagnostic possibilities include hepatitis, congenital bile duct disorders (biliary atresia, paucity of bile ducts, Byler disease), cholestasis, inborn errors of metabolism, CF, congenital hemosiderosis, sepsis, and neonatal hepatic failure syndromes (Table 137.4).

Table 137.3 Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	COMMENTS
		APPEARS	DISAPPEARS	MG/DL	AGE IN DAYS		
"Physiologic jaundice"							Usually relates to degree of maturity
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia caused by metabolic factors							Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Full-term	Indirect	2-3 days	Variable	>12	First wk	<5	Hormonal influences: hypothyroidism, hormones, Gilbert syndrome
Premature	Indirect	3-4 days	Variable	>15	First wk	<5	Genetic factors: Crigler-Najjar syndrome, Gilbert syndrome
Hemolytic states and hematoma	Indirect	May appear in first 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drug: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and hepatoxic factors	Indirect and direct	May appear in first 24 hr	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis, pyelonephritis, hepatitis, toxoplasmosis CMV HSV Rubella, syphilis
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by second wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis, infection, hepatic failure syndromes*

*Gestational alloimmune liver disease, hemophagocytic lymphocytosis, mitochondrial hepatic disorders, inborn errors of metabolism
CMV, Cytomegalovirus; HSV, herpes simplex virus.
From Brown AK. Neonatal jaundice. Pediatr *Clin North Am.* 1962;9:575–603.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

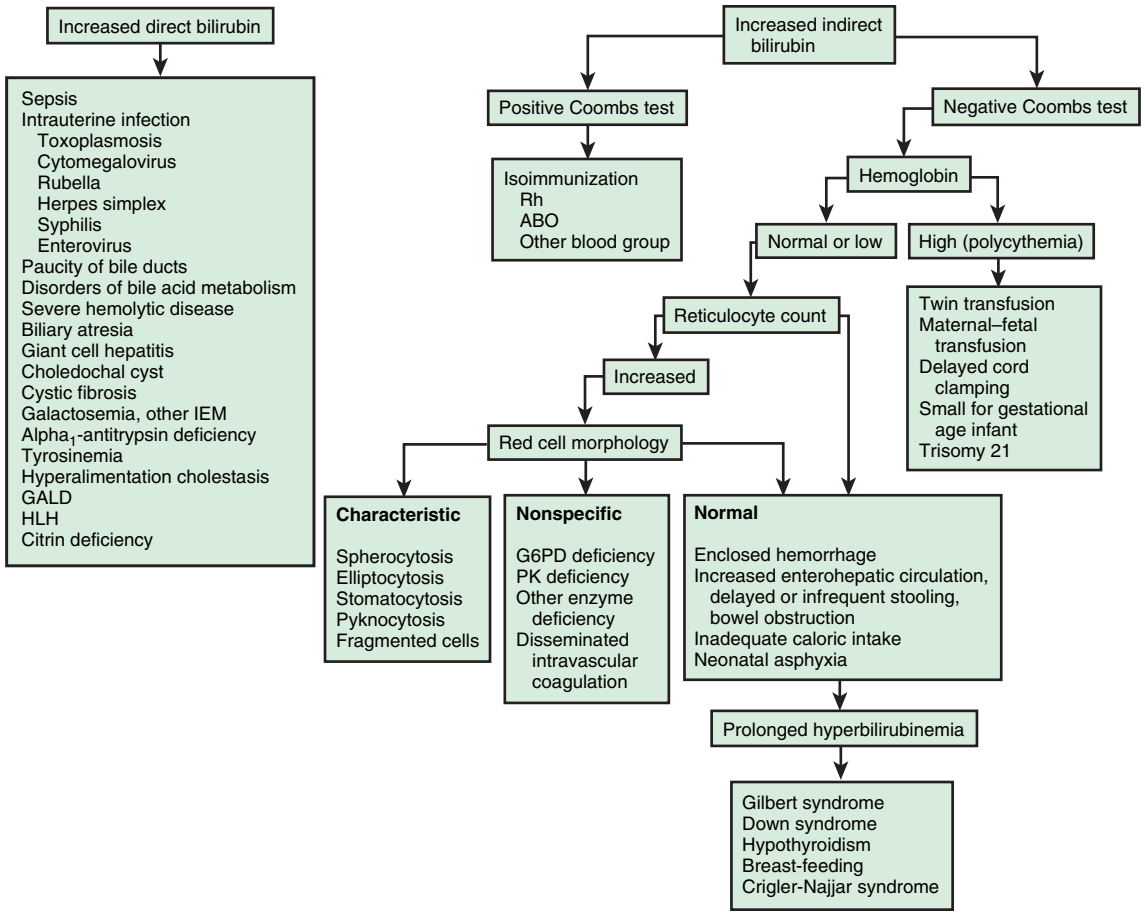

Fig. 137.2 Algorithmic approach to the diagnosis of neonatal jaundice. G6PD, Glucose-6-phosphate dehydrogenase; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis; IDM, infants of diabetic mothers; IEM, inborn error of metabolism; PK, pyruvate kinase. *(From Oski FA. Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, eds. Schaffer and Avery's Diseases of the Newborn. 6th ed. Philadelphia: Saunders; 1991.)*

Table 137.4 Typical Laboratory Findings in Neonatal Liver Failure

	GALD	HLH	MITOCHONDRIAL	VIRAL	ISCHEMIC
Transaminase levels (IU/L)	Normal/mild increase <100	Moderate/significant increase (>1,000)	Moderate increase (100-500)	Significant increase (>1,000)	Significant increase (>1,000-6,000)
INR	Significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase
Ferritin level (ng/mL)	800-7,000	Significant increase (>20,000)	Variable	Significant increase (>20,000)	Variable depending on underlying cause of ischemia
Triglyceride levels	Normal	Increased	Normal	Normal	Normal
Hypoglycemia	Yes	Often	Yes	Often	Variable
Lactic acidosis	Normal	Normal	Increased	Normal	Often
α-Fetoprotein level (for age)	Increased	Normal	Normal/increased	Normal	Normal
Cholestasis	Progressive after birth	Moderate/significant	Moderate	None/mild at presentation	Mild/moderate

HLH, Hemophagocytic lymphohistiocytosis; GALD, gestational alloimmune liver disease; INR, international normalized ratio.
From Larson-Nath C, Vitola BE. Neonatal acute liver failure. *Clin Perinatol*. 2020;47:25–39. Table 2 with data from Sundaram SS, Alonso EM, Narkewicz, MR, et al. *J Pediatr* 2011;159:813–818; Taylor SA, Whitington, PF. *Liver Transpl*. 2016;22(5):677–685; Bitar R, Thwaites R, Davison S, et al. *J Pediatr Gastroenterol Nutr*. 2017;64(1):70–75; Fellman V, Kotarsky H. *Semin Fetal Neonatal Med*. 2011;16(4):222–228.

PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus jaundice becomes visible on the second or third day, usually peaking between the second and fourth days at 5-6 mg/dL and decreasing to <2 mg/dL between the fifth and seventh days after birth. Jaundice associated with these changes is designated *physiologic* and is believed to be the result of increased bilirubin production from the breakdown of fetal RBCs combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6–7% of full-term infants have indirect bilirubin levels >13 mg/dL, and <3% have levels >15 mg/dL. Risk factors for elevated indirect bilirubin include maternal age, ethnicity (Chinese, Japanese, Korean, Native American), maternal diabetes, prematurity, drugs, altitude, polycythemia, male, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breastfeeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history of, or a sibling who had, physiologic jaundice (see Table 137.1). In infants without these variables, indirect bilirubin levels rarely rise >12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels. A combination of breastfeeding, variant-glucuronosyltransferase activity (1A1), subclinical glucose-6-phosphate dehydrogenase (G6PD) deficiency, and alterations of the organic anion transporter-2 gene increases the risk of hyperbilirubinemia. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on *hour-specific* bilirubin levels in the first 24-72 hours of life (Fig. 137.3). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 weeks suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be the result of caloric deprivation, relative deficiency of hepatic UDP–glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from an ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the fourth to seventh day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice based on the history, clinical findings, and laboratory data (see Table 137.3). In general, a search to determine the cause of jaundice should be made if (1) it appears in the first 24-36 hours after birth, (2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr, (3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant, (4) jaundice persists after 10-14 days after birth, or (5) direct bilirubin fraction is >2 mg/dL at any time. Other factors suggesting a pathologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, bleeding disorder, and signs of kernicterus (see Chapter 137.1).

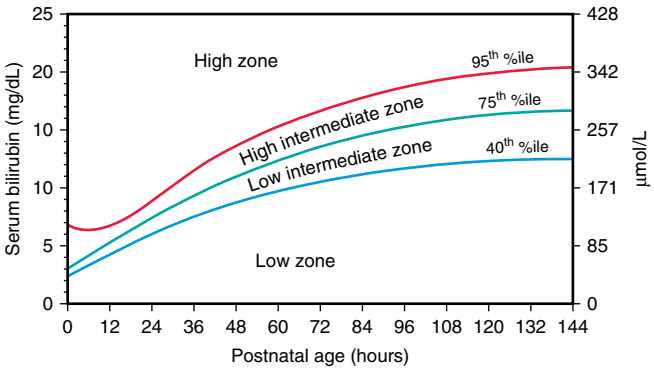

Fig. 137.3 Neonatal bilirubin nomogram. Percentile designation of well newborns ≥35 weeks' gestational age based on their hour-specific serum bilirubin values. The high zone is subdivided by the 95th percentile track. The intermediate zone is subdivided into upper and lower zones by the 75th percentile track. The low zone has been electively and statistically defined by the 40th percentile track. *(Modified from Bahr TM, Henry E, Christensen RD, et al. A new hour-specific serum bilirubin nomogram for neonates ≥35 weeks of gestation. J Pediatr. 2021;236:28–33. Fig. 2.)*

PATHOLOGIC HYPERBILIRUBINEMIA

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice, or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of unconjugated bilirubin, but many infants with this finding have associated risk factors such as ethnicity, prematurity, breastfeeding, and weight loss. Frequently, the terms *exaggerated physiologic jaundice* and *hyperbilirubinemia of the newborn* are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase **(Gilbert syndrome)** rather than an excessive load of bilirubin for excretion (see Table 137.1). *The combination of G6PD deficiency and a pathogenic variant of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis.*

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels (see Chapter 137.1). The development of kernicterus **(bilirubin encephalopathy)** depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, sepsis, meningitis, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. *The exact serum indirect bilirubin level that is harmful for very low birthweight (VLBW) infants is unclear.*

JAUNDICE ASSOCIATED WITH BREASTFEEDING

Significant elevation in unconjugated bilirubin **(breast milk jaundice)** develops in an estimated 2% of breastfed term infants after the seventh day, with maximal concentrations as high as 10-30 mg/dL reached during the second to third week. If breastfeeding is continued, the bilirubin gradually decreases but may persist for 3-10 weeks at lower levels. Phototherapy may be of benefit (see Chapter 137.1). Although very uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear, although intestinal β-glucuronidase resulting in deconjugation of bilirubin and increased enterohepatic circulation and other factors in breast milk that might interfere with bilirubin conjugation (e.g., pregnanediol, free fatty acids) have been implicated.

The late jaundice associated with breast milk should be distinguished from an *early onset*, accentuated unconjugated hyperbilirubinemia known as suboptimal intake hyperbilirubinemia or **breastfeeding jaundice**, which occurs during the first week after birth in breastfed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 137.4). Lower milk intake before breast milk production is established can result in various degrees of dehydration, which hemoconcentrates bilirubin, while also causing fewer bowel movements, which in turn increases the enterohepatic circulation of bilirubin. Prophylactic supplements of glucose water to breastfed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk and *are not indicated*. Frequent breastfeeding (>10 in 24 hours), rooming-in with night feeding, and ongoing lactation support may reduce the incidence of

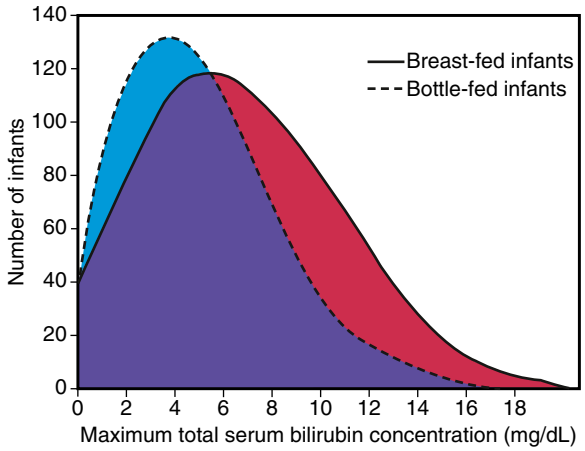

Fig. 137.4 Distribution of maximal bilirubin levels during the first week of life in breastfed and formula-fed White infants weighing >2,500 g. *(From Maisels MJ, Gifford K. Normal serum bilirubin levels in the newborn and the effect of breast-feeding. Pediatrics. 1986;78:837–843.)*

early breastfeeding jaundice. In addition, supplementation with formula or more preferred expressed breast milk is appropriate if the intake seems inadequate, weight loss is excessive, or the infant appears dehydrated.

NEONATAL CHOLESTASIS

See Chapter 404.

CONGENITAL ATRESIA OF THE BILE DUCTS

See Chapter 404.1.

Jaundice persisting for >2 weeks or associated with acholic stools and dark urine suggests biliary atresia. All infants with such findings require immediate diagnostic evaluation, including determination of direct bilirubin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

137.1 Kernicterus and Therapy of Hyperbilirubinemia

Kelsey S. Ryan and Robert M. Kliegman

Kernicterus, or **bilirubin encephalopathy**, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the BBB, and neuronal susceptibility to injury. Disruption of the BBB by disease, asphyxia, infection, and other factors and maturational changes in BBB permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable. In a large series, however, kernicterus occurred only in infants with a bilirubin >20 mg/dL (more often >25-30 mg/dL), 90% of whom were previously healthy, predominantly breastfed, term and near-term infants. The duration of exposure to high bilirubin levels needed to produce toxic effects is unknown; the more immature the infant, and possibly age (day 1 vs day of life ≥4), the greater the susceptibility to kernicterus.

CLINICAL MANIFESTATIONS

Signs and symptoms of kernicterus usually appear 2-5 days after birth in term infants and as late as the seventh day in preterm infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, apnea, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill, high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 137.5). Rigidity is rare at this late stage.

Table 137.5 Clinical Features of Kernicterus

ACUTE FORM
Phase 1 (first 1-2 days): poor suck, stupor, hypotonia, seizures
Phase 2 (middle of first week): hypertonia of extensor muscles, opisthotonos, retrocollis, fever
Phase 3 (after the first week): hypertonia
CHRONIC FORM
First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills
After first year: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

From Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med* 2001;344:581–590.

Many infants who progress to these severe neurologic signs die; the survivors usually have serious sequalae but may appear to recover and for 2-3 months show few abnormalities. Later in the first year, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the second year the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 years of age, the complete neurologic syndrome is often apparent: bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or "minimal brain dysfunction," occurring singly or in combination; these problems may be unapparent until the child enters school (see Table 137.5).

INCIDENCE AND PROGNOSIS

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2–16% and is related to the risk factors discussed in this chapter. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs carry a grave prognosis; >75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Developmental delay, deafness, and spastic quadriplegia are common.

PREVENTION

The aim of bilirubin management is prevention of kernicterus. Although kernicterus has been thought to be a disease of the past, there are reports of neurotoxic effects of bilirubin in term and near-term infants who were discharged as healthy newborns. Effective prevention requires ongoing vigilance and a practical, system-based approach to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Predischarge universal screening for hyperbilirubinemia and assessment of clinical risk factors for severe jaundice and bilirubin-induced neurologic dysfunction include either total serum bilirubin or transcutaneous bilirubin measurement (interchangeably), although transcutaneous instruments may be less accurate at higher bilirubin levels (>15 mg/dL) or for infants with darker skin or if phototherapy has been used. If transcutaneous levels are documented as ≥15 mg/dL or rising rapidly, confirmation with a total serum bilirubin is recommended. Serum

values should also be measured once infants begin phototherapy, because transcutaneous measurement may falsely underestimate total bilirubin in this setting.

Protocols using the hour-specific bilirubin nomogram (see Fig. 137.3), physical examination, and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. Potentially preventable causes of kernicterus include (1) early discharge (<48 hours) with no early follow-up (within 48 hours of discharge), a problem that is particularly important in near-term infants (35-37 weeks of gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the first 24 hours; (3) failure to recognize the presence of risk factors for hyperbilirubinemia, especially hemolysis; (4) underestimation of the severity of jaundice by clinical (visual) assessment, which is inaccurate; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. Figure 137.5 provides a consensus-based (expert opinion) management plan for neonates with significant hyperbilirubinemia that relies on consensus-recommended (expert opinion) phototherapy thresholds for gestational ages ≥35 weeks (Figs. 137.6 and 137.7) in well appearing neonates.

The following approach is further recommended: (1) any infant who is jaundiced before 24 hours requires measurement of total *and* direct serum bilirubin levels and, if elevated, evaluation for possible hemolytic or primary hepatic diseases, and (2) follow-up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48 hours after birth. Early follow-up is particularly important for infants <38 weeks of gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hours is necessary. Postdischarge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about the infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Parents should be advised to nurse their infants 8-12 times in 24 hours and to avoid supplementation with water or glucose water to ensure adequate hydration and caloric intake.

TREATMENT OF HYPERBILIRUBINEMIA

Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while causing no undue harm. Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Table 137.6; see Figs. 137.6 and 137.7). The risk of injury to the central nervous system from bilirubin must be balanced against the potential risk of treatment. Because phototherapy may require 6-12 hours to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion. When identified, underlying

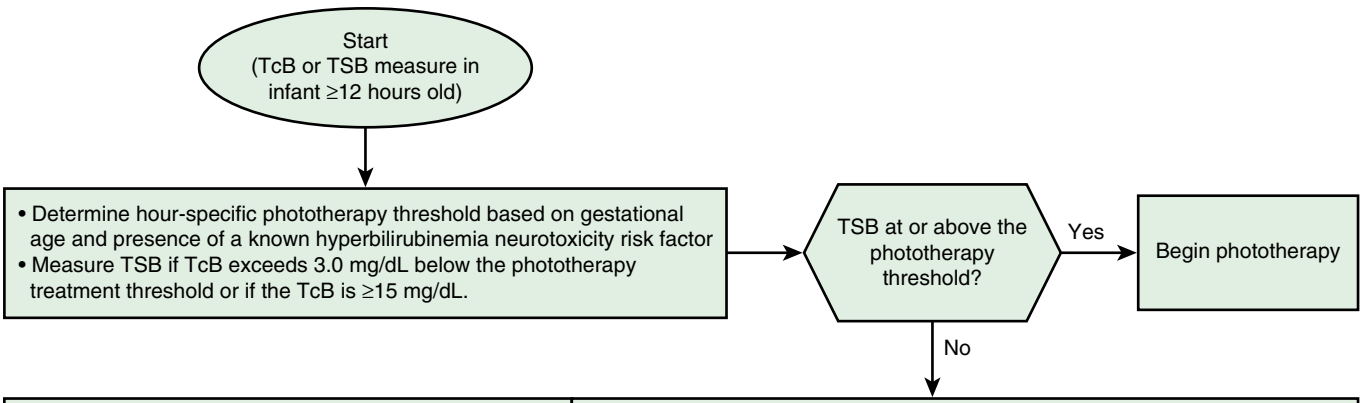

Phototherapy threshold minus TcB or TSDB		Discharge recommendations
0.1-1.9 mg/dL	Age <24 hours	Delay discharge, consider phototherapy, measure TSB in 4 to 8 hours
	Age ≥24 hours	Measure TSB in 4 to 24 hours[a] Options: • Delay discharge and consider phototherapy • Discharge with home phototherapy if all considerations in the guideline are met • Discharge without phototherapy but with close follow-up
2.0-3.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 4 to 24 hours[a]
3.5-5.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 1-2 days
5.5-6.9 mg/dL	Discharging <72 hours	Follow-up within 2 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]
≥7.0 mg/dL	Discharging <72 hours	Follow-up within 3 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]

Fig. 137.5 Algorithm to determine postdischarge follow-up for infants who have not received phototherapy during the birth hospitalization. [a]Use clinical judgment and shared decision-making to determine when to repeat the bilirubin measure within this 4–24-hour time window. [b]Clinical judgment decisions should include physical examination, the presence of risk factors for the development of hyperbilirubinemia or hyperbilirubinemia neurotoxicity risk factors, feeding adequacy, weight trajectory, and family support. TcB, Transcutaneous bilirubin; TSB, total serum bilirubin. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022; 150[3]:e2022058859. Fig. 7.)*

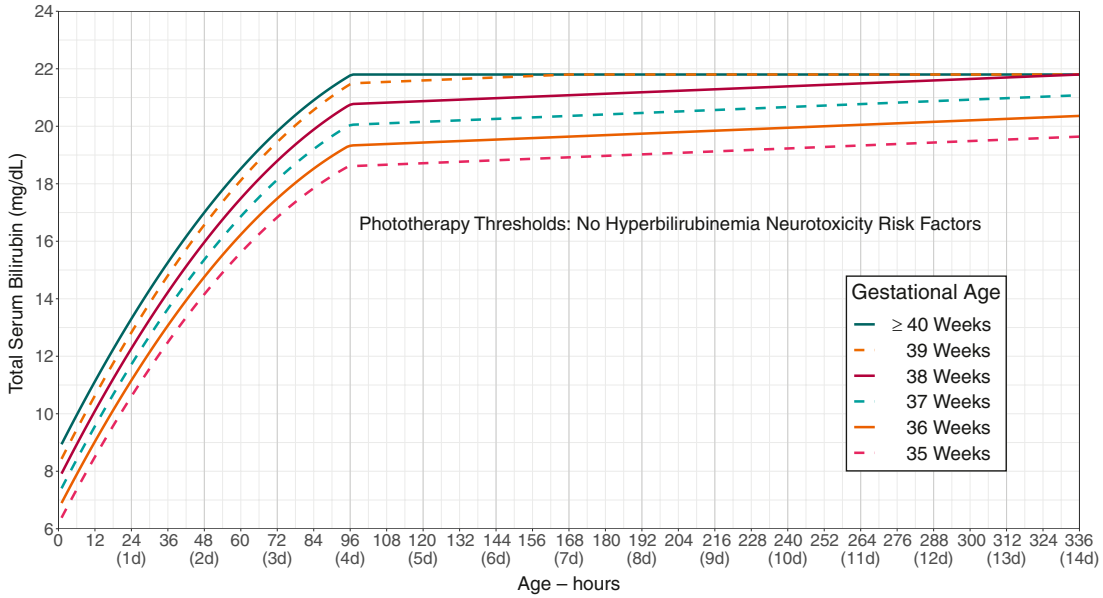

Fig. 137.6 Phototherapy thresholds by gestational age and age in hours for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Note that infants <24 hours old with a TSB at or above the phototherapy threshold are likely to have a hemolytic process and should be evaluated for hemolytic disease. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 2.)*

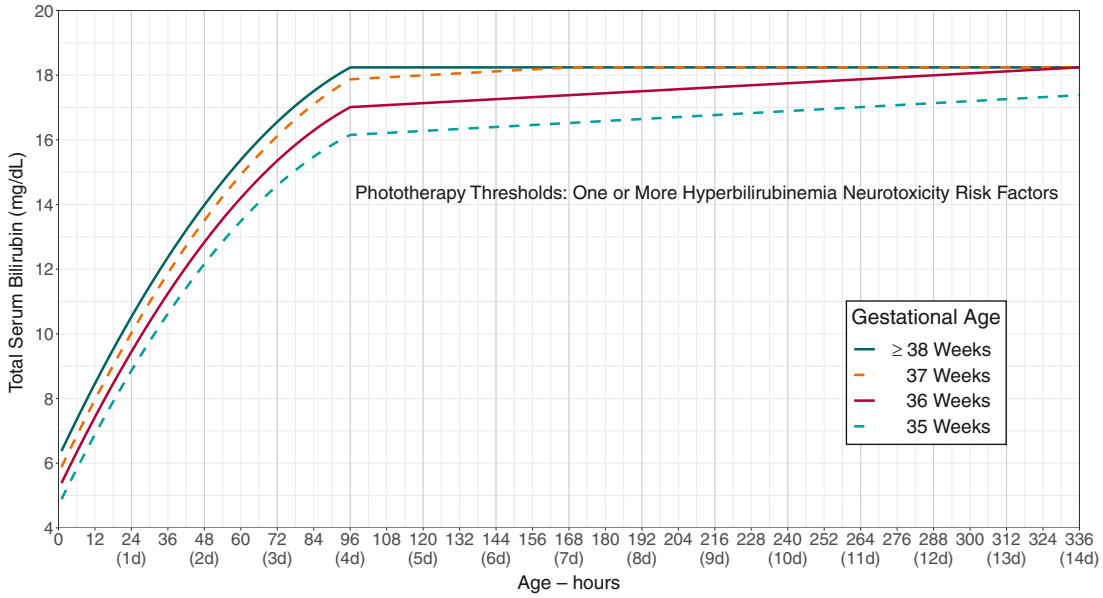

Fig. 137.7 Phototherapy thresholds by gestational age and age in hours for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract the direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022:150[3]:e2022058859. Fig. 3.)*

medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated, such as antibiotics for sepsis, correction of acidosis, and dehydration (Fig. 137.8).

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to high-intensity light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photoisomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of hemolysis and in vivo metabolism and excretion of bilirubin. Available commercial phototherapy units vary considerably in spectral output and the intensity of radiance emitted; therefore the wattage can be accurately measured only at the patient's skin surface. Dark skin does not reduce the efficacy of phototherapy. Maximal intensive phototherapy should be used when indirect bilirubin levels approach those noted in Figures 137.6 and 137.7. Such therapy includes using LED lamps and/or putting a fiberoptic phototherapy blanket under the infant's back to increase the exposed surface area.

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic *and* nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis. Conventional phototherapy is applied continuously (except for breastfeeding). It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant's age and condition. Serum bilirubin levels and hematocrit should be monitored every 4-8 hours in infants with hemolytic disease and those with bilirubin levels near toxic range. Serum bilirubin monitoring should continue for at least 24 hours after cessation of phototherapy in *patients with hemolytic disease*, because unexpected rises in bilirubin may occur, requiring further treatment. Skin color, visual assessment, or transcutaneous bilirubin levels cannot be relied on for evaluating the effectiveness of phototherapy; the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia. Although not necessary for *all* affected infants, intravenous fluid supplementation added to oral feedings are beneficial in dehydrated patients or infants with bilirubin levels nearing those requiring exchange transfusion.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, hypothermia from exposure, and a benign condition called "bronze baby syndrome," which occurs in the presence of direct hyperbilirubinemia. Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage and fluorescent bulb use. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development

Table 137.6 Suggested Maximal Indirect Serum Bilirubin Concentrations (mg/dL) in Preterm Infants

BIRTHWEIGHT (g)	UNCOMPLICATED*	COMPLICATED*
<1,000	12-13	10-12
1,000-1,250	12-14	10-12
1,251-1,499	14-16	12-14
1,500-1,999	16-20	15-17
2,000-2,500	20-22	18-20

*Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50–70% of the maximal indirect level. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.

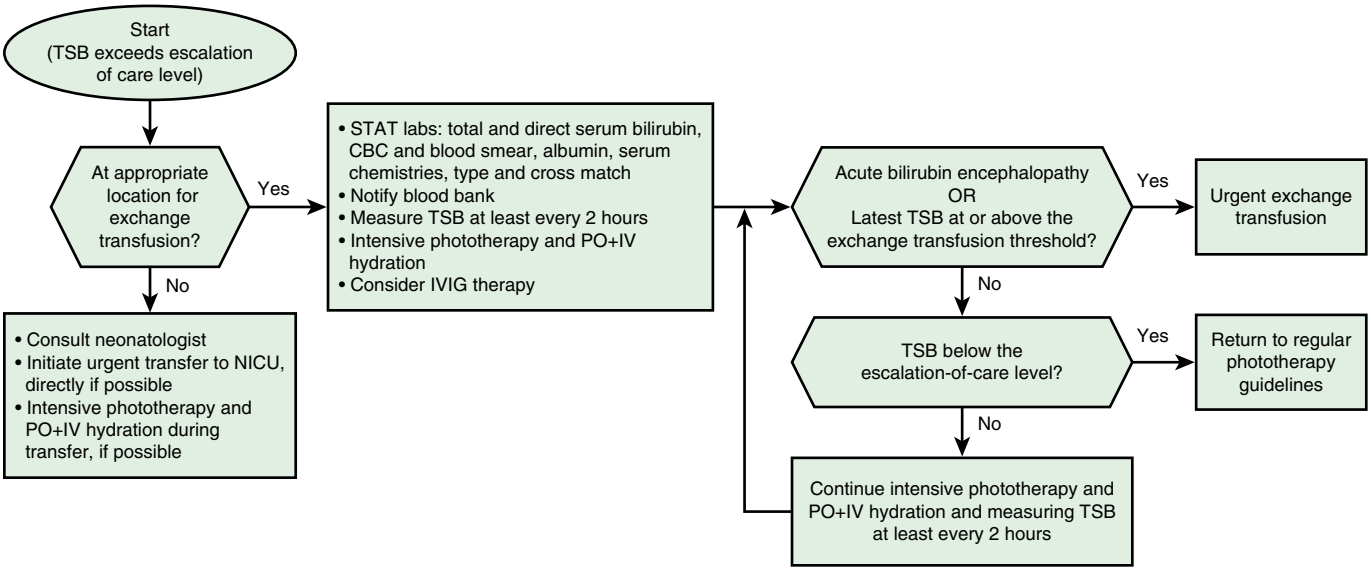

Fig. 137.8 Approach to escalation of care. The escalation-of-care threshold is 2 mg/dL below the exchange transfusion threshold. IVIG, Intravenous immunoglobulin; NICU, neonatal intensive care unit; PO, orally; TSB, total serum bilirubin. *(Modified from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 4.)*

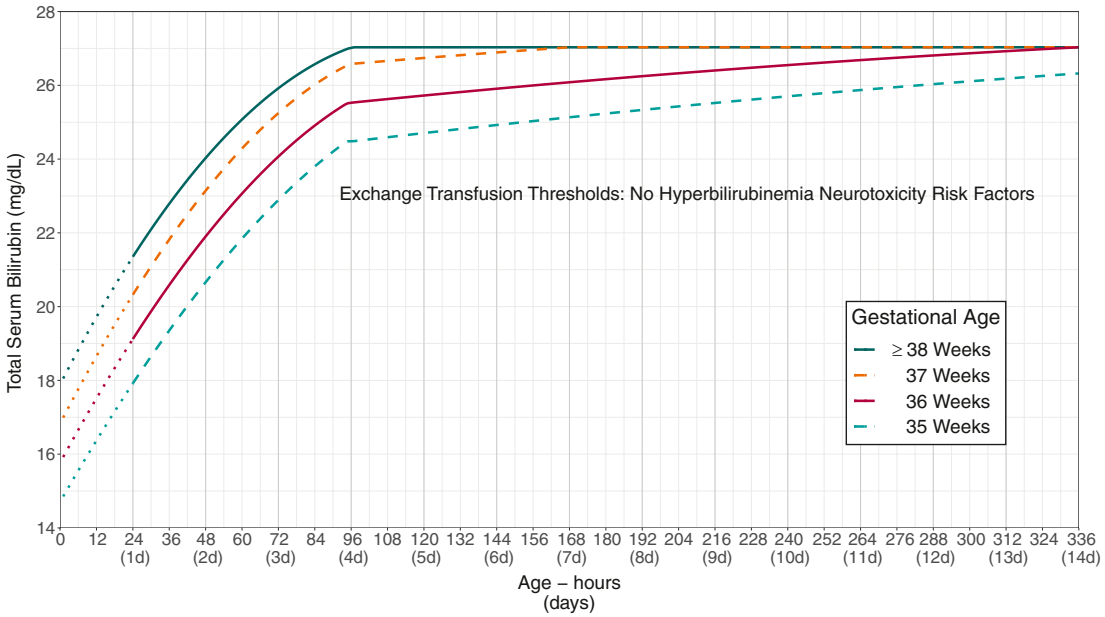

Fig. 137.9 Exchange transfusion thresholds by gestational age for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 5.)*

of anemia, which may require transfusion; *anemia may develop despite lowering of bilirubin levels.* Clinical experience suggests that long-term adverse biologic effects of phototherapy are absent, minimal, or unrecognized.

The term **bronze baby syndrome** refers to a dark, grayish brown skin discoloration sometimes noted in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may result from photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin

The administration of intravenous immunoglobulin (IVIG) is an adjunctive treatment for hyperbilirubinemia caused by *isoimmune hemolytic disease*. It has been used when serum bilirubin is approaching exchange levels despite maximal interventions, including phototherapy. IVIG (0.5-1.0 g/kg/dose; repeat in 12 hours) may reduce the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis. The effectiveness is unclear.

Exchange Transfusion

Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and the risk of kernicterus exceeds the procedural risk. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, necrotizing enterocolitis (NEC), infection, graft versus host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (Fig. 137.9). Ideally the exchange transfusion should be performed with leukocyte-depleted, washed fresh-packed RBC's, reconstructed with fresh-frozen plasma to a hematocrit of ~40%. It should be cross matched against the neonate and the mother.

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient (see Fig. 137.8). The appearance of clinical signs suggesting kernicterus is an absolute indication for exchange transfusion at any level of serum bilirubin. A hydropic jaundiced neonate with erythroblastosis from Rh disease will be critically ill and requires exchange transfusion at much lower levels than recommended in Figures 137.9 and 137.10. See other risk factors affecting exchange transfusion threshold in Figure 137.10.

A healthy full-term infant with physiologic or breast milk jaundice may tolerate a bilirubin concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level. A level approaching that considered critical for the individual infant may be an indication for exchange transfusion during the first or second day after birth, when a further rise is anticipated, but not typically after the fourth day in a term infant or after the seventh day in a preterm infant, because an imminent decrease in bilirubin levels may be anticipated as the hepatic conjugating mechanism becomes more effective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

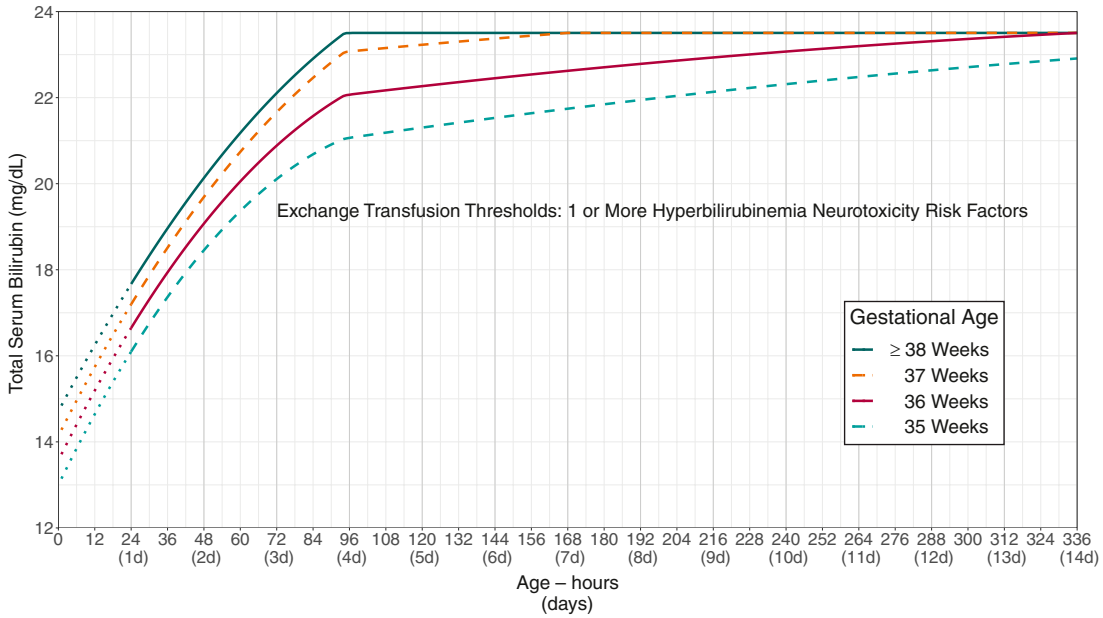

Fig. 137.10 Exchange transfusion thresholds by gestational age for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 6.)*

Chapter 138

Blood Disorders

Christopher S. Thom and Michele P. Lambert

NORMAL ERYTHROPOIESIS AND HEMOGLOBIN FUNCTIONS

The diagnosis of anemia or polycythemia, and interpretation of laboratory values, requires understanding normal hemoglobin-oxygen binding and delivery physiology. Heterotetrameric **hemoglobin**, comprising two α-globin and two β-globin monomers, has an exquisite ability to cooperatively bind and release oxygen molecules in response to environmental conditions. Hemoglobin switching refers to the normal transitions in gene expression among embryonic, fetal, and adult globins that occur before and after birth (Fig. 138.1). Fetal hemoglobin (HbF) is the predominant hemoglobin molecule produced during late gestation. Its increased oxygen affinity compared with maternal adult hemoglobin (HbA) facilitates oxygen transfer in the hypoxic in utero environment, which lacks direct atmospheric gas exchange. Relative in utero hypoxia explains the elevated hemoglobin levels normally seen in newborns, which can be exacerbated by pathologic chronic intrauterine hypoxia.

NORMAL RED BLOOD CELL INDICES IN NEONATES AND INFANTS

Diagnosing anemia or polycythemia in infants also relies on comparisons to normal reference ranges, which vary based on gestational and postnatal age. Normal reference ranges for hemoglobin, hematocrit, and other erythrocyte indices are based on measurements from more than 25,000 preterm and term infants through the first 28 days of life (Fig. 138.2). Hemoglobin and hematocrit levels exhibit linear increases between 22 and 40 weeks of gestation.

Erythrocyte mean corpuscular volume (MCV) in neonates is typically higher than toddlers or older children, with normal values ranging from approximately 100-115 fL at birth (see Fig. 138.2C). Reasons for this finding are multifactorial. An elevated MCV can reflect an increase in circulating reticulocytes (immature erythrocytes), although a relative reticulocytosis in neonates is inadequate to fully explain the MCV elevation. Indeed, mature erythrocytes are larger in neonates than in adults. The size discrepancy may be related to the presence of different hemoglobin molecules, as mature erythrocytes containing HbF (termed F cells) may be larger than HbA-containing cells. Conversely, MCV <100 fL in a neonate should prompt suspicion for underlying α-thalassemia/thalassemia trait, maternal iron deficiency, or chronic fetal to maternal blood loss.

At any age, increased MCV can indicate hemolysis or other processes that enhance erythropoietic drive. Persistent microcytic anemia can result from thalassemia or iron deficiency.

Platelet Count Abnormalities in Pediatric Patients

Hematopoiesis, megakaryopoiesis, and thrombopoiesis produce ~10^{11} platelets per day to facilitate normal blood clotting and fulfill important vascular functions (see Chapter 495). Processes that disrupt platelet production or consumption can significantly alter steady-state platelet quantities in circulation. This can be clinically relevant and require intervention, although many etiologies are transient and/or benign. Here we describe common etiologies that increase or decrease platelet counts. Chapter 533 includes a full description of these and other platelet defects.

Thrombocytosis is defined as >450 × 10^9 platelets/L blood, although for neonates this limit can be raised to >600 × 10^9 platelets/L. Thrombocytosis can be stratified from mild to extreme, the latter defined as >1,000 × 10^9

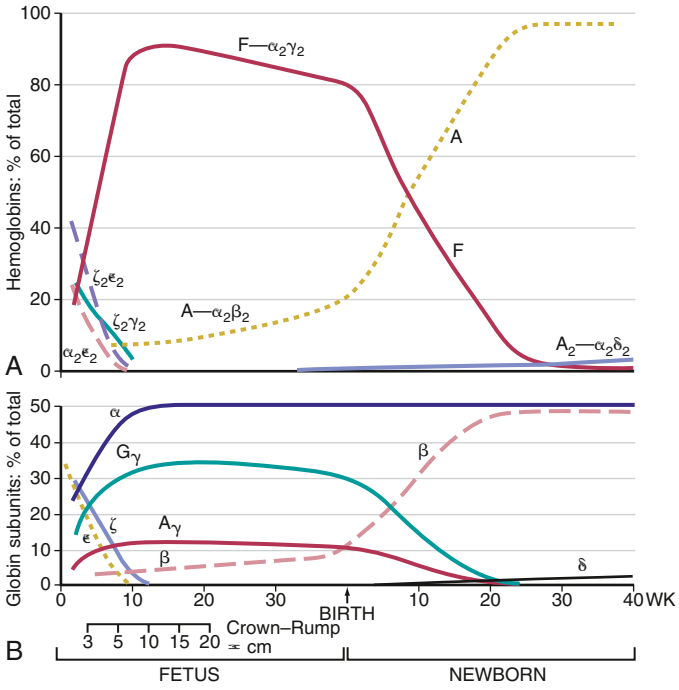

Fig. 138.1 Developmental changes in (A) hemoglobin tetramers and (B) globin subunit expression from early gestation through infancy. (*From Polin RA, Fox WW. Fetal and Neonatal Physiology. 2nd ed. Philadelphia: Saunders; 1998. p. 1769.*)

platelets/L. Immature immune or hematopoietic systems may underlie an increased rate of thrombocytosis in infants and young children.

Myeloproliferative disorders can cause primary thrombocytosis, but this is rare in children. More often, thrombocytosis reflects a secondary or reactive process as part of an acute phase response. This is usually due to an inflammatory process and does not increase thrombotic risk in children. Extreme thrombocytosis is rare, and it can be more worrisome for infection, iron deficiency, or other inflammatory pathology. However, even extremely elevated platelet counts do not seem to increase risk of hemorrhage or thrombosis. Thus most often, thrombocytosis will resolve spontaneously, or after treatment of the inciting etiology, without adverse sequelae.

Thrombocytopenia is defined as platelets count <150 × 10^9 platelets/L blood. However, increased bleeding risk does not typically occur unless platelet counts decline to <20 × 10^9 platelets/L. Congenital and acquired processes underlie a broad differential diagnosis for thrombocytopenia that is described in Chapter 533. Different immune and nonimmune processes can cause thrombocytopenia at different stages of infancy or later childhood, with wide-ranging health implications.

NEUTROPENIA

White blood cells provide innate and adaptive immune functions. The neutrophil is a key component of innate immune surveillance, and disorders that affect neutrophil number and function can result in varied clinical consequences (see Chapter 168).

Neutropenia is defined as an absolute neutrophil count (ANC) <1,500/μL blood, but typically increases infection risk only when ANC falls <500/μL. Many processes affecting the survival of neutrophils and their precursor cells can cause neutropenia, including situations wherein antineutrophil antibodies increase neutrophil destruction and clearance.

Autoimmune neutropenia results from a patient's own neutrophil-targeted antibodies. It is among the most common etiologies of neutropenia in infants and toddlers, rarely results in significant infections or complications, and generally resolves by the time the child is school age. Neonatal isoimmune neutropenia results from transplacental passage of maternal antineutrophil antibodies in a process akin to red blood cell (RBC) antigen-targeted antibodies in hemolytic disease of the fetus and newborn (see Chapter 140). Importantly, these scenarios do not typically incur additional infection risks for patients. In fact, they are typically diagnosed incidentally after noting abnormalities on a complete blood count obtained for other reasons. Reassurance, with or without repeat laboratory testing, is typically all that is required. Counts will virtually always normalize spontaneously.

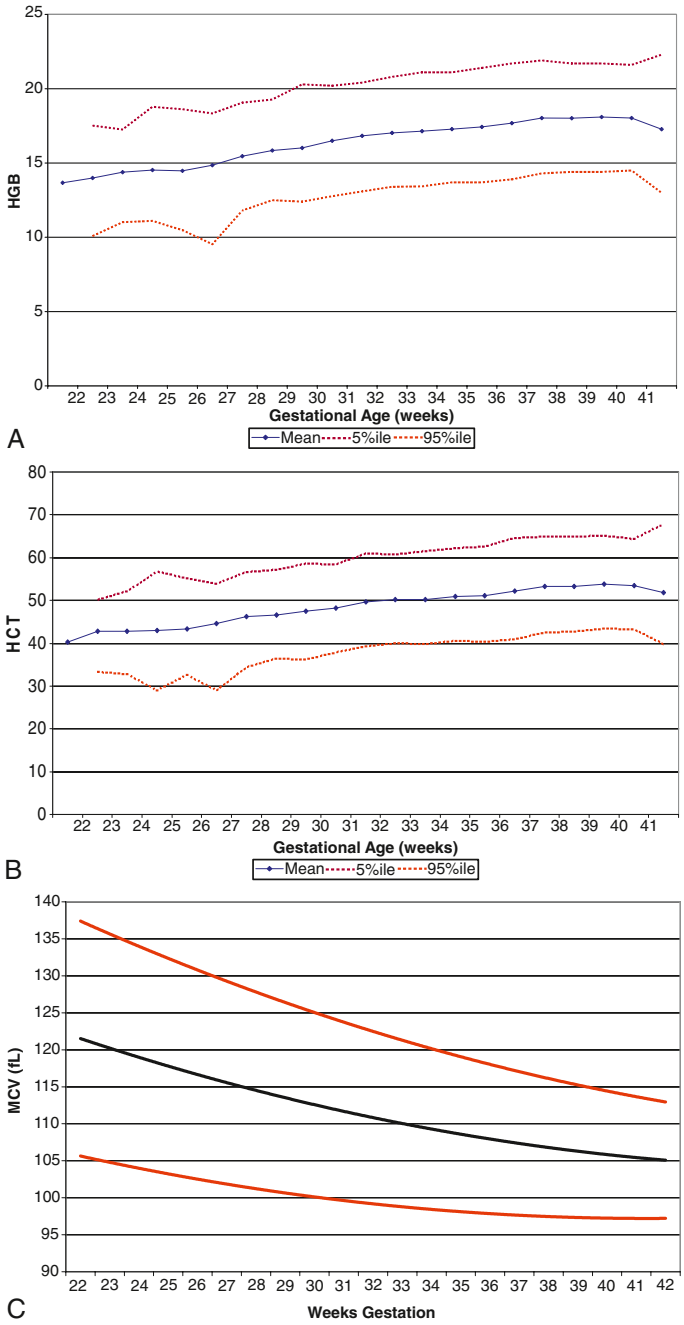

Fig. 138.2 Reference range for hematocrit (HCT) and hemoglobin (HGB) concentration according to gestational age. A and B, Reference ranges (5th percentile, mean, and 95th percentile) are shown for blood HGB (A) and HCT (B). Concentrations were obtained during the first 6 hours after birth, among patients at 22-42 weeks of gestation. Values were excluded if the diagnosis included abruption, placenta previa, or known fetal anemia, or if a blood transfusion was given before the first HGB was measured. C, Reference ranges for mean corpuscular volume (MCV) in neonates on first day after birth. The *lower line* shows the 5th percentile values, the *middle line* shows the mean values, and the *upper line* shows the 95th percentile values. (*From Christensen RD, Jopling HE, Jopling J, Wiedmeier SE. The CBC: Reference ranges for neonates. Semin Perinatol. 2009;33[1]:3–11.*)

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 139

Anemia in the Newborn Infant

Christopher S. Thom and Michele P. Lambert

Anemia is extremely common worldwide, affecting an estimated 25% of the global population, and carries a broad differential diagnosis in infants and children. Etiologies may be acute or chronic, with clinical manifestations ranging from an asymptomatic laboratory finding to life-threatening signs and symptoms. Because anemia can result from decreased erythrocyte production, increased erythrocyte destruction, erythrocyte dysfunction, or blood loss, the differential diagnosis of anemia can be complex (Table 139.1). Careful consideration of details related to the patient's history and presentation can facilitate rapid diagnosis. Additional relevant details in neonates include gestational age and general health, perinatal course and delivery, and maternal health from early pregnancy through delivery and the postpartum period.

THE PHYSIOLOGIC NADIR DURING INFANCY

An abrupt increase in oxygen tension and arterial hemoglobin saturation, a shift in the oxygen dissociation curve due to a switch from high oxygen affinity fetal hemoglobin (HbF) to low oxygen affinity adult hemoglobin (HbA), increased postnatal 2,3-diphosphoglycerate (increasing oxygen delivery through cooperativity), and adaptive cardiovascular mechanisms all contribute to increased oxygen delivery to tissues and can rapidly reduce erythropoietin levels postnatally. These mechanisms result in reduced erythropoiesis in the bone marrow after a week of life. Combined with the shorter half-life of neonatal erythrocytes compared to adult erythrocytes (60 days vs 120 days), full-term infants normally experience a slow decline in hemoglobin to 9-11 g/dL over 6-10 weeks (Fig. 139.1). Eventually, the reduction in hemoglobin concentration reduces oxygen delivery enough to stimulate erythropoietic drive, and hemoglobin levels subsequently rebound to "normal" levels for later life (see Fig. 139.1). These typical developmental and physiologic processes culminating in a decreased hemoglobin level are termed the **physiologic nadir**.

Preterm infants experience a more pronounced, earlier nadir, with hemoglobin levels falling to 8-9 g/dL over 4-8 weeks. One reason for the more dramatic nadir in preterm infants is reduced iron stores, because most iron is normally transferred to the fetus during the third trimester. The nadir in preterm infants is also a consequence of a reduced starting hemoglobin at birth; iatrogenic blood loss; and more significant cardiorespiratory disease, inadequate nutrition, and infections. Still, a hemoglobin level <8 typically prompts a transfusion and/or hematologist consultation.

Normal physiologic changes in hemoglobin concentration should be considered when diagnosing anemia in neonates and early infants. For example, a neonate may be considered anemic if the hemoglobin level declines below the 5th percentile for age (see Fig. 139.1, lower dashed lines). *Interventions should occur only in response to clinical signs and symptoms that occur as disease sequelae with referral to subspecialty care for further evaluation and management as appropriate.*

ANEMIA CLASSIFICATIONS AND KEY DIAGNOSTIC MODALITIES

Anemia can result from blood loss, erythrocyte destruction (hemolysis), or underproduction of erythrocytes. Common etiologies are summarized in Table 139.1. In many cases, the clinical context, physical examination, and medical history, including review of the patient's history and clinical course, can be diagnostic. However, a simple and efficient laboratory workup can facilitate rapid definitive diagnosis and suggest an effective treatment strategy (Fig. 139.2).

In many cases, a CBC and the reticulocyte count can identify the diagnosis. Additional testing that is particularly helpful in neonatal diagnosis includes a direct antiglobulin test, serum bilirubin, infant blood type, and maternal blood type (ABO and Rh). Prenatal screening routinely includes indirect (serum) antiglobulin testing for maternal erythrocyte alloantibodies. The infant's peripheral blood smear can identify nucleated erythrocytes secondary to compensatory active erythropoiesis, as well as distinct erythrocyte morphologies (e.g., elliptocytes, acanthocytes) reflecting hemolytic anemia. Spherocytes and microspherocytes can suggest immune-mediated hemolysis or hereditary spherocytosis (HS), which can be differentiated by the direct antiglobulin test (DAT; formerly the direct Coombs test; Fig. 139.3). Importantly, neonatal blood smears often include atypical erythrocyte morphology with macrocytosis, poikilocytosis, and anisocytosis, which can result from normal erythropoiesis at that age and preclude definitive diagnosis. An experienced hematology-pathologist is needed to identify truly pathologic features (Table 139.2; see Chapter 496).

Specialized testing to diagnose various red cell membrane disorders and enzyme deficiencies, as well as hemoglobin quantitation for evaluation for specific hemoglobin disorders, may be performed in consultation with a specialist. Some states routinely screen newborns for glucose-6-phosphate-dehydrogenase (G6PD) deficiency. Further, universal screening in the United States for sickle cell disease has markedly improved health outcomes by facilitating early penicillin prophylaxis, although much work remains to be done.

Inadequate Red Blood Cell Production

Whereas normal RBC underproduction after birth results in the **physiologic nadir**, this process can be more significant in preterm infants, requiring transfusions and other supportive therapy. **Anemia of prematurity** is largely due to iatrogenic losses (phlebotomy) and is exacerbated by acute or chronic illness, comorbidities of prematurity, and decreased iron stores.

Iron-deficiency anemia is the most common cause of anemia worldwide, and can occur during infancy or in older children. Iron is required

Table 139.1 Differential Diagnosis of Neonatal Anemia

BLOOD LOSS	↑ RBC DESTRUCTION	↓ RBC PRODUCTION
• Iatrogenic blood loss (phlebotomy) • Placental hemorrhage • Placental previa • Injury of umbilical or placental vessels • Fetomaternal transfusion • Fetoplacental transfusion • Twin-twin transfusion • Acute perinatal hemorrhage (e.g., cesarean birth, other obstetric trauma) • Chronic in utero blood loss	*Immune-Mediated Hemolysis* • Rh incompatibility • ABO incompatibility • Minor antigen incompatibility *RBC Membrane Disorders* • Hereditary spherocytosis • Hereditary elliptocytosis • Hereditary pyropoikilocytosis • Hereditary stomatocytosis *RBC Enzyme Disorders* • G6PD deficiency • Pyruvate kinase deficiency	• Physiologic anemia and anemia of prematurity • Infection (rubella, CMV, parvovirus B19) • Bone marrow suppression (acute stress in perinatal period) • Hemoglobinopathy (γ-globin mutation, unstable β-hemoglobinopathy, α-thalassemia major) • Bone marrow suppression (CMV, EBV) • Diamond-Blackfan anemia • Schwachman-Diamond syndrome • Congenital dyserythropoietic anemia • Fanconi anemia • Pearson syndrome • Congenital leukemia

CMV, Cytomegalovirus, EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase.

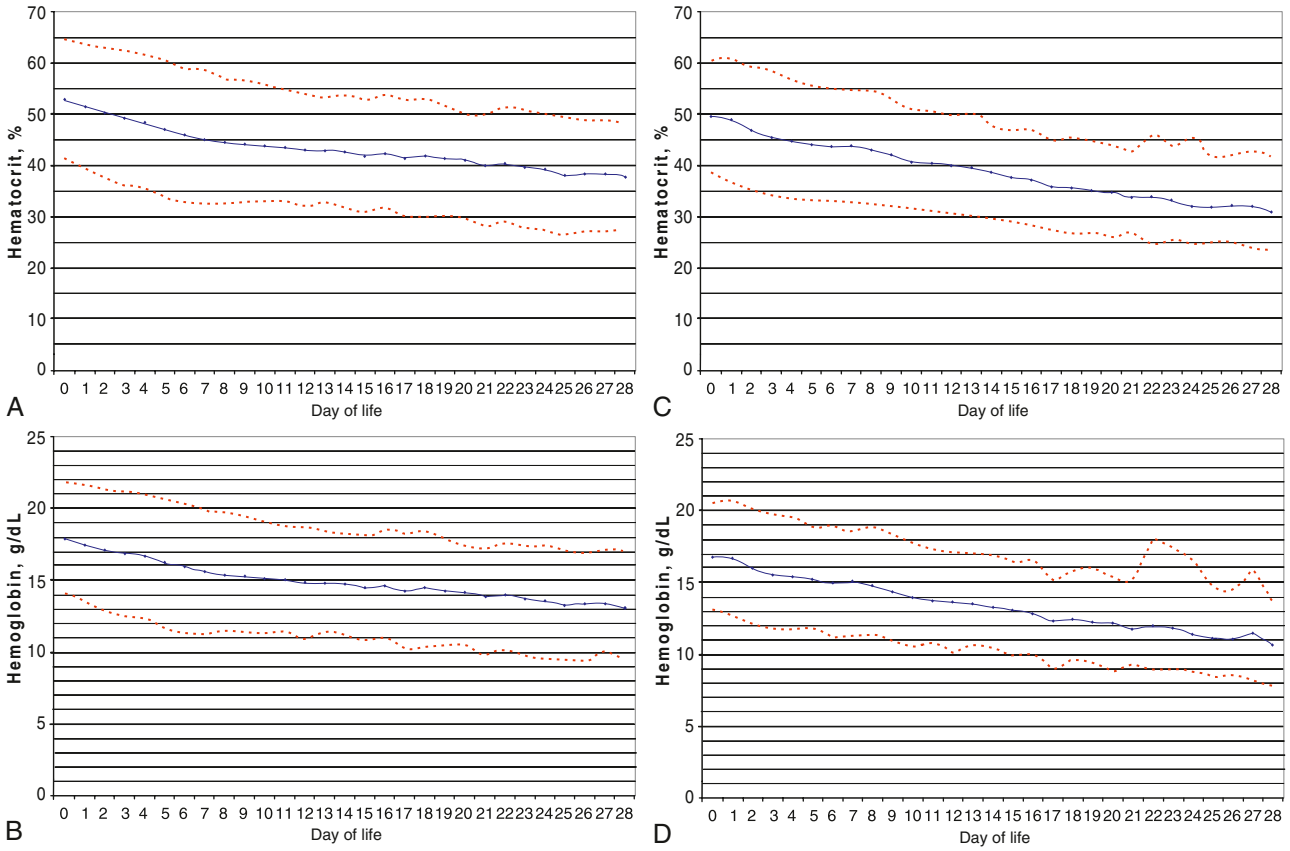

Fig. 139.1 Reference range for hematocrit and hemoglobin concentration during the first 28 days of life. **A** and **B**, Late preterm and term infants (35-42 weeks' gestation). **C** and **D**, Preterm infants (29-34 weeks' gestation). The reference ranges are shown for hematocrit (**A** and **C**) (41,957 patients) and blood hemoglobin (**B** and **D**) (39,559 patients) during the 28 days after birth. Values were divided into two groups (A/B and C/D) on the basis of gestational age at delivery. Patients were excluded when their diagnosis included abruption, placenta previa, or fetal anemia, or when a blood transfusion was given. Analysis was not possible for patients <29 weeks' gestation because virtually all these had repeated phlebotomy and erythrocyte transfusions. (*From Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. Pediatrics. 2009;123[2]:e333–e337.*)

for hemoglobin tetramer construction, so erythropoiesis demands ample iron be present to form hemoglobinized RBCs. Insufficient iron stores, either through chronic blood loss or inadequate iron intake, hinder erythropoiesis. RBCs will be uniformly microcytic (mean corpuscular volume [MCV] <80 fL) and hypochromic on the blood smear. Ferritin, transferrin, and reticulocyte quantities will be low. In addition to anemia, iron deficiency predisposes to thrombocytosis. This is a result of effects on hematopoietic progenitor cell lineage commitment, among potential mechanisms. Iron supplementation at doses of 3-6 mg/kg/day can effectively treat this condition; once-daily treatment is better than divided doses due to potential induction of hepcidin with frequent iron supplementation.

Acquired conditions may also suppress bone marrow erythrocyte production in neonates and older children (Table 139.3). Numerous bacterial and viral infections may suppress erythropoiesis and contribute to anemia, from prenatal TORCH (toxoplasmosis, other viral agents, rubella, cytomegalovirus [CMV], herpes simplex) infections and parvovirus B19 to sepsis. Congenital conditions may result in anemia due to decreased red cell production. These rare disorders may manifest early in the neonatal period, but more commonly present in later infancy or early childhood. Etiologies include the bone marrow failure syndromes (Fanconi anemia, Schwachman-Diamond syndrome, Diamond-Blackfan anemia, Aase syndrome congenital dyserythropoietic anemia, dyskeratosis congenita, Pearson syndrome), the thalassemias (α, β, or HbE), and infant leukemias, among others (see Tables 139.1 and 139.3).

Increased Red Cell Destruction: The Hemolytic Anemias

Increased rates of RBC destruction cause hemolytic anemia. This most often occurs via immune-mediated mechanisms, when RBC antigen incompatibilities exist between infants and mothers, or as a result of autoimmune disease in later childhood. However, intrinsic abnormalities in the erythrocyte membrane, hemoglobin, or other enzymes can also increase hemolysis. Severe hemolytic anemias can cause hyperbilirubinemia necessitating intervention (Fig. 139.4). For example**, hemolytic disease of the fetus and newborn (HDFN),** also known as erythroblastosis fetalis, results in often severe alloimmune hemolysis from maternal antibodies targeting paternally derived RBC antigens (see Chapter 140).

Congenital erythrocyte membrane disorders can cause clinically significant hemolytic anemia and jaundice in the neonatal period and beyond. Key structural proteins and lipid components are necessary to produce durable, flexible, biconcave erythrocyte membranes capable of deforming and squeezing through tiny capillaries. Genetic abnormalities in integral membrane proteins (e.g., ankyrin, band 3, α-spectrin, β-spectrin, protein 4.2) destabilize the RBC membrane and decrease cellular deformability, increasing splenic entrapment. HS is the most common RBC membrane disorder, affecting 1 in 2,500-5,000 individuals of European descent. HS is most often caused by pathogenic variants in genes coding for ankyrin or spectrin and is characterized by spherical erythrocytes on the blood smear (see Fig. 139.3; see Chapter 507). Most infants born with HS will develop jaundice early in the newborn period. *Treatment is largely supportive. Most patients with mild disease require little intervention, whereas those with more severe hemolysis sometimes require RBC transfusions or splenectomy.* Hereditary elliptocytosis (HE), another erythrocyte membranopathy, is typically less severe than HS. HE is characterized by elliptical-shaped erythrocytes on the peripheral blood smear and may be underdiagnosed given the extremely mild clinical presentation.

A more clinically significant membranopathy is hereditary pyropoikilocytosis (HPP), an autosomal recessive disorder with striking dysmorphology (poikilocytosis) on the peripheral blood smear. HPP is most common

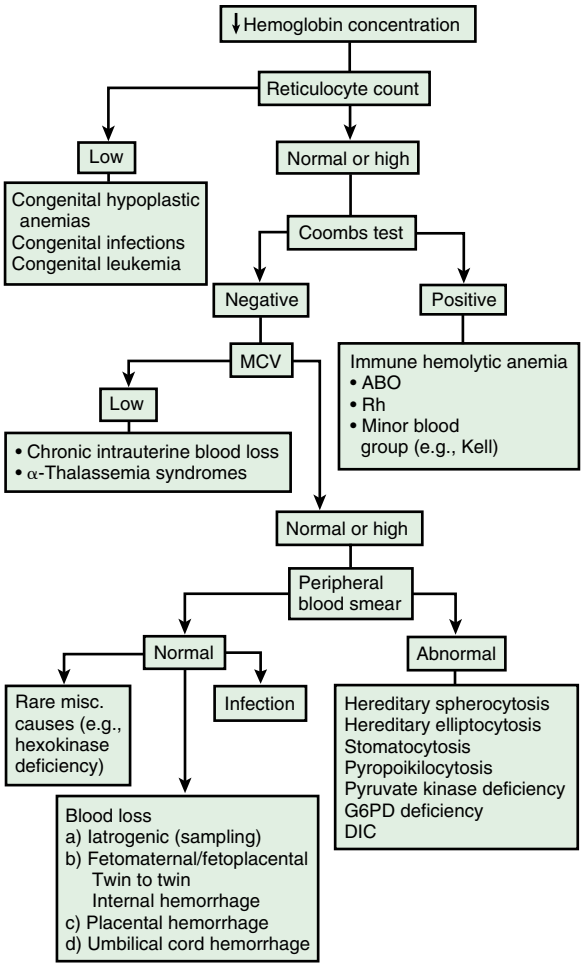

Fig. 139.2 Diagnostic algorithm showing the approach to anemia in newborn infants. DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; MCV, mean corpuscular volume. (*Modified from Blanchette VS, Zipursky A. Assessment of anemia in newborn infants. Clin Perinatol. 1984;11:489–510.*)

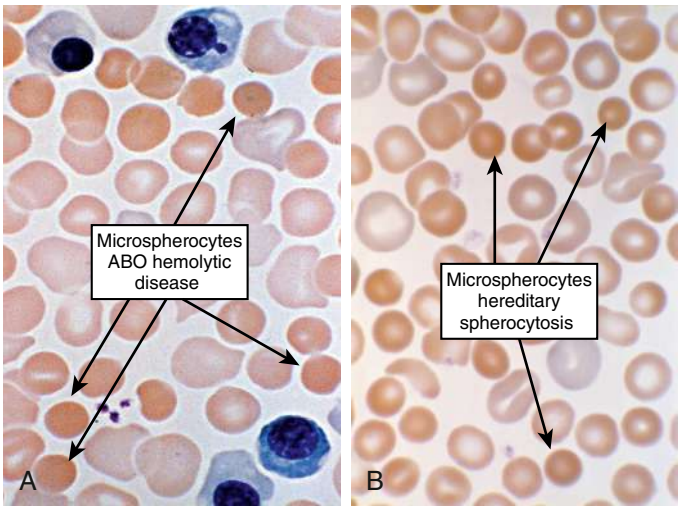

Fig. 139.3 Microspherocytes. **A,** Neonate with ABO hemolytic disease. **B,** Neonate with hereditary spherocytosis. (*From Christensen RD. Neonatal erythrocyte disorders. In Gleason CA, Juul SE, eds. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018: Fig. 81-8.*)

in infants of African descent and can be associated with severe anemia and hemolysis during infancy and throughout life. There is substantial clinical and genetic overlap between HPP and HE, because infants with HPP often have a family history of HE and may develop a milder condition resembling HE later in childhood (see Chapter 508).

In infants with significant jaundice in the first day of life without a blood type mismatch, a family history of hemolytic anemia should prompt clinical suspicion for an erythrocyte membranopathy. Beyond a negative DAT, diagnostic evaluation should include serial bilirubin and reticulocyte monitoring, along with a peripheral blood smear. Previously, osmotic fragility testing was the only way to establish the diagnosis, but it is significantly impacted by hemoglobin F concentrations. Some laboratories can instead diagnose certain membranopathies by flow cytometry based on binding of eosin-5-maleimide (EMA). Treatment is directed by the degree of anemia and hyperbilirubinemia, which can be highly variable.

Erythrocyte enzymopathies can also cause neonatal anemia. Circulating RBC survival relies on critical metabolic pathways to limit oxidative stress. Inadequate antioxidant systems can result in membrane instability and cell lysis that manifest clinically as hemolytic anemia. For example, G6PD is abundant in RBCs to limit oxidative stress. G6PD deficiency, the most common RBC enzymopathy, is an X-linked disorder affecting >400 million people worldwide. Different classes of G6PD deficiency vary in clinical severity. Although affected individuals are generally asymptomatic, some are prone to develop acute hemolytic anemia in the setting of oxidative stress triggered by sulfa drugs, infections, or certain foods like fava beans. There is an increased incidence of clinically significant jaundice in G6PD deficient neonates, who sometimes have severe and prolonged hyperbilirubinemia that can present in the first few days of life. Although severe anemia with reticulocytosis is uncommon, many infants require increased monitoring or therapy. Newborn screening for G6PD deficiency varies across the United States. G6PD activity can be tested in erythrocytes (<1–2% suggests G6PD deficiency). However, testing may be inaccurate during acute hemolysis or reticulocytosis because, for the most common variants, reticulocytes have higher enzyme activity.

Another common RBC enzymopathy is pyruvate kinase deficiency (PKD), which affects an estimated 3.2-8.5 per million individuals of European descent. Pyruvate kinase is a critical glycolytic enzyme. In its absence, metabolic derangements can cause RBC lysis and hemolytic anemia. Though clinical severity varies, PKD may be associated with sometimes life-threatening complications, prolonged jaundice, and lifelong blood transfusions.

HEMOGLOBINOPATHIES

Hemoglobinopathies result from genetic variants in γ-globin, β-globin, or α-globin genes. The clinical presentation of hemoglobin variants reflects aberrant biochemical properties of the mutated hemoglobin molecule. Individuals can be anemic (most commonly), cyanotic, polycythemic, prone to hemolysis, have high methemoglobin levels, or asymptomatic. Thousands of variants have been identified, with wide-ranging clinical severity.

Hemoglobin variants can also clinically manifest at different times according to when the affected globin chain is produced (see Fig. 138.1). The common β-hemoglobinopathies, sickle cell disease and β-thalassemia, do not typically present in the neonatal period due to protective effects from high HbF levels. In fact, novel therapeutic approaches aim to maintain HbF persistence in sickle cell patients. In contrast, infants with rare γ-globin variants can present with complications in the neonatal period that resolve in the first few months of life as normal gene expression changes to reduce or abrogate γ-globin expression.

Hemorrhage and Red Blood Cell Loss

Blood loss or hemorrhage in utero or in the newborn period can also result in anemia. In fact, iatrogenic or pathologic blood loss is the most common cause of neonatal anemia. For critically ill and/or premature infants in the neonatal intensive care unit (NICU), laboratory monitoring can require phlebotomy of 15–30% of an infant's blood volume every week (~11-22 mL/kg/week). Most other blood loss etiologies occur just before or during delivery, often from placental abruption or fetal hemorrhage (see Table 139.1). Infants can also become anemic from occult gastrointestinal blood losses due to milk protein allergy. Other causes of blood loss are restricted

Table 139.2 Morphologic Abnormalities of Erythrocytes in Neonates with Jaundice

ABNORMAL ERYTHROCYTE MORPHOLOGY	MOST LIKELY CAUSES	SUGGESTED LABORATORY TESTING/FINDINGS	OTHER FEATURES
Microspherocytes	Hereditary spherocytosis	DAT (–) EMA flow (+) Persistent spherocytosis Reticulocytosis	MCHC/MCV elevated (>36, likely >40)
	ABO hemolytic disease	DAT (+) Transient spherocytosis Reticulocytosis	MCHC/MCV normal (<36, likely <34)
Elliptocytes	Hereditary elliptocytosis	DAT (–)	MCHC normal MCV normal
Bite and blister cells	G6PD deficiency Unstable hemoglobin	G6PD enzyme activity Heinz body preparation	Typically affects males, but rarely females are also affected Ethnicity of equatorial origin
Echinocytes	PK deficiency Other glycolytic enzyme deficiency	PK enzyme activity Quantify activity of other glycolytic enzymes	Autosomal recessive, likely to have no family history
Schistocytes	DIC and/or perinatal asphyxia	Low levels of FV and FVIII, elevated levels of D-dimers	Low or falling platelet count Normal to high IPF
	Heinz body HA	Positive result of Heinz body preparation	Normal to high MPV DIC, perinatal asphyxia
	ADAMTS-13 deficiency (TTP)	Severely decreased ADAMTS-13 activity (<0.1 U/mL) high levels of LDH	ADAMTS-13 deficiency, early neonatal HUS, and giant hemangiomas all involve platelet consumption from endothelial injury and all have a similar neonatal presentation
	Neonatal hemolytic-uremic syndrome	Acute renal failure	
	Homozygous protein C deficiency	Severely decreased functional protein C activity (<1%)	
	Giant hemangioma	May be internal or external	

DAT, Direct antiglobulin test; DIC, disseminated intravascular coagulation; EMA, eosin 5-maleimide; FV, factor V; FVIII, factor VIII; G6PD, glucose-6-phosphate dehydrogenase; HA, hemolytic anemia; HUS, hemolytic uremic syndrome; IPF, immature platelet fraction; LDH, lactic dehydrogenase; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PK, pyruvate kinase; TTP, thrombotic thrombocytopenic purpura.
From Christensen RD, Yaish HM. Hemolytic disorders causing severe neonatal hyperbilirubinemia. *Clin Perinatol*. 2015;42:515–527. Table 3.

Table 139.3 Syndromes Associated with Congenital Hyporegenerative Anemia

SYNDROME	PHENOTYPIC FEATURES	GENOTYPIC FEATURES
Adenosine deaminase deficiency	Autoimmune hemolytic anemia, reduced erythrocyte adenosine deaminase activity	AR, 20q13.11
Congenital dyserythropoietic anemias	*Type I (rare):* megaloblastoid erythroid hyperplasia and nuclear chromatin bridges between nuclei *Type II (most common):* hereditary erythroblastic multinuclearity with positive acidified serum test result, increased lysis to anti-I antibodies *Type III:* erythroblastic multinuclearity ("gigantoblasts"), macrocytosis	*Type I:* 15q15.1-q15.3 *Type II:* 20q11.2 *Type III:* 15q21
Diamond-Blackfan syndrome	Steroid-responsive hypoplastic anemia, often macrocytic after 5 mo of age	AR; sporadic gene variants and AD inheritance described; 19q13.2, 8p23.3-p22
Dyskeratosis congenita	Hypoproliferative anemia usually presenting between 5 and 15 yr of age	X-linked recessive, locus on Xq28; some cases with AD inheritance
Fanconi syndrome	Steroid-responsive hypoplastic anemia, reticulocytopenia, some macrocytic RBCs, shortened RBC life span Cells are hypersensitive to DNA cross-linked agents	AR, multiple genes: complementation; group A 16q24.3; group B Xp22.3; group C 9q22.3; group D2 3p25.3; group E 6p22-p21; group F 11p15; group G 9p13
Osler hemorrhagic telangiectasia syndrome	Hemorrhagic anemia	AD, 9q34.1
Osteopetrosis	Hypoplastic anemia from marrow compression; extramedullary erythropoiesis	AR, 16p13, 11q13.4-q13.5; AD, 1p21; lethal, reduced levels of osteoclasts
Pearson syndrome	Hypoplastic sideroblastic anemia, marrow cell vacuolization	Pleioplasmatic rearrangement of mitochondrial DNA; X-linked or AR
Peutz-Jeghers syndrome	Iron-deficiency anemia from chronic blood loss	AD, 19p13.3
ATR-X and ATR-16 syndromes	ATR-X: hypochromic, microcytic anemia; mild form of hemoglobin H diseaseATR-16: more significant hemoglobin H disease and anemia are present	ATR-16, 16p13.3, deletions of α-globin locus

AD, Autosomal dominant; AR, autosomal recessive; ATR-16, chromosome 16–related α-thalassemia/mental retardation; ATR-X, X-linked α-thalassemia/mental retardation.
From Christensen RD. Neonatal erythrocyte disorders. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*. 10th ed. Philadelphia: Elsevier; 2018: Table 81-2.

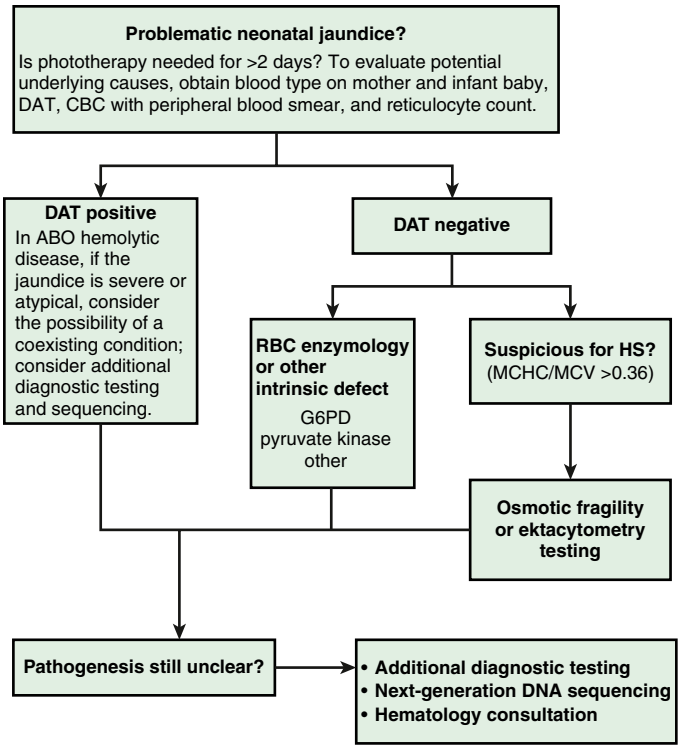

Fig. 139.4 Algorithm for the evaluation of the neonate with problematic jaundice of unclear cause. Not all neonates who receive phototherapy for 2 days or more have hemolytic jaundice. However, if hemolytic jaundice is suspected, this algorithm for stepwise evaluation of the cause might be useful. DAT, Direct antiglobulin test; G6PD, glucose 6-phosphate dehydrogenase; HS, hereditary spherocytosis; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume. (*From Christensen RD. Neonatal erythrocyte disorders. In Gleason CA, Juul SE, eds. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018: Fig. 81-15.*)

to older children, including celiac disease or menstrual bleeding. Diagnosis and treatment of hemorrhage in the newborn period are discussed in Chapter 142.

Fetomaternal hemorrhage (FMH) is caused by abnormal bleeding from fetal to maternal circulation before or during delivery. Although small amounts of FMH can be normal, more substantial pathologic FMH (>30 mL of fetal blood) occurs in 3 per 1,000 births. In comparison, large (>80 mL) or massive (>150 mL) FMH occurs in 0.9 and 0.2 per 1,000 births, respectively. Clinical signs of FMH vary due to differential fetal compensation. Decreased or absent fetal movement is the most common antenatal presentation and should prompt clinical suspicion. Postnatally, infant pallor, tachycardia, hypotension, and poor perfusion can indicate clinically significant anemia.

A standard diagnostic modality for FMH is the Kleihauer-Betke test, which leverages the differential stability of HbF vs HbA on acid exposure to identify fetal erythrocytes in the maternal circulation from a maternal blood smear (Fig. 139.5). However, this test requires technical skill, expert interpretation, and may not be available in a timely manner. Some laboratories now offer flow cytometry–based assays to quantify fetal RBCs in maternal circulation.

ANEMIA MANAGEMENT PRINCIPALS

Red Blood Cell Transfusions

The decision to transfuse packed RBC for anemia depends on the severity of symptoms, the hemoglobin concentration, and the presence of comorbidities that can alter oxygen delivery, such as pulmonary hypertension, bronchopulmonary dysplasia, cyanotic congenital heart disease, or other respiratory pathology. Benefits should be balanced against risks, including volume overload, hemolytic and nonhemolytic reactions, exposure to blood product preservatives and toxins, graft-versus-host reaction, and transfusion-acquired infections such as

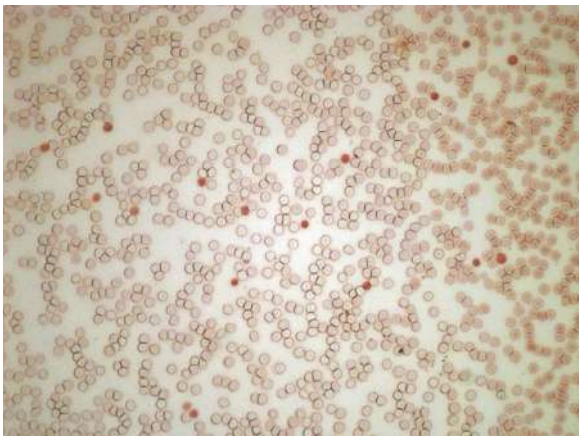

Fig. 139.5 Acid elution technique of Kleihauer (Kleihauer-Betke test). Fetal red blood cells stain with eosin and appear dark. Adult RBCs do not stain and appear as "ghosts." (*From Liley HG, Gardener G, Lopriore E, Smits-Wintjens V. Immune hemolytic disease. In Orkin SH, Nathan DG, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier; 2015: Fig. 3-2.*)

Table 139.4 Suggested Transfusion Thresholds

	PRESENCE OF RESPIRATORY SUPPORT	ABSENCE OF RESPIRATORY SUPPORT
POSTNATAL AGE	HEMOGLOBIN CONCENTRATION g/dL (HEMATOCRIT %)	
Week 1	11.0 (33%)	10.0 (30%)
Week 2	10.0 (30%)	8.5 (25%)
Week 3	8.5 (25%)	7.0 (21%)

Values based on thresholds described in Kirpalani H, Bell EF, Hintz SR, et al. Higher or lower hemoglobin transfusion thresholds for preterm infants. *N Engl J Med.* 2020;383(27):2639–2651.

CMV, HIV, parvovirus, hepatitis B, and hepatitis C (see Chapter 523). Transfusion decisions should also consider the time course in which anemia developed, whether ongoing blood loss or hemolysis are anticipated, and if there are any planned surgical interventions.

Many neonates in the NICU require RBC transfusions, particularly among premature and very low birthweight (VLBW) infants. Several trials to compare restrictive (lower) to liberal (higher) transfusion thresholds have shown no significant differences in death or serious morbidity, with restrictive thresholds modestly reducing blood product exposure. These studies provide the basis for neonatal transfusion guidelines based on postnatal age and respiratory support needs (Table 139.4). *In full-term anemic infants, RBC transfusions should be similarly based on hemodynamic stability, respiratory status, clinical status, and expected clinical trajectory.*

To reduce blood product-associated CMV transmission to vulnerable infants, it is important that transfused RBCs are leukocyte reduced or CMV seronegative. There remains a small risk of transfusion-associated graft versus host disease even after RBC irradiation. Although data do not support specific transfusion volumes, the typical range is from 10-20 mL/kg. Infants at risk of volume overload, including neonates with congenital cardiac disease or who were born in the setting of chronic abruption, are typically given smaller volume transfusions (often 5 mL/kg). *One logical goal of RBC transfusions is to target a specific goal hemoglobin concentration.* Each 5 mL/kg of transfused RBCs is expected to raise the hemoglobin concentration by 1 g/dL.

Transfusion of RBCs is typically delivered at a rate of 3-5 mL/kg/hr, with a slower rate preferred for very small, acutely ill infants with a tenuous fluid status. Each transfusion should be completed within 4 hours, or before a given blood product expires.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 140

Hemolytic Disease of the Fetus and Newborn

Christopher S. Thom and Michele P. Lambert

Hemolytic disease of the fetus and newborn (HDFN), also known as **erythroblastosis fetalis**, is a broad diagnosis that applies to any fetus or neonate who develops alloimmune hemolysis caused by the transplacental passage of maternal antibodies directed against paternally derived red blood cell (RBC) antigens. Although more than 60 different RBC antigens can elicit a maternal antibody response, clinically significant disease is most often associated with incompatibility in ABO blood groups or rhesus (Rh) antigen (Table 140.1). HDFN caused by anti-RhD antibodies, occurring in RhD-positive infants born to RhD-negative mothers, is the most severe form because of the highly immunogenic nature of the RhD antigen. Less frequently, hemolytic disease may be caused by differences in other Rh system antigens, or by other RBC antigens such as C^W, C^X, D^U, K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. *Early recognition and diagnosis facilitate timely interventions to prevent adverse sequelae.*

HDFN CAUSED BY Rh INCOMPATIBILITY

Pathogenesis

Rh antigenic determinants are genetically transmitted from each parent and determine Rh blood type by directing the production of Rh C, c, D, E, or e proteins to be expressed on the RBC surface. RhD alloimmunization is responsible for 90% of HDFN cases involving the Rh antigen system, but other Rh antigens, particularly E and c, can be causal. Rh sensitization usually occurs in the first pregnancy when small amounts of blood (usually >1 mL) enter maternal circulation so that most instances of sensitization occur around the time of delivery. Although sensitization may occur earlier in the first pregnancy resulting in some hemolysis, HDFN rarely occurs during a first pregnancy. After sensitization, smaller doses of antigen can stimulate antibody production, so all subsequent infants expressing the cognate antigen are at risk for HDFN. For this reason, the severity of HDFN also typically worsens with successive pregnancies. *Routine administration of Rh immunoglobulin (RhoGAM) to mothers at risk for Rh alloimmunization, both at 28 and 32 weeks' gestation and within 72 hours after delivery of Rh-positive infants, has reduced initial sensitization to an estimated <0.1% of at-risk pregnancies in high-income countries.*

Clinical Manifestations

The severity of HDFN is variable, ranging from mild hemolysis without overt symptoms to severe anemia with compensatory hyperplasia of erythropoietic tissues, including massive hepatosplenomegaly. When hemolysis exceeds the compensatory regenerative capacity of the hematopoietic system, profound anemia, thrombocytopenia, coagulopathy, cardiomegaly, respiratory distress, massive anasarca, and circulatory collapse can result. Perinatal hemoglobin concentrations may be as low as 3-4 g/dL.

HDFN can also cause abnormal fluid collection in two or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), a clinical scenario termed **hydrops fetalis,** which frequently results in significant clinical morbidity or death in utero or shortly after birth. Hydrops results from heart failure along with subsequent hepatic congestion and dysfunction. This leads to reduced serum albumin and loss of intravascular oncotic pressure. Consequent edema can lead to extravascular fluid accumulation in the lungs (pleural effusion), abdomen (ascites), and elsewhere, which can compromise ventilation and lead to a range of life-threatening complications (Fig. 140.1). Hydrops is typically present when the fetal hemoglobin level is <5 g/dL but can occur when hemoglobin levels are between 7 and 9 g/dL. Hydrops does not invariably occur with low hemoglobin concentration, instead depending on the duration of anemia and the gestational age when anemia developed.

Infants affected by HDFN may not be jaundiced at birth because of effective placental clearance of lipid-soluble unconjugated bilirubin. However, in severe cases, bilirubin pigments can stain the amniotic fluid, cord, and vernix. In either case, hyperbilirubinemia is generally evident within 24 hours of birth, as hemolysis overwhelms the infant's bilirubin clearance system. Extremely high levels of unconjugated bilirubin levels present a risk of bilirubin encephalopathy **(kernicterus)**, which is worsened in patients with concomitant hypoxia or acidosis.

Hypoglycemia may further complicate clinical management of infants with severe HDFN. This may be related to islet cell hypertrophy and hyperinsulinism due to growth stimulatory effects of anti-RhD antibodies on the pancreas.

Table 140.1 Etiologies of Hemolytic Disease of the Fetus and Newborn

	Rh	ABO	KELL
BLOOD GROUPS			
Mother	Rh-negative	O (occasionally B)	K1-negative
Infant	Rh-positive (D is most common)	A (sometimes B)	K1-positive
CLINICAL FEATURES			
Occurrence in firstborn	5%	40–50%	Rare
Severity in subsequent pregnancies:	Predictable	Difficult to predict	Somewhat predictable
Stillbirth/hydrops	Frequent (less with Rh-immunoglobulin use)	Rare	10%
Severe anemia	Frequent	Rare	Frequent
Jaundice	Prominent, severe	Mild-moderate	Mild
LABORATORY TESTS			
Direct antiglobulin test (infant)	Positive	Positive or negative	Positive or negative
Reticulocyte count	Elevated	Elevated	Variable
RBC antibodies (mother)	Usually detectable Antibody titers may help predict severity of fetal disease	May not be detectable Antibody titers may not correlate with fetal disease	Usually detectable Antibody titers may not correlate with fetal disease; fetus can be affected at titers lower than for Rh-mediated hemolysis

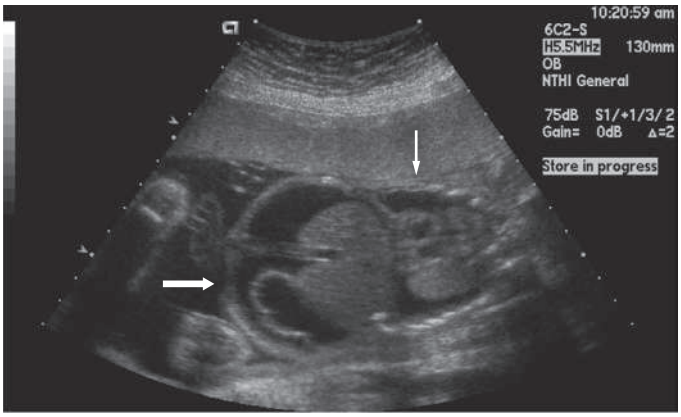

Fig. 140.1 Hydrops fetalis. Longitudinal sonographic image of the fetus, with ascitic fluid outlining the liver *(large arrow)*. The *small arrow* shows pleural effusion above the diaphragm. *(From Wilkins I: Nonimmune hydrops. In Creasy RK, Resnick R, Iams JD, et al., eds. Creasy & Resnik's Maternal-Fetal Medicine. 7th ed. Philadelphia: Elsevier; 2014: Fig. 37-2.)*

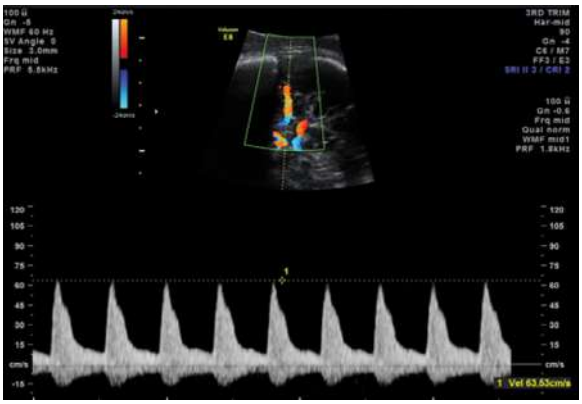

Fig. 140.2 Middle cerebral artery (MCA) Doppler study of elevated peak systolic velocity (PSV). MCA-PSV can predict fetal anemia with sufficient accuracy to determine management, including the need for intrauterine transfusion or, in the mid to late third trimester, early delivery. Fetal hemoglobin is typically measured at the start and end of intravascular transfusion to validate the prediction from MCA-PSV results. The reliability of MCA-PSV can decrease after intrauterine transfusion because of the altered rheostatic characteristics of transfused adult blood. This is now the method of choice for detecting fetal anemia. *(From Liley HG, Gardener G, Lopriore E, Smits-Wintjens V. Immune hemolytic disease. In Orkin SH, Nathan DG, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier' 2015: Fig. 3-6.)*

Diagnosis, Prevention, and Treatment

Definitive diagnosis of HDFN requires demonstration of blood group incompatibility between mother and infant, and corresponding maternal antibody bound to the infant's RBCs. However, severe clinical presentations strongly suggest the diagnosis. Emergent interventions may be required before definitive test results become available.

During pregnancy, expectant parents should have blood tested for potential blood type incompatibility, including ABO and Rh antigens. If RhD incompatible, maternal anti-RhD IgG titers should be measured early in pregnancy. Paternal blood can be tested to determine the fetal risk of inheriting the cognate antigen, typically either 50% or 100% depending on whether the father is heterozygous or homozygous. However, as paternal serologic testing alone is not fully accurate, molecular genotyping may be recommended for both parents.

Fetal genotyping provides an accurate prediction for the development of HDFN in sensitized mothers. Fetal Rh status is available by isolating fetal cells or cell-free fetal DNA from the maternal circulation. These methods are replacing amniocentesis and chorionic villus sampling methods and associated risks. Elevated antibody titers, or rising titers, correspond to increased HDFN risk.

Without Rh immunoglobulin prophylaxis, any Rh-negative woman with a previous pregnancy or abortion, prior exposure to transfused blood products, or receipt of an organ transplant is at risk for Rh sensitization. If a mother has had a previously affected infant or stillbirth, the Rh-positive infant is usually equally or more severely affected than the previous infant. Although there can be poor correlation between the anti-RhD titer level and disease severity, Rh-negative mothers found to have RhD antibody titers of ≥1:16 (15 IU/mL in Europe) at any time during a subsequent pregnancy warrant close monitoring for fetal anemia.

Pregnancies at risk for HDFN should be managed by maternal-fetal specialists. In some cases, monitoring must begin at 16-24 weeks' gestation. This is typically done via noninvasive Doppler ultrasonography of middle cerebral artery (MCA) flow velocity, which can be used to monitor for increased vascular resistance in fetal arteries indicative of **fetal anemia** (Fig. 140.2). Moderate to severe anemia increases MCA blood flow, so peak MCA flow velocity can be a quantitative correlate for anemia severity. Real-time ultrasound is used to detect signs of hydrops (skin or scalp edema, pleural or pericardial effusions, and ascites) and fetal heart rate monitoring. Early ultrasonographic signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. *In the setting of concerning ultrasonographic findings, percutaneous umbilical blood sampling (PUBS) can provide more direct assessment of fetal hemoglobin level and facilitate intrauterine transfusions.*

Although cord blood hemoglobin content typically varies in proportion to disease severity, hemoglobin may be within the normal range due to compensatory bone marrow and extramedullary hematopoiesis. Reticulocytosis will be present and a peripheral blood smear will show polychromasia with abundant nucleated RBCs. Thrombocytopenia may develop in severe cases. Umbilical cord bilirubin levels are generally between 3 and 5 mg/dL, including elevated direct bilirubin levels from cholestasis. Indirect-reacting bilirubin content rises rapidly in the first 6-12 hours of life.

Indications for delivery include fetal distress, complications during in utero interventions, and pulmonary maturity. Many affected infants are delivered preterm due to concerns for fetal well-being, after balancing risks of prematurity. The birth should be attended by a skilled neonatal resuscitation team familiar with the infant's prenatal course. *Because severe hemolytic anemia can cause rapid cardiovascular compromise, a team skilled in evaluation in management of HDFN should be involved when the diagnosis is suspected or confirmed, especially when there is a history of prior infants affected by HDFN.* Small packed RBC (PRBC) transfusions can be used to partially correct anemia, although volume expansion (e.g., large transfusions) risks worsening cardiac failure. Phototherapy may be necessary to treat hyperbilirubinemia in the first 24 hours of life if bilirubin levels exceed safe limits on an age-based nomogram (see Chapter 137). Although it is the indirect bilirubin fraction that crosses the blood-brain barrier to cause kernicterus, clinical decision-making is often based on total serum bilirubin levels.

Despite adequate resuscitation, phototherapy, and/or other empiric treatments, some infants with HDFN require exchange transfusions to treat anemia and/or hyperbilirubinemia. The decision to proceed with exchange transfusion is typically based on clinical status and trajectories in hemoglobin or serum bilirubin values, specifically the likelihood that serum bilirubin, plotted against postnatal hours of life, will reach a dangerous level (see Chapter 137). Signs and symptoms of kernicterus are absolute indications for exchange transfusion. Previous kernicterus or severe HDFN in a sibling, severe reticulocytosis >15%, or prematurity (with increased kernicterus risk) are additional factors to be considered in the decision to proceed with exchange transfusion (see Chapter 137).

Complications related to HDFN can also present weeks after birth, irrespective of the prenatal or perinatal course. Late anemia can present after 4-6 weeks of life, sometimes clinically manifesting as poor feeding or growth. This can result from ongoing hemolysis caused by persistent circulating maternal alloantibodies, or from hyporegenerative anemia caused by suppression of bone marrow erythropoiesis. These etiologies can be distinguished by reticulocyte count and bilirubin level, with ongoing hemolysis driving reticulocytosis and hyperbilirubinemia.

Neutropenia may also be observed in association with hyporegenerative anemia. Outpatient blood and reticulocyte counts should be monitored serially under the supervision of an expert hematologist to determine the need for interventions through bone marrow recovery. Iron supplementation or erythropoietin therapy can be helpful. In some cases, PRBC transfusions can be required for months after birth, until the infant's own erythropoietic system becomes more robust.

Hemolysis and hyperbilirubinemia can also cause late-onset complications. Jaundice typically resolves spontaneously within a few weeks or months with conservative management. Portal vein thrombosis and portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. This complication is thought to be seen in infants with prolonged, traumatic, or septic umbilical vein catheterization. Inspissated bile syndrome is another rare complication, associated with persistent icterus and significant elevations in both direct and indirect bilirubin levels.

The outcome for Rh-incompatible fetuses varies greatly, depending on the characteristics of both the RBC antigen and the maternal antibodies. Although fetal transfusions and prenatal interventions can ameliorate some complications, those with severe hydrops remain at risk for cerebral palsy, developmental delay, and deafness, requiring medical and procedural interventions for hydrops prenatally or after birth. Infants should be monitored closely for late complications by pediatric hematologists in the outpatient setting.

HDFN CAUSED BY ABO INCOMPATIBILITY

ABO incompatibility is the most common cause of HDFN, with approximately 20% of live births at theoretical risk. Of at-risk infants, clinical manifestations develop in 1–10% and are usually less severe than Rh disease, rarely requiring aggressive clinical management or therapeutic intervention aside from phototherapy. This is because naturally occurring maternal antibodies against ABO blood group antigens are mostly IgM and therefore do not cross the placenta. However, some group O mothers will naturally produce anti-A or anti-B IgG antibodies that can cross the placenta to cause immune-mediated hemolysis. For this reason, ABO incompatibility can cause hemolysis even in a firstborn infant. Another reason for mild disease manifestations is that fetal and neonatal RBCs have relatively low ABO expression, limiting binding sites for maternal antibodies.

Clinical Manifestations

Affected infants will typically develop jaundice in the first day of life. Severe clinical manifestations, such as hydrops, severe anemia, or hepatosplenomegaly, are rare. Diagnosis requires serologic ABO incompatibility between the mother and infant, a positive DAT, and hyperbilirubinemia with or without anemia. Affected infants often have mild anemia and reticulocytosis, with peripheral blood smears showing polychromasia, nucleated RBCs, and spherocytes. *Phototherapy may be required based on bilirubin level and postnatal age, and is typically effective in lowering serum bilirubin levels* (see Chapter 137). In some cases, hemolysis can persist for weeks until maternal antibodies are cleared. Intravenous immunoglobulin (IVIG) administration can help to limit hemolysis and potentially avoid exchange transfusion and/or PRBC transfusions in cases with dangerous levels of hyperbilirubinemia or anemia, respectively. Rarely, affected infants who also have hyporegenerative anemia can require PRBC transfusions several weeks after birth. For this reason, outpatient monitoring is essential for newborns with ABO hemolytic disease. However, the persistence of hemolytic anemia or spherocytosis beyond 2 weeks of age can indicate an alternative diagnosis, such as hereditary spherocytosis (see Fig. 139.3).

OTHER ETIOLOGIES OF HDFN

Incompatibility in blood group antigens other than Rh or ABO account for <5% of HDFN. Minor RBC antigen mismatch is emerging as a common cause of HDFN in the developed countries in which anti-RhD immune globulin is routinely used. The likelihood of minor antigen mismatches is a function of population frequency, antigen surface density on RBCs, and immunogenicity in the mother. In most cases, the infant's direct antiglobulin test (DAT) will be positive and maternal serum will have alloantibodies against infant (and paternal) erythrocytes. Elution techniques can identify the antigen specificity.

Common RBC antigens that can lead to clinically relevant incompatibility include those in the Kell, Duffy, and MNS blood groups. Kell incompatibility can be the most clinically relevant, as the severity of the hemolytic anemia is difficult to predict based on previous obstetric history, amniotic fluid bilirubin determinants, or maternal antibody titer (Table 140.2). Kell-alloimmunized infants often have inappropriately low numbers of circulating reticulocytes caused by erythroid suppression, and even low maternal titers of anti-Kell antibodies may cause significant anemia due to loss of precursors expressing the antigen as well as mature erythrocytes. No pharmacologic therapies are available to prevent sensitization with these minor antigens. As with cases of Rh and ABO incompatibility, treatment is supportive, including exchange transfusion for severe presentations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 140.2 Red Cell Antigens That Cause Hemolytic Disease of the Fetus and Newborn (HDFN)

MILD HDFN	MODERATE HDFN	SEVERE HDFN
ABO (A, B)	Rh (EW, hrs, Tar, Rh32, HrBE, Hr_o)	Rh (D, c, f, Ce, C^w, cE)
Rh (C, e, C^x, VS, CE, Be^a, JAL)	Diego (Di^a, Di^b, Wr^a, ELO)	Kell (K, k, Ku, Js^b)
Kell (Kp^a, Js^a, Ul^a)	Duffy (Fy^a)	Globoside (PP_1P_k)
Junior (Jra)	Gerbich (Ge3)	MNSs (Vw, Mur, MUT)
Kidd (Jk^a, Jk^b, Jk3)	H (H)	Mittenberger (Mi^a)
Duffy (Fy^b)	Kell (K, k, Ku, Js^b)	MNSs (Vw, Mur, MUT)
Langereis (Lan)	MNSs (U, Ss S, s, Mt^a, M^v)	Gerbich (PP1Pk)
MNSs (M, N, Hil, Or)	Colton (Co^a)	(HJK)
Colton (Co^b, Co^3)	(Kg)	—
Scianna (Rd, SC2)	(Sara)	—
Xg (Xg^a)	—	—
(At^a)	—	—

Mild HDFN, published reports of needing phototherapy for postnatal jaundice; *moderate HDFN*, published reports of needing postnatal exchange transfusion; *severe HDFN*, published reports of hydrops fetalis or intrauterine transfusions.
Note that some antigens have no system as per International Society of Blood Transfusion classification.
From Jackson ME, Baker JM. Hemolytic disease of the fetus and newborn. *Clin Lab Med.* 2021;41:133–151. Table 1.

Chapter 141

Neonatal Polycythemia

Christopher S. Thom and Michele P. Lambert

Neonatal polycythemia is broadly defined as an elevated hemoglobin or hematocrit level. This can be due to primary myeloproliferative disorders (e.g., polycythemia vera) or reactive processes, such as from chronic hypoxemia or living at high altitudes.

In infants, polycythemia is inferred from a hematocrit level >2 standard deviations above the normal value for gestational and postnatal age (Figs. 138.2 and 139.1). Full-term infants are therefore considered polycythemic with a hemoglobin level above ~22 g/dL or hematocrit >65%. It is important that these values are obtained from a "central" venous or arterial puncture, as heelstick or capillary samples can report artificially elevated values. Due to fluid shifts in the newborn period, hematocrit levels typically peak at 2-3 hours of life.

Although most polycythemic individuals are asymptomatic, symptomatic blood **hyperviscosity** from polycythemia can cause sluggish blood flow that decreases tissue perfusion and leads to metabolic disturbances. Signs and symptoms are vague, including irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Thus a high index of suspicion is often required for diagnosis and coincident respiratory, cardiovascular, and neurologic disorders should be investigated. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis (NEC), renal vein thrombosis, and renal failure in newborns. Related symptoms often appear in the first hours of life but can be delayed by up to 2-3 days depending on clinical context.

Dehydration should be considered as a potential contributing cause in symptomatic polycythemic infants. Neonatal polycythemia can also result from processes that lead to passive RBC transfusion into the fetus or increased intrauterine erythropoiesis. Passive fetal RBC transfusions may occur from prolonged delayed umbilical cord clamping but can also present in recipients of twin-twin transfusions or unrecognized maternal-fetal transfusions from the placenta.

Most cases of increased fetal erythropoiesis are thought to result from chronic intrauterine hypoxia, which stimulates erythropoietin and RBC production. Increased fetal erythropoiesis is associated with polycythemia in postterm (3%) and term (1–2%) infants; small-for-gestational-age (8%) or large-for-gestational-age (3%) infants; infants of diabetic mothers; infants of hypertensive mothers or those taking propranolol; and infants with trisomy 13, 18, or 21, adrenogenital syndrome, neonatal Graves disease, hypothyroidism, or Beckwith-Wiedemann syndrome. Delayed cord clamping does not increase the incidence of polycythemia. Contraindications to delayed cord clamping include suspected chronic intrauterine hypoxia (e.g., severe growth restriction) and maternal diabetes, which independently increase RBC production. The frequency of neonatal polycythemia is also increased for births at higher altitudes (5% at high altitude vs 1–2% at sea level).

Asymptomatic polycythemia can be treated conservatively, with consideration for supplemental enteral or intravenous hydration. Treatment for symptomatic infants should also begin with supplemental hydration, after considering potential comorbidities (e.g., heart failure). All polycythemic infants should have intake and output, blood glucose, and bilirubin levels followed closely. Infants with hyperviscosity symptoms may benefit from partial exchange transfusions, particularly if the hematocrit reaches ≥75% and symptoms worsen despite aggressive intravenous hydration.

Outcomes are more closely determined by etiologies contributing to chronic intrauterine hypoxia than polycythemia per se. Although infants treated with partial exchange transfusion may be at increased risk of NEC, it is unclear whether adverse long-term speech, fine motor, cognitive, and behavioral outcomes are affected.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 142

Hemorrhage in the Newborn Infant

Christopher S. Thom and Michele P. Lambert

Congenital and acquired bleeding disorders can manifest at varying times in infants and older children. Hemorrhage in an otherwise healthy newborn may suggest an inherited coagulation defect (e.g., hemophilia) or concurrent thrombocytopenia. Bleeding in otherwise sick neonates is frequently caused by underproduction or consumption of coagulation factors and/or platelets. Common acquired hemorrhagic disorders include hemorrhage due to vitamin K deficiency (see Chapter 71 and below), disseminated intravascular coagulation (DIC: see Chapter 532), or immune-mediated thrombocytopenia (see Chapter 533).

The neonatal hemostatic system differs from older children and adults. This impacts bleeding risk and laboratory assessment, and should enter into management considerations. Plasma levels of vitamin K–dependent coagulation factors (II, VII, IX, X, protein C, protein S) and antithrombin are initially low at birth and do not reach adult ranges until approximately 6 months of age. Note that overall the neonatal hemostatic system tends toward hypercoagulability, given low levels of protein C, protein S, and antithrombin. This may explain why neonatal platelets are hypofunctional in response to some agonists, and why neonatal platelet content differs from adults (Chapters 525 and 526).

HEMORRHAGIC DISEASE OF THE NEWBORN

Bleeding from vitamin K deficiency, otherwise known as **hemorrhagic disease of the newborn**, results from transient but profound deficiencies in vitamin K–dependent coagulation factors. Vitamin K normally facilitates carboxylation of factors II, VII, IX, and X, which is necessary for enzymatic activities. Decarboxylated factors are biologically inactive. Without vitamin K, decarboxylated *proteins induced in vitamin K absence (PIVKA)* are secreted. The classic form of this disease can be prevented with intramuscular injection of vitamin K (phytonadione) just after birth.

The disease process most often affects exclusively breastfed infants who did not receive intramuscular vitamin K prophylaxis at birth. Maternal breastmilk lacks free vitamin K, and newborns lack the intestinal flora normally responsible for vitamin K synthesis. Premature infants with nutritional deficiencies are also at risk of vitamin K deficiency and bleeding.

Laboratory testing typically reveals prolonged prothrombin time (PT) and partial thromboplastin time (PTT) in affected infants, with low plasma levels of prothrombin (II) and factors VII, IX, and X. Soluble **PIVKA** measurement can also act as a laboratory marker for vitamin K status. Factors V and VIII, fibrinogen, bleeding time, clot retraction, platelet count, and platelet function will be within normal newborn ranges.

Intramuscular administration of 1 mg vitamin K_1 (phytonadione) soon after birth can prevent bleeding complications from vitamin K deficiency in most full-term infants. Low birthweight infants may be given 0.5 mg phytonadione, although weight-based dosing varies between institutions. Phytonadione is the only form of vitamin K available in the United States. Vitamin K_2, also known as menaquinones, constitutes a minority of the vitamin K consumed by humans or produced by intestinal flora. Vitamin K prophylaxis does not prevent all hemorrhagic disease of the newborn. Although rare, cases can occur in full-term infants, preterm infants with significant nutritional deficiencies, and infants with malabsorption.

Chapter 141

Neonatal Polycythemia

Christopher S. Thom and Michele P. Lambert

Neonatal polycythemia is broadly defined as an elevated hemoglobin or hematocrit level. This can be due to primary myeloproliferative disorders (e.g., polycythemia vera) or reactive processes, such as from chronic hypoxemia or living at high altitudes.

In infants, polycythemia is inferred from a hematocrit level >2 standard deviations above the normal value for gestational and postnatal age (Figs. 138.2 and 139.1). Full-term infants are therefore considered polycythemic with a hemoglobin level above ~22 g/dL or hematocrit >65%. It is important that these values are obtained from a "central" venous or arterial puncture, as heelstick or capillary samples can report artificially elevated values. Due to fluid shifts in the newborn period, hematocrit levels typically peak at 2-3 hours of life.

Although most polycythemic individuals are asymptomatic, symptomatic blood **hyperviscosity** from polycythemia can cause sluggish blood flow that decreases tissue perfusion and leads to metabolic disturbances. Signs and symptoms are vague, including irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Thus a high index of suspicion is often required for diagnosis and coincident respiratory, cardiovascular, and neurologic disorders should be investigated. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis (NEC), renal vein thrombosis, and renal failure in newborns. Related symptoms often appear in the first hours of life but can be delayed by up to 2-3 days depending on clinical context.

Dehydration should be considered as a potential contributing cause in symptomatic polycythemic infants. Neonatal polycythemia can also result from processes that lead to passive RBC transfusion into the fetus or increased intrauterine erythropoiesis. Passive fetal RBC transfusions may occur from prolonged delayed umbilical cord clamping but can also present in recipients of twin-twin transfusions or unrecognized maternal-fetal transfusions from the placenta.

Most cases of increased fetal erythropoiesis are thought to result from chronic intrauterine hypoxia, which stimulates erythropoietin and RBC production. Increased fetal erythropoiesis is associated with polycythemia in postterm (3%) and term (1–2%) infants; small-for-gestational-age (8%) or large-for-gestational-age (3%) infants; infants of diabetic mothers; infants of hypertensive mothers or those taking propranolol; and infants with trisomy 13, 18, or 21, adrenogenital syndrome, neonatal Graves disease, hypothyroidism, or Beckwith-Wiedemann syndrome. Delayed cord clamping does not increase the incidence of polycythemia. Contraindications to delayed cord clamping include suspected chronic intrauterine hypoxia (e.g., severe growth restriction) and maternal diabetes, which independently increase RBC production. The frequency of neonatal polycythemia is also increased for births at higher altitudes (5% at high altitude vs 1–2% at sea level).

Asymptomatic polycythemia can be treated conservatively, with consideration for supplemental enteral or intravenous hydration. Treatment for symptomatic infants should also begin with supplemental hydration, after considering potential comorbidities (e.g., heart failure). All polycythemic infants should have intake and output, blood glucose, and bilirubin levels followed closely. Infants with hyperviscosity symptoms may benefit from partial exchange transfusions, particularly if the hematocrit reaches ≥75% and symptoms worsen despite aggressive intravenous hydration.

Outcomes are more closely determined by etiologies contributing to chronic intrauterine hypoxia than polycythemia per se. Although infants treated with partial exchange transfusion may be at increased risk of NEC, it is unclear whether adverse long-term speech, fine motor, cognitive, and behavioral outcomes are affected.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 142

Hemorrhage in the Newborn Infant

Christopher S. Thom and Michele P. Lambert

Congenital and acquired bleeding disorders can manifest at varying times in infants and older children. Hemorrhage in an otherwise healthy newborn may suggest an inherited coagulation defect (e.g., hemophilia) or concurrent thrombocytopenia. Bleeding in otherwise sick neonates is frequently caused by underproduction or consumption of coagulation factors and/or platelets. Common acquired hemorrhagic disorders include hemorrhage due to vitamin K deficiency (see Chapter 71 and below), disseminated intravascular coagulation (DIC: see Chapter 532), or immune-mediated thrombocytopenia (see Chapter 533).

The neonatal hemostatic system differs from older children and adults. This impacts bleeding risk and laboratory assessment, and should enter into management considerations. Plasma levels of vitamin K–dependent coagulation factors (II, VII, IX, X, protein C, protein S) and antithrombin are initially low at birth and do not reach adult ranges until approximately 6 months of age. Note that overall the neonatal hemostatic system tends toward hypercoagulability, given low levels of protein C, protein S, and antithrombin. This may explain why neonatal platelets are hypofunctional in response to some agonists, and why neonatal platelet content differs from adults (Chapters 525 and 526).

HEMORRHAGIC DISEASE OF THE NEWBORN

Bleeding from vitamin K deficiency, otherwise known as **hemorrhagic disease of the newborn**, results from transient but profound deficiencies in vitamin K–dependent coagulation factors. Vitamin K normally facilitates carboxylation of factors II, VII, IX, and X, which is necessary for enzymatic activities. Decarboxylated factors are biologically inactive. Without vitamin K, decarboxylated *proteins induced in vitamin K absence (PIVKA)* are secreted. The classic form of this disease can be prevented with intramuscular injection of vitamin K (phytonadione) just after birth.

The disease process most often affects exclusively breastfed infants who did not receive intramuscular vitamin K prophylaxis at birth. Maternal breastmilk lacks free vitamin K, and newborns lack the intestinal flora normally responsible for vitamin K synthesis. Premature infants with nutritional deficiencies are also at risk of vitamin K deficiency and bleeding.

Laboratory testing typically reveals prolonged prothrombin time (PT) and partial thromboplastin time (PTT) in affected infants, with low plasma levels of prothrombin (II) and factors VII, IX, and X. Soluble **PIVKA** measurement can also act as a laboratory marker for vitamin K status. Factors V and VIII, fibrinogen, bleeding time, clot retraction, platelet count, and platelet function will be within normal newborn ranges.

Intramuscular administration of 1 mg vitamin K_1 (phytonadione) soon after birth can prevent bleeding complications from vitamin K deficiency in most full-term infants. Low birthweight infants may be given 0.5 mg phytonadione, although weight-based dosing varies between institutions. Phytonadione is the only form of vitamin K available in the United States. Vitamin K_2, also known as menaquinones, constitutes a minority of the vitamin K consumed by humans or produced by intestinal flora. Vitamin K prophylaxis does not prevent all hemorrhagic disease of the newborn. Although rare, cases can occur in full-term infants, preterm infants with significant nutritional deficiencies, and infants with malabsorption.

Table 142.1 Vitamin K Deficiency Bleeding (Hemorrhagic Disease of the Newborn)

	EARLY-ONSET DISEASE	CLASSIC DISEASE	LATE-ONSET DISEASE
Age	0-24 hr	2-7 days	1-6 mo
Potential sites of hemorrhage	Cephalohematoma Subgaleal Intracranial Gastrointestinal Umbilicus Intraabdominal	Gastrointestinal Ear-nose-throat-mucosal Intracranial Post circumcision Cutaneous Injection sites	Intracranial Gastrointestinal Cutaneous Ear-nose-throat-mucosal Injection sites Thoracic
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K levels or absorption Inherited coagulopathy	Vitamin K deficiency Exclusive breastfeeding	Cholestasis: malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis) Abetalipoprotein deficiency Idiopathic in Asian breastfed infants Warfarin ingestion
Prevention	Avoidance of high-risk medication Possibly antenatal vitamin K to treatment of mother (20 mg) before birth and postnatal administration to infant soon after birth	Prevented by parenteral vitamin K at birth Oral vitamin K regimens require repeated dosing	Prevented by parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
Incidence	Very rare	~2% if infant not given vitamin K soon after birth	Dependent on primary disease

Infants who present with hemorrhage should be given 1-5 mg of vitamin K_1 intravenously, typically on 3 consecutive days. This regimen generally improves coagulation defects and bleeding ceases within hours. Serious bleeding, particularly in premature infants or those with liver disease, may also require intravenous transfusion of fresh-frozen plasma to correct coagulopathy. Packed RBCs (PRBCs) or whole blood transfusions may also be required to correct anemia.

Bleeding episodes most frequently occur between days of life 2 and 7. Mild bleeding may precede more severe manifestations, which are most frequently gastrointestinal, nasal, subgaleal, intracranial, or occur after circumcision.

Early-onset vitamin K deficiency bleeding can occur in the first day of life in infants born to mothers chronically treated with drugs that interfere with vitamin K absorption or function, including warfarin, phenytoin, phenobarbital, or some cholesterol-lowering medications. Usually, bleeding is promptly ameliorated by vitamin K administration, although some infants can have poor or delayed improvements in bleeding. Thus infants born to mothers who took these medications late in gestation should be given 1-2 mg intravenous vitamin K immediately after birth, and serial newborn PT monitoring should begin using cord blood. If the PT is greatly prolonged and fails to improve, or significant hemorrhage presents, fresh-frozen plasma administration can temporarily correct factor deficiencies.

Late-onset vitamin K deficiency bleeding after 2 weeks of life is most often associated with conditions that cause fat-soluble vitamin malabsorption, including cystic fibrosis, neonatal hepatitis, or biliary atresia (Table 142.1). Bleeding can be severe and is not responsive to vitamin K treatment if there is hepatocellular injury; bleeding will respond to intravenous vitamin K if there is malabsorption.

Bleeding unresponsive to vitamin K should prompt consideration for congenital clotting factor deficiencies (see Chapter 525). These conditions may present with hematomas, melena, post circumcision bleeding, or bleeding from the umbilicus. Up to 70% cases of hemophilia (factor VIII or IX deficiency) are clinically apparent in the newborn period. Congenital factor deficiency treatment requires specific factor replacement, or fresh-frozen plasma if factor concentrate is not available.

Although *oral* vitamin K administration has been investigated as an alternative to intramuscular prophylaxis, oral regimens *do not* prevent late-onset vitamin K deficiency bleeding. Thus intramuscular vitamin K prophylaxis remains the method of choice.

Prompt recognition of infants who do present with bleeding from vitamin K deficiency is critical. A presumptive diagnosis can often be made based on a complete history, even before laboratory confirmation, facilitating rapid treatment initiation. With timely therapy and supportive care, the associated mortality rate is low.

DISSEMINATED INTRAVASCULAR COAGULOPATHY

Critical illness that results in consumption of circulating coagulation factors and platelets is termed disseminated intravascular coagulation. In neonates and other patients, DIC can result in either bleeding or thrombosis. DIC occurs secondary to an array of primary processes, including but not limited to sepsis or asphyxia. Rarely, hemangiomas will cause consumption of coagulation factors and initiate this process. In addition to clinical context, coagulation studies, factor levels, and platelet counts can provide evidence of ongoing DIC. Management centers on treatment of the underlying etiology, although supportive care may include blood, plasma, vitamin K, or platelet transfusions to replace consumed factors. Usually, affected infants are critically ill, with evidence of end-organ damage. Those with DIC can have high rates of morbidity and mortality, dependent on the underlying etiology (see Chapter 532).

Diagnosis and Treatment

Diagnostic modalities for hemorrhage in neonates vary based on clinical suspicion. For example, noninvasive imaging can be used to identify hemorrhage or bleeding sequelae. Premature infants who become acutely anemic out of proportion to phlebotomy are frequently monitored for intraventricular hemorrhage or investigated for bleeding elsewhere. These diagnostic measures can help to explain the pathology leading to anemia and any related risks. In turn, diagnosis can facilitate prognostication, and in rare cases lead to potentially definitive interventions (e.g., for some vascular malformations).

Treatment for blood loss typically includes transfusion of crossmatched PRBCs, which should be given more slowly in the setting of chronic blood loss or in patients at risk of volume overload. Therapies and interventions should also focus on correcting coexisting coagulopathy and/or comorbidities that increase further bleeding risk.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 143

Nonimmune Hydrops

Dalal Taha

Nonimmune hydrops, a significant contributor to neonatal morbidity and mortality, is the leading cause of fetal hydrops. **Hydrops fetalis** is defined by ≥2 abnormal fetal fluid collections, such as ascites, pleural, pericardial, or cutaneous edema (>5 mm) (Fig. 143.1). In addition, there may be associated placental edema (>6 mm), polyhydramnios (50%), and the rare occurrence of **mirror syndrome**, in which the mother becomes edematous. In cases in which hydrops is not caused by red cell alloimmunization, it is referred to as nonimmune hydrops. Nonimmune hydrops is the result of a range of underlying etiologies, such as high-output cardiac failure secondary to anemia or fetal arrhythmia, alterations in lymphatic development, fetal inflammation, and capillary leak or elevated central venous pressure due to structural cardiac disease. Despite advances in recognition of the underlying cause, mortality remains high with prognosis dependent on the underlying cause, degree of prematurity, and extent of disease burden at birth.

INCIDENCE AND ETIOLOGY

Estimates of incidence range between 1 in 1,700 pregnancies and 1 in 4,000 pregnancies. Population studies provide lower estimates, but this may be an underrepresentation due to a lack of information on fetuses who died in utero.

The etiologies are broad; cardiovascular, lymphatic, hematologic, and chromosomal disorders are the most common identifiable underlying causes (Table 143.1). The etiology is unknown in approximately 10–20% of cases. However, improved understanding of the lymphatic system and its contribution to the development of nonimmune hydrops has led to increased identification of the underlying etiology. Lymphatic causes of nonimmune hydrops are congenital lymphovenous atresia, in which the thoracic duct outlet is not connected to the venous circulation, and complete absence of the thoracic duct or pulmonary lymphatic perfusion syndrome, in which the pulmonary lymphatic channels abnormally conduct to the pleural space resulting in chylothorax. Other mechanisms for the development of nonimmune hydrops are not well established (Fig. 143.2).

PRENATAL DIAGNOSIS AND TREATMENT

Hydrops fetalis is identified in utero by ultrasonographic findings of excess fluid. After ruling out immune-mediated hydrops (Rh alloimmunization), other diagnostic testing may include screening for hemoglobinopathies, testing for fetal-maternal hemorrhage (Kleihauer-Betke test), and testing for infection (i.e., TORCH infections, syphilis, and parvovirus B19). Fetal echocardiography should be performed to assess for structural heart defect or arrhythmia. Commonly diagnosed causes of nonimmune hydrops in fetuses greater than 24 weeks' gestation are cardiac disorders. Amniotic fluid can be obtained for fetal genetic testing to evaluate for chromosomal and specific gene abnormalities. In cases with fetal pleural effusions, a fluid sample may be collected via thoracentesis and tested for lymphocyte count to determine whether the underlying cause of hydrops is due to lymphatic dysfunction.

In utero treatment has been successful for fetal supraventricular tachycardia (SVT), twin-twin transfusion syndrome, nonimmune fetal anemias, large vascular masses, congenital diaphragmatic hernia, and other chest occupying lesions, such as congenital cystic adenomatoid malformation (CCAM) and pulmonary sequestration. In cases in which initial ultrasound is not useful in identifying a cause, repeat ultrasound or fetal magnetic resonance imaging (MRI) can be used to reassess fetal anatomy, monitor progression of hydrops, determine an underlying diagnosis, and direct fetal intervention. The finding of nutmeg lung on fetal MRI signifies abnormal pulmonary lymphatic flow that results in chylothorax. To treat fetal pleural effusions, in the absence of an infectious etiology, fetal thoracentesis and/or thoracoamniotic shunt placement can be performed.

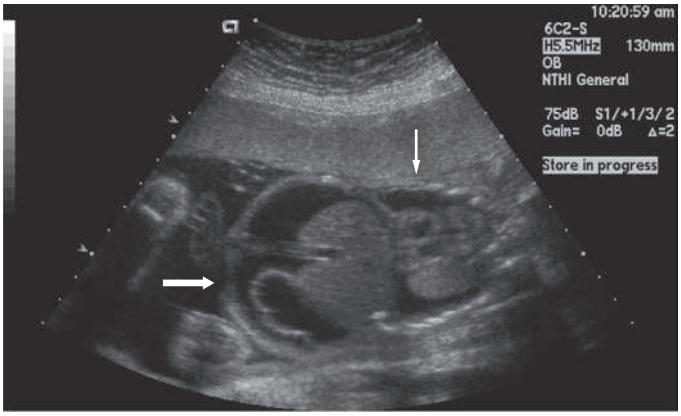

Fig. 143.1 Hydrops fetalis. Longitudinal sonographic image of the fetus, with ascitic fluid outlining the liver *(large arrow)*. The *small arrow* shows pleural effusion above the diaphragm. *(From Wilkins I. Nonimmune hydrops. In Creasy RK, Resnick R, Iams JD, et al., eds.* Creasy & Resnik's Maternal-Fetal Medicine, *7th ed. Philadelphia: Elsevier; 2014: Fig. 37-2.)*

POSTNATAL DIAGNOSIS AND TREATMENT

Postnatal therapy includes a team approach to the delivery room management that often requires immediate endotracheal tube intubation for predicted respiratory failure secondary to pleural, peritoneal, or pericardial effusions, pulmonary hypoplasia, surfactant deficiency, pulmonary edema, or poor chest wall compliance due to soft tissue edema. Immediate transfusion of packed red blood cells (RBCs) may also be required in the delivery room in the presence of anemias. Drainage of large pleural, peritoneal, or pericardial effusions may aid in achieving effective mechanical ventilation and ensure successful resuscitation. High ventilatory pressures may be needed to overcome poor chest compliance but may result in pneumothoraces or pulmonary interstitial emphysema, especially in cases with pulmonary hypoplasia.

Once the infant is stabilized, additional intensive care includes fluid and electrolyte management. Maintenance fluids should be restricted as much as possible with the goal of resolving or improving the degree of hydrops. In cases with ongoing drainage of pleural or peritoneal fluid, fluid replacement may be necessary to replete serum sodium levels and maintain hemodynamic stability. If the fluid drained is secondary to a lymphatic disorder, albumin may need to be administered to maintain adequate serum levels.

Diagnostic testing should be performed if an underlying etiology of hydrops is unknown at the time of birth to direct additional therapies. Whole exome (or genome) sequencing and microarray duplication/deletion studies are recommended to establish a diagnosis. Analysis of fluid from the pericardial, pleural, or peritoneal space may confirm an underlying lymphatic disorder if there is a lymphocyte predominance. Hypoalbuminemia and the presence of soft tissue edema is also suggestive of a lymphatic disorder. Additional evaluation of the lymphatic system includes the use of T2 weighted MRI, dynamic contrast-enhanced magnetic resonance lymphangiogram (DCMRL), and direct or conventional lymphangiogram. Interventions for congenital lymphatic disorders include ethiodized oil injection to treat pulmonary lymphatic perfusion syndrome and lymphovenous anastomosis for lymphovenous atresia.

OUTCOMES

Mortality from nonimmune hydrops remains high at approximately 50% despite recent advances in diagnosis and treatment. Predictors of survival include gestational age at birth and degree of illness at the time of birth. Infants with parvovirus, isolated neonatal chylothorax, and SVT have the highest survival.

Table 143.1 Principal Diagnoses Associated with Nonimmune Hydrops Fetalis

CARDIOVASCULAR (21%)
STRUCTURAL
- Hypoplasias (left or right heart)
- AV canal defect
- Single ventricle
- Transposition of great arteries
- Septal defects (VSD/ASD)
- Tetralogy of Fallot
- Ebstein anomaly
- Ductus arteriosus closure
- Truncus arteriosus
- Valvular (stenosis/insufficiency)

ARRYTHMIAS
- Atrial (flutter/tachyarrhythmia)
- Wolff-Parkinson-White
- Supraventricular tachycardia
- Long QT interval
- Heart block

CARDIOMYOPATHY
- Tumors
- Neoplasias
- Myopathies
- Cardiosplenic syndromes
- Hereditary cardiomyopathies

INFECTION (6.7%)
- Cytomegalovirus
- Parvovirus B19
- Syphilis
- Herpes simplex
- Rubella
- Coxsackievirus
- Leptospirosis
- *Trypanosoma cruzi*

INBORN STORAGE DISEASE (1.1%)
- Gaucher disease
- GM1 gangliosidosis
- Sialidosis
- MPS IVA and VII
- Mucolipidosis type I+II
- Galactosialidosis
- Niemann-Pick type C

TTTS-PLACENTAL (5.6%)
Twin
- TTTS
- Acardiac twin

Placental
- Umbilical vein thrombosis
- Umbilical cord angiomyxoma
- True cord knot
- Chorionic vein thrombosis
- Rare placenta disorders

THORACIC/EXTRATHORACIC MASS/LYMPHATIC (12.4%)
Mass Effect
- Diaphragmatic hernia
- Congenital pulmonary adenomatoid malformation
- Intrathoracic mass
- Pulmonary sequestration
- Chylothorax
- Airway obstruction
- Pulmonary lymphangiectasia
- Bronchogenic cyst

Other
- Milroy syndrome
- Generalized lymphatic dysplasia
- Lymphedema-distichiasis syndrome

Skeletal Dysplasias
- Thanatophoric dysplasia
- Short rib polydactyly
- Hypophosphatasia
- Osteogenesis imperfecta chondrogenesis
- Campomelic dysplasia
- Lethal achondroplasia
- Nager syndrome

IDIOPATHIC (17.8%)
CHROMOSOMAL (13.4%)
TRISOMY
- 21
- 18
- 13

MONOSOMY
- 45, X
- 45, X (mosaic)

DUPLICATIONS
- 18 q +
- 11p

DELETIONS
- 13 q −
- 17 q −

TRIPLOIDY

HEMATOLOGIC (10.4%)
- Alpha-thalassemia
- Hereditary stomatocytosis
- Fetomaternal hemorrhage
- Glucose-6-phosphate deficiency
- Leukemia
- Pyruvate kinase deficiency
- Red blood cell aplasias
- Diamond-Blackfan syndrome

GASTROINTESTINAL (0.5%)
- Duodenal atresia
- Duodenal diverticulum
- Jejunoileal atresia
- Volvulus
- Imperforate anus
- Meconium peritonitis
- Intestinal malrotation
- Intestinal duplication
- Hepatic fibrosis
- Cholestasis
- Biliary atresia
- Hepatic vascular malformations
- Hepatitis
- Hepatic necrosis
- Liver tumor or cysts

SYNDROMIC/MISCELLANEOUS (8.1%)
- Noonan syndrome and other RASopathies
- Arthrogryposis
- Multiple pterygium syndrome
- Neu-Laxova syndrome
- Pena-Shokeir syndrome
- Myotonic dystrophy
- Saldino-Noonan syndrome
- Francois syndrome, type III
- Familial nuchal bleb
- Elejalde syndrome
- Thoracoabdominal syndrome

URINARY TRACT MALFORMATION (2.3%)
- Urethral stenosis
- Urethral atresia
- Posterior urethral valve
- Finnish type nephrosis
- Edwards (prune belly) syndrome

OTHER
- HLH
- IPEX
- Nemaline myopathy
- Multiple pterygium syndrome
- Hyper IgE syndrome

ASD, Atrial septal defect; AV, arteriovenous; HLH, hemophagocytic lymphohistiocytosis; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked, MPS, mucopolysaccharide; TTTS, twin-twin transfusion syndrome; VSD, ventricular septal defect.
Modified from Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine Diseases of the Fetus and Infant*, 11th ed. Philadelphia: Elsevier; 2020: Table 23.4, p 381.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

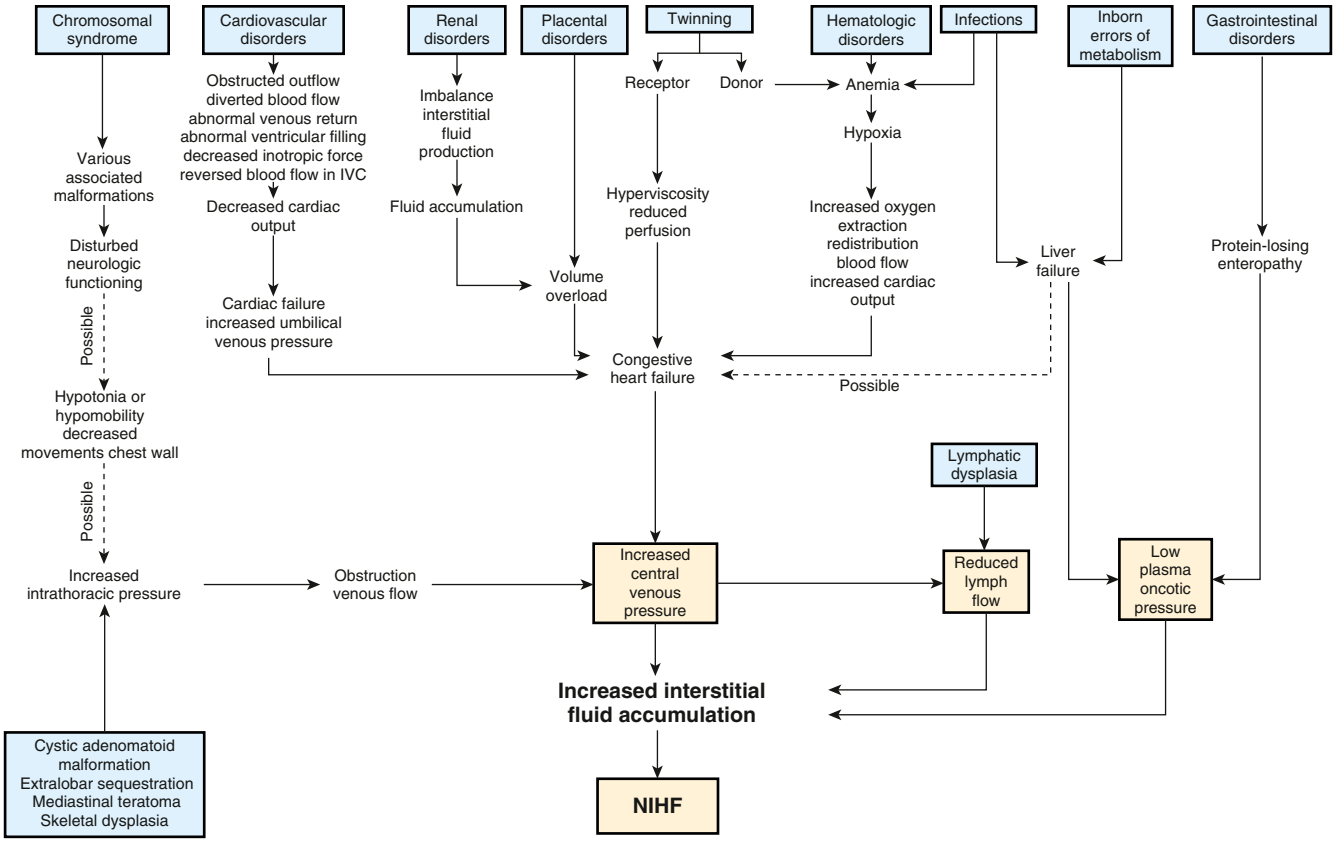

Fig. 143.2 Impact of various etiologies for nonimmune hydrops on fluid homeostasis. IVC, Inferior vena cava; NIHF, nonimmune hydrops fetalis. *(Adapted from Bellini C, Hennekam RCM. Non-immune hydrops fetalis: a short review of etiology and pathophysiology.* Am J Med Genet. *2012;158A:597–605.)*

Chapter 144

The Umbilicus

Eric C. Eichenwald

The umbilical cord typically consists of two umbilical arteries, the umbilical vein, and a gelatinous substance called Wharton jelly, all contained within a sheath derived from the amnion and coiled into a helical shape. The muscular umbilical arteries carry deoxygenated blood from the fetus to the placenta and are contiguous with the fetal internal iliac arteries. The umbilical vein carries oxygenated blood from the placenta back to the fetus, where it flows into the inferior vena cava by way of the ductus venosus. The placenta contains an estimated 20 mL/kg of blood; current recommendations are to delay clamping of the cord at delivery for 30-60 seconds in both term and preterm infants, to facilitate placental transfusion. At term, a normal umbilical cord is approximately 55 cm long. Abnormally short cords are associated with conditions causing decreased fetal movement, including fetal hypotonia, oligohydramnios, and uterine constraint, and lead to increased risk for complications during labor and delivery for both mother and infant. Long cords (>70 cm) increase the risk for true knots, wrapping around the fetus, and/or prolapse. Straight uncoiled cords are associated with anomalies, fetal distress, and intrauterine fetal demise.

When the cord is cut after birth, portions of these structures remain in the base but gradually become obliterated. The blood vessels are functionally closed but anatomically patent for 10-20 days. The umbilical arteries become the lateral umbilical ligaments; the umbilical vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. The umbilical cord stump usually sloughs within 2 weeks. Delayed separation of the cord, after more than 1 month, has been associated with neutrophil chemotactic defects and overwhelming bacterial infection (see Chapter 168).

A single umbilical artery is present in approximately 5-10/1,000 births; the frequency is higher (35-70/1,000) in twin births. It is estimated that 20–30% of infants with a single umbilical artery have other (and often multiple) congenital structural abnormalities. The presence of multiple anomalies is suggestive of an abnormal karyotype, including trisomies. Infants with an isolated single umbilical artery are not thought to be at increased risk of having a chromosomal anomaly, and no specific evaluation is indicated for these infants aside from a thorough physical examination.

The **omphalomesenteric duct (OMD)** is an embryonic connection between the developing midgut and the primitive yolk sac. It typically involutes at 8-9 weeks' gestation, but failure of this process can leave an abnormal connection between the umbilical cord and the gastrointestinal (GI) tract. The most common remnant of the OMD is a **Meckel diverticulum** (see Chapter 377), whereas abnormalities that would become symptomatic in the neonatal period include a **sinus** or **fistula** that would drain mucus or intestinal contents through the umbilicus. An umbilical **polyp** is one of the least common OMD remnants and represents exposed GI mucosa at the umbilical stump. The tissue of the polyp is bright red, firm, and has a mucoid secretion. Therapy for all OMD remnants is surgical excision of the anomaly.

A **persistent urachus** (urachal cyst, sinus, patent urachus, or diverticulum) is a result of failure of closure of the allantoic duct and may be associated with bladder outlet obstruction. Patency should be suspected if a clear, light-yellow, urine-like fluid is being discharged from the umbilicus. Symptoms include drainage, a mass or cyst, abdominal pain, local erythema, and infection. Urachal anomalies should be investigated by ultrasonography and a cystogram. Therapy for a persistent urachus is surgical excision of the anomaly and correction of any bladder outlet obstruction if present.

UMBILICAL HEMORRHAGE

Hemorrhage from the umbilical cord may be the result of trauma, inadequate ligation of the cord, or failure of normal thrombus formation. It may also indicate hemorrhagic disease of the newborn or other coagulopathies (especially factor XIII deficiency), septicemia, or local infection. The infant should be observed frequently during the first few days of life so that if hemorrhage does occur, it will be detected promptly.

UMBILICAL GRANULOMA

The umbilical cord stump usually dries and separates within 1-2 weeks after birth. The raw surface becomes covered by a thin layer of skin; scar tissue forms, and the wound is usually healed within 12-15 days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection or incomplete epithelialization may result in a moist, granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

Persistence of granulation tissue at the base of the umbilicus is common. The tissue is soft, 3-10 mm in size, vascular and granular, colored dull red or pink, and may have a seropurulent discharge. Granulation tissue is treated by cauterization with silver nitrate, repeated at intervals of several days until the base is dry.

UMBILICAL INFECTIONS

The devitalized umbilical cord provides an ideal medium for bacterial growth and a potential portal of entry for microbes. The term **omphalitis** refers to infection of the umbilical cord stump, navel, or the surrounding abdominal wall. Omphalitis must be distinguished from local irritation from the umbilical cord clamp. Erythema that extends to the abdominal wall, particularly tracking superiorly is concerning. Most term infants with mild localized omphalitis appear well and are afebrile. However, ~10–15% are acutely ill and at risk for bacteremia, spreading cellulitis, necrotizing fasciitis, and extension into the portal vein and liver. **Necrotizing fasciitis** (which is often polymicrobial) is associated with a high mortality rate and is often associated wth neutropenia. Treatment of omphalitis includes prompt antibiotic therapy with agents effective against *Staphylococcus aureus* and *Escherichia coli*, such as an antistaphylococcal penicillin or vancomycin in combination with an aminoglycoside. If abscess formation or necrotizing fasciitis has occurred, surgical consultation for incision and drainage or debridement may be required.

In community and primary care settings in developing countries, topical application of chlorhexidine to the umbilical cord has been shown to reduce omphalitis and neonatal mortality. In hospital settings in developed countries, there is no convincing evidence that application of antiseptics (including triple dye, alcohol, or chlorhexidine) is superior to *dry cord care* in minimizing the risk of omphalitis for infants in these settings, although these treatments do reduce bacterial colonization.

UMBILICAL HERNIA

Often associated with **diastasis recti**, an umbilical hernia is caused by incomplete closure or weakness of the muscular umbilical ring. Predisposing factors include Black race and low birthweight. The hernia appears as a soft swelling covered by skin that protrudes during crying, coughing, or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from <1 cm in diameter to as much as 5 cm (2 inches), but larger defects are rare. Most umbilical hernias that appear before age 6 months disappear spontaneously by 1 year. Even large hernias (5-6 cm in all dimensions) have been known to disappear spontaneously by 5-6 years. Strangulation of intestinal contents is *extremely rare*. Surgery is not advised unless the hernia persists to age 4-5 years, causes symptoms, becomes strangulated, or becomes progressively larger after age 1-2 years. Defects exceeding 2 cm are less likely to close spontaneously.

CONGENITAL OMPHALOCELE

An **omphalocele** is a herniation or protrusion of the abdominal contents into the base of the umbilical cord (Fig. 144.1). In contrast to the more common umbilical hernia, the sac is covered with peritoneum without overlying skin, and the insertion of the distal umbilical cord into the sac itself distinguishes this condition from other abdominal wall defects such as gastroschisis. The size of the sac that lies outside the abdominal cavity depends on its contents. Herniation of intestines into the cord occurs in approximately 1/5,000 births, and herniation of liver and intestines in 1/10,000 births. The abdominal cavity may be proportionately small because of the lack of space-occupying viscera. Treatment for an omphalocele consists of covering the sac with moist, sterile dressings, then initiating prompt surgical repair if the abdomen is able to accommodate the eviscerated organs. If the omphalocele is too large to allow immediate repair, continued dressings may temporize and encourage epithelialization of the sac. Occasionally, mesh or similar synthetic material may be used to cover the viscera if the sac has ruptured or if excessive mobilization of the tissues would be necessary to cover the mass and its intact sac.



Fig. 144.1 A, Omphalocele with umbilical cord insertion into the sac and intestine visible. B, Omphalocele with sac containing liver. (*Courtesy Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.*)

Many infants with omphalocele (50–70%) have associated malformations, and about 30% have chromosomal abnormalities. The likelihood of an abnormal karyotype is increased when the liver is *intracorporeal* (not within the sac). Omphalocele can be part of well-defined syndromes, including **Beckwith-Wiedemann syndrome**, characterized by omphalocele, macrosomia, and hypoglycemia. The survival rate for affected infants is largely determined by the presence of associated malformations or chromosomal abnormalities. For patients with isolated omphalocele, the survival rate is >90%.

UMBILICAL TUMORS

Tumors of the umbilicus are rare and include angioma, enteroteratoma, dermoid cyst, myxosarcoma, and cysts of urachal or OMD remnants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 145

Neonatal Abstinence Syndrome

Stephen W. Patrick

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome that occurs among some substance-exposed infants shortly after birth. The syndrome most commonly occurs after in utero exposure to opioids and is also called neonatal opioid withdrawal syndrome (NOWS). Between 2000 and 2017, the rate of NAS in the United States increased sixfold reaching 7.2 per 1,000 hospital births, which mirrors the rise of other population-wide opioid-related complications including overdose deaths. The opioid overdose crisis in the United States was first driven by prescription opioids (e.g., oxycontin), then heroin, and more currently by illicitly produced fentanyl. For pregnant women opioid use disorder (OUD), or continued use of an opioid despite adverse consequences, often begins before pregnancy and is associated with myriad social risks including trauma and physical abuse. Treatment of OUD, especially with medications for OUD (MOUD), is effective in improving pregnancy outcomes. MOUD, including buprenorphine and methadone, has been shown to reduce risk of relapse, overdose death, HIV and hepatitis C virus (HCV), and preterm birth. **Methadone** is a full μ-opioid agonist, generally given once daily, and is administered through highly regulated opioid treatment programs. **Buprenorphine** is a partial μ-opioid agonist and a partial k-antagonist, can be prescribed in the outpatient setting, and is more widely available. Accessing treatment can be challenging for pregnant women, with studies showing they are nearly 20% less likely to be accepted for treatment than nonpregnant women. Notably, MOUD such as methadone and buprenorphine can cause NAS; however, this is generally thought of as a preferable outcome when compared to preterm birth or overdose.

The clinical signs of NAS are generally associated with neurologic (e.g., tremor), gastrointestinal (e.g., poor feeding), and autonomic signs (e.g., tachypnea) and can be documented using the NAS score (Fig. 145.1) as well as the Eat, Sleep, Console (ESC) assessment tool (Table 145.1).

NEONATAL ABSTINENCE SCORE

Date: _____ Weight: _____

System	Signs & Symptoms	Score	Time AM / PM	Comments
Central Nervous System Disturbances	Excessive High Pitched Cry	2		
	Continuous High Pitched Cry	3		
	Sleeps < 1 Hour After Feeding	3		
	Sleeps < 2 Hours After Feeding	2		
	Sleeps < 3 Hours After Feeding	1		
	Hyperactive Moro Reflex	2		
	Markedly Hyperactive Moro Reflex	3		
	Mild Tremors Disturbed	1		
	Moderate - Severe Tremors Disturbed	2		
	Mild Tremors Undisturbed	3		
	Moderate - Severe Tremors Undisturbed	4		
	Increased Muscle Tone	2		
	Excoriation (Specific Area)	1		
	Myoclonic Jerks	3		
	Generalized Convulsions	5		
Metabolic / Vasomotor / Respiratory Disturbances	Sweating	1		
	Fever < 101° F (37.2° - 38.2° C)	1		
	Fever ≥ 101.1° F (≥38.4° C)	2		
	Frequent Yawning (> 3 - 4 Times/Interval)	1		
	Mottling	1		
	Nasal Stuffiness	1		
	Sneezing (> 3 - 4 Times/Interval)	1		
	Nasal Flaring	2		
	Respiratory Rate - 60/min	1		
	Respiratory Rate - 60/min with Retractions	2		
Gastrointestinal Disturbances	Excessive Sucking	1		
	Poor Feeding	2		
	Regurgitation	2		
	Projectile Vomiting	3		
	Loose Stools	2		
	Watery Stools	3		
	TOTAL SCORE			
	Initials of Scorer			

Fig. 145.1 Data from Amin A, Frazie M, Thompson S, Patel A. Assessing the Eat, Sleep, Console model for neonatal abstinence syndrome management at a regional referral center. *J Perinatol*. 2023 Apr 25:1–7; Blount T, Painter A, Freeman E, et al. Reduction in length of stay and morphine use for NAS with the "Eat, Sleep, Console" Method. *Hosp Pediatr*. 2019;9:615–623; Glait M, Moyer A, Saudek K, et al. Addressing drivers of healthcare utilization for neonatal opioid withdrawal syndrome. *J Perinatol*. 2023;43):392–401; Grossman M. Eat, Sleep, Console (ECS) care tool. 2017 ESC 3rd ed. 1.30.20; Young LW, Ounpraseuth ST, Merhar SL, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. 2023;388:2326–2336.)

Table 145.1 Eat, Sleep, Console (ESC) Assessment Approach to Neonatal Opioid Withdrawl

EATS
Takes > 10 min to coordinate feeding with hunger cues
< 10 min for breastfeeds
< 10 mL of a feed

SLEEPS
< 1 hr after a feed

CONSOLES
Takes > 10 min to be consoled
Cannot stay consoled for 10 min

Nonpharmacologic interventions include rooming in, caregiver presence, skin to skin contact, holding/cuddling, safe swaddling (avoid face), feed on demand after hunger cues, breastfeeding, non-nutritive sucking, quiet low stimulation low-light environment, rhythmic motion, additional caregiver support, minimal disruptions in environment, cluster care to awake times, safe sleep, caregiver self-care and rest.

These parameters suggest withdrawl.
Data from Amin A, Frazie M, Thompson S, Patel A. Assessing the Eat, Sleep, Console model for neonatal abstinence syndrome management at a regional referral center. *J Perinatol*. 2023 Apr 25:1–7; Blount T, Painter A, Freeman E, et al. Reduction in length of stay and morphine use for NAS with the "Eat, Sleep, Console" Method. *Hosp Pediatr*. 2019;9:615–623; Glait M, Moyer A, Saudek K, et al. Addressing drivers of healthcare utilization for neonatal opioid withdrawal syndrome. *J Perinatol*. 2023;43):392–401; Grossman M. Eat, Sleep, Console (ECS) care tool. 2017 ESC 3rd ed. 1.30.20; Young LW, Ounpraseuth ST, Merhar SL, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. 2023;388:2326–2336.

The timing of NAS onset can be related to several factors, including the last maternal use and half-life of the opioid. NAS signs can rarely begin within 24 hours of birth but more commonly occur within 48 hours after short-acting opioids, and 72-96 hours after exposure to long-acting or maintenance opioids (e.g., methadone). For these reasons, it is recommended to observe opioid-exposed infants for at least 3 days after birth for an infant exposed to short-acting opioids and 5 days for longer half-life opioids such as buprenorphine. Tremors, poor feeding, excessive crying, poor sleeping, and hyperirritability are the most prominent signs of NAS. Other signs include sneezing, yawning, hiccups, myoclonic jerks, skin breakdown and abrasions, vomiting, loose stools, nasal stuffiness, and seizures. Many prenatal and postnatal factors can influence the severity and duration of withdrawal. Polysubstance use, particularly with cigarettes, gabapentin, benzodiazepines, and selective serotonin reuptake inhibitors, has been associated with a higher risk or more severe NAS, whereas breastfeeding after delivery, rooming-in, and standardizing care processes (i.e., following protocols) have been associated with lower risk or less severe NAS (see Table 145.1 for nonpharmacologic interventions).

Identifying substance use as early as possible in pregnancy is critical to improving pregnancy outcomes. For that reason, it is recommended to perform universal screening for substance use using a standardized and validated tool such as the four Ps:

- **Parents:** Did any of your parents have problems with alcohol or other drug use?
- **Partner:** Does your partner have a problem with alcohol or drug use?
- **Past:** In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?
- **Present:** In the past month, have you drunk any alcohol or used other drugs?

Screening can be augmented with toxicology testing of the mother or infant; it is important to recognize that toxicology testing has limitations and for some substances may only capture a short window of exposure. Toxicology testing of pregnant women requires informed consent but is not needed for infants if done as part of routine care.

Testing urine of mothers or infants can capture recent exposures, whereas umbilical cord and meconium testing will capture a longer window of substance use. Toxicology testing may not be needed if women are in treatment and receive routine testing in pregnancy.

TREATMENT AND SETTING

Hospitals should have standardized protocols for the observation, scoring, and treatment of the opioid-exposed infant. The first line of treatment for all opioid-exposed infants is **nonpharmacologic support**, including rooming-in, breastfeeding, and tailoring the environment to not overstimulate the infant. Importantly, care for opioid-exposed infants and those diagnosed with NAS does not require admission to a neonatal intensive care unit (NICU); admission to a NICU may cause undue separation of the maternal–infant dyad as well as exacerbate clinical signs of withdrawal by placing the infant in a loud environment. Breastfeeding, in addition to its well-documented benefits, can also reduce NAS severity and can safely occur with maternal treatment using MOUD. Although there are no evidence-based guidelines, consensus guidelines suggest breastfeeding can be encouraged if there has been no relapse within 30 days of birth and should be encouraged if there has been no relapse within 90 days of birth. Untreated HIV is a contraindication to breastfeeding; however, breastfeeding is safe with HCV unless there are cracked or bleeding nipples.

The decision for pharmacologic treatment has been traditionally based on the nursing scoring assessment tool, and the most widely used tool is a modification of the Finnegan scoring tool (see Fig. 145.1). Other scoring tools include the Neonatal Narcotic Withdrawal Index, Neonatal Withdrawal Inventory, and MOTHER NAS Scale.

The **ESC model** is very useful and is an evidenced-based approach for improved outcomes and fewer pharmacologic interventions (Table 145.1). An inability to eat, sleep, or be consoled in at least two of the three parameters in the presence of nonpharmacologic interventions warrants pharmacologic therapy, usually with oral liquid morphine plus continued nonpharmacologic interventions. Other etiologies of poor eating, sleeping, and consolability must be evaluated. The main objectives when initiating pharmacologic treatment is to control clinical signs of withdrawal and to prevent adverse events (e.g., seizure). Excessive weight loss may be an indication for pharmacotherapy regardless of other clinical signs.

Pharmacologic treatment for NAS, when necessary, should be done with an opioid, and the most commonly used are morphine or methadone (Table 145.2). **Morphine** is a short-acting opioid given every 3 hours as a weight-based or clinical sign-based regimen. **Methadone** is a long-acting opioid that can generally be given twice a day after loading doses. **Buprenorphine** is an effective agent that may be superior to morphine; its use may be associated with a short duration of treatment and length of stay, as well as few adverse effects and less use of additional medications. Clinical trials have shown methadone and buprenorphine to decrease length of treatment when compared with morphine. Buprenorphine and some methadone formulations contain high ethanol levels, which may be deleterious to the infant and should be avoided. Closely adhering to NAS treatment protocols with guidelines on initiation and weaning have been shown to decrease both length of treatment and length of stay.

Adjuvant therapy is generally initiated in the unusual situation when the primary opioid is not effective in controlling the signs of NAS. The two medications used as adjuvant therapy are **phenobarbital** and **clonidine**. American Academy of Pediatrics (AAP) guidelines suggest clonidine be used as adjuvant therapy; phenobarbital should be avoided if possible as some studies suggest long-term use can be associated with developmental delay.

Long-term studies of opioid-exposed infants are lacking, and many are confounded by co-exposures (e.g., alcohol), maternal health (e.g., poor nutrition), or social risk (e.g., trauma), all of which could influence developmental outcomes. Still, infants should be closely monitored to optimize developmental trajectory. In many states a diagnosis of NAS qualifies for early intervention services, which are part of the Individuals with Disability and Education Act Part C, and infants should be referred to this service. Other supportive referrals should be

Table 145.2 Medications Used in Pharmacologic Treatment of Neonatal Abstinence Syndrome

DRUG	INITIAL DOSING	DOSING INCREASES	WEANING SCHEDULE	ADD ADJUVANT THERAPY
Morphine	0.05 mg/kg/dose q3h	Increase dose 10–20%	10% of stabilizing dose q24h	>1 mg/kg/day of morphine Unable to wean for 2 days
Methadone	0.1 mg/kg/dose q6h for 4 doses	Increase to q4h if unable to capture	0.7 mg/kg/dose q12h × 2 doses, then 0.05 mg/kg/dose q12h × 2 0.04 mg/kg/dose q12h × 2 0.03 mg/kg/dose q12h × 2 0.02 mg/kg/dose q12h × 2 0.01 mg/kg/dose q12h × 2 0.01 mg/kg/dose q24h × 1	Unable to wean for 2 days
Buprenorphine	4 µg/kg q8h	2 µg/kg until maximum of 15 µg/kg	3 µg/kg/dose q8h × 3 doses 2 µg/kg/dose q8h × 3 2 µg/kg/dose q8h × 2 2 µg/kg/dose q24h × 1	Unable to wean for 2 days
Phenobarbital	20 mg/kg	—	5 mg/kg daily	N/A
Clonidine	1.5 µg/kg/dose q3h	25% dose escalation q24h	10% every day	N/A

N/A, Not available; q24h, every 24 hours.

considered, including home visitation programs and Early Head Start. Further, in the discharge process clinicians should also assess other risk, including HIV and HCV exposure, which must be followed in the outpatient setting. Hospitals should standardize the discharge process for opioid-exposed infants to ensure connection to postdischarge services.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 146

Fetal Alcohol Spectrum Disorder

Susan A. Friedman and Hallam Hurt

Alcohol is a known teratogen that can cause irreversible central nervous system (CNS) damage. Injury can include reduced brain volume, particularly for the frontal lobe, and thinning of the corpus callosum. These injuries can lead to CNS dysfunction that can range from relatively mild to severe. Prenatal alcohol exposure (PAE) affects all stages of brain development from neurogenesis to myelination, through mechanisms that include disrupted cell-cell interactions, altered gene expression, and oxidative stress leading to abnormalities such as reduced brain volume in the frontal lobe, striatum and caudate nucleus, thalamus, and cerebellum; thinning of the corpus callosum; and abnormal functioning of the amygdala.

PAE can result in a spectrum of outcomes. The term fetal alcohol spectrum disorder (FASD) is the umbrella term that encompasses a group of conditions associated with PAE. The FASD group of disorders includes fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defect (ARBD), and neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE).

EPIDEMIOLOGY

According to the CDC, approximately 1 in 7 pregnant women report consuming alcohol within the past 30 days. Approximately 20-30% report drinking at some point during the pregnancy, and more than 5% report binge drinking. consuming alcohol within the last 30 days, with ~20% reporting binge drinking. Because almost 50% of pregnancies in the United States are unplanned, unintentional PAE can occur before a woman knows she is pregnant.

PREVALENCE

FASDs are the most common causes of preventable developmental delay and intellectual disability. Prevalence rates vary across reports. The US Centers for Disease Control and Prevention (CDC) FAS Surveillance Network reported prevalence rate across several populations of 0.3 out of 1,000 children from 7 to 9 years of age. This prevalence rate is much lower than that obtained by active case ascertainment studies in the United States and Western Europe, which have estimated prevalence rates of 2–5%. Another study reported similar rates, 24-48 cases per 1,000 children (2.4–4.8%) for all FASDs, and 6-9 cases per 1,000 (0.6–0.9%) for FAS specifically. Studies that have examined PAE by anonymous meconium testing demonstrate 4.26 times greater identification of alcohol use during pregnancy compared with maternal self-report. Rates of FASDs have been reported to be higher in children living in poverty, in Indigenous populations, and in children living in foster care. The rate of FASDs for children in foster care has been found to be 10 to 15 times higher than that for children in the general population. FASDs often go undetected in these children, and as many as 86.5% of foster and adopted youth with FASDs go undiagnosed or are diagnosed incorrectly within the FASD spectrum. Children adopted internationally represent another high-risk group, particularly those adopted from Eastern Europe. Children adopted from orphanages and other children with a history of early trauma, such as those in foster care, may also exhibit symptoms of posttraumatic stress disorder (PTSD) and other neurobehavioral and developmental issues that can overlap with those of FASD, including those without physical features (ARND or ND-PAE). The impairments seen in children with an FASD may also include the negative impact of additional prenatal and postnatal risk factors.

DIAGNOSTIC SYSTEMS

The most widely used diagnostic guidelines are the Hoyme FASD diagnostic guidelines (revised 2016), the University of Washington 4-Digit Diagnostic Code (2004), the CDCFAS guidelines (revised

2004, only includes FAS), and the Canadian FASD guidelines (revised 2016).

These FASD diagnostic guidelines overlap but also have important distinctions. The Hoyme system uses more stringent alcohol exposure criteria than the 4-Digit Diagnostic Code. Both the Hoyme system (2016), and the 4-Digit Diagnostic Code system use the three diagnostic criteria of facial findings, growth restriction, and CNS abnormalities and both include a spectrum of disorders under the umbrella term of *fetal alcohol spectrum disorder* (FASD). However, they do differ in diagnostic tools, specific criteria used to define each category, and in diagnostic nomenclature. The result of these differences and others is that there may not be total agreement between the two in the diagnosis of a given patient. The CDC guidelines establish criteria only for FAS and require the three diagnostic criteria of facial findings, growth restriction, and CNS abnormalities, with or without documented PAE. In the updated Canadian guidelines, "fetal alcohol spectrum disorder" is considered a diagnostic term with two categories: FASD with sentinel facial features and FASD without sentinel facial features. These guidelines eliminate growth restriction as a required diagnostic criterion. They include an at-risk category for children with confirmed PAE who were too young to meet the criteria for neurodevelopmental deficits, or in whom assessment was incomplete. They also include a category for children with cardinal facial features without documentation or evidence of severe impairment in neurodevelopmental domains. There is no universal acceptance of one system. If less stringent criteria are used, the sensitivity increases, which may lead to overdiagnosis. Additional expert evaluation is then needed to confirm a diagnosis. In contrast, using more stringent criteria leads to greater specificity but may underdiagnose FASD.

Historical and Clinical Features

The historical and clinical features shared by all previously described diagnostic systems (although not required by all of the disorders) include five categories: (1) PAE, (2) three key facial features, (3) prenatal/postnatal growth restriction, (4) deficient brain growth and/or significant structural brain abnormalities, and (5) neurobehavioral impairment.

Prenatal Alcohol Exposure

A safe threshold or pattern of alcohol consumption during pregnancy has not been identified, and any PAE at any stage of gestation is believed to present a risk to a developing fetus. Significant alcohol exposure has been carefully defined in the 2016 updated Hoyme guidelines as follows.

One or more of the following exposures, beginning 3 months before pregnancy and continuing until delivery, with a standard drink defined as 1.5 oz of hard liquor, 5 oz of wine, or 12 oz of beer or wine cooler:

- ≥6 drinks/week for ≥2 weeks during pregnancy
- ≥3 drinks per occasion on ≥2 occasions
- Documented alcohol-related social or legal problems before or during pregnancy or a history of treatment for an alcohol-related condition
- Documentation of intoxication of blood, breath, or urine alcohol testing
- Positive testing with an established biomarker of alcohol exposure during pregnancy or at birth
- Positive finding on a validated screening tool for drinking during pregnancy

Information can be obtained from a variety of sources in addition to the birth mother, including family members, foster or adoptive parents, social service agencies who observed maternal alcohol consumption during pregnancy, or medical records that document PAE, alcohol treatment, or social, legal, or medical problems related to drinking during pregnancy. Binge drinking (4 or more drinks per occasion) has been shown to be the most harmful to fetal development. PAE in the first trimester leads to the classic facial dysmorphia associated with FAS and other structural defects. PAE can have other deleterious effects (e.g., spontaneous abortion, growth defect, CNS effects) on the fetus throughout the pregnancy.

Several well-validated screens are used to identify alcohol use in pregnant and nonpregnant women of childbearing years, including the assessments of Tolerance, Annoyance, Cut Down, Eye-Opener (T-ACE), Cut Back, Annoyed, Guilty, Eye-Opener (CAGE); Car; Relax; Alone; Forget; Friends; Trouble (CRAFFT); Alcohol Use Disorders Identification Test (Audit-C); and Tolerance, Worried, Eye-Opener, Amnesia, Kut Down (TWEAK). There are, however, no well-validated screens designed to ask about past consumption of alcohol. Pediatricians can ask the following two questions to determine the likelihood of significant PAE: "In the 3 months before you knew you were pregnant, how many times did you have 4 or more alcohol drinks in a day?" and "During your pregnancy, how many times did you have any alcohol?" If a positive response is given to either question, the clinician can follow up to determine the level of PAE by asking the following: (1) "During your pregnancy, on average, how many days per week did you have any alcohol?"; (2) "During your pregnancy, on a typical day when you had an alcoholic beverage, how many drinks did you have?"; and (3) "During your pregnancy, what was the maximum number of drinks that you had in a day?"

Dysmorphologic Facial Features

The three key, facial dysmorphologic features include short palpebral fissures, a thin vermilion border of the upper lip, and a smooth philtrum (Fig. 146.1). Measurement of the **palpebral fissure length (PFL)** is shown in Figure 146.2. There are several different PFL charts that can be used to plot this measurement. That of Hall is included here (Fig. 146.3), with additional charts listed under Additional Resources for Healthcare Providers. In addition, different diagnostic systems have different cutoffs to define the criteria. Evaluation of the philtrum and upper lip utilizes the Lip-Philtrum



Fig. 146.1 Examples of facial features of FAS in children of different ethnicities. **A**, White. **B**, Native American. **C**, Black. **D**, Asian. (*Copyright 2021 Susan (Astley) Hemingway PhD, University of Washington.*)

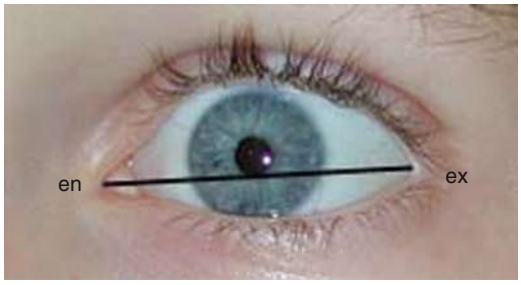

Fig. 146.2 The palpebral fissure length is defined by the distance between the endocanthion *(en)* and exocanthion *(ex)* landmarks. (*Copyright 2021 Susan (Astley) Hemingway PhD, University of Washington.*)

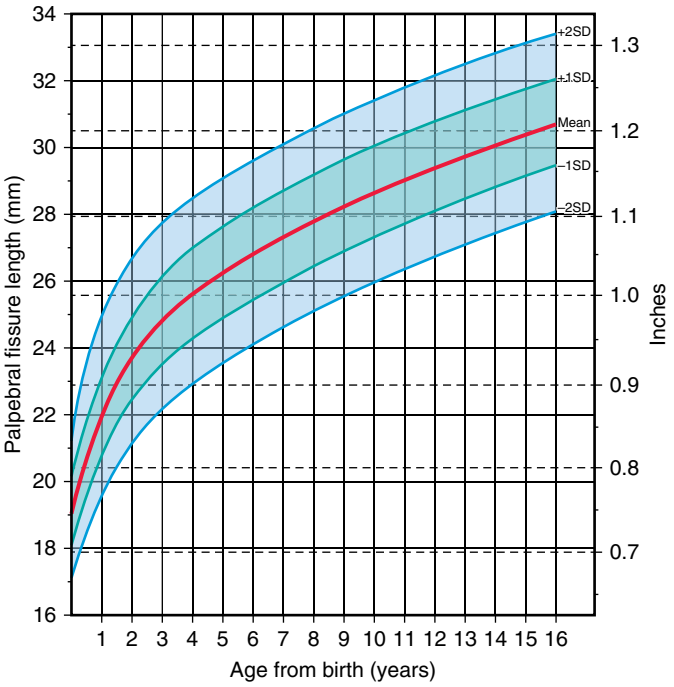

Fig. 146.3 Palpebral fissure measurements. (*From Hall JG, Froster-Iskenius UG, Allanson J, eds. Handbook of Normal Physical Measurements. Oxford: Oxford University Press; 1989: p. 150.*)

Guide developed at the University of Washington (Fig. 146.4), which can be obtained on request in digital format or as a laminated card from the University of Washington. Although this guide includes norms for White and Black children, additional work is needed on establishing norms for the three facial features across a wider range of racial groups.

Additional minor anomalies may also occur in association with PAE but are not included in the diagnostic criteria: mid-face hypoplasia, epicanthal folds, ptosis, strabismus, altered palmar crease ("hockey stick" and clinodactyly of the fifth finger [Fig. 146.5], "railroad track ears" [Fig. 146.6], hypoplastic nails, limited elbow supination, camptodactyly, hypertrichosis).

Prenatal/Postnatal Growth Deficiency

This is defined as ≤10th percentile for age (Hoyme and CDC) or ≤3rd percentile (4-Digit Diagnostic Code) for *either* height or weight. The systems also vary in the timing of the growth problems (prenatal/at birth, or at any point in life).

Deficient Brain Growth and Significant Structural Brain Abnormalities

Deficient brain growth is defined as an occipitofrontal head circumference (OFC) <10% for age, abnormal morphogenesis, or abnormal neurophysiology. The criteria additionally state that if the child has weight and height <10th percentile, then the OFC should be at or below the 3rd percentile. Structural brain abnormalities seen on brain imaging may include abnormalities of the corpus callosum, the cerebellum, or basal ganglia.

Neurobehavioral/Neurodevelopmental Impairment

These criteria can include abnormal findings on neurologic exam or seizures, and/or functional neurobehavioral or neurodevelopmental abnormalities. There is tremendous variability in the presentation of the neurobehavioral and neurocognitive features of children with FASD due to the timing and amount of PAE and unique characteristics of the birth mother and the child. The assessment of neurobehavioral impairment is also different for children under 3 years of age than for children 3 years or older.

The degree of developmental impairment can range from relatively mild delays to severe intellectual disability, although approximately 75% of individuals with an FASD *do not* have intellectual disability. In *infants*, the symptoms can be nonspecific and may include irritability, poor feeding, sleep difficulties, a tendency to become easily overstimulated, or difficulty forming attachments with caregivers. *Young children* may demonstrate developmental delays, inattention, impulsivity, internalizing and externalizing problems, social impairments and difficulty with peers, and behavioral difficulties such as mood lability, frequent tantrums, or aggression. The neurocognitive profile of children with an FASD that emerges at *elementary or middle school age* includes challenges with processing speed, memory, visual-spatial reasoning, math, auditory comprehension, use of pragmatic language, and executive functioning skills. In *adolescents*, difficulties with abstract reasoning, time and money management, and social and adaptive skills may become more pronounced.

The most common comorbid mental health condition seen in children with an FASD is attention-deficit/hyperactivity disorder (ADHD; see Chapter 50), which occurs in >50% of children. Individuals with FASD may also present with problems of self-regulation, impulse control, and adaptive functioning. Additional mental health disorders typically seen in children and adolescents include oppositional defiant and conduct disorder, anxiety disorder, adjustment disorder, sleep disorder, mood disorders (e.g., depression, bipolar disorder), and disinhibited social engagement disorder. FASD may increase the severity or complexity of these conditions.

DIAGNOSTIC CRITERIA

Five diagnoses included under the FASD umbrella include the following:

1. Fetal alcohol syndrome (FAS)
2. Partial fetal alcohol syndrome (pFAS)
3. Alcohol related neurodevelopmental disorder (ARND)
4. Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)
5. Alcohol related birth defects (ARBD)

The previously described clinical features with or without a history PAE are used to define the disorders within the FASD spectrum (Tables 146.1-146.5). As noted earlier, the criteria do vary somewhat depending upon which diagnostic system is used.

DIFFERENTIAL DIAGNOSIS

It is important to consider other causes of the facial features of FAS and pFAS, as each of these can be seen in certain genetic and teratogenic exposure conditions. Genetic conditions can include Williams syndrome, Dubowitz syndrome, Noonan syndrome, 22q11.2 deletion (velocardiofacial syndrome), Cornelia de Lange syndrome, chromosome 15q duplication syndrome, and others. Teratogenic exposure conditions include fetal valproate syndrome, fetal hydantoin syndrome, maternal phenylketonuria

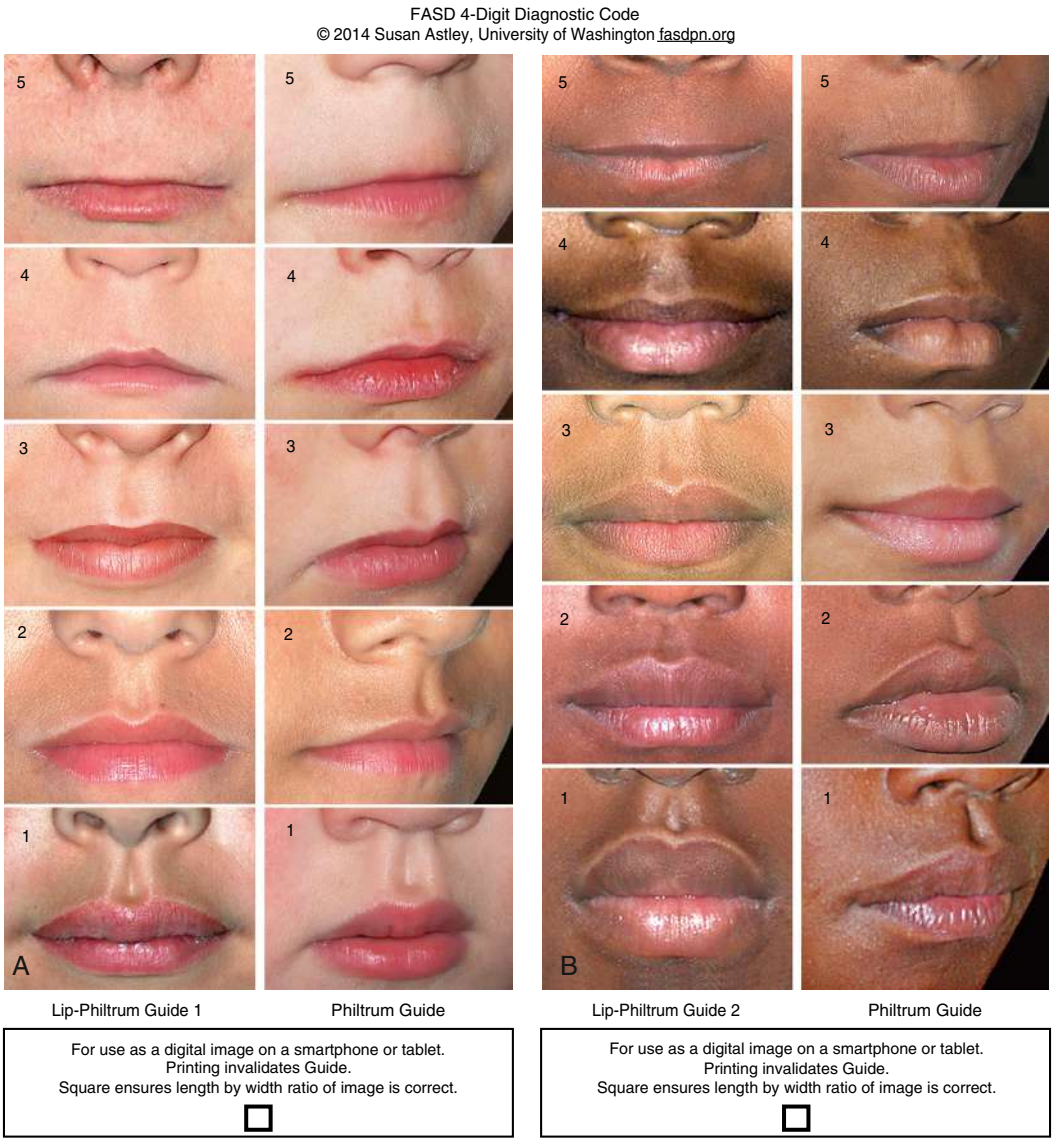

Fig. 146.4 University of Washington Lip-Philtrum Guides 1 (A) and 2 (B) are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip thickness and philtrum depth with Rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterize the FAS facial phenotype. Guide 1 is used for Whites and all other races with lips like Whites. Guide 2 is used for Blacks and all other races with lips like Blacks. Free digital images of these guides for use on smartphones are available from astley@uw.edu. (*Copyright 2021 Susan (Astley) Hemingway PhD, University of Washington.*)

(PKU) effects, toluene embryopathy, and others. Therefore a genetics evaluation may be warranted, especially when there is unconfirmed PAE.

The neurobehavioral issues associated with FASD can be difficult to distinguish from those of other behavioral health disorders, such as autism spectrum disorder, ADHD, intellectual disability, reactive attachment disorder, PTSD, exposure to other maternal substance use during pregnancy, and others. This is particularly the case when the FASD facial features are not present. Children who experience "adverse childhood experiences" (ACEs), such as neglect, abuse, poverty, and parental substance abuse, can have similar findings of hyperactivity, poor impulse control, emotional dysregulation, deficits in executive function, and memory weaknesses as children with FASD. Furthermore, these disorders are not mutually exclusive and more than one underlying disorder can result in the neurobehavioral issues found.

OUTCOMES

Children with an FASD are at higher risk for victimization and bullying, often due to poor social judgment. Children and adolescents who are not identified early and treated aggressively are significantly more likely to have secondary disabilities, including encounters with juvenile justice and incarceration, substance abuse problems, severe mental health problems, sexual promiscuity and other inappropriate sexual behaviors, high rates of school failure, dropout and under- or unemployment, health problems, and premature death. Children and adolescents with an FASD have a 95% lifetime likelihood of having a mental health diagnosis and are at higher risk for suicide. Although an FASD cannot be cured, the long-term negative effects of the brain injury caused by PAE can be reduced through aggressive, sustained intervention initiated early. Factors associated with a better outcome include early diagnosis (under age 6 years), a stable and nurturing home, lack of exposure to violence, full assessment for disabilities and adequate provision of appropriate education, therapies, and social services. Prevention of FASD and early identification and interventions for children with an FASD is essential and has become an important goal of the CDC and other organizations.



Fig. 146.5 Characteristic hand findings that can be seen in a child with an FASD: curved fifth finger (clinodactyly) and upper palmar crease that widens after the bend and ends between the second and third fingers ("hockey stick" crease). (*Courtesy Darryl Leja, NHGRI, National Institutes of Health.*)



Fig. 146.6 Ear findings that can be seen in a child with an FASD: "railroad track" appearance of ear creases. (*Courtesy Darryl Leja, NHGRI, National Institutes of Health.*)

Table 146.1 Diagnostic Criteria for Fetal Alcohol Syndrome

ALL of the following, *with or without* documented prenatal alcohol exposure:

Facial features (Hoyme system requires two or more, 4-Digit Diagnostic Code requires all three):
- Palpebral fissures ≤10th percentile (Hoyme system) or ≤3rd percentile (4-Digit code)
- Thin upper lip (ranking of 4 or 5 on racially normed Lip-Philtrum Guide*)
- Smooth philtrum (ranking of 4 or 5 on racially normed Lip-Philtrum Guide*)

Prenatal and/or postnatal growth deficiency:
- Height and/or weight ≤10% for age and sex at any point of time (prenatal or postnatal)
- Adjust for gestational age if preterm. (4-Digit Diagnostic Code puts emphasis on short stature)

Deficient brain growth, abnormal brain formation or neurophysiology: one or more of following:
- Head circumference ≤10th % (Hoyme system) or ≤3rd percentile (4-Digit Diagnostic Code)
- Structural brain abnormalities
- Recurrent nonfebrile seizures with other causes excluded (Hoyme system)

Neurobehavioral impairment:
- For children <3 y/o: Developmental delay ≥1.5 SD below the mean
- For children 3 y/o or older (either of the following):
  - Cognitive impairment: Scores ≥1.5 SD below mean (Hoyme) or ≥2 SD below mean (4-Digit Diagnostic Code) either for global abilities or for at least one neurobehavioral domain (executive function, specific learning impairment, memory impairment, or visual-spatial impairment). The Hoyme system defines impairment domain as normal or abnormal. The 4-Digit Diagnostic Code has three domains defined: normal, moderate, severe.
  - Behavioral impairment without cognitive impairment: ≥1.5SD below mean in self-regulation (mood or behavioral regulation), attention deficit, or impulse control.

*The Hoyme system and the 4-Digit Diagnostic Code have different Lip-Philtrum Guides.
SD, Standard deviation.

INTERVENTIONS AND TREATMENTS

Given the heterogeneity of presenting problems associated with the FASDs, interventions need to be tailored to address each individual child's or adolescent's profile of strengths and difficulties. Studies support that the most successful interventions begin early and continue across the life span, include a preventive focus, are intensive and individualized, address multiple domains of functioning, include parent education and training, and are coordinated across systems of care.

Behavioral issues seen in children with FASD can be difficult for parents to manage and can cause significant stress within the home. These children often have impaired cause-and-effect understanding and therefore may not respond to traditional behavior modification strategies. Pediatricians can help support families by providing parenting tips suggested by the CDC, such as providing a structured environment and stable routines, using simple concrete language and lots of repetition, viewing the difficult behaviors as brain based rather than willful misbehavior, focusing on strengths, and providing an abundance of positive reinforcement. Specific programs include *Families Moving Forward* and *Parents and Children Together* teaching parents strategies designed to improve self-regulation and executive function, and decreasing child behavior problems. Children with FASD often have significant difficulties with social functioning, such as interpreting social cues and communicating in social settings. Programs such as *Children's Friendship Training* provides group-based, parent-assisted intervention that teaches social skills, which have been shown to improve standardized rating of social skills. Programs such as *Good Buddies* provide classes that address issues related to impaired social skills. Children with FASD may have decreased safety awareness, poor judgement, and impulsivity, which can place them at increased risk for unintentional injuries. A video-based intervention, *Fire and Street Safety,* was developed to address this. Children who participated showed significant improvement in safety-related knowledge and appropriate behavioral responses following the training and were also able to apply this training to real-world situations.

Young children with FASD are generally eligible for early intervention therapies (occupational therapy, physical therapy, speech therapy, and developmental instruction) and should be referred for these services as needed. Older children with an FASD often have difficulties with verbal and spatial learning, executive functioning, adaptive skills, social skills and peer relations, and mental health, which can interfere with academic performance. High rates of school failure and disruption are reported for this population. Difficulties with memory often require simplification of instructions, repetition, and patience. A home and school environment that is structured and predictable can also help to address this issue. To enhance generalizability of skills and to ensure they are encoded into memory, children with an FASD require consistent and predictable interventions, simplified directions, repeated instructions, and reduced distractions in the classroom. Classroom intervention programs such as *Cognitive Control Therapy* have been found to result in significant improvements in classroom behavior and academic achievement. Programs have also been developed that

Table 146.2 Diagnostic Criteria for Partial Fetal Alcohol Syndrome

- WITH documented prenatal alcohol exposure (requires A and B):
  - A. Facial features (at least two of three)
  - B. Neurobehavioral impairment (same as for FAS), i.e., leaves out brain abnormalities and growth deficiency
- WITHOUT documented prenatal alcohol exposure (requires A, B, and C):
  - A. Facial features (at least two of three)
  - B. Growth deficiency OR deficient brain growth/structural brain abnormalities/recurrent seizures (at least one of these)
  - C. Neurobehavioral impairment (same as for FAS), i.e., same as FAS except it is EITHER growth deficiency OR brain growth/structural brain abnormalities/recurrent seizures (does not require both)

Note that the diagnosis of FAS and pFAS are the only FASDs that can be diagnosed in the absence of a confirmed maternal history of PAE.

FAS, Fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome.

Table 146.3 Diagnostic Criteria for Alcohol-Related Neurodevelopmental Disorder

Requires A *and* B:

Note: *Cannot* be diagnosed definitively in children <3 yr old

A. Documented prenatal alcohol exposure

B. Neurobehavioral impairment:
- WITH cognitive impairment: Global delay OR deficit in at least TWO neurobehavioral domains (executive function, specific learning impairment, memory impairment, visual-spatial impairment)
- WITHOUT cognitive impairment: Behavioral deficit in at least TWO domains (behavioral regulation, attention, impulse control)

Table 146.4 Diagnostic Criteria for Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

ND-PAE is a mental health disorder (rather than a medical disorder) included in the DSM-5 (2013) as a "new clarifying term" that encompasses the range of developmental disabilities associated with PAE that affect function and are not due to other conditions. This diagnosis requires:
- ≥1 deficit in neurocognition
- ≥2 deficits in adaptive functioning (at least one in communication or social communication and interaction)
- ≥1 deficit in self-regulation
- History of maternal consumption of more than 13 alcoholic drinks in any 30-day period of the pregnancy or more than 2 alcoholic drinks in one sitting
- Onset of the disorder in childhood
- The findings cause clinically significant distress or impairment in important areas of functioning and are not better explained by other causes (medication, medical conditions, genetic disorders, or environmental neglect)

Although the diagnosis of ND-PAE overlaps with ARND, ND-PAE aims to describe the *behavioral and mental health effects* on an individual with PAE. Unlike ARND, a diagnosis of ND-PAE can be given with or without the physical characteristics of FAS (ARND does not include physical characteristics) and the diagnosis of ND-PAE can be given in addition to FAS or pFAS.

ARND, Alcohol-related neurodevelopmental disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; FAS, fetal alcohol syndrome; ND-PAE, neurobehavioral disorder associated with prenatal alcohol exposure; pFAS, partial fetal alcohol syndrome.

address specific areas of learning, such as *Language and Literacy Training Math Interactive Learning Experience*. A cognitive-based intervention, the *Alert Program* has been adapted to address self-regulation and executive function difficulties in children with FAS or ARND living in foster care or adoptive homes. A video game, *GoFar*, was developed by to address issues of self-regulation. An intervention that uses rehearsal training interventions has been shown to result in improvement in working memory. Children with FASD have been found to show deficits in adaptive functioning more significant than expected based on their cognitive testing. Occupational therapy to address this issue can help to decrease the significant level of supervision and support required of parents and caregivers.

Table 146.5 Alcohol-Related Birth Defects

This diagnosis refers to a pattern of structural birth defects and other congenital abnormalities that can be characteristic of FASD.

Requires both A *and* B

A. Documented prenatal alcohol exposure

B. One or more specific major malformations found to be the result of prenatal alcohol exposure:
- Cardiac: ASD, VSD, aberrant great vessels, conotruncal heart defects
- Skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis
- Renal: kidney/ureteral malformations
- Eyes: strabismus, ptosis, retinal vascular abnormalities, optic nerve hypoplasia
- Ears: conductive or neurosensory hearing loss

ASD, Atrial septal defect; FASD, fetal alcohol spectrum disorder; VSD, ventricular septal defect.

There are no medications that are approved specifically for FASDs, but some medications may be used for symptom management. These can include stimulants (for hyperactivity, inattention, and poor impulse control), antidepressants, neuroleptics, and antianxiety drugs. Children with an FASD are often treated with a higher number of drugs and at higher doses, likely because of atypical or less favorable responses. Such atypical responses may require an adjustment in medication or discontinuation. Stimulant medication use in patients with FASD is controversial but is often considered, since there is a high prevalence of ADHD-like symptoms in this population. Stimulants can lead to some improvement in hyperactivity but may be less helpful for impulsivity and attention, and the rate of efficacy in general is not as high as in idiopathic ADHD. A diagnosis in the FASD spectrum should, in fact, be considered in a child with ADHD who has an atypical response to such medications. The efficacy of nonstimulant medications used for ADHD, such as alpha-2 agonists is being studied and may be shown to be helpful. Studies are also underway for use of choline supplementation and treatment with atomoxetine (a selective norepinephrine reuptake inhibitor). Data regarding the use of SSRI (selective serotonin reuptake inhibitors) medications, antipsychotics, and mood stabilizers are limited in terms of efficacy and safety.

THE PEDIATRICIAN/PRIMARY CARE PROVIDER'S ROLE

Pediatricians and other primary care providers need to document findings related to PAE and refer the child for a full evaluation. Indications for referral for further evaluation for FASD include confirmed history of significant PAE, concern raised by the caregiver about the possibility of FASD, all three facial features present, one or more facial features plus growth deficits, and one or more facial features along with one or more CNS abnormalities ± growth deficits. Evaluation for an FASD is best done by a multidisciplinary team that can provide a medical, genetic, and neuropsychologic assessment. This team might include a developmental behavioral pediatrician, psychologist/psychiatrist, geneticist, social worker, speech therapist, occupational therapist, physical therapist, and educational therapist/special education teacher. Evaluations by audiology and ophthalmology should be included if not already completed.

Once a diagnosis of an FASD is made, the pediatrician's/primary care providers role is important in establishing a medical home for the child that provides coordinated care between medical and mental health professionals, therapists, and educators who can help and support the child and family. The American Academy of Pediatrics (AAP) has developed an FASD toolkit (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/fetal-alcohol-spectrum-disorders-toolkit/Pages/default.aspx) that includes a "Flow Diagram for Medical Home Evaluation of Fetal Alcohol Spectrum Disorders" to assist primary care providers in identifying children with an FASD and managing their challenges in an effort to reduce the lifelong adverse consequences.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 147

Infants of Diabetic Mothers

Kesi C. Yang

Diabetes (type 1, type 2, or gestational) in pregnancy increases the risk of complications and adverse outcomes in the mother and the baby. Complications related to diabetes are milder in gestational vs pregestational (preexisting type 1 or type 2) diabetes. Pregnancy outcomes are correlated with onset, duration, and severity of maternal hyperglycemia. Preconception planning and tight glycemic control (hemoglobin A_{1c} [HbA_{1c}] <6.5%) is crucial in pregestational diabetes to achieve the best outcomes for the mother and the baby. The risk of **diabetic embryopathy** (neural tube defects, cardiac defects, caudal regression syndrome) and spontaneous abortions is highest in those with pregestational diabetes who have poor control (HbA_{1c} >7%) in the first trimester. The risk of congenital malformations in **gestational diabetes** is only slightly increased compared to the general population, because the duration of diabetes is less and hyperglycemia occurs later in gestation (typically >25 weeks).

Mothers with pregestational and gestational diabetes have a high incidence of complications during the pregnancy. Polyhydramnios, preeclampsia, preterm labor (induced and spontaneous), and chronic hypertension occur more frequently in mothers with diabetes. Accelerated fetal growth is also common, and 36–45% of **infants of diabetic mothers (IDMs)** are born large for gestational age (LGA). Restricted fetal growth is seen in mothers with pregestational diabetes and vascular disease, but it is less common. Fetal mortality rate is greater in both pregestational and gestational diabetic mothers than in nondiabetic mothers, but the rates have dropped precipitously over the years. Fetal loss throughout pregnancy is associated with poorly controlled maternal diabetes, especially **diabetic ketoacidosis**. The neonatal mortality rate of IDMs is >5 times that of infants of nondiabetic mothers and is higher at all gestational ages and in every birthweight for gestational age category. The rate is higher in women with pregestational diabetes, smoking, obesity, hypertension, and poor prenatal care.

PATHOPHYSIOLOGY

The probable pathogenic sequence is that maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia, or hyperinsulinism. It is important to recognize that while maternal glucose crosses the placenta, maternal and exogenous insulin does not. Fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis (Fig. 147.1). Related pathologic findings are hypertrophy and hyperplasia of the pancreatic β cells, increased weight of the placenta and infant organs (except the brain), myocardial hypertrophy, increased amount of cytoplasm in liver cells, and extramedullary hematopoiesis. Hyperinsulinism and hyperglycemia produce fetal acidosis, which may result in an increased rate of stillbirth. Separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on hyperinsulinism, leading to hypoglycemia during the first few hours after birth. The risk of rebound hypoglycemia can be diminished by tight blood glucose control during labor and delivery.

Hyperinsulinemia has been documented in infants of mothers with pregestational and gestational diabetes. The infants of mothers with *pregestational* diabetes have significantly higher fasting plasma insulin levels than normal newborns, despite similar glucose levels, and respond to glucose with an abnormally prompt elevation in plasma insulin. After arginine administration, they also have an enhanced insulin response and increased disappearance rates of glucose compared with normal infants. In contrast, fasting glucose production and utilization rates are diminished in infants of mothers with *gestational* diabetes. Although hyperinsulinism is probably the main cause of hypoglycemia, the diminished epinephrine and glucagon responses that occur may be contributing factors. Infants of mothers with pregestational and gestational diabetes are at risk for neonatal hypoglycemia in the first hours of life, with an increased risk in both large- and small-for-gestational-age infants. Aggressive screening and treatment is recommended as outlined later.

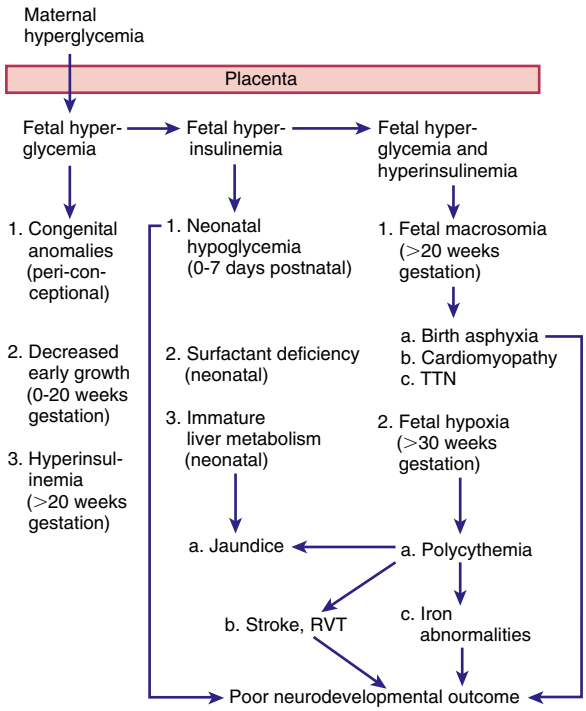

Fig. 147.1 The fetal and neonatal events attributable to fetal hyperglycemia *(column 1)*, fetal hyperinsulinemia *(column 2)*, or both in synergy *(column 3)*. Time of risk is denoted in parentheses. RVT, Renal vein thrombosis; TTN, transient tachypnea of the newborn. (*From Nold JL, Georgieff MK. Infants of diabetic mothers. Pediatr Clin North Am. 2004;51:619–637.*)

CLINICAL MANIFESTATIONS

Infants of mothers with pregestational diabetes and those of mothers with gestational diabetes often bear a surprising resemblance to each other (Fig. 147.2). They tend to be macrosomic as a result of increased body fat and enlarged viscera, with puffy, plethoric facies resembling those of patients who have been receiving corticosteroids. These infants may also be of normal birthweight if diabetes is well controlled or low birthweight if they are delivered before term or if their mothers have associated diabetic vascular disease. Infants that are macrosomic or LGA are at high risk of birth trauma (brachial plexus injury) and birth asphyxia because of not only their large size but also their decreased ability to tolerate stress, especially if they have cardiomyopathy and other effects of fetal hyperinsulinemia (Table 147.1).

Hypoglycemia develops in approximately 25–50% of infants of mothers with pregestational diabetes and 15–25% of infants of mothers with gestational diabetes, but only a small percentage of these infants become symptomatic. The probability that hypoglycemia will develop in such infants increases with higher cord or maternal fasting blood glucose levels. The nadir in an infant's blood glucose concentration is usually reached between 1 and 3 hours of age. Hypoglycemia can persist for 72 hours and in rare cases last up to 7 days. Frequent feedings can be used to treat the hypoglycemia, but some infants require intravenous (IV) dextrose.



Fig. 147.2 Macrosomic, plethoric infant of a mother with gestational diabetes. The baby was born at 38 weeks of gestation but weighed 9 lb, 11 oz (4,408 g). Mild respiratory distress was the only symptom other than appearance.



Fig. 147.3 Caudal dysplasia sequence. Newborn male infant with a normal upper body and a short lower segment. (*Modified from Jones KL, Jones MC, Del Campo M, eds. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 1, p. 897.*)

Table 147.1 Morbidity in Infants of Diabetic Mothers

Congenital anomalies
Heart failure and septal hypertrophy of heart
Surfactant deficiency, respiratory distress syndrome, transient tachypnea of the newborn, persistent pulmonary hypertension
Hyperbilirubinemia
Hypoglycemia, hypocalcemia, hypomagnesemia
Macrosomia, nerve injury related to birth trauma
Renal vein thrombosis
Small left colon
Unexplained intrauterine demise
Polycythemia
Visceromegaly
Predisposition to later-life obesity, insulin resistance, and diabetes

From Devaskar SU, Garg M. Disorders of carbohydrate metabolism in the neonate. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine*, 10th ed. Philadelphia: Elsevier; 2015: Box 95-3.

The infants tend to be jittery, tremulous, and hyperexcitable during the first 3 days after birth, although hypotonia, lethargy, and poor feeding may also occur. Early appearance of these signs is more likely to be related to hypoglycemia but can also be caused by hypocalcemia and hypomagnesemia, which also occur in the first 24-72 hours of life due to delayed response of the parathormone system. Perinatal asphyxia is associated with increased irritability and also increases the risk of hypoglycemia, hypomagnesemia, and hypocalcemia.

Tachypnea develops in many IDMs during the first 2 days after birth and may be a manifestation of hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia. IDMs have a higher incidence of **respiratory distress syndrome** (RDS) than do infants of nondiabetic mothers born at comparable gestational age. The greater incidence is likely related to an inhibitory effect of insulin on surfactant protein expression. **Polycythemia** often occurs with RDS as they are both a result of fetal hyperinsulinism.

Cardiomegaly is common, and heart failure occurs in 5–10% of IDMs. Interventricular septal hypertrophy may occur and may manifest as **transient idiopathic hypertrophic subaortic stenosis**. This is thought to result from chronic hyperglycemia and chronic hyperinsulinism leading to glycogen loading in the heart. Inotropic agents worsen the obstruction and are contraindicated. β-Adrenergic blockers have been shown to relieve the obstruction, but ultimately the condition resolves spontaneously over time.

Acute neurologic abnormalities (lethargy, irritability, poor feeding) can be seen immediately after birth. The symptoms will resolve with treatment of the underlying cause but may persist for weeks if caused by birth asphyxia. Neurologic development and ossification centers tend to be immature and to correlate with brain size (which is not increased) and gestational age rather than total body weight in infants of mothers with gestational and pregestational diabetes. In addition, IDMs have an increased incidence of hyperbilirubinemia, polycythemia, iron deficiency, and renal vein thrombosis. Renal vein thrombosis should be suspected in the infant with a flank mass, hematuria, and thrombocytopenia.

There is a fourfold increase in **congenital anomalies** in infants of mothers with pregestational diabetes, and the risk varies with HbA_{1c} during the first trimester when organogenesis occurs. The recommended goal for periconceptual HbA_{1c} is <6.5%. Although the risk of congenital malformations increases with increasing HbA_{1c} levels, there may still be an increased risk in the therapeutic goal range. Congenital anomalies of the central nervous system and cardiovascular system are most common, including failure of neural tube closure (encephalocele, meningomyelocele, and anencephaly), transposition of great vessels, ventricular septal defect (VSD), atrial septal defect (ASD), hypoplastic left heart, aortic stenosis, and coarctation of the aorta. Other less common anomalies include caudal regression syndrome (Fig. 147.3), intestinal atresia, renal agenesis, hydronephrosis, and cystic kidneys. **Small left colon syndrome** is a rare anomaly that develops in the second and third trimester because of rapid fluctuations in maternal and therefore fetal glucose, leading to impaired intestinal motility and subsequent intestinal growth. Prenatal ultrasound and a thorough newborn physical examination will identify most of these anomalies. High clinical

suspicion and a good prenatal history will help identify needed screening for subtle anomalies.

TREATMENT

Preventive treatment of IDMs should be initiated before birth by means of preconception and frequent prenatal evaluations of all women with preexisting diabetes and pregnant women with gestational diabetes. This involves evaluation of fetal maturity, biophysical profile with nonstress testing (NST), Doppler velocimetry, and planning of the delivery of IDMs in hospitals where expert obstetric and pediatric care is continuously available. Preconception glucose control reduces the risk of anomalies and other adverse outcomes in women with pregestational diabetes, and glucose control during labor reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy (average daily glucose levels <95 mg/dL and $HgbA_{1c}$ <6.5%, if safely achievable without hypoglycemia) deliver infants with birthweight and anthropomorphic features similar to those of infants of nondiabetic mothers. Treatment of gestational diabetes (diet, glucose monitoring, insulin, and oral antihyperglycemic treatment with metformin or glyburide as needed) decreases the rate of serious perinatal outcomes (death, shoulder dystocia, bone fracture, or nerve palsy). Continuous glucose monitoring has been increasingly used in pregnancy to achieve these purposes. In these mothers, the incidence of macrosomia and neonatal hypoglycemia is similar to that in mothers with insulin-treated gestational diabetes.

Regardless of size, IDMs should initially receive close observation and care. All infants should initiate feedings within 1 hour after birth. A screening glucose test should be performed no sooner than 30 minutes of life but no later than 2 hours and should be performed immediately in symptomatic infants. Defining precise glucose thresholds in neonates remains a challenge. The American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) have both published guidelines based on observational data and expert opinion. These guidelines are adapted within individual institutions, with one example included in Figure 147.4. The AAP recommends maintaining a blood glucose level greater than 40 mg/dL (2.2 mmol/L) in the first 4 hours of life and greater than 45 mg/dL in the first 4 to 24 of life (2.5 mmol/L). In comparison, the PES recommends maintain a threshold of greater than 50 mg/dL (2.8 mmol/L) in the first 48 hours.

Feeding is the initial treatment for *asymptomatic* hypoglycemia. Oral or gavage feeding with breast milk or formula per maternal preference can be given. **Dextrose gel** has been shown to be a safe and

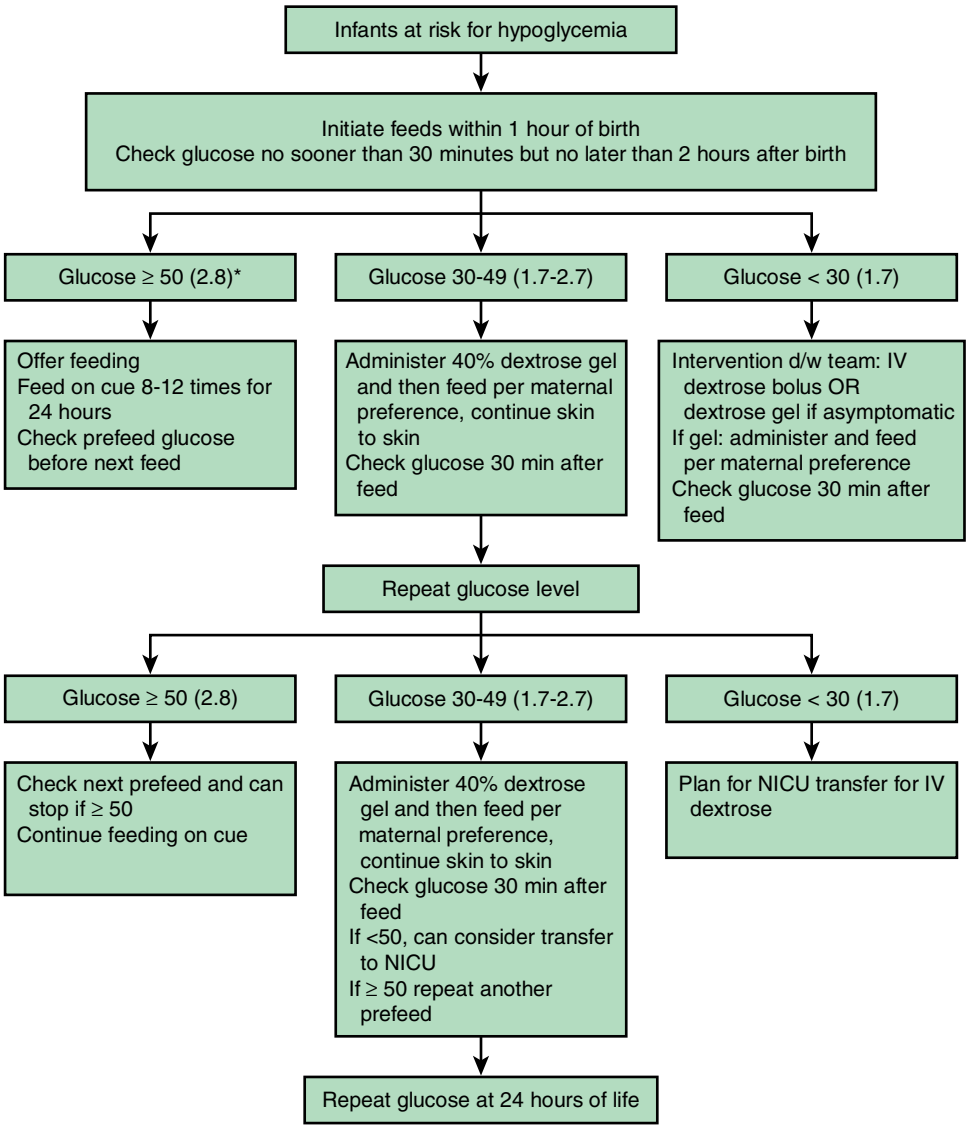

Fig. 147.4 Neonatal hypoglycemia algorithm at the Hospital of the University of Pennsylvania. This was derived from institutional consensus and meant to serve as a sample management protocol as there is no defined threshold for neonatal hypoglycemia in the first day of life. IV, Intravenous; NICU, neonatal intensive care unit. *Units are mg/dL (mmol/L).

effective adjunct to feeding and should be administered if available. Infants with *persistent* (and unresponsive to oral therapy) hypoglycemia should be treated with IV glucose (bolus followed by continuous infusion), especially if symptomatic. If question arises about an infant's ability to tolerate oral feeding, a continuous peripheral IV infusion at a rate of 4-8 mg/kg/min should be given. Neurologic symptoms of hypoglycemia *must* be treated with IV glucose. Bolus injections of hypertonic (25%) glucose should be avoided because they may cause further hyperinsulinemia and potentially produce rebound hypoglycemia (see Chapter 113). For treatment of hypocalcemia and hypermagnesemia, see Chapters 121.4 and 121.5; for RDS treatment, see Chapter 126; and for treatment of polycythemia, see Chapter 141.

PROGNOSIS

The subsequent incidence of diabetes mellitus in IDMs is higher than that in the general population because of genetic susceptibility in all types of diabetes. Infants of mothers with either pregestational diabetes or gestational diabetes are at risk for obesity and impaired glucose metabolism in later life as a result of intrauterine exposure to hyperglycemia. Disagreement persists about whether IDMs have a slightly increased risk of impaired intellectual development because of the many confounding factors (e.g., parental education, maternal age, neonatal complications). In general, the outcomes have improved over the last several decades due to increased awareness, screening, and improved prenatal care for pregnant women with diabetes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 148

Epidemiology of Infections

Dustin D. Flannery

Neonatal infections are often classified by their timing relative to birth and include congenital, perinatal, early-onset, and late-onset disease. This categorization is clinically useful because infectious mechanisms, etiologies, and outcomes are fairly distinct for each, although there is some overlap between the different types. **Congenital infection** denotes infection acquired in utero. Such infections are often associated with injury to developing organs, depending on the timing of infection during gestation (see Chapter 149). **Perinatal infection** indicates acquisition around the time of delivery. Perinatally acquired organisms include both bacteria and viruses, some of which are the same as those causing congenital infection, but often manifest with different features. **Early-onset infection** occurs in the first 3 days after birth and is generally the consequence of infection caused by organisms acquired during the perinatal period. **Late-onset infection** occurs after 3 days and is caused by organisms that are typically acquired in the postnatal period. Notably, some studies categorize early-onset and late-onset infections as within the first 7 days of age and after 7 days, respectively, particularly for infants not continuously admitted to the hospital from birth, who are exposed to pathogens in the community.

Neonates are prone to infection for multiple reasons, namely because of their lack of fully responsive innate immunity (Fig. 148.1). Attenuated immune responses often result in minimal or nonspecific clinical manifestations, and effective treatment requires attention to subtle signs of infection and known risk factors. Compared with older infants, neonates are often treated empirically with systemic antimicrobials while awaiting results of laboratory investigations. Preterm infants are particularly susceptible to infection because of their decreased innate immune and barrier defenses, need for invasive medical devices such as central venous catheters, and prolonged hospitalizations. The term "neonatal sepsis" typically refers to culture-confirmed infection of the blood, cerebrospinal fluid, and/or urine, though definitions vary across studies.

INCIDENCE

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. Neonatal infections are more common in areas with limited access to healthcare than in areas with a well-established healthcare infrastructure. Estimated incidence rates vary based on the case definition, geographical region, and the population studied. The overall global incidence of neonatal sepsis and other severe infections remains unknown given the lack of data from many countries, though the disease is common and often fatal. The global incidence is estimated at 2,824 cases per 100,000 live births; ~18% are fatal. For congenital infections, the incidence varies greatly depending on the specific infectious etiology and geographic region, though low- and middle-income countries have the greatest burden of disease.

The overall incidence of early-onset infection in the United States is approximately 1 per 1,000 live births and is dramatically higher among infants born preterm. The incidence varies significantly by gestational age (GA) and is highest among infants with a GA of 22 to 28 weeks (18.5 cases per 1,000 births). A 2021 report of over 84,000 very preterm infants at centers in the United States estimated the incidence of early-onset infection at 13.5 per 1,000 births; the incidence again varied substantially by GA (Table 148.1) and was highest for infants born <24 weeks (45.4 per 1,000 births). Similar to early-onset infection, late-onset infection incidence is inversely related to the degree of prematurity with significant variation across centers and geography. Among hospitalized newborns, 0.6–14% develop late-onset infection, with up to 40% of very preterm infants suffering from at least one episode.

MICROBIOLOGY

Infection microbiology is critically important to inform preventative strategies, as well as empiric and targeted antimicrobial therapies. A number of bacterial and nonbacterial pathogens can infect fetuses and newborns. Although there is overlap, pathogen types may be distinguished by timing of infection (Table 148.2).

The TORCH pneumonic, although not all-encompassing, is used to describe common causes of most often congenital or perinatal but also postnatal infection (see Table 148.2): toxoplasmosis, *Treponema pallidum* (syphilis), rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and other pathogens including parvovirus B19, varicella, and tuberculosis (TB). For pathogens causing congenital (prenatal), perinatal, and postnatal infection, modes of transfer include transplacental infection, exposure during labor and delivery through an infected or colonized birth canal, or from contact with an infected caretaker and/or infected breast milk (see Chapter 149). Some viral infections (e.g., CMV) can be substantial causes of disease whether acquired during gestation or acquired postpartum, whereas others (e.g., respiratory syncytial virus) are typically acquired only in the postnatal period (Fig. 148.2).

The two most common bacterial causes of **early-onset infection** are group B *Streptococcus* (GBS) and *Escherichia coli*; GBS is most common among term infants, whereas *E. coli* is the predominant pathogen among preterm infants. Approximately 30% of early-onset infections are caused by organisms other than GBS or *E. coli* (see Table 148.2). Coagulase-negative staphylococci (CONS) are the predominant cause of **late-onset infection** in hospitalized neonates, often accounting for 50–80%. Other common causes (see Table 148.2) include *Staphylococcus aureus*, gram-negative bacilli (*E. coli, Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp.), and fungi (*Candida* spp.). In Asia and Africa additional pathogens cause early-onset sepsis (*Acinetobacter* spp., *Klebsiella pneumoniae*); these pathogens are often resistant to first-line antibiotics.

Microorganisms causing pneumonia acquired during labor and delivery include GBS, gram-negative enteric aerobes, *Listeria monocytogenes,*

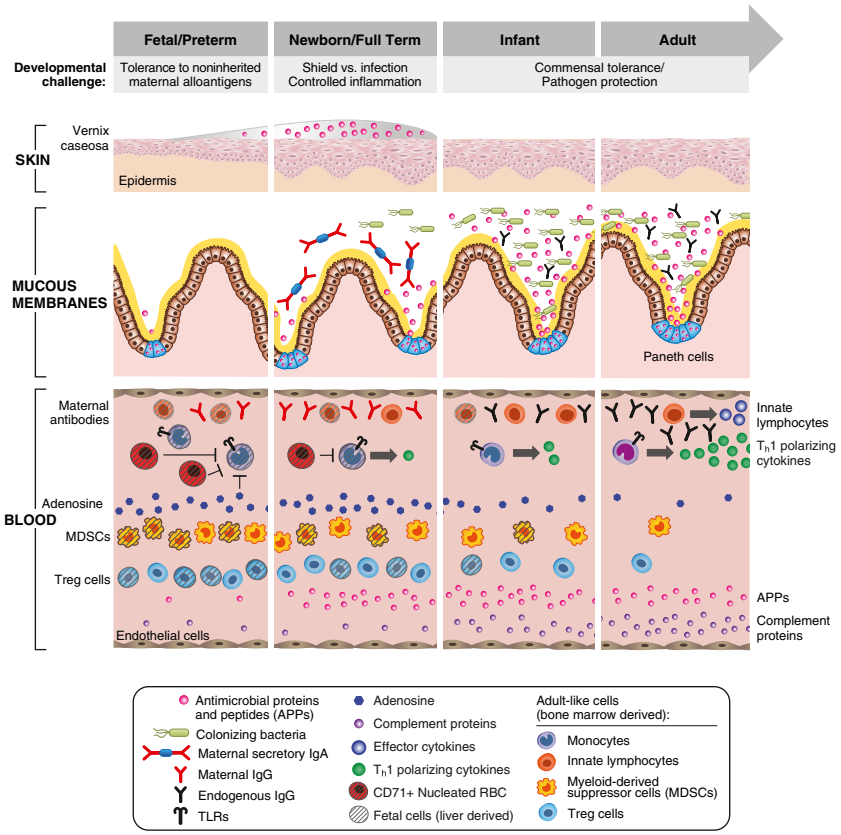

Fig. 148.1 Ontogeny of skin, soluble, and cellular innate defense systems. Host-protective barrier functions include physical, chemical, and functional components of the skin and mucous membrane epithelia of the fetus, neonate (birth to 28 days of age), and infant (1 month to 1 year of age). Skin: while physical and chemical barriers are impaired in early in life, especially in the preterm newborn, the vernix caseosa and skin epithelia of full-term newborns robustly express antimicrobial proteins and peptides (APPs). Mucous membranes: in parallel with and induced by an increasingly complex microbiota, the newborn intestinal mucosal epithelium rapidly changes structurally, with an increase in the population of crypts and crypt-based Paneth cells, as well as functionally with increasing APP expression. Blood: the composition of neonatal blood is distinct, with relatively low concentrations of complement components and APPs and high concentrations of the immunosuppressive purine metabolite adenosine. Plasma also contains maternal antibodies that are transferred beginning midgestation and supplemented by postnatal factors derived from breast milk. Innate immunity is detectable from the end of the first month of gestation, with changes driven largely by the increasing exposure to environmental microbes. Neonatal antigen-presenting cells such as blood monocytes express pattern recognition receptors (e.g., toll-like receptors [TLRs]) with distinct functional responses, including limited Th1-polarizing cytokine production, to most stimuli. Adaptive immunity develops from 4 weeks of gestation onward, with changes driven by an evolving chimerism reflecting fetal (liver-derived, *shaded cells*) regulatory T (Treg)-cell–rich lymphocytes, and more adultlike (bone marrow derived, *unshaded cells*) lymphocytes with distinct, epigenetically encoded functional programs. Ig, Immunoglobulin; RBC, red blood cell. *(Modified from Kollmann TR, Kampmann B, Mazmanian SK, et al. Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny. Immunity. 2007;46:350–363.)*

Table 148.1 Incidence of Early-Onset Infection Among Very Preterm Infants

CATEGORY	INCIDENCE RATE PER 1,000 BIRTHS (99% CI)
Overall	13.5 (12.5-14.6)
Gestational age, completed weeks	
≤23	45.4 (38.3-53.7)
24-25	26.0 (22.6-29.9)
26-27	15.5 (13.2-18.2)
28-29	10.1 (8.5-11.9)

Adapted from Flannery DD, Edwards EM, Puopolo KM, et al. Early-onset sepsis among very preterm infants. *Pediatrics.* 2021;148(4):e2021052456.

Mycoplasma, Chlamydia trachomatis, CMV, HSV, and *Candida* spp. (Table 148.3). The most common bacterial causes of neonatal meningitis are GBS, *E. coli, L. monocytogenes, Streptococcus pneumoniae,* other streptococci, *Haemophilus influenzae,* both coagulase-positive and coagulase-negative staphylococci, and other gram-negative bacilli. *Treponema pallidum* and TB infection involving the central nervous system (CNS) may also result in meningitis.

PATHOGENESIS

Early-Onset Infections

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extrauterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or

Table 148.2 Most Common Pathogens Causing Neonatal Infections, Grouped by Timing of Infection

CONGENITAL/PERINATAL
- Toxoplasmosis
- *Treponema pallidum* (syphilis)
- Rubella
- Cytomegalovirus
- Herpes simplex virus
- Hepatitis B and C
- Human immunodeficiency virus
- Varicella
- Parvovirus B19
- Tuberculosis
- Zika virus

EARLY-ONSET
- Group B *Streptococcus*
- *Escherichia coli*
- *Haemophilus* species
- *Staphylococcus aureus*
- *Klebsiella* species
- *Enterococcus* species
- Herpes simplex virus
- *Streptococcus anginosus*
- *Listeria monocytogenes*
- *Enterobacter* species
- *Citrobacter* species
- *Streptococcus pneumoniae*
- *Morganella morganii*
- *Pseudomonas* species
- *Serratia* species
- *Bacteroides* species

LATE-ONSET
- Coagulase-negative staphylococci
- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida* species
- *Enterococcus* species
- *Group B Streptococcus*
- *Klebsiella* species
- *Enterobacter* species
- *Pseudomonas* species
- Respiratory syncytial virus
- Herpes simplex virus
- Enteroviruses
- *Listeria monocytogenes*

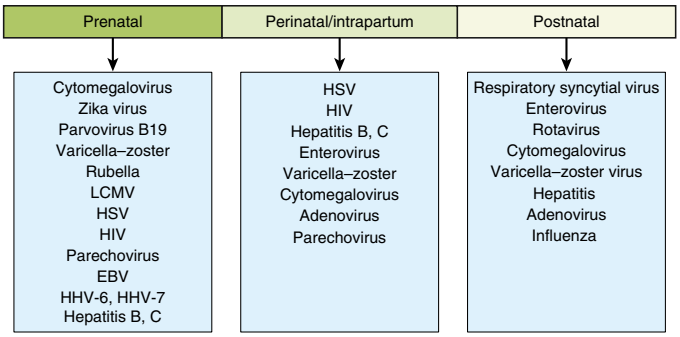

Fig. 148.2 Relative importance of neonatal viral infections related to the timing of acquisition of infection. Viruses are listed in declining order of importance relative to prenatal, perinatal (intrapartum), and postnatal timing of typical infection. Some neonatal virus infections (e.g., cytomegalovirus) can be substantial causes of disease whether acquired during gestation or acquired postpartum, whereas others (e.g., respiratory syncytial virus) are typically acquired in the postnatal period. EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus. *(From Schleiss MR, Marsh KJ. Viral infections of the fetus and newborn. In: Gleason CA, Juul SE, eds. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018: Fig. 37.1.)*

colonization of the neonate at birth. Vertical transmission of agents that infect the amniotic fluid and vaginal canal, and contamination from the gastrointestinal tract, may occur in utero or, more often, during labor and delivery (Fig. 148.3).

Chorioamnionitis results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term *chorioamnionitis* refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis (uterine tenderness, foul-smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, diagnosed only by amniotic fluid analysis or pathologic examination of the placenta. The rate of histologic chorioamnionitis is inversely related to GA at birth (Fig. 148.4) and directly related to duration of membrane

Table 148.3 Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

TRANSPLACENTAL
Cytomegalovirus (CMV)
Herpes simplex virus (HSV)
Mycobacterium tuberculosis
Rubella virus
Treponema pallidum
Varicella-zoster virus (VZV)
Listeria monocytogenes

PERINATAL
Anaerobic bacteria
Chlamydia
CMV
Enteric bacteria
Group B *Streptococci*
Haemophilus influenzae
HSV
Listeria monocytogenes
Mycoplasma

POSTNATAL
Adenovirus
Candida spp.*
Coagulase-negative staphylococci
CMV
Enteric bacteria*
Enteroviruses
Influenza viruses A, B
Parainfluenza
*Pseudomonas**
Respiratory syncytial virus (RSV)
Staphylococcus aureus
Mycobacterium tuberculosis
Legionella

*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

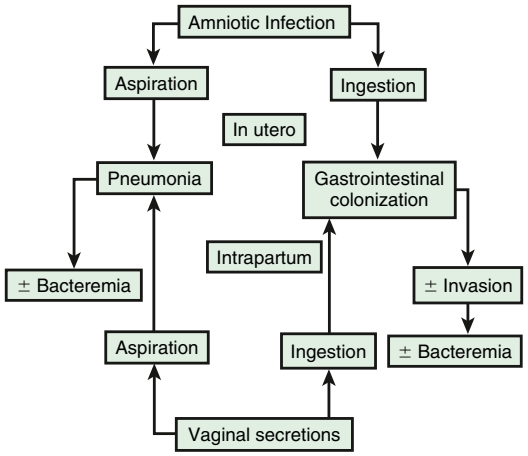

Fig. 148.3 Pathways of ascending or intrapartum infection.

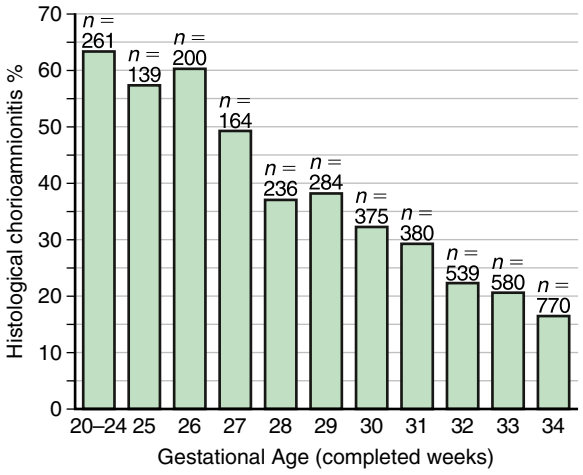

Fig. 148.4 Histologic chorioamnionitis in liveborn preterm babies by gestational age (n = 3,928 babies). *(From Lahra MM, Jeffery HE. A fetal response to chorioamnionitis is associated with early survival after preterm birth. Am J Obstet Gynecol. 2004;190:147–151.)*

rupture. Chorioamnionitis increases the risk of neonatal sepsis; however, most infants exposed to chorioamnionitis do not develop sepsis.

Chorioamnionitis was thought to result from infection of the amniotic fluid but is now better defined by the term *intrauterine inflammation* or *infection* at birth *(Triple I)*. This is defined by fetal tachycardia, maternal leukocytosis (>15,000 cells in the absence of corticosteroids), purulent fluid from the cervical os, biochemical or microbiologic amniotic fluid changes consistent with infection, and fever (≥39.0°C) (see Chapter 149.2).

Bacterial colonization does not always result in fetal or neonatal disease. Factors influencing which colonized infant will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies (Fig. 148.5). Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (apnea, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

Late-Onset Infections

After birth, neonates are exposed to infectious agents in the hospital or in the community (including family and caretakers). Postnatal infections may be transmitted by direct contact with hospital personnel, the mother, or other caretakers; from breast milk (e.g., HIV, CMV); or from inanimate sources such as contaminated equipment or surfaces. The most common source of postnatal infections in hospitalized newborns is *hand contamination* of healthcare personnel, underscoring the importance of hand hygiene. Contaminated milk, especially powdered formula *(Cronobacter sakazakii, Salmonella)*, equipment, other objects, or the environment are rare sources of neonatal infections but should be suspected during outbreaks of single organism disease.

Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or penetrating wounds from fetal scalp sampling or internal fetal electrocardiographic monitors. Cerebral abscess formation, ventriculitis, septic infarcts, hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children. Metabolic factors, including hypoxia, acidosis, hypothermia, and inherited metabolic disorders (e.g., galactosemia), are likely to contribute to risk for and severity of neonatal infection.

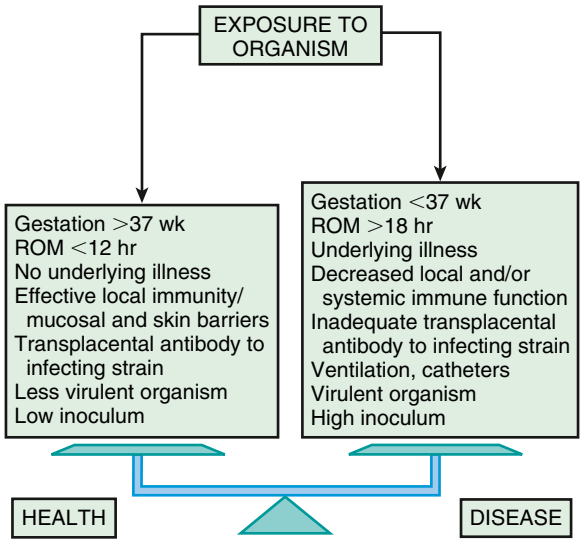

Fig. 148.5 Factors influencing the balance between health and disease in neonates exposed to a potential pathogen. ROM, Rupture of membranes. *(Adapted from Baker CJ. Group B streptococcal infections. Clin Perinatol 1997;24:59–70.)*

Infection in Premature Infants

The most important neonatal factors predisposing to infection are prematurity and low birthweight. Premature infants have a 3- to 10-fold higher incidence of infection than full-term normal birthweight infants. Possible explanations include the following: (1) maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn; (2) the frequency of intraamniotic infection is inversely related to GA (see Figs. 148.1 and 148.5); (3) premature infants have documented immune dysfunction; and (4) premature infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, putting them at continued risk for hospital-acquired infections.

CLINICAL MANIFESTATIONS

The maternal history and circumstances of delivery provide important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis). Signs and symptoms in the neonate are often subtle and nonspecific. Temperature instability, tachypnea, lethargy, apnea, and poor feeding are common initial signs and should raise suspicion for systemic or focal infection (Table 148.4).

Bacterial Sepsis

Neonates with bacterial sepsis may have either nonspecific manifestations or focal signs of infection (see Table 148.4), including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. Table 148.5 lists World Health Organization *international criteria* for sepsis. The initial manifestation may involve only limited symptomatology and only one system, such as apnea alone or tachypnea with retractions, or tachycardia, or the infant may present with an acute catastrophic manifestation

Table 148.4 Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL	**CARDIOVASCULAR**
Fever, temperature instability	Pallor; mottling; cold, clammy skin
Hypothermia	Tachycardia
"Not doing well"	Hypotension
Poor feeding	Bradycardia
Edema	
GASTROINTESTINAL	**CENTRAL NERVOUS**
Abdominal distention	Irritability, lethargy
Vomiting	Tremors, seizures
Diarrhea	Hyporeflexia, hypotonia
Hepatomegaly	Abnormal Moro reflex
	Irregular respirations
RESPIRATORY	Full fontanel
Apnea, dyspnea	High-pitched cry
Tachypnea, retractions	
Flaring, grunting	**HEMATOLOGIC**
Cyanosis	Jaundice
	Splenomegaly
RENAL SYSTEM	Pallor
Oliguria	Petechiae, purpura
	Bleeding

Table 148.5 Clinical Criteria for the Diagnosis of Sepsis in the International Setting: IMCI and WHO Criteria for Severe Infections in Children

- *Neurologic:* Convulsions, drowsy or unconscious, decreased activity, bulging fontanel
- *Respiratory*: Respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
- *Cardiac*: Poor perfusion, rapid and weak pulse
- *Gastrointestinal*: Jaundice, poor feeding, abdominal distention
- *Dermatologic*: Skin pustules, periumbilical erythema or purulence
- *Musculoskeletal*: Edema or erythema overlying bones or joints
- Other: Temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

IMCI, Integrated Management of Childhood Illness; WHO, World Health Organization. Adapted from WHO. *Pocket Book Of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses.* 2nd ed. Geneva: WHO. 2013. p 45–69. http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/.

with multiorgan dysfunction and shock. Infants should be reevaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).

A variety of noninfectious conditions can occur together with neonatal infection or can make the diagnosis of infection more difficult. Respiratory distress syndrome (RDS) secondary to surfactant deficiency can mimic and/or coexist with bacterial pneumonia in premature infants. Because bacterial sepsis can be rapidly progressive, the physician must be alert to the signs and symptoms of possible infection and must initiate diagnostic evaluation and empirical therapy in a timely manner for infants at risk. The differential diagnosis of many of the signs and symptoms that suggest infection is extensive; noninfectious disorders must also be considered (Table 148.6).

Systemic Inflammatory Response Syndrome

The clinical manifestations of infection depend on the virulence of the infecting organism and the body's inflammatory response. The term *systemic inflammatory response syndrome* (SIRS) is most frequently used to describe this unique process of infection and the subsequent systemic response (see Chapter 85). In addition to infection, SIRS may result from trauma, hemorrhagic shock, other causes of ischemia and inflammation, necrotizing enterocolitis, and pancreatitis.

Patients with SIRS have a spectrum of clinical symptoms that represent progressive stages of the pathologic process. In adults, SIRS is defined by the presence of two or more of the following: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea, and (4) abnormal white blood cell (WBC) count or an increase in immature forms. In neonates and pediatric patients, SIRS manifests as temperature instability, respiratory dysfunction (altered gas exchange, hypoxemia, acute RDS), cardiac dysfunction (tachycardia, delayed capillary refill, hypotension), and perfusion abnormalities (oliguria, metabolic acidosis) (Table 148.7). Increased vascular permeability results in capillary leak into peripheral tissues and the lungs, with resultant peripheral and pulmonary edema. DIC results in the more severely affected cases. The cascade of escalating tissue injury may lead to multisystem organ failure and death.

There are neonates who appear to have sepsis or SIRS but no bacterial or viral pathogen has been recovered. Culture negative sepsis may be due to a hard-to-culture bacteria (anaerobes) or virus, as well as noninfectious inflammatory conditions. In addition, an undetected localized source with transient bacteremia (osteomyelitis), prior antibiotic treatment, and poor culture technique (too small blood sample for culture may miss bacteremia) may be responsible.

Table 148.6 Serious Systemic Illness in Newborns: Differential Diagnosis of Neonatal Sepsis

CARDIAC
Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)
Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN

GASTROINTESTINAL
Necrotizing enterocolitis
Spontaneous gastrointestinal perforation
Midgut volvulus
Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)

HEMATOLOGIC
Neonatal purpura fulminans
Immune-mediated thrombocytopenia
Immune-mediated neutropenia
Severe anemia
Malignancies (congenital leukemia)
Langerhans cell histiocytosis
Hereditary clotting disorders
Familial hemophagocytic lymphohistiocytosis

METABOLIC
Hypoglycemia
Adrenal disorders: adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia
Inborn errors of metabolism: organic acidurias, lactic acidoses, urea cycle disorders, galactosemia

NEUROLOGIC
Intracranial hemorrhage: spontaneous, caused by child abuse
Hypoxic-ischemic encephalopathy
Neonatal seizures
Infant botulism

RESPIRATORY
Respiratory distress syndrome
Aspiration pneumonia: amniotic fluid, meconium, or gastric contents
Lung hypoplasia
Tracheoesophageal fistula
Transient tachypnea of the newborn

Table 148.7 Definitions of Systemic Inflammatory Respiratory Response Syndrome (SIRS) and Sepsis in Pediatric Patients

SIRS: The systemic inflammatory response to a variety of clinical insults, manifested by two or more of the following conditions:
Temperature instability <35°C (95°F) or >38.5°C (101.3°F)
Respiratory dysfunction:
  Tachypnea >2 SD above the mean for age
  Hypoxemia (Pa_{O_2} <70 mm Hg on room air)
Cardiac dysfunction:
  Tachycardia >2 SD above the mean for age
  Delayed capillary refill >3 sec
  Hypotension >2 SD below the mean for age
Perfusion abnormalities:
  Oliguria (urine output <0.5 mL/kg/hr)
  Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)
  Altered mental status
Sepsis: The systemic inflammatory response to an infectious process

SD, Standard deviation.
From Adams-Chapman I, Stoll BJ. Systemic inflammatory response syndrome. *Semin Pediatr Infect Dis.* 2001;12:5–16.

Temperature Instability

Fever or hypothermia may be the only initial manifestation of serious infection in newborns. However, only approximately 50% of infected newborn infants have a temperature >37.8°C (see Chapter 220). Fever in newborn infants does not always signify infection; it may be caused

by increased ambient temperature, isolette or radiant warmer malfunction, dehydration, CNS disorders, hyperthyroidism, familial dysautonomia, or ectodermal dysplasia. A single temperature elevation is infrequently associated with infection; sustained fever is more likely to be caused by infection. Most febrile infected infants have additional signs compatible with infection, although a focus of infection is not always apparent. Acute febrile illnesses occurring later in the neonatal period may be caused by urinary tract infection, meningitis, pneumonia, osteomyelitis, or gastroenteritis and viral infections (enteroviruses, others) in addition to sepsis, thus underscoring the importance of a diagnostic evaluation that includes blood culture, urine culture, lumbar puncture (LP), and other studies as indicated. Numerous pathogens may cause these late infections (see Table 148.2), including HSV, enteroviruses, respiratory syncytial virus, and bacterial organisms. In premature infants, hypothermia or temperature instability requiring increasing ambient (isolette, warmer) temperatures is more likely to accompany infection.

Respiratory and Cardiovascular Symptoms

Early signs and symptoms of pneumonia may be nonspecific, including poor feeding, lethargy, irritability, cyanosis, temperature instability, and the overall impression that the infant is not well. Respiratory symptoms of increasing severity include grunting, tachypnea, retractions, nasal flaring, cyanosis, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be *superimposed* on RDS or bronchopulmonary dysplasia (BPD). For mechanically ventilated infants, the need to increase ventilator support may indicate infection. Although a common finding in neonatal sepsis, tachycardia is nonspecific. Bradycardia may also occur. Poor perfusion and hypotension are more sensitive indicators of sepsis but tend to be late findings. In a prospective national surveillance study, 40% of neonates with sepsis required volume expansion, and 29% required vasopressor support.

Signs of pneumonia on physical examination, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate. Radiographs of the chest may reveal new infiltrates or an effusion, but if the neonate has underlying RDS or BPD, it is very difficult to determine whether the radiographic changes represent a new process or worsening of the underlying disease.

The progression of neonatal pneumonia can be variable. Fulminant infection is most frequently associated with pyogenic organisms such as GBS (see Chapter 230). Onset may occur during the first hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. With early-onset pneumonia in premature infants, the clinical course and chest radiographs may be indistinguishable from those with severe RDS, particularly for GBS pneumonia.

In contrast to the rapid progression of pneumonia caused by pyogenic organisms, an indolent course may be seen in nonbacterial infection. The onset can be preceded by upper respiratory tract symptoms or conjunctivitis. The infant may demonstrate a nonproductive cough, and the degree of respiratory compromise is variable. Fever is usually absent or low grade, and radiographic examination of the chest shows focal or diffuse interstitial pneumonitis or hyperinflation. Infection can be caused by *C. trachomatis,* CMV, *Ureaplasma urealyticum,* and other respiratory viruses. Rhinovirus has been reported to cause severe respiratory compromise in infants, particularly those who are preterm.

Conjunctivitis

Conjunctival infection is relatively common and may be caused by a variety of organisms. The presentation includes periorbital swelling, conjunctival injection, and purulent conjunctival drainage. *C. trachomatis* and *Neisseria gonorrhoeae* are common causes; other gram-positive and gram-negative organisms are occasionally involved. *Pseudomonas aeruginosa* is an important pathogen in hospitalized preterm infants and may be a precursor to invasive disease. Viral infections (e.g., HSV, adenovirus) are occasionally seen. Recognition of HSV infection is important to prevent corneal injury and dissemination to systemic sites.

Skin and Soft Tissue Infection

Cutaneous manifestations of infection include omphalitis, cellulitis, mastitis, and subcutaneous abscesses. Pustules likely indicate the presence of staphylococcal infection but must be distinguished from the vesicular rash of HSV infection. Staphylococcal pustulosis results in larger, pus-filled lesions often scattered around the umbilicus, whereas HSV infection often appears as tiny vesicles in crops, often on the scalp. The presence of small, salmon-pink papules suggests *L. monocytogenes* infection. Mucocutaneous lesions suggest *Candida* spp. (see Chapter 280.1). Petechiae and purpura may be the result of systemic viral or bacterial infection. Neonatal **mastitis** is caused by *S. aureus* and in an otherwise well appearing afebrile neonate is a localized infection.

Omphalitis

Omphalitis is a neonatal infection resulting from unhygienic care of the umbilical cord, which continues to be a problem, particularly in developing countries. The umbilical stump is colonized by bacteria from the maternal genital tract and the environment (see Chapter 144). The necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. Omphalitis may remain a localized infection or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, and the liver. Abdominal wall cellulitis or necrotizing fasciitis, with associated sepsis and a high mortality rate, may develop in infants with omphalitis. Prompt diagnosis and treatment are necessary to avoid serious complications. *S. aureus* and gram-negative organisms are common involved pathogens.

Tetanus

Neonatal tetanus remains a serious infection in resource-limited countries (see Chapter 257). It results from unclean delivery and unhygienic management of the umbilical cord in an infant born to a mother who has not been immunized against tetanus. The surveillance case definition of neonatal tetanus requires the ability of a newborn to suck at birth and for the first few days of life, followed by an inability to suck. Neonatal tetanus typically occurs in infants 5-7 days after birth (range: 3-24 days) and is complicated by difficulty swallowing, spasms, stiffness, seizures, and death. Bronchopneumonia, presumably resulting from aspiration, is another complication and cause of death. Neonatal tetanus can be prevented by immunizing mothers before or during pregnancy and by ensuring a clean delivery, sterile cutting of the umbilical cord, and proper cord care after birth.

LABORATORY FINDINGS

Maternal history and infant signs should guide diagnostic evaluation (Table 148.8). Additionally, signs of systemic infection in newborn infants may be unrevealing, so laboratory investigation plays a particularly important role in diagnosis. Cultures and cell counts are obtained from blood and urine. Cerebrospinal fluid (CSF) should be sent for Gram stain, routine culture, cell count with differential, and protein/glucose concentrations. Surface swabs, blood, and CSF are often obtained for HSV testing. Except for culture and directed pathogen testing, no single laboratory test is completely reliable for diagnosis of invasive infection in the newborn. CBC may demonstrate elevated or decreased WBC count, often with a shift toward more immature forms. Thrombocytopenia can be seen in systemic bacterial, fungal, or viral infection. Hyponatremia, acidosis, and other electrolyte abnormalities can be seen. Hyperbilirubinemia is nonspecific but may be an indication of systemic infection, particularly of the urine tract. Elevated serum transaminases may be a clue to systemic HSV, enterovirus, or other viral infection.

Various **serum biomarkers** have been investigated for their ability to identify infants with serious bacterial infection (SBI). An immature-to-total phagocyte count (I/T ratio) (≥0.2) has the best sensitivity of the neutrophil indices for predicting neonatal sepsis. After the newborn period, serum C-reactive protein (CRP), procalcitonin, and ferritin have demonstrated reasonable sensitivity and specificity for SBI.

Table 148.8 Evaluation of a Newborn for Infection or Sepsis

HISTORY (SPECIFIC RISK FACTORS)
Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy):
- Urinary tract infection
- Chorioamnionitis
- Maternal colonization with group B *Streptococci*, *Neisseria gonorrhoeae*, herpes simplex
- Low gestational age/birthweight
- Multiple birth
- Duration of membrane rupture
- Complicated delivery
- Fetal tachycardia (distress)
- Age at onset (in utero, birth, early postnatal, late)
- Location at onset (hospital, community)

Medical intervention:
- Vascular access
- Endotracheal intubation
- Parenteral nutrition
- Surgery

EVIDENCE OF OTHER DISEASES*
Congenital malformations (heart disease, neural tube defect)
Respiratory tract disease (respiratory distress syndrome, aspiration)
Necrotizing enterocolitis
Metabolic disease (e.g., galactosemia)

EVIDENCE OF FOCAL OR SYSTEMIC DISEASE
General appearance, neurologic status
Abnormal vital signs
Organ system disease
Feeding, stools, urine output, extremity movement

LABORATORY STUDIES
Evidence of Infection
Culture from a normally sterile site (blood, CSF, other)
Demonstration of a microorganism in tissue or fluid
Molecular detection (blood, urine, CSF) by specific PCR and/or 16S ribosomal DNA
Maternal or neonatal serology (syphilis, toxoplasmosis)

Evidence of Inflammation
Leukocytosis, increased immature/total neutrophil count ratio
Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate, procalcitonin, ferritin
Cytokines: interleukin-6, interleukin-B, tumor necrosis factor
Pleocytosis in CSF or synovial or pleural fluid
Disseminated intravascular coagulation: fibrin degradation products, D-dimer

Evidence of Multiorgan System Disease
Metabolic acidosis: pH, P_{CO_2}
Pulmonary function: P_{O_2}, P_{CO_2}
Renal function: blood urea nitrogen, creatinine
Hepatic injury/function: bilirubin, alanine transaminase, aspartate transaminase, ammonia, prothrombin time, partial thromboplastin time
Bone marrow function: neutropenia, anemia, thrombocytopenia

*Diseases that increase the risk of infection or may overlap with signs of sepsis.
CSF, Cerebrospinal fluid; PCR, polymerase chain reaction.

CRP may be monitored serially in newborn infants to assess response to therapy. Their value in the initial diagnosis of sepsis in the newborn period has yet to be clarified. The American Academy of Pediatrics (AAP) Committee on the Fetus and Newborn reiterated in a 2018 early-onset sepsis guideline update that lab tests alone should not be used to diagnose sepsis. Cytokines (both proinflammatory cytokines such as interleukin [IL]-6 and tumor necrosis factor-α and antiinflammatory cytokines such as IL-4 and IL-10), chemokines, and other biomarkers are increased in infected infants.

Tables 148.8 and 148.9 list clinical features and laboratory parameters that are useful in the diagnosis of neonatal infection or sepsis.

GENERAL APPROACH TO MANAGEMENT

In the absence of specific signs of focal infection, therapy for presumed infection in the neonate is often empirical and initiated on the basis of fever or hypothermia, listlessness, irritability, or apneic episodes. Antibiotics are chosen to cover the organisms typically causing neonatal sepsis, including GBS, gram-negative organisms, *Listeria*, and *Enterococcus*. Because the latter two organisms are intrinsically resistant to cephalosporins, ampicillin is generally included in the empirical treatment of infants with presumed neonatal infection (Table 148.10). Initiation of antibiotics within 1 hour of onset is recommended and has a survival advantage.

An empirical regimen for suspected **early-onset infection** in a term or late preterm infant includes ampicillin and gentamicin. This has long been a standard regimen for early-onset sepsis and provides coverage for the most prevalent organisms, predominantly GBS and *E. coli*. Resistance of *E. coli* to ampicillin or gentamicin has been reported; approximately 1 in 10 isolates are resistant to both ampicillin and gentamicin. Ampicillin plus cefotaxime (if available) or cefepime may be substituted if the patient presents with infection after discharge from the nursery, or when infection with resistant *E. coli* is suspected. Ceftriaxone is typically not used in the neonatal period due to precipitation with intravenous calcium and displacement of bound bilirubin causing hyperbilirubinemia. There is concern that cephalosporins may be associated with higher rates of mortality in neonates compared to ampicillin and gentamicin. Alterations to the standard regimen may be appropriate in some circumstances, such as for critically ill newborns, with illness out of proportion to degree of prematurity, at highest risk of infection given maternal risk factors and delivery characteristics.

HSV infection may present without cutaneous signs, in the absence of maternal history of infection, and in mothers receiving suppressive antiviral therapy. Therefore management of the ill newborn requires a high index of suspicion for HSV infection. Surface swabs, blood, and CSF are obtained for HSV culture or polymerase chain reaction (PCR), and empirical acyclovir is often recommended while the results of these studies are pending (see Chapters 220 and 299).

Systemic infection caused by *Candida* spp. is a concern in hospitalized infants, particularly extremely preterm infants with central venous access catheters and prior antibiotic and steroid exposure. Empirical therapy for fungal infection may be indicated for those at highest risk, as well as those with specific clinical signs such as erythematous rash, thrombocytopenia, hyperglycemia, and invasive devices.

Definitive therapy is based on identification and susceptibility of the offending organism. In almost all circumstances, the *narrowest* antibiotic with activity against the organism is chosen. Duration of therapy depends on the organism and the site of infection. In neonates with culture-proven sepsis, the usual course of therapy is typically 7-10 days. Longer treatment courses may be warranted if a specific focus of infection is identified (e.g., meningitis, osteomyelitis, septic arthritis). Antimicrobial therapy should be altered based on the susceptibility profile of the pathogen isolated. In infants with a negative blood culture but a clinical status that remains concerning for a systemic inflammation, other etiologies and potential focal sources of infection should be investigated. Sepsis is unlikely in these infants if appropriately obtained blood cultures are sterile by 48 hours.

PREVENTION

Intrapartum antibiotics are used to reduce vertical transmission of GBS (Table 148.11), as well as to lessen neonatal morbidity associated with preterm labor and preterm premature rupture of membranes (see Chapter 230). With introduction of selective intrapartum antibiotic prophylaxis to prevent perinatal transmission of GBS, rates of early-onset neonatal GBS infection in the United States declined from 1.7/1,000 live births to 0.25/1,000. Intrapartum chemoprophylaxis does *not* reduce the rates of late-onset GBS disease and has no effect on the rates of infection with non-GBS pathogens. Of concern is a possible increase in gram-negative infections (especially *E. coli*) despite a reduction in early GBS sepsis by intrapartum antibiotics.

Table 148.9 Culture-Based and Non–Culture-Based Diagnostics for Neonatal Sepsis

CATEGORY	PARAMETER	OPTIMAL TIMING, VOLUME OF SPECIMEN, ROUTINE/INVESTIGATIONAL*	APPLICABILITY FOR NEONATAL SEPSIS
CULTURE BASED			
Blood	Culture	>1 mL of whole blood, from two sites	Gold standard for bacteremia
CSF	Culture	When clinically feasible	Gold standard for bacterial meningitis
Urine	Culture	>72 hr of life	Not useful for EOS; indicated for LOS evaluation
Tracheal aspirate	Culture	Neonates with endotracheal tube in place and signs of progressive respiratory distress	Usually reflects colonization
NON–CULTURE BASED			
Neutrophil indices	Neutropenia Absolute neutrophil count Absolute immature neutrophil count	After 12 hr of life Consider GA, delivery mode, altitude, arterial versus venous sampling, time since birth	Neutropenia better predictor for sepsis than leukocytosis
Neutrophil markers	CD64	Elevated for 24 hr after infection Requires 50 μL blood Results within hours Investigational	Cut points between 2.38 and 3.62 optimal sensitivity, specificity, and NPV for EOS
Platelet count	Thrombocytopenia and thrombocytosis	Late findings; slow to respond	Thrombocytopenia associated with fungal infection
CSF cell count	CSF WBC	Uninfected neonates: mean 10 cells/mm^3; range up to 20 cells/mm^3	Does not predict culture-proven meningitis
CSF chemistries	CSF protein CSF glucose	Term <100 mg/dL Preterm higher; 70–80% of serum glucose	Elevated in fungal meningitis Low glucose specific for bacterial meningitis
Acute phase reactants	CRP Procalcitonin	8-24 hr after infection 2-12 hr after infection	Good NPV Better sensitivity but less specificity than CRP

**Investigational* refers to an assay or parameter that is undergoing evaluation for clinical use and applicability.
CSF, Cerebrospinal fluid; EOS, early-onset sepsis; GA, gestational age; LOS, late-onset sepsis; MHC II, major histocompatibility complex class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.
From Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *Am J Perinatol.* 2013;30(2):131–141.

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS and early-onset GBS disease is significantly reduced by selective intrapartum chemoprophylaxis (see Fig. 230.4) but does still occur. Neonatal infection with *Chlamydia* can be prevented by identification and treatment of infected pregnant women (see Chapter 272). Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, by cesarean delivery before rupture of membranes, and by antiretroviral treatment of the infant after birth (see Chapter 322).

Prevention of congenital and perinatal infections predominantly focuses on maternal health. The Centers for Disease Control and Prevention (CDC) recommends the following screening tests and treatment when indicated:

1. All pregnant women should be offered voluntary and confidential HIV testing at the first prenatal visit, as early in pregnancy as possible. HIV screening should be part of routine prenatal testing, unless the mother declines testing (opt-out screening). For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use, HIV-infected partners), repeat testing in the third trimester is recommended. Rapid HIV screening is indicated for any women who presents in labor with an undocumented HIV status, unless she declines testing.
2. A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit. Repeat screenings early in the third trimester and again at delivery are recommended for women in whom syphilis test results in the first trimester were positive and for those at high risk for infection during pregnancy. Infants should not be discharged from the hospital unless the syphilis status of the mother has been determined at least once during pregnancy and preferably again at delivery.
3. Serologic testing for hepatitis B surface antigen (HBsAg) should be performed at the first prenatal visit, even if the woman has been previously vaccinated or tested. Women who were not screened prenatally, those who are at high risk for infection (multiple sexual partners, intravenous drug use, HBsAg-positive sex partner), and those with clinical hepatitis should be retested at the time of delivery.
4. A maternal genital culture for *C. trachomatis* should be performed at the first prenatal visit. Young women (<25 years) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the third trimester.
5. A maternal culture for *N. gonorrhoeae* should be performed at the first prenatal visit. Those at high risk for infection should be retested in the third trimester.
6. All pregnant women at high risk for hepatitis C infection (intravenous drug use, blood transfusion or organ transplantation before 1992) should be screened for hepatitis C antibodies at the first prenatal visit.
7. Evidence does not support routine testing for bacterial vaginosis in pregnancy. For asymptomatic women at high risk for preterm delivery, testing may be considered. Symptomatic women should be tested and treated.
8. The CDC recommends universal screening for vaginorectal GBS colonization of all pregnant women at 36 0/7 and 37 6/7 weeks of gestation and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS (see Table 148.11) (see Figs. 230.2 and 230.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 148.10 Management and Prevention of Neonatal Sepsis

CONDITION	THERAPY	ADDITIONAL CONSIDERATIONS
EMPIRICAL MANAGEMENT		
Early-onset sepsis	Ampicillin + aminoglycoside 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections	• Consider a third-generation cephalosporin or carbapenem for meningitis or severe illness with high suspicion for gram-negative infection • Tailor therapy to pathogen • Should discontinue empiric therapy if pathogen not isolated
Late-onset sepsis	Vancomycin or antistaphylococcal penicillin (i.e., nafcillin, oxacillin) + aminoglycoside Duration dependent on pathogen and site	• Gram-positive coverage should be based on local epidemiology, MRSA colonization, CONS risk factors, and clinical presentation • Aminoglycoside-based regimen preferred to cephalosporin given reduced risk of resistance • Consider cephalosporin if meningitis suspected • Consider a carbapenem if third-generation cephalosporin recently received • Consider amphotericin for fungal etiologies • Tailor therapy to pathogen • Consider discontinuation of therapy if pathogen not isolated
NONANTIMICROBIAL TREATMENT STRATEGIES		
Recombinant G-CSF Recombinant GM-CSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections
IVIG	Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis
PREVENTION STRATEGIES		
IAP	Administration of penicillin or ampicillin 4 hr before parturition	Successfully reduces rates of EOS caused by GBS No effect on LOS GBS
Fluconazole prophylaxis	Administration of weight-based dosing to neonates <1,500 g	Most beneficial in NICUs with high baseline rates of invasive candidiasis
BLF supplementation with a probiotic, *Lactobacillus rhamnosus* (GG)	BLF is a human milk glycoprotein with a role in innate immune response LGG enhances the activity of lactoferrin	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT Additional confirmatory studies warranted

BLF, Bovine lactoferrin supplementation; CONS, coagulase-negative staphylococci; EOS, early-onset sepsis; GBS, group B *Streptococcus*; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin, LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; RCTs, randomized controlled trials; VLBW, very low birthweight.
Data from Carr R, Modi N, Doré C. G-CSF and GM-CSF for treating or preventing neonatal infections. *Cochrane Database Syst Rev*. 2003;(3):CD003066. Brocklehurst P, Farrell B, King A, et al. INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med*. 2011;365:1201–1211. Manzoni P, Decembrino L, Stolfi I, et al. Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology: Lactoferrin and prevention of late-onset sepsis in the pre-term neonates. *Early Hum Dev*. 2010;86(Suppl 1):59–61.
From Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *Am J Perinatol*. 2013;30(2):131–141.

Table 148.11 Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset Group B *Streptococcus* Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F)† Intrapartum NAAT‡ positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Chapter 230.
†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.
‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 wk gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C/100.4°F) is present, intrapartum antibiotic prophylaxis is indicated.
GBS, Group B streptococcus; NAAT, nucleic acid amplification test.
From Verani J, McGee L, Schrag S. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10):1–36.

Chapter 149

Congenital and Perinatal Infections

Sallie R. Permar and Emma L. Mohr

Infections are a frequent and important cause of neonatal morbidity and mortality. **Congenital** or **intrauterine** infections (i.e., those transmitted across the placenta) and **perinatal** infections (i.e., those transmitted from the mother to the fetus or newborn infant during the birth process) represent two major routes of neonatal infection.

149.1 Congenital Infections

Sallie R. Permar and Emma L. Mohr

In utero infections are caused by a variety of etiologic agents, including bacteria, viruses, fungi, and protozoa. Clinical manifestations of congenital infectious diseases in neonates can range from asymptomatic or subclinical to life-threatening disease. History and physical examination findings, in addition to laboratory testing and/or radiologic imaging, provide insight into the best approach for prevention and treatment of congenital infectious diseases in this immunologically immature population (see Fig. 148.2 and Table 148.2).

GENERAL APPROACH

Prenatal counseling on methods to prevent congenital infections is the best approach for improving infant outcomes. Once a fetus or infant is suspected of having a congenital or perinatal infection, infectious as well as noninfectious processes, such as underlying congenital heart disease, genetic disorders, and inborn errors of metabolism, should be considered in the differential diagnosis. Because maternal infection is a prerequisite for infection in the fetus, a thorough history is essential to assess the mother for her symptoms, travel, diet, medication use, occupational exposures, and any **sexually transmitted infections (STIs)** during pregnancy. Clinical manifestations are varied and overlap for many of the pathogens causing intrauterine infection. Laboratory testing and/or radiologic imaging is often required to confirm the diagnosis. Treatment depends on the specific pathogen and can range from symptomatic management with close follow-up for long-term sequelae to targeted antimicrobial therapy.

PATHOGENESIS

The route and timing of infection can provide helpful clues as to the potential infectious etiology (Fig. 149.1 and Table 149.1). First-trimester infection may alter embryogenesis and result in malformations of the heart and eyes, as seen in congenital rubella syndrome. Third-trimester infection (e.g., congenital toxoplasmosis) can result in active infection with signs of hepatomegaly, splenomegaly, and generalized lymphadenopathy at birth. Infections that occur late in gestation (e.g., congenital syphilis) may lead to a delay in clinical manifestations until weeks to years after birth.

Intrauterine infection from cytomegalovirus (CMV), *Treponema pallidum*, *Toxoplasma gondii*, rubella virus, varicella-zoster virus (VZV), and human parvovirus B19 may cause minimal or no symptoms in the mother but still may be transmitted across the placenta to the fetus. The presence of maternal antibodies to rubella prevents maternal infection and congenital transmission, but transmission across the placenta of CMV can occur despite preexisting immunity, albeit at a lower rate compared to primary maternal CMV infection. Regardless of the mother's immune status, the placenta may act as a barrier, and the fetus may or may not be infected. If infection occurs, signs may or may not be noted in the fetus during pregnancy. Infection can result in spontaneous abortion, congenital malformation, intrauterine growth restriction (IUGR), premature birth, stillbirth, acute or delayed disease in the neonate, or asymptomatic persistent infection with sequelae later in life.

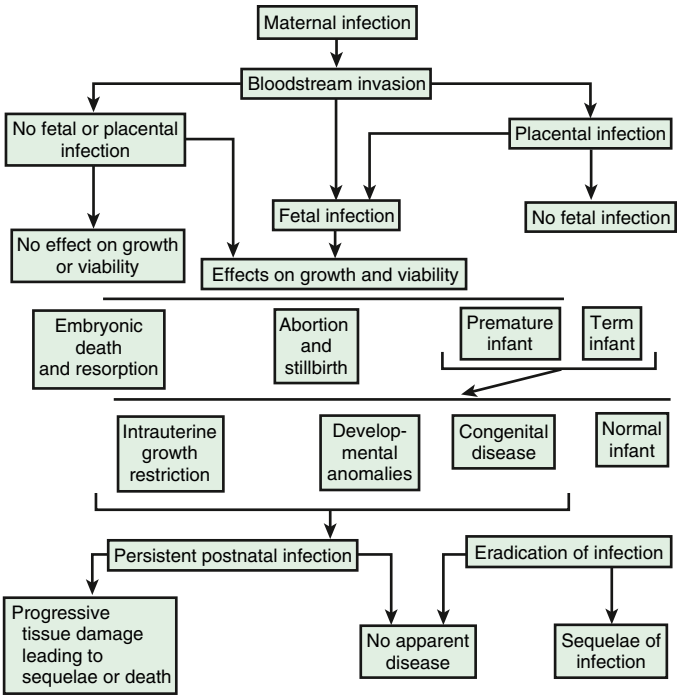

Fig. 149.1 Pathogenesis of hematogenous transplacental infections. (*Adapted from Klein JO, Remington JS. Current concepts of infections of the fetus and newborn infant. In: Remington JS, Klein JO, eds. Infectious Diseases of the Fetus and Newborn Infant, 8th ed. Philadelphia: Saunders; 2002.*)

PREVENTION

Prevention of congenital infections includes behavioral and therapeutic interventions. Counseling-based interventions are effective in reducing CMV infection, but few healthcare providers report counseling their patients on CMV prevention. Counseling on hygienic practices, such as washing hands after diaper changes and avoiding contact with saliva, decreases CMV transmission risk. Safer sex practices, safe food preparation practices, and preventing mosquito bites are some of the recommendations that prevent congenital and perinatal infections. Prenatal and maternal vaccination and control of existing maternal infections are other strategies of preventing congenital infection. Prevention recommendations are presented in Table 149.2.

CLINICAL MANIFESTATIONS

The clinical manifestations of intrauterine infections can range from asymptomatic to severe multiorgan system complications. For some agents (e.g., CMV, *T. pallidum*), ongoing injury after birth can lead to late sequelae as well. The specific clinical signs in the newborn period are usually not sufficient to make a definitive diagnosis but are useful to guide more specific laboratory testing. Symptomatic congenital infections often affect the central nervous system (CNS; brain and eyes) and the reticuloendothelial system (RES; bone marrow, liver, and spleen). Table 149.3 presents the clinical manifestations of some specific congenital infections. Congenital Zika virus infection has features that are rarely seen with other congenital infections (Table 149.4). For example, no hematologic or hepatic laboratory abnormalities have been documented in infants with congenital Zika virus infection. Table 149.5 provides late sequelae of some congenital infections.

Table 149.1 Specific Agents in Effects of Transplacental Fetal Infection on the Fetus and Newborn Infant

	DISEASE				
ORGANISM	**PREMATURITY**	**INTRAUTERINE GROWTH RESTRICTION/LOW BIRTHWEIGHT**	**DEVELOPMENTAL ANOMALIES**	**CONGENITAL DISEASE**	**PERSISTENT POSTNATAL INFECTION**
Viruses	CMV HSV Rubeola Smallpox HBV HIV* SARS-CoV-2 Zika	CMV Rubella VZV* HIV Zika	CMV Rubella VZV Coxsackievirus B* HIV Zika	CMV Rubella VZV HSV Mumps* Rubeola Vaccinia Smallpox Coxsackievirus B Poliovirus HBV HIV LCV Parvovirus Zika	CMV Rubella VZV HSV HBV HIV Zika
Bacteria	*Treponema pallidum* *Mycobacterium tuberculosis* *Listeria monocytogenes* *Campylobacter fetus* *Salmonella typhi*			*T. pallidum* *M. tuberculosis* *L. monocytogenes* *C. fetus* *S. typhi* *Borrelia burgdorferi*	*T. pallidum* *M. tuberculosis*
Protozoa	*Toxoplasma gondii* *Plasmodium** *Trypanosoma cruzi*	*T. gondii* *Plasmodium* *T. cruzi*		*T. gondii* *Plasmodium* *T. cruzi*	*T. gondii* *Plasmodium*

*Association of effect with infection has been suggested and is under consideration.
CMV, Cytomegalovirus; HBV, hepatitis B virus; HSV, herpes simplex virus; LCV, lymphocytic choriomeningitis virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VZV, varicella-zoster virus.
From Maldonado YA, Nizet V, Klein JO, et al. Current concepts of infections of the fetus and newborn infant. In: Wilson CB, Nizet V, Maldonado Y, et al., eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn*, 8th ed. Philadelphia: Elsevier; 2016. Tables 1–5; and from Woodworth KR, Olsen EO, Neelam V, et al. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1635–40.

DIAGNOSIS

During Pregnancy

The presence of IUGR or a physical abnormality on a prenatal fetal ultrasound raises concern for a congenital infection. The well-known acronym **TORCH**—***T****. gondii*, **O**ther (*T. pallidum*, human parvovirus B19, HIV, Zika virus, others), **R**ubella, **C**ytomegalovirus, and **H**erpes simplex virus (HSV)—is a historical mnemonic but is less useful given the number of *other* infections that need to be considered. The routine ordering of TORCH serology panels *is not* recommended because the presence of a pathogen-specific IgG response in the mother indicates past infection but does not establish if the infection occurred during pregnancy. Maternal IgM titers to *specific* pathogens are only moderately sensitive, and a negative result cannot be used to exclude infection. Testing the mother for the pathogen of concern itself, such as testing for CMV, HIV, or Zika viremia, can shed some light onto the potential congenital pathogens of concern.

In certain cases, a fetal blood sample with cordocentesis can be obtained and tested for total and pathogen-specific IgM assays, polymerase chain reaction assays (PCRs), or cultures. A positive *pathogen-specific* IgM test is strongly suggestive of infection, but a negative test does not rule out the organism as the cause of the fetopathy. Amniotic fluid can also be obtained and sent for PCR or culture. The presence of CMV, *T. gondii*, or human parvovirus B19 in amniotic fluid indicates the fetus likely is infected but cannot establish the severity of disease. Although HSV is included in the TORCH acronym, it is rarely isolated from amniotic fluid and is rarely transmitted across the placenta from mother to fetus. Fetal blood can be collected to test for human parvovirus B19 IgM and PCR.

Newborn Infant

When a congenital infection is suspected because clinical signs are present at birth, a complete blood count with differential and platelet count along with measurements of transaminases and total/direct bilirubin are routinely performed. Additional evaluations may include a dilated funduscopic examination for retinopathy, auditory brainstem response (ABR) for those failing the newborn hearing screen, and CNS imaging. If available, pathologic examination of the placenta and/or cord may be informative. Infectious diseases consultation is valuable in guiding the evaluation.

Neonatal antibody titers for specific pathogens are often difficult to interpret because IgG is acquired from the mother by transplacental passage, and a positive result may reflect the mother's past infection and not infection of the newborn. Neonatal IgM antibody titers to specific pathogens have high specificity and only moderate sensitivity; a negative result cannot be used to exclude infection. Paired maternal and fetal-neonatal IgG antibody titers showing higher or rising infant IgG antibodies can diagnose some congenital infections (e.g., syphilis). Total cord blood IgM and IgA are not actively transported across the placenta to the fetus yet are not specific or sensitive enough for intrauterine infection.

PCR testing of infant saliva, urine, and/or blood for CMV and other viral infections is sensitive, specific, and widely accepted over virus cultures, yet should be performed within the first 2 weeks of life to distinguish congenital infection from perinatal or postnatal infection. The Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL; Palo Alto, CA: www.pamf.org/serology/; telephone: (650) 853-4828; e-mail: remingtonlab@sutterhealth.org) offers specialized tests and physician experts to aid in the diagnosis of congenital toxoplasmosis. Testing for Zika virus with real-time reverse-transcription PCR (rRT-PCR) from neonatal urine and serum and IgM enzyme-linked immunosorbent assay (ELISA) from neonatal serum is recommended. However, the most reliable method of testing has not been established. In endemic areas, this workup

Table 149.2 Prevention Strategies for Congenital and Perinatal Infections

PATHOGEN	PREVENTION STRATEGY
CMV	Hygienic education to avoid direct contact with toddler urine/saliva, avoid new sexual partners
HSV	Prevention of maternal STI near delivery and exposure of newborn to active maternal lesions
VZV	Vaccination of nonpregnant women of childbearing age with a negative varicella history or vaccine immunity
Rubella virus	Vaccination of nonpregnant women of childbearing age with no immunization history
HIV	Safe sex practices; maternal treatment with HAART on infection
SARS-CoV-2	Prenatal and maternal vaccination, masking, and social distancing
Zika virus	Prevention of mosquito bites and safe sex practices with persons who have recently traveled to endemic areas
Toxoplasma gondii	Avoiding undercooked meat, avoiding unpasteurized goat milk, avoiding raw mollusks, avoid contact with litter or soil potentially contaminated with cat feces
Treponema pallidum	Safe sex practices; screening in nonpregnant populations

HSV, Herpes simplex virus; CMV, cytomegalovirus; VZV, varicella-zoster virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STI, sexually transmitted infection; HAART, highly active antiretroviral therapy.

From Auriti C, De Rose DU, Santisi A, et al. Pregnancy and viral infections: Mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. *Biochim Biophys Acta Mol Basis Dis.* 2021;1867:1–17; Maldonado YA, Read JS. American Academy of pediatrics committee on infectious diseases: diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. *Pediatrics.* 2017;139(2):e20163860; US Preventive Services Task Force: Screening for syphilis infection in pregnant women, February 2018.

should be done soon after delivery because it is difficult to distinguish congenital from perinatal and postnatal infection if testing is done later.

SPECIFIC INFECTIOUS AGENTS

Important congenital infections include more than the TORCH agents. The following is a list of pathogens that may be transmitted across the placenta and the respective chapters where they are discussed in more detail, including treatment.

Bacteria

Listeria monocytogenes (Chapter 234)
Syphilis *(Treponema pallidum)* (Chapter 264)

Viruses

Cytomegalovirus (Chapter 302)
Hepatitis B (Chapter 406)
Hepatitis C (Chapter 406)
Herpes simplex virus (Chapter 299)
Human immunodeficiency virus (Chapter 322)
Human parvovirus B19 (Chapter 298)
Lymphocytic choriomeningitis virus (Chapter 318)
Rubella (Chapter 294)
Varicella-zoster virus (Chapter 300)
Zika virus (Chapter 314.12)

Parasite

Toxoplasmosis (*Toxoplasma gondii)* (Chapter 336)

149.2 Perinatal Infections

Sallie R. Permar and Emma L. Mohr

Perinatal infections are defined as those that are transmitted from the mother to the fetus or newborn infant during the birth process. Despite recommended universal screening of pregnant women for *Chlamydia trachomatis*, gonorrhea, and group B streptococcus (GBS), transmission to the newborn still occurs. In addition to these STIs, other bacteria, viruses, and *Candida* spp. may cause perinatal infections. Similar to congenital infections, their presentation can range from asymptomatic to a sepsis-like syndrome.

GENERAL APPROACH

The general approach is like that for congenital infections and includes a detailed maternal history and a careful examination of the newborn (see Chapter 148). Many clinical syndromes overlap; therefore laboratory testing is usually required to establish a specific microbiologic etiology and guide management decisions.

PATHOGENESIS

The human birth canal is colonized with aerobic and anaerobic bacteria. **Ascending amniotic infection** may occur with either apparently intact membranes or relatively brief duration of membrane rupture. Infectious agents can also be acquired as the newborn infant passes through the vaginal canal. This acquisition may result in either colonization or disease. Factors influencing which colonized infants will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies.

Chorioamnionitis has been historically used to refer to microbial invasion of the amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane for >18 hours. The term *chorioamnionitis* is confusing because it does not convey the spectrum of inflammatory or infectious diseases, it leaves out other intrauterine components that can be involved (e.g., decidua), and it results in significant variability in clinical practice, with the potential for a significant number of well newborns being exposed to antimicrobial agents. The term **intrauterine inflammation or infection at birth**, abbreviated as **Triple I**, is preferred because of the heterogeneous nature of conditions that can affect the mother and neonate (Table 149.6). Regardless of the definition used, prematurity (<37 weeks) is associated with a greater risk of early-onset sepsis, especially with GBS.

Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

CLINICAL MANIFESTATIONS

Most perinatal infections present clinically during the first month of life. Initial signs and symptoms may be either nonspecific or focal (see Chapter 148). Additional information on specific infectious agents and their management are reviewed in the chapters indicated below.

SPECIFIC INFECTIOUS AGENTS

Bacteria

Chlamydia trachomatis (Chapter 272)
Escherichia coli (Chapter 246)
Genital mycoplasmas (Chapter 270)
Group B streptococci (Chapter 230)
Neisseria gonorrhoeae (Chapter 238)
Syphilis *(Treponema pallidum)* (Chapter 264)

Table 149.3 Clinical Manifestations of Specific Neonatal Infections Acquired in Utero or at Delivery

RUBELLA VIRUS	CYTOMEGALOVIRUS	*TOXOPLASMA GONDII*	HERPES SIMPLEX VIRUS	*TREPONEMA PALLIDUM*	ENTEROVIRUSES	ZIKA VIRUS
Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Adenopathy Hearing deficits Myocarditis Congenital defects* Bone lesions* Glaucoma* Chorioretinitis *or* retinopathy* Cataracts* Microphthalmia	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Microcephaly* Intracranial calcifications* Hearing deficits Chorioretinitis *or* retinopathy Optic atrophy	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus* Microcephaly Maculopapular exanthems Intracranial calcifications* Myocarditis Bone lesions Chorioretinitis *or* retinopathy* Cataracts Optic atrophy Microphthalmia Uveitis Sensorineural hearing loss*	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Microcephaly Maculopapular exanthems Vesicles* Myocarditis Chorioretinitis *or* retinopathy Cataracts Conjunctivitis *or* keratoconjunctivitis*	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Adenopathy Maculopapular exanthems* Bone lesions* Glaucoma Chorioretinitis *or* retinopathy Uveitis	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Adenopathy Maculopapular exanthems Paralysis* Myocarditis* Conjunctivitis Keratoconjunctivitis	Fetal brain disruption sequence* Cortical thinning Ventriculomegaly Microcephaly Microphthalmia *or* coloboma Cataracts Contractures Hearing deficits Epilepsy Hyper/hypotonia

*Has diagnostic significance for this infection.
Adapted from Maldonado YA, Nizet V, Klein JO, et al. Current concepts of infections of the fetus and newborn infant. In: Wilson CB, Nizet V, Maldonado Y, et al., eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn*, 8th ed. Philadelphia: Elsevier; 2016: Tables 1–6; with data from Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital zika syndrome for pediatric clinicians. *JAMA Pediatr.* 2017;171(3):288–295.

Table 149.4 Syndromes in the Neonate Caused by Congenital Infections

ORGANISM	SIGNS
Toxoplasma gondii	Hydrocephalus, diffuse intracranial calcification, chorioretinitis
Rubella virus	Cardiac defects, sensorineural hearing loss, cataracts, microcephaly, "blueberry muffin" skin lesions, hepatomegaly, interstitial pneumonitis, myocarditis, disturbances in bone growth, intrauterine growth restriction
CMV	Microcephaly, periventricular calcifications, jaundice, petechiae or purpura, hepatosplenomegaly, intrauterine growth restriction, sensorineural hearing loss
HSV	Skin vesicles or scarring, eye scarring, microcephaly or hydranencephaly, vesicular skin rash, keratoconjunctivitis, meningoencephalitis, sepsis with hepatic failure
Treponema pallidum	Bullous, macular, or eczematous skin lesions involving palms and soles; rhinorrhea; dactylitis and other signs of osteochondritis and periostitis; hepatosplenomegaly; lymphadenopathy
VZV	Limb hypoplasia, cicatricial skin lesions, ocular abnormalities, cortical atrophy
Parvovirus B19	Nonimmune hydrops fetalis
HIV	Severe thrush, failure to thrive, recurrent bacterial infections, calcification of basal ganglia
Zika virus	Microcephaly, lissencephaly, cerebellar hypoplasia, akinesia syndrome, macular scarring, retinal mottling, subcortical calcifications, hypertonia

HSV, Herpes simplex virus; CMV, cytomegalovirus; VZV, varicella-zoster virus.
From Maldonado YA, Nizet V, Klein JO, et al. Current concepts of infections of the fetus and newborn infant. In Wilson CB, Nizet V, Maldonado Y, et al., eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn*, 8th ed. Philadelphia: Elsevier; 2016: Tables 1–7.

Table 149.5 Late Sequelae of Intrauterine Infections

	INFECTION				
CLINICAL SIGN	CMV	RUBELLA VIRUS	*TOXOPLASMA GONDII*	*TREPONEMA PALLIDUM*	ZIKA VIRUS
Hearing loss	+	+	+	+	+
Dental/skeletal problems	(–)	+	(–)	+	+
Developmental delays	+	+	+	+	+
Seizures	+	+	+	+	+

+, Present; (–), rare or absent; CMV, cytomegalovirus.

Table 149.6 Classification of Triple I and Isolated Maternal Fever

TERMINOLOGY	FEATURES
Isolated maternal fever	Maternal oral temperature ≥39°C is considered a "documented fever" If the oral temperature is ≥38°C but ≤39°C, repeat the measurement in 30 min If the repeat value is ≥38°C, it is considered a "documented fever"
Suspected Triple I	Fever without a clear source with *any* of the following: 1. Baseline fetal tachycardia (>160 beats/min for 10 min) 2. Maternal WBC >15,000/mm^3 in the absence of corticosteroids 3. Purulent fluid from the cervical os
Confirmed Triple I	All the above (from suspected Triple I) with *any* of the following: 1. Amniocentesis-proven infection through positive Gram stain 2. Low glucose of amniotic fluid or positive amniotic fluid culture 3. Placental pathology consistent with infection

Triple I, Intrauterine inflammation or infection at birth; WBC, white blood cell count.
Adapted from Higgins RD, Saade G; Chorioamnionitis Workshop participants: Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. *Obstet Gynecol* 2016;127(3):426–436.

Table 149.7 Laboratory Tests in the Diagnosis of Specific Perinatal Infections

INFECTIOUS AGENT	ACCEPTABLE SPECIMEN(S) FROM INFANT UNLESS OTHERWISE INDICATED	LABORATORY TEST
Chlamydia trachomatis	Conjunctiva, nasopharyngeal swab, tracheal aspirate	DFA or culture using special transport media NAATs are not FDA-approved for specimens from neonates*
Genital mycoplasmas (*Mycoplasma hominis, M. genitalium, Ureaplasma urealyticum*)	Tracheal aspirate, blood, CSF	Culture using special transport media NAATs
Neisseria gonorrhoeae	Conjunctiva, blood, CSF, synovial fluid	Finding gram-negative intracellular diplococci on Gram stain is suggestive Culture on special media establishes the diagnosis
Syphilis *(Treponema pallidum)*	Serum (mother)	A nontreponemal test (RPR or VDRL) and if reactive, a specific treponemal test† or reverse-sequence screening: specific treponemal test and if reactive, a quantitative nontreponemal test
	Serum	RPR/VDRL
	CSF	VDRL
Cytomegalovirus	Urine, saliva (with confirmational urine), blood, or CSF (if CNS involvement)	CMV DNA PCR Obtained within 3 wk of birth
Enteroviruses	Blood, nasopharyngeal swab, throat swab, conjunctival swab, tracheal aspirate, urine, stool, rectal swab, vesicle fluid, CSF	PCR Cell culture (sensitivity depends on serotype and cell lines used)
Hepatitis B	Serum (mother) Serum	HBsAg If mother's HBsAg is positive, at age 9 mo, test the infant for HBsAg and hepatitis B surface antibody
Herpes simplex viruses 1 and 2	Conjunctiva, skin vesicle scraping, whole blood, mouth vesicles	PCR or cell culture
	CSF	PCR
	"Surface cultures" (mouth, nasopharynx, conjunctiva, and anus)	PCR or cell culture
HIV	Serum (mother) Whole blood (infant)	Fourth-generation HIV antigen/antibody test HIV DNA PCR (performed on peripheral blood mononuclear cells) or RNA PCR (performed on plasma)
Candida species	Blood, skin biopsy, or CSF	Culture
Zika virus	Blood, urine	RNA PCR Also assay CSF for RNA if obtained for other reasons
	Blood	IgM antibodies Also assay CSF for IgM if obtained for other reasons
SARS-CoV-2	Nasopharynx, oropharynx, nose, saliva, trachea	RT-PCR or direct antigen testing

*Published evaluations of NAATs for these indications are limited, but sensitivity and specificity is expected to be at least as high as those for culture.
†Treponemal tests include the *T. pallidum* particle agglutination (TP-PA) test, *T. pallidum* enzyme immunoassay (TP-EIA), *T. pallidum* chemiluminescent assay (TP-CIA), and fluorescent treponemal antibody absorption (FTA-ABS) test.
DFA, Direct immunofluorescence assay; NAAT, Nucleic acid amplification test; FDA, U.S. Food and Drug Administration; CSF, Cerebrospinal fluid; VDRL, Venereal Disease Research Laboratories; RPR, rapid plasma reagin; HBsAg, hepatitis B surface antigen; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse-transcription polymerase chain reaction.
Created with data from pathogen-specific chapters within Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Redbook: 2021-2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2018; p. 729–744.

Viruses

Cytomegalovirus (Chapter 302)
Enteroviruses (Chapter 297)
Hepatitis B (Chapter 406)
Herpes simplex virus (Chapter 299)
Human immunodeficiency virus (Chapter 322)
Severe acute respiratory syndrome coronavirus 2 (Chapter 311)

Fungi

Candida spp. (Chapter 280)

DIAGNOSIS

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, chorioamnionitis). STIs acquired by a pregnant woman, including syphilis, *N. gonorrhoeae*, and *C. trachomatis,* have the potential for perinatal transmission.

Neonates with perinatal infections often present with nonspecific symptoms and signs; therefore the general diagnostic evaluation for the ill neonate as discussed in Chapter 202 should be followed. Table 149.7 provides a summary of laboratory tests that are useful to diagnose specific perinatal infections.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Adolescent Medicine

PART XI

Chapter 150

Adolescent Physical and Social Development

Cynthia M. Holland-Hall and Maria D. Brown

See also Part XXIV and Chapters 599 and 600.

During the preteen, teenage, and young adult years, young people undergo not only dramatic changes in physical appearance but also rapid changes in physiologic, psychologic, and social functioning. Hormonally driven physiologic changes and ongoing neurologic development occur in the setting of social structures that foster the transition from childhood to adulthood. This period of development comprises **adolescence**, which is divided into three phases—early, middle, and late adolescence—each marked by a characteristic set of biologic, cognitive, and psychosocial milestones (Table 150.1). Although individual variations in the timing and pace of development undoubtedly exist, these changes follow a predictable pattern of occurrence. Gender and culture profoundly affect the developmental course, as do physical, social, and environmental influences (Fig. 150.1). Given the interaction of these domains, a biopsychosocial perspective is best suited to approach the healthcare of the adolescent.

PHYSICAL DEVELOPMENT

Puberty is the biologic transition from childhood to adulthood. Pubertal changes include the appearance of the secondary sexual characteristics, increase in height, change in body composition, and development

Table 150.1 Milestones in Early, Middle, and Late Adolescent Development

VARIABLE	EARLY ADOLESCENCE	MIDDLE ADOLESCENCE	LATE ADOLESCENCE
Approximate age range	10-13 yr	14-17 yr	18-21 yr
Sexual maturity rating*	1-2	3-5	5
Physical	• *Females:* secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt • *Males:* testicular enlargement, start of genital growth	• *Females:* peak growth velocity, menarche (if not already attained) • *Males:* growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes • Change in body composition • Acne	• Physical maturation slows • Increased lean muscle mass in males
Cognitive and moral	• Concrete operations • Egocentricity • Unable to perceive long-term outcome of current decisions • Follow rules to avoid punishment	• Emergence of abstract thought (formal operations) • May perceive future implications, but may not apply in decision-making • Strong emotions may drive decision-making • Sense of invulnerability • Growing ability to see others' perspectives	• Future-oriented with sense of perspective • Idealism • Able to think things through independently • Improved impulse control • Improved assessment of risk vs reward • Able to distinguish law from morality
Self-concept/identity formation	• Preoccupied with changing body • Self-consciousness about appearance and attractiveness	• Concern with attractiveness • Increasing introspection	• More stable body image • Attractiveness may still be of concern • Consolidation of identity
Family	• Increased need for privacy • Exploration of boundaries of dependence vs independence	• Conflicts over control and independence • Struggle for greater autonomy • Increased separation from parents	• Emotional and physical separation from family • Increased autonomy • Reestablishment of "adult" relationship with parents
Peers	• Same-gender peer affiliations	• Intense peer group involvement • Preoccupation with peer culture • Conformity	• Peer group and values recede in importance
Sexual	• Increased interest in sexual anatomy • Anxieties and questions about pubertal changes • Limited capacity for intimacy	• Testing ability to attract partner • Initiation of relationships and sexual activity • Exploration of sexual identity	• Consolidation of sexual identity • Focus on intimacy and formation of stable relationships • Planning for future and commitment

*See text and Figures 150.2 and 150.3.

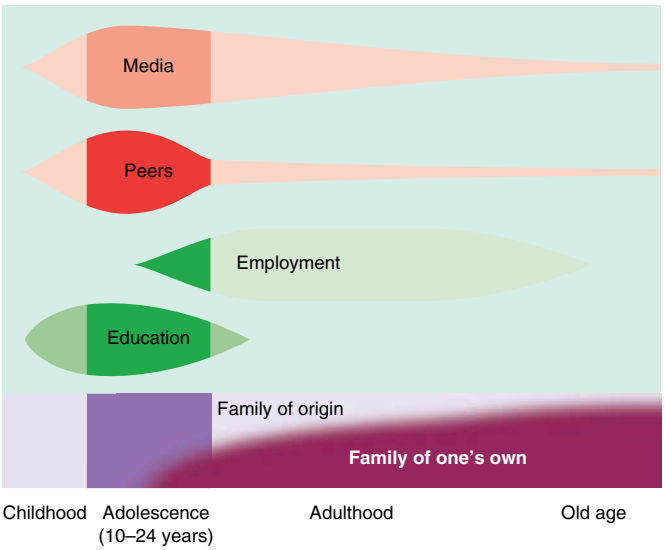

Fig. 150.1 Changing proximal social determinants of health across the life course. During adolescence, social determinants from outside the family become greater, with major influences of peers, media, education, and the beginning of workplace influences. Community and structural determinants remain consistently influential, as shown by the background shading. *(From Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. Lancet. 2016;387:2423–2478, Fig. 2.)*

of reproductive capacity. Two principal physiologic events occur during puberty: adrenarche and gonadarche. Adrenal androgen production, chiefly dehydroepiandrosterone sulfate (DHEAS), rises in response to adrenocorticotropic hormone (ACTH). Increases in serum concentrations of DHEAS result in the development of adult-like body odor and faint genital hair **(adrenarche)**, occurring as early as 6-8 years of age. Gonadal sex steroid production occurs with activation of the hypothalamic-pituitary-gonadal (HPG) axis **(gonadarche)**. Maturation of the gonadotropin-releasing hormone (GnRH) pulse generator is among the earliest neuroendocrine changes associated with the onset of puberty. Under the influence of GnRH, the pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH); initially this occurs in a pulsatile fashion primarily during sleep, but this diurnal variation diminishes throughout puberty. LH and FSH stimulate corresponding increases in gonadal androgens and estrogens. The triggers for these changes are incompletely understood. The activation of the HPG axis may be mediated by increasing adiposity and associated insulin resistance, hyperinsulinemia, elevated androgens, and leptin. Both genetic and environmental (epigenetic) factors contribute to the regulation of pubertal timing.

Sexual Development

The progression of the development of the secondary sex characteristics may be described using the **sexual maturity rating (SMR)** scale (ranging from 1, prepubertal, to 5, fully mature adolescent) or **Tanner stages**. Figures 150.2 and 150.3 depict the physical findings of breast and pubic hair maturation at each SMR (Tables 150.2 and 150.3). Although the ages at which individual pubertal changes occur may vary, the timing and sequence of these changes relative to one another is predictable (Figs. 150.4 and 150.5). The wide range of normal progress through sexual maturation is affected by genetics, the psychosocial environment, nutrition, and overall health status. Environmental exposures may also play a role.

In **males** the first visible sign of puberty and the hallmark of SMR 2 is testicular enlargement, beginning as early as 9.5 years, followed by the development of pubic hair. This is followed by penile growth during SMR 3. Peak growth occurs when testis volumes reach approximately 9-10 cm^3 during SMR 4. Under the influence of LH and testosterone, the seminiferous tubules, epididymis, seminal vesicles, and prostate

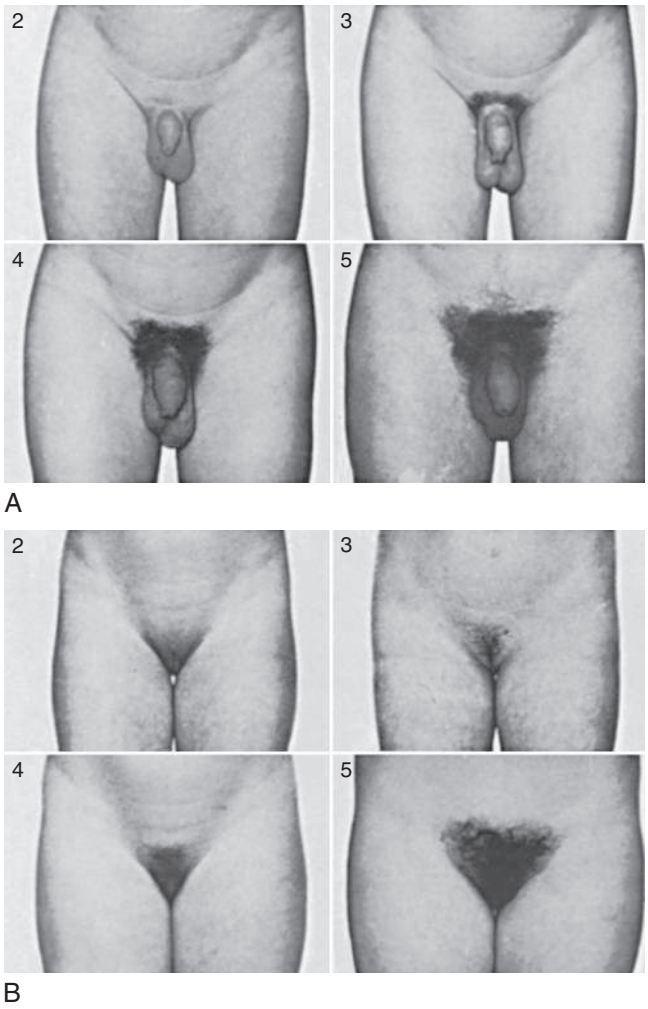

Fig. 150.2 Sexual maturity ratings (2-5) of pubic hair changes in adolescent males (A) and females (B) (see Tables 150.2 and 150.3). *(Courtesy J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London.)*

enlarge. Sperm may be found in the urine by SMR 3; nocturnal emissions may be noted at this time as well. Some degree of breast tissue growth, typically bilateral, occurs in 40–65% of males during SMR 2-4 as a presumed consequence of a relative excess of estrogenic stimulation. This usually resolves with ongoing maturation.

In **females**, typically the first visible sign of puberty and the hallmark of SMR 2 is the appearance of breast buds **(thelarche)**, between 7 and 12 years of age. A significant minority of females develops pubic hair **(pubarche)** prior to thelarche. Less visible changes include enlargement of the ovaries, uterus, labia, and clitoris and thickening of the endometrium and vaginal mucosa. A clear vaginal discharge may be present before menarche (physiologic leukorrhea). Menses typically begins within 3 years of thelarche, during SMR 3-4 (average age 12.5 years; normal range 9-15 years) (see Fig. 150.5). The timing of **menarche** is determined largely by genetics; contributing factors likely include adiposity, chronic illness, nutritional status, and the physical and psychosocial environment. Early menstrual cycles often are anovulatory and thus somewhat irregular, but typically occur every 21-45 days and include 3-7 days of bleeding, even during the first year after menarche.

The **onset of puberty** and menarche appear to be occurring at earlier ages than previously reported in the United States (see Chapter 599). Several studies from 1948 to 1981 identified the average age for the onset of breast development as ranging from 10.6 to 11.2 years of age. A subsequent prospective study suggests an earlier average age of onset of 8.8 years in Black females and 9.6 years in White females. Almost 25% of Black females and 10% of White females initiate breast development

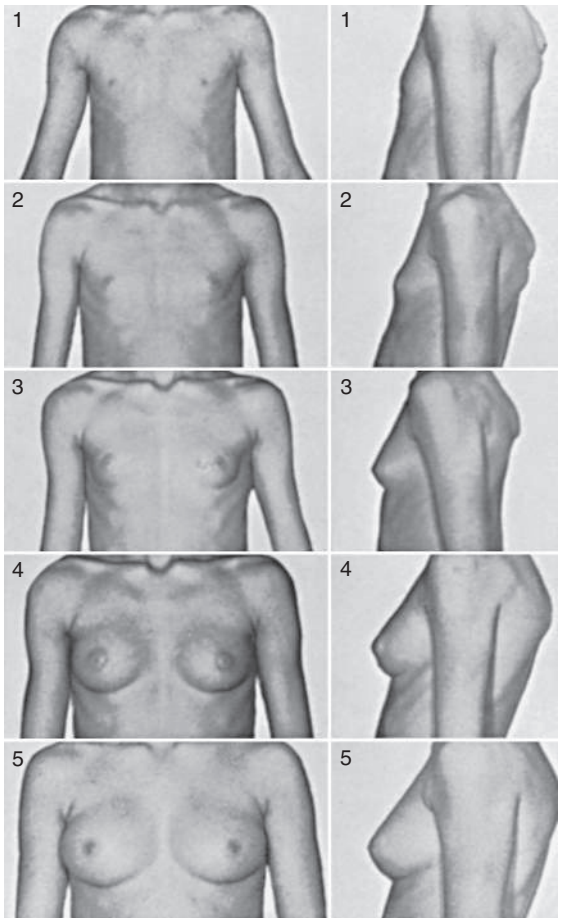

Fig. 150.3 Sexual maturity ratings (1-5) of breast changes in adolescent females. *(Courtesy J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London.)*

by 7 years of age. A 2020 systematic review and meta-analysis demonstrated an almost 3 months per decade decrease in age of thelarche between 1977 and 2013 worldwide. Early breast development may be associated with a slower tempo of puberty (i.e., longer time to menarche). There also appears to be a trend toward decreasing ages for the onset of pubic hair development and menarche. Data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative, longitudinal survey in the United States, show a decline in the average age of menarche of 4.9 months between the 1960s and 2002. This may be partially explained by changes in the ethnic makeup of the sample. Changes in the timing of menarche *within* ethnic groups were significantly smaller. The reasons for the larger decrease in age for breast development have been postulated to include the epidemic of childhood obesity and exposure to estrogen-like environmental agents (endocrine disruptors), but further research in this area is needed.

Although fewer data are available on changes in the timing of puberty in males, they appear to be experiencing a similar trend. Although the method of assessing the onset of puberty (i.e., inspection vs palpation of the testes) varies between studies, it appears that the average age for the onset of genital and pubic hair development may have decreased by 1-2 years over the past several decades in many industrialized countries. Evidence for an association of obesity with the timing of puberty in males has been inconsistent.

Somatic Growth

Linear growth acceleration begins in early adolescence for all genders, with 15–20% of adult height accrued during puberty. Females attain a **peak height velocity (PHV)** of 8-9 cm/year at SMR 2-3, approximately 6 months before menarche. Males typically begin their growth acceleration at a later SMR stage and achieve a PHV of 9-10 cm/year later in the course of puberty (SMR 3-4). Males continue their linear growth for approximately 2-3 years after females have stopped growing, accounting for an average difference of 11-13 cm in height between adult males and females (Fig. 150.6). The growth spurt begins distally, with enlargement of the hands and feet, followed by the arms and legs, and finally the trunk and chest. This growth pattern imparts a characteristic "awkward" appearance to some early adolescents. Body

Table 150.2 Sexual Maturity Rating (SMR) Stages in Females

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

From Tanner JM. *Growth at Adolescence,* 2nd ed. Oxford, England: Blackwell Scientific; 1962.

Table 150.3 Sexual Maturity Rating (SMR) Stages in Males

SMR STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scant, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

From Tanner JM. *Growth at Adolescence,* 2nd ed. Oxford, England: Blackwell Scientific; 1962.

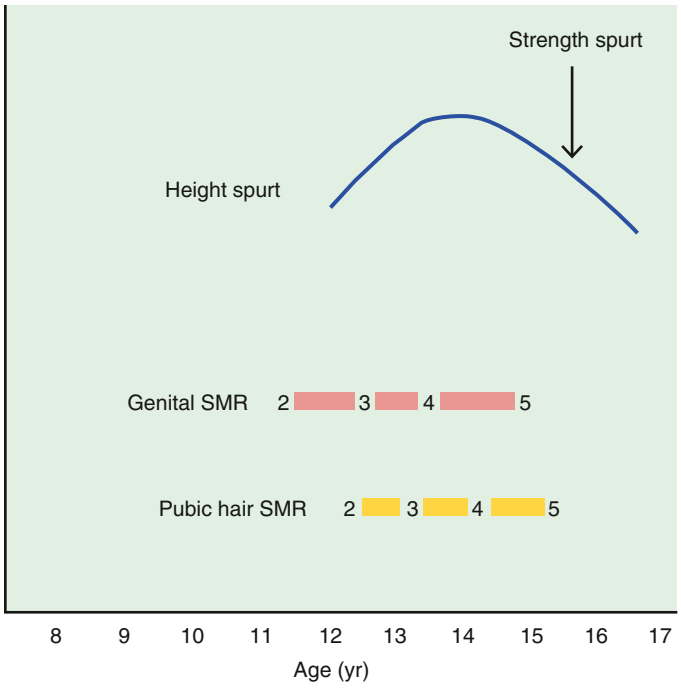

Fig. 150.4 Sequence of pubertal events in males. Although the age of onset of puberty is variable, the sequence of events relative to one another is predictable. SMR, Sexual maturity rating.

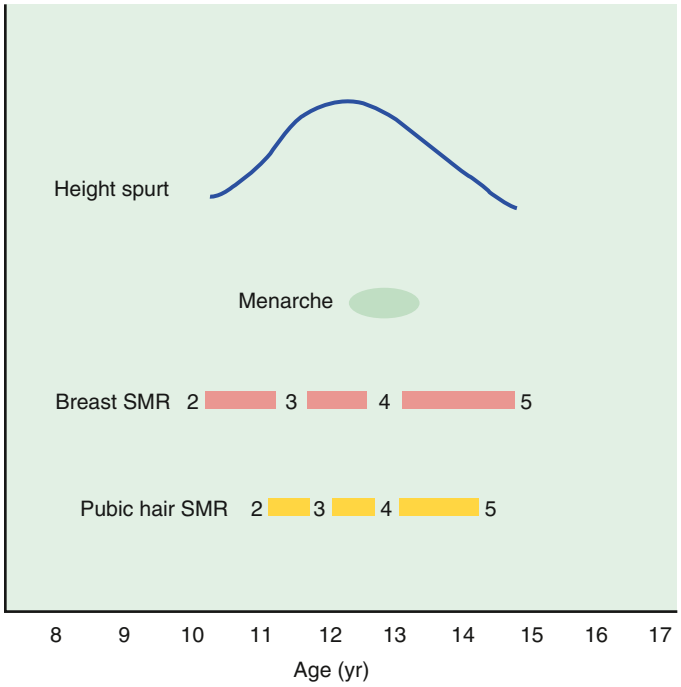

Fig. 150.5 Sequence of pubertal events in females. Although the age of onset of puberty is variable, the sequence of events relative to one another is predictable. SMR, Sexual maturity rating.

composition changes as well after attainment of PHV. Males undergo an increase in lean body mass ("strength spurt"), whereas females develop a higher proportion of body fat. Scoliosis, if present, may progress with rapid axial skeleton growth (see Chapter 720.1). From 50% to 65% of total body calcium is laid down during puberty. Bone growth precedes increases in bone mineralization and bone density, which may increase the adolescent's risk of fracture during times of rapid growth.

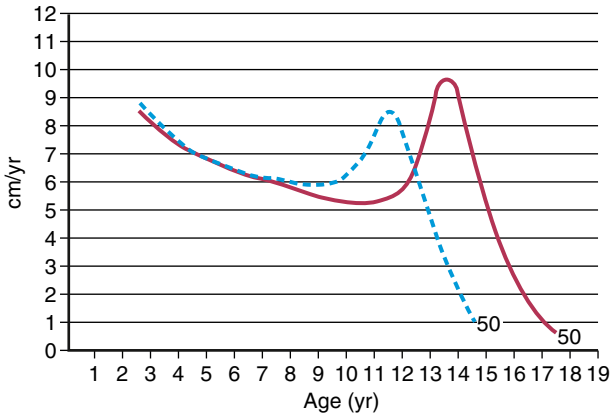

Fig. 150.6 Height velocity curves for American males *(solid line)* and females *(dashed line)* who have their peak height velocity at the average age (i.e., average growth tempo). *(From Tanner JM, Davies PSW. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985;107:317.)*

Because skeletal growth precedes muscle and tendon growth, sprains and strains may be more common during this time as well.

Cardiovascular changes in middle adolescence include increased heart size, higher blood pressure, and increases in blood volume and hematocrit, particularly in males. Coupled with an increase in lung vital capacity, these changes lead to greater aerobic capacity. Androgenic stimulation of sebaceous and apocrine glands may result in acne and body odor. Rapid enlargement of the larynx, pharynx, and lungs leads to changes in vocal quality in males, typically preceded by vocal instability (voice cracking). Elongation of the optic globe may result in the development of myopia (see Chapter 660). Dental changes include jaw growth, loss of the final deciduous teeth, and eruption of the permanent cuspids, premolars, and finally, molars (see Chapter 353). Orthodontic appliances may be needed, secondary to growth exacerbations of bite disturbances. Physiologic changes in sleep patterns and increased sleep requirements occur, causing many adolescents to delay sleep onset at night, with subsequent difficulty awakening for early school start times in the morning (see Chapter 31). The mechanism of delayed circadian rhythm has not been elucidated but likely involves changes in both circadian and homeostatic sleep regulatory processes.

NEUROLOGIC, COGNITIVE, AND MORAL DEVELOPMENT

As children progress through adolescence, they develop and refine their ability to use formal operational thought processes. Abstract, symbolic, and hypothetical thinking replaces the need to manipulate concrete objects. Middle and late adolescents develop the ability to consider multiple options and to assess the long-term consequences of their actions. The capacity for verbal expression is enhanced. Because adolescents' decision-making and subsequent behaviors are the primary determinants of their mortality and morbidity, understanding these cognitive processes is of critical importance.

Both structural and functional brain development continue throughout adolescence. Cortical gray matter volume peaks in preadolescence, then decreases because of selective "pruning" of rarely used synaptic connections, slowly declining as the third decade of life is approached. Cerebral white matter volume increases until mid-to-late adolescence, reflecting increasing myelination and subsequent facilitation of integrated brain activity and more efficient transmission of information between different regions of the brain, enhancing the "signal-to-noise" ratio. Although the frontal lobes and prefrontal cortex, regions of the brain associated with executive function, have been considered to be among the last regions to mature, other cortical regions show similarly prolonged trajectories of maturation. Without question, adolescents are capable of the complex cognitive processes attributed to frontal lobe function. *Cognitive control,* however, continues to improve into adulthood, with progressive maturation and *integration* of component

processes such as working memory, inhibition and impulse control, performance monitoring, and motivational circuitry.

The behavioral correlates of adolescent neurodevelopment remain speculative but are increasingly supported by a rapidly expanding body of research. Adolescents appear to demonstrate a unique sensitivity to the effects of dopamine on reward-relevant subcortical structures such as the ventral striatum and the ventral tegmental area, with some studies demonstrating increased activation in this region when receiving rewards relative to children or adults. Other studies show reduced responsiveness to aversive stimuli in adolescents. This altered responsiveness to risk vs reward, paired with incomplete frontal lobe myelination and thus immature impulse control, may underlie the increased risk taking and novelty seeking seen in adolescents. Early maturation and distinct patterns of neural reactivity in the amygdala and other limbic structures may explain the strong role that social and emotional stimuli play in adolescents, sometimes overwhelming the frontal executive function systems that facilitate the interpretation and regulation of those social and emotional experiences. This may explain why adolescents are more likely to make poor decisions in highly emotionally charged situations relative to mature adults. These "hot cognition" processes may result in the adolescent making a different decision in the context of a strong affective experience than he or she would in a less emotional state ("cool cognition"). These two types of cognitive processes may not develop at the same rate; the adolescent may be able to use higher brain structures and functions more effectively when in states of lower emotional arousal.

Early adolescents often continue to employ the concrete operational cognitive processes of childhood. Although formal operational cognition is developing, it may be applied inconsistently across different domains. A young adolescent may be able to use abstract thought when completing schoolwork, but not when working through a personal dilemma. Early adolescence also is characterized by egocentricity—the belief of some adolescents that they are the center of everyone's attention. Despite being largely imagined, this perception of always being "on stage" can be stressful for adolescents, who may feel that others are constantly judging or evaluating them. Early adolescents express a greater need for privacy than they did in childhood and begin to appreciate the privacy of their own thoughts. With ongoing cognitive development, **middle adolescents** are more able to consider the needs and feelings of other people. Their creativity and intellectual abilities are enhanced. Because of their increased capacity for abstract thought in combination with a persistent perception of uniqueness, middle adolescents may feel a sense of immortality and immunity to the consequences of risky behaviors. **Late adolescents** are more future oriented and able to delay gratification. They can think more independently, consider others' views, and compromise. They have a stronger sense of self and more stable interests. Under times of stress, adolescents may temporarily revert to the cognitive processes and coping strategies used at younger ages.

Moral development generally accompanies cognitive development. Preadolescents, concrete and individualistic, follow rules to please authority figures and avoid punishment. As they move into early adolescence, they develop a stronger sense of right and wrong but are likely to perceive these as absolute and unquestionable. Middle and late adolescents may establish a sense of morality driven by their desire to be seen as a good person, to behave in a manner according to their perceived place in society, or by their sense of obligation to care for others. Moral decision-making, however, still may be highly subject to emotional context. Late adolescents may develop a rational conscience and an independent system of values, although these often are largely consistent with parental values. While going through this complex developmental process, religious or political organizations that promote simple answers to complex social or moral questions may hold great appeal to the adolescent.

PSYCHOSOCIAL DEVELOPMENT

In contrast to cognitive development, psychosocial development correlates more strongly with pubertal status and physical maturation than with chronological age. Whereas cognitive development is more biologically determined, psychosocial development is subject to greater environmental and cultural influences. Indeed, cultural variation can be dramatic. Some late adolescents move immediately from high school into marriage, childbearing, working, and financial independence; others remain dependent on the parents while pursuing their own education for several more years, in a period sometimes referred to as *emerging adulthood*. Psychosocial development also may be nonlinear, with different domains of growth progressing along different timelines. An overriding theme of psychosocial development is the concept of identity formation and consolidation as the adolescent moves away from the nurturing protection of the family, develops an increased affiliation with the peer group(s), and ultimately defines himself or herself as an individual.

Separation from the parents is a hallmark of adolescent development. Early adolescents start to seek out more privacy at home, spending less time with the parents. They begin to reject parental advice and involvement in their decision-making as they explore the boundaries of their dependence on, and independence from, their parents. With evolving cognitive skills, an adolescent can conceive of an ideal parent and contrast this ideal with his or her own parents. Adolescents may seek out alternative adult role models, such as teachers, coaches, or parents of friends. Parent–child conflict often peaks during middle adolescence, with disagreements over privileges, independence, and other limits set by the parents. Adolescents may appear intermittently to seek and reject parental acceptance. It is theorized that perhaps the adolescent *needs* to conceive of the parents as "wrong" in order to ameliorate the pain of separating from them. Throughout this time, however, the parents remain a critical source of nurturing and support for the adolescent and continue to exert significant influence over the adolescent's decision-making. Paradoxically, frequent arguments and conflict may coexist with strong emotional bonds and closeness. The late adolescent may reestablish a more "adult–adult" type of relationship with the parents, once again seeking out and considering parental advice and guidance as they enter adulthood.

Increasing importance of the **peer group** also may buffer the emotional trauma of separating from the parents (see Fig. 150.1). Early adolescents tend to socialize largely with same-gender peers, both in their individual friendships and larger groups. Females' peer groups tend to be more relationship oriented, whereas males' peer groups are more likely to be centered around a particular interest or activity. In both cases, group cohesion and a sense of belonging become important. Peers become increasingly important in middle adolescence, during which time the adolescent may experiment with being a part of different groups and "try on" different identities. These groups may include all genders. Peer groups may arise from organized activities, such as sports or clubs, or may simply be friendship based. Gang membership is another form of peer acceptance. **Conformity** with the peers in manners of dress, speech, and behavior is a normal part of this process and should not necessarily be viewed negatively. Similarly, **peer pressure** may exist, but its influence over the adolescent's decision-making may be positive, negative, or negligible. Acceptance and successful navigation of peer groups during adolescence may give the individual more confidence to move into and out of various social, academic, and professional groups in the future. Late adolescents are less vulnerable to peer group influence, having moved closer to establishing their own stable identity. Their cognitive skills allow them to choose selectively among different peer groups, endorsing and adopting individual values and behaviors that best reflect who they are becoming.

Early adolescents have increased **sexual awareness and interest**, which may manifest as sexual talk and gossip, and often is focused on sexual anatomy. Masturbation and other sexual exploration, sometimes with same-sex peers, are common. The prevalence of other forms of sexual behavior varies by culture; in general, these behaviors are less common in early adolescents. Romantic relationships, if they exist at all, lack emotional depth. Sexual curiosity, experimentation, and activity become more common among

middle adolescents. Same-sex attraction is common; sexual orientation may become clear to some adolescents, but still may be evolving in others during this time. Dating behaviors may be seen, but this is culture dependent and may not be a popular construct for all adolescents. Individual relationships often continue to emphasize sexual attraction over emotional intimacy. Relationships that occur during middle adolescence may be short and intense. Emotional intimacy and more permanent relationships may not be seen until late adolescence. At that time, relationships increasingly involve love and commitment and demonstrate greater stability.

Body image may affect (and be affected by) adolescents' psychosocial development as well. Early and middle adolescence are usually the ages during which poor or distorted body image and eating disorders develop. Early adolescents undergo rapid physical changes and may experience uncertainty about whether all these anatomic and physiologic changes are progressing normally. Reassurance from adults, including their healthcare providers, may be comforting. As puberty comes to an end and these changes slow, the middle adolescent's preoccupation may shift to whether they are attractive to others. A strong emphasis on physical appearance during this time is common. Although this focus on physical appearance may continue into adulthood, late adolescence generally is characterized by a shifting balance toward introspection, with somewhat less emphasis placed on external characteristics.

The **timing of pubertal changes** also can affect psychosocial development and well-being. The progression of pubertal changes in males is generally associated with a positive self-image. Early-maturing males tend to have greater self-confidence, social, and academic success, whereas later-maturing males are at risk for more internalizing behaviors and diminished self-esteem. Females may initially perceive changes in their physical appearance more negatively. This appears to be especially true for early-maturing females, some of whom experience greater decreases in self-esteem, engage in more disruptive behaviors, and have more conflict with their parents than do on-time or late-maturing females. Early-maturing females may be more comfortable associating with older peers and may subsequently be exposed to peer pressure around things like sexual activity and substance use at younger ages. Still lacking the cognitive skills to effectively navigate these situations, they may be vulnerable to making poor decisions that place their health and safety at risk. Many other factors influence how adolescents experience puberty, and supportive peers and adults can have a positive impact on psychosocial development at any maturational stage. With successful navigation of these domains, emerging adults move into the world with a strong sense of personal identity and their place in society. They are able to work toward a vocation and financial independence and to manage the responsibilities of adulthood.

IMPLICATIONS FOR PROVIDERS, PARENTS, AND POLICYMAKERS

Providers can help parents approach their child's adolescent years by reframing some of the "challenges" of adolescence as normal developmental milestones that should be anticipated and accepted. Puberty and emerging sexuality should be approached as positive and health-affirming life changes, rather than focusing discussions only on the negative reproductive risks and outcomes. Even good-natured teasing about bodily changes can be detrimental to the adolescent's self-image. Early-maturing females and late-maturing males should be supported, recognizing their potential increased exposure to psychosocial challenges. Identification of strengths and emerging positive coping strategies should be promoted in all youth, particularly those with chronic illness or other challenges. Providers need to determine the young adolescent's cognitive development and capacity for abstract thought and tailor their communication and counseling style accordingly. Physical examinations should be performed in private with the parent outside the exam room (provided the adolescent is comfortable with this), which also affords the adolescent and provider an opportunity to discuss confidential issues. Reassurance of normal development should be provided.

As adolescents develop more independence and parent–child conflict peaks, providers should remind parents that this is typical and that arguing does not mean the adolescent does not value the parents' input and perspectives. Although some may rebel initially, most adolescents ultimately adopt a value system very similar to that of their parents. Even if discussions feel ineffective to parents, they should continue to demonstrate and model these values to their child. Similarly, rather than categorically dismissing their child's "negative" interests, such as playing a violent video game, parents should be encouraged to use these opportunities to model critical thinking about the impact of such an activity. Potentially negative peer groups may be approached the same way, while fostering the development of positive peer networks. **Authoritative parenting**, in which clear and appropriate negotiated limits are set in the context of a caring and mutually respectful parent–child relationship, is most strongly associated with positive psychosocial development. Parental connectedness and close supervision or monitoring of the youth's activities and peer group can be protective against early onset of sexual activity and involvement in behaviors that may threaten their safety and can foster positive youth development. Parents should also assume an active role in their adolescent's transition to adulthood to ensure that their child receives appropriate preventive health services.

Parents and providers may each work with adolescents to foster good decision-making. In addition to providing adolescents with accurate and complete health information, the adolescent's cognitive ability to use this information in various contexts must be considered. Visits with providers can be used to promote independence among adolescents by spending time separately with both caregivers and the adolescent, allowing the adolescent space to voice concerns and receive appropriate information about making healthy decisions and recognizing behaviors that may be placing their health at risk.

Adolescents may find themselves needing to make important decisions in highly charged situations where they may be unable to manage their emotions and use their higher cognitive functions to examine the consequences of their decision. For example, a couple in a sexual situation with high emotional arousal may make the decision to proceed with unprotected intercourse. By anticipating this situation ahead of time, under conditions of lower emotional arousal, and making a plan to deal with this, they may make a different decision (e.g., stick with their prior decision never to have sex without protection) when the time comes. Parents and healthcare providers are in a position to encourage and foster this anticipation and planning under conditions of "cool cognition."

Providers may need to help parents distinguish normal adolescent development and risk-taking behaviors from possible signs of a more serious mental health or conduct problem. Bids for **autonomy**, such as avoiding family activities, demanding privacy, and increasing argumentativeness, are normal; extreme **withdrawal** or **antagonism** may be dysfunctional, signaling a mental health or substance use concern. Bewilderment and dysphoria at the start of middle school are normal; continued failure to adapt several months later suggests a more serious problem. Although some degree of risk taking is normal, progressive escalation of risk-taking behaviors is problematic. In general, when the adolescent's behaviors cause significant dysfunction in the domains of home life, academics, or peer relationships, they should be addressed by the parents and healthcare provider, and referral to a mental health provider may be considered. In most cases, parents can be reassured that although adolescence can pose unique challenges, their adolescent, like most adolescents, will come through it to become a successful and happy adult.

At national and international levels, adolescents are at risk for environmental, health, behavioral, and societal challenges. Table 150.4 provides suggestions to address these issues.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 150.4 Recommended Action Bundles* for Adolescent and Young Adult Health Problems and Risks

PROBLEM/ RISK AREA	STRUCTURAL	SOCIAL MARKETING	COMMUNITY INTERVENTIONS, INCLUDING FAMILY	ELECTRONIC HEALTH, MOBILE HEALTH	SCHOOLS	HEALTH SERVICE SECTOR
Sexual and reproductive health, including HIV	***Legislation*** *18 yr as the minimum age of marriage* *Allow provision of contraception to legal minors* *Legalize abortion*	*Promote community support for sexual and reproductive health and HIV health access for adolescents*	**Cash transfer programs, with payments linked to staying in school** *Positive youth development* *Peer education*	*Target knowledge, attitudes, and risk behaviors*	**Quality secondary education** **Comprehensive sexuality education** **Safe schools with clean toilets and facilities for menstrual care** **School-based health services with condoms and modern contraceptives**	**Condoms and affordable modern contraception, including long-acting reversible contraception** **Early HIV and STI diagnosis and treatment** **Male circumcision** **Antenatal, delivery, and postnatal care** *Transition to adult care for HIV*
Undernutrition	**Fortification of foods (e.g., iron, folate)**		**Micronutrient supplements (particularly in pregnancy)** **Protein-energy supplementation** **Deworming** *Cash transfer program* *Nutrition education*		**Micronutrient supplements** **Healthy school meals**	**Screening and micronutrient supplementation**
Infectious diseases			*Deworming* *Bed net distribution*		**HPV vaccination** *Deworming*	**Early identification and treatment** **Adolescent vaccinations (HPV, childhood catch-up)** *Deworming* *Bed net distribution* *Seasonal malaria chemoprevention*
Violence	**Gun control** *Legalize homosexuality and protect women from violence and sexual coercion* *Youth justice reforms to promote second chances and diversion from custody* *16 yr as the minimum age for criminal responsibility*	*Promote knowledge of the effects of violence and available services*	*Promote parent skills and parent–child communication* *Positive youth development* *Promote gender equality* *Economic empowerment* *Group training for awareness, knowledge, and skills*		**Multicomponent interventions that target violent behavior and substance use**	**Trauma care**
Unintentional injury	**Graduated licensing** **Mandatory helmet wearing** **Multicomponent traffic injury control**	*Promote knowledge of risks*	*Police enforcement of traffic injury control*			**Trauma care, including first responders (e.g., ambulances)**
Alcohol and illicit drugs	**Limit alcohol sales to underage adolescents** **Taxation on alcohol** **Drunk-driving legislation** **Restrict illicit alcohol** **Interventions in licensed premises** **Diversion from youth justice and custody** *Graduated drinking*	**Advertising restrictions** *Campaigns to build community awareness*	*Promote parent–child communication and parenting skills* *Needle-syringe exchange access* *Mentoring*	*Target knowledge, attitudes, and risk behaviors*	*Alcohol-free policies*	*Risk screening and motivational interviewing*

Continued

Table 150.4 Recommended Action Bundles for Adolescent and Young Adult Health Problems and Risks—cont'd

PROBLEM/ RISK AREA	STRUCTURAL	SOCIAL MARKETING	COMMUNITY INTERVENTIONS, INCLUDING FAMILY	ELECTRONIC HEALTH, MOBILE HEALTH	SCHOOLS	HEALTH SERVICE SECTOR
Tobacco	**Tobacco control, including taxation, pricing, and advertising control** **Youth access restrictions** **Legislation for smoke-free air**	**Anti-tobacco campaigns**	*Interventions to promote parent skills and parent–child communication*	*Text messaging adjunct to quitting*	*Smoke-free policies* *Multicomponent*	*Routine screening and motivation interviewing to promote cessation*
Mental disorders and suicide	**Restriction of access to means**	*Promote adolescent mental health literacy*	*Gatekeeper training*	*Electronic mental health interventions*	*Educational interventions* *Gatekeeper training* *School-based mental health services*	**Practitioner training in depression recognition and treatment** *Routine assessment of mental health, including self-harm and suicide risk*
Chronic physical disorders			*Peer support initiatives*		*School-based health services*	*Promote self-management* *Promote transition to adult healthcare*
Overweight and obesity	**Taxation of high-sugar, high-salt, and high-fat foods** *Front-of-pack nutrition labels* *Restriction of fast-food advertising*	*Promote physical activity*	*Create opportunities for maintenance of physical activity in daily life*	*Interactive or personalized feedback interventions*	*Multicomponent interventions involving education about healthy diet and increasing opportunities for physical education*	**Manage comorbidities of obesity**

*Actions in **bold** have an evidence base in adolescents and young adults; actions in *italics* are promising but without yet a strong evidence base in adolescents and young adults.
HIV, Human immunodeficiency virus; HPV, human papillomavirus; STI, sexually transmitted infection.
From Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet*. 2016;387:2423–2478, p. 2458.

Chapter 151

Delivery of Healthcare to Adolescents

Samantha V. Hill and Tamera Coyne-Beasley

Healthcare providers play an important role in nurturing healthy behaviors among adolescents, because the leading causes of death and disability among adolescents are preventable. Adolescence provides a unique opportunity to prevent or modify health conditions arising from behaviors that develop in the second decade of life and that can lead to substantial morbidity and mortality, such as trauma, suicide, cardiovascular and pulmonary disease, type 2 diabetes, reproductive health issues, and cancer (see Chapter 150, Table 150.4).

Health systems in each community should be in place to ensure comprehensive and high-quality care to adolescents. **Health insurance coverage** that is affordable, continuous, confidential, and not subject to exclusion for preexisting conditions should be available for all adolescents and young adults. **Comprehensive, coordinated benefits** should meet the developmental needs of adolescents, particularly for reproductive, mental health, dental, and substance use services. **Safety net providers and programs** that provide confidential services, such as school-based health centers, federally qualified health centers, family planning services, and clinics that treat sexually transmitted infections **(STIs)** in adolescents and young adults, need to have assured funding for viability and sustainability. **Quality-of-care** data should be collected and analyzed by age so that the performance measures for age-appropriate healthcare needs of adolescents are monitored. **Affordability** is important for access to preventive services. Family involvement should be encouraged, but **confidentiality** and adolescent consent are critically important and should be addressed with intentionality at each visit.

Healthcare providers, trained and experienced in adolescent care, should be available in all communities. Healthcare providers should be adequately compensated to support the range and intensity of services required to address the developmental and health service needs of adolescents. The development and dissemination of provider education about **adolescent preventive health guidelines** have been demonstrated to improve the content of recommended care (Table 151.1). The ease of recognition or expectation that an adolescent's needs can be addressed in a setting relates to the visibility and flexibility of sites and services. Staff at sites should be approachable, linguistically capable, culturally humble, and able to balance trauma-informed care with healing-centered engagement approaches with attention to equity and social determinants of health. Health services should be coordinated to respond to goals for adolescent health at the local, state, and national levels. The coordination should address service financing and delivery in a manner that reduces disparities in care.

Although most adolescents in the United States have seen a healthcare provider in the past year and report a usual source of healthcare, adolescents are less likely to receive preventive care services. According to the 2019 National Health Interview Survey, an estimated 92% of 12- to 17-year-old U.S. adolescents had a well child visit within the past year. Uninsured adolescents are the least likely to receive care. The National Health Interview Survey found that 8% of 15- to 18-year-olds were uninsured, whereas 61% and 31% had private and public insurance in 2016, respectively.

Table 151.1 Bright Futures/American Academy of Pediatrics Recommendations for Preventive Healthcare for 11- to 21-Year-Olds

	PERIODICITY AND INDICATIONS
HISTORY	Annual
MEASUREMENTS	
Body mass index	Annual
Blood pressure	Annual
SENSORY SCREENING	
Vision	At 12 yr and 15 yr visits or if risk assessment positive
Hearing	Screen with audiometry, including 6,000- and 8,000-Hz high frequencies once at 11-14 yr, once at 15-17 yr, and once at 18-21 yr.
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT	
Developmental surveillance	Annual
Psychosocial/behavioral assessment	Annual
Depression screening	Annual for 12 yr and older
Tobacco, alcohol, and drug use assessment	If risk assessment positive
PHYSICAL EXAMINATION	Annual
PROCEDURES	
Immunization*	Annual
Hematocrit or hemoglobin	If risk assessment positive
Tuberculin test	If risk assessment positive
Dyslipidemia screening	Once at 9-11 yr, and once at 17-21 yr
STI screening	If sexually active
HIV screening†	Once between ages 15 and 18 yr Discuss and offer at earlier age and annually if risk assessment positive.
Cervical dysplasia screening‡	Beginning at age 21 yr
ORAL HEALTH	Annual; refer to dental home
ANTICIPATORY GUIDANCE	Annual§

*Schedules per the Advisory Committee on Immunization Practices, published annually at http://www.cdc.gov/vaccines/schedules/hcp/index.html and http://redbook.solutions.aap.org/SS/Immunization_Schedules.aspx.

†The CDC recommends universal, voluntary HIV screening of all sexually active people beginning at age 13 yr. The American Academy of Pediatrics recommends offering routine HIV screening to all adolescents at least once by 16-18 yr of age and to those younger if at risk. The U.S. Preventive Services Task Force recommends offering routine HIV screening to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

‡Screening for cervical cancer, April 2012, U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

§Refer to specific guidance by age as listed in *Bright Futures* guidelines.

HIV, Human immunodeficiency virus; STI, sexually transmitted infection.

Adapted from Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, 4th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017.

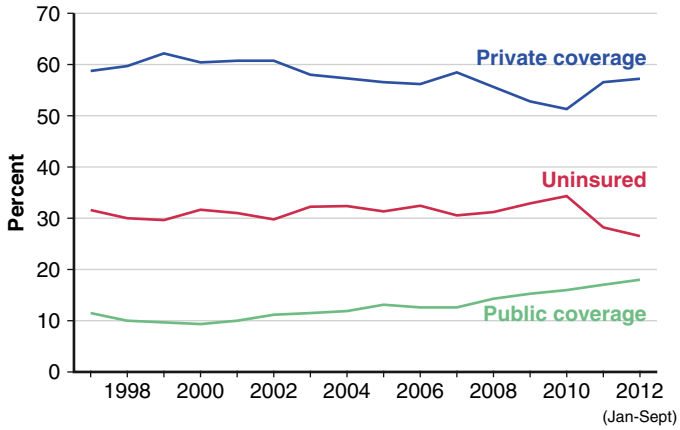

Fig. 151.1 Percentage of adults 19-25 years of age with health insurance by coverage type and percentage uninsured at the time of the interview: United States, 1997 to September 2012. *Note:* Estimates for 2012 are based on data collected in January through September. Data are based on household interviews of a sample of the civilian noninstitutionalized population. (*Data from CDC/NCHS, National Health Interview Survey, 1997–2012, Family Core Component.*)

The **Patient Protection and Affordable Care Act (ACA)** has expanded access to both commercial health plans and Medicaid for young adults age 19-26 years (Fig. 151.1); the proportion of young adults with insurance increased from 65.7% to 73.8%. ACA provisions require that commercial health plans continue dependent coverage to 26 years, regardless of the young adult's financial or dependent status, marriage, or educational enrollment; mandate university and college student health plans enhance consumer protections for students; provide financial assistance for young adults to enroll into health insurance exchanges with incomes ranging from 133% to 399% of the federal poverty level in Medicaid expansion states; and offer preventive healthcare services (to include contraceptive care) free of any cost sharing, deductibles, or copayments. In states that have expanded Medicaid coverage, all adults with incomes <133% of the federal poverty level are eligible to enroll. After passage of the ACA, 14% of 18- to 24-year-olds still remained uninsured.

The complexity and interaction of physical, cognitive, and psychosocial developmental processes during adolescence require sensitivity and skill on the part of the health professional (see Chapter 150). Health education and promotion, as well as disease prevention, should be the focus of every visit (Table 151.2).

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) currently recommends routine adolescent vaccines for universal administration beginning at the 11- to 12-year-old visit or as soon as possible: (1) tetanus-diphtheria-acellular pertussis vaccine (Tdap), (2) the meningococcal conjugate vaccine (MCV4) with a booster at age 16 years, (3) the human papillomavirus vaccine (HPV) series, and (4) the COVID-19 vaccine (see Chapter 215). ACIP recommends annual influenza vaccination and hepatitis A virus (HAV) vaccination to adolescents and young adults who have not previously received the HAV vaccine series if immunity against HAV is desired or for those at increased risk for infection, such as men who have sex with men (MSM), injection drug users (IDUs), and those with chronic liver disease or clotting factor disorders, or those who live in endemic areas. Although another meningococcal vaccine (MenB) is not routinely recommended for all adolescents, the ACIP recommends a MenB vaccine series for people ages 16-23 based on shared clinical decision-making with the patient (or parent/guardian) to provide short-term protection against serogroup B meningococcal disease.

The time spent on various elements of the screening will vary with the issues that surface during the assessment. However, time for screening and assessment is important for all adolescents, and the ideal model of adolescent care requires a minimum of 20 minutes per visit. For lesbian, gay, bisexual, trans, intersex, and asexual youth (see Chapters 153 and 154), emotional and psychologic concerns related to their experiences, from fear of disclosure to the trauma of discrimination or bullying or violence, may direct the clinician to spend more time assessing emotional and psychologic supports in the young person's environment. For youth with chronic illnesses or special needs, the assessment of at-risk behaviors should not be omitted or deemphasized by assuming they do not experience the "normal" adolescent vulnerabilities.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 151.2 Adolescent Screening Recommendations

UNIVERSAL SCREENING	11- TO 14-YR-OLD VISIT ACTION	15- TO 17-YR-OLD VISIT ACTION	18- TO 21-YR-OLD VISIT ACTION
Cervical dysplasia*	N/A	N/A	Pap smear all young women at 21 yr visit
Depression	Annual adolescent depression screen beginning at 12 yr visit	Annual adolescent depression screen	Annual adolescent depression screen
Dyslipidemia	Lipid screen once at 9-11 yr	Lipid screen once at 17-21 yr	Lipid screen once at 17-21 yr
Hearing	Once at 11-14 yr Audiometry, including 6,000- and 8,000-Hz high frequencies	Once at 15-17 yr Audiometry, including 6,000- and 8,000-Hz high frequencies	Once at 18-21 yr Audiometry, including 6,000- and 8,000-Hz high frequencies
HIV†	Selective screening (see later)	HIV test once at 15-18 yr	HIV test once at 15-18 yr
Tobacco, alcohol, or drug use	Annual tobacco, alcohol, or drug use screen	Annual tobacco, alcohol, or drug use screen	Annual tobacco, alcohol, or drug use screen
Vision	At 12 yr visit Objective measure with age-appropriate visual acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	At 15 yr visit Objective measure with age-appropriate visual acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	N/A

SELECTIVE SCREENING	RISK ASSESSMENT (RA)	11-14 YR OLD VISIT ACTION IF RA+	15-17 YR OLD VISIT ACTION IF RA+	18-21 YR OLD VISIT ACTION IF RA+
Anemia	Positive on risk screening questions	Hemoglobin or hematocrit	Hemoglobin or hematocrit	Hemoglobin or hematocrit
Dyslipidemia (if not universally screened at this visit)	Positive on risk screening questions and not previously screened with normal results	Lipid profile	Lipid profile	Lipid profile
HIV†	Positive on risk screening questions	HIV test	HIV test (if not universally screened at this visit)	HIV test (if not universally screened at this visit)
Oral health (through 16 yr visit)	Primary water source fluoride deficient	Oral fluoridation supplementation	Oral fluoridation supplementation	N/A
STIs				
Chlamydia	Sexually active females	Chlamydia and gonorrhea NAAT (test at all sites where patient engages in sex)	Chlamydia and gonorrhea NAAT (test at all sites where patient engages in sex)	Chlamydia and gonorrhea NAAT (test at all sites where patient engages in sex)
Gonorrhea	Sexually active females			
Syphilis	Sexually active and positive on risk screening questions	Syphilis test	Syphilis test	Syphilis test
Tuberculosis	Positive on risk screening questions	Tuberculin skin test	Tuberculin skin test	Tuberculin skin test
Vision at other ages	Positive on risk screening questions at 11, 13, and 14 yr visits	Objective measure with age-appropriate visual acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	Objective measure with age-appropriate visual acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	Objective measure with age-appropriate visual acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters

*Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force.

†The Centers for Disease Control and Prevention recommends universal, voluntary HIV screening of all sexually active people beginning at age 13 yr. The American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. The U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

NA, Not applicable; NAAT, nucleic acid amplification test; STIs, sexually transmitted infections.

Adapted from Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, 4th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017 and Bright Futures/American Academy of Pediatrics: Recommendations for Preventive Pediatric Health Care (Periodicity Schedule), 2017. https://www.aap.org/en-us/Documents/periodicity_schedule.pdf.

151.1 Legal Issues

Samantha V. Hill and Tamera Coyne-Beasley

The rights of an individual, including those of adolescents, vary widely between nations. In the United States, the right of a minor to consent to treatment without parental knowledge differs between states and is governed by **state-specific minor consent laws**. Some consent laws are based on a minor's status, such as minors who are emancipated, parents, married, pregnant, in the armed services, or mature. In some states, minors can be considered *emancipated* if they are or have served in the armed services or are living apart from parents and are economically independent through gainful employment. A *mature minor* is a minor who is emotionally and intellectually mature enough to give informed consent and who lives under the supervision of a parent or guardian. Courts have held that if a minor is mature, a physician is not liable for providing beneficial treatment. There is no formal process for recognition of a mature minor. The determination is made by the healthcare provider.

Some minor consent laws are based on services a minor is seeking, such as emergency care, sexual healthcare, substance abuse, or mental healthcare (Table 151.3). All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for **STIs**. Approximately 25% of states require that minors be a certain age (generally 12-14 years) before they can consent for their own care for STIs. No state requires parental consent for STI care or requires that providers notify parents that an adolescent minor child has received STI services, except in limited or unusual circumstances.

Minors' right to consent for **contraceptive services** varies from state to state. Almost 50% of states and the District of Columbia explicitly authorize all minors to consent for their own contraceptive services, and 50% of states permit minors to consent for their own contraceptive services under specific circumstances, such as being married, a parent, currently or previously pregnant, over a certain age, or a high school graduate, or per physician's discretion. The FDA has approved a nonprescription daily oral contraceptive (norgestrel) intended to reduce barriers to access to an effective birth control measure.

A minor's right to consent for **mental healthcare** and **substance use** treatment services varies by state and age of the minor, whether care is medical vs nonmedical (e.g., counseling), and whether care is delivered as an inpatient vs outpatient basis. Minor consent laws often contain provisions regarding confidentiality and disclosure, even when general state consent laws do not have such provisions.

The **confidentiality** of medical information and records of a minor who has consented for his or her own *reproductive healthcare* is governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI or contraceptive services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents.

The confidentiality of medical information and records of a minor who has consented for their own healthcare is also governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI, contraceptive, or mental health services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents. Title X and Medicaid both provide confidentiality protection for family planning services provided to minors with funding from these programs.

Federal regulations issued under the Federal Health Insurance Portability and Accountability Act, known as the **HIPAA Privacy Rule**, defer to state and "other applicable laws" with respect to the question of whether parents have access to information about care for which a minor has given consent. Thus both the state laws that either prohibit or permit disclosure of confidential information and the federal Title X and Medicaid laws that protect the confidentiality of care for adolescents are important under the HIPAA Privacy Rule in determining when confidential information about health services for minors can be disclosed to parents.

Billing for confidential services is complex. Commercial health plans send home an *explanation of benefit (EOB)* to the primary insured or the primary beneficiary, listing services rendered by the provider and reimbursed by the health plan. An EOB documenting that confidential health services were rendered to their adolescent dependent that is received by a parent may disclose those services. In addition, copayments automatically generated with certain billing codes for office visits and medications can be a barrier for adolescents receiving care, including treatment. One way to circumvent a breach of confidentiality from EOBs is to have the adolescent call the insurance company; however, this can be a time-consuming process.

Table 151.3 Types of Minor Consent Statutes or Rules of Common Law That Allow for Medical Treatment of a Minor Patient Without Parental Consent

LEGAL EXCEPTIONS TO INFORMED CONSENT REQUIREMENT	MEDICAL CARE SETTING
The "emergency" exception	• The child is suffering from an emergent condition that places his or her life or health in danger • The child's legal guardian is unavailable or unable to provide consent for treatment or transport • Treatment or transport cannot be safely delayed until consent can be obtained • The professional administers only treatment for emergent conditions that pose an immediate threat to the child
The "emancipated minor" exception	• Married • Economically self-supporting and not living at home • Active-duty status in the military • In some states, a minor who is a parent or pregnant • Some states might require a court to declare the emancipation of a minor
The "mature minor" exception	Most states recognize a mature minor, in which a minor, usually ≥14 yr, displays sufficient maturity and intelligence to understand and appreciate the benefits, risks, and alternatives of the proposed treatment and to make a voluntary and reasonable choice on the basis of that information; states vary or whether a judicial determination is required
Exceptions based on specific medical condition (state laws vary)	Minor seeks: • Mental health services • Pregnancy and contraceptive services • Testing or treatment for HIV infection or AIDS • Sexually transmitted infection testing and treatment • Drug and alcohol addiction treatment

Data from American Academy of Pediatrics: consent for emergency medical services for children and adolescents. *Pediatrics* 2011;128:427–433.

In March 2020, in response to the COVID-19 pandemic, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) was passed. Part of this act requires rapid release of all patient documentation (e.g., notes, laboratory results, problem and medication lists) and poses a new challenge to the provision of confidential health services to adolescents.

Providers may elect to establish a policy of discussing with their adolescent patients when medical records and other information will be disclosed and developing a mechanism to alert office staff as to what information in the chart is confidential. For legal and other reasons, a chaperone should be present whenever an adolescent patient's genitalia is examined.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

151.2 Screening Procedures

Samantha V. Hill and Tamera Coyne-Beasley

INTERVIEWING THE ADOLESCENT

The preparation for a successful interview with an adolescent patient varies based on the history of the relationship with the patient. Patients (and their parents) who are going from preadolescence to adolescence while seeing the same provider should be guided through the transition. Although the rules for confidentiality are the same for new and continuing patients, the change in the **physician–patient relationship**, allowing more privacy during the visit and more autonomy in the health process, may be threatening for the parent and the adolescent. For new patients, the initial phases of the interview are more challenging given the need to establish rapport rapidly with the patient in order to meet the goals of the encounter. Issues of **confidentiality and privacy** should be explicitly stated along with the conditions under which that confidentiality may need to be altered, that is, in life- or safety-threatening situations. For new patients, the parents should be interviewed with the adolescent or before the adolescent to ensure that the adolescent does not perceive a breach of confidentiality. The clinician who takes time to listen, avoids judgmental statements and the use of street jargon, and shows respect for the adolescent's emerging maturity will have an easier time communicating with the adolescent. The use of *open-ended questions,* rather than closed-ended questions, will further facilitate history taking. (The closed-ended question, "Do you get along with your father?" leads to the answer "yes" or "no," in contrast to the question, "What might you like to be different in your relationship with your mother?" which may lead to an answer such as, "I would like her to stop always worrying about me.")

The goals of the interview or clinical encounter are to establish an information base, identify problems and issues from the patient's perspective, and identify problems and issues from the perspective of the clinician, based on knowledge of the health and other issues relevant to the adolescent age-group. The adolescent should be given an opportunity to express concerns and the reasons for seeking medical attention. The adolescent and the parent should be allowed to express the strengths and successes of the adolescent, in addition to communicating problems.

The effectiveness of an interview can be compromised when the interviewer is distracted by other events or individuals in the office, when extreme time limitations are obvious to either party, or when there is expressible discomfort with either the patient or the interviewer. The need for an **interpreter** when a patient is hearing impaired or **a translator** if the patient and interviewer are not language compatible provides a challenge, but not necessarily a barrier, under most circumstances (see Chapter 12). Observations during the interview can be useful to the overall assessment of the patient's maturity, presence or absence of depression, and the parent–adolescent relationship. Given the key role of a successful interview in the screening process, excellent training and experience should be sought by clinicians providing comprehensive care to adolescent patients.

PSYCHOSOCIAL ASSESSMENT

A few questions should be asked to identify the adolescent who is having difficulty with **peer relationships** (Do you have a best friend with whom you can share even the most personal secret?), **self-image** (Is there anything you would like to change about yourself?), **depression** (In the past year have you felt depressed or sad most days, even if you felt okay sometimes?), **school** (How are your grades this year compared with last year?), **personal decisions** (Are you feeling pressured to engage in any behavior for which you do not feel you are ready?), **substance use** (Have you ever tried smoking, vaping, alcohol, weed, or prescription drugs that were not prescribed for you?), and an **eating disorder** (Do you ever feel that food controls you, rather than vice versa?). Standardized screening for depression with validated tools such as the PH-Q9 modified for teens is also helpful. The **HEADS/SF/FIRST** mnemonic, basic or expanded, can be useful in guiding the interview if encounter forms are not available (Table 151.4). Based on the assessments,

Table 151.4 Adolescent Psychosocial Assessment: HEADS/SF/FIRST Mnemonic

***H*ome.** Space, privacy, frequent geographic moves, neighborhood
***E*ducation/School.** Frequent school changes, repetition of a grade/in each subject, teachers' reports, vocational goals, after-school educational clubs (e.g., language, speech, math), learning disabilities
***A*buse.** Physical, sexual, emotional, verbal abuse; parental discipline
***D*rugs.** Tobacco, electronic cigarettes or vaping devices, alcohol, marijuana, inhalants, "club drugs," "rave" parties, others; drug of choice, age at initiation, frequency, mode of intake, rituals, alone or with peers, quit methods, number of attempts
***S*afety.** Seat belts, helmets, sports safety measures, hazardous activities, driving while intoxicated
***S*exuality/*S*exual Identity.** Reproductive health (use of contraceptives, presence of sexually transmitted infections, feelings, pregnancy)
***F*amily and *F*riends**
Family: Family constellation; genogram; single/married/separated/divorced/blended family; family occupations and shifts; history of addiction in first- and second-degree relatives; parental attitude toward alcohol and drugs; parental rules; chronically ill, physically or mentally challenged parent
Friends: Peer cliques and configuration ("preppies," "jocks," "nerds," "computer geeks," cheerleaders), gang or cult affiliation
***I*mage.** Height and weight perceptions, body musculature and physique, appearance (including dress, jewelry, tattoos, body piercing as fashion trends or other statement)
***R*ecreation.** Sleep, exercise, organized or unstructured sports, recreational activities (television, video games, computer games, internet and chat rooms, church or community youth group activities [e.g., Boy (BSA)/Girl Scouts; Big Brother/Sister groups, campus groups]). How many hours per day, days per week involved?
***S*pirituality and Connectedness.** Use HOPE* or FICA† acronym; adherence, rituals, occult practices, community service or involvement
***T*hreats and Violence.** Self-harm or harm to others, running away, cruelty to animals, guns, fights, arrests, stealing, fire setting, fights in school

*HOPE, *H*ope or security for the future; *o*rganized religion; *p*ersonal spirituality and *p*ractices; *e*ffects on medical care and end-of-life issues.
†FICA, *F*aith beliefs; *i*mportance and influence of faith; *c*ommunity support.
From Dias PJ: Adolescent substance abuse: assessment in the office. *Pediatr Clin North Am* 2002;49:269–300.

appropriate counseling or referrals are recommended for more thorough probing or for in-depth interviewing.

PHYSICAL EXAMINATION

Vision Testing

The pubertal growth spurt may involve the optic globe, resulting in its elongation and myopia in genetically predisposed individuals (see Chapter 658). Vision testing should therefore be performed to detect this problem before it affects school performance.

Audiometry

Highly amplified music of the kind enjoyed by many adolescents may result in hearing loss or tinnitus (see Chapter 676). A hearing screening is recommended by the *Bright Futures* guidelines for adolescents who are exposed to loud noises regularly, have had recurring ear infections, or report problems.

Blood Pressure Determination

Criteria for a diagnosis of hypertension are based on age-specific norms that increase with pubertal maturation (see Chapter 471). Individuals younger than 13 years old whose blood pressure (BP) exceeds the 95th percentile for their age are suspect for having hypertension, regardless of the absolute reading, and a BP between the 90th and 95th percentiles should receive appropriate counseling relative to weight and have a follow-up examination in 6 months. Individuals 13-18 years old with a BP of 130-139/80-89 are suspect for having hypertension, and those with a BP of 120-129/80 should receive appropriate counseling relative to weight and have a follow-up examination in 6 months. Those with elevated BPs should have their BP measured on three separate occasions to determine the stability of the elevation before moving forward with an intervention strategy. The technique is important; false-positive results may be obtained if the cuff covers less than two thirds of the upper arm. The patient should be seated, and an average should be taken of the second and third consecutive readings, using the change rather than the disappearance as the diastolic pressure. Most adolescents with BP elevation have labile hypertension. If BP is below 2 standard deviations (SD) for age, anorexia nervosa and Addison disease should be considered.

Scoliosis

See Chapter 720.

Approximately 5% of male and 10–14% of female adolescents have a mild curvature of the spine. This is 2-4 times the rate in younger children. Scoliosis is typically manifested during the peak of the height velocity curve, at approximately 12 years in females and 14 years in males. Females should be screened twice, once between 11 and 12 and again between 13 and 14, and males should be screened between 12 and 13. Curves measuring >10 degrees should be monitored by an orthopedist until growth is complete.

Breast Examination

See Chapters 158 and 588.

Visual inspection of the young and middle adolescent female's breasts is performed to evaluate progression of sexual maturation and provide reassurance about development. The American Cancer Society no longer recommends a clinical breast exam as a screening method for women in the United States. Breast self-exam is also no longer recommended as an option for women of any age.

Scrotum Examination

Visual inspection of the young and middle adolescent male testicles is performed to evaluate progression of sexual maturation and provide reassurance about development. The peak incidence of germ cell tumors of the testes is in late adolescence and early adulthood. Because varicoceles often appear during puberty, the examination also provides an opportunity to explain and reassure the patient about this entity (see Chapter 582). Self-examination is no longer recommended because of the low incidence and high recovery rates of testicular cancer in this age-group. Palpation of the scrotum along with visual inspection should be performed to document bilaterally descended testicles.

Pelvic Examination

See Chapter 585.

Laboratory Testing

The increased incidence of iron-deficiency anemia after menarche directs the performance of a hematocrit annually in females with moderate to heavy menses. The reference standard for this test changes with progression of puberty, as estrogen suppresses erythropoietin (see Chapter 496). Populations with nutritional risk should also have the hematocrit monitored. Androgens have the opposite effect, causing the hematocrit to rise during male puberty; sexual maturity rating (SMR) 1 males have an average hematocrit of 39%, whereas those who have completed puberty (SMR 5) have an average value of 43%. **Tuberculosis (TB)** testing is important in adolescents with risk factors, such as an adolescent with HIV, living in a household with someone with HIV, incarcerated, homeless, from a country where TB is common, or those with other risk factors, because puberty has been shown to activate this disease in those not previously treated. **Hepatitis C virus (HCV)** screening should be offered to all adolescents 18 years and older regardless of their risks. It should also be offered to adolescents who report risk factors, such as IDU, received blood products or organ donation before 1992, or long-term hemodialysis. The rate of acute hepatitis C has remained the highest among persons age 20-39 years, similar to age-groups at highest risk for fatal overdose in the United States and age at initiation of IDU among certain U.S. populations. Compared with 2018, the greatest increase in the rates of acute hepatitis C were observed among those age 40-49 years (31% increase), followed by those age 30-39 years (23% increase). For the first time in more than a decade, the rate of acute hepatitis C decreased slightly among those age 20-29 years. Rates have consistently been lowest among those age <20 years or ≥60 years. Sexually active adolescents should undergo screening for **STIs** per CDC guidelines, regardless of symptoms (see Chapter 163). There are clear indications for chlamydia and gonorrhea screening of females ≤24 years old, but less sufficient evidence to support routine screening in young men. Based on feasibility, efficacy, and cost-effectiveness, evidence is insufficient to recommend routine chlamydia screening in all sexually active young men. However, screening of sexually active young males should be considered in clinical settings associated with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, sexually transmitted disease clinics) and should be offered to all young MSM. **HIV** screening should be discussed and offered at least once to all adolescents age 15-18 years and to younger and older adolescents who are at increased risk. Routine screening of adolescents who are asymptomatic for certain STIs (e.g., syphilis, trichomoniasis, herpes simplex virus, HPV) is not recommended. However, young MSM and pregnant adolescent females might require more thorough evaluation for all sexually transmitted diseases. Because cervical cancer incidence is low and complications from procedures may outweigh benefits of screening adolescent females, cervical cancer screening should not begin until age 21 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 152

Transitioning to Adult Care

Joseph M. Truglio and Nikita Barai

The importance of thoughtfully and intentionally transitioning care of adolescents from pediatric to adult services, particularly for adolescents with **special healthcare needs (SHCN)**, has been recognized for more than 2 decades. The Society of Adolescent Health and Medicine defines health care transitions as "the purposeful, planned movement of adolescents and young adults (AYA) with chronic physical and medical conditions from child-centered to the adult-oriented health care system." For adolescents with SHCN, successful transition is associated with improved health outcomes and quality of life, whereas poorly managed transitions may lead to loss of a medical home and worsening of chronic disease control. All adolescents, regardless of SHCN, are likely to benefit from the autonomy, continuity of care, and self-management skills that are facilitated by a successful transition.

Guidelines emphasize that **transition** is a process, not an event, and encompasses much more than simply the transfer of care from one clinician to another. The guidelines make recommendations and provide practice-based resources for implementing elements of transition support in pediatric, family medicine, internal medicine, and combined internal medicine–pediatric practices. This includes providing assistance for the patient in adapting to an adult model of healthcare delivery as they transition from one practice/clinician to another or as they transition between models of care within the same practice. It also emphasizes the importance of the many members of the patient's care team (primary and specialty care, physical and occupational therapy, school and/or vocational support, mental health clinicians, and so on) that support the patient before, during, and after the transition process. Table 152.1 represents the key elements of healthcare transition. Tools to assist providers with these steps are available online from the National Center for Health Care Transition Improvement (www.gottransition.org).

The process begins with the development of a transition policy and its dissemination to all families of young adolescents, ensuring families understand that transition planning will be an element of health maintenance and chronic care management visits throughout the adolescent years. By middle adolescence, a transition plan should be developed with the youth and family caregivers and updated at subsequent visits until the patient is ready for implementation of the adult care model in early adulthood. Periodic **readiness assessments** are key to planning and anticipating challenges. Critical to the transition process is **skills training** for the adolescent in communication, self-advocacy, and self-care. Some youth with SHCN depend on caregivers for navigating the healthcare system on their behalf, and it is not realistic to expect increased independence. For these youth, addressing guardianship, long-term care planning, and advance directives are important. **Care coordination** facilitates navigation and engagement in an adult-oriented health system, especially for adolescents with SHCN. The goal is to help all youth maximize their potential as they become young adults.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 152.1 Key Elements of the Transition of Healthcare Process

- **Written transition policy** to be shared with youth, families, providers, and staff, explaining the process and the responsibilities of all team members
- **Transitioning youth registry** to track the progress of each patient through the transition process
- **Longitudinal readiness checklists** assessing the youth's ability for independence, self-management, and communicating with the adult healthcare system, as well as the family's readiness to assist the patient in achieving these goals
- **Written transition plan** documenting the steps to be conducted to meet the needs identified in the readiness assessment and identifying appropriate adult care resources
- For youth with SHCN, expanded transition services, including attention to insurance, entitlements, guardianship, and vocational needs, in addition to adult subspecialty care
- Appropriate communication between the pediatric and adult medical home and subspecialists, including a **portable medical summary** and care plan delivered to the patient and caregivers
- Transfer of care, within the 18- to 21-yr-old range, to adult providers, to whom pediatric providers continue to serve as a resource until transition is complete

Chapter 153

Gender Identity and Transgender Care

Abby Walch and Stephen M. Rosenthal

TERMINOLOGY

Sex refers to the physical or genetic characteristics that differentiate between biologic maleness or femaleness (e.g., sex chromosomes, gonads, internal and external genital structures). **Sex designated (assigned) at birth** is typically based on the appearance of the external genitalia. In the absence of atypical genitalia, which may indicate a difference of sexual development requiring further evaluation, sex is designated at birth as either male or female.

Gender identity refers to one's internal core sense of gender. Gender is not binary, and although most people identify their gender as being male (boy or man) or female (girl or woman), others may identify as both, neither, or another gender completely. The gender identity of an individual cannot be known until they reach a certain level of psychosocial development and self-awareness to identify it themself. Development of gender identity likely results from a complex interplay of biologic, environmental, and cultural factors. This concept is supported by compelling studies in several biomedical disciplines including genetics, endocrinology, and neurology. **Gender expression** refers to one's external manifestations of gender (e.g., choice of name, pronouns, clothing, hairstyle), whereas **gender role** describes the behaviors, attitudes, and personality traits considered to be masculine or feminine by a society or culture during a particular period.

Many cultures recognize and accept as normal more than two genders. In the Philippines, *Bakla* is considered a third gender; many are community leaders. In India, the third gender is *Hijras,* and Aboriginal (Australian) terms such as *brotherboy* and *sistergirl* are used to refer to transgender and gender-diverse people.

Indigenous Nations (America) peoples may have three to five genders: male, female, Two Spirits female, Two Spirits male, and transgender. Navajo refer to Two Spirits as *Nádleehí* (transformed), and the Cheyenne term for Two Spirits is *Hemaneh* (half man, half woman). In all these societies, Two Spirits people are honored and often leaders in their tribe.

Cisgender refers to people who have a gender identity that aligns with their sex designated at birth. **Gender incongruence** is the term used when gender identity does not align with the sex designated at birth. **Transgender and gender diverse (TGD)** is an umbrella term used to describe a diverse group of people with gender incongruence. *All TGD gender identities are normal, healthy variations within the spectrum of possible gender identities.* Individuals with gender identities that are not exclusively male or female may describe themselves as **gender nonbinary**, **genderqueer**, or **genderfluid**. Some of these individuals may also identify as transgender while others may not.

Gender dysphoria refers to the distress experienced by TGD individuals caused by gender incongruence. This term replaced "gender identity disorder" in the most recent *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5 published in 2013, focusing the clinical concern on the distress an individual may experience because of gender dysphoria and underscoring the *nonpathologic* nature of TGD gender identities. Not all TGD individuals experience gender dysphoria, and use of this term, although sometimes necessary to obtain gender-affirming therapies, may be considered offensive and stigmatizing by some.

It is important to distinguish gender identity as separate from **sexual orientation**, which refers to an individual's sexual attraction to another person. Gender identity does not predict sexual orientation, and a person with any gender identity may have any sexual orientation.

EPIDEMIOLOGY

Early studies likely underestimated the size of the TGD population due to reliance on reports of individuals who accessed gender-related mental health or medical care and because of the lack of questions related to gender identity on population-based surveys. With newer study methods and increased societal recognition and acceptance of the diverse spectrum of genders, it is now evident that the prevalence of TGD persons is higher than previously thought. With improved access to multidisciplinary gender clinics, TGD youth are seeking gender-affirming medical treatment at increasing rates.

In 2022, a report from the Williams Institute of the University of California Los Angeles School of Law, informed by the Center for Disease Control and Prevention's (CDC's) Behavior Risk Factor Surveillance System and the Youth Risk Behavior Survey carried out from 2017 to 2020 and 2017 to 2019, respectively, revealed that 0.5% of U.S. adults (18 years and older) and 1.4% of adolescents and young adults (13-17 years) identify as transgender. A population-based study of self-reported gender identity in high school students carried out in Minnesota in 2016 reported a 2.7% prevalence of TGD individuals. An international review in 2016 estimated the TGD population worldwide to be 25 million with 0.5–1.3% of birth-designated males and 0.4–1.2% of birth-designated females having TGD gender identities.

There has been a striking inversion in the sex ratio of TGD youth seeking services for gender dysphoria. Reports from Europe and North America prior to 2005–2006 revealed a predominance of birth-designated males. Since then, and for unclear reasons, there has been a predominance of birth-designated females. A 2017 survey of 25 gender centers in the United States, Europe, and Chile demonstrated that 63% of youth being treated were transitioning from female to male.

Clinical Presentation

TGD youth may recognize and reveal their gender identity to others at any age. Some will communicate their identity in early childhood as soon as they are able to talk. Others may not acknowledge or share their identity until adulthood, largely influenced by a cis-heteronormative society in which TGD individuals encounter significant oppression and discrimination. What is evident is the importance of accepting and valuing the gender identities as reported by TGD children at any point in time and the recognition that gender may not be binary and may change over time.

Gender incongruence that occurs in young children does not invariably persist into adolescence and adulthood. Studies based on earlier versions of the DSM demonstrate that gender dysphoria or gender incongruence in prepubertal children persists in a minority of these individuals. Future studies may reveal different persistence rates, as DSM-5 criteria for the diagnosis of gender dysphoria are narrower compared to previous versions. Although it is currently not possible to predict which children will persist in their asserted TGD identity, certain factors are associated with persistence of a TGD identity. Receipt of a gender dysphoria diagnosis in childhood, increased intensity of gender dysphoria as measured on gender dysphoria scales, social gender transition in childhood, sex designated as female at birth, and older age at clinic intake have been associated with higher persistence rates of TGD identities. Although not well studied, the assigned male at birth verbal toddler who asserts "I am a girl" (rather than "I want to be a girl") has a high likelihood of persistence.

Recognition that social gender transition in prepubertal children is associated with a higher likelihood of persistence should not prevent children from making this transition. Social transition, when completed early, may result in more favorable outcomes for some TGD children and should be done with input from a qualified mental health provider. Currently, persistence of gender incongruence and gender dysphoria can only reliably be assessed after the onset of puberty. Gender dysphoria that emerges or worsens with puberty onset is associated with a very high rate of persistence of that individual's TGD identity into adulthood, an observation that is fundamental to the rationale for the provision of medical interventions in TGD youth who meet criteria for treatment.

Diagnostic Evaluation

Optimally, the diagnostic evaluations of TGD youth are performed by a multidisciplinary team comprising medical and mental health professionals. Current clinical practice guidelines recommend that gender incongruence and gender dysphoria be diagnosed by a qualified mental health gender specialist after a thorough psychodiagnostic evaluation. Specific criteria for the mental health gender specialist in their role providing care for TGD youth are outlined elsewhere, whereas the recommendations in this chapter are intended for medical providers.

Although the involvement of a mental health gender specialist in the diagnostic evaluation of TGD youth is recommended by current clinical practice guidelines prior to initiating any medical therapies, it is recognized that this may not always be possible. Mental health gender specialists may be inaccessible in certain areas, and the insistence that a TGD child establish mental healthcare in this circumstance could delay care indefinitely. Additionally, if an early pubertal TGD child presents with significant gender dysphoria, and if requiring input from a mental health gender specialist before initiating puberty blockers would create a significant delay in care, resulting in the development of irreversible secondary sexual characteristics, this could be harmful. Therefore in limited circumstances it may be reasonable to initiate gender-affirming medical therapies without input from a mental health gender specialist, though with the increasing use of telehealth, there may be greater access to mental health gender specialists. Providers involved in the diagnostic evaluation of TGD youth should be thoughtful about their strengths and limitations and refer for further evaluation as needed to provide optimal care.

At the initial clinic visit, medical providers should obtain information from TGD youth and their families about the child's gender journey. This information should include their current understanding of their gender identity, challenges faced in addition to support received in their families and surrounding communities, any distress associated with their body and if so whether it changed with puberty, and a full medical and mental health history. After obtaining this information, in TGD youth seeking gender-affirming medical therapies, the medical provider then must decide whether the individual fulfills criteria for treatment (Table 153.1) for gender dysphoria/gender incongruence according to the DSM-5 (Table 153.2).

Table 153.1 Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A QUALIFIED MHP HAS CONFIRMED THAT:
   - The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed)
   - Gender dysphoria worsened with the onset of puberty
   - Any coexisting psychologic, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment
   - The adolescent has sufficient mental capacity to give informed consent/assent to this (reversible) treatment
2. AND THE ADOLESCENT:
   - Has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility
   - Has given informed consent/assent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process
3. AND A PEDIATRIC ENDOCRINOLOGIST OR OTHER CLINICIAN EXPERIENCED IN PUBERTAL ASSESSMENT:
   - Agrees with the indication for GnRH agonist treatment
   - Has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2)
   - Has confirmed that there are no medical contraindications to GnRH agonist treatment

Adolescents are eligible for subsequent sex hormone treatment if:

1. A QUALIFIED MHP HAS CONFIRMED:
   - The persistence of gender dysphoria
   - Any coexisting psychologic, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment
   - The adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent/assent to this (partly) irreversible treatment
2. AND THE ADOLESCENT:
   - Has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility)
   - Has given informed consent/assent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process
3. AND A PEDIATRIC ENDOCRINOLOGIST OR OTHER CLINICIAN EXPERIENCED IN PUBERTAL INDUCTION:
   - Agrees with the indication for sex hormone treatment
   - Has confirmed that there are no medical contraindications to sex hormone treatment

MHP, mental health professional.
Data from Coleman E, Radix AE, Bouman WP, et al. Standards of care for the health of transgender and gender diverse people, Version 8. *Int J Transgend Health*. 2022;23(Suppl 1):S1-S259.

Table 153.2 DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender
   4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning

Specify if:

1. The condition exists with a disorder of sex development
2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females)

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Copyright 2013. American Psychiatric Association.

Gender-Affirmative Care

TGD youth have historically faced high rates of discrimination and barriers in medical care settings. Pediatric primary care providers play a vital role in assessing the gender identities of their patients during routine well child checks, and they should be relied upon as a trusted source of validation, support, and reassurance to TGD youth and their families (Table 153.3). If a provider feels unable to address gender-related issues, then referral to another provider who can is recommended. If additional information on gender-affirming medical therapies is desired, referral to a provider with expertise in the care of TGD youth is appropriate. Available resources for youth, family, and providers are noted in Table 153.4.

Pediatric providers should follow a gender-affirmative care model (GACM) in their practices. In a GACM, providers offer a supportive, open-minded environment while facilitating discussion and exploration of their patients' gender identities. Within this care model, the following messages are relayed: (1) TGD identities and diverse gender expressions are normal, healthy variations, (2) gender identity develops through a complex interplay of biologic, environmental, and cultural factors, and (3) coexisting mental health issues are more often *caused* by stigma and discrimination than by internal psychologic disturbances within the TGD child. Key components of gender-affirming clinics are highlighted in Figure 153.1.

Pediatric providers should help TGD youth explore the various options available for gender affirmation. Some TGD youth will require medical or surgical interventions for affirmation of their gender, whereas others will not. Social transition is a nonmedical intervention that may occur gradually or all at once. It may occur in only some environments and not in others, or it may occur in all spaces in which TGD individuals find themselves. Social transition may include adaptions to name and/or pronouns, changes to hairstyle and/or clothing, use of devices to hide unwanted physical features (e.g., binders to create a smoother contour of the chest) or to create the appearance of desired physical features (e.g., packers to achieve the appearance of a genital bulge), and steps to access appropriate restroom facilities at school, work, or other public locations. Social transition may also include legal

Table 153.3 Strategies for Supporting TGD Youth

DOMAIN	STRATEGIES
Clinical settings	Use of affirmed name and pronouns in clinical spaces and inclusion of this information in the electronic medical record (EMR) Training for clinical staff Use of affirming imagery, inclusive intake forms Gender-neutral bathroom spaces Open-ended, nonjudgmental discussion about gender identity Sensitive, trauma-informed care History taking using nongendered language
Relationships with family/ caregivers	Assistance with disclosure of identity to family when desired by the youth Psychoeducation on gender development and the benefits of supporting TGD youth Promoting practices such as use of affirmed name and pronouns Education about social transitioning Providing space and support for parents to express concerns without youth present Support for disclosure to extended family or other important people Referrals to support groups or family counseling
Educational settings	Education for school staff on gender concepts and zero tolerance for transphobia Advocating for the use of affirmed name and pronouns Advocacy for inclusive sexual education curriculum Advocacy for youth to use preferred bathrooms, locker rooms, and dorms and participate with desired sports teams
Public identification	Assistance with documentation for changing legal name and/or gender marker Documentation of the patient's gender identity to ensure safe passage during travel

From Voss RV, Simons L. Supporting the health of transgender and gender-diverse youth in primary care settings. *Prim Care Clin Office Pract.* 2021;48:259–270, Table 2; with data from Guss CE, Woolverton GA, Borus J, et al. Transgender adolescents' experiences in primary care: a qualitative study. *J Adolesc Health.* 2019;65:344–349.

Table 153.4 Resources for Youth, Parents, and Providers

	ONLINE RESOURCE
Resources for youth	Gender Spectrum (genderspectrum.org) The Trevor Project (thetrevorproject.org) Transgender Law Center (transgenderlawcenter.org) TransAthlete (transathlete.com) TransLifeline (translifeline.org)
Resources for families and caregivers	PFLAG/PTI (pflag.org) Family Acceptance Project (familyproject.sfsu.edu) Gender Spectrum (genderspectrum.org) National Center for Transgender Equality (transequality.org) Trans Youth Family Allies (imatyfa.org)
Resources for providers	World Professional Association for Transgender Health Standards of Care (wpath.org) Endocrine Society Gender Dysphoria/ Gender Incongruence Practice Guidelines (www.endocrine.org) UCSF Transgender Center for Excellence (transcare.ucsf.edu/guidelines) National LGBTQIA + Health Education Center (lgbtqiahealtheducation.org)

From Voss RV, Simons L. Supporting the health of transgender and gender-diverse youth in primary care settings. *Prim Care Clin Office Pract.* 2021;48:259–270, Table 3.

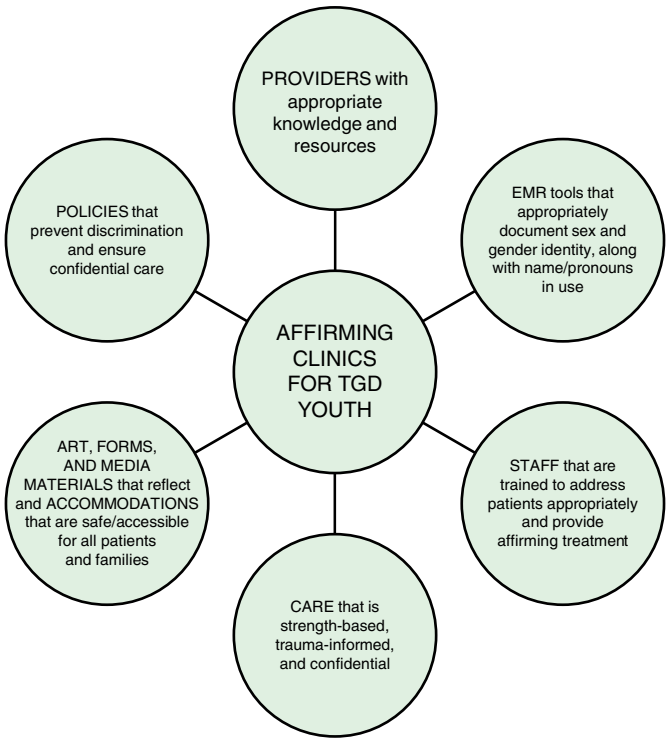

Fig. 153.1 Key components of an affirming clinic for TGD youth. *(Adapted from Allen BJ, Rosenthal SM. Care of transgender, nonbinary, and gender diverse youth. In Allen DB, Nadeau K, Kappy MS, Geffner ME, eds. Pediatric Endocrinology: Principles and Practice, 3rd ed. New York: McGraw Hill; 2020: Fig. 7-2.)*

affirmation in which an individual updates their name and/or gender marker on legal documents.

MENTAL HEALTH CONSIDERATIONS

Although the vast majority of TGD youth do not have any underlying severe psychiatric illnesses, they are at increased risk of internalizing disorders and life-threatening behaviors. Studies have demonstrated an increased prevalence of anxiety, depression, obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, self-harm behavior, suicidal ideation, and suicide attempts in TGD youth compared to cisgender controls. These conditions and behaviors are not inherent to an individual's gender identity, but rather often occur secondary to a lack of societal acceptance, stigma, discrimination, and poor

access to gender-affirming mental health and medical care. A higher co-occurrence of autism spectrum disorder among individuals with gender dysphoria and vice versa has also been demonstrated in addition to higher rates of homelessness, physical violence, substance abuse, and high-risk sexual behaviors compared to the general population.

In addition to determining the presence or absence of gender dysphoria as part of the psychodiagnostic evaluation, there are many important reasons to consider involving a mental health gender specialist in the evaluation and care of TGD youth *before* and *during* the provision of gender-affirming medical care. Mental health gender specialists may (1) evaluate for the presence of and provide treatment for coexisting mental health concerns, (2) provide family counseling and supportive psychotherapy to assist youth with the exploration of their gender identity and alleviate any distress secondary to gender dysphoria, (3) provide education, assist in decision-making, and refer as indicated for gender-affirming medical therapies, (4) educate and advocate for TGD youth and their families in their community, and (5) provide TGD youth and their families with information for support groups. An emphasis should be placed on the nonpathologic nature of TGD gender identities, and conversion or reparative therapies aimed at changing an individual's gender identity are ineffective and unethical (and illegal in certain places) practices that should not be pursued.

Despite the increased risk for mental health comorbidities in TGD youth, studies have provided evidence of protective factors resulting in positive mental health outcomes. Education regarding and access to gender-affirming medical interventions at early pubertal stages resulted in less gender dysphoria and better mental health and well-being in TGD youth. Additionally, TGD youth with supportive family environments have better mental health outcomes and quality of life. This knowledge underscores the importance of involving a qualified mental health professional to facilitate supportive home environments as needed and educating TGD youth and their families on options for gender-affirming medical therapies.

Another aspect of support is to provide access to other children/adolescents who are TGD. Many have identified like-minded friends in their own community, but others may develop a community through summer camps, group meetings associated with a treatment center, or the internet.

Gender-Affirming Medical Care

Affirming medical and surgical options in TGD individuals who require them to bring their body into alignment with their gender identity are essential, medically necessary interventions that have clear mental health benefits, some of which might even be lifesaving. Mental health benefits of gender-affirming medical therapies include the alleviation of gender dysphoria and the avoidance of worsening of any underlying psychologic distress. Options available to TGD youth vary depending on their pubertal and developmental stage, and care should be individualized based on the goals of the child rather than applied as a blanket algorithm. At each decision point, careful consideration should be given to the potential risks, benefits, and likely outcomes of each treatment, and use of signed consent forms, or informed assent forms in the case of individuals <18 years of age, attesting to an understanding of these considerations are advised before initiating any gender-affirming medical therapies. Medical care for TGD youth is based primarily on the World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) published in 2022 and the Endocrine Society's clinical practice guidelines, last published in 2017. TGD seeking gender-affirming hormone therapy must satisfy certain criteria before proceeding (see Table 153.1).

Current standards of care and clinical practice guidelines for the gender-affirming medical care of TGD youth are based on compelling research from short- to medium-term studies, a 22-year follow-up case report, and expert opinion. Although large longitudinal observational outcome studies are ongoing, there remains a paucity of long-term outcome data currently available. Nevertheless, refusing to deliver timely medical interventions for TGD youth is not a neutral option. A delay or withholding of care may prolong or worsen gender dysphoria and mental health and lead to the development of irreversible physical changes that may require invasive surgical interventions in the future.

PUBERTY BLOCKERS

Treatment Criteria and Timing

Pubertal hormone suppression is recommended in TGD youth who meet criteria for treatment (see Table 153.1). No medical interventions are recommended before the onset of puberty. TGD youth are eligible for treatment *only after* the onset of puberty. Medical providers should monitor for physical exam findings consistent with Tanner stage 2, including breast buds in youth designated female at birth and testicular volume ≥4 mL in youth designated male at birth. Laboratory assays, including ultrasensitive gonadotropin and sex steroid levels obtained in the early morning, can be used to confirm the onset of puberty. However, gonadotropin-releasing hormone (GnRH) is released from the hypothalamus in a pulsatile manner, and in early puberty, gonadotropin and sex steroid hormone levels may overlap with prepubertal ranges if checked at random times.

Goals of Therapy

When initiated early in puberty, pubertal suppression allows for expansion of the diagnostic phase with additional time for gender identity exploration before deciding whether or not to proceed with gender-affirming sex hormone (GAH) therapy. Pubertal suppression also prevents the development of undesirable, irreversible secondary sex characteristics not aligned with the individual's gender identity. These irreversible characteristics include breast development, female body habitus, and possibly short stature in individuals designated female at birth and low voice, laryngeal prominence, male bone configuration, tall stature, and male hair pattern on the face and extremities in individuals designated male at birth. Some, but not all, of these features can only be addressed later with surgery, but pubertal suppression is preferred. Pubertal suppression initiated in early puberty is thought to be fully reversible; if suspended or discontinued, endogenous puberty will resume.

Pubertal suppression can also be considered in TGD youth in later stages of puberty with the goal of achieving menstrual suppression in individuals designated female at birth or the goal of blocking androgen effects in individuals designated male at birth. However, studies do not currently exist that inform whether pubertal blockers can be used as a monotherapy (and for how long) in adolescents older than 14 without posing a risk to skeletal health, given that prolonged deficiency of sex steroids could result in impaired bone mineral density (BMD) during later adolescence and adulthood.

Treatment Options

GnRH agonists are the preferred agents for pubertal suppression in TGD youth. GnRH agonists are long-acting medications that are highly effective in suppressing gonadotropin release through GnRH receptor desensitization. Once started, GnRH agonists may result in some regression of previously developed secondary sex characteristics, including atrophy of breast tissue and a reduction in testicular size. GnRH agonists are available as injectables given every 1-6 months or as subcutaneous implants that last 1-2 years.

Although GnRH agonists are the most effective and preferred option for pubertal suppression, they are costly and may be inaccessible to TGD individuals without insurance coverage. Antiandrogens and progestins with antiandrogen properties, including spironolactone, cyproterone, bicalutamide, and medroxyprogesterone, provide additional options for pubertal suppression. These medications are not as efficacious in suppressing the HPG axis as compared to GnRH agonists, and concern regarding potential side effects have limited their use. The various medications available for pubertal suppression can be found in Table 153.5.

Potential Adverse Effects

Before initiating treatment for pubertal suppression, it is important to discuss potential adverse effects with TGD youth and their guardians. The primary risks of treatment with GnRH agonists

Table 153.5 Available Formulations of Medications Used for Pubertal Blockade

	MEDICATION	ROUTE OF ADMINISTRATION	DOSING FREQUENCY	DOSE
GnRH agonists	Leuprolide acetate	Intramuscular	Every 1-3 mo	11.25-30 mg
	Triptorelin	Intramuscular	Every 24 wk	22.5 mg
	Histrelin	Subcutaneous implant	Every 1-2 yr	50 mg
Progestins	Medroxyprogesterone	Oral	Daily	Up to 40 mg
		Intramuscular	Every 3 mo	150 mg
Antiandrogens	Spironolactone	Oral	1-2 times/day	25 mg initially, up to 100-300 mg divided twice daily
	Cyproterone acetate	Oral	Daily	Up to 100 mg
	Bicalutamide	Oral	Daily	50 mg

GnRH, Gonadotropin-releasing hormone.
Adapted from Allen BJ, Rosenthal SM. Care of transgender, nonbinary, and gender diverse youth. In: Allen DB, Nadeau K, Kappy MS, Geffner ME, eds. *Pediatric Endocrinology: Principles and Practice,* 3rd ed. New York: McGraw Hill; 2020.

Table 153.6 Baseline and Follow-Up Protocol During Suppression of Puberty

EVERY 3-6 MO
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
EVERY 6-12 MO
Laboratory: LH, FSH, E2/T, 25-OH vitamin D
EVERY 1-2 YR
Bone density using DXA
Bone age on x-ray of the left hand (if clinically indicated)

DXA, Dual-energy x-ray absorptiometry; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; T, testosterone.
Adapted from Hembree WC, Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ, et al; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94(9):3132–3154.

include impaired bone mineralization, compromised fertility (if followed by GAH therapy), and unknown effects on brain development and metabolism.

Bone Health

GnRH agonist treatment initiated early in puberty is associated with an increased risk of compromised BMD. Assessment of BMD in TGD individuals is challenging in part because it is not clear whether scores should be compared to norms for the individual's sex designated at birth or to norms for their gender identity. Previous studies have demonstrated an expected stabilization or decline in BMD Z-scores during treatment with GnRH agonists without recovery to baseline after treatment with GAH therapy in all instances. In one study, BMD Z-scores normalized in transmales but remained below zero in transfemales 3 years after the addition of GAH therapy. Potential explanations for differences include differences in lifestyle, exercise, and vitamin D levels. In early pubertal TGD youth treated with GnRH agonists, vitamin D status should be monitored and supplemented, if necessary, and adequate dietary calcium intake and weight-bearing exercise should be encouraged to optimize bone health. BMD should also be monitored every 1-2 years during GnRH agonist treatment and, if the individual undergoes phenotypic transition with gender-affirming sex hormones, should continue to be monitored as described in the Endocrine Society's clinical practice guideline (Tables 153.6 and 153.7).

Fertility

Before initiating treatment for pubertal suppression, counseling must be provided regarding options for fertility preservation. TGD adolescents and their families should be given the opportunity to meet with a specialist in reproductive endocrinology before initiating therapy or at any point during gender-affirming medical therapy as desired. When initiated early in puberty, GnRH agonists inhibit gonadal tissue maturation. If discontinued, the effects of GnRH agonists on fertility are reversible, and gamete maturation will resume. However, if followed by GAH therapy, fertility is likely to be compromised. If TGD youth desire fertility preservation, delaying or temporarily discontinuing pubertal suppression to promote spermatogenesis and oocyte maturation to allow for gamete collection is an option. The attainment of mature gametes occurs during the later stages of puberty when irreversible secondary sexual characteristics have developed, however, features that are undesirable for many TGD youth. Individuals who decide to continue pubertal suppression may elect to preserve immature gonadal tissue in the hopes that ongoing studies and future preservation techniques will allow for the maturation and preservation of viable gametes. Although in vitro maturation of human germ cells has not yet been accomplished, a report described in vivo maturation and subsequent cryopreservation of oocytes in a transgender male adolescent treated with a GnRH agonist starting in early puberty. This was achieved 2 years after the initiation of GnRH agonist therapy and without the discontinuation of pubertal suppression.

In contrast to TGD youth who initiate GnRH agonist therapy in early puberty, cryopreservation of mature sperm or eggs is an option before initiating gender-affirming medical therapy in late puberty or postpuberty (Table 153.8). If GAH therapy is initiated without fertility preservation in these individuals, it may be possible to discontinue hormone therapy in the future to allow for recovery of the hypothalamic-pituitary-gonadal (HPG) axis and subsequent gamete maturation. Stopping estrogen in individuals designated male at birth may allow for recovery of testicular function and collection of sperm. Discontinuation of testosterone in individuals designated female at birth may allow for ovarian recovery and release of eggs, and some who have desired this have had successful pregnancies. Unfortunately, even when counseling is provided, very few TGD youth pursue fertility preservation because of the high associated costs and invasiveness of some procedures and concerns regarding potential delays to medical transition.

Brain Development

Very few studies thus far have assessed the impact of GnRH agonist therapy on brain development. Attainment of executive functioning is a milestone that is typically achieved during puberty. A single cross-sectional study comparing TGD adolescents treated with GnRH agonists

Table 153.7 Baseline and Follow-Up Protocol During Induction of Puberty

Anthropometry	Height,* sitting height,* weight, blood pressure, Tanner stages*	Every 3-6 mo
Laboratory studies	Testosterone: testosterone, hemoglobin/hematocrit, lipids, 25-OH vitamin D* Estrogen: estradiol, prolactin, 25-OH vitamin D*	Every 3-12 mo
Imaging*	DXA to evaluate bone mineral density†	Every 1-2 yr
	Left hand radiograph to evaluate bone age (as clinically indicated)	

*Only indicated in individuals previously treated with pubertal blockers.
†BMD should be monitored into adulthood (until the age of 25-30 yr or until peak bone mass has been reached).
DXA, Dual-energy x-ray absorptiometry.
Adapted from Hembree WC, Cohen-Kettenis PT, Delemarre-van de Waal HA , Gooren LJ , et al; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94(9):3132–3154.

Table 153.8 Fertility Preservation Options for Transgender Patients

FERTILITY PRESERVATION METHOD	PROCEDURE	TIMING OF INTERVENTION
ASSIGNED MALE AT BIRTH		
Sperm cryopreservation	Sperm is collected from ejaculated semen ± electrical or vibratory stimulation	1. Before initiation of gender-affirming hormone therapy or surgery 2. If gender-affirming hormone therapy already initiated, consider 3-mo cessation of estrogen
Surgical sperm extraction	Sperm is obtained surgically from the testis (TESE) or epididymis (PESA)	1. Before initiation of gender-affirming hormone therapy or surgery 2. If gender-affirming hormone therapy already initiated, consider 3-mo cessation of estrogen
ASSIGNED FEMALE AT BIRTH		
Oocyte cryopreservation	Ovarian stimulation followed by surgical egg retrieval and egg freezing	1. Before initiation of gender-affirming hormone therapy or surgery 2. If gender-affirming hormone therapy already initiated, consider 3-mo cessation of testosterone
Embryo cryopreservation	Ovarian stimulation followed by surgical egg retrieval, IVF, and embryo freezing	1. Before initiation of gender-affirming hormone therapy or surgery 2. If gender-affirming hormone therapy already initiated, consider 3-mo cessation of testosterone
Ovarian tissue cryopreservation	Surgical removal and freezing of ovarian tissue	Before gender-affirming surgery involving removal of ovaries

PESA, Percutaneous epididymal sperm aspiration; TESE, testicular sperm extraction; IVF, in vitro fertilization.
From Montoya MN, Peipert BJ, Whicker D, Gray B. Reproductive considerations for the LGBTQ+ community. *Prim Care Clin Office Pract.* 2021;48:283–297, Table 2.

to untreated TGD adolescents found no significant differences in executive functioning. However, animal studies have suggested that GnRH agonists may affect cognitive function, and one transgender adolescent was reported to demonstrate a lack of expected variation in white matter fractional anisotropy (a measure of brain maturation thought to typically occur during puberty) and a 9-point drop in operational memory testing after approximately 2 years of treatment with a GnRH agonist. A subsequent systematic review and meta-analysis found no adverse impacts of hormone therapy on cognitive function in transgender young adults. Additional long-term studies are necessary to assess the impact of GnRH agonist therapy more fully on brain development in TGD youth.

Metabolism and Other Effects

A few studies have evaluated the effects of GnRH agonists on various metabolic and physiologic parameters and future surgical outcomes. A decrease in lean body mass, an increase in fat percentage, and weight gain have been reported in studies of TGD adolescents treated with GnRH agonists. TGD youth designated female at birth who start GnRH agonist therapy may also experience hot flashes, especially if this treatment is initiated in the later stages of puberty. TGD youth designated male at birth who initiate pubertal suppression in early puberty will have limited growth of their genitalia, which may require alternative techniques for penile inversion-vaginoplasty if gender-affirming genital surgery is desired in the future, and counseling should be provided in this regard before initiating treatment with a pubertal blocker.

Alternative Therapy Side Effects

GnRH agonist therapy for pubertal suppression may not be an option for all TGD youth, and alternative therapies are also associated with potential adverse effects. Spironolactone may cause electrolyte abnormalities, polyuria, and orthostasis. Concern for potential hepatotoxicity associated with cyproterone acetate and bicalutamide treatment has limited their use. Progestin treatment may cause hot flashes, headaches, acne, depression, weight gain, lipid changes, and irregular menstrual bleeding in individuals designated female at birth.

Monitoring Protocol

Efficacy and potential adverse effects of treatment should be monitored closely in TGD youth treated with pubertal suppression according to the protocol outlined in Table 153.6. For individuals treated with spironolactone, serum electrolytes should be monitored every 3 months for the first year of therapy and then annually.

A clear endpoint for pubertal suppression can be difficult to determine. It is generally recommended that GnRH agonists not be continued as monotherapy past age 14 years (nor initiated as a monotherapy past age 14 years) because of the potential adverse effects on bone health. The decision must ultimately be made to discontinue pubertal suppression all together or to initiate concurrent treatment with GAH therapy. It is recognized that this decision point can be difficult for TGD adolescents, particularly for some with nonbinary gender identities who may not desire certain physical changes that may occur with sex hormone therapy. Although current guidelines suggest that GnRH

Table 153.9 Protocol Induction of Puberty

	MEDICATION	ROUTE OF ADMINISTRATION	DOSING FREQUENCY	INITIAL DOSE	DOSE ESCALATION	ADULT DOSE
Estrogen	17β–estradiol	Oral/sublingual	Daily	PB: 5 μg/kg/day	5 μg/kg every 6 mo	2-6 mg/day
				PP: 1 mg	1 mg every 6 mo	
		Transdermal	Every 3-5 days	PB: 6.25-12.5 μg/24 hr	12.5 μg/24 hr every 6 mo	50-200 μg/24 hr
				PP: 25-50 μg/24 hr	25 μg/24 hr every 6 mo	
Testosterone	Testosterone enanthate/ cypionate	Subcutaneous	Weekly	PB: 12.5 mg/m^2	12.5 mg/m^2 every 6 mo	30-100 mg/wk
				PP: 37.5 mg	37.5 mg every 6 mo	
		Intramuscular	Every 2 wk	PB: 25 mg/m^2	25 mg/m^2 every 6 mo	60-200 mg every 2 wk
				PP: 75 mg	75 mg every 6 mo	

PB, Pubertal blocker initiated in early puberty; PP, postpuberty.
Adapted from Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102:3869–3903, Table 8; and from Allen BJ, Rosenthal SM. Care of transgender, nonbinary, and gender diverse youth. In: Allen DB, Nadeau K, Kappy MS, Geffner ME, eds. *Pediatric Endocrinology: Principles and Practice*, 3rd ed. New York: McGraw Hill; 2020, Fig. 7-2.

agonist therapy may be continued in conjunction with sex hormone therapy until gonadectomy (if pursued), it is often possible to discontinue this therapy in individuals designated female at birth who initiate treatment with testosterone once adult levels of testosterone have been reached.

GENDER-AFFIRMING SEX HORMONE THERAPY

Treatment Criteria and Timing

GAH therapy is a medically necessary intervention for many TGD adolescents. GAH therapy is partially reversible, and it is the responsibility of the medical provider to ensure the adolescent meets criteria for treatment before initiating therapy (see Table 153.1). *GAH treatment may be initiated in TGD adolescents who request this therapy after a multidisciplinary team of medical and mental health providers has confirmed the persistence of gender dysphoria/gender incongruence and if the adolescent has sufficient mental capacity to give informed consent/assent.* Most adolescents are felt to have sufficient mental capacity to provide informed consent by age 16 years; however, there may be compelling reasons to initiate therapy earlier. TGD youth treated with pubertal suppression at Tanner stage 2, which may occur as early as 8-9 years of age, may incur certain risks if this treatment is continued as monotherapy until 16 years of age. Prolonged pubertal suppression may be detrimental to bone health, and it may have detrimental effects on mental health if puberty is delayed well beyond the majority of an individual's peers. Treatment with GAH therapy therefore should be individualized with consideration given to earlier initiation as clinically indicated. Initiation of GAH should follow an evaluation by a qualified mental health gender specialist (separate from any evaluation focused on prior use of pubertal suppression), the signing of consent/assent forms, the obtainment of baseline labs, and consideration of fertility preservation.

Goals of Therapy

The goals of GAH therapy are (1) to reduce *endogenous* sex hormone levels to prevent the development of secondary sex characteristics in individuals previously treated with pubertal blockers or to reduce secondary sex characteristics in those who have already progressed through any degree of puberty and (2) to provide *exogenous* sex hormones to allow for phenotypic changes aligned with an individual's gender identity. GAH therapy must be individualized based on the adolescent's goals rather than applying a one-size-fits-all approach, though it is important to achieve a level of either testosterone or estrogen that is in the normal range for a person's developmental stage.

Treatment Options

In TGD adolescents whose puberty was blocked in early Tanner stages, puberty induction with GAH treatment should be initiated using a gradually increasing dose schedule (Table 153.9). Initial exogenous sex hormone levels are insufficient to suppress endogenous sex hormone secretion, and pubertal blockade should be continued. As sex hormone doses increase, GnRH agonist treatment may often be discontinued in individuals designated female at birth who are treated with testosterone therapy. Adult doses of exogenous testosterone therapy are often sufficient to suppress the HPG axis. In contrast, pubertal suppression must often be continued in individuals designated male at birth who are treated with estrogen therapy. Adult doses of estrogen therapy are insufficient in suppressing the HPG axis and testosterone release. Ongoing adjunctive therapy with a GnRH agonist or antiandrogen therapy (e.g., spironolactone) to block testosterone secretion and/or action is required indefinitely or until gonadectomy, if pursued. Not all TGD adolescents will pursue gonadectomy, and long-term studies are needed to determine the potential risks of prolonged treatment with GnRH agonists.

In TGD adolescents who present for gender-affirming medical therapy in late puberty or after completion of puberty, pubertal induction with sex hormones can start at higher doses and can occur more rapidly (see Table 153.9).

At this time, no evidence has demonstrated that any of the following medically approved types or methods of administering hormones is superior to others in yielding the desired phenotypic changes. Protocols for some formulations of estrogen and testosterone are not available. Protocols that do exist are outlined in Table 153.9. It is important to emphasize to patients that individual variations in outcomes will occur based on several factors including genetics, body type, and compliance.

Estrogen

Estrogen can be given via transdermal, oral, or injectable routes. The naturally occurring form, 17β–estradiol, is preferred to synthetic (e.g., ethinyl estradiol) and conjugated estrogens (e.g., Premarin), which cannot easily be monitored in the serum. Compared to synthetic estrogens, 17β–estradiol is also associated with a lower risk of venous thromboembolism (VTE). Serum estradiol levels can be monitored, with the eventual goal of achieving values in the normal range for premenopausal females (100-200 pg/mL).

TGD individuals who pursue estrogen therapy should be educated on the expected timeline of physical changes (Table 153.10).

Table 153.10 Timeline of Effects from Gender-Affirming Sex Hormone Therapy

	EFFECT	ONSET	MAXIMUM	REVERSIBILITY
Estrogen	Redistribution of body fat	3-6 mo	2-3 yr	Likely
	Decreased muscle mass/strength	3-6 mo	1-2 yr	Likely
	Softening of skin/decreased oiliness	3-6 mo	Unknown	Likely
	Decreased sexual desire	1-3 mo	3-6 mo	Likely
	Decreased spontaneous erections	1-3 mo	3-6 mo	Likely
	Breast growth	3-6 mo	2-3 yr	Not possible without surgery
	Decreased testicular volume	3-6 mo	2-3 yr	Unknown
	Decreased sperm production	Unknown	>3 yr	Unknown
	Decreased terminal hair growth	6-12 mo	>3 yr	Possible
	Scalp hair	Variable		
Testosterone	Skin oiliness/acne	1-6 mo	1-2 yr	Likely
	Facial/body hair growth	6-12 mo	4-5 yr	Unlikely without electrolysis
	Scalp hair loss	6-12 mo		Unlikely
	Increased muscle mass/strength	6-12 mo	2-5 yr	Likely
	Fat redistribution	1-6 mo	2-5 yr	Likely
	Cessation of menses	1-6 mo		Likely
	Clitoral enlargement	1-6 mo	1-2 yr	Unknown
	Vaginal atrophy	1-6 mo	1-2 yr	Unknown
	Deepening of voice	6-12 mo	1-2 yr	Not possible without surgery

Adapted from Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102:3869–3903, Table 12; and from Allen BJ, Rosenthal SM. Care of transgender, nonbinary, and gender diverse youth. In Allen DB, Nadeau K, Kappy MS, Geffner ME, eds. *Pediatric Endocrinology: Principles and Practice*, 3rd ed. New York: McGraw Hill; 2020, Tables 7-11 and 7-12.

Treatment will lead to some changes that are likely reversible and others, such as breast development, that are irreversible without surgery.

Testosterone

Naturally occurring testosterone may be given transdermally via gels or patches, through subcutaneous or intramuscular injections, or via implantation of subcutaneous pellets. Oral testosterone undecanoate is Food and Drug Administration (FDA)–approved for use in the United States but is not currently in wide use. It is important to counsel patients on the potential transfer to others via direct contact when transdermal formulations are used. Testosterone levels can be monitored in the serum, with the eventual goal of achieving values in the normal male range (typically 320-1,000 ng/dL, depending on the specific assay).

TGD individuals treated with testosterone should be educated on the expected timeline of physical changes (see Table 153.10). Treatment will lead to some changes that are likely reversible and others that are not, such as facial hair growth, which is irreversible without electrolysis. Adult levels of testosterone are typically sufficient to suppress the HPG axis and induce amenorrhea in TGD individuals designated female at birth. However, unplanned pregnancies have been reported, emphasizing the need for *ongoing contraceptive counseling* in these individuals. If undesired uterine bleeding persists, or if menstruation is causing significant dysphoria before the initiation of testosterone therapy, a progestin or other agent may be used for menstrual suppression. If estrogen is tolerable, combined continuous oral contraceptives (with limited intervals for breakthrough menses) are more effective in achieving menstrual suppression and are better for maintaining bone health than progestin-only options. For TGD adolescents who prefer nonestrogen-containing medications, progesterone-only pills, medroxyprogesterone acetate shots, and progesterone-containing intrauterine or implantable devices are available.

Potential Adverse Effects

Clinicians should inform TGD adolescents of the potential for adverse effects of GAH treatment. Risk for adverse effects is higher when supraphysiologic or inadequate doses of sex hormones are used, which should be avoided. Before initiating therapy, risk factors for adverse effects should be assessed and minimized when possible. GAH treatment has implications for fertility, which must be discussed before initiating therapy as noted previously.

Risks with Estrogen

The most serious risks associated with estrogen therapy include VTE, cardiovascular disease, and cerebrovascular accident. The risk increases with higher estrogen doses and supraphysiologic estradiol levels. Risk factors for these conditions should be assessed and addressed before initiating estrogen therapy. Tobacco cessation counseling should be provided as indicated. Oral ethinyl estradiol in particular appears to increase the risk of VTE, and it should not be used for GAH therapy in individuals at high risk. Estrogen may also cause growth of pituitary lactotroph cells and hyperprolactinemia, which resolves with a reduction or discontinuation of therapy in most individuals. Other potential adverse effects include weight gain, cholelithiasis, and hypertriglyceridemia. TGD adults treated with estrogen therapy have been shown to have an increased risk for developing breast cancer compared with a general population of men in a retrospective Dutch study, although the risk was still lower than in the general population of women. Another retrospective Dutch study spanning five decades demonstrated an increased mortality risk in TGD individuals treated with estrogen therapy compared with a general population of men and general population of women with high risks of death because of cardiovascular

disease, lung cancer, HIV-related disease, and suicide; however, the study was not designed to attribute the cause of the increased mortality risk to a specific effect of estrogen therapy. Absolute contraindications to estrogen therapy include previous VTE related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm, and end-stage chronic liver disease.

Risks with Testosterone

Testosterone therapy is primarily associated with potential risks of developing acne, weight gain, hypertension, polycythemia, and a more atherogenic lipid profile (i.e., elevated low-density lipoprotein, elevated triglyceride, and decreased high-density lipoprotein cholesterol levels). Risk increases with sustained, supraphysiologic testosterone levels. Risk factors for these conditions should be assessed and addressed before initiating testosterone therapy. Despite being associated with a more atherogenic lipid profile, numerous studies have shown no increased risk of cardiovascular disease in individuals treated with testosterone. Additional studies are needed to determine if therapy is associated with an increased risk for cerebrovascular disease. Historically, oral testosterone formulations have been associated with increased risk for transaminitis and severe liver dysfunction, whereas injectable formulations are not. Because of the concern that aromatization of testosterone to estradiol may increase risk in patients with a history of estrogen-sensitive malignancies, consultation with an oncologist should be considered before initiating therapy in such patients. Absolute contraindications to testosterone therapy include current pregnancy, unstable coronary artery disease, and untreated polycythemia (hematocrit ≥55%).

Monitoring Protocol

Efficacy and potential adverse effects of treatment should be monitored closely in TGD youth treated with GAH therapy at baseline and follow-up according to the protocol outlined in Table 153.7. Clinical evaluation and laboratory monitoring are recommended every 3 months during the first year of GAH therapy and then 1-2 times annually thereafter. All evaluations should include a physical exam, including measurement of weight and blood pressure. Chest and genitourinary exams may be sensitive issues for TGD youth and should only be conducted as needed to guide management. Evaluations should include questions regarding occurrence of potential adverse events and satisfaction with phenotypic changes on medical therapies. Medication dosing adjustments should occur as needed with the goal of avoiding supraphysiologic and subphysiologic hormone levels that may increase the risk for adverse effects.

Surgical Therapy

Gender-affirming surgeries may be pursued by some TGD individuals to better align their bodies with their gender identities. In these individuals, surgery is medically necessary and an essential step to alleviate their gender dysphoria. Surgeries are irreversible interventions, and most, including those that directly affect fertility such as gonadectomy and/or hysterectomy, are not recommended until an individual reaches age 18 years or the age of legal majority in their country. The Endocrine Society clinical practice guideline and WPATH SOC acknowledge that mastectomy may be considered in TGD adolescents before age 18 years, taking into consideration the physical and mental health status of the individual. Hormone therapy should not be considered a prerequisite to accessing gender-affirming surgical procedures in individuals who do not desire hormone therapy nor in those in whom it is medically contraindicated. Surgeries may occur after the appropriate assessments by qualified medical and mental health professionals responsible for the care of the TGD individual have been performed and confirm that criteria for surgery are met. Individuals who undergo gonadectomy will require ongoing hormone replacement therapy to prevent adverse effects, including osteoporosis.

Table 153.11 Recommendations for Breast and Reproductive Tract Cancer Screening

ORGAN	TRANSGENDER WOMEN	TRANSGENDER MEN
Breast/chest	Discuss mammography in transwomen age >50 yr with additional risk factors for breast cancer (body mass index >35 kg/m^2, estrogen and/or progestin use >5 yr, family history) • Family history of *BRCA* mutations: prophylactic mastectomy could be recommended, with consecutive primary reconstruction	Patients who have not undergone bilateral mastectomy should follow cisgender women recommendations for breast cancer screening Patients who have undergone chest reconstructive surgery should be offered physical examination and/or chest ultrasound
Cervix	Not recommended (transwomen do not have a cervix) • Patients should be routinely examined to detect HPV-related lesions	Patients with an intact cervix should follow the recommendations for cisgender women • Consider self-collected vaginal swabs to test for high-risk HPV DNA • Pathologists should be aware if patient is taking testosterone • Patients who have undergone total hysterectomy and have no history of high-grade cervical precancerous lesion or cervical cancer can discontinue cervical cancer screening
Ovarian	N/A	Do not routinely screen • Transmen at increased risk (identified *BRCA* gene mutation and family history) should be referred for genetic counseling • Consider risk-reduction salpingo-oophorectomy
Endometrial	N/A	Do not routinely screen • Unexplained bleeding (in patients under testosterone who had reached amenorrhea) should be evaluated
Prostate	Monitor the following framework for cisgender men • PSA cutoffs may be lower in transgender men receiving antiandrogens • Consider transvaginal digital examination and ultrasound	N/A

N/A, Not applicable; *PSA*, prostate-specific antigen.
From Labanca T, Manero I, Pannunzio M. Transgender patients: considerations for routine gynecologic care and cancer screening. *J Gynecol Cancer*. 2020;30:1990–1996, Table 4.

Primary Care: Screening

Not all TGD adults have had gender-affirming chest or reproductive organ surgery. Because of this, they may be at risk for cancers not typically screened for based on their affirmed or biologic gender. Suggested breast and reproductive cancer screening recommendations are noted in Table 153.11.

THERAPY FOR NONBINARY YOUTH

Youth with nonbinary gender identities are increasingly presenting for gender-affirming medical care. Although current clinical care guidelines recognize that gender exists on a spectrum and may not always be binary, research and guidelines to date have been largely grounded in the binary gender narrative. Some individuals with nonbinary gender identities will seek treatment as outlined in current clinical practice guidelines, but not all will. The Endocrine Society clinical practice guidelines state that tailoring of current protocols to the individual may be acceptable if done within the context of accepted safety guidelines using a multidisciplinary approach including mental health support. Additionally, the WPATH SOC state they are intended to be flexible to meet the diverse healthcare needs of the individual, and health professionals may modify them in consultation with their TGD patients. However, evidence-based protocols are not yet available for nonbinary individuals, and neither the Endocrine Society nor the WPATH provide guidelines specific to the care of nonbinary youth. Nonbinary individuals have been shown to have higher rates of depression, anxiety, and self-harm compared to their binary transgender peers. In addition, they often encounter more barriers in their attempts to access gender-affirming medical care, even when care is accessed at specialized gender clinics. As a result, some feel forced to identify within the gender binary to obtain desired medical therapies or choose to not seek care.

Until future studies inform clinical practice guidelines outlining therapeutic approaches specific to nonbinary youth, gender-affirming care for nonbinary youth should be individualized. Providers should frame care using the concept of *embodiment rather than transition,* the latter implying a linear path within the gender binary. Ongoing dialogue and support are essential in helping nonbinary youth navigate a potentially nonlinear path. Providers should explore the individual's internal awareness of self, specific areas of gender dysphoria, and their embodiment goals to offer specific therapies toward affirming the individual's gender. Specific expected outcomes of the possible interventions (e.g., increased facial hair with testosterone or chest growth with estrogen) should be discussed rather than describing therapies as masculinizing or feminizing in nature. Difficult decisions may need to be made, particularly for nonbinary youth treated with pubertal suppression who do not desire any secondary sex characteristics. There is the potential for negative impacts on bone health from prolonged monotherapy with pubertal blocking agents, and this should be avoided. Providers should expect to have conversations about balancing the individual's priorities in their specific embodiment goals and to discuss the known potential risks and benefits of various treatment options in order to provide optimal care to their nonbinary patients. Patients should be counseled about the importance of maintaining a minimum threshold level of sex steroids—typically a normal adult range of either estrogen or testosterone—to preserve general health.

Like TGD youth with binary gender identities, available medical interventions for nonbinary youth may include pubertal suppression, sex hormones, and surgeries. Desired and unwanted effects should be discussed and balanced in decision-making regarding therapies. Existing treatment protocols may be modified to achieve patient embodiment goals if deemed safe with a plan for close follow-up monitoring. Potential modifications may include gradual titration or tapering of doses, low-dose or limited testosterone therapy, lower doses of estrogen therapy, intermittent hormone dosing, use of both estrogen and testosterone, and use of adjunctive medications. After initiating a new treatment, follow-up visits should include a discussion of physical changes noted and whether they are in alignment with the patient's embodiment goals, with adjustments made as needed.

Mental Health Outcomes of Treatment

Multiple studies have demonstrated the positive impact of gender-affirming medical and surgical interventions on mental health outcomes in TGD adolescents. A prospective study of 55 TGD adolescents and young adults in the Netherlands published in 2014 demonstrated resolution of gender dysphoria and improvement in general psychologic functioning after sequential treatment with GnRH agonist therapy, GAH treatment, and gender reassignment surgery. These individuals were also shown to have a sense of well-being equivalent or superior to that seen in age-matched controls from the general population, and none regretted treatment. A cross-sectional survey administered by the National Center for Transgender Equality to more than 20,000 U.S. TGD adults age 18-36 years demonstrated that those treated with GnRH agonists for pubertal suppression during adolescence had a significantly lower odds of lifetime suicidal ideation compared to those who wanted, but did not receive, such treatment. The largest observational study assessing the impact of gender-affirming medical care on the mental health of TGD adolescents and young adults in the United States (n = 315, age 12-20 years) demonstrated significant improvements in psychosocial functioning, decreases in depression and anxiety, and increases in appearance congruence, positive affect, and life satisfaction. Other studies have also reported on improvement of mental health measures, quality of life, global psychosocial functioning, and body image in response to treatment with gender-affirming medical care.

Challenges to Care

TGD youth not only face high levels of discrimination in their lived environments, but those who succeed in accessing medical care often encounter stigma and discrimination within healthcare settings. Research on the experiences of TGD persons of color, a group that faces startingly high rates of violence and homicide, is an area in need of much attention. In the United States, gender-affirming medical therapies are currently not FDA-approved for use in TGD youth, and insurance companies often deny coverage of these medically necessary, essential, and even lifesaving interventions. Some families can pay out-of-pocket for treatments when coverage is denied, whereas others cannot, furthering the socioeconomic divide between wealthy and impoverished. Efforts in multiple U.S. states to criminalize the medical care of TGD youth are ongoing and in need of significant advocacy and education. In addition, participation in same-gender sporting activities has created significant barriers among TGD athletes. Some athletic bodies have placed barriers to same-gender participation, requiring transfemales to start suppressive therapy early in puberty or to monitor testosterone levels, with a cutoff level prohibiting participation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 154

Gay, Lesbian, and Bisexual Adolescents

Stewart L. Adelson and Mark A. Schuster

Understanding a child's or adolescent's sexual and emotional development is an essential part of any comprehensive pediatric evaluation. For youth who are or might be gay, lesbian, or bisexual **(GLB also noted as LGB in the LGBT abbreviation)**, such understanding is particularly important. GLB youth as a group have the same health and developmental needs typical of youth in general, and their sexual orientation is part of the normal spectrum of human sexuality. However, they encounter distinct developmental challenges and can have additional physical and mental health needs related to their orientation and others' reaction to it. Their sexual orientation may be different from that expected by some families, peers, and society; they are at risk of peer rejection, bullying, violence, or family nonacceptance more frequently than most youth. Although the majority of GLB adolescents grow up physically and mentally healthy, they are at increased risk for certain health problems as a result of these stresses and the epidemiology of health threats such as HIV and other sexually transmitted infections (STIs). In addition, healthcare providers may also have biases and assumptions about the GLB community (Table 154.1).

Sexual orientation refers to an individual's attraction to others based on sex or gender. It encompasses emotional and erotic desires, physiologic arousal, sexual behavior, sexual identity, and social role. As sexuality develops, youth can be oriented entirely toward a particular sex or gender, or more than one, to various degrees on a continuum. **Homosexuality** involves orientation toward people of one's same sex or gender, and **bisexuality** involves orientation toward males and females. **Gay** is a common term for both males and females who have same-sex attractions; **lesbian** refers to gay females. Increasing numbers of youth describe themselves as having a nonbinary gender identity (see Chapter 153). Accordingly, some do not fit binary categories of sexual orientation and use other terms to describe themselves, such as **pansexual** (attracted to all genders). Those unsure of their orientation are **curious** or **questioning**. The term **young men who have sex with men (YMSM)** is sometimes used in the research literature to denote male youth who engage in sexual activity with other males, regardless of how they identify themselves.

PREVALENCE OF HOMOSEXUALITY AND BISEXUALITY IN YOUTH

Some junior high and high school students self-identify as gay, lesbian, or bisexual (Fig. 154.1). Some who do not identify as GLB report same-sex attraction, fantasies, or behavior. Some are unsure of their sexual orientation. Certainty about sexual orientation tends to increase through adolescence with sexual experience, although one can be aware of one's orientation without having had sexual partners. Those who fear nonacceptance may try to suppress or deny their orientation. Consequently, various aspects of an individual's orientation—attraction, behavior, and identity—may not always be consistent with each other throughout development. Not all youth with homosexual attraction or experience identify as *gay,* consistent in part with reluctance about having or revealing a gay identity and underscoring the differences among attraction, behavior, and identity. A report providing national estimates of the number of high school students with GLB identity in 2019 found that 2.5% said they were gay or lesbian, 8.7% said they were bisexual, and 4.5% reported being unsure of their sexual orientation (see Fig. 154.1).

Table 154.1 Common Assumptions to Avoid When Caring for Lesbian, Gay, Bisexual, and Queer Patients

ASSUMPTION TYPE	DO NOT ASSUME THAT…
Identity	• Lesbian, gay, or bisexual people are cisgender • A person has to identify as either male or female • A person's gender or sexual orientation is a major aspect of a person's identity • Being lesbian, gay, bisexual, or queer is always hard • LGBQ people cannot adjust to stressors
Sexual orientation	• All patients are heterosexual • People exploring their sexuality have a need to categorize into established sexual orientations • Bisexuality is a phase or that bisexual people are confused • Sexual orientation aligns with sexual behavior
Sexual behavior	• All LGBQ people are sexually active (some are celibate or asexual) • Gay men do not have sex with women or lesbian women do not have sex with men • All gay men have multiple partners and engage in high-risk behavior • Sexual behavior will remain stable over time • Lesbians are not at risk of HPV or other STIs • Bisexual people are promiscuous or are always unfaithful
Relationships and family	• Lesbian women do not want to be pregnant or are not at risk of pregnancy • Interpersonal violence does not occur in LGBQ couples • LGBQ patients do not have children or do not wish to have children • All adults of reproductive age have an interest in parenting • LGBQ people do not have strong family ties • LGBQ patients have ties to their families of origin
Anatomy	• Queer people all want to change their bodies with surgeries or hormones • Anything about the body of an LGBQ patient

HPV, Human papillomavirus; STI, sexually transmitted illness.
Adapted from Makadon HJ, Mayer KH, Potter J, Goldhammer H. *The Fenway Guide to Lesbian, Gay, Bisexual, and Transgender Health*, 2nd ed. Philadelphia: American College of Physicians, 2015; and Suarez Lupez E, Siegel J, Streed Jr C. The annual examination for lesbian, gay, and bisexual patients. *Prim Care Clin Office Pract*. 2021;48:191–212, Table 1.

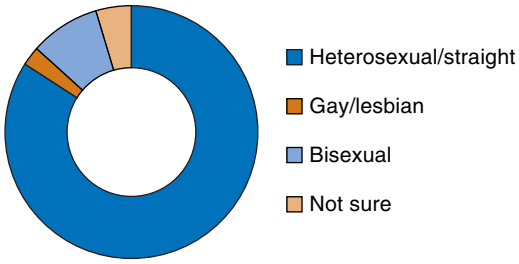

Fig. 154.1 Sexual identities among high school students. YRBS; Youth Risk Behavior Study. *(From HHS Youth Risk Behavior Survey from 2019: US Department of Health and Human Services, Centers for Disease Control and Prevention. (2020, Aug 21). Youth Risk Behavior Surveillance -- United States, 2019. MMWR Supplement, 69(1) https://www.cdc.gov/healthyyouth/data/yrbs/pdf/2019/su6901-H.pdf.)*

DEVELOPMENT OF SEXUAL ORIENTATION IN CHILDHOOD AND ADOLESCENCE

Sexual orientation development appears to begin prenatally and continue through childhood and adolescence and into adulthood. Both gender role behavior in childhood and sexual orientation in puberty and adolescence are partly influenced by prenatal genetic and neuroendocrine factors. Sociocultural and psychologic factors also influence sexual development. A gay or lesbian sexual orientation is sometimes preceded developmentally in childhood by nonconforming gender expression or variation from population averages in expression of gender-related behavior such as activities, interests, styles, and other attributes recognized as masculine or feminine, like toy preferences and preference for playmates of a particular gender. Childhood gender nonconformity is significantly associated with nonheterosexual orientation, especially in males. However, it is not experienced by all gay or lesbian people, and not all children with nonconforming gender role behavior are gay or lesbian. When present, however, nonconformity causes many gay people to feel different from peers during childhood, even before sexual desire or identity emerges. Depending on the setting, gender-nonconforming children may experience ostracism, bullying, or family nonacceptance. These reactions to gender nonconformity can lead to later difficulty with gender-related self-esteem and long-term mental health problems.

Less frequently, gay or lesbian sexual orientation in adolescence is preceded by childhood **gender variant identity**, a phenomenon in which the gender identity of an individual at any age differs from phenotypic sex and assigned sex at birth (see Chapter 153).

STIGMA, RISK, AND RESILIENCE

People experiencing same-sex attraction and behavior exist in all societies. The meaning, acceptance, and legality of non-heterosexual attraction vary greatly with cultural, historical, and social contexts. Although gay people are more visible and accepted in some societies, youth are often exposed to antigay attitudes. For many GLB youth, revealing their sexual orientation *(coming out)* to family, peers, healthcare providers, and others is a significant step. Specific racial, ethnic, religious, and other demographic groups may experience distinct developmental stressors. A comprehensive understanding of a youth's sexual development and health must consider intersecting sociodemographic factors influencing a youth's experience of a nonheterosexual orientation. For example, race, ethnicity, and religious affiliation—and the reactions of others to one's demographic characteristics—can influence comfort disclosing an GLB identity, involvement in GLB socialization, access to religious affirmation, and processes of coming out.

Some GLB youth experience difficulty coping with **stigma**. A longitudinal study that investigated **bullying** and **victimization** among youth from 5th through 10th grade found that the females and males who identified as GLB in 10th grade were more likely than their peers to report that they had been bullied and victimized across grades. GLB youth may be perceived by others as different before they themselves have any GLB attraction or experience or identify as GLB. Even when not overtly threatened, GLB youth frequently encounter negative attitudes that force them to hide at a time when family and peer acceptance holds great developmental significance. Family nonacceptance, feeling unsafe due to school harassment, and peer bullying related to sexual orientation elevate risk in GLB adolescents for depression, anxiety, substance abuse, suicidal thoughts and attempts, and social problems such as truancy, dropping out, running away, and homelessness. Mental health problems, sexual risk-taking, or substance use may increase exposure to HIV and other STIs. Stigma may also impede access to healthcare in some communities.

Nevertheless, most GLB youth are resilient, with good physical and mental health despite possible pervasive stresses. Family connectedness and school support and safety are important protective factors against depression, suicidal thoughts and attempts, and substance abuse. GLB antiharassment policies and organizations such as **genders and sexualities alliances** (also sometimes called gay-straight alliances) and antibullying programs are associated with increased school safety for GLB youth. It is therefore important to reduce stigma, support acceptance, and promote resilient coping.

HEALTH

Depression and Suicidality

Compared to their heterosexual peers, GLB youth and those who are not sure of their sexual orientation have a higher prevalence of suicidality. Family rejection, bullying, and other victimization motivated by homophobia account statistically for increased depression and suicidal thoughts and attempts in GLB adolescents. Suicidal thoughts or attempts are highest during the interval after recognition of same-sex attraction or a same-sex sexual experience but before self-acceptance as gay.

Sexually Transmitted Infections

The epidemiology of STIs, related to specific sexual practices and prevalence of certain STIs in GLB communities, informs recommended counseling, screening, and treatment strategies (Table 154.2). Anal intercourse has been shown to be the most efficient route of infection by hepatitis B (see Chapter 406), cytomegalovirus (see Chapter 302), and HIV (see Chapter 322). Oral-anal and digital-anal contact can transmit enteric pathogens, such as hepatitis A. Unprotected oral sex also can lead to oropharyngeal disease in the receptive partner and gonococcal and nongonococcal urethritis in the insertive partner. Certain STIs, particularly ulcerative diseases, such as syphilis and herpes simplex virus infection, facilitate spread of HIV. YMSM are also at risk for infections with Shigella spp. and Mpox (see Chapter 163).

Among U.S. adolescents and young adults, YMSM, and especially Black YMSM, continue to face the greatest prevalence of HIV/AIDS. Although possible, female-to-female sexual transmission of HIV is inefficient, and females who only engage in sex with females are less likely than other youth to acquire an STI. However, males and females who identify as gay or lesbian may engage in sexual activity with partners who are not of the same gender; counseling and screening for all types of STIs are still relevant.

Substance Abuse

Compared with their heterosexual peers, GLB youth appear to use alcohol and other substances at higher rates, including more binge drinking and earlier onset and more rapid trajectory of substance use.

More substantial substance use may be greatest in youth who, although they do not identify as GLB, have attraction to or engage in sexual behavior with others of their gender.

Obesity and Disordered Eating

Compared with heterosexual females, lesbian and bisexual females are generally more likely to be obese or overweight. In contrast, young gay and bisexual males are more likely to have body image concerns and to restrict eating or engage in compensatory weight loss strategies compared to heterosexual boys. Binge eating may also be more common in GLB youth.

Psychosocial Problems

Academic underachievement, truancy, and dropping out of school are frequently associated in GLB adolescents with homophobic victimization, harassment, violence, and feeling unsafe at school. Studies suggest that youth who eventually identify as GLB have higher rates than other youth of experiencing child abuse and of running away or being kicked

Table 154.2 The 6 Ps of a Complete Sexual History

P	OBJECTIVES	QUESTIONS
Partners	• Determine the number and gender/sex of partners • Determine partner risk factors (other partners, drug use)	"Are you currently sexually active?" "Have you ever been sexually active?" "When you have sex, what is the gender of your partners? What anatomy is used for sex?" "How do you describe your sexual orientation?" "How many partners have you had in the past 6 (or 12) months?" "Has anyone ever forced themselves on you sexually or touched you sexually in an unwanted way?"* Remember to ask about opposite-sex partners
Practices	• If a patient has had more than one partner in the past 12 mo (or has a partner who has other sex partners) • Explore their sexual practices and behaviors, because they will guide assessment of risk and determination of testing	"What types of sex are you having?" "When having sex, do you have vaginal, anal, and/or oral sex?" "If you have anal sex, do you have insertive sex, receptive sex, or both?" In colloquial words, "Are you a top, a bottom, or vers?" "Do you have any alternative sexual practices?" (i.e., kinks, BDSM, fisting) "Do you use alcohol or drugs during sex?" "Have you ever exchanged sex for money, drugs, food, or shelter?" "Do you use lubricants during sex? What kind?" "Do you use sex toys? How often? Do you share them? Do you clean them?" Put bluntly, questions should aim to answer who is putting what, where, when, and how
Protection from STI	• If a patient has had more than one partner in the past 12 mo (or has a partner who has other sex partners)† • Based on patient risk profile, ask these questions accordingly • Explore the patient's use of barrier methods • Explore the patient's use of PrEP	"How do you keep yourself safe during sex" "Do you use condoms/dental dams when having vaginal, anal, and/or oral sex? How often? All the time? Most of the time? About half of the time? Rarely?" If no, "Why not?" "Do you and your partners use any other protection against STI?" "Do you or your partner use PrEP? "Are you interested in starting PrEP?"
Past history of STI	• Explore patient STI history as a risk factor for future STI	"Have you ever been tested for HIV or other STIs?" "Have you ever been diagnosed with an STI?" If yes, "When were you diagnosed? How were you treated?" "Would you like to be tested? And which parts of your body should we check?" "Has your current or any former partners ever been diagnosed with an STI?" If yes, "Have you been tested for the same STI?"
Pleasure/pain	• Recognize the importance of pleasure in sexual intimacy and well-being	"Are you satisfied with your sexual life?" "Do you have any pain with sex?" "Do you have any problems with erection, lubrication, ejaculation, or orgasm?"
Prevention/planning of pregnancy	• Evaluate desire for/risk of pregnancy	"Are you concerned about getting pregnant or getting your partner pregnant?" "Are you using contraception or practicing any form of birth control?" "Do you need any information on birth control?"

*For more information, please see, "Sexual Health and the LGBTQ+ Community," by Taylor NM, King CK.. *Prim Care Clin Office Pract.* 2021;48:271-282.
†For patients who report one or fewer partners in the last 12 mo, ask whether they have any concerns about STI.
BDSM, Bondage and discipline, dominance and submission, sadism and masochism; HIV, human immunodeficiency virus; PrEP, preexposure prophylaxis.
From Suarez S, Lupez E, Siegel J, Streed Jr C. The annual examination for lesbian, gay, and bisexual patients. *Prim Care Clin Office Pract.* 2021;48:191–212, Table 2.

out of their homes. GLB young people are overrepresented among homeless and runaway populations across the United States, which can expose them to drugs, sexual abuse, and other health risks.

RECOMMENDATIONS FOR CARE

Evaluation

The goal of GLB pediatric care is physical health, social and emotional well-being, and healthy development. Physicians should provide nonjudgmental care to all adolescents, including those who are GLB or questioning (see Chapter 153, Table 153.1, and Table 154.1). They should receive the age-appropriate history, examination, and anticipatory guidance recommended for adolescents in general. The physical examination and laboratory evaluation of GLB and questioning adolescents are the same as for any teenager. However, providers should appropriately screen for special potential medical and psychosocial threats to GLB teenagers' health.

A nonjudgmental healthcare environment is important, with open communication and a positive relationship with youth and families. In the waiting room, written material about sexual orientation, support groups, and community resources will signal openness to discussing sexuality. Registration forms recognizing the possibility of same-gender parents signal a safe setting (e.g., forms can list parent/guardian #1, parent/guardian #2). Sexual history questions should avoid heterosexual assumptions (e.g., ask "Are you dating someone?" vs "Do you have a boyfriend/girlfriend?"). This is important at all ages. For example, asking a 6-year-old male if he has a girlfriend may convey an unsupportive message if he discovers later that he would like a boyfriend. Explaining confidentiality and incorporating into each adolescent visit private time with no parent in the room (see Chapter 137) may facilitate discussing sexual orientation, as may use of appropriate health history forms such as the American Medical Association's Guidelines for Adolescent Prevention Services Questionnaire.

Clinicians should remember that any youth might be GLB whether or not they are identified or perceived as such, so clinicians should not presuppose a particular orientation (see Table 154.1). Competency in conveying sensitivity, acceptance, and respectfulness; effective communication skills; and appropriate attention to privacy and confidentiality (including practices related to billing and record requests) are fundamental to providing high-quality care. While remaining attuned to youth's preferences, explicit or implied, for discussing sexual orientation, providers can tactfully take the lead, if necessary, regarding any pressing areas of clinical concern.

Medical and Sexual Health

STIs are covered in Chapter 163, but issues specific to GLB youth are included here. Use of latex condoms for fellatio, and dental dams and cut-open latex condoms for anilingus and cunnilingus, should be discussed with adolescents. Recommendations also include use of latex condoms for sexual appliances. In addition, it is important to emphasize that people who have been using alcohol or other drugs are at increased likelihood for engaging in riskier sexual activity. It is important not to assume that a gay male or female who does not identify as bisexual has not had sex with someone of a different sex or gender; lesbians can still have an unplanned pregnancy. Therefore prevention counseling about unintended pregnancy is relevant to all adolescents. Similarly, youth who identify as heterosexual and whose attractions are not to those of the same sex or gender may still have sexual activity with a partner of the same sex or gender.

Although vaccination against hepatitis A and B is recommended for all children, it is particularly recommended that nonvaccinated adolescent males who are having (or are likely to have) sex with males receive catch-up vaccines. The same recommendation applies to the human papillomavirus (HPV) vaccine for males. The Centers for Disease Control and Prevention (CDC) recommends that males who are engaging in sexual activity with males have annual testing for HIV, hepatitis A, hepatitis B, syphilis, urethral gonorrhea, and chlamydia (if engaging in insertive oral or anal intercourse), oral gonorrhea (if engaging in receptive oral intercourse), and rectal gonorrhea and chlamydia (if engaging in receptive anal intercourse). The CDC also recommends HIV pre-exposure prophylaxis (PrEP) for adolescents who are engaging in or plan to engage in sexual behavior placing them at "substantial ongoing risk of HIV exposure and acquisition."

Mental Health

Awareness of mental health and social problems is important when caring for GLB youth, as for all youth. Clinicians should monitor for depression, suicidality, anxiety, and substance abuse and know their community's mental health resources. Minor psychosocial problems might be handled by referral to a support group for patients (e.g., a school gay-straight or genders-sexualities alliance, other community support group) or for parents and others (e.g., Parents, Families and Friends of Lesbians and Gays). In some communities, agencies and organizations serving the GLB community can help with social, educational, vocational, housing, and other needs.

Individuals or families who harbor negative attitudes may inquire about mental health treatment to avert or change a gay or bisexual orientation (conversion therapy). However, a GLB orientation is not an illness, and all leading health organizations have concluded that such change is neither possible nor warranted. Conversion therapy is illegal in 18 states; 22 states have no law or policy.

It is important to distinguish between a GLB orientation, which is not a mental illness, and mental health problems (e.g., depression) for which GLB youth are at elevated risk. While understanding different families' values, clinicians must recognize the morbidity and mortality associated with stigma and attempt to foster physical and emotional health. Individual or family therapy might be indicated.

Clinicians should also monitor for specific stressors, such as bullying and other homophobic victimization, family nonacceptance, and abuse. Failure to confront harassment constitutes tacit assent. Anticipatory guidance, referral, and substance abuse treatment should be considered for the subset of GLB youth who use alcohol, drugs, or tobacco, some of whom may be using these to manage painful feelings related to conflicts over their sexuality.

Adolescents with serious psychiatric symptoms, such as suicidality, depression, and substance abuse, should be referred to mental health specialists with competency in treating GLB adolescents (see Chapter 40).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 155

The Epidemiology of Adolescent Health Problems

Samantha V. Hill and Tamera Coyne-Beasley

Adolescence is the first period of life where the major determinants of morbidity and mortality are *behavioral* rather than congenital or infectious. As adolescents make the transition from childhood to adulthood, they establish behaviors that affect both their current and future health. Adolescence is a time of immense biologic, psychologic, and social change (see Chapter 150). Many of the psychologic changes have a biologic substrate in the development and eventual maturation of the central nervous system, particularly the frontal lobe areas responsible for executive functioning (Fig. 155.1). In addition to cognitive development, there are both risk and protective factors for adverse adolescent health behaviors that are dependent on the social environment and the mental health of an adolescent (Table 155.1).

Many adolescents continually confront the task of making healthy choices while struggling with impulsivity that can lead to unintentional consequences, such as injuries, sexually transmitted infections (STIs), or drug overdoses. Adolescents are also challenged with adopting behaviors that will affect their future adult health, such as eating nutritiously; engaging in physical activity; and choosing not to use tobacco (including vapes and e-cigarettes), alcohol, cannabis, or illicit substances. Environmental factors and social determinants of health in and among an individual's family, peers, school, and community also contribute to adolescents' health and risk behaviors. The U.S. Centers for Disease Control and Prevention (CDC) **Youth Risk Behavior Surveillance Survey**, a school-based survey of a nationally representative sample of U.S. high school students, demonstrates that youth begin engaging in behaviors that place their health at risk during adolescence (Fig. 155.2).

Although according to the 2018 CDC National Health Interview Survey (https://www.cdc.gov/nchs/nhis/shs/tables.htm), a probability sample survey conducted annually, an estimated 83% of 12- to 17-year-olds report excellent or very good health, 11% reported limitation in usual activities because of one or more chronic conditions, 10% missed 6-10 school days in the past year, 6% are uninsured, 5% have no usual place of healthcare, 10% have asthma, 12% have respiratory allergies, 10% have a learning disability, 13% have attention-deficit/hyperactivity disorder, and 18% take prescription medications routinely. In 2018 the mortality rate among adolescents 15-19 years of age was 49 deaths per 100,000 population. Although varying by gender, the leading causes of death overall among adolescents 15-19 years of age are (1) unintentional injuries, (2) suicide, and (3) homicide (Table 155.2).

Within the adolescent population, **disparities in health** occur. Adolescent health outcomes and behaviors vary among populations that can be defined by being Black, ethnicity, gender, education, income, disability, geographic location (e.g., rural or urban), or sexual orientation. Health disparities result from multiple factors affecting social determinates of health, including poverty, environmental threats, inadequate access to healthcare, individual and behavioral factors, racism and other systemic biases, and educational and other inequalities (Table 155.3).

ACCESS TO HEALTHCARE

Adolescents in the United States make fewer visits to physicians for ambulatory office visits than any other age-group; school-age children and adolescents are more likely than younger children to have unmet health needs and delayed medical care. Adolescents who actually receive preventive care may still not have access to time alone with their provider to discuss confidential health issues such as STIs, HIV, or pregnancy prevention. Less than half (22% of 13- to 14-year-olds and 43% of 15- to 18-year-olds) of adolescents have time alone with their healthcare provider during a preventive healthcare visit; sexually experienced teens report sexual health discussions more often than nonsexually experienced teens, but the frequency is still low at 81% and 65% for sexually experienced young women and men, respectively.

The 2010 Patient Protection and Affordable Care Act (ACA) has improved access to care for young adults 18 to 24 years old. The ACA permits children to receive benefits from their parents' health plans through age 26 years. Although accomplishments have been made in improving adolescent health, *Healthy People* provides science-based, 10-year national objectives for measuring and improving the health of all Americans by establishing benchmarks and monitoring progress over time. The ***Healthy People 2030*** agenda includes 24 adolescent-specific objectives with a goal of improving the healthy development, health, safety, and well-being of adolescents and young adults over the next 10 years (Table 155.4). This science-based initiative is centered around a framework for public health prevention priorities and actions to improve the health status of U.S. youth.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

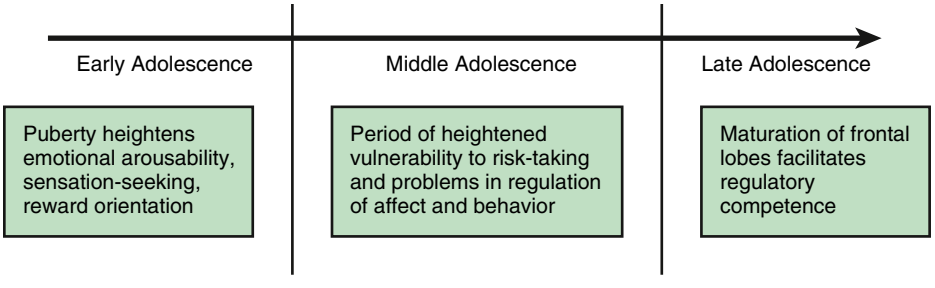

Fig. 155.1 It has been speculated that the impact of puberty on arousal and motivation occurs before the maturation of the frontal lobes is complete. This gap may create a period of heightened vulnerability to problems in the regulation of affect and behavior, which might help to explain the increased potential in adolescence for risk-taking, recklessness, and the onset of emotional and behavioral problems. *(From Steinberg L. Cognitive and affective development in adolescence. Trends Cogn Sci. 2005;9:69–74.)*

Table 155.1 Identified Risk and Protective Factors for Adolescent Health Behaviors

BEHAVIOR	RISK FACTORS	PROTECTIVE FACTORS
Smoking	Depression and other mental health problems, alcohol use, disconnectedness from school or family, difficulty talking with parents, minority ethnicity, low school achievement, peer smoking	Family connectedness, perceived healthiness, higher parental expectations, low prevalence of smoking in school
Alcohol and drug misuse	Depression and other mental health problems, low self-esteem, easy family access to alcohol, working outside school, difficulty talking with parents, risk factors for transition from occasional to regular substance misuse (smoking, availability of substances, peer use, other risk behaviors)	Connectedness with school and family, religious affiliation
Teenage pregnancy	Deprivation, city residence, low educational expectations, sexual intercourse, lack of access to sexual health services, drug and alcohol use	Connectedness with school and family, religious affiliation
Sexually transmitted infections	Mental health problems, substance misuse, exploration of sexuality and sexual identity (sexual activity)	Connectedness with school and family, religious affiliation

Adapted from McIntiosh N, Helms P, Smyth R, eds. *Fofar and Arneil's Textbook of Pediatrics*, 6th ed. Edinburgh: Churchill Livingstone; 2003:1757–1768; and Viner R, Macfarlane A. Health promotion. *BMJ*. 2005;330:527–529.

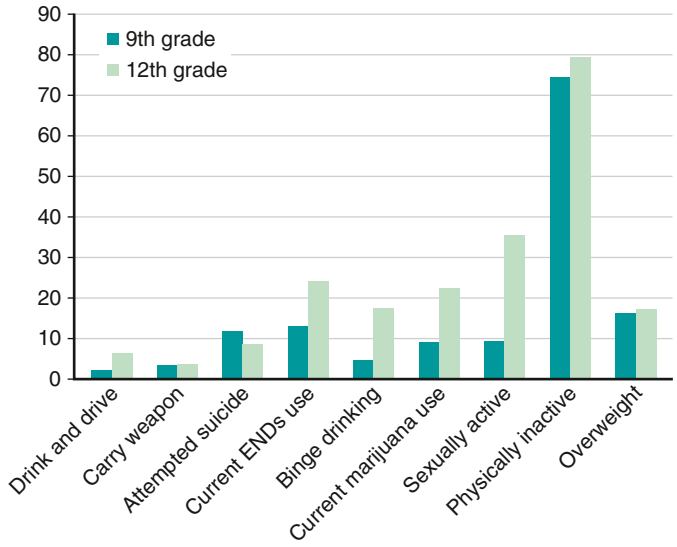

Fig. 155.2 Selected health behaviors among 9th-and 12th-grade high school students. ENDs, Electronic nicotine delivery systems. *(Data from Centers for Disease Control and Prevention: 1991-2021 High school youth risk behavior survey data. http://nccd.cdc.gov/youthonline.)*

Table 155.2 Leading Causes of Death Among 15- to 19-Year-Olds by Gender, United States, 2018-2021*

LEADING CAUSES OF DEATH	MALE		FEMALE	
	CAUSE OF DEATH	MORTALITY RATE PER 100,000 POPULATION	CAUSE OF DEATH	MORTALITY RATE PER 100,000 POPULATION
#1	Unintentional injuries	32.4	Accidents (unintentional injuries)	14.3
#2	Assault (homicide)	21.6	Intentional self-harm (suicide)	5.2
#3	Intentional self-harm	16.1	Malignant neoplasms	3.6

*Based on data from Heron M. Deaths: leading causes for 2018-2019, CDC WONDER Online Database 2021. https://wonder.cdc.gov/

Table 155.3 Adolescent Health Outcomes by Ethnicity, United States, 2018-2019

OUTCOME	WHITE	BLACK	AI/AN	API	HISPANIC
Deaths*	45.4	79.8	62.8	23.4§	29.3
Births†	11.4	25.8	29.2	2.7§	18.2
Obese‡‡	12.5	18.2	7.9	33.3§	37.1
Asthma‡	10.1	18.0	17.8	8.2§	12.5
Depressed**	14.0	9.5	16.3	11.5§	13.8
Chlamydia*	857.5	4,894.0	2343.1	310.3§	1080.4
Gonorrhea*	134.5	1506.1	559.9	44.9§	179.8
HIV*	2.1	34.8	5.6	12.2§	7.4

*2019 rates per 100,000 15- to 19-yr-old population by race/ethnicity.
†2019 rates of births in per 1,000 15- to 19-yr-old females by race/ethnicity.
‡Percent high school students reporting health outcome in 2018.
**Prevalence of 12- to 17-yr-olds reporting health outcome in 2017.
‡‡Percent high school students reporting health outcome in 2017.
§Rates of Asian-only race.
AI/AN, American Indian or Alaska Native; API, Asian or Pacific Islander; HIV, human immunodeficiency virus.

Table 155.4 *Healthy People 2030* Adolescent Health (AH) Objectives

- **AH-01:** Increase the proportion of adolescents who had a preventive healthcare visit in the past year.
- **AH-02:** Increase the proportion of adolescents who speak privately with a provider at a preventive medical visit.
- **AH-03:** Increase the proportion of adolescents who have an adult they can talk to about serious problems.
- **AH-04**: Increase the proportion of students participating in the School Breakfast Program.
- **AH-05:** Increase the proportion of 4th-graders with reading skills at or above the proficient level.
- **AH-06:** Increase the proportion of 4th-graders with math skills at or above the proficient level.
- **AH-07:** Reduce chronic school absence among early adolescents.
- **AH-08:** Increase the proportion of high school students who graduate in 4 years.
- **AH-09:** Reduce the proportion of adolescents and young adults who are not in school or working.
- **AH-10:** Reduce the rate of minors and young adults committing violent crimes.
- **AH-D01:** Increase the proportion of trauma-informed early childcare settings and elementary and secondary schools.
- **AH-D02:** Increase the proportion of children and adolescents with symptoms of trauma who get treatment.
- **AH-D03**: Reduce the proportion of public schools with a serious violent incident.
- **AH-R01:** Increase the proportion of adolescents who get support for their transition to adult healthcare.
- **AH-R02:** Increase the proportion of adolescents in foster care who show signs of being ready for adulthood.
- **AH-R03:** Increase the proportion of eligible students participating in the Summer Food Service Program.
- **AH-R04:** Increase the proportion of 8th-graders with reading skills at or above the proficient level.
- **AH-R0:** Increase the proportion of 8th-graders with math skills at or above the proficient level.
- **AH-R06:** Increase the proportion of schools requiring students to take at least two health education courses from 6 to 12.
- **AH-R07:** Increase the proportion of secondary schools with a start time of 8:30 AM or later.
- **AH-R08:** Increase the proportion of secondary schools with a full-time registered nurse.
- **AH-R09**: Increase the proportion of public schools with a counselor, social worker, and psychologist.
- **AH-R10:** Increase the proportion of students served under the Individuals with Disabilities Education Act who earn a high school diploma.
- **AH-R11:** Reduce the rate of adolescents and young adult victimization from violent crimes.

From U.S. Department of Health and Human Services: *Healthy People 2030*, available at: https://health.gov/healthypeople/about/workgroups/adolescent-health-workgroup.

Chapter 156

Violent Behavior

Michael N. Levas and Marlene D. Melzer-Lange

Violence is recognized by the World Health Organization (WHO) as a leading worldwide public health problem. The WHO defines violence as "the *intentional* use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in *injury*, death, psychologic harm, maldevelopment or deprivation" (see Chapter 15). Youths may be perpetrators, victims, or observers of violence (or any combination of the three roles, wherein the roles are unclear), with varying severity of impact on the individual, family, and larger community. Risk factors for youth violence include poverty, socially disorganized communities, war and other regional conflicts, substance misuse (in the child or family), behavioral health disorders (attention-deficit, hyperactivity, conduct disorder), poor school performance, social isolation, child trafficking, runaway youth, criminal or gang involvement (child or family), bullying, and low parental involvement.

EPIDEMIOLOGY

In 2019 (and 2021), **homicide** in the United States was the third leading cause of death for 10- to 24-year-olds, totaling 4,965 deaths, which were largely males (85%) killed by a handgun (79%). The 2019 homicide rate for teens age 12-17 years was 3.43/100,000 youth, down 63% from 8.4/100,000 youth in 1993. The WHO reports that other than the United States, where the youth and young adult homicide rate was 11/100,000, most countries with homicide rates above 10/100,000 are developing nations or countries with socioeconomic instability. In the United States the prevalence of behaviors that contribute to violence has not decreased, as fighting, weapon carrying, and cyberbullying remain prevalent among youth. Furthermore, the rate of homicide in youth had been declining since the peak in the 1990s but showed an increase in 2017 that has continued (Fig. 156.1). Adolescent reports of **physical fighting** have decreased from 42% in 1991 to 22% in 2019.

Violence at U.S. schools remains a significant problem, with 8.1% of students reporting being in a physical fight on school property one or more times in the preceding 12 months in 2019. The 2019 Youth Risk Behavior Surveillance System reported 13.1% of youths overall carried a weapon such as a gun, knife, or club in the last 30 days; 2.8% carried the weapon to school; and 7.4% reported being threatened or injured with a type of weapon on school property. Males are more likely than females to carry a gun or weapon and therefore may need more support and engagement at home and at school. These **violence-related behaviors** at school affect the general students' perception of safety. More than 8.7% of students did not go to school on one or more days in the preceding 30 days because they felt it was unsafe. School-based prevention programs initiated at the elementary school level have been found to decrease violent behaviors in students. Increased surveillance of students is warranted both on and around school property to improve student safety.

Adolescent relationship abuse (dating violence/reproductive coercion) occurs between two people in a close relationship and can be physical (punching, kicking, hitting, shoving), emotional (shaming, bullying, controlling, stalking), or sexual (forcing a partner to engage in a sexual act when he or she does not consent to it). Incidents of adolescent relationship abuse are not uncommon, with 22.4% of females and 15% of males experiencing some type of partner violence between the ages of 11 and 17 years. It may start with teasing, name calling, or shaming but often progresses electronically, with frequent calls, texting, or posting sexual pictures of a partner on social media. Risk factors for being a victim of adolescent relationship abuse include those who use alcohol, believe violence is acceptable, have a lack of adult supervision, or have a peer who is in a violent relationship. Most teens do not report the behaviors because of fear of retaliation from the partner. Teens who are victims of adolescent relationship abuse are more likely to experience decreased school performance, have thoughts about suicide, use drugs and alcohol, develop an eating disorder, experience depression, and are more likely to be victimized during college and into adulthood. School-based prevention programs that address attitudes and behaviors linked with adolescent relationship abuse, such as **Safe Dates** and **Dating Matters**, offer training experiences to change social norms among teens.

ETIOLOGY

The WHO places youth violence in a model within the context of three larger types of violence: self-inflicted, interpersonal, and collective. **Interpersonal violence** is subdivided into violence largely between family members or partners and includes child abuse. **Community violence** occurs between individuals who are unrelated. **Collective violence** incorporates violence by people who are members of an identified group

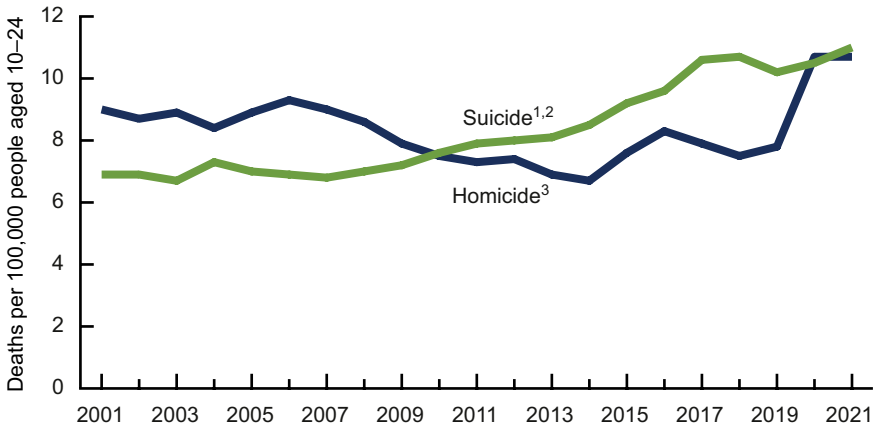

Fig. 156.1 Suicide and homicide death rates among people aged 10–24, United States, 2001–2021. [1]No statistically significant trend from 2001–2007, then significant increasing trend from 2007–2021 ($p < 0.05$). [2]Rate significantly lower than the rates for homicide from 2001–2009 and significantly higher from 2011–2019 ($p < 0.05$). [3]No statistically significant trend for homicides from 2001–2006, then significant decreasing trend from 2006–2014, and a significant increasing trend from 2014–2021 ($p < 0.05$). The rate in 2021 was not significantly different than the rate in 2020 ($p < 0.05$). NOTES: Suicides are identified with International Classification of Diseases, 10th Revision codes U03, X60–X84, and Y87.0, and homicides with codes U01–U02, X85–Y09, and Y87.1. Access data table at: https://www.cdc.gov/nchs/data/databriefs/db471-tables.pdf#1. SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality data file. *(From Curtin SC, Garnett MF. Suicide and Homicide Death Rates Among Youth and Young Adults Aged 10–24: United States, 2001–2021. NCHS Data Brief. 2023 Jun;(471):1–8. Fig 1.)*

against another group of individuals with social, political, or economic motivation. The types of violence in this model have behavioral links, such that child abuse victims are more likely to experience violent and aggressive interpersonal behavior as adolescents and adults. Overlapping risk factors for the types of violence include firearm availability, alcohol use, and socioeconomic inequalities. The benefit to identifying common risk factors for the types of violence lies in the potential for intervening with prevention efforts and gaining positive outcomes for more than one type of violent behavior. The model further acknowledges four categories that explore the potential nature of violence as involving physical, sexual, or psychologic force and deprivation.

The social-ecologic model of public health focuses on both population-level and individual-level determinants of health and their respective interventions. On the individual level, there may be two types of antisocial youth: life course persistent and limited. **Life course–limited offenders** have no childhood aberrant behaviors and are more likely to commit *status* offenses such as vandalism, running away, and other behaviors symbolic of their struggle for autonomy from parents. **Life course–persistent offenders** exhibit aberrant behavior in childhood, such as problems with temperament, behavioral development, and cognition; as adolescents they participate in more *victim-oriented* crimes. The existence of **adverse childhood experiences** foretells future health issues and subsequent violence. This hypothesis proposes that precursors such as child abuse and neglect, a child witnessing violence, adolescent sexual and physical abuse, and adolescent exposure to violence and violent assaults predispose youths to outcomes of violent behavior, violent crime, delinquency, violent assaults, suicide, or premature death. This public health model also emphasizes the community environment and resiliency of the individual and family. An additional common paradigm for high-risk violence behavior poses a balance of risk and protective factors at the individual, family, and community levels.

CLINICAL MANIFESTATIONS

The identified risk factors for youth violence include poverty, association with delinquent peers, poor school performance or low education status, disconnection from adult role models or mentors, prior history of violence or victimization, poor family functioning, childhood abuse, substance misuse, and certain mental health disorders. The most common disorders associated with **aggressive behavior** in adolescents are intellectual disabilities, learning disabilities, moderately severe language disorders, and mental health disorders such as attention-deficit/hyperactivity disorder (ADHD) and mood disturbances. In general, youth with mental health disorders are not violent. However, the link between severe mental illness and violent behaviors is strongest for those with coexisting alcohol or substance abuse or dependence.

Inability to master prosocial skills such as the establishment and maintenance of positive family/peer relations and poor resolution of conflict may put adolescents at higher risk of physical violence and other risky behaviors. The single, most protective factor is the existence of one or more significant adult mentors in the child's life. **Conduct disorder** and **oppositional defiant disorder** are specific psychiatric diagnoses whose definitions are associated with violent behavior (Table 156.1). They occur with other disorders such as ADHD (see Chapter 50) and increase an adolescent's vulnerability for juvenile delinquency, substance use or abuse, sexual promiscuity, adult criminal behavior, incarceration, and antisocial personality disorder. Other co-occurring risk factors for youth violence include use of anabolic steroids, gang tattoos, belief in one's premature death (inability to see oneself as surviving to adulthood), preteen alcohol use, and placement in a juvenile detention center.

DIAGNOSIS

The assessment of an adolescent at risk or with a history of violent behavior or victimization should be a part of the health maintenance visit of all adolescents. The answers to questions about recent history of involvement in a physical fight, carrying a weapon, or firearms in the household, as well as concerns that the adolescent may have about personal safety, may suggest a problem requiring a more in-depth evaluation. The **FISTS** mnemonic provides guidance for structuring the assessment (Table 156.2). Another screening tool, **Violence Injury Protection and Risk Screen (VIPRS)**, has been validated to predict *future* violence among youth in the primary care setting (Table 156.3). The additional factors of physical or sexual abuse, serious problems at school, poor school performance and attendance, multiple incidents of trauma, substance use, and symptoms associated with behavioral disorders are indications for evaluation by a behavioral health professional. In a situation of acute trauma, assault victims are not always forthcoming about the circumstances of their injuries for fear of retaliation or police involvement. Stabilization of the injury or the gathering of forensic evidence in sexual assault is the treatment priority; however, once this is achieved, addressing a more comprehensive set of issues surrounding the assault is appropriate.

Table 156.1 Oppositional Defiant Disorder and Conduct Disorder

OPPOSITIONAL DEFIANT DISORDER	CONDUCT DISORDER
• Often being angry or losing one's temper • Often arguing with adults or refusing to comply with adults' rules or requests • Often resentful or spiteful • Deliberately annoying others or becoming annoyed with others • Often blaming other people for one's own mistakes or misbehavior	• Breaking serious rules, such as running away, staying out at night when told not to, or skipping school • Being aggressive in a way that causes harm, such as bullying, fighting, or being cruel to animals • Lying, stealing, or damaging other people's property on purpose

Courtesy Centers for Disease Control and Prevention: Children's Mental Health, https://www.cdc.gov/childrensmentalhealth/behavior.html, accessed August 4, 2021.

Table 156.2 FISTS Mnemonic to Assess an Adolescent's Risk of Violence

F: Fighting (How many fights were you in last year? What was the last?)
I: Injuries (Have you ever been injured? Have you ever injured someone else?)
S: Sex (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?)
T: Threats (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?)
S: Self-defense (What do you do if someone tries to pick a fight? Have you carried a weapon in self-defense?)

Adapted with permission from the Association of American Medical Colleges. Alpert EJ, Sege RD, Bradshaw YS. Interpersonal violence and the education of physicians. *Acad Med.* 1997;72:S41–S50.

TREATMENT

In the patient with acute injury secondary to violent assault, the treatment plan should follow standard protocols, which include the stabilization of the injury, evaluation and treatment of the injury, evaluation of the assault circumstance, psychologic evaluation and support, social service evaluation of the circumstances surrounding the assault, and a treatment plan on discharge that is designed to protect the adolescent from subsequent injury episodes, prevent retaliation, and minimize the development of psychologic disability. Victims and *witnesses* of violence are at risk for posttraumatic stress disorder and future aggressive or violent behavior. Using a **trauma-informed care** approach enables providers to help these victims and witnesses so that they can develop linkages to recovery and resilience. **Hospital-based violence intervention programs** have shown success by supporting violently injured youth and their families in the emergency department, hospital, or community. Credible messenger and violence interrupter programs have shown promise in decreasing the cycle of violence and retaliation in the community after violent events.

Table 156.3 Violence Injury and Perpetration Risk Screen (VIPRS Scale): Percent and Odds of Future Violence Perpetration by Question Type

PROTECTIVE FACTORS	%	ODDS OF ASSOCIATION WITH VIOLENCE PERPETRATION IF PROTECTIVE FACTOR NOT PRESENT OR (95% CI)
1. Do your parents expect you to do well at school?		6.1 (1.1-33.83)
Most of the time	93	
Sometimes	6.1	
Rarely/never	0.6	
2. Are your grades mostly		5.8 (1.7-19.2)
A/B average	77.9	
C average	16.6	
D/F average	5.5	
RISK FACTORS	**% POSITIVE**	**ODDS OF ASSOCIATION WITH FUTURE VIOLENCE PERPETRATION IF RISK FACTOR PRESENT (OR 95% CI)**
3. Have you been suspended from school in the last year?		
Yes	17	47 (11.1-201)
4. How many fights have you been in during the last year?		
0	82	
1-5	18	10.7 (3.2-35.6)
5. Have you ever smoked marijuana or used other drugs?		
Yes	23	4.6 (1.5-14.2)
6. Have you or your friends ever been in trouble with the law?*		
Yes	38.2	2.1 (0.72-6.2)
Males	40.8	8.6 (1.4-54.2)
Females	36.2	0.85 (0.19-3.8)
7. Are you or your friends involved with a gang or tagging crew?		
Yes	7.0	4.6 (0.93-23.0)
8. Do you feel you are hyperactive, or have you ever been diagnosed with ADHD*		
Yes	14.8	3.0 (0.88-10.3)
Males	15.9	0.83 (0.08-8.5)
Females	14.0	6.4 (1.3-30.7)
9. Have you had any friends who have committed suicide?		
Yes	11	3.7 (0.93-14.4)
10. Have you ever been injured in a fight?		
Yes	10	4.3 (1.1-17.6)
11. When was the last time you hurt someone else in a fight?		
In the past month	4.3	
Between 1 and 6 mo ago	6.7	
Between 6 and 12 mo ago	3.7	
Over 1 yr ago	11.6	
Never	73.8	
Positive if ≤12 mo ago	14.6	24.6 (4.3-138.7)
12. When was the last time you watched a fight?		
In the past month	25	
Between 1 and 6 mo ago	13.4	
Between 6 and 2 mo ago	11.6	
Over 1 yr ago	22.6	
Never	27.4	
Positive if ≤12 mo ago	50	6.1 (1.6-22)

Continued

Table 156.3 Violence Injury and Perpetration Risk Screen (VIPRS Scale): Percent and Odds of Future Violence Perpetration by Question Type—cont'd

RISK FACTORS	% POSITIVE	ODDS OF ASSOCIATION WITH FUTURE VIOLENCE PERPETRATION IF RISK FACTOR PRESENT (OR 95% CI)
13. How many times has someone beat you up in the last 6 mo?		
0	91.2	
1-6	9.8	6.2 (1.1-34.2)
14. How many times has someone asked you to fight in the last 6 mo?		
0	75	
1-6	25	3.6 (1.1-11.7)

*Questions 6 and 8 display gender differences, because these two questions reveal statistically significant differences between genders.
Modified from Sigel EJ, Hoffenberg A, Hart J, Dodge M. Development and psychometric properties of a violence screening tool for primary care. *J Adolesc Health*. 2011;48:358–365, Table 4.

Table 156.4 Preventing Youth Violence (CDC)

STRATEGY	APPROACH
Promote family environments that support healthy development	Early childhood home visitation Parenting skill and family relationship programs
Provide quality education early in life	Preschool enrichment with family engagement
Strengthen youth skills	Universal school-based programs
Connect youth to caring adults and activities	Mentoring programs After-school programs
Create protective community environments	Modify the physical and social environment Reduce exposure to community-level risks Street outreach and community norm change
Intervene to lessen harms and prevent future risk	Treatment to lessen the harms of violence exposures Treatment to prevent problem behavior and further involvement in violence Hospital-community partnerships

From David-Ferdon, C, Vivolo-Kantor AM, Dahlberg LL, et al. *A Comprehensive Technical Package for the Prevention of Youth Violence and Associated Risk Behaviors.* Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2016.

Table 156.5 Prevention of Youth Violence (WHO)

Promising prevention programs include:
- Life skills and social development programs designed to help children and adolescents manage anger, resolve conflict, and develop the necessary social skills to solve problems
- Whole-school approaches to violence prevention in educational facilities
- Programs that support parents and teach positive parenting skills
- Preschool programs that provide children with academic and social skills at an early age
- Therapeutic approaches for youths at high risk of being involved in violence
- Reducing access to alcohol
- Interventions to reduce the harmful use of drugs
- Restrictive firearm licensing
- Community and problem-oriented policing
- Interventions to reduce concentrated poverty and to upgrade urban environments

Preventing youth violence requires a comprehensive approach that addresses the social determinants of violence, such as income inequality, rapid demographic and social change, and low levels of social protection.
Courtesy World Health Organization: Youth Violence. https://www.who.int/news-room/fact-sheets/detail/youth-violence, accessed August 11, 2022.

Multiple treatment modalities are used simultaneously in managing adolescents with persistent violent and aggressive behavior and range from cognitive-behavioral therapy involving the individual and family to specific family interventions (parent management training, multisystemic treatment) and pharmacotherapy. Treatment of comorbid conditions, such as ADHD, depression, anxiety, and substance abuse, appears to reduce aggressive behavior.

PREVENTION

The WHO recognizes a multifactorial approach to prevention: parenting and early childhood development strategies, school-based academic and social skills development strategies, strategies for young people at higher risk of or already involved in violence, and community- and society-level strategies (Tables 156.4 and 156.5). **Parenting and early childhood development approaches** concentrate on working with families to provide nonviolent parenting through home visitation and parent groups as well as teaching coping strategies and nonviolent conflict resolution for all children and families. **School-based social skills development strategies** focus on students' families and peer relationships, especially those with the potential to trigger aggressive or violent responses. Solutions include improving coping or problem-solving skills, anti-bullying campaigns, peer mediation, adolescent relationship abuse prevention, and after-school programs. **Strategies for young people at higher risk of, or already involved in, violence** include therapeutic behavioral health approaches, crime victim services, vocational training, mentoring, and gang intervention. These youth are at highest risk for repeat injury or incarceration. **Community- and societal-level approaches** include broader advocacy and legislative actions and changing the cultural norm toward violent behaviors.

A specific prevention strategy can incorporate several approaches, such as the handgun/firearm prevention recommendations that include gun-lock safety, public education, and legislative advocacy. Other efforts are directed toward establishing a national database to track and define the problem of youth violence. The **National Violent Death Reporting System** collects and analyzes violent death data from all 50 states, the District of Columbia, and Puerto Rico and aims to improve surveillance of current trends, to share information state to state, to build partnerships among state and community organizations, and to develop and implement prevention and intervention programs. The Centers for Disease Control and Prevention characterizes specific successful prevention programs, including Striving to Reduce Youth Violence Everywhere (STRYVE), and summarizes program content on its website (www.cdc.gov).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 157
Substance Use Disorder

Cora Collette Breuner

Many adolescents engage in the use of a wide range of substances, including alcohol, tobacco products, natural marijuana and synthetic cannabinoids, opiates, psychoactive agents (amphetamine, cocaine, MDMA, 3,4-methylenedioxymethamphetamine), hallucinogens, inhaled products (glue, organic solvents, nitrous oxide), and stimulants. Their reactions to and the consequences of these exposures are influenced by a complex interaction among biologic and psychosocial development, environmental messages, legality, and societal attitudes. The potential for adverse outcome with occasional use, such as motor vehicle crashes, violence, and other injuries, is sufficient justification to consider any substance use in adolescents a considerable risk.

Individuals who initiate substance use at an early age are at a greater risk for developing a **substance use disorder** than those who begin using substances in early adulthood. Substance use disorder is diagnosed when the recurrent use of the substance causes clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home. Substance use in younger adolescents may act as a substitute for developing age-appropriate coping strategies and enhance vulnerability to poor decision-making. Most (88%) people report that their age of first alcohol use was <21 years old, the legal drinking age in the United States. Inhalants have been identified as a popular first substance for youth in eighth grade (age 13-14 years).

Substance use disorder is a pervasive phenomenon and infiltrates every socioeconomic and cultural segment of the population. It is one of the costliest and most challenging public health problems facing all societies and cultures. The challenge to the clinician is to identify youth at risk for substance use disorder and offer early intervention. The challenge to the community and society is to create norms that decrease the likelihood of adverse health outcomes for adolescents and promote and facilitate opportunities for adolescents to choose healthier and safer options. Recognizing those substances with the greatest harm, and at times focusing on harm reduction with or without abstinence, is essential in the approach to the adolescent with substance use disorder (Fig. 157.1).

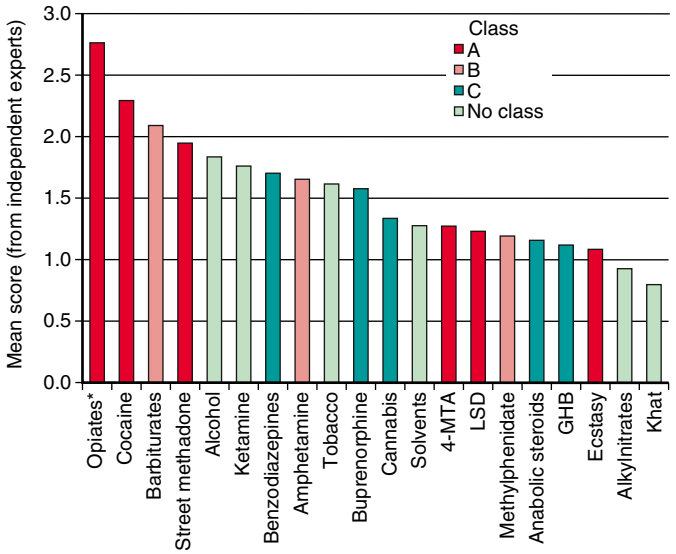

Fig. 157.1 Mean harm scores for 20 substances as determined by an expert panel based on three criteria: physical harm to user, potential for dependence, and effect on family, community, and society. Classification under the Misuse of Substances Act, when appropriate, is shown by the color of each bar. Class A substances are deemed potentially most dangerous; class C least dangerous. *Heroin, fentanyl, fentanyl derivatives. *(From Nutt D, King LA, Saulsbury W, et al. Development of a rational scale to access the harm of substances of potential misuse. Lancet 2007;369:1047–1053.)*

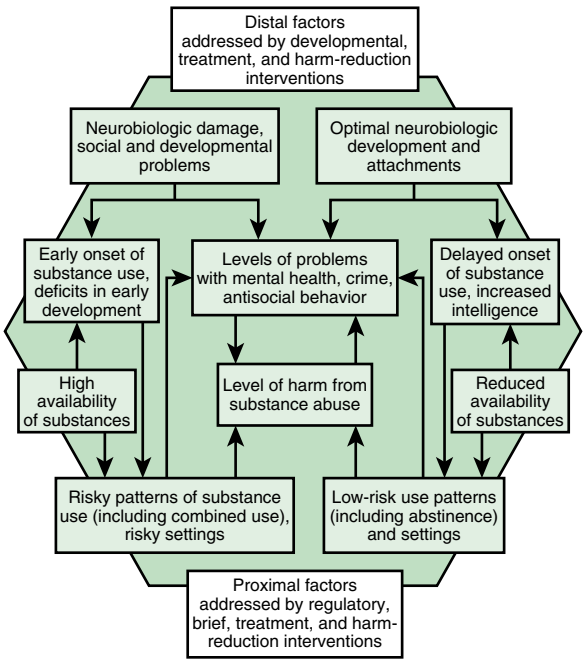

Fig. 157.2 Protection and risk model for distal and proximal determinants of risky substance use disorder and related harms. *(From Toumbourou JW, Stockwell T, Neighbors C, et al. Interventions to reduce harm associated with adolescent substance use. Lancet 2007;369:1391–1571.)*

ETIOLOGY

Substance use disorder has multifactorial origins (Fig. 157.2). Social determinants of health, including economic stability, education, health and healthcare, neighborhood environment, and social and community context, all have an impact on adolescents and can lead to substance use disorder and use. Biologic factors, including genetic predisposition, are established contributors. Behaviors such as ineffective self-control, poor school performance, involvement with the juvenile justice system, and emotional trends such as low self-esteem are frequently associated with or predate the onset of substance use. Psychiatric disorders often coexist with adolescent substance use. Conduct disorders and antisocial personality disorders are the most common diagnoses coexisting with substance use, particularly in males. Teens with depression (see Chapter 39.1), attention-deficit disorder (Chapter 50), anxiety (Chapter 38), and eating disorders (Chapter 41) have high rates of substance use. The determinants of adolescent substance use disorder and substance use are explained using numerous theoretical models and include factors at the individual level, the level of significant relationships with others, and the level of the setting or environment. These models include a balance of risk and protective or coping factors contributing to individual differences among adolescents with similar risk factors who escape adverse outcomes.

Risk factors for adolescent *substance use disorder* may differ from those associated with adolescent substance use. Adolescent substance use is more commonly related to social and peer factors, whereas *use disorder* is more often a function of psychologic and biologic factors. The likelihood that an otherwise normal adolescent would experiment with substances may depend on the availability of the substance to the adolescent, the perceived positive or otherwise functional value to the adolescent, the perceived risk associated with use, and the presence or absence of restraints, as determined by the adolescent's cultural or other important value systems.

Specific historical questions can assist in determining the severity of the substance problem through a rating system (Table 157.1). The type of substance used (marijuana vs cocaine), the circumstances of use (alone or in a group setting), the frequency and timing of use (daily before school vs occasionally on a weekend), current mental health status, and general functional status, including sleep habits and screen use, should all be considered in evaluating any adolescent found to be using a substance. The stage of substance use should also be considered (Table 157.2). A teen may spend months or years in the experimentation phase trying a variety of illicit substances, including the most common substances: alcohol, tobacco products, and marijuana. Often it is not until regular use of substances results in negative consequences (problem use) that the adolescent is identified as having a problem, either by parents, friends, teachers, or a healthcare provider. Having emotionally supportive parents with open communication styles, involvement in organized school activities, having mentors or role models outside the home, and recognition of the importance of academic achievement are examples of important protective factors against developing problematic use.

EPIDEMIOLOGY

Alcohol, tobacco products, and marijuana are the most commonly reported substances used among U.S. teens (Table 157.3). The prevalence of substance use and associated risky behaviors vary by age, gender, race/ethnicity, and other sociodemographic factors. Younger teenagers tend to report less use of substances than do older teenagers, except for inhalants (in 2016, 4.4% in 8th grade, 2.8% in 10th grade, 1.0% in 12th grade). In 2019, a total of 50.1% of U.S. high school students had ever used electronic vapor products, and 24.1% had ever tried cigarette smoking. Current electronic vapor product use was 32.7%, current cigarette smoking was 6.0%, current cigar smoking was 5.7%, and current smokeless tobacco use was 3.8%. Approximately 36.5% of students were current users of any tobacco product, and 8.2% were current users of two or more tobacco products. Males have higher rates of substances use than females, with greatest differences seen in their higher rates of use of tobacco products including vaping, chewing and cigarettes/cigars, and anabolic steroids.

Fewer students engaged in some high-risk substance use–related behaviors from 2009 through 2019. However, approximately one in seven students are still reporting lifetime use of any illicit drug or misuse of prescription medicine.

Marijuana use has been trending down over the past several years among adolescents, though there is variation in the extent and rate of use in different racial/ethnic groups. Use also depends on grade level, urban vs rural location, class size, and state laws regarding legalization of recreational or medical marijuana. The magnitude of the increase was greater in states with legal medical or recreational marijuana. Synthetic cannabinoids have significant psychotropic effects and addictive potential. Severe neuropsychiatric toxicity is often different from and more severe than marijuana.

The number of 12th graders who report using any of the **prescription psychotherapeutic** substances, including amphetamines, sedatives (barbiturates), tranquilizers, and narcotics other than heroin, decreased in 2019. Prevalence was 14% for ever used and 7.0% for 30-day use, indicating that a substantial portion of adolescents still misuse prescription substances including opioids. Rural adolescents are also more likely than urban adolescents to misuse prescription substances. In a large-scale study of 16,209 adolescent exposures to prescription substances, 52.4% were females, and the mean age was 16.6 years. The five most frequently misused substances were hydrocodone (32%),

Table 157.2 Stages of Adolescent Substance Use

STAGE	DESCRIPTION
1	Potential for use • Decreased impulse control • Need for immediate gratification • Available substances, alcohol, inhalants • Need for peer acceptance
2	Experimentation: learning the euphoria • Use of inhalants, tobacco, marijuana, and alcohol with friends • Few, if any, consequences • Use may increase to weekends regularly • Little change in behavior
3	Regular use: seeking the euphoria • Use of other substances (e.g., stimulants, LSD, sedatives) • Behavioral changes and some consequences • Increased frequency of use; use disorder alone • Buying or stealing substances
4	Regular use: preoccupation with the "high" • Daily use of substances • Loss of control • Multiple consequences and risk taking • Estrangement from family and "straight" friends
5	Burnout: use of substances to feel normal • Polysubstance use/cross-addiction • Guilt, withdrawal, shame, remorse, depression • Physical and mental deterioration • Increased risk taking, self-destructive, suicidal

Table 157.1 Assessing the Seriousness of Adolescent Substance Use

VARIABLE	0	+1	+2
Age (yr)	>15	<15	
Sex	Male	Female	
Family history of substance use		Yes	
Setting of substance use	In group		Alone
Affect before substance use	Happy	Always poor	Sad
School performance	Good, improving		Recently poor
Use disorder before driving	None		Yes
History of accidents	None		Yes
Time of week	Weekend	Weekdays	
Time of day		After school	Before or during school
Type of substance	Marijuana, beer, wine	Hallucinogens, amphetamines	Whiskey, opiates, cocaine, barbiturates

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.

Table 157.3 Trends in Annual Prevalence (%) of Use Disorder of Various Substances for Grades 8, 10, and 12 Combined

																	PEAK YEAR–2021 CHANGE		LOW YEAR–2021 CHANGE	
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019[E]	2020	2021	2020–2021 CHANGE	ABSOLUTE CHANGE	PROPORTIONAL CHANGE (%)[a]	ABSOLUTE CHANGE	PROPORTIONAL CHANGE (%)[a]
Any illicit drug[c]	24.8	24.9	25.9	27.3	27.6	27.1	28.6‡	27.2	26.8	25.3	26.5	27.1	**27.7**	27.3	*19.9*	−7.4 sss	−7.8 sss	−28.1	—	—
Any illicit drug other than marijuana[c]	12.4	11.9	11.6	11.8	11.3	10.8	11.4‡	**10.9**	10.5	9.7	9.4	9.3	9.0	9.2	*5.6*	−3.6 sss	−5.3 sss	−48.7	—	—
Any illicit drug including inhalants[c]	27.6	27.6	28.5	29.7	29.8	29.0	30.5‡	28.5	28.4	26.3	28.3	28.8	29.0	**29.2**	*21.5*	−7.8 sss	−7.8 sss	−26.6	—	—
Marijuana/hashish	21.4	21.5	22.9	24.5	25.0	24.7	25.8	24.2	23.7	22.6	23.9	24.3	25.2	2	*17.9*	−6.7 sss	−12.1 sss	−40.3	—	—
Synthetic marijuana	—	—	—	—	—	**8.0**	6.4	4.8	4.2	3.1	2.8	2.6	2.9	2.2	*1.6*	−0.6 ss	−6.4 sss	−80.3	—	—
Inhalants	6.4	6.4	6.1	6.0	5.0	4.5	3.8	3.6	3.2	*2.6*	2.9	2.9	2.9	3.4	2.9	−0.5	−7.3 sss	−71.6	+0.2	+0.3
Hallucinogens	3.8	3.8	3.5	3.8	3.7	3.2	3.1	2.8	2.8	2.8	2.7	2.7	2.9	3.4	*2.4*	−1.0 s	−3.6 sss	−60.4	—	—
LSD	1.7	1.9	1.6	1.8	1.8	1.6	1.6	1.7	1.9	2.0	2.1	2.0	2.2	2.5	1.5	−0.9 ss	−4.8 sss	−75.6	+0.1	+0.6
Hallucinogens other than LSD	3.3	3.2	3.0	3.3	3.1	2.7	2.5	2.1	1.9	1.8	1.8	1.7	1.9	2.0	*1.7*	−0.3	−2.4 sss	−58.3	—	—
Ecstasy (MDMA)[d]	3.0	2.9	3.0	3.8	3.7	2.5	2.8‡	**3.4**	2.4	1.8	1.7	1.5	1.6	1.3	*0.8*	−0.5 s	−2.6 sss	−76.0	—	—
Salvia	—	—	—	3.5	**3.6**	2.7	2.3	1.4	1.2	1.2	0.9	0.8	0.8	0.8	*0.5*	−0.3 s	−3.1 sss	−85.1	—	—
Cocaine	3.4	2.9	2.5	2.2	2.0	1.9	1.8	1.6	1.7	1.4	1.6	1.5	1.4	1.4	*0.7*	−0.8 ss	−3.8 sss	−85.0	—	—
Crack	1.5	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.8	0.6	0.7	0.6	0.7	0.6	*0.4*	−0.2	−2.0 sss	−82.6	—	—
Other cocaine	2.9	2.6	2.1	1.9	1.7	1.7	1.5	1.5	1.5	1.2	1.3	1.3	1.3	1.4	*0.5*	−0.9 sss	−3.5 sss	−86.6	—	—
Heroin	0.8	0.8	0.8	0.8	0.7	0.6	0.6	0.5	0.4	0.3	0.3	0.3	0.3	0.2	*0.2*	−0.1	−1.1 sss	−85.5	—	—
With a needle	0.5	0.5	0.5	0.6	0.5	0.4	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	*0.1*	0.0	−0.6 sss	−84.3	—	—
Without a needle	0.7	0.6	0.5	0.6	0.5	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	0.1	*0.1*	0.0	−1.0 sss	−92.7	—	—
OxyContin	3.5	3.4	**3.9**	3.8	3.4	2.9	2.9	2.4	2.3	2.1	1.9	1.7	1.7	1.4	*0.9*	−0.5	−3.0 sss	−77.3	—	—
Vicodin	6.2	6.1	6.5	5.9	5.1	4.3	3.7	3.0	2.5	1.8	1.3	1.1	1.0	0.9	*0.6*	−0.2	−5.9 sss	−90.6	—	—
Amphetamines[c]	6.5	5.8	5.9	6.2	5.9	5.6	7.0‡	**6.6**	6.2	5.4	5.0	5.0	4.6	4.6	*2.7*	−1.9 sss	−3.9 sss	−59.5	—	—
Ritalin	2.8	2.6	2.5	2.2	2.1	1.7	1.7	1.5	1.4	1.1	0.8	0.8	0.9	1.0	*0.5*	−0.6	−3.7 sss	−88.3	—	—
Adderall	—	—	4.3	**4.5**	4.1	4.4	4.4	4.1	4.5	3.9	3.5	3.5	3.1	3.3	*1.7*	−1.6 sss	−2.8 sss	−61.3	—	—
Methamphetamine	1.4	1.3	1.3	1.3	1.2	1.0	1.0	0.8	0.6	0.5	0.5	0.5	0.5	0.7	*0.2*	−0.5 ss	−3.9 sss	−96.1	—	—
Bath salts (synthetic stimulants)	—	—	—	—	—	0.9	**0.9**	0.8	0.7	0.8	*0.5*	0.7	—	—	—	—	—	—	—	—
Tranquilizers	4.5	4.3	4.5	4.4	3.9	3.7	3.3	3.4	3.4	3.5	3.6	3.2	3.1	2.7	*1.2*	−1.4 sss	−4.3 sss	−77.8	—	—
OTC cough/cold medicines	5.0	4.7	5.2	4.8	4.4	4.4	4.0	3.2	3.1	3.2	3.0	3.2	2.8	3.7	*2.7*	−1.1 s	−2.7 sss	−50.3	—	—
Rohypnol	0.8	0.7	0.6	0.8	0.9	0.7	0.6	0.5	0.5	0.7	0.5	0.4	0.5	**1.0**	*0.2*	−0.7 sss	−0.7 sss	−71.3	—	—
GHB[b]	0.7	0.9	0.9	0.8	*0.8*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Ketamine[b]	*1.0*	1.2	1.3	1.2	1.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Continued

Table 157.3 Trends in Annual Prevalence (%) of Use Disorder of Various Substances for Grades 8, 10, and 12 Combined—cont'd

																	PEAK YEAR–2021 CHANGE		LOW YEAR–2021 CHANGE	
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019[E]	2020	2021	2020–2021 CHANGE	ABSOLUTE CHANGE	PROPORTIONAL CHANGE (%)[a]	ABSOLUTE CHANGE	PROPORTIONAL CHANGE (%)[a]
Alcohol	50.2	48.7	48.4	47.4	45.3	44.3	42.8	40.7	39.9	36.7	36.7	36.1	35.9	38.3	*30.2*	−8.1 sss	−31.1 sss	−50.7	—	—
Been drunk	29.7	28.1	28.7	27.1	25.9	26.4	25.4	23.6	22.5	20.7	20.4	20.0	19.5	22.1	*15.5*	−6.6 sss	−21.4 sss	−57.9	—	—
Flavored alcoholic beverages	40.8	39.0	37.8	35.9	33.7	32.5	31.3	29.4	28.8	25.3	25.9	26.1	24.6	26.5	*20.0*	−6.5 sss	−24.5 sss	−55.1	—	—
Alcoholic beverages containing caffeine	—	—	—	—	**19.7**	18.6	16.6	14.3	13.0	11.2	10.6	10.1	9.2	8.6	*7.8*	−0.8 sss	−11.9 sss	−60.3	—	—
Any vaping	—	—	—	—	—	—	—	—	—	—	*21.5*	28.9	**31.9**	30.7	22.1	−8.6 sss	−9.9 sss	−30.9	+0.6	+2.6
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	*13.9*	21.6	**27.3**	27.1	19.2	−7.9 sss	−8.1 sss	−29.7	+5.3 sss	+37.7
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	*6.8*	9.9	15.6	**16.3**	11.6	−4.7 ss	−4.7 ss	−28.9	+4.8 sss	+69.7
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	17.2	**21.8**	18.6	15.8	*10.0*	−5.8 sss	−11.8 sss	−54.3	—	—
Juul	—	—	—	—	—	—	—	—	—	—	—	—	**23.8**	20.6	*9.1*	−11.5 sss	−14.7 sss	−61.7	—	—
Dissolvable tobacco products	—	—	—	—	—	**1.4**	1.4	1.2	1.1	0.9	0.9	1.0	1.0	0.9	*0.7*	−0.2	−0.7 s	−48.7	—	—
Snus	—	—	—	—	—	**5.6**	4.8	4.1	3.8	3.6	2.6	3.0	2.2	2.7	*1.6*	−1.1 ss	−4.0 sss	−72.0	—	—
Steroids	1.1	1.1	1.0	0.9	0.9	0.9	0.9	0.9	1.0	0.8	0.8	0.8	0.9	1.1	*0.4*	−0.7 sss	−1.6 sss	−79.5	—	—

[a]The proportional change is the percent by which the most recent year deviates from the peak year (or the low year) for the drug in question. So, if a drug was at 20% prevalence in the peak year and declined to 10% prevalence in the most recent year, that would reflect a proportional decline of 50%.

[b]Question was discontinued among 8th and 10th graders in 2012.

[c]In 2013, for the questions on the use of amphetamines, the text was changed on two of the questionnaire forms for 8th and 10th graders and four of the questionnaire forms for 12th graders. This change also affected the any illicit drug indices. Data presented here include only the changed forms beginning in 2013.

[d]In 2014, the text was changed on one of the questionnaire forms for 8th, 10th, and 12th graders to include "molly" in the description. The remaining forms were changed in 2015. Data for both versions of the question are presented here.

[e]Drug prevalence results in 2019 combine results from paper-and-pencil surveys with those completed using electronic tablets. In 2019, students in a randomly selected half of schools completed MTF surveys on paper-and-pencil and students in the other half completed the surveys using electronic tablets. Analysis of this randomized controlled trial demonstrated that these results did not significantly differ across survey mode (Miech RA, Couper MP, Heeringa SG, et al. The impact of survey mode on US national estimates of adolescent drug prevalence: results from a randomized controlled study, *Addiction*). Results for student attitudes and beliefs in 2019 are based on answers from paper-and-pencil surveys only because these appear more susceptible to survey mode effects.

Notes: – indicates data not available. ‡ indicates a change in the question text. When a question change occurs, peak levels after that change are used to calculate the peak year to current year difference. Values in bold equal peak levels since 1991. Values in *italics* equal peak level before wording change. Level of significance of difference between classes: s = 0.05, ss = 0.01, sss = 0.001. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is the result of rounding.

Modified from Miech RA, Johnston LD, O'Malley PM, et al. *Monitoring the Future National Survey Results on Drug Use, 1975–2021: Volume I, Secondary School Students.* Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2022. Available https://monitoringthefuture.org/wp-content/uploads/2022/12/mtf2022.pdf

amphetamines (18%), oxycodone (15%), methylphenidate (14%), and tramadol (11%). Many of these substances can be found in the home of friends; some are over-the-counter (OTC) substances (dextromethorphan, pseudoephedrine), whereas others are purchased from substance dealers at schools and colleges. Adolescents often combine opioids with marijuana, alcohol, cocaine, and tranquilizers, putting them at risk for serious complications and overdose.

CLINICAL MANIFESTATIONS

Although manifestations vary by the specific substance of use, adolescents who use substances often present in an office setting with no obvious physical findings. Substance use disorder is more frequently detected in adolescents who experience trauma such as motor vehicle crashes, bicycle injuries, or violence. Eliciting appropriate historical information regarding substance use, followed by blood alcohol and urine substance screens, is recommended in emergency settings. Although waning in popularity, the illicit substances known as "club drugs" still need to be considered in the differential diagnosis of a teen with an altered sensorium. An adolescent presenting to an emergency setting with an impaired sensorium should be evaluated for substance use as a part of the differential diagnosis (Table 157.4). Screening for substance use is recommended for patients with psychiatric and behavioral diagnoses. Other clinical manifestations of substance use are associated with the route of use; intravenous substance use is associated with venous "tracks" and needle marks, and nasal mucosal injuries are associated with nasal insufflation of substances. Seizures can be a direct effect of substances such as cocaine, synthetic marijuana, and amphetamines or an effect of substance withdrawal in the case of barbiturates or tranquilizers.

SCREENING FOR SUBSTANCE USE DISORDERS

In a primary care setting the annual health maintenance examination provides an opportunity for identifying adolescents with substance use disorder. The direct questions and the assessment of school performance, family relationships, and peer activities may necessitate a more in-depth interview if there are suggestions of difficulties in those areas. Several self-report screening questionnaires also are available, with varying degrees of standardization, length, and reliability. The **CRAFFT mnemonic** is specifically designed to screen for adolescents' substance use in the primary care setting (Table 157.5). Privacy and confidentiality must be established when asking the teen about specifics of their substance experimentation or use. Interviewing the parents can provide additional perspective on early warning signs that go unnoticed or disregarded by the teen. Examples of early warning signs of teen substance use disorder are change in mood, appetite, or sleep pattern; decreased interest in school or school performance; loss of weight; secretive behavior about social plans; or valuables such as money or jewelry missing from the home. The use of urine substance screening is recommended when select circumstances are present: (1) psychiatric symptoms to rule out comorbidity or dual diagnoses, (2) significant changes in school performance or other daily behaviors, (3) frequently occurring accidents, (4) frequently occurring episodes of respiratory problems, (5) evaluation of serious motor vehicular or other injuries, and (6) as a monitoring procedure for a recovery program. Most initial screening uses an immunoassay method, such as the enzyme-multiplied immunoassay technique, followed by a confirmatory test using highly sensitive, highly specific gas chromatography–mass spectrometry. The substances that can cause false-positive results should be considered, especially when there is a discrepancy between

Table 157.4 Most Common Toxic Syndromes

ANTICHOLINERGIC SYNDROMES	
Common signs	Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimsonweed and *Amanita muscaria*).
SYMPATHOMIMETIC SYNDROMES	
Common signs	Delusions, paranoia, tachycardia (or bradycardia if the substance is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxyamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxyethamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), some synthetic marijuana, and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
OPIATE, SEDATIVE, OR ETHANOL INTOXICATION	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.
CHOLINERGIC SYNDROMES	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.

From Kulig K. Initial management of ingestions of toxic substances. *N Engl J Med* 1992;326:1677–1681.

Table 157.5 CRAFFT Mnemonic Tool

- Have you ever ridden in a **C**ar driven by someone (including yourself) who was high or had been using alcohol or substances?
- Do you ever use alcohol or substances to **R**elax, feel better about yourself, or fit in?
- Do you ever use alcohol or substances while you are by yourself (**A**lone)?
- Do you ever **F**orget things you did while using alcohol or substances?
- Do your **F**amily or **F**riends ever tell you that you should cut down on your drinking or substance use?
- Have you ever gotten into **T**rouble while you were using alcohol or substances?

From the Center for Adolescent Substance Use Research (CeASAR). *The CRAFFT Screening Interview.* (Copyright John R. Knight, MD, Boston Children's Hospital, 2015.)

the physical findings and the urine substance screen result. Current guidelines strongly discourage routine home-based or school-based testing.

DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) no longer identifies substance use disorder as those of *abuse* or of *dependence*. A substance use disorder is defined by a cluster of cognitive, behavioral, and physiologic symptoms that indicate that an adolescent is using a substance even though there is evidence that the substance is harming the adolescent. Even after detoxification, a substance use disorder may leave persistent changes in brain circuits with resulting behavioral changes. There are 11 criteria that describe a pathologic pattern of behaviors related to use of the substance, falling into four categories: impaired control, social impairment, increased risk, and pharmacologic criteria. The first category, **impaired control**, describes an individual taking increasing amounts of the substance who expresses a persistent desire to decrease use, with unsuccessful efforts. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects and expresses an intense desire for the substance, usually in settings where the substance had been available, such as a specific type of social situation. The second cluster of criteria (5-7) reflects **social impairment,** including the inability to perform as expected in school, at home, or at a job; increasing social problems; and withdrawing from the family. The third cluster addresses **increased risk** associated with use of the substance, and the fourth cluster addresses **pharmacologic responses** (tolerance and/or withdrawal). The total number of criteria present is associated with a determination of a *mild, moderate,* or *severe* disorder.

These criteria may have limitations with adolescents because of differing patterns of use, developmental implications, and other age-related consequences. Adolescents who meet diagnostic criteria should be referred to a program for substance use disorder treatment unless the primary care physician has additional training in addiction medicine.

COMPLICATIONS

Substance use disorder in adolescence is associated with significant comorbidities and acts of juvenile delinquency. Youth may engage in other high-risk behaviors such as robbery, burglary, substance dealing, or prostitution for the purpose of acquiring the money necessary to buy substances. Regular use of any substance eventually diminishes judgment and is associated with unprotected sexual activity with its consequences of pregnancy and sexually transmitted infections, including HIV, as well as physical violence. Substance use disorder is closely associated with trauma in the adolescent population. Several studies of adolescent trauma victims have identified cannabinoids and cocaine in blood and urine samples in significant proportions (40%), in addition to the more common identification of alcohol. Any use of injected substances involves the risk of hepatitis B and C viruses and HIV (see Chapter 322).

TREATMENT

Adolescent substance use disorder is a complex condition requiring a multidisciplinary approach that attends to the needs of the individual, not just substance use. Fundamental principles for treatment include accessibility to treatment, using a multidisciplinary approach, employing individual or group counseling, offering mental health services, monitoring of substance use while in treatment, and understanding that recovery from substance use/addiction may involve multiple relapses. For most patients, remaining in treatment for a minimum period of 3 months may result in a significant improvement.

PROGNOSIS

For adolescent substance users who have been referred to a substance treatment program, positive outcomes are directly related to regular attendance in posttreatment groups. Outcomes are worse for males with learning problems or conduct disorder than for those without such disorders. Peer use patterns and parental use have a major influence on outcome for males. The chronicity of a substance use disorder makes **relapse** an issue that must always be considered when managing patients after treatment, and appropriate assistance from a healthcare professional qualified in substance use disorder treatment should be obtained.

Table 157.6 Domains of Risk and Protective Factors for Substance Use Prevention

RISK FACTORS	DOMAIN	PROTECTIVE FACTORS
Early aggressive behavior	Individual	Self-control
Lack of parental supervision	Family	Parental monitoring
Substance use	Peer	Academic competence
Substance availability	School	Anti–substance use disorder policies
Poverty	Community	Strong neighborhood attachment

From National Institute on Substance Use. Preventing Substance Use Disorder Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders, NIH Pub No 04-4212(B), 2nd ed. Bethesda, MD: NIDA; 2003.

PREVENTION

Preventing substance use disorder among adolescents requires prevention efforts aimed at the individual, family, school, and community levels. The National Institute on Drug Abuse (NIDA) of the U.S. National Institutes of Health has identified essential principles of successful prevention programs. Programs should enhance *protective factors* (parent support) and reduce *risk factors* (poor self-control), should address all forms of substance use (legal and illegal), should address the specific type(s) of substance use within an identified community, and should be culturally competent to improve effectiveness (Table 157.6). Prevention programs need to target emotionally and socially intense times such as life/school transitions for adolescents to adequately anticipate potential substance use disorder. Examples of effective research-based substance use prevention programs featuring a variety of strategies are listed on the NIDA website (www.drugabuse.gov) and on the Center for Substance Abuse Prevention website (www.prevention.samhsa.gov).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.1 Alcohol

Cora Collette Breuner

Alcohol is the most widely used substance of abuse among America's youth, and a higher proportion use alcohol than use tobacco or other substances, but the numbers are trending down. According to the 2020 *Monitoring the Future (MTF)* study, by the end of high school, 61.5% of students had reported ever using alcohol and 26% of eighth graders had reported ever using alcohol. Early initiation of alcohol use increases the risk for a variety of developmental problems during adolescence and is frequently an indicator of future substance use. Drinking by children, adolescents, and young adults has serious negative consequences for the individuals, their families, their communities, and society as a whole. Underage drinking contributes to a wide range of costly health and social problems, including motor vehicle crashes (the greatest single mortality risk for underage drinkers); suicide; interpersonal violence (e.g., homicides, assaults, rapes); unintentional injuries such as burns, falls, and drowning; brain impairment; alcohol dependence; risky sexual activity; academic problems; and alcohol and other drug poisoning.

Multiple factors can affect a young teen's risk of developing a drinking problem at an early age (Table 157.7). One third of high school seniors admit to combining drinking behaviors with other risky behaviors, such as driving or taking additional substances. **Binge drinking**

Table 157.7 Risk Factors for a Teen Developing a Drinking Problem

FAMILY RISK FACTORS

- Low parental supervision
- Poor parent to teen communication
- Family conflicts
- Severe or inconsistent family discipline
- Having a parent with an alcohol or substance problem

INDIVIDUAL RISK FACTORS

- Poor impulse control
- Emotional instability
- Thrill-seeking behaviors
- Behavioral problems
- Perceived risk of drinking is low
- Begins drinking before age 14 yr

remains especially problematic among older teens and young adults; 31% of high school seniors report having five or more drinks in a row in the last 30 days. Higher rates of alcohol use disorder are seen in males (23.8%) than in females (19.8%). Teens with binge-drinking patterns are more likely to be assaulted, engage in high-risk sexual behaviors, have academic problems, and be injured than those teens without binge-drinking patterns.

Alcohol contributes to more deaths in young individuals in the United States than all the illicit substances combined. Among studies of adolescent trauma victims, alcohol is reported to be present in 32–45% of hospital admissions. Motor vehicle crashes are the most frequent type of event associated with alcohol use, but the injuries span several types, including self-inflicted wounds.

Alcohol is often mixed with energy drinks (caffeine, taurine, sugars), which can result in a spectrum of alcohol-related negative behaviors. Caffeine may counter the sedative effects of alcohol, resulting in more alcohol consumption and a perception of not being intoxicated, thus leading to risk-taking behavior such as driving while intoxicated. In addition, aggressive behavior, including sexual assaults and motor vehicle or other injuries, has been reported. Both alcohol and caffeine overdoses have also been reported.

PHARMACOLOGY AND PATHOPHYSIOLOGY

Alcohol (ethyl alcohol or ethanol) is rapidly absorbed in the stomach and is transported to the liver and metabolized by two pathways. The primary metabolic pathway contributes to the excess synthesis of triglycerides, a phenomenon that is responsible for producing a **fatty liver**, even in those who are well nourished. Engorgement of hepatocytes with fat causes necrosis, triggering an inflammatory process **(alcoholic hepatitis)**, later followed by fibrosis, the hallmark of **cirrhosis**. Early hepatic involvement may result in elevation in γ-glutamyltransferase (GGT) and serum glutamic-pyruvic transaminase (alanine transaminase). The second metabolic pathway, which is used at high serum alcohol levels, involves the microsomal enzyme system of the liver, in which the cofactor is reduced to nicotinamide-adenine dinucleotide phosphate. The net effect of activation of this pathway is to decrease metabolism of substances that share this system and to allow for their accumulation, enhanced effect, and possible toxicity.

CLINICAL MANIFESTATIONS

Alcohol acts primarily as a central nervous system (CNS) depressant. It produces euphoria, grogginess, talkativeness, impaired short-term memory, and an increased pain threshold. Alcohol's ability to produce vasodilation and hypothermia is also centrally mediated. At very high serum levels, respiratory depression occurs. Its inhibitory effect on pituitary antidiuretic hormone release is responsible for its diuretic effect. The gastrointestinal (GI) complications of alcohol use can occur from a single large ingestion. The most common is acute **erosive gastritis**, manifesting as epigastric pain, anorexia, vomiting, and heme-positive stools. Less frequently, vomiting and mid-abdominal pain may be caused by acute alcoholic **pancreatitis**; the diagnosis is confirmed by the finding of elevated serum amylase and lipase levels.

DIAGNOSIS

Primary care settings provide the opportunity to screen teens for alcohol use disorder or problem behaviors. Brief alcohol screening instruments such as CRAFFT (see Table 157.5) perform well in a clinical setting as techniques to identify alcohol use disorders A score of 2 or higher is a positive screen, indicating a need for additional assessment.

Teenagers in the early phases of alcohol use exhibit few physical findings. Recent use of alcohol may be reflected in elevated GGT and aspartate transaminase levels.

In acute care settings the **alcohol overdose syndrome** should be suspected in any teenager who appears disoriented, lethargic, or comatose. Although the distinctive aroma of alcohol may assist in diagnosis, confirmation by analysis of blood is recommended. At levels >200 mg/dL, the adolescent is at risk of death, and levels >500 mg/dL (median lethal dose) are usually associated with a fatal outcome. *When the level of obtundation appears excessive for the reported blood alcohol level, head trauma, hypoglycemia, or ingestion of other substances should be considered as possible confounding factors.*

TREATMENT

The usual mechanism of death from alcohol overdose syndrome is **respiratory depression**; artificial ventilatory support must be provided until the liver can eliminate sufficient amounts of alcohol from the body. In a patient *without* chronic alcohol use, it generally takes 20 hours to reduce the blood level of alcohol from 400 mg/dL to zero. Dialysis should be considered when the blood level is >400 mg/dL. As a follow-up to acute treatment, referral for treatment of the alcohol use disorder is indicated. Group counseling, individualized counseling, and multifamily educational intervention have proved to be effective interventions for teens.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.2 Tobacco, E-Cigarettes, and Other Tobacco Products

Brian P. Jenssen

CIGARETTES

Tobacco use and addiction often start in childhood or adolescence, a period when the brain has heightened susceptibility to nicotine addiction. Nearly 90% of adult cigarette smokers began smoking before age 18. Factors associated with youth tobacco use include exposure to smokers (friends, parents), tobacco availability, low socioeconomic status, poor school performance, low self-esteem, lack of perceived risk of use, and lack of skills to resist influences to use tobacco.

The landscape of tobacco product use among youth has shifted dramatically over the past decade. Various sources are used to capture data on tobacco use. Similar trends have been observed across cross-sectional surveys with data on youth use, including, for example, the National Youth Tobacco Survey, Monitoring the Future, and the Youth Risk Behavior Surveillance system.

Based on 2022 data, current use of any tobacco product was reported by 11.3% (3.08 million) of all students, including 16.5% (2.51 million) of high school and 4.5% (530,000) of middle school students. E-cigarettes were the most used tobacco product among high school (14.1%; 21.4 million) and middle school (3.3%; 380,000) students. Among high school students, 5.2% reported current use of any combustible tobacco product. By product, current use among high school students was highest for e-cigarettes (14.1%), followed by cigars (2.8%), cigarettes (2.0%), smokeless tobacco (1.6%), hookahs (1.5%), nicotine pouches (1.4%), heated tobacco products (1.1%), and pipe tobacco (0.7%). Among middle school students, 1.6% reported current use of any combustible tobacco product. By type of product, current use among middle school students

was highest for e-cigarettes (3.3%), followed by cigarettes (1.0%), smokeless tobacco (0.7%), heated tobacco products (0.7%), cigars (0.6%), hookahs (0.5%), nicotine pouches (0.5%), and pipe tobacco (0.3%).

Tobacco use tends to be higher among males compared to females and by those identifying as lesbian, gay, or bisexual compared to heterosexual or uncertain sexual identity. Tobacco is used by teens in all regions of the world, although the form of tobacco used differs. In the Americas and Europe, cigarette smoking is the predominant form of tobacco use, followed by cigars and smokeless tobacco; in the Eastern Mediterranean, hookah use is prevalent; in Southeast Asia, smokeless tobacco products are used; in the Western Pacific, betel nut is chewed with tobacco; and pipe, snuff, and rolled tobacco leaves are used in Africa. Cigarette use by teens in low- and middle-income nations is increasing.

PHARMACOLOGY

Nicotine, the primary active ingredient in cigarettes, is addictive. Nicotine is absorbed by multiple sites in the body, including the lungs, skin, GI tract, and buccal and nasal mucosa. The action of nicotine is mediated through nicotinic acetylcholine receptors located on noncholinergic presynaptic and postsynaptic sites in the brain and causes increased levels of dopamine. Nicotine also stimulates the adrenal glands to release epinephrine, causing an immediate elevation in blood pressure, respiration, and heart rate. The dose of nicotine delivered to the user in a cigarette depends on a variety of factors, including puffing characteristics. A smoker typically takes 10 puffs within the span of 5 minutes and absorbs 1-2 mg of nicotine (range: 0.5-3 mg). The Food and Drug Administration (FDA) is planning to reduce the permissible amount of nicotine in cigarettes. **Cotinine**, the major metabolite of nicotine, has a biologic half-life of 19-24 hours and can be detected in urine, serum, and saliva.

CLINICAL MANIFESTATIONS

Cigarettes are addictive by design and result in life-shortening diseases in half of their long-term users. Each year, approximately 480,000 deaths are attributable to smoking, responsible for 1 of every 5 deaths and 1 of every 3 cancer deaths in the United States. Cigarette smoking has severe adverse health consequences for youth and young adults, including increased prevalence of chronic cough, sputum production, wheezing, and worsening asthma. Smoking during pregnancy increases prenatal and perinatal morbidity and mortality, either causing or exacerbating the risks of preterm birth, low birthweight, congenital malformations, stillbirth, and sudden infant death syndrome (SIDS) and sudden unexplained infant death (SUID). **Withdrawal** symptoms, including irritability, decreased concentration, increased appetite, and strong cravings for tobacco, can occur when adolescents try to quit.

ELECTRONIC CIGARETTES (E-CIGARETTES)

E-cigarettes are handheld devices that produce an aerosol created from a solution of nicotine, flavoring chemicals, humectants such as propylene glycol, and often other constituents unknown and unadvertised to the consumer. There is wide variability in terminology, product design, and engineering of these products, with alternative names including e-cigs, electronic cigars, electronic hookah, e-hookah, and vaping devices. The tobacco industry continues to develop new products that contain nicotine but may not be recognized as a tobacco product by teens. The unique flavors offered in e-cigarette solutions, the majority of which are confectionary in nature and appealing to children, have been shown to encourage youth experimentation, regular use, and addiction.

Known harmful toxicants and carcinogens have been found in e-cigarette solutions, in device emissions, and within the bodies of adolescent users. Multiple systematic reviews and meta-analyses have found e-cigarette use is associated with an increased risk of subsequent cigarette smoking initiation and current cigarette smoking in young people. There is a critical need for e-cigarette regulation, legislative action, and counter-promotion to prevent children, adolescents, and young adults from transitioning from e-cigarettes to traditional cigarettes and minimize the potential public health harm from e-cigarette use. The FDA should regulate all tobacco and nicotine products to protect public health.

HOOKAH

Hookah (water pipe) smoking uses specially treated tobacco that comes in a variety of flavors. Many teens believe incorrectly that hookah does not contain nicotine. Emerging evidence indicates that hookah may involve comparable health risks to cigarettes, including nicotine dependence. Both human and machine simulation studies of hookah use consistently find that smoke content and user toxicant exposure, including carbon monoxide, tar, and nicotine, are at least comparable to that of cigarettes. Secondhand smoke from hookahs can be a health risk for nonsmokers exposed to harmful toxicants.

TREATMENT

The 2020 U.S. Surgeon Report on smoking cessation emphasizes that smoking cessation is beneficial at any age, reducing the risk of premature death, adding as much as a decade to life expectancy, while also reducing the risk of many adverse health effects. More than half of adolescents who use tobacco products report that they want to quit, and more than half report making at least one quit attempt in the past year. Thus for adolescents who want to stop tobacco or e-cigarette use, it is reasonable to consider referral to behavioral cessation supports. Behavioral interventions for adults have significant evidence supporting their effectiveness, and many youth and young adult supports are modeled off of these programs.

Little research has been conducted assessing the effectiveness of pharmacologic therapies for combustible tobacco use among adolescents. The 2020 U.S. Preventive Services Task Force recommendation concluded there was inadequate evidence on the benefits and harms of medications for tobacco cessation in children and adolescents. Nonetheless, consensus panels recommend that for adolescents who want to stop tobacco or e-cigarette use with moderate to severe tobacco dependence, it is reasonable to consider pharmacotherapy, especially nicotine replacement therapy (NRT). Cessation medications are not approved by the FDA for use with children or adolescents, and NRT cannot be purchased OTC by persons younger than 18 years of age. However, cessation medications can be prescribed for and used by youth under the supervision of a physician. NRT is also available as a patch, gum, inhaler, nasal spray, lozenge, or microtab (Table 157.8). Tobacco dependence treatment for youth should be tailored to the patient's level of nicotine dependence and readiness for change. Given the very high rates of nonadherence during therapy and relapse after discontinuation of therapy among adolescents in the trials of these medications, close follow-up is recommended.

Pediatric clinicians can connect patients to effective behavioral interventions, including telephone, text message, smartphone app, internet, and community-based resources. Free telephone-based treatment (800-QUIT-NOW) has been shown to improve smoking cessation rates. Smoke-free TXT, offered by the National Cancer Institute, engages teens to quit smoking using free, daily text messaging. Teens can sign up online (teen.smokefree.gov) or text QUIT to iQUIT (47848). A smartphone-based app, quitSTART, helps teens track cravings, monitor moods, use cessation tips, and follow quitting attempts. Truth Initiative has an evidence-based program, This Is Quitting, which is targeted to teens who want to stop using e-cigarettes (https://truthinitiative.org/thisisquitting). The American Academy of Pediatrics offers a brief, practical guide that is designed to support pediatric health clinicians in providing behavioral and pharmacologic support to help youth quit (https://services.aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 157.8 Smoking Cessation Pharmacotherapy Available in the United States*

THERAPY BRAND	NAME	STRENGTHS	FDA-APPROVED ADULT DOSING	AVAILABILITY†	STUDIED IN ADOLESCENTS
NICOTINE REPLACEMENT THERAPY					
Gum‡	Nicorette	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke ≥25 cigarettes a day; otherwise, 2-mg strength should be used. Wk 1-6: 1 piece every 1-2 hr Wk 7-9: 1 piece every 2-4 hr Wk 10-12: 1 piece every 4-8 hr	OTC*	Yes
Inhaler	Nicotrol Inhaler	4 mg	6-16 cartridges a day for up to 12 wk	Rx	No
Lozenge	Commit, Nicorette mini	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke their first cigarette within 30 min of waking; otherwise, 2-mg strength should be used. Wk 1-6: 1 lozenge every 1-2 hr Wk 7-9: 1 lozenge every 2-4 hr Wk 10-12: 1 lozenge every 4-8 hr	OTC	No
Nasal spray	Nicotrol NS	0.5 mg/spray	1-2 sprays/hr up to a maximum of 80 sprays per day	Rx	Yes
Transdermal patch‡	NicoDerm CQ	7, 14, 21 mg/24 hr	For patients who smoke >10 cigarettes daily: Step 1: one 21-mg patch daily for wk 1-6 Step 2: one 14-mg patch daily for wk 7-8 Step 3: one 7-mg patch daily for wk 9-10 For patients who smoke <10 cigarettes daily: Begin with 14-mg patch daily for 6 wk, followed by 7-mg patch for 2 wk.	OTC	Yes
NONNICOTINE THERAPY					
Bupropion SR‡	Zyban	150-mg sustained-release tablets	150 mg PO in morning for 3 days, then increase to 150 mg PO bid	Rx	Yes
Varenicline	Chantix	0.5-, 1-mg tablets	0.5 mg PO in morning for 3 days; increase to 0.5 mg PO bid for 4 days, then increase to 1 mg PO bid	Rx	Yes

*None are FDA approved for use in patients younger than 18 years of age.
†OTC, Over the counter; Rx, prescription product; PO, by mouth (orally); bid, twice daily.
‡Generics are available.
From JP Karpinski et al: Smoking cessation treatment for adolescents. *J Pediatr Pharmacol Ther* 2010;15:249–260

157.3 Marijuana

Cora Collette Breuner

Marijuana (cannabis, pot, weed, hash, grass), derived from the *Cannabis sativa* hemp plant, is the most commonly used illicit substance. The main active chemical, tetrahydrocannabinol **(THC)**, is responsible for its hallucinogenic properties. THC is absorbed rapidly by the nasal or oral routes, producing a peak of subjective effect at 10 min and 1 hour, respectively. Marijuana is generally smoked as a cigarette (reefer, joint), in a pipe, or ingested (edibles). Although there is much variation in content, each cigarette contains 8–10% THC. Another popular form that is smoked, a "blunt," is a hollowed-out small cigar (tobacco leaf) refilled with marijuana, and thus also contains nicotine. Marijuana products (hash oil or leaf) can also be used in some vaping devices or hookah pens. **Hashish** is the concentrated THC resin in a sticky black liquid or oil. Although marijuana use by U.S. teens has declined in the last decade, ~25% of high school students have used marijuana at least once during the previous 30 days. About 8% of students report having tried marijuana before age 13, with a range of 4.3–18.5% across various states, indicating the need for early prevention efforts. Adolescents living in states where medical marijuana is legal report a higher use of cannabis edibles. It is important to recognize that as perceived harm drops, marijuana use increases. (Fig. 157.3). In addition, the potency of cannabis has increased substantially in part to marketing and legal sales.

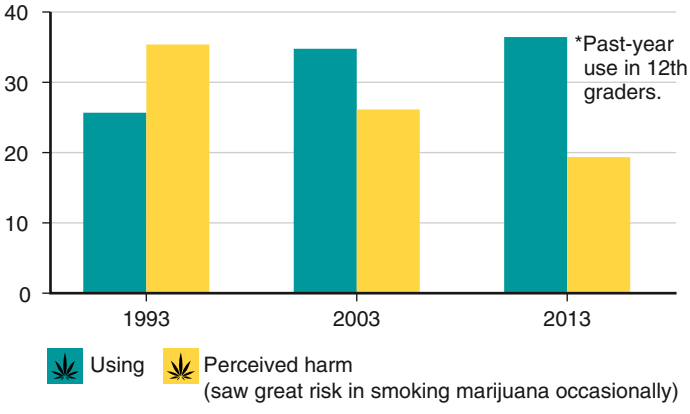

Fig. 157.3 As the perceived harm of marijuana drops, use disorder goes up. The 36.4% using in 2013 equates to about 11 students in the average class. *(From NIH National Institute on Substance Use.)*

Table 157.9 Acute and Chronic Adverse Effects of Cannabis Use

ACUTE ADVERSE EFFECTS

- Anxiety and panic, especially in naïve users
- Psychotic symptoms (at high doses)
- Road crashes if a person drives while intoxicated
- Cannabis hyperemesis syndrome

CHRONIC ADVERSE EFFECTS

- Cannabis dependence syndrome (in about 1 in 10 users)
- Chronic bronchitis and impaired respiratory function in regular smokers
- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders
- Impaired educational attainment in adolescents who are regular users
- Subtle cognitive impairment in those who are daily users for 10 yr or more
- Impaired tasks of sequencing ability, cognitive processing speed, inhibition, and sustained attention

Modified from Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374:1383–1390.

Table 157.10 Rome IV Criteria for CHS Diagnosis

CATEGORY	FEATURES
Essential	Stereotypical episodic vomiting resembling CVS in terms of onset, duration, and frequency Presentation after prolonged, excessive cannabis use Relief of vomiting episodes by sustained cessation of cannabis use
Supportive remarks	May be associated with pathologic bathing behavior (prolonged hot baths or showers)

CHS, Cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome.
From Zhu JW, Gonsalves CL, Issenman RM, Kam AJ. Diagnosis and acute management of adolescent cannabinoid hyperemesis syndrome: a systematic review. *J Adolesc Health*. 2021;68:246–254, Table 1, p. 248.

CLINICAL MANIFESTATIONS

In addition to the desired effects of elation and euphoria, marijuana may cause impairment of short-term memory, poor performance of tasks requiring divided attention (e.g., those involved in driving), loss of critical judgment, decreased coordination, and distortion of time perception (Table 157.9). Visual hallucinations and perceived body distortions occur rarely, but "flashbacks" or recall of frightening hallucinations experienced under marijuana's influence may occur, usually during stress or with fever.

Smoking marijuana for a minimum of 4 days/week for 6 months appears to result in dose-related suppression of plasma testosterone levels and spermatogenesis, prompting concern about the potential deleterious effect of smoking marijuana before completion of pubertal growth and development. There is an antiemetic effect of oral THC or smoked marijuana, often followed by appetite stimulation, which is the basis of the substance's use in patients receiving cancer chemotherapy.

An **amotivational syndrome** has been described in long-term marijuana users who lose interest in age-appropriate behavior; proof of the causative relationship remains equivocal. Chronic use is associated with increased anxiety and depression, learning problems, poor job performance, hyperemesis, and respiratory problems such as pharyngitis, sinusitis, bronchitis, and asthma (see Table 157.9).

Cannabinoid hyperemesis syndrome (CHS) is characterized by recurrent episodes of vomiting associated with abdominal pain and nausea; patients often find relief by taking a hot shower or bath (Table 157.10). Cannabis use typically has been chronic (>1-2 year) and frequent (multiple times per week). There is considerable similarities between CHS and cyclic vomiting syndrome (see Chapter 390). Treatment of CHS includes stopping marijuana use, antiemetics, and topical capsaicin.

The increased THC content of marijuana of 5- to 15-fold compared to that of the 1970s is related to the observation of a **withdrawal syndrome** occurring 24-48 hours after discontinuing the substance. Heavy users experience malaise, irritability, agitation, insomnia, substance craving, shakiness, diaphoresis, night sweats, and GI disturbance. The symptoms peak by the fourth day and resolve in 10-14 days. Certain substances may interact with marijuana to potentiate sedation (alcohol, diazepam) and stimulation (cocaine, amphetamines) or may be antagonistic (propranolol, phenytoin).

Behavioral interventions, including **cognitive-behavioral therapy (CBT)** and motivational incentives, have shown to be effective in treating marijuana dependency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.4 Inhalants

Cora Collette Breuner

Inhalants, found in many common household products, comprise a diverse group of volatile substances whose vapors can be inhaled to produce psychoactive effects. The practice of inhalation is popular among younger adolescents and decreases with increasing age. Young adolescents are attracted to these substances because of their rapid action, easy availability, and low cost. Products that are abused as inhalants include *volatile solvents* (paint thinners, glue, e-cigarette solvents known as "dripping," toluene, acetone, refrigerants, gasoline, cleaning fluids, correction fluids), *aerosols* (spray paint, nitrous oxide, hair spray), *gases* (propane tanks, lighter fluid), *nitrites* ("poppers" or "video head cleaner"), and *propellants* used in whipped cream dispensers. The most popular inhalants among young adolescents are glue, shoe polish, and spray paint. The various products contain a wide range of chemicals with serious adverse health effects (Table 157.11). **Huffing**, the practice of inhaling fumes, can be accomplished using a paper bag containing a chemical-soaked cloth; spraying aerosols directly into the nose/mouth; or using a balloon, plastic bag, or soda can filled with fumes. The percentage of adolescents using inhalants has remained stable, with 5.8% of high school students reporting having ever used inhalants. Eighth and ninth graders report highest use, suggesting targeted prevention strategies for this age-group.

CLINICAL MANIFESTATIONS

The major effects of inhalants are psychoactive (Table 157.12). The intoxication lasts only a few minutes, so a typical user will huff repeatedly over an extended period (hours) to maintain the high. The immediate effects of inhalants are similar to alcohol: euphoria, slurred speech, decreased coordination, and dizziness. **Toluene**, the main ingredient in model airplane glue and some rubber cements, causes relaxation and pleasant hallucinations for up to 2 hours. Euphoria is followed by violent excitement; coma may result from prolonged or rapid inhalation. **Volatile nitrites**, such as amyl nitrite, butyl nitrite, and related compounds marketed as room deodorizers, are used as euphoriants, enhancers of musical appreciation, and sexual enhancements among older adolescents and young adults. They may result in headaches, syncope, and lightheadedness; profound hypotension and cutaneous flushing followed by vasoconstriction and tachycardia; transiently inverted T waves and depressed ST segments on electrocardiography; methemoglobinemia; increased bronchial irritation;

Table 157.11 Hazards of Chemicals Found in Commonly Used Inhalants

Amyl nitrite, butyl nitrite ("poppers," "video head cleaner"): sudden sniffing death syndrome, suppressed immunologic function, injury to red blood cells (interfering with oxygen supply to vital tissues)

Benzene (found in gasoline): bone marrow injury, impaired immunologic function, increased risk of leukemia, reproductive system toxicity

Butane, propane (found in lighter fluid, hair and paint sprays): sudden sniffing death syndrome via cardiac effects, serious burn injuries (because of flammability)

Freon (used as a refrigerant and aerosol propellant): sudden sniffing death syndrome, respiratory obstruction and death (from sudden cooling/cold injury to airways), liver damage

Methylene chloride (found in paint thinners and removers, degreasers): reduction of oxygen-carrying of blood, changes to the heart muscle and heartbeat

Nitrous oxide ("laughing gas, Whippits, i.e., whipped cream dispensers), **hexane**: death from lack of oxygen to the brain, altered perception and motor coordination, loss of sensation, limb spasms, blackouts caused by blood pressure changes, depression of heart muscle functioning; vitamin B_{12} deficiency

Toluene (found in gasoline, paint thinners and removers, correction fluid): brain damage (loss of brain tissue mass, impaired cognition, gait disturbance, loss of coordination, loss of equilibrium, limb spasms, hearing and vision loss), liver and kidney damage

Trichloroethylene (found in spot removers, degreasers): sudden sniffing death syndrome, cirrhosis of the liver, reproductive complications, hearing and vision damage

Table 157.12 Stages in Symptom Development After Use of Inhalants

STAGE	SYMPTOMS
1: Excitatory	Euphoria, excitation, exhilaration, dizziness, hallucinations, sneezing, coughing, excess salivation, intolerance to light, nausea and vomiting, flushed skin and bizarre behavior
2: Early CNS depression	Confusion, disorientation, dullness, loss of self-control, ringing or buzzing in the head, blurred or double vision, cramps, headache, insensitivity to pain, and pallor or paleness
3: Medium CNS depression	Drowsiness, muscular incoordination, slurred speech, depressed reflexes, and nystagmus or rapid involuntary oscillation of the eyeballs
4: Late CNS depression	Unconsciousness that may be accompanied by bizarre dreams, epileptiform seizures, and EEG changes

CNS, Central nervous system; EEG, electroencephalogram.
From Harris D. Volatile substance use. *Arch Dis Child Educ Pract Ed.* 2006;91:ep93–ep100.

Table 157.13 Documented Clinical Presentations of Acute and Chronic Volatile Substance Use

Ventricular fibrillation	Muscle weakness
Asystolic cardiac arrest	Abdominal pain
Myocardial infarction	Cough
Ataxia	Aspiration pneumonia
Agitation	Chemical pneumonitis
Limb and trunk incoordination	Coma
Tremor	Visual and auditory hallucinations
Visual loss	Acute delusions
Tinnitus	Nausea and vomiting
Dysarthria	Pulmonary edema
Vertigo	Photophobia
Hyperreflexia	Rash
Acute confusional state	Jaundice
Conjunctivitis	Anorexia
Acute paranoia	Slurred speech
Depression	Diarrhea
Oral and nasal mucosal ulceration	Weight loss
Halitosis	Epistaxis
Convulsions/fits	Rhinitis
Headache	Cerebral edema
Peripheral neuropathy	Visual loss
Methemoglobinemia	Burns
Acute trauma	Renal tubular acidosis

and increased intraocular pressure. There may be dermatologic findings, including perianal/perioral dermatitis ("huffer rash"), frostbite, and contact dermatitis, as well as epistaxis, nasal ulcers, and conjunctivitis.

COMPLICATIONS

Model airplane glue is responsible for a wide range of complications related to chemical toxicity, to the method of administration (in plastic bags, with resultant suffocation), and to the dangerous setting in which the inhalation occurs (roof tops). Common neuromuscular changes reported in chronic inhalant users include difficulty coordinating movement, gait disorders, muscle tremors, and spasticity, particularly in the legs (Table 157.13). Chronic use may cause pulmonary hypertension, restrictive lung defects or reduced diffusion capacity, peripheral neuropathy, hematuria, tubular acidosis, and possibly cerebral and cerebellar atrophy. Chronic inhalant use has long been linked to widespread brain damage and cognitive abnormalities that can range from mild impairment (poor memory, decreased learning ability) to severe dementia. High-frequency inhalant users were significantly more likely than moderate- and low-frequency users to experience adverse consequences of inhalant intoxication, such as behavioral, language, and memory problems. Certain risky behaviors and consequences, such as engaging in unprotected sex or fighting while high on inhalants, were dramatically more common among high-frequency than low-frequency inhalant users. Death in the acute phase may result from cerebral or pulmonary edema or myocardial involvement (see Table 157.13).

DIAGNOSIS

Diagnosis of inhalant abuse is difficult because of the ubiquitous nature of the products and decreased parental awareness of the dangers. In the primary care setting, providers need to ask parents if they have witnessed any unusual behaviors in their teen; noticed high-risk products in the teen's bedroom; seen paint on the teen's hands, nose, or mouth; or found paint- or chemical-coated rags. Complete blood count, coagulation studies, and hepatic and renal function studies may identify the complications. In extreme intoxication, a user may manifest symptoms of restlessness, general muscle weakness, dysarthria, nystagmus, disruptive behavior, and occasionally hallucinations. Toluene is excreted rapidly in the urine as hippuric acid, with the residual detectable in the serum by gas chromatography.

TREATMENT

Treatment is generally supportive and directed toward control of arrhythmia and stabilization of respirations and circulation. Withdrawal symptoms do not usually occur.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.5 EVALI

E-cigarette or vaping use–associated lung injury.
See Chapter 450.

157.6 Hallucinogens

Cora Collette Breuner

Several naturally occurring and synthetic substances are used by adolescents for their hallucinogenic properties. They have chemical structures similar to neurotransmitters such as serotonin, but their exact mechanism of action remains unclear. Lysergic acid diethylamide **(LSD)**, methylenedioxymethamphetamine **(ecstasy**, **MDMA)**, and hallucinogenic magic mushrooms **(psilocybins)** are the most commonly reported hallucinogens used. Peyote **(mescaline)** derived from a cactus flower is chemically related to MDMA. **Ayahuasca** is another plant-derived hallucinogen found in South America whose active agents are N,N-dimethyltryptamine **(DMT)** and harmala alkaloids, which act as a monoamine oxidase inhibitor. Another hallucinatory agent is derived from a poisonous toad *(Bufo alvarius),* native to the Sonoran Desert, which produces **5-MeO-DMT** in its venom gland. 251-NBOMe **(N-Bomb)** is a designer substance that interacts with the 5HT-2a receptor and has sympathomimetic and hallucinogenic properties (Table 157.14).

LYSERGIC ACID DIETHYLAMIDE

LSD (acid, big "d," blotters) is a very potent hallucinogen that is made from lysergic acid found in ergot, a fungus that grows on rye and other grains. Its high potency allows effective doses to be applied to absorbent paper, or it can be taken as a liquid or a tablet. The onset of action can be 30-60 minutes, and it peaks at 2-4 hours. By 10-12 hours, individuals return to the preingestion state. Among U.S. 12th graders, 4% report trying LSD at least once.

Clinical Manifestations

The effects of LSD can be divided into three categories: somatic (physical effects), perceptual (altered changes in vision and hearing), and psychic (changes in sensorium). The common somatic symptoms are dizziness, dilated pupils, nausea, flushing, elevated temperature, and tachycardia. The sensation of *synesthesia,* or "seeing" smells and "hearing" colors, as well as major distortions of time and self, have been reported with high doses of LSD. Delusional ideation, body distortion, and suspiciousness to the point of toxic psychosis are the more serious of the psychic symptoms. LSD is not considered to be an addictive substance because it does not typically produce substance-seeking behavior.

Treatment

An individual is considered to have a "bad trip" when the sensory experiences cause the user to become terrified or panicked. These episodes should be treated by removing the individual from the aggravating situation and placing them in a quiet room with a calming friend. In situations of extreme agitation or seizures, use of benzodiazepines may be warranted. "Flashbacks," or LSD-induced states after the drug has worn off, and tolerance to the effects of the drug are additional complications of its use.

METHYLENEDIOXYMETHAMPHETAMINE

MDMA ("X," ecstasy, Molly), a phenylisopropylamine hallucinogen, is a synthetic compound similar to hallucinogenic cactus-derived mescaline and the stimulant methamphetamine. Like other hallucinogens, this substance is proposed to interact with serotoninergic neurons in the CNS. It is the preferred substance at "raves," all-night dance parties, and is also known as one of the "club substances" along with γ-hydroxybutyrate (GHB) and ketamine. Nationwide, the prevalence of having ever used MDMA was 8.4% of college students; 12th-grade lifetime use was 2.8% in 2021.

Clinical Manifestations

Euphoria, a heightened sensual awareness, and increased psychic and emotional energy are acute effects. Compared to other hallucinogens, MDMA is less likely to produce emotional lability, depersonalization, and disturbances of thought. Nausea, jaw clenching, teeth grinding, and blurred vision are somatic symptoms, whereas anxiety, panic attacks, and psychosis are the adverse psychiatric outcomes. A few deaths have been reported after ingestion of the substance. In high doses, MDMA can interfere with the body's ability to regulate temperature. The resultant hyperthermia in association with vigorous dancing at a "rave" has resulted in severe liver, kidney, and cardiovascular system failure and death. No specific treatments are recommended for acute toxicity.

Chronic MDMA use can lead to changes in brain function, affecting cognitive tasks and memory. These symptoms may occur because of MDMA's effects on neurons that secrete serotonin as a neurotransmitter. The serotonin system plays an important role in regulating mood, aggression, sexual activity, sleep, and sensitivity to pain. A high rate of dependence has been found among MDMA users. MDMA exposure may be associated with long-term neurotoxicity and damage to serotonin-containing neurons. In nonhuman primates, exposure to MDMA for only 4 days caused damage to serotonin nerve terminals that was evident 6-7 years later. There are no specific pharmacologic treatments for MDMA addiction. Substance use recovery groups are recommended.

PHENCYCLIDINE

Phencyclidine **(PCP)** (Sernyl, angel dust, hog, peace pill, sheets) is an arylcyclohexalamine whose popularity is related in part to its ease of synthesis in home laboratories. One of the by-products of home synthesis can cause cramps, diarrhea, and hematemesis. It is a "dissociative substance" that produces feelings of detachment from the surrounding environment and self. The substance is thought to potentiate adrenergic effects by inhibiting neuronal reuptake of catecholamines. PCP is available as a tablet, liquid, or powder, which may be used alone or sprinkled on cigarettes (joints). The powders and tablets generally contain 2-6 mg of PCP, whereas joints average 1 mg for every 150 mg of tobacco leaves, or approximately 30-50 mg per joint. The prevalence of PCP use (a hallucinogenic substance) among U.S. 12th graders is approximately 1%.

Clinical Manifestations

The clinical manifestations are dose related and produce alterations of perception, behavior, and autonomic functions. Euphoria, nystagmus, ataxia, and emotional lability occur within 2-3 minutes after smoking 1-5 mg and last for 4-6 hours. At these low doses the user is likely to experience shallow breathing, flushing, generalized numbness of extremities, and loss of motor coordination. Hallucinations may involve bizarre distortions of body image that often precipitate panic reactions. With doses of 5-15 mg, a toxic psychosis may occur, with disorientation, hypersalivation, and abusive language lasting for >1 hour. Hypotension, generalized seizures, and cardiac arrhythmias typically occur with plasma concentrations of 40-200 mg/dL. Death has been reported during psychotic delirium from hypertension, hypotension, hypothermia, seizures, and trauma. The coma of PCP may be distinguished from that of the opiates by the absence of respiratory depression; the presence of muscle rigidity, hyperreflexia, and nystagmus; and lack of response to naloxone. PCP psychosis may be difficult to distinguish from schizophrenia. In the absence of a history of use, the diagnosis depends on urinalysis.

Treatment

Management of the PCP-intoxicated patient includes placement in a darkened, quiet room on a floor pad, safe from injury. Acute alcohol intoxication may also be present. For recent oral ingestion, gastric absorption is poor, and induction of emesis or gastric lavage is useful. Diazepam, in a dose of 5-10 mg orally or 2-5 mg intravenously, may

Table 157.14 Classes of Hallucinogens

CHEMICAL NAMES	PLANTS OR NATURAL SOURCES; SYNTHETIC AGENTS; "SLANG NAMES"
INDOLEAMINES	
Lysergamides (Ergolines)	
d-Lysergic acid diethylamide	LSD; Delysid; "acid," "blotter," "stamps," "dots," "trips," "paper," "a-bombs," "pyramids"
d-Lysergic acid amide	*Ipomoea violacea* (morning glory), *Rivea corymbosa* (Mexican ololiuqui), *Argyreia nervosa* (Hawaiian baby woodrose), *Merremia tuberose* (Hawaiian woodrose)
Alkytryptamines	
α-Methyltryptamine	AMT; "alpha"
N,N-dimethyltryptamine (DMT)	*Piptadenia peregrina, Anadenanthera peregrina, Prestonia amazenicum, Mimosa hostilis, Vivola calophylla*; "businessman's trip"
5-Methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT)	*Bufo alvarius*
Psilocybin (4-phophoryloxy-DMT)	*Psilocybe* sp, *Panaeolus* sp, *Conocybe* sp, *Inocybe* sp, *Gymnopilus* sp, *Lycoperdon* sp, *Pluteus* genus; "magic mushrooms," "shrooms," "alice"
Psilocin (4-OH-DMT)	
5-Methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT)	"Foxy methoxy," "foxy"
Bufotenine (5-OH-DMT)	Ch'an Su
Diethyltryptamine	DET
Ibogaine	*Tabernanthe iboga*
PHENYLETHYLAMINES	
Mescaline (3,4,5-trimethoxyphenethylamine)	Peyote cactus *(Lophophora williamsii)*
3,4-methylenedioxymethamphetamine (MDMA)	Ecstasy; "XTC," "X," "E," "Adam," "the hug drug"
3,4-methylenedioxyethamphetamine (MDEA)	"Eve"
Methylenedioxyamphetamine (MDA)	
4-Bromo-2,5-dimethoxyamphetamine (DOM)	"Serenity, tranquility, and peace" [STP]
Paramethoxyamphetamine (PMA)	
ARYLCYCLOHEXYLAMINES (PIPERIDINE DERIVATIVES)	
Phencyclidine (PCP)	Angel dust; "hog," "wacky weed," "T," "killer weed"
Ketamine	Ketalar, ketaject, ketanest, "special K," "K," "K-hole," "vitamin K"
Dextromethorphan	"DXM," "dex," "robotripping," "CCC," "skittles," "red devils"
PIPERAZINES	
Benzylpiperazine (BZP)	"Legal E," "legal X," "A2"
Trifluoromethylphenylpiperazine (TFMPP)	
Methylenedioxybenzylpiperazine (MDBP)	
m-Chlorophenylpiperazine (mCPP)	
p-Methoxyphenylpiperazine (MeOPP)	
TETRAHYDROCANNABINOIDS	
Tetrahydrocannabinol (Δ^9-THC, Δ^1-THC)	Dronabinol (Marinol); *Cannabis sativa* (marijuana, hashish)
DITERPENE ALKALOIDS	
Salvinorin A, C	*Salvia divinorum*; sage
Myrisicin, saffron	*Myristica fragrans* (nutmeg, mace)
ANTICHOLINERGIC AGENTS	
Atropine (d,l-hyoscyamine)	*Atropa belladonna* (deadly nightshade), *Datura stramonium* (jimson weed)
Scopolamine (L-hyoscine)	Transderm Scop; *Datura stramonium* (jimson weed), *Hyoscyamus niger* (henbane)

From Traub SJ. Hallucinogens. In Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: Elsevier; 2007: Table 45.1.

be helpful if the patient is agitated and not comatose. Rapid excretion of the substance is promoted by acidification of the urine. Supportive therapy of the comatose patient is indicated with particular attention to hydration, which may be compromised by PCP-induced diuresis. Inpatient and/or behavioral treatments can be helpful for chronic PCP users.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.7 Cocaine

Cora Collette Breuner

Cocaine, an alkaloid extracted from the leaves of the South American *Erythroxylum coca*, is supplied as the hydrochloride salt in crystalline form. With **snorting**, it is rapidly absorbed into the bloodstream from the nasal mucosa, detoxified by the liver, and excreted in the urine as benzoylecgonine. Smoking the cocaine alkaloid **(freebasing)** involves inhaling the cocaine vapors in pipes or cigarettes mixed with tobacco

or marijuana. Accidental burns are potential complications of this practice. With **crack** cocaine, the crystallized rock form, the smoker feels "high" in <10 seconds. The risk of addiction with this method is higher and more rapidly progressive than from snorting cocaine. Tolerance develops, and the user must increase the dose or change the route of administration, or both, to achieve the same effect. To sustain the high, cocaine users repeatedly use cocaine in short periods known as "binges." Substance dealers often place cocaine in plastic bags or condoms and swallow these containers during transport. Rupture of a container produces a sympathomimetic crisis (see Table 157.4). Cocaine use disorder among U.S. high school students has decreased in the last decade, with 2.5% of 12th graders having tried the substance (any route) at least once.

CLINICAL MANIFESTATIONS

Cocaine is a strong CNS stimulant that increases dopamine levels by preventing reuptake. Cocaine produces euphoria, increased motor activity, decreased fatigability, and mental alertness. Its sympathomimetic properties are responsible for pupillary dilation, tachycardia, hypertension, and hyperthermia. Snorting cocaine chronically results in loss of sense of smell, nosebleeds, and chronic rhinorrhea. Injecting cocaine increases risk for HIV infection. Chronic users experience anxiety, irritability, and sometimes paranoid psychosis. Lethal effects are possible, especially when cocaine is used in combination with other substances, such as heroin, in an injectable form known as a "speedball." When taken with alcohol, cocaine is metabolized by the liver to produce cocaethylene, a substance that enhances the euphoria and is associated with a greater risk of sudden death than with cocaine alone. Pregnant adolescents who use cocaine place their fetus at risk of premature delivery, complications of low birthweight, and possibly developmental disorders.

TREATMENT

There are no FDA-approved medications for treatment of cocaine addiction. CBT has been shown to be effective when provided in combination with additional services and social support. Oral sustained-release dexamphetamine has been shown to be partially effective in adults with cocaine dependence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.8 Amphetamines

Cora Collette Breuner

Methamphetamine, commonly known as **meth**, is a nervous system stimulant and Schedule II substance with a high potential for abuse. Most of the methamphetamine currently used is produced in illegal laboratories. It is a white, odorless, bitter-tasting powder that is particularly popular among adolescents and young adults because of its potency and ease of absorption. It can be ingested orally, smoked, needle-injected, or absorbed across mucous membranes. Amphetamines have multiple CNS effects, including release of neurotransmitters and an indirect catecholamine agonist effect. Approximately 0.6% of 12th graders reported using methamphetamine at least once.

CLINICAL MANIFESTATIONS

Methamphetamine rapidly increases the release and blocks the reuptake of dopamine, a powerful "feel good" neurotransmitter (Table 157.15). The effects of amphetamines can be dose related. In small amounts, amphetamine effects resemble other stimulants: increased physical activity, rapid and/or irregular heart rate, increased blood pressure, and decreased appetite. High doses produce slowing of cardiac conduction in the face of ventricular irritability. Hypertensive and hyperpyrexic episodes can occur, as can seizures (see Table 157.4). Binging may result in the development of psychotic ideation with the potential for sudden violence. Cerebrovascular damage, psychosis, severe receding of the gums with tooth decay, and infection with HIV and hepatitides B and C can result from long-term use. A withdrawal syndrome is associated with amphetamine use, with early, intermediate, and late phases (see Table 157.15). The early phase is characterized as a "crash" phase with depression, agitation, fatigue, and desire for more of the substance. Loss of physical and mental energy, limited interest in the environment, and anhedonia mark the intermediate phase. In the final phase, substance craving returns, often triggered by particular situations or objects.

TREATMENT

Acute agitation and delusional behaviors can be treated with haloperidol or droperidol. Phenothiazines are contraindicated and may cause

Table 157.15 Signs and Symptoms of Intoxication and Withdrawal

	OPIATES	AMPHETAMINES/COCAINE	BENZODIAZEPINES
INTOXICATION			
Behavior	Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment	Euphoria and sensation of increased energy; hypervigilance; grandiosity, aggression, argumentative; labile mood; repetitive stereotyped behaviors; hallucinations, usually with intact orientation; paranoid ideation; interference with personal functioning	Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning
Signs	Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdose—dilation); decreased level of consciousness	Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of weight loss; dilated pupils; chest pain; convulsions	Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters
Overdose	Respiratory depression; hypothermia	Sympathomimetic symptoms	Hypotension; hyperthermia; depression of gag reflex; coma
Withdrawal	Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep	Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams	Tremor of tongue, eyelids, or outstretched hands; nausea or vomiting; tachycardia; postural hypotension; psychomotor agitation; headache; insomnia; malaise or weakness; transient visual, tactile, or auditory hallucinations or illusions; paranoid ideation; grand mal convulsions

From Haber PS, Demirkol A, Lange K, et al. Management of injecting substance users admitted to hospital. *Lancet.* 2009;374:1284–1292.

a rapid drop in blood pressure or seizure activity. Other supportive treatment consists of a cooling blanket for hyperthermia and treatment of the hypertension and arrhythmias, which may respond to sedation with lorazepam or diazepam. For the chronic user, comprehensive CBT interventions have been demonstrated as effective treatment options.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.9 Stimulant Use and Diversion

Cora Collette Breuner

In MTF 2021, 4.6% of 12th graders reported using OTC diet pills in their lifetime and 1.1% in the past 30 days. These include nonprescription stimulants of two general types: pseudoamphetamines, usually sold by internet/mail order, and OTC stimulants, primarily diet and "stay-awake" pills. These substances usually contain caffeine, ephedrine, and/or phenylpropanolamine.

The *misuse* of a stimulant medication, defined as taking a stimulant not prescribed by a healthcare provider and not in accordance with healthcare provider guidance, has been growing over the past two decades, with an increase in prevalence rates of nonprescription stimulant use among both adolescents and young adults in the past 10 years. Nonprescription use of methylphenidate **(MPH)** in 2000 was 1.2%, increasing to 2% for MPH and 7.5% for nonprescription mixed amphetamine salts **(AMPs)** in 2015.

The majority of nonprescription stimulant users reported obtaining the substances by **diversion**, a process for obtaining the substance from peers. Diversion occurs quite often and can begin in childhood, adolescence, or young adulthood. Lifetime rates of diversion ranged from 16–29% of students with stimulant prescriptions. One survey reported that 23.3% of middle and high school students taking prescribed stimulants had been solicited to divert their medication to others at a rate that increased from middle to high school. It has been shown that 54% of college students prescribed stimulants for attention-deficit/hyperactivity disorder (ADHD) had been approached to divert their medication.

In U.S. college students, nonprescription use of stimulants is more prevalent among particular subgroups (males; members of fraternities/sororities; with lower grade point averages; more likely to use alcohol, cigarettes, marijuana, MDMA, or cocaine) and types of colleges (northeastern region, with more competitive admission standards). Lifetime prevalence of nonprescription stimulant use was 6.9% and past-month prevalence 2.1%. According to a survey of 334 ADHD-diagnosed college students taking prescription stimulants, 25% misused their own prescription medications. Scholastic pressures, including the need to succeed academically, and persistent social and financial demands place many students at an increased risk for misuse of various substances, especially at the end of school terms. A web-based survey of medical and health profession students found that the most common reason for nonprescription stimulant use was to focus and concentrate during studying.

CLINICAL MANIFESTATIONS

Misuse of stimulants is associated with psychosis, seizures, dysrhythmias, myocardial infarction, cardiomyopathy, and even sudden death. Intentional misuse of MPH or AMPs in combination with other substances leads to adverse medical consequences. Importantly, 14% of the emergency department (ED) visits for stimulant use were associated with cardiovascular (CV) events. Psychosis includes visual hallucinations, delusions, anorexia, flattening of affect, and insomnia mediated by dopaminergic excess. The CV effects include hypertension, arrhythmias, tachycardia, cardiomyopathy, cardiac dysrhythmias, necrotizing vasculitis, and CV accidents. Case reports include serious CV adverse drug reactions (ADRs), sudden death, and psychiatric disorders. Many patients report sleep difficulties (72%), irritability (62%), dizziness and lightheadedness (35%), headaches (33%), stomachaches (33%), and sadness (25%). Other health risks include loss of appetite, weight loss, and nervousness. Many users are involved in heavy episodic alcohol use while using MPH or AMPs. Most users of MPH or AMPs are unaware of these adverse effects and predominantly "feel good" about taking these medications.

Despite reports that MPH misuse is a healthcare issue, >82% of primary care physicians did not suspect misuse of prescribed ADHD medication in one report, and <1% thought that their patients were diverting prescribed ADHD medication. Improved monitoring for malingering and patient misuse may assist stopping diversion of these medications. An ADHD diagnosis should be confirmed in those requesting ADHD medication, and they should be screened for use of other substances.

TREATMENT

Treatment for nonprescription stimulant overdose is similar as that for amphetamine overdose. Haloperidol or droperidol is recommended for acute agitation and delusional behaviors. Phenothiazines are contraindicated and may cause a rapid drop in blood pressure or seizure activity. Hyperthermia may require use of a cooling blanket, and sedation with a benzodiazepine is recommended for treatment of the hypertension and arrhythmias. In those with chronic use, inpatient or outpatient substance use interventions using CBT have been shown to be the most effective treatment option.

Monitoring of the diversion and misuse of pharmaceutical stimulants must be a priority. More data need to be obtained on the prevalence, patterns, and harmful effects in adolescents and young adults.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.10 Opiates/Opioids

Cora Collette Breuner

Opiates refers to natural derived drugs (morphine, codeine, opium), whereas opioids refers to natural, semisynthetic, and synthetic agents. **Heroin** is a highly addictive synthetic opiate substance made from a naturally occurring substance **(morphine)** in the opium poppy plant. It is a white or brown powder that can be injected (intravenously or subcutaneously), snorted/sniffed, or smoked. Intravenous (IV) injection produces an immediate effect, whereas effects from the subcutaneous route occur in minutes, and from snorting, in 30 minutes. After injection, heroin crosses the blood-brain barrier, is converted to morphine, and binds to opiate receptors. Tolerance develops to the euphoric effect, and the chronic user must take more heroin to achieve the same intense effect. Heroin use among U.S. teens peaked in the mid-1990s but is resurgent in some suburban communities, as is the use of **prescription opioids** found in the home. Nationwide, 2.9% of high school students report having tried heroin at least once. **Fentanyl** is a more potent opiate and is responsible for many opiate overdoses. Other opioid drugs are noted in Table 157.16. Synthetic opioid fentanyl-derived analogues or nitrazene drugs (novel potent opioids:NPO) are much more potent than fentanyl and require higher and multiple doses of naloxone to reverse an overdose. NPOs include brorphine, isotonitazene, metonitazene, and N-piperidinyl etonitazene. Fentanyl is often illicitly manufactured and may be mixed with other substances, including xylazine, a nonopioid sedative. Xylazine, also known as *tranq*, is a veterinary drug that in humans produces central nervous system and respiratory depression, as well as bradycardia and hypotension. Xylazine also produces poorly healing cutaneous ulcerations at the site of injection and at distal sites. In 2022, fentanyl-xylazine combinations have been responsible for a significant number of overdose deaths; there is no antidote for xylazine.

CLINICAL MANIFESTATIONS

The clinical manifestations are determined by the purity of the heroin or its adulterants, combined with the route of administration (oral vs injection). The immediate effects include euphoria, diminution in pain, flushing of the skin, and pinpoint pupils (see Table 157.15). An effect on the hypothalamus is suggested by the lowering of body temperature. The most common dermatologic lesions are the "tracks," the hypertrophic linear scars that follow the course of large veins. Smaller, discrete peripheral scars, resembling healed insect bites, may be easily overlooked. The adolescent who injects heroin subcutaneously may have fat necrosis, lipodystrophy, and atrophy over portions

Table 157.16 Types and Actions of the Most Commonly Prescribed and Used Opioids

	TYPE OF OPIOID	ACTION ON OPIOID RECEPTOR
Alfentanil	Fully synthetic	Agonist of μ-receptors
Buprenorphine	Semisynthetic	Partial agonist of μ-receptors and NOP receptors; antagonist of κ-receptors
Codeine	Natural	Weak agonist of μ-receptors
Diamorphine (heroin)	Semisynthetic	Agonist of μ-receptors, δ-receptors, and κ-receptors; predominant binding to μ-receptors
Dihydrocodeine	Semisynthetic	Agonist of μ-receptors
Fentanyl	Fully synthetic	Agonist of μ-receptors, δ-receptors, and κ-receptors; predominant binding to μ-receptors
Hydromorphone	Semisynthetic	Agonist of μ-receptors and κ-receptors; predominant binding to μ-receptors
Methadone	Fully synthetic	Agonist of μ-receptors
Morphine	Natural	Agonist of μ-receptors, δ-receptors, and κ-receptors; predominant binding to μ-receptors
Oxycodone	Semisynthetic	Weak agonist of μ-receptors, δ-receptors, and κ-receptors; predominant binding to μ-receptors
Pentazocine	Fully synthetic	Partial agonist of δ-receptors and κ-receptors; antagonist of μ-receptors
Pethidine (meperidine)	Fully synthetic	Agonist of κ-receptors
Tramadol	Fully synthetic	Weak agonist of μ-receptors

Information presented is from the DrugBank and PubChem databases.
NOP, Nociceptin opioid peptide.
From Fountas A, Van Uum S, Karavitaki N. Opioid-induced endocrinopathies. *Lancet Diabetes Endocrinol*. 2020;8:68–80.

of the extremities. Attempts to conceal these stigmata may include amateur tattoos in unusual sites. Skin abscesses secondary to unsterile techniques of substance administration are usually found. There is a loss of libido; the mechanism is unknown. The chronic heroin user may resort to prostitution to support the habit, thus increasing the risk of sexually transmitted diseases (including HIV), pregnancy, and other infectious diseases. Constipation results from decreased smooth muscle propulsive contractions and increased anal sphincter tone. The absence of sterile technique in injection may lead to cerebral microabscesses or endocarditis, usually caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Abnormal serologic reactions are also common, including false-positive Venereal Disease Research Laboratories and latex fixation tests. Infectious complications are usually not seen with oral prescription opioid use unless the pills are dissolved and injected.

WITHDRAWAL

After ≥8 hours without heroin, the addicted individual undergoes a series of physiologic disturbances over 24-36 hours, referred to collectively as "withdrawal" or **abstinence syndrome** (see Table 157.15). The earliest sign is yawning, followed by lacrimation, mydriasis, restlessness, insomnia, "goose flesh," cramping of the voluntary musculature, bone pain, hyperactive bowel sounds and diarrhea, tachycardia, and systolic hypertension. Although the administration of **methadone** is the most common method of detoxification, **buprenorphine**, an opiate agonist-antagonist, is available for detoxification and maintenance treatment of heroin and other opiates. Buprenorphine has the advantage of offering less risk of addiction, overdose, and withdrawal effects and can be dispensed in the privacy of a physician's office. Combined with behavioral interventions, it has a greater success rate of detoxification. A combination substance, buprenorphine plus naloxone, has been formulated to minimize use during detoxification. Clonidine and tramadol have also been used to manage opioid withdrawal.

Substances used to treat **opioid use disorder**, a chronic relapsing problem, traditionally include methadone maintenance and buprenorphine. Use-deterrent opioid pill formulations (when pain control requires an opioid) include pills resistant to crushing that form a viscous gel when dissolved or pills with a sequestered opioid antagonist (naltrexone).

OVERDOSE SYNDROME

Overdose syndrome is an acute reaction after administration of an opiate. It is the leading cause of death among substance users. Many opiate overdoses are complicated by polydrug use (Fig. 157.4). The clinical signs include stupor or coma, seizures, miotic pupils (unless severe anoxia has occurred), respiratory depression, cyanosis, and pulmonary edema. The differential diagnosis includes CNS trauma, diabetic coma, hepatic (and other) encephalopathy, Reye syndrome, and overdose of alcohol, barbiturates, PCP, or methadone. Diagnosis of opiate toxicity is facilitated by IV administration of naloxone 0.1 mg/kg, not to exceed 2 mg, which causes dilation of pupils constricted by the opiate. Diagnosis is confirmed by the finding of opiates in the urine and/or serum.

TREATMENT

Treatment of acute heroin overdose consists of maintaining adequate oxygenation and continued administration of **naloxone**, a pure opioid antagonist (see Chapter 94). It may be given intravenously, intramuscularly, subcutaneously, as a nasal spray, or by endotracheal tube. Naloxone has an ultra-rapid onset of action (1 minute) and duration of action of 20-60 minutes. Naloxone is often available in the field, carried by first responders. Take-home naloxone may also be given to substance users, their family, or friends; such programs have been effective in treating overdoses. If there is no response, other etiologies for the respiratory depression must be explored. Naloxone may have to be repeated if given by nasal route or continued for 24 hours if methadone, rather than shorter-acting heroin, has been taken. Higher and prolonged naloxone dosing is required for novel potent opioid overdoses. Admission to the intensive care unit is indicated for patients who require continuous naloxone infusions (rebound coma, respiratory depression) and for those with life-threatening arrhythmias, shock, and seizures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

157.11 Synthetic Cannabinoids

Cora Collette Breuner

Bath salts refers to a group of previously OTC, but now illicit, often home synthesized, substances containing one or more chemicals similar to **cathinone**, an amphetamine-like stimulant found in the khat

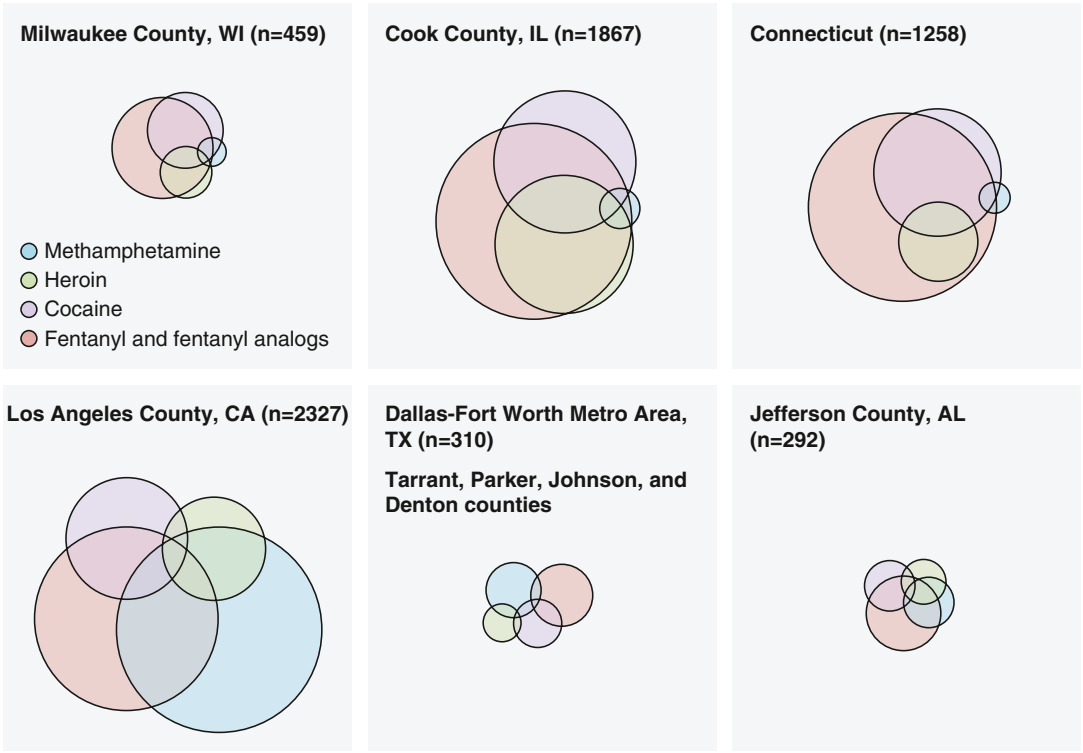

Fig. 157.4 Proportional drug combinations involved in fatal overdoses in U.S. jurisdictions with detailed medical examiner data available, 2020. Based on death investigations that were completed at the time of data request. Official counts by jurisdictions may differ as all investigations are completed. These areas were chosen to provide a country-wide view. *(From Humphreys K, Shover CL, Andrews CM, et al. Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-Lancet commission. Lancet. 2022;399:555–604, Fig. 5.)*

plant. The bath salts, marketed under ever-changing brand names (e.g., Lunar Wave, Cloud Nine, Vanilla Sky), are sold online or in substance paraphernalia stores as a white or brown crystalline powder and can be ingested, inhaled, or injected. The most current information about teen use of bath salts is from the 2016 MTF survey of 8th, 10th, and 12th graders, who report use of 0.9%, 0.8%, and 0.8%, respectively. The synthetic cathinones found in bath salts include methylone, mephedrone, and 3,4-methylenedioxypyrovalerone (MDPV), all of which are chemically similar to amphetamines and MDMA (ecstasy).

CLINICAL MANIFESTATIONS

The chemicals in bath salts raise brain dopamine levels, causing the user to feel a surge of euphoria, with increased sociability and sex drive. In addition, the user may experience a surge in norepinephrine, causing reactions such as an elevated heart rate, chest pain, vasoconstriction, diaphoresis, hyperthermia, dilated pupils, seizures, arrhythmias, and high blood pressure. Users also experience psychiatric symptoms such as aggressive behavior, panic attacks, paranoia, psychosis, delirium, self-mutilation, and hallucinations caused by elevated serotonin levels. Intoxication from bath salts may cause **excited delirium syndrome**, which includes dehydration, rhabdomyolysis, and kidney failure.

TREATMENT

Treatment of overdose should be directed at specific complications but often includes benzodiazepines or propofol for agitation and other neuropsychiatric manifestations. The synthetic cathinones in bath salts are highly addictive, triggering intense cravings in those who consume them frequently. This may result in dependence, tolerance, and strong withdrawal symptoms, as seen in other highly addictive substances. The sale of two of the synthetic cathinones, mephedrone and MDPV, is illegal in the United States.

SYNTHETIC CANNABINOIDS (MARIJUANA)

Spice, K2, crazy clown, aroma, black mamba, blaze, dream, and funky monkey are some of the common street names for synthetic marijuana, which is a mixture of herbs or plant materials that have been sprayed with artificial chemicals similar to THC, the psychoactive ingredient in marijuana. One active group of chemicals is the **carboxamides**, which *are not detected* by standard assays to detect THC. In the United States the chemicals in "spice" are designated a Schedule I controlled substance (as is marijuana) by the Drug Enforcement Administration (DEA), thereby making it illegal to sell, buy, or possess them. Nonetheless, synthetic marijuana is the second most common illicit substance used by high school seniors. More than 10% of high school seniors used synthetic marijuana in the last year.

Synthetic marijuana is mainly used by smoking, or mixed with marijuana, or brewed as a tea for drinking. The chemicals in synthetic marijuana affect the same receptors as THC and produce similar effects as seen in cannabis use, such as relaxation, elevated mood, and altered perception. In addition, sympathomimetic symptoms are quite common and are the cause of significant toxicity. Symptoms of **intoxication** depend on the individual compounds in the community and include vomiting, tachycardia, hypertension, hyperthermia, confusion, extreme anxiety, profuse sweating, agitation, aggression, dysphoria, hallucinations, seizures, rhabdomyolysis, dystonia, unresponsiveness, confusion, catatonia, "zombie-like" behaviors, psychosis, coma, and myocardial ischemia. Some of the neuropsychiatric manifestations may last for 1-4 weeks and at times resemble autoimmune encephalitis syndromes. Patients often require psychopharmacology for agitation or frank psychosis. In response to legislation to ban the chemicals in OTC synthetic marijuana products, manufacturers alter and substitute the chemicals in the product, keeping it on the legal market and leaving teens particularly vulnerable to potential health effects.

Synthetic marijuana is not detected by standard toxicology screening but can be identified in specialized laboratories.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 158

The Breast

Cynthia M. Holland-Hall

Breast development is often the first visible sign of puberty in the adolescent female. Pediatric practitioners must be able to distinguish normal breast development, including normal variants, from pathologic breast disorders. Visual inspection of the breast tissue should routinely be a component of the adolescent's general physical examination. Breast development during puberty is described using the **Sexual Maturity Rating (SMR)** scale, progressing from SMR 1 to SMR 5 as the breast becomes more mature (see Chapter 150, Fig. 150.2).

FEMALE DISORDERS

See Chapter 588.

MALE DISORDERS

Pubertal gynecomastia, benign glandular proliferation in the male breast, occurs in up to 65% of healthy adolescent males (see Chapter 625). The incidence of gynecomastia has increased over the past 20 years, suggesting that changes in the endogenous or exogenous sex-steroid environment have occurred. It is thought that an imbalance of estrogen and androgen concentrations contributes, at least in part, to the development of gynecomastia. Elevations of insulin-like growth factor (IGF)-1 have also been demonstrated. The onset of physiologic gynecomastia typically is between 10 and 13 years, peaking at SMR 3-4. Careful physical examination is essential to distinguish between **true gynecomastia**, characterized by a discrete disk of palpable glandular tissue under the nipple-areolar complex, and **pseudogynecomastia**, characterized by more diffuse, bilateral adiposity of the anterior chest wall. Physiologic gynecomastia regresses spontaneously in up to 90% of adolescents within 18-24 months but may transition into lipomastia. Reassurance and continued observation are recommended in most patients; surgery may be indicated in severe or persistent cases. No medical therapies for gynecomastia have been approved for use in adolescents by the U.S. Food and Drug Administration. Small, noncontrolled trials of antiestrogens, such as tamoxifen, appear promising, but more evidence is needed. Conditions associated with nonphysiologic gynecomastia include endocrine disorders, liver disease, neoplasms, chronic disease, and trauma. It can also be seen as a late effect in childhood cancer survivors. Although dozens of medications are implicated as possible causes of gynecomastia, convincing evidence exists only for a few, including several antiandrogens and other exogenous hormones, isoniazid, antiretrovirals, and histamine-2 receptor blockers. Calcium channel blockers, isotretinoin, statins, certain antipsychotics, proton pump inhibitors, lavender, and tea tree oil may be causative. Among drugs of misuse, alcohol, opioids, and anabolic steroids may be associated with gynecomastia, but minimal evidence supports an association with marijuana or amphetamines.

Other breast pathology in males is uncommon. Benign masses such as neurofibromas, lipomas, and dermoid cysts have been reported in the male breast. Males with Klinefelter syndrome have an elevated risk of breast cancer (see Chapter 623), but this malignancy is otherwise exceedingly rare in adolescents.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 159

Menstruation-Related Disorders

Fareeda Haamid and Gina S. Sucato

See also Chapter 587.

At least 400 lifetime episodes of menstruation are predicted in those who menstruate, yet many adolescents consistently report stigma, inadequate health education, and hesitance to discuss their menses with trusted adults. Clinicians should normalize menstruation and avoid unnecessarily medicalizing this natural process. Menstrual disturbances, including delayed onset, irregularity, heavy flow, and pain, occur in 75% of adolescent females. For adolescents with minor variations from normal (Table 159.1), an explanation of symptoms and reassurance may be all that is needed. Severe dysmenorrhea or prolonged menstrual bleeding can be not only frightening but a cause of persistent morbidity requiring more intensive management, potentially including referral to a specialist in adolescent gynecology.

NORMAL MENSTRUATION

The average age of **menarche**, or first menses, was thought to vary according to ethnic origin and socioeconomic status (SES). A prospective U.S. study of nearly 1,100 diverse females demonstrated no correlation between SES and menarche yet a statistically significant correlation with SES and thelarche; lower SES was associated with earlier pubertal onset. There is often a close concordance of the age at menarche between mother and daughter, which suggests genetic factors are determinants in addition to individual factors such as weight, exercise level, and chronic medical conditions. The age of menarche has declined in countries and populations experiencing improved nutritional standards and other living conditions. In U.S. females, the average age of menarche, 12.5 years, has been relatively stable over the last few decades. Higher body mass index (BMI) is associated with earlier onset of menarche.

The onset of breast budding **(thelarche)** is the first sign of puberty in most females, though it has decreased worldwide by a mean of roughly 3 months per decade from 1977 to 2013. Menarche typically occurs within 2-3 years of thelarche during breast **sexual maturity rating** (**SMR**; i.e., Tanner stage) 4. Longer cycle lengths ranging between 21 and 45 days occur initially then periods gradually become more regular. However, for most adolescents, by 3 years postmenarche, menstrual cycle patterns are similar to adults, occurring every 21-35 days.

MENSTRUAL IRREGULARITIES

In young adolescents, many menstrual variations are explained by **anovulation** caused by immaturity of the hypothalamic-pituitary-ovarian

Table 159.1 Characteristics of Normal Menses*

Cycle length**	21-35 days 21-45 days during first 3 yr after menarche
Duration of menses	7 or fewer days
Blood flow	6 or fewer soaked menstrual products per day Infrequent overflow of menstrual cups

*Adolescents with two or more cycles outside this range or who skip their period for 3 consecutive months warrant evaluation.

**A cycle begins with the first day of one period and extends to the first day of the next.

axis governing the menstrual cycle. Significant deviations from normal should prompt a search for organic pathology in a logical and cost-effective manner. An accurate menstrual history is an important, but often lacking, first step toward a diagnosis. At menarche, all patients should be encouraged to track their periods.

A range of terms has previously been used to describe abnormal menstrual bleeding. Terms such as "menorrhagia and metrorrhagia" are imprecise, confusing, and not linked to any specific underlying pathology. **Abnormal uterine bleeding (AUB)** is the preferred term for uterine bleeding that is abnormal in regularity, volume, frequency, or duration. AUB is further specified by adding descriptive terms such as *heavy menstrual* bleeding or *intermenstrual* bleeding. A qualifier is added to categorize the etiology of abnormal bleeding. Of the nine categories, the three most relevant to adolescents are **ovulatory dysfunction** (AUB-**O**), previously referred to as *dysfunctional uterine bleeding* and discussed in Chapter 159.2; **coagulopathy** (AUB-**C**); and **not otherwise classified** (AUB-**N**).

In addition to a standard medical history noting hospitalizations, chronic illness, and medication and supplement use, a complete history for evaluating a patient with menstrual irregularity should include the timing of pubertal milestones, such as onset of pubic and axillary hair and breast development; a detailed patient menstrual history; age of menarche and overall menstrual pattern of mother and sisters; and a family history of gynecologic problems. The complete review of systems should elicit any changes in headache pattern or vision; the presence of galactorrhea; and any changes in skin, hair, or bowel patterns. Changes in diet, level of exercise, and sports participation are also important factors when generating a differential diagnosis. The patient should be interviewed alone, and the confidential history should assess substance use, consensual sexual activity, forced sexual behavior, abuse, and other psychosocial stressors.

Assessment of basic growth parameters should include weight, height, and BMI and a thorough review of the growth chart. Physical examination should document heart rate, blood pressure, SMR, signs of androgen excess, such as hirsutism or severe acne, and signs suggestive of an eating disorder (see Chapter 41), such as bradycardia, cachexia, lanugo, or knuckle calluses. A careful external genital examination should be performed. An internal pelvic examination is rarely necessary in the absence of sexual activity. Any internal exam being considered for young adolescents should be performed with proper equipment and technique by a clinician with expertise in this age-group. Transabdominal pelvic ultrasound can be a useful adjunct for evaluating anatomic abnormalities in the adolescent; when indicated, MRI can provide greater detail of pelvic anatomy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

159.1 Amenorrhea

Fareeda Haamid and Gina S. Sucato

Amenorrhea, the absence of menstruation, generally requires evaluation at age 15 years, or if there has been no menstruation within 3 years of the onset of puberty **(primary amenorrhea)**, or if there has been no menstruation for the length of three previous cycles in a postmenarchal patient **(secondary amenorrhea)**. However, the following caveats exist: lack of any pubertal signs by age 13 years in a female should prompt evaluation for pubertal delay; in sexually active patients, or those with other symptoms suggesting pathology, evaluation should be initiated without waiting for three missed cycles; in patients whose breast development started between age 8 and 9 years, observation for >3 years may be warranted in some cases, given data suggesting that the age of thelarche has decreased but the age of menarche has not. Conversely, expectant management with close follow-up can be considered in a patient whose history, physical examination showing some pubertal development, and family history suggest constitutional delay of puberty.

Table 159.2 Causes of Primary or Secondary Amenorrhea

Pregnancy (regardless of history can cause primary or secondary amenorrhea)
Functional hypothalamic states (stress, weight loss, undernutrition, high levels of exercise, energy deficit even at normal weight)
Relative energy deficiency in sport (RED-S) (inadequate energy intake causing impaired physiologic function, including amenorrhea, bradycardia, and low bone density)
Eating disorders
Premature ovarian insufficiency (autoimmune, idiopathic, galactosemia, or secondary to radiation or chemotherapy)
Hypothalamic and/or pituitary damage (e.g., irradiation, tumor, traumatic brain injury, surgery, hemochromatosis, midline central nervous system defects such as septooptic dysplasia, autoimmune pituitary hypophysitis)
Thyroid disease (hyper- or hypo-; hypothyroidism more likely to be associated with increased bleeding)
Prolactinoma
Systemic disease (e.g., inflammatory bowel disease, cyanotic congenital heart disease, sickle cell disease, cystic fibrosis, celiac disease)
Hyperandrogenism (polycystic ovary syndrome, nonclassic congenital adrenal hyperplasia, adrenal tumor or dysfunction)
Drugs and medications (e.g., illicit drugs, atypical antipsychotics, hormones)
Turner syndrome (including mosaicism)

Table 159.3 Additional Causes of Primary Amenorrhea

Physiologic/constitutional delay
Anatomic abnormalities
Müllerian agenesis
Imperforate hymen
Transverse vaginal septum
Genetic disorders
46,XY disorders of sexual development (e.g., androgen insensitivity syndrome, 5α-reductase deficiency, 17α-hydroxylase deficiency)
Mixed gonadal dysgenesis (associated with various chromosome patterns)
Turner syndrome (resulting from 45,X or a variety of mosaic or other abnormal karyotypes)
Genetic hypogonadotropic hypogonadism (e.g., X-linked Kallmann syndrome)

The differential diagnosis of amenorrhea is broad (Table 159.2) and requires a careful history and physical exam to guide any necessary diagnostic studies. Understanding the timing and tempo of the patient's pubertal milestones is key to the evaluation. The first step in the amenorrhea evaluation is to ascertain whether the patient has ever had any menstrual bleeding. Conditions that can interrupt the menstrual cycle can also prevent menarche; therefore some aspects of the evaluation of primary and secondary amenorrhea are identical. In females with primary amenorrhea, genetic and anatomic conditions must also be considered (Table 159.3).

HISTORY AND PHYSICAL EXAMINATION

Important historical elements include dietary intake, exercise level, and a thorough review of any ongoing symptoms, including fever, headache, vision changes, chronic respiratory or gastrointestinal (GI) complaints, bowel habit changes, galactorrhea, changes in hair or nails, excessive body hair, severe acne, unexplained musculoskeletal complaints, and changes in

vaginal discharge, which may decrease in females who are hypoestrogenic. Any underlying medical conditions and the adequacy of their control should be noted, as well as the presence of any renal or skeletal anomalies, some of which may have associated reproductive system anomalies. Clinicians should document medications, particularly those for psychiatric conditions. Family history of menarcheal age, eating disorders (see Chapter 41), and **polycystic ovary syndrome (PCOS**; see Chapter 589) should be elicited. A thorough social history is necessary, especially concerning the presence or absence of sexual activity or abuse (see Chapter 16.1).

Physical examination should begin with careful attention to growth chart trajectories. In addition to a search for undiagnosed systemic disease, clues to an eating disorder, thyroid disease, or hyperandrogenism should be sought. The exam should assess for BMI, orthostatic pulses, blood pressure, abnormal dentition, anosmia or hyposmia (suggestive of Kallmann syndrome; see Chapter 623.2), parotid enlargement, thyroid gland palpation, hepatosplenomegaly, abdominal mass, lymphadenopathy, and SMR (see Chapter 150). Skin examination should note any lanugo, dry or doughy skin, loss of hair from scalp or eyebrows, striae, acanthosis nigricans, or acne. Clinicians should assess for glandular breast tissue via palpation in patients with primary amenorrhea. The external genital exam should note SMR and appearance of the vagina, which should be pink and moist; thin, dry, reddened mucosa suggests estrogen deficiency. The clitoral width should be <1 cm. In the patient with primary amenorrhea, vaginal patency can be painlessly assessed using a slender saline-moistened swab and careful avoidance of the hymen. If physical assessment of the cervix and uterus is not tolerated, a transabdominal pelvic ultrasound is advisable in patients with primary amenorrhea, followed by MRI if more detail is needed.

LABORATORY STUDIES

A urine pregnancy test, serum prolactin levels, thyroid-stimulating hormone, and follicle-stimulating hormone (FSH) are reasonable to measure in all patients presenting with amenorrhea (Fig. 159.1). Elevation of FSH (>30 mIU/mL) in an amenorrheic female suggests ovarian insufficiency, and if confirmed with repeat testing, should be followed with a pelvic ultrasound, karyotype, and specialist referral. Diagnostic tests in the patient presenting with amenorrhea should be tailored to the history and physical exam.

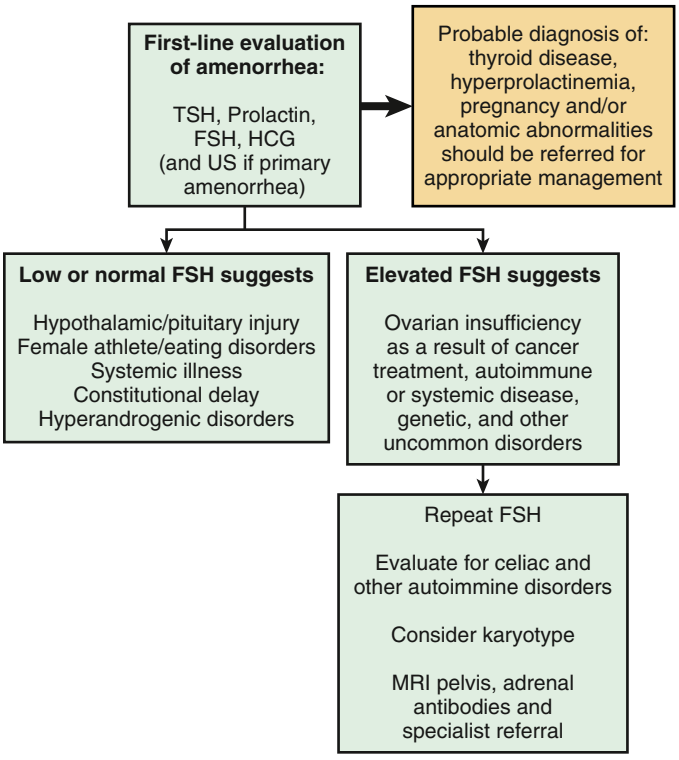

Fig. 159.1 Initial diagnostic testing algorithm to evaluate amenorrhea. FSH, Follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; US, ultrasound.

In patients with signs of androgen excess (e.g., severe acne or hirsutism) or other physical stigmata associated with PCOS (rapid pubertal weight gain, acanthosis nigricans) consider measuring levels of 17-hydroxyprogesterone (17-OHP), free and total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione; all preferably collected in the morning. PCOS affects up to 15% of females; diagnostic criteria for adolescents are controversial but include variations of menstrual irregularity (ranging from amenorrhea to AUB) and clinical or biochemical hyperandrogenism. The interpretation of polycystic ovarian morphology identified on ultrasound in adolescents can be challenging, and an ultrasound is not necessary for diagnosis in adolescents.

With the exceptions of pregnancy, constitutional delay, and imperforate hymen, conditions causing primary amenorrhea are associated with reduced fertility; thus their diagnosis may cause profound emotional responses in patients and families. Therefore before ordering studies to confirm these diagnoses (e.g., karyotype, MRI of reproductive anatomy), the clinician should carefully consider the implications and be prepared to refer to specialists with experience managing the long-term treatment of such diagnoses.

In patients presumed to have hypothalamic amenorrhea, based on prepubertal luteinizing hormone (LH) and low FSH levels using an ultrasensitive assay and consistent history and physical exam, MRI of the brain is not necessary in all patients. However, MRI should be considered for patients presenting with a headache history that has changed from baseline; persistent emesis; change in thirst, urination, or vision; elevated prolactin or galactorrhea; or other neurologic symptoms.

TREATMENT

Treatment for amenorrhea widely varies depending on the underlying cause. Many diagnoses require referral to clinicians in specialties such as endocrinology, adolescent medicine, and gynecology; often, collaboration with other disciplines such as psychology or nutrition is indicated. The mainstay of PCOS treatment is suppression of ovarian androgens, typically with **combined hormonal contraception** (i.e., estrogen and progestin) and **lifestyle modifications** to decrease obesity and insulin resistance. Patients with abnormal glucose tolerance may benefit from the addition of **metformin**. **Spironolactone**, an androgen receptor blocker, can also be used to reduce androgen effects, including hirsutism. **Metabolic syndrome** is highly prevalent in PCOS; thus clinicians should evaluate for comorbid diabetes and hyperlipidemia with periodic lipid and hemoglobin A_{1c} screening. It is crucial to normalize weight and improve nutritional status for patients with eating disorders or other hypoestrogenic conditions of energy imbalance. It is not routinely recommended to initiate hormonal therapy in these patients. However, short-term use of **transdermal estrogen therapy** (E2) to protect bone health may be considered for those who remain amenorrheic after a trial of nutritional and activity modification. For females with amenorrhea due to partial or total ovarian insufficiency, exogenous hormones are required for all pubertal development. Experts recommend starting at age 10-12 years with low-dose transdermal estrogen, progressing to increased doses of estrogen and cyclic progestin. Continued maintenance therapy can be accomplished with higher-dose combination products, as found in typical combined hormonal contraceptive pills, patches, and vaginal rings.

In the absence of a clear indication such as PCOS, hormonal medications (e.g., combined hormonal methods) to produce monthly bleeding are not recommended for patients with **secondary amenorrhea** because it will mask the patient's subsequent menstrual pattern. However, in patients with normal postpubertal estrogen levels, progesterone can be useful to periodically (every 4-12 weeks) induce shedding of the endometrial lining to avoid buildup and subsequent heavy menses. One commonly used regimen is **medroxyprogesterone** 10 mg PO daily for the first 7-14 days of the month.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

159.2 Abnormal Uterine Bleeding

Fareeda Haamid and Gina S. Sucato

Abnormal uterine bleeding (AUB) is a broad term used to describe any menstrual bleeding pattern that deviates from physiologic patterns. Clinicians are encouraged to categorize the abnormal pattern based on the patient's complaint, which is typically irregular (AUB/**IMB: intermenstrual bleeding**) or heavy (AUB/**HMB: heavy menstrual bleeding**).

IRREGULAR MENSTRUAL BLEEDING

Menstrual status should be treated as a *vital sign;* at every preventative care or comprehensive visit clinicians should document the first day of the last menstrual period and the menstrual pattern. Although menses are frequently irregular in the early postmenarcheal years, further evaluation is necessary when menstrual patterns vary too widely from what is normal for age. Even in the first postmenarcheal year, menses are usually not less frequent than every 45 days. Menses become increasingly regular with age, and by 3 years after menarche typically occur every 21-35 days, lasting 3-7 days. Personal cycle duration is usually established by age 19 or 20 years.

In the early postmenarcheal years, the most common cause of AUB in adolescents is anovulation caused by immaturity of the hypothalamic-pituitary-ovarian axis. In the absence of a mid-cycle LH surge to stimulate ovulation, there is no corpus luteum production of progesterone. Without the stabilizing effects of progesterone on the endometrial lining, there is increased risk of irregular bleeding. **AUB caused by ovulatory dysfunction (AUB-O**; previously termed *dysfunctional uterine bleeding*), describes irregular bleeding in the absence of specific anatomic, systemic, or endocrinologic disease. Although it is the most common cause of abnormal menstrual bleeding in adolescents, AUB-O is a diagnosis of exclusion. It is important to remember that most conditions that cause amenorrhea can first cause anovulation, which is a key risk for heavy irregular bleeding. Table 159.4 lists the causes of AUB and vaginal bleeding. Adolescents rarely present with complaints of unusually short or light menses. However, short, light, or infrequent menstrual patterns that have changed from a previously established pattern may need to be evaluated similarly to secondary amenorrhea.

Unscheduled bleeding during the use of hormonal contraception frequently occurs, particularly with progestin-only methods. Common causes include medication nonadherence, interactions with prescribed or over-the-counter medications, and smoking. Patients should be reassured such bleeding is benign and not an indication to stop an otherwise satisfactory contraceptive method.

HEAVY AND PROLONGED MENSTRUAL BLEEDING

Irregular bleeding, particularly from anovulation, can be long and heavy (see Table 159.4). However, a hematologic cause **(AUB-C)** should be strongly considered in patients with regular, cyclic menses that are long and/or heavy, especially if heavy menses occurs at the onset of menarche and bleeding disorder symptoms are present. **von Willebrand disease** and other coagulation disorders are found in up to 13% and 20%, respectively, of patients with heavy menstrual bleeding. Other symptoms suggestive of bleeding disorders include changing

Table 159.4 Causes of Vaginal Bleeding in Adolescence

CAUSES OF VAGINAL BLEEDING	EXAMPLES	FEATURES
Immature hypothalamic-pituitary-ovarian axis (AUB-O)	Patient within 2 yr of menarche	Patient responds to hormonal treatment.
Weight changes, disordered eating, or excessive exercise	Anorexia nervosa, bulimia, weight gain or loss of more than 10 pounds from any etiology	Weight loss more frequently results in lighter, less frequent menses.
Endocrinologic causes	Thyroid disease, polycystic ovary syndrome (PCOS)	Bleeding typically increases with hypothyroidism and decreases with PCOS and hyperthyroidism.
Pregnancy complication	Threatened abortion, postpartum or postabortal endometritis	History of sexual activity and/or pregnancy
Infection	Cervicitis, condyloma, pelvic inflammatory disease	Bleeding is usually not heavy and may occur during or after sexual intercourse.
Trauma	Sexual assault, straddle injuries	History will be evident in patients of menstruating age unless there is cognitive disability.
Vaginal foreign body	Toilet paper, broken condoms, tampons	Associated with odor and vaginal discharge, but usually not heavy bleeding.
Hematologic causes (AUB-C)	Type 1, 2, 3 von Willebrand disease, platelet function disorders, thrombocytopenia (idiopathic thrombocytopenic purpura, drug induced), symptomatic hemophilia carrier, clotting factor deficiency, leukemia, aplastic anemia	Bleeding is heavy and/or long and frequently regular, may present at menarche, and may be accompanied by a suggestive personal or family history (hysterectomy, uterine ablation, cautery for epistaxis) or physical exam (ecchymoses, petechiae).
Medications	Estrogens and progestins in combined hormonal contraception Androgens Drugs that affect prolactin (estrogens, phenothiazines, tricyclic antidepressants, metoclopramide) Anticoagulants (heparin, warfarin, aspirin, NSAIDs) SSRIs	Affect the hypothalamic-pituitary-ovarian axis, endometrial lining, platelets, or coagulation pathway.
Anatomic	Partial obstruction of vagina or uterus causing asynchronous bleeding; cervical or endometrial polyps or myomas; hemangioma; uterine vascular malformation; genital/reproductive tract cancer	Most of these entities are extremely rare, especially reproductive tract cancers.
Systemic disease	Celiac disease, rheumatoid arthritis, Ehlers-Danlos syndrome and other connective tissue disorders	Accompanied by other condition-specific signs.

a pad or tampon more than hourly, passing clots larger than 1 inch in diameter, iron deficiency, menses longer than 7 days, a history of hemorrhagic ovarian cysts, excessive bleeding from wounds or postoperatively, mucosal bleeding (epistaxis or GI tract), and first-degree relatives with heavy menses or epistaxis requiring medical treatment. Inherited collagen disorders such as Ehlers-Danlos syndrome are associated with vascular collagen abnormalities; thus patients with heavy menses and manifestations of joint hyperflexibility may require a hematology referral.

LABORATORY FINDINGS

Table 159.5 lists laboratory tests to consider in patients with long, heavy bleeding. Females with persistent heavy bleeding despite negative first-line testing should be referred to a hematologist for testing for platelet function disorders, factor deficiencies, and other less common disorders. In the initial evaluation, rapidity of blood loss in conjunction with the hemoglobin establishes the **bleeding severity**: **mild** (hemoglobin 10-11 g/dL), **moderate** (hemoglobin 7-10 g/dL), or **severe** (hemoglobin <7 g/dL). Iron deficiency is defined as serum ferritin of <15 µg/mL.

TREATMENT

In bleeding that has resulted in **mild** anemia, the patient should keep a menstrual calendar to follow the subsequent flow patterns. **Nonsteroidal antiinflammatory drugs** (NSAIDs; e.g., naproxen) are more effective than placebo in treating heavy bleeding and can also treat concurrent dysmenorrhea. Clinicians may need to educate patients and families about the noncontraceptive medical indications for hormonal contraception given the unnecessary stigma commonly associated with these medications. Active bleeding typically responds well to cycling with any **combined hormonal contraceptive method** containing estrogen and progestin starting with once-daily dosing; up to twice-daily dosing may be considered until bleeding stops. Patients with estrogen contraindications such as migraine with aura, uncontrolled hypertension, or thrombotic risks can be treated with progestins alone, such as medroxyprogesterone 10 mg orally daily or norethindrone acetate 5-10 mg PO daily, either continuously or for 10-14 days per month. The latter regimen will be followed by monthly bleeding.

Iron deficiency with or without anemia should be treated with **65 mg elemental oral iron** once daily until serum ferritin >30 µg/mL. Dosing more frequently than daily has not been shown to be beneficial. Ferritin and hemoglobin should be repeated 4 weeks after treatment is initiated. Once anemia is corrected, iron should be continued once daily for 3 months to replenish iron stores. A referral to hematology may be warranted for insufficient response or intolerance of oral iron for consideration of **intravenous (IV) iron therapy**.

With **moderate** anemia, any of the hormonal regimens noted earlier can be used. However, it may be necessary in patients with more brisk bleeding to start with three to four **combined oral contraceptive (COC) pills** (or three to four doses of **medroxyprogesterone** 10 mg) per day, with additional medication to control nausea. The dose can usually be tapered to daily dosing over the next 2 weeks. Patients with ongoing rapid bleeding, syncope or lightheadedness, hemodynamic instability, or hemoglobin of <7 g/dL should be treated in the hospital.

Patients with **severe** anemia should be treated with one of the hormone tapers described earlier, in addition to **IV fluid or blood products** as indicated; it is advisable to draw necessary hematologic laboratory studies before transfusion. Patients with emesis or other significant symptoms may be initially treated with **conjugated estrogens** 25 mg IV every 4-6 hours for 1-2 days. A COC or progestin regimen should be added within 24-48 hours because progestin is needed to stabilize the endometrial lining and can be used as maintenance therapy after hospital discharge. In the exceptionally rare case of a patient whose bleeding cannot be controlled hormonally, options for gynecologic interventions include **intrauterine Foley balloon placement** or **uterine packing** to tamponade the uterus mechanically. Dilation and curettage, performed frequently in adults, is almost never indicated in adolescents and can increase blood loss in patients with bleeding disorders.

Hormonal AUB treatment should continue for at least 3-6 months, depending on the patient's age, prior menstrual history, and severity of presentation, before reassessing the need for ongoing therapy. Additional options for maintenance therapy include **combined hormonal transdermal patches and vaginal rings**; **depot medroxyprogesterone acetate** 150 mg intramuscularly (IM) or 104 mg subcutaneously (SC) every 3 months; and placement of a **levonorgestrel intrauterine device** (IUD), depending on the patient's preference and/or concurrent need for long-term contraception. For patients who need or choose to avoid hormonal therapy, **antifibrinolytics such as tranexamic acid** 1,300 mgPO 3 times daily can be used for up to 5 days during monthly menstruation in patients who do not have an increased risk of thrombosis.

Females with a known bleeding disorder may be up to 5 times more likely to develop heavy menstrual bleeding. Therefore it can be helpful while the patient is premenarcheal to devise a proactive plan in collaboration with the patient's hematology team in the event of acute heavy menstrual bleeding, which can occur at menarche.

Table 159.5 Laboratory Tests to Evaluate Patients with Abnormal Uterine Bleeding

Complete blood count with platelets
Ferritin
Urine pregnancy test (regardless of history)
Thyroid function studies
Total and free testosterone*
Liver and kidney function studies
Nucleic acid amplification test (NAAT) or equivalent testing for *Chlamydia trachomatis, Neisseria gonorrhoeae*, and *Trichomonas vaginalis*
Prothrombin time and partial thromboplastin time
von Willebrand factor antigen, vWF activity (such as ristocetin cofactor), and factor VIII† activity
Pelvic ultrasound (if palpable mass or bleeding persists despite treatment)

*In patients with signs or symptoms suggestive of polycystic ovary syndrome, such as acne, hirsutism, obesity, acanthosis nigricans, and a history of infrequent menses.
†Any abnormalities should be referred to a hematologist. False-negative von Willebrand tests and false-positive platelet function studies have been observed in the setting of anemia. It is preferable to obtain tests before estrogen treatment is started to minimize false-negative results. Repeat testing is common in patients for whom there is a high pretest suspicion.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

159.3 Dysmenorrhea

Fareeda Haamid and Gina S. Sucato

Dysmenorrhea, painful uterine cramps that precede and accompany menses, occur in up to 90% of 17- to 24-year-olds. Although dysmenorrhea is frequently severe enough to interfere with school and other activities, many adolescents undertreat their symptoms, and fewer seek medical care.

Dysmenorrhea may be primary or secondary. **Primary dysmenorrhea**, characterized by the absence of any specific pelvic pathologic condition, is the more commonly occurring form, accounting for approximately 90% of cases. After ovulation, withdrawal of progesterone results in synthesis of prostaglandins by the endometrium, which stimulates local vasoconstriction, uterine ischemia and pain, and smooth muscle contraction, explaining uterine and GI symptoms.

Secondary dysmenorrhea results from underlying pathology, such as anatomic abnormality, or infection, such as pelvic inflammatory disease. However, the most common cause of secondary dysmenorrhea in adolescents is **endometriosis**, a condition in which implants of endometrial tissue are found outside the uterus, usually near the fallopian tubes and ovaries. Often, other family members have endometriosis. Severe menstrual pain is characteristic of endometriosis; however, adolescents may also have noncyclic pain. Although primary dysmenorrhea is almost always the cause, a careful history and physical examination are required for adolescents who present with **pelvic pain**. An internal pelvic exam is not required in females who are not sexually experienced and whose presentation is consistent with primary dysmenorrhea. Constipation can vary cyclically in many females, especially those with irritable bowel syndrome, and often significantly contributes to the pain. **Mittelschmerz**, brief severe pain with ovulation, occurs at mid-cycle. Table 159.6 lists the differential diagnosis and "red flags" for secondary dysmenorrhea. Ovarian cysts, a frequent concern of families, are usually transient and painless.

Treatment for primary dysmenorrhea is aimed at preventing or decreasing prostaglandin production. The mainstay of first-line treatment is prostaglandin synthetase inhibition with **NSAIDs** (Table 159.7) beginning at,

Table 159.6 Differential Diagnosis of Dysmenorrhea in Adolescents*

	PRESENTATION	DIAGNOSIS
Primary	Crampy pelvic pain may be accompanied by aching/heaviness in lower back and upper thighs, nausea, emesis, diarrhea, headache, mastalgia, fatigue, and dizziness; symptoms begin at or shortly before menstrual flow onset and last 1-3 days.	Normal physical exam; internal exam only for sexually active adolescents. Ultrasound can be reserved for patients with atypical presentations (e.g., onset at menarche) or pain despite NSAIDs and hormonal therapy.
Endometriosis and adenomyosis†	**Increasingly severe dysmenorrhea despite adequate therapy**; pain exacerbated during menses or noncyclical pain.	Increased risk in patients with obstructive anomalies and possibly bleeding disorders; however, most adolescents with endometriosis have normal anatomy and bleeding indices; visual diagnosis is made during surgery and confirmed by tissue sample.
Müllerian anomalies with partial outflow obstruction	**Pain begins at or shortly after menarche** and occurs with bleeding; presence of **known renal tract anomaly** (often coexists with müllerian anomaly).	Pelvic ultrasound will demonstrate uterine anomalies (e.g., rudimentary uterine horn); MRI may be required to identify some lesions (e.g., obstructed hemivagina).
Pelvic inflammatory disease	Abrupt onset of dysmenorrhea more severe than baseline in a sexually active adolescent; presentation can range from mild discomfort to acute abdomen.	Clinical diagnosis made by finding **lower abdominal tenderness plus cervical motion tenderness, uterine or adnexal tenderness** on bimanual pelvic examination (see Chapter 146); supporting features include dysuria, dyspareunia, **vaginal discharge**, fever, and increased white blood cell count.
Pregnancy complication	Coincident pain and bleeding may be misdiagnosed as dysmenorrhea.	Urine test positive for human chorionic gonadotropin.

*__Bold__ entries indicate "red flags" for diagnosis.
†Adenomyosis is the presence of endometrial tissue within the uterine myometrium.

Table 159.7 Treatment for Dysmenorrhea

	MEDICATION	REGIMEN	COMMENTS
NSAIDs (for up to 5 days)	Ibuprofen 200 mg	2 tablets PO q4-6h	Over-the-counter
	Naproxen sodium 275 mg	550 mg loading dose, then 275 mg PO q6h	Patients may prefer the equivalent 550 mg PO q12h dosing regimen.
	Celecoxib (cyclooxygenase [COX]-2 inhibitor)*	400 mg loading dose, then 200 mg PO q12h prn pain	Can be used for patients with bleeding disorders.
Hormonal contraception	Combined hormonal contraceptive	Continuous hormone regimens vs standard 21 hormone days followed by 7 placebo days may offer better relief but may increase the risk of unscheduled intermenstrual bleeding.	Treatment can be based on patient preference.
	Progestin-only methods	DMPA 150 mg IM or 104 mg SC q3mo; levonorgestrel intrauterine device for up to 8 yr; etonogestrel implant	DMPA has potential side effects of weight gain, interference with expected bone density increase during adolescence, and higher discontinuation rates than LARC methods.
Gonadotropin-releasing hormone agonist	Depot leuprolide	11.25 mg IM q3mo	Consider for presumed endometriosis unresponsive to hormonal methods; add-back hormones advised to prevent bone loss.

*This medication may cause serious cardiovascular and gastrointestinal events. Use with caution in patients with impaired renal or liver dysfunction, heart failure, or a history of GI bleeding or ulcer. Full prescribing information can be found at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020998s050lbl.pdf
DMPA, Depot medroxyprogesterone acetate; LARC, long-acting reversible contraceptive; NSAIDs, nonsteroidal antiinflammatory drugs.

Table 159.8 Criteria for Premenstrual Dysphoric Disorder

A. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to *improve* with a few days after the onset of menses, and become *minimal* or absent in the week post menses.
B. One (or more) of the following symptoms must be present:
   1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
   2. Marked irritability or anger or increased interpersonal conflicts.
   3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
   4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.
C. One (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from criterion B.
   1. Decreased interest in usual activities (e.g., work, school, friends, and hobbies).
   2. Subjective difficulty in concentration.
   3. Lethargy, easy fatigability, or marked lack of energy.
   4. Marked change in appetite, overeating, or specific food cravings.
   5. Hypersomnia or insomnia.
   6. A sense of being overwhelmed or out of control.
   7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain.

Note: The symptoms in criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).
E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).
F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (*Note:* The diagnosis may be made provisionally prior to this confirmation.)
G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

From the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., pp. 171–172. Copyright 2013. American Psychiatric Association.

or preferably the day before, menstruation. High doses of around-the-clock treatment are rarely needed for more than the first 2 days. More data are needed to make specific treatment recommendations regarding exercise, but females should be reassured that participation in usual sports and extracurricular activities is not only permissible but a benchmark of adequate treatment.

For those adolescents whose pain does not optimally respond to dosed NSAIDs, or who also require contraception, the currently available forms of **hormonal contraception** will improve dysmenorrhea. Up to three cycles may be required to appreciate the full benefit. Methods and regimens that eliminate a placebo interval may provide better relief. Despite various studies of adjuvant treatments including heat, aromatherapy, acupressure, acupuncture, transcutaneous nerve stimulation, herbal remedies, yoga, and dietary supplements, hormonal medications are the mainstay of second-line treatment. Females whose pain persists despite more than 3 months of adequate hormonal therapy require further evaluation and treatment and referral to a specialist, as endometriosis has been found in up to 69% of adolescents who underwent laparoscopy for persistent pelvic pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

159.4 Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Fareeda Haamid and Gina S. Sucato

Premenstrual syndrome (PMS), which occurs in up to 30% of adolescents, is marked by symptoms such as mood changes, bloating, and breast tenderness that begin in the luteal phase of the menstrual cycle (i.e., the time between ovulation and the first day of bleeding) and improve within a few days after the onset of menses. Adolescents are often reassured by education about the relationship of symptoms to the menstrual cycle. Lifestyle interventions such as exercise and stress reduction sometimes provide adequate relief. For more severe symptoms, cognitive-behavioral therapy may be useful. Current data do not support routine recommendations for any vitamin, mineral, or other dietary supplements in the absence of documented deficiency. There is not strong evidence supporting the effectiveness of combined hormonal contraceptive methods for PMS. However, some experts suggest this treatment option for adolescents who also have dysmenorrhea, acne, or contraceptive needs.

Premenstrual dysphoric disorder (PMDD) is distinguished from other depressive disorders by its timing; mood symptoms are precipitated by ovulation, recur in the luteal phase, and disappear at the end of menstruation. It is distinguished from PMS by the severity and consequences of the affective symptoms. PMDD causes significant distress and functional impairment and may be accompanied by physical and behavioral symptoms (Table 159.8). It is a distinct, treatment-responsive depressive disorder. PMDD occurs in 2–6% of menstruating females worldwide. Accurate diagnosis requires use of a menstrual calendar to prospectively document cyclic symptoms. Other mental health conditions such as depression and anxiety disorders may be exacerbated before or during menses, but symptoms will occur throughout the cycle.

Selective serotonin reuptake inhibitors (SSRIs) are first-line therapy for PMDD and severe PMS. In contrast to the treatment of depression, SSRIs can be rapidly effective for premenstrual symptoms and thus can be prescribed either continuously or intermittently, beginning at ovulation (or whenever in the luteal phase symptoms begin) and ending when symptoms resolve. Adolescents can be prescribed the standard regimens used for adults, such as fluoxetine 20 mg PO daily. For adolescents who also need contraception, the drospirenone 3 mg and ethinyl estradiol 0.02 mg combination pill delivered for 24 days followed by 4 inactive days has been approved by the Food and Drug Administration for PMDD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 160
Contraception

Mary E. Romano and Elizabeth M. Alderman

The consequences of sexual activity, including unintended pregnancy (see Chapter 161) and sexually transmitted infections (STIs; Chapter 163), occur in adolescents at higher rates than in adults. Significant barriers, including access to confidential care, may delay an adolescent's ability to access reproductive healthcare until after initiation of sexual activity, and many may become pregnant and/or acquire an STI during this interval. Early and appropriate counseling and education with adolescents, including direct discussion of the risks of unintended pregnancy and STI prevention, can help to mitigate these risks; adolescents who plan sexual initiation are 75% more likely to use contraception at sexual debut. Therefore appropriate patient-centered counseling and provision of contraception as warranted are an essential component of comprehensive healthcare for adolescents. *Female* refers to cisfemale but theoretically would include all those with a uterus engaging in sexual behaviors that put them at risk for pregnancy.

CONTRACEPTIVE EFFECTIVENESS

To decrease rates of unintended pregnancy, the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) recommend that healthcare providers counsel about and ensure access to all contraceptive methods for their adolescent patients. Comparing typical effectiveness of contraceptive methods, Figure 160.1 illustrates a tiered system of contraceptive methods ranging from more effective to least effective. These tiers are categorized by **typical-use failure rates**, which reflect the effectiveness of a method for the average person who may not always use the method consistently or correctly (Table 160.1). For example, for oral contraceptive pills, the typical-use failure rate is 7%, whereas the *perfect-use* failure rate is <1%. **Tier 1** methods, the most effective, include those with failure rates of <1 pregnancy per 100 women in a year of typical use, and reversible Tier 1 methods include intrauterine devices (IUDs) and implants. **Tier 2** methods have failure rates of 4-7 pregnancies per 100 women in a year of typical use and include injectable contraception, oral contraceptive pills, contraceptive patches, and the vaginal ring. **Tier 3** methods have failure rates of >13 pregnancies per 100 women per year of typical use and include the male and female condom, the diaphragm, withdrawal, the sponge, fertility awareness–based methods, and spermicides.

160.1 Contraceptive Use

Mary E. Romano and Elizabeth M. Alderman

SEXUAL ACTIVITY

According to the 2021 Youth Risk Behavior Surveillance System, 30% of U.S. high school students had ever had sexual intercourse and approximately 22% reported being currently sexually active. These numbers have been decreasing since 2015. However, significant decreases noted from 2019 to 2021 may be attributable to the effect of the COVID pandemic on behaviors.

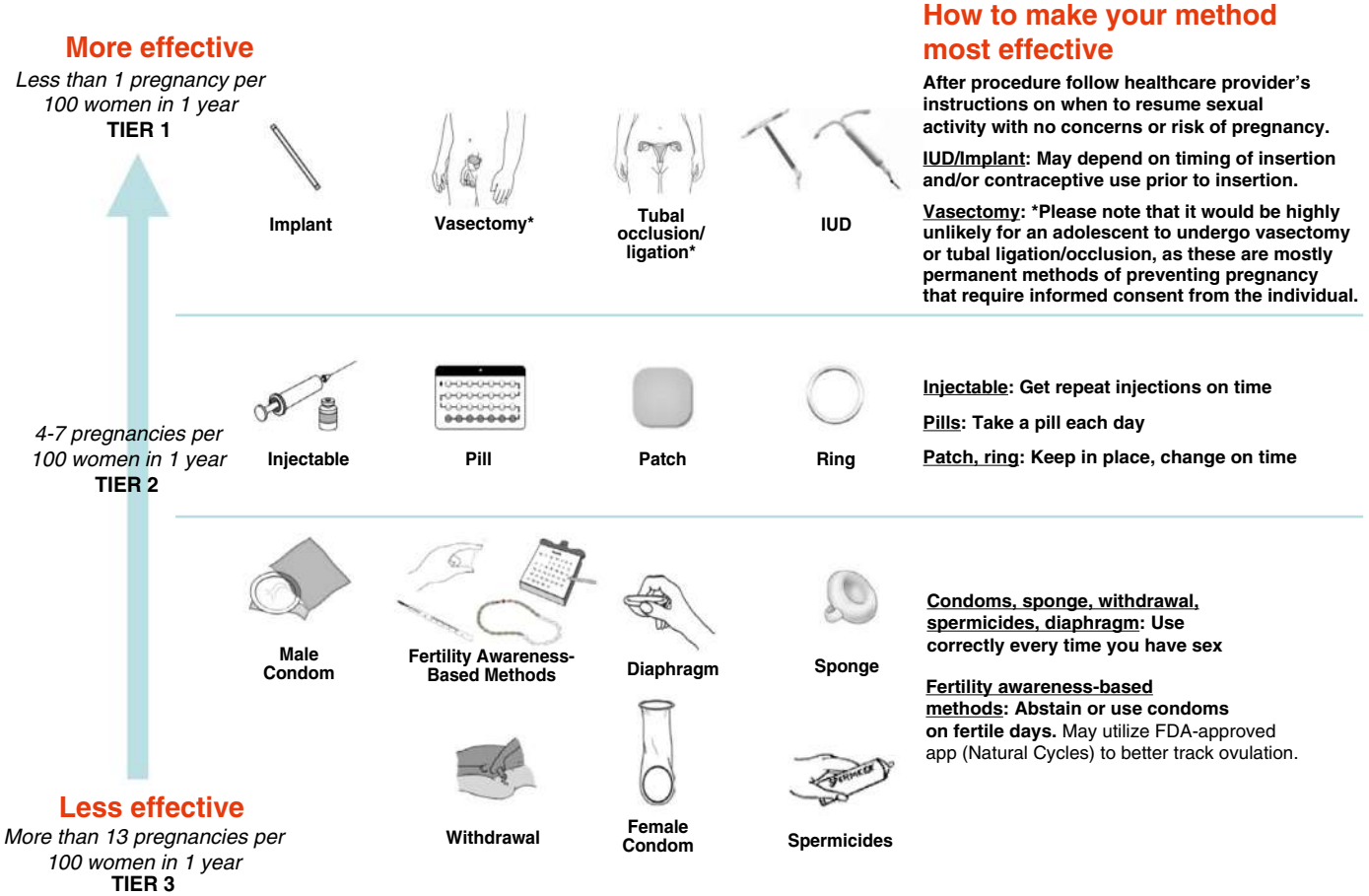

Fig. 160.1 Effectiveness of contraceptive methods. (*Modified from Trussell J, Aiken ARA, Micks E, Guthrie K. Contraceptive efficacy, safety, and personal considerations. In: Hatcher RA, Nelson AL, Trussell J, et al., eds. Contraceptive Technology, 21st ed. New York: Ayer Company Publishers; 2018:102.*)

Table 160.1 Efficacy of Contraceptives

METHOD	FAILURE RATE (%)* TYPICAL USE	PERFECT USE	SOME ADVANTAGES	SOME ADVERSE EFFECTS AND DISADVANTAGES
Implant				
Nexplanon	0.1	0.1	Convenience; long-term contraception; efficacy not dependent on patient adherence; rapid return of fertility after removal	Irregular bleeding; amenorrhea, insertion and/or removal complications
Intrauterine Devices (IUDs)			Convenience; long-term contraception; efficacy not dependent on patient adherence; rapid return of fertility after removal	Rare uterine perforation; risk of infection with insertion
ParaGard T380A	0.8	0.6	Effective for 10 yr; nonhormonal	Irregular/heavy bleeding and dysmenorrhea
Mirena	0.1	0.1	Effective for 8 yr; decreased menstrual bleeding and improved symptoms of dysmenorrhea	Irregular bleeding in first 3-6 mo, followed by amenorrhea; unpredictable suppression of ovulation and potential ovulatory SE (ovarian cysts, PMS, dysmenorrhea)
Liletta	0.1	0.1	Decreased menstrual bleeding and improved symptoms of dysmenorrhea	Irregular bleeding in first 3-6 mo; unpredictable suppression of ovulation and potential ovulatory SE (ovarian cysts, PMS, dysmenorrhea)
Kyleena	0.2	0.2	Smaller T-frame and narrower insertion tube	Irregular bleeding in first 3-6 mo; unpredictable suppression of ovulation and potential ovulatory SE (ovarian cysts, PMS, dysmenorrhea), unpredictable bleeding pattern for the duration of use
Skyla	0.4	0.3	Smaller T-frame and narrower insertion tube	Irregular bleeding in first 3-6 mo; unpredictable suppression of ovulation and potential ovulatory SE (ovarian cysts, PMS, dysmenorrhea), unpredictable bleeding pattern for the duration of use
Injectable				
Depo-Provera	4	0.2	Convenience of q3mo injections; same as progestin-only oral contraceptives	Delayed return to fertility, irregular bleeding, and amenorrhea; weight gain; decreased bone mineral density while receiving injections
Combination Oral Contraceptives	7	0.3	Protection against ovarian and endometrial cancer; suppresses ovulation, which can improve symptoms of PMS, PMDD, and dysmenorrhea; quick return to fertility upon discontinuation	Increased rate of thromboembolism, which increases with age and in those with underlying risks for blood clots, nausea; headache; contraindicated with breastfeeding
Progestin-Only Oral Contraceptives	7	0.3	Safe in breastfeeding women and those with underlying risk of blood clots	Irregular, unpredictable bleeding; must take at same time every day, unpredictable suppression of ovulation
Transdermal Patch	7	0.3	Convenience of once-weekly application; same benefits as combination oral contraceptives	Application site reactions; detachment; increased estrogen exposure as compared with oral contraceptives
Vaginal Ring	7	0.3	Convenience of once-monthly application, benefits similar to combination oral contraceptive pills	Discomfort of ring or with insertion; vaginal discharge
Diaphragm with Spermicide	17	16	Low cost	High failure rate; cervical irritation; there can be increased risk of urinary tract infection and toxic shock syndrome with improper and prolonged use; some require fitting by healthcare professional; may be difficult to obtain; available only by prescription
Condoms Only				
Female	21	5	Protection against STIs; covers external genitalia; OTC	High failure rate; difficult to insert; may be less appealing because of need to stop during sexual activity
Male	13	2	Protection against STIs, OTC, male participation	High failure rate; allergic reactions; may be less appealing because of need to stop during sexual activity; breakage possible
Cervical Cap	16–32	9–26	Effective for 48 hr; can be used for ~2 yr	High failure rate, cervical irritation, risk of toxic shock, limited sizes, requires prescription
Withdrawal	20	4	No drugs or devices	High failure rate
Sponge	14–27	9–20	OTC; low cost; no fitting required; provides 24 hr of protection	High failure rate; contraindicated during menses; increased risk of toxic shock syndrome with improper and prolonged use

Continued

Table 160.1 Efficacy of Contraceptives—cont'd

METHOD	FAILURE RATE (%)* TYPICAL USE	PERFECT USE	SOME ADVANTAGES	SOME ADVERSE EFFECTS AND DISADVANTAGES
Fertility Awareness–Based Methods	15	—	Low cost; no drugs or devices	High failure rate; can be difficult to use properly if periods/ovulation are not well established/regular, requires periods of abstinence
Spermicide			Available OTC	High failure rate; local irritation; must be reapplied with repeat intercourse; unknown effect on HIV transmission, cost
Nonoxynol-9	21	16	—	
Phexxi	14	5	Microbicidal effect, increased viscosity as compared to other spermicides	Requires a prescription, local irritation; must be reapplied with repeat intercourse; cannot be used with vaginal ring, cost/insurance coverage
No Method	85	85	—	—

*Risk of unintended pregnancy during first year of use; data from Trussel J et al: In: Hatcher RA, Nelson AL, Trussell J, et al., eds. *Contraceptive Technology,* 21st ed. New York: Ayer Company Publishers; 2018.
STIs, Sexually transmitted infections; OTC, over the counter; N-9, Nonoxynol 9.
Adapted from Choice of contraceptives. *Med Lett* 2018;60(1557):161.

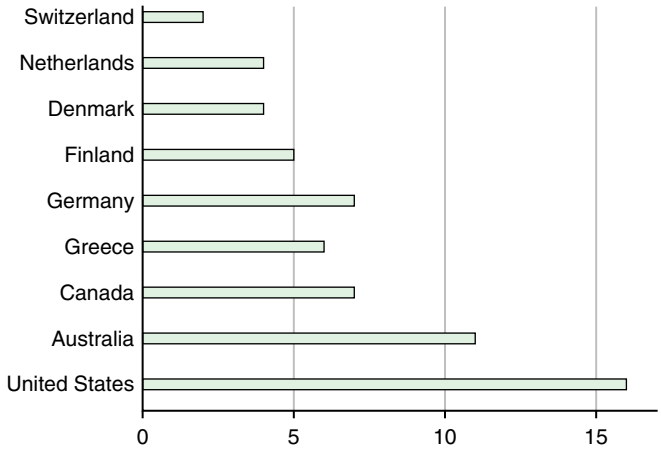

Fig. 160.2 Teen birthrates in high-income countries, 2020. Live births per 1,000 females age 15-19 yr. (*Data from The World Bank Group. United Nations Population Division, World Population Prospects.* https://data.worldbank.org/indicator/SP.ADO.TFRT.)

Although U.S. teens and European teens have similar levels of **sexual activity** and ages of **sexual debut**, U.S. teens are less likely to use contraception and less likely to use the most effective methods. Teen pregnancy rates have been declining worldwide—a result of delayed initiation of sexual activity and increased contraceptive use. Despite this decline, the United States still had the highest teen birthrate in the Western industrialized world as of 2020, with 16.7 live births per 1,000 females age 15-19 years (Fig. 160.2). This is 8 times higher than the teen birthrate in Switzerland, which has the lowest rate in Western Europe. As of 2020 the teenage pregnancy rate in the United States is 31 pregnancies per 1,000 women, with a rate of 13.6/1,000 in those 15-17 years and 56.9/1,000 in those 18-19 years. The majority of these pregnancies are unintended, and one in five births are a repeat birth, indicating an unmet need for reliable, effective contraception that teens will correctly and consistently use.

USE OF CONTRACEPTION AMONG TEENS

According to the 2017–2019 National Survey of Family Growth, 78% of females and 89% of males who had their first sexual intercourse before age 20 years used a contraceptive method at first intercourse. The method most used by teenage females is the condom, followed by withdrawal (both least effective methods) and then the pill (a moderately effective method). IUDs and implants, the most effective reversible methods, are used by 20% of females 15-19 years, with the implant being more commonly used (15%). Use of contraception at first sex has greatly increased over the last 50 years. Factors associated with contraceptive use at first sex include increasing age among teens up to age 17 years, time spent in college, and planning their sexual debut.

More than half of sexually experienced female teens are currently using the most effective reversible contraceptives or moderately effective contraceptive methods. U.S. teens' use of hormonal methods at last intercourse is less frequent compared with teens in other developed countries. A higher likelihood of female current contraceptive use is associated with older age at sexual initiation, aspirations for higher academic achievement, acceptance of one's own sexual activity, and a positive attitude toward contraception. Despite the importance of dual-method use to protect against both unwanted pregnancy and STIs, only 33% of sexually active female U.S. teens report using a barrier method (condoms) plus another method of contraception at last sexual activity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.2 Contraceptive Counseling

Mary E. Romano and Elizabeth M. Alderman

The adolescent preventive health visit offers opportunities for confidential discussions with all adolescents and the opportunity to identify and discuss sexual practices that may be putting the adolescent at risk for STIs or unintended pregnancy. It is also a time to discuss safe sexual behaviors, including abstinence (see Chapter 151). It is important to ask specifically about adolescents' sexual behaviors to make sure your counseling is appropriate for their sexual activity. Adolescents with medical conditions, either chronic or acute, are particularly vulnerable to having sexual and reproductive health omitted from their visits, although they have similar sexual health and contraceptive needs (see Chapter 756). Their comorbidities or concurrent medication use may make STIs and unintended pregnancy an increased health risk and may affect contraceptive counseling/options. The **U.S. Medical Eligibility Criteria for Contraceptive Use** (MEC) outlines medical conditions associated with increased risk for adverse health events with pregnancy and provides recommendations for who can safely use specific contraceptive methods.

The goals of adolescent contraceptive counseling are to (1) understand adolescent experiences, preferences, perceptions, and misperceptions about pregnancy and use of contraceptives; (2) help adolescents understand the risks of unprotected sexual intercourse, including STIs and unintended pregnancy; (3) educate adolescents about the various contraceptive methods available using information that is medically accurate, balanced, and provided in a nonjudgmental manner; and (4) engage in patient-centered counseling so the adolescent feels empowered to choose a safe and effective method that can either be

provided on site or be easily obtained through prescription or by referral. If adolescents are comfortable and willing to include their parents in this discussion, it is also always helpful to engage parents in the decision-making process and address any parental questions and concerns. Providers should be aware of state laws affecting confidentiality and an adolescent's ability to access confidential contraceptive services (see Chapter 151). Most states allow adolescents confidential access to contraceptive services, but given that many adolescents are under their parents' insurance plan, confidentiality may be unintentionally breached through billing and explanation of benefit statements, as well as through the open notes mandate. This should be discussed with adolescents, especially those who are very concerned about disclosing sexual health information to their parents or guardians.

Counseling should include a review of all contraceptive methods available that the adolescent can use safely (see U.S. MEC). **Long-acting reversible contraception** (LARC/IUDs and implants) is a safe and effective option for many adolescents, including those who have not been pregnant or given birth. The adolescent should be counseled about method effectiveness using typical-use failure rates. Although it is important to highlight the methods most effective at preventing pregnancy, it is also imperative to provide contraceptive counseling within the framework of reproductive justice and to avoid any coercion due to provider preference or bias. The focus of contraceptive counseling should be on the priorities of the adolescent, and the adolescent should be allowed to explore all options and determine which method is most appropriate for their contraceptive needs and priorities. It is important to ask about use of **withdrawal** and discuss its risks given that 60% of female teens have used it for contraception and it has a typical-use failure rate of 20%. **Abstinence** should also be discussed as an option even if teens have engaged in sexual intercourse in the past. Abstinence may be the best option if adolescents do not have another method available at a particular time.

Necessary concepts to address while discussing individual methods include how effective the method is, how long the method works, what behaviors are required for correct and consistent use, what side effects may be seen, any noncontraceptive benefits of the method (e.g., reduced menstrual bleeding, protection from STIs), and what signs or symptoms of complications should prompt a return visit. Reviewing common side effects allows teens to anticipate and cope with any changes with reassurance and may avoid method discontinuation. Weighing the possibility of certain side effects with the possibility of an unintended pregnancy may also help with the conversation. It is also important to address any specific misperceptions teens may have for certain contraceptives regarding side effects, effectiveness, or effect on future fertility.

Once an adolescent chooses a method, the provider and adolescent should discuss clear plans on correct and consistent use of the chosen method and strategies for appropriate follow-up (see Table 160.1). Providers should help the adolescent consider potential barriers to correct and consistent use (e.g., forgetting to take a pill daily) and develop strategies to deal with each barrier (e.g., use of reminder systems such as daily text messages or phone alarms). The provider should assess whether the teen understood the information discussed and may confirm by asking the teen to repeat back key concepts.

The U.S. Selected Practice Recommendations for Contraceptive Use provides guidance for providers regarding when to start contraception, how to be certain the woman is not pregnant at contraception initiation, and what examinations and tests are recommended before initiating contraception. Generally, women may start a contraceptive method other than an IUD at any time, and an IUD may be placed when a provider is reasonably certain that a woman is not pregnant. The Centers for Disease Control and Prevention (CDC) defines this as a patient who has no symptoms or signs of pregnancy, is ≤7 days after the start of normal menses, has not had sexual intercourse since the start of last normal menses, and has been correctly and consistently using a reliable method of contraception

Most women do not require any special exam or additional screening for STIs before initiating contraception if they have been recently screened according to the CDC's STI treatment guidelines. A blood pressure reading is advisable. A pelvic examination is only required for placement of an IUD, unless otherwise indicated. STI screening is appropriate at and/or before IUD placement, even if a patient does not report sexual activity, as some patients may choose to not disclose this information to their provider. Gonorrhea and chlamydia screening using a self- or provider-collected vaginal swab or urine sample is recommended unless symptoms require a pelvic exam. IUD placement should not be delayed to receive screening results. Cervical cancer screening is not recommended until age 21.

Providers should offer confidential services to adolescents and observe all relevant state laws and legal obligations (e.g., notification or reporting of sexual abuse). Chapter 151 discusses confidentiality and consent issues related to contraceptive management. Providers should also encourage adolescents to involve parents or guardians in their healthcare decisions, while giving parents clear information on their teen's right to confidentiality, privacy, and informed consent. All services should be provided in a youth-friendly manner, meaning that they are accessible, equitable, acceptable, appropriate, comprehensive, effective, and efficient. Resources are available that describe ways to ensure a **teen-friendly** reproductive health visit.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.3 Long-Acting Reversible Contraception

Mary E. Romano and Elizabeth M. Alderman

Long-acting reversible contraception **(LARC)** includes four **levonorgestrel (LNG)** IUDs, the **copper (Cu)** IUD, and the etonogestrel subdermal implant. LARC methods are the only Tier 1 methods that are reversible (see Fig. 160.1). Their efficacy is the result of the fact that LARC does not require frequent office or pharmacy visits and does not depend on user adherence for effectiveness. In the Contraceptive CHOICE Project in St. Louis, Missouri, >9,000 women were given the contraceptive method of their choice at no cost and were followed for 2-3 years. The failure rates among women of all ages, including adolescents who used oral contraceptive pills, transdermal patch, or vaginal ring, were >20 times higher than the failure rates for those using a LARC method. Acceptance, continuation, and satisfaction in this project were also higher among adolescents using LARC compared with adolescents using non-LARC methods. *ACOG and AAP support the use of LARC methods for adolescents.* The U.S. MEC supports safe use of both IUDs and implants for adolescents and nulliparous women. Implants are considered Category 1 for all ages, and IUDs are considered Category 2 for women <20 years old and for nulliparous women (Table 160.2).

INTRAUTERINE DEVICES

IUDs are small, flexible, plastic objects introduced into the uterine cavity through the cervix. They differ in size, shape, presence or absence of hormone, and dose of hormone delivered daily. In the United States, five IUDs are currently approved by the Food and Drug Administration (FDA): the CuT380A (Paragard) and four LNG IUDs (Liletta, Kyleena, Mirena, and Skyla).

The LNG IUDs also have various actions, from thickening of cervical mucus and inhibiting sperm survival to suppressing the endometrium. LNG IUDs are effective and approved for use from 3 to 8 years. The Cu IUD releases copper ions into the uterine cavity, which induces an inflammatory response within the endometrium. Copper also impairs sperm motility/migration, inhibits the acrosomal reaction, and impairs implantation. As with the other IUDs, the Cu IUD is reversible, safe for use in nulliparous women, and effective for at least 10 years. All IUDs have typical-use failure rates of <1% (see Fig. 160.1). All LARC methods are appropriate and safe to use in the postpartum period.

Mirena is FDA approved for the treatment of heavy menstrual bleeding, and studies in adults have demonstrated an 80% reduction in menstrual blood loss in Mirena users, with 50% of users reporting amenorrhea after 2 years of use. Among the other LNG IUDs,

Table 160.2 Categories of Medical Eligibility Criteria for Contraceptive Use

Category 1: A condition for which there is no restriction for the use of the contraceptive method
Category 2: A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
Category 3: A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
Category 4: A condition that represents an unacceptable health risk if the contraceptive method is used

Table 160.3 Conditions Classified as Category 3 and 4 for Combined Hormonal Contraceptive Use

Category 4 (a condition that represents an unacceptable health risk if the contraceptive method is used)
Complicated valvular heart disease
Current breast cancer
Severe decompensated cirrhosis
Deep venous thrombosis/pulmonary embolism (acute; history, not on anticoagulation or on established therapy for at least 3 mo with higher risk recurrence; major surgery with prolonged immobilization)
Complicated diabetes with nephropathy, retinopathy, neuropathy, or other vascular disease or duration of diabetes >20 yr
Migraine with aura
Poorly controlled hypertension (blood pressure >160/100 mm Hg) or hypertension with vascular disease
Ischemic heart disease (history of or current)
Hepatocellular adenoma
Malignant liver tumor
Peripartum cardiomyopathy (diagnosed <6 mo before or with moderately or severely impaired cardiac function)
Postpartum <21 days
History of cerebrovascular accident
Systemic lupus erythematosus with positive antiphospholipid antibodies
Thrombogenic pathogenic variants
Viral hepatitis (acute or flare)
Category 3 (a condition for which the theoretical or proven risks usually outweigh the advantages of using the method)
Past breast cancer with no evidence of disease for 5 yr
Breastfeeding and <1 mo postpartum
Deep venous thrombosis/pulmonary embolism (history of DVT/PE with lower risk recurrence)
Gallbladder disease (current, medically treated)
History of malabsorptive bariatric surgery
History of cholestasis and past combined oral contraceptive–related
Hypertension (adequately controlled or blood pressure <160/100 mm Hg)
Peripartum cardiomyopathy with mild impairment or >6 mo
Postpartum 21-42 days with other risk factors for venous thromboembolism
Drug interactions (ritonavir-boosted protease inhibitors; certain anticonvulsants; rifampin or rifabutin)
First-degree family member with a history of a blood clot/clotting disorder/thromboembolic event

From Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016, *MMWR Recomm Rep* 2016;65(RR-3):1–104.

amenorrhea at 2 years is reported at 26% for Liletta users, and Kyleena and Skyla report prolonged and irregular bleeding at 1 year in 5–20% of users. Heavier bleeding patterns and increased dysmenorrhea are reported in users of the Cu-IUD. Patients should be counseled on bleeding patterns and expected changes to their menstrual bleeding after IUD insertion (Table 160.3).

Common misconceptions of IUDs among healthcare providers are that IUDs can cause or increase the risks of infections, cause infertility, and generally are not safe or tolerated by teens or nulliparous women; these misconceptions can be a barrier for teens desiring an IUD to access these highly effective and safe methods. IUDs do not increase risk of infertility and may be inserted safely in teenagers regardless of parity (Category 2; see Table 160.2).

Although early studies suggested an increased risk for upper genital tract infection, because of the passing of a foreign body through the cervix, new studies have refuted these concerns. Therefore clinicians are encouraged to consider the use of IUDs in adolescents despite relatively high prevalence rates of STIs in this population. Teens should be screened for gonorrhea and chlamydia at and/or before IUD placement, although placement should not be delayed if results have not returned and there are no signs of current infection (e.g., purulent discharge, erythematous cervix). If STI testing is positive with an IUD in place, the patient may be treated without removing the IUD if she wants to continue the method.

There has been evidence that rates of IUD expulsion are higher in adolescents as compared to older women. The data are limited, but the risk seems to be higher with Cu-IUD vs hormonal IUD, previous IUD expulsion, and concomitant use of the menstrual cup. A paracervical block with lidocaine may reduce patient discomfort during placement and, along with other medications (e.g., NSAIDs, anxiolytics), may be considered on an individual patient basis, but these are not routinely recommended.

IMPLANTS

One contraceptive implant is available in the United States. The single rod that releases 60 μg/day of **etonogestrel** has been updated to a radiopaque rod with a new inserter. This **progestin-only method** keeps etonogestrel at steady serum levels for at least 3 years and primarily works to inhibit ovulation. Similar to the levonorgestrel IUD, the progestin acts on the uterus to cause an atrophic endometrium and thicken cervical mucus to block sperm penetration; its typical-use failure rate is also <1% (see Fig. 160.1). Unlike the IUD, no pelvic exam is required for insertion. A trained provider can quickly place or remove the implant in the upper arm under local anesthesia. The most common side effect of the contraceptive implant is irregular and unscheduled/unpredictable bleeding. This can include irregular or infrequent bleeding, amenorrhea, and less often, prolonged or frequent bleeding. Although the continuation rates are favorable and comparable to the IUD, the most common reason for discontinuation is dissatisfaction with bleeding patterns. It is important that adolescents be appropriately counseled on the potential for changes to their bleeding pattern before insertion of the implant. Adolescents who present with troublesome bleeding should be evaluated for any underlying gynecologic abnormalities, bleeding or blotting disorders, and the presence of an STI. If these are not present and adolescents desire treatment, they can be treated with a short course of NSAIDs (5-7 days) or low-dose combined oral contraceptives (COCs) if no contraindications to estrogen exist (10-20 days). Any and all adolescents desiring implant removal because of side effects should be offered prompt removal as indicated.

One potential unique complication of this method relates to localized infection and other side effects after implantation, such as bleeding, hematoma, or scarring, and if inserted too deeply into the muscle, neural damage or migration; however, these events are rare, occurring in <1% of patients. Minor side effects, such as bruising or skin irritation, are more common but most often resolve without treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.4 Other Progestin-Only Methods

Mary E. Romano and Elizabeth M. Alderman

Several progestin-only contraceptive methods are available and include the LNG IUDs and implant (see Chapter 160.3), as well as an injectable and progestin-only pills. These methods do not contain estrogen and may be useful for teens with contraindications to estrogen use or in

Table 160.4 Hormonal Intrauterine Devices

	MIRENA	KYLEENA	LILETTA	SKYLA
Duration of use	FDA approved 8 yr	FDA approved 5 yr	FDA approved 8 yr	FDA approved 3 yr
Daily hormone delivery over time	20 mcg LNG/day → 9 mcg/day (52 mcg total)	17.5 mcg LNG/day → 7.4 mcg/day (19.5 mcg total)	19.5 mcg LNG/day → 9.8 mcg/day (52 mcg total)	14 mcg LNG/day → 5 mcg/day (13.5 mcg total)
Device size	32 mm × 32 mm	28 mm × 30 mm	32 mm × 32 mm	28 mm × 30 mm
Diameter of insertion rod	4.4 mm	3.8 mm diameter	4.4 mm diameter	3.8 mm diameter

FDA, Food and Drug Administration; LNG, levonorgestrel.

patients who prefer a method without estrogen such as gender-diverse adolescents and young adults (Table 160.4). They are considered safe for use in teens (Category 1 or 2; see Table 160.2). Progestins thicken cervical mucus to block sperm entry into the uterine cavity and induce an atrophic endometrium leading to either amenorrhea or less menstrual blood loss; the implant and injectable also suppress ovulation, whereas the progestin-only pills and LNG IUDs may affect the frequency of ovulation but do not suppress it completely. Teens should be provided anticipatory counseling regarding bleeding irregularities that may normally occur in the first 3-6 months of any hormonal contraception use.

DEPO-PROVERA

An *injectable progestin,* depot **medroxyprogesterone acetate** (**DMPA**, Depo-Provera) is a Tier 2 contraceptive method available as a deep intramuscular (IM) injection (150 mg) or as a subcutaneous (SC) injection (104 mg) with typical-use failure rates of 4% (see Table 160.1). Both preparations must be readministered every 3 months (13 weeks). When appropriate, DMPA can be given up to 3 weeks before or 7 days after the 13 weeks scheduled interval without any effect on contraceptive efficacy. DMPA works by inhibiting ovulation and thickening cervical mucus. DMPA may be preferred by patients or parents who are caring for a child with intellectual disabilities. Common concerns with DMPA include bleeding changes, bone effects, and weight gain. After 1 year of use, 50% of DMPA users develop amenorrhea, which may be an added advantage for teens with heavy menstrual bleeding, dysmenorrhea, anemias, or blood dyscrasias. It may also be advantageous for those desiring menstrual suppression because of physical or developmental disabilities that make hygiene difficult or those in whom menstruation causes gender dysphoria. Studies have demonstrated bone mineral density (BMD) loss in adolescents with DMPA use, but this has not been shown to directly increase fracture risk. It is unclear how this decrease in BMD affects the risk for osteoporosis later in life. Other studies have found that BMD is recovered after discontinuation of this method, and it is thus considered safe for use in this population with appropriate counseling and consideration of other risk factors for bone health. Healthcare providers should speak at length with teens and parents, when appropriate, who are already at high risk for low BMD, such as those receiving chronic corticosteroid therapy or those with eating disorders (see Chapter 749). They should discuss and decide together if DMPA is an appropriate contraceptive choice. Patients and providers need to balance the potential bone effects of DMPA with the bone effects that can occur with a teenage pregnancy. Although the FDA issued a black box warning in 2004 because of Depo's BMD effects, the AAP and ACOG do not recommend limiting duration of DMPA use and do not recommend routine BMD screening for females using it. Early weight gain may be predictive of progressive gain over time; thus those teens gaining weight in the first 3-6 months after the initiation of DMPA should be monitored and continue to engage in discussions about healthy eating and exercise habits.

PROGESTIN-ONLY PILLS

Progestin-only oral contraceptive pills **(POPs)** are available and safe for use in adolescents. POPs **(mini pills)** are quickly effective after 2 days of initiation in thickening cervical mucus, but do not reliably inhibit ovulation. Prior to 2019, the only progestin pill available in the United States contained 0.35 mg of norethindrone. Norethindrone has a short half-life, and it is important that this pill is taken at the same time every day, which can make adherence difficult. If a pill is >3 hours late from normal time, an unintended pregnancy may occur. POPs have a typical-use failure rate of 7% (see Table 160.1). Norethindrone POPs are taken continuously, and as a result, the bleeding pattern is variable—ranging from amenorrhea to irregular and unpredictable breakthrough bleeding. Acceptance by adolescents is limited by the necessity of taking the pill at the same time daily, and bleeding irregularities

In 2019 the FDA approved a new POP—Slynd—which contains 4 mg of drospirenone. This is higher than the dose found in COCs. Drospirenone is an analog of spironolactone with a longer half-life of ~25-30 hours, which allows for more flexibility with timing of pills. It also has some antimineralocorticoid activity and therefore should be used with caution in those who may take other medications or have medical comorbidities that can put them at risk for hyperkalemia. Slynd comes in a 28-day pill pack with four inactive pills intended to cause a scheduled withdrawal bleed. Slynd primarily suppresses ovulation. Studies have demonstrated its safety and efficacy along with high rates of satisfaction among users (85%). There may still be unscheduled bleeding, but it seems to be more favorable than what is experienced with norethindrone use.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.5 Combined Hormonal Contraceptives

Mary E. Romano and Elizabeth M. Alderman

Combined hormonal contraceptives **(CHCs)** are methods that include an estrogen in combination with a progestin that has progestational, estrogenic, and androgenic properties. Methods available in the United States include several formulations of **COCs**, a transdermal patch, and a vaginal ring. The major mechanism of action of the **estrogen-progestin** combination is to prevent the surge of luteinizing hormone and thereby inhibit ovulation. Additional effects to the reproductive tract include thickening of the cervical mucus, which prevents sperm penetration, and thinning of the endometrial lining, which may decrease menstrual blood loss. Typical-use failure rates for all CHCs are the same at 7%.

The COCs, patch, and vaginal ring are classified together as CHCs in the U.S. MEC for Contraceptive Use, and recommendations mostly consider estrogen exposure for a given condition or characteristic (see Tables 160.3 and 160.4). Thromboembolic events such as venous thromboembolism (VTE), pulmonary embolism, or stroke are some of the more serious potential complications of exogenous estrogen use. These serious adverse events are exceedingly rare in adolescents who do not have other risk factors for thromboembolic events. Although the risk of blood clots is increased in those who smoke cigarettes, the likelihood of its occurrence is very small in adolescents, and thus clinically insignificant, compared to the risk of morbidity and mortality from other pregnancy-related complications, including blood clots

associated with the high estrogen levels that occur during pregnancy and in the postpartum period.

COMBINED ORAL CONTRACEPTIVES

Oral contraceptive pills (OCs) can be either COCs or POPs and are commonly referred to as "the pill." The pill is one of the most common contraceptive methods used among women of all ages. To decrease risk of pregnancy and increase continuation, providers are encouraged to provide OCs at the time of patient presentation to start immediately rather than waiting for next menses, as long as the provider is reasonably sure that the patient is not pregnant. Providers are also encouraged to provide up to 13 pill packs at a time, based on evidence that more pill packs provided is associated with higher continuation rates. However, it is important to see an adolescent in follow-up once starting contraception to discuss adherence and satisfaction with the method selected. Advanced provision of emergency contraceptive pills is also recommended should patients miss pills and have unprotected sex. The effectiveness of COCs depends on adherence, and it can be difficult for any patient to remember to take a pill each day. Figures 160.3 and 160.4 list the rules for missed pills or after vomiting or diarrhea.

COCs contain between 50 μg and 10 μg of an estrogenic substance, typically **ethinyl estradiol**, and as many as 10 progestins are available in the United States for combined pills. Multiple preparations are available to help select the formulation that satisfies an individual patient, with minimal side effects. Studies looking at the effects of estrogen dosing on bone health have found lower rates of bone accrual in those taking COCs containing 20 mcg as compared with nonusers. It is recommended that adolescents start on a COC containing 30-35 μg of an estrogenic substance.

COCs can be packaged as 28-day *monophasic* pills, which contain the same dose of active pills for 21 or 24 days, followed by 7 or 4 days of placebo pills, respectively. Monophasic formulations are also available for extended cycles of 91 days or 1 year so that withdrawal bleeding does not occur each month, but at the end of each extended cycle. **Extended cycling** of monophasic COCs for adolescents has some anticipated benefits associated with increased ovarian activity suppression and may decrease failure rates. Other advantages include menstrual suppression in those patients in whom that is a priority and diminished frequency of hormonal withdrawal (premenstrual) effects, including headaches and migraines, mood changes, and heavy monthly bleeding. The most common side effect of extended-cycle OCs is intermenstrual bleeding and/or spotting, with the total days of bleeding over the first year of treatment being similar for extended-cycle users and users following a 28-day-cycle regimen. The unscheduled bleeding pattern diminishes over time. *Multiphasic* pill packs contain various levels of estrogen and progestin for 21 active pills and contain 7 placebo pills. Multiphasic formulations are not available for extended-cycle use. Providers can refer to the U.S. Selected Practice Recommendations for Contraceptive Use to counsel patients on how to manage late or missed COCs.

The short-term adverse effects of COCs, such as nausea and weight gain, often interfere with compliance in adolescent patients. These effects are usually transient and may be overlooked by the beneficial effects of a shortened menses and the relief of dysmenorrhea. The inhibition of ovulation or the suppressant effect of estrogens on prostaglandin production by the endometrium makes COCs effective in preventing dysmenorrhea (see Chapter 159). Acne is typically improved by COCs, as estrogen can reduce the effects of circulating androgens. There is no evidence that one particular COC is superior to

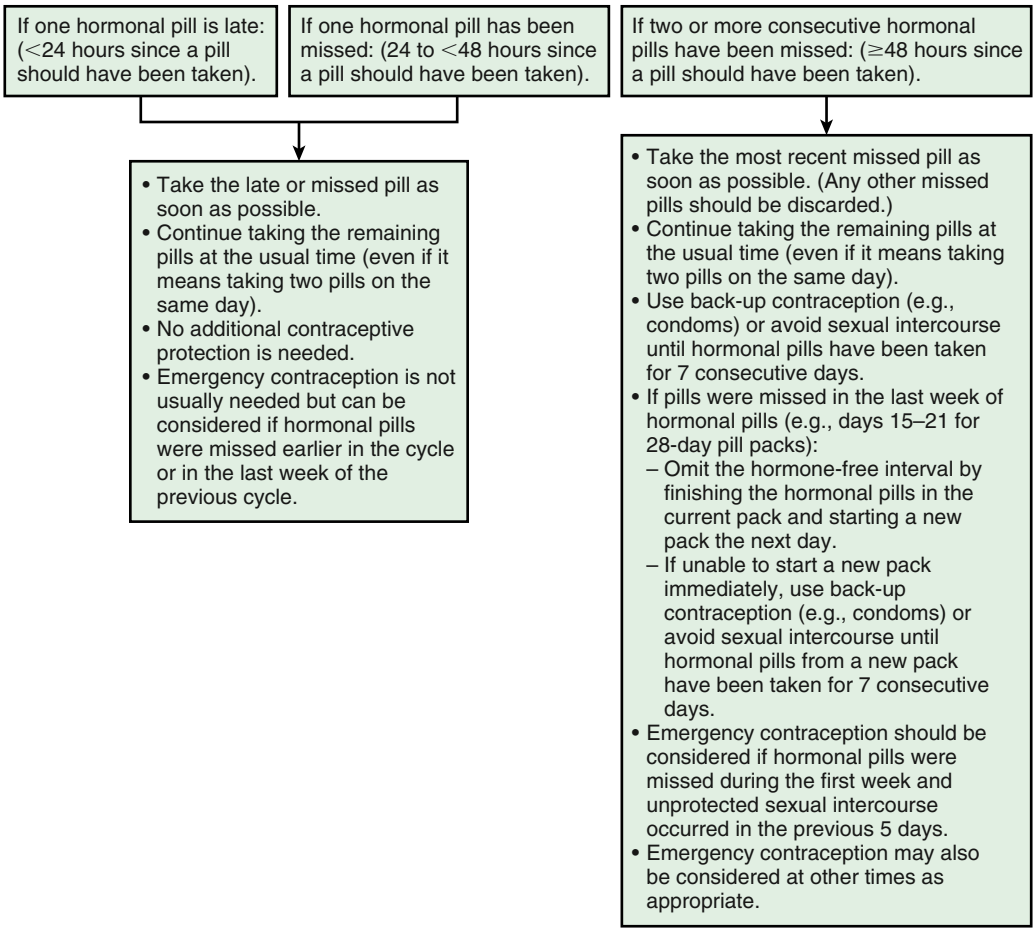

Fig. 160.3 Algorithm showing recommended actions after late or missed combined oral contraceptives. (*From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep 2016;65[RR-4]:1–66, Fig. 2, p. 28.*)

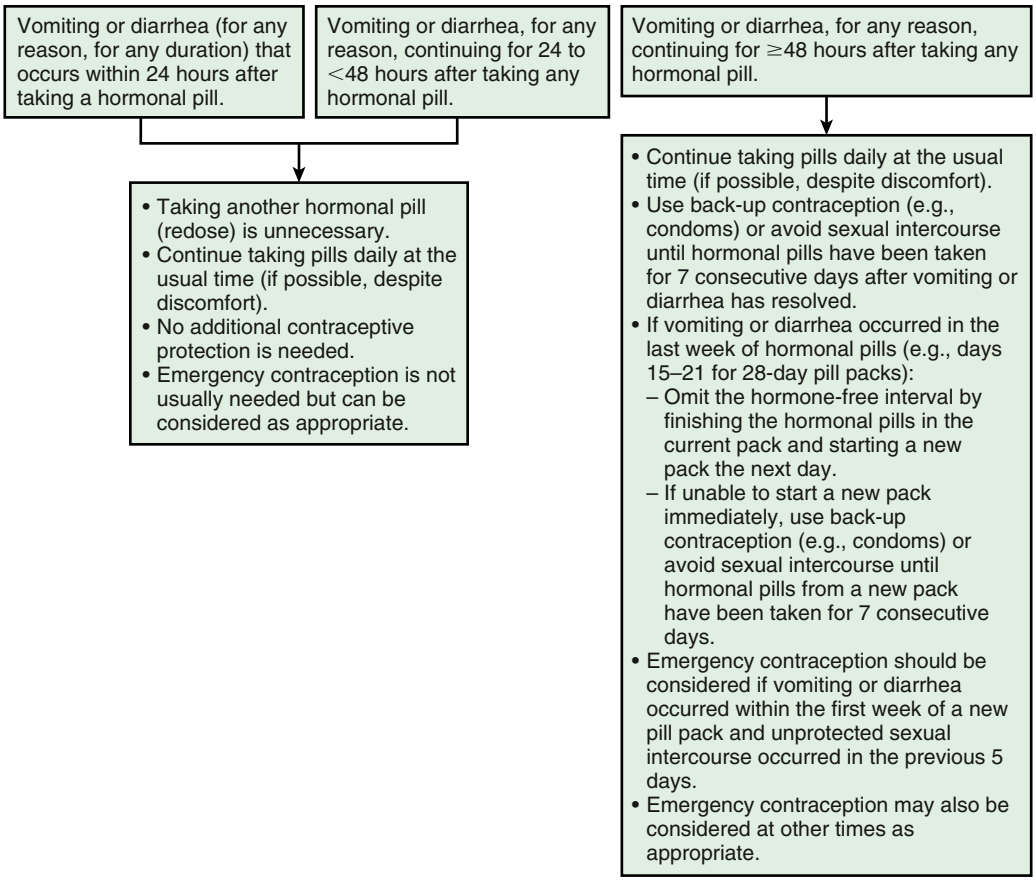

Fig. 160.4 Algorithm showing recommended steps after vomiting or diarrhea while using combined oral contraceptives. (*From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep 2016;65[RR-4]:1–66, Fig. 5, p. 30.*)

another in targeting acne, but theoretically it would be better to use a pill with nonandrogenic progestins (see Chapter 710). **Drospirenone**, a progestin with antimineralocorticoid activity, has been shown to reduce premenstrual symptomatology, but the potential for hyperkalemia as a side effect eliminates patients with renal, liver, or adrenal diseases and patients taking certain medications.

The FDA has concluded that drospirenone-containing OCs may be associated with a higher risk of VTE than other progestin-containing pills. Although no studies have provided consistent estimates of the comparative risk of VTE between OCs that contain drospirenone and those that do not, or accounted for patient characteristics that may affect VTE risk, there has been a threefold increased risk of VTE reported for drospirenone-containing pills as compared with products containing levonorgestrel or other progestins. As a result, the FDA requires that labeling be revised for the OCs marketed under the Beyaz, Safyral, Yasmin, and Yaz brands. This clot risk has not been established for Slynd, which contains 4 mg of drospirenone and no estrogenic component. Despite the risk of VTE with all OCs, the absolute risk remains lower than the risk of developing VTE during pregnancy or the postpartum period.

TRANSDERMAL PATCH

The transdermal patch releases a combination of ethinyl estradiol and a progestin daily. It is applied to the lower abdomen, buttocks, or upper body, excluding the breasts. It is worn continuously for 1 week and changed weekly for a total of 3 weeks, then no patch is worn for the fourth week, at which time bleeding occurs (see Table 160.1). Limited studies in adolescents suggest higher rates of partial or full detachment compared with adults, with high patient satisfaction and 50–83% continuation rates from 3 to 18 months of use (Fig. 160.5). As with other combined hormonal methods, the patch is a Tier 2 contraceptive. Providers can refer to the U.S. Selected Practice Recommendations to counsel patients on how to manage delayed application or detachment of the patch.

The first patch available was Ortho Evra, now available only in a generic version called Xulane. It releases 35 μg ethinyl estradiol and 150 μg norelgestromin daily. Compared with the pharmacokinetics of COCs, the area under the curve for the patch is about 55% higher for patch users. This caused concerns about increased risk of clots with higher estrogen exposure, although there have been no data to confirm this risk. Studies to date have had conflicting data on the risk of VTE in patients using nonoral combined hormonal contraception. There is also concern for efficacy of the patch in those whose weight was >90 kg, and this should be discussed with patients in consideration of use. The Xulane patch can be used to extend cycles similar to COC extended-cycle pills. Patients may choose to wear patches consecutively without any "patch-free week" but should be aware that this can carry a risk of breakthrough bleeding, as occurs with extended-cycle COC use.

In 2020 Twirla was developed to address the need for a lower-dose product to reduce the cumulative estrogen exposure from patch use. Twirla releases 30 μg ethinyl estradiol (EE) and 120 μg levonorgestrel (LNG) daily, and the maximum steady-state concentrations were 60% (EE) and 18% (LNG) as compared with Xulane. Initial studies did not demonstrate a significantly decreased clot risk as compared to other methods of combined hormonal contraception, but as with Xulane, efficacy seemed to be affected by body mass index (BMI), in particular in those who were categorized by BMI as obese. Twirla was not studied for extended use.

VAGINAL RING

The vaginal contraceptive ring is a flexible, transparent, colorless vaginal ring that is inserted into the vagina by the patient. It releases a daily dose of ethinyl estradiol and a progestin. It remains in place for 3 weeks, during which time these hormones are absorbed. It is then typically

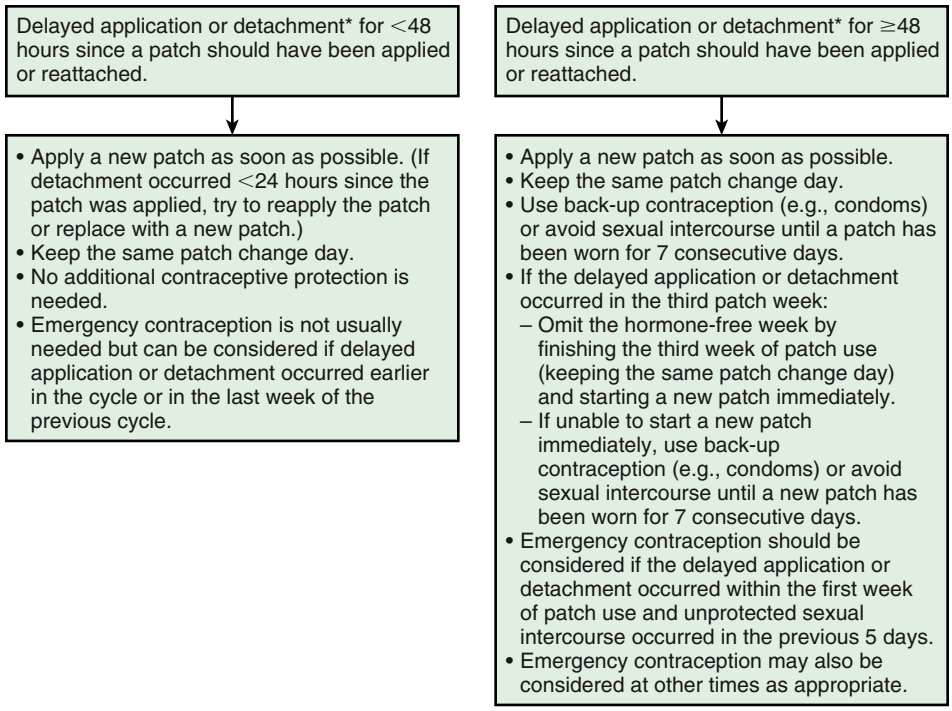

Fig. 160.5 Algorithm showing recommended actions after delayed application or detachment with combined hormonal patch. (*From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep 2016;65[RR-4]:1–66, Fig. 3, p. 28.*)

removed for 7 days during which time a withdrawal bleed should occur. If the ring is accidentally expelled or removed for intercourse, it should be reinserted; however, if it is out of place ≥48 hours or the ring is not replaced within 7 days after removal, a backup method of contraception should be used (Fig. 160.6). The vaginal ring is a Tier 2 contraceptive. Providers can refer to the U.S. Selected Practice Recommendations to counsel patients on how to manage delayed insertion or reinsertion with the vaginal ring.

The first contraceptive ring available was NuvaRing, which measures about 2.1 inches in diameter and releases 1 μg ethinyl estradiol and 120 μg etonogestrel daily. Users use one ring per 4-week cycle with 3 weeks in and 1 week out and a scheduled withdrawal bleed. It should be noted that although it is labeled for 28 days of use, it contains enough hormones to be used for up to 35 days and can be replaced once every calendar month. The ring can be used to extend cycles similar to COC extended-cycle pills. Patients may choose to use the Nuva Ring consecutively without any "ring-free week" but should be aware that this can carry a risk of breakthrough bleeding, as occurs with extended-cycle COC use. Annovera is FDA approved and offers a single ring, which can be reused for 13 consecutive cycles and does not require refrigeration when not in use. Annovera has a diameter of about 2.2 inches and releases 13 μg of EE and 150 μg of segesterone acetate daily. It has not been studied for extended use, and initial studies did not include those with a BMI >29 kg/m^2.

CONTRAINDICATIONS

Contraceptive counseling should include a discussion and assessment for any absolute or relative contraindications to estrogen use. Contraindications to the use of estrogen-containing methods include those conditions for which CHCs pose an unacceptable health risk (Category 4) in the U.S. MEC for Contraceptive Use (see Table 160.3); current breast cancer; severe cirrhosis, acute deep venous thrombosis/pulmonary embolism (DVT/PE) or history of DVT/PE with higher risk for recurrence, major surgery with prolonged immobilization, diabetes with nephropathy, retinopathy, or neuropathy, migraines with focal neurologic aura, stage II hypertension, vascular disease, ischemic heart disease, hepatocellular adenoma or malignant liver tumors, multiple risk factors for cardiovascular disease, peripartum cardiomyopathy, postpartum <21 day, complicated solid-organ transplantation, history of cerebrovascular accident, systemic lupus erythematosus with positive antiphospholipid antibodies, thrombogenic pathogenic variants, and complicated valvular heart disease. The initial history taken before prescribing CHCs should specifically address these risks. The U.S. MEC provides contraceptive safety guidance with >1,800 recommendations for >120 medical conditions or characteristics. According to the MEC, obesity is not a contraindication to estrogen or contraceptive use, and these adolescents would be considered at high risk for pregnancy complications. Therefore adolescents with obesity should be counseled on and offered contraception when indicated and if desired by the patient.

Other things to discuss and consider when evaluating an adolescent for COC use are a family history of blood clots or clotting disorders and any medications that might interact with COCs. If a patient has a first-degree relative with history of VTE, evaluation for a familial thrombophilia is advisable. There are few medication interactions for progestin-only methods, but there are medications that may be affected by or affect levels of COCs. This includes certain anticonvulsants and psychotropic medications as well as herbal supplements, which may affect COC levels. The CDC has a resource for antiretrovirals and their potential for interactions with hormonal contraception. Lexicomp and UpToDate provide additional information on interactions with COCs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.6 Emergency Contraception

Mary E. Romano and Elizabeth M. Alderman

Unprotected intercourse at mid-cycle carries a pregnancy risk of 20–30%. At other times during the cycle, the risk is 2–4%. Emergency

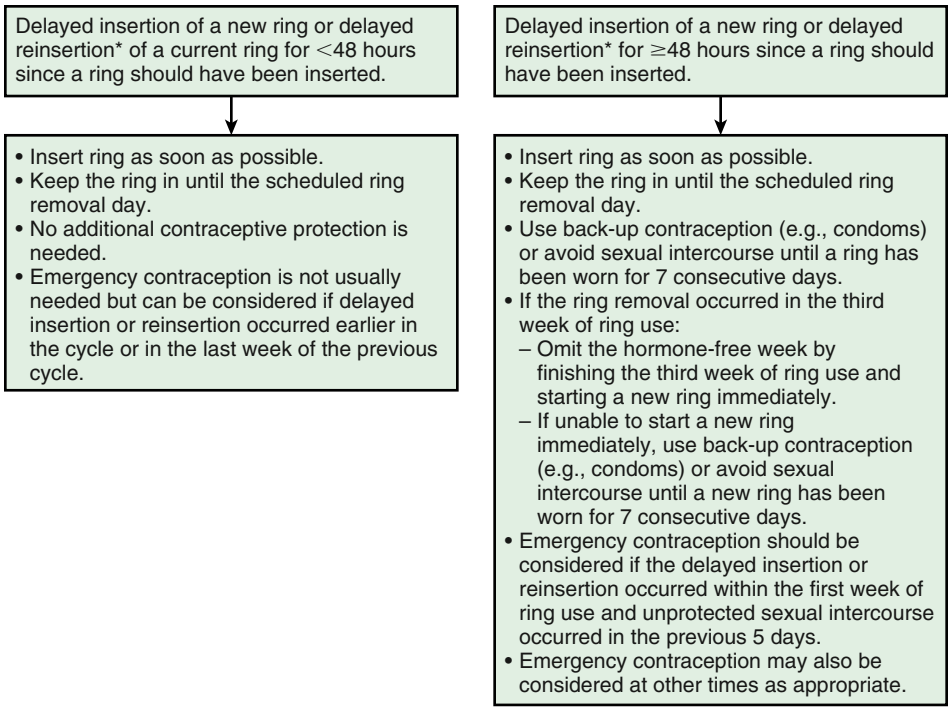

Fig. 160.6 Algorithm showing recommended actions after delayed insertion or reinsertion with combined vaginal ring. (*From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep 2016;65[RR-4]:1–66, Fig. 4, p. 29.*)

Table 160.5 Possible Indications for Emergency Contraception

SEXUAL ASSAULT
HIGH-RISK SEXUAL ACTIVITY
No contraception during intercourse
Intoxication (alcohol, drugs)
Coitus interruptus
CONTRACEPTION FAILURES
Condom breaking, spillage, leaks, intentional removal
Dislodgement and/or breaking of diaphragm, female condom, cervical cap
Expulsion of IUD
Spermicide failure to melt before coitus
DELAYED OR MISSED CONTRACEPTION
2 consecutive missed days of combined oral contraceptive
1 missed day of progestin-only oral contraceptives
>2-wk late injection of depot medroxyprogesterone
≥2 days late start of vaginal ring or patch cycle
Incorrect timing of spermicide/gel before sexual activity
OTHER
Exposure to teratogens in the absence of contraception

IUD, Intrauterine device.

contraception (EC) refers to methods of contraception that are used after sexual intercourse to reduce the risk of pregnancy but do not interrupt an existing pregnancy. EC may be used up to 120 hours after unprotected intercourse or contraceptive failure. Table 160.5 lists the indications for use of EC. EC methods include the Cu IUD, LNG 52-mg IUD, and emergency contraceptive pills, which include ulipristal acetate, LNG, and COCs following the Yuzpe method. Although the mechanism of action of the IUD as EC is unclear, all emergency contraceptive pills work to delay ovulation and are effective only for intercourse that occurs before administration. Initiation of a regular contraceptive method is necessary to prevent pregnancy for any intercourse that occurs for the remainder of the cycle and for future cycles. If pregnancy has already occurred, emergency contraceptive pills will not terminate an existing pregnancy or have teratogenic effects on the fetus.

Teens can access EC information through a hotline at 888-NOT-2-LATE to obtain EC pills over the counter (OTC). The Guttmacher Institute maintains an up-to-date listing on EC. The ACOG and AAP recommend advance provision of EC pills for at-risk adolescents to remove barriers to access and increase awareness of the utility of EC. No examination or testing is required before use of EC, but a follow-up appointment is recommended to determine the effectiveness of treatment and to diagnose a possible early pregnancy. The visit also provides an opportunity to counsel the adolescent, explore the situation leading up to the unprotected intercourse or contraceptive failure, test for STIs, offer HIV testing, and engage in a discussion about contraception when appropriate. It is also important to engage adolescent males in discussions about the availability and use of EC if they have engaged in unprotected intercourse, especially when and how to access Plan B, which is available OTC.

COPPER IUD

The CuT380A (Paragard) is not FDA approved for EC, but it has been shown to be >99% effective if used within 5 days (120 hours) after unprotected sex. The additional benefit of using the Cu IUD for EC is that it also provides long-term reversible contraception. Efficacy of the Cu-IUD is not affected by BMI.

LNG 52-mg IUD

The Mirena IUD is not FDA approved for EC, but studies have shown it is as effective/noninferior to the Cu-IUD for EC if used within 5 days (120 hours) after unprotected sex. Similar to the Cu-IUD, it also provides long-term reversible contraception and efficacy is not affected by BMI.

ULIPRISTAL ACETATE

Ulipristal acetate (UPA) is available for EC and is FDA approved for use up to 120 hours after unprotected sex. UPA is available only by prescription regardless of age. A few studies have shown it to be more effective than LNG at and beyond 72 hours. If starting OC pills after taking UPA, it is recommended to start or resume pills no sooner than 5 days after taking UPA to avoid decreased efficacy of contraceptive pills as a result of its antiestrogenic effect. Studies have shown an increased risk of ovulation if COC pills are started immediately after UPA use. Studies have not looked at UPA efficacy when Depo or a progestin-containing LARC is initiated immediately after UPA use. If starting a method requires an extra visit (e.g., IUDs, implant, Depo-Provera), starting the method at the time of ulipristal use may be considered, weighing the risk of decreasing the effectiveness of ulipristal with the risk of not starting a contraceptive method. Patients should be encouraged to take a pregnancy test within 3 weeks after UPA use either in the office or on their own. Studies have suggested UPA is less effective in overweight and obese women (BMI >25). This should be discussed with patients, and all attempts should be made to provide UPA as soon as possible after unprotected sexual activity.

LEVONORGESTREL

In 2013 the FDA approved the emergency contraceptive drug **Plan B** One-Step as an OTC option for all persons of childbearing potential. Experience with adolescents has demonstrated more effective use of EC with advance provision, and this is not associated with more frequent unprotected intercourse or less condom and/or pill use. Nausea and vomiting are uncommon side effects, and LNG has been shown to be more effective at preventing pregnancy than the Yuzpe method. However, LNG has been shown to be less effective than UPA when taken ≥72 hours and in women who are obese and overweight (BMI >25). This should be discussed with women in deciding with EC method is most appropriate for use. Patients should be encouraged to take a pregnancy test within 3 weeks after EC use either in the office or on their own.

Yuzpe Method

The **Yuzpe method** has been replaced by the more effective methods of EC, but may be useful for women who do not have access to other methods and/or already have COCs at home and desire EC. It is most effective when taken up to 72 hours after unprotected intercourse. For EC, COC pills with 200 µg ethinyl estradiol and 2 mg norgestrel or 1 mg levonorgestrel should be taken in two doses, 12 hours apart. This method is effective in reducing the risk of pregnancy by 75%. The most common side effects are nausea (50%) and vomiting (20%), prompting some clinicians to prescribe or recommend antiemetics along with the COCs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.7 Condoms

Mary E. Romano and Elizabeth M. Alderman

The use of condoms is the only contraceptive method that protects against pregnancy and STIs, including HIV. Condoms, also referred to as *barrier contraception,* prevent sperm from being deposited in the vagina. The use of condoms in conjunction with hormonal contraception (or Cu IUD) is always recommended to reduce the risk of pregnancy and protect against STIs. This is sometimes referred to as *dual protection.* Although correct and consistent condom use with every act of sexual intercourse theoretically protects against pregnancy and STIs, providers should encourage adolescents to use condoms for STI/HIV protection along with a more effective method for pregnancy protection.

No major medical side effects are associated with condom use, and condoms are available for use by males and females. Nonlatex condoms are available for those with a latex allergy, and these include lambskin and synthetic polyurethane condoms. Lambskin condoms do not protect against HIV and other viral infections, although they do work to prevent pregnancy. Although condom use at last sexual intercourse had steadily increased from the early 1990s to the mid-2000s, the percentage of students reporting condom use at last intercourse has remained stable, with 54% of adolescents reporting condom use at last intercourse. Earlier increases in condom use were thought to be the result of increased awareness of HIV risks. Only 9% of high school students reported using dual methods of contraception (condom plus something else) at last intercourse. The main advantages of condoms are their low price, availability without prescription, male involvement in the responsibility for contraception, and effectiveness in preventing transmission of STIs, including HIV and human papillomavirus (HPV). The typical-use failure rate for male condoms is 18% for all users and is thought to be higher in adolescents. For the most effective dual protection, male latex condoms are recommended as protection against STIs and should be used in conjunction with another method of contraception. According to the National Survey of Family Growth, only 21.3% of females used another contraceptive method along with a condom at last sex during the past 12 months.

There is only one female condom available in the United States. It is available OTC or can be ordered online. It is nonlatex. It can be harder to use properly and has a higher typical-use failure rate (21%) than the male condoms. There are no human studies demonstrating its effectiveness against STIs. Adolescents intending to use this method should be provided education on proper use and hands-on practice to ensure effective use.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

160.8 Other Barrier Methods

Mary E. Romano and Elizabeth M. Alderman

Although these methods are not widely available or used, they are important to know about for patients who wish to use nonhormonal contraception at the time of intercourse.

DIAPHRAGM, CERVICAL CAP, AND SPONGE

These methods have few side effects but are much less likely to be used by teenagers. Typical-use failure rates exceed 14%. The sponge has limited OTC availability in the United States, and the cervical cap and diaphragm require a visit with a healthcare provider for fitting. The **cervical cap** and **sponge** have lower failure rates in nulliparous women, whereas the **diaphragm** has similar rates among nulliparous and parous women. The sponge is used with water, whereas the cervical cap and diaphragm are used with spermicide before being placed over the cervix. Adolescents may feel less comfortable and be less likely to use these methods because of the messiness of the jelly or the need for insertion and removal interrupting the spontaneity of sex (to be inserted before sex and left in for several hours afterward). Spermicide must be reapplied before every act of intercourse. Adolescents may also be less comfortable touching their genitals.

160.9 Other Contraceptive Methods

Mary E. Romano and Elizabeth M. Alderman

The only OTC spermicide available in the United States is Nonoxynol-9 (N-9). It is available as a foam, film, gel, cream, suppository, and tablet. It must be placed in the vagina no more than 1 hour before intercourse and again before each act of intercourse/ejaculation. Side effects, although rare, include local irritation or contact vaginitis. There have been concerns about the vaginal and cervical mucosal damage observed with N-9 and its impact on HIV transmission. Results thus far have been inconclusive. There were some studies that suggested that N-9 is gonococcicidal and spirocheticidal, but this has not been substantiated in randomized clinical trials. Spermicides should be used in combination with barrier methods because their typical-use failure rate alone is 21%

Phexxi is a prescription vaginal gel that is FDA approved. It is nonhormonal and user controlled. It can be used alone or in conjunction with other methods, although it is not recommended for use with the intravaginal ring. It is prepackaged in a single-dose applicator and must be inserted intravaginally up to 1 hour before vaginal intercourse. It works to maintain vaginal pH in an acidic range (~3.5 to 4.5) despite the presence of alkaline semen/sperm, which limits motility and incapacitates sperm. When compared with other OTC spermicidal gels, Phexxi has a higher viscosity, which minimizes vaginal leakage of the product and is thought to further affect sperm motility and provide an additional barrier to cervical penetration. Data also suggest Phexxi may have microbicidal effects in that by maintaining an acidic vaginal pH, Phexxi may enhance the vagina's natural microbicidal mechanisms. This effect seems more consistent and reliable than what has been found with the use of N-9. As with N-9, the most commonly reported side effect was vaginal discomfort and irritation. There has been no evidence that it affects HIV transmission. It should not be used in women with recurrent urinary tract infections (UTIs) or any urinary tract abnormalities.

WITHDRAWAL

The pregnancy risk with use of withdrawal as a contraceptive method is probably underestimated in adolescents, and a high typical-use failure rate of 20% should be specifically addressed with all adolescents, given that up to 60% of teens have reported using withdrawal for contraception.

FERTILITY AWARENESS–BASED METHODS

Fertility awareness methods require that one be aware of the fertile days of their menstrual cycle and either avoid intercourse during that time or use barrier contraception. Methods typically involve calculating the length of one's menstrual cycle, observing changes in body temperature and/or cervical secretions. Fertility awareness methods are based on regular ovulatory cycles, which are less common in teens, and therefore fertility awareness methods may be difficult for a teenager to use effectively. Methods include the Standard Days method, basal body temperature method, Billings method, and lactational amenorrhea. Be aware that the lactational amenorrhea method may be a highly effective, temporary contraceptive method if the following criteria are met: (1) no return of menses, (2) the infant is <6 months old, and (3) the woman is exclusively breastfeeding. There is an FDA-approved mobile application—Natural Cycles—that may be used to best predict fertility days to plan for abstinence or barrier contraceptive use. Other apps do exist, but they are not FDA approved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 161

Adolescent Pregnancy

Cora Collette Breuner

EPIDEMIOLOGY

There has been a trend of decreasing teen births and pregnancies since 1991 (Fig. 161.1). Teen birthrates in the United States are at a historic low secondary to increased use of contraception at first intercourse, use of dual methods of condoms and hormonal contraception among sexually active teenagers, and access to abortion (see Chapter 161.1). Despite these data, the United States continues to lead other industrialized countries in having high rates of adolescent pregnancy, with >700,000 pregnancies per year. Nonetheless, the National Survey of Family Growth (NSFG) 2006–2010 revealed that less than one third of 15- to 19-year-old females consistently used contraceptive methods at last intercourse.

The improvement in U.S. female teen birthrates is attributed to three factors: more teens are delaying the onset of sexual intercourse, are using some form of contraception when they begin to have sexual intercourse, and are using long-lasting contraceptive agents such as injections, implants, and intrauterine devices (IUDs).

Most pregnancies among U.S. adolescents are **unintended** (unwanted or mistimed); 88% of births to teenagers 15-17 years old were the result of unintended pregnancies. Birthrate statistics underestimate actual adolescent pregnancy rates because the birthrate numerator includes the number of actual births per 1,000 individuals in that age-group, but the pregnancy rate includes actual births, abortions, and best estimates of fetal loss per 1,000 adolescents in that age-group.

The *reported* **abortion** rate among adolescents in 2019 for those <15 years of age was 0.4 per 1,000 females (of the same age-group), and for those 15-19 years, it was 6.0 per 1,000; this compares to the most common age for having an abortion (20-29) of 18-19 per 1,000 females. It is unknown how many abortions go unreported (see Chapter 161.1).

ETIOLOGY

In industrialized countries with policies supporting access to protection against pregnancy and sexually transmitted infections **(STIs)**, older adolescents are more likely to use hormonal contraceptives and condoms, resulting in a lowered risk of unplanned pregnancy. Younger teenagers are likely to be less deliberate and logical about their sexual decisions, and their sexual activity is likely to be sporadic or even coercive, contributing to inconsistent contraceptive use and a greater risk of unplanned pregnancy. Better personal hopes for employment and higher educational goals are associated with lowered probability of childbearing in most groups. In nonindustrialized countries, laws permitting marriage of young and mid-teens, poverty, and limited female education are associated with increased adolescent pregnancy rates.

CLINICAL MANIFESTATIONS

Adolescents may experience the traditional symptoms of pregnancy: morning sickness (vomiting, nausea that may also occur *any* time of the day), swollen tender breasts, weight gain, and amenorrhea. Often the presentation is less classic; headache, fatigue, abdominal pain, dizziness, and scanty or irregular menses are common presenting complaints.

In the pediatric office, some teens are reluctant to divulge concerns of pregnancy. Denial of sexual activity and menstrual irregularity should not preclude the diagnosis in face of other clinical or historical information. An unanticipated request for a complete checkup or a visit for contraception may uncover a suspected pregnancy. *Pregnancy is still the most common diagnosis when adolescents present with secondary amenorrhea.*

DIAGNOSIS

Table 161.1 provides classic symptoms, laboratory tests, and physical changes in the diagnosis of pregnancy.

On physical examination, the findings of an enlarged uterus, cervical cyanosis **(Chadwick sign)**, a soft uterus **(Hegar sign)**, or a soft cervix **(Goodell sign)** are highly suggestive of an intrauterine pregnancy. A confirmatory pregnancy test is always recommended, either *qualitative* or *quantitative*. Modern **qualitative** urinary detection methods are efficient at detecting pregnancy, whether performed at home or in the office. These tests are based on detection of the beta subunit of human chorionic gonadotropin **(hCG)**. Although claims for nonprescription home pregnancy tests may indicate 98% detection on the day of the first missed menstrual period, sensitivity and accuracy vary considerably. Office or point-of-care tests have increased standardization and generally have increased sensitivity, with the possibility of detecting a pregnancy within 3-4 days after implantation. However, in any menstrual cycle, ovulation may be delayed, and in any pregnancy, the day of implantation may vary considerably, as may rate of production of hCG. This variability, along with variation of urinary concentration, may affect test sensitivity. *Consequently, each negative test should be*

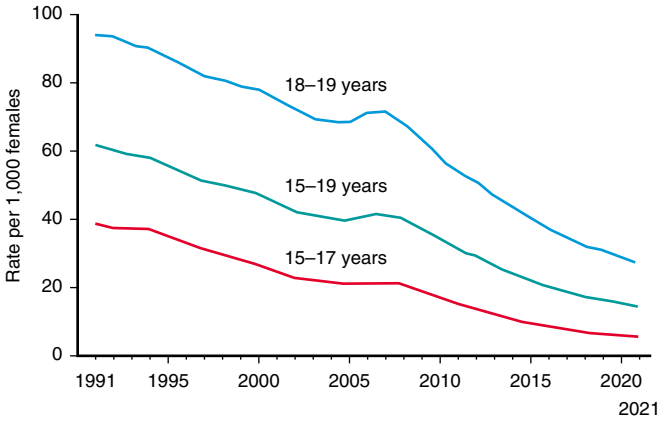

Fig. 161.1 Birth rates for teenagers by age of mother: United States, final 1991–2020 and provisional 2021. Source: National Center for Health Statistics, National Vital Statistics System, Natality. (*From Hamilton BE, Martin JA, Osterman JA, Division of Vital Statistics, National Center for Health Statistics. Births: provisional data for 2021. Nat Vital Stats Rapid Release. 2022;20, Fig. 2.*)

Table 161.1 Diagnosis of Pregnancy Dated from First Day of Last Menstrual Cycle

CLASSIC SYMPTOMS
Missed menses, breast tenderness, nipple sensitivity, nausea, vomiting, fatigue, abdominal and back pain, weight gain, urinary frequency.
Teens may present with unrelated symptoms that enable them to visit the doctor and maintain confidentiality.
LABORATORY DIAGNOSIS
Tests for human chorionic gonadotropin in urine or blood may be positive 7-10 days after fertilization, depending on sensitivity.
Irregular menses make ovulation/fertilization difficult to predict.
Home pregnancy tests have a high error rate.
PHYSICAL CHANGES
2-3 wk after implantation: cervical softening and cyanosis.
8 wk: uterus size of orange.
12 wk: uterus size of grapefruit and palpable suprapubically.
20 wk: uterus at umbilicus.
If physical findings are not consistent with dates, ultrasound will confirm.

repeated in 1-4 weeks if there is a heightened suspicion of pregnancy. The most sensitive pregnancy detection test is a serum **quantitative βhCG radioimmunoassay**, with reliable results within 7 days after fertilization. This more expensive test is used primarily during evaluations for ectopic pregnancy, to detect retained placenta after pregnancy termination, or in the management of a molar pregnancy. It is used when serial measurements are necessary in clinical management.

Although not used for primary diagnosis of pregnancy, pelvic or vaginal **ultrasound** can be helpful in detecting and dating a pregnancy. Pelvic ultrasound will detect a gestational sac at about 5-6 weeks (dated from last menstrual period) and vaginal ultrasound at 4.5-5 weeks. This tool may also be used to distinguish diagnostically between intrauterine and ectopic pregnancies.

PREGNANCY COUNSELING AND INITIAL MANAGEMENT

Once the diagnosis of pregnancy is made, it is important to begin addressing the psychosocial and the medical aspects of the pregnancy. The patient's response to the pregnancy should be assessed and her emotional issues addressed. It should not be assumed that the pregnancy was unintended. Discussion of the patient's options should be initiated. These options include (1) releasing the child to an adoptive family, (2) electively terminating the pregnancy, and (3) raising the child herself with the help of family, father of the baby, friends, and/or other social resources. Options should be presented in a supportive, informative, nonjudgmental fashion; for some young women, they may need to be discussed over several visits. Physicians who are uncomfortable in presenting options to their young patients should refer their patients to a provider who can provide this service expeditiously. Pregnancy terminations implemented early in the pregnancy are generally less risky and less expensive than those initiated later. These include the prescription use of mifepristone and misoprostol within 10 weeks (the World Health Organization [WHO] recommends 12 weeks) of the pregnancy (see Chapter 161.1).

Other issues that may need discussion are how to inform and involve the patient's parents and the father of the infant; implementing strategies for ensuring continuation of the young mother's education; discontinuation of tobacco, alcohol, and illicit drug use; discontinuance and avoidance of any medications that may be considered teratogenic; starting folic acid, calcium, and iron supplements; proper nutrition; and testing for STIs. Especially in younger adolescents, the possibility of **coercive sex** (see Chapter 162) must be considered and appropriate social work/legal referrals made if abuse has occurred, although most pregnancies are not a result of coercive sex. Patients who elect to continue their pregnancy should be referred as soon as possible to an adolescent-friendly obstetric provider.

Risk factors for teen pregnancy include growing up in poverty, having parents with low levels of education, growing up in a single-parent family, fewer opportunities in their community for positive youth involvement, neighborhood physical disorder, foster care (such teens are more than twice as likely to become pregnant than those not in foster care), and having poor performance in school (see "Psychosocial Outcomes/Risks for Mother and Child" later).

The Importance of Prevention

Teen pregnancy and childbearing bring substantial social and economic costs through immediate and long-term impacts on teen parents and their children. In 2010, teen pregnancy and childbirth accounted for at least $9.4 billion in costs for increased healthcare and foster care, increased incarceration rates among children of teen parents, and lost tax revenue because of lower educational attainment and income among teen mothers.

ADOLESCENT FATHERS

Those who become fathers as adolescents also have poorer educational achievement than their age-matched peers. They are more likely than other peers to have been involved with illegal activities and with the use of illegal substances. Adult men who father the children of teen mothers are poorer and educationally less advanced than their age-matched peers and tend to be 2-3 years older than the mother, but any combination of age differences may exist. Younger teen mothers are more likely to have a greater age difference between themselves and the father of their child, raising the issue of coercive sex or statutory rape (see Chapter 162).

Male partners have a significant influence on the young woman's decision/desire to become pregnant and to parent her child. Sensitively and appropriately including the male partner in discussions of family planning, contraception, and pregnancy options may be a useful strategy in improving outcomes for all. This can only be successful if the young female patient is willing to have her partner involved in such discussions.

MEDICAL COMPLICATIONS OF MOTHERS AND BABIES

Although pregnant teens are at higher-than-average risk for some complications of pregnancy, most teenagers have pregnancies that are without major medical complications, delivering healthy infants. The

miscarriage/stillbirth risk for adolescents is estimated at 15–20%. In the United States, elective pregnancy termination rates peaked from 1985 to 1988 at 41–46%, decreasing since then to approximately 30% in 2008. Teen mothers have low rates of age-related chronic disease (diabetes or hypertension) that might affect the outcomes of a pregnancy. They also have lower rates of twin pregnancies than older women. They tolerate childbirth well with few operative interventions. However, compared with 20- to 39-year-old mothers, teens have higher incidences of low birthweight infants, preterm infants, neonatal deaths, passage of moderate to heavy fetal meconium during parturition, and infant deaths within 1 year after birth. The highest rates of poor outcomes occur in the youngest and most economically disadvantaged mothers. *Gastroschisis,* although rare, has a much higher incidence in infants of teen mothers, for reasons that are unclear. Teen mothers also have higher rates of anemia, pregnancy-associated hypertension, and eclampsia, with the youngest teens having rates of pregnancy-associated hypertension higher than the rates of women in their 20s and 30s. The youngest teens also have a higher incidence of poor weight gain (<16 lb) during their pregnancy. This correlates with a decrease in the birthweights of their infants. Poor maternal weight gain also has correlated strongly with teens' late entrance into prenatal care and with inadequate use of prenatal care. Sexually active teens have higher rates of STIs than older sexually active women.

Globally, many young women who become pregnant have been exposed to violence or abuse in some form during their lives. There is some evidence that teenage women have the highest rates of **violence** during pregnancy of any group. Violence has been associated with injuries and death as well as preterm births, low birthweight, bleeding, substance abuse, and late entrance into prenatal care. An analysis of the Pregnancy Mortality Surveillance System indicates that in the United States 1991–1999, homicide was the second leading cause of injury-related deaths in pregnant and postpartum women. Women age 19 years and younger had the highest pregnancy-related homicide rate (see Chapter 156).

Ectopic pregnancy occurs in 1–2% of conceptions and is more common in women with a previous history of an ectopic pregnancy, pelvic inflammatory disease, prior appendicitis, infertility, in utero exposure to diethylstilbestrol, and possibly an IUD. Most ectopic pregnancies are in the fallopian tube (tubal pregnancy). Manifestations include vaginal spotting after a missed menstrual period that may progress to more intense vaginal bleeding (suggestive of spontaneous abortion); vaginal bleeding is absent in 10–20%. Abdominal pain is associated with distention of the fallopian tube; tubal rupture results in more intense pain, hemorrhagic shock, and peritonitis. Some women have nonspecific abdominal complaints and are misdiagnosed with gastroenteritis. Cervical motion and adnexal tenderness (and adnexal mass) may be present. **Transvaginal sonography** (not transabdominal) is the diagnostic test of choice to detect an ectopic pregnancy and reveals an adnexal mass and no uterine pregnancy. Nonetheless, some women will have pregnancy of unknown location by transvaginal sonography; approximately 20% of these will have an ectopic pregnancy. Measurement of sensitive quantitative serum βhCG levels together with transvaginal sonography has value in diagnosing an ectopic pregnancy. If the initial βhCG is above the *discriminatory zone* (level at which one expects an intrauterine pregnancy) but on transvaginal sonography there is no intrauterine pregnancy, there may be an ectopic pregnancy or an abnormal uterine pregnancy. In addition, if the βhCG is below the discriminatory level (usually <3,000 mIU/mL) with no definitive diagnosis by sonography, serial βhCG testing should be performed every 48 hours. In a normal uterine pregnancy, βhCG levels should increase approximately 50% every 48 hours; declining levels may suggest a miscarriage or an ectopic pregnancy. Some would perform a dilation and curettage and check for products of conception or follow serial βhCG levels. If there are no products of conception or if βhCG levels plateau or increase, an ectopic pregnancy is present. Treatment of unstable or advanced patients is usually by laparoscopic surgery or by laparotomy. Because of early detection, many patients remain stable *(unruptured).* Stable patients with an unruptured ectopic pregnancy may be treated with single-dose, or more often, multidose methotrexate to induce abortion. Contraindications to methotrexate in a stable patient include size of the ectopic mass (>3.5 cm) and embryonic cardiac motion.

Prematurity and low birthweight increase the perinatal morbidity and mortality for infants of teen mothers. These infants also have higher-than-average rates of sudden infant death syndrome (see Chapter 423), possibly because of less use of the supine sleep position or cosleeping, and are at higher risk of both intentional and unintentional injury (see Chapter 17). One study showed that the risk of homicide is 9-10 times higher if a child born to a teen mother is not the mother's firstborn compared with the risk to a firstborn of a woman age 25 years or older. The perpetrator is often the father, stepfather, or boyfriend of the mother.

After childbirth, **depressive symptoms** may occur in as many as 50% of teen mothers. Depression seems to be greater with additional social stressors and with decreased social supports. Support from the infant's father and the teen's mother seems to be especially important in preventing depression. Pediatricians who care for parenting teens should be sensitive to the possibility of depression, as well as to inflicted injury to mother or child; appropriate diagnosis, treatment, and referral to mental health or social agencies should be offered and facilitated.

PSYCHOSOCIAL OUTCOMES/RISKS FOR MOTHER AND CHILD

Educational Issues

Pregnancy and birth are significant contributors to high school dropout rates among girls. Only about 50% of teen mothers receive a high school diploma by age 22, whereas approximately 90% of women who do not give birth during adolescence graduate from high school. Mothers who have given birth as teens generally remain 2 years behind their age-matched peers in formal educational attainment at least through their third decade. Maternal lack of education limits the income of many of these young families (see Chapter 1).

The children of teenage mothers are more likely to have lower school achievement and to drop out of high school, have more health problems, and face unemployment as a young adult.

Substance Use

See also Chapter 157.

Teenagers who abuse drugs, alcohol, and tobacco have higher pregnancy rates than their peers. Most substance-abusing mothers appear to decrease or stop their substance use while pregnant. Use begins to increase again about 6 months postpartum, complicating the parenting process and the mother's return to school.

Repeat Pregnancy

In the United States, approximately 20% of all births to adolescent mothers (age 15-19) are second order or higher. Prenatal care is begun even later with a second pregnancy, and the second infant is at higher risk of poor outcome than the first birth. Mothers at risk of early repeat pregnancy (<2 years) include those who do not initiate long-acting contraceptives after the index birth, those who do not return to school within 6 months of the index birth, those with mood disorders, those receiving major childcare assistance from the adolescent's mother, those who are married or living with the infant's father, those having peers who were adolescent parents, and those who are no longer involved with the baby's father and who meet a new boyfriend who wants to have a child. To reduce repeat pregnancy rates in these teens, programs must be tailored for this population, preferably offering comprehensive healthcare for both the young mother and her child. Healthcare providers should remember to provide positive reinforcement for teen parenting successes (i.e., compliment teen parents when they are doing a good job).

Children Born to Teen Mothers

Many children born to teen mothers have behavioral problems that may be seen as early as the preschool period. Many drop out of school early (33%), become adolescent parents (25%), or, if male, are incarcerated (16%). Explanations for these poor outcomes include poverty, parental learning difficulties, negative parenting styles of teen parents,

maternal depression, parental immaturity, poor parental modeling, social stress, exposure to surrounding violence, and conflicts with grandparents, especially grandmothers. Continued positive paternal involvement throughout the child's life may be somewhat protective against negative outcomes. Many of these poor outcomes appear to be attributable to the socioeconomic/demographic situation in which the teen pregnancy has occurred, not solely to maternal age. Even when socioeconomic status and demographics are controlled, infants of teen mothers have lower achievement scores, lower high school graduation rates, increased risk of teen births themselves, and, at least in Illinois (where records include age of birth mother), a higher probability of abuse and neglect.

Comprehensive programs focused on supporting adolescent mothers and infants using life skills training, medical care, and psychosocial support demonstrate higher employment rates, higher income, and less welfare dependency in participating adolescents.

PREVENTION OF TEEN PREGNANCIES

Adolescent pregnancy is a multifaceted problem that requires multifactorial solutions. The provision of contraception and education about fertility risk from the primary care physician is important but insufficient to address the problem fully. Family and community involvement are essential elements for teen pregnancy prevention. Strategies for primary prevention (preventing first birth) are different from the strategies needed for secondary prevention (preventing second or more births). Over the past 30 years, many models of teen pregnancy prevention programs have been implemented and evaluated. Table 161.2 lists the common components of successful evidence-based programs.

Abstinence-only sexual education aims to teach adolescents to wait until marriage to initiate sexual activity but, unfortunately, does not mention contraception. Abstinence education is sometimes coupled with "virginity pledges" in which teenagers pledge to remain abstinent until they marry. Other educational programs emphasize HIV and STI prevention and in the process prevent pregnancy, whereas others include both abstinence and contraception in their curricula. Sex education and teaching about contraception do not lead to an increase in sexual activity. Teenagers who participate in programs with **comprehensive** sex education components generally have lower rates of pregnancy than those exposed solely to abstinence-only programs or no sex education at all.

In many U.S. communities, programs that engage youth in community service and that combine sex education and youth development are also successful in deterring pregnancy. Programs vary in their sites of service from schools to social agencies, health clinics, youth organizations, and churches. Programs must be tailored to the cultural background, ethnicity, age-group, and gender of the group being targeted for the prevention services.

Table 161.2 Common Components of Most Successful Evidence-Based Programs to Prevent Teen Pregnancy

- Information is provided about the benefits of abstinence.
- Information is provided about contraception for those who are already sexually active.
- Information is provided about the signs and symptoms of STIs and how to prevent STIs.
- Interactive sessions on peer pressure are presented.
- Teenagers are taught communication skills.
- Programs are tailored to meet the needs of specific groups of young people (e.g., young men or young women, cultural groups, younger or older teens).

STI, Sexually transmitted infection.
Adapted from Suellentrop K. *What Works 2011–2012: Curriculum-Based Programs That Help Prevent Teen Pregnancy*. Washington, DC: National Campaign to Prevent Teen and Unplanned Pregnancy, http://www.c-hubonline.org/sites/default/files/resources/main/What_Works_0.pdf.

Secondary prevention programs are fewer in number. In the United States, some communities have tried to "pay" young mothers not to become pregnant again, but these efforts have not always been fruitful. **Home visiting** by nurses has been successful in some areas, and many communities have developed "Teen Tot" clinics that provide a "one-stop shopping model" for healthcare for both the teen mother and the baby in the same site at the same time. Both programs have reported some successes.

In the practice setting, the identification of the sexually active adolescent through a confidential clinical interview is a first step in pregnancy prevention. The primary care physician should provide the teenager with factual information in a nonjudgmental manner and then guide the teenager in the decision-making process of choosing a contraceptive (see Chapter 160). The practice setting is an ideal setting to support the teenager who chooses to remain abstinent. When a teenager does become pregnant and requires prenatal care services, healthcare providers should remember that the pregnant teenager is an adolescent who has become pregnant, not a pregnant woman who happens to be an adolescent.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

161.1 Abortion

Alison S. Kliegman and Robert M. Kliegman

Abortion is a safe, common, and essential reproductive healthcare evidence–based intervention. Worldwide ~30% of all pregnancies and ~60% of all unintended pregnancies are voluntarily terminated. In the past by age 45 ~25% of U.S. pregnant persons had an abortion. The WHO defines abortion as the termination of pregnancy before 20 weeks' gestation. Abortions can be voluntary or spontaneous (miscarriages). Access to reproductive care, including abortion care, is considered by all health organizations as a basic human right. The American Academy of Pediatrics supports a young person's right of "access to comprehensive, evidence-based reproductive healthcare services, including abortion." Abortion should be available to any person requesting it without a specific indication. The most common indication is unintended (unplanned) pregnancy, which includes not being able to afford a child, poorly timed pregnancy, and not having a suitable partner; additional indications include being subjected to coercive sexual encounters, as well as medical conditions that place the pregnant person at risk and certain fatal fetal conditions.

EPIDEMIOLOGY

Most abortions occur in patients between 20 and 30 years of age (Table 161.3). In addition, the majority of abortions occur in the first trimester (Fig. 161.2). The highest ratio of abortion (number of abortions per 1,000 live births) is noted in persons <15 years (Fig. 161.3). Among 15- to 19-year-olds, the United States has one of the highest rates of adolescent pregnancy but among one of the lowest rates of adolescent pregnancies ending in abortion when compared to other developed countries (Fig. 161.4). Seventy-five percent of adolescent pregnancies in the United States are unplanned, while ~30% end with an abortion (among those 15-17 years).

Abortion Care

The WHO 2022 report recommends that:

- Abortions must be decriminalized
- Be made available at request
- Be made available by telemedicine
- Be made available for self-management, not just in clinic
- Have a wide range of eligible providers
- Provide an enabling environment (Fig. 161.5)

The National Academies of Sciences, Engineering and Medicine provides an outline for continuum of abortion care; preabortion, pregnancy termination, and post-abortion care (Fig. 161.6).

Table 161.3 Characteristics of Persons Who Had an Abortion in an Outpatient Setting in 2014, by Percent

CHARACTERISTIC	PERCENT
Age*	
<15-17	3.6
18-19	8.2
20-24	33.6
25-29	26.3
30-34	16.0
35+	12.2
Prior Pregnancies*	
No prior pregnancies	29.2
Prior birth only	26.0
Prior abortion only	11.7
Prior birth and abortion	33.1
Education*	
Not a high school graduate	12.2
High school graduate or GED	29.0
Some college or associate's degree	39.2
College graduate	19.7
Family Income as a Percentage of Federal Poverty Level†	
<100	49.3
100-199	25.7
≥200	25.0

Note: Percentages may not sum to 100 because of rounding.
Sources: *Jones RK, Jerman J. Characteristics and circumstances of U.S. women who obtain very early and second trimester abortions. *PLoS One.* 2017b;12:e0169969 (n = 8,098); †Jerman J, Jones RK, Onda T. Characteristics of U.S. abortion patients in 2014 and changes since 2008. 2016. [October 17, 2016]. https://www.guttmacher.org/sites/default/files/report_pdf/characteristics-us-abortion-patients-2014.pdf (n = 8,380).
Modified from National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Population Health and Public Health Practice; Committee on Reproductive Health Services. *Assessing the Safety and Quality of Abortion Care in the U.S.* Washington, DC: National Academies Press; 2018: Table 1-2.

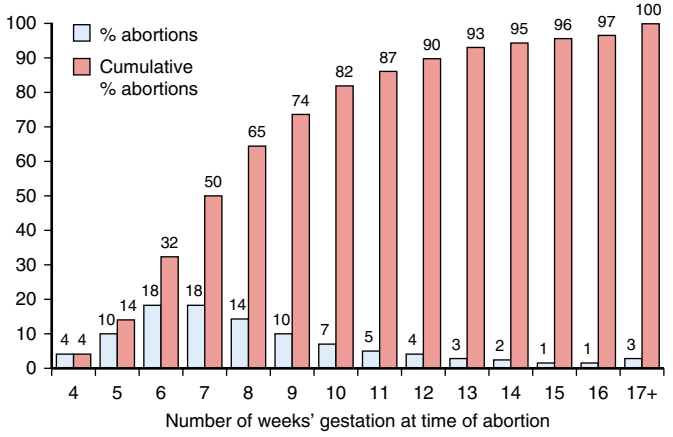

Fig. 161.2 Percentage and cumulative percentage of outpatient abortions by weeks' gestation, 2014–2015. (*From Jones RK, Jerman J. Characteristics and circumstances of US women who obtain very early and second trimester abortions. PLoS One 2017; 12(1):e0169969.*)

Methods

Abortion methods vary depending on gestational age, location (in clinic vs self-managed), and procedure (medical vs surgical). Medically managed abortion ("abortion pill") is FDA approved up to 10 weeks, although the WHO suggests up to 12 weeks and has also been used "off label" at later gestational ages. It consists of mifepristone

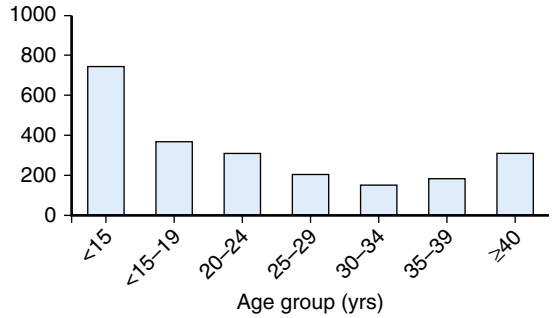

Fig. 161.3 Abortion ratio by age-group of persons who obtained a legal abortion in selected states of the United States in 2001. Abortion ratio refers to number of abortions per 1,000 live births. (*From Strauss LT, Herndon J, Chang J, et al. Abortion surveillance–United States, 2001. MMWR Surveill Summ. 2004;53:1–32.*)

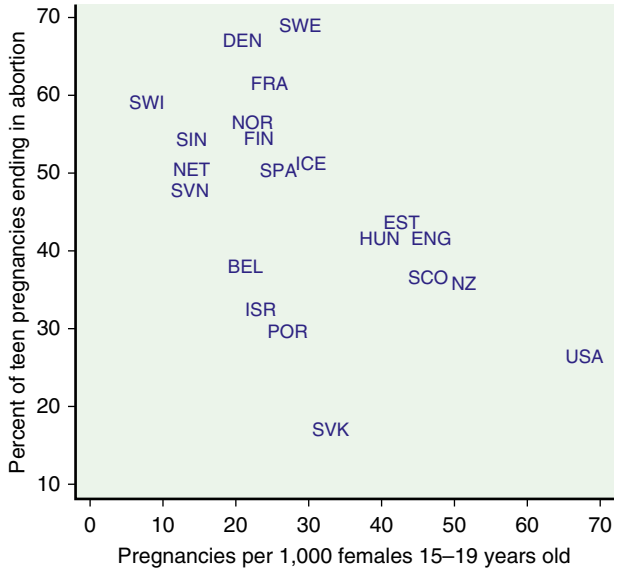

Fig. 161.4 Percentage of teen pregnancies ending in abortion is inversely correlated with teen pregnancy rate. BEL, Belgium; DEN, Denmark; ENG, England and Wales; EST, Estonia; FIN, Finland; FRA, France; HUN, Hungary; ICE, Iceland; ISR, Israel; NET, The Netherlands; NOR, Norway; NZ, New Zealand; POR, Portugal; SCO, Scotland; SIN, Singapore; SPA, Spain; SVK, Slovakia; SVN, Slovenia; SWE, Sweden; SWI, Switzerland; USA, United States. (*From Sedgh G, Finer LB, Bankole A, et al. Adolescent pregnancy, birth, and abortion rates across countries: levels and recent trends. J Adolesc Med. 2010;56:223–230, Fig. 1.*)

(a potent progesterone antagonist) 200 mg PO × one dose, followed within 24-48 hours by misoprostol 800 µg (a prostaglandin to induce uterine contractions) by buccal, sublingual, or vaginal routes. Medical abortion represents ~50% of abortions in the United States (Fig. 161.7). This treatment is available in clinic but also via telehealth, where a prescriber then mails the medication to be taken at home (self-managed medical abortion). This latter mail order availability is FDA-approved. Self-managed medical abortion is safe and ~96% effective; complications are rare (~1%) and include hemorrhage or infection; no deaths have been reported from self-managed medical abortion. Contraindications include porphyria, a bleeding disorder, taking anticoagulants, adrenal insufficiency, long-term systemic steroid use, ectopic pregnancy, and the presence of an IUD.

Acute side effects during a self-managed abortion are to be expected and include nausea and vomiting, headaches, diarrhea, and flulike symptoms and, once the abortion starts, cramping and bleeding. Excessive bleeding (two or more pads per hour for >2 hours), fever (>100°F), or severe abdominal pain requires medical attention. After

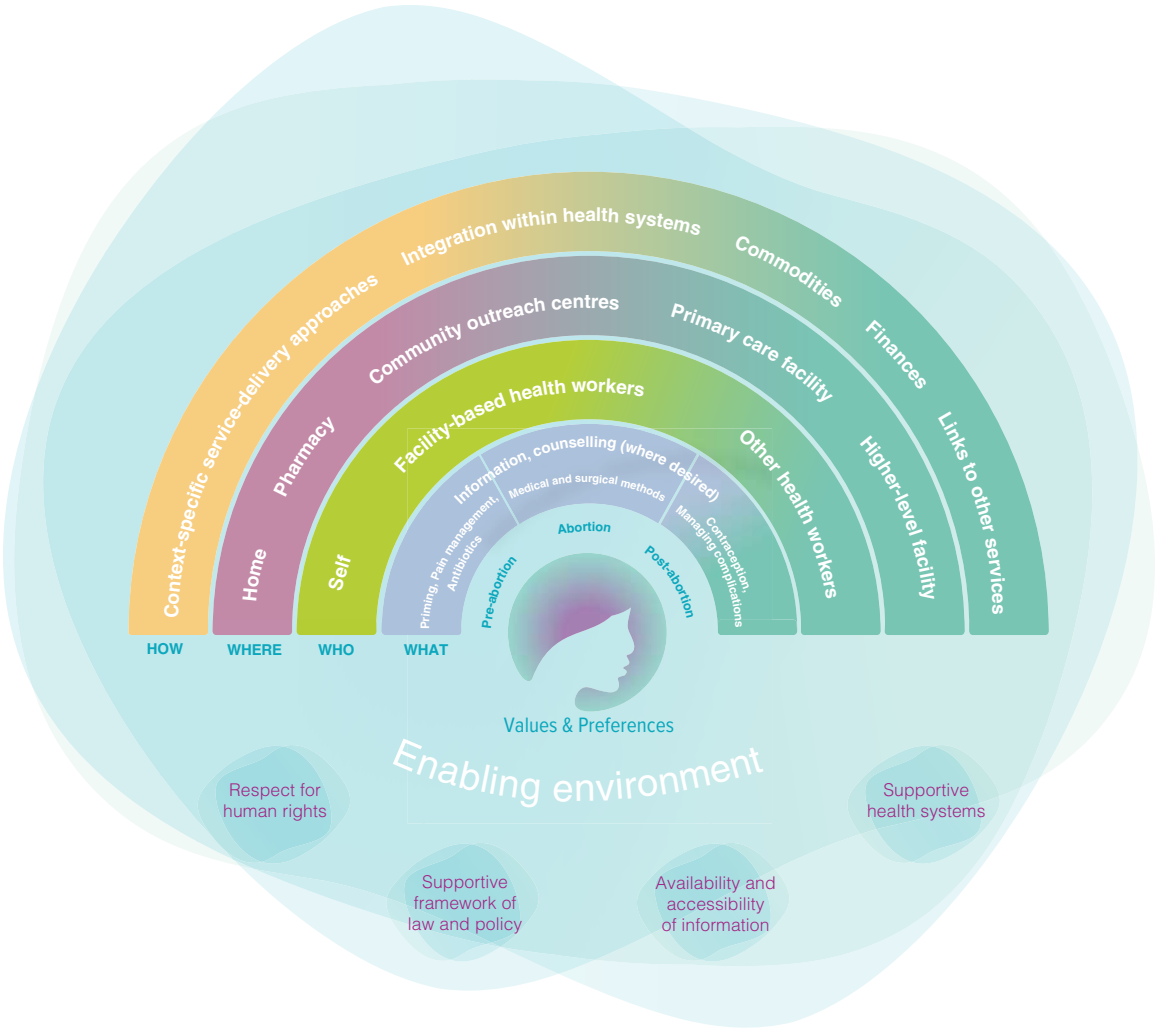

Fig. 161.5 Conceptual framework of the WHO abortion care guidelines. (*From World Health Organization. Abortion Care Guideline. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO. Fig.1* https://www.who.int/publications/i/item/9789240039483.)

the abortion, do not use tampons for ~5 days and get a pregnancy test ~3 weeks later to ensure a complete abortion. After that, a contraceptive should be started in sexually active individuals (may not be indicated in cases of rape or incest). Medical abortion has an exceptional safety record; long-term studies demonstrate no adverse effect on fertility, premature birth, breast cancer, or mental health issues.

The medications can be available by online consultation from Aid Access (aidaccess.org); pills will be mailed directly from Aid Access to persons in all states permitting self-managed abortion. "Shield laws" protect telemedicine providers serving patients in states where abortion is illegal.

Surgical methods for abortion require in-clinic presence and a skilled provider. These include suction curettage (aspiration method) used between ~6 and 16 weeks' gestation, dilation, and evacuation (~12-24 weeks); induction of labor; and, if necessary, rarely a hysterotomy (C-section) at >24 weeks. Anesthesia (local or general) is needed for these procedures.

Restricting access to or banning legal abortions will not reduce the total number of abortions but increases the risk of criminalization and potentially the number of unsafe procedures. On a global basis, unsafe abortions represent ~45% of all abortions. Unsafe abortion increases the risk of incomplete abortion (retained products of conception), hemorrhage, infection, uterine perforation, other organ injury, and infertility. Restricting access to abortion with resultant pregnancy will have adverse economic and educational consequences for the pregnant adolescent (see Chapter 161). In addition, the United States has one of the highest maternal mortality rates (23.8 deaths per 100,000 live births in 2020) of developed countries. The risk of death from pregnancy is much higher than from any form of legal abortion.

Challenges and Barriers

There are multiple logistic and legal challenges to obtaining an abortion. Some are generalizable to all ages, whereas others are specific to adolescent patients.

Some states have a complete ban against abortions, necessitating travel to another state or country. In other states, there is a limit to gestational age (usually first trimester). Many are limiting abortion to 6 weeks or when fetal heart beats are detected. The majority of states require a physician to perform an abortion. Some states restrict the use of public funding, and others restrict private insurance use for abortions. In one study, ~45% of fees were paid by the pregnant person; in states that ban Medicaid funding for abortion, the patient pays the full cost. States vary in the requirement for preabortion "counseling" and a waiting period. If "counseling" is needed, it should be from an abortion provider, not a state mandated program, which may be biased against abortion.

The criminalization of abortion (the pregnant person, the provider, others involved) has created a climate of enhanced surveillance and added barriers. Laws have been proposed to require abortion providers to register all patients requesting an abortion. These reporting mandates will compromise patient-provider confidentiality and possibly violate Health Insurance Portability and Accountability Act (HIPAA) regulations. Nonetheless HIPAA may not be applicable if legal action is filed against a patient and/or provider. Other laws will

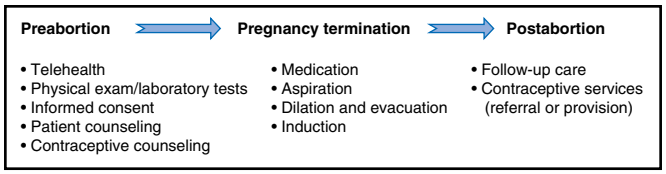

Fig. 161.6 Continuum of abortion care. (*Modified from National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Population Health and Public Health Practice; Committee on Reproductive Health Services. Assessing the Safety and Quality of Abortion Care in the U.S. Washington, DC: National Academies Press; 2018: Fig.1-1.*)

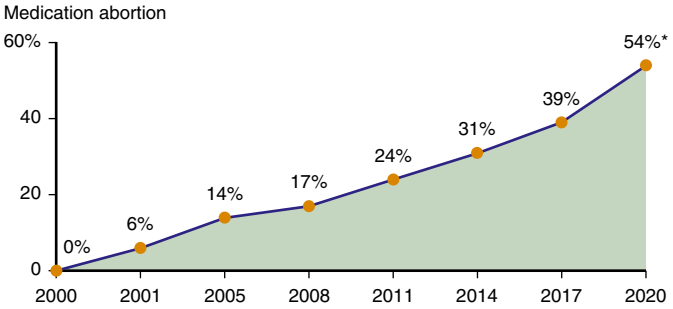

Fig. 161.7 As of 2020, medication abortions account for the majority of all U.S. abortions. *Based on preliminary data. (*From Guttmacher Institute. Medication abortion now accounts for more than half of all US abortions, 2022. https://www.guttmacher.org/print/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions.*)

permit private citizens to sue pregnant persons having an abortion or those who help (even those transporting the pregnant person to another state). With these legal obstacles in place, patients seeking an abortion must be vigilant in keeping abortion-seeking behaviors private and unavailable to litigious prosecution. This should include internet browsing and searches, text messages, period tracking apps, payments, and travel plans, all of which may be used as evidence. Although a self-managed medically induced abortion is clinically indistinguishable from a spontaneous miscarriage, a prosecutor may use electronic information as evidence to identify an induced abortion.

The concept of fetal personhood and laws defining this as starting at conception add another legal concern. Fetal personhood proponents suggest that the unborn fetus has rights similar to a child after birth and that any action thought to harm the fetus will be considered illegal. Pregnant persons can thus be detained or arrested for actions perceived as harmful to the fetus (beginning in the first trimester). Most of the cases have been related to a pregnant person's use of drugs; such patients have been accused of child abuse or even distributing drugs to a minor. In addition to the effects that the concept of fetal personhood will have on abortions, it may have implications for persons with an IUD, those using emergency contraception, embryos created for IVF, and those experiencing an ectopic pregnancy.

In addition to challenges experienced by all persons seeking an abortion, adolescents who are minors have age-specific barriers. Minors may not be able to travel to locations providing abortion (finances, driver's license, purchase airline ticket) and in most states, they are required to have some form of parental (grandparent or other adult relative in some states) involvement by notification or actual consent (PNA). PNA can be avoided by using a judicial bypass after appealing to a judge. In this case, the judge will determine if the adolescent requesting an abortion is "mature and informed." States with legal access to abortion may eliminate PNA altogether (e.g., Illinois).

Various organizations have facilitated access to self-managed abortions or to provide referrals to the nearest abortion provider. Aid Access (http://www.aidaccess.org) is an online international abortion consult service that will make mifepristone/misoprostol available by mail (including minors). Another site (http://www.ineedana.com) helps locate the nearest abortion provider, and http://www.elevatedaccess.org helps arrange flights to legal abortion sites.

Other resources include Women on Web http://www.womenonweb.org/en/ and Planned Parenthood as a patient navigator or provider of abortions.

To get help with funding: National Network of Abortion Funds https://abortionfunds.org/ or https://prochoice.org/

Locating Plan C pills: https://www.plancpills.org/?gclid=CjwKCAjw_b6WBhAQEiwAp4HyIKGkcL2gncj28MXzfN1eONGC4a3p_I9FLRxf_4I_v8NZ5HqDD04JwxoC6LQQAvD_BwE

Help with a self-managed abortion: https://www.mahotline.org/

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 162

Adolescent Sexual Assault

Allison M. Jackson, Adrianne R. Artis, and Norrell K. Atkinson

Rape is an act of violence, not an act of sex. Rape is historically defined as coercive sexual intercourse involving physical force or psychologic manipulation of a female or a male. Recognizing that sexual intercourse is not a requirement for the definition, the U.S. Department of Justice (DOJ) defines rape as "the penetration, no matter how slight, of the vagina or anus with any body part or object, or oral penetration by a sex organ of another person, without the consent of the victim." Though definitions may vary by state, **sexual assault** is a more inclusive term that according to the U.S. DOJ "means any nonconsensual sexual act proscribed by Federal, tribal, or State law, including when the victim lacks capacity to consent."

EPIDEMIOLOGY

Exact figures on the incidence of rape are unavailable because sexual assault is underreported. In the 2019 National Crime Victimization Survey, only 0.56 per 1,000 persons over 12 years of age reported sexual assault to police. According to the National Intimate Partner and Sexual Violence Survey of 2015 (NISVS 2015), over 43% women and nearly 25% of men experienced some form of **sexual violence** in their lifetime. Females exceed males as reported rape victims, but male rape may be more underreported than female rape.

Adolescence is a high-risk age-group for sexual assault, with 43.2% of females and 51.3% of males experiencing their first sexual assault before the age of 18 years, and 81.3% of females and 70.8% males experiencing their first sexual assault before the age of 25 years (NISVS 2015). Between 1995 and 2013 the rate of rape and sexual assault was highest for adolescent females between ages 18 and 24 years. The National Survey of Children's Exposure to Violence (NatSCEV 2014) revealed that 12.9% of 14- to 17-year-olds experienced any sexual victimization in the past year, 21.7% had experienced any sexual victimization in their lifetime, 4.2% experienced sexual assault in the past year, and 10.2% in their lifetime. This survey also demonstrated how other experiences with violence compound the risk for sexual victimization. Youth with a history of maltreatment by a caregiver were four times more likely to experience sexual victimization and more than four times more likely to experience sexual victimization if they were a witness to violence. Among older adolescents age 18-24 years, the rate of rape and sexual

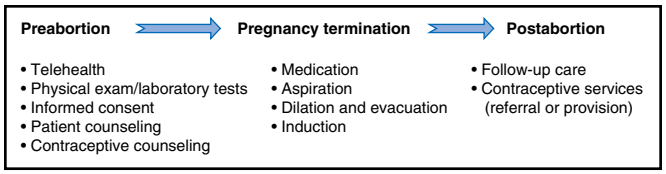

Fig. 161.6 Continuum of abortion care. (*Modified from National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Population Health and Public Health Practice; Committee on Reproductive Health Services. Assessing the Safety and Quality of Abortion Care in the U.S. Washington, DC: National Academies Press; 2018: Fig.1-1.*)

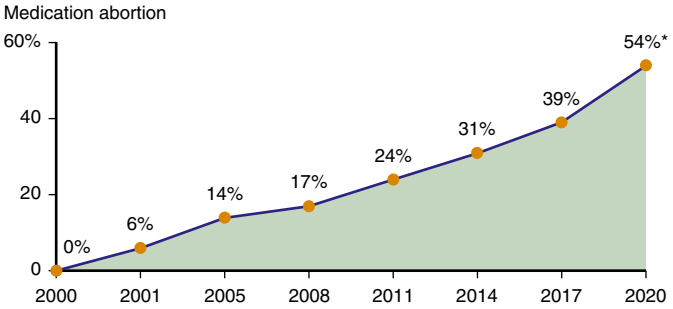

Fig. 161.7 As of 2020, medication abortions account for the majority of all U.S. abortions. *Based on preliminary data. (*From Guttmacher Institute. Medication abortion now accounts for more than half of all US abortions, 2022. https://www.guttmacher.org/print/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions.*)

permit private citizens to sue pregnant persons having an abortion or those who help (even those transporting the pregnant person to another state). With these legal obstacles in place, patients seeking an abortion must be vigilant in keeping abortion-seeking behaviors private and unavailable to litigious prosecution. This should include internet browsing and searches, text messages, period tracking apps, payments, and travel plans, all of which may be used as evidence. Although a self-managed medically induced abortion is clinically indistinguishable from a spontaneous miscarriage, a prosecutor may use electronic information as evidence to identify an induced abortion.

The concept of fetal personhood and laws defining this as starting at conception add another legal concern. Fetal personhood proponents suggest that the unborn fetus has rights similar to a child after birth and that any action thought to harm the fetus will be considered illegal. Pregnant persons can thus be detained or arrested for actions perceived as harmful to the fetus (beginning in the first trimester). Most of the cases have been related to a pregnant person's use of drugs; such patients have been accused of child abuse or even distributing drugs to a minor. In addition to the effects that the concept of fetal personhood will have on abortions, it may have implications for persons with an IUD, those using emergency contraception, embryos created for IVF, and those experiencing an ectopic pregnancy.

In addition to challenges experienced by all persons seeking an abortion, adolescents who are minors have age-specific barriers. Minors may not be able to travel to locations providing abortion (finances, driver's license, purchase airline ticket) and in most states, they are required to have some form of parental (grandparent or other adult relative in some states) involvement by notification or actual consent (PNA). PNA can be avoided by using a judicial bypass after appealing to a judge. In this case, the judge will determine if the adolescent requesting an abortion is "mature and informed." States with legal access to abortion may eliminate PNA altogether (e.g., Illinois).

Various organizations have facilitated access to self-managed abortions or to provide referrals to the nearest abortion provider. Aid Access (http://www.aidaccess.org) is an online international abortion consult service that will make mifepristone/misoprostol available by mail (including minors). Another site (http://www.ineedana.com) helps locate the nearest abortion provider, and http://www.elevatedaccess.org helps arrange flights to legal abortion sites.

Other resources include Women on Web http://www.womenonweb.org/en/ and Planned Parenthood as a patient navigator or provider of abortions.

To get help with funding: National Network of Abortion Funds https://abortionfunds.org/ or https://prochoice.org/

Locating Plan C pills: https://www.plancpills.org/?gclid=CjwKCAjw_b6WBhAQEiwAp4HyIKGkcL2gncj28MXzfN1eONGC4a3p_I9FLRxf_4I_v8NZ5HqDD04JwxoC6LQQAvD_BwE

Help with a self-managed abortion: https://www.mahotline.org/

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 162

Adolescent Sexual Assault

Allison M. Jackson, Adrianne R. Artis, and Norrell K. Atkinson

Rape is an act of violence, not an act of sex. Rape is historically defined as coercive sexual intercourse involving physical force or psychologic manipulation of a female or a male. Recognizing that sexual intercourse is not a requirement for the definition, the U.S. Department of Justice (DOJ) defines rape as "the penetration, no matter how slight, of the vagina or anus with any body part or object, or oral penetration by a sex organ of another person, without the consent of the victim." Though definitions may vary by state, **sexual assault** is a more inclusive term that according to the U.S. DOJ "means any nonconsensual sexual act proscribed by Federal, tribal, or State law, including when the victim lacks capacity to consent."

EPIDEMIOLOGY

Exact figures on the incidence of rape are unavailable because sexual assault is underreported. In the 2019 National Crime Victimization Survey, only 0.56 per 1,000 persons over 12 years of age reported sexual assault to police. According to the National Intimate Partner and Sexual Violence Survey of 2015 (NISVS 2015), over 43% women and nearly 25% of men experienced some form of **sexual violence** in their lifetime. Females exceed males as reported rape victims, but male rape may be more underreported than female rape.

Adolescence is a high-risk age-group for sexual assault, with 43.2% of females and 51.3% of males experiencing their first sexual assault before the age of 18 years, and 81.3% of females and 70.8% males experiencing their first sexual assault before the age of 25 years (NISVS 2015). Between 1995 and 2013 the rate of rape and sexual assault was highest for adolescent females between ages 18 and 24 years. The National Survey of Children's Exposure to Violence (NatSCEV 2014) revealed that 12.9% of 14- to 17-year-olds experienced any sexual victimization in the past year, 21.7% had experienced any sexual victimization in their lifetime, 4.2% experienced sexual assault in the past year, and 10.2% in their lifetime. This survey also demonstrated how other experiences with violence compound the risk for sexual victimization. Youth with a history of maltreatment by a caregiver were four times more likely to experience sexual victimization and more than four times more likely to experience sexual victimization if they were a witness to violence. Among older adolescents age 18-24 years, the rate of rape and sexual

assault was 1.2 times higher for those not enrolled in college than those in college. Further, several studies of youth in the juvenile justice system demonstrate a particularly high prevalence of prior sexual victimization of young females in that setting. Rape occurs worldwide and is especially prevalent in war and armed conflicts. The World Health Organization estimates that rape and domestic violence are responsible for 5–16% of healthy years of life lost by females of reproductive age.

Female adolescents and young adults have the highest rates of rape compared to any other age-group. The normal developmental growth tasks of adolescence may contribute to this vulnerability in the following ways: (1) the emergence of independence from parents and the establishment of relationships outside the family may expose adolescents to environments with which they are unfamiliar and situations that they are unprepared to handle; (2) dating and becoming comfortable with one's sexuality may result in activities that are unwanted, but the adolescent is too inexperienced to avoid the unwanted actions; and (3) young adolescents may be naïve and more trusting than they should be (see Chapter 150). Many teens are technologically competent, which gives sexual perpetrators access to unsuspecting vulnerable populations who were previously beyond their reach. Social media and online dating sites represent a major risk for adolescents, as they facilitate correspondence with individuals unknown to them or protective family members, while simultaneously providing a false sense of security because of remote electronic communications. A determined perpetrator can obtain specific information to identify the adolescent and arrange for a meeting that is primed for sexual victimization.

Some adolescents are at higher risk of being victims of rape than others (Table 162.1).

TERMINOLOGY

Sexual violence is a term that broadly encompasses criminal acts including **sexual assault**, **rape** and **sexual abuse**, and which disproportionately affects adolescents and young adults. Because of the prevalence of sexual violence in the adolescent population, it is important for healthcare providers to have a general understanding of the types of sexual violence that may affect children and adolescents. Providers should also be aware that every state carries their own legal definition of these crimes. These definitions dictate if or how a crime is prosecuted, which could affect survivors who have disclosed sexual violence.

Delayed disclosures of sexual violence are common. The circumstances and relationship of the assailant to the survivor can often affect if, when, and how a child or youth discloses an assault. Sexual violence is typically perpetrated by someone who knows their victim; less frequently the assailant is a stranger. The gender of the survivor may also affect the disclosure process. Males are less likely to disclose sexual violence compared with females. Individuals who are transgender, gender nonconforming, nonbinary, or other noncisgender identities are less likely to disclose sexual assault than those who identify as cisgender.

Table 162.1 Adolescents at High Risk of Rape Victimization

MALE, FEMALE, NONBINARY ADOLESCENTS
Drug and alcohol users
Runaways
Those with intellectual disability or developmental delay
Street youths
Transgender youth
Youths with a history of sexual abuse
PRIMARILY FEMALES
Survivors of prior sexual assault
Newcomers to a town or college
PRIMARILY MALES
Those in institutionalized settings (detention centers, prison)
Gay males

In any scenario where rape is facilitated by threats, coercion, physical force, or illicit and/or legal substances, the disclosure process for a survivor of sexual assault can be impacted.

TYPES OF SEXUAL VIOLENCE

Sexual assault is defined as sexual contact or behavior that occurs without explicit consent of the victim. It can include things such as attempted rape, rape, fondling, or forcing a person to perform sexual acts. It is important to remember that force is not always physical, but it can also be intimidation or coercive control of the person. Force may also include threatening to hurt the person or those close to them.

Rape is a form of sexual assault involving penetration. Not all sexual assaults are rape. Rape can further be defined as **stranger rape** vs **acquaintance rape**. **Intimate partner sexual violence** is a form of acquaintance rape. An intimate partner is defined as a person with which the survivor has had a close personal or sexual relationship; thus this form of sexual violence can be prevalent among adolescents. Intimate partner sexual violence can often start with controlling or emotionally abusive behaviors, which then escalate to assault.

Rape can frequently involve illicit and/or legal substances to facilitate the assault. Drug-facilitated rape involves perpetrators administering substances such as γ-hydroxybutyric acid (GHB), flunitrazepam (Rohypnol), and ketamine hydrochloride to their victim. More commonly, substances such as alcohol, tetrahydrocannabinoids (THC), benzodiazepines, stimulants, barbiturates, opioids, or other drugs are used during the course of an assault. Detection of these drugs requires a high index of suspicion, and a medical evaluation within 8-12 hours is necessary for prompt detection of these substances, Specific testing is used that is more sensitive than routine toxicology screens, which are often insufficient.

Sexual abuse is a type of child abuse (see Chapter 17). The American Academy of Pediatrics defines child sexual abuse as a child or adolescent who engages in sexual activities that they cannot comprehend, for which they are developmentally unprepared and unable to give informed consent, and/or when there is a violation of the legal or social taboos of society. It includes many things ranging from oral, genital, or anal contact and fondling by or of the child, to noncontact abuses, such as exhibitionism, voyeurism, or various forms of child exploitations such as pornography.

The **commercial sexual exploitation of children (CSEC)**, also known as **sex trafficking**, is a more complex form of sexual violence and is considered a form of child abuse (see Chapter 16). Sex trafficking is federally defined as the recruiting, harboring, transporting, providing, obtaining, patronizing, or soliciting of an individual through the means of force, fraud, or coercion for commercial sex. Although a pimp often personally recruits victims, they may use others to recruit. These youth may experience physical and sexual assault by the pimp as well as the "johns." Many of these youth have a history of child maltreatment, increasing their vulnerability to this form of abuse. Fear of the consequences of disclosure and the survival skills acquired often yield a very guarded presentation in the healthcare setting.

Survivors of sexual violence often experience long-term symptoms related to the trauma they have sustained. Untreated trauma can negatively affect the physical and emotional health of an adolescent into adulthood. Engagement in trauma-focused therapy, combined with a supportive environment for the adolescent to grow, can help to mitigate the effects of the trauma that they have sustained. Providers should be knowledgeable of trauma-focused therapists in their community where adolescent survivors of sexual violence can receive care.

CLINICAL MANIFESTATIONS

The adolescent's acute presentation after a rape may vary considerably, from histrionics to near-mute withdrawal. Even if they do not appear afraid, most victims are extremely fearful and very anxious about the incident, the rape report, the examination, and the entire process, including potential repercussions. Because adolescents are between the developmental lines of childhood and adulthood, their responses to rape may have elements of both child and adult behaviors. Many teens,

particularly young adolescents, may experience some level of cognitive disorganization.

Adolescents may be reluctant to report rape for a variety of reasons, including self-blame, fear, embarrassment, or in the circumstances of drug-facilitated rape, uncertainty of event details. Adolescent victims, unlike child victims who elicit sympathy and support, often face intense scrutiny regarding their credibility and inappropriately misplaced societal blame for the assault. This view is baseless and should not be used during an evaluation of any teenage victim of sexual violence. When adolescents do not report a rape, they may present at a future date with concerns for pregnancy; symptoms of or concerns for a sexually transmitted infection (STI); and symptoms of posttraumatic stress disorder (see Chapter 38), such as sleep disturbances, nightmares, mood swings, and flashbacks. Other teens may present with psychosomatic complaints or difficulties with schoolwork. All adolescents should be screened for possible sexual victimization at health examination visits.

INTERVIEW AND PHYSICAL EXAMINATION

The purpose of the adolescent medical evaluation after a sexual assault is to provide medical care for the teen and to collect and document evidence of the assault when applicable. Although many teens delay seeking medical care, others present to a medical facility within 72 hours (or up to 96 hours depending on the protocol used) of the rape, at which time forensic evidence collection should be offered to the patient. Whether presenting acutely or more remotely, a comprehensive physical exam is recommended to the extent that the patient allows. Experienced clinicians with training and knowledge of forensic evidence collection and medical-legal procedures should complete the rape evaluation or supervise the evaluation when possible.

The clinician's responsibilities are to provide support, obtain the history in a nonjudgmental and noncoercive manner, conduct a complete examination without retraumatizing the victim, and collect forensic evidence. The clinician must complete laboratory testing, administer prophylaxis treatment for STIs and emergency contraception, arrange for counseling services, and file a report to appropriate authorities in accordance with the law. In some jurisdictions, healthcare professionals are required to report all sexual assaults of minors regardless of the relationship of the victim to the perpetrator. Although healthcare professionals are legally mandated to report sexual abuse, when the perpetrator is an acquaintance or stranger, some jurisdictions leave the decision of reporting up to the victim, requiring the victim to report the sexual assault. It is not the clinician's responsibility to decide whether a sexual assault has occurred; the legal system will make that determination. Furthermore, absence of injury does not exclude the possibility that sexual assault occurred.

Ideally, a clinician trained in forensic interviewing should obtain the history. In all cases, the history should be obtained by asking *only* open-ended questions to obtain information about (1) what happened, (2) where it happened, (3) when it happened, and (4) who did it. After obtaining a concise history, including details of the type of physical contact that occurred between the victim and the assailant, the clinician should conduct a thorough and complete physical examination and document all injuries (nongenital and genital). Clinicians should provide sensitive, nonjudgmental support during the entire evaluation, as the adolescent victim has experienced a major trauma and is susceptible to retraumatization during this process. Each component of the evaluation should be explained in detail to the victim, allowing the adolescent as much control as possible, including refusal to complete any part or all of the forensic evidence collection process. For sensitive examinations like these, a chaperone should be offered. Additionally, it is often useful to permit a trusted supportive person, such as a family member, friend, or rape crisis advocate, to be present during the evaluation if that is the adolescent's wish.

The examining clinician should be familiar with **forensic evidence collection** and the physical evidence recovery kit (PERK) before initiating the examination. In the United States, each state's PERK is different, but most include some or all of the following components: swabs of suspected semen deposits, swabs of bite mark impressions to collect genetic markers (DNA, ABO group); swabs of any penetrated orifice or body surface where saliva may be present; and documentation of acute cutaneous injuries using body diagram charts and photographs with visible standard measurements. Areas of restraint should be carefully inspected for injuries; these areas include the extremities and neck. Inspection of the skin may also reveal suction injuries or bite impressions. Inspection of the mouth, with particular attention to the oral frenula and palate, may reveal mucosal injury. Although use of alternative light sources, such as the Wood lamp or blue light, enhance detection of semen and saliva, other common substances such as urine and lotion also fluoresce with alternative light sources. Swabs of sites that fluoresce under such light should be obtained for further forensic analysis.

The genital examination of a female rape victim should be undertaken with the patient in the lithotomy position. The prone knee-chest position may be used as an exam-clarifying technique, specifically to evaluate the posterior rim of the hymen and perianal area. The genital exam of a male rape victim should be undertaken with the patient in the supine position. The clinician's exam should include careful inspection of the entire pelvic, genital, and perianal areas. The clinician should document any acute injuries such as edema, erythema, petechiae, bruising, hemorrhage, or tearing. Aqueous solution of toluidine blue (1%), which adheres to nucleated cells, may be used during the acute examination to improve visualization of microtrauma in the perianal area. Any disruption to the superficial epidermis will allow for dye uptake and thus cannot differentiate between disruption of the skin from trauma, irritation, or infection. Additionally, a colposcope may be used to provide magnification and photo documentation of injuries.

LABORATORY DATA

When adolescents present for medical care within 72-120 hours of a sexual assault, a forensic evidence collection kit should be offered to the patient. The time frames of eligibility for forensic evidence collection vary according to jurisdiction, so it is important to know the criteria of the jurisdiction investigating the assault. Regardless of an adolescent's decision to have evidence collection completed, medical care, including physical examination, laboratory testing (Table 162.2), and prophylactic therapies, should be offered to the patient. Follow-up evaluations should be scheduled to repeat these laboratory studies.

TREATMENT

Treatment includes **prophylactic antimicrobials** for STIs (see Chapter 163) and emergency contraception (see Chapter 160.6). The Centers for Disease Control and Prevention (CDC) reports that trichomoniasis, bacterial vaginosis, gonorrhea, and chlamydia are the most frequently diagnosed infections among women who have been sexually assaulted. Antimicrobial prophylaxis is recommended for adolescent rape victims because of the risk of acquiring an STI and the risk of pelvic inflammatory disease (Table 162.3). HIV **postexposure prophylaxis (PEP)** must be considered and an infectious disease specialist consulted if higher transmission risk factors are identified (e.g., knowing that the perpetrator is HIV-positive, significant mucosal injury of the victim) to prescribe a triple-antiretroviral regimen (Fig. 162.1). Hepatitis B infection can be prevented with immunoglobulin and/or vaccination depending on the victim's immunization status and the perpetrators status; thus similar considerations should be made for possible exposure

Table 162.2 Laboratory Evaluation of Sexual Assault

Within 8-12 hr (if Indicated by History)
- Urine and blood for date rape drugs (GHB, Rohypnol, and ketamine)

Within 24 hr (if Indicated by History)
- Blood for comprehensive toxicology screen (for other classes of drugs)

Within 72 hr (or up to 96 hr Depending on Protocol Used)
- Forensic evidence kit
- Pregnancy test
- Hepatitis B screen (hepatitis B surface antigen, surface antibody, and core antibody)
- Syphilis (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL])
- HIV (HIV 1/2 Ag/Ab immunoassay, point-of-care testing can be useful in persons unlikely to follow up with a provider)
- Bacterial vaginosis (BV) and candidiasis: point-of-care testing and/or wet mount of vaginal secretions with measurement of pH and KOH application for whiff test
- Trichomonas vaginalis: nucleic acid amplification tests (NAATs) by urine or vaginal specimen or point-of-care testing (i.e., DNA probes) from vaginal specimen
- Chlamydia and *Neisseria gonorrhoeae*: NAATs at sites of penetration or attempted penetration:
  - *N. gonorrhoeae:* oropharynx (*), rectum (*), urine (**)
  - *Chlamydia*: rectum (*), urine (**)

*Men who have sex with men (MSM) should be offered screening of gonorrhea and chlamydia if they report receptive oral or anal sex during the preceding year even if there was not contact at these sites during the assault.
**NAAT can be obtained on a dirty urine sample as an alternative to a genital swab.
From Centers for Disease Control and Prevention. Sexually transmitted diseases: treatment guidelines 2015, *MMWR Recomm Rep*. 2015;64(RR-3):1–140; and Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:458.

to the hepatitis B virus in vaccinated/unvaccinated individuals. Human papilloma virus (HPV) vaccination is also recommended because persons who have been sexually assaulted are also at risk for infection, and the efficacy of the HPV vaccine is high. Clinicians should review the importance for the patient's compliance with medical treatment, psychologic treatment, and follow-up care. Counseling should be provided about the symptoms of STIs and the need for urgent follow-up if symptoms develop. Abstinence from sexual intercourse should be recommended until the completion of the STI prophylactic course.

At the time of presentation, the clinician should address the need for follow-up care, including psychologic counseling. Adolescent victims are at increased risk of posttraumatic stress disorder, depression, self-abusive behaviors, suicidal ideation, delinquency, substance abuse, eating disorders, and sexual revictimization. It is important for the adolescent victim and parents to understand the value of timely counseling services to decrease these potential long-term sequelae. Counseling services should be arranged during the initial evaluation, with follow-up arranged with the primary care physician to improve compliance.

FOLLOW-UP

Follow-up evaluation should be arranged within 1 week of the initial evaluation with a child abuse pediatrician or a Child Advocacy Center to provide an opportunity for prompt review of STI test results, to monitor for medication adherence and possible side effects, to ensure healing and documentation of injuries, and to evaluate for the resolution of symptoms initially present, the development of new physical symptoms, or emerging mental health concerns. If no STI prophylaxis was given, follow-up testing for gonorrhea, chlamydia, and trichomonas can be repeated in 1-2 weeks after the assault. If prophylaxis was provided, follow-up testing is not needed unless symptoms develop. If infection in the assailant cannot be ruled out, serologic testing for syphilis can be repeated in 4-6 weeks and 3 months, and for HIV in 6 weeks and 3 months.

Table 162.3 Postexposure Prophylaxis (PEP) for Acute Sexual Assault Victims

ROUTINE	
Recommended regimen for STI prophylaxis	• Ceftriaxone 500 mg IM once in a single dose* PLUS • Doxycycline 100 mg orally twice a day for 7 days (azithromycin 1 g orally in a single dose should be considered in persons at high risk for noncompliance) PLUS (for females) • Metronidazole 500 mg orally twice a day for 7 days (2 g orally in a single dose should be considered in persons at high risk for noncompliance)
Pregnancy prophylaxis	Levonorgestrel (Plan B) 1.5 mg orally in a single dose ***Ulipristal acetate (Ella) 30 mg is effective for up to 120 hr*
HPV	Assess HPV vaccination history; vaccine should be provided at initial evaluation if unimmunized or partially immunized • If unimmunized and >15 yr at the time of the initial exam, give first dose and, two follow-up doses at 1-2 mo and 6 mo • If <15 yr, a single follow-up dose at 6-12 mo • If partially immunized, a follow-up dose if >5 mo since the first dose or >12 wk since the second dose
AS INDICATED	
HIV†	*Preferred regimen* • Tenofovir 300 mg and fixed-dose combination emtricitabine 200 mg (Truvada) once daily PLUS • Raltegravir 400 mg orally twice a day OR • Dolutegravir 50 mg orally once a day All persons with a potential exposure within 72 hours should be offered PEP, which includes a 28-day course of a three-drug antiretroviral regimen.
Hepatitis B	*Alternative regimens available.* Specific indications for vaccine, immunoglobulin, and/or booster depend on assailant's status

*If ≥150 kg, give 1 g of ceftriaxone IM once.
**Provided for patients with negative urine pregnancy screen. In addition, an antiemetic (Compazine, Zofran) can be prescribed for patients receiving emergency contraception.
†HIV PEP is provided for patients with penetration and when the assailant is known to be HIV-positive or at high risk because of a history of incarceration, intravenous drug use, or multiple sexual partners. If provided, laboratory studies must be drawn before administration of medication (HIV, CBC, LFTs, BUN/Cr, amylase, lipase), and follow-up must be arranged.
Data from Workowski, KA, Bachmann, LH, Chan, PA Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep* 2021;70:128-135.

PREVENTION

Primary prevention may be accomplished through education of preadolescents and adolescents on the issues of consent, rape, healthy

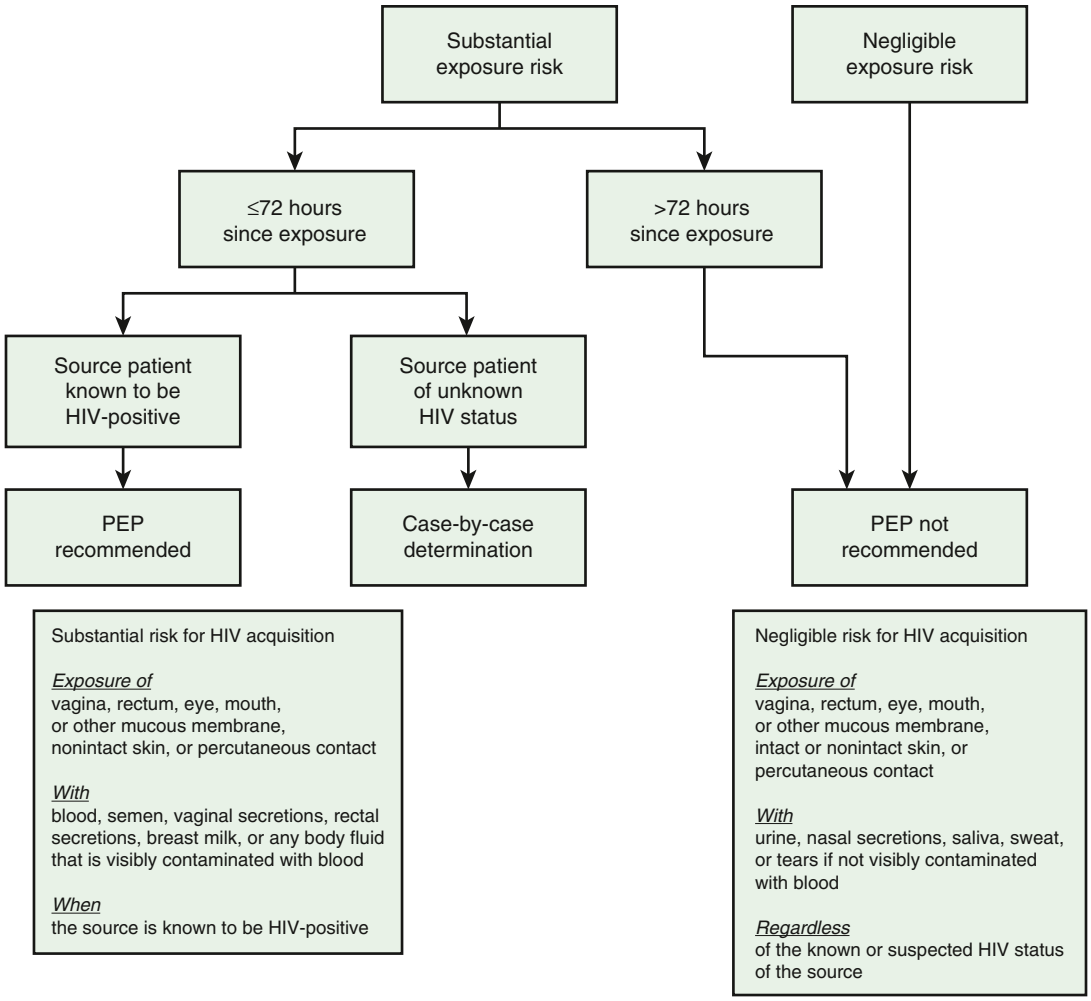

Fig. 162.1 Algorithm to evaluate the need for nonoccupational HIV postexposure prophylaxis among adult and adolescent survivors of sexual assault. *(From Workowski, KA, Bachmann, LH, Chan, PA. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70:128–135; adapted from Announcement: updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV—United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65:458.)*

relationships, internet dangers, and drug- and alcohol-facilitated rape. Prevention messages should be targeted at males, females, and nonbinary youth at high schools and colleges. Particular emphasis on prevention efforts during college orientation is highly recommended. High-risk situations that may increase the likelihood of a sexual assault should be discouraged, such as the use of drugs or alcohol, drinking from a container that has been left unattended, and accepting drinks from strangers. **Secondary prevention** includes informing adolescents of the benefits of timely medical evaluations when rape has occurred. Individual clinicians should ask adolescents about past experiences of forced and unwanted sexual behaviors and offer help in dealing with those experiences. The importance of prevention cannot be overstated because adolescents are disproportionately affected by sexual assault, and they are particularly vulnerable to long-term consequences.

Counseling services for family members of the victim may improve their ability to provide appropriate support to the adolescent victim. Caution parents not to use the assault as a validation of their parental guidance, as it will only serve to place blame inappropriately on the adolescent victim.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 163

Sexually Transmitted Infections

Tamera Coyne-Beasley, Nefertiti H. Durant, and Samantha V. Hill

Age-specific rates of many sexually transmitted infections **(STIs)** are highest among sexually experienced adolescents and young adults, after controlling for sexual activity. Although some STI pathogens present as STI syndromes with a specific constellation of symptoms, most are asymptomatic and only detected by a laboratory test. The approach to prevention and control of these infections lies in education, screening, and early diagnosis and treatment.

ETIOLOGY

Any adolescent who has had oral, vaginal, or anal sexual intercourse is behaviorally vulnerable to acquiring an STI. Not all adolescents are at equal risk; physical, behavioral, and social factors contribute to an adolescent's risk. Adolescents who initiate sex at a younger age; youth residing in detention facilities; youth attending STI clinics; youth involved in commercial sex exploitation or survival sex and exchange sex for drugs, money, food, or housing; young males having sex with males (YMSM); adolescent women and young adult women having sex with older men; transgender youth; youth with disabilities; and youth who are injection drug users are at higher risk for STIs. Risky behaviors, such as sex with multiple concurrent partners or multiple sequential partners of limited duration, failure to use barrier protection consistently and correctly, and increased biologic susceptibility to infection also contribute to risk (Table 163.1). Although all 50 states and the District of Columbia explicitly allow minors to consent for their own sexual health services (at varying ages), many adolescents encounter multiple obstacles to accessing this care, including poverty, insurance coverage, and fears of lack of confidentiality (see Table 163.1). Adolescents who are survivors of sexual assault need reassurance, protection, and appropriate intervention when these circumstances are uncovered (see Chapter 162).

Table 163.1 Circumstances Contributing to Adolescents' Susceptibility to Sexually Transmitted Infections

PHYSICAL
Younger age at puberty
Cervical ectopy
Smaller introitus leading to traumatic sex
Asymptomatic nature of sexually transmitted infection
Uncircumcised penis
BEHAVIOR INFLUENCED BY DEVELOPMENTAL STAGES
Early adolescence: Lack ability to think abstractly
Middle adolescence: Believe in uniqueness and lack of vulnerability
SOCIAL FACTORS
Poverty
Limited access to "adolescent-friendly" healthcare services
Adolescent health-seeking behaviors (forgoing care because of confidentiality concerns or denial of health problem)
Sexual abuse, trafficking, and violence
Lower levels of condom use
Mental health issues and substance use/abuse
Decreased access to confidential medical care leading complexity in seeking care
Homelessness
Young adolescent females with older partners
Young men having sex with men

Data from Wangu, G Burstein. Adolescent sexuality: updates to the Sexually Transmitted Infection Guidelines. *Ped Clin North Am.* 2017;64:389–341; and Spear LP. Adolescent neurodevelopment. *J Adolesc Health.* 2013;52:S7–S13.

EPIDEMIOLOGY

STI prevalence varies by age, gender, race, and ethnicity. In the United States, although adolescents and young adults ages 15-24 represent 25% of the sexually experienced population, this age-group accounts for almost 50% of all incident STIs each year.

Chlamydia is the most frequently reported infectious disease in the United States and is the second most common STI in U.S. adolescents and young adults after human papillomavirus (HPV). In 2019, young adult females ages 20-24 (3,797.8 cases per 100,000 females) followed by females ages 15-19 (2,697.0 cases per 100,000 females) had the highest rates of chlamydia in the United States (Fig. 163.1). Notably age-specific rates of reported cases of chlamydia among males, although substantially lower than rates among females, were still highest in young adult males 20-24 years (1,680.0 cases per 100,000 males). Chlamydia remains common among all races and ethnic groups. In 2021, a total of 1,644,416 cases of *Chlamydia trachomatis* infection were reported to the CDC, making it the most common notifiable sexually transmitted infection in the United States for that year. This case count corresponds to a rate of 495.5 cases per 100,000 population, an increase of 3.9% compared with the rate in 2020. During 2020 to 2021, rates of reported chlamydia increased among both males and females, in all regions of the United States, among most age groups, and among all race/Hispanic ethnicity groups. Rates of reported chlamydia are highest among adolescents and young adults. In 2021, almost two-thirds (58%) of all reported chlamydia cases were among persons aged 15–24 years.

Reported rates of other bacterial STIs are also high among adolescents and young adults. In 2021, gonorrhea rates among adolescents were 360.1/100,000 for males ages 15-19 compared to 587.8/100,000 for young women ages 15-19. Gonorrhea rates for young adult males ages 20-24 years old (844.2/100,000) were significantly higher than rates for males at any other age/sex group and slightly lower than for young women ages 20-24 (873.2/100,000).

Pelvic inflammatory disease (PID) is a clinical syndrome that results from the ascension of microorganisms from the cervix and vagina to the upper genital tract. PID is a serious complication of chlamydia and gonorrhea, two of the most common reportable infectious diseases and STIs in the United States. PID rates are highest among females ages 15-24 compared with older women.

Syphilis rates have increased at an alarming rate, especially among males, since 2000. In 2021, young adult males age 20-24 had the third highest rate of primary and secondary syphilis at 51.2 per 100,000. Rates among adolescent males ages 15-19 were lower at 12.0 per 100,000.

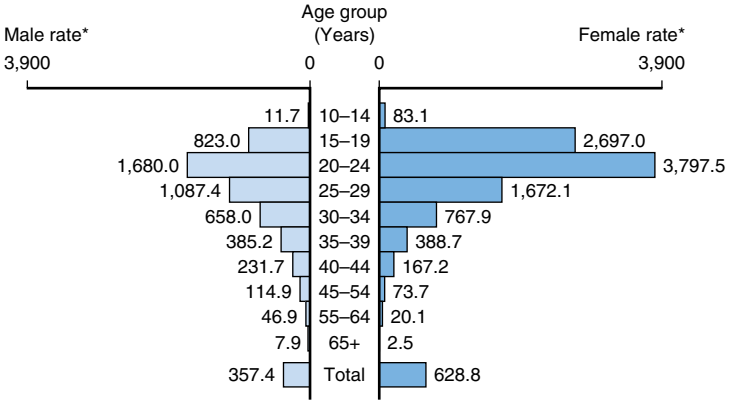

Fig. 163.1 Chlamydia: Rates of reported cases by age group and sex, United States, 2021. (*Data from the Centers for Disease Control and Prevention:* www.cdc.gov/std/statistics/2021/data.zip.)

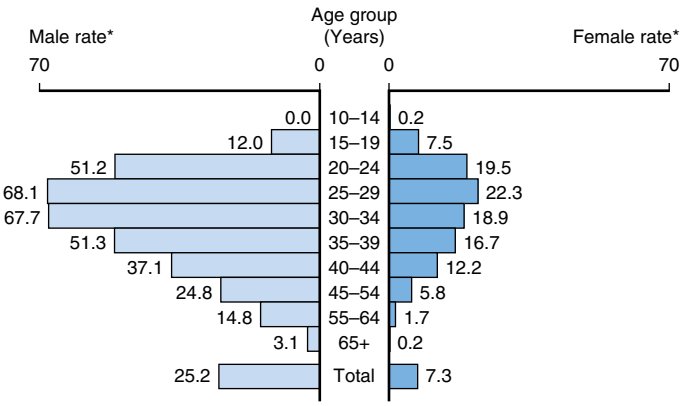

Fig. 163.2 Primary and secondary syphilis—Rates of reported cases by age group and sex, United States, 2021. (*Data from the Centers for Disease and Control and Prevention:* www.cdc.gov/std/statistics/2021/data.zip.)

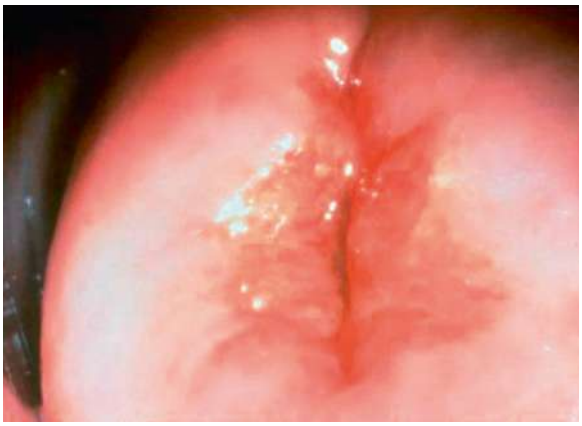

Fig. 163.3 Cervical ectopy. (*From Seattle STD/HIV Prevention Training Center, University of Washington, Claire E. Stevens.*)

Rates of female primary and secondary syphilis are much lower than male rates (7.5/100,000 among 15-19 year olds; 19.5/100,000 among 20-24 year olds).

Adolescents also carry a large burden of viral STIs. U.S. youth are at persistent risk for **HIV infection**. However, according to the 2021 Youth Risk Behavior Survey, only 6% of high school students have ever been tested for HIV. Adolescents (persons aged 13–19 years) and young adults (persons aged 20–24 years) accounted for 21% of the 36,801 diagnoses of HIV infection in 2019 in the United States and 6 dependent areas. They are the least likely of any age group to be aware of their HIV infection, retained in care, or have a suppressed viral load. From 2015 through 2019 in the United States and 6 dependent areas, the number of diagnoses of HIV infection among adolescents and young adults for males, females, and transgender MTF decreased. In 2019, diagnoses of HIV infection among adolescent and young adult males (85%) and females (12%) accounted for approximately 97% of HIV diagnoses. Transgender MTF adolescents and young adults accounted for 3% of annual diagnoses. From 2015 through 2019 in the United States, the rate of diagnosis of HIV infection for Asian, Black/African American, and multiracial adolescents decreased. The rates of diagnosis of HIV infection for Hispanic/Latino and White adolescents remained stable. In 2019, the highest rate was 23.5 for Black/African American adolescents, followed by 6.3 for Hispanic/Latino, and 4.2 for multiracial adolescents. Racial and ethnic disparities persist.

Human papillomavirus (HPV) is the most frequently acquired STI in the United States. According to the National Health and Nutrition Examination Survey (NHANES), prevalence of HPV vaccine types 6, 11, 16, and 18 **(4vHPV)** declined between the prevaccine (2003–2006) and vaccine (2009–2012) eras: from 11.5% to 4.3% among females ages 14-19 and from 18.5% to 12.1% among females ages 20-24. Within 6 years of introduction of the HPV vaccine, there was a 64% decrease in 4vHPV-type prevalence among female youth ages 14-19 and a 34% decrease among young adult women ages 20-24. Efforts are ongoing to improve vaccination among all youth.

Herpes simplex virus type 2 (HSV-2) is the most prevalent viral STI (see Chapter 299). According to NHANES data, prevalence of both HSV-1 and HSV-2 decreased from 1999–2000 to 2015–2016 (from 59.4% to 48.1% and from 18.0% to 12.1%, respectively). According to Centers for Disease Control and Prevention (CDC) data, seroprevalence for HSV-2 for adolescents ages 14-19 was low, at 0.8. It is important to note that among young adults ages 20-29, HSV-2 prevalence is higher, at 7.6%. Prevalence of HSV-1 among 14- to 19-year-olds was 27% compared to 41% among those ages 20-29. There are notable ethnic, racial, and gender disparities in HSV prevalence. Prevalence of HSV-1 was highest among Mexican American persons and lowest among non-Hispanic White persons. HSV-2 prevalence was highest among Hispanic Black persons and lowest among non-Hispanic Asian persons. Both HSV-1 and HSV-2 were higher among females than males.

PATHOGENESIS

During puberty, increasing levels of estrogen cause the vaginal epithelium to thicken and cornify and the cellular glycogen content to rise, with the latter causing the vaginal pH to fall. These changes increase the resistance of the vaginal epithelium to penetration by certain organisms (including *Neisseria gonorrhoeae*) and increase the susceptibility to others (*Candida albicans* and *Trichomonas*; see Chapter 330). The transformation of the vaginal cells leaves columnar cells on the ectocervix, forming a border of the two cell types on the ectocervix known as the *squamocolumnar junction*. The appearance is referred to as *ectopy* (Fig. 163.3). With maturation, this tissue involutes. Before involution, it represents a unique vulnerability to infection for adolescent females. The association of early sexual debut and younger gynecologic age with increased risk of STIs supports this explanation of the pathogenesis of infection in young adolescents.

SCREENING

Early detection and treatment are primary *STI control strategies*. Some of the most common STIs in adolescents, including HPV, HSV, chlamydia, and gonorrhea, are usually asymptomatic and, if undetected, can be spread inadvertently by the infected host. **Screening** initiatives for chlamydial infections have demonstrated reductions in PID cases by up to 40%. Federal and professional medical organizations recommend annual chlamydia and gonorrhea screening for sexually active females <25 years old (Table 163.2). The lack of a dialog about STIs or the provision of STI services at annual preventive service visits to sexually experienced adolescents is a missed opportunity for screening and education. Comprehensive, confidential, reproductive health services, including STI screening, should be offered to all sexually experienced adolescents (see Table 163.2).

COMMON INFECTIONS AND CLINICAL MANIFESTATIONS

STI syndromes are generally characterized by the location of the manifestation (vaginitis, enteritis) or the type of lesion (genital ulcer). Certain constellations of presenting symptoms suggest the inclusion of a possible STI in the differential diagnosis.

Urethritis

Urethritis is an STI syndrome characterized by inflammation of the urethra, usually caused by an infectious etiology. Urethritis may present with urethral discharge, dysuria, urethral irritation, or meatal pruritus. Urgency, frequency of urination, erythema of the urethral meatus, and urethral pain or burning are less common clinical presentations. Approximately 30–50% of males are asymptomatic but may have signs of discharge on diagnosis. On examination, the classic finding is mucoid or purulent discharge from the urethral meatus (Fig. 163.4). If no discharge is evident on exam, providers may attempt to

Table 163.2 Routine Laboratory Screening Recommendations for Sexually Transmitted Infections in Sexually Active Adolescents and Young Adults

CHLAMYDIA TRACHOMATIS AND *NEISSERIA GONORRHOEAE*

- Routine screening for *C. trachomatis* and *N. gonorrhoeae* of all sexually active females age <25 yr is recommended annually.
- Extragenital chlamydia and gonorrhea screening (pharyngeal or rectal) can be considered on the basis of reported sexual behaviors and exposure, through shared clinical decision-making between the patient and the provider.
- Routinely screen sexually active adolescent and young adult MSM at sites of contact for chlamydia (urethra, rectum) and gonorrhea (urethra, rectum, pharynx) at least annually regardless of condom use. NAAT is preferred for provider or self-collected specimens. More frequent screening (i.e., at 3- to 6-mo intervals) is indicated for MSM, including those taking PrEP and those with HIV infection, if risk behaviors persist or if they or their sex partners have multiple partners or anonymous partners or have sex with illicit drug use.
- Consider screening for *C. trachomatis* of sexually active adolescent and young adult males annually who have a history of multiple partners in clinical settings with high prevalence rates, such as jails or juvenile correction facilities, national job training programs, STD clinics, high school clinics, or adolescent clinics.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The following recommendations apply to testing for HIV:

- HIV testing is recommended for all adolescents and young adults seeking STI evaluation and/or treatment who are not already known to have HIV infection. Testing should be routine at the time of the STI evaluation, regardless of whether the patient reports any specific behavioral risks for HIV.
- The CDC and USPSTF recommend HIV screening at least once for all persons age 13-64 yr or 15-65, respectively.
- Persons at higher risk for HIV acquisition, including sexually active gay, bisexual, and other MSM, should be screened for HIV at least annually. Providers can consider the benefits of offering more frequent screening (e.g., every 3-6 months) among MSM at increased behavioral risk for acquiring HIV.
- All pregnant adolescents should be tested for HIV during the first prenatal visit. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered and is recommended for adolescents and young adults who are at high risk for acquiring infection.
- HIV screening should be voluntary and free from coercion. Patients should not be tested without their knowledge.
- Providers should use a laboratory-based antigen/antibody (Ag/Ab) combination assay as the first test for HIV, unless persons are unlikely to follow up with a provider to receive their HIV test results; in those cases screening with a rapid POC test can be useful.
- Providers should test for HIV RNA if initial testing according to the HIV testing algorithm recommended by the CDC is negative or indeterminate when concerned about acute HIV infection (https://stacks.cdc.gov/view/cdc/50872).
- HIV screening should be discussed and offered to all adolescents at least once by age 16-18 yr and throughout young adulthood in healthcare settings. HIV risk should be assessed annually for >13 yr and offered if HIV risk factors are identified.
- Routinely screen sexually active adolescent and young adult MSM at least annually regardless of condom use. More frequent screening (i.e., at 3- to 6-mo intervals) is indicated for MSM who have multiple or anonymous partners or who have sex with illicit drug use.

SYPHILIS

- Syphilis screening should be offered to sexually active adolescents reporting risk factors, including MSM.
- Routinely screen sexually active adolescent and young adult MSM at least annually regardless of condom use. More frequent screening (i.e., at 3- to 6-mo intervals) is indicated for MSM who have multiple or anonymous partners or who have sex with illicit drug use.
- Screen women at 1st prenatal visit, at 28 weeks, at delivery if at greater behavioral risk.
- Screen asymptomatic women who may have increased behavioral vulnerability (history of incarceration, transactional sex, higher rate in community).
- Providers should consult with their local health department regarding local syphilis prevalence and associated risk factors that are associated with syphilis acquisition.

HEPATITIS B VIRUS

- All MSM should be screened with HBsAg, HBV core antibody, and HBV surface antibody.
- Vaccination against both HAV and HBV is recommended for all MSM when a previous infection or vaccination cannot be documented.

HEPATITIS C VIRUS AND UNIVERSAL HEPATITIS C SCREENING

- The CDC recommends hepatitis C screening at least once in a lifetime for all adults age 18 yr and older, except in settings where the prevalence of HCV infection (HCV RNA positivity) is <0.1%.
- Hepatitis C screening for all pregnant women during each pregnancy, except in settings where the prevalence of HCV infection (HCV RNA positivity) is less than 0.1%.
- Screening adolescents younger than 18 yr old for HCV who report risk factors, that is, injection drug use, receipt of an unregulated tattoo, received blood products or organ donation before 1992, received clotting factor concentrates before 1987, or long-term hemodialysis.
- Given the high HCV prevalence among young injection drug users, screening should be strongly considered.
- All people living with HIV should be screened during the initial HIV evaluations and at least annually thereafter.
- Screening should be performed using HCV antibody assays followed by HCV RNA testing for those with a positive antibody test.
- Routine screening of adolescents and young adults who are asymptomatic for certain STIs (i.e., syphilis, trichomoniasis, BBV, HSV, HAV, and HB) is not typically recommended.

From Centers for Disease Control and Prevention: https://www.cdc.gov/std/treatment-guidelines/screening-recommendations.htm and https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm.

express discharge by applying gentle pressure to the urethra from the base distally to the meatus 3-4 times. *Chlamydia trachomatis* and *N. gonorrhoeae* are the most commonly identified pathogens. *Mycoplasma genitalium* has been associated with urethritis, but data supporting *Ureaplasma urealyticum* have been inconsistent. *Trichomonas vaginalis* can cause nongonococcal urethritis (NGU), but the prevalence varies. HSV-1, HSV-2, and Epstein-Barr virus (EBV) are also potential urethritis pathogens in some cases. Sensitive diagnostic *C. trachomatis* and *N. gonorrhoeae* tests are available for the evaluation of urethritis. However, other pathogens can be considered when NGU is not responsive to treatment. Noninfectious causes of urethritis include urethral trauma or foreign body. Unlike in females, urinary tract infections (UTIs) are rare in males who have no genitourinary medical history. In the typical sexually active adolescent male, dysuria and urethral discharge suggest the presence of an STI unless proven otherwise.

Epididymitis

The inflammation of the epididymis in adolescent males is most often associated with an STI, most frequently *C. trachomatis* or *N. gonorrhoeae*. The presentation of unilateral scrotal swelling and tenderness, often accompanied by a hydrocele and palpable swelling of the epididymis, associated with the history of urethral discharge constitute the presumptive diagnosis of epididymitis. Males who practice insertive anal intercourse are also vulnerable to *Escherichia coli* infection. **Testicular torsion**, a surgical emergency usually presenting with sudden onset of severe testicular pain, should be considered in the differential



Fig. 163.4 Gonococcal urethral discharge. (*From Seattle STD/HIV Prevention Training Center, University of Washington, Connie Celum and Walter Stamm.*)

diagnosis (see Chapter 582). The evaluation for epididymitis should include obtaining evidence of urethral inflammation by physical exam, Gram stain of urethral secretions, urine leukocyte esterase test, or urine microscopy. A *C. trachomatis* and *N. gonorrhoeae* nucleic acid amplification test (NAAT) should be performed.

Vaginitis

Vaginitis is a superficial infection of the vaginal mucosa frequently presenting as vaginal discharge, with or without vulvar involvement (see Chapter 586). **Bacterial vaginosis**, **vulvovaginal candidiasis**, and **trichomoniasis** are the predominant infections associated with vaginal discharge. Bacterial vaginosis is caused by replacement of the normal hydrogen peroxide (H_2O_2)–producing *Lactobacillus* species vaginal flora by an overgrowth of anaerobic microorganisms, as well as *Gardnerella vaginalis, Ureaplasma,* and *Mycoplasma*. It is diagnosed based on an individual having at least three out of four of **Amsel's criteria**: (1) thin, gray, homogenous discharge, (2) vaginal pH >4.5, (3) fishy odor after the addition of potassium hydroxide (KOH) to discharge, and (4) at least 20% clue cells present on wet prep. It is important to note that research has shown there to be significant variability in providers' abilities to read wet preps; thus standardization of wet prep analysis via laboratories is recommended. BV NAATs are also available but should be used only by symptomatic women because accuracy has not been determined for asymptomatic women. Researchers do not know the cause of bacterial vaginosis or how some women acquire it. We do know the condition typically occurs in sexually active women. We also know that sexual activity is associated with increased frequency of bacterial vaginosis. Additionally, history of a diagnosis of bacterial vaginosis increases the risk of acquisition of other STIs. Vulvovaginal candidiasis, usually caused by *C. albicans,* can trigger vulvar pruritus, pain, swelling, redness, and dysuria. Findings on vaginal examination include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. Trichomoniasis is caused by the protozoan *T. vaginalis*. Infected females may present with symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation or may be diagnosed by screening an asymptomatic patient. Cervicitis can sometimes cause a vaginal discharge. Laboratory confirmation is recommended because clinical presentations may vary and patients may be infected with more than one pathogen.



Fig. 163.5 Mucopurulent cervical discharge positive swab test. (*From Seattle STD/HIV Prevention Training Center, University of Washington, Claire E. Stevens and Ronald E. Roddy.* http://www2a.cdc.gov/stdtraining/ready-to-use/pid.htm.)



Fig. 163.6 Inflamed cervix caused by gonococcal cervicitis. (*From Centers for Disease Control and Prevention: STD clinical slides.* http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm.)

Cervicitis

The inflammatory process in cervicitis involves the deeper structures in the mucous membrane of the cervix uteri. Vaginal discharge can be a manifestation, but cervicitis is frequently asymptomatic. Patients also present with complaints of irregular or postcoital bleeding. Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (e.g., swab sign; Fig. 163.5), called **mucopurulent cervicitis** or cervicitis, and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os, signifying friability. Cervical changes associated with cervicitis must be distinguished from cervical ectopy in the younger adolescent to avoid the overdiagnosis of inflammation (Fig. 163.6 and see Fig. 163.3). The pathogens identified most frequently with cervicitis are *C. trachomatis* and *N. gonorrhoeae,* although no pathogen is identified in most cases. HSV is a less common pathogen associated with ulcerative and necrotic lesions on the cervix.

Pelvic Inflammatory Disease

PID encompasses a spectrum of inflammatory disorders of the female upper genital tract, including **endometritis**, **salpingitis**, **tuboovarian abscess**, and **pelvic peritonitis**, usually in combination rather than as separate entities. *N. gonorrhoeae* and *C. trachomatis* predominate as the involved pathogenic organisms in younger adolescents (see Chapters 238 and 271), although PID should be approached as having

a multiorganism etiology, including pathogens such as anaerobes, *G. vaginalis, Haemophilus influenzae*, enteric gram-negative rods, and *Streptococcus agalactiae.* In addition, cytomegalovirus, *Mycoplasma hominis*, *U. urealyticum*, and *M. genitalium* may be associated with PID. PID (tuboovarian abscess) has rarely been reported in virgins and is usually caused by *E. coli* and associated in some patients with obesity and possible pooling of urine in the vagina.

PID is difficult to diagnose because of the wide variation in symptoms and signs. Many females with PID have subtle or mild symptoms, resulting in many unrecognized cases. Healthcare providers should consider the possibility of PID in young, sexually active females presenting with vaginal discharge or abdominal pain.

The clinical diagnosis of PID is based on the presence of at least one of the minimal criteria, either cervical motion tenderness, uterine tenderness, or adnexal tenderness, to increase the diagnostic sensitivity and reduce the likelihood of missed or delayed diagnosis. Providers should also consider that adolescents are the population in whom PID is typically diagnosed and thus should have a low threshold for initiating empirical treatment. In addition, the majority of females with PID have either mucopurulent cervical discharge or evidence of white blood cells (WBCs) on a microscopic evaluation of a vaginal fluid–saline preparation. If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated. Specific, but not always practical, criteria for PID include evidence of endometritis on biopsy, transvaginal sonography or MRI evidence of thickened, fluid-filled tubes, or Doppler evidence of tubal hyperemia or laparoscopic evidence of PID.

Enteritis

Among men who have sex with men (MSM), both *Chlamydia* and the gonococcus can cause enteric (colitis, proctitis) symptoms. In addition, infections with enteric pathogens (*Shigella, Campylobacter, Ameba)* have been noted.

Sepsis

Although there are rare urogenital tract cases of meningococcal infections with heterosexual intercourse (similar to gonococcus), men who have sex (particularly oral sex) with men are at increased risk for invasive meningococcal infections, which often occur as an outbreak. Meningococcus may colonize the pharyngeal, anal, or urethral mucosa. Meningococcemia must be distinguished from disseminated gonococcal infection (DGI), which will manifest with a gram-negative diplococci-positive blood culture along with tenosynovitis, septic arthritis, petechial/pustular rash, and less often, endocarditis.

Genital Ulcer Syndromes

An **ulcerative lesion** in a mucosal area exposed to sexual contact is the unifying characteristic of infections associated with genital ulcer syndromes. Genital ulcer lesions are most frequently seen on the penis and vulva, but also occur on oral and rectal mucosa, depending on the adolescent's sexual practices. HSV and *Treponema pallidum* (syphilis) are the most common organisms associated with genital ulcer syndromes. Table 163.3 presents the clinical characteristics differentiating the lesions of the most common infections associated with genital ulcers, along with the required laboratory diagnosis to identify the causative agent accurately.

Genital herpes, the most common ulcerative STI among adolescents, is a chronic, lifelong viral infection. Two sexually transmitted HSV types have been identified: HSV-1 and HSV-2. The majority of cases of recurrent genital herpes are caused by HSV-2. However, among young women and MSM, an increasing proportion of anogenital herpes has been HSV-1. Most HSV-2–infected persons are unaware of their diagnosis because they experience mild or unrecognized infections but continue to shed virus intermittently in the genital tract. Therefore most genital herpes infections are transmitted by asymptomatic persons who are unaware of their infection.

Although the initial herpetic lesion is a vesicle, by the time the patient presents clinically, the vesicle often has ruptured spontaneously, leaving a shallow, painful ulcer (Fig. 163.7A). Recurrences are generally less intense and painful (see Fig. 163.7B). Up to 50% of first genital herpes episodes are caused by HSV-1. However, recurrences and subclinical shedding are much more frequent for genital HSV-2 infection.

Syphilis is a less common cause of genital ulcers in adolescents than in adults. Syphilis is caused by *T. pallidum*. Primary syphilis presents as a single painless ulcer or chancre at the site of infection. However, it can also present with multiple atypical or painful lesions. Secondary syphilis manifestations include skin rash,

Table 163.3 Signs, Symptoms, and Presumptive and Definitive Diagnoses of Genital Ulcers

SIGNS/SYMPTOMS	HERPES SIMPLEX VIRUS	SYPHILIS (PRIMARY)	CHANCROID
Ulcers	Vesicles rupture to form shallow ulcers	Ulcer with well-demarcated, indurated borders and a clean base (chancre)	Nonindurated and undermined borders and a purulent base
Painful	Painful	Painless*	Painful
Number of lesions	Usually multiple	Usually single	Multiple
Inguinal lymphadenopathy	First-time infections may cause constitutional symptoms and lymphadenopathy	Usually mild and minimally tender	Unilateral or bilateral painful adenopathy in >50% Inguinal bubo formation and rupture may occur
Clinical suspicion	Typical lesions; positive HSV-2 type–specific virologic test from the lesion by NAAT or culture OR Type-specific serologic testing	A presumptive diagnosis requires two laboratory serologic tests, a nontreponemal test (i.e., VDRL or RPR), and a treponemal test (TP-PA] assay, various EIAs, chemiluminescence assays [CIA], and immunoblots or rapid treponemal assay)	If all four criteria are met: 1. ≥1 Painful genital ulcers 2. Typical ulcers and regional lymphadenopathy 3. No evidence of *T. pallidum* 4. HSV-1 or HSV-2 NAAT or HSV culture performed on the ulcer exudate or fluid are negative
Definitive diagnosis	Detection of HSV by culture or PCR from ulcer scraping or aspiration of vesicle fluid	Identification of *Treponema pallidum* from a chancre or lymph node aspirate on dark-field microscopy	Detection of *Haemophilus ducreyi* by culture

*Primary syphilitic ulcers may be painful if they become coinfected with bacteria or one of the other organisms responsible for genital ulcers.
EIA, Enzyme immunoassay; HSV, herpes simplex virus; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.
From https://www.cdc.gov/std/treatment-guidelines/default.htm



Fig. 163.7 A, Initial herpes infection showing multiple erosions with polycyclic outlines surrounded by an erythematous halo and associated with intense pain. B, Erosions surrounded by an erythematous halo. Clinical signs and symptoms of recurrences are usually less intense than those of initial infection. (*From Martín JM, Villalón G, Jordá E. Update on treatment of genital herpes. Actas Dermosifiliogr. 2009;100:22–32, Figs. 1 and 2.*)

mucocutaneous lesions, and lymphadenopathy in addition to other nonspecific symptoms (e.g., sore throat, malaise), gastrointestinal symptoms (e.g., hepatitis), and renal symptoms. Tertiary syphilis presents with cardiac involvement, gummatous lesions, tabes dorsalis, and general paresis. Latent syphilis lacks clinical manifestations and is detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as *early latent syphilis*. Latent syphilis acquired at least 1 year prior is referred to as *late latent syphilis*. Infections of the central nervous system (CNS) (neurosyphilis), of the visual system (ocular syphilis), or auditory system (otosyphilis) can occur at any stage.

Lymphogranuloma venereum caused by *C. trachomatis* serovars L1-L3 is uncommon, although outbreaks do occur in MSM. In these circumstances, proctitis or proctocolitis is the usual manifestation. HIV is often present in affected men. Unusual infectious causes of genital, anal, or perianal ulcers in the United States and other industrialized countries include chancroid and donovanosis.

Monkeypox (see Chapter 767) has been reported after sexual contact, particularly among MSM.

The differential diagnosis of genital ulcers also includes Behçet disease (see Chapter 202), Crohn disease (see Chapter 382.2), aphthous ulceration, and acute genital ulcers caused by cytomegalovirus (see Chapter 302) or EBV (see Chapter 301). Acute genital ulcers often follow a flu or mononucleosis-like illness in an immunocompetent person and are unrelated to sexual activity. The lesions are 0.5-2.5 cm in size, bilateral, symmetric, multiple, painful, and necrotic and are associated with inguinal lymphadenopathy. This primary infection is also associated with fever and malaise. The diagnosis may require EBV titers or polymerase chain reaction (PCR) testing. Treatment is supportive care, including pain management.

Genital Lesions and Ectoparasites

Lesions that present as outgrowths on the surface of the epithelium and other limited epidermal lesions are included under this categorization of syndromes. HPV can cause genital warts and genital-cervical abnormalities that can lead to cancer (see Chapter 313). **Genital HPV** types are classified according to their association with cancer. Infections with low-risk types, such as **HPV types 6 and 11**, can cause benign or low-grade changes in cells of the cervix, genital warts, and recurrent respiratory papillomatosis. High-risk HPV types can cause cervical, anal, vulvar, vaginal, head, and neck cancers. **High-risk HPV types 16 and 18** are detected in approximately 70% of **cervical cancers**. Persistent infection increases the risk of cervical cancer. **Molluscum contagiosum** and **condyloma latum** associated with secondary syphilis complete the classification of genital lesion syndromes.

As a result of the close physical contact during sexual contact, common ectoparasitic infestations of the pubic area occur as **pediculosis pubis** or the papular lesions of **scabies** (see Chapter 709.2).

HIV, Hepatitis B, and Hepatitis C

HIV and hepatitis B virus (HBV) present as asymptomatic, unexpected occurrences in most infected adolescents. High vaccination coverage rates among infants and adolescents have resulted in substantial declines in acute HBV incidence among U.S.-born adolescents. Risk factors identified in the history or routine screening during prenatal care are much more likely to result in suspicion of infection, leading to the appropriate laboratory screening, than are clinical manifestations in this age-group (see Chapters 322 and 406). HIV incidence among adolescents has also declined, though disparities based on race, ethnicity, gender, and region persist. Young adults continue to be affected by HIV as well. The US Preventive Services Task Force (USPSTF) recommends all individuals between ages 15 and 65 be tested for HIV at least once in their life, and the CDC recommends HIV testing once between 13 and 64 and once a year based on behaviors. Hepatitis C virus (HCV) incidence continues to be on the rise not only among individuals known to be part of the "baby boomer" generation but also among young adults. Because of the rise in injection opioid use and HCV, the American Association for the Study of Liver Disease and Infectious Disease Society of America (AASLD–IDSA), and CDC recommend HCV screening among all individuals 18 years old and older. They also recommend screening based on risk behaviors among individuals younger than age 18 (see Table 163.2).

DIAGNOSIS

Most often, adolescents infected with bacterial and viral STI pathogens do not report symptoms suggestive of infection. With the use of very sensitive, noninvasive chlamydia and gonorrhea NAAT, providers are finding that most genital infections in females and many males are asymptomatic. A thorough sexual history is key to identifying adolescents who should be screened for STIs and for identifying those who require a laboratory diagnostic evaluation for an STI syndrome.

When eliciting a sexual health history, discussions should be appropriate for the patient's developmental level. In addition to questions regarding vaginal or urethral discharge, genital lesions, and lower abdominal pain among females, one should ask about prior treatment of any STI symptoms, including self-treatment using nonprescription medications. **Dyspareunia** is a consistent symptom in adolescents with **PID**. Providers must ask about oral or anal sexual activity to determine sites for specimen collection.

Urethritis should be objectively documented by evidence of inflammation or infectious etiology. Patient complaint without objective clinical or laboratory evidence does not fulfill diagnostic criteria. Inflammation can be documented by (1) observing urethral mucopurulent discharge, (2) ≥2 WBCs per high-power field on microscopic examination of Gram stain urethral secretions, (3) urine microscopic findings of ≥10 WBCs per high-power field of first-void urine specimen, or (4) a positive urine leukocyte esterase test of a first-void specimen. Laboratory evaluation is essential to identify the involved pathogens to determine treatment, partner notification, and disease control. *C. trachomatis* and *N. gonorrhoeae* NAATs of a urine specimen are recommended. The presence of gram-negative intracellular diplococci on microscopy obtained from a male urethral specimen confirms the diagnosis of gonococcal urethritis.

An essential component of the diagnostic evaluation of vaginal, cervical, or urethral discharge is a chlamydia and gonorrhea NAAT. NAATs are the most sensitive tests available in such cases and are licensed for use with urine, urethral, vaginal, and cervical specimens. Many of the chlamydia NAATs are approved by the U.S. Food and Drug Administration (FDA) to test patient-collected vaginal swabs in the clinical setting and liquid cytology specimens. Female vaginal swab specimens and male first-void urine are considered the optimal specimen types. Female urine remains an acceptable chlamydia and gonorrhea NAAT specimen, but it may have slightly reduced performance when compared with cervical or vaginal swab specimens. Urine is the recommended specimen for male urethral infection. Gonorrhea and chlamydia NAATs perform well on rectal and oropharyngeal specimens and can be performed by clinical laboratories that have completed the appropriate verification studies to obtain Clinical Laboratory Improvement Amendments (CLIA) approval.

Evaluation of adolescent females with **vaginitis** includes laboratory data. Traditionally, the cause of vaginal symptoms was determined by pH and microscopic examination of the discharge. However, CLIA-waived point-of-care vaginitis tests are available. Using pH paper, an elevated pH (i.e., >4.5) is common with bacterial vaginosis and trichomoniasis. Because pH testing is not highly specific, discharge should be further examined. For microscopic exam, a slide can be made with the discharge diluted in 1-2 drops of 0.9% normal saline solution and another slide with discharge diluted in 10% KOH solution. Examining the saline specimen slide under a microscope may reveal motile or dead *T. vaginalis* or clue cells (epithelial cells with borders obscured by small bacteria), which are characteristic of **bacterial vaginosis**. WBCs without evidence of trichomonads or yeast are usually suggestive of cervicitis. This evaluation has been consistently shown to be highly subjective, which is why there are more NAAT tests available for diagnosis. The yeast or pseudohyphae of ***Candida*** species are more easily identified in the KOH specimen (Fig. 163.8). The sensitivity of microscopy is approximately 50% and requires immediate evaluation of the slide for optimal results. Therefore lack of findings does not eliminate the possibility of infection. More sensitive point-of-care vaginitis tests include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), an immunochromatographic capillary flow dipstick technology with reported 83% sensitivity. The OSOM BVBLUE Test (Sekisui) detects

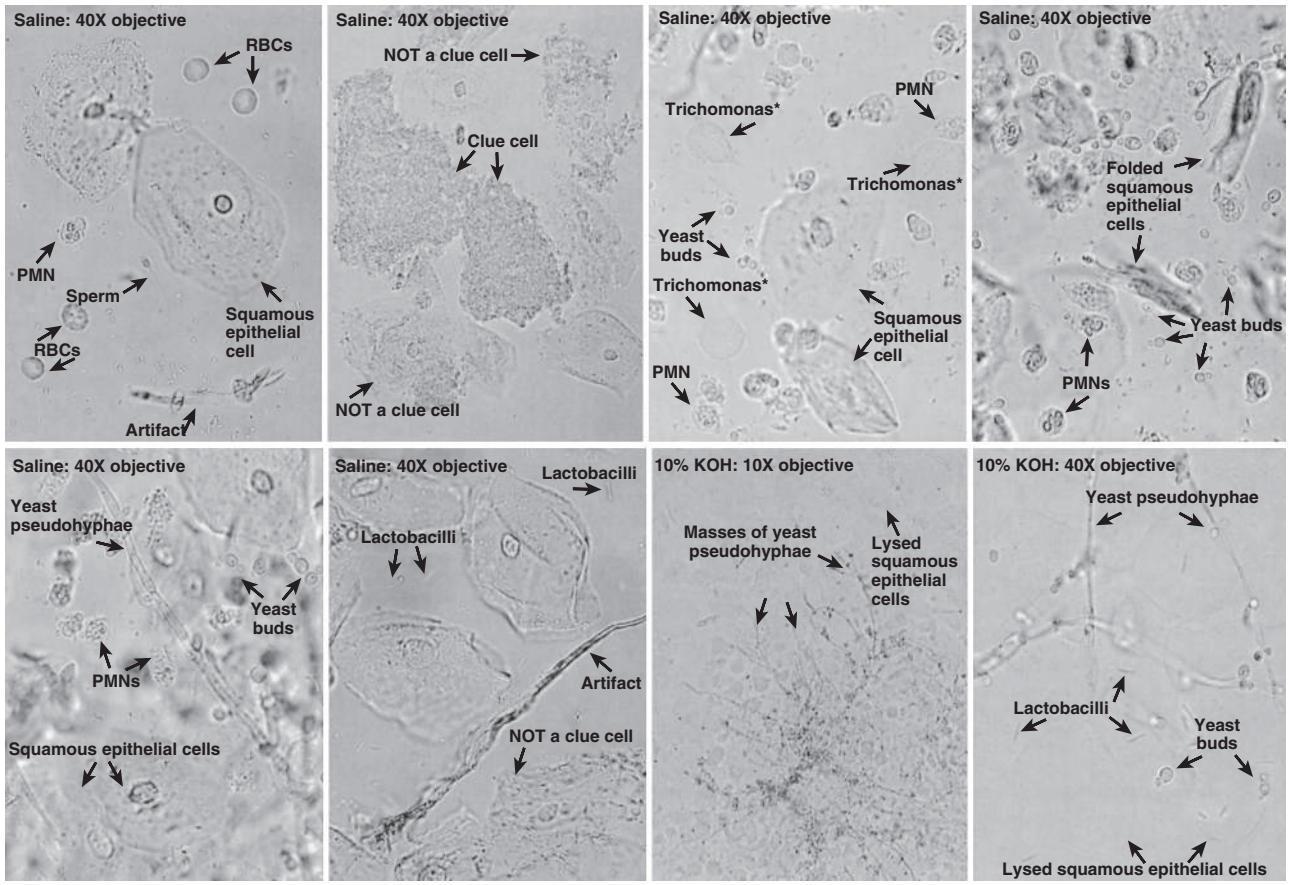

Fig. 163.8 Common normal and abnormal microscopic findings during examination of vaginal fluid. KOH, Potassium hydroxide solution; PMN, polymorphonuclear leukocyte; RBCs, red blood cells. (*From Adolescent Medicine: State of the Art Reviews, vol. 14, no. 2. Philadelphia: Hanley & Belfus; 2003:350–351.*)

Table 163.4 Pathologic Vaginal Discharge

INFECTIVE DISCHARGE	OTHER REASONS FOR DISCHARGE
COMMON CAUSES *Organisms* *Candida albicans* *Trichomonas vaginalis* *Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium* *Conditions* Bacterial vaginosis Acute pelvic inflammatory disease Postoperative pelvic infection Postabortal sepsis Puerperal sepsis LESS COMMON CAUSES *Ureaplasma urealyticum* Syphilis *Escherichia coli*	COMMON CAUSES Retained tampon or condom Chemical irritation Allergic responses Ectropion Endocervical polyp Intrauterine device Atrophic changes LESS COMMON CAUSES Physical trauma Vault granulation tissue Vesicovaginal fistula Rectovaginal fistula Neoplasia Cervicitis

From Mitchell H. Vaginal discharge—causes, diagnosis, and treatment. *BMJ.* 2004;328:1306–1308; and Sexually Transmitted Infections Treatment Guidelines, 2021: Vulvovaginal Itching, Burning, Irritation, Odor or Discharge: https://www.cdc.gov/std/treatment-guidelines/vaginal-discharge.htm.

Table 163.5 Evaluation for Pelvic Inflammatory Disease (PID)

2021 CDC DIAGNOSTIC CRITERIA

Minimal Criteria

- Cervical motion tenderness

or

- Uterine tenderness

or

- Adnexal tenderness

Additional Criteria to Enhance Specificity of the Minimal Criteria

- Oral temperature >38.3°C (101°F)
- Abnormal cervical or vaginal mucopurulent discharge*
- Presence of abundant numbers of WBCs on saline microscopy of vaginal secretions*
- Elevated ESR or C-reactive protein
- Laboratory documentation of cervical *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection

Most Specific Criteria to Enhance the Specificity of the Minimal Criteria

- Transvaginal sonography or MRI techniques showing thickened, fluid-filled tubes, with or without free pelvic fluid or tuboovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
- Endometrial biopsy with histopathologic evidence of endometritis
- Laparoscopic abnormalities consistent with PID

Differential Diagnosis (Partial List)

- Gastrointestinal: appendicitis, constipation, diverticulitis, gastroenteritis, inflammatory bowel disease, irritable bowel syndrome
- Gynecologic: ovarian cyst (intact, ruptured, or torsed), endometriosis, dysmenorrhea, ectopic pregnancy, mittelschmerz, ruptured follicle, septic or threatened abortion, tuboovarian abscess
- Urinary tract: cystitis, pyelonephritis, urethritis, nephrolithiasis
- ESR, Erythrocyte sedimentation rate; WBCs, white blood cells

*If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely and alternative causes of pain should be investigated.

Adapted from Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/std/treatment-guidelines/pid.htm.

elevated vaginal fluid sialidase activity, an enzyme produced by bacterial pathogens associated with bacterial vaginosis, including *Gardnerella, Bacteroides, Prevotella,* and *Mobiluncus,* and has a reported 90% sensitivity. Both tests are CLIA waived, with results available in 10 minutes.

Clinical laboratory–based vaginitis tests are also available. The Affirm VPIII (Becton Dickenson) is a moderate-complexity nucleic acid probe test that evaluates for *T. vaginalis, G. vaginalis,* and *C. albicans* and has a sensitivity of 63% and specificity of >99.9%, with results available in 45 minutes. Some gonorrhea and chlamydia NAATs also offer an assay for *T. vaginalis* testing of female specimens tested for *N. gonorrhoeae* and *C. trachomatis,* considered the gold standard for *Trichomonas* testing.

Objective signs of vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of vaginal discharge, suggest the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva (Table 163.4).

The **definitive diagnosis of PID** is difficult based on clinical findings alone. Clinical diagnosis is imprecise, and no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Clinical criteria have a positive predictive value of only 65–90% compared with laparoscopy. Although healthcare providers should maintain a low threshold for the diagnosis of PID, additional criteria to enhance the specificity of diagnosis, such as transvaginal ultrasonography, can be considered (Table 163.5).

Cell culture and PCR are the preferred **HSV tests**. Viral culture sensitivity is low, and intermittent viral shedding causes false-negative results. NAATs, including PCR assays for HSV DNA, are more sensitive and increasingly available for diagnosing genital HSV. The Tzanck test is insensitive and nonspecific and should not be considered reliable.

Accurate type-specific **HSV serologic assays** are based on the HSV-specific glycoproteins G2 (HSV-2) and G1 (HSV-1). Both laboratory-based point-of-care tests are available. Because almost all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. The presence of HSV-1 antibody alone is more difficult to interpret because of the frequency of oral HSV infection acquired during childhood. Type-specific HSV serologic assays might be useful in the following scenarios: (1) recurrent genital symptoms or atypical symptoms with negative HSV cultures; (2) a clinical diagnosis of genital herpes without laboratory confirmation; and (3) a patient with a partner with genital herpes, especially if considering suppressive antiviral therapy to prevent transmission.

For **syphilis testing**, nontreponemal tests, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratories (VDRL), and treponemal testing, such as fluorescent treponemal antibody absorbed tests, the *T. pallidum* passive particle agglutination (TP-PA) assay, and various enzyme and chemiluminescence immunoassays (EIA/CIA), are recommended. However, many clinical laboratories have adopted a *reverse sequence* of screening in which a treponemal EIA/CIA is performed first, followed by testing of reactive sera with a nontreponemal test (e.g., RPR). Treponemal tests often remain positive for life, with only 15-25% becoming serologically nonreactive, if treated early in primary syphilis. A positive treponemal EIA or CIA test can identify both *previously treated and untreated or incompletely treated syphilis.* False-positive results can occur, particularly among populations with low syphilis prevalence. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer (RPR or VDRL) to guide patient management decisions. If EIA/CIA and RPR/VDRL results are discordant, the laboratory should perform a different treponemal test to confirm the results of the initial test. Patients with discordant serologic results by EIA/CIA and RPR/VDRL testing whose sera are reactive by TP-PA testing are considered to have past or present syphilis; if sera is TP-PA nonreactive, syphilis is unlikely (Fig. 163.9).

Rapid HIV testing with third- and fourth-generation test results available in 10-20 minutes can be useful when the likelihood of adolescents returning for their results is low. Point-of-care CLIA-waived tests for whole blood finger stick (fourth generation) and oral fluid specimen (third generation) testing are available. Clinical studies have demonstrated that the rapid HIV test performance is comparable to those of EIAs. Because some reactive test results may be false positive, every reactive rapid test must be confirmed.

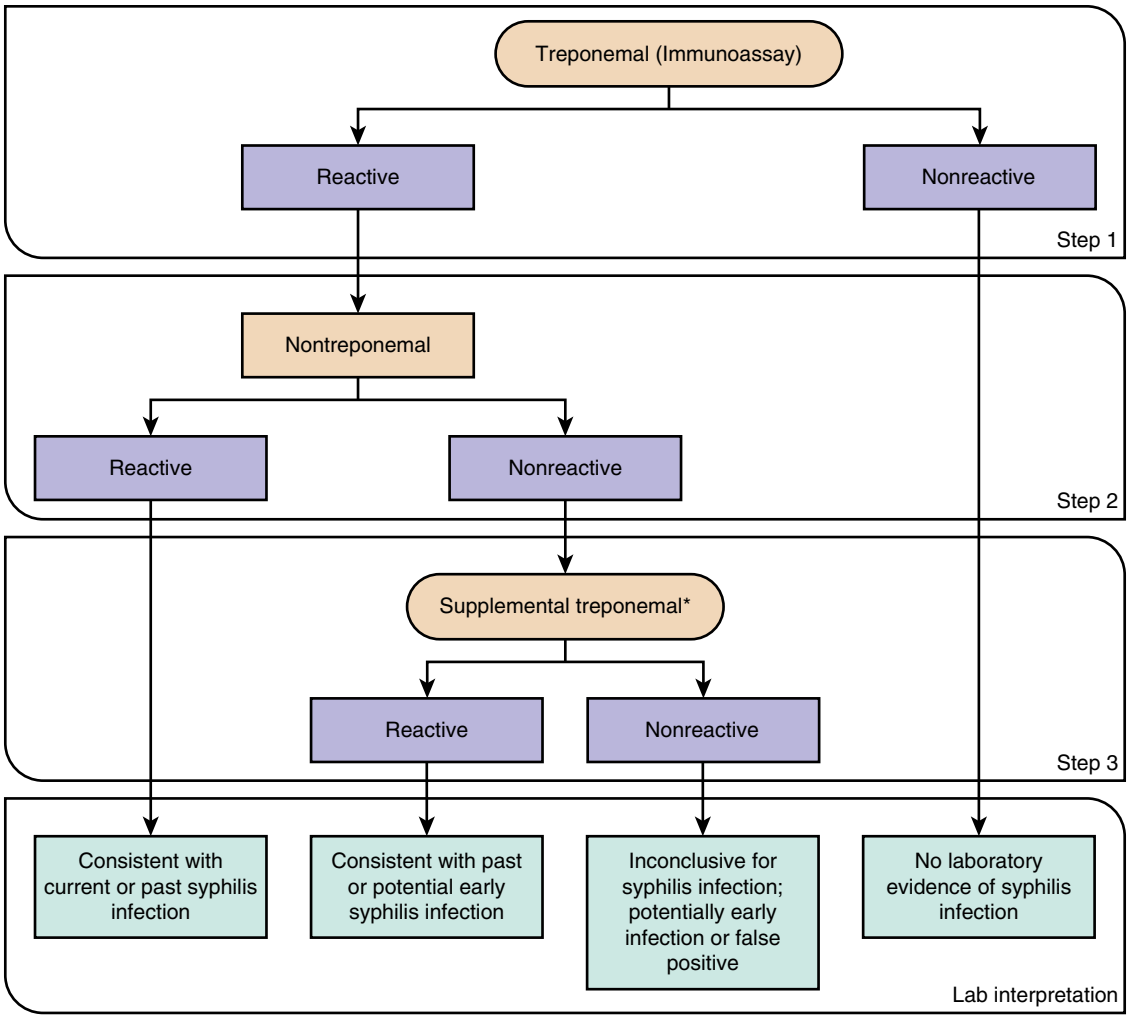

Fig. 163.9 Centers for Disease Control and Prevention (CDC)–recommended algorithm for reverse-sequence syphilis screening: Treponemal test screening followed by nontreponemal test confirmation. *The supplemental treponemal test should use a unique platform and/or antigen different from the first treponemal test. (*From Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serological Testing. Association of Public Health Laboratories August 2020* https://www.aphl.org/programs/infectious_disease/std/Documents/ID-2020Aug-Syphilis-Reporting-Language.pdf.)

Table 163.6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Chlamydia trachomatis	Doxycycline 100 mg orally 2×/day for 7 days **For pregnancy:** Azithromycin 1 g orally in a single dose	Azithromycin 1 g orally in a single dose **OR** Levofloxacin 500 mg orally 1×/day for 7 days **For pregnancy:** Amoxicillin 500 mg orally 3×/day for 7 days
Neisseria gonorrhoeae (cervix, urethra, and rectum)	Ceftriaxone 500 mg IM in a single dose for persons weighing <150 kg If chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2×/day for 7 days For person weighing >150 kg, ceftriaxone 1g should be administered	**If cephalosporin allergy or unavailable:** Gentamicin 240 mg IM in a single dose **PLUS** Azithromycin 2 g orally in a single dose **OR** Cefixime 800 mg orally in a single dose
Neisseria gonorrhoeae (pharynx)	Ceftriaxone 500 mg IM in a single dose for person weighing <150 kg Ceftriaxone 1g IM for a person weighing ≥150 kg	
Treponema pallidum (primary and secondary syphilis or early latent syphilis, i.e., infection <12 mo)	Benzathine penicillin G 2.4 million units IM in a single dose	**Penicillin allergy:** Doxycycline 100 mg orally twice daily for 14 days or tetracycline 500 mg orally 4 times daily for 14 days; limited data suggest ceftriaxone 1-2 g daily either IM or IV for 10-14 days **OR** Azithromycin 2 g orally in a single dose has been effective, but treatment failures have been documented

Continued

Table 163.6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults—cont'd

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Treponema pallidum (late latent syphilis or syphilis of unknown duration)	Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-wk intervals	**Penicillin allergy:** Doxycycline 100 mg orally twice daily for 28 days or tetracycline 500 mg orally 4 times daily for 28 days, with close serologic and clinical follow-up
Treponema pallidum (neurosyphilis, ocular syphilis, and otosyphilis)	Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units by IV every 4 hr or continuous infusion, for 10-14 days	Procaine penicillin G 2.4 million units IM 1×/day for 10-14 days **PLUS** Probenecid 500 mg orally 4×/day for 10-14 days
Haemophilus ducreyi (chancroid: genital ulcers, lymphadenopathy)	Azithromycin 1 g orally in a single dose **OR** Ceftriaxone 250 mg IM in a single dose **OR** Ciprofloxacin 500 mg orally 2× daily for 3 days **OR** Erythromycin base 500 mg orally 3× daily for 7 days	
Chlamydia trachomatis serovars L1, L2, or L3 (lymphogranuloma venereum)	Doxycycline 100 mg orally 2× daily for 21 days	**Alternative:** Erythromycin base 500 mg orally 4× daily for 21 days **OR** Azithromycin 1 g orally once weekly for 3 wk

IM, Intramuscularly; IV, intravenously; NAAT, nucleic acid amplification test.
Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases: treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70:1–187, https://www.cdc.gov/std/treatment-guidelines/default.htm.

Table 163.7 Management Guidelines for Uncomplicated Miscellaneous Sexually Transmitted Infections in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Trichomoniasis	**Women:** Metronidazole 500 mg orally 2×/day for 7 days **Men:** Metronidazole 2 g orally in a single dose	For women and men: Tinidazole 2 g orally in a single dose
Phthirus pubis (pediculosis pubis, e.g., pubic lice)	Permethrin 1% cream rinse applied to affected areas and washed off after 10 min **OR** Pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 min Launder clothing and bedding	Malathion 0.5% lotion applied for 8-12 hr and washed off **OR** Ivermectin 250 μg/kg orally, repeat in 7-14 days
Sarcoptes scabiei (scabies)	Permethrin 5% cream applied to all areas of the body (from neck down), wash after 8-14 hr **OR** Ivermectin 200 μg/kg body weight orally, repeated in 14 days Launder clothing and bedding	Lindane (1%) 1 oz of lotion or 30 g of cream in thin layer to all areas of body from neck down; wash off after 8 hr

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases: treatment guidelines. *MMWR*. 2021;64(RR-3); https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf.

TREATMENT

See Part XV for chapters on the treatment of specific microorganisms and Tables 163.6-163.8. Treatment regimens using nonprescription products for candidal vaginitis and pediculosis reduce financial and access barriers to rapid treatment for adolescents, but potential risks for inappropriate self-treatment and complications from untreated, more serious infections must be considered before using this approach. Minimizing noncompliance with treatment, notifying and treating the sexual partners, addressing prevention and contraceptive issues, offering available vaccines to prevent STIs, and making every effort to preserve fertility are additional physician responsibilities.

Chlamydia- and gonorrhea-infected males and females should be retested approximately 3 months after treatment, regardless of whether they believe that their sex partners were treated, or whenever persons next present for medical care in the 12 months after initial treatment. Adolescents who are pregnant with chlamydia and gonorrhea infections should be retested in approximately 1 month after treatment. Adolescents with oral gonorrhea should be retested in 7-14 days. Once an infection is diagnosed, partner evaluation, testing, and treatment are recommended for sexual contacts within 60 days of symptoms or diagnosis, or the most recent partner if sexual contact was >60 days, even if the partner is asymptomatic. Abstinence is recommended for at least 7 days

Table 163.8 Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
HUMAN PAPILLOMAVIRUS (HPV)		
External anogenital warts (penis, groin, scrotum, vulva, perineum, external anus, and perianus)	**Patient applied:** Imiquimod 3.75–5% cream self-applied to warts at bedtime nightly for up to 16 wk; wash off after 6-10 hr ***OR*** Podofilox 0.5% solution or gel self-applied to warts twice daily for 3 consecutive days each wk followed by 4 days of no therapy. May be repeated for up to four cycles. ***OR*** Sinecatechins 15% ointment self-applied 3 times daily for up to 16 wk. Do not wash off after use, and avoid genital, anal, and oral sexual contact while ointment is on skin. **Provider-administered:** Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1-2 wk. ***OR*** Surgical removal either by tangential scissor excision, electrocautery, tangential shave excision, curettage, laser or electrosurgery. ***OR*** Trichloroacetic acid (TCA) or bichloracetic acid (BCA) 80–90%; small amount applied only to warts and allowed to dry, when white "frosting" develops; can be repeated weekly.	**Provider administered:** Podophyllin resin 10–25% in a compound tincture of benzoin applied to each wart and then allowed to air-dry; thoroughly wash off after 1-4 hr; can be repeated weekly. Systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hr. Many persons with external anal warts also have **intraanal warts** and might benefit from inspection of anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.
Cervical warts	Cryotherapy with liquid nitrogen ***OR*** Surgical removal ***OR*** TCA or BCA 80–90% solution Management should include consultation with a specialist.	
Vaginal warts	Cryotherapy with liquid nitrogen; avoid cryoprobe use because of risk for vaginal perforation and fistula formation. ***OR*** Surgical removal ***OR*** TCA or BCA 80–90%; small amount applied only to warts and allowed to dry, when white "frosting" develops; can be repeated weekly.	
Urethral meatal warts	Cryotherapy with liquid nitrogen ***OR*** Surgical removal	
Intraanal warts	Cryotherapy with liquid nitrogen ***OR*** Surgical removal ***OR*** TCA or BCA 80–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly.	Management of intraanal warts should include consultation with a specialist.
HERPES SIMPLEX VIRUS (HSV; GENITAL HERPES)		
First clinical episode	**Treat for 7-10 days with one of the following:** Acyclovir 400 mg orally 3× daily Valacyclovir 1 g orally 2× daily Famciclovir 250 mg orally 3× daily	Consider extending treatment if healing is incomplete after 10 days of therapy.
Episodic therapy for recurrences	**Treat with one of the following:** Acyclovir 800 mg orally 2× daily for 5 days Acyclovir 800 mg orally 3× daily for 2 days Valacyclovir 500 mg orally 2× daily for 3 days Valacyclovir 1,000 mg orally once daily for 5 days Famciclovir 1,000 mg orally 2× daily for 1 day Famciclovir 500 mg orally once, then 250 mg 2× daily for 2 days Famciclovir 125 mg orally twice daily for 5 days	Effective episodic treatment of recurrences requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.
Suppressive therapy to reduce frequency of recurrences	**Treat with one of the following:** Acyclovir 400 mg orally 2× daily Valacyclovir 500 mg orally once daily* or 1 g orally once daily Famciclovir 250 mg orally 2× daily	All patients should be counseled regarding suppressive therapy availability, regardless of number of outbreaks per year. Because the frequency of recurrent outbreaks diminishes over time in many patients, providers should periodically discuss the need to continue therapy.

Continued

Table 163.8 Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults—cont'd

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Daily suppressive therapy in persons with HIV infection	Acyclovir 400-800 mg orally 2-3× daily ***OR*** Famciclovir 500 mg orally 2× daily ***OR*** Valacyclovir 500 mg orally 2× daily	If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected and a viral culture obtained for phenotypic sensitivity testing. Consultation with an infectious disease specialist is recommended.
Episodic infection in persons with HIV	Acyclovir 400 mg orally 3× daily for 7-10 days ***OR*** Famciclovir 250 mg orally 3×/day for 7-10 days ***OR*** Valacyclovir 1g orally 2× for 7-10 days	If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected and a viral culture obtained for phenotypic sensitivity testing. Consultation with an infectious disease specialist is recommended.
Daily suppressive therapy of recurrent genital herpes in pregnant women	**Treatment is recommended to start at 36 wk gestation:** Acyclovir 400 mg orally 3× daily ***OR*** Valacyclovir 500 mg orally 2× per day	

*Valacyclovir 500 mg once daily might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per yr).
Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases: treatment guidelines, *MMWR* 2021;64(RR-3): https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf.

Table 163.9 Option for Pre-Exposure Prophylaxis (PrEP) for HIV Prevention

GENERIC	DOSE	FREQUENCY	POPULATION
Tenofovir disproxil fumarate + emtricitabine (F/TDF)*	200 mg/300 mg	Daily pill	Any person weighing at least 35 kg
Tenofovir alafenamide +emtricitabine (F/TAF)	200 mg/25 mg	Daily pill	Individuals engaging in anal sex who are cis male, transwomen weighing at least 35 kg
Cabotegravir	200 mg/mL	Every 2 month injection	Any person weighing at least 35 kg

*F/TDF is also available by brand name and generic depending on insurance. It can also be used as intermittent dosing for cis-men and transwomen engaging in anal sex.

after both patient and partner have completed treatment. A test for pregnancy should be performed for all females with suspected PID because the test outcome will affect management. Repeat testing 3 months after treatment is also recommended for *Trichomonas* infection.

Diagnosis and therapy are often carried out within the context of a **confidential** relationship between the physician and the patient. Therefore the need to report certain STIs to health department authorities should be clarified at the outset. Health departments are Health Insurance Portability and Affordability Act (HIPAA) exempt and will not violate confidentiality. The health department's role is to ensure that treatment and case finding have been accomplished and that sexual partners have been notified of their STI exposure. **Expedited partner therapy (EPT)**, the clinical practice of treating sex partners of patients diagnosed with chlamydia or gonorrhea by providing prescriptions or medications to the patient to take to the partner without the healthcare provider first examining the partner, is a strategy to reduce further transmission of infection. In randomized trials, EPT has reduced the rates of persistent or recurrent gonorrhea and chlamydia infection. Serious adverse reactions are rare with recommended chlamydia and gonorrhea treatment regimens, such as doxycycline, azithromycin, and ceftriaxone. Transient gastrointestinal side effects are more common but rarely result in severe morbidity. Most states expressly permit EPT or may allow its practice. Resources for information regarding EPT and state laws are available at the CDC website.

PREVENTION

Healthcare providers should integrate comprehensive **sexuality education** into clinical practice with children from early childhood through adolescence. Providers should counsel adolescents regarding sexual behaviors associated with risk of STI acquisition and should educate using evidence-based prevention strategies, which include a discussion of abstinence and other risk reduction strategies, such as consistent and correct condom use, and distribution of educational materials for reinforcement. The USPSTF recommends **high-intensity behavioral counseling** to prevent STIs for all sexually active adolescents.

The following recommendations for the primary prevention of STIs through vaccination are based on published guidelines from the Advisory Committee on Immunization Practices:

- HPV vaccination is recommended through age 26 years for males and females not vaccinated previously at the routine age of 11 or 12 years. Vaccination can be started at age 9. Two doses of HPV vaccine are recommended for most persons starting the series before their 15th birthday; three doses are recommended at ≥ 15 years.
- The HBV vaccination series is recommended for all adolescents and young adults who have not previously received the universal HBV vaccine series during childhood.
- Mpox vaccination is recommended for gay, bisexual, transgender persons and if the patient has had sexual or intimate contact with someone who may have mpox. Mpox vaccination is a two-dose schedule separated by 4 weeks.

Preexposure prophylaxis (PrEP) offers another strategy to specifically prevent HIV infection (Table 163.9).

The CDC and USPSTF recommend offering HIV PrEP to adolescents weighing ≥35 kg and young adults who are HIV negative and

Immunology

PART XII

Section 1

Evaluation of the Immune System

Chapter 164

Orientation to the Consideration of Inborn Errors of Immunity

Soma Jyonouchi and Kathleen E. Sullivan

Primary immune deficiency diseases (PIDDs) comprise more than 450 disorders that impair the development or function of the immune system. Most these disorders result from a single gene pathogenic variant, although more complex inheritance patterns can also occur.

The initial diagnosis and subsequent treatment of PIDDs are often delayed due to a low index of suspicion, a rare individual disease incidence, protein manifestations including infection, autoimmunity, cutaneous lesions, and failure to thrive all in the background of a higher frequency of more common childhood illnesses (nonspecific viral illness, allergy). This diagnostic delay can lead to irreversible end-organ damage or death.

Newborn screening for severe combined immune deficiency (SCID) has helped the early detection of SCID and other immune deficiencies associated with very low T cells. However, the vast majority of immune deficiencies will not be detected by this method. Physicians must be aware of concerning manifestations or events that suggest an underlying PIDD. The varied presentations and complex phenotypes, some of which have minimal or no infectious manifestations, make the initial diagnosis of PIDDs difficult (Table 164.1). Manifestations of PIDD include recurrent and/or sentinel infections, fever without a focus, periodontitis, poor formation of pus at a site of infection, and unusual inflammatory (including autoimmune) diseases. PIDDs may involve defects in one or more host defense mechanism, or they may be an independent isolated disorder or part of a recognizable syndrome (Table 164.2).

The immune system is primarily responsible for protecting the body against invading infectious pathogens. Recurrent (often in multiple sites), severe, or unusual infections are typical presentations of PIDDs. Viral, bacterial, fungal, and mycobacterial infections each require distinct arms of the immune system for eradication; identification of the microbe causing an infection is helpful in directing the evaluation of a patient with suspected PIDD (see Table 164.1; Table 164.3). Children who exceed the normal *frequency* of infections or who have very *prolonged* symptoms suggesting failure of pathogen clearance may also warrant evaluation. The typical preschool child can have 6-10 viral respiratory infections per year, making this assessment less than straightforward. Patients with PIDD are significantly more likely to have severe infections requiring hospitalization and prolonged or unsuccessful treatment with IV antibiotics. Infections with unusual pathogens (opportunistic organisms) or infections resulting from live attenuated virus vaccines (rotavirus, varicella, MMR) are important warning signs. Neutropenia or lymphocytopenia may be present.

In addition to pathogen defense, the immune system must demonstrate tolerance to the host and prevent excessive inflammation that can result in tissue damage. In addition to infections, patients can present with autoimmune disease and/or autoinflammatory conditions. The presence of a family history of PIDD or consanguinity should increase suspicion for these conditions.

The patient's clinical presentation can help guide the initial laboratory evaluation (Fig. 164.1).

INFECTION RED FLAGS

Infections are one of the more common reasons to initiate an immunologic evaluation. The pattern and etiology of the infections dictate the appropriate diagnostic evaluation. A high burden of infections in a child is the most common reason for referral to an immunology

Table 164.1 Patterns of Infections and Other Conditions in Primary Immunodeficiency

	ILLNESSES	
DISORDER	**TYPE OF INFECTION**	**OTHER CONDITIONS**
Antibody defects	Sinopulmonary infections (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Mycoplasma sp.*) Gastrointestinal (enteroviruses, *Salmonella, Campylobacter, Giardia,* norovirus)	Autoimmune disease (thrombocytopenia, hemolytic anemia, neutropenia) Inflammatory bowel disease Lymphadenopathy, splenomegaly Otitis, mastoiditis
Cell-mediated immunity defects	Pneumonia *(Pneumocystis jirovecii), Mycobacterium avium-intracellulare* Severe Epstein-Barr infection Gastrointestinal disease (viruses, cytomegalovirus) Fungi of the skin, nails, mucous membranes	Failure to thrive Splenomegaly, lymphadenopathy
Defects of phagocytosis	Skin, liver, lymph nodes, abscesses (*Staphylococcus,* gram-negative bacteria, fungi)	Inflammatory bowel disease Granulomatous infiltrations
Defects of complement	Sepsis and other blood-borne encapsulated bacteria; meningitis, *(Streptococcus, Pneumococcus, Neisseria)*	Autoimmune disease (systemic lupus erythematosus, ANA+, glomerulonephritis)

ANA, Antinuclear antibodies.
From Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice.* 4th ed. Philadelphia: Elsevier; 2021. Table 4.1, p. 32.

Table 164.2 Types of Primary Immune Defects

IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY	
$T^-B^+NK^-$ SCID	Common gamma chain (IL2RG, X-linked), JAK3
$T^-B^+NK^+$ SCID	IL7-α, T-cell receptor defects, CD45, PNP deficiency
T^-B^- SCID	RAG1, RAG2 defects, adenosine deaminase deficiency
COMBINED IMMUNODEFICIENCIES, GENERALLY LESS SEVERE	
MHC class I and II defects; T-cell receptor defects; DOCK8, IL21, and IL21R, and others	
COMBINED IMMUNODEFICIENCIES WITH SYNDROMIC OR OTHER FEATURES	
With thrombocytopenia	Wiskott-Aldrich syndrome
DNA repair defects	Ataxia telangiectasia, Nijmegen breakage syndrome; Bloom syndrome, dyskeratosis congenital, LIG-4
Hyper-IgE syndromes	STAT3 loss of function, and others
Immuno-osseous dysplasias	Cartilage hair hypoplasia Schimke immuno-osseous dysplasia
Ectodermal dysplasia	IKBKG deficiency (NEMO)
THYMIC DEFECTS WITH ADDITIONAL CONGENITAL ANOMALIES	
DiGeorge, velocardiofacial syndrome CHARGE syndrome	
ANTIBODY DEFECTS	
Agammaglobulinemias	X-linked and autosomal forms of agammaglobulinemia
Hyper-IgM syndromes	X-linked and autosomal forms
IgG or IgA deficiency	IgG subclass and IgA deficiency
IgG, and IgA and or IgM deficiency	Common variable immunodeficiency
DISEASES OF IMMUNE DYSREGULATION	
Familial hemophagocytic lymphohistiocytosis	Perforin deficiency; UNC13D.
With hypopigmentation	Chédiak-Higashi, Griscelli, Hermansky-Pudlak syndromes
With autoimmunity	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, autoimmune lymphoproliferative syndrome
With defects of regulatory T cells	X-linked immune dysregulation, polyendocrinopathy enteropathy (IPEX), defects of CTLA4, STAT3
Leading to severe Epstein-Barr virus	X-linked autoimmune lymphoproliferative syndrome, XIAP deficiency, magnesium transporter 1 (MAGT1)
With colitis	IL-10 defects
CONGENITAL DEFECTS OF PHAGOCYTE NUMBER OR FUNCTION	
Neutropenia	Elastase deficiency, HAX1 deficiency, and others
Defects of motility	Leukocyte adhesion deficiency
Defects of respiratory burst	Chronic granulomatous disease
Other nonlymphoid defects	GATA2 deficiency
DEFECTS IN INTRINSIC AND INNATE IMMUNITY	
Mycobacterial disease	IL-12, IL-23, INF-γ, STAT1 defects, and others
Warts	Epidermodysplasia verruciformis (EVER), hypogammaglobulinemia, infections, myelokathexis syndrome (WHIM)
Viral infections	STAT1, STAT2, IRF7, and others
Herpes simplex encephalitis	TLR3, UNC93B1
Fungal diseases	CARD9, IL17 defects, STAT1
Bacterial susceptibility	IRAK4, MYD88, IRAK1, and others
COMPLEMENT DEFICIENCY	
Classical pathway	C1q-C9 defects
Alternative pathway	Factors B, D, I, H, properdin, and others
Regulatory and membrane controls	Co-factor proteins

CHARGE defect, Disorder with coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities; Ig, immunoglobulin; MHC, major histocompatibility complex; NK, natural killer; PNP, purine nucleoside phosphorylase; SCID, severe combined immunodeficiency.
From Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice.* 4th ed. Philadelphia: Elsevier; 2021. Table 4.2, p. 33-34.

center; there are certain patterns that can collectively be thought of as **red flags**, mandating an immunologic evaluation.

Recurrent Sinopulmonary Infections

Recurrent bacterial sinopulmonary infections (ear, sinus, pneumonia) with encapsulated organisms are a common presentation for PIDDs. It can be challenging to define a number of infections that represent a threshold to begin an immunologic evaluation. Typically, most patients with a PIDD will have a diversity of sites impacted by infection; the frequency will be higher or the severity more severe than the clinician would expect. Recurrent sinopulmonary infections are highly suggestive of patients with antibody deficiencies, such as common variable immunodeficiency (CVID; see Chapter 165) or X-linked agammaglobulinemia (XLA; see Chapter 166). Patients often require *longer courses*

Table 164.3 Sentinel Infections and Related Genes

INFECTIONS	RECOGNIZED GENE DEFECTS AND WELL-CHARACTERIZED SYNDROMES
VIRUSES	
Herpes simplex encephalitis	*TBK1, TLR3, TRAF3, TRIF, UNC93B*
Cutaneous herpes simplex	Severe T-cell defects, *DOCK8, GATA2, WAS*
EBV—chronic	*CD21, CD27, CORO1A, ITK, MAGT1, PRKCD, CXCR4*
EBV—HLH	*AP3B1, LYST1, PRF1, RAB27A, SH2D1A, STX11, UNC13D, XIAP*
CMV	Severe T-cell defects, Good syndrome, *DOCK8, GATA2, STIM1, WAS*
Papilloma virus	Idiopathic CD4 lymphopenia, *ATM, CD40L, EVER1, EVER2, DOCK8, GATA2, IKBKG, MST1, RORH, STK4, CXCR4*
FUNGI	
Candida	*AIRE, CARD9, IL17F, IL17RA, STAT1*
Aspergillus	Idiopathic CD4 lymphopenia, *CYBA, CYBB, DOCK8, GATA2, ITGB2, NCF1, NCF2, NCF4, STAT3*
BACTERIA	
Pseudomonas	Congenital neutropenia, *IRAK4, ITGB2, MYD88, BTK* (neutropenia), *CD40LG* (neutropenia)
Salmonella	*CYBB, IFNGR1, IFNGR2, IL12B, IL12RB1*
Serratia	*CYBA, CYBB, NCF1, NCF2, NCF4*
Neisseria	*C5, C6, C7, C8A, C8B, C8G, C9, CFD, CFH, CFI, CFP*
Streptococcus pneumoniae	*C1QA, C1QB, C1QC, C4A + C4B, C2, C3, IRAK4, MYD88*
MYCOBACTERIA	
Mycobacteria	*CYBA, CYBB, GATA2, IFNGR1, IFNGR2, IKBKG, IL12, IL12RB1, IRF8, NCF1, NCF2, NCF4, STAT1, TYK2*

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis. From Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies.* 2nd ed. London: Elsevier; 2020. Table 1.2.

of antibiotics to clear infections and may not have improvement with standard interventions such as bilateral myringotomy tubes or sinus surgery.

Recurrent Invasive Pneumococcal Infections

Invasive pneumococcal infections (sepsis, septic arthritis, meningitis) may occur in patients with antibody deficiency (Table 164.4). A single episode need not imply a PIDD. Recurrent invasive pneumococcal infections should elicit an evaluation. Pneumococcus has a polysaccharide capsule that permits it to evade the immune system. Antibodies bind to these bacteria (opsonization), which facilitates phagocytosis and bacterial killing. The early complement fragment C3b also opsonizes bacteria, labeling it for destruction. Patients with **early classical complement component deficiencies** (see Chapter 173) have an increased risk of invasive infections with encapsulated bacteria such as pneumococcus. The spleen plays a key role in the phagocytosis and clearance of nonopsonized bacteria. Thus **primary or secondary asplenia** is associated with an increased risk of disseminated infections with pneumococcus (and meningococcus) requiring patients to take antibiotic prophylaxis. Patients with **toll-like receptor (TLR) defects** (IRAK4, MyD88, and NEMO deficiency) develop invasive pneumococcal and *Staphylococcus aureus* infections. These patients uniquely fail to (or minimally) manifest signs of inflammation (fevers, elevated CRP, ESR) despite having invasive infections; this is the result of a block in the pathway that produces inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, critical for recruitment of neutrophils and fever generation.

Severe Papillomavirus

A number of PIDDs are characterized by recurrent, severe human papillomavirus (HPV) infections (see Table 164.3). Warts are common in the general population but high numbers should suggest a PIDD. Patients with WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency, myelokathexis) have a unique susceptibility to HPV-induced warts in addition to bacterial sinopulmonary infections and cutaneous abscesses (immunity to other viral infections is intact) (see Fig. 708.6). One of the hallmarks of **DOCK8 deficiency** is severe cutaneous viral infections with HPV, molluscum contagiosum, herpes simplex, and varicella zoster. Patients with **epidermodysplasia verruciformis** have markedly increased susceptibility to cutaneous HPV infections. Patients with **GATA2 deficiency** can suffer from severe disseminated HPV, including genital locations, and molluscum contagiosum infections. Treatment is distinct for each condition, but knowing

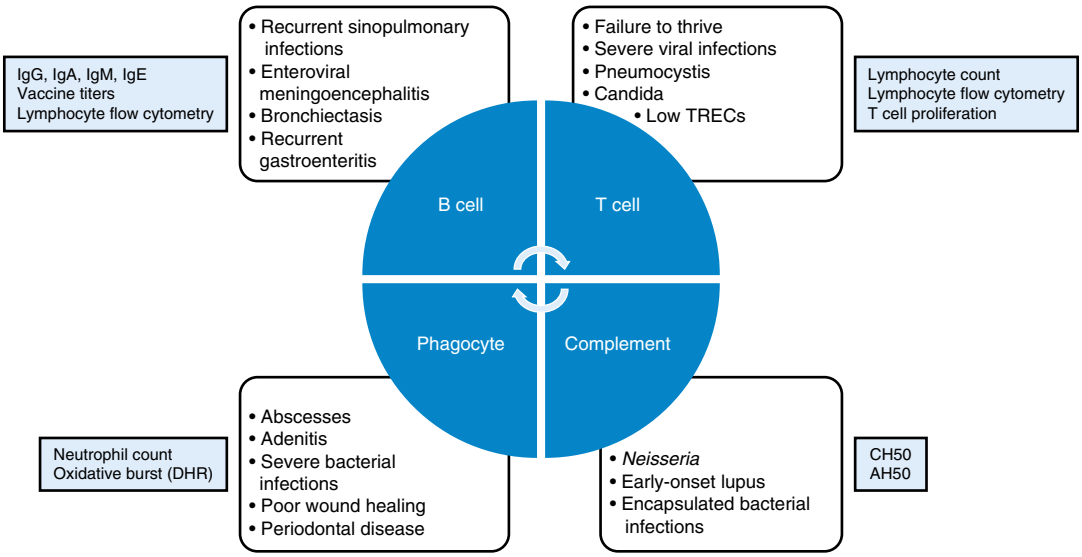

Fig. 164.1 When infections are the major manifestation of the inborn error of immunity, several types of laboratory tests can yield a diagnosis. The specific type of infection suggests the effector arm of the immune system that may be dysfunctional, and the testing can be applied in a targeted fashion. Laboratory evaluation is noted in the light blue boxes. DHR, dihydrorhodamine, Ig, immunoglobulin; TRECs, T cell receptor excision circles.

Table 164.4 Recurrent Invasive Pneumococcal Infections

CONDITION	GENE/CONDITION SUBSET	INHERITANCE	OTHER FEATURES
Asplenia	*ATRX*	XL	Developmental delay, low-set ears, single palmar crease
Asplenia	*HMOX1*	AR	Hemolysis, nephritis
Asplenia	*NKX2-5*	AD	
Asplenia	*RPSA*	AD	
Asplenia	*ZEB2*	AD	Mowat-Wilson syndrome, microcephaly, Hirschsprung disease, defects in corpus callosum
Asplenia	Gene unknown/syndromic		Can occur in heterotaxy syndromes
Antibody deficiency	*BTK*	XL	
Antibody deficiency	Hypogammaglobulinemia	Various	
Antibody deficiency	Specific antibody deficiency	Various	
Antibody deficiency	IgG subclass deficiency	Various	
Antibody deficiency	CVID	Various	
Innate immune deficiency	*MYD88*	AR	Poor fever formation
Innate immune deficiency	*IRAK4*	AR	Poor fever formation
Innate immune deficiency	*IKBKG*	XL	Peg teeth, ectodermal dysplasia
Complement deficiency	C2	AR	Can have lupus
Complement deficiency	C1	AR	Can have lupus
Complement deficiency	C4	AR	Can have lupus
Complement deficiency	C3	AR	Glomerulonephritis

AD, Autosomal dominant; AR, autosomal recessive; CVID, common variable immunodeficiency; XL, X-linked.

the immune etiology is critical because of the substantial morbidity associated with continually spreading warts.

Herpes Simplex Virus Encephalitis

Several innate PIDDs uniquely present with recurrent herpes simplex virus (HSV) encephalitis (without mucosal HSV infections) due to disruption of the signaling pathways regulating antiviral cytokines interferon (IFN)-α and -β, which are critical for control of HSV infections (see Table 164.3). Examples of these PIDDs include TLR3 deficiency, UNC93b deficiency, and interferon regulatory factor 3 (IRF3) deficiency. The importance of recognition relates to the likelihood of recurrence, with the attendant central nervous system (CNS) dysfunction that can result.

Epstein-Barr Virus

Severe life-threatening infections with fulminant Epstein-Barr virus (EBV) are a hallmark of certain PIDDs, whereas typical outpatient infectious mononucleosis infections are not concerning (see Chapter 301) (see Table 164.3). Patients with **familial hemophagocytic lymphohistiocytosis** (HLH) have a block in the cytotoxic lymphocyte (NK and CD8 T cell) pathway necessary to control EBV infections (see Chapter 556). Patients develop uncontrolled immune hyperactivation (cytokine storm) from unchecked EBV infections resulting in life-threatening HLH. Clinical symptoms include fever, hepatosplenomegaly, pancytopenia, and multi-system organ failure. There may be evidence of hemophagocytosis activated by macrophages in a bone marrow biopsy. Patients with **X-linked lymphoproliferative syndrome (XLP)** are predisposed to fatal fulminant EBV with or without HLH, as well as lymphoma. Patients with XLP who survive acute EBV infections will often go on to develop hypogammaglobulinemia. Multiple PIDD disorders have an increased risk of HLH (Table 164.5). These conditions are more likely to require hematopoietic cell transplantation (see Chapter 176) than HLH occurring in the non-PIDD community.

Severe *Candida*

Severe oral thrush from *Candida albicans* (as well as other opportunistic infections such a *Pneumocystis jiroveci*) can be seen in patients with SCID who have very low CD3 T cells (classically <300) and poor T-cell function; this mirrors the clinical phenotype of infants with HIV who also have low T cells (see Table 164.3). Intact T-cell IL-17 immunity is essential for control of *Candida* infections and overall decrements in the entire T-cell population or selective defects in the Th17 population are strongly associated with *Candida*. Patients with specific gene pathogenic variants in IL-17 signaling (IL-17RA, IL-17RC, IL-17F, and ACT1) present with **chronic mucocutaneous candidiasis** (CMCC; *Candida* infections of the skin, nails, mucosa). ***STAT1*** gain-of-function pathogenic variants result in decreased IL-17 production that also predisposes patients to skin and mucosal *Candida* infections. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is an autosomal recessive disease caused by mutations in the autoimmune regulator (AIRE) gene. Patients develop CMCC and autoimmune endocrine disorders such as hypoparathyroidism and adrenal insufficiency.

Aspergillus

Neutrophils are responsible for engulfing and killing fungal organisms. *Aspergillus* species are a major cause of infections in chronic granulomatous disease (CGD), a PIDD characterized by defective neutrophil function (see Table 164.3). CGD patients most commonly develop *Aspergillus* pneumonia or osteomyelitis, although all sites are susceptible to fungal infection. *Aspergillus nidulans* infections occur almost exclusively in CGD and result in a much higher rate of osteomyelitis and mortality than *A. fumigatus*. Exposure to *Aspergillus* through handling of mulch with gardening or exposure to hay can cause fulminant pneumonitis in CGD patients. Patients with **GATA2 deficiency** and ***STAT1*** gain-of-function pathogenic variants can develop fungal infections such as aspergillus and histoplasmosis as well as atypical mycobacteria. Patients with autosomal dominant **hyper-IgE syndrome**

Table 164.5 Primary Immune Deficiency Disease and Risk of Hemophagocytic Lymphohistiocytosis*

CONDITION	GENE/CONDITION SUBSET	INHERITANCE	RISK OF HLH	OTHER FEATURES
CD48 deficiency	*CD48*	AD	High	
Chédiak-Higashi syndrome	*LYST*	AR	High	Pigmentary dilution
NLRC4	*NLRC4*		High	IBD
Perforin deficiency (FHL2)	*PRF1*	AR	High	
Griscelli syndrome, type 2	*RAB27A*	AR	High	Pigmentary dilution
X-linked lymphoproliferative disease 1	*SH2D1A*	XL	High	
Syntaxin 11 deficiency (FHL4)	*STX11*	AR	High	
STXBP2/Munc18-2 deficiency (FHL5)	*STXBP2*	AR or AD	High	Hypogammaglobulinemia, IBD
UNC13D/Munc13-4 deficiency (FHL3)	*UNC13D*	AR	High	
X-linked lymphoproliferative disease 2	*XIAP*	XL	High	
CD27 deficiency	CD27	AR	Medium	Unable to control EBV
Chronic granulomatous disease	*All genetic types*	XL, AR	Low	Infections, granulomas
Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR	Low	Pigmentary dilution
Hermansky-Pudlak syndrome, type 10	*AP3D1*	AR	Low	Pigmentary dilution
Lysinuric protein intolerance SLC7A7 deficiency	*SLC7A7*	AR	Low	Lung disease, feeding intolerance

*Other primary immune deficiency diseases, including most T-cell deficiencies have been associated with HLH in rare patients.
AD, Autosomal dominant; AR, autosomal recessive; HLH, Hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease.

(STAT3 deficiency) commonly develop lung pneumatoceles (cavities), which can then become superinfected with *Aspergillus*.

Sentinel Bacterial Infections

Certain bacterial infections are considered *sentinel infections* because the pathogen is highly associated with specific PIDDs. The following bacteria are considered highly suspicious for CGD: *Burkholderia cepacia*, *Nocardia*, *Serratia marcescens*, *Chromobacterium violaceum*, and *Granulibacter bethesdensis*. Unlike patients with cystic fibrosis, *B. cepacia* in CGD can cause pneumonia but also rapidly fatal sepsis. Terminal complement (C5-C9) and alternative complement defects (properdin or factor D deficiency) have increased susceptibility to recurrent invasive *Neisseria* species (recurrent meningococcal and disseminated gonococcal infections). Complement deficiencies are also found more frequently in patients with meningitis due to unusual serotypes of *Neisseria*.

Mycobacterial Infections

Intact IL-12 and IFN-γ signaling is required to activate phagocytes such as macrophages to clear intracellular pathogens such as mycobacteria (see Table 164.3). Patients who have defects along this pathway such as IL-12 p40, IL-12 receptor, and **IFN-γ receptor deficiency** present with atypical mycobacterial infections; these infections can spread to bones and visceral organs (rather than isolated uncomplicated cervical lymphadenitis, which does not suggest a PIDD). STAT1 deficiency is associated with mycobacterial infections because STAT1 is required for IFN-γ signaling. Patients with NEMO deficiency due to pathogenic variants in *IKBKG* develop mycobacterial disease due to impaired IL-12 production in response to infection and impaired TLR signaling. Atypical mycobacteria also cause pulmonary disease in patients with CGD. Patients with the PIDDs mentioned previously born outside of the United States who receive the bacilli Calmette-Guérin (BCG) attenuated vaccine can present with disseminated BCG strain mycobacterial infection often complicating subsequent hematopoietic cell transplantation.

Severe Cryptosporidia

Cryptosporidium is a protozoan parasite that causes diarrheal disease in humans. Exposure occurs from contaminated drinking water sources as well as fresh water and public swimming pools. Patients with PIDD can develop infections outside of the GI tract such as the lungs, biliary tract, and pancreas. Intact T-cell immunity appears to play a critical role in resolution of *Cryptosporidium* infection as evidenced by the high incidence of this infection in patients with HIV. PIDDs with impaired T-cell immunity are characterized by increased risk for developing *Cryptosporidium*. In X-linked hyper-IgM syndrome, major histocompatibility complex (MHC) class II deficiency, DOCK8 deficiency, IL-21 receptor deficiency, sclerosing cholangitis, and cirrhosis from chronic *Cryptosporidium* infection can occur. The presence of liver disease from *Cryptosporidium* appears to increase the risk of mortality from curative hematopoietic cell transplantation.

SCHEMA FOR DIAGNOSIS

Clues to the diagnosis of a PIDD may be obtained by the past and current history and the physical exam (Tables 164.6 and 164.7)

Laboratory studies typically used in the diagnosis of PIDD are rudimentary. Typical laboratory studies measure the amount of antibody or count the numbers of a given cell type (T cells as an example). There is a relatively limited ability to test function. Figures 164.1 and 164.2 outline a strategy to approach the diagnostic testing for PIDDs.

NONINFECTIOUS PRESENTATIONS SUGGESTING PIDD

Autoimmunity and inflammation can be indicators of a possible PIDD. Infections may be falsely attributed to the medications used to control the autoimmunity or inflammation. Often the usual immunologic testing is normal. Many of the autoimmune or autoinflammatory disorders associated with PIDD may need to be identified through genetic sequencing.

Autoimmunity

Autoimmunity can be the presenting manifestation of a PIDD. Rather than having the more familiar infectious phenotype, these patients have defects in tolerance or lymphocyte function that compromise their homeostasis. HLH is a profound form of immune dysregulation (see Chapter 556.2). These conditions are important to recognize because *targeted* therapies can be beneficial and because they can evolve to complex phenotypes with severe morbidity. The typical laboratory

Table 164.6 Clinical Aids to the Diagnosis of Immunodeficiency

SUGGESTIVE OF B-CELL DEFECT (HUMORAL IMMUNODEFICIENCY)
Recurrent bacterial infections of the upper and lower respiratory tracts
Recurrent skin infections, meningitis, osteomyelitis secondary to encapsulated bacteria *(Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Neisseria meningitidis)*
Severe *Giardia lamblia* infections
Paralysis after vaccination with live attenuated poliovirus
Reduced levels of immunoglobulins
SUGGESTIVE OF T-CELL DEFECT (COMBINED IMMUNODEFICIENCY)
Systemic illness after vaccination with any live virus or BCG
Unusual life-threatening complication after infection with benign viruses (giant cell pneumonia with measles; varicella pneumonia)
Chronic oral candidiasis after 6 mo of age
Chronic mucocutaneous candidiasis
Graft versus host disease after blood transfusion
Reduced lymphocyte counts for age
Low level of immunoglobulins
Absence of lymph nodes and tonsils
Small thymus
Chronic diarrhea
Failure to thrive
Recurrent infections with opportunistic organisms
Generalized, recurrent, recalcitrant warts
SUGGESTIVE OF MACROPHAGE DYSFUNCTION
Disseminated atypical mycobacterial infection, recurrent *Salmonella* infection
Fatal infection after BCG vaccination
CONGENITAL SYNDROMES WITH IMMUNODEFICIENCY
Ataxia-telangiectasia: ataxia, telangiectasia
Autoimmune polyglandular syndrome: hypofunction of one or more endocrine organs, chronic mucocutaneous candidiasis
Cartilage-hair hypoplasia: short-limbed dwarfism, sparse hair, neutropenia
Wiskott-Aldrich syndrome: thrombocytopenia, male gender, eczema
Chédiak-Higashi syndrome: oculocutaneous albinism, nystagmus, recurrent bacterial infections, peripheral neuropathies
DiGeorge syndrome (22q deletion syndrome): unusual facies, heart defect, hypocalcemia
CHARGE syndrome: coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness
Short-limb skeletal dysplasia with combined immune deficiency: metaphyseal dysplasia, ADA deficiency, or Omenn syndrome
X-linked agammaglobulinemia with growth hormone deficiency: hypogammaglobulinemia, growth hormone deficiency
Kabuki syndrome: long palpebral fissures, prominent eyelashes, congenital heart disease
Timothy syndrome: prolonged QT, congenital heart disease, developmental delay
PTEN tumor hamartoma syndrome: multiple hamartomas, cancer
SUGGESTIVE OF ASPLENIA
Heterotaxia, complex congenital heart disease, Howell-Jolly bodies on blood smear, sickle cell anemia

ADA, Adenosine deaminase; BCG, bacille Calmette-Guérin.
From Verbsky JW, Routes JM. Recurrent fever, immune deficiency, and autoinflammatory disorders. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis.* 2nd ed. Philadelphia: Elsevier; 2023.Table 54.7, p. 1028.

evaluations used in the diagnosis of the PIDD are often unrevealing or minimally abnormal, leading to delay in diagnosis and implementation of appropriate therapy. The prognosis may be poor; hematopoietic cell transplantation is recommended.

Early-Onset Systemic Lupus Erythematosus

Prepubertal systemic lupus erythematosus (SLE) is uncommon and onset of SLE before 5 years of age is exceptionally unusual (Table 164.8); onset before 5 years of age suggests a monogenic condition such as early complement component deficiencies (see Chapter 173). Complement deficiencies also have an infection phenotype. SLE is the dominant phenotype for C1 and C4 deficiencies. The mechanism by which these complement deficiencies lead to susceptibility to SLE is through impaired clearance of apoptotic material and compromised tolerance. SLE may present in infancy in C1 and C4 deficiencies and it is typically severe. C2 deficiency, in contrast, is associated with a milder susceptibility to SLE and proportionally higher susceptibility to infection. Other gene defects associated with early-onset SLE include lymphocyte defects such as *PRKCD*, *FAS*, and *FASL*. Manifestations of the **interferonopathies** such as Aicardi Goutières can resemble SLE and may have a high rate of antinuclear antibodies (ANA). CNS involvement and a cutaneous vasculopathy are hallmarks of interferonopathies (see Chapter 205).

Early-Onset Enteropathy

Small bowel enteropathy in these conditions is defined as non–gluten sensitive and associated with villous blunting or atrophy (Table 164.9). A key component of the differential diagnosis is the congenital diarrheas associated with either solute carrier defects or altered epithelial function (see Chapter 385). However, many of the solute carrier defects do not have villous blunting or atrophy. The early-onset enteropathy conditions are most often related to T-cell defects in intolerance and are classically associated with dysfunctional regulatory T cells such as in **IPEX** (immune dysregulation enteropathy X-linked). Identical but milder enteropathy is also seen in patients with **STAT5B deficiency** and **IL2RA deficiency**. Both of these molecules are required for critical signal transduction in regulatory T cells. Although enteropathy is often the presenting manifestation in these regulatory T-cell deficiency states, many of these patients will develop additional autoimmune features. The progression of autoimmune involvement of different organ systems can only be altered through hematopoietic cell transplantation. Enteropathy can also be seen in older individuals with one of the immune dysregulation conditions associated with **CVID**. In these conditions, the enteropathy may appear in early childhood or as late as middle age. The key to suspecting a monogenic immune dysregulation condition is the finding of villous atrophy that is not gluten-restriction responsive. Expanded populations of intraepithelial lymphocytes are also common.

Pleomorphic Autoimmunity

Autoimmunity in children usually does not imply an inherited monogenic condition (Table 164.10). In a setting where there is a strong family history and a suspected autosomal dominant condition, the first onset of autoimmunity may prompt a genetic evaluation; a single organ autoimmune disease does not strongly suggest that there is a monogenic condition underlying that autoimmune disease.

Pleomorphic autoimmunity refers to autoimmune disease affecting multiple organs in a pattern that is not typical for either age of onset or evolution. SLE can affect a number of organs as can mixed connective tissue disease, but it would be unusual for those conditions to also be associated with diabetes mellitus or autoimmune hepatitis. When autoimmunity does not fall cleanly into a particular diagnosis, it is suggestive of pleomorphic autoimmunity.

There is a broad range of defects in T- and B-cell tolerance and conditions associated with impaired regulation of T-cell behavior that can lead to an array of autoimmune conditions. The organs affected by autoimmunity typically accrue over time and in a pattern that is not standard for the known sporadic systemic autoimmune conditions. In some cases, these conditions may also have peculiar pathologic features that represent a clue that the underlying diagnosis is something other than a standard autoimmune disease of childhood. Table 164.10 attempts to categorize conditions according to the pathway implicated. There is wide heterogeneity in the timing of the autoimmune disease, the penetrance of the disease, and the end organs affected. This combination makes this particular subset of PIDD extraordinarily difficult to conceptualize. Only a high index of suspicion and the use of genetic evaluations can identify these patients who will often benefit from targeted therapeutics.

Table 164.7 Special Physical Features Associated with Immunodeficiency Disorders

CLINICAL FEATURES	DISORDERS
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage-hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft versus host disease, Comèl-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver, and rectum especially	CGD
Recurrent abscesses or cellulitis	CGD, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	CGD, SCID, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, IL-17, and IL-23 deficiencies; *CARD9* deficiency; STAT1 deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of nails	Chronic lung disease caused by antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, CGD
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T-cell and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage-hair hypoplasia

ADA, Adenosine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.
From Goldman L, Ausiello D, ed. *Cecil Textbook of Medicine.* 22nd ed. Philadelphia: Saunders; 2004. p 1599.

Inflammatory Diseases

Many of the recognized inflammatory diseases are the periodic fever (autoinflammatory) syndromes (see Chapter 204). Distinguishing fevers related to infection and those fevers that are driven by endogenous immune dysfunction is often initially difficult. The first contact with the healthcare system may be by a subspecialist who may only recognize the initial presenting manifestation. The inflammatory diseases are typically managed according to the pathway that is defective; therefore the distinction between these conditions and the autoimmune conditions is critically important.

Very Early Onset Inflammatory Bowel Disease

A key setting where a monogenic inflammatory condition should be considered is infantile-onset inflammatory bowel disease or early-onset inflammatory bowel disease with additional autoimmune features (see Chapter 382.1). Overall, approximately 20% of children who develop inflammatory bowel disease prior to 6 years of age will have a monogenic immune-based condition. The frequency increases with infantile onset or with panenteric disease. The diagnosis is most often established through genetic sequencing because the implicated genes are numerous and diverse (see Chapters 174 and 382.3). These conditions are managed with targeted biologic or small molecule agents with a few select patient subsets requiring hematopoietic cell transplantation.

Fever Syndromes

The central feature of the inherited fever syndromes is fever arising in the absence of infectious trigger (see Chapter 204). Infants and toddlers may have infections with a frequency of one per month and take as long as 2 weeks to recover. Nevertheless, the parents will often remark that the fevers "came out of the blue" or no one else in the household was ill at the time and express surprise at the frequency with which their child has been diagnosed with a viral infection with no viral symptoms. Some of the fever syndromes have fever that is typically isolated with no additional end-organ effects, whereas others have fever as a component of a much larger systemic inflammatory picture.

The most familiar inherited fever syndromes are those associated with inflammasome activation and typically treated with IL-1 inhibitors. A key consideration in the differential diagnosis for these conditions is the nongenetic condition called periodic fever aphthous stomatitis pharyngitis adenitis (PFAPA; see Chapter 204).

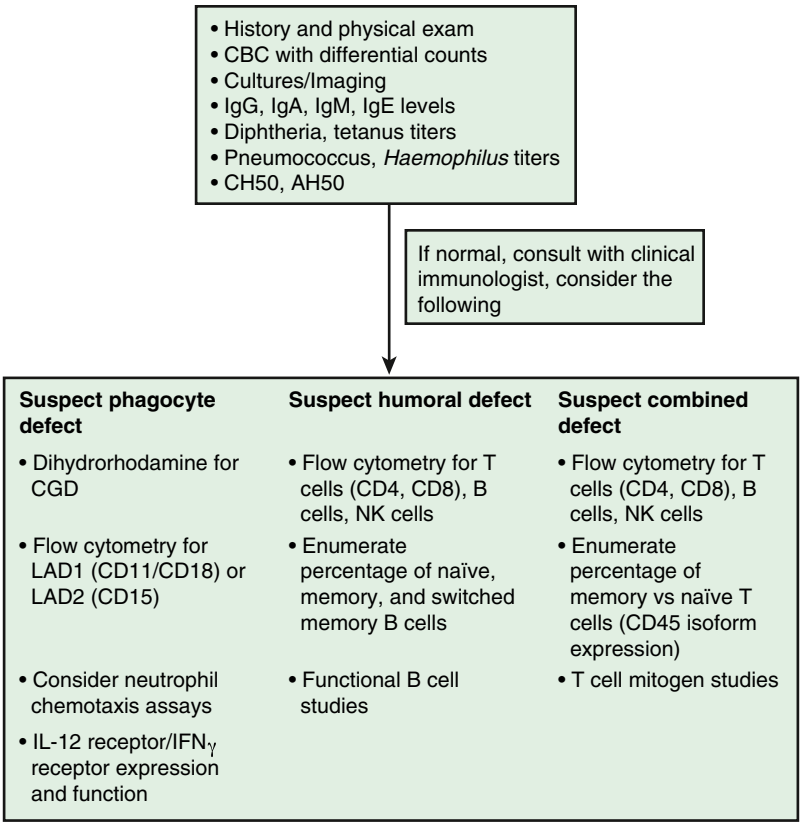

Fig. 164.2 Initial work-up and follow-up studies of patients with suspected immune deficiency. Consultation with a clinical immunologist is recommended to guide advanced testing and interpret results. CGD, Chronic granulomatous disease; Ig, immunoglobulin; LAD, leukocyte adhesion defect; NK, natural killer; IL, interleukin; IFN, interferon. *(From Verbsky JW, Routes JM. Recurrent fever, immune deficiency, and autoinflammatory disorders. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. 2nd ed. Philadelphia: Elsevier; 2023. Fig. 54.9, p. 1029.)*

Table 164.8 Early-Onset Monogenic Systemic Lupus Erythematosus

PATHWAY	GENE	INHERITANCE	SLE FREQUENCY	OTHER FEATURES
Complement	*C1QA*	AR	High	Infections
Complement	*C1QB*	AR	High	Infections
Complement	*C1QC*	AR	High	Infections
Complement	*C1R*	AR	High	Infections
Complement	*C1S*	AR	High	Infections
Complement	*C2*	AR	Low	Infections
Complement	*C3*	AR	Low	Infections, GN
Complement	*C4*	AR	High	Infections
Type I Interferon-AGS	*ADAR*	AR or AD (DN)	Low	AGS, CNS
Type I Interferon-AGS	*IFIH1*	AD (GOF)	Low	AGS, arthropathy, CNS
Type I Interferon-AGS	*RNASEH2A/B/C*	AR	Low	AGS
Type I Interferon-AGS	*SAMHD1*	AR	Low	AGS, FCL, CNS
Type I Interferon-AGS	*TREX1*	AR or AD (DN)	Low	AGS, FCL
Type I Interferon	*ACP5*	AR	High	Bone, CNS
Type I Interferon	*DNASE1*	AR	High	
Type I Interferon	*DNASE2*	AR	High	GN
Type I Interferon	*DNASE1L3*	AR	High	HUVS
Type I Interferon	*OTUD1*	AD	Medium	Arthritis, IBD
Type I Interferon	*STING*	AD (GOF)	Medium	Vasculopathy, arthritis, ILD

Continued

Table 164.8 Early-Onset Monogenic Systemic Lupus Erythematosus—cont'd

PATHWAY	GENE	INHERITANCE	SLE FREQUENCY	OTHER FEATURES
RAS/MAPK	*KRAS*	AD	Low	Short stature
RAS/MAPK	*PTPN1*	AD	Low	Short stature
RAS/MAPK	*SHOC2*	AD	Low	Noonan-like syndrome
Proteasome	*PSMA3*	AD	Low	Dermatosis, lipodystrophy
Proteasome	*PSMB4*	AD	Low	Dermatosis, lipodystrophy
Proteasome	*PSMB8*	AD	Low	Dermatosis, lipodystrophy
Proteasome	*PSMB9*	AD	Low	Dermatosis, lipodystrophy
Apoptosis	*FASLG*	AD	Medium	ALPS
Apoptosis	*TNFRSF6*	AD	Medium	ALPS
Tolerance	*PRKCD*	AR	High	Infections
Tolerance	*RAG1/2*	AR	Medium	Infections, granulomas
Oxidase	*CYBB*	XL	Low	Males, CGD; females, discoid SLE
AKT	*PTEN*	AD	Medium	Malignancy risk
Collagen	*PEPD*	AR	Low	Leg ulcers
Amino acids	*SLC7A7*	AR	Low	Lysinuric protein intolerance
Carbohydrate	*MAN2B1*	AR	Low	Mannosidase
NFKappaB	*TNFAIP3*	AD	Medium	Vasculitis, ALPS
Adenosine	*ADA2*	AR	Low	Vasculitis, CNS, ALPS
Transcription factor	IKZF1	AD	Low	Leukemia, infections

AD, Autosomal dominant; AGS, Aicardi Goutières syndrome; ALPS, autoimmune lymphoproliferative syndrome; AR, autosomal recessive; CNS, central nervous system; DN, dominant negative; FCL, familial chilblains lupus; GOF, gain of function; GN, glomerulonephritis; HUVS, hypocomplementemic urticarial vasculitis; IBD, inflammatory bowel disease; ILD: interstitial lung disease; SLE, systemic lupus erythematosus; XL, X-linked.

Table 164.9 Early-Onset Enteropathy (Not Gluten Sensitive)

CONDITION	GENE	INHERITANCE	ENTEROPATHY FREQUENCY	OTHER FEATURES
Microvillous inclusion disease	*MYO5B*	AR	Always	Neonatal onset
Microvillous inclusion disease	*STX3*	AR	Always	Neonatal onset
Tufting enteropathy	*EPCAM*	AR	Always	Neonatal onset
Tufting enteropathy	*SPINT2*	AR	Always	Keratitis, anal/choanal atresia
Trichohepatoenteric syndrome	*SKIV2L*	AR	Always	Trichorrhexis nodosa, IUGR
Trichohepatoenteric syndrome	*TTC37*	AR	Always	Trichorrhexis nodosa, IUGR
Multiple intestinal atresia	*TTC7A*	AR	High	Lymphopenia, IA
Immune dysregulation	*CARD11*	AD	Low	CVID, alopecia, atopy
Immune dysregulation	*CTLA4*	AD	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*DEF6*	AR	Medium	Cardiomyopathy, infections
Immune dysregulation	*FOXP3*	XL	Always	Diabetes
Immune dysregulation	*ICOS*	AR	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*IL2RA*	AR	Low	Lymphopenia, infections, LP
Immune dysregulation	*LRBA*	AR	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*MALT1*	AR	High	Infections, LP, eczema
Immune dysregulation	*RLTPR*	AR	Medium	Infections, EBV
Immune dysregulation	*STAT1*	AD (GOF)	High	*Candida,* diabetes
Immune dysregulation	*STAT3*	AD (GOF)	High	Short, LP
Immune dysregulation	*XIAP*	XL	High	EBV, HLH
MHC class II deficiency	*RFXANK*	AR	Low	Infection, cytopenias
MHC class II deficiency	*CIITA*	AR	Low	Infection, cytopenias
MHC class II deficiency	*RFX5*	AR	Low	Infection, cytopenias
MHC class II deficiency	*RFXAP*	AR	Low	Infection, cytopenias

AD, Autosomal dominant; AR, autosomal recessive; CVID, Common variable immune deficiency; EBV, Epstein-Barr virus; GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; IA, intestinal atresia and fibrosis; IUGR, intrauterine growth retardation; LP, lymphocytic infiltrates in multiple organs; MHC, major histocompatibility complex; XL, X-linked.

Table 164.10 Pleomorphic Autoimmunity (Autoimmunity Not Limited to a Single Organ)

PATHWAY	GENE	INHERITANCE	MAIN ORGANS INVOLVED	NONIMMUNE FEATURES	INFECTIONS
B-cell tolerance	*AID*	AR	Lymphoid hyperplasia, cytopenias, GI		High IgM, frequent infections
T-cell tolerance	*AIRE*	AR/AD	Endocrine organs, lung, skin	Nail dystrophy	*Candida*
T-cell tolerance	*ARPC1B*	AR	Cytopenias, GI	Thrombocytopenia	Frequent infections
T-cell tolerance	*CTLA4*	AD	GI, lung, CNS		Frequent infections
T-cell tolerance	*COPA*	AD	Lung, joint, renal		
T-cell tolerance	*FOXP3*	XL	GI, endocrine, skin		
T-cell tolerance	*HAVCR2*	AR	HLH, panniculitis, SLE-like, joint	Lymphoma	
T-cell tolerance	*IL2RA*	AR	Skin, GI, endocrine		Viral
T-cell tolerance	*IL2RB*	AR	GI, skin		Viral
T-cell tolerance	*ITCH*	AR	Joints, lung, enteropathy	Developmental delay	
T-cell tolerance	*JAK1*	AD (GOF)	Skin, renal, GI		
T-cell tolerance	*LRBA*	AR	GI, lung, CNS		
T-cell tolerance	*ORAI1*	AR	Cytopenias, vasculitis	Myopathy, poor dental enamel	Frequent infections
T-cell tolerance	*PRKCD*	AR	SLE-like		Frequent infections
T-cell tolerance	*PTEN*	AD	Cytopenias, GI, endocrine	Malignancy, macrocephaly, developmental delay	
T-cell tolerance	*STAT1*	AD (GOF)	GI, endocrine		*Candida*
T-cell tolerance	*STAT3*	AD (GOF)	GI, lung, endocrine	Short stature	
T-cell tolerance	*STIM1*	AR	Cytopenias, Sjögren syndrome	Myopathy, poor dental enamel	Frequent infections
T-cell tolerance	*TPP2*	AR	Hematopoietic	CNS	Viral
T-cell tolerance	*WAS*	XL	Cytopenias, GI	Thrombocytopenia	Frequent infections
T-cell tolerance	*WIP*	AR	Cytopenias, GI	Thrombocytopenia	Frequent infections
Inflammatory pathway	*RBCK1*	AR	Joints, skin, GI	Amylopectin deposits in muscle	Frequent infections
Inflammatory pathway	*RIPK1*	AD	GI, joint	HSM episodic	Fevers
Inflammatory pathway	*RNF31*	AR	Joints, skin	Amylopectin deposits in muscle	Frequent infections, CVID-like
Inflammatory pathway	*TNFAIP3*	AD	Mucosal ulcers, GI, arthritis, skin		Fevers
Lysinuric protein intolerance	*SLC7A7*	AR	HLH, SLE, PAP	HSM, poor growth, osteoporosis, renal	Infections trigger metabolic decompensation

AD, Autosomal dominant; AR, autosomal recessive; CNS, central nervous system; CVID, common variable immune deficiency; GI, gastrointestinal, GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; HSM, hepatosplenomegaly; PAP, pulmonary alveolar proteinosis; SLE, systemic lupus erythematosus; XL, X-linked.

Although genetic fever syndromes may have a cutaneous component, abdominal pain, or nausea, fever is by far the dominant manifestation. There may be a family history or there may be an ethnic background that suggests the diagnosis (e.g., familial Mediterranean fever).

Other fever syndromes are related to proteasome dysfunction. These often have a very strong cutaneous component that can be a neutrophilic dermatosis or more of a vasculopathic picture with chilblains affecting the ears, fingers, and toes. Over time, these conditions may develop lipodystrophy. Fever is often seen in these conditions before 5 years of age. Treatment often includes a Jak inhibitor.

In their most severe form, interferonopathies present with the infantile-onset leukoencephalopathy called **Aicardi Goutières syndrome**. There are milder variants leading to interferon production that can be associated with later onset and a picture more typical for SLE. The earlier the onset the more likely there is to be significant brain involvement. These conditions are treated with Jak inhibitors.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

The T-, B-, and NK-Cell Systems

Chapter 165

T-Cell and Combined Deficiencies

Ramsay L. Fuleihan

T-CELL AND COMBINED DEFICIENCIES

T lymphocytes (T cells) play a central role in the orchestration and regulation of the adaptive immune response. CD4 T cells help B cells synthesize specific IgG, IgA, and IgE antibodies and develop into memory B cells, help macrophages kill intracellular pathogens, and regulate the immune response. CD8 T cells kill virus-infected or malignant cells. Immune deficiency diseases that disrupt T-cell development or function are usually severe, affecting multiple aspects of adaptive immunity, and are thus *combined immune deficiency diseases*. A hallmark of the adaptive immune response is specific recognition of pathogen proteins via antigen receptors, the T-cell receptor (TCR) in T cells and immunoglobulin in B cells. Antigen receptors have a variable region that is formed by random rearrangement of two to three gene segments, V(D)J, allowing a large variety of antigen recognition. TCRs recognize a fragment of a protein that is presented by the major histocompatibility complex (MHC) molecules; therefore the randomly generated variable region of the TCR needs to be able to interact with the individual's MHC molecules. During T-cell development in the thymus, only thymocytes with TCRs that recognize the individual's MHC molecules are selected to survive (positive selection) and all other thymocytes die (by neglect). Among the thymocytes that survive, those with self-reactive TCRs are eliminated (negative selection) or develop into regulatory T cells to prevent autoimmune disease (Fig. 165.1). There is a symbiotic relationship between the thymus and developing thymocytes, where the absence of a thymus affects T-cell development and the absence of thymocytes leads to disruption of the thymic architecture. Pathogenic gene variants affecting any of the signaling pathways, DNA recombination, and repair enzymes as well as the thymic environment can lead to T-cell and combined immune deficiency diseases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography

165.1 Severe Combined Immunodeficiencies

Ramsay L. Fuleihan

Severe combined immunodeficiency (SCID) is caused by diverse pathogenic gene variants that lead to absence of T- and B-cell function. Patients with this group of disorders have the most severe immunodeficiency.

GENETICS AND PATHOGENESIS

SCID is caused by pathogenic variants in genes crucial for lymphoid cell development or function (Table 165.1 and Fig. 165.2). All patients with SCID have very small thymuses that contain no thymocytes and lack corticomedullary distinction and lack Hassall's corpuscles. The thymic epithelium appears histologically normal. Both the follicular and the paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

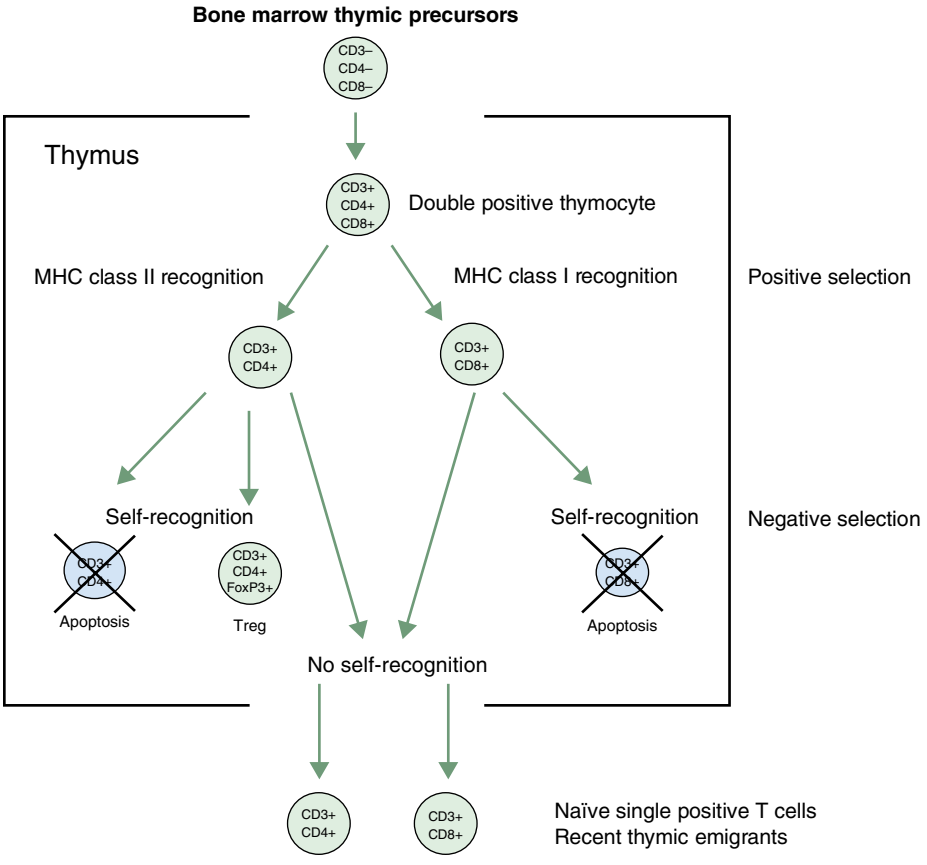

Fig. 165.1 Schematic representation of T-cell development in the thymus. Thymocyte precursors leave the bone marrow and enter the thymus with no expression of CD3, CD4, or CD8 (double negative T cells). Later the thymocytes express CD3 and both CD4 and CD8. If the newly formed T-cell receptor (TCR) recognizes major histocompatibility complex (MHC) class I or class II molecules, the thymocytes receive a positive selection signal and develop into CD8 or CD4 single positive thymocytes, respectively. Single positive thymocytes with TCR that recognize self-proteins will be killed by apoptosis or develop into regulatory T cells (Treg) to prevent autoimmune disease. Single positive thymocytes that are non–self-reactive leave the thymus as naïve single positive T cells ready to engage in the immune response when needed.

Table 165.1 Genetic Basis of Severe Combined Immunodeficiency and SCID Variants

DISEASE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
T^-B^- SCID				
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness Pathogenic variants in adenylate kinase 2	GCSF, HSCT
Reticular dysgenesis	AD	Impaired hematopoiesis	Severe neutropenia but no deafness, gain-of-function variant in RAC2	HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, skeletal, bone marrow abnormalities	HSCT, PEG-ADA, gene therapy
RAG1 and RAG2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	*DCLERE1C* pathogenic gene variants	HSCT
DNA-PK deficiency	AR	Defective V(D)J recombination	None	HSCT
DNA ligase IV deficiency	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bone marrow abnormalities, lymphoid malignancies	HSCT
Cernunnos-XLF	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, birdlike facies, bone defects	HSCT
T^-B^+ SCID				
γ_c (CD132) deficiency	XL	Abnormal signaling via γ_c-ILRs (IL-2, 4, 7, 9, 15, 21)	None	HSCT, gene therapy
Jak3 deficiency	AR	Abnormal signaling downstream of γ_c	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at $CD4^-CD8^-$ stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at $CD4^-CD8^-$ stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size Attention deficit disorder	HSCT
LAT deficiency	AR	Defective T-cell development in the thymus	Autoimmune disease	HSCT
SLP76	AR	Abnormal signaling	Neutrophil defect, skin abscesses, rash, autoimmunity	HSCT attempted

γ_c, Common gamma chain; AD, Autosomal dominant; AR, Autosomal recessive; GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; Jak3, Janus kinase 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; R, receptor; RAG1, RAG2, recombinase-activating genes 1 and 2; SCID, severe combined immune deficiency; V(D)J, variable, diversity, joining domains; XL, X-linked.

Adapted from Roifman CM, Grunebaum E. Primary T-cell immunodeficiencies. In: Rich RR, Fleisher TA, Shearer WT, et al., eds. *Clinical Immunology*. 4th ed. Philadelphia: Saunders; 2013. pp. 440-441.

The 4 most common types of SCID are the X-linked forms caused by pathogenic variants in *CD132*, autosomal recessive *RAG1* and *RAG2* deficiencies, and adenosine deaminase (ADA) deficiency. Additional forms are listed in Table 165.1. For X-linked SCID and *ADA* deficiency, gene therapy exists, but genetic counseling is the most compelling reason for genetic sequencing to identify the pathogenic gene variant. Several specific pathogenic gene variants are associated with increased sensitivity to radiation and chemotherapy, and their early identification can lead to a better transplant experience by avoiding or reducing dosages of conditioning agents.

CLINICAL MANIFESTATIONS

SCID is included in the newborn screening program in all states in the United States and in several countries around the world. Thus infants can be identified and treated prior to development of symptoms, which has dramatically improved the survival of infants with SCID. A few genetic types of SCID are not detected by newborn screening, and there are many countries where newborn screening for SCID is not yet performed. Therefore an awareness of the clinical presentation of SCID remains important in the early diagnosis and treatment of patients.

When infants with SCID are not detected through newborn screening, they most often present with **infection** during infancy. Diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections are common presentations. Infections with a variety of opportunistic organisms, either through direct exposure or immunization, can lead to death. Potential infectious threats include *Candida albicans, Pneumocystis jiroveci* (PJP), parainfluenza 3 virus, adenovirus, respiratory syncytial virus (RSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus, measles virus, and attenuated organisms from the MMRV (measles, mumps, rubella, varicella), rotavirus, oral polio, nasal influenza, yellow fever, or bacille Calmette-Guérin (BCG) vaccines. Disseminated BCG infection may be the presenting feature of SCID in countries where the vaccine is given at birth. Infants with SCID also lack the ability to reject foreign tissue and are therefore at risk for severe or fatal **graft versus host disease (GVHD)** from T lymphocytes in nonirradiated blood products or maternal immunocompetent T cells

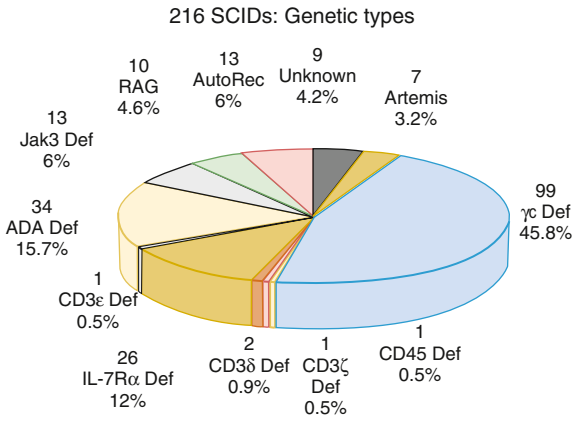

Fig. 165.2 Relative frequencies of the different genetic types of severe combined immunodeficiency (SCID) among 216 patients seen consecutively. *(From Buckley RH, Orange JS. Primary immunodeficiency diseases. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. Middleton's Allergy: Principles and Practice. 9th ed. Philadelphia: Elsevier; 2020. Fig. 69.2, p. 1126.)*



Fig. 165.3 Typical clinical features in an infant with Omenn syndrome. Note generalized erythroderma with scaly skin, alopecia, and edema. *(From Notarangelo LD. T cell immunodeficiencies. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig 6.1.)*

that crossed the placenta during pregnancy. The latter is usually not fatal but can be severe. This devastating presentation is characterized by expansion of the allogeneic cells, rash, hepatosplenomegaly, and diarrhea. A third presentation is often called **Omenn syndrome**, caused by hypomorphic pathogenic variants in SCID-causing genes, which allow few T cells to be generated in the infant that then expand, unregulated, and cause a clinical picture similar to GVHD (Fig. 165.3) with a severe dermatitis, lymphadenopathy, and diarrhea. The difference in this case is that the cells are the infant's own cells. Dermatitis, especially if it is difficult to treat, failure to thrive, and infection in the first 6 months of life, particularly severe infections from commonly mild pathogens or opportunistic organisms, should raise the suspicion of SCID.

All genetic types of SCID are associated with profound immunodeficiency. A small number have other associated features or atypical features that are important to recognize. ADA deficiency can be associated with pulmonary alveolar proteinosis and chondroosseous dysplasia. Adenylate kinase 2 (AK2) deficiency causes a picture referred to as **reticular dysgenesis** where neutrophils, myeloid cells, and lymphocytes are all low. This condition is also often associated with deafness.

DIAGNOSIS

A high index of suspicion is very important in the diagnosis of SCID. A key feature of SCID is that almost all patients will have a low lymphocyte count. Some patients may have a normal lymphocyte count from proliferation of B cells and/or natural killer (NK) cells. A combination of infection and a persistently low lymphocyte count is an indication to test for SCID. The diagnostic strategy both for symptomatic infants and those detected by newborn screening or with a family history of SCID is to perform flow cytometry to quantitate the T, B, and NK cells in the infant (Fig. 165.4). The CD45RA (naïve T-cell) and CD45RO (memory T-cell) markers can be helpful to identify patients with maternal engraftment or Omenn syndrome with predominantly memory T cells. Identification of a limited TCR repertoire is also helpful in the diagnosis of Omenn syndrome. T-cell function is often assessed by measuring proliferative responses to stimulation with mitogens.

Gene sequencing is often done by requesting a SCID gene panel or a more extensive primary immunodeficiency (PID) gene panel. There are certain laboratory features that predict specific gene defects. When both T and B cells are low with normal numbers of NK cells, often a gene encoding a protein involved in V(D)J recombination is the cause such as *RAG1* and *2*. Similarly, certain cytokine receptor defects are associated with specific SCID lymphocyte phenotypes, such as absent T cells and NK cells, but normal or elevated numbers of B cells in X-SCID caused by pathogenic variants in the common gamma chain (CD132) of cytokine receptors. Pathogenic variants in Janus kinase *(JAK)3*, which signal downstream of CD132, cause an autosomal recessive form of SCID affecting both females and males, with an identical lymphocyte phenotype as X-SCID.

The diagnosis of SCID can be established by the presence of a known pathogenic gene variant, low T-cell counts with proliferative response to the mitogen phytohemagglutinin (PHA) less than 10% of a normal control, or the identification of maternal T cells in the child. In male infants, this can be determined by fluorescence in situ hybridization (FISH) for the X and Y chromosomes.

Newborn Screening

Newborn screening for SCID has allowed the early diagnosis and treatment of SCID, improving the outcome of therapy and changing the natural history of the disease. Newborn screening is based on quantitative polymerase chain reaction (PCR) of T-cell receptor excision circles (TRECs), which are formed during V(D)J rearrangement of the variable region of the TCR chains. These TRECs do not replicate during cell division; they are thus present in most or all recent thymic emigrants but get diluted out as T cells divide in the periphery. The TREC assay identifies low numbers of recent thymic emigrants, which is not diagnostic of SCID, but raises suspicion to proceed with an evaluation of lymphocyte subsets and function followed by confirmation with genetic testing. Other diseases with low T-cell counts may also be identified by newborn screening and include 22Q11.2 deletion syndrome, Rac2 deficiency, trisomy 21, and idiopathic lymphopenia, which was not well appreciated until newborn screening was implemented. In many countries, kappa excision circles (KRECs), generated during B-cell development, are assayed simultaneously with TRECs allowing a larger number of types of SCID to be identified as well as allowing identification of infants with agammaglobulinemia.

TREATMENT

SCID is a true pediatric immunologic emergency. Unless immunologic reconstitution is achieved through hematopoietic stem cell transplantation (HSCT) or gene therapy, death usually occurs during the first year of life and almost invariably before 2 years of age. HSCT in the first 100 days of life or in an infant prior to infection is associated with a 95% survival rate. In patients with SCID, 92% have survived after T-cell–depleted parental marrow is given soon after birth when the infant is healthy, without pretransplant chemotherapy or posttransplant GVHD prophylaxis, although T-cell reconstitution is improved with pretransplant conditioning including reduced-intensity protocols.

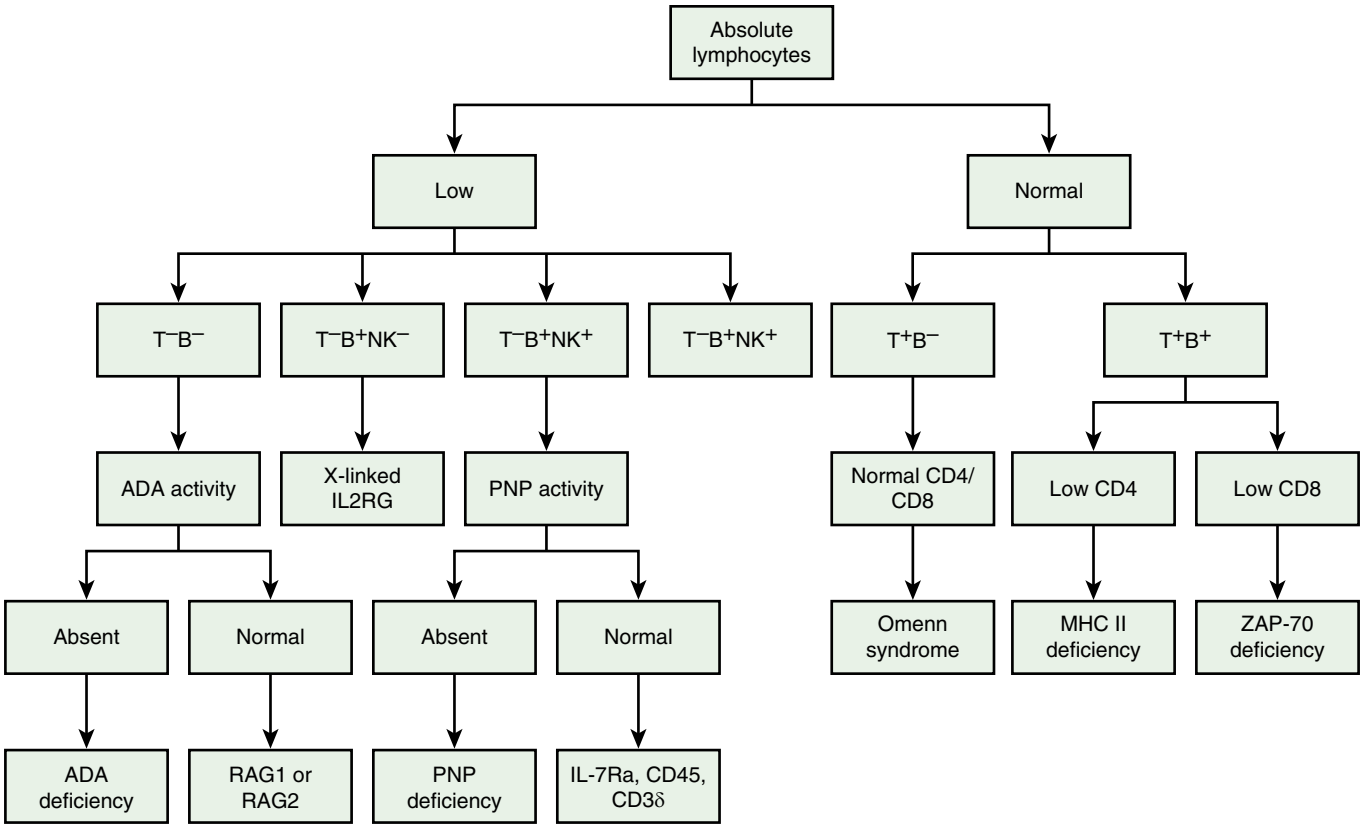

Fig. 165.4 Using the absolute lymphocytes count as a starting place to suggest the type of severe combined immunodeficiency (SCID) that may be present. ADA, Adenosine deaminase; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase. *(From Cunningham-Rundles C. Approach to the child with recurrent infections and molecular diagnosis. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig. 4.2.)*

Bone marrow transplantation remains the most important and effective therapy for SCID. In ADA-deficient and X-linked SCID, there has been success in correcting the immune defects with ex vivo gene transfer to autologous hematopoietic stem cells. Initial protocols of gene therapy for X-linked SCID resulted in **insertional mutagenesis** with the development of leukemic-like clonal T cells or lymphoma in some patients. Modification of the gene therapy protocol has greatly reduced the risk of insertional mutagenesis. ADA-deficient SCID can also be treated with enzyme replacement by repeated injections of polyethylene glycol-ADA (PEG-ADA), although the immune reconstitution achieved is not as effective as with HSCT or gene therapy. Until definitive therapy can be achieved, SCID patients should be treated with supportive care for prevention and treatment of infections with immunoglobulin replacement and microbial prophylaxis starting at 4-6 weeks of age including PJP prophylaxis as well as viral and fungal prophylaxis. Breastfeeding should be avoided if the mother is CMV or EBV positive as infection can be transmitted via breast milk.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

165.2 Combined Immunodeficiencies

Ramsay L. Fuleihan

Combined immunodeficiency (CID) is distinguished from SCID by the presence of low but not absent T-cell function. CID is a syndrome of diverse genetic causes and, therefore, diverse clinical and laboratory characteristics. Patients with CID may have recurrent or chronic pulmonary infections, opportunistic infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, gram-negative bacterial sepsis, urinary tract infections, or severe varicella in infancy. Although they usually survive longer than infants with SCID, patients with CID fail to thrive and often die before reaching adulthood. Neutropenia and eosinophilia are common. Serum immunoglobulins may be normal or elevated for all classes; selective IgA deficiency, marked elevation of IgE, and elevated IgM levels occur in some cases. Although antibody-forming capacity is impaired in most patients, it may not be absent.

Studies of cellular immune function may show lymphopenia, deficiencies of T cells, specific T-cell subsets, or switched memory B cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, or allogeneic cells in vitro. Peripheral lymphoid tissues may demonstrate paracortical lymphocyte depletion. The thymus is usually small, with a paucity of thymocytes and usually no Hassall's corpuscles.

There is a large number and variety of CIDs caused by pathogenic variants in many different genes. A list of known causes of CID with some of their characteristic features can be found in Tables 165.2 to 165.7.

COMBINED IMMUNODEFICIENCIES THAT ARE GENERALLY LESS PROFOUND THAN SCID

Several types of CID are characterized by a severe immunodeficiency but affected patients tend to survive longer than patients with SCID (see Table 165.2). These patients are susceptible to severe viral, opportunistic, and/or fungal infections. Their laboratory features are variable from normal lymphocyte subsets to a severe deficiency of CD4, CD8, or both cell types. Invariably, T-cell function is decreased but proliferative responses to mitogens and, in some cases, to antigens may be normal, making it difficult to have unifying laboratory characteristics for this group of diseases. The severity of clinical infection and/or the presence of a family history of CID should raise suspicion and initiate a laboratory evaluation for these diseases.

COMBINED IMMUNODEFICIENCY FROM DEFICIENCY IN CD4 T-CELL HELPER FUNCTION

CD4 T cells play an important role in orchestrating the immune response. Helper function from CD4 T cells is critical for immunoglobulin isotype switching, somatic hypermutation, and B-cell memory

Table 165.2 Combined Immunodeficiencies Generally Less Profound Than SCID

DISEASE (DEFICIENCY)	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
CD40 Ligand (CD154)	XL	Defective CD40 ligand:CD40 signaling	Opportunistic infections, neutropenia, biliary tract and liver disease/cancer, neuroectodermal cancer	HSCT
CD40	AR	Defective CD40 ligand:CD40 signaling	Opportunistic infections, neutropenia, biliary tract and liver disease	HSCT
ICOS	AR		Autoimmunity, gastroenteritis, granulomas	
ICOS Ligand	AR	Decreased T and B cells	Neutropenia	
CD3γ	AR	Low TCR expression	Autoimmunity of variable severity	
CD8	AR	Absent CD8 T cells	May be asymptomatic	
ZAP-70 LOF	AR	Low CD8 T cells, poor CD4 T-cell function	May have immune dysregulation, autoimmunity	HSCT
ZAP-70 LOF/GOF	AR	Low CD8 T cells	Severe autoimmunity, bullous pemphigoid, inflammatory colitis	HSCT
MHC class I (TAP1, TAP2, TAPBP, β_2-microglobulin)	AR	Low CD8 T cells, absent MHC I on lymphocytes and thymic epithelium	Vasculitis, pyoderma gangrenosum	
MHC class II (CIITA, RFX5, RFXANK, RFXAP)	AR	Low CD4 T cells absent MHC II on lymphocytes and thymic epithelium	Failure to thrive, liver biliary tract disease	HSCT
IKAROS	AD	No memory T cells or B cells	Opportunistic infections, early CID onset	
DOCK2	AR	Low T cells and poor NK cell function	Invasive herpesvirus infections, poor interferon responses	
Polymerase and (POLD1, POLD2)	AR	Low CD4 T cells	Skin infections, warts and molluscum, short stature, intellectual disability	
RHOH	AR	Restricted TCR repertoire	HPV infection, lung granulomas, molluscum, lymphoma	
STK4	AR	Low CD4 T cells	Intermittent neutropenia, viral and *Candida* infection, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease	
TCRα	AR	Absent TCRαβ	Immune dysregulation, autoimmunity, diarrhea	
LCK	AR	Poor TCR signaling, low CD4 T cells and low regulatory T cells, restricted TCR repertoire	Immune dysregulation, autoimmunity	
ITK	AR	Decreased T-cell activation, progressive decline in CD4 T cells	EBV-associated B-cell lymphoproliferation, immune dysregulation	
MALT1	AR	Poor T-cell proliferation		
CARD11 LOF	AR	Poor T-cell proliferation	Opportunistic infections	
BCL10	AR	Poor T-cell antigen or anti-CD3 proliferation, few memory T cells and Tregs	Candidiasis, gastroenteritis	
IL-21	AR	Low T-cell function, low memory/switched B cells	Opportunistic infections, liver disease	
IL-21R	AR	Low cytokine production, low T-cell antigen proliferation		
OX40	AR	Low Ag-specific memory CD4 T cells	Impaired immunity to HHV8, Kaposi's sarcoma	
IKBKB	AR	Impaired TCR activation, absent Treg and γ/δ T cells	Opportunistic infections	HSCT
NIK	AR	Poor T-cell antigen proliferation, low switched memory B cells	*Cryptosporidium* infection	
RelB	AR	Reduced TCR diversity with poor proliferation to mitogens and absent to antigens		

Continued

Table 165.2 Combined Immunodeficiencies Generally Less Profound Than SCID—cont'd

DISEASE (DEFICIENCY)	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
RelA haploinsufficiency	AD	Impaired NFκB activation with decreased inflammatory cytokines	Chronic mucocutaneous ulceration	
Moesin	XL	Defective T-cell migration and proliferation	Varicella infections, neutropenia	
TFRC	AR	Poor T-cell proliferation, low memory B cells	Neutropenia, thrombocytopenia	
c-Rel	AR	Poor T- and B-cell proliferation, low memory CD4 and low memory B cells	*Mycobacteria* and *Salmonella* infections, opportunistic infections, defective innate immunity	
FCHO1	AR	Poor T-cell proliferation	Mycobacterial infections, lymphoproliferation, failure to thrive	

Ag, antigen; AD, Autosomal dominant; AR, autosomal recessive; CID, combined immune deficiency; EBV, Epstein-Barr virus; HHV8, human herpesvirus-8; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; IL, interleukin; GOF, gain of function; LOF, loss of function; MHC, major histocompatibility complex; NK, natural killer; R, receptor; TCR, T-cell receptor; Treg, regulatory T cell; XL, X-linked.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.3 DNA Repair Defects Other Than Causing SCID

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Ataxia-telangiectasia	*ATM*	AR	Progressive decrease in T cells, poor T-cell proliferation	Ataxia, telangiectasia, elevated IgM, lymphoreticular malignancy, increased radiosensitivity, chromosomal instability and translocations	Ig replacement, supportive care, avoid ionizing radiation
Nijmegen breakage syndrome	*NBS1*	AR	Progressive decrease in T cells	Microcephaly, dysmorphic features, lymphomas and solid tumors, hyper-IgM	Ig replacement, supportive care, avoid ionizing radiation
Bloom syndrome	*BLM*	AR	Marrow failure, low Ig	Short stature, dysmorphic facies, sun-sensitive erythema, leukemia, lymphoma, chromosomal instability	Ig replacement, supportive care, avoid ionizing radiation
Immunodeficiency with centromeric instability and facial anomalies (ICF types 1, 2, 3, 4)	*DNMT3B* *ZBTB24* *CDCA7* *HELLS*	AR	Decreased T cells, decreased response to PHA, hypogammaglobulinemia with variable antibody deficiency	Facial dysmorphism, developmental delay, macroglossia, opportunistic infections, malabsorption, cytopenias, malignancies, multiradial configurations of chromosomes 1, 9, 16	Ig replacement, supportive care, avoid ionizing radiation
PMS2 deficiency	*PMS2*	AR	Low B cells, abnormal antibody responses	Café-au-lait spots, hyper-IgM, lymphoma, colorectal carcinoma, brain tumors	Ig replacement, supportive care, avoid ionizing radiation
Radiosensitivity, immune deficiency, dysmorphic features, learning difficulties (RIDDLE) syndrome	*RNF168*	AR	Low IgG or IgA	Short stature, mild defects of motor control to ataxia, may have learning difficulties	Ig replacement, supportive care, avoid ionizing radiation
MCM4 deficiency	*MCM4*	AR	Low number and function of NK cells	Short stature, B-cell lymphoma, adrenal failure	Supportive care, avoid ionizing radiation
Polymerase ε subunit 1 deficiency (FILS syndrome)	*POLE1*	AR	Decreased T-cell proliferation	Short stature, facial dysmorphism, livedo	Ig replacement, supportive care, avoid ionizing radiation

Continued

Table 165.3 DNA Repair Defects Other Than Causing SCID—cont'd

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Polymerase ε subunit 2 deficiency	*POLE2*	AR	Lymphopenia, absent T-cell proliferation to Ags, hypogammaglobulinemia	Disseminated BCG, autoimmunity (type 1 diabetes), hypothyroidism, facial dysmorphism	Ig replacement, supportive care, avoid ionizing radiation
Ligase 1 deficiency	*LIG1*	AR	Lymphopenia, increased γ/δ T cells, decreased T-cell proliferation, hypogammaglobulinemia antibody deficiency	Growth restriction, sun sensitivity, radiation sensitivity, macrocytic RBC	Ig replacement, supportive care, avoid ionizing radiation
NSMCE3 deficiency	*NSMCE3*	AR	Decreased T cells and T-cell response to mitogens and antigens	Thymic hypoplasia, severe lung disease, chromosomal breakage, radiation sensitivity	Ig replacement, supportive care, avoid ionizing radiation
ERCC6L2 deficiency	*ERCC6L2*	AR	Lymphopenia	Facial dysmorphism, microcephaly, bone marrow failure	Supportive care, avoid ionizing radiation
GINS1 deficiency	*GINS1*	AR	Low NK cells, high IgA with low IgM and IgG	Neutropenia, IUGR	Supportive care, avoid ionizing radiation

Ag, Antigen; AR, Autosomal recessive; BCG, bacilli Calmette-Guérin; FILS, facial dysmorphism, immunodeficiency, livedo, and short stature; ICF, instability, centromeric, facial anomalies; Ig, immunoglobulin; IUGR, intrauterine growth retardation; NK, natural killer; PHA, phytohemagglutinin; RBC, red blood cell.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.4 Immunoosseous Dysplasias

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Cartilage hair hypoplasia	*RMRP*	AR	Normal to severely decreased T-cell counts Decreased T-cell proliferation	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	HSCT for the immunodeficiency
Schimke immuno-osseous dysplasia	*SMARCAL1*	AR	Decreased T cells	Short stature, spondyloepiphyseal dysplasia, intrauterine growth restriction; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure	HSCT for the immunodeficiency
MYSM1 deficiency	*MYSM1*	AR	Decreased T cells, naïve T cells, and NK cells B-cell deficiency with hypogammaglobulinemia	Short stature; recurrent infections; congenital bone marrow failure, myelodysplasia; immunodeficiency affecting B cells and granulocytes; skeletal anomalies; cataracts; developmental delay	HSCT for the immunodeficiency
MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	AR	Decreased NK cell function Decreased total and memory B cells Hypogammaglobulinemia, variably decreased specific antibodies	Recurrent bacterial infections; lymphadenopathy; spondyloepiphyseal dysplasia, extreme intrauterine growth restriction; retinal dystrophy; facial dysmorphism; may present with microcephaly; short stature	HSCT for the immunodeficiency
Immunoskeletal dysplasia with neurodevelopmental abnormalities (*EXTL3* deficiency)	*EXTL3*	AR	Decreased T cells, decreased to normal Ig levels	Short stature; cervical spinal stenosis, neurodevelopmental impairment; eosinophilia; may have early infant mortality	HSCT for the immunodeficiency

AR, Autosomal recessive; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; NK, natural killer; SCID, severe combined immune deficiency.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.5 Other Combined Immunodeficiencies

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
PNP deficiency	*PNP*	AR	Progressive decrease in T cells	Autoimmune hemolytic anemia, neurologic impairment	HSCT
Immunodeficiency with multiple intestinal atresias	*TTC7A*	AR	Variable T-cell counts but may be as low as SCID with low TRECs at NBS	Multiple intestinal atresias, intrauterine polyhydramnios, early demise, bacterial (sepsis), viral and fungal infections	HSCT for severe T-cell deficiency
Trichohepatoenteric syndrome (THES)	*TTC37* *SKIV2L*	AR	Impaired IFNγ production, variably low switched memory B cells, hypogammaglobulinemia, may have low antibody responses	Respiratory infections; IUGR; facial dysmorphic features, wooly hair; early-onset intractable diarrhea, liver cirrhosis; platelet abnormalities	
Hepatic venoocclusive disease with immunodeficiency (VODI)	*SP110*	AR	Decreased memory T and B cells; low IgG, IgA, and IgM; absent germinal centers and tissue plasma cells	Hepatic venoocclusive disease Susceptibility to opportunistic infections: PJP, CMV, *Candida* Thrombocytopenia, hepatosplenomegaly, cerebrospinal leukodystrophy	
BCL11B deficiency	*BCL11B*	AD	Decreased T-cell counts with poor proliferation	Congenital abnormalities, neonatal teeth, dysmorphic facies; absent corpus callosum, neurocognitive deficits	
EPG5 deficiency (Vici syndrome)	*EPG5*	AR	Very low CD4 T cells, decreased Ig levels especially IgG2, defective B cells	Chronic mucocutaneous candidiasis, recurrent infections, agenesis of the corpus callosum, microcephaly, cataracts; cardiomyopathy, skin hypopigmentation, intellectual disability	
HOIL1 deficiency	*RBCK1*	AR	Decreased memory B cells with poor antibody response to polysaccharide antigens	Bacterial infections, autoinflammation, amylopectinosis	
HOIP deficiency	*RNF31*	AR	Decreased memory B cells with decreased Ig levels	Bacterial infections, autoinflammation, amylopectinosis, lymphangiectasia	
Hennekam lymphangiectasia-lymphedema syndrome	*CCBE1 FAT4*	AR	Variably decreased T- and B-cell counts, decreased Ig levels	Facial anomalies and other dysmorphic features, lymphangiectasia and lymphedema	
Activating de novo mutations in nuclear factor, erythroid 2-like (NFE2L2)	*NFE2L2*	AD	Decreased switched memory B cells, hypogammaglobulinemia and decreased antibody responses	Recurrent respiratory and skin infections; growth restriction, developmental delay; white matter cerebral lesions; increased level of homocysteine; increased expression of stress response genes	
STAT5b deficiency	*STAT5B*	AR	Slightly decreased T cells, decreased Treg number and function, hypogammaglobulinemia with elevated IgE	Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity	
STAT5b deficiency	*STAT5B*	AD (dominant negative variants)	Increased IgE	Growth failure, eczema, lack immune defects of AR STAT5b deficiency	
Kabuki syndrome (type 1 and 2)	*KMT2D* *KDM6A*	AD XL (females may be affected)	Low IgA, occasionally low IgG	Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature; intellectual disability; congenital heart defects; recurrent infections (otitis media, pneumonia); autoimmunity	

Continued

Table 165.5 Other Combined Immunodeficiencies—cont'd

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
KMT2A deficiency (Wiedemann-Steiner syndrome)	*KMT2A*	AD	Decreased memory B cells, hypogammaglobulinemia with decreased antibody responses	Respiratory infections; short stature; hypertelorism; hairy elbows; developmental delay, intellectual disability	

AD, Autosomal dominant; AR, Autosomal recessive; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IFN, interferon; Ig, immunoglobulin; IUGR, intrauterine growth retardation; NBS, newborn screening; PJP, *Pneumocystis jiroveci*; PNP, purine nucleoside phosphorylase; SCID, severe combined immune deficiency; TREC, T-cell receptor excision circle; Treg, regulatory T cells; XL, X-linked.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.6 Thymic Disorders

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
DiGeorge/Velocardio-facial syndrome/ chromosome 22Q11.2 deletion syndrome *TBX1* deficiency	22Q11.2del including *TBX1, TBX1* Unknown	AD (Unknown defects are sporadic)	Variable T-cell counts, may have low TRECs at NBS, may have hypogammaglobulinemia	Conotruncal cardiac defects, hypoparathyroidism, abnormal facies, velopalatal insufficiency, intellectual disability, autoimmunity	Thymic transplant for severe T-cell deficiency
CHARGE syndrome	*CHD7* *SEMA3E* Unknown	AD AD	Variable T-cell counts, may have low TRECs at NBS, may have hypogammaglobulinemia	Coloboma of eye; heart anomaly; choanal atresia; intellectual disability; genital and ear anomalies (CHARGE), CNS malformation	Thymic transplant for severe T-cell deficiency
Winged helix nude *FOXN1* deficiency	*FOXN1*	AR	Very low T cells, decreased Ig levels	Severe infections, abnormal thymic epithelium, congenital alopecia, nail dystrophy, neural tube defect	Thymic transplant attempted
FOXN1 haploinsufficiency	*FOXN1*	AD	Severe T-cell lymphopenia at birth, normal by adulthood	Recurrent, viral and bacterial respiratory tract infections; (eczema, dermatitis), nail dystrophy	
Chromosome 10p13-p14 deletion syndrome (10p13-p14DS)	10p13-p14del	AD	T-cell lymphopenia rarely with decreased proliferation to mitogens and antigens, may have hypoplastic thymus	Hypoparathyroidism, renal disease, deafness, growth retardation, facial dysmorphism, cardiac defects may be present, may have recurrent infections	
Chromosome 11q deletion syndrome (Jacobsen syndrome)	11q23del	AD	T-, B-, and NK cell lymphopenia, low switched memory B cells, variable Ig levels and antibody responses	Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation	Ig replacement for antibody deficiency
PAX1	*PAX1*	AR	Absent thymus	Omenn-like syndrome	HSCT attempted, thymic transplantation attempted

AD, Autosomal dominant; AR, Autosomal recessive; del, deletion; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; TREC, T-cell receptor excision circle; NBS, newborn screening; Ig, immunoglobulin.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.7 Hyper IgE Syndromes

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
HIE (Job syndrome)	*STAT3*	AD (DN LOF)	Decreased response to *STAT3*-activating cytokines; decreased Th17, T follicular helper, MAIT, NKT cells, reduced memory B cells, elevated IgE	Coarse facial features, broad nasal bridge; staphylococcal abscesses, eczema, pneumatoceles, pulmonary *Aspergillus,* PJP, mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retained primary teeth; coronary and cerebral aneurysms	Bacterial and fungal prophylaxis
DOCK8 deficiency	*DOCK8*	AR	T-cell lymphopenia with poor proliferation, few Tregs with poor function, reduced MAIT and NKT cells, very high IgE	Low NK cells with poor function Eosinophilia, recurrent infections, cutaneous viral, fungal and staphylococcal infections, severe atopy/allergic disease, cancer diathesis	HSCT
IL-6 receptor deficiency	*IL6R*	AR	Decreased switched memory B cells, very high IgE	Recurrent pyogenic infections, cold abscesses, elevated IL-6 levels	Bacterial prophylaxis
IL-6 signal transducer (IL6ST) deficiency	*IL6ST*	AR	Decreased Th17 cells, reduced memory B cells, high IgE, variable antibody responses	Bacterial infections, abscesses, eczema, pulmonary abscesses, pneumatoceles; bone fractures; scoliosis; retention of primary teeth; craniosynostosis	Bacterial prophylaxis
IL6ST	*IL6ST*	AD (DN)	Increased Th2, naïve T cells, low memory T and B cells, low to normal NK cell counts, elevated IgE with normal or low IgG	Similar to AD HIE syndrome: dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiectasis, pneumatoceles, pulmonary aspergillosis, connective tissue defects (scoliosis, face, joints, fractures, palate, tooth retention)	Bacterial and fungal prophylaxis
IL6ST	*IL6ST*	AR (LOF)	Death in utero or in neonatal period	Fatal Stuve-Wiedemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia, dermatitis, eczema, defective acute phase response, complete unresponsiveness to IL-6 family cytokines	None
ZNF341 deficiency	*ZNF341*	AR	Decreased Th17 and NK cells, reduced memory B cells, decreased response to *STAT3*-activating cytokines	Similar to AD-HIE: mild facial dysmorphism; early-onset eczema, mucocutaneous candidiasis, bacterial skin infections, *Staphylococcus aureus* abscesses, recurrent bacterial respiratory infections, pneumatoceles; hyperextensible joints; bone fractures and retention of primary teeth	Bacterial and fungal prophylaxis
ERBIN deficiency	*ERBB2IP*	AD	Increased Treg, moderate increased IgE	Susceptibility to *S. aureus,* eczema, recurrent respiratory infections, hyperextensible joints, scoliosis, arterial dilatation in some patients	Bacterial prophylaxis
Loeys-Dietz syndrome	*TGFBR1, TGFBR2*	AD	Elevated IgE	Recurrent respiratory infections; eczema, food allergies; hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurysms	Bacterial prophylaxis
Comèl-Netherton syndrome	*SPINK5*	AR	Low memory B cells, elevated IgE and IgA, variable antibody responses	Congenital ichthyosis, bamboo hair, atopic diathesis, bacterial infections, failure to thrive	Bacterial prophylaxis; Ig replacement for antibody deficiency
PGM3 deficiency	*PGM3*	AR	May have low T cells, B cells, memory B cells, normal or elevated IgG, IgA, and high IgE, eosinophilia	Severe atopy; autoimmunity; bacterial and viral infections; short stature, brachydactyly, dysmorphic facial features; intellectual disability and cognitive impairment, delayed CNS myelination in some patients	
CARD11 deficiency	*CARD11 DN LOF*	AD	Defective T-cell activation and proliferation, high IgE, Th2 skewing, poor specific antibody production, impaired activation of the NF-κB and mTORC1 pathways	Variable atopy, eczema, food allergy, eosinophilia; cutaneous viral infections, recurrent respiratory infections; lymphoma; CID	Ig replacement for antibody deficiency

AD, Autosomal dominant; AR, Autosomal recessive; CID, combined immunodeficiency; CNS, central nervous system; DN, dominant negative; HIE, hyper-IgE; Ig, immunoglobulin; IL, interleukin; IL6ST, gp130 common signal transducer of the IL-6 cytokine family; LOF, loss of function; MAIT, mucosal-associated invariant T cells; NKT, natural killer T cells; PJP, *Pneumocystis jiroveci*; Th, T helper; Treg, regulatory T cells.

Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

formation as well as helping macrophages kill intracellular pathogens. In addition, patients with poor or absent CD4 T-cell helper function are susceptible to opportunistic infection. The consequences of defects in CD40 ligand and CD40 highlight the role CD4 T-cell–dependent helper function plays in immunity.

CD40 LIGAND AND CD40 DEFICIENCY

CD40 ligand (CD154) deficiency (X-linked) and similarly, CD40 deficiency (autosomal recessive), cause a severe form of **hyper-IgM syndrome** that is a CID.

Genetics and Pathogenesis

Pathogenic variants in the CD40 ligand or CD40 genes, disrupt the interaction between CD4 T cells and antigen-presenting cells (APCs): dendritic cells, monocytes/macrophages, and B cells. CD40 ligand is expressed on activated CD4 T cells and delivers signals to APC via CD40 to stimulate expression of co-stimulatory molecules that help T-cell activation and differentiation, immunoglobulin isotype switching and somatic hypermutation in B cells as well as memory B-cell development, and signals to macrophages to kill intracellular pathogens. Therefore disruption of the CD40 signaling pathway affects several key elements of the adaptive immune response leading to a CID disease characterized by failure of immunoglobulin isotype switching, a process important for synthesis of IgG, IgA, and IgE antibodies; failure of somatic hypermutation, a process by which B cells generate antibodies of higher affinity; and absent B-cell memory, susceptibility to opportunistic infections including PJP, and *Cryptosporidium* and enhanced susceptibility to some cancers especially of the liver or of neuroectodermal origin.

Clinical Manifestations

Recurrent and opportunistic infections usually develop in the first year of life. About half the patients present with PJP pneumonia. Recurrent bacterial sinopulmonary infections are also common as well as *Cryptosporidium* infection and sclerosing cholangitis. Chronic or recurrent neutropenia is also a feature of this disease, although the pathogenesis of neutropenia is not well known. Patients have a higher susceptibility to cancer of the liver or biliary tree as well as primitive neuroectodermal carcinoma, which usually develop after the first 10 years of life. Few patients survive beyond 30 years of age. Some patients with milder genetic variations present in adolescence with parvovirus-induced aplastic anemia.

Diagnosis

Serum immunoglobulin levels show very low or absent IgG, IgA, and IgE, with normal or elevated IgM. Some patients have normal serum IgA levels, likely the result of a non–CD40-dependent isotype switching mechanism. The term hyper-IgM is a misnomer because most patients are identified before they have elevation of serum IgM levels. Lymphocyte subsets as well as lymphocyte proliferation to mitogens are usually normal. Characteristically, there is an absence or paucity of switched memory B cells. Patients may or may not have neutropenia, which can be severe. Flow cytometry for expression of CD40 on resting B cells or CD40 ligand on activated T cells can identify patients with these defects. Staining for CD40 ligand expression with soluble CD40 will identify all CD40 ligand variants that prevent binding to CD40. Gene sequencing of CD40 and CD40 ligand can be done separately or within a larger PID gene panel with known pathogenic variants confirming the disease.

Treatment

Patients should be treated with immunoglobulin replacement therapy and PJP prophylaxis as soon as the diagnosis is suspected. Attention to hygiene and clean drinking water as well as avoiding swimming in lakes will help prevent exposure to opportunistic organisms such as *Cryptosporidium*. HSCT can be curative and is recommended if the patient has a matched related or unrelated donor. Outcomes after stem cell transplantation have a trend toward improved survival and a reduced risk for cancer and improved quality of life.

MHC CLASS II DEFICIENCY AND OTHER CAUSES OF CD4 T-CELL DEFICIENCY

MHC class I and II molecules play an important role in T-cell development and function by presenting a peptide fragment from a pathogen-derived protein to the TCR of CD8 or CD4 T cells, respectively. MHC class II molecules are required for processing and presentation of peptides derived from exogenous antigens to CD4 T cells and for positive selection of CD4 T cells in the thymus. Therefore MHC class II deficiency is a severe form of **bare lymphocyte syndrome** resulting in decreased CD4 T cells and impairment in their function.

Clinical Manifestations

Patients with low, or occasionally normal, CD4 T-cell numbers from MHC class II deficiency are susceptible to bacterial, viral, fungal, and opportunistic infections. Patients usually present in the first year of life with respiratory infections, chronic diarrhea, and failure to thrive. *Cryptosporidium* infections may be associated with sclerosing cholangitis and liver failure.

Genetics and Pathogenesis

MHC class II deficiency results from defects in genes encoding for transcription factors necessary for expression of MHC class II molecules from the HLA-DR, HLA-DP, and HLA-DQ loci including CIITA, RFXANK, RFX5, and RFXAP, which explains the concomitant loss of expression from all three loci.

Diagnosis

Immunodeficiencies with MHC class II deficiency can be identified by absent or low CD4 T cells on lymphocyte phenotyping by flow cytometry and absent MHC class II molecules. In some cases, CD8 T-cell numbers are also decreased. Lymphocyte proliferation to mitogens is normal but absent in response to antigens.

Treatment

The prognosis for MHC class II deficiency is poor with most patients dying in the first decade of life. HSCT has been performed and improves CD4 T-cell proliferation but not numbers because it does not correct the expression of MHC class II molecules on thymic epithelial cells. The outcome of HSCT in MHC class II deficiency is not as good as in SCID and other severe immunodeficiency diseases.

MHC CLASS I DEFICIENCY AND OTHER CAUSES OF CD8 T-CELL DEFICIENCY

MHC class I molecules play an important role in T-cell development and function by presenting a peptide fragment from an intracellular pathogen, such as viruses, or cancer-derived proteins to the TCR of CD8 T cells. In the thymus, MHC class I molecules provide the positive selection signal for thymocytes to develop into CD8 T cells. Therefore the absence of MHC class I molecules in the thymus (and on all nucleated cells) is associated with very low or absent CD8 T cells. There are several other pathogenic gene variants that cause a deficiency in CD8 T cells.

Genetics and Pathogenesis

MHC class I deficiency results from pathogenic variants in the transporter associated with antigen processing (TAP) 1 or 2, TAP binding protein, or β_2-microglobulin genes. The TAP proteins play an important role in allowing the expression of MHC class I molecules on the surface of all nucleated cells and β_2-microglobulin associates with MHC class I molecules on the surface of cells.

Clinical Manifestations

Patients with low CD8 T cells from MHC class I deficiency may be asymptomatic in some cases but may present with chronic respiratory infections including bronchiectasis and granulomatous skin ulcers.

Diagnosis

Immunodeficiency patients with MHC class I deficiency can be identified by absent or low CD8 T cells on lymphocyte phenotyping by flow

cytometry and absent MHC class I molecules. Lymphocyte proliferation is normal.

Treatment
MHC class I deficiency is treated with supportive therapy and avoidance of immunosuppression if possible.

OTHER FORMS OF CD8 DEFICIENCY
CD8 α Gene Defects
CD8 deficiency also results from pathogenic variants in the CD8 α gene. Patients are susceptible to bacterial and viral respiratory infections. CD8 T-cell numbers are low and there is an increase in CD4- CD8- T cells. Lymphocyte proliferation is normal. CD8 α deficiency is also treated with supportive therapy and avoidance of immunosuppression if possible.

Defects in the Zeta-Associated Protein 70
The zeta-associated protein (ZAP-70) is a severe immunodeficiency similar to SCID with absent or very low numbers of CD8 T cells. Although CD4 T cells develop in adequate numbers, they are defective in proliferation and function. Patients with ZAP-70 deficiency are susceptible to all types of infection including opportunistic infections, disseminated varicella, and mucocutaneous candidiasis with failure to thrive and diarrhea. The diagnosis of ZAP-70 deficiency can be made by low CD8 T-cell counts and deficient T-cell proliferation to mitogens that can be rescued by bypassing ZAP-70 signaling with phorbol ester and ionomycin, helping confirm that the defect is in the proximal signaling pathway in T cells. The diagnosis is confirmed by identification of a homozygous or combined heterozygous pathogenic variant in the ZAP-70 gene. Treatment of ZAP-70 deficiency requires HSCT. Immunoglobulin replacement and microbial prophylaxis should be initiated until immune reconstitution after HSCT is achieved.

COMBINED IMMUNODEFICIENCIES WITH CONGENITAL THROMBOCYTOPENIA
Wiskott-Aldrich Syndrome
Wiskott-Aldrich syndrome (WAS) is an X-linked recessive disorder characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and susceptibility to infection.

Genetics and Pathogenesis
The Wiskott-Aldrich syndrome protein (WASP) controls the assembly of actin filaments required for cell migration and cell-cell interactions. Specific pathogenic variants in the WASP gene cause X-linked thrombocytopenia (XLT) without immunodeficiency and gain-of-function variants cause X-linked severe congenital neutropenia. A similar phenotype to WAS occurs with pathogenic variants in the WASP interactive Protein (WIP) that is an autosomal recessive disease affecting both females and males.

Clinical Manifestations
Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not caused initially by antiplatelet antibodies, although autoimmunity may develop later in life. **Atopic dermatitis** and **recurrent infections** usually develop during the first year of life. *Streptococcus pneumoniae* and other bacteria having polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later, infections with agents such as *P. jiroveci* and the herpesviruses become more frequent. Infections, bleeding, and EBV-associated malignancies are major causes of death.

Diagnosis
The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed. The presence of low numbers of platelets that are small in size is typical. Immunologically, patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or greatly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. In addition, antibody responses to protein and conjugate vaccines may also be diminished.

Treatment
Good supportive care includes appropriate nutrition, immunoglobulin replacement, use of killed vaccines, and aggressive management of eczema and associated cutaneous infections. Because of their profound antibody deficiency, these patients should be given immunoglobulin replacement regardless of their serum levels of the different immunoglobulin isotypes. HSCT is the treatment of choice when a high-quality matched donor is available and is usually curative. Gene therapy has resulted in sustained benefits in several patients. As in X-SCID, early trials of gene therapy were associated with the development of malignancy.

In addition to WAS and WIP deficiency, there is a third cause of immunodeficiency with thrombocytopenia from pathogenic variants in the *ARPC1B* gene affecting Arp2/3-mediated filament branching presenting with mild thrombocytopenia but normal-sized platelets and recurrent infections. Patients have high IgA and IgE as in WAS.

DNA REPAIR DEFECTS OTHER THAN THOSE CAUSING SCID
DNA repair plays an important role during lymphocyte development and differentiation including V(D)J recombination and immunoglobulin isotype switching. Therefore defects in DNA repair enzyme are frequently associated with CID and many have other characteristic features to identify them (see Table 165.3).

ATAXIA-TELANGIECTASIA
Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.

Genetics and Pathogenesis
The ataxia-telangiectasia pathogenic variant *(ATM)* gene encodes a protein critical for responses to DNA damage. Cells from patients, as well as from heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. Percentages of CD3 and CD4 T cells are moderately reduced, with normal or increased percentages of CD8 T cells and elevated numbers of γ/δ T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall's corpuscles.

Clinical Manifestations
The most prominent clinical features are progressive cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, a high incidence of malignancy, and variable humoral and cellular immunodeficiency. Ataxia typically becomes evident soon after these children begin to walk and progresses until they are confined to a wheelchair, usually by age 10-12 years. The telangiectasias begin to develop at 3-6 years of age, contributing to a delay in diagnosis. Recurrent sinopulmonary infections occur in approximately 80% of patients. Although common viral infections have not usually resulted in untoward sequelae, fatal varicella has occurred. The malignancies associated with ataxia-telangiectasia are usually of the lymphoreticular type, but adenocarcinomas also occur. Carriers of pathogenic variants have an increased incidence of malignancy.

Diagnosis
Patients have elevated serum α-fetoprotein levels. The most frequent humoral immunologic abnormality is the selective absence of IgA, which occurs in 50–80% of these patients. IgG2 or total IgG levels may be decreased, and specific antibody levels may be decreased or normal. Some patients have an elevated serum IgM level. Identification of homozygous or compound heterozygous pathogenic variants in the *ATM* gene confirms the diagnosis.

Treatment
Therapy in ataxia-telangiectasia is supportive but includes immunoglobulin replacement and avoidance of ionizing radiation unless absolutely necessary to establish a clinical diagnosis and initiate appropriate treatment.

Immunoosseous Dysplasias
Immunoosseous dysplasias are a group of combined immune deficiency diseases affecting bone development as well as T-cell development or function. They are characterized by skeletal abnormalities and recurrent infections (see Table 165.4).

CARTILAGE-HAIR HYPOPLASIA
Cartilage-hair hypoplasia (CHH) is an unusual form of **metaphyseal dysplasia** with frequent and severe infections. It occurs with a high frequency among the Amish and Finnish people (Chapter 741).

Genetics and Pathogenesis
CHH is an autosomal recessive condition. Numerous pathogenic variants that cosegregate with the CHH phenotype have been identified in the untranslated RNase MRP *(RMRP)* gene. The RMRP endoribonuclease consists of an RNA molecule bound to several proteins and has at least two functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of pre-RNA. Defects in *RMRP* cause CHH by disrupting a function of *RMRP* RNA that affects multiple organ systems. In vitro studies show decreased numbers of T cells and defective T-cell proliferation because of an intrinsic defect related to the G1 phase, resulting in a longer cell cycle for individual cells. NK cells are increased in number and function.

Clinical Manifestations
Clinical features include short, pudgy hands; redundant skin; hyperextensible joints of hands and feet but an inability to extend the elbows completely; and fine, sparse, light hair and eyebrows. Infections range from mild to severe (Fig. 165.5). Associated conditions include deficient erythrogenesis, Hirschsprung disease, and an increased risk of malignancies. The bones radiographically show scalloping and sclerotic or cystic changes in the metaphysis and flaring of the costochondral junctions of the ribs.

Diagnosis
The diagnosis of CHH is suspected by the clinical constellation of skeletal dysplasia and immune deficiency and supporting laboratory findings. Homozygous or compound heterozygous pathogenic variants in the *RMRP* gene confirms the diagnosis.

Treatment
Treatment of CHH is supportive. Some patients have been treated with HSCT, which will correct the T-cell immunodeficiency and erythrogenesis but will not affect other organ systems.

ANHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNODEFICIENCY
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) is a CID characterized by susceptibility to infection, thin sparse hair, abnormal dentition (conical teeth), and absence of salivary gland (Chapter 690).

Genetics and Pathogenesis
X-linked EDA-ID results from hypomorphic gene variants in the *IKKγ* gene that encodes the NF-κB essential modulator **(NEMO)**. Complete loss-of-function (LOF) variants are deleterious early in embryogenesis. Carriers of LOF variants have features of incontinentia pigmenti. NEMO is a member of the IKK complex that phosphorylates the inhibitor of NF-κB (IκB), which then allows NF-κB to translocate to the nucleus and turn on gene expression. In lymphocytes, NF-κB is involved in signaling via the antigen receptors, the tumor necrosis factor (TNF) receptor family, and toll-like receptors as well as the interleukin (IL)-1 receptor. Defects in NEMO affect both the innate and adaptive immune systems and can be severe. Autosomal dominant gain-of-function variants in IκBα also result in a similar phenotype



Fig. 165.5 Metaphyseal dysplasia, McKusick type. Note the fine, sparse hair and short limbs. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation. 8th ed. Philadelphia: Elsevier; 2022. Fig.1, p. 529.)*

that affects both females and males as well as gain-of-function variants in IKBKB. The latter is also associated with recurrent bacterial, viral, and fungal infections, but the ectodermal defects are variable.

Clinical Manifestations
Patients with EDA-ID suffer from recurrent and severe infections from gram-positive and gram-negative bacteria, mycobacteria, viruses, and fungi. Patients have thin sparse hair and conical teeth and may have colitis. More severe variants may be associated with osteopetrosis and lymphedema; their disease is termed OL-EDA-ID (osteopetrosis, lymphedema, EDA-ID).

Diagnosis
The diagnosis can be suspected from the clinical features of anhidrosis, ectodermal dysplasia, and recurrent infections. Patients frequently present with hypogammaglobulinemia as in the hyper-IgM syndrome because CD40 signaling involves NF-κB, with elevated IgM in some patients. Most if not all patients have poor NK cell function. The diagnosis can be confirmed by identification of hypomorphic variants in the *IKKγ* gene or gain-of-function variants in the *IκBα* gene.

Treatment
Patients are usually treated with immunoglobulin replacement and close monitoring. The outcome is dependent on the severity of the phenotype. HSCT has been successful in some patients, but it may not correct the colitis or other features of the disease.

Calcium Channel Defects
Calcium signaling plays an important role in T-cell activation, where initially calcium is released from the endoplasmic reticulum into the cytoplasm, which is sensed by STIM1 that in turn activates calcium release activated channels (CRACs), which are made up of the pore-forming subunit ORAI-1, to bring in additional calcium from outside the cell. Intracellular calcium activates calcium-dependent enzymes including calcineurin, which activates the nuclear factor of activated T cells (NFAT), which

translocates to the nucleus and activates gene transcription including IL-2 and the CD40 ligand. Pathogenic variants in *ORAI-1* or *STIM1* result in a CID associated with hypotonia because calcium is also important for muscle function.

Clinical Manifestations

Patients with calcium channel defects have recurrent and severe infections with bacteria, viruses, and fungi. They typically have pneumonia but may present with a variety of infections including BCG lymphadenitis, chronic rotavirus diarrhea, and mucocutaneous candidiasis. They may also present with failure to thrive, ectodermal dysplasia defective dental enamel, and mydriasis. Patients also have a nonprogressive hypotonia.

Diagnosis

Patients have normal numbers of T cells, but the T cells have decreased or have absent proliferation to mitogens, antigens, or anti-CD3. Although serum immunoglobulins are normal or increased, specific antibody levels are diminished and NK cell function may also be decreased as B cells and NK cells also depend on calcium signaling for their activation. The clinical features and laboratory test results are similar for both *ORA-1* and *STIM1* deficiency. Therefore genetic testing is required to identify the specific pathogenic variants, which will aid in genetic counseling and prenatal diagnosis.

Treatment

HSCT is the optimal treatment for the immunodeficiency; however, it does not correct the hypotonia, which may contribute to recurrent pneumonia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

165.3 Thymic Disorders

Ramsay L. Fuleihan

The thymus is the organ where T-cell development occurs and central T-cell tolerance to self-proteins develops by negative selection of self-reactive thymocytes or development of regulatory T cells. Defects in thymic development affect T-cell development causing a variable degree of T-cell immunodeficiency and are associated with higher risk for the development of autoimmunity.

DIGEORGE/VELOCARDIOFACIAL SYNDROME/ CHROMOSOME 22Q11.2 DELETION SYNDROME (22Q11.2DS)

Chromosome 22q11.2 deletion syndrome is the most common of the T-cell disorders, occurring in about 1 in 3,000 births in the United States. Chromosome 22q11.2 deletions disrupt development of the third and fourth pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and posteriorly rotated ears (see Chapter 99) (Fig. 165.6). With advanced fetal ultrasound and fetal echocardiography, the diagnosis is often identified prenatally. Other patients may be identified by low TREC counts on newborn screening for SCID or sometimes by the development of hypocalcemic seizures during the neonatal period.

Genetics and Pathogenesis

Chromosome 22q11.2 deletions occur with high frequency because complex repeat sequences that flank the region represent a challenge for DNA polymerase. This condition is inherited in an autosomal dominant fashion and occurs with comparable frequency in all populations. Within the deleted region, haplosufficiency for the TBX1 transcription factor appears to underlie the majority of the phenotype. The phenotype is highly variable; a subset of patients has a phenotype that has also been called **DiGeorge syndrome**, **velocardiofacial syndrome**, or **conotruncal anomaly face syndrome**.



Fig. 165.6 Typical facial appearance of a child with DiGeorge syndrome. Notice the microstomia, hypertelorism, upturned nose, and posteriorly rotated and small, low-set ears. *(From Chinn IK, Chinen J, Shearer WT. Primary immunodeficiency diseases. In: Cherry JD, Harrison GJ, Kaplan SL, et al., eds. Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 8th ed. Philadelphia: Elsevier; 2019. Fig. 67.1, p. 641.)*

Variable hypoplasia of the thymus occurs in 75% of the patients with the deletion, which is more frequent than total aplasia; aplasia is present in <1% of patients with 22q11.2 deletion syndrome. Slightly less than half of patients with complete thymic aplasia are hemizygous at chromosome 22q11.2. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately 30% of infants with complete DiGeorge syndrome have **CHARGE association** (*c*oloboma, *h*eart defect, choanal *a*tresia, growth or developmental *r*etardation, *g*enital hypoplasia, and *e*ar anomalies including deafness). Pathogenic variants in the chromodomain helicase DNA-binding protein 7 *(CHD7)* gene on chromosome 8q12.2 are found in approximately 60–65% of individuals with CHARGE syndrome; some have pathogenic variants in *SEMA3E*.

Clinical Manifestations

Children with partial thymic *hypoplasia* may have little trouble with infections and grow normally. Patients with thymic *aplasia* (complete DiGeorge syndrome) resemble patients with SCID in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and *P. jiroveci*, and to GVHD from nonirradiated blood transfusions. Patients with thymic aplasia can develop an atypical phenotype in which oligoclonal T-cell populations appear in the blood associated with rash and lymphadenopathy. These atypical patients appear phenotypically similar to patients with **Omenn syndrome** or maternal T-lymphocyte engraftment.

It is critical to ascertain in a timely manner whether an infant has thymic aplasia, because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, and conotruncal cardiac anomalies with syndromic features. Some but not all infants are identified by newborn screening for SCID and when 22q11.2 deletion is suspected, a calcium level should be obtained at the time of T-cell evaluation. The three manifestations with the highest morbidity in early infancy are profound immunodeficiency, severe cardiac anomaly, and seizures from hypocalcemia. Thus an early focus on these concerns is warranted even before the diagnosis is confirmed. Affected patients may also develop autoimmune cytopenias, juvenile idiopathic arthritis, atopy, and malignancies (lymphomas).

Diagnosis

The clinical features of DiGeorge/CHARGE/22Q11.2DS will help in establishing the diagnosis, but there is a wide variety of clinical phenotypes. In most patients, absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Immunoglobulin levels are often normal, but there is an increased frequency of IgA deficiency, low IgM levels, and some patients develop progressive hypogammaglobulinemia. FISH for 22Q11.2 may identify patients with 22Q11.2DS as well as the more sensitive DNA microarray. Pathogenic variants in *TBX1* may be found in DiGeorge syndrome, and pathogenic variants in *CHD7* or *SEMA3E* in CHARGE syndrome.

Treatment

The immunodeficiency in thymic aplasia is correctable by cultured allogenic (donor derived) thymic tissue transplants. Following thymic tissue transplantation, a cytokine release syndrome may develop. Some infants with thymic aplasia have been given nonirradiated unfractionated bone marrow or peripheral blood transplants from a human leukocyte antigen–identical sibling, with subsequent improved immune function because of adoptively transferred T cells. Infants and children with low T-cell counts but not low enough to consider transplantation should be monitored for evolution of immunoglobulin defects as well as autoimmunity. Infections in these patients are multifactorial. Their anatomy may not favor drainage of secretions; they have a higher rate of atopy, which may complicate infections; and their host defense may allow persistence of infections. Interventions range from hand hygiene, probiotics, prophylactic antibiotics, and risk management to immunoglobulin replacement for those who have demonstrated defective humoral immunity. Live-viral vaccines should be avoided until adequate CD4 and CD8 T-cell counts are confirmed and normal response to antigens is documented with T-cell proliferation to antigens or a protective antibody response to a protein vaccine such as tetanus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

165.4 Inborn Errors of Immunity with a Strong Atopic Diathesis

Ramsay L. Fuleihan

AUTOSOMAL DOMINANT HYPER-IgE SYNDROME *STAT3* DEFICIENCY (JOB SYNDROME)

This syndrome is associated with early-onset atopy and recurrent skin and lung infections.

Genetics and Pathogenesis

The autosomal dominant hyper-IgE syndrome is caused by heterozygous pathogenic variants in the gene encoding signal transducer and activator of transcription 3 *(STAT3)*. These pathogenic variants result in a dominant negative effect. The many clinical features are caused by compromised signaling downstream of the IL-6, type I interferon, IL-22, IL-10, and epidermal growth factor (EGF) receptors.

Clinical Manifestations

The characteristic clinical features are staphylococcal abscesses, pneumatoceles, osteopenia, and unusual facial features. There is a history from infancy of recurrent staphylococcal abscesses involving the skin, lungs, joints, viscera, and other sites. Persistent pneumatoceles develop as a result of recurrent pneumonia. Patients often have a history of sinusitis and mastoiditis. *C. albicans* is the second most common pathogen. Allergic respiratory symptoms are usually absent. The pruritic dermatitis that occurs is not typical of atopic eczema and does not always persist. There can be a prominent forehead, deep-set wide-spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy, although these are most evident in adulthood. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.



Fig. 165.7 Mucocutaneous inflammation and infections in DOCK8-HIES. Severe eczema, molluscum contagiosum and fungal skin infections, and benign tumorous mucosa proliferations progressing from the inner eyelid and from oral mucosa are clinical signs of DOCK8-HIES. *(From Hagl B, Heinz V, Schlesinger A, et al. Key findings to expedite the diagnosis of hyper-IgE syndromes in infants and young children. Pediatr Allergy Immunol. 2016;27[2]:177-184. Fig. 1)*

These patients demonstrate an *exceptionally high serum IgE concentration*; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; and poor antibody and cell-mediated responses to neoantigens. Although IgE levels >2,000 IU/mL are characteristic, IgE levels may fluctuate and even decrease in adulthood. In neonates and infants with the pruritic pustular dermatosis, IgE levels will be elevated *for age* and are usually in the 100s. In vitro studies show normal percentages of blood T, B, and NK lymphocytes, except for a decreased percentage of T cells with the memory (CD45RO) phenotype and an absence or deficiency of T-helper type 17 (Th17) cells. Most patients have normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens or allogeneic cells from family members. Blood, sputum, and histologic sections of lymph nodes, spleen, and lung cysts show striking eosinophilia. Hassall's corpuscles and thymic architecture are normal.

Treatment

Therapy is generally directed at prevention of infection using antimicrobials including antibiotics and antifungals as well as immunoglobulin replacement.

DOCK8 DEFICIENCY

Deficiency of DOCK8 (dedicator of cytokinesis 8) is an autosomal recessive severe immunodeficiency that most often presents with impressively severe eczema in infancy and toddlerhood, food allergy, and eosinophilic esophagitis. Patients commonly have cutaneous viral infections with herpes simplex virus (HSV), varicella, or molluscum contagiosum; susceptibility to infection by CMV and EBV; recurrent pneumonia leading to bronchiectasis; and opportunistic infections with PJP. In some patients, cryptosporidia causes sclerosing cholangitis (Fig. 165.7). The infectious susceptibility tends to worsen over time, as do the laboratory features of immune dysfunction, most often low T-cell counts and poor proliferative function. Serum IgE levels tend to be elevated with eosinophilia, whereas other immunoglobulin levels may be decreased, especially IgM. Specific antibody levels are variably decreased. Patients are also susceptible to autoimmune disease as well as cancer. Although these patients can survive to adulthood without transplantation, they suffer many complications and their quality of life is often poor. For this reason, most patients are now transplanted early in life to avoid the later complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 166

B-Cell and Antibody Deficiencies

Vivian P. Hernandez-Trujillo and Camile Ortega

Of the primary immunodeficiency diseases (PIDDs), those affecting antibody production are the most prevalent. Selective absence of IgA is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria, predominantly in the upper and lower respiratory tracts. Some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections. These conditions have a complex and likely polygenic inheritance, as do the common variable immunodeficiency (CVID) syndromes. The gene defects for many primary antibody deficiency disorders have been identified (Table 166.1). Sometimes the defect is not in the B cell itself but in T cells, which are required for complete B-cell function. Some disorders are caused by unknown factors or are secondary to an underlying disease or its treatment.

166.1 Agammaglobulinemia

Vivian P. Hernandez-Trujillo and Camile Ortega

X-LINKED AGAMMAGLOBULINEMIA

Patients with X-linked agammaglobulinemia (XLA), or **Bruton agammaglobulinemia**, have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes. These patients present with an increased susceptibility to infection (Fig. 166.1) and have increased risk of neutropenia and autoimmunity, particularly presenting as colitis.

Genetics and Pathogenesis

The variant gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B-cell protein tyrosine kinase Btk (Bruton tyrosine kinase). Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases and is expressed at high levels in all B-lineage cells, including pre-B cells. Some pre-B cells are found in the bone marrow, but the percentage of peripheral blood B lymphocytes is <1%. The percentage of T cells is increased, ratios of T-cell subsets are normal, and T-cell function is intact. The thymus is normal.

Several autosomal recessive defects have also been shown to result in agammaglobulinemia with an absence of circulating B cells (see Table 166.1; Table 166.2), including pathogenic variants in the genes encoding the (1) μ heavy chain gene; (2) Igα and (3) Igβ signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); (7) p85α subunit of phosphatidylinositol-3 kinase; (8) p110 δ subunit of phosphatidylinositol-3 kinase; (9) TCF3; (10) SLC39A7; and (11) TOP2B. These are rare but are clinically indistinguishable from the X-linked form (see Fig. 166.1).

Clinical Manifestations/Complications

Most males afflicted with XLA remain well during the first 6-9 months of life by virtue of maternally transmitted IgG antibodies. Thereafter they acquire infections with extracellular pyogenic organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis (Fig. 166.2). Infections with *Mycoplasma* are also particularly problematic, specifically as they can affect the joints. Chronic fungal infections are seen; *Pneumocystis jirovecii* pneumonia rarely occurs. Viral infections are usually handled normally, with the exceptions of hepatitis viruses and enteroviruses. There are examples of paralysis when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system (CNS) infections with various echoviruses and coxsackieviruses have occurred in a significant number of patients. An enterovirus-associated myositis resembling dermatomyositis has also been observed. Enteroviral encephalitis can also be life-threatening in patients with XLA. **Neutropenia**, typically seen at diagnosis when infected, can be associated with *Pseudomonas* or staphylococcal infections. In addition, *Pseudomonas* can lead to severe and life-threatening invasive infections. *Giardia* can also lead to diarrhea and weight loss. A sudden decrease in serum IgG level should prompt an evaluation for *Giardia*.

Long-term complications include bronchiectasis and colitis, presenting like an inflammatory bowel disease. Gastrointestinal (GI) disease has been increasingly reported in patients with XLA. Although immune globulin replacement decreased severe infectious complications, the chronic lung disease persisted in a recent cohort study. In addition, in a separate cohort, infections were highest before initiation of antibody replacement; however, patients continued to have infections despite adequate IgG levels.

Diagnosis

The diagnosis of XLA should be suspected if lymphoid hypoplasia is found on physical examination (minimal or no tonsillar tissue and no palpable lymph nodes), and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls; total immunoglobulins are usually <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in XLA, whereas they are typically normal in transient hypogammaglobulinemia of infancy. In infants below the age of 6 months, care should be taken when interpreting normal IgG, which can represent maternal IgG passed in utero. In this case, flow cytometry is essential in making the diagnosis of XLA. Flow cytometry is an important test to demonstrate the absence of circulating B cells, which will distinguish XLA from most types of **CVID**, the hyper-IgM syndrome, and transient **hypogammaglobulinemia** of infancy (Fig. 166.3). Genetic testing is also available to detect absence of Btk.

AUTOSOMAL RECESSIVE AGAMMAGLOBULINEMIA

Autosomal recessive agammaglobulinemia (ARA) is a clinically indistinguishable disorder from XLA presenting in males and females. The successful assembly and subsequent signaling capacity of the pre-B cell receptor complex (pre-BCR) in the bone marrow is central to the production of B cells and antibody-secreting plasma cells. A pathogenic variant in any of the components of the pre-BCR, or in the downstream signaling cascade, results in these rare forms of agammaglobulinemia (see Fig. 166.1).

Genetics and Pathogenesis

Hematopoietic stem cells develop into B cells in the bone marrow. The maturation into antibody-secreting plasma cells occurs in peripheral lymphoid tissues. B-cell development relies on a tightly regulated sequence of events from the pro-B cell stage to the formation of the pre-BCR and onward (see Fig. 166.1).

The pre-BCR is composed of the membrane form of the μ heavy chain, the surrogate light chain composed of VpreB and λ5/14.1 and the immunoglobulin-associated signal transducing chains, Igα and Igβ. An autosomal pattern of inheritance occurs in approximately 10% of agammaglobulinemic syndromes, and, in some affected families, there is known consanguinity. Approximately half of these pathogenic variants are in μ heavy (IGHM) and have a clinical picture that

Table 166.1 Genetic Basis of the Most Common Primary Antibody Deficiency Disorders

GENE	PHENOTYPE	DISORDER
BAFFR	CVID	Hypogammaglobulinemia
CD19	CVID	Hypogammaglobulinemia
CD20	CVID	Hypogammaglobulinemia
CD21	CVID	Hypogammaglobulinemia
CD81	CVID	Hypogammaglobulinemia
CTLA4	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
ICOS	CVID	Hypogammaglobulinemia, autoimmunity, neoplasia
LRBA	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
NFKB2	CVID	Hypogammaglobulinemia, autoimmunity
NFKB1	CVID	Hypogammaglobulinemia, autoimmunity
PIK3CD (AD)	CVID	Hypogammaglobulinemia, adenopathy
PI3KR1 (AD)	CVID	Hypogammaglobulinemia
TNFRSF13B	CVID	Hypogammaglobulinemia, low penetrance of disease
Unknown	CVID	Hypogammaglobulinemia, autoimmunity Majority of patients with CVID have no known gene variant
Unknown	IgG subclass deficiency	Variable association with infection
Unknown	Specific antibody deficiency	Normal immunoglobulin levels with poor vaccine responses
Unknown	Transient hypogammaglobulinemia of infancy	Vaccine responses are usually preserved, and most children outgrow this by age 3 yr
Unknown	Selective IgA deficiency	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
BLNK	Agammaglobulinemia	Absence of antibody production, lack of B cells
BTK	Agammaglobulinemia	Absence of antibody production, lack of B cells, X-linked agammaglobulinemia
CD79A	Agammaglobulinemia	Loss of the Igα required for signal transduction, absence of antibody production, lack of B cells
CD79B	Agammaglobulinemia	Loss of the Igβ required for signal transduction, absence of antibody production, lack of B cells
IGHM	Agammaglobulinemia	Loss of the Ig heavy chain, absence of antibody production, lack of B cells
IGLL1	Agammaglobulinemia	Loss of the surrogate light chain, absence of antibody production, lack of B cells
PI3KR1 (AR)	Agammaglobulinemia	Loss of signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
PIK3CD δ (AR)	Agammaglobulinemia	Severely impaired signal transduction through B-cell receptor, absence of antibody production, lack of B cells
SLC39A7	Agammaglobulinemia	Impaired signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
TCF3	Agammaglobulinemia	Loss of a key transcription factor for B-cell development, absence of antibody production, lack of B cells
AID	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD40	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
CD154	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
INO80	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
MSH6	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, malignancy
UNG	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD27	EBV lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Phenotype highly variable but includes specific antibody deficiency and CVID

AD, autosomal dominant; AR, autosomal recessive; CVID, common variable immunodeficiency; EBV, Epstein-Barr virus.

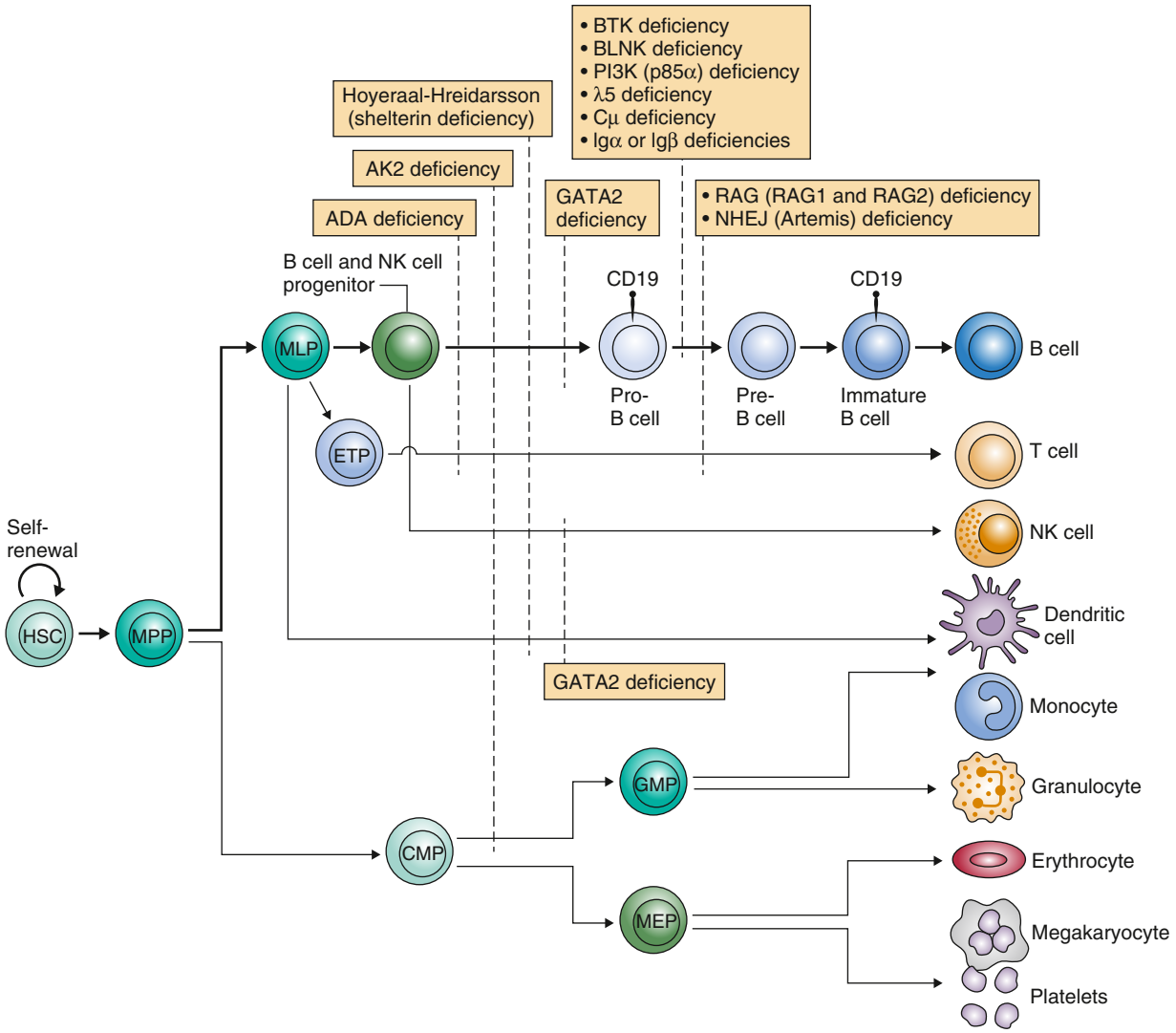

Fig. 166.1 B-cell development defects in primary antibody deficiencies (PADs) result from developmental defects that are either B-cell specific or affect several hematopoietic cell lineages. B-cell development occurs in the bone marrow, where hematopoietic stem cells (HSCs) undergo B-cell lineage specification. Some autosomal-recessive forms of severe combined immunodeficiency (SCID) are associated with an early defect in both B and T cells and are diagnosed in the first few months or years of life. For example, adenosine deaminase (ADA) deficiency leads to an accumulation of adenosines and thus the death of the lymphocytes. Moreover, adenylate kinase 2 (AK2) deficiency (also known as reticular dysgenesis) is a metabolic defect that mostly affects T cells, natural killer (NK) cells, neutrophils, and (in some cases) B cells. It is associated with very early onset hypogammaglobulinaemia or even agammaglobulinaemia. Dyskeratosis congenita is caused by mutations in genes encoding components of the telomerase or shelterin complexes; it is a rare inherited bone-marrow failure syndrome that leads to progressive B- and T-cell lymphopenia and hypogammaglobulinaemia. Finally, mutations in GATA2 (which encodes a transcription factor required for early differentiation of hematopoietic cells in the bone marrow) also lead to B-cell, dendritic cell, monocyte, and NK cell deficiencies. Successive B-cell differentiation stages are characterized by ordered gene expression and stochastic immunoglobulin gene rearrangements. The V(D)J recombination of the immunoglobulin locus is achieved by the lymphocyte-specific RAG molecules and the non–lymphocyte-specific nonhomologous end joining (NHEJ) complex and leads to the expression of the pre-B cell receptor (BCR). Defects in V(D)J recombination (as observed in RAG deficiency and NHEJ deficiency) typically result in the absence of mature B and T cells. The pre-BCR is affected in these cases, leading to PADs as V(D)J recombination is required for heavy chain expression. The dashed lines indicate a block of differentiation. BLNK, B-cell linker; Btk, Bruton tyrosine kinase; CMP, common myeloid progenitor; ETP, early T-cell precursor; GMP, granulocyte/macrophage progenitor; MEP, megakaryocyte/erythrocyte progenitor; MLP, multi-lymphoid progenitor; MPP, multipotent progenitor; PI3K, phosphoinositide 3-kinase. *(From Durandy A, Kracker S, Fischer A. Primary antibody deficiencies.* Nat Rev Immunol. *2013;13:519-533. Box 1, p. 520.)*

is similar to XLA. Variants in the genes encoding for Igα (CD79a), Igβ (CD79b), λ5 (IGLL1), BLNK, and p85α (PI3KR1) have been identified as other, more rare, causes for ARA in humans (see Fig. 166.1). Autosomal dominant forms of agammaglobulinemia have also been identified in patients with an unusual phenotype characterized by an increased expression of CD19, but with the absence of the BCR. Genetic studies demonstrated a de novo variant in the broadly expressed transcription factor E47, which functions as a quality control mechanism of enforcing a block to prevent cells that lack a pre-BCR from further development.

Clinical Manifestations

Absent peripheral B cells and severe hypogammaglobulinemia due to a developmental arrest at the pro-B stage to pre-B stage is characteristic of ARA. Although these patients generally have clinical findings that are indistinguishable from Btk mutations, patients with the pathogenic variants in any of the components of the BCR leading to ARA tend to have a more severe phenotype. ARA is diagnosed at a mean age of 11 months, rather than 35 months in patients with XLA. There is also a higher incidence of enteroviral infections and *Pseudomonas* sepsis with neutropenia. These differences suggest there is protective value in

Table 166.2 Patterns of Inheritance for Different Forms of Agammaglobulinemia

DISEASE	GENE/PROTEIN AFFECTED	PATTERN OF INHERITANCE
XLA	Btk	X-linked
IGHM	μ heavy chain	Autosomal recessive
Igα	CD79a	Autosomal recessive
Igβ	CD79b	Autosomal recessive
λ5	IGLL1	Autosomal recessive
BLNK	BLNK scaffolding protein	Autosomal recessive
PIK3R1	PIK3 regulatory subunit	Autosomal recessive
PIK3CD	PIK3 regulatory subunit	Autosomal recessive
SLC39A7	Zinc transporter protein ZIP7	Autosomal recessive
TCF3	Transcription factors E12 and E47	Autosomal recessive or autosomal dominant
LRRC8	LRRC8 deficiency	Autosomal dominant
Hoffman syndrome	TOP2B	Autosomal dominant

XLA, X-linked agammaglobulinemia.

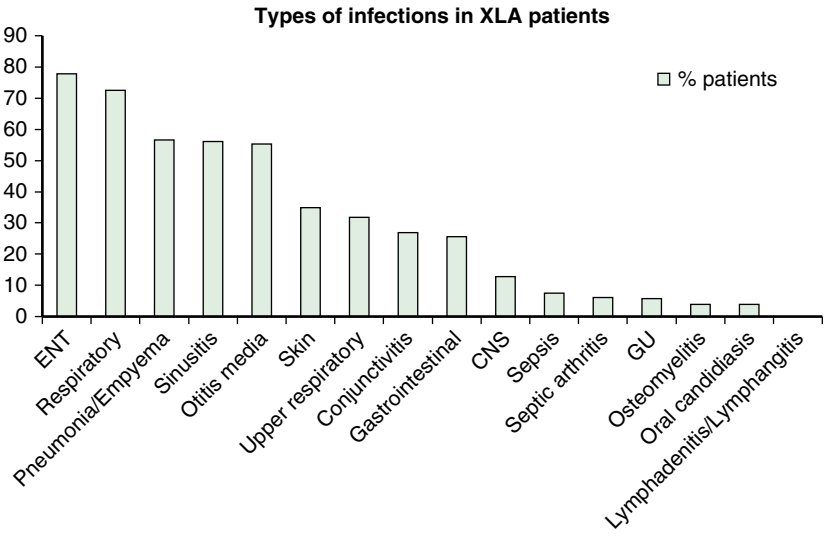

Fig. 166.2 Types of Infections in a cohort of X-linked agammaglobulinemia (XLA) patients. USIDNET Registry. Infections affect many body systems in XLA patients. CNS, Central nervous system: ENT, ear, nose, and throat; GU, genitourinary. *(Data from Groth D, Wright H, Marsh R, et al. X-linked agammaglobulinemia: Infection frequencies in 226 patients from the USIDNET Registry.* J Allergy Clin Immunol. *2020;145[2 Supplement]:AB80.)*

the small amount of immunoglobulins produced by patients with XLA. Treatment using immunoglobulin and aggressive use of antibiotics is identical to that for patients with XLA.

Diagnosis

Due to the early B-cell developmental arrest, ARA variants have been associated with the complete absence of $CD19^+$ B cells in the peripheral circulation and profound hypogammaglobulinemia. Identifying a genetic cause of ARA is challenging, and there is a need for a better understanding of susceptibility genes and modifying genetic factors. The goal of further areas of investigation should include the identification of variant genes in patients who do not appear to have defects in the genes already associated with immunodeficiency.

Whole genome sequencing will greatly facilitate the molecular diagnosis of abnormalities in additional genes that can cause ARA.

Inheritance Patterns

XLA affects males, as it is an X-linked disorder. The inheritance patterns include all female offspring as carriers, and none of the male offspring will be affected. Autosomal recessive forms of agammaglobulinemia result in both males and females affected, as each parent passes on the affected gene. Patients with agammaglobulinemia tend to have more severe disease, often presenting earlier in life compared with patients with hypogammaglobulinemia, specific antibody deficiency (SAD), or CVID.

Treatment with antibody replacement and prophylactic antibiotics for patients with any form of agammaglobulinemia is essential in preventing infections and will be further reviewed later.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

166.2 Hypogammaglobulinemia, Transient Hypogammaglobulinemia of Infancy, Specific Antibody Deficiency, and Common Variable Immunodeficiency

Vivian P. Hernandez-Trujillo and Camile Ortega

Patients with low IgG may present at different ages. Hypogammaglobulinemia results from low, but not absent, levels of serum immunoglobulins. If a patient is diagnosed with a specific pathologic genetic variant, this aids in making a specific diagnosis. Otherwise, in patients with a low IgG, the diagnosis may be arbitrary when considering the differential of hypogammaglobulinemia, SAD, and CVID (Tables 166.3 and 166.4).

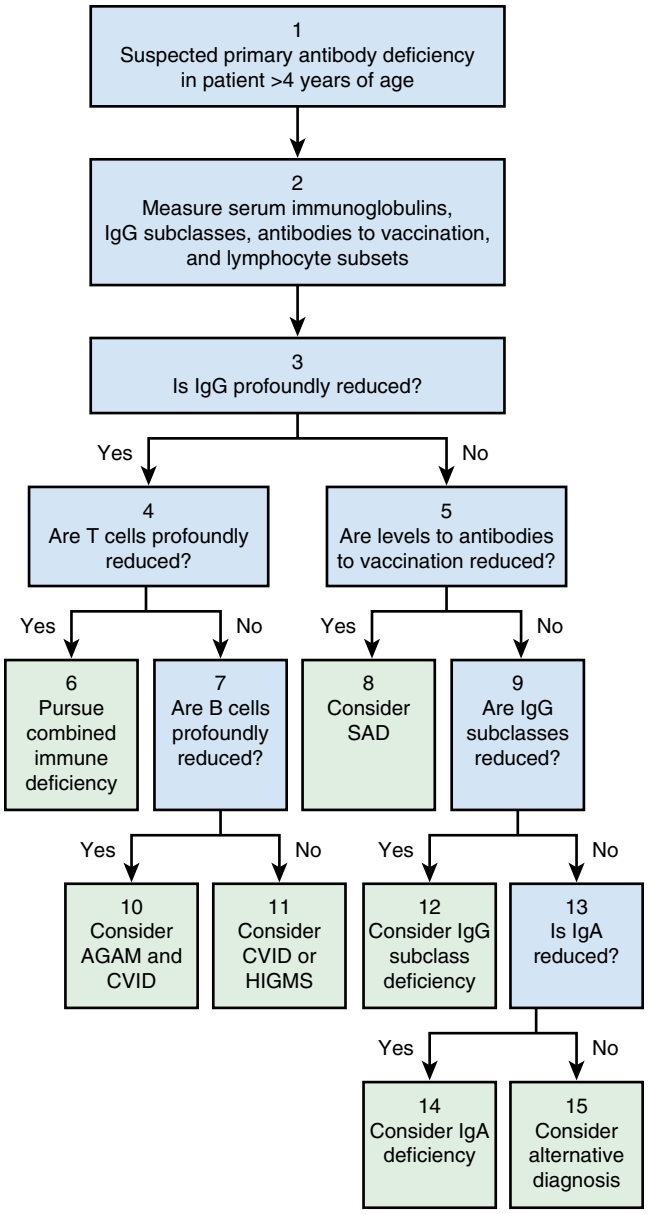

Fig. 166.3 Algorithm for evaluation of a patient with suspected primary antibody deficiency. AGAM, Congenital agammaglobulinemia; CVID, common variable immunodeficiency; HIGMS, hyperIgM syndrome; SAD, specific antibody deficiency. *(From Maglione PJ. Primary antibody deficiency. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds.* Pediatric Allergy Principles and Practice. *4th ed. Philadelphia: Elsevier, 2021. Fig. 5.1.)*

HYPOGAMMAGLOBULINEMIA

The most common types of PIDD are antibody deficiencies characterized by hypogammaglobulinemia and recurrent infections and are usually present in childhood. Primary hypogammaglobulinemia represents a spectrum of disease, with more severe phenotypes characterized by profound hypogammaglobulinemia or agammaglobulinemic states, as was described in the previous section. SAD and CVID are presented in the following sections, and onset may occur later in childhood and adolescence. This is in contrast to transient hypogammaglobulinemia of infancy, which presents in the first few months of life.

The secondary forms are more common in adults and are a result of decreased production or increased loss. Decreased production can be drug induced (rituximab, glucocorticoids, and antiepileptics), from malignancy or premalignant disorders (chronic lymphocytic leukemia, lymphoma, multiple myeloma, or Waldenström macroglobulinemia), and from Good syndrome (thymoma with hypogammaglobulinemia). Increased loss can result from protein-losing enteropathies, intestinal lymphangiectasia, nephrotic syndrome, burns, and trauma.

Specific Antibody Deficiency

SAD is defined as patients, 2 years old and older, with recurrent infections and normal immunoglobulin isotypes who lack antibody response to purified *S. pneumoniae* capsular polysaccharide antigens, while responding normally to protein antigens.

Genetics and Pathogenesis

Infants demonstrate robust antibody responses to protein antigens through T-cell–dependent activation. Response to purified polysaccharide vaccines (PPVs) does not involve T-cell activation, and is only considered to be fully developed by 2 years of age. The response to protein antigens, including those contained in the protein conjugated vaccines (PCVs), typically remains intact in patients with SAD. In SAD, some patients' lack of response to PPV may represent physiologic immaturity of the immune system, and may resolve over time. In SAD patients with recurrent infections requiring antibiotics, there is likely an underlying immunologic abnormality. The cause for this delay in maturation remains unknown. Abnormalities in a specific pathogen-associated molecular pathway may be responsible for the variability in which individuals respond to specific protein or polysaccharide antigens despite normal total immunoglobulin levels. A number of cellular pathways produce antibodies against purified or conjugate polysaccharides and are likely to be altered by different defects. The response seen to PPV, which can occur in patients who lack a response to PCV, demonstrates how conjugate and purified polysaccharides induce antibodies through different activation pathways. The variation in phenotypes of SAD also supports the likelihood of different pathogenic mechanisms resulting in polysaccharide antibody deficiencies. The use of large-scale DNA studies, along with IgM memory and class-switched memory B cells as immunologic markers, is expected to provide useful information for the evaluation and management of patients with SAD in the future.

Clinical Manifestations

Patients with SAD present in a manner consistent with those with defects of humoral immunity. Frequent, severe, or prolonged sinopulmonary infections are most common. Rapid recurrence of infection on discontinuation of antibiotics, following initial improvement, is also common. Invasive and life-threatening infections are not frequent. Approximately half of children show resolution of SAD in 3 years and treatment may be temporary. A new diagnosis of SAD during adolescence or adulthood could indicate a previously missed diagnosis or progression of a mild phenotype. Pathogen susceptibility is not specific and not limited to *S. pneumoniae.* Other encapsulated bacteria, (*H. influenzae* and *Moraxella catarrhalis*), *Staphylococcus aureus* and respiratory viruses cause significant disease in SAD.

SAD patients with allergic disease are among the most challenging to identify due to increased risk of sinopulmonary infections resulting from persistent inflammation and anatomic dysfunction associated with asthma and rhinitis. It is important to consider underlying SAD in this population, as IgE-mediated sensitization is only present in some of these patients. Mucociliary or anatomic defects should also be considered in those who have developed high titers in response to natural infection, but maintain an abnormal pattern of infections.

Although lack of antibody response to polysaccharide antigens is found frequently in patients without any associated immune deficiency, selective antibody deficiencies are also common in patients with known PIDDs with normal total immunoglobulin levels such as ataxia telangiectasia, asplenia, hyper-IgE syndrome, selective IgA deficiency, IgG subclass deficiencies, Wiskott-Aldrich syndrome, and partial DiGeorge syndrome. A subset of adolescents and adults with SAD may progress to more severe forms of PIDD, including other forms of hypogammaglobulinemia and CVID.

Diagnosis

The gold standard for the diagnosis of SAD involves evaluating the response to the 23-valent pneumococcal polysaccharide vaccine (PPV23). In patients immunized with protein conjugated

Table 166.3 Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL FEATURES
Agammaglobulinemia	Bacterial infections (in respiratory tract) and enterovirus infections	Absence of CD19 B cells
Common variable immunodeficiency	Bacterial infections (in respiratory tract and gut), autoimmunity, cancer, and increased risk of granuloma	Highly variable; may see decreased memory B cells
Class switch defects	Bacterial and opportunistic infections	Decreased frequency of memory B cells
Selective IgA deficiency	Most often asymptomatic	Normal
IgG subclass deficiency	Frequent bacterial infections; diagnosis after age 2 yr	B-cell subsets normal
Selective polysaccharide antibody deficiency	Bacterial infections (after age 2 yr)	Normal IgG (including IgG2 and IgG4) levels, normal B-cell subsets

Table 166.4 Antibody Deficiency Disorders with Laboratory Evaluation

LABORATORY VALUES	XLA/AR AGAMMA	SELECTIVE IgA	SPECIFIC ANTIBODY DEFICIENCY	COMMON VARIABLE IMMUNODEFICIENCY	TRANSIENT HYPOGAMMA-GLOBULINEMIA
IgG	Decreased	Normal	Normal	Decreased to normal	Decreased
IgA	Decreased	Decreased	Normal	Decreased to normal	Normal
IgM	Decreased	Normal	Normal	Varies	Normal
LYMPHOCYTES					
B $CD19^+$	Decreased to absent	Normal	Normal	Decreased to normal memory B cells	Normal
T $CD4^+/CD3^+$	Normal to increased	Normal	Normal	Normal	Normal
$CD8^+/CD3^+$	Normal to increased	Normal	Normal	Normal	Normal
NK $16^+/56^+$	Normal to increased	Normal	Normal	Normal	Normal
SPECIFIC ANTIBODY TITERS					
Protein	Decreased	Normal	Normal	Decreased to normal	Normal
Polysaccharide	Decreased	Normal	Decreased	Decreased to normal	Normal

AR, Autosomal recessive; NK, natural killer; XLA, X-linked agammaglobulinemia.

pneumococcal vaccines (PCV-7, PCV-13, PCV-10, PCV-15, PCV-20), the evaluation must be based on the serotypes not present in conjugate vaccines. In unimmunized patients, a complete absence of protective titers to all serotypes is unusual, as most individuals would be expected to have developed some in response to natural infection by 2 years of age. The standard and reproducible method used for analysis is the third-generation World Health Organization enzyme-linked immunosorbent assay (ELISA) and the antigens are individual serotype specific capsular polysaccharides of pneumococci. Antibody titers are expressed as mg/mL and although titers as low as 0.35 mg/mL have been considered protective against invasive infections, a titer of 1.3 mg/mL is used as the threshold of response to PPV23 and generally considered protective against mucosal infections. **Four different phenotypes of SAD** have been described based on the response to the available pneumococcal vaccines: mild, moderate, severe, and memory. Although all phenotypes presume an abnormal pattern of infection, severity or susceptibility to infection may or may not correlate clinically. The severe phenotype is defined as nearly absent protective titers to ≤2 serotypes following PPV23. The moderate phenotype is based on age: for those less than 6 years old, less than 50% protective serotypes and those age 6 years old and greater, less than 70% protective serotypes. Many patients fall in the mild phenotype, which is less well defined as a failure of response to multiple phenotypes. The memory phenotype, also dependent on age, is defined as an adequate initial response and subsequent loss of protective titers within 6 months. The evaluation of specific antibodies against *S. pneumoniae* polysaccharides provides guidance in determining the need for additional immunization, antibiotic therapy, or IgG replacement therapy in SAD patients. Children and adults who have not been immunized and have not developed protective titers in response to natural infection should be immunized with PCV followed by PPV23, as they have been shown to respond both clinically and serologically. Patients who fail to respond to the initial challenge with PPV23 may respond to the conjugated vaccine, when given ≥1 year after PPV23. Most patients have an excellent prognosis with appropriate treatment.

COMMON VARIABLE IMMUNODEFICIENCY

CVID is a syndrome characterized by hypogammaglobulinemia after an initial period of apparent normal immune function. Serum IgG must be <2 standard deviations below the *age-adjusted* norms, with low IgA and/or IgM levels. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that enterovirus meningoencephalitis is rare in patients with CVID. In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later, and infections may be less severe. CVID is the most common of the antibody defects.

Genetics and Pathogenesis

CVID is a phenotypic diagnosis with a polygenic inheritance in most cases. Genes known to produce the **CVID** phenotype when pathogenic variants occur include *ICOS* (inducible co-stimulator) deficiency, *SH2DIA* (responsible for X-linked lymphoproliferative disease [XLP]), *CD19, CD20, CD21, CD81, BAFF-R* (B-cell–activating factor of the tumor necrosis factor family of receptors), *NFKB1* and *NFKB2*, *IKZF1*, *ATP6AP1*, *MOGS*, *TACI*, and *TRNT1* (Fig. 166.4). With rare exceptions, management of CVID does not depend on a genetic diagnosis. In the setting of atypical infections or autoimmunity, pursuing a genetic diagnosis can be useful because some genetic etiologies can have a poor prognosis and transplantation should be considered. Targeted treatment options may also be available to treat some forms of CVID related to *LRBA* or *CTLA4* pathogenic variants.

Despite normal numbers of circulating B cells in many patients and the presence of lymphoid cortical follicles, blood B cells from CVID patients do not differentiate normally into immunoglobulin-producing cells. They may have a deficiency of switched memory B cells.

Clinical Manifestations

The serum immunoglobulin and antibody deficiencies in CVID are associated with recurrent sinopulmonary infections (sinusitis, otitis, pneumonia). Most patients present before age 20. Close monitoring for the development of chronic lung disease is needed. Repeated pulmonary infections may produce bronchiectasis; interstitial lung disease is common (Fig. 166.5). Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. Patients with recurrent infections as their only manifestation typically have a normal life expectancy and do well with immunoglobulin replacement. The presence of autoimmune disease or lymphoproliferation confers a poor prognosis, as antibody replacement does not improve these conditions. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; about 25% of patients have splenomegaly. CVID has also been associated with a spruelike enteropathy with or without nodular lymphoid hyperplasia of the intestine. Other autoimmune diseases include alopecia areata, hemolytic anemia, thrombocytopenia, gastric atrophy, achlorhydria, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs (**granulomatous and lymphocytic interstitial lung disease [GLILD]**), spleen, skin, and liver also occur. Patients should be monitored closely over time for symptoms involving multiple tissues.

166.3 Class Switch Defects

Vivian P. Hernandez-Trujillo and Camile Ortega

The **hyper-IgM syndrome** is genetically heterogeneous and characterized by normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class switch recombination (CSR) process. Causative pathogenic variants have been identified in the CD40 ligand gene on the X chromosome and three genes on autosomal chromosomes: the activation-induced cytidine deaminase (AID) gene, the uracil DNA glycosylase gene (UNG), and the CD40 gene on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of pathogenic variants in these patients, thereby aiding proper choice of therapy. All such patients should undergo molecular analysis to ascertain the affected gene for purposes of genetic counseling, carrier detection, and decisions regarding definitive therapy.

X-LINKED HYPER-IgM CAUSED BY MUTATIONS IN CD40 LIGAND GENE

X-linked hyper-IgM is caused by pathogenic variants in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper (Th) cells. Males with this syndrome have very low serum concentrations of IgG and IgA, with a usually normal or sometimes elevated concentration of polyclonal IgM; may or may not have small tonsils; usually have no palpable lymph nodes; and often have profound neutropenia. This disease, unlike the autosomal recessive forms of hyper-IgM, affects both B and T cells.

Genetics and Pathogenesis

The B cells are normal in this condition; the defect is in the T cells. CD40L is the ligand for CD40, which is present on B cells and monocytes. CD40L is upregulated on activated T cells. Mutations result in an inability to signal B cells to undergo isotype switching, and thus the B cells produce only IgM. The failure of T cells to interact with B cells through this receptor-ligand pair also causes a failure of upregulation of the B-cell and monocyte surface molecules CD80 and CD86 that

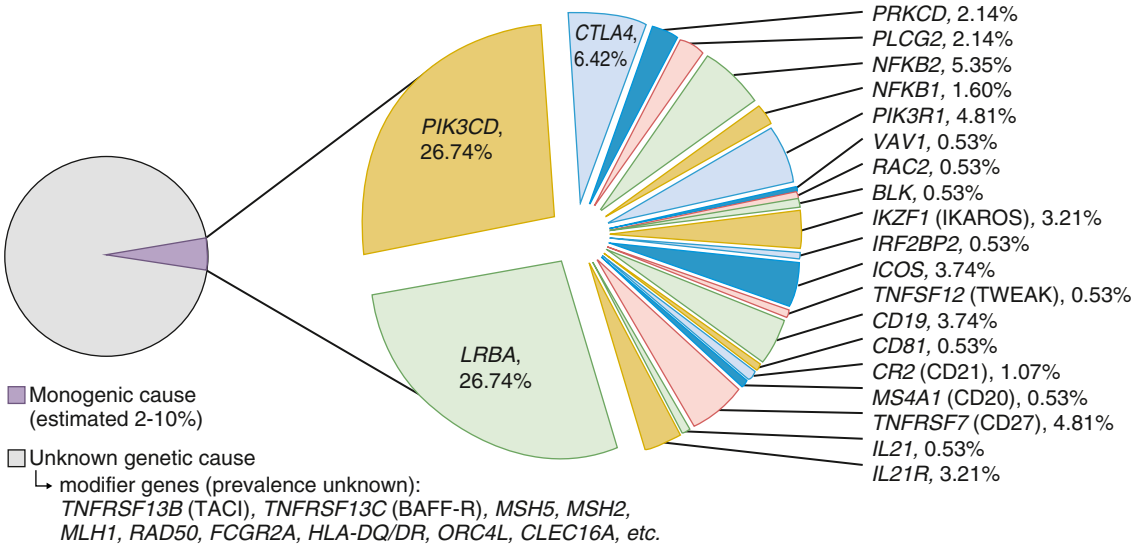

Fig. 166.4 Known genetic etiology of common variable immunodeficiency (CVID). **The majority of cases of CVID do not have a defined genetic cause.** Many of these are likely to be multifactorial, and the genomic duplication and deletion burden in CVID suggests this to be the case; 115 of the mutations have been identified. The colored pie chart represents their breakdown and relative frequency. *(From Bogaert DJ, Dullaers M, Lambrecht BN, et al. Genes associated with common variable immunodeficiency: One diagnosis to rule them all?* J Med Genet. *2016;53[9]:575-590. Fig 1.)*

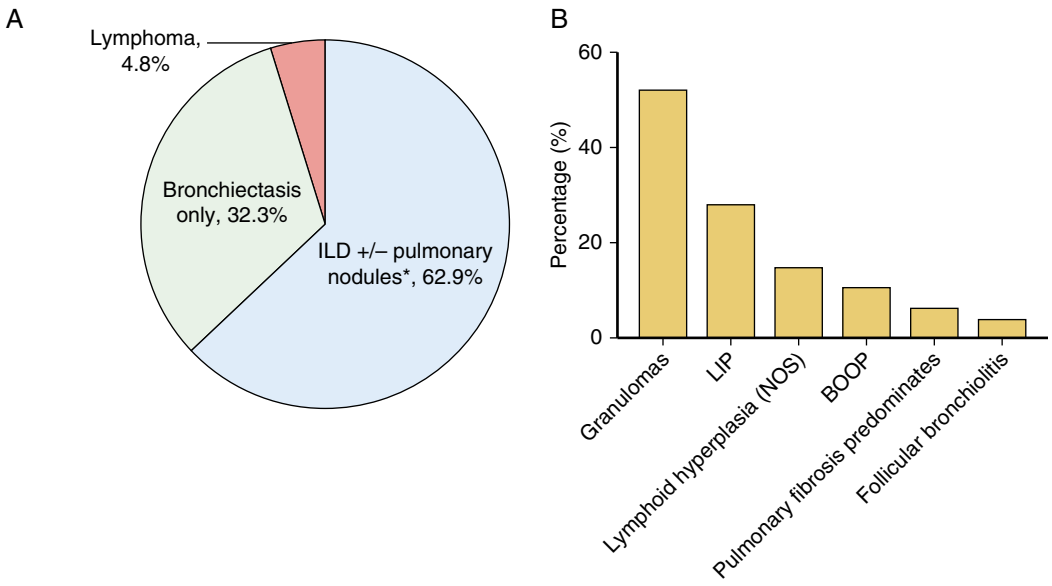

Fig. 166.5 Chronic lung disease in common variable immunodeficiency. **A**, Lung disease types by radiographs and/or pathology reports (n = 124). **B**, Interstitial lung disease pathologies (n = 46). *Thirteen of 65 subjects with ILD had concurrent bronchiectasis. BOOP, bronchiolitis obliterans organizing pneumonia; ILD, interstitial lung disease; LIP, lymphoid interstitial pneumonia. *(From Ho HE, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: Updated clinical spectrum, sequelae, and insights to pathogenesis.* Front Immunol. *2020;11:149. Fig. 1)*

interact with CD28/CTLA4 on T cells, resulting in failure of "crosstalk" between immune system cells.

Clinical Manifestations

Males with the CD40 ligand defect become symptomatic during the first or second year of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jirovecii* pneumonia and can be neutropenic. Lymph node histology shows only abortive germinal center formation with severe depletion and phenotypic abnormalities of follicular dendritic cells. These patients have normal numbers of circulating B lymphocytes, but a decreased frequency of $CD27^+$ memory B cells. Circulating T cells are also present in normal numbers and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In addition to opportunistic infections such as *P. jirovecii* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy.

Treatment

Because of the poor prognosis, the treatment of choice is an HLA-identical hematopoietic stem cell transplant at an early age. Alternative treatment for this condition is lifelong infusions of immune globulin. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

AUTOSOMAL RECESSIVE HYPER-IgM

Genetics and Pathogenesis

In contrast to patients with the CD40L defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when co-cultured with normal T cells. The defects are all B-cell intrinsic. The most common autosomal recessive defect is in a gene that encodes AID. AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in three hyper-IgM patients reported to have UNG deficiency. Their clinical characteristics were similar to those with AID deficiency, with increased susceptibility to bacterial infections and lymphoid hyperplasia. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times > normal) filled with highly proliferating B cells. Autosomal recessive hyper-IgM can be caused by defects in CD40. Clinical manifestations included recurrent sinopulmonary infections, *P. jirovecii* pneumonia, and *Cryptosporidium parvum* infections, very similar to the manifestations seen in X-linked hyper-IgM syndrome. Patients with *INO80* deficiency may present with severe bacterial infections; whereas in *MSH6* deficiency patients may have increased IgM, family or personal history of cancer, and low switch memory B cells.

Clinical Manifestations

Concentrations of serum IgG, IgA, and IgE are very low in AID, UNG, and CD40 deficiencies. In contrast to the CD40 ligand defect, however, the serum IgM concentration in patients with AID deficiency is usually markedly elevated and polyclonal. Patients with AID and UNG mutations have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jirovecii* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. The lymphoid hyperplasia distinguishes these patients from many others with antibody deficiency, particularly agammaglobulinemia, which leads to a paucity of lymphoid tissue. They have a tendency, however, to develop autoimmune and inflammatory disorders, including diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn disease, and chronic uveitis.

Treatment and Prognosis

With early diagnosis and antibody replacement, as well as good management of infections with antibiotics, patients with AID and UNG mutations generally have a more benign course than do those with the CD40L or CD40 defects. CD40 deficiency is rare but appears to mimic the manifestations of CD40L quite closely.

Treatment of Antibody Deficiency

Except for the CD40 ligand defect, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of immunoglobulin are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immune globulin (IVIG or SCIg). Broad antibody deficiency should be carefully documented before such therapy is initiated. The rationale for the use of IVIG or SCIg is to provide missing antibodies, not to raise the serum IgG or IgG subclass level. The development of safe and effective immunoglobulin preparations is a major advancement in the treatment of patients with severe antibody deficiencies, although it is expensive and there have been national shortages.

Almost all commercial preparations are isolated from normal plasma by the Cohn alcohol fractionation method or a modification of it. Cohn fraction II is then further treated to remove aggregated IgG. Additional stabilizing agents such as sugars, glycine, and albumin are added to prevent reaggregation and protect the IgG molecule during lyophilization. The ethanol used in preparation of immunoglobulin inactivates

HIV, and an organic solvent/detergent step inactivates hepatitis B and C viruses. Some preparations are also nanofiltered to remove infectious agents. Most commercial lots are produced from plasma pooled from 10,000 to 60,000 donors and therefore contain a broad spectrum of antibodies. Each pool must contain adequate levels of antibody to antigens in various vaccines, such as tetanus and measles. However, there is no standardization based on titers of antibodies to more clinically relevant organisms, such as *S. pneumoniae* and *H. influenzae* type b.

The IVIG and SCIg preparations available in the United States have similar efficacy and safety. Rare transmission of hepatitis C virus has occurred in the past, but this has been resolved by the additional treatment step. There has been no documented transmission of HIV by any of these preparations. IVIG or SCIg at a dose of 400-600 mg/kg per month achieves trough IgG levels close to the normal range. Higher doses are indicated in patients with chronic or severe respiratory infections. Systemic reactions may occur, but rarely are these true anaphylactic reactions. Neutropenia associated with B-cell defects has responded to granulocyte colony-stimulating factor. Treatment of inflammatory bowel disease is essential in maintaining adequate IgG levels.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

166.4 Isotype Defects

Vivian P. Hernandez-Trujillo and Camile Ortega

SELECTIVE IgA DEFICIENCY

An isolated absence or near absence (<5 mg/dL) of serum and secretory IgA is the most common well-defined immunodeficiency disorder, with a disease frequency as high as 0.33% in some populations. Patients may be asymptomatic or may develop sinopulmonary or gastrointestinal (GI) infections (especially *Giardia*). IgA deficiency is also associated with celiac disease and other autoimmune disorders. The diagnosis cannot be made until about 4 years of age, when IgA levels should be matured to adult levels.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. In these patients, normal levels of other isotypes and normal specific antibody levels are seen. This defect also often occurs in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID over time. IgA deficiency is noted in patients treated with the same drugs associated with producing CVID (phenytoin, D-penicillamine, gold, and sulfasalazine), suggesting that environmental factors may trigger this disease in a genetically susceptible person.

Clinical Manifestations

Infections occur predominantly in the respiratory, GI, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG2 (and other) subclass deficiency has been reported.

Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. These antibodies can cause nonhemolytic transfusion reactions. Washed erythrocytes (frozen blood would have this done routinely) or blood products from other IgA-deficient individuals should be administered to patients with IgA deficiency. Many immune globulin preparations contain sufficient IgA to cause reactions. It is important to note that administration of immune globulin, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

IgG Subclass Deficiencies

Some patients have deficiencies of one or more of the four subclasses of IgG despite normal or elevated total IgG serum concentration. Most patients may be asymptomatic. Some patients with absent or very low concentrations of IgG2 also have IgA deficiency. They may present with bacterial infections. Other patients with IgG subclass deficiency have gone on to develop CVID, suggesting that the presence of IgG subclass deficiency may be a marker for more generalized immune dysfunction. The biologic significance of the numerous moderate deficiencies of IgG subclasses that have been reported is difficult to assess. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infections. The more relevant issue is a patient's capacity to make specific antibodies to protein and polysaccharide antigens, because profound deficiencies of antipolysaccharide antibodies have been noted even in the presence of normal concentrations of IgG2. For this reason, immune globulin should not be administered to patients with IgG subclass deficiency unless they are shown to have a deficiency of antibodies to a broad array of antigens.

Immunoglobulin Heavy- and Light-Chain Deletions

Some completely asymptomatic individuals have been documented to have a total absence of IgG1, IgG2, IgG4, and/or IgA1 as a result of gene deletions. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate immune globulin therapy in IgG subclass–deficient patients. Low or undetectable levels of IgG subclasses alone is, therefore, not an indication for antibody replacement.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

166.5 Transient Hypogammaglobulinemia of Infancy

Vivian P. Hernandez-Trujillo and Camile Ortega

A common laboratory finding in infants, transient hypogammaglobulinemia represents developmental delay in the production of immunoglobulin. It is thought to occur in as many as 1:1,000 children. Most infants begin to produce IgG in the first 3 months of life, and the quantity produced increases throughout infancy. For reasons incompletely understood, a small number of infants either begin late or do not increase their production as expected. This condition will resolve with no intervention, but represents a source of diagnostic confusion. A key distinction is that responses to vaccines are usually preserved in this condition, whereas in the others, including SAD, antibody responses will be low to absent.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 167

Natural Killer Cells

Jessica M. Palmieri, Vibha A. Szafron*, and Lisa Forbes Satter*

Natural killer (NK) cells are lymphocytes that have a critical role in the innate immune response to pathogenic challenge and cellular stress. NK cells are capable of rapid target cell killing and can quickly secrete large amounts of preformed granzymes and perforins in response to viral infections, especially those of the herpesvirus family. They are also crucial in tumor surveillance. NK cells are found in the circulating blood as approximately 3–15% of lymphocytes and are also found in both primary and secondary lymphoid tissues where they are in a constant state of surveillance for cellular abnormalities. NK cells use a detection system composed of a wide range of germline-encoded cell surface receptors that contribute to simultaneous NK activating and inhibitory signals. NK cells are constantly receiving both activating and inhibitory signals with the balance of signals tilted toward inactivation until NK cell recognition of a target cell occurs. With target cell recognition, the balance between inhibitory and activating signals leans in favor of activation and NK cell killing is initiated.

NK cells are defined as *innate immune lymphocytes* because unlike B and T lymphocytes, they do utilize recombination-activating gene (RAG) proteins required for DNA rearrangement and assemblage of diverse antigen-specific receptors in response to antigen exposure. However, they can develop long-lived and highly antigen-specific immunologic memory responses to different antigens through *RAG-independent adaptive immunity,* which provides lifelong immune memory responses. This means that despite a lack of receptor diversity accrued via DNA rearrangement like B cells and T cells, NK cells do have characteristics associated with the adaptive immune system; distinguishing healthy from diseased cells, producing robust antiviral responses, and maintaining a collection of long-lived cells that expand during cellular stress responses.

NK CELL MARKERS, SUBSETS, AND MATURATION

Mature NK cells are traditionally defined as non-T, non-B lymphocytes that can rapidly produce interferon gamma (IFN-γ) and can mediate cellular cytotoxicity. Like all lymphocytes, they express cluster of differentiation (CD) markers that identify their cell type and stage of development that are also upregulated or downregulated for cell homing purposes. However, there are no surface markers that are unique and specific for NK cells. NK cells have been traditionally identified by using flow cytometry to exclude the cellular surface presence of leukocyte expressing markers specific to other leukocytes, such as CD3 and CD5 (T cells), CD19 and CD20 (B cells), and CD13 and CD14 (myelomonocytic cells). Further identification of NK cells follows via their expression of CD56 (neural cell adhesion molecule-1) and/or CD16, their low-affinity Fc gamma receptor that mediates **antibody-dependent cellular cytotoxicity** (ADCC). Neither CD56 nor CD16 is specific or unique to the NK cell lineage; however, these CD markers are functionally important and thus used to characterize major subsets of NK cells.

NK cells develop from CD34 hematopoietic stem cells (HSCs) in the bone marrow and then undergo maturation in secondary lymphoid tissues. NK cell development occurs through a series of six functionally distinct developmental stages distinguishable by cellular expression of cell surface markers including CD34, CD117, CD94/NKG2A (surface inhibitory receptor), NKp80 (surface activating receptor), CD16, and CD57. Once mature, NK cells then circulate through the peripheral blood (PB) or are found in organ tissues such as the secondary lymphoid tissues, liver, lungs, uterus, kidneys, or gut. For example, stage 1 cells found in the bone marrow are marked by the presence of only CD34, and subsequent stages occur through the upregulation and downregulation of previously mentioned cell surface markers; whereas, stage 6 mature NK cells in the PB express Nkp80, CD16, and CD57 (Fig. 167.1).

NK cells express CD56 at different levels of development. $CD56^{bright}$ NK cells that express high levels of CD56, without expressing much CD16, are considered stage 4b and are approximately 3–10% of circulating PB NK cells. Most PB NK cells express CD16 and low levels of CD56 and are referred to as $CD56^{dim}$ NK cells. Distinguishing cells as $CD56^{bright}$ and $CD56^{dim}$ refers to the increased fluorescent intensity for $CD56^{+}$ cells seen in comparison to cells negative for CD56. $CD56^{bright}$ and $CD56^{dim}$ cells are functionally different. $CD56^{bright}$ NK cells are considered to be developmentally immature and produce higher levels of cytokines such as IFN-γ with less cytotoxic capacity. They can rapidly produce large amounts of cytokines and chemokines; however, they contain low levels of perforin and granzymes and have low or absent CD16, making them poor mediators of direct cytotoxicity and ADCC. In contrast, $CD56^{dim}$ cells are developmentally more mature, contain high levels of perforin, are cytotoxic, and recognize antibody-coated cells through CD16. $CD56^{dim}$ cells are able to produce large amounts of cytokines but not to the degree of $CD56^{bright}$ cells.

The cell surface marker expression for NK cells in the PB and tissues are phenotypically distinct due to the influence of each tissue's unique microenvironment. Similarly, the ratio of $CD56^{bright}$ and $CD56^{dim}$ NK subsets in the tissues is not the same as the ratios found in the PB. In the bone marrow, lung, spleen, subcutaneous adipose tissue, and breast tissue, $CD56^{dim}$ NK cells predominate, whereas $CD56^{bright}$ NK cells predominate in the mucosa-associated lymphoid tissues (MALTs; e.g., gastric and intestinal mucosa), liver, uterus, visceral adipose tissue, adrenal gland, and kidney.

NK Cell Functions

NK cells have a critical role in the control of tumor growth and metastasis and are vital for the innate immune response against infections, particularly certain viruses. Additionally, there is increasing recognition of the importance of NK cells in immunoregulation, coordination of immunity, and modulation of autoreactivity.

NK cell activity is a balance between inhibitory and activating signals. NK cell surfaces contain a wide range of receptors that affect NK cell expression. Healthy host cells express high amounts of major histocompatibility complex class I (MHC I) molecules that ligate NK cell inhibitory receptors and prevent unwanted killing of healthy cells. Infected or malignant host cells downregulate their MHC I expression and express ligands for NK cell activating receptors, which triggers NK cell killing of the diseased cell. The balance of signals for NK cell inhibition by MHC I expression in healthy cells and NK cell activation by MHC I downregulation during cellular stress allows NK cells to defend against viruses and tumors and have protective roles in fungal, extracellular bacterial, intracellular bacterial, and parasitic infections. Many viruses have evolved to specifically downregulate MHC I in cells they infect to prevent the host cell from presenting antigenic peptides to virus-specific cytotoxic T lymphocytes (CTLs). Although this strategy does allow virus-infected cell evasion from CTLs, it makes the infected cell more susceptible to recognition by NK cells.

The three main functions of NK cells include cytokine/chemokine production, contact-dependent co-stimulation, and cytotoxicity. Additionally, NK cells are capable of interfacing with the adaptive immune system through their IgG Fc receptor, CD16, which allows them to engage in antibody-dependent killing.

Cytokine/Chemokine Production

Activated NK cells secrete a wide variety of cytokines and chemokines in response to stimulation by interleukin (IL)-12, IL-15, and IL-18. IFN-γ is one of the most potent cytokines released by

*These authors contributed equally to this work.

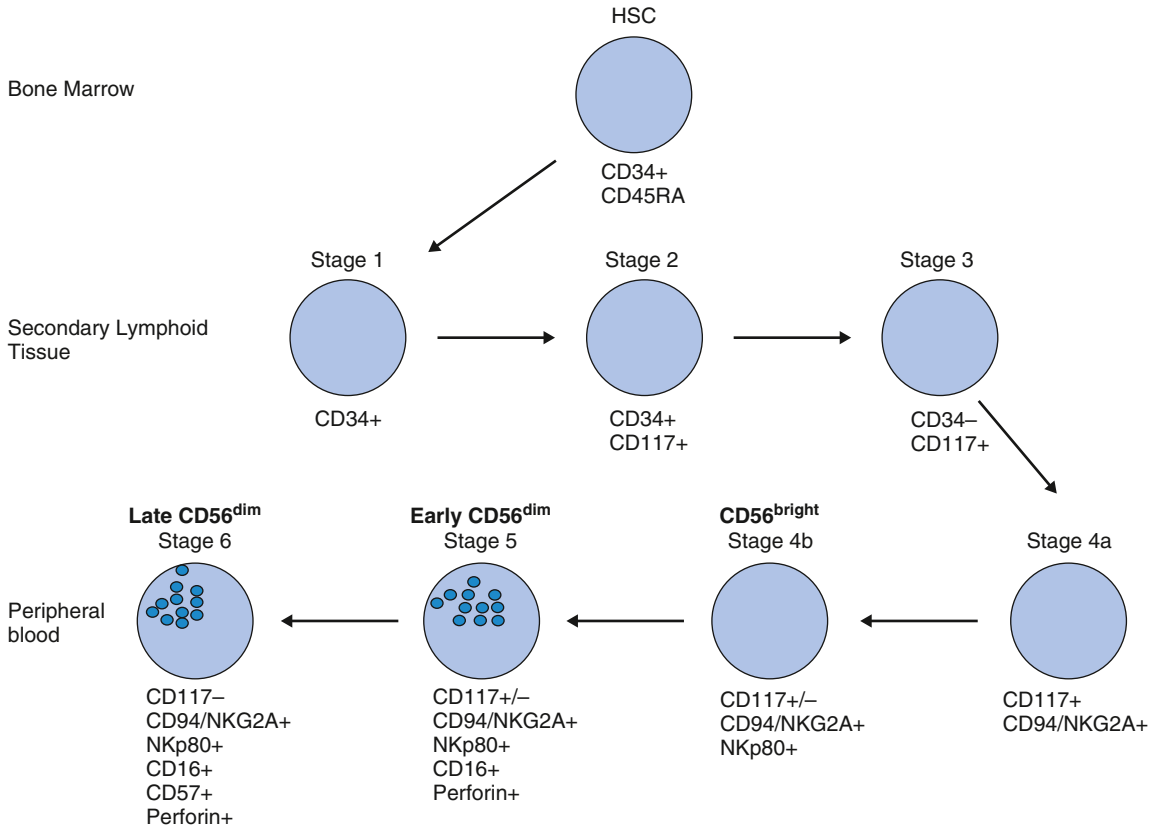

Fig. 167.1 Stages of NK cell development. HSC, Hematopoietic stem cell.

NK cells. It is crucial for the antiviral, antibacterial, and antitumor activity of NK cells through modulating death ligand expression of caspase, FasL, and TRAIL. NK cells are thus able to target cells for death through expression of these death ligands. Death ligand killing is not as rapid as lytic granule killing. Additional NK cell–released cytokines include TNF-α, IL-10, IL-5, and IL-13. NK cells also produce chemokines (chemotactic agents) such as MIP-1α, MIP-1β, IL-8, and RANTES. It is important to note that cytokines and chemokines in NK cells are compartmentalized separately from the lytic granules allowing them to be accessed separately from their cytotoxicity function.

Contact-Dependent Co-Stimulation

NK cells can promote and regulate immunity through direct receptor-ligand interactions with other cells, or contact-dependent co-stimulation. NK cells express or can be induced to express a variety of co-stimulatory and inhibitory ligands including the CD40 ligand, CD28, and PD-1, which can then interact with other types of immune cells to alter immune responses.

NK CELL SPONTANEOUS CYTOTOXICITY

Similar to cytotoxic T cells, NK cells secrete specialized lysosome-related organelles known as **lytic granules**. However, unlike CTLs, the lytic granules inside NK cells are preformed and abundant while the cell is at rest, which allows for their rapid killing response on recognition of cellular distress/disease. Lytic granule contents include **perforin** (pore-forming molecule) and pro-apoptotic enzymes such as **granzymes**. Once an NK cell recognizes an activation signal from a distressed cell, the NK cell will polarize its lytic granules toward the portion of the NK cell membrane in contact with the target cell where the lytic granules will then dock. This is followed by fusion of the secretory lysosome with the plasma membrane of the target cells. The site of NK cell connection with the target cell is called the **lytic immunologic synapse.**

Once a stable connection is formed at the lytic immunologic synapse, cellular killing by the lytic granules will be completed in less than 2 hours. Perforin will insert into the target cell membrane, which will allow for pro-apoptotic granzymes to travel to the target cell and initiate cellular killing.

NK CELL ANTIBODY-DEPENDENT KILLING

NK cells are also able to kill target cells via ADCC. NK cells have an IgG Fc receptor, CD16, expressed on their cell surfaces that allows them to recognize IgG-opsonized targets to promote killing without priming via lysing of the target cell. ADCC also causes NK cell secretion of cytokines like INF-γ for recruitment of adaptive immune cells.

Etiologies of NK Cell Deficiency

NK cells are lymphocytes that are critical for the immune response to viral infections. Patients with recurrent severe and refractory cutaneous viral and herpes viral infections should be evaluated for **NK cell deficiency (NKD)** with both enumeration and functional studies. However, ultimate evaluation should be completed with immunogenetic analysis as patients with diagnosed NKD may benefit from antiviral prophylaxis and eventual HSC transplant.

NKD accounts for a small subset of primary immunodeficiencies (PIDs) that often present as clinical and diagnostic challenges. In general, NKD is suspected in patients who appear to have increased susceptibility to herpesvirus infections as well as select other viral pathogens such a human papillomavirus (HPV).

NK cells can be decreased in number or function for many reasons. More commonly, severe illness and emotional stress can cause decreases of these cells. In addition, immunosuppressive medications such as corticosteroids, mycophenolate, cyclosporine, azathioprine, and 6-mercaptopurine can depress NK cells. Given many factors are known to affect the stability of NK cells, repetition of the test is required to document true deficiency. If a patient is found to have abnormal NK cell studies 3 times, drawn at least 1 month

apart, inborn errors in immunity should be also considered, as described next.

More than 50 PIDs include abnormalities in NK cells as part of their immunophenotypes. This occurs secondary to disruption in maturation, proliferation, or survival of NK cells. Forms of **severe combined immune deficiency (SCID)** including *IL2RG, JAK3,* and *AK2* deficiency are known to present with low or absent NK cell numbers. In addition, given the importance of lytic granule secretion to NK cytotoxicity, conditions with abnormal granule secretion, such as primary **hemophagocytic lymphohistiocytosis**, or abnormal cytoskeletal function, such as **Wiskott-Aldrich syndrome**, also can lead to NK cell aberrations.

NKDs are classified as classical or functional. In **classical NKD**, there is a significantly decreased or absent number of $CD3^{-}CD56^{+}$ cells, making up less than 1% of the total peripheral lymphocytes. Alternatively, although the number of NK cells can be normal in **functional NKD**, these cells are functionally impaired.

Classical NK Cell Deficiency

Classical NKDs include pathogenic variants in *MCM4*, *MCM10*, *GINS1*, *GATA2, RTEL1,* and *IRF8.*

MCM4 and *MCM10*

MCM (mini-chromosome maintenance complex member) 4 and 10 are a part of the MCM replisome progression complex important for DNA replication. *MCM4* is part of the *Cdc45-MCM2-7-GINS1* (CMG) helicase complex and *MCM10* is a replication factor associated with this complex. In times of cellular stress, variant complexes have resulted in abnormal DNA breakage (Fig. 167.2). These patients have a decreased number of NK cells, specifically $CD56^{dim}$ NK cells. $CD56^{dim}$ NK cells are mature NK cells that express CD16 (Fc receptor) and are important for ADCC. It is possible that $CD56^{dim}$ NK cells are particularly reliant on the MCM complex for survival. Alternatively, the pathogenic variant may cause an interruption along development before mature NK cell expansion. Patients with biallelic pathogenic variants in *MCM4* have Epstein-Barr virus (EBV)-driven lymphoproliferation and viral pneumonitis. As *MCM4* is widely expressed in many cells, these patients can also have adrenal insufficiency, short stature, and development delay.

MCM10-deficient patients have a similar immunologic phenotype related to their NK cell abnormalities and the patients reported were found to have severe cytomegalovirus (CMV) infection.

GINS1

Go-Ichi-Ni-San complex subunit 1 (GINS1) is a protein involved in the CMG helicase complex that is important for DNA replication. Biallelic pathogenic variants in *GINS* have been seen to cause growth retardation, neutropenia, and NKD. It is important to note that both $CD56^{dim}$ and $CD56^{bright}$ cells are affected in this disorder. *MCM4, MCM10,* and *GINS1* defects causing classical NKD suggests that chromosomal maintenance is critical to NK cell development and function.

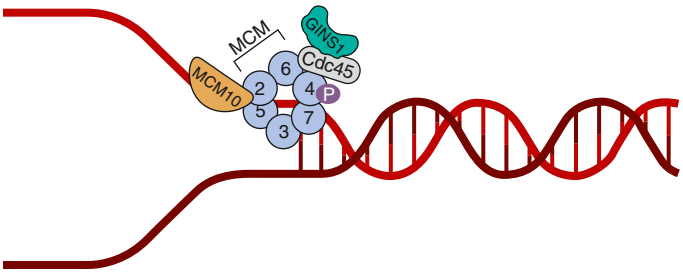

Fig. 167.2 Cell division cycle complex pathogenic variants associated with NK cell deficiency: *MCM4, MCM10, and GINS1*. Schematic illustration of the cell division cycle complex including the CMG (Cdc45, mini-chromosome maintenance [MCM 2-7], GINS1) helicase complex and *MCM10.*

GATA2

Pathogenic variants in *GATA2* (GATA-binding protein-2), inherited in an autosomal dominant manner, can cause immune aberrations affecting many different cell lines. The pathogenic variant prevents appropriate NK cell development with specific deficiency of immature $CD56^{bright}$ NK cells causing an absence of the $CD56^{bright}$ population, leaving a functionally impaired $CD56^{dim}$ population. These patients are known to have refractory HPV infections, among other cutaneous viral infections, myelodysplasias, cytopenias, and a risk of acute and chronic myeloid leukemias.

RTEL1

Biallelic pathogenic variants in regulator of telomerase elongation (*RTEL1)*, a DNA helicase, cause a form of **dyskeratosis congenita**, bone marrow failure, and immunodeficiency known as **Hoyeraal-Hreidarsson syndrome**. One patient reported with a history of disseminated varicella infection was found to have abnormal NK cells in number and function.

IRF8

Interferon regulatory factor 8 *(IRF8)* is a transcription factor involved in B-cell, dendritic cell, granulocyte, monocyte, and NK cell production. *IRF8* is vital for the NK cell response to viral infections and patients have been found to have severe EBV infections. Terminal NK cell maturation is disrupted and $CD56^{dim}$ cells are decreased in patients with biallelic *IRF8* pathogenic variants.

FUNCTIONAL NK CELL DEFICIENCY (FNKCD)

CD16 Deficiency

Patients with CD16 deficiency have severe infections with herpes viral pathogens such as varicella-zoster virus (VZV), herpes simplex virus (HSV) and EBV. One patient was reported to have EBV-driven Castleman disease. The deficiency is caused by a homozygous pathogenic variant in the *FCGR3A* gene, which encodes CD16. CD16 is the Fc receptor on NK cells required for ADCC. As CD16 deficiency is an FNKCD, patients have normal levels of NK cells, but abnormal function. Although CD16's main function is to facilitate ADCC, patients with CD16 deficiency have been found to have abnormal spontaneous cytotoxicity with normal antibody-dependent cytotoxicity (Fig. 167.3). Further analysis helped uncover a new function of the CD16 protein related to spontaneous cytotoxicity, which clarifies this unexpected finding. The variant sequence in CD16 deficiency encodes for the distal B73.1 domain of the CD16 molecule. Studies from patients with this pathogenic variant revealed that this region is needed for co-activation of the NK cell CD2 stimulatory receptor, which is required for spontaneous cytotoxicity. Alternatively, immunoglobulin binding, which is integral to ADCC, occurs at the proximal 3G8 domain of CD16, which is not affected by the variant. For diagnostic purposes, two anti-CD16 monoclonal antibodies are utilized against the distal B73.1 and proximal 3G8 domains. Therefore patients with CD16 deficiency will have absent B73.1 expression and normal 3G8 expression. These diagnostic tests can help identify patients with CD16 deficiency in addition to genetic analysis of *FCGR3A*.

ELF4

E74-like ETS transcription factor 4 (ELF4) is a protein involved in transactivation of gene promoters through DNA binding. Perforin expression, an important component of NK cell activity, has been shown to be dependent on ELF4-regulated promoters. Pathogenic variants in ELF4 can result in poor terminal NK cell maturation

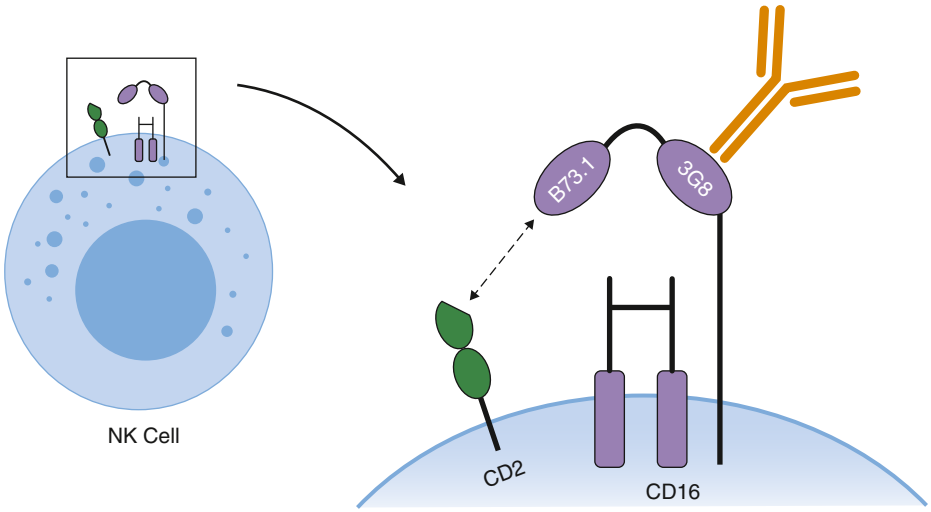

Fig. 167.3 Functional natural killer (NK) cell deficiency secondary to CD16 pathologic variants. Schematic of the CD16 (Fc) NK cell receptor. The proximal domain of the CD16 receptor, 3G8, binds the Fc portion of immunoglobulin, which is important for antibody-depending cytotoxicity. The distal domain of the CD16 receptor, B73.1, co-localizes with the CD2 stimulatory receptor facilitating spontaneous cytotoxicity. In *CD16* deficiency, the B73.1 domain of the CD16 receptor is not adequately expressed causing impaired spontaneous cytotoxicity.

from CD56^{bright} to CD56dim (cytotoxic) NK cells. A rare, hemizygous variant in ELF4, located on the X chromosome, has been described as a novel cause of NK cell deficiency. Patients with this variant can present with recurrent sinopulmonary and varicella zoster infections, as well as lymphoproliferative and malignant disease. Laboratory analysis has shown decreased number and function of NK cells, specifically with an abnormal immature NK cell CD56^{bright} to mature CD56dim NK cell ratio. Because these patients also can present with decreased B cells and hypogammaglobinemia, further work is needed to elucidate the role of ELF4 in B cell development and function.

NK Cell Diagnostic Tests

When evaluating for possible NK cell defects, it is important to examine the total NK cell count and percentage, the distribution of NK cell subsets, and NK cell function.

NK Cell Count and Percentage

The absolute NK cell count and NK cell percentage of total lymphocytes is often calculated using a lymphocyte subset analysis or enumeration assay. This test is performed using flow cytometry and will identify the CD16 and CD56 markers of NK cells. The majority of lymphocyte enumeration assays use a combined CD56/16 antibody and cannot distinguish between CD56^{bright} and CD56^{dim} NK cells. Further delineation of NK cell subsets (CD56^{dim}, CD56^{bright}, etc.) can be obtained with further flow cytometry for additional NK cell markers. Evaluation of NK cell phenotypes and ratios such as the CD56 bright to dim ratio becomes important in evaluating for NK cell defects such as *GATA2* deficiency.

FUNCTIONAL ASSAYS AVAILABLE FOR CLINICAL EVALUATION

NK Cell Cytotoxicity Assay

NK cytotoxic killing ability can be evaluated using a flow cytometry–based assay to quantify NK cell cytotoxic activity or a chromium release (^{51}CR) cytotoxicity assay. The ^{51}CR is technician dependent and requires the use of radioactive material. Many laboratories are doing the flow cytometry-based assay.

Individual clinical laboratories have normal ranges that are particular to their specific assay; however, the values for this assay are dependent on the percentage of NK cells present in the sample. A peripheral blood mononuclear cell (PBMC) sample with lower numbers of NK cells may not identify as much NK cell cytotoxicity as a sample with higher levels of NK cells, thus it is essential to take the percentage of NK cells into account when interpreting these assays.

CD107a Degranulation

Lysosomal-associated membrane protein-1 (LAMP-1) or CD107a is contained in NK cell lytic granules. CD107a is significantly upregulated on the surface of NK cells following lytic granule fusion with the NK cell membrane after activation by MHC I downregulated target cells. CD107a is thus often used as a way to evaluate activation-induced NK cell degranulation. In this test, NK cells are stimulated and the upregulation of CD107a is measured using flow cytometry.

CD107a degranulation has advantages and disadvantages when compared to the NK cell cytotoxicity assay. The main advantage is that CD107a degranulation can be measured in individual cells and is therefore independent of the NK cells percentage. The disadvantage is that it does not directly measure NK cell killing ability. NK cell killing can be impaired despite appropriate degranulation for reasons such as abnormal lytic effector molecules. Ten to 30% of resting NK cells can be induced to degranulate when measured by flow cytometry, and in normal individuals CD107a degranulation reasonably correlates with killing ability.

NK CELL DEFICIENCY TREATMENT

Primarily, treatment of NKD targets the infectious complications that occur in these patients. Specifically, HSV infections should be treated with antiviral therapy such as acyclovir. Long-term prophylaxis should be considered after completion of treatment. HPV infections can be significant and recurrent, and patients should be referred to dermatology for medical and surgical management.

Additional therapies such as immunoglobulin replacement and antimycobacterial prophylaxis can be utilized depending on the genetic cause of NKD. The only curative therapy for classical NKDs at this time is HSC transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

The Phagocytic System

Chapter 168

Neutrophils

Thomas D. Coates

THE PHAGOCYTIC INFLAMMATORY RESPONSE

The phagocyte system includes both granulocytes (neutrophils, eosinophils, and basophils) and mononuclear phagocytes (monocytes and tissue macrophages). Neutrophils and mononuclear phagocytes share primary functions, including the defining properties of large-particle ingestion and microbial killing. Phagocytes participate primarily in the innate immune response but also help initiate acquired immunity.

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hours (Table 168.1), but on encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues. There they ingest and kill microbes and release chemotactic signals to recruit more neutrophils and to attract dendritic cells and other initiators of the acquired immune response.

HEMATOPOIESIS

The hematopoietic progenitor system can be viewed as a continuum of functional compartments, with the most primitive compartment composed of very rare **pluripotential stem cells**, which have high self-renewal capacity and give rise to more mature stem cells, including cells that are committed to either lymphoid or myeloid development (Fig. 168.1). Common lymphoid progenitor cells give rise to T- and B-cell precursors and their mature progeny. Common myeloid progenitor cells eventually give rise to committed single-lineage progenitors of the recognizable precursors through a random process of lineage restriction in a stepwise process (see Chapter 495). The capacity of lineage-specific committed progenitors to proliferate and differentiate in response to demand provides the hematopoietic system with a remarkable range of response to changing requirements for mature blood cell production.

Table 168.1 Neutrophil and Monocyte Kinetics

NEUTROPHILS	
Average time in mitosis (myeloblast to myelocyte)	7-9 days
Average time in postmitosis and storage (metamyelocyte to neutrophil)	3-7 days
Average half-life in the circulation	6 hr
Average total body pool	6.5×10^8 cells/kg
Average circulating pool	3.2×10^8 cells/kg
Average marginating pool	3.3×10^8 cells/kg
Average daily turnover rate	1.8×10^8 cells/kg
MONONUCLEAR PHAGOCYTES	
Average time in mitosis	30-48 hr
Average half-life in the circulation	36-104 hr
Average circulating pool (monocytes)	1.8×10^7 cells/kg
Average daily turnover rate	1.8×10^9 cells/kg
Average survival in tissues (macrophages)	Months

From Boxer LA. Function of neutrophils and mononuclear phagocytes. In: Bennett JC, Plum F, eds. *Cecil Textbook of Medicine*. 20th ed. Philadelphia: Saunders; 1996.

The proliferation, differentiation, and survival of immature hematopoietic progenitor cells are governed by hematopoietic growth factors, a family of glycoproteins (see Chapter 495). Along with regulating proliferation and differentiation of progenitors, these factors influence the survival and function of mature blood cells. During granulopoiesis and monopoiesis, multiple cytokines regulate the cells at each stage of differentiation from pluripotent stem cells to nondividing, terminally differentiated cells (monocytes, neutrophils, eosinophils, and basophils). As cells mature, they lose receptors for most cytokines, especially those that influence early cell development; however, they retain receptors for cytokines that affect their mobilization and function, such as granulocyte and macrophage colony-stimulating factors. Mature phagocytes also express receptors for chemokines, which help direct the cells to sites of inflammation. Chemokine receptors such as CXCR4 and its ligand SDF-1 play a key role in retention of developing myeloid cells within bone marrow.

NEUTROPHIL MATURATION AND KINETICS

The process of intramedullary granulocyte maturation involves changes in nuclear configuration and accumulation of specific intracytoplasmic granules. The bone marrow microenvironment supports the normal steady-state renewal of peripheral blood neutrophils through the generation of growth and differentiation factors by stromal cells. Growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) not only stimulate cell division, but also induce the expression of transcription factors that regulate the biosynthesis of functional components of the neutrophil, such as granule proteins. The transcription factor PU.1 is essential for myelopoiesis, both as a positive regulatory element and as a suppressor of GATA1, a transcription factor that directs nonmyeloid differentiation. Other transcription factors, such as Runx1 (AML1), c-myb, CDP, C/EBPα, C/EBPγ, and MEF, are expressed in the myeloblast and promyelocyte, and some of these are required for azurophil granule protein expression. As cells enter the myelocyte stage, Runx1 and myb are downregulated, whereas PU.1 and C/EBPε expression rise to initiate terminal differentiation.

Granulocytes survive for only 6-12 hours in the circulation; therefore daily production of 2×10^4 granulocytes/μL of blood is required to maintain a level of circulating granulocytes of 5×10^3/μL (see Table 168.1). The relatively small peripheral blood pool includes the rapidly interchanging circulating and marginating pools; the latter provides entrance into the tissue phase, where neutrophils may survive for hours or days. The circulating pool is fed and buffered by a much larger marrow population of mature neutrophils and myeloid precursors, representing the marrow reserve and proliferating pools, respectively. Proliferation of myeloid cells, encompassing approximately five mitotic divisions, takes place only during the first three stages of neutrophil development, in myeloblasts, promyelocytes, and myelocytes. After the myelocyte stage, the cells terminally differentiate into nondividing, maturing metamyelocytes, bands, and neutrophils.

Neutrophil maturation is associated with nuclear condensation and lobulation and the sequential production of characteristic granule populations. A **myeloblast** is a relatively undifferentiated cell with a large oval nucleus, a sizable nucleolus, and a deficiency of granules. **Promyelocytes** acquire peroxidase-positive azurophilic (primary) granules, and then **myelocytes** and **metamyelocytes** acquire specific (secondary) granules; tertiary granules and secretory vesicles develop in the final stage of neutrophil maturation.

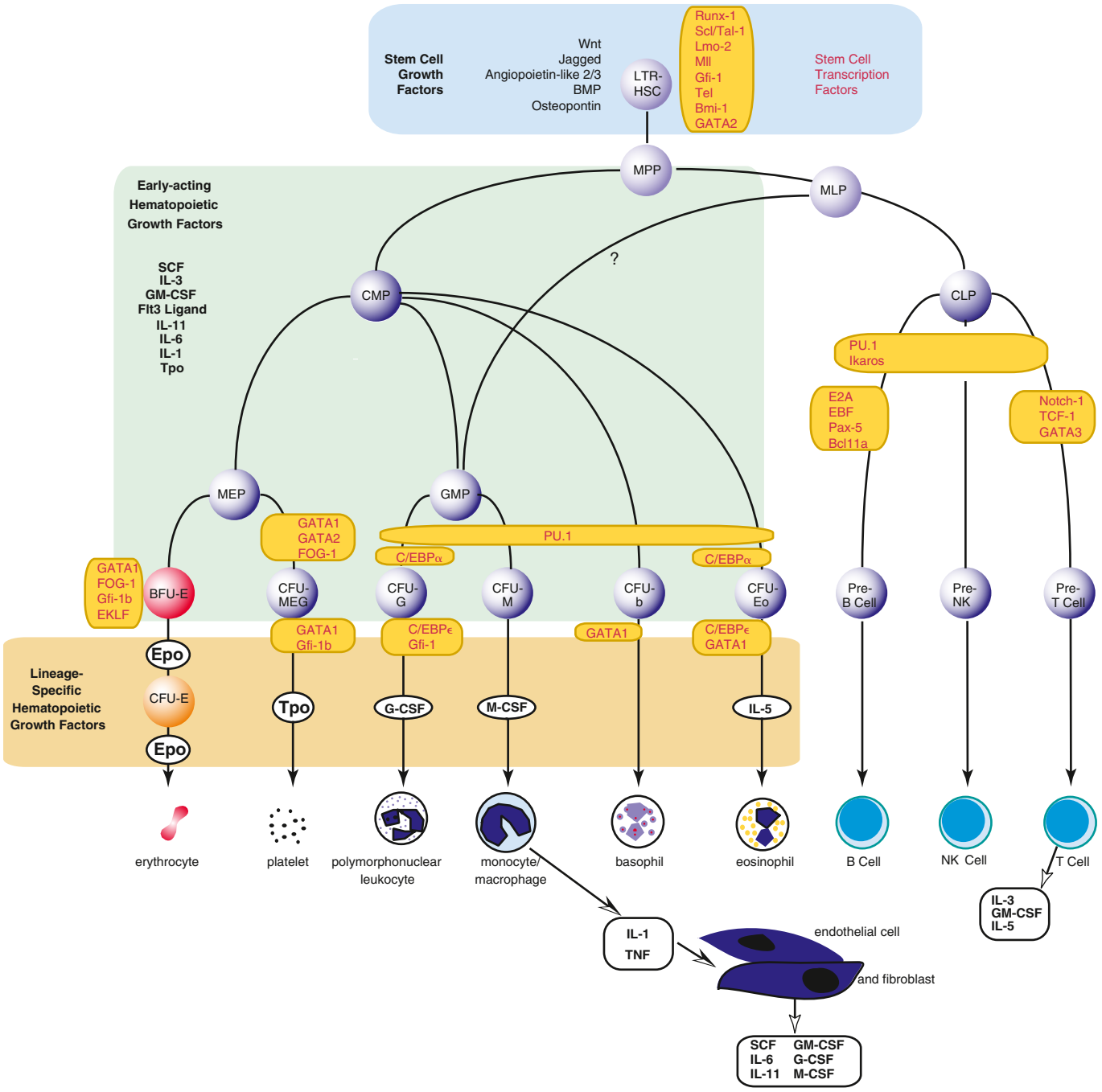

Fig. 168.1 Major cytokine sources and actions and transcription factor requirements for hematopoietic cells. Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblastoid cells, produce macrophage, granulocyte-macrophage, and granulocyte colony-stimulating factors (M-CSF, GM-CSF, G-CSF), interleukin-6 (IL-6), and probably stem cell factor (SCF) (cellular sources not precisely determined) after induction with endotoxin (macrophage) or IL-1/tumor necrosis factor (TNF) (endothelial cells and fibroblasts). T cells produce IL-3, GM-CSF, and IL-5 in response to antigenic and IL-1 stimulation. These cytokines have overlapping actions during hematopoietic differentiation, as indicated, and for all lineages, optimal development requires a combination of early-acting and late-acting factors. Transcription factors important for survival or self-renewal of stem cells are shown in *red* at the *top*, whereas stages of hematopoiesis blocked after the depletion of indicated transcription factors are shown in *red* for multipotent and committed progenitors. *(From Sieff CA, Daley GQ, Zon LI. Anatomy and physiology of hematopoiesis. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier; 2015. Fig 1.7.)*

NEUTROPHIL FUNCTION

Neutrophil responses are initiated as circulating neutrophils flowing through the postcapillary venules detect low levels of chemokines and other chemotactic substances released from a site of infection. The sequence of events as the neutrophil moves from circulating in the blood to the encounter and destruction of bacteria is carefully orchestrated by a series of biochemical events, defects of which are associated with genetic disorders of neutrophil function (Fig. 168.2). In fact, these disorders of neutrophil function lead to our understanding of the cell biology of phagocyte function. A subset of circulating neutrophils loosely adheres to the endothelium through low-affinity receptors called **selectins** and rolls along the endothelium, forming the marginated pool. Soluble effectors of inflammation trigger subtle changes in surface adhesion molecules

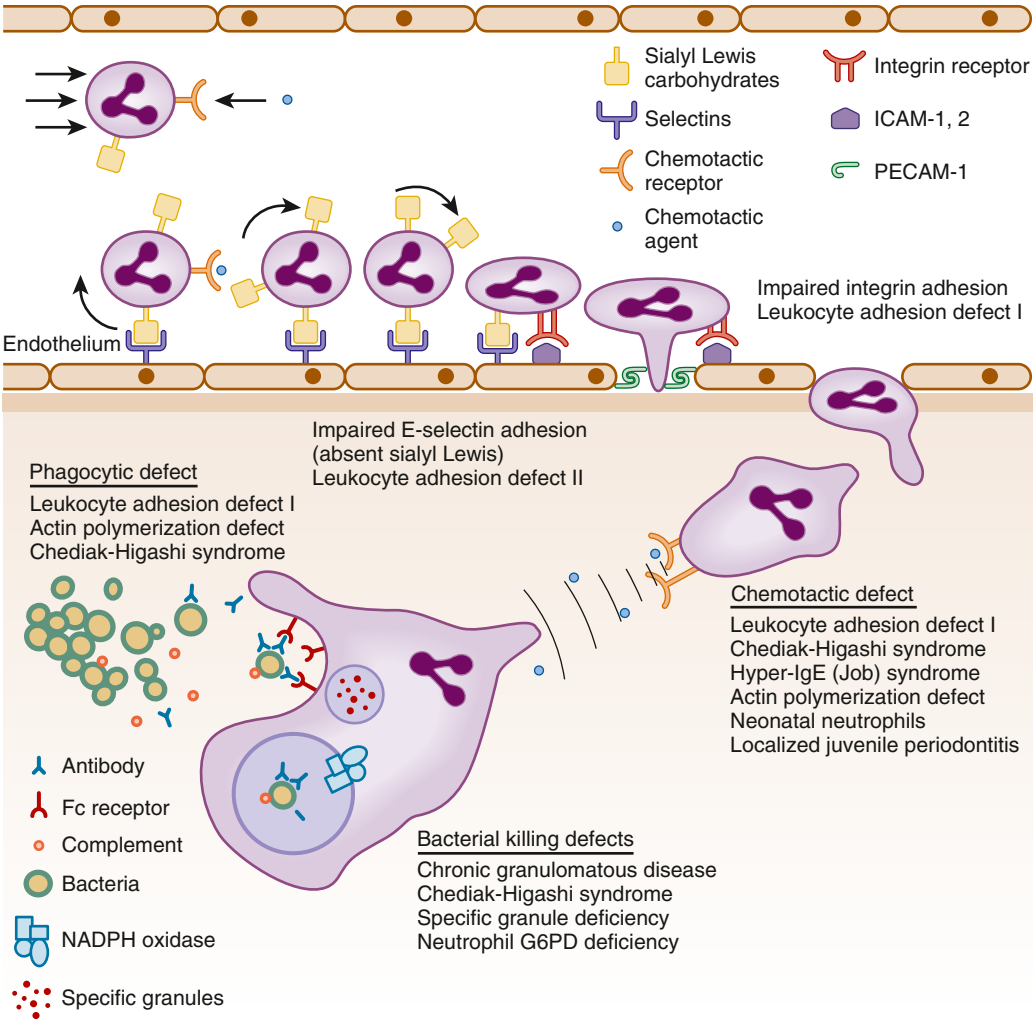

Fig. 168.2 The neutrophil-mediated inflammatory response and associated neutrophil dysfunction syndromes. Circulating neutrophils loosely attach to endothelium via selectins and roll along the vessel wall until they arrive at the site of infection. Inflammatory monokines, interleukin-1 (IL-1), and tumor necrosis factor (TNF) activate endothelial cells to express E- and P-selectins. E- and P-selectins serve as counter-receptors for neutrophils sialyl Lewis X and Lewis X to cause low-avidity neutrophil rolling. Activated endothelial cells express intracellular adhesion molecule (ICAM)-1, which serves as a counter-receptor for neutrophil β_2-integrin molecules, leading to high-avidity leukocyte spreading and the start of transendothelial migration at the infection site. Neutrophils invade through the vascular basement membrane with the release of proteases and reactive oxidative intermediates, causing local destruction of surrounding tissue at sites of high concentrations of chemotactic factors, and migrate to the site of infection, where they ingest and kill the bacteria. NADPH, Nicotinamide-adenine dinucleotide phosphate; PECAM, platelet endothelial cell adhesion molecule. *(Modified from Kyono W, Coates TD. A practical approach to neutrophil disorders. Pediatr Clin North Am. 2002;49:929.)*

on endothelial cells at the site of infection. The rolling of neutrophils allows more intense exposure of neutrophils to activating factors such as tumor necrosis factor or interleukin-1 (see Fig. 168.2). Exposure of neutrophils to these same activating factors induces qualitative and quantitative changes in the family of β_2-integrin adhesion receptors (the CD11/CD18 group of surface molecules), leading to tight adhesion between neutrophils and endothelial cells at the site of inflammation and ultimately to transmigration of the neutrophil into the tissue.

Once through the endothelium, the neutrophil senses the gradient of chemokines or other chemoattractants and migrates to sites of infection. **Neutrophil migration** is a complex process involving rounds of receptor engagement, signal transduction, and remodeling of the actin microfilaments composing in part the cytoskeleton. Actin polymerization-depolymerization occurs in approximately 8-second cycles and drives cyclic extension and retraction of the actin-rich lamella at the front of the neutrophil. Receptors at the leading edge of the lamella detect the gradient of attractant and follow microorganisms, then ingest and destroy them. When the neutrophil reaches the site of infection, it recognizes pathogens by means of Fc immunoglobulin and complement receptors, toll-like receptors, fibronectin receptors, and other adhesion molecules.

The neutrophil ingests microbes that are coated by **opsonins**, serum proteins such as immunoglobulin and complement component **C3**. The pathogens are engulfed into a closed vacuole, the **phagosome** (Fig. 168.3), where two cellular responses essential for optimal microbicidal activity occur concomitantly: degranulation and activation of nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent oxidase. Fusion of neutrophil granule membranes with the phagosome membrane delivers potent antimicrobial proteins and small peptides into the phagosome.

Assembly and activation of NADPH oxidase occur at the phagosome membrane as well (see Fig. 168.3), generating large amounts of superoxide (O_2^-) from molecular oxygen, which in turn decomposes to produce hydrogen peroxide (H_2O_2) and singlet oxygen. **Myeloperoxidase,** a major azurophil granule component, catalyzes the reaction

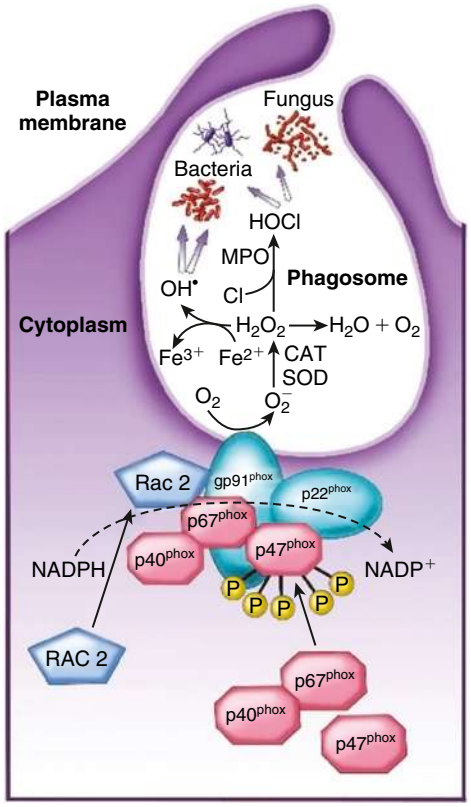

Fig. 168.3 Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components and activation. On activation of phagocytic cells, the 3 cytosolic components *(red)* of the NADPH oxidase (p67^{phox}, p47^{phox}, and p40^{phox}), plus the small guanosine triphosphatase (GTPase) protein Rac2, are translocated to the membrane of the phagocytic vacuole. The p47^{phox} subunit binds to the flavocytochrome$_{b558}$ membrane component *(blue-green)* of the NADPH oxidase (gp91^{phox} plus p22^{phox}). The NADPH oxidase catalyzes the formation of superoxide by transferring an electron from NADPH to molecular oxygen (O_2), thereby forming the superoxide free radical. The unstable superoxide anion is converted to hydrogen peroxide, either spontaneously or by superoxide dismutase (SOD). H_2O_2 can follow different metabolic pathways into more potent reactive oxidants, such as OH• or HOCl) or degradation to $H_2O + O_2$. *(Adapted from Stiehm ER, Ochs HD, Winkelstein JA. Immunologic Disorders in Infants and Children, 5th ed. Philadelphia: Saunders; 2004, p. 622.)*

of H_2O_2 with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. H_2O_2 and HOCl are potent microbicidal agents that break down and clear pathogens from sites of infection.

In addition, neutrophils secrete a wide variety of cytokines and chemokines that recruit more neutrophils to fight the infection, attract monocytes and macrophages that possess both microbicidal and scavenger functions, and promote antigen presentation to help initiate the adaptive immune response. Also, the reactive oxidants can inactivate chemotactic factors and may serve to terminate the process of neutrophil influx, thereby attenuating the inflammatory process. Finally, the release of reactive oxygen species, granule proteins, and cytokines can also damage local tissues, leading to the classic signs of inflammation or to more permanent impairment of tissue integrity and function. In addition to the role of neutrophils in tissue damage, they are now known to play a significant role in regulation of inflammation and promoting tissue repair. Turning off inflammation and removing tissue debris is an important role and, like seeking and destroying bacteria, this process is highly regulated as well.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 169

Eosinophils

Benjamin L. Wright and Brian P. Vickery

Eosinophils are nondividing, fully differentiated cells with a diameter of approximately 8 μm and a bilobed nucleus that are distinguished from other leukocytes by their morphology, constituent products, and association with specific diseases. Their characteristic membrane-bound specific granules stain bright pink with eosin and are cytotoxic for the larval stages of helminthic parasites and are also thought to contribute to much of the inflammation associated with chronic allergic diseases such as asthma (see Chapter 185). Eosinophil granule proteins including major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase are thought to inflict epithelial cell damage, although recent studies indicate their role may be more nuanced and not purely destructive. Eosinophil granule contents activate other proinflammatory cells, including mast cells, basophils, neutrophils, and platelets and have the capacity to generate large amounts of the lipid mediators, which can cause vasoconstriction, smooth muscle contraction, and mucus hypersecretion (Fig. 169.1). Eosinophils are a source of several proinflammatory cytokines and have also been shown to influence T-cell recruitment and immune polarization in inflammatory settings. Thus eosinophils have considerable potential to initiate and sustain the inflammatory response of the innate and acquired immune systems.

Eosinophil migration from the vasculature into the extracellular tissue is mediated by the binding of leukocyte adhesion receptors (e.g., VLA-4) to their ligands or counterstructures (VCAM-1) on the postcapillary endothelium. Eosinophils are recruited to tissues in inflammatory states by a group of chemokines known as **eotaxins** (eotaxin 1, 2, and 3). These unique pathways account for selective accumulation of eosinophils in allergic and inflammatory disorders. Eosinophils normally dwell primarily in tissues, especially tissues with an epithelial interface with the environment, including the respiratory, gastrointestinal (GI), and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

Interleukin (IL)-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophilopoiesis. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 (mepolizumab, reslizumab, benralizumab) decrease sputum eosinophils and reduce exacerbations in a subset of patients with asthma. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated on activation, normal T-cell expressed and secreted), eotaxin, and monocyte chemotactic proteins 3 and 4. These chemokines appear to be key mediators in the induction of tissue eosinophilia.

DISEASES ASSOCIATED WITH EOSINOPHILIA

The **absolute eosinophil count (AEC)** is used to quantify peripheral blood eosinophilia. Calculated as the white blood cell (WBC) count/μL × percentage of eosinophils, it is usually <450 cells/μL and varies diurnally, with eosinophil numbers higher in the early morning and diminishing as endogenous glucocorticoid levels rise.

Many diseases with allergic, infectious, hematologic, autoimmune, or idiopathic origins are associated with moderate (AEC 1,500-5,000 cells/μL) or severe (AEC >5,000 cells/μL) eosinophilia in peripheral blood (Table 169.1). These disorders may range from mild and transient to chronic and life-threatening. Importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in tissues and degranulation products may more accurately reflect disease activity. Because prolonged eosinophilia is associated with end-organ

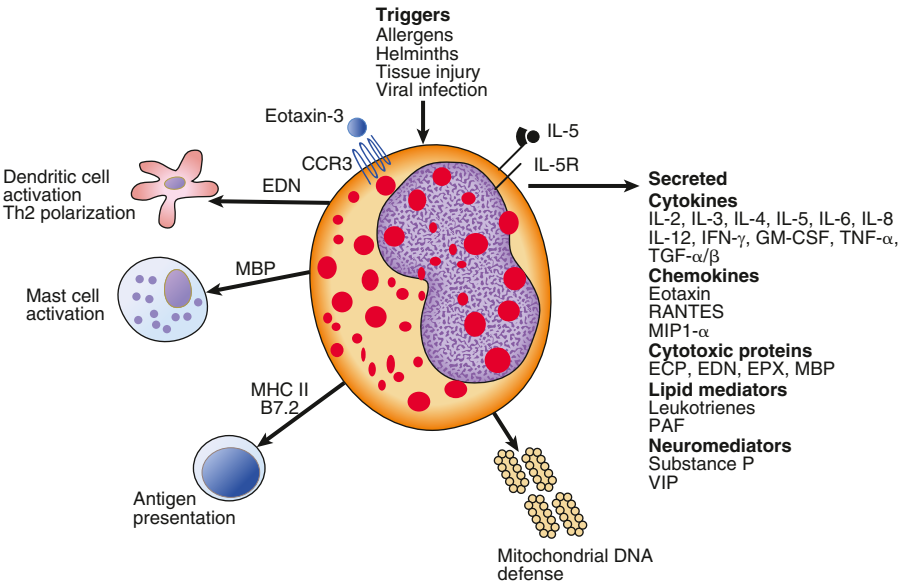

Fig. 169.1 Schematic diagram of an eosinophil and its diverse properties. Eosinophils are bilobed granulocytes that respond to diverse stimuli, including allergens, helminths, viral infections, allografts, and nonspecific tissue injury. Eosinophils express the receptor for interleukin (IL)-5, a critical eosinophil growth and differentiation factor, as well as the receptor for eotaxin and related chemokines (CCR3). The secondary granules contain four primary cationic proteins designated eosinophil peroxidase (EPX), major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). All four proteins are cytotoxic molecules; also, ECP and EDN are ribonucleases. In addition to releasing their preformed cationic proteins, eosinophils can release a variety of cytokines, chemokines, and neuromediators and generate large amounts of leukotriene C4 (LTC4). Last, eosinophils can be induced to express major histocompatibility complex (MHC) class II and co-stimulatory molecules and may be involved in propagating immune responses by presenting antigen to T cells. PAF, platelet activating factor; VIP, vasoactive intestinal peptide. *(From Leung YM, Szefler SJ, Bomilla FA, Akdis CA, Sampson HA. Pediatric Allergy: Principles and practice. 3rd ed. Philadelphia: Elsevier; 2016. p. 42.)*

damage, especially involving the heart, patients with persistently elevated AECs should undergo a thorough evaluation to search for an underlying cause.

Allergic Diseases

Allergy is the most common cause of eosinophilia in children in the United States. Patients with allergic asthma typically have eosinophils in the blood, sputum, and/or lung tissue. **Hypersensitivity drug reactions** can elicit eosinophilia, and when associated with organ dysfunction (e.g., DRESS [drug rash with eosinophilia and systemic symptoms]), these reactions can be serious (see Chapter 193). If a drug is suspected of triggering eosinophilia, biochemical evidence of organ dysfunction should be sought, and if found, the drug should be discontinued. Various skin diseases have also been associated with eosinophilia, including atopic dermatitis/eczema, pemphigus, urticaria, and toxic epidermal necrolysis.

Eosinophilic gastrointestinal diseases (EGIDs) are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 383). In these conditions, eosinophils are recruited to the esophagus, stomach, and/or intestine, where they may cause tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, or diarrhea. Eosinophilic esophagitis is the most common EGID. Treatment options include proton pump inhibitors, allergen elimination diets, topical corticosteroids, and biologics (e.g. dupilumab). Patients with nonesophageal EGIDs often require treatment with systemic steroids.

Infectious Diseases

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 169.1 includes examples of specific organisms. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion, especially by larvae such as **visceral larva migrans** (see Chapter 344). Eosinophilia often *does not* occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the GI tract, such as *Giardia lamblia* and *Enterobius vermicularis* infection.

In evaluating patients with unexplained eosinophilia, the dietary history and geographic or travel history may indicate potential exposures to helminthic parasites. It is frequently necessary to examine the stool for ova and larvae at least three times. Additionally, the diagnostic parasite stages of many of the helminthic parasites that cause eosinophilia never appear in feces. Thus normal results of stool examinations do not absolutely preclude a helminthic cause of eosinophilia; diagnostic blood tests or tissue biopsy may be needed. *Toxocara* causes visceral larva migrans usually in toddlers with pica (see Chapter 344). Most young children are asymptomatic, but some develop fever, pneumonitis, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohemagglutinins are frequently elevated, and serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 283) and **coccidioidomycosis** (see Chapter 286) following primary infection, especially in conjunction with erythema nodosum. HIV infection can also be associated with peripheral eosinophilia.

Hypereosinophilic Syndrome

The idiopathic hypereosinophilic syndrome is a heterogeneous group of disorders characterized by sustained overproduction of eosinophils. The three diagnostic criteria for this disorder are (1) AEC >1,500 cells/μL persisting for 6 months or longer or at least on two occasions or with evidence of tissue eosinophilia; (2) absence of another diagnosis to explain the eosinophilia; and (3) signs and symptoms of organ involvement. The clinical signs and symptoms of hypereosinophilic syndrome can be heterogeneous because of the diversity of potential organ (pulmonary, cutaneous, neurologic, serosal, GI) involvement. Organ-specific signs and symptoms direct the diagnostic evaluation, but common initial tests used to evaluate hypereosinophilia and potential end-organ complications include a comprehensive metabolic panel, inflammatory markers, troponin level, urinalysis, antineutrophil cytoplasmic antibodies, immunoglobulin levels, vitamin B_{12} level, tryptase level, stool examination for ova and parasites, parasite serologies, HIV testing, and a chest x-ray. Eosinophilic endomyocardial disease, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Screening for cardiac involvement should also include an electrocardiogram, an echocardiogram, and in some cases a cardiac MRI. Evaluation of the hypereosinophilic syndrome requires morphologic review of the blood and marrow, cytogenetics, fluorescence in situ hybridization, immunophenotyping by flow cytometry, and T-cell clonality assessment to detect histopathologic or clonal evidence for hematolymphoid neoplasm. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome

Table 169.1 Causes of Eosinophilia

ALLERGIC DISORDERS
- Allergic rhinitis
- Asthma
- Acute and chronic urticaria
- Atopic dermatitis
- Angioedema
- Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
- Eosinophilic gastrointestinal disorders
- Interstitial nephritis
- Mastocytosis

INFECTIOUS DISEASES

Tissue-Invasive Helminth Infections and Other Infections
- Trichinosis
- Toxocariasis
- Strongyloidiasis
- Ascariasis
- Filariasis
- Schistosomiasis
- Echinococcosis
- Amebiasis
- Malaria
- Scabies
- Toxoplasmosis
- *Pneumocystis jirovecii*
- Scarlet fever
- Allergic bronchopulmonary aspergillosis (ABPA)
- Coccidioidomycosis
- Human immunodeficiency virus (HIV)

MALIGNANT DISORDERS
- Hodgkin disease and T-cell lymphoma
- Acute myelogenous leukemia
- Myeloproliferative disorders
- Eosinophilic leukemia
- Brain tumors

GASTROINTESTINAL DISORDERS
- Inflammatory bowel disease
- Peritoneal dialysis
- Chronic active hepatitis

Eosinophilic Gastrointestinal Disorders
- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic enteritis
- Eosinophilic colitis

RHEUMATOLOGIC DISEASE
- Rheumatoid arthritis
- Eosinophilic fasciitis
- Scleroderma
- Dermatomyositis
- Systemic lupus erythematosus
- IgG4-related disease
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)

IMMUNODEFICIENCY/IMMUNE DYSREGULATION DISEASE
- Hyperimmunoglobulin E syndromes
- Wiskott-Aldrich syndrome
- Graft-versus-host disease
- Omenn syndrome
- Severe congenital neutropenia
- Autoimmune lymphoproliferative syndromes (ALPS)
- Immune dysregulation, polyendocrinopathy, X-linked (IPEX) and IPEX-like syndrome
- Transplant rejection (solid organ)

MISCELLANEOUS
- Thrombocytopenia with absent radii
- Hypersensitivity pneumonitis
- Adrenal insufficiency
- Postirradiation of abdomen
- Histiocytosis with cutaneous involvement
- Hypereosinophilic syndromes
- Cytokine infusion
- Pemphigoid

by demonstrating a clonal interstitial deletion on chromosome 4q12 that fuses the platelet-derived growth factor receptor-α *(PDGFRA)* and FIP1-like-1 *(FIP1L1)* genes; this disorder is treated with imatinib mesylate, a tyrosine kinase inhibitor, which helps target the fusion oncoprotein (Fig. 169.2).

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Patients with possible exposure to *Strongyloides* should receive concomitant empiric treatment with ivermectin to prevent corticosteroid-associated hyperinfection syndrome. Imatinib mesylate may be effective in FIP1L1-PDGFRA–negative patients. Hydroxyurea or interferon-alfa may be beneficial in patients unresponsive to corticosteroids. Specific anti–IL-5 monoclonal antibodies (mepolizumab) target this cytokine, which has a central role in eosinophil differentiation, mobilization, and activity. With therapy, the eosinophil count declines and corticosteroid doses may be reduced. For patients with prominent organ involvement who fail to respond to therapy, the mortality is about 75% after 3 years.

Miscellaneous Diseases

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyper-IgE syndrome, Wiskott-Aldrich syndrome, and Omenn syndrome (see Chapter 165). Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include GI disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis), mastocytosis, and adrenal insufficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

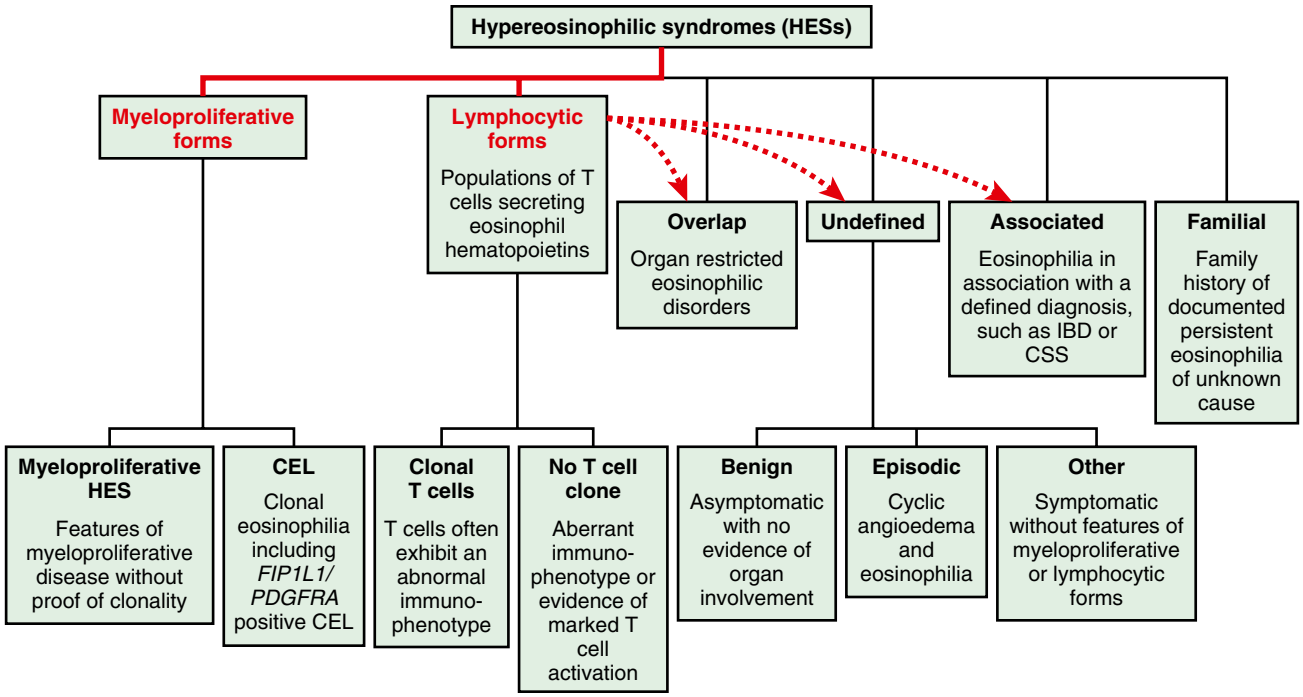

Fig. 169.2 Revised classification of hypereosinophilic syndromes. Changes from the previous classification are indicated in *red*. *Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin–producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CEL, Chronic eosinophilic leukemia; CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. *(From Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol. *2010;126:45-49.)*

Chapter 170

Disorders of Phagocyte Function

Thomas D. Coates

Neutrophils are the first line of defense against microbial invasion. They arrive at the site of inflammation during the critical 2-4 hours after microbial invasion to contain the infection and prevent hematogenous dissemination. Much of our knowledge about neutrophil function derives from studies done in patients with genetic errors in neutrophil function. These critical functions and their associated disorders are depicted in Figure 168.2. Children with phagocytic dysfunction present at a young age with recurrent infections that often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise <20% of immunodeficiencies, and there is significant overlap in the presenting signs and symptoms between phagocytic disorders and lymphocyte and humeral disorders. Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, cutaneous lesions, or osteomyelitis rather than bloodstream infections (Tables 170.1 and 170.2; Fig. 170.1). In the past, diagnosis of these disorders relied on very specialized biologic assays. Because the genes for most of these disorders have been identified, the first step in diagnosis for all of these disorders is to obtain DNA analysis through commercially available genetic panels for immunodeficiency.

Chemotaxis, the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 168). Disorders of adhesion or granule abnormalities can have intermediate or profound motility defects, and the propensity to infections is related to a combination of these functional deficits. One family with recessively inherited neutrophil actin dysfunction demonstrated that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children with various clinical conditions. However, unless chemotaxis is essentially absent, it is difficult to establish whether frequent infections arise from a primary chemotactic abnormality or occur as secondary medical complications of the underlying disorder. Dental infection with *Capnocytophaga* is associated with a clear neutrophil motility defect that resolves when the infection is eliminated.

Motility defects present with significant skin and mucosal infections. Tender cutaneous nodular lesions may also be present and characteristically do not contain neutrophils. In fact, the presence of a true abscess makes the diagnosis of a significant chemotactic defect less likely.

Laboratory tests of chemotaxis are biologic assays and have high variability except in the most experienced hands. The assays must be done on freshly obtained blood and are affected by many factors related to the blood sampling. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

Table 170.1 Infections and White Blood Cell Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	**DIAGNOSIS TO CONSIDER**	**SITE OF INFECTION**	**DIAGNOSIS TO CONSIDER**	**MICRO-ORGANISM**	**DIAGNOSIS TO CONSIDER**	**SITE OF INFECTION**	**DIAGNOSIS TO CONSIDER**
Cellulitis	Neutropenia, LAD, CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrophil motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, Bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyper-IgE syndrome; LAD, leukocyte adhesion deficiency; MPO, myeloperoxidase; MSMD, mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.
From Leung DYM. *Pediatric Allergy: Principles and Practice*. 2nd ed. Philadelphia: Saunders; 2010. p. 134.

Table 170.2 Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome (CHS)	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is *CHSI/LYST*, which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections; propensity to develop marked hepatosplenomegaly as a manifestation of hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a pathogenic variant or arising from reduced expression of *Gfi-1* or *C/EBPε*, which regulates specific granule formation	Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B_{12}–binding protein, and lactoferrin	Recurrent deep-seated abscesses
ADHESION ABNORMALITIES			
Leukocyte adhesion deficiency 1 (LAD-1)	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β_2-integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of iC3b to neutrophils and impaired adhesion to ICAM-1 and ICAM-2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2 (LAD-2)	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol conjugates arising from pathogenic variants of GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from pathogenic variants of *FERMT3*, which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia, recurrent infections, bleeding tendency

Continued

Table 170.2 Clinical Disorders of Neutrophil Function—cont'd

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DISORDERS OF CELL MOTILITY			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16, which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, possibly the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, amyloidosis
DEPRESSED MOTILE RESPONSES			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, CHS, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express β_2-integrins, and there is a qualitative impairment in β_2-integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is *STAT3*	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome–AR	Autosomal recessive; more than one gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
MICROBICIDAL ACTIVITY			
Chronic granulomatous disease (CGD)	X-linked and AR; failure to express functional $gp91^{phox}$ in the phagocyte membrane in $p22^{phox}$ (AR) Other AR forms of CGD arise from failure to express protein $p47^{phox}$ or $p67^{phox}$	Failure to activate neutrophil respiratory burst, leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	<5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase; hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense variant	H_2O_2-dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by variant protein of Rac2-mediated functions	Failure of membrane receptor–mediated O_2^- generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H_2O_2	Excessive formation of H_2O_2	Minimal problems with recurrent pyogenic infections

AMP, Adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; IL-1, interleukin-1; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Adapted from Curnutte JT, Boxer LA. Clinically significant phagocytic cell defects. In: Remington JS, Swartz MN, eds. *Current Clinical Topics in Infectious Disease*. 6th ed. New York: McGraw-Hill; 1985. p. 144.

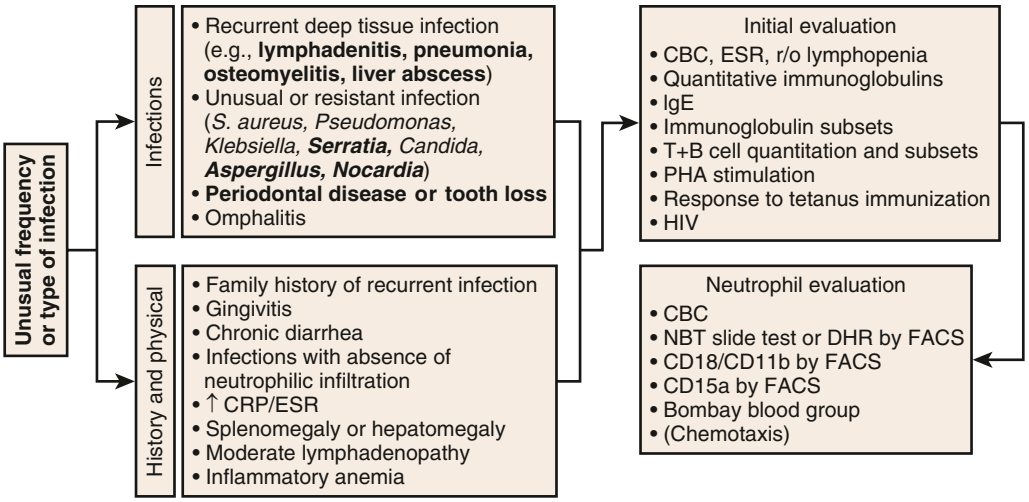

Fig. 170.1 Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The complete blood count (CBC) can detect marked leukocytosis in leukocyte adhesion deficiency (LAD) and giant granules of Chédiak-Higashi syndrome may be seen on the smear. Chemotaxis and all other neutrophil function assays require highly specialized research laboratories. CD, Cluster of differentiation; CRP, C-reactive protein; DHR, dihydrorhodamine; ESR, erythrocyte sedimentation rate; FACS, fluorescence-activated cell sorter; HIV, human immunodeficiency virus; IgE, immunoglobulin E; NBT, nitroblue tetrazolium; PHA, phytohemagglutinin. *(Adapted from Dinauer, MC, Coates TD: Disorders of neutrophil function. In: Hoffman R, Benz EJ, Silberstein LE, et al., eds.* Hematology: Basic Principles and Practice. *6th ed. Philadelphia: Saunders; 2012.)*

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency types 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about 1 per 10 million individuals and is characterized by recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 170.3).

Genetics and Pathogenesis

LAD-1 results from pathogenic variants of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β_2-leukocyte transmembrane integrin subunit. Normal neutrophils express four heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and $\alpha_{1\beta2}$ (CD11d/CD18). These four transmembrane adhesion molecules are composed of unique extracellular α_1 encoded on chromosome 16, and they share a common β_2 subunit (CD18) that links them to the membrane and connects them to intracellular signal transduction machinery. This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms, which promotes phagocytosis and particulate activation of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Some pathogenic variants of CD11/CD18 allow a low level of assembly and activity of integrin molecules, resulting in retention of some neutrophil integrin adhesion function and a moderate phenotype.

Because of their inability to adhere firmly to intercellular adhesion molecules 1 (ICAM-1) and 2 (ICAM-2) expressed on inflamed endothelial cells (see Chapter 168), neutrophils cannot transmigrate through the vessel wall and move to the site infection. Furthermore, neutrophils that do arrive at inflammatory sites fail to recognize microorganisms opsonized with complement fragment **iC3b**, an important stable opsonin formed by the cleavage of C3b. Therefore other neutrophil functions such as degranulation and oxidative metabolism normally triggered by iC3b binding are also greatly compromised in LAD-1 neutrophils, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Monocyte function is also impaired, with poor fibrinogen-binding function, an activity that is promoted by the CD11/CD18 complex. Consequently, such cells are unable to participate effectively in wound healing.

Children with **LAD-2** share the clinical features of LAD-1 but have normal CD11/CD18 integrins. Features unique to LAD-2 include neurologic defects, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen (**Bombay** phenotype). LAD-2 (also known as **congenital disorder of glycosylation IIc (CDG-IIc)** derives from pathogenic variants in the gene encoding a specific guanosine diphosphate (GDP)-L-fucose transporter of the Golgi apparatus. This abnormality prevents the incorporation of fucose into various cell surface glycoproteins, including the carbohydrate structure sialyl Lewis X that is critical for low-affinity rolling adhesion of neutrophils to vascular endothelium. This is an important initial step necessary for subsequent integrin-mediated activation, spreading, and transendothelial migration. Infections in LAD-2 are milder than that in LAD-1.

LAD-3 is characterized by a **Glanzmann thrombasthenia–like** bleeding disorder, delayed separation of the umbilical cord, and serious skin and soft tissue infections similar to those seen in LAD-1, and failure of leukocytes to undergo β_2- and β_1-integrin–mediated adhesion and migration. Pathogenic variants in *KINDLIN3* affect integrin activation.

Clinical Manifestations

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β_2-integrin molecules, whereas patients with the moderate phenotype may express 2–7% of the normal amount. Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. Significant neutrophilic leukocytosis, often >25,0000/mm^3, is a prominent feature. They may have a history of delayed separation of the umbilical cord, usually with associated infection of the cord stump. The presence of significant omphalitis is an important feature that distinguishes these rare patients from the 10% of healthy infants who can have cord separation at age 3 weeks or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 170.2). The ulcers heal slowly, need months of antibiotic treatment, and often require plastic surgery grafting. Severe gingivitis can lead to early loss of primary and secondary teeth (Fig. 170.3). Infected areas characteristically have very little neutrophilic infiltration (absent pus).

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 171) and

Table 170.3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD-1)	TYPE 2 (LAD-2 OR CDG-IIc)	TYPE 3 (LAD-3)	E-SELECTIN DEFICIENCY	Rac2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	β_2-Integrin common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis X, CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

CDG-IIc, Congenital disorder of glycosylation IIc, OMIM, Online Mendelian Inheritance in Man.
From Leung DYM. *Pediatric Allergy: Principles and Practice.* 2nd ed. Philadelphia: Saunders; 2010. p. 139.



Fig. 170.2 Skin infection of a patient with leukocyte adhesion deficiency type 1. Failure to form pus, inability to demarcate the fibrotic skin debris, and limited inflammation. *Enterococcus gallinarium* was cultured from the wound. *(From Rich RR. Clinical Immunology:* Principles and Practice. *4th ed. Philadelphia: Saunders; 2013, p. 273.)*

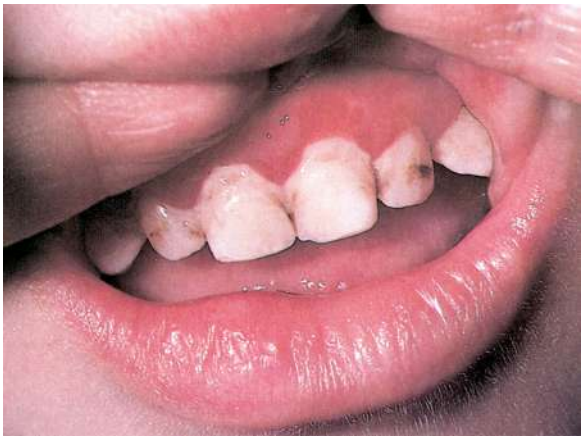

Fig. 170.3 Oral pathology in a patient with leukocyte adhesion deficiency type 1 (LAD-1). Gingivitis and severe periodontitis are hallmarks of LAD-1. *(From Rich RR.* Clinical Immunology: Principles and Practice. *4th ed. Philadelphia: Saunders; 2013, p. 273.)*

include *Staphylococcus aureus* and enteric gram-negative organisms such as *Escherichia coli.* These patients are also susceptible to opportunistic infection by fungi such as *Candida* and *Aspergillus.* Typical signs of inflammation, such as swelling, erythema, and warmth, may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/μL and can surpass 100,000/μL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/μL. LAD-1 genotypes with only moderate, rather than absent, amounts of functional integrins at the surface of the neutrophil have significantly reduced severity and frequency of infections compared with children with the severe form, although gingival disease is still a prominent feature.

Laboratory Findings

The diagnosis of LAD-1 is established most readily by flow cytometric measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and iC3b-mediated phagocytosis demonstrate striking abnormalities. However, these assays are not clinically available. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis, although some patients have impaired T-lymphocyte–dependent antibody responses. The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils. It is important to note that the flow cytometric assays are not done the same as the more common lymphocyte subset analysis and require specialized approaches to detect levels of surface expression, especially to detect milder phenotypes.

Treatment

Treatment of LAD-1 depends on the phenotype, as determined by the level of expression of functional CD11/CD18 integrins. Early allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for severe LAD-1 (and LAD-3). One patient was successfully treated with ustekinumab, an inhibitor of interleukins 12 and 23. Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim/sulfamethoxazole (TMP/SMX) and should have close surveillance for early identification of infections and initiation of empirical treatment with broad-spectrum antibiotics. Specific determination of the etiologic agent by culture or biopsy is important because of the prolonged antibiotic treatment required in the absence of neutrophil function.

Some LAD-2 patients have responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules, accompanied by marked improvement in leukocyte adhesion.

Prognosis

The severity of infectious complications correlates with the degree of β_2-integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by defective degranulation of neutrophils, a mild bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening form of **hemophagocytic lymphohistiocytosis** (see Chapter 556.2). CHS is caused by a fundamental defect in granule morphogenesis that results in abnormally large granules in multiple tissues. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes. Neurologic deficits are associated with a failure of decussation of the optic and auditory nerves. Patients exhibit an increased susceptibility to infection that can be explained only in part by defects in neutrophil function. The patients have progressive neutropenia as well as abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene variant in CHS, is located at chromosome 1q2-q44. The LYST/CHS protein is thought to regulate vesicle transport by mediating protein-protein interaction and protein-membrane associations. Loss of function may lead to indiscriminate interactions with lysosomal surface proteins, yielding giant granules through uncontrolled fusion of lysosomes with each other.

Almost all cells of patients with CHS show some oversized and dysmorphic lysosomes, storage granules, or related vesicular structures. Melanosomes are oversized, and delivery to the keratinocytes and hair follicles is compromised, resulting in hair shafts devoid of pigment granules. This abnormality in melanosomes leads to the macroscopic impression of hair and skin that is lighter than expected from parental coloration. The same abnormality in melanocytes leads to the partial ocular albinism associated with light sensitivity.

Beginning early in neutrophil development, spontaneous fusion of giant primary granules with each other or with cytoplasmic membrane components results in huge secondary lysosomes with reduced contents of hydrolytic enzymes, including proteinases, elastase, and cathepsin G. This deficiency of proteolytic enzymes may be responsible for the impaired killing of microorganisms by CHS neutrophils.

Clinical Manifestations

Patients with CHS have light skin and silvery hair and frequently complain of solar sensitivity and photophobia that is associated with rotary nystagmus. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous membranes, skin, and respiratory tract. Affected children are susceptible to gram-positive bacteria, gram-negative bacteria, and fungi, with *S. aureus* being the most common offending organism. The **neuropathy** may be sensory or motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem.

Patients with CHS have prolonged bleeding times with normal platelet counts, resulting from impaired platelet aggregation associated with a deficiency of the dense granules containing adenosine diphosphate and serotonin.

The most life-threatening complication of CHS is the development of an accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. The onset of the accelerated phase, which can occur at any age, is now recognized to be a genetic form of hemophagocytic lymphohistiocytosis. This occurs in 85% of patients and usually results in death.

Laboratory Findings

The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films and are accentuated by a peroxidase stain. Because of impaired egress from the bone marrow, cells containing the large inclusions may be missed on peripheral blood smear but readily identified on bone marrow examination. The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.

Treatment

High-dose ascorbic acid (200 mg/day for infants; 2,000 mg/day for adults) may improve the clinical status of some children in the stable phase. Although controversy surrounds the efficacy of ascorbic acid, given the safety of the vitamin, it is reasonable to administer ascorbic acid to all patients.

The only curative therapy to prevent the accelerated phase is HSCT. Normal stem cells reconstitute hematopoietic and immunologic function, correct the NK cell deficiency, and prevent conversion to the accelerated phase, but cannot correct or prevent the neuropathy. If the patient is in the accelerated phase with active hemophagocytic lymphohistiocytosis, HSCT often fails to prevent death. While HSCT can cure the neutrophil defect and hemophagocytic lymphohistiocytosis, it does nothing for neurologic complications.

MYELOPEROXIDASE DEFICIENCY

Myeloperoxidase (MPO) deficiency is an autosomal recessive disorder of oxidative metabolism and is one of the most common inherited disorders of phagocytes, occurring at a frequency approaching 1 per 2,000 individuals. MPO is a green heme protein located in the azurophilic lysosomes of neutrophils and monocytes and is the basis for the greenish tinge to pus accumulated at a site of infection.

Clinical Manifestations

MPO deficiency is usually clinically silent. Rarely, patients may have disseminated candidiasis, usually in conjunction with diabetes mellitus. Acquired partial MPO deficiency can develop in acute myelogenous leukemia and in myelodysplastic syndromes.

Laboratory Findings

Deficiency of neutrophil and monocyte MPO can be identified by histochemical analysis. Severe MPO deficiency can cause the dihydrorhodamine (DHR) flow cytometric assay for chronic granulomatous disease (CGD) to be falsely positive. Unlike CGD, eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy for MPO deficiency. Aggressive treatment with antifungal agents should be provided for candidal infections. The prognosis is usually excellent.

CHRONIC GRANULOMATOUS DISEASE

CGD is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but unable to kill **catalase-positive microorganisms** because of a defect in the generation of microbicidal oxygen metabolites. CGD is a rare disease, affecting 4-5 per 1 million individuals; it is caused by four genes: one X-linked and three autosomal recessive inheritance (Table 170.4).

Genetics and Pathogenesis

Activation of the phagocyte NADPH oxidase requires stimulation of the neutrophils and involves assembly from cytoplasmic and integral membrane subunits (see Fig. 168.3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, $p47^{phox}$ (47-kDa phagocyte oxidase protein). Phosphorylated $p47^{phox}$, together with two other cytoplasmic components of the oxidase, $p67^{phox}$ and the low-molecular-weight guanosine triphosphatase Rac2, translocates to the membrane, where they combine with the cytoplasmic domains of the transmembrane flavocytochrome b_{558} to form the active oxidase complex. The flavocytochrome is a heterodimer composed of $p22^{phox}$ and highly glycosylated $gp91^{phox}$. The

Table 170.4 Classification of Chronic Granulomatous Disease

COMPONENT AFFECTED	INHERITANCE	SUBTYPE*	FLAVOCYTOCHROME b SPECTRUM	NBT SCORE (% POSITIVE)	INCIDENCE (% OF CASES)
gp91^{phox}	X	X91^{0}	0	0	60
		X91^{-}	Low	80-100 (weak)	5
		X91^{-}	Low	5-10	<1
		X91^{+}	0	0	1
p22^{phox}	A	A220	0	0	4
		A22^{+}	N	0	<1
p47^{phox}	A	A470	N	0†	25
p67^{phox}	A	A670	N	0	5
		A67^{+}	N	0	<1
p40^{phox}	A	A40^{-}	N	100	<1

*In this nomenclature, the first letter represents the mode of inheritance (X-linked [X] or autosomal recessive [A]), whereas the number indicates the *phox* component that is genetically affected. The superscript symbols indicate whether the level of protein of the affected component is undetectable (^{0}), diminished ($^{-}$), or normal ($^{+}$), as measured by immunoblot analysis.

†Can be weakly positive.

NBT, Nitroblue tetrazolium.

From Dinauer MC, Newburger PE, Borregaard N. Phagocyte system and disorders of granulopoiesis and granulocyte function. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Elsevier; 2015. Table 22.12, p. 833.

gp91^{phox} glycoprotein catalyzes electron transport through its NADPH-binding, flavin-binding, and heme-binding domains. Defects in any of these NADPH oxidase components can lead to CGD.

Approximately 65% of patients with CGD are males who inherit their disorder as a result of pathogenic variants in *CYBB*, an X-chromosome gene encoding gp91^{phox}. Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from pathogenic variants in the *NCF1* gene on chromosome 7, encoding p47^{phox}. Defects in the genes encoding p67^{phox} (*NCF2* on chromosome 1) and p22^{phox} (*CYBA* on chromosome 16) are inherited in an autosomal recessive manner and account for approximately 5% of cases of CGD.

The CGD phagocytic vacuoles lack microbicidal reactive oxygen species and remain acidic, so bacteria are not killed or digested properly (Fig. 170.4). Hematoxylin-eosin–stained sections from patients' tissues show multiple granulomas that give CGD its descriptive name.

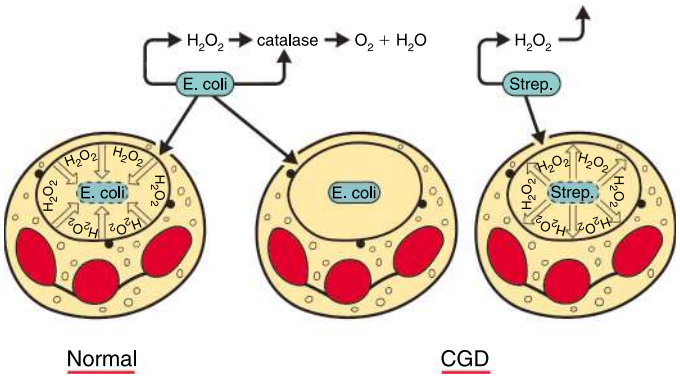

Fig. 170.4 Pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide (H_2O_2) in the phagosome containing ingested *Escherichia coli*. Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the *closed circles*. In this setting, H_2O_2 acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of H_2O_2 produced by the normal neutrophil is sufficient to exceed the capacity of catalase, an H_2O_2-catabolizing enzyme of many aerobic microorganisms, including *Staphylococcus aureus,* most gram-negative enteric bacteria, *Candida albicans,* and *Aspergillus.* When organisms such as *E. coli* gain entry into CGD neutrophils, they are not exposed to H_2O_2 because the neutrophils do not produce it, and the H_2O_2 generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough H_2O_2 to result in a microbicidal effect. As indicated *(middle),* catalase-positive microbes such as *E. coli* can survive within the phagosome of the CGD neutrophil. *(Adapted from Boxer LA. Quantitative abnormalities of granulocytes. In: Beutler E, Lichtman MA, Coller BS, et al., eds.* Williams Hematology. *6th ed. New York: McGraw-Hill; 2001. p. 845.)*

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. These include any patient with *recurrent* pneumonia, lymphadenitis, hepatic, subcutaneous, or other abscesses, osteomyelitis at multiple sites, family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation (Fig. 170.5). Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or bloodstream infection caused by *Salmonella*, *Burkholderia cepacia,* or *Candida*.

The onset of clinical signs and symptoms usually occurs in early infancy, although a few patients with very rare CGD subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable; however, the infection incidence decreases in the second decade, coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is *S. aureus,* but any catalase-positive microorganism may be involved. Other organisms frequently causing infections include *Serratia marcescens, B. cepacia, Aspergillus, Candida albicans, Nocardia,* and *Salmonella.* There may also be increased susceptibility to mycobacteria, including the bacille Calmette-Guérin vaccine. Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occurs but is much less common than focal infections and usually only occurs when local infections have been inappropriately treated for long periods. Patients may have sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydronephrosis, esophageal dysmotility, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus, also suggest CGD.

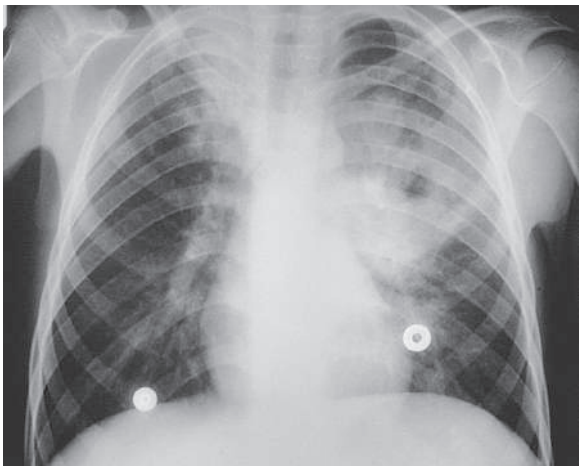

Fig. 170.5 Chest radiograph of a 10-year-old boy with chronic granulomatous disease shows a left-sided pulmonary infiltrate and cavitary lung lesion. Biopsy revealed an *Aspergillus fumigatus* infection. *(From Chinn IK, Chinen J, Shearer WT. Primary immunodeficiency diseases. In Cherry JD, Harrison GJ, Kaplan SL, et al., eds.* Feigin and Cherry's Textbook of Pediatric Infectious Diseases. *8th ed. Philadelphia: Elsevier; 2019. Fig. 67.6, p. 652.)*

Granuloma formation and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, or rectal fistulas and granulomatous colitis simulating Crohn disease. More than 80% of CGD patients have positive serology for Crohn disease. Persistent fever, especially with splenomegaly and cytopenia, warrants an evaluation for secondary macrophage activation syndrome. This has been seen in CGD and may require treatment with corticosteroids and discontinuation of interferon-γ treatment.

Laboratory Findings

The diagnosis is most often made by performing flow cytometry using DHR to measure oxidant production through its increased fluorescence when oxidized by hydrogen peroxide (H_2O_2). The nitroblue tetrazolium dye test is frequently cited in the literature but is only rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence through a bimodal response to stimulation. It is important to test the mother as some extremely lyonized carriers with <5% positive cells may have chronic clinical problems as well. Ideally, at least the first patient in a kindred should have DNA analysis to facilitate prenatal diagnosis and for genetic counseling purposes.

A few individuals have been described with apparent CGD caused by severe glucose-6-phosphate dehydrogenase deficiency, leading to insufficient NADPH substrate for the phagocyte oxidase. The erythrocytes of these patients also lack the enzyme, leading to chronic hemolysis.

Treatment

HSCT is the only known cure for CGD, although gene therapy has been transiently successful in a few patients and is the topic of active research. HSCT transplant for all patients with CGD is strongly recommended if a suitable sibling or unrelated donor can be identified. The long-term outcome for survival late into adulthood is not good, even in the hands of experienced CGD physicians. Curative therapy at an early age is strongly recommended by many experts.

Patients with CGD should be given daily oral TMP/SMX because it reduces the number of bacterial infections. A placebo-controlled study found that interferon-γ 50 μg/m^2 three times per week significantly reduces the number of hospitalizations and serious infections, although the mechanism of action is unclear. Itraconazole (200 mg/day for patients weighing >50 kg and 100 mg/day for patients <50 kg and ≤5 years old) administered prophylactically reduces the frequency of fungal infections.

Management of infection is dramatically different than in normal children. CGD patients are always at risk for deep-seated, indolent bacterial infections that can become widespread if not treated properly. They also develop the same kinds of infections that occur in normal children, so determination of the appropriate treatment can be difficult. The ESR can be quite helpful. If the child does not have a deep-seated infection, the ESR will be normal or will normalize within several days with standard management. If it does not, however, a search for deep tissues is warranted, as is consideration of empirical antibiotics. Cultures should be obtained, but are usually negative. Because all neutrophil functions in CGD except killing are normal, there is often an exuberant inflammatory reaction to a very small number of organisms. Thus blood cultures and direct cultures of biopsy samples are usually negative unless there are many organisms. Most abscesses require surgical drainage for therapeutic and diagnostic purposes. Prolonged use of antibiotics is required even for common bacterial infections. A simple pneumonia may require 6-8 weeks or more of parenteral antibiotics. Infections should be treated for at least 1 week past normalization of ESR to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, many support an "antibiotic sensitivity by sedimentation rate response" approach to treatment. The ESRs are often 40-80 mm/hr or more with severe infection and will decrease monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day because of moderate variability in this test, and changes in treatment need to be based on trends rather than individual values. If there is a clear downward trend over 3-10 days, continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus*. Failure of the ESR to decrease suggests another antimicrobial approach needs to be tried. This sequential addition of antimicrobials offers some insight into the nature of the infection. If both antibacterials and antifungal are started at the same time, one cannot know what caused a response.

Because of the rarity of this disorder, it is critical to seek counsel from someone with significant direct experience with management of several CGD patients. Granulocyte transfusions have been used, but their benefit is unclear. The ESR should be regularly monitored in well patients and whenever they appear ill. A high ESR itself is usually not enough to trigger treatment. However, in the presence of symptoms, one should search for sources at least by contrast CT of the sinus, chest, and abdomen. If the patient is unstable or has very high fevers, *B. cepacia* should be considered and empirically covered. This organism can cause septic shock quickly, unlike the usual smoldering infections seen in CGD. The patient can be treated with antibiotics until the ESR is normal and radiographic evidence of infection has been cleared, if possible. The overall incidence of infection decreases in the second decade of life as nonneutrophil immunity matures, but increased risk of infection is lifelong.

Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis. Corticosteroids can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. Short (4-6 days) pulses of 1-2 mg/kg of prednisone are recommended, with rapid taper to avoid long-term side effects and risk of fungus. Pulses can be repeated if clinical effect has not been achieved.

Genetic Counseling

Identifying a patient's specific genetic subgroup by DNA analysis is useful primarily for genetic counseling and prenatal diagnosis. In X-linked CGD, all possibly affected females should be tested by DHR to exclude carrier state. Diagnosis by DNA is strongly recommended in suspected carriers with normal DHR who are related to a known proband, because rarely DHR testing is normal in obligate carriers and may indicate that the patient has a spontaneous mutation and the mother may not be a carrier at all. Counseling is best done by a physician who has direct knowledge of the clinical manifestations of CGD.

Prognosis

The overall mortality rate for CGD is about two patient deaths per year per 100 cases, with the highest mortality among young children. The development of effective infection prophylaxis regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions have improved the prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 171

Leukopenia

Thomas F. Michniacki and Kelly J. Walkovich

Leukopenia refers to an abnormally low number of white blood cells (WBCs) in the circulating blood secondary to a paucity of lymphocytes, granulocytes, or both. Because there are marked developmental changes in normal values for WBC counts during childhood, normal ranges must be considered in the context of age. For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hours through the first week of life. Thereafter, values are stable until 1 year of age, after which a slow, steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence. Evaluation of patients with leukopenia begins with a thorough history, physical examination, and at least one confirmatory complete blood count with differential. Further evaluation then depends on whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 171.1). Treatment depends on the etiology and clinical manifestations of the leukopenia.

NEUTROPENIA

Neutropenia is defined as a decrease in the absolute number of circulating segmented neutrophils and bands in the peripheral blood. The **absolute neutrophil count (ANC)** is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands. Normal neutrophil counts must be stratified for age and race. Neutrophils predominate at birth but rapidly decrease in the first few days of life. During infancy, neutrophils constitute 20–30% of circulating leukocyte populations. Near-equal numbers of neutrophils and lymphocytes are found in the peripheral circulation at 5 years of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For White children >12 months old, the lower limit of normal for the ANC is 1,500/μL; for Black children >12 months old, the lower limit of normal is 1,200/μL. The relatively lower limit of normal in Black individuals likely reflects the prevalence of the **Duffy negative** (Fy−/−) blood group, which is enriched in populations in the malarial belt of Africa and is associated with ANCs 200-600/μL less than those who are Duffy positive.

Neutropenia may be characterized as **mild** (ANC 1,000-1,500/μL), **moderate** (ANC 500-1,000/μL), or **severe** (ANC <500/μL). ANC <200 is also termed **agranulocytosis**. This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia resulting from disorders of bone marrow production, because only patients with severe neutropenia have a significantly increased susceptibility to life-threatening infections. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared with isolated neutropenia. *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection,* because of their often robust ability to generate additional neutrophils from their functioning marrow when needed.

Acute neutropenia evolves over a few days and is often a result of rapid neutrophil use and compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 months and arises from reduced production, increased destruction, or excessive splenic sequestration of neutrophils. The etiology of neutropenia can be classified as either an acquired disorder or extrinsic insult (Table 171.2) or more rarely an inherited, intrinsic defect (Table 171.3).

Clinical Manifestations of Neutropenia

Individuals with neutrophil counts <500/μL are at substantial risk for developing infections, primarily from their endogenous flora as well as from nosocomial organisms. However, some patients with isolated chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact or because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias (AINs). In contrast, children whose neutropenia is secondary to acquired disorders of production, as occurs with cytotoxic therapy, immunosuppressive drugs, or radiation therapy, are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised and the ability of the marrow to robustly generate new phagocytes is impaired. Neutropenia associated with additional monocytopenia or lymphocytopenia is more highly associated with serious infection than neutropenia alone. The integrity of skin and mucous membranes, the vascular supply to tissues, and nutritional status also influence the risk of infection.

The most common clinical presentation of profound neutropenia includes fever, frequent infections, aphthous stomatitis, and gingivitis. Infections frequently associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, warts, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis. The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and gram-negative bacteria. Isolated neutropenia does not heighten a patient's susceptibility to parasitic or viral infections or to bacterial meningitis but does increase the risk of fungal pathogens causing disease. The usual signs and symptoms of local infection and inflammation (e.g., exudate, fluctuance, regional lymphadenopathy) may be diminished in the absence of neutrophils because of the inability to form pus, but patients with agranulocytosis still experience fever and feel pain at sites of inflammation.

Laboratory Findings

Isolated absolute neutropenia has a limited number of causes (see Tables 171.2 to 171.6). The duration and severity of the neutropenia greatly influence the extent of laboratory evaluation. Patients with chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis should have WBC counts and differential counts determined 3 times a week for 6-8 weeks to evaluate for periodicity suggestive of **cyclic neutropenia**. Bone marrow aspiration and biopsy should be performed on select patients to assess cellularity and myeloid maturation. Additional marrow studies, such as cytogenetic analysis and flow cytometry for detecting leukemia and other malignant disorders, should be obtained for patients with suspected intrinsic defects in the myeloid progenitors and for patients with suspected malignancy. Children of African or Arabic descent with mild to moderate neutropenia should have Duffy null, Fy(a-b-) variant, screening completed. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 171.1).

Acquired Neutropenia

Infection-Related Neutropenia

Transient neutropenia often accompanies or follows **viral infections** and is the most frequent cause of neutropenia in childhood (Table 171.4). Viruses causing acute neutropenia include influenzas A and B, SARS-CoV-2, adenovirus, respiratory syncytial virus, enteroviruses, human herpesvirus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitis A or B may also cause neutropenia,

Table 171.1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
History of acute or chronic leukopenia	
General medical history including prior serious, recurrent or unusual infections and malignancy Physical examination: stomatitis, gingivitis, dental defects, warts, lymphedema, congenital anomalies	Congenital syndromes (severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport, GATA2 haploinsufficiency, and primary immunodeficiencies)
Spleen size	Hypersplenism
History of drug exposure	Drug-associated neutropenia
Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/μL	
Evaluation of Acute-Onset Neutropenia	
Repeat blood counts in 3-4 wk	Transient myelosuppression (e.g., viral)
Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
Test for antineutrophil antibodies	Autoimmune neutropenia
Measure quantitative immunoglobulins (IgG, IgA, IgM, IgE), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/μL ON THREE SEPARATE TESTS	
Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia; reticular dysgenesis
Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropenias
Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
Exocrine pancreatic function	Shwachman-Diamond syndrome
Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1,000/μL	
Repeat blood counts in 3-4 wk	Transient leukopenia (e.g., viral)
IF ALC <1,000/μL THREE SEPARATE TESTS	
HIV antibody or RNA test	HIV infection, AIDS
Quantitative immunoglobulins (IgG, IgA, IgM, IgE), vaccine titers, lymphocyte subsets; qualitative lymphocyte proliferation to mitogens/antigens	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
Bone marrow cytogenetics and flow cytometry	Myelodysplasia, leukemia
Copper, vitamin B12 and folate levels	Vitamin deficiencies

ALC, Absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

but are more often associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the first 24-48 hours of illness and usually persists for 3-8 days, which generally corresponds to the period of viremia. The neutropenia is related to virus-induced redistribution of neutrophils from the circulating to the marginating pool. In addition, neutrophil sequestration may occur after virus-induced tissue damage or splenomegaly.

Significant neutropenia also may be associated with severe bacterial, protozoal, rickettsial, or fungal infections (see Table 171.4). **Bacterial sepsis** is a particularly serious cause of neutropenia, especially among younger infants and children. Premature neonates are especially prone to exhausting their marrow reserve and rapidly succumbing to bacterial sepsis.

Chronic neutropenia often accompanies infection with Epstein-Barr virus, cytomegalovirus, or HIV and certain immunodeficiencies

Table 171.2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrested" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Myelofibrosis, malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, marrow fibrosis, malignant cells in bone marrow sites of extramedullary hematopoiesis
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 171.3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12}, copper, or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hyper-segmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birthweight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to *PIGA* gene variant	Pancytopenia, thrombosis (hepatic vein thrombosis)

Table 171.4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella, HHV-6, SARS-CoV-2
Bacterial	*Brucella,* paratyphoid, pertussis, tuberculosis (disseminated), tularemia, *Shigella*, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum,* psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

HHV-6, Human herpesvirus-6.

such as X-linked agammaglobulinemia (XLA), hyper-IgM syndrome and AIDS. The neutropenia associated with AIDS likely arises from a combination of viral bone marrow suppression, antibody-mediated destruction of neutrophils, and effects of antiretroviral or other drugs.

Drug-Induced Neutropenia

Drugs constitute a common cause of neutropenia (Table 171.5). The incidence of drug-induced neutropenia increases dramatically with age; only 10% of cases occur among children and young adults. The majority of cases occur among adults >65 years, likely reflecting the more frequent use of multiple medications in that age-group. Almost any drug can cause neutropenia. The most common offending drug classes are antimicrobial agents, antithyroid drugs, antipsychotics, antiepileptics, antipyretics, and antirheumatics. **Drug-induced neutropenia** has several underlying mechanisms (immune-mediated, toxic, idiosyncratic, hypersensitivity, idiopathic) that are distinct from the severe neutropenia that predictably occurs after administration of antineoplastic drugs or radiotherapy.

Drug-induced neutropenia from immune mechanisms usually develops abruptly, is accompanied by fever, and lasts for about 1 week after the discontinuation of the drug. The process likely arises from effects of drugs such as propylthiouracil or penicillin that act as haptens to stimulate antibody formation, or drugs such as quinine that induce immune complex formation. Other drugs, including the antipsychotic drugs such as the phenothiazines, can cause neutropenia when given in toxic amounts, but some individuals, such as those with preexisting neutropenia, may be susceptible to levels at the high end of the usual therapeutic range. Late-onset neutropenia can occur after rituximab therapy. Idiosyncratic reactions,

Table 171.5 Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

for example to chloramphenicol, are unpredictable with regard to dose or duration of use. Hypersensitivity reactions are rare and may involve arene oxide metabolites of aromatic anticonvulsants. Fever, rash, lymphadenopathy, hepatitis, nephritis, pneumonitis, and aplastic anemia are often associated with hypersensitivity-induced neutropenia. Acute hypersensitivity reactions such as those caused by phenytoin or phenobarbital may last for only a few days if the offending drug is discontinued. Chronic hypersensitivity may last for months to years.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs most commonly associated with neutropenia. Usually, the neutropenia will resolve soon after withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient is symptomatic with infection or stomatitis, subcutaneous administration of recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim, 5 μg/kg/day) should be considered. Drug-induced neutropenia may be asymptomatic and noted only as an incidental finding or because of regular monitoring of WBC counts during drug therapy. For patients who are asymptomatic, continuation of the suspected offending drug depends on the relative risks of neutropenia vs discontinuation of a possibly essential drug. If the drug is continued, blood counts should be monitored for possible progression to agranulocytosis.

Neutropenia usually and predictably follows the use of anticancer drugs or radiation therapy, especially radiation directed at the pelvis or vertebrae, secondary to cytotoxic effects on rapidly replicating myeloid precursors. A decline in the WBC count typically occurs 7-10 days after administration of the anticancer drug and may persist for 1-2 weeks. The neutropenia accompanying malignancy or following cancer chemotherapy is frequently associated with compromised cellular immunity and barrier compromise secondary to central venous lines and mucositis, thereby predisposing patients to a much greater risk of infection than found in disorders associated with isolated neutropenia. Patients with chemotherapy/radiation-related neutropenia and fever must be treated aggressively with broad-spectrum antibiotics.

Nutrition-Related Neutropenia

Poor nutrition can contribute to neutropenia. Ineffective myelopoiesis may result in neutropenia caused by acquired dietary **copper, vitamin B_{12}, or folic acid deficiency**. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim/sulfamethoxazole that inhibit folic acid metabolism and from the use of phenytoin, which may impair folate absorption in the small intestine, or from surgical resection of the small intestine. Neutropenia also occurs with starvation and marasmus in infants, with anorexia nervosa, and occasionally among patients receiving prolonged parenteral nutrition without vitamin supplementation. Patients receiving prolonged parenteral nutrition and supplemental lipids are additionally at risk for neutropenia given hepatosplenomegaly-related sequestration and marrow infiltration by abnormal macrophages filled with blue-staining pigment granules and atypical lipid vacuoles; these cells are termed **sea-blue histiocytes**.

Immune-Mediated Neutropenia

Immune-mediated neutropenia is usually associated with the presence of circulating antineutrophil antibodies, which may mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of opsonized neutrophils, or by accelerated apoptosis of mature neutrophils or myeloid precursors.

Alloimmune neonatal neutropenia occurs after transplacental transfer of maternal alloantibodies directed against antigens on the infant's neutrophils, analogous to Rh-hemolytic disease. Prenatal sensitization induces maternal IgG antibodies to neutrophil antigens on fetal cells. The neutropenia is often severe and infants may present within the first 2 weeks of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 weeks of age, the neutrophil count usually returns to normal, reflecting the decay of maternal antibodies in the infant's circulation. Treatment consists of supportive care and appropriate antibiotics for clinical infections, plus G-CSF for severe infections without neutrophil recovery.

Mothers with autoimmune disease may give birth to infants who develop transient neutropenia, known as **neonatal passive AIN**. The duration of the neutropenia depends on the time required for the infant to clear the maternally transferred circulating IgG antibody. It persists in most cases for a few weeks to a few months. Neonates almost always remain asymptomatic.

AIN of infancy is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 years of age. Antineutrophil antibodies are inappropriately created by the child during an inflammatory episode, most commonly a mild viral infection. Patients usually have severe neutropenia on presentation, with ANC <500/μL, but the total WBC count is generally within normal limits. Monocytosis or eosinophilia may occur but does not impact the low rate of infection. The median age of presentation is 8-11 months, with a range of 2-54 months. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection or when a routine complete blood count is obtained at the 12-month well-child visit. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be supported by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antineutrophil antibodies does not exclude the diagnosis, and a positive result does not exclude other conditions. Therefore the diagnosis is best made clinically based on a benign course and, if obtained, a normal or hyperplastic myeloid maturation in the bone marrow. There is considerable overlap between AIN of infancy and "**chronic benign neutropenia**."

Treatment is not generally necessary because the disease is only rarely associated with severe infection and usually remits spontaneously. Low-dose G-CSF may be useful for severe infections, to promote wound healing following surgery, or to avert emergency room visits or hospitalizations for febrile illnesses. Longitudinal studies of infants with AIN demonstrate median duration of disease ranging from 7-30 months. Affected children generally have no evidence or risk of other autoimmune diseases.

AIN in older children can occur as an isolated process, as a manifestation of other autoimmune diseases, or as a secondary complication of infection, drugs, or malignancy. In primary AIN, low circulating neutrophil counts are the only hematologic finding, and associated diseases or other factors that cause neutropenia are absent. Secondary AIN associated with immune dysregulation or other factors is more often identified in older children and is less likely to remit spontaneously. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats previously discussed) and myeloid hyperplasia on bone marrow examination. The most common antineutrophil antibody targets are human neutrophil antigens 1a, 1b, and 2.

Treatment of AIN relies on management of any underlying disorders. In addition, judicious use of appropriate antibiotics for bacterial infections is generally beneficial, as is family and primary care provider education. Regular dental hygiene, always strongly recommended, is even more important. Infections tend to be less frequent in AIN than with the corresponding degree of neutropenia from other causes, probably because tissue delivery of neutrophils is greater than that in conditions resulting from impaired production. Prophylactic antibiotics may be helpful for the management of recurrent minor infections. For patients with serious or recurrent infections, G-CSF is generally effective at raising the ANC and preventing infection. Very low doses (<1-2 μg/kg/day) are usually effective, and administration of standard doses can lead to severe bone pain from marrow expansion.

Neutropenia Secondary to Bone Marrow Replacement

Various acquired bone marrow disorders lead to neutropenia, usually accompanied by anemia and thrombocytopenia. Hematologic malignancies, including leukemia, lymphoma, and metastatic solid tumors, suppress myelopoiesis by infiltrating the bone marrow with tumor cells. Neutropenia may also accompany aplastic anemia, myelodysplastic disorders, or preleukemic syndromes, which are characterized by multiple cytopenias and often macrocytosis. Treatment requires management of the underlying disease.

Neutropenia Secondary to Reticuloendothelial Sequestration

Splenic enlargement resulting from intrinsic splenic disease (storage disease), portal hypertension, or systemic causes of splenic hyperplasia (inflammation or neoplasia) can lead to neutropenia. Most often the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. The reduced neutrophil survival corresponds to the size of the spleen, and the extent of the neutropenia is inversely proportional to bone marrow compensatory mechanisms. Usually, the neutropenia can be corrected by successfully treating the underlying disease. In select cases, splenectomy may be necessary to restore the neutrophil count to normal, but results in increased risk of infections by encapsulated bacterial organisms. Patients undergoing splenectomy should receive appropriate preoperative immunizations and may benefit from antibiotic prophylaxis after splenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency (CVID), autoimmune lymphoproliferative disease, and other immunodeficiency syndromes because of the higher risk of sepsis.

Inherited Neutropenia

Intrinsic disorders of proliferation or maturation of myeloid precursor cells are rare. Table 171.6 presents a classification based on genetics (Fig. 171.1) and molecular mechanisms; other organ involvement or physical features may suggest an etiology (Table 171.7).

Primary Disorders of Granulopoiesis

Cyclic neutropenia is an autosomal dominant congenital granulopoietic disorder occurring with an estimated incidence of 0.5-1 cases per 1 million population. The disorder is characterized by regular, periodic oscillations, with the ANC ranging from normal to <200/μL, mirrored by reciprocal cycling of monocytes. Cyclic neutropenia is sometimes termed *cyclic hematopoiesis* because of the secondary cycling of other blood cells, such as platelets and reticulocytes. The mean oscillatory period of the cycle is 21 days (±4 days). During the neutropenic nadir, many patients develop malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Before the availability of G-CSF, approximately 10% of patients developed fatal clostridial or gram-negative infections. Cyclic neutropenia arises from a regulatory abnormality involving early hematopoietic precursor cells and is almost invariably associated with pathologic variants in the neutrophil elastase gene, *ELANE*, that lead to accelerated apoptosis as a result of abnormal protein folding. Many patients experience abatement of symptoms with age. The cycles tend to become less noticeable in older patients, and the hematologic picture often begins to resemble that of chronic idiopathic neutropenia.

Cyclic neutropenia is diagnosed by obtaining blood counts 3 times a week for 6-8 weeks. The requirement for repeated blood counts is necessary because some of the elastase variants overlap with those in patients who have **severe congenital neutropenia (SCN)**. Demonstrating oscillation or a lack thereof in the blood counts helps to identify patients' risks for progression to **myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML)**, a risk that is only associated with SCN. The diagnosis can be confirmed with genetic studies demonstrating a pathologic variant in *ELANE*. Affected patients with neutrophil nadirs <200/μL are treated with G-CSF, and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to 9-11 days with 1 day of less profound neutropenia. The dose needed to maintain nadirs >500/μL is usually 2-4 μg/kg/day administered daily or every other day.

SCN is a rare, genetically heterogeneous, congenital granulopoietic disorder with an estimated incidence of 1-2 cases per 1 million population. The disorder is characterized by an arrest in myeloid maturation at the promyelocyte stage in the bone marrow, resulting in ANCs consistently <200/μL and may occur sporadically, with autosomal dominant or recessive inheritance. The **dominant** form is caused most often by pathologic variants in ***ELANE***, which accounts for 60–80% of SCN cases, whereas **recessive** forms arise from variants in ***HAX1*** (the form also known as **Kostmann disease**) or *G6PC3* (encoding a myeloid-specific isoform of glucose-6-phosphatase). Pathologic alterations in *GFI1, CSF3R,* and *JAGN1* additionally may lead to the condition. *HAX1* variants may be associated with neurologic deficits, and *G6PC3* with heart defects, urogenital abnormalities, and venous angiectasia. In addition to severe neutropenia, peripheral blood counts generally show monocytosis and many also exhibit eosinophilia; chronic inflammation may lead to secondary anemia and thrombocytosis. Patients who have SCN experience frequent episodes of fever, skin infections (including omphalitis), oral ulcers, gingivitis, pneumonia, and perirectal abscesses, typically appearing in the first few months of life. Infections often disseminate to the blood, meninges, and peritoneum and are usually caused by *S. aureus*, *Escherichia coli,* and *Pseudomonas* species. Without filgrastim therapy, most patients die of infectious complications within the first 1-2 years of life despite prophylactic antibiotics.

Table 171.6 Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI1* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1, JAGN1, CSF3R)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angioectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS, DNAJC21, EFL1, SRP54)*	Pancreatic insufficiency, metaphyseal dysostosis, bone marrow failure, MDS/AML
Telomere biology disorders/ dyskeratosis congenita	Telomere length abnormality: XL *(DKC1)*, AD or AR *(ACD, RTEL1, TERC, TERT)*, AD *(NAF1, TINF2)*, AR *(CTC1, NHP2, NOP10, PARN, STN1, WRAP53)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure, various malignancies, Coats plus syndrome (*CTC1* and *STN1*)
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired NK cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired NK cell function, neurologic impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3B1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	AR *(MAPBPIP)*	Partial albinism, coarse facial features, decreased B and T cells
VPS45 defects	AR *(VPS45)*	Neutrophil dysfunction, bone marrow fibrosis, nephromegaly
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Methylmalonic/propionic acidemia/ aciduria	AR (*CLPB*) Mutase or cobalamin transporters/ propionyl coenzyme A carboxylase	Ketoacidosis, metabolic stroke, depressed consciousness, megaloblastic anemia
3-Methylglutaconic aciduria	AR (*CLPB*)	Nonspecific finding indicative of mitochondrial dysfunction or associated with known syndromes
Barth syndrome	XL *(TAZ)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR *(RMRP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	XL (Bruton tyrosine kinase (*BTK*))	Agammaglobulinemia, neutropenia in ~25%
GATA2 haploinsufficiency	AD (*GATA2*)	Pulmonary alveolar proteinosis, lymphedema, monocytopenia, decreased B and NK cells, risk for severe fungal/mycobacterial/viral infections, susceptibility to leukemia/MDS, MonoMAC syndrome

AD, Autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndrome; NK, natural killer; XL, X-linked.

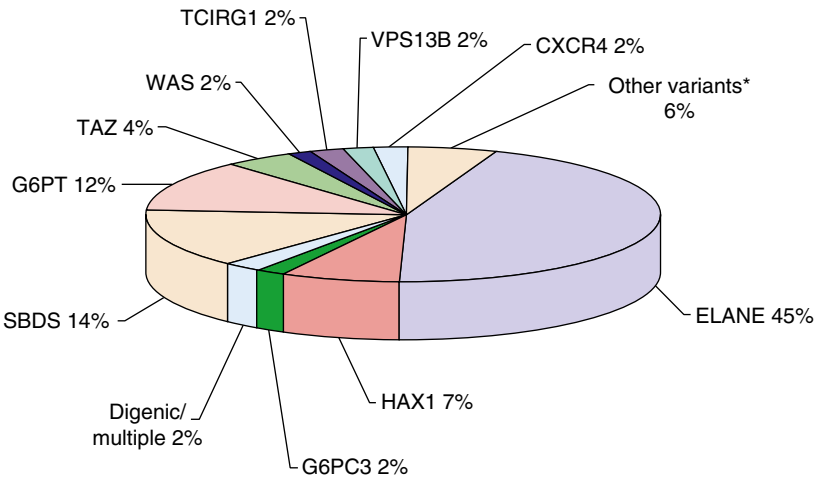

Fig. 171.1 Genes with germline variants associated with severe congenital neutropenia. Data based on 650 patients with severe congenital neutropenia registered in the European and North American Branches of the Severe Chronic Neutropenia International Registry. *Pathogenic variants in *JAGN1, LAMTOR2, GFI1, LYST, USB1,* or mitochondrial DNA. *(From Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. Nat Rev Dis Primers. 2017;3:17032. Fig. 3.)*

More than 95% of SCN patients respond to filgrastim (G-CSF) treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1,000/μL vary greatly. A starting dose of filgrastim at 5 μg/kg/day is recommended; the dose should be gradually increased, if necessary, to as high as 100 μg/kg/day to attain an ANC of 1,000-2,000/μL. The 5% of patients who do not respond to filgrastim or who require high doses (>8 μg/kg/day) should be considered for hematopoietic stem cell transplantation (HSCT). Along with infections, patients with SCN are at risk for developing MDS associated with monosomy 7 and AML. For this reason, regular monitoring with blood counts and yearly bone marrow surveillance, including karyotyping and fluorescence in situ hybridization, should be performed on all SCN patients. Although clonal cytogenetic abnormalities may spontaneously remit, their appearance should be considered a strong indication for HSCT, which is much more likely to be successful before progression to MDS/AML.

Disorders of Molecular Processing

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder classically characterized by neutropenia, pancreatic insufficiency, and short stature with skeletal abnormalities. SDS is most commonly caused by pro-apoptotic pathologic variants of the *SBDS* gene, which encodes a protein that plays a role in ribosome biogenesis and RNA processing. The initial symptoms are usually steatorrhea and failure to thrive because of malabsorption secondary to pancreatic insufficiency, which usually develops by 4 months of age, although the gastrointestinal symptoms may be subtle in some patients and go unrecognized. Patients have also been reported to have respiratory problems with frequent otitis media, pneumonia, and eczema. Virtually all patients with SDS have neutropenia, with the ANC periodically <1,000/μL. Some children have hypogammaglobulinemia, defects in chemotaxis, or a reduction in the number or function of B, T, and natural killer (NK) cells that may contribute to the increased susceptibility to pyogenic infection. The diagnosis of SDS is based on clinical phenotype; approximately 90% of patients have pathologic variants identified in *SBDS* with additional disease-causing variants now recently discovered in *DNAJC21, EFL1,* and *SRP54*. SDS may progress to bone marrow hypoplasia or MDS/AML; identification of increasing *TP53* variants or cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so routine bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus G-CSF in patients with severe neutropenia.

Telomere biology disorders (TBDs), including **dyskeratosis congenita**, are disorders of telomere length that most often present as bone marrow failure rather than isolated neutropenia. Various pathologic variants have now been identified to cause such conditions (see Table 171.6), including alterations in *ACD, PARN, DKC1, RTEL1, TERC,* and *TERT*. Moreover, the classic phenotype includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features. Pulmonary and hepatic fibrosis is also a concern in individuals with TBDs. Patients are at risk for not only hematologic dysplasia/malignancy but additionally neoplasms involving the gastrointestinal tract, skin, and head and neck. Early and routine screening for these malignancies can be lifesaving.

Vesicular Trafficking Disorders

This group of rare **primary immunodeficiency syndromes** (see Table 171.6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. The syndromes share phenotypic characteristics, including defects in melanosomes contributing to partial albinism, abnormal platelet function, and immunologic defects involving not only neutrophil number, but also the function of neutrophils, B lymphocytes, NK cells, and cytotoxic T lymphocytes. The syndromes share a high risk of hemophagocytic lymphohistiocytosis (HLH) as a result of defects in T and NK cells.

Chédiak-Higashi syndrome has characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, and is a disorder of subcellular vesicular dysfunction caused by pathologic variants in the *LYST* gene, with resultant giant granules in all granule-bearing cells. Patients have increased susceptibility to infections, mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening HLH. The only curative treatment is HSCT, but transplant does not treat all aspects of the disorder.

Griscelli syndrome type II also features neutropenia, partial albinism, and a high risk of HLH, but peripheral blood granulocytes do not show giant granules. Patients often have hypogammaglobulinemia. The disorder is caused by alterations in *RAB27a*, which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is HSCT.

Disorders of Metabolism

Recurrent infections with neutropenia are a distinctive feature of **glycogen storage disease (GSD) type Ib**. As in classic von Gierke disease (GSDIa), glycogen storage in GSDIb causes massive hepatomegaly and severe growth retardation. Pathologic variants in glucose-6-phosphate transporter 1, *G6PT1*, inhibit glucose transport in GSDIb, resulting in both defective neutrophil motility and increased apoptosis associated with neutropenia and recurrent bacterial infections. Treatment with

Table 171.7 Main Organ Associated Features and Genetic Subtypes of Congenital Neutropenia

SYSTEM	HEMATOLOGIC OR ASSOCIATED FEATURES	DISEASE	GENE
Blood/bone marrow maturation	Maturation arrest	Severe congenital neutropenia Severe congenital neutropenia Wiskott-Aldrich syndrome *Neutropenia G6PC3* *G-CSF receptor*	*ELANE* *HAX1* *WAS* *G6PC3* Extracellular domain of *CSF3R*
	No maturation arrest	GSDIb WHIM Shwachman Diamond disease Cohen disease Hermansky-Pudlak type 2	*G6PT1* *CXCR4* *SBDS* *VPS13B* *AP3B1*
	Myelokathexis	WHIM	*CXCR4*
Pancreas	External pancreatic insufficiency	Shwachman Diamond disease	*SBDS*
Eyes	Congenital cataract	Charcot-Marie-Tooth	*Dynamin 2*
	Retinochoroidal dystrophy	Cohen disease	*VPS13B*
Heart	Heart: arrhythmias	Neutropenia G6PC3	*G6PC3*
	Dilated cardiomyopathy	Barth diseases	*TAZ*
	Cardiomyopathy	Shwachman Diamond disease	*SBDS*
	Various cardiac abnormalities	Shwachman Diamond disease WHIM Neutropenia G6PC3	*SBDS* *CXCR4* *G6PC3*
Skin	Skin xerosis eczema	Shwachman Diamond disease	*SBDS*
	Skin: prominent superficial veins	Neutropenia G6PC3	*G6PC3*
	Skin poikiloderma	SCN with poikiloderma type Clericuzio	*16ORF57*
	Skin: Partial or complete albinism	Hermansky-Pudlak type 2 AP14 defect Chédiak Higashi disease Griscelli disease	*AP3B1* *AP14* *LYST* *RAB27A*
	Hair: fine, sparse, and light-colored	Cartilage-hair hypoplasia	*RMRP*
Bone	Metaphyseal dysplasia	Shwachman Diamond disease Cartilage-hair hypoplasia	*SBDS* *RMRP*
	Facial dysmorphia	Cohen disease	*VPS13B*
Central nervous system	Mental retardation	Kostmann disease Shwachman Diamond disease Cohen disease	*HAX1* *SBDS* *VPS13B*
Muscle	Weakness	Neutropenia G6PC3 Axonal Charcot-Marie-Tooth disease	*G6PC3* *Dynamin 2*
Metabolic pathway	Fasting intolerance and glycogenosis	Glycogen storage disease type Ib	*SLC37A4*
Inner ear	Inner ear defect	GFI 1/severe chronic neutropenia Reticular dysgenesia	*GFI1* *AK2*
Urogenital tract	Uropathy	Neutropenia G6PC3	*G6PC3*
	Cryptorchidism	Cohen disease Neutropenia G6PC3	*VPS13B* *G6PC3*

G-CSF, Granulocyte colony-stimulating factor; SCN, severe congenital neutropenia; WHIM, warts, hypogammaglobulinemia, infections, myelokathexis.
From Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. *Orphanet J Rare Dis.* 2011;6:26. Table 2.

G-CSF can correct the neutropenia but does not correct the underlying functional neutrophil defects.

Neutropenia in Disorders of Immune Dysfunction

Congenital immunologic disorders that have severe neutropenia as a clinical feature include XLA, CVID, the severe combined immunodeficiencies (SCIDs), autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, GATA2 haploinsufficiency, and a number of even rarer immunodeficiency disorders (see Table 171.6).

Unclassified Neutropenic Disorders

Chronic benign neutropenia of childhood represents a common group of disorders characterized by mild to moderate neutropenia that does not lead to an increased risk of pyogenic infections. Spontaneous remissions are often reported, although these may represent misdiagnosis of AIN of infancy, in which remissions often occur during

Table 171.8 Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid, COVID-19
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage/chylothorax
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure, sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, Psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

childhood. Chronic benign neutropenia may be sporadic or inherited in either dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 years of age, with no identifiable etiology. Patients with an ANC persistently <500/μL may have recurrent pyogenic infections involving the skin, mucous membranes, lungs, and lymph nodes. Bone marrow examination reveals variable patterns of myeloid formation with arrest generally occurring between the myelocyte and band forms. The diagnosis overlaps with chronic benign and AINs.

Treatment

The management of acquired transient neutropenia associated with malignancies, myelosuppressive chemotherapy, or immunosuppressive chemotherapy differs from that of congenital or chronic forms of neutropenia. In the former situation, infections sometimes are heralded only by fever, and sepsis is a major cause of death. Early recognition and treatment of infections may be lifesaving. Therapy of severe chronic neutropenia is dictated by the clinical manifestations. Patients with benign neutropenia and no evidence of repeated bacterial infections or chronic gingivitis require no specific therapy. Superficial infections in children with mild to moderate neutropenia may be treated with appropriate oral antibiotics. In patients who have invasive or life-threatening infections, broad-spectrum intravenous antibiotics should be started promptly.

Subcutaneously administered G-CSF can provide effective treatment of severe chronic neutropenia, including SCN, cyclic neutropenia, and chronic symptomatic idiopathic neutropenias. Treatment leads to dramatic increases in neutrophil counts, resulting in marked attenuation of infection and inflammation. Doses range from 2-5 μg/kg/day for cyclic, idiopathic, and AINs, to 5-100 μg/kg/day for SCN. The long-term effects of G-CSF therapy include a propensity for the development of moderate splenomegaly, reduced bone density, thrombocytopenia, and rarely vasculitis; only patients with SCN are at risk for MDS/AML.

Patients with SCN or SDS who develop MDS or AML respond only to HSCT; chemotherapy is ineffective. HSCT is also the treatment of choice for aplastic anemia or familial HLH.

LYMPHOPENIA

The definition of lymphopenia, as with neutropenia, is age dependent and can have acquired or inherited causes. **The absolute lymphocyte count (ALC)** is determined by multiplying the total WBC count by the percentage of total lymphocytes. For children <12 months old, lymphopenia is defined as an ALC <3,000 cells/μL. For older children and adults, an ALC <1,000 cells/μL is considered lymphopenia. In isolation, mild to moderate lymphopenia is generally a benign condition often detected only in the evaluation of other illnesses. However, severe lymphopenia can result in serious, life-threatening illness. Lymphocyte subpopulations can be measured by flow cytometry, which uses the pattern of lymphocyte antigen expression to quantitate and classify T, B, and NK cells.

Acquired Lymphopenia

Acute lymphopenia is most often a result of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 171.8). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, hepatitis, COVID-19), bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, brucellosis), and malaria. The mechanisms behind infection-associated lymphopenia are not fully elucidated but probably include lymphocyte redistribution and accelerated apoptosis. Corticosteroids are a common cause of medication-induced lymphopenia, as are lymphocyte-specific immunosuppressive agents (e.g., antilymphocyte globulin, alemtuzumab, rituximab), chemotherapy drugs, and radiation. In most cases, infectious and iatrogenic causes of acute lymphopenia are reversible, although full lymphocyte recovery from chemotherapy and lymphocyte-specific immunosuppressive agents may take several months to years. Prolonged lymphopenia (see Table 171.8) may be caused by recurrent infection, persistent infections (mostly notably HIV), malnutrition, mechanical loss of lymphocytes through protein-losing enteropathy or thoracic duct leaks, or systemic diseases such as lupus erythematosus, rheumatoid arthritis, sarcoidosis, renal failure, lymphoma, and aplastic anemia.

Inherited Lymphopenia

Primary immunodeficiencies and bone marrow failure syndromes are the main cause of inherited lymphopenia in children (see Table 171.8). Primary immunodeficiency may result in a severe quantitative defect, as in XLA and SCID, or a qualitative or progressive defect, as in Wiskott-Aldrich syndrome and CVID. XLA is characterized by a near-absence of mature B cells because of a pathologic alteration in *BTK* that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogeneous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, by analysis of T-cell receptor excision circles (TRECs) from dried blood spot Guthrie cards, aids in the rapid identification and treatment of infants with SCID and other T-cell disorders. Quantitative defects in lymphocytes can also be appreciated in select forms of inherited bone marrow failure such as reticular dysgenesis, SCN secondary to *GFI1* variants, and dyskeratosis congenita.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 172

Leukocytosis

Thomas F. Michniacki and Kelly J. Walkovich

Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 standard deviations (SDs) above the mean for age. It is most often caused by elevated numbers of neutrophils (i.e., neutrophilia), although marked increases in monocytes, eosinophils, basophils, and lymphocytes can be seen. Before extensive evaluation, it is important to assess for spurious elevations in the WBC count caused by platelet clumping (secondary to insufficient sample anticoagulation or the presence of EDTA-dependent agglutinins), high numbers of circulating nucleated red blood cells (RBCs), and the presence of cryoglobulins by review of the peripheral smear.

Malignancy, namely leukemia and lymphoma, is a primary concern for patients with leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 544. Nonmalignant WBC counts exceeding 50,000/μL have historically been termed a **leukemoid reaction.** Unlike leukemia, leukemoid reactions show relatively small proportions of immature myeloid cells, consisting largely of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. Leukemoid reactions are most often neutrophilic and are frequently associated with severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia; physiologic stressors; and certain medications.

The presence of a **left shift**, defined as having >5% immature neutrophils in the peripheral blood, is consistent with marrow stress. Higher degrees of left shift with more immature neutrophil precursors are indicative of serious bacterial infections and may be a dire sign of depletion of the bone marrow reserve pool of neutrophils. Marked left shift may occasionally be encountered with trauma, burns, surgery, acute hemolysis, or hemorrhage.

NEUTROPHILIA

Neutrophilia is an increase in the total number of blood neutrophils that is 2 SD above the mean count for age. Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, migration out of the marrow compartments into the circulation, and neutrophil destruction. Neutrophilia may arise either alone or in combination with enhanced mobilization into the **circulating pool** from either the bone marrow storage compartment or the peripheral blood **marginating pool**, by impaired neutrophil egress into tissues, or by expansion of the circulating neutrophil pool secondary to increased granulopoiesis. Myelocytes are not released to the blood except under extreme circumstances.

Acute Acquired Neutrophilia

Neutrophilia is usually an acquired, secondary finding associated with inflammation, infection, injury, or an acute physical or emotional stressor (Table 172.1). Bacterial infections, trauma (especially with hemorrhage), and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heat stroke, burns, diabetic ketoacidosis, vaccines, pregnancy, or cigarette use.

Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF) and recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF). Epinephrine causes release into the circulation of a sequestered pool of neutrophils that normally marginate along the vascular endothelium. Corticosteroids accelerate the release of neutrophils and bands from a large storage pool within the bone marrow and impair the migration of neutrophils from the circulation into tissues. G-CSF and GM-CSF cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and stimulating neutrophil production.

Acute neutrophilia in response to inflammation and infections occurs because of release of neutrophils from the marrow storage pool. The postmitotic marrow neutrophil pools are approximately 10 times the size of the blood neutrophil pool, and about half of these cells are bands and segmented neutrophils. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia, followed by neutrophilia secondary to release of bone marrow neutrophils. Reactive neutrophils often have toxic granulation and Döhle bodies present.

Chronic Acquired Neutrophilia

Chronic acquired neutrophilia is usually associated with continued stimulation of neutrophil production resulting from persistent inflammatory reactions or chronic infections (e.g., tuberculosis), vasculitis, postsplenectomy states, Hodgkin disease, chronic myelogenous leukemia, chronic blood loss, sickle cell disease, some chronic hemolytic anemias, and prolonged administration of corticosteroids (see Table 172.1). Chronic neutrophilia can arise after expansion of cell production secondary to stimulation of cell divisions within the mitotic precursor pool, which consists of promyelocytes and myelocytes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hematopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 week to develop.

Lifelong Neutrophilia

Congenital or acquired asplenia is associated with lifelong neutrophilia. Some patients with trisomy 21 also have neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiency and Rac2 deficiency (see Chapter 170) and systemic disorders such as familial cold urticaria, periodic fever syndromes, and familial myeloproliferative disease (see Table 172.1). Rare patients with an autosomal dominant hereditary neutrophilia have been reported.

Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly almost zero, from reactive or secondary neutrophilia, which features normal to elevated levels.

ADDITIONAL FORMS OF LEUKOCYTOSIS

Monocytosis

The average absolute blood monocyte count varies with age, which must be considered in the assessment of monocytosis. Given the role of monocytes in antigen presentation and cytokine secretion and as effectors of ingestion of invading organisms, it is not surprising that many clinical disorders give rise to monocytosis (Table 172.2). Typically, monocytosis occurs in patients recovering from myelosuppressive chemotherapy and is a harbinger of the return of the neutrophil count to normal. Monocytosis is occasionally a sign of an acute bacterial, viral, protozoal, or rickettsial infection and may also occur in some forms of chronic neutropenia and postsplenectomy states. Chronic inflammatory conditions can stimulate sustained monocytosis, as can preleukemia, chronic myelogenous leukemia, and lymphomas.

Eosinophilia

Eosinophilia is defined as an absolute eosinophil count >1500 cells/μL. The majority of eosinophilic conditions are reactive, including infections (especially parasitic diseases), connective tissue disorders, allergic and hyperinflammatory diseases, pulmonary disorders, and dermatologic conditions (see Chapter 169). Drug reaction with eosinophilia and systemic symptoms (DRESS) is a particularly important condition

Table 172.1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Neutrophil disorder	Leukocyte adhesion defects
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis, cigarette exposure
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease, pregnancy, Sweet syndrome
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Table 172.2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis, typhoid
Nonbacterial	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

to consider in those with prominent eosinophilia as severe cases are associated with significant morbidity and mortality (see Chapter 686.2). Hypereosinophilic syndrome and systemic mastocytosis are additional important causes of an elevated eosinophil count. However, persistent eosinophilia can also herald a malignancy such as leukemia, lymphoma, or carcinoma.

Basophilia

Basophilia is defined as an absolute basophil count >120 cells/μL. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance. Basophilia is most often present in hypersensitivity reactions and frequently accompanies the leukocytosis of chronic myeloid leukemia.

Lymphocytosis

The most common cause of lymphocytosis is an acute viral illness, as part of the normal T-cell response to the infection. In infectious mononucleosis, the B cells are infected with the Epstein-Barr virus, and the T cells react to the viral antigens present in the B cells, resulting in **atypical lymphocytes** with characteristic large, vacuolated morphology. Other viral infections classically associated with lymphocytosis are cytomegalovirus and viral hepatitis. Chronic bacterial infections such as tuberculosis and brucellosis may lead to a sustained lymphocytosis. Pertussis is accompanied by marked lymphocytosis in approximately 25% of infants infected before 6 months of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis. Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography

Section 4

Complement System

Chapter 173

Complement System

Anete Sevciovic Grumach

173.1 Complement Components, Pathways, and Evaluation

Anete Sevciovic Grumach

The complement system (CS) forms a network of soluble and cell surface–bound components, pattern-recognition proteins (PRPs), proteases, receptors, effectors, and regulators to perform multiple sensor and effector functions as part of the *innate* immune system (Tables 173.1 and 173.2). It represents an essential part of immunity, having a major role in host defense against pathogens, homeostasis, and inflammation, such as promoting phagocytic removal of senescent cells, molecular debris, and weak or superfluous synapses during brain formation. Complement acts not only in the extracellular space but also within cells and subcellular compartments, where it is involved in the regulation of basic processes of the cell, suggesting that complement directs both innate and adaptive immune responses. Cells are generally protected from amplification and effector insult by a group of complement regulators, which are expressed on their surface or mobilized from the circulation. However, if the equilibrium between complement activation and regulation is disturbed, complement can harm the host and precipitate or worsen adverse processes that result in diseases.

Circulating complement proteases are zymogens and, once activated, they initiate an amplification cascade through cleavage of specific targets and/or interaction with other proteins. Depending on the activating surface, the CS can be triggered by the **classical** (CP), **lectin** (LP), and **alternative** (AP) **pathways**. Each pathway is triggered by different interactions. The CP is initiated by immune complexes through binding of complement protein C1q to immune complexes containing IgM or IgG, in solution or bound to antigens on the cell surface. Certain bacteria, RNA viruses, and the lipid A component of bacterial endotoxin as **pathogen-associated molecular patterns (PAMPs)** on microbial surfaces can activate C1q directly and trigger the full complement cascade. The LP is activated when **mannose-binding lectin (MBL),** or ficolins, recognize unique carbohydrate structures present on the surface of pathogens or altered glycosylation patterns (DAMPs, danger-associated molecular patterns) on abnormal host cells. **The mannose-binding lectin-associated serine proteases (MASPs)** cleave C2 and C4, following the same sequence as CP.

The **AP** is rapidly activated after contact with pathogens, independent of antibody; however, antibody will accelerate the rate of activation. The fluid phase C3 convertase complex C3(H2O)Bb is generated with the spontaneous hydrolysis of C3, referred to as "tick over." An amplification loop leads to rapid opsonization stabilized by properdin. Therefore each of these pathways converge toward the cleavage of the abundant plasma protein C3 by a C3 convertase, followed by the formation of a C5 convertase, which cleaves C5 into C5a and C5b, and induces the activation of the common lytic effector **terminal pathway (TP).** The interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration. The subsequent insertion of TP components into the cell wall leads to lysis via the **membrane attack complex (MAC),** which is composed of complement proteins C5b to C9.

Cell membrane receptors bind complement components or fragments to mediate complement activity, and a large array of serum and membrane regulatory proteins control the activation of CS (Fig. 173.1). The circulating components and regulators together comprise approximately 15% of the globulin fraction and 4% of the total serum proteins. The normal concentrations of serum complement components vary by age; newborn infants have mild to moderate deficiencies of all components.

CLASSICAL AND LECTIN PATHWAYS

The CP sequence begins with fixation of C1, by way of C1q, to the Fc non–antigen-binding part of the antibody molecule after antigen-antibody interaction. On binding, the C1 complex changes conformation, activating the C1r and C1s protease subunits; the C1s subcomponent becomes an active enzyme, **C1 esterase**. The activation leads to cleavage of C2 and C4 and the formation of the CP C3 convertase (C4bC2a).

As part of the **innate immune response**, broadly reactive "natural" antibodies and C-reactive protein (CRP), which react with carbohydrates from microorganisms and with dying cells, can substitute for specific antibodies in the fixation of C1q and initiate reaction of the entire sequence. Endogenous substances, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells, such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. In this case, however, the ligand-C1q complex interacts strongly with the inhibitor's C4-binding protein and factor H, allowing some C3-mediated **opsonization** and **phagocytosis** but limiting the full inflammatory response typically triggered by microbes.

Table 173.1 Nomenclature for Complement Components

	EXAMPLES
Classical pathway components are labeled with a C and a number	C1, C2, C4
Alternative pathway components are lettered	B, P, D
Some components are called factors	Factor B, factor D
Activated components or complexes have a bar over to indicate activation	$\overline{\text{C4bC2a}}$
Cleavage fragments are designated with a small letter	C3a, C3b
Cell membrane receptor	CR1, CR2, CR3, CR4

Table 173.2 Components of Complement System

SERUM COMPONENTS THAT ARE THE CORE OF THE COMPLEMENT SYSTEM
Classical pathway: C1q, C1r, C1s, C4, C2, C3
Alternative pathway: factor B, factor D
Lectin pathway: Mannose-binding lectin (MBL), ficolins 1/2/3, MBL-associated serine proteases (MASPs) 1/2/3
Membrane attack complex: C5, C6, C7, C8, C9
Regulatory protein, enhancing: properdin
Regulatory proteins, downregulating: C1 inhibitor (C1-INH), C4-binding protein (C4-bp), factor H, factor I, vitronectin, clusterin, carboxypeptidase N (anaphylatoxin inactivator)
MEMBRANE REGULATORY PROTEINS
CR1 (CD35), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF, CD55), CD59 (membrane inhibitor of reactive lysis)
MEMBRANE RECEPTORS
CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11c/CD18)
C3a receptor, C5a receptor, C1q receptors, complement receptor of the immunoglobulin superfamily (CRIg)

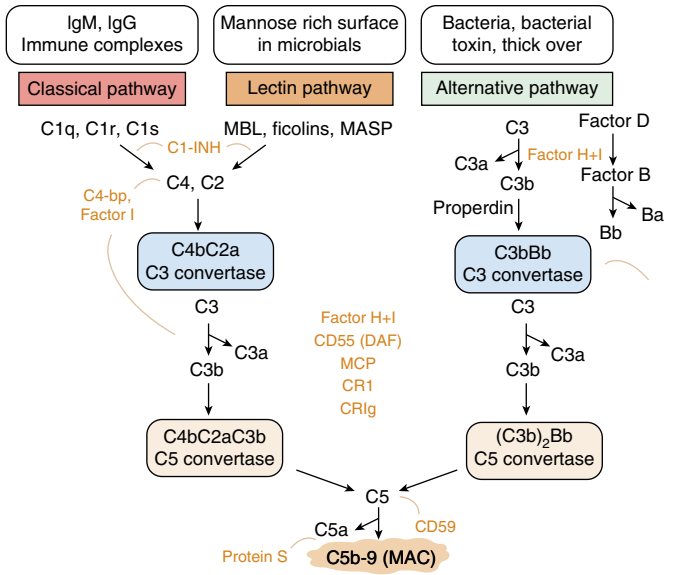

Fig. 173.1 Activation and control of the complement system. C1-INH, C1 inhibitor; C4-bp, C4-binding protein; CD59, cell membrane–associated protein; CR1 (CD35), complement receptor 1; CRIg, complement receptor of the immunoglobulin superfamily; DAF, CD55, decay-accelerating factor; MASP, mannose-binding lectin–associated serine protease; MAC, membrane attack complex; MCP, membrane cofactor protein.

C1q synthesized in the brain and retina fixes to superfluous synapses, which then can be cleared through C1q receptors on microglia, clearing the way for fresh synapses to populate the developing nervous system.

Recognition molecules in the **LP** are **MBL**, **ficolins, or collectins** (**CL-11** or kidney collectin or CL-K1; **CL-10**, collectin liver 1). MBL is the prototype of the collectin family of carbohydrate-binding proteins (**lectins**) that play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. Three ficolins have been identified in humans: **L-ficolin (ficolin-2), H-ficolin (ficolin-3),** and **M-ficolin (ficolin-1).** Ficolins show specificity for *N*-acetylglucosamine residues in complex oligosaccharides, but not for mannose or high-mannose-type oligosaccharides. Individual members display additional specificities, e.g., H-ficolin binds to *N*-acetyl-D-galactosamine and D-fucose, M-ficolin binds to sialic acid, and L-ficolin recognizes lipoteichoic acid and 1,3-β-D-glucan, the major component of yeast and fungal cell walls. These lectins, in association with **MASP-1, -2, and -3,** can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. There, MASPs then function like C1s to cleave C4 and C2 and activate the complement cascade. The peptide C4a has weak **anaphylatoxin** activity and reacts with mast cells to release the chemical mediators of immediate hypersensitivity, including histamine. The activation of C3 and C5 also liberates potent chemotactic fragments (i.e., the anaphylatoxins C3a and C5a) that recruit immune cells to the site of activation and prime them. Fixation of C4b to the complex permits it to adhere to neutrophils, macrophages, B cells, dendritic cells, and erythrocytes. MASP-2 can activate clotting by generating thrombin from prothrombin, which could prevent microbial spread.

Cleavage of C3 and generation of **C3b** is the next step in the sequence. The serum concentration of C3 is the highest of any component, and its activation is the most crucial step in terms of biologic activity. Cleavage of C3 can be achieved through the **C3 convertase** of the CP, C142, or of the AP, $\overline{C3bBb}$. Once C3b is fixed to a complex or dead or dying host cell, it can bind to cells with receptors for C3b (complement receptor 1, **CR1**), including B lymphocytes, erythrocytes, and phagocytic cells (neutrophils, monocytes, and macrophages). Efficient **phagocytosis** of most microorganisms, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that frequently occur in C3-deficient patients illustrate this point. The biologic activity of C3b is controlled by cleavage by **factor I** to iC3b, which promotes phagocytosis on binding to the **iC3b receptor (CR3)** on phagocytes. Further degradation of iC3b by factor I and proteases yields C3dg, then C3d; C3d binds to CR2 on B lymphocytes, thereby serving as a co-stimulator of antigen-induced B-cell activation.

ALTERNATIVE PATHWAY

The AP can be activated by C3b generated through CP activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by a low-grade, spontaneous reaction of native C3 with a molecule of water, or a tick over that occurs constantly in plasma. Once formed, C3b or the hydrolyzed C3 can bind to any nearby cell or to factor B. **Factor B** attached to C3b in the plasma or on a surface can be cleaved to Bb by the circulating protease **factor D**. The complex C3bBb becomes an efficient C3 convertase, which generates more C3b through an amplification loop. **Properdin** can bind to C3bBb, increasing stability of the enzyme and protecting it from inactivation by **factors I and H**, which modulate the loop and the pathway.

Certain activating surfaces promote AP activation if C3b is fixed to them, including bacterial teichoic acid and endotoxin, virally infected cells, antigen–immunoglobulin A complexes, and cardiopulmonary bypass and renal dialysis membranes. These surfaces act by protecting the C3bBb enzyme from the control otherwise exercised by factors I and H. Rabbit red blood cell (RBC) membrane is such a surface, which serves as the basis for an assay of serum AP activity. Conversely, sialic acid on the surface of microorganisms or cells prevents the formation of an effective AP C3 convertase by promoting the activity of factors I and H. Significant activation of C3 can occur through the AP, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142.

MEMBRANE ATTACK COMPLEX

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the CP, $\overline{C4b2a3b}$, or from the AP, $\overline{C3bBb3b}$. C6 is bound to C5b without being cleaved, stabilizing the activated C5b fragment. The C5b6 complex then dissociates from C423 and reacts with C7. C5b67 complexes must attach promptly to the membrane of the parent or a bystander cell, or they lose their activity. Next, C8 binds, and the C5b678 complex then promotes the addition of multiple C9 molecules. The C9 polymer of at least 3-6 molecules forms a transmembrane channel, and lysis ensues.

CONTROL MECHANISMS

Without control mechanisms acting at multiple points, there would be unbridled consumption of components, which would generate severe, potentially lethal host damage. Cells are generally protected from amplification and effector insult by a panel of complement regulators, which are expressed on their surface or recruited from circulation At the first step, **C1 inhibitor (C1-INH)** inhibits C1r and C1s enzymatic activity and thus the cleavage of C4 and C2. C1-INH also inhibits MASP-2, factors XIa and XIIa of the clotting system, and kallikrein of the contact system. Activated C2 has a short half-life, and this relative instability limits the effective life of C42 and C423. The AP enzyme that activates C3, $\overline{C3bBb}$, also has a short half-life, although it can be prolonged by the binding of **properdin** to the enzyme complex. Properdin can also bind directly to microbes and promote assembly of the AP C3 convertase.

The serum contains the enzyme carboxypeptidase N, which cleaves the N-terminus arginine from C4a, C3a, and C5a, thereby limiting their biologic activity. Factor I inactivates C4b and C3b; factor H accelerates inactivation of C3b by factor I; and an analogous factor, **C4-binding protein (C4-bp)**, accelerates C4b cleavage by factor I, thus limiting assembly of the C3 convertase. Three protein constituents of cell membranes (**CR1**, **membrane cofactor protein** [**MCP**], and **decay-accelerating factor** [**DAF**]) promote the disruption of C3 and C5 convertases assembled on those membranes. Another **cell membrane–associated protein**, **CD59**, can bind C8 or both C8 and C9, thereby interfering with the insertion of the MAC (C5b6789). The serum proteins **vitronectin** and **clusterin** can inhibit attachment of the C5b67 complex to cell membranes, bind C8 or C9 in a full MAC, or

interfere with the formation or insertion of this complex. Vitronectin also promotes macrophage uptake of dying neutrophils. The genes for the regulatory proteins factor H, C4-bp, MCP, DAF, CR1, and CR2 are clustered on chromosome 1.

PARTICIPATION IN HOST DEFENSE

Neutralization of virus by antibody can be enhanced with C1 and C4 and further enhanced by the additional fixation of C3b through the classical or alternative pathway. Complement may therefore be particularly important in the early phases of a viral infection when the antibody titer is limited. Antibody and the full complement sequence can also eliminate infectivity of at least some viruses by the production of typical complement "holes," as seen by electron microscopy. Fixation of C1q can opsonize (promote phagocytosis) through binding to the phagocyte C1q receptor.

C4a, **C3a**, and **C5a** can bind to mast cells and thereby trigger the release of histamine and other mediators, leading to vasodilation and the swelling and redness of inflammation. C5a can enhance macrophage phagocytosis of C3b-opsonized particles and induce macrophages to release the cytokines tumor necrosis factor and interleukin-1. C5a is a major **chemotactic factor** for neutrophils, monocytes, and eosinophils, which can efficiently phagocytize microorganisms opsonized with C3b or cleaved C3b (iC3b). Further inactivation of cell-bound C3b by cleavage to C3d and C3dg removes its opsonizing activity, but it can still bind to B cells. Fixation of C3b to a target cell can enhance its lysis by natural killer cells or macrophages (Fig. 173.2).

Insoluble immune complexes can be solubilized if they bind C3b, apparently because C3b disrupts the orderly antigen-antibody lattice. Binding C3b to a complex also allows it to adhere to **C3 receptors (CR1)** on RBCs, which then transport the complexes to hepatic and splenic macrophages for removal. This phenomenon may at least partially explain the immune complex disease found in patients who lack C1, C4, C2, or C3.

The CS serves to link the innate and adaptive immune systems. C4b or C3b coupled to immune complexes promotes their binding to antigen-presenting macrophages, dendritic cells, and B cells. The coupling of antigens to C3d allows binding to CR2 on B cells, which greatly reduces the amount of antigen needed to trigger an antibody response.

Neutralization of endotoxin in vitro and protection from its lethal effects in experimental animals require C1-INH and later-acting components of complement, at least through C6. Activation of the entire complement sequence can result in lysis of virus-infected cells, tumor cells, and most types of microorganisms. **Bactericidal activity** of complement has not appeared to be important to host defense, except for the occurrence of *Neisseria* infections in patients lacking later-acting components of complement.

Complement Evaluation

Good quality blood sampling requires that after clotting (about 20-120 minutes), the serum must be separated by centrifugation as soon as possible, and stored under controlled conditions. In case complement testing cannot be performed on the day of blood sampling, the serum and plasma samples must be stored in a deep freezer (−20°C) for up to 3 months or in an ultra-deep freezer (−70°C) for a longer storage until analysis. If the analysis will be done by a specialized laboratory, the samples must be shipped on dry ice by courier. Repeated freezing and thawing should be avoided because of the risk of in vitro activation. The serum is sufficient for the analysis of the total function of complement proteins and regulators as well as of autoantibodies. A quantitation of activation products requires the use of EDTA plasma because it blocks the in vitro activation of the CS by way of its Mg^{2+} and Ca^{2+} complexing properties. Heparin and citrate are less useful. The utilization of the less invasive dried blood spot (DBS)-based assays can also be used for diagnosis; enzyme activities could be retained, facilitating the samples' transportation.

The indication for using assays for complement evaluation is to detect genetic, acquired, or the effect of complement inhibitory therapy. Functional assays can screen and direct the following steps for the evaluation of specific protein deficiencies (Fig. 173.3). Assays including hemolysis of RBCs **(CH50, AP50)** check the activation of classical and alternative pathways. In both cases, CH50 and AP50, the functional result is the lytic destruction of erythrocytes on membrane insertion of C5b-9 (MAC). Low but not absent CH50 results could reflect complement consumption due to active immune complex disease, diminished hepatic production due to liver disease, and immaturity of hepatic production seen in young infants. *Screening with hemolytic assays is not adequate for C9, properdin, MBL, MASP-2, or ficolin deficiencies.* In patients with these defects, the hemolytic assay value may be minimally decreased or normal. An alternative assay, popular in Europe, is a plate-based activation assay, which more specifically detects complement

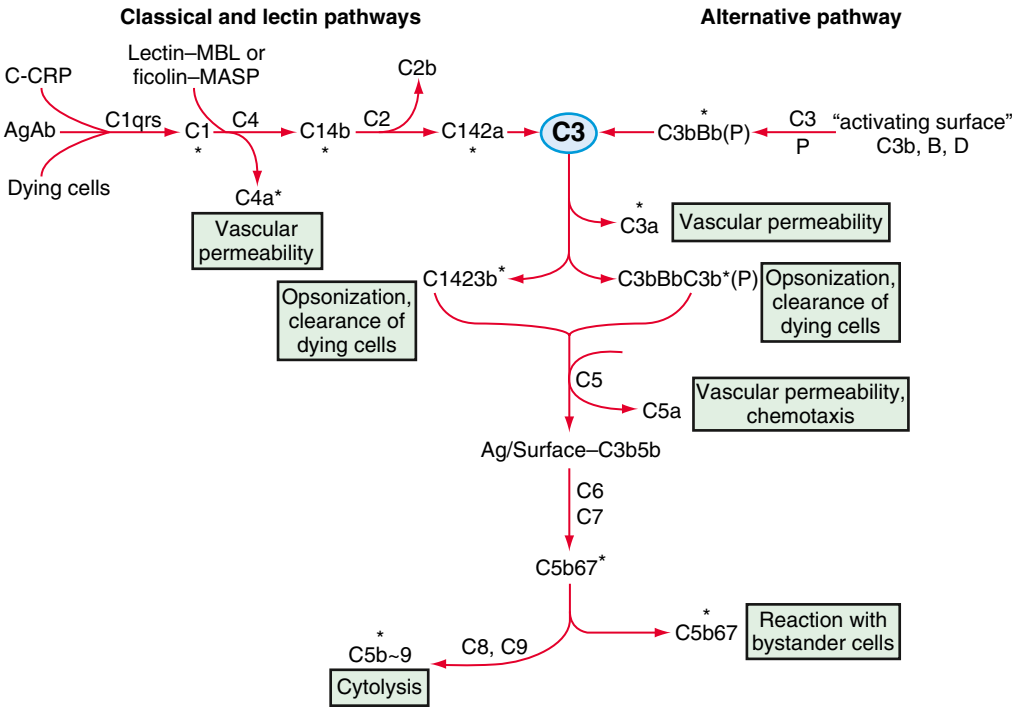

Fig. 173.2 Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. Functional activities generated during activation are enclosed in boxes. The multiple sites at which inhibitory regulator proteins (not shown) act are indicated by asterisks. Ab, Antibody (immunoglobulin G or M class); Ag, antigen (bacterium, virus, tumor, or tissue cell); B, D, P, factors B, D, and properdin; C-CRP, carbohydrate–carbohydrate-reactive protein; MBL, mannose-binding lectin; MASP, MBL-associated serine protease.

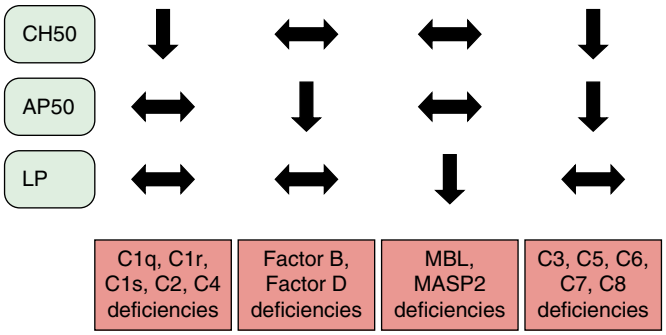

Fig. 173.3 Laboratory screening of complement system. LP, Lectin pathway; MBL, mannose-binding lectin; MASP, MBL-associated serine protease.

activation through CP, LP, and AP ("CS screen" test). Although the result target of these enzyme-linked immunosorbent assays (ELISAs) is principally the same as for the lytic assays, it is based on detecting full assembly of C5b-9 by using an antibody to a C9 neoantigen when serum is added to microtiter wells coated with the activation agent for the different pathways (e.g., IgM for CP, mannan for LP, and lipopolysaccharides for AP).

Once an abnormal CH50 or AP50 has been confirmed, immunochemical tests can be used to define the serum levels of specific components, the second step for defining complement deficiencies. Normal concentrations of single components do not exclude functional defects. The functional activity of a single component can be tested. Sera depleted of the actual component and patient's fresh serum are mixed to see whether the activity can be restored by using hemolysis as a result. Reduced functional activity of individual complement components either reflects a deficiency state, or indicates consuming complement activation. To distinguish primary or acquired defects, activation products generated by CS activation could be measured. Different approaches can be applied for this aim: detection of split fragments, generated after enzymatic cleavage of certain components, e.g., C4 (C4a, C4b/c, C4d), C3 (C3a, C3b/c, iC3b, C3d), factor B (Ba, Bb), and C5 (C5a), or the identification of protein complexes where activated components are bound to their respective regulators, like C1rs-C1-inhibitor, the properdin-containing AP convertase, C3bBbP, and sC5b-9 (soluble terminal complement complex). Detection of complement activation products like C3d and C4d on red cells using *flow cytometry* has been used to evaluate in vivo complement activation in autoimmune diseases and trauma. The terminal **C5b-9 complement complex** exists in two forms, the MAC and the soluble form (sC5b-9). The in vitro–generated surface-bound C5b-9 must not be confused with sC5b-9, which is found in plasma and if increased is a useful marker of complement activation in vivo reflecting diseases with disturbed complement function. sC5b-9 can be quantified by ELISA and is based on the same C9 neoepitope principle. In the case of efficient C5 blockade, there should ideally be no sC5b-9 present.

C4 levels have been used as a screening test for **C1-INH deficiency** in **hereditary angioedema (HAE)**; this test does not substitute quantitative and/or functional evaluation of C1-INH. C4 concentrations can be within normal range between episodes in approximately 5–10% of the patients. Also, a defective C1-INH protein can reflect only a functional assay with normal quantitative values. **Deficiency of factor I or H** permits persistence of the classical and alternative pathway convertase and thus consumption of C3, with reduction in the CH50 value. If multiple components are decreased, it is possible that sample handling was improper, a regulatory protein was deficient, or autoantibodies were present. Flow cytometry is the standard technique for the diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH)** by detecting reduced levels of CD55 and CD59 on blood cells.

Autoantibodies to complement components could simulate deficiencies and assays for their detection would be relevant according to clinical information. They are often associated with specific diseases, e.g., anti-C1q antibody is associated with hypocomplementemic urticarial vasculitis and/or proliferative systemic lupus erythematosus (SLE) nephritis.

Assessment of cell surface expression of receptors and tissue deposition of complement proteins or fragments are further steps for complement evaluation. Specific gene panels are another accessible tool that could supply additional information (Table 173.3).

Table 173.3 The Steps for Complement System Evaluation

COMPLEMENT EVALUATION	EXAMPLES
Total complement activity	CH50, AP50, lectin pathway
Quantification of single components	C3, C4, MBL, properdin
Functional activity of single components	Functional C1 inhibitor
Products of complement activation	C3d; C3dg
Autoantibodies to complement components	Anti-C1q; nephritic factor
Cell surface expression	CD55; CD59; CR3/4
Tissue deposition of complement proteins or fragments	Deposition of C3 or factor H in injury burns
Genetic evaluation	Next generation sequencing or specific gene panels

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

173.2 Complement Pathway Deficiencies

Anete Sevciovic Grumach

Most genetically determined complement deficiencies are inherited in an autosomal recessive fashion. Exceptions are properdin deficiency, which is X-linked, and C1-INH deficiency, which is autosomal dominant. In most cases, it is possible to predict the effects of a particular deficiency based on understanding the normal physiologic function of that protein. Increased susceptibility to **infections** caused by encapsulated bacteria and **autoimmunity** are the most common presentations of complement deficiencies. Deficiency of components of TP and properdin deficiency are associated with neisserial infections. When there is an imbalance between complement activation and regulation, complement can quickly attack the host and trigger and/or exacerbate adverse processes that result in diseases and clinical complications. Genetic variants in the **complement factor H (CFH)** and **complement factor I (CFI)** genes have been associated with **atypical hemolytic uremic syndrome (aHUS)** and **aging macular degeneration (AMD).** A distinct clinical manifestation is described for deficiency of C1-INH causing recurrent **angioedema.**

CLASSICAL PATHWAY DEFICIENCIES

Patients deficient in the initial components of the CP are prone to autoimmune connective tissue diseases (Table 173.4). Most patients with primary **C1q deficiency** have SLE; some have SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). The association with SLE is due to compromised clearance of apoptotic debris and impaired B-cell tolerance. Some C1q-deficient children have serious infections, including septicemia and meningitis. Only a few patients with **inherited deficiencies of C1r and C1s** have been described. It is thought that neither component is stable without the other so that a pathogenic variant in one often leads to diminished levels of both. Glomerulonephritis and lupus have been reported in C1r/C1s-deficient patients.

Table 173.4 Pathway Deficiencies of Complement System

DEFICIENCY	INHERITANCE	ASSOCIATED SYMPTOMS/DISORDERS
C1q, C1r/s (often combined), C2, C4 (total C4 deficiency)	AR	SLE, systemic infections with encapsulated organisms; heterozygous C2 deficiency may have a reduced CH50 but remain asymptomatic
C4A or C4B	Complex	Susceptibility to infections and/or autoimmunity (SLE); mostly asymptomatic
C3 GOF	AD	aHUS (2–10% of the cases)
C3	AR	Pyogenic infections, neisserial infections, glomerulonephritis, AMD
C5, C6, C7, C8α–γ/C8β	AR	Neisserial infections; recurrent meningitis
C9	AR	Neisserial infections (mostly asymptomatic)
Factor B	AR*	Neisserial and pneumococcal infections, aHUS (1–4% of the cases)
Factor D	AR	Bacterial infections
MBL	Polymorphism	Bacterial infections (mostly asymptomatic) and susceptibility to autoimmunity in some cases
Ficolin-3 (H-ficolin)	Polymorphism	Various clinical phenotypes
MASP-1	AR	3MC syndrome
MASP-2	AR	Respiratory infections, mostly asymptomatic

*AR, Autosomal recessive non-codominant.
AR, Autosomal recessive; AD, Autosomal dominant; C4A and C4B, isotypes encoded by C4A and C4B genes, respectively; GOF, gain of function; SLE, systemic lupus erythematosus; aHUS, atypical hemolytic uremic syndrome; AMD, aging macular degeneration; 3MC, Mingarelli, Malpuech, Michels and Carnevale.

Complement component **C4** is a central protein in the classical and lectin pathways within the CS. **C4A** and **C4B genes** encode the two isoforms of the component C4, an essential element for the effector arm of the humoral immune response. The two isotypes of C4, which differ by only four amino acids, demonstrate differential chemical reactivities: C4A displays a higher affinity for amino group–containing antigens or immune complexes, and C4B for hydroxyl group-containing antigens. The presence of one C4A or C4B gene is called *heterozygous* C4A or C4B deficiency, whereas the presence of no functional C4A or C4B genes causes *complete* C4A or C4B deficiency and is called **homozygous C4 deficiency**. Homozygous deficiencies of complement C4A or C4B are detected in 1–10% of populations. Homozygous deficiency of C4A is associated with an increased frequency of SLE; whereas homozygous C4B deficiency has been associated with increased susceptibility to bacterial and enveloped viral infections. Within each C4 gene, there can be deletions or duplications or simple inactivating variants; therefore interpretation of a serum level is difficult.

C2 deficiency is found with a frequency of 1/10,000 in the White population. The lowest frequency of autoimmunity (10–42%), among the proteins of the CP, is observed in C2-deficient patients. Individuals with C2 deficiency also carry the risk of life-threatening septicemic illnesses, usually caused by pneumococci; however, most have not had problems, presumably because of protective effects of other complement pathways. The genes for C2, factor B (AP), and C4 are situated close to each other on chromosome 6, and a partial depression of factor B levels can occur in conjunction with C2 deficiency.

Patients with C1, C2, or C4 deficiency have an increased occurrence of **autoantibodies**; antinuclear antibodies are present in 75% of patients with C1 or C4 deficiency and 25–55% of patients with C2 deficiency. Anti-dsDNA antibodies are present in 20% of patients with C1q/C4 deficiency and 33% of patients with C2 deficiency. Individuals with heterozygous C2 or C4 deficiency often remain asymptomatic. Also, there is an increased incidence of **bacterial infections** associated with deficiency of components in CP, including meningitis, pneumonia, arthritis, or septicemia. Other infections such as epiglottitis, and peritonitis have been described. The most common organisms identified in C2-deficient patients have been *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.

C3 Deficiency

C3 deficiency is rare and the disease manifests early in life. Severe infections (pneumonia, meningitis, osteomyelitis, or bacteremia) caused by encapsulated bacteria *(H. influenzae*, *Neisseria meningitidis)* occur. The infections reflect the impairment in the C3b opsonization, generation of chemotactic factor, influence in B-cell stimulation, and failure of complete complement activation. **MPGN** is noted in approximately 30% of the cases of C3 deficiency. Slightly more common is a partial deficiency of C3, termed *hypomorphic* C3. This partial deficiency has been seen in some autoimmune disorders. Rare C3 gain-of-function (GOF) variants may lead to **aHUS** and endothelial damage in the glomerulus. One common and several rare variants in C3 have been associated with increased risk of AMD. A unique feature of C3 deficiency is a vasculitic rash that may appear during infections; symptoms of serum sickness may occasionally be seen. These unusual findings are due to the lack of immune complex solubilization by C3. They typically are transient in nature but can cause confusion with lupus, particularly in the presence of glomerulonephritis.

DEFICIENCY OF TERMINAL COMPONENTS (C5, C6, C7, C8, C9)

Terminal components are shared by the classical, lectin, and alternative pathways, and are ultimately responsible for the formation of the **MAC**. The risk of developing **meningococcal sepsis or meningitis** is markedly increased in people who have a deficiency of one terminal component. In contrast to the immunocompetent population (median age for meningococcal infection: 3 years), the onset of symptoms in patients with terminal deficiencies is 17 years. However, infections generally lead to lower mortality, may be recurrent, and have a milder course than in an immunocompetent person. Rarely, SLE or other autoimmune disorders has been identified in these defects. Disseminated ***Neisseria gonorrhoeae*** infections have also been described; an increased frequency of other bacterial infections is not observed. A terminal component deficiency should be suspected if there is a family history of meningococcal infections, repeated neisserial infections, or if the causative meningococcal serotype is W-135, X, Y, or Z, which less frequently cause infections in healthy individuals. Early vaccination of children could change the profile of serotypes causing infection in those patients.

C6 deficiency occurs more frequently in African Americans and in people from South Africa. Two variations of C6 deficiency have been described. In one case, a splice defect leads to a smaller than usual protein, C6SD. This protein functions less efficiently than wild-type C6; however, it is not clear whether bearing C6SD leads to compromised host defense. The other variation is combined C6 and C7 deficiency. **C7 deficiency** is rare and in the few reported cases, the clinical presentations have varied.

C8 is composed of three chains: α, β, and γ. **C8β deficiency** is more common in White people, whereas **C8α-γ deficiency** is more common among African Americans. Approximately 1 patient in 1000 carries a homozygous common nonsense variant causing **C9 deficiency** as described in Japan and Korea. It is more difficult to diagnose than most of the other complement deficiencies because the CH50 is diminished but not absent. Lytic activity can be generated in the absence of C9. The neisserial disease can occur, although the penetrance appears to be less than that with other terminal component deficiencies.

ALTERNATIVE PATHWAY DEFICIENCIES

The AP is a highly conserved surveillance system that is continuously turning over (tick over) due to a labile thioester bond in C3 and thus does not require antibodies or lectins for activation. **Properdin** is a positive regulator of AP activity and works by stabilizing AP convertases. **Properdin deficiency** is rare, hereditary, and is the only X-linked complement deficiency. A small number of patients have been identified with properdin deficiency; these patients are unusually susceptible to ***Neisseria* infections.** There is a particularly high fatality rate for meningococcal disease in properdin-deficient patients, in contrast with the protection from early death seen in patients with terminal complement component deficiencies. It manifests with either complete absence of the molecule (type I), partial deficiency (type II), or a normal level of dysfunctional protein (type III). Properdin-deficient individuals are susceptible to **meningococcal disease**, which is frequently complicated by sepsis and most commonly occurs in adolescence. **Factor D** and **Factor B deficiencies** were described in few cases and the association with *Neisseria* infections was also identified. Systemic streptococcal infections have also been involved in factor D deficiency. GOF pathogenic variants in factor B are associated with the aHUS.

LECTIN PATHWAY DEFICIENCIES

The **LP** is focused on the recognition of repetitive carbohydrate patterns found on the surface of microbial pathogens. Lectin **pattern recognition molecules (PRMs)**, which include MBL, ficolin-1, ficolin-2, ficolin-3, collectin-10, and collectin-11, activate the pathway in an analogous manner to antibodies in the CP. **MASPs**, which act in a similar fashion to C1r and C1s, associate with MBL and activate C4 and C2 by proteolytic cleavage (see Fig.173.1). Among White populations, approximately 5–7% of people have inherited MBL deficiency. LP impairment due to insufficient production of any of these components is common and may be associated with no clear clinical phenotype. However, MBL insufficiency is, in combination with other factors, associated with more severe forms of sepsis and fatal outcomes. The deficiency appears to represent a modest risk factor for infection, typically revealed in a high-risk setting. Similarly, it may subtly alter the course or contribute to the overall risk of developing several autoimmune diseases. MBL deficiency has been associated as an additional severity influence for common variable immunodeficiency, cystic fibrosis, and hepatitis. In contrast, low MBL levels have been described as protective for mycobacterial infection. MBL deficiency is not typically associated with absent levels, and it has been difficult to define the normal range in healthy people.

MASP-1, the most abundant protease of the LP, has a central role in pathway activation via MASP-2. MASP-1 may be involved in coagulation, renal, gastrointestinal, and myocardial ischemia/reperfusion-related pathology; there is no firm evidence for this type of pathology in humans.

The **Malpuech, Michels, Mingarelli, Carnevale (3MC) syndrome** is a rare, autosomal recessive genetic disorder associated with pathogenic variants in the **MASP1/3; COLEC11; or COLEC10** genes. The number of 3MC patients with known pathogenic variants in these three genes reported so far remains very small. The clinical manifestations of the 3MC syndrome consist of developmental delay, facial dysmorphia, and various skeletal anomalies. Developmental defects include cleft lip and palate, postnatal growth deficiency, cognitive impairment, and hearing loss. Excess or unusual infections and autoimmunity have not yet been described in this syndrome. The proposed mechanism was revealed by an unexpected role for these proteins in cuing neural crest cell migration.

MASP-2 deficiency was initially described in a patient with serious infections and autoimmune disease. MASP-2 deficiency has been included in the classification of primary immunodeficiencies. Asymptomatic individuals have been described; the frequency is 6/10,000, suggesting that the phenotype is mild. Healthy individuals homozygous for p.D120G have also been found by chance in genetic association studies. These findings suggest that MASP-2 deficiency could no longer be associated to a specific clinical phenotype. In contrast, increased levels of MBL or MASP-2 may contribute to poor disease outcome associated with mycobacterial infections or pneumococcal meningitis.

Complete **ficolin-3 (or H-ficolin) deficiency** was initially associated with increased susceptibility to infections and necrotizing enterocolitis. A heterogeneous range of clinical manifestations have been described in patients with complete ficolin-3 deficiency, and the first case described was later diagnosed with Wiskott-Aldrich syndrome. Respiratory and nervous system involvement in the few reported cases of FCN3 deficiency raises awareness regarding the significance of ficolin-3 in respiratory and nervous immunity.

DEFICIENCIES OF COMPLEMENT REGULATION

The CS has several levels of **regulation** at the initiation, amplification (formation of convertases), and membrane attack phases, thereby preventing inadvertent tissue damage. Deficiency of complement inhibitors leads to dysregulation either in the fluid phase or on cell surfaces and consequent recurrent infections (mostly bacterial), inflammatory disorders, and presentations with a broader clinical phenotype. These include angioedema (**C1-INH deficiency**), kidney and eye diseases (**factor H, factor I, or CD46/MCP deficiency**), **protein-losing enteropathy (CD55/DAF deficiency)**, and **PNH (CD55 + CD59 deficiency**). In addition, there are seven complement receptors (C1qR, C3aR, C5aR, CR1, CR2, CR3, and CR4). The same disease spectrum may be caused and shaped by a broad variety of different alterations in complement activators and/or regulators. The individual complement profile of a patient (sometimes referred to as **complotype**) often determines the course and severity of the disease. Disorders such as AMD, aHUS, or C3 glomerulopathy (C3G) are among the most well-described examples in this context.

Approximately 50% of patients with aHUS have genetic pathogenic variants of factors H and I, C3, factor B, and/or MCP, and deletion of complement factor H–related proteins 1 and 3 (CFHR1/CFHR3). Approximately 20% of patients with aHUS have pathologic variants in more than one gene and patients with autoantibodies to regulatory proteins also comprise a significant subset. The majority of aHUS cases are sporadic and occur in the absence of prior family history. Furthermore, even in familial forms of aHUS, penetrance is incomplete.

Thrombomodulin (CD141) also has a regulatory role and binds to factor H and C3b, thereby inhibiting complement activation. Interestingly, pathologic variants in factor H, MCP, and factor I have also been reported in **C3** MPGN, as well as preeclampsia and hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome.

Several complement proteins, their activation products, and regulators have also been related to **AMD**, particularly, C3 and factors H and I.

Hereditary Angioedema

HAE comprises a group of diseases characterized by recurrent angioedema without wheals, showing an autosomal dominant inheritance pattern. It was first recognized in patients with heterozygous **deficiencies of C1-INH** and the estimated prevalence is 1:50,000 (Chapter 189.1). Patients with angioedema without wheals have also been described with normal C1-INH levels. Several pathogenic variants

were associated with this group of patients with **primary angioedema**: factor XII (FXII-HAE), plasminogen (PLG-HAE), angiopoietin-1 (ANGPT1-HAE), kininogen-1 (KNG1-HAE), myoferlin (MYOF-HAE), and heparan sulfate-glucosamine 3-*O*-sulfotransferase 6 (HS-HAE). However, a significant proportion do not have a defined molecular explanation.

The angioedema is self-limited and recurrent, affecting the deep layers of skin and mucosa, commonly causing swelling of extremities (hands, feet, limbs), face, lips, tongue, genitalia, bowels, and the upper airway. The involvement of the gastrointestinal tract causes severe abdominal pain, distension, vomiting, and, less frequently, diarrhea. The symptoms can be misdiagnosed, and unnecessary surgery may be performed. The obstruction of upper airways due to edema of the glottis is associated with asphyxia if the attacks are not prevented. Swelling attacks are transitory and usually last from 2-5 days, but their severity and frequency vary widely from patient to patient. Approximately 5% of people who carry a C1-INH pathologic variant are asymptomatic.

In the most frequent subtype, HAE with C1-INH deficiency (HAE-C1INH, OMIM #106100), the first HAE episodes occur at a mean age of 10 years; however, the onset of symptoms may occur at an early age (Chapter 189.1). This type of HAE is classified as **type I** when there is low quantitative and functional C1-INH levels (85% of the cases) and **type II** for decreased functional C1-INH values. A typical functional level is approximately 25–40% of normal in both types. Attacks, when identified, are triggered by stress, trauma, hormones (estrogen), infections, extreme temperatures, and alcohol. Although many patients can identify triggers, many episodes have no identifiable trigger, which increases anxiety and contributes to feelings of loss of control. The symptoms are preceded by prodromes, such as erythema marginatum, irritability, nausea, and flulike symptoms. Consumption of C2 and C4 increases the risk for the development of SLE. Positive family history occurs in 75% of the cases and de novo pathogenic variants are described in 25% of the cases.

The **third type** of HAE referred to as **HAE with normal C1-INH** (previously called type III), is not a complement deficiency. It is characterized by normal serum levels and functional activity of C1-INH. It has been described primarily in females; however, both sexes are affected.

Acquired C1-INH deficiency is rarer than HAE-C1-INH (1:9) and is clinically indistinguishable from inherited C1-INH deficiency except that onset is later in life (>40 years old). Patients with acquired C1-INH deficiency require careful surveillance for malignancy; B-cell malignancies, autoimmunity, and monoclonal gammopathies are the most common. The laboratory features are similar to those of hereditary C1-INH deficiency, except that C1q levels are diminished in these patients. Anti–C1-INH can be detected in approximately 70% of the cases.

C4 Binding Protein Deficiency

C4 binding protein deficiency has been described in one family. The proband presented with angioedema, vasculitis, and arthritis. The manifestations were thought to relate to uncontrolled activation of the CP and the release of anaphylatoxins.

Factor H Deficiency

Factor H (CFH), which is present at high concentrations (500 μg/mL) in plasma, works in both the liquid and solid phases and attenuates the activity of C3 convertase in the AP and acts as a cofactor for factor I in the cleavage of C3b and C4b. It is a multifunctional molecule that has the function of decay acceleration and plays a very important role in regulating complement activation. Infections, aHUS, glomerulonephritis, and macular degeneration are the main disease phenotypes seen in patients with factor H deficiency. Infections occur due to secondary consumption of C3 with consequent partial deficiency. Diagnosis is suggestive when C3 has diminished levels and low but not absent CH50 and AP50 is found. The antigenic levels of factor H are typically low.

Several people with **MPGN** were identified with factor H deficiency. CFH deficiency was found to be the underlying basis for the pathophysiologic changes in 15–30% of patients with **aHUS**. aHUS is a thrombotic microangiopathy characterized by hemolytic anemia, thrombocytopenia, and renal failure, which occurs in the absence of its usual cause (infection with a Shiga toxin–producing organism). It is called "atypical" because it lacks the common trigger of infectious diarrhea. CFH deficiency probably affects the ability to protect the fenestrated endothelium in the glomerulus from complement-mediated damage. Recurrent aHUS also has been seen in patients with antibodies to factor H, defining an acquired form as well. This form may be slightly more amenable to therapy. Both autosomal recessive and heterozygous pathogenic variants have been seen. The age at onset is quite young in most cases, and the disease is recurrent. Mortality is not uncommon. These patients have a diminished C3 level, although the antigenic level of factor H typically is normal or elevated. Normal C3 levels are sometimes seen, and the only way in which this disorder can be identified is with direct genetic analysis.

A common tyrosine-histidine polymorphism of factor H was identified as a significant risk factor for **macular degeneration** with a higher risk of the development of macular degeneration and blindness subsequently. In macular degeneration, the central region of the retina is gradually destroyed by a process that leaves deposits of protein that contain factor H and terminal complement components. It has been hypothesized that the abnormal factor H provides less protection to the choroidal vessels, allowing smoldering complement activation with gradual damage to the endothelium.

FACTOR I DEFICIENCY

Not only factor H but also factor I is a key regulator of the AP. Deficiency of factor I results in uncontrolled activation of the AP with subsequent secondary C3 deficiency and a reduction in circulating factor H levels. Distinct clinical manifestations have been associated with **factor I deficiency.** Marked susceptibility to infections relates to the role of factor I as a cofactor for C3bBb dissociation. When factor I is lacking, C3bBb continues to cleave C3 resulting in secondary C3 deficit. Both the CH50 and the AP50 are depressed but not absent, and C3 antigen levels are low. In factor I deficiency, infections are similar to those seen in true C3 deficiency. Neisserial disease has been reported, as well as infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae.* Partial factor I deficiency has been described. aHUS, or MPGN II, has also been associated with factor I deficiency, probably related to the capacity of complement regulatory proteins to protect vascular endothelium from activating complement after microtrauma. These cases of factor I deficiency are difficult to identify because complement studies often give normal results. C3 may be depressed but is not necessarily affected. The pathogenic variants inactivate certain binding sites like surface-bound C3b and polyanion surfaces such as the fenestrated endothelium of the glomerulus, which exposes the basement membrane. A third phenotype resembles an autoinflammatory process and has been described in a small number of patients. Central nervous system inflammation has been the hallmark. Partial factor I deficiency has also been previously associated with clinical manifestations including recurrent tonsillitis, urinary infections, otitis, pyelonephritis, severe meningitis, and sepsis.

Membrane Cofactor Protein (CD46) Deficiency

MCP is a membrane protein, and its defect is intrinsic to the kidney. Deficiencies of MCP are associated with a later onset of atypical HUS compared with factor H and factor I deficiencies and it accounts for approximately 10% of all cases. There is no other known phenotype for MCP deficiency. Findings on traditional complement analysis are normal, although the mechanism is thought to be the same as for factor H and factor I deficiencies. Considering the local defect, renal transplantation can be successful.

CD59 Deficiency

CD59 is the key membrane regulator of the TP that prevents insertion of the MAC into host tissue. It is expressed on most hematopoietic cells and endothelial cells, where it confers protection from intravascular complement-mediated lysis. Isolated CD59 deficiency manifests by chronic hemolytic anemia, recurrent stroke, and severe Guillain-Barré–like neurologic symptoms with hemolysis. This defect

Table 173.5 Protein Regulators and Receptor Deficiencies of Complement System

DEFICIENCY	INHERITANCE	ASSOCIATED SYMPTOMS/DISORDERS
C1 inhibitor	AD	HAE with C1-INH deficiency
C4-binding protein	Unknown	Atypical Morbus Behçet, angioedema, protein S deficit
Properdin	X-linked recessive	Meningitis (*Neisseria*)
Factor H	AR	Membranoproliferative glomerulonephritis, AMD, aHUS (20–30% of the cases)
Factor I	AR	Pyogenic infections, neisserial infections, glomerulonephritis, aHUS (5–10% of the cases), central nervous system inflammation
CFHR1 (FHR3)	Complex	aHUS, C3G, AMD, RA, SLE
Thrombomodulin (CD141)	AD	aHUS (3–5% of the cases)
CD46/MCP	Most often heterozygous or compound heterozygous pathogenic variants	aHUS (10–15% of the cases)
CD55/DAF	AR	Protein losing enteropathy
CD55 (DAF) or CD59	AR	PNH
CD59	AR	Chronic hemolysis and relapsing peripheral demyelinating disease, cerebral infarction
CR2 (CD21)	AR	Infections, associated with CVID
CR3 (CD18/CD11b); CR4 (CD18/CD11c, LFA-1)	AR	LAD

CFHR1, Complement factor H related 1; MCP, membrane cofactor protein; DAF, decay-accelerating factor; LFA-1, integrin called lymphocyte function-associated antigen 1; AR, autosomal recessive; AD, autosomal dominant; aHUS, atypical hemolytic uremic syndrome; C3G, C3 glomerulopathy; SLE, systemic lupus erythematosus; AMD, aging macular degeneration; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; PNH, paroxysmal nocturnal hemoglobinuria; CVID, common variable immunodeficiency; LAD, leukocyte adhesion deficiency.

in CD59 was suspected in cases of chronic hemolysis because of the phenotypic resemblance to **PNH**. PNH is caused by acquired somatic variants of phosphatidylinositol glycan class A (PIG-A) or phosphatidylinositol glycan class M (PIG-M) in a clone of bone marrow progenitor cells. The protein product of PIG-A is an anchoring structure for C8 binding protein, DAF (CD55), and CD59. Glycosylphosphatidylinositol (GPI)-anchored proteins protect hematopoietic cells from complement-mediated lysis. PNH is characterized by recurrent episodes of hemoglobinuria secondary to intravascular hemolysis and can be associated with thrombosis and aplastic anemia. The red cells are the most vulnerable because they have no ability to repair membrane damage. When the cells develop from the variant-bearing progenitor, they lack all GPI-anchored membrane proteins, although the major features relate to loss of CD59. The diagnosis of PNH is made by flow cytometry for CD59 or CD55 (DAF).

Decay-Accelerating Factor (CD55) Deficiency

DAF (CD55) is a membrane-bound regulator that dissociates both classical and alternative C3 convertases. In certain kindreds, DAF deficiency has been associated with protein-losing enteropathy, whereas in others, all of the members have been completely healthy, with the deficiency being identified at the time of blood donation or cross matching for a transfusion. The *Cromer blood group* antigens reside on DAF. The RBCs of people with the Cromer-null phenotype, Inab, lack DAF but do not appear to show increased susceptibility to hemolysis. This finding suggests that CD59 is substantially more important in regulating red cell lysis by complement.

DEFICIENCIES OF COMPLEMENT RECEPTORS

CR1 Deficiency

CR1 (CD35) is a multiple modular protein that binds C3b/C4b-opsonized foreign antigens, mediating the immune adherence phenomenon. No cases of complete inherited CR1 deficiency have been reported; however, acquired mild C1R deficiency is quite common in patients with immune complex diseases and serum sickness. Similarly, a polymorphic variant of CR1 with diminished levels and function has been described, although it does not appear to be a risk factor for autoimmune disease.

CR3/CR4 Deficiency

CR3/CR4 deficiency (LFA-1) is a defect in the 3 β_2-integrin adhesion molecules. Pathogenic variants in the common β chain (CD18) lead to failure to express adequate α chains: CD11a, CD11b, and CD11c. **Leukocyte adhesion deficiency (LAD)** is an autosomal recessive disorder of neutrophil function resulting from a deficiency of β_2-integrin subunit of the leukocyte cell adhesion molecule (Table 173.5; see Chapter 170). The leukocyte cell adhesion molecule is present on the surface of peripheral blood mononuclear leukocytes and granulocytes and mediates cell-cell and cell-extracellular matrix adhesion. LAD is characterized by a delayed separation of the umbilical cord, recurrent bacterial and fungal infections, and impaired pus formation and wound healing associated with heavy mortality; bone marrow transplantation often is recommended. The infections are characteristic in that necrosis predominates, with little neutrophilic infiltrate. With some residual β_2-integrin expression, the patient may be able to survive without a bone marrow transplant and infections are common.

The manifestations of the disorder are due to the combined effects of ineffective opsonization and an inability to traverse the vascular endothelium to phagocytose bacteria. β_2-Integrins are essential for the firm adhesion step and diapedesis. Lacking β_2-integrins, the neutrophils remain in the vascular space, where they are unable to participate in the defense against bacteria. This explains the lack of pus at sites of active infection.

Two other forms of LAD are recognized: **LAD type II** is due to a defect in fucosylation of selectin ligands and **LAD type III** is due to an activation defect of integrins. The major manifestations are the infection pattern just described and a moderate to severe bleeding tendency secondary to impaired activation of platelet adhesion molecules. LAD-III results from pathogenic variants in FERMT3, or KINDLIN3, which encodes an intracellular protein that interacts with β-integrins in hematopoietic cells. In LAD-III, the adhesive functions of integrins on both leukocytes and platelets are disrupted, most likely due

to defects in activation-dependent alterations of surface integrins that enable high-avidity binding to ligands on target cells, a process termed inside-out signaling.

MANAGEMENT OF COMPLEMENT DEFICIENCIES

Prophylactic antibiotics may offer additional protection from serious infection. With the onset of unexplained fever, cultures should be obtained and antibiotic therapy instituted rapidly and with less stringent indications than in an unaffected child. The parent or patient should be given a written action plan describing any predisposition to systemic bacterial infection or autoimmune disease associated with the patient's deficiency, along with the recommended initial approach to management, for possible use by school, camp, or emergency department physicians. Therapy for infection is not standardized, but it is usually directed to prevent infections caused by encapsulated bacteria. Early complement component deficiencies have major risks to acquire infections caused by *S. pneumoniae* and *H. influenzae.*

Patients should also be vaccinated against encapsulated organisms to maintain high titers. In the case of terminal component, factor D, and properdin deficiencies, high levels of antibody after vaccination may partially compensate for the complement deficiency. Effective vaccines are available; high titers of antibody may offer protection. Repeat immunization of patients is advisable because complement deficiency can be associated with a blunted or shorter-lived antibody response than normal. Immunization of household members may reduce the risk of exposing patients to these pathogens.

Patients under immunosuppression for rheumatologic disorders such as SLE will require more vigilance for severe infection. Individuals with SLE and a complement defect generally respond as well to therapy as do those without complement deficiency. Management of cardiac risk factors is of heightened importance in early complement component–deficient individuals because of their accelerated atherosclerosis. C1q deficiency has a poor prognosis and this protein is produced to a large extent by myeloid cells. Bone marrow transplantation has been curative and should be considered for C1q deficiency.

MBL purified from plasma or recombinant material has been administered in trials; however, no prospective study has been performed. In addition, the role of MBL deficiency in significant infections is not well established.

The treatment of **HAE with C1-INH deficiency** is noted in Chapter 189.1. General guidance includes avoiding the use of estrogens or drugs that can induce angioedema, such as angiotensin-converting enzyme inhibitors (ACEis) and gliptins. If possible, trigger factors could be avoided. Vaccination is not contraindicated, and hepatitis A and B vaccinations are recommended. The approach includes long-term prophylaxis (LTP), short-term prophylaxis (STP), and on-demand therapy (Table 173.6; see Chapter 189.1).

STP is used for dental procedures, surgical procedures, endoscopies, or other situations in which significant trauma may be expected. Attenuated androgens can be used for this indication; C1-INH concentrates have largely supplanted androgens in this setting. A recombinant C1-INH, conestat alfa, is effective for both HAE attacks and for STP. Fresh-frozen plasma (FFP) is another alternative in this setting.

Despite prophylaxis, breakthrough episodes do occur. **On-demand therapy** should also be an option for patients with sporadic attacks or who may not be on any active prophylaxis. There are several options to treat the attacks: C1-INH concentrate; ecallantide, a kallikrein inhibitor; and icatibant, a bradykinin β_2-receptor antagonist.

On-demand treatment and STP is the same for **HAE with normal C1-INH**. LTP shows improvement with tranexamic acid and progestins.

PNH/aHUS Treatment

Eculizumab, a humanized monoclonal IgG2/4-antibody targeting C5, prevents the generation of the MAC C5b9 and is an effective treatment for PNH and aHUS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 173.6 Therapies for Hereditary Angioedema with C1 Inhibitor Deficiency

LONG-TERM PROPHYLAXIS	
Androgens (danazol, oxandrolone, stanozolol)	Avoid use If necessary: Danazol: 10 mg/kg/day (max 200 mg/day) Oxandrolone: ≤ 0.1 mg/kg/day (no max) Stanozolol: 2-6 mg/day (dose and max) after puberty (Tanner 5) Oral
Antifibrinolytics (tranexamic acid, epsilon aminocaproic acid)	Tranexamic acid: 10 mg/kg/day bid to 25 mg/kg/day tid Limit dosage 3 g/day Oral
pdC1-INH nanofiltrated*	Approved for ≥12 yr in some countries, ≥6 yr in others 1,000 IU in ≥12 yr 6-12 yr 500 IU q 3-4 days IV
SC pdC1-INH nanofiltrated	60 IU/kg twice weekly >12 yr SC
Lanadelumab	300 mg every 2 wk After 6 mo, if no attacks: 300 mg every 4 wk >12 yr SC
Berotralstat	Approved in some countries for 12 yr or older 150 mg/day Oral
SHORT-TERM PROPHYLAXIS	
pdC1-INH nanofiltrated*	20 IU/kg IV (no age limits) 1-6 hr before procedure/trigger IV
rhC1-INH/conestat alfa	Approved for ≥12 yr in some countries, ≥2 yr in others 50 IU/kg, max. 4,200 IU (50 IU/kg <84 kg, 4,200 IU >85 kg) IV
Androgens (danazol, oxandrolone, stanozolol)	Avoid use Danazol: 10 mg/kg/day (max 200 mg/day) Oxandrolone: ≤0.1 mg/kg/day (no max) Stanozolol: 2-6 mg/day (dose and max) 5 days before and 2-3 days after procedure/trigger Oral
Fresh-frozen plasma	May be used, if other STP medications not available 10 mL/kg IV No age limits
ON-DEMAND THERAPY	
Ecallantide	Approved in some countries for ≥12 yr 30 mg SC Self-administration is not allowed due to anaphylaxis
Icatibant	Approved for ≥18 yr in some countries, ≥2 yr in others 30 mg/3 mL Dose adjustment is needed for adolescent/children <65 kg/≥2 yr SC
pdC1-INH nanofiltrated*	20 IU/kg IV (no age limits)
rhC1-INH/conestat alfa	Approved for ≥12 yr in some countries, ≥2 yr in others 50 IU/kg, max. 4,200 IU (50 IU/kg <84 kg, 4,200 IU >85 kg) IV
Fresh-frozen plasma	May be used if other on-demand medications are not available 10 mL/kg IV No age limits

*Commercial name for pdC1-INH nanofiltered indicated for LTP is Cinryze and for STP is Berinert.
IV, Intravenous; LTP, long-term prophylaxis; pd, plasma derived; rh, recombinant; SC, subcutaneous; STP, short-term prophylaxis.

Section 5

Immune Dysregulation

Chapter 174

Immune Dysregulation

Danielle E. Arnold and Jennifer W. Leiding

Primary immune dysregulatory diseases (PIRDs) are a recognized subset of primary immunodeficiencies that are characterized by hyperinflammation, organ-specific and systemic autoimmunity, endocrinopathy, enteropathy, and nonmalignant lymphoproliferation. Clinical manifestations of immune dysregulation should lead to a consideration of PIRD. Genetic testing can confirm a diagnosis. Targeted treatments are available for many PIRDs and hematopoietic cell transplant (HCT) is often curative.

174.1 Tregopathies

Danielle E. Arnold and Jennifer W. Leiding

Tregopathies are a subset of primary immunodeficiency diseases recognized by the International Union of Immunologic Societies. The clinical manifestations of these diseases are variable, but all involve some degree of immune dysregulation manifesting as autoimmunity, hyperinflammation, cancer predisposition, and/or lymphoproliferative disease.

PATHOPHYSIOLOGY

T regulatory (Treg) cells are specialized T cells responsible for the maintenance and self-tolerance of immune responses (Fig. 174.1). These cells are responsible for suppressing production of proinflammatory cytokines and growth factors and suppressing T-cell proliferation. The transcription factor FOXP3 is essential for the regulatory function of Treg cells. Several subsets of Treg cells exist, each characterized by unique features. Thymic-derived Treg cells (tTreg) ($CD4^+CD25^+FOXP3^+$) account for ~5% of total $CD4^+$ T cells in the peripheral blood. $FOXP3^+$ Treg cells can also differentiate outside of the thymus in peripheral tissues. These cells are known as peripherally induced regulatory (pTreg) cells. A number of monogenic diseases (Table 174.1) of the immune system that affect the number and/or function of Treg cells have been described. By reducing the effect of Treg cells, T-cell activation and proliferation are unrestrained. This lack of regulation or inhibition manifests as immune dysregulation. Clinical symptoms of these disorders include early onset multiorgan autoimmunity, endocrinopathy, enteropathy, colitis, and lymphoproliferation.

Diagnosis

In a patient with early-onset, severe, or difficult to control autoimmunity, endocrinopathy, colitis, or nonmalignant lymphoproliferative disease, a diagnosis of a Tregopathy should be considered. Next generation sequencing via a targeted panel and/or whole exome sequencing is necessary to establish a genetic diagnosis.

Treatment

Targeted treatment is available for several Tregopathies (see Table 174.1). Abatacept, a CTLA4-Ig fusion protein, has been used successfully in the treatment of refractory cytopenias, interstitial lung disease, and lymphoproliferation in CTLA4 haploinsufficiency and lipopolysaccharide-responsive and beigelike anchor protein (LRBA) deficiency. Jakinibs are a class of medications that inhibit Janus kinase activation of certain STAT transcription factors. Jakinibs have been used successfully to treat immune dysregulatory and autoimmune symptoms in gain-of-function of STAT1 and STAT3 diseases. HCT can provide a curative option for many Tregopathies.

IMMUNE DYSREGULATION POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME

This immune dysregulation syndrome is characterized by onset within the first few weeks or months of life with watery diarrhea (autoimmune enteropathy), an eczematous rash (erythroderma in neonates), insulin-dependent diabetes mellitus, hyperthyroidism or more often hypothyroidism, severe allergies, and other autoimmune disorders (Coombs-positive hemolytic anemia, thrombocytopenia, neutropenia). Psoriasiform or ichthyosiform rashes and alopecia have also been reported.

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked **(IPEX)** syndrome is caused by a pathogenic variant in the *FOXP3* gene, which encodes a forkhead-winged helix transcription factor *(scurfin)* involved in the function and development of $CD4^+$ $CD25^+$ Tregs. The absence of Tregs may predispose to abnormal activation of effector T cells. Variants in multiple other genes also produce an **IPEX-like syndrome** (see Table 174.1; Fig. 174.2).

Clinical Manifestations

Watery diarrhea with intestinal villous atrophy leads to failure to thrive in most patients. Cutaneous lesions (usually eczema) and insulin-dependent diabetes begin in infancy. Lymphadenopathy and splenomegaly are also present. Serious bacterial infections (meningitis, sepsis, pneumonia, osteomyelitis) may be related to neutropenia, malnutrition, or immune dysregulation. Laboratory features reflect the associated autoimmune diseases, dehydration, and malnutrition. In addition, serum IgE levels are elevated,

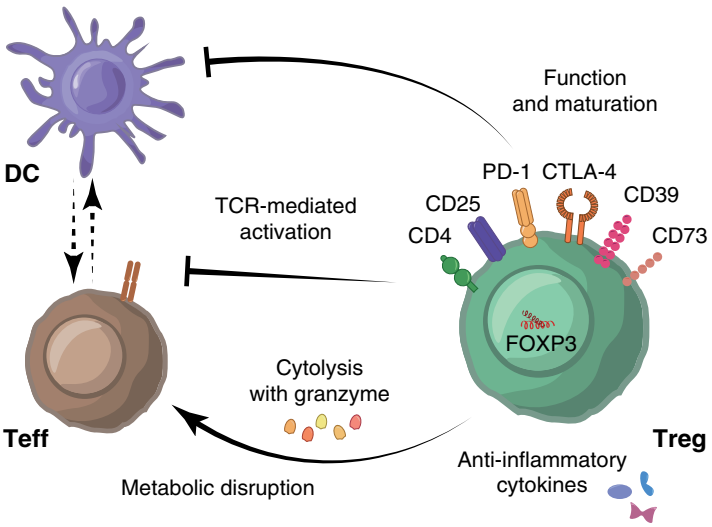

Fig. 174.1 Immunosuppressive mechanisms underlying Treg-mediated immune suppression. Tregs are characterized by expression of the cell surface markers $CD4^+$, CD25high and $CD127^{low/-}$, and transcription factor FOXP3. Tregs modulate the immune system using their suppressive molecules PD-1, CTLA-4, and CD39, and various surface receptors through inhibition of dendritic cell (DC) function and maturation, through the secretion of anti-inflammatory cytokines such as IL-10, TGF-β, and IL-35, and/or through direct inhibition of Teff via induction of cytolysis using granzyme and metabolic disruption. Moreover, Tregs can reduce Teff activation by limiting TCR-ligand binding. DC, dendritic cell; TCR, T cell receptor; Teff, effector T cell; Treg, regulatory T cell. (*From Kempkes RWM, Joosten I, Koenen HJPM, He X. Metabolic pathways involved in regulatory T cell functionality. Front Immunol. 2019;10:2839. Fig. 1.*)

Table 174.1 Tregopathies

GENE (PROTEIN)	DISORDER	INHERITANCE	CLINICAL PHENOTYPE	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT
FOXP3	IPEX syndrome	XL	Enteropathy, type 1 diabetes, eczema, FTT, autoimmune cytopenias, thyroiditis, hepatitis	Tacrolimus, cyclosporine Allogeneic HCT
IL2RA	CD25 deficiency	AR	Enteropathy, eczema, lymphoproliferation, recurrent infections	Allogeneic HCT
CTLA-4 *ALPSV*	CTLA4 haploinsufficiency	AD	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Sirolimus Abatacept, belatacept Allogeneic HCT
LRBA	LRBA deficiency	AR	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Abatacept, belatacept Allogeneic HCT
BACH2	BACH2 deficiency	AD	Enteropathy, lymphoproliferation, recurrent respiratory tract infections, infections	Allogeneic HCT
STAT3	STAT3 GOF	AD, GOF	Enteropathy, autoimmune cytopenias, lymphoproliferation, type 1 diabetes, recurrent infections	Jakinibs Allogeneic HCT
STAT5B	STAT5B	AD, AR	Eczema, growth hormone deficiency, infections, enteropathy, JIA, ITP, chronic lung disease	Symptom specific therapy, HCT

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; XL, X-linked; FTT, failure to thrive; HCT, hematopoietic cell transplant; AR, autosomal recessive; CTLA, cytotoxic T-lymphocyte protein; ALPSV, autoimmune lymphoproliferative disease V; AD, autosomal dominant; LRBA, lipopolysaccharide-responsive and beigelike anchor protein; BACH, broad complex-tramtrack-bric a brac and Cap'n'collar homology; STAT, signal transducer and activator of transcription; GOF, gain of function; JIA, juvenile idiopathic arthritis; ITP, immune thrombocytopenic purpura.

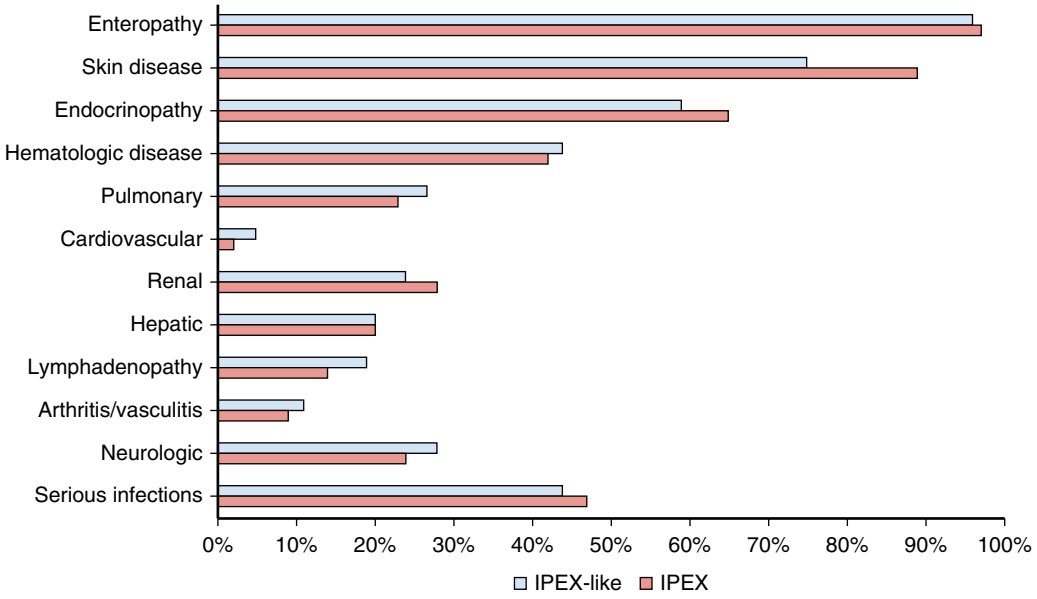

Fig. 174.2 Clinical manifestations in the IPEX-like cohorts. (*Modified from Gambineri E, Ciullini Mannurita S, Hagin D, et al. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Front Immunol. 2018;9:2411. Fig. 5.*)

with normal levels of IgM, IgG, and IgA. The diagnosis is initially made clinically and confirmed by genetic testing (exome or panels).

Treatment

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with corticosteroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. These agents are typically used as a bridge to transplant. HCT is the only possibility for curing IPEX. Janus kinase inhibitors have been used in patients with IPEX-like syndromes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

174.2 Hemophagocytic Lymphohistiocytosis

Danielle E. Arnold and Jennifer W. Leiding

Hemophagocytic lymphohistiocytosis (HLH) is a severe systemic hyperinflammatory syndrome that can be aggressive and life-threatening. Classic features include fever, cytopenia, hepatosplenomegaly, coagulopathy, and elevations in inflammatory markers.

Primary or genetic HLH is due to pathogenic variants in genes that predispose patients to HLH by a variety of mechanisms and includes classic familial HLH due to pathogenic variants in *PRF1*, *UNC13D*, *STX11*, and *STXBP2*; certain pigmentary disorders; and other primary

immunodeficiencies or immune regulatory disorders (see Chapter 556.2; Fig. 174.3). Primary HLH is seen most frequently in pediatric patients but may occur at all ages.

Secondary HLH occurs in the setting of a medical condition that results in intense immune activation such as severe infection, malignancy, or rheumatologic disease. Many primary immune deficiencies (PIDs) are also associated with an increased risk of HLH, usually in the setting of infection. HLH has been reported in patients with severe combined immune deficiency and chronic granulomatous disease, but secondary HLH has been seen in a wide variety of PID. Several inborn errors of metabolism can also present with secondary HLH.

Of note, patients with primary or genetic HLH often present with HLH triggered by or "secondary" to infection or other immune activating events.

For more details see Chapter 556.2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

174.3 Epstein-Barr Virus Susceptibility Disorders

Danielle E. Arnold and Jennifer W. Leiding

Epstein-Barr virus (EBV) is a gamma-herpes family virus with a marked tropism for B cells. Most individuals experience asymptomatic infection or infectious mononucleosis, a self-limiting lymphoproliferative disease that is particularly common in adolescents. EBV is also an oncogenic virus and may induce several types of neoplasms, including B-cell, T-cell, and natural killer (NK) cell lymphomas; nasopharyngeal and gastric carcinomas; and EBV-associated smooth muscle cell tumors.

During primary infection, EBV-infected B cells are eliminated by EBV-specific cytotoxic T cells as well as other innate cytotoxic lymphocytes such as NK cells, γδ T cells, and invariant natural killer T (iNKT) cells. However, some EBV-infected B cells escape the immune response, establishing a reservoir for EBV that may reactivate

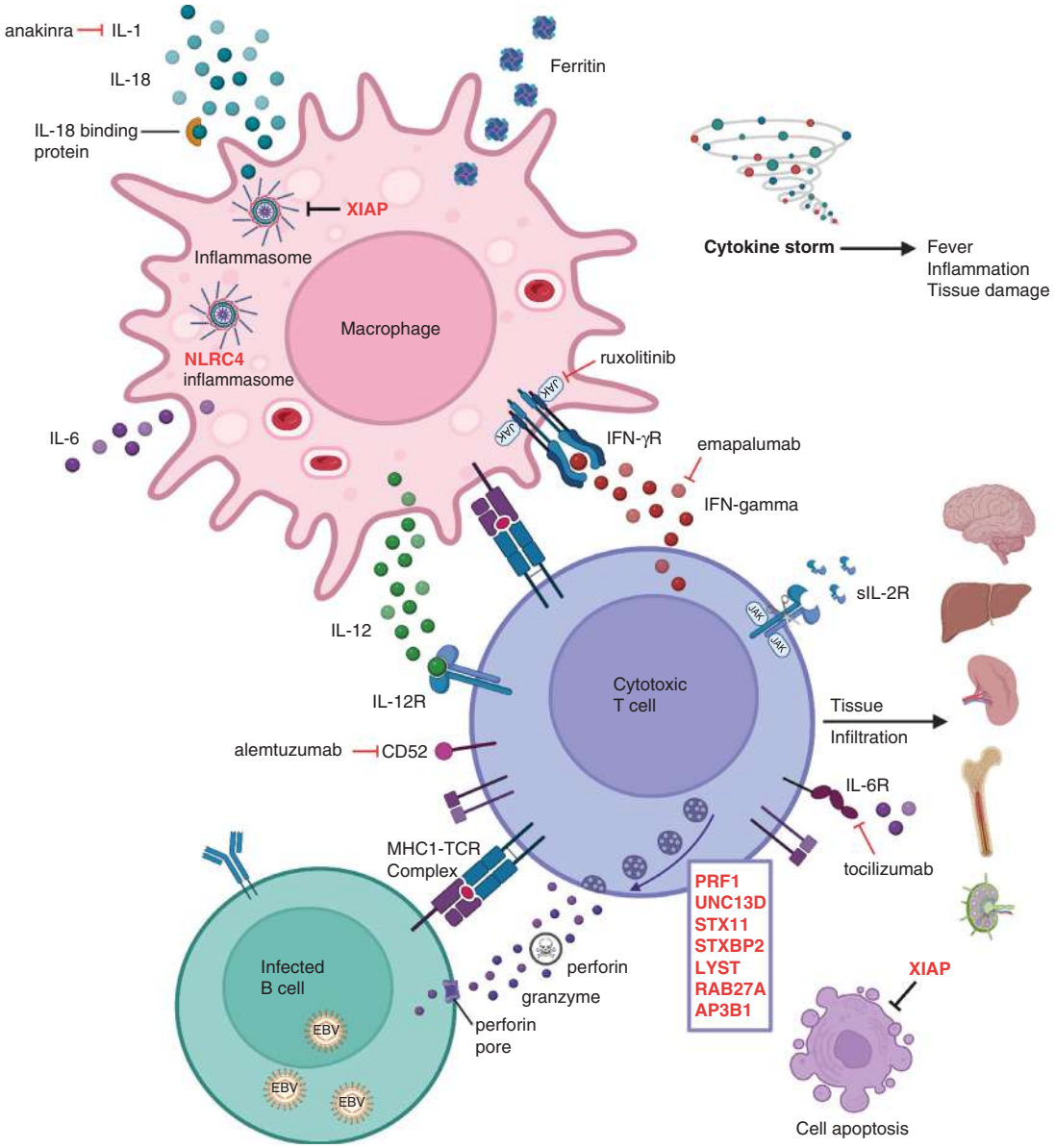

Fig. 174.3 Hemophagocytic lymphohistiocytosis (HLH). HLH is a severe systemic inflammatory syndrome due to abnormal reciprocal macrophage and cytotoxic lymphocyte hyperactivation, resulting in cytokine storm, hemophagocytosis, and tissue infiltration by activated immune cells. Primary HLH genes associated with defective granule-mediated cytotoxicity or inflammasome dysregulation are shown in red. Common nonsteroidal immunosuppressive agents frequently used to treat HLH are also shown. EBV, Epstein-Barr virus; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; XIAP, X-linked inhibitor of apoptosis.

throughout an individual's life. These reactivations are typically asymptomatic in healthy individuals; however, in immunocompromised persons, EBV reactivations and persistence and expansion of latently infected B lymphoblasts may result in symptomatic and often severe disease.

PATHOPHYSIOLOGY

There are several primary combined immunodeficiencies characterized by a very high predisposition to EBV infection, some of which are listed in Table 174.2. These disorders are due to defects in pathways involved in T- and B-cell interaction and crosstalk (Fig. 174.4). Disruption of these pathways results in aberrant cytotoxic T-cell activation, migration, proliferation, and/or cytolytic activity in response to antigenic stimulation and, thus, impaired immune surveillance of B cells by T cells. Marked decrease or absence of iNKT cells, mucosal-associated invariant T (MAIT) cells, and/or NK cells and impaired NK cell function are also often observed.

Clinical Manifestations, Diagnosis, and Treatment

More than 50% of patients with EBV susceptibility disorders experience at least one episode of EBV lymphoproliferative disease. Patients are also susceptible to other EBV-driven pathologies, including HLH and both Hodgkin and non-Hodgkin lymphoma. Other severe viral infections (e.g., other herpesviruses, human herpesvirus 6 [HHV-6]), bacterial infections, particularly recurrent pulmonary infections, and hypogammaglobulinemia and/or dysgammaglobulinemia are also common. Diagnosis for these disorders is with a full immune evaluation and genetic testing. Treatment includes rituximab (anti-CD20 antibody) to eliminate EBV-infected B cells, treatment of infections, and immunoglobulin

Table 174.2 Primary or Genetic EBV Susceptibility Disorders

GENE (PROTEIN)	DISORDER	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT*
MAGT1	XMEN (X-linked immunodeficiency w/Mg^{2+} defect, EBV infection and neoplasia)	XL	Defective Mg^{2+} transporter; ↓ NKG2D expression results in defective cytotoxicity	Chronic EBV infection rather than full-scale HLH, viral infections, lung infections, autoimmune cytopenia, lymphoma	Allogeneic HCT
ITK	Lymphoproliferative syndrome 1	AR	Defective tyrosine kinase function; defective cytotoxic T-cell expansion, and cytolytic capacity; ↓ iNKT cells	Chronic EBV infection, lung infections, PJP, autoimmune cytopenia, lymphoma	Allogeneic HCT
CD27	Lymphoproliferative syndrome 2	AD	CD27 is a co-stimulatory molecule on T cells; required for normal T-cell proliferation and cytotoxicity against EBV-infected B cells; ↓ iNKT cells	Chronic EBV infection, lung infections, uveitis, oral and anal ulcers, hypogammaglobulinemia, lymphoma	Allogeneic HCT
CD70	Lymphoproliferative syndrome 3	AR	CD70 expressed by EBV-infected B cells interacts with CD27 on T cells; required for normal expansion and cytotoxicity of T cells; ↓ NKG2D and 2B4 expression; ↓ iNKT cells	Chronic EBV infection, lung infections, lymphoma	Allogeneic HCT
CTPS1	CTPS1 deficiency	AR	Enzyme involved in de novo synthesis of cytidine nucleotide triphosphate (CTP); deficiency leads to impaired T-cell proliferation; ↓ iNKT cells	Chronic EBV infection, viral infections, lung infections, meningitis, eczema, lymphoma	Allogeneic HCT
CORO1A	CORO1A deficiency	AR	Actin regulator; T lymphopenia, impaired immunologic synapse formation and intracellular signaling; ↓ iNKT cells	Chronic EBV infection rather than HLH, viral infections, lung infections, neurologic involvement, lymphoma	Allogeneic HCT
RASGRP1	RASGRP1 deficiency	AR	Activates RAS, which leads to MAPK pathway activation; defects in T-cell activation, proliferation, and migration; ↓ iNKT cells	Chronic EBV infection, viral infections, lung infections, autoimmune cytopenia, EBV negative lymphoproliferative disease, lymphoma	Allogeneic HCT

*Treatment should include HLH-directed therapy, treatment of infections and malignancy, and other supportive care measures as appropriate.
EBV, Epstein-Barr virus; AR, autosomal recessive; XL, X-linked; AD, autosomal dominant; TNF, tumor necrosis factor; iNKT, invariant NK T cell; CNS, central nervous system; HSM, hepatosplenomegaly; PJP, *Pneumocystis jiroveci* pneumonia; HCT, hematopoietic cell transplantation.

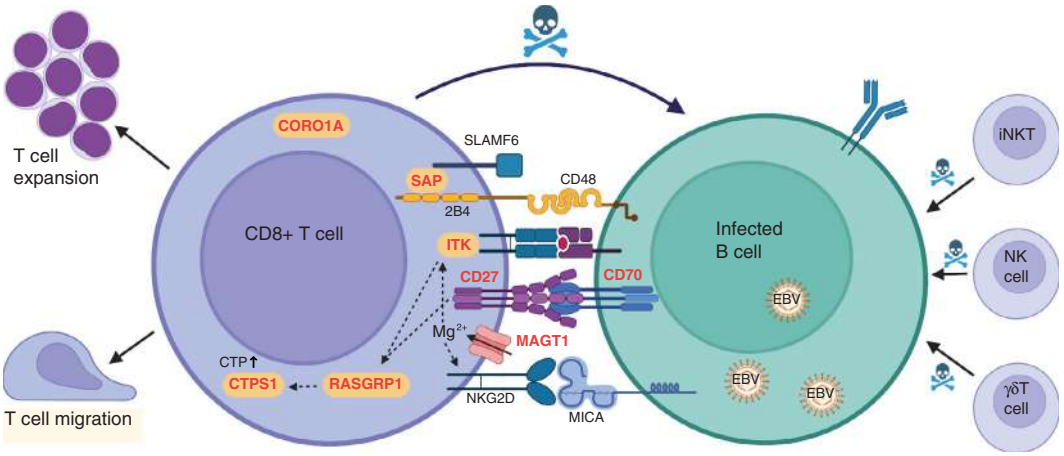

Fig. 174.4 Epstein-Barr virus (EBV) susceptibility disorders. Combined immunodeficiencies characterized by a very high predisposition to EBV lymphoproliferative disease are shown in red. These genes/proteins play essential roles in the recognition of EBV-infected B cells by T cells and in cytotoxic T-cell activation, migration, proliferation, and/or cytotoxic activity. As such, defects in any of these components allow for EBV-infected B-cell immune escape. Invariant natural killer T (iNKT) cell, NK cell, and γδT-cell numbers and/or function may also be low or aberrant, respectively.

replacement when indicated. Allogeneic HCT is the only curative treatment available.

Other Primary Immunodeficiencies Associated with Epstein-Barr Virus Lymphoproliferative Disease

Herpesvirus infections and EBV lymphoproliferative disease are also seen to a lesser extent in several other combined immunodeficiencies associated with T-cell defects, particularly those affecting T-cell survival and mobilization. Classic examples include Wiskott-Aldrich syndrome, DOCK8 deficiency, GATA2 haploinsufficiency, and activated PI3K-delta syndrome, among others. Severe EBV infections may also be seen in patients with hypomorphic or leaky severe combined immunodeficiency.

Any patient who presents with prolonged and/or severe EBV lymphoproliferative disease or EBV-positive lymphoma warrants evaluation for an underlying primary immunodeficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

174.4 Chronic Active Epstein-Barr Virus

Danielle E. Arnold and Jennifer W. Leiding

Chronic active EBV (CAEBV) is a rare systemic EBV lymphoproliferative disorder characterized by fever, persistent lymphadenopathy, hepatosplenomegaly, and hepatitis in the absence of an underlying primary or secondary immunodeficiency, malignancy, or autoimmune disorder.

GENETIC PREDISPOSITION

CAEBV is seen primarily in persons of East Asian (Japan, Korea, China, and Taiwan) or Latin American (Indigenous people in Mexico and Central/South America) ancestry; in these patients, EBV is predominantly present in T cells or NK cells. Conversely, while rare, persons of Western European descent typically have B-cell CAEBV. The uneven geographic distribution of CAEBV suggests that underlying genetic factors may contribute to the development of CAEBV; heterozygous pathogenic variants in HLH predisposing genes (e.g., perforin) have been identified in patients with CAEBV. Causative genetic defects have not been identified in most cases.

Pathophysiology

The mechanism of EBV entry into T cells or NK cells is unclear, but T cells and NK cells can express low levels of CD21, the EBV receptor, during primary infection. The pathogenesis of CAEBV is less clear. Evidence suggests that EBV infection directly induces T-cell or NK cell survival via activation of several survival-promoting molecules or pathways, including upregulation of co-stimulatory molecules that suppress apoptosis, activation of the NF-κB pathway, and upregulation of activation-induced cytidine deaminase, which acts as a genomic disruptor and has been shown to play a role in EBV-induced lymphomagenesis in B cells.

Table 174.3 Chronic Active EBV (CAEBV) Diagnostic Criteria

All 4 criteria must be present:

1. Sustained or recurrent infectious mononucleosis-like symptoms persisting for >3 mo
2. EBV PCR >$10^{2.5}$ copies/μg DNA in the peripheral blood or tissue lesion
3. Evidence of EBV infection of T or NK cells in the peripheral blood or affected tissues
4. Exclusion of other diagnoses: primary EBV infection, primary or secondary immunodeficiency, malignancy, autoimmune disease

EBV, Epstein-Barr virus; NK, natural killer; PCR, polymerase chain reaction.

Clinical Manifestations and Diagnosis

Clinical manifestations of CAEBV are heterogenous, ranging from a mild and indolent clinical course to a more aggressive and potentially fatal illness due to complications such as HLH, multisystem organ failure, and/or progression to leukemia or lymphoma. Clinical manifestations may by episodic, but patients typically have persistently and markedly elevated levels of EBV in the blood throughout their disease course. Infiltration of tissues by EBV-positive lymphocytes may result in organ failure (liver failure is commonly seen), and EBV-infected T cells and NK cells may undergo malignant transformation. The diagnostic criteria for CAEBV are listed in Table 174.3; CAEBV should be suspected in any patient with sustained inflammation of unknown origin and chronically elevated EBV polymerase chain reaction (PCR) levels.

Evaluations to determine whether EBV is predominantly present in T cells or NK cells should be undertaken, if possible, in patients with CAEBV. One method is EBV PCR on peripheral blood mononuclear cells that have been sorted by flow cytometry, although this test is not widely available. Histologic examination of tissue that has been infiltrated by EBV-infected lymphocytes by immune staining and in situ hybridization of EBV-encoded mRNA (EBER) is another approach.

Treatment

Treatment options in severe cases are limited, and clinical responses are mostly transient. Some therapeutic approaches include

immunomodulatory therapy, combination bortezomib and ganciclovir, and EBV-specific T cells. Patients with HLH should receive HLH-directed therapy. Standard antiviral therapy is not effective. Cytotoxic chemotherapy is also used to reduce disease activity and burden of EBV-infected lymphocytes, primarily as a bridge to HCT. Allogeneic HCT is the only definitive therapy available with overall survival rates as high as 87% in some reports. Patients with progressive disease remain difficult to transplant. As such, some advocate rapidly proceeding to HCT early in the disease process, although the timing of HCT remains controversial.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

174.5 Very Early Onset Inflammatory Bowel Disease

Danielle E. Arnold and Jennifer W. Leiding

Inflammatory bowel disease that presents in children less than 6 years of age is known as very early onset inflammatory bowel disease (VEO-IBD). Monogenic defects involved in primary immunodeficiency and intestinal barrier processes are enriched in children with VEO-IBD (Fig. 174.5). Targeted therapies in children with VEO-IBD with a monogenic defect have been successful in treating disease manifestations (see Chapter 382.3).

DISEASE CLASSIFICATION AND CLINICAL PRESENTATION

Children diagnosed with IBD <2 years of age are referred to as *infantile*-onset IBD and those 2-6 years as VEO-IBD. Children present with classic symptoms of IBD including weight loss, failure to thrive, abdominal pain, fever, constipation, diarrhea, hematochezia. The phenotype is heterogenous with some children having mild disease and others presenting with or developing more severe disease over time. Approximately 40% have extensive pancolonic disease at presentation. Extent, location, and histology can progress or change over time.

For more details see Chapter 382.3.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

174.6 Autoimmune Cytopenias

Danielle E. Arnold and Jennifer W. Leiding

Autoimmune cytopenias are a group of disorders in which there is immune destruction of differentiated hematopoietic cells. Immune destruction can be autoantibody mediated or non-autoantibody mediated. Single lineage disease can affect red cells (autoimmune hemolytic anemia [AIHA]), platelets (idiopathic thrombocytopenia purpura [ITP]), or neutrophils (autoimmune neutropenia [AIN]). Bilineage or trilineage disease can affect any combination of these cell lines. **Evan disease** is a combination of AIHA and ITP.

PATHOPHYSIOLOGY

The etiology of autoimmune cytopenias as a manifestation of an inborn error of immunity is often multifactorial with autoantibody-mediated destruction or cellular-mediated destruction of red blood cells, platelets, or neutrophils as the major causes of hemolysis (Table 174.4). In disorders with intrinsic B-cell defects and disrupted T- and B-cell interactions, autoantibody production toward hematopoietic cells can

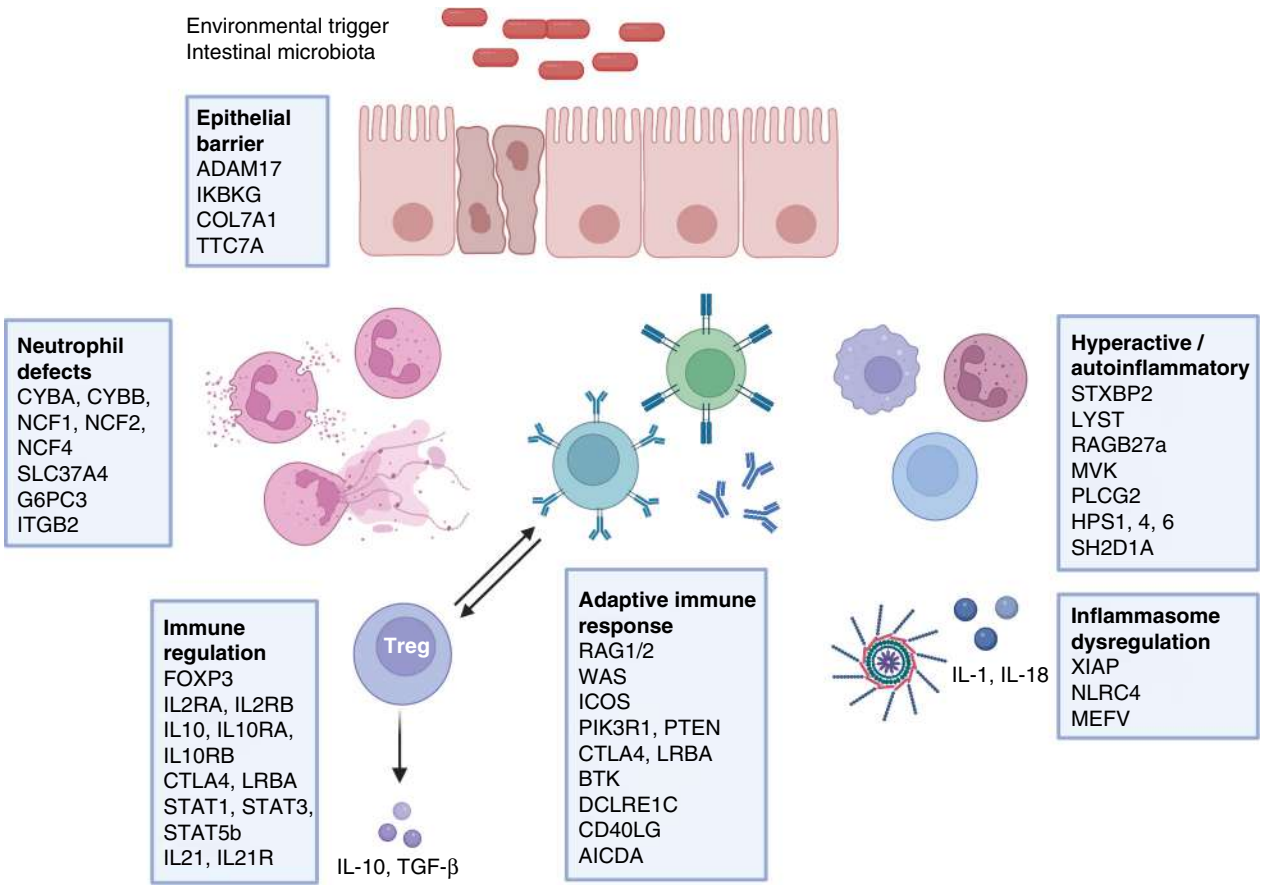

Fig. 174.5 Very early onset inflammatory bowel disease. Complex host interactions between the environment, intestinal microbiota, and immune-related genes maintain gut health. Mutations in genes involved in epithelial barrier, neutrophil function, control of inflammation, and T- and B-cell function can manifest as very early onset inflammatory bowel disease. IL, Interleukin; TGF, transforming growth factor; Treg, T regulatory cell.

Table 174.4 Monogenic Causes of Autoimmune Cytopenias and Primary Immunodeficiency

GENE (PROTEIN)	DISORDER	MOI	CLINICAL PHENOTYPE	IMMUNE FEATURES	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT
PIK3 defects	Activated PI3K-delta syndrome	AD, LOF AD, GOF AD	Insulin resistance, short stature, nodular lymphoid hyperplasia, lymphoma, bronchiectasis	High IgM, low IgG, low CD4/CD45RA	Allogeneic HCT *Leniolisib, sirolimus
STAT3	STAT3 GOF	AD, GOF	Enteropathy, autoimmune cytopenias, lymphoproliferation, recurrent infections	Elevated DNTs Variable decreases in IgG, IgA, IgM, B- and T-cell quantities	Jakinibs Allogeneic HCT
STAT1	STAT1 GOF	AD, GOF	Chronic mucocutaneous candidiasis, cerebral aneurysms, interstitial lung disease, enteropathy, colitis	Variable decreases in IgG, IgA, IgM, B- and T-cell quantities	Jakinibs Allogeneic HCT
CTLA-4	CTLA4 haploinsufficiency	AD	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Low IgG, low T-cell quantities	Sirolimus Abatacept, belatacept Allogeneic HCT
LRBA	LRBA deficiency	AR	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Low IgG, low T-cell quantities	Abatacept, belatacept Allogeneic HCT
TNFRSF6 *TNFSF6* *FADD* *CASP8* *CASP10*	ALPS	AR GOF	Lymphadenopathy, lymphoma	Elevated DNTs	Mycophenolate mofetil Sirolimus

PI3K, Phosphoinositide 3 kinase; AD, autosomal dominant; LOF, loss of function; AD, autosomal dominant; GOF, gain of function; HCT, hematopoietic cell transplant; STAT, signal transducer and activator of transcription; CTLA, cytotoxic T-lymphocyte protein; LRBA, lipopolysaccharide-responsive and beigelike anchor protein; ALPS, autoimmune lymphoproliferative syndrome; DNT, double negative T cell.

occur. When B-cell maturation is impaired, vital steps in the induction of tolerance are omitted. In addition to the humoral B-cell defects that can lead to autoimmune cytopenias, intrinsic defects in T-cell effector function can lead to cellular autoimmunity. Impaired T-cell development can cause a lack of functional effector cells against non-self or "dangerous" antigens while allowing production of autoreactive clones with T-cell receptors directed against self-antigens. Additionally, T-cell defects may lead to a reduction in $FOXP3^+$ Treg cells.

Clinical Manifestations and Diagnosis

The clinical presentation of AIHA commonly includes dizziness, fatigue, pallor, jaundice, and exertional dyspnea (see Chapter 513). Complete blood count will show anemia and reticulocytosis. Additional features of hemolysis include hyperbilirubinemia, elevated lactate dehydrogenase, and decreased haptoglobin levels. Direct antiglobulin testing is most often positive. ITP typically presents with bleeding episodes that can range from mild bruising, petechiae, and epistaxis to oral purpura, hematuria, menorrhagia, gastrointestinal hemorrhage, or intracranial bleeding (see Chapter 533.1). Severe life-threatening bleeding is rare. Laboratory findings include acute thrombocytopenia. Mean platelet volume is elevated or variable indicating that large new platelets are being generated to compensate for loss. Autoantibodies against platelet glycoproteins may be positive but are not helpful in elucidating immune thrombocytopenia as they are positive in less than 65% of patients with immune thrombocytopenia and are not predictive, specific, or prognostic. AIN presents with low absolute neutrophil count (see Chapter 171). Clinical manifestations include aphthous stomatitis, periodontal disease, and increased frequency of soft tissue infections. Invasive infections and sepsis are rare. Antigranulocyte antibodies can be present.

Immunodeficiencies Associated with Autoimmune Cytopenias

Autoimmune cytopenias, especially those that include bilineages and trilineages, are often a presenting symptom of or associated with primary immunodysregulatory disorders. Other organ-specific immunodysregulatory and autoimmune conditions are often present. Next generation sequencing via whole exome sequencing or panel-based sequencing can aid in establishing a diagnosis. When an inborn error of immunity is suspected with the presence of autoimmune cytopenias, a general immune screen should be performed including serum quantities of IgG, IgM, IgA, and IgE. Quantities of T cell, B cell, and NK cells should also be measured. Additional labs that may be helpful in narrowing a diagnosis of immunodeficiency include quantification of $\alpha\beta^+$double negative T cells ($CD4^-CD8^-$), $CD27^+IgD^+$ and $CD27^+IgD^-$ memory B cells, serum ferritin, soluble interleukin (IL)-2 receptor, IL-18, soluble Fas ligand, vitamin B_{12}, and folate.

Treatment

Targeted treatment of the primary immunodysregulatory disorder can control or resolve autoimmune cytopenias. Standard treatment of autoimmune cytopenias with or without a primary immunodysregulatory disorder include corticosteroids, intravenous immunoglobulin (IVIG), and biologic therapies such as rituximab and daratumumab (monoclonal antibody against CD38 expressed on long-lived plasma cells). Control of symptoms is often more difficult and may increase the suspicion for an underlying primary immunodysregulatory disorder.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

174.7 Autoimmune Lymphoproliferative Syndrome

Danielle E. Arnold and Jennifer W. Leiding

Autoimmune lymphoproliferative syndrome **(ALPS)**, also known as Canale-Smith syndrome, is a disorder of abnormal lymphocyte apoptosis leading to polyclonal populations of T cells (double-negative T cells), which express CD3 and α/β antigen receptors but do not have CD4 or CD8 co-receptors ($CD3^+$ T-cell receptor α/β^+, $CD4^-CD8^-$). These T cells respond poorly to antigens or mitogens and do not produce growth or survival factors (IL-2). The genetic deficit in most patients is a germline or somatic pathologic variant in the *FAS* gene, which produces a cell surface receptor of the tumor necrosis factor (TNF) receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 174.5). Persistent survival of these lymphocytes leads to immune dysregulation and autoimmunity. ALPS is also caused by other genes in the Fas pathway (*FASLG* and *CASP10*). In addition, ALPS-like disorders are associated with other mutations: RAS-associated autoimmune lymphoproliferative disorder (RALD), caspase-8 deficiency, Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immunodeficiency, autoimmunity, and lymphoproliferation.

CLINICAL MANIFESTATIONS

ALPS is characterized by **autoimmunity, chronic persistent or recurrent lymphadenopathy**, splenomegaly, hepatomegaly (in 50%), and hypergammaglobulinemia (IgG, IgA). Many patients present in the first year of life, and most are symptomatic by age 5 years. Lymphadenopathy can be striking (Fig. 174.6). Splenomegaly

Table 174.5 Revised Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome*

REQUIRED

1. Chronic (>6 mo), nonmalignant, noninfectious lymphadenopathy, splenomegaly or both
2. Elevated $CD3^+$ $TCR\alpha\beta^+$ $CD4^-CD8^-$ DNT cells (≥1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or elevated lymphocyte counts

ACCESSORY

Primary

1. Defective lymphocyte apoptosis (in two separate assays)
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or *CASP10*

Secondary

1. Elevated plasma sFasL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B_{12} levels (>1500 ng/L) OR elevated plasma interleukin-18 levels >500 pg/mL
2. Typical immunohistologic findings as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

*A *definitive* diagnosis is based on the presence of both required criteria plus one primary accessory criterion. A *probable* diagnosis is based on the presence of both required criteria plus one secondary accessory criterion.

DNT, Double-negative T cell; TCR, T-cell receptor.

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, eds. *Textbook of Pediatric Rheumatology*. 7th ed. Philadelphia: Elsevier; 2016. Box 46-2.

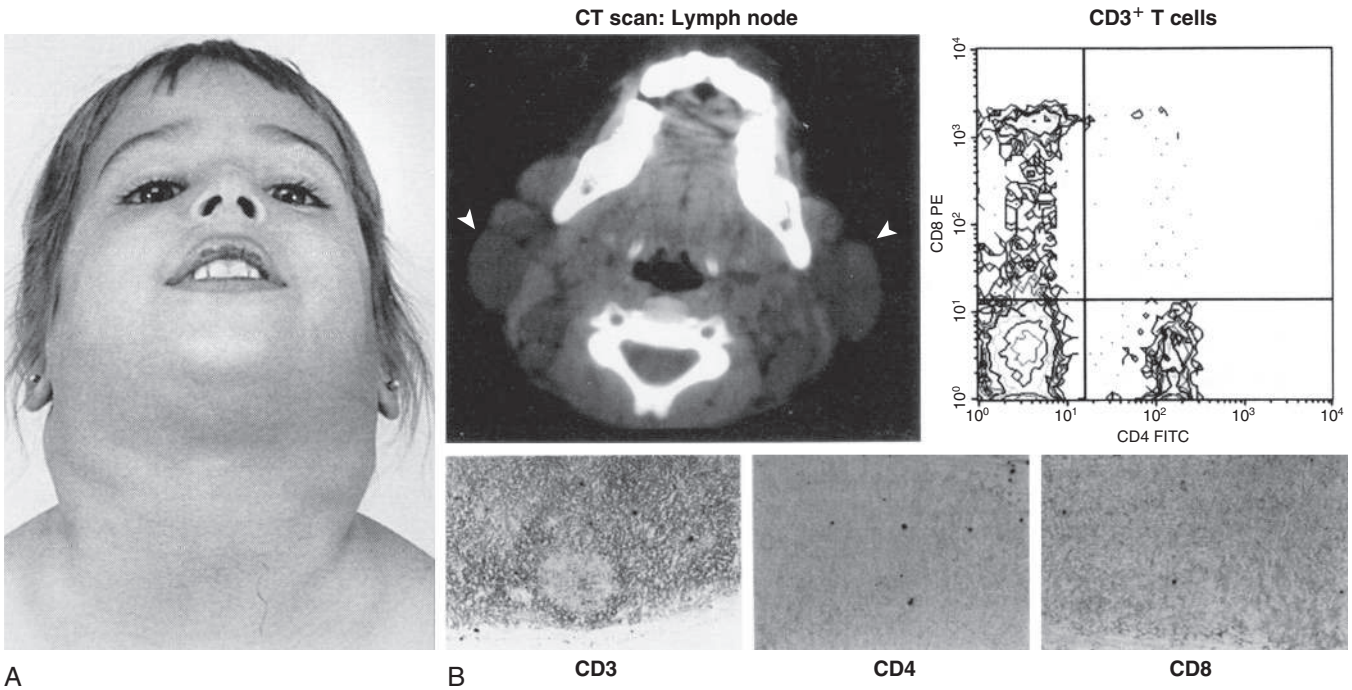

Fig. 174.6 Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. **A,** Front view of the National Institutes of Health patient. **B,** *Top left,* CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. *Top right,* Flow cytometric analysis of peripheral blood T cells from a patient with autoimmune lymphoproliferative syndrome (ALPS), with CD8 expression on the vertical axis and CD4 on the horizontal axis. *Lower left quadrant,* Contains $CD4^-CD8^-$ (double-negative) T cells, which are usually present at <1% of T cells expressing the αβ T-cell receptor. *Bottom,* CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS. Large numbers of $DNCD3^+$ $CD4^-CD8^-$ (double-negative) T cells are present in the interfollicular areas of the lymph node. (*Adapted from Siegel RM, Fleisher TA. The role of Fas and related death receptors in autoimmune and other disease states. J Allergy Clin Immunol. 1999;103[5 Pt 1]:729–738.*)

may produce hypersplenism. Autoimmunity also produces anemia (Coombs-positive hemolytic anemia) or thrombocytopenia or a mild neutropenia. The lymphoproliferative process (lymphadenopathy, splenomegaly) may regress over time, but autoimmunity does not regress and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, panniculitis, arthritis, premature ovarian failure, thyroiditis, myocarditis, pancreatitis, and CNS involvement (seizures, headaches, encephalopathy, transverse myelitis, Guillain-Barré syndrome, ataxia).

Malignancies are also more common in patients with ALPS and include Hodgkin and non-Hodgkin lymphomas and solid-tissue tumors of thyroid, skin, heart, or lung. ALPS is one cause of Evan syndrome (immune thrombocytopenia and immune hemolytic anemia).

Diagnosis

Laboratory abnormalities depend on the lymphoproliferative organ response (hypersplenism) or the degree of autoimmunity (anemia, thrombocytopenia). There may be lymphocytosis or lymphopenia. Table 174.5 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 174.6). Functional genetic analysis for the *TNFRSF6* gene often reveals a heterozygous mutation. The differential diagnosis of ALP-related syndromes is noted in Table 174.6.

Table 174.6 Autoimmune Lymphoproliferative Syndrome (ALPS)-Related Syndromes That Are Potentially Similar to But Genetically Distinct from ALPS or Meet Characteristics of ALPS with Undetermined Genetic Defects (ALPS-U)

DISEASE	NOMENCLATURE	MUTATION	CLINICAL FEATURES	LABORATORY BIOMARKERS	POTENTIAL TARGETED THERAPIES
Ras-associated autoimmune leukoproliferative disorder	RALD	Germline or somatic *NRAS* and *KRAS* pathogenic variants RAS markedly decreases Bim protein expression leading to impaired lymphoid withdrawal and T-cell receptor (TCR)-induced apoptosis	Primary immunodeficiency disorder of defective apoptosis leading to lymphadenopathy, massive splenomegaly, increased circulating B cells, hypergammaglobulinemia, and autoimmunity increased risk for hematopoietic malignancies	Persistent absolute or relative monocytosis, hypergammaglobulinemia, B lymphocytosis Does not exhibit elevated "double-negative T cells" (DNTs), vitamin B_{12} Activating somatic mutations in *KRAS* or *NRAS*	Mitogen-activated pathway kinase (MAPK) inhibitors (for example, trametinib), mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus)
Dianzani autoimmune lymphoproliferative disease	DALD	No causative genes identified Overexpression of the cytokine osteopontin Perforin	Exhibit autoimmunity, lymphoproliferation, splenomegaly, and defective Fas without expansion of DNT cells	Absent DNTs FAS resistance but without *FAS* or *FASL* mutations	
Caspase-8 deficiency state	CEDS	Loss-of-function pathogenic variants in *CASP8* thought to play a dual role in the induction of the nuclear factor-kappa B (NF-κB) transcription factor during lymphocyte activation as well as in apoptosis mediated by the Fas death-inducing signaling complex (DISC)	Exhibits lymphoproliferation and apoptosis defects observed in ALPS, but manifests immunodeficiency rather than autoimmunity; recurrent sinopulmonary infections Increased risk for malignancy	Serum Ig levels, antibody function, lymphocyte activation Defective activation of T, B and natural killer (NK) cells *CASP8* deficiency	
Fas-associated death domain deficiency	*FADD* deficiency	Autosomal recessive (AR) *FADD* deficiency	Characterized by severe bacterial and viral infections, congenital heart defects, and recurrent episodes of fever, liver, dysfunction, and seizures	*FADD* deficiency	
Common variable immunodeficiency 9	Protein kinase C delta *(PRKCD)* deficiency	AR *PRKCD* primary immunodeficiency	Characterized by recurrent infections, lymphadenopathy, hepatosplenomegaly, autoimmunity, and NK cell dysfunction	IL-10 overexpression by B cells	

Table 174.6 Autoimmune Lymphoproliferative Syndrome (ALPS)-Related Syndromes That Are Potentially Similar to But Genetically Distinct from ALPS or Meet Characteristics of ALPS with Undetermined Genetic Defects (ALPS-U)—cont'd

DISEASE	NOMENCLATURE	MUTATION	CLINICAL FEATURES	LABORATORY BIOMARKERS	POTENTIAL TARGETED THERAPIES
Activated PI3K delta syndrome	APDS, also known as PASLI	Heterozygous gain-of-function pathogenic variants in *PI_3KCD* or *PI_3KR1*	Recurrent respiratory infections and increased susceptibility to viral infections with both B- and T-cell defects	Decreased naïve T cells, low IgG, IgA, and normal or elevated IgM	mTOR inhibitors, PI3K inhibitors
X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection and neoplasia	XMEN disease	Loss-of-function pathogenic variants in magnesium transporter 1 *(MAGT1)*; X-linked	Chronic high-level EBV with increased EBV-infected B cells and increased susceptibility to EBV-associated lymphomas	Mg deficiency	Magnesium
Gain-of-function mutations in signal transducer and activator of transcription 1 defect	GOF *STAT1* defect	*STAT1* gain-of-function pathogenic variants	Chronic mucocutaneous candidiasis, recurrent *Staphylococcus aureus* infections, cerebral aneurysms, and multiple autoimmune features	Decreased TH17 response	JAK/STAT inhibitors (for example, ruxolitinib)
Gain-of-function mutations in signal transducer and activator of transcription 3	GOF *STAT3*-mutations	*STAT3*-gain of function pathogenic variants	Lymphoproliferation and childhood-onset autoimmunity thought to result from dysregulated cytokine signaling and interstitial lung disease		Anti–IL-6R monoclonal antibody (tocilizumab)
Cytotoxic T lymphocyte antigen *(CTLA4)* haploinsufficiency with autoimmune infiltration	CHAI	Heterozygous loss-of-function pathogenic variants in *CTLA4*	Hypogammaglobulinemia and autoantibody-mediated cytopenias, lymphadenopathy, splenomegaly, organ-specific autoimmunity, and lymphocytic infiltration of nonlymphoid organs CHAI more commonly seen in older children or young adults, whereas disease onset in LATAIE is typically earlier		CTLA4-Ig fusion drug (Abatacept) mTOR inhibitors
Common variable immune deficiency caused by defect in lipopolysaccharide-responsive and beigelike anchor protein LRBA deficiency with autoantibodies, regulatory T-cell defects, autoimmune infiltration, and enteropathy	*LRBA* deficiency LATAIE	*LRBA* encodes the lipopolysaccharide-responsive and beigelike anchor protein, thought to regulate CTLA4	Antibody deficiency, infection, autoimmunity, and lymphoproliferation, often linked with enteropathy or inflammatory bowel disease Lymphocyte infiltration also seen in lungs and brain		CTLA4-Ig fusion drugs Hydroxy-chloroquine or chloroquine mTOR inhibitors

Note: The majority of these syndromes have been defined based on the genomic defect with associated symptoms.
From Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease. *F1000Res.* 2017;6:1928. Table 1.

Treatment

Rapamycin (sirolimus) will often control the adenopathy and autoimmune cytopenias. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

174.8 Nuclear Factor-κB Pathway Defects

Danielle E. Arnold and Jennifer W. Leiding

The NF-κB pathways consist of canonical (NF-κB1) and noncanonical (NF-κB2) pathways. On cellular activation, both pathways lead to activation and translocation of NF-κB proteins into the nucleus, where they initiate downstream inflammatory responses. Defects in many proteins in both pathways have been described. Table 174.7 describes immune defects of the NF-κB pathways that cause symptoms of immune dysregulation or autoimmunity. Treatment of NF-κB defects includes prevention of infections and replacement of immunoglobulin and has included HSCT.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 174.7 Defects of Nuclear Factor-κB Pathways Associated with Immune Dysregulation

PROTEIN	INHERITANCE	AUTOIMMUNE OR INFLAMMATORY COMPLICATIONS	OTHER MANIFESTATIONS	IMMUNOLOGIC PHENOTYPE
IKBKG (NEMO)	XL	Colitis	• Ectodermal dysplasia • Osteopetrosis • Lymphedema • Bacterial infections • Opportunistic infections • DNA viral infections	• Hypogammaglobulinemia • Hyper-IgM • Hyper-IgA • Hyper-IgD • Poor antibody responses • Decreased NK cell function • Decreased TLR responses
NF-κB1	AD	• Pyoderma gangrenosum • Lymphoproliferation • Cytopenia • Hypothyroidism • Alopecia areata • Enteritis • LIP • NRH	• Atrophic gastritis • Squamous cell carcinoma • Respiratory tract infections • Superficial skin infections • Lung adenocarcinoma • Respiratory insufficiency • Aortic stenosis • Non-Hodgkin lymphoma	• Hypogammaglobulinemia • IgA deficiency
NF-κB2	AD	• Alopecia totalis • Trachyonychia • Vitiligo • Autoantibodies: thyroid peroxidase, glutamate decarboxylase, thyroglobulin • Central adrenal insufficiency	• Viral respiratory infections • Pneumonias • Sinusitis • Otitis media • Recurrent herpes • Asthma • Type 1 Chiari malformation • Interstitial lung disease	• Early-onset hypogammaglobulinemia • Low vaccine responses • Variable B-cell counts • Low switched memory B cells ($CD19^+CD27^+IgD^-$) • Low marginal zone B cells ($CD19^+CD27^+IgD^+$)

XL, X-linked; AD, autosomal dominant; LIP, lymphocytic interstitial pneumonitis; NRH, nonregenerative hyperplasia; TLR, toll like receptor.

Chapter 175

Defects of Innate Immunity

Jenna R.E. Bergerson and Alexandra F. Freeman

The innate immune system is the body's first defense against pathogens, and includes barriers such as the skin as well as neutrophils, natural killer (NK) cells, the toll-like receptors (TLRs) for microbial pathogen recognition, cytokines, and the complement system. Breakdown of different parts of this system can predispose primarily to different pathogens, such as viruses, fungi, bacteria, and mycobacteria. The innate immune system also plays an important role in engaging the adaptive immune response.

175.1 Predisposition to Fungal Infections

Jenna R.E. Bergerson and Alexandra F. Freeman

Despite constant exposure to environmental fungi at sites like the respiratory and gastrointestinal tracts and the skin, immunocompetent individuals do not develop invasive fungal disease because highly sophisticated host defenses have evolved with time. The genetic basis for inborn errors of immunity (IEIs) presenting with mucocutaneous and/or invasive fungal disease have provided valuable insight into the immunologic mediators necessary for antifungal host defense. Certain IEIs whose phenotype includes fungal disease, such as chronic granulomatous disease (CGD), APECED, GATA2 deficiency, and dominant negative STAT3 pathogenic variants (Job syndrome), are examples.

Candida and *Aspergillus* are the two most commonly encountered opportunistic fungi in clinical practice; both of these fungi are recognized in host tissues by pattern recognition receptors (PRRs) on the cell surface. When triggered by a relevant ligand, activation of these receptors results in pathogen uptake and killing. Most relevant to antifungal immunity is the C-type lectin receptor (CLR) family, which recognizes specific fungal cell wall components called pathogen-associated molecular patterns, like β-glucans or mannans. When CLRs like Dectin-1 bind ligand, the CARD9/BCL10/MALT1 complex (BCM complex) is formed. Signaling via downstream pathways ultimately results in production of proinflammatory cytokines and promotes fungal uptake and killing by myeloid phagocytes.

The molecular mechanisms that protect against host *mucosal* infections with *Candida* spp. are vastly different than those that confer protection against *systemic* infection. Neutrophils, monocytes, and macrophages are seemingly dispensable for immunity to mucosal *Candida* infection; chronic mucocutaneous candidiasis (CMC) is not seen in neutropenic patients or those with CGD. Instead, mucocutaneous candidiasis seems to correlate with impairments in T-lymphocyte number or function. Interleukin (IL)-17 signaling is also a critical pathway for protection against CMC. On receptor activation, the adaptor molecule ACT1 is recruited to the IL-17 receptor and mediates the induction of signaling pathways that upregulate the transcription of cytokines and antimicrobial peptides (AMPs) that help clear *Candida* from the mucosal surfaces. Control of endemic fungi, such as *Histoplasma,* is dependent on the IL-12/IFNg/STAT1 pathway.

Chronic mucocutaneous candidiasis is characterized by severe, persistent, or recurrent symptomatic infection of the nails, skin, oral, or genital mucosa by the *Candida* genus. CMC has been associated with a number of IEIs, in which it is one of many disease features along with other infections and/or autoimmune manifestations. However, CMC can also be a main feature of a primary immunodeficiency disease (PIDD) (Table 175.1).

Antifungal therapy is the hallmark of treatment in these diseases. Episodes of CMC typically respond to either topical or oral therapy. Recurrences are common without secondary prophylaxis. Prophylaxis should be initiated in those patients with frequent and early recurrences after discontinuation of antifungal therapy. Prophylaxis is important not only to reduce the morbidity associated with recurrent episodes of CMC, but also to prevent mucosal inflammation, which can increase the risk of squamous cell carcinoma. Repeated courses of antifungal therapy increase the risk of developing resistance to antifungal therapy. All cases of CMC should be confirmed with culture, and susceptibility testing should guide the choice of antifungal if a therapeutic response is not observed.

Systemic fungal disease should be guided by culture and susceptibility data with consideration of antifungal penetration in the affected tissue. Additional factors to consider include concomitant medications (triazoles are metabolized by P450 and prolong the QT interval with the exception of isavuconazole, which shortens it), liver function, and kidney function (amphotericin use). It is important to also consider that voriconazole is associated with additional toxicities including an increased risk of squamous cell carcinoma of the skin, fluorosis, peripheral neuropathy, and visual disturbances. Survival of life-threatening fungal infection should also mandate secondary antifungal prophylaxis unless the underlying immunodeficiency is cured by hematopoietic stem cell transplantation (HSCT).

CARD9 DEFICIENCY

CARD9 deficiency is caused by biallelic loss-of-function (LOF) pathogenic variants in *CARD9.* CARD9 contributes to antifungal host defense in a pathogen- and organ-specific manner with a striking predilection for *Candida albicans* central nervous system (CNS) infections. CARD9 deficiency is the only known IEI in which patients are predisposed to both mucocutaneous and systemic candidiasis, with *C. albicans* typically isolated. The CNS is the most common site of systemic involvement, with CNS candidiasis often presenting as either meningoencephalitis or an intracranial abscess ± obstructive hydrocephalus. The next most common site of systemic involvement is bone. Neutrophils are absent in all involved exudates and tissues.

Deep dermatophytosis and subcutaneous phaeohyphomycosis infections can also be seen in CARD9 deficiency. *Trichophyton rubrum* and *Trichophyton violaceum* were the most common dermatophyte species. Severe complications like lymphadenitis, extension into adjacent organs with fistula formation, and dissemination to the CNS have been seen. Dermal biopsies show necrotizing granulomatous inflammation, subcutaneous nodules, and severe ulceration of the superficial tissues. Subcutaneous phaeohyphomycosis with a predilection for facial involvement has also been reported. Granulomatous inflammation with scattered lymphocytes and eosinophils are seen on biopsy. Extrapulmonary aspergillosis and a variety of dematiaceous fungi have also been reported including *Phialophora verrucosa, Exophiala spinifera, Ochroconis musae,* and *Corynespora cassiicola.*

Clinical manifestations of CARD9 deficiency are fully penetrant by the fourth or fifth decade of life with about 40% of patients presenting in adulthood. Sequencing of CARD9 is required to establish the diagnosis, and determination of functional consequences of CARD9 variants is difficult. Lymphocyte phenotyping is usually normal, as are absolute neutrophil and monocyte counts despite a lack of neutrophils in infected CSF. Nearly 60% of affected patients have findings of elevated serum IgE and/or hypereosinophilia. Treatment of fungal infection follows the tenets outlined earlier, frequently with infectious diseases consultation followed by lifelong antifungal prophylaxis unless HSCT is successfully performed. Two patients with CARD9 deficiency have been successfully treated with HSCT leading to clinical remission. There is a potential role for treatment of fungal disease with granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy in CARD9 deficiency, but there is variability in response that may relate to the underlying pathogenic variant(s) responsible for disease; thus seeking expert advice is recommended.

Table 175.1 Medelian Susceptibility to Mycobacterial Disease Defects

	GENE/INHERITANCE	CLINICAL PHENOTYPE	TREATMENT
Complete IFNgR1/R2 deficiency	*IFNgR1* or I*FNgR2*/AR	Early-onset disseminated NTM or BCG	Antimycobacterials; HSCT
Autosomal dominant IFNgR1 deficiency	IFNgR1/AD	NTM or BCG osteomyelitis, disseminated *Salmonella,* disseminated endemic mycoses	Antimycobacterials; adjuvant IFN-γ
IL-12RB1 deficiency	*IL12RB1*/AR	Disseminated NTM, BCG, *Salmonella* Mucocutaneous candidiasis Variable penetration	Antimycobacterials; consider IFN-γ with careful monitoring
IL-12p40 deficiency	*IL12B*/AR	Disseminated NTM, BCG, *Salmonella* Variable penetration	Antimycobacterials; consider IFN-γ with careful monitoring
IL-12Rb2 deficiency	*IL12RB2*/AR	NTM, BCG, and tuberculosis	Antimycobacterials
IL-23R deficiency	*IL23R*/AR	NTM, BCG, and tuberculosis	Antimycobacterials
STAT1 LOF	*STAT1*/AD	Disseminated BCG/NTM, often osteomyelitis	Antimycobacterials; consider IFN-γ
SPPL2a deficiency	*SPPL2A*/AR	Disseminated BCG	Antimycobacterials
TYK2 deficiency	*TYK2*/AR	Disseminated BCG, tuberculosis, viral infections	Antimycobacterials
Macrophage gp91 phox deficiency	*CYBB*/XL; distinct variants than those causing CGD	Disseminated BCG	Antimycobacterials
IRF8 deficiency (dominant)	*IRF8*/AD	Disseminated BCG, NTM	Antimycobacterials
IRF8 deficiency (recessive)	*IRF8*/AR	Viral, mycobacterial, mucocutaneous candidiasis	Antimicrobials, consider HSCT
ISG15 deficiency	*ISG15*/AR	Disseminated BCG	Antimycobacterials
RORγt deficiency	*RORC*/AR	Disseminated BCG and mucocutaneous candidiasis	Antimicrobials
JAK1 LOF	*JAK1*/AR	Bacterial, viral, and disseminated NTM	Antimicrobials

AD, Autosomal dominant; AR, autosomal recessive; BCG, bacilli Calmette-Guérin; CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation; IFN, interferon; LOF, loss of function; NTM, nontuberculous mycobacteria.

STAT1 GOF

STAT1 gain-of-function (GOF) pathogenic variants present with CMC, autoimmunity, intracranial aneurysms, and/or squamous cell carcinoma. This condition likely accounts for more than 50% of CMC cases; CMC affects most patients with this diagnosis and typically presents in the first year of life. *Candida* involvement of the oropharynx is most common, but esophagitis, genital, and skin and nail disease are also common. *C. albicans* is the most common cause of CMC, but other *Candida* species have also been isolated. Azole resistance is a major challenge over time making treatment difficult.

Invasive fungal infections are less common in this disease but can be quite severe. Disseminated *Histoplasmosis, Cryptococcus, Coccidioides,* and *Paracoccidioides* can be difficult to treat and, in some cases, have been fatal. Pulmonary and disseminated mold infections have been reported infrequently and include organisms such as *Aspergillus, Nannizziopsis,* and *Mucorales. Pneumocystis jiroveci* pneumonia has been reported rarely.

A wide range of other types of pathogens cause infections in this patient population as well including recurrent bacterial sinopulmonary infections, typically due to *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Staphylococcus aureus*. Bronchiectasis, when present, may further produce susceptibility to pathogens such as *Pseudomonas*. Less commonly skin infections such as folliculitis or cellulitis are also observed. Mycobacterial infections are typically due to BCG in those from countries that routinely immunize against tuberculosis (TB), and nontuberculous mycobacteria (NTM) adenitis or TB, or NTM lung infections. NTM infections do not usually disseminate widely in STAT1 GOF as they do in autosomal recessive or dominant STAT1 LOF.

Severe or recurrent viral infections, most commonly due to herpesviruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], Epstein-Barr virus (EBV), cytomegalovirus [CMV], BK, and JC), are also troublesome in over 30% of patients. Recurrent oral mucocutaneous disease due to HSV or recurrent VZV infection are the most frequent viral disease manifestations. EBV and CMV viremias are commonly detected, but CMV disease is infrequent as is symptomatic EBV disease. Human papillomavirus (HPV)-driven warts and molluscum are seen in a small number of these patients and are difficult to treat. Although rare, progressive multifocal leukoencephalopathy (PML) from JC virus is of particular concern due to its high mortality. PML has been seen with and without additional immune modulation; therapies that are sometimes indicated for the autoimmunity seen in STAT1 GOF, such as rituximab, need to be used with caution.

Additional disease manifestations include autoimmunity, vasculopathy, and malignancy. Autoimmune thyroid disease is most common, but type 1 diabetes mellitus, vitiligo, alopecia, pernicious anemia, autoimmune cytopenias, inflammatory bowel disease, and lupus-like disease have all been observed and, in many cases, the autoimmune manifestations can be quite refractory and difficult to control. Aphthous ulcers are also especially common and can be very painful. Cerebral aneurysms are the most common vasculopathy seen, but extracerebral vascular abnormalities occur as well. These aneurysms may be the result of vasculitis, perhaps from pathogens like VZV; serial

prospective imaging should be a part of routine screening. The most common malignancy observed is squamous cell carcinoma, mainly of the skin, oropharynx, and esophagus. Chronic inflammation caused by mucosal *Candida* infections may play an important role, as well as inflammation driven by increased STAT1 activity.

Management has been largely targeted against the infections and treatment of autoimmunity when present. Many of the patients need antifungal prophylaxis, and azole resistance may emerge and limit therapeutic choices to topical nystatin or amphotericin washes, or IV echinocandins. It is worth highlighting that voriconazole is not recommended in this patient population due to its photosensitivity and long-term skin cancer risk. In those patients with recurrent sinopulmonary infections and/or bronchiectasis, antibiotic prophylaxis is likely to be beneficial. Azithromycin prophylaxis, if pulmonary NTM is not present, may be beneficial not only for prevention of recurrent airway infections, but also will yield some antiinflammatory benefits. Recurrent HSV or VZV infections suggest the need for prophylaxis with acyclovir or valacyclovir. The autoimmunity is typically treated with immune suppression, and many have received long courses of corticosteroids. However, there are positive reports of success controlling this inflammation and autoimmunity with JAK inhibition. Ruxolitinib has been used in STAT1 GOF to treat alopecia, enteropathy, autoimmune cytopenias, and hepatitis. There is one report of JAK inhibition being used early in the course of associated insulin-dependent diabetes, with resolution of the need for insulin and remission of the diabetes. JAK inhibition also can be highly effective in the treatment of CMC because there is growing evidence that the CMC observed in this disease is due to exuberant inflammation rather than infection susceptibility. *Severe or disseminated infections have progressed while on JAK inhibition, thus, it is best to start this treatment only when invasive infections are adequately controlled.* Some patients develop hypogammaglobulinemia over time; immune globulin replacement may be indicated. HSCT is not yet the preferred option for treatment of STAT1 GOF. HSCT in this population of patients has been difficult with high morbidity and mortality, although it is important to note that many of these transplants were done before the genetic diagnosis was known and a variety of conditioning regimens were used.

IL-17F DEFICIENCY

A dominant-negative missense pathogenic variant in *IL17F* was reported in multiple patients from one kindred with CMC. About 65% of these patients had CMC manifesting as persistent thrush, vulvovaginal candidiasis, and interdigital intertrigo. Lymphocyte phenotyping and quantitative immunoglobulin levels were normal in the one patient who had such testing. Diagnosis relies on sequencing of IL-17F, but can also be suspected if flow cytometry shows absent intracellular IL-17F producing $CD3^+$ cells in patients with detectable IL-17A and IL-22 producing $CD3^+$ cells. Although there is insufficient clinical information to suggest ideal management of patients with IL-17F deficiency, we recommend a similar approach as outlined for management of CMC.

IL-17RA DEFICIENCY

IL-17RA deficiency also presents with CMC, but usually with onset within the first year of life. Candidiasis involved the oropharynx in 95% of patients, the genitals in 38% (60% females), the skin or scalp in 67%, and the nails in 19%. Episodes of CMC seemed to respond to topical or oral therapy. Staphylococcal skin infections were seen in 65% of the cohort, with such lesions also manifesting in the first year of life. Bacterial recurrent sinopulmonary infections occur in just over one-third of these patients, and all responded to antibiotic therapy.

Lymphocyte phenotyping is normal, and diagnosis should be made by sequencing of the *IL17RA* gene, particularly when early-onset CMC and concurrent *S. aureus* skin infections are present.

As CMC is a presenting feature of all reported patients with IL-17RA deficiency, oral antifungal prophylaxis should be initiated. Strong consideration should be given to also initiating antibiotic prophylaxis in those who have culture-proven bacterial infections that are recurrent or severe. In those with recurrent sinopulmonary infections, although the spectrum of organisms is not known, covering for common bacterial etiologies like *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis* should be sufficient to prevent disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

175.2 Innate Immunity Defects with Predominant Susceptibility to Viral Infections

Jenna R.E. Bergerson and Alexandra F. Freeman

Defects in innate immunity that predispose to viral infections are divided into three main groups: those primarily predisposing to HPV, those predisposing primarily to HSV encephalitis, and those predisposing to other viruses, many of which interfere with interferon (IFN) signaling. Some of these defects are described in the following sections along with other rare defects highlighted in Table 175.2.

PREDOMINANT HPV SUSCEPTIBILITY

Epidermodysplasia verruciformis (EV) is the main clinical presentation for diseases with autosomal recessive pathogenic variants in the transmembrane channel-like 6 and 8 (*TMC6* and *TMC8*) genes and more recently described in the calcium- and integrin-binding protein 1 *(CIB1)* gene, encoding for the proteins EVER1, EVER2, and CIB1, respectively. EVER1, EVER2, and CIB1 complex together for keratinocyte intrinsic immunity, and disruption of this complex leads to HPV susceptibility. The typical warts affecting healthy individuals are from α-HPV types; however, in EV, β-HPV causes symptomatic disease, which is usually asymptomatic in healthy individuals but associated with cancer in some immune compromised individuals. The warts are frequently not the typical verrucous appearance seen in healthy children, but are usually flat warts, and can look like tinea versicolor with pigment changes. The warts appear in sun-exposed areas and have a high incidence of cancer transformation. Individuals with EV do not usually have increased risk of other infections; they have normal immune evaluations including normal lymphocyte number and function. Diagnosis is with genetic testing after suspicion with atypical widespread HPV disease. There is no specific treatment, although warts are treated with standard therapies (see Chapter 708). Patients needed to be counseled to avoid UV and radiation exposure, and these individuals need frequent screening for skin cancer.

WHIM (wart, hypogammaglobulinemia, infections, myelokathexis) syndrome is an autosomal dominant (AD) disease caused by GOF pathogenic variants in *CXCR4*. Increased responsiveness of the CXCR4 receptor to its ligand CXCL12 (also known as SDF-1) results in increased retention of the neutrophils in the bone marrow and thus the finding of myelokathexis (neutropenia related to the inability of neutrophils to leave the marrow). Patients also have lymphopenia with decreased B-, T- and NK lymphocytes, along with hypogammaglobulinemia. Although recurrent infections are common, they tend not to be as severe as expected from the neutropenia because the neutrophils often are released from the bone marrow with infection; dental issues likely related to the neutropenia are common. Recurrent sinopulmonary infections likely relate more to the hypogammaglobulinemia, and some patients develop bronchiectasis. Warts typically start in childhood or adolescence and are often particularly severe with poor response to therapy. Evolution into squamous cell carcinomas can occur; patients require monitoring. Treatment traditionally has been supportive in treating infections and preventive with immune globulin therapy and G-CSF, which usually needs to be dosed at lower concentrations due to frequently experienced debilitating bone pain. Plerixafor, an antagonist of CXCR4, may provide a specific therapy.

There are several other PIDDs that primarily affect lymphocytes that have HPV susceptibility as a major component and are discussed in

other chapters. Many of these diseases, such as DOCK8 deficiency and GATA2 deficiency, have broader susceptibility than just HPV. CD28 deficiency has susceptibility specific for HPV resulting in warts and cutaneous horns. Compared to EV, those with CD28 deficiency have predisposition to the more common α- and γ-HPV types.

Predisposition to Severe Viral Infections

Host control of viral infections is predominately dependent on normal type 1 IFN signaling (Fig. 175.1; see Table 175.2). Type 1 IFNs, including the IFN-α subtypes and IFN-β, bind to their heteroreceptor comprising IFNAR1 and IFNAR2 leading to phosphorylation of TYK2 and JAK1. Activation of TYK2 and JAK1 leads to phosphorylation of STAT1 and STAT2, which then cause upregulation of **interferon-stimulated genes (ISGs)**. There are multiple potential defects along this pathway that can lead to viral susceptibility. The role of this pathway has been highlighted with the COVID-19 pandemic, with not only genetic defects but also autoantibodies against type I IFNs leading to more severe disease.

Autosomal recessive pathogenic variants in *IFNAR1* and *IFNAR2* lead to a lack of TYK2 phosphorylation for IFNAR1 defects, and both TYK2 and JAK1 phosphorylation for IFNAR2 with subsequent downstream deficiency of ISG upregulation. Despite the severe in vitro findings, the viral infection susceptibility appears more limited. Both are rare diseases, with most patients developing severe or fatal illness after live viral vaccination with the measles mumps rubella (MMR) vaccine (largely measles component) or yellow fever vaccine. Herpes viral control is variable, with a fatal case of herpes encephalitis reported in IFNAR1 deficiency, and poor control of human herpesvirus 6 (HHV6) in IFNAR2. Variants have been described with severe SARS-CoV-2 infection. These diseases appear to have incomplete penetrance, with some affected individuals having better control of viral infections or vaccination. Naturally acquired viral infections have been controlled much more than live viral vaccinations. These diseases are rare and therapy remains unclear, but avoiding live viral vaccines, considering antiviral prophylaxis for HSV/VZV infections, and vaccination of affected individuals and close contacts for influenza and COVID-19 appears prudent.

Genetic defects in *STAT1* can be activating (STAT1 GOF) or can be heterozygous or recessive with LOF. Autosomal recessive complete STAT1 deficiency is the most severe defect with most cases being fatal early in life. As IFN-α, IFN-β, and IFN-γ all signal through STAT1, completely impaired signaling predisposes individuals to both severe early-onset viral disease in addition to disseminated mycobacterial disease. Herpes family infections are common as well as live viral disseminated infection. The disease is fatal without HSCT early in life, but HSCT outcomes have been poor with several children having herpes family inflammatory complications after HSCT, such as with hemophagocytic lymphohistiocytosis (HLH) or severe CMV disease. There are also patients with autosomal recessive hypomorphic *STAT1* pathogenic variants who have some residual STAT1 disease that appears to have a less severe phenotype. Treatment is with aggressive antimicrobials to treat presenting infections and prevent new infections until HSCT is performed.

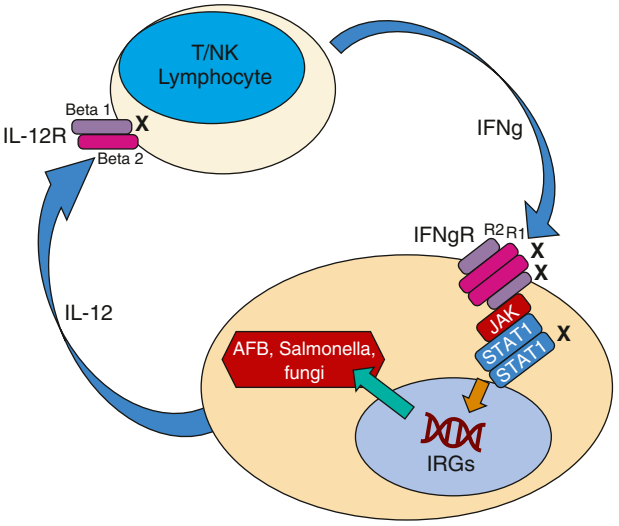

Fig. 175.1 Host control of mycobacteria. Macrophages ingest mycobacteria leading to secretion of cytokine IL-12, which then binds to its heterodimer receptor on the T lymphocytes and NK cells leading to the secretion of IFN-γ. IFN-γ binds to its heterodimer receptor, IFN-γR1 and IFN-γR2, leading to JAK1 and JAK2 phosphorylation, and then STAT1 phosphorylation. Where defects lead to MSMD are marked by an X.

Autosomal recessive complete STAT2 deficiency presenting early in life with severe viral infections is not as severe as STAT1 deficiency due to maintenance of IFN-γ signaling. Compared to IFNAR1 and IFNAR2 deficiency, there is more severe disease with naturally acquired viral infections such as respiratory syncytial virus (RSV) and enteroviruses, but similarly severe disease has been seen with MMR vaccine. Some children have been described to have a Kawasaki-like inflammatory presentation. The phenotype has been variable with some deaths early in life and some surviving to adulthood. Treatment remains uncertain with few patients reported, but live viral vaccines should be avoided, antiviral prophylaxis provided, and influenza vaccination given to those affected and close contacts.

Autosomal recessive IRF9 deficiency appears to present similarly to STAT2 deficiency. After IFN-α or IFN-β stimulation leads to STAT1 and STAT2 phosphorylation, these STAT proteins can heterodimerize with IRF9 to lead to ISG upregulation. This is a very rare defect presenting with naturally occurring or vaccine strain viruses. Life-threatening influenza and severe enterovirus infections have been described in addition to vaccine strain varicella and MMR dissemination. Treatment remains uncertain with few patients reported, but live viral vaccines should be avoided, antiviral prophylaxis considered, and influenza and COVID-19 vaccination given to those affected and close contacts.

Defects have been described in cytosolic sensors of viral DNA or RNA replication by-products that lead to fairly specific viral susceptibility. Melanoma differentiation-associated protein 5 (MDA5), encoded by the *IFIH1* gene, is a cytosolic sensor of double-stranded RNA by-products of RNA viral replication. Several patients have been described with LOF variants, either autosomal recessive or dominant, with presumed dominant negative effect, resulting in severe susceptibility to respiratory viruses including rhinovirus and influenza. Retinoic acid-inducible gene I (RIG-I), encoded by the *DDX58* gene, plays a similar role, and a patient has been described with LOF variants having severe influenza infection. RNA polymerase III deficiency (POL III) is a cytosolic DNA sensor detecting replication by-products of DNA viruses. AD pathogenic variants have been reported in POL III in children and adults with severe varicella-zoster disease causing pneumonitis, encephalitis, and CNS vasculitis. Treatment is not defined, but avoiding live viral vaccines, providing antiviral prophylaxis, and providing non-live annual influenza and COVID-19 vaccination to affected individuals and family members appear prudent.

NK functional and quantitative defects can occur on their own or as part of combined immune deficiencies and are associated with viral infections (see Chapter 167). Pathogenic variants in the *FCGR3A* gene, encoding CD16, which is a Fc receptor on NK cells, impair NK cytotoxicity. A few patients have been described who have susceptibility to herpes family viruses with EBV-related disease such as Castleman disease or HSV and VZV infections. Patients also develop significant warts from HPV infection. Antiviral prophylaxis should be given to prevent HSV/VZV infections, in addition to HPV vaccination.

Predominant HSV Encephalitis

Defects that affect TLR3 signaling predispose quite specifically to HSV encephalitis due to their role in the activation of type 1 IFNs in the CNS (Fig. 175.2; see Table 175.2). Double-stranded RNA is detected by TLR3, which then recruits the adaptor TRIF to activate TRAF3 to induce IFN-α, IFN-β, and inflammatory cytokines through TBK1 and IRF3 and other proteins. UNC93B1 acts as a transporter protein to

Table 175.2 Defects with Predominant Susceptibility to Viral Infections

GENE/INHERITANCE	CLINICAL PHENOTYPE	SPECIFIC TREATMENT	GENE/INHERITANCE
Epidermodysplasia verruciformis	*EVER1, EVER2, CIB1*/AR	Diffuse flat warts, with increased skin cancers	Avoid UV/radiation exposure, skin cancer screening.
WHIM syndrome	*CXCR4*/AD	Warts, squamous cell cancer, sinopulmonary infections, neutropenia, hypogammaglobulinemia	G-CSF, IgRT, plerixafor
IFNAR1 deficiency	*IFNAR1*/AR	Severe disease after live viral vaccination (MMR, yellow fever), herpesviruses	Avoid live viral vaccination, consider HSV/VZV prophylaxis
IFNAR2 deficiency	*IFNAR2*/AR	Severe disease after live viral vaccination (MMR, yellow fever), herpesviruses	Avoid live viral vaccination, consider HSV/VZV prophylaxis
Complete STAT1 deficiency	*STAT1*/AR	Early-onset severe viral and disseminated *Mycobacteria*	Early HSCT
STAT2 deficiency	*STAT2*/AR	Severe respiratory viruses, enterovirus; some live viral vaccine disease	Avoid live viral vaccines
IRF9 deficiency	*IRF9*/AR	Severe respiratory viruses, enterovirus; some live viral vaccine disease	Avoid live viral vaccines
IRF7 deficiency	*IRF7*/AR	Severe influenza	Influenza vaccination*
MDA5 deficiency	*IFIH1*/AR or AD	Severe respiratory tract infections	Influenza vaccination
RNA polymerase III deficiency	*POL3A,POL3C, POL3F*/AD	Severe varicella-zoster	Antiviral prophylaxis
CD16 deficiency	*FCGR31*/AR	Herpes family infections, HPV	Antiviral prophylaxis
IL-18BP deficiency	*IL18BP/AR*	Fulminant hepatitis A	Hepatitis A vaccination
TLR3 deficiency	*TLR3*/AD and AR	HSV encephalitis, severe influenza, zoster	Antiviral prophylaxis
TRAF3 deficiency	*TRAF3*/AD	HSV encephalitis	Antiviral prophylaxis
TRIF deficiency	*TRIF*/AD and AR	HSV encephalitis	Antiviral prophylaxis
UNC93B1 deficiency	*UNC93B1*/AR	HSV encephalitis	Antiviral prophylaxis
TBNK1 deficiency	*TBNK1*/AD	HSV encephalitis	Antiviral prophylaxis
IRF3 deficiency	*IRF3*/AD	HSV encephalitis	Antiviral prophylaxis
DRB1 deficiency	*DRB1*/AR	Brainstem encephalitis	Antiviral prophylaxis

*Although influenza vaccination is highlighted for certain inborn errors of immunity (IEIs), influenza vaccination should be given to all those with IEIs and their close contacts unless there is a contraindication. In addition, HPV vaccination should be given per the recommended schedule. Vaccination at an earlier age can be considered for certain defects with HPV predisposition.

AD, Autosomal dominant; AR, autosomal recessive; G-CSF, granulocyte colony-stimulating factor; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus IFN, interferon; MMR, measles mumps rubella; UV, ultraviolet; VZV, varicella-zoster virus; WHIM, (wart, hypogammaglobulinemia, infections, myelokathexis) syndrome.

transport TLR3 and other TLRs from the endoplasmic reticulum to the endosome to allow RNA binding. The TLR3 pathway is redundant for leukocyte immunity, but it is essential for CNS host viral immunity; thus the infection susceptibility of these defects is primarily CNS HSV disease. The defects in signaling are not found in leukocytes but required fibroblasts and inducible pluripotent stem cell generation of CNS cells to demonstrate abnormal IFN-α responses with HSV infection.

Pathogenic variants in multiple genes along this pathway have similar presentations with HSV encephalitis including autosomal recessive and dominant LOF variants in *TLR3*, dominant pathogenic variants in *TRAF3*, dominant and recessive pathogenic variants in *TRIF*, recessive pathogenic variants in *UNC93B1*, and dominant pathogenic variants in *TBK1* and *IRF3*. The HSV encephalitis tends to present in infancy and early childhood on HSV exposure, with frontal and temporal lobes predominantly affected. Dominant pathogenic variants in *TLR3* have also been associated with severe influenza and varicella-zoster encephalitis in a few adults. Genetic diagnosis is essential as routine immunologic studies are normal. Treatment is supportive with acyclovir or similar prophylaxis.

Rarely children can have brainstem CNS infections, including HSV; defects in the TLR3 pathway have not been found in these cases. Autosomal recessive hypomorphic pathogenic variants in *DBR1* (debranching enzyme 1) have been identified in children with brainstem encephalitis caused by HSV, norovirus, and influenza virus. DBR1 is an RNA lariat-debranching enzyme that degrades spliced RNA introns, which is ubiquitously expressed in humans but with highest amounts in the brainstem and peripheral nervous system. With decreased function, there is increased accumulation of lariat introns that presumably interfere with viral recognition and control. Genetic diagnosis can allow prophylaxis with antivirals such as acyclovir and influenza vaccination of the affected individual and close contacts.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

175.3 Susceptibility to Invasive Bacterial Infections

Jenna R.E. Bergerson and Alexandra F. Freeman

Inborn errors of immunity (IEIs) with predominant susceptibility to invasive bacterial infections such as meningitis, sepsis, arthritis, osteomyelitis, and deep-seated abscesses are rare, and are mostly due to neutrophil defects or defects in innate immunity. Inherited disorders of the Toll and IL-1 receptor (TIR)-pathway are innate immunity defects with a very distinct phenotype with invasive pyogenic bacterial infections and usually the absence of fever and inflammatory markers. TLRs on white blood cell surfaces sense bacterial peptides leading to activation of the NF-κB and MAPK pathway leading to inflammatory mediators (Fig. 175.3). IEIs associated with impaired TLR signaling include pathogenic variants in *NEMO, IKBA, MyD88,* and *IRAK4* (Table 175.3).

IRAK4 DEFICIENCY

IRAK4 deficiency presents in infancy and early childhood with severe, recurrent bacterial infections, specifically due to *S. pneumoniae, S. aureus*, and *Pseudomonas aeruginosa*. Unique to this disorder, clostridial infections have also been reported. An impairment in mounting a fever at the beginning of infection with a corresponding rise in CRP are also hallmark features of this disease. Most patients with IRAK4 deficiency present with their first bacterial infection before 2 years of age; there is a high mortality rate in the early years. However, the frequency and severity of infections in IRAK4 deficiency improves with age, with none of the reported patients having invasive bacterial infections after the onset of adolescence, even those not on prophylactic antibiotics. Approximately 50% of IRAK4-deficient patients continue to have noninvasive skin and upper respiratory infections after adolescence. Delayed separation of the umbilical cord has been reported in IRAK4-deficient patients due to an unclear mechanism.

Diagnosis relies on clinical suspicion and genetic testing because other immunologic studies are variable or require research laboratory testing. All T- and B-cell and NK cell subsets are unremarkable, but there may be a deficiency of unswitched memory B cells with normal levels of switched memory B cells. Specific antibody levels to pneumococcal and allohemagglutinins of the ABO system are impaired in up to 30% of patients. Serum IgE and IgG4 concentrations are elevated in up to 65% and 30%, respectively. Defective IL-6 production leads to the inability to increase plasma CRP or mount fevers. Without the clinical findings of fever and inflammatory markers, there may be a low threshold for diagnostic imaging and initiating empiric parenteral antibiotic treatment against *S. pneumoniae, S. aureus,* and *P. aeruginosa*. Antibiotic prophylaxis should be implemented with agents like clotrimazole plus penicillin, and immunizations against pneumococcus serotypes, *H. influenzae,* and *Neisseria meningitidis* given. If patients have a poor response to vaccination, immunoglobulin replacement should be considered. There is a paucity of data to support the duration of antibiotic prophylaxis, but given that invasive pyogenic infections seem to resolve by adolescence a trial discontinuation could be considered at this time. Nonetheless these patients continue to have skin and upper respiratory infections and may benefit from lifelong antibiotic prophylaxis targeting pyogenic bacteria.

MYD88 DEFICIENCY

MyD88 deficiency resembles the clinical and laboratory findings in IRAK4 deficiency (Fig. 175.4; see Table 175.1). These patients have a susceptibility to serious bacterial infections due primarily to *S. pneumoniae, S. aureus,* and *P. aeruginosa*, including an inability to mount fever at the beginning of infection. CRP does not rise early during infection, likely due to impaired IL-6 production. Invasive bacterial infections begin before age 2 years and seem to improve with age, although noninvasive bacterial infections similarly persist after adolescence. Diagnosis is similar to IRAK4 deficiency relying on genetics, as routine immunologic testing is nondiagnostic. MyD88-deficient patients may have elevated serum IgE and IgG4 concentrations in up to 50% and

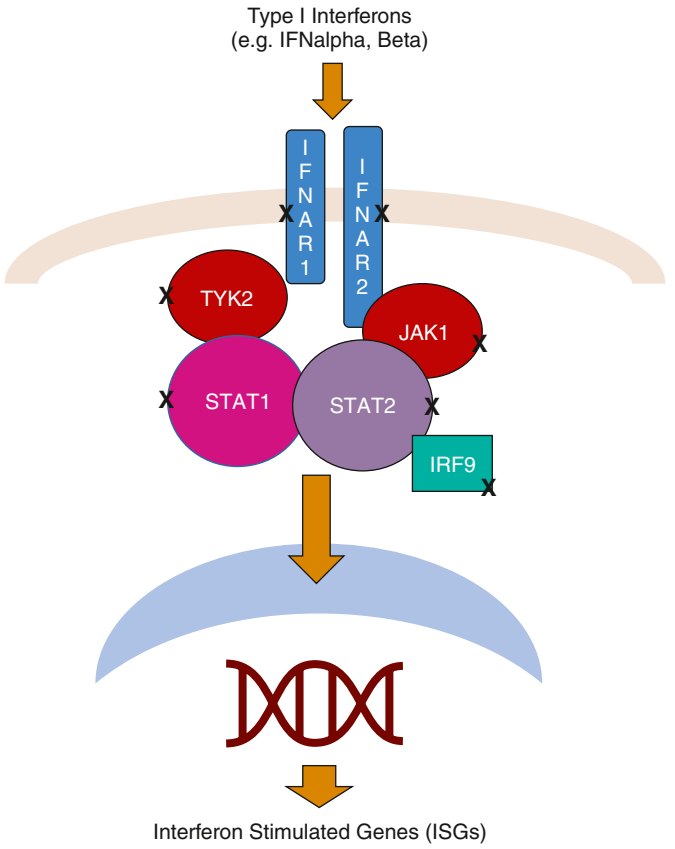

Fig. 175.2 Defects along type 1 interferon (IFN) signaling lead to viral susceptibility. Type 1 IFNs bind to their heteroreceptor comprising IFNAR1 and IFNAR2 leading to TYK2 and JAK1 phosphorylation followed by phosphorylation of STAT1 and STAT2, which then cause upregulation of IFN-stimulated genes (ISGs). IRF9 can also heterodimerize with STAT2 leading to ISG upregulation. Multiple genetic defects along this pathway (marked with X) can lead to viral susceptibility.

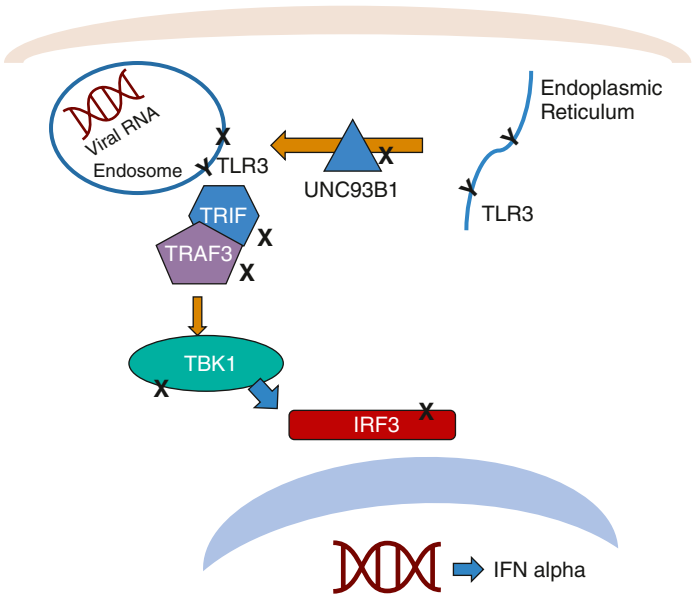

Fig. 175.3 Defects that affect toll-like receptor (TLR) 3 signaling predispose to HSV encephalitis by impairing type I interferon (IFN) activation. Double-stranded RNA is detected by TLR3, which then recruits the adaptor TRIF to activate TRAF3 and then through TBK1 and IRF3 to induce IFN-α and other inflammatory cytokines. UNC93B1 transports TLR3 from the endoplasmic reticulum to the endosome.

Table 175.3 Innate Defects with Bacterial Susceptibility

DISEASE	GENE/INHERITANCE	CLINICAL PHENOTYPE	LABORATORY PARAMETERS
IRAK4 deficiency	*IRAK4*, AR	Early-onset invasive pyogenic bacterial infections resolving in adolescence Persistence of noninvasive skin and URT infections	↓ IL-6, undetectable CRP in setting of infection ↓ CSM B cells Poor specific antibody levels to pneumococcus
MyD88 deficiency	*MYD88*, AR	Early-onset invasive pyogenic bacterial infections resolving in adolescence Persistence of noninvasive skin and URT infections	↓ IL-6, undetectable CRP in setting of infection ↓ CSM B cells
IRAK1 deficiency	*IRAK1*, XL	Undefined as reported in only one patient with Rett syndrome	Unknown
TIRAP deficiency	*TIRAP*, AR	Undefined Identified in nine members of one family with only one affected (pneumonia and sepsis from PVL-associated *Staphylococcus aureus*	Selectively ↓CSM B cells
Isolated congenital asplenia	*RPSA*, AD	Sepsis with encapsulated bacteria, absent spleen	HJB on blood smear
	PBX1, NKX2-5, BAPX1, POD1, AR	Sepsis with encapsulated bacteria, absent spleen	HJB on blood smear

AD, Autosomal dominant; AR, autosomal recessive; CSM; class switched memory; HJB; Howell-Jolly bodies; IL, interleukin; PVL, Panton-Valentine leukocidin; URT, upper respiratory tract; XL, X-linked.

33% of patients tested (respectively), as well as a specific deficiency of unswitched memory B cells. Treatment of MyD88 deficiency should follow the same principles as outlined previously for IRAK4 deficiency.

Other inherited disorders of the TIR pathway like IRAK1 deficiency and TIRAP deficiency will be addressed in Table 175.3.

ISOLATED CONGENITAL ASPLENIA

Asplenia refers to the complete lack of splenic tissue and includes a heterogenous group of conditions ranging from surgical asplenia to congenital asplenia. Congenital asplenia can be part of a syndrome of multiple congenital anomalies (see Chapter 480.11) or, less often, it can be isolated (see Table 175.3).

A diagnosis of isolated congenital asplenia (ICA) is made on the basis of the presence of Howell-Jolly bodies (HJBs) on blood smear and the lack of a detectable spleen at ultrasound in the absence of cardiovascular malformations. Some cases are due to an AD inheritance; relatives of those with ICA should be evaluated because the outcome is typically poor without initiation of antibiotic prophylaxis and pneumococcal vaccination. Half of all isolated cases are due to pathogenic variants in *RPSA*, a protein component of the small ribosomal subunit. Involvement of related key spleen patterning genes involved during embryogenesis can also result in splenic agenesis.

Presentation is typically with overwhelming, refractory infections due to encapsulated bacteria, particularly *S. pneumoniae*, but also other encapsulated bacteria like *H. influenzae* and *N. meningitidis*. Diseases like malaria and babesiosis also affect asplenic patients more severely due to defective removal of intra-erythrocytic parasites. In all cases of pneumococcal sepsis, a blood smear should be evaluated for HJBs in addition to an abdominal ultrasound to identify patients with ICA.

Immunization against pneumococcal serotypes and meningococcal serotypes is essential. Conjugated vaccines are preferred to unconjugated vaccines. Influenza vaccination should also occur yearly due to the risk of pneumococcal superinfection. Long-term oral penicillin prophylaxis (amoxicillin 10 mg/kg twice daily to max 250 mg OR ≤3 years: penicillin V 125 mg twice daily, ≥3 years: penicillin 250 mg twice daily) is recommended, as is early initiation of IV antibiotics in the setting of febrile illnesses. Patient education is a critical part in management. Patients should recognize and react to fever as a life-threatening emergency with initiation of antibiotic therapy at home (pediatric dosage of amoxicillin-clavulanate 45 mg/kg twice daily or levofloxacin 10 mg/kg for penicillin allergic patients) even before seeking medical care. Animal bites (risk of *Capnocytophaga*) also should be recognized as a medical emergency requiring local wound care and debridement, and a short course of antibiotic therapy (amoxicillin-clavulanate for 3-5 days). Lastly, when traveling patients should know what to do in case of fever, and if in a tropical area recognize the increased risk for malaria.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

175.4 Mendelian Susceptibility to Mycobacterial Diseases

Jenna R.E. Bergerson and Alexandra F. Freeman

The group of diseases referred to as mendelian susceptibility to mycobacterial diseases (MSMDs) centers around the synthesis and signaling of IFN-γ required for the ability of macrophages to control intracellular infections including mycobacteria as well as some other intracellular bacteria, fungi and viruses (see Table 175.1).

Control of mycobacterial infections relies on the IL-12/IFN-γ/STAT1 pathway (see Fig. 175.4). When the macrophages ingest mycobacteria or other intracellular organisms, they secrete the cytokine IL-12, which binds to its receptor, a heterodimer comprising IL-12RB1 plus IL-21RB2, on the T lymphocytes and NK cells. This then leads to the secretion by the T/NK lymphocytes of IFN-γ. IFN-γ binds to its heterodimer receptor, IFN-γR1 and IFN-γR2, leading to JAK1 and JAK2 phosphorylation, and then STAT1 phosphorylation. STAT1 is a transcription factor that leads to the upregulation of IFN-regulated genes (IRGs), which leads to the clearance of these infections. Control of mycobacteria relies on this pathway, but also other intracellular microorganisms such as endemic fungi (e.g., *Histoplasma* and *Coccidioides*), *Salmonella,* leishmaniasis, and, in part, some viruses, such as those in the herpes virus family.

The MSMD defects typically present with disseminated BCG or with extrapulmonary nontuberculous and environmental mycobacteria (NTM); individuals with disseminated mycobacterial disease with either bone or visceral involvement should be evaluated. Depending on the type of defect, the infection may be more localized, such as the osteomyelitis seen frequently with dominant LOF defects in *IFN-γR1* or *STAT1*,

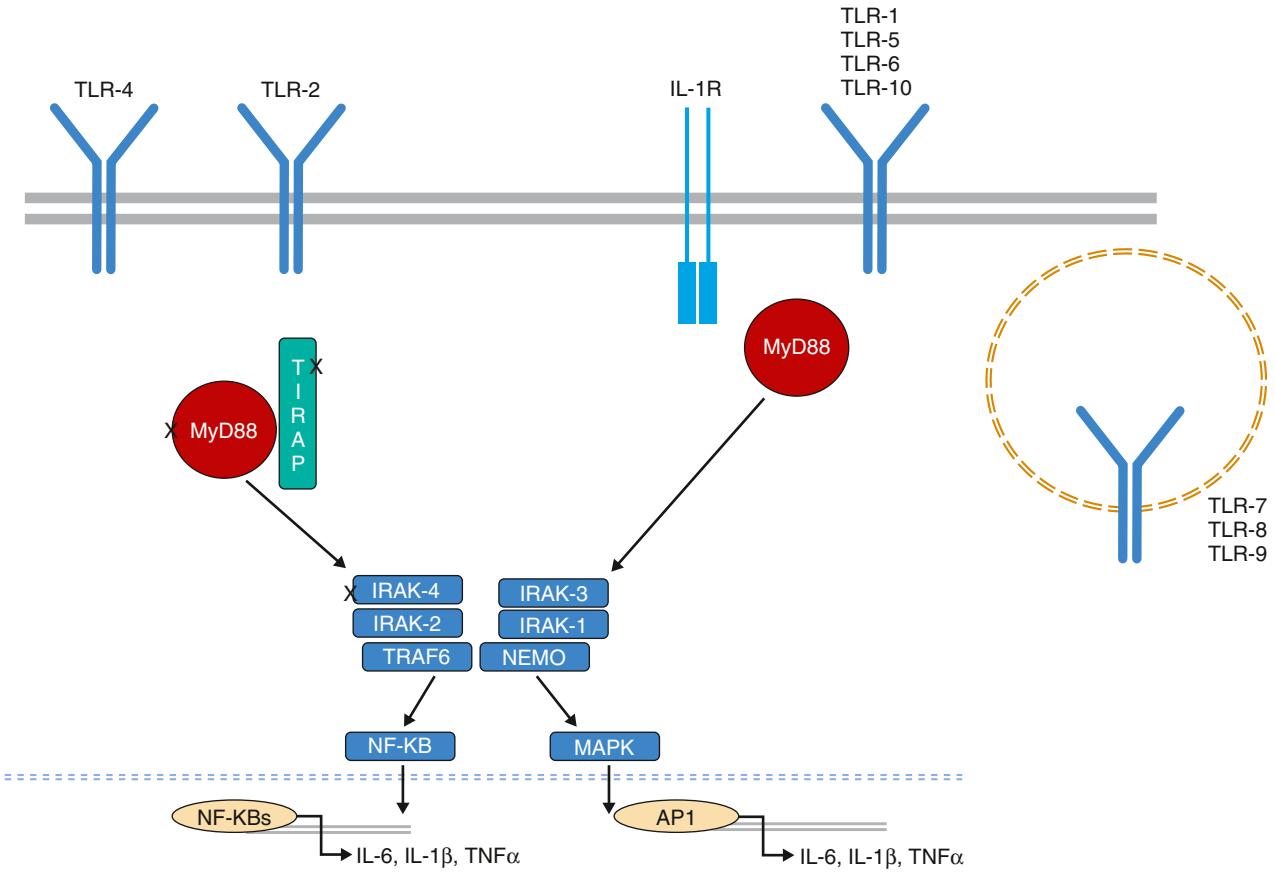

Fig. 175.4 TLR/IL-1R pathways. MyD88 is a cytosolic adaptor protein that bridges TLRs and IL-1Rs to the IRAK complex and subsequently allows for the downstream production of cytokines and interferons (IFNs) through the NF-κB and MAPK pathways. All TLRs, except TLR3, as well as multiple IL-1Rs use MyD88 and IRAK4. Where defects lead to predominant susceptibility to invasive bacterial infections are marked by an X.

or with more disseminated disease often with lymph node, bowel, and hepatosplenic involvement. Extrapulmonary TB should also raise suspicion of MSMD in young BCG-vaccinated children. Mycobacterial disease restricted to the lungs is much less frequently associated with MSMD, but more often with diseases predisposing to bronchiectasis. In addition, young children with isolated cervical adenitis from NTM do not usually have MSMD; the evaluation can be limited to those with recurrent or difficult to treat disease.

Therapy relies on targeted antimicrobials, but cytokine adjuvants, such as IFN-γ, and consideration of HSCT varies based on the defect. Related defects that predispose to CMC are noted in Table 175.4.

IFN-γR Defects

The IFN-γ receptor is a heterodimer comprised of IFN-γR1 and IFN-γR2, and defects in both components lead to abnormal signaling. There are biallelic and heterozygous pathogenic variants that lead to differing presentations.

Autosomal Recessive Complete IFN-γR1/IFN-γR2 Deficiency

The most severe defect of the IFN-γR defects are homozygous or compound heterozygous pathogenic variants that block all IFN-γ signaling. The variants are in the extracellular domains of the protein and lead to no surface receptor expression. In countries where BCG is given, these patients typically present in infancy with disseminated BCG; in other countries affected patients present usually in early childhood with disseminated NTM, such as *Mycobacterium avium* complex (MAC). *Salmonella* and *Listeria* can also cause severe infection; there may be more severe disease with common respiratory viruses and herpes family viruses. Diagnosis is with genetic testing, but some laboratories can also suggest the diagnosis by performing flow cytometry showing no surface expression of the IFNg-γ on monocytes or lack of intracellular STAT1 phosphorylation after stimulation with IFN-γ.

Treatment of complete IFN-γR1 deficiency is aggressive antimicrobial therapy until HSCT. Adjuvant IFN-γ is not helpful because signaling is blocked; addition of IFN-α has been used successfully in some cases of disseminated MAC. These patients usually have disseminated NTM or BCG and require combination antibiotics through HSCT, with breakthrough infections being seen often if antibiotics are withdrawn. High serum IFN-γ levels in the blood are typical when infection is present and has been correlated with a poor HSCT outcome; these levels can be followed and HSCT optimally performed when they decline.

Autosomal Dominant IFN-γR1 Deficiency

Compared with complete γ/2 deficiency, AD IFN-γR1 deficiency allows partial IFNg signaling, and thus a typically less severe clinical course. Most pathogenic variants are small frameshift deletions in the intracellular domain of the *IFNGR1* gene, thus blocking both the JAK binding site as well as the receptor recycling domain, eliminating the removal of the nonfunctional receptor from the cell surface. Clinical presentation is usually later in childhood or adolescence with more focal NTM infections, which is usually osteomyelitis. BCG can present with osteomyelitis as well, at a younger age than is usually seen for the environmental NTM. Disseminated endemic fungi infections with *Histoplasma* and *Coccidioides* are seen, in addition to disseminated *Salmonella* infections. Diagnosis relies on genetic testing, but in laboratories able to perform flow cytometry for IFN-γR expression, diagnosis is suspected by increased IFN-γR expression due to the inability to recycle the receptor. Intracellular STAT1 phosphorylation is reduced after IFN-γ stimulation, although not absent such as with the complete defects.

Treatment involves antimicrobials guided by the specific infection, with combination antibiotics needed for NTM/BCG. The addition of IFN-γ is

Table 175.4 Chronic Mucocutaneous Candidiasis Associated Inborn Errors of Immunity

SYNDROME	GENE	INHERITANCE	FUNGAL SPECIES	OTHER MANIFESTATIONS
CARD9 deficiency (30% CMC)	*CARD9*	AR	*Candida* spp. (often CNS involvement), CMC *Aspergillus* spp. (extrapulmonary), dermatophytes, phaeohyphomycosis	Some with increased IgE and eosinophilia
IL-17F deficiency (67% CMC)	*IL17F*	AD	CMC	Asthma, folliculitis
IL-17RA deficiency (100% CMC)	*IL17RA*	AR	CMC	Folliculitis, susceptibility to *Staphylococcus aureus* (skin) bacterial infections
IL-17RC (100% CMC)	*IL17RC*	AR	CMC	None
ACT1 (100%)	*TRAF3IP2*	AR	CMC	Seborrheic dermatitis
STAT1 GOF (95% CMC)	*STAT1*	AD	CMC, *Histoplasma capsulatum, Coccidioides* spp. *Talaromyces marneffei, Trichophyton, Cryptococcus, Aspergillus, Mucorales*	Herpes viral infections, bacterial sinopulmonary and skin infections, mycobacterial pulmonary and disseminated infections, CNS aneurysms, autoimmunity

AD, Autosomal dominant; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; GOF, gain of function; IL, interleukin.

often helpful to clear the infection because some IFN-γ signaling remains. After clearance of the infection, lifelong prophylaxis is suggested such as with azithromycin therapy, and consideration of fluconazole for *Coccidioides* endemic regions. IFN-γ is not usually long term for prophylaxis. HSCT has been performed in rare cases but is typically not considered necessary.

Autosomal Recessive IL-12 Receptor Beta 1 (IL-12RB1) Deficiency

Biallelic typically missense or nonsense pathogenic variants in *IL-12RB1* result in complete loss of IL-12 signaling leading to disseminated NTM or other intracellular infections. Compared with complete IFN-γR deficiency, the penetration and expressivity of IL-12RB1 deficiency is much more variable. Some patients are asymptomatic, even if BCG is given, whereas others develop severe disease early in life with early mortality; even within families the disease can have very different presentations. This defect is also more common than IFN-γR deficiency. Disseminated BCG is common in countries in which the vaccine is given and disseminated environmental NTM presents at much more variable ages in other countries. Although there is increased childhood mortality from this defect, patients who clear disseminated BCG infection have lower rates of subsequent NTM infection than those who did not have a BCG infection. Disseminated *Salmonella* is seen frequently. IL-12RB1 forms a heterodimer with IL-23R, so perturbation of this signaling cascade also results in an increased rate of mucocutaneous candidiasis. Diagnosis is confirmed with genetic testing, but some laboratories can test the lymphocyte response to IL-12 signaling, noting absence of STAT4 phosphorylation or IFN-γ secretion.

Treatment is aimed at antimicrobials for the diagnosed infection. Secondary prophylaxis is suggested after clearance of mycobacterial infections, such as with azithromycin. Adjuvant IFN-γ therapy has been used in cases where antimicrobials do not adequately clear the infection. Increased doses than are used in CGD may be needed, with prudence being to titrate up the dose slowly as hyperinflammatory presentations can complicate the therapy. There is very little experience with HSCT in IL-12RB1 deficiency.

AD STAT1 Loss of Function

Although GOF and complete LOF *STAT1* defects can be associated with NTM infections, NTM infections occur with the highest frequency in AD *STAT1* LOF, which is to be expected because STAT1 is downstream of the IL-12/IFN-γ pathway. Presentation is typically with more focal NTM or BCG infections, often with osteomyelitis, similar to that seen with AD IFN-γR1 deficiency. Diagnosis requires genetic testing. Patients typically respond well to combination antimicrobials and can then be placed on long-term prophylaxis. Infants with complete *STAT1* deficiency have had disseminated BCG; this defect also has severe viral infections.

TYK2 Deficiency

JAK proteins and TYK2 are part of the JAK/STAT signal transduction pathway. TYK2 is downstream of IFN-α and -β, as well as IL-12/IL-23, with its activation leading to STAT1 phosphorylation. Patients have had disseminated BCG, TB, and viral infections.

DIFFERENTIAL DIAGNOSIS FOR MSMD

MSMD centers around the control of intracellular organisms including *Mycobacteria* by the lymphocyte/macrophage interactions involving the IL-12/IFN-γ/STAT1 pathway. However, other primary and secondary immune deficiencies should be included in the differential diagnosis of those presenting with disseminated NTM. Disseminated NTM is a common infection for those with **GATA2 deficiency**, which typically presents in adolescence or adulthood, and is often associated with monocytopenia and myelodysplasia, susceptibility to HPV, and pulmonary alveolar proteinosis. **Nuclear factor-κ-B (NEMO)** deficiency and other genetic defects involved in NF-κB activation, such as defects in IkBα, are combined immune deficiencies that present with recurrent bacterial, viral, and disseminated mycobacterial disease; NEMO and IKBα may both have ectodermal dysplasia as part of the phenotype. Disseminated NTM is a less frequent complication for other myeloid and lymphocyte IEIs such as CGD, NFKB1 deficiency, and severe combined immune deficiency (SCID). Disseminated NTM is also associated with **autoantibodies against IFN-γ;** these should be considered for adult-onset disease. In the United States, anti–IFN-γ autoantibody disease with disseminated NTM is much more common in Asian females but is seen in males and females in East Asian countries. HIV/AIDS should always be ruled out for those with disseminated NTM. Disseminated NTM can also be seen secondary to immune suppressive medications, with TNF-α blockade being the most common cause. Hairy cell leukemia has an increased incidence of disseminated NTM.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 176

Approaches to Treatment of Primary Immune Deficiency Diseases

Alissa McInerney, Stefani Su, and Artemio M. Jongco III

GENERAL INFECTION PREVENTION AND MANAGEMENT STRATEGIES

Whenever possible, precautionary measures to reduce or minimize exposure to infection should be implemented. Whereas patients with severe immunologic defects (e.g., severe combined immunodeficiency [SCID]) would benefit from strict isolation, patients with other, less severe types of primary immunodeficiency disease (PID) usually do not require such restrictive measures. It is imperative to maximize the patient's quality of life while implementing appropriate infection mitigation strategies. Using shared decision-making, the clinician, patient, and caregivers should regularly discuss the risks, benefits, and alternatives of infection mitigation strategies, as the patient's clinical situation and risk change over time. Universal precautions, including but not limited to proper and thorough hand hygiene, should be frequently practiced by patients as well as their close contacts. The use of masks that cover the nose and mouth should be considered to avoid infection, especially when highly transmissible infections (e.g., SARS-CoV-2) are prevalent in the community. This is especially important in those PID patients before hematopoietic stem cell transplant (HSCT) while on immunosuppressive medications and afterward while awaiting immune reconstitution. *There is a low threshold to do further diagnostic testing to identify acute infections early and to start antimicrobial therapy or admit the patient to hospital for aggressive treatment if needed.*

It is also important to practice standard routine *oral* hygiene. Guidelines for antibiotic prophylaxis prior to dental procedures in PID patients has not been well established. Antibiotic prophylaxis is recommended for patients with PIDs requiring invasive dental procedures such as root canals and tooth extraction. In particular, those patients with PID with ongoing odontogenic infections require antibiotics before and during dental treatment. There is not enough evidence for antibiotic prophylaxis for noninvasive dental procedures such as oral examinations.

IMMUNIZATIONS

Some PID patients *will not* mount an adequate immune response to vaccinations because of their underlying immunologic defect. Nonetheless, immunizations should be given to prevent infections to PID patients who are able to respond to vaccination. Specific immunization practices are covered in Chapter 215. Immunization with live viral or bacterial vaccines (BCG) is contraindicated in many PIDs due to the risk of acquiring the live vaccine–related disease. Specific recommendations for vaccines in PID are shown in Table 176.1.

Patients who are on immunoglobulin G (IgG) replacement therapy (IgRT) do not require routine vaccinations because they receive *passive* immunization. Protective levels of antibodies against tetanus toxoid, diphtheria toxoid, measles, varicella, pertussis, pneumococci, and three meningococcal serotypes are documented in patients receiving IgRT.

GUIDANCE FOR CLOSE CONTACTS

Household members and other close contacts should not receive live oral polio virus or live influenza vaccine because they may shed the virus and transmit infection. Household members should generally be vaccinated to all recommended vaccines, including MMR and varicella, to facilitate herd immunity. Transmission of MMR vaccine viruses has not been reported. The risk of transmission of varicella vaccine virus from a healthy person to an immunocompromised person is rare. If a close contact develops varicella rash after immunization with the varicella or zoster vaccines, isolation of the patient and administration of varicella-zoster immune globulin is recommended.

COVID-19 VACCINE

The impact and severity of SARS-CoV-2 infection likely varies depending on the underlying immune defect. Small case series have suggested that B-cell lymphopenia (such as in X-linked agammaglobulinemia [XLA]) may actually be a protective factor and correlates with milder COVID-19 course. Meanwhile, patients with biallelic loss-of-function variants in *AIRE,* who have autoimmune polyendocrine syndrome type-1 (APS-1), appear to have higher risk for life-threatening COVID-19 pneumonia due to the presence of autoantibodies to type I interferons (IFNs). Although all PID patients will benefit from infection prevention and mitigation practices, it is becoming apparent that morbidity and mortality is variable among PID patients.

The most effective COVID prevention practices include the standard infection prevention strategies for all diseases including frequent handwashing, minimizing exposure to sick contacts, self-isolation/quarantining while ill, and mask wearing when in crowded public areas or areas with suboptimal ventilation. The most effective prevention strategy against COVID-19 is vaccination. Although this is a rapidly changing situation, a variety of organizations have created recommendations for immunodeficiency patients. The consensus is that PID patients should be vaccinated with non-live vaccines based on what has been approved for the age-group in their country. Patients with humoral deficiencies who do not respond with measurable antibody titers should still be considered for vaccination as vaccines can induce cellular immunity as well.

In the United States, the Centers for Disease Control and Prevention (CDC) recommends administration of a third or fourth dose in high-risk patients, such as immunocompromised patients, including PID patients with moderate to severe immunodeficiency and patients on chronic immunosuppressive therapy.

PROPHYLAXIS

Antimicrobial Prophylaxis

Prophylactic antibiotics are one of the mainstays for infection prevention in patients with PID. The specific antimicrobial prophylaxis recommended differs depending on the type of PID because patients with different PIDs are susceptible to different pathogens.

IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY

Severe Combined Immunodeficiency

Patients with SCID will require definitive treatment with allogeneic HSCT to correct the immune defect. It is crucial that patients remain infection free to maximize chances of long-term survival. With the implementation of newborn screening for SCID, infants with SCID are being detected before they develop infections. When SCID is suspected, the number of people in contact with the infant should be limited. Due to risk of transmission of cytomegalovirus (CMV) through breast milk, many PID transplant centers recommend cessation of breastfeeding until the CMV status of both the mother and infant is established.

Antimicrobial prophylaxis should be directed toward pneumonia caused by *Pneumocystis jiroveci* with a combination of sulfamethoxazole and trimethoprim. However, in infants under 2 months of age, there is a concern for bilirubin displacement from albumin and subsequent risk of kernicterus. In these young infants, close monitoring of bilirubin levels is recommended or alternatives such as atovaquone, dapsone, and pentamidine can be considered. Fluconazole to prevent mucocutaneous candidiasis and acyclovir for viral prophylaxis can be considered as well. In countries where BCG vaccine is commonly administered in early infancy, daily chemoprophylaxis until definitive treatment with HSCT and immune reconstitution is needed with isoniazid and rifampin due to the risk of disseminated BCG infection.

Table 176.1 Immunizations in Patients with Primary Immunodeficiency Diseases

PRIMARY DEFECT	EXAMPLE OF SPECIFIC IMMUNODEFICIENCY	NOT RECOMMENDED	RECOMMENDED
Predominantly antibody deficiencies	Hypogammaglobulinemias (X-linked agammaglobulinemia, common variable immunodeficiency) Other antibody deficiencies (selective IgA deficiency, IgG subclass deficiencies, specific antibody deficiency with normal immunoglobulins)	Live-attenuated vaccines excluding BCG Live-attenuated influenza, OPV, adenovirus, typhoid, yellow fever	Inactivated vaccines All vaccines likely effective Pneumococcal and *Hib*
Combined immunodeficiencies	Complete defects (SCID, complete DiGeorge syndrome) Partial defects (partial DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia)	All live vaccines Live-attenuated influenza, OPV, rotavirus, adenovirus, smallpox, typhoid, yellow fever, BCG	All vaccines likely ineffective Inactivated vaccines, live-attenuated MMR, varicella, and herpes zoster if documentation of adequate T-cell number*
Complement		None	All routine vaccines, especially pneumococcal and meningococcal vaccines
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects	Live-attenuated influenza, adenovirus, typhoid, BCG	All inactivated vaccines, other live-attenuated viral vaccines
IFN-γ-IL-12 pathway defects		BCG	

*Age-related levels of immunocompetence proposed by the CDC: <1 yr, 1500; 1-5 yr, 1,000; and >6 yr, 500 $CD4^+$ T cells/mm^3 for HIV may also be used.
BCG, Bacille Calmette-Guérin; OPV, oral poliovirus vaccine; SCID, severe combined immune deficiency; MMR, measles, mumps, rubella; IFN-γ, interferon gamma; IL-12, interleukin-12.
Data from Medical Advisory Committee of the Immune Deficiency Foundation, Shearer WT, Fleisher TA, et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. *J Allergy Clin Immunol*. 2014;133(4):961–966.

Palivizumab, a humanized monoclonal antibody against respiratory syncytial virus (RSV), can be considered for children under 2 years of age with SCID during the RSV season to prevent serious disease. The specific RSV seasonal patterns differ between countries.

HYPER-IgM/*CD40LG* DEFICIENCY

Patients with hyper-IgM or CD40LG deficiency are especially susceptible to *P. jiroveci* pneumonia (PJP) and require prophylaxis with a combination of sulfamethoxazole and trimethoprim. These patients are also at special risk for developing sclerosing cholangitis, which can be associated with *Cryptosporidium parvum* infection. To prevent the risk of cryptosporidium infection, steps need to be taken to avoid drinking contaminated water and places where risk of infection is higher, such as at recreational water parks.

COMBINED IMMUNODEFICIENCIES WITH ASSOCIATED OR SYNDROME FEATURES

DiGeorge Syndrome/22q11 Deletion Syndrome

Most patients with DiGeorge syndrome do not require antimicrobial prophylaxis as most patients do not have severe immunodeficiency (i.e., partial DiGeorge syndrome). Less than 1% of patients have significant thymic aplasia and profound T- and B-cell lymphopenia (i.e., complete DiGeorge syndrome), putting them at risk of PJP and CMV; PJP prophylaxis is recommended.

Wiskott-Aldrich Syndrome

Patients with Wiskott-Aldrich syndrome (WAS) are susceptible to a variety of viral and bacterial infections. *Prophylactic antimicrobials against infection by PJP and herpes simplex virus are often recommended.* If splenectomy is necessary for severe refractory thrombocytopenia, those patients would then require penicillin prophylaxis to protect against infection by encapsulated organisms.

Ataxia Telangiectasia

Opportunistic infections in patients with ataxia telangiectasia are infrequent; however, sinopulmonary infections are common. Prophylactic azithromycin is commonly used empirically, however, efficacy data are sparse.

STAT3 HYPER-IgE SYNDROME (JOB SYNDROME)

These patients are susceptible to skin infections predominantly with *Staphylococcus aureus* causing "cold" abscesses with diminished inflammatory response. Chronic mucocutaneous candidiasis occurs in over 70% of patients. Pneumonia is a frequent infection with risk of leading to bronchiectasis and pneumatoceles. Common causative pathogens include *Staphylococcus, Streptococcus pneumoniae, Haemophilus influenzae,* and fungal organisms such as *Aspergillus* and *P. jiroveci. Antimicrobial prophylaxis with a combination of sulfamethoxazole and trimethoprim and antifungal medications such as itraconazole is recommended.*

NF-κB ESSENTIAL MODULATOR (NEMO) DEFICIENCY

Patients with NF-κB essential modulator (NEMO) deficiency are susceptible to nontuberculous mycobacteria (NTM), similar to patients with IFN-γ and interleukin (IL)-12 defects. Prophylaxis with azithromycin should be considered. However, these patients are also at risk for many bacterial infections, viral infections such as herpesviruses, and opportunistic infections such as PJP. *Acyclovir for viral prophylaxis and a combination of sulfamethoxazole and trimethoprim for PJP prophylaxis should be considered as well.*

PREDOMINANTLY ANTIBODY DEFICIENCIES

Hypogammaglobinemias

Lifelong IgRT is the mainstay of infection prevention for patients with major antibody deficiencies such as agammaglobulinemia and common variable immunodeficiency (CVID). Prophylactic antibiotics can be used in conjunction with IgRT for patients who develop recurrent respiratory tract infections, which can lead to severe complications of bronchiectasis. Macrolide antibiotics such as azithromycin are commonly used for prophylaxis due to their anti-inflammatory properties in chronic lung disease. Low-dose oral azithromycin reduces the number of exacerbation episodes per patient-year, with a consequent reduction in additional courses of antibiotics and risk of hospitalization.

Other Antibody Deficiencies

Patients with minor antibody deficiencies such as **transient hypogammaglobulinemia of infancy (THI),** selective IgA deficiency, IgG

subclass deficiency, or specific antibody deficiency with normal immunoglobulins can usually be managed without need for IgRT. Patients who experience chronic or recurrent infections may benefit from prophylactic antibiotics. Prophylactic antibiotics and IgRT are equally effective as first-line treatment in preventing infections in specific antibody deficiency patients.

CONGENITAL PHAGOCYTE DEFECTS

Chronic Granulomatous Disease

Patients with chronic granulomatous disease (CGD) are susceptible to severe bacterial and fungal infections. The most common bacterial organisms include *S. aureus*, *Serratia marcescens, Burkholderia cepacia,* and *Nocardia* species. The majority of fungal infections in CGD are attributed to *Aspergillus* species causing invasive aspergillosis. *Prophylaxis with a combination of sulfamethoxazole and trimethoprim and itraconazole is recommended.*

Leukocyte Adhesion Deficiency

Antibiotic prophylaxis to protect against infections with *S. aureus* or gram-negative bacilli is recommended.

DEFECTS IN INTRINSIC AND INNATE IMMUNITY

Interferon-γ/IL-12 Pathway Defects

Patients with IFN-γ/IL-12 pathway defects are at special risk for infections with intracellular pathogens such as nontuberculosis *Mycobacterium* species as well as *Salmonella*. *Prophylaxis with daily azithromycin or clarithromycin is recommended.*

COMPLEMENT DEFICIENCIES

Deficiency of terminal pathway components can lead to recurrent neisserial infections. Antibiotic prophylaxis with penicillin can be considered. *Immunization against S. pneumoniae, H. influenzae, and Neisseria meningitidis is strongly recommended.*

IMMUNOGLOBULIN G REPLACEMENT THERAPY

Human immunoglobulin preparations, derived from the plasma of paid donors, can be administered intravenously (IVIG), subcutaneously (SCIG), or intramuscularly (IMIG) to treat a variety of disorders, including inborn errors of immunity, acquired immunodeficiency, and autoimmune and inflammatory disorders. IgRT provides *passive immunity* through preformed antibodies against a wide range of pathogens that are encountered by the general population, leading to immediate but transient protection; IgRT has an integral role in the treatment of patients with defects in the humoral immune system. IgRT is also used for a variety of medical conditions because of its anti-inflammatory and immunomodulating effects.

Products

Although most products are approved for a specific administration route, several 10% **IVIG** solutions can be administered subcutaneously with good patient tolerability. More concentrated 20% **SCIG** and 16% **IMIG** products should not be used intravenously. Available products and their key properties are summarized in Table 176.2. **IMIG** is rarely used because of its inferior safety and tolerability profile. Injections are painful, the injectable volume is limited, and the risk of local injury and adverse reactions is higher. Both **IVIG** and **SCIG** products are effective in treating humoral immunodeficiencies, without significant differences in the infection rates between the two routes. Incidence of infection is inversely correlated with dose regardless of route.

INDICATIONS FOR IgRT

IgRT is indicated for the treatment of primary immunodeficiencies characterized by absent or deficient antibody production, which comprises the majority of PIDs. The utility of IgRT in decreasing the frequency and severity of infection is well accepted for agammaglobulinemia (e.g., XLA) and hypogammaglobulinemia (e.g., CVID). There are six distinct phenotypes of primary immunodeficiency for which IgRT is or may be indicated: (1) agammaglobulinemia due to absence of B cells, (2) hypogammaglobulinemia with poor antibody function, (3) normal immunoglobulin levels with impaired specific antibody production, (4) hypogammaglobulinemia with normal antibody function, (5) isolated IgG subclass deficiency with normal immunoglobulin levels and normal quality antibody responses, and (6) recurrent infections related to an unknown immune mechanism.

Agammaglobulinemia Due to Absence of B cells

IgRT reduces both acute and chronic infections in this patient population; the number and severity of infectious complications are inversely correlated with IgRT dose. When IgG trough levels are maintained above 800 mg/dL, serious bacterial illness and enteroviral meningoencephalitis are prevented; increasing trough levels up to 1,000 mg/dL are associated with decreased risk for pneumonia. In the setting of SCID, IgRT is warranted at diagnosis because maternally derived IgG wanes after birth, during the posttransplant period, or gene therapy or enzyme replacement (for adenosine deaminase [ADA] deficiency) until B-cell function reconstitution, or indefinitely if B-cell function is not restored.

Hypogammaglobulinemia with Poor Antibody Function

Patients with recurrent infections who demonstrate decreased immunoglobulin concentrations and/or impaired response to protein and/or polysaccharide vaccines benefit from IgRT. CVID falls in this category. Initiation of IgRT is associated with decreased infection rate compared with pretreatment. Adequate IgRT dosing is associated with decreased frequency of sinopulmonary infections, which can mitigate the development of lung inflammation, bronchiectasis, and chronic lung disease. Growing evidence and expert consensus support individualizing IgRT dosing to keep the patient relatively infection free, achieving a "biologic trough or biologic steady-state level," and following clinical outcomes rather than using a standardized dose in all patients by disease. In addition to CVID, patients with class-switching defects, such as autosomal recessive and X-linked hyper-IgM syndromes, also demonstrate decreased infection rates from a variety of pathogens.

NORMAL IMMUNOGLOBULIN LEVELS WITH IMPAIRED SPECIFIC ANTIBODY PRODUCTION

Determining whether and when IgRT is indicated for these patients can be challenging. Available evidence and expert consensus suggest that IgRT should be given when there is well-documented nonresponsiveness to polysaccharide vaccines and recurrent infections that are inadequately managed by antibiotic prophylaxis. Protective concentration of antibody to polysaccharide antigens is considered 1.3 μg/mL and conversion from nonprotective to protective titers. In children 2-5 years, >50% of concentrations tested are considered protective, with an observed increase of at least twofold postvaccination, while the threshold is >70% in patients aged 6-65 years. Selective antibody deficiency has been categorized into four phenotypes—mild, moderate, severe, and memory (where the patient can mount an adequate initial response that wanes within 6 months). If an IgRT trial is started, it should be discontinued after a period of time so that antibody responses can be reevaluated a minimum of 3 months after discontinuation. Some children can demonstrate clinical improvement and improved response after pneumococcal polysaccharide vaccine challenge after a short trial of IgRT, whereas others continue to have recurrent infections and restart IgRT.

Hypogammaglobulinemia with Normal Antibody Function

Age-specific normal ranges differ among laboratories and having IgG levels below the lower limit of normal for age without accompanying infections may not be clinically significant. The IgG levels of children experiencing **THI** normalize with time. THI may be exacerbated by preterm birth. In the absence of significant infections, IgRT is not routinely recommended for these children. Acquired hypogammaglobulinemia arising from medication (e.g., seizure medications, B-cell depletion therapy) can also fall in this category. Severe hypogammaglobulinemia, conventionally defined as IgG levels ≤150 mg/day, is considered a risk

Table 176.2 Available Immunoglobulin Replacement Therapy Products

ROUTE	PRODUCT	DOSAGE FORM	DILUENT	REFRIGERATION REQUIRED?	FILTRATION REQUIRED?	OSMOLALITY (mOsm/kg)	SODIUM	PH	IgA (mcg/mL)	STABILIZER OR REGULATOR*	PATHOGEN INACTIVATION/ REMOVAL†
IV	Asceniv	10% liquid	NA	Yes	No	Not available	0.100-0.140 mol/L	4.0-4.6	<200	Glycine and polysorbate 80	FP, S/D, VF
	Bivigam	10% liquid	NA	Yes	No	<510	100-140 mM	4.0-4.6	≤200	Glycine	FP, S/D, NF
	Flebogamma DIF 5%	5% liquid	NA	No‡	Optional	240-370	Trace	5.0-6.0	<50	D-sorbitol	Past, S/D, dsNF, FP, PEG, pH 4
	Flebogamma DIF 10%	10% liquid	NA	No‡	No	240-370	Trace	5.0-6.0	<100	D-sorbitol	Past, S/D, dsNF, FP, PEG, pH 4
	Gammagard 5% S/D	Lyophilized	Sterile water	No	Yes	636	8.5 mg/mL	6.8	<1	2% glucose and glycine	CEF, CHROM, S/D
	Gammaplex	5% liquid	NA	No‡	15-20-μm filter preferred	420-500	30 to 50 mmol/L	4.8-5.0	<4	Sorbitol and glycine and polysorbate 80	S/D, VF, low pH
	Gammaplex	10% liquid	NA	No‡	No	≥280	<30 mM/L	4.9-5.2	<20	Glycine and polysorbate 80	S/D, VF, low pH
	Octagam	5% liquid	NA	No‡	Optional	310-380	0.03 mEq/mL	5.1-6.0	<200	Maltose	CEF, UF, CHROM, S/D, pH 4
	Octagam	10% liquid	NA	No‡	Optional	310-380	<30 mmol/L	4.5-5.0	106	Maltose	CEF, S/D, pH 4, UF, CHROM
	Panzyga	10% liquid	NA	No§	Optional	240-310	Trace	4.5-5.0	100	Glycine	S/D, CEF, NF, CHROM
	Privigen	10% liquid	NA	No**	No	240-440	Trace	4.6-5.0	<25	L-proline	CEF, CHROM, pH 4, DF, NF, OAF
IV or SC	Gammagard liquid	10% liquid	NA	No‡	Optional	240-300	None added	4.6-5.1	37	Glycine	CEF, CHROM, S/D, pH 4, NF
	Gammaked	10% liquid	NA, incompatible with saline	No**	No	258	None added	4.0-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM, NF
	Gamunex-C	10% liquid	NA, incompatible with saline	No**	No	258	None added	4.0-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM, NF

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 176.2 Available Immunoglobulin Replacement Therapy Products—cont'd

ROUTE	PRODUCT	DOSAGE FORM	DILUENT	REFRIGERATION REQUIRED?	FILTRATION REQUIRED?	OSMOLALITY (mOsm/kg)	SODIUM	PH	IgA (mcg/mL)	STABILIZER OR REGULATOR*	PATHOGEN INACTIVATION/ REMOVAL†
SC	Cutaquig	16.5% liquid	NA	Yes¶	No	310-380	<30 mmol/L	5.0-5.5	≤600	Maltose	CEF, UF, CHROM, S/D, pH 4
	Cuvitru	20% liquid	NA	No***	No	208-290	None	4.6-5.1	80	Glycine	CEF, CHROM, NF, S/D
	Hizentra	20% liquid	NA	No	No	380	Trace, <10 mmol/L	4.6-5.2	≤50	Proline	CEF, CHROM, pH 4.2, DF, NF, VF, OAF
	HyQvia	10% liquid + recombinant human hyaluronidase	NA	No	No††	240-300	None added	4.6-5.1	37	Glycine	CEF, CHROM, S/D, pH 4, NF
	Xembify	20% liquid	NA	2-8°C	No	280-404	None	4.1-4.8	≤70	Glycine	CEF, CHROM, CAP, NF, DF, low pH
IM	GamaSTAN	16.5% liquid	NA	2-8°C	No	Not available	Not measured	4.1-4.8	Not measured	Glycine	CEF, CAP, CHROM, NF, low pH, DF
	GamaSTAN S/D‡‡	15–18% liquid	NA	2-8°C	No	Not available	0.4-0.5%	6.4-7.2	Not measured	Glycine	CEF, S/D, UF

*Precautions and laboratory abnormalities associated with specific stabilizers include the following:
- Glucose: May alter glycemic control in patients with diabetes mellitus.
- L-proline: Cannot be used in patients with hyperprolinemia.
- Maltose: Falsely elevates glucose readings in certain blood glucose monitoring systems, may contain trace corn protein (potential allergen), and may increase plasma osmolality (usually not clinically important).
- Polysorbate 80: Some patients may be hypersensitive (also known as Tween 80); reactions can be delayed type.
- Sorbitol, D-sorbitol: Cannot be used in patients with hereditary fructose intolerance.
- Sucrose: Avoid in patients with renal impairment or increased risk of acute kidney injury.

†Pathogen inactivation/removal using CEF, DF, UF, CAP, CHROM, Nano, dsNF, VF, S/D, Past, FP, or OAF.
‡Not required (+2 to 25°C).
§Storage is 2-8°C for 24 months or 25°C for 9 months.
**Storage is 2-8°C for 36 months or 25°C for 6 months.
¶Storage is 2-8°C for 24 months or 25°C for 6 months.
***Storage is 2-8°C for 36 months or 25°C for 12 months.
††Storage is 2-8°C for 36 months or 25°C for 3 months.
‡‡GamaSTAN S/D has been discontinued in the United States.
Note: Brand names and descriptions refer to products available in the United States and some other countries; product availability, specific composition, and other details regarding individual products vary in other countries.
IgA, Immunoglobulin A; IV, intravenous; NA, not applicable; FP, fraction precipitation; S/D, solvent detergent; VF, virus filtration; Nano, NF, nanofiltration; DIF, dual inactivation and filtration; Past, pasteurization; dsNF, double sequential nanofiltration; PEG, polyethylene glycol precipitation; CEF, cold ethanol fractionation; DF, depth filtration; UF, ultrafiltration; CHROM, chromatography; SC, subcutaneous; CAP, caprylate; OAF, octanoic acid fractionation; IM, intramuscular.
Adapted from Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017;139(3S):S1–S46; with data from Immune Deficiency Foundation. Characteristics of Immunoglobulin Products Used to Treat Primary Immunodeficiencies. Accessed 8/10/21. https://primaryimmune.org/sites/default/files/publications/IDF_IG%20Booklet%202020.pdf

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

factor for infection, and empiric trial of IgRT is reasonable. However, patients with levels between 150 and 250 mg/dL deserve further consideration of antibody function and individual clinical history.

Isolated IgG Subclass Deficiency with Normal Immunoglobulin Levels and Normal Quality Antibody Responses

Most patients with subclass deficiency are asymptomatic, but a few may have recurrent infections and poor antibody responses to specific antigens. *First-line management includes prophylactic antibiotics and treatment of other comorbidities, such as allergic rhinitis, that can contribute to the development of sinopulmonary infections.* IgRT is not routinely recommended for these patients; some case studies have demonstrated reduced infection rate, decreased antibiotic use, and improved quality of life among patients on therapy.

Recurrent Infections Related to an Unknown Immune Mechanism

There are defined immunodeficiencies, such as ataxia telangiectasia, WAS, and *STAT3* deficiency, as well as syndromic immunodeficiencies, such as Jacobsen syndrome, which can present with variable humoral immune defects. IgRT can prevent infections in select patients, and the decision to start IgRT and dosing considerations should be tailored to individual needs.

INDIVIDUALIZING IgRT

Clinicians, patients, and caregivers need to consider each patient's specific clinical situation and comorbidities, incorporate patient and caregiver preferences, and consider flexibility in dosing route and frequency. Children and adolescents may object to the multiple and more frequent needlesticks associated with SCIG. Once the decision is made to start IgRT, the clinician, patient, and caregivers need to periodically reassess and adjust as needed. Available IgRT products differ from one another and are not interchangeable; the product used should be matched carefully to the patient characteristics to maximize patient safety. There are eight guiding principles on the safe, effective, and appropriate use of IgRT in patients with primary immunodeficiency (Table 176.3).

Table 176.3 Guiding Principles for Effective Use of IgRT for Patients with Primary Immunodeficiency

GUIDING PRINCIPLE	RATIONALE
Indication for IgRT	IgG is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production; PI is an FDA-approved indication for IgRT
Diagnoses	A large number of PI diagnoses exist for which IgRT is indicated and recommended; many diagnoses have low total IgG levels, but some have a normal level with documented specific antibody deficiency
Frequency of IgRT	Treatment is indicated as ongoing replacement therapy for PI; treatment should not be interrupted once a definitive diagnosis has been established
Dose	IVIG is indicated for PI patients at a starting dose of 400-600 mg/kg every 3-4 wk; SCIG is generally used at a starting dose of 100-200 mg/kg/wk; SCIG dosing frequency is flexible
IgG trough levels	IgG trough levels can be useful in some diagnoses to guide care but should not be a consideration in access to IgRT
Site of care	The decision to infuse IgRT in a hospital, outpatient infusion center, community office, or home-based setting must be based on patient clinical characteristics
Route	Administration route must be based on patient characteristics; throughout life, certain patients may be more appropriate for IV or SC therapy depending on many factors, and patients should have access to either route as needed
Product	IVIG/SCIG are not generic drugs and products are not interchangeable; a specific product needs to be matched to patient characteristics to ensure patient safety; product change should only occur with active participation of the prescribing physician

IgRT, Immunoglobulin replacement therapy; IgG, immunoglobulin G; PI, primary immunodeficiency; FDA, US Food and Drug Administration; SCIG, subcutaneous immunoglobulin; IV, intravenous; SC, subcutaneous; IVIG, intravenous immunoglobulin.
Data from Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1–S46; with data from Yong PL, Boyle J, Ballow M, et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. *Clin Immunol.* 2010;135(2):255–263.

CONSIDERATIONS FOR PRODUCT SELECTIONS

IVIG

IgA Content

The amount of IgA in various products varies. Rarely, severe allergic reactions, including anaphylaxis, have been reported in patients with IgE anti-IgA or IgG anti-IgA. In these cases, use of low IgA-containing IVIG products or SCIG, which appears to be tolerated by these patients despite having higher IgA content, is recommended. Anaphylaxis due to IgA in SCIG has not been reported.

Adverse Reactions

All IgRT products are associated with a potential risk for adverse reactions, but historically IVIG is associated with higher risk. Most IVIG adverse reactions are rate related, mild, and occur in 5–15% of infusions. Slowing or stopping the infusion for 15-30 minutes usually leads to complete resolution. Premedication regimens can also help. Ensuring adequate hydration or switching to SCIG has been used successfully to mitigate this risk. Risk factors for experiencing adverse reactions include (1) having IVIG for the first time, (2) having or recently having a bacterial infection, (3) having underlying chronic inflammation, (4) using higher concentration products, (5) using lyophilized product, and (6) fast infusion rates. Future reactions become less likely after subsequent infusions with the same product. However, patients can develop adverse reactions at any point even to products they have tolerated previously; clinicians and patients need to remain vigilant. For enhanced safety, patients who have experienced prior adverse reactions may benefit from getting infusions at a medical facility, instead of at home with an infusion nurse.

Serious adverse events, including acute renal failure, neurodegeneration, and thromboembolic events, can occur during or soon after infusion. Thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism are rare, but they need to be watched for and require timely intervention when they occur. Risk factors include preexisting cardiovascular disease, diabetes mellitus, dehydration, sepsis, increased blood viscosity, hypercholesterolemia, and hypertension. The use of indwelling venous catheters solely for IVIG administration is not recommended due to the increased risk for thromboembolism and infection with these devices.

SCIG

Products

Available products range from 10–20% concentration and offer much dosing flexibility for patients. Facilitated SCIG (fSCIG) involves recombinant human hyaluronidase to facilitate the SC administration of large volumes of IgG among multiple sites and a variety of dosing schedules. Many studies demonstrate equivalence and noninferiority of SCIG and IVIG for management of PIDs.

Adverse Reactions

SCIG is well tolerated by many patients, including children and IgA-deficient patients, and its safety profile is well documented. The most common adverse reaction is local infusion site reactions that can range from mild to severe, but severe local reactions are rare. The prevalence of these local site reactions appears to diminish when infusions are continued. Carefully cleaning the skin of the infusion site with alcohol and using appropriately sized infusion needles or catheters can further decrease risk of local reactions. IV administration of 10% products that are approved for both IV and SC administration is unlikely to be problematic, but 20% products should not be used intravenously. Premedication is usually not needed for SCIG, but pretreatment of the infusion site with local anesthetic creams may improve tolerability in children.

In the United States, patients are routinely provided epinephrine autoinjectors as part of an anaphylaxis kit for home infusions, regardless of prior history of allergic reactions to IgRT.

DOSING CONSIDERATIONS

The IgRT dose that keeps a patient relatively infection free varies between patients and can vary in the same patient over time, so the goal of IgRT should be to maximize clinical outcomes and not to achieve a specific IgG level.

Conversion from IVIG to SCIG

The bioavailability of SCIG is approximately 67% lower compared to IVIG. Thus the monthly dose of SCIG required to achieve an equivalent monthly area under the curve (AUC) is 1.37 times the IVIG dose for 16% products and 1.53 for 20% products. No significant differences in infection incidence or outcome have been shown between studies that do not utilize this dose adjustment compared to studies with this dose adjustment. In clinical practice, AUC dose adjustment is rarely used.

IVIG Dosing

For IVIG, many clinical immunologists use 400-600 mg/kg every 3-4 weeks as an acceptable starting point for maintenance therapy, while continuing to check annual trough levels. Infusion rates start slowly (e.g., 0.01 mL/kg/min) to minimize adverse reactions, and the rate can be increased as tolerated. Clinicians should monitor weight changes and adjust dosing accordingly. Also, IgG levels may need to be checked more frequently if the patient experiences breakthrough infections, develops new medical conditions (e.g., protein losing conditions), or is not responding to treatment as expected. Because pharmacokinetics also differs among patients, a specific IVIG dose can result in different trough levels in patients with similar body mass. There is insufficient evidence to routinely recommend higher loading IVIG doses in patients with low IgG levels at presentation; this practice has been associated with higher risk for adverse reactions at IgRT start. There is limited data on optimal dosing intervals for IVIG, and current practices vary widely.

SCIG Dosing

For traditional **SCIG**, a starting dose of 100-200 mg/kg of body weight per week is commonly used. For hyaluronidase fSCIG, a starting dose of 400-600 mg/kg via one or two sites every 3-4 weeks is common. When fSCIG is given every 3-4 weeks, the initial peak will still be lower than that of IVIG given at the same intervals, but the trough serum levels will be similar. Patients have more dosing frequency flexibility because there are products approved for daily, weekly, biweekly, or monthly dosing. Infusion rates generally range from 10-35 mL/hr per site by pump with volumes of 15-40 mL per site. The number of sites depends on the total volume for the target dose, and typical infusion sites include abdomen, outer thigh, upper arm, and buttocks. Manual rapid-push protocols that do not require infusion pumps have been reported to be safe and tolerable by patients in small nonrandomized trials. Steady-state serum IgG levels should be monitored periodically after approximately 3 months and can be used to assess patient adherence.

Facilitated SCIG

The dosing of hyaluronidase fSCIG is similar to IVIG. In the United States, fSCIG is approved for use in patients 2 years or older. Unlike traditional SCIG, a four-dose/7-week "ramp-up" period is recommended when starting fSCIG, even in patients who have used other IgRT products successfully. Once established on therapy, **fSCIG** infusion rates can be increased as tolerated by the patient from 50 mL/hr up to 300 mL/hr. The IgG is infused via peristaltic pump or large volume battery-operated pump, similar to IVIG, which has been programmed to account for the higher pressure of fSCIG compared with IV.

ADMINISTRATION DETAILS

Premedication

Many patients tolerate IVIG infusions without premedication. Pediatric pretreatment regimens include oral acetaminophen or ibuprofen, oral or IV or IM diphenhydramine, or alternatively a nonsedating antihistamine and/or a glucocorticoid such as oral prednisolone or IV hydrocortisone. Maintaining adequate hydration before infusion orally or via IV fluids with normal saline may be beneficial, especially for patients with preexisting renal disease or other risk factors (e.g., concomitant use of nephrotoxic agents). *Premedication is usually not required for SCIG.*

VACCINATION WHILE ON IgRT

Administration of IgRT may interfere with vaccination efficacy because the antibodies in the product might bind to the antigens in the vaccine and inhibit the immune response. The IgG in the IgRT product may hinder the viral replication that is needed to induce the desired immune response in live-virus vaccines such MMR or varicella (varicella-zoster virus [VZV]). Antibody-containing blood products from the United States do not interfere with the immune response to yellow fever vaccine and are not believed to interfere with the response to live typhoid, live-attenuated influenza, rotavirus, or zoster vaccines. The duration of inhibition ranges from 3-11 months and is related to the amount of antigen-specific antibody contained in the immune globulin or blood product. *For patients on IgRT, 8 months since last IVIG infusion is the suggested waiting time before administering live vaccines.* Although no specific recommended waiting time has been suggested for SCIG, many clinicians will also wait for 8 months since last infusion.

- If the antibody-containing product is administered *before* the vaccine is scheduled, the vaccine should be delayed for the suggested interval. If a dose of MMR or VZV vaccine is administered after an antibody-containing product but at an interval shorter than the suggested interval, the vaccine dose should be repeated at the suggested interval unless an antibody response to the vaccine is documented.
- If the antibody-containing product is necessary within 14 days *after* administration of MMR or VZV vaccine, the vaccine dose should be repeated after the suggested interval, unless an antibody response to the vaccine is documented.

Caution is advised when checking and interpreting IgG-based serologies while on IgRT. Stopping IgRT to assess vaccine efficacy in immunodeficient patients is generally not recommended. Neoantigen vaccines such as *Salmonella typhi Vi* can be used to assess a patient's ability to make specific antibodies while on IgRT, but this is not widely available.

Annual inactivated influenza vaccine is generally recommended for immunodeficient patients, including those on IgRT, presumably to stimulate T-cell immunity, although data are lacking that demonstrate induction of protective antibodies. The influenza vaccine may be given simultaneously or at any time interval before or after IgRT infusion.

Clinical trials using gene therapy with retroviral vectors have been conducted for several inborn errors of immunity including ADA-SCID, X-linked SCID, X-linked CGD, and WAS in which immunity was restored but with leukoproliferative complications due to insertion of the vector into oncogenes, in all except for ADA-SCID. The use of lentiviral vectors represented a breakthrough in the field with clinical recovery and immune reconstitution while minimizing vector-related complications. For further details on HSCT and gene therapy/editing, see Chapters 177 and 178.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 6

Hematopoietic Stem Cell Transplantation

Chapter 177

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Rachel A. Phelan and David Margolis

Allogeneic (from a donor) or autologous (from the same individual) hematopoietic stem cells have been used to cure both malignant and nonmalignant disorders. **Autologous** transplantation is employed as a rescue strategy after delivering otherwise lethal doses of chemotherapy with or without radiotherapy in children with hematologic malignancies such as relapsed lymphoma or selected solid tumors (e.g., neuroblastoma, brain tumors). **Allogeneic** transplantation is used to treat children with genetic diseases of blood cells, such as hemoglobinopathies, primary immunodeficiency diseases, various inherited metabolic diseases, and bone marrow failure. Allogeneic transplant is also used as treatment for hematologic malignancies, such as leukemia and myelodysplastic syndromes. Bone marrow had originally represented the only source of hematopoietic progenitor cells. Growth factor (granulocyte colony-stimulating factor)–mobilized peripheral blood hematopoietic stem cells and umbilical cord blood hematopoietic progenitors have also been regularly used in clinical practice to perform hematopoietic stem cell transplantation **(HSCT)**.

A **human leukocyte antigen (HLA)**-matched sibling was traditionally the only type of donor employed. Matched unrelated volunteers, full-haplotype mismatched family members, and unrelated cord blood donors have been largely utilized to transplant patients lacking an HLA-identical relative.

Protocols for allogeneic HSCT consist of two parts: the preparative regimen and transplantation itself. During the **preparative conditioning regimen**, chemotherapy, at times in conjunction with irradiation, is administered to eliminate the patient's hematopoietic system and to suppress the immune system, especially T cells, so that graft rejection is prevented. In patients with malignancies, the preparative regimen also serves to significantly reduce the tumor burden. The patient then receives an intravenous infusion of hematopoietic cells from the donor. Less aggressive conditioning regimens, known as **reduced-intensity conditioning regimens**, are also used in pediatric patients. These regimens are mainly immunosuppressive and aim at inducing a state of reduced immune competence of the recipient to avoid the rejection of donor cells.

The immunology of HSCT is distinct from that of other types of transplant because, in addition to stem cells, the graft contains mature blood cells of donor origin, including T cells, B cells, natural killer cells, and dendritic cells. These cells repopulate the recipient's lymphohematopoietic system and give rise to a new immune system, which helps eliminate residual leukemia cells that survive the conditioning regimen. This effect is known as the **graft-versus-leukemia (GVL) effect.**

The donor immune system exerts its T-cell–mediated GVL effect through alloreactions directed against histocompatibility antigens displayed on recipient leukemia cells. However, because some of these histocompatibility antigens are also displayed on tissues, unwanted T-cell–mediated alloreactions may ensue. Specifically, donor alloreactive immune cells may attack recipient tissues, particularly the skin, gastrointestinal (GI) tract, and liver, causing acute or chronic **graft-versus-host disease (GVHD)**, a condition of varying severity that in some cases can be life-threatening or even fatal (see Chapter 179).

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. **HLA**, including HLA-A, HLA-B, and HLA-C major histocompatibility complex (MHC) class I molecules, present peptides to $CD8^+$ T cells, whereas the HLA-DR, HLA-DQ, and HLA-DP MHC class II molecules present peptides to $CD4^+$ T cells. There are hundreds of variant forms of each class I and class II molecule, and even small differences can elicit alloreactive T-cell responses that mediate graft rejection and/or GVHD. Disparities for HLA-A, HLA-B, HLA-C, or HLA-DRB1 alleles in the donor-recipient pair are independent risk factors for both acute and chronic GVHD. There is also increasing evidence that HLA-DQ and HLA-DP may play a role, prompting some transplant centers to also explore matching at these alleles.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. These antigens result from polymorphisms of non-HLA proteins, differences in the level of expression of proteins, or genetic differences between males and females. An example of the latter is represented by the H-Y antigens encoded by the Y chromosome, which can stimulate GVHD when a female donor is employed to transplant an HLA-identical male recipient. Thus, from this evidence, GVHD may occur even when the donor and recipient are HLA identical.

The preferred donor for any patient undergoing HSCT has traditionally been an HLA-identical sibling. Because polymorphic HLA genes are closely linked and usually constitute a single genetic locus, *any pair of siblings has a 25% chance of being HLA identical.* Thus, also in view of the limited family size in the developed countries, <25–30% of patients in need of an allograft can receive their transplant from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders because affected siblings will not be considered donor candidates.

HSCT FROM AN HLA–IDENTICAL SIBLING DONOR

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematologic malignancies and various congenital or acquired diseases (Table 177.1). Best results are achieved in patients with congenital or acquired nonmalignant disorders because the risk of disease recurrence is low and the cumulative transplantation-related mortality is lower than in children receiving transplants for hematologic malignancies.

ACUTE LYMPHOBLASTIC LEUKEMIA

Allogeneic HSCT is used for pediatric patients with acute lymphoblastic leukemia (ALL), either in the first complete remission when a child is considered at *high risk* of leukemia recurrence (e.g., those carrying poor-risk cytogenetic characteristics or with high levels of minimal residual disease), or in second or further complete remission after previous marrow relapse. ALL is the most common indication for HSCT in childhood. Several patient-, donor-, disease-, and transplant-related variables may influence the outcome of patients with ALL given an allogeneic HSCT. The probabilities of 3-year overall survival (OS) for US patients <18 years of age with ALL transplanted in the first or second complete remission is 70–80% and 60–70%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases (50–60%; Fig. 177.1). The use of total body irradiation (TBI) during the preparative regimen offers an advantage in terms of better event-free survival (EFS) compared to a regimen consisting of cytotoxic drugs alone, but it can induce more long-term side effects. This has prompted more investigation into TBI-sparing alternatives. Less intensive GVHD prophylaxis is also associated with a better outcome. Bone marrow is generally the preferred source of stem cells to be employed for transplantation, although this differs among transplant centers.

Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immunocompetent cells, disease recurrence remains the main cause of treatment

Table 177.1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

MALIGNANCY
- ALL
  - First complete remission for patients at very high risk of relapse
  - T-cell immunophenotype and poor response to corticosteroid therapy
  - Not in remission at the end of the induction phase
  - Marked hypodiploidy (<43 chromosomes)
  - Minimal residual disease at the end of consolidation therapy
- High-risk infant ALL
  - Second complete remission
  - Third or later complete remission
- Acute myeloid leukemia in first complete remission or in advanced-disease phase
- Philadelphia chromosome–positive chronic myeloid leukemia
- Myelodysplastic syndromes
- Hodgkin and non-Hodgkin lymphomas
- Selected solid tumors
  - Metastatic neuroblastoma
  - Rhabdomyosarcoma refractory to conventional treatment
  - Very high risk Ewing sarcoma
  - High-risk CNS tumors

ANEMIAS
- Severe acquired aplastic anemia
- Fanconi anemia
- Paroxysmal nocturnal hemoglobinemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Shwachman-Diamond syndrome

IMMUNOLOGIC DISORDERS
- Variants of severe combined immunodeficiency
- Hyper-IgM syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Zap-70 kinase deficiency
- Cartilage-hair hypoplasia
- PNP deficiency
- CD40 ligand deficiency
- MHC class II deficiency
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Kostmann syndrome (infantile malignant agranulocytosis)
- Chronic granulomatous disease
- Autoimmune lymphoproliferative syndrome
- X-linked lymphoproliferative disease (Duncan syndrome)
- IPEX syndrome
- Interleukin-10 receptor deficiency
- Hemophagocytic lymphohistiocytosis
- Interferon-γ receptor deficiency
- Griscelli disease
- Granule deficiency

OTHER DISORDERS
- Selected severe variants of platelet function disorders (e.g., Glanzmann thrombasthenia, congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (e.g., Hurler disease) or other liposomal/peroxisomal disorders (e.g., Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

ALL, Acute lymphoblastic leukemia; CNS, central nervous system; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase.

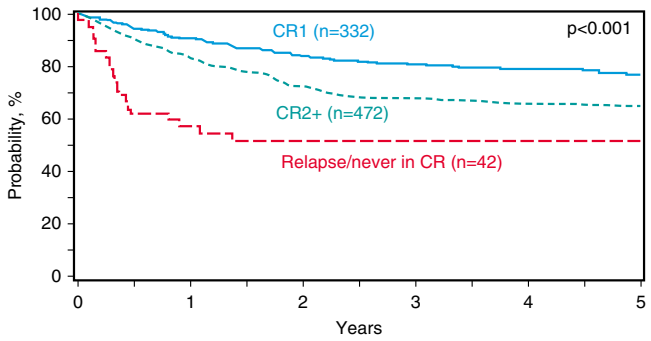

Fig. 177.1 Survival after matched related donor hematopoietic stem cell transplantation for acute lymphoblastic leukemia (ALL), age <18 years, 2008-2018. CR1, first complete remission; CR2+, second or greater remission. *(From Phelan R, Arora M, Chen M. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides 2020.* http://www.cibmtr.org.*)*

failure. The risk of failing to eradicate leukemia is influenced by many variables, including disease phase, molecular lesions of tumor cells, and disparity for major or minor histocompatibility antigens in the donor/recipient pairs. To overcome the hurdle of tumor elusion caused by HLA loss on malignant cells, the use of non–HLA-restricted **chimeric antigen receptors (CARs)** has also been used. This therapeutic strategy is based on genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by leukemic cells. When expressed by T cells, CARs mediate antigen recognition and tumor cytolysis in an MHC-unrestricted fashion and can target any molecule (protein, carbohydrate, or glycolipid) expressed on the surface of tumor cells, thus bypassing one of the major tumor escape mechanisms based on the downregulation of MHC molecules. CARs are composed of an extracellular specific antigen-binding moiety, obtained from the variable regions of a monoclonal antibody, linked together to form a single-chain antibody (scFv), and of an intracellular signaling component derived from the ζ chain of the T-cell receptor (TCR)-CD3 complex. The addition to the *CAR* gene construct of co-stimulation signals and cytokines promoting T-cell expansion and survival improves the antitumor efficiency of the engineered T cells and their survival in the tumor milieu. Gamma retrovirus and lentiviruses are usually used to transduce CARs into T lymphocytes to be employed in the clinical setting. These vectors have been shown to efficiently infect T lymphocytes, integrate into the host genome, and produce robust expression of the gene in human T cells and their progeny.

ACUTE MYELOID LEUKEMIA

Allogeneic HSCT is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (AML) who meet certain high-risk disease criteria. This subset of children with AML in first complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of EFS than those treated with either chemotherapy alone or autologous transplantation. Results obtained in patients given HSCT after either a TBI-containing or a chemotherapy-based preparative regimen are similar. Therefore, for AML, conditioning regimens generally omit the use of TBI because of associated long-term side effects. Children with acute promyelocytic leukemia in

molecular remission at the end of treatment with chemotherapy and all-*trans*-retinoic acid, or with AML and translocation t(8;21) inversion of chromosome 16 (inv16), translocation t(16;16), or normal cytogenetics and presence of *NPM1* or *CEPBα* pathogenic variants are no longer considered eligible for allogeneic HSCT in first complete remission in view of their improved prognosis with alternative treatments. Studies suggest restricting the use of HSCT to those patients with poor molecular lesions, such as FLT3-internal tandem duplication or mixed-lineage leukemia abnormalities, or with high levels of minimal residual disease at the end of induction therapy. Approximately 40–60% of pediatric patients with AML in the second complete remission can be rescued by HSCT. The probabilities of 3-year OS for US patients <18 years of age with AML transplanted in the first or second complete remission is 60–70%. Similar to ALL, inferior results are obtained in patients receiving transplants in more advanced disease phases (30–40%).

CHRONIC MYELOGENOUS LEUKEMIA

For many years, allogeneic HSCT has been considered the only proven curative treatment for children with Philadelphia-positive (Ph+) chronic myelogenous leukemia. Leukemia-free survival of chronic myelogenous leukemia patients after an allograft is 45–80%. The phase of disease (chronic phase, accelerated phase, blast crisis), recipient age, type of donor employed (related or unrelated), and time between diagnosis and HSCT are the main factors influencing the outcome. The best results are obtained in children transplanted during the chronic phase from an HLA-identical sibling within 1 year from diagnosis. Unlike other forms of pediatric leukemia, infusion of donor leukocytes can reinduce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib, nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, has modified the natural history of the disease and thus the indications for transplantation. The indication for HSCT in this population is generally reserved for patients with a poor response to tyrosine kinase inhibitors or those who do not tolerate their side effects.

JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. JMML is characterized by hepatosplenomegaly and organ infiltration, with excessive proliferation of cells of monocytic and granulocytic lineages. Hypersensitivity to granulocyte-macrophage colony-stimulating factor (GM-CSF) and pathologic activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signaling pathway play an important role in the pathophysiology. JMML usually runs an aggressive clinical course, with a median duration of survival for untreated children of <12 months from diagnosis. Rare patients with *CBL1* or *N-RAS* mutations can survive for years without an allograft.

HSCT can cure approximately 50–60% of patients with JMML. Patients who receive a transplant from an unrelated donor have comparable outcome to those given HSCT from an HLA-compatible related donor. Cord blood transplantation represents a suitable alternative option. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, with the relapse rate as high as 40–50%. Because children with JMML frequently have massive spleen enlargement, splenectomy has been performed before transplantation. Spleen size at the time of HSCT and splenectomy before HSCT do not appear to affect the posttransplantation outcome. Donor leukocyte infusion is not useful to rescue patients experiencing disease recurrence; a second allograft can induce sustained remission in approximately 30% of children with JMML relapsing after a first HSCT.

MYELODYSPLASTIC SYNDROMES OTHER THAN JUVENILE MYELOMONOCYTIC LEUKEMIA

Myelodysplastic syndromes are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenia and a propensity to evolve toward AML. HSCT is the treatment of choice for children with **refractory anemia with excess of blasts (RAEB)** and for those with RAEB in transformation (RAEB-t). The probability of survival without evidence of disease for these children is 65–70%. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation is also considered in children with refractory cytopenia associated with monosomy 7, GATA 2 deficiency, complex karyotype, life-threatening infections, profound neutropenia, or transfusion dependency. For children with **refractory cytopenia**, the probability of EFS after HSCT may be as high as 80%, and disease recurrence is rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

NON-HODGKIN LYMPHOMA AND HODGKIN DISEASE

Childhood non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) are very responsive to conventional chemoradiotherapy; some patients have refractory disease or are at high risk for relapse. HSCT can cure a proportion of patients with relapsed NHL and HD and should be offered early after relapse, while the disease is still sensitive to therapy. If an HLA-matched donor is available, allogeneic transplantation can be offered to patients with NHL to take advantage of the GVL effect. Patients with sensitive disease and limited tumor burden have favorable outcomes, with EFS rates of 50–60%. Patients with relapsed or refractory HD do well after autologous HSCT, with EFS of 50–60%. HD patients may also benefit from a GVL effect when given an allograft.

ACQUIRED APLASTIC ANEMIA

Because the probability of long-term survival for a matched-sibling bone marrow transplant (BMT) is reproducibly >80% for children and young adults, BMT is the treatment of choice for children and young adults with acquired severe aplastic anemia. Historically, the treatment of choice for children and young adults without an HLA-matched sibling has been intensive immunosuppression. Because the outcomes of matched unrelated donor transplant for children with acquired aplastic anemia have improved substantially over the years, the use of unrelated donor HSCT upfront *without* prior immunosuppressive therapy is being considered more frequently.

For patients who do not have a matched-sibling donor or well-matched unrelated donor, historically the transplant options were very disappointing. Fortunately, there is hope in using haploidentical transplant for this disease. The use of a reduced intensity conditioning regimen combined with GVHD prophylaxis, including posttransplant cyclophosphamide, have shown significant improvement over prior experiences with survival approaching transplants using well matched unrelated donors.

INHERITED BONE MARROW FAILURE SYNDROMES

Fanconi anemia (FA) and dyskeratosis congenita are genetic disorders associated with a high risk of developing pancytopenia. FA is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA crosslinking agents, including clastogenic compounds such as diepoxybutane, mitomycin C, and melphalan. Patients with FA, along with being at risk for pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, FA patients have an exquisite sensitivity to alkylating agents and radiation therapy. Thus they must be prepared for the allograft with reduced doses of cyclophosphamide and only judicious use of radiation. Many FA patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of posttransplantation head and neck cancers. Low-dose cyclophosphamide combined with fludarabine has been very well tolerated in patients with FA who have a matched-related donor. The addition of low-dose TBI and antithymocyte globulin (ATG) for those with an unrelated donor has shown similar success. Currently, the 5-year OS is >90% in patients with FA who receive HSCT before the transformation to hematologic malignancy. Because of their underlying disorder, however, patients with FA must be monitored closely in

the years after transplant to assess for late effects, including secondary malignancies and endocrinopathies.

Allogeneic HSCT remains the only potentially curative approach for severe bone marrow failure associated with **dyskeratosis congenita**, a rare congenital syndrome characterized also by atrophy and reticular pigmentation of the skin, nail dystrophy, and leukoplakia of mucous membranes. Results of allograft in these patients have been relatively poor, with a 10-year survival of 20–30%, because of both early and late complications, reflecting increased sensitivity of endothelial cells to radiotherapy and alkylating agents.

THALASSEMIA

Conventional treatment (i.e., regular blood transfusion and iron-chelation therapy) has dramatically improved both the survival and the quality of life of patients with thalassemia, changing a previously fatal disease with early death to a chronic, slowly progressive disease compatible with prolonged survival. However, HSCT remains the only curative treatment for patients with thalassemia. In these patients the risk of dying from transplant-related complications depends primarily on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially with chronic active hepatitis, have a poorer outcome than children. Among children, three classes of risk have been identified on the basis of three parameters: regularity of previous iron chelation, liver enlargement, and presence of portal fibrosis. In pediatric patients *without* liver disease who have received regular iron chelation (class 1 patients), the probability of survival with transfusion independence is >90%, whereas for patients with low compliance with iron chelation and signs of severe liver damage (class 3 patients), the probability of survival has been 60%.

With improvements in supportive care and conditioning regimens, even patients with more advanced liver disease have had excellent outcomes (Fig. 177.2). The most effective pharmacologic combinations (e.g., including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported similar to that of HLA-identical sibling recipients. The increased use of umbilical cord blood and haploidentical donors in this population is being explored to expand the number of patients eligible for HSCT. Also, advancements in gene therapy are being made in thalassemia in clinical trials, which may eventually change the approach to this disease.

SICKLE CELL DISEASE

Disease severity varies greatly among patients with sickle cell disease, with 5–20% of the overall population suffering significant morbidity from vasoocclusive crises and pulmonary, renal, or neurologic damage. Hydroxyurea, an agent favoring the synthesis of fetal hemoglobin, reduces the frequency and severity of vasoocclusive crises and improves the quality of life for patients with sickle cell disease; however, allogeneic HSCT is the only curative treatment for this disease currently. Although HSCT can cure homozygous hemoglobin S, hemoglobin Sβ0, or hemoglobin sickle cell disease, selecting appropriate candidates for transplantation is difficult. Patients with sickle cell disease may survive for decades, but some patients have a poor quality of life, with repeated hospitalizations for painful vasoocclusive crises and central nervous system (CNS) infarcts. The main indications for performing HSCT in patients with sickle cell disease are history of strokes or abnormal transcranial Doppler ultrasound, recurrent acute chest syndrome, and/or recurrent vasoocclusive crises. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80–90%. However, the use of alternative donor transplants in this population, including matched unrelated donors and haploidentical donors, is being investigated through a number of clinical trials and may increase the number of patients eligible to undergo potentially curative HSCT. Reduced-intensity and reduced-toxicity regimens are also being explored to further decrease transplant-related morbidity and mortality, although graft failure remains an important issue in this patient population. Gene therapy for sickle cell disease is currently being investigated in clinical trials.

IMMUNODEFICIENCY DISORDERS

HSCT is the treatment of choice for children affected by severe combined immunodeficiency (SCID), as well as for other inherited immunodeficiencies, including Wiskott-Aldrich syndrome, leukocyte adhesion deficiency (LAD), and chronic granulomatous disease (see Table 177.1). With an HLA-identical sibling, the probability of survival approaches 100%, with less favorable results for patients transplanted from an HLA–partially matched relative. Some children with SCID, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen; the donor lymphoid cells are usually the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, hemophagocytic lymphohistiocytosis (HLD), or LAD. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient's outcome after HSCT. Because of this, patients with the most severe immunodeficiencies must be transplanted as early as possible to prevent infectious complications.

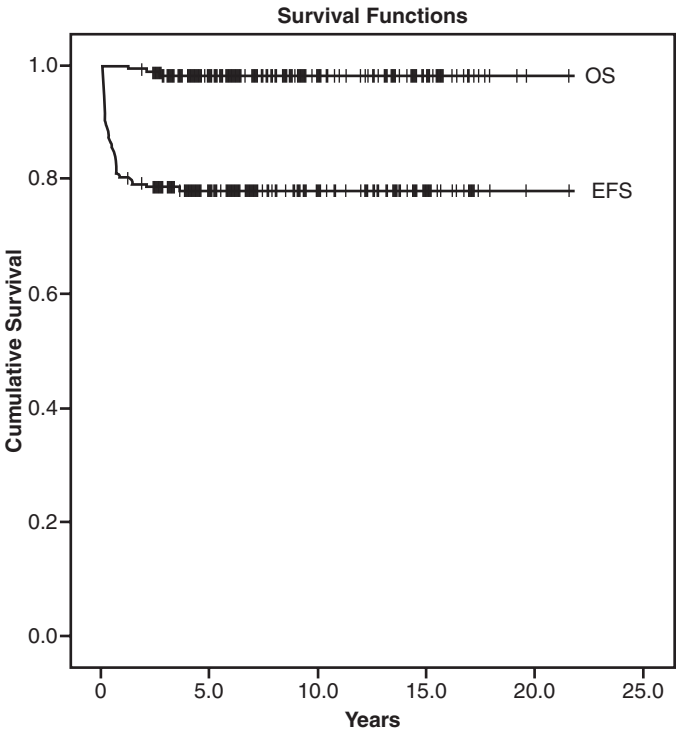

Fig. 177.2 Overall survival (OS) and event-free (graft failure) survival (EFS) after hematopoietic stem cell transplantation in children ≥1 year from transplant for β-thalassemia major. *(From Chaudhury S, Ayas M, Rosen C, et al. A Multicenter Retrospective Analysis Stressing the Importance of Long-Term Follow-Up after Hematopoietic Cell Transplantation for β-Thalassemia. Biol Blood Marrow Transplant. 2017;23(10):1695–1700.)*

INHERITED METABOLIC DISEASES

Inherited metabolic diseases are a broad group of diseases that result from the accumulation of substrate within tissues caused by dysfunction of the lysosome or peroxisome. The use of HSCT has been established for a variety of inherited metabolic diseases, including mucopolysaccharidosis type 1 (Hurler syndrome) and adrenoleukodystrophy (ALD). Although some of these diseases are treatable with exogenous enzyme replacement therapy, the clinical manifestations of disease tend to progress over time, especially disease in the CNS, where enzyme is unable to be reliably delivered. It is thought that undergoing HSCT results in the engraftment of microglial cells that are able to provide new enzyme to the areas where enzyme replacement therapy, if available, cannot have a substantial impact. Multiple studies have shown significantly improved outcomes for patients who are diagnosed with their underlying conditions relatively early and are able to undergo HSCT expeditiously, before significant damage from accumulated substrate that may be irreversible.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 178

Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors

Rachel A. Phelan and David Margolis

Two thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available HLA-identical sibling. Alternative sources of hematopoietic stem cells (HSCs) are being increasingly used and include **matched unrelated donors, unrelated umbilical cord blood**, and **HLA-haploidentical relatives**. Each of these three options has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary strategies to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation; patient-, disease-, and transplant-related factors; center experience; and physician preference.

UNRELATED DONOR TRANSPLANTS

One of the most widely used strategies for children who need an allograft and do not have an available HLA-identical sibling is to identify an unrelated HLA-matched donor in a registry. Worldwide international registries include almost 27 million HLA-typed volunteer donors. HLA-A, HLA-B, HLA-C class I loci, and the DRB1 class II locus are the HLA loci that most influence outcome after HSCT from an unrelated volunteer. Other class II loci (namely, DQB1 and DP1 loci), as well as **killer cell immunoglobulin-like receptor (KIR)** haplotypes, are also increasingly considered when choosing a donor, although their impact on outcome is less well elucidated.

Although in the past serologic (low-resolution) typing was used for HLA-A and HLA-B loci, currently the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, HLA-B, HLA-C, and -DRB1. The chance of finding an HLA-matched unrelated donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors. Data from the National Marrow Donor Program (NMDP) donor registry and banked cord blood units estimated that essentially every patient in need of a transplant would be able to find a donor in a timely fashion, despite the recipient's race/ethnic group, donor availability, and cell dose. However, many of those patients may not have access to an "ideal" graft, defined as HLA matching of a minimum of 8/8 for bone marrow and 6/6 for cord blood.

Initially, HLA polymorphism and the intrinsic limitations of conventional (i.e., serologic) HLA-typing techniques unfavorably affected the accuracy of matching, thus increasing rejection rates and the incidence of acute and chronic graft-versus-host disease (GVHD). The advent of both high-resolution molecular HLA classes I and II loci typing coupled with progress in the prophylaxis and treatment of GVHD has resulted in a reduction of transplantation-related mortality and improvement in outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling. The outcomes of haploidentical transplantation are similarly reaching that of matched unrelated donors as well as matched sibling donors.

Although a single locus disparity in patients with leukemia may be seen as beneficial by a reduction in the relapse rate caused by the graft-versus-leukemia (GVL) effect, in patients with nonmalignant disorders in whom GVL is not beneficial, optimal results are obtained only when a donor matched at the allelic level with the recipient is selected. In general, a single HLA disparity in the donor-recipient pair, irrespective of whether antigenic or allelic in nature, predicts a greater risk of nonleukemia mortality; multiple allelic disparities at different HLA loci have an additive detrimental effect and are associated with an even worse outcome. To reduce the risk of acute GVHD, *ex vivo T-cell depletion of the graft* has been employed, with variable efficacy. Studies are looking at selectively depleting donor α/β T cells, which are the T cells that drive GVHD, while preserving the T cells and natural killer (NK) cells, which may be responsible for GVL and protection from infection.

Although the majority of patients who have required a matched unrelated donor transplant have received a bone marrow or peripheral stem cell graft, for patients who urgently need a transplant, the time required to identify a suitable donor from a potential panel, establish eligibility, and harvest the cells may lead to relapse and failure to transplant. For this subset of patients who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

UMBILICAL CORD BLOOD TRANSPLANTS

Umbilical cord blood transplantation (UCBT) is a viable option for children who need allogeneic HSCT. UCBT offers the advantages of absence of risks to donors, reduced risk of transmitting infections, and for transplants from unrelated donors, immediate availability of cryopreserved cells, with the median time from start of search to transplantation of only 3-4 weeks. Compared with bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence of chronic GVHD and the possibility of using donors showing HLA disparities with the recipient. Despite these advantages, the large experience gained over the last 2 decades has demonstrated that UCBT patients may be exposed to an increased risk of early fatal complications, mainly because of a lower engraftment rate of donor hematopoiesis, delayed kinetics of neutrophil recovery (risk of infection), and lack of adoptive transfer of pathogen-specific memory T cells. Transfer of donor-derived, memory T cells significantly contributes to early immunologic reconstitution of children after unmanipulated allogeneic bone marrow or peripheral blood stem cell transplantation.

Concerning the issues of engraftment and hematopoietic recovery, it has been demonstrated that an inverse correlation exists between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes. In particular, engraftment is a major concern when the nucleated cells are $<2.5 \times 10^7$/kg of recipient body weight. Because a cord blood unit usually contains between 1×10^9 and 1.8×10^9 cells, it is not surprising that UCBT has been less frequently employed for adolescents or adults with body weight >40 kg. Indeed, it can be estimated that only 30% of the UCB units available in the bank inventory could suffice for a 75 kg patient, according to the recommended threshold cell dose. Efforts have focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units or infusion of 2 units in the same recipient (i.e., double UCBT) have been explored to improve the results of UCBT. The results of these studies have been mixed, with one large study demonstrating no survival advantage for children and adolescents that receive double UCBT. Preliminary studies of ex vivo expansion of a single umbilical cord sample with UM171, an HSC self-renewal agonist, have suggested improved engraftment, reduced infection, and low rates of severe acute GVHD.

The long-term results of UCB transplants are similar to those after transplantation from other sources of HSCs for pediatric hematologic malignancies. In patients with hematologic malignancies, recipients of UCBT may be transplanted from donors with greater HLA disparities, receive 1-log fewer nucleated cells, have delayed neutrophil and platelet recovery, and show reduced incidence of GVHD compared with children given BMT from unrelated donors. In one study, there were similar rates of acute GVHD, but significantly less chronic GVHD in patients who received UCBT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. Thus, in the absence of an HLA-identical family donor, unrelated UCBT can be considered a suitable option for children with malignant and nonmalignant disorders. Results of UCBT have been of particular interest in children with certain nonmalignant disorders to proceed to transplant quickly and prevent further progression of disease.

HAPLOIDENTICAL TRANSPLANTS

HSCT from an HLA-haploidentical **(haplo-HSCT)** donor offers an immediate source of HSCs to almost all patients who fail to find a matched donor, whether related or unrelated, or a suitable cord blood unit. Indeed, almost all children have at least one haploidentical–3 loci mismatched family member who is promptly available as donor. The few patients who reject the haploidentical transplant also have the advantage of another immediately available donor within the family. Moreover, this may represent an approach that would be attractive in the global health setting, where more sophisticated donor registries and cell-processing techniques are less unavailable.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidentical parental grafts. This can be done ex vivo or in vivo with the use of chemotherapeutic agents before and after cell infusion. The use of post-transplant cyclophosphamide is one such in vivo technique now being widely incorporated into haploidentical transplant regimens. The benefits of T-cell depletion were first demonstrated in transplantation of children with severe combined immunodeficiency (SCID). More than 300 transplants in SCID patients using haploidentical donors have been performed worldwide, with a high rate of long-term partial or complete immune reconstitution.

The elimination of mature T cells from the graft, necessary for preventing GVHD in a context of great immune genetic disparity, results in recipients being unable to benefit from the adoptive transfer of donor memory T lymphocytes, through their peripheral expansion, are the main factor responsible for protection from infections in the first few months after transplantation. A state of profound immunodeficiency lasts for at least 4-6 months after transplantation in haplo-HSCT recipients. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (Epstein-Barr virus [EBV], human cytomegalovirus, *Aspergillus*, adenovirus) have been successfully tested in trials to protect the recipients in the early posttransplant period.

For many years the absence of the T-cell–mediated GVL effect has been considered as rendering the recipients of a T-cell–depleted allograft more susceptible to leukemia relapse. However, it has been demonstrated that a GVL effect displayed by donor NK cells can compensate for this lack of T-specific alloreactivity when an HLA-disparate NK-alloreactive relative is employed as a donor.

Selective approaches of graft manipulation in haploidentical and unrelated donor transplant have also been developed. In particular, promising results have been obtained through a negative depletion of T lymphocytes carrying the α/β chains of the T-cell receptor, which are believed to be the mediators of GVHD. B lymphocytes are also depleted to prevent EBV-related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature NK cells and γ/δ^+ T cells, which can confer a protection against life-threatening infections as well as provide a GVL effect.

The outcomes of haplo-HSCT have been more extensively reported in adults than in children. The reported probability of survival at 3-4 yr after a haplo-HSCT in children with acute leukemia ranged from 18–48%. Survival was influenced by many factors, most importantly the state of remission at transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. In haplotype-mismatched parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates compared with recipients of paternal grafts, translating into better event-free survival.

DONOR VERSUS RECIPIENT NK CELL ALLOREACTIVITY

NK cells are the first lymphocytes derived from the donor to recover after allogeneic HCT. Donor versus recipient NK cell alloreactivity derives from a mismatch between donor NK clones, carrying specific inhibitory receptors for self–major histocompatibility complex (MHC) class I molecules, and MHC class I ligands on recipient cells. NK cells are primed to kill by several activating receptors, which play an important role in the NK cell–mediated GVL effect. Human NK cells discriminate allelic forms of MHC molecules via **KIRs,** which are clonally distributed with each cell in the repertoire bearing at least one receptor that is specific for self-MHC class I molecules. Because NK cells co-express inhibitory receptors for self–MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets, NK cells sense the missing expression of self–class I alleles and mediate alloreactions. In mismatched transplants, there are many donor recipient pairs in which the donor NK inhibitory cells do not recognize the recipient's class I alleles as self. Consequently, the donor NK cells are not blocked and are activated to lyse the recipient's lymphohematopoietic cells.

Haplo-HSCT trials demonstrate that MHC class I mismatches, which generate an alloreactive NK cell response in the graft-versus-host direction, eradicate leukemia cells, improve engraftment, and protect from T-cell–mediated GVHD. The potential for donor versus recipient NK cell alloreactivity, which can be predicted by standard HLA typing, is increasingly being examined when selecting the donor of choice. The importance of KIR haplotype in transplants other than haploidentical transplantation in preventing GVHD as well as relapse has been shown to be increasingly beneficial.

Table 178.1 Indications for Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Autologous transplantation, using the patient's own stored marrow, is associated with a low risk of life-threatening transplant-related complications, although the main cause of failure is disease recurrence. Bone marrow was once the only source of stem cells employed in patients given an autograft. The majority of patients treated with autologous HSCT receive hematopoietic progenitors mobilized in peripheral blood by either cytokines alone (mainly granulocyte colony-stimulating factor) or by cytokines plus cytotoxic agents. A CXCR4 antagonist can be extremely effective in mobilizing hematopoietic progenitors in the periphery. Compared with bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome.

Autologous HSCT is employed primarily for selected children with relapsed lymphomas and select solid tumors (Table 178.1).

Patients with sensitive lymphomas and minimal tumor burden have favorable outcomes after autologous HSCT, with disease-free survival rates of 50–60%, whereas high-risk patients with bulky tumor or poorly responsive disease have a poor outcome, with survival rates of 10–20%.

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome than conventional chemotherapy. A Children's Oncology Group (COG) study demonstrated further survival advantage by performing two sequential, or tandem, transplants that use different chemotherapeutic agents. Because of these improved outcomes, tandem autologous transplants are now considered the standard recommended treatment. In these patients, posttransplantation infusion of a monoclonal antibody directed against a molecule (GD2) expressed on the surface of neuroblastoma cells confers a protection against the risk of tumor recurrence.

For children with brain tumors at high risk of relapse, or resistant to conventional chemotherapy and irradiation, the dose-limiting toxicity for intensifying therapy is myelosuppression, thus providing a role for stem cell rescue. Several studies provide encouraging results for patients with different histologic types of brain tumors treated with autologous HSCT.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography

Chapter 179

Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Rachel A. Phelan and David Margolis

A major cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (HSCT) is **graft-versus-host disease (GVHD)**, which is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host who shows histocompatibility differences with the donor. These differences between the donor and the host may result in donor T-cell activation against either recipient major histocompatibility complex (MHC) antigens or minor histocompatibility antigens. GVHD is usually subdivided in two forms: **acute GVHD**, which occurs within 3 months after transplantation, and **chronic GVHD**, which, although related, is a different disease, occurring later and displaying some clinical and pathologic features that resemble those observed in selected autoimmune disorders (e.g., systemic sclerosis, Sjögren syndrome).

ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD is caused by the alloreactive, donor-derived T cells contained in the graft, which attack nonshared recipient's antigens on target tissues. A 3-step process generates the clinical syndrome. First, conditioning-induced tissue damage activates recipient antigen-presenting cells, which present recipient alloantigens to the donor T cells transferred with the graft and secrete **cytokines**, such as interleukin (IL)-12, favoring the polarization of T-cell response in the type 1 direction. Second, in response to recipient antigens, donor T cells become activated, proliferate, expand, and generate cytokines such as tumor necrosis factor (TNF)-α, IL-2, and interferon (IFN)-γ. In the third step of the process, these cytokines cause tissue damage and promote differentiation of cytotoxic $CD8^+$ T cells, which, together with macrophages, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops 2-8 weeks after transplantation. The primary manifestations depend on the sites of involvement and may include an erythematous maculopapular rash (Figs. 179.1 and 179.2), persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). Diagnosis may benefit from skin, liver, or gastrointestinal (GI) biopsy for confirmation. Endothelial damage and lymphocytic infiltrates are seen in all affected organs. The epidermis and hair follicles of the skin are damaged, the hepatic small bile ducts show segmental disruption, and there is destruction of the crypts and mucosal ulceration of the GI tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often requires no treatment, or topical treatment alone. Grade II GVHD is a moderately severe multiorgan disease requiring immunosuppressive therapy. Grade III GVHD is a severe multiorgan disease, and grade IV GVHD is a life-threatening, often fatal condition (Table 179.1).

The standard pharmacologic prophylaxis of GVHD after an unmanipulated allograft relies mainly on posttransplant administration of immunosuppressive drugs, such as cyclosporine or tacrolimus or combinations of either with methotrexate or prednisone, anti–T-cell antibodies, mycophenolate mofetil (MMF), and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +4 after transplantation has been used as a strategy to deplete alloreactive donor T lymphocytes that become activated after exposure to recipient antigens. This approach has been successful in patients undergoing haploidentical transplantation. Pretransplantation infusion of either antithymocyte globulin (ATG) or monoclonal antibodies (mAbs) such as alemtuzumab is largely used to modulate alloreactivity of donor T cells, in particular in patients given the allograft from either an unrelated donor or a partially matched relative. An alternative approach is the removal of T lymphocytes from the graft **(T-cell depletion)**. Other approaches are being used to selectively remove the α/β T cells, which are thought to be responsible for the development of GVHD, while preserving the γ/δ T cells in order to sustain graft-versus-leukemia (GVL) and the ability to fight infection. Any form of GVHD prophylaxis may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. Traditional T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from an HLA-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in approximately 30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. These numbers are estimates, and the actual risk of acute GVHD is highly variable depending on several factors. Risk for development of GVHD is increased by diagnosis of malignant disease, older donor and recipient age, and in patients given an unmanipulated allograft. The most important risk factor for acute GVHD is the presence of disparities for HLA molecules in the donor-recipient pair.

Acute GVHD is usually initially treated with glucocorticoids; approximately 40–50% of patients show a complete response to



Fig. 179.1 Acute graft-versus-host disease. Involvement of the scalp, ears, palms, and soles is common. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier, 2016. p 577.*)



Fig. 179.2 Acute graft-versus-host disease. Almost confluent eruption of erythematous macules and papules in an immunodeficient neonate treated with extracorporeal membrane oxygenation (ECMO) and transfusion of nonirradiated blood. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier; 2016. p 577.*)

Table 179.1 Clinical Staging and Grading* of Acute Graft-Versus-Host Disease

STAGE	SKIN (ACTIVE ERYTHEMA ONLY)	LIVER (BILIRUBIN)	UPPER GI	LOWER GI (STOOL OUTPUT/DAY)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	*Adult:* <500 mL/day or <3 episodes/day *Child:* <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	*Adult:* 500-999 mL/day or 3-4 episodes/day *Child:* 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1-6 mg/dL		*Adult:* 1,000-1,500 mL/day or 5-7 episodes/day *Child:* 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		*Adult:* >1,500 mL/day or >7 episodes/day *Child:* >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

*Overall clinical grade (based on most severe target organ involvement):
Grade 0: no stage 1-4 of any organ.
Grade I: stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.
GI, Gastrointestinal; GVH, graft-versus-host; BSA, body surface area.
From Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant.* 2016;22(1):4–10.

corticosteroids. The risk of transplantation-related mortality is much higher in patients who do not respond to corticosteroids than in those showing a complete response. Ruxolitinib, targeting the JAK signaling pathway, or other drugs targeting molecules expressed on T cells or cytokines released during the inflammatory cascade (including infliximab and etanercept targeting TNF, vedolizumab targeting $\alpha_4\beta_7$-integrin, and tocilizumab targeting IL-6), which underlies the pathophysiology of GVHD, have been used in patients with steroid-resistant acute GVHD. Extracorporeal photopheresis is another second-line treatment for GVHD and is most efficacious for skin GVHD. A patient's peripheral blood is exposed to a photosensitive compound and then exposed to ultraviolet light. The cells are then reinfused into the patient. It is thought that this process results in an increase in apoptosis of lymphocytes responsible for GVHD as well as the upregulation of anti-inflammatory cytokines and regulatory T cells. Promising results in children with steroid-resistant acute GVHD have also been obtained using **mesenchymal stromal cells**, which are able to blunt the inflammatory response associated with acute GVHD.

CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic GVHD develops or persists >3 months after transplantation and is the most frequent late complication of allogeneic HSCT with an incidence of approximately 25% in pediatric patients. Chronic GVHD is the major cause of nonrelapse mortality and morbidity in long-term HSCT survivors. Acute GVHD is recognized as the most important factor predicting the development of the chronic form of the disease. The use of matched unrelated volunteers as donors and use of unmanipulated peripheral blood as the stem cell source have increased the incidence and severity of chronic GVHD. Other factors that predict occurrence of chronic GVHD include older donor and recipient ages, female donor for male recipient, diagnosis of malignancy, and use of total body irradiation (TBI) as part of the preparative regimen.

Chronic GVHD is a disorder of immune regulation characterized by autoantibody production, increased collagen deposition and fibrosis, and clinical symptoms similar to those seen in patients with autoimmune diseases (Table 179.2). The predominant cytokines involved in the pathophysiology of chronic GVHD are usually

Table 179.2 Clinical Findings in Chronic Graft-Versus-Host Disease

ORGAN SYSTEM	SYMPTOMS AND SIGNS
Systemic	Immunodeficiency and recurrent infections
Skin	Lichen planus, scleroderma, hyperpigmentation or hypopigmentation, erythema, freckling, ichthyosis, ulcerations Flexion contractures Vaginal scars Onycholysis Nail loss
Hair	Alopecia; scarring or nonscarring
Mouth	Sicca syndrome, lichen planus, depapillation of tongue with variegations, scalloping of lateral margins, xerostomia, mucocele
Joints	Diffuse myositis/tendonitis, arthritis, contractures
Eyes	Decreased tearing, injected sclerae, scarring conjunctivitis, keratopathy
Liver	Increased enzymes, cholestasis, hepatomegaly, cirrhosis
Gastrointestinal	Failure to thrive, malabsorption, chronic diarrhea Esophageal strictures
Lung	Cough, dyspnea, wheezing Bronchiolitis obliterans, chronic rales, pneumothorax, fibrosis
Hematology	Thrombocytopenia, eosinophilia, Howell-Jolly bodies (splenic dysfunction)

type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia and B-cell hyperactivity with elevated IgM, IgG, and IgE titers. Associated monoclonal gammopathies indicate clonal dysregulation. Chronic GVHD is dependent on the development and persistence of donor T cells that are not tolerant to the recipient. Maturation of transplanted stem cells within a damaged thymus could lead to errors in negative selection and production of cells that have not been tolerized to recipient antigens and are therefore autoreactive or, more accurately, **recipient reactive**. This ongoing immune reactivity results in clinical features resembling a systemic autoimmune disease with lichenoid and sclerodermatous skin lesions, malar rash, sicca syndrome, arthritis, joint contractures, bronchiolitis obliterans, and bile duct degeneration with cholestasis.

Patients with chronic GVHD involving only the skin and liver have a favorable course (Figs. 179.3 and 179.4). Extensive multiorgan disease may be associated with a very poor quality of life, recurrent infections associated with prolonged immunosuppressive regimens to control GVHD, and a high mortality rate. Morbidity and mortality are highest in patients with a progressive onset of chronic GVHD that directly follows acute GVHD, intermediate in those with a **quiescent onset** after resolution of acute GVHD, and lowest in patients with **de novo onset** in the absence of acute GVHD. Chronic GVHD can be classified as mild, moderate, or severe depending on extent of involvement. Single-agent prednisone is the standard treatment, although other agents have been employed with variable success. Ruxolitinib, a Janus kinase inhibitor, has been a beneficial treatment for steroid-dependent or refractory chronic GVHD. In addition, ibrutinib, a Bruton tyrosine kinase inhibitor, has been approved by the FDA for the treatment of chronic GVHD. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been effective in some patients with chronic GVHD and sclerotic features. As a consequence of prolonged immunosuppression, patients with chronic GVHD are particularly susceptible to infections and should receive appropriate antibiotic prophylaxis, including trimethoprim/sulfamethoxazole (TMP/SMX). Chronic GVHD resolves in most pediatric patients but may require 1-3 years of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes the development of secondary neoplasms, in particular in patients with Fanconi anemia, and has a significant impact on quality of life.



Fig. 179.3 Chronic graft-versus-host disease (GVHD), lichenoid. After bone marrow transplantation, this patient had acute GVHD and subsequently developed cutaneous scaling papules and plaques typical of lichen planus. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier; 2016. p 577.*)



Fig. 179.4 Chronic graft-versus-host disease. Note the extensive alopecia of the scalp with dyschromia and numerous sclerodermatous plaques of the scalp and back. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier; 2016. p 579.*)

GRAFT FAILURE

Graft failure is a serious complication exposing patients to a high risk of fatal infection. **Primary graft failure** is defined as failure to achieve a neutrophil count of 0.5×10^9/L after transplantation. **Secondary graft failure** is loss of peripheral blood counts following initial transient engraftment of donor cells. Causes of graft failure after autologous and allogeneic transplantation include transplantation of an inadequate stem cell dose (more frequently observed in children given cord blood transplantation) and viral infections such as with cytomegalovirus or human herpesvirus type 6, which are often associated with activation of recipient macrophages. Graft failure after allogeneic transplantation, however, is mainly caused by immunologically mediated rejection of the graft by residual recipient-type T cells that survive the conditioning regimen.

Diagnosis of graft failure resulting from immunologic mechanisms is based on examination of peripheral blood and marrow aspirate and biopsy, along with molecular analysis of chimerism status. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic rejection. The risk of immune-mediated graft rejection is higher in patients given HLA-disparate, T-cell–depleted grafts, reduced-intensity conditioning regimens, and transplantation of low numbers of stem cells, and in recipients who are sensitized toward major HLA antigens or, less frequently, minor histocompatibility antigens. Allosensitization develops as a consequence of preceding blood product transfusions and is observed particularly in recipients with aplastic anemia, sickle cell disease, and thalassemia. In HSCT for nonmalignant diseases, such as mucopolysaccharidoses, graft failure is also facilitated by the absence of previous treatment with cytotoxic and immunosuppressive drugs. In thalassemia, graft failure is promoted by expansion of recipient hematopoietic cells. GVHD prophylaxis with methotrexate, an antimetabolite, and antiinfective prophylaxis with TMP/SMX or ganciclovir may also delay engraftment.

Treatment of graft failure usually requires removing all potentially myelotoxic agents from the treatment regimen and attempting a short trial of hematopoietic growth factors, such as granulocyte colony-stimulating factor. A second transplant, usually preceded

Table 179.3 Severity Grading Thresholds of Sinusoidal Obstructive Syndrome Among Children, Adolescents, and Young Adults

	MILD	MODERATE	SEVERE	VERY SEVERE
ALT, AST, GLDH (mg/dL)	<2× normal	2-5× normal	2-5× normal	>5× normal
Bilirubin (mg/dL)	<2	<2	≥2	Bilirubin doubles in 48 hr
Coagulopathy (not responsive to vitamin K administration; INR)	<1.5	1.5-1.9	>2	Need for replacement of coagulation factors
Ascites	Mild (minimal fluid by liver, spleen or pelvis)	Moderate (<1 cm fluid)	Severe (fluid in all 3 regions with >1 cm fluid in at least 2 regions)	Requires paracentesis
Weight gain (from baseline)	2.5%	5–10% despite diuretic use	>10%	Persistent rise
Renal function score	KDIGO 1: serum creatinine 1.5-1.9× baseline or ≥0.3 mg/dL (≥26.5 mmol/L) increase or urine output <0.5 mL/kg/hr for 6-12 hr	KDIGO 2: serum creatinine 2.0-2.9× baseline or urine output <0.5 mL/kg/hr for ≥12 hr	KDIGO 3: serum creatinine 3.0× baseline or increase in serum creatinine ≥4.0-mg/dL (≥353.6 mmol/L) or initiation of renal replacement therapy or decrease in eGFR to <35 mL/min per 1.73 m^2 (patients <18 years) or urine output <0.3 mL/kg/hr for ≥24 hr or anuria for ≥12 hr (patients <18 years)	Persistent need for renal replacement therapy
Encephalopathy	CAPD <9	CAPD <9	CAPD ≥9	CAPD ≥9
Persistent RT	<3 days	3-7 days	—	>7 days
Pulmonary function	<2 L	<2 L	NIV/IMV	IMV

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; GLDH, glutamate dehydrogenase; INR, international normalized ratio; KDIGO, Kidney Disease: Improving Global Outcomes score; eGFR, estimated glomerular infiltration rate; CAPD, Cornell Assessment of Pediatric Delirium; RT, refractory thrombocytopenia; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation.

From Mahadeo KM, Bajwa R, Abdel-Azim H, et al. Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syndrome: An international expert position statement. *Lancet Haematol*. 2020;7(1):e61–e72.

by a highly immunosuppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a first transplant because of cumulative toxicities, but this risk must be balanced with the risk of infection from prolonged neutropenia and lymphocytopenia.

VENOOCCLUSIVE DISEASE

Hepatic venoocclusive disease (VOD), also known as sinusoidal obstruction syndrome, presents with hepatomegaly, right upper quadrant tenderness, jaundice, coagulopathy, thrombocytopenia, and weight gain from fluid retention and ascites (Table 179.3). It results from endothelial damage within the liver, which can then progress to multiorgan dysfunction. Onset is usually within 30 days of transplantation, with an incidence of approximately 15%, depending on the intensity of the conditioning protocol. Risk factors include young age, prior hepatic disease (fibrosis, cirrhosis), abdominal radiation, repeated transplantations, neuroblastoma, osteopetrosis, and familial hemophagocytic lymphohistiocytosis. The severe form of VOD has a high mortality rate (>80%) without treatment.

Prophylaxis has traditionally used ursodeoxycholic acid and occasionally heparin; only **defibrotide** has demonstrated efficacy in treating VOD. A phase 3 study demonstrated improvement in survival and response rate to VOD in patients treated with defibrotide. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells. Defibrotide is FDA approved for the treatment of VOD in adult and pediatric patients with renal or pulmonary dysfunction after HSCT. Defibrotide is often used as prophylaxis in Europe, with data showing efficacy, but this use is not yet approved in the United States.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 180

Infectious Complications of Hematopoietic Stem Cell Transplantation

Anna R. Huppler

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. The risk of infection depends on the stage after transplantation (pre- vs postengraftment), ongoing immunosuppression, disruption in barrier functions (indwelling catheters, graft-versus-host disease [GVHD], mucositis, and preexisting infections (Fig. 180.1). Management approaches may include the use of prophylactic antimicrobials, preemptive antimicrobials for infection prior to symptomatic disease, or antimicrobial treatment of documented or suspected infection.

Immediately after transplantation, the absence or paucity of neutrophils **(neutropenia)** renders patients susceptible to bacterial and fungal infections. Consequently, consideration is given to the use of antipseudomonal and antifungal prophylaxis during the conditioning regimen. Evidence is moderate quality against systemic antibacterial prophylaxis and for systemic antifungal prophylaxis, which is reflected in published society guidelines. Even with the use of prophylactic measures, the majority of patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric gram-negative bacteria and fungi. An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for infection. Staphylococcal species and *Candida* species are the most frequent pathogens in catheter-related infections (see Chapter 224). Multidrug-resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* can cause infection, with prevalence highly variable among centers. Severe lower respiratory tract disease caused by seasonal respiratory viruses, such as influenza, respiratory syncytial virus (RSV), parainfluenza virus, and human metapneumovirus, can occur during the pre- or postengraftment phase. Emerging infections, such as SARS-CoV-2, can also cause severe or persistent infection in immunocompromised individuals. Published guidelines from the International Pediatric Fever and Neutropenia Guideline Panel address the management of fever and neutropenia after HSCT (Table 180.1).

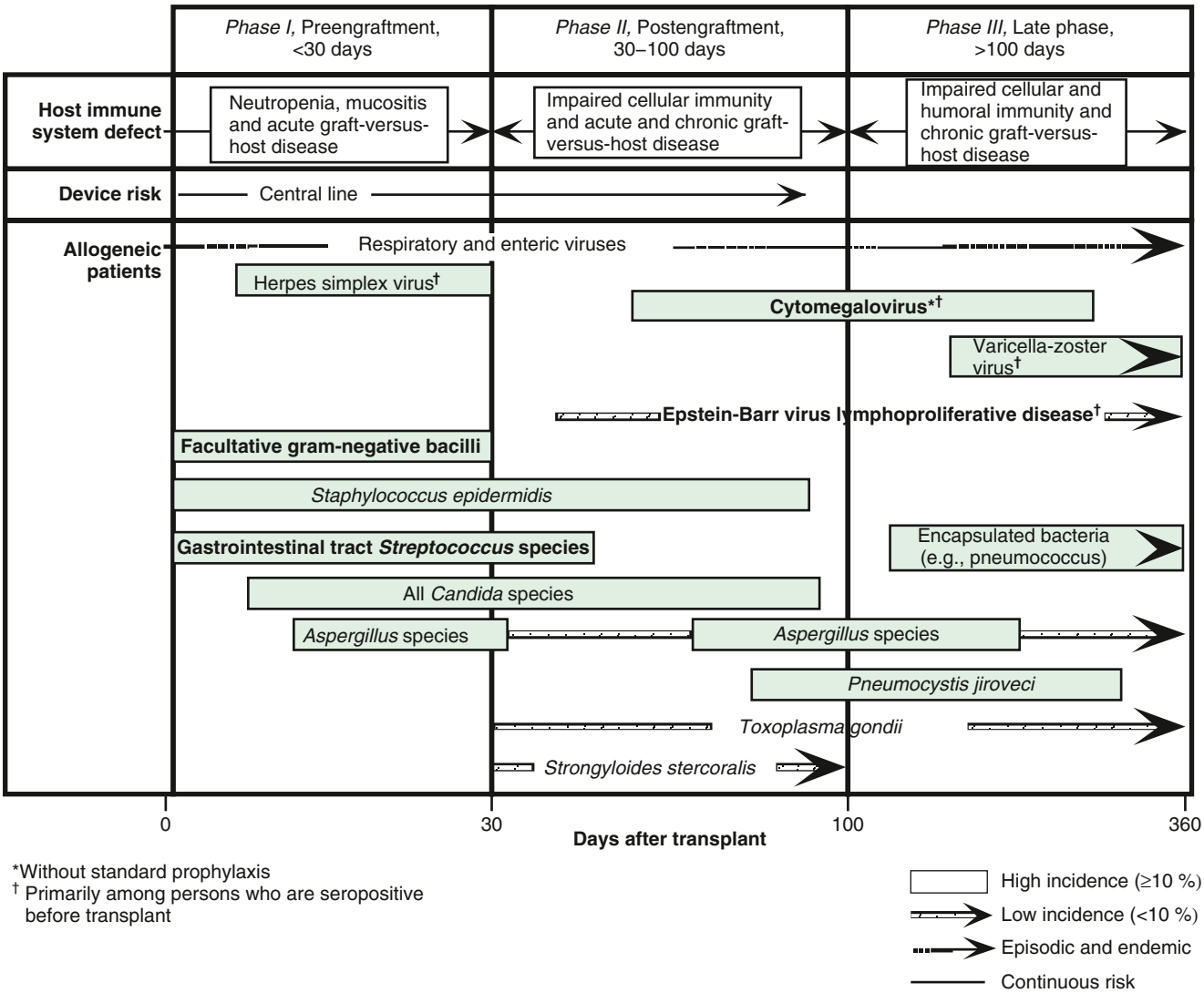

Fig. 180.1 Phases of opportunistic infections among allogeneic HSCT recipients. (*From Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients [published correction appears in MMWR Recomm Rep. 2004 May 14;53(19):396]. MMWR Recomm Rep. 2000;49(RR-10):1–CE7.*)

Table 180.1 Overall Summary of Recommendations for Management of Fever and Neutropenia

INITIAL MANAGEMENT

Risk Stratification

A1. Adopt a validated risk stratification strategy and incorporate it into routine clinical management (strong recommendation, low-quality evidence).

Evaluation

A2. Obtain blood cultures at the onset of FN from all lumens of central venous catheters (strong recommendation, low-quality evidence).

A3. Consider obtaining peripheral blood cultures concurrent with central venous catheter cultures (weak recommendation, moderate-quality evidence).

A4. Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available (weak recommendation, low-quality evidence).

A5. Obtain chest radiography only in patients with respiratory signs or symptoms (strong recommendation, moderate-quality evidence).

Treatment

A6. In high-risk FN:

A6a. Use monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk FN (strong recommendation, high-quality evidence).

A6b. Reserve addition of a second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (strong recommendation, moderate-quality evidence).

A7. In low-risk FN:

A7a. Consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (weak recommendation, moderate-quality evidence).

A7b. Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (weak recommendation, moderate-quality evidence).

ONGOING MANAGEMENT

Modification of Treatment

B1. In patients who are responding to initial empirical antibiotic therapy, discontinue double coverage for gram-negative infection or empirical glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (strong recommendation, moderate-quality evidence).

B2. Do not modify the initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable (strong recommendation, low-quality evidence).

B3. In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (strong recommendation, very low-quality evidence).

Cessation of Treatment

B4. In all patients, discontinue empirical antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery (strong recommendation, low-quality evidence).

B5. In patients with low-risk FN, consider discontinuation of empirical antibiotics at 72 hours in patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured (weak recommendation, moderate-quality evidence).

EMPIRICAL ANTIFUNGAL THERAPY

Risk Stratification

C1. Patients at high risk of IFD are those with AML, high-risk ALL, or relapsed acute leukemia, and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of IFD. All others should be categorized as IFD low risk (strong recommendation, low-quality evidence).

Evaluation

C2. In terms of biomarkers to guide empirical antifungal management for prolonged (≥96 hours) FN in IFD high-risk patients:

C2a. Consider not using serum GM (weak recommendation, moderate-quality evidence).

C2b. Do not use β-d-glucan (strong recommendation, low-quality evidence).

C2c. Do not use fungal PCR testing in blood (strong recommendation, moderate-quality evidence).

C3. In terms of imaging for the evaluation of prolonged (≥96 hours) FN in IFD high-risk patients:

C3a. Perform CT of the lungs (strong recommendation, low-quality evidence).

C3b. Consider imaging of abdomen in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).

C3c. Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).

Table 180.1 Overall Summary of Recommendations for Management of Fever and Neutropenia—cont'd

Treatment

C4. In IFD high-risk patients with prolonged (≥96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy (strong recommendation, high-quality evidence).

C5. In IFD low-risk patients with prolonged (≥96 hours) FN, consider withholding empirical antifungal therapy (weak recommendation, low-quality evidence).

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; FN, fever and neutropenia; GM, galactomannan; HSCT, hematopoietic stem cell transplantation; IFD, invasive fungal disease; PCR, polymerase chain reaction.

Modified from Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 Update. *J Clin Oncol.* 2017;35(18):2082–2094. Table 1, p. 2084–2086.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized because of prolonged depression in T-cell number and function. The manifestations of GVHD, as well as the associated immunosuppressive therapy, are additional risk factors for fungal and viral opportunistic infections. After umbilical cord blood transplant (UCBT), infections are the consequence of both slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, T-cell depletion results in an increased risk of infection in the first 4-6 months. Recipients of this type of transplantation, as well as those receiving UCBT, do not have the benefit of adoptive transfer of donor-derived, antigen-experienced T cells. For HSCT recipients after engraftment, **invasive fungal disease (IFD),** herpesviruses, and adenovirus infections represent life-threatening complications that significantly affect outcomes. Additional pathogens to consider include nontuberculous mycobacteria, BK virus, *Clostridium difficile,* and norovirus.

IFD remains a significant cause of infectious morbidity and mortality in allogeneic HSCT recipients. Empirical treatment for IFD is considered for HSCT patients with persistent fever despite 96 hours of broad-spectrum antibiotic treatment. The most common organisms are *Aspergillus* and *Candida* species. Infections also occur with non-*Aspergillus* molds, including *Mucor* and *Rhizopus* species (among other agents of mucormycosis), *Fusarium,* and *Scedosporium* species. *Pneumocystis jiroveci* is a unique, noncultivatable cause of fungal pneumonia in immunocompromised patients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of IFD carry case fatality rates of 20–70%. IFD can present early after transplant, although there is a shift toward presentation of infection in the postengraftment period in the presence of GVHD. The risk of developing IFD is mainly influenced by history of previous fungal infection, duration of neutropenia, use of corticosteroid therapy, mucosal tissue damage (GVHD, posttransplant cytomegalovirus [CMV] infection, viral respiratory tract infections), and for candidiasis, presence of central venous catheters.

Disseminated candidiasis presents frequently as a central venous catheter–associated infection. However, up to 50% of patients with disseminated candidiasis do not present with positive blood cultures. Patients with and without candidemia can have infection of normally sterile organs, including liver, spleen, kidney, brain, heart, and eye. Mortality rates in pediatric series range from 10–25%. Echinocandins (micafungin, caspofungin) are the initial drugs of choice for candidiasis in immunocompromised patients with pediatric data supporting reduced 14-day failure rates compared to initial triazole or amphotericin B therapy.

Pulmonary disease is the common presentation of invasive **aspergillosis**. The upper airway mucosa (nose and sinuses) can also be a site of initial infection. Infection progresses from lung or sinus sites by direct extension across tissue or angioinvasion resulting in hematogenous dissemination to brain and other organs. The earliest imaging finding is classically one or more small pulmonary nodules (Figs. 180.2 and 180.3). As a nodule enlarges, the dense central core of infarcted tissue may become surrounded by edema or hemorrhage, forming a hazy rim known as the *halo sign.* When bone marrow function recovers, the infarcted central core may cavitate, creating the *crescent sign.* Unfortunately, radiographic signs, including the halo sign, crescent sign, and cavitation, have low sensitivity in pediatric patients. Clinical criteria are used to diagnose proven or probable IFD, requiring direct or indirect microbiologic data. Direct, culture-based diagnosis requires invasive

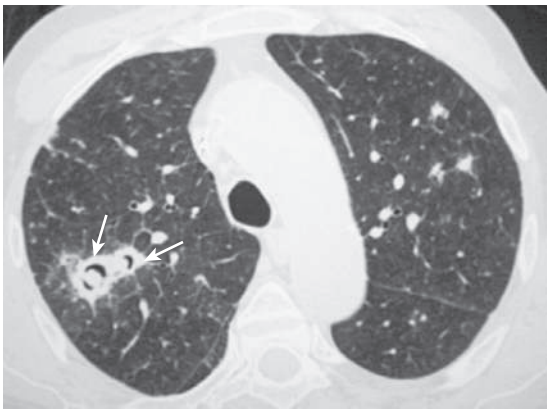

Fig. 180.3 Angioinvasive aspergillosis. CT section at the level of the lower trachea shows a consolidation with an eccentric cavitation and air crescent sign *(arrows).* This finding in this neutropenic patient is highly diagnostic of angioinvasive aspergillosis. (*From Franquet T. Nonneoplastic parenchymal lung disease. In Haaga JR, Boll DT, eds.* CT and MRI of the Whole Body, *6th ed. Philadelphia: Elsevier; 2017. Fig 36.14.*)

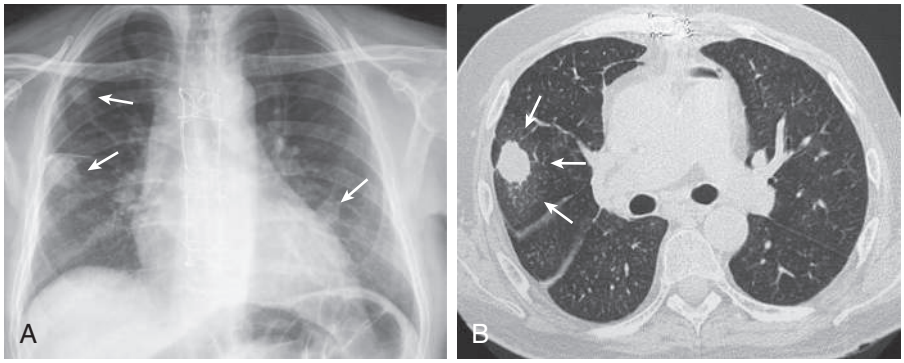

Fig. 180.2 Angioinvasive aspergillosis. **A,** Posteroanterior radiograph shows multiple nodules in the lungs *(arrows).* **B,** CT section at the level of the intermediary bronchus shows a nodule surrounded by a halo of ground-glass attenuation *(arrows).* (*From Franquet T. Nonneoplastic parenchymal lung disease. In Haaga JR, Boll DT, eds.* CT and MRI of the Whole Body, *6th ed. Philadelphia: Elsevier; 2017. Fig 36.13.*)

procedures, such as sinus endoscopy or lung biopsy. Indirect measures, including *fungal biomarkers,* are used in HSCT patients to screen for or diagnose probable aspergillosis. Galactomannan from serum or bronchoalveolar lavage fluid is an adjunct to diagnostic strategies because of a high negative predictive value for aspergillosis; however, lack of detection of mucormycosis limits its utility as a single diagnostic test. Other limitations include poor positive predictive values due to false-positive test results and lack of validation in patients without neutropenia. Another widely available biomarker, (1→3)-β-D-glucan, is insufficiently studied for routine use in pediatric patients.

Fungal infection prevention includes isolation of the patient in a laminar airflow or positive pressure room. Universal prophylaxis to prevent *Pneumocystis* pneumonia is advocated until the return of T-cell function in HSCT patients; the primary agent for prophylaxis is trimethoprim/sulfamethoxazole. Alternative agents are pentamidine, dapsone, and atovaquone. For prevention and treatment of other IFDs, liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole, isavuconazole), and echinocandins (caspofungin, micafungin) are used. Voriconazole represents the treatment of choice for adult patients with invasive aspergillosis, but achieving adequate trough levels can be challenging in young children. The agents of mucormycosis are resistant to most azole and echinocandin medications, which makes liposomal amphotericin B the initial drug of choice. IFD often does not respond satisfactorily to antifungal agents alone, and infection may persist until adequate source control is achieved with surgical debridement and immune function recovers.

Herpesviruses, including CMV, Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), herpes simplex virus (HSV-1 and HSV-2), and varicella-zoster virus (VZV) are pathogens that can cause significant disease after HSCT. Because herpesviruses can establish latency in the human host, symptomatic infection can occur from viral reactivation as well as acquisition from the donor or de novo infection. Baseline susceptibility to disease and viremia before symptom development can be established with laboratory monitoring (pretransplant donor-recipient serology, posttransplant viral load monitoring) and can inform decisions on prophylactic and preemptive antiviral treatment.

CMV infection remains the most common and potentially severe viral complication in patients receiving allogeneic HSCT. Risk factors for CMV viremia include recipient seropositivity, UCBT, and acute GVHD. The period of maximal risk for CMV disease is 1-4 months after transplantation. Late presentation of CMV disease is associated with GVHD. Until CMV-specific T-cell responses develop months after transplant, CMV infection may result in a variety of syndromes, including fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, retinitis, esophagitis, gastritis, and colitis. CMV pneumonia has been reported to occur in up to 15–20% of bone marrow transplant recipients, with a case fatality rate of 85% in the absence of early treatment. Tachypnea, hypoxia, and nonproductive cough signal respiratory involvement. Chest radiography often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon with complications of bleeding or perforation. Fatal CMV infections are often associated with persistent viremia and multiorgan involvement.

CMV disease has largely been prevented through prophylaxis or preemptive approaches. Prophylaxis is based on administration of antiviral drugs to at-risk transplanted patients for a median duration of 3 months after transplantation. The major drawbacks of this approach are drug toxicity, late CMV disease after withdrawal of prophylaxis, potential unnecessary treatment of patients who would not have reactivated CMV infection, and low cost-effectiveness. Preemptive therapy aims at treating only patients who experience CMV reactivation and thus are at risk of developing overt disease; it starts on detection of CMV in blood but before symptom development. The major drawback of this strategy is the need of serial monitoring of CMV by polymerase chain reaction (PCR) in blood. First-line therapy is usually ganciclovir, with foscarnet as an alternative for resistant strains or ganciclovir intolerance.

EBV-related posttransplant lymphoproliferative disease (PTLD) is a major complication in HSCT and solid-organ transplantation. In patients receiving HSCT, selective procedures of T-cell depletion–sparing B lymphocytes and use of HLA–partially matched family and unrelated donors are risk factors for the development of PTLD. PTLD usually presents in the first 4-6 months after transplantation as high-grade, diffuse, large-cell B-cell lymphomas that are oligoclonal or monoclonal. High EBV viral loads in blood by PCR predict development of PTLD. Standard treatment of PTLD includes the reduction of immunosuppression, monoclonal antibodies directed against CD20 on B cells (rituximab), or cytotoxic chemotherapy. Prophylactic strategies with rituximab for EBV-positive recipients during conditioning for HSCT have also been employed. Histologic diagnosis of PTLD is required to assess for the emergence of neoplasms in which cells are $CD19^+$ but $CD20^-$, thus eliminating susceptibility to rituximab.

Disseminated adenovirus infection is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children or recipients of donor cells naïve to adenovirus (T-cell–depleted grafts or UCBT) are at particular risk of developing this complication. Diagnosis is based on the demonstration of high viral loads by PCR in blood or recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is with the antiviral **cidofovir**, which has significant renal toxicity and limited potency at controlling viral replication. The enterally available prodrug brincidofovir showed initial promise in allogeneic pediatric HSCT recipients with refractory adenovirus infection but is not available clinically for this indication. Recovery of immune system function is associated with improved survival with disseminated adenovirus infection.

In immunocompromised hosts, severe viral infections, including PTLD and adenovirus infection, originate from a deficiency of virus-specific **cytotoxic T lymphocytes** (CTLs). This finding provides the rationale for developing strategies of adoptive cell therapy to restore virus-specific immune competence. Multiple protocols are in clinical trials and available at some centers for the rapid generation of specific CTL lines of donor or third-party origin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 181

Late Effects of Hematopoietic Stem Cell Transplantation

Rachel A. Phelan and David Margolis

Pediatric hematopoietic stem cell transplantation (HSCT) is considered standard-of-care treatment for several malignant and nonmalignant conditions. Treatment generally involves exposure to chemotherapy and occasionally radiation to encourage engraftment of donor stem cells and prevent donor and recipient rejection. The period immediately after transplant is associated with the risk for a number of serious acute complications, including profound immunosuppression and subsequent risk for infection, graft-versus-host disease (GVHD), and organ toxicities (see Chapters 179 and 180). Fortunately, significant progress has been made in supportive care strategies to reduce the risk of acute complications and treat them more effectively if they do arise. This has resulted in a growing number of pediatric patients who are now long-term survivors following HSCT. The estimated total number of HSCT survivors in 2009 was 108,900, and this is expected to increase 5 times by 2030 to over 500,000. Of these survivors, approximately 14% (64,000) in 2030 will have received a transplant in childhood (<18 years of age).

Exposure to chemotherapy, radiation, or a combination of both, places patients at similar long-term risks as the pediatric cancer population; the high doses and types of chemotherapy and radiation often amplify the risk for issues such as ovarian failure/infertility and neurocognitive difficulties. Total body irradiation (TBI) has been shown to increase dramatically the risk for late complications after transplant. In addition, late effects may be additive if the patient received therapy before HSCT for their underlying malignancy. Moreover, the indication for transplant in pediatric patients is not always related to malignancy, but rather an underlying immunodeficiency, bone marrow failure syndrome, or metabolic disorder. These patients are potentially at risk for late effects related to this underlying disease and require different types of monitoring.

Essentially, every organ system can be impacted by the long-term effects of therapy, and each must be considered when undergoing late effects surveillance (Table 181.1). As a result of growing evidence of the importance of lifelong care for HSCT survivors, multiple groups have published consensus guidelines to help in caring for this patient population. As the field of survivorship continues to expand, *we recommend the following reference for real-time evidence-based recommendations from the* ***Children's Oncology Group*** (see http://survivorshipguidelines.org).

ENDOCRINE EFFECTS

Children given HSCT before puberty may develop **growth impairment**, precluding achievement of the genetic target for adult height. The decrease in growth velocity is similar for boys and girls and is more frequently observed in patients given TBI as part of the preparative regimen. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment.

Growth impairment of patients given TBI is mainly a result of direct damage of cartilage plates and to the effect of TBI on the hypothalamic-pituitary axis, which leads to an inappropriately low production of growth hormone (GH). GH deficiency is susceptible to at least partial correction through administration of hormonal replacement therapy. Annual growth evaluation should be performed in all children after HSCT. Children showing a decreased growth velocity should be further investigated through evaluation of bone age and secretion of GH in response to pharmacologic stimulus.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in **hypothyroidism**. Younger children are at greater risk of developing hypothyroidism. Chemotherapy-only preparative regimens have far fewer adverse effects on normal thyroid function. The site of injury by irradiation is at the level of the thyroid gland rather than at the pituitary or hypothalamus. Therapy with thyroxine is very effective for overt hypothyroidism. The cumulative incidence of hypothyroidism increases over time, underscoring the importance of annual thyroid function studies.

Gonadal hormones are essential for normal pubertal growth, as well as for development of secondary sexual characteristics. A significant proportion of patients receiving TBI-containing preparative regimens as well as high doses of alkylating agents show delayed development of secondary sexual characteristics, resulting from primary ovarian or testicular failure. Laboratory evaluation of these patients reveals elevated follicle-stimulating hormone and luteinizing hormone levels with depressed estradiol and testosterone serum levels. These patients benefit from careful follow-up with evaluation of annual sexual maturity rating (Tanner) scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. **Infertility** during adulthood remains a significant risk for these patients, especially those undergoing traditional myeloablative conditioning for HSCT. The use of reduced-intensity regimens may result in sparing fertility in a large proportion of patients, although conditioning regimens vary and studies are limited.

Bone health of HSCT survivors can also be impacted by hormonal changes as well as lifestyle practices, such as inadequate exercise and/or dietary intake of vitamin D. Prior exposures, including corticosteroid use, can result in changes to bone density as well as predispose to the development of avascular necrosis. Dual-energy x-ray absorptiometry (DXA) scans are routinely incorporated into the care of those patients at risk for low bone mineral density.

CARDIOVASCULAR EFFECTS

Survivors of childhood HSCT are at risk for the future development of cardiovascular complications. This population can be prone to developing **metabolic syndrome** (dyslipidemia, hypertension, diabetes mellitus, obesity), especially those with a history of TBI exposure and subsequent hormonal derangements. Prior exposures such as anthracycline chemotherapy and chest radiation further increase the risk for **cardiomyopathy** as well as **atherosclerosis**. As a result, routine anthropometric, imaging, and laboratory screening should be performed in survivors of childhood HSCT to assess and monitor their cardiovascular health.

SECONDARY MALIGNANCY

The overall risk of developing a secondary form of cancer is significantly higher after HSCT than in the general population. Although few studies have specifically analyzed pediatric patients, available evidence indicates that the cumulative incidence of second malignancies shows a slight, but continuous, tendency to increase over time. The development of myelodysplastic syndrome as well as secondary leukemias must be considered in survivors of HSCT. Several other types of secondary tumors have been identified in patients given HSCT. The most frequently diagnosed neoplasms are thyroid carcinoma, brain tumors, and epithelial cancers. Young age, male gender, use of TBI during the preparative regimen, chronic GVHD, and an intrinsic genetic predisposition to develop cancer (Fanconi anemia) have been reported to be risk factors for development of secondary malignancies after HSCT. Routine physical exams, including yearly skin in exams, in those that received TBI are important in the care of these patients.

GRAFT-VERSUS-HOST DISEASE

In the posttransplant period, multiple studies have shown that quality of life is severely impacted by the presence of GVHD, which is an issue that is also unique to HSCT (see Chapter 179).

OTHER EFFECTS

HSCT patients can also experience complications related to their pulmonary function, renal function, dental health, and gastrointestinal system, often related to prior exposures as well as their conditioning regimen. It is also important to note that long-term survivors must be monitored for psychologic issues because of their prior and current underlying health conditions. They may need extra assistance

Table 181.1 Summary of Late Effects After Hematopoietic Stem Cell Transplantation in Childhood

EXPOSURE	LATE EFFECT*
HSCT experience in general	Dental abnormalities Renal toxicity Hepatic toxicity Low BMD Avascular necrosis Increased risk of second cancers Adverse psychosocial/quality-of-life effects Mental health disorders, risk behaviors Psychosocial disability caused by pain or fatigue
TRANSPLANTATION CONDITIONING	
Alkylating agent	Cataract (busulfan) Pulmonary fibrosis (busulfan) Renal toxicity Urinary tract toxicity Gonadal dysfunction Therapy-related AML/MDS Bladder cancer
Epipodophyllotoxin[†] DNA intersecting and cross linking agents (i.e., platinum, heavy metal)	Therapy-related AML/MDS Ototoxicity Renal toxicity Gonadal toxicity
TBI[‡]	Neurocognitive deficits Leukoencephalopathy Cataract Dental abnormalities GH deficiency Hypothyroidism, thyroid nodule Pulmonary toxicity Breast tissue hypoplasia Cardiac toxicity Renal toxicity Gonadal dysfunction Uterine vascular insufficiency Diabetes Dyslipidemia Musculoskeletal growth problems Second cancers
PRETRANSPLANTATION EXPOSURES (NOT LISTED ABOVE)	
Anthracycline/anthraquinone	Cardiac toxicity Therapy-related AML/MDS
Bleomycin	Pulmonary toxicity
Cytarabine	Neurocognitive deficits Leukoencephalopathy
Methotrexate	Neurocognitive deficits Leukoencephalopathy Renal toxicity Low BMD
Corticosteroid	Cataract Low BMD Avascular necrosis
Cranial radiation[§]	Neurocognitive deficits Leukoencephalopathy Cerebrovascular disease Cataract Craniofacial abnormalities Dental abnormalities, xerostomia GH deficiency Hypothyroidism thyroid nodule Increased obesity Precocious puberty Brain tumor
Spinal radiation (in addition to cranial dose)	Cardiac toxicity Scoliosis/kyphosis, musculoskeletal problems
AFTER TRANSPLANTATION (NOT LISTED ABOVE)	
Chronic GVHD	Xerophthalmia Xerostomia, dental abnormalities Pulmonary toxicity Gastrointestinal strictures Genitourinary strictures Skin and joint changes Immunodeficiency Second cancers, especially skin, oral, cervical, lymphoma
Tyrosine kinase inhibitor	Acute cardiac toxicity reported, but not known to cause late cardiotoxicity
OTHER EXPOSURES	
Blood transfusions	Hepatitis C, HIV

*Focused on those late effects that can develop or persist even after cessation of therapy.
[†]Includes etoposide, teniposide.
[‡]At given total dose, risks greater for single-fraction vs fractionated total body irradiation (TBI); single-fraction myeloablative TBI (>500 cGy) now rarely used.
[§]Effects listed are those more likely to be associated with doses used in HSCT survivors (e.g., those given for leukemia treatment, <25 Gy); late effects are more likely if TBI also given.
AML/MDS, Acute myeloid leukemia/myelodysplastic syndrome; BMD, bone mineral density; GH, growth hormone; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.
From Chow EJ, Anderson L, Baker KS, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. *Biol Blood Marrow Transplant.* 2016;22(5):782–795.

with school and vocational attainment. These patients are also often at higher risk for depression and anxiety; yearly psychosocial assessments can identify survivors who need additional therapy or psychotropic medication. Parents may also have posttraumatic stress from the experience.

SPECIAL CONSIDERATIONS

Certain patient populations who undergo HSCT are at increased risk for late effects. Young children appear to be at a heightened risk for late complications related to TBI, especially those related to growth, thyroid function, and neurocognition. Patients with an *underlying genetic condition* must also be monitored more closely for specific consequences of therapy, such as specific secondary malignancies in the Fanconi anemia population caused by an underlying DNA repair defect and patients with sickle cell anemia and thalassemia who are predisposed to iron overload.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Allergic Disorders

PART XIII

Chapter 182

Allergy and the Immunologic Basis of Atopic Disease

Cezmi A. Akdis and Scott H. Sicherer

Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin E (IgE) antibodies to the antigens that trigger their illness. The term *allergy* represents the clinical expression of IgE-mediated allergic diseases that have a familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal (GI) tract, and nose. The significant increase in the prevalence of allergic diseases in the last few decades is attributed to changes in environmental factors such as exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity, and perhaps a decline in certain infectious diseases (hygiene hypothesis).

The incidence of allergic asthma and atopic dermatitis started to grow to epidemic proportions after the 1960s. Since 2000, the prevalence of food allergy, eosinophilic esophagitis, and drug-induced anaphylaxis has also risen to epidemic proportions. Currently more than 1 billion patients worldwide are expected to have at least one kind of allergic disease. The hygiene hypothesis, biodiversity hypothesis and epithelial barrier hypothesis are the three main hypotheses that propose mechanisms for the development of allergic diseases.

HYGIENE HYPOTHESIS

The relatively recent onset of the epidemics of allergic, autoimmune, and metabolic conditions leads to the question of what might underlie their development. A prominent hypothesis is the hygiene hypothesis, which proposes that certain microorganisms or infections protect against inflammatory diseases, and that their loss, due to hygiene measures, results in an increase in allergy, asthma, and autoimmunity. Growing up on a traditional farm has a protective effect from asthma and allergies, which provides a prominent example of the hygiene hypothesis. Children in Amish communities in the United States, where traditional dairy farming is practiced, are highly protected from asthma and allergies. In contrast, Hutterite communities have a significantly higher prevalence of asthma and allergies in children. Interestingly, they practice industrialized farming with extensive cleaning measures. Early development of a **T-helper type 1 (Th1)** response together with **T-regulatory cell (Treg)** response were proposed to play a role in prevention of allergic diseases.

BIODIVERSITY HYPOTHESIS

Allergic diseases are associated with a microbiome with increased colonization of opportunistic pathogens. The biodiversity hypothesis states that the observed increase in allergies is due to a loss of symbiotic relationships with bacteria and dysbiosis caused by changes in the microbiome of the gut, skin, and respiratory system. Healthy microbiota on the surface of the mucosal barrier regulates many aspects of epithelial barrier homeostasis, such as the modulation of barrier permeability and expression of epithelial barrier molecules, angiogenesis, vascular permeability, local microinflammation, and mucosal tolerance. Young children at risk of developing allergies have been shown to suffer from gut microbiome dysbiosis with an overall reduced microbiome diversity. The dysbiotic microbiota has been characterized by an underrepresentation of certain bacterial taxa that may produce immune regulatory and epithelial barrier healing or protective factors, such as short-chain fatty acids, retinoic acid, and vitamin D.

Several shortcomings of the hygiene and biodiversity hypotheses include the fact that water sanitation was established in many western cities in the 1920s, but allergy and asthma epidemics only started in the 1960s. The protective role of parasitic infections that increase biodiversity has been questioned for the same reason. Many parasitic infections started to decrease in 1910 in New York, whereas allergies started to increase after the 1960s. Allergic asthma is still on the rise in some cities in Asia and Africa, which have low standards of hygiene. Another limitation of the hygiene hypothesis and biodiversity hypothesis is that probiotics are not viable alternatives for the prevention or treatment of allergies. Moreover, studies of migrants who move from developing countries to affluent regions demonstrate a rapid increase in asthma and allergic diseases. It appears that domestic living conditions, increased birth by cesarean section, antibiotic usage, dietary practices, urbanization, and indoor air pollution are more prominent factors compared with general public hygiene.

EPITHELIAL BARRIER HYPOTHESIS

The epithelial barrier hypothesis is a broader hypothesis that covers hygiene and biodiversity hypotheses and adds further insights in the pathogenesis and recent development of allergic diseases. The defective epithelial barrier concept also applies to many autoimmune and metabolic diseases showing increased prevalence during the last few decades, such as diabetes, rheumatoid arthritis, multiple sclerosis, liver steatosis, and obesity. There is epidemiologic evidence from humans and disease models in laboratory animals that demonstrate that even trace amounts of certain toxic substances can damage epithelial barriers, initiate inflammation of the epithelium, and increase microbial dysbiosis and bacterial translocation toward the inside and beneath the epithelium. The epithelial barrier consists of four main components: the epithelial microbiota; the epithelial cell; structural proteins, such as filaggrin, loricrin, and involucrin and tight junctions and adherence junctions; and secreted epithelial products, such as mucus, antimicrobial peptides and fatty acids. Humans are exposed daily to a variety of toxins and chemicals, and substantial data demonstrate disruption of the epithelial barrier by allergens, certain bacteria and their toxins, fungi, viruses, laundry and dishwasher detergents, household cleaners, surfactants, enzymes and emulsifiers used in the food industry, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics.

Epithelial cell activation and release of epithelial cell cytokines, such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) play a major role in the development and exacerbation of allergic diseases. Local tissue inflammation opens epithelial barriers. Open epithelial barriers in the mucosa allow the entrance of foreign substances, including allergens, into deeper tissues. Both Th1 and **T-helper type 2 (Th2)** inflammation affect the skin and mucosal epithelial barriers. Th2 cells and group 2 innate lymphoid cells (ILCs-2) play major roles utilizing IL-13 as major cytokines in the opening of the tight junction barrier.

Microbial dysbiosis caused by transepithelial translocation of commensal microbes, colonization by opportunistic pathogens, and decreased biodiversity are hallmarks of barrier damaged tissues. Colonization by opportunistic pathogens in the microbiota takes place in tissues with a defective epithelial barrier. A dysregulated subepithelial immune response, local inflammation, and incorrect regeneration and remodeling take place as the continuum and chronicity of the local inflammation. Migration of inflamed cells to other affected tissues and systemic low-level immune activation and microinflammation are additional players in the development and exacerbation of many chronic inflammatory diseases (Fig. 182.1).

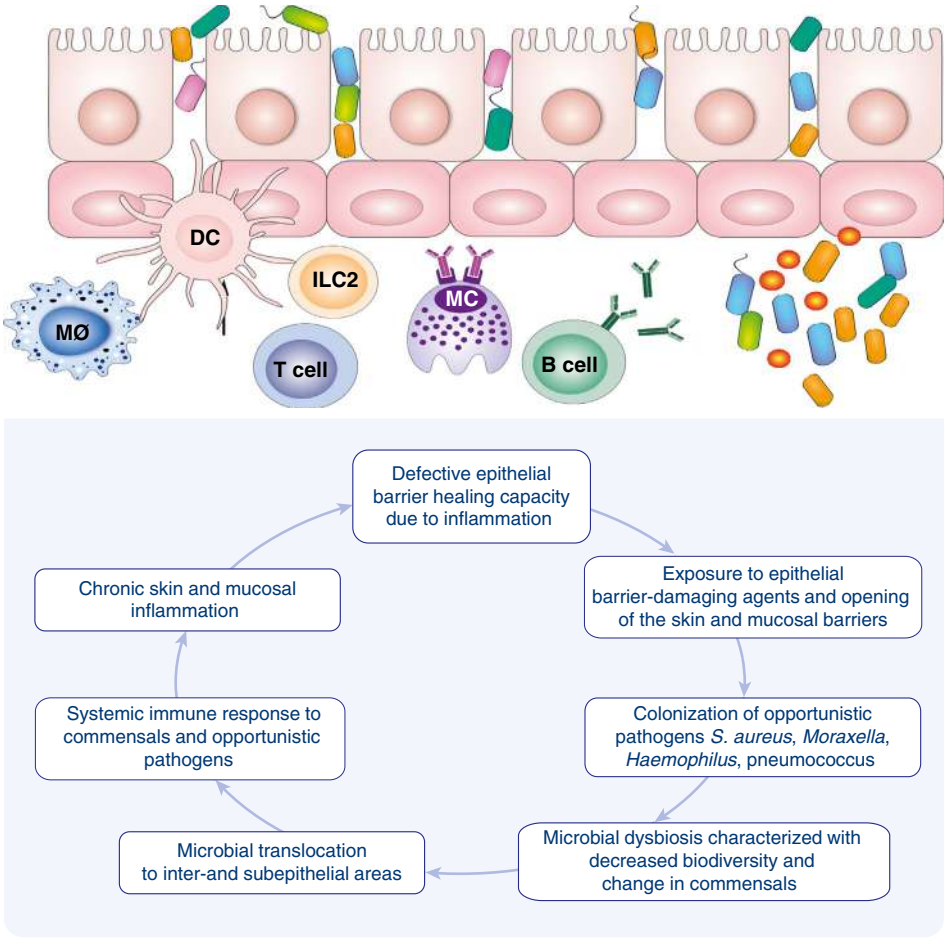

Fig. 182.1 The physiopathology of the epithelial barrier hypothesis. Genetic defects in barrier-related molecules or exposure to epithelial barrier-damaging agents cause an opening of the skin and mucosal tight junction barriers. This is followed by translocation of microbiota to inter- and subepithelial areas and colonization of opportunistic pathogens, such as *Staphylococcus aureus*, *Moraxella*, *Haemophilus* and pneumococcus. An immune response develops toward commensals and opportunistic pathogens in the gut and respiratory system and systemic inflammation takes place. In most cases of allergic diseases, a systemic type 2 inflammation predominates, and is directed against allergens, but also commensals and opportunistic pathogens. Anti–*S. aureus* antibodies show a very high prevalence in asthma, chronic sinusitis, and atopic dermatitis. This is associated with microbial dysbiosis and decreased biodiversity of commensals. Chronic inflammation in the subepithelial area develops as the main pathogenetic feature of these diseases. Defective epithelial barrier healing capacity due to inflammation and epigenetic changes take place, developing a vicious circle of leaky barriers, microbial dysbiosis, and chronic inflammation. DC, Dendritic cell; IL, interleukin; ILC, innate lymphoid cells; MC, mast cell; Mø, macrophage.

KEY ELEMENTS OF ALLERGIC DISEASES

Allergens

Allergens are almost always *proteins,* but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response on subsequent exposure to the same protein. Biochemical properties of the allergen; stimulating factors of the innate immune response around the allergen substances at the time of exposure; stability of the allergen in the tissues, digestive system, skin, or mucosa; and the dose and time of stay in lymphatic organs during the interaction with the immune system are factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins with a molecular weight of 10-70 kDa. Molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils. Most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach **antigen-presenting cells (APCs)** for stimulation of the immune system. Allergens frequently contain **proteases**, which promote skin and mucosal epithelial barrier dysfunction and increase allergen penetration into host tissues. A relatively high dose of exposure and stability of the allergenic protein in body fluids to reach the immune cells are important determinants of an allergen. Low molecular weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of *biologics* in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose.

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of **Th2** cells that secrete cytokines, such as IL-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on skin-prick testing. The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 182.2). IL-5 and IL-9 are important in the differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. T-cell and eosinophil migration to allergic inflammation areas are controlled by IL-4 and IL-13 upregulating their adhesion to endothelial cell walls. IL-9 is responsible for mucus production. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and **TSLP** secreted from epithelial cells on exposure to allergens and respiratory viruses contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergens results in activation and proliferation of **Th1** cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because

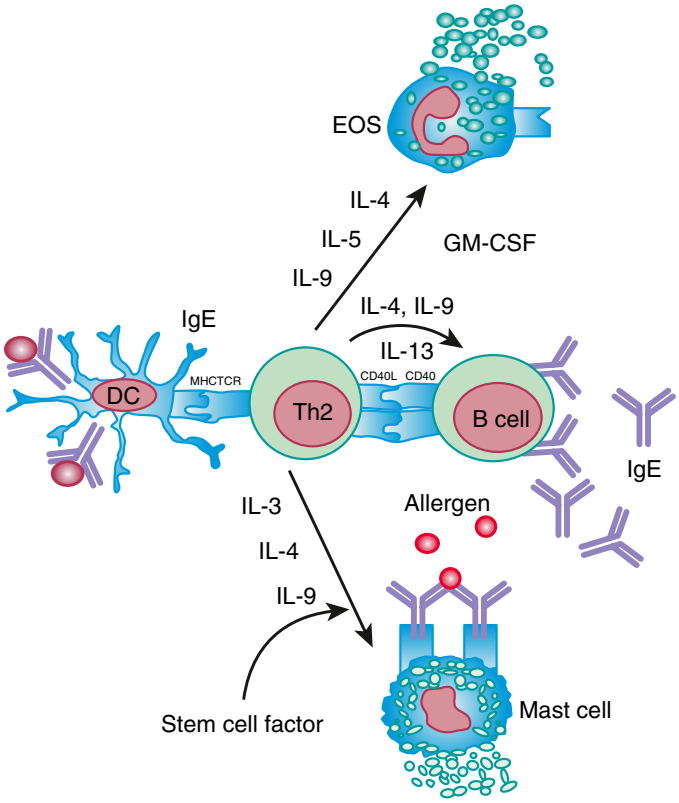

Fig. 182.2 Role of Th2 cytokines in allergic cascade. DC, Dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin.

of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor (TNF)-α, and Fas-ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and **Th17 cells**. This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils, thereby contributing to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Figure 182.3 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17, and Th22 cells.

Tregs are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of Th1, Th2, Th9, Th17, and Th22 phenotypes (Fig. 182.4). Tregs express $CD4^+CD25^+$ surface molecules and immunosuppressive cytokines such as IL-10, IL-35, and transforming growth factor-β (TGF-β_1). The forkhead box/winged-helix transcription factor gene *FOXP3* is expressed specifically by $CD4^+CD25^+$ Tregs and programs their development and function. Adoptive transfer of Tregs inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Tregs. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat

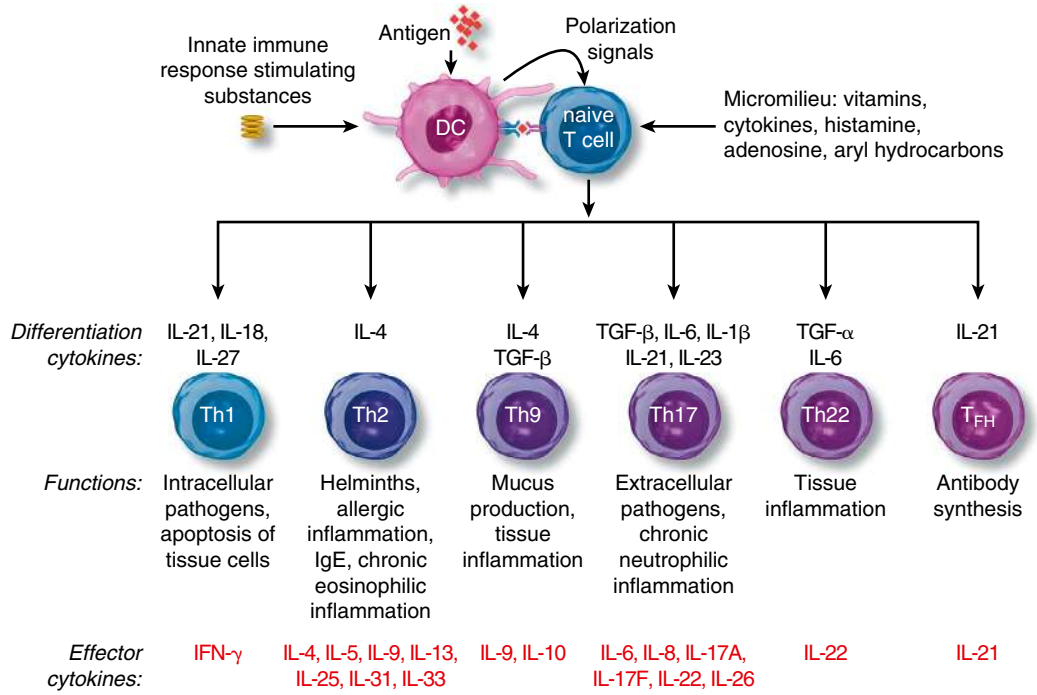

Fig. 182.3 Effector T-cell subsets. Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper (TFH) effector subsets. Their differentiation requires cytokines and other cofactors that are released from DCs and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, Interferon-γ; TGF-β, transforming growth factor-β. *(From Akdis M, Palomares O, van de Veen W, et al. TH17 and TH22 cells: A confusion of antimicrobial response with tissue inflammation versus protection. J Allergy Clin Immunol. 2012;129:1438–1449.)*

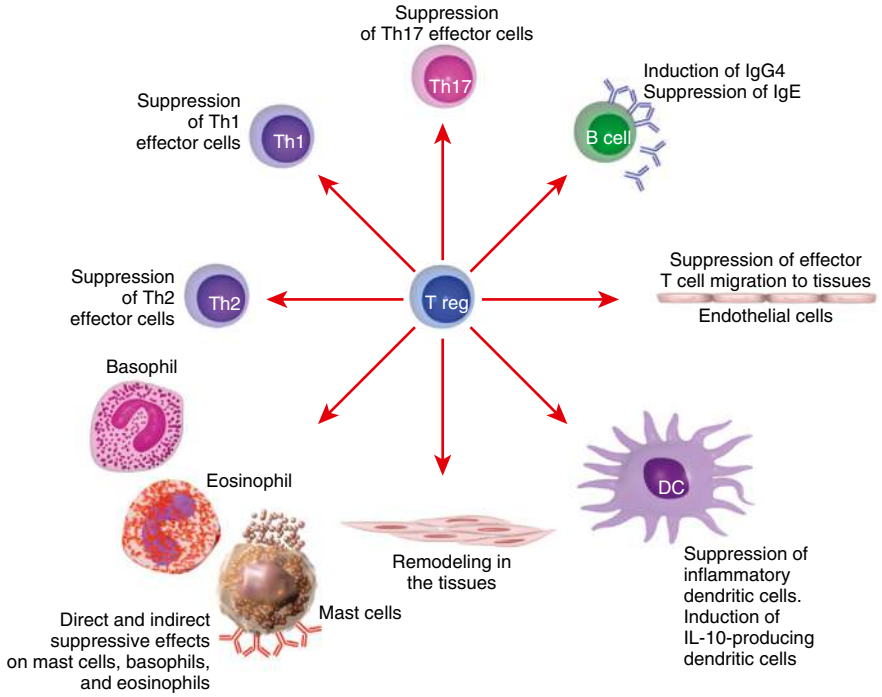

Fig. 182.4 Control of allergen-specific immune responses. FoxP3$^+$, CD4$^+$, CD25$^+$, and Tr1 cells contribute to the control of allergen-specific immune responses in several major ways: suppression of dendritic cells (DCs) that support the generation of effector T cells; suppression of Th1, Th2, and Th17 cells; suppression of allergen-specific IgE, and induction of IgG_4 and/or IgA; suppression of mast cells, basophils, and eosinophils; interaction with resident tissue cells and remodeling; and suppression of effector T-cell migration to tissues. IL, Interleukin. *(From Akdis CA, Akdis M. Mechanisms and treatment of allergic disease in the big picture of regulatory T cells. J Allergy Clin Immunol. 2009;123:735–746.)*

owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Tregs. It is thought that CD4$^+$CD25$^+$ Tregs play an important role in mitigating the allergic immune response, and that the lack of such cells may predispose to the development of allergic diseases. Patients with pathogenic variants in the human *FOXP3* gene lack CD4$^+$CD25$^+$ Tregs and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/IPEX disease) (see Chapter 165.4). In addition to Treg cells, IL-10–secreting and allergen-specific Breg cells increase during allergen-specific immunotherapy and may play a role in allergen tolerance.

Innate Lymphoid Cells

Immune responses in populations of lymphoid cells that lack rearranged T- and B-cell antigen receptors and surface markers for myeloid and lymphoid lineages, such as T, B, and natural killer (NK) cells, show similarities to Th1, Th2, and Th17/Th22 types of immune responses. These latter cells are defined as **ILC1s, ILC2s,** and **ILC3s,** respectively, based on their transcription factors and cytokine production patterns. ILC1s mainly produce IFN-γ; ILC2s produce IL-5, IL-9, and IL-13; and ILC3s produce IL-17 and IL-22 without any need of antigen/allergen exposure. Strong evidence indicates that ILCs play substantial roles in protection against infection and the pathogenesis of inflammatory diseases, such as asthma, allergic diseases, and autoimmune diseases. ILCs control the mucosal environment through close interaction with epithelial cells and other tissue cells, cytokine production, and induction of chemokines that recruit suitable cell populations to initiate and promote distinct types of immune response development and tissue inflammation. ILC2s are likely involved in the induction of asthma, allergic rhinitis, eosinophilic esophagitis, and atopic dermatitis through activation by epithelium-derived cytokines (e.g., IL-33, IL-25, TSLP) and interaction with other immune cells. IL-10–secreting ILCs with an immune regulatory function have been reported. These cells develop from ILC2s and play suppressive roles in allergic inflammation, particularly through IL-10.

Antigen-Presenting Cells

Dendritic cells (DCs), Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells, thereby modulating allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. DCs and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the **sensitization phase** of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses on reexposure to allergen, which characterizes the **elicitation phase** of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and co-stimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as **myeloid** or **plasmacytoid** on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. In contrast, plasmacytoid DCs have low levels of IL-12. Plasmacytoid DCs particularly play a role in antiviral immunity by rapid production of high amounts of IFN-α and help B cells for antibody production. There is considerable interest in the role of TSLP, which is overexpressed in the mucosal surfaces and skin of atopic individuals. TSLP enhances Th2 differentiation by inducing expression of OX40L on immature myeloid DCs in the absence of IL-12 production.

Tissue macrophages are also acting as APCs. They show two main effector subsets in tissues, namely the M1 and M2 macrophages. M1 macrophages are classically activated, typically by IFN-γ or lipopolysaccharide (LPS) like innate immune response stimulating substances, and produce proinflammatory cytokines, phagocytize microbes, and initiate an immune response. M1 macrophages produce nitric oxide (NO) or reactive oxygen intermediates (ROIs) to protect against bacteria and viruses. M2 macrophages are alternatively activated by allergen exposure and certain cytokines such as IL-4, IL-10, or IL-13. M2 macrophages will produce either polyamines to induce proliferation or proline to induce collagen production. These macrophages are associated with wound healing and tissue repair remodeling and activation of Th2 cells and ILC2s.

Presence of allergen-specific IgE on the cell surfaces of APCs is a unique feature of atopy. Importantly, the formation of high-affinity IgE receptor I (**FcεRI**)/IgE/allergen complexes on APC surfaces greatly facilitates allergen uptake and presentation. The clinical importance of this phenomenon is supported by the observation that FcεRI-positive Langerhans cells bearing IgE molecules are a prerequisite for skin-applied, aeroallergen provocation of eczematous lesions in patients with atopic dermatitis. The role of the low-affinity IgE receptor II **(FcεRII, CD23)**

on monocytes/macrophages is less clear, although under certain conditions it apparently can also facilitate antigen capture. Cross linking of FcεRII, as well as FcεRI, on monocytes/macrophages leads to the release of inflammatory mediators. There is a critical role for DCs in induction of oral tolerance; tolerogenic DCs are compartmentalized within the mucosa and present antigen through a mechanism designed to produce a Th1/Treg-suppressive response that ablates allergen-specific T cells.

Immunoglobulin E and Its Receptors

The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade, followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross linking and FcεRI aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 174). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires two major signals. The first signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The second signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in DNA switch recombination. Interactions between several co-stimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ), IL-10 from Tregs, Breg cells, and regulatory DCs and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

Eosinophils

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins (see Fig. 169.1). These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and **leukotrienes (LTs);** in particular, cysteinyl LT C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and ROIs, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated on activation, normal T-cell expressed and secreted), macrophage inflammatory protein-1α (MIP-1α), and eotaxins are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5–dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

Mast Cells

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. On entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand, the stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are instead widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, GI tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least two subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the GI submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell–derived lipid mediators are the **cyclooxygenase** and **lipoxygenase** metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is **prostaglandin D_2**, and the major lipoxygenase products are the sulfidopeptide **LTs:** LTC_4 and its peptidolytic derivatives LTD_4 and LTE_4. Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α, IL-6) and regulate tissue remodeling (TGF, vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in patients receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

MECHANISMS OF ALLERGIC TISSUE INFLAMMATION

IgE-mediated immune responses can be classified chronologically according to three reaction patterns. The **early-phase response** is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of 1-30 minutes after allergen exposure and resolving within 1-3 hours. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and GI tract, respectively, depending on the targeted organ.

A second, **late-phase response** can occur within hours of allergen exposure, reaching a maximum at 6-12 hours and resolving by 24 hours. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils, followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., $\alpha_4\beta_1$-integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells. ILC2s receive signals from the epithelial cells, such as IL-33, TSLP, and IL-25, and are activated and start to release their cytokines IL-5 and IL-13 to initiate a type 2 immune response.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemoattractants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemoattractants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the third reaction pattern, **chronic allergic disease**, tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, **remodeling** involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Generally, it is considered that a type 2 immune response underlines a majority of asthma cases, atopic dermatitis, chronic rhinosinusitis, and allergic rhinitis as a general characteristic of an immune/inflammatory response. Type 2 immune response involves Th2 cells, type 2 B cells, ILC2, IL-4–secreting NK T cells, basophils, eosinophils, and mast cells and their major cytokines. From a complex network of cytokines, IL-4, IL-5, IL-9, and IL-13 are mainly secreted from the immune system cells, and IL-25, IL-31, IL-33, and TSLP from tissue cells, particularly epithelial cells. Many asthma-related antigens, such as protease allergens, fungal extracts, and viral infection, trigger IL-33, TSLP, and IL-25 production from epithelial cells and various immune cells and induce eosinophilic asthma–like airway inflammation through activation of lung ILC2s.

IL-31 plays a role in pruritus in atopic dermatitis. Th2 cytokines do not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGF-β produced by eosinophils and fibroblasts can also enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating due to a general type 2 immune response and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1-cell and Th17-cell autoreactivity.

GENETIC BASIS OF ATOPY

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) and that are usually expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., skin in atopic dermatitis, lung in asthma, GI tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses (Fig. 182.5). Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23-35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, *IL4* is a well-studied potential candidate gene. A nucleotide change at position 589 of the *IL4* promoter region is associated with the formation of a unique binding site for **n**uclear **f**actor for **a**ctivated **T** cells (NF-AT) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, *IL13* coding region variants have been associated with asthma and atopic dermatitis. An association has been found between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen *Der p* I, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma. A recent genome-wide association study showed that genetic polymorphisms in the gene encoding IL-33, which is a major activator of ILC2s, and its receptor IL-1RL1 (ST2) are strongly linked to asthma development.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. **Filaggrin** is a protein that is essential in the formation of the stratum corneum. Null pathogenic variants of the filaggrin gene are strongly associated with early-onset and severe atopic dermatitis. Pathogenic variants in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause **Netherton disease**, a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical to neutralizing the proteolytic activity of *Staphylococcus aureus* and common allergens such as *Der p* I, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding tight junctions. Epithelial tight junctions form a strong barrier on the apical side of mucosal epithelial cells and stratum granulosum of the skin. Epithelial tight junction defects shown in asthma and atopic dermatitis have been linked to two mechanisms, such as polymorphisms in certain claudin molecules or epigenetic regulation of the tight junction molecules. Epithelial cells obtained from asthmatic tissues cannot form a strong barrier in cultures. Chemical inhibition of histone deacetylases strengthens the barrier development capacity of these epithelial cells.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: *GPRA* (G-protein–coupled receptor for asthma susceptibility on chromosome 7p14), *ADAM-33* (a disintegrin and metalloproteinase 33 on chromosome 20p), and

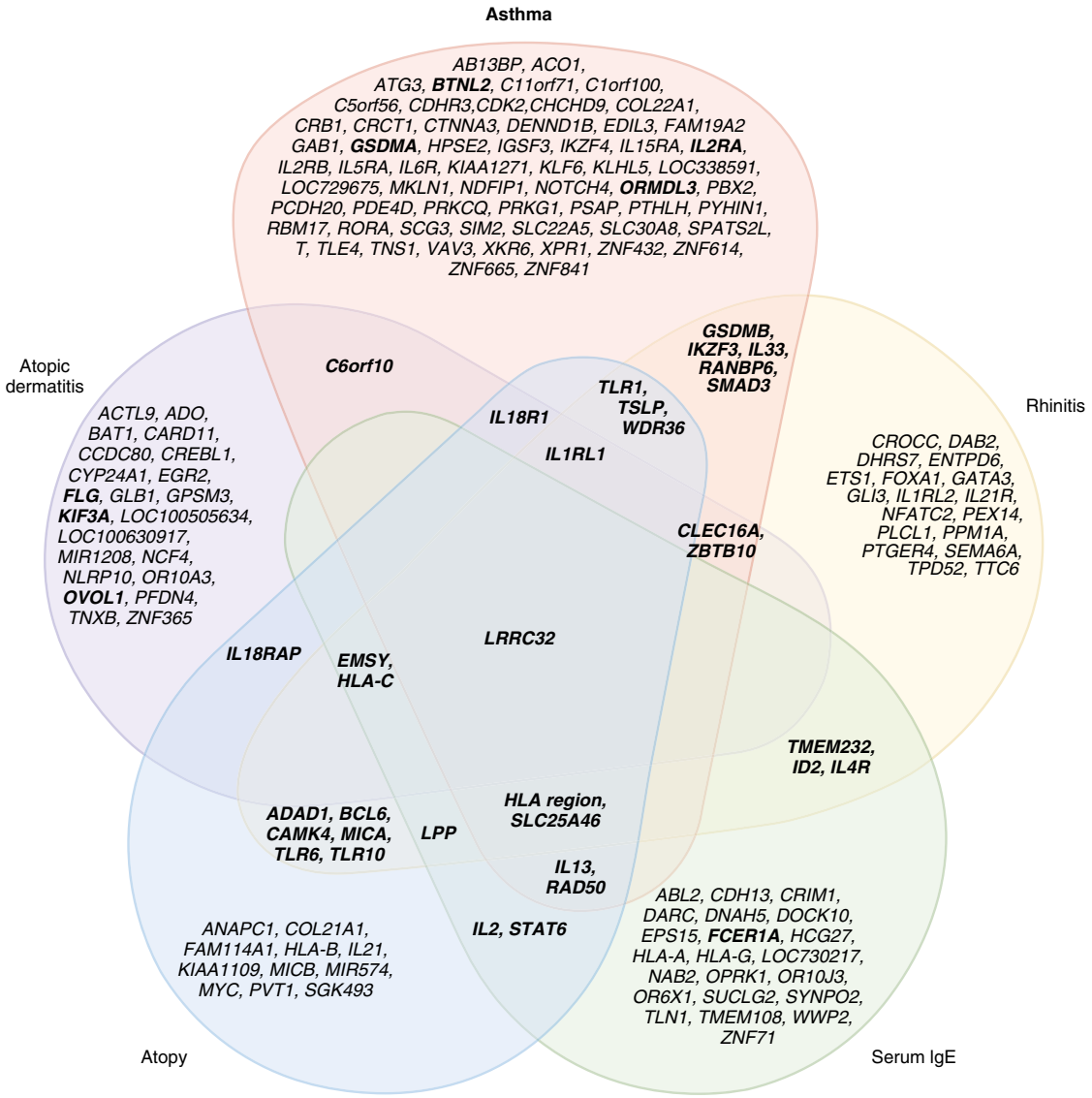

Fig. 182.5 Overlapping sets of genes have been reported in genome-wide association studies (GWASs) for asthma, rhinitis, serum immunoglobulin E (IgE) levels, atopy, and atopic dermatitis, supporting a common genetic element within the mechanisms predisposing individuals toward different allergic disease phenotypes. GWASs have also identified many genes in association with only one allergic disease phenotype; these most likely represent the tissue-specific component of each allergic disease (e.g., *FLG* in the epidermal barrier in atopic dermatitis). More GWASs have been conducted analyzing genetic variants associated with asthma than with other allergic diseases. In the future it is likely that more risk variants for other allergic diseases will be identified. Genes reported in more than one GWAS are shown in bold font. The genes reported for SNPs detected to be significantly associated ($P \leq 1 \times 10^{-5}$) with each allergic disease phenotype were obtained by searching the National Human Genome Research Institute GWAS catalog. *(From Holloway JW. The genetics of allergic disease and asthma. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig. 3.3, p 22.)*

DPP10 (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. *GPRA* encodes a G-protein–coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. *ADAM-33* is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. *DPP10* encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial components. Polymorphisms in CD14 (engages endotoxin), Toll-like receptor 2 (which engages *S. aureus*), and T-cell immunoglobulin domain and mucin domain (which engage hepatitis A virus) correlate with asthma and/or atopic dermatitis susceptibility. Dysregulation of these frontline immune defense systems would permit abnormal response to common environmental allergens.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Bibliography

Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;32(22):749–751.

Akdis CA, Arkwright PD, Brüggen MC, et al. Type 2 immunity in the skin and lungs. *Allergy*. 2020;75(7):1582–1605.

Bachert C, Akdis CA. Phenotypes and emerging endotypes of chronic rhinosinusitis. *J Allergy Clin Immunol Pract*. 2016;4(4):621–628.

Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol*. 2020;145(6):1517–1528.

Cevhertas L, Ogulur I, Maurer DJ, et al. Advances and recent developments in asthma in 2020. *Allergy*. 2020;75(12):3124–3146.

Kortekaas Krohn I, Shikhagaie MM, Golebski K, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: Clinical implications. *Allergy*. 2018;73(4):837–850.

Kuo IH, Yoshida T, De Benedetto A, et al. The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2013;131:266–278.

Liu AH, Anderson 3rd WC, Dutmer CM, et al. Advances in asthma 2015: across the lifespan. *J Allergy Clin Immunol*. 2016;138(2):397–404.

Mjösberg J, Spits H. Human innate lymphoid cells. *J Allergy Clin Immunol*. 2016;138(5):1265–1276.

Morita H, Kubo T, Rückert B, Ravindran A, et al. Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid. *J Allergy Clin Immunol*. 2019;143(6). 2190–2201.e9.

Palomares O, Akdis M, Martín-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. *Immunol Rev*. 2017;278(1):219–236.

Tang TS, Bieber T, Williams HC. Does "autoreactivity" play a role in atopic dermatitis? *J Allergy Clin Immunol*. 2012;129:1209–1215.

Van de Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol*. 2013;131:1204–1212.

Vercelli D. Remembrance of things past: HLA genes come back on the allergy stage. J Allergy Clin Immunol 129:846–847

Wang M, Tan G, Eljaszewicz A, et al. Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier integrity in human bronchial epithelial cells. *J Allergy Clin Immunol*. 2019;143(5):1892–1903.

Zabielinski M, McLeod MP, Aber C, et al. Trends and antibiotic susceptibility patterns of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* in an outpatient dermatology facility. *JAMA Dermatol*. 2013;149(4):427–432.

Chapter 183

Diagnosis of Allergic Disease

Supinda Bunyavanich, Jacob Kattan, and Scott H. Sicherer

ALLERGY HISTORY

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than one allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy, should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when one parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal **pruritus** and **rhinorrhea**, children with allergic rhinitis often perform the **allergic salute** by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the **nasal crease**, a horizontal wrinkle over the bridge of the nose. Characteristic vigorous **rubbing** of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The **allergic cluck** is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens, such as **pollens** and fungal spores, are prominent causes of allergic disease. The concentrations of these allergens in outdoor air fluctuate seasonally. Correlating symptoms with **seasonal** pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States, with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollens may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to **perennial allergens** usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as *Aspergillus* and *Penicillium,* are found indoors, whereas *Alternaria* is found in both indoor and outdoor environments. Cockroach and rodent allergens are often problematic in urban environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are often first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory and cardiovascular symptoms. Symptoms of immediate or IgE-mediated hypersensitivity food reactions typically develop within minutes to 2 hours after ingestion of the offending food. Symptoms of non–IgE-mediated food allergies are often delayed or chronic (see Chapter 192).

Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough **environmental** survey should be performed, focusing on potential sources of allergen and/or irritant exposure, particularly when respiratory symptoms (upper/lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the use of dust mite covers on pillows and mattresses, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers living in the home, and what and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in other environments where the child spends long periods, such as a relative's home or school setting.

PHYSICAL EXAMINATION

In patients with **asthma**, *spirometry* should be performed. If respiratory distress is observed, *pulse oximetry* should be performed.

The child presenting with a chief complaint of **rhinitis** or **rhinoconjunctivitis** should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing **pruritus**; see Chapter 184). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional change in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may experience growth suppression, an accurate height should be plotted at regular intervals. The

use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (1 cm) that may persist as a reduction in adult height. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus**, defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airway obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child's lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners** (Fig. 183.1). They are found in up to 60% of allergic patients and almost 40% of patients *without* allergic disease. Thus "shiners" may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atopy (see Fig. 183.1). These are prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

In patients with **allergic conjunctivitis**, involvement of the eyes is typically bilateral (see Chapter 188). Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as "stringy" or "ropy." In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus**, or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atopic dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.



Fig. 183.1 Bilateral Dennie-Morgan folds. Several linear wrinkles beneath the lower eyelashes *(arrow)* associated with bilateral allergic shiners: dark circles beneath the lower eyelid *(arrowheads)*. *(From Blanc S, Bourrier T, Albertini M, et al. Dennie-Morgan fold plus dark circles: suspect atopy at first sight. J Pediatr. 2015;166:1541.)*

The external ear should be examined for eczematous changes in patients with atopic dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyps. Nasal polyps in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple compared with the beefy-red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort **(lip licker's dermatitis)**. Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia ("cobblestoning").

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles (retractions), wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests **foreign body aspiration**. Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with **vocal cord dysfunction.** Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of **urticaria/angioedema** or **atopic dermatitis** (see Chapters 189 and 186). **Xerosis**, or dry skin, is the most common skin abnormality of allergic children. **Keratosis pilaris**, often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases **(hyperlinearity)** in children with moderate to severe atopic dermatitis.

DIAGNOSTIC TESTING

In Vitro Tests

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. **Eosinophilia**, defined as the presence of >500 eosinophils/μL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence

Table 183.1 Differential Diagnosis of Childhood Eosinophilia

PHYSIOLOGIC
Prematurity
Infants receiving hyperalimentation
Hereditary

INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)

PULMONARY
Allergic (rhinitis, asthma)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia

DERMATOLOGIC
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)

HEMATOLOGIC/ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis

IMMUNOLOGIC
T-cell immunodeficiencies
Hyper-IgE (Job) syndromes
Wiskott-Aldrich syndrome
Autoimmune lymphoproliferative syndrome (ALPS)
Sarcoidosis
Graft-versus-host disease
Drug hypersensitivity including drug reaction with eosinophilia and systemic symptoms (DRESS)
Postirradiation
Postsplenectomy

ENDOCRINE
Addison disease
Hypopituitarism

CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis

GASTROINTESTINAL
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α; HTLV, human T-lymphotropic virus 1.

of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy; eosinophil counts >1,500 without an identifiable etiology should suggest one of the two hypereosinophilic syndromes (Table 183.1; see Chapter 169).

Nasal and bronchial secretions may be examined for the presence of eosinophils and neutrophils. The presence of eosinophils in the sputum of patients with atopic asthma is frequently seen. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis.

An elevated **IgE** value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels, whereas patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such that the diagnostic value of a total IgE level is poor. Approximately half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of **allergic bronchopulmonary aspergillosis** is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 283.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 183.2).

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of **allergen-specific IgE (sIgE)** levels in the serum (Table 183.3). The first test for documenting the presence of sIgE was called the radioallergosorbent test (RAST) because it used a radiolabeled anti-IgE antibody. RAST has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These immunoassays typically use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient's serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient's sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE–antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample, kU_A/L). Laboratory reports may specify classes, counts, or units, but quantification of results in kU_A/L is most useful. sIgE immunoassays are available for foods, environmental allergens, insect venoms, natural rubber latex, and a small number of β-lactam drugs. The sensitivity and specificity of immunoassays for particular allergens vary widely from 30–95%. These immunoassays are not diagnostic for allergy and should not be used for allergy screening. Only targeted sIgE levels for specific antigens should be measured when there is a clinical indication to suspect a specific allergy.

Table 183.2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

PARASITIC INFESTATIONS
Ascariasis
Capillariasis
Echinococcosis
Fascioliasis
Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans

INFECTIONS
Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
HIV type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections

IMMUNODEFICIENCY
Autosomal dominant hyper-IgE syndrome (*STAT3* variants)
Autosomal recessive hyper-IgE syndrome (*DOCK8, TYK2* variants)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome

NEOPLASTIC DISEASES
Hodgkin disease
IgE myeloma
Bronchial carcinoma

OTHER DISEASES AND DISORDERS
Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medication related
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Juvenile idiopathic arthritis

Table 183.3 Determination of Allergen-Specific IgE by Skin Testing vs In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermatographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

*Skin testing may be the prick test or intradermal (ID) injection.

Component testing refers to diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut, Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

In Vivo Tests

Allergen skin testing is the primary in vivo procedure for the diagnosis of allergic disease. Mast cells with sIgE antibodies attached to high-affinity receptors on their surface reside in the skin of allergic patients. The introduction of minute amounts of an allergen into the skin of the sensitized patient results in cross linking of IgE antibodies on the mast cell surface, thereby triggering local mast cell activation. Once activated, these mast cells release a variety of preformed and newly generated mediators that act on surrounding tissues. **Histamine** is the mediator most responsible for the immediate **wheal and flare reactions** observed in skin testing. Examination of the site of a positive skin test result reveals a pruritic wheal surrounded by erythema. The time course of these reactions is rapid in onset, reaching a peak within 10-20 minutes and usually resolving over the next 30 minutes.

Skin testing is performed using the **prick/puncture technique.** With this technique, a small drop of allergen is applied to the skin surface, and a tiny amount is introduced into the epidermis by lightly pricking or puncturing the outer layer of skin through the drop of extract with a small needle or other device. When the **skin-prick test (SPT)** result is negative but the history suggestive, selective skin testing (for vaccines, venom, drugs, and aeroallergens) using the **intradermal technique** may be performed. This technique involves using a 26-gauge needle to inject 0.01-0.02 mL of an allergen extract diluted 1,000- to 10-fold into the dermis of the arm. Intradermal skin tests are *not recommended for use with food allergens* because of the risk of triggering anaphylaxis. Irritant rather than allergic reactions can occur with intradermal skin testing if higher concentrations of extracts are used. Although skin-prick testing is less sensitive than intradermal skin testing, positive SPT results tend to correlate better with clinical symptoms.

The number of skin tests performed should be individualized, with the allergens suggested by the history. A positive and negative control SPT, using histamine and saline, respectively, is performed with each set of skin tests. A negative control is necessary to assess for **dermatographism**, in which reactions are caused merely by applying pressure to overly sensitive skin. A positive control is necessary to establish the presence of a cutaneous response to histamine. Medications with antihistaminic properties, in addition to adrenergic agents such as ephedrine and epinephrine, suppress skin test responses and should be avoided for appropriate intervals (approximately five half-lives) before skin testing. Prolonged courses of systemic corticosteroids may suppress cutaneous reactivity by decreasing the number of tissue mast cells as well as their ability to release mediators.

Whether identified via serologic or skin testing, detection of sIgE denotes a sensitized state (i.e., atopy or a tendency toward development of allergic disease) but is not equivalent to a clinically relevant allergic diagnosis. **Many children with positive tests have no clinical symptoms on exposure to the allergen**. Increasingly strong test results (higher serum sIgE results or larger SPT wheal sizes) generally correlate with increasing likelihood of clinical reactivity (but not severity). Neither serologic testing nor skin testing for allergy is predictive of reaction severity or threshold of reactivity, and these tests will be negative when the allergy is not IgE mediated, such as in food protein–induced enterocolitis syndrome. The limitations of these test modalities underscore the need for a detailed medical history that can guide the selection and interpretation of test results. **Large panels of indiscriminately performed screening tests may provide misleading information and are not recommended.**

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. The benefits of the serologic immunoassays are that performance is not limited by the presence of skin disease (i.e., active atopic dermatitis) or medication use (i.e., antihistamines). Advantages of skin testing are that they provide rapid results to the patient/family during the clinic visit, do not require venipuncture, and are less costly.

Under certain circumstances, **provocation testing** is performed to examine the association between allergen exposure and the development of symptoms. The bronchial provocation test most frequently performed clinically is the **methacholine challenge,** which causes potent bronchoconstriction of asthmatic but not of normal airways; it is performed to document the presence and degree of bronchial hyperreactivity in a patient with suspected asthma. After baseline spirometry values are obtained, increasing concentrations of nebulized methacholine are inhaled until a drop occurs in lung function, specifically a 20% decrease in FEV_1 (forced expiratory volume in the first second of expiration), or the patient is able to tolerate the inhalation of a set concentration of methacholine, typically 25 mg/mL.

Oral **food challenges** are performed to determine whether a specific food causes symptoms or whether a suspected food can be added to the diet. Food challenges are performed when the history and results of skin tests and immunoassays for sIgE are insufficient to clarify the diagnosis of an allergy. These challenges may be performed in an open single-blind, double-blind, or double-blind placebo-controlled manner and involve the ingestion of gradually increasing amounts of the suspected food at set intervals until the patient either experiences a reaction or tolerates a normal portion (i.e., one serving size) of the food openly. Although the double-blind placebo-controlled food challenge is currently the gold standard test for diagnosing food allergy, it is typically only performed in research studies due to the time and labor-intensive nature of this method. Because of the potential for significant allergic reactions, oral food challenges should be performed only in an appropriately equipped facility with personnel experienced in the performance of food challenges and the treatment of anaphylaxis, including cardiopulmonary resuscitation.

Upper gastrointestinal **endoscopy** is required to confirm the diagnosis of **eosinophilic esophagitis**. One or more biopsy specimens from the proximal and distal esophagus must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils per high-power field (peak value) is considered a minimum threshold for the diagnosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Bibliography

Adkinson Jr NF, Bochner BS, Burks AW, et al., eds. *Middleton's allergy: principles & practice*. 9th ed. Philadelphia: Elsevier/Saunders; 2019.

Cevhertas L, Ogulur I, Maurer DJ, et al. Advances and recent developments in asthma in 2020. *Allergy*. 2020;75(12):3124–3146.

Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020. A practice parameter update. *J Allergy Clin Immunol*. 2020;146(4):721–767.

Gonsalves NP, Aceves SS. Diagnosis and treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2020;145(1):1–7.

Hew M, Menzies-Gow A, Hull JH, et al. Systematic Assessment of Difficult-to-Treat Asthma: Principles and Perspectives. *J Allergy Clin Immunol Pract*. 2020;8(7):2222–2233.

Khan DA, Banerji A, Blumenthal K et al. Drug allergy: A 2022 practice parameter Update. *J Allergy Clin Immunol* 2022;150(6)1333–1393.

Nowak-Wegrzyn A, Berin MC, Mehr S. Food Protein-Induced Enterocolitis Syndrome. *J Allergy Clin Immunol Pract*. 2020;8(1):24–35.

Rodrigues J, Kuruvilla ME, Vanijcharoenkarn K, Patel N, Hom MM, Wallace DV. The spectrum of allergic ocular diseases. *Ann Allergy Asthma Immunol*. 2021;126(3):240–254.

Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food Allergy from Infancy Through Adulthood. *J Allergy Clin Immunol Pract*. 2020;8(6):1854–1864.

Worm M, Vieths S, Mahler V. An update on anaphylaxis and urticaria. *J Allergy Clin Immunol*. 2022;150(6):1265–1278.

Chapter 184

Allergic Rhinitis

Tamara T. Perry and Scott H. Sicherer

Allergic rhinitis (AR) is a common chronic disease affecting 20–30% of children. AR is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children derives from its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a threefold increase in risk for asthma at an older age. Over the past 50 years an upsurge in AR has been observed throughout the world, with some symptom surveys reporting incidence rates approaching 40%. Heritability of allergic conditions attests to genetic factors, but the increase stems from changes in the environment, diet, and the microbiome. The symptoms may appear in infancy, with the diagnosis generally established by the time the child reaches age 6 years. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum IgE higher than 100 IU/mL before age 6 years. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children who are exposed to tobacco smoke prenatally, and above all before the infants reach 1 year, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible child is at greatest risk of sensitization. Delivery by cesarean section is associated with AR and atopy in children with a parental history of asthma or allergies. This association may be explained by the lack of exposure to the maternal microbiota through fecal/vaginal flora during delivery.

Children between 2 and 3 years old who have elevated anticockroach and antimouse IgE are at increased risk of wheezing, AR, and atopic dermatitis. The occurrence of three or more episodes of rhinorrhea in the first year of life is associated with AR at age 7 years. Favorably, the exposure to dogs, cats, and endotoxin early in childhood protects against the development of atopy. Prolonged breastfeeding, not necessarily exclusive, is beneficial. There is also a decreased risk of asthma, AR, and atopic sensitization with early introduction to wheat, rye, oats, barley, fish, and eggs. However, reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age.

ETIOLOGY AND CLASSIFICATION

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent.** The two sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent, moderate-severe intermittent, mild-persistent,** and **moderate-severe persistent** (Fig. 184.1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR, symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and there is no incapacity at work or school. Severe symptoms result in sleep disturbance and impairment in daily activities and school performance.

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates they persist throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of symptom occurrence, the regional patterns of pollination and mold sporulation, and the patient's allergen-specific IgE **(sIgE)** is necessary to recognize the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the United States. The allergens from saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners' clothing into such "cat-free" settings as schools and hospitals.

PATHOGENESIS

The exposure of an atopic host to an allergen leads to the production of sIgE, which is strongly associated with eczema throughout childhood and with asthma and rhinitis after age 4 years. The clinical reactions on reexposure to the allergen have been designated as *early-phase* and *late-phase* allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates the early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators, including histamine, prostaglandin 2, and the cysteinyl leukotrienes. The late-phase allergic response appears 4-8 hour following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin (IL)-3, IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes "priming," which is a more brisk response even with a lesser provocation. Over the course of an allergy season, a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease.

CLINICAL MANIFESTATIONS

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the **allergic salute**, an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the **nasal crease**, a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include

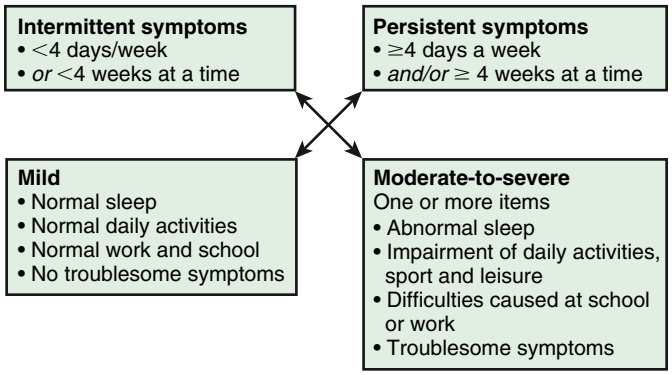

Fig. 184.1 Global Allergic Rhinitis and Its Impact on Asthma (ARIA) classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-severe persistent seasonal rhinitis in June and July and may be suitable for specific allergen immunotherapy. *(From Scadding GK, Durham SR, Mirakian R, et al. BASCI guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy. 2008;38:19–42.)*

intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste, though this has also been noted as a symptom of mild COVID-19 or other viral upper respiratory infections. Some experience headaches, wheezing, and coughing. Preschoolers with chronic wheezing and rhinitis experience more severe wheezing than children without rhinitis. Nasal congestion is often more severe at night, inducing mouth breathing and snoring, interfering with sleep, and rousing irritability.

Signs on physical examination include abnormalities of facial development, dental malocclusion, the **allergic gape** (continuous open-mouth breathing), chapped lips, **allergic shiners** (dark circles under the eyes; see Fig. 183.1), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

DIFFERENTIAL DIAGNOSIS

Evaluation of AR entails a thorough history, including details of the patient's environment and diet and a family history of allergic conditions (e.g., eczema, asthma, AR), physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms such as sneezing, rhinorrhea, nasal itching, and congestion and lab findings of elevated IgE, sIgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. **Nonallergic rhinitides** give rise to sporadic symptoms; their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. **Vasomotor rhinitis** is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis, structural problems (e.g., nasal polyps, septal deviation), **rhinitis medicamentosa** (caused by overuse of topical vasoconstrictors), hormonal rhinitis associated with pregnancy or hypothyroidism, neoplasms, vasculitides, and granulomatous disorders may mimic AR (Table 184.1 and Fig. 184.2). Occupational risks for rhinitis include exposure to allergens (grain dust, insects, latex, enzymes) and irritants (wood dust, paint, solvents, smoke, cold air).

COMPLICATIONS

AR is associated with complications and comorbid conditions. Undertreated AR detracts from the quality of life, aggravates asthma, and enhances its progression. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness, and swelling of the conjunctivae, has been reported in at least 20% of the population and >70% of patients with AR, most frequently in older children and young adults. The two conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 188). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia.

Aspirin-exacerbated respiratory disease (AERD) is characterized by the presence of chronic rhinosinusitis with nasal polyposis, asthma, and aspirin sensitivity. The pathophysiology of AERD is not fully understood and symptoms often respond poorly to therapy such as leukotriene modifiers, intranasal or systemic steroids, and aspirin desensitization. Surgical removal of nasal polyps is also a common intervention; however, the rate of recurrence is high with frequent regrowth of polyps. New biologic therapies are available for patients with chronic rhinosinusitis with nasal polyposis and patients with AERD may benefit from the addition of these new therapies.

Table 184.1 Causes of Rhinitis

ALLERGIC RHINITIS
Seasonal
Perennial
Perennial with seasonal exacerbations
NONALLERGIC RHINITIS
Structural/Mechanical Factors
Deviated septum/septal wall anomalies
Hypertrophic turbinates
Adenoidal hypertrophy
Foreign bodies
Nasal tumors
Benign
Malignant
Choanal atresia
CSF leakage
Infectious
Acute infections
Chronic infections
Congenital syphilis
Inflammatory/Immunologic
Granulomatosis with polyangiitis
Sarcoidosis
Midline granuloma
Systemic lupus erythematosus
Sjögren syndrome
Nasal polyposis
Physiologic
Primary ciliary dyskinesia
Atrophic rhinitis
Hormonally induced
Hypothyroidism
Pregnancy
Oral contraceptives
Menstrual cycle
Exercise
Atrophic
Drug induced
Rhinitis medicamentosa
Oral contraceptives
Antihypertensive therapy
Aspirin
Nonsteroidal antiinflammatory drugs
Cocaine
Reflex induced
Gustatory rhinitis
Chemical or irritant induced
Posture reflexes
Nasal cycle
Environmental factors
Odors
Temperature (cold air)
Weather/barometric pressure
Occupational (irritants)
OTHER
Nonallergic rhinitis with eosinophilia syndrome
Perennial nonallergic rhinitis (vasomotor rhinitis)
Emotional factors

From Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(1 Suppl);108:S2–S8.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction

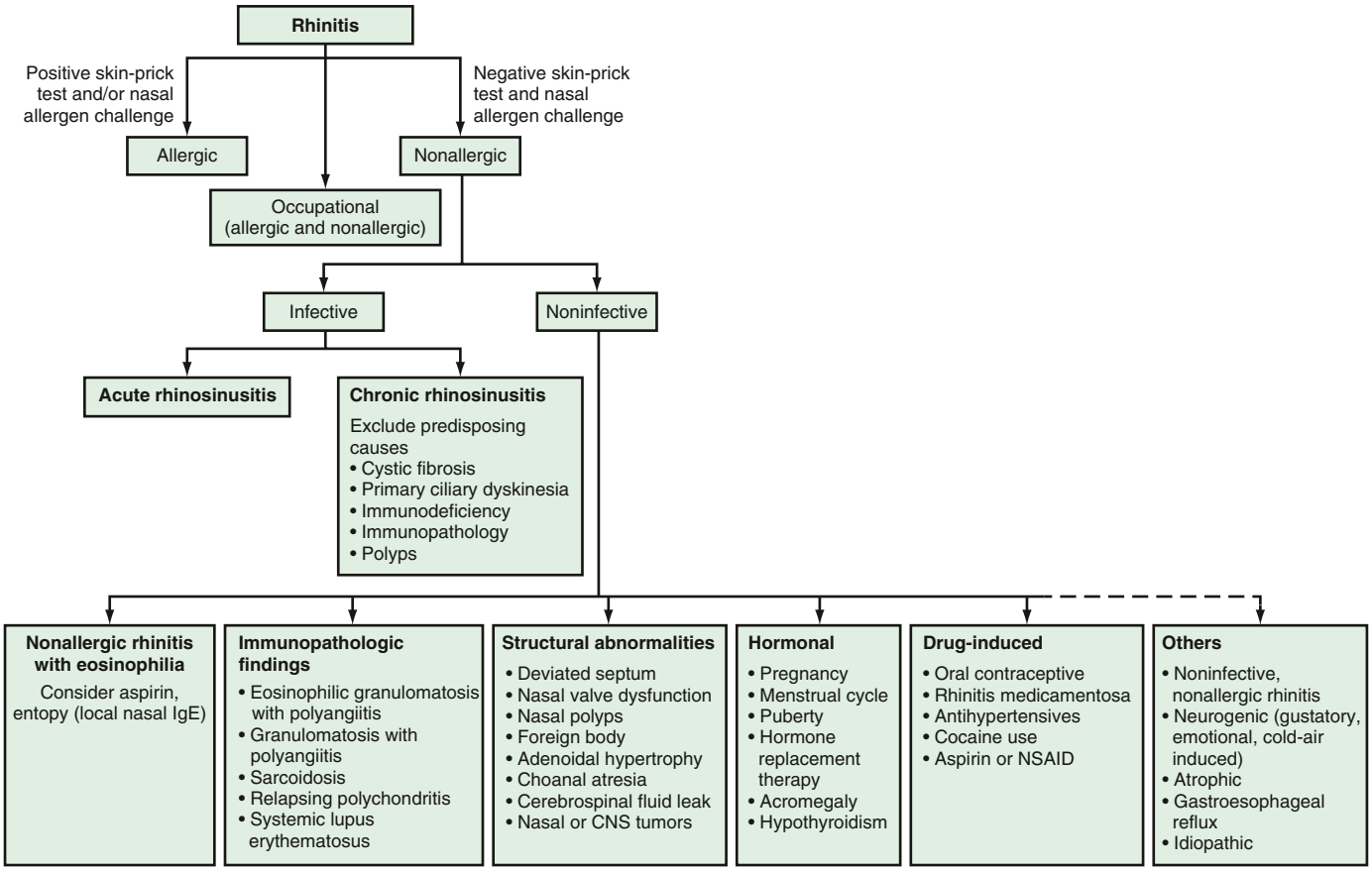

Fig. 184.2 Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. CNS, Central nervous system; NSAID, nonsteroidal antiinflammatory drug. *(From Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet. 2011;378:2112–2120.)*

and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented and may require multidisciplinary intervention.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 years old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 years old. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. AR causes an estimated 824,000 missed school days and 4,230,000 days of decline in quality-of-life activities. Patients with AR report an impairment in the activities of daily living similar to patients with moderate to severe asthma. Some (but not many) patients improve during their teenage years, only to develop symptoms again as young adults. Symptoms often abate in the fifth decade of life.

LABORATORY FINDINGS

Epicutaneous skin tests provide the best method for detection of sIgE, with a positive predictive value (PPV) of 48.7% for epidemiologic diagnosis of AR. Skin tests are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before two seasons of exposure, and children <1 year old seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and nonsedating antihistamines for 5-7 days. Serum immunoassays for sIgE provide a suitable alternative (PPV of 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in the nasal smear supports the diagnosis of AR, and neutrophils suggest infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

TREATMENT

Guideline-directed management has been shown to improve disease control. **Global Allergic Rhinitis and its Impact on Asthma (ARIA)** provides an evidence-based approach to treatment and includes quality-of-life measures useful for the evaluation of symptoms and the assessment of the response to therapy. Safe effective prevention and relief of symptoms are the current goals of treatment. **Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease.** Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergen. Bed linen and blankets should be washed every week in hot water (>54.4°C [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air (HEPA) filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea, and ocular symptoms. Administered as needed, antihistamines provide acceptable treatment for mild-intermittent disease. Antihistamines have been

Table 184.2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES *Desloratadine*			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo to 5 yr: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr: 2.5 mg once daily
			Adults and adolescents ≥12 yr: 5 mg once daily
LEUKOTRIENE ANTAGONIST† *Montelukast*			
Singulair	10 mg	Tablets	6 mo to 5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine
†As advised by the FDA, montelukast should be used to treat allergic rhinitis only in patients who are not treated effectively with or cannot tolerate other alternative therapies.
Dosing recommendations taken in part from Kleinman K, McDaniel L, Molloy M for the Johns Hopkins Hospital. *The Harriet Lane Handbook*. 22nd ed. Philadelphia: Elsevier; 2021.

classified as **first generation** (relatively sedating) or **second generation** (relatively nonsedating). Antihistamines usually are administered by mouth but are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. **Second-generation antihistamines are preferred because they cause less sedation.** Preparations containing **pseudoephedrine**, typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. These are not considered first-line agents and should be used with caution. Pseudoephedrine is available without prescription generally in fixed combination with other agents such as first-generation antihistamines (brompheniramine, chlorpheniramine, triprolidine), second-generation antihistamines (desloratadine, fexofenadine, loratadine), antipyretics (acetaminophen, ibuprofen), antitussives (guaifenesin, dextromethorphan), and an anticholinergic (methscopolamine). Pseudoephedrine is an oral vasoconstrictor distrusted for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 years) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children <4 years old. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Tables 184.2, 184.3, and 184.4 provide examples of prescription, nonprescription, and combined oral agents, respectively, for treatment of AR. Oral leukotriene receptor antagonists are not recommended for initial treatment of AR because of reduced efficacy compared to other agents and serious neuropsychiatric events that have been reported with montelukast.

The anticholinergic **nasal spray** ipratropium bromide is effective for the treatment of *serous* rhinorrhea (Table 184.5). **Intranasal decongestants** (oxymetazoline and phenylephrine) should be used for <5 days and should not to be repeated more than once a month to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, every 4 hours. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 185 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require **intranasal corticosteroids**, the most effective therapy for AR, which may also be beneficial for concomitant allergic conjunctivitis (Table 184.6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Allergen-specific immunotherapy is a well-defined treatment for IgE-mediated allergic disease. It may be administered by subcutaneous or sublingual routes. **Sublingual immunotherapy** (SLIT) has been used successfully in Europe and South America and is now approved by the U.S. Food and Drug Administration. **Allergy immunotherapy** (AIT) is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Immunotherapy for AR prevents the onset of asthma. Moreover, progress in molecular characterization of allergens raises the possibility of defined vaccines for allergen immunotherapy. Omalizumab (anti-IgE antibody) is effective for difficult-to-control asthma and is likely to have a beneficial effect on coexisting AR. Dupilumab (IL-4 antagonist) is approved *in adults* for the treatment of chronic rhinosinusitis with nasal polyposis and has shown improvement in nasal symptoms scores as well as improvements in lung function among patients with AERD.

Typically, treatment of AR with oral antihistamines and nasal corticosteroids provides sufficient relief for most patients with coexisting **allergic conjunctivitis**. If it fails, additional therapies directed primarily at allergic conjunctivitis may be added (see Chapter 188). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but ophthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy, although they carry the risk of adverse effects such as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataracts. Ophthalmic corticosteroids are only suited for the treatment of allergic conjunctivitis that does not respond to the medications previously discussed. Sound practice calls for the assistance of an ophthalmologist.

Table 184.3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton OTC	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (max 6 mg/day) 6-11 yr: 2 mg every 4-6 hr (max 12 mg/day)
Chlor-Trimeton Syrup OTC	2 mg/5 mL	Syrup	>12 yr: 4 mg every 4-6 hr (max 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup OTC	1 mg/mL	Syrup	6-11 mo: 2.5 mg daily
Children's Zyrtec Chewable OTC	5 mg, 10 mg	Chewable tablets	12-23 mo: initial 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec Tablets OTC	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to max of 5 mg/day given either as a single dose or divided into two doses
Zyrtec Liquid Gels OTC	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into two doses
Levocetirizine Xyzal	5 mg 0.5 mg/mL	Tablet Oral solution	6 mo-5 yr: 1.25 mg daily in the evening 6-11 yr: 2.5 mg daily in the evening ≥12 yr: 5 mg daily in the evening
Desloratadine			
Clarinex	0.5 mg/mL	Oral solution	6-11 mo: 1 mg daily 1-5 yr: 1.25 mg daily 6-11 yr: 2.5 mg daily
Clarinex	5 mg	Tablet	≥12 yr 5 mg daily
Fexofenadine HCl OTC	30 mg, 60 mg, 180 mg	Tablet	6-11 yr: 30 mg twice daily 12-adult: 60 mg twice daily; 180 mg daily
Children's Allegra OTC ODT*	30 mg	ODTs	6-11 yr: 30 mg twice daily
Children's Allegra Oral Suspension OTC	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra OTC	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg daily
Loratadine			
Children's Claritin OTC	5 mg/5 mL	Syrup	2-5 yr: 5 mg daily 6-adult: 10 mg daily
Alavert OTC ODT*	10 mg 10 mg 10 mg 5 mg 1 mg/mL	ODTs Tablets Liquid-filled caps Chewable tablets Syrup	2-5 yr: 5 mg daily >6 yr: 10 mg once daily or 5 mg twice daily

*Contains phenylalanine.
ODT, Orally disintegrating tablet; OTC, over the counter.
Dosing recommendations taken in part from Kleinman K, McDaniel L, Molloy M for the Johns Hopkins Hospital. *The Harriet Lane Handbook*. 22nd ed. Philadelphia: Elsevier; 2021.

Table 184.4 Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine HCl Sudafed Sinus & Allergy	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr, not to exceed 6 tablets per day
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended-release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Kleinman K, McDaniel L, Molloy M for the Johns Hopkins Hospital. *The Harriet Lane Handbook*. 22nd ed. Philadelphia: Elsevier; 2021.

Table 184.5 Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established *Adverse effects:* Epistaxis, nasal dryness, nausea
Atrovent nasal spray (0.06%)	Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril tid ≥12 yr and adults: 2 sprays in each nostril tid-qid	
Azelastine	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus *M:* Antagonism of histamine H_1 receptor	May cause drowsiness *Adverse effects:* Headache, somnolence, bitter taste
Astelin	6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	
Cromolyn sodium	*I:* AR *M:* Inhibition of mast cell degranulation	Not effective immediately; requires frequent administration
NasalCrom	>2 yr: 1 spray tid-qid; max 6 times daily	
Oxymetazoline Afrin Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril bid; therapy should not exceed 3 days	Excessive dosage may cause profound CNS depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, or diabetes *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, dizziness
Neo-Synephrine	2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed *Note:* Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed *Note:* Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion *Note:* Therapy should not exceed 3 continuous days	

bid, 2 times daily; CNS, central nervous system; tid, 3 times daily; qid, 4 times daily.

Table 184.6 Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Beconase AQ (42 μg/spray) Qnasl (80 μg/spray) OTC	6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	
Flunisolide OTC	6-14 yr: 1 spray in each nostril tid *or* 2 sprays in each nostril bid; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays in each nostril bid (morning and evening); may increase to 2 sprays tid; maximum dose: 8 sprays/day in each nostril (400 μg/day)	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth

Table 184.6 Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone Nasacort AQ (55 µg/spray) OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as generic preparation) OTC	2-6 yr: 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	
	I: AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flonase (50 µg/spray) OTC	≥4 yr: 1-2 sprays in each nostril qd	
Fluticasone furoate Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril qd (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril qd (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg qd Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril qd (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril qd (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day	
Mometasone	*I:* AR *M:* Antiinflammatory, immune modulator	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk before pollen season Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Nasonex (50 µg/spray)	2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	
Budesonide OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Rhinocort Aqua (32 µg/spray) OTC	6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (max dose)	
Ciclesonide	*I:* AR *M:* Antiinflammatory, immune modulator	Before initial use, gently shake, then prime the pump by actuating 8 times If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Omnaris Zetonna (50 µg/spray)	2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	
Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista	≥6 yr: 1 spray in each nostril bid	Shake bottle gently before using Blow nose to clear nostrils Keep head tilted downward when spraying Insert applicator tip 1/4 to 1/2 inch into nostril, keeping bottle upright, and close off the other nostril Breathe in through nose While inhaling, press pump to release spray

OTC, Over the counter; AR, allergic rhinitis; qd, once daily; bid, 2 times daily; tid, 3 times daily.

PROGNOSIS

Therapy with nonsedating antihistamines and topical corticosteroids, when taken appropriately, improves health-related quality-of-life measures in patients with AR. The reported rates of remission among children are 10–23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Bibliography

Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol*. 2013;131:1288–1296.

Codispoti CD, Bernstein DI, Levin L, et al. Early-life mold and tree sensitivity is associated with allergic eosinophilic rhinitis at 4 yr of age. *Ann Allergy Asthma Immunol*. 2015;114:193–198.e4.

Cox LS. Sublingual immunotherapy for allergic rhinitis—is 2-year treatment sufficient for long-term benefit? *JAMA*. 2017;317(6):591–593.

Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. 2020;146(4):721–767.

Federal Drug Administration. *Singulair (montelukast) and all montelukast generics: strengthened boxed warning – due to restricting use for allergic rhinitis*. https://www.fda.gov/safety/medical-product-safety-information/singulair-montelukast-and-all-montelukast-generics-strengthened-boxed-warning-due-restricting-use.

Garcia-Aymerich J, Benet M, Saeys Y, et al. Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. *Allergy*. 2015;70:973–984.

Kim JM, Lin SY, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics*. 2013;131(6):1155–1167.

Laidlaw TM, Mullol J, Fan C, et al. Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and AERD. *J Allergy Clin Immunol Pract*. 2019;7:2462.

Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013;309:1278–1288.

Patil VK, Kurukulaaratchy RJ, Venter C, et al. Changing prevalence of wheeze, rhinitis and allergic sensitisation in late childhood: Findings from 2 Isle of Wight birth cohorts 12 yr apart. *Clin Exp Allergy*. 2015;45:1430–1438.

Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2013;68:1102–1116.

Scadding GK. Optimal management of allergic rhinitis. *Arch Dis Child*. 2015;100:576–582.

Schmitt J, Schwarz K, Stadler E, et al. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol*. 2015;136:1511–1516.

The Medical Letter. Allergic rhinitis. *Med Lett Drugs Ther*. 2017;59:71–80.

Valenta R, Campana R, Focke-Tejkl M, et al. Vaccine development for allergen-specific immunotherapy based on recombinant allergens and synthetic allergen peptides: lessons from the past and novel mechanisms of action for the future. *J Allergy Clin Immunol*. 2016;137:351–357.

Wallace DV, Dykewicz MS, Oppenheimer J, et al. Pharmacologic treatment of seasonal allergic rhinitis: synopsis of guidance from the 2017 joint task force on practice parameter. *Ann Intern Med*. 2017;167:876–881.

Westman M, Lupinek C, Bousquet J, et al. Early childhood IgE reactivity to pathogenesis-related class 10 proteins predicts allergic rhinitis in adolescence. *J Allergy Clin Immunol*. 2015;135. 1199-1206.e1–1199-1206.e11.

Wheatly LM, Togias A. Allergic rhinitis. *N Engl J Med*. 2015;372(15):456–462.

bronchiolitis in the first year of life is a significant predisposing factor for asthma at age 5 years. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in early childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures and are causally linked to disease severity, exacerbations, and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air; hyperventilation from physical play or exercise; and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental features underlying the development of host susceptibilities to the various common airway exposures are not as well defined. Living in rural or farming communities may be a protective environmental factor.

EPIDEMIOLOGY

Asthma is a common chronic disease, causing considerable morbidity. In 2020 >7 million children (~11% of U.S. children) had been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the United States. About 13% of males vs 9% of females have had asthma, and ~15% of all children living in poor families (family income less than poverty threshold) have asthma. Childhood asthma is among the most common causes of childhood emergency department (ED) visits, hospitalizations, and missed school days. In the United States in 2019, childhood asthma accounted for >750,000 ED visits, nearly 75,000 hospitalizations, and 178 deaths. However, there are ethnic disparities in asthma outcomes, with nearly three times more deaths as a result of asthma in Black non-Hispanic vs White non-Hispanic children.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Although childhood asthma may have plateaued in the United States after 2008, numerous studies conducted in other countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6–7-year-old children (2.4–37.6%) and 13–14-year-old children (0.8–32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset before 6 years of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 185.1) and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. *Allergen sensitization (allergy) in young children with recurrent cough and/or wheeze* is the strongest identifiable factor for the persistence of childhood asthma.

Types of Childhood Asthma

There are two common types of childhood asthma based on different natural courses: (1) **recurrent wheezing** in *early* childhood, primarily triggered by common respiratory viral infections, that usually resolves during the preschool/lower school years and (2) **chronic asthma** associated with *allergy* that persists into later childhood and often adulthood

Table 185.1 Early Childhood Risk Factors for Persistent Asthma

Parental asthma*
Allergy
• Atopic dermatitis (eczema)*
• Allergic rhinitis
• Food allergy
• Inhalant allergen sensitization*
• Food allergen sensitization
Severe lower respiratory tract infection
• Pneumonia
• Bronchiolitis requiring hospitalization
Wheezing apart from colds
Male sex
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth
Formula feeding rather than breastfeeding

*Major risk factors.

(Table 185.2). School-age children with mild to moderate persistent asthma generally improve as teenagers. About 40% of these children, most of whom have milder disease, will develop intermittent disease. Inhaled corticosteroid (ICS) controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, reduced lung growth and progressive decline in lung function can be features of persistent, problematic disease.

Asthma is also classified by **disease severity** (e.g., intermittent or persistent [mild, moderate, or severe]) or **control** (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as (1) **easy to control** (well controlled with low levels of controller therapy); (2) **difficult to control** (not as well controlled with multiple and/or high levels of controller therapies); (3) **exacerbators** (despite being controlled, continue to have severe exacerbations); and (4) **refractory asthma** (continue to have poorly controlled asthma despite multiple and high levels of controller therapies; see Table 185.2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

PATHOGENESIS

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airway's lumen. T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 185.3) can lead to airways inflammation, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion, which are all processes that contribute to the clinical manifestations of asthma. Although most children with asthma manifest this proallergic "type 2" immunity and inflammation, other pathologic pathways can underlie asthma.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Asthma is characterized by repeated episodes of intermittent dry coughing and expiratory wheezing. Older children and adults report

Table 185.2 Asthma Patterns in Childhood, Based on Natural History and Asthma Management

TRANSIENT NONATOPIC WHEEZING

Common in early preschool years

Recurrent cough/wheeze, primarily triggered by common respiratory viral infections

Usually resolves during the preschool and lower school years, without increased risk for asthma in later life

Reduced airflow at birth, suggestive of relatively narrow airways; AHR near birth; improves by school age

PERSISTENT ATOPY-ASSOCIATED ASTHMA

Begins in early preschool years

Associated with atopy in early preschool years

- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum IgE, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities

- Those with onset before 3 yr of age acquire reduced airflow by school age
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood

ASTHMA WITH DECLINING LUNG FUNCTION

Children with asthma with progressive increase in airflow limitation

Associated with hyperinflation in childhood, male gender

ASTHMA MANAGEMENT TYPES

(From national and international asthma management guidelines)

*Severity Classification**

- Intrinsic disease severity while not taking asthma medications

Intermittent

Persistent

- Mild
- Moderate
- Severe

*Control Classification**

- Clinical assessment while asthma being managed and treated

Well controlled

Not well controlled

Very poorly controlled

Management Patterns

- *Easy-to-control:* well controlled with low levels of daily controller therapy
- *Difficult-to-control:* inadequately controlled with multiple and/or high levels of controller therapies
- *Frequent exacerbators:* have severe exacerbations
- *Refractory:* continue to have poorly controlled asthma despite multiple and high levels of controller therapies

*From National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): *Guideline for the Diagnosis and Management of Asthma,* NIH Pub No 07-4051, Bethesda, MD, 2007, US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report.

AHR, Airways hyperresponsiveness.

Table 185.3 Asthma Triggers

COMMON VIRAL INFECTIONS OF THE RESPIRATORY TRACT

AEROALLERGENS IN SENSITIZED ASTHMATIC PATIENTS

Indoor Allergens

- Animal dander
- Dust mites
- Cockroaches
- Molds

Seasonal Aeroallergens

- Pollens (trees, grasses, weeds)
- Seasonal molds

AIR POLLUTANTS

- Environmental tobacco smoke
- Ozone
- Nitrogen dioxide
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Mycotoxins
- Endotoxin
- Dust

STRONG OR NOXIOUS ODORS OR FUMES

- Perfumes, hairsprays
- Cleaning agents

OCCUPATIONAL EXPOSURES

- Farm and barn exposures
- Formaldehydes, cedar, paint fumes
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

DRUGS

- Aspirin and other nonsteroidal antiinflammatory drugs
- β-Blocking agents

OTHER

- Cold dry air
- Exercise
- Crying, laughter, hyperventilation
- Comorbid conditions

associated shortness of breath and chest congestion and tightness; younger children may report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators and/or corticosteroids) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 185.3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, RSV, enterovirus, coronavirus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae, Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry, cold air and irritant exposures. An environmental history is essential for optimal asthma management.

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma typically present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal.

Deeper breaths with forced exhalation can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 minutes) or convincing improvement in symptoms and signs of asthma with administration of an **inhaled short-acting β-agonist** (**SABA**; e.g., albuterol) is supportive of the diagnosis of asthma.

Asthma exacerbations can be classified by their severity based on symptoms, signs, and functional impairment (Table 185.4). Coughing and shortness of breath are common. Expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lung field, are consistent with regional hypoventilation caused by airways obstruction. **Rhonchi** and **crackles** (or **rales**) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard **(silent chest)**.

DIFFERENTIAL DIAGNOSIS

Many childhood respiratory conditions can present with symptoms and signs like those of asthma (Table 185.5). Along with asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

In early life, consideration of congenital and anatomic conditions is essential. Chronic coughing and wheezing can indicate recurrent aspiration, **tracheobronchomalacia** (congenital anatomic abnormality of airways), vascular ring/sling, foreign body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, **vocal cord dysfunction (VCD)** can manifest as intermittent daytime wheezing, most often in the setting of exercise (Table 185.6). The vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals truncated and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Hypercarbia and severe hypoxia are uncommon in uncomplicated VCD. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. Before the diagnosis, patients with VCD are often treated unsuccessfully

Table 185.4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant: softer, shorter cry, difficulty feeding)	While at rest (infant: stops feeding)	Extreme dyspnea Anxiety
	Can lie down	Prefers sitting	Sits upright	Upright, leaning forward
Talks in…	Sentences	Phrases	Words	Unable to talk
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate†	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)‡	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40–69% or response lasts <2 hr	<40%	<25%§
Pa_{O_2} (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
P_{CO_2}	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
Sa_{O_2} (breathing air) at sea level	>95% (test not usually necessary)	90–95% (test not usually necessary)	<90%	Hypoxia despite oxygen therapy
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

*Notes:
- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other; thus they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

†Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.
‡Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.
§Peak expiratory flow testing may not be needed in very severe attacks.
Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). *Guideline for the Diagnosis and Management of Asthma*, NIH Pub No 07-4051, Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program: 2007. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report.

Table 185.5 Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS

Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body

LARGE/CENTRAL AIRWAYS CONDITIONS

Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Endobronchial or mediastinal tumor
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Repaired tracheoesophageal fistula
Toxic inhalations

PERIPHERAL AIRWAYS CONDITIONS

Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis
- Cystic fibrosis
- Immunodeficiency
- Allergic bronchopulmonary mycoses (e.g., aspergillosis)
- Chronic aspiration

Primary ciliary dyskinesia
Bronchiolitis obliterans
Interstitial lung diseases
Hypersensitivity pneumonitis (acute or chronic)
Loeffler syndrome
Eosinophilic granulomatosis with angiitis
Eosinophilic pneumonia
Tropical pulmonary eosinophilia
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Pulmonary vascular congestions (congenital or acquired heart disease)
Vasculitis
Sarcoidosis
Visceral larva migrans
Medications associated with chronic cough
- Acetylcholinesterase inhibitors
- β-Adrenergic antagonists
- Angiotensin-converting enzyme inhibitors
- Daptomycin

*More common asthma masqueraders.

Table 185.6 Features Distinguishing Paradoxical Vocal Cord Motion Disorder from Asthma

FEATURE	PVCM	ASTHMA
Incidence	Less common	More common
Age and sex	Young, female	Any
Triggers	Usually exercise or emotional stress	Many triggers
History of allergy	Usually absent	May be present
Family history	Usually absent	May be present
Sensation of tightness	Throat	Chest
Inspiratory stridor	More common, heard loudly over larynx	Rare
Sputum production	Rare	Common
Nocturnal awakening with symptoms	Rare	Common
Response to bronchodilators and steroids	No response	Good response
Hypoxemia	Rare	Common
Eosinophilia	Rare	Common in allergic asthma
Chest radiograph	Usually normal	May show hyperinflation and peribronchial thickening
Residual volume and total lung capacity	Normal	May be increased
Flow volume loop	Flattening of inspiratory loop	Obstructive pattern
Bronchial provocation test	May be positive	Usually positive
Laryngoscopy	Inspiratory adduction of the anterior two thirds of vocal folds with posterior chink	Usually normal

PVCM, Paradoxical vocal cord motion.
Modified from Ibrahim WH, Gheriani HA, Almohamed AA, Raza T. Paradoxical vocal cord motion disorder: Past present and future. *Post Grad Med J*. 2007;83:164–172. Table 2, p 168.

with multiple different classes of asthma medications. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be causes of chronic coughing and/or wheezing. Rare mimics of asthma in childhood are noted in Table 185.5.

Chronic pulmonary diseases often produce clubbing (e.g., in cystic fibrosis), but clubbing is a very unusual finding in childhood asthma.

LABORATORY FINDINGS

Laboratory tests such as blood eosinophil counts and allergen-specific IgE testing may be useful for ascertaining allergy, but are not diagnostic for asthma itself. Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

Pulmonary Function Testing

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction, or when physical signs of asthma do not occur until airflow obstruction is severe.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. **Spirometry** is a helpful objective measure of airflow limitation (Fig. 185.2). It is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >4-5 years old (with some younger exceptions).

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 185.2). Because asthmatic patients typically have hyperinflated lungs, forced expiratory volume in 1 second (FEV_1) can be simply adjusted for full expiratory lung volume (the forced vital capacity [FVC]) with an FEV_1/FVC ratio, which is generally an FEV_1/FVC ratio below the lower limit of normal (Table 185.7). Normative values for these measures of lung function have been determined for children by height, gender, and age. Abnormally low FEV_1 as a percentage of predicted norms is one of six criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the **Global Initiative for Asthma (GINA)**.

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow limitation. In addition, approximately 50% of children with mild to moderate persistent asthma will have normal spirometric values when well. **Bronchodilator**

Table 185.7 Lung Function Abnormalities in Asthma

Spirometry (in clinic)*†:

Airflow limitation

- Low FEV_1 (relative to percentage of predicted norms), although many children with asthma have normal FEV_1
- FEV_1/FVC ratio below the lower limit of normal for age

Bronchodilator response (to inhaled β-agonist) assesses *reversibility* of airflow limitation

Reversibility is determined by an increase in either FEV_1 >9–12% or predicted FEV_1 >10% after inhalation of a short-acting β-agonist (SABA)‡

Exercise challenge

- Worsening in FEV_1 ≥15%‡

Daily peak expiratory flow (PEF)* or FEV_1 monitoring: day-to-day and/or am-to-pm variation ≥20%‡

*PEF variability is insensitive, while being highly specific for asthma.
†Of note, >50% of children with mild to moderate asthma will have a normal FEV_1 and will not have a significant bronchodilator response.
‡Main criteria consistent with asthma.
FEV_1, Forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroid; ppb, parts per billion.

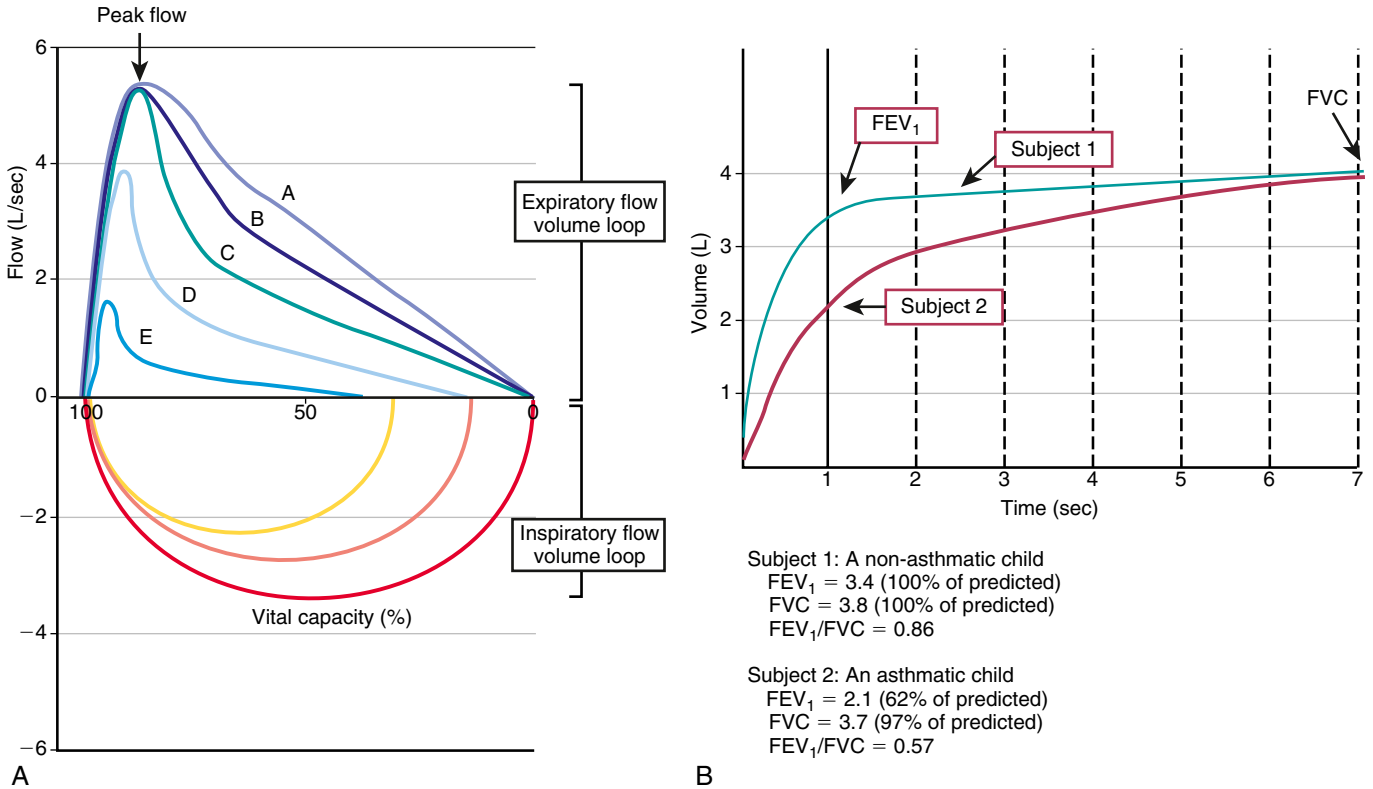

Fig. 185.2 Spirometry. **A**, Spirometric flow-volume loops. *Loop A* is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. *Loops B through E* are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." **B**, Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV_1 and FVC lung volumes are obtained. The FEV_1 is the volume of air exhaled in the first second of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV_1 and FEV_1:FVC ratio are smaller than subject 1's ratio, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

Table 185.8 Interpretations of FeNO Test Results for Asthma Diagnosis in Nonsmoking Individuals Not Taking Corticosteroids

FeNO LEVEL		
<25 PPB (<20 IN CHILDREN AGE 5-12 YR)	**25-50 PPB (20-35 IN CHILDREN AGE 5-12 YR)**	**>50 PPB (>35 IN CHILDREN AGE 5-12 YR)**
• Recent or current corticosteroid use • Alternative diagnoses • Phenotype less likely to benefit from ICS • Noneosinophilic asthma • COPD • Bronchiectasis • CF • Vocal cord dysfunction • Rhinosinusitis • Smoking • Obesity	• Evaluate in clinical context • Consider other diagnoses • Consider other factors influencing result • Eosinophilic asthma less likely	• Eosinophilic airways inflammation likely • Phenotype more likely to respond to ICS • Allergic asthma • Eosinophilic bronchitis

CF, Cystic fibrosis; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; ppb, parts per billion.
From NAEPPCC Expert Panel Working Group: 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol.* 2020;146(6):1217–1269. Table II.

response to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV_1 ≥12% is consistent with asthma. However, many children will not demonstrate an improvement with bronchodilator when well. **Bronchoprovocation challenges** can be helpful in diagnosing asthma. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. **Exercise challenges** (aerobic exertion or "running" for 6-8 minutes) can help to identify children with exercise-induced bronchospasm (EIB). Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV_1 slightly (5–10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV_1 typically decreases during or after exercise by >15% (see Table 185.7). The onset of EIB usually begins within 5 minutes, reaching a peak at 15 minutes after vigorous exercise, and often spontaneously resolves within 30-60 minutes. Studies of exercise challenges in school-age children typically identify an additional 5–10% with EIB and previously unrecognized asthma. There are two caveats regarding exercise challenges: (1) treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field and (2) exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for both bronchoprovocation and exercise challenges and preparedness for severe asthma exacerbations are required.

Peak expiratory flow (PEF) monitoring devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in some circumstances. Like spirometry in clinics, poor perceivers of asthma may benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction; they are less sensitive and reliable than spirometry to detect airflow obstruction, such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore PEF monitoring should be started by measuring morning and evening PEFs (best of three attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a "personal best," and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Table 185.7). If PEF monitoring is employed, morning measurements are preferable when peak flows are typically lower.

Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is a noninvasive measure of allergic/eosinophilic airways inflammation measured in exhaled breath (Table 185.8). FeNO can be used in children as young as 5 years to help distinguish asthma from other airways diseases that are mediated by nonallergic/noneosinophilic inflammation, such as GER, VCD, and cystic fibrosis. FeNO can substantiate the diagnosis of asthma in untreated patients, complement the assessment of asthma control, predict response to ICS and biologic therapy, assess adherence with ICS therapy, predict loss of control with ICS tapering, and predict future asthma exacerbations. However, an elevated FeNO level alone is not diagnostic of asthma and can be seen in children with allergic rhinitis without asthma.

Additional Tests to Consider

Other tests, such as allergy testing to assess sensitization to inhalant allergens (skin testing or allergen specific IgE levels) and peripheral blood total eosinophil counts, are markers of allergic "type 2" immunity and inflammation and can help with the management and prognosis of asthma. In a comprehensive U.S. study of 5–12-year-old asthmatic children, the Childhood Asthma Management Program (CAMP), 88% of patients had inhalant allergen sensitization according to results of allergy skin-prick testing.

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 185.3). Chest radiographs can help identify abnormalities that are hallmarks of asthma mimics (retained foreign body, vascular rings, aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. **Bronchiectasis**, which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implicates an asthma mimic such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

TREATMENT

National and international guidelines have been published to help promote evidence-based asthma management. These include the NIH-sponsored National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 4 (EPR4), *Guidelines for the Diagnosis and Management of Asthma*,* and The *Global Strategy for Asthma Management and Prevention (GINA), 2022*.† NAEPP and GINA guidelines are generally consistent in their management recommendations for children with asthma, with some key differences that are noted in this chapter.

The key components to optimal asthma management are specified (Fig. 185.4). Management of asthma should have the following

* https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates
† https://ginasthma.org/gina-reports/

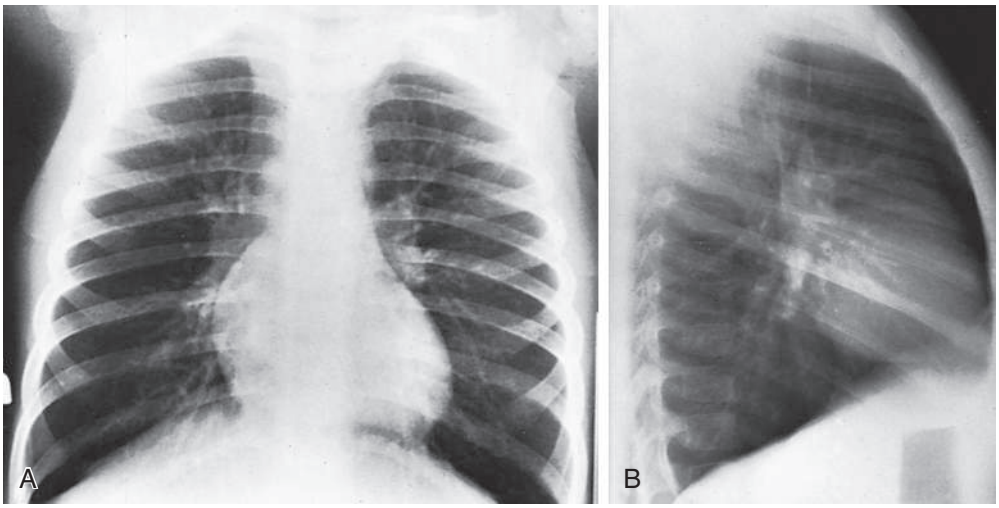

Fig. 185.3 Frontal (A) and lateral (B) radiographs of a 4-year-old with asthma show pulmonary hyperinflation, flattening of the diaphragms, and minimal peribronchial thickening. No asthmatic complication is apparent.

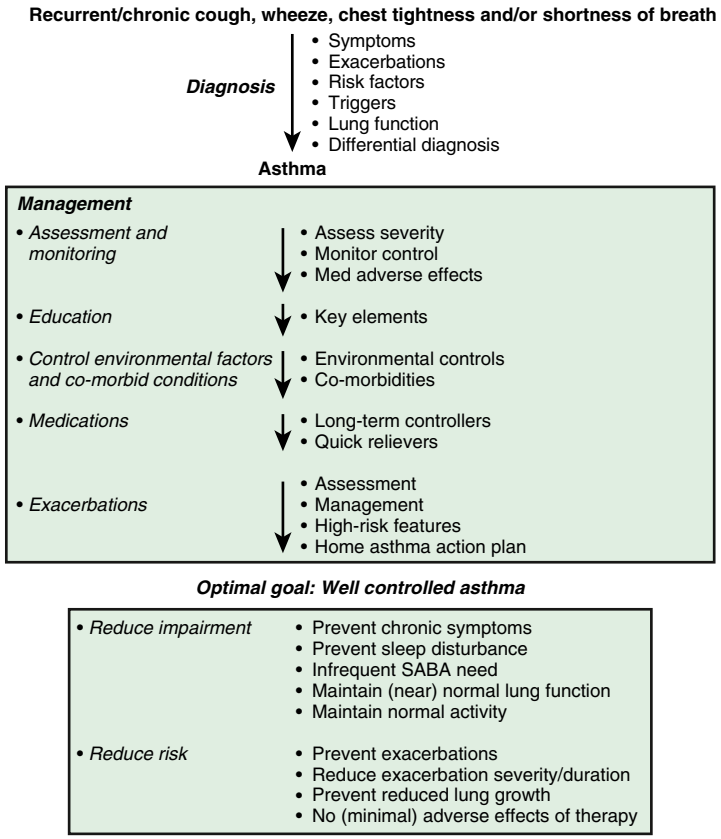

Fig. 185.4 The key elements to optimal asthma management. SABA, Short-acting β-agonist.

components: (1) assessment and monitoring of disease activity, (2) education to enhance patient and family knowledge and skills for self-management, (3) identification and management of precipitating factors and comorbid conditions that worsen asthma, and (4) appropriate selection of medications to address the patient's needs. The long-term goals of asthma management are to attain and maintain asthma control, to reduce risk of severe exacerbations, and to minimize impairment of daily activities.

Component 1: Regular Assessment and Monitoring

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. **Asthma severity** is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Therefore assessing asthma severity directs the initial level of therapy. The two general categories are **intermittent** asthma and **persistent** asthma, the latter being further subdivided into **mild, moderate,** and **severe.** In contrast, **asthma control** is dynamic and refers to the day-to-day variability of an asthmatic patient. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized into three levels: well controlled, not well controlled, and very poorly controlled. **Responsiveness to therapy** is the ease or difficulty with which asthma control is attained by treatment.

Classification of asthma severity and control is based on the domains of **impairment** and **risk**. These domains do not necessarily correlate with each other and may respond differently to treatment. Childhood asthma is often characterized by minimal day-to-day impairment, with the potential for frequent, severe exacerbations most often triggered by viral infections. The NIH and GINA guidelines have distinct criteria for three childhood age-groups, 0-4 years (GINA 0-5 years), 5-11 years (GINA 6-11 years), and ≥12 years, for the evaluation of both severity (Table 185.9) and control (Table 185.10). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, **impairment** consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the three age-groups), SABA use for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children ≥5 years. **Risk** refers to the likelihood of developing severe asthma exacerbations. Of note, even in the absence of frequent symptoms, persistent asthma can be diagnosed and long-term controller therapy initiated. For children ≥5 years, two exacerbations requiring oral corticosteroids (OCSs) in 1 year, and for infants and preschool-age children who have risk factors for asthma (see earlier) and four or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or two or more exacerbations in 6 months requiring systemic corticosteroids, qualifies them as having persistent asthma.

Asthma management can be optimized through regular clinic visits every 2-6 weeks until good asthma control is achieved. For children on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the three age-groups (see Table 185.10). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA use for quick relief, ability to engage in normal or desired activities, and for older children, airflow measurements. Validated asthma control questionnaires such as the **Asthma Control Test** (ACT, for adults and children ≥12 years), the **Childhood ACT** (C-ACT, for children 4-11 years), and the **Test for Respiratory and Asthma Control in Kids** (TRACK, for children <4 years) can also be used to assess level of control. An ACT score of ≥20 indicates a child with **well-controlled** asthma, a value of 16-19 indicates **not well-controlled** asthma, and ≤15 indicates **very poorly controlled** asthma. For the C-ACT, a score ≥20 indicates *well controlled*, 13-19 indicates *not well controlled*, and ≤12 indicates *very poorly controlled*. For the TRACK, a score of less than 80 points suggests that a child's breathing problems might not be controlled.

Assessment of risk, in addition to considering severity and frequency of exacerbations requiring systemic corticosteroids, includes tracking the lung growth of older children to identify those with reduced and/or progressive loss of lung function, and monitoring adverse effects of

Table 185.9 Assessing Asthma Severity*

	CLASSIFICATION OF ASTHMA SEVERITY			
		PERSISTENT		
	INTERMITTENT	MILD	MODERATE	SEVERE
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2-agonist use for symptoms (not for EIB prevention)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60–80% predicted	<60% predicted
FEV_1/FVC ratio†:				
Age 5-11 yr	>85%	>80%	75–80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic CS *or* ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.				

*Notes:
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma, may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

†Normal FEV_1/FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV_1, Forced expiratory volume in 1 sec; FVC, forced vital capacity; CS, corticosteroid; EIB, exercise-induced bronchospasm.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94–S138.

Table 185.10 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	WELL CONTROLLED	**NOT WELL CONTROLLED**	**VERY POORLY CONTROLLED**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2-agonist use for symptoms (not for EIB pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60–80% predicted or personal best	<60% predicted or personal best
FEV_1/FVC:	>80%	75–80%	<75%
Age ≥12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60–80% predicted or personal best	<60% predicted or personal best
Validated questionnaires†:			
Age ≥12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome; the level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care		
RECOMMENDED ACTION FOR TREATMENT			
	Maintain current step Regular follow-up every 1-6 mo to maintain control Consider step down if well controlled for at least 3 mo	Step up‡ (1 step) and reevaluate in 2-6 wk If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy For side effects, consider alternative options	Consider short course of oral corticosteroids Step up§ (1-2 steps) and reevaluate in 2 wk If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy For side effects, consider alternative options

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not well-controlled asthma, even in the absence of impairment levels consistent with not well-controlled asthma.

†Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0.
- ACQ, Asthma Control Questionnaire; MID = 0.5.
- ACT, Asthma Control Test; MID not determined.

‡ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

§Before step-up therapy: (1) review adherence to medications, inhaler technique, and environmental control and (2) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV_1, Forced expiratory volume in 1 sec; FVC, forced vital capacity; EIB, exercise-induced bronchospasm; N/A, not available.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR 3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94–S138.

medications. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well controlled, not well controlled, or very poorly controlled. Children with *well-controlled asthma* have daytime symptoms ≤2 days/week and need a rescue bronchodilator ≤2 days/week, an FEV_1 of >80% of predicted (and FEV_1/FVC ratio >80% for children 5-11 years), no interference with normal activity, and <2 exacerbations in the past year and an ACT score of ≥20. The impairment criteria vary slightly depending on age-group. Children whose status does not meet all the criteria of well-controlled asthma are determined to have either *not well-controlled* or *very poorly controlled* asthma, which is determined by the single criterion with the poorest rating.

Two to four asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, is inadequately controlled, and/or lung function is abnormally low.

Component 2: Patient Education

Asthma education that focuses on home management and medication adherence is critical for optimal clinical care of children with asthma (Table 185.11). Asthma education should consider sociocultural and ethnic factors and provide an open forum for concerns about asthma and its treatment. Families should be active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 184.4). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

All children with asthma should benefit from a written Asthma Action Plan (Fig. 185.5). This plan has two main components: (1) a daily "routine" management plan describing regular asthma medication use and other measures to keep asthma under good control and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Regular follow-up visits are recommended to help to maintain optimal asthma control. Follow-up visits provide the opportunity to reassess asthma medication perceptions and delivery techniques. The Asthma Action Plan can be revised as needed.

Table 185.11 Key Elements of Productive Clinic Visits for Asthma

Standardize assessment of asthma control (e.g., Asthma Control Test, exacerbations in past 12 mo)
Specify goals of asthma management
Explain basic facts about asthma
• Contrast normal vs asthmatic airways
• Link airways inflammation, "twitchiness," and bronchoconstriction
• Long-term-control and quick-relief medications
• Address concerns about potential adverse effects of asthma pharmacotherapy
Teach, demonstrate, and have patient show proper technique
• Inhaled medication use (spacer use with metered-dose inhaler)
Investigate and manage factors that contribute to asthma severity
• Environmental exposures
• Comorbid conditions
Create written two-part Asthma Action Plan (see Fig. 185.5)
• Daily management
• Action plan for asthma exacerbations
Regular follow-up visits
• Twice yearly (more often if asthma not well controlled)
• Monitor lung function at least annually

Adherence

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane and exacerbations may be infrequent. A natural tendency is to reduce or discontinue daily controller therapies once asthma symptoms improve. As such, adherence to a daily controller regimen is frequently suboptimal; ICSs are underused 60% of the time. In one study, children with asthma who required an OCS course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

Component 3: Control of Factors Contributing to Poor Asthma Control

Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 185.12).

Eliminating and Reducing Problematic Environmental Exposures

Steps should be taken to investigate and minimize exposures in asthmatic patients. These exposures include allergens as well as irritants (e.g., smoke, pollutants, and other chemicals such as perfumes), in the patient's home or school. However, patients often cannot identify potential triggers. **Allergy testing** should be considered for all patients with persistent asthma to identify allergens that may contribute to airway inflammation, asthma symptoms, and exacerbations. For asthmatic patients who are allergic to allergens in their homes and/or schools or daycare centers, reducing or eliminating these indoor allergen exposures can reduce asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home, school, and daycare allergen exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats, cockroaches), and occult indoor allergens such as dust mites and molds.

Allergen mitigation strategies can be used in patients with allergy of all ages and asthma severities, but these strategies should be tailored to the individual. Multicomponent interventions are recommended to control indoor allergens, because single component interventions are often not effective. Examples of single component interventions for dust mite allergy include (1) encasing bedding and pillows in allergen-impermeable covers, (2) washing bedding weekly in hot water (>130°F), (3) removing wall-to-wall carpeting and upholstered furniture, or (4) reducing and maintaining indoor humidity <50%. In contrast, a multicomponent strategy for dust mite allergy might include all of these measures. Integrated pest management strategies are also recommended for patients exposed to cockroaches, mice, or rats in the home who have sensitization to these allergens. Integrated pest management can also be used with other interventions to reduce exposures to pest-related allergens. Families should be educated that it can take ≥6 months for the levels of these indoor allergens to drop significantly and for asthma control to improve after intervention. Allergen mitigation strategies are not recommended for patients with no allergy to indoor allergens.

Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants (e.g., nitrogen dioxide from inadequately vented gas stoves and furnaces) can also aggravate asthma. These airway irritants should be eliminated from or reduced in the homes, schools/daycare centers, and automobiles/school transportation used by children with asthma. Care providers can be strong influencers of smoking cessation by parents, caregivers, and adolescent patients (see also Chapters 157.2 and 759.1). Secondhand marijuana smoke contains many of the same chemicals and

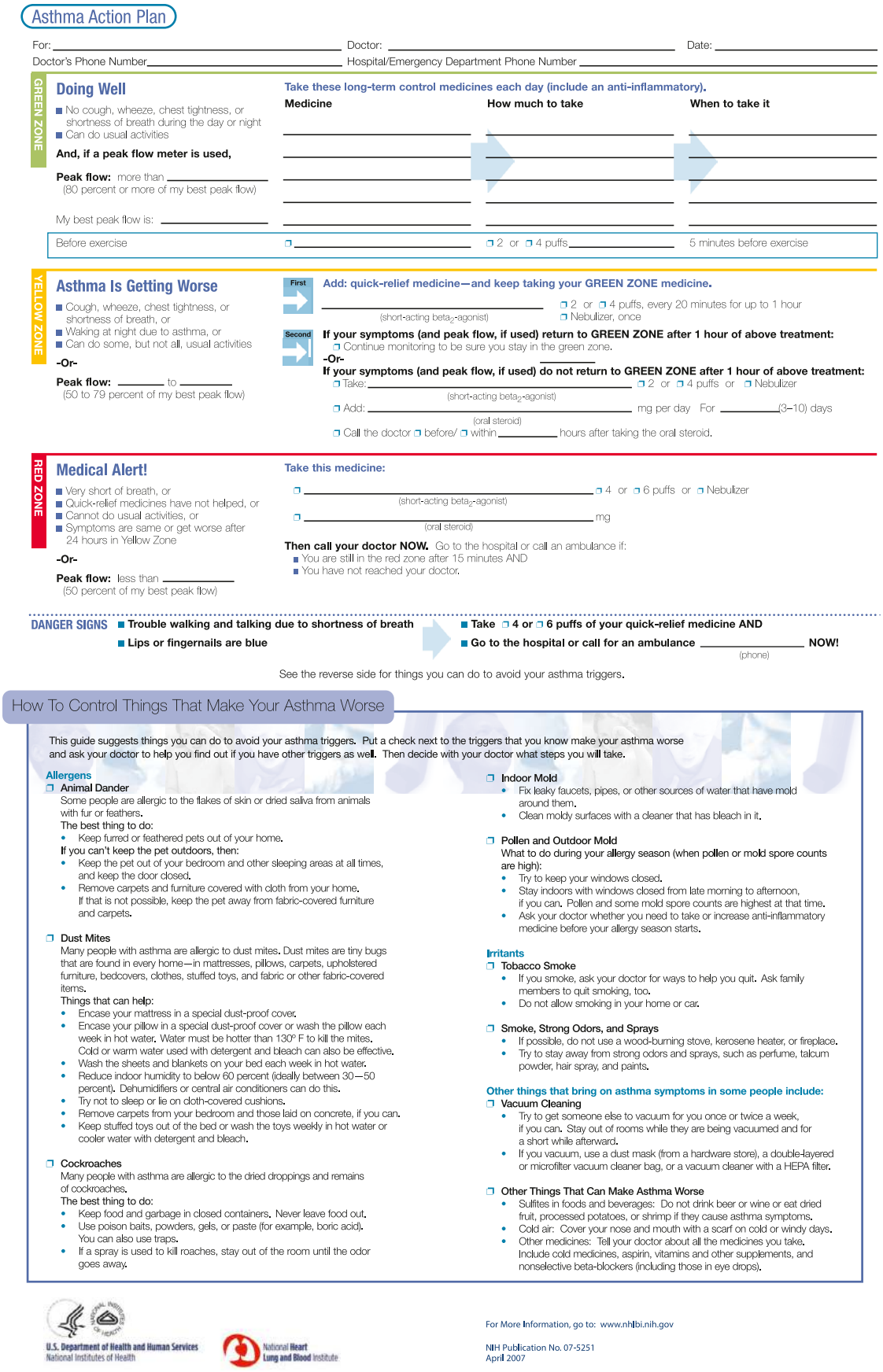

Asthma Action Plan

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number _____ Hospital/Emergency Department Phone Number _____

GREEN ZONE

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____ (80 percent or more of my best peak flow)

My best peak flow is: _____

Take these long-term control medicines each day (include an anti-inflammatory).

Medicine	How much to take	When to take it
Before exercise	❒ _____	❒ 2 or ❒ 4 puffs _____	5 minutes before exercise

YELLOW ZONE

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____ (50 to 79 percent of my best peak flow)

First

Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

_____ (short-acting beta$_2$-agonist) ❒ 2 or ❒ 4 puffs, every 20 minutes for up to 1 hour ❒ Nebulizer, once

Second

If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:

❒ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:

❒ Take: _____ (short-acting beta$_2$-agonist) ❒ 2 or ❒ 4 puffs or ❒ Nebulizer

❒ Add: _____ (oral steroid) mg per day For _____ (3–10) days

❒ Call the doctor ❒ before/ ❒ within _____ hours after taking the oral steroid.

RED ZONE

Medical Alert!

- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____ (50 percent of my best peak flow)

Take this medicine:

❒ _____ (short-acting beta$_2$-agonist) ❒ 4 or ❒ 6 puffs or ❒ Nebulizer

❒ _____ (oral steroid) mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:

- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS

- **Trouble walking and talking due to shortness of breath**
- **Lips or fingernails are blue**

- **Take ❒ 4 or ❒ 6 puffs of your quick-relief medicine AND**
- **Go to the hospital or call for an ambulance _____ (phone) NOW!**

See the reverse side for things you can do to avoid your asthma triggers.

How To Control Things That Make Your Asthma Worse

This guide suggests things you can do to avoid your asthma triggers. Put a check next to the triggers that you know make your asthma worse and ask your doctor to help you find out if you have other triggers as well. Then decide with your doctor what steps you will take.

Allergens

❒ **Animal Dander**

Some people are allergic to the flakes of skin or dried saliva from animals with fur or feathers.

The best thing to do:

- Keep furred or feathered pets out of your home.

If you can't keep the pet outdoors, then:

- Keep the pet out of your bedroom and other sleeping areas at all times, and keep the door closed.
- Remove carpets and furniture covered with cloth from your home. If that is not possible, keep the pet away from fabric-covered furniture and carpets.

❒ **Dust Mites**

Many people with asthma are allergic to dust mites. Dust mites are tiny bugs that are found in every home—in mattresses, pillows, carpets, upholstered furniture, bedcovers, clothes, stuffed toys, and fabric or other fabric-covered items.

Things that can help:

- Encase your mattress in a special dust-proof cover.
- Encase your pillow in a special dust-proof cover or wash the pillow each week in hot water. Water must be hotter than 130° F to kill the mites. Cold or warm water used with detergent and bleach can also be effective.
- Wash the sheets and blankets on your bed each week in hot water.
- Reduce indoor humidity to below 60 percent (ideally between 30—50 percent). Dehumidifiers or central air conditioners can do this.
- Try not to sleep or lie on cloth-covered cushions.
- Remove carpets from your bedroom and those laid on concrete, if you can.
- Keep stuffed toys out of the bed or wash the toys weekly in hot water or cooler water with detergent and bleach.

❒ **Cockroaches**

Many people with asthma are allergic to the dried droppings and remains of cockroaches.

The best thing to do:

- Keep food and garbage in closed containers. Never leave food out.
- Use poison baits, powders, gels, or paste (for example, boric acid). You can also use traps.
- If a spray is used to kill roaches, stay out of the room until the odor goes away.

❒ **Indoor Mold**

- Fix leaky faucets, pipes, or other sources of water that have mold around them.
- Clean moldy surfaces with a cleaner that has bleach in it.

❒ **Pollen and Outdoor Mold**

What to do during your allergy season (when pollen or mold spore counts are high):

- Try to keep your windows closed.
- Stay indoors with windows closed from late morning to afternoon, if you can. Pollen and some mold spore counts are highest at that time.
- Ask your doctor whether you need to take or increase anti-inflammatory medicine before your allergy season starts.

Irritants

❒ **Tobacco Smoke**

- If you smoke, ask your doctor for ways to help you quit. Ask family members to quit smoking, too.
- Do not allow smoking in your home or car.

❒ **Smoke, Strong Odors, and Sprays**

- If possible, do not use a wood-burning stove, kerosene heater, or fireplace.
- Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, and paints.

Other things that bring on asthma symptoms in some people include:

❒ **Vacuum Cleaning**

- Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- If you vacuum, use a dust mask (from a hardware store), a double-layered or microfilter vacuum cleaner bag, or a vacuum cleaner with a HEPA filter.

❒ **Other Things That Can Make Asthma Worse**

- Sulfites in foods and beverages: Do not drink beer or wine or eat dried fruit, processed potatoes, or shrimp if they cause asthma symptoms.
- Cold air: Cover your nose and mouth with a scarf on cold or windy days.
- Other medicines: Tell your doctor about all the medicines you take. Include cold medicines, aspirin, vitamins and other supplements, and nonselective beta-blockers (including those in eye drops).

U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute

For More Information, go to: www.nhlbi.nih.gov

NIH Publication No. 07-5251
April 2007

Fig. 185.5 Asthma action plan for home use. This plan has two main components: (1) a daily management plan to keep asthma in good control and (2) an action plan to recognize and manage worsening asthma. *(From U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Pub No 07-5251, April 2007.* https://www.nhlbi.nih.gov/health/asthma/treatment-action-plan.*)*

Table 185.12 Control of Factors Contributing to Asthma Severity

ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES
Environmental tobacco smoke elimination or reduction in home and automobiles
Allergen exposure elimination or reduction in sensitized asthmatic patients
• Pets (cats, dogs, rodents, birds)
• Pests (mice, rats)
• Dust mites
• Cockroaches
• Molds
Other airway irritants
• Wood- or coal-burning smoke
• Strong chemical odors and perfumes (e.g., household cleaners)
• Dusts
TREAT COMORBID CONDITIONS
Rhinitis
Sinusitis
Gastroesophageal reflux

particulates as tobacco smoke, and should also be avoided (see Chapter 759.2). Exposure to electronic cigarette aerosol may also aggravate asthma.

Annual influenza vaccination (both inactivated and live attenuated) is safe in children with asthma and continues to be recommended for all children with asthma to reduce the risk of severe complications, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

Identifying and Treating Comorbid Conditions

Rhinitis, sinusitis, GER, and obesity often accompany asthma and may make the asthma difficult to treat. These conditions can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions, along with asthma, are the most common causes of chronic cough. Poor conditioning from obesity may also be confused with asthma-related dyspnea. Effective management of these comorbid conditions may improve asthma symptoms, such that less asthma medication is needed to achieve good asthma control.

Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2020) provides treatment recommendations that vary by level of asthma severity and age-groups (Table 185.13). There are six treatment steps. Patients at **Treatment Step 1** have intermittent asthma. Children with mild persistent asthma are at **Treatment Step 2**. Children with moderate persistent asthma can be at **Treatment Step 3 or 4**. Children with severe persistent asthma are at **Treatment Steps 5 and 6**. The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing or minimizing symptoms, infrequently needing quick-reliever medications, maintaining "normal" lung function and normal activity levels) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medication adverse effects). The recommendations for initial therapy are based on assessment of asthma severity, whereas level of control determines any modifications of treatment in children who are already using controller therapy. **A major objective of this approach is to identify and treat all "persistent" and inadequately controlled asthma with anti-inflammatory controller medication.** *Treatment Step 1 (intermittent asthma)* management is simply the use of a SABA as needed for symptoms and for pretreatment in those with EIB. For children <5 years with recurrent episodic wheeze in the setting of viral illness, a short course of daily high-dose ICS may also be considered.

The preferred treatment for all patients with persistent asthma includes an ICS-containing therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating.

At *Treatment Step 2 (mild persistent asthma)*, low-dose daily ICS therapy is the treatment of choice for all children. Common alternative medications include a leukotriene receptor antagonist (LTRA) such as montelukast.

At *Treatment Step 3 (moderate persistent asthma)*, for school-age children, the preferred treatment has recently been modified to the daily and as-needed use of a low-dose ICS/formoterol (a rapid onset, long-acting β_2-agonist [LABA]) combination inhaler, used twice daily as both maintenance therapy and as-needed reliever therapy (in place of a separate SABA inhaler).

Single maintenance and reliever therapy (SMART) is a fundamental change from the conventional distinct daily controllers vs quick reliever medications. Although SMART has been determined to be effective in reducing asthma exacerbations relative to use of SABA as a reliever (i.e., favorable benefit-harm ratio), some current challenges to implementation for providers and patients include ICS/formoterol availability/affordability, FDA approval for use as a reliever therapy, and asthma management and action plan reeducation for home and school, including the appropriate use of SABA in asthma care (e.g., exercise pretreatment). A SABA/ICS combination inhaler (albuterol/budesonide 90 mcg/80 mcg per actuation) is FDA approved for as-needed use as a quick reliever in adults ages 18 years and older (not in children).

Common alternate choices for the treatment of school-age children at Treatment Step 3 include (1) medium-dose ICS or (2) low-dose ICS used in combination with an inhaled LABA. In a study of children with uncontrolled asthma receiving low-dose ICS, the addition of LABA was more likely to provide improvement than either adding an LTRA or increasing ICS dosage. However, some children had a good response to medium-dose ICS or the addition of an LTRA, justifying them as step-up controller therapy options. Thus if a child is not well controlled with a given step 3 treatment, trials of the alternate treatment approaches should be considered before stepping up to step 4. In patients 12 years and older with uncontrolled persistent asthma for whom a LABA is not used, current guidelines recommend addition of a LABA or a long-acting muscarinic antagonist (LAMA) to the ICS as a step-up approach. Adding a LAMA is not more efficacious than adding a LABA, so LAMAs should not be selected over a LABA unless necessary. LAMAs also have a less favorable benefit-harm profile and should not be used in patients with a risk of urinary retention or glaucoma. LAMAs can also be added to ICS/LABA combination therapy if the patient remains symptomatic.

For young children (≤4 years) at Treatment Step 3, NAEPP guidelines recommend daily medium dose ICS, whereas GINA recommends three co-equal preferred options: (1) daily low-dose ICS/LABA, (2) daily low-dose ICS + LTRA, or (3) daily medium-dose ICS.

At *Treatment Step 4 (moderate persistent asthma)*, the preferred therapy for school-age children is daily and as-needed use of a medium-dose ICS/formoterol combination inhaler, used twice daily for maintenance and as needed for reliever therapy. Alternatives include daily medium-dose ICS with either a LABA, LTRA, or other controller (such as a LAMA in patients 12 years and older). For preschool-age children at Treatment Step 4, daily medium-dose ICS/LABA is recommended.

For children age ≥5 years with allergic asthma requiring Treatment Steps 2-4 care, *subcutaneous allergen immunotherapy (SCIT)* can be considered. Current guidelines recommend SCIT as an adjunct treatment to standard pharmacotherapy in patients whose asthma can be adequately controlled and managed at the initiation, buildup, and maintenance phases of SCIT. Some requirements for effective and safe SCIT include (1) allergen sensitization evaluation using either immediate hypersensitivity skin testing or in vitro antigen-specific IgE antibody testing, and by a trained healthcare professional skilled in proper testing and result interpretation; (2) before each SCIT injection, evaluation to ensure that asthma is well controlled because poorly controlled asthma is a major risk factor for life-threatening and fatal

Table 185.13 Stepwise Approach for Managing Asthma in Children*

Age	Treatment	Intermittent Asthma	Persistent Asthma				
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
0–4 years	**Preferred**	PRN SABA And At the start of RTI: Add short course daily ICS	Daily low-dose ICS and PRN SABA	Daily low-dose ICS-LABA and PRN SABA Or Daily low-dose ICS + montelukast or daily medium-dose ICS and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroids and PRN SABA
	Alternative		Daily montelukast or Cromolyn and PRN SABA		Daily medium-dose ICS + montelukast and PRN SABA	Daily high-dose ICS + montelukast and PRN SABA	Daily high-dose ICS-LABA + montelukast + oral systemic corticosteroids and PRN SABA
				For children age 4 years only, see Step 3 and Step 4 for ages 5–11 years			
5–11 years	**Preferred**	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol	Daily and PRN combination medium-dose ICS-formoterol	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroids and PRN SABA
	Alternative		Daily LTRA, or Cromolyn, or Nedocromil, or Theophylline, and PRN SABA	Daily medium-dose ICS and PRN SABA Or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA, or daily low-dose ICS + theophylline, and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA Or Daily medium-dose ICS + LTRA, or daily medium-dose ICS + theophylline, and PRN SABA	Daily high-dose ICS + LTRA or daily high-dose ICS + Theophylline, and PRN SABA	Daily high-dose ICS + LTRA + oral systemic corticosteroid or daily high-dose ICS + Theophylline + oral systemic corticosteroid, and PRN SABA
			Steps 2–4: Conditionally recommend use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy			Consider omalizumab	
12+ years	**Preferred**	PRN SABA	Daily low-dose ICS and PRN SABA Or PRN concomitant ICS and SABA	Daily and PRN combination low-dose ICS-formoterol	Daily and PRN combination medium-dose ICS-formoterol	Daily medium-high dose ICS-LABA + LAMA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroids and PRN SABA
	Alternative		Daily LTRA and PRN SABA Or Cromolyn, or Nedocromil, or Theophylline, and PRN SABA	Daily medium-dose ICS and PRN SABA Or Daily low-dose ICS-LABA, or Daily low-dose ICS + LAMA, or daily low-dose ICS + LTRA, or daily low-dose ICS + theophylline, and PRN SABA	Daily medium-dose ICS or daily medium-dose ICS + LAMA, and PRN SABA Or Daily medium-dose ICS + LTRA, or daily medium-dose ICS + theophylline, and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA, and PRN SABA	
			Steps 2–4: Conditionally recommend use of subcutaneous allergen immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy			Consider adding asthma biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13R, anti-TSLP)	

Assess control

- First check adherence, inhaler technique, environmental factors, and comorbid conditions.
- **Step up** if needed, reassess in 4–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 3 or higher is required for those 0–4 years of age (and consider consultation at Step 2) or if Step 4 is required for those 5+ years of age (and consider consultation at Step 3).

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Continued

Table 185.13 Stepwise Approach for Managing Asthma in Children*—cont'd

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited.
- Clinicians who administer allergen immunotherapy or biologic therapy should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels. The 2016 GINA guidelines do not recommend the use of theophylline as a controller medication and in IV forms to treat status asthmaticus due to its severe adverse effects profile.

†Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.

ICS, Inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; prn, as needed; SABA, inhaled short-acting β_2-agonist.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma --summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94-S138, 2007 and 2020 Focused Updates to Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group.

allergic reactions from SCIT; and (3) being well prepared to respond to systemic allergic/anaphylactic reactions to SCIT injections. Patients with allergic asthma may also benefit from improvements in comorbid allergic rhinitis and conjunctivitis, which could additionally improve quality of life. SCIT efficacy with regard to asthma medication use and exacerbations is not clear. SCIT is not recommended in patients with severe asthma given the potential for systemic reactions of potentially great severity. Sublingual immunotherapy is not currently recommended based on available data.

At *Treatment Steps 5 and 6 (severe persistent asthma)*, all children should receive daily high-dose ICS plus LABA as the preferred approach; alternative secondary controllers to LABA include LTRA or LAMA. Long-term administration of OCSs as controller therapy may be effective but is rarely required and should be avoided whenever possible due to potential for significant corticosteroid side effects. In addition, biologics should be considered in children with specific asthma phenotypes: (1) omalizumab can be used in children ≥6 years old with severe allergic asthma; (2) mepolizumab (≥6 years), dupilumab (≥6 years), and benralizumab (≥12 years) can be used in children with severe eosinophilic asthma; and (3) tezepelumab (≥12 years) can be used in children with severe asthma. A rescue course of systemic corticosteroids may be necessary at any step for very poorly controlled asthma.

Adjusting Asthma Pharmacotherapy

By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. ***Asthma controller therapy can be stepped down after good asthma control has been achieved and maintained for at least 3 months.*** Stopping ICS controller therapy should be given careful consideration in children with a history of exacerbations. For example, in children with a history of fall seasonal asthma exacerbations and whose asthma becomes well controlled in the summer, ICS may be reduced but not completely discontinued. Regular follow-up is still emphasized because the variability of asthma's course is well recognized. When asthma is not well controlled, adherence, inhaler technique, and comorbidities should be considered first before increasing controller treatment. If increased treatment is required, the recommendation is to step up by one level and closely monitor for clinical improvement. For a child with very poorly controlled asthma, the recommendations are to consider a short course of prednisone and/or to increase therapy by two step levels, with reevaluation in 2 weeks.

Referral to Asthma Specialist

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining good asthma control. For children ≤4 years, referral is recommended if the patient requires at least Treatment Step 3 care, and should be considered if the patient requires Treatment Step 2 care. For children ≥5 years, consultation with a specialist is recommended if the patient requires Treatment Step 4 care or higher, and should be considered if Treatment Step 3 is required. Referral is also recommended if allergen immunotherapy (AIT) or biologic therapy is being considered.

Long-Term Controller Medications

All levels of persistent asthma should be treated with an ICS-containing therapy to reduce airway inflammation, improve long-term control, and reduce exacerbation risk (see Table 185.13). Other long-term controller medications include LABAs, leukotriene modifiers, LAMAs, SCIT, cromolyn, sustained-release theophylline, and tiotropium in adolescents. Omalizumab and mepolizumab are approved by the FDA for use as an add-on therapy in children ≥6 years who have severe allergic asthma or eosinophilic asthma, respectively, that remains difficult to control. For adolescents 12 years and older, benralizumab is approved by the FDA for severe asthma with an eosinophilic phenotype. Dupilumab is approved by the FDA for moderate to severe asthma with an eosinophilic phenotype for children 6 years and older. Tezepelumab is approved by the FDA for severe asthma in adolescents 12 years and older (see Tables 185.13 and 185.14).

Inhaled Corticosteroids

ICS therapy serves as the cornerstone of therapy in persistent asthma, as it improves lung function; reduces asthma symptoms, AHR, and use of "rescue" medications; improves quality of life; and most importantly reduces exacerbations, the need for systemic corticosteroids, urgent care visits, and hospitalizations. Epidemiologic studies have also shown that ICS therapy in adults substantially lowers the risk of death attributable to asthma if used regularly. Because ICS therapy frequently achieves all the goals of asthma management, it is viewed as first-line treatment for persistent asthma. The selection of the initial ICS dose is based on the determination of disease severity.

Seven ICSs are approved by the FDA for use in children. The NIH and GINA guidelines provide equivalence classifications (Table 185.15), although direct comparisons of efficacy and safety outcomes are lacking. ICSs are available in metered-dose inhalers (MDIs) using hydrofluoroalkane (HFA) as their propellant, in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, and to a lesser extent budesonide are considered "second-generation" ICSs, in that they have greater antiinflammatory potency and less systemic bioavailability.

Even though ICSs are very effective in most patients, there has been some reluctance to treat children with ICSs due to parental and occasionally physician concerns regarding their potential for adverse effects with chronic use. The most serious adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency of administration (Table 185.16). High doses (≥1,000 μg/day in children) and frequent administration (4 times per day) are more likely to have both local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require frequent systemic corticosteroid courses for asthma exacerbations, further increasing their risk of corticosteroid adverse effects.

The most common ICS adverse effects are local: oral **candidiasis** (thrush) and **dysphonia** (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression, and dysphonia

Table 185.14 Usual Dosages for Long-Term Control Medications

MEDICATION	AGE 0-4 YR	5-11 YR	≥12 YR
INHALED CORTICOSTEROID MONOTHERAPIES (SEE TABLE 185.13)			
Inhaled Corticosteroid/Long-Acting β-Agonist (ICS/LABA) Combination Therapies:			
Fluticasone/salmeterol (Advair):	N/A		
DPI: 100, 250, or 500 µg/50 µg		1 inhalation bid; dose depends on level of severity or control (the 100/50 dosage is indicated in children ≥4 yr)	1 inhalation bid; dose depends on level of severity or control
HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg			2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol (Symbicort): HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	N/A		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol (Dulera): HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Leukotriene Receptor Antagonists:			
Montelukast (Singulair): 4 or 5 mg chewable tablet; 4 mg granule packets; 10 mg tablet **Black box warning** (see text)	4 mg qhs (1-5 yr)	5 mg qhs (6-14 yr)	10 mg qhs (indicated in children ≥15 yr)
Zafirlukast (Accolate): 10 mg or 20 mg tablet	N/A	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
Biologic Therapies:			
Omalizumab (anti-IgE; Xolair): SC injection, 150 mg	N/A	75-375 mg SC q 2-4 wk (6-11 yr), depending on body weight and pretreatment serum IgE level	75-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level
Mepolizumab (anti–IL-5; Nucala): SC injection, 100 mg	N/A	40 mg SC q 4 wk (6-11 yr)	100 mg SC q 4 wk
Benralizumab (anti–IL-5 Rα; Fasenra) SC injection, 30 mg	N/A	N/A	30 mg SC q 4 wk × 3 doses, then 30 mg SC q 8 wk
Dupilumab (anti–IL-4 Rα; Dupixent) SC injection, 200 mg, 300 mg	N/A	15 to <30 kg:100 mg q 2 wk or 300 mg q 4 wk ≥30 kg: 200 mg q2 wk	400 mg or 600 mg SC starting dose, then 200 or 300 mg SC q 2 wk
Tezepelumab (anti-TSLP; Tezspire) SC injection, 210 mg	N/A	N/A	210 mg SC q 4 wk

bid, Two times daily; DPI, dry powder inhaler; HFA, hydrofluoroalkane; IL, interleukin; q, every; qhs, every night; SC, subcutaneous(ly).

is the result of vocal cord myopathy. These effects are dose dependent and are most common in individuals receiving high-dose ICS or OCS therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI with the ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use had been an unanswered concern. A long-term, prospective NIH-sponsored study (CAMP) followed the growth and bone mineral density (BMD) of >1,000 children (age 6-12 years at entry) with mild to moderate asthma until they reached adulthood and found slight growth suppression and osteopenia in some children who received long-term ICS therapy. A small (1.1 cm), limited (1 year) growth suppressive effect was noted in children receiving budesonide, 200 µg twice daily, after 5 years of therapy. Height was then followed until all children had reached adulthood (mean age 25 years). Those who received ICS therapy remained approximately 1 cm shorter than those who received placebo. Thus children treated with long-term low-dose ICS therapy may be about 1 cm shorter than expected as an adult, which is of little clinical significance. BMD was no different in those receiving budesonide vs placebo during the duration of the study, whereas a follow-up study after a mean of 7 years found a slight dose-dependent effect of ICS therapy on bone mineral accretion only among males. A much greater effect on BMD was observed with increasing numbers of OCS bursts for acute asthma, as well as an increase in risk for osteopenia, which was again limited to males. These findings were with use of low-dose budesonide; higher ICS doses, especially of agents with increased potency, are likely to have a greater potential for adverse effects. Thus osteoporosis screening and prevention measures are recommended for patients receiving higher ICS doses, because these patients are also likely to require systemic courses for exacerbations (see Table 185.16).

Systemic Corticosteroids

The development of second-generation ICSs, especially when used in combination with a LABA in a single device, along with the addition of biologics, have allowed almost all children with asthma to achieve and maintain good control without need for maintenance OCS therapy. Thus short courses of OCSs are used primarily to treat asthma exacerbations and, very rarely, as maintenance therapy in children with very severe disease. In these patients, every attempt should be made to exclude comorbid conditions and to keep the OCS dose at ≤20 mg every other day. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 615). To determine the need for continued OCS therapy, tapering of the OCS dose over several weeks should be attempted, with close monitoring of the patient's symptoms and lung function.

Prednisone, prednisolone, methylprednisolone, and dexamethasone are rapidly and completely absorbed, with peak plasma

Table 185.15 Estimated Comparative Inhaled Corticosteroid Doses

GLUCOCORTICOID	LOW DAILY DOSE	MEDIUM DAILY DOSE	HIGH DAILY DOSE
Beclomethasone (Qvar) MDI: 40 or 80 μg (Approved for children ≥5 yr)	80-160 μg	160-320 μg	>320 μg
Budesonide (Pulmicort Flexhaler) DPI: 90, 180 μg (Approved for children ≥6 yr)	200 μg	200-400 μg	>400 μg
Budesonide suspension for nebulization (Generic and Pulmicort Respules) 0.25 mg, 0.5 mg, 1 mg (Approved for children 1-8 yr)	0.5 mg	1.0 mg	2.0 mg
Ciclesonide (Alvesco) MDI: 80, 160 μg (Approved for children ≥12 yr)	80 μg	80-160 μg	160 μg
Flunisolide (Aerospan) MDI: 80 μg/puff (Approved for children ≥6 yr)	80 μg	80-160 μg	160 μg
Fluticasone propionate (Flovent, Flovent Diskus) MDI: 44, 110, 220 μg DPI: 50, 100, 250 μg (44 and 50 μg approved for children ≥4 yr)	88-176 μg 100-200 μg	176-440 μg 200-500 μg	>440 μg >500 μg
Fluticasone furoate (Arnuity Ellipta) DPI: 100, 200 μg (Approved for children ≥12 yr)	100 μg	100-200 μg	200 μg
Mometasone Furoate (Asmanex, Asmanex Twisthaler) MDI: 100, 200 μg DPI: 110, 220 μg (Approved for children ≥4 yr)	110 μg 100 μg	110 μg 100 μg	110 μg 100 μg

DPI, Dry powder inhaler; MDI, metered-dose inhaler.
Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94–S138.

concentrations occurring within 1-2 hours. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. For asthma exacerbations in children, oral dexamethasone is also commonly used given its long half-life of 36-54 hours and association with less vomiting when compared with oral prednisone. These corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketoconazole, oral contraceptives) can significantly delay corticosteroid metabolism. Some macrolide antibiotics, such as erythromycin and clarithromycin, delay the clearance of only methylprednisolone.

Long-term OCS therapy can cause numerous adverse effects over time (see Chapter 617). Some occur immediately (metabolic effects), whereas others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of OCSs, especially with concurrent high-dose ICSs and often intranasal corticosteroids, should receive corticosteroid adverse effects screening (see Table 185.16) and osteoporosis preventive measures (see Chapter 749).

Long-Acting Inhaled β-Agonists

Although considered daily controller medications, LABAs (salmeterol, formoterol) are not intended for use as monotherapy for persistent asthma because they can increase the risk for serious asthma exacerbations (ICU admission, endotracheal intubation) and asthma-related deaths when used without an ICS. The likely mechanism involves the ability of LABAs to "mask" worsening asthma inflammation and asthma severity, leading to a delay in seeking urgent care and increased risk of a life-threatening exacerbation. Although both salmeterol and formoterol have a prolonged duration of effect (≥12 hours), salmeterol has a prolonged onset of effect (60 minutes), whereas formoterol's onset of effect is rapid (5-10 minutes) after administration. Given their long duration of action, LABAs are well suited for patients with nocturnal asthma and for individuals who require frequent use of SABA inhalations during the day to prevent EIB, but only in combination with ICSs. The FDA recommends that once a patient is well controlled on combination ICS/LABA therapy, the LABA component should be discontinued while continuing treatment with the ICS, although many patients experience disease worsening on LABA discontinuation.

Combination ICS/LABA Therapy

Combination ICS/LABA therapy is recommended for patients who are suboptimally controlled with ICS therapy alone and those with moderate or severe persistent asthma. In most patients who are inadequately controlled with ICS alone, combination ICS/LABA therapy is superior to add-on therapy with either an LTRA or LAMA or doubling the ICS dose. Benefits include improvement in baseline lung function, less need for rescue SABA therapy, improved quality of life, and fewer asthma exacerbations. A large study found that in children inadequately controlled with low-dose ICS therapy, combination low-dose fluticasone/salmeterol (100 μg/21 μg) twice daily was almost twice as likely to be effective as other step-up regimens, including fluticasone (250 μg) twice daily or low-dose fluticasone (100 μg twice daily) plus montelukast once daily, with the greatest improvement in reducing exacerbations requiring prednisone and study withdrawals due to poorly controlled asthma. In addition, combination fluticasone/salmeterol was as likely to be effective as medium-dose fluticasone and

Table 185.16 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 185.13)	Monitor blood pressure and weight with each physician visit Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay Encourage regular physical exercise Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed. Avoid smoking and alcohol Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 185.13) At least four courses of OCS per year	As above, *plus*: Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma Baseline bone densitometry (DEXA scan) Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥7 OCS burst treatments per year Very-high-dose ICS (e.g., fluticasone propionate ≥800 μg/day)	As above, *plus*: DEXA scan: if DEXA *z* score ≤1.0, recommend close monitoring (every 12 mo) Consider referral to a bone or endocrine specialist Bone age assessment Complete blood count Serum calcium, phosphorus, and alkaline phosphatase determinations Urine calcium and creatinine measurements Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin Urine telopeptides for those receiving long-term systemic or frequent OCS treatment Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, alcohol intake).

DEXA, Dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; OCS, oral corticosteroid; TSH, thyroid-stimulating hormone.

was superior to combination fluticasone/montelukast therapy in Black children, arguing against the notion that Black children are more prone to serious asthma exacerbations than White children when treated with combination ICS/LABA therapy.

Despite their efficacy and widespread use, the long-term safety of LABAs, even when used in combination with ICS in a single inhaler, has been questioned. To address this concern of rare, severe asthma-related events with LABA/ICS use, large randomized controlled trials (RCTs) compared the safety of combination ICS/LABA vs ICS monotherapy. Two studies of >23,000 adults and adolescents ≥12 years old with various levels of asthma severity were randomized to receive ICS (low or medium dose) monotherapy vs equivalent ICS/LABA (fluticasone vs fluticasone/salmeterol; budesonide vs budesonide/formoterol) over 26 weeks to determine whether small but significant differences might occur in asthma hospitalization, intubation, or death attributable to ICS/LABA. No intubations or asthma deaths occurred during the study, and no differences in asthma hospitalizations between treatment groups were observed. The similar pediatric study enrolled >6,000 children age 4-11 years with various levels of asthma severity to receive either fluticasone (low or medium dose) or equivalent fluticasone/salmeterol dose over 26 weeks, with similar findings of no significant differences in severe asthma-related events between treatment groups. *These results strongly suggest that the use of combination ICS/LABA products in children and adults with moderate to severe persistent asthma is both effective and safe.*

Leukotriene-Modifying Agents

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. LTRAs may be an alternative treatment for mild persistent asthma and as an add-on medication with ICS for moderate persistent asthma. Two LTRAs with FDA-approved use in children are montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and modestly improve lung function. **Montelukast** is approved for use in children ≥1 year of age and is administered once daily, whereas **zafirlukast** is approved in children ≥5 years and is given twice daily. LTRAs are less effective than ICSs in patients with mild persistent asthma (e.g., ICSs improve baseline lung function 5–15%, whereas LTRAs improve lung function 2.5–7.5%). *The FDA has identified serious behavior and mood-related changes in some patients treated with montelukast and suggests that the benefits of montelukast may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with other medicines.* When initially prescribing montelukast, a precaution is to inform the child and family that, if mood changes are noted after starting montelukast, they should discontinue its use and contact their physician.

Long-Acting Inhaled Anticholinergics

Tiotropium is a LAMA (24-hour duration of action) that is approved by the FDA for use in children with asthma ≥6 years old. In studies in children and adolescents with moderate persistent asthma, tiotropium improved lung function as an add-on therapy to ICS. Adding a LAMA is not more efficacious than adding a LABA, so LAMAs should not be selected over a LABA unless necessary. LAMAs can also be added to ICS/LABA combination therapy if the patient remains symptomatic.

Allergen Immunotherapy

AIT involves administering gradually increasing doses of allergens to a person with allergic disease to reduce or eliminate the patient's allergic response to those allergens, including allergic rhinoconjunctivitis and asthma. Conventional AIT is given subcutaneously (**SCIT**) under the direction of an experienced allergist. The goal of SCIT is to increase the dose of allergen extract administered to reach a therapeutic maintenance dose of each major allergen, in a manner that minimizes the likelihood of systemic allergic reactions. Allergen extracts are formulated for each patient based on documented allergen sensitizations

and problematic exposures. Maintenance doses are generally given monthly, to complete a 3–5-year course. A meta-analysis of 20 trials examining the effects of SCIT on allergic asthma revealed significant improvement with fewer symptoms, improved lung function, less need for medication, and AHR reduction.

Although AIT is regarded as safe, the potential for **anaphylaxis** always exists when patients receive extracts containing allergens to which they are sensitized. Local transient allergic reactions at the injection site are common. Systemic allergic reactions can also occur with SCIT, with fatal anaphylaxis occurring in approximately 1 per 2 million injections. Because of the risks of systemic allergic reactions to SCIT, standard precautions include administering SCIT in medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 190). Patients should be observed in the office for 30 minutes after each injection because most systemic reactions to SCIT begin within this time frame. *SCIT should never be given at home or by untrained personnel.* Because of the complexities and risks of administration, SCIT should only be administered by an experienced allergist. SCIT is not recommended for patients with severe and uncontrolled asthma.

AIT should be discontinued in patients who have not shown improvement after 1 year of receiving maintenance doses of an appropriate allergen extract(s), or who have a serious systemic allergic or adverse reaction.

Biologic Therapies

Biologic therapies are genetically engineered proteins derived from human genes and designed to inhibit specific immune mediators of disease. Several are approved by the FDA as add-on controller therapies (i.e., in addition to conventional controller therapies) for severe asthma in adults and children.

Omalizumab (Anti-IgE Antibody). Omalizumab is a humanized monoclonal antibody (mAb) that binds IgE and prevents its binding to the high-affinity IgE receptor on mast cells and basophils, thereby blocking IgE-mediated allergic responses and inflammation. It is approved by the FDA for patients >6 years old with severe allergic asthma who continue to have inadequate disease control despite treatment with high-dose ICS and/or OCS. Omalizumab is given every 2-4 weeks subcutaneously, with the dosage based on body weight and serum IgE levels. Omalizumab can improve asthma control while allowing ICS and/or OCS dose reduction. Omalizumab has been studied in inner-city children with exacerbation-prone asthma. When added to guideline-based controller management, omalizumab reduced exacerbations (50%), particularly those that peak in the spring and fall seasons. A follow-up prospective preseasonal treatment study confirmed the effect on fall seasonal exacerbations and demonstrated how omalizumab restores antiviral (interferon [IFN]-α) immune responses to rhinovirus (the most common infectious trigger of exacerbations) that are impaired by IgE-mediated mechanisms. Omalizumab is generally well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) have been reported following approximately 0.1% of injections. As a result, omalizumab has an FDA black box warning of potentially serious and life-threatening anaphylactic adverse reactions, and an epinephrine autoinjector should be available to all patients receiving omalizumab.

Mepolizumab and Reslizumab (Anti–IL-5 Antibodies). **Mepolizumab**, an anti–IL-5 mAb that blocks IL-5-mediated eosinophilopoiesis, reduces severe asthma exacerbations and lowers sputum and blood eosinophils while allowing for a significant reduction in OCS dose in adults and adolescents with severe exacerbation-prone eosinophilic asthma. It is administered subcutaneously every 4 weeks and is approved by the FDA for severe eosinophilic asthmatic children ≥6 years old. **Reslizumab**, another anti–IL-5 mAb therapeutic, is administered intravenously and is approved by the FDA for severe asthmatics ≥18 years old (i.e., not currently approved for use in children).

Benralizumab (Anti–IL-5Ra Antibody). Benralizumab is also an mAb that binds to the IL-5 receptor α subunit, resulting in apoptosis of eosinophils and basophils. Benralizumab is approved for patients ≥12 years old with severe eosinophilic asthma with a suggested absolute blood eosinophil count of at least 300 cells/μL. Benralizumab is administered subcutaneously every 4 weeks for three doses followed by every 8-week dosing.

Dupilumab (Anti–IL-4 Receptor α Antibody). Dupilumab, an anti–IL-4 receptor α human mAb that inhibits both IL-4 and IL-13 production (both cytokines share the same IL-4 receptor α chain) and atopic immune responses, reduces exacerbations and symptoms and improves lung function in moderate to severe asthmatic patients with an eosinophilic phenotype. Dupilumab is administered subcutaneously every 2 weeks and is approved by the FDA for patients ≥6 years old with moderate to severe eosinophilic asthma. It is suggested that patients have an absolute eosinophil count of at least 150 cells/μL or an exhaled nitric oxide level of at least 25 parts per billion (ppb). In meta-analysis, dupilumab was associated with significant reductions of the annualized rate of severe asthma exacerbations and OCS use and a statistical improvement in lung function.

Tezepelumab (Anti-Thymic Stromal Lymphopoietin [TSLP] Antibody). Tezepelumab, an anti-TSLP human mAb, binds and blocks TSLP's inflammatory actions, reduces asthma exacerbations and symptoms, and improves lung function. Tezepelumab is administered subcutaneously every 4 weeks and is approved by the FDA for patients ≥12 years old with severe asthma.

Quick-Reliever Medications

Quick-reliever or "rescue" medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 185.17).

Short-Acting Inhaled β-Agonists

Given their rapid onset of action, effectiveness, and 4–6-hour duration of action, SABAs (albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute asthma symptoms ("rescue" medication) and for preventing EIB. β-Adrenergic agonists cause bronchodilation by inducing airway smooth muscle relaxation, reducing vascular permeability and airways edema, and improving mucociliary clearance. Levalbuterol, the R-isomer of albuterol, is associated with less tachycardia and tremor, which can be bothersome to some asthmatic patients. Overuse of β-agonists is associated with an increased risk of death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on the frequent use of SABAs as a "quick fix" for their asthma, rather than using controller medications in a preventive manner. It is helpful to monitor the frequency of SABA use, in that use of one or more MDIs per month or three or more MDIs per year (200 inhalations per MDI) indicates inadequate asthma control and necessitates improving other aspects of asthma therapy and management. Of note, a SABA/ICS combination inhaler (albuterol/budesonide 90 mcg/80 mcg per actuation) has recently been FDA approved for as-needed use as a quick reliever in adults ages 18 years and older (not in children).

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (e.g., ipratropium bromide) are less potent than the β-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the ED with acute asthma. Ipratropium has few central nervous system adverse effects and is available in both MDI and nebulizer formulations. Although widely used in all children with asthma exacerbations, it is approved by the FDA for use in children >12 years old. A combination ipratropium/albuterol product is also available in both nebulized and mist formulations.

Table 185.17 Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION	
Focused history	Onset of current exacerbation Frequency and severity of daytime and nighttime symptoms and activity limitation Frequency of rescue bronchodilator use Current medications and allergies Potential triggers History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes
Clinical assessment	Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status Pulse oximetry Lung function (defer in patients with moderate to severe distress or history of labile disease)
Risk factors for asthma morbidity and death	See Table 185.18

TREATMENT

DRUG AND TRADE NAME	MECHANISMS OF ACTION AND DOSING	CAUTIONS AND ADVERSE EFFECTS
Oxygen (mask or nasal cannula)	Treats hypoxia	Monitor pulse oximetry to maintain O_2 saturation >92% Cardiorespiratory monitoring
Inhaled short-acting β-agonists	Bronchodilator	During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume.
Albuterol MDI (90 µg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids	Antiinflammatory	If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis For daily dosing, 8 AM administration minimizes adrenal suppression Children may benefit from dosage tapering if course exceeds 7 days Adverse effects monitoring: frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 615); see Table 185.14 for adverse effects screening recommendations
Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution	Short course oral "burst" for exacerbation: 1-2 mg/kg/day divided qd or bid for 3-7 days (maximum 40 mg/day)	
Depo-Medrol (IM); Solu-Medrol (IV)	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day qd or bid	
Dexamethasone: 0.5, 0.75, 1, 1.5, 2, 4, 6 mg tablets; 0.5 mg/5 mL, 1 mg/mL Intensol solution	Short course oral "burst" for exacerbation: 0.6 mg/kg, maximum 16 mg; can be repeated next day	
Anticholinergics	Mucolytic/bronchodilator	Should not be used as first-line therapy; added to β_2-agonist therapy
Ipratropium Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 µg/inhalation)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine	Bronchodilator	For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)

Continued

Table 185.17 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	
Terbutaline		Terbutaline is β-agonist–selective relative to epinephrine Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 μg/kg loading dose, followed by 0.1-0.4 μg/kg/min Titrate in 0.1-0.2 μg/kg/min increments every 30 min, depending on clinical response.	
Other medications		
Magnesium sulfate	25-75 mg/kg over 20 min Max 2 gm	Flushing, headache, hypotension (rare)
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 185.10	

IM, Intramuscular; IV, intravenous; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; $\dot{V}/\dot{Q}$, ventilation/perfusion; bid, 2 times daily; tid, 3 times daily; qid, 4 times daily; qd, every day.

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in an MDI, as a DPI formulation, or in a suspension form delivered via a nebulizer. **Spacer devices, recommended for the administration of all MDI medications, are simple and inexpensive tools that (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of drug and propellant-mediated oropharyngeal adverse effects (dysphonia and thrush)**. Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5-second) inhalation, then a 5–10-second breath hold. No waiting time is required between puffs of medication. Preschool-age children cannot perform this inhalation technique. As a result, MDI medications in this age-group are delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 seconds or 5-10 breaths; a tight seal must be maintained; and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

DPI devices (e.g., Diskus, Flexhaler, Autohaler, Twisthaler, Aerolizer, Ellipta) are popular because of their simplicity of use, although adequate inspiratory flow is needed. DPIs are breath-actuated devices (the drug comes out only as it is breathed in), and spacers are not needed. Mouth rinsing is recommended after ICS use to remove ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrush.

Nebulizers are the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants greatly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include the need for a power source, inconvenience in that treatments take a significantly longer time, are more expensive, and have the potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 AM), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airways obstruction is not resolved with SABA use, ventilation/perfusion mismatching can cause hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis (common) and air leaks in the chest (pneumomediastinum, pneumothorax; rare).

A severe exacerbation of asthma that does not improve with standard therapy is termed **status asthmaticus**. Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (Fig. 185.6; see Tables 185.4 and 185.17). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient's asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they have severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 185.18).

Follow this plan for After Hours patients only. Nurse may decide not to follow this home management plan if:
- Parent does not seem comfortable with or capable of following plan
- Nurse is not comfortable with this plan, based on situation and judgment
- Nurse's time does not allow for callbacks

In all cases, tell parent to call 9-1-1 if signs of respiratory distress occur during the episode
NOTE: If action plan has already been attempted without success, go to "RED ZONE — poor response" or "YELLOW ZONE — incomplete response" as symptoms indicate.

Assess symptoms/peak flow

YELLOW ZONE
Mild-to-moderate exacerbation
PEF 50–80% predicted or personal best
or
Signs and symptoms
- Coughing, shortness of breath or chest tightness (correlate imperfectly with severity of exacerbation), or
- Unable to sleep at night due to asthma, or
- Decreased ability to perform usual activities
- With or without wheezing

RED ZONE
Severe exacerbation
PEF < 50% predicted or personal best or
Signs and symptoms
- Very hard time breathing; constant coughing
- Trouble walking or talking due to asthma (unable to complete sentences; only using 2- to 3-word phrases)
- Nails blue
- Suprasternal or supraclavicular retractions
- Albuterol not relieving symptoms within 10–15 minutes
- With or without wheezing

Instructions to patient
Inhaled short-acting β_2-agonist:
- 2–4 puffs of inhaler or nebulizer treatment every 20 minutes up to 3 times in 1 hour
- Assess asthma symptoms and/or peak flow 15–20 minutes after each treatment
- Nurse to call family after 1 hour
- If patient worsens during treatment, have parent call back immediately or call 9-1-1

GREEN ZONE — Good response
Mild exacerbation
PEF > 80% predicted or personal best
or
Signs and symptoms
- No wheezing, shortness of breath, cough or chest tightness, and
- Response to β_2-agonist sustained for 4 hours

Instructions to patient
- May continue 2–4 puffs (or nebulizer) β_2-agonist every 3–4 hours for 24–28 hours prn
- For patients on inhaled steroids, double dose for 7–10 days
- Contact PCP within 48 hours for instructions

YELLOW ZONE — Incomplete response
Moderate exacerbation PEF
50–80% predicted or personal best
or
Signs and symptoms
- Persistent wheezing, shortness of breath, cough or chest tightness

Instructions to patient
- Take 2–4 puffs (or nebulizer) β_2-agonist every 2–4 hours for 24–48 hours prn
- Add oral steroid* (see contraindications below)
- Contact PCP urgently (within 24 hours) for instructions

RED ZONE — Poor response
Severe exacerbation
PEF < 50% predicted or personal best
or
Signs and symptoms
- Marked wheezing, shortness of breath, cough, or chest tightness
- Distress is severe and nonresponsive
- Response to β_2-agonist last < 2 hours

Instructions to patient
- Proceed to ED, or call ambulance or 9-1-1 and repeat treatment while waiting

Instructions to patient
IMMEDIATELY:
- Take 4-6 puffs (or nebulizer) β_2-agonist
- Start oral steroids* if available (see contraindications below)
- Instruct parent to call back in 5 minutes after treatment finished
- If still in **RED ZONE** proceed to ED, or call ambulance or 9-1-1 and repeat treatment while waiting
- If in **YELLOW ZONE**, move to **YELLOW ZONE** protocol (top left box)

Documentation faxed or given to PCP within 24 hours; phone or verbal contact sooner as indicated.

* Ask patient about preexisting conditions that may be contraindications to oral steroids (including type 1 diabetes, active chicken pox, chicken pox exposure or varicella vaccine within 21 days, MMR within 14 days). If so, nurse to contact PCP before initiating steroids. Oral steroid dosages: Child: 2 mg/kg/day, maximum 60 mg/day, for 5 days.

Date: _____
Signature _____

Fig. 185.6 Algorithm for treatment of acute asthma symptoms. ED, Emergency department; PCP, primary care physician; PEF, peak expiratory flow. *(Courtesy BJC Healthcare/Washington University School of Medicine, Community Asthma Program, January 2000.)*

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that develop over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure because of fatigue can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (Pco_2) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

Home Management of Asthma Exacerbations

Families of all children with asthma should have a **written Asthma Action Plan** (see Fig. 185.5) to guide their recognition and management of exacerbations, along with the necessary education, medications, and tools to manage them. Early recognition of asthma exacerbations to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. The NIH guidelines recommend immediate treatment with "rescue" medication (inhaled SABA, 2-4 puffs, up to 3 times every 20 minutes in 1 hour). A good response is characterized by resolution of symptoms within 1 hour and no further symptoms over the next 4 hours. The child's physician should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hours. If the child has an incomplete response to initial treatment with rescue medication, a short course of OCS therapy (for example, prednisone, 1-2 mg/kg/day [not to exceed 40 mg/day] for 4 days) should be instituted, in addition to inhaled β-agonist therapy. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (e.g., previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if abrupt in onset, an epinephrine autoinjector and perhaps portable oxygen at home can be considered. Use of either of these extreme measures for home management of asthma exacerbations would be an indication to call 911 for emergency support services.

Table 185.18 Risk Factors for Asthma Morbidity and Mortality

BIOLOGIC
Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
Sudden asphyxia episodes (respiratory failure, arrest)
Two or more hospitalizations for asthma in past year
Three or more emergency department visits for asthma in past year
Increasing and large diurnal variation in peak flows
Use of >2 canisters of short-acting β-agonists per month
Poor response to systemic corticosteroid therapy
Male sex
Low birthweight
Non-White
Sensitivity to *Alternaria*
ENVIRONMENTAL
Allergen exposure
Environmental tobacco smoke exposure
Air pollution exposure
Urban environment
ECONOMIC AND PSYCHOSOCIAL
Poverty
Crowding
Mother <20 yr old
Mother with less than high school education
Inadequate medical care
Inaccessible
Unaffordable
No regular medical care (only emergency)
Lack of written Asthma Action Plan
No care sought for chronic asthma symptoms
Delay in care of asthma exacerbations
Inadequate hospital care for asthma exacerbation
Psychopathology in the parent or child
Poor perception of asthma symptoms or severity
Alcohol or substance abuse

Emergency Department Management of Asthma Exacerbations

In the ED, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors associated with asthma morbidity and mortality (see Table 185.18). Indicators of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV_1 value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 minutes for 1 hour, and, if necessary, oral, injectable or IV systemic corticosteroids (see Tables 185.4 and 185.17, and Fig. 185.6). Inhaled ipratropium may be added to the β-agonist treatment, especially if no significant response is seen with the first inhaled β-agonist treatment. In the ED, single oral, IV, or intramuscular (IM) dose dexamethasone (0.6 mg/kg, maximum 16 mg) is an effective alternative to prednisone and with a lower incidence of emesis. A second dose of dexamethasone can be given the next day whether discharged or admitted to the hospital. An IM injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 minutes after SABA administration to compensate for possible ventilation/perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the first hour suggests that the exacerbation will not remit quickly. The patient may be discharged home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, and oxygen saturation >92% while the patient is breathing room air for 4 hours. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hours plus a short course of an OCS. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of OCS in the ED setting reduces the risk of exacerbation recurrence over the subsequent month.

Hospital Management of Asthma Exacerbations

For patients with severe exacerbations that do not adequately improve within 1-2 hours of intensive treatment, observation and/or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 185.18). Admission to an ICU is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 185.17). Supplemental oxygen is administered because many children hospitalized with acute asthma have or will eventually have hypoxemia, especially at night and with increasing

SABA administration. SABAs can be delivered frequently (every 20 minutes to 1 hour) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs, and thus continuous nebulization can obviate the need for IV β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia; lactic acidosis is an uncommon complication. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation/perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium is often added to albuterol every 6 hours if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium may be beneficial in patients who have mucus hypersecretion or who are receiving β blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as IV corticosteroids. Accordingly, OCS therapy can often be used, although children with sustained respiratory distress and those unable to tolerate oral preparations or liquids are obvious candidates for IV corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluation, such as complete blood count, arterial blood gases, serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased antidiuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are not recommended during asthma exacerbations because they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (e.g., air leaks) related to asthma exacerbations increase with intubation and assisted ventilation, so every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including parenteral β-agonists, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 minutes), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of magnesium sulfate requires monitoring of serum levels and cardiovascular status. Noninvasive positive pressure ventilation (e.g., continuous positive airway pressure [CPAP] or biphasic positive airway pressure [BiPAP]) might improve severe asthma exacerbations through a variety of mechanisms. Their use in the care of children with severe persistent asthma exacerbations has increased in efforts to avert mechanical ventilation, even though evidence supporting the intervention has been considered weak, and current NAEPP and GINA guidelines do not recommend the intervention. Parenteral (SC, IM, or IV) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because inhaled medication may not reach the lower airway in such patients.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. **Mechanical ventilation** in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum; see Chapter 461). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to moderate hypercapnia (Pco_2 50-70 mm Hg) to minimize barotrauma. As measures to relieve mucus plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by corticosteroid-induced myopathy, which can lead to severe muscle weakness requiring prolonged rehabilitation.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 weeks of a child's discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

Special Management Circumstances

Management of Infants and Young Children

Recurrent wheezing episodes in preschool-age children are common, occurring in as much as one-third of this population. Of these, most improve and even become asymptomatic during the prepubescent school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems. The NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 185.9, 185.10, 185.13, and 185.14). **For young children with recurrent episodic wheeze in the setting of viral illness, a short course of daily high-dose ICS may also be considered.** For young children with a history of moderate to severe exacerbations, nebulized budesonide is approved by the FDA, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are two delivery systems for inhaled medications for this age-group: the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred because of limited published information and lack of FDA approval for children <4 years of age.

Asthma Management During Surgery

Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, which may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment to improve asthma stability before surgery, if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV_1 or PEF values <80% of the patient's personal best. In addition, patients who have received >2 weeks of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide "stress" replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period.

PROGNOSIS

Recurrent coughing and wheezing occur in 35% of preschool-age children. Of these, approximately one third continue to have persistent asthma into later childhood, and approximately two thirds improve on their own through their teen years. Concomitant atopic disorders (such as allergen sensitization or atopic dermatitis) are associated with greater likelihood of disease persistence. Asthma severity by ages 7-10 years is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years).

PREVENTION

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional antiinflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling through early microbiome and innate immune development. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, these findings may foster new strategies for asthma prevention.

Several nonpharmacologic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 months), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Care providers can be strong influencers of smoking cessation by parents, caregivers, and adolescent patients (see Chapters 157.2 and 759.1). Immunizations are not considered to increase the likelihood of development of asthma; therefore all standard childhood immunizations are recommended for children with asthma, including varicella, SARS-CoV-2, and annual influenza vaccines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 186

Atopic Dermatitis (Atopic Eczema)

Donald Y.M. Leung and Scott H. Sicherer

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to the development of food allergy, allergic rhinitis, and asthma later in childhood, a process called *the atopic march*.

ETIOLOGY

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and primarily type 2 adaptive immune responses to environmental allergens and microbes that lead to chronic skin inflammation.

PATHOLOGY

Acute AD skin lesions are characterized by **spongiosis**, or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells (APCs) in the epidermis, such as Langerhans cells, exhibit surface-bound IgE molecules with cell processes that reach into the upper epidermis to sense allergens and pathogens. These APCs play an important role in cutaneous responses to type 2 immune responses (see Chapter 182). There is marked perivascular T-cell and inflammatory monocyte-macrophage infiltration in acute AD lesions. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

PATHOGENESIS

AD is associated with multiple phenotypes and endotypes that have overlapping clinical presentations. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70–80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20–30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of T-helper type 2 (Th2) cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another type 2 cytokine, IL-5, plays an important role in eosinophil development and IL-31 is a key itch cytokine (Fig. 186.1). Nonatopic eczema is associated with lower IL-4 and IL-13 but increased IL-17 and IL-23 production than in atopic eczema. Age has also been found to affect the immune profile in AD.

Compared with the skin of healthy individuals, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4, IL-13, and IL-31. Chronic AD skin lesions, by contrast, have fewer cells that express IL-4 and IL-13, but they have more cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Despite increased type 1 and type 17 immune responses in chronic AD, IL-4 and IL-13 as well as other type 2 cytokines (e.g., thymic stromal lymphopoietin [TSLP], IL-31, IL-33) predominate and reflect increased numbers of type 2 innate lymphoid cells and Th2 cells. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia. The importance of IL-4 and IL-13 in driving severe persistent AD has been validated by multiple clinical trials now demonstrating that biologics blocking IL-4 and IL-13 action lead to clinical improvement in moderate to severe AD.

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. *Severely dry skin is a hallmark of AD.* This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin**, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function, including moisturization of the skin. Genetic pathogenic variants in the filaggrin gene *(FLG)* family have been identified in patients with ichthyosis vulgaris (dry skin, palmar hyperlinearity) and in up to 50% of patients with severe AD. *FLG* pathogenic variant is strongly associated with the development of food allergy and eczema herpeticum. Nonetheless, up to 60% of carriers of an *FLG* pathogenic variant do not develop atopic diseases. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, and IL-25, and tumor necrosis factor, can also reduce filaggrin

PROGNOSIS

Recurrent coughing and wheezing occur in 35% of preschool-age children. Of these, approximately one third continue to have persistent asthma into later childhood, and approximately two thirds improve on their own through their teen years. Concomitant atopic disorders (such as allergen sensitization or atopic dermatitis) are associated with greater likelihood of disease persistence. Asthma severity by ages 7-10 years is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years).

PREVENTION

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional antiinflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling through early microbiome and innate immune development. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, these findings may foster new strategies for asthma prevention.

Several nonpharmacologic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 months), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Care providers can be strong influencers of smoking cessation by parents, caregivers, and adolescent patients (see Chapters 157.2 and 759.1). Immunizations are not considered to increase the likelihood of development of asthma; therefore all standard childhood immunizations are recommended for children with asthma, including varicella, SARS-CoV-2, and annual influenza vaccines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 186

Atopic Dermatitis (Atopic Eczema)

Donald Y.M. Leung and Scott H. Sicherer

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to the development of food allergy, allergic rhinitis, and asthma later in childhood, a process called *the atopic march*.

ETIOLOGY

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and primarily type 2 adaptive immune responses to environmental allergens and microbes that lead to chronic skin inflammation.

PATHOLOGY

Acute AD skin lesions are characterized by **spongiosis**, or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells (APCs) in the epidermis, such as Langerhans cells, exhibit surface-bound IgE molecules with cell processes that reach into the upper epidermis to sense allergens and pathogens. These APCs play an important role in cutaneous responses to type 2 immune responses (see Chapter 182). There is marked perivascular T-cell and inflammatory monocyte-macrophage infiltration in acute AD lesions. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

PATHOGENESIS

AD is associated with multiple phenotypes and endotypes that have overlapping clinical presentations. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70–80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20–30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of T-helper type 2 (Th2) cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another type 2 cytokine, IL-5, plays an important role in eosinophil development and IL-31 is a key itch cytokine (Fig. 186.1). Nonatopic eczema is associated with lower IL-4 and IL-13 but increased IL-17 and IL-23 production than in atopic eczema. Age has also been found to affect the immune profile in AD.

Compared with the skin of healthy individuals, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4, IL-13, and IL-31. Chronic AD skin lesions, by contrast, have fewer cells that express IL-4 and IL-13, but they have more cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Despite increased type 1 and type 17 immune responses in chronic AD, IL-4 and IL-13 as well as other type 2 cytokines (e.g., thymic stromal lymphopoietin [TSLP], IL-31, IL-33) predominate and reflect increased numbers of type 2 innate lymphoid cells and Th2 cells. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia. The importance of IL-4 and IL-13 in driving severe persistent AD has been validated by multiple clinical trials now demonstrating that biologics blocking IL-4 and IL-13 action lead to clinical improvement in moderate to severe AD.

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. *Severely dry skin is a hallmark of AD.* This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin**, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function, including moisturization of the skin. Genetic pathogenic variants in the filaggrin gene *(FLG)* family have been identified in patients with ichthyosis vulgaris (dry skin, palmar hyperlinearity) and in up to 50% of patients with severe AD. *FLG* pathogenic variant is strongly associated with the development of food allergy and eczema herpeticum. Nonetheless, up to 60% of carriers of an *FLG* pathogenic variant do not develop atopic diseases. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, and IL-25, and tumor necrosis factor, can also reduce filaggrin

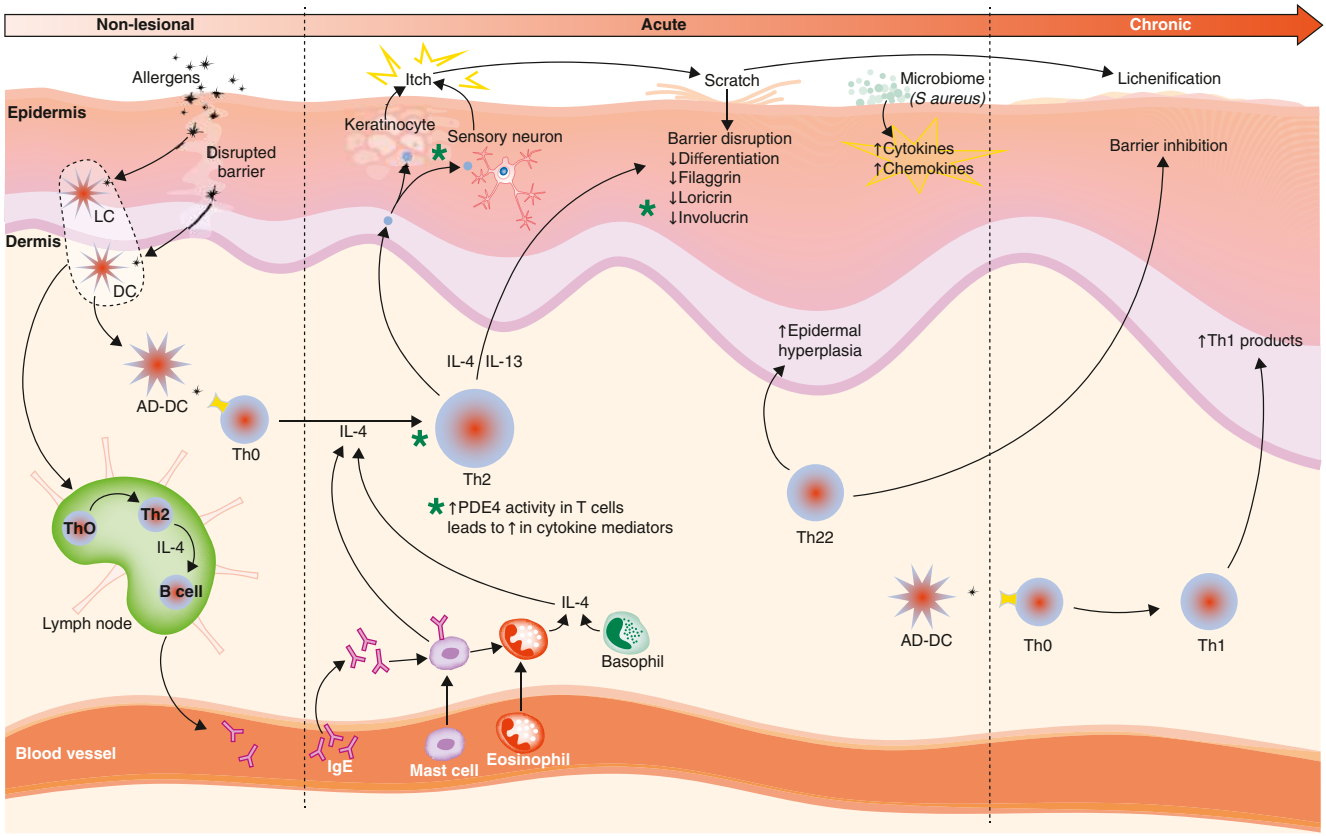

Fig. 186.1 Pathogenic pathways and immunologic targets in atopic dermatitis (AD). Skin barrier defects in nonlesional atopic dermatitis leads to penetration by allergens, which encounter antigen-presenting Langerhans cells (LCs) in the epidermis and dendritic cells (DCs) in the dermis, resulting in immune activation and inflammatory cell recruitment. Elevated T-helper type 2 (Th2) cell counts in the acute state leads to increased secretion of cytokines, especially interleukin (IL)-4 and IL-13, which disrupt the skin barrier by decreasing expression of barrier proteins (i.e., filaggrin, loricrin, and involucrin). In addition, Th2 cytokines recruit eosinophils and basophils to lesional sites, and increase B-cell IgE production. Eosinophils, basophils, and activated IgE-bound mast cells release proinflammatory mediators, further potentiating pathogenesis. Th2 cytokines also impair antimicrobial peptide responses to pathogens which, in combination with barrier disruption, increases the risk of colonization and barrier penetration by allergens and pathogens (i.e., *Staphylococcus aureus*). Chronic atopic dermatitis results in a skewed Th1 response, leading to further inflammation and immune activation. Processes mediated by Janus kinase (JAK) receptors are marked with a green asterisk. PDE4, phosphodiesterase-4. *(From Vahharia PP, Silverberg JI. New and emerging therapies for paediatric atopic dermatitis. Lancet Child Adolesc. 2019;3:343–352.)*

and other epidermal proteins and lipids. AD patients are at increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, disturbances in the microbiome, skin epithelial dysfunction, and overexpression of polarized immune pathways, which dampen host antimicrobial responses. Patients with the combination of AD and food allergy have significantly lower levels of filaggrin and increased type 2 immune activation than patients with AD only.

CLINICAL MANIFESTATIONS

AD typically begins in infancy. Approximately 50% of patients experience symptoms in the first year of life, and an additional 30% are diagnosed between 1 and 5 years of age. Intense **pruritus**, especially at night, and **cutaneous reactivity** are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow's milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (*Staphylococcus aureus*, herpes simplex, coxsackievirus, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can trigger pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 186.2 and 186.3). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by **lichenification** (Fig. 186.4), or thickening of the skin with accentuated surface markings, and **fibrotic papules**. In chronic AD, all three types of skin reactions may coexist in the same individual. Most patients with AD have dry, lackluster skin regardless of their stage of illness. Skin reaction pattern and distribution vary with the patient's age and disease activity. AD is generally more acute in infancy and involves the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared. Older children and children with chronic AD have lichenification and localization of the rash to the flexural folds of the extremities. AD can go into remission as the patient grows older; however, many children with AD have persistent eczema as an adult (see Fig. 186.2*C*).

LABORATORY FINDINGS

There are no specific laboratory tests to diagnose AD. Many patients have peripheral blood eosinophilia, increased serum IgE levels, and T cells expressing type 2 cytokines. Serum IgE measurement or skin-prick testing can identify the allergens (foods, inhalant/microbial allergens) to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

AD is diagnosed on the basis of three major features: pruritus, an eczematous dermatitis that fits into a typical pattern of skin inflammation, and a chronic or chronically relapsing course (Table 186.1). Associated features, such as a family history of asthma, hay fever, food



Fig. 186.2 Typical clinical appearance and locations of atopic dermatitis at different ages. A, In infants, atopic dermatitis is generally acute, with lesions mainly on the face and the extensor surfaces of the limbs. The trunk might be affected, but the napkin area is typically spared. B, From age 1-2 years onward, polymorphous manifestations with different types of skin lesions are seen, particularly in flexural folds. C, Adolescents and adults often present lichenified and excoriated plaques at flexures, wrists, ankles, and eyelids; in the head and neck type, the upper trunk, shoulders, and scalp are involved. Adults might have only chronic hand eczema or present with prurigo-like lesions. (*From Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387:1111.*)

allergy, elevated IgE, and immediate skin test reactivity, reinforce the diagnosis of AD.

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Tables 186.2 and 186.3). Severe combined immunodeficiency (see Chapter 165.1) should be considered for infants presenting in the first year of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis should be excluded in any infant with AD and failure to thrive (see Chapter 556). Wiskott-Aldrich syndrome, an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD (see Chapter 165.4). One of the hyper-IgE syndromes is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant *STAT3* pathogenic variants. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a dedicator of cytokinesis 8 gene *(DOCK8)* pathogenic variants. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic **contact dermatitis**. A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis receiving topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyosis, and seborrheic dermatitis.

TREATMENT

The treatment of AD requires a systematic, multifaceted approach that incorporates skin moisturization, topical antiinflammatory therapy, identification and elimination of flare factors (Table 186.4), and, if necessary, systemic therapy (Fig. 186.5). Assessment of the severity also helps direct therapy (Table 186.5; see Fig. 186.5).

Cutaneous Hydration

Because patients with AD have impaired skin barrier function from reduced filaggrin and skin lipid levels, they present with diffuse, abnormally dry skin, or **xerosis**. **Moisturizers are first-line therapy**. Lukewarm soaking baths or showers for 15-20 minutes followed by the



Fig. 186.3 Crusted lesions of atopic dermatitis on the face. (*From Eichenfield LF, Friedan IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001. p 242.*)



Fig. 186.4 Lichenification of the popliteal fossa from chronic rubbing of the skin in atopic dermatitis. (*From Weston WL, Lane AT, Morelli JG. Color Textbook of Pediatric Dermatology. 2nd ed. St Louis: Mosby; 1996. p 33.*)

application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient's preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these patients, less occlusive agents should be used. Several prescription (classified as a medical device) "therapeutic moisturizers" or "barrier creams" are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are minimal data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

Table 186.1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES
Pruritus
Facial and extensor eczema in infants and children
Flexural eczema in adolescents
Chronic or relapsing dermatitis
Personal or family history of atopic disease
ASSOCIATED FEATURES
Xerosis
Cutaneous infections (*Staphylococcus aureus*, group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
Nonspecific dermatitis of the hands or feet
Ichthyosis, palmar hyperlinearity, keratosis pilaris
Nipple eczema
White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum IgE levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors
Lichenification
Perioral, periauricular sites
Prurigo

Topical Corticosteroids

Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD. Patients should be carefully instructed on their use of topical glucocorticoids to avoid potential adverse effects. There are seven classes of topical glucocorticoids, ranked according to their potency, as determined by vasoconstrictor assays (Table 186.6). Because of their potential adverse effects, the ultra-high-potency glucocorticoids should not be used on the face or intertriginous areas and should be used only for very short periods on the trunk and extremities. Mid-potency glucocorticoids can be used for longer periods to treat chronic AD involving the trunk and extremities. Long-term control can be maintained with twice-weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to relapse, once control of AD is achieved after a daily regimen of topical corticosteroids. Compared with creams, ointments have a greater potential to occlude the epidermis, resulting in enhanced systemic absorption.

Adverse effects of topical glucocorticoids can be divided into local adverse effects and systemic adverse effects, the latter resulting from suppression of the hypothalamic-pituitary-adrenal axis. *Local* adverse effects include the development of striae and skin atrophy. *Systemic* adverse effects are related to the potency of the topical corticosteroid, site of application, occlusiveness of the preparation, percentage of the body surface area covered, and length of use. The potential for adrenal suppression from potent topical corticosteroids is greatest in infants and young children with severe AD requiring intensive therapy.

Topical Calcineurin Inhibitors

The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 years whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable

Table 186.2 Differential Diagnosis of Atopic Dermatitis

	MAIN AGE GROUP AFFECTED	FREQUENCY*	CHARACTERISTICS AND CLINICAL FEATURES
OTHER TYPES OF DERMATITIS			
Seborrheic dermatitis	Infants	Common	Salmon-red greasy scaly lesions, often on the scalp (cradle cap) and napkin area; generally presents in the first 6 wk of life; typically clears within weeks
Seborrheic dermatitis	Adults	Common	Erythematous patches with yellow, white, or grayish scales in seborrheic areas, particularly the scalp, central face, and anterior chest
Nummular dermatitis	Children and adults	Common	Coin-shaped scaly patches, mostly on legs and buttocks; usually no itch
Irritant contact dermatitis	Children and adults	Common	Acute to chronic eczematous lesions, mostly confined to the site of exposure; history of locally applied irritants is a risk factor; might coexist with AD
Allergic contact dermatitis	Children and adults	Common	Eczematous rash with maximum expression at sites of direct exposure but might spread; history of locally applied irritants is a risk factor; might coexist with AD
Lichen simplex chronicus	Adults	Uncommon	One or more localized, circumscribed, lichenified plaques that result from repetitive scratching or rubbing because of intense itch
Asteatotic eczema	Adults	Common	Scaly, fissured patches of dermatitis overlying dry skin, most often on lower legs
INFECTIOUS SKIN DISEASES			
Dermatophyte infection	Children and adults	Common	One or more demarcated scaly plaques with central clearing and slightly raised reddened edge; variable itch
Impetigo	Children	Common	Demarcated erythematous patches with blisters or honey-yellow crusting
Scabies	Children	Common†	Itchy superficial burrows and pustules on palms and soles, between fingers, and on genitalia; might produce secondary eczematous changes
HIV	Children and adults	Uncommon	Seborrhea-like rash
CONGENITAL IMMUNODEFICIENCIES (SEE TABLE 186.3)			
KERATINIZATION DISORDERS			
Ichthyosis vulgaris	Infants and adults	Uncommon	Dry skin with fine scaling, particularly on the lower abdomen and extensor areas; perifollicular skin roughening; palmar hyperlinearity; full form (i.e., 2 *FLG* pathogenic variants) is uncommon; often coexists with AD
NUTRITIONAL DEFICIENCY–METABOLIC DISORDERS			
Zinc deficiency (acrodermatitis enteropathica)	Children	Uncommon	Erythematous scaly patches and plaques, most often around the mouth and anus; rare congenital form accompanied by diarrhea and alopecia
Biotin deficiency (nutritional or biotinidase deficiency)	Infants	Uncommon	Scaly periorofacial dermatitis, alopecia, conjunctivitis, lethargy, hypotonia
Pellagra (niacin deficiency)	All ages	Uncommon	Scaly crusted epidermis, desquamation, sun-exposed areas, diarrhea
Kwashiorkor	Infants and children	Geographic dependent	Flaky scaly dermatitis, swollen limbs with cracked peeling patches
Phenylketonuria	Infants	Uncommon	Eczematous rash, hypopigmentation, blonde hair, developmental delay
NEOPLASTIC DISEASE			
Cutaneous T-cell lymphoma	Adults	Uncommon	Erythematous pink-brown macules and plaques with a fine scale; poorly responsive to topical corticosteroids; variable itch (in early stages)
Langerhans cell histiocytosis	Infants	Uncommon	Scaly and purpuric dermatosis, hepatosplenomegaly, cytopenias

*Common = approximately 1 in 10 to 1 in 100; uncommon = 1 in 100 to 1 in 1,000; rare = 1 in 1,000 to 1 in 10,000; very rare = <1 in 10,000.
†Especially in developing countries.
AD, Atopic dermatitis; FLG, filaggrin gene.

because of potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, patients with steroid phobia, and those with face and neck dermatitis, in whom ineffective, low-potency topical corticosteroids are typically used because of fears of steroid-induced skin atrophy.

Phosphodiesterase Inhibitor

Crisaborole (Eucrisa) is an approved nonsteroidal topical antiinflammatory phosphodiesterase-4 (PDE-4) inhibitor indicated for the treatment of mild to moderate AD of children 3 months or older. It may be used as an alternative to topical corticosteroids or calcineurin inhibitors.

Table 186.3 Features of Primary Immunodeficiencies Associated with Eczematous Dermatitis

DISEASE	GENE	INHERITANCE	CLINICAL FEATURES	LAB ABNORMALITIES
AD-HIES	*STAT3*	AD, less commonly sporadic	Cold abscesses Recurrent sinopulmonary infections Mucocutaneous candidiasis Coarse facies Minimal trauma fractures Scoliosis Joint hyperextensibility Retained primary teeth Coronary artery tortuosity or dilation Lymphoma	High IgE (>2,000 IU/μL) Eosinophilia
DOCK8 deficiency	*DOCK8*	AR	Severe mucocutaneous viral infections Mucocutaneous candidiasis Atopic features (asthma, allergies) Squamous cell carcinoma Lymphoma	High IgE Eosinophilia With or without decreased IgM
PGM3 deficiency	*PGM3*	AR	Neurologic abnormalities Leukocytoclastic vasculitis Atopic features (asthma, allergies) Sinopulmonary infections Mucocutaneous viral infections	High IgE Eosinophilia
WAS	*WASP*	XLR	Hepatosplenomegaly Lymphadenopathy Atopic diathesis Autoimmune conditions (especially hemolytic anemia) Lymphoreticular malignancies	Thrombocytopenia (<80,000/μL) Low mean platelet volume Eosinophilia is common Lymphopenia Low IgM, variable IgG
SCID	Variable, depends on type	XLR and AR most common	Recurrent, severe infections Failure to thrive Persistent diarrhea Recalcitrant oral candidiasis Omenn syndrome: lymphadenopathy, hepatosplenomegaly, erythroderma	Lymphopenia common Variable patterns of reduced lymphocyte subsets (T, B, natural killer cells) Omenn syndrome: high lymphocytes, eosinophilia, high IgE
IPEX	*FOXP3*	XLR	Severe diarrhea (autoimmune enteropathy) Various autoimmune endocrinopathies (especially diabetes mellitus, thyroiditis) Food allergies	High IgE Eosinophilia Various autoantibodies
Netherton syndrome	*SPINK5*	AR	Hair shaft abnormalities Erythroderma Ichthyosis linearis circumflexa Food allergies Recurrent gastroenteritis Neonatal hypernatremic dehydration Upper and lower respiratory infections	High IgE Eosinophilia

AD, Autosomal dominant; AD-HIES, autosomal-dominant hyper-IgE syndrome; AR, autosomal recessive; *DOCK8*, dedicator of cytokinesis 8 gene; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PGM3, phosphoglucomutase 3; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; XLR, X-linked recessive.
From Kliegman RM, Bordini BJ, eds. Undiagnosed and rare diseases in children. *Pediatr Clin N Amer*. 2017;64(1):41–42.

Tar Preparations

Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, their antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Therefore topical tar preparations are not a preferred approach for management of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines

Systemic antihistamines act primarily by blocking the histamine H_1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H_1- and H_2-receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria. For children, melatonin may be effective in promoting sleep because production is deficient in AD.

Systemic Corticosteroids

Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, as during an asthma exacerbation, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids, and frequent bathing, followed by application of emollients or proactive topical corticosteroids, to prevent rebound flaring of AD.

Table 186.4 Counseling and Aggravating Factors for Patients with Atopic Dermatitis

Maintain cool temperature in bedroom, and avoid too many bed covers.
Increase emollient use with cold weather.
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect.
Clothing: Avoid skin contact with irritating fibers (wool, large-fiber textiles).
Do not use tight and too-warm clothing to avoid excessive sweating.
New, nonirritating clothing designed for AD children is being evaluated.
Tobacco: Avoid exposure.
Vaccines: Normal schedule in noninvolved skin, including egg-allergic patients (see text).
Sun exposure: No specific restriction.
Usually helpful because of improvement of epidermal barrier.
Encourage summer holidays in altitude or at beach resorts.
Physical exercise, sports: No restriction.
If sweating induces flares of AD, progressive adaptation to exercise.
Shower and emollients after swimming pool.
Food allergens:
Maintain breastfeeding exclusively to 4-6 mo if possible.
Consider evaluation for early introduction of allergens (see Chapter 192).
Otherwise normal diet, unless an allergy workup has proved the need to exclude a specific food.
Indoor aeroallergens: House dust mites.
Use adequate ventilation of housing; keep the rooms well aerated even in winter.
Avoid wall-to-wall carpeting.
Remove dust with a wet sponge.
Vacuum floors and upholstery with an adequately filtered cleaner once a week.
Avoid soft toys in bed (cradle), except washable ones.
Wash bedsheets at a temperature higher than 55°C (131°F) every 10 days.
Use bed and pillow encasings made of Gore-Tex or similar material.
Furred pets: Advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal.
Pollen: Close windows during peak pollen season on warm and dry weather days and restrict, if possible, time outdoors.
Windows may be open at night and early in the morning or during rainy weather.
Avoid exposure to risk situations (lawn mowing).
Use pollen filters in motor vehicles.
Clothes and pets can vectorize aeroallergens, including pollen.

Adapted from Darsow U, Wollenberg A, Simon D, et al. ETFAD/EADV Eczema Task Force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2010;24:321.

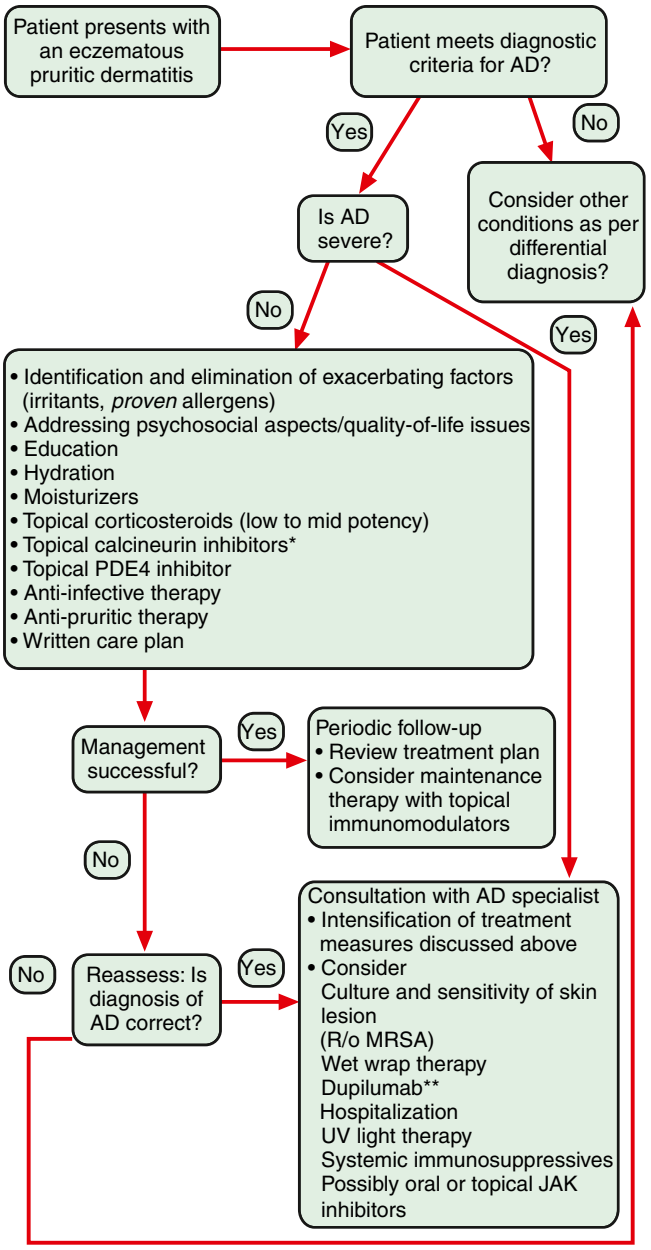

Fig. 186.5 Approach to the patient with atopic dermatitis (AD). *Per boxed warning: second-line, intermittent therapy for patients ≥2 years of age. **Approved for patients ≥12 years of age with moderate to severe AD. JAK, Janus kinase; MRSA; methicillin-resistant *Staphylococcus aureus*; PDE, phosphodiesterase; UV, ultraviolet. (*Modified from Boguniewicz M, Fonacier L, Leung DYM. Atopic dermatitis and allergic contact dermatitis. In Hershey GKK, Sheikh A, O'Hehir RE, Holgate ST, eds. Allergy Essentials. 2nd ed. Philadelphia: Elsevier; 2022. Fig 11.5.*)

Dupilumab

A monoclonal antibody that binds to the IL-4 receptor α subunit, dupilumab (Dupixent) inhibits the signaling of IL-4 and IL-13, cytokines associated with AD. In children with moderate to severe AD not controlled by standard topical therapy, dupilumab reduces pruritus and improves skin clearing. Dupilumab is approved for children 6 years or older. Lebrikizumab, an IgG4 monoclonal antibody that targets IL-13, has shown efficacy in adolescents and adults with moderate to severe atopic dermatitis.

Phototherapy

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription and has been shown to be effective in the control of severe AD. Cyclosporine forms a complex with an intracellular protein, cyclophilin, and this complex in turn inhibits calcineurin, a phosphatase required for activation of nuclear factor of activated T cells (NFAT), a transcription factor necessary for cytokine

Table 186.5 Categorization of Physical Severity of Atopic Eczema

Clear: Normal skin, with no evidence of atopic eczema
Mild: Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate: Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe: Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA, Guideline Development Group. Management of atopic eczema in children aged up to 12 years: summary of NICE guidance. *BMJ.* 2007;335:1263–1264.

gene transcription. Cyclosporine (5 mg/kg/day) for short-term and long-term (1 year) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

Janus Kinase Inhibitors

Oral and topical Janus kinase (JAK) inhibitors have demonstrated rapid improvement in adults and older children with severe AD. These inhibitors also have potential side effects including infections (tuberculosis), malignancy (cutaneous lymphoma), and headaches. Topical therapy is effective and has fewer side effects. Clinical trials are in progress to address the efficacy and safely of JAK inhibitors.

Antimetabolites

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex retinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore mycophenolate mofetil should be discontinued if the disease does not respond within 4-8 weeks.

Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis.

Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyltransferase levels may identify individuals at risk.

Before any of these drugs are used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

Unproven Therapies

Other therapies may be considered in patients with refractory AD.

Interferon-γ

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are common side effects during the treatment course.

Omalizumab

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials supporting omalizumab as a preferred therapy for moderate to severe AD. Most reports show inconsistent responses to anti-IgE.

Table 186.6 Selected Topical Corticosteroid Preparations*

GROUP 1
Clobetasol propionate (Temovate) 0.05% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel
Fluocinonide (Vanos) 0.1% cream
GROUP 2
Mometasone furoate (Elocon) 0.1% ointment
Halcinonide (Halog) 0.1% cream
Fluocinonide (Lidex) 0.05% ointment/cream
Desoximetasone (Topicort) 0.25% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% cream
GROUP 3
Fluticasone propionate (Cutivate) 0.005% ointment
Halcinonide (Halog) 0.1% ointment
Betamethasone valerate (Valisone) 0.1% ointment
GROUP 4
Mometasone furoate (Elocon) 0.1% cream
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
Fluocinolone acetonide (Synalar) 0.025% ointment
GROUP 5
Fluocinolone acetonide (Synalar) 0.025% cream
Hydrocortisone valerate (Westcort) 0.2% ointment
GROUP 6
Desonide (DesOwen) 05% ointment/cream/lotion
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
GROUP 7
Hydrocortisone (Hytone) 2.5%, 1%, 0.5% ointment/cream/lotion

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).
Adapted from Stoughton RB. Vasoconstrictor assay-specific applications. In: Malbach HI, Surber C, eds. *Topical Corticosteroids*. Basel, Switzerland: Karger; 1992. p 42–53.

Allergen Immunotherapy

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest that specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical corticosteroid use.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the first 2 years of life. The treatment response has been found to be more pronounced in patients with positive skin-prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

Chinese Herbal Medications

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The patients had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

Vitamin D

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation, and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease, especially in patients with low baseline vitamin D, as during winter, when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

AVOIDING TRIGGERS

It is essential to identify and eliminate triggering factors for AD, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 186.4).

Irritants

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. *Patients with AD should use soaps with minimal defatting properties and a neutral pH.* New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a second rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be as normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high sun protection factor (SPF) sunscreens should be used to avoid sunburn.

Foods

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 192). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet may lead to clinical improvement but also carries a risk of the patient developing immediate type allergic reactions to the food allergen removed.

Potential allergens can be identified by a careful history and performing selective skin-prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple positive skin test results, the majority of patients react to fewer than three foods under controlled challenge conditions.

Aeroallergens

In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections

Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *S. aureus*. Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus*. Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic clindamycin or trimethoprim/sulfamethoxazole needed for methicillin-resistant *S. aureus* (MRSA). Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus*. This finding supports the importance of combining effective antiinflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus*. Dilute bleach baths (½ cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial, the group who received the bleach baths plus intranasal mupirocin (5 days/month) had significantly decreased severity of AD at 1 and 3 months compared with placebo. Patients rinse off after the soaking. Bleach baths may not only reduce *S. aureus* abundance on the skin but also have antiinflammatory effects.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection (Fig. 186.6). The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical

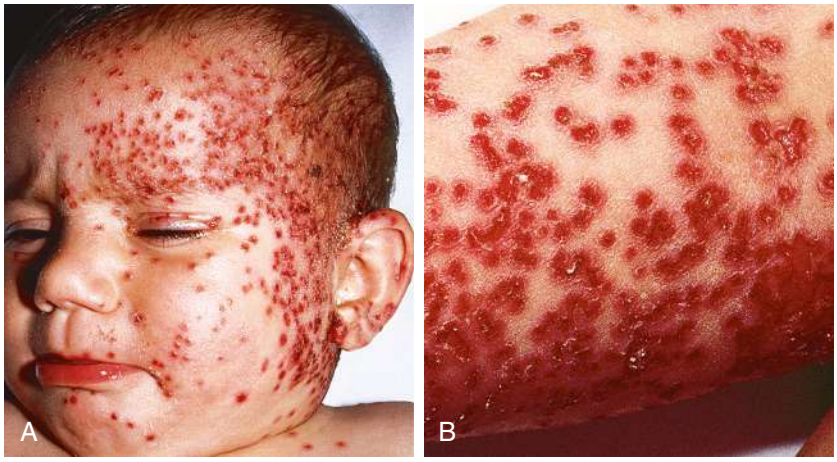

Fig. 186.6 Eczema herpeticum infection in a patient with atopic dermatitis. Numerous punched-out vesicles and erosions involving the face (**A**) and extremities (**B**). (*From Papulosquamous eruptions. In Cohen BA, ed. Pediatric Dermatology. Philadelphia: Saunders; 2013. pp 68–103.*)

corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to **eczema vaccinatum**, which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination.

Cutaneous warts, coxsackievirus, and molluscum contagiosum are additional viral infections affecting children with AD.

Dermatophyte infections can also contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic controls. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in these patients after treatment with antifungal agents.

COMPLICATIONS

Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma.

Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. **Atopic keratoconjunctivitis** is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. **Keratoconus** is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

PROGNOSIS

AD generally tends to be more severe and persistent in young children, particularly if they have homozygous null pathogenic variants in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 years in 40–60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as *hand dermatitis,* especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, *FLG* null pathogenic variants, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

PREVENTION

Breastfeeding may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breastfeeding mother may need to eliminate the implicated food allergen from her diet. For infants with severe eczema, introduction of infant-safe forms of peanut as early as 4-6 months, after other solids are tolerated, is recommended after consultation with the child's pediatrician and/or allergist for allergy testing. This approach may prevent peanut allergy (see Chapter 192). Identification and elimination of triggering factors are the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the first few months of life may enhance the cutaneous barrier and reduce the risk of eczema.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 187

Insect Allergy

Julie Wang and Scott H. Sicherer

Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. **Allergic reactions** caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and asthma.

ETIOLOGY

Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are usually attributed to IgE antibody–mediated responses, which are caused primarily by stings from venomous insects of the order **Hymenoptera** and more rarely from ticks, spiders, scorpions, and *Triatoma* (kissing bug). Members of the order Hymenoptera include *apids* (honeybee, bumblebee), *vespids* (yellow jacket, wasp, hornet), and *formicids* (fire and harvester ants) (Fig. 187.1). Among winged stinging insects, yellow jackets are the most notorious for stinging because they are aggressive and ground dwelling, and they linger near activities involving food. Hornets nest in trees, whereas wasps build honeycomb nests in dark areas such as under porches; both are aggressive if disturbed. Honeybees are less aggressive and nest in tree hollows; unlike the stings of other flying Hymenoptera, honeybee stings almost always leave a barbed stinger with venom sac.

In the United States, fire ants are found in the Southeast, living in large mounds of soil. When disturbed, the ants attack in large numbers, anchor themselves to the skin by their mandibles, and sting multiple times in a circular pattern. Sterile pseudopustules form at the sting sites. Systemic reactions to stinging insects occur in 0.4–0.8% of children and 3% of adults and account for approximately 40 deaths each year in the United States.

Although reactions to insect bites are common, IgE-mediated reactions are infrequently reported and anaphylaxis is rare. The *Triatoma* (kissing bug) bite causes an erythematous plaque that is painless. Mosquito bites generally result in local reactions that are pruritic. Large,

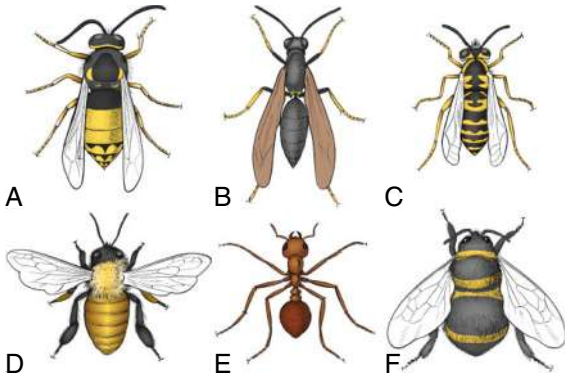

Fig. 187.1 Representative venomous Hymenoptera. **A,** Hornet *(Vespula maculata).* **B,** Wasp *(Chlorion ichneumerea).* **C,** Yellowjacket *(Vespula maculiforma).* **D,** Honeybee *(Apis mellifera).* **E,** Fire ant *(Solenopsis invicta).* **F,** Bumblebee *(Bombus species). (From Erickson TB, Marquez A. Arthropod envenomation and parasitism. In: Auerbach PS, Cushing TA, Harris NS, eds. Auerbach's Wilderness Medicine. 7th ed. Philadelphia: Elsevier; 2017: Fig 41-1, p 937.)*

local reactions to mosquito bites can occur in some young children; this is known as **skeeter syndrome** and is often misdiagnosed as cellulitis. The *tabanid* species (horsefly, deerfly), typically found in rural and suburban areas, are large flies that induce painful bites.

IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. **Perennial allergy** is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has eight rather than six legs.

PATHOGENESIS

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross reactivity among vespid venoms, but these venom allergies are distinct from honeybee venom allergies.

Localized skin responses to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva; they rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

CLINICAL MANIFESTATIONS

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple **local reactions** involve limited swelling and pain and generally last <24 hours. **Large local reactions** develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. **Generalized cutaneous reactions** typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. **Systemic reactions** are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. A subset of patients with hypotension and persistently elevated (once recovered) tryptase levels may have mast cell activation syndrome (see Chapter 190). Stings from numerous insects at once may result in **toxic reactions** of fever, malaise, emesis, and nausea because of the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as **delayed/late reactions** to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. **Papular urticaria** affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large, local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, or asthma.

DIAGNOSIS

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by skin-prick testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when **venom immunotherapy** (**VIT**) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of five Hymenoptera (honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp), as well as the jack jumper ant in Australia and whole body extract of fire ant, are available for skin testing. Although skin tests are considered to be the most sensitive modality for detection of venom-specific IgE, additional evaluation with an in vitro serum assay for venom-specific IgE is recommended if skin test results are negative in the presence of a convincing history of a severe systemic reaction. In vitro tests have a 20% incidence of both false-positive and false-negative results, so it is not appropriate to exclude venom hypersensitivity based on this test alone. If initial skin-prick and in vitro test results are negative in the context of a convincing history of a severe reaction, repeat testing is recommended before concluding that allergy is unlikely. Skin tests are usually accurate within 1 week of a sting reaction, but occasionally a refractory period is observed that warrants retesting after 4-6 weeks if the initial results are negative.

An elevated **basal tryptase** level is associated with more severe reactions to venom stings. Therefore basal tryptase should be measured if there is a history of severe reaction to a sting, hypotensive reaction, lack of urticaria in a systemic sting reaction, or negative venom IgE in a patient who has a history of systemic reaction to a sting. As many as 40% of skin test–positive patients may not experience anaphylaxis on sting challenge, so testing without an appropriate clinical history is potentially misleading.

The diagnosis of inhalant insect allergy may be evident from a history of typical symptoms. A chronic respiratory symptom during long-term exposure, as may occur with cockroach allergy, is less amenable to identification by history alone. Skin-prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy. Allergy tests may be particularly warranted for potential cockroach allergy in patients with persistent asthma and known cockroach exposure.

TREATMENT

For local cutaneous reactions caused by insect stings and bites, treatment with cold compresses, topical medications to relieve itching, and occasionally a systemic antihistamine and oral analgesic are appropriate. Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom. Sting sites rarely become infected, possibly because of the antibacterial actions of venom constituents. Vesicles left by fire ant stings that are scratched open should be cleansed to prevent secondary infection.

Anaphylactic reactions after a Hymenoptera sting are treated the same as anaphylaxis from any cause; *epinephrine is the drug of choice.* Adjunctive treatment includes antihistamines, corticosteroids, intravenous fluids, oxygen, and transport to the emergency department (see Chapter 190). Referral to an allergist-immunologist should be considered for patients who have experienced a generalized cutaneous or systemic reaction to an insect sting, who need education about avoidance and emergency treatment, who may be candidates for VIT, or who have a condition that may complicate management of anaphylaxis (e.g., use of β blockers).

Venom Immunotherapy

Hymenoptera VIT is highly effective (95–97%) in decreasing the risk for **severe anaphylaxis**. The selection of patients for VIT depends on several factors (Table 187.1). Individuals with local reactions,

Table 187.1 Risk of Systemic Reaction in Untreated Patients with History of Sting Anaphylaxis and/or Positive Venom Skin Test Results

ORIGINAL STING REACTION		RISK OF SYSTEMIC REACTION	
SEVERITY	**AGE**	**ANY SYSTEMIC (%)**	**ANAPHYLAXIS (%)**
No reaction	Adult	5-15	<3
Large local	All	4-10	<
Cutaneous systemic	All	10	<3
Anaphylaxis	Child	40	30
	Adult	60	40

From Golden DBK: Insect allergy. In Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy Principles and Practice*, ed 9, vol 2, Philadelphia: Elsevier, 2020, Table 76.2, p. 1253.

regardless of age, are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large, local reaction is approximately 7%; testing or VIT is usually not recommended, and prescription of self-injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. **Those who experience severe systemic reactions, such as airway involvement or hypotension, and who have specific IgE to venom allergens, should receive immunotherapy.** Immunotherapy against winged Hymenoptera is generally not required when stings have caused only generalized urticaria or angioedema, because the risk for a systemic reaction after a subsequent sting is approximately 10% and the chance of a more severe reaction is <3%. VIT may be considered if there are potential high-risk cofactors such as comorbid cardiovascular disease or use of specific cardiovascular medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, β blockers), elevated basal tryptase level, or high likelihood of future stings. VIT is usually not indicated if there is no evidence of IgE to venom.

The incidence of adverse effects in the course of *treatment* is not trivial in adults; 50% experience large, local reactions, and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT; thus some experts recommend basal tryptase level for risk assessment purposes.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, treatment duration of 3-5 years is recommended because >80% of adults who have received 5 years of therapy tolerate challenge stings without systemic reactions for 5-10 years after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 years of children with moderate to severe insect sting reactions who received VIT for a mean of 3-5 years and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Extended or lifelong treatment may be considered for those who have had life-threatening anaphylaxis with insect stings or severe reaction during VIT, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Lifelong VIT should also be considered for patients with mast cell disorders because they have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat patients who have only cutaneous systemic reactions with VIT. Only whole body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

Inhalant Allergy

The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 184), conjunctivitis (see Chapter 188), and asthma (see Chapter 185).

PREVENTION

Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should have known or suspected nests near the home removed by trained professionals, should wear gloves when gardening, should wear long pants and shoes with socks when walking in the grass or through fields, and should avoid or be cautious about eating or drinking outdoors. Typical insect repellents do not guard against Hymenoptera.

Individuals who are at high risk for future severe reactions to Hymenoptera stings should have immediate access to self-injectable epinephrine. High-risk individuals include those who have a history of severe reactions or have elevated basal tryptase level. Adults responsible for allergic children and older patients who can self-treat must be carefully taught the indications and technique of administration for this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear medical identification jewelry indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly for those living in apartments, where eradication of cockroaches may be problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 188

Ocular Allergies

Leonard Bielory, Brett P. Bielory, and Scott H. Sicherer

The ocular surface of the eye, the conjunctiva, is the most immunologically active tissue of the external eye. The conjunctiva is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. Ocular allergies can occur as isolated target organ disease or more often in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

CLINICAL MANIFESTATIONS

Allergic eye diseases represent a spectrum of conditions that require allergic sensitization and range from acute (seasonal) progressing to the perennial and then to the more chronic forms and potentially sight-threatening forms, vernal and atopic keratoconjunctivitis (Table 188.1).

Allergic Conjunctivitis

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to *chemosis,* or conjunctival swelling, and a watery discharge (Fig. 188.1).

Allergic conjunctivitis occurs in a seasonal or, less frequently, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 184) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons vary significantly in different parts of the United States. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/week or for <4 weeks) and persistent (symptoms present >4 days/week and for >4 weeks) has been proposed.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in two forms, limbal or palpebral. It may threaten eyesight if there is corneal involvement. Vernal keratoconjunctivitis is only associated with positive cutaneous allergic reactivities in 50% of cases, although it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects males twice as often as females

Table 188.1 Allergic Diseases of the Eye

DISEASE	CLINICAL PARAMETERS	SIGNS/SYMPTOMS	DIFFERENTIAL DIAGNOSIS
Seasonal allergic conjunctivitis (SAC)	• Sensitized individuals • Both females and males • Bilateral involvement • Seasonal allergens • Self-limiting	• Ocular itching • Tearing (watery discharge) • Chemosis, redness • Often associated with rhinitis • Not sight threatening	• Infective conjunctivitis • Preservative toxicity • Medicamentosa • Dry eye • PAC/AKC/VKC
Perennial allergic conjunctivitis (PAC)	• Sensitized individuals • Both females and males • Bilateral involvement • Year-round allergens • Self-limiting	• Ocular itching • Tearing (watery discharge) • Chemosis, redness • Often associated with rhinitis • Not sight threatening	• Infective conjunctivitis • Preservative toxicity • Medicamentosa • Dry eye • SAC/AKC/VKC
Atopic keratoconjunctivitis (AKC)	• Sensitized individuals • Peak incidence 20-50 years of age • Both females and males • Bilateral involvement • Seasonal/perennial allergens • Atopic dermatitis • Chronic symptoms	• Severe ocular itching • Red flaking periocular skin • Mucoid discharge, photophobia • Corneal erosions • Scarring of conjunctiva • Cataract (anterior subcapsular) • Sight threatening	• Contact dermatitis • Infective conjunctivitis • Blepharitis • Pemphigoid • VKC/SAC/PAC/GPC
Vernal keratoconjunctivitis (VKC)	• Some sensitized individuals • Peak incidence 3-20 years of age • Males predominate 3:1 • Bilateral involvement • Warm, dry climate • Seasonal/perennial allergens • Chronic symptoms	• Severe ocular itching • Severe photophobia • Thick, ropy discharge • Cobblestone papillae • Corneal ulceration and scarring • Sight threatening	• Infective conjunctivitis • Blepharitis • AKC/SAC/PAC/GPC
Giant papillary conjunctivitis (GPC)	• Sensitization not necessary • Both females and males • Bilateral involvement • Prosthetic exposure • Occurs anytime • Chronic symptoms	• Mild ocular itching • Mild mucoid discharge • Giant papillae • Contact lens intolerance • Foreign body sensation • Protein buildup on contact lens • Not sight threatening	• Infective conjunctivitis • Preservative toxicity • SAC/PAC/AKC/VKC

From Barney NP. Allergic and immunologic diseases of the eye. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy: Principles and Practice.* 9th ed. Philadelphia: Elsevier, 2020: Table 38.1, p. 607)

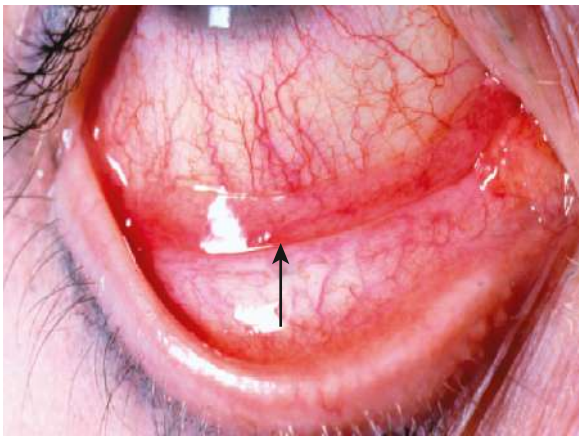

Fig. 188.1 Allergic conjunctivitis. *Arrow* indicates area of chemosis in the conjunctivitis. *(From Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy: Principles & Practice. 8th ed. St Louis: Elsevier, 2014: p. 619.)*

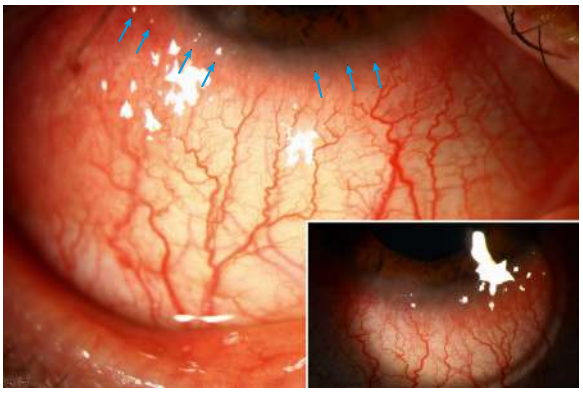

Fig. 188.3 Horner-Trantas dots. Classic appearance of small white-yellow chalky concretions with collections of degenerated epithelial cells and eosinophils around the corneal limbus *(arrows). (From Cheng J, Jiang L, Morrow NC, et al. Recognition of atopic keratoconjunctivitis during treatment with dupilumab for atopic dermatitis. J Am Acad Dermatol. 2021;85(1):265–267. Fig 1.)*

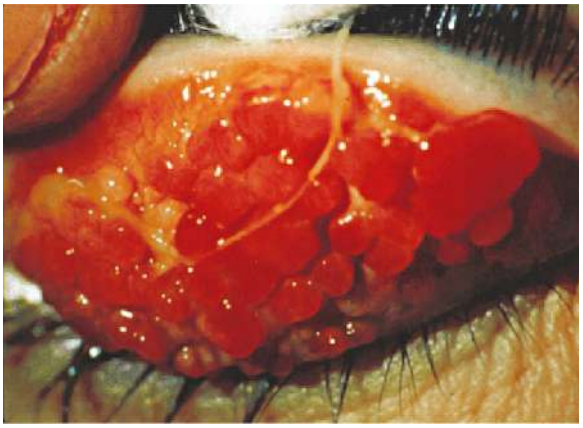

Fig. 188.2 Vernal keratoconjunctivitis. Cobblestone papillae and ropey discharge are seen on the underside (tarsal conjunctiva) of the upper eyelid. *(From Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy: Principles & Practice. 8th ed. St Louis: Elsevier, 2014: p. 627.)*

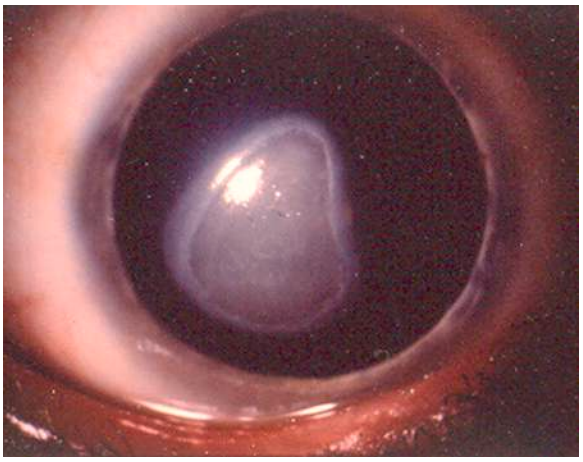

Fig. 188.4 Corneal shield ulcer classic depiction of sterile plaques containing fibrin and mucous that accumulate into macro-erosions forming a shield ulcer. *(From LaMattina K, Thompson L. Pediatric conjunctivitis. Dis Mon. 2014;60(6):231–238. Fig 6.)*

and is more common in the Mediterranean basin and in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer, but can occur throughout the year. Symptoms include intense ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia due to corneal involvement, foreign body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as *cobblestoning* (Fig. 188.2). Other signs include a stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points at the corneal limbus *(Trantas dots)* (Fig. 188.3) and conjunctiva *(Horner points)*, corneal "shield" ulcers (Fig. 188.4), and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a chronic inflammatory ocular disorder most often involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have atopic dermatitis, and a significant number have asthma. Atopic keratoconjunctivitis rarely presents before late adolescence. Symptoms include severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge that are much more severe than in allergic conjunctivitis and persist throughout the year. The bulbar conjunctiva is injected and chemotic; cataracts may occur. Trantas dots at the corneal limbus or giant papillae typically found in inferior palpebral conjunctiva may also be present. Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling. Secondary staphylococcal blepharitis is common because of eyelid induration and maceration. Chronic eye rubbing associated with vernal and atopic keratoconjunctivitis can lead to **keratoconus**, a noninflammatory cone-shaped corneal ectasia. This may lead to corneal thinning and perforation.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis is not associated with IgE sensitization, but has been linked to chronic exposure to foreign bodies, such

as contact lenses (both hard and soft), ocular prostheses, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is frequently associated with increased exposure to topical medications, contact lens solutions, and preservatives.

DIAGNOSIS

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral, but can be bilateral with symptoms initially developing in one eye (see Chapter 666). Symptoms include stinging or burning rather than itching and often a foreign body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharoconjunctivitis, dry eye, uveitis, and trauma.

Dry Eye

Dry eye conditions are being increasingly recognized as a concomitant and comorbid condition in children directly correlated with increased use of computers and gaming and mobile devices that are associated with decreased blinking time and increased evaporative tear film dysfunction.

TREATMENT

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. Secondary treatment regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 188.2). Drugs with dual antihistamine and mast cell–blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictor is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a nasoocular reflex.

Table 188.2 Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	COMMENTS, CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride, 0.05% Optivar	Antihistamine *Children ≥3 yr:* 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Emedastine difumarate, 0.05% Emadine	Antihistamine *Children ≥3 yr:* 1 gtt qid	Soft contact lenses should not be worn if the eye is red Wait at least 10 min after administration before inserting soft contact lenses
Levocabastine hydrochloride, 0.05% Livostin	Antihistamine *Children ≥12 yr:* 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms Not for use with contact lenses
Naphazoline hydrochloride, 0.3% 0.025% Naphcon-A, Opcon-A	*Children >6 yr:* 1-2 gtt qid	Avoid prolonged use (>3-4 days) to avoid rebound symptoms Not for use with contact lenses
Cromolyn sodium, 4% Crolom, Opticrom	Mast cell stabilizer *Children >4 yr:* 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis Not for use with contact lenses
Lodoxamide tromethamine, 0.1% Alomide	Mast cell stabilizer *Children ≥2 yr:* 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis Not for use in patients wearing soft contact lenses during treatment
Nedocromil sodium, 2% Alocril	Mast cell stabilizer *Children ≥3 yr:* 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis
Pemirolast potassium, 0.1% Alamast	Mast cell stabilizer *Children >3 yr:* 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Epinastine hydrochloride, 0.05% Elestat	Antihistamine/mast cell stabilizer *Children ≥3 yr:* 1 gtt bid	Contact lenses should be removed before use Wait at least 15 min after administration before inserting soft contact lenses Not for the treatment of contact lens irritation

Table 188.2 Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	COMMENTS, CAUTIONS AND ADVERSE EVENTS
Ketotifen fumarate, 0.025% Zaditor	Antihistamine/mast cell stabilizer *Children ≥3 yr:* 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Olopatadine hydrochloride, 0.1%, 0.2%, 0.7% Patanol, Pataday, Pazeo	Antihistamine/mast cell stabilizer *Children ≥3 yr:* 1 gtt bid (8 hr apart) *Children ≥2 yr:* 1 gtt qd	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer *Children >2 yr:* 1 gtt bid q8-12h	Contact lenses should be removed before application; may be inserted after 10 min Not for the treatment of contact lens irritation
Bepotastine besilate, 1.5% Bepreve	Antihistamine/mast cell stabilizer *Children >2 yr:* 1 gtt bid q8-12h	Contact lenses should be removed before application; may be inserted after 10 min Not for the treatment of contact lens irritation
Cetirizine, 0.24% Zerviate	Antihistamine *Children >2 yr:* 1 gtt bid	Contains lubricant hydrocellulose, preservative free unit doses
Ketorolac tromethamine, 0.5% Acular	NSAID *Children ≥3 yr:* 1 gtt qid	Avoid with aspirin or NSAID sensitivity Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight threatening *Do not use while wearing contact lenses*
Fluorometholone, 0.1%, 0.25% suspension and 0.1% ointment FML, FML Forte, Flarex	Fluorinated corticosteroid *Children ≥2 yr:* 1 gtt into conjunctival sac of affected eye(s) bid-qid During initial 24-48 hr, dosage may be increased to 1 gtt q4h Ointment (~1.3 cm in length) into conjunctival sac of affected eye(s) 1-3 times daily May be applied q4h during initial 24-48 hr of therapy.	If improvement does not occur after 2 days, patient should be reevaluated Patient should remove soft contact lenses before administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 min after administration Close monitoring for development of glaucoma and cataracts
Cyclosporine ophthalmic solution, 01.% Verkazia	Immunomodulation *Children >3 yr:*1 gtt qid	Unpreserved single dose units Approved for treatment of vernal keratoconjunctivitis
loteprednol, 0.5% Lotemax, Alrex	Steroid, antiinflammatory *Children >2 yr:*1-2 gtt qid	Lowest steroid associated with cataract formation or increase in intraocular pressure Comes in suspension and gel formulations

NSAID, Nonsteroidal antiinflammatory drug; bid, 2 times daily; gtt, drops; qid, 4 times daily; q4-6h, every 4-6 hr; qd, every day.

Tertiary treatment of ocular allergy includes topical (or rarely oral) corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine, are used as steroid-sparing agents. Allergen immunotherapy is very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist. *Symptoms that should prompt referral to an ophthalmologist include unilateral red eye with pain, photophobia, change in vision, refractory dry eyes, or corneal abnormality.*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 189

Urticaria (Hives) and Angioedema

David A. Khan, Aleena Banerji, and Scott H. Sicherer

Urticaria affects 20% of individuals at some point in their life. Episodes of hives that last for <6 weeks are considered *acute,* whereas those that occur on most days of the week for >6 weeks are designated *chronic.* The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

ETIOLOGY AND PATHOGENESIS

Urticaria is defined as the presence of wheals (hives), angioedema, or both. **Acute urticaria** is often caused by an allergic IgE–mediated reaction (Table 189.1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging-insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells, caused by viral infections, nonsteroidal anti-inflammatory drugs (NSAIDs), and opiates. The diagnosis of **chronic urticaria** is established when lesions occur on most days of the week for >6 weeks (Tables 189.2 and 189.3). In about half the cases, chronic urticaria is accompanied by angioedema. In 20% of chronic urticaria patients, angioedema occurs without wheals. Acute angioedema without wheals is often a result of allergy, but recurrent isolated angioedema raises the possibility of other diagnoses.

A typical **hive** is an erythematous, pruritic, raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with systemic lupus erythematosus (SLE), or other vasculitides in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hours, do not blanch, blister, heal with scarring, or that are associated with bleeding into the skin (purpura) suggest urticarial vasculitis, which is a rare condition in children. Atypical aspects of the gross appearance of the hives or associated systemic symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process (Table 189.4).

Table 189.1 Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, direct mast cell degranulation
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	**Bacterial** (streptococcal pharyngitis, *Mycoplasma*, sinusitis); **Viral** (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); **Parasitic** (*Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella*); **Fungal** (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or intravenous immune globulin administration

From Lasley MV, Kennedy MS, Altman LC. Urticaria and angioedema. In: Altman LC, Becker JW, Williams PV, eds. *Allergy in Primary Care.* Philadelphia: Saunders; 2000: p. 232.

INDUCIBLE URTICARIA

Inducible urticaria and angioedema (previously referred to as physical urticaria) share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (Table 189.5; see also Table 189.2). In contrast to chronic spontaneous urticaria (CSU), the wheals of inducible urticaria are more short-lived, often lasting <1 hour.

Cold-Dependent Disorders

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total body exposure, as seen with swimming in cold water, can cause anaphylaxis, resulting in hypotension, loss of consciousness, and even death if not promptly treated. The diagnosis is most easily confirmed by challenge testing by holding an ice cube in place on the patient's skin for 5 minutes. In patients with cold urticaria, a urticarial lesion develops about 10 minutes after removal of the ice cube and on rewarming of the chilled skin. Most cases of acquired cold urticaria are idiopathic. Cold urticaria is rarely associated with the presence of **cryoproteins** such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis (paroxysmal cold hemoglobinuria). Multiple subtypes of atypical cold urticaria with a negative ice cube test have also been reported. Cold

Table 189.2 Etiology of Chronic Urticaria

Spontaneous/autoimmune	Approximately 30% of chronic urticaria cases are inducible urticaria, and 60–70% are spontaneous; of the spontaneous cases approximately 20–60% have autoantibodies (see text)
Inducible	Dermographism Cholinergic urticaria Cold urticaria (see Table 189.6) Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid disease (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Urticarial vasculitis
Autoinflammatory/periodic fever syndromes	See Tables 189.3 and 189.6.
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema Acquired angioedema Angiotensin-converting enzyme inhibitors

Modified from Lasley MV, Kennedy MS, Altman LC. Urticaria and angioedema. In: Altman LC, Becker JW, Williams PV, eds. *Allergy in Primary Care.* Philadelphia: Saunders; 2000: p. 234.

Table 189.3 Febrile Autoinflammatory Diseases Causing Urticaria in Children

DISEASE	GENE (PROTEIN)	INHERITANCE	ATTACK LENGTH	TIMING OF ONSET	CUTANEOUS FEATURES	EXTRACUTANEOUS CLINICAL FEATURES
FCAS	*NLRP3* (cryopyrin)	AD	Brief; minutes to 3 days	Neonatal or infantile	Cold-induced pseudourticaria	Arthralgia Conjunctivitis Headache
Muckle-Wells syndrome	*NLRP3* (cryopyrin)	AD	1-3 days	Neonatal, infantile, childhood (can be later)	Widespread pseudourticaria	Arthralgia/arthritis Sensorineural hearing loss Conjunctivitis/episcleritis Headache Amyloidosis
Neonatal-onset multisystem inflammatory disease (aka chronic infantile neurologic cutaneous articular syndrome)	*NLRP3* (cryopyrin)	AD	Continuous flares	Neonatal or infantile	Widespread pseudo-urticaria	Deforming osteoarthropathy, epiphyseal overgrowth Sensorineural hearing loss Dysmorphic facies Chronic aseptic meningitis, headaches, papilledema, seizures Conjunctivitis/uveitis, optic atrophy Growth retardation Developmental delay Amyloidosis
HIDS	*MVK* (mevalonate kinase)	AR	3-7 days	Infancy (<2yr)	Intermittent morbilliform or urticarial rash Aphthous mucosal ulcers Erythema nodosum	Arthralgia/arthritis Cervical lymphadenopathy Severe abdominal pain Diarrhea/vomiting Headache Elevated IgD and IgA antibody levels Elevated urine mevalonic acid during attacks
Tumor necrosis factor receptor–associated periodic syndrome	*TNFRSF1A* (TNFR1)	AD	>7 days	Childhood	Intermittent migratory erythematous macules and edematous plaques overlying areas of myalgia, often on limbs Periorbital edema	Migratory myalgia Conjunctivitis Serositis Amyloidosis
Systemic-onset juvenile idiopathic arthritis (SoJIA)	Polygenic	Varies	Daily (quotidian)	Peak onset at 1-6yr	Nonfixed erythematous rash; may be urticarial With or without dermographism With or without periorbital edema	Polyarthritis Myalgia Hepatosplenomegaly Lymphadenopathy Serositis
PLAID	*PLCG2*	AD	N/A	Infancy	Urticaria induced by evaporative cooling Ulcers in cold-exposed areas	Allergies Autoimmune disease Recurrent sinopulmonary infections Elevated IgE antibody levels Decreased IgA and IgM antibody levels Often elevated antinuclear antibody titers

AD, Autosomal dominant; AR, autosomal recessive; HIDS, hyperimmunoglobulinemia D syndrome; FCAS, familial cold-induced autoinflammatory syndrome; N/A, not available; PLAID, PLCG2-associated antibody deficiency and immune dysregulation.

From Youseff MJ, Chiu YE. Eczema and urticaria as manifestations of undiagnosed and rare diseases. *Pediatr Clin North Am.* 2017;64:39–56. Table 2, pp. 49–50.

urticaria must be distinguished from the **familial cold autoinflammatory syndrome** (see later, Diagnosis) (Table 189.6; see also Table 189.3 and Chapter 204). Because 20% of pediatric patients with cold urticaria may experience anaphylaxis, counseling on risks of anaphylaxis and prescribing epinephrine autoinjectors should be considered.

Cholinergic Urticaria

Cholinergic urticaria is characterized by the onset of small, punctate pruritic wheals surrounded by a prominent erythematous flare and associated with exercise, hot showers, emotional stress, and sweating. Once the patient cools down, the rash usually subsides in 30-60 minutes. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

Table 189.4 Distinguishing Features Between Urticaria and Systemic Urticarial Syndromes

COMMON URTICARIA	URTICARIAL SYNDROMES (≥1 OF FOLLOWING)
Only typical wheals:	Atypical "wheals":
Erythematous edematous lesions	Infiltrated plaques
Transient (<24-36 hr)	Persistent (>24-36 hr)
Asymmetric distribution	Symmetric distribution
Resolution without signs	Resolution with signs (hypo/hyperpigmentation, bruising, or scarring)
No associated different elementary lesions (papules, vesicles, purpura, crustae)	Associated different elementary lesions (papules, vesicles, purpura, scaling, crustae)
Pruritic (rarely stinging/burning)	Not pruritic; rather painful or burning
Possibly associated with angioedema	Usually no associated angioedema
No associated systemic symptoms	Often associated with systemic symptoms (fever, malaise, arthralgia, abdominal pain, weight loss, acral circulatory abnormalities, neurologic signs

From Peroni A, Colato C, Zanoni G, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria. *J Am Acad Dermatol*. 2009;62(4):559.

Symptomatic Dermographism

Symptomatic dermographism (also called *dermatographism* or *urticaria factitia*) may occur as an isolated disorder or may accompany chronic urticaria or other inducible urticarias. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear wheal caused by secondary dilation of the vessel and extravasation of plasma. Symptomatic dermographism is distinct from the more common "simple dermographism," affecting 4% of the population, whereas whealing but no itch occurs with stroking the skin.

Delayed Pressure Urticaria

Delayed pressure urticaria differs from other inducible urticaria in that symptoms typically occur 4-6 hours after pressure has been applied. Some patients may complain of swelling, with or without pruritus, secondary to pressure, without hives. Other lesions are predominantly wheals and may or may not be associated with significant swelling. When wheals are present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in CSU. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with CSU or can occur separately. The diagnosis is confirmed by challenge testing, most commonly via the "sand bag test." This test can be performed by using 15 lb of weights attached to a strap applied to the shoulder, thigh, or forearm for 15 minutes and observing the site over the next 24 hours for evidence of hives or edema.

Solar Urticaria

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 seconds, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hours after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into six types, depending on the wavelength of light that induces skin lesions and the ability or inability to transfer the disorder passively with serum IgE.

Aquagenic Urticaria

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. Rarely, chlorine or other trace contaminants may be responsible for the reaction.

CHRONIC SPONTANEOUS URTICARIA

CSU is the most common form of chronic urticaria and is associated with normal routine laboratory values and no evidence of systemic disease. CSU differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and shape but generally rounded.

Biopsy of a typical lesion reveals nonnecrotizing, perivascular, mononuclear cellular infiltration. Varying histopathologic processes can occur in the skin and manifest as urticaria. Patients with urticarial **vasculitis** can have urticaria and/or angioedema. Biopsy of these lesions in patients who may present with urticaria, arthralgias, myalgias, an elevated erythrocyte sedimentation rate (ESR), and in some cases **hypocomplementemia** as manifestations of urticarial vasculitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. Although urticarial vasculitis lesions are typically less blanchable, the lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

The immunopathogenesis of CSU is not entirely clear; however, mast cell activation is thought to have a key role. A key activating receptor in mast cells is the high-affinity IgE receptor (FcεRI). Two theories suggest that autoimmune factors may lead to FcεRI activation. In **type 1 autoimmunity (aka autoallergy)**, patients have IgE autoantibodies to self-antigens such as thyroperoxidase or interleukin (IL)-24, which can cross link the IgE autoantibodies leading to mast cell activation and urticaria. In **type II autoimmunity**, patients have autoantibodies (IgG, IgM, IGA) directed against FcεRI or IgE itself, which can similarly lead to mast cell activation. Direct measurement of these autoantibodies is limited to research studies with no clear clinical utility at present. However, the autoallergy theory is an attractive explanation for the effectiveness of anti-IgE therapies like omalizumab.

Diagnosis

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the clinician be aware of the various forms of urticaria (wheals and angioedema).

Hives are transient, pruritic, erythematous, raised wheals that may become tense and painful. The lesions may coalesce and form polymorphous, serpiginous, or annular lesions (Figs. 189.1 and 189.2). Individual lesions usually last minutes to several hours and rarely more than 24 hours. The lesions often disappear, only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, and in the case of hereditary angioedema (HAE), the wall of the gastrointestinal (GI) tract (see Chapter 189.1).

Viral infections, drugs, and foods are the most common identifiable causes of acute urticaria in children. Allergy skin testing for foods can be helpful in identifying a cause of acute urticaria, but only when supported by historical evidence. The role of an offending food can then be proved by elimination and food challenge, when needed. In the absence of information implicating an ingestant cause, skin testing for foods and implementation of elimination diets are generally not useful for either acute or chronic urticaria. Patients with delayed urticaria 3-6 hours after a meal consisting of mammalian meat should be evaluated for IgE to galactose-α-1,3-galactose **("alpha-gal")**, a carbohydrate allergen. Alpha-gal has been identified as a trigger in this circumstance,

Table 189.5 Comparison of the Physical Urticarias

URTICARIA	RELATIVE FREQUENCY	PRECIPITANT	TIME OF ONSET	DURATION	LOCAL SYMPTOMS	SYSTEMIC SYMPTOMS	TESTS	MECHANISM	TREATMENT
Symptomatic dermographism	Most frequent	Stroking skin	Minutes	2-3 hr	Irregular pruritic attacks	None	Stroke skin	Passive transfer, IgE, histamine, possible role of adenosine triphosphate, substance P, possible direct pharmacologic mechanism	Continual antihistamines
Delayed dermographism	Rare	Stroking skin	30 min to 8 hr	<48 hr	Burning, deep swelling	None	Stroke skin, observe early and late	Unknown	Avoidance of precipitants
Pressure urticaria	Frequent	Pressure	3-12 hr	8-24 hr	Diffuse, tender swelling	Flulike symptoms	Apply weight	Unknown	Avoidance of precipitants; if severe, omalizumab
Solar urticaria	Frequent	Various wavelengths of light	2-5 min	15 min to 3 hr	Pruritic wheals	Wheezing, dizziness, syncope	Phototest	Passive transfer, reverse passive transfer, IgE, possible histamine	Avoidance of precipitants; antihistamines, sunscreens, antimalarials
Familial cold urticaria	Rare	Change in skin temperature	30 min to 3 hr	<48 hr	Burning wheals	Tremor; headache; arthralgia; fever	Expose skin to cold air	Unknown	Avoidance of precipitants
Essential acquired cold urticaria	Frequent	Cold contact	2-5 min	1-2 hr	Pruritic wheals	Wheezing, syncope, drowning	Apply ice-filled copper beaker to arm, immerse	Passive transfer, reverse passive transfer, IgE (IgM), histamine; vasculitis can be induced	Cyproheptadine hydrochloride, other antihistamines; desensitization; avoidance of precipitants
Heat urticaria	Rare	Heat contact	2-5 min (rarely delayed)	1 hr	Pruritic wheals	None	Apply hot water–filled cylinder to arm	Possibly histamine; possibly complement	Antihistamines, desensitization; avoidance of precipitants
Cholinergic urticaria	Very frequent	General overheating of body	2-20 min	30 min to 1 hr	Papular, pruritic wheals	Syncope; diarrhea; vomiting, salivation; headaches	Bathe in hot water; exercise until perspiring, inject methacholine chloride	Passive transfer; possible immunoglobulin; product of sweat gland stimulation; histamine, reduced protease	Application of cold water or ice to skin; antihistamines; omalizumab
Aquagenic urticaria	Rare	Water contact	Several minutes	30-45 min	Papular, pruritic wheals	None reported	Apply water compresses to skin	Unknown	Avoidance of precipitants; antihistamine; application of inert oil
Vibratory angioedema	Very rare	Vibrating against skin	2-5 min	1 hr	Angioedema	None reported	Apply vibration to forearm	Unknown	Avoidance of precipitants

Ig, Immunoglobulin.
From Lee AD, Jorizzo JL. Urticaria. In: Callen JP, Jorizzo JL, Bolognia JL, et al., eds. *Dermatological Signs of Internal Disease*. 4th ed. Philadelphia: Elsevier; 2009: p. 59, Table 6.4.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 189.6 Hereditary Diseases with Cold-Induced Urticaria

		EPISODIC SYMPTOMS	SUSTAINED/PROGRESSIVE SYMPTOMS
CAPS	FCAS	Urticarial rash, arthralgia, myalgia, chills, fever, swelling of extremities	Renal amyloidosis
	MWS	Urticarial rash, arthralgia, chills, fever	Sensorineural deafness, renal amyloidosis
	CINCA	Fever	Rash, arthritis, chronic meningitis, visual defect, deafness, growth retardation, renal amyloidosis
NAPS12 (FCAS2)		Fever, arthralgia, myalgia, urticaria, abdominal pain, aphthous ulcers, lymphadenopathy	Sensorineural deafness
PLAID (FCAS3)		Urticaria induced by evaporative cooling, sinopulmonary infections	Serum low IgM and IgA levels; high IgE levels; decreased B and NK cells; granulomata; antinuclear antibodies

CAPS, Cryopyrin-associated periodic syndromes; FCAS, familial cold-induced autoinflammatory syndrome; MWS, Muckle-Wells syndrome; CINCA, chronic infantile neurologic cutaneous articular syndrome; NAPS, NLRP-12–associated periodic syndrome; PLAID, PLCG2-associated antibody deficiency and immune dysregulation; NK, natural killer; Ig, immunoglobulin.
From Kanazawa N. Hereditary disorders presenting with urticaria. *Immunol Allergy Clin N Amer.* 2014;34:169–179. Table 4, p. 176.



Fig. 189.1 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion. *(From Eichenfield LF, Friedan IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001: p. 300.)*



Fig. 189.2 Annular urticaria of unknown etiology. *(From Eichenfield LF, Friedan IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001: p. 301.)*

with sensitization linked to tick bites in specific geographic regions, such as the mid-Atlantic area of the United States. Skin testing for aeroallergens is not indicated unless there is a concern about contact urticaria (animal dander or grass pollen).

Autoimmune diseases are very rare causes of chronic urticaria or angioedema. Clinically available tests marketed for chronic urticaria such as basophil activation tests (used as surrogates for detecting type 2 autoantibodies) are generally not recommended. The **differential diagnosis** of chronic urticaria includes atopic or contact dermatitis, cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blistering disorders (e.g., bullous pemphigoid; see Table 189.2). Routine laboratory testing in chronic urticaria in the absence of other history has not been found to be cost-effective as it rarely changes management. Urticaria guidelines recommend either no testing or limited laboratory testing such as a complete blood cell count with differential and ESR or CRP. Further studies are warranted if the patient has fever, arthralgias, or elevated ESR (Table 189.7; see also Table 189.4). **HAE** is potentially life-threatening, usually associated with deficient C1 inhibitor (C1-INH) activity, and the most important familial form of angioedema (see Chapter 189.1), but it is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A rare syndrome of episodic (approximately 3- to 4-week intervals) angioedema less often with urticaria, weight gain, and occasionally fever with associated **hypereosinophilia** has been described in both adults and children.

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the *same location* for >24 hours, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as SLE may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivenular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

Mastocytosis is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. Maculopapular cutaneous mastocytosis (aka **urticaria pigmentosa)** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching **(Darier sign)**. This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Inducible urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Tables 189.2 and 189.5). Papular "urticaria" often occurs in small children, generally on the extremities, but the lesions are more persistent than true urticaria. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, or hypotension after exercise (see Chapter 190). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence

Table 189.7 Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Chronic spontaneous urticaria	No testing required for diagnosis
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50}, C1q, C4, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Cold urticaria	Ice cube test usually positive but may be negative in familial autoinflammatory disorders
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermographism	Stroking with narrow object (e.g., tongue blade)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C1-INH testing by protein and function
Familial cold autoinflammatory syndrome	Genetic testing for *NALP3* pathogenic variants

Table 189.8 Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg	Twice daily
	>12 yr: 60 mg	
	Adult: 180 mg	Once daily
Loratadine	2-5 yr: 5 mg	Once daily
	>6 yr: 10 mg	
Desloratadine	6-11 mo: 1 mg	Once daily
	12 mo-5 yr: 1.25 mg	
	6-11 yr: 2.5 mg	
	>12 yr: 5 mg	
Cetirizine	6-23 mo: 2.5 mg	Once daily
	2-6 yr: 2.5-5 mg	
	>6 yr: 5-10 mg	
	>12 yr: 10 mg	Once daily
Levocetirizine	6 mo-5 yr: 1.25 mg	Once daily
	6-11 yr: 2.5 mg	Once daily
	>12 yr: 5 mg	Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day	Divided q6-12h
	Children: 20-40 mg/kg/day	
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day	Divided q12h
	1-16 yr: 1-2 mg/kg/day	
LEUKOTRIENE PATHWAY MODIFIERS		
Montelukast	12 mo-5 yr: 4 mg	Once daily
	6-14 yr: 5 mg	
	>14 yr: 10 mg	
Zafirlukast	5-11 yr: 10 mg	Twice daily
IMMUNOMODULATORY DRUGS		
Omalizumab (anti IgE)	>11 yr: 300 mg	Every 28 days
Cyclosporine	1-4 mg/kg/day	Divided q12h*

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

of anaphylactic shock. The combination of ingestion of various food allergens and postprandial exercise has been associated with urticaria/angioedema and anaphylaxis. In patients with this combination disorder, the offending food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and familial cold autoinflammatory syndrome are rare, autosomal dominantly inherited conditions associated with recurrent urticaria-like lesions. **Muckle-Wells syndrome** is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR (see Tables 189.3 and 189.6), hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. **Familial cold autoinflammatory syndrome** is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea.

Treatment

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and frequently used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced sedation (Table 189.8). Epinephrine 1:1,000, 0.01 mg/kg (maximum 0.5 mg) intramuscularly, usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids may be given for more severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

The best treatment of inducible urticaria is avoidance of the stimulus; however, for some conditions like cholinergic urticaria, this can be very difficult. Antihistamines with appropriate updosing, should be tried in all inducible urticarias but may not be effective in many patients.

Management of chronic urticaria through dietary manipulation is not recommended by U.S. guidelines. The mainstay of therapy for chronic urticaria is the use of nonsedating or low-sedating H_1 antihistamines. In those patients not showing response to standard doses, increasing the dose up to fourfold the recommended dose is recommended; however, studies on the safety and efficacy of this approach in children are lacking. The addition of H_2 antihistamines and/or leukotriene receptor antagonists (e.g., montelukast) is controversial. These medications are generally benign but evidence supporting their efficacy is weak. For chronic urticaria patients that are not well controlled, brief courses of oral corticosteroids may be considered, but long-term corticosteroid use is not recommended. The monoclonal antibody omalizumab (anti-IgE) is approved by the US Food and Drug Administration (FDA) for the treatment of chronic urticaria in children 12 years and older. Other agents that have been used for chronic urticaria but are not approved by the FDA include cyclosporine, tacrolimus, mycophenolate, dapsone, hydroxychloroquine, sulfasalazine, and azathioprine. Ultraviolet light therapy may also be beneficial in refractory cases. Bruton tyrosine kinase (BTK) inhibitors have demonstrated efficacy in treating chronic spontaneous urticaria and have a rapid onset of action with few side effects.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

189.1 Hereditary Angioedema

Aleena Banerji, David A. Khan, and Scott H. Sicherer

ETIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, AND DIAGNOSTIC APPROACH

HAE (types 1 and 2) is an inherited autosomal dominant genetic disease caused by low functional levels of the plasma protein **C1-INH**. Patients typically report unpredictable episodic attacks of angioedema or deep localized swelling, most often on a hand or foot, that begin during childhood or adolescence. Cutaneous nonpitting and nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about several hours and then resolves over 2-5 days when left untreated. However, the duration of attacks can be quite variable. In some patients, attacks are preceded by the development of a rash, **erythema marginatum**, that is erythematous, not raised, and not pruritic. A second major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery, including appendectomy. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks. Patients may have a *prodrome,* a tightness or tingling in the area that will swell, usually lasting several hours, followed by the development of angioedema.

Laryngeal edema, the most worrisome complication of HAE, can cause complete respiratory obstruction with a high risk of mortality when untreated. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Laryngeal edema can be triggered by local trauma but can also occur spontaneously without any identifiable trigger. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over hours. Soft tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. As symptoms are bradykinin mediated, patients with HAE typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients, trauma, infections or emotional stress clearly precipitates attacks. Drugs such as estrogen or angiotensin-converting enzyme (ACE) inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse. In some females, menstruation can be associated with an increase in attacks. The frequency of attacks varies greatly among affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1:1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with elevated serum C1-INH levels. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene variation, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks. Figure 189.3 shows the diagnostic approach.

Although named for its action on the first component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin-activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classical complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the proteins following in the complement cascade. Levels of C3 are normal. C1-INH also inhibits serine proteases associated with activation of the lectin activation pathway. The major factor responsible for the edema formation is bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high molecular weight kininogen by the plasma enzyme kallikrein.

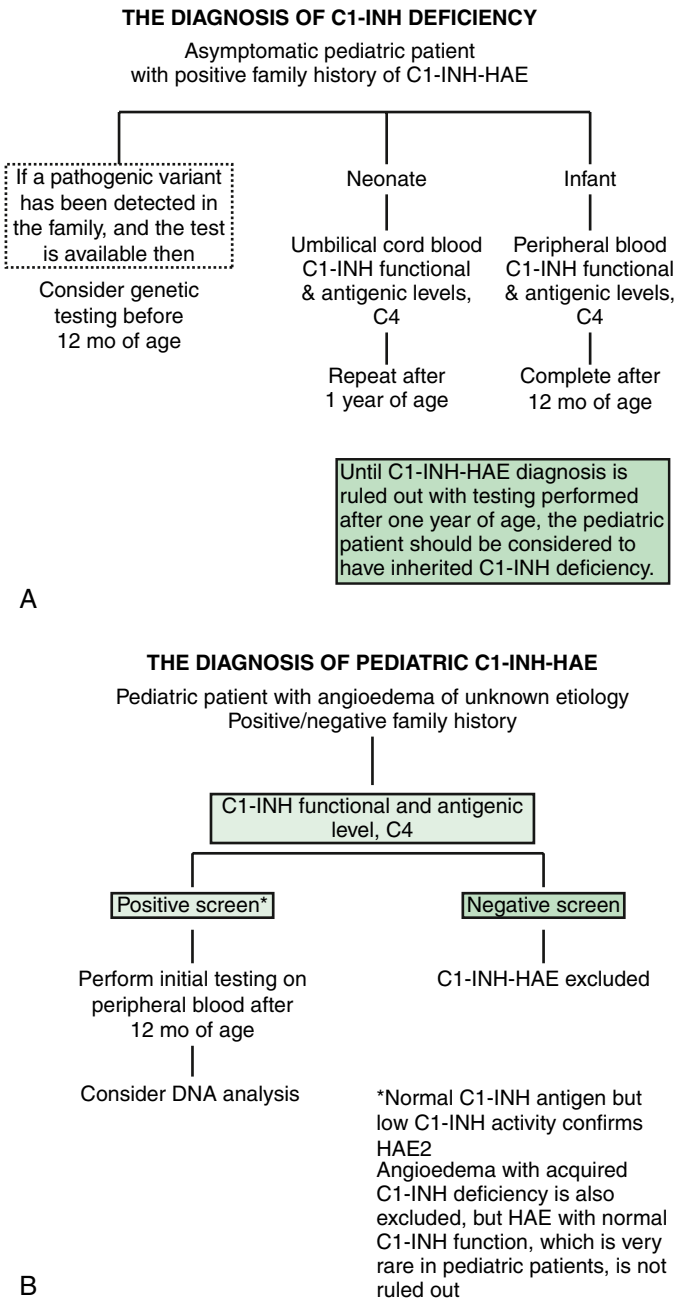

Fig. 189.3 A, Diagnosis of C1-INH deficiency in families with known C1-INH hereditary angioedema (HAE). B, Diagnosis of C1-INH HAE in pediatric patients with angioedema of unknown etiology. *(From Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Eur J Allergy Clin Immunol. 2017;72:300–313. Fig. 1, p. 304.)*

Two major genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The *C1-INH* gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the variant gene can have a clinical spectrum ranging from asymptomatic to severely affected. **Type 1** HAE is the most common form, accounting for approximately 80–85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele, or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH approximately 20–40% of normal. **Type 2** HAE accounts for approximately 15–20% of cases. Pathogenic variants of one of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein but low values in assays of C1-INH function.

A clinical syndrome resembling HAE termed **HAE with normal C1-INH** has been described that more commonly affects females, with a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. A small number of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause of this syndrome is still unknown. Additional pathogenic variants including ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-*O*-sulfotransferase 6) have been identified. Acquired C1-INH is associated with low levels of C4, C1-INH, and C1q (Table 189.9).

TREATMENT

Treatment of HAE is aimed at use of on-demand treatment when an attack starts along with long-term prophylaxis to prevent attacks. Short-term prophylaxis is used prior to a known trigger such as a surgical or dental procedure. The medical management of HAE has improved significantly in recent years with the availability of several new safe and effective therapies approved by the FDA in the United States. To provide optimal care and restore a normal quality of life, treatment of patients with HAE needs to be individualized based on patient-specific factors including patient preference and access to emergency care.

Options for **long-term prophylaxis** in patients with HAE include an intravenous formulation of plasma-derived C1-INH concentrate (Cinryze) given twice a week. Cinryze was FDA approved in 2008 for adolescents and adults. The half-life of this plasma protein is relatively short, about 40 hours, and the approved regimen is 1,000 units twice a week. In 2017, a **subcutaneous C1-INH** concentrate formulation given twice a week was approved for long-term prophylaxis in adolescents and adults. **Lanadelumab**, a monoclonal antibody that inhibits plasma kallikrein, given subcutaneously once every 2-4 weeks, along with **berotralstat,** an oral once a day pill, which inhibits plasma kallikrein, are the newest treatment options available for long-term prophylaxis in patients with HAE (see Table 189.10). Garadacimab, a fully human recombinant monoclonal antibody targeting activated factor XII, has shown efficacy as a prophylactic agent.

Androgens, like the gonadotropin inhibitor danazol, were previously used more frequently for long-term prophylaxis to prevent attacks. Weak androgens have many side effects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are

Table 189.9 Complement Evaluation of Patients with Recurrent Angioedema

	C4	C1-INH LEVEL	C1-INH FUNCTION	C1q
Idiopathic angioedema	Normal	Normal	Normal	Normal
Type 1 HAE	Low	Low	Low	Normal
Type 2 HAE	Low	Normal	Low	Normal
HAE-nlC1-INH	Normal	Normal	Normal	Normal
Acquired C1-INH deficiency	Low	Low	Low	Low
Urticarial vasculitis	Low or normal	Normal	Normal	Low or normal

C1-INH, C1 inhibitor; HAE-nlC1-INH, hereditary angioedema with normal C1-INH; nl, normal.
From Joshi SR, Khan DA. Urticaria and angioedema. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice*. 4th ed. Philadelphia: Elsevier; 2021: Table 39.3, p. 338.

Table 189.10 Long-Term Prophylactic Treatment Options for Patients with Hereditary Angioedema in the United States

DRUG	DATE OF FDA APPROVAL IN US	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	OTHER CONSIDERATIONS
Intravenous plasma-derived C1-INH	2008	Replacing missing protein	Intravenous	Dependent on plasma supply Extensive clinical experience
Subcutaneous plasma-derived C1-INH	2017	Replacing missing protein	Subcutaneous	Dependent on plasma supply Improved steady-state C1-INH levels
Lanadelumab	2018	Plasma kallikrein inhibitor	Subcutaneous	Unknown safety in pregnancy Infrequent dosing every 2-4 wk
Berotralstat	2020	Plasma kallikrein inhibitor	Oral	Unknown safety in pregnancy Once a day pill
Attenuated androgens	1976	Increases circulating levels of C1-INH protein	Oral	Significant adverse effects Contraindicated in pregnancy, lactation and children
Antifibrinolytics	1986	Reduces complement activation and C1-INH protein consumption	Oral	Significant adverse effects Inferior efficacy compared with other agents

Table 189.11 On-Demand Treatment Options for Patients with Hereditary Angioedema in the United States

DRUG	DATE OF FDA APPROVAL IN US	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	OTHER CONSIDERATIONS
Intravenous plasma-derived C1-INH	2009	Replacing missing protein	Intravenous	Dependent on plasma supply Extensive clinical experience
Recombinant C1-INH	2014	Replacing missing protein	Intravenous	No human virus risk Scalable supply
Ecallantide	2009	Plasma kallikrein inhibitor	Subcutaneous	No infectious risk 3–4% risk of anaphylaxis Requires administration by a healthcare provider
Icatibant	2011	B2 bradykinin receptor antagonist	Subcutaneous	No infectious risk Stable at room temperature Local injection reactions

not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid **(EACA)** is also effective in preventing attacks and has been used in children, but its use is attenuated by the development of severe fatigue and muscle weakness over time. A cyclized analog of EACA, **tranexamic acid**, has been used extensively in Europe; because of side effects and increased availability of other novel treatment options, it has been used less extensively in the United States. Tranexamic acid is believed to be more effective than EACA and has lower toxicity, but there have been few direct studies. Its mechanism of action is not clearly defined, and not all patients respond to this agent.

There are four **on-demand treatment** options FDA approved in the United States for patients with HAE. The first, approved in 2009, is a purified C1-inhibitor product **(Berinert)** that is administered as 20 U/kg intravenously. It was approved for the *treatment* of attacks. In 2009 the FDA approved a kallikrein inhibitor, **ecallantide**, given subcutaneously, for *acute treatment* in patients age 16 years and older. This 60–amino acid peptide causes anaphylaxis rarely and is approved only for administration by medical personnel. In 2010 a bradykinin type 2 receptor antagonist, **icatibant**, was approved for *acute treatment* in patients age 18 years and older. An intravenous **recombinant C1-INH** product has been FDA approved in 2014 for *treatment* of acute attacks (and in Europe) in adolescents and adults (see Table 189.11). All treatments are most effective when given early in an attack and begin to have a noticeable effect about 1-4 hours after treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 190

Anaphylaxis

Hugh A. Sampson, Julie Wang, and Scott H. Sicherer

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, may be underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent, biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (GI; nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 190.1 and Fig. 190.1).

Table 190.1 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

And at least one of the following:

   A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   B. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

OR

2. Two or more of the following that occur rapidly after exposure to a **likely allergen** (or other trigger) for that patient (minutes to several hours)
   A. Involvement of the skin/mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   B. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   C. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   D. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

OR

3. Reduced blood pressure after exposure to a **known allergen** or other trigger for that patient (minutes to hours).
   A. Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   B. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

From Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117(2):391-7.

ETIOLOGY

The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. **Food allergy** is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 190.2). **Peanut allergy** is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products.

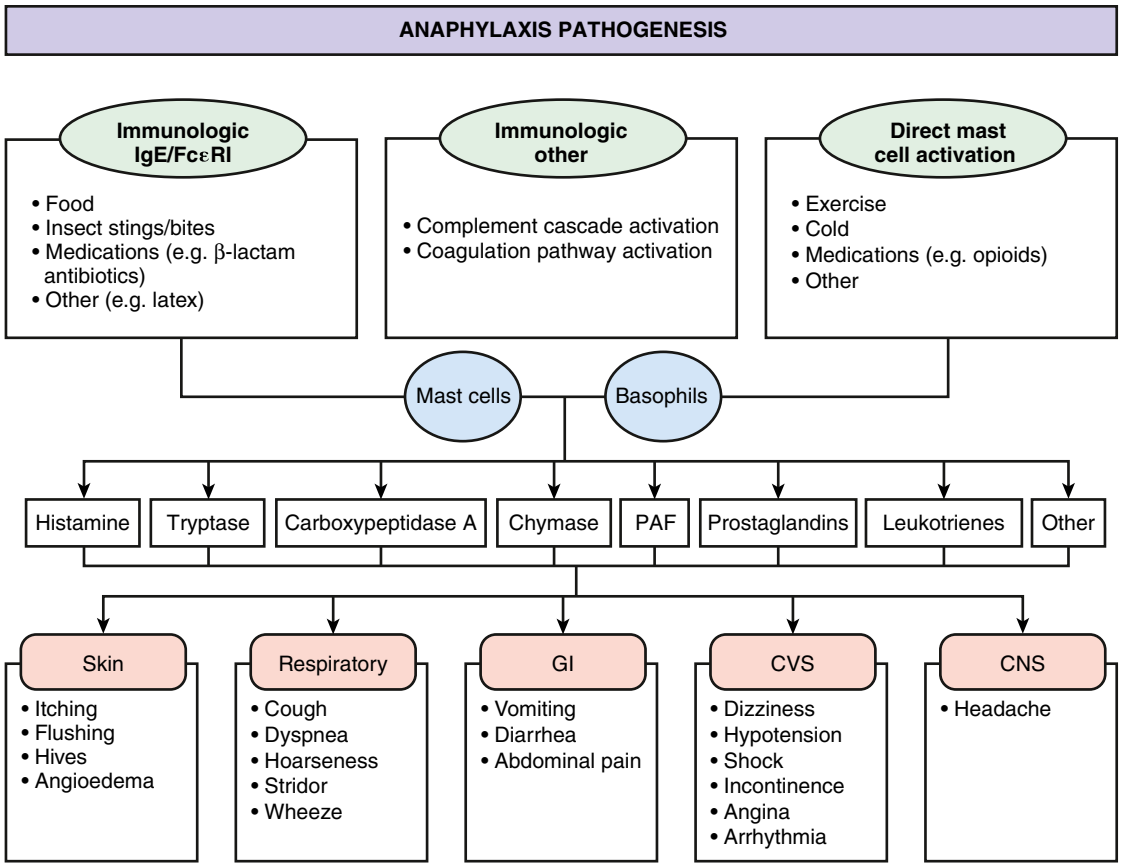

Fig. 190.1 Summary of the pathogenesis of anaphylaxis. See text for details about mechanisms, triggers, key cells, and mediators. Two or more target organ systems are typically involved in anaphylaxis. CNS, Central nervous system; CVS, cardiovascular system; GI, gastrointestinal; PAF, platelet-activating factor. *(From Leung DYM, Szefler SJ, Bonilla FA Akdis CA, Sampson HA, eds. Pediatric Allergy Principles and Practice. 3rd ed. Philadelphia: Elsevier; 2016: p. 525.)*

Table 190.2 Anaphylaxis Triggers in the Community*

ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)*	OTHER IMMUNE MECHANISMS (IgE INDEPENDENT)
Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])	IgG mediated (infliximab, high molecular weight dextrans)
Food additives (e.g., spices, colorants, vegetable gums, contaminants)	Immune aggregates (IVIG)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, fire ants)	Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Medications (e.g., β-lactam antibiotics, ibuprofen)	Complement activation
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])	Physical factors (e.g., exercise,† cold, heat, sunlight/ultraviolet radiation)
Natural rubber latex	Ethanol
Vaccines	Idiopathic*
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)	

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.
†Exercise with or without a co-trigger, such as a food or medication, cold air, or cold water.
IVIG, Intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.
Adapted from Leung DYM, Sampson HA, Geha RS, et al. *Pediatric Allergy Principles and Practice*. Philadelphia: Elsevier; 2010. p. 652.

Patients with **latex allergy** may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hours after eating red meat (see Chapter 189). Anaphylaxis may be **idiopathic** and in some of these patients related to mast cell activation syndrome (Fig. 190.2; see Chapter 700.1) or familial hypertryptasemia. **Exercise-induced anaphylaxis** has been associated with the combination of certain foods *and* exercise. Ingestion of the food without exercise does not produce allergic symptoms or anaphylaxis.

EPIDEMIOLOGY

The overall annual incidence of anaphylaxis in the United States is estimated at 42 cases per 100,000 person-years, totaling >150,000 cases per year. Food allergens are the most common trigger in children, with an incidence rate of approximately 20 per 100,000 person-years. An Australian parental survey found that 0.59% of children 3-17 years of age had experienced at least one anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 190.3). In addition, patients with systemic

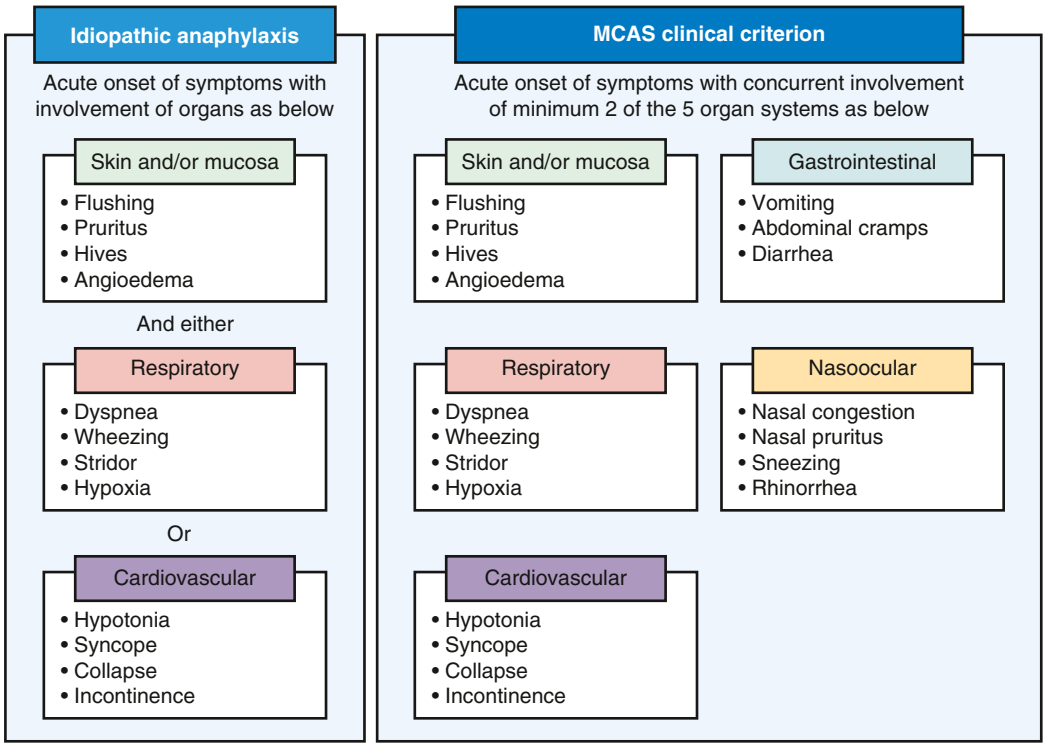

Fig. 190.2 The criteria of idiopathic anaphylaxis versus mast cell activation syndrome. Note that when there is no likely cause of the reactions, if the onset of illness is acute, a diagnosis of idiopathic anaphylaxis can only be made when either reduced blood pressure (or its symptoms such as syncope) and/or respiratory compromise are present accompanied by the involvement of the skin mucosal tissue symptoms. (*From Gulen T, Akin C. Idiopathic anaphylaxis: A perplexing diagnostic challenge for allergists. Curr Allergy Asthma Rep. 2021;21[2]:11. Fig. 1.*)

mastocytosis or monoclonal mast cell–activating syndrome are at increased risk for anaphylaxis, as are patients with an elevated baseline serum tryptase level.

PATHOGENESIS

Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific IgE molecules (see Fig. 190.1). Patients initially must be exposed to the responsible allergen to generate allergen-specific IgE antibodies. In many cases the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or exposure to inflamed skin (e.g., eczematous lesions). When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (opiates, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high molecular weight dextran, chimeric or humanized monoclonal antibodies) (see Table 190.2).

Idiopathic anaphylaxis (IA) is a diagnosis of exclusion when no inciting agent is identified, and other disorders have been excluded (see Chapter 700.1). Symptoms are similar to IgE-mediated causes of anaphylaxis; episodes often recur (see Fig. 190.2). IA may be secondary to mast cell activation syndrome with bone marrow expansion of mast cells exhibiting a D816V *KIT* pathologic variant or aberrant mast cell clonality on flow cytometry expressing CD117, CD2, or CD25 markers. Associated features of IA-associated mast cell activation syndrome include insect (venom) sting anaphylaxis with hypotension and persistent (once recovered) elevations of tryptase at times associated with autosomal dominant familial hypertryptasemia.

CLINICAL MANIFESTATIONS

The onset of symptoms may vary depending on the cause of the reaction. Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hours) compared with those from injected allergens (insect sting, medications) and tend to have more GI symptoms. Initial symptoms may include any of the following constellation of symptoms: pruritus about the mouth and face; flushing, urticaria and angioedema, and oral or cutaneous pruritus; a sensation of warmth, weakness, and apprehension (sense of doom); tightness in the throat, dry staccato cough and hoarseness, periocular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 10% of cases, and the *acute* onset of severe bronchospasm in a previously well person with asthma should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 189.1). Symptoms in infants may not be easy to identify. Infants may manifest nonspecific symptoms such as sudden crying, fussiness, flushing, dysphonia, drooling, vomiting, and becoming quiet or drowsy.

Table 190.3 Patient Risk Factors for Anaphylaxis

AGE-RELATED FACTORS
Infants: anaphylaxis can be difficult to recognize, especially if the first episode; patients cannot describe symptoms
Adolescents and young adults: increased risk-taking behaviors, such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently
Pregnancy: risk of iatrogenic anaphylaxis, as from β-lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
Older people: increased risk of death because of concomitant disease and drugs
CONCOMITANT DISEASES
Asthma and other chronic respiratory diseases
Cardiovascular diseases
Systemic mastocytosis or monoclonal mast cell–activating syndrome
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse
DRUGS
NSAIDs
β-Adrenergic blockers†
Mast cell destabilizers
ACE inhibitors†
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms.
Caffeine
FACTORS THAT MAY INCREASE RISK FOR ANAPHYLAXIS OR MAKE IT MORE DIFFICULT TO TREAT
Age
Asthma
Eczema
Drugs
Alcohol
Other cofactors such as exercise, infection, menses

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings.
†Those taking β-blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.
ACE, Angiotensin-converting enzyme; NSAID, nonsteroidal antiinflammatory drugs.
Adapted from Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341–384. Table I-9.

Table 190.4 Differential Diagnosis of Anaphylaxis

Anaphylaxis to exogenously administered agents
Physical factors
Exercise
Cold, heat, sunlight
Idiopathic
VASODEPRESSOR (VASOVAGAL) RESPONSES
Flushing syndromes
Carcinoid, pheochromocytoma, medullary carcinoma of the thyroid
Menopause
Side effects of chlorpropamide, alcohol, calcium channel blockers
Autonomic epilepsy
FOOD-ASSOCIATED SYNDROMES
Scombroidosis
Sulfites
Monosodium glutamate (MSG)
OTHER FORMS OF SHOCK
Cardiogenic
Septic
Vascular
EXCESS ENDOGENOUS PRODUCTION OF HISTAMINE SYNDROMES
Mast cell activation syndrome
Systemic mastocytosis
Cutaneous mastocytosis
Mast cell leukemia
Acute promyelocytic leukemia
NONORGANIC DISEASE
Panic attacks
Munchausen stridor
Vocal cord dysfunction
Undifferentiated somatoform anaphylaxis
MISCELLANEOUS
Acute urticaria with or without angioedema
Hereditary angioedema
Idiopathic angioedema
Neurologic (seizure, stroke)
Red man syndrome (vancomycin)
Capillary leak syndrome

From Dreskin SC, Stitt JM. Anaphylaxis. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy: Principles and Practice*. 9th ed. Philadelphia: Elsevier; 2020: Box 75.6, p. 1237.

LABORATORY FINDINGS

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. **Plasma tryptase** is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions. Plasma tryptase may also be elevated with chronic renal disease, eosinophilic GI disorders, parasitic infections, Gaucher disease, and mast cell activation syndrome or as a familial trait.

DIAGNOSIS

A National Institutes of Health (NIH)–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (see Table 190.1). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic), vasopressor reactions, including flushing syndromes (e.g., carcinoid syndrome), ingestion of monosodium glutamate, scombroidosis, and hereditary angioedema (Table 190.4). In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and vancomycin-induced flushing should be considered.

TREATMENT

Anaphylaxis is a medical emergency requiring aggressive management with intramuscular (IM, first line) or intravenous (IV) epinephrine. Oral (PO), IM, or IV H_1 and H_2 antihistamine antagonists, oxygen, IV fluids, inhaled β-agonists, and corticosteroids are adjunctive medications that may be used (Table 190.5 and Fig. 190.3). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. **Epinephrine** is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the IM route to the lateral thigh (1:1000 dilution, 0.01 mg/kg; maximum 0.5 mg). Children weighing 25 kg or more should receive 0.3 mg IM, with many recommending 0.5 mg IM for older adolescents. The IM dose can be repeated at intervals of 5-15 minutes if symptoms persist or worsen. If there is no response to multiple doses of epinephrine, IV epinephrine using the 1:10,000 dilution

Table 190.5 Management of a Patient with Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.3 mg IM in lateral thigh (0.5 mg autoinjectors are not available in the United States) Epinephrine autoinjector: 0.1 mg for 7.5-13 kg 0.15 mg for <25 kg 0.3 mg for 25 kg or more A second dose may be given in 5 min if symptoms worsen or do not improve	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 mL 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, paradoxical excitement
Transport to an emergency facility			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.1 mg for 7.5-13 kg 0.15 mg for <25 kg 0.3 mg for 25 kg or more 0.01 mL/kg/dose of 1:1,000 (vial) solution, up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/dose of 1:10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor
Supplemental oxygen and airway management			
Volume Expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in first hour	Rate titrated against BP response If tolerated, place patient supine with legs raised
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against BP response If tolerated, place patient supine with legs raised
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 mL 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg, up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg, up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alternative: Cimetidine	Antihistamine (competitive of H_2 receptor)	4 mg/kg, up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV): 1-2 mg/kg, up to 125 mg IV Depo-Medrol (IM): 1 mg/kg, up to 80 mg IM	Hypertension, edema, nervousness, agitation
Prednisone	Antiinflammatory	1 mg/kg up, to 75 mg PO	Hypertension, edema, nervousness, agitation
Nebulized albuterol	β-Agonist	0.83 mg/mL (3 mL) via mask with O_2	Palpitations, nervousness, CNS stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
Preventive Treatment Prescription for epinephrine autoinjector and antihistamine Provide written plan outlining patient emergency management (may download form from http://www.aap.org or http://www.foodallergy.org; English and Spanish versions available) Follow-up evaluation to determine/confirm etiology Immunotherapy for insect sting allergy *Patient Education* Instruction on avoidance of causative agent Information on recognizing early signs of anaphylaxis Stress early treatment of allergic symptoms to avoid systemic anaphylaxis Encourage wearing medical identification jewelry			

BP, Blood pressure; CNS, central nervous system; IM, Intramuscularly; IV, intravenously; PO, orally; qd, every day.

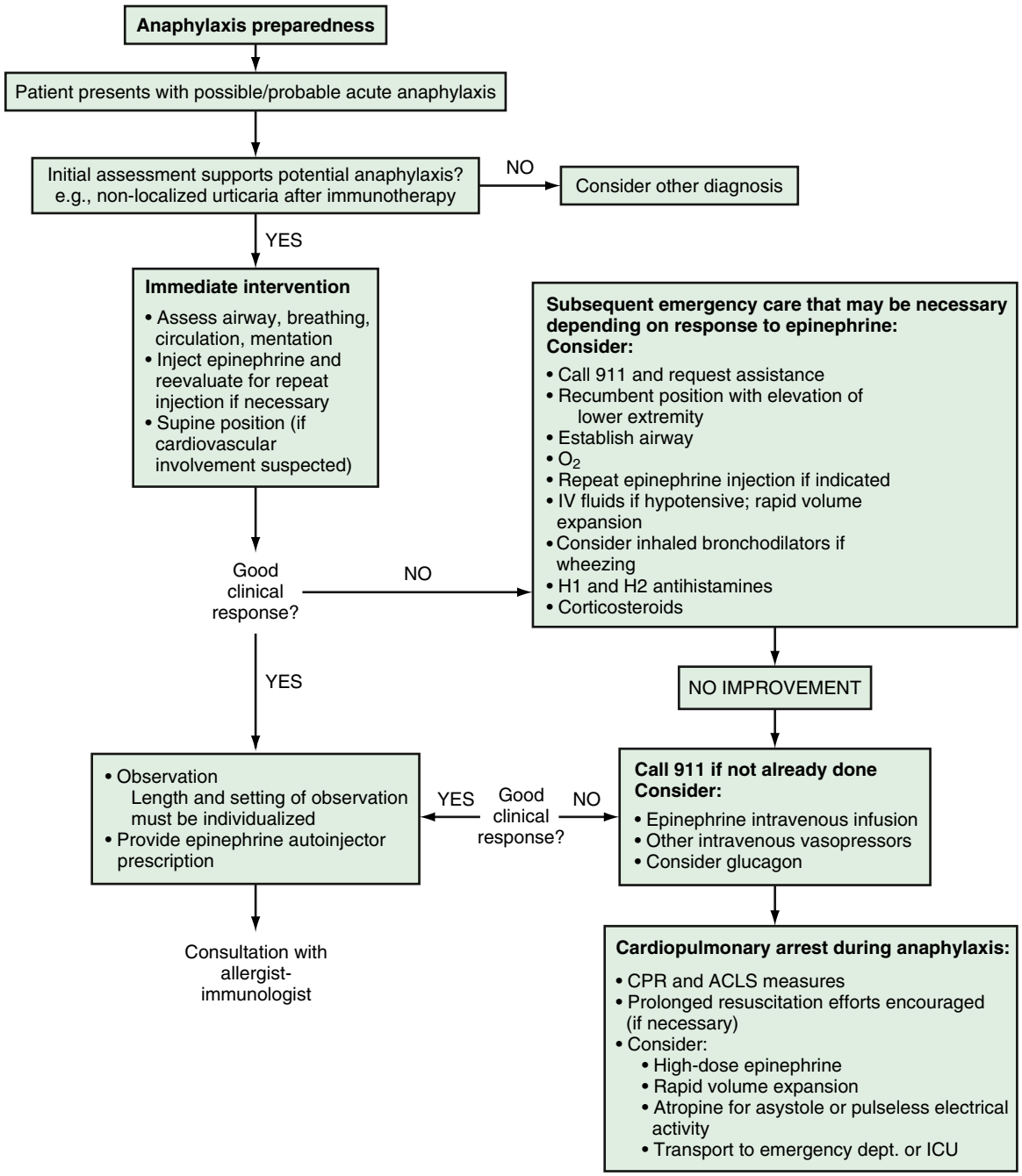

Fig. 190.3 Algorithm for treatment of anaphylactic event in outpatient setting. ACLS, Advance cardiac life support; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IV, intravenous. (*From Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126:477–480 e471-442.*)

may be needed. If IV access is not readily available, epinephrine can be administered via the endotracheal or intraosseous routes.

For refractory hypotension, other vasopressors may be needed. Anaphylaxis refractory to repeated doses of epinephrine in a patient receiving β-adrenergic blockers has anecdotally been treated with glucagon. The patient should be placed in a supine position when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis.

Patients may experience **biphasic anaphylaxis**, which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but more severe initial presentation and the need for more than one dose of epinephrine to treat initial symptoms are risk factors for biphasic anaphylaxis. Treatment with antihistamines or corticosteroids do not provide clear benefit for prevention of biphasic reactions. Extended observation after resolution of initial anaphylaxis symptoms should be considered for patients with risk factors for biphasic anaphylaxis. At discharge,

Table 190.6 Considerations with Epinephrine Injection for Anaphylaxis

WHY HEALTHCARE PROFESSIONALS FAIL TO INJECT EPINEPHRINE PROMPTLY

- Lack of recognition of anaphylaxis symptoms; failure to diagnose anaphylaxis
- Episode appears mild, or there is a history of previous mild episode(s)*
- Inappropriate concern about transient mild pharmacologic effects of epinephrine (e.g., tremor)
- Lack of awareness that serious adverse effects are almost always attributable to epinephrine overdose or IV administration, especially IV bolus, rapid IV infusion, or IV infusion of a 1:1,000 epinephrine solution instead of an appropriately diluted solution (1:10,000 concentration)

WHY PATIENTS AND CAREGIVERS FAIL TO INJECT EPINEPHRINE PROMPTLY

- Lack of recognition of anaphylaxis symptoms; failure to diagnose anaphylaxis
- Episode appears mild, or there is a history of previous mild episode(s)*
- H_1 antihistamine or asthma puffer is used initially instead, relieving early warning signs such as itch or cough, respectively
- Prescription for epinephrine autoinjectors (EAIs) is not provided by physician
- Prescription for EAIs is provided but not filled at pharmacy (e.g., not affordable)
- Patients do not carry EAIs consistently (due to size and bulk, or "don't think they'll need it")
- Patients and caregivers are afraid to use EAIs (concern about making an error when giving the injection or about a bad outcome)
- Patients and caregivers are concerned about injury from EAIs
- Competence in using EAIs is associated with regular allergy clinic visits; it decreases as time elapses from first EAI instruction; regular retraining is needed
- Difficulty in understanding how to use EAIs (15% of mothers with no EAI experience could not fire an EAI immediately after a one-on-one demonstration)
- Errors in EAI use can occur despite education, possibly related to the design of some EAIs

WHY PATIENTS OCCASIONALLY FAIL TO RESPOND TO EPINEPHRINE INJECTION

- Delayed recognition of anaphylaxis symptoms; delayed diagnosis
- Error in diagnosis: problem being treated (e.g., foreign body inhalation) is not anaphylaxis
- Rapid progression of anaphylaxis†

Epinephrine†:

- Injected too late; dose too low on mg/kg basis; dose too low because epinephrine solution has degraded (e.g., past the expiration date, stored in a hot place)
- Injection route or site not optimal; dose took too long to be absorbed
- Patient suddenly sits up or walks or runs, leading to the empty ventricle syndrome
- Concurrent use of certain medications (e.g., β-adrenergic blockers)

*Subsequent anaphylaxis episodes can be more severe, less severe, or similar in severity.
†Median times to respiratory or cardiac arrest are 5 min in iatrogenic anaphylaxis, 15 min in stinging-insect venom anaphylaxis, and 30 min in food anaphylaxis; however, regardless of the trigger, respiratory or cardiac arrest can occur within 1 min in anaphylaxis.
Adapted from Leung DYM, Szefler SJ, Bonilla FA Akdis CA, Sampson HA, eds. *Pediatric Allergy Principles and Practice*. Philadelphia: Elsevier; 2016: p. 531.

referrals should be made to appropriate specialists for further evaluation and follow-up.

PREVENTION

For patients experiencing anaphylactic reactions, the triggering agent should be avoided, and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma and a peanut, tree nut, fish, or shellfish allergy or a previous systemic reaction should be given an epinephrine autoinjector. The expert panel also indicates that epinephrine autoinjectors should be considered for any patient with IgE-mediated food allergy. In addition, liquid cetirizine (or alternatively, diphenhydramine) and a written emergency plan should also be provided in case of accidental ingestion or allergic reaction. A form can be downloaded from the American Academy of Pediatrics (www.aap.org) or Food Allergy Research & Education (www.foodallergy.org).

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-4 hours of ingesting the triggering food; children with exercise-induced anaphylaxis should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth, facial pruritus), and stop exercising and seek help immediately if symptoms develop. Foods associated with exercise-induced anaphylaxis include wheat, vegeas, nuts, fruits, and shellfish.

Children experiencing a systemic anaphylactic reaction, including respiratory symptoms, to an insect sting should be evaluated and treated with immunotherapy, which is >90% protective. Reactions to medications can be reduced and minimized by using oral medications instead of injected forms and avoiding cross-reacting medications. Low-osmolarity radiocontrast dyes and pretreatment can be used in patients with suspected reactions to previous radiocontrast dye. Nonlatex gloves and materials should be used in children undergoing multiple operations.

Any child at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications (Table 190.6), and a written emergency plan in case of accidental exposure. They should be encouraged to wear medical identification jewelry.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 191

Serum Sickness

Anna H. Nowak-Wegrzyn and Scott H. Sicherer

Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 191.1).

ETIOLOGY

Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse, sheep, or rabbit are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (antithymocyte globulin [ATG]). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. However, rabbit-generated ATGs, which target human T cells, continue to be widely used as immunosuppressive agents during treatment of kidney allograft recipients; serum sickness is associated with a late graft loss in kidney transplant recipients. A **serum sickness–like reaction** may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor, trimethoprim-sulfamethoxazole, anticonvulsants, prolonged high-dose intravenous penicillin G), infections (streptococcal infections, hepatitis B), or rabies vaccine. In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

Table 191.1 Proteins and Medications That Cause Serum Sickness*

PROTEINS FROM OTHER SPECIES
Antibotulinum globulin
Antithymocyte globulin
Antitetanus toxoid
Antivenin (Crotalidae) polyvalent (horse serum based)
Crotalidae polyvalent immune Fab (ovine serum based)
Antirabies globulin
Infliximab
Rituximab
Etanercept
Omalizumab
Adalimumab
Natalizumab
Anti-HIV antibodies ([PE]HRG214)
Hymenoptera stings
Streptokinase
H1N1 influenza vaccine
Rabies vaccine
DRUGS
Antibiotics
Cefaclor
Penicillins
Trimethoprim sulfamethoxazole
Minocycline
Meropenem
Neurologic
Bupropion
Carbamazepine
Phenytoin
Sulfonamides
Barbiturates

*Based on review of the most current literature. Other medications that are not listed might also cause serum sickness.

Adapted from Aceves SS. Serum sickness. In: Burg FD, Ingelfinger JR, Polin RA, Gershon AA, eds. *Current Pediatric Therapy*. 18th ed. Philadelphia: Elsevier; 2006: p. 1138.

PATHOGENESIS

Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen-antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen-antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, because of the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to IgE or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

CLINICAL MANIFESTATIONS

The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 weeks afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous. Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions (Fig. 191.1). In a prospective study of serum sickness induced by administration of equine ATG, an initial rash was noted in most patients. It began as a thin, serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients the band of erythema was replaced by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 weeks of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 months. Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. **Serum sickness–like reactions** from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 weeks after drug exposure. The urticarial skin eruption becomes increasingly



Fig. 191.1 Serum sickness–like reaction (SSLR). Note the swollen hand and large urticarial wheals in this girl with SSLR and arthralgias. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology. 5th ed. Philadelphia: Elsevier; 2016: p. 476.)*

erythematous as the reaction progresses and can evolve into dusky centers with round plaques. Serum sickness and serum sickness–like reactions are more likely to occur with higher doses and intermittent exposures of culprit antigens.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serum sickness and serum sickness–like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic-onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis, autoinflammatory syndromes, acute annular urticaria (urticaria multiforme), Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and erythema multiforme (see Chapters 193 and 686.2).

DIAGNOSIS

In most patients the diagnosis of serum sickness is made clinically based on the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit. Patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

- Complete blood count and differential: Thrombocytopenia is often present.
- Erythrocyte sedimentation rate (ESR) and C-reactive protein: ESR is usually elevated.
- Urinalysis: Mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
- Serum chemistries: Including blood urea nitrogen, creatinine, and liver function tests.
- Complement studies, including CH_{50}, C3, and C4: Serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
- Testing for specific infectious diseases: If indicated by the history or physical examination.
- Appropriate viral or bacterial cultures: If an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

TREATMENT

There are no evidence-based guidelines or controlled trials on which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory drugs and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day; maximum 60 mg/day) for 1-2 weeks is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 weeks. Symptoms lasting longer suggest another diagnosis.

PREVENTION

The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk/benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 192

Food Allergy and Adverse Reactions to Foods

Anna H. Nowak-Wegrzyn, Hugh A. Sampson, Amanda L. Cox, and Scott H. Sicherer

Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into **food intolerances** and **food allergies.** Food intolerances are nonimmunologic physiologic responses and can include metabolic, toxic, pharmacologic, or other mechanisms. **Food allergies** are adverse *immunologic* responses and can be IgE mediated, non–IgE mediated, or mixed (Tables 192.1 and 192.2). Food allergies appear to have increased over the past 3 decades, primarily in westernized/industrialized countries. Worldwide, estimates of food allergy prevalence range from 1–11% with regional variations. The vast majority of food allergies are due to peanut, tree nuts, seeds, milk, egg, soy, wheat, fish, and

Table 192.1 Adverse Food Reactions

FOOD INTOLERANCE (NON–IMMUNE SYSTEM MEDIATED, NONTOXIC, NONINFECTIOUS)
Host Factors
Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia, alcohol dehydrogenase deficiency
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)
Food Factors (Toxic or Infectious or Pharmacologic)
Infectious organisms—*Escherichia coli*, *Staphylococcus aureus*, *Clostridium perfringens*, *Shigella*, botulism, *Salmonella*, *Yersinia*, *Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics
FOOD ALLERGY
IgE Mediated
Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise-induced anaphylaxis
Mixed IgE Mediated and Non–IgE Mediated
Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma
Non–IgE Mediated
Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, Immunoglobulin E.

shellfish, with regional variations in prevalence. It has been estimated that 8–11% of children have food allergy, with 2.4% having multiple food allergies. Up to 6% of children experience food allergic reactions in the first 3 years of life, including approximately 2.5% with cow's milk allergy, 2% with egg allergy, and 2–3% with peanut allergy. Most children "outgrow" milk and egg allergies, with approximately 50% doing so by school-age. In contrast, 80–90% of children with peanut, tree nut, or seafood allergy retain their allergy for life (Table 192.3).

Table 192.2 Differential Diagnosis of Adverse Food Reactions

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)
Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
Enzyme deficiencies (primary or secondary)
Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
Galactosemia
Malignancy with obstruction
Other: pancreatic insufficiency (cystic fibrosis), peptic disease
CONTAMINANTS AND ADDITIVES
Flavorings and preservatives—rarely cause symptoms
Sodium metabisulfite, monosodium glutamate, nitrites
Dyes and colorings—very rarely cause symptoms (urticaria, eczema)
Tartrazine
Toxins
Bacterial, fungal (aflatoxin), fish related (scombroid, ciguatera)
Infectious organisms
Bacteria (*Salmonella, Escherichia coli, Shigella*)
Virus (rotavirus, enterovirus)
Parasites (*Giardia,* Akis simplex [in fish])
Accidental contaminants
Heavy metals, pesticides
Pharmacologic agents
Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)
PSYCHOLOGIC REACTIONS
Food phobias

GENETIC AND ENVIRONMENTAL RISK FACTORS

Allergic sensitization and food allergy development is influenced by genetics, environment, and genome-environment interactions (possible epigenetic effects). Family and twin studies show that family history confers a 2- to 10-fold increased risk, depending on the study setting, population, specific food, and diagnostic test. Candidate gene studies suggest that genetic variants in the HLA-DQ locus (HLA-DQB1*02 and DQB1*06:03P), filaggrin, interleukin (IL)-10, *STAT6*, and *FOXP3* genes are associated with food allergy, although the results are inconsistent across different populations. In a genome-wide association study, differential methylation at the HLA-DR and -DQ regions was associated with food allergy. Epigenetic studies implicate DNA methylation effects on IL-4, -5 and -10, and interferon (IFN)-γ genes and in the mitogen-activated protein kinase (MAPK) pathway.

Many environmental factors have been observed to influence the development of food allergy. Skin exposure to foods in the setting of infantile eczema, characterized by impaired skin barrier and inflammation, can lead to sensitization and allergy. Decreased microbial exposure ("hygiene hypothesis"), decreased microbiome diversity, and the specific makeup of microbial communities in the gastrointestinal (GI) tract, airway, and skin, influence allergic conditions, including food allergy (see Chapter 182). Additional environmental factors that may be associated with increased risk of food allergy include reduced diversity of the diet, delayed introduction of allergenic foods, vitamin D deficiency, and other factors.

PATHOGENESIS

Food intolerances are the result of a variety of nonimmunologic mechanisms, whereas food allergy is predominantly caused by IgE-mediated and cell-mediated immune mechanisms. In food allergy, normal physiologic oral tolerance of food, which is induced largely by regulatory T cells (Tregs) and the microbiome of the gut mucosa, breaks down. Susceptible individuals exposed to certain allergens generate food-specific IgE antibodies that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells, resulting in allergic sensitization. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells, basophils, and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. During acute IgE-mediated reactions, mast cell and basophil

Table 192.3 Natural History of Food Allergy

FOOD	USUAL AGE AT ONSET OF ALLERGY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	5 yr (76% of cases resolve)*
Peanut	1-2 yr	Persistent (20% of cases resolve)
Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Persistent†
Shellfish (crustacean)	Adulthood (in 60% of patients with this allergy)	Persistent
Wheat*	6-24 mo	5 yr (80% of cases resolve)
Soybean*	6-24 mo	2 yr (67% of cases resolve)
Kiwi	Any age	Unknown
Apple, carrot, and peach‡	Late childhood and adulthood	Unknown

*Studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A/L.
†Fish allergy that is acquired in childhood can resolve.
‡Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is typically caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.
Adapted from Lack G. Food allergy. *N Engl J Med.* 2008;359:1252–1260.

degranulation elicits symptoms that can affect the skin (urticaria, angioedema, flushing, pruritus), GI tract (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), respiratory tract (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and cardiovascular system (dysrhythmias, hypotension, loss of consciousness). In non-IgE food allergies, lymphocytes, primarily food allergen–specific T cells, secrete excessive amounts of various cytokines that lead to a "delayed," more chronic inflammatory process affecting the skin (pruritus, erythematous rash), GI tract (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), and respiratory tract (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders, such as atopic dermatitis, asthma, eosinophilic esophagitis (EoE), and eosinophilic gastroenteritis.

Children who develop IgE-mediated food allergies may be sensitized by food allergens penetrating the inflamed skin barrier, e.g., eczema, or GI barrier (referred to as **class 1 food allergens**), or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract (referred to as **class 2 food allergens**). Any food may serve as a class 1 food allergen, but *egg, milk, peanuts, tree nuts, seeds, fish, soy,* and *wheat* account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Class 2 food allergens are typically vegetable, fruit, or nut proteins that are partially homologous to pollen proteins. With the development of seasonal allergic rhinitis from birch/oak, grass, ragweed, or mugwort weed pollens, subsequent ingestion of certain nuts, uncooked fruits, or vegetables provokes the **pollen-food allergy syndrome (also called oral allergy syndrome)**. *Intermittent ingestion* of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas *prolonged exposure* may lead to poor control of chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1 allergens.

The **galactose-α-1,3-galactose (alpha-gal) syndrome** is an IgE-mediated allergy to a carbohydrate allergen, and manifests as delayed allergic reactions 2-6 hours after ingestion of mammalian meats (pork, beef, lamb, venison) and rarely gelatin or milk. Sensitization occurs after multiple tick bites, in particular by the lone star tick *(Amblyomma americanum)*. This unique form of food allergy is seen more often in teenagers and adults.

CLINICAL MANIFESTATIONS

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 192.4) and immune mechanism (see Table 192.1).

Gastrointestinal Manifestations

GI food allergies are often the first form of allergy to affect infants and young children and typically manifest as irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as skin-prick tests and in vitro tests for food-specific IgE antibodies of little diagnostic value. The non–IgE-mediated GI food-allergic disorders food protein–induced enterocolitis syndrome (FPIES), food protein–induced allergic proctocolitis (FPIAP), and eosinophilic GI disorders are discussed in Chapter 192.1.

Pollen-food allergy syndrome (oral allergy syndrome) is an IgE-mediated hypersensitivity to certain uncooked or unprocessed plant-based foods that occurs in many older children who have pollen-induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus; tingling and angioedema of the lips, tongue, palate, and throat; and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short-lived and are caused by local mast cell activation following contact with fresh raw fruit and vegetable proteins that cross react with birch tree pollen (including but not limited to apple, carrot, potato, celery, hazelnuts, peanuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi),

Table 192.4 Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough Dyspnea Wheezing
Gastrointestinal (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
Gastrointestinal (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Other	Uterine contractions Sense of "impending doom"	

From Boyce JA, Assa'ad A, Burks AW, et al. Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010;126(6):S1–S58. Table IV, p. S19.

mugwort weed pollen (celery, fennel, mustard, peach), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

Acute GI allergy generally manifests as acute abdominal pain, vomiting, or diarrhea that accompanies IgE-mediated allergic symptoms in other target organs.

Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronic relapsing course, and association with asthma and allergic rhinitis (see Chapter 186). Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have IgE-mediated food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a pathogenic role in the disorder. Atopic dermatitis is a risk factor for the development of food allergy rather than a result of food allergy.

Acute urticaria and angioedema are among the most common symptoms of food allergic reactions (see Chapter 189). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly implicated in children include egg, milk, peanuts, and tree nuts, although reactions to various seeds (sesame, sunflower, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are very rarely caused by food allergies. **Contact urticaria** may occur in the perioral region of infants and young children, especially in those with eczema, when otherwise tolerated food causes small, self-resolving hives on direct skin contact while eating. In the absence of any other symptoms, food exclusion is not generally needed and the rash could be avoided by wiping the face during feeding or using a barrier ointment (such as petroleum jelly) in the perioral area before feeding.

Perioral dermatitis is a contact dermatitis often caused by substances in toothpaste, gums, lipstick, or medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoic acid in the food. It may also occur in nursing infants. In both situations the effect is benign. Flushing may also be caused by **auriculotemporal nerve (Frey) syndrome** (familial, forceps delivery), which resolves spontaneously.

Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe nasal congestion in infants to be caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periocular pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only 10% of asthmatic patients have food-induced respiratory symptoms.

Anaphylaxis

Anaphylaxis (see Chapter 190) is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the most common cause of anaphylaxis seen in U.S. hospital emergency departments. Fatal food-induced anaphylaxis is rare, with death affecting 0.03-0.3 per million per year. In addition to the rapid onset of cutaneous, respiratory, and GI symptoms, patients with anaphylaxis may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-dependent exercise-induced anaphylaxis** is a special form of acute IgE-mediated food allergy in which moderate intensity exercise performed within a few hours of ingestion of a particular food, most commonly wheat or shellfish, results in anaphylaxis but when ingested without exercise, there is no allergic reaction.

DIAGNOSIS

A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse food reaction (see Table 192.2), whether it is an intolerance or food allergic reaction, and, if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response (Fig. 192.1). An understanding of the basic pathophysiology and clinical presentations of different adverse food reactions is essential and if allergy is suspected, referral to an allergist-immunologist is recommended. The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, because most reactions occur within minutes to 2 hours of ingestion, (3) the types of symptoms elicited by the ingestion, which may suggest the pathophysiology of the adverse reaction, (4) whether ingesting the suspected food produced similar symptoms on other occasions because reproducibility is expected, (5) whether other inciting factors, such as exercise, are necessary, and (6) time interval since last reaction to the food because evaluation for potential resolution of the allergy may be warranted.

Skin-prick tests and in vitro laboratory tests are useful for demonstrating *IgE sensitization,* defined as presence of food-specific IgE antibodies. **Sensitization alone is not diagnostic of a food allergy.** In general, increasingly higher serum food-specific IgE levels or increasingly large skin-test wheal size (especially >8 mm diameter) indicate a higher chance of clinical allergy. A negative serum food-specific IgE test or skin test result virtually excludes an IgE-mediated form of food allergy. In limited studies, serum food-specific IgE levels ≥15 kU_A/L for milk (≥5 kU_A/L for children ≤1 year), ≥7 kU_A/L for egg (≥2 kU_A/L for children <2 years), and ≥14 kU_A/L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected allergy. Evaluation of IgE-binding to specific digestion-resistant allergens that trigger reactions or labile proteins unlikely to cause significant reactions in a food, termed molecular or **component-resolved diagnostic (CRD) testing**, can provide additional clinically relevant information. Identification of sensitization to digestion-resistant proteins (components) in the foods correlates with a greater chance of systemic allergic reactions. Examples of tests for digestion-resistant proteins include Ara h 1, 2, 3, and 6 for peanut; Jug r 1 and Jug r 3 for walnut; Ana o 3 for cashew; Ber e 1 for Brazil nut; and Cor a 9 and Cor a 14 for hazelnut. Ara h 8 in peanut is a labile, birch pollen–related protein generally not associated with significant allergic reactions, and isolated sensitization to this component is typically associated with no or only mild oral reactions.

Importantly, most children with positive serum food-specific IgE or skin test responses do not react when the food is ingested. It is therefore crucial to avoid indiscriminate testing (i.e., sending panels of food tests). In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, and/or a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Table 192.5). When the earlier diagnostic modalities are not definitive,

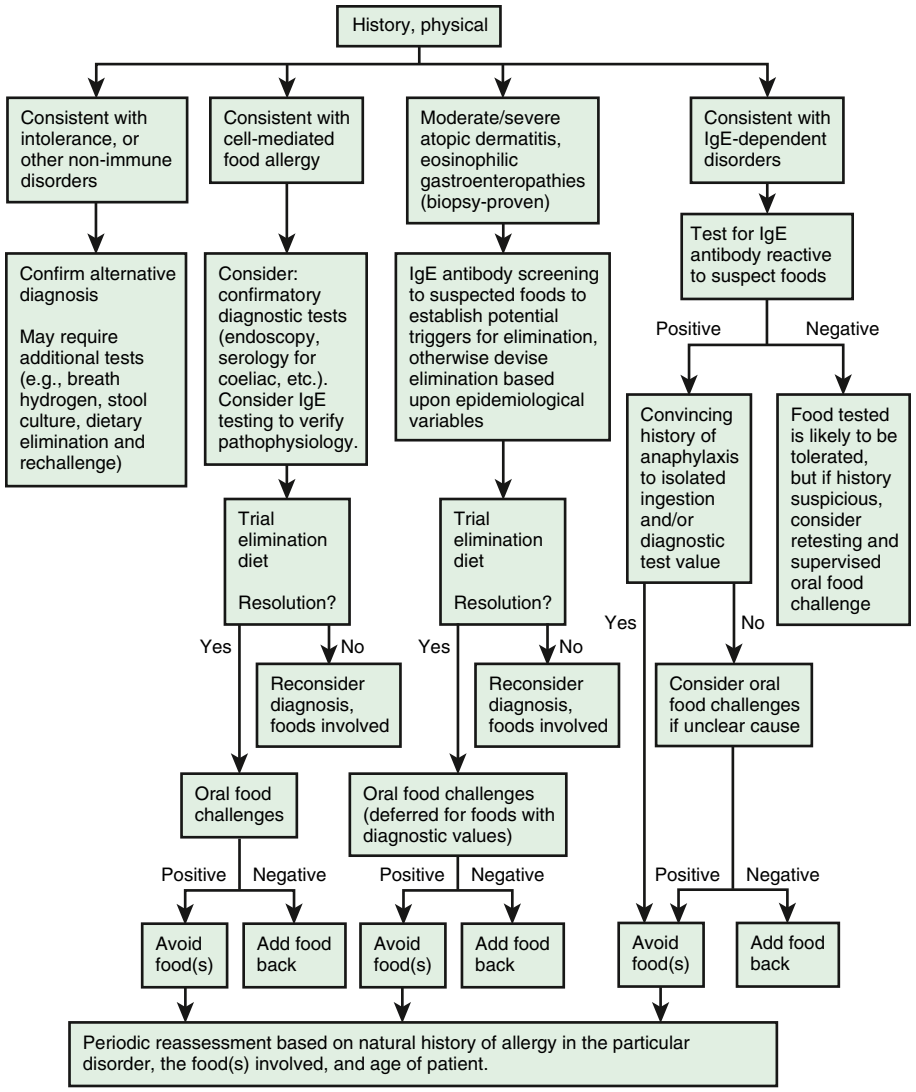

Fig. 192.1 Algorithm for diagnosis of food allergy. *(From Sicherer SH. Food allergy. Lancet. 2002;360:701–710.)*

Table 192.5 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)	FEATURE(S)
Legumes	5–50	If allergic to peanut, 5-20% likelihood of allergy to other legumes (lupine, green bean, green pea, soy) If allergic to chickpea (garbanzo bean), >50% likelihood of allergy to lentil and/or pea.
Tree nuts (e.g., almond, cashew, hazelnut, walnut, Brazil)	15–33	Reactions are often severe
Fish	50	Reactions can be severe
Shellfish (crustaceans)	75 (other crustaceans) 50 (mollusks)	Reactions can be severe
Grains	20	Wheat shows cross-reactivity with barley and rye
Mammalian milks	90	Cow's milk is highly cross reactive to goat's or sheep's milk (92%) but not with mare's milk (4%)
Rosaceae (pitted fruits)	55	Risk of reactions to >3 related foods is very low (<10%); symptoms are usually mild (pollen food allergy syndrome)

Modified from Sicherer SH. Food allergy. *Lancet.* 2002;360:701–710.

which is a common scenario, oral food challenges (OFCs), observed incremental feedings of a food performed under physician supervision, are useful in ruling out or confirming the presence or resolution of a food allergy. *Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges.*

There are no laboratory studies to help identify foods that are already in the diet but may be responsible for non–IgE and cell-mediated food reactions. Consequently, elimination diets followed by OFCs are the only way to establish the diagnosis. This approach may be recommended for atopic dermatitis, eosinophilic GI diseases, and some forms of contact dermatitis. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 weeks for some cell-mediated disorders, such as EoE (see Chapter 192.1). Some children with cell-mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

TREATMENT

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the most established and validated management strategies for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organizations Food Allergy Research and Education (FARE; www.foodallergy.org) and the Asthma & Allergy Foundation of America (Kids with Food Allergies Division; www.kidswithfoodallergies.org/recipes-diet.aspx) provide excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Egg allergy is not a contraindication for vaccination with measles, mumps, rubella, or influenza vaccines, but remains a concern for the yellow fever vaccine where referral to an allergist is recommended.

Children at risk of food-induced anaphylaxis should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 190). Because many food allergies resolve, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are evaluating the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies. Immunotherapy is not typically curative but aims to provide temporary "desensitization," or an increase in the threshold of a food that can be consumed without triggering an allergic reaction. Success depends on continuous treatment exposure. An FDA-approved peanut oral immunotherapy (OIT) agent is commercially available for use in children. Combining OIT with anti-IgE treatment (omalizumab) or other biologic agents is under study and may improve safety or efficacy compared to OIT alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg–allergic children. Regular ingestion of baked products with milk and egg may accelerate resolution of milk and egg allergy.

PREVENTION

It was once thought that avoidance of allergenic foods and delayed introduction to the diet would prevent allergy, but the opposite is probably true; delayed introduction of these foods may increase the risk of allergy, especially in children with atopic dermatitis. A trial of early introduction of dietary peanut randomized 640 infants age 4-11 months with severe eczema, egg allergy, or both to consume or avoid peanut until the age 60 months. The early introduction of peanut dramatically decreased the development of peanut allergy among children at high risk for this allergy. A theory behind this approach is that early oral introduction of peanut induces oral tolerance that precedes the potential sensitization to peanut that can occur with environmental exposure to peanut via the inflamed, disrupted skin barrier seen in infants with eczema. Infants with severe eczema or egg allergy in the first 4-6 months of life might benefit from evaluation by an allergist or physician trained in management of allergic diseases to diagnose any food allergy and assist in promptly implementing appropriate early peanut introduction. For this high-risk group, the clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response or serum peanut-specific IgE >0.35 kU_A/L to determine whether they are clinically reactive before initiating at-home introduction of infant-safe forms of peanut. Additional details for the early introduction of peanut are available from the National Institute of Allergy and Infectious Diseases (NIAID).* Analyses of several early introduction studies have shown that early egg introduction may be associated with reduced egg allergy, while review of data for other allergenic foods is not conclusive. There is however no evidence that delaying the introduction of typically allergenic foods prevents food allergy or other allergic diseases.

There is no compelling evidence to support the practice of restricting the maternal diet during pregnancy or while breastfeeding, or for delaying introduction of various allergenic foods to infants from atopic families. Exclusive breastfeeding for the first 4-6 months of life is strongly encouraged but has not been shown to reduce the development of food allergies. Potentially allergenic foods (eggs, milk, wheat, soy, peanut/tree nut products, fish) should be introduced and maintained in the diet in infant-appropriate forms after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Recent meta-analyses have not supported the use of hydrolyzed infant formulas in cases where breastfeeding cannot be continued for 4-6 months or after weaning to prevent eczema or food allergies in high-risk families. Modulation of the microbiome with probiotics has been an area of interest, where it may affect oral tolerance induction; however, specific interventions have not been proven effective. Probiotic supplements in the third trimester and to the newborn infant may reduce the incidence and severity of eczema, but have not demonstrated effects on food allergy prevention. Other potential influences on the infant/child microbiome are currently being studied, including mode of delivery (vaginal vs C-section), diet diversity, vitamin D supplementation, and household pet exposure. With the recognition that infantile eczema increases the risk of allergic sensitization and food allergy, attention has also focused on early skin care and aggressive treatment of infantile eczema as potential preventive measures. Because some **skin preparations** contain peanut or nut oils, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided. Table 192.6 summarizes approaches to food allergy prevention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 192.6 Approaches to Prevention of Food Allergy

RECOMMENDED
Infant-safe forms of peanut, egg introduced around age 6 mo, not before 4 mo
Other allergens may be introduced around this time as well
Allergy testing before introduction not usually needed (see text)
Infants with severe eczema or egg allergy may benefit from evaluation for early peanut introduction at 4-6 mo
Diverse infant diet
UNPROVEN/NOT RECOMMENDED
Hydrolyzed formulas
Maternal allergen avoidance during pregnancy or lactation
Purposeful delay in introducing allergens to infants

* https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy..

192.1 Non-IgE Gastrointestinal Food Allergy Disorders

Anna H. Nowak-Wegrzyn, Hugh A. Sampson, Amanda L. Cox, and Scott H. Sicherer

CLINICAL MANIFESTATIONS

GI food allergies are often the first form of allergy to affect infants and young children, and typically manifest as chronic irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement (non-IgE) predominate, making standard allergy tests such as skin-prick tests and in vitro tests for food-specific IgE antibodies of little diagnostic value (Table 192.7).

FPIES is a non-IgE, cell-mediated food allergy that can have dramatic GI symptoms and in its severe form is considered an allergic emergency. FPIES can present as acute or chronic phenotypes (Fig. 192.2).

EPIDEMIOLOGY

Prevalence: The prevalence of FPIES ranges between 0.34% and 0.7% of infants in Israel and Spain; in a population-based survey, physician-diagnosed FPIES was reported in 0.51% (95% confidence interval [CI]; 0.420.62) of U.S. children.

Food triggers: Globally, cow's milk is the most common trigger of FPIES, although in countries with higher rates of breastfeeding rather than formula feeding, complementary foods introduced into infants' diets early are also reported. Commonly reported triggers include soy, oat, rice, vegetables (avocado, sweet potato), fruits (banana), egg, fish, chicken, turkey, peanut, tree nuts, and fish. Most infants (50–75%) react to one food; however, about 10–15% report more than three food triggers.

Pathophysiology: FPIES is characterized by a strong inflammatory response with significant elevation of CRP, neutrophils, and platelets. There is evidence of innate immune compartment activation (monocytes, neutrophils) along with the pan-activation of T lymphocytes and significant elevation in levels of various cytokines and chemokines in the peripheral blood, including IL-17A, IL-22, IL-17C, and tumor necrosis factor (TNF)-α, and a preferential activation of nonconventional T-cell populations, including γδT cells.

Clinical manifestations: FPIES typically manifests in the first year of life in an **acute** form as projectile, repetitive vomiting within 1-4 hours of food ingestion, frequently accompanied by lethargy, pallor (or dusky appearance), and low muscle tone; in a smaller subset, vomiting is followed by watery diarrhea in 5-10 hours (see Fig. 192.2). Prolonged ingestion of the causal allergen may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive, referred to as **chronic FPIES.** Acute FPIES is considered to be an allergic emergency because hypotension occurs in approximately 5–10% of patients after allergen ingestion, which initially may be attributed to sepsis.

Diagnosis: Acute FPIES is diagnosed based on the recognition of a constellation of symptoms, (Table 192.8; see Fig. 192.2) and allergy tests detecting food-specific IgE are typically negative. OFCs are rarely required for the confirmation of the initial diagnosis, but are utilized for evaluating resolution of FPIES. Chronic FPIES is diagnosed based on the chronic GI symptoms that resolve within days to weeks following elimination of the allergen and recur acutely within 1-2 hours following a subsequent feeding.

Differential diagnosis: The differential diagnosis includes GI infections (viral, bacterial), sepsis, necrotizing enterocolitis, metabolic disorders that induce emesis and lethargy (hyperammonemias, organic acidemias, congenital adrenal hyperplasia), very early onset inflammatory bowel disease and other immune enteropathies (IPEX), gastroesophageal reflux (GER) disease, ileus, anatomical small bowel obstruction, celiac disease, anaphylaxis, cyclic vomiting syndrome, poisoning, pyloric stenosis, seizures, and primary immunodeficiencies.

Emergency management: Severe FPIES reactions are considered allergic emergencies due to the risk of hypotension (in extreme cases, hypovolemic shock), dehydration, and metabolic derangements including acidemia and methemoglobinemia (Fig. 192.3). Acute management entails vigorous intravenous hydration. Additional therapies include intravenous or intramuscular ondansetron as an antiemetic, and a single dose of steroid (e.g., methylprednisolone) may be administered due to a strong inflammatory response. Mild to moderate reactions can be managed with oral rehydration and oral ondansetron. Epinephrine autoinjectors and oral antihistamines are not prescribed for home management; however, vasopressors may be used for treatment of shock in the medical setting.

Dietary management: Breastfeeding mothers rarely need to restrict the foods that trigger symptoms in an infant following direct feeding, unless the infant exhibits symptoms of acute or chronic FPIES during breast milk feeding or has impaired growth. Hypoallergenic infant formulas (extensively hydrolyzed or amino acid) are recommended in non-breastfed infants to avoid cow's milk and soy. Timely introduction of solids is important for nutrition and for the development of oromotor skills. Following acute FPIES reactions to a solid food, foods from an unrelated food group can be chosen for introduction. Tolerance to one food from a food group usually indicates a favorable likelihood of tolerance to the related foods. Table 192.9 discusses practical guidelines for dietary management of FPIES.

Monitoring for resolution: The natural history of infantile FPIES is favorable, with the majority becoming tolerant by 3-5 years of age; persistent FPIES is rare. FPIES to fish and shellfish may start in older children and in adults; the natural history of adult FPIES is unknown. Reintroduction of foods that have caused FPIES is usually done during a physician-supervised OFC. Timing of reintroduction varies based on the nutritional and social importance of the foods; usually attempts are done 6-24 months following the most recent FPIES reaction to the offending food. FPIES induced by cow's milk may (~10%) evolve into IgE-mediated food allergy.

Comorbidities: FPIES is associated with an increased risk of IgE-mediated food allergy to other foods, atopic dermatitis, allergic rhinitis, asthma, and EoE.

FPIAP presents in the first few months of life as blood-streaked stools in otherwise healthy infants that are breastfed and/or formula-fed (see Table 192.7). Blood loss is typically mild, but can occasionally result in anemia. The most commonly implicated dietary triggers are cow's milk and soy proteins, followed by egg; their elimination, either by maternal dietary restriction if breastfeeding or by use of hypoallergenic formulas, leads to symptom and gross blood resolution within 48-72 hours in most infants. FPIAP is diagnosed clinically based on the presence of blood in the stool; sigmoidoscopy with biopsy, confirming an eosinophilic inflammatory response, is no longer done in routine practice for diagnosis of FPIAP. Blood in the infant's stool can be attributed to multiple causes other than food allergy (see Table 192.7). Therefore diagnosis based on clinical observation carries the risk of overdiagnosis (especially when FPIAP is diagnosed based on detection of microscopic blood in stool) and unnecessary dietary restrictions resulting in delayed introduction of foods and an associated increased risk of developing IgE sensitization. Therefore, considering benign, nonspecific nature of the symptoms and favorable natural history, in cases of mild to moderate FPIAP, many authorities recommend a trial of the culprit food 2-3 months following symptom resolution to determine whether the infant has "outgrown" the sensitivity.

Table 192.7 Food Protein–Induced Gastrointestinal Syndromes

	FPIES	FPIAP	FPE	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day to 1 year, later for fish and shellfish	1 day to 6 months	Dependent on age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
FOOD PROTEINS IMPLICATED				
Most common	Cow's milk, egg, oat, rice	Cow's milk, soy	Cow's milk, soy	Cow's milk, wheat, egg white, soy, peanut, seafood
Less common	Soy, chicken, turkey, fish, pea, peanut, avocado, sweet potato	Egg	Wheat, egg	Meats, corn, rice, fruits, vegetables, legumes
Multiple food hypersensitivities	>50% both cow's milk and soy if younger than 6 mo; 40–50% react to more than one grain, 30% react to more than one fish	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breastfeeding	Formula	Formula
ATOPIC BACKGROUND				
Family history of atopy	40–70%	25%	Unknown	~50% (often history of EoE)
Personal history of atopy	30%	22%	22%	~50%
SYMPTOMS				
Emesis	Projectile, repetitive, severe	No	Intermittent	Intermittent
Diarrhea	Severe in chronic FPIES	No	Moderate	Moderate
Bloody stools	Occasionally severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Differential diagnosis	Infection: viral, bacterial Necrotizing enterocolitis, GI obstruction (ileus, pyloric stenosis, Meckel diverticulum); gastroesophageal reflux disease; very early onset inflammatory bowel disease, seizure disorder, metabolic disorder, cardiac disease, anaphylaxis	Rectal fissure, bleeding disorder, vit K deficiency, GI infection e.g., *Shigella*, inflammatory bowel disease	Celiac disease, primary immunodeficiency, inflammatory bowel disease	Gastroesophageal reflux disease, recurrent vomiting due to other causes, parasitic and fungal infections, congenital rings, Crohn disease, periarteritis, allergic vasculitis, connective tissue diseases, bullous pemphigoid, pemphigoid vegetans, graft-versus-host disease, achalasia, drug hypersensitivity, celiac disease, vasculitis, carcinoma, hypereosinophilic syndrome
LABORATORY FINDINGS				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
ALLERGY EVALUATION				
Food skin-prick test	Majority negative†	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Majority negative†	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
BIOPSY FINDINGS				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation, and basal zone hyperplasia
Food challenge	Emesis in 1-4 hr; diarrhea in 5-8 hr (in a subset)	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge under supervision in 0.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate; resume/continue breastfeeding on maternal antigen-restricted diet; reintroduce at home after 9-12 mo of age	Protein elimination, symptoms clear in 1-3 wk; rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent (>90%) response to elemental diet; symptoms clear in 2-3 wk, excellent acute response to oral steroids but with high rate of relapse following discontinuation; in EoE 30–50% response to proton pump inhibitors, 70% to swallowed corticosteroids; rechallenge by introducing food at home and biopsy in 1-2 yr

Continued

Table 192.7 Food Protein–Induced Gastrointestinal Syndromes—cont'd

	FPIES	FPIAP	FPE	EOSINOPHILIC GASTROENTEROPATHIES*
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 mo	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Supervised food challenge	At home, gradually advancing from 1 oz to full feedings over 2 wk	Home, gradually advancing	Home, gradually advancing

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, and gastroenterocolitis.
†If positive, may be a risk factor for persistent disease, referred to as "atypical" FPIES.
FPIES, Food protein–induced enterocolitis syndrome; FPIAP, food protein–induced allergic proctocolitis; FPE, food protein–induced enteropathy; GI, gastrointestinal; EoE, eosinophilic esophagitis.

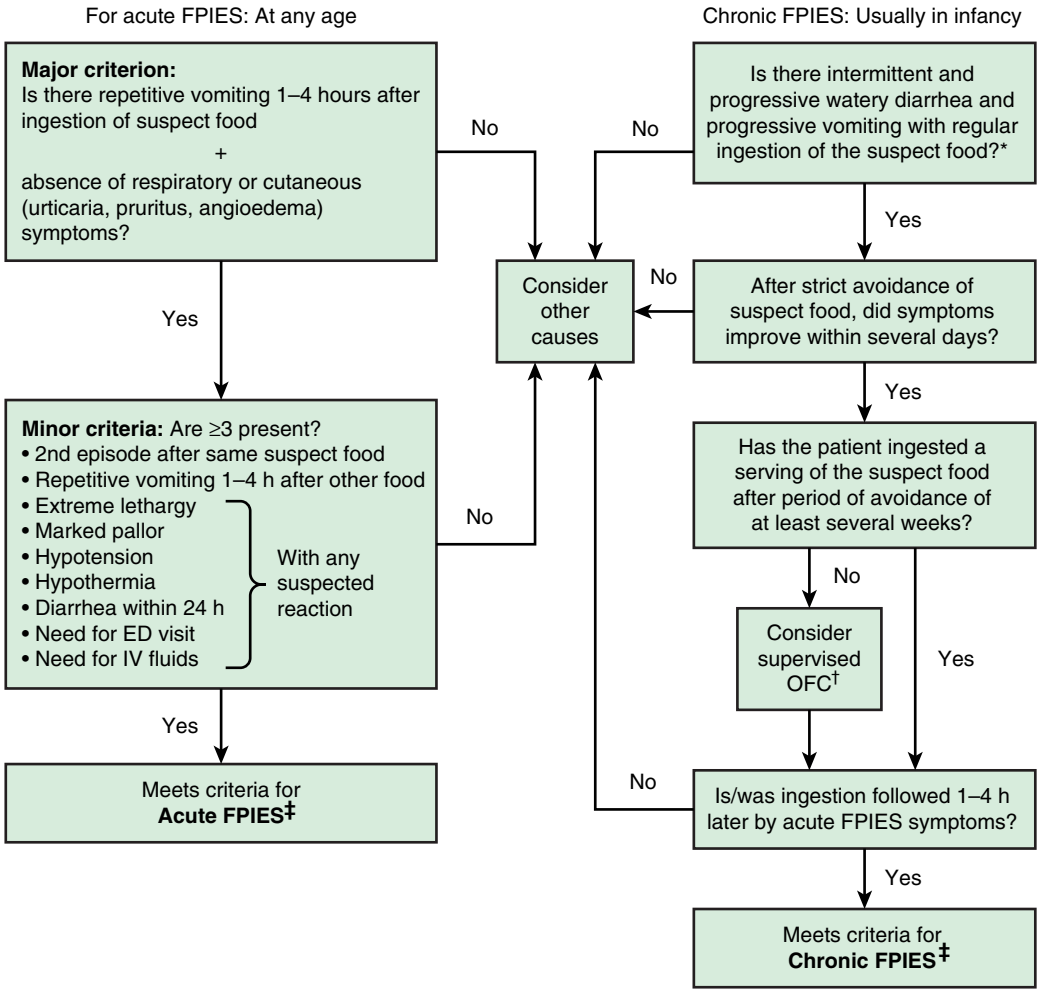

Fig. 192.2 Diagnostic algorithm for food protein–induced enterocolitis syndrome (FPIES). ED, Emergency department; IV, intravenous; OFC, oral food challenge. *Chronic FPIES is described almost exclusively with cow's milk or soy in young infants. †Without a confirmatory OFC or other ingestion with emesis onset in 1-4 hours, diagnosis of chronic FPIES is presumptive. ‡Based on Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2017;139:1111–1126. *(From Sicherer SH, Nowak-Węgrzyn A. Enterocolitis, proctocolitis, and enteropathies. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021: Fig. 33.2.)*

Table 192.8 FPIES Diagnostic Criteria

ACUTE FPIES*	
MAJOR CRITERIA (BOTH MUST BE MET), PLUS	MINOR CRITERIA (≥3 OCCURRING WITH EPISODE)
• Vomiting 1-4 hr after suspect food ingestion • Absence of immediate, IgE-mediated allergic symptoms (hives, itching, swelling, wheezing, cough)	• ≥2 episodes with same food • One episode with a different food • Lethargy • Pallor • Need for ER visit • Need for IV fluid support • Diarrhea within 24 hr (usually 5-10 hr) • Hypotension • Hypothermia
CHRONIC FPIES†	
SYMPTOMS AND SEVERITY	CRITERIA
Milder (lower doses with intermittent ingestion): • Intermittent vomiting and/or diarrhea • Growth faltering • No dehydration or metabolic acidosis **Severe** (higher doses with chronic ingestion): • Intermittent but progressive vomiting and watery diarrhea (occasionally with blood) • Poor weight gain or failure to thrive • Possible dehydration and metabolic acidosis, anemia, hypoproteinemia, neutrophilia, thrombocytosis	• Resolution of symptoms within days to weeks after elimination of offending food(s) • Acute recurrence of symptoms (vomiting in 1-4 hr, diarrhea in <24 hr, usually 5-10 hr) when the food is reintroduced, following a period of elimination • Confirmatory OFC required for conclusive diagnosis; if OFC not performed diagnosis remains presumptive

*Major criterion must be met (both) plus at least three minor criteria.
†General criteria because of paucity of available data.
FPIES, Food protein–induced enterocolitis syndrome; ER, emergency room; IV, intravenous; OFC, oral food challenge.
Adapted from Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111–1126.e4.

Food protein–induced enteropathy (FPE) often manifests in the first several months of life as diarrhea, often with steatorrhea and poor weight gain (see Table 192.7). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally. **Cow's milk sensitivity** is the most common cause of FPE in young infants, but it has also been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease**, the most severe form of FPE, occurs in about 1 per 100 of the U.S. population, although it may be "silent" in many patients (see Chapter 384). The classic form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

EoE may present from infancy through adolescence, more frequently in boys (see Chapter 370). EoE is a cell-mediated disorder, which is often associated with IgE-mediated food allergies in infants and young children, and manifests as chronic GER, intermittent emesis, food refusal, abdominal pain, dysphagia, food impaction, irritability, sleep disturbance, and failure to respond to conventional GER medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are seen on esophageal biopsies. Treatment is possible with elimination of dietary allergens but management with medications is typically included (see Chapter 370). **Eosinophilic gastritis and gastroenteritis** are additional **eosinophilic GI disorders** that are far less common and can occur at any age. **Eosinophilic gastritis** often presents with nausea and abdominal pain or bloating, while **eosinophilic enteritis** may also present with nausea, abdominal pain or bloating with additional diarrhea, anemia, or protein loss. **Eosinophilic colitis** may present with loose stool or blood in stool associated with abdominal cramping/pain. More than 50% of patients with these disorders are atopic; however, food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked **protein-losing enteropathy**.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

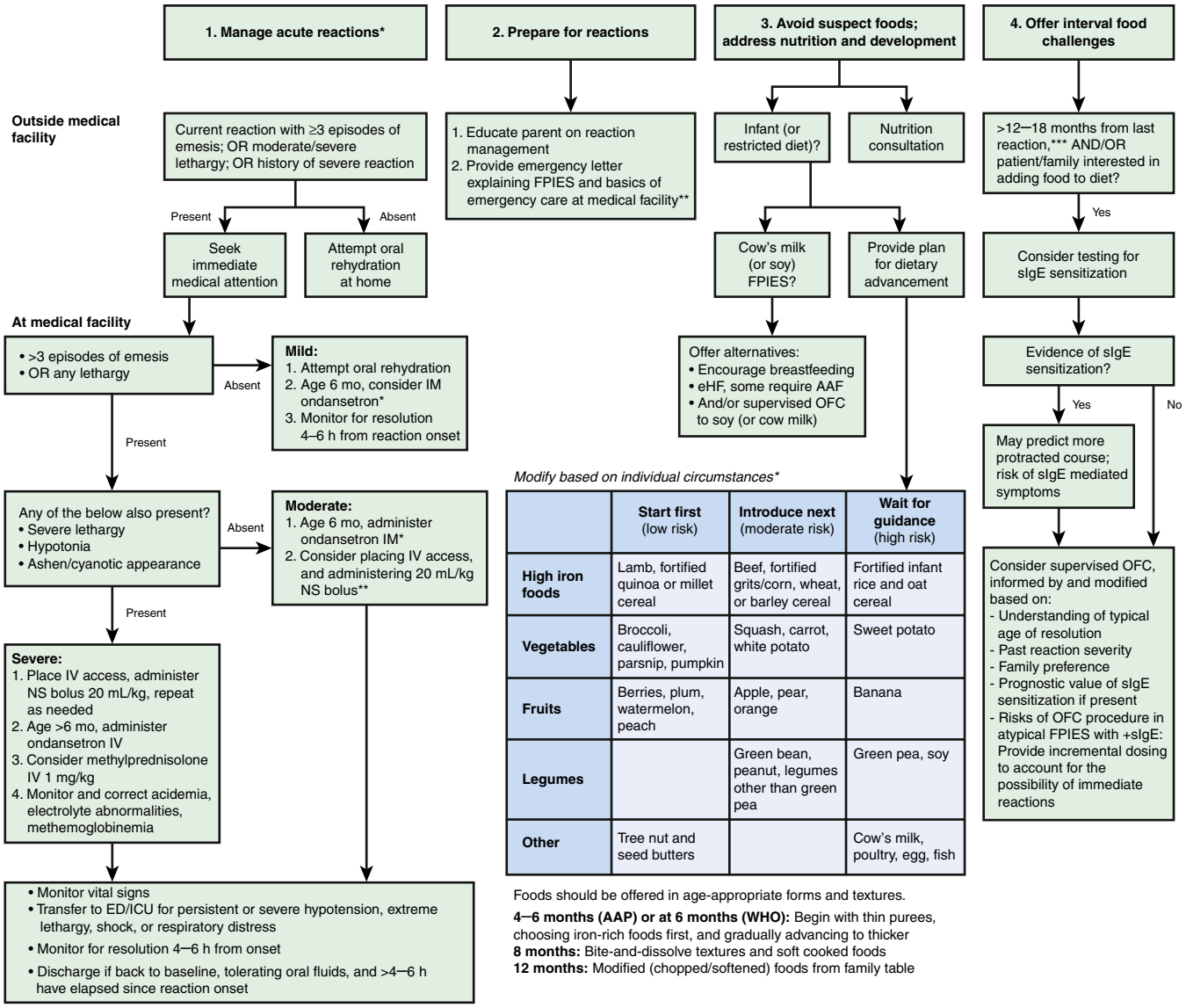

*0.15 mg/kg/dose; maximum, 16 mg
AAF, amino acid–based formula
ED, emergency department
FPIES, food protein–induced enterocolitis syndrome
ICU, intensive care unit
IM, intramuscular
IV, intravenous
mo, months
NS, normal saline
OFC, oral food challenge
sIgE, specific immunoglobulin E
WHO, World Health Organization

** Template may be downloaded at https://www.fpies.org/wp-content/uploads/2018/08/IFPIES-ER-Letter-2018.pdf
*** Interval can be modified at the discretion of the treating physician.

Fig. 192.3 Treatment algorithm for food protein–induced enterocolitis syndrome (FPIES). *Modified from Nowak-Wegrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139:1111–1126. **Template may be downloaded at https://www.fpies.org/wp-content/uploads/2018/08/IFPIES-ER-Letter-2018.pdf. ***Interval can be modified at the discretion of the treating physician. *(From Sicherer SH, Nowak-Węgrzyn A. Enterocolitis, proctocolitis, and enteropathies. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021: Fig. 33.3.)*

Table 192.9 Empiric Guidelines for Selecting Weaning Foods in Infants with FPIES

AGES AND STAGES[a,b]	LOWER RISK FOODS*	MODERATE RISK FOODS*	HIGHER RISK FOODS†
4-6 MO (AS PER AAP, CON) If developmentally appropriate and safe and nutritious foods are available • Begin with smooth, thin, purees and progress to thicker purees • Choose foods that are high in iron • Add vegetables and fruits	**VEGETABLES**		
	Broccoli, cauliflower, parsnip, turnip, pumpkin, kale	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
	FRUITS		
	Blueberries, strawberries, plum, watermelon, peach	Apple, pear, orange	Avocado, banana
6 MO (AS PER WHO) Complementary feeding should begin no later than 6 mo of age • In the breastfed infant, high-iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 mo of age • Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated	**HIGH-IRON FOODS**		
	Lamb, beef, pork, fortified quinoa cereal, millet, amaranth	Fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Fortified, infant rice and oat cereals.
8 MO OF AGE OR WHEN DEVELOPMENTALLY APPROPRIATE • Offer soft-cooked and bite-and-dissolve textures from around 8 mo of age or as tolerated by infant	**OTHER**		
	Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish, shellfish
12 MO OF AGE OR WHEN DEVELOPMENTALLY APPROPRIATE • Offer modified tolerated foods from the family table, chopped meats, soft cooked vegetables, grains, and fruits			

*Risk assessment is based on the clinical experience and the published reports of FPIES triggers.
†This is not an exhaustive list and feeding should not be limited to this list of lower and moderate risk foods. Many other foods are appropriate for infant feeding. One may consider delaying the introduction of higher risk foods until there is a nutritional need for the food, the infant already has a diverse diet, or other lower and moderate risk foods are tolerated.
[a]Exclusive breastfeeding until 4-6 mo of age and continuing breastfeeding through the first year of life or longer as long as mutually desired by both mother and child.
[b]If an infant tolerates a variety of early foods, subsequent introduction may be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered as a favorable prognostic indicator for tolerance of other foods from the same group (legumes).
AAP, CON, American Academy of Pediatrics, Committee on Nutrition; WHO, World Health Organization.
Adapted from Nowak-Wegrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive Summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2017;139(4):1111–1126.e4

Chapter 193

Adverse and Allergic Reactions to Drugs

Roland Solensky and Scott H. Sicherer

Adverse drug reactions (ADRs) can be divided into predictable (type A) and unpredictable (type B) reactions. **Predictable drug reactions**, including drug toxicity, drug interactions, and adverse effects, are dose dependent, are related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. **Unpredictable drug reactions** are generally dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically or otherwise predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. **Allergic reactions** are immune-mediated and require prior sensitization. They manifest as signs and symptoms characteristic of an underlying allergic mechanism (Table 193.1). Anaphylaxis is due to production of drug-specific IgE antibodies, and delayed cutaneous reactions are due to drug-specific T cells. **Pseudoallergic reactions** resemble allergic reactions but are caused by non–IgE-mediated release of mediators from mast cells and basophils, such as vancomycin-induced flushing. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-α-1,3-galactose. This antigen is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group. Sensitization to galactose-α-1,3-galactose may occur from tick bites caused by cross-reactive tick salivary antigens.

EPIDEMIOLOGY

The incidence of ADRs in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal ADRs. Databases such as the U.S. Food and Drug Administration (FDA) MedWatch program (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) likely suffer from underreporting. Cutaneous reactions are the most common form of ADRs, with ampicillin, amoxicillin, penicillin, and trimethoprim/sulfamethoxazole (TMP/SMX) being the most frequently implicated drugs (Tables 193.2 and 193.3). Although the majority of ADRs do not appear to be allergic in nature, 6–10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of re-exposure.

Table 193.1 Classification of Drug Allergies

TYPE	TYPE OF IMMUNE RESPONSE	PATHOPHYSIOLOGY	CLINICAL SYMPTOMS	TYPICAL CHRONOLOGY OF THE REACTION
1	IgE	Mast cell and basophil degranulation	Anaphylactic shock Angioedema Urticaria Bronchospasm	Within 1-6 hr after the last intake of the drug
2	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5-15 days after the start of the eliciting drug
3	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness Urticaria Vasculitis	7-8 days for serum sickness/urticaria 7-21 days after the start of the eliciting drug for vasculitis
4a	Th1 (IFN-γ)	Monocytic inflammation	Eczema	1-21 days after the start of the eliciting drug
4b	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthem, DRESS	1 to several days after the start of the eliciting drug for MPE 2-6 wk after the start of the eliciting drug for DRESS
4c	Cytotoxic T cells (perforin, granzyme B, FASL)	Keratinocyte death mediated by CD4 or CD8	Maculopapular exanthem, SJS/TEN, pustular exanthem	1-2 days after the start of the eliciting drug for fixed drug eruption 4-28 days after the start of the eliciting drug for SJS/TEN
4d	T cells (IL-8/CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1-2 days after the start of the eliciting drug *(but could be longer)*

CXCL8, C-X-C motif chemokine ligand 8; DRESS, drug reaction with eosinophilia and systemic symptoms; FASL, FAS ligand; FcR, Fc receptor; IFN-γ , interferon gamma; IgE, immunoglobulin E; IL, interleukin; MPE, malignant pleural effusion; SJS , Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Th1, Th2, T-helper cell type 1 and type 2.
From Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69(4):420–437.

Table 193.2 Heterogeneity of Drug-Induced Allergic Reactions

ORGAN-SPECIFIC REACTIONS	CLINICAL FEATURES	EXAMPLES OF CAUSATIVE AGENTS
CUTANEOUS		
Exanthems	Diffuse fine macules and papules evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Usually IgE mediated	β-Lactam antibiotics Platinum agents
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, sulfonamides, NSAIDs, carbamazepine
Pustules	Acneiform Acute generalized exanthematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium channel blockers, ACEIs
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillins, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
MULTIORGAN REACTIONS		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, platins
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

ACEI, Angiotensin-converting enzyme inhibitor; DRESS, drug reaction with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Adapted from Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125:S126–S137. Table 1, p. S127.

Table 193.3 Delayed Hypersensitivity Drug Rashes by Category

MACULOPAPULAR EXANTHEMS: ANY DRUG CAN PRODUCE A RASH SEVERAL DAYS INTO THE COURSE
Allopurinol
Antibiotics: penicillins, ampicillin, sulfonamides
Antiepileptics: phenytoin, phenobarbital
Antihypertensives: thiazide diuretics, calcium channel blockers
Radiocontrast material
Gold salts
Hypoglycemic drugs
Meprobamate
Phenothiazines
Quinine
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)
Anticonvulsants: phenytoin, phenobarbital, valproate, lamotrigine, carbamazepine
Antibiotics: sulfonamides, minocycline, dapsone, ampicillin, ethambutol, isoniazid, linezolid, metronidazole, rifampin, streptomycin, vancomycin
Allopurinol
NSAIDs: celecoxib, ibuprofen, diclofenac
Phenothiazines
STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS
Sulfonamides, phenytoin, barbiturates, carbamazepine, allopurinol, amikacin, phenothiazines, acetazolamide, gold, nitrofurantoin, pentazocine, tetracycline, quinidine
ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS
Antibiotics: penicillins, macrolides, cephalosporins, clindamycin, imipenem, fluoroquinolones, isoniazid, vancomycin, minocycline, doxycycline, linezolid, gentamicin, sulfonamides
Antimalarials: chloroquine, hydroxychloroquine
Antifungals: terbinafine, nystatin, amphotericin B, fluconazole, itraconazole
Anticonvulsants: carbamazepine
Calcium-channel blockers
Furosemide, thiazides
Systemic corticosteroids
Protease inhibitors
COLLAGEN VASCULAR OR LUPUS-LIKE REACTIONS
Procainamide, hydralazine, phenytoin, penicillamine, trimethadione, methyldopa, carbamazepine, griseofulvin, nalidixic acid, oral contraceptives, propranolol
ERYTHEMA NODOSUM
Oral contraceptives, penicillins, sulfonamides, diuretics, gold, clonidine, propranolol, opiates
FIXED DRUG REACTIONS
Phenolphthalein, barbiturates, gold, sulfonamides, penicillins, tetracycline, quinolones, carbamazepine, NSAIDs

Note: See Chapter 686 and Table 686.5.
NSAID, Nonsteroidal antiinflammatory drug.
Adapted from Duvic M. Urticaria, drug hypersensitivity rashes, nodules and tumors, and atrophic diseases. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier; 2016: Table 440.3.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Immunologically mediated ADRs have been classified according to the Gell and Coombs classification: immediate hypersensitivity reactions **(type I)**, cytotoxic antibody reactions **(type II)**, immune complex reactions **(type III)**, and delayed-type hypersensitivity reactions **(type IV)** (see Table 193.1). **Immediate hypersensitivity reactions** occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasm, or anaphylaxis. **Cytotoxic antibody reactions** involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte-macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. **Immune complex reactions** are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 weeks into the course of the offending drug and persist for days to weeks after the drug is discontinued. **Delayed-type hypersensitivity reactions** are mediated by cellular immune mechanisms. They are subdivided into four categories involving activation and recruitment of monocytes (type IVa), eosinophils (type IVb), $CD4^+$ or $CD8^+$ T cells (type IVc), and neutrophils (type IVd). Examples include drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and Stevens-Johnson syndrome (SJS) (see Chapter 686.2). Not all allergic drug reactions can be easily classified using the Gell and Coombs system.

Non–IgE-mediated immediate-type reactions mimic Gell and Coombs type I reactions, with indistinguishable symptoms and signs. The most common drugs associated with these reactions are vancomycin, fluoroquinolones, and opiates, which cause nonspecific mast cell degranulation via interaction with the surface receptor MrgprX2. Because these reactions do not require prior sensitization (unlike IgE-mediated reactions), they may occur with first exposure.

The pharmacologic interaction with immune receptors concept **(p-i concept)** is another type of drug hypersensitivity classification. In this scheme, a drug binds noncovalently to a T-cell receptor, which leads to an immune response through interaction with a major histocompatibility complex (MHC) receptor. In this scenario, no sensitization (i.e., previous exposure) is required because there is direct stimulation of memory and effector T cells analogous to the concept of superantigens. Although the various mechanistic schemes of drug-induced allergic reactions are useful, not all drug allergic reactions can be categorized using these various classification systems.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and toxic epidermal necrolysis (TEN; see Chapters 686.2, 695.2 and 695.3). Although their pathophysiology remains incompletely understood, HLA associations including HLA-B*1502 with carbamazepine-induced TEN have been recognized, and the pathogenic roles of drug-specific cytotoxic T cells and granulysin have been reported. SJS is defined as the epidermal detachment of <10%, TEN is >30% detachment, and overlap syndrome is 10–30% detachment. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than one mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. The risks of infection and mortality remain high, but improved outcomes have been demonstrated by immediate withdrawal of the implicated drug, early transfer to a burn unit, and aggressive supportive care. Additional management is reviewed in Chapter 695.3.

Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS (i.e., drug-induced hypersensitivity syndrome) is a potentially life-threatening reaction that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 193.2 and 193.3; see Chapter 686.2). It is likely less common in children compared with adults. DRESS is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of one or more organs, usually hepatic or renal. Onset is delayed, usually 2-8 weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten-protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. Penicillins are highly reactive with proteins and can directly haptenate protein carriers, without prior metabolism, possibly accounting for the higher frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are *slow acetylators* appear to be at increased risk. In addition, cutaneous reactions in patients with AIDS treated with TMP/SMX, rifampin, and other drugs may be caused by glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions due to cefaclor may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for ADRs include prior exposure, previous reactions, age (20-49 years), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), and genetic predisposition. Atopy does not appear to predispose patients to allergic reactions to low molecular weight compounds, but asthmatics who experience allergic reactions are likely at increased risk of more serious reactions, analogous to food-allergic patients. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiocontrast media (RCM). Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions.

DIAGNOSIS

Skin testing is the most rapid and sensitive method of demonstrating the presence of IgE antibodies to a specific allergen. It can be performed with high molecular weight compounds, such as foreign antisera, hormones, enzymes, and toxoids. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated ADRs are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal and flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

In vitro tests (radioallergosorbent test or enzyme-linked immunoassay) for IgE-mediated penicillin allergy have lower sensitivity and comparable specificity compared with skin testing. The positive and negative predictive values (NPVs) of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses using nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum **tryptase** is elevated with systemic mast cell degranulation and can be seen with drug-associated reactions such as anaphylaxis; however, not all patients with well-defined anaphylaxis show increased serum tryptase levels. **Patch testing** is the most reliable technique for diagnosis of contact dermatitis caused by topically applied drugs. **Graded drug challenge** is an incremental (usually two-step) administration of a drug under medical supervision and is used in patients who are deemed unlikely to be allergic to the drug. Unlike desensitization, there is no attempt to modify the underlying immune response. Patients who pass a graded challenge are proven to not be allergic to the drug.

TREATMENT

Drug desensitization alters the immune response to a medication and allows allergic patients to receive it safely. However, the induced tolerance is temporary and if treatment is interrupted, hypersensitivity returns, and patients are again at risk of reacting to the drug. Drug desensitization has classically been used for IgE-mediated allergy, such as penicillin, but the procedure has been successfully applied to immediate non–IgE-mediated reactions, such as taxanes. Rapid desensitization is indicated in patients who are either proven or are strongly suspected to have an immediate-type drug allergy and for whom an alternate drug is not available or appropriate. The procedure warrants close monitoring and preparedness to treat possible anaphylaxis. Depending on the clinical stability of the patient and the severity of the previous reaction (or symptoms during a previous desensitization), it may be performed in outpatient or inpatient settings. Premedications are used for non–IgE-mediated hypersensitivity (such as taxanes and biologic agents), but not for IgE-mediated allergy (such as antibiotics). Desensitization can be performed via parenteral or oral routes. The starting dose is typically 1/10,000 of the full dose, and the dose is doubled every 15 minutes until the full dose is reached. Desensitization has a very high success rate and breakthrough allergic reactions occur about 20–30% of the time, but they are usually mild and do not necessitate aborting the procedure.

Penicillin Allergy

Penicillin allergy is self-reported by approximately 10% of patients, but following evaluation, about 95% of these individuals are shown to not be allergic and able to tolerate penicillins. This incongruity is due to the reaction being the result of the underlying infection (or interaction between the infectious agent and the antibiotic), mislabeling a predictable reaction as allergic, and the waning of penicillin-specific IgE. Being labeled as penicillin allergic is not benign, because patients are more likely to be treated with less effective, more toxic, or more expensive antibiotics such as fluoroquinolones, vancomycin, later generation cephalosporins, and clindamycin. This prescribing practice compromises optimal medical care and increases costs. Penicillin "allergy" has been associated with increased antimicrobial resistance (such as vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus*), increased *Clostridium difficile* colitis, increased surgical site infections, prolonged length of hospital stays, increased intensive care admissions, increased hospital readmissions, and increased mortality. Removal of the penicillin allergy label leads to improved antibiotic selection with decreased use of broad-spectrum antibiotics and decreased healthcare utilization (fewer outpatient visits, fewer emergency department [ED] visits, and fewer hospital days). Therefore a proactive effort should be made to de-label penicillin allergy whenever possible. Ideally, this is done electively such as when patients are well and not in immediate need of antibiotic treatment. De-labeling of penicillin allergy is endorsed by the CDC, allergy/immunology, and infectious disease societies.

The penicillin β-lactam ring opens to form various reactive intermediates, which then interact with self-proteins to stimulate immune reactions. Penicillin skin test reagents are based on the immunochemistry, and they are broadly grouped into major and minor allergenic determinants. (Table 193.4) The positive predictive value of penicillin skin testing is ~80% for immediate type reactions. Alternatively, 95% or more of penicillin skin test–negative patients tolerate these antibiotics. The major determinant (penicilloyl-polylysine [PPL]) should always be used for skin testing, but there is controversy regarding the relative importance of various minor determinants (penicillin G, penicilloate, penilloate and ampicillin/amoxicillin) and what effect this has on the NPV. Although PPL is commercially available in the United States as Pre-Pen, the minor determinants are not. Penicillin G and IV ampicillin can be diluted and used off-label for skin testing, but penicilloate and penilloate require synthesis; therefore they are more difficult to obtain.

Patients who are positive on penicillin skin testing should avoid penicillins but consider being reevaluated at a later time, because penicillin allergy wanes and resolves in most (but not all) individuals. If administration of penicillin is deemed necessary, desensitization can be performed. Skin test–negative patients should ideally undergo an amoxicillin challenge, to unequivocally prove lack of allergy. This alleviates the fear and reluctance on the part of the patient, patient's family, or future prescribing clinicians to treat with penicillins. Additionally, effort should be made to remove the penicillin allergy label in all electronic medical systems (hospitals, clinics, private offices, pharmacies, etc.).

The traditional approach to de-label penicillin allergy has been to first perform penicillin skin testing in all patients with suggestive penicillin allergy histories and then challenge with amoxicillin (if skin testing is negative). However, in recent years several publications have challenged this standard, particularly in the pediatric population, by instead directly challenging "low-risk" patients with amoxicillin (without preceding skin testing). Patients deemed appropriate for direct amoxicillin challenge are those with maculopapular and urticaria eruptions, without other respiratory, cardiovascular, oropharyngeal symptoms, angioedema, and vesicular or exfoliative eruptions. Using this strategy, the rate of observed reactions ranged from 5% to 10% and were no more severe than the historical reactions. For comparison, up to 7% of children (without a previous history of allergy) treated with aminopenicillins develop cutaneous eruptions. The cause of these rashes is presumed to be the underlying infection (typically viral) or an interaction between the infectious agent and the antibiotic. The best characterized example is patients with Epstein-Barr infection, almost 100% of whom develop a nonpruritic morbilliform rash when treated with ampicillin. Pediatric patients who undergo direct amoxicillin challenge should be observed in a clinical setting for at least 1 hour, with preparedness to treat potential allergic reactions including anaphylaxis.

Resensitization is the redevelopment of penicillin allergy after initial resolution. Resensitization after oral treatment with penicillins is rare in both pediatric and adult patients, including after repeated courses, and comparable to the rate of sensitization. Therefore repeat penicillin skin testing is not indicated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin. Data on resensitization after parenteral treatment with penicillins is more limited, but routine repeat penicillin skin testing is likely not necessary in patients with a history of penicillin allergy who have tolerated one or more courses of parenteral penicillin. Consideration may be given to retesting individuals with recent or particularly severe previous reactions.

Table 193.4 Penicillin Skin Test Reagents

REAGENT*	CONCENTRATION USED FOR SKIN TESTING
Penicilloyl-polylysine (PPL)	6×10^{-5} M
Penicillin G	10,000 units/mL
Penicilloate	0.01 M
Penilloate	0.01 M
Ampicillin/amoxicillin	3-25 mg/mL

*PPL is the major allergenic determinant; all the other reagents are minor determinants.

β-Lactam Cross Reactivity

Penicillins, cephalosporins, carbapenems, and aztreonam share a common β-lactam ring and hence the potential for allergic cross reactivity. Additionally, some penicillins and cephalosporins share identical R group side chains, and these are another source of potential allergic cross reactivity (Table 193.5). Combining published reports of patients proven to be allergic via positive penicillin skin testing and then challenged with cephalosporins, only about 2% experienced allergic reactions. This is similar to the incident rate of new drug reactions to structurally dissimilar medications in patients with prior drug allergies (because patients with a history of drug allergy are more likely to react to structurally unrelated drugs). If cephalosporin skin testing (using nonirritating concentrations) is performed in penicillin skin test–positive subjects before challenging with cephalosporins, the reaction rate decreased to 0%.

In general, the preferred approach to patients with a history of penicillin allergy is to electively de-label the allergy because this greatly simplifies all future β-lactam administration recommendations by allowing treatment with any β-lactam antibiotics. Given that less than 5% of patients with an unverified penicillin allergy are truly allergic and 2% of those who are allergic cross react with cephalosporins, the chance

Table 193.5 Groups of β-Lactam Antibiotics That Share Identical Side Chains*

IDENTICAL R1-GROUP SIDE CHAINS					
Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			
IDENTICAL R2-GROUP SIDE CHAINS					
Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

*Each column represents a group with identical side chains.
From Solensky R, Khan DA. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:273e1–273e78. Tables 16, 17, p. 273e49.

of a cephalosporin reaction is extremely low at approximately 0.1% (5% × 2% = 0.1%). *Therefore most experts and guidelines recommend that for patients with a history of nonanaphylactic penicillin allergy, cephalosporins may be administered without prior testing or additional precautions.* In patients with a history of penicillin anaphylaxis (or those positive on penicillin skin testing), cephalosporin graded challenge is preferred because the chance of reaction is still very low.

There are rare patients who have selective IgE-mediated allergy to aminopenicillins but tolerate penicillin VK and penicillin G. The allergic determinant is an R-group side chain, rather than the core β-lactam portion of the molecule. In these patients, the positive challenge rate to cephalosporins sharing identical side group chains (such as ampicillin/cephalexin or amoxicillin/cefadroxil; see Table 193.5) is higher, or about 16%. Therefore, in such patients, administration of cephalosporins with identical side group chains should be avoided, given via two-step graded challenge or desensitization, whereas treatment with other cephalosporins does not require a more cautious approach.

The data on allergic cross reactivity between penicillins and carbapenems mirror the discussion on penicillin/cephalosporin cross reactivity. Patients with unconfirmed penicillin allergy treated with carbapenems showed a higher reaction rate compared to patients without a history of penicillin allergy. In studies of penicillin skin test–positive patients challenged with carbapenems, none of 680 reacted; four carbapenem skin test–positive patients were not challenged. Therefore it is recommended that patients with a history of penicillin allergy may receive carbapenems in usual fashion or via two-step graded challenge.

Aztreonam is the only monobactam and the only β-lactam antibiotic that contains a monocyclic ring structure, in contrast to the bicyclic core of other β-lactams. In vitro, skin testing and challenge studies have demonstrated no evidence of allergic cross reactivity between penicillins and aztreonam, including no positive aztreonam challenges in penicillin skin test–positive patients. Therefore patients with a history of penicillin allergy may receive aztreonam in the usual fashion. The only β-lactam that shows cross reactivity with aztreonam is ceftazidime, because these two antibiotics share an identical R-group side chain. Hence, patients allergic to aztreonam or ceftazidime should avoid the other antibiotic.

Sulfonamides

The most common type of reaction to sulfonamide antibiotics is a maculopapular eruption that occurs about a week into treatment. The incidence of immediate reactions, such as urticaria/angioedema or anaphylaxis, is rare and less frequent than with β-lactam antibiotics. On the other hand, sulfonamides are the most common antibiotic to cause severe cutaneous delayed reactions (SCARs), such as SJS, TEN, and DRESS. Hypersensitivity reactions to sulfonamides occur with greater frequency in HIV-infected individuals. For patients with history of typical delayed maculopapular rashes, both graded one- or two-step challenge and desensitization protocols have been shown to be effective in HIV-positive and non–HIV-positive patients. Because the success rate of graded challenge and desensitization appears comparable, it is not clear that the various desensitization protocols truly modify the immune response. These regimens are not intended for individuals with a history of SJS or TEN. There is no evidence of allergic cross reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides (such as celecoxib, thiazides, furosemide, acetazolamide, sumatriptan, and others).

Macrolides

Macrolides cause allergic reactions less frequently than penicillins, cephalosporins, or sulfonamides. The most common reactions are delayed onset maculopapular eruptions and urticaria, and they occur in about 1% of patients. IgE-mediated reactions are uncommon, limited to case series, and anaphylactic reactions are extremely rare. When pediatric patients with convincing histories of allergic reactions undergo formal evaluation, less than 10% are confirmed to be allergic. Skin testing with a nonirritating concentration of macrolides may provide useful information in those patients with immediate reaction histories. However, in patients with an anticipated clinical need for macrolides, graded challenge without preceding testing is used most commonly, given the high likelihood of success and rare nature of anaphylaxis.

Antiretroviral Agents

There are several categories of antiretroviral drugs to treat HIV (reverse transcriptase inhibitors, protease inhibitors, entry inhibitors, and integrase inhibitors) and all have been implicated in hypersensitivity reactions, which usually present as delayed onset and range from mild self-limited maculopapular eruptions to life-threatening SJS/TEN or DRESS. Hypersensitivity to abacavir is a well-recognized, multiorgan, potentially life-threatening reaction that occurs in HIV-infected children and adults. Rechallenge is strictly contraindicated, because subsequent reactions may be more rapid and severe than the initial reaction. Importantly, these reactions have been associated with the presence of the MHC class I allele HLA-B*5701, and HLA testing has shown very high sensitivity and NPV. Therefore genetic screening for HLA-B*5701 is part of guideline-based therapy when abacavir is initially prescribed.

Chemotherapeutic Agents

Hypersensitivity reactions to chemotherapeutic drugs have been described, most notably to platinum agents and taxanes. The clinical pattern of immediate reactivity to platinum agents, along with skin test findings, is consistent with an IgE-mediated mechanism. Hence reactions occur after patients tolerated several previous treatments. In contrast, immediate reactions to paclitaxel and docetaxel usually occur with first exposure and the risk lessens with repeated exposure. They are believed to be due to emulsifying agents such as Cremophor-EL, which result in complement activation and generation of anaphylatoxins. Rapid desensitization (most typically a 12-step protocol) is effective for both IgE and non–IgE-mediated type reactions.

Biologics

An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of ADRs, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a black box warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 185).

Vaccines

Anaphylactic reactions to vaccines are very rare, occurring at a rate of approximately one event per million administrations, and they may be due to various vaccine components such as antibiotics, preservatives, stabilizers, virus-inactivating compounds, residual animal proteins, and latex. Measles mumps rubella (MMR) vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). Egg-allergic patients are not at higher risk of reacting to both inactivated and live influenza vaccine than those without egg allergy. Skin testing with the influenza vaccine is no longer recommended for egg-allergic patients but may be helpful if allergy to the vaccine itself is suspected. The American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI) Joint Task Force on Practice Parameters recommend that "Influenza vaccines should be administered to individuals with egg allergy of any severity, just as they would be to individuals without egg allergy." The incidence of anaphylactic reactions following mRNA COVID-19 vaccines may be higher (2.5-4.7 events per million). However, following evaluation by allergists/immunologists, most patients reporting immediate-type reactions to the first vaccine dose are able to tolerate the second dose, arguing against an IgE-mediated mechanism. Therefore the true rate of anaphylaxis is likely lower.

It is uncertain whether patients with underlying atopic conditions or other allergies are at increased risk of reacting to these vaccines. Although polyethylene glycol (PEG) (a component of mRNA COVID vaccines) has been proposed to be a possible culprit, there is limited evidence for the relationship.

Perioperative Agents

In North America, perioperative anaphylaxis is most frequently due to antibiotics, whereas in European series, neuromuscular blockers are the most common culprit. Other potential causes include induction agents, opioids, colloids and plasma expanders, chlorhexidine, sugammadex, and latex. The mechanism responsible may be IgE-mediated or non–IgE-mediated. Previous surgeries are a risk factor for IgE-mediated reactions because they require prior sensitization. Patients who have experienced perioperative anaphylaxis should be screened for possible mast cell disease. Skin testing with agents known to cause IgE-mediated reactions is useful and can help prevent recurrent reactions during subsequent surgeries. Sometimes, despite a thorough evaluation, an underlying cause for perioperative anaphylaxis is not detected.

Local Anesthetics

ADRs associated with local anesthetic agents are primarily nonallergic and include vasovagal, psychomotor, sympathetic stimulation, and toxic reactions. IgE-mediated reactions are exceedingly rare. Patients with suspected local anesthetic allergy should be referred to an allergist/immunologist for skin testing followed by a graded challenge. This procedure invariably finds a local anesthetic the patient is able to tolerate, in the rare individuals who are allergic to one of these agents. Although local anesthetics can be broadly grouped into esters (group I) and amides (group II), allergic cross reactivity within these groups is only relevant for delayed Gell and Coombs type IV reactions, not type I reactions.

Insulin

Insulin use has been associated with a spectrum of ADRs, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergenic than porcine insulin, which is less allergenic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergenic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly because of IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reinstitution of insulin therapy in sensitized patients.

Insulin therapy should not be interrupted if a systemic reaction to insulin occurs, and continued insulin therapy is essential. Skin testing may identify a less antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2- to 5-unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for >24-48 hours.

Radiocontrast Media

Immediate type allergic reactions to RCM may occur after intravascular administration, and during myelograms or retrograde pyelograms. The pathogenic mechanism has classically been thought to be non–IgE-mediated mast cell activation (anaphylactoid). However, there is growing evidence that some immediate reactions are IgE mediated. This may be because use of older high-osmolar RCM agents has been replaced by low- and iso-osmolar agents. One approach to patients with previous RCM reactions who require another diagnostic study is to choose an alternate agent and premedicate with prednisone and diphenhydramine. Another approach is to perform skin testing with the culprit and alternate RCM agents, with the results guiding the choice of treatment. The latter method appears to be more useful when the historical reactions are severe (i.e., anaphylactic). There is no evidence that seafood or iodine allergy is associated with or predisposes to RCM reactions.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Acetylsalicylic acid (ASA) and other NSAIDs have been associated with several types of allergic reactions. Reactions that are caused by modifying effects on arachidonic acid metabolism, namely respiratory reactions (in patients with underlying aspirin-exacerbated respiratory disease [AERD]) and urticarial reactions (in patients with underlying chronic idiopathic urticaria), show cross reactivity with other NSAIDs, as one would expect. Patients with AERD and aspirin-sensitive patients with chronic idiopathic urticaria tolerate drugs that selectively block the cyclooxygenase-2 (COX-2) enzyme, such as celecoxib. On the other hand, acute urticarial or anaphylactic reactions in otherwise normal individuals are medication specific. There are no skin or in vitro tests to identify patients allergic to ASA or other NSAIDs.

Except for respiratory reactions in asthmatics, there are no data on the incidences of reactions to ASA/NSAIDs in children; however, clinical experience suggests that it is much lower than in adults. Furthermore, only 20% of children reporting NSAID allergy are confirmed to be allergic when challenged. The incidence of AERD in children with asthma has been investigated in six prospective studies, the rate varied from 0% to 28%, and there was a trend for more respiratory reactions in adolescents compared with younger children. Overall, the data indicate that ASA sensitivity in asthmatic children under the age of 10 is rare and increases thereafter.

Patients with AERD whose nasal disease or asthma is poorly controlled with use of medications are candidates for ASA desensitization. This procedure, unlike antibiotic or chemotherapy desensitization, involves administration of the drug to cautiously induce a respiratory reaction (rather than prevent it), following which patients enter a refractory phase that can be maintained with continued administration of ASA. Long-term studies of adults maintained on chronic ASA desensitization demonstrated improved clinical outcomes for both upper and lower respiratory diseases. ASA desensitization is rarely performed in children because severe, poorly controlled AERD is encountered very infrequently in the pediatric population, and aspirin is not routinely recommended for children because of the risk of Reyes syndrome.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Rheumatic Diseases of Childhood (Connective Tissue Disease, Collagen Vascular Diseases)

PART XIV

Chapter 194

Evaluation of Suspected Rheumatic Disease

C. Egla Rabinovich

Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune markers and other serologic tests, tissue pathology, and imaging. Defined diagnostic criteria exist for most rheumatic diseases. Recognition of *clinical patterns* remains essential for diagnosis because there is no single diagnostic test, and tests may be positive in the absence of disease. Further complicating diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease (overlap syndromes). The primary mimics of rheumatic diseases are infection and malignancy but also include metabolic, orthopedic, immune deficiencies, autoinflammatory diseases, and chronic pain conditions. Exclusion of possible mimicking disorders is essential before initiation of treatment for a presumptive diagnosis, especially corticosteroids. After careful evaluation has excluded nonrheumatic causes, referral to a pediatric rheumatologist for confirmation of the diagnosis and treatment should be considered.

SYMPTOMS SUGGESTIVE OF RHEUMATIC DISEASE

There are no classic symptoms of rheumatic diseases, but common symptoms include joint pain, fever, fatigue, and rash. Presenting signs and symptoms help direct the evaluation and limit unnecessary testing. Once a differential diagnosis is developed based on history and physical findings, a directed assessment assists in determining the diagnosis.

Arthralgias are common in childhood and are a frequent reason for referral to pediatric rheumatologists. Arthralgias without physical findings for arthritis suggest infection, malignancy, orthopedic conditions, benign syndromes, or pain syndromes such as fibromyalgia (Table 194.1). Although rheumatic diseases may manifest as arthralgias, **arthritis** is a stronger predictor of the presence of rheumatic disease and a reason for referral to a pediatric rheumatologist. The timing of joint pain along with associated symptoms, including poor sleep and interference with normal activities, provides important clues. Poor sleep, debilitating generalized joint pain that worsens with activity, school absences, and normal physical and laboratory findings in an adolescent suggest an amplified **pain syndrome** (see Chapter 212). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, or cold intolerance, testing for **thyroid disease** is merited. Nighttime awakenings because of severe pain along with decreased platelet or white blood cell (WBC) count or, alternatively, a very high WBC count, may lead to the diagnosis of malignancy, especially marrow-occupying lesions such as **acute lymphocytic leukemia** and **neuroblastoma**. Pain with physical activity suggests a mechanical problem such as an overuse syndrome or orthopedic condition. An adolescent presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has **patellofemoral syndrome**. Children age 3-10 years with a history of episodic pain occurring at night, especially after increased daytime physical activity, that is relieved by rubbing but who have no limp or complaints in the morning likely have **growing pains**. There is often a positive family history for growing pains, which may aid in this diagnosis. Intermittent pain in a child, especially a girl 3-10 years old, that is increased with activity and is associated with hyperextensible joints on examination likely has **benign hypermobility syndrome**. Many febrile illnesses cause arthralgias that improve when the temperature normalizes, and arthralgias are part of the diagnostic criteria for **acute rheumatic fever** (**ARF**; see Chapter 229.1).

Arthralgia may also be a presenting symptom of pediatric **systemic lupus erythematosus** (**SLE**) and chronic childhood arthritis such as **juvenile idiopathic arthritis (JIA)**. Interestingly, many children with JIA do not complain of joint symptoms at presentation. Other symptoms more suggestive of arthritis include morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever, and fatigue or stiffness after physical inactivity *(gelling phenomenon)*. A diagnosis of JIA cannot be made without the finding of arthritis on physical examination (see Chapters 196 and 197). No laboratory test is diagnostic of JIA.

Fatigue is a nonspecific symptom that may point to the presence of a rheumatic disease but is also common in nonrheumatic causes, such as viral infections, pain syndromes, depression, and malignancy. Fatigue, rather than the specific complaints of muscle weakness, is a common presenting complaint in **juvenile dermatomyositis (JDM)**. It is also frequently present in SLE, vasculitis, and chronic childhood arthritis. Overwhelming fatigue with inability to attend school is more suggestive of chronic fatigue syndrome, pediatric fibromyalgia, or other amplified pain syndrome.

SIGNS SUGGESTIVE OF RHEUMATIC DISEASE

A complete physical examination is essential in any child with suspected rheumatic disease, because subtle physical findings may further refine the differential diagnosis. In addition, many rheumatic diseases have multisystem effects, and a stepped assessment should focus on delineating the extent of organ system involvement (e.g., skin, joints, muscle, hepatic, renal, cardiopulmonary).

Presence of a **photosensitive malar rash** that spares the nasolabial folds is suggestive of SLE (Table 194.2; see Fig. 199.1A). Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears may represent discoid lupus (see Fig. 199.1D). A palpable purpuric rash on the extensor surfaces of the lower extremities points to **IgA vasculitis (Henoch-Schönlein purpura)** (see Fig. 210.2A). Less localized purpuric rashes and petechiae are present in systemic vasculitis or blood dyscrasias, including coagulopathies. Nonblanching erythematous papules on the palms are seen in vasculitis, SLE, and endocarditis. Gottron papules (see Fig. 200.3) and heliotrope rashes (see Fig. 200.2) along with erythematous rashes on the elbows and knees are pathognomonic

Table 194.1 Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and postinfectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP*
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile idiopathic arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis-related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.
*Also know as IgA vasculitis.

Table 194.2 Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically spares nasolabial folds	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with genital ulcers	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis (e.g., ANCA-associated vasculitis), HSP*	HSP* typically starts as small lesions on lower extremities and buttocks that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated heliotrope rash, periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP*, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	Chronic joint swelling (>6 wk) required for diagnosis of JIA; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, Antineutrophil cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; SLE, systemic lupus erythematosus.
*Also know as IgA vasculitis.

of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 200.4) are common in JDM, scleroderma, and secondary Raynaud phenomenon. An evanescent macular rash associated with fever is part of the diagnostic criteria for systemic-onset arthritis (see Fig. 196.12). Sun sensitivity or photosensitive rashes are indicative of SLE or JDM but can also be caused by antibiotics.

Mouth ulcers are part of the diagnostic criteria for SLE and Behçet disease (see Fig. 199.1C); painless nasal ulcers and erythematous macules on the hard palate are also common in SLE. Cartilage loss in the nose, causing a saddle nose deformity, is classically present in granulomatosis with polyangiitis (formerly Wegener granulomatosis; see Fig. 210.8) but is also seen in relapsing polychondritis and syphilis. Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 201.4) and JDM. **Raynaud phenomenon** may be a primary benign idiopathic disorder or can be a presenting complaint in the child with scleroderma, lupus, mixed connective tissue disease (MCTD), or an overlap syndrome. Diffuse lymphadenopathy is present in many rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA. Irregular pupils may represent the insidious and unrecognized onset of **uveitis** associated with JIA. Erythematous conjunctivae may be a result of uveitis or episcleritis associated with JIA, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

A pericardial rub and orthopnea are suggestive of **pericarditis**, often seen in systemic JIA, SLE, and sarcoid. Coronary artery dilation is strongly suggestive of Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) but may also be a finding in systemic arthritis and other forms of systemic vasculitis. Interstitial lung disease, suggested by dyspnea on exertion or the finding of basilar rales with decreased carbon monoxide diffusion capacity, occurs in SLE, MCTD, and systemic sclerosis. Signs consistent with pulmonary hemorrhage point to granulomatosis with polyangiitis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or two or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all the chronic childhood arthritis syndromes, along with SLE, JDM, vasculitis, Behçet disease, sarcoidosis, Kawasaki disease, and Henoch-Schönlein purpura. Nonrheumatic causes of arthritis include malignancy, septic arthritis, Lyme disease, osteomyelitis, viral infections (e.g., rubella, hepatitis B, parvovirus B19, chikungunya), and postinfectious etiologies such as Epstein-Barr virus (EBV), ARF, and reactive arthritis. ARF typically involves a migratory (lasting hours to days), painful arthritis. Pain on palpation of long bones is suggestive of malignancy. Specific muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, because both these symptoms may be manifestations of muscle inflammation.

LABORATORY TESTING

There are no specific screening tests for rheumatologic disease. Once a differential diagnosis is determined, appropriate testing can be performed (Tables 194.3 and 194.4). Initial studies are generally performed in standard local laboratories. Screening for specific autoantibodies can be performed in commercial laboratories, but confirmation of results in a tertiary care center immunology laboratory is often necessary.

Table 194.3 Autoantibody Specificity and Disease Associations

ANTIBODY	DISEASE	PREVALENCE (%)	SPECIFICITY
Antinuclear antibody (ANA)	SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD	—	Associated with increased risk of uveitis in JIA and psoriatic arthritis Up to 30% of children testing positive for ANAs have no underlying rheumatic disease
Double-stranded DNA (dsDNA)	SLE	60-70	High specificity for SLE; associated with lupus nephritis
Smith (Sm)	SLE	20-30	Highly specific for SLE; associated with lupus nephritis
Smooth muscle (Sm)	Autoimmune hepatitis	—	—
Pm-Scl (polymyositis-scleroderma)	Sclerodermatomyositis	—	—
SSA (Ro)	SLE, Sjögren syndrome	25-30	Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia
SSB (La)	SLE, Sjögren syndrome	25-30	Usually coexists with anti-SSA antibody
Ribonuclease protein (RNP)	MCTD, SLE	30-40	Suggestive of MCTD unless meets criteria for SLE
Histone	Drug-induced lupus, SLE	—	—
Centromere	Limited cutaneous systemic sclerosis	70	Nonspecific for systemic sclerosis
Topoisomerase I (Scl-70)	Systemic sclerosis	—	Rare in childhood
Antineutrophil cytoplasmic antibodies (ANCAs)	Vasculitis	—	—
Cytoplasmic (cANCAs)/PR3-ANCA		—	cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis
Perinuclear (pANCAs)/MPO-ANCA		—	pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis, primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome
Anticitrullinated protein (ACPA); also called anti–cyclic citrullinated protein (anti-CCP)	RF-positive JIA	50-90	Specific for JIA (RF+), may be positive before RF

MCTD, Mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.
Adapted from Aggerwal A. Clinical application of tests used in rheumatology. *Indian J Pediatr* 2002;69:889–892.

For initial workup of rheumatic disease, a CBC with differential, alanine transaminase/aspartate transaminase (ALT/AST), albumin, BUN/creatinine, urinalysis, creatine phosphokinase/lactate dehydrogenase (CPK/LDH), and inflammatory markers (sedimentation rate and CRP) are recommended. Further appropriate testing depends on clinical concern (see Table 194.4).

One essential laboratory test for rheumatic disease assessment is the *complete blood count* (CBC), because it yields many diagnostic clues. Elevated WBC count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be postinfectious, especially viral, or caused by SLE or malignancy. Lymphopenia is more specific for SLE than is leukopenia. Platelets are acute-phase reactants and are therefore elevated with inflammatory markers. Exceptions are a bone marrow–occupying malignancy, such as leukemia or neuroblastoma, SLE, and early Kawasaki disease. **Anemia** is nonspecific and may be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor (RF) is present in <10% of children with JIA and thus has poor sensitivity as a diagnostic tool; RF may be elevated by infections such as endocarditis, tuberculosis, syphilis, and viruses (parvovirus B19, hepatitis B and C, mycoplasma), as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, RF serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, CRP, ferritin, procalcitonin) are nonspecific and are elevated in infections, malignancies, and rheumatic diseases (Table 194.5). Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. The advantages of a CRP include rapid response to inflammatory stimuli, wide range of clinically relevant values, the fact that it is unaffected by age or gender, it is precise and reproducible, and it can be measured on stored sera. Sedimentation rates have classically been used as markers of inflammation, but they can be affected by anemia, red cell morphology, and drugs such as intravenous immunoglobulin (IVIG); they require a fresh blood sample; and they are slow to respond to clinical changes. Inflammatory marker measurements in general are more useful in rheumatic diseases for following response to treatment than as diagnostic tests.

Muscle enzymes include AST, ALT, CPK, aldolase, and LDH, any of which may be elevated in JDM and in other diseases causing muscle breakdown. Muscle-building supplements, medications, and extreme physical activity may also cause muscle breakdown and enzyme elevations. AST, ALT, and aldolase may also be elevated in liver disease, and a γ-glutamyltransferase (GGT) measurement may help differentiate muscle or liver source.

The use of an antinuclear antibody (ANA) measurement as a screening test is *not* recommended because it has low specificity. A positive ANA test result may be induced by infection, especially EBV infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children, and ANA level is

Table 194.4 Evaluation Based on Suspected Diagnosis of Rheumatic Disease

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
Systemic lupus erythematosus (SLE) Mixed connective tissue disease (MCTD)	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If ANA test result is positive: anti-SSA (Ro), anti-SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2-glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
Juvenile dermatomyositis (JDM)	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
Juvenile idiopathic arthritis (JIA)	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP	MRI
Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants (see Chapter 200); HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum IgG, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper GI radiography series

Ab, Antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine transaminase; ANA, antinuclear antibody; anti-dsDNA Ab, anti–double-stranded DNA antibody; AST, aspartate transaminase; BP, blood pressure; CBC, complete blood count; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest x-ray; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor; RNP, ribonucleoprotein.

Table 194.5 Conditions Associated with Elevated C-Reactive Protein Levels

NORMAL OR MINOR ELEVATION (<1 mg/dL)
Vigorous exercise
Common cold
Pregnancy
Gingivitis
Seizures
Depression
Insulin resistance and diabetes
Several genetic polymorphisms
Obesity
MODERATE ELEVATION (1-10 mg/dL)
Myocardial infarction
Malignancies
Pancreatitis
Mucosal infection (bronchitis, cystitis)
Most systemic autoimmune diseases
Rheumatoid arthritis
Influenza and adenovirus infections
MARKED ELEVATION (>10 mg/dL)
Acute bacterial infection (80–85%)
Major trauma, surgery
Systemic vasculitis
MIS-C

MIS-C, Multisystem inflammatory syndrome in children.
From Firestein GS, Budd RC, Gabriel SE, et al., eds. *Kelley & Firestein's Textbook of Rheumatology*, 10th ed. Philadelphia: Elsevier; 2017, Table 57-4, p. 849.

increased in those with a first-degree relative with a known rheumatic disease. In the majority of children with a positive ANA without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop over time, so this finding does not necessitate referral to a pediatric rheumatologist. A positive ANA test result is found in many rheumatic diseases, including JIA, in which it serves as a predictor of the risk for inflammatory eye disease (see Chapter 196). Once a positive ANA test result is discovered in a child, the need for specific autoantibody testing is directed by the presence of clinical signs and symptoms (see Table 194.3).

IMAGING STUDIES

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings may be abnormal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Musculoskeletal ultrasound can be useful in evaluation of synovitis and joint effusion. MRI findings are abnormal in inflammatory myositis and suggest the optimal site for biopsy. *MRI is more sensitive than plain radiographs in detecting the presence of early erosive arthritis and demonstrates increased joint fluid, synovial enhancement, and sequela of trauma with internal joint derangement.* MRI is also helpful in ruling out infection or malignancy. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and lung, including SLE, systemic scleroderma, MCTD, JDM, and sarcoid, as clinical manifestations may be subtle. This evaluation, which may include echocardiogram, pulmonary function tests, and high-resolution CT of the lungs along with consideration of bronchoalveolar lavage, is generally performed by a pediatric rheumatologist to whom the patient is referred (see Table 194.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 195.1 Multidisciplinary Treatment of Rheumatic Diseases in Childhood

Accurate diagnosis and education of family	Pediatric rheumatologist Pediatrician Nurse • Disease-related education • Medication administration (injection teaching) • Safety monitoring Social worker • Facilitation of school services • Resource identification (community, government, financial, advocacy groups, vocational rehabilitation)
Physical medicine and rehabilitation	Physical therapy • Addressing deficits in joint or muscle mobility, limb-length discrepancies, gait abnormalities, and weakness Occupational therapy • Splinting to reduce joint contractures/deformities and lessen stress on joints; adaptive devices for activities of daily living
Consultant team	Ophthalmology • Eye screening for uveitis • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids) Nephrology Orthopedics Dermatology Gastroenterology
Physical and psychosocial growth and development	Nutrition • Addressing undernourishment from systemic illness and obesity/overnourishment from glucocorticoids School integration • Individualized educational plan (IEP) or 504 plan Peer-group relationships Individual and family counseling
Coordination of care	Involvement of patient and family as active team members Communication among healthcare providers Involvement of school (school nurse) and community (social worker) resources

qualitatively different from that observed with treatment of neoplasms. Adverse effects include elevated liver enzyme values (15%); GI toxicity (13%); stomatitis (3%); headache (1–2%); and leukopenia, interstitial pneumonitis, rash, and alopecia (<1%). Hepatotoxicity observed among adults with rheumatoid arthritis (RA) treated with MTX has raised concern about similar problems in children. Analysis of liver biopsy specimens in children with JIA undergoing long-term MTX treatment has revealed occasional mild fibrosis but no evidence of even moderate liver damage. Patients receiving MTX should be counseled to avoid alcohol, smoking, and pregnancy. *Folic acid* (1 mg daily) is given as an adjunct to minimize adverse effects. Lymphoproliferative disorders have been reported in adults treated with MTX, primarily in association with Epstein-Barr virus (EBV) infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 8-12 weeks for the first 3-6 months of treatment, then every 12 weeks, with more frequent intervals after dosing adjustments or in response to abnormal values.

Hydroxychloroquine

Hydroxychloroquine sulfate is an antimalarial drug important in the treatment of SLE and dermatomyositis, particularly cutaneous manifestations of disease and to reduce lupus flares. It is not indicated to treat JIA because of lack of efficacy. The most significant potential adverse effect is *retinal toxicity,* which occurs rarely but results in irreversible color blindness or loss of central vision. Complete ophthalmologic examinations, including assessment of peripheral vision and color fields, are conducted at baseline and every 6-12 months to screen for retinal toxicity. Retinal toxicity is rare (1/5,000 patients) and is associated with weight-based dosing exceeding 6.5 mg/kg/day; therefore recommended dosing is 5 mg/kg/day, not to exceed 400 mg/day. Other potential adverse effects include rash, skin discoloration, gastric irritation, bone marrow suppression, central nervous system (CNS) stimulation, and myositis.

Leflunomide

Leflunomide is a DMARD approved for treatment of RA and also offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 weeks, 89% of patients receiving MTX achieved a 30% response rate vs 68% of those receiving leflunomide), although both drugs were effective. Dosing is oral, once daily, and weight based: 10 mg for children 10 to <20 kg, 15 mg for children 20-40 kg, and 20 mg for children >40 kg. Adverse reactions include paresthesias and peripheral neuropathy, GI intolerance, elevated liver transaminases and hepatic failure, cytopenias, alopecia, and teratogenesis. Leflunomide has a long half-life, and in cases in which discontinuation of the agent is required, a drug elimination protocol with cholestyramine may be indicated. Avoidance of pregnancy is essential. Laboratory tests (e.g., CBC, LFTs) are monitored every 4 weeks for the first 6 months of treatment, then every 8-12 weeks.

Sulfasalazine

Sulfasalazine is used to treat children with polyarticular JIA, oligoarticular JIA, and the peripheral arthritis and enthesitis associated with juvenile ankylosing spondylitis. In JIA, sulfasalazine 50 mg/kg/day (adult maximum: 3,000 mg/day, divided bid) achieves greater improvement in joint inflammation, global assessment parameters, and laboratory parameters than placebo. More than 30% of sulfasalazine-treated patients withdraw from the treatment because of adverse effects, primarily GI irritation and skin rashes. Sulfasalazine is associated with severe systemic hypersensitivity reactions, including Stevens-Johnson syndrome. Sulfasalazine is generally considered contraindicated in children with active systemic JIA because of increased hypersensitivity reactions. Sulfasalazine should not be used in patients with sulfa or salicylate hypersensitivity or porphyria.

Monitoring laboratory tests for sulfasalazine toxicity include CBC, LFTs, serum creatinine/blood urea nitrogen (BUN), and urinalysis, every other week for the first 3 months of treatment, monthly for 3 months, then every 3 months.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. MMF is used primarily for treatment of lupus, uveitis, and autoimmune skin manifestations. In adult clinical trials, MMF was noninferior to cyclophosphamide for induction therapy of lupus nephritis, with a potential for fewer adverse effects (infection, gonadal toxicity). Dosing is based on body surface area (BSA): 600 mg/m^2 orally twice daily, with maximum dosage limits varying by formulation and BSA. The most common adverse reaction is GI intolerance; infections, cytopenias, and secondary malignancies are also reported.

Glucocorticoids

Glucocorticoids are given through oral, intravenous (IV), ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. Oral corticosteroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with many well-described, dose-dependent complications, including linear growth suppression, cushingoid features, osteoporosis, avascular necrosis, hypertension, impaired glucose tolerance, mood disturbance, and increased infection risk. Glucocorticoids should be tapered to the lowest effective dose over time and DMARDs introduced as steroid-sparing agents.

Table 195.2 Therapeutics for Childhood Rheumatic Diseases*

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Nonsteroidal antiinflammatory drugs (NSAIDs)‡	Etodolac[a]	PO once-daily dose: 20-30 kg: 400 mg 31-45 kg: 600 mg 46-60 kg: 800 mg >60 kg: 1,000 mg	JIA Spondyloarthropathy Pain Serositis Cutaneous vasculitis Uveitis	GI intolerance (abdominal pain, nausea), gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis, headache, renal disease	CBC, LFTs, BUN/creatinine, urinalysis at baseline, then every 6-12 mo
	Ibuprofen[a]	40 mg/kg/day PO in 3 divided doses Max 2,400 mg/day			
	Naproxen[a]	15 mg/kg/day PO in 2 divided doses Max 1,000 mg/day			
	Celecoxib[a]	10-25 kg: 50 mg PO bid >25 kg: 100 mg PO bid			
	Meloxicam[a]	0.125 mg/kg PO daily Max 7.5 mg			
Disease-modifying antirheumatic drugs (DMARDs)	Methotrexate[a]	10-20 mg/m^2/wk (0.35-0.65 mg/kg/wk) PO 20-30 mg/m^2/wk (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection	JIA Uveitis	GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis	CBC, LFTs at baseline, monthly ×3, then every 8-12 wk
	Leflunomide	PO once daily: 10 to <20 kg: 10 mg 20-40 kg: 15 mg >40 kg: 20 mg	JIA	Hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy	CBC, LFTs, at baseline, monthly ×6, then every 8-12 wk
	Hydroxychloroquine	5 mg/kg PO daily; do not exceed 5 mg/kg/daily Max 400 mg daily	SLE JDMS Antiphospholipid antibody syndrome	Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)	Ophthalmologic screening every 6-12 mo
	Sulfasalazine[a]	30-50 mg/kg/day in 2 divided doses Adult max 3 g/day	Spondyloarthropathy, JIA	GI intolerance, rash, hypersensitivity reactions, Stevens-Johnson syndrome, cytopenias, hepatitis, headache	CBC, LFTs, BUN/creatinine, urinalysis at baseline, every other wk ×3 mo, monthly ×3, then every 3 mo
Janus kinase inhibitor	Tofacitinib[a]	Oral solution (1 mg/mL) Use for ≥2 yr and ≥10 kg; 10 to <20 kg: 3.2 mg twice daily 20 to <40 kg: 4 mg twice daily ≥40 kg: 5 mg twice daily **or** Immediate-release tablet (5 mg), 5 mg twice daily	Polyarticular JIA	Infection, headache, increased HDL, cytopenias, potential increased malignancy risk, potential increased thrombosis risk	CBC, LFTs at baseline, then every 3 mo; lipids 4-8 wk after initiation, then periodically

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 195.2 Therapeutics for Childhood Rheumatic Diseases —cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Tumor necrosis factor (TNF)-α antagonists	Adalimumab[a]	SC once every other wk: 10 to <15 kg: 10 mg 15 to <30 kg: 20 mg ≥30 kg: 40 mg	JIA Spondyloarthropathy Psoriatic arthritis Uveitis	Injection site reaction, infection, rash, cytopenias, lupus-like syndrome, potential increased malignancy risk	TB test; anti-dsDNA, CBC
	Etanercept[a]	0.8 mg/kg SC once weekly (max 50 mg/dose) or 0.4 mg/kg SC twice weekly (max 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk	TB test; CBC
	Golimumab[a]	80 mg/m^2 IV at 0 and 4 wk, then every 8 wk	Polyarticular JIA Spondyloarthropathy Psoriatic arthritis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs
	Infliximab	5-10 mg/kg IV every 4-8 wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs
Modulate T-cell activation	Abatacept[a]	IV every 2 wk ×3 doses, then monthly for ≥6 yr of age: <75 kg: 10 mg/kg 75-100 kg: 750 mg >100 kg: 1,000 mg SC once weekly: 10 to <25 kg: 50 mg ≥25 to <50 kg: 87.5 mg ≥50 kg: 125 mg	JIA	Infection, headache, potential increased malignancy risk	
Anti-CD20 (B-cell) antibody	Rituximab	575 mg/m^2, max 1,000 mg, IV on days 1 and 15	SLE	Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML	CBC, BMP; consider monitoring quantitative IgG
Anti-BLyS antibody	Belimumab[e]	10 mg/kg IV every 2 wk ×3 doses, then every 4 wk	SLE	Infusion reactions, infection, depression	
Interleukin (IL)-1 antagonist	Anakinra	1-2 mg/kg/daily Adult max 100 mg	Systemic JIA CAPS	Injection site reactions, infection	CBC
	Canakinumab[b]	Given SC every 8 wk (CAPS) every 4 wk (systemic JIA): 15-40 kg: 2 mg/kg (up to 3 mg/kg if needed) >40 kg: 150 mg	CAPS Systemic JIA	Injection site reaction, infection, diarrhea, nausea, vertigo, headache	
		IV: <30 kg: 10 mg/kg/dose every 4 wk ≥30 kg: 8 mg/kg/dose every 4 wk; maximum dose: 800 mg/dose SC: <30 kg: 162 mg/dose once every 3 wk ≥30 kg: 162 mg/dose once every 2 wk	Polyarticular JIA		

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 195.2 Therapeutics for Childhood Rheumatic Diseases —cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
IL-6 antagonist	Tocilizumab[a]	≥2 yr and ≥30 kg: 8 mg/kg/dose every 2 wk ≥2 yr and ≤30 kg: 12 mg/kg/dose every 2 wk	Systemic JIA	Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections	CBC, LFTs, platelet count, serum lipid profile
Intravenous immune globulin	IVIG[c]	1,000-2,000 mg/kg IV infusion For JDMS, give monthly	Kawasaki disease JDMS SLE	Infusion reaction, aseptic meningitis, renal failure	Serum creatinine, BUN, IgG level
Cytotoxic	Cyclophosphamide	0.5-1 g/m^2 IV (max 1.5 g) monthly for 6 mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; max 150 mg/daily	SLE Vasculitis JDMS Pulmonary hemorrhage	Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy	CBC
Immunosuppressive	Mycophenolate mofetil	Oral suspension: max 1,200 mg/m^2/day PO (up to 2 g/day) divided bid Capsules: max 1,500 mg/day PO for BSA 1.25-1.5 m^2, 2 g/day PO for BSA >1.5 m^2 divided bid	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML	CBC, BMP
Glucocorticoids	Prednisone[a,d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; max varies by individual (80 mg/daily) Adverse effects are dose dependent; lowest effective dose should be used	SLE JDMS Vasculitis JIA Uveitis Sarcoidosis	Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis	Blood glucose, potassium Blood pressure
	Methylprednisolone[a,d-g]	0.5-1.7 mg/kg/day or 5-25 mg/m^2/day IM/IV in divided doses every 6-12 hr For severe manifestations: 30 mg/kg/dose (max 1 g) daily for 1-5 days	SLE JDMS Vasculitis Sarcoidosis Localized scleroderma		
	Intraarticular	Dose varies by joint and formulation	JIA	Subcutaneous atrophy, skin hypopigmentation, calcification, infection	
	Prednisolone ophthalmic suspension	1-2 drops into eye up to every hr while awake Needs monitoring by ophthalmologist	Uveitis	Ocular hypertension, glaucoma, nerve damage, cataract, infection	Ophthalmologic exam

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines and complete list of known adverse effects.
†Therapeutics used in practice may not have an FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: *a*, JIA; *b*, CAPS; *c*, Kawasaki disease; *d*, sarcoidosis; *e*, SLE; *f*, uveitis; *g*, dermatomyositis.
‡Many more products are available in this class.
bid, Twice daily; BLys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immune globulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Intravenous corticosteroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The IV route allows for higher doses to obtain an immediate, profound antiinflammatory effect. Methylprednisolone 10-30 mg/kg/dose up to a maximum of 1 g, given over 1 hour daily for 1-5 days is the IV preparation of choice. Although generally associated with fewer adverse effects than oral corticosteroids, IV steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular corticosteroids are prescribed by ophthalmologists as ophthalmologic drops or injections into the soft tissue surrounding the globe (sub–Tenon capsule injection) for active uveitis. Long-term ocular corticosteroid use leads to cataract formation and glaucoma. Current ophthalmologic management with methotrexate and biologic therapy, especially TNF inhibitors, have significantly decreased the frequency of eye complications of JIA-associated uveitis.

Intraarticular corticosteroids are frequently used as initial therapy for children with oligoarticular JIA or as bridge therapy while awaiting efficacy of a DMARD in polyarticular disease. Most patients have significant clinical improvement within 3 days. Duration of response depends on steroid preparation used, joint affected, and arthritis subtype; the anticipated response rate to knee injection is 60–80% at 6 months. Intraarticular administration may result in subcutaneous atrophy and hypopigmentation of the skin at the injection site, as well as subcutaneous calcifications along the needle track.

JANUS KINASE INHIBITORS

Another effective class of DMARDs is the Janus kinase inhibitors, collectively known as **JAKinibs**. In immune cells, these drugs inhibit intracellular signaling through the JAK-STAT pathway in immune cells by binding to various Janus kinases (in humans, JAK 1, JAK 2, JAK 3, and TYK2), thereby negating the response to extracellular cytokine ligation of immune cell receptors. Inhibition affects lymphocyte activation, function, and survival. Many JAKinibs are currently available, including tofacitinib, baricitinib, ruxolitinib, and upadacitinib. Currently, only tofacitinib has FDA approval in pediatric rheumatic disease.

Tofacitinib is a small-molecule, oral JAKinib of the JAK1, JAK3, and, to a lesser extent, JAK2 enzymes. Tofacitinib has FDA approval for treatment of polyarticular JIA (age ≥2 years and weight ≥10 kg) with twice-daily dosing: 3.2 mg bid for 10-20 kg, 4 mg bid for 20-40 kg, and 5 mg bid for >40 kg. It is available as an oral solution (1 mg/mL) and as oral tablets (5 mg). Adverse reactions include increased risk of serious infections, thrombosis including pulmonary and deep venous/arterial, and gastrointestinal perforations; the most common adverse reactions are upper respiratory infections, diarrhea, and headache.

Biologic Agents

Biologic agents are proteins that have been engineered to target and modulate specific components of the immune system, with the goal of decreasing the inflammatory response. Antibodies have been developed to target specific cytokines such as IL-1 and IL-6 or to interfere with specific immune cell function through depletion of β cells or suppression of T-cell activation (Table 195.3). Biologic agents have increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies, and in some cases biologics are first-line interventions. A primary concern is the increased risk of malignancy when biologics are combined with other immunosuppressants.

Tumor Necrosis Factor-α Antagonists

Three TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept, adalimumab, and golimumab). *Etanercept* is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular TNF receptor monomer fused with the Fc domain of human immunoglobulin G_1. Etanercept binds both TNF-α and lymphotoxin-α (formerly called TNF-β) and inhibits their activity. Three fourths of children with active polyarticular JIA that fails to respond to MTX demonstrate response to etanercept after 3 months of therapy. Dosing is 0.8 mg/kg subcutaneously weekly (max 50 mg/dose) or 0.4 mg/kg SC twice weekly (max 25 mg/dose). *Adalimumab* is a fully human anti-TNF monoclonal antibody (mAb) used alone or in combination with MTX. In a placebo-controlled withdrawal-design study, children continuing to receive adalimumab were less likely to experience disease flares (43% vs 71%) even if they were also taking MTX (37% vs 65%). Adalimumab is administered subcutaneously every other week at a dose of 10 mg for children weighing 10 to <15 kg, 20 mg for children weighing 15 to <30 kg, and 40 mg for those weighing ≥30 kg. *Golimumab* is a human mAb that binds to both soluble and transmembrane bioactive forms of TNF. It has FDA approval for use in polyarticular JIA at dosing of 80 mg/m^2 IV with initial doses at 0 and 4 weeks and then every 8 weeks thereafter. Non-FDA approved uses include psoriatic arthritis.

Infliximab, a chimeric mouse-human mAb, was tested in a randomized controlled trial (RCT) for use in JIA but did not achieve study end-points. However, it is FDA approved for pediatric inflammatory bowel disease and has been used "off label" for treatment of polyarticular JIA, uveitis, Behçet syndrome, and sarcoidosis. *Certolizumab pegol*, a pegylated humanized antibody against TNF, is approved by the FDA for RA, psoriatic arthritis, and ankylosing spondylitis in adults and is currently in pediatric trials for treatment of polyarticular JIA.

The most common adverse effects are injection site reactions that diminish over time. TNF blockade is associated with an increased frequency of serious systemic infections, including sepsis, dissemination of latent tuberculosis (TB), and invasive fungal infections in endemic areas. TNF blockade should not be initiated in patients with a history of chronic or frequent recurrent infections. TB testing should be done before initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. Theoretically, the risk of malignancy increases with TNF-α antagonists. Case reports describe the development of lupus-like syndromes, leukocytoclastic vasculitis, interstitial lung disease, demyelinating syndromes, antibody formation to the drug, rashes, cytopenias, anaphylaxis, serum sickness, and other reactions. The benefit/risk profile appears favorable after a decade of experience with this therapeutic class; the safety of longer-term suppression of TNF function is unknown.

Modulator of T-Cell Activation

Abatacept is a selective inhibitor of T-cell costimulation resulting in T-cell anergy. It is FDA approved for treatment of moderate to severe polyarticular JIA. In a double-blind withdrawal RCT in children whose disease had not responded to DMARDs, 53% of placebo-treated patients vs 20% of abatacept-treated patients experienced disease flares during the withdrawal period. The frequency of adverse events did not differ between the

Table 195.3 Method of Action of Biologic Therapies Studied in Juvenile Idiopathic Arthritis

DRUG	METHOD OF ACTION
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
Adalimumab	A humanized IgG_1 monoclonal antibody that binds to TNF-α
Abatacept	Soluble, fully human fusion protein of the extracellular domain of CTLA-4, linked to a modified Fc portion of the human IgG_1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
Tocilizumab	A humanized anti–human IL-6 receptor monoclonal antibody
Anakinra	An IL-1 receptor antagonist (IL-1RA)

CTLA, Cytotoxic T lymphocyte–associated antigen; IL, interleukin; TNF, tumor necrosis factor.

From Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis. Part 2. The era of biologicals. *Arch Dis Child Educ Pract Ed.* 2009;94:151–156.

groups. Abatacept is administered IV every other week for three doses (<75 kg: 10 mg/kg/dose; 75-100 kg: 750 mg/dose; >100 kg: 1,000 mg/dose; maximum 1,000 mg/dose at 0, 2, and 4 weeks) and then monthly thereafter. Abatacept administered by SC injection was given FDA approval in March 2017 for children ≥4 years old for treatment of polyarticular JIA at doses given weekly: 50 mg for 10-25 kg, 87.5 mg for ≥25 to <50 kg, and 125 mg for ≥50 kg.

B-Cell Depletion

Rituximab is a chimeric mAb to the antigen CD20, a transmembrane protein on the surface of B-cell precursors and mature B lymphocytes. This antibody induces B-cell apoptosis and causes depletion of circulating and tissue-based B cells. Antibody production is not completely abrogated because plasma cells are not removed. Rituximab has FDA approval for treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children greater than 2 years of age. It is approved for treatment of adult RA and may also have a role in treatment of SLE, particularly its hematologic manifestations. Adverse events include serious infusion reactions, cytopenias, hepatitis B virus reactivation, hypogammaglobulinemia, infections, serum sickness, vasculitis, and a rare but fatal side effect, *progressive multifocal leukoencephalopathy*. Resistance to rituximab may develop over time in patients being treated for lymphoma.

Belimumab is a human mAb to B-lymphocyte stimulator **(BLys)** that negatively affects B-cell proliferation, differentiation, and long-term survival by inhibiting binding of BLys to its receptors on B cells. It is FDA approved for treatment of pediatric SLE in children age 5 years and older. For this indication, it is given as an IV infusion (10 mg/kg) every 2 weeks for the first three doses, then every 4 weeks thereafter. Side effects associated with belimumab include increased risk of serious infections, allergic (hypersensitivity) reactions, and changes in mood.

Interleukin-1 Antagonists

Anakinra, a recombinant form of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the natural receptor, interrupting the cytokine proinflammatory cascade. Anakinra has been approved for RA in adults. In meta-analyses of treatments for RA, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of systemic JIA (sJIA) and other autoinflammatory syndromes, such as cryopyrin-associated periodic syndrome (CAPS). The medication is dosed SC, 1-2 mg/kg, once daily. An IL-1β mAb, *canakinumab,* is FDA approved for use in CAPS, dosed SC every 8 weeks, and sJIA, dosed SC every 4 weeks. Adverse reactions include significant injection site reactions and increased bacterial infections.

Interleukin-6 Receptor Antagonist

Tocilizumab is an anti–IL-6 receptor antibody binding to both soluble and membrane-associated receptors. Tocilizumab has FDA approval for treatment of sJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 weeks (sJIA) to 4 weeks (polyarticular JIA), and SC for polyarticular JIA 162 mg every 3 weeks for those <30 kg and every 2 wk for ≥30 kg.

Intravenous Immune Globulin

Intravenous immunoglobulin (IVIG) is thought to be beneficial in various clinical conditions. IVIG significantly improves the short- and long-term natural history of Kawasaki disease. Open studies have supported benefit for juvenile dermatomyositis, lupus-associated thrombocytopenia, and polyarticular JIA. IVIG is given as 1-2 g/kg/dose, administered once monthly. It has been occasionally associated with severe, systemic allergy-like reactions and postinfusion aseptic meningitis (headache, stiff neck) (Table 195.4).

Table 195.4 Predisposing Factors for Immunoglobulin-Induced Adverse Effects

ADVERSE EFFECT	PREDISPOSING FACTORS
Flulike symptoms	High dose, rapid infusion rate, accompanying infection, previous adverse effects
Dermatologic adverse effects	High dose, rapid infusion rate, accompanying infection, male patients with chronic inflammatory demyelinating polyneuropathy
Arrhythmia and hypotension	History of heart disease
Transfusion-related acute lung injury	Rapid infusion rate
Thrombotic events	High dose, rapid infusion rate, advanced age, being bedridden, diabetes mellitus, hypertension, dyslipidemia, prior/current thrombosis, preexisting atherosclerotic disease, elevated serum viscosity, oral contraceptive use, hereditary hypercoagulable state, idiopathic thrombocytopenic purpura
Aseptic meningitis	High dose
Renal impairment	Rapid infusion rate, advanced age, renal insufficiency, nephrotic syndrome, diabetes mellitus, dehydration, sepsis paraproteinemia, nephrotoxic drugs, hemolysis, sucrose-containing preparations
Hemolysis	High dose, rapid infusion rate, non-O blood group, underlying inflammatory state

From Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. *Frontiers Immunol.* 2018;9:1299, Table 2.

Cytotoxics

Cyclophosphamide

Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by inhibition of the S2 phase of mitosis. The subsequent decrease in numbers of T and B lymphocytes results in diminished humoral and cellular immune responses. Cyclophosphamide infusions (500-1,000 mg/m^2) given monthly for 6 months, then every 3 months for 12-18 months, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe CNS lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody (ANCA)–associated vasculitis and other forms of systemic vasculitis, as well as interstitial lung disease or pulmonary hemorrhage associated with rheumatic disease.

Cyclophosphamide is a potent cytotoxic drug associated with significant toxicities. Potential short-term adverse effects include nausea, vomiting, anorexia, alopecia, mucositis, hemorrhagic cystitis, and bone marrow suppression. Long-term complications include an increased risk for sterility and cancer, especially leukemia, lymphoma, and bladder cancer. In adult women with lupus treated with IV cyclophosphamide, 30–40% become infertile; the risk of ovarian failure appears to be significantly lower in adolescent and premenarchal girls. Ovarian suppression with an inhibitor of gonadotropin-releasing hormone to preserve fertility is currently being studied.

Other Drugs

Azathioprine is sometimes used to treat ANCA-associated vasculitis after induction therapy or to treat SLE. *Cyclosporine* has been used occasionally in the treatment of dermatomyositis on the basis of uncontrolled studies and is helpful in the treatment of macrophage activation syndrome complicating sJIA (see Chapter 207). Case reports describe the successful use of *thalidomide,* or its analog *lenalidomide,* as treatment for sJIA, inflammatory skin disorders, and Behçet disease.

Several drugs commonly used in the past to treat arthritis are no longer part of standard treatment, including salicylates, gold compounds, and D-penicillamine.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 196

Juvenile Idiopathic Arthritis

Eveline Y. Wu and C. Egla Rabinovich

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult. As a result, several classification schemes exist, each with its own limitations. The former classification of the **American College of Rheumatology (ACR)** uses the term *juvenile rheumatoid arthritis* and categorizes the disease into three onset types (Table 196.1). Attempting to standardize nomenclature, the **International League of Associations for Rheumatology (ILAR)** proposed a different classification using the term *juvenile idiopathic arthritis* (Table 196.2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 197 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 196.3 and 196.4).

EPIDEMIOLOGY

The worldwide incidence of JIA ranges from 0.8 to 22.6 per 100,000 children per year, with prevalence ranges from 7 to 401 per 100,000. These wide-ranging numbers reflect population differences, particularly environmental exposure and immunogenetic susceptibility, along with variations in diagnostic criteria, difficulty in case ascertainment, and lack of population-based data. An estimated 300,000 U.S. children have arthritis, including 100,000 with a form of JIA. **Oligoarthritis** is the most common subtype (40–50%), followed by **polyarthritis** (25–30%) and **systemic JIA** (5–15%) (see Table 196.4). More females than males are affected in both oligoarticular (3:1) and polyarticular (5:1) JIA but are equally affected in systemic JIA (sJIA). The peak age at onset is 2-4 years for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 years and 10-14 years. sJIA occurs throughout childhood, with a peak at 1-5 years.

ETIOLOGY

The etiology and pathogenesis of JIA are not completely understood, although both immunogenetic susceptibility and an external trigger are considered necessary. Twin and family studies suggest a substantial role for genetic factors. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. Variants in major histocompatibility complex (MHC) class I and class II regions have indisputably been associated with different JIA subtypes. Non-HLA candidate loci are also associated with JIA, including polymorphisms in the genes encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor, interleukin (IL)-6 and its receptor, and IL-1α. Possible nongenetic triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

Table 196.1 Criteria for the Classification of Juvenile Rheumatoid Arthritis

Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in one or more joints
Duration of disease: ≥6 wk
Onset type defined by type of articular involvement in the first 6 mo after onset:
Polyarthritis: five or more inflamed joints
Oligoarthritis: four or fewer inflamed joints
Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
Exclusion of other forms of juvenile arthritis

Adapted from Cassidy JT, Levison JE, Bass JC, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum*. 1986;29:274–281.

PATHOGENESIS

JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T-lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T lymphocytes specific for synovial non–self-antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe articular disease.

sJIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an **autoinflammatory disorder**, which may transition to an autoimmune process once actual arthritis develops (Fig. 196.1). The IL-1 family of cytokines is key to disease pathogenesis, which is strongly supported by the marked responsiveness to IL-1 inhibitors. IL-18 in particular is a central driver, and serum IL-18 levels are markedly elevated in children with sJIA.

All these immunologic abnormalities cause inflammatory synovitis, characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T lymphocytes (Fig. 196.2). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 196.3 and 196.4).

CLINICAL MANIFESTATIONS

Arthritis must be present ≥6 weeks to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of two or more of the following signs: limitation in range of motion (ROM), tenderness or pain on motion, and warmth. Initial symptoms may be subtle or acute and often include morning stiffness with a limp or gelling after inactivity. Easy fatigability and poor sleep quality may be present. Involved joints are often swollen, warm to the touch, and uncomfortable on movement or palpation with reduced ROM, but usually are not erythematous. Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths. Continued inflammation stimulates rapid and premature closure of the growth plate, resulting in shortened bones.

Oligoarthritis is defined as involving four or fewer joints within the first 6 months of disease onset, and often only a single joint is involved (see Table 196.4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 196.5). Isolated involvement of upper-extremity large joints is less common. Those in whom disease never develops in four or more joints are regarded as having **persistent oligoarticular JIA**, whereas evolution of disease in five or more joints after 6 months changes the classification to **extended oligoarticular JIA** and is associated with a worse prognosis. Isolated involvement of the hip is *almost never* a presenting sign and suggests ERA (see Chapter 197) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) test confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 196.5). ANA positivity may also be correlated with younger age at disease onset, females, asymmetric arthritis, and fewer involved joints over time.

Table 196.2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic JIA	Arthritis in one or more joints with, or preceded by, fever of ≥2 wk in duration that is documented to be daily (quotidian*) for at least 3 days and accompanied by one or more of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis†	a. Psoriasis or a history of psoriasis in patient or first-degree relative b. Arthritis in an HLA-B27–positive male beginning after the sixth birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis, or history of one of these disorders in a first-degree relative d. Presence of IgM RF on at least two occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting one to four joints during the first 6 mo of disease; two subcategories are recognized: 1. Persistent oligoarthritis—affecting four or fewer joints throughout the disease course 2. Extended oligoarthritis—affecting five or more joints after the first 6 mo of disease	a, b, c, d (above) *plus* e. Presence of systemic JIA in the patient
Polyarthritis (RF negative)	Arthritis affecting five or more joints during the first 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF positive)	Arthritis affecting five or more joints during the first 6 mo of disease; two or more tests for RF at least 3 mo apart during the first 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in first-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis¶ or arthritis or enthesitis with at least two of the following: 1. Presence of or history of sacroiliac joint tenderness or inflammatory lumbosacral pain, or both** 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis in first-degree relative	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or two or more of the above categories	

**Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once daily and returns to 37°C (98.6°F) between fever peaks.
†*Serositis* refers to pericarditis, pleuritis, or peritonitis or some combination of the three.
‡*Dactylitis* is swelling of one or more digit(s), usually in an asymmetric distribution, that extends beyond the joint margin.
§A minimum of two pits on any one or more nails at any time.
¶*Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
***Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.
IBD, Inflammatory bowel disease; RF, rheumatoid factor.
From Firestein GS, Budd RC, Harris ED Jr, et al., eds. *Kelley's Textbook of Rheumatology,* 8th ed. Philadelphia: Saunders; 2009.

Table 196.3 Characteristics of ACR and ILAR Classifications of Childhood Chronic Arthritis

PARAMETER	ACR (1977)	ILAR (1997)
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
Minimum duration	≥6 wk	≥6 wk
Age at onset	<16 yr	<16 yr
Four or fewer joints in first 6 mo after presentation	Pauciarticular	Oligoarthritis: Persistent: four or fewer joints for course of disease Extended: four or more joints after 6 mo
Four or more joints in first 6 mo after presentation	Polyarticular	Polyarthritis, RF negative Polyarthritis, RF positive
Fever, rash, arthritis	Systemic onset	Systemic
Other categories included	Exclusion of other forms	Psoriatic arthritis Enthesitis-related arthritis Undifferentiated: Fits no other category Fits more than one category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 197)	Yes

ACR, American College of Rheumatology; ILAR, International League of Associations for Rheumatology; RF, rheumatoid factor.

Table 196.4 Overview of Main Features of Subtypes of Juvenile Idiopathic Arthritis (JIA)

ILAR SUBTYPE	PEAK AGE AT ONSET (yr)	FEMALE:MALE RATIO	% OF ALL JIA CASES	ARTHRITIS PATTERN	EXTRAARTICULAR FEATURES	LABORATORY INVESTIGATIONS	NOTES ON THERAPY
Systemic arthritis	1-5	1:1	5-15	Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets ↑↑ (normal or ↓ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1 or IL-6 inhibitors in resistant cases or as first-line therapy
Oligoarthritis	2-4	3:1	40-50 (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in 30% of cases	ANA positive in 60%; other test results usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular corticosteroids; MTX occasionally required
Polyarthritis:							
RF negative	2-4 and 10-14	3:1 and 10:1	20-35	Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint	Uveitis in 10%	ANA positive in 40%; RF negative; ESR ↑ or ↑↑; CRP ↑ or normal; mild anemia	Standard therapy with MTX and NSAIDs; then, if nonresponsive, anti-TNF agents or other biologics, including abatacept, indicated as first-line therapy
RF positive	9-12	9:1	<10	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/ normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	2-4 and 9-11	2:1	5-10	Asymmetric arthritis of small or medium-sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑ or normal; mild anemia	NSAIDs and intraarticular corticosteroids; MTX, anti-TNF agents
Enthesitis-related arthritis	9-12	1:7	5-10	Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis)	Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease	80% of patients positive for HLA-B27	NSAIDs and intraarticular corticosteroids; consider sulfasalazine as alternative to MTX; anti-TNF agents

ILAR, International League of Associations for Rheumatology; ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MAS, macrophage activation syndrome; MTX, methotrexate; NSAIDs, nonsteroidal antiinflammatory drugs; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.
From Firestein GS, Budd RC, Harris ED Jr, et al., eds. *Kelley's Textbook of Rheumatology*, 8th ed. Philadelphia: Saunders; 2009.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

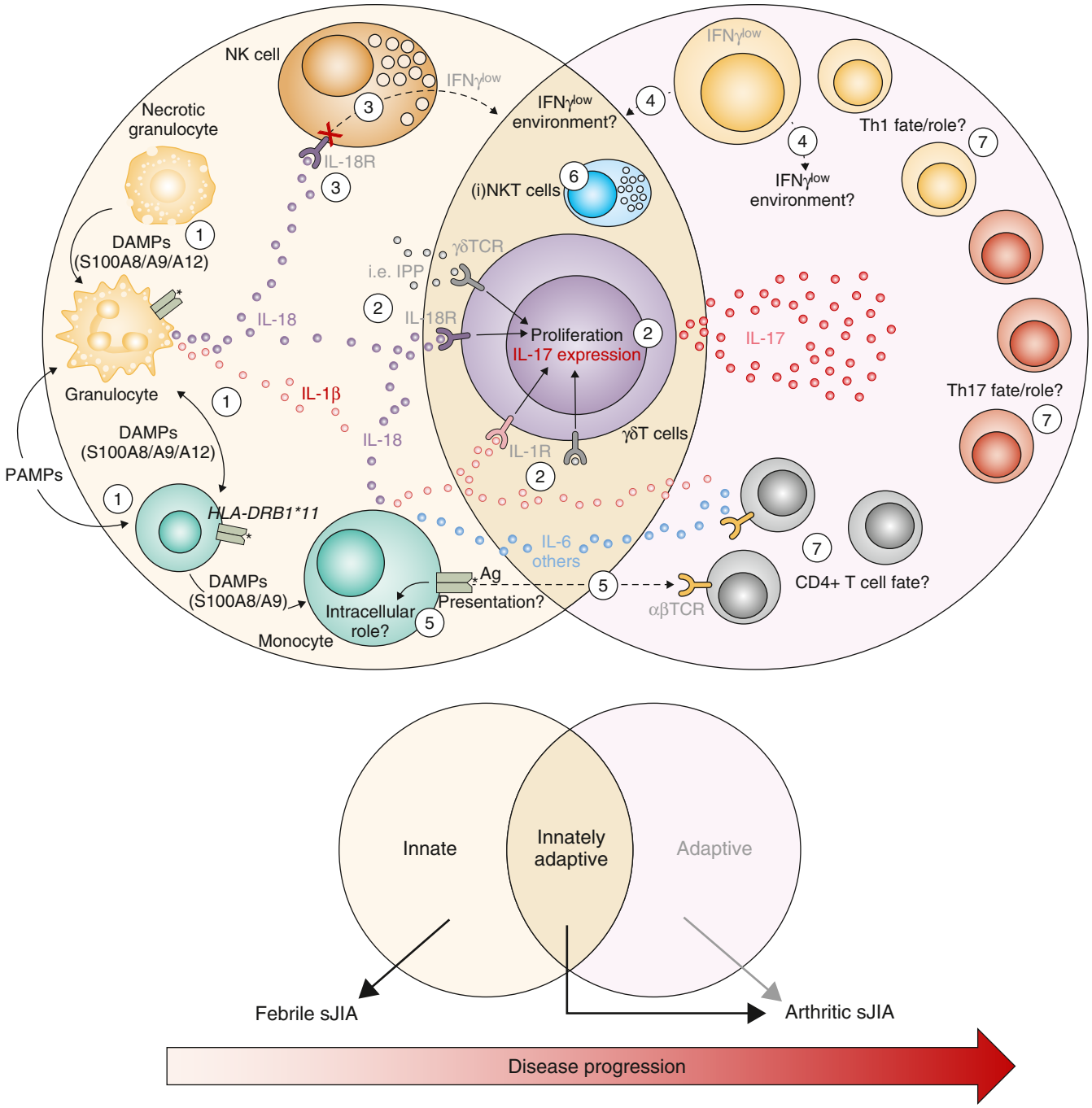

Fig. 196.1 Innately adaptive or truly autoimmune: a pathophysiologic model for disease progression in systemic juvenile idiopathic arthritis (sJIA). Innate immune cells, such as myeloid cells (granulocytes, monocytes) and natural killer (NK) cells, are relevant during the acute febrile phase of systemic JIA. *(1)* Myeloid cells release interleukin-1 (IL-1) family cytokines (IL-1β, IL-18) and other proinflammatory cytokines, which can either be triggered by infection (pathogen- associated molecular patterns [PAMPs]) or result from pattern-recognition receptor activation by damage-associated molecular patterns (DAMPs) released from stressed or necrotic cells. *(2)* Together with γδ T-cell receptor (γδ TCR) activation by endogenous ligands (i.e., isopentenyl pyrophosphate [IPP]) or bacterial ligands, IL-1 and IL-18 can trigger IL-17 expression from γδ T cells, while *(3)* IL-18 fails to trigger interferon-γ (IFNγ) expression from NK cells because of a defective IL-18 receptor (IL-18R). *(4)* Similarly, systemic JIA Th1 cells express only low levels of IFNγ. Both cell types may contribute to hypophysiologic IFNγ levels, potentially promoting IL-17 expression in disease. Although a genetic association or alterations in frequencies have been reported, the pathomechanistic roles of *(5)* HLA- DRB1*11 (whether antigen [Ag] presentation or intracellular function) or *(6)* invariant NKT (iNKT) and *(7)* CD4+ T cells in disease progression are yet largely unclear. Thus current data imply that innately adaptive immune cells bridging innate and adaptive immunity, rather than classic B or T lymphocytes, play a central role in promoting disease progression in systemic JIA. *(From Kessel C, Hedrich CM, Foeil D. Innately adaptive or truly autoimmune: is there something unique about systemic juvenile idiopathic arthritis?* Arth Rheumatol. *2020;72:210–219, Fig. 2, p. 214)*

Polyarthritis is characterized by inflammation of five or more joints in both upper and lower extremities (Figs. 196.6 and 196.7). Rheumatoid factor (RF)–positive polyarthritis resembles the characteristic symmetric presentation of adult rheumatoid arthritis. **Rheumatoid nodules** on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals (Fig. 196.8). **Micrognathia** reflects chronic temporomandibular joint



Fig. 196.2 Synovial biopsy specimen from a 10-yr-old child with oligoarticular juvenile idiopathic arthritis. There is a dense infiltration of lymphocytes and plasma cells in the synovium.



Fig. 196.3 Arthroscopy in the shoulder of a child with juvenile idiopathic arthritis showing pannus formation and cartilage erosions. *(Courtesy Dr. Alison Toth.)*

disease (Fig. 196.9). Cervical spine involvement (Fig. 196.10), manifesting as decreased neck extension, occurs with a risk of atlantoaxial subluxation and neurologic sequelae. Hip disease may be subtle, with findings of decreased or painful ROM on examination (Fig. 196.11).

Systemic JIA is characterized by arthritis (may not be evident on initial presentation), fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis). The characteristic fever, defined as spiking temperatures to ≥39°C (102.2°F), occurs on a daily or twice-daily basis for at least 2 weeks, with a rapid return to normal or subnormal temperatures (Fig. 196.12). The fever is often present in the evening and is frequently accompanied by a characteristic faint, erythematous, macular rash. The evanescent **salmon-colored lesions**, classic for sJIA, are linear or circular and are usually distributed over the trunk and proximal extremities (Fig. 196.13). The classic rash is nonpruritic and migratory with lesions lasting <1 hour. **Koebner phenomenon**, a cutaneous hypersensitivity in which classic lesions are brought on by superficial trauma, is often present. Heat can also evoke rash. Fever, rash, hepatosplenomegaly, and lymphadenopathy are present in >70% of affected children. Without arthritis, the **differential diagnosis** includes the episodic fever (autoinflammatory) syndromes (see Chapter 204), infection (endocarditis, rheumatic fever, brucellosis, multisystem inflammatory syndrome in children [MIS-C]), other rheumatic disorders (systemic lupus erythematosus [SLE], vasculitis syndromes, serum sickness, Kawasaki



Fig. 196.4 MRI with gadolinium of a 10-yr-old child with juvenile idiopathic arthritis (same patient as in Fig. 196.2). The dense white signal in the synovium near the distal femur, proximal tibia, and patella reflects inflammation. MRI of the knee is useful to exclude ligamentous injury, chondromalacia of the patella, and tumor.



Fig. 196.5 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee.

disease, sarcoidosis, Castleman disease), inflammatory bowel disease, hemophagocytic lymphohistiocytosis syndromes, and malignancy (leukemia, neuroblastoma, lymphoma). Some children initially present with only systemic features and evolve over time, but definitive

Table 196.5 Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis

REFERRAL
- Patients should be referred at the time of diagnosis, or suspicion, of JIA

INITIAL SCREENING EXAMINATION
- Should occur as soon as possible and no later than 6 wk from referral
- Symptomatic ocular patients should be seen within a week of referral

ONGOING SCREENING
- Screening at 2-monthly intervals from onset of arthritis for 6 mo
- Followed by 3-4 monthly screening for time outlined below

OLIGOARTICULAR JIA, PSORIATIC ARTHRITIS, AND ENTHESITIS-RELATED ARTHRITIS IRRESPECTIVE OF ANA STATUS, ONSET UNDER 11 YR

AGE AT ONSET (YR)	LENGTH OF SCREENING (YR)
<3	8
3-4	6
5-8	3
9-10	1

POLYARTICULAR, ANA-POSITIVE JIA, ONSET <10 YR

AGE AT ONSET (YR)	LENGTH OF SCREENING (YR)
<6	5
6-9	2

Polyarticular, ANA-negative JIA, onset <7 yr
5-yr screening for all children
Systemic JIA and rheumatoid factor–positive polyarticular JIA
- Uveitis risk very low; however, diagnostic uncertainty in the early stages and overlap of symptoms may mean initial screening is indicated

All categories, onset >11 yr
- 1-yr screening for all children

After stopping immunosuppression (e.g., methotrexate)
- Two-monthly screening for 6 mo, then revert to previous screening frequency as above

After discharge from screening
- Patients should receive advice about regular self-monitoring by checking vision uniocularly once weekly and when to seek medical advice
- Screening may need to continue indefinitely in situations where a young person may be unable to detect a change in vision or be unwilling to seek re-referral
- Annual check by optometrist as a useful adjunct

Data from Clarke SLN, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol*. 2016;14:27.



Fig. 196.6 Hands and wrists of a child with polyarticular juvenile idiopathic arthritis, rheumatoid factor negative. Notice the symmetric involvement of the wrists, metacarpophalangeal joints, and proximal and distal interphalangeal joints. In this photograph, there is cream with occlusive dressing on the patient's right hand in preparation for placement of an intravenous line for administration of a biologic agent.

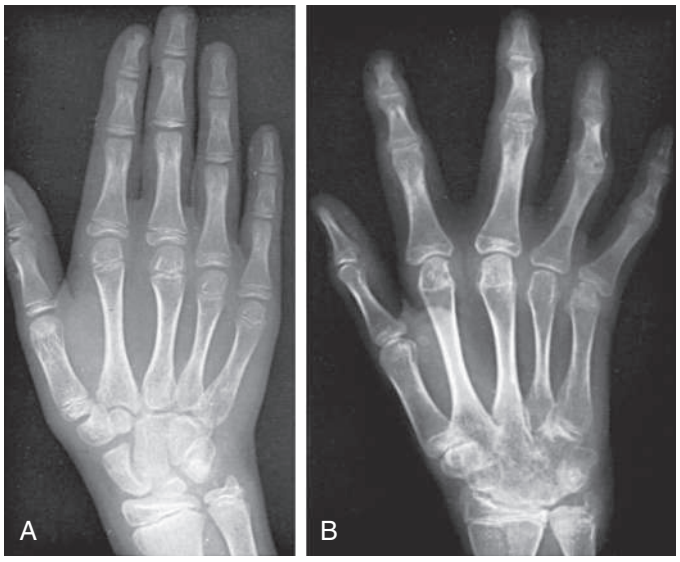

Fig. 196.7 Progression of joint destruction in a child with polyarticular juvenile idiopathic arthritis, rheumatoid factor positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between radiographs. **A,** Radiograph of the hand at onset. **B,** Radiograph taken 4 years later, showing a loss of articular cartilage and destructive changes in the distal and proximal interphalangeal and metacarpophalangeal joints as well as destruction and fusion of wrist bones.

diagnosis requires the presence of arthritis. Arthritis may affect any number of joints, but the course is classically polyarticular; may be very destructive; and can include hip, cervical spine, and temporomandibular joint involvement.

Macrophage activation syndrome (MAS; see Chapter 207) is a rare but potentially fatal complication of sJIA that can occur at any time (onset, medication change, active or remission) during the disease course. It is also referred to as *secondary hemophagocytic syndrome* or *hemophagocytic lymphohistiocytosis* (HLH) (see Chapter 556.2). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. In addition, sJIA-associated MAS and HLH share genetic variants in approximately 35% of patients with sJIA/MAS. MAS classically manifests as acute onset of high-spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. Laboratory evaluation shows thrombocytopenia and leukopenia with elevated liver enzymes, lactate dehydrogenase, ferritin, and triglycerides. Patients may have purpura and mucosal bleeding, as well as elevated fibrin split product values and prolonged prothrombin and partial thromboplastin times. The ESR falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 196.6). An international consensus panel developed a set of classification criteria for sJIA-associated MAS, including hyperferritinemia (>684 ng/mL) and any two of the following: thrombocytopenia (≤181 × 10^9/L), elevated liver enzymes (aspartate transaminase >48 U/L), hypertriglyceridemia (>156 mg/dL), and hypofibrinogenemia (≤360 mg/dL) (see Table 196.6). These criteria apply to a febrile patient suspected of sJIA *and* in the absence of disorders such as immune-mediated thrombocytopenia, infectious hepatitis, familial hypertriglyceridemia, or visceral leishmaniasis. *A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values.* A bone marrow aspiration and biopsy may be helpful in diagnosis, but



Fig. 196.8 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. *(From Rosenberg AM, Oen KG. Polyarthritis. In: Cassiday JT, Petty RE, Laxer RM, et al., eds.* Textbook of Pediatric Rheumatology, 6th ed. *Philadelphia: Saunders; 2011: Fig 15-5, p. 257.)*

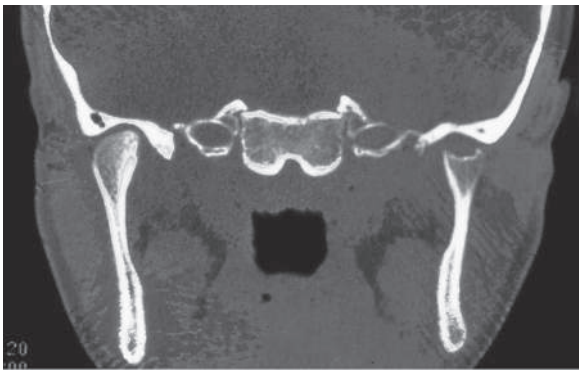

Fig. 196.9 CT scan of the temporomandibular joint of a child with juvenile idiopathic arthritis exhibiting destruction on the right.



Fig. 196.10 Radiograph of the cervical spine of a child with active juvenile idiopathic arthritis showing fusion of the neural arch between joints C2 and C3, narrowing and erosion of the remaining neural arch joints, obliteration of the apophyseal space, and loss of the normal lordosis.



Fig. 196.11 Severe hip disease in 13-yr-old male with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The child had received corticosteroids systemically for 9 years.

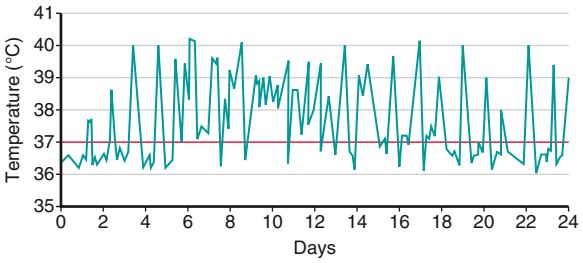

Fig. 196.12 High-spiking intermittent fever in a 3-yr-old child with systemic juvenile idiopathic arthritis. *(From Ravelli A, Martini A. Juvenile idiopathic arthritis.* Lancet *2007;369:767–778.)*

evidence of hemophagocytosis is not always evident. Emergency treatment with high-dose intravenous methylprednisolone, cyclosporine, or anakinra may be effective. Severe cases may require therapy similar to that for primary HLH (see Chapter 556.2).

An inflammatory lung disease has also recently been recognized as a rare but life-threatening complication in children with sJIA. Children can present with little to no respiratory symptoms; acute clubbing can be an early indicator. The predominant pathology is pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia. Compared with children without lung disease, children with sJIA and lung disease are younger at diagnosis, have a history of MAS, have higher serum IL-18 levels, and have higher exposure and adverse reaction rates to cytokine inhibitors. Given the more severe disease course, lung disease in children with sJIA requires a high index of suspicion and prompt evaluation.

Bone mineral metabolism and skeletal maturation are adversely affected in children with JIA, regardless of subtype. Children with JIA have decreased bone mass (osteopenia), which appears to be associated with increased disease activity. Increased levels of cytokines such as TNF-α and IL-6, both key regulators in bone metabolism, have deleterious effects on bone both within the joint and systemically in the axial and appendicular bones. Abnormalities of skeletal maturation become most prominent during the pubertal growth spurt.

DIAGNOSIS

JIA is a clinical diagnosis without any diagnostic laboratory tests. The meticulous clinical exclusion of other diseases and many mimics is therefore essential. Laboratory studies, including tests for ANA and RF,

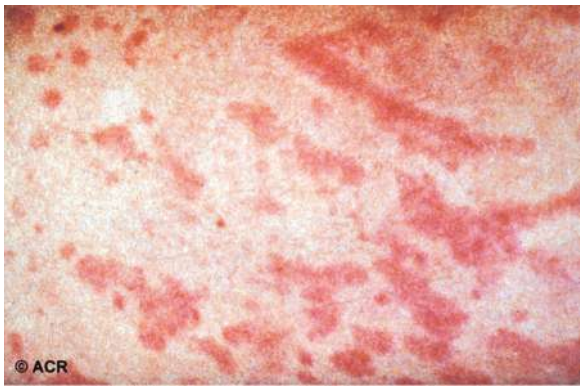

Fig. 196.13 The rash of systemic juvenile idiopathic arthritis is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. *(From American College of Rheumatology.* Clinical Slide Collection on the Rheumatic Diseases. *Atlanta, GA: ACR. Copyright 1991, 1995, 1997.)*

Table 196.6 Macrophage Activation Syndrome (MAS)

LABORATORY FEATURES*
1. Cytopenias
2. Abnormal liver function tests
3. Coagulopathy (hypofibrinogenemia)
4. Decreased erythrocyte sedimentation rate
5. Hypertriglyceridemia
6. Hyponatremia
7. Hypoalbuminemia
8. Hyperferritinemia
9. Elevated sCD25 and sCD163
CLINICAL FEATURES*
1. Nonremitting fever
2. Hepatomegaly
3. Splenomegaly
4. Lymphadenopathy
5. Hemorrhages
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)
HISTOPATHOLOGIC FEATURES*
1. Macrophage hemophagocytosis in the bone marrow aspirate
2. Increased CD163 staining of the bone marrow
PROPOSED CRITERIA FOR MAS IN SJIA†
1. Serum ferritin >684 ng/mL *and*
2. Any two of the following:
• Thrombocytopenia (≤181 × 10^9/L)
• Elevated liver enzymes (aspartate transaminase >48 U/L)
• Hypertriglyceridemia (>156 mg/dL)
• Hypofibrinogenemia (≤360 mg/dL)

*From Ravelli A, Grom A, Behrens E, Cron R. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: Diagnosis, genetics, pathophysiology and treatment. *Genes Immun.* 2012;13:289–298.

†From Ravelli A, Minoia F, Davì S, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative. *Arthritis Rheumatol.* 2016;68:566–576.

are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 196.1, 196.3, and 196.4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for arthritis is broad, and a careful, thorough investigation for other underlying etiology is imperative (Table 196.7). History, physical examination, laboratory tests, and radiography may help exclude other possible causes. Arthritis can be a presenting manifestation for any of the multisystem rheumatic diseases of childhood, including SLE (see Chapter 199), juvenile dermatomyositis (see Chapter 200), sarcoidosis (see Chapter 209), and the vasculitic syndromes (see Chapter 210). In scleroderma (see Chapter 201), limited ROM caused by sclerotic skin overlying a joint may be confused with sequelae from chronic inflammatory arthritis. **Acute rheumatic fever** is characterized by exquisite joint pain and tenderness, remittent fever, and migratory polyarthritis. **Autoimmune hepatitis** can also be associated with an acute arthritis.

Many infections are associated with arthritis, and a recent history of infectious symptoms may help make a distinction. Viruses, including parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, and HIV, can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 198). **Lyme disease** should be considered in children with oligoarthritis living in or visiting endemic areas (see Chapter 268). Although a history of tick exposure, preceding flulike illness, and subsequent rash should be sought, these are not always present. Monoarticular arthritis unresponsive to antiinflammatory treatment may be the result of chronic mycobacterial or other infection, such as *Kingella kingae,* and the diagnosis is established by synovial fluid analysis (polymerase chain reaction [PCR]) or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis (see Chapter 726). Isolated hip pain with limited ROM suggests suppurative arthritis, osteomyelitis (see Chapter 725), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 719).

Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a male child, suggest ERA (see Chapter 197). **Psoriatic arthritis** can manifest as limited joint involvement in an unusual distribution (e.g., small joints of the hand and ankle) years before the onset of cutaneous disease. **Inflammatory bowel disease** may manifest as oligoarthritis, usually affecting joints in the lower extremities, as well as gastrointestinal symptoms, elevations in ESR, and microcytic anemia.

Many conditions present solely with arthralgia (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child age 4-12 years complaining of leg pain in the evening with normal investigative studies and no morning symptoms. Nocturnal pain that awakens the child also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 211.3).

Children with **leukemia** or **neuroblastoma** may have joint or bone pain resulting from malignant infiltration of the bone, synovium, or more often the bone marrow, sometimes months before demonstrating lymphoblasts on peripheral blood smear. Physical examination may reveal no tenderness, a deeper pain with palpation of the bone, or pain out of proportion to exam findings. Malignant pain often awakens the child from sleep and may cause cytopenias. Because platelets are an acute-phase reactant, a high ESR with leukopenia and a low-normal platelet count may also be a clue to underlying leukemia. In addition, the characteristic quotidian fever of sJIA is absent in malignancy. Bone marrow examination is necessary for diagnosis. Some diseases, such as cystic fibrosis, diabetes mellitus, and the glycogen storage diseases, have associated arthropathies. Swelling that extends beyond the joint can be a sign of lymphedema or IgA vasculitis (formerly Henoch-Schönlein purpura; see Chapter 210.1). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 165), such as common variable immunodeficiency and X-linked agammaglobulinemia. Skeletal dysplasias associated with a degenerative arthropathy are diagnosed from their characteristic radiologic abnormalities.

Systemic onset of JIA often presents as a fever of unknown origin (see Chapter 222). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat-scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 204), malignancy (leukemia, lymphoma, neuroblastoma), and HLH.

Table 196.7 Conditions Causing Arthritis or Extremity Pain

RHEUMATIC AND INFLAMMATORY DISEASES
Juvenile idiopathic arthritis
Systemic lupus erythematosus
Juvenile dermatomyositis
Polyarteritis nodosa
Scleroderma
Sjögren syndrome
Behçet disease
Overlap syndromes
Antineutrophilic cytoplasmic antibody (ANCA)–associated vasculitis
Sarcoidosis
Kawasaki syndrome
IgA vasculitis (formerly Henoch-Schönlein purpura)
Chronic recurrent multifocal osteomyelitis

SERONEGATIVE SPONDYLOARTHROPATHIES
Juvenile ankylosing spondylitis
Inflammatory bowel disease
Psoriatic arthritis
Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions

INFECTIOUS ILLNESSES
Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella kingae,* pneumococcal, gonococcal, *Haemophilus influenzae*)
Lyme disease
Viral illness (parvovirus, rubella, mumps, Epstein-Barr, hepatitis B, chikungunya)
Fungal arthritis
Mycobacterial infection
Spirochetal infection
Endocarditis

REACTIVE ARTHRITIS
Acute rheumatic fever
Reactive arthritis (postinfectious caused by *Shigella, Salmonella, Yersinia, Chlamydia,* post-streptococcal, or meningococcus)
Serum sickness
Toxic synovitis of the hip
Postimmunization

IMMUNODEFICIENCIES
Hypogammaglobulinemia
Immunoglobulin A deficiency
Common variable immunodeficiency disease (CVID)
Human immunodeficiency virus (HIV)

CONGENITAL AND METABOLIC DISORDERS
Gout
Pseudogout
Mucopolysaccharidoses
Thyroid disease (hypothyroidism, hyperthyroidism)
Hyperparathyroidism
Vitamin C deficiency (scurvy)
Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome)
Fabry disease
Farber disease
Fucosidosis
Amyloidosis (familial Mediterranean fever)

BONE AND CARTILAGE DISORDERS
Trauma
Patellofemoral syndrome
Hypermobility syndromes
Osteochondritis dissecans
Avascular necrosis (including Legg-Calvé-Perthes disease)
Hypertrophic osteoarthropathy
Slipped capital femoral epiphysis
Osteolysis
Benign bone tumors (including osteoid osteoma)
Langerhans cell histiocytosis
Rickets
Idiopathic multicentric osteolysis
Camptodactyly-arthropathy-coxa vara-pericarditis syndrome
Progressive pseudorheumatoid dysplasia
Pachydermodactyly

NEUROPATHIC DISORDERS
Peripheral neuropathies
Carpal tunnel syndrome
Charcot joints

NEOPLASTIC DISORDERS
Leukemia
Neuroblastoma
Lymphoma
Bone tumors (osteosarcoma, Ewing sarcoma)
Histiocytic syndromes
Synovial tumors

HEMATOLOGIC DISORDERS
Hemophilia
Hemoglobinopathies (including sickle cell disease)

MISCELLANEOUS DISORDERS
Autoinflammatory diseases
Recurrent multifocal osteomyelitis
Pigmented villonodular synovitis
Plant-thorn synovitis (foreign body arthritis)
Myositis ossificans
Eosinophilic fasciitis
Tendinitis (overuse injury)
Raynaud phenomenon
Hemophagocytic syndromes

PAIN SYNDROMES
Fibromyalgia
Growing pains
Depression (with somatization)
Complex regional pain syndrome

LABORATORY FINDINGS

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell (WBC) and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and CRP, although it is not unusual for both to be normal in children with JIA.

Elevated ANA titers are present in 40–85% of children with oligoarticular or polyarticular JIA but are rare with sJIA. ANA seropositivity is associated with increased risk of **chronic uveitis** in JIA. Approximately 5–15% of patients with polyarticular JIA are seropositive for RF. Anti–cyclic citrullinated peptide antibody, as with RF, is a marker of more aggressive disease. Both ANA and RF seropositivity can occur in association with transient events, such as viral infection.

Children with sJIA usually have striking elevations in inflammatory markers and WBC and platelet counts. Hemoglobin levels are low, typically 7-10 g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high, except in MAS. Although immunoglobulin levels tend to be high, ANA and RF are uncommon. Ferritin values are typically elevated and can be markedly increased in MAS (>10,000 ng/mL). In the setting of MAS, all cell lines have the potential to decline precipitously because of the consumptive process. A low or normal WBC count and/or platelet count in a child with active sJIA should raise concerns for MAS.



Fig. 196.14 Early (6 month duration) radiographic changes of juvenile idiopathic arthritis. Soft tissue swelling and periosteal new bone formation appear adjacent to the second and fourth proximal interphalangeal joints.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 196.14). Continued active disease may lead to subchondral erosions, loss of cartilage with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in the cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 196.10), may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 196.15).

TREATMENT

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 195).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 196.8). Those who have no or partial response after 4-6 weeks of treatment with NSAIDs or who have functional limitations such as joint contracture or leg-length discrepancy benefit from injection of intraarticular corticosteroids. *Triamcinolone hexacetonide* is a long-lasting preparation that provides a prolonged response. A substantial fraction of patients with oligoarthritis show no response to NSAIDs and injections and therefore require treatment with *disease-modifying antirheumatic drugs (DMARDs),* including conventional synthetic DMARDs (csDMARDs) like methotrexate, and, if no response, biologic DMARDs (bDMARDs) like TNF inhibitors.

NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. *Methotrexate* is the oldest and least toxic of the csDMARDs available for adjunctive therapy. It may take 6-12 weeks to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a bDMARD. bDMARDs that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrate excellent disease control. TNF-α antagonists (e.g., *etanercept, adalimumab, golimumab*) are used to treat children with an inadequate response to methotrexate, poor prognostic factors, or severe disease onset. Early aggressive therapy with a combination of methotrexate and a TNF-α antagonist may result in earlier achievement of clinically inactive disease. *Abatacept,* a selective inhibitor of T-cell activation, and *tocilizumab,* an IL-6

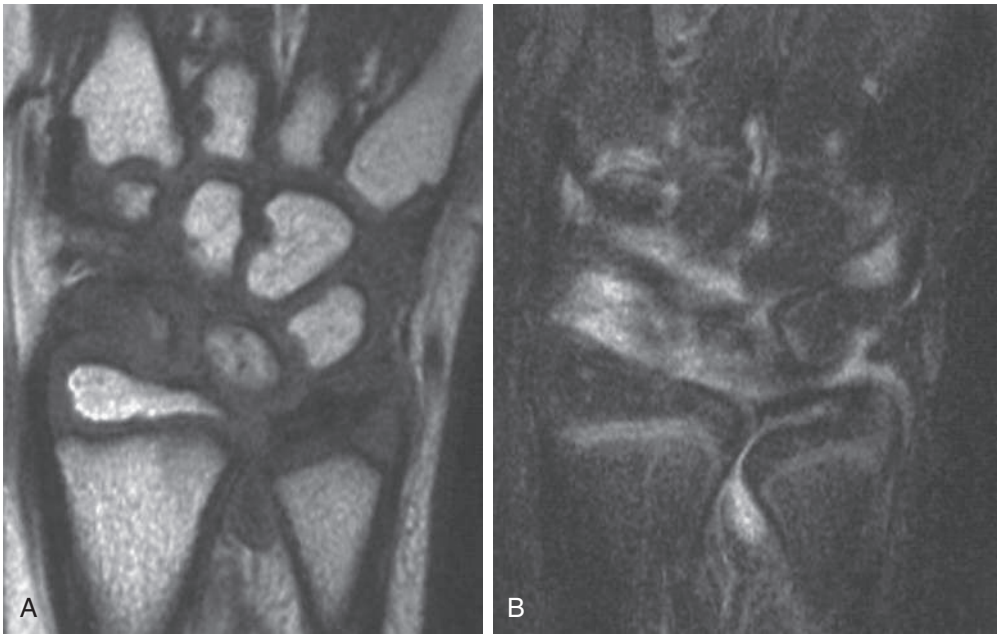

Fig. 196.15 MRI of the wrist in a child with wrist arthritis. **A,** Multiple erosions of carpal bones. **B,** After administration of gadolinium contrast agent, uptake is consistent with active synovitis.

Table 196.8 Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

TYPICAL MEDICATIONS	TYPICAL DOSES	JIA SUBTYPE	SIDE EFFECT(S)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS			
Naproxen	15 mg/kg/day PO divided bid (maximum dose 500 mg bid)	Polyarthritis Systemic Oligoarthritis	Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen	40 mg/kg/day PO divided tid (maximum dose 800 mg tid)	Same as above	Same as above
Meloxicam	0.125 mg/kg PO once daily (maximum dose 15 mg daily)	Same as above	Same as above
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS			
Methotrexate	0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine	Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)	Polyarthritis	GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide*	10-20 mg PO daily	Polyarthritis	GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
BIOLOGIC AGENTS			
Anti–Tumor Necrosis Factor-α			
Etanercept	0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab*	3-10 mg/kg IV q4-8wk	Same as above	Same as above, infusion reaction
Adalimumab	10 to <15 kg: 10 mg SC every other week 15 to <30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	Same as above	Same as above
Golimumab	80 mg/m^2 IV wk 0 and 4 and then q8 wk	Same as above	Same as above
Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin			
Abatacept	<75 kg: 10 mg/kg/dose IV q4wk 75-100 kg: 750 mg/dose IV q4wk >100 kg: 1,000 mg/dose IV q4wk SC once weekly: 10 to <25 kg: 50 mg ≥25 to <50 kg: 87.5 mg ≥50 kg: 125 mg	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction
Anti-CD20			
Rituximab*	750 mg/m^2 IV 2 wk × 2 (maximum dose 1,000 mg)	Polyarthritis	Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
Interleukin-1 Inhibitors			
Anakinra*	1-2 mg/kg SC daily	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	4 mg/kg/dose SC q4wk (maximum dose 300 mg)	Systemic	Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept*	2.2 mg/kg/dose SC weekly (maximum dose 160 mg)	Systemic	Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
Interleukin-6 Receptor Antagonist			
Tocilizumab	<30 kg: 12 mg/kg/dose IV q2wk (maximum dose 800 mg) 162 mg SC q2wk ≥30 kg: 8 mg/kg/dose IV q2wk (maximum dose 800 mg) 162 mg SC weekly	Systemic	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction
	<30 kg: 10 mg/kg/dose IV q4wk (maximum dose 800 mg) 162 mg SC q3wk ≥30 kg: 8 mg/kg/dose IV q4wk 162 mg SC q2wk	Polyarthritis	
Janus Kinase Inhibitors			
Tofacitinib	10 to <20 kg: 3.2 mg PO bid 20 to <40 kg: 4 mg PO bid ≥ 40 kg = 5 mg PO bid	Polyarthritis	Immunosuppressant, GI perforation, thrombosis

*Not indicated by the U.S. Food and Drug Administration for use in JIA as of 2021.

receptor antagonist, have demonstrated efficacy in and are approved for treatment of polyarticular JIA (see Table 196.8).

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate, systemic corticosteroids are started, followed by the initiation of IL-1 or IL-6 antagonist therapy, which often induces a dramatic and rapid response. Patients with severe disease activity may go directly to anakinra. *Canakinumab,* an IL-1β inhibitor, and tocilizumab are Food and Drug Administration (FDA)–approved treatments for sJIA in children older than 2 years (see Table 196.8). Standardized consensus guiding therapy for sJIA provide four treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab, with optional glucocorticoid use in the latter three plans as clinically indicated.

With the use of DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic corticosteroids are recommended only for management of severe systemic illness, for *bridge therapy* during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Small molecule drugs, including Janus kinase (JAK) inhibitors, are an alternative to csDMARDs and bDMARDs. Oral JAK inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. *Tofacitinib* is FDA approved for children older than 2 years with polyarticular JIA.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (Figs. 196.16 and 196.17; see Table 196.4). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist; initial management may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and TNF-α inhibitors (adalimumab and infliximab) are effective in treating severe uveitis.

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

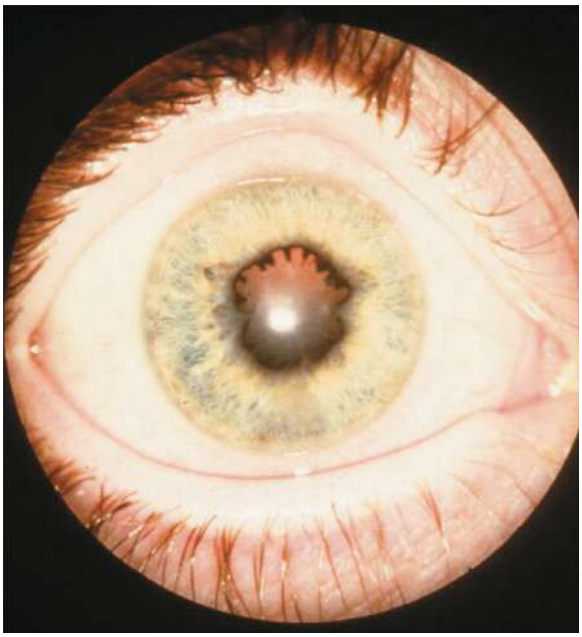

Fig. 196.16 Chronic anterior uveitis demonstrating posterior synechiae and absence of significant scleral inflammation. *(From Firestein GS, Budd RC, Gabriel SE, et al., eds.* Kelley & Firestein's Textbook of Rheumatology, 10th ed. *Philadelphia: Elsevier; 2017: Fig. 107-5, p. 1838.)*

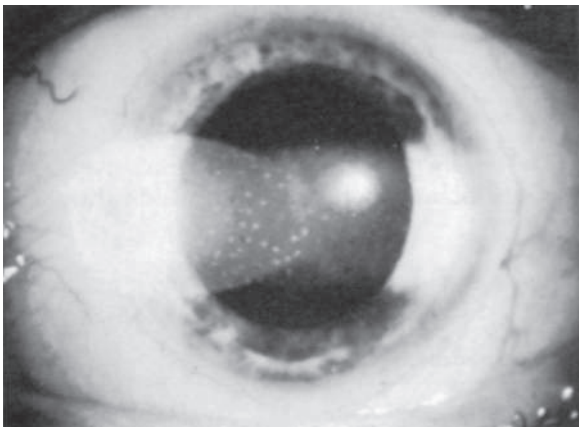

Fig. 196.17 Slit-lamp examination shows "flare" in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells. *(Courtesy Dr. H.J. Kaplan. From Petty RE, Rosenbaum JT. Uveitis in juvenile idiopathic arthritis. In Cassidy JT, Petty RE, Laxer RM, et al., eds.* Textbook of Pediatric Rheumatology, *6th ed. Philadelphia: Saunders; 2011: Fig. 20-3, p. 309.)*

PROGNOSIS

Although the course of JIA in an individual child is unpredictable, some prognostic generalizations can be made on the basis of disease type and course. Studies analyzing management of JIA in the pre–TNF-α era indicate that up to 50% of JIA patients had active disease persisting into early adulthood, often with severe limitations of physical function.

Children with persistent oligoarticular disease fare well, with a majority achieving disease remission. Those with extended oligoarticular disease have a poorer prognosis. Children with oligoarthritis, particularly females who are ANA positive and with onset of arthritis before 6 years of age, are at greatest risk for development of chronic uveitis. There is no association between the activity or severity of arthritis and uveitis. Persistent, uncontrolled anterior uveitis (see Fig. 196.16) can cause posterior synechiae, cataracts, glaucoma, and band keratopathy, with resultant blindness. Morbidity can be averted with early diagnosis and implementation of systemic therapy.

The child with polyarticular JIA often has a more prolonged course of active joint inflammation and requires early and aggressive therapy. Predictors of severe and persistent disease include young age at onset, RF seropositivity or rheumatoid nodules, presence of anti–cyclic citrullinated peptide antibodies, and many affected joints. Disease involving the hip and hand/wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

sJIA is often the most difficult to control in terms of both articular inflammation and systemic manifestations. Poorer prognosis is related to polyarticular distribution of arthritis, fever lasting >3 months, and increased inflammatory markers, such as platelet count and ESR, for >6 months. IL-1 and IL-6 inhibitors have changed the management and improved the outcomes for children with severe and prolonged systemic disease.

Orthopedic complications include leg-length discrepancy and flexion contractures, particularly of the knees, hips, and wrists. Discrepancies in leg length can be managed with a shoe lift on the shorter side to prevent secondary scoliosis. Joint contractures require aggressive medical control of arthritis, often in conjunction with intraarticular corticosteroid injections, appropriate splinting, and stretching of the affected tendons. Popliteal cysts may require no treatment if they are small or respond to intraarticular corticosteroids in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with controls, a significant number of children with JIA have problems with lifetime adjustment and employment. Disability not directly associated with arthritis may continue into young adulthood in as many as 20% of patients, together with continuing chronic pain syndromes at a similar frequency. Psychological complications, including problems with school attendance and socialization, may respond to counseling by mental health professionals.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 197

Ankylosing Spondylitis and Other Spondyloarthritides

Pamela F. Weiss

The diseases collectively referred to as *spondyloarthritides* include ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD) or psoriasis, and reactive arthritis after gastrointestinal (GI) or genitourinary (GU) infections (Table 197.1 and Table 197.2). **Spondyloarthritis** is more common in adults, but all forms can present during childhood with varying symptoms and signs. Many children with spondyloarthritis are classified in the **juvenile idiopathic arthritis (JIA)** categories of **enthesitis-related arthritis (ERA)** or psoriatic arthritis. Children and adolescents with spondyloarthritis who may not meet JIA criteria include arthritis associated with IBD, juvenile ankylosing spondylitis (JAS), and reactive arthritis.

EPIDEMIOLOGY

JIA is diagnosed in 90 per 100,000 U.S. children every year (see Chapter 196). ERA accounts for 10–20% of JIA and has a mean age at onset of 12 years. In India, ERA is the most common category of JIA, accounting for 35% of cases. Unlike other JIA categories, males are affected more often than females, accounting for 60% of ERA cases. AS occurs in 0.2–0.5% of adults, with approximately 15% of cases beginning in childhood. These disorders can be familial, largely as a result of the influence of human leukocyte antigen (HLA)-B27, which is found in 90% of JAS and 50% of ERA patients compared to 7% of healthy individuals. Approximately 20% of children with ERA have a family history of HLA-B27–associated disease, such as reactive arthritis, AS, or IBD with sacroiliitis.

ETIOLOGY AND PATHOGENESIS

Spondyloarthritides are complex diseases in which susceptibility is largely genetically determined. Only 30% of heritability has been defined, with HLA-B27 responsible for two thirds of the total, and >100 additional genetic loci accounting for only one third. Genes that influence interleukin (IL)-23 responses (e.g., *CARD9, IL23R, JAK2, TYK2, STAT3*) and the function of HLA-B27 *(ERAP1)* are particularly important. Unusual properties of HLA-B27, such as its tendency to misfold and form abnormal cell surface structures, may have a role. Infection with certain GI or GU pathogens can trigger reactive arthritis (see Table 197.2 and Chapter 198). Altered gut microbiota and an abnormal immune response to normal microbiota may also play a role in pathogenesis. Inflamed joints and entheses in spondyloarthritis contain T and B cells, macrophages, osteoclasts, proliferating fibroblasts, and osteoblasts, with activation of the IL-23/IL-17 pathway. Bone loss and osteoproliferation in and around vertebral bodies and facet joints in long-standing AS contribute to significant morbidity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations that help distinguish spondyloarthritis from other forms of juvenile arthritis include arthritis of the axial skeleton (sacroiliac joints or spine) and hips, enthesitis (inflammation at the site of a tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and GI inflammation (even in the absence of IBD) (Table 197.3, but see also Table 197.1).

Enthesitis-Related Arthritis

Children fulfill classification criteria for ERA if they have *either* arthritis and enthesitis *or* arthritis or enthesitis with at least two of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) presence of HLA-B27, (3) onset of arthritis in a male older than 6 years, (4) acute anterior uveitis, and (5) a family history of an HLA-B27–associated disease (ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis) in a first-degree relative. Patients with psoriasis (or a family history of psoriasis in a first-degree relative), a positive–rheumatoid factor (RF) test result, or systemic arthritis are excluded from this group. During the first 6 months of disease the arthritis is typically

Table 197.1 Overlapping Characteristics of the Spondyloarthritides*

CHARACTERISTIC	JUVENILE ANKYLOSING SPONDYLITIS	JUVENILE PSORIATIC ARTHRITIS	INFLAMMATORY BOWEL DISEASE	REACTIVE ARTHRITIS
Enthesitis	+++	+	+	++
Axial arthritis	+++	++	++	+
Peripheral arthritis	+++	+++	+++	+++
HLA-B27 positive	+++	+	++	+++
Antinuclear antibody positive	–	++	–	–
Rheumatoid factor positive	–	–	–	–
SYSTEMIC DISEASE				
Eyes	+	+	+	+
Skin	–	+++	+	+
Mucous membranes	–	–	+	+
Gastrointestinal tract	–	–	++++	+++

*Frequency of characteristics: –, absent; +, <25%; ++, 25–50%; +++, 50–75%; ++++, ≥75%.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021.

Table 197.2 Etiologic Microorganisms of Reactive Arthritis

PROBABLE	POSSIBLE
Chlamydia trachomatis	*Neisseria gonorrhoeae*
Shigella species	*Mycoplasma fermentans*
Salmonella enteritidis	*Mycoplasma genitalium*
Salmonella typhimurium	*Ureaplasma urealyticum*
Yersinia enterocolitica	*Escherichia coli*
Yersinia pseudotuberculosis	*Cryptosporidium*
Campylobacter jejuni and *coli*	*Entamoeba histolytica*
	Giardia lamblia
	Brucella abortus
	Clostridium difficile
	Streptococcus pyogenes
	Chlamydia pneumoniae
	Chlamydia psittaci

From Kim PS, Klausmeier TL, Orr DP. Reactive arthritis: a review. *J Adolesc Health.* 2009;44:309–315, Table 2, p. 311.

Table 197.3 Assessment in SpondyloArthritis International Society (ASAS) Classification Criteria for Spondyloarthritis (SpA)

AXIAL SpA		PERIPHERAL SpA
In patients with ≥3 months back pain and age at onset <45 years		In patients with peripheral symptoms ONLY
Sacroiliitis on imaging* *plus* one or more SpA feature(s)	***or*** **HLA-B27** *plus* two or more other SpA features	**Arthritis** *or* **enthesitis** *or* **dactylitis** *plus*
SpA features • Inflammatory back pain (IBP) • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn disease/ulcerative colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP		One or more SpA feature(s): • Uveitis • Psoriasis • Crohn disease/ulcerative colitis • Preceding infection • HLA-B27 • Sacroiliitis on imaging* *or* Two or more other SpA features: • Arthritis • Enthesitis • Dactylitis • IBP ever • Family history for SpA

*Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA. Definite radiographic sacroiliitis according to modified NY criteria.
CRP, C-reactive protein; NSAIDs, nonsteroidal antiinflammatory drugs.
Adapted from Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis. Part II. Validation and final selection. *Ann Rheum Dis.* 2009;68(6):777–783; and The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011;70(1):25–31.

Table 197.4 Symptoms Characteristic of Inflammatory Back Pain

Pain at night with morning stiffness (and improvement on arising)
No improvement with rest
Improvement with exercise
Insidious onset
Good response to nonsteroidal antiinflammatory drugs

asymmetric and involves fewer than four joints, most frequently the knees, ankles, and hips. Inflammation of the small joints of the foot, or *tarsitis*, is highly suggestive of ERA. Enthesitis is typically symmetric and affects the lower limbs. Up to 40% of children develop clinical or radiographic evidence of sacroiliac joint arthritis as part of their disease; approximately 20% have evidence of sacroiliac joint arthritis at diagnosis. When the sacroiliac or other axial joints are involved, children may experience **inflammatory back pain** (Table 197.4), hip pain, and alternating buttock pain. Patients may also experience pain with palpation of the lower back or with pelvic compression. The risk of sacroiliac joint arthritis is highest in children who are HLA-B27 positive and have an elevated C-reactive protein (CRP). Untreated sacroiliitis may, but does not always, evolve into AS; additional risk factors for progression are unclear.

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 5% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 197.1), onycholysis, and dactylitis (sausage-like swelling of fingers or toes).

Children fulfill classification criteria for psoriatic arthritis if they have arthritis and psoriasis *or* arthritis and at least two of the following: (1) dactylitis, (2) nail pitting or onycholysis, and (3) psoriasis in a first-degree relative. The presence of psoriasis aids in diagnosis but is not required. Disease onset peaks during the preschool and early adolescent years. Children with onset during the preschool years are more often female, antinuclear antibody (ANA) positive, and at risk for asymptomatic ocular inflammation. Disease onset during adolescence is equally common among males and females. In the majority



Fig. 197.1 Nail pitting in a 9-year-old with JPsA. (*From Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. Rheum Dis Clin N Am. 2021;47:565–583, Fig. 2, p. 569.*)

of children, the arthritis is asymmetric and affects four or fewer joints at presentation. Large (knees and ankles) and small (fingers and toes) joints may be involved. Although distal interphalangeal joint involvement is uncommon, it is highly suggestive of the diagnosis. Enthesitis is detectable in ~20–75% of patients and seems to be more frequent in those who present at an older age (Table 197.5, Fig. 197.2). Axial (sacroiliac) and root (hip) joints may be affected in up to 30% of children; the risk of axial arthritis is highest in those who are HLA-B27 positive.

Table 197.5 Entheseal Sites Studied in Historical JSpA Cohorts

ENTHESEAL SITES	PERCENTAGE
Insertion of infrapatellar tendon on patella	27-44
Achilles tendon	21-74
Interosseous ligaments of the sacroiliac joint	30.3
Plantar fascia insertion to calcaneus	12-39
Tibial tuberosity	23-30
Quadriceps insertion to upper poles of patella	22-46
Second MTP	21
Third MTP	16
First MTP	14
Greater trochanter	14
Iliac crest	14

JSpA, Juvenile spondyloarthritis; MTP, metatarsophalangeal.
From Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. *Rheum Dis Clin N Am.* 2021;47:565–583, Table 1, p. 567.

Juvenile Ankylosing Spondylitis

JAS frequently begins with oligoarthritis and enthesitis. The arthritis occurs predominantly in the lower extremities and often involves the hips. In comparison to adult-onset AS, axial disease and inflammatory back pain are less frequent at disease onset, whereas enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified New York (NY) criteria if there is sufficient radiographic evidence of sacroiliitis (sacroiliitis of grade 2 or greater bilaterally or at least grade 3 unilaterally) and if the patient meets at least one clinical criterion involving inflammatory back pain, limitation of motion in the lumbar spine (Fig. 197.3), or limitation of chest expansion. JAS is present if the patient is <16 years old. Juvenile-*onset* AS is frequently used to describe adult AS when the symptoms began before 16 years of age but full criteria were not met until later.

To fulfill the modified NY criteria for AS, patients must have radiographic changes in the sacroiliac joints and clinical sequelae of axial disease. Because radiographic sacroiliitis can take many years to develop in adults and even longer in children, and clinical sequelae may lag further behind, criteria to identify preradiographic axial spondyloarthritis were developed by the **Assessment of SpondyloArthritis International Society**. To meet criteria for axial spondyloarthritis (SpA), patients must have at least 3 months of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by NY criteria) plus one feature of SpA (inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for SpA, HLA-B27, or elevated CRP). Alternatively, patients can fulfill axial SpA criteria if they are HLA-B27 positive and have at least two SpA features. These criteria have low sensitivity and specificity in the pediatric population but, in the absence of alternative pediatric criteria, may be useful as a guide to evaluating preradiographic axial SpA.

Arthritis with Inflammatory Bowel Disease

The presence of erythema nodosum, pyoderma gangrenosum, oral ulcers, abdominal pain, diarrhea, fever, weight loss, or anorexia in a child with chronic arthritis should raise suspicion of IBD. Two patterns of arthritis complicate IBD. **Polyarthritis** affecting large and small joints is most common and often reflects the activity of the intestinal inflammation. Less frequently, **arthritis of the axial skeleton**, including the sacroiliac joints, occurs. As with psoriatic arthritis, the presence of HLA-B27 is a risk factor for the development of axial disease. The severity of axial involvement is independent of the activity of the GI inflammation.

LABORATORY FINDINGS

Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate (ESR) and/or CRP value is variable in most spondyloarthritides and may or may not be present at the onset of disease. RF and ANAs are absent, except in children with psoriatic arthritis, as many as 50% of whom are ANA positive. HLA-B27 is present in approximately 90% of children with JAS, compared with 7% of healthy individuals, but is less frequent in ERA and other SpA types.

Imaging

Conventional radiographs detect chronic bony changes and damage but not active inflammation and are unreliable in the assessment of pediatric disease. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions. **Sclerosis** typically starts on the iliac side of the joint (Fig. 197.4). Peripheral joints may exhibit periarticular **osteoporosis**, with loss of sharp cortical margins in areas of enthesitis, which may eventually show erosions or bony spurs (enthesophytes). Squaring of the corners of the vertebral bodies and syndesmophyte formation resulting in the classic "bamboo spine" characteristic of advanced AS are rare in early disease, particularly in childhood. CT, like radiographs, can detect chronic bony changes but not active inflammation and has the disadvantage of more radiation exposure. The gold standard for early visualization of sacroiliitis is evidence of bone marrow edema adjacent to the joint on MRI with fluid-sensitive sequences such as short-T1 inversion recovery (STIR) (Figs. 197.5 and 197.6). Gadolinium does not add value to the study of the sacroiliac joints if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole

Anatomic region	Enthesitis exam
Foot and ankle	Achilles tendon insertion to calcaneus Plantar fascia insertion to calcaneus Plantar fascia insertion to metatarsal heads Plantar fascia insertion to base of fifth metatarsal
Knee	Quadriceps tendon insertion to patella (2 and 10 o'clock) Infrapatellar ligament insertion to patella (6 o'clock) and tibial tuberosity
Pelvis	Hip extensor insertion at greater trochanter of femur Sartorius insertion at anterior superior iliac spine Posterior superior iliac spine Abdominal muscle insertions to iliac crest Gracilis and adduction insertion to pubis symphysis Hamstrings insertion to ischial tuberosity
Spine	5th lumbar spinous process
Upper extremity	Common flexor insertion at medial epicondyle of humerus Common extensor insertion at lateral epicondyle of humerus Supraspinatus insertion into greater tuberosity of humerus
Chest	Costosternal junctions (1st and 7th)

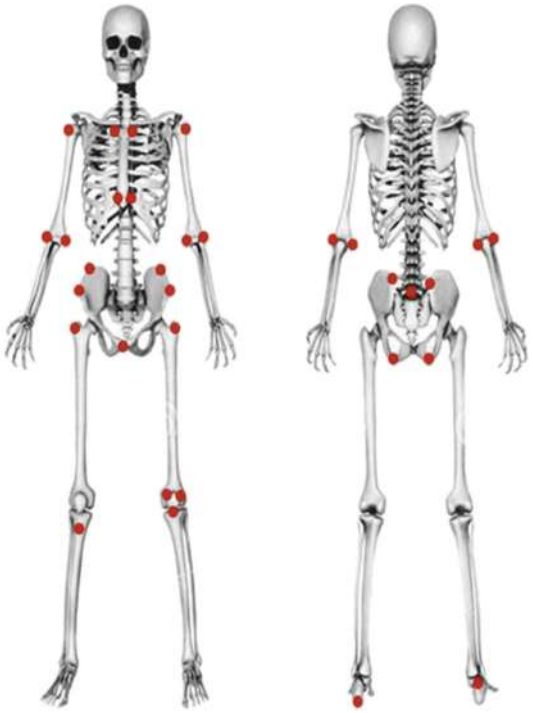

Fig. 197.2 Anatomic sites for assessment of enthesitis in ERA and JAS. (*From Petty RE, Laxer RM, Lindsley CB, et al., eds. Textbook of Pediatric Rheumatology, 8th ed. Philadelphia: Elsevier; 2021: Fig. 20.1, p. 254.*)

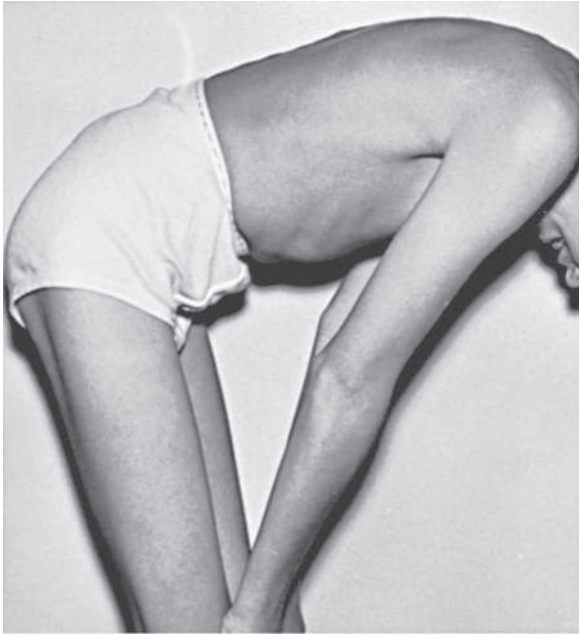

Fig. 197.3 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward.



Fig. 197.4 Well-developed sacroiliitis in a boy with ankylosing spondylitis. Both sacroiliac joints show extensive sclerosis, erosion of joint margins, and apparent widening of the joint space.

body MRI may also be used to evaluate the axial skeleton in adults with early disease because it can detect vertebral lesions in addition to sacroiliac changes.

DIFFERENTIAL DIAGNOSIS

The onset of arthritis after a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest **reactive arthritis** (see Chapter 198). Lower back pain can be caused by strain, infectious arthritis of the sacroiliac joint, osteomyelitis of the pelvis or spine, chronic nonbacterial osteomyelitis (CNO) of the pelvis or spine, osteoid osteoma of the posterior elements of the spine, pelvic muscle pyomyositis, or malignancies. In addition, mechanical conditions such as spondylolysis, spondylolisthesis, and Scheuermann disease should be considered. Back pain secondary to **fibromyalgia** usually affects the soft tissues of the upper back in a symmetric pattern and is associated with well-localized tender points and sleep disturbance (see Chapter 211.3). Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), slipped capital femoral epiphysis, and chondrolysis may also manifest as pain over the inguinal ligament and loss of internal rotation of the hip joint, but without other SpA features, such as involvement of other entheses and/or joints. Radiography and MRI are critical for distinguishing these conditions.

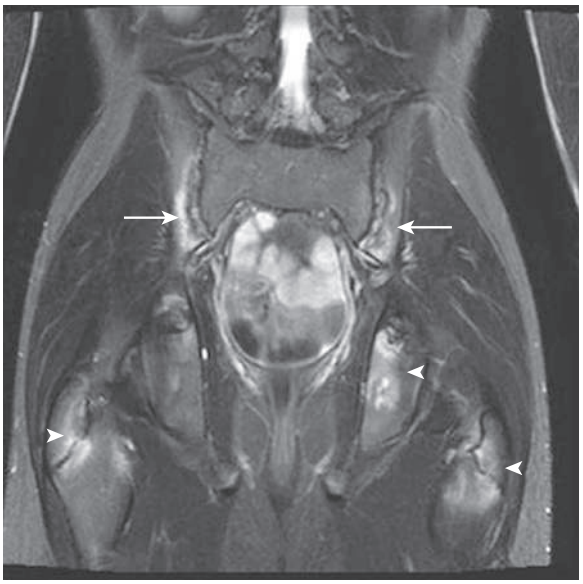

Fig. 197.5 Coronal MRI (STIR) of the pelvis in a 14-year-old boy with ERA (HLA-B27 positive). Fluid and pathology appear bright, spinal fluid also appears bright. Increased signal abnormality is observed around bilateral triradiate cartilages and greater trochanteric apophyses *(arrowheads),* common areas of involvement for ERA. Also, signal abnormality appears on the iliac side of the sacroiliac joints bilaterally around more curvilinear, dark, sclerotic subchondral areas representing erosions and sacroiliitis *(arrows).* (*From Tse SM, Laxer RM. New advances in juvenile spondyloarthritis. Nat Rev Rheumatol. 2012;10;8:269–279.*)



Fig. 197.6 Short T1 inversion recovery image from whole body MRI of a 15-yr-old boy with HLA-B27–negative JSpA. The MRI shows active corner inflammatory lesions of vertebral end plates at multiple levels *(straight arrows)* and more chronic-appearing discovertebral unit changes *(curved arrow).* (*From Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. Rheum Dis Clin N Am. 2021;47:565–583, Fig. 7, p. 574.*)

TREATMENT

The goals of therapy are to control inflammation, minimize pain, preserve function, and prevent ankylosis (fusion of adjacent bones) using a combination of antiinflammatory medications, physical therapy, and education. Treatment regimens for SpA include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs (DMARDs), or biologic agents. NSAIDs, such as naproxen (15-20 mg/kg/day), are frequently used to help relieve symptoms and may slow the progression of structural damage (syndesmophyte formation and growth) if used continually. With relatively mild monoarticular disease, intraarticular corticosteroids (e.g., triamcinolone acetonide/hexacetonide) may also help to control peripheral joint inflammation. DMARDs such as sulfasalazine (up to 50 mg/kg/day; maximum 3 g/day) or methotrexate (10 mg/m^2) may be beneficial for peripheral arthritis, but these medications have not been shown to improve axial disease in adults. For axial arthritis, it is typically necessary to add a biologic therapy. Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS. It remains unclear whether TNF inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies. Drugs that target IL-17 (secukinumab/ixekizumab), IL-23/IL-12 (ustekinumab), and the JAK/STAT pathway (tofacitinib/upadacitinib) reduce clinical disease activity in adults with AS.

Physical therapy and low-impact exercise should be included in the treatment program for all children with spondyloarthritis. Exercise to maintain range of motion in the back, thorax, and affected joints should be instituted early in the disease course. Custom-fitted insoles and heel cups are particularly useful in the management of painful entheses around the feet, and the use of pillows to position the lower extremities while the child is in bed can be helpful.

PROGNOSIS

Observational studies suggest that ongoing disease activity for >5 years in juvenile spondyloarthritis predicts disability. Disease remission occurs in <20% of children with spondyloarthritis 5 years after diagnosis. Factors associated with disease progression include tarsitis, HLA-B27 positivity, hip arthritis within the first 6 months, and disease onset after age 8. Important questions, such as which patients with ERA will go on to have JAS/AS, have yet to be addressed. Outcomes for JAS compared with adult-onset AS suggest that hip disease requiring replacement is more common in children but axial disease is more severe in adults.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 198

Reactive and Postinfectious Arthritis

Pamela F. Weiss

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 726), microbes activate innate and adaptive immune responses, which can lead to the generation and deposition of immune complexes and antibody or T-cell–mediated cross-reactivity with self. Furthermore, microbes may influence the immune system in ways that promote immune-mediated inflammatory diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), and spondyloarthritis. **Reactive arthritis** and **postinfectious arthritis** are defined as joint inflammation caused by a sterile inflammatory reaction after a recent infection. The term *reactive arthritis* is used to refer to arthritis that occurs after enteropathic or urogenital infections and *postinfectious arthritis* to describe arthritis that occurs after infectious illnesses not classically considered in the reactive arthritis group, such as infection with group A streptococcus or viruses. In some patients, nonviable components of the initiating organism have been demonstrated in affected joints, and the presence of viable, yet nonculturable, bacteria within the joint remains an area of investigation.

The course of reactive arthritis is variable and may remit or progress to a chronic spondyloarthritis, including ankylosing spondylitis (see Chapter 197). In postinfectious arthritis, the pain or joint swelling is usually transient, lasting <6 weeks, and does not necessarily share the typical spondyloarthritis pattern of joint involvement. The distinction between postinfectious arthritis and reactive arthritis is not always clear, either clinically or pathophysiologically.

PATHOGENESIS

Reactive arthritis typically follows enteric infection with Salmonella species, *Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni,* or genitourinary (GU) tract infection with *Chlamydia trachomatis*. *Escherichia coli* and *Clostridium difficile* are also causative enteric agents, although less common (see Table 197.2). Acute **rheumatic fever** caused by group A streptococcus (see Chapters 229 and 229.1), arthritis associated with infective endocarditis (see Chapter 486), and the tenosynovitis associated with *Neisseria gonorrhoeae* are similar in some respects to reactive arthritis.

Approximately 75% of patients with reactive arthritis are HLA-B27 positive. Incomplete elimination of bacteria and bacterial products, such as DNA, has been proposed as a factor in reactive arthritis. A relationship with clinical characteristics of specific infectious disorders is not present. In postinfectious arthritis, several viruses (rubella, varicella-zoster, herpes simplex, cytomegalovirus) have been isolated from the joints of patients. Antigens from other viruses (e.g., hepatitis B, adenovirus) have been identified in immune complexes from joint tissue.

Patients with reactive arthritis who are HLA-B27 positive have an increased frequency of acute and symptomatic uveitis and other extraarticular features. In addition, HLA-B27 is a risk factor for persistent gastrointestinal (GI) inflammation after enteric infections, even after resolution of the initial infection, and significantly increases the risk that the individual will develop chronic spondyloarthritis. Nevertheless, reactive arthritis also occurs in HLA-B27–negative patients, emphasizing the importance of other genes in disease susceptibility.

CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

Symptoms of reactive arthritis begin approximately 3 days to 6 weeks after infection. The classic triad of arthritis, urethritis, and conjunctivitis is relatively uncommon in children. The arthritis is typically asymmetric and oligoarticular, with a predilection for the lower extremities. Dactylitis may occur, and enthesitis is common, affecting as many as 90% of patients (Fig. 198.1). Cutaneous manifestations can occur and may include circinate balanitis, ulcerative vulvitis, erythematous oral macules or plaques or erosions, erythema nodosum, paronychia, painful erosions or pustules on fingertips, and keratoderma blennorrhagica, which is similar in appearance to pustular psoriasis (Fig. 198.2). Systemic symptoms may include fever, malaise, and fatigue. Less common features may include conjunctivitis, optic neuritis, aortic valve involvement, sterile pyuria, and polyneuropathy. Early in the disease course, markers of inflammation—erythrocyte sedimentation rate (ESR), C-reactive protein, and platelets—may be greatly elevated. The clinical manifestations may last for weeks to months.

Familiarity with other causes of postinfectious arthritis is vital when a diagnosis of reactive arthritis is being considered. Numerous viruses are associated with postinfectious arthritis and may result in particular patterns of joint involvement (Table 198.1). Rubella and hepatitis B virus typically affect the small joints, whereas mumps and varicella often involve large joints, especially the knees. **Hepatitis B arthritis–dermatitis syndrome** is characterized by urticarial rash and a symmetric migratory polyarthritis resembling that of serum sickness. Rubella-associated arthropathy may follow natural rubella infection and, infrequently, rubella immunization. It typically occurs in young women, with an increased frequency with advancing age, and is uncommon in preadolescent children and in males. Arthralgia of the knees and hands usually begins within 7 days of onset of the rash or 10-28 days after immunization. Parvovirus B19, which is responsible for erythema infectiosum (fifth disease), can cause arthralgia, symmetric



Fig. 198.1 Enthesitis—swelling of the posterior aspect of the left heel and lateral aspect of the ankle. *(Courtesy Dr. Nora Singer, Case Western Reserve University and Rainbow Babies' Hospital.)*



Fig. 198.2 Keratoderma blennorrhagica. *(Courtesy Dr. MF Rein and the Centers for Disease Control and Prevention Public Health Image Library, 1976. Image #6950.)*

Table 198.1 Viruses Associated with Arthritis

TOGAVIRUSES	HERPESVIRUSES
RUBIVIRUS	Epstein-Barr
Rubella	Cytomegalovirus
ALPHAVIRUSES	Varicella-zoster
Ross River	Herpes simplex
Chikungunya	PARAMYXOVIRUSES
O'nyong-nyong	Mumps
Mayaro	FLAVIVIRUS
Sindbis	Zika virus
Ockelbo	HEPADNAVIRUS
Pogosta	Hepatitis B
ORTHOPOXVIRUSES	ENTEROVIRUSES
Variola virus (smallpox)	Echovirus
Vaccinia virus	Coxsackievirus B
Parvoviruses	CORONAVIRUSES
ADENOVIRUSES	SARS-CoV-2
Adenovirus 7	

Adapted from Infectious arthritis and osteomyelitis. In: Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021.

joint swelling, and morning stiffness, particularly in adult women and less frequently in children. Arthritis occurs occasionally during cytomegalovirus infection and may occur during varicella infections but is rare after Epstein-Barr virus infection. Varicella may also be complicated by suppurative arthritis, usually secondary to group A streptococcus infection. HIV is associated with an arthritis that resembles psoriatic arthritis more than JIA (see Chapter 196).

Poststreptococcal arthritis may follow infection with either group A or group G streptococcus. It is typically oligoarticular, affecting lower-extremity joints, and mild symptoms can persist for months. Poststreptococcal arthritis differs from rheumatic fever, which typically manifests with painful migratory polyarthritis of brief duration. Because valvular lesions have occasionally been documented by echocardiography after the acute illness, some clinicians consider poststreptococcal arthritis to be an incomplete form of acute rheumatic fever (see Chapter 229.1). Certain HLA-DRB1 types may predispose children to development of either poststreptococcal arthritis (HLA-DRB1*01) or acute rheumatic fever (HLA-DRB1*16).

Transient synovitis (toxic synovitis), another form of postinfectious arthritis, typically affects the hip, often after an upper respiratory tract infection (see Chapter 719.2). Males 3-10 years of age are most often affected and have acute onset of severe pain in the hip (groin), with referred pain to the thigh or knee, lasting approximately 1 week. ESR and white blood cell count are usually normal. Radiologic or ultrasound examination may confirm widening of the joint space secondary to an effusion. Aspiration of joint fluid is often necessary to exclude septic arthritis and typically results in dramatic clinical improvement. The trigger is presumed to be viral, although responsible microbes have not been identified.

Nonsuppurative arthritis has been reported in children, usually adolescent males, in association with severe truncal acne. Patients often have fever and persistent infection of the pustular lesions. **Pyogenic (sterile) arthritis, pyoderma gangrenosum, and acne (cystic) syndrome**, an autosomal dominant disorder caused by a pathogenic variant in the *PSTPIP1* gene, is a difficult-to-treat but rare autoinflammatory disorder that has responded to anakinra or anti–tumor necrosis factor antibody therapy in a few patients (see Chapter 710). Recurrent episodes of erosive arthritis begin in childhood; cystic acne and the painful ulcerating lesions of pyoderma gangrenosum begin during adolescence. Recurrent episodes may also be associated with a sterile myopathy and may last for several months.

Infective endocarditis can be associated with arthralgia, arthritis, or signs suggestive of vasculitis, such as Osler nodes, Janeway lesions, and Roth spots. Postinfectious arthritis, perhaps because of immune complexes, also occurs in children with *N. gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae* type b, and *Mycoplasma pneumoniae* infections.

DIAGNOSIS

A recent GU or GI infection may suggest the diagnosis of reactive arthritis, but there is no diagnostic test. A complete blood count, acute-phase reactants, complete metabolic panel, and urinalysis may be helpful to exclude other etiologies. Although stool or urogenital tract cultures can be performed in an attempt to isolate it, the triggering organism is not typically found at the time arthritis presents. Imaging findings are nonspecific or normal. Documenting previous streptococcal infection with antibody testing (anti-streptolysin O and anti-DNAse B) may help to diagnose postinfectious arthritis. Serum sickness associated with the antibiotic treatment of preceding infection must be excluded.

Because the preceding infection can be remote or mild and often not recalled by the patient, it is also important to rule out other causes of arthritis. Acute and painful arthritis affecting a single joint suggests septic arthritis, mandating joint aspiration. Osteomyelitis may cause pain and an effusion in an adjacent joint but is more often associated with focal bone pain and tenderness at the site of infection. Arthritis affecting a single joint, particularly the knee, may also be secondary to Lyme disease in endemic areas. The diagnosis of postinfectious arthritis is often established by exclusion and after the arthritis has resolved. Arthritis associated with GI symptoms or abnormal liver function test results may be triggered by infectious or autoimmune hepatitis. Arthritis or spondyloarthritis may occur in children with IBD, such as Crohn disease or ulcerative colitis (see Chapters 382.1 and 382.2). Parvovirus infection, macrophage activation (hemophagocytic) syndrome, and leukemia should be strongly considered when two or more blood cell lines are low or progressively decrease in a child with arthritis. Persistent arthritis (>6 weeks) suggests the possibility of a chronic rheumatic disease, including JIA (see Chapter 196) and SLE (see Chapter 199).

TREATMENT

Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory drugs (NSAIDs) are often needed for management of pain and functional limitation. Unless ongoing *Chlamydia* infection is suspected, attempts to treat the offending organism are not warranted. If swelling or arthralgia recurs, further evaluation may be necessary to exclude active infection or evolving rheumatic disease. Intraarticular corticosteroid injections may be given for refractory or severely involved joints once acute infection has been ruled out. Systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs) are rarely indicated but may be considered for chronic disease. Participation in physical activity should be encouraged, and physical therapy may be needed to maintain normal function and prevent muscle atrophy. For postinfectious arthritis caused by streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 year. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

COMPLICATIONS AND PROGNOSIS

Postinfectious arthritis after viral infections usually resolves without complications unless it is associated with involvement of other organs, such as **encephalomyelitis**. Children with reactive arthritis after enteric infections occasionally experience IBD months to years after onset. Both **uveitis** and **carditis** have been reported in children diagnosed with reactive arthritis. Reactive arthritis, especially after bacterial enteric infection or GU tract infection with *C. trachomatis,* has the potential for evolving to chronic arthritis, particularly spondyloarthritis (see Chapter 197). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 199

Systemic Lupus Erythematosus

Rebecca E. Sadun and Stacy P. Ardoin

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. SLE occurs in both children and adults, disproportionately affecting females of reproductive age. Although nearly every organ may be affected, most commonly involved are the skin, joints, kidneys, blood-forming cells, blood vessels, and the central nervous system. Systemic signs of inflammation such as fever and lymphadenopathy can also be seen. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

ETIOLOGY

The pathogenesis of SLE remains largely unknown, but several factors likely influence risk and severity of disease, including genetics, hormonal milieu, and environmental exposures.

A genetic predisposition to SLE is suggested by the association with specific genetic variants, including congenital deficiencies of C1q, C2, and C4, as well as several polymorphisms (e.g., interferon regulatory factor 5 and protein tyrosine phosphatase N22) and familial clustering of SLE or other autoimmune disease (Table 199.1). In addition, certain human leukocyte antigen (HLA) types (including HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency in patients with SLE. Although SLE clearly has a genetic component, its occurrence is sporadic in families and its concordance is incomplete (estimated at 2–5% among dizygotic twins and 25–60% among monozygotic twins), suggesting nonmendelian genetics and involvement of epigenetic and environmental factors. Patients with SLE often have family members—especially mothers and sisters—with SLE or various other autoimmune diseases.

Because SLE preferentially affects females, especially during their reproductive years, it is suspected that hormonal factors are important in pathogenesis. Of individuals with SLE, 90% are female, making female sex the strongest risk factor for SLE. Estrogens are likely to play a role in SLE, and both in vitro and animal model studies suggest that estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, though the risk of flares may be increased in postmenopausal women receiving hormone replacement.

Environmental exposures that may trigger the development of SLE remain largely unknown; certain viral infections (including Epstein-Barr virus) may play a role in susceptible individuals, and ultraviolet light exposure is known to trigger SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, increasing the risk of SLE and drug-induced lupus; in mouse models, drugs such as procainamide and hydralazine can promote lymphocyte hypomethylation, causing a lupus-like syndrome.

EPIDEMIOLOGY

The reported prevalence of SLE in children and adolescents (1-6/100,000) is lower than that in adults (20-70/100,000). Prevalence of SLE is highest among patients of African, Asian, Hispanic, Native American, and Pacific Island ancestry for both adult and pediatric populations. SLE predominantly affects females, with a reported 2-5:1 ratio before puberty, 9:1 ratio during reproductive years, and return to near-prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 years of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 years. Up to 20% of all individuals with SLE are diagnosed before age 16 years. Pediatric-onset SLE (pSLE) is defined as onset of symptoms before age 16 or 18 years.

PATHOLOGY

Histologic features most suggestive of SLE include findings in the kidney and skin. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 560.2). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases the risk for renal morbidity. Renal biopsies are helpful to establish the diagnosis of SLE and to stage disease. Immune complexes are commonly found with "full house" deposition of immunoglobulin and complement. The characteristic **discoid rash** depicted in Figure 199.1D is characterized on biopsy by hyperkeratosis, follicular plugging, and infiltration of mononuclear cells into the dermal-epidermal junction. The histopathology of photosensitive rashes can be nonspecific, but immunofluorescence examination of both affected and nonaffected skin may reveal deposition of immune complexes within the dermal-epidermal junction. This finding is called the *lupus band test,* which is specific for SLE.

PATHOGENESIS

A hallmark of SLE is the generation of *autoantibodies* directed against self-antigens, particularly nucleic acids. These intracellular antigens are ubiquitously expressed but are usually inaccessible and cloistered within the cell. During cell necrosis or *apoptosis,* the antigens are released. SLE skin cells are highly susceptible to damage from ultraviolet light, and the resulting cell death leads to release of cell contents, including nucleic antigens. Individuals with SLE may have impaired apoptosis or impaired ability to clear cell debris, causing prolonged exposure to nucleic antigens in the bloodstream and increased opportunity for recognition by immune cells, leading to B-cell stimulation and autoantibody production. Circulating autoantibodies form *immune complexes* and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and, ultimately, tissue damage. Antibodies to **double-stranded DNA** (dsDNA) can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to dsDNA yet do not have nephritis, suggesting that autoantibodies are not the only pathway leading to end-organ damage in SLE.

Both the innate and adaptive arms of the immune system have been implicated in the dysregulation of the immune system seen in SLE. High levels of interferon-α production by plasmacytoid dendritic cells promote expression of other proinflammatory cytokines and chemokines, maturation of monocytes into myeloid dendritic cells, promotion of autoreactive B and T cells, and loss of self-tolerance. Nearly 85% of patients with SLE exhibit this cytokine profile, known as the *type I interferon signature*. Other cytokines with increased expression in SLE include interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-17, and IL-21; anti–tumor necrosis factor-α; interferon-γ; and *B-lymphocyte stimulator (BLyS)*, also known as *B-cell–activating factor (BAFF)*. Both B and T cells demonstrate functional impairments in SLE. In active SLE, B-cell populations have impaired tolerance and increased autoreactivity, enhancing B cells' ability to produce autoantibodies after exposure to self-antigen. In addition, cytokines such as BLyS/BAFF may promote abnormal B-cell number and function. T-cell abnormalities in SLE include increased numbers of memory T cells and decreased number and function of T-regulatory cells. SLE T cells display aberrant signaling and increased autoreactivity. As a result, they are resistant to attrition by normal apoptosis pathways. In addition, a neutrophil signature can be identified in 65% of adult SLE patients and has recently been recognized as a potential biomarker for active lupus nephritis.

Table 199.1 Reviewed Proteins and Genes Associated with Monogenic Forms of Systemic Lupus Erythematosus and Lupus-Like Phenotypes

PROTEIN	GENE	INHERITANCE	MECHANISM	FEMALE-TO-MALE PATIENT RATIO	ASSOCIATED SYMPTOMS
C1q	*C1QA, C1QB, C1QC*	Autosomal recessive	Complement deficiency	1:1	SLE (cutaneous, renal, CNS, arthritis, ANA), young age onset, recurrent bacterial infections
C1r/s	*C1R, C1S*	Autosomal recessive	Complement deficiency	1:1	SLE (fever, cutaneous, arthritis, renal, ANA, ENA), recurrent infections, encapsulated bacteria, Hashimoto thyroiditis
C2	*C2*	Autosomal recessive	Complement deficiency	7:1	SLE (cutaneous, arthritis), young age onset, type 1 diabetes
C3	*C3*	Autosomal recessive	Complement deficiency	1:1	Recurrent sinopulmonary infections, lupus-like syndrome, glomerulonephritis
C4	*C4A, C4B*	Autosomal recessive	Complement deficiency	1:1	SLE (severe photosensitive rash, renal, ANA, Ro), young age onset
TREX1/DNASE III	*TREX1*	Autosomal dominant (FCL), autosomal recessive and dominant (AGS)	Abnormal DNA clearance leading to IFN activation	Likely 1:1	FCL, AGS, SLE
MDA5	*IFIH1*	Autosomal dominant	Activation of IFN production	Likely 1:1	AGS, SLE, FCL, IgA deficiency
SAMHD1	*SAMHD1*	Autosomal recessive and dominant	Abnormal DNA or RNA clearance leading to IFN production	Likely 1:1	AGS, SLE, FCL, photosensitivity
RNaseH2	*RNASH2*	Autosomal dominant and recessive	Abnormal RNA clearance leading to IFN production	Likely 1:1	AGS, SLE
ADAR1	*ADAR1*	Mainly autosomal dominant	Abnormal RNA clearance leading to IFN production	Likely 1:1	AGS, SLE
STING	*TMEM173*	Autosomal dominant	Activation of IFN production	1:1	SAVI, FCL, SLE
DNase I	*DNASE1*	Autosomal dominant	Abnormal DNA clearance-break intolerance	Likely 1:1	SLE (dsDNA), adolescent onset, Sjögren syndrome
DNase 1-like-3	*DNASE1L3*	Autosomal recessive	Abnormal DNA clearance-break intolerance	1:2	SLE (hypocomplementemia, dsDNA, cANCA, renal), HUVS
DNASE2	*DNASE2*	Possible autosomal recessive	Abnormal DNA clearance	1:1	Neonatal-onset cytopenias, hepatosplenomegaly, arthritis, nephritis
Protein kinase C-delta	*PRKCD*	Autosomal recessive; dominant	Disrupts B-cell proliferation and apoptosis, NK-cell activity	1:1	Early onset SLE nephritis, lymphoproliferation autoimmunity
Ras/MAPK Pathway	*KRAS GoF*	Somatic mutation	Altered cell proliferation, differentiation, apoptosis	Likely 1:1	Pancytopenia, autoantibodies, arthritis, hepatosplenomegaly, pericarditis
Noonan syndrome	*NRAS GoF*	Somatic mutation	Altered cell proliferation, differentiation apoptosis	Likely 1:1	Chilblain lupus, pancytopenia, autoantibodies

AGS, Aicardi-Goutières syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen antibody; FCL, familial chilblain lupus; GOF, gain of function; HUVS, hypocomplementemic urticarial vasculitis syndrome; IFN, interferon; IgA, immunoglobulin A; SAVI, STING-associated vasculopathy with onset in infancy; SLE, systemic lupus erythematosus.

Modified from Hiraki LT, Silverman ED. Genomics of systemic lupus erythematosus: insights gained by studying monogenic young-onset systemic lupus erythematosus. *Rheum Dis Clin N Am.* 2017;43:415–434, Table 1, p. 417.

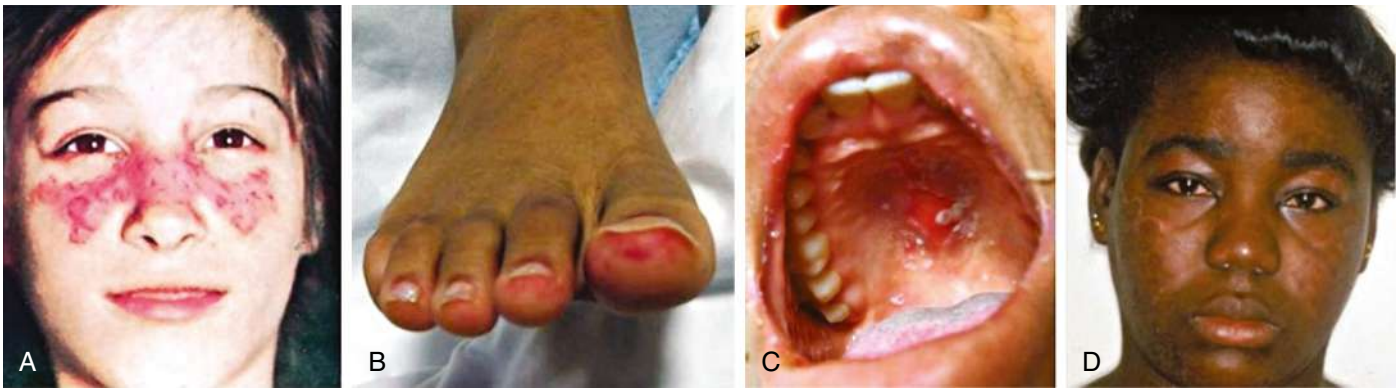

Fig. 199.1 Mucocutaneous manifestations of SLE. A, Malar rash. B, Vasculitic rash on toes. C, Oral mucosal ulcers. D, Discoid rash in malar distribution.

Table 199.2 Potential Clinical Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex), chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural and cerebral venous sinus thrombosis
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy, macrophage activation syndrome
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

CLINICAL MANIFESTATIONS

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Table 199.2). The presentation of SLE in childhood or adolescence differs somewhat from that seen in adults. The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis. Arthritis is usually present in the first year of diagnosis; arthritis may be painful or painless swelling, often with stiffness in the morning, and is usually a **symmetric polyarthritis** affecting large and small joints. Tenosynovitis is often present, but joint erosions or other radiographic changes are rare.

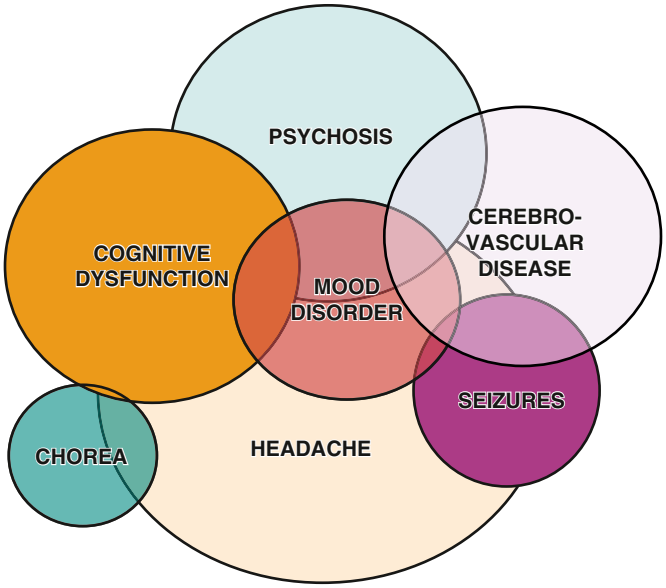

Fig. 199.2 Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE most commonly have more than one neuropsychiatric symptom—in particular for seizures. (*From Silverman E, Eddy A. Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al., eds. Textbook of Pediatric Rheumatology, 6th ed. Philadelphia: Saunders; 2011: Fig. 21-17, p. 329.*)

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE can present with **nephrotic syndrome** and/or **renal failure**, with the predominant symptoms being edema, fatigue, changes in urine color, and nausea/vomiting. Because SLE symptoms and findings may develop serially over several years and not all be present simultaneously, the diagnosis may require longitudinal follow-up. SLE is often characterized by periods of flare and disease quiescence but may follow a more smoldering disease course. The **neuropsychiatric complications** of SLE may occur with or without apparently active SLE, posing a particularly difficult diagnostic challenge in adolescents, who are already at high risk for mood disorders (Fig. 199.2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in early to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations arise even many years after diagnosis.

Table 199.3 Comparison of 1997 American College of Rheumatology and 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

	1997 ACR CRITERIA*	2012 SLICC CRITERIA*
CLINICAL CRITERIA Acute cutaneous lupus	• Malar rash†	• Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus†
Chronic cutaneous lupus	• Discoid rash	• Classic discoid rash, hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematous tumidus, chilblains lupus, or discoid lupus/lichen planus overlap
Mucosal ulcers	• Oral or nasal ulcers	• Oral (palate, buccal, tongue) or nasal ulcers
Other cutaneous	• Photosensitivity	• Nonscarring alopecia
Arthritis	• Nonerosive arthritis in ≥ two peripheral joints	• Synovitis in ≥ two peripheral joints
Serositis	• Pleuritis or pericarditis	• Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, or ECG evidence of pericarditis
Renal	• Persistent proteinuria representing > 500 mg/24 hr or cellular casts	• Urine protein/creatinine ratio representing >500 mg protein/24 hr or red blood cell casts
Neurologic	• Seizure or psychosis	• Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state
Hematologic	• Hemolytic anemia, leukopenia (<4,000/mm^3, lymphopenia (<1,500/mm^3), or thrombocytopenia (<100,000/mm^3)	• Hemolytic anemia • Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3) • Thrombocytopenia (<100,000/mm^3)
IMMUNOLOGIC	• Positive anti-double-stranded antibody or positive anti-Smith antibody • Positive antiphospholipid antibody (false-positive rapid plasma reagin test, positive lupus anticoagulant test result, or elevated anticardiolipin antibody level [IgG or IgM]) • Positive ANA	• Positive anti-double-stranded DNA antibody • Positive anti-Smith antibody • Positive antiphospholipid antibody (false-positive rapid plasma regain test, positive lupus anticoagulant test, medium to high titer anticardiolipin antibody level [IgA, IgG, IgM], or positive anti-B2-glycoprotein I antibody [IgA, IgG, IgM]) • Low C3, C4, or Ch50 level • Positive direct Coombs test (in the absence of hemolytic anemia) • Positive ANA

*For the 1997 ACR Criteria, the presence of 4 of 11 cumulative criteria establishes the classification of SLE. For the 2012 SLICC criteria, the presence of 4 cumulative criteria also establishes the classification of SLE; however, at least 1 clinical criterion and at least 1 immunologic criterion are required. In addition, the presence of biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA satisfies the 2012 SLICC criteria. For both sets of classification criteria, all items must be attributable to lupus and not an alternate cause (e.g., medication side effect).

†Each bullet point counts as a single criterion whether 1 or more definitions are satisfied.

Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, *Arthritis Rheum* 1997;40:1725; and from Petri M, et al: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, *Arthritis Rheum* 2012;64:2677-2686.

DIAGNOSIS

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Classification criteria for SLE were developed to identify appropriate subjects for clinical trials but are often used as guideposts for SLE diagnosis. Over the past several decades, SLE classification criteria have undergone serial updates. Both the **American College of Rheumatology (ACR) 1997 Revised Classification**

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE
If present, apply additive criteria

Additive criteria

- **Do not count a criterion if there is a more likely explanation than SLE.**
- **Occurrence of a criterion on at least one occasion is sufficient.**
- **SLE classification requires at least one clinical criterion and ≥10 points.**
- **Criteria need not occur simultaneously.**
- **Within each domain, only the highest weighted criterion is counted toward the total score.***

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5 g/24hr	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody† OR Anti-Smith antibody	6

Total score:

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled.

Fig. 199.3 Classification criteria for systemic lupus erythematosus (SLE). *Additional criteria items within the same domain will not be counted. †In an assay with ≥90% specificity against relevant disease controls. (*From Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus.* Arthritis Rheum. *2019;71[9]:1400–1412.*)

Criteria for SLE and the **2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria** (Table 199.3) are validated in childhood onset SLE populations, with the SLICC Criteria achieving higher sensitivity and the 1997 ACR Criteria achieving better specificity. In both the 1997 ACR and 2012 SLICC Criteria, a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE; however, ANA-negative lupus is extremely rare. The ANA test is very sensitive for SLE (95-99%) but is not very specific (~50%). The ANA may become positive many years before a diagnosis of SLE is established; however, most asymptomatic ANA-positive patients will never develop SLE. More recently, the **2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) SLE Classification Criteria** (Fig. 199.3) provided a different approach by requiring a positive antinuclear antibody (ANA) test result at a titer ≥1:80. Allthough the 2019 EULAR/ACR criteria have excellent sensitivity and specificity in the adult SLE population, they are still being validated in pediatric populations.

Anti-dsDNA and anti-Smith antibodies are specific for SLE (~98%) but not as sensitive (40–65%) as the ANA. **Hypocomplementemia** was not included in earlier classification criteria, but has been added to the two most recent classification criteria. The 2012 SLICC Criteria also added as criteria nonscarring alopecia, additional cutaneous and neurologic manifestations, and a positive direct Coombs test in the absence of hemolytic anemia.

Table 199.4 Main Differential Diagnoses of SLE (SLE Mimickers)

OTHER CONNECTIVE TISSUE DISEASES
Sjögren (SSA+), dermatomyositis (rash), mixed connective tissue disease
INFECTIOUS DISEASES
Endocarditis; hepatitis A, B, C, E; parvovirus B19; HIV; EBV; CMV; Lyme; disseminated gonococcal arthritis; toxoplasmosis; histoplasmosis; mycobacterial diseases; tinea faciei; visceral leishmaniasis; Whipple disease
HEMATOLOGIC MALIGNANCIES
Hodgkin lymphoma, myelodysplastic syndromes, angioimmunoblastic T-cell lymphoma
SOLID TUMORS AND PARANEOPLASTIC SYNDROMES
Thymoma, carcinoma of the lung, breast, and ovary with paraneoplastic syndromes
OTHER DISEASES
Meigs and Pseudo-Meigs syndrome Multiple sclerosis Castleman disease Interferonopathies (monogenic SLE) Still disease (and other autoinflammatory diseases) Evans syndrome (with primary immune deficiency) Complement deficiency Hypocomplementemic urticarial vasculitis Schizophrenia and other psychoses Kikuchi disease IgG4-related disease Chilblains (cold-induced) Ackerman syndrome and erythema elevatum diutinum with polyarthritis Drug-induced lupus and drug-induced polyarthritis Graft-versus-host disease Systemic manifestations of atrial myxoma Prolidase deficiency

From Chasset F, Richez C, Martin T, et al. Rare diseases that mimic systemic lupus erythematosus (lupus mimickers). *Joint Bone Spine*. 2019;86:165–171, Table 1, p. 166 Copyright Elsevier Masson SAS.

DIFFERENTIAL DIAGNOSIS

Multiorgan disease is the hallmark of SLE, and given its wide array of potential clinical manifestations, SLE is in the differential diagnosis of many clinical scenarios, including unexplained fevers, joint pain or arthritis, rash, cytopenias, nephritis, nephrotic syndrome, pleural or pericardial effusions or other cardiopulmonary abnormalities, and new-onset psychosis or seizures. For patients ultimately diagnosed with pediatric SLE, the initial differential diagnosis often includes infections (sepsis, Epstein-Barr virus, parvovirus B19, endocarditis), malignancies (leukemia and lymphoma), poststreptococcal glomerulonephritis, other rheumatologic conditions (juvenile idiopathic arthritis, vasculitides), and drug-induced lupus (Table 199.4).

Drug-induced lupus refers to the presence of SLE manifestations triggered by exposure to specific medications, including hydralazine, minocycline, many anticonvulsants, sulfonamides, antiarrhythmic agents, and other drugs (Table 199.5). In individuals prone to SLE, these agents may act as a trigger for true SLE, but more commonly these agents provoke a reversible lupus-like syndrome. Unlike SLE, drug-induced lupus affects males and females equally. A genetic predisposition toward slow drug acetylation may increase the risk of drug-induced lupus. Circulating **antihistone antibodies** are often present in drug-induced SLE; these antibodies are only detected in up to 20% of individuals with SLE. Hepatitis, which is rare in SLE, is more common in drug-induced lupus. Individuals with drug-induced lupus are less likely to demonstrate antibodies to dsDNA, hypocomplementemia, and significant renal or neurologic disease. In contrast to SLE, manifestations of drug-induced lupus typically resolve after withdrawal of the offending medication; however, complete recovery may take several months to years, requiring treatment, often with hydroxychloroquine, NSAIDs, and/or corticosteroids.

Table 199.5 Medications Associated with Drug-Induced Lupus

DEFINITE ASSOCIATION
Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab
PROBABLE ASSOCIATION
Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, β blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil

Table 199.6 Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE)

ANTIBODY	CLINICAL ASSOCIATION
Anti–double-stranded DNA (anti-dsDNA)	Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody (anti-Sm)	Specific for the diagnosis of SLE
Anti-ribonucleoprotein antibody (anti-RNP)	Increased risk for Raynaud phenomenon, interstitial lung disease, and pulmonary hypertension
Anti-Ro antibody (anti-SSA) Anti-La antibody (anti-SSB)	Associated with sicca syndrome May suggest diagnosis of Sjögren syndrome Increased risk of neonatal lupus in offspring (congenital heart block) May be associated with cutaneous and pulmonary manifestations of SLE May be associated with isolated discoid lupus
Antiphospholipid antibodies (including lupus anticoagulant and anti-cardiolipin or anti-beta-2 glycoprotein antibodies)	Increased risk for venous and arterial thrombotic events
Antihistone antibodies	Present in a majority of patients with drug-induced lupus May be present in SLE

LABORATORY FINDINGS

A positive ANA test is present in 95–99% of individuals with SLE. The ANA has poor specificity for SLE, as up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screen for SLE when used in isolation. After diagnosis, ANA titers are not reflective of disease activity; therefore repeat ANA testing in SLE patients is not helpful. Antibodies to dsDNA are specific for SLE, and in many individuals, anti-dsDNA levels correlate with disease activity, particularly in those with significant nephritis. Anti-Smith antibody, although found specifically in patients with SLE, does not correlate with disease activity. Serum levels of total hemolytic complement (CH_{50}), C3, and C4 are typically decreased in active disease and often improve with treatment. Table 199.6 lists autoantibodies

found in SLE along with their clinical associations. Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly the erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity; significantly elevated CRP values often reflect infection, whereas chronic mild elevation of CRP may indicate increased cardiovascular risk.

Antiphospholipid antibodies, which increase clotting risk, can be found in up to 66% of children and adolescents with SLE. The primary antiphospholipid antibodies are lupus anticoagulant, anticardiolipin, and anti–beta-2 glycoprotein antibodies. When an arterial or venous clotting event occurs in the presence of an antiphospholipid antibody, **antiphospholipid antibody syndrome** is diagnosed. Antiphospholipid antibody syndrome can occur in the context of SLE (secondary) or independent of SLE (primary) (see Chapter 528). Rarely, antiphospholipid antibodies can result in catastrophic antiphospholipid syndrome, a condition in which clots affect three or more organs/tissues simultaneously; this condition has a very high mortality rate.

TREATMENT

Treatment of SLE is tailored to the individual and is based on specific disease manifestations and medication tolerability. For all patients, sunscreen and avoidance of prolonged direct sun exposure and other ultraviolet light may help control disease and should be reinforced at every visit with the patient. **Hydroxychloroquine is recommended for all individuals with SLE when tolerated.** In addition to treating mild SLE manifestations such as rash and mild arthritis, hydroxychloroquine prevents SLE flares, improves lipid profiles, and may have a beneficial impact on mortality and renal outcomes. Potential toxicities include retinal pigmentation that leads to vision impairment; therefore *annual ophthalmology exams are recommended for patients taking hydroxychloroquine, including automated visual field testing and spectral-domain optical coherence tomography (SD-OCT)*. Given that risk factors for ocular toxicity include duration of use and dose, hydroxychloroquine in SLE should not be prescribed at doses greater than 5 mg/kg to a maximum of 400 mg daily.

Corticosteroids are a treatment mainstay for significant manifestations of SLE and work quickly to improve acute deterioration; side effects often limit patient adherence, especially in adolescence, and potential toxicities are worrisome. It is important to limit the dose and length of exposure to corticosteroids whenever possible. Potential consequences of corticosteroid therapy include growth disturbance, weight gain, striae, acne, hyperglycemia, hypertension, cataracts, avascular necrosis, and osteoporosis. The optimal dosing of corticosteroids in children and adolescents with SLE remains unknown; **severe disease is often treated with high doses of intravenous methylprednisolone (e.g., 30 mg/kg/day to a maximum of 1,000 mg for each of 3 days, sometimes followed by a period of weekly pulses) and/or high doses of oral prednisone** (often starting at **1 mg/kg/day).** As disease manifestations improve, corticosteroid dosages are gradually tapered over months. For most patients it is necessary to introduce a steroid-sparing immunosuppressive medication in order to limit cumulative steroid exposure.

Steroid-sparing immunosuppressive agents for the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, tacrolimus, cyclophosphamide, rituximab, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Cyclophosphamide, mycophenolate mofetil, and azathioprine are appropriate for the treatment of lupus nephritis, whereas mycophenolate mofetil and rituximab are often used for the treatment of significant hematologic manifestations, including severe leukopenia, hemolytic anemia, or thrombocytopenia.

Cyclophosphamide, usually administered intravenously, is reserved for the most severe, potentially life-threatening SLE manifestations, such as renal, neurologic, and cardiopulmonary disease. Although cyclophosphamide is highly effective in controlling disease, the potential toxicities are significant, including cytopenias, infection, hemorrhagic cystitis, premature gonadal failure, and increased risk of future malignancy. Attention to adequate hydration can attenuate the risk of hemorrhagic cystitis. Fortunately, young females are at much lower risk of gonadal failure than older women, and the use of gonadotropin-releasing hormone agonists, such as leuprolide acetate, may help prevent gonadal failure.

The Childhood Arthritis Rheumatology Research Alliance (CARRA) has developed a consensus treatment plan for induction therapy of newly diagnosed proliferative lupus nephritis (class III and IV) that is specific to the pSLE population; the treatment plan is considered necessary for class III and IV lupus nephritis but also appropriate for certain patients with other classes of lupus nephritis. The CARRA treatment plan advises 6 months of induction therapy with either cyclophosphamide (given per the National Institutes of Health [NIH] protocol as 500-1,000 mg/m^2 IV monthly) or mycophenolate mofetil (dosed as 600 mg/m^2 bid up to 1,500 mg bid), used in combination with one of three standardized glucocorticoid regimens. For patients who fail to achieve a partial response in 6 months, it is appropriate to switch agents. For adult-weight adolescents, the cyclophosphamide dosing regimen used in the Euro-Lupus Nephritis Trial can be considered in lieu of the previous 6-month therapy in an effort to reduce toxicity from cyclophosphamide exposure. Per this protocol, a fixed dose of 500 mg is given every 2 weeks for 3 months; in adults, this regimen is althought to reduce adverse effects while maintaining comparable efficacy for lupus nephritis, though this regimen has not been studied specifically in pediatric lupus. It should be noted that oral medication adherence is very poor in pSLE, and this must be taken into consideration when weighing the benefits of an IV infusion versus a twice daily oral medication such as mycophenolate mofetil. After the 6-month induction therapy, maintenance therapy for lupus nephritis consists of quarterly IV cyclophosphamide (dosed 500-1,000 mg/m^2 once every 3 months), mycophenolate, or azathioprine, with mycophenolate generally being the preferred agent. Maintenance therapy is typically continued for a minimum of 30 months after the completion of induction therapy, but in many circumstances, it is continued longer.

Calcineurin inhibitors such as tacrolimus are often adjunct therapy in the treatment of refractory lupus nephritis. Voclosporin, Food and Drug Administration (FDA)–approved for adults with lupus nephritis, awaits pediatric study. Clinical trial data on the use of rituximab in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but post hoc analysis from the LUNAR study suggests there may be benefit for subpopulations of SLE patients. The FDA has approved the use of belimumab, a monoclonal antibody against BLyS/BAFF, for the treatment of lupus in adults and children; when added to standard SLE therapy, belimumab improves markers of disease activity in renal and nonrenal lupus. Belimumab has been shown to improve renal outcomes in adults, and while it is not used as monotherapy to treat lupus nephritis, it can be used in addition to standard therapy to help achieve renal remission without substantial increase in risk of infectious complications. Anifrolumab (a monoclonal antibody to the interferon-α receptor), achieved 2021 FDA approval for treatment of adult nonrenal SLE, and studies in lupus nephritis and pediatric lupus are forthcoming. Several novel therapies are in the pipeline for the treatment of SLE and lupus nephritis, including Janus kinase inhibitors.

Given the lifelong nature of SLE, optimal care of children and adolescents with this disease also involves preventive practices. Owing to the enhanced risk of atherosclerosis in SLE, attention to cholesterol levels, smoking status, body mass index, blood pressure, and other traditional cardiovascular risk factors is warranted. Even though the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study failed to support placing all children with SLE on a statin, post hoc analyses suggest that statins can be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP.

Table 199.7 Morbidity in Childhood Lupus

Renal	Hypertension, dialysis, transplantation
Central nervous system	Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction
Cardiovascular	Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease
Immune	Recurrent or severe infection, functional asplenia, malignancy
Musculoskeletal	Osteopenia, compression fractures, avascular necrosis
Ocular	Cataracts, glaucoma, retinal detachment, blindness
Endocrine	Diabetes, obesity, growth failure, infertility, fetal wastage

From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*, 6th ed. Philadelphia: Saunders; 2011.

SLE patients with antiphospholipid antibody syndrome (antiphospholipid antibodies and a history of arterial or venous clot or pregnancy morbidity) are treated with long-term anticoagulation to prevent thrombotic events; for SLE patients who are antiphospholipid antibody positive without a history of clots, many pediatric rheumatologists prescribe aspirin 81 mg daily.

For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis, particularly as vitamin D levels are lower in pSLE patients compared with age-matched healthy controls. It is worth noting recent studies suggest a link between hypovitaminosis D and SLE susceptibility and also offer an emerging role for vitamin D in immunomodulation.

Infections, particularly pneumococcal disease, commonly complicate SLE, so routine immunization is recommended, including the annual influenza vaccination, SARS-CoV-2 vaccination, and vaccination against human papilloma virus (HPV). In addition, pSLE patients age 6 or older should receive a dose of PPSV23 at least 8 weeks after completing all recommended pneumococcal vaccine series with PCV13 or PCV15. Many of the immunosuppressant medications used in SLE contraindicate administration of live vaccines. Prompt attention to febrile episodes should include an evaluation for serious infections. Because pSLE patients are at high risk for developing anxiety and depression, screening for depression is important. Peer support and cognitive-behavioral therapy interventions reduce pain and enhance resilience in pSLE.

Pregnancy can worsen SLE, and obstetric complications are common. In addition, many medications used to treat SLE are teratogenic. As a consequence, it is important to counsel adolescent girls about these risks and facilitate access to appropriate contraceptive options. Hydroxychloroquine is recommended throughout pregnancy for all SLE patients, whereas other medications may need to be adjusted.

COMPLICATIONS

Within the first several years of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease (Table 199.7). Over the long term, the most common causes of mortality are atherosclerosis and malignancy. The increased risk of premature atherosclerosis in SLE is not explained by traditional risk factors and is partly a result of the chronic immune dysregulation and inflammation associated with SLE. Increased malignancy rates may be caused by immune dysregulation and exposure to medications with carcinogenic potential. Potential lupus emergencies are noted in Table 199.8.

Table 199.8 A Summary of Signs and Symptoms Indicative of Lupus Emergencies

SIGNS/SYMPTOMS	DIFFERENTIAL CONSIDERATIONS
Fever	Evaluate for infection Consider disease flare Consider macrophage activation syndrome
Thrombosis/hemoptysis	May be arterial or venous Evaluate for antiphospholipid syndrome
Chest pain	Pleurisy, pericarditis, pulmonary infarction/embolus
Dyspnea	Pneumonitis, alveolar hemorrhage, pleural effusions, congestive heart failure
Headache	Vascular headaches, meningitis, thrombus, cerebrovascular accident, hypertensive crisis
Altered mental status	Cerebritis, hypertensive crisis, macrophage activation syndrome, stroke, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome
Rash	Vasculitis lesions, palpable purpura, infarction
Icterus	Autoimmune hemolysis Autoimmune hepatitis
Petechiae	Thrombotic thrombocytopenia purpura
Seizure	Cerebritis, infection, metabolic causes, hypertensive crisis

From Harry O, Yasin S, Brunner H. Childhood-onset systemic lupus erythematosus: a review and update. *J Pediatr.* 2018;196:22–30, Table IV.

PROGNOSIS

SLE disease severity is higher in childhood-onset SLE compared with adult-onset SLE. Fortunately, advances in the diagnosis and treatment of SLE have led to dramatically improved survival over the past 50 years. The 5-year and 10-year survival rates for pSLE are 99% and 97%, respectively, in high-income countries, although these survival rates are 85% and 79%, respectively, in low- and middle-income countries. Infection contributes significantly to mortality in pediatric lupus. In addition, early in the disease course, lupus nephritis, lupus cerebritis, and complications such as macrophage activation syndrome are primary causes of mortality, whereas later in the disease course, atherosclerosis and malignancy become larger contributors to mortality. Given their long burden of disease, children and adolescents with SLE face high risks of future morbidity and mortality from the disease and its complications, as well as medication side effects. Because pSLE is a complex, chronic disease with a high risk for morbidity and mortality, optimal care for children and adolescents with SLE includes treatment by pediatric rheumatologists in a multidisciplinary clinic with access to a full complement of pediatric subspecialists. Furthermore, because SLE is a lifelong disease, it is critically important to ensure an appropriate transition to an adult model of care, which helps avoid interruptions in rheumatology care.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

199.1 Neonatal Lupus

Deborah M. Friedman, Jill P. Buyon, Rebecca E. Sadun, and Stacy P. Ardoin

Neonatal lupus erythematosus (NLE), an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. NLE is not an autoimmune disease of the fetus, but instead results from passively acquired autoimmunity, when maternal immunoglobulin G autoantibodies cross the placenta and enter the fetal circulation. In contrast to SLE, neonatal lupus is not characterized by ongoing immune dysregulation, although infants with neonatal lupus may be at some increased risk for development of future autoimmune disease. The vast majority of NLE cases are associated with maternal anti-Ro (also known as SSA), anti-La antibodies (also known as SSB), or anti-RNP autoantibodies.

Despite the clear association with maternal autoantibodies, their presence alone is not sufficient to cause disease, as only ~2% of offspring born to mothers with anti-Ro and anti-La antibodies develop neonatal lupus. Increasing evidence supports the observation that generally high maternal anti-Ro titers are necessary for fetal clinical disease. In the prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) study, the median anti-Ro titer for pregnancies resulting in heart block was 5 times as high as the median anti-Ro titer in unaffected pregnancies. Another group identified heart block in 8% of cases with very high anti-Ro antibody titers, with no cases among women with low or moderate titers.

Siblings of infants with NLE have a 15–20% chance of developing NLE. Neonatal lupus seems to be independent of the maternal health because many mothers are asymptomatic and only identified to have anti-Ro/anti-La antibodies subsequent to the diagnosis of NLE. Roughly half of the infants with NLE are born to the mothers with a defined rheumatic disease such as Sjogren syndrome or SLE.

Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 199.4). The rash can be present at birth but more often appears within the first 6-8 weeks of life, after exposure to ultraviolet light, and typically lasts 3-4 months. Infants may also have cytopenias and hepatitis, each occurring in ~25% of cases, but the most concerning complication is congenital heart block.

Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive cardiomyopathy in the most severe cases. The noncardiac manifestations of neonatal lupus are usually reversible, whereas third-degree congenital heart block is permanent. Conduction system abnormalities can be detected in utero by fetal echocardiogram beginning at 16 weeks of gestational age. Neonatal lupus cardiac disease has a mortality rate of ~20%. Cardiac NLE can manifest as heart block, cardiomyopathy, valvular dysfunction, and endocardial fibroelastosis. Fetal bradycardia from heart block can lead to hydrops fetalis.

In vitro studies suggest that during cardiac development via apoptosis, Ro and La antigens may be exposed on the surface of cardiac cells in the proximity of the atrioventricular node, making the antigens accessible to maternal autoantibodies. Binding incites a local immune response, resulting in fibrosis within the conduction system and more extensive disease in fatal cases. In the skin, exposure to ultraviolet light results in cell damage and the subsequent exposure of Ro and La antigens, inducing a similar local inflammatory response that produces the characteristic rash.

Although the scant clinical trial data have been mixed, fluorinated corticosteroids (dexamethasone or betamethasone), intravenous immunoglobulin (IVIG) at 1-2 g/kg maternal weight, plasmapheresis, hydroxychloroquine, and terbutaline (combined with steroids) have been used in pregnant women with anti-Ro or anti-La antibodies to prevent occurrence or progression of fetal cardiac abnormalities.



Fig. 199.4 Neonatal lupus syndrome. Typical rash, often photosensitive with a malar distribution, appearing as annular plaques with erythema and scaling. (*From Pain C, Beresford MW. Neonatal lupus syndrome.* Paediatr Child Health. *2007;17:223–227.*)

Most encouraging are retrospective cohort studies suggesting maternal treatment with hydroxychloroquine may reduce the frequency and recurrence of congenital heart block. In a multicenter, single-arm, open-label clinical trial assessing the efficacy of hydroxychloroquine to prevent recurrent autoantibody-associated congenital heart block, hydroxychloroquine treatment reduced the risk of recurrent heart block compared to historical controls by over 50%, from 17.5% to less than 8% of pregnancies.

Significant conduction system abnormalities after birth are treated with cardiac pacing and occasionally IVIG and steroids, whereas severe cardiomyopathy may require cardiac transplantation. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. With cardiac pacing, however, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis. In a long-term follow-up study of 239 subjects enrolled in the Research Registry for Neonatal Lupus, 22% of subjects had cardiac dysfunction in the first year of life. Cardiac dysfunction often regressed; nevertheless, some dysfunction did appear later in childhood. Risk factors for cardiac dysfunction were being male or of low socioeconomic status and having low fetal heart rates, a longer period of pacing, or extranodal cardiac disease. In a Swedish cohort of 119 children with congenital heart block, 16.8% developed cardiomyopathy ± congestive heart failure. Congenital heart block increased the risk of cerebral infarctions and infections. Pacemaker treatment was associated with decreased risk of developing cerebral infarction but increased risk of infection and cardiomyopathy.

Noncardiac manifestations are typically transient and are conservatively managed, often with supportive care alone. Topical steroids can be used to treat moderate to severe NLE rash. Cytopenias may improve over time but severe cases occasionally require IVIG. Supportive care is usually appropriate for hepatic and neurologic manifestation. When the neonate clears maternal autoantibodies over the first 6 months of life, these inflammatory manifestations gradually resolve.

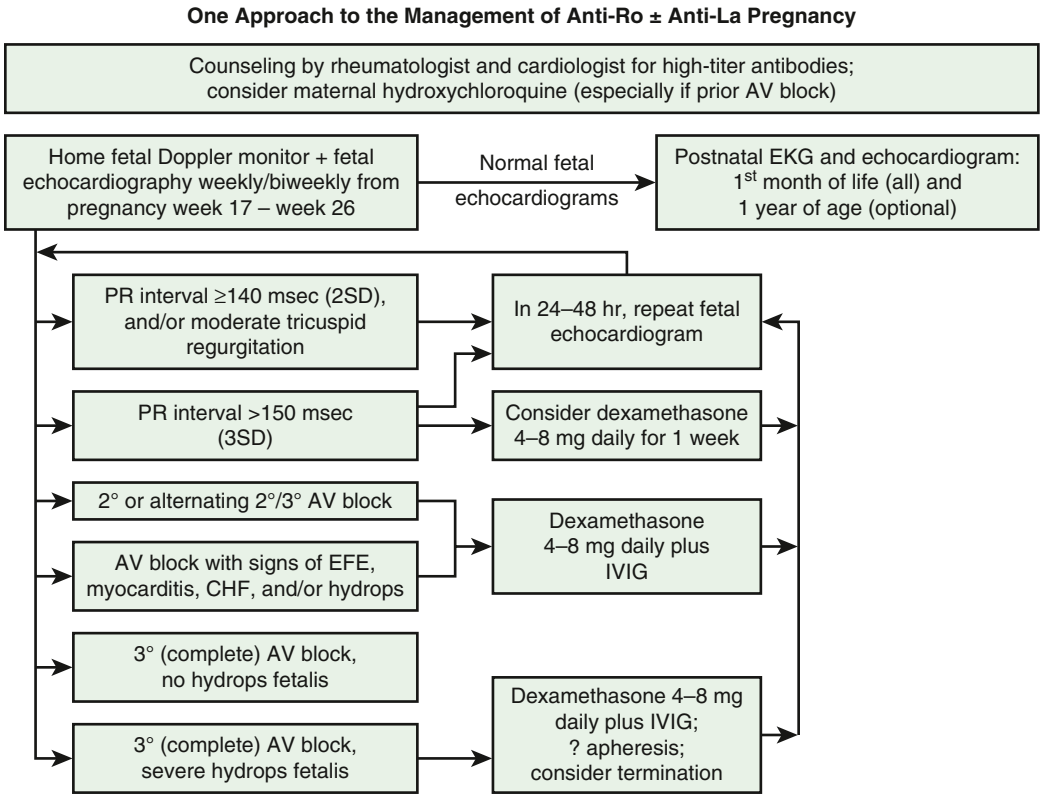

Fig. 199.5 Suggested algorithm for the management of anti-Ro ± anti-La pregnancy. All such pregnancies should include counseling and serial fetal echocardiograms.

Because maternal autoantibodies begin to gain access to the fetus through the placenta via FcRn at about 12 weeks gestation, all pregnant women with circulating anti-Ro and/or anti-La antibodies, or those with a history of offspring with neonatal lupus or congenital heart block, are generally advised to be monitored by a pediatric cardiologist, with screening fetal echocardiography performed weekly or biweekly from 17-26 weeks of gestation. The period of greatest vulnerability is usually 18-24 weeks. If fetal bradycardia is found during routine in utero monitoring in a mother never evaluated for the putative antibodies and if fetal echocardiography confirms a conduction defect, screening for maternal anti-Ro and anti-La antibodies is warranted. In pregnancies at risk for congenital heart block, maternal home monitoring of fetal heart rate using a handheld fetal heart rate monitor 2-3 times daily allows for accurate and early detection of heart rate abnormalities.

A proposed management algorithm is presented in Figure 199.5.

A multicenter retrospective study concluded that *maternal treatment* with dexamethasone and/or intravenous gamma globulin should be initiated in all cases of anti-SSA/Ro antibody cardiac manifestations, including significant first-degree or any higher atrioventricular block, isolated endocardial fibroelastosis, or sinus bradycardia. However, other studies suggest that treatment should be individualized to fetuses at high risk and not universally instituted for isolated complete third-degree block, which is generally considered immutable.

The negative predictive value of antibody titers to identify pregnancies at low risk of fetal atrioventricular block has also been studied. Excluding women with previously affected children, leveraging samples obtained from anti-SSA/Ro exposed pregnancies with and without fetal atrioventricular block, no case of heart block developed among subjects with anti-Ro52 and anti-Ro60 titers of <110 arbitrary units per milliliter using the multiplex bead assay of the Associated Regional and University Pathologists Laboratories (n=141). Applying these 100% negative predictive value thresholds, approximately 50% of the anti-Ro/SSA antibody pregnancies that ultimately had no fetal atrioventricular block could be excluded from surveillance.

Emerging data suggest that not all mothers with anti-SSA/Ro antibodies require surveillance. Based on review of the literature, the Society for Maternal-Fetal Medicine published guidelines that recommended "…that serial fetal echocardiograms for assessment of the PR interval not be routinely performed in patients with anti-SSA/SSB antibodies outside of a clinical trial setting" but rather that, "Doppler assessment of fetal heart rate during routine prenatal visits can be used to screen for fetal complete heart block. Once complete heart block develops, management is expectant, with weekly ultrasound examinations recommended to assess for hydrops."

Guidelines in this domain continue to evolve as new data advances our approach to risk stratification

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 200

Juvenile Dermatomyositis

Jeffrey A. Dvergsten and Ann M. Reed

Juvenile dermatomyositis (JDM) is the most common of the *juvenile idiopathic inflammatory myopathies (JIIMs),* representing up to 85% of all patients with these rare vasculopathic diseases. It is characterized by proximal muscle weakness and distinctive rashes of the face and extensor joint surfaces.

EPIDEMIOLOGY

The incidence of JDM is approximately 3 cases/1 million children/yr, with an incidence similar in White and Black non-Hispanics and an apparent lower incidence in Hispanics. The peak age of onset is 7 years with a second peak of onset in late adulthood (45-64 years); however, adult-onset dermatomyositis appears to be a distinctly separate entity, both in prognosis and etiology. In the United States the ratio of females to males with JDM is 2:1. Multiple cases of myositis in a single family are rare, but familial autoimmune disease may be increased in families with children who have JDM when compared to families of children without autoimmune disease. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

ETIOLOGY

A precise understanding of the etiology and pathogenesis of JDM remains elusive; many factors that affect elements of innate and adaptive immunity have been identified as contributing to onset and perpetuation of disease. Evidence suggests that the etiology of JDM is multifaceted, with a genetic predisposition influenced by an environmental factor triggering events leading to disease pathogenesis.

Genetic factors that are associated with increased susceptibility to JDM include human leukocyte antigen (HLA) alleles DRB1*0301, DQA1*0501, and DQA1*0301. Additionally, HLA-DQA1*0501 is found on maternal cells present in blood and tissue samples of children with JDM, an example of maternal microchimerism, which has been proposed to play an etiologic role in JDM by creating an immune response comparable to graft-versus-host disease (GVHD). Other polymorphisms implicated in JDM include those affecting cytokine genes such as the tumor necrosis factor (TNF)-α promoter and the variable-number tandem repeats of the interleukin (IL)-1 receptor antagonist A1 gene. An increase in TNF-α may be associated with persistent immune activation leading to a longer disease course. The IL-1 receptor antagonist A1 allele is associated with the development of JIIM in White but not in Black persons, in whom the A3 allele, instead, is a possible risk factor. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported. Short-term increases in ultraviolet (UV) index before the onset of disease have been reported; however, no clear theory of etiology has emerged. A history of infection in the 3 months before disease onset is usually reported; multiple studies have failed to produce a causative organism. Constitutional signs and upper respiratory symptoms predominate, but one third of patients report preceding gastrointestinal (GI) symptoms. Group A streptococcus, upper respiratory infections, GI infections, coxsackievirus B, toxoplasma, enteroviruses, parvovirus B19, and multiple other organisms have been postulated as possible pathogens in the etiology of JDM. Despite these concerns, results of serum antibody testing and polymerase chain reaction amplification of the blood and muscle tissue for multiple infectious diseases have not been revealing.

PATHOGENESIS

JDM and related immune myositis syndromes are believed to be an autoimmune vasculopathic inflammatory disease affecting capillaries of multiple organs, but most notably, the skin, muscles, and GI tract (Table 200.1). Pathogenic mechanisms are both immune and nonimmune with cellular and soluble constituents of the innate and adaptive immune systems and pathways of cellular injury involved. Type I interferons (IFNs), principally α and β, are cytokines of the innate immune system that play a significant role in the pathogenesis of JDM by modulating several immune mechanisms, including upregulation of major histocompatibility complex (MHC) class I molecules on muscle cells; induction of proinflammatory cytokine, chemokine, and adhesion molecule production; and supporting cytotoxic effects of innate and adaptive immune cells. Plasmacytoid dendritic cells (pDCs) play an important role in JDM and are principal producers of type I IFN upon activation of Toll-like receptor (TLR) 9 on their surface by viruses. Cells involved in the inflammatory cascade include monocytes/macrophages (CD14), T-cell subsets (CD4, CD8, Th17), natural killer (NK) cells (CD56), and dendritic cells (DCs). MHC class I upregulation induces endoplasmic reticulum (ER) stress, which results in the degradation of contractile proteins; additional downstream effects of type I IFN include autoantibody production and B-cell proliferation. Galectin-9 and CXCL10 (IP-10) are two IFN-related proteins that have been validated as sensitive and specific peripheral biomarkers of disease activity in JDM.

CLINICAL MANIFESTATIONS

Children with JDM present with either rash, insidious onset of weakness, or both. Fevers, dysphagia or dysphonia, arthritis, muscle tenderness, and fatigue are also commonly reported at diagnosis (Tables 200.2 and 200.3). Certain myositis-specific antibodies are associated with different phenotypic patterns of disease (Fig. 200.1).

Rash develops as the first symptom in 50% of patients and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to UV light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the **shawl sign**. Erythema is also commonly seen over the knees and elbows. The characteristic **heliotrope rash** is a blue-violet discoloration of the eyelids that may be associated with periorbital edema (Fig. 200.2). Facial erythema crossing the nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus (SLE). Classic **Gottron papules** are bright-pink or pale, shiny, thickened, or atrophic plaques over the metacarpal phalangeal joints, proximal interphalangeal joints, and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli (Fig. 200.3). The rash of JDM is sometimes mistaken for eczema or psoriasis. Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as **mechanic's hands**) and soles along the flexor tendons, which is associated with anti–Jo-1 antibodies.

Evidence of small vessel inflammation is often visible in the nail folds and gums as individual capillaries display changes including loops, thickening, tortuosity, or loss (Fig. 200.4C). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with another magnifier (e.g., ophthalmoscope). Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

Early in disease, weakness associated with JDM is often insidious and difficult to differentiate from fatigue. It is typically symmetric, affecting proximal muscles such as the neck flexors, shoulder girdle, and hip flexors. Parents may report difficulty climbing stairs, combing hair, and getting out of bed. Examination reveals inability to perform a sit-up, head lag in a child after infancy, and **Gower sign** (use of hands climbing on thighs to help stand from a sitting position). Patients with JDM may roll to the side rather than sit straight up from lying to compensate for truncal weakness. Approximately half of children exhibit muscle tenderness because of muscle inflammation.

Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure. It is essential to assess for dysphonia or nasal speech, palatal elevation with gag, dysphagia, and gastroesophageal reflux by means of history and physical examination. If any of these are abnormal, a swallow study should be pursued. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure.

Table 200.1 Clinical Associations: Myositis-Specific Antibodies (MSA) and Myositis-Associated Antibodies (MAA) in Juvenile-Onset Myositis (JOM)

AUTOANTIBODY	TARGET AUTOANTIGEN	PREVALENCE (%) IN PATIENTS WITH JOM	CLINICAL ASSOCIATIONS
Common myositis-specific autoantibodies are found in 45–55% of patients with juvenile-onset myositis			
Anti-Mi2	Nucleosome remodeling deacetylase complex (NuRD)	3–4	• "Classic" dermatomyositis • Responds well to standard therapies • Favorable prognosis
Anti-TIF1g (p155/140, TRIM33)	Transcriptional intermediary factor 1 gamma (TIF1-γ)	18–35	• Severe cutaneous disease • Rashes in photoexposed pattern • Chronic disease course • Lipodystrophy
Anti-NXP2 (p140, MJ)	Nuclear matrix protein 2 (NXP2)	15–22	• Calcinosis • More severe muscle disease • Gastrointestinal bleeding, ulcers, and dysphagia • Worse disease outcome and functional status
Anti-MDA5 (CADM-140)	Melanoma differentiation–associated gene 5 (MDA5)	6	• More common in East Asia, where associated with clinically amyopathic myositis, rapidly progressive interstitial lung disease, and a high mortality rate • In White populations associated with mild muscle disease, interstitial lung disease, arthritis, and ulceration
Rare but clinically important myositis-specific autoantibodies are found in 5–8% of patients with juvenile-onset myositis antisynthetases (Jo-1, PL12, PL7, OJ, EJ, KS, Zo, and Ha)			
ANTISYNTHETASES			• Antisynthetase syndrome: myositis, interstitial lung disease, fever, mechanic's hands, Raynaud phenomenon, and arthritis • Occurs in older children • Increased mortality
- Jo-1	- Histidyl	2–3	
- PL12	- Alanyl	2–3	
- PL7	- Threonyl	2–3	
- OJ	- Isoleucyl	2–3	
- EJ	- Glycyl	2–3	
- KS	- Asparaginyl	2–3	
- Zo	- Phenylalanyl	2–3	
- Ha	- Tyrosyl	2–3	
Anti-SRP	Signal recognition particle (SRP)	2	• Necrotizing autoimmune myositis • Severe weakness, muscle necrosis, high CK • Cardiac involvement • Occurs in older children • No rash • May be refractory to standard treatment
Anti-HMGCR	HMGCR	1	• Necrotizing autoimmune myositis, muscle necrosis, high CK, dysphagia, no statin exposure
Anti-SAE	Small ubiquitin-like modifier–activating enzyme (SAE)	1	• Initially amyopathic disease with muscle involvement occurring later
Myositis-associated autoantibodies are found in 16–20% of patients with juvenile-onset myositis. Some may occur in conjunction with a myositis-specific autoantibody.			
Anti-PmScl	Exosome-associated PM- Scl-75; PM-Scl-100; C1D	5	• Overlap syndromes
Anti-U1RNP	U1RNP	2	• Overlap syndromes
Anti-Ro52	Ro52	5	• Overlap syndromes • May be found in conjunction with other MSA, particularly antisynthetases

Common MSAs are present in 45–55% of the U.S. pediatric population with juvenile-onset myositis. Rare MSAs are present in 5–8%. Myositis-associated autoantibodies (MAAs) are found in 16–20% of juvenile-onset myositis, with or without an accompanying MSA.

CK, Creatine kinase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme reductase; MDA, melanoma differentiation-associated; NuRD, nucleosome remodeling deacetylase; SAE, small ubiquitin-like modifier–activating enzyme; SRP, signal recognition particle; TIF, transcriptional intermediary factor.

Modified from Pachman LM, Khojah AM. Advances in juvenile dermatomyositis: myositis specific antibodies aid in understanding disease heterogeneity. *J Pediatr*. 2018;195:16–27.

Table 200.2 Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus three of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate transaminase Lactate dehydrogenase Aldolase
Electromyographic changes	Short, small polyphasic motor unit potentials Fibrillations Positive sharp waves Insertional irritability Bizarre, high-frequency repetitive discharges
Muscle biopsy	Necrosis Inflammation

Data from Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med.* 1975;292:403–407.

Table 200.3 Clinical Features of Juvenile Dermatomyositis During Disease Course

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-75
Skin lesions	85-100
Heliotrope rash of eyelids	66-95
Gottron papules	57-95
Erythematous rash of malar/facial area	42-100
Periungual (nail fold) capillary changes	80-90
Photosensitive rash	5-42
Ulcerations	22-30
Calcinosis	12-30
Lipodystrophy	11-14
Raynaud phenomenon	2-15
Arthritis and arthralgia	22-58
Joint contractures	26-27
Fever	16-65
Gastrointestinal signs and symptoms	8-37
Restrictive pulmonary disease	4-32
Interstitial lung disease	1-7
Cardiac involvement	0-3

From Rider LG, Lindsley CB, Cassidy JT. Juvenile dermatomyositis. In: Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology,* 6th ed. Philadelphia: Saunders; 2011: Table 24.20, p. 410.

Children with respiratory muscle weakness do *not* manifest typical symptoms of impending respiratory failure with increased work of breathing, instead demonstrating hypercarbia rather than hypoxemia. Evaluation of respiratory muscle function by negative inspiratory force (NIF) measurement can be performed in the clinic or at the bedside.

DIAGNOSIS

Diagnosis of dermatomyositis requires the presence of a characteristic rash and at least three signs of muscle inflammation and weakness (see Table 200.2). Diagnostic criteria developed in 1975 predate the use of MRI and have not been validated in children. Diagnosis is often delayed because of the insidious nature of disease onset.

Electromyography (EMG) shows signs of myopathy (increased insertional activity, fibrillations, sharp waves) and muscle fiber necrosis (decreased action potential amplitude and duration). Nerve conduction studies are typically normal unless severe muscle necrosis and atrophy are present. It is important that EMG be performed in a center with experience in pediatric EMG and its interpretation. **Muscle biopsy** is typically indicated when the diagnosis is in doubt or for grading disease severity (see Fig. 200.4A). Biopsy of involved muscle reveals focal necrosis and phagocytosis of muscle fibers, fiber regeneration, endomysial proliferation, inflammatory cell infiltrates and vasculitis, and tubuloreticular inclusion bodies within endothelial cells. Findings of lymphoid structures and vasculopathy may portend more severe disease.

Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called **amyopathic JDM** or **dermatomyositis sine myositis**. It is unclear whether these children have isolated skin disease or mild undetected muscle inflammation, risking progression to more severe muscle involvement with long-term sequelae such as calcinosis and lipodystrophy if untreated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myositis or myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (e.g., Duchenne, Becker), myasthenia gravis, Guillain-Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, TNF receptor–associated periodic syndrome (TRAPS), and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, staphylococcal pyomyositis, and SARS-CoV-2. Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria. Myositis in children may also be associated with vaccinations, drugs, growth hormone, and GVHD. The rash of JDM may be confused with dyshidrotic eczema, psoriasis, erythema nodosa, malar rash from SLE, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with SLE, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Necrotizing immune-mediated myopathies are characterized by muscle necrosis without lymphocytic infiltration. Antibodies to signal recognition particle (SRP) or 3-hydr oxy-3-methylglutaryl-coenzyme A (HMG-CoA) distinguish the two types from each other and from JDM. Table 200.4 compares other juvenile idiopathic inflammatory myositis disorders: JDM, juvenile polymyositis, and juvenile connective tissue myositis.

LABORATORY FINDINGS

Elevated serum levels of muscle-derived enzymes (creatine kinase [CK], aldolase, aspartate transaminase, alanine transaminase [ALT], lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; ALT is usually elevated on initial presentation, whereas CK level may be normal.

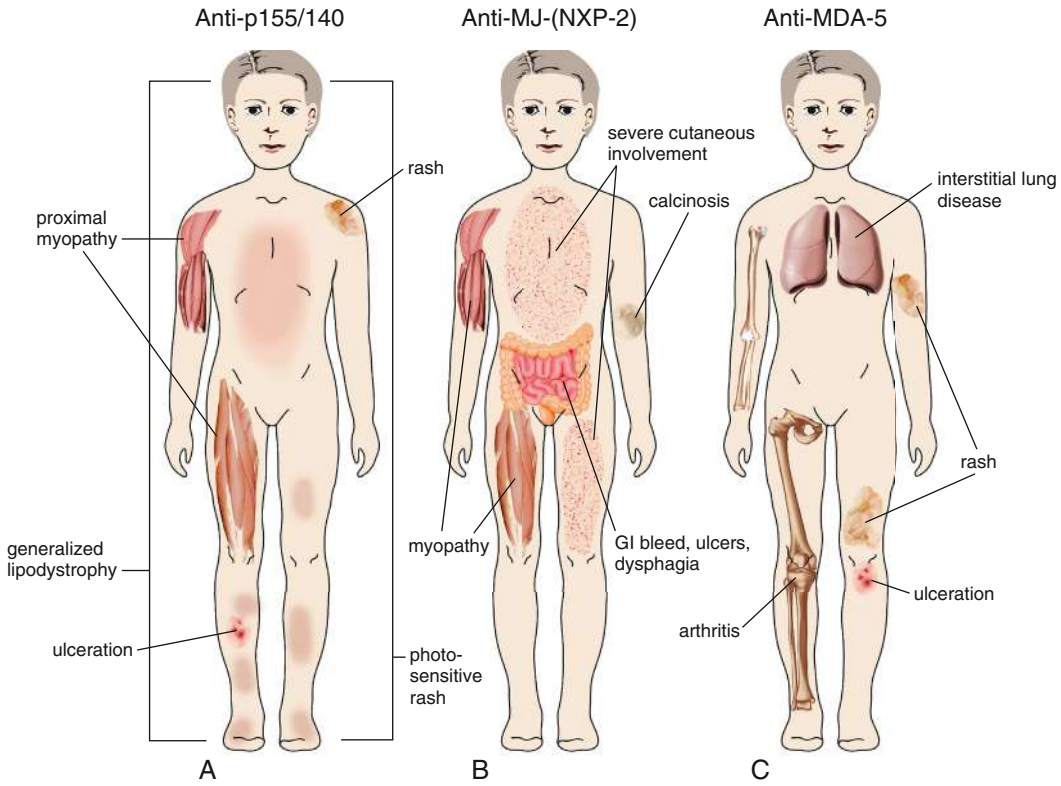

Fig. 200.1 Phenotypes associated with the three most common myositis specific antibodies in children with myositis: anti-p155/140, anti-MJ, and antiMDA-5. **A,** Anti-p155/140, present in 18–30% of idiopathic juvenile inflammatory myopathies, displays an extensive photosensitive rash that ulcerates, a chronic disease course, and generalized lipodystrophy. **B,** Fifteen to twenty-three percent of children positive for anti-MJ (nuclear matrix protein 2 in the United Kingdom) may have disease onset at a younger age and have dysphonia, muscle cramps, atrophy, and contractures, with increased weakness, and they are more likely to develop calcifications and gastrointestinal symptoms; their rash often spares the truncal area. **C,** Anti–MDA-5 is increased in the Japanese population (33%) vs the United Kingdom (6%) and is associated with inflammatory lung disease, oral and cutaneous ulcers, arthritis, and a milder form of muscle involvement. GI, gastrointestinal. *(Modified from Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: Pathogenesis, clinical and autoantibody phenotypes, and outcomes.* J Intern Med. *2016;280:24–38, Fig 3.)*



Fig. 200.2 The facial rash of juvenile dermatomyositis. There is erythema over the bridge of the nose and malar areas with violaceous (heliotropic) discolorations of the upper eyelids.



Fig. 200.3 The rash of juvenile dermatomyositis. The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

The erythrocyte sedimentation rate (ESR) is often normal, and the rheumatoid factor (RF) test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody (ANA) is present in >80% of children with JDM. Serologic testing results are divided into two groups: **myositis-associated antibodies (MAAs)** and **myositis-specific antibodies (MSAs)** (see Table 200.1). MAAs are associated with JDM but are not specific and can be seen in both overlap conditions and other rheumatic diseases. The presence of MAAs such as SSA, SSB, Sm, ribonucleoprotein (RNP), and double-stranded (ds) DNA may increase the likelihood of overlap disease or connective tissue myositis. Antibodies to Pm/Scl identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and cardiac involvement. MSAs are specific for myositis and are identified in

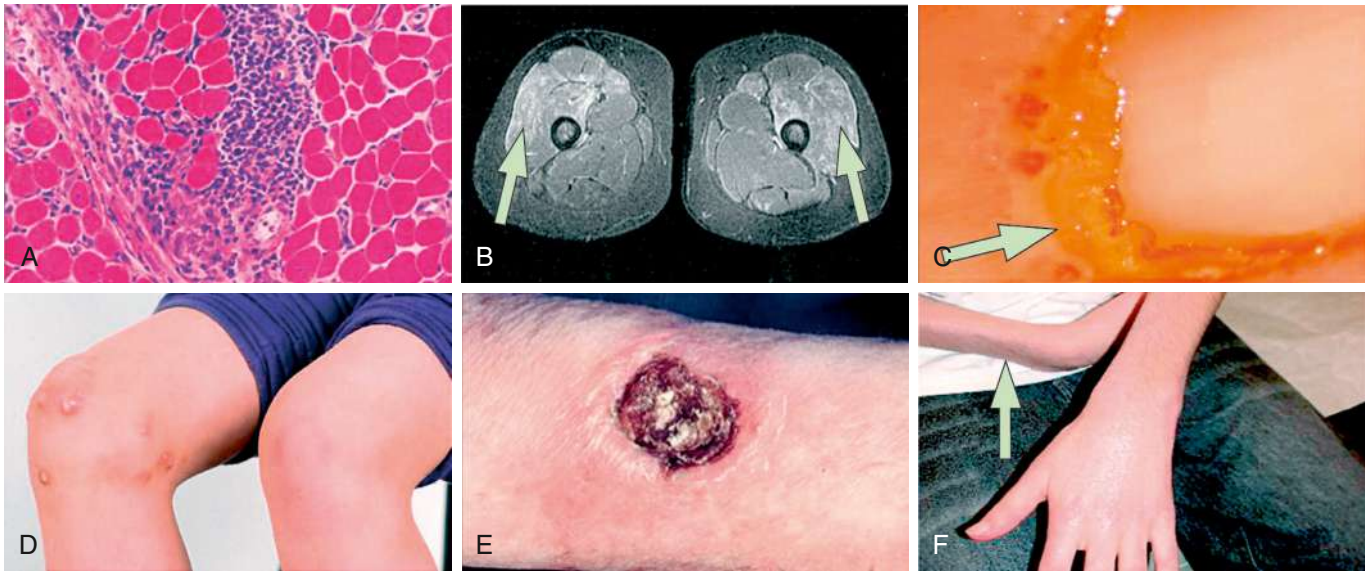

Fig. 200.4 Features of juvenile dermatomyositis. **A,** Perivascular and perifascicular inflammatory infiltrates with necrotic fibers, perifascicular atrophy, and regeneration in a muscle biopsy. **B,** MRI is a sensitive indicator of myositis. Inflamed areas appear bright on short-tau inversion recovery–weighted images *(arrows).* **C,** Capillaries are most often abnormal when viewed at the nail fold. Typical changes of dilation with adjacent dropout *(arrow)* are seen. **D,** About 30% of juvenile dermatomyositis (JDM) patients have dystrophic calcinosis. **E,** Cutaneous ulceration with central necrosis, crust, and surrounding erythema at the elbow of 10-year-old boy with severe JDM. **F,** Lipoatrophy of the forearm *(arrow)* in a boy with JDM. *(From Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood.* Lancet. *2008;371:2201–2212, Fig. 3, p. 2205.)*

approximately 40–60% of children with JIM. These antibodies suggest a diagnosis of myositis, and their presence may define distinct clinical subsets and may predict prognosis. Anti-TIF-1-γ antibodies are reported in 23–30% of children with JDM and are associated with photosensitive rashes, ulceration, and lipodystrophy. Unlike in adults, this antibody is not associated with malignancy in children with JDM. Anti-NXP2 antibodies are reported in 12–23% of children with JDM and are associated with cramps, muscle atrophy, contractures, and dysphonia. Anti-**MDA5** antibodies are found in approximately 7% of children with JDM and may predict the development of interstitial lung disease (ILD). Because certain MSAs have defined clinical phenotypes in JDM and IFN-related biomarkers that may correlate with disease activity, there is interest in assessing IFN signature by MSA type.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (see Fig. 200.4B) identifies active sites of disease, reducing sampling error and increasing the sensitivity of muscle biopsy and EMG, results of which are nondiagnostic in 20% of cases if the procedures are not directed by MRI. Extensive rash and abnormal MRI findings may be found despite normal serum levels of muscle-derived enzymes. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

A contrast swallow study may document palatal dysfunction and risk of aspiration. Pulmonary function testing detects a restrictive defect consistent with respiratory weakness and reduced diffusion capacity of carbon monoxide from alveolar fibrosis associated with other connective tissue diseases. Serial measurement of vital capacity or negative inspiratory force can document changes in respiratory weakness, especially in an inpatient setting. **Calcinosis** is seen easily on radiographs, along the fascial planes, and within muscles (see Figs. 200.4D and E and Fig. 200.5).

TREATMENT

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Before the advent of corticosteroids, one third of patients spontaneously improved; a third had a chronic, lingering course; and a third died from the disease. Corticosteroids have altered the course of the disease, lowering morbidity and mortality. Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous (IV) gamma globulin is frequently used as an adjunct for the treatment of severe disease and can be given at 2 g/kg (maximum 70 g) every 2 weeks for three doses, then every 4 weeks as needed. The efficacy and safety have been reported in open-label studies. In the 2010 **Childhood Arthritis and Rheumatology Research Alliance (CARRA)** treatment utilization report, IVIG was used most frequently for initial treatment of severe disease and treatment of refractory disease. It is also a steroid-sparing agent. Consensus treatment plans for guiding treatment of children with JDM are available from CARRA online through PubMed and Figure 200.6.

Corticosteroids remain the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is recommended. Children with GI involvement may have decreased absorption of oral corticosteroids and require IV administration. In more severe cases with respiratory or oropharyngeal weakness, high-dose pulse methylprednisolone is used (30 mg/kg/day for 3 days, maximum dose 1 g/day) with ongoing weekly or monthly IV dosing along with daily oral corticosteroids as needed. Corticosteroid dosage is slowly tapered over 12 months, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, IV, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m^2) is often used as a steroid-sparing agent in JDM. The concomitant use of methotrexate halves the cumulative dosage of steroids needed for disease control. Risks of methotrexate include immunosuppression, blood count dyscrasias, chemical hepatitis, pulmonary toxicity, nausea/vomiting, and teratogenicity. *Folic acid is typically given with methotrexate starting at a dose of 1 mg daily to reduce toxicity and side effects of folate inhibition (oral ulcers, nausea, anemia).* Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly. An international trial found the combination of methotrexate plus corticosteroids to perform better than corticosteroids alone and with fewer side effects than corticosteroids plus cyclosporine A.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission.

Table 200.4 Frequency of Manifestations of Juvenile Dermatomyositis (JDM), Juvenile Polymyositis (JPM), and Overlap Myositis

	FREQUENCY AT ONSET (%)		
MANIFESTATION	**JDM**	**JPM**	**OVERLAP MYOSITIS**
Progressive proximal muscle weakness	82-100	100	100
Easy fatigue	80-100	85	84
Gottron papules	57-91	0	74-80
Heliotrope rash	66-87	0	40-59
Erythematous rash of malar/facial area	42-100	0-6	20-51
Periungual nailfold capillary changes	35-91	33	67-80
Muscle pain or tenderness	25-83	61-66	55
Weight loss	33-36	52	53
Falling episodes	40	59	29
Arthritis	10-65	0-45	69-80
Fever	16-65	0-41	0-49
Lymphadenopathy	8-75	0-12	20-22
Dysphagia or dysphonia	15-44	39	40
Joint contractures	9-55	17-42	57-60
V- or shawl-sign rashes	19-29	3-6	8-14
Dyspnea on exertion	5-43	17-42	40
Gastrointestinal symptoms	5-37	9-33	6-53
Photosensitive rashes	5-51	0-6	22-40
Raynaud phenomenon	9-28	0-24	41-60
Edema	11-34	15	20
Gingivitis	6-30	9	0-37
Cutaneous ulceration	5-30	3	20-22
Calcinosis	3-34	6	24
Cardiac involvement	2-13	36	19
Interstitial lung disease	5	15	26
Lipodystrophy	4-14	3	0-6
Gastrointestinal bleeding or ulceration	3-4	3	4-10

From Rider LG, Lindsley CB, Miller FW. Juvenile Dermatomyositis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn L, eds. *Textbook of Pediatric Rheumatology,* 7th ed. Philadelphia: Elsevier; 2016: Table 26.4.

Typically, it is administered at doses of 4-6 mg/kg/day orally in either tablet or liquid form. Ophthalmologic follow-up one time per year to monitor for rare retinal toxicity is recommended. Other side effects include hemolysis in patients with glucose-6-phosphate deficiency, GI intolerance, and skin/hair discoloration.

The use of **rituximab** in a trial of steroid-dependent patients with resistant inflammatory myopathies, including JDM, did not meet the primary study end-point showing a difference in time to improvement between individuals given rituximab at baseline or at 8 weeks, but overall, 83% of all patients met the definition of improvement in the trial. Additionally, rituximab was noted to have a significant steroid-sparing effect.

Other medications used to treat severe refractory disease include mycophenolate mofetil, cyclosporine, and cyclophosphamide. Given the strong type I IFN signal in JDM and that these cytokines activate intracellular signaling through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway, consideration of JAK inhibitors, including *tofacitinib,* baricitinib, and ruxolitinib, as potential therapeutic candidates has been bolstered by case reports and case series that report generally promising results with these drugs in off-label treatment of JDM.

Children with pharyngeal weakness may need nasogastric or gastrostomy feedings to avoid aspiration, whereas those with GI vasculitis require full bowel rest. Rarely, children with severe respiratory weakness require ventilator therapy and even tracheostomy until the respiratory weakness improves.

Physical therapy and **occupational therapy** are integral parts of the treatment program, initially for passive stretching early in the disease course and then for direct reconditioning of muscles to regain strength and range of motion. Therapy may improve muscle strength measures and cardiovascular fitness. Bed rest is not indicated, because weight bearing improves bone density and prevents contractures. Social work and psychology services may facilitate adjustment to the frustration of physical impairment in a previously active child and aid with sleep disturbances associated with rheumatic disease.

All children with JDM should avoid sun exposure and apply high–sun protection factor (SPF) sunscreen daily, even in winter and on cloudy days. Vitamin D and calcium supplements are indicated for all

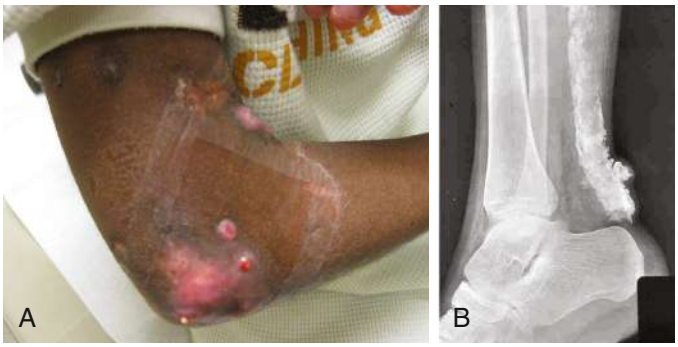

Fig. 200.5 Calcifications in dermatomyositis. A, Skin effects of calcification. B, Radiographic evidence of calcification.

MODERATE JDM
Plan 1 Methotrexate[a] 15 mg/m^2 or 1 mg/kg weekly AND Prednisone[b] 2 mg/kg/d for 4 wk then decrease by 20%
Plan 2 *Plan 1* AND IV methylprednisolone 30 mg/kg for 3 d, then weekly[c]
Plan 3 *Plan 2* AND IVIG 2 g/kg[d] q2wk × 3 doses then monthly
SKIN PREDOMINANT JDM
Plan 1 Hydroxychloroquine 5 mg/kg/d[e]
Plan 2 *Plan 1* AND Methotrexate[a] 15 mg/m^2 or 1 mg/kg weekly
Plan 3 *Plan 2* AND Prednisone[b] 2 mg/kg/d for 4 wk then decrease by 20%
SKIN RESISTANT JDM
Plan 1 IVIG 2 g/kg[d] q2wks × 3 doses then monthly
Plan 2 *Plan 1* AND Mycophenolate mofetil[f] BID 10 mg/kg/dose OR 600 mg/m^2
Plan 3 Cyclosporine 3 mg/kg[g]

Fig. 200.6 Recommended consensus treatment plans from CARRA for JDM patients with moderate, skin-predominant, and skin-resistant disease. IV, intravenous; IG, immunoglobulin. [a]Lesser of 15 mg/m^2 or 1 mg/kg (max 40 mg), [b]max 60 mg, [c]optional, [d]max 70 g, [e]max 400 mg, [f]max 1,500 mg bid, [g]higher doses based on toxicity, efficacy. *(From Kim H, Huber AM, Kim S. Updates on juvenile dermatomyositis from the last decade: classification to outcomes.* Rheum Dis Clin N Am. *2021;47:669–690, Fig. 1, p. 679.)*

children undergoing long-term corticosteroid therapy to reduce drug-induced osteopenia and osteoporosis.

COMPLICATIONS

Most complications from JDM are related to prolonged and severe weakness from muscle atrophy to cutaneous calcifications and scarring or atrophy to lipodystrophy. Secondary complications from medical treatments are also common. Children with acute and severe weakness are at risk for aspiration pneumonia and respiratory failure and occasionally require nasogastric feeding and mechanical ventilation until weakness improves. Rarely, **vasculitis** of the GI tract develops in children with severe JDM. Crampy abdominal pain and occult GI bleeding may indicate bowel wall vasculitis and lead to ischemia, GI bleeding, and perforation if not treated with complete bowel rest and aggressive treatment for the underlying inflammation. Surgery should be avoided, if possible, because the GI vasculitis is diffuse and not easily amenable to surgical intervention. Contrast-enhanced CT may show dilation or thickening of the bowel wall, intraluminal air, or evidence of bowel necrosis.

Involvement of the cardiac muscle with pericarditis, myocarditis, and conduction defects with arrhythmias has been reported, as has reduced diastolic and systolic function related to ongoing disease activity.

Lipodystrophy and **calcinosis** are thought to be associated with long-standing or undertreated disease (see Fig. 200.4D-F). Dystrophic deposition of calcium phosphate, hydroxyapatite, or fluoroapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid. Calcification is found in up to 40% of large cohorts of children with JDM. Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of TNF-α-308. Calcium deposits tend to form in subcutaneous tissue and along muscle. Some ulcerate through the skin and drain a soft calcific liquid, and others manifest as hard nodules along extensor surfaces or embedded along muscle. Draining lesions serve as a nidus for cellulitis or osteomyelitis. Nodules cause skin inflammation that may mimic cellulitis. Spontaneous regression of calcium deposits may occur, but there is no evidence-based recommendation for treatment of calcinosis. Some experts recommend aggressive treatment of underlying myositis. Others have recommended bisphosphonates, TNF inhibitors, and sodium thiosulfate, but no evidence-based trials have been conducted for this condition.

Lipodystrophy manifests in 10–40% of patients with JDM and can be difficult to recognize. Lipodystrophy results in progressive loss of subcutaneous and visceral fat, typically over the face and upper body, and may be associated with a metabolic syndrome similar to polycystic ovarian syndrome with insulin resistance, hirsutism, acanthosis, hypertriglyceridemia, and abnormal glucose tolerance. Lipodystrophy may be generalized or localized.

Children receiving prolonged corticosteroid therapy are prone to complications such as cessation of linear growth, weight gain, hirsutism, adrenal suppression, immunosuppression, striae, cushingoid fat deposition, mood changes, osteoporosis, cataracts, avascular necrosis, and steroid myopathy. Families should be counseled on the effects of corticosteroids and advised to use medical alert identification and to consult a nutritionist regarding a low-salt, low-fat diet with adequate vitamin D and calcium supplementation.

An association with malignancy at disease onset is observed in adults with dermatomyositis but very rarely in children.

PROGNOSIS

The mortality rate in JDM has decreased since the advent of corticosteroids, from 33% to currently approximately 1%; little is known about the long-term consequences of persistent vascular inflammation. The period of active symptoms has decreased from about 3.5 years to <1.5 years with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 years of follow-up, 75% of patients have little to no residual disability, but 25% continue to have chronic weakness and 40% have chronic rash. Up to one-third may need long-term medications to control their disease. Children with JDM appear able to repair inflammatory damage to vasculature and muscle, but there is some emerging concern about long-term effects on cardiovascular risk.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 201

Scleroderma and Raynaud Phenomenon

Heather A. Van Mater and C. Egla Rabinovich

Juvenile scleroderma encompasses a range of conditions unified by the presence of fibrosis of the skin. Juvenile scleroderma is divided into two major categories, **juvenile localized scleroderma** (**JLS**, also known as **morphea**), which is largely limited to the skin, and **juvenile systemic sclerosis (JSSc)**, with multisystem organ involvement. Localized disease is the predominant type seen in pediatric populations (>95%), but systemic sclerosis is associated with mortality and severe multiorgan morbidity.

ETIOLOGY AND PATHOGENESIS

The etiology of scleroderma is unknown, but the mechanism of disease appears to be a combination of a vasculopathy, autoimmunity, immune activation, and fibrosis. Triggers, including trauma, infection, and, possibly, subclinical graft versus host reaction from persistent maternal cells *(microchimerism)*, injure vascular endothelial cells, resulting in increased expression of adhesion molecules. These molecules entrap platelets and inflammatory cells, resulting in vascular changes with manifestations such as Raynaud phenomenon and pulmonary hypertension. Inflammatory cells infiltrate the area of initial vascular damage, causing further vascular damage and resulting in thickened artery walls and reduction in capillary numbers. Macrophages and other inflammatory cells then migrate into affected tissues and secrete cytokines that induce fibroblasts to reproduce and synthesize excessive amounts of collagen, resulting in fibrosis and subsequent lipoatrophy and dermal fibrosis, with loss of sweat glands and hair follicles. In late stages the entire dermis may be replaced by compact collagen fibers.

Autoimmunity is believed to be a key process in the pathogenesis of both localized and systemic scleroderma, given the high percentage of affected children with autoantibodies (Table 201.1). Children with localized disease often have a positive antinuclear antibody (ANA) test result (42%), and 47% of this subgroup have antihistone antibodies. Children with JSSc have higher rates of ANA positivity (80.7%) and may have anti–Scl-70 antibody (34%, antitopoisomerase I). The relationship between specific autoantibodies and the various forms of scleroderma is not well understood, and all antibody test results may be negative, especially in JLS.

CLASSIFICATION

Localized scleroderma is distinct from systemic scleroderma and rarely progresses to systemic disease. The category of JLS includes several subtypes differentiated by both the distribution of the lesions and the depth of involvement (Tables 201.2 and 201.3). Up to 15% of children have a combination of two or more subtypes.

EPIDEMIOLOGY

Juvenile scleroderma is rare, with an estimated prevalence of 1 in 100,000 children. Localized scleroderma (LS) is much more common than systemic sclerosis (SSc) in children, by a 10:1 ratio, with **linear scleroderma** being the most common subtype. LS is predominantly a pediatric condition, with 65% of patients diagnosed before age 18 years. After age 8 years the female/male ratio for both LS and SSc is approximately 3:1, whereas in patients younger than 8 years, the prevalence is equal.

CLINICAL MANIFESTATIONS

Localized Scleroderma

The onset of scleroderma is generally insidious, and manifestations vary according to disease subtype. The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting

Table 201.1 Clinical Subtypes of Systemic Sclerosis: Associated Organ Manifestations and Autoantibody Association

SUBTYPE	ORGAN SYSTEM	ORGAN SYSTEM FEATURES	ANTIBODY ASSOCIATION
Diffuse cutaneous (dc)	Skin	Thickness proximal to elbows and knees Rapid progressive thickening	Topoisomerase (Scl-70) RNA Polymerase III U3-RNP (fibrillarin)
	Cardiac	Congestive heart failure Conduction abnormalities	
	Renal	Scleroderma renal crisis	
	Pulmonary	Interstitial lung disease	
Limited cutaneous (lc)	Skin	Thickness limited to distal extremities (and face) Restricted and nonprogressive thickening	Centromere Th/To
	Gastrointestinal	Esophageal dysmotility GI strictures Malabsorption	
	Pulmonary	Pulmonary arterial hypertension	
Overlap syndrome	Skin	Either dcSSc or lcSSc pattern Skin manifestations of other CTD, such as Gottron papules (DM) and malar rash (SLE)	PM-Scl U1-RNP Ku
	Musculoskeletal	Arthritis	
		Myositis	
	Cardiac	Can have any of the dcSSc or lcSSc manifestations Additional organ involvement in association with other CTD feature, such as lupus nephritis	
	Renal		
	Pulmonary		
	Gastrointestinal		

CTD, Connective tissue disease; DM, dermatomyositis; PM-Scl, polymyositis-scleroderma antibody; SLE, systemic lupus erythematosus; U1-RNP, U1 ribonucleoprotein antibody.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Table 27.3, p. 382.

Table 201.2 Classification of Pediatric Scleroderma (Morphea)

LOCALIZED SCLERODERMA
Plaque morphea
Confined to dermis, occasionally superficial panniculus
Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral
Generalized morphea
Involves dermis primarily, occasionally panniculus
Defined as confluence of individual morphea plaques or lesions in three or more anatomic sites; more likely to be bilateral
Bullous morphea
Bullous lesions that can occur with any of the subtypes of morphea
Linear scleroderma
Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral
Limbs/trunk:
One or more linear streaks of the extremities or trunk
Flexion contracture occurs when lesion extends over a joint; limb-length discrepancies
En coup de sabre:
Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches
Parry-Romberg syndrome:
Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement
Deep Morphea
Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral
Subcutaneous morphea:
Primarily involves the panniculus or subcutaneous tissue
Plaques are hyperpigmented and symmetric
Eosinophilic fasciitis:
Fasciitis with marked blood eosinophilia
Fascia is the primary site of involvement; typically involves extremities
Classic description is "peau d'orange," or orange peel texture, but early disease manifests as edema (see Fig. 201.2)
Morphea profunda:
Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on the trunk
Disabling pansclerotic morphea of childhood:
Generalized full-thickness involvement of skin on the trunk, face, and extremities, sparing fingertips and toes
SYSTEMIC SCLEROSIS
Diffuse
Most common type in childhood
Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera
Limited
Rare in childhood
Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome

Table 201.3 Provisional Criteria for Classification of Juvenile Systemic Sclerosis (JSSc)

MAJOR CRITERION (REQUIRED)*
Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints
MINOR CRITERIA (AT LEAST TWO REQUIRED)
Cutaneous: Sclerodactyly
Peripheral vascular: Raynaud phenomenon, nail fold capillary abnormalities (telangiectasias), digital tip ulcers
Gastrointestinal: Dysphagia, gastroesophageal reflux
Cardiac: Arrhythmias, heart failure
Renal: Renal crisis, new-onset arterial hypertension
Respiratory: Pulmonary fibrosis (high-resolution CT/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension
Neurologic: Neuropathy, carpal tunnel syndrome
Musculoskeletal: Tendon friction rubs, arthritis, myositis
Serologic: Antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin, or anti-RNA polymerase I or III)

*Diagnosis requires at least one major and at least two minor criteria.
From Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. *Arthritis Rheum.* 2007;57:203–212.

sign (Fig. 201.1). Edema and erythema are followed by indurated, hypopigmented or hyperpigmented atrophic lesions (Fig. 201.2). LS varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients may present with arthralgias, synovitis, or flexion contractures (Fig. 201.3). Children also experience limb-length discrepancies as a result of growth impairment caused by involvement of muscle and bone. Children with **en coup de sabre** may have symptoms unique to central nervous system (CNS) involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes (Fig. 201.4). Up to 25% of children with LS have extracutaneous manifestations, most frequently arthritis (47%) in linear disease and neurologic symptoms (17%) associated with en coup de sabre.

Systemic Scleroderma

SSc is a severe disease in children, starting with an insidious onset followed by a prolonged course characterized by periods of remission and exacerbation, commonly resulting in chronic disability and death, with a 5-year mortality rate of 7.5%.

The **skin manifestations** of SSc include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face. An eventual decrease in edema is followed by induration and fibrosis of skin, ultimately resulting in loss of subcutaneous fat, sweat glands, and hair follicles. Later, atrophic skin becomes shiny and waxy in appearance. As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy. In the face, this process results in a small oral stoma with decreased mouth aperture. Skin ulceration over pressure points, such as the elbows, may be associated with subcutaneous calcifications. Severe **Raynaud phenomenon** (RP; Fig. 201.5) causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers **(sclerodactyly)** (Fig. 201.6). Resorption of the distal tufts of the distal phalanges may occur **(acroosteolysis)**. Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation give a salt-and-pepper appearance to skin. Over years, remodeling of lesions sometimes results in focal improvement in skin thickening.

Pulmonary disease is the most common visceral manifestation of SSc and includes both arterial and interstitial involvement (alveolitis). Symptoms range from asymptomatic disease to exercise intolerance, dyspnea at

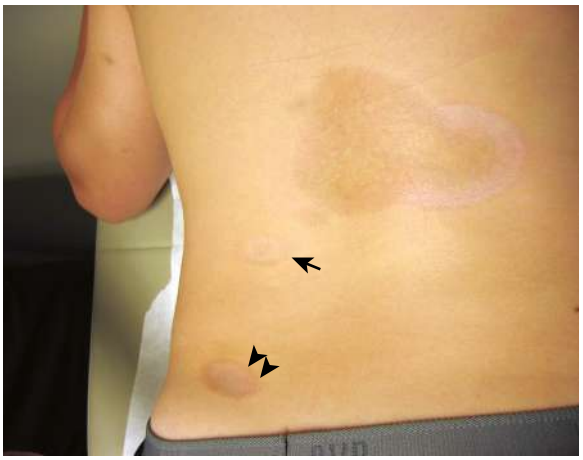

Fig. 201.1 Child with generalized morphea. Note the active circular lesion *(arrowheads)* with a surrounding rim of erythema. The largest lesion has areas of postinflammatory hyperpigmentation and depression with an area of erythema on the right. The small lesion *(arrow)* demonstrates depression caused by lipoatrophy.



Fig. 201.2 Inactive linear scleroderma demonstrating hyperpigmented lesion with areas of normal skin (skip lesions).



Fig. 201.3 Child with untreated linear scleroderma resulting in knee contracture, immobility of ankle, chronic skin breakdown of scar on the lateral knee, and areas of hypopigmentation and hyperpigmentation. The affected leg is 1 cm shorter.

rest, and right-sided heart failure. **Pulmonary arterial hypertension** is a poor prognostic sign, developing because of lung disease or independently as part of the vasculopathy. Clinical manifestations of pulmonary arterial hypertension in children appear late in the course, are subtle, and include cough and dyspnea on exertion. Pulmonary evaluation should include pulmonary function tests (PFTs) such as diffusion capacity of carbon monoxide (DLco), bronchoalveolar lavage (BAL), and high-resolution chest computed tomography (HRCT). PFTs reveal decreased vital capacity and decreased DLco, whereas neutrophilia or eosinophilia on BAL suggests active alveolitis. Chest CT is much more sensitive than chest radiographs, which are often normal, showing typical basilar ground-glass abnormalities, reticular linear opacities, nodules, honeycombing, and mediastinal adenopathy.

Gastrointestinal tract disease is seen in 25% of children with SSc. Common manifestations include esophageal and intestinal dysmotility resulting in dysphagia, reflux, dyspepsia, gastroparesis, bacterial overgrowth, dilated bowel loops and pseudoobstruction, and dental caries, as well as malabsorption and failure to thrive. **Renal** arterial disease can cause chronic or severe episodic hypertension; unlike adult disease, renal



Fig. 201.4 Child with en coup de sabre lesion on scalp extending down to forehead. Before treatment, the skin on the scalp was bound down with chronic skin breakdown. Note the area of hypopigmentation extending down the forehead *(arrows)*.



Fig. 201.5 Active Raynaud phenomenon with well-demarcated pallor at the fingertips in a patient with scleroderma. *(From Firestein GS, Budd RC, Gabriels SE, et al., eds.* Firestein & Kelley's Textbook of Rheumatology, *11th ed. Philadelphia: Elsevier; 2021: Fig. 89.2, p. 1507.)*



Fig. 201.6 Sclerodactyly and finger ulcerations in a patient with systemic sclerosis who is poorly compliant with treatment.

crisis is rare. **Cardiac** fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is usually a result of cardiopulmonary disease. A scoring system helps identify the severity of the multiorgan involvement (Table 201.4).

Table 201.4 Medsger Systemic Sclerosis Severity Scale*

ORGAN SYSTEM	0 (NORMAL)	1 (MILD)	2 (MODERATE)	3 (SEVERE)	4 (END STAGE)
General	Wt loss <5% Hct 37%+ Hb 12.3+ g/dL	Wt loss 5–10% Hct 33–37% Hb 11.0-12.2 g/dL	Wt loss 10–15% Hct 29–33% Hb 9.7-10.9 g/dL	Wt loss 15–20% Hct 25–29% Hb 8.3-9.6 g/dL	Wt loss 20%+ Hct 25% Hb <8.3 g/dL
Peripheral vascular	No RP; RP not requiring vasodilators	RP requiring vasodilators	Digital pitting scars	Digital tip ulcerations	Digital gangrene
Skin	TSS 0	TSS 1-14	TSS 15-29	TSS 30-39	TSS 40+
Joint/tendon	FTP 0-0.9 cm	FTP 1.0-1.9 cm	FTP 2.0-3.9 cm	FTP 4.0-4.9 cm	FTP 5.0+ cm
Muscle	Normal proximal muscle strength	Proximal weakness, mild	Proximal weakness, moderate	Proximal weakness, severe	Ambulation aids required
Gastrointestinal tract	Normal esophagogram; normal small bowel series	Distal esophageal hypoperistalsis; small bowel series abnormal	Antibiotics required for bacterial overgrowth	Malabsorption syndrome; episodes of pseudoobstruction	Hyperalimentation required
Lung	DLCO 80%+ FVC 80%+ No fibrosis on radiograph sPAP <35 mm Hg	DLCO 70–79% FVC 70–79% Basilar rales; fibrosis on radiograph sPAP 35-49 mm Hg	DLCO 50–69% FVC 50–69% sPAP 50-64 mm Hg	DLCO <50% FVC <50% sPAP 65+ mm Hg	Oxygen required
Heart	ECG normal LVEF 50%+	ECG conduction defect LVEF 45–49%	ECG arrhythmia LVEF 40–44%	ECG arrhythmia requiring therapy LVEF 30–40%	CHF LVEF <30%
Kidney	No history of SRC with serum creatinine <1.3 mg/dL	History of SRC with serum creatinine <1.5 mg/dL	History of SRC with serum creatinine 1.5-2.4 mg/dL	History of SRC with serum creatinine 2.5-5.0 mg/dL	History of SRC with serum creatinine >5.0 mg/dL or dialysis required

*If two items are included for a severity grade, only one is required for the patient to be scored as having disease of that severity level.
CHF, Congestive heart failure; DLCO, diffusing capacity for carbon monoxide, % predicted; ECG, electrocardiogram; FTP, fingertip-to-palm distance in flexion; FVC, forced vital capacity, % predicted; Hb, hemoglobin; Hct, hematocrit; LVEF, left ventricular ejection fraction; RP, Raynaud phenomenon; sPAP, estimated pulmonary artery pressure by Doppler echo; SRC, scleroderma renal crisis; TSS, total skin score; Wt, weight.
Modified from Medsger TA Jr, Bombardieri S, Czirjak L, et al. Assessment of disease severity and prognosis, *Clin Exp Rheumatol*. 2003;21(3 Suppl 29):S51, Table 1, p. S-43.

Raynaud Phenomenon

Raynaud phenomenon is the most frequent initial symptom in pediatric SSc, present in 70% of affected children months to years before other manifestations and seen in nearly all over the course of the disease. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced by cold exposure and/or emotional stress (see Fig. 201.5). RP is typically independent of an underlying rheumatic disease (Raynaud disease) but can result from rheumatic diseases such as scleroderma, systemic lupus erythematosus (SLE), and mixed connective tissue disease (Fig. 201.7). The color changes are brought about by (1) initial arterial vasoconstriction, resulting in hypoperfusion and pallor (blanching), (2) venous stasis (cyanosis), and (3) reflex vasodilation caused by the factors released from the ischemic phase (erythema). The color change is classically reproduced by immersing the hands in iced water and reversed by warming. During the blanching phase, there is inadequate tissue perfusion in the affected area, associated with pain and paresthesias and resulting in ischemic damage only when associated with a rheumatic disease. The blanching usually affects the distal fingers but may also involve thumbs, toes, ears, and tip of the nose. The affected area is usually well demarcated and uniformly white. *Digital ulcers* associated with RP are indicative of underlying rheumatic disease.

Raynaud disease often begins in adolescence and is characterized by symmetric occurrence, the absence of digital ulcers, tissue necrosis and gangrene, and the lack of manifestations of an underlying rheumatic disease. Children have normal nail fold capillaries (absence of periungual telangiectasias). RP should be distinguished from acrocyanosis and chilblains. **Acrocyanosis** is a vasospastic disorder resulting in cool, painless, bluish discoloration in the hands and feet despite normal tissue perfusion. It may be exacerbated by stimulant medications used to treat attention-deficit disorder. **Chilblains** is a condition with episodic color changes and the development of nodules related to severe cold exposure and spasm-induced vessel and tissue damage; it has been associated with SLE and is also referred to as *lupus pernio*, but the majority of children with chilblains do not have lupus.

DIAGNOSIS

The diagnosis of JLS is based on the distribution and depth of characteristic lesions. Biopsy is helpful to confirm the diagnosis. The diagnosis of JSSc requires proximal sclerosis/induration of the skin and the presence of 2 of 20 minor criteria (see Table 201.3).

DIFFERENTIAL DIAGNOSIS

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those caused by LS by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, diabetic cheiroarthropathy, pseudoscleroderma, and scleredema. **Pseudoscleroderma** comprises a group of unrelated diseases characterized by patchy or diffuse cutaneous fibrosis without the other manifestations of scleroderma. These include phenylketonuria, syndromes of premature aging, and localized idiopathic fibrosis. **Scleredema** is a transient, self-limited disease of both children and adults that has sudden onset after a febrile illness (especially streptococcal infections) and is characterized by patchy sclerodermatous lesions on the neck and shoulders and extending to the face, trunk, and arms.

Laboratory Findings

No laboratory studies are diagnostic of either localized or systemic scleroderma. Although the results of complete blood counts, serum chemistry analyses, and urinalysis are normal, children may have elevated erythrocyte sedimentation rate, eosinophilia, or hypergammaglobulinemia, all of which normalize with treatment. Elevations of muscle enzymes, particularly aldolase, can be seen with muscle

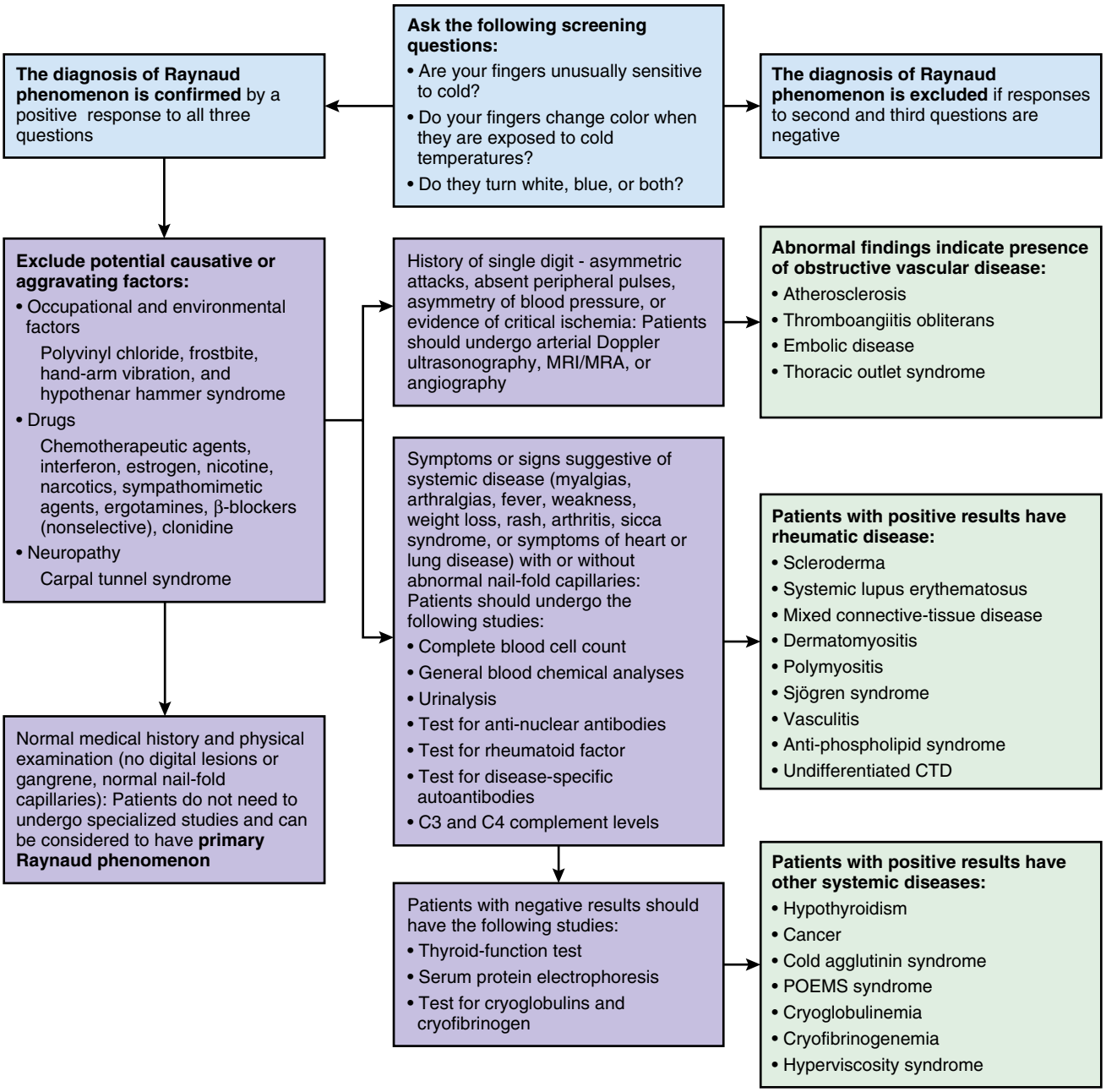

Fig. 201.7 Diagnostic algorithm for Raynaud phenomenon. CTD, Connective tissue disease; MRA, magnetic resonance angiography; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. *(From Firestein GS, Budd RC, Gabriel SE, et al., eds.* Kelley & Firestein's Textbook of Rheumatology*, 10th ed. Philadelphia: Elsevier; 2017: Fig 84-3.)*

involvement. Patients with JSSc may have anemia, leukocytosis, and eosinophilia and autoantibodies (ANA, anti–Scl-70). Imaging studies delineate the affected area and can be used to follow disease progression. MRI is useful in en coup de sabre and Parry-Romberg syndrome (facial hemiatrophy) for determination of CNS or orbital involvement. Infrared thermography uses the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to examine lesion activity is evolving. HRCT, PFTs, echocardiography, and manometry are useful tools for diagnosing and monitoring visceral involvement in JSSc.

TREATMENT

Treatment for scleroderma varies according to the subtype and severity. **Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy.** For lesions involving deeper structures, systemic therapy is recommended. A combination of *methotrexate* and *corticosteroids* is effective in treating JLS by preventing lesion extension and resulting in significant skin softening and improved range of motion of affected joints. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans for JLS include (1) weekly subcutaneous (SC) methotrexate at 1 mg/kg (maximum dose 25 mg); (2) weekly SC methotrexate (1 mg/kg; max 25 mg) *plus* either 3 months of high-dose intravenous (IV) corticosteroids (30 mg/kg; max 1,000 mg) for 3 consecutive days a month *or* weekly corticosteroids at the same dose for 3 months; or (3) high-dose daily oral corticosteroids (2 mg/kg/day, max 60 mg) with a slow taper over 48 weeks (Fig. 201.8). *Mycophenolate mofetil* (MMF) and abatacept have shown promise as second-line agents for recalcitrant

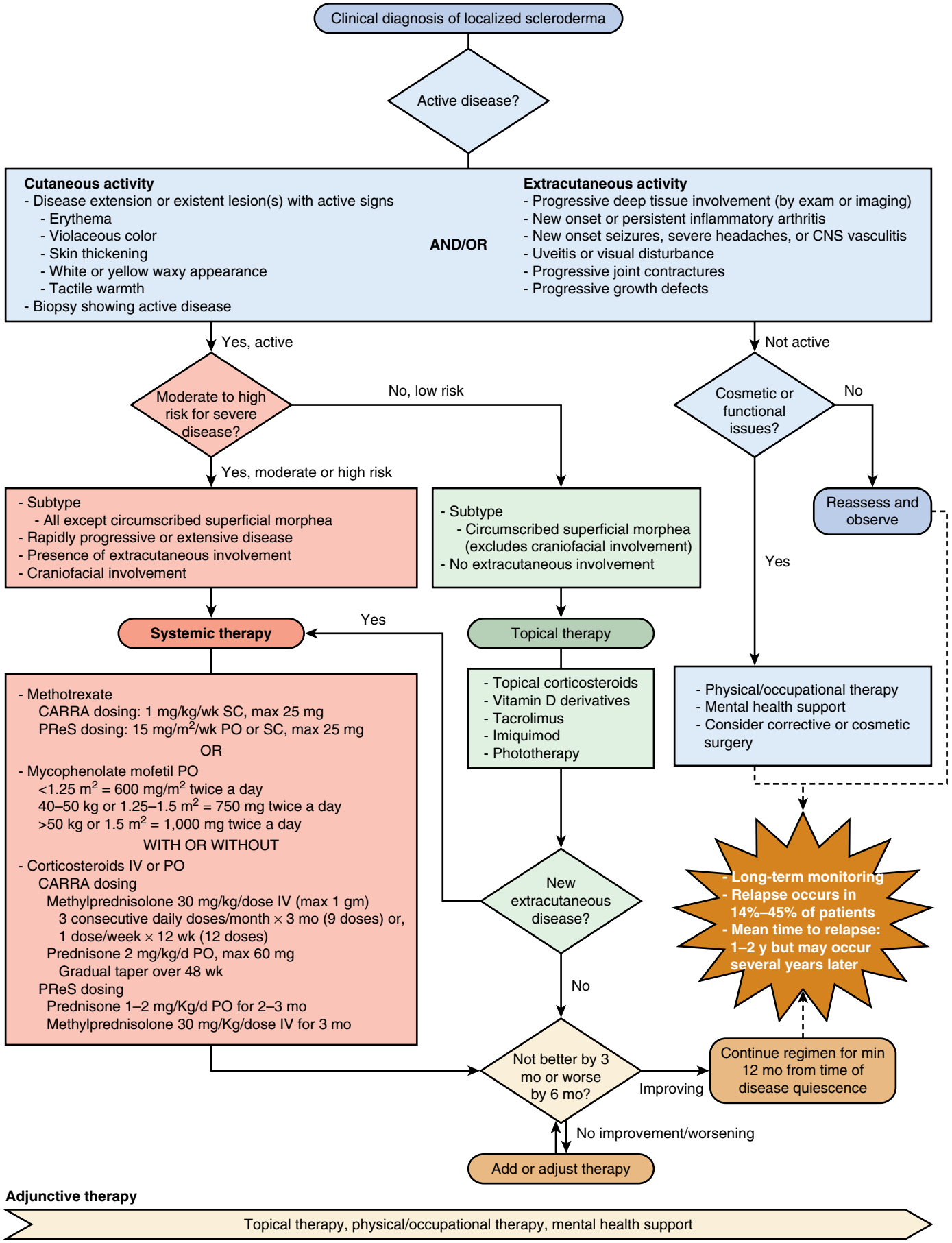

Fig. 201.8 LS treatment recommendations. This algorithm outlines factors to consider when deciding upon treatment and CARRA- and PReS-recommended treatments. Careful and long-term monitoring for both cutaneous and extracutaneous activity is important. The algorithm is based upon the authors' experiences and not intended to serve as prescriptive instructions. CARRA, Childhood Arthritis and Rheumatology Research Alliance; IV, intravenous; max, maximum; min, minimum; PO, by mouth; PReS, Pediatric Rheumatology European Society; SC, subcutaneous. *(From Vasquez-Canizares N, Li SC. Juvenile localized scleroderma – updates and differences from adult-onset disease.* Rheum Dis Clin N Am. *2021;47:737–755, Fig. 5, p. 749.)*

disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate. Close follow-up is necessary in JLS given high rates of relapse—up to 40%.

Treatments for JSSc target specific disease manifestations (Tables 201.5 and 201.6). RP is treated with cold avoidance, and pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine 30-60 mg sustained-release form daily; amlodipine 2.5-10 mg daily) are the most common pharmacologic interventions. Additional potential therapies for RP include losartan, prazosin, bosentan, and sildenafil. Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or MMF may be beneficial for skin manifestations. Cyclophosphamide and MMF are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in SSc because of an association with renal crisis. Adults with SSc have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin, and autologous stem cell transplantation. Systemic sclerosis–associated interstitial lung disease has been managed with nintedanib, a tyrosine kinase inhibitor, which has antiinflammatory and antifibrotic effects. Nintedanib combination therapy with MMF is also effective as an initiation therapy or when escalation of therapy is needed.

The treatment of RP begins with avoiding cold stimuli, using hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg three times daily—adult dose) reduces, but does not eliminate, the number and severity of episodes. Side effects include headache, flushing, and hypotension. Topical nitrates may result in digital vasodilation and may reduce the severity of an episode.

PROGNOSIS

JLS is ultimately generally self-limited, with the initial inflammatory stage followed by a period of stabilization and then softening, for an average disease duration of 3-5 years, although there are reports of active disease lasting up to 20 years. Prolonged disease activity is associated primarily with linear and deep disease subtypes. JLS, especially linear and deep subtypes, can result in significant morbidity, disfigurement, and disability as a result of joint contractures, muscle atrophy, limb shortening, facial asymmetry, and hyperpigmentation and hypopigmentation. Death from an en coup de sabre lesion with progressive neurologic decline has been reported.

JSSc has a more variable prognosis. Although many children have a slow, insidious course, others demonstrate a rapidly progressive form with early organ failure and death. Skin manifestations reportedly soften years after disease onset. Overall, the prognosis of JSSc is better than that of the adult form, with 5-, 10-, and 15-year survival rates, respectively, in children of 89%, 80–87%, and 74–87%. The most common cause of death is heart failure caused by myocardial and pulmonary fibrosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 201.5 Organ-Specific Treatment of Systemic Sclerosis

MANIFESTATION	FIRST-LINE	SECOND-LINE	VERY SEVERE
Raynaud phenomenon	Calcium channel blockers*	PDE-5 inhibitors† Fluoxetine Angiotensin II receptor antagonists‡ Topical nitrates§	Prostacyclins (iloprost)¶ Sympathectomy Botulism toxin Fat grafting
Digital ulcers	PDE-5 inhibitors†	Endothelin receptor antagonists#	Prostacyclins (iloprost)
Pulmonary hypertension	PDE-5 inhibitors† Endothelin receptor antagonists	Prostacyclins (epoprostenol)¶ Riociguat	
Interstitial lung disease	Cyclophosphamide Mycophenolate mofetil Corticosteroids	Rituximab	Hematopoietic stem cell transplantation
Skin	Methotrexate Mycophenolate mofetil Corticosteroids (low dose)	Abatacept Immune globulin	Cyclophosphamide Rituximab
Renal crisis	ACE inhibitors**		
Musculoskeletal	NSAIDs Hydroxychloroquine Methotrexate Corticosteroids (low dose)	Rituximab Abatacept Tocilizumab	

*Calcium channel blockers (nifedipine, amlodipine).
†PDE-5 inhibitors (sildenafil, tadalafil).
‡Angiotensin receptor antagonists (losartan).
§Topical nitrates (glyceryl trinitrate).
¶Prostacyclins (iloprost, epoprostenol).
#Endothelin receptor antagonist (bosentan, ambrisentan, macitentan).
**ACE inhibitors (captopril, enalapril).
ACE, Angiotensin converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs; PDE-5, phosphodiesterase-5.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Table 27.8, p. 395.

Table 201.6 Treatment of Gastrointestinal Manifestations of Juvenile SSc

ORGAN	MANIFESTATION	TREATMENT
Oral	Buccal, lingual fibrosis Tooth decay Mandibular resorption Gingival recession Dysphagia	Dental hygiene Fluoride treatments every 3 months Dental sealant Soft foods, small portions, adequate fluids Gingival mucosa grafting Dietary restriction (low sugar, soft foods)
Esophageal	Dysmotility Reflux Constriction	Metoclopramide, erythromycin Weight loss; small, frequent meals; avoid eating 3 hr before bed; raise head of bed 6 inches Avoid tight clothes, heavy lifting, bending Proton pump inhibitors, H2 blockers Dilatation
Stomach	GAVE (watermelon stomach) Fructose intolerance	Metoclopramide Erythromycin* Octreotide
Small intestines	Bacterial overgrowth Bezoars Malabsorption leading to malnutrition Pseudoobstruction	FODMAP diet Vitamin supplementation Low-residue, elemental diet Metoclopramide Antibiotics Octreotide
Colon	Fibrosis of lymphatics Ischemia	Erythromycin Metamucil High-fiber diet
Anorectal	Internal anal sphincter atrophy	Biofeedback Pelvic floor exercises Sacral nerve stimulation

*Side effects of erythromycin can be avoided by using low doses (rather than antibiotic-level doses).
FODMAP, Fermentable oligosaccharides, disaccharides, monosaccharides, and polyol; GAVE, gastric antrum vascular ectasia; SSc, systemic sclerosis.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Table 27.9, p. 398.

Chapter 202

Behçet Disease

Seza Ozen

Behçet disease (BD) is classified as a primary *multisystem variable vessel vasculitis* because of the involvement of any size and type (arterial, venous) of blood vessel. BD is probably underdiagnosed in children as a result of the heterogeneity in clinical features, the large spectrum of differential diseases, and lack of specific tests. Originally described with recurrent oral ulcerations, uveitis, and skin abnormalities, the BD spectrum is much broader.

EPIDEMIOLOGY

BD has a high prevalence in countries along the *Silk Road,* extending from Japan to the Eastern Mediterranean. It is increasingly recognized among people of European ancestry as well. BD has a prevalence of 5-7 per 100,000 adults. The increased disease recognition might have had a role in the rising prevalence of BD as well as the migrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in Eastern Mediterranean countries; boys and girls are equally affected. A family history of BD is present in approximately 20% of the cases. Onset in children is usually 8-12 years of age. Newborns of affected mothers have demonstrated symptoms of BD.

ETIOLOGY AND PATHOGENESIS

The etiology of BD is unknown. It is a polygenic disorder with autoinflammatory features. The autoinflammatory nature of BD is suggested by its episodic nature, the prominent innate immune system activation, the absence of identifiable autoantibodies, and the coassociation with the *MEFV* gene. However, there is evidence supporting the role of the adaptive immune system as well. BD has also been considered to be an MHC-I-opathy because of the strong association with HLA-B51. Genetic contribution to BD is evident through this well-known association with HLA-B5101, the familial cases, the sibling and twin recurrence rate, the specific frequency of the disease among people along the Silk Road, evidence for genetic anticipation, and genome-wide analysis. Genome-wide analysis studies among Turkish and Japanese BD patients confirm the marked association with HLA-B5101. Other significant associations include interleukin (IL)-10 and IL-23R/IL-12Rβ_2 genes. Other possible susceptibility loci demonstrate associations with *STAT4* (a transcription factor in a signaling pathway related to cytokines such as IL-12, type I interferons, and IL-23) and *ERAP1* (an endoplasmic reticulum–expressed

aminopeptidase that functions in the processing of peptides onto major histocompatibility complex class I).

An infectious agent may be responsible for inducing the aberrant innate immune system attacks in the genetically predisposed host. A number of infectious agents have been implicated and include streptococci and herpes simplex virus type 1. A microbiome study in BD proposed a distinct salivary signature.

BD has some genetic and immune similarities to periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome and recurrent aphthous stomatitis, suggesting a spectrum of these disorders.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The course of BD is characterized by exacerbations and remissions. There is marked heterogeneity in disease manifestations.

The mean age of the first symptom is between 8 and 12 years. The most frequent initial symptom is a *painful* **oral ulcer** (Fig. 202.1). The oral ulcers are often recurrent, may be single or multiple, range from 2 to 10 mm, and may be in any location in the oral cavity. They are often very painful. The oral ulcers last 3-10 days and heal without scarring. In contrast, the genital ulcers heal with scars. Genital scars are noted in 60–85% of the patient, usually occur after puberty, and are seen on the labia, scrotum, penis, or anal area.

Another key feature of BD that has significant morbidity is the bilateral eye involvement seen in 30–60% of pediatric patients. The main symptoms of **anterior uveitis** are blurred vision, redness, periorbital or global pain, and photophobia. Although it is often in the form of panuveitis, anterior uveitis may be seen in females. Uveitis in general is more common in males. Vitritis and retinal vasculitis are the most prominent features of *posterior* involvement. Complications of uveitis include blindness (unusual with treatment), glaucoma, and cataracts. Retinal vasculitis, retinal detachment, and retrobulbar neuritis (optic neuritis) are less common eye manifestations of BD.

The skin lesions are the third most common symptom of BD. They range from erythema nodosum (seen in approximately 50% of patients) to papulopustular acneiform lesions (85%), folliculitis, purpura, and ulcers. Pathergy (seen in 50%) is another skin feature associated with BD and is a pustular reaction occurring 24-48 hours after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

The vasculitis of BD involves both arteries and veins, thrombosis and aneurysm formation, occlusions, or stenosis in arteries of any size. In children, deep venous thrombosis of the lower limbs is the most frequent vasculitic feature. If the hepatic vein is thrombosed, Budd-Chiari syndrome may occur. Pulmonary artery aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki or multisystem inflammatory syndrome in children (MIS-C) disease. Microvascular involvement may be noted in the nail bed capillaries.

Central nervous system (CNS) manifestations (approximately 10%) in children include meningoencephalitis (headache, meningismus, cerebrospinal fluid pleocytosis), encephalomyelitis, pseudotumor cerebri, dural sinus thrombosis, and organic psychiatric disorders (psychosis, depression, dementia). Dural sinus thrombosis is the most common CNS manifestation in children.

Gastrointestinal (GI) involvement (seen in 10–30%) manifests with abdominal pain, diarrhea, and intestinal ulcerations, most often in the ileocecal region. Gastrointestinal BD may be difficult to distinguish from inflammatory bowel disease. Oligoarticular arthritis/arthralgia is present in >50% of patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

The International Study Group for Behçet Disease (ISG) criteria used to be the most widely used and require the presence of oral ulcers (at least 3 times per year) along with two other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions. If only one of the criteria is present along with oral ulcerations, the term *incomplete* or *partial Behçet disease* is applied. The revised International Criteria for Behçet Disease (ICBD) have been reported to have a much better performance than the 1990 ISG criteria.

Additional classification criteria for children have been suggested by the use of an international prospective observational cohort. According to these criteria, BD is diagnosed when three of the following criteria are present: recurrent oral aphthosis, genital ulcers, skin involvement (necrotic folliculitis, acneiform lesions, erythema nodosum), ocular involvement, neurologic involvement, and vascular involvement (venous thrombosis, arterial thrombosis, arterial aneurysm). These criteria performed better than the ISG criteria in the pediatric cohort (Table 202.1).

There are no specific laboratory tests. Acute-phase reactants are often mildly elevated. The diagnosis relies on the constellation of symptoms and excluding other causes.

Hughes-Stovin syndrome is characterized by thrombophlebitis and multiple bronchial or pulmonary artery aneurysms. This vasculitic



Fig. 202.1 A deep aphthous ulcer in a patient with Behçet disease.

Table 202.1 Consensus Classification of Pediatric Behçet Disease

ITEM	DESCRIPTION
Recurrent oral aphthosis	At least three attacks/year
Genital ulceration or aphthosis	Typically with scar
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum
Ocular involvement	Anterior uveitis, posterior uveitis, retinal vasculitis
Neurologic signs	With the exception of isolated headaches
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm

From Koné-Paut I, Shahram F, Darce-Bello M, et al, for PEDBD group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis.* 2016;75:958–964.

process is regarded as a clinical variant of BD (partial or incomplete) but without ulcerations.

TREATMENT AND PROGNOSIS

Azathioprine is highly recommended to treat inflammatory eye disease. Anti–tumor necrosis factor (TNF) treatment and interferon (IFN)-α should be considered for refractory eye disease. For oral and genital ulcers, topical treatment and colchicine are recommended (sucralfate, corticosteroids). **Apremilast**, an oral phosphodiesterase-4 inhibitor, is effective in treating the oral ulcers of BD. In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. There is no evidence-based treatment for GI disease, but 5-ASA derivatives, corticosteroids, azathioprine, and anti-TNF agents have been recommended. For CNS disease and venous thrombosis, corticosteroids, azathioprine, and anti-TNF agents are recommended. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, GI, and CNS involvement, respectively. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients with pulmonary arterial or cardiac involvement, cyclophosphamide is typically used initially.

Mortality in children with BD is low except for the pulmonary aneurysms. However, BD is a chronic disease associated with significant morbidity. Early diagnosis and effective treatment improve the outcome of BD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 203

Sjögren Syndrome

C. Egla Rabinovich

Sjögren syndrome is a chronic, inflammatory autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, especially salivary and lacrimal (parotid being prototypical), with potential for systemic manifestations. It is rare in children and has classic symptoms of dry eyes **(keratoconjunctivitis sicca)** and dry mouth **(xerostomia)**.

EPIDEMIOLOGY

Sjögren syndrome typically manifests at 35-45 years of age, with 90% of cases among females, but it is underrecognized in children because symptoms often start in childhood. The mean age at diagnosis in children is 9-10 years; 75% are female. The disease can occur as an isolated disorder, referred to as **primary** Sjögren syndrome **(sicca complex)**, or as a **secondary** Sjögren syndrome in association with other rheumatic disorders, such as systemic lupus erythematosus (SLE), scleroderma, or mixed connective tissue disease, which usually precedes the associated autoimmune disease by years.

ETIOLOGY AND PATHOGENESIS

The etiology of Sjögren syndrome is complex and includes genetic predisposition and possibly an infectious trigger. Lymphocytes and plasma cells infiltrate salivary glands, forming distinct periductal and periacinar foci that become confluent and may replace epithelial structure. Several genes regulating apoptosis influence the chronicity of lymphocytic infiltration.

CLINICAL MANIFESTATIONS

International classification criteria have been developed for the diagnosis of Sjögren syndrome in adult patients, but these criteria apply poorly to children. Although diagnostic criteria in children have been proposed, they have not been validated (Table 203.1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas **sicca syndrome** (dry mouth, painful mucosa, halitosis, widespread dental caries) predominates in adults. Children tend to have a higher prevalence of systemic symptoms, including fevers and adenopathy, compared to adults. In a cross-sectional study of children with Sjögren syndrome, manifestations included recurrent parotitis (72%), sicca symptoms (38%), polyarthritis (18%), vulvovaginitis (12%), hepatitis (10%), Raynaud phenomenon (10%), fever (8%), renal tubular acidosis (9%), lymphadenopathy (8%), and central nervous system (CNS) involvement (5%).

Table 203.1 Proposed Pediatric Criteria for Diagnosis of Sjögren Syndrome (SS)

JUVENILE SS
CLINICAL SYMPTOMS
1. Recurrent parotitis or parotid enlargement
2. Recurrent conjunctivitis (nonallergic and noninfectious)
3. Recurrent vaginitis
4. Systemic: fever of unknown origin, arthralgias, hypokalemic paralysis, or abdominal pain
OBJECTIVE
5. Ocular dryness (ocular staining or a Schirmer test)
6. Abnormal sialography
7. Elevated serum amylase
8. Leukopenia or elevated ESR
9. Hyperimmunoglobulinemia (polyclonal)
10. Renal tubular acidosis
SEROLOGY
11. At least one of anti-SSA, anti-SSB, high titer ANA (speckled pattern), RF
HISTOPATHOLOGY
12. Lymphocytic infiltration of salivary glands or other organs
DIAGNOSIS OR CLASSIFICATION REQUIREMENTS
13. Diagnosis requires at least 4 of 12 items

Modified from Yokogawa N, Lieberman SM, Sherry DD, Vivino FB. Features of childhood Sjögren's syndrome in comparison to adult Sjögren's syndrome: considerations in establishing child-specific diagnostic criteria. *Clin Exper Rheumatol.* 2016;34:343–351, Table 1.

Subjective symptoms of xerostomia complaints are relatively rare in juvenile cases, perhaps indicating that Sjögren syndrome is a slowly progressive disease; however, increased dental caries is seen clinically in children. Serologic markers (antinuclear antibodies [ANAs], antibodies to Ro [SSA] and La [SSB]) and articular manifestations are significantly more common in adults. Reported frequencies of ANAs and SSA and SSB antibodies in children are 78%, 75%, and 65%, respectively, with rheumatoid factor present in 67%. Additional clinical manifestations from a variety of organ involvement patterns include a decreased sense of smell; hoarseness; chronic otitis media; leukocytoclastic vasculitis (purpura); and internal organ exocrine disease involving the lungs (diffuse interstitial lymphocytosis), pancreas, hepatobiliary system, gastrointestinal tract, kidneys (renal tubular acidosis), musculoskeletal (arthritis and arthralgia), hematologic (cytopenias), peripheral nervous system (sensory and autonomic neuropathy), and CNS (optic neuritis, transverse myelitis, meningoencephalitis).

Nonexocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (skin, muscle and joints, serosal surfaces, CNS, peripheral nervous system), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, fever), and autoimmune endocrinopathy (thyroiditis).

DIAGNOSIS

Clinical presentation of recurrent **parotitis** and/or recurrent parotid gland swelling in a child or adolescent is characteristic and should raise the suspicion for Sjögren syndrome. The diagnosis is based on clinical features supported by biopsy of salivary or parotid glands demonstrating foci of lymphocytic infiltration, the current gold standard for diagnosis. Children are more likely to have normal minor salivary gland but abnormal parotid gland biopsies. Supporting laboratory abnormalities include cryoglobulinemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, and presence of SSA and SSB antibodies. The Schirmer test detects abnormal tear production (≤5 mm of wetting of a filter paper strip in 5 minutes). Special dyes (e.g., fluorescein, Lissamine green) detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium (^{99m}Tc) scintigraphy, parotid ultrasound, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 203.1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Sjögren syndrome in children includes **juvenile recurrent parotitis**, characterized by intermittent *unilateral* parotid swelling typically lasting only a few days; it is frequently associated with fever and may undergo remission with puberty. Unlike in Sjögren syndrome, there is a male predominance, juvenile recurrent parotitis is seen in the younger children (3-6 years), and there is a lack of focal lymphocytic infiltrates on biopsy. Other conditions in the differential diagnosis include eating disorders, infectious parotitis (mumps, streptococcal and staphylococcal infections, Epstein-Barr virus, cytomegalovirus, HIV, parainfluenza, influenza enterovirus), and local trauma to the buccal mucosa. Rarely, polycystic parotid disease, tumors, and sarcoidosis may present with recurrent parotid swelling.

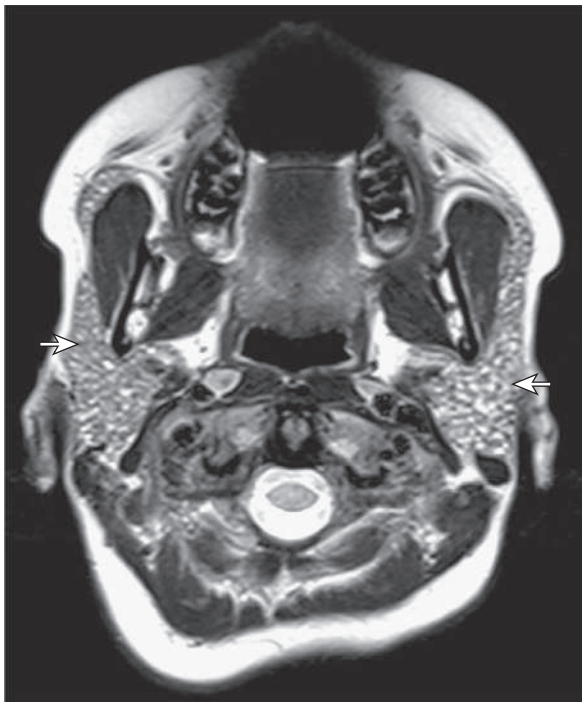

Fig. 203.1 T2-weighted MRI of a child with Sjögren syndrome showing parotitis *(arrows)*.

In these conditions, sicca complex, rash, arthralgia, and ANAs are usually absent.

TREATMENT

Symptomatic treatment of Sjögren syndrome includes the use of artificial tears, massage of the parotids, oral lozenges, and fluids to limit the damaging effects of decreased secretions. Corticosteroids, nonsteroidal antiinflammatory drugs, and hydroxychloroquine are among the more commonly used agents for treatment, with reports of methotrexate and etanercept used for treatment of arthritis. Stronger immunosuppressive agents, such as cyclosporine and cyclophosphamide, are reserved for severe manifestations (e.g., lung involvement) and life-threatening complications.

COMPLICATIONS AND PROGNOSIS

The symptoms of Sjögren syndrome develop and progress slowly. Diminished salivary flow typically remains constant for years. Because monoclonal B-lymphocyte disease originates chiefly from lymphocytic foci within salivary glands or from parenchymal internal organs, there is increased risk for mucosa-associated lymphoid tissue lymphoma. Maternal Sjögren syndrome can be an antecedent to neonatal lupus syndrome (see Chapter 199.1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 205

Interferonopathies

Sara E. Sabbagh and James W. Verbsky

Type I interferonopathies refer to a group of inherited autoinflammatory disorders that are characterized by dysregulation of the type I interferon (IFN) pathway (Table 205.1). Type I interferonopathies were recognized when a report described the phenotypic overlap between Aicardi-Goutières syndrome (AGS) encephalopathy, congenital viral infections, and monogenic systemic lupus erythematosus (SLE). The clinical similarities of these diseases stimulated the theory of a shared pathologic mechanism. Pathogenic variants involved in type I IFN signaling were identified to be causative for AGS and monogenic forms of SLE. Several other novel monogenic disorders with aberrant IFN signaling have been identified.

Type I IFNs are ubiquitously expressed inflammatory polypeptides that are induced by microbial and viral nucleic acids. During viral replication, accumulation of viral nucleic acids is sensed by several different cellular mechanisms, which leads to downstream IFN production (Fig. 205.1). Type I IFNs are released from the cell and bind to IFN receptors (IFNRs) through autocrine and paracrine action. The IFNR then activates signal translation through Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways, which promotes the expression of IFN-simulated genes (ISGs), which stops cell replication and protein translation of the infected cell. There are several molecular mechanisms that lead to altered regulation of IFN signaling: (1) loss-of-function variants of genes that encode enzymes responsible for DNA or DNA-RNA hybrid molecule degradation; (2) variants that lead to constitutive activation or reduction of the activation threshold of intracytosolic nucleic acid sensors; (3) gain-of-function variants of positive IFN signaling regulators; (4) loss-of-function variants of negative IFN signaling regulators; and (5) proteasomal dysfunction leading to the unfolded protein response and downstream IFN pathway activation. Examples of these altered molecular mechanisms and the associated

Table 205.1 Mutated Gene, Protein Function, Pattern of Inheritance, and Main Symptoms of Known Type 1 Interferonopathies

DISEASE	GENE	PROTEIN FUNCTION	INHERITANCE	SYMPTOMS
Aicardi-Goutières syndrome (AGS) type 1	*TREX-1*	3′-5′ DNA exonuclease	AR and AD	Classical AGS
AGS2	*RNASEH2B*	Components of RNase H2 complex. Removes ribonucleotides from RNA-DNA hybrids	AR	Classical AGS
AGS3	*RNASEH2C*			Classical AGS
AGS4	*RNASEH2A*			Classical AGS with dysmorphic features
AGS5	*SAMHD1*	Restricts the availability of cytosolic deoxynucleotides	AR	Mild AGS, mouth ulcer, deforming arthropathy, cerebral vasculopathy with early-onset stroke
AGS6	*ADAR*	Deaminates adenosine to inosine in endogenous dsRNA, preventing recognition by MDA5 receptor	AR and AD	Classical AGS, bilateral striatal necrosis
AGS7	*IFIH1*	Cytosolic receptor for dsRNA	AD	Classic or mild AGS, asymptomatic
Retinal vasculopathy with cerebral leukodystrophy (RVCL)	*TREX-1*	3′-5′ DNA exonuclease	AD	Adult-onset loss of vision, stroke, motor impairment, cognitive decline, Raynaud, and liver involvement
Spondyloenchondrodysplasia (SPENCD)	*ACP5*	Lysosomal phosphatase activity	AR	Spondyloenchondrodysplasia, immune disregulation, and in some cases combined immunodeficiency
STING-associated vasculopathy with onset in infancy (SAVI)	*TMEM173*	Transduction of cytoplasmic DNA-induced signal	AD	Systemic inflammation, cutaneous vasculopathy, pulmonary inflammation
Proteasome-associated autoinflammatory syndrome (PRAAS)	*PSMB8*	Part of the proteasome complex	AR	Autoinflammation, lipodystrophy, dermatosis, hyperimmunoglobulinemia, joint contractures, short stature
ISG15 deficiency	*ISG15*	Stabilizes USP18, a negative regulator of type 1 interferon	AR	Brain calcifications, seizures, mycobacterial susceptibility
Singleton-Merten syndrome (SMS)	*IFIH1*	Cytosolic receptor for dsRNA	AD	Dental dysplasia, aortic calcifications, skeletal abnormalities, glaucoma, psoriasis
Atypical SMS	*DDX58*	Cytosolic receptor for dsRNA	AD	Aortic calcifications, skeletal abnormalities, glaucoma, psoriasis
Trichohepatoenteric syndrome (THES)	*SKIV2L*	RNA helicase	AR	Severe intractable diarrhea, hair abnormalities (trichorrhexis nodosa), facial dysmorphism, immunodeficiency in most cases

From Volpi S, Picco P, Caorsi R, Candotti F, Gattorno M. Type I interferonopathies in pediatric rheumatology. *Pediatr Rheumatol Online J.* 2016;14(1):35.

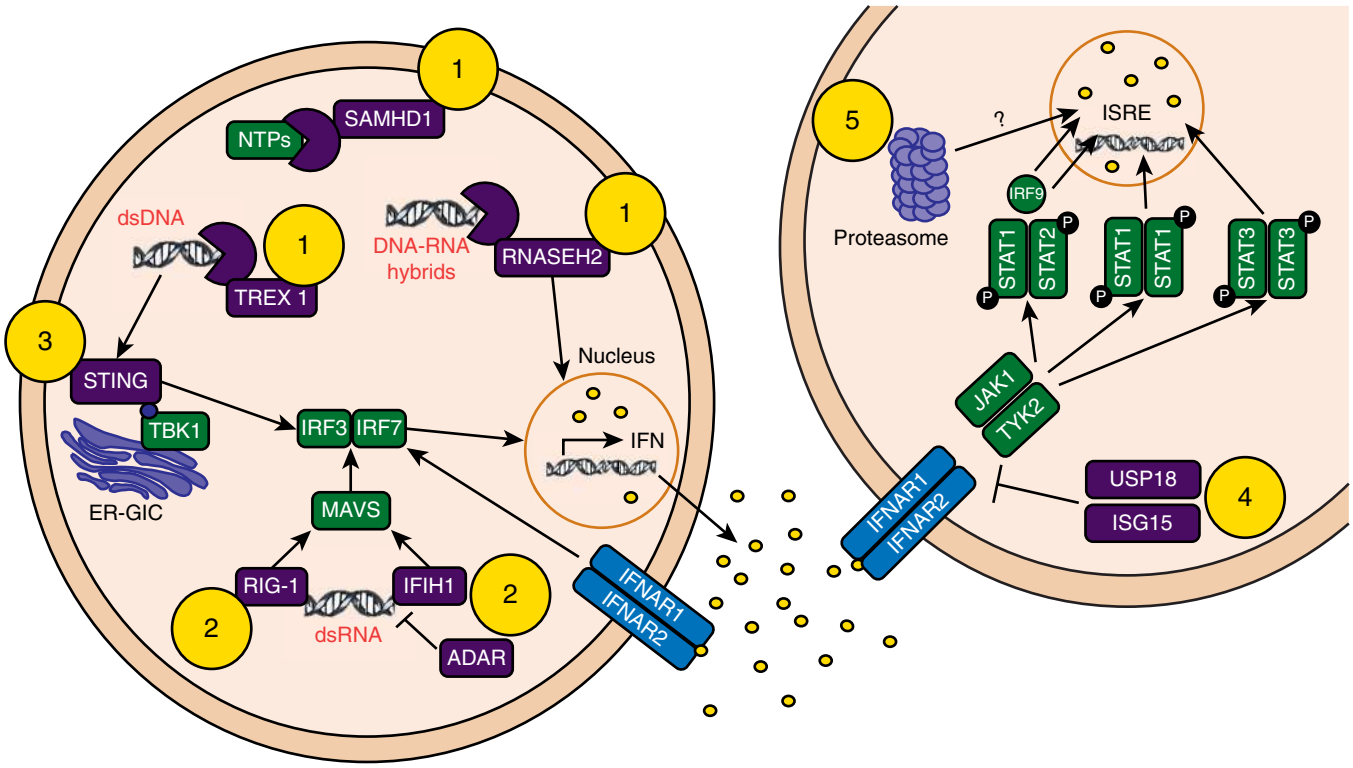

Fig. 205.1 Schematic representation of various pathways affected in genetic interferonopathies. *Purple rectangle*s indicate variant proteins in type I interferonopathies. Numbered *yellow circles* indicate the common mechanistic defect. *1.* Loss-of-function pathogenic variants of genes that encode enzymes responsible for DNA or DNA-RNA hybrid molecule degradation. *2.* Pathogenic variants that lead to constitutive activation or reduction of activation threshold of intracytosolic nucleic acid sensors. *3.* Gain-of-function pathogenic variants of positive IFN signaling regulators; *4.* Loss-of-function pathogenic variants of negative IFN signaling regulators; and *5.* Proteasomal dysfunctional leading to the unfolded protein response and downstream IFN pathway activation. STING: stimulator of interferon genes; SAMHD1: SAM domain and HD domain deoxynucleoside triphosphate triphosphohydrolase 1; NTPs: nucleoside triphosphates; TREX1: DNA 3′ repair exonuclease 1; ISG15: interferon-stimulated gene 15; MAVS: mitochondrial antiviral-signaling protein; RIG-I: retinoic acid-inducible gene I; TBK1: TANK-binding kinase 1; USP18: ubiquitin-specific peptidase 18; RNASEH2, ribonuclease H domain 2; IFIH1: IFN-induced helicase C domain-containing protein 1; ADAR: RNA adenosine deaminase; IRF3: interferon regulatory factor 3; IRF7: interferon regulatory factor 7; IRF9: interferon regulatory factor 9; ERGIC: endothelial reticulum–Golgi intermediate compartment; IFNAR: interferon-α receptor; ISGF3: the transcriptional activator induced by interferon-α; ISRE: interferon-sensitive response element; JAK1: Janus kinase 1; TYK2: tyrosine kinase 2; STAT: signal transducer and activator of transcription. P indicates phosphorylation.

genetic variants are depicted in Figure 205.1. Each genetic variant that leads to dysregulation of IFN signaling is causative of a unique clinical syndrome or subtype of a clinical syndrome that has been classified as a type I interferonopathy. Despite some disease heterogeneity, interferonopathies have a characteristic clinical phenotype, which may include recurrent fevers, early onset of skin vasculopathy with chilblains, livedo reticularis, panniculitis, lipodystrophy, interstitial lung disease with fibrosis, and encephalopathic CNS involvement (Fig. 205.2 and Table 205.2).

AUTOINFLAMMATORY INTERFERONOPATHIES

Aicardi-Goutières Syndrome

AGS is a clinically heterogeneous disease with a spectrum of associated phenotypes. AGS is characterized by an early-onset progressive encephalopathy with basal ganglia calcifications, leukoencephalopathy, and cerebral atrophy with elevated type I IFN cerebrospinal fluid (CSF) levels and CSF pleocytosis. Cutaneous features, seen in about 30% of patients, include chilblains, or cold-induced acral dermatosis of the digits and auricles secondary to peripheral inflammatory vasculopathy. Other common manifestations include thrombocytopenia, hepatosplenomegaly, transaminitis, psoriasis, interstitial lung disease, and intermittent fever. Most frequently, AGS has an infantile onset in which patients develop abrupt irritability, sterile pyrexias, and developmental regression within the first few months of life. Neurologic symptoms may include limb hypertonia with truncal hypotonia, dystonia, excessive startle, abnormal eye movements, epileptic seizures, and slowing of head growth. *RNASEH2B* variants are commonly seen in this context; however, variants of any associated AGS-related genes may present with this clinical scenario. AGS may also present prenatally with a striking similarity to transplacentally acquired infections (pseudo-TORCH), with onset of disease in utero. At birth, patients may have irritability, feeding difficulties, jitteriness, microcephaly, abnormal movements, epileptic seizures, thrombocytopenia, anemia, and liver dysfunction. This presentation is most frequently associated with *TREX1* pathogenic variants and leads to profound developmental sequelae and increased risk of death in infancy. In both clinical presentations, neuroimaging shows a highly characteristic pattern of diffuse abnormal white matter, intracranial calcifications, swelling of temporal or frontal lobes, and cerebral atrophy, similar to radiologic findings seen in congenital infections. Patients may also develop autoimmunity, including type 1 diabetes mellitus, hypothyroidism, hypergammaglobulinemia, and hemolytic anemia. Rarely, AGS can have a later onset with abrupt profound neurologic regression after an extended period of normal development.

There are seven recognized genetic variants and corresponding disease subtypes of AGS (AGS 1-7), all of which are responsible for RNA/DNA degradation or detection, resulting in type I

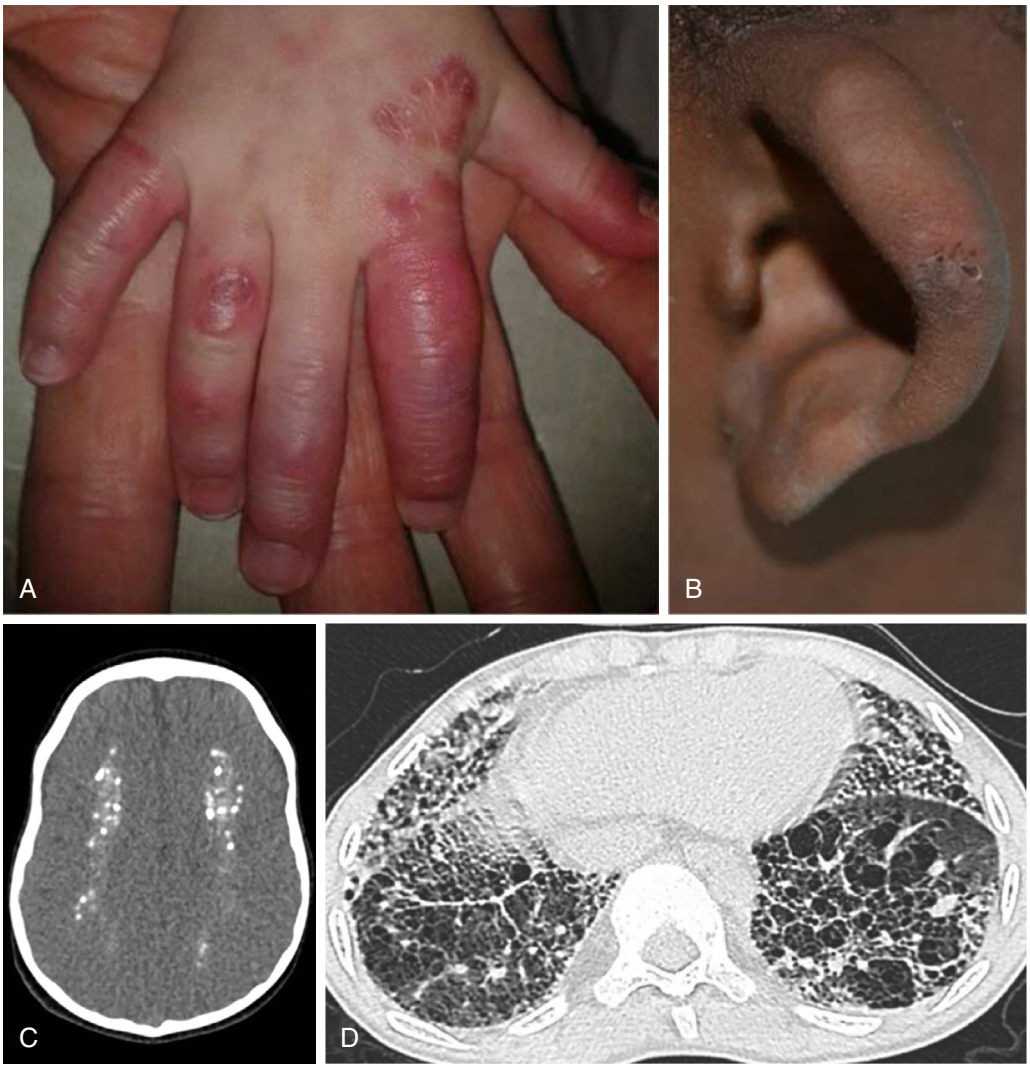

Fig. 205.2 Characteristic clinical phenotypes of interferonopathies. Chilblain lesions typical of monogenic type I interferonopathies, seen most frequently on the toes, fingers (A), ears (B), and nose. The lesions are generally worse in the cold months. C, Representative brain CT scan of intracranial calcifications seen in a patient with Aicardi-Goutières syndrome due to *TREX1* homozygous pathogenic variants. D, Chest CT scan of a SAVI patient (performed at the age of 12.5 years) showing evidence of interstitial lung disease (interlobular septal thickening, intralobular lines, cystic lesions, and some ground-glass lesions) and fibrosis (honeycombing). *(Modified from Melki I, Fremond ML. Type I interferonopathies: from a novel concept to targeted therapeutics.* Curr Rheum Reports. *2020;22:32, Fig. 1.)*

IFN production and upregulation of ISGs. These include variants of *3′-5′ DNA exonuclease-TREX1* **(AGS1)**; ribonucleases including *RNASEH2B* **(AGS2)**, *RNASEH2C* **(AGS3)**, and *RNASEH2A* **(AGS4)**; SAM and HD domain-containing deoxynucleoside *triphosphate triphosphohydrolase 1-SAMHD1* **(AGS5)**; adenosine deaminase acting on *RNA 1-ADAR1* **(AGS6)**; and IFN-induced helicase C domain–containing protein-*IFIH1* **(AGS7)**. The majority of AGS subtypes are autosomal recessive; however, heterozygous gain-of-function variants can also occur in AGS1 and AGS6, and variants causing AGS7 are autosomal dominant.

There are several manifestations that are strongly associated with distinct AGS subtypes. Bilateral striatal necrosis with severe dystonia is associated with variants in *ADAR1* (AGS6), and spastic paraparesis has been associated with variants in *ADAR1* (AGS6), *IFIH1* (AGS7), and *RNASEH2B* (AGS2). Variants involving *SAMHD1* (AGS5) have the most variable phenotype with cutaneous involvement, glaucoma, progressive contractures, stroke, and cerebral aneurysms. Beyond the phenotype diversity between different AGS variants, there are descriptions of marked intrafamilial variation in siblings harboring identical homozygous variants, which raises questions regarding how environmental factors influence disease expression and penetrance.

Spondyloenchondrodysplasia

Spondyloenchondrodysplasia (SPENCD) is a rare autosomal recessive disorder best characterized as a skeletal dysplasia with sclerosis, enchondromas, short stature, platyspondyly, and irregularity of vertebral end plates. Patients may also develop intracranial calcifications, spasticity, and a spectrum of autoimmunity that bears resemblance to SLE, including hemolytic anemia, thrombocytopenia, glomerulonephritis, malar rash, myositis, antiphospholipid syndrome, and autoantibody positivity. Patients have also developed hypothyroidism, Raynaud phenomenon, Sjögren syndrome, and vitiligo. SPENCD is caused by variants of the *ACP5* gene on chromosome 19p13, which encodes tartrate-resistant acid phosphatase (TRAP). Loss of TRAP expression impairs inactivation of osteopontin (Opn), a protein involved in bone metabolism and Th1 differentiation, via signaling through TLR9 in plasmacytoid dendritic cells (pDCs). Increased levels of Opn thus leads to increased IFN-α production.

STING-Associated Vasculopathy with Onset in Infancy

STING-associated vasculopathy with onset in infancy (SAVI) is a rare disorder that presents with systemic inflammation, fevers, and elevated inflammatory markers in the first months of life.

Table 205.2 Suggestive Features of Type I Interferonopathies

Familial history	Several affected individuals, even if phenotypic spectrum might be variable within the same family
Age of onset	• Young age at onset, in favor of monogenic disease • Later onset also reported
Neurologic phenotypes	**Clinical signs:** • Spasticity, spastic paraparesis • Acute or subacute dystonia • Encephalopathy with seizures and progressive microcephaly • Cortical blindness • Variable developmental delay • Ataxia • Psychosis • Vascular neurologic disease (Moyamoya)/strokes • Rare demyelinating or multifocal neuropathies **Lumbar puncture:** • Meningitis (inconstant) • Elevated pterins/neopterins in the CSF • Elevated IFN-α activity or protein in the CSF **Morphologic imaging features:** • CT scans: ICC, basal ganglia calcifications or progressive cerebral atrophy • Cerebral MRI: leukoencephalopathy, white matter rarefaction, delayed myelination, bilateral striatal necrosis, deep white matter cysts, or intracranial aneurysms
Cutaneous features	• Chilblains/FCL; necrotizing vasculitis of fingers, toes, helix, cheeks, and nose, telangiectasia, cutaneous ulcerations • Livedo reticularis • Panniculitis, violaceous periorbital rash • Lentigines • Psoriasis • Nail dystrophy, sparse hair
Failure to thrive/short stature	• Secondary to osseous dysplasia (ACP5) • Secondary to the inflammatory status (TMEM173)
Systemic inflammation and immune features	• Recurrent fevers • Autoimmune features/SLE/autoantibodies (not necessarily specific) • Inconstant immune deficiency • Elevated IFN I pathway in whole blood/serum/plasma
Hematologic	• AI anemia, dyserythropoiesis • Thrombocytopenia or thrombocytosis • Malignancies (chronic lymphocytic leukemia, cutaneous T cell lymphoma, *SAMHD1*)
Lung features	• Interstitial lung disease (isolated or not) • Lung fibrosis • Intraalveolar hemorrhage • Macrophagic alveolitis
Vascular features	• Calcification of the aorta or blood vessels
Musculoskeletal features	• Joint pain, arthritis • Contractures and joint retractions • Jaccoud arthropathy, tendon rupture • Muscle weakness and pain/myositis • Calcinosis • X-rays: acro-osteolysis, wide medullar cavities phalange, deforming arthropathies/joint subluxation with conserved interarticular space, calcinosis
Ophthalmologic features	• Glaucoma • Papillary edema[a]
Kidney features	• Lupus nephritis
Gastrointestinal features	• VEO-IBD (very severe protein-losing enteropathy)
Dental anomalies	• Retained primary teeth[b] • Early loss of permanent teeth

[a]Reported in one SAVI patient treated with JAK1/2 inhibitor.
[b]Data not published.
Ab, Autoantibodies; AI, autoimmune; CSF, cerebrospinal fluid; CT, computerized tomography; FCL, familial chilblain lupus; ICC, intracranial calcifications; IFN, interferon; IFN I, type I interferon; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; VEO-IBD, very-early-onset inflammatory bowel disease.
From Melki I, Fremond ML. Type I interferonopathies: From a novel concept to targeted therapeutics. *Curr Rheum Reports.* 2020;22:3, Table 2.



Fig. 205.3 Clinical manifestations of stimulator of interferon genes (STING)–associated vasculopathy with onset in infancy (SAVI). **A,** Typical facial distribution of telangiectatic lesions on the nose and cheeks with atrophy and scarring of the skin with loss of deep tissue of the nose. **B,** Violaceous, scaling, atrophic plaques on both hands and progressive autoamputations of several fingers. **C,** Hilar lymphadenopathy and bilateral interstitial infiltrates on high-resolution computed tomography (CT) image. **D,** Ulcerated lesions on the pinna of the ear with scales and crusts. *(Courtesy Dr. Raphaela Goldbach-Mansky. From Petty RE, Laxer RM, Lindsley CB, et al., eds.* Textbook of Pediatric Rheumatology, *8th ed. Philadelphia: Elsevier; 2021: Fig. 39.11, p. 541.)*

Cutaneous involvement is characterized by vasculopathic rashes in acral areas (Fig. 205.3). These lesions present as violaceous plaques or nodules on the face, ears, or nose or as distal ulceration and may become necrotic. Lesional skin biopsy reveals leukocytoclastic vasculitis, microthrombotic angiopathy, neutrophilia, and occasional immune complex deposition. As STING is expressed in alveolar macrophages, type 2 pneumocytes, and bronchial epithelium, patients with SAVI also develop pulmonary complications. Paratracheal adenopathy, interstitial lung disease, and lung fibrosis have been described to a variable extent. Patients may also develop myositis, arthritis, arthralgia, oral ulcers, aphthosis, and nasal septum perforation. Low-titer autoantibodies (e.g., antinuclear antibody, anticardiolipin antibodies, and antibodies against β2 glycoprotein I) may be seen. Notably, the presence of antineutrophil cytoplasmic antibodies (cANCA) may lead to misdiagnosis of childhood granulomatosis with polyangiitis. SAVI is caused by a dominant gain-of-function variant in *TMEM173,* which encodes the stimulator of interferon genes (STING). Working as both a direct cytosolic DNA sensor and as an adaptor protein in type I IFN signaling, STING mediates the production of IFN-α/β.

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature/ Proteasome-Associated Autoinflammatory Syndromes

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a rare autoinflammatory disease caused by abnormal functioning of the proteasome-immunoproteasome. CANDLE presents in early infancy with fevers, systemic inflammation, and cutaneous involvement including neutrophilic dermatosis, annular erythema, violaceous eyelid swelling, and erythema nodosum–like panniculitis. Histology reveals a characteristic mononuclear interstitial infiltrate, which includes "immature" neutrophils in the dermis. Lipodystrophy, usually of the face, trunk, and upper limbs, begins in early childhood. Arthralgias, without radiographic evidence of arthritis, are common in children, and severe joint contractures may develop into adulthood. Acute attacks of inflammatory myositis, aseptic meningitis, sterile epididymitis, conjunctivitis, nodular episcleritis, parotitis, pneumonitis, nephritis, carditis, and otitis have been reported. Autoimmunity can occur, including Coombs-positive hemolytic anemia and hypothyroidism. Most commonly, CANDLE is due to loss-of-function variants in the *PSMB8* gene, which encodes the proteasome β5i subunit. More recently, variants in other genes encoding other proteasome-immunoproteasome subunits or the regulatory protein POMP have been discovered in patients with CANDLE syndrome. The defective proteasome function may lead to an accumulation of damaged proteins, resulting in cellular stress and type 1 IFN upregulation.

ISG15 Deficiency/USP18 Deficiency

Ubiquitin-like protein IFN stimulated gene-15 *(ISG15)* deficiency has only been reported in a few individuals and leads to a phenotype similar to AGS, with intracranial calcifications and seizures. ISG15 is an IFN-induced protein that that plays a central role in the host antiviral response, although, in humans, ISG15 deficiency does not cause an increased susceptibility to viral infection. Rather, the absence of intracellular ISG15 prevents the accumulation of ubiquitin-specific peptidase 18 (USP18), a potent negative regulator of IFN-α/β signaling, which results in an unchecked IFN-α/β

response. Notably, loss-of-function recessive variants of USP18 have been reported in five patients, all of whom had neonatal demise soon after birth owing to the dysregulation of type 1 IFN responses.

Singleton-Merten Syndrome

Singleton-Merten syndrome (SMS) is an autosomal dominant disorder characterized by early-onset severe aortic and valvular calcification, dental anomalies, acro-osteolysis, osteoporosis, and glaucoma. There is a broad spectrum of disease with variable expressivity, and patients have been reported to have an SLE or AGS phenotype. SMS is caused by gain-of-function variants in *IFIH1* and *DDX58,* which encode retinoic acid–inducible gene-I (RIG-I)–like receptor family members melanoma differentiation-associated gene 5 *(MDA5)* and *RIG-I,* respectively. MDA5 and RIG-I are cytosolic pattern recognition receptors that detect viral RNA and promote type I and III IFN expression. The phenotype variability of SMS suggests that other genetic and/or environmental factors may influence the clinical presentation.

X-Linked Reticulate Pigmentary Disorder

X-linked reticulate pigmentary disorder (XLPDR) is an X-linked dominant disorder that manifests in the first few months of life in affected males with recurrent pneumonia, bronchiectasis, diarrhea, and failure to thrive. Diffuse skin hyperpigmentation occurs in early childhood, and distinct facial features develop. Female carriers typically exhibit only pigmentary changes along the lines of Blaschko. Hypohidrosis, corneal scarring, enterocolitis, and urethral strictures can develop. The defect in XLPDR is in an intron of the *POLA1* gene, which encodes the catalytic subunit of DNA polymerase-a. Although this defect does not affect DNA replication, it does appear to increase IFN production and IFN-induced genes as well as NF-κB–induced genes in response to dsDNA, cytosolic dsRNA, and TNF-α.

DNAse II Deficiency

Deoxyribonucleases (DNAses) degrade double-stranded DNA molecules and exist in several forms. DNAse II degrades DNA contained in lysosomes, and recently deficiency of DNAse II was shown to cause a form of monogenic SLE. This autosomal recessive disease presents with severe anemia, thrombocytopenia, and hepatosplenomegaly at birth that may resolve over time. In childhood patients may then develop membranoproliferative glomerulonephritis, arthropathy, lipodystrophy, chilblain-like vasculitis, and hypogammaglobulinemia. Laboratory testing shows high titer ANA and dsDNA antibodies and high levels of serum IFNs and IFN-stimulated gene expression. In addition to DNAse II, there are two extracellular DNAses (DNAse1 and DNAse1L3) that do cause a monogenic form of SLE. Although these are likely to exhibit high IFN signatures, no data are available on these two diseases, and thus they are not classically considered interferonopathies.

AUTOIMMUNE INTERFERONOPATHIES

Systemic Lupus Erythematosus

There were descriptions of increased levels of IFN in the serum of patients with SLE. Further rationale for IFN contributing to SLE pathogenesis was supported by observational studies of patients who developed a lupuslike disease with autoantibody formation after treatment with IFN-α. Several groups showed that the majority of patients with SLE have an increased expression of type I IFN–regulated genes and that active SLE could be distinguished by an IFN-induced gene expression pattern. Many clinical features of SLE are associated with increased production of IFN, and a high IFN signature has been correlated with cytopenia, autoantibody formation, and cutaneous disease activity. There are a large number of possible inducers of IFN production in SLE. Neutrophil extracellular TRAP formation, transposable elements, and immune complexes have all been associated with IFN production in SLE patients. From a genetic standpoint, over 100 risk loci have been associated with SLE, many of which encode proteins with functions linked to type I IFN production or response. There are also several *rare* forms of monogenic SLE that are due to pathogenic variants involving type I IFN signaling. Monogenic forms of SLE, including loss-of-function variants in *DNAse II, DNASE1L3,* and *DNASE1,* are classically grouped under the umbrella of interferonopathies and are characterized by typical SLE clinical manifestations with autoantibody formation and immune complex deposition (see Chapter 199). Success of targeting the IFN pathway has been documented in SLE, and multicenter phase 3 randomized placebo-controlled trials are currently underway in extrarenal disease.

Juvenile Dermatomyositis

Dermatomyositis has become recognized as a disease partly driven by aberrant IFN signaling. An elevated IFN signature was first discovered in muscle tissue and later identified in peripheral blood cells of patients with adult and juvenile-onset dermatomyositis (DM, JDM). Subsequently, multiple studies have shown an association between type I IFN in the circulation and disease activity in myositis. Targeting the IFN pathway has shown success in treatment of DM and JDM, and there are several ongoing clinical trials evaluating small-molecule Janus kinase (JAK) inhibitors for the treatment of dermatomyositis.

Therapeutics Targeting the Interferon Pathway

Treatments for interferonopathies has been historically empiric. Numerous immunosuppressive medications, including corticosteroids and a variety of biologics, have been tried in case reports with variable results. However, because interferonopathies have a common pathway involving IFN signaling, the use of small-molecule JAK inhibitors (JAKinibs) has gained interest as a targeted therapy for these disorders. Signaling through the IFN pathway involves JAKs that phosphorylate signal transducers and activators of transcription (STAT) proteins that then dimerize and enter the nucleus to drive transcription of IFN-stimulated genes. JAKinibs block activation of JAK proteins and have been used to treat various autoimmune diseases. There is Food and Drug Administration (FDA) approval of several JAKinibs, including tofacitinib, baricitinib, and upadacitinib, for the treatment of rheumatoid arthritis; tofacitinib is also approved for the treatment of psoriatic arthritis, ulcerative colitis, and polyarticular juvenile idiopathic arthritis. Clinical trials are underway to test the utility of JAKinibs in interferonopathies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 206

Amyloidosis

Deborah L. Stone and Karyl S. Barron

Amyloidosis is the result of extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues. It may be caused by a hereditary abnormality in an amyloidogenic protein or occur as a result of chronic inflammation associated with some infectious and rheumatologic diseases.

ETIOLOGY

Amyloidosis is a result of protein misfolding. These misfolded proteins aggregate and form insoluble fibrils that can affect the normal function of several vital organs. In the amyloidosis nomenclature, a distinction is made between amyloidosis that develops from pathogenic gene variants in the amyloid fibril proteins **(hereditary amyloidoses)** and amyloidosis associated with genetic mutation in nonamyloid proteins. The hereditary amyloidoses include diseases caused by pathogenic variants in the genes for transthyretin and apolipoprotein A and usually do not present in childhood. However, children may be affected by **amyloid A (AA) amyloidosis**, which develops in patients with chronic inflammatory states. It is estimated that approximately 45% of all amyloid cases worldwide are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. Since the development of effective treatments for these infections, other causes of AA have become more common.

Individuals with chronic inflammatory rheumatic diseases, such as **rheumatoid arthritis (RA)**, **juvenile idiopathic arthritis (JIA)**, and **ankylosing spondylitis**, as well as **hereditary autoinflammatory diseases**, have an increased risk for the development of AA amyloidosis. AA amyloidosis has also been associated with sarcoidosis, cystic fibrosis, Crohn disease, malignancies (mesothelioma and Hodgkin disease), intravenous drug use disorders, and HIV infection. Approximately 6% of AA amyloidosis cases have no identified disease association.

EPIDEMIOLOGY

Only AA amyloidosis affects children in appreciable numbers. The factors that determine the risk for amyloidosis as a complication of inflammation are not clear. Many individuals with long-standing inflammatory disease do not demonstrate tissue amyloid deposition, but some children with relatively recent onset of disease may develop amyloid. In developed countries, before therapy with disease-modifying antirheumatic drugs (DMARDs) and biologic agents was available, **rheumatoid arthritis** was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of severe and poorly controlled disease with extraarticular manifestations were at the greatest risk of developing amyloidosis, and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 months. The use of DMARDs and biologic therapy has resulted in a sustained decline in the number of new cases of RA-associated amyloidosis.

JIA may be associated with AA amyloidosis, with the highest prevalence occurring in patients with systemic JIA, followed by those with polyarticular disease. AA amyloidosis has been observed in JIA patients as soon as 1 year after diagnosis. Before the availability of DMARDs and biologics, the prevalence of AA amyloidosis in JIA patients ranged from 1% to 10%. Higher prevalence was seen in Northern European patients, especially Polish patients, who had a prevalence of 10.6%; a lower prevalence was observed in North American patients. The reasons for this discrepancy are not completely understood, although it is speculated that selection bias, genetic background, and tendency toward earlier, more aggressive therapy in North Americans may have played a role. As with RA, the occurrence of new amyloid cases in patients with JIA has significantly decreased in the past 20 years because of the increased efficacy of treatment with DMARDs and biologics.

The **hereditary autoinflammatory diseases** define a group of illnesses characterized by attacks of seemingly unprovoked recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases. These attacks often appear to be initiated by stress, immunizations, or trauma. Common findings of autoinflammatory diseases include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense elevations in inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some, but not all, hereditary autoinflammatory diseases.

Familial Mediterranean fever (FMF) is the most common of the Mendelian autoinflammatory diseases and is seen most frequently in the Armenian, Arab, Turkish, and Sephardic Jewish populations. FMF is an autosomal recessive disease that results from pathogenic variants in the *MEFV* gene, which encodes the pyrin protein. *MEFV* pathogenic variants affecting the M680 and M694 amino acid residues are associated with early onset of symptoms, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arab countries have an increased risk of developing AA amyloidosis compared with patients with the same *MEFV* mutations living in North America. While one might assume that FMF patients who have frequent, severe attacks would be at the highest risk for the development of AA amyloidosis, this is not always the case. Some patients with a history of frequent attacks never develop amyloidosis, whereas others develop amyloidosis at an early age.

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is associated with pathogenic variants in the *TNFRSF1A* gene, which encodes the 55-kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14–25% of untreated patients with TRAPS will develop AA amyloidosis. The risk of amyloidosis appears to be greater among patients with cysteine pathogenic variants or the T50M pathogenic variant. These cysteine residues normally create disulfide bonds within the protein, and disruption of these bonds by amino acid substitutions is thought to interfere with protein folding.

Pathogenic variants in the *NLRP3* (NLR family pyrin domain containing 3) gene encoding the NLRP3 or cryopyrin protein cause three clinically distinct diseases or cryopyrinopathies: **familial cold autoinflammatory syndrome (FCAS**, or ***NLRP3*-AID mild)**, **Muckle-Wells syndrome (MWS**, or ***NLRP3*-AID moderate**), and **neonatal-onset multisystem inflammatory disease (NOMID**, or ***NLRP3*-AID severe)**, also known as **chronic infantile neurologic cutaneous and articular (CINCA) syndrome**. Pathogenic variants in *NLRP3* are inherited in an autosomal dominant fashion or as de novo variants in patients with the most severe disease. A few patients have been found to carry somatic variants in *NLRP3*.

FCAS is the least severe of the cryopyrinopathies and is rarely associated with AA amyloidosis. MWS presents with fevers, myalgias, arthralgias, urticarial-like rash, and progressive sensorineural hearing loss. AA amyloidosis is quite common in MWS, affecting up to one third of the patients. NOMID/CINCA is the most severe cryopyrinopathy. NOMID patients have not developed AA amyloidosis as often as MWS patients, but this may be attributable to the fact that before the availability of effective treatments, 20% of NOMID patients died before reaching adulthood.

Mevalonate kinase deficiency (MKD) – mild (**formally known as Hyper-IgD syndrome**, or **HIDS**) is an autoinflammatory disease that presents in early childhood with high fevers, abdominal pain, lymphadenopathy, and occasional rash. MVK-mild is an autosomal recessive disease that involves loss-of-function variants in the *MVK* gene that encodes the mevalonate kinase enzyme. Patients with MVK-mild retain a low level of enzyme activity, whereas patients with MVK-severe **(mevalonic aciduria)** have severe *MVK* variants that completely abolish enzyme activity, causing recurrent fevers, dysmorphic features, and developmental delays. Inflammatory markers are high during

MVK-mild attacks and may remain elevated between attacks. AA amyloidosis is rare in patients with MVK-mild but has been reported, most often associated with the V377I/I268T genotype.

Although seen less frequently than in the hereditary periodic fever syndromes, AA amyloidosis occurs in an estimated 1% of U.S. patients and up to 3% of Northern European patients with **Crohn disease**. Conversely, AA amyloidosis in patients with ulcerative colitis is extremely rare, with an estimated prevalence of 0.07%. Patients with Crohn disease and AA usually have a long-standing history of aggressive, poorly controlled disease, although there are reports of amyloidosis in patients with well-controlled inflammatory markers.

Thirty-six proteins have been identified as being amyloidogenic in humans, but most of these rarely cause disease during childhood. **Transthyretin-related hereditary amyloidosis** is an autosomal dominant disorder with variable penetrance and onset in the second to third decades of life. Manifestations include familial amyloidotic polyneuropathy, familial amyloid cardiomyopathy, nephropathy, and ocular disease.

PATHOGENESIS

The deposition of AA amyloid fibrils is a result of a prolonged inflammatory state that leads to misfolding of the AA amyloid protein and deposition into tissues. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein called **serum amyloid A**. SAA is expressed by three different genes on chromosome 11p15.1. SAA1 and SAA2 are two isoforms that are acute-phase reactants synthesized by the liver. SAA is produced in response to proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF-α, and can increase more than 1,000-fold during inflammation.

It has been speculated that SAA has a role as a chemoattractant and in lipid metabolism. Supporting this theory is the finding that amyloid deposition occurs initially in organs that are major sites of lipid and cholesterol metabolism, such as the kidney, liver, and spleen. Approximately 80% of secreted SAA1 and SAA2 is bound to lipoproteins. Usually SAA secreted by the liver is completely degraded by macrophages. The secreted SAA protein is 104 amino acids in length and is primarily secreted in an α-helix structure. For reasons not completely understood, patients with AA amyloidosis have incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome where the c-terminal portion of the 104–amino acid SAA protein is cleaved, allowing the remaining 66-76 amino acid proteins to fold into a β-pleated sheet configuration. These cleaved fragments polymerize, form fibrils that are deposited in the extracellular space, and bind proteoglycans and other proteins such as serum amyloid P. These fibrils are resistant to proteolysis and deposit in organ tissues.

CLINICAL MANIFESTATIONS

Although organ involvement may vary, AA amyloidosis most frequently affects the kidneys; 90% of patients have some degree of renal involvement. Unexplained proteinuria may be the presenting feature in some patients. Nephrotic syndrome and renal failure may develop if the underlying inflammatory condition is not well-controlled. Patients with higher SAA levels have a significantly higher risk of death than those with lower SAA levels. Gastrointestinal (GI) involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, GI bleeding, abdominal pain, and malabsorption. When biopsied, the testes are frequently discovered to be involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. The heart, tongue, and skin are rarely involved.

DIAGNOSIS

The diagnosis of amyloidosis is established by a biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues tested may include kidney, rectum, abdominal fat pad, and gingiva. Amyloid deposits are composed of seemingly homogeneous eosinophilic material that stains with Congo red dye and demonstrates the pathognomonic "apple-green birefringence" in polarized light. Tissue staining and genetic testing are useful for diagnosing transthyretin amyloidosis.

LABORATORY FINDINGS

In the United States, specific laboratory testing is not commercially available for AA amyloid, but SAA levels are available in some other countries and can be monitored to guide response to treatment.

TREATMENT

There is no established therapy for AA amyloidosis, and thus the primary approach is aggressive management of the underlying inflammatory or infectious disease. As newer therapies are developed to treat the underlying conditions, emerging evidence shows that the incidence of AA amyloidosis is decreasing. **Colchicine** is effective not only in controlling the attacks of FMF but also in preventing the development of amyloidosis associated with FMF. AA amyloidosis associated with other autoinflammatory diseases and chronic rheumatic diseases does not respond to colchicine. Biologic agents against proinflammatory cytokines used to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases appear to decrease the risk of developing AA amyloidosis and may even reverse the deposition of amyloid.

The class of medications referred to as the **TNF inhibitors** have been paramount in the management of RA and other autoimmune diseases, and there are reports documenting the effectiveness of anti-TNF agents in blunting the progression of amyloidosis. Adverse effects of anti-TNF medications include reactivation of tuberculosis and hepatitis B, and thus screening should be performed before instituting therapy. Caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, because their use may cause exacerbations of underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of three biologic medications used in autoimmune and autoinflammatory diseases. The available IL-1 antagonists are **anakinra** (IL-1 receptor antagonist), **rilonacept** (soluble IL-1 receptor decoy), and **canakinumab** (long-acting fully humanized IgG_1 anti–IL-1β monoclonal antibody). **A trial of canakinumab in patients with colchicine-resistant FMF, MKD, and TRAPS showed that it was effective in controlling and preventing flares.** The various IL-1 inhibitors have been successful at slowing the progression of AA amyloidosis, and in some cases treatment results in regression of amyloid proteinuria.

Tocilizumab, an anti–IL-6 receptor antibody, has been shown to attenuate experimental AA amyloid and to reverse AA amyloidosis complicating JIA and RA. A trial using **eprodisate disodium** in AA amyloid patients failed to meet its primary end-point of reducing progression to end-stage renal disease and was halted in 2016.

Transthyretin amyloidosis has been treated with liver transplantation, which removes the source of mutated transthyretin molecules, and several medications that inhibit the synthesis of the mutated protein, stabilize tetramers of the protein, or disrupt fibrils.

PROGNOSIS

End-stage renal failure is the underlying cause of death in 40–60% of patients with amyloidosis. According to a large-scale study of 374 patients with AA amyloidosis, the factors associated with a poor prognosis include older age, a lower albumin serum level, end-stage renal disease at baseline, and prolonged serum elevation of SAA. An elevated SAA value was the most powerful risk factor for end-stage renal disease and death from AA amyloidosis.

PREVENTION

The primary means of preventing AA amyloidosis is treatment of the underlying inflammatory or infectious disease, resulting in decreases in the level of SAA protein and the risk of amyloid deposition. Although the period of latency between the onset of inflammation from the underlying disease and the initial clinical signs of AA amyloidosis may vary and is often prolonged, progression of the amyloid depositions can be rapid.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 207

Macrophage Activation Syndrome

Rebecca Trachtman and Edward M. Behrens

Macrophage activation syndrome (MAS) is a potentially fatal complication of rheumatic diseases thought to be caused by excessive activation and expansion of macrophages and T cells. These events lead to an overwhelming inflammatory reaction, involving fever, hepatosplenomegaly, lymphadenopathy, cytopenias, liver dysfunction, and coagulopathy resembling disseminated intravascular coagulation (DIC). Extreme hyperferritinemia is a characteristic laboratory feature that separates MAS from primary disease flare.

Inflammatory infiltrates composed predominantly of T lymphocytes and hemophagocytic macrophages are commonly seen in the bone marrow; they are also found in the liver, spleen, or lymph nodes. These hemophagocytic macrophages can infiltrate most organs in the body. Both the systemic and local inflammation can cause severe organ damage, which can be life-threatening and progress to multiple organ failure. The abundance of tissue macrophages exhibiting hemophagocytic activity in inflammatory lesions in MAS suggests that MAS is related to a group of histiocytic disorders collectively known as *hemophagocytic lymphohistiocytosis* (HLH).

EPIDEMIOLOGY

Although MAS can occur in many rheumatic diseases, it is seen most frequently in systemic juvenile idiopathic arthritis (SJIA) and in its adult equivalent, adult-onset Still disease (AOSD). The reasons for this association remain unclear; elevated interleukin (IL)-18 may be a causative factor. Approximately 7–17% of patients with SJIA develop severe disease, whereas more mild subclinical MAS may be seen in as many as 30% of patients with SJIA.

Systemic lupus erythematosus (SLE) and Kawasaki disease are other rheumatologic conditions in which MAS occurs somewhat more frequently than in other rheumatic diseases. In SLE, MAS occurs in approximately 1–9% of patients.

MAS most often occurs subsequent to the onset of rheumatologic disease; MAS has also been known to occur at the initial presentation of a rheumatic illness. Approximately 23% of episodes of MAS have occurred at the onset of SJIA. MAS typically occurs in the setting of active primary rheumatic disease. However, it can occur despite good control of underlying rheumatic disease. Many cases occur in the setting of infections and/or modifications in drug therapy. Both of these triggers are possibly related to subsequent active rheumatic disease.

PATHOPHYSIOLOGY AND OTHER HYPERINFLAMMATORY SYNDROMES

The exact mechanisms behind MAS remain unclear; however, much has been extrapolated from the pathogenesis of primary HLH (pHLH). Consistent with parallels to pHLH, in MAS there is an abundance of interferon-gamma (IFN-γ)–producing $CD8^+$ T cells in inflammatory lesions. Further suggesting a role for T-cell–mediated inflammation, cyclosporine A, a therapeutic agent that acts predominantly on T cells, is very effective in the treatment of the majority of MAS patients. CXCL9, a biomarker of IFN-γ activity, is also elevated in patients during an MAS episode. Cytotoxic function appears to be impaired in certain subsets of SJIA patients, perhaps specifically in those at risk for MAS, although this finding has been inconsistent. Some studies have demonstrated an enrichment of heterozygous pathogenic variants in known pHLH genes in MAS populations, suggesting that *hypomorphic* lesions in cytolytic pathways may result in disease.

Translational studies in SJIA patients suggest that elevated serum IL-18 is a risk factor for the development of SJIA/MAS. A common link to the "IFN-γ-centric" models is that IL-18 is perhaps most noted for its ability to stimulate IFN-γ production by T cells and natural killer cells. In the case of MAS caused by activating pathogenic variants in the *NLRC4* gene, IL-18 has been shown to be highly elevated, and case reports of IL-18 blockade leading to resolution of both disease and IFN-γ activity suggest a causal link.

Cytokine Storm

A "cytokine storm" is the common pathophysiologic state in many hyperinflammatory diseases. There is increasing interest in the relative roles of cytokines in MAS pathophysiology, and the similarities and differences to HLH, multisystem inflammatory syndrome in children (MIS-C) related to SARS-CoV-2 virus, and sepsis.

HLH

MAS belongs to a group of hemophagocytic disorders, which includes HLH. The current classification of histiocytic disorders distinguishes primary, or familial, HLH and secondary, or reactive, HLH (see Chapter 556.2). Clinically, they may be difficult to distinguish from each other. pHLH is a constellation of rare autosomal recessive immune disorders linked to genetic defects in various genes all affecting the cytolytic pathway. The clinical symptoms of pHLH usually become evident within the first months of life. Secondary HLH tends to occur in older children or adults. It may be associated with an identifiable infectious episode, most often Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection. However, when EBV-associated HLH occurs as part of a genetic syndrome, such as the X-linked proliferative disorders, it is more properly considered pHLH. The group of secondary hemophagocytic disorders also includes malignancy-associated HLH. Some consider MAS to be a form of secondary HLH, whereas others make a distinction and prefer the moniker "Rheuma-HLH" to separate MAS from other secondary HLH conditions. The distinction between primary and secondary HLH is becoming less distinct because of other genetic causes, some of which are associated with less severe and more distinct clinical presentations. Some of these may present later in life because heterozygous or compound heterozygous pathogenic variants in cytolytic pathway genes that confer a partial dominant negative effect on the cytolytic function.

The exact relationship between HLH and MAS is an area of extensive investigation, and some rheumatologists believe that MAS should be categorized as secondary HLH occurring in a setting of a rheumatic disease (or MAS-HLH). Although there are multiple attempts to try to standardize the nomenclature for these various syndromes, at this point, best practice would be to use the term *primary HLH* for cases with known molecular diagnoses or a clear genetic component. For secondary cases, there is not yet a prescribed specific terminology, but inclusion of known secondary causes can add clarity to the specific syndromes being described (e.g., SJIA-MAS, EBV-HLH).

Multisystem Inflammatory Syndrome in Children (MIS-C)

Children may develop a postinfectious hyperinflammatory syndrome after SARS-CoV-2 virus exposure that bears some resemblance to MAS. Approximately 4-8 weeks after infection, children developed multiorgan dysfunction, frequently involving persistent fever, abdominal pain, and rash, and sometimes accompanied by abnormal cardiac function or hypotension. Laboratory evaluation is significant for elevation of markers of inflammation and sometimes hyperferritinemia, coagulopathy, and liver dysfunction. Similar to MAS, this phenomenon occurred after infectious trigger, and cytokine storm has been invoked in multiple studies, especially involving IL-18, IL-10, IL-6, and the IFN-γ–induced CXCL9.

CLINICAL AND LABORATORY MANIFESTATIONS

The clinical findings in overt MAS are dramatic and often evolve rapidly. High persistent fever, hepatosplenomegaly, generalized lymphadenopathy, liver dysfunction, and changes in mental status are common. Coagulopathy resembling DIC can be associated with hemorrhagic

skin rashes ranging from mild petechiae to extensive ecchymotic lesions. These can progress to epistaxis and hematemesis secondary to upper gastrointestinal bleeding. Mental status changes, seizures, and coma are the most common manifestations of CNS disease. Cerebrospinal fluid examination in these patients usually reveals pleocytosis with mildly elevated protein. Deterioration in renal function has been noted in several series and may be associated with particularly high mortality. Pulmonary infiltrates can occur, and hemophagocytic macrophages can be found in bronchoalveolar lavage fluid.

These clinical symptoms are associated with notable laboratory features. A precipitous fall in at least two of three blood cell lines (leukocytes, erythrocytes, or platelets) is one of the early findings, caused in part by increased destruction of cells by phagocytosis and consumption at inflammatory sites. Decreasing erythrocyte sedimentation rate (ESR) despite persistently high CRP is another characteristic laboratory feature. This parallels hypofibrinogenemia, likely secondary to fibrinogen consumption and liver dysfunction. Prolonged prothrombin and partial thromboplastin times, fibrin degradation products, and moderate deficiency of vitamin K–dependent clotting factors are usually present as well. Liver involvement is common in MAS, and most patients develop marked hepatomegaly, and sometimes mild jaundice. Liver function tests frequently reveal high serum transaminase activity and mildly elevated levels of serum bilirubin. Serum ammonia levels are typically normal or only mildly elevated. Additional laboratory findings in MAS include hypertriglyceridemia, hypoalbuminemia, and elevated lactate dehydrogenase (LDH).

Perhaps the most striking laboratory change in MAS is the elevation of serum ferritin. Although diagnostic/classification criteria set levels of 500 ng/mL and 684 ng/mL as cutoffs for HLH and SJIA-MAS respectively, levels are often greater than 10,000 ng/mL. The reasons for this elevated ferritin are not clear and are likely multifactorial. Although extremely high ferritin is often a good serologic marker of HLH and MAS, high levels are not pathognomonic and can be seen in a wide variety of conditions. Thus ferritin needs to be interpreted in the context of the other features of the disease to support a diagnosis. Further, serum ferritin is usually 60–80% glycosylated, whereas intracellular ferritin is not glycosylated. In hemophagocytic syndromes, the percentage of glycosylated ferritin in the serum is low, typically below 20%; assessment of glycosylated ferritin may also be a useful tool for MAS diagnosis.

It has been recognized that as many as one third of patients with active SJIA may have mild subclinical MAS. These patients typically have moderate hyperferritinemia, highly increased CRP, moderately decreased hemoglobin, and relatively low platelet counts. These patients may also have mild hepatosplenomegaly and mildly elevated liver enzymes. Serum fibrinogen tends to remain in the normal range despite highly increased CRP.

DIAGNOSIS

Recognition of MAS is crucial, but early diagnosis is often difficult. There is no single clinical or laboratory feature that is specific for MAS, including hemophagocytosis, and many clinical features of MAS overlap with those seen in the underlying rheumatic diseases. The MAS clinical presentation also overlaps with sepsis-like syndromes associated with infection. This is further complicated by the fact that MAS may also be triggered by a flare of the underlying rheumatic disease or infection. In a patient with active underlying rheumatologic disease, persistent fevers and decrease in ESR and platelet count in combination with increasing serum ferritin and persistently high CRP should raise suspicion for impending MAS. Increasing liver enzymes, aspartate aminotransferase in particular, is another characteristic laboratory change. The diagnosis of MAS might be confirmed by bone marrow biopsy, with the presence of increased hemophagocytosis. However, demonstration of hemophagocytosis may be limited by sampling error, particularly at the early stages of the syndrome. In such cases, additional staining of the bone marrow with anti-CD163 antibodies may be helpful. Features consistent with MAS include massive expansion of highly activated histiocytes. The diagnosis of MAS is supported by elevated levels of soluble IL2Rα and soluble CD163 in serum.

Table 207.1 The Classification Criteria for Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

A *febrile* patient with *known or suspected systemic juvenile idiopathic arthritis* is classified as having macrophage activation syndrome if the following criteria are met:
Ferritin >684 ng/mL and any two of the following:
Platelet count ≤181 × 10^9/L
Aspartate aminotransferase >48 U/L
Triglycerides >156 mg/dL
Fibrinogen ≤360 mg/dL

Evidence is mounting that IFN-γ is the pivotal cytokine in MAS; however, peripheral measurement of IFN-γ can be difficult because of retention in tissues. Therefore the IFN-induced chemokine CXCL9 may be a more reliable serum biomarker of MAS. Although substantial elevation in the serum levels of soluble IL2Rα receptors and CXCL9 in an SJIA patient is highly suggestive of MAS, these assessments remain nonspecific, and elevation can be associated with some malignancies and viral infections, such as viral hepatitis.

Striking clinical similarities between MAS and HLH have led some to advocate for the use of the HLH-2004 diagnostic guidelines developed by the HLH Study Group of the International Histiocyte Society (see Chapter 556.2). However, the application of the HLH diagnostic criteria to SJIA patients with suspected MAS is problematic, both because there is significant overlap with common features of active rheumatic disease and because SJIA patients may reach some of the criteria only later in the clinical course. NK function testing as a means to assess cytotoxic activity is problematic, as defects in this pathway are only variably associated with SJIA and MAS.

Criteria for the diagnosis of MAS complicating SJIA are noted in Table 207.1. In cross-validation analyses, the criteria revealed a sensitivity of 0.72-0.76 and a specificity 0.97-0.99. It should be noted that these criteria were developed for classification for studies and trials and were not optimized for clinical diagnostic purposes. One limitation of the MAS classification criteria is that background treatment with biologics might modify the clinical presentation of MAS. Although IL-1 and IL-6 inhibitors effectively control the disease in the majority of SJIA patients, they do not provide full protection against MAS and may impede diagnosis. Furthermore, the MAS classification criteria are less likely to classify tocilizumab-treated patients as having MAS compared with historical controls or canakinumab-treated patients.

DIFFERENTIAL DIAGNOSIS

It is most important to distinguish MAS from a flare of an underlying rheumatologic disease and from intercurrent infection. Further, one must consider other clinical entities associated with hyperferritinemia, hepatic dysfunction, coagulopathy, cytopenias, or encephalopathy, specifically DIC, thrombotic thrombocytopenic purpura (TTP), and malignancy-associated HLH. Some other important differential diagnoses include sepsis and drug reactions; a thorough infectious workup is necessary for the majority of MAS patients. Hyperferritinemia is not specific for hemophagocytic syndromes and may be observed in various liver and kidney diseases, hematologic malignancies, or conditions requiring chronic blood transfusions.

TREATMENT

MAS is still associated with high mortality rates; therefore prompt recognition and initiation of immediate therapeutic intervention are critical. To achieve rapid reversal of coagulation abnormalities and cytopenias, most clinicians start with intravenous methylprednisolone pulse therapy (30 mg/kg for three consecutive days) followed by 2 to 3 mg/kg/day in four divided doses.

If response to glucocorticoids is not satisfactory, cyclosporine A (2-7 mg/kg/day) is usually added to the treatment regimen based on several reports describing the rapid resolution of MAS features in response to this medication. Cyclosporine is preferentially used orally, and careful monitoring for toxicity is required, especially if it is administered intravenously. In many patients, administration of cyclosporine A not only provides rapid control of symptoms but also avoids excessive use of steroids. Case reports support the use of tacrolimus as an alternative to cyclosporine A, as it is often effective and has a desirable safety profile.

There is also reported efficacy with the use of anakinra for MAS. Because MAS episodes may be triggered by disease flare, biologics that neutralize IL-1 could extinguish the underlying inflammation driving the cytokine storm. There are several case reports and two case series of anakinra treatment for MAS with promising results, particularly when used in higher doses. However, in established SJIA, continuous treatment with standard doses of anti–IL-1 and anti-IL-6 biologic therapies does not absolutely protect against MAS even if the underlying disease responds well to the treatment. In the phase 3 clinical trial of canakinumab, IL-1 blockade did not confer full protection from MAS even in patients with fully controlled SJIA. These results suggest that IL-1 inhibition effectively treats MAS in many patients, but does not completely prevent the occurrence of MAS, particularly in the setting of viral infection in treated subjects.

Intravenous immune globulin treatment has been successful in virus-associated reactive HLH. Rituximab—a treatment that depletes B lymphocytes, the main type of cells harboring EBV virus—has been successfully used in EBV-induced lymphoproliferative disease and could be considered in EBV-driven MAS.

If MAS remains active despite the use of corticosteroids, anakinra, and cyclosporine A, the HLH-2004 treatment protocol developed by the HLH Study Group of the International Histiocyte Society may be considered. In addition to steroids and cyclosporine A, this protocol includes etoposide (or VP16), a podophyllotoxin derivative that inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. However, this protocol is limited by the toxicity of etoposide and its likelihood of causing kidney and liver damage. In addition, severe bone marrow suppression, overwhelming infection, and death have been reported. The use of lower doses of etoposide (50-100 mg/m^2 range rather than 150 mg/m^2, as suggested by the HLH-2004 protocol) has been advocated by some groups.

It has also been suggested that antithymocyte globulin (ATG) might be a safer alternative to etoposide, particularly in patients with renal and hepatic impairment. ATG depletes both CD4$^+$ and CD8$^+$ T cells through complement-dependent cell lysis. Mild depletion of monocytes is noted in some patients as well. Although this treatment was tolerated well in reported cases, infusion reactions are frequently reported with the use of ATG, and adequate laboratory and supportive medical resources must be readily available if this treatment is used. Occasional reports describe successful use of cyclophosphamide to control MAS, mainly in patients with SLE.

The monoclonal antibody tocilizumab is very effective in treating SJIA. However, in a phase 3 clinical trial of tocilizumab in SJIA, several patients developed MAS. Similar to canakinumab, at the time of MAS presentation, underlying SJIA in most of these patients was well controlled. Furthermore, tocilizumab can cause normalization of some of the laboratory parameters of MAS, without actually altering the course of MAS activity itself, providing false reassurance of disease control.

In a patient with an inflammasomopathy caused by gain-of-function pathogenic variants in *NLRC4,* administration of the recombinant IL-18BP resulted in rapid and sustained improvement, including the resolution of all MAS-like features. It remains unclear whether a similar therapeutic intervention might be effective in MAS as well. Based on their essential roles in transmitting cytokine-induced signals, particularly from IFN-γ, the JAK/STAT pathways have become a target for pharmacologic manipulation in inflammatory diseases. Ruxolitinib, a potent inhibitor of JAK1 and JAK2, has been shown to ameliorate the disease-influencing patterns of JAK/STAT-dependent gene expression in animal models of pHLH, but it remains to be determined whether this treatment will be routinely effective in patients with MAS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 208

Kawasaki Disease

Mindy S. Lo, Mary Beth F. Son, and Jane W. Newburger

Kawasaki disease (KD), formerly known as *mucocutaneous lymph node syndrome* and *infantile polyarteritis nodosa,* is an acute febrile illness of childhood seen worldwide, with the highest incidence occurring in Asian children. KD is a systemic inflammatory disorder manifesting as a vasculitis with a predilection for the coronary arteries. Approximately 20–25% of untreated children develop **coronary artery abnormalities (CAAs)**, including aneurysms, whereas <5% of children treated with intravenous immunoglobulin (IVIG) develop CAA. Nonetheless, KD is the leading cause of acquired heart disease in children in most developed countries, including the United States and Japan.

ETIOLOGY

The cause of KD remains unknown. Certain epidemiologic and clinical features support an infectious origin, including the young age-group affected; epidemics with wavelike geographic spread of illness; the self-limited nature of the acute febrile illness; and the clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants <3 months old, possibly the result of protective maternal antibodies, and the rarity of cases in adults, possibly the result of prior exposures with subsequent immunity. Furthermore, the number of hospitalizations per year for KD significantly decreased during the COVID-19 pandemic, both in Japan and the United States, possibly due to low circulating causative viruses. However, there are also features that are not consistent with an infectious origin; it is unusual to have multiple cases present at the same time within a family or daycare center. Furthermore, no single infectious etiologic agent has been successfully identified, despite an exhaustive search. Other environmental triggers such as airborne toxins and climate shifts have also been speculated to play a role.

Genetic factors clearly influence the pathogenesis of KD, as evidenced by the higher risk of KD in Asian children regardless of country of residence and in siblings and children of individuals with a history of KD. The concordance rate among identical twins is approximately 13%. Linkage studies and genome-wide association studies (GWAS) have identified significant potential associations between polymorphisms in the *ITPKC* gene, a T-cell regulator, with increased susceptibility to KD and more severe disease. Other candidate genes for KD identified by GWAS include *CASP3, BLK,* and *FCGR2A*. Lastly, multiple alleles in different human leukocyte antigen (HLA) regions have been reported to influence risk for KD.

EPIDEMIOLOGY

For the majority of patients, KD is a disease of early childhood, and nearly all epidemiologic studies show a higher susceptibility to KD in males. Large database studies suggest that the hospitalization rate for KD in the United States has been mostly stable over time, although the proportion of hospitalizations complicated by "KD shock syndrome" has increased over time. In 2017, the Kids' Inpatient Database estimated 19.3 hospitalizations/100,000 children <4 years of age. Children of Asian/Pacific Islander descent had the highest rates of KD among all racial groups.

In other countries, such as the United Kingdom, South Korea, and Japan, the rate of KD seems to be increasing. In Japan, nationwide surveys have been administered every 2 years to monitor trends in KD incidence. In 2018 the highest recorded rate thus far of 359 per 100,000 children ages 0-4 years was described, with the highest rate in young children ages 9-11 months. Fortunately, the proportion of Japanese

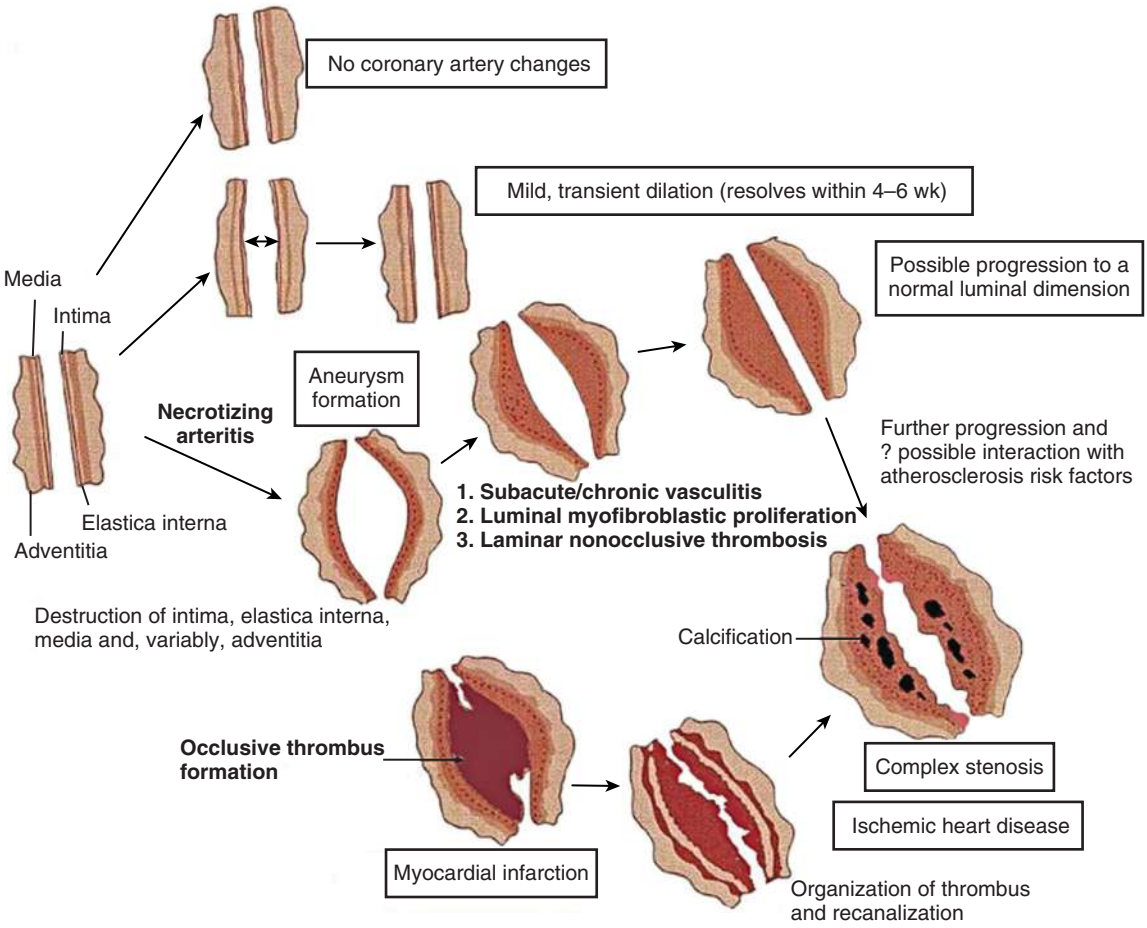

Fig. 208.1 Natural history of coronary artery abnormalities. *(Modified from Kato H. Cardiovascular complications in Kawasaki disease: coronary artery lumen and long-term consequences. Prog Pediatr Cardiol. 2004;19:137–145.)*

patients with coronary aneurysms and myocardial infarction has decreased over time, at 2.6% for the former in the most recent survey.

Several risk-stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Predictors of poor outcome across several studies include young age; being male; persistent prolonged fever; poor response to IVIG; and laboratory abnormalities, including neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal brain natriuretic protein, and elevated C-reactive protein (CRP) levels. Asian, Pacific Islander, and Hispanic ethnicity are also risk factors for CAA. Three risk scores for IVIG resistance, which refers to incomplete response to the first treatment, have been constructed by Japanese researchers; of these, the **Kobayashi score** is the most widely used and has high sensitivity and specificity. Unfortunately, when applied to non-Japanese populations, these scores do not appear to be as accurate in identifying children at risk for IVIG resistance and CAA. Body surface area (BSA)–adjusted coronary artery dimensions on initial echocardiography are good predictors of CAA development. In a North American cohort, coronary artery *z* scores ≥2.0 are predictive of CAA development; similar findings have been reported in Japanese cohorts as well. Accordingly, coronary artery *z* scores at initial presentation are useful imaging biomarkers that can be used to guide adjunctive therapy for high-risk patients.

PATHOLOGY

KD is a vasculitis that predominantly affects medium-size arteries. The coronary arteries are most often involved, although other arteries (e.g., axillary, subclavian, femoral, popliteal, brachial) can also develop dilation. A three-phase process to the arteriopathy of KD has been described. The first phase is a neutrophilic necrotizing arteritis occurring in the first 2 weeks of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis. The second phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which may cause diminution of internal lumen dimension and progressive stenosis in the third phase. Thrombi may form in the lumen and obstruct blood flow (Fig. 208.1).

CLINICAL MANIFESTATIONS

Fever is characteristically high (≥38.3°C [101°F]), persistent, and unresponsive to antipyretics. The duration of fever without treatment is generally 1-2 weeks but may be as short as 5 days or may persist for 3-4 weeks. In addition to fever, the **five principal clinical criteria** of KD are (1) bilateral *nonexudative* conjunctival injection with limbal sparing; (2) erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; (3) edema (induration) and erythema of the hands and feet; (4) rash of various forms (maculopapular, urticarial, erythema multiforme–like, scarlatiniform, and rarely, micropustular or psoriatic-like); and (5) nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 208.1 and Figs. 208.2-208.5). Superficial perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 weeks after the onset of illness and may progress to involve the entire hand and foot (Fig. 208.6).

Additional symptoms other than the principal clinical criteria are common in the 10 days before diagnosis of KD, which may be explained in part by the finding that up to a third of patients with KD have confirmed, concurrent infections. Gastrointestinal (GI)

Table 208.1 Clinical and Laboratory Features of Kawasaki Disease

EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*

Fever persisting at least 5 days†

Presence of at least four principal features:
- Changes in extremities
  - Acute: erythema of palms, soles; edema of hands, feet
  - Subacute: periungual peeling of fingers, toes in wk 2 and 3
- Polymorphous exanthem
- Bilateral bulbar conjunctival injection without exudate
- Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral

Exclusion of other diseases with similar findings‡

These features do not have to occur concurrently.

OTHER CLINICAL AND LABORATORY FINDINGS

Cardiovascular System
- Myocarditis, pericarditis, valvular regurgitation, cardiogenic shock
- Coronary artery abnormalities
- Aneurysms of medium-sized noncoronary arteries
- Peripheral gangrene
- Aortic root enlargement

Respiratory System
- Peribronchial and interstitial infiltrates on chest radiograph
- Pulmonary nodules

Musculoskeletal System
- Arthritis, arthralgias (pleocytosis of synovial fluid)

Gastrointestinal Tract
- Diarrhea, vomiting, abdominal pain
- Hepatitis, jaundice
- Hydrops of gallbladder
- Pancreatitis
- Parotitis

Central Nervous System
- Extreme irritability
- Aseptic meningitis (pleocytosis of cerebrospinal fluid)
- Facial nerve palsy
- Sensorineural hearing loss

Genitourinary System
- Urethritis/meatitis, hydrocele

Other Findings
- Desquamating rash in groin
- Retropharyngeal phlegmon
- Anterior uveitis by slit-lamp examination
- Erythema, induration at bacille Calmette-Guérin inoculation site

LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE
- Leukocytosis with neutrophilia and immature forms
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Elevated nitrogen-terminal pro B-type natriuretic peptide (NT-proBNP)
- Anemia
- Abnormal plasma lipids
- Hypoalbuminemia
- Hyponatremia
- Thrombocytosis after wk 1§
- Sterile pyuria
- Elevated serum transaminase
- Elevated serum γ-glutamyl transpeptidase
- Pleocytosis of cerebrospinal fluid
- Leukocytosis in synovial fluid

*Patients with fever at least 5 days and fewer than four principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by two-dimensional echocardiography or angiography.

†In the presence of four or more principal criteria, particularly when redness and swelling of the hands and feet are present, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish a diagnosis before day 4 in rare cases.

‡See the differential diagnosis (Table 208.3).

§Rarely infants present with thrombocytopenia and disseminated intravascular coagulation.

From McCrindle BW, Rowley A, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927–e999.

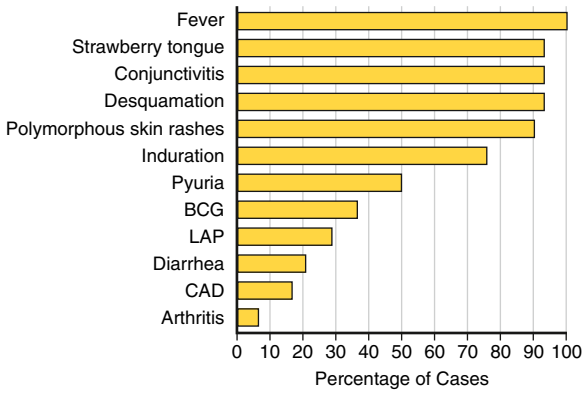

Fig. 208.2 Clinical symptoms and signs of Kawasaki disease. Summary of clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, Lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. *(From Wang CL, Wu YT, Liu CA, et al. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24:998–1004.)*



Fig. 208.3 Kawasaki disease. Strawberry tongue in patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*



Fig. 208.4 Kawasaki disease. Congestion of bulbar conjunctiva in a patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*



Fig. 208.5 Kawasaki disease. Indurative edema of the hands in a patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*



Fig. 208.6 Kawasaki disease. Desquamation of the fingers in a patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*

symptoms (vomiting, diarrhea, or abdominal pain) occur in >60% of patients, and at least one respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings can include significant irritability that is especially prominent in infants and likely caused by aseptic meningitis, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, uveitis, and arthritis. Arthritis may occur early in the illness or may develop in the second or third week. Small or large joints may be affected, and the arthralgias may persist for several weeks. Patients previously vaccinated with bacillus Calmette-Guerin (BCG) may show reactivation at the inoculation site. Clinical features that are *not consistent* with KD include exudative/purulent conjunctivitis; exudative pharyngitis; generalized lymphadenopathy; discrete oral lesions (e.g., ulceration); splenomegaly; and bullous, petechial, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis may occur in patients with acute KD and may manifest as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock **(KD shock syndrome)**, with hypotension and greatly diminished left ventricular function. In addition, KD shock syndrome may manifest with thrombocytopenia, a high band count, and a high CRP. Case series of KD shock syndrome indicate that these patients may be at higher risk for coronary artery dilation. Pericarditis with a small pericardial effusion can also occur during the acute illness. Mitral regurgitation of at least mild severity is evident on echocardiography in 10–25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease. Up to 25% of untreated patients develop CAA by Japanese Ministry of Health criteria in the second to third week of illness; initially these are usually asymptomatic and detected by echocardiography. Almost all the morbidity and mortality in KD occur in patients with **large or giant coronary artery aneurysms**, defined by the 2017 American Heart Association (AHA) scientific statement on the diagnosis and treatment of KD as having a *z* score ≥10 or an absolute dimension of ≥8 mm. Specifically, large or giant aneurysms are associated with the greatest risk of later thrombosis or stenosis, angina, and myocardial infarction (Figs. 208.7 and 208.8A). Rupture of a giant aneurysm is a rare complication that generally occurs in the first month after illness onset and may present as hemopericardium with tamponade. Axillary, popliteal, iliac, or other systemic medium-sized muscular arteries may also become aneurysmal, but always in the setting of giant coronary aneurysms (see Fig. 208.8B); these usually regress.

Occasionally KD presents initially with only fever and lymphadenopathy **(node-first KD)**. This presentation may be confused with bacterial or viral cervical lymphadenitis and may delay the diagnosis and treatment. Persistence of high fever, lack of response to antibiotics, and subsequent development of other signs of KD suggest the diagnosis. Children with node-first KD tend to be older (4 vs 2 years) and have more days of fever and higher CRP levels. In addition to cervical adenopathy, many node-first patients had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 208.9). Patients with node-first KD have a higher incidence of coronary aneurysms. Patients with infectious adenitis usually respond to antibiotics; they may have abscesses noted on imaging studies (ultrasonography or CT).

KD can be divided into three clinical phases. The **acute febrile phase** is characterized by fever and the other acute signs of illness and usually lasts 1-2 weeks. The **subacute phase** is associated with desquamation, thrombocytosis, development of CAA, and the highest risk of sudden death in patients who develop aneurysms; it generally lasts 3 weeks. The **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically 6-8 weeks after the onset of illness.

LABORATORY AND RADIOLOGY FINDINGS

There is no diagnostic test for KD, but patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common. The platelet count is generally normal in the first week of illness and rapidly increases by the second to third week of illness, sometimes exceeding 1 million/mm^3. An elevated ESR or CRP value is universally present in the acute phase of illness. The ESR may remain elevated for weeks, in part from the effect of IVIG. Sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis may also be present. KD is unlikely if the ESR, CRP, and platelet counts are normal after 7 days of fever.

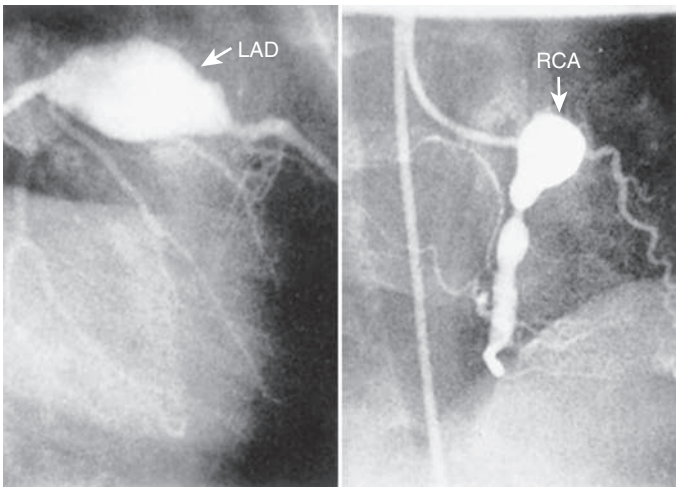

Fig. 208.7 Coronary angiograms in 6-yr-old boy with Kawasaki disease. *Left,* Giant aneurysm of the left anterior descending coronary artery (LAD) with obstruction. *Right,* Giant aneurysm of the right coronary artery (RCA) with an area of severe narrowing. *(From Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease. Pediatrics. 2004;114:1708–1733.)*

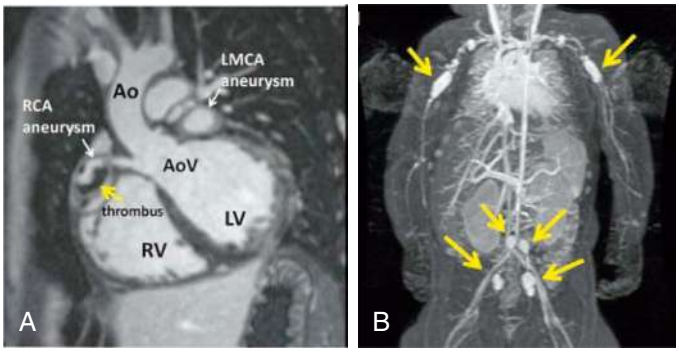

Fig. 208.8 MRI of coronary and peripheral artery aneurysms in Kawasaki disease. **A,** Image of left ventricular outflow tract showing a giant right coronary artery (RCA) aneurysm with nonocclusive thrombus *(yellow arrow)* and a giant left main coronary artery (LMCA) aneurysm. Ao, Aorta; AoV, aortic valve; LV, left ventricle; RV, right ventricle. **B,** Aneurysms in the axillary and subclavian arteries and the iliac and femoral arteries *(arrows). (From McCrindle BW, Rowley A, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135[17]:e927–e999, Fig. 2G and H, p. e935.)*

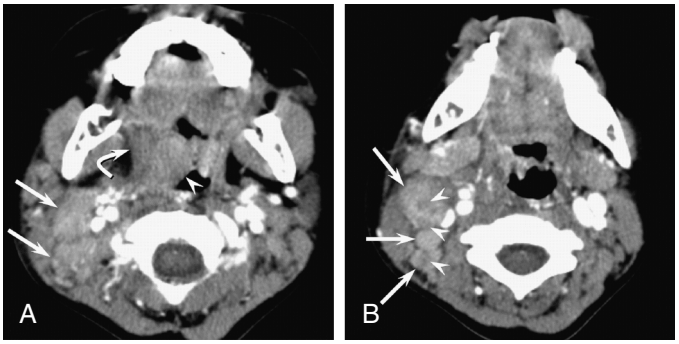

Fig. 208.9 Contrast-enhanced CT in 3-yr-old boy with Kawasaki disease. **A,** Right-sided cervical lymphadenopathy *(arrows),* peritonsillar hypodense area *(curved arrow),* and swelling of right palatine tonsil *(arrowhead).* **B,** Right-sided cervical lymphadenopathy with perinodal infiltration *(arrows)* and intranodal focal low attenuation *(arrowheads). (From Kato H, Kanematsu M, Kato Z, et al. Computed tomographic findings of Kawasaki disease with cervical lymphadenopathy. J Comput Assist Tomogr. 2012;36[1]:138–142, Fig. 1, p. 139.)*

Two-dimensional echocardiography is the most useful test to monitor for development of CAA. Although frank aneurysms are rarely detected in the first week of illness, coronary arteries are commonly dilated. Coronary artery dimensions, adjusted for BSA (*z* scores), may increase over the first 6 weeks of illness, and higher *z* scores at the time of diagnosis are the strongest risk factor for the presence of coronary aneurysms 2-8 weeks after illness onset. Children with non-KD febrile illnesses also have mildly increased *z* scores compared with nonfebrile controls, but to a lesser degree than patients with KD. Aneurysms have been defined with the use of absolute dimensions by the Japanese Ministry of Health and are classified as small (≤4 mm internal diameter [ID]), medium (>4 to ≤8 mm ID), or giant (>8 mm ID). Some experts believe that a *z* score–based system for classification of aneurysm size may be more discriminating, because it adjusts the coronary dimension for BSA. The AHA *z* score classification system is noted in Table 208.2.

Echocardiography should be performed at diagnosis and again after 1-2 weeks of illness. If the results are normal, a repeat study should be performed 6-8 weeks after onset of illness. If results of either of the initial studies are abnormal or the patient has recurrent fever or symptoms, more frequent echocardiography or other studies may be necessary. In patients in whom CAA has not developed in the first 4-6 weeks of illness, the patient may be discharged from cardiology care, although follow-up through 12 months may be considered. Children and families should be counseled regarding healthy diet and the importance of exercise at regular primary care visits. For patients with CAA, the type of testing and the frequency of cardiology follow-up visits are tailored to the patient's coronary artery status (see Table 208.2).

DIAGNOSIS

The diagnosis of KD is based on the presence of characteristic clinical signs. For **classic KD**, the diagnostic criteria require the presence of fever for at least 5 days and at least four of five of the other principal characteristics of the illness (see Table 208.1). The diagnosis of KD should be made within 10 days, and ideally within 7 days, of fever onset to improve coronary artery outcomes. In **incomplete KD**, patients have persistent fever but fewer than four of the five characteristic clinical signs. In patients with incomplete KD, laboratory and echocardiographic data can assist in the diagnosis (Fig. 208.10). Incomplete cases occur most frequently in infants, who also have the highest likelihood of development of CAA. Ambiguous cases should be referred to a center with experience in the diagnosis of KD. Establishing the diagnosis with prompt initiation of treatment is essential to prevent potentially devastating coronary artery disease. For this reason, it is recommended that *any infant age ≤6 months with fever for ≥7 days and signs of systemic inflammation without explanation undergo echocardiography to assess the coronary arteries.*

DIFFERENTIAL DIAGNOSIS

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 208.3). Children with **adenovirus** typically have exudative pharyngitis and exudative conjunctivitis, allowing differentiation from KD. A common clinical problem is the differentiation of **scarlet fever** from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hours with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Features of **measles** that distinguish it from KD include exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, and leukopenia. **Cervical lymphadenitis** can be the initial diagnosis in children who are ultimately recognized to have KD. Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD. **Rocky Mountain spotted fever** is a potentially lethal bacterial infection, and appropriate antibiotics should not be withheld if the diagnosis is under consideration. Its distinguishing features include pronounced myalgias and headache at onset, centripetal rash, and petechiae on the palms and soles. **Leptospirosis** can also be an illness of considerable severity. Risk factors include exposure to water contaminated

Table 208.2 Classification of Coronary Artery Dilation or Aneurysms (after AHA Guidance with Modification)

CLASSIFICATION OF RISK LEVEL	DESCRIPTION OF CORONARY ARTERIES	FOLLOW-UP INTERVAL	IMAGING REQUIRED TO ASSESS FOR INDUCIBLE ISCHEMIA (STRESS ECHO OR STRESS MRI)	PSP	REGIONAL SPECIALIST KAWASAKI DISEASE CLINIC
1	No involvement at any time point (*z* score<2)	2 wk 6 wk 6 mo 12 mo Discharge if normal at 12 mo	None	No	No—annual cardiac and general health review with GP recommended*
2	Dilation only (2< *z* score ≤2.5): resolves within 1 year	2 wk 6 wk 6 mo 12 mo Discharge if normal at 12 mo	None	No	No—annual cardiac and general health review with GP recommended*
3	Small aneurysm (2.5≤ *z* score <5): (a) current or persistent (b) decreased to normal or *z* score <2.5	2 wk 6 wk 6 mo 12 mo Annual review	Coronary angiography (preferably CT) at 12 mo as baseline Consider stress imaging for inducible myocardial ischemia every 2 years Imaging (echo) for coronary surveillance annually	Yes	Yes
4	Medium aneurysm (5 ≤*z* score <10): (a) persistent aneurysm (b) decreased to normal or *z* score <2.5	2 wk 6 wk 6 mo 12 mo Annual review	Coronary angiography (preferably CT) at 12 mo as baseline Consider stress imaging for inducible myocardial ischemia annually Imaging (echo, CT,† or MRI) for coronary thrombus surveillance annually	Yes	Yes
5	Giant aneurysm (*z* score ≥10 or ≥8 mm): (a) persistent giant aneurysm (b) persistent aneurysm (but regressed to medium or small aneurysms) (c) regressed to normal dimensions	2 wk 6 wk 3 mo 6 mo 9 mo 12 mo Then every 6 mo	Coronary angiography (preferably CT) at 6-12 mo as baseline Consider stress imaging for inducible myocardial ischemia annually Imaging (echo, CT,† or MRI) for coronary thrombus surveillance every 6 mo	Yes	Yes

*GP review should include clinical examination, blood pressure measurement, general health discussion, and advice on avoidance of cardiovascular risk factors and lifestyle choices, including maintaining a healthy weight, reducing the risk of diabetes, avoiding smoking, and taking regular exercise. This provides the opportunity to discuss any parent or patient questions and concerns.

†CT should not be used repeatedly if possible. Use MRI or ultrasound where possible to reduce radiation exposure.

ADP, Adenosine diphosphate; AHA, American Heart Association; FBC, full blood count; GP, general practitioner; PSP, person-specific protocol.

From McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation*. 2019 Jul 30;140(5):e181-e184]. *Circulation*. 2017;135(17):e927–e999.).

with urine from infected animals. The classic description of leptospirosis is of a biphasic illness with a few asymptomatic days between an initial period of fever and headache and a late phase with renal and hepatic failure. In contrast, patients with KD have consecutive days of fever at diagnosis and rarely have renal or hepatic failure.

Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of oral ulcerations and a normal or minimally elevated ESR are not seen in KD. **Systemic juvenile idiopathic arthritis** (sJIA) is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis may or may not be present in the initial illness. Fevers typically show a quotidian or double-quotidian pattern, in contrast to the unremitting fevers seen in KD. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with sJIA who have echocardiographic evidence of CAA. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, granulomatosis with polyangiitis, lupus, infantile polyarteritis nodosa, hyper-IgE syndrome, hyper-IgD syndrome (mevalonic aciduria), and meningococcemia.

Children with KD may present with **Kawasaki disease shock syndrome,** with a clinical picture similar to that of toxic shock syndrome or of the multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C; see Chapter 311). Features of **toxic shock syndrome** that are not usually seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. With COVID-19 disease, some children developed a KD-like illnesses presenting in cardiogenic shock. **multisystem inflammatory syndrome in children (MIS-C)**, also known as *pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2* (PIMS-TS), occurs 2-6 weeks after infection with SARS-CoV-2. The initial infection may be asymptomatic. Children with MIS-C may show conjunctival injection, oropharyngeal changes, and rashes similar to that seen in KD. CAAs have also been described in MIS-C, but the risk of CAA in MIS-C does not strictly correlate with criteria for incomplete or complete KD. Furthermore, patients are often older and have a greater degree of myocardial dysfunction as compared with KD; distinguishing laboratory features include greater hyperferritinemia, more pronounced cytopenias, and elevated D-dimer in MIS-C (Table 208.4).

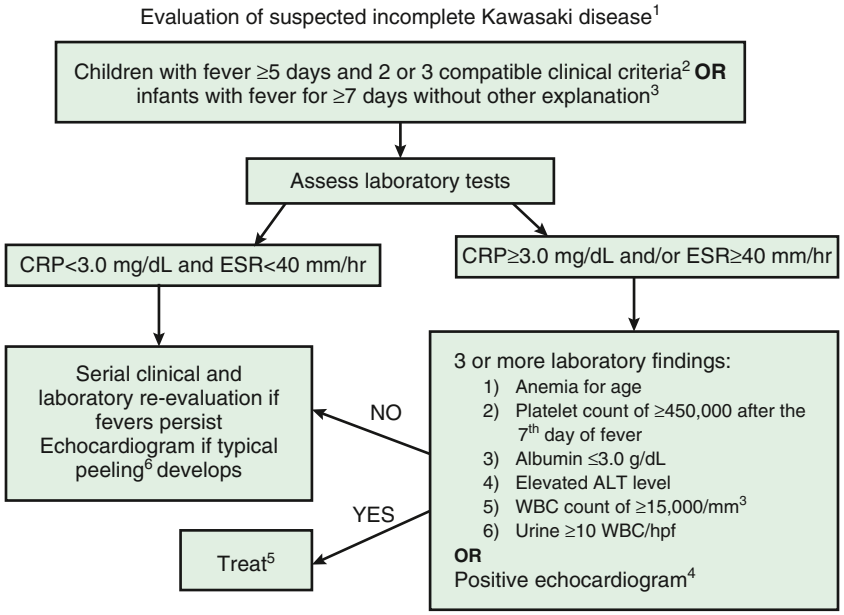

Fig. 208.10 Algorithm for the evaluation of suspected incomplete Kawasaki disease (KD). [1]In the absence of a gold standard for diagnosis of KD, this algorithm cannot be evidence based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. [2]Clinical findings of KD are listed in Table 208.1. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, and splenomegaly. [3]Infants ≤6 months of age are most likely to develop prolonged fever without other clinical criteria for KD; these infants are at particularly high risk of developing coronary artery abnormalities. [4]Echocardiography is considered positive for purposes of this algorithm if any of three conditions are met: *z* score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or three or more other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or *z* scores in the left anterior descending coronary artery or right coronary artery of 2-2.5. [5]If the echocardiogram is positive, treatment should be given within 10 days of fever onset or after the 10th day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. [6]Typical peeling begins under the nail beds of fingers and toes. ALT, Alanine transaminase; WBC, white blood cell. *(From McCrindle BW, Rowley A, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation. 2017;135:e927–e999, Fig. 2, p. e937.)*

Table 208.3 Differential Diagnosis of Kawasaki Disease

VIRAL INFECTIONS*
Adenovirus
Enterovirus
Measles
Epstein-Barr virus
Cytomegalovirus
BACTERIAL INFECTIONS
Scarlet fever
Rocky Mountain spotted fever
Leptospirosis
Bacterial cervical lymphadenitis ± retropharyngeal phlegmon
Meningococcemia
Urinary tract infection
RHEUMATOLOGIC DISEASE
Systemic-onset juvenile idiopathic arthritis
Behçet disease
Rheumatic fever
Polyarteritis nodosa
Takayasu arteritis
OTHER
Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19
Toxic shock syndromes
Serum sickness
Staphylococcal scalded skin syndrome
Macrophage activation syndrome (may also complicate Kawasaki disease)
Hemophagocytic lymphohistiocytosis
Drug hypersensitivity reactions
Stevens-Johnson syndrome
Aseptic meningitis
Autoinflammatory diseases

*Detection of a virus does not exclude Kawasaki disease in the presence of the principal clinical features (see Table 208.1).

Table 208.4 Comparing and Contrasting Multisystem Inflammatory Syndrome in Children (MIS-C) with Kawasaki Disease

MIS-C	KAWASAKI DISEASE
Mean age 8-12 years	Mean age <5 years
Fever >24 hr	Fever >5 days
GI symptoms common (severe abdominal pain) (50–90%)	GI complaints not common (~20%)
Myocarditis/myocardial dysfunction (left ventricular dysfunction)	Myocardial function normal/ mildly reduced*
Coronary artery dilation or aneurysms (25–50%)	Coronary artery abnormalities such as aneurysms common if untreated
Hypotension	Normal BP*
Renal involvement more common	Renal involvement rare
Proinflammatory state common	Proinflammatory state common
Lymphopenia common	Lymphopenia not common
Thrombocytopenia	Thrombocytosis
Elevated ferritin	Ferritin usually normal

*Except in Kawasaki shock syndrome (~5%).
GI, Gastrointestinal.
Modified from Naka F, Melnick L, Gorelik M, et al. A dermatologic perspective on multisystem inflammatory syndrome in children. *Clin Dermatol*. 2021;39(1):163–168, Table 5.

TREATMENT

Patients with acute KD should be treated with 2 g/kg of IVIG as a single infusion, usually administered over 10-12 hours within 10 days of disease onset, and ideally as soon as possible after diagnosis (Table 208.5).

In addition, moderate-dose (30-50 mg/kg/day divided every 6 hours) aspirin should be administered until the patient is afebrile, then lowered to antiplatelet doses (3-5 mg/kg/day). Other NSAIDs should *not* be given during therapy with aspirin because they may block aspirin's antiplatelet effect. The mechanism of action of IVIG in KD is likely multifaceted, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. Using Japanese Ministry of Health criteria, the prevalence of coronary disease is 20–25% in children treated with aspirin alone and falls to <5% in those treated with IVIG and aspirin within the first 10 days of illness. In children diagnosed after the 10th day of fever, IVIG should still be offered to patients with persistent fever, abnormal dimensions of the coronary arteries, or signs of systemic inflammation. Low-dose aspirin is continued for its antithrombotic effect until 6-8 weeks after illness onset and is then discontinued in patients who have had normal echocardiography findings throughout the course of their illness. Patients with CAA continue with aspirin therapy longer and may require anticoagulation, depending on the degree of coronary dilation (see later).

Glucocorticoids have been used as primary therapy with the first dose of IVIG in hopes of improving coronary outcomes. A North American trial using a single pulse dose of intravenous methylprednisolone (30 mg/kg) with IVIG as primary therapy did not improve coronary outcomes. However, a trial in Japan using the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of methylprednisolone/prednisolone (2 mg/kg/day, divided every 12 hours) plus IVIG as primary therapy. Furthermore, a systematic review and meta-analysis of 16 comparative studies demonstrated that early treatment with glucocorticoids improved coronary artery outcomes in children with KD. These data suggest that primary glucocorticoid therapy in addition to standard of care (IVIG plus aspirin) may be helpful in children at *high risk* for CAA. Fewer data are available to support the use of TNF alpha inhibitors for prevention of coronary artery aneurysms.

IVIG-resistant KD (nonresponders) occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hours after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Therapeutic options for the child with IVIG resistance include a second dose of IVIG (2 g/kg), a tapering course of glucocorticoids, infliximab, or possibly anakinra (Table 208.6). For the most severely affected patients with enlarging coronary aneurysms, additional therapies such as cyclosporine or cyclophosphamide may be administered, with consultation from specialists in pediatric rheumatology and cardiology.

Table 208.5 Treatment of Kawasaki Disease

ACUTE STAGE
Standard risk: Intravenous immune globulin 2 g/kg over 10-12 hr
and
Aspirin 30-50 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr
High risk for coronary artery abnormalities:* Intravenous immune globulin and aspirin as above, *plus* methylprednisolone 2 mg/kg/d IV divided q12hr until afebrile, then prednisolone orally until CRP normalized, then taper over 2-3 wk
CONVALESCENT STAGE
Aspirin 3-5 mg/kg once daily orally until 6- after illness onset if normal coronary findings throughout course

*High risk for coronary artery abnormalities is defined as age <6 months or baseline left anterior descending (LAD) or right circumflex artery (RCA) z-score greater than or equal to 2.5.

COMPLICATIONS

Acute KD is complicated in 1–2% of patients by macrophage activation syndrome (MAS; see Chapter 207), a syndrome of life-threatening hyperinflammation on the spectrum of hemophagocytic lymphohistiocytosis. MAS may mimic MIS-C. These patients may present with hyperferritinemia, coagulopathy, thrombocytopenia, and shock, warranting more aggressive immunosuppressive therapy.

In all phases of KD, patients with giant coronary aneurysms may experience myocardial infarction, angina, and sudden death due to thrombosis. For this reason, aspirin is continued indefinitely in children with coronary aneurysms (Table 208.7). When aneurysms are moderate-sized, dual antiplatelet therapy (e.g., aspirin and clopidogrel) is sometimes administered. For those with large or giant aneurysms, anticoagulation with warfarin or low-molecular-weight heparin is added to aspirin. For acute thrombosis that occasionally occurs in an aneurysmal or stenotic coronary artery, thrombolytic therapy may be lifesaving. In very rare circumstances of severe, giant aneurysms, rupture can occur.

Long-term follow-up of patients with CAAs is tailored to the past (i.e., worst-ever) and current coronary status, with a schedule of testing recommended in the 2017 AHA scientific statement on KD (see Table 208.2). Testing may include echocardiography, assessment for inducible ischemia, advanced imaging (CT, MRI, or invasive angiography), physical activity counseling, and cardiovascular risk factor assessment and management. Patients with coronary artery stenosis and inducible ischemia may be managed with coronary artery bypass grafting (CABG) or catheter

Table 208.6 Treatment Options for IVIG-Resistant Patients with Kawasaki Disease*

AGENT	DESCRIPTION	DOSE
MOST FREQUENTLY ADMINISTERED		
IVIG: second infusion	Pooled polyclonal IG	2 g/kg IV
IVIG + methylprednisolone/ prednisolone	IVIG + glucocorticoid	IVIG: 2 g/kg IV + methylprednisolone 2 mg/kg/d IV divided every 12 hr until afebrile, then oral prednisolone 2 mg/kg/d divided twice daily
Infliximab	Monoclonal antibody against TNF-α	Single infusion: 5-10 mg/kg IV
ALTERNATIVE TREATMENTS		
Anakinra	Recombinant IL-1β receptor antagonist	2-8 mg/kg/day given by subcutaneous injection or IV infusion
Cyclosporine	Inhibitor of calcineurin-NFAT pathway	IV: 3 mg/kg/d divided every 12 hr PO: 4-8 mg/kg/d divided every 12 hr Adjust dose to achieve trough 50-150 ng/mL; 2 hr peak level 300-600 ng/mL
Cyclophosphamide	Alkylating agent blocks DNA replication	10-15 mg/kg IV, 1 or 2 doses
Plasma exchange	Replaces plasma with albumin	1-5 cycles

*IVIG resistance is defined as persistent or recrudescent fever at least 36 hr and <7 days after completion of first IVIG infusion. The top three treatments have been most frequently used, although no comparative effectiveness trial has been performed. Pulsed high-dose corticosteroid treatment is not recommended. The alternative treatments have been used in a limited number of patients with KD.

CRP, C-reactive protein; IG, immunoglobulin; IL, interleukin; IV, intravenous(ly); IVIG, intravenous immune globulin; NFAT, nuclear factor of activated T cells; PO, oral; TNF, tumor necrosis factor.

Table 208.7 Anticoagulation for Coronary Artery Abnormalities in Kawasaki Disease

LONG TERM THERAPY
Small aneurysms: Aspirin 3-5 mg/kg/d
Medium aneurysms: Aspirin +/- clopidogrel 1 mg/kg/d (max 75 mg/d)
Giant aneurysms: Aspirin + anticoagulation with warfarin, low molecular weight heparin, or direct oral anticoagulants (e.g. apixaban)
ACUTE CORONARY THROMBOSIS
Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under the supervision of a pediatric cardiologist

interventions, including percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation.

Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome. A different antiplatelet agent can be substituted for aspirin during the 6 weeks after varicella vaccination. IVIG may interfere with the immune response to live virus vaccines as a result of a specific antiviral antibody, so the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 months after IVIG administration. Nonlive vaccinations do not need to be delayed.

PROGNOSIS

The vast majority of patients with KD return to normal health; timely treatment reduces the risk of coronary aneurysms to <5%. Acute KD recurs in 1–3% of cases. Published fatality rates are very low, generally <1%. The prognosis for patients with CAA depends on the severity of coronary disease; therefore recommendations for follow-up and management are stratified according to coronary artery status. A 6-week echocardiogram may be unnecessary in patients with normal coronary artery measurements at baseline and at 2 weeks of illness, as these children very rarely develop new abnormalities over time. Overall, ~50% of CAAs remodel to normal lumen diameter by 1-2 years after the illness, with smaller aneurysms being more likely to regress. Intravascular ultrasonography has demonstrated that regressed aneurysms are associated with marked myointimal thickening and abnormal vascular function. Giant aneurysms are less likely to regress to normal lumen diameter and are more likely to lead to thrombosis or stenosis. Bypass grafting may be required if there is inducible ischemia; it is best accomplished with the use of arterial grafts, which grow with the child and are more likely than venous grafts to remain patent over the long term. Heart transplantation has been required in rare cases where revascularization is not feasible because of distal coronary stenoses, distal aneurysms, or severe ischemic cardiomyopathy. A study from Japan reported outcomes in adult patients with a history of KD and giant aneurysms. These patients required multiple cardiac and surgical procedures, but the 30-years survival rate approached 90%.

The long-term outcomes of children who have had KD and never had coronary artery abnormalities, based upon reliable echocardiograms performed early in the course of disease, appear to be similar to those in the normative population. Although studies of endothelial dysfunction in children with a history of KD and normal coronary dimensions have produced conflicting results, reassuring data suggest that the standardized mortality ratio among adults in Japan who had KD in childhood without aneurysms is indistinguishable from that of the general population. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. Among children with coronary aneurysms, the AHA recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 209

Sarcoidosis

Laura Cannon and Eveline Y. Wu

Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. There appears to be two distinct, age-dependent patterns of disease among children with sarcoidosis. The clinical features in older children are similar to those in adults (pediatric-onset adult sarcoidosis), with frequent systemic features (fever, weight loss, malaise), pulmonary involvement, and lymphadenopathy. In contrast, early-onset sarcoidosis manifesting in children <4 years of age is characterized by the triad of rash, uveitis, and polyarthritis.

ETIOLOGY

The etiology of sarcoidosis remains obscure but likely results from exposure of a genetically susceptible individual to one or more unidentified antigens. This exposure initiates an exaggerated immunologic response that ultimately leads to the formation of granulomas. The human major histocompatibility complex is located on chromosome 6, and specific human leukocyte antigen (HLA) class I and class II alleles are associated with disease phenotype. Genetic polymorphisms involving various cytokines and chemokines may also have a role in development of sarcoidosis. Familial clustering supports the contribution of genetic factors to sarcoidosis susceptibility. Environmental and occupational exposures are also associated with disease risk. There are positive associations between sarcoidosis and agricultural employment, occupational exposure to insecticides, and moldy environments typically associated with microbial bioaerosols.

Blau syndrome is an autosomal dominant, familial form of sarcoidosis and is typified by the early onset of granulomatous inflammation involving the skin, eyes, and joints. Pathogenic genetic variants in the *CARD15/NOD2* gene have been found in affected family members and appear to be associated with development of sarcoidosis. Similar genetic variants have been found in individuals with a sporadic **early-onset sarcoidosis (EOS)** (rash, uveitis, arthritis), suggesting that this nonfamilial form and Blau syndrome are genetically and phenotypically identical (see Chapter 204).

EPIDEMIOLOGY

A nationwide patient registry of childhood sarcoidosis in Denmark estimated the annual incidence to be 0.22-0.27 per 100,000 children. The incidence increases with age, and peak onset occurs at 20-39 years. The most common age of reported childhood cases is 13-15 years. In comparison, an international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 months and 36 months, respectively. There is no clear gender predilection in any form of childhood sarcoidosis. The majority of U.S. childhood sarcoidosis cases are reported in the southeastern and southcentral states.

PATHOLOGY AND PATHOGENESIS

Noncaseating, epithelioid granulomatous lesions are a cardinal feature of sarcoidosis. Activated macrophages, epithelioid cells, and multinucleated giant cells, as well as $CD4^+$ T lymphocytes, accumulate and become tightly packed in the center of the granuloma. The causative agent that initiates this inflammatory process is unknown. The periphery of the granuloma contains a loose collection of monocytes, $CD4^+$ and $CD8^+$ T lymphocytes, and fibroblasts. The interaction between the macrophages and $CD4^+$ T lymphocytes is important in the formation and maintenance of the granuloma. The activated macrophages secrete high levels of tumor necrosis factor (TNF)-α and other proinflammatory mediators. The $CD4^+$ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon (IFN)-γ, promoting proliferation of lymphocytes. Granulomas may heal or resolve with complete preservation of the parenchyma. In approximately 20% of the

lesions, the fibroblasts in the periphery proliferate and produce fibrotic scar tissue, leading to significant and irreversible organ dysfunction.

The sarcoid macrophage is able to produce and secrete 1,25-$(OH)_2$-vitamin D, or *calcitriol,* an active form of vitamin D typically produced in the kidneys. The hormone's natural functions are to increase intestinal absorption of calcium and bone resorption and decrease renal excretion of calcium and phosphate. An excess of calcitriol may result in hypercalcemia and hypercalciuria in patients with sarcoidosis.

CLINICAL MANIFESTATIONS

Sarcoidosis is a multisystem disease, and granulomatous lesions may occur in any organ of the body. The clinical manifestations depend on the extent and degree of granulomatous inflammation and are extremely variable. Children may present with nonspecific symptoms, such as fever, weight loss, and general malaise. In adults and older children, pulmonary involvement is most frequent, with infiltration of the thoracic lymph nodes and lung parenchyma. Isolated bilateral hilar adenopathy on chest radiograph is the most common finding (Fig. 209.1), but parenchymal infiltrates and miliary nodules may also be seen (Figs. 209.2, 209.3, and 209.4). Patients with lung involvement are usually found to have restrictive changes on pulmonary function testing. Symptoms of pulmonary disease are seldom severe and generally consist of a dry, persistent cough.

Extrathoracic lymphadenopathy and infiltration of the liver, spleen, and bone marrow also occur often (Table 209.1). Infiltration of the liver and spleen typically leads to isolated hepatomegaly and splenomegaly, respectively, but actual organ dysfunction is rare. Cutaneous disease, such as plaques, nodules, erythema nodosum in acute disease, or lupus pernio in chronic sarcoidosis, appears in one quarter of cases and is usually present at onset. Red-brown to purple maculopapular lesions <1 cm on the face, neck, upper back, and extremities are the most common skin finding (Fig. 209.5). Papulonodular granulomatous lesions have been reported to develop in cosmetic (eyebrows) and decorative tattoos (tattoo sarcoidosis). Ocular involvement is frequent and has variable manifestations, including anterior or posterior uveitis, conjunctival granulomas, eyelid inflammation, and orbital or lacrimal gland infiltration. The arthritis in sarcoidosis can be confused with **juvenile idiopathic arthritis** (JIA). Central nervous system (CNS) involvement is rare in early childhood but may manifest as seizures, cranial nerve involvement, intracranial mass lesions, and hypothalamic dysfunction (Fig. 209.6). Kidney disease occurs infrequently in children but typically manifests as renal insufficiency, proteinuria, transient pyuria, or microscopic hematuria caused by early monocellular infiltration or granuloma formation in kidney tissue. Only a small fraction of children have hypercalcemia or hypercalciuria. Sarcoid granulomas can also infiltrate the heart and lead to cardiac arrhythmias and, rarely, sudden death. Other



Fig. 209.1 Sarcoidosis. Chest radiograph demonstrating stage I disease with enlarged mediastinal and hilar lymph nodes. *(From Iannuzzi M. Sarcoidosis. In Goldman L, Schafer AI, eds. Goldman's Cecil Medicine, 24th ed. Philadelphia: Saunders; 2012: Fig. 95-1, p. 582.)*



Fig. 209.2 Sarcoidosis. Chest radiograph of 10-year-old girl showing widely disseminated peribronchial infiltrates, multiple small nodular densities, hyperaeration of the lungs, and hilar lymphadenopathy.

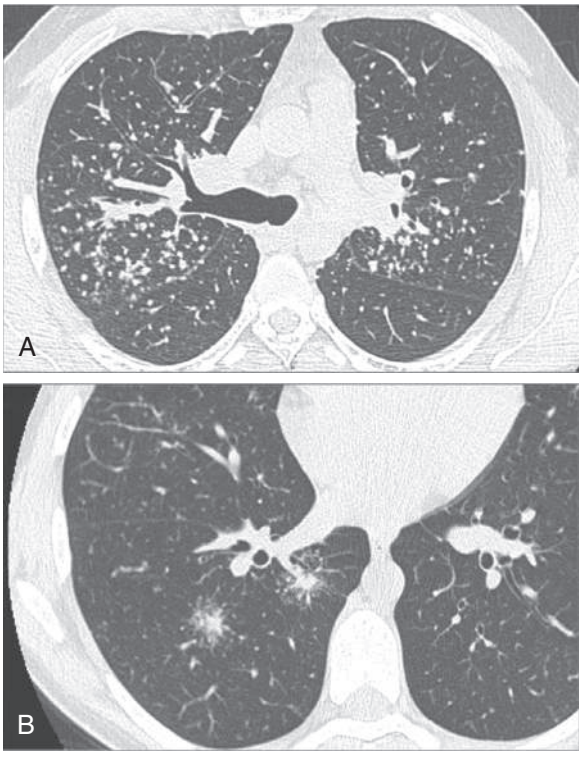

Fig. 209.3 Typical features of lung sarcoidosis on CT. **A,** Usual perilymphatic distribution of micronodules with fissural spreading. **B,** Typical nodules with irregular margins and satellite micronodules known as the *galaxy sign. (From Valerye D, Prasse A, Nunes H, et al. Sarcoidosis. Lancet. 2014;383:1155–1167, Fig. 2, p. 1158.)*

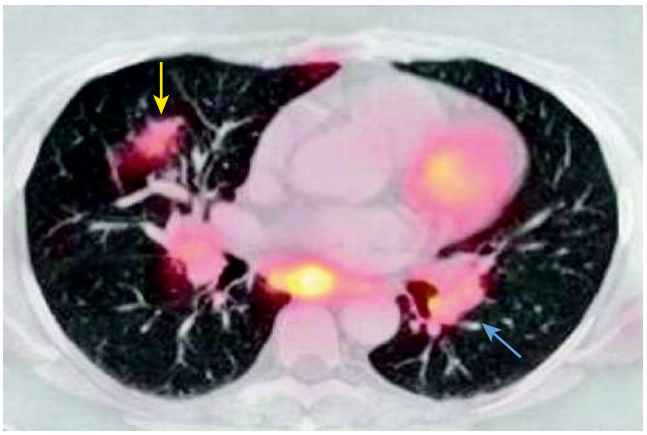

Fig. 209.4 Confluent parenchymal lung nodules and mediastinal and bilateral hilar lymphadenopathy with increased FDG uptake in a female with biopsy-proven sarcoidosis. PET/CT shows confluent parenchymal lung nodules *(yellow arrow)* and mediastinal and bilateral hilar lymphadenopathy *(blue arrow)*. These abnormalities show increased FDG uptake on fused PET/CT. *(Modified from Prabhakar HB, Rabinowitz CB, Gibbons FK, et al. Imaging features of sarcoidosis on MDCT, FDG PET, and PET/CT. AJR Am J Roentgenol. 2008;190:S1–S6, Fig. 6, p. S4.)*

rare sites of disease involvement include blood vessels of any size, the gastrointestinal tract, parotid gland, muscles, bones, and testes.

In contrast to the variable clinical presentation of sarcoidosis in older children, **Blau syndrome and EOS** (NOD2-associated sarcoidosis) classically manifest as the triad of uveitis, arthritis, and rash (see Chapter 204). **Infantile-onset panniculitis with uveitis and systemic granulomatosis** is an uncommon manifestation of sarcoidosis.

LABORATORY FINDINGS

There is no single standard laboratory test diagnostic of sarcoidosis. Anemia, leukopenia, and eosinophilia may be seen. Other nonspecific findings include hypergammaglobulinemia and elevations in acute-phase reactants, including ESR and CRP. Hypercalcemia and/or hypercalciuria occur in only a small proportion of children with sarcoidosis. Angiotensin-converting enzyme (ACE) is produced by the epithelioid cells of the granuloma, and *its serum value may be elevated, but this finding lacks diagnostic sensitivity and specificity*. ACE levels are estimated to be elevated in >50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose–positron emission tomography (FDG-PET) (with either CT or MRI) can help identify nonpulmonary (lymph nodes, bone, cardiac, liver, spleen) sites for a diagnostic evaluation or biopsy (Fig. 209.7).

DIAGNOSIS

Definitive diagnosis ultimately requires demonstration of the characteristic noncaseating granulomatous lesions in a biopsy specimen (usually taken from the most readily available affected organ) and exclusion of other known causes of granulomatous inflammation. Skin and transbronchial lung biopsies have higher yield, greater specificity, and fewer associated adverse events than biopsy of mediastinal lymph nodes or liver. Additional diagnostic testing includes chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential because ocular inflammation is frequently present and may be asymptomatic in sarcoidosis, and vision loss is a sequela of untreated disease.

Bronchoalveolar lavage may be used to assess for disease activity, and the fluid typically reveals an excess of lymphocytes with an increased $CD4^+/CD8^+$ ratio of 2-13:1. In addition to flexible bronchoscopy with transbronchial biopsy, endosonographic-guided intrathoracic node aspiration has been valuable in obtaining tissue to assess for noncaseating granulomas.

Table 209.1 Sarcoidosis: Extrapulmonary Localizations

	SYMPTOMS
Skin	Papules, nodules, plaques, scar sarcoidosis, lupus pernio, subcutaneous sarcoidosis, granuloma annulare, lip granulomas, vitiligo, erythema nodosum, Lofgren syndrome*
Peripheral lymphadenopathy	Mostly cervical or supraclavicular; inguinal, axillary, epitrochlear, or submandibular lymph node sites also possible; painless and mobile
Eye	Anterior, intermediate, or posterior uveitis; retinal vascular change; conjunctival nodules; lacrimal gland enlargement
Liver	Often symptom free; abnormal liver function tests in 20–30% of patients; hepatomegaly; rarely hepatic insufficiency, chronic intrahepatic cholestasis, or portal hypertension
Spleen	Splenomegaly; rarely, pain or pancytopenia; very rarely, splenic rupture
Heart	Atrioventricular or bundle branch block; ventricular tachycardia or fibrillation; congestive heart failure; pericarditis; impairment of sympathetic nerve activity; sudden death
Nervous system	Facial nerve palsy, optic neuritis, leptomeningitis, diabetes insipidus, hypopituitarism, seizures, cognitive dysfunction, deficits, hydrocephalus, psychiatric manifestations, spinal cord disease, polyneuropathy, small-fiber neuropathy
Kidney	Rare symptoms; increased creatinine sometimes associated with hypercalcemia; nephrocalcinosis; kidney stones
Parotitis	Symmetric parotid swelling; Heerfordt syndrome when associated with uveitis, fever, and facial palsy
Nose	Nasal stuffiness, nasal bleeding, crusting, anosmia
Larynx	Hoarseness, breathlessness, stridor, dysphagia
Bones	Often asymptomatic; hands and feet classically most involved, also large bones and axial skeleton
Skeletal muscles	Proximal muscle weakness, amyotrophy, myalgia, intramuscular nodules
Genitourinary tract	All organs can be involved, including breast, uterus, epididymis, and testicle
Gastrointestinal tract	Most often symptom free, but the esophagus, stomach, small intestine, and colon can be involved

*Lofgren syndrome: acute arthritis, erythema nodosum, and hilar adenopathy.
Adapted from Valerye D, Prasse A, Nunes H, et al. Sarcoidosis. *Lancet.* 2014;383:1155–1167, Table 1.



Fig. 209.5 Sarcoidosis nodules on the face. *(From Shah BR, Laude TA. Atlas of Pediatric Clinical Diagnosis. Philadelphia: Saunders; 2000.)*

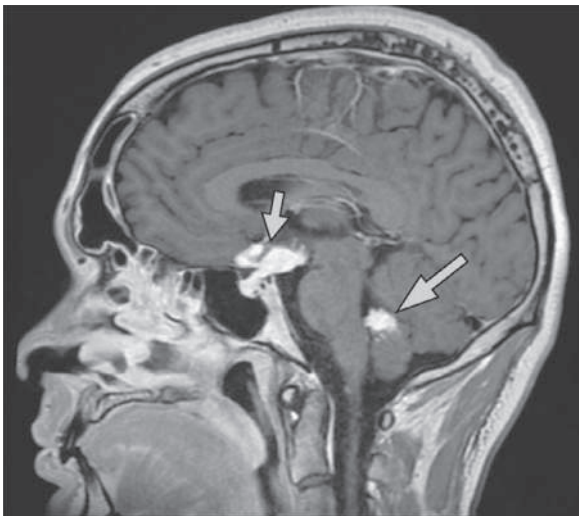

Fig. 209.6 Neurologic involvement in sarcoidosis. Typical involvement of hypothalamus, pituitary gland, and optic chiasm seen on a sagittal gadolinium-enhanced T1-weighted sequence MRI *(small arrow)*. Abnormal nodular enhancement of the fourth ventricle is seen *(large arrow)*. *(Modified from Valerye D, Prasse A, Nunes H, et al. Sarcoidosis. Lancet. 2014;383:1155–1167, Fig. 3D, p. 1160.)*

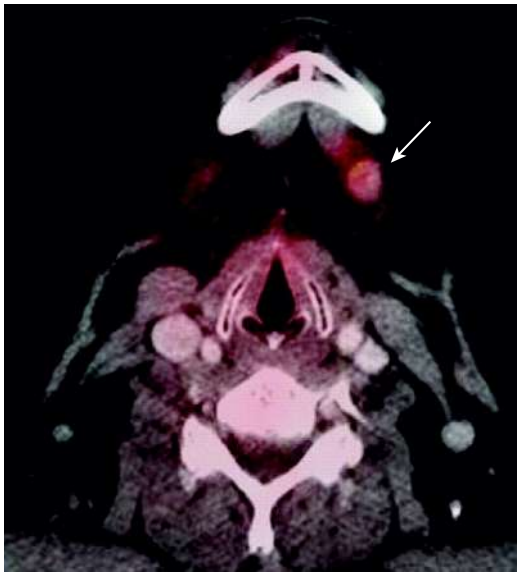

Fig. 209.7 Palpable submental lymph node with FDG uptake. Axial fused contrast-enhanced PET/CT image shows enlarged left submental lymph node *(arrow)* with increased FDG uptake. Lesion was biopsied and was consistent with sarcoidosis. *(From Prabhakar HB, Rabinowitz CB, Gibbons FK, et al. Imaging features of sarcoidosis on MDCT, FDG PET, and PET/CT. AJR Am J Roentgenol. 2008;190:S1–S6, Fig. 5, p. S3.)*

DIFFERENTIAL DIAGNOSIS

Because of its protean manifestations, the differential diagnosis of sarcoidosis is extremely broad and depends largely on the initial clinical manifestations. **Granulomatous infections**, including tuberculosis, cryptococcosis, pulmonary mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), brucellosis, tularemia, and toxoplasmosis, must be excluded. Other causes of granulomatous inflammation are granulomatosis with polyangiitis (formerly Wegener granulomatosis), hypersensitivity pneumonia, chronic berylliosis, and other occupational exposures to metals. Localized granulomatous lesions of the head and neck may be due to **orofacial granulomatosis (Melkersson-Rosenthal syndrome)**. Other granulomatous lesions involving the head, neck, and orofacial regions are noted in Table 209.2. Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective IgA deficiency, chronic granulomatous disease, ataxia telangiectasia, and severe combined immunodeficiency. Granulomas of the lung, skin, or lymph nodes have been reported in patients treated with anti-TNF agents. Lymphoma should be ruled out in cases of hilar or other lymphadenopathy. Sarcoid arthritis may mimic JIA. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

Table 209.2 Granulomatous Disorders with Head and Neck Manifestations

AUTOIMMUNE
GPA (Wegener granulomatosis)
Churg-Strauss syndrome
Behçet disease
INFECTIOUS
Tuberculosis
Cat-scratch fever
Syphilis
Leprosy
Fungal (blastomycosis, histoplasmosis)
Actinomycosis
IDIOPATHIC/INFLAMMATION
Sarcoidosis
Orofacial granulomatosis (Melkersson-Rosenthal syndrome)
HEREDITARY
CGD
OTHER DISEASES WITH SECONDARY GRANULOMATOUS MANIFESTATIONS
Relapsing polychondritis
LCH
SLE
Rheumatoid arthritis
Chemical exposure (e.g., cocaine, talc, beryllium)

CGD, chronic granulomatous disease; GPA, Granulomatosis with polyangiitis; LCH, Langerhans cell histiocytosis; SLE, systemic lupus erythematosus.
Modified from Nwawka OK, Nadgir R, Fujita A, Sakai O. Granulomatous disease in the head and neck: Developing a differential diagnosis. *RadioGraphics.* 2014;34(5):1240–1256, Table 1.

TREATMENT

Treatment should be based on disease severity and the number and type of organs involved. *Corticosteroids are the mainstay of treatment for most acute and chronic disease manifestations.* The optimal dose and duration of corticosteroid therapy in children have not been established. Induction treatment typically begins with oral prednisone or prednisolone (1-2 mg/kg/day up to 40 mg daily) for 8-12 weeks until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 months to the minimal effective maintenance dose (e.g., 5-10 mg/day) that controls symptoms, or discontinued if symptoms resolve. *Methotrexate* or *leflunomide* may be effective as a corticosteroid-sparing agent. On the basis of the role of TNF-α in the formation of granulomas, there is rationale for the use of TNF-α antagonists. Results of small clinical trials showed modest effects with *infliximab* and *adalimumab* treatment of selected disease manifestations (CNS, lupus pernio, pulmonary, ocular), whereas etanercept does not appear to be particularly effective. Other therapeutics used for sarcoidosis manifestations include topical corticosteroids (eye), inhaled corticosteroids (lung), azathioprine (CNS), cyclophosphamide (cardiac, CNS), hydroxychloroquine (skin), mycophenolate mofetil (CNS, skin), thalidomide or its analogs (skin), and nonsteroidal antiinflammatory drugs (joints).

PROGNOSIS

The prognosis of childhood sarcoidosis is not well defined. The disease may be self-limited with complete recovery or may persist with a progressive or relapsing course. Outcome is worse in the setting of

multiorgan or CNS involvement. Most children requiring treatment experience considerable improvement with corticosteroids, although a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with early-onset sarcoidosis have a poorer prognosis and generally experience a more chronic, progressive disease course. The greatest morbidity is associated with ocular involvement, including cataract formation, development of synechiae, and loss of visual acuity or blindness. Long-term systemic treatment may be required for the eye disease. Progressive polyarthritis may result in joint destruction. The overall mortality rate in older children with sarcoidosis is low.

Serial pulmonary function tests and chest radiographs are useful in following the course of lung involvement. Monitoring for other organ involvement should also include electrocardiogram with consideration of an echocardiogram, urinalysis, renal function tests, and measurements of hepatic enzymes and serum calcium. Other potential indicators of disease activity include inflammatory markers and serum ACE, although changes in ACE level do not always correlate with other indicators of disease status. Given the frequency of asymptomatic eye disease and the ocular morbidity associated with pediatric sarcoidosis, all patients should have an ophthalmologic examination at presentation with monitoring at regular intervals, perhaps every 3-6 months, as recommended in children with JIA.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

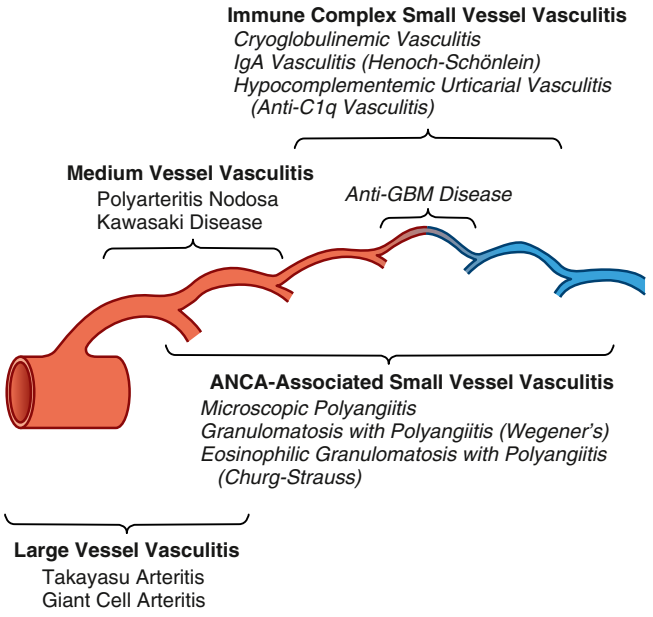

Fig. 210.1 Distribution of vessel involvement in large, medium, and small vessel vasculitis. There is substantial overlap with respect to arterial involvement, and all three major categories of vasculitis can affect any size artery. Large vessel vasculitis affects large arteries more often than other vasculitides. Medium vessel vasculitis predominantly affects medium arteries. Small vessel vasculitis predominantly affects small vessels, but medium arteries and veins may be affected, although immune complex small vessel vasculitis rarely affects arteries. Not shown is *variable vessel vasculitis*, which can affect any type of vessel, from aorta to veins. The diagram depicts (from *left* to *right*) aorta, large artery, medium artery, small artery/arteriole, capillary, venule, and vein. ANCA, Antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane. *(From Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11, Fig. 2, p. 4.)*

Chapter 210

Vasculitis Syndromes

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

INTRODUCTION

Childhood vasculitis encompasses a broad spectrum of diseases that share inflammation of the blood vessels as the central pathophysiology. The pathogenesis of the vasculitides is generally idiopathic. Some forms of vasculitis are associated with infectious agents and medications, whereas others may occur in the setting of preexisting autoimmune or autoinflammatory diseases. The pattern of vessel injury provides insight into the form of vasculitis and serves as a framework to delineate the different vasculitic syndromes. The distribution of vascular injury includes *small vessels* (capillaries, arterioles, and postcapillary venules), *medium vessels* (renal arteries, mesenteric vasculature, and coronary arteries), and *large vessels* (the aorta and its proximal branches) (Fig. 210.1). Additionally, some forms of small vessel vasculitis are characterized by the presence of **antineutrophil cytoplasmic antibodies (ANCAs)**, whereas others are associated with **immune complex** deposition in affected tissues. A combination of clinical features, histologic appearance of involved vessels, and laboratory data is used to classify vasculitis (Tables 210.1-210.4). A nomenclature system from the 2012 International Chapel Hill Consensus Conference (see Table 210.1) has proposed using the pathologic diagnosis rather than eponyms for vasculitis nomenclature. For example, Henoch-Schönlein purpura would be referred to as IgA vasculitis. Additionally, the classification criteria endorsed by the European League Against Rheumatism (EULAR), Pediatric Rheumatology International Trial Organization (PRINTO), and Pediatric Rheumatology European Society (PRES) have been validated in childhood vasculitis (see Table 210.2).

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura (IgA vasculitis) to catastrophic disease with end-organ damage, as seen in granulomatosis with polyangiitis (formerly Wegener granulomatosis). Vasculitis generally manifests as a heterogeneous multisystem disease. Although some features, such as purpura, are easily identifiable, others, such as hypertension secondary to renal artery stenosis or glomerulonephritis, can be subtler. Ultimately, the key to recognizing vasculitis relies heavily on *pattern recognition*. Demonstration of vessel injury and inflammation on biopsy or vascular imaging is required to confirm a diagnosis of vasculitis.

Clues to the diagnosis of a vasculitis disorder are noted in Table 210.3, and a broad diagnostic approach is noted in Table 210.5.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

210.1 Henoch-Schönlein Purpura (IgA Vasculitis)

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Henoch-Schönlein purpura (**HSP**) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney. HSP is also referred to as **IgA vasculitis**, based on the presence of vasculitis with predominance of IgA deposits affecting small vessels.

Table 210.1 2012 Chapel Hill Consensus Conference on Nomenclature of Systemic Vasculitis

LARGE VESSEL VASCULITIS (LVV)*	
Giant cell (temporal) arteritis (GCA)	Granulomatous arteritis of the aorta and its major branches with a predilection for the extracranial branches of the carotid artery *Often involves the temporal artery* *Usually occurs in patients older than 50 yr of age and often associated with polymyalgia rheumatica*†
Takayasu arteritis (TAK)	Granulomatous inflammation of the aorta and its major branches *Usually occurs in patients much younger than 50 yr of age*
MEDIUM VESSEL VASCULITIS (MVV)*	
Polyarteritis nodosa (PAN)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with ANCAs
Kawasaki disease (KD)	Arteritis involving large, medium-sized, and small arteries associated with mucocutaneous lymph node syndrome *Coronary arteries are often involved* *Aorta and veins may be affected* *Usually occurs in children*
SMALL VESSEL VASCULITIS (SVV)*	
ANCA-associated vasculitis (AAV)	
Granulomatosis with polyangiitis (Wegener) (GPA)	Granulomatous inflammation involving the respiratory tract associated with necrotizing vasculitis affecting small- to medium-sized vessels *Necrotizing glomerulonephritis is common*
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophilic and granulomatous inflammation involving the respiratory tract accompanied by necrotizing vasculitis affecting small to medium-sized vessels associated with asthma and eosinophilia
Microscopic polyangiitis (MPA)	Necrotizing vasculitis with few or no immune deposits, affecting small vessels *Necrotizing arteritis involving small and medium-sized arteries may be present* *Necrotizing glomerulonephritis is common* *Pulmonary capillaritis often occurs*
Immune Complex Small Vessel Vasculitis	
IgA vasculitis (Henoch-Schönlein) (IgAV)	Vasculitis characterized by immunoglobin A–dominant immune deposits affecting small vessels *Typically involves skin, gut, and glomeruli. Arthralgias and arthritis are common*
Cryoglobulinemic vasculitis (CPV)	Vasculitis with cryoglobulin immune deposits affecting small vessels associated with cryoglobulinemia *Skin and glomeruli are often involved*
Anti–glomerular basement membrane (anti-GBM) disease	Vasculitis affecting pulmonary and renal capillaries with deposition of anti–glomerular basement membrane antibodies
Hypocomplementemic urticarial vasculitis	Associated with anti-Clq antibodies *Affects kidney, joints, lungs, and eyes*
VARIABLE VESSEL VASCULITIS (VVV)	
Behçet disease (BD)	Affects arteries and veins with thrombosis, arteritis, and arterial aneurysms *Oral and/or genital aphthous ulcers and can involve skin, eyes, joints, and central nervous system*
Cogan syndrome (CS)	Affects small, medium, or large arteries; aortitis, aortic, and mitral valvulitis
SINGLE-ORGAN VASCULITIS (SOV)	
Cutaneous leukocytoclastic angiitis	Vasculitis Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis
Cutaneous arteritis	Cutaneous vasculitis not associated with systemic vasculitis
Primary central nervous system vasculitis	CNS vasculitis not associated with systemic vasculitis
Isolated aortitis	Aortitis not associated with systemic vasculitis
Others	
VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE	
Lupus vasculitis	
Rheumatoid vasculitis	
Sarcoid vasculitis	
Others	
VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY	
Hepatitis C–associated cryoglobulinemia vasculitis	
Hepatitis B–associated vasculitis	
Syphilis-associated vasculitis	
Drug-associated immune complex vasculitis	
Drug-associated ANCA associated vasculitis	
Cancer-associated vasculitis	
Others	

*Large vessels: aorta and its larger branches directed toward major anatomic regions; medium vessels: renal, hepatic, coronary, and mesenteric arteries; small vessels: venules, capillaries, arterioles, and intraparenchymal distal arteries and arterioles.
†Essential components are in normal type; *italicized type* represents usual, but not essential, components.
Adapted from Jennette JC, Falk RJ, Bacon P, et al. *Arthritis Rheum*. 2013;65(1):1–11.

Table 210.2 EULAR/PRES Classification of Childhood Vasculitis

I. PREDOMINANTLY LARGE-SIZED VESSEL VASCULITIS
- Takayasu arteritis

II. PREDOMINANTLY MEDIUM-SIZED VESSEL VASCULITIS
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

III. PREDOMINANTLY SMALL-SIZED VESSEL VASCULITIS

A. Granulomatous
- Wegener granulomatosis*
- Churg-Strauss syndrome*

B. Nongranulomatous
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV. OTHER VASCULITIDES
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs (including hypersensitivity vasculitis)
- Vasculitis associated with connective tissue diseases
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

*This classification predated the removal of eponyms and histopathologic subclassification by the CHCC 2012.

From Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis.* 2006;65:936–941.

Table 210.3 Features that Suggest a Vasculitic Syndrome

CLINICAL FEATURES
- Fever, weight loss, fatigue of unknown origin
- Skin lesions (palpable purpura, fixed urticaria, livedo reticularis, nodules, ulcers)
- Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
- Arthralgia or arthritis, myalgia, or myositis, serositis
- Hypertension, hematuria, renal failure
- Pulmonary infiltrates or hemorrhage
- Myocardial ischemia, arrhythmias

LABORATORY FEATURES
- Increased erythrocyte sedimentation rate or C-reactive protein level
- Leukocytosis, anemia, thrombocytosis
- Eosinophilia
- Antineutrophil cytoplasmic antibodies
- Elevated factor VIII–related antigen (von Willebrand factor)
- Cryoglobulinemia
- Circulating immune complexes
- Hematuria

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR. *Textbook of Pediatric Rheumatology,* 7th ed. Philadelphia: Saunders; 2016.

EPIDEMIOLOGY

HSP occurs worldwide and affects all ethnic groups. The incidence is estimated at 14-20 per 100,000 children per year and affects males more than females, with a 1.2-1.8:1 male/female ratio. Approximately 90% of HSP cases occur in children, usually between ages 3 and 10 years. HSP is distinctly less common in adults, who often have severe and chronic complications. HSP is more common in the winter and spring and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

PATHOLOGY

Skin biopsies demonstrate **leukocytoclastic vasculitis** of the dermal capillaries and postcapillary venules. The inflammatory infiltrate includes neutrophils and monocytes. Renal histopathology typically shows endocapillary proliferative glomerulonephritis, ranging from a focal segmental process to extensive crescentic involvement. In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels (Fig. 210.2), accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

PATHOGENESIS

The exact pathogenesis of HSP remains unknown. Given the seasonality of HSP and the frequency of preceding upper respiratory infections, infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus, Mycoplasma,* and adenovirus have been suspected. The common finding of deposition of IgA, specifically IgA_1, suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component. HLA-B34 and HLA-DRB1*01 alleles have been linked to HSP nephritis. Patients with familial Mediterranean fever, hereditary periodic fever syndromes, and complement deficiencies are at increased risk for developing HSP, suggesting that genetically determined immune dysregulation may contribute.

CLINICAL MANIFESTATIONS

The hallmark of HSP is its **rash**: palpable purpura starting as pink macules or wheals and developing into petechiae, raised purpura, or larger ecchymoses. Occasionally, bullae and ulcerations develop. The skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities), the extensor aspect of the upper extremities, or on pressure points (buttocks) (Figs. 210.2 and 210.3). The skin lesions often evolve in groups, typically lasting 3-10 days, and may recur up to 4 months after initial presentation. Subcutaneous edema localized to the dorsa of the hands and feet, periorbital area, lips, scrotum, or scalp is also common.

Musculoskeletal involvement, including arthritis and arthralgias, is common, occurring in up to 75% of children with HSP. The arthritis tends to be self-limited and oligoarticular, with a predilection for large joints such as the knees and ankles, and does not lead to deformities. Periarticular swelling and tenderness without erythema or effusions are common. The arthritis usually resolves within 2 weeks but can recur.

Gastrointestinal (GI) manifestations occur in up to 80% of children with HSP and include abdominal pain, vomiting, diarrhea, paralytic ileus, and melena. Intussusception, mesenteric ischemia, and intestinal perforation are rare but serious complications. Endoscopic evaluation is usually not needed but may identify vasculitis of the intestinal tract.

Renal involvement occurs in up to 30% of children with HSP, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure. However, progression to end-stage renal disease (ESRD) is uncommon in children (1–2%) (see Chapter 560.3). Renal manifestations can be delayed for several months after the initial illness, so close follow-up with serial urinalyses and blood pressure monitoring is necessary.

Neurologic manifestations of HSP, caused by hypertension (posterior reversible encephalopathy syndrome) or central nervous system (CNS) vasculitis, may also occur, including intracerebral hemorrhage, seizures, headaches, depressed level of consciousness, cranial or peripheral neuropathies, and behavior changes. Other, less common potential manifestations of HSP are inflammatory eye disease, carditis, pulmonary hemorrhage, orchitis, and testicular torsion.

DIAGNOSIS

The diagnosis of HSP is clinical and often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis challenging.

Table 210.4 Clinicopathologic Characteristics of Vasculitides in Childhood

SYNDROME	FREQUENCY	VESSELS AFFECTED	CHARACTERISTIC PATHOLOGY
POLYARTERITIS			
Polyarteritis nodosa	Rare	Medium-size and small muscular arteries and sometimes arterioles	Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution
Kawasaki disease	Common	Coronary and other muscular arteries	Thrombosis, fibrosis, aneurysms, especially of coronary vessels
LEUKOCYTOCLASTIC VASCULITIS			
Henoch-Schönlein purpura (IgA vasculitis)	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, IgA deposits in affected vessels
Hypersensitivity angiitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
GRANULOMATOUS VASCULITIS			
Granulomatosis with polyangiitis (Wegener granulomatosis)	Rare	Small arteries and veins, occasionally larger vessels	Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Rare	Small arteries and veins, often arterioles and venules	Necrotizing extravascular granulomata; lung involvement; eosinophilia
GIANT CELL ARTERITIS			
Takayasu arteries	Uncommon	Large arteries	Granulomatous inflammation, giant cells; aneurysms, dissection
Temporal arteritis	Rare	Medium-size and large arteries	Granulomatous inflammation, giant cell arteries

Adapted from Cassidy JT, Petty RE. *Textbook of Pediatric Rheumatology,* 6th ed. Philadelphia: Saunders; 2011.

Table 210.6 summarizes the EULAR/PRES classification criteria for HSP. Most patients are afebrile.

The **differential diagnosis** for HSP depends on specific organ involvement, but usually includes other small vessel leukocytoclastic vasculitides (Table 210.7), infections, acute poststreptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes. Additional disorders in the differential include papular-purpuric glove and sock syndrome, systemic lupus erythematosus (SLE), other vasculitides (urticarial, hypersensitivity), and thrombocytopenia.

Infantile acute hemorrhagic edema (AHE), an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 years of age, resembles HSP clinically. AHE manifests as fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities (Fig. 210.4). The trunk is spared, but petechiae may be seen in mucous membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated, and the urinalysis results are normal. The younger age, nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish infantile AHE from HSP.

LABORATORY FINDINGS

No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). *The platelet count is normal in HSP*. Occult blood is frequently found in stool specimens. Serum albumin levels may be low because of renal or intestinal protein loss. Autoantibody testing such as antinuclear antibody (ANA) is not useful diagnostically except to exclude other diseases. Serum IgA values are often elevated but are not routinely measured. Assessment of renal involvement with blood pressure, urinalysis, and serum creatinine is necessary.

Ultrasound is often used in the setting of GI complaints to look for bowel wall edema or the rare occurrence of an associated intussusception. Barium enema can also be used to both diagnose and treat intussusception. Although often unnecessary in typical HSP, biopsies of skin and kidney can provide important diagnostic information, particularly in atypical or severe cases, and characteristically show leukocytoclastic vasculitis with IgA deposition in affected tissues.

TREATMENT

Treatment for mild and self-limited HSP is *supportive,* with an emphasis on ensuring adequate hydration, nutrition, and analgesia. Corticosteroids are most often used to treat significant GI involvement or other life-threatening manifestations. Glucocorticoids such as oral prednisone (1-2 mg/kg/day), or in severe cases, intravenous (IV) methylprednisolone for 1-2 weeks, followed by taper, reduce abdominal and joint pain but do not alter the overall prognosis. Corticosteroids are not routinely recommended for prevention of complications such as nephritis. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immunoglobulin (IVIG) and plasma exchange are sometimes used for severe disease. In some patients, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. ESRD develops in <5% of children with HSP nephritis.

COMPLICATIONS

Acutely, serious GI involvement, including intussusception and intestinal perforation, imparts significant morbidity and mortality. Renal disease is the major long-term complication, occurring in 1–2% of children with HSP. Renal disease can develop up to 6 months after diagnosis but rarely does so if the initial urinalysis findings are normal. Therefore, it is recommended that children with HSP undergo serial monitoring of blood pressure and urinalysis for at least 6 months after diagnosis to monitor for development of nephritis.

PROGNOSIS

Overall, the prognosis for childhood HSP is excellent, and most children experience an acute, self-limited course lasting on average 4 weeks. However, 15–60% of children with HSP experience one or more recurrences, typically within 4-6 months of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children

Table 210.5 Recommendations on the Diagnosis of Rare Pediatric Systemic Vasculitides

RECOMMENDATION

1. In any pediatric patient with ongoing or a history of unexplained systemic inflammation, the diagnosis of systemic vasculitis should be considered and referral to a pediatric rheumatologist should be made, particularly in the presence of unexplained organ involvement.
2. Clinical features combined with laboratory evidence of inflammation that suggest a vasculitic syndrome warranting referral to a pediatric rheumatologist are included in the following nonexhaustive list:
   - Pyrexia of unknown origin
   - Vasculitic skin rash
   - PNS or CNS involvement
   - Unexplained arthritis, myalgia, serositis
   - Unexplained pulmonary, gastrointestinal, cardiovascular, or renal disease
3. When vasculitis is suspected, the diagnosis is often difficult and differential diagnoses are broad. The general workup for diagnosis of a specific vasculitic syndrome should include tissue histology, imaging, and determination of ANCA.
4. In every patient in whom a specific vasculitic syndrome is suspected, basic screening investigations, along with blood pressure measurement, should include:
   - Hematology and acute-phase reactants:
     - Full blood count, ESR, CRP, clotting, prothrombotic screen (if patchy ischemia of digits or skin)
     - Peripheral blood smear
   - Basic biochemistry:
     - Renal function, liver function, CPK, LDH
     - Urine dipstick test of urine with UA:UC ratio or UP:UC ratio
   - Infection:
     - Routine pediatric infection screen
     - Anti–streptolysin O antibody titer (ASOT) and/or anti–DNase b
     - VZV antibody status
   - Immunologic tests:
     - ANA, ENA antibodies, ANCA, antiphospholipid antibodies
     - Immunoglobulins IgG/IgA/IgM/IgE
     - Complement (C3, C4)
     - RF (if nephritis or interstitial lung disease)
     - GBM antibody
   - Radiologic/other:
     - CXR
     - Doppler abdominal ultrasound scan
     - ECG; echocardiography
     - Digital clinical photography of lesions
5. When considering a specific vasculitic syndrome, depending on presenting symptoms, tests with specific indications should be considered:
   - The following may be useful if blood pressure abnormalities:
     - Four limb blood pressure measurements
     - 24-hr ambulatory blood pressure monitor
   - The following may be useful if evidence/suspicion of specific organ involvement:
     - CT (e.g., thorax, abdomen, brain)
     - MRI
     - MRI/MRA of aorta and major branches
     - Selective contrast visceral arteriography
     - Tissue biopsy (e.g., skin, nasal or sinus, kidney, sural nerve, lung, liver, gut, temporal artery, brain)
     - Nail fold capillaroscopy
     - Possible bone/joint involvement: radiograph of suspected sites
     - Eye symptoms: ophthalmology screen
     - Pulmonary symptoms: V/Q scan
     - Renal involvement: Tc-99m DMSA scan
     - Peripheral vascular symptoms: ultrasound scan Doppler of peripheral arteries
     - Neuropathy: nerve conduction studies
     - Cerebral involvement: MRI/MRA of brain and cerebral contrast angiography
     - Organ-specific autoantibodies (e.g., ASCAs, brain/neuronal specific autoantibodies)
     - Cryoglobulins or cryoprecipitants (technical expertise required), particularly if skin involved predominantly at peripheral sites
   - The following may be useful when the differential diagnosis includes malignancy:
     - Lymph node excision biopsy
     - Bone marrow analysis
     - PET-CT
   - The following may be useful when the differential diagnosis includes infection:
     - Tuberculosis screen
     - PCR for viral infection (e.g., CMV, EBV, enterovirus, adenovirus, VZV, HBV, HCV)
     - Serology for HIV, rickettsiae, *Borrelia burgdorferi, Mycoplasma*
     - Viral serology for hepatitis B and C, parvovirus B19
     - Cryoglobulins or cryoprecipitants (technical expertise required)
   - The following may be useful when the differential diagnosis includes autoinflammatory syndromes:
     - DNA analysis for MEFV (familial Mediterranean fever), TNFRSF1A (TNF-α receptor–associated periodic fever syndrome [TRAPS]), MVK (mevalonate kinase deficiency; previously referred to as hyper-IgD syndrome [HIDS]), NLRP3 (cryopyrin-associated periodic syndrome [CAPS]), NOD2 (Crohn/Blau/juvenile sarcoid mutations), ADA2 (deficiency of ADA2), genetic screening for SAVI (TMEM173) and CANDLE (PSMB8, 4, 9, and other proteasome genes if available).
6. In the clinical assessment of suspected systemic vasculitis, a structured multiorgan assessment should take place.
7. For suspected systemic vasculitis, the Pediatric Vasculitis Activity Score (PVAS) may facilitate structured multiorgan assessment. The PVAS can be found here: http://ard.bmj.com/content/72/10/1628.short
8. At diagnosis and in ongoing follow-up of systemic vasculitis, a PVAS score should be performed to assess disease activity.
9. At diagnosis and in ongoing follow-up of systemic vasculitis, a multiorgan assessment of damage should be undertaken.
10. There is no currently validated tool to assess pediatric vasculitis damage. This is an ongoing unmet need. The PVDI, while unvalidated, can be assessed here: https://ard.bmj.com/content/73/Suppl_2/696.4

PNS, Peripheral nervous system; PVAS, pediatric vasculitis activity score; PVDI, pediatric vasculitis damage index; CNS, central nervous system; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; UA:UC, urine albumin to urinary creatinine ratio; UP:UC, urine protein to urinary creatinine ratio; VZV, varicella-zoster virus; CXR, chest x-ray; ECG, electrocardiogram; MRA, magnetic resonance angiography; V/Q, ventilation/perfusion; DMSA, dimercaptosuccinic acid; ASCA, anti–*Saccharomyces cerevisiae* antibodies; SAVI, STING-associated vasculitis of infancy; CANDLE, chronic atypical neutrophilic dermatosis lipodystrophy and elevated temperature.

Modified from de Graeff N, Groot N, Brogan P, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides – the SHARE initiative. *Rheumatology*. 2019;58(4):656–671, Table 1.

with a more severe initial course are at higher risk for relapse. The long-term prognosis usually depends on the severity and duration of GI or renal involvement. Chronic renal disease develops in 1–2% of children with HSP, and <5% of those with HSP nephritis go on to have ESRD. The risk of HSP recurrence and graft loss after renal transplantation is estimated at 7.5% after 10 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

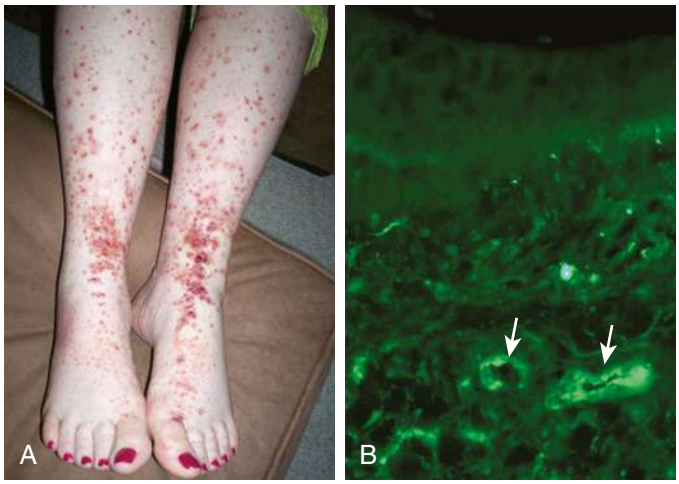

Fig. 210.2 Henoch-Schönlein purpura. **A,** Typical palpable purpura in lower extremities. **B,** Skin biopsy of lesion shows direct immunofluorescence of IgA *(arrows)* within the walls of dermal capillaries.

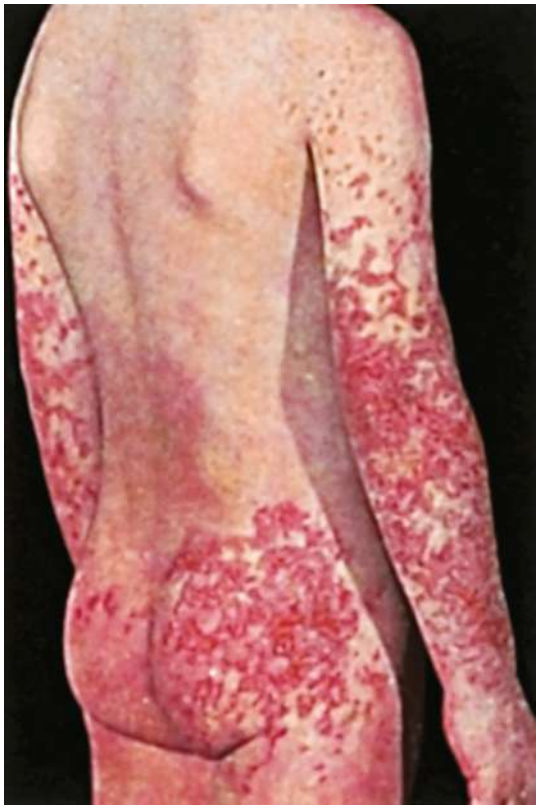

Fig. 210.3 Henoch-Schönlein purpura. *(From Korting GW. Hautkrankheiten bei Kindern und Jungendlichen, 3rd ed. Stuttgart: FK Schattaur Verlag; 1982.)*

Table 210.6 Classification Criteria for Henoch-Schönlein Purpura*

EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA†
Palpable purpura (in absence of coagulopathy or thrombocytopenia) and one or more of the following criteria must be present:
• Abdominal pain (acute, diffuse, colicky pain)
• Arthritis or arthralgia
• Biopsy of affected tissue demonstrating predominant IgA deposition
• Renal involvement (proteinuria >0.3 g/24 hr), hematuria, or red cell casts

*Classification criteria are developed for use in research and are not validated for clinical diagnosis.
†Developed for use in pediatric populations only.
Adapted from Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. *Ann Rheum Dis.* 2010;69:798–806.

Table 210.7 Conditions Associated with Leukocytoclastic Vasculitis

Immunoglobulin (Ig) A vasculitis (Henoch-Schönlein)
Hypersensitivity vasculitis
Hypocomplementemic urticarial vasculitis
Mixed cryoglobulinemia
Cutaneous polyarteritis
Antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis*
Goodpasture syndrome
Rheumatic disorders: systemic lupus erythematosus (SLE), juvenile dermatomyositis, mixed connective tissue disease (MCTD), scleroderma, juvenile idiopathic arthritis (JIA)
Mucha-Habermann disease
Relapsing polychondritis
Köhlmeier-Degos syndrome
Antiphospholipid antibody syndrome
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome
Malignancy-associated disease
Sweet syndrome
Cronkhite-Canada syndrome
Stevens-Johnson syndrome
Erythema elevatum diutinum
COVID-19/MIS-C

*Leukocytoclastic vasculitis may occur in cutaneous lesions in some patients with ANCA-associated vasculitis and collagen vascular diseases.
Modified from Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Box 33.1, p. 457.

210.2 Takayasu Arteritis

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Takayasu arteritis (TA), also known as *pulseless disease,* is a chronic large vessel vasculitis of unknown etiology that predominantly involves the aorta and its major branches.

EPIDEMIOLOGY

Although TA occurs worldwide and can affect all ethnic groups, the disease is most common in those of Asian descent. Age of onset is typically between 10 and 40 years. Most children are diagnosed as adolescents, on average at age 13 years. Up to 20% of individuals with TA are diagnosed before 19 years. Younger children may be affected, but diagnosis in infancy is rare. TA preferentially affects females, with a reported 2-4:1 female/male ratio in children and adolescents and a 9:1 ratio among adults. Occlusive complications are more common in the United States, Western Europe, and Japan, whereas aneurysms predominate in Southeast Asia and Africa.

PATHOLOGY

TA is characterized by inflammation of the vessel wall, starting in the vasa vasorum. Involved vessels are infiltrated by T cells, natural killer cells, plasma cells, and macrophages. Giant cells and granulomatous inflammation develop in the media. Persistent inflammation damages the elastic lamina and muscular media, leading to blood vessel



Fig. 210.4 Infantile acute hemorrhagic edema. Typical lesions on the arm of an infant. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001.)*

dilation and the formation of aneurysms. Progressive scarring and intimal proliferation can result in stenotic or occluded vessels. The subclavian, renal, and carotid arteries are the most commonly involved aortic branches; pulmonary, coronary, and vertebral arteries may also be affected.

PATHOGENESIS

The etiology of TA remains unknown. The presence of abundant T cells with a restricted repertoire of T-cell receptors in TA vascular lesions points to the importance of cellular immunity and suggests the existence of a specific but unknown aortic tissue antigen. Expression of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α is reported to be higher in patients with active TA than in patients with inactive TA and in healthy controls. In some patient populations, IL-1 genetic polymorphisms are linked to TA. Some individuals with TA have elevated serum values of antiendothelial antibodies. The increased prevalence of TA in certain ethnic populations and its occasional occurrence in monozygotic twins and families suggest a genetic predisposition to the disease.

CLINICAL MANIFESTATIONS

The diagnosis of TA is challenging because early disease manifestations are often nonspecific. As a result, diagnosis can be delayed for several months, and the time to diagnosis is usually longer in children than in adults. Fever, malaise, weight loss, headache, hypertension, myalgias, arthralgias, dizziness, and abdominal pain are common early complaints in the *prepulseless* phase of the disease. Among children, hypertension and headache are particularly common presenting manifestations and should prompt consideration of TA when present without alternative explanation. Some individuals with TA report no systemic symptoms and instead present with vascular complications. It is only after substantial vascular injury that evidence of hypoperfusion becomes clinically evident. Later manifestations of disease include diminished pulse, asymmetric blood pressure, claudication, Raynaud phenomenon, renal failure, and symptoms of pulmonary or cardiac ischemia. Inflammation can extend to the aortic valve, resulting in valvular insufficiency. Other findings may include pericardial effusion, pericarditis, pleuritis, splenomegaly, and arthritis.

Supradiaphragmatic (aortic arch) disease often manifests with CNS (stroke, transient ischemic attack) and cardiac (heart failure, palpitations) symptoms. **Infradiaphragmatic** (midaortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

Table 210.8 Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between arms or legs of >10 mm Hg
- Bruits over the aorta and/or its major branches
- Hypertension (defined by childhood normative data)
- Elevated acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Adapted from Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. *Ann Rheum Dis.* 2010;69:798–806.

DIAGNOSIS

Specific pediatric criteria for TA have been proposed (Table 210.8). The 2022 ACR/ EULAR classification criteria for Takayasu arteritis propose a criterion-based scoring system in adults (Table 210.9). *Radiographic demonstration of large vessel vasculitis is necessary*. A thorough physical examination is required to detect an aortic murmur, diminished or asymmetric pulses, and vascular bruits. Four extremity blood pressures should be measured; >10 mm Hg asymmetry in systolic pressure is indicative of disease.

DIFFERENTIAL DIAGNOSIS

In the early phase of TA, when nonspecific symptoms predominate, the differential diagnosis includes a wide array of systemic infections, autoimmune conditions, and malignancies. Although **giant cell arteritis**, also known as *temporal arteritis,* is a common large vessel vasculitis in older adults, this entity is rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

LABORATORY FINDINGS

The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP values are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies, including ANA and ANCA, are not useful in diagnosing TA except to help exclude other autoimmune diseases.

Radiographic assessment is essential to establish large vessel arterial involvement. Conventional arteriography of the aorta and major branches, including carotid, subclavian, pulmonary, renal, and mesenteric branches, can identify luminal defects, including dilation, aneurysms, and stenoses, even in smaller vessels such as the mesenteric arteries. Figure 210.5 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) also provide important information about vessel wall thickness and enhancement, although they may not image smaller vessels as well as conventional angiography. Positron emission tomography (PET) may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color flow Doppler imaging may identify vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular

Table 210.9 2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu Arteritis

Considerations when applying these criteria: • These classification criteria should be applied to classify the patient as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made. • Alternate diagnoses mimicking vasculitis should be excluded before applying the criteria.	
ABSOLUTE REQUIREMENTS	
Age ≤ 60 yr at time of diagnosis	
Evidence of vasculitis on imaging[1]	
ADDITIONAL CLINICAL CRITERIA	
Female sex	+1
Angina or ischemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit[2]	+2
Reduced pulse in upper extemity[3]	+2
Carotid artery abnormality[4]	+2
Systolic blood pressure difference in arms ≥20 mm Hg	+1
ADDITIONAL IMAGING CRITERIA	
Number of affected arterial territories (select one)[5]	
One arterial territory	+1
Two arterial territories	+2
Three arterial territories	+3
Symmetric involvement of paired arteries[6]	+1
Abdominal aorta involvement with renal or mesenteric involvement[7]	+3
	*TOTAL:

*Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of Takayasu arteritis.

[1]Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (e.g., computed tomographic/catheter-based/magnetic resonance angiography, ultrasonography, positron emission tomography).

[2]Bruit detected by auscultation of a large artery, including the aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral arteries.

[3]Reduction or absence of pulse by physical examination of the axillary, brachial, or radial arteries.

[4]Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery.

[5]Number of arterial territories with luminal damage (e.g., stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography from the following nine territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal arteries.

[6]Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography in any of the following paired vascular territories: carotid, subclavian, or renal arteries.

[7]Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries.

From Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. Ann Rheum Dis. 2022;81(12):1654–1660. Fig. 1.

involvement. Serial vascular imaging is usually necessary to assess response to treatment and to detect progressive vascular damage.

TREATMENT

Glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone or methylprednisolone IV) followed by gradual dosage tapering. When TA progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. *Cyclophosphamide* is reserved for severe or refractory disease. Results of small case series also suggest that *mycophenolate mofetil* or anti–TNF-α therapy may be beneficial in select patients. Anti–IL-6 therapy with tocilizumab has shown promising results in a small case series

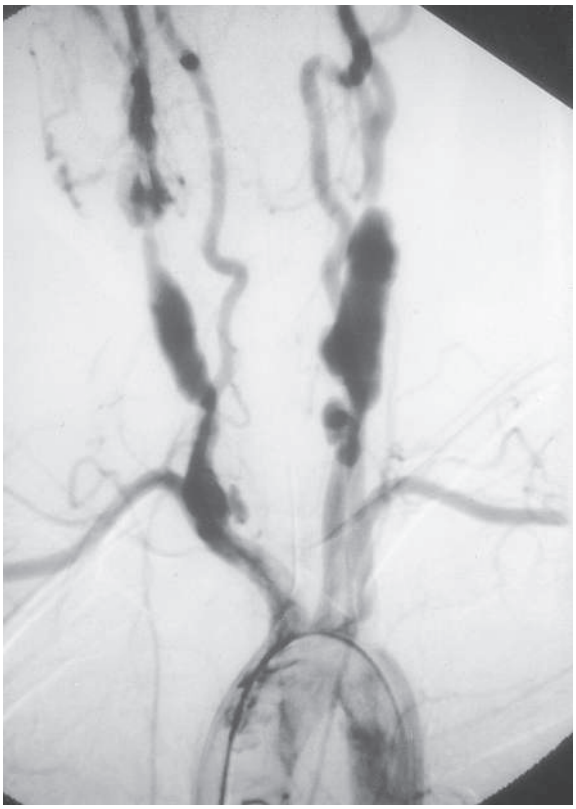

Fig. 210.5 Child with Takayasu arteritis. Conventional angiogram shows massive bilateral carotid dilation, stenosis, and poststenotic dilation.

of children with TA. Antihypertensive medications are often necessary to control blood pressure caused by renovascular disease.

COMPLICATIONS

Progressive vascular damage can result in arterial stenoses, aneurysms, and occlusions, which produce ischemic symptoms and can be organ or life threatening. Potential ischemic complications include stroke, renal impairment or failure, myocardial infarction, mesenteric ischemia, and limb-threatening arterial disease. When these complications occur or are imminent, intervention with *surgical* vascular grafting or catheter-based angioplasty and stent placement may be necessary to restore adequate blood flow. A high rate of recurrent stenosis has been reported after angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

PROGNOSIS

Although up to 20% of individuals with TA have a monophasic course and achieve sustained remission, most suffer relapses. Survival for individuals with TA has improved considerably over the decades, although higher mortality rates are reported in children and adolescents. The overall estimated survival for individuals with TA is 93% at 5 years and 87% at 10 years. However, morbidity from vascular complications remains high, particularly when there is evidence of ongoing active inflammation as detected by elevated CRP or ESR. Given the chronic endothelial insult and inflammation, children and adolescents with TA are probably at high risk for accelerated atherosclerosis. Early detection and treatment are critical to optimizing outcomes in TA.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

210.3 Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting small and medium-size arteries. Aneurysms and stenoses form at irregular intervals throughout affected arteries. Cutaneous PAN is limited to the skin.

EPIDEMIOLOGY

PAN is rare in childhood. Males and females are equally affected, and the mean age at presentation is 9 years. The cause is unknown, but the development of PAN after infections, including group A streptococcus and chronic hepatitis B, suggests that PAN may represent a postinfectious autoimmune response. Infections with other organisms, including Epstein-Barr virus, *Mycobacterium tuberculosis*, cytomegalovirus, parvovirus B19, and hepatitis C virus, have also been associated with PAN. There is a possible association between PAN and familial Mediterranean fever.

PATHOLOGY

Biopsies show **necrotizing vasculitis** with granulocytes and monocytes infiltrating the walls of small and medium-size arteries. Involvement is usually segmental and tends to occur at vessel bifurcations. Granulomatous inflammation is not present, and deposition of complement and immune complexes is rarely observed. Different stages of inflammation are found, ranging from mild inflammatory changes to panmural fibrinoid necrosis associated with aneurysm formation, thrombosis, and vascular occlusion.

PATHOGENESIS

Immune complexes are believed to be pathogenic, but the mechanism is poorly understood. It is not known why PAN has a predilection for small and medium-size blood vessels. The inflamed vessel wall becomes thickened and narrowed, impeding blood flow and contributing to end-organ damage characteristic of this disease. Although there is no clear genetic association with PAN, PAN-like vasculitis is a component of three recently described monogenic autoinflammatory conditions.

Deficiency in **adenosine deaminase 2 (DADA2)**, caused by mutations in the *CECR1* gene, causes a familial form of vasculitis with an autosomal recessive inheritance (see Chapter 204).

CLINICAL MANIFESTATIONS

The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Weight loss and severe abdominal pain suggest mesenteric arterial inflammation and ischemia. Renovascular arteritis can cause hypertension, hematuria, or proteinuria, although glomerulonephritis is not typical. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischemia, and painful nodules (Fig. 210.6). Arteritis affecting the nervous system can result in cerebrovascular accidents, transient ischemic attacks, psychosis, and ischemic motor or sensory peripheral neuropathy **(mononeuritis multiplex)**. Myocarditis or coronary arteritis can lead to heart failure and myocardial ischemia; pericarditis and arrhythmias have also been reported. Arthralgias, arthritis, or myalgias are frequently present. Less common symptoms include testicular pain that mimics testicular torsion, bone pain, and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

DIAGNOSIS

The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography (Table 210.10). Biopsy of cutaneous lesions shows small or medium vessel vasculitis. Kidney biopsy in patients with renal manifestations may show necrotizing arteritis. Electromyography in children with peripheral neuropathy identifies affected nerves, and sural nerve biopsy may reveal vasculitis. Conventional arteriography is the gold-standard diagnostic imaging study for PAN and reveals areas of aneurysmal dilation and segmental stenosis, the classic "beads on a string" appearance (Fig. 210.7). MRA and CTA, less invasive imaging alternatives, are gaining acceptance but may not be as effective in identifying small vessel disease or in younger children.



Fig. 210.6 Purpuric and necrotic lesions on the legs of a child with polyarteritis nodosa. *(From Petty RE, Laxer RM, Lindsley CB, et al., eds. Textbook of Pediatric Rheumatology, 8th ed. Philadelphia: Elsevier; 2021: Fig. 34.1, p. 468.)*

DIFFERENTIAL DIAGNOSIS

Early skin lesions may resemble those of HSP, although the finding of nodular lesions and the presence of systemic features help distinguish PAN. Because pulmonary vascular involvement is very rare in PAN, pulmonary lesions suggest ANCA-associated vasculitis or Goodpasture disease. Other rheumatic diseases, including SLE, have characteristic target-organ involvement and associated autoantibodies distinguishing them from PAN. Prolonged fever and weight loss should also prompt consideration of inflammatory bowel disease or malignancy.

Deficiency of DADA2 is a mimic of PAN and should be suspected in the presence of vasculitic rash (Fig. 210.8), hypogammaglobulinemia, cytopenias, and strokes. In addition, **SAVI** (STING-associated vasculopathy with onset in infancy) presents in infancy with ulcerating skin lesions that form eschars, cytopenias, interstitial lung disease, and failure to thrive (see Chapter 204).

LABORATORY FINDINGS

Nonspecific laboratory findings include elevations of ESR and CRP, anemia, leukocytosis, and hypergammaglobulinemia. Abnormal urine sediment, proteinuria, and hematuria indicate renal disease. Laboratory findings may be normal in cutaneous PAN or similar to those of systemic PAN. Elevated hepatic enzyme values may suggest hepatitis B or C infection. Serologic tests for hepatitis (hepatitis B surface antigen and hepatitis C antibody) should be performed in all patients.

Table 210.10 Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*

CRITERION	FINDINGS
Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of medium or small artery not from noninflammatory cause
Cutaneous findings	Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions, or splinter hemorrhages
Muscle involvement	Myalgia or muscle tenderness
Hypertension	Systolic or diastolic blood pressure >95th percentile for height
Peripheral neuropathy	Sensory peripheral neuropathy, motor mononeuritis multiplex
Renal involvement	Proteinuria (>300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal)

*The presence of five criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood-onset polyarteritis nodosa.
Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. *Ann Rheum Dis.* 2010;69:798–806.



Fig. 210.7 Child with polyarteritis nodosa. Abdominal aortogram shows bilateral renal artery aneurysms *(arrows)*, superior mesenteric artery aneurysm *(asterisk)*, and left common iliac artery occlusion *(arrowhead)*. *(Courtesy Dr. M. Hogan.)*

TREATMENT

Oral *prednisone* (1-2 mg/kg/day) or IV pulse *methylprednisolone* (30 mg/kg/day) are the mainstay of therapy. Oral or IV cyclophosphamide is often used as adjunctive therapy, and plasma exchange may be warranted for life-threatening disease. If hepatitis B is identified, appropriate antiviral therapy should be initiated (see Chapter 406). Most cases of cutaneous PAN can be treated with less intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory drugs (NSAIDs), and methotrexate. Azathioprine, mycophenolate mofetil, IVIG, thalidomide, cyclosporine, and anti-TNF agents such as infliximab have all been reported as successful in the treatment of refractory cutaneous or systemic PAN. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.



Fig. 201.8 Retiform purpura in a child with deficiency of adenosine deaminase type 2. *(From Petty RE, Laxer RM, Lindsley CB, et al., eds. Textbook of Pediatric Rheumatology, 8th ed. Philadelphia: Elsevier; 2021, Fig. 34.3, p. 469.)*

COMPLICATIONS

Cutaneous nodules may ulcerate and become infected. Hypertension and chronic renal disease may develop from renovascular involvement in PAN. Cardiac involvement may lead to decreased cardiac function or coronary artery disease. Mesenteric vasculitis can predispose to bowel infarction, rupture, and malabsorption. Stroke and rupture of hepatic arterial aneurysm are uncommon complications of this disorder.

PROGNOSIS

The course of PAN varies from mild disease with few complications to a severe, multiorgan disease with high morbidity and mortality. Poor prognostic factors in PAN include elevated serum creatinine, proteinuria, severe GI involvement, cardiomyopathy, and CNS involvement. Early and aggressive immunosuppressive therapy increases the likelihood of clinical remission. Compared with disease in adults, childhood PAN is associated with less mortality. Cutaneous PAN is unlikely to transition to systemic disease. Early recognition and treatment of the disease are important to minimizing potential long-term vascular complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

210.4 Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCAs, and a paucity of immune complex deposition in affected tissues, thus the term **pauci-immune vasculitis**. ANCA-associated vasculitis is categorized into three distinct forms: **granulomatosis with polyangiitis (GPA)** (Table 210.11),

Table 210.11 2022 American College of Rheumatology/ EULAR Classification Criteria for Granulomatosis with Polyangiitis

Considerations when applying these criteria:
- These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small-vessel or medium-vessel vasculitis has been made.
- Alternate diagnoses mimicking vasculitis should be excluded before applying the criteria.

CLINICAL CRITERIA	
Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity	+2
Conductive or sensorineural hearing loss	+1
LABORATORY, IMAGING, AND BIOPSY CRITERIA	
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/ paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	–1
Blood eosinophil count ≥ 1×10^9/liter	–4
	*TOTAL:

*Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of granulomatosis with polyangiitis.
From Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis*. 2022;81(3):315–320. Fig. 1.

Table 210.12 Presenting Manifestations (Reported as Percentages) in Children with Granulomatosis with Polyangiitis and Microscopic Polyangiitis from the ARChiVe Cohort (n = 231)

CLINICAL FEATURE	GPA (n = 183)	MPA (n = 48)
CONSTITUTIONAL/GENERAL	88	85
Malaise, fatigue	83	77
Fever	53	52
Weight loss	44	31
RENAL	83	75
Proteinuria	72	69
Hematuria	72	60
Biopsy proven glomerulonephritis	94 (101 of 108)	94 (30 of 32)
Elevated serum creatinine	54	58
PULMONARY	74	44
Hemoptysis/alveolar hemorrhage	42	15
Nodules	54	0
Fixed pulmonary infiltrates	36	0
Oxygen dependency	22	13
Pleurisy	14	8
Requiring ventilation	12	4
EAR, NOSE, THROAT	70	4
Nasal involvement	53	0
Sinusitis	39	0
Otitis/mastoiditis	17	0
Subglottic involvement	10	0
Hearing loss	10	0
Oral ulcers	15	4
MUSCULOSKELETAL	65	52
Arthralgia/arthritis	61*	42
Myalgia, muscle weakness, or myositis	14	19
CUTANEOUS	47	52
Palpable purpura/petechia	27	31
EYES	43	31
Nonspecific red eye	10	2
Conjunctivitis	11	6
Scleritis/episcleritis	8	4
GASTROINTESTINAL	36	58
Nonspecific abdominal pain	22	38
Chronic nausea	12	33
NERVOUS SYSTEM	20	21
Severe headache	11	13
Dizziness	7	4
CARDIOVASCULAR	5	6

*Arthralgias and arthritis at disease onset were not reported separately.
GPA, Granulomatosis with polyangiitis; MPA, microscopic polyangiitis.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology*, 8th ed. Philadelphia: Elsevier; 2021: Table 36.2, p. 487.

formerly Wegener granulomatosis; **microscopic polyangiitis (MPA)** (Table 210.12); and **eosinophilic granulomatosis with polyangiitis** (Table 210.13), formerly Churg-Strauss syndrome **(CSS)**. The 2022 ACR/ EULAR classification criteria for adults with GPA, MPA and EGPA employ a criterion-based scoring system for classification of these vasculitides.

EPIDEMIOLOGY

GPA is a necrotizing, granulomatous, small and medium vessel vasculitis that occurs at all ages and targets the upper and lower respiratory tracts and the kidneys. Most cases of GPA occur in adults; the disease also occurs in children with a mean age at diagnosis of 14 years. There is a female predominance of 3-4:1, and pediatric GPA is most prevalent in the White population.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA, but without granulomas and upper airway involvement. CSS is a small vessel necrotizing granulomatous (allergic granulomatosis) vasculitis associated with a history of refractory asthma and peripheral eosinophilia. MPA and CSS are rare in children, and there does not appear to be a gender predilection in either disease.

PATHOLOGY

Necrotizing vasculitis is the cardinal histologic feature in both GPA and MPA. Kidney biopsies typically demonstrate crescentic glomerulonephritis with little or no immune complex deposition ("pauci-immune"), in contrast to biopsies from patients with SLE. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS from both MPA and GPA.

Table 210.13 American College of Rheumatology Criteria for Classification of Eosinophilic Granulomatosis with Polyangiitis Syndrome

CRITERION*	DESCRIPTION
Asthma	History of wheezing or diffuse high-pitched rales on expiration
Eosinophilia	Eosinophils >10% of differential white blood cell count
History of allergy	History of seasonal allergy (e.g., allergic rhinitis) or documented allergies, including food, contactants, and others (except for drug allergies)
Mononeuropathy or polyneuropathy	Mononeuropathy, multiple mononeuropathies or polyneuropathy (i.e., glove/stocking distribution) attributable to a systemic vasculitis
Pulmonary infiltrates	Migratory or transitory pulmonary infiltrates on radiographs attributable to a systemic vasculitis
Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
Extravascular eosinophils	Biopsy including artery, arteriole, or venule, showing accumulation of eosinophils in extravascular areas

*For classification purposes, a patient is said to have EGPA if at least four of these criteria are present. The presence of any four or more criteria has a sensitivity of 85% and a specificity of 99.7%.

From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021, Fig. 36.7, p. 495.

PATHOGENESIS

The etiology of ANCA-associated vasculitis remains unknown, although neutrophils, monocytes, and endothelial cells are involved in disease pathogenesis. Neutrophils and monocytes are activated by ANCAs, specifically by the ANCA-associated antigens proteinase-3 (PR3) and myeloperoxidase (MPO), and release proinflammatory cytokines such as TNF-α and IL-8. Localization of these inflammatory cells to the endothelium results in vascular damage characteristic of the ANCA vasculitides. Why the respiratory tract and kidneys are preferential targets in GPA and MPA is unknown.

CLINICAL MANIFESTATIONS

The early disease course is characterized by nonspecific constitutional symptoms, including fever, malaise, weight loss, myalgias, and arthralgias. In GPA, upper airway involvement can manifest as sinusitis, nasal ulceration, epistaxis, otitis media, and hearing loss. Lower respiratory tract symptoms in GPA include cough, wheezing, dyspnea, and hemoptysis. Pulmonary hemorrhage can cause rapid respiratory failure. Compared with adults, childhood GPA is more frequently complicated by subglottic stenosis (Fig. 210.9). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (see Fig. 210.9). Ophthalmic involvement includes conjunctivitis, scleritis, uveitis, optic neuritis, and invasive orbital pseudotumor (causing proptosis). Perineural vasculitis or direct compression on nerves by granulomatous lesions can cause cranial and peripheral neuropathies. Hematuria, proteinuria, and hypertension in GPA signal renal disease. Cutaneous lesions include palpable purpura and ulcers. Venous thromboembolism is a rare but potentially fatal complication of GPA. The frequencies of organ system involvement throughout the disease course in GPA are as follows: respiratory tract, 74%; kidneys, 83%; joints, 65%; eyes, 43%; skin, 47%; sinuses, 70%; and nervous system, 20%. Table 210.11 lists the classification criteria for pediatric-onset GPA.

The clinical presentation of MPA closely resembles that of GPA, although sinus disease is less common; systemic features of fever, malaise, weight loss, myalgias, and arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes (see Table 210.12).

CSS frequently causes inflammation of the upper and lower respiratory tracts, but cartilage destruction is rare. CSS may initially demonstrate chronic or recurrent rhinitis/sinusitis, nasal polyposis, nonfixed pulmonary lesions, and difficult-to-treat asthma. Eosinophilia (>10% of leukocytes) with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral neuropathy, GI tract, and muscle. Renal involvement in CSS is uncommon.

DIAGNOSIS

GPA should be considered in children who have recalcitrant sinusitis, pulmonary infiltrates, and evidence of nephritis. Chest radiography often fails to detect pulmonary lesions, and chest CT may show nodules, ground-glass opacities, mediastinal lymphadenopathy, and cavitary lesions (Fig. 210.10). The diagnosis is confirmed by the presence of c-ANCA with anti-PR3 specificity (PR3-ANCAs) and the finding of necrotizing granulomatous vasculitis on pulmonary, sinus, or renal biopsy. The ANCA test result is positive in approximately 90% of children with GPA, and the presence of anti-PR3 increases the specificity of the test.

In MPA, ANCAs are also frequently present (70% of patients) but are usually p-ANCA with reactivity to MPO (MPO-ANCAs). MPA can be distinguished from PAN by the presence of ANCAs and the tendency for small vessel involvement. The ANCA test result is positive in 50–70% of cases of CSS, and MPO-ANCAs are more common than PR3-ANCAs. In addition, the presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

DIFFERENTIAL DIAGNOSIS

ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. **Goodpasture syndrome** is characterized by antibodies to glomerular basement membrane. Medications such as propylthiouracil, hydralazine, and minocycline are associated with drug-induced ANCA (usually perinuclear ANCA) vasculitis. SLE and HSP can manifest as pulmonary hemorrhage and nephritis.

LABORATORY FINDINGS

Nonspecific laboratory abnormalities include elevated ESR and CRP values, leukocytosis, and thrombocytosis, which are present in most patients with an ANCA-associated vasculitis but are nonspecific. Anemia may be caused by chronic inflammation or pulmonary hemorrhage. ANCA antibodies show two distinct immunofluorescence patterns: *perinuclear* (p-ANCA) and *cytoplasmic* (c-ANCA). In addition, ANCAs can be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with c-ANCAs/anti-PR3 antibodies, whereas 75% of patients with MPA have a positive p-ANCA. There is no clear correlation between ANCA titers and disease activity or relapse.

TREATMENT

When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of prednisone (oral 2 mg/kg/day oral or IV methylprednisolone 30 mg/kg/day × 3 days) in conjunction with daily oral or monthly IV cyclophosphamide. *Rituximab,* a monoclonal antibody to CD20 on activated B cells, is an option for induction therapy in ANCA-positive vasculitides, although it has been studied primarily in adults. *Plasmapheresis* in conjunction with methylprednisolone has a role in the therapy of patients with severe disease manifestations such as pulmonary hemorrhage or ESRD, with the potential for reducing dialysis dependency. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or

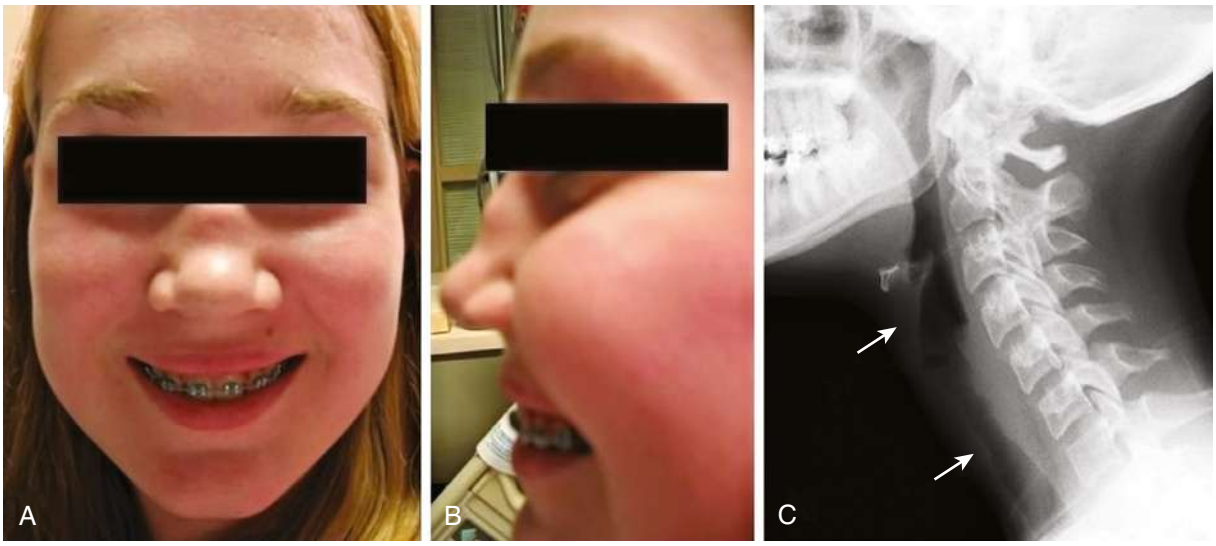

Fig. 210.9 Adolescent with granulomatosis with polyangiitis. **A** and **B**, Anterior and lateral views of saddle nose deformity. **C**, Segment of subglottic posterior tracheal irregularity (between *arrows*) on lateral neck radiograph.

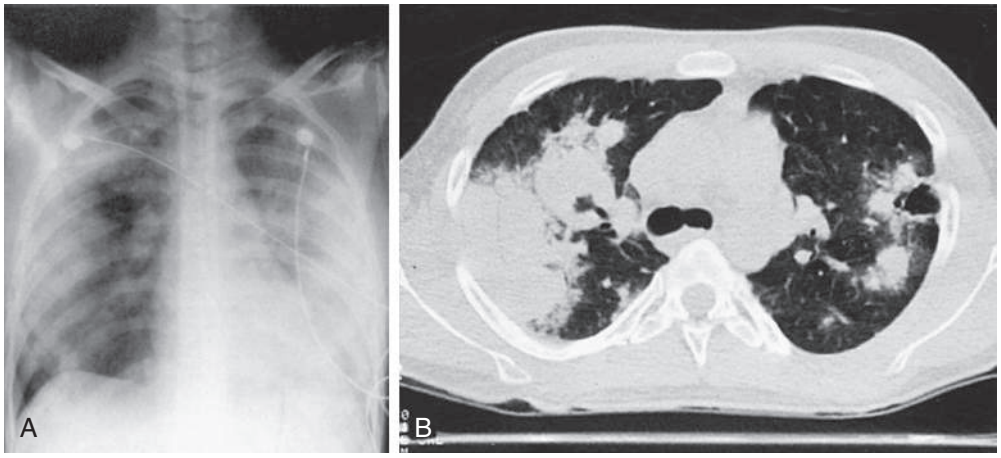

Fig. 210.10 Radiographs of lower respiratory tract disease in granulomatosis with polyangiitis (GPA). **A**, Chest radiograph of 14-yr-old girl with GPA and pulmonary hemorrhage. Extensive bilateral, fluffy infiltrates are visualized. **B**, Chest CT scan in 17-yr-old boy with GPA. Air space consolidation, septal thickening, and a single cavitary lesion are present. (**A** *from Cassidy JT, Petty RE. Granulomatous vasculitis, giant cell arteritis and sarcoidosis. In Textbook of Pediatric Rheumatology, 3rd ed. Philadelphia: Saunders; 1995;* **B** *from Kuhn JP, Slovis TL, Haller JO. Caffey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby; 2004.)*

mycophenolate mofetil) within 3-6 months once remission is achieved. The Childhood Arthritis and Rheumatology Research Alliance has published treatment guidelines for the induction and maintenance therapy of children with severe ANCA-associated vasculitides consisting of induction therapy with cyclophosphamide or rituximab and maintenance therapy with rituximab, methotrexate, or azathioprine. Trimethoprim-sulfamethoxazole (one 160 mg/800 mg tablet 3 days/week) is often prescribed both for prophylaxis against *Pneumocystis jirovecii* infection and to reduce upper respiratory bacterial colonization with *S. aureus*, which may trigger disease activity. If disease is limited to the upper respiratory tract, corticosteroids (1-2 mg/kg/day) and methotrexate (0.5-1.0 mg/kg/week) may be first-line treatment. *Avacopan*, a C5a receptor inhibitor, has been shown to be effective in reducing the need for corticosteroids in addition to standard therapy in adults with ANCA-associated vasculitis but has not been studied in children.

Mepolizumab, an anti–IL-5 monoclonal antibody, may have a role in the treatment of eosinophilic granulomatosis with polyangiitis (CSS).

COMPLICATIONS

Upper respiratory tract lesions can invade the orbit and threaten the optic nerve, and lesions in the ear can cause permanent hearing loss. Respiratory complications include potentially life-threatening pulmonary hemorrhage and upper airway obstruction caused by subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to ESRD in a subset of patients with advanced or undertreated disease.

PROGNOSIS

The course is variable, but disease relapse occurs in up to 60% of patients. Mortality has been reduced with the introduction of cyclophosphamide and other immunosuppressive agents. Compared with adults, children are more likely to develop multiorgan involvement, renal involvement, and subglottic stenosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

210.5 Other Vasculitis Syndromes: Hypersensitivity, CNS, and COVID-19 Related

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Other vasculitic conditions can occur in childhood; the most common is **Kawasaki disease** (see Chapter 208). **Behçet disease** is a rare form of vasculitis seen in children of Turkish and Mediterranean descent, characterized by the triad of recurrent aphthous stomatitis, genital ulcers, and uveitis (see Chapter 202).

Hypersensitivity vasculitis is a cutaneous vasculitis triggered by medication or toxin exposure. The rash consists of palpable purpura or other nonspecific rash. Skin biopsies reveal characteristic changes of **leukocytoclastic vasculitis** (small vessels with neutrophilic perivascular or extravascular neutrophilic infiltration) (Table 210.14). **Hypocomplementemic urticarial vasculitis** involves small vessels and manifests as recurrent urticaria that resolves over several days but leaves residual hyperpigmentation. This condition is associated with low levels of complement component C1q and systemic findings that include fever, GI symptoms, arthritis, and glomerulonephritis. Some patients with urticarial vasculitis have normal complement levels. **Cryoglobulinemic vasculitis** can complicate mixed essential cryoglobulinemia and is a small vessel vasculitis affecting skin, joints, kidneys, and lungs.

Primary angiitis of the central nervous system represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. **Large vessel disease** (angiography positive) may be progressive or nonprogressive and may manifest with focal deficits similar to an occlusive stroke, with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits and behavioral disorders are seen in 30–40% of patients. **Small vessel disease** (angiography negative, biopsy positive) more often results in language problems and diffuse deficits, such as cognitive, memory, behavior, and concentration problems, as well as focal seizures. In both types of cerebral angiitis, patients may have an elevated ESR or CRP and abnormal CSF findings (increased protein, pleocytosis), although these are not consistent findings in all patients. Diagnosis remains a challenge, and brain biopsy is often indicated to confirm the diagnosis and exclude vasculitis mimics such as infections that could worsen with immunosuppressive therapy (Table 210.15).

Table 210.14 Criteria for Diagnosis of Hypersensitivity Vasculitis*

CRITERION	DEFINITION
Age at onset >16yr	Development of symptoms after 16yr of age
Medication at disease onset	Medication that may have been a precipitating factor was taken at the onset of symptoms
Palpable purpura	Slightly elevated purpuric rash over one or more areas; does not blanch with pressure and is not related to thrombocytopenia
Maculopapular rash	Flat and raised lesions of various sizes over one or more areas of the skin
Biopsy, including arteriole and venule	Histologic changes showing granulocytes in a perivascular or extravascular location

*For purposes of classification, a patient is said to have hypersensitivity vasculitis if at least three of these criteria are present. The presence of three or more criteria has a diagnostic sensitivity of 71.0% and specificity of 83.9%. The age criterion is not applicable for children.

Adapted from Calabrese LH, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. *Arthritis Rheum.* 1990;33:1108–1113, Table 2, p. 1110; and Petty RE, Laxer RM, Lindsley CB, Wedderburn LR. *Textbook of Pediatric Rheumatology,* 7th ed. Philadelphia: Saunders; 2016: Table 38.2, p. 511.

Table 210.15 Differential Diagnosis of Small Vessel Primary Central Nervous System (CNS) Vasculitis in Children

CNS VASCULITIS COMPLICATING OTHER DISEASES

Infections

- Bacterial: *Mycobacterium tuberculosis, Mycoplasma pneumoniae, Streptococcus pneumoniae*
- Viral: Epstein-Barr virus, cytomegalovirus, enterovirus, varicella-zoster virus, hepatitis C virus, parvovirus B19, West Nile virus
- Fungal: *Candida albicans, Actinomyces, Aspergillus*
- Spirochetal: *Borrelia burgdorferi, Treponema pallidum*

Rheumatic and Inflammatory Diseases

- Systemic vasculitis such as granulomatosis with polyangiitis, microscopic polyangiitis, Henoch-Schönlein purpura, Kawasaki disease, polyarteritis nodosa, Behçet disease
- Systemic lupus erythematosus, juvenile dermatomyositis, morphea
- Inflammatory bowel disease
- Autoinflammatory syndromes
- Hemophagocytic lymphohistiocytosis
- Neurosarcoidosis
- Adenosine deaminase-2 deficiency

Other

- Drug-induced vasculitis
- Malignancy-associated vasculitis

NONVASCULITIS INFLAMMATORY BRAIN DISEASES

Demyelinating Diseases

- Multiple sclerosis, acute demyelinating encephalomyelitis (ADEM), optic neuritis, transverse myelitis

Antibody-Mediated Inflammatory Brain Disease

- Anti–NMDA receptor encephalitis, neuromyelitis optica (NMO), antibody-associated limbic encephalitis (antibodies against LGI, AMP, AMP-binding protein), Hashimoto encephalopathy, celiac disease, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

T-Cell–Associated Inflammatory Brain Disease

- Rasmussen encephalitis

Other

- Febrile infection-related epilepsy syndrome (FIRES)

NONINFLAMMATORY VASCULOPATHIES

- Hemoglobinopathies (sickle cell disease), thromboembolic disease
- Radiation vasculopathy, graft versus host disease
- Metabolic and genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy lactic acidosis and strokelike episodes (MELAS), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Moyamoya disease, Fabry disease
- Malignancy (lymphoma)

Modified from Gowdie P, Twilt M, Benseler SM. Primary and secondary central nervous system vasculitis. *J Child Neurol.* 2012;27:1448–1459.

Table 210.16 Diagnostic Considerations for Other Vasculitis Syndromes

VASCULITIS SYNDROME	APPROACH TO DIAGNOSIS
Hypersensitivity vasculitis	Skin biopsy demonstrating leukocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Low levels of circulating C1q
Cryoglobulinemic vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Measurement of serum cryoglobulins Exclusion of hepatitides B and C infections
Primary angiitis of CNS	Conventional, CT, or MRA evidence of CNS vasculitis Consideration of dura or brain biopsy
Nonprogressive angiography-positive CNS vasculitis	Conventional, CT, or MRA evidence of CNS vasculitis
Cogan syndrome	Ophthalmology and audiology evaluations Conventional, CT, or MRA evidence of CNS or aortic vasculitis

Table 210.17 Acral and Nonacral Potential Cutaneous Manifestations of Pediatric COVID-19

ACRAL	NONACRAL
Pernio-like lesions	Urticaria
EM-like lesions	Erythematous patches
Plantar papules	EM-like lesions
Retiform purpura	Vesicles/papulovesicles
Ecchymotic-like lesions	Herpetiform oral eruption
Livedo reticularis	Roseola-like rash
	Maculopapular rash
	Macular eruption
	Lingual papillitis
	Eccrine hidradenitis
	Erythema nodosum
	Petechiae
	Purpura

Modified from Neale H, Hawryluk EB. COVID-19 pediatric dermatology. *Dermatol Clin.* 2021;39:505–519, Table 4, p. 513.

Nonprogressive angiography-positive CNS vasculitis, also known as *transient CNS angiopathy,* represents a more benign variant and can be seen after varicella infection. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms; inflammatory eye disease such as uveitis, episcleritis, or interstitial keratitis; vestibuloauditory dysfunction (vertigo, hearing loss, tinnitus); arthritis; and large vessel vasculitis or aortitis. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy **(CADASIL)** is caused by pathogenic variants in the *NOTCH3* gene and manifests with stroke, mood changes, cognitive decline, and migraines; it is a vasculitis mimic and demonstrates osmophilic granules in cerebral arteries. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (**CARASIL**) is another mimic of angiitis caused by pathogenic variants in the *HTRA1* gene. It manifests with early-onset hair loss, spasticity, stroke, memory loss, and personality changes.

Identification of these vasculitis syndromes requires a comprehensive history and physical examination. Table 210.16 outlines other diagnostic considerations. Although tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day). Potent immunosuppressive medications, such as cyclophosphamide, are often indicated, particularly in primary angiitis of the CNS to prevent rapid neurologic decline. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

COVID-19, including multisystem inflammatory syndrome in children (**MIS-C**), has been associated with a variety of cutaneous lesions that resemble vasculitis, vasculopathy, and vasoocclusive etiologies (see Chapter 311) (Table 210.17, Fig. 210.11). Lesions include pernio (chilblain: COVID toes)–like lesions suggestive of a vasculitis. Other cutaneous manifestations include urticarial vasculitis and livedo reticularis–like or livedo racemosa—both resemble a pauci-inflammatory occlusive vasculitis. Sweet syndrome and erythema multiforme–like lesions have also been described. Most cutaneous lesions associated with known COVID-19 or MIS-C do not require a biopsy, but some of those that were biopsied have demonstrated a leukocytoclastic vasculitis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 210.11 Pernio-like lesions in children. **A,** A child with purpuric papules on the first, second, fourth, and fifth right digits and second proximal left digit. **B,** Digits on the same child appearing with increased erythema. **C,** Right toes of a child appearing with pink and dusky papules and plaques, also involving the child's left digits **(D)**. *(From Neale H, Hawryluk EB. COVID-19 pediatric dermatology. Dermatol Clin. 2021;39:505–519, Fig. 3, p. 511.)*

Chapter 211

Musculoskeletal Pain Syndromes

James J. Nocton

Musculoskeletal pain is a frequent reason for children to visit a healthcare provider and is the most common problem referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from 10% to 40%. Although inflammatory diseases such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) are associated with musculoskeletal pain, noninflammatory conditions such as trauma, hypermobility, overuse, and **idiopathic pain syndromes** are much more common causes of musculoskeletal pain in children.

CLINICAL MANIFESTATIONS

Acute and subacute musculoskeletal pain in children is most commonly the result of trauma, overuse, hypermobility, or some combination of these. The history and physical findings of trauma are most often readily apparent, and the pain associated with overuse or hypermobility is most often described as related to activities and improving with rest. The physical examination of children with pain related to overuse, hypermobility, and other mechanical causes of pain does not reveal signs of inflammation such as warmth, swelling, or limited range of motion and most often reveals hypermobility with perhaps mild tenderness over tendons and their insertion points.

Chronic idiopathic musculoskeletal pain syndromes are defined by pain of at least 3 months duration in the absence of objective abnormalities on physical examination or laboratory screening (see Chapter 212). The prevalence of chronic idiopathic musculoskeletal pain syndromes increases with age and is higher in females. These syndromes often persist despite treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and other analgesics. Chronic pain may occur anywhere and is most often diffuse and poorly localized, but may sometimes involve only a single extremity or part of an extremity. Pain may start in one location before potentially developing in other areas over time.

Psychologic and emotional distress, including anxiety, depression, stress, or a combination of these, is quite common in those with chronic idiopathic musculoskeletal pain syndromes. Frequent crying, school and social stress, poor concentration, and excessive worry are often described. Sleep disturbance in children with chronic pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep-wake cycles with increased daytime sleeping, nonrestorative sleep, and fatigue.

Children who are high achievers, excellent students, mature, and responsible, with high expectations of themselves have a predisposition to the development of pain syndromes in general, including chronic musculoskeletal pain. As a result, headaches and abdominal pain or other gastrointestinal symptoms are also frequently present in those with chronic idiopathic musculoskeletal pain syndromes.

The constellation of chronic pain, psychologic distress, and sleep disturbance often leads to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, along with changes in gait and posture, as children avoid the use of the area affected by pain. Peer relationships may also be disrupted by decreased opportunities for social interaction because of pain. Loneliness and social isolation characterized by few friends and lack of participation in extracurricular activities are common.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of a musculoskeletal pain syndrome is based primarily on history and physical examination. Children with pain require a thorough clinical history, including a complete social history and review of systems, and a careful, comprehensive physical examination. The specific characteristics of the pain should be defined, evidence of potential systemic disease should be sought, and any additional associated symptoms and signs should be elicited.

The need for laboratory testing and imaging studies should be individualized, depending on the information elicited in the history and discovered with the physical examination. Possible indicators of an inflammatory cause for musculoskeletal pain include objective joint warmth, swelling, limited range of joint motion on physical examination, localized bone tenderness, and muscle weakness; potential indicators of a systemic disease include poor linear growth, weight loss, and constitutional symptoms. The lack of these symptoms and objective abnormalities on physical examination is more suggestive of a noninflammatory cause for pain (Table 211.1). The complete blood count (CBC) and erythrocyte sedimentation rate (ESR) are often abnormal in children whose pain is secondary to a bone or joint infection, rheumatic disease, or a malignancy. Bone tumors, fractures, and other focal pathology resulting from infection, malignancy, or trauma can often be identified through imaging studies, including plain radiographs or MRI.

The presence of chronic, persistent pain, accompanied by psychologic distress, sleep disturbance, and/or functional impairment, in the absence of objective laboratory or physical examination abnormalities, suggests the diagnosis of an **idiopathic musculoskeletal pain syndrome**. Table 211.2 outlines common causes of pediatric musculoskeletal pain according to anatomic location, including **growing pains** (see Chapter 211.1), diffuse **amplified pain syndromes** and chronic widespread pain (see Chapter 211.3), **complex regional pain syndrome** (see Chapter 211.4), localized pain syndromes, low back pain, and chronic overuse-related pain (e.g., Osgood-Schlatter disease). A differential diagnosis of more serious conditions is noted in Table 211.3.

TREATMENT

The primary goal of treatment for acute and subacute musculoskeletal pain related to trauma, hypermobility, overuse, or other mechanical factors is to minimize the discomfort as much as possible and to promote normal activities. Rest, topical analgesics, mechanical joint support to be worn with activities, ice, oral analgesics, and physical therapy may all be used. Education of children and families regarding pain related to these mechanical factors is critical in helping them to understand what to expect. Although it is common for the discomfort related to hypermobility and overuse to be recurrent, the prognosis for these mechanical pains is excellent, and most children learn to manage their discomfort with few, if any, restrictions on activities.

The primary goal of treatment of chronic idiopathic musculoskeletal pain syndromes is to improve function and relieve pain; these outcomes may not occur simultaneously or quickly. Pain may persist even as children resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes whose school attendance has been affected by their symptoms, regular school attendance is a primary initial goal. The dual nature of treatment, targeting both *function* and *pain,* needs to be clearly explained. Children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing the equally imperative goal of improved functioning.

Recommended treatment modalities include physical and/or occupational therapy, pharmacologic interventions, and cognitive-behavioral and/or other psychotherapeutic interventions. The overarching goal of **physical therapy** is to improve children's physical function and should emphasize participation in aggressive but graduated aerobic exercise. **Pharmacologic** interventions should be used judiciously. Low-dose

Table 211.1 Potential Indicators of Inflammatory vs Noninflammatory Causes of Musculoskeletal Pain

CLINICAL FINDING	NONINFLAMMATORY	INFLAMMATORY
Effects of rest vs activity on pain	Relieved by rest and worsened by activity	Present at rest and may be relieved by activity
Time of day pain and/or stiffness occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bone tenderness	No	Possible
Muscle strength	Normal	Possible weakness
Gait	Normal	Limp
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms	Fatigue without other constitutional symptoms	Possible
Laboratory findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Imaging findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bone destruction

*Cancer pain is often severe and worst at night.
CBC, Complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.
Data from Malleson PN, Beauchamp RD. Diagnosing musculoskeletal pain in children. *CMAJ* 2001;165:183–188.

Table 211.2 Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMIC REGION	PAIN SYNDROMES
Shoulder	Impingement syndrome
Elbow	"Little League elbow" Avulsion fractures Osteochondritis dissecans Tennis elbow Panner disease
Arm	Localized hypermobility syndrome Complex regional pain syndrome
Pelvis and hip	Avulsion injuries Legg-Calvé-Perthes syndrome Slipped capital femoral epiphysis Congenital hip dysplasia
Knee	Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome Patellofemoral syndrome Malalignment syndromes
Leg	Growing pains Complex regional pain syndrome Localized hypermobility syndrome Shin splints Stress fractures Compartment syndromes
Foot	Plantar fasciitis Tarsal coalition Stress fractures Achilles tendonitis Juvenile bunion
Spine	Musculoskeletal strain Spondylolisthesis Spondylolysis Scoliosis Scheuermann disease (kyphosis) Low back pain
Generalized	Hypermobility syndrome Diffuse amplified pain syndrome Chronic widespread pain

Adapted from Anthony KK, Schanberg LE. Assessment and management of pain syndromes and arthritis pain in children and adolescents. *Rheum Dis Clin North Am.* 2007;33:625–660, Box 1.

tricyclic antidepressants (amitriptyline 0.1 mg/kg at bedtime; can increase to 0.5 to 2 mg/kg as tolerated) may improve sleep; selective serotonin reuptake inhibitors (sertraline 25-100 mg daily) may help to alleviate symptoms of depression and anxiety if present. **Cognitive-behavioral therapy (CBT)** and/or other psychotherapeutic interventions are designed to teach children and adolescents coping skills for controlling the behavioral, cognitive, and physiologic responses to pain. Specific components often include cognitive restructuring, relaxation, distraction, and problem-solving skills. Parent education and involvement in the psychologic intervention are important to ensure maintenance of progress. More intensive family-based approaches are warranted if barriers to treatment success are identified at the family level. These could include parenting strategies or family dynamics that serve to maintain children's pain complaints, such as overly solicitous responses to the child's pain and maladaptive models for coping with pain.

COMPLICATIONS AND PROGNOSIS

Musculoskeletal pain related to hypermobility and/or overuse may be recurrent and related to specific activities, but is typically mild, does not usually significantly limit activities, and is most often managed symptomatically. Conversely, chronic idiopathic musculoskeletal pain syndromes have a much greater potential to negatively affect development and future role functioning. Worsening pain and the symptoms of depression and anxiety associated with chronic pain can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with chronic idiopathic musculoskeletal pain syndromes may fail to achieve the level of autonomy and independence necessary for age-appropriate activities, such as attending college, living away from home, and maintaining a job. Fortunately, not all children and adolescents with these syndromes experience this degree of impairment. Factors that contribute to the persistence of pain are increasingly understood and include female gender, pubertal stage at pain onset, older age of pain onset, increased psychologic distress associated with the pain, and greater functional impairment. The likelihood of positive health outcomes is increased with multidisciplinary treatment addressing the pain, the functional disabilities, and the psychologic comorbidities associated with pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 211.3 Differential Diagnosis of Idiopathic Musculoskeletal Pain Syndrome

CHANNELOPATHIES
Erythromelalgia: primary (associated with the *SCN9A* gene) or secondary
Paroxysmal extreme pain disorder (*SCN9A* gene)
Small fiber neuropathy (*SCN9A, SCN1OA* genes)
Familial episodic pain syndrome (*SCN11A, TRPA1* genes)
CONNECTIVE TISSUE DISORDERS
Ehlers-Danlos syndrome
Marfan syndrome
IMMUNE/AUTOIMMUNE
Systemic lupus erythematosus
Sarcoidosis
Juvenile idiopathic arthritis
Sjögren syndrome
Familial Mediterranean fever and other autoinflammatory recurrent fever syndromes
Hereditary angioedema
Chronic nonbacterial osteomyelitis
Mononeuritis multiplex associated with vasculitis
METABOLIC/NUTRITION
Fabry disease
Gaucher disease
Porphyria
Mitochondrial neuropathies
Vitamin deficiency (thiamine, B_{12}, C, D)
X-linked adrenoleukodystrophy
OTHER
Guillain-Barré syndrome
Multiple sclerosis
Toxic: lead, arsenic, chemotherapy
HIV
Familial amyloid neuropathy
Complex regional pain syndrome types 1 and 2
Sickle cell anemia
Thalamic stroke
Primary, metastatic, or recurrent malignancy (acute lymphocytic leukemia, neuroblastoma)
Neurofibromatosis
Radiculopathy
Nerve entrapment syndromes
1. Peroneal
2. Suprascapular
3. Anterior, posterior hip
4. Anterior cutaneous nerve (abdominal)

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 33.2, p. 547.

211.1 Growing Pains (Benign Limb Pain of Childhood)

James J. Nocton

The cause of benign limb pain of childhood, historically referred to as **growing pains**, is unknown. Low pain threshold, overuse, and behavioral causes have been postulated, and it is possible that there are multiple causes for these pains. This pain affects 10–20% of children, with peak incidence between age 4 and 12 years. Benign limb pains of childhood are intermittent and usually bilateral, poorly localized, and predominantly affecting the anterior thigh, shin, and calf. Occasionally, bilateral upper extremity pain may be associated with leg pain. Children typically describe cramping or aching that occurs most often in the late afternoon or evening. Pain may wake the child from sleep, may be severe, and may last a few minutes to hours, but typically resolves quickly with massage or analgesics; pain is nearly always resolved by the following morning (Table 211.4). Pain may often follow a day with increased or excessive physical activity. Physical examination is normal, and gait is not impaired.

Treatment should focus on reassurance, education, and healthy sleep hygiene while preparing parents and children for the possibility that the pain may occur intermittently for years, with eventual resolution. Massage, acetaminophen, or NSAIDs during the episode are nearly always effective.

Restless legs syndrome (RLS), seen more frequently among adolescents and adults, is a sensorimotor disturbance that may be confused with growing pains (see Chapter 31). Often familial, RLS is a difficult-to-control *urge* to move the leg that is exacerbated during rest and at night and is relieved by movement (see Table 211.4). There is significant overlap in the diagnostic features of growing pains and RLS. Moreover, these conditions can be comorbid, and there is a high incidence of RLS in the parents of children with growing pains. RLS appears to be best distinguished from growing pains by the *urge* to move the legs, associated uncomfortable leg sensations that may not be described as painful; worsening with periods of rest; and relief through movement. Iron supplementation may benefit pediatric patients with RLS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

211.2 Small Fiber Polyneuropathy

James J. Nocton

Some patients with juvenile-onset widespread pain syndromes have evidence of a small fiber polyneuropathy causing dysfunctional or degeneration of small-diameter unmyelinated C fibers and thinly myelinated A delta fibers that mediate nociception and the autonomic nervous system. In addition to pain, these children may have dizziness, postural orthostatic tachycardia syndrome (POTS), constipation and/or gastrointestinal dysmotility, and other symptoms suggestive of dysautonomia (Fig. 211.1).

The diagnosis of small fiber polyneuropathy requires distal leg immunolabeled skin biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovagal, adrenergic, and sudomotor small fiber function. Genetic testing for pathogenic variants in genes coding for sodium channels may reveal *SCN9A, SCN10A,* or *SCN11A* variants. Some small studies have reported the presence of autoantibodies to trisulfated disaccharide and fibroblast growth factor receptor 3, suggestive of immune-mediated pathogenesis. Other potential etiologies for small fiber neuropathy are noted in Table 211.5; most cases are idiopathic. In addition, other genetic painful neuropathies should be considered (Table 211.6).

Optimal treatment of patients with small fiber polyneuropathy is unknown. Corticosteroids and intravenous immune globulin have been effective in very small numbers of patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

211.3 Diffuse Amplified Pain Syndromes

James J. Nocton

Diffuse amplified pain syndrome is more common in children than localized amplified pain. In addition to widespread pain, children frequently have associated chronic fatigue, sleep disturbance, headaches, chronic abdominal pain and gastrointestinal symptoms, stress, anxiety, and/or symptoms of depression (see also Chapter 212). The terms *diffuse amplified pain syndrome, chronic widespread pain syndrome, chronic myofascial pain syndrome,* and *juvenile primary fibromyalgia syndrome* are often used to describe the same constellation of symptoms. Some of these children have findings that fulfill the criteria that have been developed for adult patients with fibromyalgia by either the American College of Rheumatology (Table 211.7) or the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society (Table 211.8 and

Table 211.4 Inclusion and Exclusion Criteria for Growing Pains Including Features of Restless Legs Syndromes (RLS)

	INCLUSIONS	EXCLUSIONS	RLS FEATURES
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day	Urge to move legs often accompanied by unpleasant sensations in legs, but may not be painful
Unilateral or bilateral	Bilateral	Unilateral	
Location of pain	Anterior thigh, calf, posterior knee—in muscles not the joints	Articular, back, or groin pain	Urge to move and discomfort throughout leg
Onset of pain	Late afternoon or evening	Pain still present next morning	Worse later in day or night but also present at periods of rest or inactivity throughout the day
Physical findings	Normal	Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass	
Laboratory findings	Normal	Objective evidence of abnormalities; increased erythrocyte sedimentation rate or C-reactive protein; abnormal complete blood count, radiography, bone scan, or MRI	

Adapted from Evans AM, Scutter SD. Prevalence of "growing pains" in young children. *J Pediatr*. 2004;145:255–258; and Walters AS, Gabelia D, Frauscher B. Restless legs syndrome (Willis-Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research. *Sleep Med*. 2013;14:1247–1252.

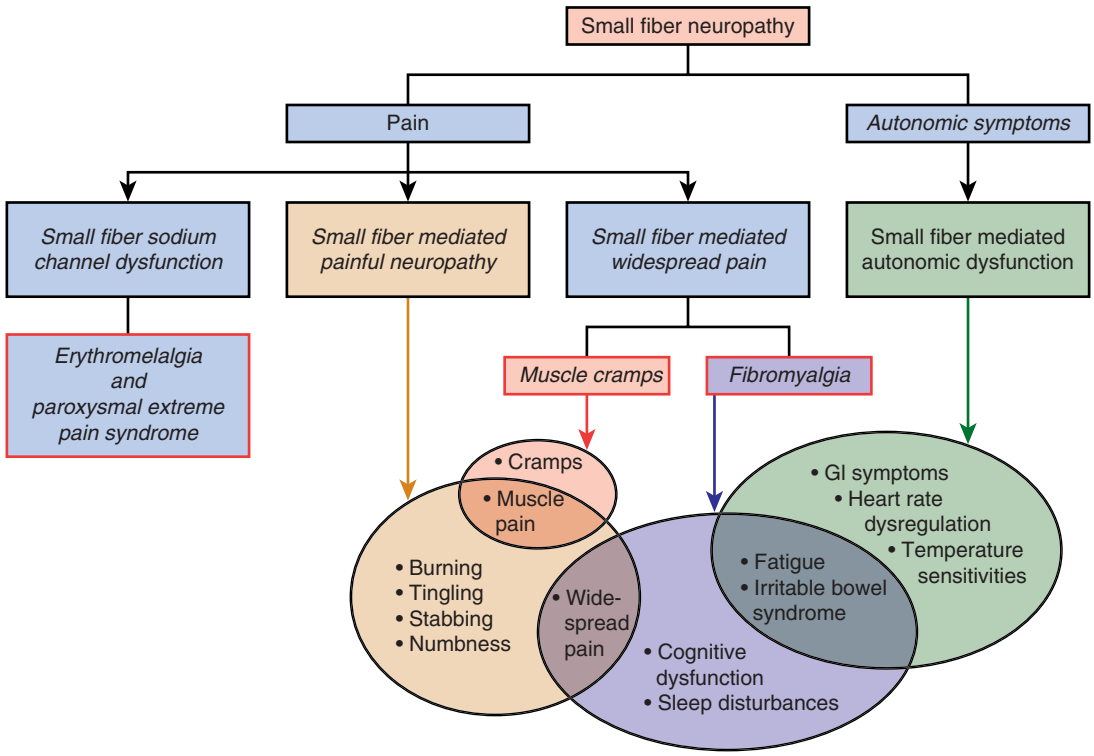

Fig. 211.1 Small fiber neuropathy symptom clusters and neuropathy classifications. *(From Levine TD. Small fiber neuropathy: disease classification beyond pain and burning. J Central Nervous Sys Dis. 2018;10:1–6, Fig. 1, p. 3).*

Fig. 211.2). Separate criteria for the diagnosis of juvenile primary fibromyalgia syndrome in children have been proposed, but these have not been validated (Table 211.9). The evaluation of fibromyalgia tender points has not been useful or diagnostic.

Although the precise cause of diffuse amplified pain is unknown, there is an emerging understanding that the development and maintenance of chronic pain are related both to biologic and psychologic factors. Diffuse amplified pain likely has multifactorial causes and is hypothesized to be an abnormality of central pain processing associated with disordered sleep physiology, enhanced pain perception, disordered mood, and dysregulation of hypothalamic-pituitary-adrenal and other neuroendocrine axes, resulting in lower pain thresholds and increased pain sensitivity. Children and adolescents with diffuse amplified pain often find themselves in a vicious cycle of pain, where symptoms build on one another and contribute to the onset and maintenance of new symptoms.

Diffuse amplified pain has a chronic course that can detrimentally affect child health and development. Adolescents who do not

Table 211.5 Causes of Small Fiber Neuropathy

PRIMARY	SECONDARY
IDIOPATHIC Idiopathic small fiber neuropathy Burning mouth syndrome	METABOLIC Impaired glucose tolerance Diabetes mellitus Rapid glycemic control Vitamin B_{12} deficiency Dyslipidemia Hypothyroidism Chronic kidney disease
HEREDITARY/GENETIC Familial amyloid polyneuropathy Fabry disease Tangier disease Sodium channelopathies (see text)	INFECTIONS HIV Hepatitis C Influenza TOXINS AND DRUGS Antiretrovirals Antibiotics—metronidazole, nitrofurantoin, linezolid Chemotherapy—bortezomib Flecainide Statin Alcohol Vitamin B_6 toxicity IMMUNE MEDIATED Celiac disease Sarcoidosis Sjögren syndrome Rheumatoid arthritis Systemic lupus erythematosus Vasculitis Inflammatory bowel disease Paraneoplastic Monoclonal gammopathy/amyloid

Note that a number of these conditions may present as a small fiber neuropathy and then evolve to include large fibers.
Modified from Themistocleous AC, Ramirez JD, Serra J, Bennett DLH. The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol.* 2014;14:368–379, Table 1.

receive treatment or who are inadequately treated may withdraw from school and the social milieu, complicating their transition to adulthood. **Treatment** of diffuse amplified pain is ideally multidisciplinary. The major goals are to restore function and alleviate pain and to improve comorbid mood and sleep disorders. Treatment strategies include parent/child education, pharmacologic interventions, exercise-based interventions, and psychologic interventions. Graduated **aerobic exercise** is the recommended exercise-based intervention, whereas psychologic interventions should include training in pain coping skills, stress management skills, emotional support, and sleep hygiene. CBT is particularly effective in reducing symptoms of depression in children and adolescents with chronic pain and helps to reduce functional disability.

Drug therapies, although largely unsuccessful in isolation, may include tricyclic antidepressants (amitriptyline 0.1 mg/kg at bedtime; can increase to 0.5 to 2 mg/kg as tolerated), selective serotonin reuptake inhibitors (sertraline 25-100 mg daily), and anticonvulsants. Pregabalin and duloxetine hydrochloride are approved by the U.S. Food and Drug Administration (FDA) for treatment of fibromyalgia in adults (≥18 years of age); however, data regarding the efficacy of these medications in children are limited.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

211.4 Complex Regional Pain Syndrome

James J. Nocton

Complex regional pain syndrome (CRPS) is characterized by chronic, persistent limb pain, often burning in character. **CRPS type 1**, also termed *reflex sympathetic dystrophy*, has no evidence of nerve injury, whereas the less common **CRPS type 2** is associated with a known mechanism of nerve injury. The pain of CRPS is typically extreme and disproportionate to the inciting event. Associated features include **allodynia** (a heightened pain response to normally non-noxious stimuli), **hyperalgesia** (exaggerated pain reactivity to noxious stimuli), swelling of the affected extremity, and indicators of **autonomic dysfunction** (cyanosis, mottling, hyperhidrosis).

There are no diagnostic criteria specifically for pediatric CRPS; in adults, several sets of criteria have been developed (Table 211.10); the clinical utility of these criteria is controversial. The diagnosis of CRPS is clinical and can be made when continuous pain is present that is disproportionate to any potential inciting event with associated allodynia, or hyperalgesia, evidence of edema, skin blood flow abnormalities, or excessive sweating activity, and exclusion of other disorders. Other features that may be present include atrophy of hair or nails, loss of joint mobility, weakness, tremor, and dystonia.

Although many pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a significant proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 years, and females outnumber males with the disease by as much as 6:1. Childhood CRPS differs from the adult form in that lower extremities, rather than upper extremities, are most often affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late. Left untreated, CRPS can have severe consequences for children, including bone demineralization, muscle wasting, and joint contractures.

The **treatment** of CRPS, like that of more diffuse pain syndromes, is ideally multidisciplinary. Aggressive physical therapy (PT) should be initiated as soon as the diagnosis is made, and CBT added as needed. **PT** is recommended three to four times a week, and children may need analgesic premedication at the onset, particularly before PT sessions. PT is initially limited to desensitization and then moves to weight bearing, range of motion, and other functional activities. CBT used as an adjunctive therapy targets psychosocial obstacles to fully participating in PT and provides pain-coping skills training. The goal of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. Multiple studies have shown that noninvasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

211.5 Erythromelalgia

James J. Nocton

Children with erythromelalgia experience episodes of intense burning pain, erythema, edema, and heat, most often in the hands and feet (Fig. 211.3) and less frequently in other locations. Symptoms are most often triggered by exposure to heat or exercise and typically last for hours to days. Erythromelalgia is more common in females during adolescence, and the diagnosis is often delayed for many years. Although many cases are sporadic, an autosomal dominant hereditary form results most often from gain-of-function pathogenic variants of the *SCN9A* gene, which encodes the alpha subunit of the sodium channel $Na_V1.7$ found in nociceptive neurons that transmit pain signals. Age of onset for the

Table 211.6 Clinical Features of Human Disorders Caused by Pathogenic Gene Variants in Ion-Channel Genes that Lead to Altered Pain Perception and Are Inherited in a Mendelian Manner

	GENE (PROTEIN)	TYPE AND EFFECT OF GENE VARIANT	MAIN PHENOTYPE	ADDITIONAL FEATURES
Inherited erythromelalgia	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset by age 20 yr; episodic pain triggered by warmth; feet affected more frequently than hands	Erythema of feet
Paroxysmal extreme pain disorder	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset at birth; episodic pain; sacral region is affected most frequently; face is affected more often than the limbs; physical triggers include defecation	Erythema of the sacrum; tonic attacks
Small-fiber neuropathy	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset at any age but more common in early adulthood; persistent burning pain; feet affected more frequently than hands	Could be autonomic features
Small-fiber neuropathy	*SCN10A* ($Na_v1.8$)	Heterozygous, activating	Persistent burning pain	Could be autonomic features
Familial episodic pain syndrome type I	*TRPA1* (TRPA1)	Heterozygous, activating	Onset at birth or in infancy; episodic chest or arm pain; triggers are hunger and cold	
Familial episodic pain syndrome type III	*SCN11A* ($Na_v1.9$)	Heterozygous, activating	Onset in first decade; episodic hand and foot pain; triggers are intercurrent illness or exercise	

Na_v Sodium ion channel.
Modified from Bennett DLH, Woods CG. Painful and painless channelopathies. *Lancet Neurol*. 2014;13:587–599, Table 1.

Table 211.7 American College of Rheumatology Fibromyalgia Diagnostic Criteria (2016 Revision)

The following three conditions must be met:

1. Widespread Pain Index (WPI) ≥7 and Symptom Severity Scale (SSS) score ≥5 *or* WPI 4-6 and SSS score ≥9.
2. Generalized pain, defined as pain in at least four of five regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
3. Symptoms have been generally present for at least 3 mo.

ASCERTAINMENT OF WPI

The WPI is the number of areas in which a patient has had pain over the last week. The score will be between 0 and 19: Left Upper Region: left jaw, left shoulder girdle, left upper arm, left lower arm; Right Upper Region: right jaw, right shoulder girdle, right upper arm, right lower arm; Left Lower Region: left hip (buttock, trochanter), left upper leg, left lower leg; Right Lower Region: right hip (buttock, trochanter), right upper leg, right lower leg; Axial Region: chest, abdomen, upper back, lower back, and neck.

ASCERTAINMENT OF SSS SCORE

The SSS score is the sum of the severity of three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) over the past week (each given a score from 0 to 3) *plus* the sum of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 mo: headaches, pain or cramps in the lower abdomen, and depression (each given a score from 0 to 1). The final score will be between 0 and 12. For fatigue, waking unrefreshed, and cognitive symptoms, the level of severity over the past week is rated using the following scale:

0 = No problem

1 = Slight or mild problems, generally mild or intermittent

2 = Moderate, considerable problems, often present and/or at a moderate level

3 = Severe: pervasive, continuous, life-disturbing problems

- For headaches, pain or cramps in the lower abdomen, and depression, the severity for each is scored as 0 or 1.

Adapted from Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46(3):319–329.

Table 211.8 Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (AAPT) Fibromyalgia Diagnostic Criteria

Core diagnostic criteria:

1. Musculoskeletal pain defined as 6 or more pain sites from a total of 19 possible sites (see Fig. 211.2)
2. Moderate to severe sleep problems OR fatigue
3. Musculoskeletal pain plus fatigue or sleep problems must have been present for at least 3 mo

NOTE: The presence of another pain disorder or related symptoms does not rule out a diagnosis of fibromyalgia. However, a clinical assessment is recommended to evaluate for any condition that could fully account for the patient's symptoms or contribute to the severity of the symptoms.
Adapted from Arnold LM, Bennett RM, Crofford LJ, et al. AAPT Diagnostic Criteria for Fibromyalgia. *J Pain*. 2019;20:611–628.

familial form ranges from 1 to 16 years. **Secondary** erythromelalgia is associated with many disorders, including myeloproliferative diseases, peripheral neuropathies, frostbite, and rheumatic diseases. The differential diagnosis includes Fabry disease, Raynaud phenomenon or disease, reflex sympathetic dystrophy, and peripheral neuropathies. In contrast to Raynaud phenomenon, the pain in erythromelalgia is relieved by cooling the affected area. Treatment includes avoidance of heat exposure and other precipitating situations and the use of cooling techniques that do not cause tissue damage during attacks. There is no proven reliably efficacious treatment, and NSAIDs, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), antidepressants, sodium nitroprusside, magnesium, mexiletine, and misoprostol, as well as biofeedback, medical and surgical nerve blocks, and hypnosis have had variable efficacy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Widespread Pain Index
(1 point per circle; score range: 0–19 points)

Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Fill in the circles on the diagram for each area in which you have had pain or tenderness.

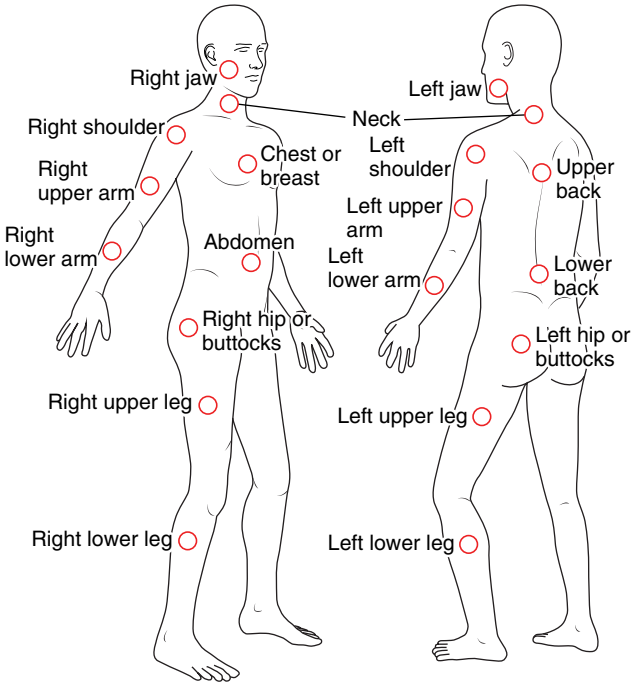

Fig. 211.2 Widespread pain index. *(Modified from Fraix M. Fibromyalgia. In Tallia AF, Scherger JE, Dickey NW (eds). Swanson's Family Medicine Review, 9th ed. Philadelphia: Elsevier, 2022. Fig 47.1.)*

Table 211.9 Suggested Diagnostic Criteria for Juvenile Primary Fibromyalgia Syndrome (JPFS)

MAJOR CRITERIA
1. Generalized musculoskeletal aching at three or more sites for ≥3 mo
2. Absence of an underlying condition/cause
3. Normal laboratory tests
4. Five or more typical tender points*
MINOR CRITERIA
1. Chronic anxiety or tension
2. Fatigue
3. Poor sleep
4. Chronic headaches
5. Irritable bowel syndrome
6. Subjective soft tissue swelling
7. Numbness
8. Pain modulated by physical activities
9. Pain modulated by changes in weather
10. Pain modulated by anxiety/stress

*Thirty-one potential tender points were listed for these criteria when proposed in 1985. JPFS is diagnosed when all major criteria are met, plus three of the minor criteria or when there are four tender points and five minor criteria.
Adapted from Coles M, Weissmann R, Uziel Y. Juvenile primary fibromyalgia syndrome: Epidemiology, etiology, pathogenesis, clinical manifestations and diagnosis. *Pediatr Rheumatol Online J.* 2021;19(1):22.

Table 211.10 Budapest Clinical Diagnostic Criteria for Complex Regional Pain Syndrome

All of the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in each of the following four categories:
   - *Sensory*: Hyperesthesia and/or allodynia
   - *Vasomotor*: Temperature asymmetry, skin color changes, and/or skin color asymmetry
   - *Sudomotor/edema*: Edema, sweating changes, and/or sweating asymmetry
   - *Motor/trophic*: Decreased range of motion, motor dysfunction (tremor, weakness, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following four categories:
   - *Sensory*: Evidence of hyperesthesia (to pin prick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure, and/or joint movement)
   - *Vasomotor*: Evidence of temperature asymmetry (>1°C), skin color changes, and/or skin color asymmetry
   - *Sudomotor/edema*: Edema, sweating changes, and/or sweating asymmetry
   - *Motor/trophic*: Decreased range of motion, motor dysfunction (tremor, weakness, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

Adapted from Harden RN, Bruel S, Stanton-Hicks, et al. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med.* 2007;8:326–331.



Fig. 211.3 Characteristic redness and edema of the foot associated with erythromelalgia. *(From Pfund Z, Stankovics J, Decsi T, Illes Z. Childhood steroid-responsive acute erythromelalgia with axonal neuropathy of large myelinated fibers: a dysimmune neuropathy? Neuromuscul Disord. 2009;19:49–52, Fig. 1A, p. 50.)*

Chapter 212

Chronic Overlapping Pain Conditions

Thomas C. Chelimsky and Gisela G. Chelimsky

In chronic overlapping pain conditions **(COPCs)**, several painful symptoms affecting different body systems coexist without clear underlying pathophysiology. Other terms for COPCs include **medically unexplained symptoms**, **functional somatic syndromes** (FSS), and **central sensitivity syndromes**. These disorders are probably highly prevalent; for example, two COPCs, irritable bowel syndrome (IBS) and migraine, *each* affect 10–20% of the population. Pediatric COPC studies usually focus on populations with one painful condition (headaches) and their psychiatric comorbidities, rather than somatic comorbidities. The overlap of these disorders with psychiatric conditions has led both the public and the medical specialists to dichotomize these disorders artificially into "physical," by implication, "real" disorders and "psychologic," by implication, "not real" disorders. This classification ignores the unity of brain and body and hinders progress in understanding these disorders. COPC connotes a nonassumptive neutral position, appropriately attributing no assumed pathophysiology to the disorder, in contrast to other terms, such as "medically unexplained syndrome," subtly suggesting a psychologic process, more strongly implied in the term "functional."

PREVALENCE

The prevalence of COPCs is unknown depending on which symptom is being assessed and how much overlap exists across disorders. A large study from 28 countries (about 400,000 participants) found a prevalence of headache of 54%, stomachache 50%, and backache 37%, occurring at least once a month for at least 6 months. Females had a higher prevalence of having all three complaints when compared with males; the prevalence increased with age. These three pain syndromes, headache, stomachache, and backache, frequently coexist.

IBS and chronic abdominal pain affect 6–20% of children and adolescents. Idiopathic musculoskeletal pain affects about 16% of schoolchildren age 5-16 years and is often associated with sleep disturbances, headache, abdominal pain, daytime tiredness, and feeling sad. Migraines present >6 months occur in about 8% of the population (children and adolescents <20 years). Fibromyalgia is present in 1.2–6%. The prevalence of chronic disabling fatigue increases during adolescence from about 1.9% at age 13 to 3% at 18 years. As with most COPCs, fibromyalgia has many comorbid disorders, such as sleep disturbance, fatigue, headache, sore throat, joint pain, and abdominal pain. The American College of Rheumatology definition of fibromyalgia incorporates some of these comorbid conditions.

SYMPTOM/DISORDER OVERLAP

Diagnostic criteria of many of these disorders overlap with one another, making differentiation between two disorders more of a semantic issue rather than a clinical differentiation. **Chronic fatigue syndrome (CFS)**, clinically the most concerning symptom, shares many of the diagnostic criteria with fibromyalgia. Patients with a single pain condition, such as fibromyalgia, CFS, IBS, multiple chemical sensitivity (MCS), headaches, or temporomandibular joint disorder (TMJD), will typically have another disorder. This overlap of symptoms may reflect a shared pathophysiology, possibly a central nervous system (CNS) dysfunction, as was implied in the prior term "central sensitization syndrome." A CNS pathophysiology would also explain the "invisibility" of these disorders to usual screening tools that most often target an end organ.

COPCs also harbor many symptoms that are not strictly "pain," although they may be equally or more disabling. Adolescents seen in a tertiary referral center with a **functional gastrointestinal disorder (FGID)** also manifest dizziness, chronic nausea, chronic fatigue, and sleep disturbance, as well as migraines. Up to 50% of adolescents complain of weekly fatigue, and 15%, daily fatigue. COPCs are studied in their discipline-specific silos rather than collectively as a group.

Migraine headaches are frequently associated with anxiety and depression. **Anxiety** also predicts the persistence of migraine headaches. Sleep disturbance and migraine also interact closely. Poor sleep can trigger a migraine or a migraine cluster; migraine headache itself disturbs sleep. Juvenile fibromyalgia is associated with sleep disturbances such as prolonged sleep latency, frequent awakening, less total sleep time, and periodic limb movements. Adult patients with IBS also have sleep disturbances, correlating with anxiety, depression, and stress.

The *comorbidities* of **hypermobility Ehlers-Danlos (hEDS)** and **postural orthostatic tachycardia syndrome (POTS)** with COPC have been significant. Patients with hEDS may complain of widespread and sometimes debilitating pain with or after activity, severe fatigue, handwriting difficulties, "cracking" of joints, joint swelling, joint dislocation, subluxation, or back pain. The chronic pain reduces exercise tolerance, with poorer quality of life and an ever-worsening cycle because exercise is a key piece of management. Patients with FGID may also have hEDS, fibromyalgia, chronic pain, and higher somatizations scores than those with organic gastrointestinal (GI) disorders.

The diagnosis of pediatric POTS requires an increase in heart rate >40 beats/min in the first 10 minutes of upright tilt test associated with orthostatic symptoms. POTS is also associated with multiple comorbidities, including sleep disruption, chronic pain, Raynaud-like symptoms, GI abnormalities, and less frequently, headaches, syncope, and urinary complaints. Patients with both POTS and hEDS usually have more migraines and syncope than those with POTS alone. The prevalence of comorbid disorders in children with COPC is identical whether they have POTS or hEDS.

PSYCHIATRIC COMORBIDITIES

Many of these disorders have significant psychiatric comorbidities. Juvenile fibromyalgia is associated with anxiety disorders and major mood disorders. Children with medically unexplained symptoms generally have more anxiety and depression than children with other chronic disorders. Other associations include disruptive behaviors, symptom internalization, fearfulness, greater dependency, hyperactivity, and concern about sickness.

PREDISPOSING FACTORS

Female gender and older age (adolescence) increase the risk of COPCs. Certain conditions (e.g., headache) are more common in males or have similar prevalence across genders during childhood, but the prevalence in females increases after puberty. Trauma or posttraumatic stress disorder increases psychologic comorbidities in juvenile fibromyalgia. Some studies suggest that anxiety predisposes to chronic pain. A population-based study following children from 18 months to 14 years of age suggested that maternal psychologic distress in early childhood and depressive and pain complaints in preadolescence increase the risk of recurrent abdominal pain at age 14. Postinfectious IBS is an identifiable risk factor for new-onset anxiety, depression, and sleep disruption in adults. Children with recurrent abdominal pain often have parents with abdominal pain. It is unclear if this association is caused by a common environmental/genetic factor or a learned behavior of the child imitating the parent.

NATURAL HISTORY

The natural history of COPC is not well known. Chronic disabling fatigue in the general adolescent population persists 2-3 years in about 25% of patients, but only 8% of youth affected at age 13 still had the complaints at ages 16 and 18. A meta-analysis suggests that the prognosis of CFS in children is usually good, with a small minority having persistent disabling symptoms. The patient's belief in an underlying

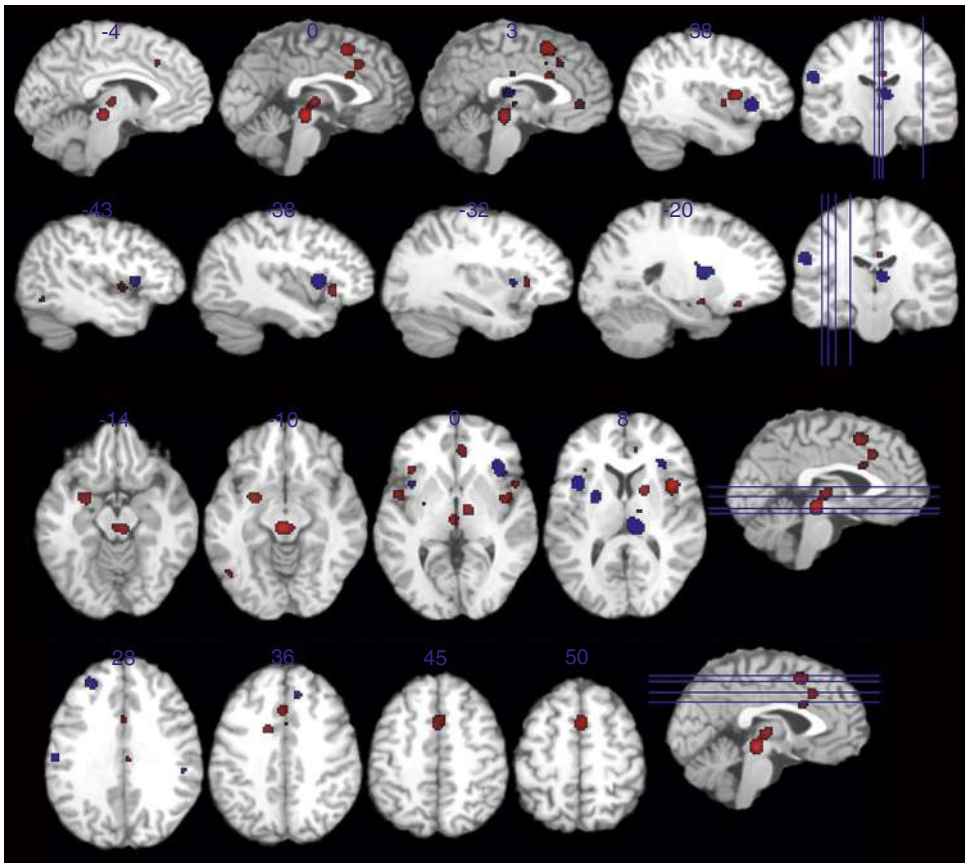

Fig. 212.1 Brain areas demonstrating more *(red)* or less *(blue)* activation in irritable bowel syndrome compared with healthy control in a meta-analysis of rectal distention. *(From Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastroenterology. 2011;140:91–100, Fig. 3.).*

physical disorder and the presence of psychiatric comorbidities predict a poorer outcome.

In a study of children with FGID, the outcome depended on specific variables. Those who perceived their abdominal pain as more threatening, with high levels of pain catastrophization and little capacity to cope with pain because of reduced activity levels, had a poorer outcome. This "high pain dysfunctional profile" subgroup was predominantly female (70%) with a mean age of 12.2 years. Two thirds of this subgroup still complained of FGID at follow-up vs about one third of those in the other groups. These groups included a "high pain adaptive profile" group with similar pain levels but better adaptive skills and less catastrophization, predominantly slightly younger (11.8 years) females, and a "low pain adaptive profile" group, slightly younger (11.1 years), with equal males and females but less abdominal pain, better coping mechanisms, and less impairment of daily activities. In the high pain dysfunctional profile group, 41% had both FGID and nonabdominal chronic pain at follow-up vs 11% in the high pain adaptive and 17% in the low pain adaptive group. Another study following children ages 4-16.6 years with IBS demonstrated resolution of symptoms in 58%, usually without medication. The differences between these studies may result from the age of the groups, with better outcome in the younger patients, as well as the number of comorbidities and psychologic profile. Similarly, in juvenile fibromyalgia, symptoms are still present 2-6 years later in about 60% of affected children. The psychiatric comorbidities, mainly depression, and controlling family environments are associated with a poor prognosis.

PROPOSED PATHOPHYSIOLOGY

There may be dysfunction in the hypothalamic-hypophyseal-adrenal axis, circadian patterns, autonomic responses, some aspects of CNS processing, the inflammatory immune response, and the musculoskeletal system. Vagal tone measured by heart rate variability is decreased in some children with FGID symptoms and in children with COPCs. Alterations in the autonomic nervous system may affect the immune system and circadian patterns. The stress response may increase muscle tone, which in turn leads to body aches and tension headaches. In fibromyalgia the cortisol response is altered, with lower cortisol levels on awakening and throughout the day. **Orthostatic intolerance** from autonomic abnormalities may also contribute to poor concentration from brain hypoperfusion and blood pooling in the lower extremities.

The pathophysiology has been better studied in myalgic encephalomyelitis (ME)/CFS. ME/CFS has been associated with joint hypermobility, orthostatic intolerance, decreased range of motion, and reduced activity. These patients demonstrate excessive glial activation resulting in neuroexcitation, neuroinflammation, and possibly neurodegeneration. These features may contribute to the cognitive issues and fatigue present in this disorder.

Neuroinflammation and other changes in processing may lead to abnormal descending inhibitory pain pathways, resulting in distal pain and "central sensitization." The malfunction of descending antinociceptive pathways allows pain to spread in the body, associated with increased activity of the nociceptive facilitator pathways. These facilitator pathways are further activated by psychologic factors, such as catastrophization, depression, lack of acceptance, and hypervigilance. Other signals such as pressure, sound, heat, and cold are also aberrantly processed, with activation of areas of the brain that are typically activated only by acute pain stimuli, such as the insula, prefrontal cortex, and anterior cingulate cortex, as well as some regions usually not involved in pain processing.

The neuromechanisms involved in dysregulated brain-gut interactions in patients with FGID include changes in functional connectivity between brain regions associated with nociceptive processing and the somatosensory cortexes. Enhanced sensory processing of the gut homeostasis (homeostatic afferent) and attentive responses to salience stimuli (salience network) as well as changes in certain brain regions are noted in patients with FGID (Fig. 212.1). These alterations affect the perception of pain and may affect the endocrine and autonomic nervous systems. What was once called FGIDs is currently considered disorders of gut-brain interactions. Proposed mechanisms are noted in Figure 212.2. Research investigating the role of the microbiome in regulating microglia, astrocytes, and immune cells may lead to central sensitization and chronic pain.

TREATMENT

In general, *chronic pain should never be treated with opioids*; **cognitive-behavioral therapy (CBT) and a gradually progressive exercise program**

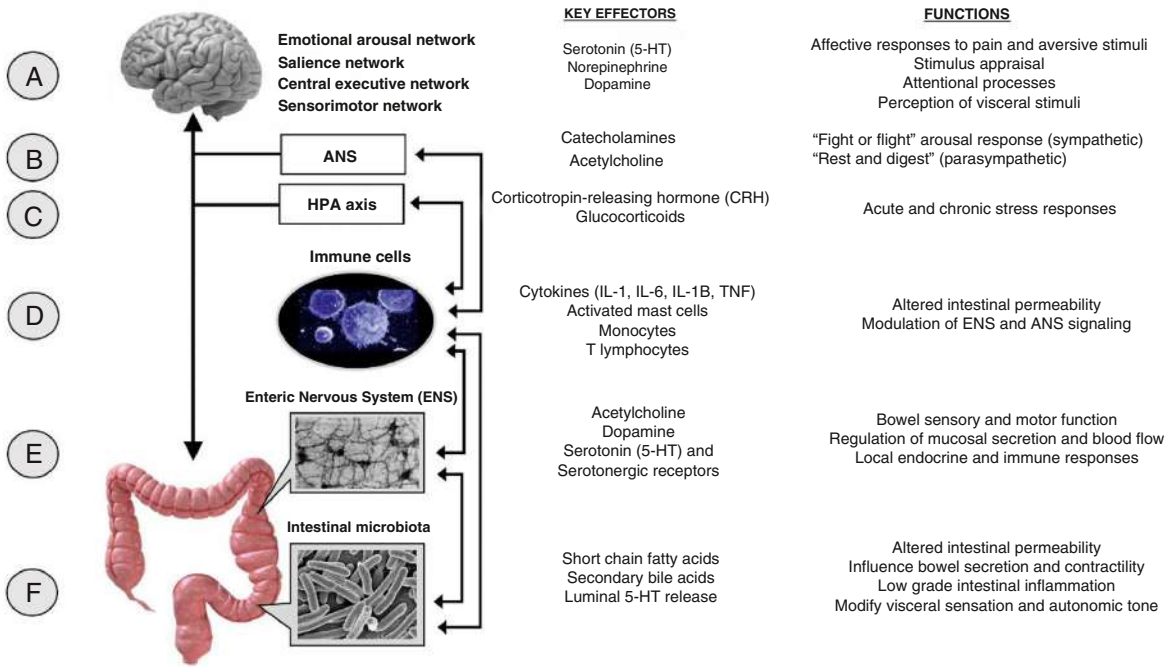

Fig. 212.2 Key effectors and functions of the brain-gut-microbiota axis. ANS, autonomic nervous system; HPA, hypothalamic pituitary axis. *(From Tait C, Sayuk GS. The brain-gut-microbial axis: A framework for understanding functional GI illness and their therapeutic interventions. Eur J Int Med. 2021;84:1–9, Fig. 2.)*

constitute the cornerstones of treatment. The complex comorbid nature of COPCs typically requires a multidisciplinary approach. Because neither CBT nor exercise will have any effect in the absence of full patient engagement and understanding, the team must include the family and the patient, a pain psychologist with experience in CBT, a physical therapist, and the primary care physician. Depending on comorbid conditions, rheumatology, neurology, or gastroenterology may have important roles for symptom management and a possible alternative diagnosis. Depending on the initial symptomatology, the differential diagnosis should include inflammatory bowel disease, celiac disease, juvenile idiopathic arthritis, systemic lupus erythematosus, dermatomyositis, autoinflammatory disorders, Fabry disease, porphyrias, hereditary sensory-autonomic neuropathies, and Ehlers-Danlos syndrome. Red flags suggesting a medical/organic etiology for abdominal pain (Table 212.1), headache (Tables 212.2 and 212.3), and musculoskeletal pain (Table 212.4) must be assessed.

When a thorough evaluation for a structural cause of symptoms is unrevealing, an important next step is patient and family education. This should include the common presentation, the expectation that "markers" for these types of disorders would typically be absent, and the presence of solid management tools with high probability of improvement. Families and patients need to receive encouragement to stop seeking a "magic diagnosis and cure" and to begin the path to full recovery. Without this step, critical patient engagement in the treatment will not occur. In our practice, we sometimes call *functional* disorders a problem of "software," in contrast to *structural* issues that would involve "hardware." We explain that successful management must change the software, not just mask symptoms. Approaches that accomplish such a goal include CBT and a rehabilitative program that may require physical therapy, a vigorous exercise program with interval training, meditation, and/or yoga. Patients are often deconditioned and may need to start with a very low level of physical activity. In addition, their exercise tolerance may be significantly hampered by an orthostatic intolerance syndrome (e.g., POTS). For these reasons, we frequently recommend starting with a *water aerobics* program, which provides several benefits: (1) very low gravitational force, so the patient can be set up for success, working only on conditioning and not simultaneously fighting an orthostatic challenge; (2) builds both limb and core strength; and (3) gentle on joints for those with arthralgias or a hypermobility syndrome. When water is unavailable, we recommend starting with a recumbent exercise program such as a recumbent stationary bike. In both circumstances, we then slowly introduce upright aerobic activities on land over 2-3 months. Strength exercises are also useful. A Cochrane review in adults with painful disorders showed exercise to have minimal side effects and to improve functionality, reduce pain, and improve quality of life. Patients with fibromyalgia who undergo a 3-month multidisciplinary program with twice-weekly physical therapy and CBT benefited in function and physical activity level, and most importantly continued to exercise regularly at 1 year follow-up. Pharmacologic interventions have less impact than nonmedical treatments.

When children are missing school or are homebound, it is important to work closely with the school to encourage reentry. This may require modifying the school schedule initially, starting with fewer hours at school, and providing extra time for homework on days that the children are not feeling well.

Although medications such as tricyclic antidepressants are often added to the treatment, the improvement with these medications for chronic pain is minimal, and the side effects need to be considered. Nonetheless, amitriptyline and anticonvulsants like gabapentin are often used because they help in treating headaches and abdominal pain and improve sleep quality, a critical element to manage any chronic pain condition.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

212.1 Chronic Fatigue Syndrome

Mark R. Magnusson

Chronic fatigue syndrome **(CFS)**, also known as **myalgic encephalomyelitis (ME)**, is a complex, diverse, and debilitating illness characterized by chronic or intermittent fatigue accompanied by select symptoms and occurring in children, adolescents, and adults. The combination of fatigue and other symptoms interferes significantly with daily activities and has no identified medical explanation (Fig. 212.3). The fatigue does not require exertion by the patient, nor does rest relieve it. Some consider **postexertion malaise**, or worsening of

Table 212.1 Red Flags and Clues to an Organic Cause of Abdominal Pain

Age <4 yr old
Localized pain in nonperiumbilical site
Referred pain
Sudden onset of excruciating pain
Crescendo nature of pain
Sudden worsening of pain
Fever (high fever >39.4°C suggests pneumonia, pyelonephritis, dysentery, cholangitis, more than perforation or abscess)
Jaundice
Distention*
Dysphagia
Dysuria
Emesis (especially bilious)
Anorexia
Weight loss, failure to thrive
Positive family history (metabolic disorders, peptic ulcer disease)†
Change in urine or stool color (blood, acholic) or frequency
Vaginal discharge
Menstrual abnormalities (amenorrhea)
Sexual activity
Delayed sexual development (chronic pain)
Anemia
Elevated erythrocyte sedimentation rate
Elevated stool calprotectin
Specific physical findings (hepatomegaly, splenomegaly, absent bowel sounds, adnexal tenderness, palpable mass, involuntary guarding, focal or diffuse tenderness, positive rectal examination results, perianal disease, joint swelling, rashes)

*Consider the five Fs: fat, feces, flatus (aerophagia, obstruction), fluid (ascites, hydronephrosis, cysts), fetus (pregnancy or fetal-like abnormal growth [e.g., tumors]).
†Family history is also positive for chronic pain syndromes (constipation, irritable bowel, dysmenorrhea, and lactase or sucrase deficiency).
Modified from Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 13.8, p. 229.

Table 212.3 Physical Examination Red Flags for Secondary Headaches

Abnormal vital signs:
Hypertension
Growth failure
Increased head circumference or bulging fontanel
Fever
Meningeal signs with or without fever
Evidence of cranial trauma
Cranial bruit
Frontal bony tenderness
Macrocephaly
Abnormal ophthalmologic findings:
Papilledema
Abnormal ocular movements
Squinting
Pathologic pupillary response
Visual field defects
Abnormal neurologic findings:
Impaired mental status
Cranial nerve palsy
Ataxia
Abnormal gait
Abnormal coordination
Abnormal reflexes
Asymmetric motor or sensory examination
Hemiparesis
Developmental regression
Precocious, delayed, or arrested puberty
Skin findings:
Café-au-lait or ash leaf macules
Petechiae or purpura
Facial hemangioma
Malar rash

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.6, p. 553.

Table 212.2 History-Related Red Flags for Secondary Headaches

Quality:
"Thunderclap" rapid-onset headache or the "worst headache of my life"
Recent worsening in severity or frequency
Change in quality
New-onset symptoms consistent with cluster headache
Location:
Unilateral without alteration of sides
Chronic or recurrent occipital headache
Timing:
Awakens from sleep
Occurs in morning or causes morning vomiting
Acute or chronic progressive pattern
Positional or activity-related variations:
Worsened in the recumbent position or when bending over
Headache experienced or worsened with cough or the Valsalva maneuver
Associated neurologic history:
Neurologic dysfunction other than typical aura
Altered sensorium during headache
Sensory deficits or changes in vision, gait, or coordination
Other focal neurologic deficits
Seizures or syncope
Decreased visual acuity
Mental status changes (e.g., confusion or disorientation)
Regression in fine or gross motor developmental skills
Decline in cognition or school performance
Change in mood, behavior, or personality
Associated general history:
Vomiting without nausea and morning/fasting nausea or vomiting
Polyuria or polydipsia
Preschool or younger age
History of head trauma
Neck pain:
Medical comorbidities
History of ventriculoperitoneal shunt
Certain medications
Signs of systemic or localized head/neck infection
Negative family history of primary headache disorders

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.5, p. 553.

Table 212.4 Musculoskeletal/Joint Pain Warning Signals Requiring Further Workup

- Arthritis: Erythema, warmth, swelling, pain on palpation
- Pain/stiffness in the morning
- Abnormal radiographic findings
- Pain at rest, relieved by activity
- Pain at night: Worsened by massage, analgesics ineffective
- Refusal to walk
- Extremity atrophy
- Bony tenderness
- Poor growth
- Weight loss
- Fever
- Rash
- Abnormal blood results: Including complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate

Modified from Friedrichsdorf SJ, Giordano J, Dakoji KD, et al. Chronic pain in children and adolescents: Diagnosis and treatment of primary pain disorders in head, abdomen, muscles and joints. *Children*. 2016;3:42, Table 3.

the fatigue with additional symptoms after mental or physical exertion and lasting >24 hours, to be characteristic of CFS. A definitive causal agent or process has not been identified, although the differential diagnosis includes infectious, inflammatory, metabolic, genetic, and autoimmune diseases. Our understanding of this condition is largely from studies of adults and adolescents, with limited descriptions of chronic fatiguing illnesses in younger children.

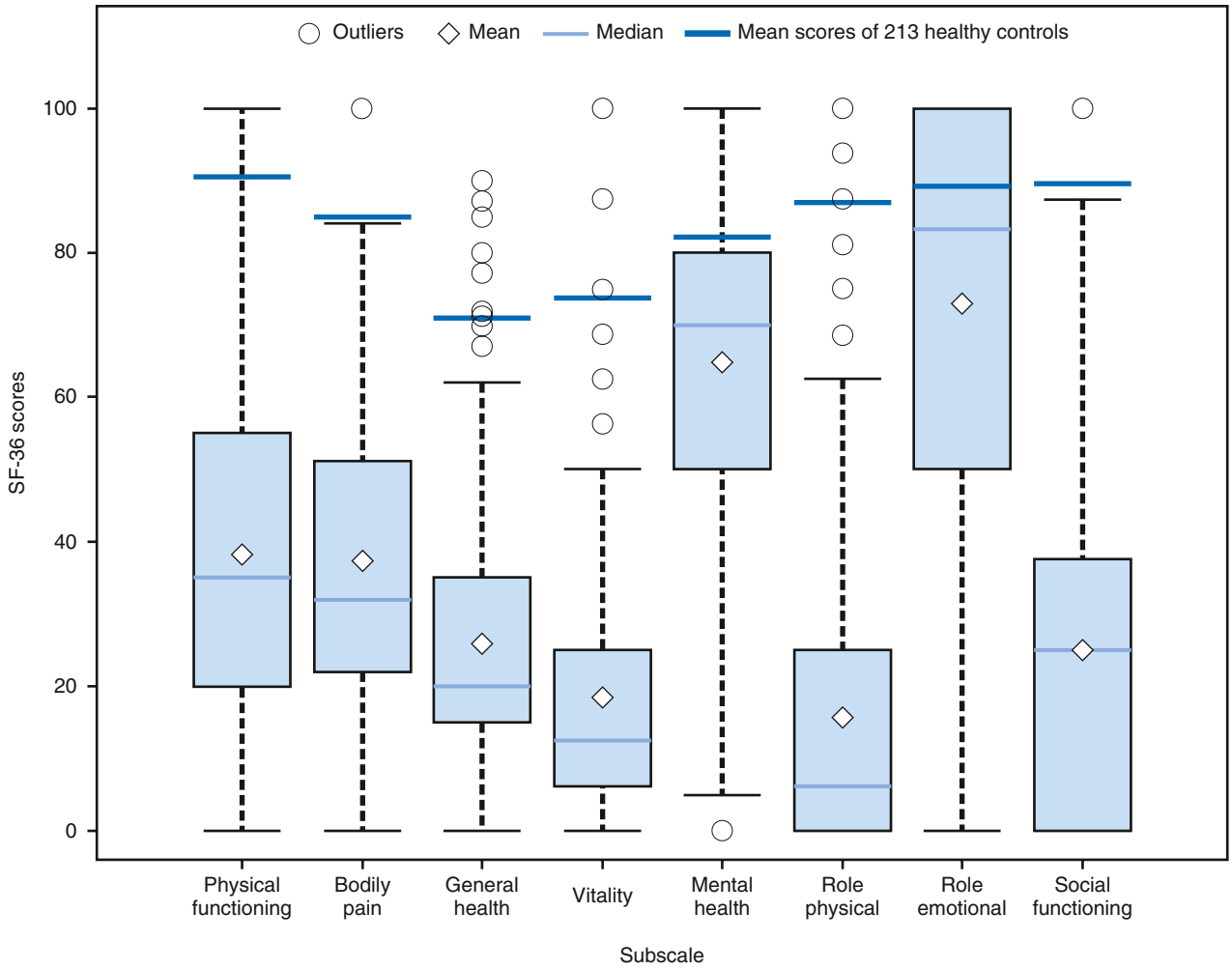

Fig. 212.3 Functional status* of 471 patients enrolled in the CDC Multisite Clinical Assessment† of ME/CFS§—United States, September 2015. *Measured by box plots of scores in the eight subscales of Short-Form Health Survey (SF-36) scores (25th and 75th percentile at *bottom* and *top* of box). SF-36 scores range from 0 to 100, with higher scores indicating better functioning. †https://www.cdc.gov/cfs/programs/clinical-assessment/index.html. §ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) patients show significant impairment, particularly in vitality and physical functioning subscale scores, but with preservation of mental health and emotional role functioning. *(From Unger ER, Lin JMS, Brimmer DJ, et al. CDC Grand Rounds: Chronic fatigue syndrome—advancing research and clinical education. MMWR. 2016;65[50–51]:1434–1438.)*

The illness was formally defined in 1988 as *chronic fatigue syndrome* because persistent unexplained fatigue was considered the principal and invariable physical symptom. A variety of other names have been used to describe the illness, including *chronic mononucleosis, chronic Epstein-Barr virus (EBV) infection, postinfection syndrome,* and *immune dysfunction syndrome.* Several case definitions have been developed and are in use in both clinical care and research (Table 212.5).

The Institute of Medicine (IOM) 2015 recommendations apply to all ages and include a special focus on pediatrics. The IOM suggested new diagnostic criteria and a new name, **systemic exertion intolerance disease (SEID)**, to emphasize the postexertion malaise criterion and better understand the illness (Table 212.6).

EPIDEMIOLOGY

Based on worldwide studies, 0.2–2.3% of adolescents or children have CFS. Most epidemiology studies use the 1994 definition. CFS is more prevalent in adolescents than in younger children. The variation in CFS prevalence estimates may result from variations in case definition, study methodology and application, study population composition (specialty vs general practice or general population), and data collection (parent, self-reporting vs clinician evaluation). Gender distribution in children differs from that in adults, with a more equal distribution in children <15 years old, while remaining two-fold to three-fold higher in females 15-18 years old. Few studies have reported the incidence of CFS among children <10 years old. In adolescents in the Netherlands, the pediatrician-diagnosed incidence of CFS/ME was 0.01%, and in the United Kingdom, 0.5%.

PATHOGENESIS

Although the etiology and pathophysiology of CFS are unknown, some patients and clinicians correlate the onset with a recent episode of a viral illness such as infectious mononucleosis (10–12%) (EBV; see Chapter 301). A pathophysiologic relationship of CFS to infection is suggested because the symptoms and biologic markers elicited by the nonspecific innate host responses to infections in general are present in CFS. CFS-like illness after infectious mononucleosis is not predicted by viremia or altered host response to EBV infection, but is associated with the severity of the primary infection. A wide variety of other candidate viral infections have been associated with postinfectious fatigue syndromes, particularly in adolescents and adults. SARS CoV-2/COVID-19 infection has also been implicated, as patients with a history of COVID-19 infection have presented with symptoms similar to patients with ME/CFS, labeled long COVID, post-acute sequalae of SARS CoV-2 infection (PASC), or post–COVID-19 conditions (Table 212.7) (see

Table 212.5 Overview of Current Case Definitions for Systemic Exertion Intolerance Disease (SEID) and Past Definitions of Chronic Fatigue Syndrome or Myalgic Encephalomyelitis

SYMPTOM	SEID	CFS	ME
Fatigue and impairment of daily function	≥6 mo	≥6 mo	≥6 mo
Sudden onset	Yes	Yes	
Muscle weakness			Yes
Muscle pain		Yes	
Postexertional symptoms	Yes	Yes	Yes
Sleep disturbance	Yes		Yes
Memory or cognitive disturbances	Yes		Yes
Autonomic symptoms			Yes
Sore throat		Yes	
Lymph node involvement		Yes	
Cardiovascular symptoms	Yes		
Headaches		Yes	
Arthralgias		Yes	Yes

CFS, Chronic fatigue syndrome; ME, myalgic encephalomyelitis.
Data from Institute of Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Redefining an Illness*. Washington, DC: National Academies Press; 2015; Jason L, Evans M, Porter N, et al. The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. *Am J Biochem Biotechnol*. 2010;6:120–135; Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome—a clinically empirical approach to its definition and study. *BMC Med*. 2005;3:19.

Table 212.6 Criteria for Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Patient has each of the following three symptoms at least half the time to at least a moderately severe degree:

- A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for >6 mo and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.
- Postexertional malaise*
- Unrefreshing sleep*

Plus at least one of the two following manifestations (chronic, severe):

- Cognitive impairment*
- Orthostatic intolerance

*Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.
From Institute of Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*. Washington, DC: National Academies Press; 2015.

Table 212.7 WHO Definition of Long (Post)–COVID-19 Condition

- Post–COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 mo from the onset of COVID-19, with symptoms that last for at least 2 mo and cannot be explained by an alternative diagnosis.
- Common symptoms include fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on everyday functioning.
- Symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness.
- Symptoms might also fluctuate or relapse over time; a separate definition might be applicable for children.

Modified from Munblit D, O'Hara ME, Akrami A, et al. Long COVID: Aiming for a consensus. *Lancet Respir Med*. 2022;10(7):632–634.

Chapter 449.1). Similar features have been described in **post–intensive care syndrome.**

Similarities between CFS symptoms and those experienced by patients with autoimmune and other inflammatory disorders suggests primary perturbation of immune function in the pathogenesis of CFS. Hypogammaglobulinemia and hypergammaglobulinemia, immunoglobulin subclass deficiencies, elevated levels of circulating immune complexes, altered helper/suppressor lymphocyte ratios, natural killer cell dysfunction, elevated cytokines, and monocyte dysfunction have been inconsistently reported in adult patients with CFS. These findings have not been consistent among studies. CFS patients as a group differ from healthy controls, but most laboratory values of the immune parameters are not outside the normal range.

Autonomic nervous system (ANS) changes are suggested by the **orthostatic intolerance** (OI) experienced by some patients with CFS. OI syndromes with circulatory dysfunction include **neutrally mediated hypotension** and **POTS** and have been observed in some patients with CFS and could contribute to the syndrome. The pathophysiology of these manifestations among adolescents with CFS is unclear, but in postinfectious states could be associated with unreplenished fluid and electrolyte losses associated with acute infection or immune-mediated injury (autoantibodies directed against ANS).

Because the widespread musculoskeletal pain in CFS is similar to **fibromyalgia**, and because some consider these to be overlapping syndromes, fibromyalgia and CFS may share similarities in pathogenesis. Other hypotheses under investigation for the biologic basis of CFS involve alterations in energy metabolism (e.g., mitochondrion, particularly as related to exercise intolerance and postexertion malaise), alterations in sleep, the stress response, and the hypothalamic-pituitary axis. Understanding CFS has proved so challenging because it likely represents more than one underlying pathophysiology. Current studies and guidelines are attempting to stratify or subgroup patients to address this possibility.

CLINICAL MANIFESTATIONS

The dominant symptom expressed by adolescents and adults is a substantial reduction or impairment in the ability to engage in pre-illness levels of activity, accompanied by fatigue (see Fig. 212.2). In younger children, who often do not spontaneously report symptoms, exertion induces behavioral changes, manifested by a lack of their usual energy and reduced participation in activities. In adolescents, fatigue and postexertion malaise may lead to decreased participation in school, family activities, and social exchange.

Cognitive impairment includes reported difficulties in concentrating, which are common and indicated by reduced participation in school, difficulty keeping up with homework, and a drop in grades. Sleep may be impaired, and nonrestorative sleep is common. Other sleep complaints include difficulty falling asleep and staying asleep, whereas diagnosed sleep disorders, including restless legs syndrome, parasomnias, and sleep apnea, are less common. Myalgia and arthralgia may accompany fatigue and altered sleep. Sore throat and cervical lymph node tenderness can occur but may be part of an inciting illness. Adolescents also have increased reports of headache, abdominal pain, nausea, and sensitivity to light and sound with amplified pain.

Patients diagnosed with CFS in primary care practices are more likely to report abrupt onset of their symptoms, often as part of an initial virus-like illness, whereas gradual onset is more common in those identified in population-based studies. School absenteeism is a major social issue. In one study, two thirds of adolescents missed >2 weeks over a 6-week observation period, and one third required home tutoring. Unlike school phobia, inactivity due to CFS persists on the weekends and during holidays the same as it does during the school week.

Although fatigue and accompanying symptoms are subjective, the magnitude of impairment of each component can be measured by questionnaires addressing pain and function or, in the case of suspected orthostatic instability, by recording routine supine and standing heart rate and blood pressure measurements. Fatigue cannot be dismissed as a minor ailment. It generally manifests as lassitude, profound tiredness, intolerance of exertion with easy fatigability, and general malaise.

Abnormal physical examination findings are conspicuously absent, providing both reassurance and consternation for the patient, family, and physician. The presence of "alarm symptoms" such as weight loss, chest pain with exertion, paresthesia, dry mouth and eyes, fevers, diarrhea, cough, night sweats, and rash is uncommon and warrants consideration of a diagnosis other than CFS.

DIAGNOSIS

There are no pathognomonic signs or diagnostic tests for CFS. The diagnosis is clinically defined based on inclusion and exclusion criteria (Fig. 212.4). The diagnostic criteria are applicable to adults and adolescents >11 years old because of the current requirement for a self-generated history. Whereas duration of symptoms is 3-6 months depending on age, symptom management should not wait until this criterion is met.

CFS is difficult to diagnose in children, who may have difficulty describing their symptoms and articulating their concerns. Sole reliance on parental history can be fraught with confusion because parents may also struggle to interpret their children's symptoms and feelings in providing accurate historical information. A combination of child and parent reporting is most effective. It is important to document the child's activity levels and worsening of symptoms after physical or mental endeavors. Changes in participation in hobbies and family or other social activities can help identify the impact of CFS on function.

The diagnosis of CFS can be established only after other medical and psychiatric causes of fatigue and other symptoms, many of which are treatable, have been excluded. These include medical conditions presenting with chronic symptoms, such as hypothyroidism,

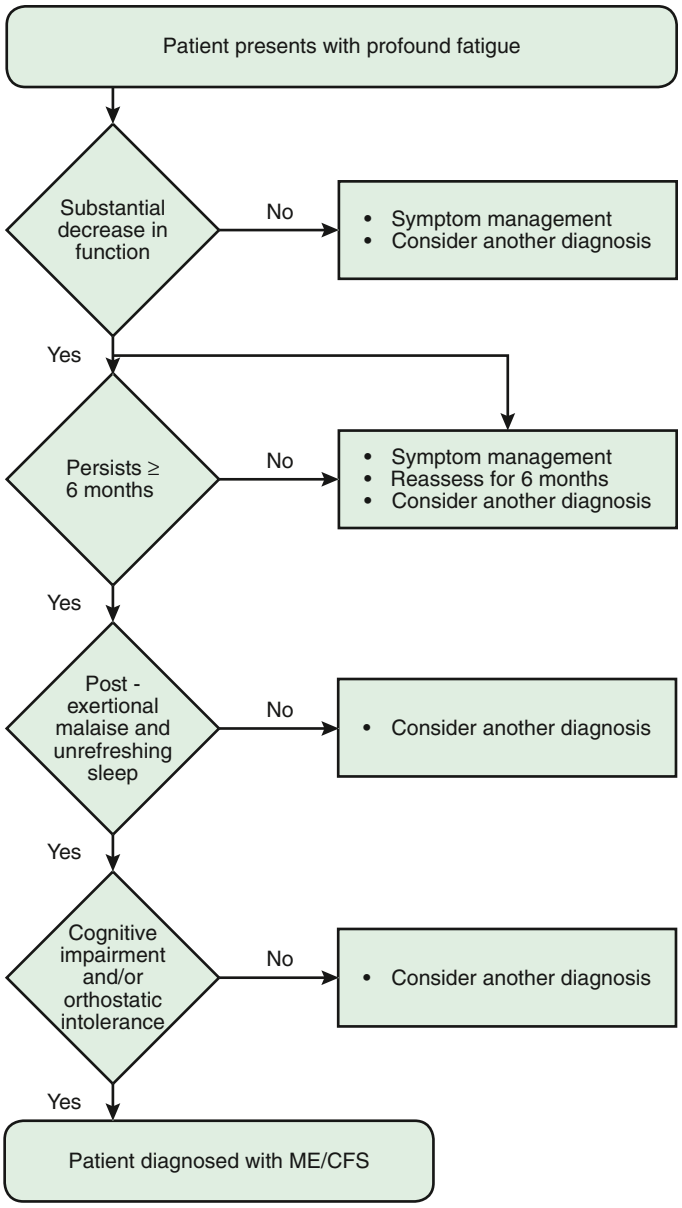

Fig. 212.4 Diagnostic algorithm for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). ANS, autonomic nervous system; HPA, hypothalamic-pituitary axis. *(From Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: National Academies Press; 2015.)*

adrenal insufficiency, respiratory and food allergies, sleep apnea, narcolepsy, substance abuse, posttraumatic stress disorder, adverse drug reactions, and obesity. A previously diagnosed medical condition with incomplete or uncertain resolution that may explain fatigue needs be considered.

Certain illnesses (e.g., fibromyalgia), amplified pain syndrome, post–COVID-19 condition, post–intensive care syndrome, and depression share similar symptoms with CFS but are not exclusionary diagnoses. These should be considered in the differential diagnosis in select cases. There is concern that CFS might be mistaken for readily identifiable psychiatric disorders such as anxiety and mood disorders, but evidence supports differences in their clinical presentation from CFS. CFS should not be diagnosed in persons with a prior diagnosis of major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia

of any subtype, delusional disorders of any subtype, dementia of any subtype, eating disorder of any type, or alcohol or other substance abuse within 2 years before the onset of the chronic fatigue or any time thereafter.

Although evaluation of each patient should be individualized, initial laboratory evaluation should be limited to screening laboratory testing sufficient to provide reassurance of the lack of significant medical illness. Further evaluation should be directed primarily toward excluding treatable illnesses that may be suggested by the history, symptoms, signs, or physical exam findings present in specific patients.

MANAGEMENT

Management of CFS is based on relief of the core and most disruptive symptoms in the individual patient. The diagnostic criterion of 6 months duration of illness should not delay evaluation and symptom management, because these may be initiated as soon as the child or adolescent presents with a CFS-like picture. Problems with sleep can be addressed by encouraging patients to adopt good sleep habits using standard sleep hygiene techniques. It may be beneficial to refer the patient to a sleep medicine specialist for the identification and treatment of sleep disorders and disturbances. Once pain is found not to be related to other specific disease or illness, nonpharmacologic treatment is indicated.

One of the nonpharmacologic approaches to pain management, CBT, may also assist the patient in managing and coping with CFS. Through explanation and changes in perception of the illness, CBT may help patients and their families develop coping skills and provide emotional support. Improved methods of coping may allow some improved function while living with the illness. Comorbid psychiatric conditions such as anxiety require appropriate evaluation and intervention. Guided graded-exercise therapy may be beneficial and added to CBT.

Although the overall goal is to help patients with CFS tolerate activity, children and adolescents with CFS should limit physical or mental efforts that result in aggravated symptoms. Return to school should be initiated gradually and systematically with the goal to return to full-time attendance. Home tutoring, cyber-school, and partial attendance can be interim steps. Parents and clinicians can work with teachers and school administrators to define appropriate expectations for attendance and performance for children with CFS. Because of the crucial importance of learning socialization skills, even brief attendance in school or participation in school activities should be encouraged, remembering that too rapid remobilization usually exacerbates symptoms and should be avoided.

Continued empathy and support by the treating physician are crucial in maintaining a physician-parent-patient relationship that is conducive to managing this illness. Careful attention must be directed to family dynamics to identify and resolve family problems or psychopathology that may be contributing to children's perception of their symptoms.

PROGNOSIS

The natural history of CFS is highly variable, and patients and families understand that the symptoms will wax and wane. Children and adolescents with CFS appear to have a more optimistic outcome than adults, typically with an undulating course of gradual improvement over several years. Overall, a good functional outcome has been reported in up to 80% of patients. Poor prognostic factors include gradual onset, increased school absenteeism, lower socioeconomic status, chronic maternal health problems, and untreated comorbid individual and family psychiatric disorders. Favorable prognostic factors include patient control of the rehabilitation program, with continuing support from health professionals and family members, and improvement in orthostatic intolerance.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 213

Miscellaneous Conditions Associated with Arthritis

Angela Byun Robinson and C. Egla Rabinovich

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (RP) is a rare condition characterized by episodic chondritis causing cartilage destruction and deformation of the ears (sparing the earlobes), nose, larynx, and tracheobronchial tree. Antibodies to matrillin-1 and collagen (types II, IX, and XI) are present in approximately 60% of patients with RP, suggesting an autoimmune pathogenesis. Patients may experience arthritis, uveitis, and hearing loss resulting from inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations may include erythema nodosum, maculopapular rash, and purpura. Cardiac involvement, including conduction defects and coronary vasculitis, has been reported. Severe, progressive, and potentially fatal disease resulting from destruction of the tracheobronchial tree and airway obstruction is unusual in childhood. **Diagnostic criteria** established for adults are useful guidelines for evaluating children with suggestive symptoms (Table 213.1). The clinical course of RP is variable; flares of disease are often associated with elevations of acute-phase reactants and may remit spontaneously. Although seen more often in the adult population, RP may coexist with other rheumatic disease (e.g., systemic lupus erythematosus, Sjögren syndrome, Henoch-Schönlein purpura) in up to 30% of patients. The differential diagnosis includes **ANCA-associated vasculitis** (granulomatosis with polyangiitis) (see Chapter 210.4) and **Cogan syndrome**, which is characterized by auditory nerve inflammation and keratitis but not chondritis. **MAGIC** (mouth and genital ulcers with inflamed cartilage) syndrome has many similarities to Behçet disease (see Chapter 202). A genetic syndrome named vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is caused by somatic pathogenic variants affecting the *UBA1* gene. Adolescent and adult patients (most are male) with this syndrome may have fevers, myalgia, arthralgia, auricular chondritis, and erythema nodosum. Approximately 50% of patients with VEXAS meet criteria for relapsing polychondritis. Between 5% and 10% of patients originally thought to have RP have pathogenic variants in *UBA1*. Affected patients have a high CRP and ESR in addition to lower platelet counts when compared with patients with only RP.

Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents

Table 213.1 Suggested Criteria for Relapsing Polychondritis*

MAJOR
Typical inflammatory episodes of ear cartilage
Typical inflammatory episodes of nose cartilage
Typical inflammatory episodes of laryngotracheal cartilage
MINOR
Eye inflammation (conjunctivitis, keratitis, episcleritis, uveitis)
Hearing loss
Vestibular dysfunction
Seronegative inflammatory arthritis

*The diagnosis is established by the presence of two major or one major and two minor criteria. Histologic examination of affected cartilage is required when the presentation is atypical.

Data from Michet CJ Jr, McKenna CH, Luthra HS, et al. Relapsing polychondritis: Survival and predictive role of early disease manifestations. *Ann Intern Med.* 1986;104:74–78.



Fig. 213.1 Pityriasis lichenoides et varioliformis acuta (PLEVA). Symmetric, oval and round, reddish brown macular, papular, necrotic, and crusted lesions on the chest of 9-yr-old boy. *(From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology*, 5th ed. Philadelphia: Elsevier; 2016: Fig. 4-33, p. 87.)*

(azathioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor [TNF] agents), as reported in small series and case reports.

MUCHA-HABERMANN DISEASE/PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA

Pityriasis lichenoides et varioliformis acuta **(PLEVA)** is a benign, self-limited cutaneous vasculitis characterized by episodes of macules, papules, and papulovesicular lesions that can develop central ulceration, necrosis, and crusting (Fig. 213.1). Different stages of development are usually seen at once. **PLEVA fulminans** or febrile ulceronecrotic Mucha-Habermann disease **(FUMHD)** is the severe, life-threatening form of PLEVA. Large, coalescing, ulceronecrotic lesions are seen, accompanied by high fever and elevated ESR. Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. PLEVA has a male predominance and occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions, which reveals perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. Phototherapy has been used in some cases of PLEVA. When disease is severe, corticosteroids have been used with questionable effect, and methotrexate has been reported to induce rapid remission in resistant cases. Cyclosporine and anti-TNF agents have also been efficacious in case reports.

SWEET SYNDROME

Sweet syndrome, or **acute febrile neutrophilic dermatosis**, is a rare entity in children. It is characterized by fever, elevated neutrophil count, and raised, tender erythematous plaques and nodules over the face, extremities, and trunk. Skin biopsy reveals neutrophilic perivascular infiltration in the upper dermis. Female predominance is seen in the adult population, whereas gender distribution is equal in children. Established criteria are useful for diagnosis (Table 213.2). Children can also have arthritis, multifocal nonbacterial osteomyelitis, myositis, and other extracutaneous manifestations. Sweet syndrome may be idiopathic or secondary to malignancy (particularly acute myelogenous leukemia), drugs (granulocyte colony-stimulating factor, tretinoin, azathioprine, or trimethoprim-sulfamethoxazole), or rheumatic diseases (Behçet disease, antiphospholipid antibody syndrome, systemic lupus erythematosus). It has also been reported in association with COVID-19, VEXAS, CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), Majeed syndrome, and deficiency of interleukin-1 receptor antagonist (DIRA) and pyrin associated autoinflammation with neutrophilic dermatosis (PAAND) syndromes (see Chapter 204). **The condition usually responds to treatment with corticosteroids, treatment of underlying disease, or removal of the associated medication.**

HYPERTROPHIC OSTEOARTHROPATHY

Children with chronic disease, especially pulmonary or cardiac disease, can demonstrate clubbing of the terminal phalanges and have associated periosteal reaction and arthritis. These findings characterize the classic presentation of hypertrophic osteoarthropathy (HOA). HOA can be **primary** (idiopathic) or secondary. Although rare, **secondary** HOA is more common in children and is seen in those with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancy (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). It may precede a diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of secondary HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling; in adults, management with bisphosphonates has been reported. Evaluation of children presenting with HOA should include a chest radiograph to evaluate for pulmonary disease or intrathoracic mass. Autosomal recessive pathogenic variants in prostaglandin pathway genes have been described in primary HOA, also described as **pachydermoperiostosis**.

Table 213.2 Diagnostic Criteria for Classic Sweet Syndrome*

MAJOR CRITERIA
Abrupt onset of painful erythematous plaques or nodules
Histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
MINOR CRITERIA
Pyrexia >38°C
Association with underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy *or* preceded by an upper respiratory or gastrointestinal infection or vaccination
Excellent response to systemic corticosteroids or potassium iodide
Abnormal laboratory values at presentation (three of four):
Erythrocyte sedimentation rate >20 mm/hr
Positive C-reactive protein test result
>8,000 leukocytes/mm^3
>70% neutrophils/mm^3

*The diagnosis is established by the presence of two major criteria plus two of the four minor criteria.

Adapted from Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: Case report and review of drug induced Sweet's syndrome. *J Am Acad Dermatol.* 1996;34:918–923.

PLANT THORN SYNOVITIS

A diagnosis of plant thorn synovitis should be considered in children with monoarticular arthritis nonresponsive to antiinflammatory therapy. Acute or chronic arthritis can occur after a plant thorn or other foreign object penetrates a joint. Unlike septic arthritis, children with plant thorn synovitis are usually afebrile. The most common organism seen with plant thorn synovitis is *Pantoea agglomerans,* although cultures are often negative. The initial injury may be unknown or forgotten, making the diagnosis difficult. Ultrasound or MRI can be useful in identifying the foreign body. **Removal of the foreign body using arthroscopy, followed by an antibiotic course, is the accepted therapy.**

PIGMENTED VILLONODULAR SYNOVITIS

Proliferation of synovial tissue is seen in pigmented villonodular synovitis (PVNS). This proliferation is localized or diffuse and can affect the joint, tendon sheath, or bursa. Macrophages and multinucleated giant cells with brownish hemosiderin are present histologically. It is unclear if the etiology of PVNS is inflammatory or neoplastic in nature. Although findings are not pathognomonic, MRI with contrast is a useful diagnostic tool by which PVNS can be seen as a mass or bone erosion. Brown or bloody synovial fluid is seen with arthrocentesis, but the diagnosis is made by tissue biopsy. **Surgical removal of the affected tissue is the therapeutic modality, and with diffuse disease, a total synovectomy is recommended**.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Infectious Diseases

PART XV

Section 1

General Considerations

Chapter 214

Public Health Approach to Pandemics

Kevin P. O'Callaghan

INTRODUCTION

Public health as a field aims to promote healthy lifestyles and communities and to protect the public at large from health threats from known and emerging diseases, chronic noncommunicable diseases, and environmental risks and vulnerabilities. In this context, public health authorities have a core role in prevention, preparedness, and response to epidemic and pandemic infectious diseases. The field of public health has a long and storied history in investigating and ending outbreaks of infectious diseases, extending back to one of the founders of modern epidemiology, John Snow, and the Broad Street pump cholera outbreak. Modern epidemiology and public health practices have an integral role in the management of outbreaks, epidemics, and pandemics, using both traditional methodologies that look like the "shoe leather epidemiology" of John Snow's time, meshed with modern best practices that leverage genomic sequencing, data analytics, and medical innovations in therapeutics and vaccination.

DEFINITIONS

Infectious disease outbreak response hinges on an understanding of current and ongoing incidence and prevalence of the disease in the affected community. The transmission dynamics of a disease will look different in a population that is entirely **susceptible** (e.g., a novel or emerging disease) than in a population in which some members are **recovered/immune** (e.g., a disease has been present for some time).

Sporadic diseases occur infrequently and irregularly in a population. **Endemic** diseases are continually circulating, often at low levels, maintaining a constant presence among members of the community. **Epidemic** disease occurs when there is a substantial increase above the baseline amount of a disease. This may occur as an increase in a disease that is already endemic at low levels or by the introduction of a novel disease that has not been seen in the affected population. A **pandemic** refers to an epidemic that has spread over several countries and continents, affecting large numbers of people. This is frequently defined and declared by international public health authorities, for example, the World Health Organization.

Public Health Authorities and Partners

Although describing "public health" as a specialty may sound somewhat monolithic, the majority of public health work is done collaboratively across a variety of partners, including local, city, state, and national public health authorities, city and state governments, healthcare systems, individual clinical providers, and members of the affected communities. The most important aspect of public health work is often community involvement, whether as part of outbreak investigations, public-facing communications, or education around prevention and response measures.

At an international level, the World Health Organization operates as an international collaborative agency set up in 1948 under the auspices of the United Nations. One of its core responsibilities is to direct and coordinate the world's response to health emergencies, working with national governments, international organizations, researchers, and health systems. At a national level, responsibility for public health management typically devolves to national and federal government departments (e.g., the Department of Health and Human Services in the United States) and their constituent agencies, such as the Centers for Disease Control and Prevention (CDC). The CDC coordinates national surveillance systems for a variety of health conditions, including endemic and newly emergent diseases.

The bulk of regional and local public health surveillance, preparedness, and response work falls under the purview of city, county, and state public health departments. These agencies liaise closely with healthcare systems, specialty and primary care practices, and individual clinicians within their region to help facilitate their public health goals, as well as with nonmedical partners, including school districts, other government agencies, and community groups.

Aims of Public Health Response to Infectious Diseases

Broadly, the aims of a public health response are to prevent the emergence of novel diseases in human hosts, prevent the spread of new diseases or the increase in prevalence of a known endemic disease, and mitigate the health effects of any spread that may occur. Based on these goals, the arms of public health response for epidemic and pandemic infectious diseases fall into four groupings: mitigation/prevention, preparedness, response, and recovery. These areas stem from a common approach to emergency management in general but have specific meanings and impact in the context of pandemic response. Some active public health measures, such as education and public-facing communication, occur across all four arms.

Arms of Intervention

Mitigation/Prevention

A primary approach to pandemic management includes proactive activities to prevent new human infections with target diseases, both to prevent endemic diseases from becoming epidemic and to arrest emergence of novel diseases. Some recent epidemics and pandemics likely represent "spillover" events from animal populations, with these zoonoses then becoming prevalent in human populations through human-to-human transmission (e.g., Zika, SARS-CoV-2). There is a complex interplay between human and animal populations related to farming, deforestation, changes in land use, water management, and climate change that makes the emergence of new zoonotic diseases intermittently more likely and unfortunately somewhat unpredictable. Prevention of emergence of these diseases is best approached through a One Health approach, which is an international project using a "collaborative, multisectoral, and transdisciplinary approach" at local, national, and international levels to optimize health outcomes, recognizing the interconnectedness of people, animals, plants, and their environment. Individual approaches to prevent disease outbreaks of this type may require the involvement of agricultural regulators and inspectors, veterinarians, and environmental health specialists, among others.

A more concrete example of a salient mitigation effort involving human healthcare providers is antimicrobial stewardship. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms in response to the selection pressure of antimicrobial usage is a critical vulnerability in epidemic and pandemic preparedness. Stewardship efforts at a grassroots, individual patient level provide a necessary bulwark against the proliferation of further MDR and XDR strains of currently endemic diseases.

Preparedness

Separate from mitigation and prevention, a preparedness stance plans for the potentially inevitable outcome of the emergence of a novel epidemic or pandemic disease. Preparedness efforts can be targeted against specific disease threats (e.g., seasonal and pandemic influenza, which has predictable seasonality) or against previously unknown or less predictable threats (e.g., SARS-CoV-2, Ebola virus disease). Given the broad range of potential pathogens that may pose a threat over time, much preparedness planning takes place in an "all hazards" stance, where the preparation is necessarily agnostic as to the specific pathogen, with surveillance and resources that can be quickly pivoted to cover a broad variety of potential risks.

A core element of preparedness involves case-based surveillance or the active observation and documentation of incidence and prevalence of a specific disease or syndrome at local, regional, and national levels. Robust surveillance infrastructure requires both regulatory and material support, including both voluntary and mandatory reporting requirements, as well as a reporting infrastructure that includes clear and consistent case definitions that are reproducible across venues of care. In the United States, the National Notifiable Diseases Surveillance System (NNDSS) coordinates case definitions and reporting requirements for approximately 120 nationally notifiable diseases. A coherent and centralized reporting infrastructure such as that provided by NNDSS allows for a more global understanding of burden of disease and disease trends over time. However, case surveillance as described here remains dependent on close partnership with healthcare systems, clinical laboratories, and individual providers at a local level to ensure that these systems are both sensitive and specific. Case-based surveillance is also predicated on a good understanding of both the pathophysiology and available diagnostics for a specific disease. For newly emergent diseases, where a coherent case definition is less readily available, early warning systems seek to detect syndromic clusters that elude identification on routine diagnostics. Expansion of such programs in the wake of the 2019 SARS-CoV-2 pandemic have received governmental support and may use novel approaches such as wastewater screening and genomic sequencing within syndromic clusters.

In terms of tangible supplies that may be required for an acute response, personal protective equipment (PPE) and medical countermeasures (MCMs, e.g., vaccines, therapeutics) may be needed in high volume on short notice, at which point a "just in time" supply chain approach may prove lacking. Stockpiling of critical supply needs is a necessary part of pandemic preparedness, particularly with regard to high-risk, low-frequency, unpredictable events such as international travel of a patient with undiagnosed Ebola virus disease. For a longer-term outbreak or epidemic, such as that seen with the 2020 response to COVID-19, even the most aggressive stockpiling cannot support a protracted pandemic response, and close collaboration with manufacturers of durable medical supplies, therapeutics, and vaccines may be necessary to ensure sustained availability and a flexible supply chain.

Lastly, healthcare capacity is a separate but critically important resource with concrete limits (e.g., total bed spaces, provider person-days, and critical care and ventilator availability). In responding to the exponential growth of a rapidly reproducing pathogen, hospital capacity may be rapidly overwhelmed, as seen in some early surges of COVID-19 in 2020. Infrastructure planning for healthcare systems can help alleviate some of these pressures through rapidly accessible, flexible patient care space normally kept in reserve and through thoughtful capacity management, such as plans that allow for restriction of elective or nonemergent care for short periods. Ultimately, such efforts need to be matched with public-facing interventions described later, which can "flatten the curve" of epidemic transmission.

Response

Pandemic response begins with identification of the emergence of a specific risk (through surveillance systems described previously), followed by activation of applicable plans developed during the preparedness phase. Early pandemic response may be, by necessity, nonspecific to a known disease, particularly if the identification of risk is predicated on a syndromic cluster or a novel, not-yet-identified pathogen.

For novel pathogens, short-term goals will include rapid identification of the pathogen at a genus and species level, sequencing of its genome, development of accurate and readily available diagnostic tests, and development of targeted therapeutics and vaccines. As these individual targets may take weeks to months to come to fruition, early response will focus on mitigation of disease transmission through the application of standard public health measures, including social distancing, transmission-based precautions, isolation of cases, contact tracing, and quarantine of known contacts. All of these approaches occur simultaneously and require extensive public communication and education to ensure their effectiveness. **Social distancing** involves the temporary application of new social norms and social constructs designed to keep individuals, particularly those from separate households, physically distanced so that the likelihood of disease transmission between individuals is substantially reduced or eliminated. This may include infrastructural changes that promote contactless payment options at stores, physical barriers in offices and at public-facing service desks, and others. This distancing is assisted by application of **transmission-based precautions**, which are PPE recommendations based on the transmission modality of a specific pathogen. In non-healthcare settings, the most common application of PPE is facial masking designed to protect oral and nasal mucosa from diseases spread by droplets (e.g., influenza). **Isolation of cases** is a public health measure that strongly encourages or, depending on regulatory support, legally requires diagnosed cases of a specific disease to isolate for the duration of their period of infectivity, usually at home, in a healthcare setting, or at a designated isolation facility. After identification of a case, **contact tracing** should occur, during which identification of potential contacts of the known case (during the period of infectivity) is made. Completion of contact tracing involves notification of the affected contacts and a recommendation that they quarantine, typically for the duration of the upper bound of the incubation period for the disease. All of these responses require a large commitment in terms of time, personnel, and resources, and in a rapidly accelerating epidemic, these resources may ultimately be overwhelmed.

While these core public health responses are ongoing, rapid development of diagnostics, therapeutics, and vaccine candidates will continue. Of these, the earliest steps involve genomic sequencing and targeted diagnostics, the latter of which ultimately will greatly assist with consistent case definitions and subsequent contact tracing, isolation, and quarantine. The timeline for development of suitable vaccine candidates has greatly decreased in recent decades, with development of messenger RNA (mRNA) vaccine candidates during the COVID-19 pandemic being a hallmark example. Regulatory changes in timelines for vaccine assessment and approval for emergency use have assisted in these efforts, while not altering safety and efficacy oversight.

Recovery

Termination of pandemic response is rarely clear-cut, as elimination or eradication of specific pathogens from human population is rare. Most epidemic or pandemic responses end with a slow decrease in case counts and ultimate quiescence for a period (e.g., Ebola virus disease outbreaks) or the attainment of endemicity—the low-level constant circulation of a pathogen within remaining susceptible human hosts. Ultimately, transition from response to recovery is predicated on ongoing case counts, pressure on healthcare infrastructure, and an amalgamation of other metrics that may include test positivity, case severity, vaccine uptake, and hospitalization rates.

A core aspect of the recovery phase is an analysis of pandemic response measures as a whole, including their relative success, their tolerability, and their tangible and intangible costs. Future pandemic response, for the same and other pathogens, can be informed and improved by this analysis, typically developed in an after-action report or similar post hoc analytic framework.

Communication and Education

A core element of public health response to epidemic and pandemic disease, which spans across all four stances, is public communication and education. At each stage of pandemic preparedness and response, public engagement is key. This is particularly true in a response phase, where data become available rapidly and contradictory findings in early reports can cause confusion and mistrust. Clear, concise messaging

that focuses on core concepts of preparedness and response is key. A large portion of public health response may be spent in developing and promulgating this messaging, but it can be extremely worthwhile insofar as it can lead to dramatic increases in tolerability and uptake of other public health interventions, including social distancing, isolation and quarantine, and vaccines.

Viruses, bacteria, fungi, and other microbes are a fact of life on this earth and are an integral part of the biodiversity upon which we as humans depend. Although infectious diseases may also be a dependable fact of life, their broader societal impact can be shifted, reduced, and controlled in the ways described here. Pandemic preparedness and response can be difficult and time-consuming, but done well, with engaged partners at all levels, can be lifesaving on a societal level.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

Preventive Measures

Chapter 215

Immunization Practices

Alexandra Kilinsky, Henry H. Bernstein, and Walter A. Orenstein

Immunization is one of the most beneficial and cost-effective disease prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States. However, cases of vaccine-preventable diseases, including measles, mumps, and pertussis, continue to occur in the United States. Incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from representative 20th-century annual morbidity, usually before development of the corresponding vaccines (Table 215.1), with most of the newer vaccines not achieving quite the same percentage decrease (Table 215.2). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force (USPSTF) reported that childhood immunization received a perfect score based on clinically preventable disease burden and cost-effectiveness.

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either passively or actively. **Passive immunity** is generated through administration of an antibody-containing preparation. **Active immunity** is achieved by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2023, infants, children, and adolescents in the United States are recommended to be routinely immunized against **19 pathogens**: *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis,* polio virus, *Haemophilus influenzae* type b **(Hib)**, hepatitis A, hepatitis B, measles virus, mumps virus, rubella virus, rotavirus, varicella-zoster virus, SARS-CoV-2, pneumococcus, meningococcus, influenza virus, human papillomavirus **(HPV)**, and respiratory syncytial virus **(RSV)**.

PASSIVE IMMUNITY

Rather than producing antibodies through the body's own immune system, passive immunity is achieved by administration of preformed antibodies. Protection is immediate, yet transient, lasting weeks to months. Products used include:

- Immunoglobulin administered intramuscularly **(IMIG)**, intravenously **(IVIG)**, or subcutaneously **(SCIG)**
- Specific or hyperimmune immunoglobulin preparations administered IM or IV

Table 215.1 Comparison of 20th-Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

DISEASE	20TH-CENTURY ANNUAL MORBIDITY*	2019 REPORTED CASES†	PERCENT DECREASE
Smallpox	29,005	0	100
Diphtheria	21,053	2	>99
Measles	530,217	1275	>99
Mumps	162,344	3780	98
Pertussis	200,752	18,617	91
Polio (paralytic)	16,316	0	100
Rubella	47,745	6	>99
Congenital rubella syndrome	152	1	>99
Tetanus	580	26	95
Haemophilus influenzae type b (Hib)	20,000	18‡	>99

*Data from Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298(18):2155–2163.

†Data from Centers for Disease Control and Prevention. *National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data.* Atlanta, GA: CDC Division of Health Informatics and Surveillance Available at https://wonder.cdc.gov/nndss/static/2019/annual/2019-table1.html.

‡Hib <5 yr of age. An additional 667 cases of *Haemophilus influenzae* invasive disease (<5 yr of age)—non-b serotype (213 cases), nontypeable (200 cases), and unknown serotype (254 cases)—are estimated to have occurred.

Table 215.2 Comparison of Pre–Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

DISEASE	PRE–VACCINE ERA ANNUAL ESTIMATE*	2019 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333*	18,846†	86
Hepatitis B (acute)	66,232*	3544†	95
Pneumococcus (invasive)			
All ages	63,067*	19,689†	69
<5yr of age	16,069*	1091†	93
Rotavirus (hospitalizations, <3yr of age)	62,500‡	30,625‖	51
Varicella	4,085,120*	8297†	>99

*Data from Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298(18):2155–2163.

†Data from Centers for Disease Control and Prevention. *National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data.* Atlanta, GA: CDC Division of Health Informatics and Surveillance Available at: https://wonder.cdc.gov/nndss/static/2019/annual/2019-table1.html

‡Data from Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2009;58(RR-2):1–25.

‖Data from New Vaccine Surveillance Network 2017 data: U.S. rotavirus disease now has biennial pattern (unpublished).

that focuses on core concepts of preparedness and response is key. A large portion of public health response may be spent in developing and promulgating this messaging, but it can be extremely worthwhile insofar as it can lead to dramatic increases in tolerability and uptake of other public health interventions, including social distancing, isolation and quarantine, and vaccines.

Viruses, bacteria, fungi, and other microbes are a fact of life on this earth and are an integral part of the biodiversity upon which we as humans depend. Although infectious diseases may also be a dependable fact of life, their broader societal impact can be shifted, reduced, and controlled in the ways described here. Pandemic preparedness and response can be difficult and time-consuming, but done well, with engaged partners at all levels, can be lifesaving on a societal level.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

Preventive Measures

Chapter 215

Immunization Practices

Alexandra Kilinsky, Henry H. Bernstein, and Walter A. Orenstein

Immunization is one of the most beneficial and cost-effective disease prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States. However, cases of vaccine-preventable diseases, including measles, mumps, and pertussis, continue to occur in the United States. Incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from representative 20th-century annual morbidity, usually before development of the corresponding vaccines (Table 215.1), with most of the newer vaccines not achieving quite the same percentage decrease (Table 215.2). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force (USPSTF) reported that childhood immunization received a perfect score based on clinically preventable disease burden and cost-effectiveness.

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either passively or actively. **Passive immunity** is generated through administration of an antibody-containing preparation. **Active immunity** is achieved by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2023, infants, children, and adolescents in the United States are recommended to be routinely immunized against **19 pathogens**: *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis,* polio virus, *Haemophilus influenzae* type b **(Hib)**, hepatitis A, hepatitis B, measles virus, mumps virus, rubella virus, rotavirus, varicella-zoster virus, SARS-CoV-2, pneumococcus, meningococcus, influenza virus, human papillomavirus **(HPV)**, and respiratory syncytial virus **(RSV)**.

PASSIVE IMMUNITY

Rather than producing antibodies through the body's own immune system, passive immunity is achieved by administration of preformed antibodies. Protection is immediate, yet transient, lasting weeks to months. Products used include:

- Immunoglobulin administered intramuscularly **(IMIG)**, intravenously **(IVIG)**, or subcutaneously **(SCIG)**
- Specific or hyperimmune immunoglobulin preparations administered IM or IV

Table 215.1 Comparison of 20th-Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

DISEASE	20TH-CENTURY ANNUAL MORBIDITY*	2019 REPORTED CASES†	PERCENT DECREASE
Smallpox	29,005	0	100
Diphtheria	21,053	2	>99
Measles	530,217	1275	>99
Mumps	162,344	3780	98
Pertussis	200,752	18,617	91
Polio (paralytic)	16,316	0	100
Rubella	47,745	6	>99
Congenital rubella syndrome	152	1	>99
Tetanus	580	26	95
Haemophilus influenzae type b (Hib)	20,000	18‡	>99

*Data from Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298(18):2155–2163.

†Data from Centers for Disease Control and Prevention. *National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data.* Atlanta, GA: CDC Division of Health Informatics and Surveillance Available at https://wonder.cdc.gov/nndss/static/2019/annual/2019-table1.html.

‡Hib <5 yr of age. An additional 667 cases of *Haemophilus influenzae* invasive disease (<5 yr of age)—non-b serotype (213 cases), nontypeable (200 cases), and unknown serotype (254 cases)—are estimated to have occurred.

Table 215.2 Comparison of Pre–Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

DISEASE	PRE–VACCINE ERA ANNUAL ESTIMATE*	2019 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333*	18,846†	86
Hepatitis B (acute)	66,232*	3544†	95
Pneumococcus (invasive)			
All ages	63,067*	19,689†	69
<5yr of age	16,069*	1091†	93
Rotavirus (hospitalizations, <3yr of age)	62,500‡	30,625‖	51
Varicella	4,085,120*	8297†	>99

*Data from Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298(18):2155–2163.

†Data from Centers for Disease Control and Prevention. *National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data.* Atlanta, GA: CDC Division of Health Informatics and Surveillance Available at: https://wonder.cdc.gov/nndss/static/2019/annual/2019-table1.html

‡Data from Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2009;58(RR-2):1–25.

‖Data from New Vaccine Surveillance Network 2017 data: U.S. rotavirus disease now has biennial pattern (unpublished).

- Antibodies of animal origin
- Monoclonal antibodies

Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. This transfer can provide protection during an infant's first few months of life; other antibodies (IgA) are transferred to the infant during breastfeeding. Protection for some diseases can persist for as long as 1 year after birth, depending on the quantity of antibody transferred and the time until levels fall below those considered protective.

The major indications for inducing passive immunity are immunodeficiencies in children with B-lymphocyte defects who have difficulty making antibodies (e.g., hypogammaglobulinemia, secondary immunodeficiencies), who have exposure to infectious diseases or to imminent risk of exposure when there is inadequate time for them to develop an active immune response to a vaccine (e.g., newborn exposed to maternal hepatitis B), and who have infectious diseases that require antibody administration as part of the specific therapy (Table 215.3).

Intramuscular Immunoglobulin

Immunoglobulin is a sterile antibody-containing solution, usually derived through cold ethanol fractionation of large pools of human plasma from adults. Antibody concentrations reflect the infectious disease exposure and immunization experience of plasma donors. IMIG contains 15–18% protein and is predominantly IgG. Intravenous use of human IMIG is contraindicated. Immunoglobulin is not known to transmit infectious agents, including viral hepatitis and HIV. The major indications for immunoglobulin are:

- Replacement therapy for children with antibody deficiency disorders
- Measles prophylaxis
- Hepatitis A prophylaxis

For **replacement therapy**, the usual dose of IMIG is 100 mg/kg (equivalent to 0.66 mL/kg) monthly. The usual interval between doses is 2-4 weeks depending on trough IgG serum concentrations and clinical response. In practice, IVIG has replaced IMIG for replacement therapy.

IMIG can be used to prevent or modify **measles** if administered to susceptible children within 6 days of exposure (usual dose: 0.5 mL/kg body weight; maximum dose: 15 mL). The recommended dose of IVIG is 400 mL/kg. Data suggest that measles vaccine, if given within 72 hours of measles exposure, will provide protection in some cases to infants ≥6 months of age. Measles vaccine and immunoglobulin should not be administered at the same time.

Two methods are available for **postexposure prophylaxis** against **hepatitis A** depending on the patient's age: Children 6-11 months old should receive a dose of hepatitis A vaccine before international travel. However, the dose of hepatitis A vaccine received before 12 months should not be counted in determining compliance with the recommended two-dose schedule. In those 12 months to 40 years of age, hepatitis A immunization is preferred over immunoglobulin for postexposure prophylaxis and for protection of people traveling to areas where hepatitis A is endemic. Persons age >40 years, persons with immunocompromising conditions, and persons with chronic liver disease planning on traveling to an area with high or intermediate hepatitis A virus (HAV) endemicity should receive a single dose of hepatitis A vaccine as soon as travel is considered. Persons traveling in <2 weeks should receive the initial dose of hepatitis A vaccine and simultaneously may be administered immunoglobulin in a different anatomic injection site (e.g., separate limbs). A second dose of hepatitis A vaccine is not required for postexposure prophylaxis; however, for long-term immunity, the vaccination series should be completed with a second dose at least 6 months after the first dose.

The most common adverse reactions to immunoglobulin are pain and discomfort at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious adverse events are rare and include chest pain, dyspnea, anaphylaxis, and systemic collapse. Immunoglobulin should *not* be administered to people with selective IgA deficiency who can produce antibodies against the trace amounts of IgA in immunoglobulin preparations and can develop reactions after repeat doses. These reactions can include fever, chills, and a shocklike syndrome. Because these reactions are rare, testing for selective IgA deficiencies is not recommended.

Intravenous Immunoglobulin

IVIG is a highly purified preparation of immunoglobulin antibodies prepared from adult plasma donors using alcohol fractionation and is

Table 215.3 Immunoglobulin and Animal Antisera Preparations

PRODUCT	MAJOR INDICATIONS
Intramuscular immunoglobulin (IMIG)	Replacement therapy in antibody-deficiency disorders Hepatitis A prophylaxis Measles prophylaxis Rubella prophylaxis (pregnant women)
Intravenous immunoglobulin (IVIG)	Replacement therapy in antibody-deficiency disorders Kawasaki disease Pediatric HIV infection Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia Varicella postexposure prophylaxis Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy Toxic shock syndrome Postexposure measles prophylaxis for immunocompromised contacts May be useful in a variety of other conditions
Subcutaneous immunoglobulin (SCIG)	Treatment of patients with primary immunodeficiencies
Hepatitis B immunoglobulin (IM)	Postexposure prophylaxis Prevention of perinatal infection in infants born to hepatitis B surface antigen–positive mothers
Rabies immunoglobulin (IM)	Postexposure prophylaxis
Tetanus immunoglobulin (IM)	Wound prophylaxis Treatment of tetanus
Varicella-zoster immunoglobulin (VariZIG, IM)	Postexposure prophylaxis of susceptible people at high risk for complications from varicella
Cytomegalovirus (IV)	Prophylaxis of disease in seronegative transplant recipients
Vaccinia immunoglobulin (IV)	Reserved for certain complications of smallpox immunization and has no role in treatment of smallpox
Human botulism (IV), BabyBIG	Treatment of infant botulism
Diphtheria antitoxin, equine	Treatment of diphtheria
Heptavalent botulinum antitoxin against all seven (A-G) botulinum toxin types (BAT)	Treatment of noninfant food and wound botulism
Palivizumab (monoclonal antibody), humanized mouse (IM)	Prophylaxis for infants against respiratory syncytial virus (see Chapter 307)
Nirsevimab (monoclonal antibody) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. (IM)	Passive immunization to prevent RSV-associated lower respiratory tract infection among infants and younger children (see Chapter 307)
Crotalidae immune F(ab')2 (equine)	Effective for viper and pit viper bites, including rattlesnakes, copperheads, moccasins

Data from Passive Immunization. In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021–2024 Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021. (Recommendations for use of specific immunoglobulins are located in the sections for specific diseases in Section 3 of *Red Book*.)

modified to allow IV use. IVIG is more than 95% IgG and is tested to ensure minimum antibody titers to *C. diphtheriae,* hepatitis B virus, measles virus, and poliovirus. Antibody concentrations against other pathogens vary widely among products and even among lots from the same manufacturer. Liquid and lyophilized powder preparations are available. IVIG does not contain thimerosal.

Not all IVIG products are approved by the U.S. Food and Drug Administration (FDA) for all indications. The major recommended FDA-approved indications for IVIG are:

- Replacement therapy for primary immunodeficiency disorders
- Kawasaki disease to prevent coronary artery abnormalities and shorten the clinical course
- Replacement therapy for prevention of serious bacterial infections in children infected with HIV
- Prevention of serious bacterial infections in people with hypogammaglobulinemia in chronic B-lymphocyte leukemia
- Immune-mediated thrombocytopenia to increase platelet count

IVIG may be helpful for patients with severe toxic shock syndrome, Guillain-Barré syndrome, and anemia caused by parvovirus B19. IVIG is also used for many other conditions based on clinical experience, such as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. IVIG may be used for varicella after exposure when varicella-zoster immunoglobulin is not available.

Reactions to IVIG may occur in up to 25% of patients. Some of these reactions appear to be related to the rate of infusion and can be mitigated by decreasing the rate. Such reactions include fever, headache, myalgia, chills, nausea, and vomiting. More serious reactions, including anaphylactoid events, thromboembolic disorders, aseptic meningitis, hemolytic anemia, and renal insufficiency, have rarely been reported. Renal failure occurs mainly in patients with preexisting renal dysfunction.

Specific or hyperimmune immunoglobulin preparations are derived from donors with high titers of antibodies to specific agents and are designed to provide protection against those agents (see Table 215.3).

Subcutaneous Immunoglobulin

(SCIG) is safe and effective in children and adults with primary immune deficiency disorders. Smaller doses administered weekly result in less fluctuation of serum IgG concentrations over time. Systemic reactions are less frequent than with IVIG, and the most common adverse effects of SCIG are injection site reactions. There are no data on administration of IMIG by the subcutaneous route.

Hyperimmune Animal Antisera Preparations

Animal antisera preparations are derived from horses. The immunoglobulin fraction is concentrated using ammonium sulfate, and some products are further treated with enzymes to decrease reactions to foreign proteins. The following two equine antisera preparations are available for humans (as of 2018):

- **Diphtheria antitoxin**, which can be obtained from the U.S. Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/diphtheria/dat.html) and is used to treat diphtheria.
- **Heptavalent botulinum antitoxin**, available from the CDC for use in adults with botulism. To request it, one can call the CDC's 24-hour line at 770-488-7100. This product contains antitoxin against all seven (A-G) botulinum toxin types.

Great care must be exercised before administering animal-derived antisera because of the potential for severe allergic reactions. Due caution includes testing for sensitivity before administration, desensitization if necessary, and treating potential reactions, including febrile events, serum sickness, and anaphylaxis. For infant botulism, IVIG (BabyBIG), a human-derived antitoxin, is licensed and should be used.

Monoclonal Antibodies

Monoclonal antibodies (mAbs) are antibody preparations produced against a single antigen. They are mass-produced from a hybridoma, a hybrid cell used as the basis for production of large amounts of antibodies. A hybridoma is created by fusing an antibody-producing B lymphocyte with a fast-growing immortal cell such as a cancer cell. There are two injectable monoclonal antibody products that help protect infants and young children from lower respiratory tract infection caused by RSV: nirsevimab and palivizumab. **Palivizumab** is used for prevention of severe disease from respiratory syncytial virus (RSV) among children ≤24 months old with bronchopulmonary dysplasia (BPD, a form of chronic lung disease), a history of premature birth, or congenital heart lesions or neuromuscular diseases. The American Academy of Pediatrics (AAP) has developed specific recommendations for the use of palivizumab. **Nirsevimab** is recommended for infants younger than 8 months of age who were born shortly before or are entering their first RSV season if the mother did not receive RSV vaccine (Abrysvo) during pregnancy, if the mother's RSV vaccination status is unknown, or the infant was born within 14 days of maternal RSV vaccination. Additionally, a dose of nirsevimab is recommended for some children 8 to 19 months of age who are at increased risk for severe RSV disease and entering their second RSV season. Given the atypical interseasonal change in RSV epidemiology in 2021-2023, the AAP strongly supports the use of palivizumab and nirsevimab in patients who would be candidates per the current eligibility recommendations. See https://publications.aap.org/redbook/resources/25379/ for details (see Chapter 307).

mAbs also are used to prevent transplant rejection and to treat some types of cancer, autoimmune diseases, and asthma. Use of mAbs against interleukin (IL)-2 and tumor necrosis factor (TNF)-α are being used as part of the therapeutic approach to patients with a variety of malignant and autoimmune diseases.

Serious adverse events associated with palivizumab are rare, primarily including cases of anaphylaxis and hypersensitivity reactions. Adverse reactions to nirsevimab are rare and mild to moderate in severity, including rash and injection site reactions. Adverse reactions to mAbs directed at modifying the immune response, such as antibodies against IL-2 or TNF-α, can be more serious and include cytokine release syndrome, fever, chills, tremors, chest pain, immunosuppression, and infection with various organisms, including mycobacteria.

ACTIVE IMMUNIZATION

Vaccines are defined as whole or parts of microorganisms administered to prevent an infectious disease. Vaccines can consist of whole inactivated microorganisms (e.g., polio, hepatitis A), parts of the organism (e.g., acellular pertussis, HPV, hepatitis B), polysaccharide capsules (e.g., pneumococcal and meningococcal polysaccharide vaccines), polysaccharide capsules conjugated to protein carriers (e.g., Hib, pneumococcal, and meningococcal conjugate vaccines), live-attenuated microorganisms (e.g., measles, mumps, rubella, varicella, rotavirus, and live-attenuated influenza vaccines), and toxoids (e.g., tetanus, diphtheria) (Table 215.4). In addition, vaccines against SARS-CoV-2 are messenger RNA (mRNA) vaccines, viral vector vaccines, or protein subunit vaccines. A **toxoid** is a bacterial toxin modified to be nontoxic but still capable of inducing an active immune response against the toxin.

Vaccines can contain a variety of other constituents besides the immunizing antigen. *Suspending* fluids may be sterile water or saline but can be a complex fluid containing small amounts of proteins or other constituents used to grow the immunobiologic culture. Preservatives, stabilizers, and antimicrobial agents are used to inhibit bacterial growth and prevent degradation of the antigen. Such components can include gelatin, 2-phenoxyethanol, and specific antimicrobial agents. Preservatives are added to multidose vials of vaccines, primarily to prevent bacterial contamination on repeated entry of the vial. In the past, many vaccines for children contained thimerosal, a preservative containing ethyl mercury. Removal of thimerosal as a preservative from vaccines for children began as a precautionary measure in 1999 in the absence of any data on harm from the preservative. This objective was accomplished by switching to single-dose packaging. Of the vaccines recommended for young children, only some preparations of influenza vaccine contain thimerosal as a preservative.*

Adjuvants are used in some vaccines to enhance the immune response. In the United States, the only adjuvants currently licensed by the FDA to be part of vaccines are **aluminum salts**: AsO_4, composed of 3-O-desacyl-4′-monophosphoryl 301 lipid A (MPL) adsorbed on to aluminum (as hydroxide salt) and MF59 and 1018 adjuvant. **AsO_4** is

*The thimerosal content in U.S.-licensed vaccines currently being manufactured is listed at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228.htm#pres.

Table 215.4 Currently Available* Vaccines and Immunizing Agents in the United States by Type

PRODUCT	TYPE
Adenovirus	Live, oral vaccine indicated for active immunization for the prevention of febrile acute respiratory disease caused by adenovirus types 4 and 7 for use in military populations 17-50 yr of age
Anthrax vaccine adsorbed	Cell-free filtrate of components including protective antigen
Bacille Calmette-Guérin (BCG) vaccine	Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances
Cholera vaccine	Oral vaccine containing live-attenuated *Vibrio cholerae* CVD 103-HgR strain for protection against serogroup O1 in adults age 18-64 traveling to cholera-affected areas
COVID-19 vaccines	Two messenger mRNA-based: Comirnaty (Pfizer-BioNTech) and Spikevax (Moderna). A single adjuvanted, protein subunit-based vaccine, is a Novavax product.
Dengue vaccine	Tetravalent live-attenuated dengue virus (DENV) manufactured by Sanofi Pasteur Use in children age 9-16 yr, with laboratory-confirmed previous dengue virus infection and living in an area where dengue is endemic
Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine	Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis*
DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)	DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses
DTaP with IPV and *Haemophilus influenzae* type b (Hib) (DTaP-IPV/Hib)	DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid
DTaP with inactivated polio vaccine, *Haemophilus influenzae* type b, and hepatitis B (DTaP-IPV-Hib-HepB)	DTaP with inactivated whole polioviruses, Hib conjugate, and hepatitis B vaccine
DTaP and inactivated polio vaccine (DTaP-IPV)	DTaP with inactivated whole polioviruses
Ebola	Live, recombinant viral vector vaccine: backbone: vesicular stomatitis virus (VSV), with gene encoding for envelope glycoprotein of *Zaire ebolavirus*. Approved for individuals 18 yr of age and older as a single-dose administration.
Hib conjugate vaccine (Hib)	Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein
Hepatitis A vaccine (HepA)	Inactivated whole virus
Hepatitis A–hepatitis B vaccine (HepA-HepB)	Combined hepatitis A and B vaccine
Hepatitis B vaccine (HepB)	HBsAg produced through recombinant techniques in yeast
Human papillomavirus vaccine 9-valent (9vHPV)	The L1 capsid proteins of HPV types 6 and 11 to prevent genital warts and types 16 18, 31, 33, 45, 52, and 58 to prevent cervical cancer (9vHPV)
Influenza virus vaccine inactivated (IIV†)	Available as quadrivalent inactivated formulations that contain hemagglutinin-derived influenza A(H1N1)pdm09 and influenza A(H3N2) components, along with two influenza B viruses (one from each Victoria and Yamagata lineage) Flucelvax is a cell-based inactivated quadrivalent vaccine
Influenza virus vaccine live-attenuated, intranasal (LAIV4)	Live-attenuated, temperature-sensitive, cold-adapted quadrivalent intranasal vaccine containing the hemagglutinin and neuraminidase genes from the wild strains reassorted to have the six other genes from the cold-adapted parent; recommended for 2-49 yr of age
Recombinant influenza vaccine (RIV4)	A quadrivalent formulation of influenza vaccine approved for persons 18 yr old and older
Japanese encephalitis vaccine	Purified, inactivated whole virus
Measles, mumps, rubella (MMR) vaccine	Live-attenuated viruses
Measles, mumps, rubella, varicella (MMRV) vaccine	Live-attenuated viruses
Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MenACWY)	Polysaccharide from each serogroup conjugated to diphtheria toxoid CRM_{197} protein
Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4)	Polysaccharides from each of the serogroups conjugated to diphtheria toxoid protein. No longer available in the United States.
Meningococcal B (MenB)	Recombinant proteins from serogroup B developed in *Escherichia coli*
Mpox vaccine	Live replication-deficient modified vaccinia Ankara vaccine
Pneumococcal conjugate vaccine (15, 20 valent PCV15, PCV20)	Pneumococcal polysaccharides conjugated to diphtheria toxin CRM_{197}, containing 15 and 20 pneumococcal serotypes, respectively. These serotypes accounted for >80% of invasive disease in young children before vaccine licensure
Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)	Pneumococcal polysaccharides of 23 serotypes responsible for 85–90% of bacteremic disease in the United States
Poliomyelitis (inactivated, enhanced potency) (IPV)	Inactivated whole virus highly purified from monkey kidney cells, trivalent types 1, 2, and 3
Rabies vaccines (human diploid and purified chicken fibroblasts)	Inactivated whole virus
Respiratory syncytial virus vaccines	RSVPreF3 (Arexvy) and RSVpreF (Abrysvo). Both vaccines are recombinant protein vaccines and are currently approved as a single dose in adults ages 60 and older. Arexvy is adjuvanted. For pregnant women during RSV season, one dose of Abrysvo is recommended
RSV immunization	Human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Table 215.4 Currently Available* Vaccines and Immunizing Agents in the United States by Type—cont'd

PRODUCT	TYPE
Rotavirus vaccines (RV5 and RV1)	Bovine rotavirus pentavalent vaccine (RV5), live reassortment attenuated virus, and human live-attenuated virus (RV1)
Smallpox vaccine	Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox (variola)
Tetanus and diphtheria toxoids, adsorbed (Td, adult use)	Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared with diphtheria toxoid used for children <7 yr of age
Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine	Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7-10 yr of age who have not been appropriately immunized with DTaP
Tickborne encephalitis vaccine	Whole tickborne-encephalitis virus (TBE) inactivated vaccine. Currently no ACIP/CDC recommendations available for this vaccine
Typhoid vaccine (polysaccharide)	Vi capsular polysaccharide of *Salmonella* Typhi Ty2 strain
Typhoid vaccine (oral)	Live-attenuated Ty21a strain of *S. typhi*
Varicella vaccine	Live-attenuated Oka/Merck strain
Yellow fever vaccine	Live-attenuated 17D-204 strain
Herpes zoster (shingles) vaccine	Zoster vaccine recombinant, adjuvanted (Shingrix) for use in adults ≥50 yr and in adults age 18 yr and older who are or will be at increased risk of herpes zoster because of immunodeficiency or immunosuppression caused by known disease or therapy

*As of November 2023.
†There are various types of inactivated flu vaccines—IIV4, ccIIV4, and aIIV4.
Data from U.S. Food and Drug Administration. Vaccines licensed for use in the United States. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.tm.

found in one type of HPV vaccine, no longer available in the United States but still used in Europe. **MF59** is an oil-in-water emulsion found in one type of influenza vaccine approved for people ≥65 years old; it is also being studied in children. 1018 is an immunostimulatory sequence adjuvant used in HepB-CpG, a hepatitis B vaccine approved for persons >18 years. HepB-CpG contains yeast-derived recombinant hepatitis B surface antigen (HBsAg) and is prepared by combining purified HBsAg with small synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide motifs. The 1018 adjuvant binds to toll-like receptor 9 to simulate a directed immune response to HBsAg. Vaccines with adjuvants should be injected deeply into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Vaccines can induce immunity by stimulating antibody formation, cellular immunity, or both. Protection induced by most vaccines is thought to be mediated primarily by B lymphocytes, which produce antibodies. Such antibodies can inactivate toxins, neutralize viruses, and prevent their attachment to cellular receptors, facilitate phagocytosis and killing of bacteria, interact with complement to lyse bacteria, and prevent adhesion to mucosal surfaces by interacting with the bacterial cell surface.

Most B-lymphocyte responses require the assistance of CD4 helper T lymphocytes. These T-lymphocyte–dependent responses tend to induce high levels of functional antibody with high avidity. The T-dependent responses mature over time from primarily an IgM response to a persistent, long-term IgG response and induce immunologic memory that leads to enhanced responses on boosting. **T-lymphocyte–dependent vaccines**, which include protein moieties, induce good immune responses even in young infants. In contrast, polysaccharide antigens induce B-lymphocyte responses in the absence of T-lymphocyte help. These **T-lymphocyte–independent vaccines** are associated with poor immune responses in children <2 years old and with short-term immunity and absence of an enhanced or booster response on repeat exposure to the antigen. With some polysaccharide vaccines, repeat doses actually are associated with reduced responses, as measured by antibody concentrations, compared with first doses (i.e., *hyporesponsive*). To overcome problems with plain polysaccharide vaccines, polysaccharides have been **conjugated**, or covalently linked, to protein carriers, converting the vaccine to a T-lymphocyte–dependent vaccine. In contrast to plain polysaccharide vaccines, conjugate vaccines induce higher-avidity antibody, immunologic memory leading to booster responses on repeat exposure to the antigen, long-term immunity, and community protection by decreasing carriage of the organism (Table 215.5). As of 2023 in the United States, licensed conjugate vaccines are available to prevent Hib, pneumococcal, and meningococcal diseases.

Table 215.5 Characteristics of Polysaccharide and Conjugate Vaccines

CHARACTERISTIC	CONJUGATE	POLYSACCHARIDE
T-lymphocyte–dependent immune response	Yes	No
Immune memory	Yes	No
Persistence of protection	Yes	No
Booster effect	Yes	No
Reduction of carriage	Yes	No
Community protection	Yes	No
Lack of hyporesponsiveness	Yes	No

Serum antibodies may be detected as soon as 7-10 days after initial injection of antigen. Early antibodies are usually of the IgM class that can fix complement. IgM antibodies tend to decline as IgG antibodies increase. The IgG antibodies tend to peak approximately 1 month after vaccination and with most vaccines persist for some time after a primary vaccine course. Secondary or booster responses occur more rapidly and result from rapid proliferation of memory B and T lymphocytes.

Assessment of the immune response to most vaccines is performed by measuring serum antibodies. Although detection of serum antibody at levels considered protective after vaccination can indicate immunity, loss of detectable antibody over time does not necessarily mean susceptibility to disease. Some vaccines induce immunologic memory, leading to a booster or anamnestic response on exposure to the microorganism, with resultant protection from disease. In some cases, cellular immune response is used to evaluate the status of the immune system. Certain vaccines (e.g., acellular pertussis) do not have an accepted serologic correlate of protection.

Live-attenuated vaccines routinely recommended for children and adolescents include measles, mumps, and rubella **(MMR)**; MMR and varicella **(MMRV)**; rotavirus; and varicella. In addition, a cold-adapted, live-attenuated quadrivalent influenza vaccine **(LAIV4)** is available for influenza.

Live-attenuated vaccines tend to induce long-term immune responses. They replicate, often similarly to natural infections, until an immune response inhibits reproduction. Most live vaccines are administered in one-dose or two-dose schedules. The purpose of

repeat doses, such as a second dose of the MMR or MMRV vaccine, is to induce an initial immune response in those who failed to respond to the first dose. Because influenza viruses tend to mutate to evade preexisting immunity to prior strains, at least one of the strains in influenza vaccines each year is often different than in the previous year. Thus influenza vaccines are recommended to be administered yearly.

The remaining vaccines in the recommended schedule for children and adolescents are inactivated vaccines. **Inactivated vaccines** tend to require multiple doses to induce an adequate immune response and are more likely than live-attenuated vaccines to need booster doses to maintain that immunity. However, some inactivated vaccines appear to induce long-term or perhaps lifelong immunity after a primary series, including hepatitis B vaccine and inactivated polio vaccine.

VACCINATION SYSTEM IN THE UNITED STATES

Vaccine Production

Vaccine production is primarily a responsibility of private industry. Many of the vaccines recommended routinely for children are produced by only one vaccine manufacturer. Vaccines with multiple manufacturers include Hib, hepatitis B, rotavirus, MCV4 (meningococcal conjugate vaccine against serogroups A, C, W135, and Y), COVID-19 vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP), and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines for adolescents and adults. Inactivated polio vaccine (IPV) as an IPV-only vaccine has only one manufacturer, but IPV is also available in combination products (DTaP–hepatitis B–IPV, DTaP–IPV/Hib, and DTaP–IPV) from different manufacturers. Influenza vaccine for children 6-35 months of age is produced by fewer manufacturers. MMR, MMRV, varicella, pneumococcal conjugate vaccines, and tetanus and diphtheria (Td) vaccines also are produced by single manufacturers. The FDA has authorized for emergency use the Pfizer-BioNTech and Moderna COVID-19 vaccines for the prevention of COVID-19 disease in individuals 6 months of age and older. The FDA has also authorized the Novavax COVID-19 vaccine for individuals 12 years of age and older.

Vaccine Policy

Two major committees make vaccine policy recommendations for children: the Committee on Infectious Diseases (COID) of the AAP (the *Red Book* Committee) and the Advisory Committee on Immunization Practices (ACIP) of the CDC. Annually, the AAP, ACIP, American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), American College of Nurse-Midwives (www.midwife.org), American Academy of Physician Assistants (www.aapa.org), and National Association of Pediatric Nurse Practitioners (www.napnap.org) issue a harmonized childhood and adolescent immunization schedule. (http://www.cdc.gov/vaccines/schedules/index.html). The ACIP recommendations (http://www.cdc.gov/vaccines/acip/recs/index.html) are official only after adoption by the CDC director, which leads to publication in the *Morbidity and Mortality Weekly Report (MMWR Morb Mortal Wkly Rep)*. The AAP recommendations are published in *Pediatrics* and the *Red Book*, which includes its continuously updated online version (aapredbook.org).

Vaccine Financing

Approximately 50% of vaccines routinely administered to children and adolescents <19 years of age are purchased through a contract negotiated by the federal government with licensed vaccine manufacturers. Three major sources of funds are available to purchase vaccines through this contract. The greatest portion comes from the **Vaccines for Children (VFC)** program (http://www.cdc.gov/vaccines/programs/vfc/index.html), a federal entitlement program established in 1993. The VFC program covers children receiving Medicaid, children without insurance (uninsured), and Native Americans and Alaska Natives. In addition, underinsured children whose insurance does not cover immunization can be covered through VFC, but only if they go to a federally qualified health center (http://www.cms.gov/center/fqhc.asp). In contrast to other public funding sources that require approval of discretionary funding by legislative bodies, VFC funds are immediately available for new recommendations. These funds are only available if the ACIP votes the vaccine and the recommendation for its use into the VFC program, the federal government negotiates a contract, and the Office of Management and Budget (OMB) apportions funds. The VFC program can provide free vaccines to participating private providers for administration to children eligible for coverage under the program. The second major federal funding source is the Section 317 **Discretionary Federal Grant Program** to states and selected localities. These funds must be appropriated annually by Congress, and in contrast to VFC, they do not have eligibility requirements for use. The third major public source of funds is **state appropriations**.

The VFC program itself does not cover vaccine administration costs. Medicaid covers the administration fees for children enrolled in the program. Parents of other children eligible for VFC must pay administration fees out of pocket, although the law stipulates that no one eligible for the program can be denied vaccines because of inability to pay the administration fee. The Affordable Care Act (ACA) states that all vaccines recommended by ACIP and those included in the harmonized annual immunization schedules must be provided by qualified insurance programs with no copay and no deductible. For eligible children and adults, the COVID-19 vaccine is free of charge. (https://www.cdc.gov/vaccines/programs-/bridge/index.html).

Vaccine Safety Monitoring

Monitoring vaccine safety is the responsibility of the FDA, CDC, and vaccine manufacturers. A critical part of that monitoring depends on reports provided to the **Vaccine Adverse Event Reporting System (VAERS)**, the country's early warning system for vaccine safety comanaged by the CDC and the FDA. Adverse events after immunization can be reported by completing a VAERS form, which can be obtained from http://www.vaers.hhs.gov, or by calling 800-822-7967. VAERS can rapidly detect safety signals and rare adverse events but is not designed to assess causality. Individual VAERS case reports may be helpful in identifying potential vaccine safety concerns that can generate hypotheses about whether vaccines are causing certain clinical syndromes. In general, however, the reports are not helpful in evaluating the causal role of vaccines in the adverse event, because most clinical syndromes that follow vaccination are similar to syndromes that occur in the absence of vaccination, which constitute background rates. For causality assessment, epidemiologic studies are often necessary, comparing the incidence rate of the adverse event after vaccination with the rate in unvaccinated individuals. A statistically significant higher rate in vaccinated individuals would be consistent with causation. **V-safe** is a smartphone-based tool that uses text messaging and web surveys to provide personalized health check-ins for up to a year after someone receives a COVID-19 vaccine. Through v-safe, COVID-19 vaccine recipients are able to communicate with the CDC regarding possible side effects (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/pdfs/v-safe-information-sheet-508c.pdf).

The **Vaccine Safety Datalink** gathers data from nine participating integrated healthcare organizations on over 12 million people per year. It consists of inpatient and outpatient records of some of the largest managed-care organizations in the United States and facilitates causality evaluation. In addition, the **Clinical Immunization Safety Assessment (CISA)** network has been established to advise primary care physicians on evaluation and management of adverse events (http://www.cdc.gov/vaccinesafety/Activities/CISA.html). CISA facilitates the CDC's collaboration with a network of vaccine safety experts at seven leading academic medical centers and strengthens national capacity for vaccine safety monitoring and clinical research.

The Health and Medicine Division (HMD) of the National Academies of Sciences, Engineering and Medicine, previously the Institute of Medicine (IOM), has independently reviewed a variety of vaccine safety concerns and published reports summarizing its findings.* From 2001 through 2004, the IOM released eight reports, concluding that the body of epidemiologic evidence did not show an association between vaccines and autism. In 2012 the IOM (HMD) report *Adverse Effects of Vaccines: Evidence and Causality*** reviewed a list of reported adverse effects associated with eight vaccines to evaluate the scientific evidence, if any, of an event-vaccine relationship. The IOM committee had developed 158 causality conclusions and assigned each relationship between a vaccine and

* http://nationalacademies.org/hmd/Reports.aspx?filters=inmeta:activity=Immunization+Safety+Review.
** https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality

an adverse health problem to one of four causation categories. The committee concluded that available evidence convincingly supported a causal relationship between **anaphylaxis** and MMR, varicella-zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines. Additionally, the evidence *favored rejection* of five vaccine–adverse event relationships, including MMR vaccine and autism, inactivated influenza vaccines and asthma episodes and Bell palsy, and MMR and DTaP and type 1 diabetes mellitus. For the majority of cases (135 vaccine–adverse event pairs), the evidence was inadequate to accept or reject a causal relationship because of the rarity of the events. Overall, the committee concluded that few health problems are caused by or clearly associated with vaccines.

In 2013, the HMD released the report *Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies.*[†] The HMD uncovered no evidence of major safety concerns associated with adherence to the recommended childhood immunization schedule. The HMD specifically found no links between the immunization schedule and autoimmune diseases, asthma, hypersensitivity, seizures, child developmental disorders, learning or developmental disorders, or attention-deficit or disruptive disorders. Additionally, use of nonstandard schedules is harmful, because it increases the period of risk of acquiring vaccine-preventable diseases and increases the risk of incomplete immunization.[‡] In addition, the Agency for Healthcare Research and Quality (AHRQ) contracted with the Rand Corporation for an independent systematic review of the immunization schedule. That review concluded that although some vaccines are associated with serious adverse events, these events are extremely rare and must be weighed against the protective benefits that vaccines provide. The AAP has summarized the information on a variety of safety issues and different vaccines.[§]

The **National Vaccine Injury Compensation Program (VICP)** is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. The program is funded through an excise tax of $0.75 on vaccines recommended by the CDC per disease prevented per dose (e.g., the quadrivalent influenza vaccine is taxed $0.75 because it prevents one disease; the MMR vaccine is taxed $2.25 because it prevents three diseases). As of 2023, this program covers all the routinely recommended vaccines that protect children against 16 diseases. The VICP was established to provide a no-fault system, with a table of related injuries and time frames. In April 2018 the table was modified to reflect changes in the 21st Century Cures Act, requiring that the VICP cover vaccines recommended for routine administration in pregnant women. All people alleging injury from covered vaccines must first file with the program. If the injury meets the requirements of the table, compensation is automatic. If not, the claimant has the responsibility to prove causality. If compensation is accepted, the claimant cannot sue the manufacturer or physician administering the vaccine. If the claimant rejects the judgment of the compensation system, the claimant can enter the tort system, which is uncommon. Information on the VICP is available at http://www.hrsa.gov/vaccinecompensation or by calling 800-338-2382. All vaccines included in the child and adolescent vaccine schedule are covered by VICP except dengue, PPSV23, and COVID-19 vaccines. COVID-19 vaccines that are authorized or approved by the FDA are covered by the Countermeasures Injury Compensation Program (CICP). For more information, see www.hrsa.gov/ vaccinecompensation or www.hrsa.gov/cicp. All physicians administering a vaccine covered by the program are required by law to give the approved **Vaccine Information Statement (VIS)** to the child's parent or guardian at each visit before administering vaccines. Information on the VIS can be obtained from http://www.cdc.gov/vaccines/hcp/vis/index.html. There is no VIS for COVID-19 vaccines authorized under an emergency use authorization (EUA). For each COVID-19 vaccine approved by the FDA, a Vaccine Information Fact Sheet for recipients and caregivers is available. The FDA also requires that recipients or their caregivers be provided with certain vaccine-specific information for any COVID vaccine authorized under an EUA to help make an informed decision about vaccination. This is accomplished by providing an EUA Fact Sheet for Recipients and Caregivers. The fact sheet is similar in purpose and content to VISs for licensed vaccines but differs in that the EUA fact sheet is specific to each authorized COVID-19 vaccine, is developed by the manufacturer of the vaccine, and is authorized by the FDA. EUA fact sheets are available at https://www.cdc.gov/vaccines/covid-19/eua/index.html.

[†] https://www.nap.edu/catalog/13563/the-childhood-immunization-schedule-and-safety-stakeholder-concerns-scientific-evidence.

[‡] For more information on the reports, see http://nationalacademies.org/hmd/Reports.aspx.

[§] https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Vaccine-Studies-Examine-the-Evidence.aspx.

Vaccine Delivery

To ensure potency, vaccines should be stored at recommended temperatures before and after reconstitution. A comprehensive resource for providers on vaccine storage and handling recommendations and best practice strategies is available (https://www.cdc.gov/vaccines/hcp/admin/storage/index.html). Expiration dates should be noted and expired vaccines discarded. Lyophilized vaccines often have long shelf lives. However, the shelf life of reconstituted vaccines generally is short, ranging from 30 minutes for varicella vaccine to 8 hours for MMR vaccine.

All vaccines have a preferred route of administration, which is specified in package inserts and in AAP and ACIP recommendations. Most inactivated vaccines, including DTaP, hepatitis A, hepatitis B, Hib, inactivated influenza vaccine (IIV), HPV, PCV, COVID-19 vaccines, MCV4, and Tdap, are administered IM. In contrast, the more commonly used live-attenuated vaccines (MMR, MMRV, and varicella) should be dispensed by the SC route. Rotavirus vaccine is administered orally. IPV and PPS23 (pneumococcal polysaccharide vaccine) can be given IM or SC. One influenza vaccine, LAIV4, when recommended, is administered intranasally. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children. The recommended needle length varies depending on age and size: ⅝ inch for newborn infants, 1 inch for infants 2-12 months old, and ⅝ to 1 inch for children 3-10 years of age. For adolescents and adults, the deltoid muscle of the arm is the preferred site for IM administration with needle lengths of 1-1¼ inches depending on patient size. Most IM injections can be made with 23- to 25-gauge needles. For SC injections, needle lengths generally range from ⅝ to ¾ inch with 23- to 25-gauge needles.

Additional aspects of immunization important for pediatricians and other healthcare providers are detailed on the websites listed in Table 215.6.

RECOMMENDED IMMUNIZATION SCHEDULE

All children in the United States should be immunized against 19 diseases (Fig. 215.1 and Table 215.7) (annually updated schedule available at http://www.cdc.gov/vaccines/schedules/index.html).

Hepatitis B vaccine (HepB) is recommended in a three-dose schedule starting at birth. The birth dose, as well as hepatitis B immunoglobulin, is critical for infants born to mothers who are HBsAg-positive or whose hepatitis B immune status is unknown. The recommendation is to administer the first hepatitis B vaccine to all newborns within 24 hours of birth, the second dose at 1-2 months, with a minimal interval between the first and second dose of 4 weeks, and the third dose from 6 to 18 months of age, ensuring that 8 weeks has passed between the second and third dose. If either the DTaP-HepB-IPV combination vaccine or the DTaP-IPV-Hib-HepB combination vaccine is used, a four-dose schedule is permissible, which includes the stand-alone hepatitis B vaccine at birth and the combination vaccine for the next three doses. There are multiple alternatives for catch-up vaccination with HepB vaccine depending on the child's age. See the immunization schedule notes for clarification.

The **DTaP** series consists of five doses administered at 2, 4, 6, and 15 through 18 months of age and 4 through 6 years of age. The fourth dose of DTaP may be administered as early as 12 months of age, provided at least 6 months have elapsed since the third dose. The fifth (booster) dose of DTaP vaccine is not necessary if the fourth dose was administered at 4 years or older. One dose of an adult preparation of Tdap is recommended for all adolescents 11 through 12 years of age, even if a dose of Tdap or DTaP was administered inadvertently or as part of the catch-up series at 7-9 years of age. If Tdap is administered at 10 years of age, an additional booster at 11-12 years of age is not recommended. Adolescents 13 through 18 years who missed the 11 through 12 year Tdap booster dose should receive a single dose of Tdap if they have completed the diphtheria, tetanus, and pertussis (DTP)/DTaP series. Tdap may be given at any interval after the last Td. Table 215.8 lists preparations in which DTaP is

Table 215.6 Vaccine Websites and Resources

ORGANIZATION	WEBSITE
HEALTH PROFESSIONAL ASSOCIATIONS	
American Academy of Family Physicians (AAFP)	http://www.familydoctor.org/online/famdocen/home.html
American Academy of Pediatrics (AAP)	http://www.aap.org/
American Academy of Physician Assistants (AAPA)	https://www.aapa.org
AAP Childhood Immunization Support Program	http://www.aap.org/immunization/
American Association of Occupational Health Nurses (AAOHN)	http://www.aaohn.org/
American Association of Nurse Practitioners (AANP)	https://www.aanp.org
American College Health Association (ACHA)	http://www.acha.org/
American College of Nurse-Midwives (ACNM)	https://www.midwife.org
American College of Obstetricians and Gynecologists (ACOG)–Immunization for Women	http://www.immunizationforwomen.org/
American Medical Association (AMA)	http://www.ama-assn.org/
American Nurses Association (ANA)	http://www.nursingworld.org/
American Pharmacists Association (APhA)	http://www.pharmacist.com/
American School Health Association (ASHA)	http://www.ashaweb.org/
American Travel Health Nurses Association (ATHNA)	http://www.athna.org/
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
Association of State and Territorial Health Officials (ASTHO)	http://www.astho.org/
Association of Teachers of Preventive Medicine (ATPM)	http://www.atpm.org/
National Medical Association (NMA)	http://www.nmanet.org/
Society of Teachers of Family Medicine—Group on Immunization Education	http://www.immunizationed.org/
NONPROFIT GROUPS AND UNIVERSITIES	
Albert B. Sabin Vaccine Institute	http://www.sabin.org/
Brighton Collaboration	https://brightoncollaboration.org/public
Center for Vaccine Awareness and Research—Texas Children's Center	http://www.texaschildrens.org/departments/immunization-project
Children's Vaccine Program	http://www.path.org/vaccineresources/
Every Child by Two (ECBT)	http://www.ecbt.org/
Families Fighting Flu	http://www.familiesfightingflu.org/
GAVI, the Vaccine Alliance	http://www.gavialliance.org/
Health on the Net Foundation (HON)	http://www.hon.ch/
Immunization Action Coalition (IAC)	http://www.immunize.org/
Infectious Diseases Society of America (IDSA)	http://www.idsociety.org/Index.aspx
Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu/
National Academies: Health and Medicine Division	http://www.nationalacademies.org/hmd/
National Alliance for Hispanic Health	http://www.hispanichealth.org/
National Association of Certified Professional Midwives	https://nacpm.org
National Foundation for Infectious Diseases (NFID)	http://www.nfid.org
National Foundation for Infectious Diseases (NFID)—Childhood Influenza Immunization Coalition (CIIC)	http://www.preventchildhoodinfluenza.com/
National Network for Immunization Information (NNii)	http://www.immunizationinfo.net/
Parents of Kids with Infectious Diseases (PKIDS)	http://www.pkids.org/
PATH Vaccine Resource Library	http://www.path.org/resources/vaccine-resource-library-website
Vaccine Education Center at the Children's Hospital of Philadelphia	http://www.chop.edu/service/vaccine-education-center/home.html
Vaccinate Your Baby	http://www.vaccinateyourbaby.org/
GOVERNMENT ORGANIZATIONS	
Centers for Disease Control and Prevention (CDC)	
Advisory Committee on Immunization Practices (ACIP)	http://www.cdc.gov/vaccines/acip/index.html
ACIP Vaccine Recommendations	http://www.cdc.gov/vaccines/hcp/acip-recs/index.html
Current Vaccine Delays and Shortages	http://www.cdc.gov/vaccines/vac-gen/shortages/
Epidemiology and Prevention of Vaccine-Preventable Diseases (also known as the Pink Book)	https://www.cdc.gov/vaccines/pubs/pinkbook/index.html
Manual for the Surveillance of Vaccine-Preventable Diseases	www.cdc.gov/vaccines/pubs/surv-manual/index.html
Public Health Image Library	https://phil.cdc.gov/phil/home.asp
Travelers' Health	http://www.cdc.gov/travel/
CDC Health Information for International Travel (also known as the Yellow Book)	https://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents
Vaccine Adverse Events Reporting System (VAERS)	http://www.cdc.gov/vaccinesafety/Activities/vaers.html
Vaccine Administration: Recommendations and Guidelines	http://www.cdc.gov/vaccines/recs/vac-admin/default.htm
Vaccines and Immunizations	http://www.cdc.gov/vaccines/
Vaccines for Children Program	http://www.cdc.gov/vaccines/programs/vfc/index.html
Vaccines for Children—Vaccine Price List	http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Vaccine Information Statements	www.cdc.gov/vaccines/hcp/vis/index.html

Table 215.6 Vaccine Websites and Resources—cont'd

ORGANIZATION	WEBSITE
Vaccine Safety	http://www.cdc.gov/vaccinesafety/index.html
Vaccine Storage and Handling	http://www.cdc.gov/vaccines/recs/storage/default.htm
Department of Health and Human Services (HHS)	
National Vaccine Program Office (NVPO)	http://www.hhs.gov/nvpo/
Health Resources and Services Administration	
National Vaccine Injury Compensation Program	http://www.hrsa.gov/vaccinecompensation/
National Institute of Allergy and Infectious Diseases (NIAID)	
Vaccines	https://www.niaid.nih.gov/about/vrc
World Health Organization (WHO)	
Immunization, Vaccines, and Biologicals	http://www.who.int/immunization/en/

Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 215.7).

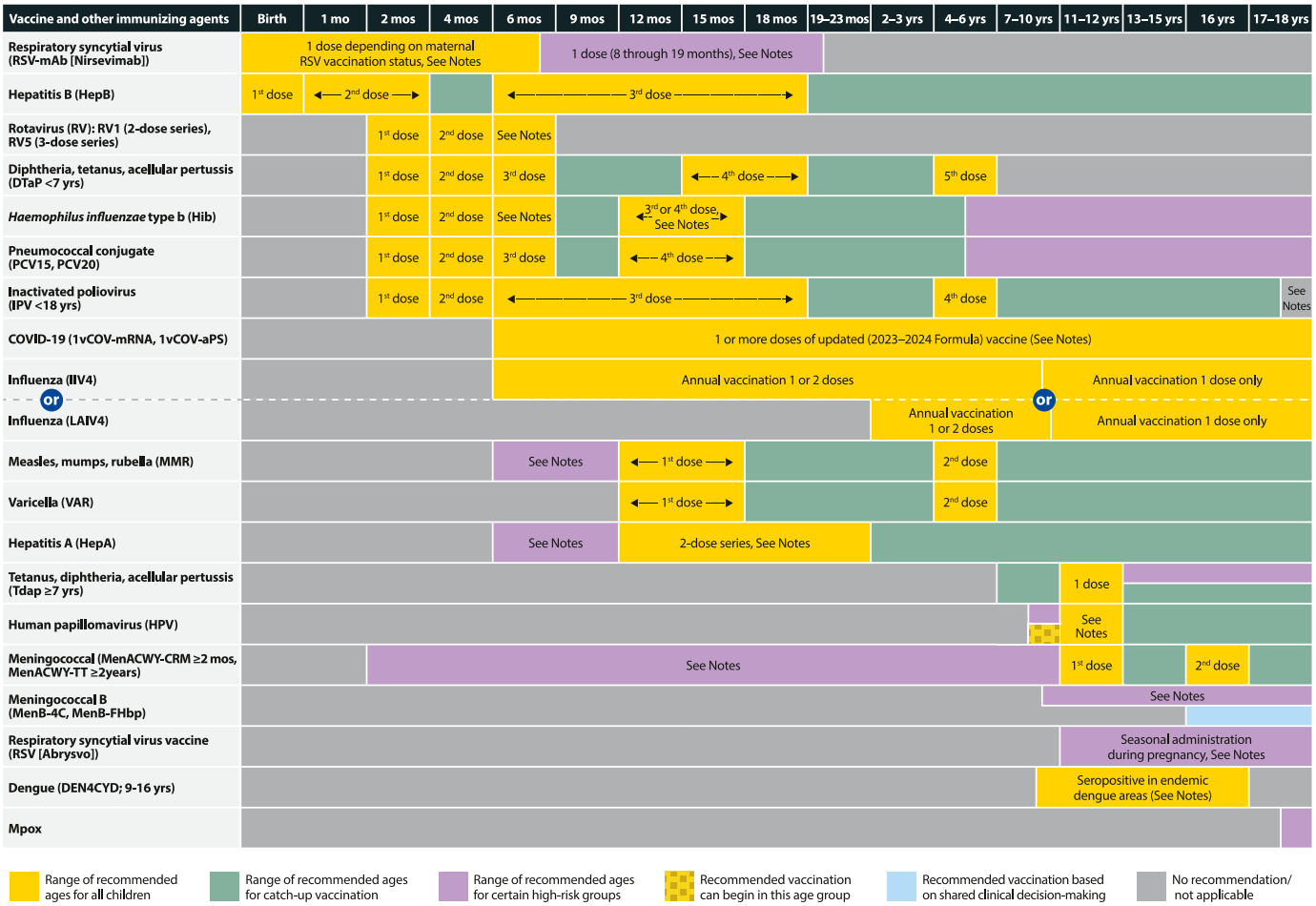

Fig. 215.1 Recommended immunization schedule for children and adolescents age 18 yr or younger—United States, 2024, including an appendix detailing contraindications and precautions for commonly used vaccines. *These recommendations must be read with the notes that follow.* For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the *green bars.* A new addendum section has been added to list any ACIP recommendations that occur by majority vote and are approved by CDC Director after the 2024 immunization schedules are approved and published. To determine minimum intervals between doses, see the Catch-Up Schedule (see Table 215.7). *(Courtesy U.S. Centers for Disease Control and Prevention, Atlanta, 2023. https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf; Appendix is adapted from the Advisory Committee on Immunization Practices [ACIP] General Best Practice Guidelines for Immunization: Contraindication and Precautions, Table 4-1, available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and from the ACIP's Recommendations for the Prevention and Control of 2023-24 seasonal influenza with vaccines available at www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm.)*

Notes

For vaccination recommendations for persons ages 19 years or older, see the Recommended Adult Immunization Schedule, 2024.

Additional information

- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age appropriate. **The repeat dose should be spaced after the invalid dose by the recommended minimum interval.** For further details, see Table 3-2, Recommended and minimum ages and intervals between vaccine doses, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccination requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Barnett ED, Lynfield Ruth, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:72–86).
- For information about vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All vaccines included in the child and adolescent vaccine schedule are covered by VICP except dengue, PPSV23, RSV, Mpox and COVID-19 vaccines. Mpox and COVID-19 vaccines are covered by the Countermeasures Injury Compensation Program (CICP). For more information, see www.hrsa.gov/vaccinecompensation or www.hrsa.gov/cicp.

COVID-19 vaccination (minimum age: 6 months [Moderna and Pfizer-BioNTech COVID-19 vaccines], 12 years [Novavax COVID-19 Vaccine])

Routine vaccination

Age 6 months–4 years

- **Unvaccinated:**
  - 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4-8 weeks
  - 3-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3-8, 11-16 weeks
- **Previously vaccinated* with 1 dose of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna 4-8 weeks after the most recent dose.
- **Previously vaccinated* with 2 or more doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 8 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 8 weeks (minimum interval between previous Pfizer-BioNTech and dose 1: 3-8 weeks).
- **Previously vaccinated* with 2 or more doses of any Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 5–11 years

- **Unvaccinated:** 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech vaccine.
- **Previously vaccinated* with 1 or more doses of Moderna or Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 12–18 years

- **Unvaccinated:**
  - 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech vaccine
  - 2-dose series of updated (2023–2024 Formula) Novavax at 0, 3-8 weeks
- **Previously vaccinated* with any COVID-19 vaccine(s):** 1 dose of any updated (2023–2024 Formula) COVID-19 vaccine at least 8 weeks after the most recent dose.

Special situations

Persons who are moderately or severely immunocompromised**

Age 6 months–4 years

- **Unvaccinated:**
  - 3-dose series of updated (2023–2024 Formula) Moderna at 0, 4, 8 weeks
  - 3-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3, 11 weeks.
- **Previously vaccinated* with 1 dose of any Moderna:** 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4 weeks (minimum interval between previous Moderna and dose 1: 4 weeks).
- **Previously vaccinated* with 2 doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 3 or more doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 8 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 8 weeks (minimum interval between previous Pfizer-BioNTech and dose 1: 3 weeks).
- **Previously vaccinated* with 2 or more doses of any Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 5–11 years

- **Unvaccinated:**
  - 3-dose series of updated (2023–2024 Formula) Moderna at 0, 4, 8 weeks
  - 3-dose series updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3, 7 weeks.
- **Previously vaccinated* with 1 dose of any Moderna:** 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4 weeks (minimum interval between previous Moderna and dose 1: 4 weeks).
- **Previously vaccinated* with 2 doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 4 weeks (minimum interval between previous Pfizer-BioNTech and dose 1: 3 weeks)
- **Previously vaccinated* with 2 doses of any Pfizer-BioNTech:** 1 dose of 2023–2024 Pfizer-BioNTech at least 4 weeks after the most recent dose.
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as age 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Special situations

- **Wound management** in children less than age 7 years with history of 3 or more doses of tetanus-toxoid-containing vaccine: For all wounds except clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus-toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB®, Hiberix®, Pentacel®, or Vaxelis®:** 4-dose series (3-dose primary series at age 2, 4, and 6 months, followed by a booster dose* at age 12–15 months)
  - *Vaxelis® is not recommended for use as a booster dose. A different Hib-containing vaccine should be used for the booster dose.
- **PedvaxHIB®:** 3-dose series (2-dose primary series at age 2 and 4 months, followed by a booster dose at age 12–15 months)

Catch-up vaccination

- **Dose 1 at age 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at age12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at age 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before age 12 months and dose 2 before age 15 months:** Administer dose 3 (final dose) at least 8 weeks after dose 2.
- **2 doses of PedvaxHIB® before age 12 months:** Administer dose 3 (final dose) at age12–59 months and at least 8 weeks after dose 2.
- **1 dose administered at age 15 months or older:** No further doses needed
- **Unvaccinated at age 15–59 months:** Administer 1 dose.

- **Previously vaccinated* with 3 or more doses of any Moderna or Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 12–18 years

- **Unvaccinated:**
  - 3-dose series of updated (2023–2024 Formula) Moderna at 0, 4, 8 weeks
  - 3-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3, 7 weeks
  - 2-dose series of updated (2023–2024 Formula) Novavax at 0, 3 weeks
- **Previously vaccinated* with 1 dose of any Moderna:** 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4 weeks (minimum interval between previous Moderna dose and dose 1: 4 weeks).
- **Previously vaccinated* with 2 doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 4 weeks (minimum interval between previous Pfizer-BioNTech dose and dose 1: 3 weeks).
- **Previously vaccinated* with 2 doses of any Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Pfizer-BioNTech at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 3 or more doses of any Moderna or Pfizer-BioNTech:** 1 dose of any updated (2023–2024 Formula) COVID-19 vaccine at least 8 weeks after the most recent dose.
- **Previously vaccinated* with 1 or more doses of Janssen or Novavax or with or without dose(s) of any Original monovalent or bivalent COVID-19 vaccine:** 1 dose of any updated (2023–2024 Formula) COVID-19 vaccine at least 8 weeks after the most recent dose.

There is no preferential recommendation for the use of one COVID-19 vaccine over another when more than one recommended age-appropriate vaccine is available.

Administer an age-appropriate COVID-19 vaccine product for each dose. For information about transition from age 4 years to age 5 years or age 11 years to age 12 years during COVID-19 vaccination series, see Tables 1 and 2 at www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#covid-vaccines.

Current COVID-19 schedule and dosage formulation available at www.cdc.gov/covidschedule. For more information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, see www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines

***Note:** Previously vaccinated is defined as having received any Original monovalent or bivalent COVID-19 vaccine (Janssen, Moderna, Novavax, Pfizer-BioNTech) prior to the updated 2023–2024 formulation.

****Note:** Persons who are moderately or severely immunocompromised have the option to receive one additional dose of updated (2023–2024 Formula) COVID-19 vaccine at least 2 months following the last recommended updated (2023–2024 Formula) COVID-19 vaccine dose. Further additional updated (2023–2024 Formula) COVID-19 vaccine dose(s) may be administered, informed by the clinical judgement of a healthcare provider and personal preference and circumstances. Any further additional doses should be administered at least 2 months after the last updated (2023–2024 Formula) COVID-19 vaccine dose. Moderately or severely immunocompromised children 6 months–4 years of age should receive homologous updated (2023–2024 Formula) mRNA vaccine dose(s) if they receive additional doses.

Dengue vaccination (minimum age: 9 years)

Routine vaccination

- Age 9–16 years living in areas with endemic dengue **AND** have laboratory confirmation of previous dengue infection
  - 3-dose series administered at 0, 6, and 12 months
- Endemic areas include Puerto Rico, American Samoa, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue endemic areas and pre-vaccination laboratory testing see www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?s_cid=rr7006a1_w and www.cdc.gov/dengue/vaccine/hcp/index.html
- Dengue vaccine should not be administered to children traveling to or visiting endemic dengue areas.

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix® or Quadracel®])

Routine vaccination

- 5-dose series (3-dose primary series at age 2, 4, and 6 months, followed by a booster doses at ages 15–18 months and 4–6 years

Fig. 215.1, cont'd

- **Previously unvaccinated children age 60 months or older who are not considered high risk:** Do not require catch-up vaccination

For other catch-up guidance, see Table 2. Vaxelis® can be used for catch-up vaccination in children less than age 5 years. Follow the catch-up schedule even if Vaxelis® is used for one or more doses. For detailed information on use of Vaxelis® see www.cdc.gov/mmwr/volumes/69/wr/mm6905a5.htm.

Special situations

- **Chemotherapy or radiation treatment:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated* persons age 5 years or older
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated* persons age 15 months or older
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated* persons age 5–18 years
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart

Special situations

- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Post-vaccination serology testing and revaccination** (if anti-HBs <10mIU/mL) is recommended for certain populations, including:
  - Infants born to HBsAg-positive mothers
  - Persons who are predialysis or on maintenance dialysis
  - Other immunocompromised persons
  - For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Note: Heplisav-B and PreHevbrio are not recommended in pregnancy due to lack of safety data in pregnant persons

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination

- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9–14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- No additional dose recommended when any HPV vaccine series **of any valency** has been completed using recommended dosing intervals.

Special situations

- **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
- **History of sexual abuse or assault:** Start at age 9 years
- **Pregnancy:** Pregnancy testing not needed before vaccination; HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

Unvaccinated* = Less than routine series (through age 14 months) **OR no doses (age 15 months or older)

Hepatitis A vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (minimum interval: 6 months) at age 12–23 months

Catch-up vaccination

- Unvaccinated persons through age 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses (separated by at least 6 months) between age 12–23 months.
  - **Unvaccinated age 12 months or older**: Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination
(minimum age: birth)

Routine vaccination

- 3-dose series at age 0, 1–2, 6–18 months **(use monovalent HepB vaccine for doses administered before age 6 weeks)**
  - Birth weight ≥2,000 grams: 1 dose within 24 hours of birth if medically stable
  - Birth weight <2,000 grams: 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).
- Infants who did not receive a birth dose should begin the series as soon as possible (see Table 2 for minimum intervals).
- Administration of 4 doses is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum intervals (see Table 2):** when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations
- **Final (3rd or 4th) dose:** age 6–18 months **(minimum age 24 weeks)**
- **Mother is HBsAg-positive**
  - **Birth dose (monovalent HepB vaccine only):** administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight.
  - **Birth weight <2000 grams:** administer 3 additional doses of HepB vaccine beginning at age 1 month (total of 4 doses)
  - **Final (3rd or 4th) dose:** administer at age 6 months **(minimum age 24 weeks)**
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose. Do not test before age 9 months.
- **Mother is HBsAg-unknown**

  If other evidence suggestive of maternal hepatitis B infection exists (e.g., presence of HBV DNA, HBeAg-positive, or mother known to have chronic hepatitis B infection), manage infant as if mother is HBsAg-positive
  - **Birth dose (monovalent HepB vaccine only):**
    - Birth weight ≥2,000 grams: administer **HepB vaccine** within 12 hours of birth. Determine mother's HBsAg status as soon as possible. If mother is determined to be HBsAg-positive, administer **HBIG** as soon as possible (in separate limb), but no later than 7 days of age.
    - Birth weight <2,000 grams: administer **HepB vaccine** and **HBIG** (in separate limbs) within 12 hours of birth. Administer 3 additional doses of **HepB vaccine** beginning at age 1 month (total of 4 doses)
  - **Final (3rd or 4th) dose:** administer at age 6 months **(minimum age 24 weeks)**
  - If mother is determined to be HBsAg-positive or if status remains unknown, test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose. Do not test before age 9 months.

Catch-up vaccination

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months. See Table 2 for minimum intervals
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB®** only).
- Adolescents age 18 years may receive:
  - **Heplisav-B®:** 2-dose series at least 4 weeks apart
  - **PreHevbrio®:** 3-dose series at 0, 1, and 6 months
  - Combined HepA and HepB vaccine, **Twinrix®:** 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV4], 18 years [recombinant influenza vaccine, RIV4])

Routine vaccination

- Use any influenza vaccine appropriate for age and health status annually:
  - **Age 6 months–8 years** who have received **fewer** than 2 influenza vaccine doses before July 1, 2023, or whose influenza vaccination history is unknown: 2 doses, separated by at least 4 weeks. Administer dose 2 even if the child turns 9 years between receipt of dose 1 and dose 2.
  - **Age 6 months–8 years** who have received **at least** 2 influenza vaccine doses before July 1, 2023: 1 dose
  - **Age 9 years or older:** 1 dose
- For the 2023-2024 season, see www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm.
- For the 2024–25 season, see the 2024–25 ACIP influenza vaccine recommendations.

Special situations

- **Close contacts (e.g., household contacts) of severely immunosuppressed persons who require a protected environment:** should not receive LAIV4. If LAIV4 is given, they should avoid contact with for such immunosuppressed persons for 7 days after vaccination.

Note: Persons with an egg allergy can receive any influenza vaccine (egg-based and non-egg-based) appropriate for age and health status.

Measles, mumps, and rubella vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series at age 12–15 months, age 4–6 years
- MMR or MMRV* may be administered

Note: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV* may be used if parents or caregivers express a preference.

Catch-up vaccination

- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart*
- The maximum age for use of MMRV* is 12 years.

Special situations

- **International travel**
  - **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.*
  - **Unvaccinated children age 12 months or older:** 2-dose series at least 4 weeks apart before departure*
- In mumps outbreak settings, for information about additional doses of MMR (including 3rd dose of MMR), see www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm

***Note:** If MMRV is used, the minimum interval between MMRV doses is 3 months

Meningococcal serogroup A,C,W,Y vaccination
(minimum age: 2 months [MenACWY-CRM, Menveo], 2 years [MenACWY-TT, MenQuadfi]), 10 years [MenACWY-TT/MenB-FHbp, Penbraya])

Routine vaccination

- 2-dose series at age 11–12 years; 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Menveo®***
  - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6, and 12 months)
  - Dose 1 at age 3–6 months: 3- or 4-dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **MenQuadfi®**
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart

Fig. 215.1, cont'd

Travel to countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (www.cdc.gov/travel/):

- Children less than age 24 months:
  - **Menveo®* (age 2–23 months)**
    - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6, and 12 months)
    - Dose 1 at age 3–6 months: 3- or 4-dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
    - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
- Children age 2 years or older: 1 dose Menveo®* or MenQuadfi®

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo®*** or **MenQuadfi®**

Adolescent vaccination of children who received MenACWY prior to age 10 years:

- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement component deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk.
- **Children for whom boosters are not recommended** (e.g., a healthy child who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

**Menveo has two formulations: lyophilized and liquid. The liquid formulation should not be used before age 10 years. See www.cdc.gov/vaccines/vpd/mening/downloads/menveo-single-vial-presentation.pdf.*

Note: For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Children age 10 years or older may receive a single dose of Penbraya™ as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day (see "Meningococcal serogroup B vaccination" section below for more information).

Meningococcal serogroup B vaccination
(minimum age: 10 years [MenB-4C, Bexsero®; MenB-FHbp, Trumenba®; MenACWY-TT/MenB-FHbp, Penbraya™])

Shared clinical decision-making

- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
  - **Bexsero®:** 2-dose series at least 1 month apart
  - **Trumenba®:** 2-dose series at least 6 months apart (if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2)

For additional information on shared clinical decision-making for MenB, see www.cdc.gov/vaccines/hcp/admin/downloads/isd-job-aid-scdm-mening-b-shared-clinical-decision-making.pdf

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Bexsero®:** 2-dose series at least 1 month apart
- **Trumenba®:** 3-dose series at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed; if dose 3 is administered earlier than 4 months after dose 2, a 4th dose should be administered at least 4 months after dose 3)

Note: Bexsero® and **Trumenba®** are not interchangeable; the same product should be used for all doses in a series.

For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Children age 10 years or older may receive a dose of Penbraya™ as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day. For age-eligible children not at increased risk, if Penbraya™ is used for dose 1 MenB, MenB-FHbp (Trumenba) should be administered for dose 2 MenB. For age-eligible children at increased risk of meningococcal disease, Penbraya™ may be used for additional MenACWY and MenB doses (including booster doses) if both would be given on the same clinic day **and** at least 6 months have elapsed since most recent Penbraya™ dose.

Mpox vaccination
(minimum age: 18 years [Jynneos®])

Special situations

- **Age 18 years and at risk for Mpox infection:** 2-dose series, 28 days apart.

  Risk factors for Mpox infection include:
  - Persons who are gay, bisexual, and other MSM, transgender or nonbinary people who in the past 6 months have had:
    - A new diagnosis of at least 1 sexually transmitted disease
    - More than 1 sex partner
    - Sex at a commercial sex venue
    - Sex in association with a large public event in a geographic area where Mpox transmission is occurring
  - Persons who are sexual partners of the persons described above
  - Persons who anticipate experiencing any of the situations described above
- **Pregnancy:** There is currently no ACIP recommendation for Jynneos use in pregnancy due to lack of safety data in pregnant persons. Pregnant persons with any risk factor described above may receive Jynneos.

For detailed information, see: www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/04-MPOX-Rao-508.pdf

Pneumococcal vaccination
(minimum age: 6 weeks [PCV15], [PCV 20]; 2 years [PPSV23])

Routine vaccination with PCV

- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV

- Healthy children ages 2–4 years with any incomplete* PCV series: 1 dose PCV
- For other catch-up guidance, see Table 2.

Note: For children **without** risk conditions, PCV20 is not indicated if they have received 4 doses of PCV13 or PCV15 or another age appropriate complete PCV series.

Special situations

Children and adolescents with cerebrospinal fluid leak; chronic heart disease; chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome); chronic liver disease; chronic lung disease (including moderate persistent or severe persistent asthma); cochlear implant; or diabetes mellitus:

Age 2–5 years

- Any incomplete* PCV series with:
  - 3 PCV doses: 1 dose PCV (at least 8 weeks after the most recent PCV dose)
  - Less than 3 PCV doses: 2 doses PCV (at least 8 weeks after the most recent dose and administered at least 8 weeks apart)
- Completed recommended PCV series but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no further PCV or PPSV23 doses needed
  - Not previously received PCV20: administer 1 dose PCV20 OR 1 dose PPSV23 administer at least 8 weeks after the most recent PCV dose.

Age 6–18 years

- Not previously received any dose of PCV13, PCV15, or PCV20: administer 1 dose of PCV15 or PCV20. If PCV15 is used and no previous receipt of PPSV23, administer 1 dose of PPSV23 at least 8 weeks after the PCV15 dose.**
- Received PCV before age 6 years but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no further PCV or PPSV23 doses needed
  - Not previously received PCV20: 1 dose PCV20 OR 1 dose PPSV23 administer at least 8 weeks after the most recent PCV dose.
- Received PCV13 only at or after age 6 years: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV13 dose.
- Received 1 dose PCV13 and 1 dose PPSV23 at or after age 6 years: no further doses of any PCV or PPSV23 indicated.

Children and adolescents on maintenance dialysis, or with immunocompromising conditions such as nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; or sickle cell disease or other hemoglobinopathies:

Age 2–5 years

- Any incomplete* PCV series:
  - 3 PCV doses: 1 dose PCV (at least 8 weeks after the most recent PCV dose)
  - Less than 3 PCV doses: 2 doses PCV (at least 8 weeks after the most recent dose and administered at least 8 weeks apart)
- Completed recommended PCV series but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no further PCV or PPSV23 doses needed
  - Not previously received PCV20: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV dose. If PPSV23 is used, administer 1 dose of PCV20 or dose 2 PPSV23 at least 5 years after dose 1 PPSV23.

Age 6–18 years

- Not previously received any dose of PCV13, PCV15, or PCV20: administer 1 dose of PCV15 or 1 dose of PCV20. If PCV15 is used and no previous receipt of PPSV23, administer 1 dose of PPSV23 at least 8 weeks after the PCV15 dose.**
- Received PCV before age 6 years but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no additional dose of PCV or PPSV23
  - Not previously received PCV20: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV dose. If PPSV23 is used, administer either PCV20 or dose 2 PPSV23 at least 5 years after dose 1 PPSV23.
- Received PCV13 only at or after age 6 years: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV13 dose. If PPSV23 is used, administer 1 dose of PCV20 or dose 2 PPSV23 at least 5 years after dose 1 PPSV23.
- Received 1 dose PCV13 and 1 dose PPSV23 at or after age 6 years: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV13 dose and at least 5 years after dose 1 PPSV23.

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series. See Table 2 in ACIP pneumococcal recommendations at stacks.cdc.gov/view/cdc/133252

***When both PCV15 and PPSV23 are indicated, administer all doses of PCV15 first. PCV15 and PPSV23 should not be administered during the same visit.*

For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app, which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

Poliovirus vaccination
(minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended on or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- **Adolescents age 18 years known or suspected to be unvaccinated or incompletely vaccinated:** administer remaining doses (1, 2, or 3 IPV doses) to complete a 3-dose primary series.* Unless there are specific reasons to believe they were not vaccinated, most persons aged 18 years or older born and raised in the United States can assume they were vaccinated against polio as children.

Series containing oral poliovirus vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_%20cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Fig. 215.1, cont'd

Special situations

- **Adolescents aged 18 years at increased risk of exposure to poliovirus and completed primary series*:** may administer one lifetime IPV booster

***Note:** Complete primary series consist of at least 3 doses of IPV or trivalent oral poliovirus vaccine (tOPV) in any combination.

For detailed information, see: www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html

Respiratory syncytial virus immunization (minimum age: birth [Nirsevimab, RSV-mAb (Beyfortus™)]

Routine immunization

- **Infants born October – March in most of the continental United States***
  - Mother did not receive RSV vaccine OR mother's RSV vaccination status is unknown: administer 1 dose nirsevimab within 1 week of birth in hospital or outpatient setting
  - Mother received RSV vaccine **less than 14 days** prior to delivery: administer 1 dose nirsevimab within 1 week of birth in hospital or outpatient setting
  - Mother received RSV vaccine **at least 14 days** prior to delivery: nirsevimab not needed but can be considered in rare circumstances at the discretion of healthcare providers (see special populations and situations at www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html)
- **Infants born April–September in most of the continental United States***
  - Mother did not receive RSV vaccine OR mother's RSV vaccination status is unknown: administer 1 dose nirsevimab shortly before start of RSV season*
  - Mother received RSV vaccine **less than 14 days** prior to delivery: administer 1 dose nirsevimab shortly before start of RSV season*
  - Mother received RSV vaccine **at least 14 days** prior to delivery: nirsevimab not needed but can be considered in rare circumstances at the discretion of healthcare providers(see special populations and situations at www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html)

Infants with prolonged birth hospitalization** (e.g., for prematurity) discharged October through March should be immunized shortly before or promptly after discharge.

Special situations

- **Ages 8–19 months with chronic lung disease of prematurity requiring medical support (e.g., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season; severe immunocompromise; cystic fibrosis with either weight for length <10th percentile or manifestation of severe lung disease (e.g., previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable)**:**
  - 1 dose nirsevimab shortly before start of second RSV season*
- **Ages 8–19 months who are American Indian or Alaska Native:**
  - 1 dose nirsevimab shortly before start of second RSV season*
- **Age-eligible and undergoing cardiac surgery with cardiopulmonary bypass**:** 1 additional dose of nirsevimab after surgery. For additional details see special populations and situations at www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html

***Note:** While the timing of the onset and duration of RSV season may vary, nirsevimab may be administered October through March in most of the continental United States. Providers in jurisdictions with RSV seasonality that differs from most of the continental United States (e.g., Alaska, jurisdiction with tropical climate) should follow guidance from public health authorities (e.g., CDC, health departments) or regional medical centers on timing of administration based on local RSV seasonality. Although optimal timing of administration is just before the start of the RSV season, nirsevimab may also be administered during the RSV season to infants and children who are age-eligible.

****Note:** Nirsevimab can be administered to children who are eligible to receive palivizumab. Children who have received nirsevimab should not receive palivizumab for the same RSV season.

For further guidance, see www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm and www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html

Respiratory syncytial virus vaccination (RSV [Abrysvo™])

Routine vaccination

- **Pregnant at 32 weeks 0 days through 36 weeks and 6 days gestation from September through January in most of the continental United States*:** 1 dose RSV vaccine (Abrysvo™). Administer RSV vaccine regardless of previous RSV infection.
  - Either maternal RSV vaccination or infant immunization with nirsevimab (RSV monoclonal antibody) is recommended to prevent respiratory syncytial virus lower respiratory tract infection in infants.
- **All other pregnant persons:** RSV vaccine not recommended.

There is currently no ACIP recommendation for RSV vaccination in subsequent pregnancies. No data are available to inform whether additional doses are needed in later pregnancies.

***Note:** Providers in jurisdictions with RSV seasonality that differs from most of the continental United States (e.g., Alaska, jurisdiction with tropical climate) should follow guidance from public health authorities (e.g., CDC, health departments) or regional medical centers on timing of administration based on local RSV seasonality.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination

- **Rotarix®:** 2-dose series at age 2 and 4 months
- **RotaTeq®:** 3-dose series at age 2, 4, and 6 months
- If any dose in the series is either **RotaTeq®** or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- **Age 11–12 years:** 1 dose Tdap (adolescent booster)
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36.

Note: Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- **Age 13–18 years who have not received Tdap:** 1 dose Tdap (adolescent booster)
- **Age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at age 7–10 years:**
  - **Age 7–9 years** who receive Tdap should receive the adolescent Tdap booster dose at age 11–12 years.
  - **Age 10 years** who receive Tdap do not need the adolescent Tdap booster dose at age 11–12 years.
- **DTaP inadvertently administered on or after age 7 years**:
  - **Age 7–9 years**: DTaP may count as part of catch-up series. Administer adolescent Tdap booster dose at age 11–12 years.
  - **Age 10–18 years**: Count dose of DTaP as the adolescent Tdap booster dose.
- For other catch-up guidance, see Table 2.

Special situations

- **Wound management** in persons age 7 years or older with history of 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap.
- For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older*

Varicella vaccination (minimum age: 12 months)

Routine vaccination

- 2-dose series at age 12–15 months, 4–6 years
- VAR or MMRV may be administered*
- Dose 2 may be administered as early as 3 months after dose 1 (a dose inadvertently administered after at least 4 weeks may be counted as valid)

***Note**: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have a 2-dose series:
  - **Age 7–12 years**: Routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)
  - **Age 13 years and older**: Routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of *MMRV* is 12 years.

Fig. 215.1, cont'd

Appendix Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

Guide to Contraindications and Precautions to Commonly Used Vaccines

Vaccines and other Immunizing Agents	Contraindicated or Not Recommended[1]	Precautions[2]
COVID-19 mRNA vaccines [Pfizer-BioNTech, Moderna]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of an mRNA COVID-19 vaccine[4]	• Diagnosed non-severe allergy (e.g., urticaria beyond the injection site) to a component of an mRNA COVID-19 vaccine[4]; or non-severe, immediate (onset less than 4 hours) allergic reaction after administration of a previous dose of an mRNA COVID-19 vaccine • Myocarditis or pericarditis within 3 weeks after a dose of any COVID-19 vaccine • Multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A) • Moderate or severe acute illness, with or without fever
COVID-19 protein subunit vaccine [Novavax]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of a Novavax COVID-19 vaccine[4]	• Diagnosed non-severe allergy (e.g., urticaria beyond the injection site) to a component of Novavax COVID-19 vaccine[4]; or non-severe, immediate (onset less than 4 hours) allergic reaction after administration of a previous dose of a Novavax COVID-19 vaccine • Myocarditis or pericarditis within 3 weeks after a dose of any COVID-19 vaccine • Multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A) • Moderate or severe acute illness, with or without fever
Influenza, egg-based, inactivated injectable (IIV4)	• Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV of any valency) • Severe allergic reaction (e.g., anaphylaxis) to any vaccine component[3] (excluding egg)	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Moderate or severe acute illness with or without fever
Influenza, cell culture-based inactivated injectable (ccIIV4) [Flucelvax Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) to any ccIIV of any valency, or to any component[3] of ccIIV4	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any egg-based IIV, RIV, or LAIV of any valency. If using ccIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, recombinant injectable (RIV4) [Flublok Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) to any RIV of any valency, or to any component[3] of RIV4	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any egg-based IIV, ccIIV, or LAIV of any valency. If using RIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, live attenuated (LAIV4) [Flumist Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV of any valency) • Severe allergic reaction (e.g., anaphylaxis) to any vaccine component[3] (excluding egg) • Children age 2–4 years with a history of asthma or wheezing • Anatomic or functional asplenia • Immunocompromised due to any cause including, but not limited to, medications and HIV infection • Close contacts or caregivers of severely immunosuppressed persons who require a protected environment • Pregnancy • Cochlear implant • Active communication between the cerebrospinal fluid (CSF) and the oropharynx, nasopharynx, nose, ear or any other cranial CSF leak • Children and adolescents receiving aspirin or salicylate-containing medications • Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Asthma in persons age 5 years old or older • Persons with underlying medical conditions other than those listed under contraindications that might predispose to complications after wild-type influenza virus infection, e.g., chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus) • Moderate or severe acute illness with or without fever

1. When a contraindication is present, a vaccine should **NOT** be administered. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization.
2. When a precaution is present, vaccination should generally be deferred but might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization.
3. Vaccination providers should check FDA-approved prescribing information for the most complete and updated information, including contraindications, warnings, and precautions. See Package inserts for U.S.-licensed vaccines.
4. See package inserts and FDA EUA fact sheets for a full list of vaccine ingredients. mRNA COVID-19 vaccines contain polyethylene glycol (PEG).

Fig. 215.1, cont'd

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Vaccines and other Immunizing Agents	Contraindicated or Not Recommended[1]	Precautions[2]
Dengue (DEN4CYD)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Lack of laboratory confirmation of a previous Dengue infection	• Pregnancy • HIV infection without evidence of severe immunosuppression • Moderate or severe acute illness with or without fever
Diphtheria, tetanus, pertussis (DTaP)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For DTaP only: Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP or DTaP	• Guillain-Barré syndrome (GBS) within 6 weeks after previous dose of tetanus-toxoid–containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine • For DTaP only: Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized • Moderate or severe acute illness with or without fever
Haemophilus influenzae type b (Hib)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Less than age 6 weeks	• Moderate or severe acute illness with or without fever
Hepatitis A (HepA)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including neomycin	• Moderate or severe acute illness with or without fever
Hepatitis B (HepB)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including yeast • *Pregnancy: Heplisav-B and PreHevbrio are not recommended due to lack of safety data in pregnant persons. Use other hepatitis B vaccines if HepB is indicated*[4].	• Moderate or severe acute illness with or without fever
Hepatitis A-Hepatitis B vaccine (HepA-HepB) [Twinrix]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including neomycin and yeast	• Moderate or severe acute illness with or without fever
Human papillomavirus (HPV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • *Pregnancy: HPV vaccination not recommended.*	• Moderate or severe acute illness with or without fever
Measles, mumps, rubella (MMR) Measles, mumps, rubella, and varicella (MMRV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Pregnancy • Family history of altered immunocompetence, unless verified clinically or by laboratory testing as immunocompetent	• Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) • History of thrombocytopenia or thrombocytopenic purpura • Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing • Moderate or severe acute illness with or without fever • For MMRV only: Personal or family (i.e., sibling or parent) history of seizures of any etiology
Meningococcal ACWY (MenACWY) MenACWY-CRM [Menveo] MenACWY-TT [MenQuadfi]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For Men ACWY-CRM only: severe allergic reaction to any diphtheria toxoid—or CRM197—containing vaccine • For MenACWY-TT only: severe allergic reaction to a tetanus toxoid-containing vaccine	• For MenACWY-CRM only: Preterm birth if less than age 9 months • Moderate or severe acute illness with or without fever
Meningococcal B (MenB) MenB-4C [Bexsero] MenB-FHbp [Trumenba]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Pregnancy • For MenB-4C only: Latex sensitivity • Moderate or severe acute illness with or without fever
Meningococcal ABCWY (MenACWY-TT/MenB-FHbp) [Penbraya]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe allergic reaction to a tetanus toxoid-containing vaccine	• Moderate or severe acute illness, with or without fever
Mpox [Jynneos]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness, with or without fever
Pneumococcal conjugate (PCV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe allergic reaction (e.g., anaphylaxis) to any diphtheria-toxoid-containing vaccine or its component[3]	• Moderate or severe acute illness with or without fever
Pneumococcal polysaccharide (PPSV23)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness with or without fever
Poliovirus vaccine, inactivated (IPV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Pregnancy • Moderate or severe acute illness with or without fever
RSV monoclonal antibody (RSV-mAb)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[5]	• Moderate or severe acute illness with or without fever
Respiratory syncytial virus vaccine (RSV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness with or without fever
Rotavirus (RV) RV1 [Rotarix] RV5 [RotaTeq]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe combined immunodeficiency (SCID) • History of intussusception	• Altered immunocompetence other than SCID • Chronic gastrointestinal disease • RV1 only: Spina bifida or bladder exstrophy • Moderate or severe acute illness with or without fever
Tetanus, diphtheria, and acellular pertussis (Tdap) Tetanus, diphtheria (Td)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For Tdap only: Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP, DTaP, or Tdap	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of tetanus-toxoid–containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine • For Tdap only: Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized • Moderate or severe acute illness with or without fever
Varicella (VAR)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Pregnancy • Family history of altered immunocompetence, unless verified clinically or by laboratory testing as immunocompetent	• Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) • Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination) • Use of aspirin or aspirin-containing products • Moderate or severe acute illness with or without fever • If using MMRV, see MMR/MMRV for additional precautions

1. When a contraindication is present, a vaccine should NOT be administered. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
2. When a precaution is present, vaccination should generally be deferred but might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
3. Vaccination providers should check FDA-approved prescribing information for the most complete and updated information, including contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at www.fda.gov/vaccines-blood-biologics/approved-products/vaccines-licensed-use-united-states.
4. For information on the pregnancy exposure registries for persons who were inadvertently vaccinated with Heplisav-B or PreHevbrio while pregnant, please visit heplisavbpregnancyregistry.com or www.prehevbrio.com/#safety.
5. Full prescribing information for BEYFORTUS (nirsevimab-alip) www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf

Fig. 215.1, cont'd

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 215.7 Recommended Catch-Up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 Month Behind United States, 2024.*

VACCINE	MINIMUM AGE FOR DOSE 1	MINIMUM INTERVAL BETWEEN DOSES			
		DOSE 1 TO DOSE 2	DOSE 2 TO DOSE 3	DOSE 3 TO DOSE 4	DOSE 4 TO DOSE 5
CHILDREN AGE 4 MONTHS THROUGH 6 YEARS					
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose** minimum age for the final dose is 24 weeks		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days.	**4 weeks**	**4 weeks** maximum age for final dose is 8 months, 0 days		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months** A fifth dose is not necessary if the fourth dose was administered at age 4 years or older ***and*** at least 6 months after dose 3
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months ***and*** at least 1 previous dose was PRP-T (ActHib®, Pentacel®, Hiberix®), Vaxelis® or unknown **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; **OR** if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday ***and*** second dose was administered at younger than 15 months; **OR** if both doses were PedvaxHIB® and were administered before the 1st birthday	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older **4 weeks** if first dose was administered before the 1st birthday **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after	**No further doses needed** for healthy children if previous dose was administered at age 24 months or older **4 weeks** if current age is younger than 12 months ***and*** previous dose was administered at <7 months old **8 weeks (as final dose for healthy children)** if previous dose was administered between 7–11 months (wait until at least 12 months old); **OR** if current age is 12 months or older ***and*** at least 1 dose was administered before age 12 months	**8 weeks (as final dose)** This dose is only necessary for children age 12 through 59 months regardless of risk, or age 60 through 71 months with any risk, who received 3 doses before age 12 months.	
Inactivated poliovirus	6 weeks	**4 weeks**	**4 weeks** if current age is <4 years**6 months (as final dose)** if current age is 4 years or older	**6 months (minimum age 4 years for final dose)**	

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 215.7 Recommended Catch-Up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 Month Behind United States, 2024.*—cont'd

VACCINE	MINIMUM AGE FOR DOSE 1	MINIMUM INTERVAL BETWEEN DOSES			
		DOSE 1 TO DOSE 2	DOSE 2 TO DOSE 3	DOSE 3 TO DOSE 4	DOSE 4 TO DOSE 5
CHILDREN AGE 4 MONTHS THROUGH 6 YEARS					
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal ACWY	2 months MenACWY-CRM 2 years MenACWY-TT	**8 weeks**	See Notes	See Notes	
CHILDREN AND ADOLESCENTS AGE 7 THROUGH 18 YEARS					
Meningococcal ACWY	Not applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday**6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday	**6 months** if first dose of DTaP/DT was administered before the 1st birthday	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose**		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older ***and*** at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years **OR** if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older			
Dengue	9 years	**6 months**	6 months		

*Always use this table in conjunction with Figure 215.1 and the notes that follow it.
This table provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.
For vaccination recommendations for persons ages 19 yr or older, see the Recommended Adult Immunization Schedule, 2024 https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.
Courtesy U.S. Centers for Disease Control and Prevention, Atlanta, Georgia. 2024. https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html#table-catchup.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

combined with other vaccines. Either Td vaccine or Tdap can be used for the decennial Td booster, for tetanus prophylaxis in wound management, or for additional required doses in the catch-up immunization schedule if a person has received at least one Tdap dose. One dose of Tdap vaccine is recommended for pregnant adolescents with each pregnancy, preferably between 27 and 36 weeks of gestation, regardless of the time since the last Tdap or Td. Current available data suggest that vaccinating earlier in the 27- through 36-week period will maximize passive antibody transfer to the infant. This recommendation was made in response to data predicting lack of infant protection when maternal Tdap had been received before pregnancy.

There are three licensed preparations of single-antigen **Hib** vaccines. The two monovalent vaccines conjugated to tetanus toxoid (PRP-T) are each given in a four-dose series at 2, 4, 6, and 12 through 15 months of age. The third Hib vaccine is conjugated to meningococcal outer membrane protein (PRP-OMP) and is recommended in a three-dose series at 2, 4, and 12 through 15 months of age. There also are several vaccines in which Hib is a component, in addition to single-antigen Hib conjugate vaccines (see Tables 215.8 and 215.9).

Influenza vaccine is recommended for all children beginning at 6 months of age, with a minimum age of 6 months for IIVs and 24 months for LAIV4. Various influenza vaccine preparations are FDA-licensed for different age-groups.* Children 6 months through 8 years of age being vaccinated for the first time should receive two doses at least 4 weeks apart. If such children only received a single dose of IIV before July 1 of the current season, they need two doses. Children who have received two doses in a prior season only need one dose annually thereafter. For additional guidelines, follow dosing instructions in the influenza policy statements, which are updated annually by both the CDC (https://www.cdc.gov/flu/professionals/acip/index.htm) and AAP (aapredbook.org). Influenza vaccine usually is given in October or November, although there are benefits even when administered as late as February or March because influenza seasons most frequently peak in February. People ≥9 years old should receive one dose of influenza vaccine annually. LAIV4 is recommended for the 2023-2024 season. Because of limited use of LAIV4, there have been no effectiveness estimates in the United States. Data from other countries have demonstrated similar protection from LAIV4 to that of standard-dose, egg-based IIV in children. Although there are no reports of additional safety risks for LAIV4 in children with immunodeficiencies, anatomic or functional asplenia, cochlear implants, or active cerebrospinal fluid leaks, it is not recommended in these populations because the vaccine is a live attenuated product (see Table 215.7). For more information see https://pediatrics.aappublications.org/content/146/4/e2020024588

IPV should be administered at 2, 4, and 6 through 18 months of age with a booster dose at 4 through 6 years. The final dose in the series should be administered on or after 4 years of age and at least 6 months after the previous dose. Four or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. The final dose in the IPV series should still be administered at 4 years or older regardless of the number of previous doses, and the minimal interval from dose 3 to dose 4 is 6 months. For series that contain oral polio vaccine (OPV), the total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. Only documentation specifying receipt of trivalent OPV constitutes proof of vaccination according to the U.S. polio vaccination recommendations. This is important because since April 2016, trivalent OPV (tOPV) is no longer available with the type 2 serotype removed. Thus children vaccinated since that time only received the type 1 and 3 components and are not immune to type 2. In contrast, IPV contains all three polio serotypes. Only IPV is available in the United States. One lifetime IPV booster should be considered for adolescents 18 years old who are at increased risk of exposure to poliovirus and completed IPV primary series. For catch-up vaccine recommendations, see the recommended childhood immunization schedule at http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html (see Table 215.7).

MMR should be administered at 12 through 15 months of age followed by a second dose at 4 through 6 years. Before all international travel, infants 6 through 11 months of age should receive one dose of MMR vaccine. These children should be revaccinated with the routinely recommended two doses of MMR vaccine beginning at 12 months of age. For children 12 months or older, administer two doses before international travel; the second dose should be administered at least 4 weeks after the first dose.

Two doses of **varicella** vaccine should be given, the first at 12 through 15 months of age and the second at 4 through 6 years. The second dose may be administered before 4 years of age provided at least 3 months have elapsed since the first dose. MMR and MMRV preparations are available. Ensure persons age 7-18 years without evidence of immunity have a two-dose series. The **quadrivalent MMRV** vaccine is preferred in place of separate MMR and varicella vaccines at the 4- to 6-year-old visit. For dose 1 in children age 12-47 months, it is recommended to administer MMR and varicella vaccines separately because of the slight increase in febrile seizures associated with the combined MMRV vaccine compared with simultaneous administration of the separate products. MMRV may be used if parents or caregivers express a preference.

Protection against pneumococcal disease can be provided by either conjugated or polysaccharide vaccines. Conjugated vaccines offer several benefits over polysaccharide vaccines (see Table 215.5). A four-dose series of either PCV15 or 20 is recommended at 2, 4, 6, and 12 to 15 months of age. In the latest immunization schedule, PCV15 and 20 are referenced. Use of either pneumococcal conjugate vaccines is recommended for all children age 2–23 months according to currently recommended PCV dosing and schedules. References to the previously available thirteen-valent (PCV13) have been removed. For children without high risk conditions, PCV20 is not indicated if they have received four doses of PCV13 or PCV15 or another age-appopriate complete PCV series. For guidance on determining which pneumococcal vaccines a patient needs and when, a mobile app has been created. (www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html. PPSV23 is recommended for select children with conditions that place them at risk for pneumococcal disease. When both PCV and PPSV23 are indicated, administer PCV first. PCV and PPSV23 should be administered during the same visit.

A two-dose series of MCV4 includes a recommended dose for *all* adolescents at 11 through 12 years of age followed by a second dose at 16 years. If the first dose is administered at 13 through 15 years of age, a booster dose should be administered at 16-18 years. No booster dose is needed if the first dose is administered at 16 years. In addition, MCV4 should be administered to people 2 months through 55 years of age with underlying conditions that place them at high risk of meningococcal disease. There are two licensed quadrivalent meningococcal vaccines and one pentavalent vaccine that additionally provides coverage against serogroup B disease. Each vaccine has a different minimum age for beginning vaccination with that product. In addition to the quadrivalent meningoccal vaccine, two other vaccines provide coverage against serogroup B meningoccal disease. Two to three doses of the meningococcal B (MenB) vaccines are recommended for persons >10 years old at increased risk of meningococcal disease. Further, consideration should be given to adolsecents not at increased risk (16-23 years, preferred age 16-18 years) based on shared clinical decision making, which involves patients and families coming together to discuss the potential benefits of vaccination (https://www.cdc.gov/vaccines/hcp/admin/downloads/isd-job-aid-scdm-mening-b-shared-clinical-decision-making.pdf).

Children 10 years of age or older may receive a single dose of the quadrivalent vaccine as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day. The two licensed MenB vaccine products are not interchangeable. MCV4 vaccines may be administered simultaneously with MenB vaccines if indicated, but at a different anatomic site if feasible.

Hepatitis A vaccine, licensed for administration to children ≥12 months old, is recommended for universal administration to all children at 12 through 23 months of age and for certain high-risk groups. The two doses in the series should be separated by at least 6 months.

* See http://www.cdc.gov/flu/protect/vaccine/vaccines.htm and http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml#flu.

Table 215.8 Combination Vaccines Licensed and Available in the United States

VACCINE PRODUCT (MANUFACTURER)*	TRADE NAME (YR LICENSED)	COMPONENTS	RECOMMENDED AGES	
			PRIMARY SERIES	BOOSTER DOSE
DTaP-IPV/Hib (Sanofi Pasteur)	Pentacel (2008)	DTaP-IPV + PRP-T	2, 4, and 6 mo	15-18 mo
DTaP-HepB-IPV (GlaxoSmithKline)	Pediarix (2002)	DTaP + HepB + IPV	2, 4, and 6 mo	
DTap-HepB-IPV-Hib (MSP Vaccine Company)	Vaxelis (2020)	DTaP + HepB+ IPV + Hib	2, 4, and 6 mo	
DTaP-IPV	Kinrix (2008), Quadracel (2015)	DTaP + IPV		Kinrix: For use as the fifth dose of DTaP and the fourth dose of IPV in children age 4-6 yr Quadracel: For use as the fifth dose in the DTaP series and as the fourth or fifth dose in the IPV series in children 4-6 yr of age
HepA-HepB (GlaxoSmithKline)	Twinrix (2001)	HepA + HepB	>18 yr of age; 0, 1, and 6 mo schedule	
MMRV (Merck & Co)	ProQuad (2005)	MMR + varicella	†	4-6 yr

*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.
†Although ProQuad is available for the first dose (at 12-15 mo of age), the CDC recommends that MMR vaccine and varicella vaccine be administered separately for the first dose in this age-group unless the parent or caregiver expresses a preference for MMRV vaccine.
DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine, PRP-T, H. influenzae type b capsular polysaccharide (polyribosyl-ribitol279 phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T).
Adapted from Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2013;62(2):1–28.

Table 215.9 Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk

VACCINES	SPECIAL SITUATIONS
Pneumococcal conjugate (and PPSV23 in certain conditions)	Cerebrospinal fluid leak Chronic heart disease Chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions) Chronic liver disease Chronic lung disease (including moderate persistent or severe persistent asthma) Cochlear implant Diabetes mellitus Immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies)
MCV4	Anatomic or functional asplenia (including sickle cell disease) Persistent complement component deficiency Complement inhibitor use Residents of or travelers to countries in African meningitis belt or pilgrims on the Hajj During outbreaks caused by a vaccine serogroup First-year college students who live in residential housing (if not previously vaccinated at age 16 yr or older) or military recruits HIV infection
MenB	Anatomic or functional asplenia (including sickle cell disease) Children with persistent complement component deficiency Complement inhibitor use During outbreaks caused by a vaccine serogroup
Hib	In addition to routine Hib vaccine recommendations. Persons at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), HIV infection, immunoglobulin deficiency, or early component complement deficiency Recipients of hematopoietic stem cell transplant (HSCT) Elective splenectomy
Hep B	In addition to routine Hep B vaccine recommendations; infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer vaccine within 12 hr of birth)
HPV	In addition to routine HPV vaccine recommendations; immunocompromising conditions, including HIV infection History of sexual abuse or assault
Tetanus	Wound management recommendations exist based on age, number of prior doses of tetanus-toxoid-containing vaccine, and type of wound.

From Centers for Disease Control and Prevention. Child and adolescent schedule. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Persons who previously received one dose at age 12 months or older should receive dose 2 at least 6 months after dose 1. Unvaccinated persons through age 18 years should complete a two-dose series with a minimum interval of 6 months. Adolescents age 18 years or older may receive the combined HepA and HepB vaccine. Immunity against hepatitis A infection is particularly important in people with chronic liver disease and clotting factor disorders, in men who have sex with men, in those who use injection or noninjection drugs, in people who are homeless, exposed to hepatitis A virus at work or travel, and those in close contact with international adoptees. Before all international travel, infants 6 through 11 months of age should receive one dose of hepatitis A vaccine. These children should be revaccinated with the routinely recommended two doses of hepatitis A vaccine beginning at 12 months of age. For unvaccinated children 12 months or older, administer dose 1 as soon as travel is considered. Preferably two doses should be administered before international travel to countries with high or intermediate endemic hepatitis A; the second dose should be administered at least 6 months after the first dose.

The **9vHPV** vaccine is recommended at age 11 or 12 years, although some advocate for routinely administering it as early as 9 years of age. Catch-up HPV vaccination is recommended for all persons through age 18 years if not adequately vaccinated. For those who initiate the series before their 15th birthday, the recommended schedule is two doses of 9vHPV vaccine. The minimum interval is 5 months between the first and second dose. If the second dose is given at a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose. For those initiating the series on or after their 15th birthday, the recommended schedule is three doses of 9vHPV vaccine. The minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose. For children with a history of sexual abuse or assault, the ACIP recommends routine HPV vaccination beginning at age 9 years. In males and females with primary or secondary immunocompromising conditions such as B-lymphocyte deficiencies, T-lymphocyte complete or partial defects, HIV, malignancy, transplantation, autoimmune disease, or immunosuppressive therapy, the ACIP recommends vaccination with three doses of 9vHPV (0, 1-2, and 6 months) because immune response to vaccination might be attenuated. 9vHPV may be used to continue or complete a vaccination series in patients who started with 4vHPV or 2vHPV, though no additional doses are recommended after completing the series with recommended dosing intervals using any HPV vaccine. If the vaccination schedule is interrupted, the series does not need to be restarted. HPV vaccination is not recommended until after pregnancy, but no intervention is needed if vaccinated while pregnant. Pregnancy testing is not needed before vaccination.

Two **rotavirus** vaccines are available: RotaTeq (RV5) and Rotarix (RV1). With both vaccines, the first dose can be administered as early as 6 weeks of age. Do not start the series on or after age 15 weeks, 0 days. The RV5 vaccine is administered in three doses at least 4 weeks apart. The RV1 vaccine is administered in two doses at least 4 weeks apart. If any dose in the series is either RotaTeq or unknown, default to a three-dose series. The maximum age for the final dose is 8 months, 0 days as stated in the immunization schedule.

A dengue vaccine (Dengvaxia) was approved by the FDA in May 2019 for use in children age 9-16 years living in dengue-endemic territories **AND** having laboratory confirmation of *previous* dengue infection. It is a three-dose series administered at 0, 6, and 12 months. Endemic areas include Puerto Rico, American Samoa, U.S. Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue-endemic areas and pre-vaccination laboratory testing see https://apps.who.int/mediacentre/factsheets/fs117/en/index.html. Dengvaxia is not approved for use in U.S. travelers who are visiting but not living in an area where dengue is endemic. See https://www.aappublications.org/news/2020/05/01/mmwr050120 for more information.

For those that are 18 years of age or older and at risk for Mpox infection, 2 doses of the Mpox vaccine are recommended. See https://www.cdc.gov/poxvirus/mpox/interim-considerations/jynneos-vaccine.html#:~:text=JYNNEOS%20is%20approved%20for%20the,22)%3A734%2D742) for more information.

To prevent RSV in infants, one dose of nirsevimab is recommended for infants younger than 8 months of age who were born shortly before or are entering their first RSV season (typically fall through spring) if: (1) the mother did not receive RSV vaccine during pregnancy, (2) the mother's RSV vaccination status is unknown, or (3) the infant was born within 14 days of maternal RSV vaccination. Additionally, a dose of nirsevimab is recommended for some children 8 to 19 months of age who are at increased risk for severe RSV disease and entering their second RSV season (https://www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm#suggestedcitation).

The present schedule, excluding influenza vaccine, can require as many as 41 doses. Of the doses, more than half are recommended before 2 years of age. Influenza vaccination, starting at age 6 months, can add an additional 20 injections through 18 years. To reduce the injection burdens, several combination vaccines are available (see Table 215.8).

The recommended childhood and adolescent immunization schedule establishes a routine adolescent visit at 11 through 12 years of age. MCV4, a Tdap booster, and 9vHPV vaccine should be administered during this visit in addition to the COVID-19 vaccine if the child is 12 years of age or older. Influenza vaccine should be administered annually. In addition, the 11- to 12-year-old visit is an opportune time to review all the immunizations the adolescent has received previously, to provide any doses that were missed, and to review other age-appropriate preventive services. The 11- to 12-year visit establishes an important platform for incorporating other vaccines. Information on the current status of new vaccine licensure and recommendations for use is available.*

For children who are at least 1 month behind in their immunizations, catch-up immunization schedules are available for children 4 months through 18 years of age (http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html) (see Table 215.7). Interactive immunization schedules are available for children from birth through 18 years of age at https://www2a.cdc.gov/vaccines/childquiz/. Only written/electronic, dated, authentic records should be accepted as evidence of immunization. In general, when in doubt, a person with unknown or uncertain immunization status should be considered "disease susceptible," and recommended immunizations should be initiated without delay on a schedule commensurate with the person's current age. No evidence suggests that administration of vaccines to already-immune recipients is harmful. A new addendum section has been added to list any ACIP recommendations that occur by majority vote and are approved by CDC Director after the 2024 immunization schedules are approved and published.

VACCINES RECOMMENDED IN SPECIAL SITUATIONS

Eight vaccines—PCV, PPSV23, MCV4, MenB, Flu, Hib, HepA, and HepB—are recommended for children and adolescents at increased risk for complications from vaccine-preventable diseases or children who have an increased risk for exposure to these diseases who are outside the age-groups for which these vaccines are normally recommended (PPSV23 and MenB are not routinely recommended for any age-group of children and are only used for children with high-risk conditions; Fig. 215.2 and Table 215.9). Specific recommendations for use of these vaccines in children with underlying conditions can be found in the recommended immunization schedule.

PCV15 or **PCV20** is recommended for children 24-71 months of age with specialized risk conditions that place them at high risk for pneumococcal disease. This recommendation includes children with sickle cell disease and other hemoglobinopathies, including hemoglobin SS, hemoglobin S-C, or hemoglobin S–β-thalassemia,

* http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml and http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

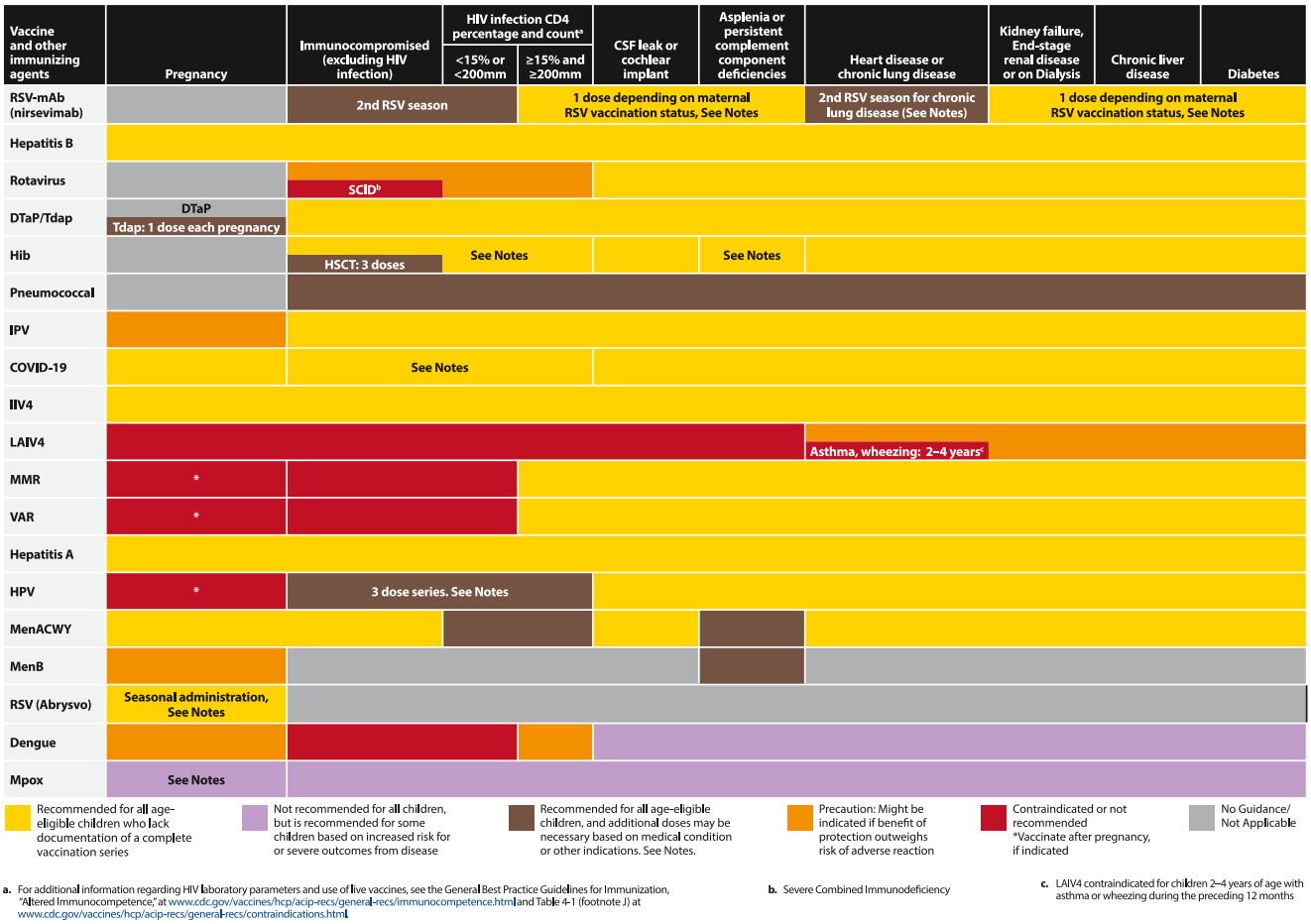

Fig. 215.2 Recommended child and adolescent immunization schedule by medical indication—United States, 2024. *Always use this figure in conjunction with Figure 215.1 and the notes that follow it. (Courtesy U.S. Centers for Disease Control and Prevention, Atlanta, Georgia. 2024. https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.)*

or children who are functionally or anatomically asplenic; children with HIV infection; and children who have chronic disease (see Table 215.9 and Fig. 215.2). (For further recommendations on pneumococcal vaccine recommendations, see https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html.)

Children at high risk for pneumococcal disease also should receive **PPSV23** to provide immunity to serotypes not contained in the 13- or 15-valent conjugate vaccine. PPSV23 should be administered on or after the second birthday and should follow completion of the PCV series by at least 8 weeks. Two doses of PPSV23 are recommended, with an interval of 5 years between doses. Immunization of children >5 years old with high-risk conditions can be performed with PCV15 or PCV20 and/or PPSV23, depending on the condition and vaccination history. When both PCV and PPSV23 are indicated, PCV should be administered first.

MCV4 is recommended for HIV-infected persons ≥2 months old, children with anatomic or functional asplenia (including sickle cell disease), children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, or factor H), or children taking a complement inhibitor (e.g., eculizumab or ravulizumab).

Meningococcal B (**MenB**) vaccine is recommended for persons ≥10 years old at increased risk of meningococcal disease. This includes people with complement deficiencies or anatomic or functional asplenia, people at increased risk because of serogroup B meningococcal disease outbreaks, and microbiologists who routinely are exposed to isolates of *Neisseria meningitidis*. Young adults age 16-23 (preferred range: 16-18 years) who are not at increased risk for meningococcal disease may be vaccinated with either of the two MenB vaccines, which are not interchangeable, to provide short-term protection against most strains of serogroup B meningococcal disease.

Hib vaccine and **HepA** vaccine are recommended for children with certain high-risk conditions. **HepB** is recommended for infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer the vaccine within 12 hours of birth) (see Table 215.9).

In addition to vaccines in the recommended childhood and adolescent schedule, a variety of vaccines are available for children who will be **traveling** to areas of the world where certain infectious diseases are common (Table 215.10). Vaccines for travelers include typhoid fever, hepatitis A, hepatitis B, Japanese encephalitis, MCV4, cholera, rabies, and yellow fever, depending on the location and circumstances of travel. **Measles** is endemic in many parts of the world. Children 6-11 months old should receive a dose of MMR and hepatitis A vaccines before international travel outside of the United States. However, doses of MMR and hepatitis A vaccines received before 12 months should not be counted in determining compliance with the recommended two-dose MMR schedule. For unvaccinated children ≥12 months old, administer two doses before international travel following the recommended schedule. (Additional information on vaccines for international travel can be found at http://wwwnc.cdc.gov/travel/.)

Vaccine recommendations for children with **immunocompromising conditions**, either primary (inherited) or secondary (acquired), vary according to the underlying condition, the degree of immune deficit, the risk for exposure to disease, and the vaccine (Table 215.11 and see Fig. 215.2). Immunization of children who are

Table 215.10 Recommended Immunizations for International Travel*

IMMUNIZATIONS	LENGTH OF STAY	
	Brief, <1 mo	Long-Term / Residential, >1 mo
Review and complete age-appropriate childhood and adolescent schedule (see text for details) • DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b (Hib) vaccines may be given at 4-wk intervals if necessary to complete recommended schedule before departure. • Influenza • MMR: two additional doses given if <12 mo old at first dose • Meningococcal disease (MenACWY)† • Rotavirus • Varicella • Human papillomavirus (HPV) • Hepatitis A: two additional doses given if <12 mo old at 1st dose‡,§ • Hepatitis B§ • Tdap	+	+
Yellow fever#	+	+
Typhoid fever¶	+	+
Rabies**	±	±
Japanese encephalitis‡	±	+
Cholera‡‡	±	±

*See disease-specific chapters in the Centers for Disease Control and Prevention's *Yellow Book* for details. For further sources of information, see text.
†Recommended for regions of Africa with endemic infection and during local epidemics and required for travel to Saudi Arabia for the Hajj.
‡For infants age 6-11 mo, first dose is recommended before departure for all international travel. For unvaccinated children 12 mo and older, this vaccine is indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
§If there is insufficient time to complete 6-mo primary series, accelerated series can be given.
#For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel). Because of the risk of serious adverse events after yellow fever vaccination, clinicians should only vaccinate people who (1) are at risk of exposure to yellow fever virus (YFV) or (2) require proof of vaccination to enter a country.
¶Indicated for travelers who will consume food and liquids in areas of poor sanitation.
**Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.
‡For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.
‡‡Cholera vaccine (CVD 103-HgR, Vaxchora) is recommended for adult (18-64 yr old) travelers to an area of active toxigenic *V. cholerae* O1 transmission.
+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.
Data from Centers for Disease Control and Prevention. Travelers' health. https://wwwnc.cdc.gov/travel.

Table 215.11 Vaccination of Persons with Primary and Secondary Immune Deficiencies

	PRIMARY			
CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[a] Smallpox[b] LAIV4 BCG Ty21a Yellow fever virus (YFV) and live-bacteria vaccines[c] No data for rotavirus vaccines	Annual IIV is the only vaccine given to patients receiving IG therapy; routine inactivated vaccines can be given if not receiving IVIG. Pneumococcal Hib (children 12-59 mo of age)	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV23). IG therapy interferes with the immune response to live vaccines MMR and VAR.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[a] BCG YFV vaccine Other live vaccines[d] appear to be safe.	Vaccines should be given as on the annual immunization schedule for immunocompetent people.[e] PPSV23 should be given beginning at 2 yr of age.[f] Pneumococcal Hib (children 12-59 mo of age)	All vaccines are probably effective. Immune response may be attenuated.
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[c,d,g]	Pneumococcal Hib (children 12-59 mo of age) and annual IIV	All inactivated vaccines are probably ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, hyper-IgM syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[c,d,g]	Routine inactivated vaccines should be given.[e] PPSV23 should be given beginning at 2 yr of age.[f] Pneumococcal Hib (children 12-59 mo of age)	Effectiveness of any vaccine depends on degree of immune suppression.
	Interferon (IFN)-γ–interleukin (IL)-12 axis deficiencies	All live vaccines for IL-12/IL-12R deficiencies, IFN-γ, IFN-α, or STAT1 deficiencies	None	None

Table 215.11 Vaccination of Persons with Primary and Secondary Immune Deficiencies—cont'd

PRIMARY

CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
Complement	Persistent complement, properdin, MBL, or factor B deficiency; secondary deficiency because taking eculizumab (Solaris)	None	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h] MenB series beginning at 10 yr of age and Hib vaccine (children 12-59 mo of age)	All routine vaccines are probably effective.
Phagocytic function	Chronic granulomatous disease	Live-bacteria vaccines[c]	None	All inactivated vaccines are safe and probably effective. Live-virus vaccines are probably safe and effective.
	Phagocytic deficiencies that are undefined or accompanied by defect in T-cell and NK-cell dysfunction (e.g., Chédiak-Higashi syndrome, leukocyte adhesion defects, myeloperoxidase deficiency)	MMR, MMRV, OPV,[a] smallpox, LAIV4, Ty21a, YF, all bacteria vaccines	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h]	All inactivated vaccines are safe and probably effective.

SECONDARY

SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
HIV/AIDS	OPV[a] Smallpox BCG Combined MMRV LAIV4 Withhold MMR, varicella, and zoster in severely immunocompromised persons. YF vaccine may have a contraindication or precaution depending on the indicators of immune function.[j]	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h] HepB vaccine Consider Hib (if not administered in infancy).[l]	Rotavirus vaccine is recommended on standard schedule. MMR and VAR are recommended for HIV-infected children who are asymptomatic or only low-level immunocompromised.[k] All inactivated vaccines may be effective.
Generalized malignant neoplasm, transplantation, autoimmune disease, immunosuppressive or radiation therapy	Live-virus and live-bacteria vaccines, depending on immune status.[c,d,m]	PPSV23 should be given beginning at 2yr of age.[f] Annual IIV (unless receiving intensive chemotherapy or anti–B-cell antibodies). Hib vaccine may be indicated.[n]	Effectiveness of any vaccine depends on degree of immune suppression; inactivated standard vaccines are indicated if not highly immunosuppressed, but doses should be repeated after chemotherapy ends.
Asplenia (functional, congenital anatomic, surgical)	LAIV4	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h] MenB series beginning at 10 yr of age. Hib (if not administered in infancy)[o]	All routine vaccines are probably effective.
Chronic renal disease	None	PPSV23 should be given beginning at 2yr of age.[f] HepB is indicated if not previously immunized.	All routine vaccines are probably effective.
CNS anatomic barrier defect (cochlear implant, congenital dysplasia of the inner ear, persistent CSF communication with naso-/oropharynx)	None	PPSV23 should be given beginning at 2yr of age.[f]	All standard vaccines are indicated.

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.
[a]OPV is no longer available in the United States.
[b]This table refers to contraindications for nonemergency vaccination (i.e., ACIP recommendations).
[c]Live-bacteria vaccines: BCG and oral Ty21a *Salmonella* Typhi vaccine.
[d]Live-virus vaccines: MMR, MMRV, VAR, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[e]Children who are delayed or underimmunized should be immunized with routinely recommended vaccines, according to age and catch-up schedule.
[f]PPSV23 is begun at 2 yr or older. If PCV13 is required, PCV13 doses should be administered first, followed by PPSV23 at least 8 wk later; a second dose of PPSV23 is given 5 yr after the first.
[g]Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

Table 215.11 Vaccination of Persons with Primary and Secondary Immune Deficiencies—cont'd

[h]Age and schedule of doses depend on the product; repeated doses are required.
[i] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV13. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.
[j]YF vaccine is contraindicated in HIV-infected children <6 yr old who are highly immunosuppressed. There is a precaution for the use of YF vaccine in asymptomatic HIV-infected children <6 yr with total lymphocyte percentage of 15–24%, and >6 yr old with $CD4^+$ T-lymphocyte counts of 200-499 cells/mm^3. Data from Centers for Disease Control and Prevention. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep*. 2010;59(RR-07); 1–27.
[k]HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella vaccine if $CD4^+$ T-lymphocyte percentage is ≥15% for those <6 yr old or $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 for those ≥6 yr old. People with perinatal HIV infection who were vaccinated with measles-, rubella-, or mumps-containing vaccine before the establishment of combination antiretroviral therapy (cART) should be considered unvaccinated and should receive two appropriately spaced doses of MMR vaccine once effective cART has been established (at least 6 mo with $CD4^+$ T lymphocytes ≥15% for children <6 yr old, or $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 for children ≥6 yr old).
[l]For patients 5-18 yr old who have not received a Hib primary series and a booster dose or at least one Hib dose after age 14 mo.
[m]Withholding inactivated vaccines also is recommended with some forms of immunosuppressive therapy, such as anti-CD20 antibodies, induction or consolidation chemotherapy, or patients with major antibody deficiencies receiving immunoglobulins. Inactivated influenza vaccine is an exception, but consideration should be given to repeating doses of any inactivated vaccine administered during these therapies.
[n]For persons <60 mo old undergoing chemotherapy or radiation therapy who have not received a Hib primary series plus a booster dose or at least one Hib dose after age 14 mo.
[o]For persons >59 mo old who are asplenic and persons ≥15 mo who are undergoing elective splenectomy and who have not received a Hib primary series and a booster dose or at least one Hib dose after age 14 mo.
BCG, Bacille Calmette-Guérin vaccine; CNS, central nervous system; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IG, immunoglobulin; IIV, inactivated influenza vaccine; LAIV4, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MMRV, measles-mumps-rubella-varicella; MCV, quadrivalent meningococcal polysaccharide vaccine; MenB, serogroup B meningococcal vaccine; OPV, oral poliovirus vaccine (live); PPSV23, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; VAR, varicella; YF, yellow fever.
Adapted from Immunization in Special Circumstances. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

immunocompromised poses the following potential concerns: the incidence or severity of some vaccine-preventable diseases is higher, and therefore certain vaccines are recommended specifically for certain conditions; vaccines may be less effective during the period of altered immunocompetence and may need to be repeated when immune competence is restored; and because of altered immunocompetence, some children and adolescents may be at increased risk for an adverse event after receipt of a live-virus vaccine. Live-attenuated vaccines generally are contraindicated in immunocompromised persons. The exceptions include **MMR**, which may be given to a child with HIV infection provided the child is asymptomatic or symptomatic without evidence of severe immunosuppression, and **varicella** vaccine, which may be given to HIV-infected children if the $CD4^+$ lymphocyte count is at least 15% and the total $CD4^+$ cell count is >200/mm^3. MMRV is not recommended in these situations.

Altered immunocompetence is considered a precaution for rotavirus; however, the vaccine is contraindicated in children with severe combined immunodeficiency disease. Inactivated vaccines may be administered to immunocompromised children, although their effectiveness might not be optimal depending on the immune deficit. Children with complement deficiency disorders may receive all vaccines, including live-attenuated vaccines. In contrast, children with phagocytic disorders may receive both inactivated and live-attenuated viral vaccines but not live-attenuated bacterial vaccines.*

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥2 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for ≥14 days should not receive live vaccines until therapy has been discontinued for at least 1 month. Children on the same dose levels but for <2 weeks may receive live-virus vaccines as soon as therapy is discontinued, although some experts recommend waiting 2 weeks after therapy has been discontinued. Children receiving lower doses of corticosteroids may be vaccinated while receiving therapy.

Children and adolescents with malignancy and those who have undergone solid organ or hematopoietic stem cell transplantation and immunosuppressive or radiation therapy should not receive live-virus and live-bacteria vaccines depending on their immune status. Children who have undergone chemotherapy for leukemia may need to be reimmunized with age-appropriate single doses of previously administered vaccines. Preterm infants generally can be vaccinated at the same chronological age as full-term infants according to the recommended childhood immunization schedule. An exception is the birth dose of HepB. When mother is HBsAg-negative, infants weighing ≥2 kg and who are medically stable should receive a birth dose within the first 24 hours of life. However, HepB should be deferred in infants weighing <2 kg at birth until chronological age 1 months or hospital discharge (whichever is earlier and even if weight is still <2 kg). All preterm, low-birthweight infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin (HBIG) and HepB vaccine (at separate anatomic sites) within 12 hours of birth. However, such infants should receive an additional three doses of vaccine starting at 30 days of age (see Fig. 215.1). Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody at 9-12 months, or 1-2 months after completion of the HepB series if the series was delayed. If the test is negative for antibody against the surface antigen (anti-HBs), an additional dose of HepB is recommended with testing 1-2 months after the dose. If the child is still antibody negative, an additional two doses of vaccine should be administered.

If the mother's HBsAg status is unknown within 12 hours of birth, administer HepB vaccine regardless of birthweight. For infants weighing <2,000 g, administer HBIG in addition to HepB within 12 hours of birth. Determine the mother's HBsAg status as soon as possible and, if the mother is HBsAg-positive, also administer HBIG to infants weighing ≥2,000 g as soon as possible, but no later than 7 days of age.

Varicella-zoster immunoglobulin **(VariZIG)** is recommended for patients without evidence of immunity to varicella who are at high risk for severe varicella and complications, who have been exposed to varicella or herpes zoster, and for whom varicella vaccine is contraindicated. This includes immunocompromised patients without evidence of immunity, newborn infants whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after), hospitalized premature infants born at ≥28 weeks of gestation whose mothers do not have evidence of immunity to varicella, hospitalized premature infants born at <28 weeks of gestation or who weigh ≤1,000 g at birth (regardless of their mother's evidence of immunity to varicella), and pregnant women without evidence of immunity.

The ACIP recommends the use of COVID-19 vaccines within the scope of the EUA or fully approved by the FDA based on a Biologics License Application for the particular vaccine. Interim ACIP recommendations for the use of COVID-19 vaccines can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html. COVID-19 vaccine and other routine vaccines may be administered on the same day. For more information about COVID-19 vaccines authorized for use in the United States, see https://www.cdc.gov/vaccines/covid-19/info-by-product/index.html. Rare serious adverse events have been reported after COVID-19 vaccination, including myocarditis in children older than 5 years of age. The ACIP continues to conclude that the benefits outweigh the risks for rare serious adverse events after COVID-19 vaccination.

*https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/a/immuno-table.pdf

Some children have situations that are not addressed directly in current immunization schedules. Physicians can use general rules to guide immunization decisions in some of these instances. General Best Practice Guidelines for Immunization (including contraindications and precautions) can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. In general, vaccines may be given simultaneously on the same day, whether inactivated or live. Different inactivated vaccines can be administered at any interval between doses. However, because of theoretical concerns about viral interference, different live-attenuated vaccines (MMR, varicella), if not administered on the same day, should be given at least 1 month apart. An inactivated and a live vaccine may be spaced at any interval from each other.

Immunoglobulin does not interfere with inactivated vaccines. However, immunoglobulin can interfere with the immune response to measles vaccine and, by inference, to varicella vaccine. In general, immunoglobulin, if needed, should be administered at least 2 weeks after the measles vaccine. Depending on the dose of immunoglobulin received, MMR should be deferred for as long as 3-11 months. Immunoglobulin is not expected to interfere with the immune response to LAIV4 or rotavirus vaccines.

Certain adult (including pregnancy) immunizations are recommended to decrease the risk of infection in their children; these include influenza virus and pertussis (Tdap).

PRECAUTIONS AND CONTRAINDICATIONS

Observation of valid precautions and contraindications is critical to ensure that vaccines are used in the safest manner possible and to obtain optimal immunogenicity. When a child presents for immunization with a clinical condition considered a **precaution**, the physician must weigh benefits and risks to that individual child. If benefits are judged to outweigh risks, the vaccine or vaccines in question may be administered. A **contraindication** means the vaccine should not be administered under any circumstances.

A general contraindication for all vaccines is **anaphylactic reaction** to a prior dose. Anaphylactic hypersensitivity to vaccine constituents is also a contraindication. However, if a vaccine is essential, there are desensitizing protocols for some vaccines. The major constituents of concern are *egg proteins* for vaccines grown in eggs; *gelatin,* a stabilizer in many vaccines; and antimicrobial agents. The recommendations for persons with egg allergy were modified as follows: A previous severe allergic reaction to influenza vaccine is a contraindication to future receipt of any influenza vaccine. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive any flu vaccine appropriate for age and health status. Persons who had symptoms other than hives (e.g., angioedema, respiratory distress, need for emergency medical services or epinephrine) should receive any influenza vaccine appropriate for age and health status annually. If using an influenza vaccine other than Flublok or Flucelvax, administer in a medical setting under supervision of a healthcare provider who is able to recognize and manage severe allergic conditions. LAIV4 should not be used for persons with a history of severe allergic reaction to any component of the vaccine (excluding egg) or to a previous dose of any influenza vaccine. The measles and mumps components of MMR are grown in chick embryo fibroblast tissue culture. However, the amount of egg protein in MMR is so small that there are no special procedures for administering the vaccine to someone with a history of anaphylaxis after egg ingestion.

Vaccines should usually be deferred in children with moderate to severe acute illnesses, regardless of the presence of fever, until the child recovers. *However, children with mild illnesses may be vaccinated.* Studies of undervaccinated children have documented opportunities that were missed because mild illness was used as an invalid contraindication.

Complete tables of contraindications and precautions by vaccine can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and as an appendix to the 2024 immunization schedule (https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#appendix).

MEDICAL EXEMPTIONS

All 50 states, the District of Columbia, and Puerto Rico have regulations requiring verification of immunization for childcare and school attendance. This provides direct protection to the immunized population and indirect protection to those unable to be immunized. It also functions to improve timely immunization of children. Regulations also allow for medical exemption from immunization requirements in all 50 states, and the majority of states also have varied regulations that allow for nonmedical exemptions. Rare, medically recognized contraindications are important to observe. Nonmedical exemptions to immunization requirements include exemptions because of religious or philosophical beliefs. Persons with exemptions are at greater risk of vaccine-preventable diseases than the general population. When children with exemptions cluster, as can happen with nonmedical exemptions, the community may be at risk for outbreaks, leading to exposure of children who cannot be protected by vaccination to vaccine-preventable diseases, such as children too young for vaccination and those with medical contraindications. (For more information, see http://pediatrics.aappublications.org/content/early/2016/08/25/peds.2016-2145.)

IMPROVING IMMUNIZATION COVERAGE

Standards for child and adolescent immunization practices have been developed to support achievement of high levels of immunization coverage while providing vaccines in a safe and effective manner and educating parents about risks and benefits of vaccines (Table 215.12).

Pediatric vaccine uptake has decreased since the start of the COVID-19 pandemic resulting in decreased vaccination coverage. This identified decline may indicate that U.S. children and their communities face increased risks for outbreaks of vaccine-preventable diseases (Fig. 215.3).

Despite benefits that vaccines have to offer, many children are underimmunized as a result of not receiving recommended vaccines or not receiving them at the recommended ages. Much of the underimmunization problem can be solved through physician actions. Most children have a regular source of healthcare. However, missed opportunities to provide immunizations at healthcare visits include but are not limited to failure to provide all recommended vaccines that could be administered at a single visit during that visit, failure to provide immunizations to children outside of well child care encounters when contraindications are not present, and referral of children to public health clinics because of inability to pay for vaccines. Simultaneous administration of multiple vaccines is generally safe and effective. When the benefits of simultaneous vaccination are explained, many parents prefer such immunization to making an extra visit. Providing all needed vaccines simultaneously should be the standard of practice.

Only valid contraindications and precautions to vaccine administration should be observed. Ideally, immunizations should be provided during well child visits; however, if no contraindications exist, it is important to administer vaccines at other visits, particularly if the child is behind in the schedule. There is no good evidence that providing immunizations outside of well child care ultimately decreases the number of well child visits.

Financial barriers to immunization should be minimized. Participation in the **VFC** program allows physicians to receive vaccines at no cost for their eligible patients, which helps such patients get immunized in their medical home.

Several interventions have been shown to help physicians increase immunization coverage in their practices. Reminder systems for children before an appointment or recall systems for children who fail to keep appointments have repeatedly been demonstrated to improve coverage. Assessment and feedback are also important interventions. Many physicians overestimate the immunization coverage among patients they serve and thus are not motivated to make any changes in their practices to improve performance. Assessing the immunization coverage of patients served by an individual physician with feedback of results can be a major motivator for improvement. Often, public health departments can be contacted to provide the assessments and feedback. Alternatively, physicians can perform self-assessment. Review of approximately 60 consecutive charts of 2-year-old children may provide

Table 215.12 Standards for Child and Adolescent Immunization Practices

AVAILABILITY OF VACCINES
Vaccination services are readily available.
Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.
Barriers to vaccination are identified and minimized.
Patient costs are minimized.
ASSESSMENT OF VACCINATION STATUS
Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
Healthcare professionals assess for and follow only medically accepted contraindications.
EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS
Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.*
Healthcare professionals offer strong and consistent recommendations for all universally recommended vaccines according to the current immunization schedule. They use presumptive language (e.g., these vaccines are routine) and deliver this recommendation in the same manner for all vaccines.
Healthcare professionals answer parents' or guardians' and patients' questions thoroughly and emphasize an unwavering commitment to the recommendation. If parents or guardians and patients are hesitant or refuse, healthcare professionals persevere and offer the vaccine again at the next most appropriate time.
PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS
Healthcare professionals follow appropriate procedures for vaccine storage and handling.
Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.
Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.
Vaccination records for patients are accurate, complete, and easily accessible.
Healthcare professionals report adverse events after vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).
Healthcare professionals and personnel review the immunization timeline with parents or guardians and patients and schedule follow-up immunization visits before the family leaves the care setting.
All personnel who have contact with patients are appropriately vaccinated and communicate consistent messages about vaccines.
IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE
Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.
Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.
Healthcare professionals practice community-based approaches.
Healthcare professionals understand cultural needs and disparities of different populations and use the most effective strategies for these populations.
Most healthcare visits (including acute care or sick visits) are viewed as opportunities to review immunization records, provide vaccines that are due, and catch up on missed vaccinations.

*Additional resources to help improve immunization rates include the following:
- Provider Resources for Vaccine Conversations with Parents from CDC, AAP, and American Academy of Family Physicians (www.cdc.gov/vaccines/hcp/conversations/index.html)
- American Academy of Pediatrics (AAP) Training Guide (https://shar.es/1JRNmJ)
- Centers for Disease Control and Prevention (CDC): *Pink Book,* Chapter 6: Vaccine administration (https://www.cdc.gov/vaccines/pubs/pinkbook/vac-admin.html) and quality improvement projects and educational materials (https://www.cdc.gov/vaccines/ed/index.html)
- Immunization Action Coalition: Suggestions to improve your immunization services (http://www.immunize.org/catg.d/p2045.pdf)

Adapted from National Vaccine Advisory Committee. Standards for child and adolescent immunization practices. *Pediatrics.* 2003;112:958–963; and Bernstein HH, Bocchini JA; AAP Committee on Infectious Diseases. The need to optimize adolescent immunization. *Pediatrics.* 2017;139(3):e20164186, and Practical approaches to optimize adolescent immunization. *Pediatrics.* 2017;139(3):e20164187.

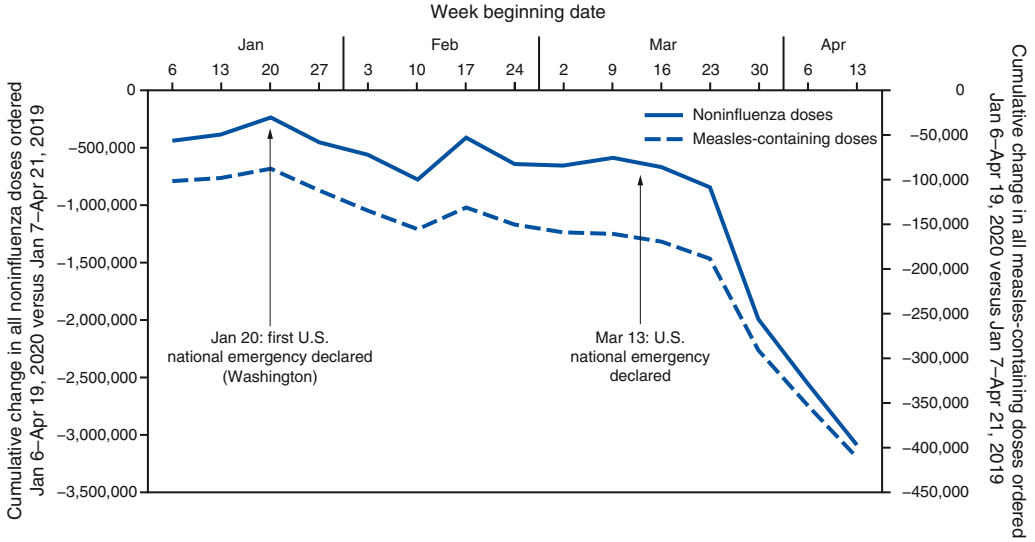

Fig. 215.3 Weekly changes in Vaccines for Children Program (VFC) provider orders* and Vaccine Safety Datalink (VSD) doses administered† for routine pediatric vaccines — United States, January 6–April 19, 2020. *VFC data represent the difference in cumulative doses of VFC-funded non-influenza and measles-containing vaccines ordered by healthcare providers at weekly intervals between Jan. 7–Apr. 21, 2019, and Jan. 6–Apr. 19, 2020; †VSD data depict weekly measles-containing vaccine doses administered by age-group (age ≤24 mo and >24 mo to 18 yr). *(From Santoli JM, Lindley MC, DeSilva MB, et al. Effects of the COVID-19 pandemic on routine pediatric vaccine ordering and administration – United States, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:591–593.)*

a reasonable estimate of practice coverage. Another approach is to have a staff member review the chart of every patient coming in for a visit and placing immunization needs reminders on the chart for the physician. Electronic medical records can be designed to accomplish this goal.

VACCINE HESITANCY

The World Health Organization (WHO) characterized *vaccine hesitancy* as a delay in acceptance or refusal of vaccines despite availability of vaccination services. The COVID-19 pandemic has also changed the way outpatient care is being delivered across the United States. Because of COVID-19, providers face the additional challenges of maintaining and strengthening routine vaccinations. As communities are reopening, it is vitally important for providers to work with parents to ensure their children stay up to date on routine, universally recommended vaccines. The pandemic is a reminder of the threat of infectious diseases. Providers are well positioned to counsel parents about the value of vaccination. Uptake is highest when parents are aware that their child is due for specific vaccines and when they feel safe about their children receiving those vaccines. Factors implicated in vaccine hesitancy include complacency, convenience, and confidence. The percentage of children having a parent reporting they were "hesitant about childhood shots" was 25.8% in 2018 and 19.5% in 2019 (https://pediatrics.aappublications.org/content/146/6/e2020007609). Concerns about vaccine safety and questions about the necessity of vaccines are often cited as reasons for refusal. Vaccine-hesitant individuals are a heterogeneous group, and their individual concerns should be respected and addressed. Multiple studies have shown that the most important factor in persuading parents to accept vaccines remains the *one-on-one contact* with an informed, caring, and concerned pediatrician. Parents should be reassured that vaccines are tested thoroughly before licensure, that ongoing mechanisms of monitoring safety exist after licensure, and that the current vaccine schedule is the only recommended schedule. It is important to stress that serious disease can occur if a child and family are not immunized, because unvaccinated children put medically exempt children who live in that same area at risk, as well as some children who have been vaccinated (although most vaccines are highly effective, no vaccine is 100% effective). Parental education can be provided through reputable sources for vaccine information (see Table 215.8). (For more information, see http://pediatrics.aappublications.org/content/early/2016/08/25/peds.2016-2146.) Provider resources for vaccine conversations with parents are available at https://www.cdc.gov/vaccines/hcp/conversations/index.html.

Physician concerns about liability should be addressed by appropriate documentation of discussions in the chart. The Committee on Bioethics of the AAP has published guidelines for dealing with parents' refusal of immunization. Physicians also might want to consider having parents sign a **refusal waiver**. A sample refusal-to-vaccinate waiver can be found at http://www2.aap.org/immunization/pediatricians/pdf/refusaltovaccinate.pdf.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

215.1 International Immunization Practices

W. William Schluter, Kari Johansen, and Tracey Goodman

Given that the epidemiology of infectious diseases varies across countries and continents, it is necessary for vaccination programs to be adapted accordingly. The WHO's Strategic Advisory Group of Experts (SAGE) on immunization evaluates the scientific evidence available for the various vaccines and products and develops advice on global policies and strategies ranging from vaccine type, recommendations for vaccine delivery, links with other health interventions, and suggested vaccine research. Its remit includes all vaccine-preventable infectious diseases for all age-groups. The WHO SAGE recommendations are summarized in the WHO Vaccine Position papers that are updated regularly. The latest information for recommended routine immunizations for children up to 18 years of age, including recommended ages for the initiation of the primary series and dose intervals, as well as recommendations for subsequent booster doses are listed in Table 215.13.

The WHO policy recommendations are adapted by the Regional and National Immunization Technical Advisory Groups making recommendations to respective country governments. As a consequence, the immunization schedules and the types of vaccines, including the specific vaccine products used, vary substantially. Country-specific immunization schedules have been compiled and are available online (https://immunizationdata.who.int/listing.html?topic=vaccine-schedule). Availability and cost play a major role in the choice of vaccine products and schedules in many countries.

According to the WHO recommended schedule, all children should be protected against 12 vaccine-preventable infectious pathogens: *Bordetella pertussis*, *Clostridium tetani*, *Corynebacterium diphtheriae, Haemophilus influenzae* type b, hepatitis B virus, human papillomavirus (HPV), measles virus, *Mycobacterium tuberculosis*, poliovirus, rotavirus, rubella virus, and *Streptococcus pneumoniae* (see Table 215.13).

BIRTH DOSE VACCINES

At birth, hepatitis B vaccine is recommended for all children within 24 hours of birth to prevent perinatal transmission. Additionally, Bacille Calmette-Guérin (BCG) vaccine is recommended at birth in countries or settings with a high incidence of tuberculosis (TB) and/or high leprosy burden, and the first dose of bivalent oral polio vaccine containing poliovirus type 1 and 3 (bOPV) is recommended to be given at birth in polio-endemic countries and in countries at high risk for importation and subsequent spread of poliovirus.

Primary Infant Series

Infant immunization visits are recommended to begin from the age of 6-8 weeks, with an interval of 4-8 weeks between doses to complete the primary series for protection against hepatitis B, polio, diphtheria, pertussis, tetanus, rotavirus, and invasive bacterial infections caused by *H. influenzae* type b and *S. pneumoniae*. To reduce the number of injections, some of these vaccines are provided in combination vaccines. Rotavirus vaccines are provided orally and can be administered concomitantly with the injectable vaccines and OPV. It should be noted that for all countries using OPV, two doses of injectable IPV are recommended from 14 weeks of age with an interval of at least 4 months between doses.

Two doses of measles vaccines are recommended, with the first dose given at 9-12 months of age and the second dose in the second year of life. Only one dose of rubella given at 9 months of age is sufficient to provide >95% protection. However, when using a rubella-containing vaccine that is combined with measles, it is often easier to provide a second dose using the same MR or MMR vaccine product for both doses, dependent on availability. HPV vaccine is recommended for girls from 9-14 years of age.

Booster Doses

In addition to the three doses provided in infancy, three booster doses of combination diphtheria toxoid– and tetanus toxoid–containing vaccine should be provided during childhood and adolescence, at 12-23 months (using DTP-containing vaccine), 4-7 years (with DT or Td), and 9-15 years of age (with Td). Ideally, there should be at least 4 years between booster doses. Depending on disease epidemiology, booster doses may also be recommended for Hib and pneumococcal conjugate vaccines. For countries where DTP/DT/Td booster doses are not provided, maternal vaccination with tetanus-containing vaccine (TT or Td) is provided to protect against neonatal and maternal tetanus.

Vaccination Against Outbreak-Prone Diseases for Endemic Areas

Cholera, Japanese encephalitis, meningococcal conjugate, typhoid, and yellow fever vaccines may be recommended for infants, children, and adolescents living in endemic areas, as shown in Table 215.14.

Table 215.13 Summary of Recommended Routine Immunization for *All* Children Up to 18 Years Based on WHO Vaccine Position Papers (updated as of September 2020)

For the most recent version of the respective position papers, the summary tables and further details per vaccine, consult the reference provided here*:

VACCINE		AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS TO BE MADE
				FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
BCG		As soon as possible after birth	1	NA	NA	NA	NA	• Universal vs selective vaccination of high-risk groups • Co-administration with hepatitis B and OPV • Birth dose and HIV • Vaccination of older age-groups
Hepatitis B	Option 1	As soon as possible after birth (<24 hr)	3	4 wk (min) with DTPCV1	4 wk (min) with DTPCV2	NA	NA	• Premature and low birthweight infants • Co-administration with other vaccines • High-risk infants
	Option 2	As soon as possible after birth (<24 hr)	4	4 wk (min) with DTPCV1	4 wk (min) with DTPCV2	4 wk with DTPCV3	NA	
Rotavirus		6 wk (min)	2 or 3 (dependent on product used)	4 wk (min) with DTPCV2	For the three-dose schedule: 4 wk with DTPCV3	NA	NA	• Not recommended if child >24 mo old
DTP-containing vaccine (DTPCV)		6 wk (min)	3	4 wk (min) to 8 wk	4 wk (min) to 8 wk	NA	3 boosters with DTPCV at 12-23 mo, 4-7 yr (Td/DT), and 9-15 yr (Td)	• Co-administration with other vaccines/combination vaccines • Maternal immunization if needed
Hemophilus influenzae type b	Option 1	6 wk (min) to 59 mo (max)	3	4 wk (min) with DTPCV2	4 wk (min) with DTPCV3	NA	At least 6 mo after last dose	• Single dose if >12 mo of age • Not recommended for children >5 yr • Co-administration with other vaccines/combination vaccines
	Option 2	6 wk (min) to 59 mo (max)	2-3	8 wk (min) if only 2 doses 4 wk (min) if 3 doses	4 wk (min) if 3 doses	NA	At least 6 mo (min) after last dose	
Pneumococcal conjugate	Option 1 3p + 0	6 wk (min)	3	4 wk (min)	4 wk	NA		• Schedule options • HIV+ • Preterm neonate booster
	Option 2 2p + 1	6 wk (min)	2	8 wk (min)		NA	9-18 mo	
Poliovirus	Option 1 bOPV + IPV	bOPV 6 wk IPV 14 wk	5 (3 bOPV + 2 IPV)	bOPV 4 wk (min) with DTPCV2 IPV 4 mo (min)	bOPV 4 wk (min) with DTPCV3			• bOPV birth dose • Fractional dose • Transmission and importation criteria
	Option 2 IPV/bOPV sequential	8 wk (IPV first)	1-2 IPV 2 bOPV	4-8 wk	4-8 wk	4-8 wk		
	Option 3 IPV-only	8 wk	3	4-8 wk	4-8 wk		Under evaluation	• IPV booster needed for early schedule (i.e., first dose given <8 wk)

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 215.13 Summary of Recommended Routine Immunization for *All* Children Up to 18 Years Based on WHO Vaccine Position Papers (updated as of September 2020)—cont'd

VACCINE	AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS TO BE MADE
			FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
Measles	9 or 12 mo	2	4 wk (min)			NA	• Combination vaccines • HIV early vaccination • Pregnancy
Rubella	9 or 12 mo with measles-containing vaccine	1				NA	• Achieve and sustain 80% vaccination coverage • Combination vaccine • Pregnancy
HPV	As soon as possible from 9 yr of age (females only)	2	6 mo (min 5 mo)			NA	• Target 9- to 14-yr-old girls • Vaccination during pregnancy to be avoided • Older age >15 yr, HIV, and immunocompromised irrespective of age need three doses

DTPCV1, DTP-containing vaccine dose 1; NA, not applicable.
*https://who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization—summary-tables
Courtesy of the World Health Organization, Department of Immunization, Vaccines and Biologicals. https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/table_2_feb_2023_english.pdf?sfvrsn=3e27ab48_11

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 215.14 Summary of Recommended Routine Immunization for Children Residing in Endemic Areas, Belonging to Identified High-Risk Populations or in Countries with More Extensive Vaccination Programs Based on WHO Vaccine Position Papers (updated as of 2020)*

VACCINE		AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS (SEE FOOTNOTES FOR DETAILS)
				FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
RECOMMENDATIONS FOR CHILDREN RESIDING IN CERTAIN REGIONS								
Japanese encephalitis	Option 1. Inactivated Vero cell derived	6 mo	2	4 wk (generally)				Vaccine options Pregnancy Immunocompromised
	Option 2. Live attenuated	8 mo	1					
	Option 3. Live recombinant	9 mo	1					
Yellow fever		9-12 mo with measles-containing vaccine	1					
Tickborne encephalitis		>1 yr FSME-Immun and Encepur >3 yr TBE-Moscow and EnceVir	3	1-3 mo FSME-Immun and Encepur 1-7 mo TBE Moscow and EnceVir	5-12 mo FSME-Immun and Encepur 12 mo TBE Moscow and EnceVir		At least 1 every 3 yr	Definition of high-risk Vaccine options Timing of booster doses
RECOMMENDATIONS FOR CHILDREN IN SOME HIGH-RISK POPULATIONS								
Typhoid	Option 1. TCV (Typbar)	>6 mo	1					Definition of high risk
	Option 2. Vi PS	2 yr (min)	1					Definition of high risk
	Option 3. Ty21a	Capsules 5 yr	3 or 4	1 day	1 day	1 day	Every 3-7 yr	Definition of high risk
Cholera	Dukoral (WC-rBS)	2 yr	3 for 2-5 yr 2 >6 yr	>7 days to 6 wk	>7 days to 6 wk		Every 6 mo Every 2 yr	Minimum age Definition of high risk
	Shancol, Euvichol and mORCVAX	1 yr	2	14 days			After 2 yr	
Meningococcal	MenA conjugate	9-18 mo	1					Definition of high risk Vaccine options 2 doses if <9 mo with 8-wk interval
	MenC conjugate	>2-11 mo	2	8 wk			After 1 yr	Definition of high-risk Vaccine options
		>12 mo	1					
	Quadrivalent (ACWY)	9-23 mo >2 yr	2 1					Definition of high risk Vaccine options

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 215.14 Summary of Recommended Routine Immunization for Children Residing in Endemic Areas, Belonging to Identified High-Risk Populations or in Countries with More Extensive Vaccination Programs Based on WHO Vaccine Position Papers (updated as of 2020)*—cont'd

VACCINE	AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS (SEE FOOTNOTES FOR DETAILS)
			FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
Hepatitis A	1 yr	At least 1					Level of endemicity Vaccine options Definition of high-risk groups
Rabies	As required	2	7 days				Preexposure vs postexposure prophylaxis Definition of high-risk groups
Dengue (CYD-TDV)	9 yr	3	6 mo	6 mo			Prevaccination screening
RECOMMENDATIONS FOR CHILDREN RECEIVING VACCINATIONS IN IMMUNIZATION PROGRAMS WITH CERTAIN CHARACTERISTICS							
Seasonal influenza Inactivated	6 mo	2 (<9 yr) 1 (≥9 yr)	4 wk			Revaccinate annually, 1 dose	Priority risk groups, especially pregnant women Lower dosage for children 6-35 mo
Mumps	12-18 mo with measles-containing vaccine	2	1 mo min to school entry				Coverage criteria >80% Combination vaccines
Varicella	12-18 mo	1-2	4 wk to 3 mo per manufacturer recommendations				Achieve and sustain >80% coverage necessary Pregnancy Co-administration with other live vaccines

*https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-rcommendations-for-routine-immunization—summary-tables

Courtesy the World Health Organization, Department of Immunization, Vaccines and Biologicals. https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/table_2_feb_2023_english.pdf?sfvrsn=3e27ab48_11&download=true

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 215.15 International Vaccine Websites and Resources

ORGANIZATION	WEBSITE
PUBLIC HEALTH ORGANIZATIONS	
WHO recommendations for routine immunization	https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization—summary-tables
WHO Vaccine Position Papers	https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers
WHO SAGE	https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/about
Global NITAG network systematic reviews	https://www.nitag-resource.org
WHO Regional Office for Africa	https://www.afro.who.int/
WHO Regional Office for the Americas or Pan American Health Organization	https://www.paho.org/en
WHO Regional Office for the Eastern Mediterranean	http://www.emro.who.int/index.html
WHO Regional Office for Europe	https://www.euro.who.int/en
WHO Regional Office for Southeast Asia	https://www.who.int/southeastasia
WHO Regional Office for the Western Pacific	https://www.who.int/westernpacific
Country-specific vaccination schedules	https://apps.who.int/immunization_monitoring/globalsummary
Canada provincial and territorial immunization schedule	https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information/provincial-territorial-routine-vaccination-programs-infants-children.html.
European Center for Disease Prevention and Control (ECDC)	https://www.ecdc.europa.eu/en
ECDC Vaccine Scheduler	https://vaccine-schedule.ecdc.europa.eu
Japan	https://www.jpeds.or.jp/uploads/files/2020%20English%20JPS%20Immunization%20Schedule.pdf
Mexico National Vaccination Schedule	https://www.gob.mx/salud/articulos/esquema-de-vacunacion.
UK immunization schedule	https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation
UK Immunisation against infectious disease – the Green Book	https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
Pan American Health Organization/WHO revolving fund for access to vaccines	https://www.paho.org/en/revolvingfund
UNICEF Supply Division	https://www.unicef.org/supply/vaccines
NONPROFIT GROUPS	
GAVI, the Alliance	http://www.gavialliance.org/
COVAX facility	https://www.gavi.org/covax-facility
Coalition for Epidemic Preparedness Innovations (CEPI)	https://cepi.net

Vaccine Supply and Production

Since 2000, the Global Alliance for Vaccines and Immunizations (GAVI, now known as *GAVI, The Vaccine Alliance*) has helped expand access to vaccines for infants, children, and adolescents in low-income countries by cost-sharing vaccine introduction and through market-sharing activities to expand vaccine production to drive down vaccine costs. There are other initiatives by the WHO and United Nations Children's Fund (UNICEF) that support pooled vaccine procurement to help expand access to vaccines in low- and middle-income countries. In many low- and middle-income countries, the private vaccine market is increasing. For relevant international vaccine websites and resources, see Table 215.15.

Vaccines are currently produced in many countries around the world, with India hosting the largest vaccine producers that serve many low- and middle-income countries. The number of countries with vaccine production capacity are expected to increase in the coming years as a result of the COVID-19 pandemic. Occasionally counterfeit vaccines have been identified, and therefore vigilant surveillance is needed to ensure safe and effective products reach the end consumer.

Vaccine Hesitancy and Demand

In addition to access, population willingness to accept vaccination is an important consideration influencing control of vaccine-preventable diseases. In 2019, the WHO declared vaccine hesitancy, which is the reluctance or refusal to accept vaccinations despite availability, as one of the top 10 threats to global health. Vaccination coverage for recommended vaccines varies between countries, and it is estimated that in 2022, 20.5 million children worldwide at the age of 1 year were considered unvaccinated or undervaccinated using DTP3 coverage data collected by UNICEF/WHO. Significant attempts to reach the unvaccinated and undervaccinated are underway, irrespective of the reasons.

Eradication and Elimination

After the success of the global eradication of smallpox, global eradication or regional disease elimination goals have been adopted for polio, measles, and rubella. In 1988 the World Health Assembly endorsed the goal of eradicating polio from the world by the end of 2000. Although that goal has not yet been reached, endemic wild poliovirus (WPV) transmission in 2023 is limited to two countries worldwide (Afghanistan and Pakistan). The principal eradication strategy has been the use of OPV both for routine immunization and mass supplemental immunization campaigns in endemic or high-risk areas, targeting all children <5 years of age for immunization, regardless of prior immunization status. In areas with low polio population immunity, the OPV virus can mutate over time to develop neurovirulence, similar to WPV. These mutated vaccine viruses are known as *vaccine-derived poliovirus* (VDPV). Since 2018, more paralytic cases have been caused by VDPVs than WPV. Once interruption of WPV transmission is achieved, the goal is to stop the use of OPV.

All six WHO regions have resolved to achieve measles elimination, and five (all but the Eastern Mediterranean region) have rubella elimination goals. In 2015, the Region of the Americas was the first region to achieve rubella elimination and has maintained that status since that time. Regional measles elimination in the Americas was verified in 2016 but was lost in 2018 when measles virus was reintroduced

and continued circulating for more than 12 months in Venezuela and Brazil. Though no other WHO region has achieved certification of regional measles or rubella elimination, national-level certification of elimination is continuing in all regions, with the European Region nearing regional elimination for both measles and rubella.

Goals to eliminate epidemics or to eliminate diseases as a public health problem have been adopted for other vaccine-preventable diseases that are not eradicable such as bacterial meningitis (*S. pneumoniae*, *N. meningitidis*), cervical cancer (HPV), cholera, hepatitis B, rabies, and tetanus (maternal and neonatal tetanus).

Vaccine Schedules in High-Income Countries

Immunization schedules in high-income countries are more variable than in low- and low-middle-income countries. In general, in high-income countries where disease incidence may be lower, doses of many vaccines are recommended to be given later than with the WHO recommended schedule. The infant primary series doses are usually given at 2, 3, and 4 months or at 2, 4, and 6 months (as in the United States) instead of starting early at 6 weeks of age. The first dose of measles-containing vaccines are often not administered until 12 months of age or later, with the second dose provided before school entry. Most middle- and high-income countries have moved to sequential IPV/OPV schedules or an IPV-only program with five or six recommended doses using combination vaccines.

Immunization recommendations for Canada are developed by the Canadian National Advisory Committee on Immunization (NACI) but vary by province. The Canadian schedule is similar to the U.S. immunization schedule, with a few exceptions. A birth dose of hepatitis B vaccine is not specifically recommended as it is in the United States, although some Canadian provinces do provide a birth dose. Conjugate meningococcal C vaccine is recommended in a one- or two-dose series, depending on the age at the time of administration (one dose if ≥12 months). In contrast to the United States, hepatitis A vaccine is not recommended in Canada as a routine pediatric immunization.

In Europe, there is significant variation in vaccines used and the immunization schedules recommended. The number of infectious diseases for which vaccines are offered vary between 12 and 17. As an example, an extensive immunization schedule is offered in the United Kingdom as recommended by the UK Joint Committee on Vaccine and Immunisation (JCVI). In 2023, it includes visits at 2, 3, and 4 months of age, when a combination DTaP-Hib-IPV-HepB vaccine is administered. Infants at high risk of developing hepatitis B infection from infected mothers are given doses of hepatitis B vaccine at birth, 4 weeks, and 1 year of age. MMR is recommended in a two-dose schedule at 12 and 40 months of age. During the second MMR visit, a booster of dTaP-IPV is provided. A Td/IPV booster is recommended at age 14 years. PCV13 is recommended at 3 and 12 months of age. Conjugate meningococcal C vaccine (MenC) is given in combination with a booster dose of Hib at 12 months, whereas MenB is offered at 2, 4, and 12 months of age, and conjugated MenACWY-135 is offered to adolescents at 14 years, with catch-up available up to 25 years of age. HPV vaccine is recommended for females and males at 12-13 years of age, with catch-up vaccination available up to 25 years of age. Rotavirus vaccination is offered at 2 and 3 months of age. Live attenuated influenza vaccine is provided to children 2-10 years of age. BCG is offered at birth in areas of the country with a TB incidence >40/100,000 or in families with a parent or grandparent born in a high-incidence country. As of June 2021, the UK schedule does not include the varicella and hepatitis A vaccines for universal childhood immunization.

Varicella vaccination has been initiated in 12 of the European Union countries, whereas hepatitis A vaccine is only offered routinely in a handful of these countries. However, hepatitis A is often provided to European children ahead of traveling to other regions of the world.

The 2020 Japanese immunization schedule differs from the U.S. schedule, in that a birth dose of hepatitis B vaccine is recommended only for infants born to mothers who test positive for HbsAg. The Japanese do not use MMR, instead recommending MR with mumps vaccine available on a voluntary basis. The recommendation for routine HPV vaccination was suspended in 2013 because of concerns about adverse events but was included for adolescent females in the 2020 schedule.

VACCINATION OF CHILDREN STARTING IMMUNIZATION OUTSIDE THE UNITED STATES

Some children come to the United States having started or completed international immunization schedules with vaccines produced outside the United States. In general, doses administered in other countries should be considered valid if administered at the same ages as recommended in the United States. For missing doses, age-inappropriate doses, lost immunization records, or other concerns, pediatricians have two options: administer or repeat missing or inappropriate doses, or perform serologic tests and, if they are negative, administer vaccines.

The childhood immunization schedule for China is unique because it recommends a sequential series for polio with IPV at 2 and 3 months of age, followed by OPV at 3 and 4 months of age. The infant primary series with diphtheria-tetanus-pertussis–containing vaccines is recommended at 3, 4, and 5 months of age. Similarly, China's schedule recommends one dose of MR vaccine at 8 months of age followed by one dose of MMR at 18 months.

India's childhood immunization schedule follows the WHO recommendations but includes two fractional doses (one fifth) of a full dose of IPV administered intradermally at 6 and 14 weeks.

Mexico recommends a schedule for pediatric immunization that is largely similar to the schedule in the United States. Some differences include that Mexico recommends the use of BCG and recommends HPV for females, but not males.

Vaccination Against Outbreak-Prone Diseases

Outbreaks spanning large geographical areas have affected several countries or continents caused by Ebola virus, influenza virus, circulating VDPV, and coronaviruses, including SARS-CoV-2 virus, have highlighted the need for preparedness to develop and assess in formal clinical trials and, if successful, rapidly produce vaccines to be used in outbreak response measures. For the Ebola virus outbreaks first identified in 2014 in West Africa and later in Democratic Republic of Congo, two new vaccines based on the recombinant vector-technology platform were developed, tested, and then used successfully in ring-vaccination outbreak vaccination campaigns.

The 2009 influenza A H1N1 pandemic triggered production of pandemic influenza vaccines (following the strain selection by WHO) by seasonal influenza vaccine producers worldwide, and adjuvants were used by several producers with the aim to be dose-sparing.

The eradication goal for polio and the chosen global strategy using a combination of OPV and IPV and the associated rare adverse event vaccine-induced paralytic polio have triggered development of a new oral poliovirus (nOPV) vaccine. This virus is more genetically stable and maintains an attenuation phenotype that will support the Global Polio Eradication Initiative during the final push to eliminate poliovirus globally, with the most immediate need in ongoing outbreak settings to control and eliminate circulating VDPVs.

The COVID-19 outbreak that started in late 2019 triggered unprecedented vaccine development, with clinical trials being conducted during the ongoing outbreak. Favorable short-term efficacy and safety data have resulted in the emergency use listing of eleven COVID-19 vaccines that were recommended by the WHO. The WHO vaccination recommendations had not been vaccine-product specific until the COVID-19 vaccines were made available. Since January 2021, each of the COVID-19 vaccine products has been recommended individually, because they are based on different technology production platforms and have been assessed in clinical trials including different age-groups and using different endpoints. Vaccination of children and adolescents 6 months of age and older is authorized for two mRNA vaccines. In June 2021, China was the first country globally that approved inactivated COVID-19 vaccines for children age 3-17 years. COVID-19 vaccines are made available globally either through direct contracts between vaccine producers and each country or through the COVAX facility, a global risk-sharing mechanism for pooled procurement and equitable distribution of COVID-19 vaccines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 216

Infection Prevention and Control

Kevin P. O'Callaghan and Julia S. Sammons

Infection prevention and control (IPC) programs are a critical and core component of ensuring patient and employee safety in pediatric healthcare systems. The scope of IPC programs is often large and requires a coordinated, well-resourced, multidisciplinary approach. At their heart, IPC programs are designed to prevent the **acquisition** and **transmission** of potentially pathogenic organisms within a healthcare setting. A robust regulatory and policy focus on the prevention of healthcare-associated infections (HAIs) is critical given their frequency. Data from the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) provides evidence that on any given day approximately 1 in 31 hospitalized patients experiences at least one HAI. Federal and state-level infrastructures that support HAI improvement efforts include the CDC NHSN, which operates a national surveillance system for HAIs, and the Joint Commission's 2022 National Patient Safety Goals. With improved surveillance and detection and focused improvement efforts, preventable events of harm (including HAIs) are now linked by many payors to reduced levels of reimbursement to offset costs associated with these events.

As our understanding of HAIs has developed over time with better surveillance metrics, reporting has expanded beyond the walls of hospitals to include HAIs occurring throughout healthcare systems. This scope includes infections in ambulatory surgical and medical settings, nursing homes, long-term acute care facilities, and even in patients' homes, especially with regard to medical device–associated infections. We have also expanded our understanding of epidemiologic risk factors, environmental pressures, and specific at-risk patient populations. Through a variety of avenues, IPC programs seek to eliminate transmission events and keep patients and employees safe.

TRANSMISSION IN THE HEALTHCARE SETTING

Fundamentally, transmission in the healthcare setting is multifaceted and multimodal. Patients, their family and caregivers, healthcare personnel, and others interact in a complex environment that is fraught with opportunity for transmission events to occur. Modern understanding of human microbiota informs us that all humans carry a plethora of microorganisms that could potentially be pathogenic in the right circumstances and in the right host. These colonizing microbiotas can be transmitted from one person to another in the healthcare setting through contaminated hands or medical equipment. The majority of infections that arise in healthcare settings occur from endogenous flora representing colonizing organisms. New HAIs require the presence of a number of independent but linked concepts, including a susceptible host, an infectious agent, a portal of entry, and modes of transmission.

Modes of transmission are a critical element of HAI prevention work and include **contact**, **droplet**, and **airborne**. Contact transmission occurs by direct contact with the patient or indirect contact with environmental surfaces or patient care items in the patient's environment that are contaminated with the offending microorganism (e.g., rotavirus). Droplet transmission occurs through large respiratory droplets, which are generated by coughing, sneezing, or talking and typically travel approximately 3 feet from an infectious person (e.g., influenza). These droplets are heavy and do not remain suspended in air for long periods. Airborne transmission occurs through small particles, which can remain suspended in air and can be widely dispersed by air currents (e.g., measles, tuberculosis). Although many infections can occur through transmission directly from an infectious host to a susceptible host, infections can also occur through contact with contaminated environments, whether through contaminated surfaces, fomites, or previously occupied air spaces.

PREVENTION STRATEGIES

Hand Hygiene

One of the most fundamental elements of infection prevention is hand hygiene; thus one of the most critical elements of an IPC program is hand hygiene education and auditing. Ignaz Semmelweis first postulated the effects of hand hygiene in 1847 when he noted epidemiologic differences in maternal mortality rates secondary to puerperal fever between physician- and midwife-delivered pregnancies. The critical difference was hand hygiene, and this proved to be a seminal finding in the field of infection prevention. Growing evidence of the importance of hand hygiene led to the first national hand hygiene guidelines in the 1980s and the development of international guidance on hand hygiene in healthcare. The World Health Organization (WHO) has developed an internationally used framework for hand hygiene education, called the *5 Moments for Hand Hygiene*. This program provides a structure for recognizing critical moments where hand hygiene can influence a transmission event, including before and after touching a patient, before a clean or aseptic procedure, after a body fluid exposure risk, and after touching patient surroundings (Table 216.1). Use of this or similar frameworks provides a structure for staff education around the practice of hand hygiene and serves as an auditing tool to assess rates of compliance with optimal practice.

Hand hygiene itself is the act of either handwashing (placing hands under running water and using friction with or without a soap product) or using a waterless hygiene product (e.g., alcohol-based foams or gels) to remove the burden of surface flora from the skin and nails of the hand. Alcohol-based hand hygiene products are widely available, are quick and easy to use, and allow for repeated in-the-moment use, such that they are the preferred method for hand hygiene for most healthcare situations. However, because they do not remove visible dirt or debris, handwashing with soap and water is recommended over alcohol-based products after dirty tasks when visible soiling is likely, such as after changing a diaper or using the restroom. Alcohol-based products are also not the preferred agents for certain hardy microbes such as norovirus or *Clostridioides difficile* spores, especially in outbreak settings.

Personal Protective Equipment

Personal protective equipment (PPE) is equipment worn to prevent or reduce exposure to potential hazards in the workplace, including infectious diseases. In the healthcare setting, PPE is targeted to prevent exposure of healthcare personnel's skin, eyes, respiratory tract, and mucous membranes to potential infectious agents but is also used to protect patients from the colonizing flora and respiratory secretions of healthcare personnel. Various types of PPE may be used in different settings, with the specific type of PPE tied to the **precautions** that are indicated for a specific patient and/or a specific pathogen. The five primary components of PPE include **gowns**, **gloves**, **masks**, **eye protection**, and **respirators (e.g., N95 or Powered Air-Purifying Respirator)**. Gowns can either be reusable (launderable) or disposable and are designed to prevent contamination of the provider's clothing, particularly from those infectious agents that are spread through a contact mechanism. Depending on the setting, gowns may be required to be resistant to liquid soaking in order to maximize their effectiveness.

Gloves are used most commonly as a component of standard precautions when performing a task where there is a reasonable expectation of soiling of the hands (e.g., changing a diaper or examining a wound). Importantly, glove use is not required for every moment of patient contact (e.g., routine physical exam), and glove use is not a substitute for effective hand hygiene in breaking the chain of transmission. Therefore gloves should never be used as the only element of infection prevention. Hand hygiene before donning of gloves and after removal of gloves is a critical and necessary step in breaking the chain of transmission.

Face masks and eye protection are intended to prevent exposure of a provider's mouth, nose, and eyes from expectorated and aerosolized pathogens. Protection of the eyes can include clear shields attached

Table 216.1 Recommendations for Application of Standard Precautions for Care of All Patients in All Healthcare Settings

COMPONENT	RECOMMENDATIONS
Hand hygiene	Before and after each patient contact, regardless of whether gloves are used. After contact with blood, body fluids, secretions, excretions, or contaminated items; immediately after removing gloves; before and after entering patient rooms. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous material or if exposure to spores (e.g., *Clostridium difficile, Bacillus anthracis)* or nonenveloped viruses (norovirus) is likely to have occurred; in these cases, soap and water is required.
PERSONAL PROTECTIVE EQUIPMENT (PPE)	
Gloves	For touching blood, body fluids, secretions, excretions, or contaminated items; for touching mucous membranes and nonintact skin. Employ hand hygiene before and after glove use.
Gown	During procedures and patient-care activities when contact of clothing or exposed skin with blood, body fluids, secretions, or excretions is anticipated.
Mask, eye protection (goggles), face shield	During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, or secretions, such as suctioning and endotracheal intubation, to protect healthcare personnel. For patient protection, use of a mask by the person inserting an epidural anesthesia needle or performing myelograms when prolonged exposure of the puncture site is likely to occur.
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment. Wear gloves if equipment is visibly contaminated. Perform hand hygiene.
ENVIRONMENT	
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient-care areas.
Textiles (linens) and laundry	Handle in a manner that prevents transfer of microorganisms to others and the environment.
PATIENT CARE	
Injection practices (use of needles and other sharps)	Do not recap, bend, break, or manipulate used needles; if recapping is required, use a one-handed scoop technique only. Use needle-free safety devices when available, placing used sharps in puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection. Single-dose medication vials preferred when medications may be administered to more than one patient.
Patient resuscitation	Use mouthpiece, resuscitation bag, or other ventilation devices to prevent contact with mouth and oral secretions.
Patient placement	Prioritize for single-patient room if patient is at increased risk for transmission, is likely to contaminate the environment, is unable to maintain appropriate hygiene, or is at increased risk for acquiring infection or developing adverse outcome after infection.
Respiratory hygiene/cough etiquette (source containment of infectious respiratory secretions in symptomatic patients) beginning at initial point of encounter, such as triage or reception areas in emergency department or physician office	Instruct symptomatic persons to cover nose/mouth when sneezing or coughing; use tissues with disposal in no-touch receptacles. Employ hand hygiene after soiling of hands with respiratory secretions. Wear surgical mask if tolerated or maintain spatial separation (>3 ft if possible).

Adapted from Kimberlin DW, Brady MT, Jackson MA, et al., eds. *Red Book 2018–2021: Report of the Committee on Infectious Diseases,* 31st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2018:148–150.

directly to surgical masks, separate face shields, or goggles, but protection of both forward-facing and lateral aspects of the ocular region is required.

In the setting of a true aerosolized pathogen, respirator use is indicated. Respirator masks include National Institute of Occupational Safety and Health (NIOSH)–approved N95s, so-called because they filter out up to 95% of particles in the air when used appropriately. Other respirator options that meet international standards include KN95 masks, but these may not meet NIOSH standards and should not be used in lieu of an N95. The use of fitted face mask respirators such as the N95 requires a fit-testing program to ensure that healthcare personnel are using a correctly sized and fitted mask at all times. Alternatives to a fitted respiratory mask include the powered air purifying respirator (PAPR), which uses a motor and fan to provide constant pressurized air flow from under a loosely fitting hood over the entire head.

Precautions and Isolation

Precautions and *isolation* are terms to describe in a specific patient-care setting which equipment, practices, and procedures should be used to best prevent against a transmission event related to a known or suspected pathogen.

Standard precautions are used in any setting in which patient care occurs to prevent transmission of a potential pathogen to or from a healthcare worker, regardless of suspected or confirmed infection status of the patient. These include consistent hand hygiene and use of barrier PPE (gown, glove, mask) as required based on risk of exposure

to blood and body fluids, including expectorations and respiratory secretions (e.g., routine use of mask and eye protection during endotracheal intubation).

Isolation procedures, or **transmission-based precautions**, are targeted to prevent transmission of known or suspected pathogens or in the setting of specific syndromes (e.g., infectious diarrhea, upper respiratory tract symptoms). **Contact isolation** typically includes gloves and gown in addition to standard precautions and is used to limit the spread of pathogens by direct contact with a patient (e.g., patients with norovirus). **Droplet isolation** includes protection of mucosal surfaces from expectorated large droplets and should include face mask and eye protection. Some pathogens may spread efficiently by both contact and droplet (e.g., rhinovirus), and thus these two isolation types may be combined as **droplet and contact**.

Airborne isolation is used for pathogens that are readily aerosolized and requires the use of eye protection and use of an appropriate respirator (either N95 or PAPR depending on the employee). Additionally, patients with airborne infections require placement in specialized airborne infection isolation rooms (AIIRs), which have specialized air handling that can maintain negative pressure compared with the surrounding environment and have increased air turnovers per unit time.

ENVIRONMENT, DISINFECTION, AND STERILIZATION

A critical component of preventing transmission of infectious pathogens in healthcare settings includes appropriate environmental cleaning, elimination of potential reservoirs, and disinfection and sterilization of medical equipment.

Maintaining cleanliness (and, where appropriate, sterility) of all patient care spaces, equipment, and medical devices requires an institutional focus on the environment of care that highlights accountability and highly reliable policies and procedures. For each individual healthcare worker, cleanliness of personal medical equipment used in patient care is key. This includes personal stethoscopes, which should be cleaned whenever they are visibly soiled and should be disinfected with an appropriate topical agent (e.g., alcohol) between each use. Similarly, shared patient devices such as thermometers, otoscopes, and ophthalmoscopes should either have disposable single-use covers or should have a cleaning protocol that is adhered to after each patient use.

Higher-level cleaning and disinfection, known as high-level disinfection, are required for reusable items that contact mucous membranes or nonintact skin (e.g., endoscopes), and sterilization is required for critical items that enter sterile tissue or the vascular system (e.g., surgical tools).

VISITATION AND PATIENT AND CAREGIVER MANAGEMENT

In pediatric healthcare settings, unlike adult settings, patients frequently are accompanied by parents, caregivers, and family members throughout their healthcare experience. Visitor and caregiver management is a critical tool in preventing healthcare transmission events in these settings. Limitation of total numbers of visitors at a bedside may be indicated in the setting of local or seasonal outbreaks of disease, such as during influenza season. Similarly, age-based limitations are commonly used to keep siblings of patients away from the healthcare setting, particularly during the winter respiratory viral season. Visitor screening at points of entry can be effective in identifying caregivers and siblings who may not be presenting for care but have evident symptoms of infection and may need to be excluded from the healthcare setting.

OCCUPATIONAL HEALTH AND CLINICIAN EDUCATION

Typically, infection prevention and control programs work closely with occupational or employee health programs because both departments have a responsibility for keeping healthcare workers safe from workplace hazards, including infection. Occupational health and IPC programs may work together to develop on-boarding requirements for vaccination for common diseases and programs for seasonal vaccination for influenza. Annual and as-needed education for healthcare workers is an important role of IPC programs, including education on best practices for hand hygiene, use of PPE, and promoting understanding of patient isolation categories.

SPECIAL POPULATIONS

Immunocompromised Hosts

Immunocompromised hosts include those patients with inborn disorders of immunity and patients with iatrogenically caused immune deficits (e.g., patients undergoing chemotherapy, solid organ, or bone marrow transplant or those using immune-modulating therapies). Immunocompromised hosts pose a special infection prevention problem, as they are typically more susceptible to infections that may be common and benign in other patients and more susceptible to infections that are highly unusual in hosts with intact immune systems, such as invasive mold.

The environment of care for these patients may have additional considerations over and above the norm. **Positive pressure ventilation** can be used to provide a protective environment for such patients during periods of highest risk (e.g., immediately after bone marrow transplantation). A focus on air handling capability, including high-efficiency particulate absorbing (HEPA) filtration, is critically important, especially in settings where construction or renovation is ongoing, as this increases the risk of aerosolization of fungal and mold spores.

Patients with Indwelling Medical Devices

Indwelling medical devices such as pacemakers, orthopedic hardware, intracranial shunts, and indwelling venous catheters pose a special infection risk because of disruption of normal immunologic barriers (e.g., skin) that can allow for communication between sterile and nonsterile spaces and because of the presence of foreign material, which can present a nidus for biofilm formation. IPC programs are frequently involved in quality improvement projects around the optimal insertion and maintenance of such devices, both in the healthcare setting and at home.

Surveillance and Reporting

In addition to the primary prevention work of an IPC program, another core element includes response to transmission events, which critically includes a surveillance and reporting mechanism. IPC programs typically monitor for events of infection within the healthcare setting, such as surgical site infection or new diagnoses of viral respiratory infection so as to generate data about current trends, detect clusters and outbreaks, and guide future policy. Most states require reporting of healthcare-associated events such as infections to a state- and/or federal-level body such as NHSN.

Preparedness, Bioresponse, and Public Health

An important additional element of IPC work is preparedness and planning for community-based outbreaks or epidemics that can affect healthcare operations. Planning for low-likelihood, high-risk pathogens such as Ebola virus requires a multidisciplinary planning team, including hospital operations, IPC, clinical teams, transport services, and others. Scheduled periodic retraining of a core group of healthcare workers can increase their comfort in managing the care of these patients and in decreasing the risk of PPE and isolation breaches that could lead to an event of transmission.

In addition to internal systemwide planning, interfacing with public health bodies is an important responsibility of IPC teams. This responsibility includes reporting of notifiable diseases (e.g., sexually transmitted infections [STIs], tuberculosis, measles), which may require a broader public health response in the community. In the absence of positive test results, individual clinician suspicion of a disease is frequently the initial trigger for public health notification, and so an understanding of reporting requirements is important for each healthcare worker.

IPC is increasingly a complex and specialized area of expertise within healthcare operations. However, at its heart it requires the active participation and commitment of every member of the healthcare team. As such, the best way to keep patients safe is to approach every moment of patient interaction as an opportunity to create a safe and clean environment of care.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 217

Childcare and Communicable Diseases

Gail V. Carter-Hamilton and Susan E. Coffin

More than 20 million children <5 years old attend a childcare facility. These facilities can include part-day or full-day programs at nursery schools or preschools and full-day programs based in either a licensed childcare center or another person's home. Regardless of the age at entry, children entering childcare settings are more prone to infections, largely from the exposure to greater numbers of children.

Childcare facilities can be classified based on the number of children enrolled, ages of attendees, health status of the attendees, and type of setting. As defined in the United States, **childcare facilities** consist of childcare centers, small and large family childcare homes, and facilities for ill children or for children with special needs. Centers are licensed and regulated by state governments and care for a larger number of children than are typically cared for in family homes. In contrast, **family childcare homes** are designated as small (1-6 children) or large (7-12 children), may be full-day or part-day, and may be designed for either daily or sporadic attendance. Family childcare homes generally are not licensed or registered, depending on state requirements.

Although many children who attend childcare facilities are cared for in family childcare homes, most studies of infectious diseases in infants and toddlers have been conducted in childcare centers. Almost any organism has the potential to be spread and to cause disease in a childcare setting. Epidemiologic studies have established that children in childcare facilities are 2-18 times more likely to acquire a variety of infectious diseases than children not enrolled in childcare (Table 217.1).

Children who attend childcare facilities are more likely to receive more courses of antimicrobial agents for longer periods and to acquire antibiotic-resistant organisms. Transmission of infectious agents in group care depends on the age and immune status of the children, season, hygiene practices, crowding, and environmental characteristics of the facilities. The pathogen characteristics, including infectivity, survivability in the environment, and virulence, also influence transmission in childcare settings. Rates of infection, duration of illness, and risk for hospitalization tend to decrease among children in childcare facilities after the first 6 months of attendance and decline to levels observed among homebound children after 3 years of age. Adult caregivers are also at increased risk for acquiring and transmitting infectious diseases, particularly in the first year of working in these settings.

EPIDEMIOLOGY

Respiratory tract infections and **gastroenteritis** are the most common diseases associated with childcare. These infections occur in children and their household contacts and in childcare workers and can spread into the community. The severity of illness caused by a given respiratory and enteric pathogen depends on the person's underlying health status, the inoculum, and prior exposures to the pathogen, either by infection or immunization. Some organisms, such as hepatitis A virus (HAV), can cause subclinical disease in young children and produce overt and sometimes serious disease in older children and adults. Other diseases, such as otitis media and varicella, usually affect children rather than adults. Both infections and infestations of the skin and hair may be acquired through contact with contaminated linens or through close personal contact, which is inevitable in childcare settings.

RESPIRATORY TRACT INFECTIONS

Respiratory tract infections account for the majority of childcare-related illnesses. Children <2 years old who attend childcare centers have more upper and lower respiratory tract infections than do age-matched children not in childcare. The organisms responsible for these illnesses are similar to those that circulate in the community and include respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses, human metapneumoviruses, adenoviruses, rhinoviruses, endemic and epidemic coronaviruses, parvovirus B19, and *Streptococcus pneumoniae.*

Upper respiratory tract infections, including **otitis media**, are among the most common manifestations of these infections. The risk for developing otitis media is 2-3 times greater among children who attend childcare centers than among children cared for at home. Most prescriptions for antibiotics for children <3 years old in childcare are to treat otitis media. These children also are at increased risk for recurrent

Table 217.1 Infectious Diseases in the Childcare Setting

DISEASE	INCREASED INCIDENCE WITH CHILDCARE
RESPIRATORY TRACT INFECTIONS	
Otitis media	Yes
Sinusitis	Probably
Pharyngitis	Probably
Pneumonia	Yes
GASTROINTESTINAL TRACT INFECTIONS	
Diarrhea (rotavirus, norovirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia, Cryptosporidium, Shigella, Escherichia coli* O157:H7, and *Clostridium difficile*)	Yes
Hepatitis A	Yes
SKIN DISEASES	
Impetigo	Probably
Scabies	Probably
Pediculosis	Probably
Tinea (ringworm)	Probably
INVASIVE BACTERIA INFECTIONS	
Haemophilus influenzae type b	No*
Neisseria meningitidis	Probably
Streptococcus pneumoniae	Yes
ASEPTIC MENINGITIS	
Enteroviruses	Probably
HERPESVIRUS INFECTIONS	
Cytomegalovirus	Yes
Varicella-zoster virus	Yes
Herpes simplex virus	Probably
BLOOD-BORNE INFECTIONS	
Hepatitis B	Few case reports
HIV	No cases reported
Hepatitis C	No cases reported
VACCINE-PREVENTABLE DISEASES	
Measles, mumps, rubella, diphtheria, pertussis, tetanus	Not established
Polio	No
H. influenzae type b	No*
Varicella	Yes
Rotavirus	Yes
COVID-19	Yes

*Not in the post–vaccine era; *yes* in the pre–vaccine era.

otitis media, further increasing the use of antimicrobial agents in this population. Studies have demonstrated reductions in both otitis media and antibiotic use subsequent to pneumococcal vaccination implementation. Pharyngeal carriage of group A *Streptococcus* occurs earlier among children in childcare; systemic illness may occur including pneumonia, empyema, septic arthritis, or osteomyelitis. **Influenza** vaccination of younger infants reduces influenza infection and secondary sequelae in both the children and the adults who care for them in their home and in childcare settings. After adoption of the acellular pertussis vaccine, increases in clusters and outbreaks of infection caused by *Bordetella pertussis* have led to the recognition of less durable immunity, with older children and adults serving as reservoirs of infection.

Transmission of these organisms typically occurs through either direct or indirect contact with the respiratory droplets of an infected child. In childcare settings, contamination of surfaces occurs frequently as children mouth toys, drool, and cough or sneeze. Additionally, some respiratory pathogens are spread through large droplets that typically can travel 3-6 feet. However, intimate contact between children is a routine part of the play and care of young children, thus facilitating transmission. The most common surfaces from which airborne droplets can be spread are the hands, so the most efficient form of infection control in the childcare setting is good hand hygiene.

GASTROINTESTINAL TRACT INFECTIONS

Acute infectious **diarrhea** is 2-3 times more common among children in childcare than among children cared for in their homes. Outbreaks of diarrhea, which occur frequently in childcare centers, are usually caused by enteric viruses, such as norovirus, caliciviruses, enteric adenoviruses, and astroviruses, or by enteric parasites such as *Giardia lamblia* or *Cryptosporidium*. A dramatic and sustained decline in the burden of rotavirus infection has been demonstrated since introduction of the rotavirus vaccination program in 2006, and this trend is likely reflected in the population of children attending childcare and early childhood education programs. Bacterial **enteropathogens** such as *Shigella* and *Escherichia coli* O157:H7 and, less often *Campylobacter, Clostridium difficile,* and *Bacillus cereus* also have caused outbreaks of diarrhea in childcare settings. *Salmonella* rarely is associated with outbreaks of diarrhea in childcare settings because person-to-person spread of this organism is uncommon.

Outbreaks of **HAV infection** in children enrolled in childcare facilities have resulted in community-wide outbreaks. HAV infection is typically mild or asymptomatic in young children and often is identified only after symptomatic illness becomes apparent among either older children or adult contacts of children in childcare. Enteropathogens and HAV are transmitted in childcare facilities by the fecal-oral route and can also be transmitted through contaminated food or water. Children in diapers constitute a high risk for the spread of gastrointestinal infections through the fecal-oral route. As such, enteric illness and HAV infection are more common in centers that care for children who are not toilet-trained and where proper hygienic practices are not followed. The most common enteropathogens, such as norovirus and *G. lamblia,* are characterized by low infective doses and high rates of asymptomatic excretion among children in childcare, characteristics that facilitate transmission and outbreaks.

SKIN DISEASES

The most recognized skin infections or infestations in children in childcare are impetigo caused by *Staphylococcus aureus* or group A *Streptococcus*, pediculosis, scabies, tinea capitis, tinea corporis, and molluscum contagiosum. Many of these diseases are spread by contact with infected linens, clothing, hairbrushes, and hats and through direct personal contact; they more often affect children >2 years old. The magnitude of these infections and infestations in children in childcare is not known.

Parvovirus B19, which causes fifth disease (erythema infectiosum), is spread through the respiratory route and has been associated with outbreaks in childcare centers. The rash of fifth disease is a systemic manifestation of parvovirus B19 infection; the child is no longer contagious once the rash is present (see Chapter 298). The greatest health hazard is for pregnant women and immunocompromised hosts because of their respective risks for fetal loss and aplastic crisis.

INVASIVE ORGANISMS AND SYSTEMIC INFECTIONS

Before universal immunization, *Haemophilus influenzae* type b invasive disease was more common among children in childcare than children in homecare. Although the largest burden of invasive *H. influenzae* infection in the pediatric population still occurs in children <5 years old, infection is now primarily caused by nontypeable *H. influenzae* or non–type b encapsulated strains of *H. influenzae;* there have been no reported outbreaks of nontypeable or type b *H. influenzae* in >5 years in the United States.

Data suggest that the risk for primary disease caused by *Neisseria meningitidis* is higher among children in childcare than among children in homecare. Childcare attendance is also associated with nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and invasive pneumococcal disease, especially among children with a history of recurrent otitis media and use of antibiotics. Secondary spread of *S. pneumoniae* and *N. meningitidis* has been reported, indicating the potential for outbreaks to occur in this setting. Routine use of pneumococcal conjugate vaccine has decreased the incidence of invasive disease and reduced carriage of serotypes of *S. pneumoniae* contained in the vaccine both in the vaccinated child and in younger siblings. A vaccine against serogroup B meningococcus has been introduced for routine use in children <2 years old in the United Kingdom. It is anticipated that infant vaccination against meningococcus will be adopted in the near future. Outbreaks of aseptic meningitis have been reported among children in childcare centers and among their parents and their teachers.

HERPESVIRUSES

As many as 70% of diapered children who become infected with **cytomegalovirus** (CMV) shed virus in urine and saliva for prolonged periods. CMV-infected children often transmit the virus to other children with whom they have contact and to their care providers and their mothers at a rate of 8–20% per year. Transmission occurs as a result of contact with either saliva or urine. The overwhelming majority of primary infections with and reactivation of CMV in otherwise healthy children results in asymptomatic shedding of CMV; nonetheless, this shedding can pose a health risk for previously uninfected pregnant childcare providers or immunocompromised persons. A licensed CMV vaccine is not yet available, but research is ongoing, with recent trials demonstrating tolerability and immunogenicity of candidate CMV vaccines (see Chapter 302).

Varicella often is transmitted in childcare centers, but routine use of varicella vaccine has reduced this risk. Vaccinated children who become infected with varicella often have mild, atypical symptoms and signs of disease that can result in delayed recognition and spread of infection to susceptible contacts. The role of childcare facilities in the spread of **herpes simplex virus**, especially during episodes of gingivostomatitis, requires further clarification.

BLOOD-BORNE PATHOGENS

Hepatitis B virus (HBV) transmission has been reported rarely in childcare settings, and transmission of hepatitis C virus (HCV), hepatitis D virus (HDV), and HIV has not been reported in a childcare setting. However, it is impossible to identify every child who might have a blood-borne infection such as hepatitis B, C, or D, or HIV, and it is critical that standard precautions be observed routinely to reduce the risk for transmitting these viruses and other pathogens.

Concerns have been raised about the risk of HIV transmission in childcare settings and the acquisition of opportunistic infections by HIV-infected children who attend childcare, but experience has revealed that this risk is minimal. Children with HIV infection enrolled in childcare facilities should be kept up to date on their vaccines and monitored for exposure to infectious diseases.

Transmission of blood-borne pathogens can theoretically occur when there is contact between blood or body fluids and a mucous membrane or an open wound. Blood-borne pathogens are unlikely to spread by toddler **biting** in a group setting. Most bites do not break the skin, and if a bite does break the skin, the mouth of the biter does not stay on the victim long enough for blood to transfer from the biter to the victim. If there are concerns about transmission of HBV, HCV, or HIV infection, it is recommended to check the status of the biter rather than the bite victim as part of the initial evaluation process.

ANTIBIOTIC USE AND BACTERIAL RESISTANCE

Antibiotic resistance has become a major global problem and threatens the health of children who attend childcare facilities because the incidence of infection by organisms resistant to frequently used antimicrobial agents has increased dramatically. It is estimated that children in childcare are 2-4 times more likely to receive an antibiotic and that they receive longer courses of antibiotics compared with age-matched children in homecare. This frequency of antibiotic use combined with the propensity for person-to-person transmission of pathogens in a crowded environment has resulted in an increased prevalence of antibiotic-resistant bacteria in the respiratory and intestinal tracts, including *S. pneumoniae, H. influenzae, Moraxella catarrhalis, E. coli* O157:H7, and *Shigella* spp.

Methicillin-resistant *S. aureus* **(MRSA)** has historically been found primarily in the healthcare setting but is now prevalent in the community setting. Traditional childcare center attendance is cited as a risk factor for colonization with MRSA, and carriage is associated with increased risk of infection and transmission. Population-based surveillance has demonstrated a rise in both invasive and noninvasive MRSA infections in community settings over the past 2 decades. Currently, large-scale studies investigating the epidemiology of *S. aureus* in the childcare setting are limited.

PREVENTION

Written policies designed to prevent or to control the spread of infectious agents in a childcare center should be available and should be reviewed regularly. All programs should use a health consultant to help with development and implementation of infection prevention and control (IPC) policies (see Chapter 216). Standards for environmental and personal hygiene should include maintenance of current immunization records for both children and staff, appropriate policies for exclusion of ill children and caretakers, targeting of potentially contaminated areas for frequent cleaning, adherence to appropriate procedures for changing diapers, appropriate handling of food, management of pets, and surveillance for and reporting of communicable diseases. Staff whose primary function is preparing food should not change diapers. Appropriate and thorough **hand hygiene** is the most important factor for reducing infectious diseases in the childcare setting. Strategies for improving adherence to these standards should be implemented. Children at risk for introducing an infectious disease should not attend childcare until they are no longer contagious (Tables 217.2 and 217.3).

Routine vaccination is proven to improve the health of children in childcare settings. In the United States, there are 17 diseases and organisms against which all children should be immunized unless there are contraindications: diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitis A and hepatitis B, varicella, *H. influenzae* type b, *S. pneumoniae,* rotavirus, *N. meningitidis,* influenza, COVID-19, and human papillomavirus (see Chapter 215). Rates of immunization among children in licensed childcare facilities are high, in part because of laws in almost all states that require age-appropriate immunizations of children who attend licensed childcare programs. Vaccines against influenza, *H. influenzae* type b, hepatitis B, rotavirus, varicella, *S. pneumoniae,* COVID-19, and hepatitis A are of particular benefit to children in childcare centers.

Childcare providers should receive all immunizations that are recommended routinely for adults, including tetanus and diphtheria toxoids and acellular pertussis (Tdap) booster, influenza, and COVID-19 vaccines and should have a preemployment health evaluation, with a tuberculin skin test or interferon-γ release blood assay. Local public health authorities should be notified of cases of reportable communicable disease that occur in children or providers in childcare settings.

STANDARDS

Every state has specific standards for licensing and reviewing childcare centers and family childcare homes. The American Academy of Pediatrics, American Public Health Association, and National Resource

Table 217.2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
COVID-19	Return to class after 10 days from onset and no fever for at least 24 hr without antipyretics.	Varies and evolving but many include being tested ≥5 days from exposure, wearing a mask, checking for symptoms, stay at home if symptoms develop (see latest recommendations at CDC) (see also Chapter 311).
Clostridium difficile	Exclusion until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Stool consistency does not need to return to normal to be able to return to childcare. Neither test of cure nor repeat testing should be performed for asymptomatic children in whom *C. difficile* was diagnosed previously.	Symptomatic contacts should be excluded until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Testing is not required for asymptomatic contacts.
Hepatitis A virus (HAV) infection	Serologic testing to confirm HAV infection in suspected cases. Exclusion until 1 wk after onset of illness.	In facilities with diapered children, if one or more cases confirmed in child or staff attendees or two or more cases in households of staff or attendees, hepatitis A vaccine (HepA) or immune globulin intramuscular (IGIM) should be administered within 14 days of exposure to all unimmunized staff and attendees. In centers without diapered children, HepA or IGIM should be administered to unimmunized classroom contacts of index case. Asymptomatic IGIM recipients may return after receipt of IGIM.
Impetigo	No exclusion if treatment has been initiated and as long as lesions on exposed skin are covered.	No intervention unless additional lesions develop.
Measles	Exclusion until 4 days after beginning of rash and when the child is able to participate.	Immunize exposed children without evidence of immunity within 72 hr of exposure. Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles.

Continued

Table 217.2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Mumps	Exclusion until 5 days after onset of parotid gland swelling.	In outbreak setting, people without documentation of immunity should be immunized or excluded. Immediate readmission may occur after immunization. Unimmunized people should be excluded for 26 or more days after onset of parotitis in last case. A second dose of MMR vaccine (or MMRV, if age appropriate) should be offered to all students (including those in postsecondary school) and to all healthcare personnel born in or after 1957 who have only received one dose of MMR vaccine. A second dose of MMR also may be considered during outbreaks for preschool-age children who have received one MMR dose. People previously vaccinated with two doses of a mumps-containing vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.
Pediculosis capitis (head lice) infestation	Treatment at end of program day and readmission on completion of first treatment. Children should not be excluded or sent home early from school because of head lice, because this infestation has low contagion within classrooms.	Household and close contacts should be examined and treated if infested. No exclusion necessary.
Pertussis	Exclusion until completion of 5 days of the recommended course of antimicrobial therapy if pertussis is suspected. Children and providers who refuse treatment should be excluded until 21 days have elapsed from cough onset.	Immunization and chemoprophylaxis should be administered as recommended for household contacts. Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy. Untreated adults should be excluded until 21 days after onset of cough.
Rubella	Exclusion for 7 days after onset of rash for postnatal infection.	During an outbreak, children without evidence of immunity should be immunized or excluded for 21 days after onset of rash of the last case in the outbreak. Pregnant contacts should be evaluated.
Infection with *Salmonella* serotypes Typhi or Paratyphi	Exclusion until three consecutive stool cultures obtained at least 48 hr after cessation of antimicrobial therapy are negative, stools are contained in the diaper or child is continent, and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program.	When *Salmonella* serotype Typhi infection is identified in a child care staff member, local or state health departments may be consulted regarding regulations for length of exclusion and testing, which may vary by jurisdiction.
Infection with nontyphoidal *Salmonella* spp., *Salmonella* of unknown serotype	Exclusion until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Stool consistency does not need to return to normal to be able to return to childcare. Negative stool culture results *not* required for nonserotype Typhi or Paratyphi *Salmonella* spp.	Symptomatic contacts should be excluded until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Stool cultures are not required for asymptomatic contacts.
Scabies	Exclusion until after treatment given.	Close contacts with prolonged skin-to-skin contact should receive prophylactic therapy. Bedding and clothing in contact with skin of infected people should be laundered.
Infection with Shiga toxin–producing *Escherichia coli* (STEC), including *E. coli* O157:H7	Exclusion until two stool cultures (obtained at least 48 hr after any antimicrobial therapy, if administered, has been discontinued) are negative, stools are contained in the diaper or child is continent, and stool frequency is no more than two stools above that child's normal frequency. Some state health departments have less stringent exclusion policies for children who have recovered from less virulent STEC infection.	Meticulous hand hygiene; stool cultures should be performed for any symptomatic contacts. In outbreak situations involving virulent STEC strains, stool cultures of asymptomatic contacts may aid in controlling spread. Center(s) with cases should be closed to new admissions during STEC outbreak.
Shigellosis	Exclusion until treatment complete and one or more posttreatment stool cultures are negative for *Shigella* spp., stools are contained in the diaper or child is continent, and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Some states may require more than one negative stool culture.	Meticulous hand hygiene; stool cultures should be performed for any symptomatic contacts.

Table 217.2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing.	Meticulous hand hygiene; cultures of contacts are not recommended.
Streptococcal pharyngitis	Exclusion until at least 12 hr after treatment has been initiated.	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive.
Tuberculosis	Most children younger than 10 yr are not considered contagious. For those with active disease, exclusion until determined to be noninfectious by physician or health department authority. No exclusion for latent tuberculosis infection (LTBI).	Local health department personnel should be informed for contact investigation.
Varicella	Exclusion until all lesions have crusted or, in immunized people without crusts, until no new lesions appear within a 24-hr period.	For people without evidence of immunity, varicella vaccine should be administered, ideally within 3 days, but up to 5 days after exposure, or when indicated, varicella-zoster immune globulin (VariZIG) should be administered up to 10 days after exposure; if VariZIG is not available, intravenous immunoglobulin (IGIV) should be considered as an alternative. If vaccine cannot be administered and VariZIG/IGIV is not indicated, preemptive oral acyclovir or valacyclovir can be considered.

From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021, Table 2.3, pp. 128–132.

Table 217.3 Recommendations for Inclusion or Exclusion of Childcare*

CHILDREN NEED NOT BE EXCLUDED FOR A MINOR ILLNESS UNLESS ANY OF THE FOLLOWING EXISTS:

- The illness prevents the child from participating comfortably in program activities.
- The illness results in a greater care need than the childcare staff can provide without compromising the health and safety of the other children.
- The child has any of the following conditions: fever, unusual lethargy, irritability, persistent crying, difficulty breathing, or other signs of possible severe illness.
- Diarrhea (defined as an increased number of stools compared with the child's normal pattern, with increased stool water and/or decreased form) that is not contained by diapers or toilet use.
- Vomiting two or more times in the previous 24 hours, unless the vomiting is determined to be caused by a noncommunicable condition and the child is not in danger of dehydration.
- Mouth sores associated with an inability of the child to control his or her saliva, unless the child's physician or local health department authority states that the child is noninfectious.
- Rash with fever or behavior change, until a physician has determined the illness to not be a communicable disease.
- Purulent conjunctivitis (defined as pink or red conjunctiva with white or yellow eye discharge, often with matted eyelids after sleep and eye pain or redness of the eyelids or skin surrounding the eye), until examined by a physician and approved to readmission, with or without treatment.
- Tuberculosis, until the child's physician or local health department authority states that the child is noninfectious.
- Impetigo, until 24 hours after treatment has been initiated.
- Streptococcal pharyngitis, until 24 hours after treatment has been initiated and unless the child has been afebrile for 24 hours.
- Head lice (pediculosis), until the morning after the first treatment.
- Scabies, until after treatment has been completed.
- Varicella, until the sixth day after the onset of rash or sooner if all lesions have dried and crusted.
- Pertussis (which is confirmed by laboratory or suspected based on symptoms of the illness or because of cough onset within 14 days of having face-to-face contact with a person in a household or classroom who has a laboratory-confirmed case of pertussis), until 5 days of appropriate antibiotic therapy (currently: erythromycin) has been completed (total course of treatment is 14 days).
- Mumps, until 9 days after onset of parotid gland swelling.
- Hepatitis A virus infection, until 1 week after onset of illness and jaundice, if present, has disappeared or until passive immunoprophylaxis (immune serum globulin) has been administered to appropriate children and staff in the program, as directed by the responsible health department.

Certain conditions do not constitute a prior reason for excluding a child from childcare unless the child would be excluded by the above criteria or the disease is determined by a health authority to contribute to transmission of the illness at the program. These conditions include the following: a symptomatic excretion of an enteropathogen; nonpurulent conjunctivitis (defined as pink conjunctiva with a clear, watery eye discharge and without fever, eye pain, or eyelid redness); rash without fever and without behavior change; cytomegalovirus infection; hepatitis B virus carrier state; and HIV infection.

*Child and caregiver-specific exclusion policies reflect the present state of knowledge.
From Centers for Disease Control and Prevention: https://dchealth.dc.gov/sites/default/files/dc/sites/doh/publication/attachments/Recommendations%20for%20Inclusion%20or%20Exclusion%20CDC.pdf

Center jointly publish comprehensive health and safety performance standards that can be used by pediatricians and other healthcare professionals to guide decisions about management of infectious diseases in childcare facilities (available at http://nrckids.org/CFOC). Additionally, the **National Association for the Education of Young Children (NAEYC)**, a professional organization supporting early childhood education efforts and volunteer accreditation, is gaining recognition as a resource for health and safety standards for childcare facilities (http://www.naeyc.org/). Specific standards set by all states can be reviewed at the U.S. Department of Health and Human Services' **National Center on Early Childhood Quality Assurance** website (https://childcareta.acf.hhs.gov/licensing).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 218

Health Advice for Children Traveling Internationally

John C. Christenson and James G. Carlucci

Children are traveling internationally with increasing frequency and to more exotic destinations that pose unique injury and disease risks. Compared to adults, children are *less* likely to receive pretravel advice and *more* likely to be seen by a medical provider or be hospitalized on return for a travel-related illness. Primary care providers are confronted with the challenge of trying to ensure safe, healthy travel for their patients, whether travel is occurring for purposes of tourism, study abroad, visiting friends and relatives, or volunteerism. Whenever possible, health professionals are encouraged to consult with **travel medicine specialists**, especially when uncertain about pretravel advice, unique travel medicine vaccines (e.g., yellow fever, Japanese encephalitis, typhoid, rabies), and recommendations for malaria medications.

Travel medicine is a unique specialty, and experienced travel medicine practitioners provide specialized guidance on the infectious and noninfectious risks based on age, itinerary, duration, season, purpose of travel, and underlying traveler characteristics (health and vaccination status). A **pretravel consultation** includes the essential elements of (1) safety and preventive counseling against injuries and diseases, (2) routine, recommended, and required vaccinations, based on individual risk assessment, (3) counseling and medications for self-treatment of traveler's diarrhea, and (4) when indicated by itinerary, malaria chemoprophylaxis (Table 218.1).

In the United States, recommendations and vaccine requirements for travel to different countries are provided by the Centers for Disease Control and Prevention (CDC) and are available online at https://wwwnc.cdc.gov/travel/page/yellowbook-home (Table 218.2). Some travel vaccines and medications may not be recommended based on specifics of travel itinerary, trip duration, or patient characteristics. Alternatively, some vaccinations are not approved for younger children because of lack of data or limited immunologic response but may still confer potential benefit to the young traveler with off-label vaccine administration. In both scenarios, consultation or referral to a knowledgeable travel medicine practitioner is encouraged, especially if uncertainty exists regarding pretravel recommendations.

THE PEDIATRIC TRAVEL MEDICINE CONSULTATION

Parents of traveling children should seek medical consultation at least 1 month before departure to review the travel itinerary, obtain safety and preventive counseling, ensure adequate vaccinations (routine, recommended, and required), receive necessary medications for chronic health conditions, and obtain important medications for self-treatment of traveler's diarrhea and, when indicated, malaria chemoprophylaxis with counseling. Advice, vaccinations, and medications should be emphasized as important measures, with the provider goal of keeping the child healthy during travel rather than to discourage traveling.

Pediatric Travelers Visiting Friends and Relatives

Compared to most children traveling internationally, the **pediatric visiting-friends-and-relatives (VFR) traveler** is the most vulnerable population uniquely at risk for travel-related illnesses. VFR travelers may include immigrants, refugees, migrants, students, or displaced persons who are traveling back to their country of origin for the purposes of visiting friends and relatives. Pediatric VFR travelers are typically children accompanying their parents or family members back to their ancestral country, where relational, social, and cultural connections remain. Compared to tourist travelers, VFR travelers are more likely to travel for longer durations, visit more remote destinations, travel by higher-risk local transportation modes, experience closer contact with the local population, and use fewer insect, food, and water precautions. Adult and pediatric VFR travelers are also less likely to perceive a risk of travel-related illnesses, seek pretravel advice, receive travel immunizations, or use effective malaria prophylaxis on arrival in the destination country. VFR travel comprises ~60% of imported malaria in U.S. children (i.e., malaria acquired outside the United States), and pediatric VFR travelers are reported to be 25 times more likely than tourist travelers to acquire malaria. Among all travelers, unvaccinated pediatric VFR travelers remain at higher risk for contracting and having symptomatic illness caused by hepatitis A virus. Several studies suggest that VFR travelers are at disproportionate risk of acquiring typhoid fever and possibly tuberculosis as well.

SAFETY AND PREVENTIVE COUNSELING TOPICS

Health and Evacuation Insurance, Underlying Health Conditions, and Medications

Parents should be made aware that their medical insurance policy might not provide coverage for hospitalizations or medical emergencies in foreign countries and is unlikely to cover the high cost of an emergency medical evacuation. Supplemental **travel medical insurance** and **evacuation insurance** may be purchased and are especially recommended for prolonged travel itineraries, for remote destinations, and for children with higher-risk preexistent health conditions going to countries where inpatient care at a level comparable to the traveler's home country may not be available. Information regarding medical and evacuation insurance providers can be found at the U.S. Department of State International Travel advisory website (https://travel.state.gov/content/travel/en/international-travel/before-you-go/your-health-abroad/insurance-providers-overseas.html) and the CDC Travel Health website (https://wwwnc.cdc.gov/travel/page/insurance).

Parents of children with medical conditions should take with them a brief medical summary and a sufficient supply of prescription medications for their children, with bottles that are clearly identified by prescription labels. For children requiring care by specialists, an international directory for that specialty can be consulted. A directory of physicians worldwide who speak English and who have met certain qualifications is available from the International Society of Travel Medicine (https://www.istm.org). If medical care is needed urgently when abroad, sources of information include the U.S. embassy or consulate, hotel managers, travel agents catering to foreign tourists, and missionary hospitals.

A travel health kit consisting of prescription medications and nonprescription items, such as acetaminophen, an antihistamine, oral rehydration solution packets, antibiotic ointment, bandages, insect repellent (DEET or picaridin), and sunscreen, is highly recommended for all children. Children with persistent asthma should have bronchodilators and oral corticosteroids prescribed for treatment of any acute asthma exacerbations encountered during overseas travel. Children with a history of angioedema, anaphylaxis, or severe allergies to food or insects should have an epinephrine autoinjector (EpiPen) and antihistamines available for use during travel.

Parents and family members should be aware of the prevalence of *counterfeit medication* and lack of quality control of medications in many areas of the world, particularly in low- and middle-income countries. Critical medications, including insulin and newly prescribed antimalarials, should be purchased before international travel and packed in original prescription containers.

Safety and Injury Prevention

Motor vehicle accidents are a leading cause of traumatic injuries, hospitalizations, and deaths, both in pediatric and adult travelers. Differences in traffic patterns and regulations (e.g., right- vs. left-hand traffic and pedestrian right of way) should be emphasized to children, and the use of safety belts should be reinforced. When possible, child safety seats should be taken on the trip. Parents should also be aware of additional risks for small children that may exist overseas, such as open balconies, windows without screens or bars, exposed wires and electrical outlets, paint chips, pest and rodent poison, and stray animals.

Table 218.1 Checklist of Items to Address in the Pretravel Consultation

CATEGORY	ISSUES THAT SHOULD BE ADDRESSED
Patient risk assessment	Obtain history: itinerary, type of travel, personal medical history, age, underlying diseases, allergies, current medications, pregnancy status, previous vaccination status
Immunizations	Update routine immunizations Provide routine travel immunizations Provide destination-specific immunizations
Malaria prophylaxis	If indicated: Provide malaria education and advice; discuss bite-avoidance measures Prescribe antimalaria prophylaxis
Traveler's diarrhea	Prescribe oral rehydration therapy and loperamide (Imodium)* Prescribe appropriate antibiotic (see Table 218.4)
Prevention against mosquito bites	Give advice regarding mosquito-borne disease Discuss personal protection measures
Rabies prevention	Give advice regarding behavior near animals Discuss measures to take if bitten or scratched by an animal—seek urgent medical advice Administer vaccine when indicated
Prevention of sexually transmitted diseases	Provide education regarding safe sex
Zika virus	Discuss potential risk of congenital Zika syndrome for pregnant women or women/men planning to conceive after return from an endemic area

Some of the recommendations are indicated only for specific destinations or specific at-risk groups.
*Contraindicated in bacterial diarrhea, dysentery.
Modified from Matson KB, Siraj DS. Travel medicine. In Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023*. Philadelphia: Elsevier; 2023: Table 2, p. 1474.

Water-related activities also are associated with significant injuries in pediatric travelers, and pools and oceanfronts are often unsupervised and without lifeguards at overseas destinations. Injuries to children on **flights** are also well-documented. Children should not sit in aisle seats, as they can be injured by aisle traffic, service carts, and falling objects from overhead storage bins.

Animal Contact

Among travelers, attacks from domestic or stray animals are much more likely to occur than attacks from wild animals. Wounds from animal bites present a risk for bacterial infections, tetanus, and rabies. **Dogs** are responsible for >95% of all **rabies** transmission in Asia, Africa, and Latin America. Globally, the World Health Organization (WHO) estimates that approximately 59,000 human deaths result from rabies each year, with the vast majority of cases occurring in South Asia, Southeast Asia, and Africa. Rabies transmission is reported less frequently after bites from cats and other carnivores, monkeys, and bats. Macaque monkeys native to Asia and North Africa can be found in urban centers and tourist sites and pose a risk for rabies and herpes B virus infections after bites and scratches.

Young children are more likely to be bitten and experience more severe facial wounds because of their short stature. They are at higher risk for rabies exposure from dogs and other animals during travel and require greater supervision. Parents should always encourage their children to report bite injuries and to avoid petting, feeding, or handling dogs, monkeys, and stray animals. Before travel, tetanus vaccinations need to be current for all travelers. Children, long-term travelers, expatriates, and all individuals likely to come into contact with animals in a rabies-endemic region (primarily Africa and South and Southeast Asia) should consider preexposure vaccination for rabies before international travel (see Rabies later). Bite or scratch wounds should be washed thoroughly and for a prolonged time (≥15 minutes) with copious water and soap. Local wound care will substantially reduce the risk of canine and other mammalian rabies transmission. Rabies **postexposure vaccination** and rabies immunoglobulin is likely indicated in most cases, and medical care should be sought emergently. Antibiotics (e.g., amoxicillin-clavulanate) may need to be administered to a child to prevent secondary infections, especially for animal bites involving the hands and head/neck areas.

ROUTINE CHILDHOOD VACCINATIONS REQUIRED FOR PEDIATRIC TRAVEL

Parents should allow at least 4 weeks before departure for optimal administration of vaccines to their children. All children who travel should be immunized according to the routine childhood immunization schedule with all vaccines appropriate for their age. The immunization schedule can be accelerated to maximize protection for traveling children, especially for unvaccinated or incompletely vaccinated children (see Fig. 215.1 in Chapter 215). Routine and catch-up childhood vaccine schedules can be found at the CDC website (https://www.cdc.gov/vaccines/schedules/).

Live-attenuated viral vaccines should be administered concurrently or ≥4 weeks apart to minimize immunologic interference. Intramuscular Immunoglobulin administration interferes with the immune response to measles immunization and possibly to varicella immunization. If a child requires measles or varicella immunization, the vaccines should be given either 2 weeks before or 3 months after immunoglobulin administration (longer with higher doses of intravenous immunoglobulin). Immunoglobulin does not interfere with the immune response to oral typhoid, poliovirus, or yellow fever vaccines.

Vaccine products produced in eggs (yellow fever, influenza) may be associated with hypersensitivity responses, including anaphylaxis in persons with known severe **egg sensitivity**. Screening by inquiring about adverse effects when eating eggs is a reasonable way to identify those at risk for anaphylaxis from receiving influenza or yellow fever vaccines. Although measles and mumps vaccines are produced in chick embryo cell cultures, children with egg allergy are at very low risk for anaphylaxis with these vaccines.

Diphtheria-Tetanus-Pertussis

Children traveling internationally should be fully vaccinated with diphtheria and tetanus toxoids and acellular pertussis (DTaP), having completed the fourth or fifth booster dose by 4-6 years of age. A single dose of an adolescent/adult preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11-12 years of age for those who have completed the recommended primary DTaP (or DTP) series.

Adolescents and adults should receive a single Tdap booster if >5 years have elapsed since the last dose, since a tetanus-containing booster (Td or Tdap) may not be readily available for tetanus-prone wounds during international travel or in remote settings (e.g., adventure travel, wilderness).

Haemophilus influenzae Type b

Haemophilus influenzae type b (Hib) remains a leading cause of meningitis in children 6 months to 3 years of age in many low- and middle-income countries. Before they travel, all unimmunized children <5 years old should be vaccinated against Hib (see Chapter 215). A single dose of Hib vaccine should also be administered to unvaccinated or

partially vaccinated children ≥5 years old if they have anatomic or functional asplenia, sickle cell disease, HIV infection, leukemia, malignancy, or other immunocompromising condition. Unvaccinated children >5 years old do not need vaccination unless they have a high-risk condition.

Hepatitis A

Hepatitis A is a routine childhood vaccine in the United States but requires special considerations in the traveling pediatric patient. Protection from hepatitis A in specific children may also involve the provision of immunoglobulin. For these reasons, hepatitis A vaccination is covered later in Specialized Pediatric Travel Vaccinations.

Hepatitis B

Hepatitis B can be a travel-associated infection. Hepatitis B is highly prevalent throughout much of the world, including areas of South America, sub-Saharan Africa, Eastern and Southeastern Asia, and most of the Pacific basin. In certain parts of the world, 8–15% of the population may be chronically infected. Disease can be transmitted by blood transfusions not screened for hepatitis B surface antigen, exposure to unsterilized needles, close contact with local children who have open skin lesions, and sexual exposure. Exposure to hepatitis B is more likely for travelers residing for prolonged periods in endemic areas. Partial protection may be provided by one or two doses, but ideally three doses should be given before travel. For unvaccinated adolescents, a three-dose hepatitis B vaccine series should be administered, with a minimum interval of 4 weeks between the first and second doses, 8 weeks between the second and third doses, and at least 16 weeks between the first and third doses.

All unvaccinated children and adolescents should receive the accelerated hepatitis B vaccine series before travel. Because one or two doses provide some protection, hepatitis B vaccination should be initiated even if the full series cannot be completed before travel.

Respiratory Viruses

Infections by respiratory viruses such as influenza and SARS-CoV-2 are well recognized as a cause of morbidity among adult and pediatric travelers. Disease caused by these viruses can be prevented through vaccination. The risk for exposure to influenza during international travel varies depending on the time of year, destination, and close contact with infected persons. During the peak of the SARS-CoV-2 pandemic, the use of lockdowns and quarantine, masks, and physical distancing used in many countries to control the spread of SARS-CoV-2 greatly altered the epidemiology of influenza and other respiratory viruses, resulting in few reported infections More recently, influenza appears to have returned to its "traditional" seasonality.

Influenza vaccination is recommended for all children older than 6 months of age and for adults. Vaccines against SARS-CoV-2 are also available (for persons ≥ 6 months of age) and are recommended to prevent severe disease, hospitalization, and death. **Oseltamivir** can be used to treat (and prevent) influenza infections. Antivirals are available to treat serious SARS-CoV-2 infections, especially for high-risk individuals.

There are no available vaccines effective against avian influenza strains such as influenza A H5N1 and H7N9, which have become a great concern worldwide. Because these strains of influenza virus are spread through contact with infected birds, precautions include avoiding direct contact with birds or surfaces with bird droppings, avoiding poultry farms or bird markets, eating only well-cooked poultry or products, and washing hands frequently. **Oseltamivir** is the antiviral of choice to treat infections caused by these viruses.

Measles-Mumps-Rubella

Measles is still endemic in many low- and middle-income countries and in some industrialized nations. It remains a leading cause of vaccine-preventable death in much of the world. Vaccine status for measles is important for all traveling children, particularly if they are traveling to low- and middle-income countries or areas with measles outbreaks. Measles vaccine, preferably in combination with mumps and rubella vaccines (MMR), should be given to all children at 12-15 months and at 4-6 years of age, unless there is a contraindication (see Chapter 215). In children traveling internationally, the second vaccination can be given as soon as 4 weeks after the first to induce immunity among those children who did not respond to the first MMR vaccine.

Children 6-12 months old traveling to low- and middle-income countries should be vaccinated early. The monovalent measles vaccine is not available in the United States, so MMR can be administered. Early vaccination (i.e., 6-12 months of age) will provide some immunity to measles, but antibody response may not be durable or lasting. Therefore any MMR vaccine administered before 12 months of age should not be counted toward the routine vaccination schedule; children vaccinated early for purposes of international travel must be revaccinated on or after their first birthday with two doses separated by at least 4 weeks. Infants <6 months old are generally protected by maternal antibodies (assuming the mother has previously been immunized against measles or had natural infection) and would not need early MMR vaccination before travel.

Pneumococcal Vaccines

Streptococcus pneumoniae is the leading cause of childhood **bacterial pneumonia** and is among the leading causes of bacteremia and bacterial meningitis in children in low- and middle-income and industrialized nations. Preparing a child to travel internationally includes routine or catch-up vaccination with 20-valent pneumococcal conjugate vaccine (PCV20) and, for children with certain high-risk conditions, use of 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV20 should be administered to previously unvaccinated children 6-18 years old with underlying high-risk medical conditions, including anatomic or functional asplenia (including sickle cell disease), HIV infection, a congenital immunodeficiency or immunocompromising condition, chronic heart or lung disease, chronic renal failure or nephrotic syndrome, diabetes mellitus, cerebrospinal fluid leak, or cochlear implant. The Advisory Committee on Immunization Practices (ACIP) also recommends that high-risk children ≥2 years old receive the PPSV23 vaccine ≥8 weeks after their last PCV13 dose. ACIP recommendations on prevention of pneumococcal disease among infants and children using PCV13 and PPSV23 can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.

Polio Vaccine

Poliomyelitis (wild type) was eradicated from the Western Hemisphere in 1991. Polio remains endemic in two countries—Afghanistan and Pakistan—with additional surrounding countries at risk for importation of polio. Unfortunately, many other countries throughout the world, mainly Africa, are experiencing infections by vaccine-derived poliovirus. The poliovirus vaccination schedule in the United States is a four-dose, all-inactivated poliovirus (IPV) regimen (see Chapter 215). Traveling infants should begin the IPV series as early as 6 weeks of age (for an accelerated dosing schedule for children, see Fig. 215.1 and Table 215.1). Length of immunity conferred by IPV immunization is not known; a single booster dose of IPV is therefore recommended for previously vaccinated adolescents and adults traveling to polio-endemic areas if approximately 10 years have elapsed since they completed their primary series. Oral poliovirus vaccine is no longer available in the United States.

Varicella

All children ≥12 months old who have no history of varicella vaccination or chickenpox should be vaccinated unless there is a contraindication to vaccination (see Chapter 215). Unlike measles vaccine (see earlier), varicella vaccine is not approved or recommended for traveling children 6-12 months of age. Infants <6 months old are generally protected by maternal antibodies. All children now require two doses, the first at 12 months of age and the second at 4-6 years. The second dose can be given as soon as 3 months after the first dose. For unvaccinated children ≥13 years old, the first and second doses can be separated by 4 weeks.

SPECIALIZED PEDIATRIC TRAVEL VACCINATIONS

Table 218.2 summarizes the dosages and age restrictions of vaccines specifically given to children traveling internationally.

Cholera

Cholera is present in many low- and middle-income countries, but the risk for infection among travelers to these countries is extremely low. Travelers entering countries reporting cholera outbreaks are at minimal risk of acquiring cholera if they take adequate safe food and water precautions and practice frequent handwashing. No country or territory currently requires cholera vaccination as a condition for entry. Of note, a live-attenuated, single-dose oral suspension vaccine is licensed in the United States to prevent disease in travelers 2-64 years of age visiting endemic regions.

Hepatitis A Vaccination and Preexposure Immunoglobulin

Hepatitis A virus (HAV) is endemic in most of the world, and travelers are at risk, even if their travel is restricted to the usual tourist routes. HAV infection can result from eating shellfish harvested from sewage-contaminated waters, eating unwashed vegetables or fruits, or eating food prepared by an asymptomatic HAV carrier. Young children infected with hepatitis A are often asymptomatic but can transmit infection to unvaccinated older children and adults, who are more likely to develop clinical hepatitis. Few areas carry no risk of HAV infection, and therefore immunization is recommended for all travelers. Hepatitis A vaccine (HepA) is recommended in the United States for universal immunization of all children ≥12 months old, administered as two doses 6 months apart. A single dose of HepA vaccine given to travelers will provide adequate protection. Protective immunity develops within 2 weeks after the initial vaccine dose. A combined three-dose HepA and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available in the United States but is licensed for use only in individuals >18 years old. Pediatric combination hepatitis A–hepatitis B vaccine (HepA-HepB) (Twinrix-Junior, GlaxoSmithKline) is licensed for use in children 1-18 years old in Canada and Europe. In many countries, a combination hepatitis A–typhoid fever vaccine is available for persons >16 years of age.

Children <1 year old are at lower risk of clinical HAV infection, especially if they are breastfed or residing in areas with safe water for formula reconstitution. Some experts recommend use of preexposure intramuscular immunoglobulin for children <6 months who are traveling internationally to higher-risk destinations, particularly low-income destinations or regions where hygienic or sanitary conditions are limited. However, administration of immunoglobulin diminishes the immunogenicity of live-virus vaccines, in particular measles vaccine, that may be needed for infant travelers. Vaccination against measles should occur ≥2 weeks before any immunoglobulin administration, and a 3-month interval is suggested between immunoglobulin administration and subsequent measles immunization.

Because measles-endemic countries frequently overlap with higher-risk travel destinations for HAV infection, HepA vaccine is recommended for infant travelers 6-11 months of age. Several studies demonstrate that infants as young as 6 months will develop antibodies after HepA, especially if there are no interfering maternal antibodies from prior maternal vaccination or disease. There is potential for a more durable immune response to the HepA vaccination, especially in later infancy, when potential interfering maternal antibody concentrations are lower. If early HepA vaccination is given rather than immunoglobulin to infant travelers (age 6-11 months), it should not count toward the routine two-dose vaccine series. Similar to MMR vaccination, an informed decision should be made with the parents, balancing the risk of travel-associated disease and vaccine adverse events with the potential protective benefit to the traveling infant.

Japanese Encephalitis

Japanese encephalitis is a disease transmitted by mosquitoes in many areas of Asia, especially in rural farming areas. Although it is a leading cause of vaccine-preventable encephalitis in children in many Asian countries and parts of western Pacific countries, the risk of disease to nonimmune travelers is low. A map showing where Japanese encephalitis transmission occurs can be found at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/japanese-encephalitis.

Most human infections with **Japanese encephalitis virus (JEV)** are asymptomatic, and <1% of individuals develop clinical disease. With symptomatic disease, the fatality rate is 20–30%, and the incidence of neurologic or psychiatric sequelae in survivors is 30–50%. The risk of JEV disease for pediatric travelers is unknown, but among all travelers, it is estimated to be less than 1 case per 1 million travelers to Asia. However, if residing in a rural area with active JEV transmission in the rainy season, the risk may increase to 5-50 cases per 100,000 population per year. Risk of Japanese encephalitis neurologic disease after mosquito-bite transmission is thought to be higher in children than in adults. The disease occurs primarily from June to September in temperate zones and throughout the entire year in tropical zones. Vaccination is recommended for travelers planning visits >1 months to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. Vaccination is recommended for shorter visits to such areas if the traveler will often be outdoors or where increased disease activity is reported. Risk for infection can be greatly reduced by following the standard precautions to avoid mosquito bites.

The inactivated Vero cell culture–derived Japanese encephalitis vaccine (Ixiaro) has replaced the older inactivated mouse brain–derived vaccine (JE-VAX), which is no longer manufactured. Japanese encephalitis vaccine efficacy is >95% in adults who receive two doses administered 7-28 days apart. The licensed range for Japanese encephalitis vaccine has been extended to include children as young as 2 months, with a dose administered on days 0 and 28.

Meningococcal Vaccines

Meningococcal vaccines currently available in the United States include two quadrivalent conjugate A/C/Y/W-135 vaccines, MenACWY-CRM (Menveo) and MenACWY-TT (MenQuadfi), and two meningococcal B vaccines (Bexsero, Trumenba).

Children traveling to those equatorial countries in sub-Saharan Africa (i.e., the "meningitis belt") where the incidence of meningococcal disease (especially group A) is highest should receive a *Neisseria meningitidis* quadrivalent vaccine, especially if travel is prolonged or occurs during the dry season of December to June. Risk is greatest in the meningitis belt of sub-Saharan Africa, with rates of meningococcal disease in endemic regions reaching up to 1,000 cases per 100,000 population per year. Vaccination programs for resident populations with a monovalent group A vaccine in highly endemic areas have resulted in a decrease in cases of invasive disease. In recent years, other serogrups have become more prevalent. Conjugate A/C/Y/W-135 vaccines are available to pediatric travelers ≥2 months of age, but the dosing schedule varies by product and age, as outlined in Table 218.2. Booster doses of conjugate A/C/Y/W-135 should occur every 3-5 years for travelers returning to endemic areas, depending on the age of the pediatric traveler. Providers may also want to consider meningococcal vaccination for other pediatric travelers, especially if there is remote or rural travel within low-income countries with limited healthcare access, because meningococcal outbreaks can occur anywhere in the world. Proof of receipt of quadrivalent meningococcal vaccination is also necessary for individuals traveling to Saudi Arabia for the annual Hajj or Umrah pilgrimage.

Serogroups A and C are most often associated with epidemics of meningitis in sub-Saharan Africa, especially in the meningitis belt of equatorial Africa during the dry season months (December to June). Serogroups Y and W-135 have also been found in meningococcal outbreaks. Serogroup B is associated with more sporadic cases of invasive meningococcal disease in industrialized countries, including the United States. Routine vaccination of travelers with meningococcal B vaccine is currently not recommended. Additional vaccine information on meningococcal vaccination regimens and booster intervals can be found at the CDC website (https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/meningococcal-disease).

Rabies

Rabies is endemic in many countries in Africa, Asia, and Central and South America. Children are at particular risk because they are less likely to report bites and because facial bites are more common in children. Rabies has the potential for an extended latency period (months) and is uniformly fatal once the clinical symptoms emerge. **Preexposure prophylaxis** is recommended for ambulatory children with extended

Table 218.2 Travel Vaccine Summary Table

VACCINE	TRADE NAME (MFR)	AGE	DOSE	ROUTE	SCHEDULE	BOOSTER
Cholera CVD 103-HgR vaccine	Vaxchora (PaxVax)	18-64 yr	100 mL (reconstituted)	Oral	1 dose[1]	Undetermined[2]
Hepatitis A vaccine, inactivated	Havrix (GlaxoSmithKline)	1-18 yr	0.5 mL (720 ELISA units)	IM	0 and 6-12 mo	None
		≥19 yr	1.0 mL (1,440 ELISA units)	IM	0 and 6-12 mo	None
Hepatitis A vaccine, inactivated	Vaqta (Merck & Co., Inc.)	1-18 yr	0.5 mL (25 U)	IM	0 and 6-18 mo	None
		≥19 yr	1.0 mL (50 U)	IM	0 and 6-18 mo	None
Hepatitis B vaccine, recombinant with novel adjuvant (1018)	Heplisav-B (Dynavax Technologies Corp.)	>18	0.5 mL (20 μg HBsAg and 3,000 μg of 1018)	IM	0, 1 mo	None
Hepatitis B vaccine, recombinant[2,3]	Engerix-B (GlaxoSmithKline)	0-19 yr	0.5 mL (10 μg HBsAg)	IM	0, 1, 6 mo	None
		0-10 yr (accelerated)	0.5 mL (10 μg HBsAg)	IM	0, 1, 2 mo	12 mo
		11-19 yr (accelerated)	1 mL (20 μg HBsAg)	IM	0, 1, 2 mo	12 mo
		≥20 yr (primary)	1 mL (20 μg HBsAg)	IM	0, 1, 6 mo	None
		≥20 yr (accelerated)	1 mL (20 μg HBsAg)	IM	0, 1, 2 mo	12 mo
Hepatitis B vaccine, recombinant[2,3]	Recombivax HB (Merck & Co., Inc.)	0-19 yr (primary)	0.5 mL (5 μg HBsAg)	IM	0, 1, 6 mo	None
		11-15 yr (adolescent accelerated)	1 mL (10 μg HBsAg)	IM	0, 4-6 mo	None
		≥20 yr (primary)	1 mL (10 μg HBsAg)	IM	0, 1, 6 mo	None
Combined hepatitis A and hepatitis B vaccine	Twinrix (GlaxoSmithKline)	≥18 yr (primary)	1.0 mL (720 ELU HAV + 20 μg HBsAg)	IM	0, 1, 6 mo	None
		≥18 yr (accelerated)	1.0 mL (720 ELU HAV + 20 μg HBsAg)	IM	0, 7, and 21-30 days	12 mo
Japanese encephalitis vaccine, inactivated	Ixiaro (Valneva)	2 mo to 2 yr	0.25 mL	IM	0, 28 days	≥1 year after primary series[4]
		3-17 yr	0.5 mL	IM	0, 28 days	≥1 yr after primary series[4]
		18-65 yr	0.5 mL	IM	0, 7-28 days	≥1 yr after primary series[4]
		>65 yr	0.5 mL	IM	0, 28 days	≥1 yr after primary series[4]
Meningococcal polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT)[5]	MenQuadfi (Sanofi Pasteur)	≥2 yr	0.5 mL	IM	1 dose[6]	If at continued risk[7]
Meningococcal oligosaccharide diphtheria CRM_{197} conjugate vaccine (MenACWY-CRM)[5]	Menveo (GSK)	2-12 mo	0.5 mL	IM	0, 2, 4, 10 mo	If at continued risk[7]
		7-23 yr	0.5 mL	IM	0, 3 mo (second dose administered in second year of life)	
		≥2 yr	0.5 mL	IM	1 dose[6]	

Table 218.2 Travel Vaccine Summary Table—cont'd

VACCINE	TRADE NAME (MFR)	AGE	DOSE	ROUTE	SCHEDULE	BOOSTER
Polio vaccine, inactivated	IPOL (Sanofi Pasteur)	≥18 yr	0.5 mL	SC or IM	1 dose if patient has completed a pediatric series	Repeat boosters may be needed for long-term travelers to polio-affected countries; see Chapter 296
Rabies vaccine (human diploid cell)	Imovax (Sanofi Pasteur)	Any	1 mL	IM	Preexposure series: days 0, 7, and 21 or 28 days	None; see Chapter 320 for postexposure immunization
Rabies vaccine (purified chick embryo cell)	RabAvert (Novartis)	Any	1 mL	IM	Preexposure series: days 0, 7, and 21 or 28 days	None; see Chapter 320 for postexposure immunization
Typhoid vaccine (oral, live, attenuated)	Vivotif (PaxVax)	≥6 yr	1 capsule[8]	Oral	0, 2, 4, 6 days	Repeat primary series after 5 yr
Typhoid vaccine (Vi capsular polysaccharide)	Typhim Vi (Sanofi Pasteur)	≥2 yr	0.5 mL	IM	1 dose	2 yr
Yellow fever	YF-Vax (Sanofi Pasteur)	≥9 mo[9]	0.5 mL[10]	SC	1 dose	Not recommended for most[11]

[1]Must be administered in a healthcare setting.
[2]In a clinical trial, vaccine efficacy was 90% at 10 days postvaccination and declined to 80% at 3 months postvaccination in prevention of severe diarrhea after oral cholera challenge. Long- term immunogenicity is unknown. Clinicians advising travelers who are at continued or repeated risk over an extended period may consider revaccination, although the appropriate interval and efficacy are unknown.
[3]Consult the prescribing information for differences in dosing for hemodialysis and other immunocompromised patients.
[4]If potential for Japanese encephalitis virus exposure continues.
[5]If an infant is receiving the vaccine before travel, two doses may be administered as early as 8 wk apart.
[6]People with HIV, anatomic or functional asplenia, and persistent complement component deficiencies (C3, C5-9, properdin, factor D, and factor H or people taking eculizumab [Soliris]) should receive a two-dose primary series 8-12 wk apart.
[7]Revaccination with meningococcal conjugate vaccine (MenACWY-D or MenACWY-CRM) is recommended after 3 yr for children who received their last dose at <7 yr of age. Revaccination with meningococcal conjugate vaccine is recommended after 5 yr for people who received their last dose at ≥7 yr of age and every 5 yr thereafter for people who are at continued risk.
[8]Must be kept refrigerated at 35.6°F to 46.4°F (2°C to 8°C); administer with cool liquid no warmer than 98.6°F (37°C).
[9]Ages 6-8 mo and ≥60 yr are precautions and age <6 mo is a contraindication to the use of yellow fever vaccine.
[10]YF Vax is available in single-dose and multiple-dose (five-dose) vials.
[11]For full details regarding revaccination, see https://wwwnc.cdc.gov/travel/page/yellow-book-resources.
ACIP, Advisory Committee on Immunization Practices; ELU, ELISA units of inactivated HAV; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; IM, intramuscular; U, units HAV antigen; SC, subcutaneous.
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Atlanta: CDC, 2024. https://wwwnc.cdc.gov/travel/yellowbook

travel to high-risk regions, especially expatriate children and younger children traveling to or living in rural areas where enzootic dog rabies is endemic. Rabies preexposure vaccination should also be considered for adventure travelers (e.g., hikers, bikers), individuals likely to come into contact with rabies vectors (e.g., students working with animal or bat conservation), or travelers with itineraries to rabies-endemic regions where timely, effective **postexposure prophylaxis** might not be available after an animal bite. Most animal bites in a rabies-endemic area should be considered a medical emergency, especially bites from stray dogs, other carnivores, and bats. Immediate and copious wound irrigation should be followed by prompt administration of appropriate postexposure rabies prophylaxis at a medical facility. Postexposure prophylaxis is required even for persons who received preexposure vaccination. Algorithms for preexposure and postexposure vaccination are the same regardless of patient age.

Numerous rabies vaccine formulations exist around the world. In the United States, two rabies vaccines are available: human diploid cell vaccine (HDCV; Imovax, Sanofi Pasteur, SA) and purified chick embryo cell vaccine (PCEC; RabAvert, Novartis). Preexposure prophylaxis is given intramuscularly (HDCV or PCEC) as two doses (1 mL) on days 0 and 7. For previously unvaccinated individuals, postexposure prophylaxis is given as four doses (1 mL) of HDCV or PCEC vaccine intramuscularly on days 0, 3, 7, and 14. A fifth dose is recommended at day 28 for immunocompromised individuals. For previously vaccinated individuals, only two doses (1 mL) intramuscularly on days 0 and 3 are recommended. Previously unvaccinated persons should also receive rabies immunoglobulin (RIG, 20 IU/kg), with as much of the dose as possible infiltrated around the wound site at the time of initial postexposure prophylaxis. Previously vaccinated persons do not require RIG. Unpurified or purified equine RIG preparations are still used in some low- and middle-income countries and are associated with a higher risk for severe reactions, including serum sickness and anaphylaxis. Purified cell culture–derived vaccines also are not always available abroad; travelers should be aware that any rabies vaccines derived from neural tissue carry an increased risk for adverse reactions, often with neurologic sequelae. If rabies prophylaxis is initiated abroad, neutralizing titers should be checked on return and immunization completed with a cell culture–derived vaccine. If rabies prophylaxis cannot be provided abroad, children with high-risk bites (e.g., stray dog) should be emergently transported to a site where they can receive prophylaxis, because the vaccinations should be started as soon as possible after the bite and ideally within 24 hours. Infants and

young children respond well to rabies vaccine, and both preexposure and postexposure vaccinations can be given at any age, using the same dose and schedule as adults. Individual travelers simultaneously receiving mefloquine or chloroquine may have limited immune reactions to intradermal (ID) rabies vaccine and should be vaccinated intramuscularly. The ID administration route is not currently recommended in the United States.

Tuberculosis

The risk for tuberculosis in the typical traveler is low. Pretravel and posttravel testing for tuberculosis is controversial and should be done on an individualized basis depending on the itinerary, duration, and activities (e.g., working in a hospital setting). Immunization with bacille Calmette-Guérin (BCG) is even more controversial. BCG vaccine has variable efficacy in reducing severe tuberculosis disease in infants and young children, is not available in the United States, and is generally not recommended for pediatric travelers. However, parents traveling with young children who plan to reside in countries with high endemic rates of tuberculosis may consider vaccination once in country to prevent disseminated disease. Infection with *Mycobacterium bovis* can be prevented through avoiding consumption of unpasteurized dairy products.

Typhoid

Salmonella Typhi infection, or **typhoid fever**, is common in many low- and middle-income countries in Asia, Africa, and Latin America (see Chapter 244). Typhoid vaccination is recommended for most children ≥2 years old who are traveling to the Indian subcontinent because the incidence of typhoid is 10-100 times higher for travelers to the Indian subcontinent than all other travel destinations. Vaccination should be strongly considered for other travelers to low- and middle-income countries, particularly if they are VFR travelers, lack access to reliable clean water and food, are traveling for a prolonged duration, or are adventurous eaters.

Two typhoid vaccines, the intramuscular (IM) Vi-polysaccharide vaccine and the oral Ty21a strain live-attenuated vaccine, are recommended for use in children in the United States. Both produce a protective response in 50–80% of recipients. The Ty21a vaccine may offer partial protection against *Salmonella* Paratyphi, another cause of enteric fever. Travelers who have had prior diagnoses of typhoid fever should still receive vaccination because past infection does not confer long-term immunity.

The IM Vi-polysaccharide vaccine is licensed for use in children ≥2 years old. It can be given any time before departure, but it should ideally be administered 2 weeks before travel, with a booster needed 2-3 years later. The oral Ty21a vaccine can only be used in children ≥6 years old and is given in four doses over 1 week. Enteric-coated capsules are to be swallowed with a cool or room-temperature drink, at least 1 hour before a meal, every other day until the four doses are completed. Oral typhoid capsules must remain refrigerated (not frozen). Capsules should never be broken open, because vaccine efficacy depends on capsules being swallowed whole in order to pass through the acidic stomach contents. The oral vaccine is associated with an immune response lasting 5-7 years (depending on national labeling). Antibiotics inhibit the immune response to the oral Ty21a vaccine; the vaccine should not be given within 72 hours of antibiotic treatment, and antibiotics should be avoided until 7 days after completing the vaccine series. Studies demonstrate that mefloquine, chloroquine, and atovaquone-proguanil can be given concurrently with the oral Ty21a vaccine without affecting the immunogenicity of the vaccine. Oral Ty21a vaccine should not be given to immunocompromised children; these children should receive the IM Vi-polysaccharide vaccine.

Yellow Fever

Yellow fever (see Chapter 316) is a mosquito-borne viral illness resembling other viral hemorrhagic fevers (see Chapter 317) but with more prominent hepatic involvement. Yellow fever is present in tropical areas of South America and Africa.

Yellow fever vaccination is indicated in children >9 months old traveling to an endemic area. Many countries require yellow fever vaccination by law for travelers arriving from endemic areas, and some African countries require evidence of vaccination from all entering travelers. Current recommendations can be obtained by contacting state or local health departments or the Division of Vector-Borne Infectious Diseases of the CDC (800-232-4636; https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/yellow-fever.

Most countries accept a medical waiver for children who are too young to be vaccinated (i.e., <6 months of age) and for persons with a contraindication to vaccination. Children with asymptomatic HIV infection may be vaccinated if exposure to yellow fever virus (YFV) cannot be avoided.

Yellow fever vaccine (0.5 mL subcutaneously), a *live-attenuated vaccine* (17D strain) developed in chick embryos, is safe and highly effective in children >9 months old, but in young infants is associated with a greatly increased risk for vaccine-associated encephalitis (0.5-4/1,000) and other severe reactions. Yellow fever vaccine should *never* be given to infants <6 months old; infants 6-8 months old should be vaccinated only in consultation with the CDC or a travel medicine expert to assess the current epidemiology, travel itinerary and duration, and whether the risk of YFV exposure is greater than vaccine risks. In children >9 months old, adverse effects are rare, although vaccine-associated neurotropic and viscerotropic disease associated with the vaccine has been reported. The risk of these reactions is higher in those with thymic disease, altered immune status, multiple sclerosis, or age <9 months (neurotropic disease) or >60 years. Yellow fever vaccination is generally contraindicated in pregnancy and for nursing mothers, unless extended travel to a yellow fever–endemic area is unavoidable.

Children with immunodeficiency or an immunosuppressed state, a thymic disorder or dysfunction (e.g., DiGeorge syndrome), or a history of anaphylactic reactions to eggs *should not receive* yellow fever vaccine. Long-lived immunity develops with this vaccine, perhaps even lasting for a lifetime. Effective July 2016, the WHO and countries following international health regulations no longer require revaccination every 10 years (i.e., a single lifetime dose is now accepted); however, individuals traveling to high-risk areas with active yellow fever transmission and who anticipate frequent or prolonged stays should still consider being reimmunized every 10 years.

TRAVELER'S DIARRHEA

Ingestion of contaminated food or water makes travel-associated diarrhea the most common health complaint among international travelers. Traveler's diarrhea, characterized by a twofold or greater increase in the frequency of unformed bowel movements, occurs in as many as 40% of all travelers overseas (see Chapter 387.1). Children, especially those <3 years old, have a higher incidence of diarrhea, more severe symptoms, and more prolonged symptoms than adults, with a reported attack rate of 60% for those <3 years old in one study.

An important risk factor for traveler's diarrhea is the country of destination. High-risk areas (attack rates of 25–50%) include low- and middle-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate risk occurs in Mediterranean countries, China, and Israel. Low-risk areas include North America, Northern Europe, Australia, and New Zealand. Fecal-oral diarrheal pathogens that children acquire during travel are similar to those acquired by adults and include enterotoxigenic and enteroaggregative *Escherichia coli*, *Campylobacter, Salmonella* (nontyphoidal serotypes predominate), and *Shigella* spp. Enteric protozoa are a much less common cause of traveler's diarrhea than bacterial pathogens; *Giardia lamblia* is the most likely protozoal cause of persistent diarrhea. Less common travel-associated protozoa include *Cryptosporidium* spp., *Entamoeba histolytica,* and *Cyclospora*. Viral infections, particularly rotavirus and norovirus infections, may also cause travel-associated diarrhea in children. Clinicians should be aware that not all diarrheal illness in children is food-borne or water-borne; for example, febrile children with malaria may also present with vomiting and/or nonbloody diarrhea and may be misdiagnosed as having traveler's diarrhea.

Guidance on Prevention of Traveler's Diarrhea

Food and water hygiene remain important measures to reduce the incidence of traveler's diarrhea in children. However, creating long lists of foods to avoid or offering the popular, simple advice of "Boil it, peel it, cook it, or forget it!" is generally an ineffective method of reducing traveler's diarrhea. Most studies show that these types of dietary directives are difficult to keep and may have little impact on the incidence of traveler's diarrhea. In adult studies, the risk of developing traveler's diarrhea appears to be more associated with *where a person eats rather than what they eat*. Eating in a relative's or friend's home is generally safer than eating in a restaurant, where restaurant kitchen hygiene and proper refrigeration may be lacking and employee handwashing may be sporadic.

In general, travel medicine providers can give some commonsense food and water advice to family travelers. Boiled or bottled water, hot beverages, and canned or bottled beverages are generally safe to consume. Ice should be avoided. In low- and middle-income countries, tap water is generally unsafe for drinking or brushing teeth. Boiling water for ≥1 minute (or 3 minutes at altitudes >2,000 meters) remains a reliable method of disinfecting water. Food that is thoroughly cooked and served hot is almost always safe to eat. Dry foods, such as pastry items, breads, and cookies, are generally safe to eat. Unpasteurized milk or other dairy products (cheese) should always be avoided. Breastfeeding should be encouraged for young children, especially infants <6 months old, to reduce exposure to contaminated water or formula. All children should be reminded to wash their hands before eating and after playing around soil or animals. Chemoprophylactic agents for traveler's diarrhea are not recommended for children.

Management of Traveler's Diarrhea

Dehydration is the greatest threat presented by a diarrheal illness in a small child. Parents should be made aware of the symptoms and signs of dehydration and given instructions on how to prepare and administer rehydration solutions. Prepackaged WHO **oral rehydration solution** packets, which are available at stores or pharmacies in almost all low- and middle-income countries, should be part of a child's travel kit. Oral rehydration solution should be mixed as directed with bottled or boiled water and given slowly, as tolerated, to the child while symptoms persist.

Antimotility agents such as diphenoxylate (Lomotil) and loperamide (Imodium) should be avoided in infants and young children. The American Academy of Pediatrics (AAP) does not recommend their routine use in acute gastroenteritis. Use of antimotility agents may be beneficial in older children and adolescents with afebrile, nonbloody traveler's diarrhea. In general, antimotility agents should not distract parents from giving frequent oral rehydration solution, because ongoing intestinal fluid losses likely continue despite a decrease in stooling. Bismuth subsalicylate for acute gastroenteritis should be avoided because of concern for toxicity and Reye syndrome.

Presumptive Antibiotic Treatment

Oral rehydration is the mainstay of treatment for pediatric traveler's diarrhea. However, antibiotics should be prescribed for the pediatric traveler, with parental instructions to start presumptive treatment early in the diarrheal illness (Tables 218.3 and 218.4). Systemic antibiotics can shorten the duration and severity of diarrheal illness, especially if presumptive antibiotics are initiated immediately after the onset of traveler's diarrhea. For children, the drug of choice is **azithromycin** (10 mg/kg once daily for up to 3 days, with a maximum daily dose of 500 mg). **Ciprofloxacin** (10 mg/kg per dose twice daily for up to 3 days, maximum dose of 500 mg twice daily) is an alternative but should not be prescribed for travelers to the Indian subcontinent or Southeast Asia, where fluoroquinolone resistance is common. Shiga toxin–producing *E. coli,* such as *E. coli* O157:H7, is an extremely uncommon cause of pediatric traveler's diarrhea in nonindustrialized countries, and the benefit of presumptive antibiotic therapy in traveling children, even with bloody diarrhea, typically outweighs the low risk of developing hemolytic-uremic syndrome. Parents need to be aware that the use of antibiotics for the treatment of traveler's diarrhea has been associated with colonization with highly resistant organisms such as extended-spectrum β-lactamase–producing Enterobacteriaceae. These organisms could later cause infections once back home.

Azithromycin is highly effective against most bacterial pathogens that cause traveler's diarrhea and is the preferred antibiotic among many travel experts. Azithromycin can be prescribed in powder form that can be reconstituted with safe water into a liquid suspension when needed. Amoxicillin, trimethoprim-sulfamethoxazole (cotrimoxazole), and erythromycin should *not* be prescribed for self-treatment of traveler's diarrhea, because of widespread resistance among diarrheal pathogens. Traveler's diarrhea that results in bloody stools, persistently high fevers, systemic chills and rigors, severe or localizing abdominal pain, or continued fluid losses should prompt additional medical evaluation.

Table 218.3 Traveler's Diarrhea Empiric Treatment Recommendations

Therapy of mild traveler's diarrhea: diarrhea that is tolerable, is not distressing, and does not interfere with planned activities.

- Antibiotic treatment is not recommended in patients with mild traveler's diarrhea.
- Loperamide or BSS may be considered in the treatment of mild traveler's diarrhea in older children.

Therapy of moderate traveler's diarrhea: diarrhea that is distressing or interferes with planned activities.

- Antibiotics may be used to treat cases of moderate traveler's diarrhea.
- Fluoroquinolones may be used to treat moderate traveler's diarrhea depending on resistance patterns of country or region.
- Azithromycin may be used to treat moderate traveler's diarrhea.
- Rifaximin may be used to treat moderate, noninvasive traveler's diarrhea.
- Loperamide may be used as adjunctive therapy for moderate to severe traveler's diarrhea. Antimotility agents alone are not recommended for patients with bloody diarrhea or those who have diarrhea and fever.
- Loperamide may be considered for use as monotherapy in moderate traveler's diarrhea in older children.

Therapy of severe traveler's diarrhea: diarrhea that is incapacitating or completely prevents planned activities: all dysentery is considered severe.

- Antibiotics should be used to treat severe traveler's diarrhea.
- Azithromycin is preferred to treat severe traveler's diarrhea.
- Fluoroquinolones may be used to treat severe, nondysenteric traveler's diarrhea depending on resistance patterns of country or region.
- Rifaximin may be used to treat severe, nondysenteric traveler's diarrhea.*
- Single-dose antibiotic regimens may be used to treat traveler's diarrhea.

*These treatment recommendations were developed before the approval of rifamycin SV in the United States. Because it is in the same category of antimicrobial drug as rifaximin and because they have the same mechanism of action, rifamycin SV can be considered as an alternative to rifaximin.

Modified from Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Atlanta: CDC, 2020. Box 2-04 and Table 2-10. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea#treatment

INSECT-BORNE INFECTIONS

Insect-borne infections for which traveling children are most at risk include malaria, dengue, chikungunya, yellow fever, Zika, and Japanese encephalitis, depending on the area of travel. **Malaria** is transmitted by nighttime biting *Anopheles* mosquitoes, whereas **dengue** occurs from mosquito species *(Culex, Aedes)* that are predominantly active during the day. Families should be encouraged to protect children against daytime and nighttime biting mosquitoes, because many regions of the world where malaria is found also have diseases transmitted by daytime

Table 218.4 Acute Diarrhea Adult Antibiotic Treatment Recommendations*

ANTIBIOTIC*	DOSE	DURATION
Azithromycin†,‡	1,000 mg	Single or divided dose§
	500 mg daily	3 days
Levofloxacin	500 mg daily	1-3 days§
Ciprofloxacin	750 mg	Single dose§
	500 mg bid	3 days
Ofloxacin	400 mg bid	1-3 days§
Rifamycin SV‖	388 mg bid	3 days
Rifaximin‖	200 mg tid	3 days

*See also Chapter 387.1. Lower weight-based dosing should be used where appropriate.
*Antibiotic regimens may be combined with loperamide 4 mg initially followed by 2 mg after each loose stool, not to exceed 16 mg in a 24-hr period. This is the adult dose of loperamide, which might be appropriate for older children and adolescents, but antimotility agents are generally not recommended for younger children, and if they are used then lower doses may be more appropriate.
†Use empirically as first-line in Southeast Asia or other areas if fluoroquinolone-resistant bacteria are suspected.
‡Preferred regimen for dysentery or febrile diarrhea.
§If symptoms are not resolved after 24 hr, continue daily dosing for up to 3 days.
‖Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella,* or other causes of invasive diarrhea. Use may be reserved for patients unable to receive fluoroquinolones or azithromycin.
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Atlanta: CDC, 2024. Table 2-09. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea#table 209

biting mosquitoes (dengue, Zika, chikungunya). Zika can also be sexually transmitted, so sexually active adolescents and young adults need to be advised on these additional risks when traveling to Zika-endemic regions. In addition to insect bite prevention using insect repellents, methods of contraception should be discussed with the traveler. Ticks, fleas, lice, and other arthropods are also known to transmit rickettsial, borrelial, and parasitic pathogens, but transmission can be prevented by close attention to measures to mitigate exposures that are appropriate when outdoors, close inspection for ticks once returning indoors, and use of insect repellents on skin and clothing with products containing DEET and permethrin, respectively.

Exposure to insect bites can be reduced by wearing appropriate attire and using insect repellents containing *N,N*-diethyl-*m*-toluamide (**DEET**) or picaridin. The AAP recommends avoiding DEET-containing repellents in children <2 months old. Rare cases of neurologic events have been reported in very young children with exposure to inappropriate, frequent applications of DEET-containing repellents (>10 times/day) or who licked off DEET. Concentrations of 25–30% DEET need be applied every 4-6 hours, as needed, whereas 5–7% DEET provides only 1-2 hours of protection time. DEET concentrations >40–50% do not confer a substantially longer protection time for children and are not recommended.

Picaridin is fragrance-free, effective, and generally well tolerated on exposed skin and faces. It has similar efficacy to DEET but with less inhalational or dermal irritation. Picaridin at concentrations of 20% or higher provides adequate protection against *Anopheles* mosquitoes that have potential to transmit malaria. When applying sunscreen and insect repellent, sunscreen should be applied first, followed by DEET or picaridin.

Spraying or treating clothing with **permethrin**, a synthetic pyrethroid, is a safe and effective method of further reducing insect bites in children. Permethrin can be applied directly to clothing, bed nets, shoes, and hats and should be allowed to dry fully before use. As an insecticide, permethrin should never be applied to skin. Permethrin-treated garments retain both repellency and insecticidal activity, even with repeated laundering. Clothing will eventually need to be retreated to maintain repellency, according to the product label. Bed nets, particularly permethrin-impregnated bed nets, also decrease the risk of insect bites, and their use is highly recommended in malarial areas.

MALARIA CHEMOPROPHYLAXIS

Malaria, a mosquito-borne infection, is the leading parasitic cause of death in children worldwide (see Chapter 334). Of the five *Plasmodium* species that infect humans, *Plasmodium falciparum* causes the greatest morbidity and mortality. Each year, >8 million U.S. citizens visit parts of the world where malaria is endemic (sub-Saharan Africa, Central and South America, India, Southeast Asia, Oceania). Children accounted for 15–20% of imported malaria cases in a WHO study in Europe. Given travel of young children with their families to endemic countries, physicians in industrialized countries are increasingly required to give advice on prevention, diagnosis, and treatment of malaria. **Risk factors** for severe malaria and death include inadequate adherence to chemoprophylaxis, delay in seeking diagnosis and medical care, and nonimmune status, but the case-fatality rate of imported malaria remains <1% in children from nonendemic countries. The CDC maintains updated information at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria, as well as a malaria hotline for physicians (770-488-7788). It is important to check this updated information, because recommendations for prophylaxis and treatment are often modified as a result of changes in the risk for developing malaria in different areas of the world, changing *Plasmodium* resistance patterns, and the availability of new antimalarial medications.

Avoidance of mosquitoes and **barrier protection** from mosquitoes are an important part of malaria prevention for travelers to endemic areas. The *Anopheles* mosquito feeds from dusk to dawn. Travelers should remain in well-screened areas, wear clothing that covers most of the body, sleep under a bed net (ideally impregnated with permethrin), and use insect repellents with DEET during these hours. Parents should be discouraged from taking a young child on a trip that will entail evening or nighttime exposure in areas endemic for *P. falciparum*.

Chemoprophylaxis is the cornerstone of malaria prevention for nonimmune children and adults who travel to malaria-endemic areas *but is not a replacement for other protective measures*. Travelers often do not take malaria prophylaxis as prescribed or at all. They are more likely to use prophylactic antimalarial drugs if their physicians provide appropriate recommendations and education before departure. However, in one survey, only 14% of persons who sought medical advice obtained correct information about malaria prevention and prophylaxis. Families with children visiting friends and relatives are particularly less likely to take malaria prophylaxis or seek pretravel medical advice.

Resistance of *P. falciparum* to the traditional chemoprophylactic agent, **chloroquine**, is widespread, and in most areas of the world other agents must be used (Table 218.5). Factors that must be considered

Table 218.5 Antimalarial Chemoprophylaxis for Children

AREA	DRUG	ADULT DOSE	PEDIATRIC DOSE	ADVANTAGES	DISADVANTAGES	COMMENTS
Chloroquine-resistant area	Mefloquine*,†	250 mg salt (228 mg base) tablets One tablet weekly	Weight <10 kg: 5 mg salt (4.6 mg base)/kg/week	Once-weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria-endemic area for ≥4 wk Children unlikely to take daily medication
			Weight 10-19 kg: ¼ tablet/week			
			Weight 20-30 kg: ½ tablet/week			
			Weight 31-45 kg: ¾ tablet/week			
			Weight >45 kg: 1 tablet/week			
	Doxycycline‡	100 mg tablet One tablet daily	2.2 mg/kg daily (max: 100 mg)	Known safety profile Readily available in most pharmacies	Prolonged (>21 days) courses should not be given to children <8 yr old Daily dosing Must take with food or causes stomach upset Photosensitivity Yeast superinfections	Children ≥8 yr old going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone-proguanil§ (Malarone)	250/100 adult tablet One tablet daily	Pediatric tablet: 62.5 mg atovaquone/25 mg proguanil	Pediatric tablet formulation available Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria-endemic area for <4 wk
			Weight 5-8 kg: ½ pediatric tablet once daily			
			Weight >8-10 kg: ¾ pediatric tablet once daily			
			Weight >10-20 kg: 1 pediatric tablet once daily			
			Weight >20-30 kg: 2 pediatric tablets once daily			
			Weight >30-40 kg: 3 pediatric tablets once daily			
			Weight >40 kg: 1 adult tablet once daily			
Chloroquine-susceptible area	Chloroquine phosphate	500 mg salt (300 mg base) One tablet weekly	8.3 mg/kg salt (5 mg/kg base) weekly, up to maximum adult dose of 500 mg salt	Once-weekly dosing Generally well tolerated Safe in pregnancy	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *P. vivax* that is chloroquine susceptible
	Hydroxychloroquine	400 mg of salt (310 mg of base)	6.5 mg/kg of salt (5 mg/kg of base) once weekly, up to maximum adult dose of 400 mg of salt	Safe in pregnancy		Alternative when chloroquine is unavailable for travelers to areas with *P. falciparum* or *P. vivax* that is chloroquine susceptible

Continued

Table 218.5 Antimalarial Chemoprophylaxis for Children—cont'd

AREA	DRUG	ADULT DOSE	PEDIATRIC DOSE	ADVANTAGES	DISADVANTAGES	COMMENTS
Terminal prophylaxis (antirelapse therapy) for regions predominantly with *P. vivax* and *P. ovale*.	Primaquine	26.3 mg salt (15 mg base) tablets; 2 tablets once daily for 14 days after departure from malarious area.	0.8 mg/kg of salt form (0.5 mg/kg of base) once daily for 14 days after departure from malarious area	Reduce risk for relapses by *P. vivax* and *P. ovale*.	May cause hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.
Short-term prophylaxis for regions with predominantly *Plasmodium vivax*	Primaquine	26.3 mg salt (15 mg base) tablets; 2 tablets. Begin 1-2 days before travel to malarious areas, continue for 7 days after leaving area.	0.8 mg/kg of salt form (0.5 mg/kg of base). Begin 1-2 days before travel to malarious areas, continue for 7 days after leaving area.	Reduce risk for relapses by *P. vivax*.	May cause hemolysis in persons with G6PD deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.
Terminal prophylaxis (antirelapse therapy) for regions predominantly with *P. vivax*	Tafenoquine **(Krintafel)**	150 mg tablets; ≥16 yr: 2 tablets, single dose	Not recommended	Single dose	May cause hemolysis in persons with G6PD deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.
Prophylaxis against all *Plasmodium* spp.	Tafenoquine **(Arakoda)**	100 mg tablets; ≥18 yr: 2 tablets, daily for 3 days before travel. Weekly during travel (starting 1 wk after last pretravel dose). Once 1 wk after travel	Not recommended	Effective against all *Plasmodium* spp.	May cause hemolysis in persons with G6PD deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.

*Chloroquine and mefloquine should be started 1-2 wk before departure and continued for 4 wk after last exposure.
†Mefloquine resistance exists in western Cambodia and along the Thailand-Cambodia and Thailand-Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.
‡Doxycycline should be started 1-2 days before departure and continued for 4 wk after last exposure. Do not use in children <8 yr old or in pregnant women.
§Atovaquone-proguanil (Malarone) should be started 1-2 days before departure and continued for 7 days after last exposure; should be taken with food or a milky drink. Not recommended in pregnant women, children who weigh <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).
Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas.

in choosing appropriate chemoprophylaxis medications and dosing schedules include age of the child, travel itinerary (including whether the child will be traveling to areas of risk within a particular country and whether chloroquine-resistant *P. falciparum* is present in the country), vaccinations being given, allergies or other known adverse reactions to antimalarial agents, and the availability of medical care during travel.

Children traveling to areas with chloroquine-resistant *P. falciparum* can be given mefloquine, atovaquone-proguanil, or doxycycline (if >8 years old) as malaria prophylaxis. For trips shorter than 4 weeks, atovaquone-proguanil is the preferred medication, because it is given for only a short period before and after travel. Atovaquone-proguanil or doxycycline is also preferred for travel of any duration to western Cambodia and the Thailand-Cambodia and Thailand-Myanmar borders because of mefloquine resistance in these areas. For periods of travel >4 weeks to all other areas with chloroquine-resistant *P. falciparum,* mefloquine is the preferred medication because it can be taken weekly.

Mefloquine is FDA approved only for children weighing >15 kg, but the CDC recommends mefloquine prophylaxis for all children regardless of weight because the risk for acquiring severe malaria outweighs the risk for potential mefloquine toxicity. Adults taking mefloquine prophylaxis have a 10–25% incidence of sleep disturbance and dysphoria and, less frequently, more serious neuropsychiatric symptoms. These side effects appear to be less common in children. Other potential side effects of mefloquine therapy include nausea and vomiting.

The lack of a liquid or suspension formulation for all antimalarial agents can make administration difficult. For children who cannot take tablets, parents should take a chloroquine or mefloquine prescription

to a compounding pharmacy, which can pulverize the tablets and place exact dosages into gel capsules. Parents can then open the gel capsules and sprinkle the powder into food. Disguising these medications, which have a bitter taste, is important; chocolate syrup has been used successfully as a vehicle for the medication. Persons with depression, neuropsychiatric disorders, seizure disorders, or cardiac conduction defects should not take mefloquine.

Atovaquone-proguanil fixed combination (Malarone) is an effective and safe chemoprophylaxis for travelers to chloroquine-resistant malaria-endemic areas. Adverse effects are infrequent and mild (abdominal pain, vomiting, and headache) and infrequently result in discontinuation of the medication. Atovaquone-proguanil prophylaxis must be taken every day with food, so it is better suited for prophylaxis during short periods of exposure. Recent data allow dosing down to 5 kg body weight, although the use of atovaquone-proguanil in children weighing 5-10 kg is considered off-label.

Daily **doxycycline** is an alternative chemoprophylaxis regimen for chloroquine-resistant *P. falciparum* malaria. Doxycycline has been used extensively and is highly effective. Use in children <8 years old should be avoided, as courses >21 days are usually required and safety data are limited in this age-group. Adverse effects (nausea, vomiting, photosensitivity, vaginal candidiasis) are relatively uncommon. Persons given doxycycline prophylaxis should be warned to decrease exposure to direct sunlight, wear protective clothing (long sleeves and brimmed hat), and use sunscreen to minimize the possibility of photosensitivity.

Primaquine has also been used successfully as chemoprophylaxis, especially in areas of high prevalence of *Plasmodium vivax* and *Plasmodium ovale,* but there are limited data about its use in nonimmune children. Primaquine prophylaxis for children should only be given in consultation with the CDC or a travel medicine specialist.

Chloroquine, chloroquine-proguanil, and azithromycin do not provide adequate protection for children traveling to a chloroquine-resistant malaria-endemic area.

In areas of the world where *P. falciparum* remains fully chloroquine-sensitive (Haiti, the Dominican Republic, Central America west of the Panama Canal, and some countries in the Middle East), weekly chloroquine is the drug of choice for malaria chemoprophylaxis. Updated information on chloroquine susceptibility and recommended malaria prophylaxis is available at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria.

On leaving an area endemic for *P. vivax* or *P. ovale* after a prolonged visit (usually >3 months), travelers should consider terminal prophylaxis with primaquine (0.5 mg/kg base) daily, up to a maximum dose of 30 mg base or 52.6 mg salt, for 14 days, to eliminate extraerythrocytic forms of *P. vivax* and *P. ovale* and prevent relapses. Screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is mandatory before primaquine treatment, because primaquine is contraindicated in G6PD-deficient persons because it can cause severe hemolysis.

Small amounts of antimalarial drugs are secreted into breast milk. The amounts of transferred drug are not considered to be either harmful or sufficient to provide adequate prophylaxis against malaria. Prolonged infant exposure to doxycycline through breast milk is not advisable.

Self-treatment of presumptive malaria during travel remains controversial. It should never be substituted for seeking appropriate medical care, but it can be considered in special circumstances such as travel to remote areas, intolerance of prophylaxis, or refusal of chemoprophylaxis by the traveler. Self-treatment medication should be different from the prescribed chemoprophylaxis. The CDC or a travel medicine specialist should be consulted if self-treatment medication is being considered for a traveler.

THE RETURNING TRAVELER

Posttravel evaluations are part of travel medicine and continuing care. Physicians unfamiliar with diseases that occur in low- and middle-income countries often misdiagnose the cause of illness in a child returning from travel abroad. Among returning patients identified from the GeoSentinel Surveillance Network sites who were ill, the most common disorders (in descending order of frequency) included malaria, giardiasis, dengue fever, campylobacteriosis, cutaneous larva migrans, enteric fever, spotted fever (rickettsiosis), chikungunya fever, hepatitis A, and influenza. Returning pediatric travelers who are severely ill or with continued fevers should be seen in consultation with a pediatric travel medicine or infectious diseases specialist. The cause of fever may be suggested by the geographic area (Table 218.6) and incubation period (Table 218.7).

Among all persons returning from travel (children and adults), three major patterns of illness have been noted (Table 218.8). The etiology of each of these disease presentations in part depends on the country or geographic region visited (see Table 218.6). Table 218.9 provides suggestive clues to a diagnosis.

Table 218.6 Common Causes of Fever by Geographic Area

GEOGRAPHIC AREA	COMMON TROPICAL DISEASE-CAUSING FEVER	OTHER INFECTIONS CAUSING OUTBREAKS OR CLUSTERS IN TRAVELERS
Caribbean	Chikungunya, dengue, malaria (Haiti), Zika	Acute histoplasmosis, leptospirosis
Central America	Chikungunya, dengue, malaria (primarily *Plasmodium vivax*), Zika	Leptospirosis, histoplasmosis, coccidioidomycosis
South America	Chikungunya, dengue, malaria (primarily *P. vivax*), Zika	Bartonellosis, leptospirosis, enteric fever, histoplasmosis
Southcentral Asia	Dengue, enteric fever, malaria (primarily non–*P. falciparum*)	Chikungunya
Southeast Asia	Dengue, malaria (primarily non–*P. falciparum*)	Chikungunya, leptospirosis
Sub-Saharan Africa	Malaria (primarily *P. falciparum*), tick-borne rickettsiae (main cause of fever in southern Africa), acute schistosomiasis, dengue	

https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/general-approach-to-the-returned-traveler
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Wilson ME. Post-travel evaluation. Atlanta: CDC, 2024. Table 11-09.

Table 218.7 Common Infections by Incubation Period

DISEASE	USUAL INCUBATION PERIOD (RANGE)	DISTRIBUTION
INCUBATION <14 DAYS		
Chikungunya	2-4 days (1-14 days)	Tropics, subtropics
Dengue	4-8 days (3-14 days)	Topics, subtropics
Encephalitis, arboviral (Japanese encephalitis, tick-borne encephalitis, West Nile virus, other)	3-14 days (1-20 days)	Specific agents vary by region
Enteric fever (typhoid/paratyphoid)	7-18 days (3-60 days)	Especially in Indian subcontinent
Acute HIV	10-28 days (10 days to 6 weeks)	Worldwide
Influenza	1-3 days	Worldwide, can also be acquired while traveling
Legionellosis	5-6 days (2-10 days)	Widespread
Leptospirosis	7-12 days (2-26 days)	Widespread, most common in tropical areas
Malaria, *Plasmodium falciparum*	6-30 days (98% onset within 3 mo of travel)	Tropics, subtropics
Malaria, *Plasmodium vivax*	8 days to 12 mo (almost half have onset >30 days after completion of travel)	Widespread in tropics and subtropics
Spotted-fever rickettsiae	Few days to 2-3 wk	Causative species vary by region
Zika virus infection	3-14 days	Widespread in Latin America, endemic through much of Africa, Southeast Asia, and Pacific Islands
INCUBATION 14 DAYS TO 6 WEEKS		
Encephalitis, arboviral; enteric fever; acute HIV; leptospirosis; malaria	See above incubation periods for relevant diseases.	See above distribution for relevant diseases
Amebic liver abscess	Weeks to months	Most common in resource-poor countries
Hepatitis A	28-30 days (15-50 days)	Most common in resource-poor countries
Hepatitis E	26-42 days (2-9 wk)	Widespread
Acute schistosomiasis (Katayama syndrome)	4-8 wk	Most common in sub-Saharan Africa
INCUBATION >6 WK		
Amebic liver abscess, hepatitis E, malaria, acute schistosomiasis	See above incubation periods for relevant diseases.	See above distribution for relevant diseases
Hepatitis B	90 days (60-150 days)	Widespread
Leishmaniasis, visceral	2-10 mo (10 days to years)	Asia, Africa, Latin America, Southern Europe, and the Middle East
Tuberculosis	Primary, weeks; reactivation, years	Global distribution, rates, and levels of resistance vary widely

https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/general-approach-to-the-returned-traveler
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Fairley JK. General approach to the returned traveler. Atlanta: CDC, 2024. Table 11-02.

Fever is a particularly worrisome symptom. Children with a febrile/systemic illness after recent travel to a malarial destination should be promptly evaluated for malaria, especially if having traveled to sub-Sahara Africa and Papua New Guinea. *P. falciparum* malaria will generally present within 1-2 months after return from travel to a malaria-endemic area, but can occur within the first year after return. In contrast, symptoms of *P. vivax* or *P. ovale* malaria are typically later in onset after travel (i.e., several months), are milder in disease severity, and may occur in a relapsing pattern if undiagnosed or improperly treated. Other symptoms of malaria can be nonspecific and include chills, malaise, headache, myalgias, vomiting, diarrhea, cough, and possible seizures. Children are more likely than adults to have higher fevers and also gastrointestinal symptoms, hepatomegaly, splenomegaly, and severe anemia. Thrombocytopenia (without increased bleeding) and fever in a child returning from an endemic area are highly suggestive of malaria.

Thick and thin blood smears need to be performed for diagnosis *if* malaria is clinically suspected. If results are negative initially, two or more additional smears should be done 12-24 hours after the initial smears. The diagnostic yield of blood smears may be higher if obtained during a febrile episode. Rapid malaria antigen tests (BinaxNOW Malaria) are also available, are FDA-approved, and are sensitive for diagnosing *P. falciparum* malaria. At times, a polymerase chain reaction (PCR) assay is necessary to confirm the malarial parasite species. Treatment should be initiated immediately once the diagnosis is confirmed or empirically if presentation is severe with suspected malaria. Treatment should be determined in consultation with a pediatric infectious disease specialist and/or the CDC for updated information on the drugs of choice, which are similar to those for adults (see Chapter 334). Great caution should be used with young children, nonimmune patients, and pregnant patients with *P. falciparum* malaria, and hospitalization of these

Table 218.8 Patterns of Illness in Returning International Travelers

SYSTEMIC FEBRILE ILLNESS
Malaria
Dengue
Zika
Enteric fever (typhoid/paratyphoid)
Chikungunya virus
Spotted fever rickettsiae
Hepatitis A
Acute HIV
Leptospirosis
Measles
Infectious mononucleosis
Respiratory causes (pneumonia, influenza)
Undetermined fever source
ACUTE DIARRHEA
Campylobacter
Shigella spp.
Salmonella spp.
Diarrheagenic *Escherichia coli* (enterotoxigenic *E. coli,* enteroadherent *E. coli*—not tested for by routine stool culture methods)
Giardiasis (acute, persistent, or recurrent)
Entamoeba histolytica
Cryptosporidium spp.
Cyclospora cayetanensis
Presumed viral enteritis
DERMATOLOGIC MANIFESTATIONS
Rash with fever (dengue)
Arthropod-related dermatitis (insect bites)
Cutaneous larva migrans (*Ancylostoma braziliense*)
Bacterial skin infections—pyoderma, impetigo, ecthyma, erysipelas
Myiasis (tumbu and botfly)
Scabies
Tungiasis
Superficial mycosis
Animal bites
Leishmaniasis
Rickettsial diseases
Marine envenomation/dermatitis
Photoallergic dermatitis and phytophotodermatitis

Table 218.9 Common Clinical Findings and Associated Infections

COMMON CLINICAL FINDINGS	INFECTIONS TO CONSIDER AFTER TRAVEL
Fever and rash	Dengue, chikungunya, Zika, rickettsial infections, enteric fever (skin lesions may be sparse or absent), acute HIV infection, measles
Fever and abdominal pain	Enteric fever, amebic liver abscess
Undifferentiated fever and normal or low white blood cell count	Dengue, malaria, rickettsial infection, enteric fever, chikungunya, Zika
Fever and hemorrhage	Viral hemorrhagic fevers (dengue and others), meningococcemia, leptospirosis, rickettsial infections
Fever and arthralgia or myalgia, sometimes persistent	Chikungunya, dengue, Zika
Fever and eosinophilia	Acute schistosomiasis, drug hypersensitivity reaction, fascioliasis and other parasitic infections (rare)
Fever and pulmonary infiltrates	Common bacterial and viral pathogens, legionellosis, acute schistosomiasis, Q fever, leptospirosis
Fever and altered mental status	Cerebral malaria, viral or bacterial meningoencephalitis, African trypanosomiasis, scrub typhus
Mononucleosis syndrome	Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, toxoplasmosis, acute HIV infection
Fever persisting >2 wk	Malaria, enteric fever, EBV infection, CMV infection, toxoplasmosis, acute HIV infection, acute schistosomiasis, brucellosis, tuberculosis, Q fever, visceral leishmaniasis (rare)
Fever with onset >6 wk after travel	*Plasmodium vivax* or *P. ovale* malaria, acute hepatitis (B, C, or E), tuberculosis, amebic liver abscess

From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Wilson ME. Post-travel evaluation. Atlanta: CDC, 2024. Table 11-4. https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/general-approach-to-the-returned-traveler.

patients should be strongly considered until reliable improvement is observed.

Enteric (typhoid) fever should be considered in children with persistent or recurrent fevers, especially after return from the Indian subcontinent. Multiple blood cultures and a stool culture may both be necessary for diagnosis of enteric fever. **Dengue** is another cause of fever and systemic illness in ill travelers, particularly when returning from Southeast Asia, the Caribbean, Central and South America, or the Indian subcontinent. Many bacterial and protozoal causes of acute traveler's diarrhea may also result in fever and systemic symptoms in children. Additional travel-associated febrile, diarrheal, and dermatologic illnesses exist, of which the most common etiologies can be found in Tables 218.8 and 218.9.

THE ADOLESCENT TRAVELER

The preparation of an adolescent interested in traveling abroad can pose a challenge for most clinicians. Study abroad, gap year, humanitarian volunteer work, adventure, and tourism are among many reasons for travel to countries with limited resources. Although many travel-related problems discussed in this chapter are relevant to this group, other high-risk activities such as sexual intercourse, alcohol consumption, driving, use of illicit drugs, and adventure travel (e.g., mountain climbing, white water rafting, kayaking, biking) require special attention and discussion with the traveler and parents/guardians. Topics such as HIV exposure, sexually transmitted infections, sexual assault, and unplanned pregnancy may require specific preventive strategies such as condom use, contraception, and postexposure HIV prophylaxis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 219

Fever

Linda S. Nield and Deepak Kamat

Fever is defined as a rectal temperature ≥38°C (100.4°F), and a fever >40°C (104°F) is called **hyperpyrexia**. Traditionally, body temperature fluctuates in a defined normal range (36.6–37.9°C [97.9–100.2°F] rectally), so that the highest point is reached in the early evening and the lowest point is reached in the morning. Any abnormal rise in body temperature should be considered a symptom and sign of an underlying condition.

PATHOGENESIS

Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature, as well as by cold and warm receptors located in skin and muscles. Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, regulation of extracellular fluid (ECF) volume by arginine vasopressin, and behavioral responses, such as seeking a warmer or cooler environmental temperature.

Three different mechanisms can produce fever: pyrogens, heat production exceeding heat loss, and defective heat loss. The first mechanism involves endogenous and exogenous pyrogens that raise the hypothalamic temperature set point. **Endogenous pyrogens** include the cytokines interleukin (IL)-1 and IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-β and IFN-γ. Stimulated leukocytes and other cells produce lipids that also serve as endogenous pyrogens. The best-studied lipid mediator is prostaglandin E_2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. Along with infectious diseases, drugs, malignancy, and inflammatory diseases can cause fever through the production of endogenous pyrogens. Some substances produced within the body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen-antibody complexes in the presence of complement components, lymphocyte products, bile acids, and androgenic steroid metabolites. **Exogenous pyrogens** come from outside the body and consist of mainly infectious pathogens and drugs. Microbes, microbial toxins, or other products of microbes are the most common exogenous pyrogens, which stimulate macrophages and other cells to produce endogenous pyrogens. **Endotoxin** is one of the few substances that can directly affect thermoregulation in the hypothalamus and stimulate endogenous pyrogen release. Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drug. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol.

Heat production exceeding heat loss is the second mechanism that leads to fever; examples include salicylate poisoning and malignant hyperthermia. **Defective heat loss**, the third mechanism, may occur in children with ectodermal dysplasia or victims of severe heat exposure.

ETIOLOGY

The causes of fever can be organized into four main categories: *infectious, inflammatory, neoplastic,* and *miscellaneous.* Self-limited viral infections (common cold, influenza, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever. The body temperature rarely rises above potentially lethal levels (42°C [107.6°F]) in the neurologically intact child unless extreme hyperthermic environmental conditions are present or other extenuating circumstances exist, such as underlying malignant hyperthermia or thyrotoxicosis.

The pattern of the fever can provide clues to the underlying etiology. Viral infections typically are associated with a slow decline of fever over several days, whereas bacterial infections are often associated with a prompt resolution of fever after effective antimicrobial treatment. Although antimicrobials can result in rapid elimination of bacteria, if tissue injury has been extensive, the inflammatory response and fever can continue for days after all microbes have been eradicated.

Intermittent fever is an exaggerated circadian rhythm that includes a period of normal temperatures on most days; extremely wide fluctuations may be termed **septic** or **hectic fever**. **Sustained fever** is persistent and does not vary by >0.5°C (0.9°F)/day. **Remittent fever** is persistent and varies by >0.5°C/day. **Relapsing fever** is characterized by febrile periods separated by intervals of normal temperature; **tertian fever** occurs on the first and third days (malaria caused by *Plasmodium vivax*), and **quartan fever** occurs on the first and fourth days (malaria caused by *Plasmodium malariae*). Diseases characterized by relapsing fevers should be distinguished from infectious diseases that tend to relapse (Table 219.1). **Biphasic fever** indicates a single illness with two distinct periods (**camelback fever** pattern); poliomyelitis is the classic example. A biphasic course is also characteristic of other enteroviral infections, leptospirosis, dengue fever, yellow fever, Colorado tick fever, spirillary rat-bite fever (caused by *Spirillum minus*), and the African hemorrhagic fevers (Marburg, Ebola, and Lassa fevers). The term **periodic fever** is used narrowly to describe fever syndromes with a regular periodicity (cyclic neutropenia and periodic fever, aphthous

Table 219.1 Fevers Prone to Relapse

INFECTIOUS CAUSES
Acute rheumatic fever
Babesiosis
Blastomycosis
Brucellosis
Chronic meningococcemia
Coccidioidomycosis
Colorado tick fever
COVID-19/SARS-CoV-2 and MIS-C
Dengue fever
Epstein-Barr virus infection
Histoplasmosis
Leptospirosis
Lyme disease *(Borrelia burgdorferi)*
Lymphocytic choriomeningitis (LCM) infection
Malaria
Melioidosis *(Pseudomonas pseudomallei)*
Noninfluenza respiratory viral infection
Oroya fever *(Bartonella bacilliformis)*
Q fever *(Coxiella burnetii)*
Rat-bite fever (*Spirillum minus*)
Relapsing fever *(Borrelia recurrentis)*
Syphilis *(Treponema pallidum)*
Tuberculosis
Typhoid fever *(Salmonella typhi)*
Visceral leishmaniasis
Yellow fever
NONINFECTIOUS CAUSES
Behçet disease
Crohn disease
Leukocytoclastic vasculitis syndromes
Sweet syndrome
Systemic lupus erythematosus and other autoimmune disorders
Weber-Christian disease (panniculitis)
Others
PERIODIC FEVER SYNDROMES (SEE CHAPTER 204)
Cyclic neutropenia
Familial Mediterranean fever
Hyper–immunoglobulin D syndrome
Muckle-Wells syndrome
Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA)
Tumor necrosis factor receptor–associated periodic syndrome [TRAPS])
Others

MIS-C, multisystem inflammatory syndrome in children.

stomatitis, pharyngitis, adenopathy) or more broadly to include disorders characterized by recurrent episodes of fever that do not follow a strictly periodic pattern (familial Mediterranean fever, TNF receptor–associated periodic syndrome [Hibernian fever], hyper-IgD syndrome, Muckle-Wells syndrome) (see Chapter 204). **Factitious fever**, or self-induced fever, may be caused by intentional manipulation of the thermometer or injection of pyrogenic material.

The **double quotidian fever** (or fever that peaks twice in 24 hours) is classically associated with juvenile idiopathic arthritis. In general, a single isolated fever spike is not associated with an infectious disease. Such a spike can be attributed to the infusion of blood products and some drugs, as well as some procedures or manipulation of a catheter on a colonized or infected body surface. Similarly, temperatures in excess of 41°C (105.8°F) are most often associated with a noninfectious cause. Causes for very high temperatures (>41°C [105.8°F]) include central fever (resulting from central nervous system dysfunction involving the hypothalamus or spinal cord injury), malignant hyperthermia, malignant neuroleptic syndrome, drug fever, or heat stroke. Temperatures that are lower than normal (<36°C [96.8°F]) can be associated with overwhelming sepsis but are more often related to cold exposure, hypothyroidism, autonomic instability, central nervous system lesions, or overuse of antipyretics.

CLINICAL FEATURES

The clinical features of fever can range from no symptoms to extreme malaise. Children might complain of feeling hot or cold, display facial flushing, and experience shivering. Fatigue and irritability may be evident. Parents often report that the child looks ill or pale and has a decreased appetite. The underlying etiology also produces accompanying symptoms. Although the underlying etiologies can manifest in varied ways clinically, there are some predictable features. For example, **fever with petechiae** in an ill-appearing patient indicates the high possibility of life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or acute bacterial endocarditis. The unusual symptom of loss of smell and taste can accompany fever in COVID-19.

Changes in heart rate, most frequently tachycardia, accompany fever. Normally heart rate rises by 10 beats/min per 1°C (1.8°F) rise in temperature for children >2 months old. Relative tachycardia, when the pulse rate is elevated disproportionately to the temperature, is usually caused by noninfectious diseases or infectious diseases in which a toxin is responsible for the clinical manifestations. **Relative bradycardia** (temperature-pulse dissociation), when the pulse rate remains low in the presence of fever, can accompany typhoid fever, brucellosis, leptospirosis, or drug fever. Bradycardia in the presence of fever also may be a result of a conduction defect resulting from cardiac involvement with acute rheumatic fever, Lyme disease, viral myocarditis, or infective endocarditis.

EVALUATION

Most acute febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few, if any, laboratory tests. Because infection is the most likely etiology of acute fever, the evaluation should initially be geared to discovering an underlying infectious cause (Table 219.2 and Chapter 220). The details of the history should include the onset and pattern of fever and any accompanying signs and symptoms. The patient often displays signs or symptoms that provide clues to the cause of the fever. Exposures to other ill persons at home, daycare, and school should be noted, along with any recent travel, animal exposures, or medications. The past medical history should include information about underlying immune deficiencies or other major illnesses and receipt of childhood vaccines.

Physical examination should begin with a complete evaluation of vital signs, which should include pulse oximetry, because hypoxia may indicate lower respiratory infection. In the acutely febrile child, the physical examination should focus on any localized complaints, but a complete head-to-toe screen is recommended, because clues to the underlying diagnosis may be found. For example, palm and sole lesions may be discovered during a thorough skin examination and provide a clue for infection with coxsackievirus.

Table 219.2 Evaluation of Acute Fever

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates, other ill individuals), travel, medications, other underlying disorders, immunizations
Physical examination: complete, with focus on localizing symptoms
Laboratory studies on a case-by-case basis:
- Blood: complete blood count, culture, C-reactive protein, procalcitonin, sedimentation rate
- Cerebrospinal fluid: cell count, culture, glucose, Gram stain, NAAT for herpes simplex virus, protein
- Nasopharyngeal: NAAT for respiratory viruses
- Pharyngeal: NAAT and culture for group A *Streptococcus*
- Stool: calprotectin, culture, NAAT for enteric pathogens
- Urine: culture, gross and microscopic analysis, NAAT for genital pathogens
- Others (such as chest radiograph or other radiologic imaging)

NAAT, Nucleic acid amplification test.

If a fever has an obvious cause, laboratory evaluation may not be required, and management is tailored to the underlying cause with as-needed reevaluation. If the cause of the fever is not apparent, further diagnostic evaluation should be considered on a case-by-case basis. The history of presentation and abnormal physical examination findings guide the evaluation. The child with respiratory symptoms and hypoxia may require a chest radiograph, rapid antigen testing for respiratory syncytial virus or influenza, or polymerase chain reaction (PCR) testing for SARS-CoV-2. The child with pharyngitis can benefit from PCR testing for group A *Streptococcus* and a throat culture. Dysuria, back pain, or a history of vesicoureteral reflux should prompt a urinalysis and urine culture, and bloody diarrhea should prompt a stool culture. A complete blood count and blood culture should be considered in the ill-appearing child, along with cerebrospinal fluid studies if the child has neck stiffness or if the possibility of meningitis is considered. Well-defined high-risk groups require a more extensive evaluation on the basis of age, associated disease, or immunodeficiency status and might warrant prompt antimicrobial therapy before a pathogen is identified. Fever in neonates and young infants (0-3 months old), fever in older children, and fever of unknown origin are discussed in Chapters 220, 221, and 222, respectively.

MANAGEMENT

Although fever is a common parental worry, no evidence supports the belief that high fever can result in brain damage or other bodily harm, except in rare instances of febrile status epilepticus and heat stroke. *Treating fever in self-limiting illnesses for the sole reason of bringing the body temperature back to normal is not necessary in the otherwise healthy child.* Most evidence suggests that fever is an adaptive response and should be treated only in select circumstances. In humans, increased temperatures are associated with decreased microbial replication and an increased inflammatory response. Although fever can have beneficial effects, it also increases oxygen consumption, carbon dioxide production, and cardiac output and can exacerbate cardiac insufficiency in patients with heart disease or chronic anemia (e.g., sickle cell disease), pulmonary insufficiency in patients with chronic lung disease, and metabolic instability in patients with diabetes mellitus or inborn errors of metabolism. Children between 6 months and 5 years of age are at increased risk for simple febrile seizures. *The focus of the evaluation and treatment of febrile seizures is aimed at determining the underlying cause of the fever.* Children with idiopathic epilepsy also often have an increased frequency of seizures associated with a fever. High fever during pregnancy may be teratogenic.

Fever with temperatures <39°C (102.2°F) in healthy children generally does not require treatment. However, as temperatures become higher, patients tend to become more uncomfortable, and treatment of fever is then reasonable. If a child is included in one of the high-risk groups previously discussed or if the child's caregiver is concerned that the fever is adversely affecting the child's behavior and causing discomfort, treatment may be given to hasten the resolution of the fever.

Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replacing fluids that are lost related to the increased metabolic demands and insensible losses of fever. Antipyretic therapy is beneficial in high-risk patients and patients with discomfort. **Hyperpyrexia** (>41°C [105.8°F]) indicates high probability of a hypothalamic disorder or central nervous system injury (hemorrhage, other etiology) and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. The most common antipyretics are **acetaminophen 10-15 mg/kg/dose every 4 hours and ibuprofen in children >6 months old at 5-10 mg/kg/dose every 8 hours**. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose one type of medication and clearly record the dose and time of administration so that overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 220

Fever Without a Focus in the Neonate and Young Infant

Laura Brower and Samir S. Shah

Fever is a common reason for neonates and young infants to undergo medical evaluation in the hospital or ambulatory setting. For this age-group (0-3 months), **fever without a focus** refers to a rectal temperature of 38°C (100.4°F) or greater without other presenting signs or symptoms. The evaluation of these patients can be challenging because of the difficulty distinguishing between a serious infection (bacterial or viral) and a self-limited viral illness. The etiology and evaluation of fever without a focus depend on the age of the child. Three age-groups are typically considered: neonates 0-28 days, young infants 29-90 days, and children 3-36 months.

ETIOLOGY AND EPIDEMIOLOGY

Serious bacterial infection (SBI) occurs in 7–13% of neonates and young infants with fever. In this group, the most common SBIs are urinary tract infection (UTI; 5–13%), bacteremia (1–2%), and meningitis (0.2–0.5%). The risk for SBI is highest in those appearing ill (in contrast to well appearing) and those with risk factors and is inversely related to postnatal age. The term **invasive bacterial infection (IBI)**, which refers to bacteremia and meningitis, recognizes that infants with UTIs may be managed differently (e.g., often with oral antibiotics) than those with bacteremia or meningitis. *Escherichia coli* is the most common organism causing SBI, followed by group B *Streptococcus* (GBS). The frequency of GBS infections has decreased as a consequence of increased screening of pregnant women and use of intrapartum antibiotic prophylaxis. Other, less common organisms include *Klebsiella* spp., *Enterococcus* spp., *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Staphylococcus aureus* (Table 220.1). *Listeria monocytogenes* is a rare cause of neonatal infections, potentially related to changes in public health education and improvements in food safety. Additional details about specific bacteria are available in the following chapters: *E. coli* (see Chapter 246), GBS (see Chapter 230), *S. pneumoniae* (see Chapter 228), *N. meningitidis* (see Chapter 237), *S. aureus* (see Chapter 227.1), and *L. monocytogenes* (see Chapter 234). Specific bacterial infections that can present with fever in this age-group, although often with symptoms other than isolated fever, include pneumonia (see Chapter 449), gastroenteritis (see Chapter 387), osteomyelitis (see Chapter 725), septic arthritis (see Chapter 726), omphalitis (see Chapter 144), cellulitis, and other skin and soft tissue infections (see Chapter 706).

Herpes simplex virus **(HSV)** infections (see Chapter 299) should also be considered in febrile neonates, particularly those under 28 days old, given the high rate of mortality and significant morbidity among survivors. Neonatal HSV is rare, with a prevalence of 0.2–0.3% among febrile neonates. Most of these infections are caused by HSV type 2, though HSV type 1 can also cause neonatal infection. Neonates with disseminated disease and skin, eye, and mouth (SEM) disease typically present at 5-12 days of life. Neonates with central nervous system (CNS) disease generally present at 16-19 days. Perinatally acquired HSV occasionally manifests beyond 28 days of age, although most cases beyond 28 days of age represent postnatal acquisition.

In febrile infants who *appear well,* viral illnesses are much more common than bacterial or serious viral infections. The most common viruses include respiratory syncytial virus (RSV; see Chapter 307), enteroviruses (see Chapter 297), influenza viruses (see Chapter 305), parainfluenza viruses (see Chapter 306), human metapneumovirus (see Chapter 308), adenovirus (see Chapter 309), parechoviruses (see Chapter 297), and rhinovirus (see Chapter 310).

CLINICAL MANIFESTATIONS

In neonates and young infants, bacterial and viral infections can present with isolated fever or nonspecific symptoms, making diagnosis of serious illnesses challenging. Some neonates and young infants will have signs of systemic illness at presentation, including abnormal temperature (hypothermia <36°C [96.8°F], fever ≥38°C [100.4°F]), abnormal respiratory examination (tachypnea >60 breaths/min, respiratory distress, apnea), abnormal circulatory examination (tachycardia >180 beats/min, delayed capillary refill >3 seconds, weak or bounding pulses), abnormal abdominal examination, abnormal neurologic

Table 220.1 Bacterial Pathogens in Neonates and Young Infants with Urinary Tract Infection, Bacteremia, or Meningitis

FREQUENCY	URINARY TRACT INFECTION	BACTEREMIA AND MENINGITIS
Common	*Escherichia coli*	*Escherichia coli* Group B *Streptococcus*
Less common	*Klebsiella* spp. *Enterococcus* spp.	*Listeria monocytogenes* *Streptococcus pneumoniae* *Staphylococcus aureus* *Klebsiella* spp.
Rare	Group B *Streptococcus* *Staphylococcus aureus* *Pseudomonas aeruginosa* *Enterobacter* spp. *Citrobacter* spp. *Proteus mirabilis*	*Neisseria meningitidis* *Salmonella* spp. *Enterobacter* spp. *Enterococcus* spp. *Cronobacter sakazakii* *Haemophilus influenzae* *Citrobacter*

Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replacing fluids that are lost related to the increased metabolic demands and insensible losses of fever. Antipyretic therapy is beneficial in high-risk patients and patients with discomfort. **Hyperpyrexia** (>41°C [105.8°F]) indicates high probability of a hypothalamic disorder or central nervous system injury (hemorrhage, other etiology) and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. The most common antipyretics are **acetaminophen 10-15 mg/kg/dose every 4 hours and ibuprofen in children >6 months old at 5-10 mg/kg/dose every 8 hours**. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose one type of medication and clearly record the dose and time of administration so that overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 220

Fever Without a Focus in the Neonate and Young Infant

Laura Brower and Samir S. Shah

Fever is a common reason for neonates and young infants to undergo medical evaluation in the hospital or ambulatory setting. For this age-group (0-3 months), **fever without a focus** refers to a rectal temperature of 38°C (100.4°F) or greater without other presenting signs or symptoms. The evaluation of these patients can be challenging because of the difficulty distinguishing between a serious infection (bacterial or viral) and a self-limited viral illness. The etiology and evaluation of fever without a focus depend on the age of the child. Three age-groups are typically considered: neonates 0-28 days, young infants 29-90 days, and children 3-36 months.

ETIOLOGY AND EPIDEMIOLOGY

Serious bacterial infection (SBI) occurs in 7–13% of neonates and young infants with fever. In this group, the most common SBIs are urinary tract infection (UTI; 5–13%), bacteremia (1–2%), and meningitis (0.2–0.5%). The risk for SBI is highest in those appearing ill (in contrast to well appearing) and those with risk factors and is inversely related to postnatal age. The term **invasive bacterial infection (IBI)**, which refers to bacteremia and meningitis, recognizes that infants with UTIs may be managed differently (e.g., often with oral antibiotics) than those with bacteremia or meningitis. *Escherichia coli* is the most common organism causing SBI, followed by group B *Streptococcus* (GBS). The frequency of GBS infections has decreased as a consequence of increased screening of pregnant women and use of intrapartum antibiotic prophylaxis. Other, less common organisms include *Klebsiella* spp., *Enterococcus* spp., *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Staphylococcus aureus* (Table 220.1). *Listeria monocytogenes* is a rare cause of neonatal infections, potentially related to changes in public health education and improvements in food safety. Additional details about specific bacteria are available in the following chapters: *E. coli* (see Chapter 246), GBS (see Chapter 230), *S. pneumoniae* (see Chapter 228), *N. meningitidis* (see Chapter 237), *S. aureus* (see Chapter 227.1), and *L. monocytogenes* (see Chapter 234). Specific bacterial infections that can present with fever in this age-group, although often with symptoms other than isolated fever, include pneumonia (see Chapter 449), gastroenteritis (see Chapter 387), osteomyelitis (see Chapter 725), septic arthritis (see Chapter 726), omphalitis (see Chapter 144), cellulitis, and other skin and soft tissue infections (see Chapter 706).

Herpes simplex virus **(HSV)** infections (see Chapter 299) should also be considered in febrile neonates, particularly those under 28 days old, given the high rate of mortality and significant morbidity among survivors. Neonatal HSV is rare, with a prevalence of 0.2–0.3% among febrile neonates. Most of these infections are caused by HSV type 2, though HSV type 1 can also cause neonatal infection. Neonates with disseminated disease and skin, eye, and mouth (SEM) disease typically present at 5-12 days of life. Neonates with central nervous system (CNS) disease generally present at 16-19 days. Perinatally acquired HSV occasionally manifests beyond 28 days of age, although most cases beyond 28 days of age represent postnatal acquisition.

In febrile infants who *appear well,* viral illnesses are much more common than bacterial or serious viral infections. The most common viruses include respiratory syncytial virus (RSV; see Chapter 307), enteroviruses (see Chapter 297), influenza viruses (see Chapter 305), parainfluenza viruses (see Chapter 306), human metapneumovirus (see Chapter 308), adenovirus (see Chapter 309), parechoviruses (see Chapter 297), and rhinovirus (see Chapter 310).

CLINICAL MANIFESTATIONS

In neonates and young infants, bacterial and viral infections can present with isolated fever or nonspecific symptoms, making diagnosis of serious illnesses challenging. Some neonates and young infants will have signs of systemic illness at presentation, including abnormal temperature (hypothermia <36°C [96.8°F], fever ≥38°C [100.4°F]), abnormal respiratory examination (tachypnea >60 breaths/min, respiratory distress, apnea), abnormal circulatory examination (tachycardia >180 beats/min, delayed capillary refill >3 seconds, weak or bounding pulses), abnormal abdominal examination, abnormal neurologic

Table 220.1 Bacterial Pathogens in Neonates and Young Infants with Urinary Tract Infection, Bacteremia, or Meningitis

FREQUENCY	URINARY TRACT INFECTION	BACTEREMIA AND MENINGITIS
Common	*Escherichia coli*	*Escherichia coli* Group B *Streptococcus*
Less common	*Klebsiella* spp. *Enterococcus* spp.	*Listeria monocytogenes* *Streptococcus pneumoniae* *Staphylococcus aureus* *Klebsiella* spp.
Rare	Group B *Streptococcus* *Staphylococcus aureus* *Pseudomonas aeruginosa* *Enterobacter* spp. *Citrobacter* spp. *Proteus mirabilis*	*Neisseria meningitidis* *Salmonella* spp. *Enterobacter* spp. *Enterococcus* spp. *Cronobacter sakazakii* *Haemophilus influenzae* *Citrobacter*

examination (lethargy, irritability, alterations in tone), or abnormal skin examination (rash, petechiae, cyanosis). Infants with **septic arthritis** or **osteomyelitis** may appear well except for signs around the involved joint or bone or may only manifest with *pseudoparalysis* (disuse) and *paradoxical irritability* (infant experiences pain during attempts to comfort the child).

DIAGNOSIS

Historically, all neonates <60 or <90 days of age were hospitalized; underwent laboratory evaluation of the blood, urine, and cerebrospinal fluid (CSF); and received empirical antibiotics. Additionally, some patients had stool cultures, had chest radiographs, had HSV evaluation, and/or received empirical antiviral agents. Under this approach, many infants without SBI or serious viral infection received evaluation, treatment, and hospitalization. Protocols were subsequently developed to identify infants at lower risk of SBI, who may be managed outside the hospital setting. The most current protocol is the American Academy of Pediatrics (AAP) guideline, which considers UTIs separately from bacteremia and meningitis (Table 220.2). Despite protocols, substantial variation continues to exist in the approach to and management

Table 220.2 Management of Fever Without Source in Infants 0-36 Months Old

GROUP	MANAGEMENT
Any toxic-appearing child 0–36 mo and temperature ≥38°C (100.4°F)	Hospitalize, cultures (blood, urine, CSF) plus other tests*, parenteral antibiotics
WELL-APPEARING CHILD	
Child <22 days and temperature ≥38°C (100.4°F)	Hospitalize, cultures (blood, urine, CSF) plus other tests*, parenteral antibiotics
Child 22–60 days and temperature ≥38°C (100.4°F)	**Three-Step Process** 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Well-appearing physical examination • Normal laboratory studies • Urine: negative leukocyte esterase and nitrite, ≤5 WBC/hpf centrifuged and <10 WBC/hpf uncentrifuged • Inflammatory markers: temperature ≤38.5°C, procalcitonin ≤0.5 ng/mL, CRP ≤20 mg/L, absolute neutrophil count ≤4,000-5,200/mm^3 • Stool studies if diarrhea (no RBC and <5 WBC/hpf) 2. If child *fulfills all low-risk criteria*, use age to determine need for LP, parenteral antimicrobials, and hospital observation. • **Age 22-28 days**: Obtain UA, blood culture, inflammatory markers. May perform LP. May administer parenteral antimicrobials. Observe in hospital. • **Age 29-60 days old**: Obtain UA, blood culture, inflammatory markers. Need not perform LP. Need not administer antimicrobials. Observe closely at home with follow-up within 24-36 hr. 3. If child does not fulfill all low-risk criteria, use age and lab results to determine need for LP, antimicrobials, and hospital observation. • **Age 22-28 days** with abnormal UA and normal inflammatory markers: May perform LP. Administer parenteral antimicrobials. Observe in hospital. • **Age 22-28 days** with abnormal inflammatory markers: Perform LP. If CSF pleocytosis, CSF uninterpretable, or abnormal UA, administer parenteral antimicrobials and observe in hospital. If CSF and UA are normal, may observe at home after parenteral antimicrobials or observe in the hospital with or without parenteral antimicrobials. • **Age 29-60 days** with abnormal UA and normal inflammatory markers: Administer oral antimicrobials. May observe closely at home with follow-up in 12-24 hr. • **Age 29-60 days** with abnormal inflammatory markers: May perform LP. If CSF pleocytosis, administer parenteral antimicrobials and observe in hospital. If CSF is normal, may administer parenteral or oral antimicrobials and may observe closely in hospital or at home. If CSF is not available or uninterpretable, administer parenteral antimicrobials and may observe closely in hospital or at home.
Child 2-36 mo and temperature 38–39°C (100.4–102.2°F)	Reassurance that diagnosis is likely self-limited viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and/or new signs and symptoms.
Child 2-36 mo and temperature >39°C (102.2°F)	**Two-Step Process** 1. Determine immunization status. 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all females, all males <6 mo old, all uncircumcised males <2 yr, and all children with recurrent urinary tract infections. If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med.* 1993;22:1198–1210).

*Other tests may include chest radiograph, stool studies, herpes simplex and other virus polymerase chain reaction.
CSF, Cerebrospinal fluid; hpf, high-powered field; LP, lumbar puncture; RBC, red blood cell; UA, urinalysis; WBC, white blood cell.
Modified from Huppler A. Fever. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 52.5, p. 971; with data from Pantell RH, Roberts KB, Adams WG, et al. Evaluation and management of well appearing febrile infants 8 to 60 days old. *Pediatrics.* 2021;148(2):e2021052228.

of the febrile infant. *It must be emphasized that these criteria apply to the well-appearing child; those who appear critically ill (septic) require prompt evaluation, resuscitation, and empiric antibiotic therapy (within 1 hour).*

In the past, experts advocated that all neonates ≤28 days old undergo a complete evaluation for serious infection, receive empirical antimicrobials, and be hospitalized. In prior risk criteria, one allowed neonates ≤28 days to be designated as "low risk" and managed outside the hospital without antimicrobials. In one study, <1% of low-risk infants ≤28 days old had SBI; however, in another study applying the other criteria to neonates, 3–4% of those classified as low risk had SBI. In the current protocols, neonates 22-28 days who meet certain low-risk criteria can be managed outside the hospital; in one study, the risk of bacteremia in this age-group was lower than in infants <22 days (1.6% vs 3.3–5.3%).

Young febrile infants ≥29 days old who *appear ill* (with signs of systemic illness) require complete evaluation for serious infection, empiric antimicrobials, and hospitalization; however, well-appearing infants can be managed safely as outpatients using low-risk criteria as indicated in Table 220.2. With each of these approaches, infants must have a normal physical examination, must be able to reliably obtain close follow-up, and must meet certain laboratory and/or radiographic criteria. Based on these protocols, all infants meeting the previous criteria would undergo lumbar puncture (LP), whereas low-risk infants meeting other criteria and following the current protocols would not. There is substantial variation in clinical practice in the performance of LPs in well-appearing infants >28 days. When deciding whether to perform an LP in this age-group, clinicians should consider multiple factors, including the home situation and the ability to contact the family.

The protocols discussed in Table 220.2 were initially developed for use in the emergency department (ED). Infants evaluated in the office setting may warrant a different approach when a relationship between the physician and family already exists to facilitate clear communication and timely follow-up. In one large study of febrile infants <3 months old who were initially evaluated for fever in the office setting, clinicians hospitalized only 36% of infants but initiated antibiotics in 61 of the 63 infants with bacteremia or bacterial meningitis. These findings suggest that, with very close follow-up (including multiple in-person visits or frequent contacts by telephone), some febrile infants perceived to be at low risk for **invasive bacterial infection** (bacteremia and meningitis) on the basis of history, physical examination, and normal but limited laboratory testing can be managed in an office-based setting. It is important to note that 3% of infants with SBI did not initially receive empiric antibiotics, necessitating careful consideration of risks and benefits of selective rather than universal testing and empiric antibiotic treatment of febrile infants evaluated in the office setting.

Viral Respiratory Illness

Several studies have demonstrated a decreased risk of SBI in infants with positive testing for influenza, RSV, and other respiratory viral illnesses, although the risk of UTI remains significant. In one prospective study, the risk of SBI in neonates <28 days old was not altered by RSV status. Given these data, young febrile infants with bronchiolitis may not require LP, particularly if they can be closely observed or have close follow-up.

Urinary Tract Infection and Bacterial Meningitis

In the past, infants with abnormal findings on urinalysis (UA) would undergo complete evaluation for infection, including LP. In well-appearing infants >28 days old with an abnormal UA, some evidence suggests that the risk of bacterial meningitis is extremely low: <0.5%. For neonates 0-28 days, the risk of concomitant bacterial meningitis with UTI is 1–2%.

CSF pleocytosis in the absence of bacterial meningitis (i.e., **sterile pleocytosis**) has been reported in ~23% infants with UTI. The cause is uncertain, with some studies attributing this phenomenon to traumatic LPs or undetected viral infection rather than inflammation in the context of systemic illness.

LABORATORY DIAGNOSIS

Complete Blood Count

The peripheral complete blood cell count (CBC) and differential are frequently obtained by providers when evaluating febrile neonates and infants. The white blood cell (WBC) count alone cannot accurately predict SBI risk. In one series, isolated use of the WBC cutoffs of outside 5,000-15,000 WBCs/mm^3 would miss at least 33% of infants with bacteremia and 40% of those with meningitis. A prospective study found no increased risk of SBI in febrile, well-appearing infants with leukopenia (WBC count <5,000/mm^3). The WBC count combined with other factors may help determine an infant's risk of SBI, but it should not be used in isolation to predict infection risk. The absolute neutrophil count (ANC) has also been used in evaluating the risk of serious infection. Two recent large studies derived ANC cutoffs of greater than 4,000 and 5,200 per mm^3 for use in specific protocols; however, these protocols used ANC in conjunction with other markers.

Blood Culture

The ability to identify pathogens in the blood depends on the volume of blood, the timing of the blood culture in relation to antimicrobial administration, and, to a lesser degree, the number of blood cultures obtained. A negative blood culture does not exclude the possibility of bacterial meningitis; in one study, 38% of infants with culture-proven bacterial meningitis had negative blood cultures. For additional information on the time to positivity of blood cultures in neonates and young infants, see "Discharge from the Hospital."

Urinalysis

Different methods can assist in making a presumptive diagnosis of UTI while awaiting results of a urine culture. *Traditional* UA consists of dipstick biochemical analysis of urine for nitrites or leukocyte esterase (LE) and microscopic examination of the urine for WBCs and bacteria. One study found that the traditional UA had a higher negative predictive value (NPV) than dipstick alone (99.2% vs 98.7%), but that dipstick alone had a higher positive predictive value (PPV, 66.8% for dipstick alone vs 51.2% for traditional UA). *Enhanced* UA includes hemocytometer cell count (to decrease variability of urine cell counts) and Gram stain on uncentrifuged urine. The enhanced UA has a higher sensitivity but comparable specificity to traditional UA. However, the enhanced UA has not been studied in the most common protocols for evaluation of the febrile infant, and many institutions/office practices do not perform this test.

Cerebrospinal Fluid

CSF evaluation consists of culture and Gram stain, cell count, glucose, and protein. Polymerase chain reaction (PCR) testing may also be sent based on the clinical scenario, usually for enterovirus or HSV (some include bacterial pathogens). Normal CSF parameters vary by age of the infant and should be interpreted in combination with other clinical and historical risk factors, given that some infants with normal CSF parameters may rarely have CNS infections (Table 220.3). The CSF Gram stain can be a useful adjunct to other CSF parameters given the high specificity of the test (99.3–99.9%; i.e., relatively few false-positive results), although the range of reported sensitivity is much broader (67–94.1%).

The interpretation of CSF can be challenging in the setting of a traumatic LP, where the CSF is contaminated with peripheral blood. Some clinicians assume a ratio of WBCs to red blood cells (RBCs) of 1:500 in the CSF. Others advocate calculating the expected CSF WBCs based on the peripheral blood WBCs and RBCs and then using the observed-to-predicted ratio of CSF WBCs to aid in the identification of bacterial meningitis. This calculation assumes that the ratio of WBCs to RBCs in the peripheral blood remains constant after introduction into the CSF. Next-generation molecular testing is helpful in identifying the most

Table 220.3 Values of Cerebrospinal Fluid (CSF) Studies in Neonates and Infants by Age

CSF WHITE BLOOD CELL COUNTS	CELLS/MM³
Upper limit of normal by age*	
1-28 days	18
29-60 days	8.5
61-90 days	8.5
Upper limit of normal by age#	
0-28 days	15
29-60 days	9
90th percentile by age†	
0-7 days	26
8-28 days	8-9
29-56 days	6-8
95th percentile by age‡	
0-28 days	19
29-56 days	9
95th percentile by age#	
0-28 days	16
29-60 days	11

CSF PROTEIN	MG/DL
Upper limit of normal by age*	
1-28 days	131
29-60 days	105.5
61-90 days	71
Upper limit of normal by age#	
0-28 days	127
29-60 days	99

CSF PROTEIN	MG/DL
90th percentile by age†	
0-7 days	153
8-28 days	84-106
29-56 days	84-105
95th percentile by age§	
0-14 days	132
15-28 days	100
29-42 days	89
43-56 days	83
95th percentile by age#	
0-28 days	118
29-60 days	91

CSF GLUCOSE	MG/DL
Lower limit of normal by age*	
1-28 days	30
29-60 days	30.5
61-90 days	33.5
Lower limit of normal by age#	
0-28 days	25
29-60 days	27
10th percentile for infants 0-56 days†	38-43
10th percentile by age#	
0-28 days	37
29-60 days	39

*Data from Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr*. 2011;158(1):130–134. All infants had nontraumatic lumbar puncture (LP) and no evidence of bacterial or viral infection.

†Data from Chadwick SL, Wilson JW, Levin JE, Martin JM. Cerebrospinal fluid characteristics of infants who present to the emergency department with fever: establishing normal values by week of age. *Pediatr Infect Dis J*. 2011;30(4):e63–e67. All infants were excluded if they had identified viral or bacterial meningitis, positive blood or urine cultures, a ventriculoperitoneal shunt, recent neurosurgery/antibiotics/seizure, or a traumatic LP.

‡Data from Kestenbaum LA, Ebberson J, Zorc JJ, et al. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics*. 2010;125(2):257–264. Infants were excluded for traumatic LP, serious bacterial infection, congenital infection, seizure, presence of ventricular shunt, or positive CSF testing for enterovirus.

§Data from Shah SS, Ebberson J, Kestenbaum LA, et al. Age-specific reference values for cerebrospinal fluid protein concentration in neonates and young infants. *J Hosp Med*. 2011;6(1):22–27. Infants were excluded for traumatic LP, serious bacterial infection, congenital infection, seizure, presence of a ventricular shunt, positive CSF testing for enterovirus, or elevated serum bilirubin.

#Data from Thomson J, Sucharew H, Cruz AT, et al. Cerebrospinal fluid reference values for young infants undergoing lumbar puncture. *Pediatrics*. 2018;141(3):e20173405. Infants were excluded for missing any component of the CSF profile, traumatic LP, serious bacterial infection, viral CNS infection, non-CNS HSV disease, or prolonged hospital length of stay.

common bacterial and viral pathogens despite a traumatic LP; results are often available within a few hours.

One retrospective cohort study concluded that an observed/predicted CSF WBC ratio of ≤0.01 was helpful in predicting the absence of bacterial meningitis; however, another retrospective cohort study and one case series of traumatic LPs concluded that adjustment of CSF WBC count does not improve the accuracy of diagnosis of meningitis in patients with traumatic LPs. Clinicians may consider hospitalization and empirical antimicrobials in patients with traumatic LPs given the challenge of interpreting the CSF WBC count when there is blood contamination of the specimen.

Treatment with antibiotics before LP can complicate the interpretation of CSF cultures. CSF cultures are negative relatively rapidly after antibiotic administration, within 2 hours for *N. meningitidis* and 4-24 hours for *S. pneumoniae*. Next-generation molecular testing is not affected by prior antibiotic treatment, thus enhancing a diagnosis despite prior antibiotic therapy. In patients with bacterial meningitis, CSF glucose increases to normal range, often within 4-24 hours of antibiotic administration, whereas CSF protein concentrations, despite decreasing, remain abnormal for >24 hours after antibiotic administration. Changes in CSF WBC count and ANC are minimal in the first 24 hours of antibiotic therapy. Therefore CSF findings can provide relevant management information even in the setting of antibiotic administration before LP.

Herpes Simplex Virus Testing

No consensus exists on which neonates should be tested and empirically treated for HSV infection. Historical and clinical features that

should raise concern for HSV include exposure to individuals infected with HSV, particularly mothers with primary HSV infections or first-time genital infections, seizure or abnormal neurologic examination, vesicular rash, ill appearance, apnea, hypothermia, petechial rash/excessive bleeding, hepatic failure, or a history of a scalp electrode. However, neonates with HSV can present *without any high-risk* clinical or historical features, particularly with early isolated CNS disease. Published approaches to neonatal HSV include (1) testing and empirical treatment of all neonates <21 days old who are evaluated for infection; (2) testing and empirical treatment of neonates with the presence of high-risk clinical features for HSV; and (3) testing and empirical treatment for all neonates with high-risk features plus testing the CSF of all neonates <21 days old while deferring empirical acyclovir in those without high-risk features, unless the CSF HSV PCR test is positive.

The AAP Committee on Infectious Diseases recommends that neonates undergoing evaluation for HSV have the following laboratory studies performed: surface cultures or PCR of the conjunctiva, mouth or nasopharynx, rectum, and any vesicles; CSF PCR (sensitivity: 75–100%); whole blood PCR; and serum levels of alanine transaminase (ALT). HSV PCR testing of the mouth, conjunctiva, nasopharynx, rectum, and vesicles has been shown to be more sensitive than culture, with comparable specificity, although no direct comparisons have been performed in neonates.

Enterovirus Testing

Enterovirus is a common and typically benign cause of fever in febrile infants, although it can be difficult to distinguish from SBI on initial presentation. Enterovirus PCR testing of the CSF is a sensitive and rapid means to diagnose infection. One retrospective study of patients with CSF enterovirus testing found no cases of bacterial meningitis in patients with positive enterovirus PCR; this study did not include neonates ≤28 days old. Several studies have demonstrated shorter length of stay, fewer antibiotics, and lower cost among infants with positive CSF enterovirus test results. These results suggest that during local enterovirus seasons, and if PCR testing is available, testing for enterovirus may be of benefit in the evaluation of febrile infants and neonates. Some centers have implemented multiplex PCR panels, which permit testing for multiple viruses, including enterovirus and HSV (and bacteria) simultaneously.

Other Inflammatory Markers

Investigations have examined the utility of inflammatory markers such as C-reactive protein (CRP) and serum procalcitonin (PCT) in the diagnosis of SBI and, more specifically, IBI (bacteremia and meningitis) (see Table 220.2). One meta-analysis reported that PCT is superior to WBC count and CRP for the detection of IBI in children <3 years old, whereas another found that PCT was inferior to prediction rules in identifying SBI in young infants. A prospective multicenter cohort study of febrile infants 7-91 days old determined that the PCT was better at identifying patients with IBI than CRP, WBC count, or ANC. Building on these results, clinical prediction rules for febrile infants, such as the **Step-by-Step** approach, incorporate PCT and CRP, along with age ≤21 days, ill appearance, ANC >10,000/mm^3, and pyuria in a stepwise approach to determine which patients are at high risk for IBI; only 0.7% of infants who met none of those criteria had IBI. In the approach from the AAP, inflammatory markers are recommended for all infants 22 days and older as part of risk stratification. If available, this approach recommends PCT along with either CRP or ANC. If PCT is unavailable, then CRP, ANC, and elevation in temperature should be considered as markers of inflammation (see Table 220.2).

Other Diagnostic Studies

Older infants with positive RSV and influenza testing have a very low risk of SBI beyond UTI. One large case-based survey demonstrated decreased admission rates and antibiotic use for infants with positive respiratory viral tests, and another study demonstrated that implementation of a care algorithm incorporating viral testing led to a shorter length of stay and antibiotic course.

Chest radiographs are unlikely to be clinically useful in the evaluation of the febrile infant without respiratory symptoms. Studies that have examined routine use of radiographs have found limited utility because in infants without respiratory symptoms, most results will be normal and abnormal results can be difficult to interpret.

TREATMENT

Antimicrobials

Ill-appearing and high-risk infants and those <22 days old hospitalized for evaluation for SBI should receive antimicrobial therapy. Commonly used regimens include (1) a third-generation cephalosporin (typically cefepime or ceftazidime), (2) a third-generation cephalosporin and ampicillin, or (3) an aminoglycoside and ampicillin.

Ampicillin is the preferred treatment of GBS and covers *L. monocytogenes* and many *Enterococcus* spp. and some *E. coli*. For neonates 0-28 days, options 2 or 3 have been recommended, given the risk of *L. monocytogenes*. For young infants >28 days, option 1 (third-generation cephalosporin: ceftriaxone) is a reasonable choice. For ill-appearing infants or those with positive CSF Gram stains, additional antibiotics may include vancomycin or broad-spectrum antibiotics such as carbapenems. Local epidemiology and resistance patterns may assist in these choices. Neonates with concern for HSV should be empirically treated with high-dose acyclovir (60 mg/kg/day).

Treatment duration and route of antimicrobial administration depend on the infection. Additional details based on specific infections and organisms are available in the following chapters: meningitis (see Chapter 148), UTI (see Chapter 575), *E. coli* (see Chapter 246), GBS (see Chapter 230), and HSV (see Chapter 299).

Discharge from the Hospital

Traditionally, infants remained in the hospital receiving antimicrobial therapy until bacterial cultures were negative for 48 hours or even longer. Multiple studies have suggested that shorter culture observation periods (i.e., 24 or 36 hours) may be reasonable because most pathogens in the blood grow within this time frame when automated blood culture monitoring systems are used. In one multicenter retrospective cross-sectional study, 91% of blood cultures were positive by 24 hours and 96% by 36 hours. Fewer studies have evaluated the *time to positivity* of CSF and urine cultures, but in one large study of febrile infants 28-90 days old, all positive CSF cultures grew within 24 hours (median time to positivity, 18 hours). For blood cultures, 1.3% grew after 24 hours (median time to positivity, 16 hours), and for urine cultures, 0.9% grew after 24 hours (median time to positivity, 16 hours). In one multicenter study including infants <60 days old, 82% of CSF cultures were positive by 24 hours and 86% by 36 hours. For neonates undergoing evaluation for HSV, it is reasonable to await results of HSV testing before discharge to home. For patients with identified bacterial infections or HSV infections, the duration of the hospital stay will be determined by the specific pathogen and site of infection.

PROGNOSIS

Most well-appearing neonates and young infants with fever recover completely and relatively quickly, depending on the etiology of the fever. Most infection-related mortality and long-term morbidity result from HSV infection and bacterial meningitis. For HSV, reported mortality rates range from 27% to 31% for disseminated disease and from 4% to 6% for CNS disease. Of those who survive, 83% of patients with disseminated disease and 31% of those with CNS disease will have normal development at 12 months old. The mortality of bacterial meningitis varies by pathogen but ranges from 4% to 15%. In one study of children who had meningitis as infants, 84% had normal development at age 5 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 221

Fever in the Older Child

Laura Brower and Samir S. Shah

Fever is the most common reason for a child to seek medical care. While most infants and children have benign viral causes of fever, a small proportion will have more serious infections. Unlike fever in young infants, pediatricians can rely more readily on symptoms and physical examination findings to establish a diagnosis in older children. Laboratory testing and radiographic studies are not routinely indicated but may be helpful when diagnostic uncertainty exists or the patient appears critically ill. Occult infections, such as urinary tract infection (UTI), may be present, and testing for such infections should be guided by demographic and contextual factors such as patient age, patient gender, and environmental exposures.

DIAGNOSIS

The many potential causes of fever in older infants and children can be broadly categorized into viral and bacterial infections, further organized by body region, as well as the less common inflammatory, oncologic, endocrine, and medication-induced causes (Table 221.1).

Viral Infections

Viral infections are the most common cause of fever, and the prevalence of specific viral infections varies by season. Typically, in the summer and early fall, enteroviruses (e.g., coxsackieviruses) predominate, usually presenting as hand-foot-and-mouth disease, herpangina, aseptic meningitis, or a variety of other manifestations. In the late fall and winter, viral upper and lower respiratory tract infections caused by respiratory viruses such as respiratory syncytial virus (RSV) and influenza and gastroenteritis caused by gastrointestinal (GI) viruses such as norovirus and rotavirus are common. Parainfluenza viruses are a common cause of **laryngotracheobronchitis (croup)** and occur primarily in the fall and spring, affecting mostly infants and toddlers. Varicella is a less common cause of fever than in the past because of childhood vaccination but still occurs, with the highest incidence in winter and early spring. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 can cause fever alone or with either upper or lower respiratory tract symptoms in young children, though asymptomatic infections also occur.

Bacterial Infections

Common bacterial infections include acute **otitis media** and **streptococcal pharyngitis (strep throat)**. Acute otitis media is diagnosed by the presence of a bulging, erythematous, and nonmobile tympanic membrane upon insufflation. Streptococcal pharyngitis occurs most frequently in the late fall and winter and is uncommon before age 3 years. The presence of focal auscultatory findings, including crackles, suggests a lower respiratory tract infection, such as bacterial pneumonia, but may also be present among children with **bronchiolitis** and viral pneumonia. **Atypical pneumonia** caused by mycoplasma typically occurs in school-age children and is often associated with headache, sore throat, malaise, and low-grade fever. The presence of neck pain (especially with neck extension for those with retropharyngeal abscess), drooling, or muffled voice may indicate a deep neck infection such as a **retropharyngeal abscess**, which occurs in infants and young children, or a **peritonsillar abscess**, which typically affects older children. Skin and soft tissue infections such as cellulitis and abscess may also present with fever, with the buttocks a common area for abscesses in young children. Bone and joint infections such as **osteomyelitis** and **septic arthritis** may present with fever and refusal to bear weight or limp in the young child. Invasive bacterial infections, including **sepsis** and **bacterial meningitis**, must be considered in young children presenting with fever. Although uncommon, these infections are potentially life-threatening and require prompt recognition and treatment. Ill appearance, lethargy, and tachycardia are typically present among children with severe sepsis, and petechiae may be an early finding among children with meningococcemia or other invasive bacterial diseases. Figures 221.1 and 221.2 show age-related diagnoses and organisms producing bacterial sepsis in infants and children. Children with fever who are immunosuppressed, such as children receiving chemotherapy or those with sickle cell disease, are at higher risk for invasive bacterial infection.

Infants and children age 2-24 months merit special consideration because they have limited verbal skills, are at risk for occult bacterial infections, and may be otherwise asymptomatic except for fever (see Chapter 220).

Occult Urinary Tract Infection

Among children 2-24 months old without symptoms or physical examination findings that identify another focal source of infection, the prevalence of UTI may be as high as 5–10%. The highest risk of UTI occurs in females and uncircumcised males, with a very low rate of infection (<0.5%) in circumcised males. Table 221.2 lists clinical risk factors for UTI.

Occult Bacteremia

Occult bacteremia is defined as a positive blood culture for a pathogen in a well-appearing child without an obvious source of infection. In the 1990s, before vaccination programs against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*, up to 5% of young children age 2 to 24 (up to 36) months with fever ≥39°C (102.2°F) had occult bacteremia, most often caused by *S. pneumoniae*. Currently, the prevalence of occult bacteremia is far less than 1% in febrile, well-appearing young children. Most cases of pneumococcal occult bacteremia are transient, with a minority of these children developing new focal infections, sepsis, or other sequelae. Unimmunized and incompletely immunized young children remain at higher risk for occult bacteremia because of pneumococcus (see Chapter 228). Bacteremia caused by Hib or meningococcus should not be considered benign because subsequent serious invasive infection may rapidly follow the bacteremia.

GENERAL APPROACH

The general approach to fever in the older child begins with an assessment of the child's overall appearance and vital signs. A detailed history of the present illness and a thorough physical examination should be performed to identify the cause of the fever.

Overall Appearance and Vital Signs

Children who are ill or appear toxic or who have abnormal vital signs (e.g., tachycardia, tachypnea, hypotension) require rapid assessment, including a focused physical examination to evaluate for the possibility of an invasive bacterial infection. A more detailed history and physical exam can be performed in the well-appearing child.

Symptoms

A thorough history should be obtained from the caregiver (and patient, when appropriate), including a characterization of the fever and any other associated symptoms. The degree and duration of the fever should be assessed, and the method of taking the temperature should be ascertained (e.g., forehead, axillary, oral, rectal). For children with prolonged fever, it is important to determine whether the fever has been episodic or persistent. Patients with prolonged fever may harbor occult infections, UTI, or bone or soft tissue infections or may have an inflammatory or oncologic condition. Additionally, Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) should be considered among children with prolonged fever, and a careful evaluation for other stigmata associated with these conditions is warranted (see Chapter 208).

After characterizing the fever, it is important to ask systematically about the presence of symptoms that may identify an etiology for the fever, including symptoms of common viral infections such as rhinorrhea, cough, vomiting, and diarrhea. Additionally, symptoms should be elicited for each body system: headache, ear pain, sore throat, neck pain or swelling, difficulty breathing, chest pain, abdominal pain, rash or changes in skin color, extremity pain or difficulty with ambulation (including refusal to bear weight in a

Table 221.1 Etiologies of Fever in Children >2 Mo of Age

INFECTIOUS

Central Nervous System
Bacterial meningitis
Viral meningitis
Viral encephalitis
Epidural abscess
Brain abscess

Ear, Nose, and Throat
Acute otitis media
Mastoiditis
Viral upper respiratory infection (i.e., common cold)
Acute bacterial sinusitis
Acute streptococcal pharyngitis
Acute viral pharyngitis
Retropharyngeal abscess
Ludwig angina
Peritonsillar abscess
Herpangina
Herpes simplex virus gingivostomatitis
Acute bacterial lymphadenitis
Viral laryngotracheobronchitis (i.e., croup)
Bacterial tracheitis
Epiglottitis
Lemierre syndrome

Face and Ocular
Parotitis (viral and bacterial)
Erysipelas
Preseptal cellulitis
Orbital cellulitis

Lower Respiratory Tract
Acute viral bronchiolitis
Pneumonia (viral and bacterial)
Complicated pneumonia (e.g., empyema, pleural effusion)
Tuberculosis

Cardiac
Pericarditis
Myocarditis
Endocarditis

Gastrointestinal
Gastroenteritis (viral and bacterial)
Mesenteric adenitis
Acute appendicitis
Hepatitis
Pancreatitis
Gallbladder disease (e.g., cholecystitis, cholangitis)
Intraabdominal abscess

Genitourinary
Urinary tract infection/pyelonephritis
Renal abscess
Epididymitis
Pelvic inflammatory disease
Tubo-ovarian abscess

Skin, Soft Tissue, and Muscle
Viral exanthemas (e.g., varicella, coxsackievirus, roseola, measles)
Scarlet fever
Syphilis
Cellulitis
Abscess
Necrotizing fasciitis
Myositis (viral and bacterial and immune)

Bone and Joint
Osteomyelitis
Septic arthritis
Transient synovitis
Spondylodiscitis

Toxin Mediated
Toxic shock syndrome
Staphylococcal scalded skin syndrome

Invasive Bacterial Infections
Occult bacteremia
Bacterial sepsis
Bacterial meningitis
Disseminated gonococcal infection

Systemic Infection
EBV
CMV
HIV
Cat scratch disease
Brucellosis
Influenza
Others (see Chapter 222)

Vector-Borne (Tick, Mosquito)
Lyme disease
Rickettsiae (e.g., Rocky Mountain spotted fever
Ehrlichiosis
Arboviruses (e.g., West Nile virus)
Dengue fever

INFLAMMATORY
Kawasaki disease
Acute rheumatic fever
Systemic lupus erythematosus
Inflammatory bowel disease
Juvenile idiopathic arthritis
IgA vasculitis (Henoch-Schönlein purpura)
Other rheumatologic diseases (e.g., dermatomyositis)
Periodic fever syndromes
Serum-like sickness syndrome
Multisystem inflammatory syndrome in children (MIS-C)

ONCOLOGIC
Leukemia
Lymphoma
Solid tumors (e.g., neuroblastoma)

ENDOCRINE
Thyrotoxicosis/thyroid storm

MEDICATION INDUCED
Serotonin syndrome
Anticholinergic toxidrome (e.g., antihistamines)
Sympathomimetic toxidrome (e.g., cocaine)
Salicylate toxicity

OTHER
Hemophagocytic lymphohistiocytosis
Macrophage activation syndrome
Ectodermal dysplasia
Dysautonomia
Factitious

young child), and overall activity level. In older children, the presence of dysuria, urinary frequency, or back pain may indicate UTI. Assessment of oral intake and urine output is also critical because dehydration may accompany common childhood infections and is associated with higher rates of morbidity. The presence of weight loss or night sweats may indicate leukemia, lymphoma, or tuberculosis. Additionally, a thorough social history should be performed, inquiring about attendance at daycare, any travel, and any sick contacts at daycare, school, or in the household.

Physical Examination

A complete physical examination includes particular attention to body systems with associated symptoms (e.g., thorough exam of oropharynx for child with sore throat). A complete physical

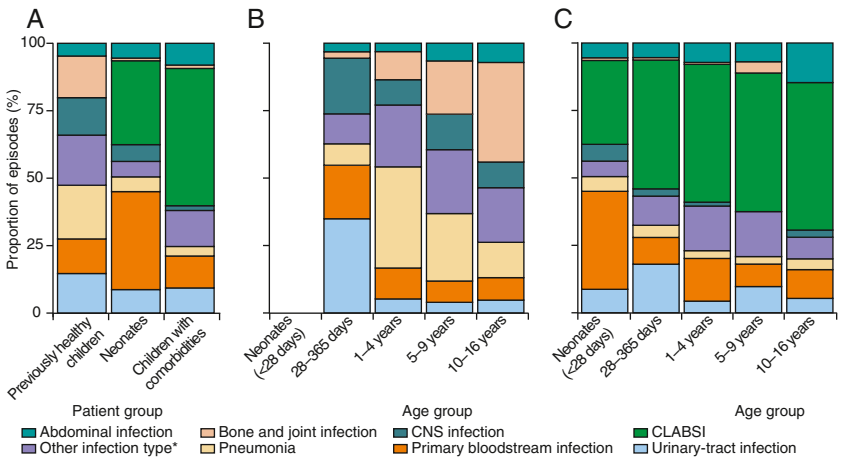

Fig. 221.1 Age distribution of sites of infection causing blood culture–proven bacterial sepsis in children. Sites of infection are shown for (A) the three patient groups together and separately for (B) previously healthy children ≥28 days old and (C) neonates and children with comorbidities ≥28 days old. CLABSI, Central line–associated bloodstream infection; CNS, central nervous system. *Skin infection, wound infection, endocarditis, toxic shock syndrome; ear, nose, and throat infection; other, nonspecified focal infection. *(From Agyeman PKA, Schlapbach LJ, Giannoni E, et al. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. Lancet Child Adolesc. 2017;1:124–133, Fig. 3.)*

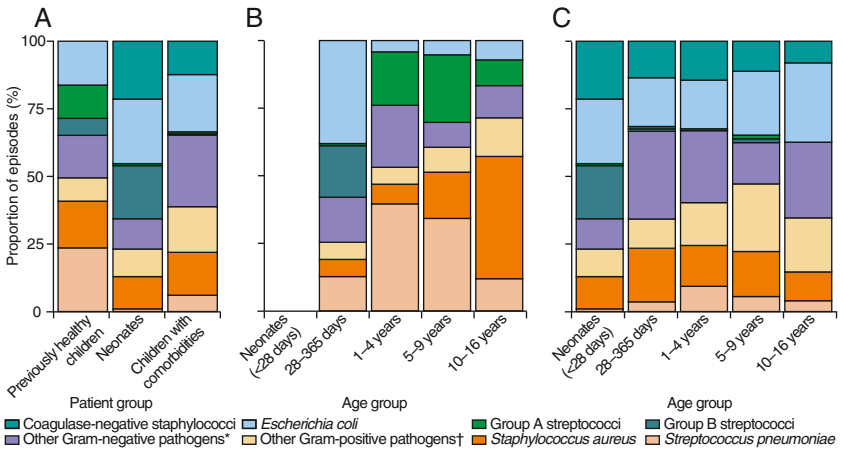

Fig. 221.2 Age distribution of pathogens causing blood culture–proven bacterial sepsis in children. Pathogens isolated in blood culture are shown for (A) the three patient groups together and separately for (B) previously healthy children ≥28 days old and (C) neonates and children with comorbidities ≥28 days old. **Pseudomonas aeruginosa, Klebsiella* spp., *Neisseria meningitidis, Haemophilus influenzae,* other gram-negative pathogens. †*Enterococcus* spp., viridans group streptococci, other gram-positive pathogens. *(From Agyeman PKA, Schlapbach LJ, Giannoni E, et al. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. Lancet Child Adolesc. 2017;1:124–133, Fig. 4.)*

examination is particularly important in young children <24 months old who have limited verbal skills to communicate localized pain. In older children the physical exam may proceed systematically from head to toe, but in younger children, who may be fearful of the exam, it is important to auscultate the heart and lungs first before proceeding to potentially painful or distressing aspects of the examination (e.g., inspection of ears or oropharynx). In addition to a careful evaluation of each body system, a complete examination should include an assessment of neck pain and mobility, which may be limited in children with **meningitis**. Additionally, the examiner should palpate carefully for the presence of **lymphadenopathy**, which may be present with infectious and oncologic causes of fever. Erythema and exudate of the tonsils with palatal petechiae suggest streptococcal pharyngitis. Erythema, bulging, and decreased mobility of the tympanic membrane are the cardinal signs of acute otitis media. Diffuse crackles and wheezes on auscultation of the lungs occur with acute viral bronchiolitis, whereas focal crackles or decreased breath sounds are more consistent with bacterial pneumonia. Focal tenderness in the right lower quadrant of the abdomen suggests **appendicitis**, and suprapubic tenderness may indicate UTI **(cystitis)**. Any focal bony tenderness may reflect a diagnosis of osteomyelitis, whereas erythema, swelling, and limitation of range of motion suggest a diagnosis of septic arthritis. Abnormal gait or pain with ambulation without focal findings may also reflect a bone or joint infection. A careful skin examination should also be performed. The presence of petechiae may suggest meningococcal or other invasive bacterial infection, whereas viral exanthems are typically associated with a blanching macular or maculopapular rash.

EVALUATION

Laboratory Testing

Laboratory testing is not routinely indicated in the well-appearing child without a focus of infection on examination. Urine testing should be considered based on the child's age, duration of fever, and risk factors for UTI (see Table 221.2). In general, the decision to perform laboratory testing should be guided by the overall appearance and vital signs of the child, the presence of specific symptoms or physical examination findings, and the child's age.

For children who are ill or appear toxic or who have vital sign abnormalities indicative of an invasive bacterial infection (tachycardia, hypotension), rapid laboratory evaluation should be performed. Testing may include a blood culture and possibly urine and cerebrospinal fluid (CSF) cultures, depending on the age of the child and the presence or absence of physical exam findings indicative of UTI or bacterial meningitis. Markers of inflammation, such as procalcitonin or C-reactive protein may also be considered. Complete blood counts (CBCs) identify leukocytosis or leukopenia, anemia, and thrombocytosis or thrombocytopenia. Children with infectious mononucleosis may have lymphocyte predominance and the presence of atypical lymphocytes. Children

who are immunosuppressed or who have a central venous catheter should also undergo diagnostic testing and receive prompt antimicrobial therapy, given their higher risk of invasive bacterial infection.

For well-appearing children with symptoms or signs indicative of a viral upper respiratory or GI infection, routine viral testing is not generally indicated. **Influenza** testing may be indicated within 48 hours of symptom onset in certain higher-risk populations, with immunosuppression, chronic respiratory or cardiac disease, sickle cell disease, hospitalization, and age <2 years influencing the decision to treat with an antiviral agent. Testing for **SARS-CoV-2** may be indicated based on local prevalence and symptoms (fever, cough, congestion, loss of taste or smell, shortness of breath, body aches, fatigue, headache, sore throat, nausea, vomiting, or diarrhea). Viral testing may also be useful with prolonged fever to identify a source of the fever and avoid extensive evaluation for inflammatory conditions such as Kawasaki disease or MIS-C.

Rapid strep testing of the oropharynx is indicated for children ≥3 years old with signs of streptococcal pharyngitis on examination. Although strep throat is uncommon in children <3 years old, this group should undergo rapid strep testing if they have signs of strep throat on exam and a household contact with streptococcal pharyngitis (see Chapter 229).

Febrile children 2 months to 2 years old with several of the risk factors for UTI listed in Table 221.2, particularly females and uncircumcised males, should undergo evaluation with urine dipstick, urine microscopy, and urine culture. Females and uncircumcised males 2-6 months old with high fever or fever that lasts ≥2 days may undergo urine testing even in the presence of respiratory tract infection, given the higher risk of UTI in this younger group (see Chapter 575).

Given the very low risk of occult bacteremia, routine performance of blood testing (e.g., CBC, blood culture) is not indicated in the vast majority of immunized children with fever. Unimmunized and underimmunized children <2 years old remain at higher risk of occult pneumococcal bacteremia, and CBC, blood culture, and/or inflammatory markers may be considered in this population in the absence of another source of infection.

Imaging

The presence of focal crackles or decreased breath sounds on auscultation in the febrile child is suggestive of **pneumonia**. Current guidelines recommend presumptive antibiotic treatment for pneumonia based on clinical grounds and reserve the use of chest radiography for children with hypoxemia or significant respiratory distress and for those who fail outpatient therapy. Chest radiography is indicated for hospitalized children to assess for complicated pneumonia, including **empyema**. The performance of other imaging should be dictated by physical exam findings. The presence of drooling and neck or throat pain in an infant or toddler may be suggestive of a retropharyngeal abscess, which is usually confirmed by imaging that may include a lateral radiograph of the soft tissue of the neck or computed tomography (CT) if clinical suspicion is high. Ultrasonography (US) may be performed to assess for **appendicitis** in children with fever and focal right lower quadrant pain or abdominal pain that is severe. However, definitive imaging, including CT or MRI, may be required if US is nondiagnostic or if clinical suspicion is high.

Table 221.2 Risk Factors for Urinary Tract Infection in Children

AMERICAN ACADEMY OF PEDIATRICS CLINICAL PRACTICE GUIDELINE* CHILDREN 2-24 MO OF AGE
Female Age <1 yr Temperature ≥39°C (102.2°F) Fever duration ≥2 days No obvious source of infection
Male *Uncircumcised males at higher risk* Temperature ≥39°C (102.2°F) Fever duration >1 day No obvious source of infection
UNIVERSITY OF PITTSBURGH UTICALC† CHILDREN 2-23 MO OF AGE
Age <12 mo Maximum temperature ≥39°C History of UTI Female or uncircumcised male Duration of fever ≥48 hr No other source of fever

*Adapted from Subcommittee on Urinary Tract Infection, et al. Urinary tract infection clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610.

†Adapted from Shaikh N, Hoberman A, Hum SW, et al. Development and validation of a calculator for estimating the probability of urinary tract infection in young febrile children. *JAMA Pediatr*. 2018;172(6):550–556 and UTICalc Version 3.0, University of Pittsburgh 2021, https://uticalc.pitt.edu/

MANAGEMENT

General Management Principles

Management should be guided by the presence of specific symptoms by history or signs on physical examination. Based on the child's age and duration of fever, management may also be guided by focused diagnostic testing, such a urinalysis and selective urine culture testing among young febrile children (Fig. 221.3 and see Table 221.2). Supportive care, including the use of antipyretics and adequate hydration, should be reviewed with the patient and caregiver for all children with fever. Children with viral infections generally require supportive care only, except for children at higher risk of severe or complicated disease with **influenza virus** (see Chapter 305) or SARS-CoV-2 (see Chapter 311). Antibiotics should

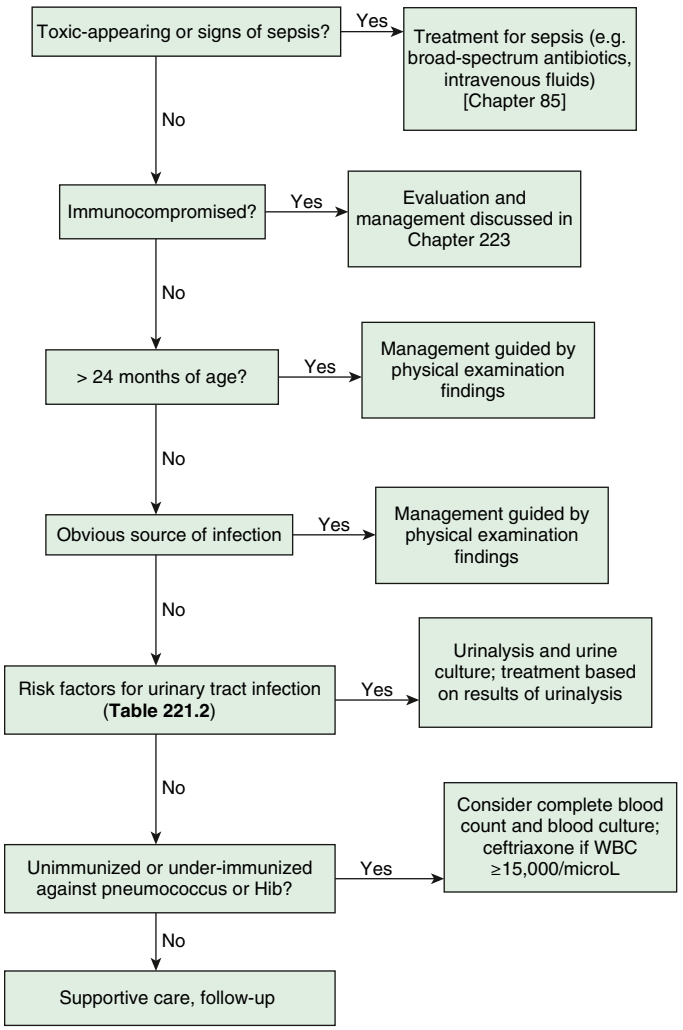

Fig. 221.3 Algorithm for evaluation and management of fever in infants and children >2 mo of age. Hib, *Haemophilus influenzae* type b; WBC, white blood cell count.

be reserved for children with evidence of bacterial infection on physical examination. A wait-and-see approach can be considered for children with acute **otitis media**, in whom a prescription for antibiotics can be provided to the family but instructions given to not fill the prescription unless severe or worsening symptoms develop (see Chapter 680). Oral antibiotics can be prescribed to young children with UTI, although children who cannot tolerate oral intake, are vomiting or dehydrated, or appear toxic require parenteral antibiotics and hospitalization.

Blood tests, including CBC and blood culture, should be considered to evaluate for occult **bacteremia** in the unimmunized child. One management strategy for these children is to administer a parenteral antibiotic (e.g., ceftriaxone) if leukocytosis (white blood cell count ≥15,000/μL), elevated absolute neutrophil count (≥10,000/μL), or elevated inflammatory markers (procalcitonin >0.5 ng/mL) are present while awaiting results of blood culture. Children who appear toxic or who have signs of either sepsis or bacterial meningitis require emergent treatment with parenteral antibiotics as well as adjunct therapies to support the child's hemodynamics (see Chapter 85).

Importantly, anticipatory guidance should be provided to all families of children with fever, including the criteria to return to care and the importance of fever control and adequate hydration.

Other Considerations

Children who are unimmunized or underimmunized are at higher risk of invasive bacterial infection, as are children who are immunocompromised. Management of fever in these children is described further in Chapter 223. Additionally, the approach to fever in the returning traveler should be focused on identifying commonly encountered infections based on the region of travel (see Chapter 218).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 222

Fever of Unknown Origin

Andrew P. Steenhoff

Fever of unknown origin **(FUO)** is a diagnostic dilemma for pediatricians because it is often difficult to distinguish clinically between benign and potentially life-threatening causes. Pediatricians face the important challenge of not missing the diagnosis of a serious illness or an easily treatable condition that can result in increased morbidity. Fortunately, FUO is usually an uncommon presentation of a common disease, with most of these common diseases being easily treatable.

The classification of FUO is best reserved for children with a temperature >38°C (100.4°F) documented by a healthcare provider and for which the cause could not be identified after at least 8 days of evaluation (Table 222.1). It is important to differentiate FUO from **fever without a source (FWS)**. FWS is fever where the source has not yet been identified and is differentiated from FUO by the duration of the fever. FWS can progress to FUO if no cause is elicited after 7 days of evaluation.

ETIOLOGY

The many causes of FUO in children are infectious, rheumatologic (connective tissue or autoimmune), autoinflammatory, oncologic, neurologic, genetic, factitious, and iatrogenic processes (Table 222.2). Although oncologic disorders should be seriously considered, most children with malignancies do not have fever alone. The possibility of **drug fever** should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hours, although certain drugs, such as iodides, are excreted for a prolonged period, with fever that can persist for as long as 1 month after drug withdrawal.

Most fevers of unknown origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease (e.g., juvenile idiopathic arthritis), but the definitive diagnosis can be established only after prolonged observation, because initially there are no associated or specific findings on physical examination, and all laboratory results are negative or normal.

In the United States the systemic infectious diseases most commonly implicated in children with FUO are bacterial enterocolitis, including salmonellosis, as well as tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases such as adenovirus infection, Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, *Angiostrongylus cantonensis* infection, and toxoplasmosis. Less common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat-bite fever. Acquired immunodeficiency syndrome (AIDS) alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 222.1).

Juvenile idiopathic arthritis (JIA) and **systemic lupus erythematosus** (SLE) are the connective tissue diseases most often associated with FUO. **Inflammatory bowel disease** (IBD) and **Kawasaki disease** are also frequently reported as causes of FUO. If **factitious fever** (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation of the patient, which can include electronic or video surveillance, is imperative. FUO lasting >6 months is uncommon in children and suggests granulomatous, autoinflammatory, or autoimmune disease. Repeat interval evaluation is required, including history, physical examination, laboratory evaluation, and imaging studies.

Historically, 90% of pediatric FUO cases in the United States had an identifiable cause: approximately 50% infectious, 10–20% collagen vascular, and 10% oncologic. Other studies had variable results: 20–44% infectious, 0–7% collagen vascular, 2–3% oncologic, and up to 67% undiagnosed. The reason for the paradoxical increase in undiagnosed cases of FUO ironically is likely caused by improved infectious and autoimmune diagnostic techniques. The advent of polymerase chain reaction (PCR), improved culture techniques, and better understanding of atypical viral and bacterial pathogenesis and autoimmune processes likely contribute to *earlier* diagnosis of these conditions and fewer children with these conditions *advancing* to the category of FUO. By contrast, causes of FUO remain primarily infectious in low and middle income settings where there is a higher infectious disease burden and advanced diagnostic techniques are more limited.

DIAGNOSIS

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation informed by the history or abnormalities on examination or initial screening tests (see Table 222.2). Occasionally the **fever pattern** helps make a diagnosis (Fig. 222.1). Nonetheless, most diseases causing an FUO do not have a typical fever pattern.

History

A detailed fever history should be obtained, including onset, frequency, duration, response or nonresponse to therapy, recurrence, and associated symptoms. Repetitive chills and temperature spikes are common in children with **septicemia** (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat-bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 years old often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or rarely, leukemia. Adolescent patients are more likely to have IBD, autoimmune processes, lymphoma, or tuberculosis in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic **animals** should be solicited. The incidence of **zoonotic infections** in the United States is

be reserved for children with evidence of bacterial infection on physical examination. A wait-and-see approach can be considered for children with acute **otitis media**, in whom a prescription for antibiotics can be provided to the family but instructions given to not fill the prescription unless severe or worsening symptoms develop (see Chapter 680). Oral antibiotics can be prescribed to young children with UTI, although children who cannot tolerate oral intake, are vomiting or dehydrated, or appear toxic require parenteral antibiotics and hospitalization.

Blood tests, including CBC and blood culture, should be considered to evaluate for occult **bacteremia** in the unimmunized child. One management strategy for these children is to administer a parenteral antibiotic (e.g., ceftriaxone) if leukocytosis (white blood cell count ≥15,000/μL), elevated absolute neutrophil count (≥10,000/μL), or elevated inflammatory markers (procalcitonin >0.5 ng/mL) are present while awaiting results of blood culture. Children who appear toxic or who have signs of either sepsis or bacterial meningitis require emergent treatment with parenteral antibiotics as well as adjunct therapies to support the child's hemodynamics (see Chapter 85).

Importantly, anticipatory guidance should be provided to all families of children with fever, including the criteria to return to care and the importance of fever control and adequate hydration.

Other Considerations

Children who are unimmunized or underimmunized are at higher risk of invasive bacterial infection, as are children who are immunocompromised. Management of fever in these children is described further in Chapter 223. Additionally, the approach to fever in the returning traveler should be focused on identifying commonly encountered infections based on the region of travel (see Chapter 218).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 222

Fever of Unknown Origin

Andrew P. Steenhoff

Fever of unknown origin **(FUO)** is a diagnostic dilemma for pediatricians because it is often difficult to distinguish clinically between benign and potentially life-threatening causes. Pediatricians face the important challenge of not missing the diagnosis of a serious illness or an easily treatable condition that can result in increased morbidity. Fortunately, FUO is usually an uncommon presentation of a common disease, with most of these common diseases being easily treatable.

The classification of FUO is best reserved for children with a temperature >38°C (100.4°F) documented by a healthcare provider and for which the cause could not be identified after at least 8 days of evaluation (Table 222.1). It is important to differentiate FUO from **fever without a source (FWS)**. FWS is fever where the source has not yet been identified and is differentiated from FUO by the duration of the fever. FWS can progress to FUO if no cause is elicited after 7 days of evaluation.

ETIOLOGY

The many causes of FUO in children are infectious, rheumatologic (connective tissue or autoimmune), autoinflammatory, oncologic, neurologic, genetic, factitious, and iatrogenic processes (Table 222.2). Although oncologic disorders should be seriously considered, most children with malignancies do not have fever alone. The possibility of **drug fever** should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hours, although certain drugs, such as iodides, are excreted for a prolonged period, with fever that can persist for as long as 1 month after drug withdrawal.

Most fevers of unknown origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease (e.g., juvenile idiopathic arthritis), but the definitive diagnosis can be established only after prolonged observation, because initially there are no associated or specific findings on physical examination, and all laboratory results are negative or normal.

In the United States the systemic infectious diseases most commonly implicated in children with FUO are bacterial enterocolitis, including salmonellosis, as well as tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases such as adenovirus infection, Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, *Angiostrongylus cantonensis* infection, and toxoplasmosis. Less common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat-bite fever. Acquired immunodeficiency syndrome (AIDS) alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 222.1).

Juvenile idiopathic arthritis (JIA) and **systemic lupus erythematosus** (SLE) are the connective tissue diseases most often associated with FUO. **Inflammatory bowel disease** (IBD) and **Kawasaki disease** are also frequently reported as causes of FUO. If **factitious fever** (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation of the patient, which can include electronic or video surveillance, is imperative. FUO lasting >6 months is uncommon in children and suggests granulomatous, autoinflammatory, or autoimmune disease. Repeat interval evaluation is required, including history, physical examination, laboratory evaluation, and imaging studies.

Historically, 90% of pediatric FUO cases in the United States had an identifiable cause: approximately 50% infectious, 10–20% collagen vascular, and 10% oncologic. Other studies had variable results: 20–44% infectious, 0–7% collagen vascular, 2–3% oncologic, and up to 67% undiagnosed. The reason for the paradoxical increase in undiagnosed cases of FUO ironically is likely caused by improved infectious and autoimmune diagnostic techniques. The advent of polymerase chain reaction (PCR), improved culture techniques, and better understanding of atypical viral and bacterial pathogenesis and autoimmune processes likely contribute to *earlier* diagnosis of these conditions and fewer children with these conditions *advancing* to the category of FUO. By contrast, causes of FUO remain primarily infectious in low and middle income settings where there is a higher infectious disease burden and advanced diagnostic techniques are more limited.

DIAGNOSIS

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation informed by the history or abnormalities on examination or initial screening tests (see Table 222.2). Occasionally the **fever pattern** helps make a diagnosis (Fig. 222.1). Nonetheless, most diseases causing an FUO do not have a typical fever pattern.

History

A detailed fever history should be obtained, including onset, frequency, duration, response or nonresponse to therapy, recurrence, and associated symptoms. Repetitive chills and temperature spikes are common in children with **septicemia** (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat-bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 years old often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or rarely, leukemia. Adolescent patients are more likely to have IBD, autoimmune processes, lymphoma, or tuberculosis in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic **animals** should be solicited. The incidence of **zoonotic infections** in the United States is

Table 222.1 Summary of Definitions and Major Features of Four Subtypes of Fever of Unknown Origin (FUO)

FEATURE	CLASSIC FUO	HEALTHCARE-ASSOCIATED FUO	IMMUNE-DEFICIENT FUO	HIV-RELATED FUO
Definition	>38°C (100.4°F), >3 wk, >2 visits, or 1 wk in hospital	≥38°C (100.4°F), >1 wk, not present or incubating on admission	≥38°C (100.4°F), >1 wk, negative cultures after 48 hr	≥38°C (100.4°F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Healthcare-associated infections, postoperative complications, drug fever	Majority caused by infections, but cause documented in only 40–60%	HIV itself, typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins	Wounds, drains, devices, sinuses, urine	Skinfolds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, Cytomegalovirus; CXR, chest radiograph; HIV, human immunodeficiency virus; IV, intravenous line.
Adapted from Mackowak PA, Durack DT. Fever of unknown origin. In: Mandell GL, Bennett, JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier; 2010: Table 51-1.

increasing, and these infections are often acquired from pets that are not overtly ill. Immunization of dogs against specific disorders such as **leptospirosis** can prevent canine disease but does not always prevent the animal from carrying and shedding leptospires, which may be transmitted to household contacts. A history of ingestion of rabbit or squirrel meat might provide a clue to the diagnosis of oropharyngeal, glandular, or typhoidal **tularemia**. A history of tick bite or travel to tick- or parasite-infested areas should be obtained.

Any history of **pica** should be elicited. Ingestion of dirt is a particularly important clue to infection with *Toxocara canis* (visceral larva migrans) or *Toxoplasma gondii* (toxoplasmosis).

A history of unusual dietary habits or travel as early as the birth of the child should be sought. Tuberculosis, malaria, histoplasmosis, and coccidioidomycosis can reemerge years after visiting or living in an endemic area. It is important to identify prophylactic immunizations and precautions taken by the patient against ingestion of contaminated water or food during foreign travel. Rocks, dirt, and artifacts from geographically distant regions that have been collected and brought into the home as souvenirs can serve as vectors of disease.

A **medication** history should be pursued rigorously. This history should elicit information about nonprescription preparations and topical agents, including eyedrops, that may be associated with atropine-induced fever.

The genetic background of a patient also is important. Descendants of the Ulster Scots may have FUO because they are afflicted with nephrogenic diabetes insipidus. **Familial dysautonomia** (Riley-Day syndrome), a disorder in which hyperthermia is recurrent, is more common among Jews than among other population groups. Ancestry from the Mediterranean region should suggest **familial Mediterranean fever**. Both familial Mediterranean fever and hyper-IgD syndrome are inherited as autosomal recessive disorders. Tumor necrosis factor receptor–associated periodic syndrome and Muckle-Wells syndrome are inherited as autosomal dominant traits.

Pseudo-FUO is defined as successive episodes of benign, self-limited infections with fever that the parents perceive as one prolonged fever episode. This needs to be carefully ruled out before undertaking an unnecessary evaluation. Usually, pseudo-FUO starts with a well-defined infection (frequently viral) that resolves but is followed by other febrile viral illnesses that may be less well defined. Diagnosis of pseudo-FUO usually requires a careful history, focusing on identifying afebrile periods between febrile episodes. If pseudo-FUO is suspected and the patient does not appear ill, keeping a *fever diary* can be helpful.

Table 222.2 Etiology of Fever of Unknown Origin (FUO) in Children

ABSCESSES
Brain
Hepatic
Intraabdominal*
Odontogenic (dental)
Pelvic*
Perinephric and renal
Psoas
Rectal
Subphrenic

BACTERIAL DISEASES
Actinomycosis
Bartonella henselae (cat-scratch disease)*
Brucellosis
Campylobacter
Chlamydia
Francisella tularensis (tularemia)
Fusobacterium (Lemierre syndrome)
Leptospirosis
Listeria monocytogenes (listeriosis)
Lymphogranuloma venereum
Meningococcemia (chronic)
Mycoplasma pneumoniae
Psittacosis
Rat-bite fever (*Streptobacillus moniliformis*; streptobacillary form of rat-bite fever)
Salmonella
Tuberculosis*
Whipple disease
Yersiniosis

LOCALIZED INFECTIONS
Bacterial endocarditis*
Cholangitis
Ludwig angina
Mastoiditis
Osteomyelitis*
Pericarditis
Pneumonia
Pyelonephritis*
Sinusitis
Spondylodiskitis

SPIROCHETES
Borrelia burgdorferi (Lyme disease)
Leptospirosis
Rat-bite fever (*Spirillum minus*; spirillary form of rat-bite fever)
Relapsing fever *(Borrelia recurrentis, Borrelia miyamotoi)*
Syphilis

FUNGAL DISEASES
Blastomycosis (extrapulmonary)
Coccidioidomycosis (disseminated)
Cryptococcosis
Histoplasmosis (disseminated)

RICKETTSIAE-LIKE ORGANISMS
Anaplasmosis
Ehrlichiosis
Q fever
Rocky Mountain spotted fever
Tick-borne typhus

VIRUSES
Arboviruses
Chikungunya
Cytomegalovirus*
Epstein-Barr virus*
Hantavirus
Hepatitis viruses
HIV
Human herpesviruses (HHV-6 and HHV-7)
Lymphocytic choriomeningitis
Respiratory viruses (especially, adenovirus and enteroviruses)*
Zika virus

PARASITIC DISEASES
Amebiasis
Babesiosis
Baylisascaris
Malaria
Naegleria
Toxoplasmosis
Trichinosis
Trypanosomiasis
Visceral larva migrans *(Toxocara)*

RHEUMATOLOGIC DISEASES
Autoimmune hepatitis
Behçet syndrome
Chronic noninfectious osteomyelitis (CNO)
Juvenile dermatomyositis
Juvenile idiopathic arthritis* ± macrophage activation syndrome
Rheumatic fever
Systemic lupus erythematosus*
Vasculitis syndromes (granulomatous, nongranulomatous)

HYPERSENSITIVITY DISEASES
Drug fever, including DRESS
Hypersensitivity pneumonitis
Hypersensitivity vasculitis/reactive arthritis*
Serum sickness
Weber-Christian disease

NEOPLASMS
Atrial myxoma
Cholesterol granuloma
Hodgkin lymphoma
Inflammatory pseudotumor
Langerhans cell histiocytosis
Leukemia
Lymphoma*
Pheochromocytoma
Neuroblastoma
Wilms tumor

GRANULOMATOUS DISEASES
Crohn disease
Granulomatous hepatitis
Polyangiitis with granulomatosis
Sarcoidosis

FAMILIAL AND HEREDITARY DISEASES
Anhidrotic ectodermal dysplasia
Autoimmune lymphoproliferative syndrome (ALPS)
Autonomic neuropathies
Fabry disease
Familial dysautonomia
Familial Hibernian fever
Familial Mediterranean fever and the many other autoinflammatory (periodic fever) diseases (see Chapter 204)
Hypertriglyceridemia
Ichthyosis
Sickle cell crisis
Spinal cord/brain injury

MISCELLANEOUS
Addison disease
Allergic alveolitis
Castleman disease
Cyclic neutropenia
Diabetes insipidus (non-nephrogenic and nephrogenic)
Erythema multiforme
Factitious fever
Hemophagocytic lymphohistiocytosis (HLH)
Hypereosinophilia syndromes
Hypothalamic-central fever
Infantile cortical hyperostosis
Inflammatory bowel disease*
Kawasaki disease*
Kikuchi-Fujimoto disease
Metal fume fever
Multisystem inflammatory syndrome in children (MIS-C)
Pancreatitis
Poisoning
Pulmonary embolism
Rosai-Dorfman disease
Thrombotic thrombocytopenia purpura
Thrombophlebitis
Thyrotoxicosis, thyroiditis

*Most common identified causes of FUO in children.
DRESS, Drug reaction with eosinophilia and systemic symptoms.
Modified from Huppler AR. Fever. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table. 52.9, pp. 980–981.

Physical Examination

A complete physical examination is essential to search for any clues to the underlying diagnosis, and often it is worthwhile to repeat a detailed examination on different days to detect signs that may have changed or been missed (Tables 222.3-222.5). The child's general appearance, including **sweating** during fever, should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration caused by vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine.

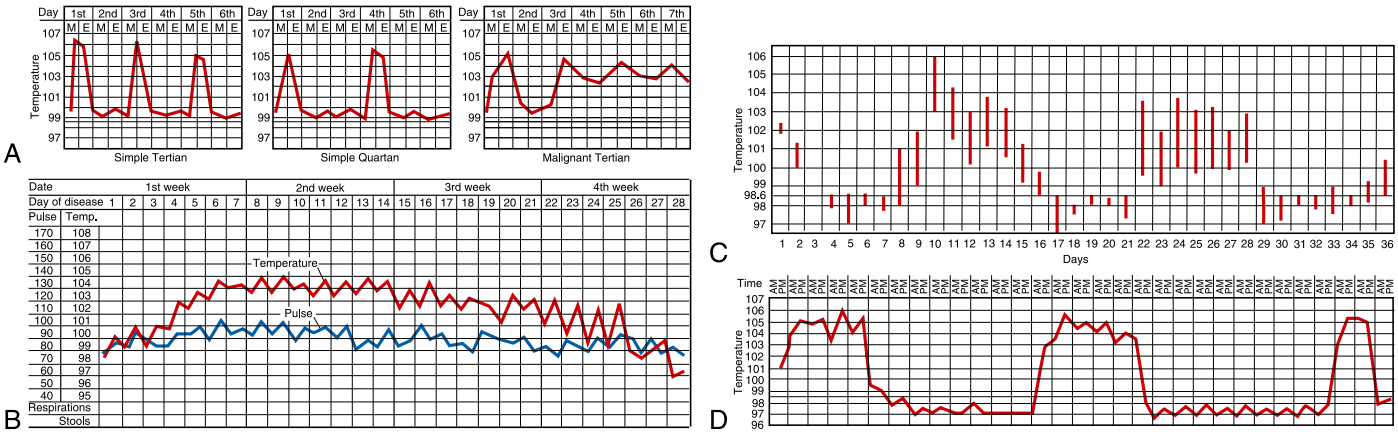

Fig. 222.1 Distinctive fever patterns. **A,** Malaria. **B,** Typhoid fever (demonstrating relative bradycardia). **C,** Hodgkin disease (Pel-Ebstein fever pattern). **D,** Borreliosis (relapsing fever pattern). *(From Woodward TE. The fever pattern as a clinical diagnostic aid. In Mackowiak PA, ed. Fever: Basic Mechanisms and Management, 2nd ed. Philadelphia: Lippincott-Raven; 1997:215–236.)*

Table 222.3 Subtle Physical Findings with Special Significance in Patients with Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis, SLE, IBD, Behçet syndrome, periodic fever syndromes
	Tender tooth	Periapical abscess, sinus referred pain
	Loose teeth	Langerhans cell histiocytosis, leukemia
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth spots	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
	Relative bradycardia	Typhoid fever, malaria, leptospirosis, psittacosis, central fever, drug fever
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
	Audible abdominal aortic or renal artery bruit	Large vessel vasculitis such as Takayasu arteritis
	Costovertebral tenderness	Chronic pyelonephritis, perinephric abscess
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa, cancer
	Epididymal nodule	Disseminated granulomatosis
Spine	Spinal tenderness	Vertebral osteomyelitis
	Paraspinal tenderness	Paraspinal collection
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Upper or lower extremities	Pseudoparesis	Syphilitic bone disease
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.
Adapted from Mackowak PA, Durack DT. Fever of unknown origin. In: Mandell GL, Bennett, JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier; 2010: Table 51-8.

Table 222.4 Examples of Potential Diagnostic Clues to Infections Presenting as Fever of Unknown Origin

ETIOLOGY	HISTORICAL CLUES	PHYSICAL CLUES
Anaplasmosis	Transmitted by bite of *Ixodes* tick in association with outdoor activity in northern-central and eastern United States	Fever, headache, arthralgia, myalgia, pneumonitis, thrombocytopenia, lymphopenia, elevated liver enzymes
Babesiosis	Transmitted by bite of *Ixodes* tick in association with outdoor activity in northeastern United States	Arthralgias, myalgias, relative bradycardia, hepatosplenomegaly, anemia, thrombocytopenia, elevated liver enzymes
Bartonellosis	Recent travel to Andes Mountains (Oroya fever; *Bartonella bacilliformis*), association with homelessness in urban settings *(Bartonella quintana)* or scratch of infected kitten or feral cat *(Bartonella henselae)*	Conjunctivitis, retroorbital pain, anterior tibial bone pain, macular rash, nodular plaque lesions, regional lymphadenopathy
Blastomycosis	Contact with soil adjacent to Mississippi and Ohio River valleys, Saint Lawrence River in New York and Canada, and North American Great Lakes or exposure to infected dogs	Arthritis, atypical pneumonia, pulmonary nodules, and/or fulminant adult respiratory distress syndrome; verrucous, nodular, or ulcerative skin lesions; prostatitis
Brucellosis	Associated with contact or consumption of products from infected goats, pigs, camels, yaks, buffalo, or cows and with abattoir work	Arthralgias, hepatosplenomegaly, suppurative musculoskeletal lesions, sacroiliitis, spondylitis, uveitis, hepatitis, pancytopenia
Coccidioidomycosis	Exposure to soil or dust in southwestern United States	Arthralgias, pneumonia, pulmonary cavities, pulmonary nodules, erythema multiforme, erythema nodosum
Ehrlichiosis	Transmitted by bite of *Amblyomma, Dermacentor,* or *Ixodes* tick in association with outdoor activity in midwestern and southeastern United States	Pneumonitis, hepatitis, thrombocytopenia, lymphopenia
Enteric fever (*Salmonella enterica* serovar Typhi)	Recent travel to a low- or middle-income country (LMIC) with consumption of potentially contaminated food or water	Headache, arthritis, abdominal pain, relative bradycardia, hepatosplenomegaly, leukopenia
Histoplasmosis	Exposure to bat or blackbird excreta in roosts, chicken houses, or caves in region surrounding Ohio and Mississippi River valleys	Headache, pneumonia, pulmonary cavities, mucosal ulcers, adenopathy, erythema nodosum, erythema multiforme, hepatitis, anemia, leukopenia, thrombocytopenia
Leptospirosis	Occupational exposure among workers in sewers, rice and sugarcane fields, and abattoirs; recreational water sports and exposure to contaminated waters or infected dogs	Bitemporal and frontal headache, calf and lumbar muscle tenderness, conjunctival suffusion, hepatic and renal failure, hemorrhagic pneumonitis
Leishmaniasis (visceral disease)	Associated with recent travel to areas endemic for sand flies	Hepatosplenomegaly, lymphadenopathy, and hyperpigmentation of face, hand, foot, and abdominal skin (kala-azar)
Malaria	Recent travel to endemic areas in Asia, Africa, and Central/South America	Fever, headaches, nausea, emesis, diarrhea, hepatomegaly, splenomegaly, anemia
Psittacosis *(Chlamydia psittaci)*	Associated with contact with birds, especially psittacine birds	Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions; erythema multiforme, marginatum, and nodosum
Q fever *(Coxiella burnetii)*	Associated with farm, veterinary, or abattoir work; consumption of unpasteurized milk; contact with infected sheep, goats, or cattle	Atypical pneumonia, hepatitis, hepatomegaly, relative bradycardia, splenomegaly
Rat-bite fever *(Streptobacillus moniliformis)*	Recent bite or scratch by rat, mouse, or squirrel; ingestion of food or water contaminated by rat excrement	Headaches, myalgias, polyarthritis, and maculopapular, morbilliform, petechial, vesicular, or pustular rash over the palms, soles, and extremities
Relapsing fever *(Borrelia recurrentis)*	Associated with poverty, crowding, and poor sanitation (louse-borne) or with camping (tick-borne), particularly in the Grand Canyon	High fever with rigors, headache, delirium, arthralgias, myalgias, and hepatosplenomegaly
Rocky Mountain spotted fever	Associated with outdoor activity in the South Atlantic or southeastern United States and exposure to *Dermacentor* tick bites	Headache, petechial rash involving the extremities, palms, and soles
Tuberculosis	Recent contact with tuberculosis; recent immigration from endemic country; work or residence in homeless shelters, correctional facilities, or healthcare facilities	Night sweats, weight loss, atypical pneumonia; on chest x-ray, hilar adenopathy is most common in younger children, with cavitary pulmonary lesions seen in youth.
Tularemia	Associated with bites by *Amblyomma* or *Dermacentor* ticks, deer flies, and mosquitoes or direct contact with tissues of infected animals such as rabbits, squirrels, deer, raccoons, cattle, sheep, and swine	Ulcerated skin lesions at a bite site, pneumonia, relative bradycardia, lymphadenopathy, conjunctivitis

Continued

Table 222.4 Examples of Potential Diagnostic Clues to Infections Presenting as Fever of Unknown Origin—cont'd

ETIOLOGY	HISTORICAL CLUES	PHYSICAL CLUES
Whipple disease (*Tropheryma whipplei*)	Potential association with exposure to sewage	Chronic diarrhea, arthralgia, weight loss, malabsorption, malnutrition

Adapted from Wright WF, Mackowiak PA. Fever of unknown origin. In: Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 56-9.

Table 222.5 Discriminating Features of Noninfectious Causes of Fever of Unknown Origin

CAUSES OF FEVER	EXPOSURE OR CONDITION	FEATURES	DIAGNOSTIC METHOD
Kikuchi-Fujimoto disease		Regional or generalized lymphadenopathy; elevated inflammatory markers	Biopsy or histology
Inflammatory pseudotumor	History of nonspecific illness (presumed host-controlled infection)	Insidious; malaise, weight loss, vague abdominal pain or tenderness; anemia; elevated inflammatory markers	Abdominal CT; biopsy or histology
Kawasaki disease (incomplete)		Asynchronous or incomplete features of Kawasaki disease; elevated inflammatory markers; thrombocytosis	Clinical constellation; echocardiogram
Juvenile idiopathic arthritis	Familial, sporadic	Hepatosplenomegaly, lymphadenopathy, exanthem; anemia, elevated inflammatory markers	Clinical constellation
Systemic lupus erythematosus	Familial, sporadic	Malaise, weight loss; then multisystem involvement (kidneys, joints, skin)	Serum antinuclear antibody, anti–double-stranded DNA, anti–smooth muscle antibody
Hemophagocytic lymphohistiocytosis	Familial, virus, or rheumatologic (macrophage activation syndrome) induced	Severe, rapidly progressive illness; hepatomegaly, lymphadenopathy, exanthem; cytopenias; extreme elevations of inflammatory markers	Ferritin, triglyceride levels, gene panel, other diagnostic criteria; erythrophagocytosis by macrophages; natural killer cell, $CD8^+$ T-lymphocyte dysfunction
Vasculitis syndromes	Familial, sporadic	Specific hallmarks (renal, neurologic, stomatitis or perianal ulcers, uveitis, pulmonary)	Clinical constellation; specific autoantibodies; biopsy or histology
Sarcoidosis	Geography; race	Fatigue, weight loss, leg pain; anemia; elevated inflammatory markers; mediastinal lymphadenopathy; uveitis	Clinical constellation; biopsy or histology; soluble interleukin-2 receptor level
Inflammatory bowel disease	Familial; sporadic	Linear growth failure, subtle gastrointestinal symptoms or abdominal tenderness; perirectal skin tag; iron-deficiency anemia; elevated inflammatory markers	Abdominal CT; barium study
Lymphoreticular malignancy		Weight loss, fatigue; nonarticular bone pain; lymphadenopathy; cytopenias	Bone marrow or tissue biopsy
Drug hypersensitivity	Prescription or nonprescription drug exposure	Preserved sense of well-being; exanthems; eosinophilia; organ dysfunction (renal, cardiac, pulmonary)	Clinical constellation; withdrawal of drug
Factitious fever or Munchausen syndrome by proxy	Predisposing parent-patient dynamic	Discordant temperature and vital signs; discordant parent-measured temperature and urine temperature; normal inflammatory markers	Clinical constellation; verification of temperature in medical setting
Hypothalamic dysfunction, diabetes insipidus, dysautonomia, or absent corpus callosum	Underlying condition; genetic syndrome; anatomic abnormality	Normal inflammatory markers; hypernatremia; no response to nonsteroidal antiinflammatory drugs	Clinical constellation; laboratory tests and imaging

Modified from Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases*, 5th ed. Philadelphia: Elsevier; 2018: Table 15.2, p. 121.

The general activity of the patient and the presence or absence of rashes should also be noted.

A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral **conjunctivitis** in a febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, or cat-scratch disease. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki disease or leptospirosis. Petechial conjunctival **hemorrhages** suggest infective endocarditis. Uveitis suggests sarcoidosis, JIA, SLE, Kawasaki disease,

Behçet disease, and vasculitis. **Chorioretinitis** suggests CMV, toxoplasmosis, and syphilis. **Proptosis** suggests an orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, granulomatosis with polyangiitis, or orbital pseudotumor.

The ophthalmoscope should also be used to examine nail-fold capillary abnormalities that are associated with connective tissue diseases such as juvenile dermatomyositis and systemic scleroderma. Immersion oil or lubricating jelly is placed on the skin adjacent to the nailbed, and the capillary pattern is observed with the ophthalmoscope set on +40.

FUO is sometimes caused by **hypothalamic dysfunction**. A clue to this disorder is failure of pupillary constriction because of absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Fever resulting from familial dysautonomia may be suggested by lack of tears, an absent corneal reflex, or a smooth tongue with absence of fungiform papillae. Tenderness to tapping over the sinuses or the upper teeth suggests sinusitis. Recurrent oral candidiasis may be a clue to various disorders of the immune system, especially involving the T lymphocytes. Hyperactive deep tendon reflexes can suggest thyrotoxicosis as the cause of FUO.

Hyperemia of the pharynx, with or without exudate, suggests streptococcal infection, EBV infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki disease, gonococcal infection, or leptospirosis.

The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiaphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki disease, or *Mycoplasma* or arboviral infection.

Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained; occult blood loss can suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

Laboratory Evaluation

The laboratory evaluation of the child with FUO and whether inpatient or outpatient are determined on a case-by-case basis. Hospitalization may be required for laboratory or imaging studies that are unavailable or impractical in an ambulatory setting, for more careful observation, or for temporary relief of parental anxiety. The **tempo** of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed in a systematic manner and can be carried out in an outpatient setting. If there are no clues in the patient's history or on physical examination that suggest a specific infection or area of suspicion, it is unlikely that diagnostic studies will be helpful. In this common scenario, continued surveillance and repeated reevaluations of the child should be employed to detect any new clinical findings.

Although ordering a large number of diagnostic tests in every child with FUO according to a predetermined list is discouraged, certain studies should be considered in the evaluation. A complete blood cell count (CBC) with a white blood cell (WBC) differential and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count (ANC) of <5,000/μL is evidence against indolent bacterial infection other than typhoid fever. Conversely, in patients with a polymorphonuclear leukocyte (PMN) count of >10,000/μL or a nonsegmented PMN count of >500/μL, a severe bacterial infection is highly likely. Direct examination of the blood smear with Giemsa or Wright stain can reveal organisms of malaria, trypanosomiasis, babesiosis, or relapsing fever.

An erythrocyte sedimentation rate (ESR) >30 mm/hr indicates inflammation and the need for further evaluation for infectious, autoimmune, autoinflammatory, or malignant diseases, tuberculosis, Kawasaki disease, or autoimmune disease. A low ESR does not eliminate the possibility of infection or JIA. C-reactive protein (CRP) is another acute-phase reactant that becomes elevated and returns to normal more rapidly than the ESR. Experts recommend checking either ESR or CRP, because there is no evidence that measuring both in the same patient with FUO is clinically useful.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should be obtained only if there are specific reasons to suspect anaerobic infection. Multiple or repeated blood cultures may be required to detect bacteremia associated with infective endocarditis, osteomyelitis, or deep-seated abscesses. Polymicrobial bacteremia suggests factitious or self-induced infection or gastrointestinal (GI) pathology. The isolation of leptospires, *Francisella,* or *Yersinia* requires selective media or specific conditions not routinely used. Therefore it is important to inform the laboratory what organisms are suspected in a particular case. Urine culture should be obtained in all cases. Next-generation sequencing of tissue or whole blood or plasma may identify undetected or unculturable bacteria, fungi, or viruses.

Tuberculin skin testing (TST) should be performed with intradermal placement of 5 units of purified protein derivative that has been kept appropriately refrigerated. In children >2 years old, it is reasonable to test for tuberculosis using an interferon-γ release assay (IGRA).

Imaging studies of the chest, sinuses, mastoids, or GI tract may be indicated by specific historical or physical findings. Radiographic evaluation of the GI tract for IBD may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow can reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic infection; histiocytosis; hemophagocytosis; or storage diseases. If a bone marrow aspirate is performed, cultures for bacteria, mycobacteria, and fungi should be obtained.

Serologic tests can aid in the diagnosis of EBV infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, cat-scratch disease, Lyme disease, rickettsial disease, and on some occasions JIA. The clinician should be aware that the reliability and the sensitivity and specificity of these tests vary; for example, serologic tests for Lyme disease outside of reference laboratories have been generally unreliable.

MRI scans may be helpful in detecting abdominal abscesses and osteomyelitis, especially if the focus cannot be localized to a specific limb or multifocal disease is suspected. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) combined with MRI or CT is a helpful imaging modality and contributed to an ultimate diagnosis in 48% of children in a Dutch study. Echocardiograms can demonstrate vegetation on the leaflets of heart valves, suggesting infective endocarditis. Ultrasonography (US) can identify intraabdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total-body CT or MRI (both with contrast) is usually the first imaging study of choice; both permit detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intraabdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT- or US-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. MRI is particularly useful for detecting osteomyelitis or myositis if there is concern about a specific limb. Diagnostic imaging can be helpful in confirming or evaluating a suspected diagnosis. With CT scans, however, the child is exposed to large amounts of radiation. PET-CT or MRI may help localize an occult tumor.

Biopsy is occasionally helpful in establishing a diagnosis of FUO. Bronchoscopy, laparoscopy, mediastinoscopy, and GI endoscopy can provide direct visualization and biopsy material when organ-specific manifestations are present. When employing any of the more invasive testing procedures, the risk/benefit ratio for the patient must always be considered before proceeding further. A diagnostic approach to an FUO is noted in Figure 222.2.

MANAGEMENT

The ultimate treatment of FUO is tailored to the underlying diagnosis. Fever and infection in children are not synonymous, and **antimicrobial agents** should only be used when there is evidence of infection, with avoidance of empirical trials of medication. An exception may be the use of antituberculous treatment in critically ill children with

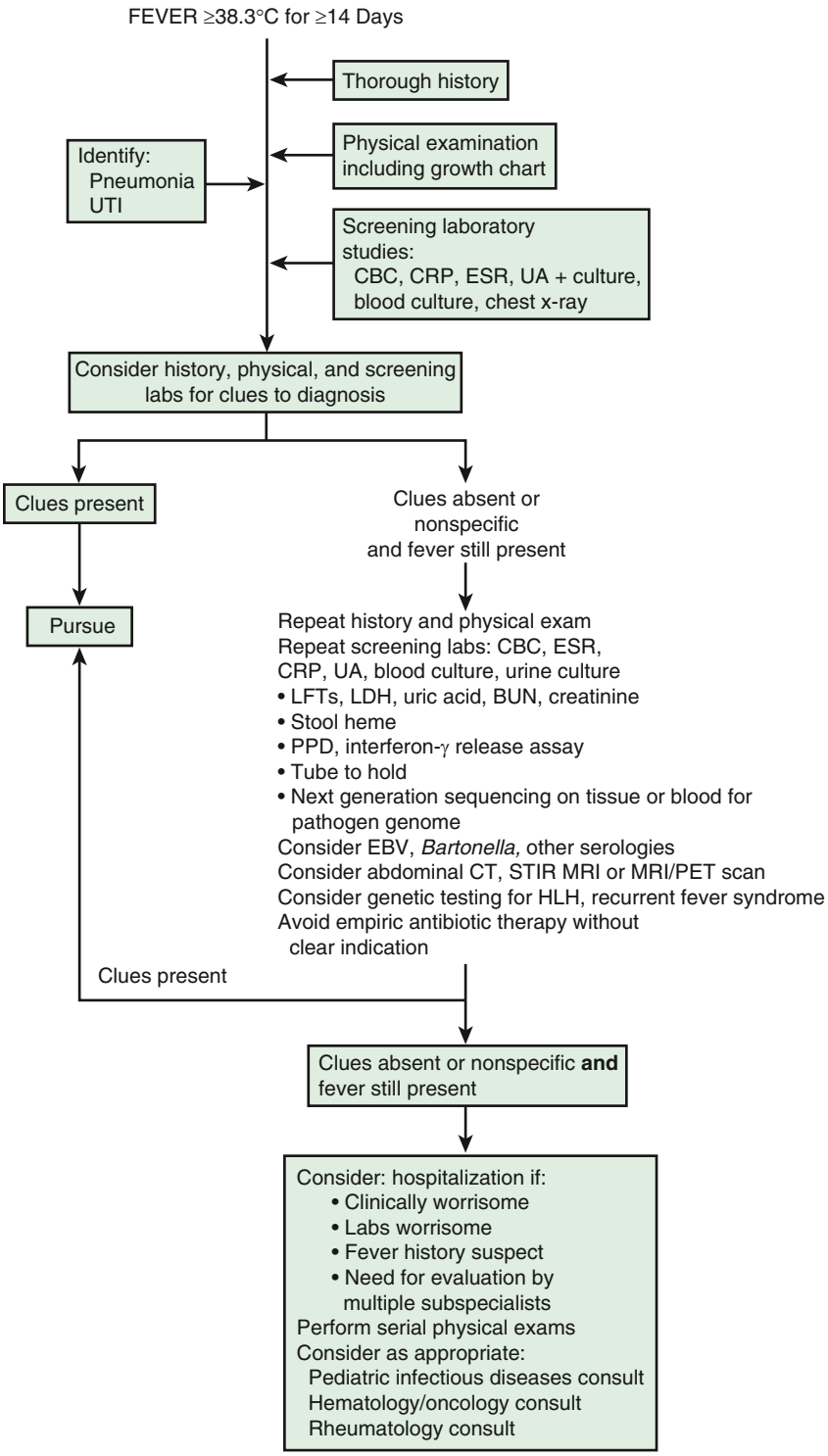

Fig. 222.2 Algorithmic approach to the evaluation of fever of unknown origin (FUO). EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; LFT, liver function test; PPD, purified protein derivative; STIR, short tau inversion recovery rapid MRI; UTI, urinary tract infection. *(Modified from Huppler AR. Fever. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023, Fig. 52.2, p. 982.)*

suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, or osteomyelitis. After a complete evaluation, **antipyretics** may be indicated to control fever associated with adverse symptoms.

PROGNOSIS

Children with FUO have a better prognosis than adults. The outcome in a child depends on the primary disease process. In many cases, no diagnosis can be established, and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear even after thorough evaluation.

In a series of 69 patients referred for "prolonged" unexplained fever, 10 were not actually having fever, and 11 had diagnoses that were readily apparent at the initial visit. The remaining 48 were classified as having FUO. The median duration of reported fever for these patients was 30 days. Fifteen received a diagnosis, and 10 (67%) had confirmed infections: acute EBV or CMV infection ($n = 5$; with 1 patient developing hemophagocytic lymphohistiocytosis), cat-scratch disease (3), and histoplasmosis (2). The other 5 patients had inflammatory conditions (systemic JIA, 2; IBD, 1), central fever (1), or malignancy (acute lymphoblastic leukemia, 1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 223

Infections in Immunocompromised Persons

Marian G. Michaels, Hey Jin Chong, and Michael Green

Infection develops when the host immune system fails to protect adequately against potential pathogens (see also Chapters 165, 166, and 180). For individuals with an intact immune system, infection occurs in the setting of naïveté to the microbe and absence of or inadequate preexisting microbe-specific immunity, or when protective barriers of the body such as the skin have been breached. Healthy children are able to meet the challenge of most infectious agents with an immunologic armamentarium capable of preventing significant disease. Once an infection begins to develop, an array of immune responses is set into action to control the disease and prevent it from reappearing. In contrast, immunocompromised children might not have this same capability. Depending on the level and type of immune defect, the affected child might not be able to contain the pathogen or develop an appropriate immune response to prevent recurrence.

Primary immunodeficiencies are compromised states that result from genetic defects affecting one or more arms of the immune system. **Acquired**, or **secondary**, **immunodeficiencies** may result from infection (e.g., infection with **HIV**), from malignancy, or as a consequence of immunomodulating or immunosuppressing medications. The latter include medications that affect T cells (corticosteroids, calcineurin inhibitors, tumor necrosis factor [TNF] inhibitors, chemotherapy), neutrophils (myelosuppressive agents, idiosyncratic or immune-mediated neutropenia), specific immunoregulatory cells (TNF blockers, interleukin-2 inhibitors), or all immune cells (chemotherapy). Perturbations of the mucosal and skin barriers or the normal microbial flora can also be characterized as secondary immunodeficiencies, predisposing the host to infections, if only temporarily.

The pathogens causing infections among *immunocompetent* hosts are also responsible for infections among children with *immunodeficiencies*. In addition, less virulent or opportunistic organisms, including normal skin flora, commensal bacteria of the oropharynx or gastrointestinal (GI) tract, environmental fungi, and common community viruses of low-level pathogenicity, can cause severe, life-threatening illnesses in immunocompromised patients (Table 223.1). Close communication with the diagnostic laboratory is critical to ensure that the laboratory does not disregard normal flora and organisms normally considered contaminants as being unimportant.

Table 223.1 Most Common Causes of Infections in Immunocompromised Children

BACTERIA, AEROBIC
Acinetobacter
Bacillus
Burkholderia cepacia
Citrobacter
Corynebacterium
Enterobacter spp.
Enterococcus faecalis
Enterococcus faecium
Escherichia coli
Klebsiella spp.
Listeria monocytogenes
Mycobacterium spp.
Neisseria meningitidis
Nocardia spp.
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus, coagulase-negative
Streptococcus pneumoniae
Streptococcus, viridans group
BACTERIA, ANAEROBIC
Bacillus
Clostridium
Fusobacterium
Peptococcus
Peptostreptococcus
Propionibacterium
Veillonella
FUNGI
Aspergillus
Candida albicans
Other *Candida* spp.
Cryptococcus neoformans
Fusarium spp.
Pneumocystis jirovecii
Zygomycoses *(Mucor, Rhizopus, Rhizomucor)*
VIRUSES
Adenoviruses
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Human herpesvirus 6
Polyomavirus (BK)
Respiratory and enteric community-acquired viruses
Varicella-zoster virus
PROTOZOA
Cryptosporidium parvum
Giardia lamblia
Toxoplasma gondii

223.1 Infections Occurring with Primary Immunodeficiencies

Marian G. Michaels, Hey Jin Chong, and Michael Green

Currently, more than 450 genes involving inborn errors of immunity have been identified, accounting for a wide array of diseases presenting with susceptibility to infection, allergy, autoimmunity, and autoinflammation, as well as malignancy (see Chapters 165 and 166).

ABNORMALITIES OF THE PHAGOCYTIC SYSTEM

Children with abnormalities of the phagocytic and neutrophil system have problems with bacteria and environmental fungi. Disease manifests as recurrent infections of the skin, mucous membranes, lungs, liver, and bones. Dysfunction of this arm of the immune system can be a result of inadequate numbers, abnormal movement properties, or aberrant function of neutrophils (see Chapter 168).

Neutropenia is defined as an absolute neutrophil count (ANC) of <1,000 cells/mm^3 and can be associated with significant risk for developing severe bacterial and fungal disease, particularly when prolonged or when the ANC is <500 cells/mm^3. Although acquired neutropenia secondary to bone marrow suppression from a virus or medication is common, practitioners should be cognizant of genetic causes of neutropenia. **Primary congenital neutropenia** most often manifests during the first year of life with cellulitis, perirectal abscesses, or stomatitis from *Staphylococcus aureus* or *Pseudomonas aeruginosa.* Episodes of severe disease, including bacteremia or meningitis, are also possible. Bone marrow evaluation shows a failure of maturation of myeloid precursors. Many of the neutropenic syndromes respond to colony-stimulating factor. Cyclic neutropenia can be associated with autosomal dominant inheritance or de novo sporadic gene variations

and manifests as fixed cycles of severe neutropenia between periods of normal granulocyte numbers. Often the ANC has normalized by the time the patient presents with symptoms, thus hampering the diagnosis. The cycles classically occur every 21 days (range: 14-36 days), with neutropenia lasting 3-6 days. Most often the disease is characterized by recurrent aphthous ulcers and stomatitis during the periods of neutropenia. However, life-threatening necrotizing myositis or cellulitis and systemic disease can occur, especially with *Clostridium septicum* or *Clostridium perfringens*.

Leukocyte adhesion deficiencies (LADs) are caused by defects of neutrophil aggregation and attachment to endothelial surfaces, rendering them unable to enter sites of infection (see Chapter 168). In the most severe form, there is a total absence of CD18, seen in LAD type 1, but genetic defects in fucose metabolism (LAD type 2) and FERMT3 (LAD type 3) have also been described. Generally, children with LAD have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract beginning early in life. Ecthyma gangrenosum also occurs. Because the defect involves leukocyte migration and adherence, the ANC in the peripheral blood is usually *extremely elevated,* but a key hallmark of LAD is that pus is not found at the site of infection. The mainstay of treatment is aggressive antibiotic use, with curative therapy being hematopoietic stem cell transplantation (HSCT).

Chronic granulomatous disease (CGD) is an inherited neutrophil dysfunction syndrome, which can be either X-linked or autosomal recessive, although spontaneous genetic changes can also occur (see Chapter 170). Neutrophils and other myeloid cells have defects in their nicotinamide-adenine dinucleotide phosphate oxidase function, decreasing superoxide production and thereby impairing intracellular killing. Accordingly, microbes that destroy their own hydrogen peroxide *(S. aureus, Serratia marcescens, Burkholderia cepacia, Nocardia* spp., *Aspergillus)* cause recurrent infections in these children. Less common but considered pathognomonic are *Granulibacter bethesdensis, Francisella philomiragia, Chromobacterium violaceum,* and *Paecilomyces* infections. Infections have a predilection to involve the lungs, liver, and bone. **Mulch pneumonitis** can be seen in patients with known CGD but also can be a unique presenting feature in adults with autosomal recessive CGD. Mulch pneumonitis can resemble hypersensitivity pneumonitis, and bronchoscopy may yield *Aspergillus* but often may not identify a clear organism. Treatment with antifungals and corticosteroids for the inflammation is recommended. *S. aureus* abscesses can occur in the liver despite prophylaxis. In addition, these children can present with recurrent abscesses affecting the skin, perirectal region, or lymph nodes. Sepsis can occur but is more common with certain gram-negative organisms such as *C. violaceum* and *F. philomiragia*.

Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), recombinant human interferon-γ, and oral antifungal agents with activity against *Aspergillus* spp., such as itraconazole or newer azoles, substantially reduces the incidence of severe infections. Patients with life-threatening infections are also reported to benefit from aggressive treatment with white blood cell transfusions along with antimicrobial agents directed against the specific pathogen. In addition, HSCT can be curative, and gene therapy trials are also a consideration. It is important to remember that patients with CGD do not make pus, and thus drainage alone for liver abscesses is not effective. Instead, patients should be treated with intravenous (IV) antibiotics as well as IV corticosteroids, with surgical resection considered if these measures fail.

DEFECTIVE SPLENIC FUNCTION, OPSONIZATION, OR COMPLEMENT ACTIVITY

Children who have congenital asplenia or splenic dysfunction associated with polysplenia or hemoglobinopathies, such as sickle cell disease, as well as those who have undergone splenectomy are at risk for serious infections from encapsulated bacteria and blood-borne protozoa such as *Plasmodium* and *Babesia.* Prophylaxis against bacterial infection with penicillin or amoxicillin should be considered for these patients, particularly children <5 years of age. The most common causative bacterial organisms include *Staphylococcus pneumoniae, Haemophilus influenzae* type b (Hib), and *Salmonella,* which can cause sepsis, pneumonia, meningitis, and osteomyelitis. Defects in the early complement components, particularly C2 and C3, may also be associated with severe infection from these bacteria. **Terminal complement defects** (C5, C6, C7, C8, and C9) are associated with recurrent infections with *Neisseria.* Patients with complement deficiency also have an increased incidence of autoimmune disorders. Vaccines for *S. pneumoniae,* Hib, and *N. meningitidis* should be administered to all children with abnormalities in opsonization or complement pathways (see Chapters 173 and 174).

B-CELL DEFECTS (HUMORAL IMMUNODEFICIENCIES)

Antibody deficiencies account for the majority of primary immunodeficiencies among humans (see Chapters 165 and 166). Patients with defects in the B-cell arm of the immune system fail to develop appropriate antibody responses, with abnormalities that range from complete **agammaglobulinemia** to isolated failure to produce antibody against a specific antigen or organism. Complete antibody deficiencies found in children with **X-linked agammaglobulinemia (XLA)** or other rarer autosomal recessive **agammaglobulinemia** predispose to infections with encapsulated organisms such as *S. pneumoniae* and Hib. Other bacteria can also be problematic in these children (see Table 223.1). Patients with XLA can also have neutropenia, with one case series showing 12 of 13 patients with XLA having neutropenia as part of the initial presentation. Because of the neutropenia, patients with XLA can present with *Pseudomonas* septicemia. Viral infections can also occur, with rotavirus leading to chronic diarrhea. Enteroviruses can disseminate and cause a chronic meningoencephalitis syndrome in these patients. Paralytic polio can develop after immunization with live polio vaccine. Protozoan infections such as giardiasis can be severe and persistent.

Children with agammaglobulinemia are usually asymptomatic until 5-6 months of age, when maternally derived antibody levels begin to wane. Around 6 months of age these children begin to develop recurrent episodes of otitis media, bronchitis, pneumonia, bacteremia, and meningitis. Many of these infections respond quickly to antibiotics, delaying the recognition of antibody deficiency, with studies showing some patients diagnosed in their teens. Children with B-cell defects can develop bronchiectasis over time after chronic or recurrent pulmonary infections and require lifelong IgG replacement therapy. Careful physical examination identifies lack of tonsils in these children, and lymphocyte subsets should confirm the lack of circulating B cells.

Selective IgA deficiency is the most common antibody deficiency and leads to a lack of production of secretory antibody at the mucosal membranes (see Chapter 166). Even though most patients have no increased risk for infections, some have mild to moderate disease at sites of mucosal barriers. Accordingly, recurrent sinopulmonary infection and GI disease are the major clinical manifestations. These patients also have an increased incidence of allergies and autoimmune disorders compared with the normal population.

Common variable immunodeficiency (CVID) is considered an antibody deficiency, with ~30% of cases found to have a monogenic cause. Diagnosis can be made in children over the age of 4, with low IgG as well as low IgM or IgA and lack of protective vaccine titers. These patients develop sinopulmonary and GI infections with common organisms, although they can have more severe presentations than their immunocompetent counterparts. They also have increased risk of autoimmunity and malignancy and often require IgG replacement.

Hyper-IgM syndrome encompasses a group of genetic defects associated with immunoglobulin class-switch recombination. The most common type is caused by a defect in the CD40 ligand on the T cell, leading to inability of the B cell to class-switch (see Chapter 166). Similar to other patients with humoral defects, these patients are at risk for bacterial sinopulmonary infections. However, unlike a true pure antibody defect, besides being important in T-cell–B-cell interactions, CD40 ligand is also important in the interaction between T cells and macrophages/monocytes, predisposing to opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and *Cryptosporidium* intestinal infection.

T-CELL DEFECTS (CELL-MEDIATED IMMUNODEFICIENCIES)

Children with primary T-cell–mediated immunodeficiencies can present early in life and are susceptible to viral, fungal, and protozoan infections. Clinical manifestations include chronic diarrhea,

mucocutaneous candidiasis, and recurrent pneumonia, rhinitis, and otitis media. In thymic hypoplasia **(DiGeorge syndrome)**, hypoplasia or aplasia of the thymus and parathyroid glands occurs during fetal development in association with the presence of other congenital abnormalities. Hypocalcemia and cardiac anomalies can be the presenting features of DiGeorge syndrome, which should prompt evaluation of the T-cell system.

Chronic mucocutaneous candidiasis (CMC) is a group of immunodeficiencies leading to susceptibility to fungal infections of the skin, nails, oral cavity, and genitals. Most frequently caused by *Candida* spp., dermatophyte infections with *Microsporum, Epidermophyton,* and *Trichophyton* have also been described. Interestingly, patients with CMC do not have an increased risk for histoplasmosis, blastomycosis, or coccidioidomycosis. Despite chronic cutaneous and mucosal infection with *Candida* spp., these patients often lack a delayed hypersensitivity to skin tests for *Candida* antigen. Several gene defects have been identified in people with CMC, including *STAT1* gain-of-function pathologic gene variations, *IL17R* defects, *CARD9* deficiency, and *ACT1* deficiency. Although patients with CMC generally do not develop invasive candidiasis, patients with CMC as a feature of an inborn error or immunity certainly do develop invasive *Candida* infection. Endocrinopathies, autoimmunity, and life-threatening vascular abnormalities can be seen as well, making genetic testing important in the prognosis and management of patients with CMC.

COMBINED B-CELL AND T-CELL DEFECTS

Patients with defects in both the B-cell and T-cell components of the immune system have variable manifestations depending on the extent of the defect (see Chapter 165). Complete or almost complete immunodeficiency is found with **severe combined immunodeficiency disorder (SCID)**, whereas partial defects can be present in such states as **ataxia-telangiectasia**, **Wiskott-Aldrich syndrome**, **hyper-IgE syndrome**, and **X-linked lymphoproliferative disorder**. Rather than one disorder, SCID represents a heterogeneous group of genetic defects that present in the first year of life with recurrent and typically severe infections caused by a variety of bacteria, fungi, and viruses. Failure to thrive, chronic diarrhea, mucocutaneous or systemic candidiasis, PJP, or cytomegalovirus (CMV) infections are common early in life. Passive maternal antibody is relatively protective against the bacterial pathogens during the first few months of life, but thereafter patients are susceptible to both gram-positive and gram-negative organisms. Exposure to live-virus vaccines can also lead to disseminated disease; accordingly, the use of live vaccines (including rotavirus vaccine) is contraindicated in patients with suspected or proven SCID. Without stem cell transplantation or gene therapy, most affected children succumb to infections within the first year of life.

Children with **ataxia-telangiectasia** develop recurrent sinopulmonary infections from both bacteria and respiratory viruses and are particularly susceptible to chronic lung infections because of their immunodeficiency and their muscular weakness leading to poor airway clearance. In addition, these children experience an increased incidence of malignancies and neurologic complications, with most patients being wheelchair bound by the second decade of life. **Wiskott-Aldrich syndrome** is an X-linked recessive disease associated with eczema, thrombocytopenia, reduced number of CD3 lymphocytes, moderately suppressed mitogen responses, and impaired antibody response to polysaccharide antigens. Accordingly, infections with *S. pneumoniae* or Hib can be seen.

Hyper-IgE syndrome (HIES) is characterized by elevated levels of IgE, infections, and eczema, with the most common cause being the result of dominant negative gene variation in *STAT3*. Pathogenic gene variants in *TYK2, PGM3, ZNF341, CARD11,* and *IL6ST* have also been reported to cause this phenotype. Patients can present with recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system. These abscesses were initially described as "cold" in that they did not have the characteristic warmth and rubor typically seen in immunocompetent patients and thereby are easily missed, delaying therapy. Patients can also develop infections caused by *Candida* and, depending on the gene defect, severe viral infections. Patients with *STAT3* HIES should receive prophylaxis against *S. aureus* with aggressive management of eczema as well.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

223.2 Infections Occurring with Acquired Immunodeficiencies

Marian G. Michaels, Hey Jin Chong, and Michael Green

Immunodeficiencies can be secondarily acquired from infections or other underlying disorders, such as malignancy, cystic fibrosis, diabetes mellitus, sickle cell disease, or malnutrition. Immunosuppressive medications used to prevent rejection after organ transplantation, to prevent graft-versus-host disease (GVHD) after stem cell transplantation, or to treat malignancies may also leave the host vulnerable to infections. Similarly, medications used to control rheumatologic or other autoimmune diseases may be associated with an increased risk for developing infection. Surgical removal of the spleen likewise puts a person at increased risk for infections. Further, any process that disrupts the normal mucosal and skin barriers (e.g., burns, surgery, indwelling catheters) may lead to an increased risk for infection.

ACQUIRED IMMUNODEFICIENCY FROM INFECTIOUS AGENTS

Infection with HIV, the causative agent of **AIDS**, remains globally an important infectious cause of acquired immunodeficiency (see Chapter 322). Left untreated, HIV infection has profound effects on many parts of the immune system but in particular T-cell–mediated immunity that leads to susceptibility to the same types of infections as with primary T-cell immunodeficiencies.

Other organisms can also lead to temporary alterations of the immune system. Very rarely, transient neutropenia associated with community-acquired viruses can lead to significant disease with bacterial infections. Secondary infections can occur because of impaired immunity or disruption of normal mucosal immunity, as exemplified by the increased risk for pneumonia from *S. pneumoniae* or *S. aureus* after influenza infection and group A streptococcal cellulitis and fasciitis after varicella.

MALIGNANCIES

The immune systems of children with malignancies are compromised by the therapies used to treat the cancer and, at times, by direct effects of the cancer itself. The type, duration, and intensity of anticancer therapy remain the major risk factors for infections in these children and often affect multiple arms of the immune system. The presence of mucous membrane abnormalities, indwelling catheters, malnutrition, prolonged exposure to antibiotics, and frequent hospitalizations adds to the risk for infection in these children.

Even though several arms of the immune system can be affected, the major abnormality predisposing to infection in children with cancer is **neutropenia**. The depth and duration of neutropenia are the primary predictors of the risk of infection in children being treated for cancer. Patients are at particular risk for bacterial and fungal infections if the ANC decreases to <500 cells/mm^3, and the risk is highest in those with counts <100 cells/mm^3. Counts of >500 cells/mm^3 but <1,000 cells/mm^3 incur some increased risk for infection, but not nearly as great. The lack of neutrophils can lead to a diminution of inflammatory response, limiting the ability to localize sites of infection and potentially leaving fever as the only manifestation of infection. Accordingly, the absence of physical signs and symptoms does not reliably exclude the presence of infection, resulting in the need for empirical antibiotics (Fig. 223.1). Because patients with **fever and neutropenia** might only have subtle signs and symptoms of infection, the presence of fever warrants an intensive investigation, including a thorough physical examination with careful attention to the oropharynx, lungs, perineum and anus, skin, nailbeds, and intravascular catheter insertion sites (Table 223.2).

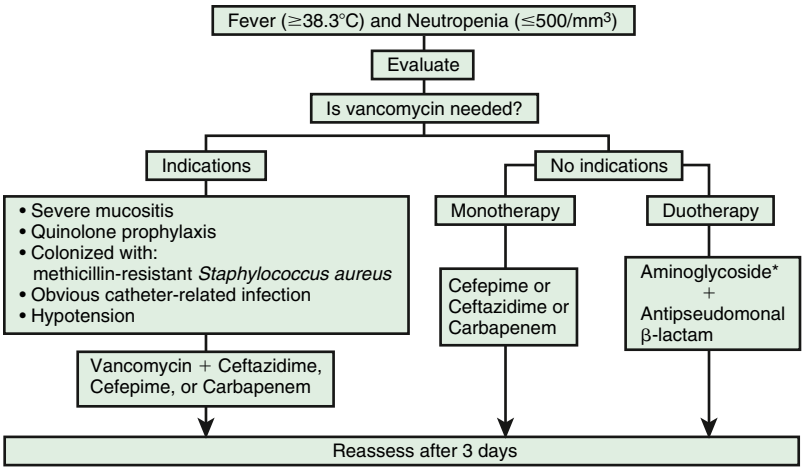

Fig. 223.1 Algorithm for the initial management of the febrile neutropenic patient. Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin–clavulanic acid. *Aminoglycoside antibiotics should be avoided if the patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (because of poor blood-brain perfusion). *(Adapted from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56–e93.)*

A comprehensive laboratory evaluation, including a complete blood cell count, serum creatinine, blood urea nitrogen, and serum transaminases, should be obtained. Blood cultures should be taken from each port of any **central venous catheter** (CVC) and from a peripheral vein and repeated if the original culture is negative. Although peripheral vein sampling is often omitted with continued fevers and neutropenia, it should be obtained before the initial antibiotic administration and reconsidered in children with one or more positive cultures from a CVC, facilitating localization (line vs systemic) of the source of the infection. Other microbiologic studies should be done if there are associated clinical symptoms, including a nasal aspirate for viruses in patients with upper respiratory findings; stool for viruses such as rotavirus or norovirus and for *Clostridium difficile* toxin in patients with diarrhea; urinalysis and culture in young children or in older patients with symptoms of urgency, frequency, dysuria, or hematuria; and biopsy and culture of cutaneous lesions. Chest radiographs should be obtained in any patient with lower respiratory tract symptoms, although pulmonary infiltrates may be absent in children with severe neutropenia. Sinus films should be obtained for children >2 years of age if rhinorrhea is prolonged. Abdominal CT scans should also be considered in children with profound neutropenia and abdominal pain to evaluate for the presence of typhlitis. Chest CT scan should be considered for children not responding to broad-spectrum antibiotics who have continued fever and neutropenia for >96 hours. Although some have considered the use of fungal biomarkers (e.g., galactomannan, β-D-glucan, fungal polymerase chain reaction [PCR]), these assays have poor positive predictive values, and their use is not routinely recommended. Biopsies for cytology, Gram stain, and culture should be considered if abnormalities are found during endoscopic procedures or if lung nodules are identified radiographically.

Past studies demonstrated that before the routine institution of empirical antimicrobial therapy for fever and neutropenia, 75% of children with fever and neutropenia were ultimately found to have a documented site of infection, suggesting that most children with fever and neutropenia will have an underlying infection (see Table 223.2). Current data suggest that bacteremia is present in ~20% of febrile neutropenic pediatric patients with leukemia; ~90% have bacterial disease (Fig. 223.2). Currently, gram-positive cocci are the most common pathogens identified in these patients; however, gram-negative organisms such as *P. aeruginosa, Escherichia coli,* and *Klebsiella* can cause life-threatening infection and must be considered in the empirical treatment regimen. Other multidrug-resistant Enterobacterales are increasingly recovered in these children. Although coagulase-negative staphylococci often cause infections in these children in association with CVCs, these infections are typically indolent, and a short delay in treatment usually does not lead to a detrimental outcome. Other gram-positive bacteria, such as *S. aureus* and *S. pneumoniae,* can cause more fulminant disease and require prompt institution of therapy. Viridans streptococci are particularly important potential pathogens in patients with the oral mucositis that is often associated with use of cytarabine and in patients who experience selective pressure from treatment with certain antibiotics such as quinolones. Infection caused by this group of organisms can present with an acute septic shock syndrome. Also, patients with prolonged neutropenia are at increased risk for opportunistic fungal infections (fungemia or tissue invasion), with *Candida* spp. and *Aspergillus* spp. being the most commonly identified fungi. Other fungi that can cause serious disease in these children include zygomycetes, *Fusarium* spp., and dematiaceous molds. In patients with repeatedly negative blood cultures but persistent fevers, next-generation sequencing in blood or plasma may help identify bacterial, viral, fungal, or protozoan pathogens.

FEVER AND NEUTROPENIA

The use of empirical antimicrobial treatment as part of the management of fever and neutropenia decreases the risk of progression to sepsis, septic shock, acute respiratory distress syndrome, organ dysfunction, and death. In 2017 the International Pediatric Fever and Neutropenia Guideline Panel updated a comprehensive guideline for the management of neutropenic children with cancer or after HSCT (see Fig. 223.1).

First-line antimicrobial therapy should take into consideration the types of microbes anticipated and the local resistance patterns encountered at each institution as well as the level of risk for severe infection associated with a given patient. In addition, antibiotic choices may be limited by specific circumstances, such as the presence of drug allergy and renal or hepatic dysfunction. Guidelines for the management of fever and neutropenia in children with cancer and/or undergoing HSCT conclude that the use of oral antimicrobial therapy as either initial or stepdown therapy can be considered in low-risk children who can tolerate oral antibiotics and in whom careful monitoring can be ensured. However, the guideline emphasizes that oral medication use may present major challenges in children, including the availability of liquid formulations of appropriate antibiotics, cooperation of young children, and the presence of mucositis potentially interfering with absorption. Accordingly, decisions to implement this approach should be reserved for a select subset of these children presenting with fever and neutropenia and institutions with an appropriate infrastructure to follow them as outpatients.

The decision to initially use IV monotherapy versus an expanded regimen of antibiotics depends on the severity of illness of the patient, history of previous colonization with resistant organisms, and obvious presence of catheter-related infection. Glycopeptide addition (such as vancomycin) to the initial empirical regimen should be implemented if the patient has hypotension or other evidence of septic shock, an obvious catheter-related infection, a history of colonization with methicillin-resistant *S. aureus,* or the patient is at high risk for infection with viridans streptococci (severe mucositis, acute myelogenous leukemia, or prior use of quinolone prophylaxis). Otherwise, use of monotherapy with an antipseudomonal β-lactam, such as piperacillin-tazobactam, a fourth-generation cephalosporin, or a carbapenem can be considered. Ceftazidime should not be used as monotherapy if concern exists for gram-positive organisms or resistant gram-negative bacteria. The addition of a second anti–gram-negative bacterial agent (e.g., aminoglycoside) for empirical therapy can be considered in patients who are clinically unstable when multidrug-resistant organisms are suspected.

Table 223.2 Host Defense Defects and Common Pathogens by Time After Bone Marrow or Hematopoietic Stem Cell Transplantation

TIME PERIOD	HOST DEFENSE DEFECTS	CAUSES	COMMON PATHOGENS
Pretransplant	Neutropenia Abnormal anatomic barriers	Underlying disease Prior chemotherapy	Aerobic gram-negative bacilli
Preengraftment	Neutropenia Abnormal anatomic barriers	Chemotherapy Radiation Indwelling catheters	Aerobic gram-positive cocci Aerobic gram-negative bacilli *Candida* *Aspergillus* Herpes simplex virus (in previously infected patients) Community-acquired viral pathogens
Postengraftment	Abnormal cell-mediated immunity Abnormal anatomic barriers	Chemotherapy Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor	Gram-positive cocci Aerobic gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens *Pneumocystis jirovecii*
Late posttransplant	Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)	Time required to develop donor-related immune function Graft-versus-host disease	Varicella-zoster virus *Streptococcus pneumoniae*

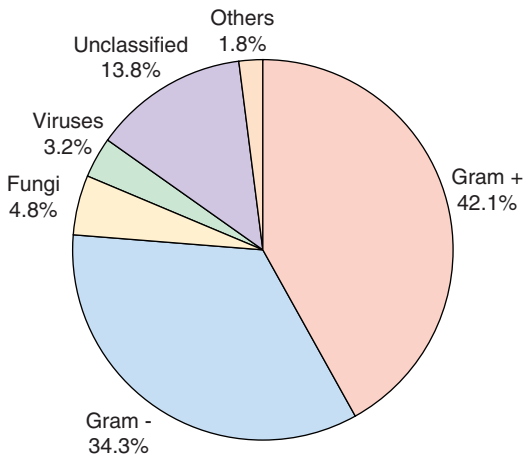

Fig. 223.2 Pathogens involved in the microbiologically documented infections in pediatric oncology patients with febrile neutropenia. *(From Boeriu E, Borda A, Dumitru D, et al. Diagnosis and management of febrile neutropenia n pediatric oncology patients – a systematic review. Diagnostics. 2022;12:1800.)*

Regardless of the regimen chosen initially, it is critical to evaluate the patient carefully and continually for response to therapy, development of secondary infections, and adverse effects. Management recommendations for these children are evolving. Patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of bone marrow recovery can have all antibiotics discontinued. However, if symptoms persist or evolve, IV antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. Pediatric guidelines advocate for discontinuing antibiotics in low-risk patients at 72 hours for children who have negative blood cultures and who have been afebrile for at least 24 hours regardless of bone marrow recovery, as long as careful follow-up is ensured.

Next-generation sequencing (NGS) during episodes of fever and neutropenia may enhance pathogen detection when blood cultures and other tests are negative. NGS has the advantage of detecting bacteria, fungi, viruses and polymicrobial infections. When fever persists despite empiric antibiotics, NGS results may help modify antimicrobial therapy based on the pathogens identified.

Patients without an identified etiology but with **persistent fever** should be reassessed daily. At day 3-5 of persistent fever and neutropenia, those remaining clinically well may continue on the same regimen, although consideration should be given to discontinuing vancomycin or double gram-negative bacterial coverage if they were included initially. Patients who remain febrile with clinical instability warrant escalation of therapy with the addition of a glycopeptide, if it was not included initially and risk factors exist, and modification of the empirical antibacterial regimen to cover potential antimicrobial resistance and anaerobic infections in these children. If fever persists for >96 hours, the addition of an **antifungal agent** with antimold activity should be considered, particularly for those at high risk for invasive fungal infection (those with acute myelogenous leukemia or relapsed acute lymphocytic leukemia or who are receiving highly myelosuppressive chemotherapies for other cancers or with allogeneic HSCT). Liposomal amphotericin products and echinocandins have been studied in children; voriconazole, itraconazole, and posaconazole have been successfully used in adults, with increasing experience in children. Azoles may have substantial drug-drug interactions; however, their use has not been thoroughly evaluated. Studies comparing caspofungin with liposomal amphotericin for children with malignancies and fever and neutropenia have shown that caspofungin is noninferior.

The use of **antiviral agents** in children with fever and neutropenia is not warranted without specific evidence of viral disease. Active herpes simplex or varicella-zoster lesions merit treatment to decrease the time of healing; even if these lesions are not the source of fever, they are potential portals of entry for bacteria and fungi. CMV is a rare cause of fever in children with cancer and neutropenia. If CMV infection is suspected, assays to evaluate viral load in the blood and organ-specific infection should be obtained. Ganciclovir, foscarnet, or cidofovir may be considered while evaluation is pending, although ganciclovir can cause bone marrow suppression and foscarnet and cidofovir can be nephrotoxic. If influenza is identified, specific treatment with an antiviral agent (oseltamivir, zanamivir) should be administered. The possibility of severe acute respiratory syndrome–coronavirus type 2 (SARS-CoV-2) infection should be evaluated by PCR, and treatment should be considered based on current recommendations and local availability of antiviral therapies.

The use of **hematopoietic growth factors** shortens the duration of neutropenia but has not been proved to reduce morbidity or mortality. Accordingly, guidelines do not endorse the routine use of hematopoietic growth factors in patients with established fever and neutropenia, although the recommendations do note that hematopoietic growth factors can be considered as prophylaxis in those with neutropenia at high risk for fever.

Prophylaxis with levofloxacin has been shown to decrease bacteremia for children with acute leukemia receiving intensive chemotherapy and may also be effective in those undergoing allogenic HSCT. However, monitoring for breakthrough bacteremia and for quinolone resistance is important.

FEVER WITHOUT NEUTROPENIA

Infections occur in children with cancer in the absence of neutropenia. Most often, these infections are viral in etiology. However, *P. jirovecii* can cause pneumonia regardless of the neutrophil count. Administration of prophylaxis against *Pneumocystis* is an effective preventive strategy and should be provided to all children undergoing active treatment for malignancy. First-line therapy remains TMP-SMX, with second-line alternatives including pentamidine, atovaquone, dapsone, or dapsone-pyrimethamine. Environmental fungi such as *Cryptococcus, Histoplasma,* and *Coccidioides* can also cause disease. *Toxoplasma gondii* is an uncommon but occasional pathogen in children with cancer. Infections caused by pathogens encountered in healthy children (*S. pneumoniae,* group A streptococcus) can also occur in children with cancer regardless of the granulocyte count.

TRANSPLANTATION

Transplantation of hematopoietic stem cells and solid organs (including heart, liver, kidney, lungs, pancreas, and intestines) is increasingly used as therapy for a variety of disorders. Children undergoing transplantation are at risk for infections caused by many of the same microbial agents that cause disease in children with primary immunodeficiencies. Although the types of infections after transplantation generally are similar among all recipients of these procedures, some differences exist between patients depending on the type of transplantation performed, the type and amount of immunosuppression given, and the child's preexisting immunity to specific pathogens.

Stem Cell Transplantation

Infections after HSCT can be classified as occurring during the **pretransplantation period**, **preengraftment period** (0-30 days after transplantation), **postengraftment period** (30-100 days), or **late posttransplantation period** (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (see Table 223.2). In addition, risk is affected by type of transplant (autologous, allogeneic, T-cell depleted, cord blood) along with the quality of the donor-recipient match. Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods after transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time after transplantation.

Pretransplantation Period

Children come to HSCT with a heterogeneous history of underlying diseases, chemotherapy exposure, degree of immunosuppression, and previous infections. Approximately 12% of all infections among adult HSCT recipients occur during the pretransplantation period. These infections are often caused by aerobic gram-negative bacilli and manifest as localized infections of the skin, soft tissue, and urinary tract. Importantly, the development of infection during this period does not delay or adversely affect the success of engraftment.

Preengraftment Period

Bacterial infections predominate in the preengraftment period (0-30 days). **Bacteremia** is the most common documented infection and occurs in as many as 50% of all HSCT recipients during the first 30 days after transplantation. Bacteremia is typically associated with the presence of either mucositis or an indwelling catheter but may also be seen with pneumonia. Similarly, >40% of children undergoing HSCT experience one or more infections in the preengraftment period. Gram-positive cocci, gram-negative bacilli, yeast, and, less frequently, other fungi cause infection during this period. *Aspergillus* has been identified in 4–20% of HSCT recipients, most often after 3 weeks of neutropenia. Infections caused by the emerging fungal pathogens *Fusarium* and *Pseudallescheria boydii* are associated with the prolonged neutropenia during the preengraftment period.

Viral infections also occur during the preengraftment period. Among adults, reactivation of herpes simplex virus (HSV) is the most common viral disease observed, but this is less common among children. A history of HSV infection or seropositivity indicates the need for prophylaxis. Nosocomial exposure to community-acquired viral pathogens, including SARS-CoV-2, respiratory syncytial virus (RSV), influenza virus, adenovirus, rotavirus, and norovirus, represents another important source of infection during this period. There is growing evidence that community-acquired viruses cause increased morbidity and mortality for HSCT recipients during this period. Adenovirus is a particularly important viral pathogen that can occur early, although it typically presents after engraftment.

Postengraftment Period

The predominant defect in host defenses in the postengraftment period is altered cell-mediated immunity. Accordingly, organisms historically categorized as *opportunistic pathogens* predominate during this period. The risk is especially accentuated 50-100 days after transplantation, when host immunity is lost and donor immunity is not yet established. *P. jirovecii* presents during this period if patients are not maintained on appropriate prophylaxis. Reactivation of *T. gondii,* a rare cause of disease among HSCT recipients, can also occur after engraftment. Hepatosplenic candidiasis often presents during the postengraftment period, although seeding likely occurs during the neutropenic phase.

Cytomegalovirus (CMV) is an important cause of morbidity and mortality among HSCT recipients. Unlike patients undergoing solid organ transplantation (SOT), where primary infection from the donor causes the greatest harm, CMV reactivation in an HSCT recipient whose donor is naïve to the virus can also cause severe disease. Disease risk from CMV after HSCT is also increased in recipients of cord blood transplants or matched unrelated T-cell–depleted transplants and those with GVHD. **Adenovirus**, another important viral pathogen, has been recovered from up to 5% of adult and pediatric HSCT recipients and causes invasive disease in approximately 20% of cases. Children receiving matched unrelated donor organs or unrelated cord blood cell transplants have an incidence of adenovirus infection as high as 14% during this early postengraftment period. **Polyomaviruses** such as BK virus have been increasingly recognized as a cause of renal dysfunction and hemorrhagic cystitis after bone marrow transplantation. Infections with other herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus 6) as well as community-acquired pathogens are associated with excess morbidity and mortality during this period, similar to the preengraftment period.

Late Posttransplantation Period

Infection is unusual after 100 days in the absence of chronic GVHD. However, the presence of chronic GVHD significantly affects anatomic barriers and is associated with defects in humoral, splenic, and cell-mediated immune function. Viral infections, including primary infection with or reactivation of varicella-zoster virus (VZV), are responsible for >40% of infections during this period. This may decrease over time, as the Oka varicella vaccine strain has a lower rate of reactivation than wild-type varicella. Pandemic SARS-CoV-2 has also been noted to have more severe outcomes in children after HSCT. Bacterial infections, particularly of the upper and lower respiratory tract, account for approximately 30% of infections. These infections may be associated with deficiencies in immunoglobulin production, especially IgG2. Fungal infections account for <20% of confirmed infections during the late posttransplantation period.

Solid Organ Transplantation

Factors predisposing to infection after organ transplantation include those that either existed before transplantation or are secondary to intraoperative events or posttransplantation therapies (Table 223.3). Some of these additional risks cannot be prevented, and some risks acquired during or after the operation depend on decisions or actions of members of the transplant team. Organ recipients are at risk for infection from potential exposure to pathogens in the donor organ. Although some donor-derived infections can be anticipated through donor screening, many pathogens are not routinely screened for, and strategies defining when and how to screen for all but a small subset of potential pathogens have not been identified or implemented. Similar to other children who have undergone surgical procedures, surgical site infections are a frequent cause of infection early after transplantation. Beyond this, the need for immunosuppressive agents to prevent rejection is the major factor predisposing to infection after transplantation. Despite efforts to

Table 223.3 Risk Factors for Infections After Solid Organ Transplantation in Children

PRETRANSPLANTATION FACTORS
Age of patient
Underlying disease, malnutrition
Specific organ transplanted
Previous exposures to infectious agents
Previous immunizations
Presence of infection in the donor
INTRAOPERATIVE FACTORS
Duration of transplant surgery
Exposure to blood products
Technical problems
Organisms transmitted with donor organ
POSTTRANSPLANTATION FACTORS
Immunosuppression
Induction immunosuppression type
Maintenance immunosuppression
Augmented treatment for rejection
Indwelling catheters
Nosocomial exposures
Community exposures

optimize immunosuppressive regimens to prevent or treat rejection with minimal impairment of immunity, all current regimens interfere with the ability of the immune system to prevent infection. The primary target of the majority of these immunosuppressive agents in organ recipients is the cell-mediated immune system, but regimens can and do impair many other aspects of the transplant recipient's immune system as well.

Timing

The timing of specific types of infections is generally predictable, regardless of which organ is transplanted. Infectious complications typically develop in one of three intervals: early (0-30 days after transplantation), intermediate (30-180 days), or late (>180 days); most infections present in the first 180 days after transplantation. Table 223.4 should be used as a general guideline to the types of infections encountered, but the timing of the presentation may be modified with the introduction of newer immunosuppressive therapies and by the use of prophylaxis.

Early infections are usually the result of a complication of the transplant surgery itself, the unexpected acquisition of a bacterial or fungal pathogen from the donor, or the presence of an indwelling catheter. In contrast, infections during the intermediate period typically result from a complication of the immunosuppression, which tends to be at its greatest intensity during the first 6 months after transplantation. This is the period of greatest risk for infections caused by opportunistic pathogens such as CMV, EBV, and *P. jirovecii*. Anatomic abnormalities, such as bronchial stenosis and biliary stenosis, that develop as a result of the transplant surgery can also predispose to recurrent infection in this period.

Infections developing late after transplantation typically result from uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Augmented immunosuppression as treatment for late acute cellular rejection or chronic rejection can increase the risk for late presentations with CMV, EBV, and other potential opportunistic infections. Acquisition of infection from community-acquired pathogens such as RSV can result in severe infection secondary to the immunocompromised state of the transplant recipient during the early and intermediate periods. Compared with the earlier periods, community-acquired infections in the late period are usually benign because immunosuppression is typically maintained at significantly lower levels. However, certain pathogens such as VZV and EBV may be associated with severe disease even at this late period.

Bacterial and Fungal Infections

Although there are important graft-specific considerations for bacterial and fungal infections after transplantation, some principles are generally applicable to all transplant recipients. Bacterial and fungal infections after organ transplantation are usually a direct consequence of the surgery, a breach in an anatomic barrier, a foreign body, or an abnormal anatomic narrowing or obstruction. With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. Infections after abdominal transplantation (liver, intestine, or renal) usually occur in the abdomen or at the surgical wound. The pathogens are typically enteric gram-negative bacteria, *Enterococcus*, and occasionally *Candida*. Infections after thoracic transplantation (heart, lung) usually occur in the lower respiratory tract or at the surgical wound. Pathogens associated with these infections include *S. aureus* and gram-negative bacteria. Patients undergoing lung transplantation for cystic fibrosis

Table 223.4 Timing of Infectious Complications After Solid Organ Transplantation

EARLY PERIOD (0-30 DAYS)
Bacterial Infections
Gram-negative enteric bacilli
• Small bowel, liver, neonatal heart
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-positive organisms
• All transplant types
Fungal Infections
• All transplant types
Viral Infections
Herpes simplex virus
• All transplant types
Nosocomial respiratory viruses
• All transplant types
MIDDLE PERIOD (1-6 MO)
Viral Infections
Cytomegalovirus
• All transplant types
• Seronegative recipient of seropositive donor
Epstein-Barr virus
• All transplant types (small bowel the highest-risk group)
• Seronegative recipient
Varicella-zoster virus
• All transplant types
• Opportunistic infections
Pneumocystis jirovecii
• All transplant types
Toxoplasma gondii
• Seronegative recipient of cardiac transplant from a seropositive donor are highest risk group
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-negative enteric bacilli
• Small bowel
LATE PERIOD (>6 MO)
Viral Infections
Epstein-Barr virus
• All transplant types, but less risk than middle period
Varicella-zoster virus
• All transplant types
Community-acquired viral infections
• All transplant types
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
• Lung transplants with chronic rejection
Gram-negative bacillary bacteremia
• Small bowel
Fungal Infections
Aspergillus
• Lung transplants with chronic rejection

Adapted from Green M, Michaels MG. Infections in solid organ transplant recipients. In: Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases*, 5th ed. Philadelphia: Elsevier; 2018: Table 95-1.

experience a particularly high rate of infectious complications because they are often colonized with *P. aeruginosa* or *Aspergillus* before transplantation. Even though the infected lungs are removed, the sinuses and upper airways remain colonized with these pathogens, and subsequent reinfection of the transplanted lungs can occur. Children receiving organ transplants are often hospitalized for long periods and receive many antibiotics; thus recovery of multidrug-resistant bacteria is common after all types of organ transplantation. Infections caused by *Aspergillus* are less common but occur after all types of organ transplantation and are associated with high rates of morbidity and mortality.

Viral Infections

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality after SOT. In addition, BK virus is a major cause of renal disease after kidney transplantation. Although SARS-CoV-2 has affected pediatric SOT recipients less than adult recipients, disease severity is increased compared with nonimmunosuppressed children. The patterns of disease associated with individual viral pathogens are generally similar among all organ transplant recipients. However, the incidence, mode of presentation, and severity differ according to the type of organ transplanted and, for many viral pathogens, pretransplant serologic status of the recipient.

Viral pathogens can be generally categorized as latent pathogens, which cause infection through reactivation in the host or acquisition from the donor (e.g., CMV, EBV) or as community-acquired viruses (e.g., SARS-CoV-2, RSV, influenza). For CMV and EBV, primary infection occurring after transplantation is associated with the greatest degree of morbidity and mortality. The highest risk is seen in a naïve host who receives an organ from a donor who previously was infected with one of these viruses. This mismatched state is frequently associated with severe disease. However, even if the donor is negative for CMV and EBV, primary infection can be acquired from a close contact or through blood products. Secondary infections (reactivation of a latent strain within the host or superinfection with a new strain) tend to result in milder illness unless the patient is highly immunosuppressed, which can occur in the setting of treatment of significant rejection.

CMV is one of the most commonly recognized transplant viral pathogens. Disease from CMV has decreased significantly with the use of preventive strategies, including antiviral prophylaxis, most commonly using ganciclovir or oral valganciclovir, as well as viral load monitoring to inform preemptive antiviral therapy. Some centers have implemented a sequential approach where surveillance viral load monitoring follows a relatively short period of chemoprophylaxis. Clinical manifestations of CMV disease can range from a syndrome of fatigue and fever to tissue-invasive disease that most often affects the liver, lungs, and GI tract.

Infection caused by **EBV** is another important complication of SOT. Clinical symptoms range from a mild mononucleosis syndrome to disseminated **posttransplant lymphoproliferative disorder (PTLD)**. EBV-associated PTLD is more common among children than adults, because primary EBV infection in the immunosuppressed host is more likely to lead to uncontrolled proliferative disorders, including posttransplant lymphoma.

Other viruses, such as adenovirus, also have the capacity to be donor associated, but appear to be less common. The unexpected development of donor-associated viral pathogens, including hepatitis B virus, hepatitis C virus, and HIV, is rare today because of intensive donor screening. However, the changing epidemiology of some viruses (e.g., dengue, chikungunya, Zika) raises concerns for the *donor-derived transmission* of these emerging viral pathogens.

Community-acquired viruses, including those associated with respiratory tract infection (SARS-CoV-2, RSV, influenza virus, adenovirus, parainfluenza virus) and GI infection (enteroviruses, norovirus, and rotavirus), can cause important disease in children after organ transplantation. In general, risk factors for more severe infection include young age, acquisition of infection early after transplantation, and augmented immune suppression. Infection in the absence of these risk factors frequently results in a clinical illness that is comparable to that seen in immunocompetent children. However, some community-acquired viruses, such as adenovirus, can be associated with graft dysfunction even when acquired late after transplantation.

Although children with SARS-CoV-2 infection after transplantation fare better than adult counterparts, they are at risk for more severe symptoms early after transplant and if they have comorbidities. Immunization remains one of the best preventive strategies against severe disease even though efficacy is less compared to nonimmunosuppressed children.

Opportunistic Pathogens

Children undergoing SOT are also at risk for symptomatic infections from pathogens that do not usually cause clinical disease in immunocompetent hosts. Although these typically present in the intermediate period, these infections can also occur late in patients, requiring prolonged and high levels of immunosuppression. *P. jirovecii* is a well-recognized cause of pneumonia after SOT, although routine prophylaxis has essentially eliminated this problem. *T. gondii* can complicate cardiac transplantations because of tropism of the organism for cardiac muscle and risk for donor transmission; less often, it complicates other types of organ transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

223.3 Prevention of Infection in Immunocompromised Persons

Marian G. Michaels, Hey Jin Chong, and Michael Green

Although infections cannot be completely prevented in children who have defects in one or more arms of their immune system, measures can be taken to decrease the risks for infection. Replacement immunoglobulin is a benefit to children with primary B-cell deficiencies. Interferon (IFN)-γ, TMP-SMX, and oral antifungal agents have long been used to reduce the number of infections occurring in children with CGD, although the relative benefit of INF-γ has been questioned. Children who have depressed cellular immunity resulting from primary diseases, advanced HIV infection, or immunosuppressive medications benefit from prophylaxis against *P. jirovecii.* Strategies for safe living for all children with immunocompromising conditions should be emphasized, including hand hygiene, avoidance of community members with communicable infections, and attention to local environmental risk factors. These strategies were stressed and employed during the era of pandemic SARS-CoV-2 circulation. Immunizations prevent many infections and are particularly important for children with compromised immune systems who do not have a contraindication or inability to respond. For children rendered immunocompromised because of medication or splenectomy, immunizations should be administered before treatment whenever possible. This timing allows for superior response to vaccine antigens, avoids the risk of live vaccines, which may be contraindicated depending on the immunosuppression, and importantly, provides protection before the immune system is compromised.

Although immunodeficient children are a heterogeneous group, some principles of prevention are generally applicable. The use of inactivated vaccines does not lead to an increased risk for adverse effects, although their efficacy may be reduced because of an impaired immune response. In most cases, children with immunodeficiencies should receive all the recommended inactivated vaccines. Live-attenuated vaccinations can cause disease in some children with immunologic defects, and therefore alternative immunizations should be used whenever possible, such as inactivated influenza vaccine rather than live-attenuated influenza vaccine or inactivated typhoid vaccine rather than the oral live typhoid vaccine for travelers. In general, live-virus vaccines should not be used in children with primary T-cell abnormalities; efforts should be made to ensure that close contacts are all immunized to decrease the risk of exposure. In some patients in whom wild-type viral infection can be severe, immunizations, even with live-virus vaccine, are warranted in the immunosuppressed child. For example, children with HIV infection and a CD4 level of >15% should receive vaccinations against measles and varicella. In addition, growing evidence suggests that select transplant recipients can safely receive live vaccines as well. Some vaccines should be given to children with immunodeficiencies in addition to routine

vaccinations. As an example, children with asplenia or splenic dysfunction should receive meningococcal vaccine and both the conjugate and the polysaccharide pneumococcal vaccines. Influenza and SARS-CoV-2 vaccination is recommended for all eligible individuals (>6 months old for influenza) and should be emphasized for immunocompromised children and all household contacts to minimize risk for transmission to the immunocompromised child.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 224

Infection Associated with Medical Devices

Hana Hakim and Joshua Wolf

Use of implanted synthetic and prosthetic devices has revolutionized pediatric practice by providing long-term venous access, limb-salvage surgery, and successful treatment of hydrocephalus, urinary retention, and renal failure. However, infectious complications of these devices remain a major concern and account for a significant number of healthcare-acquired infections (HAIs) and attributable morbidity and mortality among hospitalized patients. Several federal and hospital programs in the United States and elsewhere focus on prevention initiatives to reduce device-related HAI rates, most frequently central line–associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP). HAIs are typically defined as infections that occur at least 2 days after admission to the hospital and that were not incubating at the time of admission. Device-associated infections are related to the development of **biofilms**, organized communities of microorganisms on the device surface protected from the immune system and from antimicrobial therapy. A number of factors are important to the development of infection, including host susceptibility, device composition, duration of implantation, and exposure to colonizing or contaminating organisms.

INTRAVASCULAR ACCESS DEVICES

Intravascular access devices range from short, stainless steel needles or plastic cannulae inserted for brief periods to multilumen, implantable, synthetic plastic catheters that are expected to remain in use for years. Infectious complications include local skin and soft tissue infections, such as exit site, tunnel tract, and device pocket infections, and **catheter-related bloodstream infections (CRBSIs)**. The use of central venous devices has improved the quality of life of high-risk patients but has also increased the risk of infection.

Catheter Types

Short-term peripheral cannulae are most often used in pediatric patients, and infectious complications occur infrequently. The rate of peripheral CRBSIs in children is <0.15%. Patient age <1 year, duration of use >144 hours (6 days), and some infusates are associated with increased risk for catheter-related infection. Catheter-associated phlebitis is more common (1–6%) but is rarely infective and can be treated conservatively by cannula removal.

Central venous catheters (CVCs), which terminate in a central vein such as the superior or inferior vena cava, are widely used in both adult and pediatric patients and are responsible for the majority of catheter-related infections. These catheters are frequently used in patients with chronic illnesses such as oncologic, gastrointestinal, and cardiovascular diseases and in critically ill patients, including neonates, who have many other risk factors for nosocomial infection. Patients in an intensive care unit (ICU) with a CVC in place have a fivefold greater risk for developing a nosocomial bloodstream infection than those without. Other risk factors that have been associated with increased incidence of CLABSIs include prolonged hospital stay, total parenteral nutrition, use of multiple concurrent CVCs or a CVC with multiple lumens, and use of short-term nontunneled CVC.

The use of peripherally inserted central catheters, which are inserted into a peripheral vein and terminate in a central vein, has increased in pediatric patients. Infection rates seem to be similar to long-term tunneled CVCs, ranging between 2.0 and 3.51 per 1,000 catheter-days, but other complications such as fracture, dislodgment, and occlusion are more common.

When prolonged intravenous (IV) access is required, a cuffed silicone rubber (Silastic) or polyurethane catheter may be inserted into the superior vena cava through the subclavian, cephalic, or jugular vein. The extravascular segment of the catheter passes through a subcutaneous (SC) tunnel before exiting the skin, usually on the superior aspect of the chest (e.g., Broviac or Hickman catheter). A cuff around the catheter near the exit site induces a fibrotic reaction to seal the tunnel. Totally implanted devices comprise a tunneled central catheter attached to an SC reservoir or port with a self-sealing silicone septum immediately under the skin that permits repeated percutaneous needle access.

The incidence of local (exit site, tunnel, and pocket) infection with long-term catheters is 0.2-2.8/1,000 catheter-days. The incidence of external tunneled CRBSI is 0.5-11.0/1,000 catheter-days. The incidence of CRBSI in implantable devices is much lower at 0.3-1.8/1,000 catheter-days; however, treatment with total parenteral nutrition (TPN) eliminates this risk reduction because of a much greater relative increase in infection rate in ports. The risk for CRBSI is increased among premature infants, young children, and TPN patients.

Catheter-Associated Skin and Soft Tissue Infection

A number of local infections can occur in the presence of a CVC. The clinical manifestations of local infection include erythema, tenderness, and purulent discharge at the exit site or along the SC tunnel tract of the catheter. **Exit site infection** denotes infection localized to the exit site, without significant tracking along the tunnel, often with purulent discharge. **Tunnel tract infection** indicates infection in the SC tissues tracking along a tunneled catheter, which may also include serous or serosanguineous discharge from a draining sinus along the path. **Pocket infection** indicates suppurative infection of an SC pocket containing a totally implanted device. Bloodstream infection may coexist with local infection.

The diagnosis of local infection is established clinically, but a Gram-stained smear and culture of any exit site drainage should be performed to identify the microbiologic cause. The source is usually contamination by skin or gastrointestinal flora, and the most common organisms are *Staphylococcus aureus,* coagulase-negative staphylococci, *Pseudomonas aeruginosa, Candida* spp., and mycobacteria. Green discharge is strongly suggestive of mycobacterial infection, and appropriate stains and culture should be performed.

Treatment of local infection related to a short-term CVC should include device removal. Exit site infection may resolve with device removal alone, but systemic symptoms should initially be managed with antimicrobial therapy. In the case of long-term CVCs, exit site infections usually respond to local care with topical or systemic antibiotics alone. However, tunnel or pocket infections require removal of the catheter and systemic antibiotic therapy in almost all cases. When a tunneled CVC is removed as a result of tunnel infection, the cuff should also be removed and sent for culture if possible. In cases of mycobacterial infection, wide surgical debridement of the tissues is usually required for cure.

Catheter-Related Bloodstream Infection

CRBSI occurs when microorganisms attached to the CVC are shed into the bloodstream, leading to bacteremia. The term **catheter-related bloodstream infection** is reserved for a bloodstream infection that is demonstrated by CVC tip culture or other techniques to have been caused by colonization of the device. In contrast, the more general term **central line–associated bloodstream infection (CLABSI)** is typically

used for surveillance and can refer to any bloodstream infection that occurs in a patient with a CVC, unless there is an identified alternative source. On the device, the organisms are embedded in biofilms as organized communities. Colonization may be present even in the absence of symptoms or positive cultures.

Organisms may contaminate the external surface of the CVC during insertion or the intraluminal surface through handling of the catheter hub or contaminated infusate. Most cases of CRBSI appear to be caused by intraluminal colonization, but external colonization may play a greater role in infections related to recently inserted (<30 days) catheters or in immunocompromised patients. In most populations, gram-positive cocci predominate, with about half of infections caused by coagulase-negative staphylococci. Gram-negative enteric bacteria are isolated in approximately 20–30% of episodes, and fungi account for 5–10% of episodes.

Fever without an identifiable focus is the most common clinical presentation of CRBSI; local soft tissue symptoms and signs are usually absent. Onset of fever or rigors during or soon after flushing of a catheter is highly suggestive of CRBSI. Symptoms and signs of complicated infection, such as septic thrombophlebitis, endocarditis, and ecthyma gangrenosum, may also be present.

Blood cultures collected before beginning antibiotic therapy are generally positive from both the CVC and the peripheral blood. It is important not to collect cultures unless infection is suspected, as blood culture contamination may occur and can lead to inappropriate therapy. To help interpret positive cultures with common skin contaminants, blood cultures should be collected from at least two sites, preferably including all lumens of a CVC, before initiation of antibiotic therapy.

Tests to differentiate CRBSI from other sources of bacteremia in the presence of a CVC include culture of the catheter tip, quantitative blood cultures, and **differential time to positivity** of blood cultures drawn from different sites. Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal. Although CVC tip culture can identify CRBSI, it precludes salvage of the catheter. The most readily available technique to confirm CRBSI without catheter removal is calculation of differential time to positivity between blood cultures drawn through a catheter and from a peripheral vein or separate lumen. During CRBSI, blood obtained through the responsible lumen will usually indicate growth at least 2-3 hours before peripheral blood or uncolonized lumens because of a higher intraluminal microorganism burden. Identical volumes of blood must be collected simultaneously from each site, and a continuously monitored blood culture system is required. Specificity of this test is good (94–100%), and sensitivity is good when a peripheral blood culture is available (approximately 90%) but poorer when comparing two lumens of a CVC (64%). Where available, quantitative blood culture showing at least a threefold higher number of organisms from central compared with peripheral blood is similarly diagnostic.

Treatment of CRBSI related to **long-term vascular access devices** (e.g., Hickman, Broviac, totally implantable devices) with systemic antibiotics is successful for many bacterial infections without removal of the device. Antibiotic therapy should be directed to the isolated pathogen and given for a total of 10-14 days from the date of blood culture clearance. Until pathogen identification and susceptibility testing are available, empirical therapy, based on local antimicrobial susceptibility data and usually including **vancomycin** plus an antipseudomonal aminoglycoside (e.g., gentamicin), penicillin (e.g., piperacillin-tazobactam), or cephalosporin (e.g., ceftazidime or cefepime), is generally indicated. An echinocandin or azole antifungal should be initiated if fungemia is suspected. Patients who have a recent history of CRBSI with a resistant organism treated without CVC removal who subsequently develop severe sepsis should generally receive initial empirical therapy directed against that organism, because relapse is common.

Antibiotic lock or dwell therapy, with administration of solutions of high concentrations of antibiotics or ethanol that remain in the catheter for up to 24 hours, has been proposed to improve outcomes when used as an adjuvant to systemic therapy. Antibiotic locks are recommended in patients receiving dialysis who may not have antibiotics frequently delivered through the CVC, but evidence does not suggest that routine use of lock therapy is beneficial in other patient populations, and it may cause harm. Ethanol lock therapy increases the risk of CVC occlusion, and lock therapy can result in delays to necessary CVC removal.

If blood cultures remain positive after 72 hours of appropriate therapy, or if a patient deteriorates clinically, the device should be removed. Failure of CRBSI salvage therapy is common and can be serious in infections caused by *S. aureus* (approximately 50%), *Candida* spp. (>70%), and *Mycobacterium* spp. (>70%). Other indications for removing a long-term catheter include severe sepsis, suppurative thrombophlebitis, and endocarditis. Prolonged therapy (4-6 weeks) is indicated for persistent bacteremia or fungemia after catheter removal, because this may represent unrecognized infective endocarditis or thrombophlebitis. The decision to attempt catheter salvage should weigh the risk and clinical impact of persistent or relapsed infection against the risk of surgical intervention.

CRBSI may be complicated by other intravascular infections such as septic thrombophlebitis or endocarditis. The presence of these conditions may be suggested by preexisting risk factors (e.g., congenital heart disease), signs and symptoms, or persistent bacteremia or fungemia 72 hours after device removal and appropriate therapy. Screening for these complications in otherwise low-risk children, even those with *S. aureus* infection, is not recommended, because the overall frequency is low, and the tests can be difficult to interpret and may lead to inappropriate therapy.

Prevention of Infection

Consistent implementation of evidence-based prevention bundles has been essential to reduce HAI CLABSI rates. Prevention of CLABSI starts with preinsertion planning for the type and number of CVC lumens and selection of the venous site for CVC insertion. Insertion bundle elements include meticulous hand hygiene, aseptic skin preparation using 2% chlorhexidine gluconate, and use of maximal sterile barrier precautions in an operating room–like environment. Maintenance bundles guide the daily safe care of CVCs to prevent infections, including protecting the CVC from gross contamination with excretions or body fluids, evidence-based techniques to access and scrub the CVC hub and connectors, and assessing and changing the CVC site dressing. Regular assessment of the need for the catheter should be part of the daily medical and nursing care team discussions. In general, children with external CVCs are discouraged from swimming because of concern of subsequent CRBSI. However, existing evidence regarding risk of CRBSI related to swimming is limited. It is important to educate patient caregivers about the potential risk and the importance of maintaining a secured CVC with water-resistant dressing if patients choose to swim. Catheters should routinely be removed as soon as they are no longer needed. Although prevalence of infection increases with prolonged duration of catheter use, routine replacement of a required CVC, either at a new site or over a guide wire, results in significant morbidity and is not recommended. Other practices that have been associated with reduction in CLABSI rates include use of a chlorhexidine-impregnated sponge at the exit site and daily bathing of ICU patients with 2% chlorhexidine gluconate. Use of antibiotic, taurolidine, or ethanol lock solutions; heparin with preservatives; and alcohol-impregnated caps, as well as antimicrobial-impregnated/coated catheters may be appropriate in high-risk populations. There is no evidence that routine replacement of short-term peripheral catheters prevents phlebitis or other complications in children, so they should only be replaced when clinically indicated (e.g., phlebitis, dysfunction, dislodgment).

URINARY CATHETERS

Urinary catheters are a frequent cause of HAIs, with approximately 14 infections per 1,000 admissions, resulting in increasing duration of hospitalization, cost of patient care, morbidity, and mortality. Rates of CAUTI are highest among ICU patients. As with other devices, microorganisms adhere to the urinary catheter surface and establish a biofilm that allows proliferation. The physical presence of the catheter reduces the normal host defenses by preventing complete emptying of the bladder, thus providing a medium for growth, distending the urethra, and blocking periurethral glands. Almost all patients catheterized

for >30 days develop bacteriuria. The mechanism of the infection can be either from organisms colonizing the patient's perineal or rectal area or from organisms contaminating the hands of healthcare providers or contaminating equipment such as a collection bag. The organism burden in CAUTI is typically ≥100,000 colony-forming units/mL. Lower thresholds may be used where there is a high index of suspicion, but these episodes usually represent colonization rather than infection. Urine culture should only be performed in catheterized patients when infection is suspected, because asymptomatic colonization is ubiquitous and may lead to overtreatment and subsequent development of bacterial resistance. Gram-negative bacilli and *Enterococcus* spp. are the predominant organisms isolated in CAUTI; coagulase-negative staphylococci are implicated in approximately 15% of cases. Symptomatic UTIs should be treated with antibiotics and catheter removal. Catheter colonization with *Candida* spp. is common but rarely leads to invasive infection, and treatment does not have a long-term impact on colonization. Treatment for asymptomatic candiduria or bacteriuria is not recommended, except in neonates, immunocompromised patients, and those with urinary tract obstruction.

All urinary catheters introduce a risk for infection and thus should be used only when necessary and for the minimum required duration. Existing evidence supports the benefit of using alternatives to indwelling urethral catheters to prevent CAUTI, including external catheters in male patients, intermittent catheterization, or suprapubic catheters in selected patients. Hand hygiene and aseptic technique are part of the insertion bundles of interventions aimed at preventing CAUTI. Evidence-based urinary catheter maintenance practices are essential to prevent hospital-acquired CAUTI, including perineal hygiene, a closed drainage system, maintenance of unobstructed urine flow, and keeping the collection bag below the level of the bladder. Technologic advances have led to the development of silver- or antibiotic-impregnated urinary catheters that are associated with lower rates of infection. Prophylactic antibiotics do not significantly reduce the infection rates for long-term catheters but clearly increase the risk for infection with antibiotic-resistant organisms.

MECHANICAL VENTILATORS

Endotracheal intubation and mechanical ventilation are lifesaving technologies to support patients with respiratory failure and patients undergoing surgical procedures. However, VAP has contributed to prolonged hospital stay and increased costs in patients in medical and surgical ICUs. VAP is more frequently reported in adult than in pediatric patients. The mechanism of VAP is through microaspiration of colonizing oropharyngeal organisms to the lower respiratory tract and its associated host inflammatory response. Common pathogens causing VAP include gram-negative bacilli (e.g., *Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., and *P. aeruginosa*) and gram-positive cocci (e.g., *S. aureus* and *Streptococcus* spp.). Risk factors for VAP include medications that increase gastric pH (e.g., H_2 blockers, antacids, proton pump inhibitors), decreased level of consciousness, use of paralytics or muscle relaxant agents, and prolonged intubation. Progressive or acute-onset respiratory deterioration requiring increased mechanical setting support in a patient who has been intubated for more than 2 days should raise the suspicion of VAP. Chest diagnostic imaging and cultures of lower respiratory specimens (e.g., endotracheal aspiration or bronchoalveolar lavage) should be considered.

Evidence-based practices to prevent VAP include use of noninvasive ventilation (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP]) when possible to avoid endotracheal intubation and prevention of microaspiration by elevating the head of the bed, controlling cuff pressure, minimizing and early weaning of sedation, and maintaining closed ventilator circuits. Oral care with chlorhexidine gluconate for oropharyngeal decontamination has been included as an element in several VAP prevention bundles. Evidence regarding the efficacy and safety of other interventions such as use of probiotics or silver-coated endotracheal tubes has been inconclusive.

CEREBROSPINAL FLUID SHUNTS

Cerebrospinal fluid (CSF) shunting is required for the treatment of many children with **hydrocephalus**. The usual procedure uses a silicone rubber device with a proximal portion inserted into the ventricle, a unidirectional valve, and a distal segment that diverts the CSF from the ventricles to either the peritoneal cavity (**ventriculoperitoneal** [VP] shunt) or right atrium (**ventriculoatrial** [VA] shunt). The incidence of shunt infection ranges from 1% to 20% (average, 10%). The highest rates are reported in young infants, patients with prior shunt infections, and certain etiologies of hydrocephalus. Most infections result from intraoperative contamination of the surgical wound by skin flora. Accordingly, coagulase-negative staphylococci are isolated in more than half the cases. *S. aureus* is isolated in approximately 20% and gram-negative bacilli in 15% of cases.

Four distinct clinical syndromes have been described: colonization of the shunt, infection associated with wound infection, distal infection with peritonitis, and infection associated with meningitis. The most common type of infection is **colonization of the shunt**, with nonspecific symptoms that reflect shunt malfunction as opposed to frank infection. Symptoms associated with colonized VP shunts include lethargy, headache, vomiting, a full fontanel, and abdominal pain. Fever is often absent or may be low-grade (<39°C or 102.2°F). Symptoms usually occur within months of the surgical procedure. Colonization of a VA shunt results in more severe systemic symptoms, and specific symptoms of shunt malfunction are often absent. Septic pulmonary emboli, pulmonary hypertension, and infective endocarditis are frequently reported complications of VA shunt colonization. Chronic VA shunt colonization may cause hypocomplementemic glomerulonephritis from antigen-antibody complex deposition in the glomeruli, commonly called *shunt nephritis;* clinical findings include hypertension, microscopic hematuria, elevated blood urea nitrogen and serum creatinine levels, and anemia.

Diagnosis is by Gram stain, microscopy, biochemistry, and culture of CSF. CSF should be obtained by direct aspiration of the shunt before administration of antibiotics, because CSF obtained from either lumbar or ventricular puncture is often sterile. It is unusual to observe signs of ventriculitis, and CSF findings can be only minimally abnormal. Blood culture results are usually positive in VA shunt colonization but negative in cases of VP colonization.

Wound infection presents with obvious erythema, swelling, discharge, or dehiscence along the shunt tract and most often occurs within days to weeks of the surgical procedure. *S. aureus* is the most common isolate. In addition to the physical findings, fever is common, and signs of shunt malfunction eventually ensue in most cases.

Distal infection of VP shunts with **peritonitis** presents with abdominal symptoms, usually without evidence of shunt malfunction. The pathogenesis is likely related to perforation of the bowel at VP shunt placement or translocation of bacteria across the bowel wall. Thus gram-negative isolates predominate, and mixed infection is common. The infecting organisms are often isolated from only the distal portion of the shunt.

Common pathogens responsible for community-acquired **meningitis**, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b, cause bacterial meningitis in patients with shunts only rarely, and the clinical presentation is similar to that for acute bacterial meningitis in other children (see Chapter 643.1).

Treatment of shunt colonization includes removal of the shunt and systemic antibiotic therapy directed against the isolated organisms. Treatment without removal of the shunt is rarely successful and should not be routinely attempted. After collection of appropriate samples for culture, empirical therapy is usually with vancomycin plus an antipseudomonal agent with relatively good CSF penetration, such as ceftazidime or meropenem. Definitive therapy should be directed toward the isolate and should account for poor penetration of most antibiotics into the CSF across noninflamed meninges. Accordingly, intraventricular antibiotics may be indicated but are usually reserved unless there is evidence of treatment failure. If the isolate is susceptible, a parenteral antistaphylococcal penicillin with or without intraventricular vancomycin is the treatment of choice. If the organism is resistant to penicillins, systemic vancomycin and possibly intraventricular vancomycin are recommended. In gram-negative infections, a third-generation cephalosporin with or without an intraventricular aminoglycoside is

optimal. When using intraventricular antibiotics, monitoring CSF levels is necessary to avoid toxicity.

Removal of the colonized device is required for cure, and final replacement should be delayed until clearance of CSF cultures is documented. Many neurosurgeons immediately remove the shunt and place an external ventricular drain to relieve intracranial pressure (ICP), with a second-stage shunt replacement once CSF sterilization has been confirmed. Others opt initially to exteriorize the distal end of the shunt and replace the shunt in a single-stage procedure once CSF cultures remain sterile for 48-72 hours. Daily CSF cultures should be collected until clearance has been documented on two to three consecutive specimens, and antibiotics should be continued for at least 10 days after documented sterilization of the CSF. Gram-negative organisms may require a longer duration of therapy (up to 21 days). The CSF white cell count generally increases for the first 3-5 days of appropriate therapy, and that alone should not prompt concern for treatment failure. Distal shunt infection with peritonitis and wound infection are managed in a similar fashion.

Treatment of **bacterial meningitis** with typical community-acquired pathogens such as meningococcus or pneumococcus usually requires only systemic antibiotic therapy. Shunt replacement is not required in the absence of device malfunction, poor clinical response, persistent CSF culture positivity, or relapse of infection after antibiotic therapy.

Prevention of Infection

Prevention of shunt infection includes meticulous cutaneous preparation and surgical technique. Systemic and intraventricular antibiotics, antibiotic-impregnated shunts, and soaking the shunt tubing in antibiotics are used to reduce the incidence of infection, with varying success. Systemic prophylactic antibiotics given before and during shunt insertion can reduce the risk for infection and should be used routinely but should not be continued for more than 24 hours postoperatively. Antibiotic-impregnated catheters also appear to reduce the risk of infection and may be used in high-risk patients where the devices are available.

PERITONEAL DIALYSIS CATHETERS

During the first year of peritoneal dialysis for end-stage renal disease, 65% of children will have one or more episodes of peritonitis. Bacterial entry comes from luminal or periluminal contamination of the catheter or by translocation across the intestinal wall. Hematogenous infection is rare. Infants and young children who are in diapers are at highest risk for peritoneal dialysis catheter–associated infections. Infections can be localized at the exit site or associated with peritonitis, or both. Organisms responsible for peritonitis include coagulase-negative staphylococci (30–40%), *S. aureus* (10–20%), streptococci (10–15%), *E. coli* (5-10%), *Pseudomonas* spp. (5–10%), other gram-negative bacteria (5–15%), *Enterococcus* spp. (3–6%), and fungi (2–10%). *S. aureus* is more common in localized exit site or tunnel tract infections (42%). Most infectious episodes are caused by a patient's own flora, and carriers of *S. aureus* have increased rates of infection compared with noncarriers.

The clinical manifestations of peritonitis may be subtle and include low-grade fever with mild abdominal pain or tenderness. Cloudy peritoneal dialysis fluid may be the first and predominant sign. With peritonitis, the peritoneal fluid cell count is usually >100 white blood cells/μL. When peritonitis is suspected, the effluent dialysate should be submitted for a cell count, Gram stain, and culture. The Gram stain is positive in up to 40% of cases of peritonitis.

Patients with cloudy fluid and clinical symptoms should receive empirical therapy, preferably guided by results of a Gram stain. If no organisms are visualized, vancomycin and either an aminoglycoside or a third- or fourth-generation cephalosporin with antipseudomonal activity should be given by the intraperitoneal route. Blood levels should be measured for glycopeptides and aminoglycosides. Patients without cloudy fluid and with minimal symptoms may have therapy withheld pending culture results. Once the cause is identified by culture, changes in the therapeutic regimen may be needed. Oral **rifampin** may be added as adjunctive therapy for susceptible *S. aureus* isolates but should not be used as a standalone agent and must prompt consideration of drug interactions. Candidal peritonitis should be treated with catheter removal and intraperitoneal or oral **fluconazole** or an IV **echinocandin** such as caspofungin or micafungin, depending on the *Candida* spp.; catheter retention has been associated with almost inevitable relapse and higher risk of mortality in adult studies. The duration of therapy for peritonitis is a minimum of 14 days, with longer treatment of 21-28 days for episodes of *S. aureus, Pseudomonas* spp., and resistant gram-negative bacteria and 28-42 days for fungi. Repeat episodes of peritonitis with the same organism within 4 weeks of previous therapy should lead to consideration of catheter removal or attempt at salvage with administration of a fibrinolytic agent and a longer course of up to 6 weeks of antibiotic therapy.

In all cases, if the infection fails to clear after appropriate therapy or if a patient's condition is deteriorating, the catheter should be removed. Exit site and tunnel tract infections may occur independently of peritonitis or may precede it. Appropriate antibiotics should be administered on the basis of Gram stain and culture findings and are typically given systemically only, unless peritonitis is also present. Some experts recommend that the peritoneal catheter be removed if *Pseudomonas* spp. or fungal organisms are isolated.

Prevention of Infection

In addition to usual hygienic practices such as hand hygiene and aseptic care of the catheter exit site, regular application of **mupirocin** or **gentamicin** cream to the catheter exit site reduces exit site infections and peritonitis. Some practitioners recommend against the use of gentamicin cream because of the risk of infection with gentamicin-resistant bacteria. Systemic antibiotic prophylaxis should be considered at catheter insertion, if there is accidental contamination, and at dental procedures. Antifungal prophylaxis with oral nystatin or fluconazole should be considered during antibiotic therapy to prevent fungal infection.

IMPLANTABLE ORTHOPEDIC DEVICES

Implantable orthopedic devices are used infrequently in children. Orthopedic device infection most often follows introduction of microorganisms at surgery through airborne contamination or direct inoculation, hematogenous spread, breakdown of overlying skin, or contiguous spread from an adjacent infection. Early postoperative infection occurs within 2-4 weeks of surgery, with manifestations typically including fever, pain, and local symptoms of wound infection. Chronic infection presents >1 month after surgery and is often caused by organisms of low virulence that contaminated the implant at surgery or by failure of wound healing. Typical manifestations include pain and deterioration in function. Local symptoms such as erythema, swelling, or drainage may also occur. Acute hematogenous infections are most often observed ≥2 years after surgery and may be more common in children with immunocompromise. Options for treatment include conservative management with operative debridement and irrigation and retention of the prosthesis, followed by a 3- to 6-month course of antimicrobial therapy, or more radical intervention with removal and replacement of all hardware—as either a one- or two-stage exchange with a shorter course of antibiotic therapy (2-6 weeks). If the prosthesis is retained, suppressive oral antibiotic therapy may be considered after an initial treatment course, especially in patients who are undergoing intensive time-limited treatment such as chemotherapy. As with other long-term implanted devices, the most common organisms are coagulase-negative staphylococci and *S. aureus*. With prior antibiotic therapy, the prosthesis culture may be negative; in these situations, molecular techniques to identify the organism are available, but sensitivity and specificity are poorly understood.

Orthopedic hardware such as screws and plates are more commonly encountered in children than true implantable orthopedic devices. The management of infections associated with these kinds of hardware is similar to other orthopedic device infections, but because the hardware is typically temporary, it should generally be removed as soon as feasible.

Systemic antibiotic prophylaxis, antibiotic-containing bone cement, and operating rooms fitted with laminar airflow have been proposed to reduce infection. To date, results from clinical studies are conflicting.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3
Antibiotic Therapy

Chapter 225
Principles of Antibacterial Therapy

Mark R. Schleiss

Antibacterial therapy in infants and children presents many challenges. A daunting problem is the paucity of pediatric data regarding pharmacokinetics and optimal dosages; as a consequence, pediatric recommendations are frequently extrapolated from adult studies. A second challenge is the need for the clinician to consider important differences among pediatric age-groups with respect to the pathogenic species most often responsible for bacterial infections. Age-appropriate antibiotic dosing and toxicities must be considered, taking into account the developmental status and physiology of infants and children. Finally, the style of how a pediatrician uses antibiotics in children, particularly young infants, has some important differences compared with how antibiotics are used in adult patients.

Specific antibiotic therapy is optimally driven by a **microbiologic diagnosis**, predicated on isolation of the pathogenic organism from a sterile body site and supported by antimicrobial susceptibility testing. However, given the inherent difficulties that can arise in collecting specimens from pediatric patients and given the high risk of mortality and disability associated with serious bacterial infections in very young infants, much of pediatric infectious diseases practice is based on clinical diagnoses and **empirical** use of antibacterial agents, often administered before and/or without identification of the specific pathogen. Although there is an ever-increasing emphasis on **antimicrobial stewardship**, driven by the importance of using empirical therapy sparingly (to avoid selecting for resistant organisms), there are some settings in which antimicrobials must be administered before the presence of a specific bacterial pathogen is proven. This is particularly relevant to the care of the febrile or ill-appearing neonate or young infant under 30 days of age.

Several key considerations influence decision-making regarding the appropriate empirical use of antibacterial agents in infants and children. It is important to know the age-specific differential diagnosis with respect to likely pathogens. This information affects the choice of antimicrobial agent and also the dose, dosing interval, and route of administration (oral vs parenteral). A complete history and physical examination, combined with appropriate laboratory and radiographic studies, are necessary to identify specific diagnoses, information that in turn affects the choice, dosing, and degree of urgency of administration of antimicrobial agents. The vaccination history may confer reduced risk for some invasive infections (i.e., *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseria meningitidis*), but a history of vaccination does not necessarily eliminate risk. The threat of serious bacterial infection in pediatric practice is also affected by the child's immunologic status, which may be compromised by immaturity (neonates), underlying disease, and immunosuppressive medications used to treat other disorders (see Chapter 223). Infections in immunocompromised children may result from bacteria that are not considered pathogenic in immunocompetent children. The presence of foreign bodies (medical devices) also increases the risk of bacterial infections (see Chapter 224). The likelihood of central nervous system (CNS) involvement must be considered in all pediatric patients with serious bacterial infections, because many bacteremic pathogens in childhood carry a significant risk of hematogenous spread to the CNS.

The patterns of **antimicrobial resistance** in the community and for the potential causative pathogen being empirically covered must also be considered. Resistance to penicillin and cephalosporins is frequent among strains of *S. pneumoniae,* often necessitating the use of other classes of antibiotics. Similarly, the striking emergence of community-acquired methicillin-resistant *Staphylococcus aureus* **(MRSA)** infections has complicated antibiotic choices, both when this pathogen is isolated in culture and for empirical coverage of skin and soft tissue infections. Extended-spectrum β-lactamase **(ESBL)**–producing gram-negative bacteria (Enterobacteriaceae) have reduced the effectiveness of penicillins and cephalosporins. Furthermore, carbapenem-resistant Enterobacteriaceae **(CRE)** are an increasing problem among hospitalized patients, particularly in children with an epidemiologic connection to regions of the world, such as India, where such strains are frequently encountered.

Antimicrobial resistance occurs through many modifications of the bacterial genome (Tables 225.1 and 225.2). Mechanisms include enzyme inactivation of the antibiotic, decreased cell membrane permeability to intracellularly active antibiotics, efflux of antibiotics out of the bacteria, protection or alteration of the antibiotic target site, excessive production of the target site, and bypassing the antimicrobial site of action. CRISPR (clustered regularly interspaced short palindromic repeats) elements in bacteria have also been shown to be related to emergence of antimicrobial resistance. CRISPRs are detectable in many bacterial genomes, protecting their genomes from attack by foreign DNA during transformation, phage invasion, or plasmid insertion. The mechanism of protection is mediated by insertion of small sequences of the invading DNA between palindromic repeats within the CRISPR element. Upon re-exposure to similar DNA sequences from phage or invading bacteria, the existing sequence within the CRISPR is transcribed into a small RNA that associates with CRISPR-associated nucleases, blocking integration of the targeted foreign DNA. Deletion of CRISPR elements in *Enterococcus* is inversely related to antibiotic resistance, and CRISPR-deficient strains are selected for in the context of healthcare-associated infections. CRISPR deficiency allows for evolution of significantly larger genomes, and the attendant insertion of large sequences of DNA in turn enables expression of multiple antibiotic-resistance genes.

Antimicrobial resistance has reached *crisis proportions,* driven by the emergence of new resistance mechanisms (e.g., carbapenemases, including *Klebsiella pneumoniae*–associated carbapenemases, or **KPCs**) and by overuse of antibiotics, both in healthcare and in other venues, such as agribusiness and animal husbandry. This increase in antibiotic resistance has rendered some bacterial infections encountered in clinical practice virtually untreatable. Accordingly, there is an urgent need to develop new antimicrobials and to rediscover some older antibiotics that have been out of use in recent decades but still retain activity against resistant organisms. It is vital that practitioners use antibiotics only when truly indicated, with the narrowest feasible antimicrobial spectrum, to help thwart emergence of resistance. In addition, advocacy for **vaccines**, particularly conjugate pneumococcal vaccine, can also decrease the selective pressure that excessive antimicrobial use exerts on resistance.

Effective antibiotic action requires achieving therapeutic levels of the drug at the site of infection. Other factors to consider include the impact of pH on antibiotic activity; for example, an antibiotic may penetrate an abscess with adequate levels but may be inactive in the acidic milieu of the abscess cavity. Although measuring the level of antibiotic at the site of infection is not always possible, one may measure the serum level and use this level as a surrogate marker to achieve the desired effect at the tissue level. Various target serum levels are appropriate for different antibiotic agents and are assessed by the peak and trough serum levels and the area under the therapeutic drug level curve (Fig. 225.1). These levels in turn are a reflection of the route of administration, drug absorption (IM, PO), volume of distribution, and drug elimination half-life, as well as drug-drug interactions that might

enhance or impede enzymatic inactivation of an antibiotic or result in antimicrobial synergism or antagonism (Fig. 225.2).

AGE- AND RISK-SPECIFIC USE OF ANTIBIOTICS IN CHILDREN

Neonates

The causative pathogens associated with neonatal infections are typically acquired around the time of delivery. Thus empirical antibiotic selection must take into account the importance of these organisms (see Chapter 148). Among the causes of neonatal sepsis in infants, **group B *Streptococcus*** (GBS) is the most common. Although intrapartum antibiotic prophylaxis administered to women at increased risk for transmission of GBS to the infant has greatly decreased the incidence of this infection in neonates, particularly with respect to so-called *early-onset disease,* GBS infections are still frequently encountered in clinical practice (see Chapter 230). Gram-negative enteric organisms acquired from the maternal birth canal, in particular *Escherichia coli,* are also common causes of neonatal sepsis. Although less common, *Listeria monocytogenes* is an important pathogen to consider, in particular because this organism is intrinsically resistant to cephalosporin antibiotics, which are often used as empirical therapy for serious bacterial infections in young children. *Salmonella* bacteremia and **meningitis** on a global basis is a well-recognized infection in infants. All these organisms can be associated with meningitis in the neonate; therefore lumbar puncture should always be considered in the setting of bacteremic infections in this age-group, and antibiotic management should include agents capable of crossing the blood-brain barrier if meningitis cannot be excluded.

Older Children

Antibiotic choices in toddlers and young children were once driven by the high risk of this age-group to invasive disease caused by *H. influenzae* type b (**Hib**; see Chapter 240). With the advent of conjugate vaccines against Hib, invasive disease has declined dramatically. However, outbreaks still occur and have been observed in the context of parental refusal of vaccines. Therefore the use of antimicrobials that are active against Hib remains important in many clinical settings, particularly if meningitis is a consideration. Other important pathogens to consider in this age-group include *E. coli*, *S. pneumoniae, N. meningitidis,* and *S. aureus*. Strains of *S. pneumoniae* that are resistant to penicillin and cephalosporin antibiotics are frequently encountered in clinical practice. Similarly, MRSA is highly prevalent in children in the outpatient setting. Antibiotic resistance in *S. pneumoniae* and MRSA is a result of mutations that confer alterations in penicillin-binding proteins, the molecular targets of penicillin and cephalosporin activity (see Table 225.1).

Depending on the specific clinical diagnosis, other pathogens encountered among older children include *Moraxella catarrhalis*, nontypeable (nonencapsulated) strains of *H. influenzae*, and *Mycoplasma pneumoniae*, which cause upper respiratory tract infections and pneumonia; group A *Streptococcus*, which causes pharyngitis, skin and soft tissue infections, osteomyelitis, septic arthritis, and rarely, bacteremia with toxic shock syndrome; *Kingella kingae*, which causes bone and joint infections and bacteremia; viridians group streptococci and Enterococcus, which cause endocarditis; and *Salmonella* spp., which cause enteritis, bacteremia, osteomyelitis, and septic arthritis. Vector-borne bacterial infections, including infections with *Borrelia burgdorferi*, *Rickettsia rickettsii*, and *Anaplasma phagocytophilum*, are increasingly recognized in certain regions, with an emerging increase in prevalence related to global climate change. Zoonotic exposures, pet ownership, and uncommon dietary intake may suggest less common pathogens such as *Coxiella burnetii, Brucella abortus, Bartonella henselae, Yersinia pestis, L. monocytogenes,* and *Francisella tularensis,* all of which have unique antibiotic susceptibility profiles. These complexities

Table 225.1 Mechanisms of Resistance to β-Lactam Antibiotics

I. Alter target site (PBP)
  A. Decrease affinity of PBP for β-lactam antibiotic
    1. Modify existing PBP
      a. Create mosaic PBP
        (1) Insert nucleotides obtained from neighboring bacteria (e.g., penicillin-resistant *Streptococcus pneumoniae*)
        (2) Mutate structural gene of PBP(s) (e.g., ampicillin-resistant β-lactamase–negative *Haemophilus influenzae*)
    2. Import new PBP (e.g., *mecA* in methicillin-resistant *Staphylococcus aureus*)
II. Destroy β-lactam antibiotic
  A. Increase production of β-lactamases, carbapenemases
    1. Acquire more efficient promoter
      a. Mutate existing promoter
      b. Import new promoter
    2. Deregulate control of β-lactamase production
      a. Mutate regulator genes (e.g., *ampD* in "stably derepressed" *Enterobacter cloacae*)
  B. Modify structure of resident β-lactamase
    1. Mutate structural gene (e.g., ESBLs in *Klebsiella pneumoniae*)
  C. Import new β-lactamase(s) with different spectrum of activity
III. Decrease concentration of β-lactam antibiotic inside cell
  A. Restrict its entry (loss of porins)
  B. Pump it out (efflux mechanisms)

ESBLs, Extended-spectrum β-lactamases; PBP, penicillin-binding protein.
Adapted from Opal SM, Pop-Vicas A. Molecular mechanisms of antibiotic resistance in bacteria. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 9th ed. Philadelphia: Elsevier; 2020: Table 18-4.

Table 225.2 Aminoglycoside-Modifying Enzymes*

ENZYMES	USUAL ANTIBIOTICS MODIFIED	COMMON GENERA
PHOSPHORYLATION		
APH(2″)	K, T, G	SA, SR
APH(3′)-I	K	E, PS, SA, SR
APH(3′)-III	K ± A	E, PS, SA, SR
ACETYLATION		
AAC(2′)	G	PR
AAC(3)-I	±T, G	E, PS
AAC(3)-III, -IV, or -V	K, T, G	E, PS
AAC(6′)	K, T, A	E, PS, SA
ADENYLATION		
ANT(2″)	K, T, G	E, PS
ANT(4′)	K, T, A	SA
BIFUNCTIONAL ENZYMES		
AAC(6′)-APH(2″)	G, Ar	SA, Ent
AAC(6′)-Ibcr	G, K, T, FQ*	E

*Aminoglycoside-modifying enzymes confer antibiotic resistance through three general reactions: N-acetylation, O-nucleotidylation, and O-phosphorylation. For each of these general reactions, there are several different enzymes that attack a specific amino or hydroxyl group. The nomenclature for these enzymes lists the molecular site where the modification occurs after the type of enzymatic activity. An aminoglycoside acetyltransferase (AAC) that acts at the 3′ site is designated AAC(3′).There may be more than one enzyme that catalyzes the same reaction, however, and Roman numerals may be necessary (e.g., AAC[3′]-IV).
A, Amikacin; AAC, aminoglycoside acetyltransferase; ANT, aminoglycoside nucleotidyltransferase; APH, aminoglycoside phosphotransferase; Ar, arbekacin, E, Enterobacteriaceae; Ent, enterococci, FQ, fluoroquinolone (acetylates the piperazine ring in some fluoroquinolones), G, gentamicin; K, kanamycin; PR, *Providencia-Proteus*; PS, pseudomonads; SA, staphylococci; SR, streptococci; T, tobramycin.
Adapted from Opal SM, Pop-Vicas A. Molecular mechanisms of antibiotic resistance in bacteria. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 9th ed. Philadelphia: Elsevier; 2020: Table 18-5.

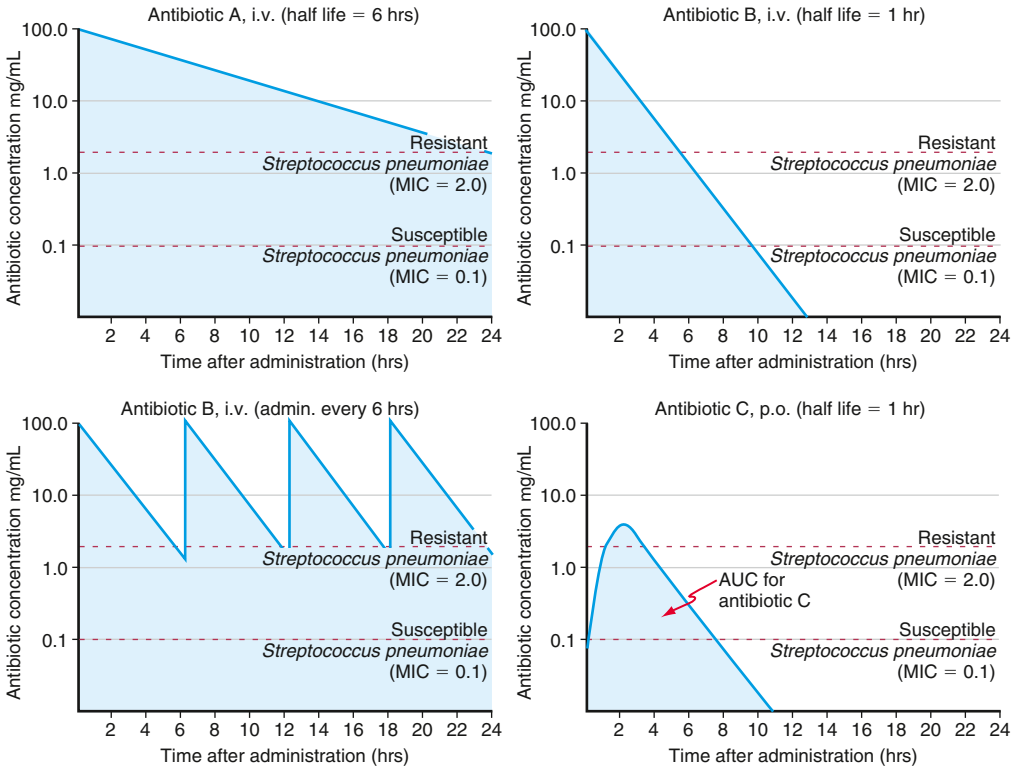

Fig. 225.1 Area under the curve (AUC; *shaded area*) for different antibiotics. The AUC provides a measure of antibiotic exposure to bacterial pathogens. The greatest exposure comes with antibiotics that have a long serum half-life and are administered parenterally (*upper left panel,* antibiotic A). The lowest exposure occurs with oral administration (*lower right panel,* antibiotic C). Dosing of antibiotic B once a day *(upper right panel)* provides far less exposure than dosing the same antibiotic every 6 hr *(lower left panel).* MIC, Minimal inhibitory concentration. *(From Pong AL, Bradley JS. Guidelines for the selection of antibacterial therapy in children. Pediatr Clin North Am. 2005;52:869–894.)*

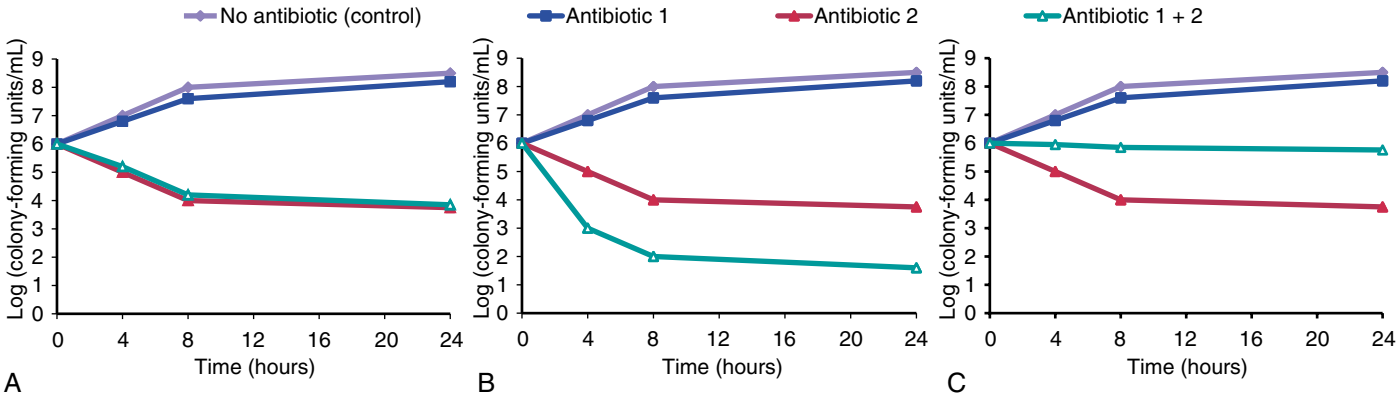

Fig. 225.2 Antibacterial effects of antibiotic combinations. **A,** Combination of antibiotics 1 and 2 is *indifferent;* killing by antibiotic 2 is unchanged when antibiotic 1 is added. **B,** Combination of antibiotics 1 and 2 results in *synergy;* killing by antibiotic 2 is significantly enhanced when antibiotic 1 is added at a subinhibitory concentration. **C,** Combination of antibiotics 1 and 2 is *antagonistic;* killing by antibiotic 2 is diminished in the presence of antibiotic 1. *(From Eliopoulos GM, Moellering RC Jr. Principles of anti-infective therapy. In: Bennett JF, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier; 2015: Fig 17-1.)*

underscore the importance of formulation of a complete differential diagnosis in children with suspected severe bacterial infections, including an assessment of the severity of the infection in parallel with consideration of local epidemiologic disease trends. Knowledge of the antimicrobial susceptibility patterns in the community is also critically important in devising an antibiotic treatment strategy.

Immunocompromised and Hospitalized Patients

It is important to consider the risks associated with immunocompromising conditions (malignancy, solid organ or hematopoietic stem cell transplantation, immunodeficiencies) and the risks conferred by conditions leading to prolonged hospitalization (intensive care, trauma, burns). Influenza infection can also predispose to invasive bacterial infections, especially those caused by *S. aureus*. Measles infection is well-known to predispose to serious bacterial infection, particularly with *Mycobacteria*. Infection with SARS-CoV-2 can also be associated with bacterial and fungal opportunistic infections. Immunocompromised children are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling catheters and caused by highly antibiotic-resistant gram-negative enteric organisms. In addition to bacterial pathogens already discussed, *Pseudomonas aeruginosa* and enteric organisms, including *E. coli, K. pneumoniae, Enterobacter,* and *Serratia,* are important opportunistic pathogens in these settings.

The so-called *ESKAPE pathogens* are a group of six highly virulent and antibiotic-resistant organisms that are being increasingly recognized in hospitalized patients, including *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species. Selection of appropriate antimicrobials is challenging because of the diverse causes and scope of antimicrobial resistance exhibited by these organisms. Many strains of enteric

organisms have resistance because of ESBLs (see Table 225.1). Class B metallo-β-lactamases (also known as *New Delhi metallo-β-lactamases*) that hydrolyze all β-lactam antibiotics except aztreonam and KPCs that confer resistance to carbapenems are increasingly being described. CRE are different from other multidrug-resistant microorganisms in that they are susceptible to few (if any) antibacterial agents.

Other modes of antimicrobial resistance exist that complicate management of common hospital-acquired infections. *P. aeruginosa* encodes proteins that function as efflux pumps to eliminate multiple classes of antimicrobials from the cytoplasm or periplasmic space. In addition to these gram-negative pathogens, infections caused by *Enterococcus faecalis* and *E. faecium* are inherently difficult to treat. Isolates of *E. faecalis* are typically susceptible to ampicillin, whereas most *E. faecium* are resistant to ampicillin, with resistance mediated by alterations in either the stoichiometry or sequence of a specific penicillin binding protein (PBP). These organisms may cause urinary tract infection (UTI) or infective endocarditis in immunocompetent children and may be responsible for a variety of syndromes in immunocompromised patients, especially in the setting of prolonged intensive care. The emergence of infections caused by **vancomycin-resistant enterococcus (VRE)** has further complicated antimicrobial selection in high-risk patients and has necessitated the development of newer antimicrobials that target these highly resistant gram-positive bacteria.

Infections Associated with Medical Devices

A special situation affecting antibiotic use is the presence of an indwelling medical device, such as a venous catheter, ventriculoperitoneal shunt, stent, or other catheter (see Chapter 224). In addition to *S. aureus,* coagulase-negative staphylococci are a major consideration. Coagulase-negative staphylococci seldom cause serious disease in the absence of risk factors such as indwelling catheters. Empirical antibiotic regimens must take this risk into consideration. In addition to appropriate antibiotic therapy, removal or replacement of the colonized prosthetic material is usually required for cure.

ANTIBIOTICS, INCLUDING NEWER AGENTS AND THERAPIES COMMONLY USED IN PEDIATRIC PRACTICE

Table 225.3 lists selected antibiotic medications, including recently licensed agents. Not all agents have formal pediatric indications, but dosage considerations for infants and children are provided, as available.

Penicillins

Although there has been ever-increasing emergence of resistance to penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

Penicillins remain the drugs of choice for pediatric infections caused by group A and group B streptococci, *Treponema pallidum* (syphilis), *L. monocytogenes,* and *N. meningitidis.* The **semisynthetic penicillins** (nafcillin, cloxacillin, dicloxacillin) are useful for management of susceptible (non-MRSA) staphylococcal infections. The **aminopenicillins** (ampicillin, amoxicillin) were developed to provide broad-spectrum activity against gram-negative organisms, including *E. coli* and *H. influenzae,* but the emergence of resistance (typically mediated by a β-lactamase) has limited their utility in many clinical settings. The **carboxypenicillins** (ticarcillin) and **ureidopenicillins** (piperacillin, mezlocillin, azlocillin) also have bactericidal activity against most strains of *P. aeruginosa.*

Resistance to penicillin is mediated by a variety of mechanisms (see Table 225.1). The production of β-lactamase is a common mechanism exhibited by many organisms that may be overcome, with variable success, by including a β-lactamase inhibitor in the therapeutic formulation with the penicillin. Such combination products (ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin–clavulanic acid [no longer available in the United States], piperacillin-tazobactam) are potentially very useful for management of resistant isolates, but only if the resistance is β-lactamase mediated. Notably, MRSA and *S. pneumoniae* mediate resistance to penicillins through mechanisms other than β-lactamase production, rendering these combination agents of little value for the management of these infections. Cephalosporin (ceftazidime/avibactam, ceftolozane/tazobactam) and carbapenem (meropenem/vaborbactam, and imipenem/relebactam) antibiotics combined with β-lactamase inhibitors have also been recently licensed by the FDA (described later). In addition, the FDA has recently approved a novel β-lactam-β-lactamase inhibitor combination, sulbactam-durlobactam (SUL-DUR), designed specifically for the treatment of carbapenem-resistant *Acinetobacter baumannii* infections, in particular, those associated with hospital-acquired and ventilator-associated pneumonias.

Table 225.4 lists adverse reactions to penicillins.

Cephalosporins

Cephalosporins differ structurally from penicillins insofar as the β-lactam ring exists as a six-member ring, compared with the five-member ring structure of the penicillins. These agents are widely used in pediatric practice, both in oral and parenteral formulations (Table 225.5). The **first-generation cephalosporins** (e.g., cefazolin, a parenteral formulation, and cephalexin, an oral equivalent) are commonly used for management of skin and soft tissue infections caused by susceptible strains of *S. aureus* and group A streptococcus. The **second-generation cephalosporins** (e.g., cefuroxime, cefoxitin) have better activity against gram-negative bacterial infections than first-generation cephalosporins and are used to treat respiratory tract infections, UTIs, and skin and soft tissue infections. A variety of orally administered second-generation agents (cefaclor, cefprozil, loracarbef, cefpodoxime) are commonly used in the outpatient management of sinopulmonary infections and otitis media. The agents cefoxitin and cefotetan are also referred to as **cephamycins**, because they were originally isolated from actinomycetes (although synthetic versions also have been developed). The **third-generation cephalosporins** (cefotaxime [no longer available], ceftriaxone, and ceftazidime) are typically used for serious pediatric infections, including meningitis and sepsis. Oral third-generation cephalosporins have been developed, including cefixime, ceftibuten, cefdinir, cefpodoxime, and cefditoren. Ceftazidime is highly active against most strains of *P. aeruginosa,* making this a useful agent for febrile, neutropenic oncology patients. The FDA approved the combination of ceftazidime and the novel β-lactamase inhibitor avibactam in 2015. Current indications include complicated intraabdominal infections and UTIs. The combination may also be useful for the treatment of infection caused by KPCs. Pediatric experience is limited. Ceftriaxone should not be mixed or reconstituted with a calcium-containing product, such as Ringer or Hartmann solution or parenteral nutrition containing calcium, because particulate formation can result. Cases of fatal reactions with ceftriaxone-calcium precipitates in the lungs and kidneys in neonates have been reported.

Cefepime is a **fourth-generation cephalosporin** and has activity against *P. aeruginosa* along with good activity against methicillin-susceptible *S. aureus*. Phase 3 studies of two new formulations of cefepime (one combined with a β-lactamase inhibitor, taniborbactam, and the other with a penicillanic acid sulfone β-lactamase inhibitor, enmetazobactam) are ongoing. *Cefpirome* is a fourth-generation cephalosporin with activity against *P. aeruginosa* and methicillin-sensitive *S. aureus* (MSSA) and is licensed for complicated UTIs and ventilator-associated pneumonia in adults, but no data on pediatric use are available. *Ceftizoxime* is a fourth-generation cephalosporin that is no longer in use in the United States. *Cefiderocol* is a novel cephalosporin that is classified as a *siderophore* antibiotic and is used for treatment of resistant gram-negative organisms, particularly *P. aeruginosa,* associated with complicated UTIs. It also recently received FDA approval for the treatment of hospital-acquired bacterial pneumonia caused by resistant gram-negative organisms. Its mechanism of action involves binding to iron, followed by active transport into bacterial cells. It was the first siderophore antibiotic to be approved by the FDA. It is approved for ages 18 and older, so pediatric experience is limited. Some classification schemes have classified it as a fourth-generation cephalosporin.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Amikacin sulfate Amikin Injection: 50 mg/mL, 250 mg/mL	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 7.5 mg/kg q12-18h IV or IM; weight >2,000 g: 10 mg/kg q12h IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 7.5 mg/kg q8-12h IV or IM; weight >2,000 g: 10 mg/kg q8h IV or IM Children: 15-25 mg/kg/24 hr divided q8-12h IV or IM Adults: 15 mg/kg/24 hr divided q8-12h IV or IM	*Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs. *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L.
Amoxicillin Amoxil, Polymox Capsule: 250, 500 mg Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL, 250 mg/5 mL Drops: 50 mg/mL	**Penicillinase-susceptible β-lactam: gram-positive pathogens except *Staphylococcus;* susceptible gram-negatives, including *Salmonella, Shigella, Neisseria* species, *E. coli,* and *Proteus mirabilis*** Children: 20-50 mg/kg/24 hr divided q8-12h PO; higher dose of 80-90 mg/kg 24 hr PO for otitis media Adults: 250-500 mg q8-12h PO	*Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally. *Drug interaction:* Probenecid.
Amoxicillin-clavulanate Augmentin Oral Tablet: 250, 500, 875 mg Tablet, chewable: 125, 200, 250, 400 mg Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL	**β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*** Neonates: 30 mg/kg/24 hr divided q12h PO Children: 20-45 mg/kg 24 hr divided q8-12h PO; higher dose 80-90 mg/kg/24 hr PO for otitis media	*Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally. *Drug interaction:* Probenecid. *Comment:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae.*
Ampicillin Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL Injection Oral	**β-Lactam with same spectrum of antibacterial activity as amoxicillin** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/kg/24 hr IV or IM q12h (meningitis: 100 mg/kg/24 hr divided q12h IV or IM); weight >2,000 g: 75 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr divided q8h IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q12h (meningitis: 100 mg/kg/24 hr divided q12h IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr divided q8hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q6h IV or IM (meningitis: 200 mg/kg/24 hr divided q6h IV or IM) Children: 100-200 mg/kg/24 hr divided q6h IV or IM (meningitis: 200-400 mg/kg/24 hr divided q4-6h IV or IM) Adults: 250-500 mg q4-8h IV or IM	*Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea. *Drug interaction:* Probenecid.
Ampicillin-sulbactam Unasyn Injection	**β-Lactam (ampicillin) and β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*** Children: 100-200 mg/kg/24 hr divided q4-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max daily dose: 8 g)	*Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally. *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae.* *Drug interaction:* Probenecid.
Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Azalide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Mycoplasma, Legionella, Chlamydia trachomatis, Babesia microti*** Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q24h for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days Adults: 500 mg PO on day 1, followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose PO	*Note:* Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited GI distress. Shorter-course regimens (e.g., 1-3 days) under investigation. For a 3-day course of therapy, use dose of (10 mg/kg/24 hr × 3 days); single-dose therapy, 30 mg/kg (not for streptococcal pharyngitis).
Aztreonam Azactam Injection	**β-Lactam (monobactam) antibiotic with activity against gram-negative aerobic bacteria, Enterobacteriaceae, and *Pseudomonas aeruginosa*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 90 mg/kg/24 hr divided q8h IV or IM; postnatal age >7 days weight <1,200 g: 60 mg/kg/24 hr divided q12h IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q8h IV or IM; weight >2,000 g: 120 mg/kg/24 hr divided q6-8h IV or IM Children: 90-120 mg/kg/24 hr divided q6-8h IV or IM. For cystic fibrosis, up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q8-12h (max dose: 8 g/24 hr)	*Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cefadroxil Generic Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus* Children: 30 mg/kg/24 hr divided q12h PO (max dose: 2 g) Adults: 250-500 mg q8-12h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q12-24h dosing. *Drug interaction:* Probenecid.
Cefazolin Ancef, Kefzol Injection	First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus* Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q12h IV or IM; >7 days 40-60 mg/kg/24 hr divided q8h IV or IM Children: 50-100 mg/kg/24 hr divided q8h IV or IM Adults: 0.5-2g q8h IV or IM (max dose: 12 g/24 hr)	*Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. *Drug interaction:* Probenecid.
Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL	Extended-spectrum, semisynthetic cephalosporin Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q24h PO	*Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart. *Drug interaction:* Probenecid.
Cefepime Maxipime Injection	Expanded-spectrum, fourth-generation cephalosporin active against many gram-positive and gram-negative pathogens, including *P. aeruginosa* and many multidrug-resistant pathogens Children: 100-150 mg/kg/24 hr q8-12h IV or IM Adults: 2-4 g/24 hr q12h IV or IM	*Adverse events:* Diarrhea, nausea, vaginal candidiasis. Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Cefiderocol Fetroja Injection 1 g vials	Expanded-spectrum, classified in some classifications as a fourth-generation cephalosporin; novel siderophore antibiotic; mechanism of action is mediated by binding to iron, followed by active transport into bacterial cells Indicated for treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-negative microorganisms and for hospital-acquired and ventilator-associated pneumonia Adults: 2 g IV q8hr for 7-14 days Children: dose not established	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Not indicated for meningitis (in contrast with cefepime).
Cefixime Suprax Oral Tablet: 200, 400 mg Suspension: 100 mg/5 mL	Third-generation cephalosporin active against streptococci, *H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, Serratia marcescens*, and *Proteus vulgaris* No antistaphylococcal or antipseudomonal activity Children: 8 mg/kg/24 hr divided q12-24h PO Adults: 400 mg/24 hr divided q12-24h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. *Drug interaction:* Probenecid.
Cefoperazone sodium Cefobid Injection	Third-generation cephalosporin active against many gram-positive and gram-negative pathogens Neonates: 100 mg/kg/24 hr divided q12h IV or IM Children: 100-150 mg/kg/24 hr divided q8-12h IV or IM Adults: 2-4 g/24 hr divided q8-12h IV or IM (max dose: 12 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable gram-positive activity. Primarily hepatically eliminated in bile. *Drug interaction:* Disulfiram-like reaction with alcohol.
Cefotaxime sodium Claforan Injection	Third-generation cephalosporin active against gram-positive and gram-negative pathogens. No antipseudomonal activity Neonates: ≤7 days: 100 mg/kg/24 hr divided q12h IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q12h IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q8h IV or IM Children: 150 mg/kg/24 hr divided q6-8h IV or IM (meningitis: 200 mg/kg/24 hr divided q6-8h IV) Adults: 1-2 g q8-12h IV or IM (max dose: 12 g/24 hr)	
Cefotetan disodium Cefotan Injection	Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter* Children: 40-80 mg/kg/24 hr divided q12h IV or IM Adults: 2-4 g/24 hr divided q12h IV or IM (max dose: 6 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile).

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cefoxitin sodium Mefoxin Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Neonates: 70-100 mg/kg/24 hr divided q8-12h IV or IM Children: 80-160 mg/kg/24 hr divided q6-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max dose: 12 g/24 hr)	*Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly. *Drug interaction:* Probenecid.
Cefpirome Cefrom Keiten Broact Cefir	**Fourth-generation cephalosporin; indicated for complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-negative microorganisms; indicated for hospital-acquired and ventilator-associated pneumonia** Adults: 2 g IV q 8hr for 7-14 days Children: Dose not established	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Not indicated for meningitis (in contrast with cefepime).
Cefpodoxime proxetil Vantin Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL, 100 mg/5 mL	**Third-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, E. coli, Klebsiella*, and *Proteus*** **No antipseudomonal activity** Children: 10 mg/kg/24 hr divided q12h PO Adults: 200-800 mg/24 hr divided q12h PO (max dose: 800 mg/24 hr) Uncomplicated gonorrhea: 200 mg PO as single-dose therapy	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food. *Drug interaction:* Probenecid; antacids and H_2 receptor antagonists may decrease absorption.
Cefprozil Cefzil Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus* spp.** Children: 30 mg/kg/24 hr divided q8-12h PO Adults: 500-1,000 mg/24 hr divided q12h PO (max dose: 1.5 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability. *Drug interaction:* Probenecid.
Ceftaroline fosamil Teflaro Injection 400 mg/vial (20 mg/mL reconstituted) 600 mg/vial (30 mg/mL reconstituted)	**Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft tissue infection), *S. pyogenes, S. agalactiae, E. coli, K. pneumoniae, H. influenzae,* and *K. oxytoca*** Children: skin/skin structure infections *or* community-acquired pneumonia, 24 mg/kg/24 hr divided q8h IV (2-23 mo old) ×5-14 days; 36 mg/kg/24 hr divided q8h IV (weight ≤33 kg) ×5-14 days; 400 mg q8h IV (weight >33 kg) Adults: 600 mg q12h IV	*Caution:* β-Lactam safety profile (rash, eosinophilia). *Drug interaction:* Probenecid.
Ceftazidime Fortaz, Ceptaz, Tazicef, Tazidime Injection	**Third-generation cephalosporin active against gram-positive and gram-negative pathogens, including *P. aeruginosa*** Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q12h IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q12h IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q8h IV or IM Children: 150 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr IV divided q8h) Adults: 1-2 g q8-12h IV or IM (max dose: 8-12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use. *Drug interaction:* Probenecid.
Ceftazidime/avibactam Avycaz Injection (2 g/0.5 g)/vial: 2.5 g Equivalent to 2.635 g of ceftazidime and 0.551 g of avibactam sodium	**Third-generation cephalosporin active against gram-positive and gram-negative pathogens, including *P. aeruginosa;* addition of β-lactamase; inhibits *K. pneumoniae* carbapenemases and AmpC-type β-lactamases that are resistant to β-lactamases, tazobactam, and clavulanic acid** **Useful for complicated intraabdominal infections, urinary tract infections, and pneumonia** Adults: 2.5 g (2 g/0.5 g) IV q8h infused over 2 hr for 7-14 days Children: 3 mo to <2 yr: 62.5 mg/kg (ceftazidime 50 mg/kg and avibactam 12.5 mg/kg) IV q8h for 5-14 days 2 yr to <18 yr: 62.5 mg/kg (ceftazidime 50 mg/kg and avibactam 12.5 mg/kg) IV q8h for 5-14 days; not to exceed 2.5 g (ceftazidime 2 g and avibactam 0.5 g)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ceftolozane/tazobactam Zerbaxa Injection	**Fifth-generation cephalosporin (with β-lactamase inhibitor) indicated for complicated intraabdominal infections; acute pyelonephritis; complicated urinary tract infections; hospital-acquired and ventilator-associated bacterial pneumonia** Adults: Community-acquired pneumonia, skin and soft tissue infections 600 mg IV q12 h ×5-7 days Children: Birth to <2 mo: 6 mg/kg IV q8h ×5-14 days 2 mo to <2 yr: 8 mg/kg IV q8h ×5-14 days 2 yr to <18 yr (≤33 kg): 12 mg/kg IV q8h ×5-14 days 2 yr to <18 yr (>33 kg): 400 mg q8h OR 600 mg q12h IV ×5-14 days	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Ceftriaxone sodium Rocephin Injection	**Third-generation cephalosporin widely active against gram-positive and gram-negative pathogens** **No antipseudomonal activity** Neonates: 50-75 mg/kg q24h IV or IM Children: 50-75 mg/kg q24h IV or IM (meningitis: 75 mg/kg dose once then 80-100 mg/kg/24 hr divided q12-24h IV or IM) Adults: 1-2 g q24h IV or IM (max dose: 4 g/24 hr) Gonorrhea: 500 mg IM, single dose	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33–65%) and bile; can cause sludging. Long half-life and dose-dependent protein binding favors q24h rather than q12h dosing. Can add 1% lidocaine for IM injection. *Drug interaction:* Probenecid. In neonates, co-administration with calcium-containing products can result in severe precipitation and attendant embolic complications.
Cefuroxime (cefuroxime axetil for oral administration) Ceftin, Kefurox, Zinacef Injection Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella,* and *Proteus*** Neonates: 40-100 mg/kg/24 hr divided q12h IV or IM Children: 200-240 mg/kg/24 hr divided q8h IV or IM; PO administration: 20-30 mg/kg/24 hr divided q8-12h PO Adults: 750-1,500 mg q8h IV or IM (max dose: 6 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability. *Drug interaction:* Probenecid.
Cephalexin Keflex, Keftab Capsule: 250, 500 mg Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella,* and *Proteus*** Children: 25-100 mg/kg/24 hr divided q6-8h PO Adults: 250-500 mg q6h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Cephradine Velosef Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella,* and *Proteus*** Children: 50-100 mg/kg/24 hr divided q6-12h PO Adults: 250-500 mg q6-12h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Ciprofloxacin Cipro Tablet: 100, 250, 500, 750 mg Injection Ophthalmic solution and ointment Otic suspension Oral suspension: 250 and 500 mg/5 mL	**Quinolone antibiotic active against *P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoeae, H. influenzae, M. catarrhalis,* some *S. aureus,* and some *Streptococcus*** Neonates: 10 mg/kg q12h PO or IV Children: 15-30 mg/kg/24 hr divided q12h PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q8-12h PO or IV Adults: 250-750 mg q12h; 200-400 mg IV q12h PO (max dose: 1.5 g/24 hr)	*Cautions:* Concerns of joint destruction in juvenile animals but not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity. *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate; probenecid; warfarin; cyclosporine.
Clarithromycin Biaxin Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis*** Children: 15 mg/kg/24 hr divided q12h PO Adults: 250-500 mg q12h PO (max dose: 1 g/24 hr)	*Cautions:* Adverse events less than erythromycin; GI upset, dyspepsia, nausea, cramping. *Drug interactions:* Same as erythromycin: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus.
Clindamycin Cleocin Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection Topical solution, lotion, and gel Vaginal cream	**Protein synthesis inhibitor active against most gram-positive aerobic and anaerobic cocci except *Enterococcus*** Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 15 mg/kg/24 hr divided q8h IV or IM; >7 days weight <1,200 g: 10 mg/kg/24 hr IV or IM divided q12h; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q8h IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q8h IV or IM Children: 10-40 mg/kg/24 hr divided q6-8h IV, IM, or PO Adults: 150-600 mg q6-8h IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)	*Cautions:* Diarrhea, nausea, *Clostridium difficile*–associated colitis, rash. Administer slow IV over 30-60 min. Topically active as an acne treatment.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cloxacillin sodium Tegopen Capsule: 250, 500 mg Suspension: 125 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 50-100 mg/kg/24 hr divided q6h PO Adults: 250-500 mg q6h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability. *Drug interaction:* Probenecid.
Colistin (colistimethate sodium; polymyxin E) Injection Inhalation	**Treatment of multidrug-resistant gram-negative organisms (*Enterobacteriaceae* including extended-spectrum β-lactamase– and carbapenemase-producing strains)** Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV Adults: 300 mg/day in 2-4 divided doses IV	*Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia). *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides.
Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) Bactrim, Cotrim, Septra, Sulfatrim Tablet: SMX 400 mg and TMP 80 mg Tablet DS: SMX 800 mg and TMP 160 mg Suspension: SMX 200 mg and TMP 40 mg/5 mL Injection	**Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci*** **Dosage based on TMP component** Children: 6-20 mg TMP/kg/24 hr or IV divided q12h PO *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q12h PO or IV *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO Adults: 160 mg TMP q12h PO	*Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure. *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine.
Dalbavancin Dalvance 500 mg/vial (20 mg/mL after reconstitution) Injection	**Glycopeptide antibiotic; bacteriocidal; disrupts cell wall synthesis** Indicated for acute bacterial skin and skin structure infections caused by susceptible gram-positive bacteria; active against MRSA Adult dose: 1-dose regimen of 1,500 mg IV or 2-dose regimen of 1000 mg IV followed 1 wk later by 500 mg IV; infuse IV over 30 min Pediatric dose: Not approved for use in children	Rapid IV infusion, as with other glycopeptide antibacterial agents, can cause reactions, including upper body flushing, urticaria, pruritus, back pain, and rash; stopping or slowing infusion may result in cessation of these reactions.
Daptomycin Cubicin Injection	**Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death** **Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft tissue infections** **Acceptable for bacteremia and right-sided endocarditis with susceptible strains** Adults: In skin and soft tissue infections, 4 mg/kg daptomycin IV once daily. For *S. aureus* bacteremia or right-sided endocarditis, 6 mg/kg IV once daily Children: For skin/skin structure infections, 12-23 mo, 10 mg/kg IV q24h; 2-6 yr, 9 mg/kg IV q24h; 7-11 yr, 7 mg/kg q24h; 12-17 yr, 5 mg/kg q24h, all for up to 14 days. For staphylococcal bacteremia, 1-6 yr, 12 mg/kg q24h; 7-11 yr, 9 mg/kg q24h; 12-17 yr, 7 mg/kg q24h; all for up to 42 days. For staphylococcal endocarditis, 1-5 yr, 10 mg/kg IV q24h for at least 6 wk; ≥6 yr, 6 mg/kg IV q24h for at least 6 wk	*Cautions:* Should not be used for pneumonia because drug inactivated by surfactants. Associated with rash, renal failure, anemia, and headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia. *Drug interactions:* Should not be administered with statins.
Delafloxacin Baxdela Injection Oral Injection, lyophilized powder for reconstitution 300 mg/vial (equivalent to 433 mg delafloxacin meglumine) Tablet, 450 mg (equivalent to 649 mg delafloxacin meglumine)	**Fluoroquinolone class of drugs; active against MSSA, MRSA, CoNS, and streptococci; retains activity against fluoroquinolone-resistant *S. aureus* strains.** **Approved for skin and soft tissue infections and community-acquired pneumonia.** Adults: 300 mg IV q12h for 5-14 days OR 300 mg IV q12h, then switch to a 450-mg tablet PO q12h for 5-14 days OR 450 mg PO q12h for 5-14 days Children: No dosage established	Similar to ciprofloxacin.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Demeclocycline Declomycin Tablet: 150, 300 mg Capsule: 150 mg	**Tetracycline active against most gram-positive cocci except *Enterococcus*, many gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 8-12 mg/kg/24 hr divided q6-12h PO Adults: 150 mg PO q6-8h Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q6-8h PO with dose reduction based on response to 600-900 mg/24 hr	*Cautions:* Teeth staining, possibly permanent (if administered <8 yr old) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections. *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption.
Dicloxacillin Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 12.5-100 mg/kg/24 hr divided q6h PO Adults: 125-500 mg q6h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renal (65%) and biliary (30%) elimination. Food may decrease bioavailability. *Drug interaction:* Probenecid.
Doripenem Doribax Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** Children: dose unknown Adults: 500 mg q8h IV	*Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70–75%); dose adjustment for renal failure. *Drug interactions:* Valproic acid, probenecid.
Doxycycline Vibramycin, Doxy Injection Capsule: 50, 100 mg Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	**Tetracycline antibiotic active against most gram-positive cocci except *Enterococcus*, many gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 2-5 mg/kg/24 hr divided q12-24h PO or IV (max dose: 200 mg/24 hr) Adults: 100-200 mg/24 hr divided q12-24h PO or IV	*Cautions:* Teeth staining, possibly permanent (<8 yr old) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections. *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, and barbiturates may decrease half-life.
Eravacycline Xerava 50 mg single-dose vials	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and CRE** Indicated for treatment of complicated intraabdominal infections in adults Dose: 1 mg/kg IV q12h ×4-14 days; infuse IV over ~60 min	Contraindications similar to other tetracyclines, including photosensitivity; pseudotumor cerebri; concerns for discoloration of tooth enamel in children under 8 yr of age.
Erythromycin E-Mycin, Ery-Tab, Eryc, Ilosone Estolate 125, 500 mg Tablet EES: 200 mg Tablet base: 250, 333, 500 mg Suspension: estolate 125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL, 400 mg/5 mL Estolate drops: 100 mg/mL; EES drops: 100 mg/2.5 mL Available in combination with sulfisoxazole (Pediazole), dosed on erythromycin content	**Bacteriostatic macrolide antibiotic most active against gram-positive organisms, *Corynebacterium diphtheriae*, and *Mycoplasma pneumoniae*** Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q12h PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q12h PO; weight >1,200 g: 30 mg/kg/24 hr divided q8h PO (give as 5 mg/kg/dose q6h to improve feeding intolerance) Children: Usual max dose: 2 g/24 hr Base: 30-50 mg/kg/24 hr divided q6-8h PO Estolate: 30-50 mg/kg/24 hr divided q8-12h PO Stearate: 20-40 mg/kg/24 hr divided q6h PO Lactobionate: 20-40 mg/kg/24 hr divided q6-8h IV Gluceptate: 20-50 mg/kg/24 hr divided q6h IV; usual max dose: 4 g/24 hr IV Adults: Base: 333 mg PO q8h; estolate/stearate/base: 250-500 mg q6h PO	*Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, and diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of GI adverse events. Rare cardiac toxicity with IV use. Dose of salts differs. Topical formulation for treatment of acne. *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus.
Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q12-18h IV or IM; weight <2,000 g: 2.5 mg/kg q12h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 2.5 mg/kg q8-12h IV or IM; weight >2,000 g: 2.5 mg/kg q8h IV or IM Children: 2.5 mg/kg/24 hr divided q8-12h IV or IM; alternatively, may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q8h IV or IM	*Cautions:* Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs. *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with intermittent daily dose regimens only.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Imipenem-cilastatin Primaxin Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*** Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/kg q18-24h IV or IM; weight >1,200 g: 40 mg/kg divided q12h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q12h IV or IM; weight >2,000 g: 60 mg/kg q8h IV or IM Children: 60-100 mg/kg/24 hr divided q6-8h IV or IM Adults: 2-4 g/24 hr divided q6-8h IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated. *Drug interaction:* Possibly ganciclovir.
Imipenem/relebactam (imipenem/cilastatin/relebactam) Recarbrio 500 mg/500 mg/250 mg per vial (i.e., 1.25 g/vial)	**Carbapenem antibiotic similar to imipenem/cilastatin; addition of relebactam restores activity against *K. pneumoniae* isolates that encode KPCs; is indicated for treatment of complicated urinary tract infections and complicated intraabdominal infections and hospital-acquired/ventilator-associated bacterial pneumonia in adults 18 yr of age and older** Adults: 1.25 g IV q6h ×4-14 days Children: No dosing information available	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated.
Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL	**Oxazolidinone antibiotic active against gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis*. Interferes with protein synthesis by binding to 50S ribosome subunit** Children: 10 mg/kg q12h IV or PO Adults: Pneumonia: 600 mg q12h IV or PO; skin infections: 400 mg q12h IV or PO	*Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache, peripheral and optic neuropathy. *Drug interaction:* Probenecid.
Loracarbef Lorabid Generic Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella,* and *Proteus*** Children: 30 mg/kg/24 hr divided q12h PO (max dose: 2 g) Adults: 200-400 mg q12h PO (max dose: 800 mg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Meropenem Merrem Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** **No activity against *S. maltophilia*** Children: 60 mg/kg/24 hr divided q8h IV; meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q8h IV Adults: 1.5-3 g q8h IV	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem; 80% renal elimination. *Drug interaction:* Probenecid.
Meropenem/vaborbactam Vabomere 1 g/1 g vials	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** **Vaborbactam protects meropenem from degradation by certain serine β-lactamases including *K. pneumoniae* carbapenemases (KPCs); added to enhance activity for complicated urinary tract infections, including pyelonephritis caused by *E. coli, K. pneumoniae,* and *E. cloacae* species complex in adults ≥18 yr** Adults: 4 g (meropenem [2 g]/vaborbactam [2 g]) IV q8h for up to 14 days; infuse over 3 hr.	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem; 80% renal elimination. *Drug interaction:* Probenecid.
Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg	**Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis** Neonates: weight <1,200 g: 7.5 mg/kg/48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q24h PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q12h PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q12h PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q12 h PO or IV Children: 30 mg/kg/24 hr divided q6-8h PO or IV Adults: 30 mg/kg/24 hr divided q6h PO or IV (max dose: 4 g/24 hr)	*Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment. *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium.
Mezlocillin sodium Mezlin Infection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia,* and *Bacteroides;* limited antipseudomonal activity** Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q12h IV; >7 days: 225 mg/kg divided q8h IV Children: 200-300 mg/kg/24 hr divided q4-6h IV; cystic fibrosis 300-450 mg/kg/24 hr IV Adults: 2-4 g/dose q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Mupirocin Bactroban Ointment	**Topical antibiotic active against *Staphylococcus* and *Streptococcus*** Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times daily	*Caution:* Minimal systemic absorption because drug metabolized within the skin.
Nafcillin sodium Nafcil, Unipen Injection Capsule: 250 mg Tablet: 500 mg	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q8h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h; weight >2,000 g: 100 mg/kg/24 hr divided q6-8h IV (meningitis: 200 mg/kg/24 hr divided q6h IV) Children: 100-200 mg/kg/24 hr divided q4-6h IV Adults: 4-12 g/24 hr divided q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended). *Adverse effect:* Neutropenia.
Nalidixic acid NegGram Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL	**First-generation quinolone effective for short-term treatment of lower UTIs caused by *E. coli, Enterobacter, Klebsiella*, and *Proteus*** Children: 50-55 mg/kg/24 hr divided q6h PO; suppressive therapy: 25-33 mg/kg/24 hr divided q6-8h PO Adults: 1 g q6h PO; suppressive therapy: 500 mg q6h PO	*Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections. *Drug interactions:* Liquid antacids.
Neomycin sulfate Mycifradin Tablet: 500 mg Topical cream, ointment Solution: 125 mg/5 mL	**Aminoglycoside antibiotic used for topical application or orally before surgery to decrease GI flora (nonabsorbable) and hyperammonemia** Infants: 50 mg/kg/24 hr divided q6h PO Children: 50-100 mg/kg/24 hr divided q6-8h PO Adults: 500-2,000 mg/dose q6-8h PO	*Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate. *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash. Like any aminoglycoside, ototoxicity and nephrotoxicity occur if absorbed.
Nitrofurantoin Furadantin, Furan, Macrodantin Capsule: 50, 100 mg Extended-release capsule: 100 mg Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL	**Effective in treatment of lower UTIs caused by gram-positive and gram-negative pathogens** Children: 5-7 mg/kg/24 hr divided q6h PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q12-24h PO (max dose: 100 mg/24 hr) Adults: 50-100 mg/24 hr divided q6h PO	*Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction. *Drug interactions:* Liquid antacids.
Ofloxacin Ocuflox 0.3% ophthalmic solution: 1, 5, 10 mL Floxin 0.3% otic solution: 5, 10 mL	**Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible gram-positive, gram-negative, anaerobic bacteria, or *C. trachomatis*** *Child >1-12 yr:* Conjunctivitis: 1-2 drops in affected eye(s) q2-4h for 2 days, then 1-2 drops qid for 5 days Corneal ulcers: 1-2 drops q30min while awake and at 4-hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q6h for 2 days Otitis externa (otic solution): 5 drops into affected ear bid for 10 days Chronic suppurative otitis media: treat for 14 days *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children	*Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed.
Omadacycline Nuzyra Injection 100 mg/single-dose vial Oral 150 mg tablet	**New subclass of tetracyclines; active against MSSA, MRSA CoNS, streptococci, including pneumococcus, and enterococci, including VRE** Adults: 200 mg IV once OR 100 mg IV × 2 doses OR 300 mg PO × 2 doses Follow with maintenance dosing starting on day 2: Maintenance dose 100 mg IV qday OR 300 mg PO qday Treatment duration: 7-14 days Children: No dosing information available	Omadacycline has comparable adverse events to other tetracyclines such as tooth discoloration, enamel hypoplasia, and inhibition of bone growth. However, no cases of photosensitivity were observed in phase 3 studies.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Oxacillin sodium Prostaphlin Injection Capsule: 250, 500 mg Suspension: 250 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q12h IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q8h IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q12h IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q6h IV Infants: 100-200 mg/kg/24 hr divided q4-6h IV Children: PO 50-100 mg/kg/24 hr divided q4-6h IV Adults: 2-12 g/24 hr divided q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia) Moderate oral bioavailability (35–65%). Primarily renally eliminated *Drug interaction:* Probenecid *Adverse effect:* Neutropenia
Penicillin G Injection Tablets	**Penicillin active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A *Streptococcus*, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q12h IV or IM (meningitis: 100,000 U/kg/24 hr divided q12h IV or IM); weight >2,000 g: 75,000 U/kg/24 hr divided q8h IV or IM (meningitis: 150,000 U/kg/24 hr divided q8h IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 U/kg/24 hr divided q12h IV (meningitis: 100,000 U/kg/24 hr divided q12h IV); weight 1,200-2,000 g: 75,000 U/kg/24 hr q8h IV (meningitis: 225,000 U/kg/24 hr divided q8h IV); weight >2,000 g: 100,000 U/kg/24 hr divided q6h IV (meningitis: 200,000 U/kg/24 hr divided q6h IV) Children: 100,000-250,000 units/kg/24 hr divided q4-6h IV or IM (max dose: 400,000 U/kg/24 hr) Adults: 2-24 million units/24 hr divided q4-6h IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, benzathine Bicillin Injection	**Long-acting repository form of penicillin effective in treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk) (e.g., group A *Streptococcus* pharyngitis, rheumatic fever prophylaxis)** Neonates weighing >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q3-4wk IM (max dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q3-4wk	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated. *Drug interaction:* Probenecid.
Penicillin G, procaine Crysticillin Injection	**Repository form of penicillin providing low penicillin concentrations for 12 hr** Neonates with weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose) Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g) Adults: 0.6-4.8 million units q12-24h IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated. *Drug interaction:* Probenecid.
Penicillin V Pen VK, V-Cillin K Tablet: 125, 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Preferred oral dosing form of penicillin, active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Children: 25-50 mg/kg/24 hr divided q4-8h PO Adults: 125-500 mg q6-8h PO (max dose: 3 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase. *Drug interaction:* Probenecid.
Piperacillin Pipracil Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q8-12h IV; >7 days; 200 mg/kg divided q6-8h IV Children: 200-300 mg/kg/24 hr divided q4-6h IV; cystic fibrosis: 350-500 mg/kg/24 hr IV Adults: 2-4 g/dose q4-6h (max dose: 24 g/24 hr) IV	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness–like reaction with high doses; increases in liver function test results. Renally eliminated. Inactivated by penicillinase. *Drug interaction:* Probenecid.
Piperacillin-tazobactam Zosyn Injection	**Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*** Children: 300-400 mg/kg/24 hr divided q6-8h IV or IM Adults: 3.375 g q6-8h IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Plazomicin Zemdri 500 mg/10 mL (50 mg/mL) vials Each vial contains plazomicin sulfate equivalent to 500 mg plazomicin free base	**Aminoglycoside active against resistant Enterobacteriaceae, including CRE** Adults: 15 mg/kg IV q24hr infused over 30 min Duration of therapy should be guided by the severity of infection and the patient's clinical status for up to 7 days; usual duration 4-7 days Children: no pediatric dose established	May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs.
Quinupristin/dalfopristin Synercid IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin	**Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*** Children and adults: VRE: 7.5 mg/kg q8h IV for VRE; skin infections: 7.5 mg/kg q12h IV	*Adverse events:* Pain, edema, or phlebitis at injection site; nausea; diarrhea. *Drug interactions*: Synercid is a potent inhibitor of CYP 3A4.
Sulfadiazine Tablet: 500 mg	**Sulfonamide antibiotic primarily indicated for treatment of lower UTIs caused by *E. coli, P. mirabilis,* and *Klebsiella*** Toxoplasmosis: Neonates: 100 mg/kg/24 hr divided q12h PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid) Children: 120-200 mg/kg/24 hr divided q6h PO with pyrimethamine 2 mg/kg/24 hr divided q12h PO ≥3 days, then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q24h PO; weight >30 kg: 1 g/24 hr q24h PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~10 hr. *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate.
Sulfamethoxazole Gantanol Tablet: 500 mg Suspension: 500 mg/5 mL	**Sulfonamide antibiotic used for treatment of otitis media, chronic bronchitis, and lower UTIs caused by susceptible bacteria** Children: 50-60 mg/kg/24 hr divided q12h PO Adults: 1 g/dose q12h PO (max dose: 3 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~12 hr. Initial dose often a loading dose (doubled). *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate.
Sulfisoxazole Gantrisin Tablet: 500 mg Suspension: 500 mg/5 mL Ophthalmic solution, ointment	**Sulfonamide antibiotic used for treatment of otitis media, chronic bronchitis, and lower UTIs caused by susceptible bacteria. Also used for *Nocardia*** ***Plasmodium falciparum* resistant to chloroquine, toxoplasmosis in combination with pyrimethamine (sulfadiazine preferred).** Children: 120-150 mg/kg/24 hr divided q4-6h PO (max dose: 6 g/24 hr) Adults: 4-8 g/24 hr divided q4-6h PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~7-12 hr. Initial dose often a loading dose (doubled). *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate.
Tedizolid Sivextro 200 mg vial 200 mg tablet	**Oxazolidinone agent; indicated for skin and soft tissue/skin structure infections caused by susceptible gram-positive organisms; active against MSSA, MRSA, streptococci, enterococci** Adults: 200 mg PO/IV qday for 6 days Children: Indicated for acute bacterial skin and skin structure infections in patients age ≥12 yr <12 yr: Safety and efficacy not established 12-18 yr: 200 mg PO/IV qday for 6 days	Similar to linezolid. Adverse events may include myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache, peripheral and optic neuropathy.
Tigecycline Tygacil Injection	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes** Children: unknown Adults: 100 mg loading dose followed by 50 mg q12h IV	*Cautions:* Pregnancy; children <8 yr old; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance). *Drug interaction:* Warfarin; mycophenolate mofetil.
Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment Inhalation capsule (28 mg); inhalation solution (60 mg/mL; 75 mg/mL)	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*** Can be administered by inhalational route Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 2.5 mg/kg q12-18h IV or IM; weight >2,000 g: 2.5 mg/kg q12h IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q8-12h IV or IM; weight >2,000 g: 2.5 mg/kg q8h IV or IM Children: 2.5 mg/kg/24 hr divided q8-12h IV or IM. Alternatively, may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate, 1 mg/24 hr; children, 1-2 mg/24 hr; adults, 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q8h IV or IM	*Cautions: S. pneumoniae*, other streptococcus, and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs. *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg	**Folic acid antagonist effective in prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* UTIs; *P. carinii* pneumonia** Children: For UTI: 4-6 mg/kg/24 hr divided q12h PO Children >12 yr and adults: 100-200 mg q12h PO. *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q6h for 21 days PO	*Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash. *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin.
Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension	**Glycopeptide antibiotic active against most gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile*–associated colitis** Neonates: Postnatal age ≤7 days, weight <1,200 g: 15 mg/kg/24 hr divided q24h IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q12-18h IV; weight >2,000 g: 30 mg/kg/24 hr divided q12h IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q24h IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q8-12h IV; weight >2,000 g: 45 mg/kg/24 hr divided q8h IV Children: 45-60 mg/kg/24 hr divided q8-12h IV; *C. difficile*–associated colitis; 40-50 mg/kg/24 hr divided q6-8h PO	*Cautions:* Ototoxicity and nephrotoxicity, particularly when co-administered with other ototoxic and nephrotoxic drugs. Infuse IV over 45-60 min. Cutaneous and systemic side effects can be observed with rapid IV infusions, fever, chills, phlebitis (central line is preferred for infusions). Renally eliminated. *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L.

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.
CNS, Central nervous system; GI, gastrointestinal; IM, intramuscular/ly; IV, intravenous/ly; PO, oral/ly; UTIs, urinary tract infections.

Table 225.4 Adverse Reactions to Penicillins

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH
ALLERGIC Immunoglobulin E antibody	0.04-0.015	Penicillin G
Anaphylaxis*		
Early urticaria* (<72 hr)		
Cytotoxic antibody	Rare	Penicillin G
Hemolytic anemia*		
Antigen-antibody complex disease	Rare	Penicillin G
Serum sickness*		
Delayed hypersensitivity	2-5	Ampicillin, amoxicillin
Contact dermatitis*		
IDIOPATHIC	2-5	Ampicillin
Skin rash		
Fever		
Late-onset urticaria		
GASTROINTESTINAL Diarrhea	3-11	Ampicillin
Clostridioides difficile (formerly *Clostridium difficile*)–associated colitis	Rare	Ampicillin
HEMATOLOGIC Hemolytic anemia	Rare	Penicillin G
Neutropenia	10-17	Penicillin G, nafcillin, oxacillin†
Platelet dysfunction	43-73	Piperacillin
HEPATIC Elevated serum aspartate transaminase	0.01-22	Flucloxacillin, oxacillin

Continued

Table 225.4 Adverse Reactions to Penicillins—cont'd

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH
ELECTROLYTE DISTURBANCE		
Hypokalemia	Rare	Nafcillin, oxacillin
Hyperkalemia, acute	Rare	Penicillin G
NEUROLOGIC		
Seizures	Rare	Penicillin G
Bizarre sensations (Hoigné syndrome)	Rare	Procaine penicillin
RENAL		
Interstitial nephritis*	Variable	Any penicillin

*Reaction can occur with any of the penicillins.
†With prolonged therapy.
Adapted from Doi Y. Penicillins and β-lactamase inhibitors. In Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 20-7.

Table 225.5 Classification of Parenteral and Oral Cephalosporins

CEPHALOSPORINS	FIRST GENERATION	SECOND GENERATION	CEPHAMYCINS	THIRD GENERATION	FOURTH GENERATION	FIFTH GENERATION (MRSA ACTIVE)
Parenteral	Cefazolin (Ancef, Kefzol)	Cefamandole (Mandol)*	Cefmetazole (Zefazone)*	Cefoperazone (Cefobid)*	Cefepime (Maxipime)	Ceftaroline (Teflaro)
	Cephalothin (Keflin, Seffin)*	Cefonicid (Monocid)*	Cefotetan (Cefotan)	Cefotaxime (Claforan)	Cefpirome (Cefrom)	Ceftobiprole (Zeftera)*
	Cephapirin (Cefadyl)*	Cefuroxime (Kefurox, Zinacef)	Cefoxitin (Mefoxin)	Ceftazidime (Fortaz)	Cefiderocol (Fetroja; Siderophore antibiotic)	Ceftolozane (combined with tazobactam; Zerbaxa)
	Cephradine (Velosef)*			Ceftizoxime (Cefizox)*		
				Ceftriaxone (Rocephin)		
				Moxalactam*		
				Ceftazidime-avibactam (Avycaz)		
Oral	Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)*	Cefaclor (Ceclor)* Cefprozil (Cefzil) Cefuroxime axetil (Ceftin) Loracarbef (Lorabid)*		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxime (Vantin) Ceftibuten (Cedax)		

*Not currently available in the United States.
Adapted from Lepak AJ, Andes DR. Cephalosporins. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 21-1.

A **fifth-generation cephalosporin** called *ceftaroline* has been licensed. Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil (which is the agent administered to the patient). Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against resistant gram-positive organisms, including MRSA, and common gram-negative pathogens. It has FDA approval and is licensed for use in children. Ceftaroline is indicated for MRSA in the treatment of skin and soft tissue infections. It is also licensed for treatment of community-acquired pneumonia but is not indicated for MRSA pneumonia. Ceftaroline's activity is attributed to its ability to bind to PBP 2a with higher affinity than other β-lactams. Another fifth-generation cephalosporin with a similar spectrum of activity, *ceftobiprole,* has been approved for use in Canada and the European Union. A third fifth-generation cephalosporin, *ceftolozane,* has been licensed. It is a derivative of ceftazidime with improved activity against *Pseudomonas* spp. It is not stable against most ESBLs or carbapenemases. It is marketed in combination with the β-lactam inhibitor tazobactam to improve its activity against β-lactamase–producing Enterobacteriaceae. Experience with children is limited.

Table 225.6 lists adverse reactions to cephalosporins.

Carbapenems

The carbapenem group of antibiotics includes imipenem (formulated in combination with cilastatin), meropenem, ertapenem, and doripenem. The basic structure of these agents is similar to that of β-lactam antibiotics, and these drugs have a similar mechanism of

Table 225.6 Potential Adverse Effects of Cephalosporins

TYPE	SPECIFIC	FREQUENCY
Hypersensitivity	Rash	1–3%
	Urticaria	<1%
	Serum sickness	<1%
	Anaphylaxis	0.01%
Gastrointestinal	Diarrhea	1–19%
	Nausea, vomiting	1–6%
	Transient transaminase elevation	1–7%
	Biliary sludge	20–46%*
Hematologic	Eosinophilia	1–10%
	Neutropenia	<1%
	Thrombocytopenia	<1–3%
	Hypoprothrombinemia	<1%
	Impaired platelet aggregation	<1%
	Hemolytic anemia	<1%
Renal	Interstitial nephritis	<1–5%
Central nervous system	Seizures	<1%
	Encephalopathy	<1%
False-positive laboratory	Coombs positive	3%
	Glucosuria	Rare
	Serum creatinine	Rare
Other	Drug fever	Rare
	Disulfiram-like reaction†	Rare
	Superinfection	Rare
	Phlebitis	Rare
	Calcium-antibiotic precipitation*	Unknown; can be associated with embolic events

*Ceftriaxone.
†Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.
Adapted from Craig WA, Andes DR. Cephalosporins. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 9th ed. Philadelphia: Elsevier; 2020: Table 21-6.

action. The carbapenems provide the broadest spectrum of antibacterial activity of any licensed class of antibiotics and are active against gram-positive, gram-negative, and anaerobic organisms. Among the carbapenems, **meropenem** is the only agent licensed for treatment of pediatric meningitis. Importantly, MRSA and *E. faecium* are *not* susceptible to carbapenems. Carbapenems also tend to be poorly active against *Stenotrophomonas maltophilia,* rendering their use for cystic fibrosis patients who are infected with this organism problematic. Ertapenem is poorly active against *P. aeruginosa* and *Acinetobacter* species and should be avoided when these pathogens are encountered. Although imipenem-cilastatin is the first carbapenem approved for clinical use and the carbapenem with the greatest clinical experience, this antibiotic unfortunately has a propensity to cause seizures in children, particularly in the setting of intercurrent meningitis. Accordingly, meropenem is typically more suitable for pediatric use, where meningitis is commonly a consideration. Carbapenems have also been combined with β-lactamase inhibitors. One example is **meropenem/vaborbactam,** where the β-lactamase inhibitor vaborbactam extends the spectrum of activity to include some ESBL- and carbapenemase-producing bacteria. No dosage recommendations exist as yet for pediatric use. Another example is **imipenem/relebactam** (imipenem/cilastatin/relebactam), which is approved for complicated urinary tract and intraabdominal infections and for ventilator-associated pneumonia.

Other carbapenems in various stages of clinical trials include benapenum, panipenem, biapenem, razupenem, and tomopenem. Tebipenem pivoxil is an orally available prodrug of tebipenem, a carbapenem with activity against multidrug-resistant gram-negative pathogens, including quinolone-resistant and ESBL-producing Enterobacteriaceae. Sulopenem/sulopenem etzadroxil/probenecid is an oral carbapenem combination. Sulopenem etzadroxil is an oral prodrug form of sulopenem, a thiopenem with broad-spectrum antibacterial activity against most gram-positive and gram-negative bacteria, not including *P. aeruginosa*. Probenecid is included to prolong half-life. Panipenem is a combination agent coformulated with betamipron, which inhibits renal uptake of panipenem (analogous to imipenem/cilastatin). Panipenem, biapenem, and tebipenem/pivoxil are licensed in Japan. There is minimal experience with pediatric dosing for all of these newer carbapenems.

Glycopeptides

Glycopeptide antibiotics include **vancomycin** and **teicoplanin**, the less commonly available analog. These agents are bactericidal and act by inhibiting cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to gram-positive organisms, including *S. aureus,* coagulase-negative staphylococci, pneumococcus, enterococci, *Bacillus,* and *Corynebacterium.* Vancomycin is frequently employed in pediatric practice and is of particular value for serious infections, including meningitis, caused by MRSA and penicillin- and cephalosporin-resistant *S. pneumoniae.* Vancomycin is also commonly used for infections in the setting of fever and neutropenia in oncology patients, in combination with other antibiotics (see Chapter 223), and for infections associated with indwelling medical devices (see Chapter 224). Oral formulations of vancomycin are occasionally used to treat pseudomembranous colitis caused by *Clostridium difficile* infections; intrathecal therapy may also be used for selected CNS infections. Vancomycin must be administered with care because of its propensity to produce **vancomycin infusion syndrome**, which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of drug infusion.

Newer FDA-approved glycopeptide antibiotics include telavancin, dalbavancin, and oritavancin; pediatric experience is limited. **Telavancin** is indicated for skin and skin structure infections caused by *S. aureus* (including MRSA), group A streptococcus, and *E. faecalis* (vancomycin-susceptible isolates only). It is also approved for hospital-acquired (including ventilator-associated) pneumonia caused by *S. aureus*. The recommended adult dose for skin and soft tissue infections, and for nosocomial pneumonia, is 10 mg/kg intravenously (IV) every 24 hours for 7-21 days. Telavancin appears to be more nephrotoxic than vancomycin and has been associated with prolongation of the QT interval. **Dalbavancin**'s unique characteristic is its long half-life, 150-250 hours. In adults with normal renal function, the dose is 1000 mg IV, followed 1 week later by 500 mg IV. This agent can be considered when MRSA is confirmed or strongly suggested. Dalbavancin is not active against vancomycin-resistant *S. aureus*. It is FDA-approved for bacterial skin and soft tissue infections. **Oritavancin** is a vancomycin derivative with indications similar to those of dalbavancin. It has a half-life of approximately 250 hours. The dosage for adults is a single 1200-mg dose administered IV over 3 hours. The FDA has approved dalbavancin and oritavancin for the treatment of acute bacterial skin and skin structure infections caused by gram-positive bacteria, including MRSA. **Cefilavancin** is a unique agent spanning two antimicrobial classes in a single agent. It is a covalently linked glycopeptide-cephalosporin heterodimer antibiotic that is highly active against gram-positive bacteria and is in a phase 3 study.

Aminoglycosides

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are **gentamicin** and **tobramycin**. They exert their action by inhibiting bacterial protein synthesis. Although they are most often used to treat gram-negative infections, the aminoglycosides are broad-spectrum agents, with activity against *S. aureus* and synergistic activity against GBS, *L. monocytogenes,* viridans streptococci, *Corynebacteria jeikeium*, *P. aeruginosa,* coagulase-negative staphylococci, and enterococci when co-administered with a β-lactam agent. Aminoglycoside use has decreased with the development of alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, UTIs, gram-negative bacterial sepsis, and complicated intraabdominal infections; infections in cystic fibrosis patients (including both parenteral and aerosolized forms of therapy); and oncology patients with fever and neutropenia. Aminoglycosides, in particular streptomycin, are also important in the management of *Francisella tularensis, Mycobacterium tuberculosis,* and nontuberculous mycobacterial infections.

Toxicities of aminoglycoside therapy include nephrotoxicity and ototoxicity (cochlear and/or vestibular), and serum levels as well as renal function and hearing should be monitored in patients on long-term therapy. Toxicities of aminoglycosides may be reduced by the use of once-daily dosing regimens with appropriate monitoring of serum levels. Hypokalemia, volume depletion, hypomagnesemia, and other nephrotoxic drugs may increase the renal toxicity of aminoglycosides. A rare complication of aminoglycosides is **neuromuscular blockade**, which may occur in the presence of other neuromuscular blocking agents and in the setting of infant botulism.

A novel aminoglycoside, **plazomicin**, has recently been approved by the FDA for adult use. It was designed to evade all of the clinically relevant aminoglycoside-modifying enzymes (Table 225.2) responsible for aminoglycoside resistance. It is approved for complicated UTIs, including pyelonephritis caused by *E. coli*, *K. pneumoniae*, *Proteus mirabilis,* and *Enterobacter cloacae.* FDA approval is pending for bloodstream infections caused by multidrug-resistant *Enterobacteriaceae*, including CRE.

Tetracyclines

The tetracyclines (tetracycline hydrochloride, doxycycline, minocycline, demeclocycline, eravacycline, omadacycline, and minocycline) are bacteriostatic antibiotics that exhibit their antimicrobial effect by binding to the bacterial 30S ribosomal subunit, inhibiting protein translation. These agents have a broad spectrum of antimicrobial activity against gram-positive and gram-negative bacteria, rickettsia, and some parasites. The oral bioavailability of these agents facilitates oral dosing for many infections, including Rocky Mountain spotted fever, anaplasmosis, ehrlichiosis, Lyme disease, and malaria. Tetracyclines must be prescribed judiciously to children <9 years old, because they can cause staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in this age-group.

Tigecycline, a semisynthetic derivative of minocycline, is a parenteral agent of a new antibiotic class **(glycylcyclines)** and is licensed in the United States. It has a broader spectrum of activity (bacteriostatic) than traditional tetracyclines but retains the side effect profile of tetracyclines. Tigecycline is active against tetracycline-resistant gram-positive and gram-negative pathogens, including MRSA and possibly VRE, but not *Pseudomonas.* **Demeclocycline** is an orally administered tetracycline with a similar antimicrobial spectrum as other agents in this class. A novel tetracycline derivative, **eravacycline** (a fluorocycline), has recently been approved for treatment of complicated intraabdominal infections in adults and has the broadest spectrum of any tetracycline, including MRSA and CRE. **Omadacycline** is another new tetracycline that is similar to that of other tetracyclines, functioning as an inhibitor of bacterial protein synthesis, but has activity against bacterial strains expressing the two main forms of tetracycline resistance, specifically, antibiotic efflux and ribosomal protection.

Complications of tetracyclines include eosinophilia, leukopenia and thrombocytopenia (tetracycline), pseudotumor cerebri, anorexia, emesis and nausea, hepatitis, photosensitivity, and a hypersensitivity reaction (urticaria, asthma exacerbation, facial edema, dermatitis) as well as a systemic lupus erythematosus–like syndrome (most common with minocycline). The FDA has issued a "black box" warning regarding tigecycline based on a meta-analysis of 10 studies that showed increased mortality among patients receiving this drug.

A salutary side effect of **demeclocycline** has been identified; it is occasionally used as an off-label treatment of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone (ADH). The mechanism of action appears to be inhibition of adenylyl cyclase activation after ADH binds to renal vasopressin receptors.

Sulfonamides

Trimethoprim and the sulfonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere

with the synthesis of dihydropteroic acid from paraaminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dihydrofolic acid. The sulfonamides are available in both parenteral and oral formulations. Although there have historically been a large number of sulfonamide antibiotics developed for clinical use, relatively few remain available for pediatric practice. The most important agent is the combination of **trimethoprim-sulfamethoxazole** (TMP-SMX), used for treatment of UTIs. TMP-SMX has also emerged as a commonly prescribed agent for staphylococcal skin and soft tissue infections, because this antibiotic generally retains activity against MRSA. TMP-SMX also plays a unique role in immunocompromised patients, as a prophylactic and therapeutic agent for *Pneumocystis jiroveci* infection. Other common sulfonamides include **sulfisoxazole**, which is useful in the management of UTIs, and **sulfadiazine**, which is a drug of choice in the treatment of toxoplasmosis.

Recently, a novel sulfonamide, **iclaprim**, demonstrated noninferiority to vancomycin in the treatment of complicated skin and soft tissue infections. Iclaprim is a diaminopyrimidine with a 20-fold higher affinity for the target molecule for sulfonamides, dihydrofolate reductase, than trimethoprim. It was granted orphan drug status by the FDA for treatment of *S. aureus* infection in patients with cystic fibrosis but has not been formally approved for general use.

Macrolides

The macrolide antibiotics most often used in pediatric practice include **erythromycin**, **clarithromycin**, and **azithromycin**. This class of antimicrobials exerts its antibiotic effect through binding to the 50S subunit of the bacterial ribosome, producing a block in elongation of bacterial polypeptides. Clarithromycin is metabolized to 14-hydroxy clarithromycin, and this active metabolite also has potent antimicrobial activity. The spectrum of antibiotic activity includes many gram-positive bacteria. Unfortunately, resistance to these agents among *S. aureus* and group A streptococcus is fairly widespread, limiting the usefulness of macrolides for many skin and soft tissue infections and for streptococcal pharyngitis. Azithromycin and clarithromycin have demonstrated efficacy for otitis media. All macrolide members have an important role in the management of pediatric respiratory infections, including atypical pneumonia caused by *M. pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila,* as well as infections caused by *Bordetella pertussis.*

Telithromycin, a ketolide antibiotic derived from erythromycin, was initially FDA-approved for the treatment in adults of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis, having good activity against the agents causing these infections (*S. pneumoniae*, *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* for community-acquired pneumonia; *M. catarrhalis* and *H. influenzae* for sinusitis). Reports of liver failure and myasthenia gravis from telithromycin prompted the withdrawal of the drug from the market. **Solithromycin** is a related next-generation oral and IV fluoroketolide in phase 3 clinical development for the treatment of community-acquired pneumonia.

Drug interactions are common with erythromycin and to a lesser extent with clarithromycin. These agents can inhibit the CYP 3A4 enzyme system, resulting in increased levels of certain drugs, such as astemizole, cisapride, statins, pimozide, and theophylline. Itraconazole may increase macrolide levels, whereas rifampin, carbamazepine, and phenytoin may decrease macrolide levels. There are few reported adverse drug interactions with azithromycin. Cross-resistance may develop between a macrolide and the subsequent use of clindamycin.

Lincosamides

The prototype of the lincosamide class of antibiotics is **clindamycin**, which acts at the ribosomal level to exert its antimicrobial effect. The 50S subunit of the bacterial ribosome is the molecular target of this agent. Its spectrum of activity includes gram-positive aerobes and anaerobes. Clindamycin has no significant activity against gram-negative organisms. An important role for clindamycin has emerged in the management of MRSA infections. Because of its outstanding penetration into body fluids (excluding the CNS) and tissues and bone, clindamycin can be used for therapy of serious infections caused by MRSA. Clindamycin is also useful in the management of invasive group A streptococcus infections and in the management of many anaerobic infections, often in combination with a β-lactam. A form of **inducible clindamycin resistance** is exhibited by some strains of MRSA; therefore consultation with the clinical microbiology laboratory is necessary before treating a serious MRSA infection with clindamycin. Pseudomembranous colitis, a common complication of clindamycin therapy in adults, is seldom observed in pediatric patients. Clindamycin also plays an important role in the treatment of malaria and babesiosis (when co-administered with quinine), *P. jiroveci* pneumonia (when co-administered with primaquine), and toxoplasmosis.

Quinolones

The **fluoroquinolones** (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, besifloxacin [ophthalmic suspension], ofloxacin, and delafloxacin) are antimicrobials that inhibit bacterial DNA replication by binding to the topoisomerases of the target pathogen, inhibiting the bacterial enzyme DNA gyrase. This class has broad-spectrum activity against both gram-positive and gram-negative organisms. Some fluoroquinolones exhibit activity against penicillin-resistant *S. pneumoniae* as well as MRSA. These agents uniformly show excellent activity against gram-negative pathogens, including the Enterobacteriaceae and respiratory tract pathogens such as *M. catarrhalis* and *H. influenzae.* Quinolones are also highly active against pathogens associated with atypical pneumonia, particularly *M. pneumoniae* and *L. pneumophila.*

Although these agents are not approved for use in children, there is a reasonable body of evidence that the fluoroquinolones are generally safe, well tolerated, and effective against a variety of bacterial infections frequently encountered in pediatric practice. Parenteral quinolones are appropriate for critically ill patients with gram-negative infections. The use of oral quinolones in stable outpatients may also be reasonable for treatment of infections that would otherwise require parenteral antibiotics (e.g., *P. aeruginosa* soft tissue infections such as osteochondritis) or selected genitourinary tract infections. However, these agents should be reserved for situations when no other oral antibiotic alternative is feasible. In 2013 the FDA changed the warning labels for the fluoroquinolones to better describe the associated risk of permanent peripheral neuropathy. Additional risks include tendonitis, arrhythmias, and retinal detachment. Moreover, in situations of overuse (e.g., typhoid fever, gonococcal infection), organisms have been demonstrated to rapidly develop resistance. The FDA has advised against the use of quinolones for uncomplicated infections such as sinusitis and bronchitis. Thus use of fluoroquinolones in pediatric practice should still be approached with continued caution, and consultation with an expert is recommended.

Streptogramins and Oxazolidinones

The emergence of highly resistant gram-positive organisms, in particular VRE, has necessitated development of new classes of antibiotics. One such class especially useful for resistant gram-positive infections is the streptogramins. The currently licensed agent in this category is **dalfopristin-quinupristin**, which is available in a parenteral formulation. It is appropriate for treatment of MRSA, coagulase-negative staphylococci, penicillin-susceptible and penicillin-resistant *S. pneumoniae,* and vancomycin-resistant *E. faecium* but not *E. faecalis.*

Another licensed class of antibiotics for highly resistant gram-positive infections is the oxazolidinone class. The prototype in this group is **linezolid**, available in both oral and parenteral formulations and approved for use in pediatric patients. Its mechanism of action involves inhibition of ribosomal protein synthesis. It is indicated for MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant

S. pneumoniae. A related drug, **tedizolid phosphate**, is also FDA-approved for acute bacterial skin and skin structure infections. It is more potent in vitro than linezolid against MRSA and may be associated with less myelosuppression. It is available in both IV and oral formulations.

There is little information on streptogramins and oxazolidinones in the treatment of CNS infections, and neither class is approved for pediatric meningitis. Linezolid can cause significant anemia and thrombocytopenia and is a monoamine oxidase inhibitor.

A novel oxazolidinone, **contezolid acefosamil** (MRX-4), was recently approved for use in China. It is an orally active prodrug of the active antimicrobial metabolite, contezolid (MRX-I), an oxazolidinone that shows potent in vitro activity against various multidrug-resistant gram-positive bacteria, including MRSA. It also has activity against *M. tuberculosis*.

Daptomycin

Daptomycin is a novel member of the cyclic lipopeptide class of antibiotics. Its spectrum of activity includes virtually all gram-positive organisms, including *E. faecalis* and *E. faecium* (including VRE) and *S. aureus* (including MRSA). The structure of daptomycin is a 13-member amino acid peptide linked to a 10-carbon lipophilic tail, which results in a novel mechanism of action of disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions, leading to depolarization of the cellular membrane and inhibition of macromolecular synthesis. A theoretical advantage of daptomycin for serious infections is its bactericidal activity against MRSA and enterococci. It is administered intravenously; experience in children is limited. Myopathy and elevations in creatine phosphokinase have been described. An FDA warning has been issued linking some cases of eosinophilic pneumonitis to the use of daptomycin. Daptomycin is inactivated by surfactant and should not be used to treat pneumonia.

Miscellaneous Agents

Metronidazole, which functions by disruption of DNA synthesis, has a unique role as an antianaerobic agent and also possesses antiparasitic and anthelmintic activity. In 2017 a related drug, **benznidazole**, was approved through the FDA's orphan drug Accelerated Approval Pathway. This antiprotozoal agent inhibits the synthesis of DNA, RNA, and proteins within *Trypanosoma cruzi* and is approved for adult and pediatric use for Chagas disease. **Rifampin** is a rifamycin antibiotic that inhibits bacterial RNA polymerase and has a major role in the management of tuberculosis. It is also of value in the management of other bacterial infections in pediatric patients, usually used as a second (synergistic) agent in the treatment of *S. aureus* infections or to eliminate nasopharyngeal colonization of Hib or *N. meningitidis*. **Rifabutin** is a related drug that has an off-label indication for treatment of tuberculosis, an orphan drug indication for Crohn disease, and an indication for prevention or treatment of disseminated *Mycobacterium avium* complex disease in patients with HIV or immune deficiency. **Rifaximin** is a *nonabsorbed rifamycin* that has been used as an adjunct agent to treat patients with multiple recurrences of *C. difficile* infection. **Fidaxomicin** is a first-in-class member of a new category of narrow-spectrum macrocyclic antibiotic drugs. It is an RNA polymerase inhibitor with activity against *C. difficile* infection.

The emerging crisis in antimicrobial resistance has also necessitated the rediscovery of antimicrobial agents seldom used in clinical practice in recent decades, such as **colistin** (colistimethate sodium), a member of the polymyxin family of antibiotics (polymyxin E). The general structure of polymyxins consists of a cyclic peptide with hydrophobic tails. After binding to lipopolysaccharide in the outer membrane of gram-negative bacteria, polymyxins disrupt both outer and inner membranes, leading to cell death. Colistin is broadly active against the Enterobacteriaceae family, including *P. aeruginosa*. It is also active against ESBL- and carbapenemase-producing strains. Toxicities are chiefly renal and neurologic.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 226

Antimicrobial Stewardship

Kathleen Chiotos and Jeffrey S. Gerber

Antibiotics are the most common class of medications prescribed to pediatric outpatients, and over 50% of pediatric inpatients receive antibiotics during their hospitalization. It is estimated that between 25% and 50% of antibiotic prescriptions are inappropriate in drug choice, dose, or duration or are unnecessary altogether.

THE NEED FOR ANTIMICROBIAL STEWARDSHIP: HARMS FROM OVERUSE

There are many negative consequences of antibiotic overuse, including contributing to the dramatic rise in **antibiotic resistance** observed over the past 30 years, which has led to antibiotic resistance being named by the World Health Organization (WHO) as one of the top 10 threats to human health. Antibiotics also carry with them a risk of individual patient-level harm, including development of ***Clostridioides difficile* infection** and **antibiotic adverse events**. For example, 21% of antibiotic courses among pediatric inpatients are complicated by an adverse event, and each additional day of antibiotic therapy is associated with 7% greater odds of experiencing an adverse event. Among pediatric outpatients receiving broad- versus narrow-spectrum antibiotics for acute respiratory tract infections, adverse events are significantly more common in patients treated with broad-spectrum therapy. Finally, an emerging area of research is the **deleterious impact of antibiotics on the developing microbiome** and its potential influence on future disease states, including childhood obesity, asthma, and other allergic diseases. Collectively, these data highlight the importance of judicious antibiotic prescribing, both on a societal and individual patient level.

DEFINING ANTIMICROBIAL STEWARDSHIP AND AN ANTIMICROBIAL STEWARDSHIP PROGRAM

Antimicrobial stewardship is defined as coordinated interventions designed to improve the use of antimicrobial agents, such that dose, duration of therapy, and route of administration are optimized. The goal of these actions is to achieve the best clinical outcome for the patient, while minimizing the development of antimicrobial resistance and risk of adverse events. **It is paramount to recognize that simply reducing antimicrobial use is *not* a primary goal of antimicrobial stewardship.** However, because inappropriate antibiotic use is so common, optimization often results in de-escalation from a broader to a narrower spectrum of therapy or discontinuing antibiotics altogether.

Antimicrobial stewardship programs (ASPs) are multidisciplinary teams designed to improve the safety and quality of patient care by deploying these coordinated interventions. ASPs are often led or co-led by infectious diseases trained physicians and clinical pharmacists and work in collaboration with the infection prevention and control department, the clinical microbiology laboratory, and numerous stakeholder groups, including hospital leadership, clinicians, nurses, and pharmacy. Multiple studies have demonstrated reductions in antibiotic use, decreasing rates of *C. difficile* infections, and cost avoidance after the implementation of ASPs, with variable impact on local antibiotic resistance rates. With this growing evidence base and the crisis of antimicrobial resistance, ASPs are now a Standard from The Joint Commission and a Centers for Medicare and Medicaid Services (CMS) Condition of Participation. **Several guidelines provide evidence-based recommendations for implementation of an ASP, including the joint Infectious Diseases Society of America (IDSA) and**

Society for Healthcare Epidemiology of America (SHEA) guideline, the Centers for Disease Control and Prevention (CDC) Core Elements of Hospital Antibiotic Stewardship Programs, the CDC Core Elements of Outpatient Antibiotic Stewardship, and the WHO Practical Toolkit for Antimicrobial Stewardship Programmes in Healthcare Facilities in Low- and Middle-Income Countries.

INPATIENT ANTIMICROBIAL STEWARDSHIP STRATEGIES

Core elements of inpatient antimicrobial stewardship include hospital leadership commitment; accountability through appointment of a leader or coleaders; pharmacy expertise; implementation of actions or interventions to improve antibiotic use (Table 226.1); tracking

Table 226.1 Summary of Inpatient Antimicrobial Stewardship Interventions

ACTION	DESCRIPTION
PRIORITY ACTIONS	
Preauthorization	Clinician must contact the stewardship program to obtain approval for use of the antimicrobial before prescribing (see also text and Table 226.2).
Prospective audit and feedback	Antimicrobials are reviewed by the stewardship program after 48-72 hr and recommendations for optimization are provided at that point (see also text and Table 226.2).
Facility-specific treatment guidelines	These local guidelines should establish clear recommendations for commonly encountered infections based on published data or national guidelines, local susceptibility data, formulary options, and patient mix. These guidelines should address diagnostic testing, empiric treatment, and definitive treatment and should be developed in collaboration with clinician stakeholders.
ADDITIONAL ACTIONS	
Antibiotic "time-outs"	A "time-out" occurs after a set duration of antimicrobial therapy (e.g., 48-72 hr) and involves a clinician-led reassessment of the need for and choice of antibiotics. This differs from prospective audit and feedback in that the review is led by the frontline clinician, not the stewardship program. Time-outs may augment prospective audit and feedback led by the ASP but should not be considered an equivalent substitute.
Assessing penicillin allergy	Although penicillin allergies are reported in 10–15% of hospitalized patients, less than 1% are true serious allergies. Patients with penicillin allergy labels receive broader-spectrum antibiotics than would otherwise be recommended, and penicillin allergy labels may be associated with worse clinical outcomes. Clinicians or stewardship personnel may be able to "delabel" patients through performing a history and/or administering a challenge dose of penicillin or amoxicillin.
Documentation of antibiotic indications in orders or prescriptions	Requiring documentation of an indication for antibiotics can improve antibiotic prescribing practices. In addition, this facilitates other interventions, such as audit with feedback, where knowledge of the intended indication is needed.
Intravenous to oral antibiotic therapy	Transitioning from intravenous to oral therapy when an oral antibiotic is available can reduce the duration of hospitalization, need for long-term intravenous access, and improve patient satisfaction.
Pharmacist-based interventions	Pharmacists are uniquely positioned to optimize antibiotic use through making recommendations for optimal antibiotic dosing and administration (e.g., extended infusions of β-lactam antibiotics, therapeutic drug monitoring for vancomycin and aminoglycosides, identifying duplicative therapy such as overlapping anaerobic coverage, and detection/prevention of antibiotic-related drug-drug interactions).
Time-sensitive automatic stop orders	Including a stop date in antibiotic orders, after which the antimicrobial order is removed from the patient's active medication orders, can promote timely discontinuation of antibiotics. This may be particularly valuable for antibiotics where durations are short and well-defined (e.g., surgical prophylaxis).
Selective reporting of susceptibility testing results	Microbiology labs can partner with stewardship programs to report select antibiotics that are consistent with hospital guidelines or use "cascade" reporting in which susceptibilities to broader-spectrum agents are reported only if resistance to narrower-spectrum drugs is demonstrated.
Comments in microbiology reports	Comments in microbiology reports may guide prescribers to making appropriate antibiotic decisions, for example, by indicating bacterial growth may reflect contamination or guiding providers to using specific preferred antibiotics.
Rapid diagnostic tests for bacterial diagnostics	Molecular diagnostic tests (for example, tests using PCR, microarrays, or mass spectroscopy) may allow more rapid identification of organisms or resistance determinants than traditional culture-based techniques. When implemented together with real-time stewardship program guidance, assays performed on positive blood cultures may reduce time to optimal antibiotic therapy and improve patient outcomes.
Nursing-based interventions	Key opportunities to engage bedside nurses in stewardship activities include optimizing the appropriate collection of microbiology cultures, encouraging intravenous to oral transitions, and prompting antibiotic timeouts.

PCR, Polymerase chain reaction.
Adapted from Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html

Table 226.2 Comparing Preauthorization and Prospective Audit and Feedback

PREAUTHORIZATION	PROSPECTIVE AUDIT AND FEEDBACK
Allows stewardship oversight from the point of antimicrobial initiation.	Stewardship oversight focuses on antimicrobial duration, de-escalation, or discontinuation.
Requires dedicated and expert personnel for "real-time" phone calls or electronic communication through at least the majority of the day.	Resource intensive, particularly if done hospital-wide, but can be scaled to available resource (e.g., focused on a single unit).
Opportunity to counsel provider on optimal diagnostic testing before starting antimicrobials.	Culture and susceptibility testing may be available at the time the intervention is made, such that recommendations for definitive therapy can be made.
Requires a coordinated process including providers, pharmacy, and the stewardship program to ensure approved antimicrobials are dispensed promptly and that antimicrobial requests that are declined are not dispensed.	Prescribers may or may not follow the recommendations made by the stewardship program.
May be seen as a threat to autonomy and/or having the potential to delay therapy.	Generally well-received by providers, with high adherence to recommendations reported.
Only the antimicrobials that are restricted are affected and only at the point of initiation.	More flexibility for the stewardship team regarding the timing of interventions, as well as the potential to act on all antimicrobials prescribed to an individual patient during a single discussion.

antibiotic use, resistance, and *C. difficile* rates; reporting antibiotic use and resistance metrics to prescribers and hospital leaders; and education.

Prospective Audit and Feedback Versus Preauthorization

Two broad approaches to antimicrobial stewardship are supported by the IDSA/SHEA guideline and the CDC Core Elements: preauthorization and prospective audit and feedback. Preauthorization is a strategy in which the clinician must contact the ASP and secure approval for use of the antimicrobial before prescribing the drug. In contrast, prospective audit and feedback is performed by the ASP 48-72 hours after the start of antimicrobial therapy, and recommendations for antimicrobial de-escalation, discontinuation, transition from intravenous to oral therapy, change in dose, or changes in duration are made. Each of these approaches has pros and cons (Table 226.2), and ASPs generally adapt these broad strategies to the local context and availability of resources, often using a hybrid approach. "Handshake stewardship" is a specific type of audit and feedback where recommendations from the ASP are delivered face-to-face to prescribers; this approach has the advantage of developing collaborative relationships but is resource intensive and therefore may not be feasible in all settings. Regardless of which strategy is used, it is critical that ASPs view the interaction with the prescriber as an opportunity to collaboratively optimize antimicrobial therapy and that the guidance provided is evidence-based and, whenever available, aligned with local clinical practice guidelines.

Development and Implementation of Local Guidelines

Creation of evidence-based **local guidelines** containing recommendations for empiric and definitive therapy for common infectious diseases diagnoses and syndromes is a key activity of ASPs. In pediatrics, key target conditions include community-acquired pneumonia, urinary tract infections, intraabdominal infections, skin and soft tissue infections, and neonatal and pediatric sepsis. Coproduction of these guidelines with relevant stakeholders, including prescribing clinicians, offers a unique opportunity to broadly improve antimicrobial prescribing through standardization of evidence-based practices. Because the approach is agreed upon a priori, adhering to these recommendations may also be more appealing to prescribers relative to more "top-down" approaches, where the ASP is either unilaterally authorizing antimicrobial use or providing directive feedback.

Education

While educational interventions alone are insufficient to improve antimicrobial use, education is critical to the success of ASPs and should be integrated along with other strategies. Education can take place in many forms, including at the point of an individual prescriber-steward interaction during preauthorization or prospective audit and feedback; as part of the implementation of a new local treatment guideline or other specific improvement intervention; or as a stand-alone or recurring lecture focused on a topic of relevance, preferably one deemed important to the learners.

OUTPATIENT ANTIMICROBIAL STEWARDSHIP STRATEGIES

The majority of antibiotic use in children occurs in the outpatient setting. Effective outpatient antimicrobial stewardship is therefore critical and requires approaches distinct from the individual-level preauthorization and prospective audit with feedback that form the foundation of inpatient antimicrobial stewardship. Relative to hospital-based stewardship, fewer studies have been conducted in outpatient settings to inform best practices. However, the CDC provides four elements to guide outpatient stewardship efforts, which include commitment to optimizing antibiotic prescribing, including appointment of an accountable leader; actions for policy and practice; tracking and reporting antibiotic use; and education and expertise.

Commitment

In addition to commitment on the part of practice or system leadership, **a written and publicly displayed commitment poster** stating that the individual clinician will only prescribe antibiotics when they are indicated is a powerful tool to reduce unnecessary antibiotic prescribing in the ambulatory setting. This strategy is particularly appealing, as it requires minimal resources to implement and may not only influence provider behavior but also stimulate a discussion between provider and patient around the importance of judicious antibiotic use. In addition, clear communication across clinic providers and staff to ensure this message is consistent and practices are aligned is paramount.

Actions to Improve Antibiotic Prescribing

As with hospital-based stewardship programs, development and implementation of **local guidelines** to inform antibiotic prescribing for relevant conditions is a key strategy for ambulatory stewardship programs. Target conditions in this setting include acute respiratory tract infections, such as pharyngitis, sinusitis, otitis media, and community-acquired pneumonia, given that these conditions account for the vast majority of ambulatory antibiotic use and are associated with significant variation in antibiotic prescribing practices across clinics. A number of strategies have been used to optimize adherence to such guidelines, including audit with feedback at the practice or provider level, clinician education, and computerized decision support. An additional evidence-based practice that may improve antibiotic use in the outpatient setting for specific conditions is use of **delayed prescriptions**, namely, prescriptions provided to patients with mild infections likely to improve without antibiotics at the time of the clinic visit, with instructions to fill the prescription only if symptoms worsen or fail to improve. Delayed prescribing is endorsed by the American Academy of Pediatrics for acute otitis media and acute sinusitis. This type of

"contingency plan" may contribute to patient and parent acceptance of an initial recommendation against antibiotics.

Education

Education is also a fundamental element of outpatient stewardship. In contrast to education in the inpatient setting, which focuses on clinicians, education in the ambulatory setting additionally requires a focus on the patient and family, as well as teaching providers to promote optimal communication. For example, a commonly cited challenge to judicious antibiotic prescribing in the pediatric outpatient setting is a perception on the part of providers that antibiotic prescriptions are strongly desired by parents, even in situations where bacterial infections are unlikely. **However, several studies have refuted this notion and instead suggest that communication of both "positive" treatment recommendations (e.g., specific measures to take to improve symptoms) and "negative" treatment recommendations (e.g., recommendations against using antibiotics when they are not indicated, antibiotic adverse events) is a driver of parent satisfaction and desired by parents.**

TRACKING AND REPORTING ANTIMICROBIAL USE MEASURES

Quantifying antimicrobial use and reporting it to key stakeholders, including clinicians and hospital leadership, are key elements for both inpatient and outpatient stewardship efforts.

Antimicrobial Use Measures

Most antimicrobial stewardship measures are process measures. **The preferred metric for inpatient antimicrobial use is antimicrobial days of therapy (DOTs) per 1,000 patient days.** Each antimicrobial prescribed on each hospital day counts as one DOT, independent of the number of doses the patient receives in the day. For example, if a patient with an intraabdominal infection receives ceftriaxone and metronidazole on the same day, each drug contributes 1 DOT and the total DOT is 2. If instead, this patient received meropenem alone, just 1 DOT would be recorded. DOT/1,000 patient days is a metric particularly useful to track antimicrobial use over time or in response to a specific stewardship intervention and can be measured for an individual drug, a specific unit, or throughout the hospital. Limitations of the measure are that it does not measure the appropriateness of therapy or spectrum of activity, and as demonstrated in the previous example, multidrug regimens will contribute a greater number of DOTs even if the spectrum of the combination of drugs is narrower than the single drug. Finally, DOT/1,000 patient days does not account for differences in patient complexity, illness severity, or comorbid conditions, a limitation that should be considered when making comparisons across units or hospitals.

Antibiotic use measures in the outpatient setting can include individual- or facility-level tracking of antibiotic prescriptions in all visits, or in visits with a certain diagnosis or collection of diagnoses. Metrics could include the proportion of visits in which antibiotics were prescribed, the appropriateness of the antibiotic choice (e.g., broad- versus narrow-spectrum, compliance with local guidelines), and/or the correct duration of antibiotics for a given condition. **Individual-level measures are preferred**, as they facilitate audit and feedback based on individual performance, as well as peer comparisons, strategies that have been used successfully to improve adherence to evidence-based guidelines for antibiotic use in the outpatient setting.

Outcome Measures

The impact of reductions in antimicrobial use through implementation of ASPs or specific interventions should ideally be linked to clinical outcomes. In practice, however, specific outcomes can be difficult to identify, particularly in children where adverse outcomes attributable to antibiotics are uncommon (e.g., *C. difficile* infection) or resource intensive to measure (e.g., drug adverse events, patient-reported outcomes). Improvement in antibiotic resistance rates over time is an appealing hospital-level measure, but improvement occurs slowly and is influenced by multiple factors other than inpatient antibiotic use, including infection prevention and control practices and outpatient prescribing patterns. Other outcome measures that may be considered include revisits, readmissions, or hospital length of stay, though few studies have evaluated these outcomes, which may be confounded by multifactorial influences. Importantly, because antibiotic exposure has been clearly linked to development of antibiotic resistance, *C. difficile* infection, and other adverse drug events, decreases in antibiotic use process measures without a worsening of clinical outcomes are relevant and should be considered sufficient for defining success, even if the reduction in antibiotic use does not result in improved clinical outcomes.

SUMMARY

Antimicrobial stewardship is an important element of patient safety and quality that is the responsibility of all clinicians prescribing antimicrobials. Formal ASPs can guide these local efforts, and abundant evidence demonstrates the positive impact of these programs on improving antibiotic use in both the inpatient and ambulatory settings. Key needs in the field of pediatric antimicrobial stewardship include development of risk-adjusted antibiotic use measures for benchmarking across centers; development of measures to quantify antibiotic-associated harm; incorporating perspectives from nursing and patients/families; and adapting stewardship strategies and organizational structures successful in acute care hospitals to other settings.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Gram-Positive Bacterial Infections

Chapter 227

Staphylococcus

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

Staphylococci are hardy, aerobic, gram-positive bacteria that grow in pairs and clusters and are ubiquitous as normal flora of humans and present on fomites and in dust. They are resistant to heat and drying and may be recovered from nonbiologic environments weeks to months after contamination. Strains are classified as *Staphylococcus aureus* if they are coagulase positive or as one of the many species of **coagulase-negative staphylococci** (e.g., *S. epidermidis, S. lugdunensis, S. saprophyticus, S. haemolyticus*). *S. aureus* has many virulence factors that mediate various serious diseases, whereas coagulase-negative staphylococci tend to be less pathogenic unless an indwelling foreign body (e.g., intravascular catheter) is present. *S. aureus* strains resistant to β-lactam antibiotics, typically referred to as **methicillin-resistant *Staphylococcus aureus* (MRSA)**, are a significant problem in both community and hospital settings.

227.1 *Staphylococcus aureus*

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

S. aureus is the most common cause of skin and soft tissue infections (SSTIs). **Bacteremia** (primary or secondary) is common and can be associated with, or can result in, musculoskeletal infection (osteomyelitis, pyomyositis, septic arthritis), pneumonia, endocarditis, and rarely meningitis. **Toxin-mediated diseases**, including food poisoning,

staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS), are caused by certain *S. aureus* strains.

ETIOLOGY

S. aureus strains produce a wide spectrum of virulence factors. These factors contribute to pathogenesis in human disease by protecting the organism from host defenses, causing local tissue damage, and affecting noninfected sites through toxin elaboration.

Most strains of *S. aureus* possess factors that protect the organism from host defenses. The microbial surface components recognizing adhesive matrix molecules **(MSCRAMMs)** are a family of cell wall–anchored proteins with a broad spectrum of virulence properties, including host tissue and cell adhesion and invasion, biofilm formation, and evasion of the host immune response. Many staphylococci produce a loose extracellular polysaccharide that promotes formation of **biofilms**, which may interfere with opsonophagocytosis. Production of clumping factor and coagulase differentiates *S. aureus* from coagulase-negative staphylococci. **Clumping factor** interacts with fibrinogen to create large clumps of organisms, interfering with effective phagocytosis. **Coagulase** causes plasma to clot by interacting with fibrinogen and may have an important role in abscess formation. **Protein A** is located on the outermost coat of the cell wall and can absorb serum immunoglobulins, preventing opsonization and thus inhibiting phagocytosis. The **chemotaxis inhibiting protein of *S. aureus* (ChIPS)** and **extracellular adherence protein (Eap)** interfere with the native host immune response by inhibiting leukocyte chemotaxis. The staphylococcal enzyme **catalase** inactivates hydrogen peroxide, promoting intracellular survival.

Many strains of *S. aureus* produce substances that cause local tissue destruction. A number of immunologically distinct **hemolysins** that act on cell membranes and cause tissue necrosis have been identified (α-toxin, β-hemolysin, δ-hemolysin). The leukocidins (LukAB, LukDE, Panton-Valentine leucocidin) are pore-forming cytotoxins resulting in increased cell membrane permeability and eventual cell death. Strains of *S. aureus* that produce **Panton-Valentine leukocidin** are associated with more severe and invasive skin disease, necrotizing pneumonia, and osteomyelitis. Many strains of *S. aureus* release one or more exotoxins. **Exfoliatins A and B** are serologically distinct proteins that produce localized (bullous impetigo) or generalized (scalded skin syndrome, staphylococcal scarlet fever) dermatologic manifestations (see Chapter 706).

S. aureus can produce >20 distinct **enterotoxins** (types A-V). Ingestion of preformed enterotoxin, particularly types A or B, can result in **food poisoning**, resulting in vomiting and diarrhea and, in some cases, profound hypotension.

Toxic shock syndrome toxin-1 (TSST-1) is associated with **toxic shock syndrome (TSS)**, related to menstruation and focal staphylococcal infection (see Chapter 227.2). TSST-1 is a superantigen that induces production of interleukin (IL)-1 and tumor necrosis factor (TNF), resulting in hypotension, fever, and multisystem involvement. Focal infections associated with enterotoxins A or B also may be associated with nonmenstrual TSS.

S. aureus also possesses intrinsic factors that can contribute to pathogenesis, including proteins that promote adhesion to fibrinogen, fibronectin, collagen, and other human proteins. Expression of proteins that mediate antibiotic resistance is also of critical importance. Although historically sensitive to penicillin, *S. aureus* isolates now almost universally produce **penicillinase** or **β-lactamase**, which inactivates many β-lactams at the molecular level and represents the major resistance mechanism against many penicillin and some cephalosporin antibiotics. Thus treatment of *S. aureus* with β-lactam antibiotics requires either a penicillinase-resistant β-lactam ring (e.g., antistaphylococcal penicillins such as oxacillin or nafcillin) or combination with a β-lactamase inhibitor (e.g., ampicillin-sulbactam). Production of altered **penicillin-binding proteins (PBPs)** in the bacterial cell wall mediates resistance to penicillinase-resistant antibiotics; an **altered PBP-2A**, encoded by the gene *mecA,* is responsible for the methicillin, cephalosporin, and carbapenem resistance of MRSA isolates.

EPIDEMIOLOGY

S. aureus is a significant cause of morbidity and mortality, particularly in pediatric healthcare-associated infections including infections of the bloodstream, surgical sites, and respiratory tract. Genetically distinct strains of MRSA are termed *community-associated MRSA* (CA-MRSA); USA300 is the predominant pulsotype circulating in the United States. These strains led to an epidemic of SSTIs, and occasionally necrotizing invasive infections, in healthy individuals without the traditional healthcare-associated risk factors for MRSA. Ambulatory visits for purulent SSTIs rose from 5 million to 11 million annually between 2000 and 2013 but have since plateaued and even declined in some populations. Additionally, the incidence of invasive nosocomial MRSA infections (e.g., bacteremia) has also declined; however, the incidence of SSTIs and bloodstream infections caused by MSSA has increased.

Approximately 20–40% of healthy individuals carry at least one strain of *S. aureus* in the anterior nares at any given time, with intermittent carriage occurring in up to 70% of individuals. In children, the oropharynx, umbilicus, inguinal folds, and rectum are also important reservoirs of *S. aureus* carriage. Many neonates are colonized within the first 2 months of life, usually by a maternal strain. The prevalence of colonization with MRSA in the general pediatric population ranges from 2% to 10%, with higher prevalence in some locales and in children with significant healthcare exposure and chronic medical conditions.

S. aureus is acquired and transmitted through close person-to-person contact and contact with contaminated objects or environmental surfaces. *S. aureus* colonization poses a risk for subsequent *S. aureus* infection. In community settings, populations traditionally at high risk for *S. aureus* infection have included athletes, military personnel, young children, veterinarians, injection drug users, and inmates in correctional facilities. However, given the high colonization prevalence in the community, *S. aureus* infections commonly occur in individuals with no identifiable risk factors. In the outpatient setting, SSTI is the most common entity caused by *S. aureus*, accounting for 8 million annual ambulatory visits.

Households are an important reservoir for *S. aureus* transmission because of close personal contact among colonized family members. Increased disease frequency occurs among household contacts of *S. aureus*–colonized or –infected individuals. Additionally, *S. aureus* can persist on environmental surfaces over time. Contamination of environmental surfaces such as hand towels, television remote controls, and bed linens can further perpetuate transmission among household members and is a risk factor for recurrent infection. Thus preventive strategies are aimed at decreasing the burden of *S. aureus* carriage in affected individuals and household members, as well as targeted household environmental surfaces.

PATHOGENESIS

Except in the case of food poisoning resulting from ingestion of preformed enterotoxins, disease associated with *S. aureus* typically begins with colonization. Subsequent disease manifestations in susceptible individuals results either directly from tissue invasion or from injury caused by various toxins and enzymes produced by the organism (Fig. 227.1).

The most significant risk factor for the development of infection is **disruption of intact skin**, including breaches from wounds, skin diseases such as eczema, epidermolysis bullosa, insect bites, burns, ventriculoperitoneal shunts, and central venous catheter placement. Additional risk factors include immunodeficiency and malnutrition, although infection can also occur in otherwise healthy children. Viral infections of the respiratory tract, especially influenza virus infection, may predispose to secondary bacterial infection with staphylococci.

Congenital defects in chemotaxis (hyper-IgE syndromes, Chédiak-Higashi, and Wiskott-Aldrich syndromes) and defective phagocytosis and killing (neutropenia, chronic granulomatous disease) increase the risk for staphylococcal infections. Patients with HIV infection have neutrophils that are defective in their ability to kill *S. aureus* in vitro. Young infants with invasive infection or individuals with *recurrent* pyogenic infection should be evaluated for immune defects, especially those involving neutrophil dysfunction. Poor mucus clearance in children with cystic fibrosis frequently leads to chronic pulmonary staphylococcal colonization and persistent inflammation in these patients.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Older children and adults develop antibodies to staphylococci as a result of colonization or minor infections. Antibody

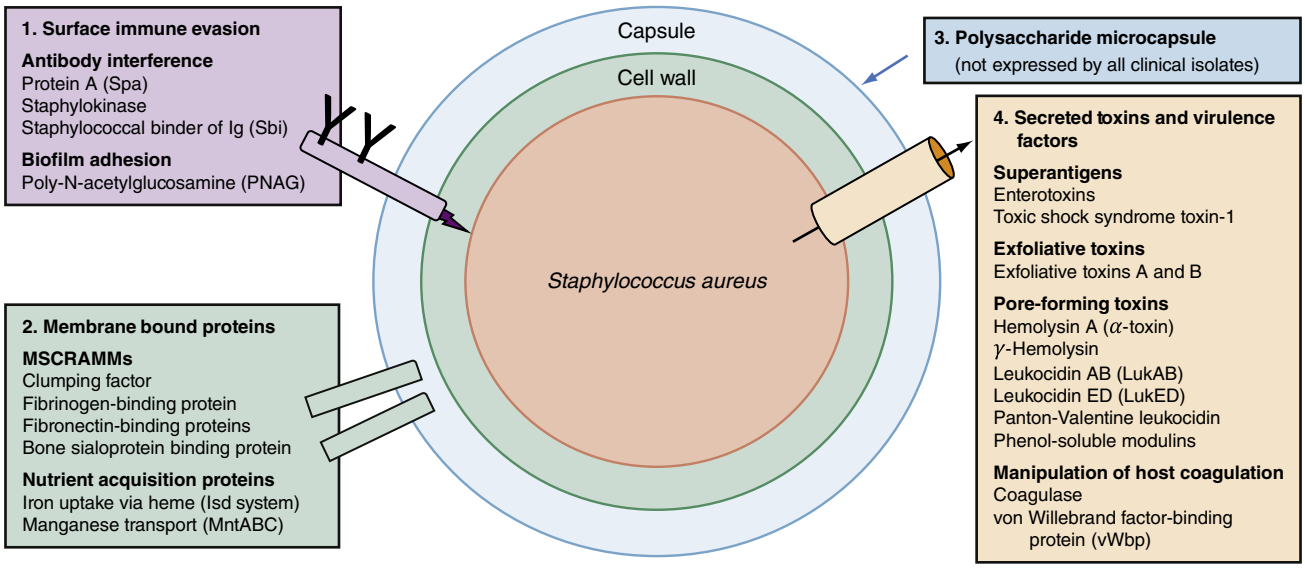

Fig. 227.1 Schematic of virulence factors and relevant surface adhesins of *Staphylococcus aureus*. YY, Immunoglobulin-binding site; MSCRAMMs, microbial surface components that recognize adhesive matrix molecules. *(From Thomsen I, Creech CB. Staphylococcus aureus. In Long SS, Prober CG, Fischer M, Kimberlin DW, eds. Principles and Practice of Pediatric Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2023, Fig. 115.1, p. 711.)*

to the various *S. aureus* toxins appears to protect against those specific toxin-mediated diseases, but humoral immunity does not necessarily protect against focal or disseminated *S. aureus* infection with the same organisms.

CLINICAL MANIFESTATIONS

S. aureus has the potential to invade any tissue. Disease severity is influenced by local suppuration, systemic dissemination with metastatic infection, or systemic effects of toxin production.

Newborn

S. aureus is an important cause of neonatal infections (see Chapter 148).

Skin

S. aureus is an important cause of **pyogenic** skin infections, including impetigo contagiosa, ecthyma, bullous impetigo, folliculitis, furuncles (boils), carbuncles (multiple coalesced boils), and paronychia. **Toxigenic** infection with skin manifestations include staphylococcal scalded skin syndrome and staphylococcal scarlet fever. *S. aureus* is a frequent cause of superinfection of underlying dermatologic conditions, such as eczema, hidradenitis suppurativa, or insect bites. Skin abscesses caused by CA-MRSA commonly affect the lower extremities and buttocks. Up to 70% of individuals with SSTI will experience a recurrent infection. *S. aureus* is also an important cause of traumatic and surgical wound infections and can cause deep soft tissue involvement, including cellulitis and, rarely, necrotizing fasciitis.

Respiratory Tract

Infections of the upper respiratory tract (otitis media, sinusitis) caused by *S. aureus* are rare, in particular considering the frequency with which the anterior nares are colonized. *S. aureus* sinusitis is relatively common in children with cystic fibrosis or defects in leukocyte function and may be the only focus of infection in some children with TSS. Suppurative **parotitis** is a rare infection, but *S. aureus* is a common cause. A membranous **tracheitis** that complicates viral croup may result from infection with *S. aureus,* although other organisms may also be responsible.

Pneumonia caused by *S. aureus* is uncommon but can present with rapidly progressive respiratory failure. Children may present with recent flulike illness (see Chapter 449). Hematogenous pneumonia may be secondary to septic emboli from right-sided endocarditis or septic thrombophlebitis, with or without intravascular devices. Inhalation pneumonia is caused by alteration of mucociliary clearance, leukocyte dysfunction, or bacterial adherence initiated by a viral infection. Common symptoms and signs include high fever, abdominal pain, tachypnea, dyspnea, and localized or diffuse bronchopneumonia or lobar disease. In particular, USA300 strains of *S. aureus* often cause a **necrotizing pneumonitis** that may be associated with early development of empyema, pneumatoceles, pyopneumothorax, and bronchopleural fistulas (Fig. 227.2). Chronic pulmonary infection with *S. aureus* contributes to progressive pulmonary dysfunction in children with cystic fibrosis (see Chapter 454).

Bacteremia and Sepsis

S. aureus bacteremia and sepsis may be primary or secondary because of a localized infection such as an infected central venous catheter or thrombus, bone, or skin and soft tissue. Risk factors for *S. aureus* bacteremia include presence of a central venous catheter, immunodeficiency, malnutrition, recent MRSA STTI, and recent surgery. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills.

Prolonged *S. aureus* bacteremia is associated with an increased risk of developing complications such as septic emboli, thrombi, and metastatic foci of infection. Methicillin resistance, musculoskeletal infection, endovascular infection, and delayed intervention for source control are risk factors for prolonged bacteremia. In general, removal of an infected central venous catheter is recommended because of the difficulty clearing *S. aureus* bacteremia in these patients.

A positive blood culture for MRSA or methicillin-sensitive *S. aureus* (MSSA) should always be considered pathogenic, and antistaphylococcus treatment should be initiated with vancomycin or daptomycin with a β-lactam until antimicrobial susceptibility is available. In the absence of an obvious source (isolated bacteremia), endocarditis must be considered. MSSA bacteremia should be treated with a β-lactam such as cefazolin or oxacillin, given poorer outcomes in children treated with vancomycin. Although vancomycin has been traditionally used as first-line treatment of MRSA bacteremia in children, daptomycin and ceftaroline, a β-lactam and fifth-generation cephalosporin, can also be considered. The duration of antibiotic therapy depends on the age and presence of associated infections. In general, 7-14 days of intravenous therapy is appropriate for uncomplicated bacteremia; however, additional studies are needed to determine the optimal duration in children. Repeat blood cultures should be obtained until negative for 2 days to document clearance of bacteremia. Prolonged positive blood cultures while on therapy suggest endocarditis, an infected thrombus, abscess formation, foreign body (central lines, bone prosthesis, or internal fixation of fractures), or other factors leading to poor source control. Whole body MRI or PET-MRI scanning may detect unrecognized metastatic foci. Infectious disease consultation has been shown to improve cure rates and outcomes in children with *S. aureus* bacteremia, including decreased mortality and decreased recurrence of bacteremia.

Muscle
Localized staphylococcal abscesses in muscle, sometimes without septicemia, have been called **pyomyositis**. This disorder is reported most frequently from tropical areas and is termed *tropical pyomyositis,* but also occurs in the United States in otherwise healthy children. Multiple abscesses occur in 30–40% of cases, most commonly affecting the pelvic and lower extremity muscles. History may include prior trauma at the site of the abscess. More commonly, pyomyositis results from seeding secondary to bacteremia, often near the site of osteomyelitis. Surgical drainage and appropriate antibiotic therapy are essential.

Bones and Joints
S. aureus is the most common cause of osteomyelitis and suppurative arthritis in children, most commonly the result of hematogenous seeding and, less often, from a contiguous focus of infection or through inoculation from trauma or a surgical procedure (see Chapters 725 and 726).

Central Nervous System
Meningitis caused by *S. aureus* is uncommon; it is associated with penetrating cranial trauma and neurosurgical procedures (craniotomy, cerebrospinal fluid [CSF] shunt placement) and, less frequently, with endocarditis, parameningeal foci (epidural or brain abscess), prematurity, complicated sinusitis, diabetes mellitus, or malignancy. The CSF profile of *S. aureus* meningitis is indistinguishable from that in other forms of bacterial meningitis (see Chapter 643.1).

Heart
S. aureus is a common cause of acute endocarditis on native valves and results in high rates of morbidity and mortality. Left-sided endocarditis is most common. The clinical presentation can be indolent with symptoms such as malaise, weight loss, or myalgias, and the typical signs of endocarditis are often not present in children (see Chapter 486).

Kidney
S. aureus is a common cause of renal and perinephric abscess, usually of hematogenous origin. Pyelonephritis and cystitis caused by *S. aureus* are unusual (see Chapter 575).

Toxic Shock Syndrome
S. aureus, more commonly MSSA than MRSA, is the principal cause of TSS, which should be suspected in anyone with fever, shock, and/or a diffuse erythroderma (see Chapter 227.2).

Intestinal Tract
Staphylococcal enterocolitis may rarely follow overgrowth of normal bowel flora by *S. aureus,* which can result from broad-spectrum oral antibiotic therapy. Diarrhea is associated with blood and mucus. Peritonitis associated with *S. aureus* in patients receiving long-term ambulatory peritoneal dialysis usually involves the catheter tunnel.

Food poisoning may be caused by ingestion of *preformed* enterotoxins produced by staphylococci in contaminated foods (see Chapter 387). The source of contamination is often colonized or infected food workers. Approximately 2-7 hours after ingestion of the toxin, sudden, severe vomiting begins. Watery diarrhea may develop, but fever is absent or low grade. Symptoms rarely persist >12-24 hours. Rarely, shock and death may occur.

DIAGNOSIS
The diagnosis of *S. aureus* infection depends on isolation of the organism in culture from the site of infection, such as cellulitis aspirates, abscess cavities, blood, bone, or joint aspirates, or other sites of infection. In patients with musculoskeletal infection, ~50% of children will have blood cultures that yield *S. aureus*. Thus surgical debridement or an aspirate or biopsy obtained by interventional radiology can maximize recovery of the organism, which is important for targeted antibiotic selection. Tissue samples or fluid aspirates in a syringe provide the best culture material. Because of the high prevalence of MRSA and the severity of *S. aureus* infections, it is important to obtain cultures before starting antibiotic treatment. The organism can be grown readily in liquid and on solid media. After isolation, identification is made on the basis of Gram stain and coagulase, clumping factor, and catalase activity. Molecular techniques and mass spectrometry are used to supplement traditional identification and antibiotic susceptibility methods. These technologies may allow for rapid species identification from positive blood cultures and simultaneously identify genetic patterns associated with methicillin resistance, such as presence of the *mecA* gene produced by MRSA. Diagnosis of *S. aureus* food poisoning is usually made on the basis of epidemiologic and clinical findings.

Differential Diagnosis
Many of the clinical entities caused by *S. aureus* can also be caused by other bacterial pathogens, and consideration of the differential diagnosis is particularly important when making empirical antibiotic choices before definitive identification of the offending pathogen. Skin lesions caused by *S. aureus* may be indistinguishable from those caused by group A streptococci, although *S. aureus* usually expands slowly and is more likely to be suppurative, whereas group A streptococci are prone to spread more rapidly and can be very aggressive. Fluctuant skin and soft tissue lesions also can be caused by other organisms, including *Mycobacterium tuberculosis,* atypical mycobacteria, *Nocardia*, *Bartonella henselae* (cat-scratch disease), *Francisella tularensis,* and various fungi. *S. aureus* pneumonia is often suspected in very ill-appearing children or after failure to improve with standard treatment that does not cover *Staphylococcus,* or on the basis of chest radiographs that reveal pneumatoceles, pyopneumothorax, or lung abscess (see Fig. 227.2). Other etiologies of cavitary pneumonias include group A streptococci, *Klebsiella pneumoniae,* and *M. tuberculosis*. In bone and joint infections, culture is the only reliable way to differentiate *S. aureus* from other etiologies, including group A streptococci and, in young children, *Kingella kingae*.

TREATMENT
Antibiotic therapy alone is rarely effective in individuals without source control of the focus of infection. Loculated collections of purulent material should be relieved by incision and drainage. Foreign bodies (e.g., orthopedic instrumentation, ventricular shunts, central venous catheters) should be removed, if possible. Therapy always should be initiated with an antibiotic consistent with the local staphylococcal susceptibility patterns, severity, and anatomic site of infection. For most patients with serious *S. aureus* infection, initial intravenous (IV) treatment is usually recommended, and transition to oral therapy can be considered based on clinical response and source of infection.

Treatment of *S. aureus* osteomyelitis (Chapter 725), meningitis (Chapter 643.1), and endocarditis (Chapter 486) is discussed in the respective chapters on these diagnoses.

Initial treatment for serious infections thought to be caused by **methicillin-susceptible *S. aureus* (MSSA)** should include a semisynthetic penicillin (e.g., nafcillin, oxacillin) or a first-generation cephalosporin (e.g., cefazolin). Penicillin and ampicillin are not appropriate, because >90% of all staphylococci isolated, regardless of source, are resistant to these agents. Addition of a β-lactamase inhibitor (clavulanic acid, sulbactam, tazobactam) to a penicillin-based drug also confers antistaphylococcal activity but has no effect on MRSA. The spectrum of these β-lactam/β-lactamase inhibitor agents (which includes gram-negative bacteria and anaerobes) can be an advantage when broad empirical coverage is needed, but narrower coverage should be selected once *S. aureus* is identified. *Antistaphylococcal penicillins and most cephalosporins do not provide activity against MRSA.*

Vancomycin is typically selected for initial treatment for penicillin-allergic individuals and those with suspected serious infections caused by MRSA. Although serum level monitoring has traditionally been used for patients receiving vancomycin, this method is no longer recommended for severe MRSA infections. Instead, calculating the ratio of area under the curve (AUC) over 24 hours to the minimum inhibitory concentration (MIC) as the primary predictor of vancomycin activity is currently recommended. Monitoring for nephrotoxicity is also important while on vancomycin therapy. Vancomycin intermediate *S. aureus* strains (VISAs), defined as having an MIC of vancomycin greater than 2 μg/mL, and, rarely, vancomycin-resistant strains of *S. aureus* (VRSA, MIC of vancomycin >16 μg/mL) have also been reported, mostly in patients being treated with vancomycin. For critically ill patients with

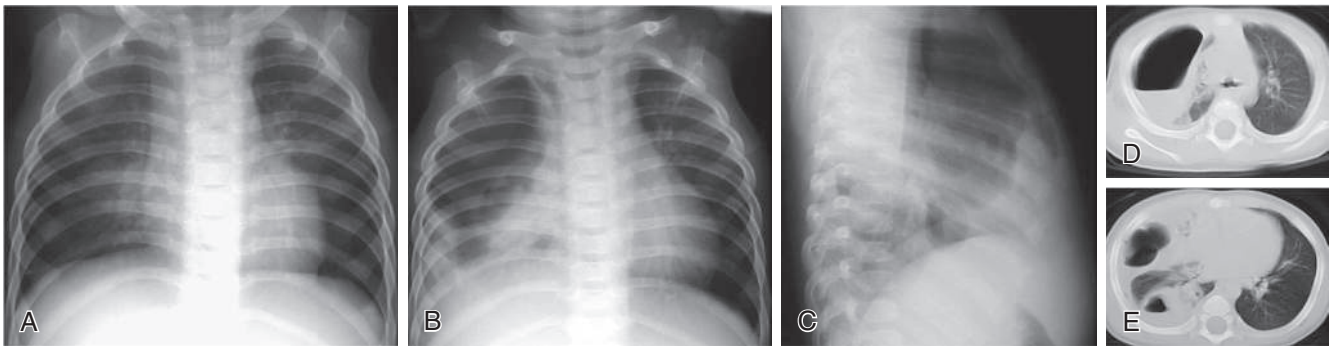

Fig. 227.2 Progressive methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia with pneumatoceles in a previously healthy 9-mo-old male. Chest radiographic findings spanning 4 days showed a perihilar right lower lobe infiltrate (**A**) progressing to a worsening infiltrate and large hydropneumothorax with mediastinal shift (**B** and **C**) despite appropriate therapy. Axial CT of the chest without contrast (lung windows) showed partial loculation of hydropneumothorax, multilobar consolidation, pneumatoceles, and atelectasis (**D** and **E**). Video-assisted thoracoscopic surgery (VATS) was performed, and a chest tube was placed for 3 days. MRSA was isolated from pleural fluid. After 2 weeks of clindamycin therapy, the chest radiograph had only minor abnormalities. *(Courtesy Dr. Sarah S. Long.)*

suspected *S. aureus* infection, empirical therapy with both vancomycin and a β-lactam (cefazolin or nafcillin) should be considered until culture results are available. Initial treatment with IV **clindamycin** followed by a transition to oral clindamycin can be considered in bone, joint, and soft tissue infection; however, not all strains of MSSA or MRSA are susceptible to clindamycin. Inducible clindamycin resistance in isolates initially reported as susceptible must be ruled out by D-test or molecular methods. Clindamycin is bacteriostatic and should not be used to treat endocarditis, persistent bacteremia, or CNS infections caused by *S. aureus*. Given that the mechanism of action of clindamycin involves inhibition or protein synthesis, many experts use clindamycin as an adjunctive agent to treat *S. aureus* toxin–mediated illnesses (e.g., TSS) to inhibit toxin production.

Although the broad-spectrum carbapenems (meropenem, ertapenem, and imipenem) have activity against MSSA, they have no activity against MRSA. As a result, carbapenems are rarely used for empirical therapy of possible staphylococcal infection and are too broad in most cases for use in identified MSSA infections. **Linezolid**, **daptomycin**, and **ceftaroline** are useful for serious *S. aureus* infections, providing excellent coverage of MRSA and MSSA (Table 227.1). A number of novel antistaphylococcal antibiotics have emerged for use in resistant or refractory MSSA and MRSA infection in adults that may be required for pediatric therapy in select patients under the guidance of a pediatric infectious disease specialist. These include the lipoglycopeptides, including **telavancin**, **oritavancin**, and **dalbavancin**, which are structurally related to vancomycin but have very long half-lives and broad activity against gram-positive organisms. **Rifampin** or **gentamicin** in addition to a β-lactam or vancomycin are recommended for prosthetic-valve endocarditis, although patients need to be monitored closely for adverse side effects; their use as combined therapy for other infections is not recommended.

In many infections, after an initial period of parenteral therapy, patients may be transitioned to oral antimicrobials to complete the course of treatment after determination of antimicrobial susceptibilities. Oral antimicrobials can be used as initial treatment in less severe infections (e.g., skin abscess). **Cephalexin** (25-100 mg/kg/24 hr divided 3-4 times daily PO) and cefadroxil (30 mg/kg/24 hr divided 2 times daily PO for noninvasive infections, 50-60 mg/kg/24 hr divided 2 times daily PO for osteoarticular infections) are absorbed well orally (PO) and are effective against MSSA. (Variable cefadroxil dosing regimens have been described, ranging from 30-150 mg/kg/day divided 2-4 times daily PO.) **Amoxicillin-clavulanate** (40-80 mg amoxicillin/kg/24 hr divided 3 times daily PO) is also effective when a broader spectrum of coverage is required. Clindamycin (30-40 mg/kg/24 hr divided 3-4 times daily PO) is highly absorbed from the intestinal tract and is frequently used for empirical coverage when both MRSA and MSSA are possible and for susceptible MRSA infections or for MSSA in penicillin/cephalosporin-allergic patients. Compliance with oral clindamycin may be limited in small children because of poor palatability of liquid formulations. **Trimethoprim-sulfamethoxazole** (TMP-SMX) may be an effective oral antibiotic for many strains of both MSSA and MRSA for SSTI. Oral linezolid is an option for severe MRSA infections that have improved but require ongoing therapy when more common options are not tolerated or are ineffective because of resistance patterns. The duration of linezolid therapy is typically limited to 2-3 weeks given toxicities such as myelosuppression and peripheral and optic neuropathy with prolonged courses. Despite in vitro susceptibility of *S. aureus* to ciprofloxacin and other quinolone antibiotics, these agents should *not* routinely be used in serious staphylococcal infections, because their use is associated with rapid development of resistance.

The **duration** of antibiotic therapy depends on the anatomic site and severity of infection and response, as determined by the clinical response and, in some cases, radiologic and laboratory findings.

PROGNOSIS

Untreated *S. aureus* septicemia is associated with a high fatality rate, which has been reduced significantly by appropriate antibiotic treatment. *S. aureus* pneumonia can be fatal at any age but is more likely to be associated with high morbidity and mortality in young infants or in patients whose therapy has been delayed. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases.

PREVENTION

S. aureus is transmitted primarily by direct contact. Strict attention to **hand hygiene** is the most effective measure for preventing the spread of staphylococci between individuals (see Chapter 216). Hospital surveillance programs to identify nosocomial acquisition of *S. aureus* colonization and/or infection are common, particularly in neonatal intensive care units. Clusters of nosocomial cases may be defined by molecular typing, and if associated with a singular molecular strain, investigation to identify any potential point sources (e.g., a colonized healthcare worker or contaminated environmental reservoir) should occur.

As *S. aureus* colonization often predisposes to infection, a number of protocols are aimed at **decolonization**, which is the application of topical antimicrobials to the skin and/or nares to eradicate *S. aureus* colonization. In healthcare settings, decolonization is often performed among vulnerable populations to prevent nosocomial infections. In community settings, decolonization is often recommended for patients with recurrent *S. aureus* skin infections. Decolonization regimens often involve combinations of decontaminating baths (hypochlorite, 1 tsp common bleach solution per gallon of water, or chlorhexidine 4% soap), nasal mupirocin twice daily for at least 5 days, and enhanced hygiene measures, including frequent laundering of household linens and targeted decontamination of frequently touched household surfaces. Although success is not universal, recurrent infections may be reduced, particularly when eradication is done in both the patient and household contacts, especially those with history of SSTI. Most cases of mild, recurrent disease will resolve in time without these measures.

Because of the potential severity of infections with *S. aureus* and concerns about emerging resistance, much work has focused on

Table 227.1 Parenteral Antimicrobial Agent(s) for Treatment of Serious *Staphylococcus aureus* Infections

SUSCEPTIBILITY	ANTIMICROBIALS	COMMENTS
I. INITIAL EMPIRICAL THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice	Vancomycin + nafcillin/oxacillin or cefazolin	For **life-threatening infections** (e.g., septicemia, endocarditis, CNS infection); linezolid, daptomycin, or ceftaroline could be substituted depending on the clinical scenario and site of infection
	Vancomycin	For **non–life-threatening infection** without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when prevalence of MRSA infection in the community is >20% of all *S. aureus* infections
	Cefazolin or nafcillin/oxacillin	For **non–life-threatening infection** when low likelihood of MRSA is suspected
	Clindamycin	For non–life-threatening infection without signs of severe sepsis when rates of MRSA infection in the community is substantial (>20% of all *S. aureus* infections) and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. AUREUS*		
Drugs of choice	Cefazolin or oxacillin/nafcillin	May change to oral therapy after infection is controlled in low-risk situations
Alternatives (depending on susceptibility results)	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	When broader coverage, including gram-negative organisms and/or anaerobes is required
III. METHICILLIN-RESISTANT *S. AUREUS* (MRSA)		
Drugs of choice	Vancomycin (some combine with a β-lactam) (some may begin with ceftaroline)	Linezolid, daptomycin, or ceftaroline* could be substituted or added depending on the clinical scenario, site of infection, or persistent bacteremia
Alternatives: susceptibility testing results available before alternative drugs are used	Clindamycin (if susceptible)	
	Trimethoprim-sulfamethoxazole	
	Doxycycline	

*Linezolid, daptomycin, and ceftaroline are agents with activity and efficacy against multidrug-resistant, gram-positive organisms, including *S. aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use. Daptomycin is ineffective for treatment of pneumonia, as it is inactivated by pulmonary surfactant.

developing a staphylococcal vaccine for use in high-risk patients, but to date, clinical trials have been disappointing. Because *S. aureus* is frequently a co-infection in severe influenza infections, an indirect preventive impact against staphylococcal pneumonia and tracheitis may be achieved through annual influenza vaccination.

To prevent *S. aureus* food poisoning, cooked foods should be eaten immediately or refrigerated within 2 hours of preparation to prevent multiplication of *S. aureus* that may have contaminated the food (see Chapter 387). Treatment is supportive.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

227.2 Toxic Shock Syndrome

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

Toxic shock syndrome (TSS) is an acute and potentially severe illness characterized by fever, hypotension, diffuse erythroderma with subsequent desquamation on the hands and feet, and multisystem involvement.

ETIOLOGY

TSS is caused by TSST-1–producing and some enterotoxin-producing strains of *S. aureus,* which may colonize the skin or mucous membranes or cause focal sites of staphylococcal infection.

EPIDEMIOLOGY

TSS continues to occur in the United States in men, women, and children, with the highest rates in menstruating women 15-25 years of age.

Nonmenstrual TSS is associated with *S. aureus*–infected nasal packing and wounds, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. The majority of strains of *S. aureus* associated with TSS are methicillin susceptible. Most strains of USA300, the predominant clone of community-associated MRSA in the United States, do not possess the genes expressing the most common TSS superantigens; however, MRSA-associated TSS can occur.

PATHOGENESIS

The primary toxin associated with TSS is TSST-1, although a significant proportion of nonmenstrual TSS is caused by one or more staphylococcal enterotoxins. These toxins act as **superantigens**, which trigger cytokine release, causing massive loss of fluid from the intravascular space and end-organ cellular injury. Epidemiologic and in vitro studies suggest that these toxins are selectively produced in a clinical environment consisting of a neutral pH, a high P_{CO_2}, and an aerobic P_{O_2}, which are the conditions found in abscesses and the vagina with tampon use during menstruation. The risk factors for symptomatic disease include a nonimmune host who is colonized with a toxin-producing organism that is exposed to focal growth conditions (menstruation plus tampon use or abscess) that in turn induce toxin production. Some hosts may have a varied cytokine response to TSST-1 exposure, helping to explain a spectrum of severity of TSS that may include staphylococcal scarlet fever. The overall mortality rate of treated patients is 3–5% when treated early.

Approximately 90% of adults have antibody to TSST-1 without a history of clinical TSS, suggesting that most individuals are colonized at some point with a toxin-producing organism at a site (e.g., anterior nares) where low-grade or inactive toxin exposure results in an immune response without disease.

CLINICAL MANIFESTATIONS

The diagnosis of TSS is based on clinical manifestations (Table 227.2). Milder cases and those with incomplete clinical characteristics may be common, particularly if the nidus of infection is addressed quickly (e.g., removal of a tampon or nasal packing). The onset of classic TSS is abrupt, with high fever, vomiting, and diarrhea, and is accompanied by sore throat, headache, and myalgias. A diffuse erythematous rash (sunburn-like or scarlatiniform) appears within 24 hours and may be associated with hyperemia of pharyngeal, conjunctival, and vaginal mucous membranes. A strawberry tongue is common. Symptoms may include alterations in the level of consciousness, oliguria, and hypotension, which in severe cases may progress to shock and disseminated intravascular coagulation. Complications, including acute respiratory distress syndrome (ARDS), myocardial dysfunction, and renal failure, are commensurate with the degree of shock. Recovery occurs within 7-10 days and is associated with desquamation, particularly of the palms and soles; hair and nail loss have also been observed after 1-2 months. Immunity to the toxins is slow to develop, so recurrences can occur, especially if there is inadequate antibiotic treatment and/or recurrent tampon use. Many cases of apparent scarlet fever without shock may be caused by TSST-1–producing *S. aureus* strains.

DIAGNOSIS

There is no specific laboratory test, and diagnosis depends on meeting certain clinical and laboratory criteria in the absence of an alternative diagnosis (see Fig. 227.2). Appropriate tests reveal involvement of multiple organ systems, including the hepatic, renal, muscular, gastrointestinal, cardiopulmonary, and central nervous systems. Bacterial cultures of the associated focus (vagina, abscess) before administration of antibiotics usually yield *S. aureus,* although this is not a required element of the definition.

Table 227.2 Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition

CLINICAL CRITERIA

1. Fever: temperature ≥102.0°F (≥38.9°C)
2. Rash: diffuse macular erythroderma
3. Desquamation: 1-2 weeks after onset of rash
4. Hypotension: systolic blood pressure ≤90 mm Hg for adults or less than fifth percentile by age for children age less than 16 years
5. Multisystem involvement (three or more of the following organ systems):
   - Gastrointestinal: vomiting or diarrhea at onset of illness
   - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
   - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
   - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (≥5 leukocytes per high-power field) in the absence of urinary tract infection
   - Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
   - Hematologic: platelets less than 100,000/mm^3
   - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

LABORATORY CRITERIA FOR DIAGNOSIS

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*)
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

CASE CLASSIFICATION

Probable

A case that meets the laboratory criteria and in which four of the five clinical criteria described above are present

Confirmed

A case that meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

From Centers for Disease Control and Prevention: https://ndc.services.cdc.gov/case-definitions/toxic-shock-syndrome-2011/

Differential Diagnosis

Group A streptococci can cause a similar TSS-like illness, termed **streptococcal TSS** (see Chapter 229), which is often associated with severe streptococcal sepsis or a focal streptococcal infection such as cellulitis, necrotizing fasciitis, or pneumonia.

Kawasaki disease closely resembles TSS clinically but is usually not as severe or rapidly progressive. Both conditions are associated with fever unresponsive to antibiotics, hyperemia of mucous membranes, and an erythematous rash with subsequent desquamation. However, many of the clinical features of TSS are rare in Kawasaki disease, including diffuse myalgia, vomiting, abdominal pain, diarrhea, azotemia, hypotension, ARDS, and shock (see Chapter 208). Kawasaki disease typically occurs in children <5 years old. Measles, scarlet fever, Rocky Mountain spotted fever, leptospirosis, toxic epidermal necrolysis, and bacterial sepsis must also be considered in the differential diagnosis.

TREATMENT

Identification and drainage/removal of any focal source of infection (e.g., abscess, tampon, nasal packing), when present, is essential. Recommended antibiotic therapy for TSS should include the combination of a β-lactamase–resistant antistaphylococcal antibiotic (nafcillin, oxacillin, or cefazolin) *plus* clindamycin to reduce toxin production. Although TSS is most often caused by MSSA, clinicians should consider use of vancomycin in addition to the β-lactam in areas where MRSA rates are very high, when hospital-acquired MRSA is suspected, and when the clinical picture overlaps with staphylococcal sepsis.

TSS often requires intensive supportive care, including aggressive fluid replacement to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; intravenous immunoglobulin may be helpful in severe cases.

PREVENTION

The risk for acquiring menstrual TSS is low (1-2 cases/100,000 menstruating women). Changing tampons at least every 8 hours is recommended. If a fever, rash, or dizziness develops during menstruation, any tampon should be removed immediately and medical attention sought. Avoidance of tampon use with subsequent menstrual cycles may also reduce the risk for recurrent menstrual TSS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

227.3 Coagulase-Negative Staphylococci

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

At present, there are approximately 50 identified species of coagulase-negative staphylococci **(CoNS)** affecting or colonizing humans. *Staphylococcus epidermidis* and, less often, *Staphylococcus hominis, S. haemolyticus,* and others are widely distributed on the skin and are significant causes of nosocomial infection, particularly in the bloodstream of neonatal and immunocompromised hosts, in surgical patients, and in those with indwelling catheters and other medical devices. *Staphylococcus saprophyticus* is a common cause of urinary tract infection (UTI). *Staphylococcus lugdunensis* and *Staphylococcus schleiferi* can cause severe infection similar to *S. aureus* and have been increasingly recognized as important pathogens since improved species identification with matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry in clinical microbiology laboratories.

EPIDEMIOLOGY

In the United States, CoNS may be the most common cause of hospital-acquired infection, particularly in neonatal intensive care units (NICUs). In many instances, growth of CoNS from clinical specimens represents contamination from skin rather than a cause of true disease, posing significant challenges for clinicians and infection prevention specialists. CoNS are normal inhabitants of the human skin, throat,

mouth, vagina, and urethra. *S. epidermidis* is the most common and persistent species, representing 65–90% of staphylococci present on the skin and mucous membranes. Colonization, sometimes with strains acquired during hospitalization, precedes infection. Alternatively, direct inoculation during surgery may initiate infection of CSF shunts, prosthetic valves, or indwelling vascular lines.

PATHOGENESIS

CoNS produce an exopolysaccharide protective biofilm, particularly on indwelling medical devices, that surrounds the organism and may enhance adhesion to foreign surfaces, resist phagocytosis, and impair penetration of antibiotics. However, the low virulence of CoNS usually requires the presence of another factor for development of clinical disease. Of these, the most significant is the presence of an indwelling catheter or other medical device, including central venous catheters (CVCs), hemodialysis shunts and grafts, CSF shunts (meningitis), peritoneal dialysis catheters (peritonitis), pacemaker wires and electrodes (local infection), prosthetic cardiac valves (endocarditis), and prosthetic joints (septic arthritis). Other risk factors for the development of infection include immature or compromised immunity and significant exposure to antibiotics.

CLINICAL MANIFESTATIONS

Bacteremia

CoNS, specifically *S. epidermidis,* are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CoNS bacteremia, with or without a CVC, can manifest as localized disease in the CNS, lungs, skin, heart, bones, and joints, or even as sepsis or necrotizing enterocolitis. Persistent positive blood cultures despite adequate antimicrobial therapy is common, particularly when catheters are not removed. In older children with intact immune systems, CoNS bacteremia is indolent and is not usually associated with overwhelming septic shock.

Endocarditis

Infection of native heart valves or the right atrial wall may occur secondary to an infected thrombosis at the end of a central line. *S. epidermidis* and other CoNS may rarely produce native valve subacute endocarditis in previously healthy hosts without a CVC. CoNS is a common cause of prosthetic valve endocarditis, presumably a result of inoculation at surgery. Infection of the valve sewing ring, with abscess formation and dissection, produces valve dysfunction or obstruction, dehiscence, or arrhythmias (see Chapter 486). *S. lugdunensis* has been increasingly associated with severe endocardial infection in adults but remains an uncommon cause in children.

Central Venous Catheter Infection

CVCs become infected through the exit site and subcutaneous tunnel, which provide a direct path to the bloodstream. *S. epidermidis* is the most frequent pathogen, in part because of its high rate of cutaneous colonization. Line sepsis is usually manifested as fever and leukocytosis; tenderness and erythema may be present at the exit site or along the subcutaneous tunnel. Catheter thrombosis may complicate line sepsis. Disease severity with CoNS is often less severe than other etiologies of line infection.

Cerebrospinal Fluid Shunts

CoNS, introduced at surgery, is the most common pathogen associated with CSF shunt meningitis. Most infections (70–80%) occur within 2 months of the operation and manifest as signs of meningeal irritation, fever, increased intracranial pressure (headache, vomiting), or peritonitis from the intraabdominal position of the distal end of the shunt tubing.

Urinary Tract Infection

S. saprophyticus is a common cause of primary UTIs in sexually active females. Manifestations are similar to those characteristics of UTI caused by *Escherichia coli* (see Chapter 575). CoNS also cause asymptomatic UTI in hospitalized patients with urinary catheters and after urinary tract surgery or transplantation.

DIAGNOSIS

Because *S. epidermidis* is a common skin inhabitant and may contaminate poorly collected blood cultures, differentiating bacteremia from contamination is often difficult. True bacteremia should be suspected if blood cultures grow rapidly (within 15 hours of incubation in a continuously monitored blood culture system), more than one blood culture is positive with the same CoNS strain, cultures from both the blood and another sterile site are positive, and clinical and laboratory signs and symptoms compatible with CoNS sepsis are present and subsequently resolve with appropriate therapy. Growth of CoNS from a blood culture in a neonate or patient with an intravascular catheter should be considered evidence of true bacteremia until careful review of the foregoing criteria and evaluation of the patient. Before initiating presumptive antimicrobial therapy in such patients, it is always prudent to draw two separate blood cultures to facilitate subsequent interpretation if CoNS is grown. Molecular and mass spectrometry assays similar to those used for identification of *S. aureus* allow for rapid identification of CoNS in positive blood cultures.

TREATMENT

Because most CoNS strains are resistant to methicillin (with the exception of *S. lugdunensis* and *S. saprophyticus,* which are generally methicillin susceptible), **vancomycin** is the initial drug of choice. Resistance to vancomycin has rarely been reported with *S. haemolyticus*. For patients with indwelling medical devices, the addition of rifampin to vancomycin may increase antimicrobial efficacy because of good penetration of this antibiotic into biofilms. Other antibiotics with good in vitro activity against CoNS may be considered in certain circumstances. These include linezolid, ceftaroline, and daptomycin. Removal of an infected catheter is ideal. However, this is not always possible because of the therapeutic requirements of the underlying disease (e.g., nutrition for short bowel syndrome, chemotherapy for malignancy). A trial of IV vancomycin (potentially with the addition of rifampin) with the retained catheter can be attempted to preserve the use of the central line, as long as systemic manifestations of infection are not severe. Antibiotic therapy given through an infected CVC and the use of antibiotic locks in conjunction with systemic therapy may increase the likelihood of curing CoNS line sepsis without line removal. Prosthetic heart valves and CSF shunts usually need to be removed to adequately treat the infection.

Peritonitis caused by *S. epidermidis* in patients on continuous ambulatory peritoneal dialysis is an infection that may be treated with IV or intraperitoneal antibiotics without removing the dialysis catheter. If the organism is resistant to methicillin, vancomycin adjusted for renal function is appropriate therapy. Unlike most CoNS, *S. saprophyticus* is usually methicillin susceptible, and UTIs can typically be treated with a first-generation cephalosporin (cephalexin), amoxicillin–clavulanic acid, or TMP-SMX.

PROGNOSIS

Most episodes of CoNS bacteremia respond successfully to antibiotics and removal of any foreign material that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CoNS infections increase the morbidity, duration of hospitalization, and mortality among patients with underlying complicated illnesses.

PREVENTION

Iatrogenic morbidity and resource use caused by contaminated blood cultures can be reduced by following recommended strategies to prevent CVC-associated bloodstream infections during catheter insertion and maintenance. These strategies include basic techniques such as central line care "bundles," which incorporate good hand hygiene, decontamination of hubs and ports before access, minimizing frequency of access, and frequent replacement of external connections and infusion materials. Antibiotic-impregnated catheters can be considered when other preventive measures have failed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 228

Streptococcus pneumoniae (Pneumococcus)

Kacy A. Ramirez and Timothy R. Peters

Streptococcus pneumoniae (pneumococcus) is an important pathogen that results in more than 1 million children deaths each year. Childhood invasive pneumococcal disease is prevalent and typically severe, causes numerous clinical syndromes, and is a major cause of life-threatening pneumonia, bacteremia, endocarditis, and meningitis; it may also cause sinusitis, otitis media, and bone and joint infections. Antimicrobial resistance in pneumococcus is a major public health problem, with 15–30% of isolates worldwide classified as **multidrug resistant** (**MDR**; resistant to at least three classes of antibiotics). Pneumococcal polysaccharide-protein conjugate vaccines (**PCVs**) developed for infants have been highly successful in the control of disease caused by virulent vaccine-specific serotypes. Epidemiologic surveillance reveals a dynamic pneumococcal ecology with emergence of highly virulent MDR serotypes. Ongoing vaccine development and distribution efforts remain the best approach to control this threat to childhood health.

ETIOLOGY

S. pneumoniae is a gram-positive, lancet-shaped, polysaccharide encapsulated diplococcus, occurring occasionally as individual cocci or in chains; >90 serotypes have been identified by type-specific capsular polysaccharides. Antisera to some pneumococcal polysaccharides cross-react with other pneumococcal types, defining serogroups (e.g., 6A and 6B). Encapsulated strains cause most serious disease in humans. Capsular polysaccharides impede phagocytosis. Virulence is related in part to capsule size, but pneumococcal types with capsules of the same size can vary widely in virulence.

On solid media, *S. pneumoniae* forms unpigmented, umbilicated colonies surrounded by a zone of incomplete (α) hemolysis. *S. pneumoniae* is bile soluble (i.e., 10% deoxycholate) and optochin sensitive. *S. pneumoniae* is closely related to the viridans groups of *Streptococcus mitis,* which typically overlap phenotypically with pneumococci. The conventional laboratory definition of pneumococci continues to rely on bile and optochin sensitivity, although considerable confusion occurs in distinguishing pneumococci and other α-hemolytic streptococci. Pneumococcal capsules can be microscopically visualized and typed by exposing organisms to type-specific antisera that combine with their unique capsular polysaccharide, rendering the capsule refractile (Quellung reaction). Specific antibodies to capsular polysaccharides confer protection on the host, promoting opsonization and phagocytosis. Additionally, $CD4^+$ T cells have a direct role in antibody-independent immunity to pneumococcal nasopharyngeal colonization. Conjugated PCVs promote T-cell immunity and protect against pneumococcal colonization, in contrast to the pneumococcal polysaccharide vaccine (PPSV23) that is used in adults and certain high-risk pediatric populations and that does not affect nasopharyngeal colonization.

EPIDEMIOLOGY

Most healthy individuals carry (colonized) various *S. pneumoniae* serotypes in their upper respiratory tract; >90% of children between 6 months and 5 years of age harbor *S. pneumoniae* in the nasopharynx at some time. A single serotype usually is carried by a given individual for an extended period (45 days to 6 months). Carriage does not consistently induce local or systemic immunity sufficient to prevent later reacquisition of the same serotype. Rates of pneumococcal carriage peak during the first and second year of life and decline gradually thereafter. Carriage rates are highest in institutional settings and during the winter and are lowest in summer. Nasopharyngeal carriage of pneumococci is common among young children attending out-of-home care, with rates of 21–59% in point prevalence studies.

Before the introduction of heptavalent pneumococcal conjugate vaccine **(PCV7)** in 2000, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F caused most invasive childhood pneumococcal infections in the United States. The introduction of PCVs resulted in a marked decrease in **invasive pneumococcal infections (IPIs)** in children. By 2005, however, IPIs began to increase slightly because of an increase in non-PCV7 serotypes, particularly serotype 19A. **Serotype replacement** can result from expansion of existing nonvaccine serotypes and from vaccine-type pneumococci acquiring the polysaccharide capsule of a nonvaccine serotype **(serotype switching)**. Since the introduction of PCV13 in 2010 in the United States, there has been a decline in IPIs caused by new vaccine serotypes, including 19A. Nonetheless, 19A remains an important cause of meningitis. Indirect protection of unvaccinated persons has occurred since PCV introduction, and this *herd protection* is likely a result of decreases in nasopharyngeal carriage of virulent pneumococcal vaccine serotypes.

S. pneumoniae is the most frequent cause of bacteremia, bacterial pneumonia, and bacterial meningitis and among the most common causes of otitis media and sinusitis in children. The decreased ability in children <2 years old to produce antibody against the T-cell–independent polysaccharide antigens and the high prevalence of colonization may explain an increased susceptibility to pneumococcal infection and the decreased effectiveness of polysaccharide vaccines. Children at increased risk of pneumococcal infections include those with sickle cell disease, asplenia, deficiencies in humoral (B-cell) immunity, deficiencies in complement-mediated immunity, toll like receptor deficiencies, HIV infection, certain malignancies (e.g., leukemia, lymphoma), chronic heart, lung, or renal disease (particularly nephrotic syndrome), cerebrospinal fluid (CSF) leak, and cochlear implants. Table 228.1 lists other high-risk groups. Some American Indian, Alaska Native, and African American children may also be at increased risk. Children <5 years old in out-of-home daycare are at increased risk (approximately twofold higher) of experiencing IPIs than other children. Males are more frequently affected than females. Because immunocompetent vaccinated children have had fewer episodes of IPI, the proportion of infected children with immunologic risk factors has increased (estimated at 20%).

Pneumococcal disease usually occurs sporadically but can be spread from person to person by respiratory droplet transmission. *S. pneumoniae* is an important cause of secondary bacterial pneumonia in patients with influenza. During influenza epidemics and pandemics, most deaths result from bacterial pneumonia, and pneumococcus is the predominant bacterial pathogen isolated in this setting. Pneumococcal co-pathogenicity may be important in disease caused by other respiratory viruses as well.

PATHOGENESIS

Invasion of the host is affected by a number of factors. Nonspecific defense mechanisms, including the presence of other bacteria in the nasopharynx, may limit multiplication of pneumococci. Aspiration of secretions containing pneumococci is hindered by the epiglottic reflex and by respiratory epithelial cell cilia, which move infected mucus toward the pharynx. Similarly, normal ciliary flow of fluid from the middle ear through the eustachian tube and sinuses to the nasopharynx usually prevents infection with nasopharyngeal flora, including pneumococci. Interference with these normal clearance mechanisms by allergy, viral infection, or irritants (e.g., smoke) may allow colonization and subsequent infection with these organisms in otherwise normally sterile sites.

Virulent pneumococci are intrinsically resistant to phagocytosis by alveolar macrophages. Pneumococcal disease frequently is facilitated by viral respiratory tract infection, which may produce mucosal injury, diminish epithelial cell ciliary activity, and depress the function of

Table 228.1 Children at Increased Risk of Invasive Pneumococcal Infection

RISK GROUP	CONDITION
Immunocompetent children	Chronic heart disease* Chronic lung disease† Chronic kidney disease (excluding dialysis and nephrotic syndrome) Chronic liver disease Diabetes mellitus Cerebrospinal fluid leaks Cochlear implant
Children with immunocompromising conditions	HIV infection Maintenance dialysis or nephrotic syndrome Congenital or acquired asplenia or splenic dysfunction Congenital or acquired immunodeficiencies Sickle cell disease and other hemoglobinopathies Congenital immunodeficiency‡ Diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasm, leukemia, lymphoma, and Hodgkin disease, or solid organ transplantation

*Particularly cyanotic congenital heart disease and cardiac failure.
†Including moderate persistent or severe persistent asthma.
‡Includes humoral or T lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3 and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
Adapted from Kobayashi M, Farrar JI, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: updated recommendations of the Advisory Committee on Immunization Practices -- United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):1174-1181; and Centers for Disease Control and Prevention. ACIP updates: Recommendations for use of 20-valent pneumococcal conjugate vaccine in children—United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(39):1072.

alveolar macrophages and neutrophils. Phagocytosis may be impeded by respiratory secretions and alveolar exudate. In the lungs and other tissues, the spread of infection is facilitated by the antiphagocytic properties of the pneumococcal capsule. Surface fluids of the respiratory tract contain only small amounts of immunoglobulin G (IgG) and are deficient in complement. During inflammation, there is limited influx of IgG, complement, and neutrophils. Phagocytosis of bacteria by neutrophils may occur, but normal human serum may not opsonize pneumococci and facilitate phagocytosis by alveolar macrophages. In tissues, pneumococci multiply and spread through the lymphatics or bloodstream or, less often, by direct extension from a local site of infection (e.g., sinuses). In bacteremia the severity of disease is related to the number of organisms in the bloodstream and to the integrity of specific host defenses. A poor prognosis correlates with very large numbers of pneumococci and high concentrations of capsular polysaccharide in the blood and CSF.

Invasive pneumococcal disease is 30- to 100-fold more prevalent in children with sickle cell disease and other hemoglobinopathies and in children with congenital or surgical asplenia than in the general population. This risk is greatest in infants <2 years old, the age when antibody production to most serotypes is poor. The increased frequency of pneumococcal disease in asplenic persons is related to both deficient opsonization of pneumococci and absence of clearance by the spleen of circulating bacteria. Children with sickle cell disease also have deficits in the antibody-independent properdin (alternative) pathway of complement activation in addition to functional asplenia. Both complement pathways contribute to antibody-independent and antibody-dependent **opsonophagocytosis** of pneumococci. With advancing age (e.g., >5 years), children with sickle cell disease produce anticapsular antibody, augmenting antibody-dependent opsonophagocytosis and greatly reducing, but not eliminating, the risk of severe pneumococcal disease. Deficiency of many of the complement components (e.g., C2 and C3) is associated with recurrent pyogenic infection, including *S. pneumoniae* infection. The efficacy of phagocytosis also is diminished in patients with B- and T-cell immunodeficiency syndromes (e.g., agammaglobulinemia, severe combined immunodeficiency) or loss of immunoglobulin (e.g., nephrotic syndrome) and is largely caused by a deficiency of opsonic anticapsular antibody. These observations suggest that opsonization of pneumococci depends on the alternative complement pathway in antibody-deficient persons and that recovery from pneumococcal disease depends on the development of anticapsular antibodies that act as opsonins, enhancing phagocytosis and killing of pneumococci. Children with HIV infection also have high rates of IPI similar to or greater than rates in children with sickle cell disease, although rates of invasive pneumococcal disease decreased after the introduction of highly active antiretroviral therapy (HAART).

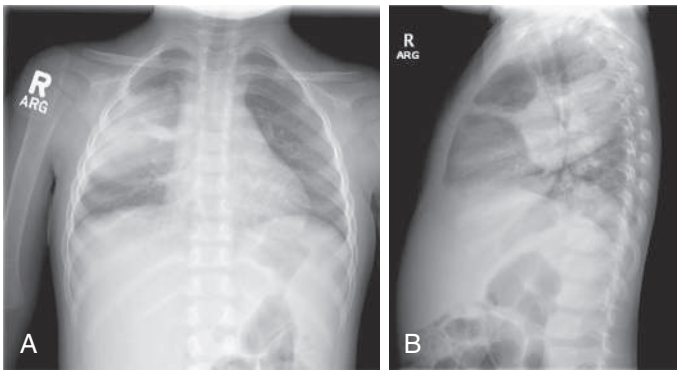

Fig. 228.1 Bacterial "round" pneumonia caused by *Streptococcus pneumoniae* in 2-yr-old child with a 2-day history of cough, high fever, leukocytosis, and back pain.

CLINICAL MANIFESTATIONS

The signs and symptoms of pneumococcal infection are related to the anatomic site of disease. Common clinical syndromes include otitis media (see Chapter 680), sinusitis (see Chapter 429), pneumonia (Fig. 228.1) (see Chapter 449), and sepsis (see Chapter 85). Before routine use of PCVs, pneumococci caused >80% of bacteremia episodes in infants 3-36 months old with fever without an identifiable source (i.e., occult bacteremia). Bacteremia may be followed by meningitis (see Chapter 643), osteomyelitis (see Chapter 725), suppurative (septic) arthritis (see Chapter 726), endocarditis (see Chapter 486), and, rarely, brain abscess (see Chapter 644). Primary peritonitis (see Chapter 419.1) may occur in children with peritoneal effusions caused by nephrotic syndrome and other ascites-producing conditions. Local complications of infection may occur, causing empyema, pericarditis, mastoiditis, epidural abscess, periorbital cellulitis, or meningitis. Hemolytic-uremic syndrome (see Chapter 533.4) and disseminated intravascular coagulation also occur as rare complications of pneumococcal infections. Epidemic conjunctivitis caused by nonencapsulated or encapsulated pneumococci occurs as well.

DIAGNOSIS

The diagnosis of pneumococcal infection is established by recovery of *S. pneumoniae* from the site of infection or the blood/sterile body fluid. Although pneumococci may be found in the nose or throat of patients with otitis media, pneumonia, septicemia, or meningitis, cultures of these locations are generally not helpful for diagnosis, because they are not indicative of causation. Blood cultures should be obtained in children with pneumonia, meningitis, endocarditis, arthritis, osteomyelitis, peritonitis, pericarditis, or gangrenous skin lesions. Because of the implementation of universal vaccination with PCVs, there has been a substantial decrease in the incidence of occult bacteremia, but blood

cultures should still be considered in febrile patients with clinical toxicity or significant leukocytosis. Leukocytosis often is pronounced, with total white blood cell (WBC) counts frequently >15,000/μL. In severe cases of pneumococcal disease, WBC count may be low.

Pneumococci can be identified in body fluids as gram-positive, lancet-shaped diplococci. Early in the course of pneumococcal meningitis, many bacteria may be seen in relatively acellular CSF. With methods of continuously monitored blood culture systems, the average time to isolation of pneumococcal organisms is 14-15 hours. Multiplex real-time polymerase chain reaction (PCR) assays are specific and more sensitive than culture of CSF and blood, particularly in patients who have recently received antimicrobial therapy. Antigen detection of C-polysaccharide in urine may be useful in adults with pneumococcal pneumonia but lacks specificity in children who may have positive results with asymptomatic colonization. Antigen immunochromatographic or PCR assays on pleural fluid are not routinely used but could be considered.

TREATMENT

Antimicrobial resistance among *S. pneumoniae* continues to be a serious healthcare concern, especially for the widely used β-lactams, macrolides, and fluoroquinolones. Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F are the most common serotypes associated with resistance to penicillin. Consequently, the introduction of the 7- and 13-valent pneumococcal conjugate vaccines (**PCV7** and **PCV13**) has altered antimicrobial resistance patterns. By 2014, only ~5% of pneumococcal strains were penicillin nonsusceptible. However, pneumococcal serotypes 11A, 35F, and 35B have contributed to steady erosion of pneumococcal antibiotic susceptibility to penicillin, third-generation cephalosporins, fluoroquinolones, and carbapenems.

Resistance in pneumococci to penicillin and cephalosporins is defined by the minimum inhibitory concentration (MIC) and clinical syndrome. Pneumococci are considered *susceptible, intermediate,* or *resistant* to various antibacterial agents based on specific MIC breakpoints. For patients with pneumococcal meningitis, penicillin-susceptible strains have MICs ≤0.06 μg/mL, and penicillin-resistant strains have MICs ≥0.12 μg/mL. For patients with nonmeningeal pneumococcal infections, breakpoints are higher; in particular, penicillin-susceptible strains have MICs ≤2 μg/mL, and penicillin-resistant strains have MICs ≥8 μg/mL. For patients with meningitis, ceftriaxone-susceptible strains have MICs ≤0.5 μg/mL, and resistant strains have MICs ≥2.0 μg/mL. For patients with nonmeningeal pneumococcal disease, breakpoints are higher, and ceftriaxone-susceptible strains have MICs ≤1 μg/mL, and resistant strains have MICs ≥4 μg/mL. In cases when pneumococcus is resistant to erythromycin but sensitive to clindamycin, *a D-test should be performed* to determine whether clindamycin resistance can be induced; if the D-test is positive, clindamycin should not be used to complete treatment of the patient. More than 30% of pneumococcal isolates are resistant to trimethoprim-sulfamethoxazole (TMP-SMX); levofloxacin resistance is low but has also been reported. All isolates from children with severe infections should be tested for antibiotic susceptibility, given widespread pneumococcal MDR strains. Resistance to vancomycin has not been seen at this time, but vancomycin-tolerant pneumococci that are killed at a slower rate have been reported, and these tolerant pneumococci may be associated with a worse clinical outcome. Linezolid is an oxazolidinone antibacterial with activity against MDR gram-positive organisms, including pneumococcus, and has been used in the treatment of MDR pneumococcal pneumonia, meningitis, and severe otitis media. Despite early favorable studies, use of this drug is limited by myelosuppression and high cost, and linezolid resistance in pneumococcus is reported.

Children ≥1 month old with suspected pneumococcal meningitis should be treated with combination therapy using **vancomycin** (60 mg/kg/24 hr divided every 6-8 hr IV) and high-dose **ceftriaxone** (100 mg/kg/24 hr divided every 12 hr IV). Proven pneumococcal meningitis can be treated with penicillin alone or ceftriaxone alone if the isolate is penicillin susceptible. If the organism is nonsusceptible (i.e., intermediate or full resistance) to penicillin but susceptible to ceftriaxone, pneumococcal meningitis can be treated with ceftriaxone alone. However, if the organism is nonsusceptible to penicillin and to ceftriaxone, pneumococcal meningitis should be treated with combination vancomycin plus ceftriaxone, not with vancomycin alone, and consideration should be given to the addition of **rifampin**. Some experts recommend use of corticosteroids in pneumococcal meningitis early in the course of disease, but data demonstrating clear benefit in children are lacking.

The 2011 Infectious Diseases Society of America guidelines recommend **amoxicillin** as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate, uncomplicated community-acquired pneumonia. **Ampicillin** or **penicillin G** may be administered to the fully immunized infant or school-age child admitted to a hospital with uncomplicated community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. Empirical therapy with parenteral ceftriaxone should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents widespread penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than ceftriaxone in the treatment of pneumococcal pneumonia, given the degree of drug resistance currently seen in the United States.

Higher doses of amoxicillin (80-90 mg/kg/24 hr) have been successful in the treatment of otitis media caused by relatively penicillin-resistant pneumococcal strains. If the patient has failed initial antibiotic therapy, alternative agents should be active against penicillin-nonsusceptible pneumococcus as well as β-lactamase–producing *Haemophilus influenzae* and *Moraxella catarrhalis*. These include high-dose oral amoxicillin-clavulanate (in the 14:1 formulation to reduce the risk of diarrhea), oral cefdinir, cefpodoxime, or cefuroxime or a 3-day course of daily intramuscular (IM) ceftriaxone if patients fail oral therapy. Empirical treatment of pneumococcal disease should be based on knowledge of susceptibility patterns in specific communities.

For individuals with a non–type I allergic reaction to penicillin, cephalosporins (standard dosing) can be used. For type I allergic reactions (immediate, anaphylactic) to β-lactam antibiotics, clindamycin and levofloxacin are preferred alternatives depending on the site of infection (e.g., clindamycin may be effective for pneumococcal infections other than meningitis). TMP-SMX may also be considered for susceptible strains but should be avoided in the absence of susceptibility results. Erythromycin and related macrolides (e.g., azithromycin, clarithromycin) should be avoided given high rates of resistance.

PROGNOSIS

Prognosis depends on the integrity of host defenses, virulence and numbers of the infecting organism, age of the host, site and extent of the infection, and adequacy of treatment. The mortality rate for pneumococcal meningitis is approximately 10% in most studies. Pneumococcal meningitis results in sensorineural hearing loss in 20–30% of patients and can cause other serious neurologic sequelae, including paralysis, epilepsy, blindness, and intellectual deficits.

Invasive pneumococcal disease is associated with various primary immunodeficiency states, leading some to suggest screening for immune defects in all or some patients with invasive diseases. In the absence of other risk factors (see Table 228.1), screening for immune defects (complement, B-cell, toll-like receptor, asplenia) may be indicated for patients with recurrent invasive disease, infection by a serotype covered by vaccination in a fully vaccinated child, children ≥2 years of age, or in some centers all patients with invasive disease.

PREVENTION

The highly successful PCVs have resulted in a marked decrease in IPIs in children. PCVs provoke protective antibody responses in 90% of infants given these vaccines at 2, 4, and 6 months of age, and greatly enhanced responses (e.g., immunologic memory) are apparent after vaccine doses given at 12-15 months of age (Table 228.2). In a large

Table 228.2 Comparison of Pneumococcal Vaccines Licensed in United States*

CARRIER PROTEIN	PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES	MANUFACTURER
Diphtheria CRM_{197} protein	**4, 6B, 9V, 14, 18C, 19F, 23F**	Wyeth Lederle (PCV7, Prevnar)
Diphtheria CRM_{197} protein	1, 3, **4,** 5, 6A, **6B,** 7F, **9V, 14, 18C,** 19A, **19F, 23F**	Wyeth Lederle (PCV13, Prevnar 13)
Diphtheria CRM_{197} protein	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 32F	Merck Sharp and Dohme (PCV15, Prevnar 15)
Diphtheria CRM_{197} protein	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 32F	Merck Sharp and Dohme (PCV20, Prevnar 20)
None	1, 2, 3, **4,** 5, **6B,** 7F, 8, 9N, **9V,** 10A, 11A, 12F, **14,** 15B, 17F, **18C,** 19A, **19F,** 20, 22F, **23F,** 33F	Sanofi Pasteur MSD (PPSV23, Pneumovax II)

*PCV7 serotypes in **bold**.

Table 228.3 Recommended Routine Vaccination Schedule for 15- or 20-Valent Pneumococcal Conjugate Vaccine (PCV15 or 20) Among Infants and Children Who Have Not Received Previous Doses of Conjugate Vaccines, by Age at First Dose—United States, 2010

AGE AT FIRST DOSE (MO)	PRIMARY PCV15 OR PCV20 SERIES*	PCV15 OR PCV20 BOOSTER DOSE†
2-6	3 doses	1 dose at age 12-15 mo
7-11	2 doses	1 dose at age 12-15 mo
12-23	2 doses	—
24-59 (healthy children)	1 dose	—
24-71 (children with certain chronic diseases or immunocompromising conditions‡)	2 doses	—

*The minimum interval between doses is 8 wk except for children vaccinated at age <12 mo, for whom the minimum interval between doses is 4 wk. The minimum age for administration of the first dose is 6 wk.
†Given at least 8 wk after the previous dose.
‡See Table 228.1. If two doses of PCV15 are used, then 1 dose of PPSV23 vaccine is given ≥8 weeks later.
Adapted from Kobayashi M, Farrar JI, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: updated recommendations of the Advisory Committee on Immunization Practices -- United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):1174-1181; and Centers for Disease Control and Prevention. ACIP updates: Recommendations for use of 20-valent pneumococcal conjugate vaccine in children—United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(39):1072.

clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by up to 97% and to reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than unvaccinated children. After PCV13, a 98% reduction in IPIs caused by vaccine serotypes has been seen, particularly in children <5 years old. The number of pneumococcal isolates and percentage of isolates with high-level penicillin resistance from cultures taken from children with otitis media or mastoiditis for clinical indications decreased, largely related to decreases in serotype 19A. Rates of hospitalization for pneumococcal pneumonia among U.S. children decreased after PCV13 introduction. The number of cases of pneumococcal meningitis in children remain unchanged, but the proportion of PCV13 serotypes has decreased significantly. In addition, pneumococcal conjugate vaccines significantly reduce nasopharyngeal carriage of vaccine serotypes. PCVs have significantly decreased rates of invasive pneumococcal disease in children with sickle cell disease, and studies suggest substantial protection for HIV-infected children and splenectomized adults. Adverse events after the administration of PCV have included local swelling and redness and slightly increased rates of fever when used in conjunction with other childhood vaccines.

Currently, the predominant non-PCV13 serotypes are 22F, 12F, 33F, 24F, 15C, 15B, 23B, 10A, 11A, 35B, 35F, and 38. Serotypes 12F and 24F have high invasive disease potential, with the latter responsible for a rebound in incidence of pneumococcal meningitis since 2015. Serotypes 11A, 35F, and 35B in nasopharyngeal and middle ear samples are increasingly resistant to antibiotics. PCV15 or PCV20, which have replaced PCV13, do not contain serotypes 24 or 35, but PCV20 includes 11A and 12F.

Immunologic responsiveness and efficacy after administration of pneumococcal polysaccharide vaccines (PPSV23) is unpredictable in children <2 years old. PPSV23 contains purified polysaccharide of 23 pneumococcal serotypes responsible for >95% of invasive disease. The clinical efficacy of PPSV23 is controversial, and studies have yielded conflicting results.

Immunization with PCV15 or PCV20 is recommended for all infants on a schedule for primary immunization, in previously unvaccinated infants, and for transition for those partially vaccinated (Table 228.3). High-risk children ≥2 years old, such as those with asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, cochlear implant, CSF leak, diabetes mellitus, and chronic lung (including moderate persistent or severe persistent asthma), heart, liver, or kidney disease (including nephrotic syndrome) or immunocompromising conditions, such as asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, etc., may also benefit from PPSV23 administered after 2 years of age after priming with the scheduled doses of PCV15 or 20. Thus it is recommended that children 2 years of age and older with these conditions receive supplemental vaccination with PPSV23. A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for persons ≥2 years old who have immunocompromising conditions including sickle cell disease and functional or anatomic asplenia. Additional doses of PPSV23 are not required, however, if the patient has ever received PCV20. Additional

TABLE 228.4 CDC Advisory Committee on Immunization Practices Recommendations for Use of PCV in Children, June 2023

AGE AND RISK GROUP	RECOMMENDATIONS
Children age <24 mo	• Use of either PCV15 or PCV20 is recommended for all children age 2–23 mo according to previously recommended PCV dosing and schedules. • If only PCV13 is available when the child is scheduled to receive a PCV, PCV13 may be given as previously recommended. • If a child started the PCV series with PCV13, the child may complete the series with PCV15 or PCV20 without giving additional doses; the PCV series does not need to be restarted. • For children who have received all recommended dosing and schedules with PCV13 or PCV15, a supplemental dose of PCV20 is not indicated.
Healthy children age 24–59 mo with an incomplete PCV vaccination status*	• A single dose of either PCV15 or PCV20 is recommended. • A supplemental dose of PCV15 or PCV20 is not indicated for healthy children who have received 4 doses of PCV13 or who completed another age-appropriate PCV13 schedule.
Children age 24–71 mo with any risk condition†	• Use either PCV15 or PCV20 according to previously recommended PCV dosing and schedules. • If only PCV13 is available when the child is scheduled to receive a PCV, PCV13 may be given as previously recommended.
Children age 2–18 yr with any risk condition who completed a recommended PCV series before age 6 yr	• Completed series includes ≥1 dose of PCV20: ○ No additional doses of any pneumococcal vaccine are indicated. ○ This recommendation may be updated as additional data become available. • Completed series using PCV13 or PCV15 (no PCV20): ○ Either a single dose of PCV20 or PPSV23 using previously recommended dosing and schedules is recommended to complete the recommended vaccine series.
Children age 6–18 yr with any risk condition with no previous PCV13, PCV15, or PCV20 vaccination	• For children age 6–18 yr with any risk condition who have not received any dose of PCV (PCV13, PCV15, or PCV20) a single dose of either PCV15 or PCV20 is recommended. • If the child has previously received PCV7 and/or PPSV23, a single dose of either PCV15 or PCV20 is recommended ≥8 wk after the most recent dose of pneumococcal vaccination. ○ PCV15 should be followed by a dose of PPSV23 if not previously given. ○ PCV20 does not need to be followed by a dose of PPSV23.
Children who have received HSCT	• Children who received HSCT are recommended to receive three doses of PCV20, 4 wk apart starting 3–6 mo after HSCT. • A fourth PCV20 dose is recommended ≥6 mo after the third PCV20 dose, or ≥12 mo after HSCT, whichever is later. • HSCT recipients who have started their pneumococcal vaccine series with PCV13 or PCV15 may complete their 4-dose pneumococcal vaccine series with PCV20 without giving extra doses. • If PCV20 is not available, three doses of PCV15, 4 wk apart starting 3–6 mo after HSCT, followed by a dose of PPSV23 ≥12 mo after HSCT may be given. • For patients with chronic graft-versus-host disease who are receiving PCV15, a fourth dose of PCV15 can be given in place of PPSV23 since these children are less likely to respond to PPSV23. A patient's clinical team is best positioned to determine the appropriate timing of vaccination.

*Routine use of PCV is not recommended for healthy children age ≥5 yr.

†Risk conditions include: cerebrospinal fluid leak; chronic heart disease; chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions); chronic liver disease; chronic lung disease (including moderate persistent or severe persistent asthma); cochlear implant; diabetes mellitus; immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease or other with these conditions who received PCV13 or PCV15 are also recommended to receive 23-valent pneumococcal polysaccharide vaccine.

PCV, pneumococcal conjugate vaccine; PCV13, 13-valent PCV; PCV15, 15-valent PCV; PCV20, 20-valent PCV; PPSV23, 23-valent pneumococcal polysaccharide vaccine; HSCT, hematopoietic stem cell transplant.

From Centers for Disease Control and Prevention. ACIP updates: Recommendations for use of 20-valent pneumococcal conjugate vaccine in children—United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(39):1072. (Table 1).

recommendations have been made for at-risk children 6-18 years old (Table 228.4).

Immunization with pneumococcal vaccines also may prevent pneumococcal disease caused by nonvaccine serotypes that are serotypically related to a vaccine strain. However, because current vaccines do not eliminate all pneumococcal invasive infections, penicillin prophylaxis is recommended for children at high risk of invasive pneumococcal disease, including children with asplenia or sickle cell disease. Oral penicillin V potassium (125 mg twice daily for children <3 years old; 250 mg twice daily for children ≥3 years old) decreases the incidence of pneumococcal sepsis in children with sickle cell disease. Once-monthly IM benzathine penicillin G (600,000 units every 3-4 weeks for children weighing <60 lb; 1,200,000 units every 3-4 weeks for children weighing ≥60 lb) may also provide prophylaxis. Erythromycin may be used in children with penicillin allergy, but its efficacy is unproven. Prophylaxis in sickle cell disease has been safely discontinued after the fifth birthday in children who have received all recommended pneumococcal vaccine doses and who had not experienced invasive pneumococcal disease. Prophylaxis is often administered for at least 2 years after splenectomy or up to 5 years of age. Efficacy in children >5 years old and adolescents is unproven. If oral antibiotic prophylaxis is used, strict compliance must be encouraged.

Given the rapid emergence of penicillin-resistant pneumococci, especially in children receiving long-term, low-dose therapy, prophylaxis cannot be relied on to prevent disease. High-risk children with fever should be promptly evaluated and treated regardless of vaccination or penicillin prophylaxis history.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 229

Group A *Streptococcus*

Stanford T. Shulman and Ami B. Patel

Group A *Streptococcus* **(GAS)**, also known as *Streptococcus pyogenes,* is a common cause of infections of the upper respiratory tract **(pharyngitis)** and the skin **(impetigo, pyoderma)** in children. Less frequently, GAS causes perianal cellulitis, vaginitis, septicemia, pneumonia, empyema, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, omphalitis, and other infections. This organism also causes distinct clinical entities **(scarlet fever** and **erysipelas)**, as well as streptococcal **toxic shock syndrome** and monomicrobial **necrotizing fasciitis**. GAS is also the cause of at least two potentially serious nonsuppurative complications: **rheumatic fever** (see Chapters 229.1 and 487) and **acute glomerulonephritis** (see Chapter 559.4).

ETIOLOGY

Group A streptococci are gram-positive, coccoid-shaped bacteria that tend to grow in chains. Streptococci are broadly classified by their hemolytic activity on mammalian (typically sheep) red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β-hemolytic (complete hemolysis) from α-hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide **(Lancefield C carbohydrate)** located in the bacterial cell wall. More than 20 serologic groups are identified, designated by the letters A through V, although only A through D are medically important. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any of a number of latex agglutination, coagglutination, molecular assays or enzyme immunoassays. Group A strains can also be distinguished from other groups by differences in sensitivity to bacitracin, as other groups are generally resistant to this antibiotic.

GAS can be subdivided into at least 220 serotypes on the basis of the **M protein** antigen, which is located on the cell surface and in fimbriae that project from the outer surface of the cell. Currently, a molecular approach to M-typing GAS isolates using the polymerase chain reaction (PCR) is based on sequencing the terminal portion of the *emm* gene of GAS that encodes the M protein. This *emm* typing system correlates with known serotypes and *emm* types. The *emm* types can be grouped into *emm* clusters that share structural and binding properties. It is important to note that immunity is largely based on type-specific opsonic anti-M antibody.

M/*emm* typing is valuable for epidemiologic studies; specific GAS diseases tend to be associated with certain M types. Types 1, 12, 28, 4, 3, and 2 (in that order) are the most common causes of uncomplicated streptococcal pharyngitis in the United States. M types usually associated with pharyngitis rarely cause skin infections, and the M types associated with skin infections rarely cause pharyngitis. A few **pharyngeal** GAS strains (e.g., M type 12) are associated with glomerulonephritis, but many more **skin** GAS strains (e.g., M types 49, 55, 57, and 60) are considered nephritogenic. Several pharyngeal serotypes (e.g., M types 1, 3, 5, 6, 18, and 29), but no proven skin strains, are associated with **acute rheumatic fever** in North America.

EPIDEMIOLOGY

Humans are the natural reservoir for GAS. These bacteria are highly communicable and can cause disease in normal individuals of all ages who do not have type-specific immunity against the particular serotype involved. Disease in neonates is uncommon in developed countries, probably because of maternally acquired antibody. The incidence of **pharyngitis** is highest in children 5-15 years of age, especially in young school-age children. Acute streptococcal pharyngitis is uncommon in children younger than 3 years, and testing is generally not recommended. These infections are most common in the northern regions of the United States, especially during winter and early spring. Children with untreated acute pharyngitis spread GAS by salivary droplets and nasal discharge. Transmission is favored by close proximity; therefore schools, military barracks, and homes are important environments for spread. GAS has the potential to be an important upper respiratory tract pathogen and to produce outbreaks of disease in the daycare setting. Foods contaminated by GAS occasionally cause explosive outbreaks of pharyngotonsillitis. The incubation period for pharyngitis is usually 2-5 days. Children are usually no longer infectious within 24 hours of starting appropriate antibiotic therapy. Chronic pharyngeal carriers of GAS rarely transmit this organism to others.

Streptococcal pyoderma (impetigo, pyoderma) occurs most frequently during the summer in temperate climates, or year-round in warmer climates, when the skin is exposed and abrasions and insect bites are more likely to occur (see Chapter 727). Colonization of healthy skin by GAS usually precedes the development of impetigo. Because GAS cannot penetrate intact skin, impetigo and other skin infections usually occur at the site of open lesions (insect bites, traumatic wounds, burns). Although impetigo serotypes may colonize the throat, spread is usually from skin to skin, not via the respiratory tract. Fingernails and the perianal region can harbor GAS and play a role in disseminating impetigo. Multiple cases of impetigo in the same family are common. Both impetigo and pharyngitis are more likely to occur among children living in crowded homes and in poor hygienic circumstances.

The incidence of **severe invasive** GAS infections, including bacteremia, pneumonia and empyema, osteomyelitis, septic arthritis, retropharyngeal abscess, lymphadenitis, streptococcal **toxic shock syndrome**, **scarlet fever**, and **necrotizing fasciitis**, has increased in recent decades. The incidence appears to be highest in very young and elderly persons. Before the routine use of varicella vaccine, varicella was the most commonly identified risk factor for invasive GAS infection in children. Other risk factors include diabetes mellitus, HIV infection, intravenous drug use, and chronic pulmonary or chronic cardiac disease. The portal of entry is unknown in almost 50% of cases of severe invasive GAS infection; in most cases, it is believed to be skin or, less often, mucous membranes. Severe invasive disease rarely follows clinically apparent GAS pharyngitis. Invasive GAS disease was reported in many children's hospitals in multiple countries during the COVID-19 pandemic. It is unclear why this has happened, but masking, social distancing, and school closures may have reduced exposure to common viral pathogens or colonization with GAS, resulting in more severe infection when mask and social distancing have stopped and schools have reopened. Co-infection with respiratory viruses (respiratory syncytial virus [RSV], other) may predispose to more severe infection.

PATHOGENESIS

The virulence of GAS depends primarily on the **M protein**, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. M protein stimulates the production of protective opsonophagocytic antibodies that are type specific, protecting against infection with a homologous M type but much less so against other M types. Therefore multiple GAS infections attributable to various M types are common during childhood and adolescence. By adult life, individuals are probably immune to many of the common M types in the environment.

GAS produces a large variety of extracellular enzymes and toxins, including erythrogenic toxins, known as **streptococcal pyrogenic exotoxins**. Streptococcal pyrogenic exotoxins A, C, and SSA, alone or in combination, are responsible for the **rash of scarlet fever** and are elaborated by streptococci that contain a particular bacteriophage. These exotoxins stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. Pathogenic variants in genes that are promoters of several virulence genes, including pyrogenic exotoxins, as well as several newly discovered exotoxins, appear to be involved in the

pathogenesis of invasive GAS disease, including streptococcal toxic shock syndrome.

The importance of other streptococcal toxins and enzymes in human disease is not yet established. Many of these extracellular substances are antigenic and stimulate antibody production after an infection. However, these antibodies do not confer immunity. The measurement of select toxins and antibodies is useful for establishing evidence of a recent streptococcal infection to aid in the diagnosis of postinfectious illnesses. Tests for antibodies against streptolysin O (anti–streptolysin O) and DNase B (anti–DNase B) are the most frequently used antibody determinations.

CLINICAL MANIFESTATIONS

The most common infections caused by GAS involve the respiratory tract and the skin and soft tissues.

Respiratory Tract Infections

GAS is an important cause of acute **pharyngitis** (see Chapter 430) and pneumonia, often with empyema (see Chapter 449).

Scarlet Fever

Scarlet fever is GAS pharyngitis associated with a characteristic rash, which is caused by an infection with **pyrogenic exotoxin** (erythrogenic toxin)–producing GAS in individuals who do not have antitoxin antibodies. It is now encountered less often and is less virulent than in the past, but the incidence is cyclic, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those for GAS pharyngitis.

The scarlet fever rash appears within 24-48 hours after the onset of symptoms, although it may appear with the first signs of illness (Fig. 229.1A). It often begins around the neck and spreads over the trunk and extremities. The rash is a diffuse, finely papular, erythematous eruption producing bright-red discoloration of the skin, which blanches on pressure. It is often accentuated in the creases of the elbows, axillae, and groin (Pastia lines). The skin has a goose-pimple appearance and feels rough. The cheeks are often erythematous with perioral pallor. After 3-4 days, the rash begins to fade and is followed by **desquamation**, initially on the face, progressing caudally, and often resembling a mild sunburn. Occasionally, sheetlike desquamation may occur around the free margins of the fingernails, the palms, and the soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with GAS pharyngitis. In addition, the tongue is usually coated and the papillae are swollen (see Fig. 229.1B). After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance (see Fig. 229.1C).

Typical scarlet fever is not difficult to diagnose; the milder form with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal infections are occasionally associated with a scarlatiniform rash. A history of recent exposure to a GAS infection is helpful. Identification of GAS in the pharynx confirms the diagnosis.

Impetigo

Impetigo (or pyoderma) has traditionally been classified into two clinical forms: bullous and nonbullous (see Chapter 706.1). **Nonbullous impetigo** is the more common form and is a superficial infection of the skin that appears first as a discrete papulovesicular lesion surrounded by a localized area of redness. The vesicles rapidly become purulent and covered with a thick, confluent, amber-colored crust that gives the appearance of having been stuck onto the skin. The lesions may occur anywhere but are most common on the face and extremities. If untreated, nonbullous impetigo is a mild but chronic illness, often spreading to other parts of the body, but occasionally self-limited. Regional **lymphadenitis** is common. Nonbullous impetigo is generally not accompanied by fever or other systemic signs or symptoms. Impetiginized excoriations around the nares are seen with active GAS infections of the nasopharynx, particularly in young children. However, impetigo is rarely associated with overt streptococcal infection of the upper respiratory tract.

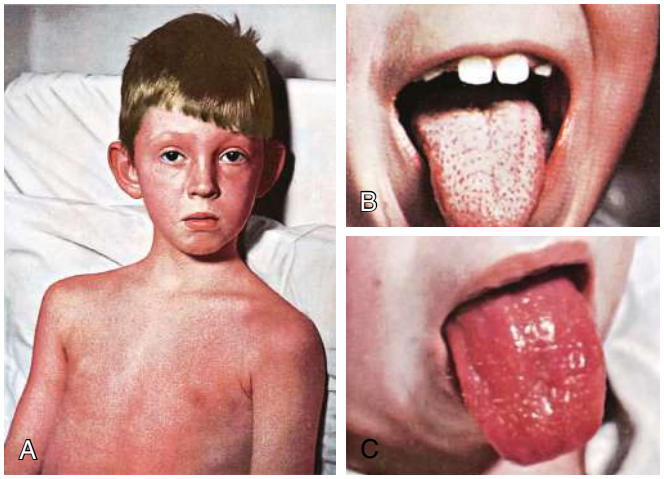

Fig. 229.1 Scarlet fever. **A,** Punctate, erythematous rash (second day). **B,** White strawberry tongue (first day). **C,** Red strawberry tongue (third day). *(Courtesy Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA, Hotez PJ, Katz SL. Krugman's Infectious Diseases of Children, 11th ed. Philadelphia: Mosby; 2004, Plate 53.)*

Bullous impetigo is less common and occurs most often in neonates and young infants. It is characterized by flaccid, transparent bullae usually <3 cm in diameter on previously untraumatized skin. The usual distribution involves the face, buttocks, trunk, and perineum.

Although *Staphylococcus aureus* has traditionally been accepted as the sole pathogen responsible for bullous impetigo, there has been confusion about the organisms responsible for nonbullous impetigo. In most episodes of nonbullous impetigo, either GAS or *S. aureus* (or both) is isolated. Earlier investigations suggested that GAS was the causative agent in most cases of nonbullous impetigo and that *S. aureus* was only a secondary invader. However, *S. aureus* has emerged as the causative agent in most cases of nonbullous impetigo. Culture of the lesions is the only way to distinguish nonbullous impetigo caused by *S. aureus* from that caused by GAS.

Erysipelas

Erysipelas is a relatively rare acute GAS infection involving the deeper layers of the skin and the underlying connective tissue. The skin in the affected area is edematous, highly erythematous, and very tender. The erythema associated with erysipelas is very bright, which differentiates it from the dusky appearance of necrotizing fasciitis. Superficial blebs may be present. The most characteristic finding is a sharply defined, slightly elevated border. At times, reddish streaks of lymphangitis project out from the margins of the lesion. The onset is abrupt, and signs and symptoms of a systemic infection, such as high fever and sepsis, are often present. Cultures obtained by needle aspirate of the advancing margin of the inflamed area often reveal the causative agent.

Perianal Dermatitis

Perianal dermatitis, also called *perianal cellulitis* or **perianal streptococcal disease**, is a distinct clinical entity characterized by well-demarcated, perianal erythema associated with anal pruritus, painful defecation, and occasionally blood-streaked stools. Most children are 2-7 years old (range: 18 days-12 years). Physical examination reveals flat, pink to beefy-red perianal erythema with sharp margins extending

as far as 2 cm from the anus. Erythema may involve the vulva and vagina. Lesions may be very tender and, particularly when chronic, may fissure and bleed. Systemic symptoms and fever are unusual. Culture or a rapid streptococcal test of a perianal swab will yield GAS or detect antigen.

Vaginitis

GAS is a common cause of vaginitis in prepubertal girls (see Chapter 586). Patients usually have a serous discharge with marked erythema and irritation of the vulvar area, accompanied by discomfort in walking and in urination.

Severe Invasive Disease

Invasive GAS infection is defined by isolation of GAS from a normally sterile body site and includes three overlapping clinical syndromes. **GAS toxic shock syndrome (TSS)** is differentiated from other types of invasive GAS infections by the presence of shock and multiorgan system dysfunction early in the course of the infection (Table 229.1). The second syndrome is **GAS necrotizing fasciitis**, characterized by extensive local necrosis of subcutaneous soft tissues and skin. The third syndrome is the group of **focal and systemic infections** that do not meet the criteria for TSS or necrotizing fasciitis and includes bacteremia with sepsis with no identified focus, meningitis, pneumonia and empyema, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound and other infections. GAS TSS, necrotizing fasciitis, and focal and systemic infections can be present in any combination.

The pathogenic mechanisms responsible for severe, invasive GAS infections, including streptococcal TSS and necrotizing fasciitis, have yet to be defined completely, but an association with **streptococcal pyrogenic exotoxins** is strongly suspected. At least two of the three original streptococcal pyrogenic exotoxins (A and C) and potentially other as yet unidentified toxins produced by GAS act as **superantigens**, which stimulate intense activation and proliferation of T lymphocytes and macrophages, resulting in the production of large quantities of proinflammatory cytokines. These cytokines are capable of inducing shock and tissue injury and appear to mediate many of the clinical manifestations of severe, invasive GAS infections.

DIAGNOSIS OF GAS PHARYNGITIS

When deciding whether to perform a diagnostic test on a patient presenting with acute pharyngitis, the clinical and epidemiologic findings should be considered. A history of close contact with a well-documented case of GAS pharyngitis is helpful, as is an awareness of a high prevalence of GAS infections in the community. The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow the requisite diagnostic precision on clinical grounds alone. The clinical diagnosis of GAS pharyngitis cannot be made with reasonable accuracy even by the most experienced physicians, and laboratory confirmation is required, except for patients with overt viral signs and symptoms (e.g., rhinorrhea, cough, mouth ulcers, hoarseness), who generally do not need a GAS diagnostic test performed, as GAS is highly unlikely.

Culture of a throat swab on a sheep blood agar plate is effective for documenting the presence of GAS and for confirming the clinical diagnosis of acute GAS pharyngitis. When performed correctly, a single throat swab has a sensitivity of 90–95% for detecting the presence of GAS in the pharynx.

The significant disadvantage of culturing a throat swab on a blood agar plate is the delay (overnight or longer) in obtaining the culture result. **Streptococcal rapid antigen detection** tests are available for the identification of GAS directly from throat swabs. Their advantage over culture is the speed in providing results, often <10-15 minutes. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk for spread of GAS, allowing the patient to return to school or work sooner, and can reduce the acute morbidity of this illness.

Almost all currently available rapid antigen detection tests have excellent specificity of >95% compared with blood agar plate cultures. False-positive test results are quite unusual, and therefore therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 70–90% when compared with blood agar plate culture. Therefore a negative rapid test does not completely exclude the presence of GAS, and a confirmatory throat culture should be performed in children and adolescents, but not necessarily in adults, who are at exceptionally low risk for developing acute rheumatic fever. Definitive studies are not available to determine whether some rapid antigen detection tests are significantly more sensitive than others or whether any of these tests is sensitive enough to be used routinely in children and adolescents without throat culture confirmation of negative test results. Some experts believe that physicians who use a rapid antigen detection test without culture backup should compare the results with that specific test to those of throat cultures to confirm adequate sensitivity in their practice.

In point-of-care settings and laboratories testing for GAS pharyngitis, culture methods are being replaced by rapid antigen and molecular assays. These molecular assays include PCR methods and **nucleic acid amplification tests** using isothermal loop amplification. Some of these methods have been reported to have a sensitivity of up to 100% and specificity of >96% compared to culture or PCR. This very high sensitivity may lead to higher numbers of positive results, which in turn may contribute to identification of more patients with asymptomatic GAS colonization and unnecessary antibiotic therapy. Therefore it is important that the appropriate clinical context to perform these highly sensitive tests be considered. However, the benefit of faster results, sometimes <10 minutes, which ensures more expedited initiation of appropriate antibiotic therapy for patients with GAS pharyngitis, may be of value.

GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The **anti–streptolysin O** assay is the streptococcal antibody test most often used. The test is not specific for group A infection because streptolysin O also is produced by groups C and G streptococci. The anti–streptolysin O response can be feeble after streptococcal skin infection. In contrast, the anti–DNase B responses are generally present after either skin or throat infections. A significant antibody increase is usually defined as an increase in titer of two or more dilution increments (≥ fourfold rise) between the acute-phase and convalescent-phase specimens, regardless of the actual height of the antibody titer. Physicians frequently misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are substantially higher among school-age children than adults. Both the traditional anti–streptolysin O and the anti–DNase B tests are neutralization assays. Newer tests use **latex agglutination** or nephelometric assays. Unfortunately, these newer tests often have not been well standardized against the traditional neutralization assays. Physicians should be aware of these potential problems when interpreting the results of streptococcal serologic testing.

Table 229.1 Definition of Streptococcal Toxic Shock Syndrome

CLINICAL CRITERIA
Hypotension *plus* two or more of the following: Renal impairment Coagulopathy Hepatic involvement Adult respiratory distress syndrome Generalized erythematous macular rash Soft tissue necrosis
DEFINITE CASE
Clinical criteria *plus* group A *Streptococcus* from a normally sterile site
PROBABLE CASE
Clinical criteria *plus* group A *Streptococcus* from a nonsterile site

Differential Diagnosis

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, and RSV are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include enteroviruses and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (e.g., splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents, including cytomegalovirus, rubella virus, measles virus, and HIV, may be associated with acute pharyngitis.

GAS is by far the most common cause of *bacterial* pharyngitis, accounting for 15–30% of cases of acute pharyngitis in children and a lower proportion in adults. Groups C and G β-hemolytic streptococcus also cause acute pharyngitis, typically in teens and young adults (see Chapter 231). *Arcanobacterium haemolyticum* and *Fusobacterium necrophorum* are additional, less common causes. *Neisseria gonorrhoeae* can occasionally cause acute pharyngitis in sexually active adolescents and adults. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica,* as well as mixed infections with anaerobic bacteria (Vincent angina), are very rare causes of acute pharyngitis. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been implicated as causes of acute pharyngitis, particularly in adults. *Corynebacterium diphtheriae* is a serious cause of pharyngitis but is very rare in areas with universal immunization (see Chapter 233). Although other bacteria (e.g., *S. aureus, Haemophilus influenzae, Streptococcus pneumoniae*) are frequently cultured from the throats of children with acute pharyngitis, their etiologic role in pharyngitis has not been established, because they are often isolated from healthy children.

GAS pharyngitis is the only common cause of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore when confronted with a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether or not the pharyngitis is attributable to GAS.

TREATMENT OF GAS PHARYNGITIS

Timely antibiotic therapy for patients with GAS pharyngitis can prevent **acute rheumatic fever** (RF), shorten the clinical course of the illness, reduce transmission of the infection to others, and prevent suppurative complications. *For the patient with classic scarlet fever, antibiotic therapy should be started immediately, but for the majority of patients, who present with much less distinctive findings, treatment should be withheld until there is laboratory confirmation by throat culture, molecular assay, or rapid antigen detection test.* Rapid antigen detection tests, because of their high degree of specificity, allow initiation of antibiotic therapy immediately for the patient with a positive test result.

GAS is exquisitely sensitive to penicillin and cephalosporins, and resistant strains have never been encountered. Penicillin or amoxicillin is therefore the drug of choice (except in patients who are allergic to penicillins) for pharyngeal infections and for suppurative complications. Oral penicillin V (250 mg/dose 2 or 3 times daily [bid-tid] for children weighing ≤60 lb and 500 mg/dose bid-tid for children >60 lb) is recommended but must be taken for a full 10 days, even though symptomatic improvement may occur within 2-3 days. Penicillin V (phenoxymethylpenicillin) is preferred over penicillin G, because it may be given without regard to mealtime. The major concern with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If the parents seem unlikely to comply with oral therapy because of family disorganization, difficulties in comprehension, or other reasons, parenteral therapy with a single intramuscular (IM) injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for children >60 lb) is the most efficacious and often the most practical method of treatment. Disadvantages include soreness around the site of injection, which may last for several days, and potential for injection into nerves or blood vessels if not administered correctly. The local reaction is diminished when the refrigerated drug is warmed to room temperature and when benzathine penicillin G is combined in a single injection with procaine penicillin G, although it is necessary to ensure that an adequate dose of benzathine penicillin G is administered.

In several comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum: 1,000 mg) for 10 days has been demonstrated to be as effective in treating GAS pharyngitis as amoxicillin administered orally multiple times per day. This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence. In addition, amoxicillin is relatively inexpensive and is considerably more palatable than penicillin V suspension.

A 10-day course of a narrow-spectrum oral cephalosporin is recommended for most **penicillin-allergic** individuals. It has been suggested that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx. Analysis of these data suggests that the difference in eradication is mainly the result of a higher rate of eradication of GAS carriage included unintentionally in these clinical trials. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should be avoided in patients with immediate (anaphylactic-type) hypersensitivity to penicillin. Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin and are more likely to select for antibiotic-resistant flora.

Oral clindamycin is an appropriate agent for treating penicillin-allergic patients, and resistance to clindamycin among GAS isolates in the United States is currently <6%. An oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is also an appropriate agent for patients allergic to penicillins. Ten days of therapy is indicated except for azithromycin, which is given at 12 mg/kg on day 1 and then 6 mg/kg on days 2-5. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than the other agents. In recent years, macrolide resistance rates among pharyngeal isolates of GAS in most areas of the United States have been approximately 5–10%. Sulfonamides and the tetracyclines are not recommended for treatment of GAS pharyngitis. However, studies showed that trimethoprim-sulfamethoxazole (TMP-SMX) is highly active in vitro against GAS and was comparable to IM penicillin for GAS impetigo in clinical trials.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal pharyngeal eradication rates of GAS and prevention of RF, but certain newer agents are reported to achieve comparable bacteriologic and clinical cure rates when given for ≤5 days. However, definitive results from comprehensive studies are not available to allow full evaluation of these proposed shorter courses of oral antibiotic therapy, which therefore cannot be recommended at this time. In addition, these antibiotics have a much broader spectrum than penicillin and are generally more expensive, even when administered for short courses.

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS is eradicated from the pharynx. Posttreatment throat cultures are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had RF or rheumatic heart disease and are therefore at unusually high risk for recurrence.

Treatment of GAS Skin Infections

Antibiotic therapy for a patient with nonbullous impetigo can prevent local extension of the lesions, spread to distant infectious foci, and transmission of the infection to others. However, the ability of antibiotic therapy to prevent poststreptococcal glomerulonephritis has not been definitively demonstrated. Patients with a few superficial, isolated lesions and no systemic signs can be treated with topical antibiotics. **Mupirocin** is a safe and effective agent that has become the topical treatment of choice. If there are widespread lesions or systemic signs, oral therapy with coverage for both GAS and *S. aureus* is needed. With the rapid emergence of methicillin-resistant *S. aureus* in many communities, one should consider using clindamycin alone or a combination

of TMP-SMX and amoxicillin as first-line therapy. Oral cefuroxime is an effective treatment of perianal streptococcal disease.

Treatment of Invasive GAS Infection

Theoretical considerations and experimental data suggest that intravenous clindamycin is a more effective agent for the treatment of severe, invasive GAS infections than IV penicillin. However, because approximately 4–6% of GAS isolates in the United States are resistant to clindamycin, clindamycin initially should be used in combination with penicillin for these infections until susceptibility to clindamycin has been established. If **necrotizing fasciitis** is suspected, immediate surgical exploration may be required to identify a deep soft tissue infection that should be debrided immediately. Patients with **streptococcal TSS** require rapid and aggressive fluid replacement, management of respiratory or cardiac failure, if present, and anticipatory management of multiorgan system failure. Limited data suggest that intravenous immune globulin (IVIG) is effective as adjunctive therapy in the management of streptococcal TSS.

COMPLICATIONS

Suppurative complications from the spread of GAS to adjacent structures were extremely common in the preantibiotic era. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or in whom treatment of the pharyngitis has been inadequate. GAS pneumonia can also occur.

Acute rheumatic fever (see Chapter 229.1) and acute poststreptococcal **glomerulonephritis** (see Chapter 559.4) are both nonsuppurative sequelae of infections with GAS that occur after an asymptomatic latent period. These complications occur after the initial GAS infection resolves and involves sites distal to the initial GAS infection site. These sequelae are thought to be the result of the immune response and not of direct GAS infection. Acute RF and acute glomerulonephritis differ in their clinical manifestations, epidemiology, and potential morbidity. In addition, acute glomerulonephritis follows a GAS infection of either the upper respiratory tract or the skin, but acute RF is only proven to follow an infection of the upper respiratory tract. Some investigators have suggested that in some highly endemic areas, particularly in New Zealand and Australia, GAS skin infection may trigger acute RF, but this remains controversial.

PROGNOSIS

The prognosis for appropriately treated GAS pharyngitis is excellent, and complete recovery is the rule. When therapy is instituted within 9 days of the onset of symptoms and continued for the full course, acute RF is almost always prevented. There is no comparable evidence that acute poststreptococcal glomerulonephritis can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

PREVENTION

The only specific indication for long-term use of an antibiotic to prevent GAS infections is for patients with a history of acute RF and/or rheumatic heart disease. Mass prophylaxis is generally not feasible except possibly to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Because the ability of antimicrobial agents to prevent GAS infections is limited, a group A streptococcal vaccine would offer the possibility of a more effective approach.

Several candidate vaccines are in development, including a 30-valent M protein–based recombinant vaccine, another recombinant vaccine that includes several conserved non–M protein epitopes that induce protective antibody, and an M-protein vaccine that includes an epitope in a highly conserved region of M protein to provide broad immunity. All these vaccines are in relatively early stages of development.

Poststreptococcal Reactive Arthritis

Poststreptococcal reactive arthritis (PSRA) describes a syndrome characterized by the onset of acute arthritis after an episode of GAS pharyngitis in a patient whose illness does not fulfill the Jones Criteria for diagnosis of acute RF. It is still unclear whether this entity represents a distinct syndrome or is a variant of acute RF. Although PSRA usually involves the large joints, similar to the arthritis of acute RF, it may also involve small peripheral joints and the axial skeleton and is typically nonmigratory, a characteristic distinct from the arthritis of acute RF. The latent period between the antecedent episode of GAS pharyngitis and PSRA may be considerably *shorter* (usually <10 days) than that typically seen with acute RF (usually 14-21 days). In contrast to the arthritis of acute RF, PSRA *does not* respond dramatically to therapy with aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs). In addition, fewer patients with PSRA than with acute RF have a temperature >38°C (100.4°F). Even though no more than half of PSRA patients with throat culture have GAS isolated, all have serologic evidence of a recent GAS infection. Because a very small proportion of patients with PSRA have been reported to develop valvular heart disease subsequently, these patients should be carefully observed for several months for clinical evidence of carditis. Some recommend that these patients receive secondary antistreptococcal prophylaxis for up to 1 year. If clinical evidence of carditis is not observed at that point, the prophylaxis can be discontinued. If valvular disease is detected, the patient should be classified as having had acute RF and should continue to receive secondary prophylaxis appropriate for RF patients.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus pyogenes*

Pediatric autoimmune neuropsychiatric disorders associated with *S. pyogenes* **(PANDAS)** is a term proposed for a group of neuropsychiatric disorders (originally obsessive-compulsive disorder [OCD], tic disorder, and Tourette syndrome, or only OCD or feeding abnormality) for which a possible relationship with GAS infections has been hypothesized (see Chapter 37). *This relationship has not been proved.* It has been proposed that this subset of patients with OCDs may produce autoimmune antibodies in response to a GAS infection that cross-react with brain tissue, similar to the autoimmune response believed to be responsible for the manifestations of **Sydenham chorea**. It has also been suggested that secondary prophylaxis that prevents recurrences of rheumatic fever, including Sydenham chorea, might also be effective in preventing exacerbations of OCDs in these patients, but clinical trials have not confirmed this. It has also been proposed that these patients may benefit from immunoregulatory therapy such as plasma exchange or IVIG, but these unproven modalities should only be used in a clinical research trial. That PANDAS may represent an extension of the spectrum of acute RF is intriguing, but it should be considered only as a yet-unproven hypothesis. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., IVIG, plasma exchange) to treat exacerbations of this disorder clearly are not recommended (see Chapter 37). It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders, which have been termed *pediatric acute-onset neuropsychiatric syndrome* (PANS), but this remains highly controversial.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

229.1 Rheumatic Fever

Stanford T. Shulman and Ami B. Patel

See also Chapter 487.

Overwhelming evidence supports the link between antecedent GAS pharyngitis and **acute rheumatic fever** (RF) and **rheumatic heart disease**. As many as two thirds of patients with an acute episode of RF have a history of an upper respiratory tract infection several weeks before; the peak age and seasonal incidence of acute RF closely parallel that of GAS pharyngitis. Patients with acute RF almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually *considerably higher* than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by community outbreaks of acute RF. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute RF, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute RF.

Not all serotypes of GAS can cause RF. When some GAS strains (e.g., M type 4) caused acute pharyngitis in a very susceptible rheumatic population, there were no recurrences of RF. In contrast, episodes of pharyngitis caused by other serotypes in the same population led to frequent recurrences of acute RF, suggesting that the latter organisms were rheumatogenic. The concept of *rheumatogenicity* is further supported by the observation that although serotypes of GAS frequently associated with skin infection can be isolated also from the upper respiratory tract, they rarely cause recurrences of RF in individuals with a previous history of RF or first episodes of RF. In addition, certain serotypes of GAS (M types 1, 3, 5, 6, 18, and 29) are more frequently isolated from patients with acute RF than are other serotypes.

EPIDEMIOLOGY

The annual incidence of acute RF in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. Worldwide, **rheumatic heart disease** remains the most common form of acquired heart disease in all age-groups, accounting for up to 50% of all cardiovascular disease and 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute RF and rheumatic heart disease among different ethnic groups are often evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility.

In the United States at the beginning of the 20th century, acute RF was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. In addition, rheumatic heart disease was a leading cause of heart disease among adults <40 years old. At that time, as many as 25% of pediatric hospital beds in the United States were occupied by patients with acute RF or its complications. By the 1940s, the annual incidence of acute RF had decreased to 50 per 100,000 population, and over the next 4 decades, the decline in incidence accelerated rapidly. By the early 1980s, the annual incidence in some areas of the United States was as low as 0.5 per 100,000 population, and rates of acute RF since the 1980s have declined substantially. This sharp decline in the incidence of acute RF has been observed in other industrialized countries as well.

The explanation for this dramatic decline in the incidence of acute RF and rheumatic heart disease in the United States and other industrialized countries is not clear but is likely related in large part to a *decline in circulating rheumatogenic strains causing acute pharyngitis*. Historically, acute RF was associated with poverty and overcrowding, particularly in urban areas. Much of the decline in the incidence of acute RF in industrialized countries during the preantibiotic era was probably the result of improved living conditions. Of the various manifestations of poverty, crowding, which facilitates the spread of GAS infections, is most closely associated with the incidence of acute RF. The decline in incidence of acute RF in industrialized countries over the past 4 decades is also attributable to the greater availability of medical care and to the widespread use of antibiotics. Antibiotic therapy of GAS pharyngitis is important in preventing initial attacks and, particularly, recurrences of the disease. In addition, the decline in the United States is attributed to a shift in the prevalent strains of GAS causing pharyngitis from mostly rheumatogenic to nonrheumatogenic.

Certain rheumatogenic serotypes (types 1, 3, 5, 6, and 18) that were isolated less often during the 1970s and early 1980s dramatically reappeared during rheumatic fever outbreaks, and their appearance in selected communities was probably a major factor. GAS that are associated with rheumatogenicity often form highly mucoid colonies on throat culture plates.

In addition to the specific characteristics of the infecting strain of GAS, the risk of developing acute RF also depends on various host factors. The incidence of both initial attacks and recurrences of acute RF peaks in children 5-15 years old, the age of greatest risk for GAS pharyngitis. Patients who have had an attack of acute RF tend to have recurrences, and the clinical features of the recurrences tend to mimic those of the initial attack. In addition, there appears to be a genetic predisposition to acute RF. Studies in twins show a higher concordance rate of acute RF in monozygotic than in dizygotic twin pairs. Preliminary studies from Oceania in a population with high rates of rheumatic heart disease have identified an allele of interest that increases one's risk of rheumatic heart disease.

PATHOGENESIS

The **cytotoxicity theory** suggests that a GAS toxin is involved in the pathogenesis of acute RF and rheumatic heart disease. GAS produces a number of enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. A major problem with the cytotoxicity hypothesis is its inability to explain the substantial latent period (usually 10-21 days) between GAS pharyngitis and onset of acute RF.

An **immune-mediated pathogenesis** for acute RF and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute RF. The immunologic cross-reactivity of several GAS cellular and extracellular epitopes with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane, group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcolemma, brain, joint).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The current **Jones Criteria**, as revised in 2015 by the American Heart Association (AHA), are intended for diagnosis of the *initial* attack of acute RF and *recurrent* attacks (Table 229.2). There are **five major and four minor criteria** and a requirement for evidence of recent GAS infection. The 2015 revision includes separate criteria for **low-risk populations** (defined as those with incidence ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population) and **moderate/high-risk populations** (defined as those with higher incidence or prevalence rates). Virtually all of the United States, Canada, and Western Europe are low-risk, whereas moderate/high-risk populations include Maoris in New Zealand, aborigines in Australia, Pacific Islanders, and most developing countries. Diagnosis of a first attack or recurrent attack of acute RF can be established when a patient fulfills **two major or one major and two minor criteria and has evidence of preceding GAS infection**. Diagnosis of recurrent acute RF can also be made only in the moderate/high-risk population by the presence of three minor criteria with evidence of preceding GAS infection. In the 2015 Jones Criteria, a major change from previous versions expands the definition of the major criterion **carditis** to include *subclinical evidence* (e.g., in the absence of a murmur, echocardiographic evidence of mitral regurgitation [MR] meeting specific criteria to distinguish physiologic from

Table 229.2 Guidelines for the Diagnosis of an Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)[1–5]

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	**Clinical features:** Arthralgia Fever **Laboratory features:** Elevated acute-phase reactants: Erythrocyte sedimentation rate C-reactive protein Prolonged P-R interval	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer

[1]**Initial attack**: Two major manifestations or one major and two minor manifestations plus evidence of recent GAS infection. **Recurrent attack**: Two major, or one major and two minor, or three minor manifestations (the latter only in the moderate/high-risk population), plus evidence of recent GAS infection (see text).
[2]**Low-risk population** is defined as acute rheumatic fever (ARF) incidence <2 per 100,000 school-age children per year or all-age rheumatic heart disease (RHD) prevalence of <1 per 1,000 population. **Moderate/high-risk population** is defined as ARF incidence >2 per 100,000 school-age children per year or all-age RHD prevalence of >1 per 1,000 population.
[3]Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 229.3.
[4]Arthritis (major) refers only to polyarthritis in low-risk populations but also to monoarthritis or polyarthralgia in moderate/high-risk populations.
[5]Minor criteria for moderate/high-risk populations only include monoarthralgia (polyarthralgia for low-risk populations), fever of >38°C (>38.5°C in low-risk populations), and ESR >30 mm/hr (>60 mm/hr in low-risk populations).
From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131(20):1806–1818.

pathologic MR) (see Table 487.1). Areas in which the Jones Criteria differ in low-risk from moderate/high-risk populations relate to the major criterion of **arthritis** and the minor criteria of arthralgia, definition of fever, and elevated inflammatory markers (see Table 229.2 and text that follows). These changes are designed to make it easier to fulfill the Jones Criteria in patients from moderate/high-risk populations. Even with strict application of the criteria, overdiagnosis and underdiagnosis of acute RF may occur. The diagnosis of acute RF can be made without strict adherence to the Jones Criteria in three circumstances: (1) when chorea occurs as the only major manifestation of acute RF, (2) when indolent carditis is the only manifestation in patients who first come to medical attention only months after the apparent onset of acute RF, and (3) in a limited number of patients with recurrence of acute RF in particularly high-risk populations.

The Five Major Criteria

Migratory Polyarthritis

Arthritis occurs in approximately 75% of patients with acute RF and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as one or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Monoarticular arthritis is unusual unless antiinflammatory therapy is initiated prematurely, aborting the progression of the migratory polyarthritis. If a child with fever and arthritis is suspected to have acute RF, it is frequently useful to withhold antiinflammatory medications like salicylates or NSAIDs and observe for migratory progression. A dramatic response to even low doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis.

Rheumatic arthritis is almost never deforming. Synovial fluid in acute RF usually has 10,000-100,000 white blood cells/μL with a predominance of neutrophils, protein level of approximately 4 g/dL, normal glucose level, and formation of a good mucin clot. Frequently, arthritis is the earliest manifestation of acute RF and may correlate temporally with peak antistreptococcal antibody titers. There is often an inverse relationship between the severity of arthritis and the severity of cardiac involvement. In moderate/high-risk populations only, monoarthritis in the absence of prior inflammatory therapies, or even polyarthralgia without frank objective signs of arthritis, can fulfill this major criterion. Before **polyarthralgia** should be considered a major criterion in the moderate/high-risk population, other potential causes should be excluded.

Carditis

A major change in the 2015 revision of the Jones Criteria is the acceptance of **subclinical carditis** (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or **clinical carditis** (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations. The echocardiographic features of subclinical carditis must meet those included in Table 487.1 in Chapter 487 to distinguish pathologic from physiologic degrees of valve regurgitation. Silent or latent rheumatic heart disease describes echocardiographic evidence of rheumatic heart disease in individuals with no known history of acute RF and no clinical symptoms. In endemic regions, active surveillance via screening echocardiography has emerged as a potential strategy to detect *asymptomatic subclinical* rheumatic heart disease.

Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute RF and account for essentially all the associated morbidity and mortality. Rheumatic carditis is characterized by **pancarditis**, with active inflammation of the myocardium, pericardium, and endocardium (see Chapter 487). Cardiac involvement during acute RF varies in severity from fulminant, potentially fatal exudative pancarditis to mild, transient cardiac involvement. **Endocarditis** (valvulitis) is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable. Myocarditis and/or pericarditis without clinical evidence of endocarditis almost never is rheumatic carditis; alternative etiologies (especially viral) need to be sought. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon. Serious and long-term illness is related entirely to the severity of valvular heart disease as a consequence of a single attack or recurrent attacks of acute RF. Valvular insufficiency is characteristic of both acute and convalescent stages of acute RF, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. However, in developing countries, where acute RF often occurs at a younger age, mitral stenosis and aortic stenosis may develop sooner after acute RF than in developed countries and can occur in young children.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial

involvement. Moderate to severe rheumatic carditis can result in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. **Mitral regurgitation** is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant MR, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50–60% of all cases of acute RF. Recurrent attacks of acute RF in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require surgical intervention.

Chorea

Sydenham chorea occurs in approximately 10–15% of patients with acute RF and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing are characteristic, all *exacerbated* by stress and *disappearing* with sleep. Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. The onset can be insidious, with symptoms being present for several months before recognition. Clinical maneuvers to elicit features of chorea include (1) demonstration of *milkmaid's grip* (irregular contractions and relaxations of the muscles of the fingers while squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue on protrusion, and (4) examination of handwriting to evaluate fine motor movements. Diagnosis is based on clinical findings with supportive evidence of GAS antibodies. However, in the usual patient with a long latent period from the inciting streptococcal infection to onset of chorea, antibody levels have often declined to normal. Although the acute illness is distressing, chorea rarely, if ever, leads to permanent neurologic sequelae.

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute RF) but characteristic rash of acute RF. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic (Fig. 229.2). It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.



Fig. 229.2 Polycyclic red borders of erythema marginatum in a febrile child with acute rheumatic fever. *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 2003:808.)*

Subcutaneous Nodules

Subcutaneous nodules are a rare (≤1% of patients with acute RF) finding and consist of firm nodules approximately 0.5-1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more *nonspecific* than major criteria, and the 2015 revised Jones Criteria have included some changes from the previous criteria. The first of the two clinical **minor criteria** involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as *polyarthralgia* in low-risk populations and *monoarthralgia* in moderate/high-risk populations. The second clinical minor manifestation is fever, defined as *at least 38.5°C* in low-risk populations and *at least 38.0°C* in moderate/high-risk populations. The two laboratory minor criteria are (1) elevated acute-phase reactants, defined as erythrocyte sedimentation rate (ESR) at least 60 mm/hr and/or C-reactive protein (CRP) at least 3.0 mg/dL (30 mg/L) in low-risk populations and ESR at least 30 mm/hr and/or CRP at least 3.0 mg/dL (30 mg/L) in moderate/high-risk populations and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A *Streptococcus* Infection

An absolute requirement for the diagnosis of acute RF is supporting evidence of a recent GAS infection. Acute RF typically develops 10-21 days after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present and when only 10–20% of patients still harbor GAS in the throat. One third of patients with acute RF have no history of an antecedent clinically symptomatic pharyngitis. Therefore evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers. If only a single antibody is measured (usually anti–streptolysin O), only 80–85% of patients with acute RF have an elevated titer; however, 95–100% have an elevation if three different antibodies (anti–streptolysin O, anti–DNase B, anti-hyaluronidase) are measured. Therefore when acute RF is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of acute RF generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least one GAS antigen. However, in patients with a long latent period from the inciting GAS infection, antibody levels may have declined to within the normal range. The diagnosis of acute RF should *not* be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones Criteria.

Differential Diagnosis

The differential diagnosis of RF includes many infectious and noninfectious illnesses (Table 229.3). When children present with arthritis, a collagen vascular disease must be considered. **Juvenile idiopathic arthritis** (JIA) must be distinguished from acute RF. Children with JIA tend to be younger and usually have less joint pain relative to their other clinical findings than those with acute RF. Spiking fevers, nonmigratory arthritis, lymphadenopathy, and splenomegaly are more suggestive of JIA than acute RF. The response to salicylate therapy is also much less dramatic with JIA than with acute RF. **Systemic lupus erythematosus** (SLE) can usually be distinguished from acute RF by antinuclear antibodies in SLE. Other causes of arthritis such as pyogenic arthritis, malignancies, serum sickness, Lyme disease, sickle cell disease, and reactive arthritis related to gastrointestinal infections (e.g., *Shigella, Salmonella, Yersinia*) should also be considered. Poststreptococcal reactive arthritis is discussed earlier (see Chapter 229).

When **carditis** is the sole major manifestation of suspected acute RF, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. Patients with infective

Table 229.3 Differential Diagnosis of Acute Rheumatic Fever

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	Systemic lupus erythematosus
Sickle cell disease	Kawasaki disease	Tic disorder
Malignancy	Congenital heart disease	Hyperactivity
Systemic lupus erythematosus	Mitral valve prolapse	Encephalitis (infectious or autoimmune)
Lyme disease (*Borrelia burgdorferi*)	Innocent murmurs	
Pyogenic arthritis	MIS-C	
Poststreptococcal reactive arthritis	Lyme disease	

MIS-C, Multisystem inflammatory syndrome in children (COVID-19).

endocarditis may present with both joint and cardiac manifestations. These patients can usually be distinguished from patients with acute RF by blood cultures and the presence of extracardiac findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When **chorea** is the sole major manifestation of suspected acute RF, Huntington chorea, Wilson disease, SLE, and various encephalitides should also be considered.

TREATMENT

All patients with acute RF should be placed on bed rest and monitored closely for evidence of **carditis**. They can be allowed to ambulate when the signs of acute inflammation have improved. However, patients with carditis require longer periods of bed rest.

Antibiotic Therapy

Once the diagnosis of acute RF has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or amoxicillin or a single IM injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. If penicillin allergic, 10 days of erythromycin, 5 days of azithromycin, or 10 days of clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis for secondary prevention should be instituted (see later).

Antiinflammatory Therapy

Antiinflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute RF. Premature treatment with one of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute RF. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute RF or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in four divided doses orally (PO) for 3-5 days, followed by 50 mg/kg/day in four divided doses PO for 2-3 weeks and half that dose for another 2-4 weeks. Determination of the serum salicylate level is not necessary unless the arthritis does not respond or signs of salicylate toxicity (tinnitus, hyperventilation) develop. There is no evidence that NSAIDs are more effective than salicylates.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in four divided doses for 2-3 weeks, followed by half the dose for 2-3 weeks, and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in four divided doses for 6 weeks to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

Termination of the antiinflammatory therapy may be followed by the reappearance of clinical manifestations or of elevation in ESR and CRP (rebound). It may be prudent to increase salicylates or corticosteroids until near-normalization of inflammatory markers is achieved.

Sydenham Chorea

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; phenobarbital (16-32 mg every 6-8 hours PO) is the drug of choice. If phenobarbital is ineffective, haloperidol (0.01-0.03 mg/kg/24 hr divided twice daily PO) or chlorpromazine (0.5 mg/kg every 4-6 hours PO) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

COMPLICATIONS

The arthritis and chorea of acute RF resolve completely without sequelae. Therefore the long-term sequelae of RF are essentially limited to the heart (see Chapter 487).

The AHA has published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis (see Chapter 486). The AHA recommendations no longer suggest routine endocarditis prophylaxis for patients with rheumatic heart disease who are undergoing dental or other procedures. However, the maintenance of optimal oral healthcare remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with a prosthetic valve or prosthetic material used in valve repair, the current AHA recommendations should be followed (see Chapter 486). These recommendations advise using an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for RF because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

PROGNOSIS

The prognosis for patients with acute RF depends on the clinical manifestations present at the initial episode, the severity of the initial episode, and the prevention of recurrences. Approximately 50–70% of patients with carditis during the initial episode of acute RF recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk for residual heart disease. Patients without carditis during the initial episode are less likely to have carditis with recurrent attacks, but there is a stepwise increase in cardiac involvement as the number of episodes increases. In contrast, patients with carditis during the initial episode are very likely to have carditis with recurrences, and the risk for permanent heart damage increases with each recurrence. Patients who have had acute RF are susceptible to recurrent attacks after reinfection of the upper respiratory tract with GAS, with approximately 50% risk with each GAS pharyngitis. Therefore these patients require long-term continuous chemoprophylaxis.

Table 229.4 Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis)

DRUG	DOSE	ROUTE
Penicillin G benzathine	600,000 IU for children weighing ≤60 lb and 1.2 million IU for children >60 lb, every 4 wk*	Intramuscular
or		
Penicillin V	250 mg, twice daily	Oral
or		
Sulfadiazine or sulfisoxazole	500 mg once daily for patients weighing ≤60 lb	Oral
	1000 mg once daily for patients weighing >60 lb	
FOR PEOPLE WHO ARE ALLERGIC TO PENICILLIN AND SULFONAMIDE DRUGS		
Macrolide or azalide	Variable	Oral

*In high-risk situations, administration every 3 wk is recommended.
Adapted from Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young. *Circulation*. 2009;119:1541–1551.

Before antibiotic prophylaxis was available, 75% of patients who had an initial episode of acute RF had one or more recurrences in their lifetime. These recurrences were a major source of morbidity and mortality. The risk of recurrence is highest in the first 5 years after the initial episode and decreases with time.

Approximately 20% of patients who present with isolated chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 years. Therefore patients with chorea, even in the absence of other manifestations of RF, require long-term antibiotic prophylaxis (Table 229.4).

PREVENTION

Prevention of both initial and recurrent episodes of acute RF depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks **(primary prevention)** depends on identification and eradication of GAS causing acute pharyngitis. A New Zealand study in a population with very high rates of acute RF showed that a school-based GAS pharyngitis screening and management program using oral amoxicillin substantially decreased pharyngeal GAS prevalence and rates of acute RF. Individuals who have already suffered an attack of acute RF are particularly susceptible to recurrences of RF with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore these patients should receive continuous antibiotic prophylaxis to prevent recurrences **(secondary prevention)**.

Primary Prevention

Appropriate antibiotic therapy instituted before the ninth day of symptoms of acute GAS pharyngitis is highly effective in preventing the first attacks of acute RF. However, approximately 30% of patients with acute RF do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention

Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent acute RF. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute RF has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute RF are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life (see Table 229.4 and Table 229.5).

Patients who did not have carditis with their initial episode of acute RF have a relatively low risk for carditis with recurrences. Antibiotic prophylaxis should continue in these patients until the patient reaches 21 years of age or until 5 years have elapsed since the last RF attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

Table 229.5 Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: AHA Recommendations

CATEGORY	DURATION
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis

*Clinical or echocardiographic evidence.
Adapted from Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association (AHA) Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young. *Circulation*. 2009;119:1541–1551.

The regimen of choice for secondary prevention is a single IM injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for those >60 lb) every 4 weeks (see Table 229.4). In certain high-risk patients and in certain areas of the world where the incidence of RF is particularly high, use of benzathine penicillin G every 3 weeks may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 weeks. In the United States, administration of benzathine penicillin G every 3 weeks is recommended only for those who have recurrent acute RF despite adherence to a 4-week regimen. In compliant patients, continuous oral antimicrobial prophylaxis can be used. Penicillin V (250 mg twice daily) and sulfadiazine or sulfisoxazole (500 mg for those weighing ≤60 lb or 1,000 mg for those >60 lb, once daily) are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) may be used. Table 229.5 notes the duration of secondary prophylaxis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 230

Group B *Streptococcus*

Thomas A. Hooven

Group B *Streptococcus* **(GBS)**, or *Streptococcus agalactiae,* is a major cause of **neonatal bacterial sepsis** worldwide. Although advances in prevention strategies have led to a decline in the incidence of neonatal disease, GBS remains a dangerous pathogen for neonates, pregnant women, and nonpregnant adults.

ETIOLOGY

Group B streptococci are facultative, anaerobic, gram-positive cocci that form chains or diplococci in broth and small, gray-white or orange-tinged colonies on solid medium. GBS is definitively identified by demonstration of the Lancefield group B carbohydrate antigen, such as with latex agglutination techniques widely used in clinical laboratories. Presumptive identification can be established on the basis of a narrow zone of β-hemolysis on blood agar, resistance to bacitracin and trimethoprim-sulfamethoxazole (TMP-SMX), lack of hydrolysis of bile esculin, and elaboration of CAMP factor (named for the discoverers, Christie, Atkins, and Munch-Petersen), an extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus,* produces a zone of enhanced hemolysis on sheep blood agar. Individual GBS strains are serologically classified according to the presence of one of the structurally distinct capsular polysaccharides, which are important virulence factors and stimulators of antibody-associated immunity. Ten GBS capsular types have been identified: types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.

EPIDEMIOLOGY

GBS emerged as a prominent neonatal pathogen in the late 1960s. For the next 2 decades, the incidence of neonatal GBS disease remained fairly constant, affecting 1.0-5.4 per 1,000 liveborn infants in the United States. Two patterns of disease were seen: **early-onset disease**, which presents at <7 days of age, and **late-onset disease**, which presents at ≥7 days of age. Since the early 1990s, widespread implementation of **maternal intrapartum antibiotic prophylaxis** has led to a striking decrease in the incidence of early-onset neonatal GBS disease in the United States, from 1.7 to 0.19 per 1,000 live births in recent years. This strategy has *not* had a significant effect on the incidence of late-onset disease, which has remained stable at approximately 0.3-0.4 per 1,000 live births (Fig. 230.1). The incidence of neonatal GBS disease is higher in premature and low birthweight infants, although most cases occur in full-term infants. Rates of both early- and late-onset disease are higher in Black infants.

Colonization by GBS in healthy adults is common. Vaginal or rectal colonization occurs in up to approximately 30% of pregnant women and is the usual source for GBS transmission to newborn infants. In the absence of maternal antibiotic prophylaxis, approximately 50% of infants born to colonized women acquire GBS colonization, and 1–2% of infants born to colonized mothers develop early-onset disease. Heavy maternal colonization increases the risk for infant colonization and development of early-onset disease. Additional risk factors for early-onset disease include prolonged rupture of membranes, intrapartum fever, prematurity, maternal bacteriuria during pregnancy, and previous delivery of an infant who developed GBS disease. Risk factors for late-onset disease are less well defined. Whereas late-onset disease may follow vertical transmission, horizontal acquisition from nursery or other community sources (such as family, healthcare providers, or environmental exposure) has also been described.

GBS is also an important cause of invasive disease in adults. GBS may cause urinary tract infections, bacteremia, endometritis, chorioamnionitis, and wound infection in pregnant and parturient women. In nonpregnant adults, especially those with underlying medical conditions such as diabetes mellitus, cirrhosis, or malignancy, GBS may cause serious infections such as bacteremia, skin and soft tissue infections, bone and joint infections, endocarditis, pneumonia, and meningitis. In the era of maternal chemoprophylaxis, most invasive GBS infections occur in nonpregnant adults. Unlike neonatal disease, the incidence of invasive GBS disease in adults has increased substantially, roughly tripling between 1990 and 2016.

The serotypes most frequently associated with neonatal GBS disease are types Ia, III, and V. Strains of serotype III are the most common subtype isolated from colonized pregnant women and are also the most frequent cause of invasive disease among newborns and adults. Global epidemiologic studies have revealed regional variation in subtype prevalence, some of which may reflect local dietary and healthcare practices.

PATHOGENESIS

A major risk factor for the development of early-onset neonatal GBS infection is maternal vaginal or rectal colonization by GBS. Infants acquire GBS by ascending infection or during passage through the birth canal. Fetal aspiration of infected amniotic fluid may occur. The incidence of early-onset GBS infection increases with the duration of rupture of membranes. Infection may also occur through transcellular passage across intact membranes. In cases of late-onset infection, GBS may be vertically transmitted or acquired later from maternal or nonmaternal sources.

Several bacterial factors are implicated in the pathogenesis of invasive GBS disease, primarily the type-specific **capsular polysaccharide**. Strains that are associated with invasive disease in humans elaborate more capsular polysaccharide than do colonizing isolates. All GBS capsular polysaccharides are high molecular weight polymers composed of repeating oligosaccharide subunits that include a short side chain terminating in *N*-acetylneuraminic acid **(sialic acid)**. Studies of type III GBS show that the sialic acid component of the capsular polysaccharide prevents activation of the alternative complement pathway in the absence of type-specific antibody. Sialylated capsular polysaccharide on the GBS surface also interacts with sialic acid–binding lectins or siglecs on human leukocytes to dampen inflammatory gene activation. Thus the capsular polysaccharide appears to exert a virulence effect by protecting the organism from opsonophagocytosis in the nonimmune host and by downregulating leukocyte activation. In addition, type-specific virulence attributes are suggested by the fact that type III strains are implicated in most cases of late-onset neonatal GBS disease and meningitis. Type III strains are taken up by brain endothelial cells

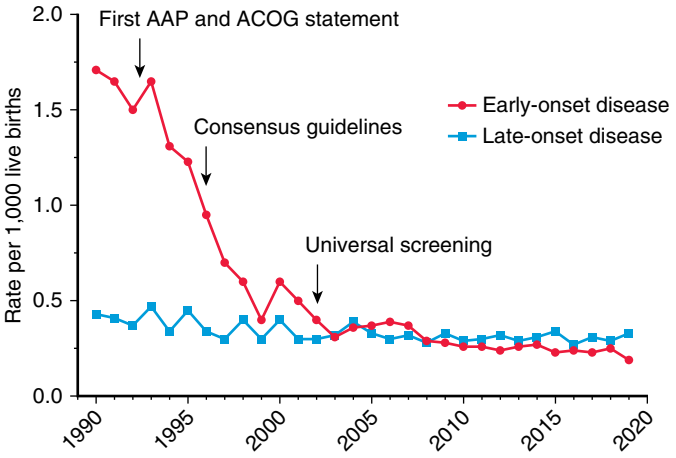

Fig. 230.1 Incidence of early- and late-onset invasive group B streptococcal (GBS) disease–active bacterial core surveillance areas, 1990-2019, and activities for prevention of GBS disease. AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists. *(Adapted from Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. Pediatr Infect Dis J. 2008;27:1057–1064.)*

more efficiently in vitro than are strains of other serotypes, although studies using acapsular mutant strains demonstrate that the capsule by itself does not facilitate cellular invasion. A single clade of type III GBS is highly associated with late-onset disease and meningitis. This clonal group, ST-17, produces a surface-anchored protein called *hypervirulent GBS adhesin* **(HvgA)** that is not present in other GBS isolates. HvgA contributes to GBS adherence to intestinal and endothelial cells and mediates invasion into the central nervous system (CNS) in an experimental infection model in mice. Other putative GBS virulence factors include GBS surface proteins, which may play a role in adhesion to host cells; C5a peptidase, which is postulated to inhibit the recruitment of polymorphonuclear cells to sites of infection; β-hemolysin/cytolysin, which has been associated with cell injury in vitro; and hyaluronidase, which has been postulated to act as a spreading factor in host tissues.

In a classic study of pregnant women colonized with type III GBS, those who gave birth to healthy infants had higher levels of capsular polysaccharide-specific antibody than those who gave birth to infants who developed invasive disease. In addition, there is a high correlation between antibody titer to GBS type III in the mother and titer in the paired infants. These observations indicate that transplacental transfer of maternal antibody is critically involved in neonatal immunity to GBS. Optimal immunity to GBS also requires an intact complement system. The classical complement pathway is an important component of GBS immunity in the absence of specific antibody; in addition, antibody-mediated opsonophagocytosis may proceed by the alternative complement pathway. These and other results indicate that anticapsular antibody can overcome the prevention of C3 deposition on the bacterial surface by the sialic acid component of the type III capsule.

The precise steps between GBS colonization and invasive disease remain unclear. In vitro studies showing GBS entry into alveolar epithelial cells and pulmonary vasculature endothelial cells suggest that GBS may gain access to the bloodstream by invasion from the alveolar space, perhaps after intrapartum aspiration of infected amniotic fluid. β-hemolysin/cytolysin may facilitate GBS entry into the bloodstream after inoculation into the lungs. Other studies have demonstrated intestinal GBS colonization preceding invasive disease among newborns, suggesting translocation across the intestinal wall as a pathogenic mechanism.

GBS induces the release of proinflammatory cytokines. The group B antigen and the peptidoglycan component of the GBS cell wall are potent inducers of tumor necrosis factor-α release in vitro, whereas purified type III capsular polysaccharide is not. Even though the capsule plays a central role in virulence through avoidance of immune clearance, the capsule does not directly contribute to cytokine release and the resultant inflammatory response.

The complete genome sequences of hundreds of GBS strains have been reported, facilitating a genomic approach to better understanding GBS. Analysis of these sequences shows that GBS is closely related to *Streptococcus pyogenes* and *Streptococcus pneumoniae.* Many known and putative GBS virulence genes are clustered in the genome in pathogenicity islands that also contain mobile genetic elements, suggesting that interspecies acquisition of genetic material plays an important role in genetic diversity.

CLINICAL MANIFESTATIONS

Two syndromes of neonatal GBS disease are distinguishable on the basis of age at presentation, epidemiologic characteristics, and clinical features (Table 230.1). **Early-onset neonatal GBS disease** presents within the first 6 days of life and is often associated with maternal obstetric complications, including chorioamnionitis, prolonged rupture of membranes, and premature labor. Infants may appear ill at the time of delivery, and most infants become ill within 24 hours of birth. In utero infection may result in septic abortion or immediate distress after birth. More than 80% of early-onset GBS disease presents as sepsis; pneumonia and meningitis are other common manifestations. Asymptomatic bacteremia is uncommon but can occur. In symptomatic patients, nonspecific signs such as hypothermia or fever, irritability, lethargy, apnea, and bradycardia may be present. Respiratory signs are prominent regardless of the presence of pneumonia and include cyanosis, apnea, tachypnea, grunting, flaring, and retractions. A fulminant course with hemodynamic abnormalities, including tachycardia, acidosis, and shock, may ensue. Persistent fetal circulation may develop. Clinically and radiographically, pneumonia associated with early-onset GBS disease is difficult to distinguish from **respiratory distress syndrome**. Patients with meningitis often present with nonspecific findings as described for sepsis or pneumonia, with more specific signs of CNS involvement initially absent.

Late-onset neonatal GBS disease presents at ≥7 days of life. Most cases occur within the first 3 months of life, but later presentations are also possible. Like early-onset disease, late-onset illness usually manifests as bacteremia (45–65%), often accompanied by meningitis (25–35%). Focal infections involving bone and joints, skin and soft tissue, the urinary tract, or lungs may also be seen. Cellulitis and adenitis are often localized to the submandibular or parotid regions. In contrast to early-onset disease, maternal obstetric complications are not risk factors for the development of late-onset GBS disease. Infants with late-onset disease are often less severely ill on presentation than infants with early-onset disease, and the disease is often less fulminant.

Invasive GBS disease in children beyond early infancy is uncommon. Bacteremia without a focus is the most common syndrome associated with childhood GBS disease beyond early infancy. Focal infections may include meningitis, pneumonia, endocarditis, and bone and joint infections.

DIAGNOSIS

A major challenge is distinguishing between respiratory distress syndrome and invasive neonatal GBS infection in preterm infants because the two illnesses share clinical and radiographic features. Severe apnea, early onset of shock, abnormalities in the peripheral leukocyte count, and greater lung compliance may be more likely in infants with GBS disease. Other neonatal pathogens, including *Escherichia coli* and *Listeria monocytogenes,* may cause illness that is clinically indistinguishable from that caused by GBS.

Table 230.1 Characteristics of Early- and Late-Onset Group B *Streptococcus* Disease

	EARLY-ONSET DISEASE	LATE-ONSET DISEASE
Age at onset	0-6 days	7-90 days
Increased risk after obstetric complications	Yes	No
Common clinical manifestations	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, osteomyelitis, other focal infections
Common serotypes	Ia, III, V	Ia, III
Case fatality rate	4.5%	3.3%

Adapted from Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the burden of Group B streptococcal disease worldwide for pregnant women, stillbirths, and children. *Clin Infect Dis.* 2017;65(Suppl 2):S200–S219.

The diagnosis of invasive GBS disease is established by isolation and identification of the organism from a normally sterile site, such as blood, urine, or cerebrospinal fluid (CSF). Isolation of GBS from gastric or tracheal aspirates or from skin or mucous membranes indicates colonization and is not diagnostic of invasive disease. CSF should be examined in all neonates suspected of having sepsis because specific CNS signs are often absent in the presence of meningitis, especially in early-onset disease. Antigen detection methods that use group B polysaccharide–specific antiserum, such as latex particle agglutination, are available for testing of urine, blood, and CSF, but these tests are less sensitive than culture. Moreover, antigen is often detected in urine samples collected by bag from otherwise healthy neonates who are colonized with GBS on the perineum or in the rectum. Commercially available methods for polymerase chain reaction (PCR) amplification of GBS-specific DNA sequences from blood or CSF samples are increasingly available, allowing earlier presumptive diagnosis than traditional culture. When possible, PCR-based diagnosis should be verified with a sterilely obtained culture; however, in certain cases the PCR result may be more accurate than the culture. A common example is a PCR performed on CSF sampled from an infant who has already received empiric antibiotic therapy, in which case the culture may remain negative despite the persistence of PCR-detectable GBS DNA. Test results must therefore be interpreted in the context of a patient's specific clinical history.

LABORATORY FINDINGS

Frequently present are abnormalities in the peripheral white blood cell count, including an increased or decreased absolute neutrophil count, elevated band count, increased ratio of bands to total neutrophils, or leukopenia. An elevated C-reactive protein level has been investigated as a potential early marker, but this test is nonspecific and cannot be used in isolation to diagnose GBS disease. Findings on chest radiograph are often indistinguishable from those of respiratory distress syndrome and may include reticulogranular patterns, patchy infiltrates, generalized opacification, pleural effusions, or increased interstitial markings. GBS meningitis is diagnosed based on a positive microbiologic test (culture or PCR), usually in combination with elevated CSF protein levels, leukocytic infiltration, and hypoglycorrhachia (decreased CSF glucose concentration).

TREATMENT

Penicillin G is the treatment of choice for confirmed GBS infection. Empirical therapy of neonatal sepsis that could be caused by GBS generally includes ampicillin and an aminoglycoside, both for the need for broad coverage pending organism identification and for synergistic bactericidal activity. Once GBS has been definitively identified and a good clinical response has occurred, therapy may be completed with penicillin alone. Especially in patients with meningitis, high doses of penicillin (450,000-500,000 units/kg/day) or ampicillin (300 mg/kg/day) are recommended because of the relatively high mean inhibitory concentration (MIC) of penicillin for GBS and the potential for a high initial CSF inoculum. The duration of therapy varies according to the site of infection and should be guided by clinical circumstances (Table 230.2). Extremely ill near-term patients with respiratory failure have been successfully treated with extracorporeal membrane oxygenation.

Although some experts recommend that, in culture-proven meningitis, additional CSF be sampled at 24-48 hours to determine whether sterility has been achieved, there is no strong evidence to support this practice. A repeat lumbar puncture, preferably paired with intracranial imaging such as MRI or CT, may be considered in patients with persistent neurologic symptoms after initiation of appropriately dosed antibiotics. The purpose in such a case is to rule out the presence of an abscess or other focal nidus of infection that may be escaping effective antibiotic exposure.

For **recurrent neonatal GBS disease**, standard intravenous antibiotic therapy recommendations for the infant should be followed. GBS recurrence can be caused by contaminated breast milk. Therefore breastfed infants with more than one episode of GBS infection should receive formula or pasteurized breast milk until expressed breast milk can be cultured for the presence of GBS. If breast milk contamination is confirmed, the mother should be counseled to consider a 5- to 7-day course of amoxicillin or rifampin to eradicate GBS carriage, followed by retesting of the milk.

Table 230.2 Recommended Duration of Therapy for Manifestations of Group B *Streptococcus* Disease

TREATMENT	DURATION
Bacteremia without a focus	10 days
Uncomplicated meningitis	14 days
Ventriculitis	At least 4 wk
Septic arthritis or osteomyelitis	3-4 wk

Data from the American Academy of Pediatrics. Group B streptococcal infections. In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases*, 32nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2021:707–713.

PROGNOSIS

Studies from the 1970s and 1980s showed that up to 30% of infants surviving GBS meningitis had major long-term neurologic sequelae, including developmental delay, spastic quadriplegia, microcephaly, seizure disorder, cortical blindness, or deafness. A study of infants who survived GBS meningitis diagnosed from 1998 through 2006 found that 19% had severe **neurologic impairment** and 25% had mild to moderate impairment at long-term follow-up. Periventricular leukomalacia and severe developmental delay may result from GBS disease and accompanying shock in premature infants, even in the absence of meningitis. The outcome of focal GBS infections outside the CNS is generally favorable.

In 2015, a global survey on the impact of GBS disease found the case fatality rates associated with early- and late-onset neonatal GBS disease in developed countries were 4.5% and 3.3%, respectively. Case fatality rates were higher in developing countries. Mortality is higher in premature infants; one study reported a case fatality rate of 30% in infants at gestational age <33 weeks and 2% in those ≥37 weeks. The case fatality rate in children age 3 months to 14 years was 9% and was 11.5% in nonpregnant adults.

PREVENTION

Persistent morbidity and mortality from perinatal GBS disease despite advances in neonatal care have spurred intense investigation into modes of prevention. Two basic approaches to GBS prevention have been investigated: elimination of colonization from the mother or infant (chemoprophylaxis) and induction of protective immunity (immunoprophylaxis).

Chemoprophylaxis

Administration of antibiotics to pregnant women *before* the onset of labor does not reliably eradicate maternal GBS colonization and is not an effective means of preventing neonatal GBS disease. **Interruption of neonatal colonization is achievable through administration of antibiotics to the mother during labor.** Infants born to GBS-colonized women with premature labor or prolonged rupture of membranes who were given **intrapartum chemoprophylaxis** had a substantially lower rate of GBS colonization (9% vs 51%) and early-onset disease (0% vs 6%) than did the infants born to women who were not treated. Maternal postpartum febrile illness was also decreased in the treatment group.

In the mid-1990s, guidelines for chemoprophylaxis were issued that specified administration of intrapartum antibiotics to women identified as *high risk* by either culture-based or risk factor–based criteria. These guidelines were revised in 2002 after epidemiologic data indicated the superior protective effect of the **culture-based** approach in the prevention of neonatal GBS disease, and further revised guidelines

were issued in 2010 and 2020. According to current recommendations, **vaginorectal GBS screening cultures or PCR testing (where available) should be performed for all pregnant women at 36 0/7 to 37 6/7 weeks of gestation, except for those with GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease**. Any woman with a positive prenatal screening culture, GBS bacteriuria during pregnancy, or a previous infant with invasive GBS disease should receive intrapartum antibiotics. Women whose culture status is unknown (culture not done, incomplete, or results unknown) and present in labor with a substantial risk of preterm birth, prolonged rupture of membranes (≥18 hr), or intrapartum fever (≥38°C [100.4°F]) should also receive intrapartum chemoprophylaxis (Table 230.3). **Routine intrapartum prophylaxis is not recommended for women with GBS colonization undergoing planned cesarean delivery who have not begun labor or had rupture of membranes.**

Penicillin remains the preferred agent for **maternal chemoprophylaxis** because of its narrow spectrum and the universal penicillin susceptibility of GBS isolates associated with human infection (Fig. 230.2). Ampicillin is an acceptable alternative. If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis. Occasional GBS isolates have demonstrated increased MICs to penicillin and other β-lactam antibiotics in association with mutations in penicillin-binding proteins. However, the clinical significance of these higher MIC values is unclear.

Table 230.3 Summary and References for GBS Prevention/Treatment Guidelines

AT-RISK POPULATION	KEY PREVENTION/ TREATMENT PRACTICES	PRACTICE GUIDELINE GOVERNING BODY
Women with history of a previous neonate with invasive GBS disease	Administer IAP during labor*	ACOG
Women with GBS bacteriuria during current pregnancy	Administer IAP during labor*	ACOG
Women with uncomplicated pregnancy	Perform prospective GBS colonization screening at 36 0/7 to 37 6/7 weeks of gestation	ACOG
	Administer IAP to colonized women during labor*	
	Women who present in term labor with unknown GBS status may qualify for IAP depending on additional clinical details	
Mothers with PROM, preterm labor, preterm intraamniotic infection, and unknown GBS colonization status	Administer IAP	ACOG
Term or late preterm (>34 wk) newborns with risk factors for GBS infection	For persistent clinical symptoms consistent with sepsis, obtain a blood culture and start empiric antibiotics with anti-GBS activity	AAP *Redbook* AAP *Pediatrics*
	In the absence of clinical symptoms, three possible approaches are available: 1. Categorical risk-based management 2. Use of an online Bayesian sepsis risk calculator to guide management 3. Serial observation of the infant	
Preterm newborns ≤34 wk with risk factors for GBS	For persistent clinical symptoms consistent with sepsis, obtain a blood culture and start empiric antibiotics with anti-GBS activity	AAP *Redbook* AAP *Pediatrics*
	If delivery followed spontaneous preterm labor, PROM, or concern for intraamniotic infection, obtain a blood culture and administer empiric antibiotics	
	If delivery followed induction of labor and there was concern for intraamniotic infection or if IAP was indicated but not provided, obtain a blood culture and administer empiric antibiotics	
Infants with signs of late-onset GBS disease	For empiric therapy of late-onset GBS disease in those who are not critically ill and in whom meningitis is not suspected, initial empiric therapy with ampicillin plus either gentamicin or cefotaxime is appropriate. If meningitis is suspected, ampicillin plus cefotaxime is recommended	AAP *Redbook*

*Infants born by cesarean section for maternal indications with no preceding labor or ROM: postnatal management should be guided by the newborn's clinical status and subsequent risk of GBS exposure.

AAP, American Academy of Pediatrics; ACOG, American College of Obstetrics and Gynecology; IAP, Intrapartum antibiotic prophylaxis; PROM, Preterm rupture of membranes

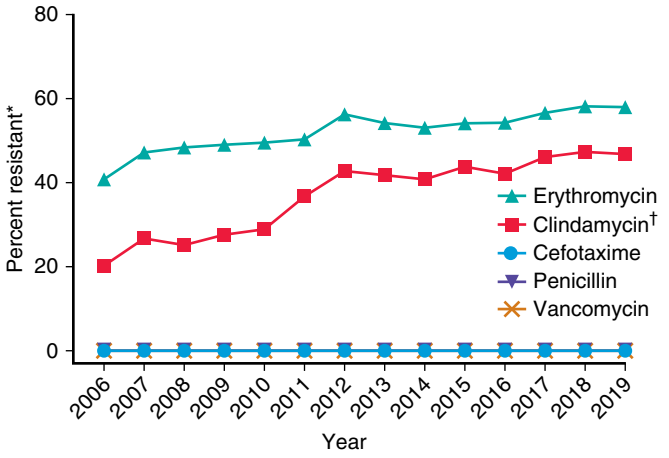

Fig. 230.2 GBS antibiotic resistance rates measured through Centers for Disease Control and Prevention active bacterial core surveillance, 2006-2019. *Resistant includes those isolates intermediate or fully resistant to antibiotics tested. †Before 2011, only constitutive resistance to clindamycin was tested. In 2011 and beyond, both constitutive and inducible resistance to clindamycin were tested. *(Courtesy Centers for Disease Control and Prevention.)*

For women who report a penicillin allergy but who have not undergone formal sensitivity testing, the American College of Obstetrics and Gynecology recommends allergy skin testing, which can be performed safely during pregnancy. Because of frequent resistance of GBS to clindamycin (up to 46%), first-generation cephalosporins (such as cefazolin) should be used for intrapartum chemoprophylaxis for penicillin-intolerant women with a low risk of anaphylaxis. For penicillin-allergic women at high risk for anaphylaxis, clindamycin should be used only if isolates are demonstrated to be susceptible. Vancomycin should be used if isolates are resistant to, or demonstrate inducible resistance to, clindamycin or if clindamycin susceptibility is unknown.

In 2019, the American Academy of Pediatrics (AAP) published updated guidelines with recommendations for prevention of early-onset GBS disease in newborns with risk factors (see Table 230.3). These replaced earlier prevention guidelines released by the AAP and Centers for Disease Control and Prevention. A key point of these revised recommendations is that **newborns with risk factors for GBS disease (such as inadequately treated maternal colonization or preterm delivery) who have persistent signs of infection after birth (beyond those attributable to transitional physiology) should undergo a laboratory evaluation that includes a blood culture and should receive empiric antibiotic therapy until infection has been ruled out**. For asymptomatic or minimally symptomatic infants born after 35 0/7 weeks of gestation, the extent of newborn evaluation and the decision to institute empiric antibiotics may be guided by one of **three systems for risk assessment**: a categorical decision chart based on the presence or absence of specific risk factors, repeated clinical evaluations, or a validated online "sepsis calculator" tool, developed from large datasets, which can estimate a newborn's risk of early-onset disease based on historical factors and clinical presentation. **For infants born before 35 0/7 weeks of gestation, the AAP recommends a blood culture and empiric antibiotics in all cases where spontaneous preterm labor, preterm rupture of the membranes, or any concern of intraamniotic infection preceded birth. Empiric treatment is also recommended in any case of a vaginal delivery before 35 0/7 weeks in which maternal chemoprophylaxis was indicated but not administered** (see Table 230.3).

Increasingly, there is recognition that decisions about whether to start empiric antibiotics for well-appearing infants with sepsis risk factors must also take into consideration the local resources available for systematic, serial examination. In medical environments where well-trained staff are available for careful, repeated observations of the newborn for 36-48 hours after birth, the threshold for initiating empiric antibiotics may be higher than sites where serial examinations are not possible. Of note, in the era of maternal chemoprophylaxis, most cases of early-onset disease are seen in infants born to women with negative prenatal screening cultures. Data from a large epidemiologic study indicate that the administration of maternal intrapartum antibiotics does not change the clinical spectrum or delay the onset of clinical signs in infants who developed GBS disease despite maternal prophylaxis.

A significant concern with maternal intrapartum chemoprophylaxis has been that large-scale antibiotic use among parturient women might lead to increased rates of antimicrobial resistance or infection in infants with organisms other than GBS, but this has not been borne out. In a population-based study of early-onset neonatal infection from 2005 to 2014, the incidence of early-onset sepsis both overall and caused by *E. coli* remained stable. At present, the substantial decline in early-onset neonatal GBS disease favors continued broad-scale intrapartum chemoprophylaxis, but continued surveillance is required.

A limitation of the maternal chemoprophylaxis strategy is that intrapartum antibiotic use is unlikely to have an impact on late-onset neonatal disease, miscarriages, or stillbirths attributed to GBS or adult GBS disease. In addition, with wider implementation of maternal chemoprophylaxis, an increasing percentage of early-onset neonatal disease has been detected in patients born to women with negative cultures, that is, false-negative screens.

Maternal Immunization

Human studies demonstrate that transplacental transfer of naturally acquired maternal antibody to the GBS capsular polysaccharide protects newborns from invasive GBS infection and that efficient transplacental passage of vaccine-induced GBS antibodies occurs. Conjugate vaccines composed of the GBS capsular polysaccharides coupled to carrier proteins have been produced for human use. In early clinical trials, conjugate GBS vaccines were well tolerated and induced levels of functional antibodies well above the range believed to be protective in >90% of recipients. A trivalent vaccine containing three subtypes of GBS capsule polysaccharide coupled to CRM_{197} was safely administered to pregnant women in a phase 2 clinical trial, eliciting functionally active type-specific antibodies that were efficiently transported to the fetus remaining detectable in the newborn. A more recent hexavalent vaccine candidate led to protective antibodies against six GBS capsular subtypes in experimental animal pregnancy models and generated robust antibody elaboration in nonpregnant adults in a phase 1/2 trial. Vaccines containing GBS surface proteins have been considered as a means to provide serotype-independent GBS protection, and availability of whole genome sequencing has enabled identification of vaccine protein candidates.

A successful GBS maternal vaccine administered before or during pregnancy should lead to transplacental passage of vaccine-induced antibody that protects the fetus and newborn against infection by several GBS serotypes. Such a vaccine would eliminate the need for cumbersome cultures during pregnancy, circumvent the various risks associated with large-scale antibiotic prophylaxis, likely have an impact on both early- and late-onset disease, and provide a prevention strategy in middle- and low-income countries, where maternal chemoprophylaxis may not be feasible. Intrapartum chemoprophylaxis will likely remain an important aspect of prevention, particularly for women in whom opportunities for GBS immunization are missed and for infants born so early that levels of transplacentally acquired antibodies may not be high enough to be protective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 231

Non–Group A or B *Streptococci*

David B. Haslam

The genus *Streptococcus* is exceptionally diverse and includes the major human pathogens *Streptococcus pyogenes* (group A *Streptococcus Streptococcus agalactiae* (group B *Streptococcus*), and *Streptococcus pneumoniae* (Table 231.1). Other important pathogens include large-colony species bearing groups C and G Lancefield antigens and numerous small-colony variants that may or may not express Lancefield carbohydrate antigen included among the viridans streptococci (see Table 231.1). This chapter focuses on *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE), commonly known as "group C and G streptococci," while Chapter 228 discusses *S. pneumoniae* and Chapter 232 discusses enterococci.

All members of the genus *Streptococcus* are gram-positive, catalase-negative organisms. Lancefield carbohydrate antigen, hemolytic activity, and colony morphology have classically been used to further distinguish and classify streptococci. These features provide a useful framework for the clinician and are still the most commonly used classification schema. However, grouping based on these phenotypic features does not precisely correlate with genetic relatedness, and it is becoming clear that disease propensity is better correlated with sequence homology than Lancefield grouping or hemolytic activity.

In this chapter, groups C and G streptococci refer exclusively to the large colony-forming organisms, often called *S. pyogenes–like,* as their microbiologic and clinical features tend to mimic those of group A *Streptococcus*. Despite their different Lancefield antigens, the large-colony-forming C and G streptococci are grouped together as SDSE. The remaining large-colony group C streptococci, predominantly animal pathogens, are grouped as *S. dysgalactiae* subspecies *dysgalactiae*. Nonhuman group G isolates are often considered part of a single species designated *Streptococcus canis* and are genetically distinct from the SDSE group G organisms.

The groups C and G streptococci share a number of virulence factors with *S. pyogenes,* including the production of streptolysin O, M protein, streptococcal pyrogenic exotoxin B, and hyaluronidase. The M protein is similar to that of *S. pyogenes* and may account for the postinfectious glomerulonephritis that is occasionally seen after infection with these organisms. A toxic shock–like syndrome associated with groups C and G streptococcal infection has been related to M protein type and production of a pyrogenic exotoxin by SDSE.

SDSE are common habitants of the pharynx, being detected in up to 5% of asymptomatic children. Other potential sites of colonization include the skin and gastrointestinal tract. Colonization of the vagina is reported and may be the source of occasional SDSE isolated from the umbilicus of healthy neonates.

Clinical manifestations of disease caused by SDSE overlap those of *S. pyogenes*. In children, these organisms are implicated most commonly in pharyngitis. The true role of these organisms as a cause of pharyngitis is difficult to determine because asymptomatic colonization is common. Nevertheless, several epidemics of SDSE pharyngitis have been reported, including foodborne outbreaks. A large study from Sweden recently demonstrated similar rates of detection of *S. pyogenes* (15%) and SDSE (14%) in children with pharyngitis. *S. pyogenes* was most prevalent in young children, whereas SDSE predominated in older children and adolescents. The clinical presentation of SDSE is indistinguishable from *S. pyogenes*–associated pharyngitis. Isolated case reports have described SDSE pneumonia in children, which is commonly complicated by abscess formation, empyema, and bacteremia. Additional respiratory infections include rare reports of epiglottitis and sinusitis.

SDSE are a significant cause of skin and soft tissue infections. As with *S. pyogenes,* lymphangitis can complicate superficial infections caused by SDSE. Necrotizing fasciitis caused by SDSE is being described with increasing frequency. Musculoskeletal infections, particularly pyogenic arthritis, occasionally are caused by SDSE. Pediatric cases are uncommon but may be increasing in incidence.

Table 231.1 Relationship of Large-Colony Streptococci Identified by Hemolysis and Lancefield Grouping to Sites of Colonization and Disease

	GROUP A *STREPTOCOCCUS* (*S. pyogenes*)	GROUP B *STREPTOCOCCUS* (*S. agalactiae*)	OTHER β-HEMOLYTIC *STREPTOCOCCI*	*VIRIDANS STREPTOCOCCI*
Hemolysis	β	β	β	α
Lancefield group	A	B	C-H, K-V Especially C and G	
Species or strains	M types (>180)	Serotypes (Ia, Ib, II, III, IV, V, VI, VII, and VIII)	*S. dysgalactiae* subspecies *equisimilis* *S. dysgalactiae* subspecies *dysgalactiae* *S. canis*	*Streptococcus bovis* *Streptococcus mitis* *Streptococcus mutans* *Streptococcus sanguis* Many others
Normal flora	Pharynx, skin, anus	Gastrointestinal and genitourinary tract	Pharynx, skin, gastrointestinal and genitourinary tracts	Pharynx, nose, skin, genitourinary tract
Common human diseases	Pharyngitis, tonsillitis, erysipelas, impetigo, septicemia, wound infections, necrotizing fasciitis, cellulitis, meningitis, pneumonia, scarlet fever, toxic shock–like syndrome, rheumatic fever, acute glomerulonephritis	Puerperal sepsis, chorioamnionitis, endocarditis, neonatal sepsis, meningitis, osteomyelitis, pneumonia	Wound infections, cellulitis, necrotizing fasciitis, pneumonia, endocarditis, brain abscess, sepsis, nosocomial infections, opportunistic infections	Endocarditis, human bite infections

α, Partial hemolysis; β, complete hemolysis; γ, no hemolysis (nonhemolytic).

Reactive arthritis has been described after SDSE infection; however, unlike *S. pyogenes,* the association between SDSE infection and acute rheumatic fever has not clearly been defined, and antibiotic prophylaxis is not recommended after reactive arthritis with this organism.

Endocarditis, bacteremia, brain abscess, and toxic shock syndrome caused by SDSE have all been described but are uncommon in children. These infections generally occur in children with immune deficits or in adolescents after delayed recognition of sinusitis.

These organisms can cause neonatal septicemia similar to early-onset group B streptococcal disease. Risk factors include prematurity and prolonged rupture of membranes. Respiratory distress, hypotension, apnea, bradycardia, and disseminated intravascular coagulation may be seen, and associated maternal infection is common. Neonatal toxic shock syndrome associated with SDSE has also been described.

Treatment of SDSE infections is similar to that of *S. pyogenes.* These organisms retain susceptibility to penicillin and other β-lactams. Other agents with reliable activity include linezolid, daptomycin, and vancomycin, though occasional isolates demonstrate tolerance to vancomycin. Clindamycin and macrolides have poor bactericidal activity against these organisms, and resistance rates are significant. Resistance to quinolones is reported, and up to 70% of SDSE are resistant to tetracycline.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 232

Enterococcus

David B. Haslam

Enterococcus has long been recognized as a pathogen in select populations and has become a common and particularly troublesome cause of hospital-acquired infection in recent years. Enterococci were formerly classified with *Streptococcus bovis* and *Streptococcus equinus* as Lancefield group D streptococci but are now placed in a separate genus and are notorious for their propensity to cause infection in compromised hosts and frequent resistance to antibiotics.

ETIOLOGY

Enterococci are gram-positive, catalase-negative facultative anaerobes that grow in pairs or short chains. Most are nonhemolytic (also called γ-hemolytic) on sheep blood agar, although some isolates have α- or β-hemolytic activity. Enterococci are distinguished from most Lancefield groupable streptococci by their ability to grow in bile and hydrolyze esculin. They are able to grow in 6.5% NaCl and hydrolyze L-pyrrolidonyl-β-naphthylamide, features used by clinical laboratories to distinguish enterococci from group D streptococcus. Identification at the species level is enabled by differing patterns of carbohydrate fermentation.

EPIDEMIOLOGY

Enterococci are normal inhabitants of the gastrointestinal tract of humans and organisms throughout the animal kingdom, suggesting they are highly evolved to occupy this niche. Oral secretions and dental plaque, the upper respiratory tract, skin, and vagina may also be colonized by these organisms. *Enterococcus faecalis* is the predominant enterococcal species, with colonization commonly occurring in the first week of life. By the time of adulthood, *E. faecalis* colonization is nearly ubiquitous. *Enterococcus faecium* colonization is less consistent, although approximately 25% of adults harbor this organism. Disruption of the normal intestinal microbiota by antibiotic exposure or hematopoietic stem cell transplantation markedly enriches for fecal enterococcal abundance and dramatically increases the risk of subsequent bloodstream infection (BSI).

E. faecalis accounts for approximately 80% of enterococcal infections, with almost all of the remaining infections caused by *E. faecium.* Only rarely are other species, such as *Enterococcus gallinarum* and *Enterococcus casseliflavus,* associated with invasive infection, but these organisms are notable for their intrinsic low-level vancomycin resistance. Whole genome sequencing suggests that the patient's indigenous flora is the source of enterococcal infection in most cases. However, direct spread from person to person or from contaminated medical devices may occur, particularly within newborn nurseries and intensive care units, where nosocomial spread has resulted in hospital outbreaks.

PATHOGENESIS

Enterococci are not aggressively invasive organisms, usually causing disease only in children with damaged mucosal surfaces or an impaired immune system. Their dramatic emergence as a cause of nosocomial infection is predominantly a result of their resistance to antibiotics commonly used in the hospital setting. Hospital-associated enterococci generally lack CRISPR (clustered regularly interspaced short palindromic repeats) elements that defend against phage-mediated horizontal gene transfer, an important source of antimicrobial-resistance genes. Secreted and cell-surface molecules are implicated in pathogenesis. Adhesion-promoting factors such as the surface protein Eps likely account for the propensity of these organisms to cause endocarditis and urinary tract infections (UTIs). The ability to form biofilms likely facilitates the colonization of urinary and vascular catheters. Other proposed virulence factors include cytolysin, aggregation substance, gelatinase, and extracellular superoxide.

Antimicrobial Resistance

Enterococci are highly resistant to cephalosporins and semisynthetic penicillins such as nafcillin, oxacillin, and methicillin. They are moderately resistant to extended-spectrum penicillins such as ticarcillin and carbenicillin. Ampicillin and penicillin are the most active β-lactams against these organisms. Some strains of *E. faecalis* and *E. faecium* demonstrate decreased resistance to β-lactam antibiotics because of mutations in one of the penicillin-binding proteins. In addition, occasional strains of *E. faecalis* produce a plasmid-encoded β-lactamase similar to that found in *Staphylococcus aureus.* These isolates are completely resistant to penicillins, necessitating the combination of a penicillin plus a β-lactamase inhibitor or the use of imipenem or vancomycin. Any active drug may be insufficient if used alone for serious infections wherein high bactericidal activity is desired (Tables 232.1 and 232.2).

All enterococci have intrinsic low-level resistance to aminoglycosides because these antibiotics are poorly transported across the *Enterococcus* cell wall. Concomitant use of a cell wall–active agent, such as a β-lactam or glycopeptide antibiotic, improves the permeability of the cell wall for the aminoglycosides, resulting in synergistic killing. However, some isolates demonstrate high-level resistance, defined as mean inhibitory concentration (MIC) >2,000 μg/mL and a result of modification or inactivation of aminoglycoside agents. Strains demonstrating high-level resistance and even some isolates with moderate-level resistance are not affected synergistically by aminoglycosides and cell wall–active antibiotics.

Table 232.1 Intrinsic Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin	Altered binding protein
Aminoglycoside (low level)	Decreased permeability, altered ribosomal binding
Clindamycin	Altered ribosomal binding
Erythromycin	Altered ribosomal binding
Tetracyclines	Efflux pump
Trimethoprim-sulfamethoxazole	Utilize exogenous folate

Table 232.2 Acquired Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin (high level)	Mutation of PBP5
Aminoglycoside (high level)	Enzyme modification
Quinolones	DNA gyrase mutation
Chloramphenicol	Efflux pump
Glycopeptide	Altered cell wall binding
Quinupristin/dalfopristin	Ribosomal modification, efflux pump
Linezolid	Point mutation
Daptomycin	Unknown

Resistance to almost all other antibiotic classes, including tetracyclines, macrolides, and glycopeptides, has been described among the enterococci, necessitating individual susceptibility testing for these antibiotics when their use is considered. Despite apparent susceptibility in vitro, trimethoprim-sulfamethoxazole has poor activity in vivo and should not be used as the primary agent against enterococcal infections.

Vancomycin has traditionally been effective against *Enterococcus* isolates, but resistance to vancomycin, defined as MIC >32 μg/mL, and other glycopeptides, including teicoplanin, is increasingly common. The emergence of vancomycin-resistant *Enterococcus* (VRE) has become a major challenge in the care of hospitalized patients. In particular, mortality in patients with VRE BSIs is considerable, and treatment is complicated by frequent resistance of VRE to most other antibiotic classes. High-level vancomycin resistance (MIC ≥64 μg/mL) can be transferred by way of conjugation and usually results from plasmid-mediated transfer of the *vanA* gene. High-level resistance is most common among *E. faecium* but is increasingly seen among *E. faecalis* isolates. Moderate-level resistance (MIC 8-256 μg/mL) results from a chromosomal homolog of *vanA* known as *vanB.* Isolates that harbor the *vanB* gene are only moderately resistant to vancomycin and initially demonstrate susceptibility to teicoplanin, although resistance can emerge during therapy. Resistance to newer agents, including linezolid and daptomycin, is rare thus far. Linezolid resistance is a result of mutations in the 26S ribosomal subunit, whereas daptomycin resistance is associated with pathogenic variants in genes required for membrane synthesis and repair.

CLINICAL MANIFESTATIONS

Enterococcus infections traditionally occurred predominantly in newborn infants; infection in older children is increasingly common. Most enterococcal infections occur in patients with breakdown of normal physical barriers such as the gastrointestinal tract, skin, or urinary tract. Other risk factors for enterococcal infection include prolonged hospitalization, indwelling vascular catheters, prior use of antibiotics, and compromised immunity.

Neonatal Infections

Enterococcus accounts for up to 15% of all neonatal bacteremia and septicemia. Like group B streptococcus infections, enterococcal infections are seen in two distinct settings in neonatal patients. Early-onset infection (<7 days of age) may mimic early-onset group B streptococcus septicemia but tends to be milder. Early-onset enterococcal sepsis most often occurs in full-term infants who are otherwise healthy. Late-onset infection (≥7 days of age) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, or necrotizing enterocolitis or follows an intraabdominal surgical procedure. Symptoms in late-onset disease are more severe than those in early-onset disease and include apnea, bradycardia, and deteriorating respiratory function. Focal infections such as scalp abscess and catheter infection are commonly associated. Mortality rates range from 6% in early-onset septicemia to 15% in late-onset infections associated with necrotizing enterocolitis.

Enterococci are an occasional cause of meningitis. In neonates in particular, meningitis usually occurs as a complication of septicemia. Alternatively, the organism may gain access to the central nervous system by way of contiguous spread, such as through a neural tube defect or in association with an intraventricular shunt. Enterococcal meningitis can be associated with minimal abnormality of cerebrospinal fluid.

Infections in Older Children

Enterococcus rarely causes UTIs in healthy children but accounts for approximately 15% of cases of nosocomially acquired UTIs in both children and adults. Presence of an indwelling urinary catheter is the major risk factor for nosocomial UTIs. *Enterococcus* is frequently isolated in intraabdominal infections after intestinal perforation or surgery. The significance of enterococci in polymicrobial infections has been questioned, although reported mortality rates are higher when intraabdominal infections include enterococci. *Enterococcus* is increasingly common as a cause of nosocomial bacteremia; these organisms accounted for approximately 10% of nosocomial BSIs in children, ranking second only to coagulase-negative staphylococci. Predisposing factors for enterococcal bacteremia and endocarditis include an indwelling central venous catheter, gastrointestinal surgery, immunodeficiency, and cardiovascular abnormalities. Risk factors for vancomycin-resistant enterococcal bacteremia include prolonged mechanical ventilation, immunosuppression, and recent vancomycin exposure.

TREATMENT

Treatment of invasive enterococcal infections must recognize that these organisms are resistant to antimicrobial agents frequently used as empirical therapy. In particular, cephalosporins should not be relied upon in situations where *Enterococcus* is known or suspected to be involved. In general, in the immunocompetent host, minor localized infections caused by susceptible *Enterococcus* can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide advantage only for the very few organisms whose resistance is caused by the production of β-lactamase. In uncomplicated UTIs, nitrofurantoin is efficacious when the organism is known to be sensitive to this antibiotic.

Invasive infections such as sepsis and meningitis have traditionally been treated with a combination of penicillin or ampicillin and an aminoglycoside when the isolate is susceptible. Recent experience suggests that adjunctive aminoglycosides may increase the risk of nephrotoxicity without improving outcomes in uncomplicated BSIs. Vancomycin can be substituted for the penicillins in allergic patients but should be used with an aminoglycoside because vancomycin alone is not bactericidal. Endocarditis from strains possessing high-level aminoglycoside resistance may relapse even after prolonged therapy. Continuous-infusion penicillin or the combination of ampicillin plus ceftriaxone has been proposed for treatment of these infections in adults, yet ultimately valve replacement may be necessary. In patients with catheter-associated enterococcal bacteremia, the catheter should be removed promptly in most cases, although salvage of infected lines has occurred with the combined use of ampicillin or vancomycin with an aminoglycoside.

Treatment of Vancomycin-Resistant Enterococci

The treatment of serious infections caused by multiresistant, vancomycin-resistant strains is particularly challenging. The two most commonly used antibiotics are linezolid and daptomycin. Linezolid, an oxazolidinone antibiotic that inhibits protein synthesis, is bacteriostatic against most *E. faecium* and *E. faecalis* isolates, including vancomycin-resistant isolates. Response rates to linezolid are generally over 90%, including cases of bacteremia and sepsis, and this antibiotic is currently the only drug approved by the FDA for treatment of VRE infections. Anecdotal reports reveal the success of linezolid in treating meningitis caused by VRE. Unfortunately, as seen with other antibiotics, linezolid resistance is documented, and nosocomial spread of resistant organisms can occur. Linezolid frequently causes reversible bone marrow suppression after prolonged use and is associated with rare occurrences of lactic acidosis and irreversible peripheral neuropathy.

Serotonin syndrome may be seen in patients taking concomitant selective serotonin uptake inhibitor antidepressants. Newer oxazolidinones include tedizolid, which has better in vitro activity against enterococci and appears to have favorable pharmacokinetic and toxicity profiles when compared to linezolid.

Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against a broad range of gram-positive organisms. The antibiotic inserts into the bacterial cell wall, causing membrane depolarization and cell death. It has been approved for the treatment of adults with serious skin and soft tissue infections, right-sided endocarditis, and bacteremia caused by susceptible organisms. Most strains of VRE (both *E. faecium* and *E. faecalis*) are susceptible to daptomycin in vitro, and daptomycin has become the first-line agent for VRE treatment in many centers. However, treatment failures occur when administered at the standard dose of 6 mg/kg/day, necessitating higher treatment doses in patients with severe invasive infections. Furthermore, daptomycin dosages may need to be higher in children when compared with adults because of more rapid renal clearance. The addition of a β-lactam antibiotic, such as ampicillin or ceftaroline, may enhance activity of daptomycin and provide benefit over daptomycin alone for severe VRE infections, including endocarditis. Daptomycin has unreliable activity in the lung and therefore should not be used as a sole agent to treat pneumonia. Resistance of both *S. aureus* and *Enterococcus* to daptomycin has rarely been described, sometimes arising during therapy.

Several studies and meta-analyses have suggested that clinical outcomes of invasive VRE infection are similar when linezolid and daptomycin are used. However, infection-related mortality remains significant, especially among adults, and alternative or combination therapies continue to be explored.

Ceftaroline, a fifth-generation cephalosporin with activity against methicillin-resistant *S. aureus,* has activity against many *E. faecalis* strains but is inadequate when used alone for the treatment of *E. faecium*.

Newer tetracyclines have been developed with activity against VRE, including tigecycline, omadacycline, and eravacycline. Tigecycline is approved for use in complicated intraabdominal and skin and soft tissue infections but fails to achieve high serum concentrations and may be associated with treatment failure for VRE BSIs. Gastrointestinal side effects are common with tigecycline and may be intolerable. Experience with omadacycline and eravacycline in treatment of pediatric patients with VRE infection is lacking.

Lipoglycopeptides are a newer class of antibiotics that possess a core structure similar to vancomycin with the addition of a lipid substituent. Lipoglycopeptides include telavancin, dalbavancin, and oritavancin. Only oritavancin has reliable activity against VRE, but resistance may develop, and thus far clinical experience in children is limited.

PREVENTION

Strategies for preventing enterococcal infections include timely removal of urinary and intravenous catheters and debridement of necrotic tissue. Infection control strategies, including surveillance cultures, patient and staff cohorting, and strict gown and glove isolation, are effective at decreasing colonization rates with VRE. Unfortunately, these organisms may persist on inanimate objects such as stethoscopes, complicating efforts to limit their nosocomial spread. In order to prevent the emergence and spread of vancomycin-resistant organisms, the Centers for Disease Control and Prevention has developed a series of guidelines for prudent vancomycin use. Antibiotics with broad activity against anaerobic organisms are also thought to contribute to colonization with VRE, suggesting that prudent use of such antibiotics may also help limit spread of VRE. Decolonization strategies have been attempted but are generally ineffective in eradicating skin or gastrointestinal carriage of VRE. In particular, antimicrobial therapy is not indicated for this purpose. The role of probiotic agents in eliminating VRE colonization is currently unclear but may be a useful adjunct to prudent antimicrobial usage and other infection control interventions in limiting nosocomial spread of VRE.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 233

Diphtheria (*Corynebacterium diphtheriae*)

Amruta Padhye and Stephanie A. Fritz

Diphtheria is an acute toxic infection caused by toxin-producing strains of *Corynebacterium diphtheriae* and, less often, by toxin-producing strains of *Corynebacterium ulcerans.* Non–toxin-producing *C. diphtheriae* can also cause disease, although less severe. *C. ulcerans* is more often isolated from animal sources and can cause human disease similar to *C. diphtheriae*.

Although respiratory and cutaneous presentations of diphtheria are the most common, mortality is substantially higher with respiratory diphtheria. Classic respiratory diphtheria caused by toxigenic *Corynebacterium* species is the main focus of World Health Organization (WHO) case surveillance. In the United States, the case definition was modified in 2019, and currently toxigenic cases of diphtheria, including respiratory and nonrespiratory (e.g., skin, wound, conjunctiva, ear, genital mucosa) forms, are reportable to the Centers for Disease Control and Prevention (CDC).

ETIOLOGY

Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, gram-positive bacilli. *C. diphtheriae* is by far the most frequently isolated agent of diphtheria. Toxigenic *C. ulcerans* can cause mastitis in cattle and respiratory infections in animals and can spread to humans through close contact with secretions. It can cause cutaneous and respiratory illnesses that are clinically indistinguishable from diphtheria in humans. Person-to-person transmission of *C. ulcerans* is possible, though not well established. A selective medium (e.g., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms is required for isolation and, when reduced by *C. diphtheriae,* renders colonies gray-black. Differentiation of *C. diphtheriae* from *C. ulcerans* is based on urease activity; *C. ulcerans* is urease-positive. Four *C. diphtheriae* biotypes *(mitis, intermedius, belfanti, gravis)* are capable of causing diphtheria and are differentiated by colony morphology, hemolysis, and fermentation reactions. The ability of either *C. diphtheriae* or *C. ulcerans* to produce diphtheritic toxin results from acquisition of a lysogenic corynebacteriophage, which encodes the diphtheritic toxin gene and confers diphtheria-producing potential in these strains. Demonstration of diphtheritic toxin production by the modified Elek test, an agar immunoprecipitin technique, alone or in conjunction with polymerase chain reaction (PCR) testing for carriage of the toxin gene, is necessary to confirm disease. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.

EPIDEMIOLOGY

Unlike other diphtheroids (coryneform bacteria), which are ubiquitous in nature, *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. In areas where diphtheria is endemic, 3–5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare in nonendemic areas. Skin infection and skin carriage are silent reservoirs of *C. diphtheriae,* and organisms can remain viable in dust or on fomites for up to 6 months.

In the 1920s, >125,000 diphtheria cases and 10,000 diphtheria-related deaths were reported annually in the United States, with the highest fatality

rates among very young and elderly persons. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the United States after World War II, declined steadily through the late 1970s. From 1996 to 2018, only 14 cases of respiratory diphtheria, including 1 fatal case, were reported in the United States, an average of ≤1 case annually. During this same period, five cases of culture-confirmed respiratory diphtheria-like illness caused by toxigenic *C. ulcerans* were also identified.

Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria. Since the introduction of toxoid immunization, the disease has shifted from affecting children <15 years old to adults who lack natural exposure to toxigenic *C. diphtheriae* in the vaccine era and have low rates of booster immunization. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990 to 1996 in the newly independent countries of the former Soviet Union, involving >150,000 cases in 14 countries. Of these, >60% of cases occurred in individuals >14 years old. Case fatality rates ranged from 3% to 23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

WHO surveillance reports indicate that most cases of diphtheria worldwide occur in the Southeast Asia and Africa regions, reporting more than 10,000 cases worldwide in 2020. India contributes a substantial proportion to the global burden of diphtheria, with an average of over 4,000 cases annually reported to the WHO in the past decade.

Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western Hemisphere in the early 20th century, recurring reminders of the fragility of this success, particularly in conflict areas, emphasize the need to continue vigorous promotion of those same control principles across the global community. The largest diphtheria outbreak in the refugee setting occurred when the Rohingya people were displaced from Myanmar to Bangladesh in 2017, eventually lasting over 2 years and with 7064 cases and 45 deaths reported as of November 2019. Along with outbreaks in Venezuela, Haiti, Yemen, and more recently Nigeria, these are stark reminders of the threat of re-emergence that vaccine-preventable diseases pose. Improving surveillance, vaccination coverage, and public awareness of the disease are key for control of disease during outbreaks.

When diphtheria was common, **cutaneous diphtheria** accounted for more than 50% of reported *C. diphtheriae* isolates in the United States. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 *C. diphtheriae* infections were documented in a Seattle neighborhood (the site of the last major U.S. outbreak) from 1971 to 1982; 86% were cutaneous, and 40% involved toxigenic strains. The incidence of *C. diphtheriae* isolates from cutaneous infections has risen dramatically over the past decade. Cutaneous diphtheria is an important source of toxigenic *C. diphtheriae* in the United States, and its importation from endemic areas is frequently the source of subsequent sporadic cases of respiratory tract diphtheria. Between 2015 and 2018, the CDC confirmed four cases of cutaneous diphtheria from toxin-producing *C. diphtheriae* in U.S. residents returning from travel to endemic areas. Cutaneous diphtheria caused by *C. ulcerans* from travel to tropical countries or animal contact has also been increasingly reported.

In Europe, increasing reports of respiratory and systemic infections have been attributed to *C. ulcerans;* animal contact is the predominant risk factor. In the United Kingdom, from 2008 to 2017, of the 33 toxigenic cases of diphtheria, just over half of the cases were caused by *C. diphtheriae,* and the remainder were caused by *C. ulcerans*. Most of the *C. diphtheriae* cases were cutaneous, while the *C. ulcerans* cases were equally respiratory and cutaneous. Travel to an endemic area was the major risk factor for *C. diphtheriae* acquisition, while contact with a companion animal was the major factor associated with acquisition of *C. ulcerans*. Incomplete vaccination status was strongly associated with the risk of hospitalization and death.

PATHOGENESIS

Both toxigenic and nontoxigenic strains of *C. diphtheriae* cause skin and mucosal infection and can rarely cause invasive disease, including endocarditis and bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing a local inflammatory reaction. The major virulence of the organism lies in its ability to produce a potent polypeptide exotoxin, the diphtheritic toxin, which inhibits protein synthesis and causes local tissue necrosis and the resultant local inflammatory response. Within the first few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, initially white and advancing to become a gray-brown, leather-like, adherent **pseudomembrane** (*diphtheria* is Greek for leather). Removal is difficult and reveals a bleeding, edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and demyelination of nerves. Because the latter two complications can occur 2-10 weeks after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21% with symptomatic nasopharyngeal infection demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

CLINICAL MANIFESTATIONS

The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin. Although 98% of infections occur in the respiratory tract, other sites include cutaneous, conjunctival, ear, and vaginal mucosa.

New estimates of epidemiologic and clinical aspects of diphtheria from a comprehensive update by Truelove et al., with systematic reviews including recent literature, are summarized in Figure 233.1.

Respiratory Tract Diphtheria

The pharynx or tonsils is the most common location of infection in the respiratory tract (75–94%), followed by the larynx (25%). Although the incubation period has traditionally been regarded to be 2-5 days (range 1-10 days), emerging data suggest that the median time from infection to onset of prodromal symptoms is only 1.4 days. An estimated 80% of untreated symptomatic cases progress to membranous diphtheria in an average of 2-3 days after symptom onset. In tonsillar and **pharyngeal diphtheria**, sore throat is the universal early symptom. Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas (Fig. 233.2). Underlying soft tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality caused by airway compromise or toxin-mediated complications (Fig. 233.3). In infants, infection of the anterior nares is more common and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic.

The characteristic adherent pseudomembrane, extension beyond the faucial area, dysphagia, and relative lack of fever help differentiate diphtheria from **exudative pharyngitis** caused by *Streptococcus pyogenes* or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre syndrome), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi

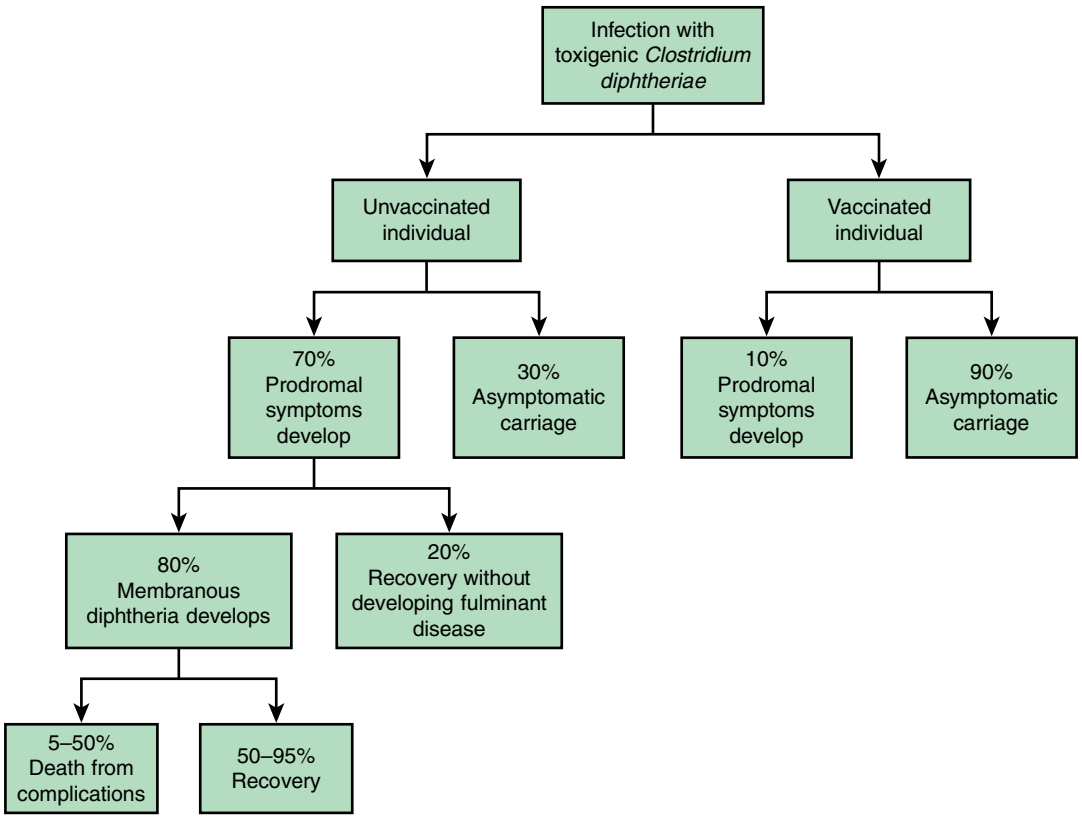

Fig. 233.1 Clinical manifestations of *Clostridium diphtheriae* infection among unvaccinated and vaccinated individuals. Among unvaccinated individuals infected with toxigenic *C. diphtheriae*, prodromal symptoms develop in ~70%, of whom 80% develop membranous diphtheria. Of those with membranous diphtheria, case fatality can be as high as 5–50%. Among vaccinated individuals infected with toxigenic *C. diphtheriae*, the toxoid vaccine provides protection from symptoms; 10% develop prodromal symptoms, whereas 90% become asymptomatic carriers. These symptomatic vaccinated individuals have a lower risk of severe disease and death and are more likely to recover. *(Adapted from Truelove SA, Keegan LT, Moss WJ, et al. Clinical and epidemiological aspects of diphtheria: a systematic review and pooled analysis. Clin Infect Dis. 2020;71[1]:89–97.)*

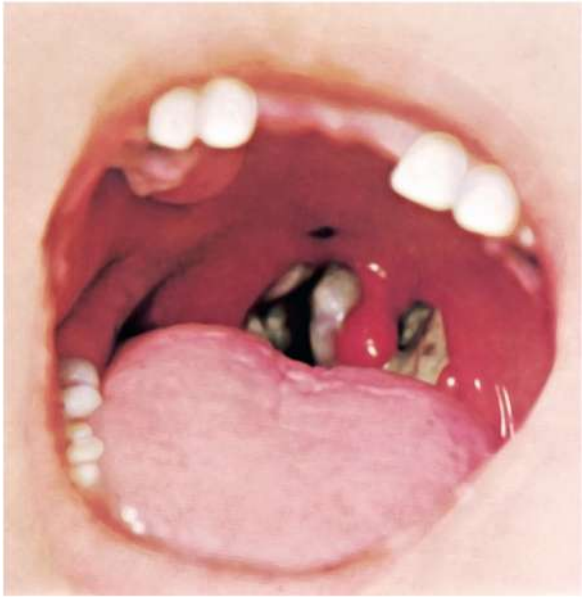

Fig. 233.2 Tonsillar diphtheria. *(Courtesy Franklin H. Top, MD, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes.)*



Fig. 233.3 Diphtheria. Bull-neck appearance of diphtheritic cervical lymphadenopathy. *(From the Centers for Disease Control and Prevention [CDC]. Public health image library [PHIL], image #5325. Available at:* https://phil.cdc.gov/Details.aspx?pid=5325.*)*

can be primary or a secondary extension from the pharyngeal infection, presenting with hoarseness, stridor, dyspnea, and croupy cough. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualization of the adherent pseudomembrane at laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft tissue edema and airway obstruction by the diphtheria membrane. This progression of airway obstruction in laryngeal infection within 1-2 weeks after symptom onset is responsible for 60–65% of overall deaths. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

Cutaneous Diphtheria

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, ecthyma-like, nonhealing ulcer with a gray-brown membrane. Diphtheria skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process, such as dermatosis, laceration, burn, bite, or impetigo, becomes secondarily infected with *C. diphtheriae.* Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria.

Infection at Other Sites

C. diphtheriae occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; the skin was the probable portal of entry, and almost all strains were nontoxigenic. Sporadic cases of pyogenic arthritis, mainly from nontoxigenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

DIAGNOSIS

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a dry swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates. It is recommended that all isolates be sent to a reference laboratory. In the United States, the CDC's Pertussis and Diphtheria Laboratory provides support to local and state health departments needing assistance with isolation, identification, and subtyping of *C. diphtheriae* and *C. ulcerans.*

COMPLICATIONS

Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of *C. diphtheriae* infection can be significantly affected by **diphtheritic toxin**: the heart and the nervous system.

Toxic Cardiomyopathy

Toxic cardiomyopathy occurs in 10–25% of patients with respiratory diphtheria, resulting in death in 35–60% of cases with this complication and responsible for 20–25% of deaths overall. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease, along with a delay in administration of antitoxin. The first evidence of cardiac toxicity characteristically occurs 7-14 days after the onset of respiratory symptoms but can appear acutely as early as the first week of illness, a poor prognostic sign, or as late as the sixth week. Tachycardia disproportionate to fever is common and may be evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged P-R interval and changes in the ST-T wave on an electrocardiographic tracing are relatively frequent findings; dilated and hypertrophic cardiomyopathy detected by echocardiogram has been described. Single or progressive cardiac **dysrhythmias** can occur, including first-, second-, and third-degree heart block. Temporary transvenous pacing may improve outcomes. Atrioventricular dissociation and ventricular tachycardia are also described, the latter having a high associated mortality. Heart failure may appear insidiously or acutely. Elevation of the serum aspartate transaminase concentration closely parallels the severity of myonecrosis. Severe dysrhythmia portends death. Histologic postmortem findings are variable: little or diffuse myonecrosis with acute inflammatory response. Recovery from toxic myocardiopathy is usually complete, although survivors of more severe dysrhythmias can have permanent conduction defects.

Toxic Neuropathy

Neurologic complications occur in 20–25% of untreated cases, resulting in death in 50% of cases who develop them and responsible for 15% of deaths overall. They parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 weeks after onset of oropharyngeal inflammation, hyperesthesia and local **paralysis** of the soft palate typically occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty in swallowing, and risk for aspiration. **Cranial neuropathies** characteristically occur in the fifth week, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric demyelinating **polyneuropathy** has onset 10 days to 3 months after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Nerve conduction velocity studies and cerebrospinal fluid findings in diphtheritic polyneuropathy are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely vasomotor center dysfunction 2-3 weeks after onset of illness can cause hypotension or cardiac failure.

Recovery from myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.

TREATMENT

Specific diphtheria **antitoxin** is the mainstay of therapy and should be administered as soon as possible, without delay on the basis of clinical diagnosis. Because it neutralizes only free toxin, antitoxin efficacy diminishes with elapsed time after the onset of mucocutaneous symptoms. Equine diphtheria antitoxin is available in the United States only from the CDC. Physicians treating a case of suspected diphtheria should contact the CDC Emergency Operations Center at 1-770-488-7100 after consulting with their state health department. Antitoxin is available from CDC under expanded access investigational new drug application protocol. Antitoxin is administered as a single empirical dose of 20,000-100,000 units based on the degree of severity, site, and duration of illness. Skin testing for hypersensitivity must be performed before administration of antitoxin. Patients with positive sensitivity testing or with a history of hypersensitivity reaction to horse equine protein should be desensitized. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but its use is prudent because toxic sequelae can occur. Commercially available intravenous immunoglobulin preparations contain low titers of antibodies to diphtheria toxin; their use for therapy of diphtheria is not proven or approved. Antitoxin is not recommended for asymptomatic carriers.

The role of **antimicrobial therapy** is to halt toxin production, treat localized infection, and prevent transmission of the organism

to contacts. Although *C. diphtheriae* is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline, only erythromycin or penicillin are recommended for treatment. Erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Resistance to erythromycin is common in populations where the drug has been used broadly, and resistance to penicillin has also been reported. Appropriate therapy is **erythromycin** (40-50 mg/kg/day divided every 6 hours by mouth [PO] or intravenously [IV]; maximum 2 g/day), **aqueous crystalline penicillin G** (150,000 - 250,000 units/kg/day divided every 6 hr IV or intramuscularly [IM], up to 2-3 million units/day), or **procaine penicillin** (300,000 units every 12 hr IM for those ≤10 kg in weight; 600,000 units every 12 hr IM for those >10 kg in weight) for 14 days. Once oral medications are tolerated, oral erythromycin (see dosing above) or penicillin V (50 mg/kg/day, divided every 6 hr, maximum 2 g per day) may be used for the remaining duration of therapy. *Antibiotic therapy is not a substitute for antitoxin therapy.* Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least two successive cultures of specimens from the nose and throat (or skin) obtained at least 24 hours apart, collected 24 hours after completion of antimicrobial therapy. Treatment with erythromycin should be repeated if either culture yields *C. diphtheriae.*

Individuals untreated with antibiotics, including those with either symptomatic or asymptomatic infection, remain colonized with *C. diphtheriae* for an average of 18.5 days, with 5% remaining colonized longer than 48 days. With antibiotic treatment, they clear *C. diphtheriae* colonization within an average of 5.2 days, reducing the duration of infectiousness by 2 weeks.

SUPPORTIVE CARE

Droplet precautions are instituted for patients with pharyngeal diphtheria; for patients with cutaneous diphtheria, **contact precautions** are observed until the results of specimen cultures taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, usually for ≥2 weeks until the risk for symptomatic cardiac damage has passed, with return to physical activity guided by the degree of toxicity and cardiac involvement.

PROGNOSIS

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies *gravis* has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality ratio for untreated, never-vaccinated cases is 29%, improving to 10% with antitoxin treatment. The risk of fatality increases with every day of delayed antitoxin treatment. Children age <5 years are more likely to die from symptomatic infection than adults >20 years of age, whereas children 5-19 years of age are less likely to die from infection than adults age >20 years. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheria toxin after infection.

PREVENTION

Protection against serious disease caused by imported or indigenously acquired *C. diphtheriae* depends on immunization. In the absence of a precisely determined minimum protective level for diphtheria antitoxin, the presumed minimum is 0.01-0.10 IU/mL. In outbreaks, 90% of individuals with clinical disease have had antibody values <0.01 IU/mL, and 92% of asymptomatic carriers have had values >0.1 IU/mL. In serosurveys in the United States and Western Europe, where almost universal immunization during childhood has been achieved, 25% to >60% of adults lack protective antitoxin levels, with typically very low levels in elderly persons. A serosurvey in the United States (1988–1994) indicated that 60% of the overall population had protective immunity against diphtheria; however, this level of protection declined from 80% in persons age 12-19 years to about 30% in persons age 60-69 years.

All suspected diphtheria cases should be reported to local and state health departments. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread. The serial interval, or time between symptom onset of the infector/infectee pair, is a median of 5.9 days, with 5% of intervals <0.8 days and 5% longer than 21 days.

Asymptomatic Case Contacts

All household contacts and people who have had intimate respiratory or habitual physical contact with a patient are closely monitored for illness for 7 days. Cultures of the nose, throat, and any cutaneous lesions are performed. Antimicrobial prophylaxis is presumed effective and is administered regardless of immunization status, using a single injection of benzathine penicillin G (600,000 units IM for patients weighing <30kg, or 1,200,000 units IM for patients weighing ≥30 kg or adults,) or erythromycin (40-50 mg/kg/day divided every 6 hr PO for 7-10 days; max 1 g/day). Diphtheria toxoid vaccine, in age-appropriate form, is given to immunized individuals who have not received a booster dose within 5 years. Children who have not received their fourth dose should be vaccinated. Those who have received fewer than three doses of diphtheria toxoid or who have uncertain immunization status should be immunized with an age-appropriate preparation on a primary schedule.

Asymptomatic Carriers

When an asymptomatic carrier is identified, antimicrobial prophylaxis is given for 10-14 days, and an age-appropriate preparation of diphtheria toxoid vaccination is administered immediately if a booster has not been given within 1 year. Droplet precautions (respiratory tract colonization) or contact precautions (cutaneous colonization only) are observed until at least two subsequent cultures obtained at least 24 hours apart, collected 24 hours after cessation of therapy, have negative results.

Repeat cultures are performed about 2 weeks after completion of therapy for cases and carriers; if results are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Susceptibility testing of isolates should be performed, as erythromycin resistance is reported. Neither penicillin nor erythromycin eradicates carriage in 100% of individuals. In one report, a single course of therapy failed in 21% of carriers. Transmission of diphtheria in modern hospitals is rare. Only those who have an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

Vaccine

Universal immunization with diphtheria toxoid throughout life, designed to provide constant protective antitoxin antibody levels and to reduce severity of *C. diphtheriae* disease, is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic *C. diphtheriae,* it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 80–85% of a population is immunized.

Full vaccination is highly effective in preventing symptomatic disease (87% with three or more doses, increasing to 99% with five doses), severe disease (defined as local and systemic symptoms plus a major complication; 81%), and death (93%). Even though vaccines do not prevent colonization, they reduce transmission by 60%, likely through reduced symptomatic shedding. Asymptomatic carriers are still able to transmit infection, albeit at only 24% the rate of symptomatic cases. In an outbreak setting, both vaccination and antibiotic treatment to clear colonization are necessary to interrupt transmission. Although full vaccination coverage can interrupt transmission in only 27% of outbreak settings, this figure increases to 70% when rapid antibiotic treatment is initiated in 90% of symptomatic cases.

The COVID-19 pandemic resulted in disruptions in immunization services in 2020, leading to 3.5 million children missing their first dose of diphtheria, tetanus, and pertussis vaccine (DTP) as compared with 2019. Global annual vaccination coverage for first-dose DTP vaccine decreased from 90% in 2019 to 87% in 2020; third-dose DTP vaccine

decreased from 86% in 2019 to 83% in 2020. The impact this will have on the resurgence of vaccine-preventable infections is yet to be determined.

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency and adsorbed to aluminum salts, enhancing immunogenicity. Two preparations of diphtheria toxoids are formulated according to the *limit of flocculation* (Lf) content, a measure of the quantity of toxoid. The pediatric (6 months to 6 years) preparations (i.e., **DTaP** [diphtheria and tetanus toxoids with acellular pertussis vaccine] and **DT** [diphtheria and tetanus toxoids vaccine]) contain 6.7-25.0 Lf units of diphtheria toxoid per 0.5 mL dose; tetanus toxoid with vaccines for ≥7 years (Td [tetanus and diphtheria toxoid vaccine] and **Tdap** [diphtheria and tetanus toxoids with acellular pertussis vaccine]) contain no more than 2-2.5 Lf units of toxoid per 0.5 mL dose. The *higher-potency* (D) formulation of toxoid is used for primary series and booster doses for children through 6 years of age, given its superior immunogenicity and minimal reactogenicity. For individuals ≥7 years old, Td or Tdap is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

For children 6 weeks to 6 years of age, five 0.5-mL doses of diphtheria-containing (D) vaccine (DTaP preferred) are given in the primary series, including doses at 2, 4, and 6 months of age, and a fourth dose, an integral part of the primary series, at 15-18 months. Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3. A booster dose is given at 4-6 years of age (unless the fourth primary dose was administered at ≥4 years). For persons ≥7 years to 18 years not previously immunized for diphtheria, three 0.5-mL doses of *lower-level* diphtheria-containing (d) vaccine are given in a primary series of two doses at least 4 weeks apart and a third dose 6 months after the second dose. The first dose should be Tdap, and subsequent doses can be Td or Tdap.

A booster dose, consisting of Tdap, is recommended at 11-12 years of age. Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine. Adolescents 13-18 years old who have not received Tdap at 11-12 years should receive a single dose of Tdap, then a Td or Tdap booster every 10 years. Pregnant women should receive a single dose of Tdap during every pregnancy, preferably during gestational weeks 27-36. Adults who have never received Tdap should receive a single dose of Tdap, regardless of when they last got Td. A Td or Tdap booster should be given every 10 years.

Updated recommendations allow for use of either Td or Tdap vaccine in situations where previously only Td was recommended. This includes the decennial Td booster, tetanus prophylaxis for wound management, and for additional required doses in the catch-up immunization schedule if a person has received at least one Tdap dose.

The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a prior dose. For children <7 years old in whom pertussis immunization is contraindicated, DT is used. Those whose immunization is begun with DTaP or DT before 1 year of age should have a total of five 0.5-mL doses of diphtheria-containing (D) vaccines by 6 years of age. For those whose immunization is begun at around 1 year old, the primary series is three 0.5-mL doses of diphtheria-containing (D) vaccine, with a booster given at 4-6 years, unless the third dose was given after the fourth birthday.

There is no association of DT or Td with seizures. Local adverse effects alone do not preclude continued use. The rare patient who experiences an Arthus-type hypersensitivity reaction or a temperature >39.4°C (103°F) after a dose of Td usually has high serum tetanus antitoxin levels and should not be given Td more frequently than every 10 years, even if the patient sustains a significant tetanus-prone injury.

The DT or Td preparation can be given concurrently with other vaccines. Meningococcal and pneumococcal conjugate vaccines containing diphtheria toxoid or a variant of diphtheria toxin, CRM197 protein, are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 234

Listeria monocytogenes

Ashley C. Howard and Thomas S. Murray

Listeriosis in humans is caused principally by *Listeria monocytogenes,* 1 of 17 species of the genus *Listeria* that are widely distributed in the environment and throughout the food chain. Human infections can usually be traced to an animal reservoir. Infection usually occurs at the extremes of age. In the pediatric population, perinatal infections predominate and usually occur secondary to maternal infection or colonization. Outside the newborn period, disease is most often encountered in *immunosuppressed* (usually T-cell deficiencies) children and adults and in elderly persons. For most people the major risk for infection with *Listeria* is **food-borne transmission**. In the United States, food-borne outbreaks are caused by improperly processed dairy products and contaminated vegetables and principally affect the same individuals at risk for sporadic disease.

ETIOLOGY

Members of the genus *Listeria* are facultatively anaerobic, non–spore-forming, motile, gram-positive bacilli that are catalase positive. The 17 *Listeria* species are divided into two genomically distinct groups on the basis of DNA-DNA hybridization studies. One group contains the species *L. grayi,* and 10 others discovered since 2009 are considered nonpathogenic. The second group contains six species: the nonhemolytic species *L. innocua*, *L. welshimeri,* and *L. marthii* and the hemolytic species *L. monocytogenes, L. seeligeri,* and *L. ivanovii. L. ivanovii* is pathogenic primarily in animals, and the vast majority of both human and animal disease is caused by *L. monocytogenes*.

Subtyping of *L. monocytogenes* isolates for epidemiologic purposes is now performed predominately with whole genome sequencing. This demonstrates the clonal structure of populations of *L. monocytogenes* as well as the sharing of populations between human and animal sources. **Subtyping** is an important component of determining whether cases are connected or sporadic but usually requires collaboration with a specialized laboratory.

Historically, selected biochemical tests, together with the demonstration of *tumbling motility,* an umbrella-type formation below the surface in semisolid medium, hemolysis, and a typical cyclic adenosine monophosphate test, are usually sufficient to establish a presumptive identification of *L. monocytogenes*. Once growth is present, *L. monocytogenes* can now be rapidly identified with matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry.

EPIDEMIOLOGY

L. monocytogenes is widespread in nature, has been isolated throughout the environment, and is associated with epizootic disease and asymptomatic carriage in >42 species of wild and domestic animals and 22 avian species. Epizootic disease in large animals (e.g., sheep, cattle) is associated with abortion and "circling disease," a form of basilar meningitis. *L. monocytogenes* is isolated from sewage, silage, and soil, where it survives for >295 days. Human-to-human transmission rarely occurs except in maternal-fetal transmission. The annual incidence of listeriosis decreased by 36% between 1996 and 2004 and has remained level since then, estimated between two and five cases per year per million people. However, **food-borne outbreaks** continue to occur. The rate of *Listeria* infections varies among states. Epidemic human listeriosis has been associated with food-borne transmission in several large outbreaks, especially in association with aged soft cheeses; improperly pasteurized milk and milk products; contaminated raw and ready-to-eat beef, pork, and poultry and packaged meats and

salads; and vegetables, both fresh and frozen, harvested from farms where the ground is contaminated with the feces of colonized animals. In 2017-2018, the largest *Listeria* outbreak ever recorded occurred in South Africa with >900 cases and 200 deaths related to a processed contaminated meat product, "polony." U.S. food-borne outbreaks from 2019 to 2020 included deli meats and cheeses, packaged hard boiled eggs, and enoki mushrooms. The ability of *L. monocytogenes* to grow at temperatures as low as 4°C (39.2°F) increases the risk for transmission from aged soft cheeses and stored contaminated food. Listeriosis is an uncommon but important recognized etiology of neonatal sepsis and meningitis. Small clusters of nosocomial person-to-person transmission have occurred in hospital nurseries and obstetric suites. Sporadic endemic listeriosis is less well characterized. Likely routes include food-borne infection and zoonotic spread. **Zoonotic transmission** with cutaneous infections occurs in veterinarians and farmers who handle sick animals.

Reported cases of listeriosis are clustered at the extremes of age. Some studies show higher rates in males and a seasonal predominance in the late summer and fall in the Northern Hemisphere. In the United States, there is an increased risk of infection in nonpregnant non-Hispanic Asians, non-Hispanic Blacks, and Hispanics compared with non-Hispanic Whites. Outside the newborn period and during pregnancy, disease is usually reported in patients with underlying immunosuppression, with a 100-300 times increased risk in HIV-infected persons and in the elderly population (Table 234.1). In a prospective cohort study for listeriosis, 82.5% of participants had at least one immunocompromising condition, and those with bacteremia and neurolisteriosis disease were found to have a fivefold increased risk of death if there was an underlying malignancy.

The incubation period, which is defined only for common-source food-borne disease, is 21-30 days but in some cases may be longer. Asymptomatic carriage and fecal excretion are reported in 1–5% of healthy persons and 5% of abattoir workers, but duration of excretion, when studied, is short (<1 month).

PATHOLOGY

One of the major concepts of *Listeria* pathology and pathogenesis is its ability to survive as an intracellular pathogen. *Listeria* incites a mononuclear response and elaboration of cytokines, producing multisystem disease, particularly pyogenic meningitis. Granulomatous reactions and microabscess formation develop in many organs, including the liver, lungs, adrenals, kidneys, central nervous system (CNS), and notably the placenta. Animal models demonstrate *translocation,* the transfer of intraluminal organisms across intact intestinal mucosa. Histologic examination of tissues, including the placenta, shows granulomatous inflammation and microabscess formation. Intracellular organisms can often be demonstrated with special stains.

Table 234.1 Types of *Listeria monocytogenes* Infections

Listeriosis in pregnancy
Neonatal listeriosis
Early onset
Late onset
Food-borne outbreaks/febrile gastroenteritis
Listeriosis in normal children and adults (rare)
Focal *Listeria* infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)
Listeriosis in immunocompromised persons
Lymphohematogenous malignancies
Collagen vascular diseases
Diabetes mellitus
HIV infection
Transplantation
Renal failure with peritoneal dialysis
Listeriosis in elderly persons

PATHOGENESIS

Listeria organisms usually enter the host through the gastrointestinal (GI) tract. Gastric acidity provides some protection, and drugs that raise gastric pH may promote infection. Studies of intracellular and intercellular spread of *L. monocytogenes* have revealed a complex pathogenesis. Four pathogenic steps are described: internalization, escape from the vacuole, nucleation of actin filaments, and cell-to-cell spread. **Listeriolysin O**, a hemolysin, mediates lysis of vacuoles and is responsible for the zone of hemolysis around colonies on blood-containing solid media. In cell-to-cell spread, locomotion proceeds via polymerization of actin filaments, which extrude the bacteria in pseudopods, which in turn are internalized by adjacent cells, necessitating escape from a double-membrane vacuole. This mechanism protects intracellular bacteria from the humoral arm of immunity and is responsible for the well-known requirement of T-cell–mediated activation of monocytes by lymphokines for clearance of infection and establishment of immunity. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear. In addition, siderophores scavenge iron from the host, enhancing growth of the organism and likely explaining the relatively high risk of listeriosis in iron overload syndromes.

CLINICAL MANIFESTATIONS

The clinical presentation of listeriosis depends greatly on the age of the patient and the circumstances of the infection.

Listeriosis in Pregnancy

Pregnant women have increased susceptibility to *Listeria* infections (approximately 20 times higher than nonpregnant women), probably because of a relative impairment in cell-mediated immunity. *L. monocytogenes* has been grown from placental and fetal cultures of pregnancies ending in spontaneous abortion. The usual presentation in the second and third trimesters is a flulike illness that may result in seeding of the uterine contents by bacteremia. Rarely is maternal listeriosis severe, but meningitis in pregnancy has been reported. Recognition and treatment at this stage are associated with normal pregnancy outcomes, but the fetus may not be infected even if listeriosis in the mother is not treated. In other instances, placental listeriosis develops with infection of the fetus that may be associated with stillbirth or premature delivery. Delivery of an infected premature fetus is associated with very high infant mortality. Disseminated disease is apparent at birth, often with a diffuse pustular rash. Infection in the mother usually resolves without specific therapy after delivery, but postpartum fever and infected lochia may occur.

Neonatal Listeriosis

Two clinical presentations are recognized for neonatal listeriosis: early-onset neonatal disease (<5 days, usually within 1-2 days of birth), which is a predominantly **septicemic** form, and late-onset neonatal disease (>5 days, mean 14 days of life), which is a predominantly **meningitic** form (Table 234.2). The principal characteristics of the two presentations resemble the clinical syndromes described for group B *Streptococcus* (see Chapter 230).

Early-onset disease occurs with milder transplacental or ascending infections from the female genital tract. There is a strong association with recovery of *L. monocytogenes* from the maternal genital tract, obstetric complications, prematurity, and neonatal sepsis with multiorgan involvement, including rash, but without CNS localization (Fig. 234.1). The mortality rate is approximately 20–30%.

The epidemiology of **late-onset disease** is poorly understood. Onset is usually after 5 days but before 30 days of age. Affected infants frequently are full-term, and the mothers are culture negative and asymptomatic. The presenting syndrome is usually purulent meningitis with parenchymal brain involvement, which, if adequately treated, has a mortality rate of <20%.

Table 234.2 Characteristic Features of Early- and Late-Onset Neonatal Listeriosis

EARLY ONSET (<5 DAYS)	LATE ONSET (≥5 DAYS)
Positive result of maternal *Listeria* culture	Negative results of maternal *Listeria* culture
Obstetric complications	Uncomplicated pregnancy
Premature delivery	Term delivery
Low birthweight	Normal birthweight
Neonatal sepsis	Neonatal meningitis
Mean age at onset 1.5 days	Mean age at onset 14.2 days
Mortality rate <30%	Mortality rate <20% Nosocomial outbreaks



Fig. 234.1 *Listeria monocytogenes.* The generalized maculopapular rash present at birth disappeared within a few hours of life. *(From Benitez-Segura I, Fiol-Jaume M, Balliu PR, Tejedor M. Listeria monocytogenes: generalized maculopapular rash may be the clue. Arch Dis Child Fetal Neonatal Ed. 2013;98[1]:F64, Fig. 1.)*

Postneonatal Infections

Listeriosis beyond the newborn period may rarely occur in otherwise healthy children but is most often encountered in association with underlying malignancies (especially lymphomas) or immunosuppression. When associated with food-borne outbreaks, disease may cause GI symptoms or any of the *Listeria* syndromes. The clinical presentation is usually meningitis, less commonly sepsis, and rarely other CNS involvement, such as cerebritis, meningoencephalitis, brain abscess, spinal cord abscess, or a focus outside the CNS, such as suppurative arthritis, osteomyelitis, endocarditis, peritonitis (associated with peritoneal dialysis), or liver abscess. It is not known whether the frequent GI signs and symptoms result from enteric infection because the mode of acquisition is often unknown.

DIAGNOSIS

Listeriosis should be included in the differential diagnosis of infections in pregnancy, of neonatal sepsis and meningitis, and of sepsis or meningitis in older children who have underlying malignancies (lymphomas), are receiving immunosuppressive therapy, or have undergone transplantation. The diagnosis is established by culture of *L. monocytogenes* from blood or cerebrospinal fluid (CSF). Cultures from the maternal cervix, vagina, lochia, and placenta, if possible, should be obtained when intrauterine infections lead to premature delivery or early-onset neonatal sepsis. Cultures from closed-space infections may also be useful. It is helpful to alert the laboratory to suspected cases so that *Listeria* isolates are not discarded as contaminating diphtheroids.

Histologic examination of the placenta is also useful. Molecular assays are now commercially available to detect *L. monocytogenes* from CNS samples and directly from positive blood culture bottles. Serodiagnostic tests are not useful.

Differential Diagnosis

Listeriosis is indistinguishable clinically from neonatal sepsis and meningitis caused by other organisms. The presence of increased peripheral blood monocytes suggests listeriosis. Monocytosis or lymphocytosis may be modest or striking. Beyond the neonatal period, *L. monocytogenes* CNS infection is associated with fever, headache, seizures, and signs of meningeal irritation. The brainstem may be characteristically affected. The white blood cell concentration may vary from normal to slightly elevated, and the CSF laboratory findings are variable and less striking than in the more common causes of bacterial meningitis. Polymorphonuclear leukocytes or mononuclear cells may predominate, with shifts from polymorphonuclear to mononuclear cells in sequential lumbar puncture specimens. The CSF glucose concentration may be normal, but a low level mirrors the severity of disease. The CSF protein concentration is moderately elevated. *L. monocytogenes* is isolated from the blood in 40–75% of cases of meningitis caused by the organism. Deep focal infections from *L. monocytogenes,* such as endocarditis, osteomyelitis, and liver abscess, are also indistinguishable clinically from such infections from more common organisms. Cutaneous infections should be suspected in patients with a history of contact with animals, especially products of conception.

TREATMENT

The emergence of multiantibiotic resistance mandates routine susceptibility testing of all isolates. The recommended therapy is **ampicillin** (100-200 mg/kg/day divided every 6 hours intravenously [IV]; 300-400 mg/kg/day divided every 6 hours IV if meningitis is present), alone or in combination with an **aminoglycoside** (2.0-3.0 mg/kg/day IV divided every 8-24 hours depending on postnatal age). The aminoglycoside enhances the bactericidal activity and is generally recommended in cases of endocarditis and meningitis. The adult dose is ampicillin 4-6 g/day divided every 6 hours plus an aminoglycoside. The ampicillin dose is doubled if meningitis is present. Special attention to dosing is required for neonates, who require longer dosing intervals because of the longer half-lives of the antibiotics in their bodies. *L. monocytogenes* is not susceptible to the cephalosporins, including third-generation cephalosporins. If these agents are used for empirical therapy for neonatal sepsis or meningitis in a newborn, ampicillin must be added for possible *L. monocytogenes* infection. Vancomycin, vancomycin plus an aminoglycoside, and trimethoprim-sulfamethoxazole are alternatives to ampicillin. The duration of therapy is usually 2-3 weeks, with 3 weeks recommended for immunocompromised persons and patients with meningitis. A longer course is needed for endocarditis, brain abscess, and osteomyelitis. Antibiotic treatment is unnecessary for gastroenteritis without invasive disease.

PROGNOSIS

Early gestational listeriosis may be associated with abortion or stillbirth, although maternal infection with sparing of the fetus has been reported. There is no convincing evidence that *L. monocytogenes* is associated with repeated spontaneous abortions in humans. The mortality rate is >50% for premature infants infected in utero, 30% for early-onset neonatal sepsis, 15% for late-onset neonatal meningitis, and <10% in older children with prompt institution of appropriate antimicrobial therapy. Mental retardation, hydrocephalus, and other CNS sequelae are reported in survivors of *Listeria* meningitis.

Table 234.3 Prevention of Food-Borne Listeriosis

GENERAL RECOMMENDATIONS TO PREVENT *LISTERIA* INFECTION

FDA recommendations for washing and handling food:

- Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
- Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
- Dry the produce with a clean cloth or paper towel.
- Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods.

Keep your kitchen and environment cleaner and safer:

- Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
- Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer −17.8°C (0°F) or lower.
- Clean up all spills in your refrigerator promptly, especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
- Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse.

Cook meat and poultry thoroughly:

- Thoroughly cook raw food from animal sources, such as beef, pork, or poultry, to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at http://www.FoodSafety.gov.

Store foods safely:

- Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
  - Hot dogs: store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
  - Luncheon and deli meat: store factory-sealed, unopened package no longer than 2 wk. Store opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
- Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.

Choose safer foods:

- Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

RECOMMENDATIONS FOR PERSONS AT HIGHER RISK*

In addition to the recommendations listed above, include:

Meats

- Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna) or fermented or dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming hot just before serving.
- Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats.
- Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, such as canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening.

Cheeses

- Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says "*Made With Pasteurized Milk.*"

Seafood

- Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product.
- Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky."
  - These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens.
- Canned and shelf-stable tuna, salmon, and other fish products are safe to eat.

Follow this general FDA advice for melon safety:

- Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew.
- Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use to avoid transferring bacteria between melons.
- Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated ≤4.5°C (40°F) (0–1.1°C [32–34°F] is best) for no more than 7 days.
- Discard cut melons left at room temperature for >4 hours.

*Including pregnant women, persons with a weakened immune system, and older adults.
FDA, Food and Drug Administration; USDA, U.S. Department of Agriculture.
Adapted from Centers for Disease Control and Prevention: *Listeria* (listeriosis): prevention. http://www.cdc.gov/listeria/prevention.html.

PREVENTION

Listeriosis can be prevented by pasteurization and thorough cooking of foods. Irradiation of meat products may also be beneficial. Consumption of unpasteurized or improperly processed dairy products should be avoided, especially aged soft cheeses, uncooked and precooked meat products that have been stored at 4°C (39.2°F) for extended periods, and unwashed vegetables (Table 234.3). This avoidance is particularly important during pregnancy and for immunocompromised persons. Infected domestic animals should be avoided when possible. Education regarding risk reduction is aimed particularly at pregnant women and people being treated for cancer.

Careful handwashing is essential to prevent nosocomial spread within obstetric and neonatal units. Immunocompromised patients given prophylaxis with trimethoprim-sulfamethoxazole are protected from *Listeria* infections. Cases, and especially outbreaks, should be reported immediately to public health authorities so that timely investigation can be initiated in order to interrupt transmission from the contaminated source.

ACKNOWLEDGMENTS

We would like to acknowledge Robert S. Baltimore, MD, for his contribution to this chapter and Michelle R. Rychalsky, PharmD, for reviewing antibiotic dosing regimens.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 235

Actinomyces

Hamid Bassiri

TAXONOMY AND MICROBIOLOGY

Members of the phylum Actinobacteria are common soil and water gram-positive bacteria with high guanine and cytosine DNA content and play important roles in the decomposition of organic materials. A proportion of Actinobacteria form filamentous and branching structures (similar to *Nocardia* spp.) that resemble fungal mycelia; these are included in the class Actinomycetia. The genus *Actinomyces* (which translates literally to "ray fungus") belongs to the order Actinomycetales (along with *Mycobacteria* and *Nocardia*) and family Actinomycetaceae and constitutes several microaerophilic to facultatively anaerobic nonmotile species that are fastidious and slow growing.

More than 50 species of *Actinomyces* have been identified using 16S rRNA sequencing, with more than half of these species associated with human infection. ***Actinomyces israelii*** is the predominant species causing human actinomycosis. Other species associated with infection include but are not limited to *A. odontolyticus, A. meyeri, A. naeslundii, A. graevenitzii, A. neuii,* and *A. turicensis.*

PATHOGENESIS AND EPIDEMIOLOGY

Actinomyces are commensal organisms of the human oropharynx and gastrointestinal and urogenital tracts, and infections by these organisms (termed **actinomycosis**) typically emanate from these anatomic sites. The hallmark of actinomycosis is contiguous spread that fails to respect tissue or fascial planes. As such, these infections can extend to contiguous structures and form abscesses and chronically suppurative granulomatous infections and sinus tracts. Cicatricial healing can then ensue, from which the organism can further spread by burrowing along fascial planes, causing deeply communicating scarred sinus tracts. Sites of infection show dense cellular infiltrates and suppuration that form many interconnecting abscesses and sinus tracts. Bacteremia and infections of more distal sites (such as endocarditis, pericarditis, and central nervous system [CNS] infections) have also been documented. Notably, polymicrobial infections are typical, especially with copathogens such as *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans,* as well as *Fusobacterium, Clostridia, Eikenella, Enterococcus, Bacteroides,* and *Peptostreptococcus* spp.

Knowledge regarding the epidemiology of actinomycosis is limited to case reports and case series. Based on these reports, actinomycosis appears to affect people of all ages, with no racial or ethnic predilection, seasonality, or occupational associations. Actinomycosis occurs in immunocompetent and immunocompromised hosts. However, pediatric actinomycosis only represents approximately 3% of reported cases. Risk factors in children include trauma, dental caries, debilitation, and poorly controlled diabetes. Although actinomycosis is not a common opportunistic infection, disease has been associated with corticosteroid use, leukemia, renal failure, congenital immunodeficiencies, HIV infection, and solid organ or hematopoietic stem cell transplantation.

Given the sites of colonization, the most common presentations of *Actinomyces* infections include cervicofacial, abdominal/pelvic, and thoracic regions (in order of frequency). Importantly, certain medical interventions can result in mucosal barrier injuries and infection. For instance, use of intrauterine contraceptive devices can predispose to pelvic actinomycosis, and aspiration events, poor dentition, and recent dental procedures can result in involvement of the thoracic region. However, more than one third of patients do not have an identifiable antecedent event that would explain the onset of actinomycosis. Importantly, actinomyces infections are not contagious.

DIAGNOSIS

Diagnosis of actinomycosis relies on identification of the organism in tissues of affected areas via culture, molecular methods, and/or histopathology. However, growth in cultures can take up to 2-3 weeks, and up to 50% of cultures may reveal no growth because of prior antibiotic exposure, failure to maintain anaerobic conditions during sample transport, or inadequate incubation.

The presence of **sulfur granules** on macroscopic or microscopic evaluation (Fig. 235.1) of involved tissue is suggestive of actinomycosis. Despite their name, these granules are not composed of sulfur, instead deriving this designation because of their typical yellow color on macroscopic appearance; they can also be white, gray, or brown. Similar granules can be formed by *Nocardia brasiliensis, Streptomyces madurae* (which can cause mycetomas), and *Staphylococcus aureus* (which can cause botryomycosis). Microscopically, these granules appear on hematoxylin-eosin or Gomori methenamine silver stains as masses of gram-positive, branching, filamentous rods surrounded by the host immune cells (e.g., polymorphonuclear neutrophils) and a milieu of eosinophilic staining inert material, often referred to as the **Splendore-Hoeppli phenomenon**. Notably, *A. meyeri* is nonbranching and *A. odontolyticus* does not form sulfur granules.

Nocardia are indistinguishable from *Actinomyces* on Gram stain, but *Nocardia* take up the modified acid-fast stain, whereas *Actinomyces* spp. do not. Although suggestive of actinomycosis, sulfur granules are often absent, and thus additional testing such as cultures are necessary for the diagnosis. Affected tissues can be cultured on

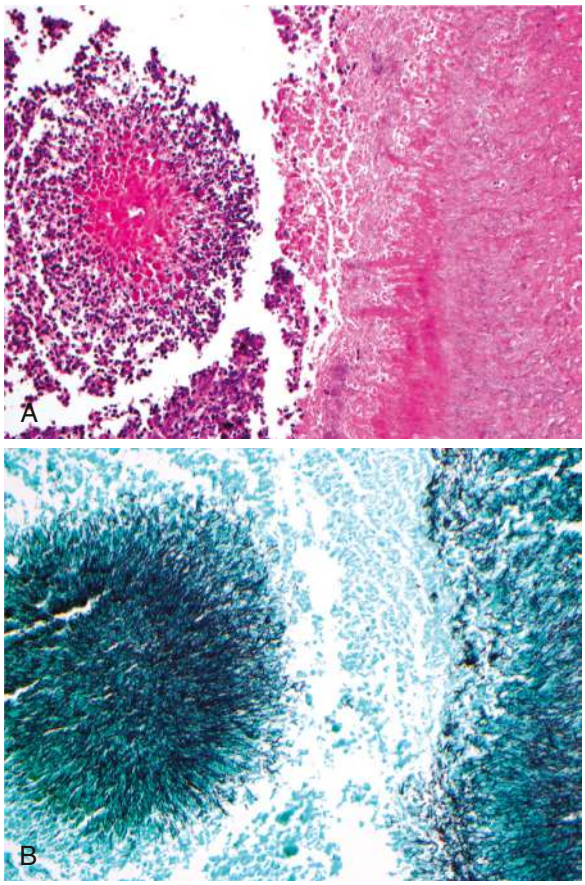

Fig. 235.1 Actinomycosis. **A,** Small cluster of *Actinomyces* on left, with sulfur granule and surrounding mixed inflammation demonstrating the Splendore-Hoeppli phenomenon (×200). **B,** Gomori methenamine silver stain of the same field, highlighting the filamentous forms (×200). *(From Johnson MM. Ear, nose, and throat infections. In: Kradin RL, ed. Diagnostic Pathology of Infectious Disease, 2nd ed. Philadelphia: Elsevier; 2018: Fig. 7.6.)*

brain-heart infusion agar incubated at 37°C anaerobically and aerobically to reveal organisms within the lines of streak at 24-48 hours. *A. israelii* colonies appear as loose masses of delicate, branching filaments with a characteristic spider-like growth. Unfortunately, even under the right conditions, it is challenging to grow *Actinomyces,* and the yield of different culturing techniques varies by species. Additionally, conventional biochemical testing for speciation is complex and may result in misclassifications. The evolution of diagnostic tools such as 16S rRNA sequence analysis and matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry has improved the accuracy of speciation of cultured organisms and highlighted the potential for detection of *Actinomyces* directly from the involved tissue without culture.

Importantly, actinomycosis is usually, if not always, **polymicrobial** in nature. In a large study of >650 cases, infection with *Actinomyces* was identified in pure culture in only 1 case. Cultures usually also identify other endogenous flora, including members of the **HACEK group**, which includes *Haemophilus* spp. (typically *H. aphrophilus, H. parainfluenzae,* or *H. paraphrophilus*), *A. actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae. A. actinomycetemcomitans* is a fastidious, gram-negative bacillus that is part of the oral flora and has been implicated in periodontal disease. Other bacteria frequently isolated concomitantly in human actinomycosis include *Fusobacterium, Bacteroides, Capnocytophaga,* and aerobic and anaerobic streptococci.

CT or MRI of involved areas is often employed in the initial patient evaluation. Imaging evidence of an invasive process spreading across tissue planes and ignoring anatomic boundaries is highly suggestive of actinomycosis. Furthermore, imaging can be helpful in establishing the extent of the infection, guiding subsequent diagnostic and therapeutic interventions, and monitoring for disease resolution.

COMMON CLINICAL PRESENTATIONS

Cervicofacial Actinomycosis

Cervicofacial disease is the most common form of pediatric actinomycosis and often manifests as a neck or submandibular mass that persists for weeks to months. Less than half of patients will have associated pain, and less than one third of patients will have fever. A minority of patients will report dysphagia or have a draining sinus (Fig. 235.2). Less frequently, cervicofacial actinomycosis manifests clinically as an acute pyogenic infection with a tender, fluctuant mass with trismus, firm swelling, and fistulas with drainage containing sulfur granules. Bone is not involved early in the disease, but periostitis, mandibular osteomyelitis, or perimandibular abscess may subsequently develop. Infection may spread through sinus tracts to cranial bones, possibly leading to meningitis. The ability of *Actinomyces* to burrow through tissue planes, including the periosteum, is a key difference between actinomycosis and nocardiosis. Whereas predisposing factors for cervicofacial actinomycosis are not well defined for children, adult cases are often preceded by a history of oral trauma, oral surgery, dental procedures, or caries, facilitating entry of organisms into cervicofacial tissues.



Fig. 235.2 A 2-yr-old male with HIV infection who has cervicofacial actinomycosis and a draining fistula.

Abdominal and Pelvic Actinomycosis

Of all the forms of actinomycosis, delayed diagnosis is most typical for abdominal and pelvic infection. A disruption of the mucosa of the gastrointestinal (GI) tract (e.g., acute GI perforation, abdominal trauma, prior abdominal surgery) is often postulated as the inciting event for adult-onset abdominopelvic actinomycosis. In pediatric patients, however, medical history sometimes fails to identify prior evidence of mucosal barrier injury. In a contemporary pediatric case series of abdominal and pelvic actinomycosis, prior abdominal surgery (all appendectomies) was reported in only 21% of patients and dental caries in 11%. In two thirds to three fourths of patients, the presenting signs are abdominal pain and a palpable mass on physical exam. Fever accompanies the abdominal pain in more than half of cases, with weight loss in almost one third. As with other forms of actinomycosis, abdominopelvic infection can spread across tissue planes by contiguous extension involving any tissue or organ, including muscle, solid abdominopelvic viscera, and walls of the intestinal tract. Imaging studies may reveal a mass with invasion of tissue planes, leading to misdiagnosis of malignancies, inflammatory bowel disease with fistulae, or abdominal tuberculosis. Genitourinary actinomycosis is often associated with use of intrauterine contraceptive devices (IUDs) in adults and can mimic gynecologic tumors, but these infections are quite rare in adolescents. Because of delays in diagnosis, more than one third of pediatric cases present with draining sinus fistulae.

Thoracic Actinomycosis

Thoracic actinomycosis may present with cough, chest pain, hemoptysis, and fever. In a retrospective review of reported pediatric cases of thoracic infection, almost half presented with a chest wall mass. Additional symptoms such as cough, fever, chest pain, and weight loss were reported in <40% of patients. Radiographic imaging may reveal hilar lymphadenopathy, endobronchial infection, tumor-like lesions, diffuse pneumonia, pleural effusions, or abscesses with or without cavitation and parenchymal lung destruction. These abscesses can also form sinus tracts to the diaphragm or mediastinum, which are often pathognomonic for actinomycosis. Other complications include bony destruction of adjacent ribs, sternum, and vertebral bodies. Multiple lobe involvement of the lungs is occasionally found. Importantly, evidence of thoracic actinomycosis can be found incidentally on radiographs ordered for noninfectious concerns. The variation in presentation and indolent nature of thoracic actinomycosis often delay the diagnosis.

Other Forms of Actinomycosis

CNS actinomycosis is often the result of hematogenous spread to the brain parenchyma from a distant site but can also ensue from contiguous spread from a cervicofacial lesion. The former often results in multiple brain abscesses. **Laryngeal** actinomycosis rarely has been reported in older teenagers. Oropharyngeal colonization with *Actinomyces* may be involved in the development of obstructive tonsillar hypertrophy. Severe forms of **periodontitis**, particularly localized juvenile periodontitis, are associated with *Actinomyces,* especially in adolescents. *Actinomyces* has a propensity for infecting heart valves, a process that results in subacute endocarditis, with fever present in less than half of cases.

DIFFERENTIAL DIAGNOSIS

Actinomycosis has been referred to as a "great imitator" with presentations that mimic appendicitis, pseudoappendicitis caused by *Yersinia enterocolitica,* amebiasis, malignancy, and inflammatory bowel disease. Actinomycosis must be differentiated from other chronic infections,

including tuberculosis, nocardiosis, polymicrobial bacterial infections, and fungal infections.

TREATMENT

Most cases of actinomycosis can be managed with antibiotics, although surgery can be adjunctive and may shorten the duration of antibiotic use. Routine susceptibility testing is not typically performed, as most *Actinomyces* spp. are susceptible to penicillin. Accordingly, penicillin G is the drug of choice for parenteral therapy, and penicillin V or amoxicillin is the preferred enteral antibiotic. Because actinomycosis is often found to be polymicrobial in nature, use of combination β-lactam/β-lactamase inhibitors (e.g., ampicillin-sulbactam or amoxicillin-clavulanate) may be warranted, especially if there is an initial poor response. In particular, ***A. actinomycetemcomitans*** is a copathogen in at least 30% of cases of actinomycosis. Failure to recognize this organism and treat it adequately has resulted in clinical relapse and deterioration.

Treating actinomycosis in a patient with a penicillin allergy can be challenging, as there is variation in susceptibility by *Actinomyces* spp. to other antibiotic classes; alternatives generally include cephalosporins, carbapenems, macrolides, and tetracyclines. Despite being anaerobic, a large percentage of *Actinomyces* are not susceptible to metronidazole, and isolates are variably susceptible to clindamycin. Fluoroquinolones and aminoglycosides have little to no activity against *Actinomyces* spp. Infectious disease specialists should be consulted to guide antibiotic usage in patients with penicillin allergy or deep-seated infections such as brain abscesses, endocarditis, or osteomyelitis. Commercially available sensitivity testing methods are available and can be employed in patients with severe disease or poor response to initial therapy.

No definitive comparative effectiveness data exist to guide the optimal route and duration of therapy. For severe or extensive infections, most experts recommend initial parenteral administration of antibiotics for 4-6 weeks and then transitioning to enteral therapy upon documentation of clinical improvement. The exceptions include endocarditis and CNS disease, which generally require parenteral administration for the entire course of therapy. In cases of mild or limited disease, enteral antibiotics could be considered even at initiation. Given concern for relapses, antibiotics are often continued for several months, with total durations ranging between 2-6 months for mild/limited disease and 6-12 months for severe/extensive disease. Shorter courses of antibiotic therapy can result in relapses, especially in cases of thoracic actinomycosis without surgical debridement. Longer courses up to 18 months have also been used in invasive disease and in immunocompromised patients. At the same time, courses of antibiotic therapy <3 months have been used successfully in cases of local disease, especially after surgical resection. Close follow-up and monitoring are indicated in patients treated with short courses of antibiotics. The total duration of treatment is often ultimately dictated by the location of the infection and follow-up clinical exams and imaging.

Traditionally, an adjunctive surgical intervention was thought to be necessary for a successful outcome. However, in some case series a subset of patients have responded well to medical management alone. In the setting of significant abscesses and/or sinus tracts, a surgical approach to establish source control and, if possible, completely resect involved issue can hasten clinical improvement. The morbidity of the surgical procedure needs to be weighed against the potential benefits for each patient.

PROGNOSIS

The prognosis is excellent with early diagnosis, prompt initiation of antibiotic therapy, adherence to a prolonged course of antibiotics, and adequate surgical debridement, if necessary. Despite a good overall prognosis, permanent scarring can still develop. Although actinomycosis can present in immunocompetent children, disseminated or recalcitrant actinomycosis should raise suspicion for immunodeficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 236

Nocardia

Coralee Del Valle Mojica

Various *Nocardia* species have been identified causing localized and disseminated disease in children and adults. These organisms are predominantly opportunistic pathogens infecting immunocompromised individuals, but cases in immunocompetent hosts are increasingly reported. Infection caused by these bacteria is termed *nocardiosis,* which consists of acute, subacute, or chronic suppurative manifestations.

ETIOLOGY

Nocardia spp. are a complex group of environmental, gram-positive bacteria that belong to aerobic actinomycetes. They can grow on diverse media (e.g., blood agar, brain-heart infusion agar, Lowenstein-Jensen media, buffered charcoal-yeast extract [BCYE], Sabouraud dextrose agar) and have been referred to as bacteria that masquerade as fungi, sometimes misdirected to the mycology or mycobacteriology section of clinical laboratories for identification. Colonies can appear as early as 48 hours, but typically growth of *Nocardia* is slower than in other bacteria and may take 1-2 weeks. Growth appears as waxy, folded, or heaped colonies at the edges, and yield is best achieved in conditions that include a temperature of 37°C (98.6°F) with 10% carbon dioxide. However, many isolates of *Nocardia* are thermophilic and will grow at temperatures up to 50°C (122°F). Microscopically, *Nocardia* spp. are weakly gram-positive, rod-shaped, filamentous bacteria. For some isolates, there may be alternating areas of gram-positive and gram-negative staining, giving a beaded appearance often described with *Nocardia*. These organisms are also weakly acid-fast, and the modified Kinyoun acid-fast staining technique can be helpful to identify organisms from clinical specimens such as a tissue biopsy or bronchoalveolar lavage (BAL).

To date, more than 80 species of *Nocardia* have been described and 50 species have been identified to be human pathogens. The distribution of *Nocardia* spp. causing disease varies across studies, partly because of revisions in taxonomic classification over time. A retrospective study looking at isolates in the United States from 1995 to 2004 reported *N. nova, N. brasiliensis,* and *N. farcinica* as the most common species. In contrast, a more recent study from China reported *N. otitidiscaviarum* as the most common species, and a systematic review from Iran from 1992 to 2021 reported *N. asteroides* and *N. cyriacigeorgica* as the two most common species. Species identification can be critical for optimal clinical outcomes because of variability in virulence strategies and antibiotic-resistance profiles. Traditional approaches to speciation require biochemical processing that can be laborious and inefficient. Techniques such as 16S rDNA polymerase chain reaction (PCR) or matrix-assisted laser desorption/ionization (MALDI) time of flight (TOF) mass spectrometry are now considered the gold standard.

EPIDEMIOLOGY

Once thought to be a rare human disease, nocardiosis is being recognized more frequently and has been diagnosed in people of all ages. Pediatric patients with compromised cellular immunity are at particular risk, including children receiving immune suppression after solid organ or stem cell transplantation, chemotherapy for malignancy, prolonged corticosteroid therapy, children with poorly controlled HIV infection, or those with a primary immunodeficiency, especially chronic granulomatous disease. Notably, nocardiosis has been described in patients without an identified immune defect, although in these clinical scenarios, other predisposing factors such as bronchiectasis are often present.

Due to the lack of a national reporting system for *Nocardia* infections and the molecular advances impacting the classification of this organism, measuring the incidence of the disease remains a challenge. Current knowledge of nocardiosis incidence in the United States is based on a historical survey of 171 infectious diseases physicians from 1974 and isolates received at the CDC reference laboratory, estimating 500-1000 cases annually. Prevalence estimates in high-risk populations have been reported to be less than 1%, with conflicting reports about the trends of infections in different geographic locations around the world.

PATHOGENESIS

Nocardia organisms are environmental saprophytes that are ubiquitous in soil and decaying vegetable matter and have been isolated from soil worldwide. Infection can be acquired via inhalation or direct cutaneous inoculation, including after arthropod and cat bites. From 70% to 80% of *Nocardia* infections originate in the pulmonary parenchyma, with 10–25% being primary cutaneous disease.

Nocardia can disseminate from the primary site of infection to any organ or any musculoskeletal location. Dissemination after primary lung infection is common, occurring in 15–50% of patients; those with an underlying immunocompromised condition are more likely to have disseminated disease. The central nervous system (CNS) is the most concerning and most common secondary site of infection, complicating as much as 25% of pulmonary disease. Although rare, isolated CNS disease has been described. Whereas most cases are the result of environmental exposure, *Nocardia* species diversity in the hospital environment has been reported as a reservoir for the development of nosocomial infections.

CLINICAL AND RADIOGRAPHIC MANIFESTATIONS

The clinical presentation can be nonspecific, with fever reported in approximately 60% of patients, cough in 30%, and dyspnea in 25%. Extrapulmonary signs and symptoms can correspond to the site of infection. In particular, neurologic deficit has been reported in up to 25% of all cases and in more than 50% of patients with CNS involvement. Neurologic complaints can include headache, confusion or altered mental status, weakness, and speech impairment. Renal nocardiosis can cause dysuria, hematuria, or pyuria, and gastrointestinal (GI) involvement may be associated with nausea, vomiting, diarrhea, abdominal distention, or melena. Skin infection can manifest with nodular lymphangitis (Fig. 236.1). Mycetoma is a chronic, progressive infection developing days to months after inoculation, usually on a distal location on the limbs. Musculoskeletal, endovascular, and ocular infections have also been reported.

Given the nonspecific symptoms and signs of nocardiosis (with the exception of cutaneous lesions), radiographic imaging is often necessary to define the location and extent of disease. Pulmonary infection can appear as a consolidation consistent with typical bacterial pneumonia or even as a necrotizing pneumonia with or without a pleural effusion. Single or multiple nodules and cavitary lesions have also been described. Cavitary lesions are more common in patients with an underlying immunocompromising condition. CNS disease can take the form of meningitis or focal lesions. Meningitis presents as neutrophil- or lymphocyte-predominant pleocytosis, elevated cerebrospinal fluid protein, and hypoglycorrhachia. For focal lesions, CT or MRI of the brain often reveals single- or multiple-ring enhancing lesions. Similar to the brain, when other organs or soft tissues are involved, CT or MRI also typically reveals single- or multiple-ring enhancing lesions, suggestive of an abscess or abscesses.

DIAGNOSIS

Microbiologic evidence is necessary to confirm the diagnosis of nocardiosis. In one systematic review, blood cultures were the only positive microbiologic specimen in 38% of cases, thus serving as an important noninvasive diagnostic test for nocardiosis. In the remaining patients, an invasive procedure such as bronchoscopy, tissue biopsy, or abscess aspiration is necessary to procure specimens for diagnostic testing. Histopathologic staining of such material can reveal beaded, weakly gram-positive or modified acid-fast filamentous bacteria. Histopathology can also show delicately branching bacteria with a proclivity to fragment.

Molecular methodologies, specifically gene sequencing, have become the most accurate for definitively identifying *Nocardia* to the species level. Speciation of *Nocardia* is becoming increasingly reliant on 16S rDNA PCR or MALDI-TOF technologies, with a specificity of 74% and a sensitivity of 88% in a multicenter study assessing the performance of 16S sequencing in 68 patients with proven or probable nocardiosis. Given that *Nocardia* spp. can colonize the respiratory airway, a sputum or BAL culture that yields a *Nocardia* species is not itself confirmatory of nocardiosis. However, a positive microbiologic test for a *Nocardia* species from one of these specimens in conjunction with the clinical and radiographic findings is strongly supportive of nocardiosis.

When a diagnosis of nocardiosis is made, strong consideration should be given to evaluation for disseminated disease, even in the absence of signs or symptoms, especially in the immunocompromised host. Although data are limited, most experts agree that, at a minimum, MRI of the brain should be performed in the immunocompromised host with nocardiosis.

TREATMENT

The choice, dose, and duration of antimicrobial treatment depend on the site and extent of infection, immune status of the patient, initial clinical response, and species and susceptibility testing of the *Nocardia* isolate. Several therapeutic options exist for the treatment of nocardiosis; however, there are no comparative effectiveness studies to inform the optimal therapeutic regimen. **Trimethoprim-sulfamethoxazole (TMP-SMX)** is the sulfonamide formulation that is recommended, although sulfadiazine and sulfisoxazole have been used. Increasing recognition of resistance to TMP-SMX across and within *Nocardia* spp. highlights the importance of speciation of *Nocardia* isolates and of performing sensitivity testing in a certified microbiology laboratory. TMP-SMX resistance rates as high as 42% have been reported. Administration of TMP-SMX as prophylaxis against *Pneumocystis jirovecii* pneumonia is not always protective against nocardiosis, and thus clinicians should not exclude this diagnosis from the differential in patients receiving TMP-SMX prophylaxis.



Fig. 236.1 A 9-yr-old healthy child with infected knee laceration (A) 10 days after falling onto concrete in his school playground, complicated by nodular lymphangitis (B). *(From Williams PCM, Bartlett AW, Palasanthiran P, McMullan B. A not so innocuous playground fall: lymphocutaneous nocardiosis in an immunocompetent boy. Arch Dis Child. 2022;107[3]:257–258, Figs. 1 and 2.)*

Other antibacterial agents with in vitro activity against *Nocardia* spp. include but are not limited to **amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, and minocycline**. A recent study profiling the antimicrobial susceptibility pattern of a diverse range of *Nocardia* revealed that among 146 isolates, the susceptibilities were 100% to linezolid, 96% to amikacin, 94% to TMP-SMX, and 76% to imipenem. A similar retrospective study conducted in the United States from 1995 to 2004 revealed that 42% of the isolates were resistant to TMP-SMX. Therefore while awaiting sensitivity testing in patients with *Nocardia* isolated from a clinical specimen, it may be reasonable to administer linezolid empirically, taking into account local susceptibility data. Subsequent therapeutic decisions should be guided by final sensitivity results and consideration of the site of infection and pharmacokinetics of the available agents. It is not clear whether parenteral administration is superior to enteral formulations. However, most experts support the use of parenteral therapy for more severe disease, including endocarditis and CNS disease.

In vitro and in vivo animal models have suggested the benefit of combination regimens for the treatment of nocardiosis. There are no clinical data to confirm the need for combination therapy; however, based on the preclinical data, there is expert support for using combination therapy in CNS nocardiosis, in disseminated disease, and in children with an underlying immunocompromising condition. A variety of combination therapies have been suggested, with many experts favoring TMP-SMX, amikacin, and a carbapenem or third-generation cephalosporin. Since data on combination therapy are limited, antibiotic choices should primarily be guided by sensitivity testing of the clinical *Nocardia* isolate.

Surgical drainage of abscesses can be helpful in hastening resolution of nocardiosis. However, no comparative data have documented improvement in overall outcomes with adjunctive surgical intervention, and success has been reported with medical management alone in resolving deep-seated abscesses, even in the CNS. A literature review showed that among patients with CNS nocardiosis, 1-year overall mortality was approximately 20%, limited by cases lost to follow-up. Among patients who were treated with a combination of antibiotics and neurosurgical procedures, mortality was lower (7%). Therefore the decision to intervene surgically needs to be balanced with the potential consequences of a surgical procedure to drain an abscess. Intraventricular antibiotics have been reported.

The necessary duration of therapy for nocardiosis varies depending on the clinical presentation and the status of the patient. The optimal duration is uncertain, but long-term therapy is common because of the propensity for relapse. Historically, superficial cutaneous infection has been treated for 3 months, pulmonary or systemic nocardiosis has been treated for 6-12 months, and CNS infection has been treated for at least 12 months. These intervals should only be considered as a guide for expected therapeutic durations. The ultimate duration should be dictated by clinical and radiographic resolution of disease.

PROGNOSIS

Historically, nocardiosis has been associated with significant mortality. Fortunately, more recent reports have documented an improved rate of complete cure to approximately 80%. Predictably, attributable case fatality rates vary by disease entity. There is no attributable case fatality associated with cutaneous disease, but 10–20% attributable case fatality has been assigned to disseminated and visceral disease. CNS disease has the highest attributable case fatality rates, reaching 25%. Importantly, much of the data on case fatality rates are informed by predominantly adult cohorts, and thus there may be fewer fatal outcomes in children. Nonetheless, early diagnosis and intervention are important to reduce the morbidity and mortality of nocardiosis, especially in immunocompromised patients at increased risk for disseminated disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 5

Gram-Negative Bacterial Infections

Chapter 237

Neisseria meningitidis (Meningococcus)

Manish Sadarangani

Neisseria meningitidis (the meningococcus) is a commensal of the human nasopharynx in approximately 10% of the population and, on rare occasions, enters the bloodstream to cause devastating invasive disease such as meningitis and meningococcal septicemia (meningococcemia). Although a rare endemic disease in most countries, the epidemiology of meningococcal disease varies widely over time and in different geographic regions, with both hyperendemic and epidemic disease patterns occurring. Onset of disease in susceptible individuals may be very rapid, within hours, and the case fatality rate is high, especially among those presenting with septic shock, despite access to modern critical care. Individual susceptibility is known to involve a complex relationship among environmental, host, and bacterial factors, and prevention of meningococcal disease through behavior modification (e.g., avoiding tobacco smoke) and vaccination offers the best prospect for control.

ETIOLOGY

N. meningitidis is a gram-negative, fastidious, encapsulated, oxidase-positive, aerobic diplococcus. Differences in the chemistry of the polysaccharide capsule allow definition of 12 (previously thought to be 13) serologically distinct meningococcal capsular groups, of which 6, designated A, B, C, W (previously designated W135), X, and Y, are responsible for almost all cases of disease. Meningococcal strains may be subclassified on the basis of antigenic variation in two porin proteins found in the outer membrane, **PorB** (serotype) and **PorA** (serosubtype), and **lipopolysaccharide** (immunotype), using serology. Serologic typing is being replaced by molecular typing methods, which target genes under immune selection to provide **antigen sequence typing** (based on amino acid variation in various surface proteins, including PorA and FetA). Sequencing of antigen genes (e.g., *porA, fHbp, nadA, nhba*) is an important means of monitoring pressure on meningococcal populations by protein-based vaccines containing these antigens. Because meningococci readily exchange genetic material, typing based on a few antigens cannot provide an accurate picture of relatedness of strains, an important goal in monitoring epidemiology. **Multilocus sequence typing**, which types meningococci using variation in seven housekeeping genes, has been widely used to map the distribution of genetic lineages of meningococci (http://pubmlst.org/neisseria/) and provides a clearer picture of the genetic and epidemiologic relatedness of strains. To provide still better definition of genetic variation, in some countries, including the United Kingdom, **whole genome sequencing** is used to type meningococci and appears set to replace both antigen and multilocus sequence typing as costs continue to fall. The application of molecular approaches to epidemiology has established that (1) endemic meningococcal disease is caused by genetically heterogeneous strains, although only a small number of genetic lineages are associated with the majority of cases of invasive disease, and (2) outbreaks are usually clonal, caused by single strains.

EPIDEMIOLOGY

Meningococci are transmitted during close contact through aerosol droplets or exposure to respiratory secretions, as by kissing. The organism does not survive for long periods in the environment. Enhanced rates of mucosal colonization and increased disease risk are associated with activities that increase the likelihood of exposure to a new strain or increase proximity to a carrier, thus facilitating transmission, including kissing, bar patronage, binge drinking, attendance at nightclubs, men having sex with men, and living in freshman college dormitories. Factors that damage the nasopharyngeal mucosa, such as smoking and respiratory viral infection (notably influenza), are also associated with increased rates of carriage and disease, perhaps by driving upregulation of host adhesion molecules that are receptors for meningococci. Carriage is unusual in early childhood and peaks during adolescence and young adulthood.

Meningococcal disease is a global problem, but disease rates vary by a factor of 10- to 100-fold in different geographic locations at one point in time and in the same location at different times. Most cases of meningococcal disease are sporadic, but small outbreaks (usually in schools or colleges, representing <3% of U.S. cases), **hyperendemic** disease (increased rates of disease persisting for a decade or more as a result of a single clone), and epidemic disease are all recognized patterns. However, over the past decade, rates of meningococcal disease have declined in most industrialized countries, partly through introduction of immunization programs and possibly aided by widespread legislation against smoking in public places. The arrival of hyperinvasive lineages and their eventual decline through development of natural immunity is recognized as a major driver of changes in disease rates over time. The U.S. disease rate was 1.1 cases per 100,000 population in 1999 but had fallen to 0.11 per 100,000 by 2019 (Fig. 237.1). By contrast, the rate of disease in Ireland in 1999 was >12 per 100,000, and rates of 1,000 per 100,000 have been described during epidemic disease in sub-Saharan Africa. Disease caused by dominant hyperendemic clones has been recognized in the past 2 decades in Oregon, United States; Quebec, Canada; Normandy, France; and across New Zealand. Laboratory data underreport meningococcal disease incidence rates because up to 50% of cases are not culture confirmed, particularly where prehospital antibiotics are recommended for suspected cases. In the United Kingdom, polymerase chain reaction (PCR) methods are used routinely for diagnosis of suspected cases, doubling the number of confirmed cases.

The highest rate of meningococcal disease occurs in infants <1 year old, probably as a result of *immunologic inexperience* (antibody that recognizes meningococcal antigens is naturally acquired during later childhood), immaturity of the alternative and lectin complement pathways, and perhaps the poor responses made by infants to bacterial polysaccharides. In the absence of immunization, incidence rates decline through childhood, except for a peak of disease among adolescents and young adults, which may be related to increased opportunity for exposure from social activities. The incidence of meningococcal disease is increased among persons with HIV infection.

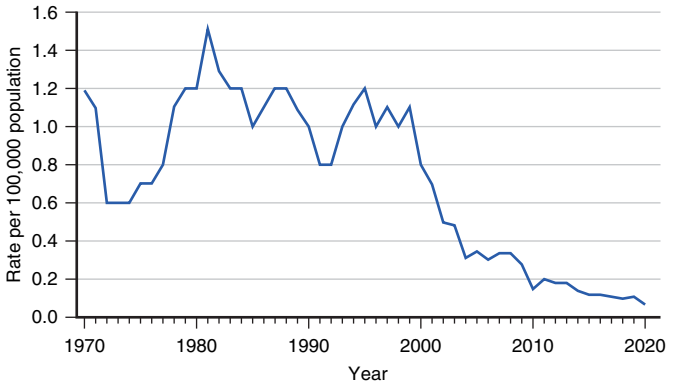

Fig. 237.1 Rate of meningococcal disease, by year—United States, 1970–2020. *(Modified from Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2013;62[RR-2]:1–28, updated with data from the CDC meningococcal surveillance data tables: https://www.cdc.gov/meningococcal/surveillance/surveillance-data.html#figure01.)*

In the United States, most cases of disease in the first 5 years of life are caused by capsular **group B** strains. After age 5 years, disease cases are mostly distributed among capsular groups C, W, and Y. In most other industrialized countries, capsular group B strains predominate at all ages, in part because of introduction of routine capsular **group C** meningococcal conjugate vaccine among infants and/or toddlers. For unclear reasons, disease in children caused by group Y strains was uncommon in the United States before the 1990s and then began to increase. Rates of disease caused by this capsular group have also increased in several other countries but are declining in the United States. Disease caused by capsular **group W** strains has increased in the United Kingdom and in other countries in Europe and Australia as a result of a hyperinvasive clone, which appears to have originated in Latin America.

Large outbreaks of capsular **group A** meningococcal disease occurred during and immediately after the First World War and Second World War in both Europe and the United States, but since the 1990s, almost all cases caused by capsular group A strains have occurred in Eastern Europe, Russia, and developing countries. The highest incidence of capsular group A disease has occurred in a band across sub-Saharan Africa, the *meningitis belt,* with annual endemic rates of 10-25 per 100,000 population. For more than a century, this region has experienced large capsular group A epidemics every 7-10 years, with annual rates as high as 1,000 per 100,000 population. The onset of cases in the sub-Saharan region typically begins during the dry season, possibly related to drying and damage to the nasopharyngeal mucosa; subsides with the rainy season; and may reemerge the following dry season. Rates of capsular group A meningococcal disease are currently falling across this region as a result of a mass vaccine implementation targeting strains bearing the A polysaccharide. However, both endemic and epidemic meningococcal disease in this region is also caused by capsular groups C, W, and X strains. Capsular group A and **group X** are infrequent causes of disease in other areas of the world, although both A and W strains have been associated with outbreaks among pilgrims returning from the Hajj.

PATHOGENESIS AND PATHOPHYSIOLOGY

Colonization of the nasopharynx by *N. meningitidis* is the first step in either carriage or invasive disease. Disease usually occurs 1-14 days after acquisition of the pathogen. Initial contact of meningococci with host epithelial cells is mediated by pili, which may interact with the host CD46 molecule or an integrin. Close adhesion is then mediated by Opa and Opc binding to carcinoembryonic antigen (CEA) cell adhesion molecule receptors and integrins, respectively. Subsequent internalization of meningococci by epithelial cells is followed by transcytosis through to the basolateral tissues and dissemination into the bloodstream. Immunoglobulin A_1 protease secreted by invasive bacteria degrades secretory IgA on the mucosal surface, circumventing this first-line host defense mechanism.

Once in the bloodstream, meningococci multiply rapidly to high levels to cause septicemia (**meningococcemia**). Patients with a higher bacterial load have a more rapid clinical deterioration and longer period of hospitalization, as well as a higher risk of death and permanent sequelae. Resistance to complement-mediated lysis and phagocytosis is largely mediated by the polysaccharide capsule and **lipopolysaccharide (LPS)**. Outer membrane vesicles released from the surface of the organism contain LPS, outer membrane proteins, periplasmic proteins, and phospholipid and play a major role in the inflammatory cascade that leads to severe disease.

Much of the tissue damage is caused by host immune mechanisms activated by meningococcal components, in particular LPS. During invasive disease LPS is bound to a circulating plasma protein known as *LPS-binding protein.* The host receptor complex for LPS consists of toll-like receptor (TLR)-4, CD14, and myeloid differentiation protein 2. Binding of LPS to TLR-4, which is upregulated on circulating leukocytes during septicemia, results in activation of a number of different cell types. An intense inflammatory reaction results from secretion of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin

(IL)-1β, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor, levels of which are closely associated with plasma levels of LPS. The major antiinflammatory cytokines IL-1Rα, IL-2, IL-4, and IL-12 and transforming growth factor-β are present at very low levels. Both high and low levels have been observed for IL-10 and interferon-γ.

The pathophysiologic events that occur during meningococcal septicemia are largely related to microvascular injury. This injury leads to increased vascular permeability and capillary leak syndrome, pathologic vasoconstriction and vasodilation, disseminated intravascular coagulation (DIC), and profound myocardial dysfunction. Increased vascular permeability can lead to dramatic fluid loss and severe hypovolemia. **Capillary leak syndrome** with or without aggressive fluid resuscitation (which is essential in severe cases) leads to pulmonary edema and respiratory failure. Initial vasoconstriction is a compensatory mechanism in response to hypovolemia and results in the clinical features of pallor and cold extremities. After resuscitation, some patients experience **warm shock**, that is, intense vasodilation with bounding pulses and warm extremities, despite persistent hypotension and metabolic acidosis. Virtually all antithrombotic mechanisms appear to be dysfunctional during meningococcal sepsis, leading to a procoagulant state and DIC. All these factors contribute to depressed myocardial function, but there is also a direct negative cytokine effect on myocardial contractility, thought to be largely mediated by IL-6. Hypoxia, acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypophosphatemia are all common features in severe septicemia and further depress cardiac function. Some patients become unresponsive to the positive inotropic effects of catecholamines and require high levels of inotropic support during intensive care management. These processes result in impairment of microvascular blood flow throughout the body and ultimately lead to **multiorgan failure**, which is responsible for much of the mortality.

After invasion of the circulation, meningococci may also penetrate the blood-brain barrier and enter the cerebrospinal fluid (CSF), facilitated by pili and possibly Opc. Once there, bacteria continue to proliferate, and LPS and other outer membrane products can stimulate a proinflammatory cascade similar to that observed in the blood. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. Central nervous system damage occurs directly by meningeal inflammation and indirectly by circulatory collapse and causes a high rate of neurologic sequelae in affected patients. Death can occur from cerebral edema, which leads to **increased intracranial pressure (ICP)** and cerebral or cerebellar herniation.

Immunity

There is an inverse correlation between the incidence of disease and the prevalence of complement-dependent **serum bactericidal antibody (SBA)**. The level of SBA is highest at birth and among adults and lowest in children between 6 months and 2 years of age, when the highest incidence of disease occurs. Such antibodies are naturally elicited by asymptomatic carriage of pathogenic and nonpathogenic *Neisseria,* such as *Neisseria lactamica,* and other antigenically related gram-negative bacteria. A similar relationship was described for capsular groups A, B, and C. Vaccine trials support these earlier findings. For the meningococcal capsular group C conjugate vaccine, an SBA titer ≥1:8 correlated strongly with postlicensure vaccine effectiveness. For capsular group B disease, the data are less certain, but the proportions of capsular group B vaccine recipients with more than fourfold rises in SBA after vaccination or SBA titers ≥1:4 have been correlated with clinical effectiveness in studies of outer membrane vesicle vaccines. These cutoffs are therefore currently used for regulatory approval of new meningococcal vaccines. The strong association between disease risk and genetic variation in human complement factor H further supports the importance of complement-mediated protection against disease.

There is evidence that mechanisms other than complement-dependent bactericidal antibodies may be important in determining protection against meningococcal disease. Disease in individuals with complement deficiency has a different age distribution, has less severe clinical features, and often involves unusual capsular groups. In particular, complement deficiency does not appear strongly related to an increased risk of capsular group B disease. Alternative surrogate markers of protection include the opsonophagocytic assay and antibody avidity, but no studies have attempted to link these laboratory tests with vaccine efficacy or even population protection, as has been found with SBA.

Host Factors

Host susceptibility is strongly related to age, as previously described, indicating that immunologic responsiveness and/or naïveté in infancy and early childhood are key determinants of risk. **Complement** is a key factor in protection against meningococcal disease. Individuals with inherited deficiencies of properdin, factor D, or terminal complement components have up to a 1,000-fold higher risk for development of meningococcal disease than complement-sufficient people. The risk of meningococcal disease is also increased in patients with acquired complement deficiencies associated with diseases such as nephrotic syndrome, systemic lupus erythematosus (SLE), and hepatic failure and in patients treated with eculizumab, a monoclonal antibody against complement protein C5.

Among those with complement deficiencies, meningococcal disease is more prevalent during late childhood and adolescence, when carriage rates are higher than in children <10 years old; meningococcal infections in these patients may be recurrent. Although meningococcal disease can occasionally be overwhelming in patients with late complement component deficiency, cases are more typically described as being less severe than in complement-sufficient persons (with properdin deficiency being the exception), perhaps reflecting that these cases are often caused by unusual capsular groups. In one study, one third of individuals with meningococcal disease caused by capsular groups X, Y, and W had a complement deficiency. Although protective against early infection, extensive complement activation and bacteriolysis may contribute to the pathogenesis of severe disease once bacterial invasion has occurred.

The sibling risk ratio for meningococcal disease is similar to that for other diseases where susceptibility shows polygenic inheritance, and a number of host genetic factors have now been identified to affect either susceptibility to meningococcal disease or severity of disease. The molecules implicated include proteins on epithelial surfaces, the complement cascade, pattern recognition receptors, clotting factors, and inflammatory mediators. Deficiencies in the complement pathways are consistently associated with an increased risk of meningococcal disease, with specific polymorphisms in mannose-binding lectin and factor H found to be associated with disease susceptibility. A genome-wide association study of 7,522 individuals in Europe identified single nucleotide polymorphisms (SNPs) within the *CFH* and *CFHR3* genes that were associated with host susceptibility to meningococcal disease. Complement-mediated bacteriolysis is known to be extremely important in protection against meningococcal disease, giving these associations biologic plausibility. In particular, factor H attaches to various binding proteins expressed on the bacterial surface, downregulating complement activation and allowing the organism to evade host responses.

In terms of disease severity, a meta-analysis of data from smaller studies found that SNPs in genes encoding plasminogen activator inhibitor 1 *(SERPINE1)*, IL-1 receptor antagonist *(IL1RN),* and IL-1β *(IL1B)* are associated with increased mortality from meningococcal disease, as reflected in pathophysiologic changes that occur during invasive disease.

CLINICAL MANIFESTATIONS

The most common form of meningococcal infection is asymptomatic carriage of the organism in the nasopharynx. In the rare cases where invasive disease occurs, the clinical spectrum of meningococcal disease varies widely, but the highest proportion of cases present with meningococcal meningitis (30–50%). Other recognized presentations include bacteremia without sepsis, meningococcal septicemia with or without meningitis, pneumonia, chronic meningococcemia, and occult bacteremia. Focal infections in various sites (e.g., myocardium, joints, pericardium, bone, eye, peritoneum, sinuses, middle ear) are well recognized, and all may progress to disseminated disease. Urethritis, cervicitis, vulvovaginitis, orchitis, and proctitis may also occur.

Acute meningococcal septicemia cannot be distinguished from other viral or bacterial infections early after onset of symptoms (Table 237.1). Typical nonspecific early symptoms include fever, irritability, lethargy, respiratory symptoms, refusal to drink, and vomiting. Less

Table 237.1 Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease, and Meningococcal Meningitis

	PREVALENCE RANGE (NUMBER OF STUDIES)		
SYMPTOM OR SIGN	**BACTERIAL MENINGITIS**	**MENINGOCOCCAL DISEASE**	**MENINGOCOCCAL SEPTICEMIA**
Fever	66–97% (10)	58–97% (7)	98% (1)
Vomiting or nausea	18–70% (10)	44–76% (6)	
Rash	9–62% (6)	59–100% (9)	70% (1)
Headache	3–59% (7)	16–49% (5)	40% (1)
Lethargy	13–87% (6)	36–65% (3)	59% (1)
Coughing	N/A (0)	15–27% (2)	33% (1)
Irritable or unsettled	21–79% (8)	36–67% (3)	32% (1)
Runny nose	N/A (0)	24% (1)	31% (1)
Muscle ache or joint pain	23% (1)	7–65% (3)	30% (1)
Refusing food or drink	26–76% (4)	13–60% (3)	27% (1)
Altered mental state*	26–93% (6)	45–81% (3)	N/A (0)
Stiff neck	13–74% (13)	5–71% (6)	N/A (0)
Impaired consciousness	60–87% (4)	10–72% (2)	N/A (0)
Unconsciousness	4–18% (4)	N/A (0)	N/A (0)
Chills or shivering	N/A (0)	39% (1)	N/A (0)
Photophobia	5–16% (2)	2–31% (5)	N/A (0)
Respiratory symptoms	25–49% (4)	16–23% (2)	N/A (0)
Breathing difficulty	13–34% (4)	11% (1)	N/A (0)
Cold hands or feet	N/A (0)	43% (1)	N/A (0)
Shock	8–16% (2)	27–29% (2)	N/A (0)
Seizures	14–38% (12)	7–17% (3)	N/A (0)
Diarrhea	21–29% (2)	7–9% (2)	N/A (0)
Abdominal pain or distention	17% (1)	4% (1)	N/A (0)
Leg pain	N/A (0)	11–37% (2)	N/A (0)
Thirst	N/A (0)	8% (1)	N/A (0)
Sore throat, coryza, or throat infection	18% (1)	24% (1)	N/A (0)
Ill appearance	N/A (0)	79% (1)	N/A (0)
Capillary refill time >2sec	N/A (0)	83% (1)	N/A (0)
Hypotension	N/A (0)	28% (1)	N/A (0)
Abnormal skin color	N/A (0)	19% (1)	N/A (0)
Bulging fontanel†	13–45% (4)	N/A (0)	N/A (0)
Ear infection or ear, nose, and throat infections‡	18–49% (5)	N/A (0)	N/A (0)
Chest infection	14% (1)	N/A (0)	N/A (0)
Brudzinski sign	11–66% (2)	N/A (0)	N/A (0)
Kernig sign	10–53% (3)	N/A (0)	N/A (0)
Abnormal pupils	10% (1)	N/A (0)	N/A (0)
Cranial nerve pair involvement	4% (1)	N/A (0)	N/A (0)

Table 237.1 Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease, and Meningococcal Meningitis—cont'd

	PREVALENCE RANGE (NUMBER OF STUDIES)		
SYMPTOM OR SIGN	**BACTERIAL MENINGITIS**	**MENINGOCOCCAL DISEASE**	**MENINGOCOCCAL SEPTICEMIA**
Toxic or moribund state	3–49% (2)	N/A (0)	N/A (0)
Back rigidity	46% (1)	N/A (0)	N/A (0)
Paresis	6% (1)	N/A (0)	N/A (0)
Focal neurologic deficit	6–47% (3)	N/A (0)	N/A (0)

*This includes confusion, delirium, and drowsiness.
†The age ranges in the four studies are 0-14 yr, 0-2 yr, 0-12 mo, and 0-13 wk.
‡One study reported the number of children and young people with ear, nose, and throat infections; the four other studies reported the number of ear infections only.
Classification of conditions presented in the table reflects the terminology used in the evidence.
N/A, Not applicable.
Data from National Collaborating Center for Women's and Children's Health (UK). Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. *NICE Clinical Guidelines, No 102.* London: RCOG Press; 2010.



Fig. 237.2 Meningococcemia. A maculopapular, nonhemorrhagic rash that subsequently became petechial. *(From Habif TP, ed. Clinical Dermatology, 6th ed. Philadelphia: Mosby; 2016: Fig 9-59.)*



Fig. 237.3 A, Purpuric rash in 3-yr-old child with meningococcemia. B, Purpura fulminans in 11-mo-old child with meningococcemia. *(From Thompson ED, Herzog KD. Fever and rash. In: Zaoutis L, Chiang V, eds. Comprehensive Pediatric Hospital Medicine. Philadelphia: Mosby; 2007: Figs. 62-6 and 62-7.)*

frequently, diarrhea, sore throat, and chills/shivering are reported. A maculopapular rash, which is indistinguishable from rashes seen after viral infections, is evident in approximately 10% of cases early in the course of infection (Fig. 237.2). Limb pain, myalgia, or refusal to walk may occur as the primary complaint in 7% of otherwise clinically unsuspected cases. As the disease progresses, cold hands or feet and abnormal skin color may be important signs, capillary refill time becomes prolonged, and a nonblanching or petechial rash will develop in >80% of cases. In fulminant meningococcal septicemia, the disease progresses rapidly over several hours from fever with nonspecific signs to septic shock characterized by prominent petechiae and purpura **(purpura fulminans)** with poor peripheral perfusion, tachycardia (to compensate for reduced blood volume resulting from capillary leak), increased respiratory rate (to compensate for pulmonary edema), hypotension (a late sign of shock in young children), confusion, and coma (resulting from decreased cerebral perfusion). Coagulopathy, electrolyte disturbance (especially hypokalemia), acidosis, adrenal hemorrhage, renal failure, and myocardial failure may all develop (Fig. 237.3). Meningitis may be present.



Fig. 237.4 Rash of chronic meningococcemia. *(From Persa OD, Jazmati N, Robinson N, et al. A pregnant woman with chronic meningococcaemia from Neisseria meningitidis with lpxL1-mutations. Lancet. 2014;384:1900.)*

Meningococcal meningitis is indistinguishable from meningitis caused by other bacteria. Nonspecific symptoms and signs (see Table 237.1), including fever and headache, predominate, especially in the young and early in the illness. Children <5 years old rarely report headache. More specific symptoms of photophobia, nuchal rigidity, bulging of the fontanel, and clinical signs of meningeal irritation may develop but are unusual in infants. Seizures and focal neurologic signs occur less frequently than in patients with meningitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*. A meningoencephalitis-like picture can occur, associated with rapidly progressive cerebral edema and death from increased ICP, which may be more common with capsular group A infection.

Occult meningococcal bacteremia manifests as fever with or without associated symptoms that suggest a minor viral infection. Resolution of bacteremia may occur without antibiotics, but sustained bacteremia leads to meningitis in approximately 60% of cases and to distant infection of other tissues.

Chronic meningococcemia, which occurs rarely, is characterized by fever, nontoxic appearance, arthralgia, headache, splenomegaly, and a maculopapular or petechial rash (Fig. 237.4). Symptoms are intermittent, with a mean duration of illness of 6-8 weeks. Blood culture results are usually positive, but cultures may initially be sterile. Chronic meningococcemia may spontaneously resolve, but meningitis may develop in untreated cases. Some cases have been associated with complement deficiency and others with sulfonamide therapy. One report indicates that up to 47% of isolates from patients with chronic meningococcemia (vs <10% in acute cases) have a pathogenic variant in the *lpxl1* gene, leading to a reduced inflammatory response and a milder course of infection.

DIAGNOSIS

The initial diagnosis of meningococcal disease should be made on clinical assessment to avoid delay in implementation of appropriate therapy. Laboratory findings are variable but may include leukocytopenia or leukocytosis, often with increased percentages of neutrophils and band forms, and anemia, thrombocytopenia, proteinuria, and hematuria. Elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may occur, but in patients with rapid onset of disease, these values may be within normal limits at presentation. Increased CRP in the presence of fever and petechiae makes the diagnosis likely. Hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, and metabolic acidosis, often with increased lactate levels, are common in patients with meningococcal septicemia. Patients with coagulopathy have decreased serum concentrations of prothrombin and fibrinogen and prolonged coagulation times.

A confirmed diagnosis of meningococcal disease is established by isolation of *N. meningitidis* from a normally sterile body fluid such as blood, CSF, or synovial fluid. Meningococci may be identified in a Gram stain preparation and/or culture of petechial or purpuric skin lesions, although this procedure is rarely undertaken, and occasionally are seen on Gram stain of the buffy coat layer of a centrifuged blood sample. Although blood culture may be positive in more than two thirds of cases before antibiotic use, culture results often are negative if the patient has been treated with antibiotics before collection of the culture specimen; data suggest that <50% are culture positive. Isolation of the organism from the nasopharynx is not diagnostic of invasive disease because the organism is a common commensal.

PCR using primers specific for meningococcal genes (e.g., *ctrA*) has high sensitivity and specificity for detection of meningococci using whole blood samples and has increased confirmation of suspected cases by >40% in the United Kingdom.

Lumbar puncture should be undertaken to establish a diagnosis of meningococcal meningitis in patients without contraindications, including presence of septic shock, coagulopathy, thrombocytopenia, respiratory distress, seizures, increased ICP, or local infection. In patients with meningococcal meningitis, the cellular and chemical characteristics of the CSF are those of acute bacterial meningitis, showing gram-negative diplococci in up to 75% of cases. CSF culture results may be positive in patients with meningococcemia in the absence of CSF pleocytosis or clinical evidence of meningitis; conversely, positive CSF specimens that are gram positive are sometimes culture negative. Overdecolorized pneumococci in Gram stain preparations can be mistaken for meningococci, and therefore empirical therapy should not be narrowed to *N. meningitidis* infection on the basis of Gram stain findings alone.

Detection of capsular polysaccharide antigens using rapid latex agglutination tests on CSF can support the diagnosis in cases clinically consistent with meningococcal disease, but the tests have not performed adequately in clinical practice (poor sensitivity and cross-reactivity of capsular group B test with *Escherichia coli* K1 antigen) and have been replaced by molecular diagnostic methods. Urine antigen testing is insensitive and should not be used. PCR-based assays for detection of meningococci in blood and CSF have been developed, and multiplex PCR assays that detect several bacterial species associated with meningitis, including the meningococcus, are used in some laboratories.

Differential Diagnosis

Meningococcal disease can appear similar to sepsis or meningitis caused by many other gram-negative bacteria, *S. pneumoniae, Staphylococcus aureus,* or group A streptococcus; to Rocky Mountain spotted fever, ehrlichiosis, or epidemic typhus; and to bacterial endocarditis. Viral and other infectious etiologies of meningoencephalitis should be considered in some cases.

Petechial **rashes** are common in viral infections (enteroviruses, influenza and other respiratory viruses, measles virus, Epstein-Barr virus, cytomegalovirus, parvovirus) and may be confused with meningococcal disease. Petechial or purpuric rashes are also associated with protein C or protein S deficiency, platelet disorders (including idiopathic thrombocytopenic purpura), Henoch-Schönlein purpura, connective tissue disorders, drug eruptions, and trauma, including nonaccidental injury. The nonpetechial, blanching maculopapular rash observed in some cases of meningococcal disease, especially early in the course, may initially be confused with a viral exanthem.

TREATMENT

Antibiotics

Empirical antimicrobial therapy should be initiated immediately after the diagnosis of invasive meningococcal infection is suspected and cultures are obtained, using a **third-generation cephalosporin** to cover the most likely bacterial pathogens until the diagnosis is confirmed. In regions with a high rate of β-lactam–resistant *S. pneumoniae,* empirical *addition* of intravenous (IV) **vancomycin** is recommended (see Chapter 643.1) while awaiting the outcome of bacterial identification and sensitivity, but this is unnecessary in other settings where cephalosporin resistance of pneumococci is very rare (in these settings a risk assessment of each case should be made). Once the diagnosis of β-lactam–sensitive meningococcal disease is confirmed in the laboratory, some authorities recommend a switch to penicillin. Even with no evidence that survival outcomes are different, however, limited evidence from one study indicates that in meningococcal purpura, necrotic skin lesions are less common among children treated with ceftriaxone than with penicillin. Furthermore, it may be cost-effective to use a once-daily dose of ceftriaxone for therapy in younger children, and this is the recommended practice in the United Kingdom (Table 237.2). No adequate studies have investigated the optimal duration of therapy for children, but the course is generally continued for 5-7 days.

Early treatment of meningococcal infections may prevent serious sequelae, but timely early diagnosis is often difficult in the absence of petechial or purpuric skin findings. Among children presenting with petechial rashes, 1–10% may have underlying meningococcal disease, and protocols have been established to ensure that these patients are identified without exposing the >90% of cases without meningococcal disease to unnecessary parenteral antibiotic therapy (Fig. 237.5).

Isolates of *N. meningitidis* with decreased susceptibility to penicillin (minimal inhibitory concentration of penicillin of 0.1-1.0 mg/mL) have been reported from Europe, Africa, Canada, and the United States (4% of isolates in 2006). Decreased susceptibility is caused at least in part by altered penicillin-binding protein 2 and does not appear to adversely affect the response to therapy. Isolates with reduced susceptibility to third-generation cephalosporins have been described in France, but the level of reduced susceptibility is not likely to affect therapeutic outcomes where these agents are used for treatment.

Supportive Care

Most children with meningococcal disease can be managed with antibiotics and simple supportive care and will improve rapidly. However, with an overall 5–10% case fatality rate, the priority in initiating management of children presenting with meningococcal disease is identification of the life-threatening features of the disease: shock and increased ICP. Delayed initiation of supportive therapy is associated with poor outcome, and protocols have therefore been established to aid clinicians in a step-by-step approach (http://www.meningitis.org). In all children presenting with meningococcal disease, assessment of the airway should be performed, because the airway could be compromised as a result of a depressed level of consciousness (elevated ICP in meningitis or poor cerebral perfusion in shock). In patients with meningococcal septicemia, supplementary oxygen should be used to treat hypoxia, which is caused by pulmonary edema (from capillary leak), and some patients will require endotracheal intubation. Hypovolemia requires both volume

Table 237.2 Treatment of *Neisseria meningitidis* Invasive Infections Beyond the Newborn Period

DRUG	ROUTE	DOSE	DOSING INTERVAL (hr)	MAXIMUM DAILY DOSE	NOTES
Penicillin G	IM or IV	300,000-400,000 units/kg/day	4-6 (4-hourly for meningitis)	12-24 million units	Does not clear carriage, and "prophylaxis" is required at the end of treatment
Ampicillin	IM or IV	200-400 mg/kg/day	4-6 (4-hourly for meningitis)	8 g	Does not clear carriage, and "prophylaxis" is required at the end of treatment
Cefotaxime‡	IM or IV	180-225 mg/kg/day	6-8 (6-hourly for meningitis)	8-12 g	Recommended in the neonate
Ceftriaxone	IM or IV	75-100 mg/kg/day	12-24	2-4 g	Preferred treatment as only once or twice daily, and may reduce skin complications
ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY					
Chloramphenicol*	IV	50-100 mg/kg/day	6	2-4 g	Adjust based on target serum concentrations (15-25 mg/L)
Meropenem†	IV	60-120 mg/kg/day	8	3-6 g	

*Monitor blood levels to avoid toxicity.
†Rate of cross-reactivity in penicillin-allergic adults is 2–3%.
‡May not be available due to manufacturing issues.
IM, Intramuscular; IV, intravenous.

replacement and inotropic support to maintain cardiac output. Because ongoing fluid resuscitation may lead to pulmonary edema, endotracheal intubation and ventilation should be initiated in a patient who remains in compensated shock after 40 mL/kg of fluid resuscitation to improve oxygenation and reduce work of breathing. Aggressive fluid resuscitation with unbuffered electrolyte solutions in febrile African children led to increased mortality; similar studies in industrialized settings are required. Metabolic and hematologic abnormalities are common in meningococcal septicemia, and protocols recommend anticipation, assessment, and correction of glucose, potassium, calcium, magnesium, phosphate, clotting factors, and anemia.

Children with meningococcal meningitis should be cautiously managed with maintenance fluids (fluid restriction is not recommended and may be harmful), and those with increased ICP should be managed with close attention to maneuvers to maintain normal cerebral perfusion. If there is shock in the presence of elevated ICP, the shock should be carefully corrected to ensure that cerebral perfusion pressure is maintained.

Many adjunctive therapies have been attempted in patients with severe meningococcal septicemia, but few have been subjected to randomized controlled trials (RCTs). Data are insufficient to recommend the use of anticoagulant or fibrinolytic agents, extracorporeal membrane oxygenation, plasmapheresis, or hyperbaric oxygen. In well-designed clinical trials, an antibody directed against endotoxin (HA1A) did not confer any benefit in children with meningococcal disease, and although initially promising in adult sepsis, activated protein C was not useful in pediatric sepsis and was associated with an increased risk of bleeding. Recombinant bactericidal permeability increasing protein was studied in an underpowered (survival endpoint) trial and showed some potentially beneficial effects against secondary end-points (amputations, transfusions, functional outcome) and requires further investigation.

Although the benefits of **corticosteroids** for adjunctive therapy in pediatric *bacterial* meningitis caused by *H. influenzae* type b (Hib) are accepted, no pediatric data specifically demonstrate benefit in *meningococcal* meningitis. However, some authorities extrapolate from animal data, from experience with Hib, and from compelling data from adult meningitis and recommend corticosteroids as adjunctive therapy in pediatric meningococcal meningitis, given with or soon after the first dose of antibiotics. Therapeutic doses of corticosteroids should not be used routinely in meningococcal septicemia. Some intensivists recommend replacement doses of corticosteroids in patients with treatment-refractory septic shock, because severe sepsis caused by meningococcus is associated with adrenal insufficiency resulting from adrenal necrosis or hemorrhage (Waterhouse-Friderichsen syndrome).

COMPLICATIONS

Adrenal hemorrhage, endophthalmitis, arthritis, endocarditis, pericarditis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts can occur during acute infection. Renal insufficiency requiring dialysis may result from prerenal failure. Reactivation of latent herpes simplex virus infections is common during meningococcal infection.

A self-limiting immune complex vasculitis may occur, usually in the first 10 days after onset of the disease, resulting in various manifestations, including fever, rash, arthritis, and rarely, iritis, pericarditis, or carditis. The arthritis is monoarticular or oligoarticular, involves large joints, and is associated with sterile effusions that respond to nonsteroidal antiinflammatory drugs. Because most patients with meningococcal meningitis become afebrile by the seventh hospital day, persistence or recrudescence of fever after 5 days of antibiotics warrants evaluation for immune complex–mediated complications.

The most common complication of acute severe meningococcal septicemia is focal skin infarction, which typically affects the lower limbs and can lead to substantial scarring and require skin grafting. Distal tissue necrosis in purpura fulminans may require amputation (which should be delayed to allow demarcation) in approximately 2% of survivors. Avascular necrosis of epiphyses and epiphyseal-metaphyseal defects can result from the generalized DIC and may lead to growth disturbance and late skeletal deformities.

Deafness is the most frequent neurologic sequela of meningitis, occurring in 5–10% of children. Cerebral arterial or venous thrombosis with resultant cerebral infarction can occur in severe cases. Meningococcal meningitis is rarely complicated by subdural effusion or empyema or by brain abscess. Other rare neurologic sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadriparesis, and obstructive hydrocephalus (manifests 3-4 weeks after the onset of illness). Behavioral and psychosocial complications of the disease are frequently reported.

PROGNOSIS

The case fatality rate for invasive meningococcal disease is 5–10%, with clear differences related to age of the patient and meningococcal genotype. Most deaths occur within 48 hours of hospitalization in children with meningococcemia. Poor prognostic factors on presentation include hypothermia or extreme hyperpyrexia, hypotension or shock, purpura fulminans, seizures, leukopenia, thrombocytopenia (including DIC), acidosis, and high circulating levels of endotoxin and TNF-α. The presence of petechiae for <12 hours before admission, absence of meningitis, and low or normal ESR indicate rapid, fulminant progression and a poorer prognosis.

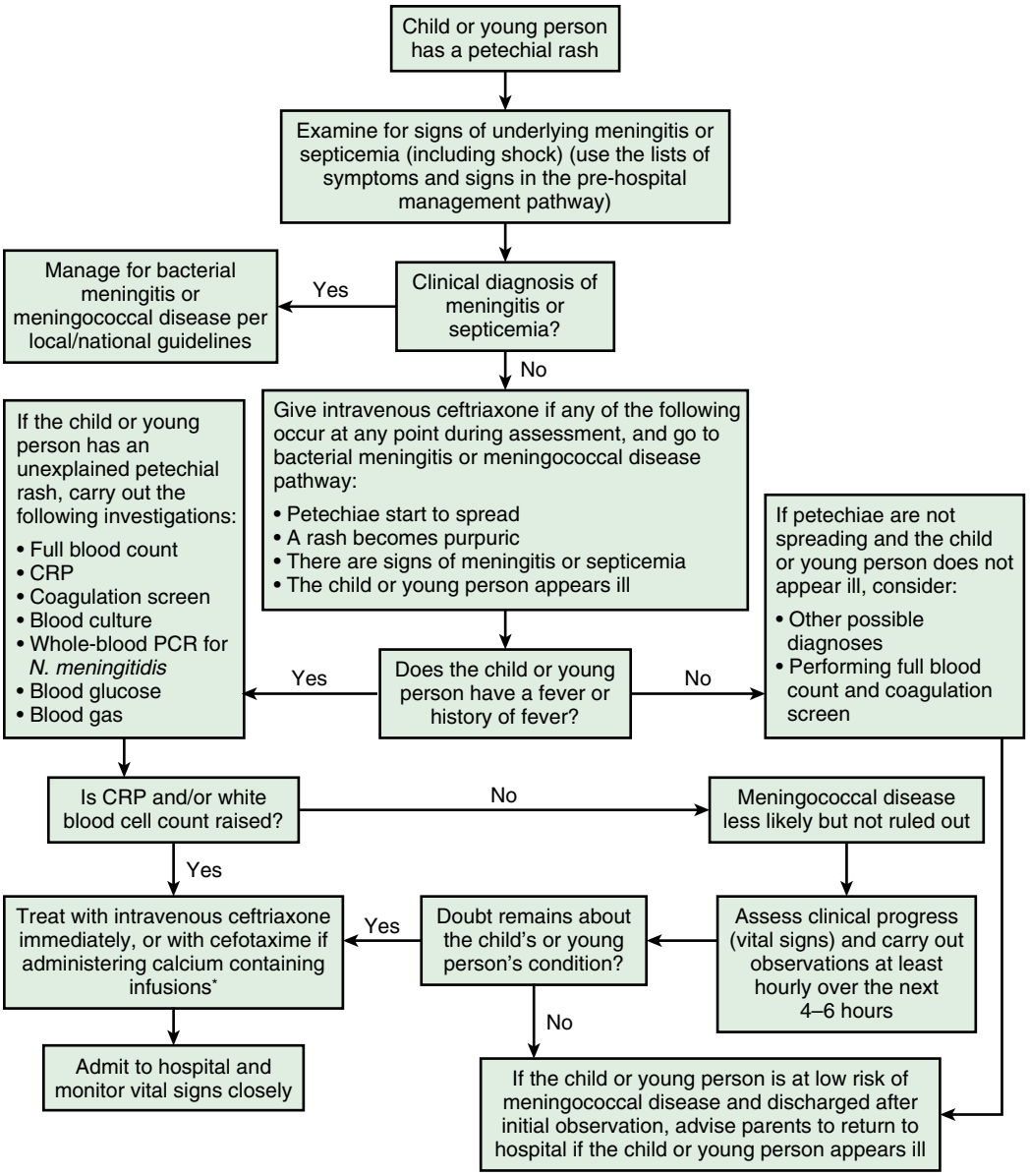

Fig. 237.5 Treatment algorithm for petechial rash. *See Medicines and Healthcare Products Regulatory Agency Drug Safety Update, 2009;3(3). Available from www.mhra.gov.uk. CRP, C-reactive protein; PCR, polymerase chain reaction. *(Data from National Collaborating Center for Women's and Children's Health (UK). Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE Clinical Guidelines, No 102. London: RCOG Press; 2010.)*

Because complement deficiency is rare in patients with capsular group B infection, screening is unlikely to be useful in detecting cases caused by this group, but some authorities recommend routine screening in these cases. However, with one third or more of cases of disease caused by groups X, Y, and W apparently associated with complement deficiency, it is clearly appropriate to screen after infection with non-B capsular groups.

PREVENTION

Secondary Prevention

Close contacts of patients with meningococcal disease are at increased risk of infection because such individuals are likely to be colonized with the index case's (hyperinvasive) strain. Antibiotic prophylaxis should be offered as soon as possible to individuals who have been exposed directly to a patient's oral secretions, for whom the risk may be 1,000 times the background rate in the population. This includes household, kissing, and close family contacts of cases, as well as child-care and recent preschool contacts in the United States. Up to 30% of cases occur in the first week, but the risk persists for up to 1 year after presentation of the index case. Although prophylaxis is effective in preventing secondary cases, coprimary cases may occur in the days after presentation of the index case, and contacts should be carefully evaluated if they develop symptoms. Advice on management of nonclose contacts, such as those in daycare, nursery settings, or school and other institutions, varies in different countries because the risk of a secondary case in this situation is low and opinion on risk assessment varies. **Ceftriaxone**, **ciprofloxacin**, and **rifampin** are 90–95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are acceptable agents for prophylaxis, with ciprofloxacin the drug of choice in some countries (Table 237.3). **Azithromycin** should not be used as the first-line choice for prophylaxis but is recommended in the rare instance of ciprofloxacin resistance. Prophylaxis is not routinely recommended for medical personnel except those with exposure to aerosols of respiratory secretions, such as through mouth-to-mouth resuscitation, intubation, or suctioning before or in the 24 hours after antibiotic therapy is initiated in the index case.

Neither penicillin nor ampicillin treatment eradicates nasopharyngeal carriage and should not be routinely used for prophylaxis. Patients with meningococcal infection treated solely with penicillin or ampicillin are therefore at risk of relapse or transmission to a close contact and should receive antimicrobial prophylaxis with one of the agents listed in Table 237.3 before hospital discharge. The preference is to use ceftriaxone for *treatment* of the index case, in which case further prophylaxis is not required. Droplet infection control precautions should be observed for hospitalized patients for 24 hours after initiation of effective therapy. All confirmed or probable cases of meningococcal infection must be reported to the local public health department according to national or regional regulations.

Table 237.3 Antibiotic Prophylaxis to Prevent *Neisseria meningitidis* Infection*

AGE-GROUP	DOSE	DURATION	EFFICACY
RIFAMPIN†			
Infants <1 mo¶	5 mg/kg PO every 12 hr	2 days (4 doses)	
Children ≥1 mo and adults	15-20 mg/kg PO every 12 hr (max 600 mg)	2 days (4 doses)	90–95%
CEFTRIAXONE			
Children <15 yr	125 mg IM	1 dose	90–95%
Children ≥15 yr and adults	250 mg IM	1 dose	90–95%
CIPROFLOXACIN			
Children ≥1 mo and adults†,‡	20 mg/kg (max 500 mg) PO	1 dose	90–95%
AZITHROMYCIN (NOT RECOMMENDED ROUTINELY)			
All ages	10 mg/kg (max 500 g) PO	1 dose	90%

*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:
- Household contact, especially children <2 yr old
- Childcare or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing, sharing toothbrushes, or eating utensils at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting more than 8 hours (gate to gate), or passengers seated within one seat in any direction from an index case on a flight of any duration if the index case was coughing or vomiting during the flight
- Always check with current local public health guidance for full recommendations

†Not recommended for pregnant women (ceftriaxone is agent of choice in this setting).
‡Use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.
¶Discussion with an expert is recommended for treatment in infants age <1 mo.
IM, Intramuscularly; PO, orally (by mouth).

Close contacts of cases could also be immunized to further reduce the risk of secondary infection, as described later.

Vaccination

Meningococcal plain *polysaccharide vaccines* containing capsular polysaccharides from capsular groups A + C or capsular groups A, C, W, and Y have been available since the 1960s and used in the control of outbreaks and epidemics and for high-risk groups. However, polysaccharide vaccines are poorly immunogenic in infants, do not induce immunologic memory, and are associated with *immunologic hyporesponsiveness* (reduced response to future doses of polysaccharide). Plain polysaccharide vaccines have been superseded by meningococcal protein-polysaccharide *conjugate vaccines,* which are generally more immunogenic than plain polysaccharides, are immunogenic from early infancy, induce immunologic memory, and are not associated with hyporesponsiveness. The conjugate vaccines contain meningococcal polysaccharides that are chemically conjugated to a carrier protein. Three carrier proteins are used in various meningococcal conjugate vaccines: tetanus toxoid, diphtheria toxoid, and the mutant diphtheria toxin CRM197. However, although plain polysaccharide vaccines should be considered redundant in most industrialized countries where the new-generation conjugates are available, they may still have a role in some regions where conjugates are not yet available.

The first meningococcal conjugate vaccine used was a monovalent capsular group C meningococcal conjugate vaccine **(MenC)**, introduced in the United Kingdom in 1999 and administered to all children and young people <19 years old in a mass catch-up campaign before establishment in the routine infant immunization schedule. The MenC vaccine has proved highly effective (>95%) in controlling disease through both direct protection of the vaccinated population and induction of herd immunity, protecting the wider population. *Herd immunity* is induced through the impact of conjugate vaccines on colonization, reducing carriage and blocking transmission of meningococci among adolescents and young adults. Monovalent MenC vaccines are used widely in the industrialized countries of Western Europe, Canada, and Australia, where disease caused by capsular group C meningococci has virtually disappeared. However, serologic surveys show that antibody levels wane, especially after infant immunization, and booster doses are now recommended during adolescence to sustain individual and population immunity.

Quadrivalent meningococcal A, C, Y, and W conjugate vaccines **(MenACWY)** have been available since 2005 and are routinely used for U.S. adolescents and as a single adolescent booster dose in some countries that had established MenC infant programs more than a decade ago. MenACWY was initially introduced as a single dose at 11 years of age in the United States, but concerns about waning immunity led to the adoption of a second dose. The initial reports on the effectiveness (>80%) of MenACWY in the U.S. program indicates that these vaccines are likely to provide control of disease caused by capsular groups C, W, and Y (capsular group A being unimportant currently), although the program has taken some time to become fully established. As the population of immunized adolescents and young adults in the United States grows, the effects of these vaccines on carriage of meningococci likely will reduce disease among other segments of the population through herd immunity, assuming the transmission dynamics of Y and W meningococci are the same as for capsular group C. Although MenACWY vaccines are not currently recommended in the United States for routine use in younger age-groups in view of the low rate of disease caused by these capsular groups in infancy, they may provide broader protection in countries that are already using MenC vaccines in infant programs. Other combination vaccines containing various conjugates, including Hib-MenC (used in the United Kingdom as a 12-month booster) and Hib-MenCY, may have a role in broadening protection beyond MenC in early life. Table 237.4 outlines the current U.S. programmatic recommendations.

Individuals of any age at high risk of meningococcal disease, such as those with complement deficiency, and travelers to regions where there is a risk of epidemic meningococcal disease caused by A or W should receive MenACWY (see Table 237.4). The risk of disease among close contacts of cases of disease caused by vaccine capsular groups may be further reduced if they are offered MenACWY in addition to antimicrobial prophylaxis. A possible association between MenACWY-diphtheria toxoid and Guillain-Barré syndrome, which caused concern early after the vaccine was first used in the United States, has not been substantiated.

A capsular group A meningococcal conjugate vaccine **(MenA)** has been developed for use in the sub-Saharan African meningitis belt, and implementation in 2010 through mass vaccination appears to have interrupted disease caused by this capsular group.

The majority of disease in infants and in most industrialized countries is caused by capsular *group B polysaccharide–bearing meningococci*. This polysaccharide capsule has chemical identity with glycosylated protein antigens in the human fetus and, as a "self" antigen, is therefore not immunogenic in humans and leads to the theoretical risk of induction of autoimmunity. Vaccine development has therefore focused on subcapsular protein antigens. Several countries (e.g., Cuba, Norway, New Zealand) successfully controlled capsular group B epidemics by immunizing with tailor-made outer membrane vesicle vaccines

Table 237.4 Recommendations for Meningococcal Vaccination (United States, 2021)

GENERAL POPULATION			
2-23 MO	**2-10 YR**	**11-23 YR**	**≥24 YR**
Not routinely recommended	Not routinely recommended	A single dose of MenACWY conjugate vaccine at age 11-12 yr with a booster dose at age 16 yr MenB series may be offered at age 16-23 yr on basis of shared clinical decision-making (2 doses of MenB-FHbp or 4CMenB)	Not routinely recommended

SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE			
RISK FACTOR	**2-23 MO**	**2-9 YR**	**≥10 YR**
Persistent complement deficiencies (including patients using a complement inhibitor), functional or anatomic asplenia	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 wk after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart* *and* MenB vaccine (2 doses of 4CMenB or 3 doses of MenB-Hbp) †
At risk during a community outbreak with a vaccine capsular group covered by the relevant vaccine	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 weeks after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart* *or* MenB vaccine (2 doses of 4CMenB or 3 doses of MenB-FHbp) † depending on the capsular group of the outbreak
Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic‡	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 weeks after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart*
Persons with HIV infection	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 weeks after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart*

*Booster every 5 yr if ongoing risk (after 3 yr if <7 yr old).
†Boosters 1 yr after primary series and every 2-3 yr thereafter if remains at increased risk.
‡For example, visitors to the "meningitis belt" of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.
Note that different MenACWY conjugate vaccines are interchangeable, but different MenB vaccines (4CMenB and MenB-FHbp) are not interchangeable
Adapted from https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html

prepared from blebs of outer membrane harvested from the respective epidemic strains. The principal limitation of outer membrane vesicle vaccines is that the bactericidal antibody responses induced by immunization are limited to the vaccine strain, because the response is largely directed against the homologous PorA (serosubtype) protein, and they are therefore not considered for use in endemic settings, including the United States or most other industrialized countries.

Promising approaches for prevention of capsular group B disease have been developed over the past decade. One vaccine that was developed for adolescent immunization was licensed in the United States in 2014 and contains two variants of factor H–binding protein (**2FHbp**; Pfizer vaccines); it appears highly immunogenic in the target population, inducing bactericidal antibodies directed against a panel of strains bearing variants of fHbp. It is currently recommended for use in high-risk groups and during outbreaks (see Table 237.4). Factor H–binding protein appears to be an important virulence determinant, aiding survival of meningococci in blood, and is expressed by virtually all strains.

A four-component meningococcal vaccine, **4CMenB** (Bexsero, GSK Vaccines), is licensed in Europe and North America and available in various other regions. This vaccine contains outer membrane vesicles (derived from the New Zealand outbreak strain) and three recombinant proteins: a single variant of factor H–binding protein (FHbp), neisserial adhesin A (NadA), and neisserial heparin-binding antigen (NHBA). 4CMenB vaccine induced bactericidal antibodies against strains containing the vaccine antigens in infants, toddlers, and adolescents in clinical trials. The vaccine appears to have a generally favorable safety profile, although induction of fever in infants and pain at the injection site in other age-groups are common. This vaccine has been used to control university outbreaks of capsular group B meningococcal disease in the United States and Canada and hyperendemic disease in Quebec, Canada. Current recommendations for use in the United States are outlined in Table 237.4. It was recommended for routine use in the infant immunization program in the United Kingdom in 2014 and deployed from September 2015. Early data reported a 75% reduction in age-groups that were fully eligible for vaccination, with a high coverage rate of 95% (a nonsignificant vaccine effectiveness of 53% after two doses and 59% after a booster dose at 1 year of age). A large cluster randomized trial in Australia found no effect of 4CMenB on carriage of disease-causing meningococci, highlighting that the benefit of this vaccine is likely to be via direct protection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 238

Neisseria gonorrhoeae (Gonococcus)

Katherine Hsu, Sanjay Ram, and Toni Darville

Neisseria gonorrhoeae is the causative agent of **gonorrhea**, an infection of the genitourinary tract mucous membranes and of the mucosa of the rectum, oropharynx, and conjunctiva. Among sexually transmissible infections, gonorrhea transmitted by sexual contact or perinatally is second only to chlamydial infections in the number of cases reported to the U.S. Centers for Disease Control and Prevention (CDC). This high prevalence and the development of antibiotic-resistant strains have led to significant morbidity.

ETIOLOGY

N. gonorrhoeae is a nonmotile, aerobic, non–spore-forming, gram-negative diplococcus with flattened adjacent surfaces. Optimal growth occurs at 35–37°C (95–98.6°F) and at pH 7.2-7.6 in an atmosphere of 3–5% carbon dioxide. The specimen should be inoculated quickly onto fresh, moist, modified Thayer-Martin or specialized transport media, because gonococci do not tolerate drying. Thayer-Martin selective medium contains antimicrobial agents that inhibit the normal flora present in clinical specimens from mucosal sites that may otherwise overgrow gonococci. Presumptive identification may be based on colony appearance, Gram stain, and production of cytochrome oxidase. Gonococci are differentiated from other *Neisseria* spp. by the fermentation of glucose but not maltose, sucrose, or lactose. Gram-negative diplococci are seen in infected material, often within polymorphonuclear leukocytes (PMNs).

As with all gram-negative bacteria, *N. gonorrhoeae* possesses a cell envelope composed of an inner cytoplasmic membrane, a middle layer of peptidoglycan, and an outer membrane. The outer membrane contains **lipooligosaccharide** (**LOS**; also called **endotoxin**), phospholipid, and a variety of proteins that contribute to cell adherence, tissue invasion, and resistance to host defenses. Systems previously used to characterize gonococcal strains included auxotyping and serotyping. **Auxotyping** is based on genetically stable requirements of strains for specific nutrients or cofactors as defined by an isolate's ability to grow on chemically defined media. **Serotyping** systems were based on specific monoclonal antibodies directed against a porin protein called **PorB** (formerly *Protein I* or *PorI*), a trimeric outer membrane protein that makes up a substantial part of the gonococcal envelope structure. Changes in the PorB protein present in a community are believed to result, at least in part, from selective immune pressure. DNA-based typing methods have now supplanted auxotyping and serotyping. Older gel-based DNA-based typing methods that included restriction fragment length polymorphism (RFLP) analysis of genomic DNA or rRNA (ribotyping) or typing of genes encoding opacity protein *(opa)* were labor intensive and sometimes lacked the ability to accurately discriminate among strains. Methods currently used include the *N. gonorrhoeae* multiantigen sequence typing **(NG-MAST)**, which examines the sequences of the variable internal fragments of two highly polymorphic *N. gonorrhoeae* genes (*porB* encoding PorB and *tbpB* encoding subunit B of transferrin-binding protein), multilocus sequence typing (**MLST**), which analyzes the sequences of seven chromosomal housekeeping genes, and whole genome sequencing.

EPIDEMIOLOGY

Since gonorrhea became a nationally notifiable disease in 1944, U.S. rates have ranged between a historic high of 467.7 cases per 100,000 population in 1975 and a historic low of 98.1 per 100,000 in 2009. However, rates of gonorrhea have increased almost every year since 2009 (with an overall increase of 118% between 2009 and 2021), with a total of 710,151 cases and a rate of 214.0/100,000 reported in 2021. Rates of reported gonorrhea are also highest in the South (242.9/100,000); among young adults age 20-24 (860.5 cases per 100,000); among males (249.7/100,000 vs 177.9/100,000 among females); and among Blacks (652.9/100,000 vs 78.9/100,000 among Whites). The higher case rate among men and the magnitude of recent increases suggest either increased transmission, increased case ascertainment (e.g., through increased extragenital screening among men who have sex with men [MSM]), or both. The concurrent increase in cases reported among women suggests parallel increases in heterosexual transmission, increased screening among women, or both.

Molecular typing methods (e.g., NG-MAST, MLST) are used to analyze the spread of individual strains of *N. gonorrhoeae* within a community. Maintenance and subsequent spread of gonococcal infections in a community are sustained through continued transmission by asymptomatically infected people and also by a **hyperendemic**, **high-risk** core group such as commercial sex workers, MSM, or adolescents with multiple sexual partners. This latter observation reflects that most persons who have symptomatic gonorrhea cease sexual activity and seek care, unless economic need or other factors (e.g., drug addiction) drive persistent sexual activity. Thus many core transmitters belong to a subset of infected persons who lack or ignore symptoms and continue to be sexually active, underscoring the importance of seeking out and treating the sexual contacts of infected persons who present for treatment. **Oral sex** has a role in sustaining gonorrhea in MSM by providing a pool of untreated asymptomatic pharyngeal infections and may account for as much as one third of symptomatic gonococcal urethritis in MSM.

Gonococcal infection of neonates usually results from peripartum exposure to infected exudate from the cervix of the mother. An acute infection begins 2-5 days after birth. The incidence of neonatal infection depends on the prevalence of gonococcal infection among pregnant women, prenatal screening for gonorrhea, and neonatal ophthalmic prophylaxis.

PATHOGENESIS AND PATHOLOGY

N. gonorrhoeae infects primarily columnar epithelium because stratified squamous epithelium is relatively resistant to invasion. Mucosal invasion by gonococci results in a local inflammatory response that produces a purulent exudate consisting of PMNs, serum, and desquamated epithelium. The gonococcal LOS (endotoxin) exhibits direct cytotoxicity, causing ciliostasis and sloughing of ciliated epithelial cells. Tumor necrosis factor (TNF) and other cytokines are thought to mediate the cytotoxicity of gonococcal infections. Complement activation also contributes to the acute inflammatory response.

Gonococci may ascend the urogenital tract, causing urethritis or epididymitis in postpubertal males and acute endometritis, salpingitis, and peritonitis (collectively termed **acute pelvic inflammatory disease** or **PID)** in postpubertal females. Dissemination from the fallopian tubes through the peritoneum to the liver capsule results in **perihepatitis** (Fitz-Hugh–Curtis syndrome). Gonococci that invade the lymphatics and blood vessels may cause inguinal lymphadenopathy; perineal, perianal, ischiorectal, and periprostatic abscesses; and **disseminated gonococcal infection** (DGI).

A number of gonococcal virulence and host immune factors are involved in the penetration of the mucosal barrier and subsequent manifestations of local and systemic infection. Selective pressure from different mucosal environments probably leads to changes in the outer membrane of the organism, including expression of variants of pili, opacity (Opa) proteins (formerly called *protein II*), and LOS. These changes may enhance gonococcal attachment, invasion, replication, and evasion of the host's immune response.

For infection to occur, the gonococcus must first attach to host cells. Gonococci adhere to the microvilli of nonciliated epithelial cells by hairlike protein structures (pili) that extend from the cell wall. Pili undergo high-frequency antigenic variation that may aid in

the organism's escape from the host immune response and may provide specific ligands for different cell receptors. Opa proteins, most of which confer an opaque appearance to colonies, function as ligands for members of the carcinoembryonic antigen–related cell adhesion molecule **(CEACAM)** family of proteins or heparin sulfate proteoglycans (HSPGs) to facilitate binding to human cells. Interactions between complement receptor 3 (CR3) on cervical epithelial cells and complement iC3b (deposited on bacteria), pili, and PorB on the gonococcal surface facilitate cellular entry of gonococci in women. In contrast, the interaction between LOS and asialoglycoprotein receptor (ASGP-R) permits gonococcal entry into male urethral epithelial cells. Gonococci that express certain Opa proteins adhere to CEACAM3 and are phagocytosed by human neutrophils in the absence of serum. The interaction of Opa with CEACAM1 on $CD4^+$ T lymphocytes may suppress their activation and proliferation and contribute to the immunosuppression associated with gonorrhea. A gonococcal IgA protease inactivates IgA1 by cleaving the molecule in the hinge region and could contribute to colonization or invasion of host mucosal surfaces.

Other phenotypic changes that occur in response to environmental stresses allow gonococci to establish infection. Examples include iron-repressible proteins such as transferrin-binding proteins (TbpA and TbpB) and lactoferrin-binding proteins (LbpA and LbpB) for binding to and extracting iron from transferrin or lactoferrin, respectively, anaerobically expressed proteins, and proteins that are synthesized in response to contact with epithelial cells. Gonococci may grow in vivo under anaerobic conditions or in an environment with a relative lack of iron.

Approximately 24 hours after attachment, the epithelial cell surface invaginates and surrounds the gonococcus in a phagocytic vacuole. This phenomenon is thought to be mediated by the insertion of the gonococcal PorB protein into the host cell, causing alterations in membrane permeability. Subsequently, phagocytic vacuoles begin releasing gonococci into the subepithelial space by means of exocytosis. Viable organisms may then cause local disease (i.e., salpingitis) or disseminate through the bloodstream or lymphatics.

Serum IgG and IgM directed against gonococcal proteins and LOS activate complement on gonococci. Gonococci have evolved several mechanisms to dampen complement activation. Scavenging cytidine monophospho-*N*-acetyl neuraminic acid (CMP-Neu5Ac, the donor molecule for sialic acid) to sialylate its LOS is one such example, which reduces binding of bactericidal antibodies and simultaneously enhances binding of a complement inhibitor called **factor H** (FH). This property is often lost on subculturing gonococci on medium that lacks CMP-Neu5Ac and is thus termed *unstable serum resistance*. In contrast, *stable serum resistance* (complement resistance independent of LOS sialylation) is often seen in gonococci that express particular porin proteins (most PorB.1As and select PorB.1Bs), which enables them to bind to complement inhibitors such as FH and C4b-binding protein (C4BP). Such strains are often associated with disseminated disease. *N. gonorrhoeae* differentially subverts the effectiveness of complement and alters the inflammatory responses elicited in human infection. Stably serum-resistant DGI isolates show less C3b deposition on their surface, inactivate C3b more rapidly, generate less C5a, and result in less inflammation at local sites. PID isolates (grown in the absence of the donor molecule for sialic acid) are serum sensitive, deposit more C3b on their surface, generate more C5a, and result in more inflammation at local sites. IgG antibody directed against gonococcal reduction-modifiable protein **(Rmp)** blocks complement-mediated killing of *N. gonorrhoeae.* Anti-Rmp blocking antibodies may harbor specificity for outer membrane protein (e.g., OmpA) sequences shared with other *Neisseria* spp. or Enterobacteriaceae, may be directed against a unique Rmp sequence upstream of the OmpA-shared region that includes a cysteine loop, or both. Preexisting antibodies directed against Rmp facilitate transmission of gonococcal infection to exposed women; Rmp is highly conserved in *N. gonorrhoeae,* and the blocking of mucosal defenses may be one of its functions. Gonococcal adaptation also appears to be important in the evasion of killing by neutrophils. Examples include sialylation of LOS, increases in catalase production, and changes in the expression of surface proteins. Neutrophil phagosomes bearing gonococci show delayed fusion with primary granules, promoting gonococcal survival within neutrophils. Other strategies gonococci employ to evade killing by neutrophils include blocking lysozyme activity (mediated by the proteins SliC and adhesin complex protein [ACP]) and degrading neutrophil extracellular traps.

Host factors may influence the incidence and manifestations of gonococcal infection. Prepubertal girls are susceptible to vulvovaginitis and rarely experience salpingitis. *N. gonorrhoeae* infects noncornified epithelium, and the thin noncornified vaginal epithelium and alkaline pH of the vaginal mucin predispose this age-group to infection of the lower genital tract. Estrogen-induced cornification of the vaginal epithelium in neonates and mature females resists infection. Postpubertal females are more susceptible to salpingitis, especially during menses, when diminished bactericidal activity of the cervical mucus and reflux of blood from the uterine cavity into the fallopian tubes facilitate passage of gonococci into the upper reproductive tract.

Populations at risk for DGI include asymptomatic carriers; neonates; menstruating, pregnant, and postpartum women; MSM; and individuals with congenital or acquired (for example, via pharmacologic inhibition) defects in complement. The asymptomatic carrier state implies failure of the host immune system to recognize the gonococcus as a pathogen, the capacity of the gonococcus to avoid being killed, or both. **Pharyngeal colonization** has been proposed as a risk factor for DGI. The high rate of asymptomatic infection in pharyngeal gonorrhea may account for this phenomenon. Women are at greater risk for development of DGI during menstruation, pregnancy, and the postpartum period, presumably because of the maximal endocervical shedding and decreased peroxidase bactericidal activity of the cervical mucus during these periods. A lack of neonatal bactericidal IgM antibody is thought to account for the increased susceptibility of neonates to DGI. Persons with terminal complement component deficiencies (C5-C9) are at considerable risk for development of recurrent episodes of DGI.

CLINICAL MANIFESTATIONS

Gonorrhea is manifested by a spectrum of clinical presentations from asymptomatic carriage, to the characteristic localized mucosal infections, to disseminated systemic infection (see Chapter 163).

Asymptomatic Gonorrhea

The incidence of asymptomatic gonorrhea in children has not been ascertained. Gonococci have been isolated from the oropharynx of young children who have been abused sexually by male contacts; oropharyngeal symptoms are usually absent. Most genital tract infections produce symptoms in children. However, as many as 80% of sexually mature females with urogenital gonorrhea infections are asymptomatic in settings in which most infections are detected through screening or other case-finding efforts. This situation is in contrast to that in men, who are asymptomatic only 10% of the time. Asymptomatic rectal carriage of *N. gonorrhoeae* has been documented in 26–68% of females with urogenital infection. Most persons with positive rectal culture results are asymptomatic. Most pharyngeal gonococcal infections are asymptomatic, although rarely **acute tonsillopharyngitis** or **cervical lymphadenopathy** can occur. Pharyngeal gonorrhea is easily acquired through fellatio and may account for a significant proportion of urethral gonorrhea in MSM. Pharyngeal gonorrhea is increasingly prevalent, particularly among adolescents and young adults, associated with overall increasing prevalence of oral sex behaviors.

Uncomplicated, Localized Gonorrhea

Genital gonorrhea has an incubation period of 2-5 days in men and 5-10 days in women. Primary infection develops in the urethra of males, the vulva and vagina of prepubertal females, and the cervix of postpubertal females. Neonatal ophthalmitis (ophthalmia neonatorum) occurs in both genders.

Urethritis is usually characterized by a purulent discharge and by dysuria without urgency or frequency. Untreated urethritis in males resolves spontaneously in several weeks or may be complicated by epididymitis, penile edema, lymphangitis, prostatitis, or seminal vesiculitis. Gram-negative intracellular diplococci are found in the discharge.

In MSM, the rectal mucosa can become infected after receptive anal intercourse. Symptoms range from painless mucopurulent discharge and scant rectal bleeding to overt proctitis with associated rectal pain and tenesmus.

In prepubertal females, **vulvovaginitis** is usually characterized by a purulent vaginal discharge with a swollen, erythematous, tender, and excoriated vulva. Dysuria may occur. Gonococcal infection should be considered in any girl with vaginal discharge, even when sexual abuse is not suspected; sexual abuse must be considered strongly when gonococcal infection is diagnosed in prepubertal children beyond the neonatal period. In postpubertal females, symptomatic gonococcal **cervicitis** and urethritis are characterized by purulent discharge, suprapubic pain, dysuria, intermenstrual bleeding, and dyspareunia. The cervix may be inflamed and tender. In urogenital gonorrhea limited to the lower genital tract, pain is not enhanced by moving the cervix and the adnexa are not tender to palpation. Purulent material may be expressed from the urethra or ducts of the Bartholin gland. Rectal gonorrhea is often asymptomatic but may cause proctitis with symptoms of anal discharge, pruritus, bleeding, pain, tenesmus, and constipation. Asymptomatic rectal gonorrhea may not be from anal intercourse but may represent translocation of infected secretions from cervicovaginal infection.

Gonococcal **ophthalmitis** may be unilateral or bilateral and may occur in any age-group after inoculation of the eye with infected secretions. **Ophthalmia neonatorum** caused by *N. gonorrhoeae* usually appears from 2-5 days after birth (see Chapter 674). Ocular infection in older patients results from inoculation or autoinoculation from a genital site. The infection begins with mild inflammation and a serosanguineous discharge. Within 24 hours, the discharge becomes thick and purulent and tense edema of the eyelids with marked chemosis occurs. If the disease is not treated promptly, corneal ulceration, rupture, and blindness may follow.

Disseminated Gonococcal Infection

Hematogenous dissemination occurs in 1–3% of all gonococcal infections, more frequently after asymptomatic primary infections than symptomatic infections. Women previously accounted for the majority of cases, with symptoms beginning 7-30 days after infection and within 7 days of menstruation in about one half of cases, but more recent case series describe more male than female cases. The most common manifestations are asymmetric arthralgia, petechial or pustular acral skin lesions, tenosynovitis, suppurative arthritis, and rarely, carditis, meningitis, and osteomyelitis. The most common initial symptom is acute onset of **polyarthralgia with fever**. Only 25% of patients complain of skin lesions. Most deny genitourinary symptoms; however, primary mucosal infection is documented by genitourinary cultures. Results of approximately 80–90% of cervical cultures are positive in women with DGI. In males, urethral culture results are positive in 50–60%, pharyngeal culture results are positive in 10–20%, and rectal culture results are positive in 15% of cases.

DGI is classified into two clinical syndromes that have some overlapping features. The more common **tenosynovitis-dermatitis syndrome** is characterized by fever, chills, skin lesions, and polyarthralgia predominantly involving the wrists, hands, and fingers. Blood culture results are positive in approximately 30–40% of cases, and results of synovial fluid cultures are almost uniformly negative. In **suppurative arthritis syndrome**, systemic symptoms and signs are less prominent and monoarticular arthritis is more common, often involving the knee. A polyarthralgia phase may precede the monoarticular infection. In cases of monoarticular involvement, synovial fluid culture results are positive in approximately 45–55%, and synovial fluid findings are consistent with septic arthritis. Blood culture results are usually negative. DGI in neonates usually occurs as a polyarticular suppurative arthritis.

Dermatologic lesions usually begin as painful, discrete, 1- to 20-mm, pink or red macules that progress to maculopapular, vesicular, bullous, pustular, or petechial lesions. The typical necrotic pustule on an erythematous base is distributed unevenly over the extremities, including the palmar and plantar surfaces, usually sparing the face and scalp. The lesions number between 5 and 40, and 20–30% may contain gonococci. Although immune complexes may be present in DGI, complement levels are normal, and the role of the immune complexes in pathogenesis is uncertain.

Acute endocarditis is an uncommon (1–3%) but often fatal manifestation of DGI that usually leads to rapid destruction of the aortic valve. **Acute pericarditis** is a rarely described entity in patients with disseminated gonorrhea. **Meningitis** with *N. gonorrhoeae* has been documented, and signs and symptoms are similar to those of any acute bacterial meningitis.

DIAGNOSIS

Laboratory confirmation of gonococcal infection is essential, given the legal implications of potential sexual abuse in children and the need to refer sex partners of adolescents and adults for treatment. Given the advent of highly sensitive and specific nucleic acid amplification tests (NAATs), the use of less sensitive, nonamplified test technologies (nucleic acid hybridization/probe tests, nucleic acid genetic transformation tests, or enzyme immunoassays) is no longer justified. Culture and susceptibility testing capability still need to be maintained, because culture is necessary to evaluate suspected cases of gonorrhea treatment failure and to monitor developing resistance to current treatment regimens.

Gram Stain and Culture

Gram stains can be useful in the initial evaluation of patients with suspected gonococcal infection. In males with symptomatic urethritis, a presumptive diagnosis of gonorrhea can be made by identification of gram-negative intracellular diplococci (within PMNs) in the urethral discharge. A similar finding in females is not sufficient because *Mima polymorpha* and *Moraxella,* which are normal vaginal flora, have a similar appearance. The sensitivity of the Gram stain for diagnosing gonococcal cervicitis and asymptomatic infections is also low. The presence of commensal *Neisseria* spp. in the oropharynx prevents the use of the Gram stain for diagnosis of pharyngeal gonorrhea.

Culture can be performed of any site, including nongenital sites. Advantages of culture include the availability of an isolate for further studies, including antibiotic susceptibility testing. Disadvantages of culture include more stringent transport and growth requirements, lower sensitivity than NAATs, and a delay in availability of results. Material for cervical cultures is obtained as follows. After the exocervix is wiped, a swab is placed in the cervical os and rotated gently for several seconds. Male urethral specimens are obtained by placement of a small swab 2-3 cm into the urethra. Rectal swabs are best obtained by passing a swab 2-4 cm into the anal canal; specimens that are heavily contaminated by feces should be discarded. For optimal culture results, specimens should be obtained with noncotton swabs, inoculated directly onto culture plates containing selective media (see later), and incubated immediately. The choice of anatomic sites to culture depends on the sites exposed and the clinical manifestations. If symptoms are present, samples from the urethra and rectum can be cultured for men, and samples from the endocervix and rectum can be cultured for all females, regardless of a history of anal intercourse. A pharyngeal culture specimen should be obtained from both men and women if symptoms of pharyngitis are present with a history of recent oral exposure or oral exposure to a person known to have genital gonorrhea. In a suspected case of **child sexual abuse**, culture or FDA approved NAAT are recommended methods of detection for *N. gonorrhoeae* in genital and extragenital specimens. Culture of the endocervix should not be attempted until after puberty.

Specimens from sites that are normally colonized by other organisms (e.g., cervix, rectum, pharynx) should be inoculated on a selective culture medium, such as modified Thayer-Martin medium (fortified with vancomycin, colistin, nystatin, and trimethoprim to inhibit growth of indigenous flora). Specimens from sites that are normally sterile or minimally contaminated (i.e., synovial fluid, blood, cerebrospinal fluid) should be inoculated on a nonselective chocolate agar medium. If DGI is suspected, blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be cultured. Cultured specimens should

be incubated promptly at 35–37°C (95–98.6°F) in 3–5% carbon dioxide. When specimens must be transported to a central laboratory for culture plating, a reduced, nonnutrient holding medium (i.e., Amies [modified Stuart] transport medium) preserves specimens with minimal loss of viability for up to 6 hours. When transport may delay culture plating by >6 hours, it is preferable to inoculate the sample directly onto a culture medium and transport it at an ambient temperature in a CO_2-enriched atmosphere. The Transgrow and John E. Martin Biological Environmental Chamber (JEMBEC) systems of modified Thayer-Martin medium are alternative transport systems.

Nucleic Acid Amplification Tests

The U.S. FDA has approved NAATs for use with genital (endocervical, vaginal, male urethral, and female and male first-catch urine) and extragenital (pharyngeal and rectal) specimens. Advantages of using NAATs include less stringent transport conditions, more rapid turnaround time, flexibility in sampling source (providing additional feasibility of testing in settings where a physical exam is not done), and patient preference for less invasive sampling. However, NAATs cannot provide antimicrobial susceptibility results, so in cases of persistent gonococcal infection after treatment, clinicians should perform both culture and antimicrobial susceptibility testing. Although urine specimens are acceptable for women, the sensitivity for screening appears to be lower than with vaginal or endocervical swab samples. In contrast, the sensitivity and specificity of urine and urethral swab specimens from men are similar, so first-catch urine is the recommended sample type for urethral screening in men. Product inserts for each NAAT vendor must be carefully examined to assess current indications and allowable specimens. Some NAAT platforms are now FDA cleared for use with specimens from the rectum and pharynx, facilitating their use for clinical management of extragenital infections (gonorrhea screening of rectal and pharyngeal sites with NAATs is recommended quarterly for some sexually active MSM, e.g., those taking HIV prophylaxis). NAATs have not yet been FDA cleared for specimens from the conjunctiva, joint fluid, blood, or cerebrospinal fluid. Rapid NAATs with shortened turnaround times of 30 minutes and waivers allowing use in point-of-care settings such as physician offices, community clinics, and other outpatient settings have now also been FDA cleared.

Although data regarding NAAT for children are more limited and performance is test-dependent, there is no evidence that performance of FDA-approved NAAT for detection of *N. gonorrhoeae* among children differs from that among adults. In a multicenter study of NAATs using strand displacement amplification or transcription-mediated amplification in children being evaluated for sexual abuse, urine from prepubertal girls was a reliable alternative to vaginal culture for detection for *N. gonorrhoeae*. Consultation with an expert is necessary before using NAAT in this context, both to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis, N. sicca, N. lactamica, N. cinerea,* or *Moraxella catarrhalis*) and to ensure correct interpretation of results. Because of the implications of a diagnosis of *N. gonorrhoeae* infection in a child, only CLIA-validated, FDA-cleared NAATs should be used, and all positive specimens should be retained for additional confirmatory testing.

TREATMENT

All patients who are presumed or proven to have gonorrhea should be evaluated for concurrent syphilis, HIV, and *Chlamydia trachomatis* infection. The incidence of *Chlamydia* co-infection is 15–25% among males and 35–50% among females. Patients beyond the neonatal period should be treated presumptively for *C. trachomatis* infection unless a negative chlamydial NAAT result is documented at the time treatment is initiated for gonorrhea. However, if chlamydial test results are not available or if a non-NAAT result is negative for *Chlamydia,* patients should be treated for both gonorrhea and *Chlamydia* infection (see Chapter 272.2). Persons who receive a diagnosis of gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present). Sexual partners exposed in the preceding 60 days should be examined, specimens collected, and presumptive treatment started.

N. gonorrhoeae has progressively developed resistance to the antibiotics used to treat it. Antimicrobial resistance in *N. gonorrhoeae* occurs as plasmid-mediated resistance to penicillin and tetracycline and chromosomally mediated resistance to penicillins, tetracyclines, spectinomycin, fluoroquinolones, cephalosporins, and azithromycin. Emergence of cephalosporin resistance worldwide has prompted designation of *N. gonorrhoeae* as antibiotic-resistance threat level "Urgent" by the CDC. Surveillance data from the CDC Gonococcal Isolate Surveillance Project reveal concerning fluctuations in minimum inhibitory concentration (MIC) for the oral cephalosporin **cefixime** and the injectable third-generation cephalosporin **ceftriaxone**, leading the CDC to revise its U.S. gonorrhea treatment guidelines in 2012 to dual therapy (usually a combination of ceftriaxone and azithromycin) in an attempt to preserve the last commercially available effective treatment. However, the CDC revised its recommendations in 2020; ceftriaxone is now the only first-line recommended treatment for gonorrhea at all sites. The change from dual therapy to monotherapy was based on (1) increasing concern for antimicrobial stewardship and the potential impact of dual therapy on commensal organisms and concurrent pathogens, (2) new pharmacokinetic and pharmacodynamic data regarding optimal dosing for gonorrhea, and (3) increasing azithromycin resistance (and therefore no optimal second drug to pair with a cephalosporin if dual therapy were the goal).

Table 238.1 summarizes first-line treatment regimens for neonate, child (weight ≤45 kg), adolescent, and adult gonococcal regimens. Mucosal, localized infections are treatable with single doses; disseminated infections are treated for a minimum of 1 week.

Alternative regimens exist for adolescents and adults but are extremely limited. For patients with cephalosporin allergy, the combination of gentamicin (240 mg intramuscularly [IM]) plus azithromycin (2 g orally [PO]) cured 100% of uncomplicated urogenital cases in a trial of U.S. patients age 15-60 years; the combination of gemifloxacin (320 mg PO) (not licensed for use in those <18 years old) plus azithromycin (2 g PO) cured >99% of uncomplicated urogenital cases in the same trial but was limited by 8% of patients vomiting within 1 hour of dual oral drug administration. For patients with azithromycin allergy, doxycycline (100 mg PO twice daily for 7 days) can be used in place of azithromycin as an alternative second antimicrobial. If ceftriaxone is not available, alternative cephalosporins include oral cefixime (800 mg PO), which has limited efficacy for pharyngeal gonorrhea, and other single-dose injectable cephalosporin regimens, such as ceftizoxime (500 mg IM) or cefoxitin (2 g IM) with probenecid (1 g PO), neither of which offers any advantage over ceftriaxone for urogenital infection, and their efficacy against pharyngeal infection is less certain.

Pregnant women with gonococcal infection should be treated with standard adult therapy. If allergy precludes standard treatment, consultation with an infectious disease specialist is recommended. HIV–co-infected patients with gonococcal infection are treated the same as HIV-negative patients.

Follow-up test of cure is not recommended for persons diagnosed with uncomplicated urogenital or rectal gonorrhea receiving recommended or alternative regimens. However, any person with pharyngeal gonorrhea should return 7-14 days after treatment for a test of cure using culture, NAAT, or both, because pharyngeal gonorrhea is more difficult to eradicate. Symptoms persisting after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT), and any gonococci isolated should be tested for antimicrobial susceptibility. **Treatment failure** should be considered in (1) persons whose symptoms do not resolve within 3-5 days after appropriate treatment and who report no sexual contact during posttreatment follow-up and (2) persons with a positive test of cure (i.e., positive culture >72 hours or positive NAAT ≥7 days after receiving recommended treatment) who report no sexual contact during posttreatment follow-up.

COMPLICATIONS

Prompt diagnosis and correct therapy ensure complete recovery from uncomplicated gonococcal disease. Complications of gonorrhea result

Table 238.1 Recommended Treatment of Gonococcal Infections

AGE GROUP	INFECTION	TREATMENT REGIMEN	LENGTH OF THERAPY
Neonates	Ophthalmia neonatorum	Ceftriaxone* 25-50 mg/kg IV or IM *OR* cefotaxime 100 mg/kg IV or IM	Once
	Disseminated infection Scalp abscess Septic arthritis	Ceftriaxone 25-50 mg/kg IV or IM every day *OR* cefotaxime 25-50 mg/kg IV or IM q8–12h†	7 days
	Meningitis	Ceftriaxone 25-50 mg/kg IV or IM every day *OR* cefotaxime 25-50 mg/kg IV or IM q8-12h	10-14 days
	Endocarditis	Ceftriaxone 25-50 mg/kg IV or IM every day *OR* cefotaxime 25-50 mg/kg IV or IM q8-12h	Minimum 28 days
Children ≤45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone 25-50 mg/kg IV or IM (max 500 mg)	Once
	Conjunctivitis	Ceftriaxone 50 mg/kg IM (max 1 g) plus consider lavage of infected eye with saline solution	Once
	Disseminated infection Septic arthritis	Ceftriaxone 50 mg/kg IV or IM every day (max 1 g daily)	7 days
	Meningitis	Ceftriaxone 50 mg/kg IV or IM q12-24h (max 4 g daily)	10-14 days
	Endocarditis	Ceftriaxone 50 mg/kg IV or IM q12-24h (max 4 g daily)	Minimum 28 days
Adults, adolescents, and children >45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone 500 mg IM (or 1 g IM for persons ≥150 kg)	Once
	Conjunctivitis	Ceftriaxone 1 g IM plus consider lavage of infected eye with saline solution	Once
	Disseminated infection Septic arthritis	Ceftriaxone 1 g IV or IM every day	7 days
	Meningitis	Ceftriaxone 1-2 g IV q12-24h	10-14 days
	Endocarditis	Ceftriaxone 1-2 g IV q12-24h	Minimum 28 days

*Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium. Consult neonatal dosing references.
†Dose or dosing frequency changes after postnatal age >7 days of life: consult neonatal dosing references.
IM, Intramuscularly; IV, intravenously; max, maximum; PO, orally.
From Wangu Z, Hsu KK. *Neisseria gonorrhoeae.* In Long SS, Prober CG, Fischer M, Kimberlin D, eds. *Principles and Practice of Pediatric Infectious Diseases,* 6th ed. Philadelphia: Elsevier; 2023: Table 126.1.

from the spread of gonococci from a local site of invasion. Complications and permanent sequelae may be associated with delayed treatment, recurrent infection, metastatic sites of infection (meninges, aortic valve), and delayed or topical therapy of gonococcal ophthalmia.

The interval between primary infection and development of a complication is usually days to weeks. In postpubertal females, endometritis may occur, especially during menses, and may progress to salpingitis, tuboovarian abscess, and peritonitis (PID). Manifestations of PID include signs of lower genital tract infection (e.g., vaginal discharge, suprapubic pain, cervical tenderness) and upper genital tract infection (e.g., fever, leukocytosis, elevated erythrocyte sedimentation rate, and adnexal tenderness or mass). The differential diagnosis includes gynecologic diseases (ovarian cyst, ovarian tumor, ectopic pregnancy) and intraabdominal disorders (appendicitis, urinary tract infection, inflammatory bowel disease). Although *N. gonorrhoeae* and *C. trachomatis* are implicated in many cases of PID, this syndrome encompasses a spectrum of infectious diseases of the upper genital tract caused by *N. gonorrhoeae, C. trachomatis,* and endogenous flora (streptococci, anaerobes, gram-negative bacilli). Treatment must therefore be broad. For women with more severe symptoms (inability to exclude surgical emergency, presence of tuboovarian abscess, severe illness, nausea, vomiting, or high fever), pregnancy, or lack of response to outpatient therapy within 72 hours, parenteral therapy should be initiated in the hospital. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women, because the clinical response to outpatient treatment is similar among younger and older women.

Recommended parenteral regimens are ceftriaxone (1 g intravenously [IV] every 24 hours [q24h]) and metronidazole (500 mg PO or IV q12h); or cefotetan (2 g IV q12h); or cefoxitin (2 g IV q6h). Each of these regimens (ceftriaxone and metronidazole; cefotetan; or cefoxitin) should be combined with doxycycline (100 mg PO or IV q12h). An alternative parenteral regimen is ampicillin-sulbactam (3 g IV q6h) plus doxycycline (100 mg PO or IV q12h) or clindamycin (900 mg IV q8h) plus a loading dose of gentamicin (2 mg/kg IV or IM) followed by maintenance gentamicin (1.5 mg/kg q8h). Clinical experience should guide the transition to oral therapy, which usually can be initiated within 24 hours of improvement. Thereafter doxycycline (100 mg PO twice daily [bid]) to complete 14 days of total therapy, with oral clindamycin (450 mg PO 4 times daily [qid]) or metronidazole (500 mg PO bid) added for more effective anaerobic coverage, is provided. Parenteral therapy and IM/PO therapy appear to be similar in terms of clinical efficacy for younger and older women with PID of mild to moderate severity. Recommended IM/PO therapy regimens are as follows: a single dose of ceftriaxone (500 mg IM); single doses of cefoxitin (2 g IM) and probenecid (1 g PO) plus doxycycline (100 mg PO bid); or another parenteral third-generation cephalosporin (e.g., ceftizoxime). Each of these regimens (ceftriaxone; cefoxitin and probenecid; other

parenteral third-generation cephalosporin) should be combined with doxycycline (100 mg PO bid) and metronidazole (500 mg PO bid) for 14 days.

Once inside the peritoneum, gonococci may seed the liver capsule, causing a perihepatitis with right upper quadrant pain **(Fitz-Hugh–Curtis syndrome)**, with or without signs of salpingitis. Perihepatitis may also be caused by *C. trachomatis*. Progression to PID occurs in approximately 20% of cases of gonococcal cervicitis, and *N. gonorrhoeae* is isolated in approximately 40% of cases of PID in the United States. Untreated cases may lead to hydrosalpinx, pyosalpinx, tubo-ovarian abscess, and eventual sterility. Even with adequate treatment of PID, the risk for sterility from bilateral tubal occlusion approaches 20% after one episode of salpingitis and exceeds 60% after three or more episodes. The risk for ectopic pregnancy is increased approximately sevenfold after one or more episodes of salpingitis. Additional sequelae of PID include chronic pain, dyspareunia, and increased risk for recurrent PID.

Urogenital gonococcal infection acquired during the first trimester of pregnancy carries a high risk for septic abortion. After 16 weeks of pregnancy, infection leads to **chorioamnionitis**, a major cause of premature rupture of the membranes and premature delivery.

In males, without treatment, gonococcal urethritis usually resolves spontaneously over several weeks to months. Epididymitis and acute or chronic prostatitis are uncommon complications; most men with gonococcal epididymitis also have overt urethritis. Even more unusual complications include penile edema associated with penile dorsal lymphangitis or thrombophlebitis, periurethral abscess or fistulas, seminal vesiculitis, and balanitis in uncircumcised men.

PREVENTION

Efforts to develop gonococcal vaccines that confer broad cross-protection have been unsuccessful thus far. A pilus vaccine elicited an antibody response and conferred protection against challenge with the homologous strain but did not protect against disease in a trial involving 3,250 volunteers. The high degree of interstrain and intrastrain antigenic variability of pili poses a formidable barrier to the development of a single effective pilus vaccine. An outer membrane vaccine that was enriched in PorB also elicited an antibody response but failed to protect male volunteers against challenge with the homologous strain, likely because small amounts of Rmp present in the vaccine preparation elicited subversive antibodies. A formalin-killed whole cell vaccine trial in 62 volunteers in an Inuvik population in Canada also failed to provide any protection. Gonococcal surface structures, such as the porin protein (isolated without contaminating Rmp), proteins expressed under various stress conditions that may be encountered in vivo and have been identified by proteomic and transcriptomic approaches, and lipooligosaccharides, may prove more promising as vaccine candidates.

A retrospective epidemiologic analysis showed that a meningococcal outer membrane vesicle vaccine (MeNZB) that was used to curb an epidemic of group B meningococcal disease in New Zealand was associated with a clinical efficacy of 31% against gonorrhea, which lends optimism for development of a gonococcal vaccine. However, efficacy was only 14% in persons co-infected with gonorrhea and chlamydia. Cross-reactive antigens shared by *N. gonorrhoeae* and *N. meningitidis* may have contributed to the efficacy of the group B outer membrane vesicle vaccine against gonorrhea.

In the absence of a vaccine, prevention of gonorrhea in adolescents and adults can be achieved through **education**, use of **barrier protection** (especially condoms), **frequent screening** of high-risk populations as recommended by the U.S. Preventive Services Task Force (PSTF) and CDC (e.g., sexually active women ≤24 years old, MSM, individuals previously infected with gonorrhea), and **early identification and treatment** of contacts—all sex partners within the 60 days preceding symptom onset or gonorrhea diagnosis or, if none, the most recent sex partner should be examined and treated presumptively. For heterosexual patients, expedited partner therapy (EPT) with cefixime (800 mg) can be delivered to partners by the patient, a public health worker, or a collaborating pharmacy, as permitted by law (https://www.cdc.gov/std/ept/legal/). EPT has been shown to be safe and effective in the prevention of reinfection with gonorrhea and is endorsed by the American Academy of Pediatrics, American Academy of Family Physicians, and Society of Adolescent Health and Medicine, along with other clinical organizations, for use when in-person evaluation and treatment of the partner is impractical or unsuccessful. (Because of limited data regarding the effectiveness of EPT in reducing persistent or recurrent gonorrhea among MSM and the high risk for coexisting undiagnosed sexually transmitted infections such as HIV, shared clinical decision-making regarding EPT for MSM is recommended.)

An infant born to a woman with cervical gonococcal infection has an approximately 30% risk of acquiring ophthalmic infection compared with a <5% risk if ocular prophylaxis is given. **Gonococcal ophthalmia neonatorum** can be prevented by instilling erythromycin (0.5%) ophthalmic ointment into each eye in a single application at birth (see Chapter 674). If erythromycin ointment is unavailable, infants at risk for *N. gonorrhoeae* (especially those born to a mother with untreated gonococcal infection or with no prenatal care) can be administered ceftriaxone 25-50 mg/kg IV or IM, not to exceed 500 mg, in a single dose.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 239
Kingella kingae

Pablo Yagupsky

Kingella kingae is being increasingly recognized as the most common etiology of skeletal system infections in young children.

ETIOLOGY

K. kingae is a fastidious, facultative anaerobic, β-hemolytic member of the Neisseriaceae family that appears as pairs or short chains of gram-negative coccobacilli with tapered ends (Fig. 239.1).

EPIDEMIOLOGY

K. kingae is asymptomatically carried in the posterior pharynx, and the colonized mucosa is the source of bloodstream invasion of the bacterium and its dissemination to the skeletal system or the endocardium, sites for which the organism has a particular tropism. **Colonization** usually starts after 6 months of age, suggesting that maternally derived immunity, coupled with limited socialization, prevents the early acquisition of the bacterium. Colonization reaches a prevalence of 10% between 12 and 24 months and decreases in older children. Carried strains are replaced after weeks or months, suggesting that carriage induces a strain-specific immune response that eradicates the colonizing strain but does not prevent the acquisition of an antigenically different organism. The vast majority of colonized children remain healthy, and the annual risk of a carrier to develop an invasive infection is <1%.

Pharyngeal colonization plays a crucial role in the **transmission** of the organism through intimate contact between siblings and playmates. Daycare attendance increases the risk for colonization and transmission, and clusters of invasive infection have been reported in childcare facilities.

The species elaborates four different polysaccharide capsules (a-d), which appear to represent important virulence factors. Whereas capsules a and b characterize 95% of all invasive strains, capsules c and d are especially found in mere pharyngeal colonizers. Colonizing *K. kingae* strains differ in their invasive potential. Whereas certain clones are commonly found as respiratory colonizers but are seldom isolated from disease sites, other clones are responsible for most of the morbidity burden worldwide.

Invasive *K. kingae* disease is most frequently diagnosed in otherwise healthy children between the ages 6 months and 4 years, coinciding

with the peak prevalence of **pharyngeal carriage** (Fig. 239.2). In contrast, older children and adults with *K. kingae* infections often have underlying chronic diseases, immunosuppressing conditions, malignancy, or cardiac valve pathology. Because of the highly fastidious nature of the organism, *K. kingae* is rarely recovered using traditional culture methods. An annual incidence of 9.4 per 100,000 culture-proven invasive infections among Israeli children <5 years old has been calculated, but this figure can be considered only a minimal estimate because of the suboptimal culture detection of the organism. When sensitive species-specific nucleic acid amplification test (NAAT) methods are consistently used, *K. kingae* appears as the most frequent etiology of skeletal system infections in children 6 months to 4 years old. In a Swiss study in which sensitive NAATs were routinely employed, the organisms caused 88% of all joint and bone infections in this age-group.

PATHOGENESIS

The pathogenesis of *K. kingae* disease begins with adherence of the organism to the pharyngeal epithelium, mediated by pili and a non-pilus adhesin. *K. kingae* secretes a potent repeats-in-toxin (RTX) toxin that is cytotoxic to respiratory epithelial cells, macrophages, and synoviocytes, suggesting that it may play a role in disrupting the respiratory mucosa, promoting survival of the bacterium in the bloodstream, and facilitating invasion of skeletal system tissues. Children with *K. kingae* disease frequently present with symptoms of an upper respiratory infection, hand-foot-and-mouth disease, herpangina, herpetic stomatitis, or buccal aphthous ulcers, suggesting that viral-induced damage to the colonized mucosal surface facilitates invasion of the bloodstream.

CLINICAL DISEASE

Septic arthritis is the most common invasive *K. kingae* infection in children, followed by bacteremia, osteomyelitis, and endocarditis (Table 239.1). Except for patients with endocarditis, the presentation of invasive *K. kingae* infections is frequently mild, and a normal body temperature <38°C (100.4°F), a normal C-reactive protein (CRP) level, and a normal white blood cell (WBC) count are common, requiring a high index of clinical suspicion. Mild to moderate thrombocytosis has been described in more than one third of patients.

Septic Arthritis

K. kingae septic arthritis primarily affects the large, weight-bearing joints and the upper extremity joints. However, *K. kingae* infections of the small metacarpophalangeal, sternoclavicular, sacroiliac, and tarsal joints and the vertebral facets are also relatively common, in contrast to traditional bacterial pathogens associated with septic arthritis (see Chapter 726). The disease has an acute presentation, and children are brought to medical attention after a median of 3 days. The leukocyte count in the synovial fluid shows <50,000 WBCs/μL in almost 25% of the patients, and the Gram stain of synovial fluid is positive in only a small percentage of cases. Involvement of the hip joint resembles toxic synovitis, and the possibility of a *K. kingae* infection should always be suspected in children <4 years old presenting with hip pain or a limp.

Osteomyelitis

K. kingae osteomyelitis usually involves the long bones of the extremities (see Chapter 725). The calcaneus, talus, sternum, and clavicle are also frequently affected (and are rarely infected by other bacterial pathogens). In contrast to *K. kingae* arthritis, the onset of *K. kingae* bone infections is insidious, and the disease follows a subacute and indolent clinical course (Fig. 239.3). In >70% of patients *K. kingae* osteomyelitis is diagnosed after ≥1 week. MRI may show a distinct involvement of cartilages that are not yet ossified, which is only accompanied by a minor soft tissue reaction. Dissemination to the apophysis or epiphysis and contiguous joints is frequent. Despite the frequent diagnostic delay, chronic osteomyelitis and functional orthopedic disabilities are unusual.

SPONDYLODISCITIS

In industrialized countries, *K. kingae* is the most common bacterium detected in children <4 years old with spondylodiscitis. The organism presumably penetrates the rich network of blood vessels that traverse the cartilaginous vertebral end plates and enters the annulus in young children during a bacteremic episode. *K. kingae* spondylodiscitis usually involves the lumbar intervertebral spaces and, with decreasing frequency, thoracolumbar, thoracic, lumbosacral, and cervical disks. Involvement of multiple disks is uncommon. Patients present with limping, lumbar pain, back stiffness, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Radiography or MRI studies demonstrate narrowing of the intervertebral space. Patients respond well to appropriate antibiotic treatment and recover without complications, although residual thinning of the intervertebral space may occur. Drainage of paraspinal abscesses is necessary when signs of cord compression appear.

Tenosynovitis

K. kingae is the etiology of most cases of hematogenous invasion of the tendon sheaths in children <4 years of age. The disease usually affects the extensor tendons of the hands and wrists and, more rarely, the ankles and the feet.

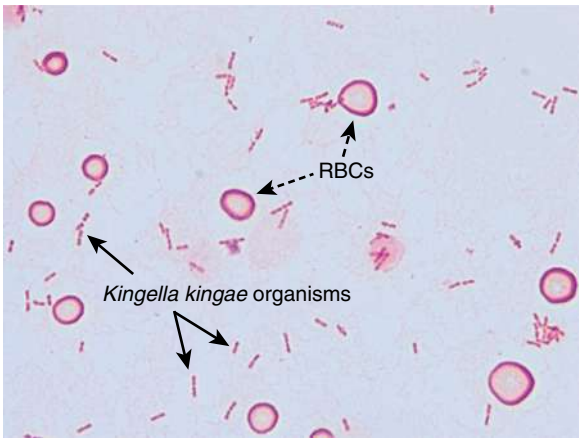

Fig. 239.1 Typical Gram stain of a positive blood culture vial from a child with *K. kingae* bacteremia showing pairs and short chains of plump gram-negative coccobacilli. RBCs, Red blood cells.

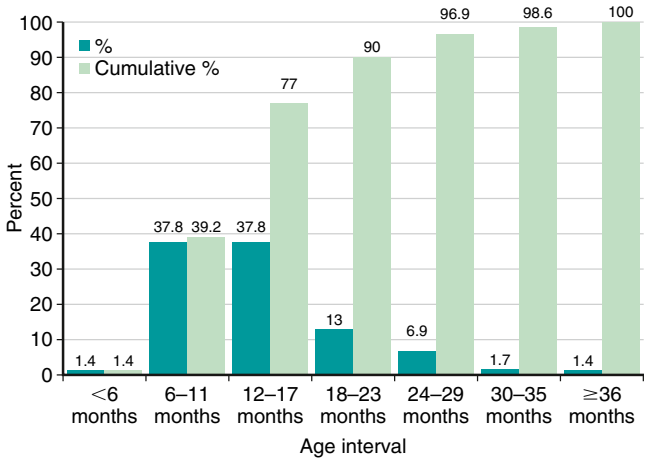

Fig. 239.2 Age distribution of 291 previously healthy children with invasive *K. kingae* infection. *(Data from Dubnov-Raz G, Ephros M, Garty BZ, et al. Invasive pediatric Kingella kingae infections: a nationwide collaborative study. Pediatr Infect Dis J. 2010;29:639–643.)*

Table 239.1 Clinical Spectrum and Relative Frequency of *K. kingae* Infections

CLINICAL DISEASE	FREQUENCY
Septic arthritis	+++
Osteomyelitis	++
Spondylodiscitis	+
Tenosynovitis	±
Bursitis	±
Bacteremia with no focus	+++
Endocarditis	+
Pericarditis	+
Laryngotracheobronchitis	±
Pneumonia	±
Pleural empyema	±
Keratitis	±
Corneal abscess	±
Endophthalmitis	±
Eyelid abscess	±

+++, Very common; ++, common; +, infrequent; ±, exceptional.

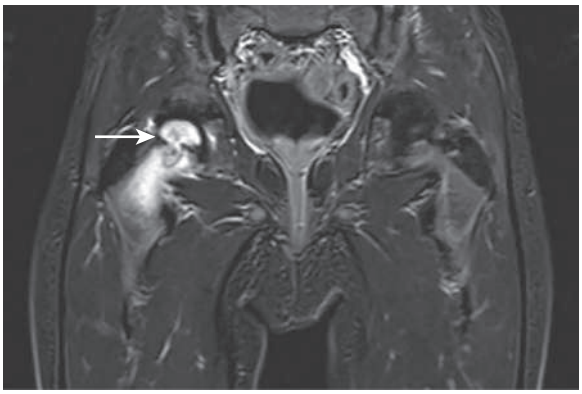

Fig. 239.3 *K. kingae* transphyseal osteomyelitis of the femur *(arrow)*. This 3-yr-old child limped for 3 weeks and was diagnosed with toxic synovitis. He was afebrile and had a leukocyte count of 9.8 × 10^9 cells/L, a C-reactive protein level of 12 mg/L, and an erythrocyte sedimentation rate of 42 mm/hr. *(Courtesy Prof. Dimitri Ceroni, Hôpitaux Universitaires de Genève.)*

Occult Bacteremia

Patients with *K. kingae* bacteremia and no focal infection (occult bacteremia) usually present with mild to moderate fever, symptoms suggestive of a viral upper respiratory infection, a mean CRP level of 2.2 mg/dL, and a mean WBC count of 12,700/μL. Children with *K. kingae* bacteremia respond favorably to a short course of antibiotics.

Endocarditis

In contrast to other *K. kingae* infections, *K. kingae* endocarditis is also diagnosed in school-age children, adolescents, and adult patients. The disease may affect native and prosthetic valves. Predisposing factors include congenital cardiac malformations or rheumatic valvular disease, but some patients have previously normal hearts. Typically, the left side of the heart is involved, usually the mitral valve. Fever and acute-phase reactants are elevated more in patients with endocarditis than in those with uncomplicated bacteremia; no particular cutoff value accurately distinguishes between the two conditions. Despite the exquisite susceptibility of *K. kingae* to antibiotics, cardiac failure, septic shock, cerebrovascular accident (stroke), and other life-threatening complications are common; the mortality rate is high (>10%); and many surviving patients later require valvular repair or replacement. Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of bacteremic children is recommended by some experts.

DIAGNOSIS

The diagnosis of *K. kingae* disease can be established by isolation of the bacterium from a normally sterile site such as blood, synovial fluid, or bone tissue. Although *K. kingae* grows on routine bacteriologic media, its recovery from exudates is frequently unsuccessful. Detection is enhanced by inoculating synovial fluid specimens into blood culture vials, suggesting that diluting samples in a large volume of nutrient broth reduces the concentration of detrimental factors. The bacteriologic diagnosis is significantly improved by the use of NAATs (polymerase chain reaction). The initial approach consisted of amplifying the 16S ribosomal RNA (rRNA) gene, which is present in all bacteria followed by sequencing the species-specific amplicon to identify the pathogen. The original molecular assays are being replaced by real-time polymerase chain reaction tests that target *K. kingae*–specific genes that can be completed in a few hours. Routine use of these assays results in a fourfold improvement in the detection of the organism compared with the blood culture vial method and reduces the fraction of culture-negative septic arthritis in young children. The three *K. kingae*–specific genes that are targeted by the current tests are the *rtx* operon that encodes the RtxA toxin; the *cpn*60 (chaperonin 60 gene), also known as *gro*EL; and the malate dehydrogenase *(mdh)* gene that combines excellent sensitivity and specificity and should be the preferred method.

Because the bacterium frequently invades joints and bones that are small or difficult to reach or intervertebral disks, exudate samples or tissues are often unavailable for analysis. An alternative noninvasive diagnostic approach has been proposed consisting of obtaining an oropharyngeal specimen and subjecting it to a sensitive *K. kingae*–specific NAAT. A compatible clinical picture, coupled with a positive test result, supports *K. kingae* as the probable cause of the disease. This strategy has the obvious limitation that the background carriage rate of the organism is around 10% in children of the relevant age and twice as high in those attending daycare centers, reducing the predictive value of a positive result. On the other hand, because the colonized oropharynx is the source of the bloodborne dissemination of the bacterium, the negative predictive value of the assay is high. For practical purposes, failure to detect *K. kingae* DNA sequences when using a sensitive molecular test virtually rules out the organism as the etiology of the infection.

Novel commercially available plasma metagenomic next-generation sequencing assays appear to be a promising tool for detecting the organism, especially in patients with endocarditis receiving antibiotics.

TREATMENT

K. kingae is usually highly susceptible to penicillin and cephalosporins but exhibits decreased susceptibility to oxacillin, precluding the use of isoxazolyl penicillins for confirmed *K. kingae* infections. Although β-lactamase production is frequently detected in colonizing *K. kingae* strains, its prevalence among invasive organisms is low and shows wide geographic variation. Testing for β-lactamase production should be routinely performed in all isolates derived from normally sterile body sites.

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens according to protocols developed for infections caused by traditional bacterial pathogens. The first-line therapy for skeletal infections in young children usually consists of intravenous (IV) administration of a second- or third-generation **cephalosporin**, pending culture or NAAT results. *K. kingae* is always *resistant* to glycopeptide antibiotics and clindamycin, a serious concern in areas where skeletal infections caused by community-associated methicillin-resistant *Staphylococcus aureus* are common, and **vancomycin** or **clindamycin** are initially

administered to children with presumptive septic arthritis or osteomyelitis. The initial antibiotic regimen is frequently changed to a cephalosporin (e.g., ceftriaxone) once *K. kingae* is identified or to ampicillin after β-lactamase production is excluded. A favorable clinical response and decreasing CRP levels to ≤20 μg/mL are used to guide switching to oral antibiotics and defining the duration of therapy. Antibiotic treatment has ranged from 2 to 3 weeks for *K. kingae* arthritis, from 3 to 6 weeks for *K. kingae* osteomyelitis, and from 3 to 12 weeks for *K. kingae* spondylodiscitis. Although some children with septic arthritis have been managed with repeat joint aspirations and lavage, most patients respond promptly to conservative treatment with appropriate antibiotics and do not require invasive surgical procedures.

Children with *K. kingae* bacteremia without focal infection are initially treated with an IV β-lactam antibiotic and are subsequently switched to an oral drug once the clinical condition has improved. In most cases, therapy is administered for 1-2 weeks.

Patients with *K. kingae* endocarditis are usually treated with an IV β-lactam antibiotic alone or in combination with an aminoglycoside for 4-7 weeks. Early surgical intervention is necessary for life-threatening complications unresponsive to medical therapy.

PREVENTION

Because the risk of asymptomatic pharyngeal carriers for developing an invasive *K. kingae* infection is low, in the absence of clinical disease, there is no indication to eradicate the organism from the colonized mucosal surfaces. Nonetheless, in 25 reported outbreaks of *K. kingae* infections in child daycare centers, 68 of 402 (17%) classmates developed a proven or presumptive infection, including fatal endocarditis, within 1 month, indicating that the causative strains combined unusual transmissibility and virulence. Under these circumstances, prophylactic antibiotic therapy to eradicate colonization in contacts and prevent further cases of the disease has been employed, consisting of either rifampin alone 10 mg/kg or 20 mg/kg twice daily for 2 days or rifampin in combination with amoxicillin (80 mg/kg/day) for 2 days or 4 days. The effectiveness of these regimens has ranged between 47% and 80%, indicating that eradication of *K. kingae* from colonized mucosae is difficult to achieve. However, after antibiotic prophylaxis administration, no further cases of the disease have been detected, suggesting that reduction of the bacterial density by antibiotics, extinction of the precipitating viral infection, and/or induction of an effective immune response by prolonged carriage is enough to decrease transmissibility and prevent additional cases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 240

Haemophilus influenzae

Nadia A. Kadry and Joseph W. St. Geme III

Effective vaccines to prevent ***Haemophilus influenzae* type b (Hib)** disease, introduced in the United States and most other countries, have resulted in a dramatic decrease in the incidence of infections caused by this organism. However, mortality and morbidity from Hib infection remain a problem worldwide, primarily in resource poor countries. Occasional cases of invasive disease caused by non–type b strains continue to occur but are infrequent. Nontypeable isolates of *H. influenzae* are an important cause of otitis media, sinusitis, and chronic bronchitis.

ETIOLOGY

H. influenzae is a fastidious, gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates are surrounded by a polysaccharide capsule and can be segregated into one of six antigenically and biochemically distinct serotypes designated types a, b, c, d, e, and f. Isolates without a polysaccharide capsule are considered nontypeable. Isolates can also be categorized based on the production of indole and the presence of ornithine decarboxylase and urease and are sorted into biotypes I-VIII.

EPIDEMIOLOGY

Before the advent of an effective Hib conjugate vaccine in 1988, Hib was a major cause of serious disease among children. There was a striking age distribution of cases, with >90% in children <5 years old and the majority in children <2 years old. The annual attack rate of invasive disease was 64-129 cases per 100,000 children <5 years old. Invasive disease caused by strains producing a non–type b capsule has been much less frequent but continues to occur. The incidence of invasive disease caused by type b and non–type b serotypes has been estimated at approximately 0.08 and 1.02 cases, respectively, per 100,000 children <5 years old per year in the United States. Nontypeable (nonencapsulated) *H. influenzae* strains also occasionally cause invasive disease, especially in neonates, immunocompromised children, and children in resource poor countries. The estimated rate of invasive disease caused by nontypeable *H. influenzae* in the United States is 1.88 per 100,000 children <5 years old per year. Nontypeable isolates are common etiologic agents in otitis media, sinusitis, and chronic bronchitis. More recent evidence also implicates nasopharyngeal colonization with nontypeable *H. influenzae* in the development of asthma and allergic airway disease.

Humans are the only natural hosts for *H. influenzae,* which is part of the normal respiratory flora in 60–90% of healthy children. Most isolates are nontypeable. Before the advent of Hib conjugate vaccines, *H. influenzae* type b could be isolated from the pharynx of 2–5% of healthy preschool and school-age children, with lower rates among infants and adults. Asymptomatic colonization with Hib occurs at a much lower rate in immunized populations.

The continued circulation of type b strains despite current vaccine coverage levels suggests that elimination of Hib disease may be a formidable task. The few cases of Hib invasive disease in the United States now occur in both unvaccinated and fully vaccinated children. Approximately 50% of cases occur in infants who are too young to have received a complete primary vaccine series. Among the cases in patients who are old enough to have received a complete vaccine series, the majority are underimmunized. To highlight this point, during a shortage of Hib vaccine, invasive disease developed in five children in Minnesota, all of whom were incompletely immunized. Continued efforts are necessary to provide currently available Hib conjugate vaccines to children in resource poor countries, where affordability remains an important issue.

In the prevaccine era, certain groups and individuals had an increased incidence of invasive Hib disease, including Alaskan Natives, American Indians (Apache, Navajo), and African Americans. Persons with certain chronic medical conditions were also known to be at increased risk for invasive disease, including individuals with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies. Unvaccinated infants with invasive Hib infection are also at increased risk for recurrence, reflecting that they typically do not develop a protective immune response to *H. influenzae.*

Socioeconomic risk factors for invasive Hib disease include childcare outside the home, the presence of siblings of elementary school age or younger, short duration of breastfeeding, and parental smoking. A history of otitis media is associated with an increased risk for invasive disease. Much less is known about the epidemiology of invasive disease caused by non–type b strains, and it is not clear whether the epidemiologic features of Hib disease apply to disease caused by non-Hib strains.

Among age-susceptible household contacts who have been exposed to a case of invasive Hib disease, there is increased risk for secondary cases of invasive disease in the first 30 days after exposure, especially in susceptible children <24 months old. Whether a similar increased risk exists for contacts of individuals with non-Hib disease is unknown.

The mode of transmission is usually direct contact or inhalation of respiratory tract droplets containing *H. influenzae.* The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Most children with invasive Hib disease are colonized in the nasopharynx before initiation of antimicrobial therapy; 25–40% may remain colonized during the first 24 hours of therapy.

With the decline of disease caused by type b organisms, disease caused by other serotypes (a, c-f) and by nontypeable strains has been recognized more clearly. There is no evidence that non–type b infections have increased in frequency. However, clusters of type a and, less often, type e and type f infections have occurred. Data from Israel suggest that nontypeable *H. influenzae* is the most common cause of invasive *H. influenzae* disease in that country.

PATHOGENESIS

The pathogenesis of Hib disease begins with adherence to respiratory epithelium and colonization of the nasopharynx, which is mediated by pilus and nonpilus adherence factors. The mechanism of entry into the intravascular compartment is unclear but appears to be influenced by cytotoxic factors. Once in the bloodstream, Hib, and perhaps other encapsulated strains, resist intravascular clearance mechanisms at least in part because of the polysaccharide capsule. In the case of Hib, the magnitude and duration of bacteremia influence the likelihood of dissemination of bacteria to sites such as the meninges and joints.

Noninvasive *H. influenzae* infections such as otitis media, sinusitis, and bronchitis are usually caused by nontypeable strains. These organisms gain access to sites such as the middle ear and sinus cavities by direct extension from the nasopharynx. Factors facilitating spread from the nasopharynx include eustachian tube dysfunction and antecedent viral infections of the upper respiratory tract.

Antibiotic Resistance

Ampicillin resistance is increasingly common among *H. influenzae* isolates. Resistance is typically driven by plasmid-mediated production of a β-lactamase. β-lactamase–negative ampicillin-resistant isolates have been identified and manifest resistance by production of a β-lactam–insensitive cell wall synthesis enzyme called *penicillin binding protein 3* (PBP 3).

Amoxicillin-clavulanate is uniformly active against *H. influenzae* clinical isolates except for the rare β-lactamase–negative ampicillin-resistant isolates. Among macrolides, azithromycin has in vitro activity against a high percentage of *H. influenzae* isolates; in contrast, the activity of erythromycin and clarithromycin against *H. influenzae* clinical isolates is poor. *H. influenzae* resistance to third-generation cephalosporins has not been documented. Resistance to quinolones is rare, and resistance to trimethoprim-sulfamethoxazole (TMP-SMX) is present in approximately 10% of isolates.

Immunity

In the prevaccine era, the most important known element of host defense was antibody directed against the type b capsular polysaccharide polyribosylribitol phosphate **(PRP)**. Anti-PRP antibody is acquired in an age-related fashion and facilitates clearance of Hib from blood, in part related to opsonic activity. Antibodies directed against antigens such as outer membrane proteins or lipopolysaccharide (LPS) may also have a role in opsonization. Both the classical and alternative complement pathways are important in defense against Hib.

Before the introduction of vaccination, protection from Hib infection was presumed to correlate with the concentration of circulating anti-PRP antibody at the time of exposure. A serum antibody concentration of >0.15 μg/mL was considered protective against invasive infection. Unimmunized infants >6 months old and young children usually lacked an anti-PRP antibody concentration of this magnitude and were susceptible to disease after encountering Hib. This lack of antibody in infants and young children may have reflected a maturational delay in the immunologic response to thymus-independent type 2 antigens such as unconjugated PRP, presumably explaining the high incidence of type b infections in infants and young children in the prevaccine era.

The conjugate vaccines act as thymus-dependent antigens and elicit serum antibody responses in infants and young children (Table 240.1). These vaccines are believed to prime memory antibody responses on subsequent encounters with PRP. The concentration of circulating anti-PRP antibody in a child primed by a conjugate vaccine may not correlate precisely with protection, presumably because a memory response may occur rapidly on exposure to PRP and provide protection. Conjugate vaccines have been shown to be highly effective against Hib disease and have been shown to reduce nasopharyngeal carriage rates.

Much less is known about immunity to other *H. influenzae* serotypes or to nontypeable isolates. For nontypeable isolates, evidence suggests that antibodies directed against one or more outer membrane proteins are bactericidal and protect against experimental challenge. A variety of antigens have been evaluated in an attempt to identify vaccine candidates for nontypeable *H. influenzae,* including outer membrane proteins (P1, P2, P4, P5, P6, D15, and Tbp A/B), LPS, various adhesins (e.g., Hap, HMW1, and HMW2), and lipoprotein D.

DIAGNOSIS

Presumptive identification of *H. influenzae* is established by direct examination of a clinical specimen after staining with Gram reagents. Because of its small size, pleomorphism, and occasional poor uptake of stain, as well as the tendency for proteinaceous fluids to have a red background, *H. influenzae* is sometimes difficult to visualize. Furthermore, given that identification of *H. influenzae* by microscopy requires at least 10^5 bacteria/mL in a clinical specimen (e.g., cerebrospinal fluid [CSF]), failure to visualize organisms does not preclude their presence.

Culture of *H. influenzae* requires prompt transport and processing of specimens because the organism is fastidious. Specimens should not be exposed to drying or temperature extremes. Primary isolation of *H. influenzae* can be accomplished on chocolate agar.

Serotyping of *H. influenzae* is accomplished by slide agglutination with type-specific antisera or through polymerase chain reaction (PCR) amplification of the capsule locus *(cap)*. Importantly, antigen-based detection methods are prone to false positives because of antigen cross-reactivity with other encapsulated organisms and are therefore not recommended as the primary diagnostic approach. Real-time PCR and nucleic acid amplification tests (NAATs) can be used to specifically detect *H. influenzae*. Accurate serotyping is essential to monitor progress toward elimination of type b invasive disease. Timely reporting of cases to public health authorities should be ensured.

CLINICAL MANIFESTATIONS AND TREATMENT

The initial antibiotic therapy for invasive infections possibly caused by *H. influenzae* should be a parenterally administered antibiotic effective

Table 240.1 *Haemophilus influenzae* Type b (Hib) Conjugate Vaccines Available in the United States

VACCINE	TRADE NAME	COMPONENTS	MANUFACTURER
PRP-T	ActHib	PRP conjugated to tetanus toxoid	Sanofi
PRP-T	Hibrix	PRP conjugated to tetanus toxoid	GlaxoSmithKline Biologicals
PRP-OMP	PedvaxHIB	PRP conjugated to OMP	Merck
PRP-T/DTaP-IPV	Pentacel	PRP-T + DTaP-IPV vaccines	Sanofi Pasteur
PRP-OMP/DTaP-IPV-HepB	Vaxelis	PRP-OMP + DTaP-IPV + HepB vaccines	Merck

DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepB, hepatitis B vaccine; IPV, trivalent inactivated polio vaccine; OMP, outer membrane protein complex from *Neisseria meningitidis*; PRP, polyribosylribitol phosphate.

in sterilizing all foci of infection and effective against ampicillin-resistant strains, usually an **extended-spectrum cephalosporin** such as ceftriaxone. After the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. **Ampicillin** remains the drug of choice for the therapy of infections caused by susceptible isolates. If the isolate is resistant to ampicillin, in selected circumstances **ceftriaxone** can be administered once daily for outpatient therapy.

Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and are typically initial therapy for noninvasive infections such as otitis media and sinusitis. If the organism is susceptible, **amoxicillin** is the drug of choice. An oral second- or third-generation cephalosporin or amoxicillin-clavulanate may be used when the isolate is resistant to ampicillin.

Meningitis

In the prevaccine era, meningitis accounted for more than half of all cases of invasive *H. influenzae* disease. Clinically, meningitis caused by Hib cannot be differentiated from meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* (see Chapter 643.1). It may be complicated by other foci of infection such as the lungs, joints, bones, and pericardium.

Antimicrobial therapy should be administered intravenously for 7-14 days for uncomplicated cases. Ceftriaxone and ampicillin cross the blood-brain barrier during acute inflammation in concentrations adequate to treat *H. influenzae* meningitis. Intramuscular therapy with ceftriaxone may be an alternative in patients with normal organ perfusion.

The prognosis of Hib meningitis depends on the age at presentation, duration of illness before appropriate antimicrobial therapy, CSF capsular polysaccharide concentration, and rapidity with which organisms are cleared from CSF, blood, and urine. Clinically manifested inappropriate secretion of antidiuretic hormone and evidence of focal neurologic deficits at presentation are poor prognostic features. Approximately 6% of patients with Hib meningitis are left with some hearing impairment, probably because of inflammation of the cochlea and the labyrinth. **Dexamethasone** (0.6 mg/kg/day divided every 6 hours for 2 days), particularly when given shortly before or concurrent with the initiation of antimicrobial therapy, decreases the incidence of hearing loss. Major neurologic sequelae of Hib meningitis include behavior problems, language disorders, impaired vision, mental retardation, motor abnormalities, ataxia, seizures, and hydrocephalus.

Cellulitis

Children with Hib cellulitis often have an antecedent upper respiratory tract infection. They usually have no prior history of trauma, and the infection is thought to represent seeding of the organism to the involved soft tissues during bacteremia. The head and neck, particularly the cheek and preseptal region of the eye, are the most common sites of involvement. The involved region generally has indistinct margins and is tender and indurated. **Buccal cellulitis** is classically erythematous with a violaceous hue, although this sign may be absent. *H. influenzae* may often be recovered directly from an aspirate of the leading edge, although this procedure is seldom performed. A blood culture may also reveal the causative organism. Other foci of infection may be present concomitantly, particularly in children <18 months old. A diagnostic lumbar puncture should be considered at diagnosis in these children.

Parenteral antimicrobial therapy is indicated until patients become afebrile, after which an appropriate oral antimicrobial agent may be substituted. A 7- to 10-day course is customary.

Preseptal Cellulitis

Infection involving the superficial tissue layers anterior to the orbital septum is termed *preseptal cellulitis,* which may be caused by *H. influenzae.* Uncomplicated preseptal cellulitis does not imply a risk for visual impairment or direct central nervous system (CNS) extension. However, concurrent bacteremia may be associated with the development of meningitis. *H. influenzae* preseptal cellulitis is characterized by fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration. Evidence of interruption of the integument is usually absent. Conjunctival drainage may be associated. *S. pneumoniae, Staphylococcus aureus,* and group A *Streptococcus* cause clinically indistinguishable preseptal cellulitis. The latter two pathogens are more likely when fever is absent and the integument is interrupted (e.g., because of an insect bite or trauma).

Children with preseptal cellulitis in whom *H. influenzae* and *S. pneumoniae* are etiologic considerations (young age, high fever, intact integument) should have a blood culture obtained. In addition, a diagnostic lumbar puncture should be considered.

Parenteral antibiotics are indicated for preseptal cellulitis. Because methicillin-susceptible and methicillin-resistant *S. aureus, S. pneumoniae,* and group A β-hemolytic streptococci are other causes, empirical therapy should include agents active against these pathogens. Patients with preseptal cellulitis without concurrent meningitis should receive **parenteral therapy for about 5 days, until fever and erythema have abated**. In uncomplicated cases, antimicrobial therapy should be given for 10 days.

Orbital Cellulitis

Infections of the orbit are infrequent and usually develop as complications of acute ethmoid or sphenoid sinusitis. Orbital cellulitis may manifest as lid edema but is distinguished by the presence of proptosis, chemosis, impaired vision, limitation of the extraocular movements, decreased mobility of the globe, or pain on movement of the globe. The distinction between preseptal and orbital cellulitis may be difficult and is best determined by CT scan.

Orbital infections are treated with **parenteral therapy for at least 14 days**. Underlying sinusitis or orbital abscess may require surgical drainage and more prolonged antimicrobial therapy.

Supraglottitis or Acute Epiglottitis

Supraglottitis is a cellulitis of the tissues of the laryngeal inlet (see Chapter 433). It has become exceedingly rare since the introduction of conjugate Hib vaccines. Direct bacterial invasion of the involved tissues is probably the initiating pathophysiologic event. This dramatic, potentially lethal condition can occur at any age. Because of the risk of sudden, unpredictable airway obstruction, supraglottitis is a medical emergency. Other foci of infection, such as meningitis, are rare. Antimicrobial therapy directed against *H. influenzae* and other etiologic agents should be administered parenterally, but only after the airway is secured, and therapy should be continued until patients are able to take fluids by mouth. The duration of antimicrobial therapy is typically 7 days.

Pneumonia

The true incidence of *H. influenzae* pneumonia in children is unknown because invasive procedures required to obtain culture specimens are seldom performed (see Chapter 449). In the prevaccine era, type b strains were believed to be the usual cause. The signs and symptoms of pneumonia caused by *H. influenzae* cannot be differentiated from those of pneumonia caused by many other microorganisms. Other foci of infection may be present concomitantly.

Children <12 months old in whom *H. influenzae* pneumonia is suspected should receive parenteral antimicrobial therapy initially because of their increased risk for bacteremia and its complications. Older children who do not appear severely ill may be managed with an oral antimicrobial. Therapy is continued for 7-10 days. Uncomplicated pleural effusion associated with *H. influenzae* pneumonia requires no special intervention. However, if empyema develops, chest tube or **surgical drainage** is generally indicated.

Suppurative Arthritis

Large joints, such as the knee, hip, ankle, and elbow, are affected most often (see Chapter 726). Other foci of infection may be present concomitantly. Although single-joint involvement is the rule, multijoint involvement occurs in approximately 6% of cases. The signs and symptoms of septic arthritis caused by *H. influenzae* are indistinguishable from those in arthritis caused by other bacteria.

Uncomplicated septic arthritis should generally be treated with an appropriate **parenteral antimicrobial for at least a few days**. If the clinical response is satisfactory, the remainder of the course of

antimicrobial treatment may be given orally. Therapy is typically given for 3 weeks for uncomplicated septic arthritis, but may be continued beyond 3 weeks, until the C-reactive protein concentration is normal and clinical symptoms are resolved.

Pericarditis

H. influenzae is a rare cause of pericarditis (see Chapter 489). Affected children often have had an antecedent upper respiratory tract infection. Fever, respiratory distress, and tachycardia are consistent findings. Other foci of infection may be present concomitantly.

The diagnosis may be established by recovery of the organism from blood or pericardial fluid. Gram stain or detection of PRP in pericardial fluid, blood, or urine (when type b organisms are the cause) may aid the diagnosis**.** Antimicrobials should be provided parenterally in a regimen similar to that used for meningitis (see Chapter 643.1). Pericardiectomy is useful for draining the purulent material effectively and preventing tamponade and constrictive pericarditis.

Bacteremia Without an Associated Focus

Bacteremia caused by *H. influenzae* may be associated with fever without any apparent focus of infection (see Chapter 220). In this situation, risk factors for occult bacteremia include the magnitude of fever (≥39°C [102.2°F]) and the presence of leukocytosis (≥15,000 cells/μL). In the prevaccine era, meningitis developed in approximately 25% of children with occult Hib bacteremia if left untreated. In the vaccine era, this *H. influenzae* infection has become exceedingly rare. When it does occur, the child should be reevaluated for a focus of infection and a second blood culture should be performed. The child should be hospitalized and given parenteral antimicrobial therapy after a diagnostic lumbar puncture and chest radiograph are obtained.

Miscellaneous Infections

Rarely, *H. influenzae* causes urinary tract infection, epididymoorchitis, cervical adenitis, acute glossitis, infected thyroglossal duct cysts, uvulitis, endocarditis, endophthalmitis, primary peritonitis, osteomyelitis, and periappendiceal abscess.

Invasive Disease in Neonates

Neonates occasionally have invasive *H. influenzae* infection. In the infant with illness within the first 24 hours of life, especially in association with maternal chorioamnionitis or prolonged rupture of membranes, transmission of the organism to the infant is likely to have occurred through the maternal genital tract (which is colonized with nontypeable *H. influenzae* in <1% of pregnant women). Manifestations of neonatal invasive infection include bacteremia with sepsis, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess or cellulitis, and meningitis. Less frequently, mastoiditis, septic arthritis, and congenital vesicular eruption may occur.

Otitis Media

Acute otitis media is one of the most common infectious diseases of childhood (see Chapter 680). It results from the spread of bacteria from the nasopharynx through the eustachian tube into the middle ear cavity. Usually, because of a preceding viral upper respiratory tract infection, the mucosa in the area becomes hyperemic and swollen, resulting in obstruction and an opportunity for bacterial multiplication in the middle ear.

The most common bacterial pathogens are *H. influenzae, S. pneumoniae,* and *Moraxella catarrhalis.* Most *H. influenzae* isolates causing otitis media are nontypeable. Ipsilateral conjunctivitis may also be present. **Amoxicillin (80-90 mg/kg/day)** is a suitable first-line oral antimicrobial agent, because the probability that the causative isolate is resistant to amoxicillin and the risk for invasive potential are sufficiently low to justify this approach. Alternatively, in certain cases, a single dose of ceftriaxone constitutes adequate therapy.

In the case of treatment failure or if a β-lactamase–producing isolate is obtained by tympanocentesis or from drainage fluid, amoxicillin-clavulanate (Augmentin) is a suitable alternative.

Conjunctivitis

Acute infection of the conjunctivae is common in childhood (see Chapter 666). In neonates, *H. influenzae* is an infrequent cause. However, it is an important pathogen in older children. Most *H. influenzae* isolates associated with conjunctivitis are nontypeable, although type b isolates and other serotypes are occasionally found. Empirical treatment of conjunctivitis beyond the neonatal period usually consists of topical antimicrobial therapy with **sulfacetamide**. Topical fluoroquinolone therapy is to be avoided because of its broad spectrum, high cost, and high rate of emerging resistance among many bacterial species. Ipsilateral otitis media caused by the same organism may be present and requires oral antibiotic therapy.

Sinusitis

H. influenzae is an important cause of acute sinusitis in children, likely the most common etiology since implementation of routine vaccination against *S. pneumoniae* (see Chapter 429). Chronic sinusitis lasting >1 year or severe sinusitis requiring hospitalization is often caused by *S. aureus* or anaerobes such as *Peptococcus, Peptostreptococcus,* and *Bacteroides.* Nontypeable *H. influenzae* and viridans group streptococci are also frequently recovered.

For uncomplicated sinusitis, **amoxicillin** is acceptable initial therapy. However, if clinical improvement does not occur, a broader-spectrum agent, such as amoxicillin-clavulanate, may be appropriate. A 10-day course is sufficient for uncomplicated sinusitis. Hospitalization for parenteral therapy is rarely required; the usual reason is suspicion of progression to orbital cellulitis.

PREVENTION

Immunization with a Hib conjugate vaccine is recommended for all infants. Prophylaxis is indicated if close contacts of an index patient with type b disease are unvaccinated. The contagiousness of non-Hib infections is not known, and prophylaxis is not recommended.

Vaccine

Several Hib conjugate vaccines are currently marketed in the United States, containing either PRP–outer membrane protein **(PRP-OMP)** or PRP–tetanus toxoid **(PRP-T)**, which differ in the carrier protein used and the method of conjugating the polysaccharide to the protein (see Table 240.1 and Chapter 215). Available combination vaccines include Pentacel (Sanofi Pasteur), which consists of PRP-T combined with DTaP vaccine (diphtheria and tetanus toxoids and acellular pertussis) and IPV vaccine (trivalent, inactivated polio vaccine), and Vaxelis (Merck), which consists of PRP-OMP combined with DTaP, IPV, and hepatitis B vaccine.

The Hib conjugate vaccines stimulate circulating anticapsular antibody and provide long-term immunity through B-cell memory.

Prophylaxis

Unvaccinated children <48 months old who are in close contact with an index case of invasive Hib infection are at increased risk for invasive infection. The risk for secondary disease for children >3 months old is inversely related to age. About half the secondary cases among susceptible household contacts occur in the first week after hospitalization of the index case. Because many children are now protected against Hib by prior immunization, the need for prophylaxis has greatly decreased. When prophylaxis is used, **rifampin** is indicated for all members of the household or close-contact group, including the index patient, if the group includes one or more children <48 months old who are not fully immunized.

Parents of children hospitalized for invasive Hib disease should be informed of the increased risk for secondary infection in other young children in the same household if they are not fully immunized. Parents of children exposed to a single case of invasive Hib disease in a childcare center or nursery school should be similarly informed, although there is disagreement about the need for rifampin prophylaxis for these children.

For prophylaxis, children should be given rifampin orally (0-1 months old, 10 mg/kg/dose; >1 month old, 20 mg/kg/dose, not to exceed 600 mg/dose) once daily for 4 consecutive days. The adult dose is 600 mg once daily. Rifampin prophylaxis is not recommended for pregnant women.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 241

Chancroid *(Haemophilus ducreyi)*

H. Dele Davies and Shirley Delair

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inguinal lymphadenopathy.

ETIOLOGY AND EPIDEMIOLOGY

Chancroid is caused by *Haemophilus ducreyi,* a fastidious gram-negative bacillus. It is most common in many low- and middle-income countries but also occurs sporadically in high-income countries. Most cases in high-income countries occur in returning travelers (90% are male) from endemic areas or occasionally in localized urban outbreaks associated with commercial sex workers. Chancroid is a risk factor for transmission of HIV. Diagnosis of chancroid in infants and children is strong evidence of sexual abuse. Male circumcision lowers the risk for chancroid. The incidence of chancroid has declined significantly since 1981 and remains low in the United States.

CLINICAL MANIFESTATIONS

The incubation period is 4-7 days, with a small, inflammatory papule on the preputial orifice or frenulum in men and on the labia, fourchette, or perineal region in women. The lesion becomes pustular, eroded, and ulcerative within 2-3 days. The ulcer edge is classically ragged and undermined. Without treatment, the ulcers may persist for weeks to months. Painful, tender inguinal lymphadenitis occurs in >50% of cases, more often among men. The lymphadenopathy can become fluctuant to form **buboes**, which can spontaneously rupture.

DIAGNOSIS

Diagnosis is usually established by the clinical presentation and the exclusion of both syphilis *(Treponema pallidum)* and herpes simplex virus infections. The ulcer of chancroid is accompanied by concurrent **lymphadenopathy** that is usually unilateral, unlike lymphogranuloma venereum (see Chapter 272.4). Genital herpes is characterized by vesicular lesions with a history of recurrence (see Chapter 299). Gram stain of ulcer secretions may show gram-negative coccobacilli in parallel clusters ("school of fish"). Culture requires expensive, special media and has a sensitivity of only 80%. There are currently no U.S. Food and Drug Administration (FDA)–approved polymerase chain reaction (PCR) tests for *H. ducreyi*. PCR and indirect immunofluorescence using monoclonal antibodies are available as research tools and are performed by some clinical laboratories using their own in-house Clinical Laboratory Improvement Amendments (CLIA)–verified kits.

TREATMENT

Most *H. ducreyi* organisms are resistant to penicillin and ampicillin because of plasmid-mediated β-lactamase production. Spread of plasmid-mediated resistance among *H. ducreyi* has resulted in lack of efficacy of previously useful drugs such as sulfonamides and tetracyclines. Chancroid is easy to treat if recognized early. The current treatment recommendation is for **azithromycin** (1 g as a single dose orally [PO]) or **ceftriaxone** (250 mg as a single dose intramuscularly) or **ciprofloxacin** (500 mg twice daily PO for 3 days) or **erythromycin** (500 mg 3 times daily PO for 7 days), the latter most often used in low- and middle-income countries, Fluctuant nodes may require drainage. Symptoms usually resolve within 3-7 days. Relapses can usually be treated successfully with the original treatment regimen. Patients with HIV infection may require a longer duration of treatment. Persistence of the ulcer and the organism after therapy should raise suspicion of resistance to the prescribed antibiotic.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, genital herpes, hepatitis B virus, HIV, chlamydia, and gonorrhea; an estimated 10% have concomitant syphilis or genital herpes. If initial HIV or syphilis testing is negative, patients should be tested again in 3 months because of the high rates of co-infections. In low- and middle-income countries, patients with a compatible genital ulcer are treated for both chancroid and syphilis. All sexual contacts of patients with chancroid should be evaluated and treated.

COMPLICATIONS

Complications include **phimosis** in men and secondary bacterial infection. **Bubo** formation may occur in untreated cases. Genital ulceration as a syndrome increases the risk for transmission of HIV.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 242

Moraxella catarrhalis

Timothy F. Murphy and Oscar G. Gómez-Duarte

Moraxella catarrhalis is an unencapsulated, gram-negative diplococcus and is a **human-specific pathogen** that colonizes the respiratory tract beginning in infancy. Patterns of colonization and infection with *M. catarrhalis* are changing in countries where pneumococcal conjugate vaccines are used widely. The most important clinical manifestation of *M. catarrhalis* infection in children is **otitis media**.

ETIOLOGY

M. catarrhalis has long been considered to be an upper respiratory tract commensal. Substantial genetic heterogeneity exists among strains of *M. catarrhalis*. Several outer membrane proteins demonstrate sequence differences among strains, particularly in regions of the proteins that are exposed on the bacterial surface. *M. catarrhalis* endotoxin lacks repeating polysaccharide side chains and is thus a lipooligosaccharide (LOS). In contrast to other gram-negative respiratory pathogens, such as *Haemophilus influenzae* and *Neisseria meningitidis,* the LOS of *M. catarrhalis* is relatively conserved among strains; only three serotypes (A, B, and C), based on oligosaccharide structure, have been identified. Genetic and antigenic differences among strains account for the observation that resolving an infection by one strain does not induce protective immunity to other strains. *M. catarrhalis* causes recurrent infections, which generally represent reinfection by new strains.

EPIDEMIOLOGY

The ecologic niche of *M. catarrhalis* is the human respiratory tract. The bacterium has not been recovered from animals or environmental sources. **Age** is the most important determinant of the prevalence of upper respiratory tract colonization. Common throughout infancy, nasopharyngeal colonization is a dynamic process with active turnover as a result of acquisition and clearance of strains of *M. catarrhalis*. Some geographic variation in rates of colonization is observed. On the basis of monthly or bimonthly cultures, colonization during the first year of life may range from 33% to 100%. Several factors likely account for this variability among studies, including living conditions, daycare attendance, hygiene, environmental factors (e.g., household smoking), and genetics of the population. The prevalence of colonization steadily decreases with age. Understanding nasopharyngeal colonization patterns is important, because the pathogenesis of otitis media involves migration of the bacterium from the nasopharynx to the middle ear via the eustachian tube.

The widespread use of pneumococcal polysaccharide vaccines in many countries has resulted in alteration of patterns of nasopharyngeal colonization in the population. A relative decrease in colonization by vaccine pneumococcal serotypes and *M. catarrhalis* has resulted in a decreased number of new upper respiratory infection episodes **associated with** *Streptococcus pneumoniae* and *M. catarrhalis*.

PATHOGENESIS OF INFECTION

Strains of *M. catarrhalis* differ in their virulence properties. The species is composed of complement-resistant and complement-sensitive genetic lineages, with the **complement-resistant** strains being more strongly associated with virulence. Strains that cause infection in children differ in several phenotypic characteristics from strains that cause infection in adults, in whom the most common clinical manifestation is lower respiratory tract infection in the setting of chronic obstructive pulmonary disease.

The presence of several **adhesin** molecules with differing specificities for various host cell receptors reflects the importance of adherence to the human respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* has long been viewed as an exclusively extracellular pathogen. However, the bacterium is now known to invade multiple cell types, including bronchial epithelial cells, small airway cells, and type 2 alveolar cells. In addition, *M. catarrhalis* resides intracellularly in lymphoid tissue, providing a reservoir for persistence in the human respiratory tract. As with many gram-negative bacteria, *M. catarrhalis* sheds vesicles from its surface during growth. These vesicles are internalized by respiratory epithelial cells and mediate several virulence mechanisms, including B-cell activation, induction of inflammation, and delivery of β-lactamases. Analysis of genomes reveals modest genetic heterogeneity among strains.

M. catarrhalis forms biofilms in vitro and in the middle ears of children with chronic and recurrent otitis media. It also promotes stable polymicrobial biofilms by enhancing the survival of other bacterial colonizing otopathogens. **Biofilms** are communities of bacteria encased in a matrix attached to a surface. Bacteria in biofilms are more resistant to antibiotics and to host immune responses than bacteria growing individually in planktonic form.

CLINICAL MANIFESTATIONS

M. catarrhalis causes predominantly mucosal infections in children. The mechanism of infection is **migration** of the infecting strains from the nasopharynx to the middle ear in the case of otitis media or to the sinuses in the case of sinusitis. The inciting event for both otitis media and sinusitis is often a preceding viral infection.

Acute Otitis Media

Approximately 80% of children have one or more episodes of otitis media by age 3 years. Otitis media is the most common reason that children receive antibiotics. On the basis of culture of middle ear fluid obtained by tympanocentesis, the predominant causes of acute otitis media are *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. *M. catarrhalis* is cultured from the middle ear fluid in 15–20% of patients with acute otitis media. When more sensitive methods (e.g., polymerase chain reaction [PCR]) are used, the number of middle ear fluid samples from children with otitis media in which *M. catarrhalis* is detected is substantially greater than by culture alone. The distribution of the causative agents of otitis media is changing as a result of widespread administration of pneumococcal conjugate vaccines, with *M. catarrhalis* and *H. influenzae* proportionally more common than *S. pneumoniae*.

Acute otitis media caused by *M. catarrhalis* is clinically milder than otitis media caused by *H. influenzae* or *S. pneumoniae,* with less fever and lower prevalence of a red, bulging tympanic membrane. However, substantial overlap in symptoms is seen, making it impossible to predict etiology in an individual child on the basis of clinical features. Tympanocentesis is required to make an etiologic diagnosis but is not performed routinely, and thus treatment of otitis media is generally empirical.

Recurrent Otitis Media and Otitis Media with Effusion

Otitis media with effusion refers to the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection. Children who experience four or more episodes of acute otitis media in a year or who have at least 8 months of middle ear effusion in a year are defined as **otitis prone**. These children have conductive hearing loss, which places them at risk for speech delays and altered language development. Analysis of middle ear fluid from children with otitis media with effusion using sensitive molecular techniques (e.g., PCR) indicates that bacterial DNA is present in up to 80% of samples from such children. Indeed, *M. catarrhalis* DNA is present, both alone and as a copathogen, in a larger proportion of cases of otitis media with effusion than of acute otitis media. Biofilms may account for these observations, although definitive evidence is lacking.

Sinusitis

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. According to findings of studies that use sinus puncture, *M. catarrhalis* accounts for approximately 20% of cases of acute bacterial sinusitis in children and a smaller proportion in adults. Sinusitis caused by *M. catarrhalis* is clinically indistinguishable from that caused by *S. pneumoniae* or *H. influenzae*.

Bacteremia

M. catarrhalis rarely causes bacteremia or invasive infections in children. When bacteremia occurs, the usual source is the respiratory tract. Some children have underlying immunocompromising conditions, but no particular immunodeficiency is associated with invasive *M. catarrhalis* infections.

Pneumonia

M. catarrhalis is an uncommon cause of community-acquired pneumonia in children. Among older patients with chronic obstructive pulmonary disease, *M. catarrhalis* is associated with acute exacerbations.

DIAGNOSIS

The clinical diagnosis of otitis media is made by demonstration of erythema and bulging of the tympanic membrane and/or fluid in the middle ear by pneumatic otoscopy. A tympanocentesis is required to establish an etiologic diagnosis, but this procedure is not performed routinely. Thus the choice of antibiotic for otitis media is empirical and generally based on guidelines. Management of bacterial sinusitis is also empirical, because determining the etiology of sinusitis requires a **sinus puncture**, also a procedure that is not performed routinely.

The key to making a microbiologic diagnosis is distinguishing *M. catarrhalis* from commensal *Neisseria* organisms that are part of the normal upper respiratory tract flora. Indeed, the difficulty in distinguishing colonies of *M. catarrhalis* from *Neisseria* spp. explains in part why *M. catarrhalis* has been overlooked in the past as a respiratory tract pathogen. *M. catarrhalis* produces round, opaque colonies that can be slid across the agar surface without disruption—the "hockey puck sign." In addition, after 48 hours, *M. catarrhalis* colonies tend to be larger than *Neisseria* and take on a pink color. A variety of biochemical tests distinguish *M. catarrhalis* from *Neisseria* spp., and commercially available kits based on these tests are available.

Sensitive tests that employ PCR to detect respiratory tract bacterial pathogens in human respiratory tract secretions are in development. In addition, metagenomics next-generation sequencing is a noninvasive option to make a diagnosis of upper or lower respiratory infections associated with *M. catarrhalis* through evaluation of bacterial-derived DNA in blood samples. Their application will likely contribute new information about the epidemiology and disease patterns of *M. catarrhalis*.

TREATMENT

A high proportion of cases of *M. catarrhalis* otitis media resolve spontaneously. Treatment of otitis media is empirical, and clinicians are advised to follow guidelines of the American Academy of Pediatrics (see Chapter 680).

Strains of *M. catarrhalis* rapidly acquired β-lactamase worldwide in the 1970s and 1980s, rendering essentially all strains resistant to amoxicillin. When *M. catarrhalis* is present as a copathogen in otitis media, its β-lactamase reduces the susceptibility of nontypeable *H. influenzae* and *S. pneumoniae* to amoxicillin. Antimicrobial susceptibility patterns have remained relatively stable for decades. However, strains of *M. catarrhalis* that are resistant to macrolides and fluoroquinolones have been isolated in several centers in Asia. Careful surveillance will be important to track the potential emergence of resistant strains more widely. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides (azithromycin, clarithromycin), trimethoprim-sulfamethoxazole, and fluoroquinolones.

PREVENTION

Vaccines to prevent otitis media and other infections caused by *M. catarrhalis* are under development, but none is yet available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 243

Pertussis (*Bordetella pertussis* and *Bordetella parapertussis*)

Emily E. Souder and Sarah S. Long

Pertussis is an acute respiratory tract infection; the term *pertussis* means "intense cough" and is preferable to *whooping cough,* because most infected individuals do not "whoop."

ETIOLOGY

Bordetella pertussis is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe and has been detected during occasional regional pertussis outbreaks in the United States. *B. pertussis* and *B. parapertussis* are exclusive pathogens of humans and some primates. *Bordetella holmesii,* first identified as a cause of bacteremia in immunocompromised hosts without cough illness, is increasingly reported to cause pertussis-like cough illness in small outbreaks in healthy persons. *Bordetella bronchiseptica* is a common animal pathogen. Occasional reports in humans describe a variety of body sites involved, and cases typically occur in immunocompromised persons or young children with intense exposure to animals. *Bordetella petrii,* frequently found in soil, has been reported in cases of osteomyelitis, mastoiditis, and chronic respiratory infection in patients with cystic fibrosis. *Bordetella hinzii* has been isolated from the respiratory tract of poultry and rodents and has rarely been associated with human disease, including endocarditis, bacteremia, and urinary tract infection. Protracted coughing (which in some cases can be paroxysmal) is attributable sporadically to *Mycoplasma,* parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial virus (RSV), or adenoviruses.

EPIDEMIOLOGY

A recent modeling study estimated that in 2014, 24.1 million cases of pertussis and 160,700 deaths caused by pertussis occurred worldwide in children <5 years, reflecting significantly higher numbers than actual case counts. Before vaccination was available, pertussis was the leading cause of death from communicable disease among U.S. children <14 years, with 10,000 deaths annually. Widespread use of whole cell pertussis vaccine (DTP) led to a >99% decline in cases. After the low U.S. number of 1,010 cases reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases per 100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989–1990, 1993, and 1996. Since then, pertussis has become increasingly endemic, with shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the United States was 8.9 cases per 100,000 in the general population and approximately 150 per 100,000 in infants <2 months, with 25,827 total cases reported, the highest since 1959. A total of 40 pertussis-related deaths were reported in 2005, and 16 pertussis-related deaths were reported in 2006; >90% of these cases occurred in infants.

Prospective and serologic studies show that pertussis is underrecognized, especially among adolescents and adults, in whom the actual number of U.S. cases is estimated to be 600,000 annually. A number of studies have documented pertussis in 13–32% of adolescents and adults with cough illness for >7 days. Responding to these changes in epidemiology, vaccination containing tetanus toxoid, reduced-content diphtheria toxoid, and acellular pertussis antigens **(Tdap)** was recommended in 2006 for 11- to 12-year-olds and was aimed to enhance control. With >70% uptake of Tdap in adolescents, the burden of disease in young adolescents fell commensurately, but without evidence of protection of the community (herd) of young infants, older adolescents, and adults. An epidemiologic shift has occurred as a result of substantial and rapid waning of protection after both DTaP and Tdap in the aging cohort of children and adolescents who were not primed with DTP (whole cell) vaccine, which was no longer used in the United States after 1997. The >42,000 cases of pertussis and 20 deaths reported in 2012 were the highest numbers in >50 years. A shift in disease burden was observed among 7- to 10-year-olds in 2010, 13- to 14-year-olds in 2012, and 14- to 16-year-olds in 2014 as the cohort of solely DTaP-vaccinated persons aged.

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis can be attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure and increased awareness and improved diagnostics. Rapidly waning vaccine-induced immunity and pathogen adaptation are the most important factors currently. Although the DTaP series is protective short-term, vaccine effectiveness wanes rapidly, with estimates of only 10% protection 8.5 years after the fifth dose. Tdap protection also is short-lived, with efficacy falling from >70% initially to 34% within 2-4 years. A retrospective cohort study of children born between 1999 and 2016 found that the risk of pertussis among immunized children was 5 times higher ≥3 years after vaccination compared with <1 year after vaccination. Divergence of circulating strains from vaccine strains began with the introduction of DTP, but with the exclusive use of acellular pertussis vaccines, **pertactin-deficient strains** emerged and have become dominant in countries where these vaccines are used. Pertactin-deficient *B. pertussis* was first reported in the United States from a Philadelphia infant case collection from 2008 to 2011. The Centers for Disease Control and Prevention (CDC) subsequently reported the earliest U.S. isolate from 1994 and rapid dominance of pertactin-deficient strains in the United States since 2010. Despite the role of pertactin as a bacterial virulence factor, illness severity in infants with pertactin-deficient *B. pertussis* is similar to that of pertactin-producing strains. Pending introduction of novel pertussis vaccine(s) that reduce colonization and transmission, pertussis will continue to be endemic, with cycling epidemics.

PATHOGENESIS

Bordetella organisms are small, fastidious, gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of DNA homology among virulence genes. Only *B. pertussis* expresses **pertussis toxin (PT),** the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction). Although injection of PT in experimental animals causes lymphocytosis immediately by rerouting lymphocytes to remain in the circulating blood pool, PT

does not cause cough. PT appears to have a central, but not a singular, role in pathogenesis. *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, **filamentous hemagglutinin (FHA)**, some **agglutinogens** (especially fimbriae [Fim] types 2 and 3), and the 69-kDa **pertactin (Prn)** protein are important for attachment to ciliated respiratory epithelial cells. **Tracheal cytotoxin**, **adenylate cyclase**, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, **dermonecrotic factor**, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT. Both antibody and cellular immune responses follow infection and immunization. Antibody to PT neutralizes toxin, and antibody to Prn enhances opsonophagocytosis. Both disease and DTP appear to drive a mixed cellular and antibody (Th1) immunologic response, whereas both DTaP and Tdap drive a narrow, antibody-dominant (Th2) response.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccination with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure, as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients—usually a sibling or related adult.

CLINICAL MANIFESTATIONS

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The **catarrhal stage** (1-2 weeks) begins insidiously after an incubation period ranging from 3 to 12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the **paroxysmal stage** (2-6 weeks). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. **Posttussive emesis** is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have one or more episodes hourly. As the paroxysmal stage fades into the **convalescent stage** (≥2 weeks), the number, severity, and duration of episodes diminish.

Infants <3 months old do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase, and whoop is infrequent. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur as the only symptom (without cough). Both are more common with pertussis than with neonatal viral infections. The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. "Exacerbations" of paroxysmal coughing can occur throughout the first year of life with subsequent respiratory illnesses; these are not a result of recurrent infection or reactivation of *B. pertussis*.

Adolescents and previously immunized children have foreshortening of all stages of pertussis. **Adults** have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Posttussive emesis and intermittency of paroxysms separated by hours of well-being are specific clues to the diagnosis. At least 30% of adolescents and adults with pertussis have nonspecific cough illness, distinguished only by duration, which usually is >21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

DIAGNOSIS

Pertussis should be suspected in any individual who has a pure or predominant complaint of cough, especially if the following features are *absent*: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. For sporadic cases, a clinical case definition of cough of ≥14 days' duration with at least one associated symptom of paroxysms, whoop, or posttussive vomiting has a sensitivity of 81% and specificity of 58% for confirmation of pertussis. Pertussis should be suspected in older children whose cough illness is *escalating* at 7-10 days and whose coughing *is not* continuous, but rather comes in bursts. Pertussis should be suspected in infants <3 months old with gagging, gasping, apnea, cyanosis, or a brief resolved unexplained event (BRUE). Sudden infant death occasionally is caused by *B. pertussis*.

Adenoviral infections usually are distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and the frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis often is included in the differential diagnosis of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales, or wheezes that typify infection by *Chlamydia trachomatis* or predominant lower respiratory tract signs that typify infection by RSV. Unless an infant with pertussis has secondary pneumonia and then appears ill, the findings on examination between paroxysms, including respiratory rate, are entirely normal. Foreign body aspiration should be considered in the differential diagnosis.

Leukocytosis (15,000-100,000 cells/μL) caused by *absolute lymphocytosis* is characteristic in the catarrhal stage. Lymphocytes are normal small cells, rather than the large, atypical lymphocytes seen with viral infections. Adults, partially immune children, and occasionally infants may have less impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with rapid-rise and extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases: 94,000 vs 18,000/μL, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases: 782,000 vs 556,000/μL, respectively). Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

Methods for confirmation of infection by *B. pertussis* (culture, polymerase chain reaction [PCR], serology) have limitations in sensitivity, specificity, or practicality, and the relative value of tests depends on the setting, phase of disease, and purpose of use (e.g., as clinical diagnostic vs epidemiologic tools). **PCR** testing on nasopharyngeal wash specimens is the laboratory test of choice for *B. pertussis* identification. Both stand-alone and multiplex assays are U.S. Food and Drug Administration (FDA) cleared and available commercially. PCR assays using only single primers (IS*481*) cannot differentiate between some *Bordetella* spp. and do not detect *B. parapertussis*. Multiplex assays using multiple targets can distinguish species. All assays detect pertactin-deficient strains. For **culture**, a specimen is obtained by deep nasopharyngeal aspiration or with the use of a flexible swab

(Dacron or calcium alginate–tipped) held in the posterior nasopharynx for 15-30 seconds (or until the cough occurs). A 1% casamino acid liquid is acceptable for holding a specimen up to 2 hours; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 μg/mL cephalexin and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35–37°C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Results of culture and PCR are expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. *However, less than 20% of culture or PCR tests have positive results in partially or remotely immunized individuals tested in the paroxysmal stage.*

Serologic tests for detection of change in antibodies to *B. pertussis* antigens between acute and convalescent samples are the most sensitive diagnostic tests in immunized individuals and are useful epidemiologically. A single serum sample showing IgG antibody to PT >90 IU/mL (>2 standard deviations [SD] above the mean of the immunized population) indicates recent symptomatic infection and usually is positive in the mid-paroxysmal phase. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for serologic diagnosis of pertussis.

TREATMENT

Infants <3 months old with suspected pertussis usually are hospitalized, as are many 3- to 6-month-old patients (i.e., unless witnessed paroxysms are not severe) and patients of any age if significant complications occur. Prematurely born young infants have a high risk for severe, potentially fatal disease, and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have increased risk of poor outcome beyond infancy. Table 243.1 lists caveats in the assessment and care of infants with pertussis. The specific, limited goals of hospitalization are to (1) assess progression of disease and likelihood of life-threatening events at peak of disease, (2) maximize nutrition, (3) prevent or treat complications, and (4) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by healthcare personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Features of typical paroxysms that are not life threatening are duration <45 seconds; red, but not blue, color change; tachycardia or bradycardia (but not <60 beats/min in infants); oxygen desaturation that spontaneously resolves rapidly at the end of the paroxysm; whooping or strength for brisk self-rescue at the end of the paroxysm; self-expectorated mucus plug; and posttussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can watchfully observe an infant's ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Table 243.1 Considerations in the Assessment and Care of Infants with Pertussis

- Infants with potentially fatal pertussis may appear well between episodes.
- A paroxysm must be witnessed before a decision is made between hospital and home care.
- Only analysis of carefully compiled cough record permits assessment of severity and progression of illness.
- Suctioning of the nose, oropharynx, or trachea should not be performed on a "preventive" schedule.
- Feeding in the period after a paroxysm may be more successful than after napping.
- Family support begins at the time of hospitalization with empathy for the child's and family's experience to date, transfer of the burden of responsibility for the child's safety to the healthcare team, and delineation of assessments and treatments to be performed.
- Family education, recruitment as part of the team, and continued support after discharge are essential.

Within 48-72 hours, the direction and severity of disease are obvious from an analysis of the recorded information. Hospital discharge is appropriate if, over 48 hours, disease severity is unchanged or diminished, intervention is not required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or a suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that lead to life-threatening events, or respiratory failure require escalating respiratory support and frequently require intubation and pharmaceutically induced paralysis.

Antibiotics

An antimicrobial agent always is given when pertussis is suspected or confirmed to decrease contagiousness and to afford possible clinical benefit. ***Azithromycin*** *is the drug of choice in all age-groups, either for treatment or postexposure prophylaxis* (Table 243.2). Macrolide resistance has been reported rarely in the United States, and recent isolates have retained susceptibility despite genetic strain adaptations. *Infantile hypertrophic pyloric stenosis (IHPS)* is associated with macrolide use in young infants, especially in those <14 days old, with higher risk in those receiving erythromycin vs azithromycin. The benefits of postexposure prophylaxis or treatment of infants far outweigh the risk of IHPS. Young infants should be managed expectantly if projectile vomiting occurs. The FDA also warns of the risk of fatal heart rhythms with the use of azithromycin in patients already at risk for cardiovascular events, especially those with prolongation of the QT interval. Trimethoprim-sulfamethoxazole (TMP-SMX) is an alternative to azithromycin for infants >2 months old and children unable to receive azithromycin. Because of its limited effectiveness, treatment of *B. parapertussis* is based on clinical judgment and is considered in high-risk populations. Agents are the same as for *B. pertussis*. Treatment of infections caused by other *Bordetella* spp. should be undertaken with consultation of a subspecialist.

Adjunct Therapies

No rigorous clinical trial has demonstrated a beneficial effect of β_2-adrenergic stimulants such as salbutamol and albuterol. Fussing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted. A randomized, double-blind, placebo-controlled trial of pertussis immunoglobulin (IGIV) was halted prematurely because of expiration/lack of additional supply of the study product; there was no indication of clinical benefit. Standard immunoglobulin has not been studied and should not be used for treatment or prophylaxis.

Isolation

Patients with suspected pertussis are placed in isolation with **droplet precautions** to reduce close respiratory or mucous membrane contact with respiratory secretions. All healthcare personnel should wear a mask on entering the room. Screening for cough should be performed on entrance of patients to emergency departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of azithromycin therapy. Children and staff with pertussis in childcare facilities or schools should be excluded until therapy has been taken for 5 days.

Care of Household and Other Close Contacts

Azithromycin should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history

Table 243.2 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis

	PRIMARY AGENTS		ALTERNATIVE AGENT*	
AGE GROUP	**AZITHROMYCIN**	**ERYTHROMYCIN**	**CLARITHROMYCIN**	**TMP-SMX**
<1 mo	Recommended agent 10 mg/kg/day in a single dose for 5 days	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants <2 mo of age (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated at age <2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses for 14 days
Infants age ≥6 mo and children	10 mg/kg in a single dose on day 1 (max 500 mg), then 5 mg/kg/day (max 250 mg) on days 2-5	40-50 mg/kg/day (max 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses (max TMP: 320 mg/day) for 14 days
Adults	500 mg in a single dose on day 1, then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day to SMX 1600 mg/day in 2 divided doses for 14 days

*Trimethoprim-sulfamethoxazole (TMP-SMX) can be used as an alternative agent to macrolides in patients ≥2 mo old who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

Adapted from Centers for Disease Control and Prevention (CDC). Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR*. 2005;54:1–16.

of immunization, or symptoms (see Table 243.2). The same drugs and age-related doses used for treatment are used for prophylaxis. Visitation and movement of coughing family members in the hospital must be assiduously controlled until therapy has been taken for 5 days. In close contacts <7 years old who have received fewer than four doses of DTaP, DTaP should be given to complete the recommended series. Children <7 years old who received a third DTaP dose >6 months before exposure, or a fourth dose ≥3 years before exposure, should be given a booster dose. Individuals ≥9 years old should be given Tdap. Unmasked healthcare personnel exposed to untreated cases should be evaluated for postexposure prophylaxis and follow-up. Coughing healthcare personnel with or without known exposure to pertussis should be evaluated promptly for pertussis.

COMPLICATIONS

Infants <2 months old have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants <4 months old account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory tract infection. The strategy of preventing pertussis in newborns through the vaccination of women with Tdap during pregnancy from 27 through 36 weeks of gestation is 80–91% effective. One study found that among infants with pertussis, disease severity was reduced in those whose mothers were vaccinated during pregnancy, with maternal vaccination being 58% effective in preventing hospitalization.

The principal complications of pertussis are **apnea**, **secondary infections** (e.g., otitis media, pneumonia), and **physical sequelae** of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms, and absolute neutrophilia are clues to pneumonia. Expected pathogens include *Staphylococcus aureus, Streptococcus pneumoniae,* and bacteria of oropharyngeal flora. Increased intrathoracic and intraabdominal pressure during coughing can result in conjunctival and scleral hemorrhage, petechiae on the upper body, epistaxis, pneumothorax and subcutaneous emphysema, umbilical or inguinal hernia, and rarely, hemorrhage in the central nervous system or retina. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation usually is limited to infants <3 months old and children with underlying conditions. Respiratory failure from apnea may mandate intubation and ventilation through the days when disease peaks; the prognosis is good. Progressive **pulmonary hypertension** in very young infants and secondary **bacterial pneumonia** are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevation of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% fatality (questioning the advisability of this procedure). Exchange transfusion or leukapheresis is associated with marked reduction in lymphocyte and platelet counts. Although recovery has been reported in several cases, the benefit is unproven. Echocardiography should be performed in critically ill infants with pertussis to detect the presence of pulmonary hypertension and to intervene expeditiously.

Acute neurologic events during pertussis almost always are the result of **hypoxemia** or **hemorrhage** associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia after an episode. Seizures usually are a result of hypoxemia, but hyponatremia from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in pertussis is parenchymal hemorrhage and ischemic necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before age 2 years may have abnormal pulmonary function into adulthood.

PREVENTION

Universal immunization of children with pertussis vaccine, beginning in infancy with reinforcing dose(s) through adolescence and adulthood, is central to the *control* of pertussis. *Prevention* of pertussis mortality in young infants depends on universal maternal immunization during each pregnancy and focused full immunization of contacts, both children and adults of all ages.

DTaP Vaccines

Several diphtheria and tetanus toxoids combined with acellular pertussis vaccines **(DTaP)** or combination products currently are licensed in the United States for children <7 years old. Acellular pertussis vaccines all contain inactivated PT and two or more additional antigens (FHA, Prn, and Fim 2 and 3). Clinical effectiveness immediately at completion of the five-dose series is approximately 80% for illness defined as "paroxysmal cough" for >21 days. Mild local and systemic adverse events are not uncommon, but more serious events (i.e., persistent crying for ≥3 hours or a hypotonic hyporesponsive episode) are rare after DTaP, are not specific to pertussis vaccine or associated with serious sequelae, and are not contraindications to subsequent doses.

Four doses of DTaP should be administered during the first 2 years of life, generally at ages 2, 4, 6, and 15-18 months. In high-risk settings, infants may be given DTaP as early as 6 weeks of age, with monthly doses through the third dose. The fourth dose may be administered as early as 12 months of age, provided that 6 months have elapsed since the third dose. When feasible, the same DTaP product is recommended for all doses of the primary vaccination series. The fifth dose of DTaP is recommended for children at 4-6 years of age; a fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

Local reactions increase modestly in rate and severity with successive doses of DTaP. Swelling of the entire thigh or upper arm, sometimes accompanied by pain, erythema, and fever, has been reported in 2–3% of vaccinees after the fourth or fifth dose of a variety of DTaP products. Limitation of activity is less than might be expected. Swelling subsides spontaneously without sequelae. The pathogenesis is unknown. Extensive limb swelling after the fourth dose of DTaP usually is not associated with a similar reaction to the fifth dose and is not a contraindication to subsequent dose(s) of pertussis vaccines.

Exempting children from pertussis immunization should be considered only within the narrow limits as recommended. Exemptors have significantly increased the risk for pertussis and play a role in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis. Pertussis vaccine (DTaP or Tdap) can be administered concurrently with any vaccine on the immunization schedule.

Tdap Vaccines

Two tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis antigen vaccine (Tdap) products were licensed in 2005 and recommended universally in 2006 for adolescents. The preferred age for Tdap vaccination is 11-12 years. All adolescents and adults of any age (including ≥65 years) who have not received Tdap should receive a single dose of Tdap promptly, regardless of interval since Td, or at least in place of one Td booster at the 10-year interval, or when indicated during wound management.

Pregnant women should be given Tdap during *every* pregnancy to provide passive antibody protection to the infant until administration of DTaP. Although Tdap can be given at any time during pregnancy, optimal administration is early in the period between 27 through 36 weeks of gestation to maximize antibody concentration at birth. The safety of Tdap during pregnancy and effectiveness in reducing fatal pertussis in infants are proven. Special effort should be made to ensure that contacts of infants have received DTaP or Tdap as recommended.

Clinical trials support the safety and immunogenicity of a second dose of Tdap; however, antipertussis antibodies decline rapidly after the first year. The CDC performed a decision analysis model of repeating Tdap at either a 5- or 10-year interval for the general population and concluded that "booster(s)" would have limited impact on pertussis disease burden. There is not a recommendation for a routine second dose of Tdap in the general population. A single dose of Tdap should be given to children 7-10 years of age who lack DTaP dose(s). Since 2019, the updated CDC recommendations allow use of either Tdap or Td when Td alone is indicated for catch-up dose(s), or for decennial immunization, or for wound management in individuals who have received Tdap.

Vaccines Under Development

Several strategies are being tested to create pertussis vaccines that elicit a Th1 response, dampen the density of mucosal infection and transmission, provide sustained protection against disease, and have tolerable reactogenicity. These include use of live attenuated *B. pertussis,* a genetically (rather than a chemically) inactivated PT component, novel antigens, and adjuvants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 244

Salmonella

Jeffrey S. McKinney

Salmonellosis is one of the most widely distributed and common food-borne and fecal-oral diseases in humans, and ***Salmonellae*** live in the intestinal tracts of multiple species. *Salmonella* infections are a major public health problem, with disproportionate morbidity and mortality among infants and children and in certain immunocompromised individuals.

Clinically, *Salmonellae* have been most broadly classified as being either nontyphoidal or typhoidal, with the latter causing typhoid (also known as *enteric*) fever. The differences in the disease manifestations from these two groups of pathogens, one predominantly causing intestinal inflammation and the other leading to systemic disease, are increasingly understood to be related to specific genes and pathogenicity islands in the genomes of the respective organisms.

Most nontyphoidal serovars of *Salmonella* (widely distributed across multiple host species) are rarely able to overcome defense mechanisms in humans that limit bacterial dissemination from the intestine. Thus in immunocompetent humans, nontyphoidal serovars usually produce a self-limiting gastroenteritis. By contrast, *S.* Typhi and *S.* Paratyphi (i.e., the typhoidal strains of *Salmonella,* notably host-restricted to only humans) possess virulence traits that more readily allow them to overcome mucosal barrier functions and then cause severe systemic illness, even in immunocompetent patients.

However, a purely binary classification of *Salmonellae* as nontyphoidal vs typhoidal can be a problematic oversimplification. For example, reports from Africa have identified strains of nontyphoidal *Salmonellae* that are highly invasive and increasingly common. Like many gram-negative bacteria, mobile or differentially expressed genetic elements can radically alter phenotypes in *Salmonellae,* sometimes in direct response to selective pressures like antimicrobial exposures given to individual patients and/or in broader settings like agricultural antimicrobial use.

Although DNA hybridization studies result in enough similarities for all *Salmonellae* to currently be classified in the single species *Salmonella enterica,* serologic studies can resolve more than 2,000 serotypes. Serotype and DNA sequencing identification has helped clinical laboratories better trace disease outbreaks, and the Centers for Disease Control and Prevention (CDC) has published recent guidelines for a more consistent terminology to help both laboratory and clinical teams confront complex classification nomenclature.

Host differences are also profoundly relevant to the outcomes of *Salmonella* exposures, infections, and disease. Infants and children, patients with certain immunologic vulnerabilities, and the extent to which a given *Salmonella* infection can evade host defenses and/or antibacterial drugs can help predict, or at least better understand, the ultimate impact of *Salmonella* on both individual and public health.

244.1 Nontyphoidal Salmonellosis

Jeffrey S. McKinney

ETIOLOGY

Salmonellae are motile, nonsporulating, gram-negative rods that grow in aerobic and facultative anaerobic conditions. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage, foods, pharmaceutical agents, and fecal material. They are resistant to many physical agents but can be killed by heat to 54.4°C (130°F) for 1 hour or 60°C (140°F) for 15 minutes.

Most serotypes of nontyphoidal *Salmonella* have a broad host spectrum, including both warm-blooded and cold-blooded vertebrates, and even insects like flies and cockroaches. Some serotypes have more limited host ranges, such as *S. dublin* in cattle (recovered in human infections associated with unpasteurized milk) and *S. choleraesuis* in pigs. In human infections, these two serotypes also have a notable propensity to cause more bacteremia and fewer gastrointestinal symptoms as compared with many other nontyphoidal *Salmonellae*. In sub-Saharan Africa, nontyphoidal *Salmonella* has become a leading cause of **bacteremia**. Up to 95% of the serovars associated with invasive *Salmonella* disease among children in this geographic region are *Salmonella* serovar Typhimurium (mostly of an unusual variant designated **multilocus sequence type 313**), a variant of sequence type 313 that does not express phase 2 flagella, or *Salmonella* serovar Enteritidis. This information represents a deviation from the historical assumption that nontyphoidal *Salmonella* is, by definition, relatively noninvasive.

In the United States, nontyphoidal *Salmonella* infections still generally cause **gastroenteritis** that is localized and self-limiting. In these uncomplicated cases, nontyphoidal *Salmonella* infection does not justify treatment with antibiotics. However, nontyphoidal infections can be severe in the young, the elderly, and patients with vulnerabilities in their immunity.

EPIDEMIOLOGY

Salmonellosis has a significant cost to society. Globally, estimates suggest there are more than 90 million cases of *Salmonella* gastroenteritis annually, causing more than 150,000 deaths. In the United States, CDC estimates suggest an annual burden of more than 1.3 million *Salmonella* infections, causing more than 26,000 hospitalizations, 420 deaths, and $400 million in direct medical costs, with approximately 30 people with unreported *Salmonella* illness for every one case confirmed by a laboratory test. Nearly half of culture-proven nontyphoidal *Salmonella* infections occur in children, with the highest incidence among infants. With the burden of HIV infections and malnutrition in Africa, nontyphoidal *Salmonella* bacteremia has emerged as a major cause of morbidity and mortality among both children and adults in Africa.

Nontyphoidal *Salmonella* has a worldwide distribution, with the incidence influenced by local standards of hygiene, sanitation, and availability of safe water and food. Modern practices of mass food production and distribution increase the potential for epidemics, which may be scattered so broadly as to only be fully appreciated via **robust national monitoring systems**, such as the CDC's **FoodNet** (https://www.cdc.gov/foodnet/foodnet-fast.html). FoodNet also helps build capacity for food-borne disease surveillance through close collaborations with PulseNet, EHS-Net, Global SalmSurv, and other partners.

Poultry meat and eggs are traditionally known to be a common source of salmonellosis, and even riding in a shopping cart next to poultry meat is a risk factor for infection of infants. However, consumption of a wide variety of foods has now been associated with outbreaks, including fruits, vegetables, and multiple factory-processed foods such as peanut butter, cookies, and infant formula.

Salmonella infections in many parts of the world may be related to **animal husbandry practices**, including drug-resistant strains that emerge in response to the widespread use of agricultural antimicrobials. Subtherapeutic antimicrobials are often added to animal feeds to promote animal growth. There is now strong evidence linking resistance to quinolones to the use of this group of antimicrobials in animal feeds. Resistance to ciprofloxacin approached 10% of all nontyphoidal *Salmonella* isolates assessed by the CDC in 2017.

In addition to the effect of antibiotic use in animal feeds, the relationship of *Salmonella* infections to prior antibiotic use in children in the month before the infection is well recognized. This association may be related to alterations in gut microbial ecology, which predisposes to colonization and infection with antibiotic-resistant *Salmonella* isolates. The CDC reports that nontyphoidal *Salmonella* isolates during the period 2015–2017 continue to manifest increasing rates of resistance, with 16% of isolates being resistant to at least one essential antibiotic (including ciprofloxacin, azithromycin, ceftriaxone, ampicillin, and trimethoprim-sulfamethoxazole). *Variation in resistance among different strains makes Salmonella culture and antibiotic susceptibility testing very important.*

It appears that some **multidrug-resistant (MDR)** strains of *Salmonella* are also more virulent than susceptible strains. Poor clinical outcomes with these infections do not relate solely to the initial empiric choice of ineffective antibiotics. Over the past 3 decades, ***S.* Typhimurium phage type DT104** has emerged as a globally disseminated MDR strain. Typically resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline, DT104 also has the capacity to acquire resistance to other antibiotics. Many of the resistance genes in DT104 are harbored on genomic islands. Integrons can also encode and disseminate virulence genes.

Several risk factors are associated with outbreaks of *Salmonella* infection. Animals constitute the principal source of human disease from nontyphoidal *Salmonella*. **High-risk pets** include reptiles, amphibians, poultry and other birds, rodents, and other small mammals. The risk of *Salmonella* from turtles was so high that the U.S. Food and Drug Administration (FDA) banned the interstate sale and distribution of turtles with shell length of less than 4 inches. Exposures can also occur from contact with cages or tanks with pets, from touching some pet foods and treats, and even at zoos *without* direct contact with an infected animal.

Animals that carry *Salmonella* still appear healthy and clean and can readily transmit nontyphoidal *Salmonella,* including in **childcare centers and schools**. When nontyphoidal serovars are identified in a childcare attendee or staff member, adherence to hygiene practices is used to control infection. Return to school is allowed as long as stools are contained in a young child's diaper, toilet-trained children do not have accidents using the toilet, and stool frequency becomes no more than two stools above the child's normal stooling frequency per day. In notable contrast to infections with typhoidal strains, demonstration of clearance of nontyphoidal *Salmonella* from stool cultures is neither sought nor required.

Given the ubiquitous nature of the organism, **nosocomial infections** with nontyphoidal *Salmonella* strains can also occur via contaminated equipment and diagnostic or pharmacologic preparations. Patient-to-patient spread can also occur in hospital settings, particularly among vulnerable hosts like neonates. Nursery nosocomial infections from *Salmonella* can be very difficult to control, sometimes taking months to stop and/or serving as a source for further spread through a hospital.

PATHOGENESIS

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthy adults is 10^6-10^8 *Salmonella* organisms. Normal gastric acidity inhibits *Salmonella* multiplication, with most organisms rapidly killed at gastric pH <2.0. Achlorhydria, buffering medications, and rapid gastric emptying after gastroenterostomy allow more viable organisms to reach the small intestine and thus lower the infectious dose. Neonates and infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to infection, even at lower inoculum exposures.

The typical intestinal response to nontyphoidal *Salmonella* infection is **enterocolitis**, with diffuse mucosal inflammation and edema, sometimes with erosions and microabscesses. Intestinal inflammation with neutrophils and macrophages usually involves the lamina propria. Underlying intestinal lymphoid tissue and mesenteric lymph

nodes enlarge and may demonstrate small areas of necrosis. Lymphoid hypertrophy may interfere with blood supply to the gut mucosa and/or serve as a leading edge for intussusception. Hyperplasia of the reticuloendothelial system can also be found in the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ.

Central to *S.* Typhimurium pathogenesis are two **type III secretion systems**. These systems secrete and translocate bacterial proteins termed **effectors** into host cells. These effectors manipulate the host cell to allow bacterial invasion and assembly of an intracellular niche conducive to bacterial survival and replication. Two **genomic pathogenicity islands** encode these type III systems.

The *Salmonella* pathogenicity island 1 (SPI-1) is involved with epithelial cell adherence and invasion (Fig. 244.1), which involves host cell membrane ruffling caused by organized actin rearrangement (Fig. 244.2). This adherent and invasive phenotype of *Salmonella* is activated under conditions like those found in the human small intestine (high osmolarity, low oxygen).

The *Salmonella* pathogenicity island 2 (SPI-2) is involved with formation of the *Salmonella*-containing vacuole (Fig. 244.3), creating a replication-permissive intracellular space (Fig. 244.4). Intracellular *S.* Typhimurium is found within special vacuoles that have diverged from the normal endocytic pathway. An ability to survive within monocytes/macrophages is a key process for *S.* Typhimurium to establish a systemic infection. Survival within host cells also shields *Salmonella* from antimicrobials. For example, gentamicin is not considered effective in vivo against *Salmonella,* even for strains found susceptible to this drug in vitro, because gentamicin does not effectively reach intracellular bacteria.

Bacteremia and systemic disease are possible with any *Salmonella* serotype, especially in individuals with reduced host defenses. Inflammatory bowel disease or gut ischemia can cause intestinal mucosal barrier defects. Malnutrition, corticosteroid therapy, interleukin (IL)-12/interferon gamma axis defects, and posttransplant immunosuppressant agents can significantly compromise cell-mediated immunity. The reticuloendothelial system can be overloaded with hemoglobin or iron or have impaired function from lymphoma or leukemia. In addition, other underlying systemic conditions can predispose to serious *Salmonella* infections, including sickle cell disease, collagen vascular diseases, HIV/AIDS, defects in T_H1 or T_H17 immunity, and chronic granulomatous disease.

As stated earlier, neonates and infants less than 3 months of age are also at higher risk of bacteremia from nontyphoidal *Salmonella*. This risk influences empiric treatment with appropriate antibiotics, even in otherwise healthy patients in this young age-group.

Patients with sickle cell disease are at very high risk for *Salmonella* septicemia and osteomyelitis. This risk may be related to the presence of numerous infarcted areas in the gastrointestinal tract, bones, and reticuloendothelial organs, along with reduced phagocytic and opsonizing capacity of patients with sickle cell disease.

CLINICAL MANIFESTATIONS

Acute Enteritis

The most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hours (mean 24 hours), there is often abrupt-onset nausea, vomiting, and crampy abdominal pain, located predominantly in the periumbilical area and the lower abdominal quadrants. These symptoms are usually followed by mild to severe watery diarrhea, sometimes containing blood, neutrophils, and mucus. Although fever is a classic feature, younger infants may exhibit a normal or subnormal temperature. Symptoms usually subside within 2-7 days in otherwise healthy children. However, some children experience a septicemia-like picture, with symptoms including high fever, drowsiness, confusion, abdominal distention, meningismus, and/or seizures.

Bacteremia

After *Salmonella* gastroenteritis, it is estimated that 1–5% of otherwise healthy children are thought to experience transient bacteremia after nontyphoidal *Salmonella* in U.S. settings. Bacteremia is usually accompanied by fever in older children but is often not associated with fever in infants. As described earlier, specific vulnerable hosts are far more likely to have systemic infection. Children with HIV can have recurrent nontyphoidal *Salmonella* septicemia, despite antibiotic therapy, even without positive stool cultures or any clear nidus of infection. Some nontyphoidal strains are more likely to result in bacteremia, even without obvious gastrointestinal symptoms, including *S. dublin* and *S. choleraesuis*. In Africa, nontyphoidal *Salmonella* is a much more common cause of pediatric bacteremia (see next).

Nontyphoidal *Salmonella* Bacteremia as Emerging Disease in Africa

In Africa, particularly sub-Saharan Africa, nontyphoidal *Salmonella* has been increasingly recognized among the most common causes of *all* bacteremia in febrile children. Children age 6-36 months are at greatest risk, and case fatality rates can reach 25%.

Clinical features among children with invasive nontyphoidal *Salmonella* infections can be confusing, as diarrhea is often *not* a prominent feature. Furthermore, 60% of these children have an apparent lower respiratory tract infection (perhaps from co-infection or comorbidity). Fever is present in 95% but may have no apparent focus. Figure 244.5 summarizes other clinical features. The lack of specificity of these features severely compromises the ability of current clinical algorithms to identify invasive nontyphoidal *Salmonella* infections. Accordingly, blood culture and clinical microbiology systems for bacterial growth, isolation, speciation, and antibiotic susceptibility testing are required for diagnosis and well-informed treatment decision-making.

It remains unclear exactly why invasive infections by nontyphoidal *Salmonella* seem so much more frequent in Africa compared with the dominance of typhoid *Salmonellae* in Asia. HIV is one identified host risk factor for nontyphoidal *Salmonella* infection. Indeed, recurrent nontyphoidal *Salmonella* infection was part of early CDC case definitions for AIDS. However, only 20% of African children with invasive nontyphoidal *Salmonella* disease are HIV positive. Other risks for invasive nontyphoidal *Salmonella* may include recent or severe malaria infections, anemia, and malnutrition.

The epidemic patterns thus far appreciated for invasive infections by nontyphoidal *Salmonella* in Africa suggest that epidemics may occur over several years, peaking in the rainy season. However, it remains unclear how relevant human diarrheal disease or gastrointestinal carriage, or even food or zoonotic sources are, for invasive nontyphoidal *Salmonella* infection in this setting. Thus optimal strategies for interrupting transmission are also not known. This is particularly problematic, given the emergence of extensive antibiotic resistance among nontyphoidal *Salmonella* isolates, including the lineage referred to as *sequence type 313* (ST313).

Recent studies have attempted to better understand the geographic spread and genetic features of ST313 lineage variants isolated internationally over time. Intriguingly, the antibiotic-resistance patterns of these lineages seem to correlate with some large-scale or sequential changes in empiric (e.g., chloramphenicol, third-generation cephalosporins, ciprofloxacin, and azithromycin) antibiotic use. ST313 lineage genomic analysis also reveals the accumulation of **pseudogenes**, in what may be crucial ***loss*-of-function genetic events** involved in ST313 stepwise evolution, perhaps as part of adaptation to a more restricted (human) host range and from an intestinal to a systemic lifestyle.

For invasive nontyphoidal *Salmonella* infections in Africa, evolving resistance patterns seem likely to force increasing reliance on more expensive treatment options. Local resistance patterns may help empirically, but given the rapid spread of various ST313 lineages, susceptibility testing of individual patient isolates will be needed to ensure appropriate antibiotic choices. Targeted resistance gene sequencing, especially for gyrase mutations related to quinolone resistance, may also be warranted as that drug class becomes more widely used.

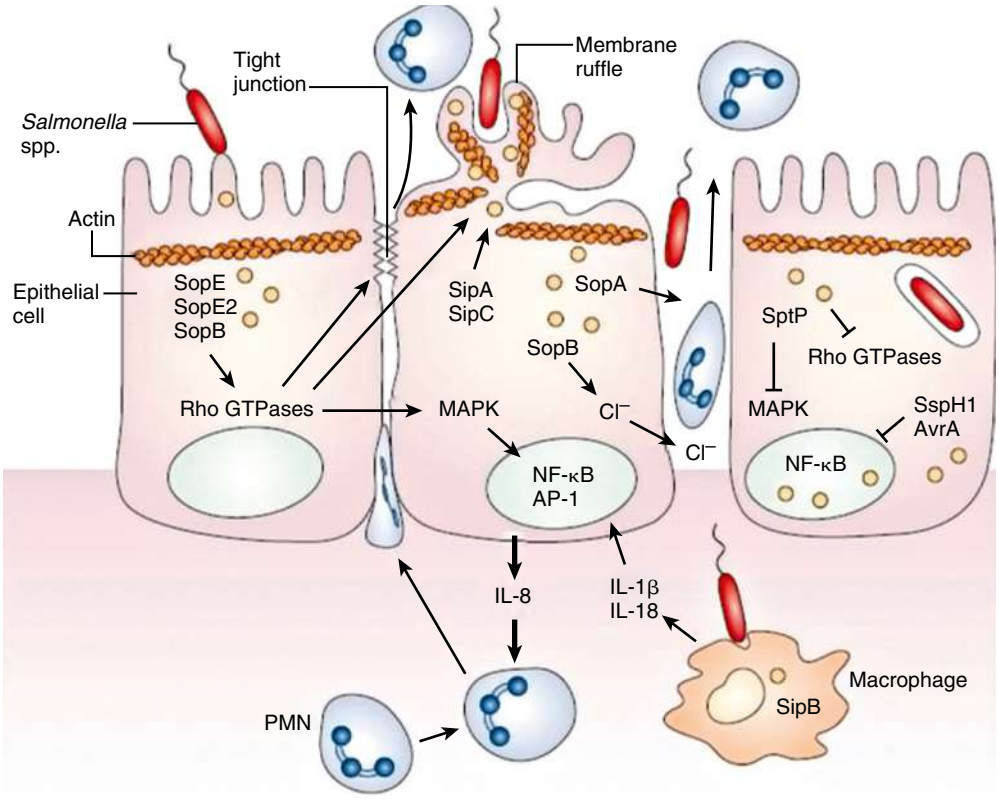

Fig. 244.1 On contact with the epithelial cell, *Salmonellae* assemble the *Salmonella* pathogenicity island 1–encoded type III secretion system (TTSS-1) and translocate effectors *(yellow spheres)* into the eukaryotic cytoplasm. Effectors such as SopE, SopE2, and SopB then activate host Rho guanosine triphosphatase (GTPase), resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton, which are further modulated by the actin-binding proteins SipA and SipC, lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which turn on production of the proinflammatory polymorphonuclear leukocyte (PMN) chemokine interleukin (IL)-8. SipB induces caspase-1 activation in macrophages, with the release of IL-1β and IL-18, augmenting the inflammatory response. In addition, SopB stimulates Cl^- secretion by its inositol phosphatase activity. The destabilization of tight junctions allows the transmigration of PMNs from the basolateral to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. However, the transmigration of PMNs also occurs in the absence of tight-junction disruption and is further promoted by SopA. The actin cytoskeleton is restored, and MAPK signaling is turned off by the enzymatic activities of SptP. This also results in the downmodulation of inflammatory responses, to which SspH1 and AvrA also contribute by inhibiting activation of NF-κB. *(From Haraga A, Ohlson MB, Miller SI. Salmonellae interplay with host cells. Nat Rev Microbiol. 2008;6:53–66.)*

Nontyphoidal *Salmonella* Bacteremia in Other Geographic Regions

The emergence of invasive, high-mortality nontyphoidal *Salmonella* infections in Africa underscores that the traditional binary division of *Salmonella* infections into typhoidal vs nontyphoidal may be a problematic oversimplification. However, in settings outside of Africa, nontyphoidal *Salmonella* infections still tend to be self-limiting and noninvasive and are low-mortality events for most children who are immunocompetent.

Risk factors for systemic spread of nontyphoidal *Salmonella* include underlying sickle cell disease, HIV/AIDS, intestinal mucosal barrier defects, malnutrition, IL-12/interferon gamma axis defects, defects in T_H1 or T_H17 immunity, corticosteroid therapy or posttransplant immunosuppressants, reticuloendothelial system dysfunction (e.g., from overload with hemoglobin or iron), lymphoma or leukemia, collagen vascular diseases, and chronic granulomatous disease. Neonates and infants less than 3 months of age are also at higher risk of bacteremia from nontyphoidal *Salmonella*.

Extraintestinal Focal Infection

After bacteremia, *Salmonellae* have the propensity to cause focal suppurative infection of many organs. The most common focal infections involve the skeletal system, meninges, and intravascular sites. The peak incidence of *Salmonella* meningitis is in infancy, and the infection may be associated with a florid clinical course, high mortality, and neurologic sequelae in survivors.

Chronic *Salmonella* Carriage

Although traditionally considered a complication among *adults* with *Salmonella* infection, chronic *Salmonella* carriage has important medical and epidemiologic implications and may occasionally occur in children. Colonization of the gallbladder by *S.* Typhi and persistent shedding from the gallbladder have long been appreciated. Reports suggest some nontyphoidal *Salmonellae* (e.g., invasive nontyphoidal *Salmonella* currently in Africa) can also establish long-term carriage states.

Antibiotic treatments of *Salmonella* infections are paradoxical in that the prospect of becoming a chronic carrier is believed to be increased by exposure to antibiotics. Yet clearance of established chronic carrier status requires prolonged medical treatment using antibiotics to which the *Salmonella* is susceptible and sometimes requires gallstone or gallbladder removal.

DIAGNOSIS

Few clinical features are specific enough to *Salmonella* to allow differentiation from other infectious causes of gastroenteritis or diarrhea. Serologic tests also do not have diagnostic value. Definitive diagnosis requires identification of *Salmonella* via stool **nucleic acid amplification test** (NAAT) or **bacterial cultures**. Stool cultures have higher yields

than rectal swabs. Blood cultures are suggested for patients at higher risk of bacteremia or endovascular focus and when enteric fever is a concern. Additionally, cultures of bone marrow (particularly valuable if antimicrobial agents have been administered or if stringent criteria are met for **fever of unknown origin**), duodenal fluid, and urine may be beneficial to detect enteric fever. In patients with sites of local suppuration, aspirated specimens should be Gram-stained and cultured.

Salmonella organisms grow well on nonselective or enriched media, such as blood agar, chocolate agar, and nutrient broth, but stool specimens containing mixed bacterial flora require a selective medium, such as McConkey, xylose-lysine-deoxycholate, bismuth sulfate, or Salmonella-Shigella (SS) agar for isolation of *Salmonella*. Given *Salmonella* variation and evolution, it is important to pursue bacterial isolation, species identification, and ***antibiotic susceptibility testing*** *to best inform the choice of effective therapeutic agents.* State public health laboratories require *Salmonella* isolates as part of outbreak detection and investigation, increasingly via genomic characterization of strains.

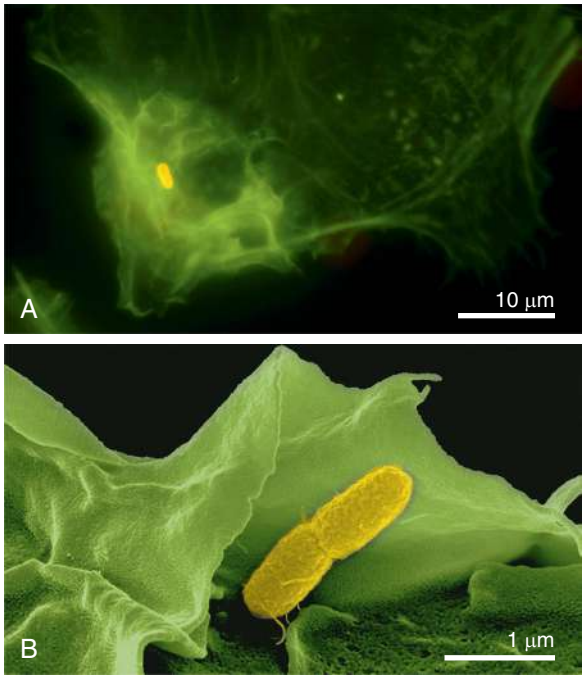

Fig. 244.2 *Salmonella* SPI-1–mediated effects include host cell actin cytoskeletal rearrangements and host cell membrane ruffling as part of *Salmonella* invasion. **A,** HeLa cell infected with *Salmonella* fixed and stained for the actin cytoskeleton with phalloidin *(green)* and for *Salmonella (yellow).* **B,** Cos cell infected with *Salmonella* and prepared for scanning electron microscopy. Cell surface extensions in the process of enveloping the bacterium are pseudocolored green, and the microbe is in yellow. *(From Rottner K, Stradal TEB, Wehland J. Bacteria-host-cell interactions at the plasma membrane: stories on actin cytoskeleton subversion. Dev Cell. 2005;9:3–17.)*

TREATMENT

Appropriate therapy depends on the specific clinical presentation of *Salmonella* infection. In children with gastroenteritis, rapid clinical assessment, correction of dehydration and electrolyte disturbances, and supportive care are key. Antimotility drugs (e.g., loperamide) should not be given to children less than 18 years of age with acute diarrhea, but antiemetic drugs (e.g., ondansetron) can be given to facilitate oral rehydration in children older than 4 years.

Antibiotics are generally *not* recommended for the treatment of isolated uncomplicated *Salmonella* gastroenteritis because they can disrupt normal intestinal flora and potentially prolong the fecal excretion of *Salmonella*.

However, empiric antibiotics are started for young infants (<3 months old) and for children with increased possibility of disseminated infection (e.g., children with HIV, malignancies, sickle cell disease, immunodeficiencies, or immunosuppression, as detailed earlier). In the United States, this empiric therapy includes a third-generation cephalosporin, with a blood culture obtained just before the initial dose. If a patient does not appear ill and does not have any evidence of disseminated infection, oral azithromycin can be started, pending blood culture results. Ampicillin, trimethoprim-sulfamethoxazole, or a fluoroquinolone may be considered as treatment options for susceptible strains.

In cases of bacteremia, blood cultures need to be repeated to confirm clearance of infection. Transition from parenteral third-generation

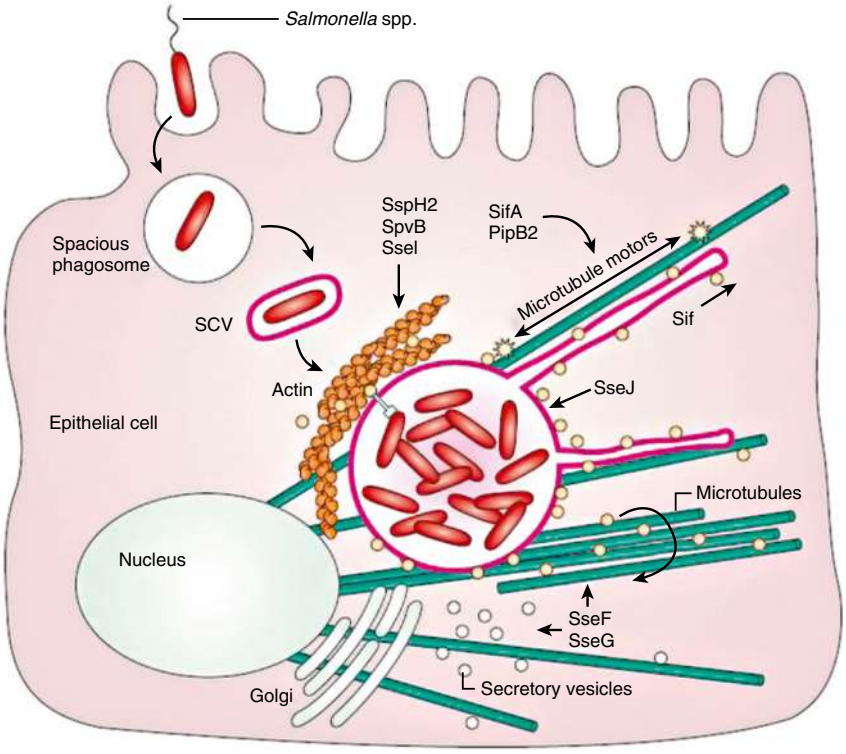

Fig. 244.3 Formation of the *Salmonella*-containing vacuole (SCV) and induction of the *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system (TTSS) within the host cell. Shortly after internalization by macropinocytosis, *Salmonellae* are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium and is called the SCV. It contains the endocytic marker lysosomal-associated membrane protein 1 (LAMP-1; *purple*). The *Salmonella* SPI-2 is induced within the SCV and translocates effector proteins *(yellow spheres)* across the phagosomal membrane several hours after phagocytosis. The SPI-2 effectors SifA and PipB2 contribute to formation of *Salmonella*-induced filament along microtubules *(green)* and regulate microtubule motor *(yellow star shape)* accumulation on the Sif and the SCV. SseJ is a deacylase that is active on the phagosome membrane. SseF and SseG cause microtubule bundling adjacent to the SCV and direct Golgi-derived vesicle traffic toward the SCV. Actin accumulates around the SCV in an SPI-2–dependent manner, in which SspH2, SpvB, and SseI are thought to have a role. *(From Haraga A, Ohlson MB, Miller SI. Salmonellae interplay with host cells. Nat Rev Microbiol. 2008;6:53–66.)*

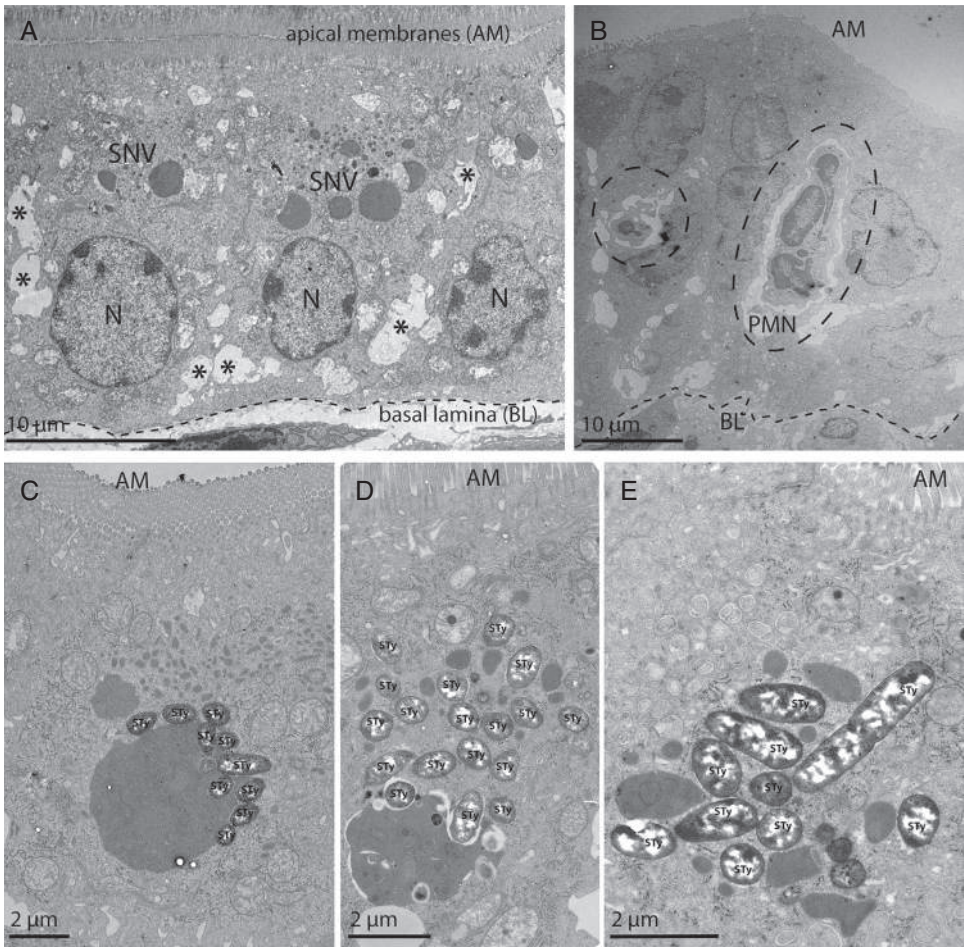

Fig. 244.4 Ultrastructural analysis of the distal small intestine with transmission electron microscopy. Distal small intestinal tissue was fixed with 1% glutaraldehyde. Short segments were cut open, post fixed with osmium tetroxide, contrasted with uranyl acetate, and dehydrated with a graded ethanol series before been embedded in epoxy resin. Thin sections were contrasted with lead citrate and analyzed in a JEM-1400 transmission electron microscope (JEOL). Images were taken with TemCam-F216 camera using EM MENU software (both TVIPS). **A,** Enterocytes in the distal intestine of healthy 5-day old neonates exhibit large supranuclear vacuoles (SNV) in their apical cytoplasm; the nuclei are situated at the basolateral site (N). SNV contain internalized milk proteins. Asterisks indicate intercellular spaces between enterocytes. **B,** 4 days after infection of 1-day-old mice with S. Typhimurium, the epithelium is infiltrated by polymorphonuclear cells (PMN). **C-E,** Intraepithelial Salmonella microcolonies are observed. Some bacteria reside in spherical vacuoles, which contain electron-dense material resembling the content of SNVs. Other bacteria appear to be localized in tight membrane-bound vesicles with few visible connections between them, or with vesicles filled with electron dense material. *(From Zhang K, Griffiths G, Repnik U, Hornef M. Seeing is understanding: Salmonella's way to penetrate the intestinal epithelium. Int J Med Microbiol. 2018 Jan;308:97-106. Fig. 2.)*

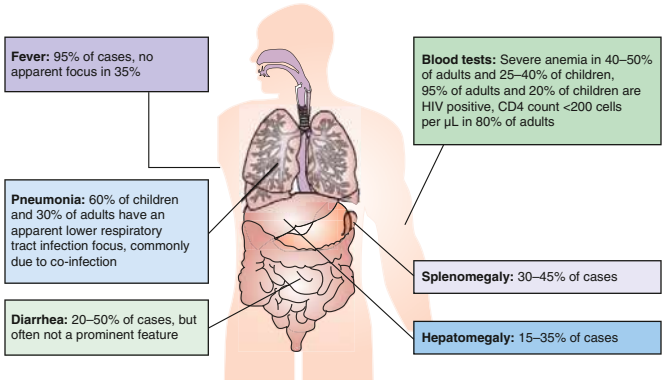

Fig. 244.5 Clinical features of invasive nontyphoidal Salmonella (NTS) disease in adults and children in Africa. *(From Feasey NA, Dougan G, Kingsley RA, et al. Invasive non-typhoidal Salmonella disease: an emerging and neglected tropical disease in Africa. Lancet. 2012;379: 2489–2499.)*

cephalosporin to oral azithromycin or a fluoroquinolone can be considered after documented clearance of blood cultures and exclusion of secondary sites, for a total 7- to 10-day course. Disseminated disease needs to be rigorously excluded, as therapy is more prolonged for meningitis (4 weeks) and osteomyelitis or other focal metastatic infections (4-6 weeks).

Given the heterogeneity, evolution, and rapid geographic spread of *Salmonella,* it is important to maintain awareness of resistance trends as related to local and national community isolate patterns, any relevant interstate outbreaks, and global patterns of emerging *Salmonella* resistance. Serially updated resources with this information include local microbiology laboratory data and open-access reporting systems like the U.S. National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). In NARMS reports from 2018, the majority (81%) of nontyphoidal *Salmonella* from humans were still *not* resistant to any of the antimicrobials tested. However, approximately 3%, 10%, and 0.3% of nontyphoidal *Salmonella* isolated from humans were intrinsically resistant to ceftriaxone, ciprofloxacin, and azithromycin, respectively.

Some contemporary nontyphoidal *Salmonellae* are of particular interest, given their resistance to antimicrobials. *S.* Typhimurium DT104 spread globally in the 1990s, when it was resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. DT104 now sometimes also has reduced susceptibility to fluoroquinolones. Nontyphoidal *Salmonella* ST313 lineages (described earlier) continue

to show resistance pattern evolution in Africa. In the United States, *S.* Infantis has now supplanted other leading serotypes in poultry and not only exhibits deceased susceptibility to fluoroquinolones because of a gyrA pathogenic variant but also contains an MDR plasmid that carries up to 10 resistance genes, conferring resistance to cephalosporins, tetracycline, chloramphenicol, and sulfonamides. This MDR strain of serovar Infantis has been reported to account for up to 35% of the nontyphoidal Salmonella infections in Israel.

PROGNOSIS

Most otherwise healthy children with *Salmonella* gastroenteritis recover fully without antimicrobial treatment. Malnourished children and those who do not receive adequate supportive care can be at risk for prolonged diarrhea and complications. Young infants and immunocompromised patients often have systemic involvement, and children with HIV can have a florid and recurring course.

After infection, nontyphoidal *Salmonella* are excreted in feces for a median of 5 weeks, during which time the recovering patient can infect others via fecal-oral routes or by contaminating foods. A prolonged carrier state is rare in children but is more common among those with biliary tract disease and/or cholelithiasis.

PREVENTION

Control of transmission of *Salmonella* infections to humans requires control of the infection in animal reservoirs, judicious use of agricultural antimicrobials, prevention of contamination of foodstuffs, and appropriate standards of food processing and inspection. Parents should be advised about the risk of various pets (especially reptiles, amphibians, and rodents).

Large outbreaks are often related to mass food production, presenting among widely geographically distributed patients. In the United States, CDC outbreak investigations are reported, via this site: https://www.cdc.gov/Salmonella/outbreaks.html, which includes maps and epidemiologic, traceback, and laboratory data, including outbreaks linked to specific foods, animals, and other sources. Awareness of these events can potentially blunt the extent of a given outbreak and/or alert caregivers of vulnerable hosts.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

244.2 Enteric Fever (Typhoid and Paratyphoid Fever)

Jeffrey S. McKinney

Enteric fever *(typhoid or paratyphoid fever)* remains endemic in many developing countries. Given the ease of modern travel, cases regularly occur in developed countries as well, usually among returning travelers or from secondary transmission from an asymptomatic carrier.

ETIOLOGY

Typhoid fever is caused by *S. enterica* serovar Typhi (*S.* Typhi). A similar but often less severe disease is caused by *Salmonella* Paratyphi A, B, and C. All are classically referred to as typhoidal *Salmonellae*. Typhoidal *Salmonellae* share more than 90% of their genes with the classic nontyphoidal strain, *S.* Typhimurium, but several genetic clusters known as *pathogenicity islands* and other genes have been acquired during evolution. The inactivation of single genes and the acquisition or loss of genes may have contributed to host adaptation and restriction of typhoidal strains. Importantly, whereas nontyphoidal *Salmonella* are found in many hosts and can be transmitted among them, typhoidal *Salmonella* only infects humans.

In contrast to the diarrheal symptoms classically encountered in gastroenteritis caused by nontyphoidal *Salmonellae,* enteric fever caused by typhoid or paratyphoid *Salmonellae* may present as abdominal pain without diarrhea, a fever without focus, and/or with extraintestinal foci of infection. Indeed, although enteric fever clearly starts in the gastrointestinal tract, the systemic nature of its presentation and symptomatology (and even its initial hard-to-detect primary bacteremia) can delay diagnosis, in particular among patients returning from or living in endemic areas, where the differential diagnosis for fevers is broad.

EPIDEMIOLOGY

Recent large-scale data and modeling efforts estimate that 14.3 million cases of typhoid and paratyphoid fevers occurred globally in 2017, a decline from 25.9 million cases in 1990. Incidence rates peak in the 5- to 9-year-old age-group, with roughly 13% of cases occurring in children younger than 5 years and roughly 56% of cases among children younger than 15 years of age. South and Southeast Asia have notably high incidence rates, whereas moderate incidence rates are reported from Central and South America, Africa, Central and East Asia, and Oceania (Fig. 244.6).

Typhoid fever is notable for the ongoing emergence of heterogeneous new patterns of drug resistance. After early outbreaks of chloramphenicol-resistant *S.* Typhi infections, *S.* Typhi strains emerged that were **multidrug resistant (MDR)**, fully resistant to all *three* of the traditional primary treatment antimicrobials: ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. There is also a considerable increase in fluoroquinolone-resistant and even ceftriaxone-resistant isolates of *S.* Typhi. In the United States, most travel-associated cases of typhoid fever are now fluoroquinolone resistant.

There are now *S.* Typhi strains that are **extensively drug resistant (XDR)** not only to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol but also to ceftriaxone and with full or intermediate resistance to ciprofloxacin. It appears that the new XDR *S.* Typhi strains came from a large outbreak in 2016 linked to contaminated water in Pakistan's Sindh province. XDR Typhi infections were then reported globally among travelers to or from Pakistan. In 2019 U.S. residents with *no* history of international travel were also diagnosed with XDR typhoid fever. The optimal therapy for these XDR isolates is still being determined, with preliminary recommendations suggesting the empiric use of a carbapenem (e.g., meropenem), azithromycin, or both.

S. Typhi is highly adapted to infections of humans, and the discovery of a large number of **pseudogenes** in *S.* Typhi suggests that its genome may have undergone degeneration as part of a specialized association with the human host. *S.* Typhi has no apparent ability to cause transmissible disease in other animals. Thus direct or indirect contact with an infected human (either sick or a chronic carrier) is a prerequisite for infection. Ingestion of foods or water contaminated with human feces is the most common mode of transmission. So-called street vendor foods outside the home are one risk factor noted in one case control study from Pakistan; such risks are included in practical guidance for travelers about food and water precautions from the CDC Yellow Book (Health Information for International Travel). However, more general water-borne outbreaks related to poor sanitation or water system contamination have also been described. Other causes of infection include consuming oysters and other shellfish cultivated in water contaminated by human sewage and the use of night soil as fertilizer.

PATHOGENESIS

Human volunteer experiments have established an infecting dose of about 10^5–10^9 organisms, with an incubation period ranging from 4 to 14 days. After ingestion, *S.* Typhi invades the gut mucosa of the terminal ileum via specialized antigen sampling cells known as *M cells* that overlie gut-associated lymphatic tissues, through enterocytes, or via a paracellular route. In contrast to nontyphoidal *Salmonella, S.* Typhi expresses factors that notably downregulate the pathogen receptor–mediated host inflammatory response. It assembles type III secretion systems to inject bacterial effectors that modulate host cell biology in elegant ways, including but not limited to rearrangements of host cell actin, facilitating invasion across the outer cell membrane and a host cell membrane ruffling process that forms a phagosome containing the bacteria. This phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the *Salmonella*-containing vacuole (SCV). This intracellular niche offers *Salmonella* a physical barrier to some

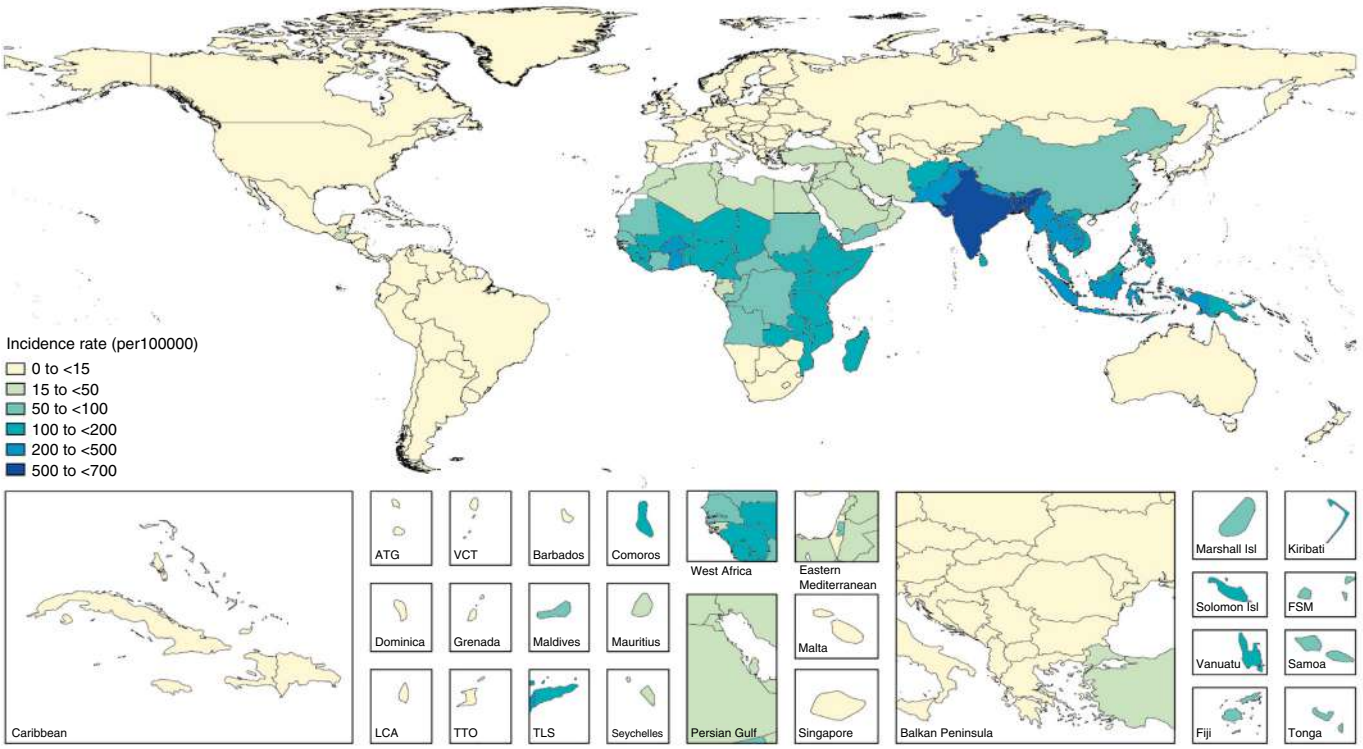

Fig. 244.6 Incidence rates (per 100,000) of typhoid and paratyphoid fevers, by country, in 2017. Inset maps detail smaller locations. ATG, Antigua and Barbuda; FSM, Federated States of Micronesia; Isl, Islands; LCA, Saint Lucia; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines. *(From GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis. 2019;19[4]:369–381.)*

drugs (e.g., gentamicin, which has very poor intracellular penetration) and an intracellular replication site and means of host cell–mediated systemic spread.

After passing through the intestinal mucosa, *S.* Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this early stage. The blood-borne bacteria are disseminated through the body and are thought to colonize the organs of the reticuloendothelial system, where they replicate within macrophages. After a period of bacterial replication, *S.* Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period (Fig. 244.7). During this secondary bacteremia, classically with fever, blood cultures are far more frequently positive, although culture of bone marrow can be even more sensitive.

Both typhoidal and nontyphoidal *Salmonellae* are members of the same species and share substantive commonalities, including more than 90% of their DNA sequences. Yet a deeper appreciation of how and why typhoidal and nontyphoidal species differ offers insights at multiple levels, ranging from genetics and ecology, to pathobiology, to more nuanced clinical recognition and care.

Despite typhoidal (and paratyphoidal, used interchangeably in this section, unless specified otherwise) fevers being synonymous with the clinical diagnosis of **enteric fever**, the initial enteric inflammation from *S.* Typhi is notably less than that caused from most nontyphoidal *Salmonellae*. Clinically, presenting symptoms of typhoid tend to include less diarrhea and far less gut mucosal inflammation. In host cell cultures, *S.* Typhi induces lower levels of IL-8 neutrophil chemoattractant and less of a toll-like receptor 5 (TLR5)–driven proinflammatory response than seen with nontyphoidal *Salmonella*. One potential implication of this is that nontyphoidal *Salmonella* may use inflammation-derived luminal substances such as electron acceptors like nitrate and tetrathionate, perhaps in competition with other fermenting gut microbes. Intriguingly, *S.* Typhi has genomic *decay* in a network of nontyphoidal *Salmonella* genes that are involved in anerobic metabolic pathways.

This is not to say that *S.* Typhi never results in intestinal lesions. In advanced stages of typhoid fever, life-threatening intestinal perforation can occur. However, the histopathology of typhoid perforation is distinct from the inflammation seen with nontyphoidal *Salmonella* gastroenteritis. With *S.* Typhi, inflammation that can finally penetrate the intestinal muscularis and serosa to cause perforation seems to originate from *deeper* sites, including underlying lymphoid tissue. In other tissues, including liver, spleen, lymph nodes, and bone marrow, **typhoid nodules** composed of macrophage aggregates can also form.

Gallbladder colonization is also a notable feature of *S.* Typhi and can result in years-long *Salmonella* carriage and shedding, with profound public health implications. The primary bacteremia of *S.* Typhi can seed the gallbladder, where exposure to bile upregulates *S.* Typhi (but seemingly *not* nontyphoidal *Salmonella*) type 3 secretion system genes that result in increased epithelial cell invasion.

S. Typhi expresses a surface **Vi (virulence) capsular polysaccharide** that is *not* present in nontyphoidal *Salmonella* or in *S.* Paratyphi A or B (which is relevant to the community-level impact of current Vi-based vaccines). Encoded as part of the *S.* Typhi pathogenicity island 7 (SPI-7), the Vi capsular polysaccharide interferes with the surface exposure of *S.* Typhi lipopolysaccharide and flagellin in ways that dampen host TLR-4 and -5 mediated **innate immune responses**. Vi also blocks complement C3 binding to the *S.* Typhi surface, interfering with **phagocytosis**.

Characterization of the **typhoid toxin** represents a major advance in understanding typhoid fever. Furthermore, in contrast to the Vi capsular polysaccharide, the typhoid toxin is expressed in both typhoidal *and* paratyphoidal *Salmonellae*. This toxin may prove important for new therapeutic or diagnostic innovations based on antitoxin

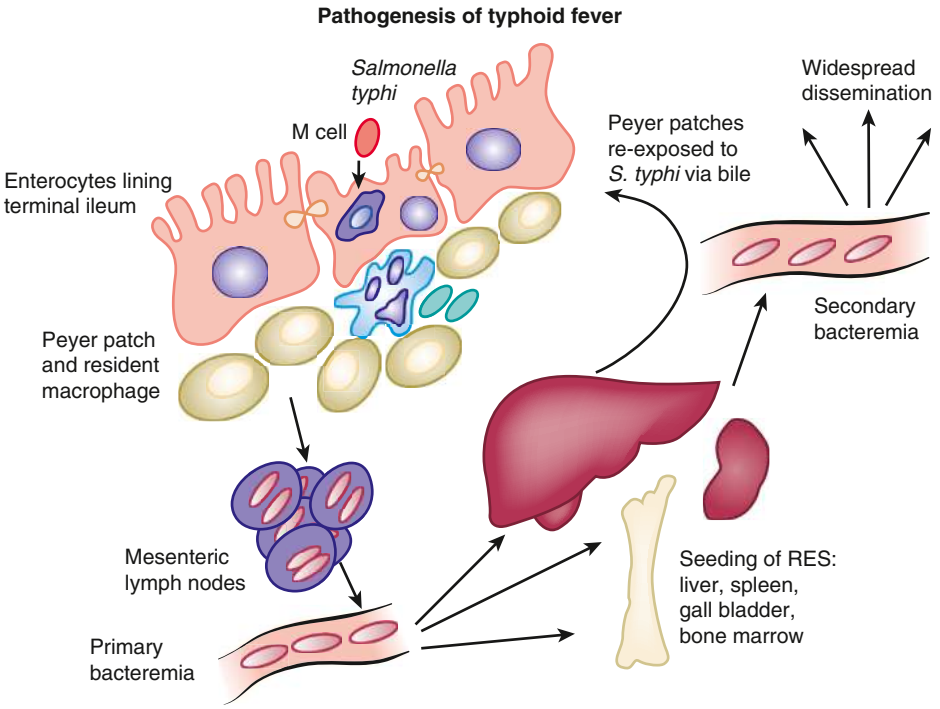

Fig. 244.7 Pathogenesis of typhoid fever, involving invasion of ileal enterocyte and Peyer patches and mesenteric lymph nodes, seeding the reticuloendothelial system (RES). Both primary and secondary bacteremia events can occur and relate to clinical stages of disease. *(Adapted from Richens J. Typhoid fever. In: Cohen J, Powderly WG, Opal SM, eds. Infectious Diseases, 2nd ed. London: Mosby; 2004:1561–1566.)*

approaches. Typhoid toxin has three subunits. Subunit CdtB has DNAse I–like nuclease activity that causes double-stranded breaks in host cell DNA, leading to host G2/M cell cycle arrest and/or cell death. Subunit PltA is a pertussis-like toxin with mono–adenosine diphosphate (ADP)–ribotransferase activity. Subunit PltB is a pertussis-like toxin with receptor binding activity to glycans, especially sialoglycans, terminated in Neu5Ac. The functional typhoid toxin is composed of one CdtB and one PltA subunit, plus five PltB subunits. Typhoid toxin genes are expressed by intracellular *S.* Typhi in the SCV of host cells. The trafficking of the toxin uses an elegant mechanism, in which PltB binding to Neu5Ac is involved in both toxin export and toxin endocytosis into target cells. The fact that Neu5Ac is the target for binding by PltB may help explain the cell tropism of typhoid toxin and also some of the human restriction of typhoidal infections and pathobiology at a molecular level.

The presence/gain/site-specific expression of certain virulence factors by typhoidal *Salmonellae* may help explain disease nuances involved in typhoid fever. Acquisition and spread of resistance genes are also a clear and present danger.

The overall quantity of **pseudogenes** in *S.* Typhi versus nontyphoidal *Salmonella* genomes is also noteworthy. Whereas *S.* Typhi's 200 pseudogenes account for roughly 4% of all its genes, the classic nontyphoidal *Salmonella* exemplar *S.* Typhimurium genome includes less than 1% pseudogenes. One broad conceptual model for this is that *S.* Typhimurium remains more of a "generalist," with a broad host range and more genes to facilitate survival in different hosts. By contrast, *S.* Typhi may have become a "specialist," evolving to infect only humans. Furthermore, *S.* Typhi may infect humans in specific ways that better evade/suppress early mucosal inflammatory events and cause more systemic spread, as well as sustained colonization and long-term shedding. This conceptual model may offer insights to understand the ongoing evolution or emergence of some new nontyphoidal *Salmonella* strains that (akin to typhoidal strains) tend to cause more systemic infections, as highlighted by the evolution of the nontyphoidal *Salmonella* ST313 strain in Africa.

In addition to the virulence of infecting organisms, host factors also influence predisposition to infection. Patients with HIV are at significantly higher risk for infection with *S.* Typhi and *S.* Paratyphi. Patients with *Helicobacter pylori* infection also have an increased risk of acquiring typhoid fever. Compared to most nontyphoidal *Salmonella* infections that are often more severe and systemic in hosts with immune abnormalities, outbreaks of typhoid fever with systemic spread often affect many hosts who do *not* have significant underlying immunocompromise.

CLINICAL MANIFESTATIONS

The incubation period of typhoid fever is usually 7-14 days but depends on the infecting dose and ranges between 3 and 30 days. The presentation varies, from mild illness with low-grade fever and malaise, to a severe clinical picture with profound abdominal discomfort and multiple complications.

Severity and clinical outcome are influenced by many factors. These include duration of illness, age, previous exposure or vaccination history, virulence of the infecting strain, and quantity of the inoculum ingested. Given the profound changes in antimicrobial susceptibility patterns, choice of appropriate antimicrobial therapy is increasingly challenging, both empirically (given multiple various patterns of resistance) and after antimicrobial susceptivity results are secured (given the increasing inadequacy of many previously effective drugs).

The presentation of typhoid fever may vary by patient age. Some reports from South Asia suggest typhoid fever may be more severe in children less than 5 years old in terms of rates of complications and hospitalization. In infancy, complications such as disseminated intravascular coagulation seem more common, with higher case fatality rates. By contrast, neurologic complications and intestinal bleeding or perforation seem less common among children.

Typhoid fever can start as a seemingly mild illness and then progress to a clinical picture that manifests as high-grade fever. It can include a wide variety of associated features, such as anorexia, vomiting, hepatomegaly or splenomegaly, abdominal pain, and/or headache (Table 244.1). In children, diarrhea may occur in earlier stages of the illness but may be followed by constipation, potentially interfering with ready access to stool for important microbial culture and susceptibility testing. In the absence of localizing signs, the early stages of the disease may be very difficult to differentiate from other endemic diseases, such as malaria and dengue fever. In some cases, a macular or maculopapular rash ("rose spots") may be visible around the seventh to tenth day of the illness. These lesions may be difficult to see in dark-skinned children and may occur in crops on the lower

chest and abdomen, typically lasting 2-3 days (Fig. 244.8). Although so-called pulse fever dissociation (relative bradycardia during fevers) has historically been invoked as a feature of typhoid fever, it has low positive predictive value, is nonspecific, and seems much less common in children than in adults.

It is recognized that MDR *S.* Typhi infection is a more severe clinical illness with higher rates of toxicity, complications, and case fatality rates. Depending on the specific infecting strain, this may be related to greater virulence and higher numbers of circulating bacteria.

If no complications occur, symptoms and physical findings gradually resolve within 2-4 weeks. However, illness may contribute to malnutrition. Although enteric fever caused by *S.* Paratyphi has traditionally been considered a more mild illness than that from *S.* Typhi, paratyphoid fever can also be severe, with significant drug resistance, morbidity, and complications.

COMPLICATIONS

Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, and cholecystitis are relatively rare and may be associated with worse outcomes. Intestinal hemorrhage and perforation are infrequent among children. Intestinal perforation may be preceded by marked increase in abdominal pain (often in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Peritoneal signs may be masked in patients receiving steroids.

Rare complications include toxic myocarditis, which may manifest as arrhythmias, sinoatrial block, or cardiogenic shock (Table 244.2). Neurologic complications are relatively uncommon among children; they include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates can be higher among patients with neurologic complications, recovery usually occurs without sequelae. Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulation, hemolytic-uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.

The propensity to become a carrier follows the epidemiology of gallbladder disease and cholelithiasis, generally increasing with patient age and antimicrobial resistance.

DIAGNOSIS

The mainstay of the diagnosis of typhoid fever is a positive culture of *S.* Typhi or *S.* Paratyphi from the blood or other anatomic site. Results of blood cultures are positive in 40–60% of patients seen early in the course of disease, but serial high-volume blood cultures may be required to identify *Salmonella* bacteremia. Stool and urine culture results may also become positive after the first week, and the stool culture may occasionally be positive even during the incubation period. NAATs for *Salmonella* can be part of diagnostic screening, but rectal swab samples are less sensitive than stool samples. In this era of increasing antibiotic resistance (not only common but also heterogeneous patterns), species identification without culture to check antibiotic susceptibilities is suboptimal. *Indeed, antibiotic susceptibility testing is now essential for determining optimal therapy.* Bone marrow culture is highly sensitive (around 90%) and remains positive in more than 50% of cases despite several days of antibiotic therapy. Bone marrow collection is relatively invasive, however, and tends to be employed as part of an extensive workup for patients meeting stringent criteria for a true fever of unknown origin. Punch biopsies from characteristic rose spots may be culture positive in up to 63% of cases, even with prior antibiotic treatment.

Results of other laboratory investigations are largely nonspecific for the diagnosis of typhoid fever. The Widal test has common false-negative and false-positive results, and as a serologic test is highly dependent on geographic area and endemicity. Tests such as coagulation studies, liver function studies, and abdominal imaging are examples of studies that may be of use in assessing for complications of typhoid fever.

Table 244.1 Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

*Data collected in Karachi, Pakistan, from 2,000 children.

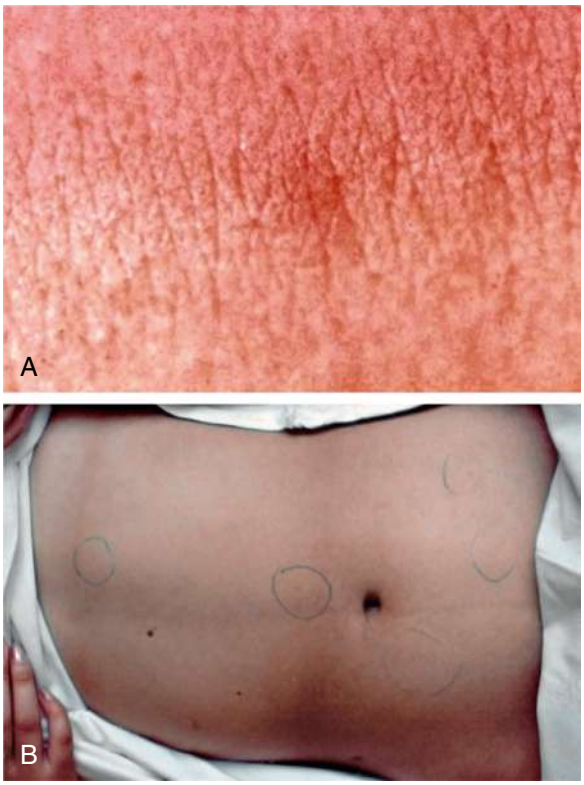

Fig. 244.8 A, "Rose spot" in volunteer with experimental typhoid fever. B, Small cluster of rose spots, usually located on lower abdomen. Lesions may be more difficult to identify in darker-skinned people. *(From Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of Salmonella enterica serotype Typhi infection. Lancet Infect Dis. 2005;5:341–348.)*

Table 244.2 Extraintestinal Infectious Complications of Typhoid Fever Caused by *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM	PREVALENCE (%)	RISK FACTORS	COMPLICATIONS
Central nervous system	3–35	Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, osteomyelitis of skull	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	1–5	Cardiac abnormalities (e.g., existing valvular abnormalities, rheumatic heart disease, congenital heart defects)	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1–6	Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1	Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, corticosteroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1–26	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1	Urinary tract abnormalities, pelvic pathology, systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue infections	At least 17 cases reported in English-language literature	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematologic	At least 5 cases reported in English-language literature		Hemophagocytosis syndrome

From Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection. *Lancet Infect Dis.* 2005;5:341–348.

DIFFERENTIAL DIAGNOSIS

Typhoid fever may mimic many febrile illnesses without localizing signs. In early stages, it can be confused with alternative conditions, such as gastroenteritis, bronchitis, and bronchopneumonia. As the disease progresses, the differential diagnosis may include bacterial sepsis, malaria, dengue fever, infectious mononucleosis, acute hepatitis, tuberculosis, brucellosis, tularemia, leptospirosis, amebiasis, Q fever, toxoplasmosis, and rickettsial diseases. A classic cause of fevers among travelers returning from endemic areas, typhoid fever can also occur in those with direct, or even unappreciated, contact with other infected people.

TREATMENT

Antibiotic resistance among *S.* Typhi strains is now so heterogeneous and dynamic that the importance of obtaining **antibiotic susceptibility tests** on clinical isolates cannot be overemphasized. Although empiric antibiotics still may be started, final decision-making about optimal treatment should be based on antibiotic susceptibility results. Molecular testing of specific resistance genes can also help assess mechanisms and evolution of resistance.

For years, third-generation cephalosporins (e.g., ceftriaxone or cefotaxime) were a mainstay of empiric therapy. They were considered effective even for **MDR** *S.* Typhi and/or for the increasing number of *S.* Typhi that were quinolone resistant. Yet now, with the recent emergence of **XDR** *S.* Typhi, third-generation cephalosporins may no longer be sufficient.

In *S.* Typhi, MDR isolates are defined as resistant to all the first line of antibiotics previously suggested by the World Health Organization (WHO): ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. XDR *S.* Typhi is not only resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol but also resistant to third-generation cephalosporins and quinolones. Gene sequencing, including one innovative study using clinical isolates from children with *S.* Typhi septicemia, found the phenotype of the XDR *S.* Typhi isolates matches with their genotypes, featured by the acquisitions of the genes bla_{TEM1}, dhfR7, sul1, catA1, qnrS, and $bla_{CTX\text{-}M\text{-}15}$ and a point mutation on gyrA.

XDR *S.* Typhi cases were first noted by Pakistani health authorities in 2016, originating in Hyderabad, Sindh. By 2018, international transmission of XDR *S.* Typhi cases had been noted. In 2019 and 2020, XDR *S.* Typhi was recovered from patients in the United States, both with and *without* a travel history. Patients without a travel history lived in six widely distributed states and did not appear to be linked or have a common source of infection. An unrelated cluster of ceftriaxone-resistant Typhi infections linked to Iraq has also been reported in the United States and the United Kingdom.

Taken together, this information led to an official CDC Health Advisory in 2021 suggesting the need for empiric carbapenem, azithromycin, or both for patients in the United States with suspected typhoid fever who traveled to Pakistan or Iraq, as well as those who had *not* traveled from the United States. Patients with severe or complicated illness should receive a carbapenem, such as meropenem. Case reports have suggested that patients who do not improve on a carbapenem alone may benefit from the addition of a second antibiotic such as azithromycin. Patients with uncomplicated illness may be treated with oral azithromycin alone. By contrast, for patients in the United States who traveled to countries other than Pakistan or Iraq, ceftriaxone *may* still be effective.

In the United States, resistance to meropenem (a carbapenem) or azithromycin was not reported during 2017–2021. By contrast, roughly 80% of Typhi strains isolated in the United States now are resistant or have decreased susceptibility to quinolones, including ciprofloxacin.

New MDR and XDR strains illustrate the profound importance of recognizing what antimicrobials will likely *not* work. Meanwhile, an encouraging relative reduction in the proportion of MDR strains in some areas of Asia means some patients with susceptible *S.* Typhi infections can be treated with agents recently considered ineffective. Namely, in some highly endemic regions of South and Southeast Asia,

strains susceptible to amoxicillin or trimethoprim-sulfamethoxazole are increasingly common.

The optimal duration of antimicrobial therapy is unclear, but most agents are suggested for at least 10-14 days, with longer courses for amoxicillin or trimethoprim-sulfamethoxazole, 21 days for chloramphenicol, and as little as 7 days for azithromycin. Relapse rates can occur in almost 20% of patients within 4 weeks, especially in immunocompromised patients.

In addition to antimicrobials, supportive treatment and maintenance of appropriate fluid and electrolyte balance are important. Although additional treatment with dexamethasone (3 mg/kg initial dose, followed by 1 mg/kg every 6 hours for 48 hours) is recommended by some for severely ill patients with shock, obtundation, stupor, or coma, corticosteroids should be administered only under strict supervision, because their use may mask signs of abdominal complications.

PROGNOSIS

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibacterial therapy. Other factors are patient age, underlying health and nutrition, the causative *Salmonella* serotype, and the appearance of complications. Infants and children with underlying malnutrition and infections with resistant isolates are at higher risk of adverse outcomes.

Despite appropriate therapy, 2–4% of infected children may experience relapse. Individuals who excrete *S.* Typhi more than 3 months after infection are regarded as chronic carriers. A chronic urinary carrier state can develop in children with schistosomiasis.

PREVENTION

Of the major risk factors for outbreaks of typhoid fever, contamination of water supplies with sewage is most important. Other risk factors are contact with another acutely infected individual or a chronic carrier and lack of water or sanitation services. During outbreaks, central chlorination and domestic water purification are important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, is recognized as an important risk factor. Human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and high-risk groups for *S.* Typhi carriage screening. Chronic carriers can be counseled as to the risk for disease transmission and the importance of handwashing.

In the United States, two vaccines have been licensed by the FDA. Systematic review and meta-analysis of randomized controlled clinical trials estimate the cumulative efficacy of these two vaccines as only roughly 50%. The Ty21a **live attenuated vaccine** can be used in people 6 years and older. It is administered orally, every other day, for a total of four doses to be completed at least 1 week before potential exposure; booster frequency is every 5 years. The Ty21a vaccine induces both cell-mediated and humoral immune responses against *S.* Typhi. It also may provide some protection against *S.* Paratyphi B. The **unconjugated** Vi capsular polysaccharide vaccine can be used in people 2 years and older. It is administered intramuscularly in a single dose to be administered at least 2 weeks before potential exposure; booster frequency is every 2 years. This unconjugated vaccine induces a **T-cell–independent humoral immune response** with lack of prolonged protection.

Conjugated vaccines have been recommended, developed, and now deployed by the WHO. By covalently conjugating the Vi capsular polysaccharide to carrier proteins, conjugate vaccines can induce a **T-cell–dependent humoral immune response**, even in young children. Conjugated typhoid vaccines are under development, using a variety of carrier proteins, including tetanus toxoid, Exoprotein A from *Pseudomonas,* and diphtheria toxoid. The WHO has recommended the introduction of a single-dose typhoid conjugate vaccine for infants and children age 6 months and older. A large study of the Typbar-TCV conjugate vaccine in Hyderabad, Pakistan, found vaccine effectiveness was 55% against suspected typhoid fever and 95% against blood culture–confirmed *S.* Typhi. The vaccine was also 97% effective against XDR *S.* Typhi. In 2019, a historic milestone was successfully achieved in Pakistan with the vaccination in Sindh province of more than 9.4 million children age from 9 months to 15 years against typhoid fever, with a coverage rate of 95%. Pakistan is the first country in the world to introduce the WHO-recommended typhoid conjugate vaccine (TCV) into its routine immunization program.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 245

Shigella

Patrick C. Seed

Shigellosis, infection by *Shigella* species, is acute invasive enteric infection clinically manifested by diarrhea that is often bloody. The term **dysentery** describes a syndrome of bloody diarrhea with fever, abdominal cramps, rectal pain, and mucoid stools. **Bacillary dysentery** is a term often used to distinguish dysentery caused by *Shigella* from amebic dysentery caused by *Entamoeba histolytica*.

ETIOLOGY

Four species of *Shigella* cause the disease shigellosis: *Shigella dysenteriae* (group A), *Shigella flexneri* (group B), *Shigella boydii* (group C), and *Shigella sonnei* (group D). Serotypes 15, 19, 19, and 1 in groups A-D, respectively, further distinguish the species. Species and group distributions vary geographically and by antimicrobial susceptibility.

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that 80-165 million cases of shigellosis occur each year worldwide, resulting in 600,000 deaths annually. *Shigella* spp. are endemic to temperate and tropical climates and are most common in countries and regions with inadequate public health sanitation and hygiene. In the U.S. Foodborne Disease Active Surveillance Network **(FoodNet)**, *Shigella* remains the third most important pathogen. In 2020, the top three diarrheagenic pathogens, *Campylobacter, Salmonella,* and *Shigella,* had laboratory-confirmed incidence rates (cases per 100,000 population) of 14.35, 13.33, and 3.05, respectively. Although infection can occur at any age, children younger than 10 years, identified as Black and of Hispanic ethnicity, have the highest incidence rates. Males have an approximately 2.7-fold higher incidence than females. Upwards of 30% of children with shigellosis are hospitalized. Death resulting from shigellosis is rare among children (<0.1%). Infection in the first 6 months of life is rare. Breast milk from women living in endemic areas contains antibodies to both virulence plasmid-encoded antigens and lipopolysaccharides, and breastfeeding might partially explain the age-related incidence.

Asymptomatic infection of children and adults occurs frequently in endemic areas. In cases of *Shigella* dysentery, up to 75% of family member contacts may have asymptomatic infection. Infection with *Shigella* occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. In industrialized societies, up to 50% of locally diagnosed cases are associated with international travel; the highest-risk travel designation is Africa, followed by Central America, South America, and parts of Asia. In recent years in the United States, travel to Haiti, the Dominican Republic, or India has been associated with acquisition of antibiotic-resistant (fluoroquinolone) *S. sonnei* infections. Additional risk factors include men who have sex with men (MSM), including recent U.S. outbreaks of azithromycin-resistant *S. sonnei* infections among affected individuals in the Midwest.

In developed countries, *S. sonnei* is the most common cause and *S. flexneri* is the second most common cause of bacillary dysentery; in preindustrial societies, *S. flexneri* is most common and *S. sonnei* second

in frequency. *S. boydii* is found primarily in India. *S. dysenteriae* serotype 1 tends to occur in massive epidemics but is also endemic in Asia and Africa, where it is associated with high mortality rates (5–15%). The epidemiologic transition has favored the emergence of *S. sonnei* as the dominant serogroup in some countries, although the reason for this epidemiologic shift is not clear.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. Exposure to both contaminated freshwater and contaminated salt water is a risk factor for infection. Rapid spread within families, custodial institutions, and childcare centers demonstrates the ability of *Shigella* to be transmitted from one individual to the next and the requirement for ingestion of very few organisms to cause illness. Human challenge studies have demonstrated the high infectivity and low infectious dose for *Shigella* spp. Ten bacteria of the species *S. sonnei* and *S. dysenteriae* can cause dysentery. In contrast, ingestion of 10^8-10^{10} *Vibrio cholerae* is necessary to cause cholera.

PATHOGENESIS

Shigella has specialized mechanisms to survive the low gastric pH. Shigella survives the acid environment in the stomach and moves through the gut to the colon, its target organ. *Shigella* spp. use a coordinated, temperature-controlled program to hijack and invade colonic epithelial cells. A large (220 kb) plasmid encodes a group of polypeptides involved in cell invasion and killing, and loss of the plasmid attenuates virulence. **Enteroinvasive** *Escherichia coli* (EIEC) that harbor a closely related plasmid containing these invasion genes behave clinically similar to *Shigellae* (see Chapter 246). The virulence plasmid encodes a type III secretion system required to trigger entry into epithelial cells and apoptosis in macrophages. This secretion system translocates effector molecules from the bacterial cytoplasm to the membrane and cytoplasm of target host cells through a needle-like appendage. The **type III secretion system** is composed of approximately 50 proteins, including the Mxi and Spa proteins involved in assembly and regulation of the type III secretion system, chaperones (IpgA, IpgC, IpgE, and Spa15), transcription activators (VirF, VirB, and MxiE), translocators (IpaB, IpaC, and IpaD), and approximately 30 effector proteins. In addition to the major plasmid-encoded virulence traits, chromosomally encoded factors are required for full virulence.

Shigellosis mostly affects the distal colon, although pancolitis can occur. *Shigella* spp. traverse the colonic epithelium through M cells in the follicle-associated epithelium overlying the Peyer patches. Localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may occur. Microscopically, ulcerations, pseudomembranes, epithelial cell death, infiltration extending from the mucosa to the muscularis mucosae by polymorphonuclear leukocytes (PMNs) and mononuclear cells, and submucosal edema occur.

After *Shigella* transcytosis through M cells, it encounters resident macrophages and subverts macrophage killing by activating the inflammasome and inducing pyroptosis, apoptosis, and proinflammatory signaling. Free bacteria invade the epithelial cells from the basolateral side, move into the cytoplasm by actin polymerization, and spread to adjacent cells. Proinflammatory signaling by macrophages and epithelial cells further activates the innate immune response involving natural killer cells and attracts PMNs. The influx of PMNs disintegrates the epithelial cell lining, which initially exacerbates the infection and tissue destruction by facilitating the invasion of more bacteria. Ultimately, PMNs phagocytose and kill *Shigella,* thus contributing to the resolution of the infection.

Some *Shigella* spp. produce toxins, including Shiga toxin and enterotoxins. **Shiga toxin** is a potent exotoxin that inhibits protein synthesis. It is produced in significant amounts by *S. dysenteriae* serotype 1, by a subset of *E. coli* known as **enterohemorrhagic** *E. coli* (EHEC) or Shiga toxin–producing *E. coli,* and occasionally by other *Shigella* spp. Shiga toxin inhibits protein synthesis to injure vascular endothelial cells and trigger the severe complication of hemolytic-uremic syndrome (see Chapter 246). Targeted deletion of the genes for other enterotoxins (*ShET1* and *ShET2*) decreases the incidence of fever and dysentery in human challenge studies. Lipopolysaccharides are virulence factors for all *Shigellae;* other traits are important for only a few serotypes (e.g., Shiga toxin synthesis by *S. dysenteriae* serotype 1 and *ShET1* by *S. flexneri* 2a).

IMMUNITY

In symptomatic infection, *Shigella* activates an intense innate immune response through triggering extracellular and intracellular pathogen recognition systems. The induction of acute inflammation with a massive recruitment of PMNs produces intensive local tissue destruction. In rectal biopsies of infected patients, acute-phase proinflammatory cytokines are induced, including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, and TNF-β. Concurrently, antiinflammatory genes encoding IL-10 and transforming growth factor-β are also upregulated to mitigate uncontrolled inflammation. Furthermore, interferon-γ expression is induced during human infection and is required to limit *Shigella* invasion in intestinal epithelial cells and macrophages. *Shigella*-specific immunity elicited upon natural infection is characterized by the induction of a humoral response. Local secretory immunoglobulin A (IgA) and serum IgG are produced against lipopolysaccharide and some protein effectors (Ipas). Protection is thought to be serotype specific. Natural protective immunity arises only after several episodes of infection, is of short duration, and seems to be effective in limiting reinfection, particularly in young children. However, children have delayed and reduced antigen-specific antibody-secreting cells with late and reduced mucosa IgA production against *Shigella*. Less effective adaptive immunity may put children at more risk for increased disease severity, mortality, and recurrences.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Shigella spp. produce intraintestinal and extraintestinal symptoms. *Bacillary dysentery is clinically similar regardless of infecting serotype or species,* but different species produce illnesses with different severity and risk for mortality, with *S. dysenteriae* type 1 most likely to produce any single manifestation and with greater severity. Ingestion of *Shigellae* is followed by an incubation period of 12 hours to several days before symptoms ensue. Severe abdominal pain, emesis, anorexia, generalized toxicity, urgency, and painful defecation characteristically occur (Table 245.1). *The typically high **fever** with shigellosis distinguishes it from EHEC.* The **diarrhea** may be watery and large volume initially, evolving into frequent, small-volume, bloody, mucoid stools. Most children never progress to the stage of bloody diarrhea, but some have bloody stools from the outset. Significant dehydration is related to the fluid and electrolyte losses in stool and emesis. Untreated diarrhea can last 7-10 days; only approximately 10% of patients have diarrhea persisting for >10 days. Persistent diarrhea occurs in malnourished infants, children with AIDS, and occasionally previously normal children. Even nondysenteric disease can be complicated by persistent illness. Physical examination initially shows abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination. **Rectal prolapse** may be present, particularly in malnourished children.

Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40% of hospitalized children. EIEC can cause similar neurologic toxicity. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea. Animal models suggest Shiga toxins activate brain endothelial cells and microglia and increase neurotransmitter levels. However, infections with Shiga toxin–positive and –negative strains can lead to neurologic features. **Seizures** sometimes occur when little fever is present, suggesting that simple febrile convulsions do not explain their appearance. Hypocalcemia or hyponatremia may be associated with seizures in a small number of patients. Although symptoms often suggest central nervous system infection, and cerebrospinal fluid pleocytosis with minimally elevated protein levels can occur, meningitis caused by *Shigellae* is rare. Based on animal studies, it has been suggested that proinflammatory mediators, including TNF-α and IL-1β, nitric oxide, and corticotropin-releasing hormone, play a role in the enhanced susceptibility to *Shigella*-mediated seizures and encephalopathy.

The most common complication of shigellosis is **dehydration** (Table 245.2). Inappropriate secretion of antidiuretic hormone with profound hyponatremia can complicate dysentery, particularly when *S. dysenteriae* is the etiologic agent. Hypoglycemia and protein-losing enteropathy are common and are decreased by early appropriate antibiotic therapy. Severe protein-losing enteropathy is associated with prolonged illness and linear growth shortfalls. **Bacteremia** is uncommon except in girls or women infected with HIV, malnourished children, young infants, and children with *S. dysenteriae* serotype 1 infection. When bacteremia occurs with dysentery (<5%), it is as likely to be caused by other enteric bacteria as by *Shigella* itself. The presence of *E. coli, Klebsiella,* and other enteric bacteria in blood cultures of children with shigellosis may reflect the loss of the barrier function during severe colitis. The mortality rate is high (approximately 20%) when sepsis occurs, with a greater likelihood of occurrence in HIV-infected persons. Other major complications include **disseminated intravascular coagulation** (DIC), particularly in very young, malnourished children. Despite the extent to which the intestinal epithelial barrier is lost, bacteremia and DIC are uncommon.

Neonatal shigellosis is rare, particularly among exclusively breastfed infants. Neonates may have only low-grade fever with mild, nonbloody diarrhea. However, complications occur more often in neonates than in older children and include septicemia, meningitis, dehydration, colonic perforation, and toxic megacolon.

Hemolysis, anemia, and **hemolytic-uremic syndrome** (HUS) frequently complicate *S. dysenteriae* serotype 1 infection. HUS is caused by Shiga toxin–mediated vascular endothelial injury. Shiga toxin–producing non-*dysenteriae Shigella* and *E. coli* that produce Shiga toxins (e.g., *E. coli* O157:H7, *E. coli* O111:NM, *E. coli* O26:H11, and less often, many other serotypes) also cause HUS (see Chapter 560.5).

Rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with *S. dysenteriae*), cholestatic hepatitis, conjunctivitis, iritis, corneal ulcers, pneumonia, arthritis (usually 2-5 weeks after enteritis), reactive arthritis, cystitis, myocarditis, and vaginitis (typically with blood-tinged discharge associated with *S. flexneri*) are uncommon events. Although rare, surgical complications of shigellosis can be severe; the most common are intestinal obstruction and appendicitis with and without perforation.

On average, the severity of illness and risk of death are least with disease caused by *S. sonnei* and greatest with infection by *S. dysenteriae* type 1. Risk groups for severe illness and poor outcomes include infants; children who are not breastfed; children with HIV; children recovering from measles; malnourished children and adults; adults >50 years old; and patients with dehydration, unconsciousness, hypothermia or hyperthermia, hyponatremia, or lesser stool frequency who have a history of convulsions when first seen. Death is a rare outcome in well-nourished older children. Multiple factors contribute to death in malnourished children with shigellosis, including illness in the first year of life, altered consciousness, dehydration, hypothermia, thrombocytopenia, anemia, hyponatremia, renal failure, hyperkalemia, hypoglycemia, bronchopneumonia, and bacteremia.

The rare shigellosis-associated Ekiri syndrome, or "lethal toxic encephalopathy," constitutes severe toxicity, convulsions, extreme hyperpyrexia, and headache, followed by brain edema and a rapidly fatal outcome without sepsis or significant dehydration.

DIFFERENTIAL DIAGNOSIS

Although clinical features suggest shigellosis, they usually are insufficiently specific to allow confident diagnosis. Infection by *Campylobacter jejuni, Salmonella* spp., EIEC, Shiga toxin–producing *E. coli* (EHEC, e.g., *E. coli* O157:H7), *Yersinia enterocolitica, Clostridioides difficile,* and *Entamoeba histolytica,* as well as inflammatory bowel disease, produce overlapping features and may challenge the clinician.

DIAGNOSIS

Presumptive data supporting a diagnosis of bacillary dysentery include the finding of fecal leukocytes (usually >50 or 100 PMNs per high-power field, confirming the presence of colitis), fecal blood, and

Table 245.2 Clinical Complications of Shigellosis

INTESTINAL COMPLICATIONS
Rectal prolapse*
Toxic megacolon
Intestinal perforation
Intestinal obstruction
Appendicitis
Persistent diarrhea
EXTRAINTESTINAL COMPLICATIONS
Dehydration
Severe hyponatremia (serum sodium <126 mmol/L)*
Hypoglycemia
Focal infections (e.g., meningitis, osteomyelitis, arthritis, splenic abscesses, vaginitis)
Sepsis, usually in malnourished or immunocompromised persons
Seizure or encephalopathy
Leukemoid reaction (peripheral leukocytes >40000/μL)*
POSTINFECTIOUS MANIFESTATIONS
Hemolytic-uremic syndrome (HUS)*
Reactive arthritis†
Irritable bowel syndrome (IBS)‡
Malnutrition

*Significantly more common in episodes with *Shigella dysenteriae* type 1 than with all other *Shigella* spp. among Bangladeshi children younger than 15 yr during the 1990s (rectal prolapse [52% vs 15%], severe hyponatremia [58% vs 26%], leukemoid reaction [22% vs 2%], and HUS [8% vs 1%]).

†Typical acute symptoms include asymmetric oligoarthritis (usually lower limb), enthesitis, dactylitis, and back pain. Extraarticular manifestations include conjunctivitis and uveitis; urethritis and other genitourinary tract manifestations; oral, skin, and nail lesions; and rarely, cardiac abnormalities.

‡IBS follows approximately 4% of *Shigella* episodes in studies from high-resource settings.

Adapted from Kotloff KL, Riddle MS, Platts-Mills JA, et al. Shigellosis. *Lancet.* 2018;391:801–810.

Table 245.1 Acute Clinical Manifestations of Shigellosis in Children <5 Years Old

MANIFESTATION	DYSENTERY (*n* = 757)	WATERY DIARRHEA (*n* = 288)
Fever	607 (80%)	207 (72%)
Abdominal cramps	616 (81%)	137 (48%)
Vomiting	136 (18%)	89 (31%)
WHO-defined dehydration	95 (13%)	134 (47%)
Tenesmus	511 (68%)	32 (11%)
Rectal prolapse	19 (3%)	4 (1%)

From Kotloff KL, Riddle MS, Platts-Mills JA, et al. Shigellosis. *Lancet.* 2018;391:801–810.

demonstration in peripheral blood of leukocytosis with a dramatic left shift (often with more bands than mature segmented neutrophils). The total peripheral white blood cell count is usually 5,000-15,000 cells/μL, although leukopenia and leukemoid reactions occur.

Culture of both stool and rectal swab specimens optimizes the chance of diagnosing *Shigella* infection. Culture media should include MacConkey agar and selective media such as xylose-lysine-deoxycholate and *Salmonella-Shigella* agar. Transport media should be used if specimens cannot be cultured promptly. Appropriate media should be used to exclude *Campylobacter* and *Salmonella* spp. and other agents. Studies of outbreaks and illness in volunteers show that the laboratory is often not able to confirm the clinical suspicion of shigellosis even when the pathogen is present. Multiple fecal cultures improve the yield of *Shigella*.

Culture-based diagnosis of *Shigella* infection, as with other enteric infections, is being displaced by molecular methods, often multiplexed, allowing testing for a panel of potential agents in a single rapid assay. Studies using molecular methods such as polymerase chain reaction (PCR) suggest that culture significantly underestimates the true frequency of infection. Quantitative PCR improves the ascertainment of *Shigella* burden in children with moderate to severe diarrhea in low-income countries. The generally **high negative predictive value** (NPV) of many molecular tests for *Shigella* (generally >95–97%) make the tests useful for decisions regarding antibiotic use and discontinuation and the necessity to test for additional etiologies of diarrhea. Molecular testing provides no information about antibiotic susceptibility. Stool cultures should be considered where antibiotic-resistant organisms are prevalent. In children who appear toxic, blood cultures should be obtained, especially in very young or malnourished infants, because of their increased risk of bacteremia.

TREATMENT

As with gastroenteritis from other causes, the first concern in a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance (see Chapter 387). Drugs that impair intestinal motility (e.g., diphenoxylate hydrochloride with atropine [Lomotil] or loperamide [Imodium]) should not be used because of the risk of more severe and prolonged illness.

Nutrition is a key concern in areas where malnutrition is common. A high-protein and high-caloric diet during convalescence enhances growth in 6 months after infection. Controlled studies show that cooked green bananas, a food rich in amylase-resistant starches, significantly improves outcome in severe disease. A single large dose of **vitamin A** (200,000 IU) lessens the severity of shigellosis in settings where vitamin A deficiency is common. **Zinc** supplementation (20 mg elemental zinc for 14 days) significantly decreases the duration of diarrhea, improves weight gain during recovery, enhances adaptive immunity to *Shigellae,* and decreases diarrheal disease in malnourished children.

The decision to use **antibiotics** remains challenging (Fig. 245.1). Many experts recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, the risk of emergence of resistant organisms, the risk of prolonging carriage (if *Salmonella* is present), or increasing the risk for HUS (EHEC). When a rapid multiplexed molecular stool pathogen detection test is available, waiting for a definitive diagnosis before administrating antibiotics should be considered. However, a counter-argument of empirical treatment for all children with suspected shigellosis has validity. Untreated illness can cause a child to have prolonged illness; chronic or recurrent diarrhea can ensue. Malnutrition can develop or worsen during prolonged illness, particularly in children in developing countries. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

Shigella antimicrobial susceptibility varies by species and geography. In the United States, strains are frequently resistant to ampicillin (74%) and trimethoprim-sulfamethoxazole (TMP-SMX) (36%). In general, the proportion of antibiotic-resistant isolates is lower in North America and Europe than in Asia or Africa. Previously, *Shigella* was widely regarded as susceptible in vitro to azithromycin, ceftriaxone, cefotaxime, cefixime, nalidixic acid, and quinolones. However, the Centers for Disease Control and Prevention (CDC) reports that 87% of *S. sonnei*–related U.S. cases are ciprofloxacin nonsusceptible, of which only approximately half followed international travel. Among MSM, clusters of shigellosis caused by *S. sonnei* and, to a lesser extent, *S. flexneri* were reported with up to 87% azithromycin resistance. International travel increases the risk for antibiotic-resistant infection. For example, Chinese isolates of *S. sonnei* are often resistant to TMP-SMX (94.5%), ampicillin (40.3%), piperacillin (36.5%), and ceftriaxone (12.8%).

Currently, in most developed and resource-poor countries, *Shigella* strains are often resistant to ampicillin and TMP-SMX. Therefore these drugs should not be used for empirical treatment of suspected shigellosis; they should be instituted only if the strain is known to be susceptible (e.g., in an outbreak caused by a defined strain). Empirical therapy in children with dysentery should be given based on considerations of regional infection cluster data and international travel history. **Ceftriaxone** (50-100 mg/kg/24 hr as a single daily dose intravenously or intramuscularly) can be used for empirical therapy, especially for small infants. The oral third-generation cephalosporin **cefixime** (8 mg/kg/24 hr divided every 12-24 hours) may be considered, although treatment failures for *S. sonnei* infections have been reported in adults; oral first- and second-generation cephalosporins are inadequate as alternative drugs despite in vitro susceptibility. **Azithromycin** (12 mg/kg/24 hr orally for the first day, followed by 6 mg/kg/24 hr for the next 4 days) has proved to be an effective alternative drug for shigellosis. **Ciprofloxacin** (20-30 mg/kg/24 hr divided into two doses) is the drug of choice recommended by the WHO for all patients with bloody diarrhea, regardless of age. Note that since 2015, the CDC has tracked increasing resistance and reduced susceptibility to ciprofloxacin and azithromycin in the United States. Concurrent zinc supplementation is recommended with antibiotic therapy.

Although **quinolones** are reported to cause arthropathy in immature animals and are associated with neuropathy, these risks are low in children and are outweighed by the value of these drugs for the treatment of this potentially life-threatening disease. However, some experts recommend that the quinolones be reserved for seriously ill children with bacillary dysentery caused by an organism suspected or known to be resistant to other agents, because overuse of quinolones promotes the development of resistance to these drugs.

Treatment of patients in whom *Shigella* infection is suspected on clinical grounds should be initiated when these patients are first evaluated. Molecular stool testing or culture is obtained to exclude other pathogens and, in the case of culture, to assist in antibiotic changes should a child fail to respond to empirical therapy. A child who has typical dysentery and who responds to initial empirical antibiotic treatment should be continued on that drug for a full 5-day course even if the stool culture is negative, because of the method's low NPV. The logic of this recommendation is based on the proven difficulty of culturing *Shigella* from stools of ill patients during adult volunteer infection studies. In a child who fails to respond to therapy of a dysenteric syndrome in the presence of initially negative stool culture results, additional cultures should be obtained, or molecular testing, where available and cost-permissive, should be performed, and the child should be reevaluated for other possible diagnoses. In the child with negative molecular stool testing for *Shigellae,* the high NPV makes the diagnosis less likely, and alternative diagnoses should be considered.

PREVENTION

Numerous measures have been recommended to decrease the risk of *Shigella* transmission to children. Mothers should be encouraged to *prolong breastfeeding* of infants. Families and daycare personnel

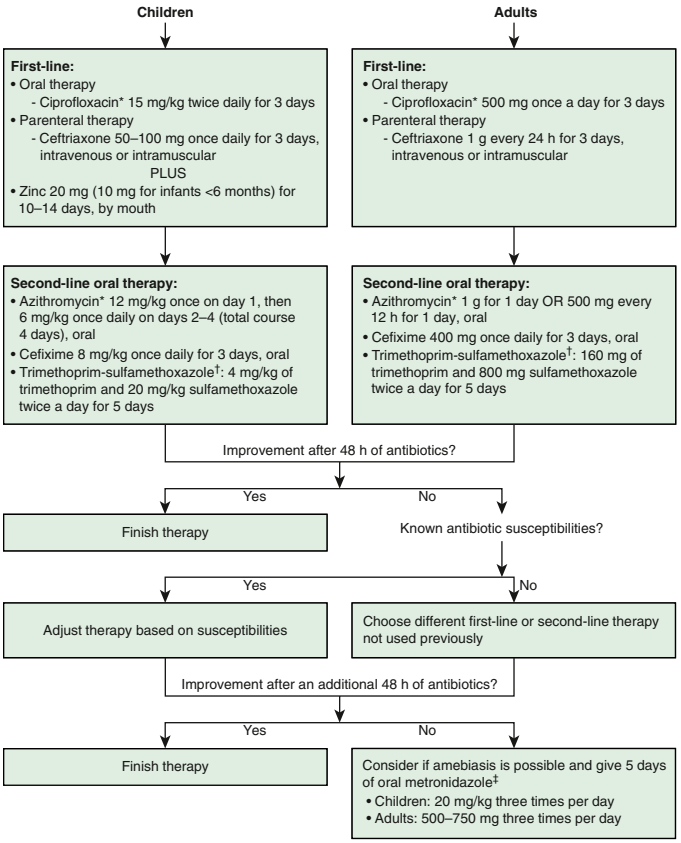

Fig. 245.1 Management algorithm: guidelines for treatment of shigellosis. Empirical therapy should be directed by hospital, clinical laboratory, or public health antibiograms whenever possible. Minimal inhibitory concentrations of 0.12-1.0 μg/mL for ciprofloxacin might be considered susceptible by laboratory standards but could harbor resistance genes known to confer decreased susceptibility. *Fluoroquinolones and azithromycin should be used with caution in patients taking the antimalarial artemether, because these drugs can prolong the QT interval on the electrocardiogram and trigger arrhythmias. †Trimethoprim-sulfamethoxazole should be used if susceptibility is known or expected based on local data. ‡Per WHO recommendations. Another acceptable regimen is a 7- to 10-day course of metronidazole followed by a luminal agent such as paromomycin or diiodohydroxyquinoline. *(Data from The selection and use of essential medicines: report of the WHO Expert Committee, 2017. Geneva: World Health Organization; 2017. WHO technical report series; no. 1006.)*

should be educated in *proper handwashing* techniques and encouraged to wash hands after using the toilet, changing diapers, or engaging in preparation of foods. They should be taught how to manage potentially contaminated materials such as raw vegetables, soiled diapers, and diaper-changing areas. Children with diarrhea should be excluded from childcare facilities. Children should be supervised when handwashing after they use the toilet. Caretakers should be informed of the risk of transmission if they prepare food when they are ill with diarrhea. Families should be educated regarding the danger of swallowing contaminated water from ponds, lakes, or untreated pools. In developing countries, a safe water supply and appropriate sanitation systems are important measures for reducing the risk for shigellosis. There is not yet a vaccine that is effective for preventing infection by *Shigella*. **Measles immunization** can substantially reduce the incidence and severity of diarrheal diseases, including shigellosis. Every infant should be immunized against measles at the recommended age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 246

Escherichia coli

Patrick C. Seed

Escherichia coli is an important cause of intraintestinal and extraintestinal infections. **Intraintestinal infections** present as diarrheal illnesses. **Extraintestinal infections** include disease of the urinary tract (see Chapter 575), bloodstream (Chapters 148, 220, and 221), and central nervous system (Chapter 643). *E. coli* causing extraintestinal and intraintestinal infections carry unique genetic attributes that encode different sets of virulence factors and genetic programs. Extraintestinal pathogenic *E. coli* increasingly harbor multidrug resistances, including transferrable plasmids resulting in extended-spectrum β-lactamase (ESBL) production and resistance to penicillins, cephalosporins, and aztreonam. Carbapenemase-bearing *E. coli* have also emerged, often in combination with multi–antibiotic class resistance, resulting in highly drug-resistant strains.

E. coli are members of the Enterobacteriaceae family and are facultative anaerobic, gram-negative bacilli that usually ferment lactose. Most fecal *E. coli* organisms are commensal, are ubiquitous among the human gut microbiota starting in the first month of life, and do not cause diarrhea. Six major groups of **diarrheagenic** *E. coli* pathotypes have been characterized based on clinical, biochemical, and molecular-genetic features: enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC); enteropathogenic *E. coli* (EPEC); *Shiga* toxin–producing *E. coli* (STEC), also known as enterohemorrhagic *E. coli* (EHEC) or verotoxin-producing *E. coli* (VTEC); enteroaggregative *E. coli* (EAEC or EggEC); and diffusely adherent *E. coli* (DAEC).

E. coli strains can also be categorized by their serogroup, where *O* refers to the lipopolysaccharide (LPS) O-antigen or serotype and *H* refers to the flagellar antigen, for example, *E. coli* O157:H7. However, because each pathotype contains many serotypes (e.g., 117 ETEC serotypes have been identified) and some serotypes can belong to more than one pathotype (e.g., O26:H11 can be either EPEC or EHEC depending on which specific virulence genes are present), serotyping usually does not provide definitive identification of pathotypes.

Virulence characteristics and the association of those traits with illness define **enteric** *E. coli* pathogenicity (Table 246.1). The mechanism by which *E. coli* produces **diarrhea** typically involves specific adherence to a glycoprotein or glycolipid receptor on a target intestinal cell, followed by production of a factor that injures or disturbs the function of intestinal cells. The genes for virulence properties and antibiotic resistance are often carried on transferable plasmids, pathogenicity islands, or bacteriophages.

In the developing world, diarrheagenic *E. coli* cause frequent infections in the first years of life and are responsible for 30–40% of all diarrhea cases in children worldwide. Cases peak during the warm months in temperate climates and during rainy season months in tropical climates. Most diarrheagenic *E. coli* strains (except STEC) require a large inoculum of organisms to induce disease, thus necessitating exposure to grossly contaminated ingestible materials. Infection is most likely when food-handling or sewage-disposal practices are suboptimal. The diarrheagenic *E. coli* pathotypes are also important in North America and Europe, although their epidemiology is less well defined in these areas than in the developing world. In North America, the various diarrheagenic *E. coli* strains may cause as much as 30% of infectious diarrhea in children <5 years old.

A significant proportion of asymptomatic healthy children living in developing countries carry diarrheagenic *E. coli* pathotypes. **Fecal contamination** (human and animal), which is common in the low-resource environments, facilitates the transmission of pathogens. Modern, highly sensitive microbiologic methods enhance the sensitivity

Table 246.1 Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli*

PATHOGEN	POPULATIONS AT RISK	CHARACTERISTICS OF DIARRHEA			MAIN VIRULENCE FACTORS		DIAGNOSIS
		WATERY	BLOODY	DURATION	ADHERENCE FACTORS	TOXINS	
ETEC	>1 yr old and travelers	+++	–	Acute	Colonization factor antigens (CFs or CFAs); ECP	Heat-labile enterotoxin (LT) Heat-stable enterotoxin (ST)	Detection of enterotoxins (LT and ST) by enzyme immunoassays or PCR *(lt, st)*
EIEC	>1 yr old	+	++	Acute	Invasion plasmid antigen (IpaA-D)		Detection of invasion plasmid antigen of *Shigella (ipaH)* by PCR
EPEC	<2 yr old	+++	+	Acute, prolonged or persistent	A/E lesion, intimin/Tir, EspABD, Bfp	EspF, Map, EAST1, SPATEs *(EspC)*	Detection of intimin gene *(eae)* ± bundle-forming pili (*bfp*A) by PCR and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA)
STEC (EHEC/ VTEC)	6 mo to 10 yr and elderly persons	+	+++	Acute	A/E lesion, intimin/Tir, EspABD	*Shiga* toxins (Stx1, Stx2, and variants of Stx2)	Detection of *Shiga* toxins by enzyme immunoassays or PCR *(Stx1, Stx2)*; stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins
EAEC	<2 yr old, HIV-infected patients, and travelers	+++	+	Acute, prolonged, or persistent	Aggregative adherence fimbriae (AAF)	SPATEs (Pic, Pet), ShET1, EAST1	Detection of *AggR*, AA plasmid, and other virulence genes: *aap, aatA, astA, set1A* by PCR; HEp-2 cells adherence assay (AA)
DAEC	>1 yr old and travelers	++	–	Acute	Afa/Dr, AIDA-I	SPATEs (Sat)	Detection of Dr adhesins (daaC or daaD) and Dr-associated genes by PCR; HEp-2 cells adherence assay (DA)

–, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili; DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat-stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli*; EspABD, *E. coli*–secreted proteins A, B, and D; ETEC, enterotoxigenic *E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine-protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli*; Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli*.

of detection in stool samples, and small numbers of bacteria can be detected in stool samples. Therefore the prevalence of various enteropathogens in children with and without diarrhea must be considered. Excretion of enteropathogens by children without diarrhea may be explained by characteristics of the pathogens (virulence heterogeneity), the host (host susceptibility, age, nutritional status, breastfeeding, immunity), and environmental factors (inoculum size).

ENTEROTOXIGENIC *ESCHERICHIA COLI*

ETEC accounts for a sizable fraction of dehydrating infantile diarrhea in the developing world (10–30%) and of **traveler's diarrhea** (20–60% of cases); ETEC is the most common cause of traveler's diarrhea. The Global Enteric Multicenter Study (GEMS) found heat-*stable* enterotoxin (ST)–expressing ETEC (with or without coexpression of *heat-labile* enterotoxin [LT]) to be a leading cause of diarrhea and increased risk for death in young children in developing countries of Asia and Africa. The typical signs and symptoms include explosive watery, nonmucoid, nonbloody diarrhea; abdominal pain; nausea; vomiting; and little or no fever. The illness is usually self-limited and resolves in 3-5 days but occasionally lasts >1 week.

Diarrhea follows ETEC colonization of the small intestine and elaboration of enterotoxin; however, ETEC causes few to no structural alterations in the gut mucosa. ETEC strains secrete one or two enterotoxins. LT, a large molecule consisting of five receptor-binding subunits

and one enzymatically active subunit, is structurally, functionally, and neutralizing antibody cross-reactive with cholera toxin produced by *Vibrio cholerae*. LT stimulates adenylate cyclase, resulting in increased cyclic adenosine monophosphate. ST is not related to cholera toxin and stimulates guanylate cyclase, resulting in increased cyclic guanosine monophosphate. Each toxin induces ion and water secretion into the intestinal lumen, resulting in profuse watery diarrhea. The toxin genes are carried on plasmids.

Colonization of the intestine requires fimbria **colonization factor antigens (CFAs)**, which promote adhesion to the intestinal epithelium. Over 25 CFA types exist and can be expressed alone or in combination. Roughly 30–50% of ETEC isolates lack a characterized CFA. However, novel CFAs continue to be identified.

CFAs are highly immunogenic, but their multiplicity and allelic variation elude vaccine development. Many strains produce a type IV pilus involved in colonization and shared among other gram-negative bacterial pathogens. ETEC express type 1 pili (the "common pilus"), produced by commensal and pathogenic *E. coli* strains. TibA, a nonfimbrial adherence factor, mediates potent bacterial attachment and invasion of cells. For many years, the O serogroup was used to distinguish pathogenic from commensal *E. coli*. Molecular classification of pathogenic *E. coli* based on specific virulence genes and whole genome phylogeny has largely replaced classic O serogroup typing.

ENTEROINVASIVE *ESCHERICHIA COLI*

EIEC infections produce watery diarrhea or dysentery with blood, mucus, and leukocytes in the stools, as well as fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency. The illness resembles **bacillary dysentery** because EIEC shares virulence genes with *Shigella* spp. Sequencing of multiple housekeeping genes indicates that EIEC is more related to *Shigella* than to noninvasive *E. coli*. EIEC diarrhea occurs mostly in outbreaks; however, endemic disease occurs in developing countries. In some areas of the developing world, as many as 5% of sporadic diarrhea episodes and 20% of bloody diarrhea cases are caused by EIEC (see Chapter 245).

EIEC behave like *Shigella* in their capacity to invade gut epithelium and cause colonic lesions with ulcerations, hemorrhage, mucosal and submucosal edema, and infiltration by polymorphonuclear leukocytes (PMNs). The invasive process involves initial entry into cells, intracellular multiplication, intracellular and intercellular spread, and host cell death. All bacterial genes necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid; these genes are closely related to those found on the invasion plasmid of *Shigella* spp. This region carries genes encoding the entry-mediating proteins, including proteins that form a needle-like injection apparatus called *type III secretion,* required for secreting the invasins (IpaA-D and IpgD). The Ipas are the primary effector proteins of epithelial cell invasion. EIEC contact with host cells triggers the syringe-like type III secretion apparatus and injection of Ipas into the host cell cytoplasm.

Like *Shigella* spp., EIEC are nonmotile (they lack H or flagellar antigens) and are usually non–lactose fermenting. The serogroups of EIEC share LPS antigens related to *Shigella* LPS.

ENTEROPATHOGENIC *ESCHERICHIA COLI*

EPEC causes acute, prolonged, and persistent diarrhea, primarily in children <2 years old in resource-poor countries, where the organism may account for 20% of infant diarrhea. In developed countries, EPEC causes occasional daycare center and pediatric ward outbreaks. Profuse watery, nonbloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged diarrhea (>7 days) and persistent diarrhea (>14 days) can lead to **malnutrition**, a potentially mortality-associated outcome of EPEC infection in infants in the developing world. Studies show that breastfeeding is protective against diarrhea caused by EPEC.

EPEC colonization causes blunting of intestinal villi, local inflammatory changes, and sloughing of superficial mucosal cells; EPEC-induced lesions extend from the duodenum through the colon. EPEC induces a characteristic attaching and effacing histopathologic lesion, which is defined by the intimate attachment of bacteria to the epithelial surface and effacement of host cell microvilli. Factors responsible for the attaching and effacing lesion formation are encoded by the *locus of enterocyte effacement* (LEE), a pathogenicity island with genes for a type III secretion system, the translocated intimin receptor (Tir) and intimin, and multiple effector proteins such as the *E. coli*–secreted proteins (EspA-B-D). Some strains adhere to the host intestinal epithelium in a pattern known as *localized adherence,* a trait that is mediated in part by the type IV bundle-forming pilus (Bfp) encoded by a plasmid (the EAF plasmid). After initial contact, proteins are translocated through filamentous appendages, forming a physical bridge between the bacteria and the host cell; bacterial effectors (EspB, EspD, Tir) are translocated through these conduits. Tir moves to the surface of host cells, where it is bound by a bacterial outer membrane protein intimin (encoded by the *eae* gene). Intimin-Tir binding triggers polymerization of actin and other cytoskeletal components at the site of attachment. These cytoskeletal changes result in intimate bacterial attachment to the host cell, enterocyte effacement, and pedestal formation.

Other LEE-encoded effectors include Map, EspF, EspG, EspH, and SepZ. Various other effector proteins are encoded outside the LEE and secreted by the type III secretion system (the non–LEE-encoded proteins, or Nle). The contribution of these putative effectors (e.g., NleA/EspI, NleB, NleC, NleD) to virulence is still under investigation. The presence and expression of virulence genes vary among EPEC strains.

The *eae* (intimin) and *bfp*A genes serve as molecular markers of EPEC and genetically subdivide EPEC into typical and atypical strains. *E. coli* strains that are *eae*$^+$/*bfp*A$^+$ are classified as "typical" EPEC; most of these strains belong to common O:H serotypes. *E. coli* strains that are *eae*$^+$/*bfp*A$^-$ are classified as "atypical" EPEC. Current data suggest that atypical EPEC are more prevalent than typical EPEC in both developed and developing countries, even in persistent diarrhea cases. In the GEMS study, typical EPEC was most associated with increased risk of mortality, particularly in infants in Africa.

ENTEROAGGREGATIVE *ESCHERICHIA COLI*

EAEC infection produces (1) acute, prolonged, and persistent pediatric diarrhea in developing countries, most prominently in children <2 years old and in malnourished children; (2) acute and persistent diarrhea in HIV-infected adults and children; and (3) acute traveler's diarrhea; EAEC is the second most common cause of traveler's diarrhea after ETEC. Typical EAEC illness is manifested by watery, mucoid, secretory diarrhea with low-grade fever and little or no vomiting. The watery diarrhea can persist for ≥14 days. Patients with EAEC may have grossly bloody stools, and EAEC cannot be excluded on stool characteristics. EAEC colonization and infection lead to growth retardation and malnutrition in infants in the developing world.

EAEC organisms form a characteristic biofilm on the intestinal mucosa and induce shortening of the villi, hemorrhagic necrosis, and inflammatory responses. The proposed model of pathogenesis of EAEC infection involves three phases: adherence to the intestinal mucosa by way of the aggregative adherence fimbriae or related adhesins, stimulation of enhanced mucus production, and toxin-mediated inflammation that results in damage to the mucosa and intestinal secretion. Diarrhea caused by EAEC is predominantly secretory. The intestinal inflammatory response (elevated fecal lactoferrin, interleukin [IL]-8 and IL-1β) may be related to growth impairment and malnutrition.

EAEC strains adhere in an aggregative, stacked-brick pattern, called *aggregative adherence* (AA), mediated by the AA fimbriae (AAF-I, -II, and -III). Some strains produce toxins, including the plasmid-encoded enterotoxin EAST1 (encoded by *ast*A), a homolog of the ETEC ST; an autotransporter toxin called Pet; other STATE toxins; and the chromosomally encoded enterotoxin ShET1 (encoded by *setA* and *setB*). Other virulence factors include outer membrane and secreted proteins, such as dispersin *(aap),* and the dispersin transport complex (aatPABCD). EAEC is a heterogeneous group of *E. coli*. A transcriptional activator called **AggR** controls the expression of plasmid-borne and chromosomal virulence factors. Identification of AggR appears to reliably identify illness-associated pathogenic EAEC strains ("typical" EAEC). EAEC *agg*R-positive strains carrying one to three of the genes *aap, ast*A, and *set1A* are significantly associated with diarrhea compared

with EAEC isolates lacking these genes. Other than the AAF and AggR factors, EAEC strains are genetically diverse, display variable virulence, and belong to multiple serogroups.

SHIGA TOXIN–PRODUCING *ESCHERICHIA COLI*

The STEC, which include EHEC, produce a range of clinical syndromes from asymptomatic colonization, to mild diarrhea, to severe hemorrhagic colitis. Watery diarrhea that becomes bloody over several days characterizes STEC illness. STEC infrequently causes fever, a distinguishing difference with shigellosis or EIEC disease. Most people with STEC recover from the infection without further complication. However, 5–10% of children with STEC hemorrhagic colitis go on within a few days to develop systemic complications such as **hemolytic-uremic syndrome** (HUS), characterized by acute kidney failure, thrombocytopenia, and microangiopathic hemolytic anemia (see Chapter 560). Severe illnesses occur most often among children 6 months to 10 years old. Young children with STEC-associated bloody diarrhea and neutrophilic leukocytosis in the early course of their diarrhea are at risk for HUS progression. Older individuals can also develop HUS or thrombotic thrombocytopenic purpura.

STEC transmits person to person (e.g., in families and daycare centers) and in contaminated food and water; a small inoculum can lead to infection. STEC food-borne outbreaks have arisen from undercooked hamburger, apple cider, lettuce, spinach, mayonnaise, salami, dry fermented sausage, and unpasteurized dairy products.

STEC primarily affects the colon, where organisms adhere to intestinal cells and produce attaching-effacing lesions such as those seen with EPEC and contain related genes (e.g., *intimin, Tir, EspA-D*). Unlike EPEC, STEC produces two major **Shiga toxins** (Stx1 and Stx2; previously called *verotoxins* and *Shiga-like*). STEC may produce one or both toxins and their closely related variants. **Stx1** is essentially identical to Shiga toxin, the protein synthesis–inhibiting exotoxin of *Shigella dysenteriae* serotype 1. **Stx2** and variants of Stx2 are more distantly related to Shiga toxin, although they share conserved sequences.

STEC Shiga toxins are composed of a single A subunit noncovalently associated with a pentamer composed of identical B subunits. The B subunits bind to globotriaosylceramide (Gb_3), a glycosphingolipid receptor on host cells. The A subunit is taken up by endocytosis. The toxin target is the 28S ribosomal RNA (rRNA), which is depurated by the toxin at a specific adenine residue, causing protein synthesis to cease and affected cells to die. These toxins are carried on bacteriophages that are normally inactive (lysogenic) in the bacterial chromosome; when the phages are induced to replicate (e.g., by the stress induced by many antibiotics), they cause lysis of the bacteria and release of large amounts of toxin. Toxin translocation across the intestinal epithelium into the systemic circulation can lead to damage of vascular endothelial cells, resulting in activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis, and ischemia.

The clinical outcome of an STEC infection depends on a strain-specific combination of epithelial attachment and the toxin factors. The Stx2 toxins are associated with a higher risk of causing HUS. Strains producing only Stx1 often cause only watery diarrhea and, infrequently, HUS.

The most common STEC serotypes are *E. coli* O157:H7, *E. coli* O111:NM, and *E. coli* O26:H11, although several hundred other STEC serotypes have also been described. *E. coli* **O157:H7** is the most virulent serotype and the serotype most frequently associated with HUS; however, other non-O157 serotypes also cause this illness.

ENTEROAGGREGATIVE HEMORRHAGIC *ESCHERICHIA COLI*

In 2011, a massive outbreak of an unusual O104:H4 strain of diarrheagenic *E. coli* began in Germany. Eventually, >4,000 individuals were sickened with hemorrhagic colitis; the outbreak involved primarily adults (<100 children were reported affected). More than 800 people developed HUS, and >50 of these individuals died. Genomic analysis suggested the outbreak strain was most closely related to EAEC and had acquired a lambdoid bacteriophage with genes for Shiga toxin Stx2a. It was thus a **hybrid** pathogen with colonization mechanisms similar to a typical EAEC strain and toxin production typical of an STEC strain. This outbreak strain carries Pic on the chromosome and a pAA-like plasmid encoding AAF, AggR, Pet, ShET1, and dispersin. A second virulence plasmid encodes multiple antibiotic resistances. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with STEC, delivering more Stx to target cells. Alternative terminology for this strain includes **enteroaggregative hemorrhagic *E. coli*** and **Shiga toxin–producing EAEC**. Whether Shiga toxin production in an EAEC background merits separate classification is unclear. Organisms with Shiga toxin genes in an atypical EPEC background were designated as a separate group (referred to as **STEC**, **EHEC**, or **verotoxin-producing *E. coli***) before the relative importance of the various genes was clear. EPEC strains are a heterogeneous group themselves. The important issue is not the nomenclature, but rather the concept that virulence genes can move between *E. coli,* resulting in new variants.

DIFFUSELY ADHERENT *ESCHERICHIA COLI*

Multiple studies in both developed and developing countries find DAEC associated with diarrhea, particularly in children after the first 1-2 years of life. DAEC strains isolated from children and adults seem to represent two different bacterial populations. **Age-dependent susceptibility** or the use of inappropriate detection methods may explain discrepancies among epidemiologic studies. Data suggest that these organisms also cause traveler's diarrhea in adults. DAEC produces prolonged watery diarrhea that is usually not dysenteric.

DAEC strains produce **diffuse adherence** on intestinal epithelial cells using the Afa/Dr-like surface fimbriae (designated F1845). The outer membrane protein AIDA-I also associates with **diffuse adherence**. DAEC secrete the serine-protease autotransporters of Enterobacteriaceae (SPATE) cytotoxin Sat. Bacteria expressing Afa/Dr adhesins interact with membrane-bound receptors, including decay-accelerating factor (DAF). The structural and functional lesions induced by DAEC include loss of microvilli and a decrease in the expression and enzyme activities of functional brush border–associated proteins. Afa/Dr DAEC isolates produce a secreted autotransporter toxin that induces marked fluid accumulation in the intestine. DAEC strains typically induce IL-8 production in vitro.

DIAGNOSIS

The features of suspected *E. coli* diarrheal illness are seldom distinctive enough to allow confident diagnosis strictly on clinical observations and routine laboratory studies such as blood counts. Practical, non–DNA-dependent methods for routine diagnosis of diarrheagenic *E. coli* have been developed primarily for STEC. Serotype O157:H7 is suggested by isolation of an *E. coli* that fails to ferment sorbitol on MacConkey sorbitol medium; latex agglutination confirms that the organism contains O157 LPS. Commercially available enzyme immunoassay or latex agglutination assays detect Shiga toxins in the routine hospital laboratory, although their variable sensitivity may limit their value.

Commercial assays such as the FilmArray Gastrointestinal Panel and Eurofins Diatherix Panel rapidly detect genetic markers for EPEC, EAEC, ETEC, STEC, and EIEC, among other pathogen genes, directly from a fecal sample in several hours and have been shown to reduce hospitalizations and treatment costs. Although some STEC (O157:H7 strains) can be detected in routine microbiology laboratories using selective media and appropriate antisera, the diagnosis of other diarrheagenic *E. coli* infection is traditionally made based on tissue culture assays (e.g., HEp-2-cells assay for EPEC, EAEC, and DAEC) or identification of specific virulence factors of the bacteria by phenotype (e.g., toxins) or genotype. Multiplex, real-time, or conventional polymerase chain reaction (PCR) can be used for presumptive diagnosis of isolated *E. coli* colonies. The genes commonly used for diagnostic PCR are *lt* and *st* for ETEC; *IpaH* or *iaL* for EIEC; *eae* and *bfp*A for EPEC; *eae, Stx1,* and *Stx2* for STEC; *AggR* or the AA plasmid for EAEC; and *daaC* or *daaD* for DAEC.

Serotyping does not provide definitive identification of pathotypes (except for selected cases such as O157:H7) because each pathotype

contains many serotypes and some serotypes can belong to more than one pathotype. Consequently, serotyping should not be used routinely for diarrheagenic *E. coli* identification in clinical laboratories (e.g., to diagnose EPEC in infantile diarrhea), except during an outbreak investigation.

Other laboratory data are, at best, *nonspecific* indicators of etiology. Fecal leukocyte examination of the stool is often positive with EIEC or occasionally positive with other diarrheagenic *E. coli*. With EIEC and STEC there may be an elevated peripheral blood PMN count with a left shift. Determination of *Stx2* blood levels in the early, post-bloody diarrhea period may be useful to identify children at risk of HUS; however, a validated clinical test is not readily available. Fecal lactoferrin, IL-8, and IL-1β can be used as inflammatory markers. Electrolyte changes are nonspecific, reflecting only fluid loss.

TREATMENT

The cornerstone of management is appropriate fluid and electrolyte therapy (Fig. 246.1). In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization (WHO). Early volume expansion during STEC infection may reduce renal injury and improve patient outcomes. Upon refeeding, continued supplementation with oral rehydration fluids is appropriate to prevent recurrence of dehydration. Early refeeding (within 6-8 hours of initiating rehydration) with breast milk or infant formula or solid foods should be encouraged. Prolonged withholding of feeding can lead to chronic diarrhea and malnutrition. If the child is malnourished, oral zinc should be given to speed recovery and decrease the risk of future diarrheal episodes.

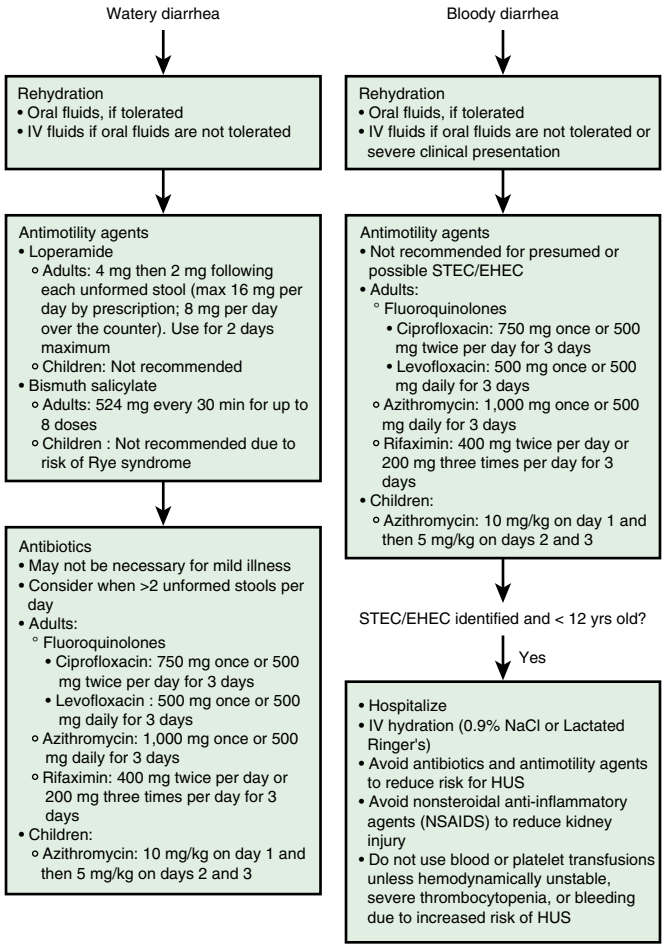

Fig. 246.1 Algorithmic treatment summary for presumed and possible *E. coli* diarrheal illness.

In children, validated criteria for antimicrobial therapy of diarrheal disease do not exist. The routine use of antimicrobials to treat childhood diarrhea is not recommended by the WHO except in severe cases. Nonbloody diarrhea rarely requires antimicrobial therapy. Antimicrobials should be reserved for dysenteric presentations, when host immunity is compromised by specific disorders, malnutrition, and chronic disease (Table 246.2). Antimicrobials should also be considered for severe traveler's diarrhea and diarrhea accompanied by fever and bloody stools. In settings of good healthcare resources, rapid molecular testing for STEC should be performed before initiating antibiotics, which can increase the risk for HUS.

Emerging antimicrobial resistance among diarrheal *E. coli* and other bacterial pathogens complicates treatment. Multiple studies in developing countries have found that diarrheagenic *E. coli* strains typically are resistant to antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX) and ampicillin (60–70%). Most data come from case series or clinical trials in adults with traveler's diarrhea. ETEC responds to antimicrobial agents such as TMP-SMX when the *E. coli* strains are susceptible. ETEC cases from traveler's diarrhea trials respond to ciprofloxacin, azithromycin, and rifaximin. However, other than for a child recently returning from travel in the developing world, empirical treatment of severe *watery diarrhea* with antibiotics is seldom appropriate.

In resource-poor settings where rapid molecular panel tests are not available, EIEC infections may be treated before culture results are finalized because the clinician suspects shigellosis and has begun empirical therapy. If the organisms prove to be susceptible, TMP-SMX is an appropriate choice. Although treatment of EPEC infection with TMP-SMX intravenously or orally for 5 days may be effective in speeding resolution, the lack of a rapid diagnostic test in the resource-poor setting makes treatment decisions difficult. Ciprofloxacin or rifaximin is useful for EAEC traveler's diarrhea, but pediatric data are sparse. Specific therapy for DAEC has not been defined.

The STEC strains represent a particularly difficult therapeutic dilemma; many antibiotics can induce bacterial stress, toxin production, and phage-mediated bacterial lysis with toxin release. Antibiotics should not be given for STEC infection because they can increase the risk of HUS (see Chapter 560). In settings with rapid molecular diagnostics, a delay in providing antibiotics is rarely consequential and can allow the clinician to more confidently recommend or exclude antibiotics from the therapeutic plan.

PREVENTION OF ILLNESS

In the developing world, prevention of disease caused by pediatric diarrheagenic *E. coli* is probably best done by maintaining prolonged breastfeeding, paying careful attention to personal hygiene, and following proper food- and water-handling procedures. People traveling

Table 246.2 Risk Factors Favoring Antibiotic Therapy in Children with Acute Diarrhea

RISK FACTOR	EVIDENCE
CHILD FACTORS	
Age <3 mo	Poor evidence in general; strong indication for neonates
Severe clinical presentation	Poor evidence but strong indications
Malnutrition	Strong evidence
Chronic disease and immune deficiency	Strong evidence (IBD and HIV); otherwise poor evidence; strong indications
SETTING FACTORS	
Daycare centers, closed institutions, hospitals	Strong evidence if bacteria spread is a potential
Traveler's diarrhea	Evidence for adult is strong; poor evidence in children

to these places can be best protected by handwashing and consuming only processed water, bottled beverages, breads, fruit juices, fruits that can be peeled, or foods that are served steaming hot.

Prophylactic antibiotic therapy is effective in adult travelers but has not been studied in children and is not recommended. Public health measures, including sewage disposal and food-handling practices, have made pathogens that require a large inoculum to produce illness relatively uncommon in industrialized countries where food screening and public health measures are robust. Food-borne outbreaks of STEC are a problem for which no adequate solution has been found. During the occasional hospital outbreak of EPEC disease, attention to enteric isolation precautions and cohorting may be critical.

Protective immunity against diarrheagenic *E. coli* remains an active area of research, and no vaccines are available for clinical use in children. Multiple vaccine candidates based on bacterial toxins and colonization factors have shown promise for prevention of ETEC in adult travelers, but long-term protection with these vaccines has not been optimal, particularly in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 247

Cholera

James P. Nataro

Cholera is a dehydrating diarrheal disease that rapidly leads to death in the absence of immediate initiation of appropriate treatment. Worldwide, 1.3 billion people are at risk for cholera, resulting in an estimated 1-4 million cases and 95,000 deaths annually. Cholera is highly prone to producing outbreaks, and the ongoing outbreaks in Yemen and Haiti emphasize how cholera and potentially other infectious diseases can easily reemerge in areas that have long been considered free of the disease after a natural disaster or war-related conflicts.

ETIOLOGY

Cholera is caused by *Vibrio cholerae,* a gram-negative, comma-shaped bacillus, subdivided into serogroups by its somatic O antigen. Of the >200 serogroups, only serogroups O1 and O139 have been associated with epidemics, although some non-O1, non-O139 *V. cholerae* strains (e.g., O75, O141) are pathogenic and can cause small outbreaks. A flagellar H antigen is present but is not used for species identification. The O1 serogroup is further divided into classical and El Tor biotypes based on its biochemical characteristics. Since the turn of the 21st century, only **O1 El Tor** has been reported; hybrids and variants of *V. cholerae* O1 El Tor possessing classical genes have been reported worldwide. These hybrid and variant strains have been associated with more severe disease.

Each biotype of *V. cholerae* can be further subdivided into Inaba, Ogawa, and Hikojima serotypes based on the antigenic determinants on the O antigen. **Inaba** strains have A and C antigenic determinants, whereas **Ogawa** strains have A and B antigenic determinants. **Hikojima** strains produce all three antigenic determinants but are unstable and rare. Recent studies reveal that serotype switching results from a selection process as yet unidentified.

EPIDEMIOLOGY

The first six cholera pandemics originated in the Indian subcontinent and were caused by classical O1 *V. cholerae*. The seventh pandemic is the most extensive of all and is caused by *V. cholerae* O1 El Tor. This pandemic began in 1961 in Sulawesi, Indonesia, and has spread to the Indian subcontinent, Southeast Asia, Africa, Oceania, Southern Europe, and the Americas. In 1991, *V. cholerae* O1 El Tor first appeared in Peru before rapidly spreading in the Americas. Cholera becomes **endemic** in areas after outbreaks when a large segment of the population develops immunity to the disease after recurrent exposure. Although the Ganges River valley is the historical home of cholera, it is estimated that >90% of global cases now occur in Africa, where the disease remains highly endemic.

In 1992 the first non-O1 *V. cholerae* that resulted in epidemics was identified in India and Bangladesh and was designated *V. cholerae* **O139**. From 1992 to 1994, this organism replaced O1 as the predominant cause of cholera in South Asia but has since been an uncommon etiologic agent.

The hybrid El Tor strains were first identified sporadically in Bangladesh. In 2004, during routine surveillance in Mozambique, isolates of *V. cholerae* O1 El Tor carrying classical genes were identified. Since then, hybrid and variant El Tor strains have been reported in other parts of Asia and Africa and have caused outbreaks in India and Vietnam. Although the classical biotype has virtually disappeared, its genes remain within the El Tor biotype. The current circulating strain in Haiti is closely related to the South Asian strain.

Humans are the only known hosts for *V. cholerae,* but free-living and plankton-associated *V. cholerae* exist in the marine environment. The organism thrives best in moderately salty water but can survive in rivers and freshwater if nutrient levels are high, as occurs when there is organic pollution such as human feces. The formation of a biofilm on abiotic surfaces and the ability to enter a viable but nonculturable state have been hypothesized as factors that allow *V. cholerae* to persist in the environment during interepidemic periods. Surface sea temperature, pH, chlorophyll content, the presence of iron compounds and chitin, and climatic conditions such as amount of rainfall and sea level rise are all important environmental factors that influence the survival of *V. cholerae* in the environment.

Consumption of **contaminated water** and ingestion of **undercooked shellfish** are the main modes of transmission, but additional food sources are becoming increasingly common. In cholera-endemic areas, the incidence is highest among children <2 years old, probably driven by the lack of previous exposure in young children. However, during cholera epidemics, all age-groups are usually affected, particularly in areas with no previous *V. cholerae* transmission. Persons with blood group O, decreased gastric acidity, malnutrition, immunocompromised states, and absence of local intestinal immunity (i.e., prior exposure) are at increased risk for developing severe disease. Household contacts of cholera-infected patients are at high risk of infection, because the stools of infected patients contain high concentrations of the pathogen. Moreover, upon repeated cycles of passage through humans, the organism becomes more virulent, demonstrating an increased number of copies of the cholera toxin-encoding genes.

PATHOGENESIS

Large inocula of bacteria (>10^8 colony-forming units [CFUs]) are required for severe cholera to occur; however, for persons whose gastric barrier is disrupted, a much lower dose (10^5 CFUs) is required, and the infectious dose may be lower after serial propagation of the pathogen through humans. After ingestion of *V. cholerae* from the environment, several changes occur in the microorganisms as they traverse the human intestine: increased expression of genes required for nutrient acquisition, downregulation of chemotactic responses, and expression of motility factors. Freshly excreted organisms (5-24 hours after shedding) are maximally infectious and may represent the predominant pathway for person-to-person transmission during epidemics.

The principal virulence factors of *V. cholerae* O1 are the cholera toxin and the toxin-coregulated pilus, a colonization factor that confers adherence to the epithelium of the small intestine (Fig. 247.1). The cholera toxin consists of five binding B subunits and one active A subunit. The B subunits are responsible for binding to the GM_1 ganglioside receptors located in the small intestinal epithelial cells. After binding, the A subunit is translocated into the cell, where it catalyzes adenosine diphosphate (ADP) ribosylation of the *alpha* subunit of the G_s signaling protein, which becomes constitutively active. G_s stimulates adenylate cyclase, leading to accumulation of cyclic adenosine

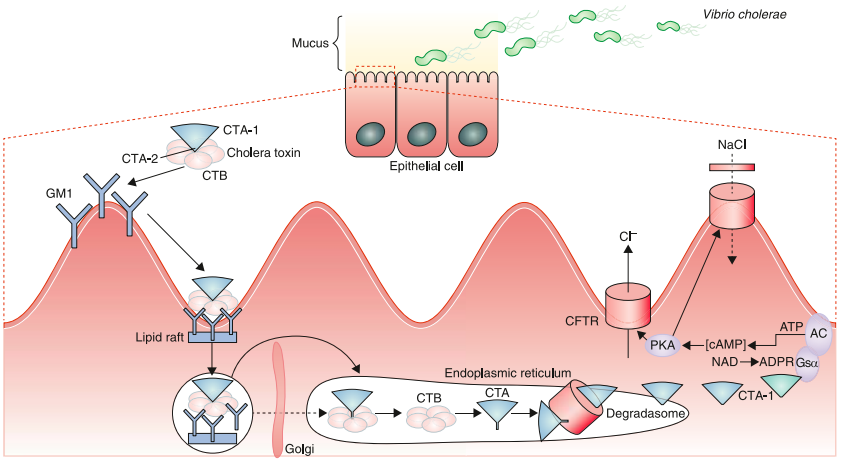

Fig. 247.1 Cholera pathogenesis and cholera toxin action. After ingestion, *Vibrio cholerae* colonize the small intestine and secrete cholera toxin, which has a doughnut-like structure with a central enzymatic toxic-active A (CTA-1 + CTA-2) subunit associated with a pentameric B subunit (CTB). After binding to GM_1 ganglioside receptors on small intestinal epithelial cells, which are mainly localized in lipid rafts on the cell surface, the cholera toxin is endocytosed and transported to the degradosome via the endoplasmic reticulum (ER) by a retrograde pathway, which, dependent on cell type, may or may not involve passage through the Golgi apparatus. In the ER, CTA dissociates from CTB, allowing CTA-1 to reach the cytosol by being translocated through the degradosome pathway. In the cytosol, CTA-1 subunits rapidly refold and bind to the Gsα subunit of adenylate cyclase (AC) in the cell membrane; on binding, CTA-1 adenosine diphosphate (ADP)-ribosylates the Gsα subunit, which stimulates AC activity, leading to an increase in intracellular concentration of cyclic adenosine monophosphate (cAMP), activation of protein kinase A (PKA), phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR), a major chloride channel, and extracellular secretion of chloride ions (Cl^-) and water. Cholera toxin–induced Cl^- (and bicarbonate ion) secretion is particularly pronounced in intestinal crypt cells, whereas the increased intracellular cAMP concentrations in villus cells mainly inhibit the uptake of sodium chloride (NaCl) and water. *(Adapted from Clemens J, Shin S, Sur D, et al. New-generation vaccines against cholera. Nat Rev Gastroenterol Hepatol. 2011;8:701–710; by permission of Nature Publishing Group.)*

monophosphate and subsequent hyperactivation of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel. Increased chloride and bicarbonate secretion by CFTR is accompanied by sodium and water loss into the small bowel, greatly exceeding the ability of the colon to reabsorb the fluid. These events eventually lead to massive purging of electrolyte-rich stool, potentially resulting in rapid dehydration and depletion of electrolytes, including sodium, chloride, bicarbonate, and potassium. Metabolic acidosis and hypokalemia then ensue.

CLINICAL MANIFESTATIONS

Most cases of cholera are mild or inapparent. Among symptomatic individuals, approximately 20% develop severe **dehydration** that can rapidly lead to death. After a typical incubation period of 1-2 days (range: several hours to 5 days), acute watery **diarrhea** and **vomiting** ensue. The onset may be sudden, with profuse watery diarrhea, but some patients have a prodrome of anorexia and abdominal discomfort and the stool may initially be brown. Diarrhea can progress to painless purging of profuse *rice-water stools* (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease (Figs. 247.2 and 247.3). Fever is infrequent and suggests a different diagnosis. Vomiting with clear watery fluid is usually present at the onset of the disease. Stool from cholera patients typically contains more sodium (along with potassium and bicarbonate) compared with stool from diarrhea caused by other pathogens; the high stool volume, coupled with the presence of electrolytes, challenges clinicians to avoid dehydration and electrolyte imbalance. Muscle cramping and weakness commonly occur as a result of potassium and calcium imbalance.

The term **cholera gravis** refers to the most severe form of the disease, characterized by rice water stools and fecal purging at rates of up to 500-1,000 mL/hr. This condition inevitably leads to dehydration, manifested by decreased urine output, a sunken fontanel (in infants), sunken eyes, absence of tears, dry oral mucosa, shriveled hands and feet ("washerwoman's hands"), poor skin turgor, thready pulse, and tachycardia. If left untreated, hypotension and vascular collapse are inevitable (see Fig. 247.3). Patients with metabolic acidosis can present with typical Kussmaul breathing. Although patients may be initially thirsty and awake, they rapidly progress to obtundation and coma. If fluid losses are not rapidly corrected, death can occur within hours.

Cholera sicca is an unusual manifestation of severe cholera in which very rapid fluid loss is confined to the intestinal lumen; such patients may succumb to dehydration without frank diarrhea.

LABORATORY FINDINGS

Findings associated with dehydration such as elevated urine specific gravity and hemoconcentration are evident. **Hypoglycemia** is a common finding that is caused by decreased food intake during the acute illness. Serum potassium may be initially normal or even high in the presence of metabolic acidosis; however, as the acidosis is corrected, hypokalemia may become evident. **Metabolic acidosis** caused by bicarbonate loss and tissue hypoperfusion is a prominent finding in severe cholera. Serum sodium and chloride levels may be normal or decreased, depending on the severity of the disease. Serum calcium may be elevated because of hemoconcentration.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In children who have acute watery diarrhea with severe dehydration residing in a cholera-endemic area or who have recently traveled to an area known to have cholera, the disease may be suspected pending laboratory confirmation. Cholera differs from other diarrheal diseases in that it often occurs in large outbreaks affecting both adults and children. Treatment of dehydration should begin as soon as possible. Diarrhea caused by other etiologies (e.g., enterotoxigenic *Escherichia coli* or rotavirus) may be difficult to distinguish from cholera clinically. Microbiologic isolation of *V. cholerae* remains the gold standard for diagnosis. Although definitive diagnosis is not required for treatment to be initiated, laboratory confirmation is necessary for epidemiologic surveillance. *V. cholerae* may be isolated from stools, vomitus, or rectal swabs. Specimens may be transported on Cary-Blair media if they cannot be processed immediately. Selective media, such as thiosulfate-citrate–bile salts sucrose (TCBS) agar, should be used; *V. cholerae* exhibits a distinctive morphology on this medium, with confirmation made by serotyping. Because most laboratories in industrialized countries do not routinely culture for *V. cholerae,* clinicians should request appropriate cultures for clinically suspected cases.

Rapid diagnostic tests are currently available and show high sensitivity and specificity. These tests may be especially useful in areas with limited laboratory capacity, allowing early identification of cases at the



Fig. 247.2 Rice-water stool in a patient with cholera. *(Modified from Harris JB, LaRocque RC, Qadri F. Cholera. Lancet. 2012;379:2466–2474.)*



Fig. 247.3 A child lying on a cholera cot showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hours was sitting up, alert, and eating normally. *(From Sack DA, Sack RB, Nair GB, et al. Cholera. Lancet. 2004;363:223–233.)*

onset of an outbreak and facilitating a timely response. Molecular identification with the use of polymerase chain reaction and DNA probes is available but often not feasible in areas where cholera exists. Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation. Dark-field microscopy may be used for rapid identification of typical *darting motility* in wet mounts of rice-water stools, a finding that disappears once specific antibodies against *V. cholerae* O1 or O139 are added.

COMPLICATIONS

When optimally treated, patients with cholera typically recover fully without complications. Most adverse outcomes occur as a result of delayed or inadequate rehydration therapy. **Renal failure** from prolonged hypotension can occur. Unless potassium supplementation is provided, **hypokalemia** can lead to nephropathy and focal myocardial necrosis. Hypoglycemia is common among children and can lead to seizures unless it is appropriately corrected. Pneumonia is a frequent complication in young children and may be the result of aspiration during vomiting.

TREATMENT

Rehydration is the mainstay of therapy (see Chapter 74). Appropriate case management substantially decreases case fatalities to <1%. Application of World Health Organization (WHO) recommendations for diarrheal rehydration is recommended for all patients with diarrhea, but particularly when cholera is in the differential diagnosis. Children with mild or moderate dehydration may be treated with oral rehydration solution (ORS) unless the patient is in shock, is obtunded, or has intestinal ileus. Careful monitoring should occur during ORS, with attention to progression to more severe dehydration. Vomiting is not a contraindication to ORS. Severely dehydrated patients (>10% body weight) require intravenous fluid, ideally with lactated Ringer solution. When available, rice-based ORS should be used when oral rehydration is attempted, because this fluid has been shown to be superior to standard ORS in children and adults with cholera. The aim of rehydration should be replacement of the entire fluid deficit within 4 hours, if possible. Careful monitoring of ongoing losses is essential. If stool volumes cannot be measured, losses may be roughly estimated at 10-20 mL/kg of body weight for each episode of diarrhea or vomiting. After initial rehydration, patients should be reassessed every 1-2 hours, or more frequently if profuse diarrhea is ongoing; diarrhea typically begins to remit after 24 hours. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less frequent, large feedings.

Antibiotics should only be given in patients with moderately severe to severe dehydration. As soon as vomiting stops (usually within 4-6 hours after initiation of rehydration therapy), an antibiotic to which local *V. cholerae* strains are sensitive must be administered. Antibiotics shorten the duration of illness, decrease fecal excretion of *Vibrio*, decrease the volume of diarrhea, and reduce the fluid requirement during rehydration. Single-dose antibiotics increase compliance and are generally recommended; **doxycycline**, **ciprofloxacin**, and **azithromycin** are effective against cholera. The most clinical evidence for efficacy exists for tetracycline antibiotics (especially a single 300-mg dose of doxycycline). However, there are increasing reports of resistance to tetracyclines and to trimethoprim-sulfamethoxazole and other drugs. Because of these multidrug-resistant strains, antibiotic treatment must be tailored based on available susceptibility results from the area. **Recommendations for single-dose therapy for children include** doxycycline 2-4 mg/kg PO as a single dose up to 300 mg; 300 mg PO should be given to children 12 years of age and older. Alternative single dose regimens include azithromycin 20 mg/kg (max 1 g) PO, or ciprofloxacin 20 mg/kg (max 1 g) PO. Children >12 years of age should receive the adult doses. Cephalosporins and aminoglycosides are not clinically effective against cholera and therefore should not be used, even if in vitro tests show strains to be sensitive.

Zinc should be given as soon as vomiting stops. Zinc deficiency is common among children in many developing countries. Zinc supplementation in children <5 years old shortens the duration of diarrhea and reduces subsequent diarrhea episodes when given daily for 14 days at the time of the illness. Children <6 months old should receive 10 mg of oral zinc daily for 2 weeks, and children >6 months should receive 20 mg of oral zinc daily for 2 weeks.

PREVENTION

Improved personal hygiene, access to clean water, and sanitation are the mainstays of cholera control. Travelers from developed countries often have no prior exposure to cholera and are therefore at risk of developing the disease. Children traveling to cholera-affected areas should avoid drinking potentially contaminated water and eating high-risk

Table 247.1 Available Oral Cholera Vaccines*

VACCINE TRADE NAME	CONTENTS	DOSING SCHEDULE
Dukoral (Crucell)	1 mg of recombinant B subunit of cholera toxin plus 2.5×10^{10} colony-forming units of the following strains of *V. cholerae*: Formalin-killed El Tor Inaba (Phil 6973) Heat-killed classical Inaba (Cairo 48) Heat-killed classical Ogawa (Cairo 50) Formalin-killed classical Ogawa (Cairo 50)	Children 2-6 yr old: 3 doses, 1-6 wk apart Adults and children >6 yr old: 2 doses, 1-6 wk apart
Shanchol (Shantha Biotech) Euvichol (Eubiologics)	*V. cholerae* O1: 600 EU Formalin-killed El Tor Inaba (Phil 6973) 300 EU Heat-killed classical Inaba (Cairo 48) 300 EU Heat-killed classical Ogawa (Cairo 50) 300 EU Formalin-killed classical Ogawa (Cairo 50) *V. cholerae* O139-600 EU of formalin-killed strain 4260B	Adults and children ≥1 yr old: 2 doses, 2 wk apart

*WHO-prequalified vaccines.

foods such as raw or undercooked fish and shellfish. No country or territory requires vaccination against cholera as a condition for entry.

Alarmed by the increasing prevalence of cholera, in 2011 the World Health Assembly recommended the use of oral cholera vaccines to complement existing water, sanitation, and hygiene initiatives for cholera control. In 2016, a live oral cholera vaccine, CVD 103-Hg-R (Vaxchora, PaxVax), was licensed in the United States for use in adults age 18-64 years traveling to cholera-affected areas.

Older-generation parenteral cholera vaccines have not been recommended by the WHO because of the limited protection they confer and their high reactogenicity. Oral cholera vaccines are safe, are protective for approximately 2-5 years and confer moderate herd protection. Three oral cholera vaccines are currently available internationally and recognized by the WHO (Table 247.1). An internationally licensed killed whole cell oral cholera vaccine with recombinant B subunit (Dukoral, Crucell) has been available in >60 countries, including the European Union, and provides protection against cholera in endemic areas as well as cross-protection against certain strains of enterotoxigenic *E. coli*. The two other vaccines (Shanchol, Shantha Biotech; and Euvichol, Eubiologics) are variants of the first vaccine and contain the *V. cholerae* O1 and O139 antigens but do not contain the B subunit. Without the B subunit, these vaccines do not require buffer for administration, thereby reducing administration costs and resources, making them easier to deploy.

Several countries are now using oral cholera vaccines in mass vaccination campaigns where cholera remains a substantial problem. A cholera vaccine stockpile, established by the WHO, is now available and can be accessed by countries at risk for cholera, supplementing efforts to lessen the impact of this ongoing cholera scourge.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 248

Campylobacter

Ericka V. Hayes

Campylobacter, typically *Campylobacter jejuni* and *Campylobacter coli,* are found globally and are among the most common causes of human intestinal infections. Clinical presentation varies by age and underlying conditions.

ETIOLOGY

More than 20 species of *Campylobacter* are recognized. Most of these have been isolated from humans, and many are considered pathogenic. The most significant of these are *C. jejuni* and *C. coli,* which are believed to cause the majority of human enteritis. More than 100 serotypes of *C. jejuni* have been identified. *C. jejuni* has been subspeciated into *C. jejuni* subsp. *jejuni* and *C. jejuni* subsp. *doylei.* Although *C. jejuni* subsp. *doylei* has been isolated from humans, it is much less common, less hardy, and more difficult to isolate. Other species, including *Campylobacter fetus, Campylobacter lari,* and *Campylobacter upsaliensis,* have been isolated from patients with diarrhea, although much less frequently (Table 248.1). Emerging *Campylobacter* spp. have been implicated in acute gastroenteritis, inflammatory bowel disease, and peritonitis, including *C. concisus* and *C. ureolyticus*. Additional *Campylobacter* spp. have been isolated from clinical specimens, but their roles as pathogens have not been established.

Campylobacter organisms are gram-negative, curved, thin (0.2-0.8 μm wide), non–spore-forming rods (0.5-5 μm long) that usually have tapered ends. They are smaller than most other enteric bacterial pathogens and have variable morphology, including short, comma-shaped or S-shaped organisms and long, multispiraled, filamentous, seagull-shaped organisms. Individual organisms are usually motile with a flagellum at one or both poles depending on the species. Such morphology enables these bacteria to colonize the mucosal surfaces of both the gastrointestinal (GI) and respiratory tracts and move through them in a spiraling motion. Most *Campylobacter* organisms are microaerophilic, occasionally partially anaerobic, and oxidase positive. Most can transform into coccoid forms under adverse conditions, especially oxidation.

EPIDEMIOLOGY

Worldwide, *Campylobacter* enteritis is a leading cause of acute diarrhea. Efforts to reduce *Campylobacter* contamination and use of safe handling practices have led to decreased incidence. *Campylobacter* infections can be both food-borne and water-borne and most frequently result from ingestion of contaminated **poultry** (chicken, turkey) or **raw milk**. Less often, the bacteria come from drinking water, household pets (cats, dogs, hamsters), and farm animals. Infections are more common in resource-limited settings, are prevalent year-round in tropical areas, and can exhibit seasonal peaks in temperate regions (late spring with a peak midsummer in most of the United States, with a smaller secondary peak in late fall). In industrialized countries, *Campylobacter* infections peak in early childhood and again in young adulthood (15-44 years). This second peak is not seen with *Salmonella* and *Shigella* infections. In resource-limited countries, repeated infections are common in childhood, leading to increased immunity and rare disease in adulthood. Each year in the United States, there are an estimated 1.5 million cases of *Campylobacter* infection; in 2022 the incidence of infections with *Campylobacter* was 19.2 infections per 100,000 population. Of these, death is rare, with 50-150 reports annually. In The Netherlands, medical record review shows that, on average, each resident acquires asymptomatic *Campylobacter* colonization every 2 years, progressing to symptomatic infection in approximately 1% of colonized people.

Table 248.1 *Campylobacter* Species Associated with Human Disease

SPECIES	DISEASES IN HUMANS	COMMON SOURCES
C. jejuni	Gastroenteritis, bacteremia, Guillain-Barré syndrome	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water
C. coli	Gastroenteritis, bacteremia	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, oysters, water
C. fetus	Bacteremia, meningitis, endocarditis, mycotic aneurysm, diarrhea	Sheep, cattle, birds, dogs
C. hyointestinalis	Diarrhea, bacteremia, proctitis	Swine, cattle, deer, hamsters, raw milk, oysters
C. lari	Diarrhea, colitis, appendicitis, bacteremia, UTI	Seagulls, water, poultry, cattle, dogs, cats, monkeys, oysters, mussels
C. upsaliensis	Diarrhea, bacteremia, abscesses, enteritis, colitis, hemolytic-uremic syndrome	Cats, dogs, other domestic pets
C. concisus	Diarrhea, gastritis, enteritis, periodontitis	Human oral cavity, dogs
C. sputorum	Diarrhea, bedsores, abscesses, periodontitis	Human oral cavity, cattle, swine, dogs
C. rectus	Periodontitis	
C. mucosalis	Enteritis	Swine, dogs
C. jejuni subsp. doylei	Diarrhea, colitis, appendicitis, bacteremia, UTI	Swine
C. curvus	Gingivitis, alveolar abscess	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water, human oral cavity
C. gracilis	Head and neck abscesses, abdominal abscesses, empyema	Dogs
C. cryaerophila	Diarrhea	Swine

Food-borne infection is most common and can be seen with the consumption of raw or undercooked meat and by cross-contamination of other foods. Although **chickens** are the classic source of *Campylobacter,* many animal sources of human food can also harbor *Campylobacter,* including seafood. *C. coli* has been linked to swine. Poultry is more likely to be heavily contaminated, whereas red meats often have fewer organisms. Unpasteurized milk products are also a documented source. Additionally, many pets can carry *Campylobacter,* and flies inhabiting contaminated environments can acquire the organism. Shedding from animals can contaminate water sources. Humans can acquire infection from water, although much less frequently than from contaminated food. **Airborne** (droplet) **transmission** of *Campylobacter* has occurred in poultry workers. Use of antimicrobials in animal foods may increase the prevalence of antibiotic-resistant *Campylobacter* isolated from humans.

Human infection can result from exposure to as few as 500 bacteria, although a higher dose (>9,000 bacteria) is often needed to cause illness reproducibly. Inoculum effectiveness is dependent on host factors, including immune status and stomach acidification. *C. jejuni* and *C. coli* spread person to person, perinatally, and at childcare centers where diapered toddlers are present. People infected with *C. jejuni* usually shed the organism for weeks, but some can shed for months, with children tending toward longer shedding. **Handwashing** is critical to preventing spread in these environments.

PATHOGENESIS

Most *Campylobacter* isolates are acid sensitive and should, in theory, be eradicated in the stomach. Therefore models for the pathogenesis of *C. jejuni* enteritis include mechanisms to transit the stomach, adhere to intestinal mucosal cells, and initiate intestinal lumen fluid accumulation. Host conditions associated with reduced gastric acidity, such as proton pump inhibitor use, and foods capable of shielding organisms in transit through the stomach may help allow *Campylobacter* to reach the intestine. Once there, *Campylobacter* is able to adhere to and invade intestinal mucosal cells through motility, including use of flagellae, and by the use of surface proteins (e.g., PEB1, CadF), large plasmids (e.g., pVir), surface adhesins (e.g., JIpA), and chemotactic factors. Lumen fluid accumulation is associated with direct damage to mucosal cells resulting from bacterial invasion and potentially from an enterotoxin and other cytotoxins. Additionally, *C. jejuni* has mechanisms that enable transit away from the mucosal surface. The factors used depend on the species involved.

Campylobacter spp. differ from other enteric bacterial pathogens in that they have both *N*- and *O*-linked glycosylation capacities. *N*-linked glycosylation is associated with molecules expressed on the bacterial surface, and *O*-linked glycosylation appears limited to flagellae. Slipped-strand mispairing in glycosylation loci results in modified, antigenically distinct surface structures. It is hypothesized that antigenic variation provides a mechanism for immune evasion.

C. fetus possesses a high molecular weight S-layer protein that mediates high-level resistance to serum-mediated killing and phagocytosis and is therefore thought to be responsible for the propensity to produce bacteremia. *C. jejuni* and *C. coli* are generally sensitive to serum-mediated killing, but serum-resistant variants exist. Some suggest these serum-resistant variants may be more capable of systemic dissemination.

Campylobacter infections can be followed by **Guillain-Barré syndrome** (GBS), **reactive arthritis**, and **erythema nodosum**. Such complications are thought to be from molecular mimicry between nerve, joint, and dermal tissue and *Campylobacter* surface antigens. Most *Campylobacter* infections are not followed by immunoreactive complications, indicating that host conditions along with other factors, in addition to molecular mimicry, are required for these complications. It is proposed that low-grade inflammation caused by *Campylobacter,* below the threshold that can be detected by endoscopy, results in cross-talk with gut nerves, leading to symptoms.

CLINICAL MANIFESTATIONS

There are a variety of clinical presentations of *Campylobacter* infections, depending on host factors such as age, immune competence, and underlying conditions. Infection presents most often as gastroenteritis, but also as bacteremia, neonatal infections, and, less often, extraintestinal infections.

Acute Gastroenteritis

Acute gastroenteritis with diarrhea is usually caused by *C. jejuni* (90–95%) or *C. coli* and, rarely, by *C. lari, C. hyointestinalis,* or *C. upsaliensis.* Infections with *C. jejuni* and *C. coli* are indistinguishable by clinical presentation. The average incubation period is 3 days (range: 1-7 days). One third of symptomatic patients can have a prodrome with fever, headache, dizziness, and myalgias; 1-3 days later, they develop cramping abdominal pain and loose, watery stools or, less frequently, mucus-containing bloody stools. In severe cases (approximately 15%), blood appears in the stools 2-4 days after the onset of symptoms. In younger children, >50% may develop blood in their stools. Some patients do not develop diarrhea at all, most often children who are 6-15 years old. Fever may be the only manifestation initially and is most pronounced in patients >1 year old. A reported 60–90% of older children also complain of abdominal pain. The abdominal pain is most frequently periumbilical and sometimes persists after the stools return to normal. The abdominal pain can mimic appendicitis, colitis, or intussusception. Nausea is common, with up to 25% of adults developing vomiting. Vomiting tends to be more common the younger the patient and is most frequent in infants. Infection with species other than *C. jejuni* and *C. coli* may have milder symptoms.

Diarrhea lasts approximately 7 days and will resolve spontaneously. More mild disease can last 1-2 days; 20–30% of patients will have symptoms for 2 weeks, and 5–10% are symptomatic for >2 weeks. Relapse can occur in 5–10% of patients. Persistent or recurrent *Campylobacter* gastroenteritis has been reported in immunocompetent patients, in patients with hypogammaglobulinemia (both congenital and acquired), and in patients with AIDS. Persistent infection can mimic chronic **inflammatory bowel disease** (IBD); therefore *Campylobacter* infection should also be considered when evaluating for IBD. Some evidence supports that *Campylobacter* infection may also be the trigger for development of IBD. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 weeks, with a range from a few days to several months. Shedding tends to occur longer in young children. Acute appendicitis, mesenteric lymphadenitis, and ileocolitis have been reported in patients who have had appendectomy during *C. jejuni* infection.

Bacteremia

Transient bacteremia has been shown in early acute infection in 0.1–1% of patients. With the exception of bacteremia caused by *C. fetus,* bacteremia with *Campylobacter* occurs most often among patients with chronic illnesses or immunodeficiency (e.g., HIV), severe malnutrition, and in extremes of age. However, bacteremia is also well described in patients without underlying disease. The majority of cases of bacteremia are asymptomatic. *C. fetus* causes bacteremia in adults with or without identifiable focal infection, usually in the setting of underlying conditions such as malignancy, immunodeficiency, or diabetes mellitus. When symptomatic, *C. jejuni* bacteremia is associated with fever, headache, malaise, and abdominal pain. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion can occur, but focal neurologic signs are unusual without cerebrovascular disease or meningitis. Moderate leukocytosis with left shift may be found. Variable presentations have been described, including transient asymptomatic bacteremia, rapidly fatal septicemia, and prolonged bacteremia of 8-13 weeks.

Focal Extraintestinal Infections

Focal infections caused by *C. jejuni* are rare and occur mainly among neonates and immunocompromised patients. Multiple sites have been reported, including meningitis, pneumonia, thrombophlebitis, pancreatitis, cholecystitis, ileocecitis, urinary tract infection, arthritis, peritonitis, pericarditis, and endocarditis. *C. fetus* shows a predilection for vascular endothelium, leading to endocarditis, pericarditis, thrombophlebitis, and mycotic aneurysms. *C. hyointestinalis* has been associated with proctitis, *C. upsaliensis* with breast abscesses, and *C. rectus* with periodontitis.

Perinatal Infections

Perinatal infections are most often acquired at birth from a mother infected with or shedding *Campylobacter.* Maternal *C. fetus* and *C. jejuni* infections may be asymptomatic and can result in abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Severe perinatal infections are uncommon and are caused most often by *C. fetus* and, rarely, by *C. jejuni*. Neonatal infection with *C. jejuni* is associated with diarrhea that may be bloody. Nosocomial infections in nurseries have also been described.

DIAGNOSIS

The clinical presentation of *Campylobacter* enteritis can be similar to that of enteritis caused by other bacterial pathogens. The differential diagnosis includes *Shigella, Salmonella, Escherichia coli, Yersinia enterocolitica, Aeromonas, Vibrio parahaemolyticus,* and amebiasis. Fecal leukocytes are found in as many as 75% of cases, and fecal blood is present in 50% of cases (higher in pediatric patients). *Campylobacter* should be considered in patients with bloody stools, fever, and abdominal pain.

The diagnosis of *Campylobacter* enteritis is usually confirmed by identification of the organism in cultures of stool or rectal swabs. Isolation is most likely from selective media such as CAMPY-agar grown in microaerophilic conditions (5–10% oxygen), 1–10% carbon dioxide, with some hydrogen. Some *C. jejuni* grow best at 42°C (107.6°F). Growth on solid media results in small (0.5-1.0 mm), slightly raised, smooth colonies. Organisms can be identified from stool microscopically in approximately 50% of known *Campylobacter* cases. Gram stain is even less sensitive. Stool culture is >90% sensitive and is the standard method of diagnosis. Visible growth on stool culture is most often present in 1-2 days. Visible growth in blood cultures is often not apparent until 5-14 days after inoculation.

Routine culture may be adequate for isolation of *C. jejuni* because of the large numbers of bacteria that are often present. However, because *Campylobacter* organisms grow more slowly under routine conditions than do other enteric bacteria, routine culture can result in failure because of overgrowth of other enteric bacteria. *Campylobacter* culture can be enhanced, when necessary, with selective media. However, selective culture media developed to enhance isolation of *C. jejuni* may inhibit the growth of other *Campylobacter* spp. Filtration methods are available and can preferentially enrich for *Campylobacter* by selecting for their small size. These methods allow subsequent culture of the enriched sample on antibiotic-free media, enhancing rates of isolation of *Campylobacter* organisms inhibited by the antibiotics included in standard selective media. Isolation of *Campylobacter* from normally sterile sites does not require enhancement procedures. Clinically, it is not necessary to speciate *Campylobacter* because the disease is the same. Speciation can be done, when needed, and specialized laboratories can perform strain typing when required for epidemiologic purposes.

For rapid diagnosis of *Campylobacter* enteritis, direct carbolfuchsin stain of fecal smear, indirect fluorescence antibody test, dark-field microscopy, or latex agglutination were used historically. Polymerase chain reaction testing is more specific and sensitive and has become more widely available for rapid testing, often grouped with testing for other bacterial, viral, and parasitic stool pathogens in a multiplex assay. At this time, the recommendation remains to confirm all positive rapid tests with culture, which also allows for susceptibility testing and epidemiologic investigations. Antigen tests are also available, although false-positive results have been reported. Serologic diagnosis is also possible and is most helpful in patients with late-onset reactive arthritis or GBS, because these patients may have negative stool cultures by the time of presentation with these late complications.

COMPLICATIONS

Severe, prolonged *C. jejuni* infection can occur in patients with immunodeficiencies, including hypogammaglobulinemia, malnutrition, and AIDS. In patients with AIDS, increased frequency and severity of *C. jejuni* infection occurs; severity correlates inversely with CD4 count. Complications can include acute complications, as described earlier, and late-onset complications that may present after the acute infection has resolved. The most common late-onset complications include reactive arthritis and GBS.

Reactive Arthritis

Reactive arthritis can accompany *Campylobacter* enteritis in adolescents and adults, especially in patients who are positive for HLA-B27 (see Chapter 198). Reactive arthritis occurs in up to 3% of patients, although up to 13% may have joint symptoms. This manifestation usually appears 1-2 weeks after the onset of diarrhea (range 5-40 days). It involves mainly large joints and resolves without sequelae. The arthritis is typically migratory and occurs without fever. Synovial fluid lacks bacteria. The arthritis responds well to nonsteroidal antiinflammatory drugs and typically resolves after 1 week, though cases are reported with symptoms lasting for several months. Reactive arthritis with conjunctivitis, urethritis, and rash (including erythema nodosum) also occurs but is less common.

Guillain-Barré Syndrome

GBS is an acute demyelinating disease of the peripheral nervous system characterized clinically by acute flaccid paralysis and is the most common cause of neuromuscular paralysis worldwide (see Chapter 656). GBS carries a mortality rate of approximately 2%, and approximately 20% of patients develop major neurologic sequelae. *C. jejuni* has been identified as the trigger in up to 40% of patients with GBS and is most closely linked to the serotypes Penner O19 and O41. It has been reported 1-12 weeks after *C. jejuni* gastroenteritis in 1 of every 1,000 *C. jejuni* infections. Stool cultures obtained from patients with GBS at the onset of neurologic symptoms have yielded *C. jejuni* in >25% of the cases. Serologic studies suggest that 20–45% of patients with GBS have evidence of recent *C. jejuni* infection. Molecular mimicry between nerve tissue GM_1 ganglioside and *Campylobacter* surface antigens may be the triggering factor in *Campylobacter*-associated GBS. The Miller Fisher variant, which more often affects cranial nerves, is characterized by ataxia, areflexia, and ophthalmoplegia and is linked to cross-reacting antibodies to the GQ1b ganglioside found in cranial nerve myelin; the most common serotype for this variant is Penner O2. When associated with *Campylobacter,* GBS is more likely to be the axonal form and has a worse prognosis with slower recovery and more neurologic disability. The management of GBS includes supportive care, intravenous immunoglobulin, and plasma exchange.

Other Complications

Immunoglobulin A nephropathy and immune complex glomerulonephritis with *C. jejuni* antigens in the kidneys have been reported. *Campylobacter* infection has also been associated with hemolytic anemia and hemolytic-uremic syndrome.

Treatment

Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays of treatment of children with *Campylobacter* gastroenteritis. Antimotility agents are contraindicated because they can cause prolonged or fatal disease. The need for antibiotic therapy in healthy patients with uncomplicated gastroenteritis is controversial. Most healthy children do not require antibiotic therapy. Data suggest a shortened duration of symptoms (by an average of 1.3 days) and intestinal shedding of organisms if antibiotics are initiated early in the disease. Antibiotics are recommended for patients with bloody stools, high fever, or a severe course and for children who are immunosuppressed or have underlying diseases and individuals at high risk of developing severe disease (e.g., pregnancy). Extraintestinal infections (e.g., bacteremia) should also be treated with antibiotics.

Most *Campylobacter* isolates are susceptible to macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and clindamycin (though there is no clinical efficacy data for these last three agents, only in vitro data) and are resistant to cephalosporins, penicillins, and trimethoprim. Resistance to tetracyclines, macrolides, and more often, fluoroquinolones has been increasingly reported. **Antibiotic resistance** among *C. jejuni* has become a serious worldwide problem. Macrolide resistance is increased in areas such as Thailand and Ireland, whereas fluoroquinolone resistance has been reported in Spain, Hungary, and multiple low and middle income countries in >50% of cultured *Campylobacter*. Fluoroquinolone resistance continues to increase in the United States and is related to the use of quinolones in veterinary medicine and food products along with acquisition from travelers and antibiotic overuse. Erythromycin-resistant *Campylobacter* isolates are less common in the United States; therefore **azithromycin** is the drug of choice if therapy is required, particularly in pediatric patients. For treatment of gastroenteritis, the duration is 3-5 days. Drug sensitivities should be determined for patients who do not respond to therapy or any patient with invasive or extraintestinal infection. Sepsis is treated with parenteral antibiotics such as meropenem or imipenem, with or without an aminoglycoside. For extraintestinal infection caused by *C. fetus,* prolonged therapy is advised. *C. fetus* isolates resistant to erythromycin and fluoroquinolones have been reported; therefore empirical therapy for serious *C. fetus* infection should avoid these agents pending susceptibilities.

PROGNOSIS

Although *Campylobacter* gastroenteritis is usually self-limited, immunosuppressed children (including children with AIDS) can experience a protracted or severe course. Septicemia in newborns and immunocompromised hosts has a poor prognosis, with an estimated mortality rate of 30–40%. Additional prognosis is based on the secondary sequelae that may develop.

PREVENTION

Most human *Campylobacter* infections are sporadic and are acquired from infected animals or contaminated foods or water. Interventions to minimize transmission include good hand hygiene; cooking meats thoroughly; preventing recontamination after cooking by not using the same surfaces, utensils, or containers for both uncooked and cooked food; and avoiding unpasteurized dairy products. Also, it is important to ensure that water sources are not contaminated and that water is kept in clean containers. Persons infected with *Campylobacter* should avoid recreational water for at least 1 week after resolution of symptoms or as guided by local public health authorities. Contact with infected animals should be avoided. No specific isolation is required; **standard precautions** are sufficient, although in a hospital or clinic setting with an incontinent child, **contact precautions** are indicated. Outbreaks can occur in childcare settings. Infants and children should be excluded from childcare centers until stools are able to be contained in the diaper or for continent children when they no longer have fecal accidents and stool frequency is no more than two stools above that child's baseline (stools may remain loose). Breastfeeding appears to decrease symptomatic *Campylobacter* disease but does not reduce colonization. All cases of *Campylopbacter* should be reported to local health departments, as it is a nationally notifiable condition.

Several approaches at immunization have been studied, including the use of live-attenuated organisms, subunit vaccines, and killed–whole cell vaccines. No vaccine is currently available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 249

Yersinia

Ericka V. Hayes

The genus *Yersinia* is a member of the order Enterobacterales, family Yersiniaceae and comprises more than 14 named species, 3 of which are established as human pathogens. *Yersinia enterocolitica* is by far the most common *Yersinia* species causing human disease and produces fever, abdominal pain that can mimic appendicitis, and diarrhea. *Y. pseudotuberculosis* is most often associated with mesenteric lymphadenitis. *Y. pestis* is the agent of **plague** and typically causes an acute febrile lymphadenitis (bubonic plague) and less often occurs as septicemic, pneumonic, pharyngeal, or meningeal plague. Other *Yersinia* species are uncommon causes of infections in humans, and their identification is often an indicator of immunodeficiency.

Yersinia is enzootic and can colonize pets. Infections in humans are incidental and most often result from contact with infected animals or their tissues; ingestion of contaminated water, milk, or meat; or for *Y. pestis,* the bite of infected fleas or inhalation of respiratory droplets (human, dog, cat). Association with human disease is less clear for *Y. frederiksenii, Y. intermedia, Y. kristensenii*, *Y. aldovae, Y. bercovieri, Y. mollaretii, Y. rohdei,* and *Y. ruckeri*. Some *Yersinia* isolates replicate at low temperatures (1–4°C [33.8–39.2°F]) or survive at high temperatures (50–60°C [122–140°F]). Thus common food preparation and storage and common pasteurization methods might not limit the number of bacteria. Most are sensitive to oxidizing agents.

249.1 *Yersinia enterocolitica*

Ericka V. Hayes

ETIOLOGY

Yersinia enterocolitica is a large, gram-negative coccobacillus that exhibits little or no bipolarity when stained with methylene blue and carbolfuchsin. It ferments glucose and sucrose but not lactose, is oxidase negative, and reduces nitrate to nitrite. These facultative anaerobes grow well on common culture media and are motile at 22°C (71.6°F) but not 37°C (98.6°F). Optimal growth temperature is 25–28°C (77–82.4°F); however, the organism can grow at refrigerator temperature. *Y. enterocolitica* includes pathogenic and nonpathogenic members. It has six different biotypes (1A, 1B, and 2-5). *Y. enterocolitica* relies on other bacteria for iron uptake, and conditions associated with **iron overload** increase the risk of infection.

EPIDEMIOLOGY

Y. enterocolitica is transmitted to humans through food, water, animal contact, and contaminated blood products. Transmission can occur from mother to newborn. *Y. enterocolitica* appears to have a global distribution but is seldom a cause of tropical diarrhea. In 2022, the Centers for Disease Control and Prevention (CDC) Foodborne Diseases Active Surveillance Network (FoodNet) reported an incidence of culture-confirmed *Y. enterocolitica* infection in the United States of 1.97 per 100,000 population (635% increase compared to 2015, and an increase of 216% since 2020). Infection may be more common in Northern Europe. Most infections occur among children <5 years old (incidence: 1.6-1.9 per 100,000 population), with the majority among children <1 year old. It is estimated that *Y. enterocolitica* accounts for 5% of illnesses secondary to major bacterial enteric pathogens in children <5 years old in the United States. Cases are more common in colder months and among males.

Natural reservoirs of *Y. enterocolitica* include pigs, rodents, rabbits, sheep, cattle, horses, dogs, and cats, with **pigs** being the major animal reservoir. Direct or indirect contact with animals, including pets, other domesticated animals, and wild animals, may be responsible for <1% of cases of enteric illnesses caused by *Y. enterocolitica*. Culture and molecular techniques have found the organism in a variety of foods and beverages, including vegetable juice, pasteurized milk, carrots, and water. Consumption of contaminated water or food, particularly undercooked pork, is the most common form of transmission to humans. A source of sporadic *Y. enterocolitica* infections is **chitterlings** (pig intestines, "chitlins"), a traditional dish in the southeastern United States and in Latin America, often in celebration of winter holidays. The infection is often seen in young infants in the household because of contamination of bottle and food preparation when chitterlings are prepared. In one study, 71% of human isolates were indistinguishable from the strains isolated from pigs. *Y. enterocolitica* is an occupational threat to butchers.

In part because of its capacity to multiply at refrigerator temperatures, *Y. enterocolitica* can be transmitted by intravenous injection of contaminated fluids, including blood products.

Patients with conditions leading to iron overload are at higher risk of developing *Yersinia* infections.

PATHOGENESIS

The *Yersinia* organisms most often enter by the gastrointestinal tract and cause mucosal ulcerations in the ileum. Necrotic lesions of Peyer patches and **mesenteric lymphadenitis** occur. If septicemia develops, suppurative lesions can be found in infected organs. Infection can trigger **reactive arthritis** and **erythema nodosum**, particularly in HLA-B27–positive individuals.

Virulence traits of pathogenic biotypes (1B and 2-5) are encoded by chromosomal genes and a highly conserved 70-kb virulence plasmid (pYV/pCD). The chromosomal genes control the production of heat-stable enterotoxins, and the plasmid allows penetration through the intestinal wall. Adherence, invasion, and toxin production are the essential mechanisms of pathogenesis. The bacteria mainly invade the intestinal epithelium in the Peyer patches of the ileum. After invasion, plasmid-encoded type III secretion of three antiphagocytic proteins protects *Yersinia* against the immunologic response of local macrophages. From Peyer patches, bacteria can disseminate to cause local or systemic disease. Motility appears to be required for *Y. enterocolitica* pathogenesis. Bioserotypes most associated with clinical illness in humans are 1B/O:8, 2/O:5,27, 2/O:9, 3/O:3, and 4/O:3, with bioserotype 4/O:3 being the most common type in the United States. *Yersinia* does not produce siderophores and uses analogous siderophores from other bacteria or host-chelated iron stores to thrive, placing patients with iron overload, as in hemochromatosis, thalassemia, and sickle cell disease, at higher risk for infection.

CLINICAL MANIFESTATIONS

Disease occurs most often as enterocolitis with diarrhea, fever, and abdominal pain. Acute enteritis is more common among younger children, and mesenteric lymphadenitis that can mimic appendicitis may be found in older children and adolescents. The incubation period is usually 4-6 days after exposure (range: 1-14 days). Stools may be watery and contain leukocytes and, less often, frank blood and mucus. Duration of diarrhea is often longer for *Y. enterocolitica* than for other causes of acute gastroenteritis, ranging from 12 to 22 days in several studies. Fever is common. Notably, prominent **pharyngitis** may be seen in 20% of patients at presentation, which may help distinguish it from other causes of gastroenteritis. *Y. enterocolitica* is excreted in stool for 1-4 weeks. Family contacts of a patient are often found to be asymptomatically colonized with *Y. enterocolitica. Y. enterocolitica* septicemia is less common and is most often found in very young children (<3 months old) and immunocompromised persons. Systemic infection can be associated with splenic and hepatic abscesses, osteomyelitis, septic arthritis, meningitis, endocarditis, and mycotic aneurysms. Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome occur infrequently.

Reactive complications include **erythema nodosum**, **reactive arthritis**, and rarely uveitis. These manifestations may be more

common in select populations (Northern Europeans), in association with HLA-B27, and in females.

DIAGNOSIS

Diagnosis is made typically through isolation of the organism, usually from the stool. *Y. enterocolitica* is easily cultured from normally sterile sites but requires special procedures for isolation from stool, where other bacteria can outgrow it. *Yersinia* should be cultured on selective agar (cefsulodin-irgasan-novobiocin [CIN]) at 25–28°C (77–82.4°F) to increase yield. If O:3 serogroup is suspected, MacConkey agar should be used at 25–28°C (77–82.4°F). Multiplex polymerase chain reaction (PCR) testing for *Y. enterocolitica* is also available, including on commercially available multiplex stool panels. Many laboratories do not routinely perform the tests required to detect *Y. enterocolitica;* procedures targeted to this organism must be specifically requested. A history indicating contact with environmental sources of *Yersinia* and detection of fecal leukocytes are helpful indicators of a need to test for *Y. enterocolitica.* The isolation of *Yersinia* from stool should be followed by tests to confirm that the isolate is a pathogen. Serodiagnosis is not readily available, and utility is limited by cross-reactivity.

Differential Diagnosis

The clinical presentation is similar to other forms of bacterial enterocolitis. The most common considerations include *Shigella, Salmonella, Campylobacter, Clostridioides difficile,* enteroinvasive *Escherichia coli, Y. pseudotuberculosis*, and occasionally *Vibrio*-related diarrheal disease. Amebiasis, appendicitis, Crohn disease, ulcerative colitis, diverticulitis, and pseudomembranous colitis should also be considered.

TREATMENT

Enterocolitis in an immunocompetent patient is a self-limited disease, and no benefit from antibiotic therapy is established. Patients with systemic infection and very young children (in whom septicemia is common) should be treated. *Y. enterocolitica* organisms are typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, third-generation cephalosporins, and quinolones, although strains resistant to quinolones have been reported. *Y. enterocolitica* produces β-lactamases, which are responsible for resistance to penicillins and first-generation cephalosporins. **TMP-SMX is the recommended empirical treatment for enterocolitis in children (generally a 5-day course) because it has activity against most strains and is well tolerated. In severe infections such as bacteremia, third-generation cephalosporins, with or without aminoglycosides, are effective, and usually a 3-week course of therapy is administered, with possible transition to oral therapy.** Patients on deferoxamine should discontinue iron chelation therapy during treatment for *Y. enterocolitica,* especially if they have complicated gastrointestinal (GI) infection or extraintestinal infection.

COMPLICATIONS

Reactive arthritis, erythema nodosum, erythema multiforme, hemolytic anemia, thrombocytopenia, and systemic dissemination of bacteria have been reported in association with *Y. enterocolitica* infection. Septicemia is more common in younger children, and reactive arthritis is more common in older patients. Arthritis appears to be mediated by immune complexes, which form as a result of antigenic mimicry, and viable organisms are not present in involved joints.

PREVENTION

Prevention centers on reducing contact with environmental sources of *Yersinia.* Families should be warned of the high risk of chitterling preparation, especially with young infants and children in the household. The CDC has developed guidance for the public regarding safe practices for chitterling preparation found here: https://www.cdc.gov/yersinia/chitlins.html. Breaking the chain of transmission from animal reservoirs to humans holds the greatest potential to reduce infections, and the techniques applied must be tailored to the reservoirs in each geographic area. There is no licensed vaccine.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

249.2 *Yersinia pseudotuberculosis*

Ericka V. Hayes

Yersinia pseudotuberculosis has a worldwide distribution; *Y. pseudotuberculosis* disease is less common than *Y. enterocolitica* disease. The most common form of disease is a **mesenteric lymphadenitis** that produces an appendicitis-like syndrome. *Y. pseudotuberculosis* is associated with a Kawasaki syndrome–like illness in approximately 8% of cases.

ETIOLOGY

Y. pseudotuberculosis is a small, gram-negative, aerobic, and facultative anaerobic coccobacillus. As with *Y. enterocolitica,* it ferments glucose and does not ferment lactose, is oxidase negative, catalase producing, urea splitting, and shares a number of morphologic and culture characteristics. It is differentiated biochemically from *Y. enterocolitica* on the basis of ornithine decarboxylase activity; fermentation of sucrose, sorbitol, and cellobiose; and other tests, although some overlap between species occurs. Antisera to somatic O antigens and sensitivity to *Yersinia* phages can also be used to differentiate the two species. Subspecies-specific DNA sequences that allow direct probe- and primer-specific differentiation of *Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica* have been described. *Y. pseudotuberculosis* is more closely related phylogenetically to *Y. pestis* than to *Y. enterocolitica.*

EPIDEMIOLOGY

Y. pseudotuberculosis is zoonotic, with reservoirs in wild rodents, rabbits, deer, farm animals, various birds, and domestic animals, including cats and canaries. Transmission to humans is by consumption of or contact with contaminated animals or contact with an environmental source contaminated by animals, often water. Direct evidence of transmission of *Y. pseudotuberculosis* to humans by consumption of lettuce and raw carrots has been reported. The organism has a worldwide distribution; however, infections are more commonly reported in Europe, in boys, and in the winter. During 1996–2014, FoodNet reported 224 cases of infections secondary to *Y. pseudotuberculosis* in the United States, with an annual average incidence of 0.03 per 100,000 persons. Compared with *Y. enterocolitica* infections, those caused by *Y. pseudotuberculosis* are more likely to be invasive and occur in adolescents and adults. Iron-overloading conditions, AIDS, other immunodeficiencies, and other debilitating diseases (including liver cirrhosis) may predispose to invasive *Y. pseudotuberculosis* infection.

PATHOGENESIS

Ileal and colonic mucosal ulceration and mesenteric lymphadenitis are hallmarks of the infection. Necrotizing epithelioid granulomas may be seen in the mesenteric lymph nodes, but the appendix is often grossly and microscopically normal. The mesenteric nodes are often the only source of isolation of the organism. *Y. pseudotuberculosis* antigens bind directly to human leukocyte antigen (HLA) class II molecules and can function as **superantigens**, which might account for the clinical illness resembling **Kawasaki syndrome**.

CLINICAL MANIFESTATIONS

Pseudoappendicitis and **mesenteric lymphadenitis** with **abdominal pain** (often right lower quadrant tenderness), fever, and leukocytosis constitute the most common clinical presentation. Enterocolitis and extraintestinal spread are uncommon. Iron overload, diabetes mellitus, and chronic liver disease are often found concomitantly with extraintestinal *Y. pseudotuberculosis* infection. Renal involvement with tubulointerstitial nephritis, azotemia, pyuria, and glucosuria can occur. *Y. pseudotuberculosis* can present as a Kawasaki syndrome–like illness with fever of 1-6 days' duration, strawberry tongue, pharyngeal erythema, scarlatiniform rash, cracked, red, and swollen lips, conjunctivitis, sterile pyuria, periungual desquamation, and thrombocytosis.

Some of these children have had coronary changes. Other uncommon manifestations include septic arthritis, massive lower GI bleeding, postaneurysmal prosthetic vascular infection, and acute encephalopathy.

DIAGNOSIS

PCR of involved tissue can be used to identify *Y. pseudotuberculosis;* isolation by culture can require an extended interval. Involved mesenteric lymph nodes removed at appendectomy can yield the organism by culture. Abdominal CT scan or ultrasound examination of children with unexplained fever and abdominal pain can reveal a characteristic picture of enlarged mesenteric lymph nodes and thickening of the terminal ileum with or without peritoneal findings, including appendiceal inflammation and periappendiceal fluid. *Y. pseudotuberculosis* is rarely recovered from stool. Serologic testing is available in specialized labs.

Differential Diagnosis

Appendicitis (most common), inflammatory bowel disease, and other intraabdominal infections should be considered. Kawasaki syndrome, staphylococcal or streptococcal disease, leptospirosis, Stevens-Johnson syndrome, and collagen vascular diseases, including acute-onset juvenile idiopathic arthritis, can mimic the syndrome with prolonged fever and rash. *C. difficile* colitis, meningitis, encephalitis, enteropathic arthropathies, acute pancreatitis, sarcoidosis, toxic shock syndrome, typhoid fever, and ulcerative colitis may also be considered.

TREATMENT

Uncomplicated mesenteric lymphadenitis caused by *Y. pseudotuberculosis* is a self-limited disease, and antimicrobial therapy is not required. Few data exist on optimal treatment and duration of therapy. Infections with *Y. pseudotuberculosis* can generally be managed the same as those caused by *Y. enterocolitica*. Culture-confirmed bacteremia should be treated with a third-generation cephalosporin with or without an aminoglycoside, TMP-SMX, fluoroquinolones, or chloramphenicol.

COMPLICATIONS

Erythema nodosum and reactive arthritis can follow infection. Coronary aneurysm formation has been described with disease presenting as Kawasaki syndrome–like illness. Rare local complications of GI disease include perforation, obstruction, and intussusception.

PREVENTION

Avoiding exposure to potentially infected animals and good food-handling practices can prevent infection. The sporadic nature of the disease makes application of targeted prevention measures difficult.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

249.3 Plague (*Yersinia pestis*)

Ericka V. Hayes

ETIOLOGY

Y. pestis is a gram-negative, facultative anaerobe that is a pleomorphic, nonmotile, non–spore-forming coccobacillus and a potential agent of bioterrorism. It evolved from *Y. pseudotuberculosis* through acquisition of chromosomal changes and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and fleas. *Y. pestis* shares bipolar staining appearance with *Y. pseudotuberculosis* and can be differentiated by biochemical reactions, serology, phage sensitivity, and molecular techniques. *Y. pestis* exists in four biovars: Antigua (Africa), Medievalis (Central Asia), Orientalis (widespread), and Microtus (Asia). Of note, Microtus, while highly virulent in mice, does not cause disease in humans.

EPIDEMIOLOGY

Plague is endemic in at least 24 countries, with Democratic Republic of the Congo, Madagascar, and Peru accounting for the highest numbers of cases. Approximately 3,000 cases are reported worldwide per year, with 100-200 deaths. Plague is uncommon in the United States (0-40 reported cases/yr); most of these cases occur west of a line from east Texas to east Montana, with 80% of cases in California, New Mexico, Arizona, and Colorado. In 2015, there was a cluster of 11 cases (with 3 deaths) in 4 months related to exposure at Yosemite National Park in California's Sierra Nevada Mountains. The epidemic form of disease killed approximately 25% of the population of Europe in the Middle Ages in a series of several epidemics and pandemics. The epidemiology of **epidemic** plague involves extension of infection from the zoonotic reservoirs to urban rats, *Rattus rattus* and *Rattus norvegicus,* and from fleas of urban rats to humans. Epidemics are no longer seen. Selective pressure exerted by plague pandemics in medieval Europe is hypothesized for enrichment of a pathogenic deletion variant in the gene encoding CCR5 (CCR5-Δ32). The enhanced frequency of this mutation in European populations endows approximately 10% of European descendants with relative resistance to acquiring HIV-1.

The most common mode of transmission of *Y. pestis* to humans is through **flea bites**. Historically, most human infections are thought to have resulted from bites of fleas that acquired infection from feeding on infected urban rats. Less frequently, infection is caused by contact with infectious body fluids or tissues or inhalation of respiratory secretions of infected animals. Currently, most cases of plague secondary to direct animal contact or inhalation of animal secretions are related to domestic **cats** or **dogs**. Direct transmission from human to human through droplet inhalation is possible but extremely rare. Laboratory transmission of *Y. pestis* has been described as well. Sylvatic plague can exist as a stable enzootic infection or as an epizootic disease with high host mortality. Ground squirrels, rock squirrels, prairie dogs, rats, mice, bobcats, cats, rabbits, and chipmunks may be infected. Transmission among animals is usually by flea bite or by ingestion of contaminated tissue. *Xenopsylla cheopis* is the flea usually associated with transmission to humans, but >30 species of fleas have been demonstrated as vector competent, and *Pulex irritans,* the human flea, can transmit plague and might have been an important vector in some historical epidemics. Both sexes are similarly affected by plague, and transmission is more common in colder regions and seasons, possibly because of temperature effects on *Y. pestis* infections in vector fleas.

PATHOGENESIS

In the most common form of plague, infected fleas regurgitate organisms into a patient's skin during feeding. The bacteria translocate via lymphatics to regional lymph nodes, where *Y. pestis* replicates, resulting in **bubonic plague**. In the absence of rapidly implemented specific therapy, **bacteremia** can occur, resulting in purulent, necrotic, and hemorrhagic lesions in many organs. Both plasmid and chromosomal genes are required for full virulence. Pneumonic plague can be secondary to bacteremia or primary when infected material is inhaled. The organism is highly transmissible from persons with pneumonic plague and from domestic cats with pneumonic infection. This high transmissibility and high morbidity and mortality have provided an impetus for attempts to use *Y. pestis* as a biologic weapon.

CLINICAL MANIFESTATIONS

Y. pestis infection can manifest as several clinical syndromes; infection can also be subclinical. The three principal clinical presentations of plague are bubonic plague, septicemic plague, and pneumonic plague. **Bubonic plague** is the most common form and accounts for 80–90% of cases in the United States. From 2 to 8 days after a flea bite, lymphadenitis develops in lymph nodes closest to the inoculation site, including the inguinal (most common), axillary, or cervical regions. These buboes are very tender. Fever, chills, weakness, prostration, headache, and the development of septicemia are common. The skin might show insect bites or scratch marks. Purpura and gangrene of the extremities can

develop as a result of disseminated intravascular coagulation (DIC). These lesions may be the origin of the name Black Death. Untreated plague results in death in >50% of symptomatic patients. Death can occur within 2-4 days after onset of symptoms.

Occasionally, *Y. pestis* establishes systemic infection and induces the systemic symptoms seen with bubonic plague without causing a bubo **(primary septicemic plague)**. Because of the delay in diagnosis linked to the lack of the bubo, septicemic plague carries an even higher case fatality rate than bubonic plague. In some regions, bubo-free septicemic plague accounts for 25% of cases.

Pneumonic plague is the least common but most dangerous and lethal form of the disease. Incubation for primary pneumonic plague is 1-6 days. Pneumonic plague can result from hematogenous dissemination or, rarely, as primary pneumonic plague after inhalation of the organism from a human or animal with plague pneumonia or potentially from a biologic attack. Signs of pneumonic plague include severe pneumonia with high fever, dyspnea, and hemoptysis.

Meningitis, tonsillitis, and gastroenteritis can occur. Meningitis tends to be a late complication after inadequate treatment. Tonsillitis and gastroenteritis can occur with or without apparent bubo formation or lymphadenopathy.

DIAGNOSIS

Plague should be suspected in patients with fever and history of exposure to small animals in endemic areas. Bubonic plague should be suspected in a patient with a painful swollen lymph node, fever, and prostration who has been potentially exposed to fleas or rodents in the western United States. A history of camping or the presence of flea bites increases the index of suspicion.

Y. pestis is readily transmitted to humans by some routine laboratory manipulations. **Thus it is imperative to clearly notify a laboratory when submitting a sample suspected of containing *Y. pestis*.** Laboratory diagnosis is based on bacteriologic culture or direct visualization using Gram, Giemsa, or Wayson stain of lymph node aspirates, blood, sputum, or exudates. *Y. pestis* grows slowly under routine culture conditions and best at temperatures that differ from those used for routine cultures in many clinical laboratories. Colonies are described as having a classic "fried egg appearance" and grow on sheep blood and chocolate agars, typically growing after 48-72 hours of incubation. Note some automated biochemical bacteria identification systems may misidentify *Y. pestis*. Suspected isolates of *Y. pestis* should be forwarded to a reference laboratory for confirmation. Special containment shipping precautions are required. A rapid antigen test detecting *Y. pestis* F1 antigen in sputum and serum samples exists. PCR testing and immunohistochemical staining for rapid identification are available in some reference and public health laboratories. Cases of plague should be reported to local and state health departments and the CDC. Serologic testing is also available. A single positive serologic test confirms the diagnosis, but in early illness seroconversion may not yet have occurred; negative tests should be interpreted with caution, particularly if there is high clinical suspicion for the diagnosis, and patients should continue to be treated.

Differential Diagnosis

The Gram stain of *Y. pestis* may be confused with *Enterobacter agglomerans*. Mild and subacute forms of bubonic plague may be confused with other disorders causing localized lymphadenitis and lymphadenopathy, including bacterial lymphadenitis, tularemia, and *Bartonella henselae* (cat scratch) lymphadenitis. Septicemic plague may be indistinguishable from other forms of overwhelming bacterial sepsis.

Pulmonary manifestations of plague are similar to those of anthrax, Q fever, and tularemia, all agents with **bioterrorism** and **biologic warfare** potential. Thus the presentation of a suspected case, and especially any cluster of cases, requires immediate reporting. Additional information on this aspect of plague and procedures can be found at https://emergency.cdc.gov/agent/plague/index.asp.

TREATMENT

Patients with suspected plague should be placed on **droplet isolation** until pneumonia is ruled out, sputum cultures are negative, and antibiotic treatment has been administered for 48 hours. The treatment of choice for bubonic plague historically has been **streptomycin** (30 mg/kg/day, maximum 2 g/day, divided every 12 hours intramuscularly [IM] for 10 days). Intramuscular streptomycin is inappropriate for septicemia because absorption may be erratic when perfusion is poor. The poor central nervous system penetration of streptomycin also makes this an inappropriate drug for meningitis. Furthermore, streptomycin might not be widely and immediately available**. Gentamicin (children, 7.5 mg/kg IM or intravenously [IV] every 24 hours; adults, 5 mg/kg IM or IV every 24 hours) has been shown to be as efficacious as streptomycin; in patients with abscesses, an additional agent may be needed in addition to an aminoglycoside because of poor abscess penetration (typically a fluoroquinolone). Dual therapy is recommended for moderate to severe septicemic or pneumonic plague as well as bubonic plague with large buboes or any suspected case of bioterrorism-related plague. Ciprofloxacin** 10 mg/kg every 8 or 12 hr IV or 15 mg/kg every 8 or 12 hr PO (maximum 400 mg/dose IV, 500 mg/dose every 8 hr PO or 750 mg/dose every 12 hr PO) and **levofloxacin** are also effective. Meningitis is usually treated with chloramphenicol or a fluoroquinolone. Resistance to these agents and relapses are rare. *Y. pestis* is susceptible in vitro to **fluoroquinolones**, which are effective in treating experimental plague in animals. *Y. pestis* is susceptible in vitro to penicillin, but penicillin is ineffective in treatment of human disease. Mild bubonic disease may be treated with oral chloramphenicol or doxycycline in children >8 years old. Clinical improvement is usually noted within 48 hours of initiating treatment. Recommended duration of therapy is 10-14 days, with a switch to oral therapy 2 days after defervescence and clinical improvement. Drainage of suppurative buboes may be needed; material is infectious, and appropriate precautions should be taken intraoperatively.

Postexposure prophylaxis should be given to close contacts of patients with pneumonic plague. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with a patient with pneumonic plague or those exposed to an accidental or bioterrorist aerosol. Recommended regimens for postexposure prophylaxis for children regardless of age include doxycycline, ciprofloxacin, or levofloxacin for a 7-day course at the treatment doses. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis. *Y. pestis* is a potential agent of bioterrorism that can require mass casualty prophylaxis.

PREVENTION

Avoidance of exposure to infected animals and fleas is the best method of prevention of infection. In the United States, special care is required in environments inhabited by rodent reservoirs of *Y. pestis* and their ectoparasites. Patients with plague should be isolated if they have pulmonary symptoms, and infected materials should be handled with extreme care. There is currently no available licensed vaccine for *Y. pestis* in the United States. Several vaccine development trials are underway, and recombinant subunit vaccines based on rF1 and rV antigens seem to be the most promising. Using baits containing live vaccines for oral immunization of wild animals may be a helpful alternative for control of epidemics.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 250

Aeromonas and *Plesiomonas*

Ameneh Khatami and Adam J. Ratner

Aeromonas and *Plesiomonas* are gram-negative bacilli that include species capable of causing enteritis and, less frequently, skin and soft tissue infections and invasive disease. They are common in freshwater and brackish water and colonize animals and plants in these environments.

250.1 *Aeromonas*

Ameneh Khatami and Adam J. Ratner

ETIOLOGY

Aeromonas is a member of the Aeromonadaceae family and includes two major groups of isolates: the nonmotile *psychrophilic* organisms that infect cold-blooded animals, most often fish, and the motile *mesophilic* organisms that infect humans and other warm-blooded animals. *Aeromonas* species are oxidase- and catalase-positive, facultatively anaerobic, gram-negative bacilli that ferment glucose. *Aeromonas* is a diverse genus with difficult taxonomy and species differentiation because of high nucleotide variability and has undergone multiple reclassifications of species and taxa in recent years. Sixteen species are recognized as clinically significant human pathogens, with *Aeromonas hydrophila, Aeromonas veronii* biotype sobria, and *Aeromonas caviae* most frequently associated with human infection. *Aeromonas dhakensis,* which was first isolated from children with diarrhea in Dhaka, Bangladesh, and was initially classified as a subspecies of *A. hydrophila,* has been recognized as a distinct species and an important cause of human infection.

EPIDEMIOLOGY

Aeromonas organisms are found in fresh and brackish aquatic environments, including rivers and streams, well water, both treated and bottled drinking water, and sewage. These organisms are most often detected in aquatic environments during warm-weather months, when they reach greater population densities. Rates of human infection may also exhibit seasonality depending on local conditions. For example, *Aeromonas* is isolated with increased frequency from May to October in the Northern Hemisphere. Some species resist chlorination of water and exhibit tolerance to high salt concentrations. *Aeromonas* has been isolated from meats, milk, seafood, seaweed, and vegetables consumed by humans. Asymptomatic colonization occurs in humans and is more common in inhabitants of tropical regions. Most human infections with *Aeromonas* are associated with exposure to contaminated water but may also be contracted via other routes, including ingestion of contaminated food. A systematic review of cases of traveler's diarrhea worldwide implicated *Aeromonas* in 0.8–3.3% of infections, with highest frequencies in travelers to Southeast Asia and Africa. A study in Bangladesh of >56,000 stool samples from patients with diarrhea found that approximately 25% had a bacterial etiology detected, 13% of which were *Aeromonas*. *Aeromonas* infections have also been acquired at various sites of natural disasters. For example, after the 2004 Thailand tsunami, *Aeromonas* was the leading cause of skin and soft tissue infection among survivors.

PATHOGENESIS

Clinical and epidemiologic data seem to support that *Aeromonas* organisms are **enteric** pathogens, although this point is not universally accepted. Reasons for uncertainty include a lack of outbreaks with clonally distinct isolates, infrequent person-to-person transmission, absence of a robust animal model, and overlapping prevalence in symptomatic and asymptomatic individuals. In addition, there are conflicting data when comparing the human challenge model with characteristics of suspected outbreaks of *Aeromonas* enteritis, further complicating interpretation.

Aeromonas isolates possess a variety of potential virulence factors, including constitutive *polar* and inducible *lateral* flagella, fimbriae, outer membrane proteins, endotoxin (lipopolysaccharide), and capsule. The mechanistic role of many of these factors in human pathogenicity remains unclear. Polar flagella provide motility in liquid media, and lateral flagella may act as adhesins. There are numerous hemolysins, proteases, and heat-labile and heat-stable enterotoxins. *Aeromonas* cytotoxic enterotoxin **(Act/aerolysin)** is secreted by a type II secretion system and is able to lyse erythrocytes, inhibit phagocytosis, and induce cytotoxicity in eukaryotic cells. *Aeromonas* also has a type III secretion system with an effector protein that causes actin reorganization and eventual apoptosis in vitro. A type VI secretion system has been described and functions analogously to a phage tail, with antimicrobial activity.

Aeromonas sobria is the most enterotoxic among clinical isolates, and cytotoxic activity with cytopathic and intracellular effects is found in 89% of isolates. A few strains produce Shiga toxin. Some clinically important species have also been shown to harbor a cholera-like toxin (**Asao toxin**). *Aeromonas* has serine proteases that can cause a cascade of inflammatory mediators, leading to vascular leakage, and in vitro studies show induction of apoptosis in murine macrophages by human isolates of *Aeromonas*. There are limited data on *quorum-sensing* molecules, which coordinate gene expression according to local density and may be involved in biofilm production or population control.

CLINICAL MANIFESTATIONS

Aeromonas may colonize humans asymptomatically or cause illness, including enteritis, focal invasive infections, and septicemia. Although apparently immunologically normal individuals may present with any of these manifestations, invasive disease is more common among immunocompromised persons.

Enteritis

The most common clinical manifestation of infection with *Aeromonas* is enteritis, which occurs primarily among children <3 years old. *Aeromonas* is the third or fourth most common cause of childhood **bacterial diarrhea** and has been isolated from 2% to 10% of patients with diarrhea and 1–5% of asymptomatic controls. One study demonstrated isolation from hospitalized neonates with diarrhea at rates of 0–19% depending on the season. Isolation from human feces also varies geographically based on food habits, level of sanitation, population demographics, aquaculture and farming practices, and laboratory isolation methods used. *Aeromonas* diarrhea is often watery and self-limited, although a dysentery-like syndrome with blood and mucus in the stool has also been described. Fever, abdominal pain, and vomiting are common in children. Choleric diarrhea with "rice-water" stools can also occur. Enteritis caused by *A. hydrophila* and *A. sobria* tends to be acute and self-limited, whereas 30% of patients with *A. caviae* enteritis have chronic or intermittent diarrhea that may last 4-6 weeks. *A. sobria* and *A. caviae* are most frequently associated with **traveler's diarrhea**. Complications of *Aeromonas* enteritis include intussusception, failure to thrive, hemolytic-uremic syndrome, bacteremia, and postinfectious chronic colitis. *Aeromonas* infection may also present as acute segmental colitis, mimicking inflammatory bowel disease or ischemic colitis.

Skin and Soft Tissue Infections

Skin and soft tissue infections are the second most common presentation of *Aeromonas,* most commonly associated with *A. hydrophila, A. veronii,* and *A. schubertii*. Predisposing factors include local trauma and exposure to contaminated fresh water. *Aeromonas* soft tissue infections have been reported after bites from a number of animal species, including alligators, tigers, bears, and snakes, and from tick

bites. These infections have also been reported after sports injuries and medicinal leech therapy. Antibiotic prophylaxis is generally used in conjunction with leech therapy because of the presence of *A. hydrophila* in the gastrointestinal (GI) tract of leeches, where they aid in the breakdown of ingested red blood cells. However, emerging reports of ciprofloxacin-resistant strains of *Aeromonas* isolated from leeches may affect this practice. The spectrum of skin and soft tissue infections is broad, ranging from a localized skin nodule to life-threatening necrotizing fasciitis, myonecrosis, and gas gangrene. Soft tissue infections are most frequently found on the extremities, are often polymicrobial, and are 3 times more likely in men than in women. *Aeromonas* **cellulitis**, the most common skin manifestation, clinically presents similar to other forms of bacterial cellulitis but should be suspected in wounds after contact with a water source, especially during the summer.

Septicemia

Aeromonas septicemia, strongly associated with *A. veronii* biovar sobria and *A. dhakensis* infection, is the third most common presentation of infection and is associated with a mortality rate of 27–73%. Higher incidence occurs during summer months or during the wet season in the tropics. Patients present with the classic signs and symptoms of gram-negative sepsis and may have GI symptoms, including abdominal pain, nausea, vomiting, and diarrhea. From 2% to 4% of patients may present with ecthyma gangrenosum–like lesions. *Aeromonas* may be the only organism isolated or may be part of a polymicrobial bacteremic illness. Most cases (approximately 80%) occur in immunocompromised adults or those with hepatobiliary disease and in young children in whom the source of infection is probably *Aeromonas* in the GI tract. Less frequently, bacteremia can be secondary to trauma-related myonecrosis or infected burns. In such patients, mortality is often higher than in those with primary bacteremia because of the underlying trauma. Rarely, *Aeromonas* bacteremia occurs in otherwise healthy adults exposed to fresh water.

Other Infections

Aeromonas is a rare cause of GI infections such as necrotizing gastroenteritis, peritonitis, cholecystitis, appendicitis, and liver and pancreas abscess formation; cardiovascular infections, including endocarditis and septic embolism; and pulmonary infections, including tracheobronchitis, pneumonia, empyema, and lung abscess formation. *Aeromonas* is also associated with musculoskeletal infections, including osteomyelitis, pyogenic arthritis, pyomyositis, and necrotizing fasciitis, as well as ocular and ear, nose, and throat infections, including endophthalmitis, keratitis, orbital cellulitis, otitis media, and epiglottitis. Other rare infections include meningitis, urinary tract infection, pelvic inflammatory disease, lymphadenitis, hot tub folliculitis, and surgical wound infections. *Aeromonas* is associated with tracheobronchitis and aspiration pneumonia after near-drowning.

DIAGNOSIS

Diagnosis is established by isolation of *Aeromonas* in culture. The organism is generally grown on standard media when the source material is normally sterile. Often, *Aeromonas* is not identified by typical laboratory protocols for examining stool specimens. If *Aeromonas* is suspected, the yield may increase if the laboratory is notified before testing, because overnight enrichment in alkaline peptone water and culture on selective agars may be useful. Most strains (approximately 90%) produce β-hemolysis on blood agar. Lactose-fermenting strains of *Aeromonas* like *A. caviae* may not be identified if the clinical laboratory does not routinely perform oxidase tests on lactose fermenters isolated on MacConkey agar. Aeromonads are resistant to vibriostatic agent O129; however, differentiation of *Aeromonas* from *Vibrio* spp. and identification of *Aeromonas* spp. and subspp. is not reliable using biochemical testing. Similarly, classification of *Aeromonas* strains at the species and subspecies level is difficult to achieve by sequencing regions of the 16S rRNA gene. Sequencing of housekeeping genes, such as *gyrB* and *rpoD,* and multilocus sequence typing are accurate for species identification but are time-, cost- and labor-intensive. Increasingly, laboratories use matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry to rapidly identify organisms because this method is accurate for *Aeromonas* as a genus and for many of the clinically important species. Because stool culture–based diagnosis is time-consuming, labor-intensive, and costly on per positive culture basis, molecular tests for various enteric bacterial pathogens, including multiplex polymerase chain reaction (PCR) assays that include targets for detection of *Aeromonas,* have been developed and are commercially available in some areas.

TREATMENT

Aeromonas **enteritis** is usually self-limited, and antimicrobial therapy may not be indicated, although some studies suggest that **antimicrobial therapy** may shorten the course of the illness. Antimicrobial therapy is reasonable to consider in patients with protracted diarrhea, dysentery-like illness, or underlying conditions such as hepatobiliary disease or an immunocompromised state. Antibiotic sensitivity varies among species and also by geography; therefore it is important to perform **susceptibility testing**. Chromosomally mediated class B, C, and D β-lactamases are found in most species and can be difficult to identify because many are inducible. These include metallo- and AmpC β-lactamases, which can lead to clinical failure if carbapenems or third-generation cephalosporins are used as monotherapy in high-organism-load infections. There is near-uniform resistance to penicillins. Surgical intervention is the primary therapeutic modality in cases of **necrotizing fasciitis**, with most patients requiring more than one **debridement** in the first 48 hours. **Septicemia** can be treated with a **fourth-generation cephalosporin** (e.g., cefepime) or **ciprofloxacin**, with or without an aminoglycoside, although specific therapy should be guided by susceptibility data. Another option for less severe infections includes trimethoprim-sulfamethoxazole (TMP-SMX). Evidence-based recommendations for duration of treatment are lacking, and thus treatment is typically guided by clinical response. In general, diarrhea is treated for 3 days, wound infections for 7-10 days, and bacteremia for 14-21 days, depending on clinical response and host characteristics.

PREVENTION

Reducing contact with contaminated environmental fresh and brackish water and contaminated foods should reduce the risk for *Aeromonas* infections. Some *Aeromonas* outer membrane proteins are immunogenic and are candidate antigens for preclinical vaccine development.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

250.2 *Plesiomonas shigelloides*

Ameneh Khatami and Adam J. Ratner

ETIOLOGY

Plesiomonas shigelloides is a facultatively anaerobic, gram-negative, non–spore-forming bacillus that ferments glucose. It is a catalase-, oxidase-, and indole-positive motile organism with polar flagella. A high level of genetic diversity has been recognized among *P. shigelloides* strains, reflecting frequent homologous recombination.

EPIDEMIOLOGY

P. shigelloides is ubiquitous in freshwater and, because it can tolerate salinity of up to 4%, can be found in estuarine or brackish water, as well as animal inhabitants of these ecosystems, including fish, shellfish, crustaceans, water mammals, amphibians, reptiles, and other vertebrates. *P. shigelloides* has been recovered from healthy (colonized)

and diseased animals, including cats. It can cause both sporadic infections and outbreaks in a range of animals. As a mesophile with optimal growth temperature of 35–39°C (95–102.2°F), *P. shigelloides* has been found most often in tropical waters or during warmer months, although there are increasing reports of isolation from surface water in colder climates. Similarly, most cases of infection occur during the warmer months of the year. *P. shigelloides* is not a usual commensal organism in the human GI tract, and infection of humans is thought to be the result of consumption of contaminated water or raw seafood or possibly through contact with colonized animals. The frequency of isolation of *P. shigelloides* from diarrheal stools in these circumstances has been reported to range from 2% to >10%. Mixed infection with *Salmonella, Aeromonas,* rotavirus, or other enteric pathogens may occur in almost one third of patients. The majority of symptomatic patients in North America have a known exposure to potentially contaminated water or seafood (notably oysters) or have traveled abroad. *Plesiomonas* has been reported to be associated with 1.3–5.4% of episodes of **traveler's diarrhea**, with the highest rates associated with travel to South and Southeast Asia. Other risk factors include immune compromise (in particular HIV infection), blood dyscrasias (including sickle cell disease), and young age. The highest rates of *Plesiomonas* **enteritis** occur in children <2 years old. Although *P. shigelloides* has a worldwide distribution, there is unexplained geographic variability in the incidence of enteritis that may be related to water temperatures and a lack of hygiene and sanitation.

PATHOGENESIS

Epidemiologic and microbiologic evidence in the form of a series of food-borne outbreaks attributable to *P. shigelloides* indicates that this organism is an **enteropathogen**. However, the pathogenic capacity of *P. shigelloides* has not been confirmed through oral challenge studies, and these organisms have been isolated from the stools of healthy individuals at a low rate. The mechanism of enteritis is not known, but putative virulence factors have been described, including cholera-like toxin, heat-labile and heat-stable enterotoxins, and lipopolysaccharide. Most strains of *P. shigelloides* also secrete a β-hemolysin, which is thought to be a major virulence factor. In vitro studies show that isolates of *P. shigelloides* can invade and induce apoptosis in cells of enteric origin, as well as exhibiting evidence of modulation of host defenses through inhibition of cathepsins involved in antigen processing and presentation.

CLINICAL MANIFESTATIONS

Clinical disease in humans generally begins 24-48 hours after exposure to the organism, although incubation periods in excess of 4 days have been reported. Diarrhea can occur in all age-groups, including neonates, is typically secretory, and less often presents as invasive dysentery. Secretory **enteritis** usually presents as a mild self-limiting disease with watery diarrhea and abdominal pain, but in 13% of cases diarrhea can persist for >2 weeks. Dehydration, hypokalemia, and peritonitis are uncommon complications; however, there have been several reports of a cholera-like presentation with severe secretory diarrhea. The frequency of secretory vs dysenteric presentation seems to cluster by individual outbreak, suggesting that either the human populations or the bacterial populations involved are associated with each particular presentation. **Dysentery** presents with macroscopic blood and/or mucus in the stool, significant abdominal pain, and vomiting, with more severe cases also associated with fever. Fatal outcomes have been reported with severe cases of *Plesiomonas* dysentery, although in most of these cases the exact role of *P. shigelloides* is unclear.

Extraintestinal infections, usually bacteremia, are rare and usually occur in patients with underlying immunodeficiency. About 90% of these cases are monomicrobial, and in almost half, *P. shigelloides* is also isolated from a site other than blood. Rarely, bacteremia accompanying enteritis has been documented in apparently otherwise normal children. Septicemia also appears to result from ingestion of contaminated water or seafood and has a high mortality rate in adults. Other extraintestinal diseases include pneumonia, meningitis, osteomyelitis, septic arthritis, reactive arthritis, abscesses, and focal infections of the GI or reproductive tracts. Almost one third of all bacteremias occur in neonates who present with early-onset sepsis and meningitis, and although rare, these make up most of the reported cases of *P. shigelloides* meningitis and have a very high mortality rate (80%). In several cases of neonatal disease, *Plesiomonas* has also been isolated from maternal feces, suggesting intrapartum vertical transmission. Compared with *Aeromonas* and *Vibrio* spp., traumatic wounds sustained in aquatic environments less often contain *P. shigelloides*.

DIAGNOSIS

P. shigelloides is a non–lactose-fermenting organism and grows well on traditional enteric media with optimal growth at 30°C (86°F), although selective techniques may be required to isolate the organism from mixed cultures and to differentiate *P. shigelloides* from *Shigella* spp. If enrichment is necessary, alkaline peptone water or bile peptone broth may be used. Colonies are nonhemolytic on 5% blood agar. Many strains cross-react with *Shigella* on serologic testing but can be differentiated easily as oxidase-positive organisms. *P. shigelloides* has a unique biochemical profile and can generally be identified using commercial kits. Rapid identification systems, including MALDI-TOF, can also be used to identify *P. shigelloides*. *P. shigelloides* is included in at least one U.S. Food and Drug Administration (FDA)–approved commercial panel that detects a range of enteropathogens directly from diarrheal stools (culture independent) by PCR.

TREATMENT

Enteritis caused by *P. shigelloides* is usually mild and self-limited. In cases associated with dehydration or with a cholera-like disease, patients usually respond favorably to **oral rehydration solution**. Consideration of **antimicrobial therapy** is reserved for patients with prolonged or bloody diarrhea, those who are immunocompromised, the elderly, and the very young. Data from uncontrolled studies suggest that antimicrobial therapy may decrease the duration of symptoms, although no difference was found in an exclusively pediatric study.

P. shigelloides produces a chromosomally encoded, noninducible β-lactamase, which generally renders strains resistant to the penicillins, including broad-spectrum penicillins. *P. shigelloides* is also usually resistant to aminoglycosides and tetracyclines. Most strains of *P. shigelloides* are susceptible to β-lactam/β-lactamase inhibitor combinations and to TMP-SMX, some cephalosporins, carbapenems, and fluoroquinolones; however, therapy should be guided by **antimicrobial susceptibility testing** because resistance to TMP-SMX, fluoroquinolones, and other agents has been reported.

Severe cases of *P. shigelloides* dysentery should be treated similarly to shigellosis (with empirical **azithromycin** or a **third-generation cephalosporin** for children and ciprofloxacin or azithromycin for adults). Antibiotics are essential for therapy of extraintestinal disease. Empirical therapy with a third-generation cephalosporin is often first-line management, because most isolates are susceptible in vitro. Alternatives include carbapenems, aztreonam, β-lactam/β-lactamase inhibitor combinations, and quinolones. Definitive therapy should be guided by the susceptibility of the individual isolate. Duration of therapy ranges from 1 to 2 weeks but may be extended depending on underlying chronic conditions and clinical response.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 251

Pseudomonas, Burkholderia, and *Stenotrophomonas*

251.1 *Pseudomonas aeruginosa*

Thomas S. Murray and Ashley C. Howard

ETIOLOGY

Pseudomonas aeruginosa is an aerobic, gram-negative rod. It can multiply in a great variety of environments that contain minimal amounts of organic compounds. Strains from clinical specimens do not ferment lactose, are oxidase positive, and may produce β-hemolysis on blood agar. Many strains produce pigments, including pyocyanin, pyoverdine, and pyorubrin, that diffuse into and color the surrounding medium. Strains of *P. aeruginosa* are differentiated for epidemiologic purposes by a variety of genotyping methods, including restriction fragment length polymorphisms using pulsed-field gel electrophoresis, multilocus sequence typing, and more recently, whole genome sequencing.

EPIDEMIOLOGY

P. aeruginosa is a classic "opportunist." It rarely causes disease in people who do not have a predisposing risk factor. Compromised host defense mechanisms resulting from trauma, neutropenia, mucositis, immunosuppression, or impaired mucociliary transport explain the predominant role of this organism in producing opportunistic infections. In pediatric settings, it is frequently seen in the respiratory secretions of children with **cystic fibrosis** (CF). In a pediatric review of 2,545 facilities from 2015 to 2017 by the National Healthcare Safety Network (NHSN), *P. aeruginosa* ranked among the top 10 organisms to cause **central line–associated bloodstream infections** in all units: 2.8% neonatal intensive care unit (NICU), 5% pediatric intensive care unit (PICU), 5% pediatric oncology units, and 3.1% pediatric wards. *P. aeruginosa* was also the second most common cause of **catheter-associated urinary tract infections** (UTIs) (18.4%) and **ventilator-associated pneumonia** (16.1%) and the third most common cause of postoperative surgical site infections (8.3%). In a multicenter U.S. prospective study of 33 sites from 2014 to 2018, *P. aeruginosa* was isolated in 2.7% of bacteremic episodes in children ≤1 year old and 3.7 % in children ≤17 years of age.

P. aeruginosa and other pseudomonads frequently enter the hospital environment on the clothes, skin, or shoes of patients or hospital personnel, with plants or vegetables brought into the hospital, and in the gastrointestinal (GI) tract of patients. Colonization of any moist or liquid substance may ensue; the organisms may be found growing in any water reservoir, including distilled water, and in hospital kitchen sinks and laundries, some antiseptic solutions, and equipment used for respiratory therapy and urinary procedures. Colonization of skin, throat, stool, and nasal mucosa of patients is low at admission to the hospital but increases to as high as 50–70% with prolonged hospitalization and with the use of broad-spectrum antibiotics, chemotherapy, mechanical ventilation, and urinary catheters. Patients' intestinal microbial flora may be altered by the broad-spectrum antibiotics, reducing resistance to colonization and permitting *P. aeruginosa* in the environment to populate the GI tract. Intestinal mucosal breakdown associated with medications, especially cytotoxic agents, and nosocomial enteritis may provide a pathway by which *P. aeruginosa* spreads to the lymphatics or bloodstream.

PATHOLOGY

The pathologic manifestations of *P. aeruginosa* infections depend on the site and type of infection. Because of its elaboration of toxins and invasive factors, the organism can often be seen invading blood vessels and causing vascular necrosis. In some infections there is spread through tissues with necrosis and microabscess formation. In patients with CF, focal and diffuse bronchitis/bronchiolitis leading to bronchiolitis obliterans has been reported.

Pathogenesis

Invasiveness of *P. aeruginosa* is mediated by a host of virulence factors. Bacterial attachment is facilitated by pili that adhere to epithelium damaged by prior injury or infection. Extracellular proteins, proteases, elastases, and cytotoxins disrupt cell membranes, and in response, host-produced cytokines cause capillary vascular permeability and induce an inflammatory response. Dissemination and bloodstream invasion follow extension of local tissue damage and are facilitated by the antiphagocytic properties of endotoxin, the exopolysaccharide, and protease cleavage of immunoglobulin G. *P. aeruginosa* also produces numerous exotoxins, including exotoxin A, which causes local necrosis and facilitates systemic bacterial invasion. *P. aeruginosa* possesses a type III secretion system composed of a needle structure that inserts into host cell membranes and allows secretion of exotoxins directly into host cells. The host responds to infection with a robust inflammatory response, recruiting neutrophils to the infection site and producing antibodies to *P. aeruginosa* proteins. There is a lack of convincing data that these antibodies are protective against the establishment of infection.

In addition to acute infection, *P. aeruginosa* is also capable of chronic persistence because of the formation of **biofilms**, organized communities of bacteria encased in an extracellular matrix. Biofilm formation requires attachment to a surface, proliferation of the organism, and production of exopolysaccharide as the main bacterial component of the extracellular matrix. A mature biofilm can persist despite an intense host immune response and is resistant to many antimicrobials.

CLINICAL MANIFESTATIONS

Most clinical patterns are related to opportunistic infections in immunocompromised hosts (see Chapter 223) or are associated with shunts and indwelling catheters (see Chapter 224). *P. aeruginosa* may be introduced into a minor wound of a healthy person as a secondary invader, and cellulitis and a localized abscess that exudes green or blue pus may follow. The characteristic skin lesions of *P. aeruginosa,* **ecthyma gangrenosum**, whether caused by direct inoculation or a metastatic focus secondary to septicemia, begin as pink macules and progress to hemorrhagic nodules and eventually to ulcers with ecchymotic and gangrenous centers with eschar formation, surrounded by an intense red areola (Table 251.1 and Fig. 251.1).

Outbreaks of dermatitis and UTIs caused by *P. aeruginosa* have been reported in healthy persons after use of pools or hot tubs. Skin lesions of folliculitis develop several hours to 2 days after contact with these water sources. Skin lesions may be erythematous, macular, papular, or pustular. Illness may vary from a few scattered lesions to extensive truncal involvement. In some children, malaise, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swollen breasts may be associated with dermal lesions. UTIs caused by *P. aeruginosa* are most often nosocomial and are often associated with the presence of an indwelling urinary catheter, urinary tract malformations, and previous antibiotic use. UTIs may be minimized or prevented by prompt removal of the catheter and by early identification and corrective surgery of obstructive lesions when present.

Burns and Wound Infection

The surfaces of burns or wounds are frequently populated by *P. aeruginosa* and other gram-negative organisms; this initial colonization with a low number of adherent organisms is a prerequisite to invasive disease. *P. aeruginosa* colonization of a burn site may develop into **burn wound sepsis**, which has a high mortality rate when the density of organisms reaches a critical concentration. Administration of antibiotics may

Table 251.1 *Pseudomonas aeruginosa* Infections

INFECTION	COMMON CLINICAL CHARACTERISTICS
Endocarditis	Native right-sided (tricuspid) valve disease with intravenous drug abuse
Pneumonia	Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid *P. aeruginosa* organisms producing capsular slime
Central nervous system infection	Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery)
External otitis	Swimmer's ear; humid warm climates, swimming pool contamination
Malignant otitis externa	Invasive, indolent, febrile, toxic, destructive, necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with seventh nerve palsy and mastoiditis
Chronic mastoiditis	Ear drainage, swelling, erythema; perforated tympanic membrane
Keratitis	Corneal ulceration; contact lens keratitis
Endophthalmitis	Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression
Osteomyelitis/septic arthritis	Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis
Urinary tract infection	Iatrogenic, nosocomial; recurrent UTIs in children, instrumented patients, and those with obstruction or stones
Intestinal tract infection	Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis
Ecthyma gangrenosum	Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses
Primary and secondary skin infections	Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic folliculitis; vesiculopustular or maculopapular, erythematous lesions



Fig. 251.1 Round, nontender skin lesion on 2-yr-old female's buttock. Note the black ulcerated center of the lesion and its red margin. *(From Ghanaiem H, Engelhard D. A healthy 2-year-old child with a round black skin lesion. J Pediatr. 2013;163:1225.)*

diminish the susceptible microbiologic flora, permitting strains of relatively resistant *P. aeruginosa* to flourish. Multiplication of organisms in devitalized tissues or associated with prolonged use of intravenous or urinary catheters increases the risk for septicemia with *P. aeruginosa*, a major problem in burned patients (see Chapter 89).

Cystic Fibrosis

P. aeruginosa is common in patients with CF, with increasing prevalence as children get older (see Chapter 454). Initial infection is caused by **nonmucoid environmental strains** of *P. aeruginosa*, but after a variable period, **mucoid strains** of *P. aeruginosa* that produce the antiphagocytic exopolysaccharide alginate, which are rarely encountered in other conditions, predominate. Repeated isolation of mucoid *P. aeruginosa* from the sputum is associated with increased morbidity and mortality. The infection begins insidiously or even asymptomatically, and the progression has a highly variable pace. In children with CF, antibody does not eradicate the organism, and antibiotics are only partially effective; thus after infection becomes chronic, it cannot be completely eradicated. Repeated courses of antibiotics select for *P. aeruginosa* strains that are resistant to multiple antibiotics.

Immunocompromised Persons

Children with leukemia or other malignancies, particularly those who are receiving immunosuppressive therapy and who are neutropenic, typically with intravascular catheters, are extremely susceptible to septicemia caused by invasion of the bloodstream by *P. aeruginosa* that is colonizing the respiratory or GI tract. Signs of sepsis are often accompanied by a generalized vasculitis, and hemorrhagic necrotic lesions may be found in all organs, including the skin (ecthyma gangrenosum) (see Fig. 251.1). Hemorrhagic or gangrenous perirectal cellulitis or abscesses may occur, associated with ileus and profound hypotension.

Nosocomial Pneumonia

Although not a frequent cause of community-acquired pneumonia in children, *P. aeruginosa* does cause nosocomial pneumonia, especially ventilator-associated pneumonia, in patients of all ages. *P. aeruginosa* has historically been found to contaminate ventilators, tubing, and humidifiers. Such contamination is uncommon now because of disinfection practices and routine changing of equipment. Nevertheless, colonization of the upper respiratory tract and the GI tract may be followed by aspiration of *P. aeruginosa*–contaminated secretions, resulting in severe pneumonia. Prior use of broad-spectrum antibiotics is a risk factor for colonization with antibiotic-resistant strains of *P. aeruginosa*. One of the most challenging situations is distinguishing between colonization and pneumonia in intubated patients. This distinction can

often only be definitively resolved by using invasive culture techniques such as quantitative bronchoalveolar lavage.

Infants

P. aeruginosa is an occasional cause of **nosocomial bacteremia** in newborns and accounts for 2–5% of positive blood culture results in NICUs. A frequent focus preceding bacteremia is **conjunctivitis**. Older infants rarely present with community-acquired sepsis caused by *P. aeruginosa.* In the few reports describing community-acquired sepsis, preceding conditions included ecthyma-like skin lesions, virus-associated transient neutropenia, and prolonged contact with contaminated bath water or a hot tub.

DIAGNOSIS

P. aeruginosa infection is rarely clinically distinctive. Diagnosis depends on recovery of the organism from the blood, cerebrospinal fluid (CSF), urine, or needle aspirate of the lung or from purulent material obtained by aspiration of subcutaneous abscesses or areas of cellulitis. In the appropriate clinical setting, recovery of *P. aeruginosa* from a coughed or suctioned sputum may represent infection; but it also may only represent colonization, and clinical judgment is required. Rarely, skin lesions that resemble *P. aeruginosa* infection may follow septicemia caused by *Aeromonas hydrophila,* other gram-negative bacilli, and *Aspergillus.* When *P. aeruginosa* is recovered from nonsterile sites such as skin, mucous membranes, or voided urine, quantitative cultures may be useful to differentiate colonization from invasive infection. In general, ≥100,000 colony-forming units/mL of fluid or gram of tissue is evidence suggestive of invasive infection. Quantitative cultures of tissue and skin are not routine and require consultation with the clinical microbiology laboratory.

TREATMENT

Systemic infections with *P. aeruginosa* should be treated promptly with an antibiotic to which the organism is susceptible in vitro. Response to treatment may be limited, and prolonged treatment may be necessary for systemic infection in immunocompromised hosts.

Septicemia and other aggressive infections should be treated with either one or two bactericidal agents. Although the number of agents required is controversial, the evidence continues to suggest that the benefit of adding a second agent is questionable, even when studies have included immunosuppressed patients. *Appropriate antibiotics for single-agent therapy include ceftazidime, cefepime, ticarcillin-clavulanate, and piperacillin-tazobactam. Gentamicin or another aminoglycoside may be used concomitantly for synergistic effect.*

Ceftazidime has proved to be extremely effective in patients with CF, at 150-400 mg/kg/day divided every 6-8 hours intravenously (IV) to a maximum of 6 g/day. Piperacillin or piperacillin-tazobactam 240-400 mg/kg/day divided every 6-8 hours IV to a maximum of 12 g/day also has proved to be effective therapy for susceptible strains of *P. aeruginosa.* Continuous infusions of β-lactam antibiotics are more effective than the same daily dose given as pulse infusions.

Additional effective antibiotics include imipenem-cilastatin, meropenem, and aztreonam. Ciprofloxacin (20-30 mg/kg/day orally every 8-12 hours up to 500 mg/dose) is the only available effective oral *P. aeruginosa* therapy, and although commonly used in children with CF, it is not approved in the United States for persons <18 years old, except for oral treatment of UTIs or when treating multidrug-resistant (MDR) *P. aeruginosa*. Inhaled therapy with either tobramycin or aztreonam is also used for chronic pulmonary infection, with inhaled colistin reserved for the treatment of resistant pseudomonads. Macrolide therapy decreases pulmonary exacerbations in patients with chronic lung disease and *P. aeruginosa* infection. The mechanism relates to altering the virulence properties of *P. aeruginosa* rather than direct bacterial killing.

It is important to base continued treatment on antimicrobial susceptibility tests because **antibiotic resistance** of *P. aeruginosa* is increasing. *P. aeruginosa* has many mechanisms for resistance to multiple classes of antibiotics, including but not limited to pathogenic variants, production of β-lactamases, and drug efflux pumps. Throughout the United States there has been an alarming increase in MDR *P. aeruginosa* isolates resistant to at least three antibiotic classes recovered from children. NHSN data from 2015 to 2017 show 2.8% NICU, 12% PICU, 6% pediatric oncology, and 5.5% pediatric ward *P. aeruginosa* isolates were MDR, with increasing rates of carbapenem and piperacillin/tazobactam resistance as well.

Several newer agents demonstrate efficacy against MDR *P. aeruginosa*. Ceftazidime-avibactam and ceftolozane-tazobactam combine cephalosporins with a β-lactamase inhibitor. Ceftolozane-tazobactam inhibits AmpC and other extended-spectrum β-lactamases but lacks activity against carbapenemases. Ceftazidime-avibactam inhibits class A carbapenemases but not metallo-β-lactamases. Cefiderocol, a siderophore cephalosporin, has enhanced stability to β-lactamases, including metallo-β-lactamases, Amp C, and carbapenemases.

Meningitis can occur by spread from a contiguous focus, as a secondary focus when there is bacteremia, or after invasive procedures. *P. aeruginosa* meningitis is best treated with ceftazidime or meropenem in combination with an aminoglycoside such as gentamicin, both given IV. Concomitant intraventricular or intrathecal treatment with gentamicin may be required when IV therapy fails but is not recommended for routine use.

SUPPORTIVE CARE

P. aeruginosa infections vary in severity from *superficial* to *intense* septic presentations. With severe infections there is often multisystem involvement and a systemic inflammatory response. Supportive care is similar to care for severe sepsis caused by other gram-negative bacilli and requires support of blood pressure, oxygenation, and appropriate fluid management.

PROGNOSIS

The prognosis is dependent primarily on the nature of the underlying factors that predisposed the patient to *P. aeruginosa* infection. In severely immunocompromised patients, the prognosis for patients with *P. aeruginosa* sepsis is poor unless susceptibility factors such as neutropenia or hypogammaglobulinemia can be reversed. The overall mortality rate was 12.3% in one series of 232 children with *P. aeruginosa* bacteremia, with 3% dying within 48 hours of admission. Resistance of the organism to first-line antibiotics also decreases the chance of survival. The outcome may be improved when there is a urinary tract portal of entry, absence of neutropenia or recovery from neutropenia, and drainage of local sites of infection.

P. aeruginosa is recovered from the lungs of most children who die of CF and adds to the slow deterioration of these patients. The prognosis for normal development is poor in the few infants who survive *P. aeruginosa* meningitis.

PREVENTION

Prevention of infections is dependent on limiting contamination of the healthcare environment and preventing transmission to patients. Effective hospital infection control programs are necessary to identify and eradicate sources of the organism as quickly as possible. In hospitals, infection can be transmitted to children by the hands of personnel, from washbasin surfaces, from catheters and other hospital equipment, and from solutions used to rinse suction catheters.

Strict attention to hand hygiene before and between contacts with patients may prevent or interdict epidemic disease. Meticulous care and sterile procedures in the suctioning of endotracheal tubes, insertion and maintenance of indwelling catheters, and removal of catheters as soon as medically reasonable greatly reduce the hazard of extrinsic contamination by *P. aeruginosa* and other gram-negative organisms. Prevention of follicular dermatitis caused by *P. aeruginosa* contamination of whirlpools or hot tubs is possible by maintaining pool water at a pH of 7.2-7.8. Antimicrobial stewardship programs that promote the appropriate use of antibiotics in the hospital setting are critical for reducing the rates of MDR *P. aeruginosa*.

Infections in burned patients may be minimized by protective isolation, debridement of devitalized tissue, and topical applications of bactericidal cream. Administration of intravenous immunoglobulin

may be used. Approaches under investigation to prevent infection include development of a *P. aeruginosa* vaccine. No vaccine is currently licensed in the United States.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

251.2 *Burkholderia cepacia* Complex

Ashley C. Howard and Thomas S. Murray

Burkholderia cepacia is a filamentous gram-negative rod now recognized to be a group of related species or **genomovars** *(B. cepacia, B. cenocepacia, B. multivorans)*. It is ubiquitous in the environment but may be difficult to isolate from respiratory specimens in the laboratory, requiring an enriched, selective media oxidation-fermentation base supplemented with polymyxin B–bacitracin-lactose agar (OFPBL) and as long as 3 days of incubation.

B. cepacia is a classic opportunist that rarely infects normal tissue but can be a pathogen for individuals with preexisting damage to respiratory epithelium, especially persons with CF or with immune dysfunction such as chronic granulomatous disease. *B. cepacia* has multiple virulence factors, including lipopolysaccharide, flagella, and a type III secretion system that promotes invasion of respiratory epithelial cells. Resistance to many antibiotics and disinfectants appears to be a factor in the emergence of *B. cepacia* as a nosocomial pathogen. In critical care units it may colonize the tubing used to ventilate patients with respiratory failure. In some patients this colonization may lead to invasive pneumonia and septic shock. Although *B. cepacia* is found throughout the environment, human-to-human spread among CF patients occurs either directly by inhalation of aerosols or indirectly from contaminated equipment or surfaces, accounting for the strict infection control measures for children with CF who are colonized with *B. cepacia*. For example, CF patients colonized with *B. cepacia* are asked not to attend events where other persons with CF will be present. *B. cepacia* infections in persons with CF may represent chronic infection in some patients, but others, especially those with *Burkholderia cenocepacia*, genomovar III, can develop an acute respiratory syndrome of fever, leukocytosis, and progressive respiratory failure, with more rapid decline in pulmonary function and lower survival rate. In 2016-2017, two healthcare-associated *B. cepacia* outbreaks among non-CF patients occurred as a result of contaminated liquid docusate that infected 63 persons from 12 states and prefilled saline flushes that infected 163 persons with 7 deaths. In August 2021, a healthcare-associated outbreak of *B. stabilis* was linked to ultrasound gel used in 59 persons in six states, with 48 cases of bloodstream infection.

Treatment in hospitals should include standard precautions and avoidance of placing colonized and uncolonized patients in the same room. The use of antibiotics is guided by susceptibility studies of a patient's isolates, because the susceptibility pattern of this species is quite variable and resistant strains are common. *Trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline or minocycline are potential oral therapies for B. cepacia complex. For IV therapy without meningitis, meropenem (20-40 mg/kg/dose every 8 hours with a maximum dose of 6 g/day) with a second agent such as TMP-SMX, doxycycline, minocycline, ceftazidime, or amikacin is recommended.* Extended infusions should be considered for difficult-to-treat infections. Even though there is primary resistance to aminoglycosides, these agents may be useful in combination with other antibiotics. Treatment with two or more agents may be necessary to control the infection and avoid the development of resistance. Cefiderocol, because of its increased stability against β-lactamases, has activity against some MDR *B. cepacia complex.*

BURKHOLDERIA MALLEI (GLANDERS)

Glanders is a severe infectious disease of horses and other domestic and farm animals that is caused by *Burkholderia mallei,* a nonmotile, gram-negative bacillus that is occasionally transmitted to humans. It is acquired by inoculation into the skin, usually at the site of a previous abrasion, or by inhalation of aerosols. Laboratory workers may acquire it from clinical specimens. The disease is relatively common in Asia, Africa, and the Middle East. The clinical manifestations include septicemia, acute or chronic pneumonitis, and hemorrhagic necrotic lesions of the skin, nasal mucous membranes, and lymph nodes. The diagnosis is usually made by recovery of the organism in cultures of affected tissue. Glanders is treated with sulfadiazine, tetracyclines, or chloramphenicol and streptomycin over many months. The disease has been eliminated from the United States, but interest in this organism has increased because of the possibility of its use as a bioterrorism agent (see Chapter 763). Although standard precautions are appropriate when caring for hospitalized infected patients, biosafety level 3 precautions are required for laboratory staff working with *B. mallei.* No vaccine is available.



Fig. 251.2 Thigh abscesses at the sites of mosquito bites in a 15-yr-old Pennsylvania resident who had recently returned from Thailand, July 2016. Photo was taken 7 wk after onset. *(From Mitchell PK, Campbell C, Montgomery MP, et al. Notes from the field: travel–associated melioidosis and resulting laboratory exposures—United States, 2016. MMWR. 2017;66[37]:1001–1002.)*

BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS)

Melioidosis is an important disease of Southeast Asia and northern Australia and occurs in the United States mainly in persons returning from endemic areas. The causative agent is *Burkholderia pseudomallei,* an inhabitant of soil and water in the tropics. It is ubiquitous in endemic areas, and infection follows inhalation of dust, ingestion, or direct contamination of abrasions or wounds. Human-to-human transmission has only rarely been reported. Serologic surveys demonstrate that asymptomatic infection occurs in endemic areas. The disease may remain latent and appear when host resistance is reduced, sometimes years after the initial exposure. Diabetes mellitus is a risk factor for severe melioidosis. In 2021, four cases of melioidosis with two deaths occurred in Kansas, Minnesota, Texas, and Georgia in persons, including children, with no known travel. The exposure is unknown but thought to be from a single source, such as a contaminated imported product or animal.

Melioidosis may present as a **primary skin lesion** (vesicle, bulla, or urticaria) (Fig. 251.2). Pulmonary infection may be subacute and mimic tuberculosis or may present as an acute necrotizing pneumonia. Occasionally, septicemia occurs and numerous abscesses are noted in various organs of the body. Myocarditis, pericarditis, endocarditis, intestinal abscess, cholecystitis, acute gastroenteritis, UTIs, septic arthritis, paraspinal abscess, osteomyelitis, mycotic aneurysm, and generalized lymphadenopathy all have been observed. Melioidosis may also present as an encephalitic illness with fever and seizures. It is also an agent of severe wound infections after contact with contaminated water after a tsunami. Diagnosis is based on visualization of characteristic small, gram-negative rods in exudates or growth on laboratory media such as eosin–methylene blue or MacConkey agar. Serologic

tests are available, and diagnosis can be established by a fourfold or greater increase in antibody titer in an individual with an appropriate syndrome. It is recognized as a possible agent of bioterrorism, and if suspected, the clinical microbiology laboratory should be notified immediately (see Chapter 763).

B. pseudomallei is susceptible to many antimicrobial agents, and the U.S. Centers for Disease Control and Prevention (CDC) recommends meropenem or ceftazidime as IV therapies and TMP-SMX or doxycycline as oral therapy. Other choices include aminoglycosides, tetracycline, chloramphenicol, and amoxicillin-clavulanate. Therapy should be guided by antimicrobial susceptibility tests; two or three agents such as ceftazidime or meropenem plus TMP-SMX, sulfisoxazole, or an aminoglycoside are usually chosen for severe or septicemic disease. For severe disease, prolonged treatment for 2-6 months is recommended to prevent relapses. Appropriate antibiotic therapy generally results in recovery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

251.3 *Stenotrophomonas*

Ashley C. Howard and Thomas S. Murray

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia* or *Pseudomonas maltophilia*) is a short to medium-sized, straight, gram-negative bacillus. It is ubiquitous in nature and can be found in the hospital environment, especially in tap water or standing water, and may contaminate sinks and hospital equipment such as nebulizers. Strains isolated in the laboratory may be contaminants, may be a commensal from the colonized surface of a patient, or may represent an invasive pathogen. The species is an opportunist and is often recovered from immunosuppressed patients and patients with CF after multiple courses of antimicrobial therapy. Serious infections usually occur among those requiring intensive care, including neonatal intensive care, typically patients with ventilator-associated pneumonia or catheter-associated infections. Prolonged antibiotic exposure appears to be a frequent factor in nosocomial *S. maltophilia* infections, probably because of its endogenous antibiotic-resistance pattern. Common types of infection include pneumonia after airway colonization and aspiration, bacteremia, soft tissue infections, endocarditis, and osteomyelitis. *S. maltophilia* bacteremia is a **nosocomial infection** associated with the presence of a central venous catheter.

Strains vary as to antibiotic susceptibility, and the treatment of *S. maltophilia* can be difficult because of inherent antimicrobial resistance. Data are lacking on whether there is clinical benefit to treat *S. maltophilia* recovered from the respiratory tract of a patient with CF. For invasive infections, ***TMP-SMX*** *(20 mg/kg/day TMP component every 6-8 hours) is the treatment of choice and is the only antimicrobial for which susceptibility is routinely reported.* ***Minocycline*** *monotherapy has recently been shown to be a viable alternative to TMP-SMX* and is reported for TMP-SMX resistance strains with fewer adverse effects and similar clinical outcomes. Mean inhibitory concentration testing is available for other antibiotics, such as ticarcillin-clavulanate, and also reserved for TMP-SMX–resistant isolates. *For resistant organisms or for patients who cannot tolerate sulfa drugs, other options based on clinical outcome include ciprofloxacin and ceftazidime alone or in combination with other agents such as aminoglycosides.*

ACKNOWLEDGMENTS

We would like to acknowledge Dr. Robert S. Baltimore for his contribution to this chapter and Dr. Michelle R. Rychalsky for antibiotic dosing regimens.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 252

Tularemia (*Francisella tularensis*)

Kevin J. Downes

Tularemia is a **zoonosis** caused by the gram-negative bacterium *Francisella tularensis.* Tularemia is primarily a disease of wild animals; human disease is incidental and usually results from **tick** or **deer fly** bites or from contact with infected live or dead wild animals. The illness caused by *F. tularensis* is manifest by multiple clinical syndromes, the most common consisting of an ulcerative lesion at the site of inoculation with regional **lymphadenopathy** or **lymphadenitis**. *F. tularensis* is also a potential agent of **bioterrorism** (see Chapter 763).

ETIOLOGY

Francisella tularensis is a small, nonmotile, pleomorphic, catalase-positive, gram-negative coccobacillus. It can be classified into four main subspecies: *F. tularensis* subsp. *tularensis* (type A), *F. tularensis* subsp. *holarctica* (type B), *F. tularensis* subsp. *mediasiatica*, and *F. tularensis* subsp. *novicida*. Type A can be further subdivided into four distinct genotypes designated A1a, A1b, A2a, and A2b, with A1b appearing to produce more serious disease in humans. Although all subspecies of *F. tularensis* can cause human infections, types A and B are most common, and type A is the most virulent. *F. tularensis* is an intracellular organism than can infect various host cell types, including macrophages, hepatocytes, and epithelial cells. It is one of the most virulent bacterial pathogens known, with as few as 10 microorganisms causing infections in humans and animals.

EPIDEMIOLOGY

Tularemia is primarily found in the Northern Hemisphere. Type A is found predominantly in North America, whereas type B is found throughout North America, Europe, and Asia. Human infections with type B are usually milder and have lower mortality rates compared to infections with type A. *F. tularensis* subsp. *mediasiatica* appears to be restricted to Central Asia, whereas *F. tularensis* subsp. *novicida* has been isolated in North America, Australia, and Southeast Asia.

According to the Centers for Disease Control and Prevention (CDC), the number of annual reported cases of tularemia in the United States from 2010 to 2019 ranged from 124 to 314 per year. In 2015 the number of cases reported in the United States was the highest it had been over the previous 50 years. Tularemia occurs all over the Unites States, with the majority of cases reported from central states (Fig. 252.1). The U.S. incidence of tularemia from 2010 to 2019 was 0.10 per 100,000 residents; Arkansas (3.1/100,000), South Dakota (1.9/100,000), and Nebraska (0.9/100,000) were the states with the highest incidence.

Although cases of tularemia occur all year, most cases and outbreaks occur in warm summer months (May-September). Tularemia is more common in males, although this is less true in children compared with adults. There is a bimodal distribution based on age with peaks in childhood (5-9 years) and later adulthood (50-69 years), potentially because of greater opportunities for environmental and animal exposures at these ages (Fig. 252.2).

PATHOGENESIS

Of all the zoonotic diseases, tularemia is unusual because of the different modes of transmission of disease. A large number of animals serve as a reservoir for this organism. In the United States, rabbits and ticks are the principal reservoirs. Dogs may be an intermediate vector. In the United States, *Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (dog tick), and *Dermacentor andersoni* (wood tick) are the most common tick vectors. These ticks usually feed on infected small

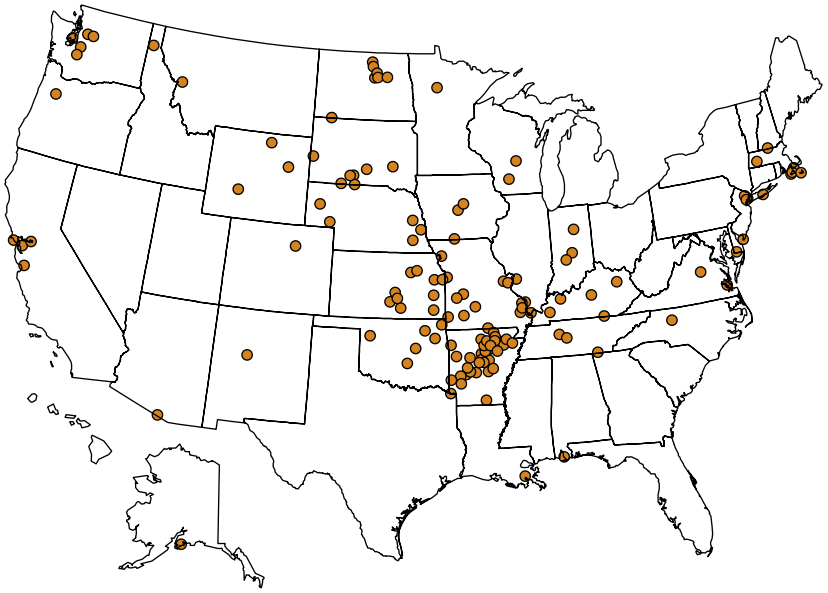

* One dot is placed randomly within county of residence for each reported case.

Fig. 252.1 Map of reported cases of tularemia—United States, 2020. *(From Centers for Disease Control and Prevention: Tularemia—Statistics, https://www.cdc.gov/tularemia/statistics/index.html, Accessed: August 25, 2021.)*

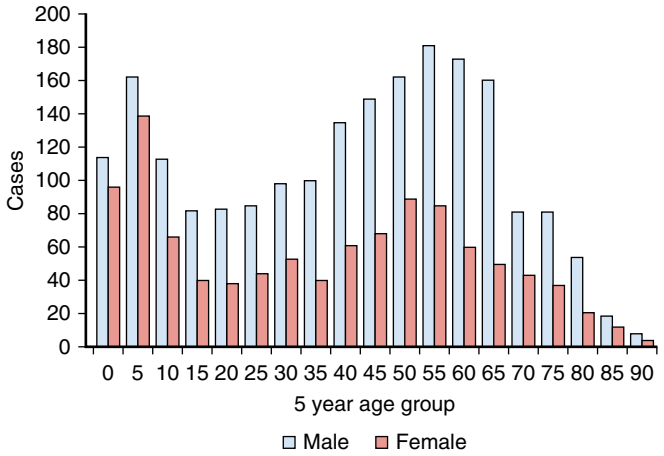

Fig. 252.2 Incidence of reported cases of tularemia by age and sex—United States, 2001–2020. *(From Centers for Disease Control and Prevention: Tularemia—Statistics, https://www.cdc.gov/tularemia/statistics/index.html, Accessed: August 25, 2021.)*

rodents and later feed on humans. Deer flies (*Chrysops* spp.) can also transmit tularemia and are present in the western United States. *F. tularensis* subsp. *tularensis* is carried by rabbits, ticks, and tabanid flies (e.g., deer flies), whereas subsp. *holarctica* is associated with aquatic habitats and transmitted primarily by mosquitoes, but also aquatic rodents (beavers, muskrats), hares, voles, ticks, tabanid flies, and ingestion of contaminated water (e.g., ponds, rivers).

The organism can penetrate both intact skin and mucous membranes (eyes, mouth, gastrointestinal [GI] tract, or lungs), which are the most common portals of entry. Transmission can occur through the bite of infected ticks or other biting insects, by contact with infected animals or their carcasses, by consumption of contaminated foods or water, or through inhalation, as might occur in a laboratory setting or if a machine (e.g., lawn mower) runs over an infected animal carcass. Hunting or skinning infected wild rodents, such as rabbits or prairie dogs, has been the source of infection in numerous reports. Domesticated animals such as cats and hamsters can also transmit tularemia. Importantly, this organism is not transmitted from person to person.

Usually >10^8 organisms are required to produce infection if *F. tularensis* bacteria are ingested, but as few as 10 organisms may cause disease if they are inhaled or injected into the skin (i.e., via an insect bite). Infection with *F. tularensis* stimulates the host to produce antibodies, which have been recognized as important in the immune response to this organism. The *F. tularensis* envelope is largely responsible for virulence and plays major roles in the ability of the organism to evade the immune system, attach to and invade cells, and cause severe disease. The body is most dependent on cell-mediated immunity to contain and eradicate *F. tularensis*. Tularemia is usually followed by specific protection; chronic infection or reinfection is therefore unlikely.

CLINICAL MANIFESTATIONS

Symptoms of tularemia vary based on the mode of transmission. The average incubation period from infection until clinical symptoms is 3 days (range: 1-21 days). Early symptoms of infection are generally nonspecific: fever, chills, myalgias, arthralgias, headache, and fatigue. Bacteremia may be common in the early stages of infection. Acute infections often present with sudden onset of fever, and a pulse-temperature dissociation may be present. Findings on physical examination may include lymphadenopathy, hepatosplenomegaly, or skin lesions. Table 252.1 shows the frequency of various symptoms and examination findings.

The clinical manifestations of tularemia have been divided into six major clinical syndromes (Table 252.2). **Ulceroglandular** and **glandular** disease are the two most common forms of tularemia in children. Infections after the bites of ticks or deer flies take these forms. Within 48-72 hours after inoculation of the skin, an erythematous, tender, or pruritic papule may appear at the portal of entry. This papule may enlarge and form an ulcer with a black base. Ulcers are generally erythematous and painful with raised borders and may last several weeks, especially if untreated. Various other skin lesions have been described, including erythema multiforme and erythema nodosum. Approximately 20% of patients may develop a generalized maculopapular rash that occasionally becomes pustular. The unifying manifestation of glandular and ulceroglandular forms of tularemia is **painful regional lymphadenopathy**. Adenopathy may develop before, concurrent with, or

Table 252.1 Common Clinical Manifestations of Tularemia in Children

SIGN OR SYMPTOM	APPROXIMATE FREQUENCY (%)
Lymphadenopathy	90
Fever (>38.3°C [100.9°F])	85
Ulcer/eschar/papule	45
Pharyngitis	40
Myalgias/arthralgias	40
Nausea/vomiting	35
Hepatosplenomegaly	35

Table 252.2 Clinical Syndromes of Tularemia in Children

CLINICAL SYNDROME	CHARACTERISTICS OF SYNDROME
Ulceroglandular	Skin ulcer/eschar at site of inoculation; painful regional adenopathy
Glandular	Painful regional adenopathy without detectable skin ulceration
Pneumonia	Nonproductive cough, dyspnea, pleuritic chest pain; multilobar/diffuse infiltrates > lobar infiltrates on chest radiography
Oropharyngeal	Pharyngitis, mucosal ulcers, cervical adenopathy
Oculoglandular	Unilateral, painful, and often purulent conjunctivitis; chemosis; conjunctival ulcers; preauricular adenopathy
Typhoidal	Severe systemic disease (sepsis-like syndrome): high fever, headaches, myalgias, arthralgias, neurologic symptoms

after skin ulceration in ulceroglandular disease. Cervical or posterior auricular nodes are involved after bites on the head or neck, whereas enlarged axillary or epitrochlear nodes signal exposure on the arms. Nodes may vary in size from 0.5 to 10 cm and appear singly or in clusters. These affected nodes may become fluctuant and drain spontaneously and are often associated with overlying skin changes. Late suppuration of the involved nodes has been described in 25–30% of patients despite effective therapy. Examination of this material from such lymph nodes usually reveals sterile necrotic material. Mortality with these forms of tularemia is rare, especially with implementation of effective treatment.

Oropharyngeal tularemia results from consumption of poorly cooked meats or contaminated water. This syndrome is characterized by acute pharyngitis, with or without tonsillitis, and cervical lymphadenitis. Infected tonsils may become large and develop a yellowish-white membrane that may resemble the membranes associated with diphtheria. GI disease may also occur and usually presents with mild, unexplained diarrhea or emesis but may progress to rapidly fulminant and fatal disease. GI bleeding can develop in more severe forms associated with intestinal ulcers.

Oculoglandular disease is uncommon, but when it does occur, the portal of entry is the conjunctiva. Contact with contaminated fingers or debris is the most common mechanism of this form of tularemia. Disease is generally unilateral. The conjunctiva is painful and inflamed with yellowish nodules and pinpoint ulcerations. Purulent conjunctivitis with ipsilateral preauricular or submandibular lymphadenopathy can develop and is referred to as **Parinaud oculoglandular syndrome**, although this term is not specific to tularemia. Corneal ulceration and perforation are uncommon but serious complications of this form of disease.

The **typhoidal** form is usually associated with a large inoculum of organisms and is a term used to describe nonlocalizing disease, regardless of the mode of transmission or portal of entry. Patients are often critically ill and bacteremic, and symptoms mimic those with other forms of sepsis: high fevers, confusion, rigors, myalgias, vomiting, and diarrhea. Clinicians practicing in tularemia-endemic regions must always consider this diagnosis in critically ill children. Complications of bacteremia with *F. tularensis* can include the development of meningitis, pericarditis, hepatitis, peritonitis, endocarditis, skin/soft tissue abscesses, and osteomyelitis. Because of its increased virulence, *F. tularensis* subsp. *tularensis* (type A disease) is more often associated with typhoidal tularemia. Patients with tularemia meningitis usually develop a marked cerebrospinal fluid (CSF) pleocytosis with a monocytic predominance. As with other causes of bacterial meningitis, CSF glucose is low and protein is high.

Pneumonia caused by *F. tularensis* **(pneumonic form)** can develop after inhalation (primary pulmonary infection) or secondary to hematogenous spread. Inhalation-related infection has been described in laboratory workers who are working with the organism and results in a relatively high mortality rate. Aerosols from farming activities involving rodent contamination (haying, threshing) or animal carcass destruction with lawn mowers have been reported to cause pneumonia as well. Patients generally complain of a nonproductive cough, dyspnea, or pleuritic chest pain. Chest radiographs of patients with pneumonic tularemia most often reveal diffuse, patchy infiltrates rather than focal areas of consolidation. Pleural effusions can also be present. In pulmonary infections, hilar or mediastinal adenopathy can develop, and in severe forms, necrotizing or hemorrhagic pneumonitis can occur. Mortality with pneumonic tularemia is high if untreated.

DIAGNOSIS

The diagnosis can be delayed because symptoms are often similar to other, more common infections. The history and physical examination of the patient may suggest the diagnosis, especially if the patient has a history of animal or tick exposure. Routine hematologic blood tests are nondiagnostic. **Definitive diagnosis is made by growth of *F. tularensis* in culture.** *F. tularensis* can be isolated in culture of lymph node biopsies or aspirates, blood, wounds, pharyngeal swabs, pleural fluid, or sputum specimens, although cultures are positive in only approximately 10% of cases. The organism can be identified on culture from skin lesions and lymph nodes for as long as a month after onset of disease. Polymerase chain reaction of tissue specimens may be more sensitive than culture but is currently used to make a presumptive diagnosis only.

F. tularensis can be cultured in the microbiology laboratory on cysteine–glucose–blood agar, but care should be taken to alert the personnel in the laboratory if this is attempted so that they can take the proper precautions to protect themselves from acquiring infection; biosafety level 3 containment is necessary to avoid occupational exposure. Histopathologic findings of involved lymph nodes demonstrate granulomas with central necrosis (early) and caseation (late). Unfortunately, these findings cannot distinguish tularemia from other causes of granulomatous lymphadenitis, such as tuberculosis, cat-scratch disease (*Bartonella henselae* infection), or sarcoidosis.

The diagnosis of tularemia is most often established via serology. In the standard tube agglutination (TA) test, a single titer of ≥1:160 in a patient with a compatible history and physical findings can establish the diagnosis. A microagglutination (MA) test is also available, and ≥1:128 is considered positive. Patients often do not produce detectable antibodies until the second week of illness, so negative testing in the acute phase does not rule out infection. A fourfold increase in titer from paired serum samples collected >2 weeks apart (i.e., acute and convalescent titers) can also be considered diagnostic. False-negative serologic responses can be obtained early in the infection or if paired sera are collected too close together. False-positive serologic tests can also result from cross-reactivity with other gram-negative organisms, such as *Brucella* or *Legionella* species, particularly at low titers. Once infected, patients may have a positive agglutination test result (1:20-1:80) that persists for life. Other testing techniques available include enzyme-linked immunosorbent assay (ELISA), analysis of urine for tularemia antigen, indirect immunofluorescent assay, and immunohistochemical staining; these studies have less well-established roles in the diagnosis of tularemia.

Differential Diagnosis

The differential diagnosis of **ulceroglandular** or **glandular** tularemia is broad and includes infection with pathogens that cause acute or subacute lymphadenitis: cat-scratch disease *(B. henselae)*, infectious mononucleosis, typical bacterial pathogens (*Staphylococcus aureus,* group A streptococcus), *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *Toxoplasma gondii, Sporothrix schenckii,* plague *(Yersinia pestis)*, anthrax *(Bacillus anthracis)*, melioidosis *(Burkholderia pseudomallei)*, and rat-bite fever *(Streptobacillus moniliformis, Spirillum minus)*. Noninfectious processes such as sarcoidosis and Kawasaki disease can also present similarly. **Oculoglandular** disease may also occur with other infectious agents, such as *B. henselae, Treponema pallidum, Coccidioides immitis,* herpes simplex virus (HSV), adenoviruses, and the bacterial agents responsible for purulent conjunctivitis. **Oropharyngeal** tularemia must be differentiated from the same diseases that cause ulceroglandular/glandular disease and from cytomegalovirus, HSV, adenovirus, and other viral or bacterial etiologies. **Pneumonic** tularemia must be differentiated from the other atypical pathogens that cause community-acquired pneumonia, such as *Mycoplasma* and *Chlamydophila,* as well as mycobacteria, fungi, and rickettsiae. Inhalation plague, anthrax, and Q fever could also present similarly. **Typhoidal** tularemia must be differentiated from other forms of sepsis and from enteric fever (typhoid and paratyphoid fever) and brucellosis.

TREATMENT

Aminoglycosides are the mainstay of treatment of tularemia: **gentamicin is the drug of choice for the treatment of tularemia in children**, and streptomycin is the drug of choice in adults. Table 252.3 displays therapeutic options for treatment of tularemia and for postexposure prophylaxis. **Ciprofloxacin is often used for mild (localized) cases**, especially those caused by subsp. *holarctica,* but is less commonly prescribed in children. Doxycycline has been used successfully, but the relapse rate is higher than with aminoglycosides, and so it is not generally recommended. Ciprofloxacin and doxycycline are often used as adjunctive therapy for treatment of tularemia meningitis because of the poor penetration of aminoglycosides in the CSF. Ciprofloxacin can also be considered in cases of moderate/severe disease after initial treatment with an aminoglycoside, if an IV-to-PO switch is warranted based on clinical improvement. β-lactam agents demonstrate poor activity against *F. tularensis* and should not be used.

Therapy with aminoglycosides is typically continued for 7-10 days, but a longer course is needed in more severe disease; 5-7 days may be sufficient for mild cases. Ciprofloxacin treatment is typically 10-14 days, although there is no FDA-approved regimen for tularemia specifically. Treatment with doxycycline should be continued for 14-21 days because of an increased risk of relapse, likely because of its bacteriostatic nature.

PROGNOSIS

Poor outcomes are associated with a delay in appropriate treatment, but with rapid recognition and treatment, fatalities are exceedingly rare. The mortality rate for severe untreated disease (e.g., pneumonia, typhoidal disease) can be as high as 30%. Otherwise, the overall mortality rate is <1%. Subspecies *tularensis* is associated with more aggressive disease and worse outcomes than subsp. *holarctica*.

Relapses are uncommon if aminoglycoside therapy is used. Patients typically defervesce within 24-48 hours after starting therapy, although lymphadenopathy can take several weeks to resolve fully. Late suppuration of involved lymph nodes may occur despite adequate therapy. Patients who have not started on appropriate therapy early may respond more slowly to antimicrobial therapy.

PREVENTION

Prevention of tularemia is based on avoiding exposure. Children living in tick-endemic regions should be taught to avoid tick-infested areas. Families should have a tick control plan for their immediate environment and for their pets. Protective clothing should be worn when entering a tick-infested area. Insect repellents can be used safely

Table 252.3 Recommended Treatment for Children with Tularemia

INDICATION	DRUG AND DOSAGE	DURATION
Moderate-severe disease	Gentamicin 5-7.5 mg/kg/day IV or IM divided every 8-12 hr* *or* Streptomycin 30-40 mg/kg/day IM divided every 12 hr (max 1 g/dose)	≥10 days
Mild disease	Gentamicin 5-7.5 mg/kg/day IV or IM divided every 8-12 hr* *or* Ciprofloxacin 20-40 mg/kg/day PO divided every 12 hr (max 500 mg/dose)	5-7 days 10-14 days
Meningitis	Streptomycin or gentamicin (in doses given for moderate-severe disease) *PLUS* Ciprofloxacin (20-40 mg/kg/day IV divided every 12 hr) *or* Doxycycline 4.4 mg/kg/day IV divided every 12 hr (max 100 mg/dose)	≥10 days
Postexposure prophylaxis	Doxycycline 4.4 mg/kg/day PO divided twice daily (max 100 mg/dose) *or* Ciprofloxacin 20-40 mg/kg/day PO divided twice daily (max 500 mg/dose)	14 days

*Once-daily dosing of gentamicin could be considered, although it has not specifically been studied for this indication.
IM, Intramuscularly; IV, intravenously; PO, per os (i.e., by mouth).

in infants and children. Children should undergo frequent tick checks during and after their time in tick-infested areas. If ticks are found on the child, forceps should be used to pull the tick straight out. The skin should be cleansed before and after this procedure. Children should also be taught to avoid sick and dead animals. Children should be encouraged to wear gloves, masks, and eye protection while cleaning wild game. Further, families should cook wild game thoroughly before eating.

Prophylactic antimicrobial agents are generally not effective in preventing tularemia and should not be used after exposure, with the exception of laboratory or bioterrorism exposures. No tularemia vaccine is currently available to the general public (one is available for high-risk laboratory workers through the Department of Defense). Standard precautions are adequate for hospitalized children with tularemia because no cases of person-to-person transmission have been identified.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 253

Brucella

Kevin J. Downes

Human **brucellosis** is caused by organisms of the genus *Brucella* and continues to be a major public health problem worldwide. Humans are accidental hosts and acquire this **zoonosis** from direct contact with an infected animal (cattle, sheep, camels, goats, and swine) or consumption of products of an infected animal. Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is food-borne and is associated with consumption of unpasteurized dairy products. *Brucella* spp. are also potential agents of bioterrorism (see Chapter 763).

ETIOLOGY

Brucella abortus (cattle), *Brucella melitensis* (goats and sheep), *Brucella suis* (swine), and *Brucella canis* (dogs) are the most common organisms responsible for human disease. These organisms are small, aerobic, non–spore-forming, nonmotile, gram-negative coccobacillary bacteria. *Brucella* spp. are fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars.

EPIDEMIOLOGY

Brucellosis is endemic in many parts of the world and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America. There are approximately 500,000 new cases annually worldwide, although accurate estimates of the prevalence of disease are lacking because of underreporting and underdiagnosis. Childhood brucellosis accounts for 10–30% of cases.

B. melitensis is the most prevalent species causing human brucellosis and is most often carried by sheep, goats, camels, and buffalo. Elk, caribou, bison, deer, moose, and swine can also be infected. Because of improved sanitation and animal vaccination, brucellosis has become rarer in countries with effective public health and domestic animal health programs, although recreational or occupational exposures continue to occur. **Consumption of raw or unpasteurized dairy products** in a child who has lived in or traveled to an endemic area is the key risk factor for pediatric brucellosis because most childhood cases are acquired via ingestion. In the United States in 2010, >50% of cases occurred in California, Arizona, Florida, and Texas. All age-groups can be infected by *Brucella,* and infections are more common in males, likely because of more frequent occupational and recreational exposures.

B. abortus cattle vaccine strain RB51 is a live, attenuated vaccine that has been used to vaccinate cattle in the United States since 1996. Very rare cases of human infection with this vaccine strain have been reported secondary to consumption of unpasteurized milk from vaccinated cows. These strains are resistant to rifampin, a primary agent used in the treatment of brucellosis, so clinicians should consider RB51 in a patient with the correct exposure history.

PATHOGENESIS

Modes of transmission for these organisms include inoculation through cuts or abrasions in the skin, inoculation of the conjunctiva, inhalation of infectious aerosols, or ingestion of contaminated meat or dairy products. **Infected livestock are the most common source of human infection.** In children the primary means of infection is through eating or drinking unpasteurized or raw dairy products. Individuals in endemic areas with occupational exposures to animals, such as farmers, veterinarians, and slaughterhouse workers, are at highest risk; exposure to an infected animal's abortion products or feces are notable risk factors in such occupations. Laboratory workers are more often exposed to infected aerosols. The risk for infection depends on the nutritional and immune status of the host, the route of inoculation, and the species of *Brucella.* For reasons that remain unclear, it has been suggested that *B. melitensis* and *B. suis* are more virulent than *B. abortus* or *B. canis.*

The major virulence factor for *Brucella* spp. appears to be its cell wall lipopolysaccharide (LPS). Strains containing smooth LPS have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes. These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system. Even though *Brucella* spp. are chemotactic for entry of leukocytes into the body, the leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement. *Brucella* spp. possess multiple strategies to evade immune responses and establish and maintain chronic infection. Specifically, during chronic stages of infection, organisms persist within the liver, spleen, lymph nodes, and bone marrow and result in granuloma formation.

Antibodies are produced against the LPS and other cell wall antigens, providing a means of diagnosis and likely playing a role in long-term immunity. The major factor in recovery from infection appears to be development of a cell-mediated immune response, resulting in macrophage activation and enhanced intracellular killing. Specifically, sensitized T lymphocytes release cytokines (e.g., interferon-γ, tumor necrosis factor-α), which activate the macrophages and enhance their intracellular killing capacity.

CLINICAL MANIFESTATIONS

Brucellosis is a systemic illness that can be quite difficult to diagnose in children. Symptoms can be acute or insidious in nature and are usually nonspecific. The incubation period is generally 2-4 weeks but may be shorter with *B. melitensis*. Fever is present in >75% of cases, and the fever pattern can vary widely. The most common physical complaints are arthralgia, myalgia, and back pain. Systemic symptoms, such as fatigue, sweats, chills, anorexia, headache, weight loss, and malaise, are reported in the majority of adult cases but are less frequent in children. Other associated symptoms include abdominal pain, diarrhea, rash, vomiting, cough, and pharyngitis.

The most common physical manifestation of brucellosis is hepatic and splenic enlargement, which is present in approximately half of cases. Whereas arthralgia is common, arthritis occurs in a minority of cases. Arthritis is typically monoarticular and most

often involves the knee or hip in children and the sacroiliac joint in adolescents and adults. Several types of skin lesions have been described with brucellosis, but there is no typical rash for this infection. Epididymo-orchitis also can occur and is more common in adolescents and adults.

In endemic countries, *Brucella* spp. are an important cause of occult bacteremia in young children. Because of the organism's ability to establish chronic infection, hepatic and splenic abscesses may develop. High-grade fever and elevations in liver enzymes are common among children with primary bacteremia. Children with positive blood cultures typically have more acute presentations with increased markers of inflammation (leukocyte count, CRP, ferritin) compared with culture-negative cases. Recurrent episodes of bacteremia can also occur (<10% of cases), especially with inadequate primary treatment. These recurrent episodes are less often associated with fever (40% of cases), potentially indicating the indolent nature of chronic *Brucella* infections in children.

Serious manifestations of brucellosis include endocarditis, meningitis, osteomyelitis, and **spondylitis**. Although headache and malaise may be demonstrated in patients with uncomplicated brucellosis, invasion of the nervous system occurs in only 1–4% of cases. Death from brucellosis is rare, occurring in less than 1% of cases. Neonatal and congenital infections with these organisms have also been described, resulting from transplacental transmission, breast milk, and blood transfusions. The signs and symptoms associated with congenital/neonatal brucellosis are nonspecific.

Hematologic abnormalities are common with brucellosis but occur in less than half of cases; leukopenia is the most common cytopenia to develop. Hemolytic complications can include microangiopathic hemolytic anemia, thrombotic microangiopathy, and autoimmune hemolytic anemia. Secondary cases of hemophagocytic lymphohistiocytosis have also been described after brucellosis in children. Elevations of liver enzymes occur in approximately half of all cases of brucellosis and are more common when bacteremia is present.

DIAGNOSIS

A definitive diagnosis of brucellosis is established by isolating and identifying the organisms from cultures of the blood (most common), bone marrow, or other fluids and tissues. Unfortunately, cultures are insensitive and positive in only a minority of pediatric cases. In a study of 436 children with brucellosis in Israel from 2005 to 2014, 76% had positive blood cultures. However, the prevalence of bacteremia in this cohort, 64% of whom were hospitalized, was much higher than most prior reports, in which less than half of cases have had positive blood cultures. Isolation of the organism from a blood culture sample may require as long as 4 weeks unless the laboratory is using an automated culture system such as the lysis-centrifugation method, where the organism can be recovered in 5-7 days. Therefore it is prudent to alert the clinical microbiology laboratory that brucellosis is suspected, so that cultures can be held longer. Bone marrow cultures may be superior to blood cultures when evaluating patients who have received previous antimicrobial therapy.

In addition to bacterial isolation, various serologic tests have been applied to the diagnosis of brucellosis. Microagglutination or serum (tube) agglutination tests are the most widely used and detect antibodies against *B. abortus, B. melitensis,* and *B. suis*. These methods do not detect antibodies against *B. canis* or *B. abortus* vaccine strain RB51, which lack the smooth LPS; *B. canis*–specific antigen is required to diagnose this species. Antibodies can also be detected by other tests such as enzyme-linked immunosorbent assay (ELISA). The Rose Bengal plate test (RBT) is a rapid agglutination test that is used as a screening test in many endemic regions. It has good sensitivity (>95%) and low cost, but confirmation of RBT results with microbiologic or other serologic tests is advised.

For a diagnosis to be made via serology alone, acute and convalescent samples taken 2-4 weeks apart are recommended; a fourfold or greater rise in titers is diagnostic of an acute infection. No single titer is ever diagnostic, but most patients with acute infections have titers of ≥1:160; lower titers may be present early in the disease course. Immunoglobulin M (IgM) antibodies can generally be detected within a week of illness onset, whereas IgG is detectable 2-4 weeks after infection.

Because patients with active infection have both an IgM and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG is measured by treatment of the serum with 2-mercaptoethanol. This fractionation is important in determining the significance of the antibody titer because low levels of IgM can remain in the serum for weeks to months after the infection has been treated. IgG titers decrease with effective therapy, and a negative 2-mercaptoethanol test after treatment indicates a favorable response.

It is important to remember that all serologic results must be interpreted in light of a patient's history and physical examination. False-positive results from cross-reacting antibodies to other gram-negative organisms, such as *Yersinia enterocolitica, Francisella tularensis,* and *Vibrio cholerae,* can occur. In addition, the prozone effect can give false-negative results in the presence of high titers of antibody. To avoid this issue, serum that is being tested should be diluted to ≥1:320.

The enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests or for the evaluation of patients in the following situations: (1) complicated cases, (2) suspected chronic brucellosis, or (3) reinfection. Polymerase chain reaction assays have been developed but are not available in most clinical laboratories.

Differential Diagnosis

Brucellosis should be considered in the differential diagnosis of fever of unknown origin in endemic areas. It may present similar to other infections such as tularemia, cat scratch disease, malaria, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis. Infections caused by *Mycobacterium tuberculosis,* atypical mycobacteria, rickettsiae, and *Yersinia* can also present similar to brucellosis.

TREATMENT

Many antimicrobial agents are active in vitro against *Brucella* spp., but clinical effectiveness does not always correlate with these results. Agents that provide good intracellular killing are required for elimination of *Brucella* infections. Because of the risk of relapse with monotherapy, combination therapy is generally recommended. Additionally, prolonged therapy (6 weeks or longer) is necessary to ensure an adequate and sustained response.

For uncomplicated infections in children 8 years of age or older, ≥6 weeks of doxycycline in combination with rifampin is recommended (Table 253.1). For children younger than age 8 years, trimethoprim-sulfamethoxazole (TMP-SMX) plus rifampin is advised because of concerns about prolonged tetracycline use in young children. Although data support that the combination of doxycycline plus an aminoglycoside (streptomycin, gentamicin) is superior to the other oral combination therapies, with fewer treatment failures and relapses, the inconvenience of parenteral therapy may limit this approach in uncomplicated cases, particularly in resource-limited settings. Fluoroquinolones may be a viable alternative to doxycycline or TMP-SMX but have not been studied in children.

In more serious infections (e.g., endocarditis, meningitis, osteoarticular infections), three-drug therapy is advised. An aminoglycoside (streptomycin, gentamicin) should be administered for the first 7-14

Table 253.1 Recommended Therapy for Treatment of Brucellosis

AGE/CONDITION	TREATMENT REGIMEN	DURATION
≥8 yr, uncomplicated infection	Doxycycline (PO; 4.4 mg/kg/day, max 200 mg/day) in 2 divided doses	≥6 wk
	plus	
	Rifampin (PO; 15-20 mg/kg/day, max 600-900 mg/day) in 1-2 divided doses	≥6 wk
	Alternative:	
	Doxycycline (PO; 4.4 mg/kg/day, max 200 mg/day) in 2 divided doses	≥6 wk
	plus	
	Streptomycin (IM/IV; 20-40 mg/kg/day, max 1 g/day) in 2-4 divided doses	2-3 wk
	or	
	Gentamicin (IM/IV; 5-7.5 mg/kg/day) once daily*	1-2 wk
<8 yr, uncomplicated infection	Trimethoprim-sulfamethoxazole (PO; trimethoprim: 10 mg/kg/day, max 480 mg/day; sulfamethoxazole: 50 mg/kg/day, max 2.4 g/day) in 2 divided doses	≥6 wk
	plus	
	Rifampin (PO; 15-20 mg/kg/day, max 600-900 mg/day) in 1-2 divided doses	≥6 wk
Complicated infection (meningitis, endocarditis, osteomyelitis, spondylitis)	Streptomycin (IM/IV; 20-40 mg/kg/day, max 1 g/day) in 2-4 divided doses	1-2 wk
	or	
	Gentamicin (IM/IV; 5-7.5 mg/kg/day) once daily*	1-2 wk
	plus	
	Doxycycline (IV/PO; 4.4 mg/kg/day, max 200 mg/day) in 2 divided doses	≥6 wk†
	(Trimethoprim-sulfamethoxazole should be used for children <8 yr of age)	
	plus	
	Rifampin (IV/PO; 15-20 mg/kg/day, max 600-900 mg/day) in 1-2 divided doses	≥6 wk†

*Gentamicin can be given in divided doses if indicated based on age.
†4-6 mo for meningitis or endocarditis.
Note: Because of resistance of *B. abortus* strain RB51 to rifampin, treatment with doxycycline plus trimethoprim-sulfamethoxazole should be used if this isolate is identified.

days of therapy, along with doxycycline (or TMP-SMX) plus rifampin, which are continued for at least 6 weeks. For meningitis and endocarditis, therapy is often continued for 4-6 months. Surgical intervention should be pursued when appropriate, such as when deep tissue abscesses have developed.

If *B. abortus* RB51 (cattle vaccine strain) is identified (or suspected) as the cause of infection, the use of rifampin should be avoided. This is because the strain was derived by selection in rifampin-enriched media and is thus inherently resistant to rifampin. As a result, a combination of doxycycline and TMP-SMX should be used as treatment.

Although relapse occurs in approximately 5–15% of cases, antimicrobial resistance is rare. Relapse is confirmed by isolation of *Brucella* within weeks to months after therapy has ended. Prolonged treatment is the key to preventing disease relapse, and steps should be taken to assure compliance with the long courses of therapy needed to achieve eradication.

PROGNOSIS

The primary indication of clinical response is resolution of symptoms, which may be slow; the average time to defervescence is 4-5 days. The prognosis after therapy is excellent if patients are compliant with the prolonged therapy. Patients should be followed clinically and serologically for 1-2 years. Before the use of antimicrobial agents, the course of brucellosis was often prolonged and associated with death. Since the institution of specific therapy, most deaths are a result of specific organ system involvement (e.g., endocarditis) in complicated cases. Initiation of antimicrobial therapy may precipitate a Jarisch-Herxheimer–like reaction, presumably because of a large antigen load, but these reactions are rarely associated with serious complications.

PREVENTION

Prevention of brucellosis depends on effective eradication of the organism from livestock. Pasteurization of milk and dairy products for human consumption remains an important aspect of prevention. It should be noted that certification of raw milk does not eliminate the risk of brucellosis acquisition. No vaccine currently exists for use in children, and therefore education of the public continues to have a prominent role in the prevention of brucellosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 254

Legionella

Jeffrey S. Gerber

Legionellosis comprises **Legionnaires' disease** (*Legionella* pneumonia), other invasive extrapulmonary *Legionella* infections, and an acute flulike illness known as **Pontiac fever**. In contrast to the syndromes associated with invasive disease, Pontiac fever is a self-limited illness that develops after aerosol exposure and may represent a toxic or hypersensitivity response to *Legionella.*

ETIOLOGY

Legionellaceae are aerobic, non–spore-forming, nonencapsulated, gram-negative bacilli that stain poorly with Gram stain when performed on smears from clinical specimens. Stained smears of *Legionella pneumophila* taken from colonial growth resemble *Pseudomonas.* Unlike other *Legionella* species, *Legionella micdadei* stains acid fast. Although more than 60 species of the genus have now been identified, the majority (90%) of clinical infections are caused by *L. pneumophila,* and most of the remainder are caused by *L. micdadei, L. bozemanii, L. dumoffii,* and *L. longbeachae.*

The organisms are fastidious and require L-cysteine, ferric ion, and α-keto acids for growth. Colonies develop within 3-5 days on buffered charcoal yeast extract agar, which may contain selected antibiotics to inhibit overgrowth by other microorganisms; *Legionella* rarely grows on routine laboratory media.

EPIDEMIOLOGY

The environmental reservoir of *Legionella* in nature is freshwater (lakes, streams, thermally polluted waters, potable water), and invasive pneumonia (Legionnaires' disease) is related to exposure to human-made water systems (plumbing, showerheads, cooling towers, certain medical devices, decorative fountains, hot tubs) via aerosols containing the bacteria. Growth of *Legionella* occurs more readily in warm water, and exposure to warm-water sources is an important risk factor for disease. Epidemic and sporadic cases (most common) of community-acquired Legionnaires' disease can be attributed to potable water in the local environment of the patient. Risk factors for acquisition of sporadic community-acquired pneumonia include exposure to cooling towers, nonmunicipal water supply, residential plumbing repairs, and lower water heater temperatures, which facilitate growth of bacteria or lead to release of a bolus of biofilm containing *Legionella* into potable water. The mode of transmission may be by inhalation of aerosols or by microaspiration. Outbreaks of Legionnaires' disease have been associated with protozoa in the implicated water source; replication within these eukaryotic cells presumably amplifies and maintains *Legionella* within the potable-water distribution system or in cooling towers. Outbreaks of community-acquired pneumonia and some nosocomial outbreaks have been linked to common sources, including hot water heaters, evaporative condensers, cooling towers, whirlpool baths, water births, humidifiers, and nebulizers. Travel-associated Legionnaires' disease and Pontiac fever are increasingly recognized in major outbreaks. Although person-to-person transmission has been reported, if it does occur, it is extremely rare.

Hospital-acquired infections are most often linked to potable water. Exposure may occur through three general mechanisms: (1) inhalation of contaminated water vapor through artificial ventilation; (2) aspiration of ingested microorganisms, including those in gastric feedings that are mixed with contaminated tap water; and (3) inhalation of aerosols from showers, sinks, and fountains. Extrapulmonary legionellosis may occur through topical application of contaminated tap water into surgical or traumatic wounds. In contrast to Legionnaires' disease, Pontiac fever outbreaks have occurred through exposure to aerosols from whirlpool baths and ventilation systems.

The incidence of legionellosis in the United States continues to rise, and nearly 10,000 cases were reported to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System in 2018. Because this is a passive reporting system, these are likely underestimates of the incidence of disease, which is estimated to occur at least twice as often as reported. An active laboratory-based and population-based surveillance system for tracking *Legionella* infections was recently launched by CDC, which will help to better assess its true incidence and epidemiology. (For up-to-date information, see https://www.cdc.gov/legionella/.)

Legionellosis demonstrates geographic differences, and the vast majority of cases are classified as Legionnaires' disease (99.5%), with a small fraction as Pontiac fever (0.5%). *Legionella* infections are reported most frequently in fall and summer, and recent studies show an association with total monthly rainfall and humidity. Approximately 0.5–5.0% of those exposed to a common source develop pneumonia, whereas the attack rate in Pontiac fever outbreaks is very high (85–100%). Although *Legionella* is associated with 0.5–10% of pneumonia cases in adults, it is a rare cause of pneumonia in children, accounting for <1% of cases; however, infrequent testing for *Legionella* might underestimate its prevalence. Acquisition of antibodies to *L. pneumophila* in healthy children occurs progressively over time, although these antibodies presumably reflect subclinical infection, mild respiratory disease, or antibodies that cross-react with other bacterial species. Community-acquired Legionnaires' disease in children is increasingly reported (1.7% of reported cases), and most cases occur in children 15-19 years old, followed by infants. The incidence in infants is reported to be 0.11 per 100,000. Legionnaires' disease is particularly severe in neonates. The epidemiology of hospital-acquired Legionnaires' disease in children is derived almost exclusively from case reports, so the true incidence of this entity is unknown.

PATHOGENESIS

Although *Legionella* can be grown on artificial media, the intracellular environment of eukaryotic cells provides the definitive site of growth. *Legionella* organisms are facultative intracellular parasites of eukaryotic cells. In nature, *Legionella* replicate within protozoa found in freshwater. In humans, the main target cell for *Legionella* is the alveolar macrophage, although other cell types may also be invaded. After entry, virulent strains of *L. pneumophila* stimulate the formation of a special phagosome that permits bacterial replication to proceed. The phagosome consists of components of the endoplasmic reticulum and escapes the degradative lysosomal pathway. Growth in macrophages occurs to the point of cell death, followed by reinfection of new cells, until these cells are activated and can subsequently kill intracellular microorganisms. Acute, severe infection of the lung provokes an acute inflammatory response and necrosis. Early on, more bacteria are found in extracellular spaces as a result of intracellular replication, lysis, and release of bacteria. Subsequently, macrophage activation and other immune responses produce intense infiltration of tissue by macrophages that contain intracellular bacteria, ultimately leading to control of bacterial replication and killing.

Corticosteroid therapy poses a high risk for infection by interfering with T-cell and macrophage function. Although community-acquired Legionnaires' disease may occur in healthy, immunocompetent patients without other comorbid conditions, those who have defects in cellular-mediated immunity are at higher risk for infection. As in other diseases caused by facultative intracellular microorganisms, the outcome is critically dependent on the specific and nonspecific immune responses of the host, particularly macrophage and T-cell responses.

Risk factors for Legionnaires' disease in adults include chronic diseases of the lung (smoking, bronchitis), older age, diabetes, renal failure, immunosuppression associated with organ transplantation, corticosteroid therapy, and episodes of aspiration. In surveys of community-acquired infection, a significant number of adults have no identified risk factors. The number of reported cases of community-acquired Legionnaires' disease in children is small. Among these cases, immunocompromised status, especially corticosteroid treatment, coupled with exposure to contaminated potable water, is the major risk factor.

Infection in a few children with chronic pulmonary disease without immune deficiency has also been reported, but infection in children lacking any risk factors is uncommon. The modes of transmission of community-acquired disease in children include exposure to mists, freshwater, water coolers, and other aerosol-generating apparatuses. Nosocomial *Legionella* infection has been reported more frequently than community-acquired disease in children and usually occurs in those who are immunocompromised (e.g., stem cell transplants, solid organ transplants), those with structural lung disease, or neonates receiving mechanical ventilation. The modes of acquisition include **microaspiration**, frequently associated with nasogastric tubes, and **aerosol inhalation**. Bronchopulmonary *Legionella* infections are reported in patients with cystic fibrosis and have been associated with aerosol therapy or mist tents. Legionnaire's disease is also reported in children with asthma and tracheal stenosis. Chronic corticosteroid therapy for asthma is a reported risk factor for *Legionella* infections in children.

CLINICAL MANIFESTATIONS

Legionnaires' disease was originally believed to cause atypical pneumonia associated with extrapulmonary symptoms and laboratory abnormalities, including diarrhea, confusion, hyponatremia, hypophosphatemia, abnormal liver function studies, and evidence of renal dysfunction. Although a subset of patients may exhibit these classic manifestations, *Legionella* infection typically causes pneumonia that is indistinguishable from pneumonia produced by other infectious agents. The incubation period for Legionnaires' disease is typically between 2 and 10 days, though it occasionally can be 3-4 weeks. Fever, cough, and chest pain are common presenting symptoms; the cough may be productive of purulent sputum or may be nonproductive. Although the classic chest radiographic appearance demonstrates rapidly progressive alveolar filling infiltrates, the chest radiographic appearance is widely variable, with tumor-like shadows, evidence of nodular infiltrates, unilateral or bilateral infiltrates, or cavitation, although cavitation is rarely seen in immunocompetent patients. This picture overlaps substantially with disease caused by *Streptococcus pneumoniae.* Although pleural effusion is less often associated with Legionnaires' disease, its frequency varies so widely that neither the presence nor absence of effusion is helpful in the differential diagnosis.

Most reports of nosocomial *Legionella* pneumonia in children demonstrate the following clinical features: rapid onset, temperature >38.5°C (101.3°F), cough, pleuritic chest pain, tachypnea, and dyspnea. Abdominal pain, headache, and diarrhea are also common. Chest radiographs reveal lobar consolidations or diffuse bilateral infiltrates, and pleural effusions may be noted. Usually there is no clinical response to broad-spectrum β-lactam (penicillins and cephalosporins) or aminoglycoside antibiotics. Concomitant infection with other pathogens, including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae,* occurs in 5–10% of cases of Legionnaires' disease; therefore, detection of another potential pulmonary pathogen does not preclude the diagnosis of legionellosis.

Pontiac Fever

Pontiac fever in adults and children is characterized by a shorter incubation period (1-3 days) followed by high fever, myalgia, headache, and extreme debilitation, lasting for 3-5 days. Cough, breathlessness, diarrhea, confusion, and chest pain may occur, but there is no evidence for invasive infection. The disease is self-limited without sequelae. Virtually all exposed individuals seroconvert to *Legionella* antigens. A very large outbreak in Scotland that affected 35 children was attributed to *L. micdadei,* which was isolated from a whirlpool spa. The onset of illness was 1-7 days (median: 3 days), and all exposed children developed significant titers of specific antibodies to *L. micdadei.* The pathogenesis of Pontiac fever is not known. In the absence of evidence of true infection, the most likely hypothesis is that this syndrome is caused by a toxic or hypersensitivity reaction to microbial antigens.

DIAGNOSIS

Culture of *Legionella* from sputum, other respiratory tract specimens, blood, or tissue is the gold standard against which indirect methods of detection should be compared. If present, pleural fluid should be obtained for culture. Specimens obtained from the respiratory tract that are contaminated with oral flora must be treated and processed to reduce contaminants and plated onto selective media. Because these are costly and time-consuming methods, many laboratories do not process specimens for culture.

The urinary antigen assay that detects *L. pneumophila* serogroup I has revolutionized the diagnosis of *Legionella* infection and has 80% sensitivity and 99% specificity. The assay is a useful method in the prompt diagnosis of Legionnaires' disease caused by this serogroup, which accounts for the majority of symptomatic infections. In the United States, this test is frequently used because it is widely available in reference laboratories. Where available, polymerase chain reaction (PCR) is used to identify *L. pneumophila* from bronchoscopic lavage and other clinical specimens to the exclusion of other respiratory pathogens. Other methods, including direct immunofluorescence, have low sensitivity and are generally not employed. Serological testing is of little clinical utility, as seroconversion may not occur for several weeks after the onset of infection, the available serologic assays do not detect all strains of *L. pneumophila* or all species, and cross reactivity occurs with several other gram-negative organisms.

In view of the low sensitivity of direct detection and the slow growth of the microorganism in culture, multiple diagnostics (culture, urine antigen, PCR if available) should be sent simultaneously and empiric antibiotic therapy considered when there is suggestive clinical evidence, including the lack of response to usual antibiotics.

TREATMENT

In community-acquired pneumonia in adults who are hospitalized, guidelines recommend empiric treatment with a β-lactam plus a macrolide or quinolone for treatment of atypical microorganisms *(Legionella, C. pneumoniae, M. pneumoniae).* Evidence-based guidelines for management of community-acquired pneumonia in children typically do not include *Legionella* in the differential diagnosis or empiric treatment recommendations. Effective treatment of Legionnaires' disease is based in part on the intracellular concentration of antibiotics. **Azithromycin** or the **quinolones** (ciprofloxacin and levofloxacin) have generally replaced erythromycin as therapy for patients with diagnosed *Legionella* infection. **Doxycycline** is an acceptable alternative. In serious infections or in high-risk patients, parenteral therapy is recommended initially, although oral conversion is favored when tolerated, particularly because of the generally high bioavailability of oral macrolides, quinolones, and tetracyclines. The duration of antibiotic therapy for Legionnaires' disease in adults is typically for a minimum of 5 days, although therapy may be continued for 10-14 days in more seriously ill or immunocompromised patients. Treatment of extrapulmonary infections, including prosthetic valve endocarditis and sternal wound infections, may require prolonged therapy. In vitro data and case reports suggest that trimethoprim-sulfamethoxazole may also be effective. A large, retrospective study of hospitalized adults with *Legionella* pneumonia found no difference in mortality between those treated with azithromycin and with quinolones. The role of combination therapy is unknown. Antibiotic treatment for Pontiac fever is not recommended.

PROGNOSIS

The mortality rate for community-acquired Legionnaires' disease in adults who are hospitalized is approximately 15% but may exceed 50% in immunocompromised patients, although reporting bias might inflate these estimates. Precise estimates for children are unknown. The prognosis depends on underlying host factors and possibly on the duration of illness before initiation of appropriate therapy. Despite appropriate antibiotic therapy, patients may succumb to respiratory complications, such as acute respiratory distress syndrome. A high mortality rate is noted in case reports of premature infants and children, virtually all of whom have been immunocompromised. Delay in diagnosis is also associated with increased mortality. Consequently, *Legionella* should be considered in the differential diagnosis of both community-acquired and nosocomial pneumonia in children, especially in cases refractory to empirical therapy or with epidemiologic risk factors for legionellosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 255

Bartonella

Rachel C. Orscheln

The spectrum of disease resulting from human infection with *Bartonella* species includes the association of **bacillary angiomatosis** and **cat scratch disease** with *Bartonella henselae.* There are more than 30 validated species of *Bartonella,* but six major species are responsible for most human disease: *B. henselae, B. quintana, B. bacilliformis, B. elizabethae, B. vinsonii,* and *B. clarridgeiae* (Table 255.1). The remaining *Bartonella* spp. have been found primarily in animals, particularly rodents and moles. However, zoonotic infections from animal-associated strains of *Bartonella* spp. have been reported. In 2013 a novel *Bartonella* agent with the proposed name *Candidatus* Bartonella ancashi *(Bartonella ancashensis)* was described as a cause of **verruga peruana**.

Members of the genus *Bartonella* are gram-negative, oxidase-negative, fastidious, aerobic rods that ferment no carbohydrates. *B. bacilliformis* is the only species that is motile, achieving motility by means of polar flagella. Optimal growth is obtained on fresh media containing ≥5% sheep or horse blood in the presence of 5% carbon dioxide. The use of lysis centrifugation for specimens from blood followed by cultivation on chocolate agar for extended periods (2-6 weeks) enhances recovery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

255.1 Cat Scratch Disease *(Bartonella henselae)*

Rachel C. Orscheln

The most common presentation of *Bartonella* infection is cat scratch disease (**CSD**), which is a subacute, regional lymphadenitis caused most frequently by *B. henselae*. CSD is the most common cause of chronic lymphadenitis that persists for >3 weeks.

ETIOLOGY

B. henselae can be cultured from the blood of healthy cats. *B. henselae* organisms are the small, pleomorphic, gram-negative bacilli visualized with Warthin-Starry stain in affected lymph nodes from patients with CSD. Development of serologic tests that showed prevalence of antibodies in 84–100% of cases of CSD, culturing of *B. henselae* from CSD nodes, and detection of *B. henselae* by polymerase chain reaction (PCR) in the majority of lymph node samples and pus from patients with CSD confirmed the organism as the cause. Occasional cases of CSD may be caused by other organisms, including *B. clarridgeiae, B. grahamii*, *B. alsatica,* and *B. quintana*.

EPIDEMIOLOGY

CSD is common, with >24,000 estimated cases per year in the United States. *B. henselae* is transmitted most frequently by cutaneous inoculation through the bite or scratch of a cat. However, transmission may occur through other routes, such as flea bites. Most patients (87–99%) with CSD have had contact with cats, many of which are kittens <6 months old, and >50% of patients have a definite history of a cat scratch or bite. Cats have high-level bacteremia with *Bartonella* spp. for months without any clinical symptoms; kittens are more frequently bacteremic than adult cats. Transmission between cats occurs through the cat flea, *Ctenocephalides felis.* In temperate zones, most cases occur between September and March, perhaps in relation to the seasonal breeding of domestic cats or to the close proximity of family pets in the fall and winter. In tropical zones, there is no seasonal prevalence. Distribution is worldwide, and infection occurs in all races.

Cat scratches appear to be more common among children, and males are affected more often than females. CSD is a sporadic illness; usually only one family member is affected, even though many siblings play with the same kitten. However, clusters do occur, with family cases within weeks of one another. Anecdotal reports have implicated other sources, such as dog scratches, wood splinters, fishhooks, cactus spines, and porcupine quills.

PATHOGENESIS

The pathologic findings in the primary inoculation **papule** and affected lymph nodes are similar. Both show a central avascular, necrotic area with surrounding lymphocytes, giant cells, and histiocytes. Three stages of involvement occur in affected nodes, sometimes simultaneously in the same node. The first stage consists of generalized enlargement with thickening of the cortex and hypertrophy of the germinal center and with a predominance of lymphocytes. Epithelioid granulomas with Langerhans giant cells are scattered throughout the node. The second stage is characterized by granulomas that increase in density, fuse, and become infiltrated with polymorphonuclear leukocytes, with beginning central necrosis. In the third stage, necrosis progresses with formation of large, pus-filled sinuses. This purulent material may rupture into surrounding tissue. Similar granulomas have been found in the liver, spleen, and osteolytic lesions of bone when those organs are involved.

Table 255.1 *Bartonella* Species Causing the Majority of Human Disease

DISEASE	ORGANISM	VECTOR	PRIMARY RISK FACTOR
Bartonellosis (Carrión disease)	*B. bacilliformis*	Sandfly *(Lutzomyia verrucarum)*	Living in endemic areas (Andes Mountains)
Cat scratch disease	*B. henselae* *B. clarridgeiae*	Cat	Cat scratch or bite
Trench fever	*B. quintana*	Human body louse	Body louse infestation during outbreak
Bacteremia, endocarditis	*B. henselae* *B. elizabethae* *B. vinsonii* *B. quintana*	Cat for *B. henselae* Rat for *B. elizabethae* Vole for *B. vinsonii* Human body louse for *B. quintana*	Severe immunosuppression
Bacillary angiomatosis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Peliosis hepatis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression

CLINICAL MANIFESTATIONS

After an incubation period of 7-12 days (range: 3-30 days), one or more 3- to 5-mm red papules develop at the site of cutaneous inoculation, often reflecting a linear cat scratch. These lesions are often overlooked because of their small size but are found in at least 65% of patients when careful examination is performed (Fig. 255.1). Lymphadenopathy is generally evident within 1-4 weeks (Fig. 255.2). **Chronic regional lymphadenitis** is the hallmark, affecting the first or second set of nodes draining the entry site. Affected lymph nodes in order of frequency include the axillary, cervical, submandibular, preauricular, epitrochlear, femoral, and inguinal nodes. Involvement of one or more groups of nodes occurs in 10–20% of patients, although at a given site, half the cases involve several nodes.

Nodes involved are usually tender and have overlying erythema but without cellulitis. They usually range between 1 and 5 cm in size, although they can become much larger. From 10% to 40% eventually suppurate. The duration of enlargement is usually 1-2 months, with persistence up to 1 year in rare cases. Fever occurs in approximately 30% of patients, usually 38–39°C (100.4–102.2°F). Other nonspecific symptoms, including malaise, anorexia, fatigue, and headache, affect less than one third of patients. Transient rashes, which may occur in approximately 5% of patients, are mainly truncal maculopapular rashes. Erythema nodosum, erythema multiforme, and erythema annulare have also been reported.



Fig. 255.1 A child with typical cat scratch disease demonstrating the original scratch injuries and the primary papule that soon thereafter developed proximal to the middle finger. *(Courtesy Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*



Fig. 255.2 Right axillary lymphadenopathy followed the scratches and development of a primary papule in this child with typical cat scratch disease. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2006:2737.)*

CSD is usually a self-limited infection that spontaneously resolves within a few weeks to months. The most common ocular presentation of CSD is **Parinaud oculoglandular syndrome**, which is unilateral conjunctivitis followed by preauricular lymphadenopathy and occurs in 5% of patients with CSD (Fig. 255.3). Direct eye inoculation as a result of rubbing with the hands after cat contact is the presumed mode of spread. A conjunctival granuloma may be found at the inoculation site. The involved eye is usually not painful and has little or no discharge but may be quite red and swollen. Submandibular or cervical lymphadenopathy may also occur.

More severe, disseminated illness occurs up to 14% of patients and is characterized by presentation with high fever, often persisting for several weeks. Other prominent symptoms include significant abdominal pain and weight loss. **Hepatosplenomegaly** may occur, although hepatic dysfunction is rare (Fig. 255.4). Granulomatous changes may be seen in the liver and spleen. Another common site of dissemination is bone, with the development of multifocal **granulomatous osteolytic lesions** associated with localized pain but without erythema,

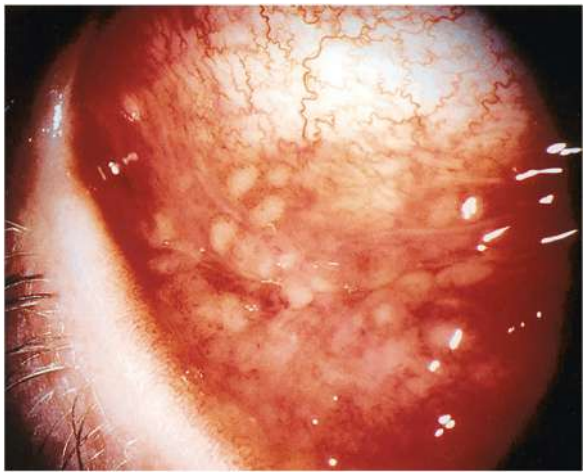

Fig. 255.3 The granulomatous conjunctivitis of Parinaud oculoglandular syndrome is associated with ipsilateral local lymphadenopathy, usually preauricular and, less often, submandibular. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2006:2739.)*

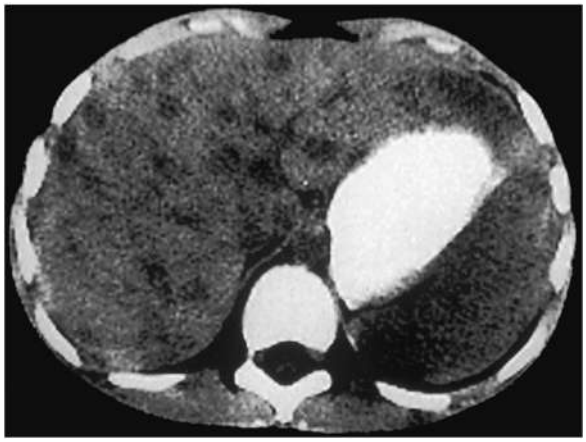

Fig. 255.4 In this CT scan of a patient with hepatic involvement of cat scratch disease, the absence of enhancement of the multiple lesions after contrast infusion is consistent with the granulomatous inflammation of this entity. Treated empirically with various antibiotics without improvement before establishment of this diagnosis, the patient subsequently recovered fully with no further antimicrobial therapy. *(Courtesy Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

tenderness, or swelling. Other uncommon manifestations are neuroretinitis with papilledema and stellate macular exudates, encephalitis, endocarditis, and atypical pneumonia.

DIAGNOSIS

In most cases the diagnosis can be strongly suspected on clinical grounds in a patient with history of exposure to a cat. Serologic testing can be used to confirm the diagnosis. Most patients have elevated IgG antibody titers at presentation. However, the IgM response to *B. henselae* has frequently resolved by the time testing is considered. There is cross reactivity among *Bartonella* spp., particularly *B. henselae* and *B. quintana*.

If tissue specimens are obtained, bacilli may be visualized with Warthin-Starry and Brown-Hopps tissue stains. *Bartonella* DNA can be identified through PCR analysis of tissue specimens. Culturing of the organism is not generally practical for clinical diagnosis. Next-generation sequencing and 16S rRNA sequencing have been used to identify *Bartonella* species on tissue that is fresh or formalin-fixed, as well as on body fluids other than blood.

Differential Diagnosis

The differential diagnosis of CSD includes virtually all causes of lymphadenopathy (see Chapter 539). The more common entities include pyogenic (suppurative) lymphadenitis, primarily from staphylococcal or streptococcal infections, atypical mycobacterial infections, and malignancy. Less common entities are tularemia, brucellosis, and sporotrichosis. Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* infections usually cause more generalized lymphadenopathy.

LABORATORY FINDINGS

Routine laboratory tests are not helpful. The erythrocyte sedimentation rate is often elevated. The white blood cell count may be normal or mildly elevated. Hepatic transaminases are often normal but may be elevated in systemic disease. Ultrasonography or CT may reveal many granulomatous nodules in the liver and spleen; the nodules appear as hypodense, round, irregular lesions and are usually multiple. However, CSD presenting as a solitary splenic lesion has been reported.

TREATMENT

Antibiotic treatment of CSD is not always needed and is not clearly beneficial. For most patients, treatment consists of conservative symptomatic care and observation. Studies show a significant discordance between in vitro activity of antibiotics and clinical effectiveness. For many patients, diagnosis is considered in the context of failure to respond to β-lactam antibiotic treatment of presumed staphylococcal lymphadenitis.

A small prospective study of oral azithromycin (500 mg on day 1, then 250 mg on days 2-5; for smaller children, 10 mg/kg/24 hr on day 1 and 5 mg/kg/24 hr on days 2-5) showed a decrease in initial lymph node volume in 50% of patients during the first 30 days, but after 30 days there was no difference in lymph node volume. No other clinical benefit was found. For the majority of patients, CSD is self-limited, and resolution occurs over weeks to months without antibiotic treatment. Azithromycin, clarithromycin, trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, ciprofloxacin, and gentamicin appear to be the best agents if treatment is considered.

Suppurative lymph nodes that become tense and extremely painful may require surgical drainage for both therapeutic and diagnostic purposes.

Children with hepatosplenic CSD appear to respond well to treatment with azithromycin with or without the addition of rifampin.

COMPLICATIONS

Encephalopathy can occur in as many as 5% of patients with CSD and typically manifests 1-3 week after the onset of lymphadenitis as the sudden onset of neurologic symptoms, which often include seizures, combative or bizarre behavior, and altered level of consciousness. Imaging studies are generally normal. The cerebrospinal fluid is normal or shows minimal pleocytosis and protein elevation. Recovery occurs without sequelae in almost all patients but may take place slowly over many months.

Other neurologic manifestations include peripheral facial nerve paralysis, myelitis, radiculitis, compression neuropathy, and cerebellar ataxia. One patient has been reported to have encephalopathy with persistent cognitive impairment and memory loss.

Stellate macular retinopathy is associated with several infections, including CSD. Children and young adults present with unilateral or, rarely, bilateral loss of vision with central scotoma, optic disc swelling, and macular star formation from exudates radiating out from the macula. The findings usually resolve completely, with recovery of vision, generally within 2-3 months. The optimal treatment for the neuroretinitis is unknown, although treatment of adults with doxycycline and rifampin for 4-6 weeks has had good results.

Hematologic manifestations include hemolytic anemia, thrombocytopenic purpura, nonthrombocytopenic purpura, and eosinophilia. **Leukocytoclastic vasculitis**, similar to Henoch-Schönlein purpura, has been reported in association with CSD in one child. A systemic presentation of CSD with pleurisy, arthralgia or arthritis, mediastinal masses, enlarged nodes at the head of the pancreas, and atypical pneumonia also has been reported.

PROGNOSIS

The prognosis for CSD in a normal host is generally excellent, with resolution of clinical findings over weeks to months. Recovery is occasionally slower and may take as long as 1 year.

PREVENTION

Person-to-person spread of *Bartonella* infections is not known. Isolation of the affected patient is not necessary. Prevention would require elimination of cats from households, which is not practical or necessarily desirable. Awareness of the risk of cat (and particularly kitten) scratches should be emphasized to parents. Cat scratches or bites should be washed immediately. Cat flea control is helpful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

255.2 Bartonellosis (*Bartonella bacilliformis*)

Rachel C. Orscheln

The first human *Bartonella* infection described was **bartonellosis**, a geographically distinct disease caused by *B. bacilliformis*. There are two predominant forms of illness caused by *B. bacilliformis*: **Oroya fever**, a severe, febrile hemolytic anemia, and **verruca peruana** (verruga peruana), an eruption of hemangioma-like lesions. *B. bacilliformis* also causes asymptomatic infection. Bartonellosis is also called **Carrión disease**.

ETIOLOGY

B. bacilliformis is a small, motile, gram-negative organism with a brush of ≥10 unipolar flagella, which appear to be important components for invasiveness. An obligate aerobe, it grows best at 28°C (82.4°F) in semisolid nutrient agar containing rabbit serum and hemoglobin.

EPIDEMIOLOGY

Bartonellosis is a zoonosis found only in mountain valleys of the Andes Mountains in Peru, Ecuador, Colombia, Chile, and Bolivia at altitudes and environmental conditions favorable for the vector, which is the **sandfly**, *Lutzomyia verrucarum*.

PATHOGENESIS

After the sandfly bite, *Bartonella* organisms enter the endothelial cells of blood vessels, where they proliferate. Found throughout the reticuloendothelial system, they then reenter the bloodstream and parasitize erythrocytes. They bind on the cells, deform the membranes, and then enter intracellular vacuoles. The resultant hemolytic anemia may involve as many as 90% of circulating erythrocytes. Patients who survive this acute phase may or may not experience the cutaneous manifestations, which are nodular hemangiomatous lesions or verrucae ranging in size from a few millimeters to several centimeters.

CLINICAL MANIFESTATIONS

The incubation period is 2-14 weeks. Patients may be totally asymptomatic or may have nonspecific symptoms such as headache and malaise without anemia.

Oroya fever is characterized by fever with rapid development of anemia. Clouding of the sensorium and delirium are common symptoms and may progress to overt psychosis. Physical examination demonstrates signs of severe hemolytic anemia, including icterus and pallor, sometimes in association with generalized lymphadenopathy.

In the preeruptive stage of **verruca peruana** (Fig. 255.5), patients may complain of arthralgias, myalgias, and paresthesias. Inflammatory reactions such as phlebitis, pleuritis, erythema nodosum, and encephalitis may develop. The appearance of verrucae is pathognomonic of the eruptive phase. Lesions vary greatly in size and number.

DIAGNOSIS

The diagnosis of bartonellosis is established on clinical grounds in conjunction with a blood smear demonstrating organisms or with blood culture. The anemia is macrocytic and hypochromic, with reticulocyte counts as high as 50%. *B. bacilliformis* may be seen on Giemsa stain preparation as red-violet rods in the erythrocytes. In the recovery phase, organisms change to a more coccoid form and disappear from the blood. In the absence of anemia, the diagnosis depends on blood cultures. In the eruptive phase, the typical verruca confirms the diagnosis. Antibody testing has been used to document infection.



Fig. 255.5 A single large lesion of verruca peruana on the leg of an inhabitant of the Peruvian Andes. Such lesions are prone to superficial ulceration, and their vascular nature may lead to copious bleeding. Ecchymosis of the skin surrounding the lesion is also evident. *(Courtesy Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City.)*

TREATMENT

B. bacilliformis is sensitive to many antibiotics, including rifampin, tetracycline, and chloramphenicol. Treatment is highly effective in rapidly diminishing fever and eradicating the organism from the blood. **Chloramphenicol** (50-75 mg/kg/day) is considered the drug of choice because it is also useful in the treatment of concomitant infections such as *Salmonella.* Fluoroquinolones are used successfully as well. Blood transfusions and supportive care are critical in patients with severe anemia. Antimicrobial treatment for verruca peruana is considered when there are >10 cutaneous lesions, if the lesions are erythematous or violaceous, or if the onset of the lesions was <1 month before presentation. Oral rifampin is effective in the healing of lesions. Surgical excision may be needed for lesions that are large and disfiguring or that interfere with function.

PREVENTION

Prevention depends on avoidance of the vector, particularly at night, by the use of protective clothing and insect repellents (see Chapter 218).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

255.3 Trench Fever *(Bartonella quintana)*

Rachel C. Orscheln

ETIOLOGY

The causative agent of trench fever was first designated *Rickettsia quintana,* was then assigned to the genus *Rochalimaea,* and now has been reassigned as *Bartonella quintana.*

EPIDEMIOLOGY

Trench fever was first recognized as a distinct clinical entity during World War I, when more than a million troops in the trenches were infected. Infection with *B. quintana* is currently rare in the United States and primarily occurs in the setting of conditions favorable to body lice infestations, such as homelessness, crowding, and poor sanitation. When pooled samples of head and body lice have been collected from homeless populations, up to 33% of individuals have lice pools that test positive for *B. quintana.*

Humans are the only known reservoir. No other animal is naturally infected, and usual laboratory animals are not susceptible. The **human body louse**, *Pediculus humanus* var. *corporis,* is the vector and is capable of transmission to a new host 5-6 days after feeding on an infected person. Lice excrete the organism for life; transovarian passage does not occur. Humans may have prolonged asymptomatic bacteremia for years.

CLINICAL MANIFESTATIONS

The incubation period for trench fever averages about 22 days (range: 4-35 days). The clinical presentation is highly variable. Symptoms can be very mild and brief. About half of infected persons have a single febrile illness with abrupt onset lasting 3-6 days. In other patients, prolonged, sustained fever may occur. More commonly, patients have periodic febrile illness with three to eight episodes lasting 4-5 days each, sometimes occurring over 1 year or more. This form is reminiscent of malaria or **relapsing fever** *(Borrelia recurrentis).* Afebrile bacteremia can occur.

Clinical findings usually consist of fever (typically with a temperature of 38.5–40°C [101.3–104°F]), malaise, chills, sweats, anorexia, and severe headache. Common findings include marked conjunctival injection, tachycardia, myalgias, arthralgias, and severe pain in the neck, back, and legs. Crops of erythematous macules or papules may occur on the trunk on as many as 80% of patients. Splenomegaly and mild liver enlargement may be noted.

DIAGNOSIS

In nonepidemic situations, it is impossible to establish a diagnosis of trench fever on clinical grounds because the findings are not distinctive. A history of body louse infection or having been in an area of epidemic disease should heighten suspicions. *B. quintana* can be cultured from the blood with modification to include culture on epithelial cells. Serologic tests for *B. quintana* are available, but there is cross-reaction with *B. henselae*.

TREATMENT

There are no controlled trials of treatment, but bacteremia with *Bartonella* treated with a combination of gentamicin and doxycycline increases the rate of cure compared with other regimens, such as doxycycline or β-lactam antibiotics alone.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

255.4 Bacillary Angiomatosis and Bacillary Peliosis Hepatis (*Bartonella henselae* and *Bartonella quintana*)

Rachel C. Orscheln

Both *B.henselae* and *B.quintana* cause vascular proliferative disease in severely immunocompromised persons, primarily adult patients with acquired immune deficiency syndrome (AIDS), persons receiving cancer chemotherapy, and organ transplant recipients. The subcutaneous and lytic bone lesions of bacillary angiomatosis can be caused by infection with either *B. henselae* or *B. quintana*. The lesions of peliosis hepatis are almost exclusively associated with *B. henselae*.

BACILLARY ANGIOMATOSIS

Lesions of cutaneous bacillary angiomatosis, also known as **epithelioid angiomatosis**, are the most easily identified and recognized form of *Bartonella* infection in immunocompromised hosts. They are found primarily in patients with AIDS who have very low CD4 counts. The clinical appearance can be quite diverse. The vasoproliferative lesions of bacillary angiomatosis may be cutaneous or subcutaneous and may resemble the vascular lesions (verruca peruana) of *B. bacilliformis* in immunocompetent persons, characterized by erythematous papules on an erythematous base with a collarette of scale. They may enlarge to form large, pedunculated lesions and may ulcerate. Trauma may result in profuse bleeding.

Bacillary angiomatosis may be clinically indistinguishable from Kaposi sarcoma. Other considerations in the differential diagnosis are pyogenic granuloma and verruca peruana *(B. bacilliformis)*. Deep soft tissue masses caused by bacillary angiomatosis may mimic a malignancy.

Osseous bacillary angiomatosis lesions typically involve the long bones. These lytic lesions are very painful and highly vascular and are occasionally associated with an overlying erythematous plaque. The high degree of vascularity produces a positive result on a technetium-99m methylene diphosphonate bone scan, resembling that of a malignant lesion.

Lesions can be found in virtually any organ, producing similar vascular proliferative lesions. They may appear raised, nodular, or ulcerative when seen on endoscopy or bronchoscopy. They may be associated with enlarged lymph nodes with or without an obvious local cutaneous lesion. Brain parenchymal lesions have been described.

BACILLARY PELIOSIS

Bacillary peliosis affects the reticuloendothelial system, primarily the liver **(peliosis hepatis)** and, less frequently, the spleen and lymph nodes. It is a vasoproliferative disorder characterized by random proliferation of venous lakes surrounded by fibromyxoid stroma harboring numerous bacillary organisms. Clinical findings include fever and abdominal pain in association with abnormal liver function test results, particularly a greatly increased alkaline phosphatase level. Cutaneous bacillary angiomatosis with splenomegaly may be associated with thrombocytopenia or pancytopenia. The vascular proliferative lesions in the liver and spleen appear on CT scan as hypodense lesions scattered throughout the parenchyma. The differential diagnosis includes hepatic Kaposi sarcoma, lymphoma, and disseminated infection with *Pneumocystis jirovecii* or *Mycobacterium avium* complex.

BACTEREMIA AND ENDOCARDITIS

B. henselae, B. quintana, B. vinsonii, and *B. elizabethae* all are reported to cause bacteremia or endocarditis. They are associated with symptoms such as prolonged fevers, night sweats, and profound weight loss. A cluster of cases in Seattle in 1993 occurred in a homeless population with chronic alcoholism. These patients with high fever or hypothermia were thought to represent *urban trench fever,* but no body louse infestation was associated. Some cases of culture-negative endocarditis may represent *Bartonella* endocarditis. One report described central nervous system involvement with *B. quintana* infection in two children.

DIAGNOSIS

The diagnosis of bacillary angiomatosis is made initially by biopsy. The characteristic small-vessel proliferation with mixed inflammatory response and the staining of bacilli by Warthin-Starry silver distinguish bacillary angiomatosis from pyogenic granuloma or Kaposi sarcoma (see Chapter 304). Travel history can usually preclude verruca peruana.

Culture is impractical for CSD but is the diagnostic procedure for suspected bacteremia or endocarditis. Lysis centrifugation technique or fresh chocolate or heart infusion agar with 5% rabbit blood and prolonged incubation may increase the yield of culture. PCR on tissue can also be a useful tool, and positive serologic testing can provide support for the diagnosis.

TREATMENT

Bartonella infections in immunocompromised hosts caused by both *B. henselae* and *B. quintana* have been treated successfully with antimicrobial agents. Bacillary angiomatosis responds rapidly to erythromycin, azithromycin, and clarithromycin, which are the drugs of choice. Alternative choices are doxycycline or tetracycline. Severely ill patients with peliosis hepatis or patients with osteomyelitis may be treated initially with a macrolide or doxycycline and the addition of rifampin or gentamicin. The use of doxycycline for 6 weeks with the addition of an aminoglycoside for a minimum of 2 weeks is associated with improved prognosis in endocarditis. A Jarisch-Herxheimer reaction may occur. Relapses may follow, and prolonged treatment for several months may be necessary.

PREVENTION

Immunocompromised persons should consider the potential risks of cat ownership because of the risks for *Bartonella* infections as well as toxoplasmosis and enteric infections. Those who elect to obtain a cat should adopt or purchase a cat >1 year old and in good health. Prompt washing of any wounds from cat bites or scratches is essential.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 6

Anaerobic Bacterial Infections

Chapter 256

Botulism (*Clostridium botulinum*)

Mark R. Schleiss

There are three naturally occurring forms of human botulism, characterized by mode of acquisition: **infant botulism** (intestinal toxemia), **food-borne botulism**, and **wound botulism**. Infant botulism is the most common form in the United States. Under rare circumstances of altered intestinal anatomy, physiology, and microflora, older children and adults may contract infant-type botulism **(adult intestinal toxemia)**. Two other forms, both human-made, also occur: **inhalational botulism**, from inhaling accidently aerosolized toxin, and **iatrogenic botulism**, from overdosage of botulinum toxin used for therapeutic or cosmetic purposes.

ETIOLOGY

Botulism is the acute, flaccid paralysis caused by the neurotoxin produced by *Clostridium botulinum* or, infrequently, an equivalent neurotoxin produced by the related species *Clostridium butyricum* and *Clostridium baratii. C. botulinum* is a gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. The organism is found in a wide variety of fresh and cooked agricultural products. Remarkably, the spores of some *C. botulinum* strains endure boiling for several hours, enabling the organism to survive efforts at food preservation. In contrast, botulinum toxin is heat labile and easily destroyed by heating at ≥85°C (185°F) for 5 minutes. Neurotoxigenic *C. butyricum* has been isolated from soils near Lake Weishan in China, the site of food-borne botulism outbreaks associated with this organism, and from vegetables, soured milk, and cheeses. Although first recognized in China, cases of infant botulism caused by *C. butyricum* have now been identified in Japan, Europe, and the United States. Little is known about the ecology of neurotoxigenic *C. baratii*.

Botulinum toxin is synthesized as a 150-kDa precursor protein that enters the circulation and is transported to the neuromuscular junction. The toxin is only released by actively replicating (vegetative) bacteria and not the spore form. At the neuromuscular junction, toxin binds to the neuronal membrane on the presynaptic side of the neural synapse. It undergoes proteolysis to a 100-kDa heavy chain and a 50-kDa light chain. These chains are joined via disulfide bond formation. The heavy chain contains the neuronal attachment sites that mediate binding to presynaptic nerve terminals. It also mediates translocation of the light chain into the cell cytoplasm after binding. The light chain, a key component of the toxin, is a member of the zinc metalloprotease family and mediates cleavage of the fusogenic SNARE (Soluble NSF Attachment REceptor) protein family member, SNAP-25. Cleavage of this protein precludes release of acetylcholine from axons at the presynaptic terminal, abrogating nerve signaling and producing paralysis. Botulinum toxin is among the most potent poisons known to humankind; indeed, the parenteral human lethal dose is estimated to be on the order of 10^{-6} mg/kg. The toxin blocks neuromuscular transmission and causes death through airway and respiratory muscle paralysis. At least nine antigenic toxin types, designated by letters A-H and X, are distinguished serologically by demonstration of the inability of neutralizing antibody against one toxin type to protect against a different type. Toxin types are further differentiated into subtypes by differences in the nucleotide sequences of their toxin genes. The gene for botulinum toxin for some toxin types and subtypes resides on a plasmid. Some toxins are fully activated by the bacteria that produce them (proteolytic strains of types A, B, and F), and some require exogenous proteolytic activation (types E and nonproteolytic types B and F).

The toxin types serve as convenient clinical and epidemiologic markers. Toxin types A, B, E, and F are well-established causes of human botulism, whereas types C and D cause illness in other animals. Toxin types A and B cause the majority of cases of infant botulism in the United States. Neurotoxigenic *C. butyricum* strains produce a type E toxin, whereas neurotoxigenic *C. baratii* strains produce a type F toxin. Type G toxin has not been established as a cause of either human or animal disease. Some strains produce two toxins such as B and A or B and F; rare strains may produce three toxins. Dual (bivalent) toxin mediated disease tends to be more severe than single toxin production.

EPIDEMIOLOGY

Infant botulism has been reported from all inhabited continents except Africa. Notably, in a typical case the infant is the only family member who is ill. The most striking epidemiologic feature of infant botulism is its age distribution: approximately 90% of cases involving infants 3 weeks to 6 months of age, with a broad peak spanning 2-4 months of age. Cases have been recognized in infants as young as 1.5 days or as old as 382 days at onset. Identified risk factors for the illness include breastfeeding, the ingestion of honey, a slow intestinal transit time (<1 stool/day), and ingestion of untreated well water (Fig. 256.1). Although breastfeeding appears to provide protection against fulminant sudden death from infant botulism, cases can occur in breastfed infants at the time of introduction of nonhuman milk for feeding.

Although infant botulism is an uncommon and often unrecognized illness, it is the most common form of human botulism in the United States, with approximately 80-140 hospitalized cases diagnosed annually. The Council of State and Territorial Epidemiologists (CSTE) maintains a **National Botulism Surveillance System** for intensive surveillance for cases of botulism in the United States (https://www.cdc.gov/botulism/surveillance.html). In 2017, 182 laboratory-confirmed botulism cases were reported to Centers for Disease Control and Prevention (CDC). Botulism was predominately observed in infants, with 141 such cases reported. A total of 19 (10%) food-borne cases and 19 (10%) wound cases were reported. Infant botulism cases were reported from 26 states and the District of Columbia, with California reporting the

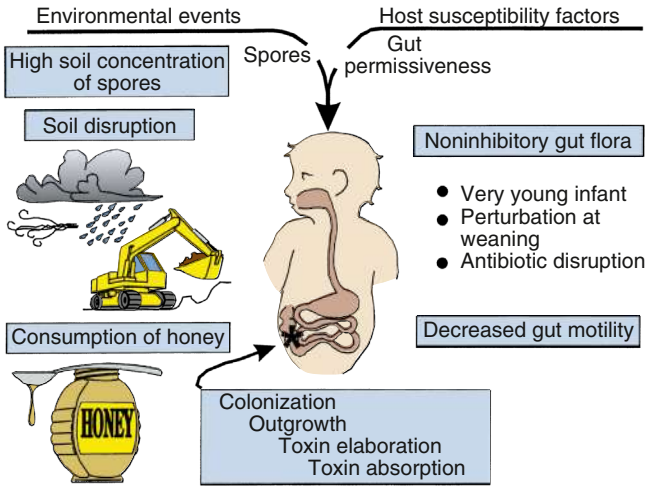

Fig. 256.1 Environmental, host, and pathophysiologic events in infant botulism. *(From Arnon SS, Long SS. Clostridium botulinum [Botulism]. In Long SS, Prober CG, Fischer M, Kimberlin DW, eds. Principles and Practice of Pediatric Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2023: Fig. 189.3, p. 1019.)*

most (n = 48, 34%). Toxin type B (n = 88) predominated. The median age of infants was 4 months (range: 0-12 months), and no deaths were reported.

Food-borne botulism results from the ingestion of a food in which *C. botulinum* has multiplied and produced toxin. Although the traditional view of food-borne botulism has been thought of as resulting chiefly from ingestion of home-canned foods, in fact, outbreaks in North America have been more often associated with restaurant-prepared foods, including nacho cheese in convenience stores, sautéed onions, chopped garlic, and seal blubber (in Alaska). Other outbreaks in the United States have occurred from commercial foods sealed in plastic pouches that relied solely on refrigeration to prevent outgrowth of *C. botulinum* spores. Uncanned foods responsible for food-borne botulism cases include peyote tea, hazelnut flavoring added to yogurt, sweet cream cheese, sautéed onions in patty melt sandwiches, potato salad, and fresh and dried fish, including botulism type E that has been acquired by eating an Egyptian salt-cured fish dish called fesikh. For food-borne botulism cases reported to the 2017 National Botulism Surveillance System, the median age of patients was 42 years (range: 14-85 years), and three deaths were reported. Most of the continental U.S. outbreaks resulted from proteolytic type A or type B strains, whereas in Alaska and Canada, most food-borne outbreaks have resulted from nonproteolytic type E strains. A further hazard of type E strains is their ability to grow at the temperatures maintained by household refrigerators (5°C [41°F]).

Wound botulism is an exceptionally rare disease, with <400 cases reported worldwide, but it is important to pediatrics because adolescents and children may be affected. Although many cases have occurred in young, physically active males who are at the greatest risk for traumatic injury, wound botulism also occurs with crush injuries in which no break in the skin is evident. In recent years, wound botulism from injection has become increasingly common in adult heroin abusers in the western United States and in Europe, not always with concomitant evidence of abscess formation or cellulitis.

A single outbreak of **inhalational botulism** was reported in 1962 in which three laboratory workers in Germany were exposed unintentionally to aerosolized botulinum toxin. Some patients in the United States have been hospitalized by accidental overdose of therapeutic or cosmetic botulinum toxin.

PATHOGENESIS

All forms of botulism produce disease through a final common pathway. Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic transmission. **Infant botulism** results from ingesting the spores of botulinum toxin–producing strains, with subsequent spore germination, multiplication, and production of botulinum toxin in the large intestine. This sequence is distinct from **food-borne botulism**, which is an intoxication that results when preformed botulinum toxin contained in an improperly preserved or inadequately cooked food is swallowed. **Wound botulism** results from spore germination and colonization of traumatized tissue by *C. botulinum;* the pathogenesis of this form of botulism is similar in this respect to that of tetanus. **Inhalational botulism** occurs when aerosolized botulinum toxin is inhaled and could conceivably be a route of exposure generated by a bioterrorist attack.

Because botulinum toxin is not a *cytotoxin,* it does not cause overt macroscopic or microscopic pathology. Pathologic changes (pneumonia, petechiae on intrathoracic organs) may be found at autopsy, but these are secondary changes and not primarily attributable to botulinum toxin. No diagnostic technique is available to identify botulinum toxin binding at the neuromuscular junction. Nerve conduction velocity studies are typically normal. Electromyography (EMG) findings are often nonspecific and nondiagnostic (see later). The healing process in botulism consists of sprouting new terminal unmyelinated motor neurons. Movement resumes when these new nerve terminals locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. In experimental animals, this process takes about 4 weeks.



Fig. 256.2 A 3-mo-old infant with botulism just before intubation. Note bilateral ptosis and facial palsy and the absence of tears. *(From Arnon SS, Long SS. Clostridium botulinum [Botulism]. In: Long SS, Prober CG, Fischer M, Kimberlin DW, eds. Principles and Practice of Pediatric Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2023: Fig. 189.4, p. 1020.)*

CLINICAL MANIFESTATIONS

The full clinical spectrum of **infant botulism** ranges from mild to fulminant sudden death. Botulinum toxin is distributed hematogenously. Because relative blood flow and density of innervation are greatest in the bulbar musculature, all forms of botulism manifest neurologically as a symmetric, *descending,* flaccid paralysis beginning with the cranial nerve musculature and progressing over hours to days. **Bulbar palsies** may manifest with such symptoms as poor feeding, weak suck, feeble cry, drooling, and even obstructive apnea. These clinical clues unfortunately may not be recognized as bulbar in origin (Fig. 256.2). Patients with evolving illness may already have generalized weakness and hypotonia in addition to bulbar palsies when first examined. The brain itself is spared in infant botulism, because botulinum toxin does not cross the blood-brain barrier.

In contrast to botulism caused by *C. botulinum,* a majority of the rare cases caused by intestinal colonization with *C. butyricum* are associated with a Meckel diverticulum accompanying abdominal distention, often leading to misdiagnosis as an acute abdomen. The also rare *C. baratii* type F infant botulism cases have been characterized by very young age at onset, rapidity of onset, and greater severity but shorter duration of paralysis.

In older children with **food-borne** or **wound botulism**, the onset of neurologic symptoms follows a characteristic pattern of diplopia, ptosis, dry mouth, dysphagia, dysphonia, and dysarthria, with decreased gag and corneal reflexes. Importantly, because the toxin acts only on motor nerves, paresthesias are not seen in botulism, except when a patient hyperventilates from anxiety. The sensorium remains clear, but this fact may be difficult to ascertain because of the slurred speech.

Food-borne botulism begins with gastrointestinal (GI) symptoms of nausea, vomiting, or diarrhea in approximately 30% of cases. These symptoms are thought to result from metabolic by-products of growth of *C. botulinum* or from the presence of other toxic contaminants in the food, because GI distress is rarely observed in wound botulism. Constipation may occur in food-borne botulism once flaccid paralysis becomes evident. Illness usually begins 12-36 hours after ingestion of

the contaminated food but can range from as short as 2 hours to as long as 8 days. The incubation period in **wound botulism** is 4-14 days. Fever may be present in wound botulism but is absent in food-borne botulism unless a secondary infection (often pneumonia) is present. All forms of botulism display a wide spectrum of clinical severity, from the very mild, with minimal ptosis, flattened facial expression, minor dysphagia, and dysphonia, to the fulminant, with rapid onset of extensive paralysis, frank apnea, and fixed, dilated pupils. *Fatigability with repetitive muscle activity* is the clinical hallmark of botulism.

Infant botulism differs in apparent initial symptoms of illness only because the infant cannot verbalize them. Clinical progression can be more rapid and more severe in very young infants. The incubation period in infant botulism is estimated to be 3-30 days. Usually, the first indication of illness is a decreased frequency or even absence of defecation, and indeed, constipation may be the chief complaint (although this sign is also frequently overlooked). Parents typically notice inability to feed, lethargy, weak cry, and diminished spontaneous movement. Dysphagia may be evident, and an increase in secretions drooling from the mouth may be noted. Gag, suck, and corneal reflexes all diminish as the paralysis advances. Oculomotor palsies may be evident. Paradoxically, the pupillary light reflex may be unaffected until the child is severely paralyzed, or it may be initially sluggish. Loss of head control is typically a prominent sign. Opisthotonos may be observed. Respiratory arrest may occur suddenly from airway occlusion by unswallowed secretions or from obstructive flaccid pharyngeal musculature. Death from botulism results either from airway obstruction or paralysis of the respiratory muscles. Occasionally, the diagnosis of infant botulism is suggested by a respiratory arrest that occurs after the infant is curled into position for lumbar puncture or after the administration of an aminoglycoside antibiotic administered for suspected sepsis (see later).

In mild cases or in the early stages of illness, the physical signs of infant botulism may be subtle and easily missed. Eliciting cranial nerve palsies and fatigability of muscular function requires careful examination. Ptosis may not be seen unless the head of the child is kept erect.

DIAGNOSIS

Definitive diagnosis of botulism is made by specialized laboratory testing that requires hours to days to complete. Therefore clinical diagnosis is the foundation for early recognition of and response to all forms of botulism. Routine laboratory studies, including those of the cerebrospinal fluid (CSF), are normal in botulism unless dehydration, undernourishment (metabolic acidosis and ketosis), or secondary infection is present.

The **classic triad** of botulism is the acute onset of a symmetric, flaccid descending paralysis with clear sensorium, no fever, and no paresthesias. Suspected botulism represents a medical and public health emergency that is immediately reportable by telephone in most U.S. health jurisdictions. State health departments (first call) and the CDC (770-488-7100 at any time) can arrange for diagnostic testing, epidemiologic investigation, and provision of equine antitoxin.

The diagnosis of botulism is unequivocally established by demonstration of the presence of botulinum toxin in serum or of *C. botulinum* toxin or organisms in wound material, enema fluid, or feces. *C. botulinum* is not part of the normal resident intestinal flora of humans, and its presence in the setting of acute flaccid paralysis is diagnostic. An epidemiologic diagnosis of food-borne botulism can be established when *C. botulinum* organisms and toxin are found in food eaten by patients.

Electromyography can sometimes distinguish between causes of acute flaccid paralysis, although results may be variable, including normal, in patients with botulism. The distinctive EMG finding in botulism is facilitation (potentiation) of the evoked muscle action potential at high-frequency (50 Hz) stimulation. In infant botulism, a characteristic pattern known as **BSAP** (Brief, Small, Abundant motor unit action Potentials) is present only in clinically weak muscles. Nerve conduction velocity and sensory nerve function are normal in botulism.

Infant botulism requires a high index of suspicion for early diagnosis (Table 256.1). "Rule-out sepsis" remains the most common admission diagnosis. If a previously healthy infant (usually 2-4 months of age) demonstrates weakness with difficulty in sucking, swallowing, crying, or breathing, infant botulism should be considered a likely diagnosis. A careful cranial nerve examination is then quite helpful. Rare instances of co-infection with *Clostridioides difficile,* respiratory syncytial virus, or influenza virus have occurred.

Table 256.1 Mimics of Initial Diagnosis of Infant Botulism

NEUROMUSCULAR
Spinal muscular atrophy (type 1)
Congenital myasthenia gravis
Guillain-Barré syndrome and its variants
Poliomyelitis
Acute flaccid paralysis
Transverse myelitis
ADEM
Congenital myopathy
Encephalitis (viral, autoimmune)
Global developmental delay
Leukodystrophy
METABOLIC
Medium chain acetyl-coenzyme A deficiency
Carnitine deficiency
Congenital disorders of glycosylation
Urea cycle defects
Mitochondrial disorders
Glutaric aciduria type 1
Maple syrup urine disease
INFECTIOUS
Enteroviral and parechovirus encephalitis
Sepsis
OTHERS
Hypothyroidism
Drug ingestion
Organophosphate poisoning
Heavy metal poisoning (lead, arsenic)

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a **polyradiculoneuropathy** (Guillain-Barré or Miller Fisher syndrome), myasthenia gravis, or a central nervous system (CNS) disease (Table 256.2). In the United States, botulism is more likely than **Guillain-Barré syndrome**, intoxication, or poliomyelitis to cause a *cluster of cases* of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its initial and prominent cranial nerve palsies that are disproportionate to milder weakness and hypotonia below the neck, in its symmetry, and in its absence of sensory nerve damage. Spinal muscular atrophy may closely mimic infant botulism at presentation.

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis. The CSF is unchanged in botulism but is abnormal in many CNS diseases. Although the CSF protein concentration is eventually elevated in Guillain-Barré syndrome, it may be normal early in the illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism, although this is rarely performed in infants. A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis. Possible organophosphate intoxication should be pursued aggressively, because specific antidotes (oximes) are available and because the patient may be part of a commonly exposed group, some of whom have yet to demonstrate illness. Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome, spinal muscular atrophy and other genetic (including mitochondrial) disorders, and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

Table 256.2 Conditions Considered in the Differential Diagnosis of Food-Borne Botulism and Wound Botulism

Acute gastroenteritis
Myasthenia gravis
Guillain-Barré syndrome
Organophosphate poisoning
Meningitis
Encephalitis
Transverse myelitis
Psychiatric illness
Cerebrovascular accident
Poliomyelitis
Hypothyroidism
Genetic disorder
Aminoglycoside-associated paralysis
Tick paralysis
Hypocalcemia
Hypermagnesemia
Carbon monoxide poisoning
Hyperemesis gravidarum
Laryngeal trauma
Diabetic complications
Inflammatory myopathy
Overexertion

TREATMENT

Human botulism immune globulin, given intravenously (BIG-IV, also referred to as *BabyBIG*), is licensed for the treatment of infant botulism caused by type A or B botulinum toxin. The purified immunoglobulin is derived from pooled adult plasma from individuals immunized with pentavalent botulinum toxoid who were selected for their high titers of neutralizing antibody against botulinum neurotoxins type A and B. Treatment with BIG-IV consists of a single intravenous infusion of 50 mg/kg (see package insert) that should be given as soon as possible after infant botulism is suspected so as to immediately end the toxemia that is the cause of the illness and arrest progression of paralysis. *When the diagnosis of infant botulism is suspected, treatment should not be delayed for laboratory confirmation.* In the United States, for clinical consultation for a patient with suspected infant botulism, the patient's physician should contact the Infant Botulism Treatment and Prevention Program (IBTPP) on-call physician at (510) 231-7600 (24/7/365). To obtain BabyBIG for a patient with suspect infant botulism, the physician must contact the IBTPP on-call physicians (https://www.infantbotulism.org/physician/obtain.php). The use of BIG-IV shortens mean hospital stay from approximately 6 weeks to 2 weeks. Most of the decrease in hospital stay results from shorter duration of mechanical ventilation and reduced days in intensive care.

Older patients with suspected food, wound, or inhalational botulism may be treated with one vial of licensed equine heptavalent (A-G) botulinum antitoxin (HBAT). (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5910a4.htm), which is available in the United States through the CDC by way of state and local health departments.

Antibiotic therapy is not part of the treatment of uncomplicated infant or food-borne botulism, because the toxin is primarily an intracellular molecule that is released into the intestinal lumen with vegetative bacterial cell death and lysis. Indeed, there is a theoretical concern that antibiotics with clostridiocidal activity may increase the amount of free toxin in the large bowel and actually worsen an infant's clinical status. Antibiotic use in infant botulism patients is indicated only for the treatment of secondary infections. In these patients, aminoglycosides in particular should be avoided, because this class of antibiotics can potentiate the action of botulinum toxin at the neuromuscular junction. Wound botulism requires aggressive treatment with antibiotics and antitoxin in a manner analogous to that for tetanus (see Chapter 257) and may require wound debridement to remove the source of the toxin.

SUPPORTIVE CARE

Management of botulism rests on the following three principles: (1) fatigability with repetitive muscle activity is the clinical hallmark of the disease, (2) complications are best avoided by anticipating them, and (3) meticulous supportive care is a necessity. The first principle applies mainly to feeding and breathing. Correct positioning is imperative to protect the airway and improve respiratory mechanics. The patient should be positioned face-up on a rigid-bottomed crib (or bed), the head of which is tilted at 30 degrees. A small cloth roll is placed under the cervical vertebrae to tilt the head back so that secretions drain to the posterior pharynx and away from the airway. In this tilted position, the abdominal viscera pull the diaphragm down, thereby improving respiratory mechanics. The patient's head and torso should not be elevated by bending the middle of the bed; in such a position, the hypotonic thorax would slump into the abdomen, and breathing would be compromised.

About half of patients with infant botulism require endotracheal intubation, which is best done prophylactically. The indications include diminished gag and cough reflexes and progressive airway obstruction by secretions. Enteral nutrition should be undertaken using a nasogastric or nasojejunal tube until sufficient oropharyngeal strength and coordination enable oral feeding by breast or bottle. Expressed breast milk is the most desirable food for infants, in part because of its immunologic components (e.g., secretory IgA, lactoferrin, leukocytes). Tube feeding also assists in the restoration of peristalsis, a nonspecific but probably essential part of eliminating *C. botulinum* from the intestinal flora. Intravenous feeding (hyperalimentation) is discouraged because of the potential for infection and the advantages of tube feeding.

Because sensation and cognitive function remain fully intact, providing auditory, tactile, and visual stimuli is beneficial. Maintaining strong central respiratory drive is essential, so sedatives and CNS depressants should be avoided. Full hydration and stool softeners such as lactulose may mitigate the protracted constipation. Cathartics are not recommended. Patients with food-borne and infant botulism excrete *C. botulinum* toxin and organisms in their feces, often for many weeks, and care should be taken in handling their excreta, with full engagement of hospital infection control staff. When bladder palsy occurs in severe cases, gentle suprapubic pressure with the patient in the sitting position with the head supported may help attain complete voiding and reduce the risk for urinary tract infection (UTI). Families of affected patients may require emotional and financial support, especially when the paralysis of botulism is prolonged.

COMPLICATIONS

Almost all the complications of botulism are *nosocomial,* and a few are iatrogenic (Table 256.3). Some critically ill, toxin-paralyzed patients who must spend weeks or months on ventilators in intensive care units inevitably experience some of these complications. Suspected "relapses" of infant botulism usually reflect premature hospital discharge or an inapparent underlying complication such as pneumonia, UTI, or otitis media.

PROGNOSIS

When the regenerating nerve endings have induced formation of a new motor end plate, neuromuscular transmission is restored. In the absence of complications, particularly those related to hypoxia, the prognosis in infant botulism is for full and complete recovery. Hospital stay in untreated infant botulism averages 5.7 weeks but differs significantly by toxin type, with patients with untreated type B disease being hospitalized a mean of 4.2 weeks and those with untreated type A disease being hospitalized a mean of 6.7 weeks.

In the United States, the case fatality ratio for hospitalized cases of infant botulism is <1%. After recovery, patients with untreated infant botulism appear to have an increased incidence of strabismus that requires timely screening and treatment. The case fatality ratio in food-borne and wound botulism varies by age, with younger patients having the best prognosis. Some adults with botulism have reported chronic weakness and fatigue for >1 year as sequelae of the illness.

Table 256.3 Complications of Infant Botulism

Acute respiratory distress syndrome
Aspiration
Clostridioides difficile enterocolitis
Hypotension
Inappropriate antidiuretic hormone secretion
Long bone fractures
Misplaced or plugged endotracheal tube
Nosocomial anemia
Otitis media
Pneumonia
Pneumothorax
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tracheal granuloma
Tracheitis
Transfusion reaction
Urinary tract infection

PREVENTION

Food-borne botulism is best prevented by adherence to safe methods of home canning (pressure cooker and acidification), by avoiding suspicious foods, and by heating all home-canned foods to 85°C (185°F) for ≥5 minutes. Wound botulism is best prevented by not using illicit drugs and by treating contaminated wounds with thorough cleansing, surgical debridement, and provision of appropriate antibiotics.

Many patients with infant botulism are presumed to have inhaled and then swallowed airborne clostridial spores; these cases cannot be prevented. However, a clearly identified and avoidable source of botulinum spores for infants is honey. *Honey is an unsafe food for any child <1 year old.* Corn syrups were once thought to be a possible source of botulinum spores, but evidence indicates otherwise. Breastfeeding appears to slow the onset of infant botulism and to diminish the risk for sudden death in infants in whom the disease develops.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 257

Tetanus (*Clostridium tetani*)

Mark R. Schleiss

ETIOLOGY

The clinical syndrome of **tetanus** involves an acute, spastic paralytic illness caused by a neurotoxin produced by *Clostridium tetani*. Thus tetanus can be considered a toxin-mediated process more than an acute infectious process per se, because there are few, if any, symptoms elicited either by the presence of replicating microorganisms or through elicitation of the host inflammatory response. Unlike other pathogenic clostridia species, *C. tetani* is not a tissue-invasive organism. Instead, it causes illness through the toxin, **tetanospasmin**, more commonly referred to as *tetanus toxin*. Tetanospasmin is the second most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be 10^{-5} mg/kg. *C. tetani* is a motile, gram-positive, spore-forming obligate anaerobe. The organism's natural habitat worldwide is soil, dust, and the alimentary tracts of various animals.

C. tetani forms spores terminally, with a classic morphologic appearance resembling a drumstick or tennis racket when viewed microscopically. The formation of spores is a critical aspect of the organism's persistence in the environment. Spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants.

EPIDEMIOLOGY

Tetanus occurs worldwide and is endemic in many developing countries, although its incidence varies considerably. Public health efforts in recent years have had an impressive impact on tetanus-associated mortality, but many challenges remain. In 1990, 314,000 people died because of tetanus, whereas in 2017 there were just slightly over 38,000 deaths. Over half of these deaths (approximately 18,000) were in children under 5 years of age (Fig. 257.1A). Individuals age 15-49 years represent the second most common group to suffer tetanus-related mortality. Global mortality in adults is largely driven by **maternal tetanus**, which results from postpartum, postabortal, or postsurgical wound infection with *C. tetani*. Most mortality related to **neonatal tetanus** (also referred to as **umbilical tetanus**) occurs in South Asia and sub-Saharan Africa. The mortality of neonatal tetanus has been substantially reduced globally, driven by increased rates of maternal tetanus vaccination, although the disease remains endemic in a number of countries (see Fig. 257.1B). Reported tetanus cases in the United States have declined more than 95% since 1947, and deaths caused by tetanus have declined by more than 99% in that same period. From 2009 to 2017, a total of 264 cases and 19 deaths from tetanus were reported in the United States. Sixty (23%) cases were in persons 65 years of age or older, 168 (64%) were in persons 20 through 64 years of age, and 36 (13%) were in persons younger than 20 years, including 3 cases of neonatal tetanus. The majority of childhood cases of tetanus in the United States have occurred in unimmunized children whose parents objected to vaccination.

Most nonneonatal cases of tetanus are associated with a traumatic injury, often a penetrating wound inflicted by a dirty object such as a nail, splinter, fragment of glass, or unsterile injection. Tetanus may also occur in the setting of illicit drug injection. The disease has been associated with the use of contaminated suture material and after intramuscular injection of medicines, most notably quinine for chloroquine-resistant falciparum malaria. The disease may also occur in association with animal bites, abscesses (including dental abscesses), ear and other body piercing, chronic skin ulceration, burns, compound fractures, frostbite, gangrene, intestinal surgery, ritual scarification, infected insect bites, and female circumcision. Rarely, cases may present to clinical attention without an antecedent history of trauma. Tetanus is not transmitted person to person.

PATHOGENESIS

Tetanus typically occurs after spores (introduced by traumatic injury) germinate, multiply, and produce tetanus toxin. A plasmid carries the toxin gene. Toxin is produced only by the vegetative cell, not the spore. It is released after the vegetative phase of replication, with replication occurring under anaerobic conditions. The low oxidation-reduction potential of an infected injury site therefore provides an ideal environment for transition from the spore to the vegetative stage of growth. After bacterial cell death and lysis, **tetanospasmin** is produced. The toxin has no known function for clostridia in the soil environment where they normally reside. Tetanus toxin is a 150-kDa simple protein consisting of a heavy chain (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport, facilitated by dyneins, to the cytoplasm of the α-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/hr. The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and γ-aminobutyric acid (GABA). Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. This aspect of pathogenesis lead to

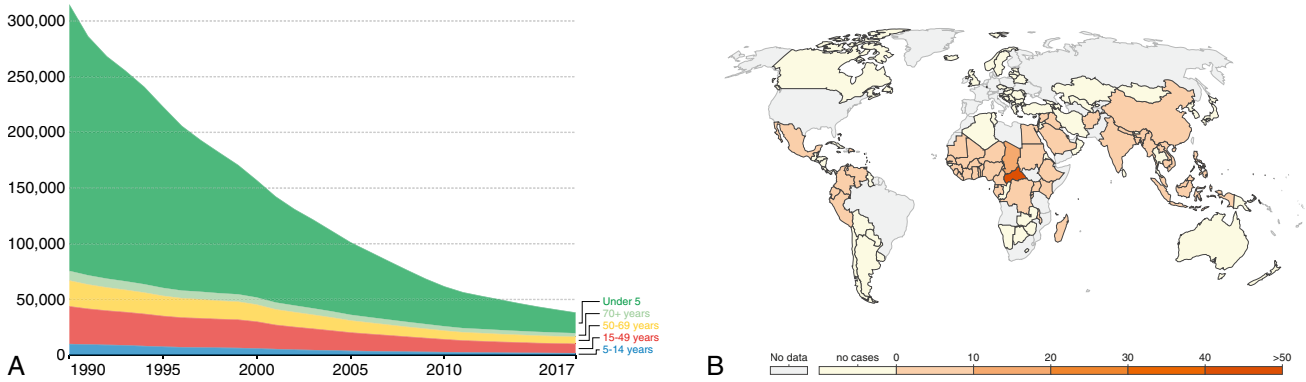

Fig. 257.1 Evolving epidemiology of tetanus. **A,** Deaths from tetanus, by age, globally from 1990 to 2017. Most cases of tetanus occur in children under the age of 5, and this group accounts for ~50% of the global mortality attributable to this infection. (Source: Institute for Health Metrics and Evaluation, Global Burden of Disease). **B,** Global distribution of neonatal tetanus. Number of new cases of neonatal tetanus per million, 2016. Sources: World Health Organization and UN Population Prospects, 2017. *(From Behrens H, Ochmann S, Dadonaite B, Roser M. Tetanus. Published online at OurWorldInData.org, 2019. Retrieved from https://ourworldindata.org/tetanus.)*

the term *lockjaw,* classically applied to the clinical manifestations of tetanus in the affected individual. Neurotransmission at neuromuscular junctions in the autonomic nervous system are also rendered unstable in tetanus, producing "autonomic storm" (described later).

The phenomenal potency of tetanus toxin is enzymatic. The 50-kDa light chain (A-chain) of tetanus toxin is a zinc-containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The cleavage of synaptobrevin is the final target of tetanus toxin, and even in low doses the neurotoxin will inhibit neurotransmitter exocytosis in the inhibitory interneurons. The blockage of GABA and glycine causes the physiologic effects of tetanus toxin. The 100-kDa heavy chain (B-chain) of the toxin contains its binding and internalization domains. It binds to disialogangliosides (GD2 and GD1b) on the neuronal membrane. The translocation domain aids the movement of the protein across that membrane and into the neuron.

Because *C. tetani* is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

CLINICAL MANIFESTATIONS

Tetanus is most often generalized but may also be localized. The incubation period typically is 2-14 days but may be as long as months after the injury. In **generalized tetanus**, the presenting symptom in about half of cases is **trismus** (masseter muscle spasm, or lockjaw). Headache, restlessness, and irritability are early symptoms, often followed by stiffness, difficulty chewing, dysphagia, and neck muscle spasm. The so-called **sardonic smile of tetanus *(risus sardonicus)*** results from intractable spasms of facial and buccal muscles. When the paralysis extends to abdominal, lumbar, hip, and thigh muscles, the patient may assume an arched posture of extreme hyperextension of the body, or **opisthotonos**, with the head and the heels bent backward and the body bowed forward. In severe cases, only the back of the head and the heels of the patient are noted to be touching the supporting surface. Opisthotonos is an equilibrium position that results from unrelenting total contraction of opposing muscles, all of which display the typical boardlike rigidity of tetanus. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxiation. Because tetanus toxin does not affect sensory nerves or cortical function, the patient unfortunately remains conscious, in extreme pain, and in fearful anticipation of the next tetanic seizure. The seizures are characterized by sudden, severe tonic contractions of the muscles, with fist clenching, flexion, and adduction of the arms and hyperextension of the legs. Without treatment, the duration of these seizures may range from a few seconds to a few minutes in length with intervening respite periods. As the illness progresses, the spasms become sustained and exhausting. The smallest disturbance by sight, sound, or touch may trigger a tetanic spasm. Dysuria and urinary retention result from bladder sphincter spasm; forced defecation may occur. Fever, occasionally as high as 40°C (104°F), is common and is caused by the substantial metabolic energy consumed by spastic muscles. Notable autonomic effects include tachycardia, dysrhythmias, labile hypertension, diaphoresis, and cutaneous vasoconstriction. The tetanic paralysis usually becomes more severe in the first week after onset, stabilizes in the second week, and ameliorates gradually over the ensuing 1-4 weeks.

Neonatal tetanus, the infantile form of generalized tetanus, typically manifests within 3-12 days of birth. It presents as progressive difficulty in feeding (sucking and swallowing), associated hunger, and crying. Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms, with or without opisthotonos, are characteristic. The umbilical stump, which is typically the portal of entry for the microorganism, may retain remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Localized tetanus results in painful spasms of the muscles adjacent to the wound site and may precede generalized tetanus. **Cephalic tetanus** is a rare form of localized tetanus involving the bulbar musculature and cranial nerves (particularly cranial nerve VII) that occurs with wounds or foreign bodies in the head, nostrils, or face. It also occurs in association with chronic otitis media. Cephalic tetanus is characterized by retracted eyelids, deviated gaze, trismus, *risus sardonicus,* and spastic paralysis of the tongue and pharyngeal musculature and may mimic a cerebrovascular accident.

DIAGNOSIS

The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an unimmunized patient (and/or mother) who was injured or born within the preceding 2 weeks, who presents with trismus, dysphagia, generalized muscle rigidity and spasm, and a clear sensorium.

Results of routine laboratory studies are usually normal. A peripheral leukocytosis may result from a secondary bacterial infection of the wound or may be stress-induced from the sustained tetanic spasms. The cerebrospinal fluid analysis is normal, although the intense muscle contractions may raise intracranial pressure. Serum muscle enzymes (creatine kinase, aldolase) may be elevated. Neither the electroencephalogram nor the electromyogram (EMG) shows a characteristic pattern, although EMG may show a continuous discharge of motor subunits and shortening or absence of the silent interval normally observed after an action potential. An assay for antitoxin levels is not readily available, although a serum antitoxin level of 0.01 IU/mL or higher is generally considered protective and makes the diagnosis of tetanus less likely. *C. tetani* is not always visible on Gram stain of wound material and is isolated by culture in only approximately 30% of cases. The **spatula test** is a simple diagnostic

bedside test that involves touching the oropharynx with a spatula or tongue blade. Normally this maneuver will elicit a gag reflex, as the patient tries to expel the spatula (negative test). If tetanus is present, patients develop a reflex spasm of the masseters and bite the spatula (positive test). This bedside diagnostic maneuver is said to have a high sensitivity and specificity.

Differential Diagnosis

Florid and generalized tetanus is typically not mistaken for any other disease. However, trismus may result from parapharyngeal, retropharyngeal, or dental abscesses or, rarely, from acute encephalitis involving the brainstem. Either rabies or tetanus may follow an animal bite, and rabies may manifest as trismus with seizures. Rabies may be distinguished from tetanus by hydrophobia, marked dysphagia, predominantly clonic seizures, and pleocytosis (see Chapter 320). Although strychnine poisoning may result in tonic muscle spasms and generalized seizure activity, it seldom produces trismus, and unlike in tetanus, general relaxation usually occurs between spasms. Hypocalcemia may produce tetany that is characterized by laryngeal and carpopedal spasms, but trismus is absent. Occasionally, epileptic seizures, narcotic withdrawal, or other drug reactions may suggest tetanus.

TREATMENT

Management of tetanus requires eradication of *C. tetani,* correction of wound environment conditions conducive to its anaerobic replication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and, finally, prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created the anaerobic growth conditions necessary for vegetative replication. Surgery should be performed promptly after administration of **human tetanus immunoglobulin (TIG)** and antibiotics. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. However, TIG should be given as soon as possible, with the goal of neutralizing toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. Most experts recommend that a **single intramuscular (IM) injection of 500 units of TIG** is sufficient to neutralize systemic tetanus toxin; although doses as high as 3,000-6,000 have been recommended by some experts, they do not seem to confer better outcomes. Infiltration of part of the dose of TIG into the wound is no longer recommended by the Red Book Committee of the American Academy of Pediatrics, and the entire dose can be administered IM. If TIG is unavailable, use of human intravenous immunoglobulin (at a dose of 200-400 mg/kg) can be considered. Intravenous immunoglobulin contains 4-90 units/mL of TIG; the optimal dosage of intravenous immunoglobulin for treating tetanus is not known, and its use is not approved for this indication. In parts of the world where it is available, another alternative may be equine-derived tetanus antitoxin (TAT). This product is no longer available in the United States. A dose of 1,500-3,000 U is recommended and should be administered after appropriate testing for sensitivity and desensitization, because up to 15% of patients given the usual dose of TAT will experience serum sickness. The human-derived immunoglobulins are much preferred because of their longer half-lives (30 days) and the virtual absence of allergic and serum sickness adverse effects. Results of studies examining the potential benefit of intrathecal administration of TIG are conflicting. The TIG preparation available for use in the United States is neither licensed nor formulated for intrathecal or intravenous use.

Oral (or intravenous) **metronidazole** (30 mg/kg per day, given at 6-hour intervals; maximum dose, 4 g/day) decreases the number of vegetative forms of *C. tetani* and is currently considered the antibiotic of choice. **Parenteral penicillin G** (100,000 U/kg per day, administered at 4- to 6-hour intervals, with a daily maximum of 12 million U) is an alternative treatment. Antimicrobial therapy for a total duration of 7-10 days is recommended (https://publications.aap.org/redbook/book/347/chapter-abstract/5757094/Tetanus-Lockjaw).

Supportive care and pharmacologic interventions targeted at control of tetanic spasms are of critical importance in the management of tetanus. In light of this goal, all patients with generalized tetanus should receive muscle relaxants. **Diazepam** provides both relaxation and seizure control. For neonatal tetanus, an initial dose of 0.1-0.2 mg/kg every 3-6 hours given intravenously is subsequently titrated to control the tetanic spasms (continuous IV infusion doses of 15-40 mg/kg/day have been recommended, titrated to control the spasm). After 5-7 days, the dosage can be decreased by 5-10 mg/day, with the drug given orally or by the nasogastric route, after which the effective dose is sustained for 2-6 weeks before a tapered withdrawal. **Magnesium sulfate** may be useful in controlling autonomic dysfunction: a loading dose of 40 mg/kg IV over 30 minutes has been recommended in a study in tetanus patients >15 years of age, in which the loading dose was followed by 2 g/hr continuously for patients weighing >45 kg, or 1.5 g/hr continuously for patients weighing <45 kg. For neonatal tetanus, a loading dose of 50 mg/kg of magnesium sulfate, followed by a maintenance infusion of 30-50 mg/kg/hr (titrated against clinical effect) has been recommended. Monitoring of serum magnesium levels at least every 6 hours is recommended. In addition to diazepam, other benzodiazepines **(midazolam)**, **chlorpromazine**, **dantrolene**, and **baclofen** are also used. Intrathecal baclofen produces such complete muscle relaxation that apnea often ensues; like most other agents listed, baclofen should be used only in an intensive care unit setting. Favorable survival rates in generalized tetanus have been described with the use of neuromuscular blocking agents such as vecuronium and pancuronium, which produce a general flaccid paralysis that is then managed by mechanical ventilation. Autonomic instability is regulated with standard α- or β- (or both) blocking agents; morphine has also proved useful.

SUPPORTIVE CARE

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch, and all therapeutic and other manipulations must be carefully scheduled and coordinated. Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for unintubated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used for this purpose (i.e., to overcome trismus). Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstipation. Prophylactic subcutaneous heparin has been suggested to be of value, but it must be balanced with the risk for hemorrhage. Enoxaparin would be an alternative for the patient for whom deep venous thrombosis (DVT) prophylaxis is warranted.

COMPLICATIONS

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions with attendant pneumonia is an important complication to consider and may be present at the time of the initial diagnosis. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema. The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or **rhabdomyolysis** with myoglobinuria and renal failure, or in long bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are described as complications. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation, reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

Table 257.1 Tetanus Vaccination and Immune Globulin Use in Wound Management

HISTORY OF ABSORBED TETANUS TOXOID	CLEAN, MINOR WOUNDS		ALL OTHER WOUNDS*	
	DTaP, Tdap, OR Td†	TIG‡	DTaP, Tdap, Or TD†	TIG‡
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more doses	No, if <10 yr since last dose of tetanus-containing vaccine	No	No, if <5 yr since last tetanus-containing vaccine‖	No
	Yes, if ≥10 yr since last dose of tetanus-containing vaccine	No	Yes, if ≥5 yr since last tetanus-containing vaccine dose	No

*Including but not limited to wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, and frostbite.
†DTaP is used for children younger than 7 yr. Tdap is preferred over Td for underimmunized children 7 yr and older who have not received Tdap previously.
‡Intravenous immune globulin should be used when TIG is unavailable.
‖More frequent boosters are not needed and can accentuate adverse events.
DT, Diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.
Data from American Academy of Pediatrics. Tetanus (lockjaw). In Kiberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics, 2021;750–755.

PROGNOSIS

Recovery in tetanus occurs through regeneration of synapses within the spinal cord that results in restoration of muscle relaxation. Interestingly, an episode of tetanus does not result in the production of toxin-neutralizing antibodies, presumably because the infinitesimally small amounts of toxin required to cause disease are not sufficient to elicit an immune response. Therefore active immunization with tetanus toxoid during convalescence and/or at discharge, with provision for completion of the primary vaccine series, is mandatory.

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in the very young and the very old. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease. An unfavorable prognosis is associated with onset of trismus <7 days after injury and with onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy, diminished mental abilities, and behavioral difficulties. Most fatalities occur within the first week of illness. Reported case fatality rates for generalized tetanus are 5–35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

PREVENTION

Tetanus is an entirely and easily preventable disease. A serum antibody titer of ≥0.01 units/mL is considered protective. Active immunization should begin in early infancy with combined diphtheria toxoid–tetanus toxoid–acellular pertussis (DTaP) vaccine at 2, 4, 6, and 15-18 months of age, with boosters at 4-6 years (DTaP) and 11-12 years (Tdap) of age, and at 10-year intervals thereafter throughout adult life with tetanus and reduced diphtheria toxoid (Td). Recovery from tetanus does not confer permanent protective immunity, so immunization is recommended in those who have survived documented infection. Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive one dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27-36 weeks of gestation. Recommended immunization schedules are regularly updated; the most current versions may be found at http://www.cdc.gov/vaccines/schedules.

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction.

Wound Management

Tetanus prevention measures after trauma consist of inducing active immunity to tetanus toxin and of passively providing antitoxic antibody (Table 257.1). Tetanus prophylaxis is an essential part of all wound management, but specific measures depend on the nature of the injury and the immunization status of the patient. Prevention of tetanus must be included in planning for the consequences of bombings, natural disasters, and other possible civilian mass-casualty events.

Tetanus toxoid should always be given after a dog or other animal bite, even though *C. tetani* is infrequently found in canine mouth flora. **Nonminor wounds require human TIG** except those in a fully immunized patient (i.e., ≥3 doses of adsorbed tetanus toxoid). In any other circumstance (e.g., patients with an unknown or incomplete immunization history; crush, puncture, or projectile wounds; wounds contaminated with saliva, soil, or feces; avulsion injuries; compound fractures; or frostbite), TIG 250 units should be administered intramuscularly, regardless of the patient's age or weight. If TIG is unavailable, use of human intravenous immunoglobulin may be considered. If neither of these products is available, then 3,000-5,000 units of equine-derived TAT (in regions of the world where it is available) may be given intramuscularly after testing for hypersensitivity. Serum sickness may occur with this agent. Human monoclonal antibodies against the tetanus neurotoxin have recently been generated and characterized, but these are not yet available for clinical use.

The wound should undergo immediate, thorough surgical cleansing and debridement to remove foreign bodies and any necrotic tissue in which anaerobic conditions might develop. Tetanus toxoid should be given to stimulate active immunity and may be administered concurrently with **TIG** (or TAT); if a tetanus toxoid-containing vaccine and TIG are administered at the same time, then separate syringes and sites should be used. A tetanus toxoid booster (preferably Tdap) is administered to all persons with any wound if the tetanus immunization status is unknown or incomplete. A booster is administered to injured persons who have completed the primary immunization series if (1) the wound is clean and minor, but 10 or more years have passed since the last booster, or (2) the wound is more serious, and 5 or more years have passed since the last booster (see Table 257.1). Persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine should not receive Td more frequently than every 10 years, even for tetanus prophylaxis as part of wound management. In a situation of delayed wound care, active immunization should be started at once.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 258

Clostridioides difficile Infection

David P. Galloway and Mitchell B. Cohen

Clostridioides difficile (formerly *Clostridium difficile*) infection **(CDI)**, also known as **pseudomembranous colitis** or *C. difficile*–associated diarrhea, refers to gastrointestinal (GI) colonization with *C. difficile* resulting in a diarrheal illness. It is a common cause of **antibiotic-associated diarrhea** and the most common cause of healthcare-associated infections in the United States, accounting for 12% of these infections. An increase in inpatient and outpatient (community) acquisition of **CDI** has been observed, and additional risk factors have been identified.

ETIOLOGY

C. difficile is a gram-positive, spore-forming, anaerobic bacillus that is resistant to killing by alcohol. It is acquired from the environment or by the fecal-oral route. Organisms causing symptomatic intestinal disease produce **toxin A** and/or **toxin B**. These toxins affect intracellular signaling pathways, resulting in inflammation and cell death. The cytotoxic **binary toxin**, which belongs to the AB toxin family, is not present in the majority of strains but has been detected in epidemic strains.

EPIDEMIOLOGY

The incidence of **CDI** is increasing in pediatric patients, and the setting of acquisition is changing. There is both high incidence in hospitalized children and an emergence of community-onset infection. National data from the Centers for Disease Control and Prevention (CDC) estimate three cases of community-acquired **CDI** in children for every healthcare-acquired case. In addition to an overall increase in all strains, a *hypervirulent strain,* denoted **NAP1/BI/027** (also called **BI**), has emerged and is estimated to cause 10–20% of pediatric infections. This strain produces **binary toxin** and exhibits 16- and 23-fold increases in the production of toxins A and B, respectively.

Asymptomatic carriage occurs with potentially pathogenic strains and is common in neonates and infants ≤1 year old. A carrier frequency rate of 50% may occur in children <1 year old. Colonization rates decrease to less than 5% in healthy children >5 years old. Asymptomatic colonization with *C. difficile* is common in recently hospitalized patients, with rates of 20%. Carriers can infect other susceptible individuals.

Risk factors for **CDI** include the use of broad-spectrum antibiotics, hospitalization, exposure to a household member with diarrhea or an asymptomatic carrier, GI surgery, inflammatory bowel disease (IBD), Hirschsprung disease, chemotherapy, enteral tube feeding, proton pump inhibitor (PPI) or H_2-receptor antagonist use, malnutrition, and chronic illness.

PATHOGENESIS

Disease is caused by GI infection with a toxin-producing strain. Any process that disrupts normal flora, impairs the acid barrier defense, alters the normal GI immune response (e.g., IBD), or inhibits intestinal motility may lead to infection. Normal bowel flora appears to be protective, conferring *colonization resistance*.

By affecting intracellular signaling pathways and cytoskeletal organization, toxins induce an inflammatory response and cell death, leading to diarrhea and pseudomembrane formation. Antibodies against **toxin A** have been shown to confer protection against symptomatic disease, and failure of antibody production occurs in patients with recurrent disease.

CLINICAL MANIFESTATIONS

Infection with toxin-producing strains of *C. difficile* leads to a spectrum of disease ranging from mild, self-limited diarrhea, to explosive, watery diarrhea with occult blood or mucus, to **pseudomembranous colitis**, and even death. **Pseudomembranous colitis** is characterized by bloody diarrhea with accompanying fever, abdominal pain/cramps, nausea, and vomiting. Rarely, small-gut involvement, **toxic megacolon**, bacteremia, abscess formation, intestinal perforation, and death can occur.

Symptoms of **CDI** generally begin less than a week after colonization and may develop during or weeks after antibiotic exposure. Symptoms are generally more severe in certain populations, including patients receiving chemotherapy, patients with chronic GI disease (e.g., IBD), and some patients with cystic fibrosis (CF). **CDI**-associated **reactive arthritis** is an occasional complication, occurring in approximately 1.4% of children with **CDI**. Reactive arthritis begins a median of 10 days after initial GI symptoms, often accompanied by fever or rash. Joint involvement may be migratory or polyarticular and may resemble septic arthritis.

DIAGNOSIS

Evaluation for **CDI** should be reserved for children with **diarrhea**, defined as the passage of at least three loose stools within a 24-hour period or bloody diarrhea (Fig. 258.1 and Table 258.1). **CDI** is diagnosed by the detection of a *C. difficile* toxin in the stool of a symptomatic patient. Most patients present with a history of recent antibiotic

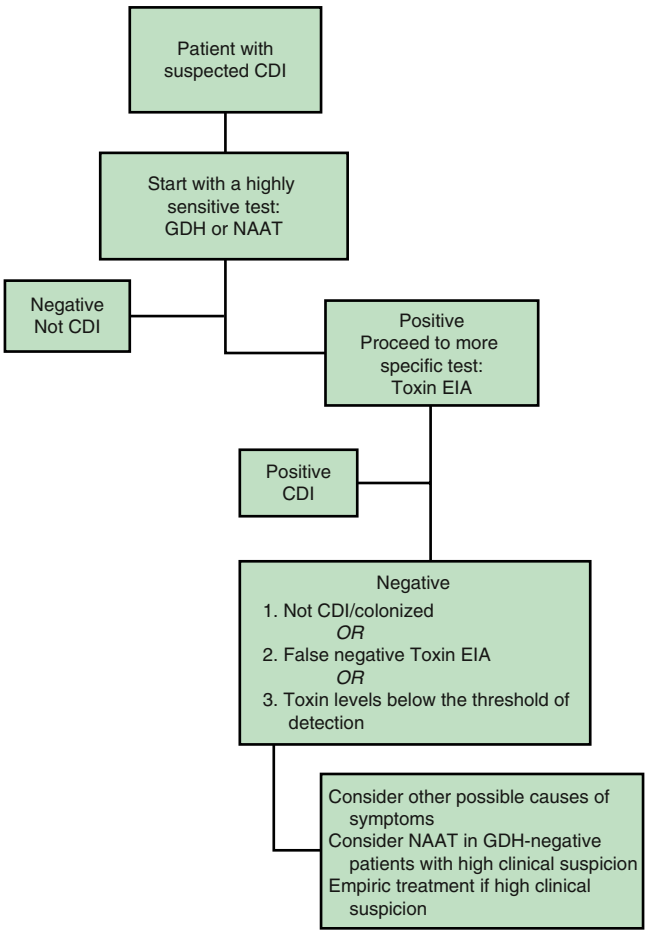

Fig. 258.1 Proposed algorithm for testing of *Clostridioides difficile* infection (CDI). EIA, Enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification testing. *(From Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of Clostridioides difficile in infections. Am J Gastroenterol. 2021;116:1124–1147, Fig. 1.)*

Table 258.1 Diagnosis of *C. difficile* Disease

- *Clostridium difficile* (renamed *Clostridioides difficile*) infection is diagnosed by a combination of clinical and laboratory findings.
- Diagnosis requires a positive test for the presence of *C. difficile* toxins.
- Glutamate dehydrogenase (GDH), produced by *C. difficile*, can be detected in stool. However, it is not specific and can be produced by nontoxigenic *C. difficile*.
- Enzyme immunoassay testing for toxin A and/or B has a variable sensitivity and specificity, a turnaround time of about 24 hours and correlates well with disease activity.
- Polymerase chain reaction testing has a high sensitivity and specificity, a turnaround time of less than 4 hours, and correlates less with disease activity, thus identifying patients with colonization and active infection. Increasingly, combination testing is being employed to improve diagnostic accuracy.
- Laboratory testing for *C. difficile* toxins should only be performed on patients with at least three unformed stools per 24 hours, who are not on laxatives, and is not useful as a test of cure.
- Pathologic findings can help to confirm the diagnosis.

From Semel JD. *Clostridioides difficile* colitis. In: Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier; 2023:561.

use, but the absence of antibiotic exposure should not dissuade the clinician from considering this diagnosis and ordering the appropriate test. Conversely, high carriage rates without illness among infants should prompt careful consideration when testing and treating children <3 years old.

The standard test for toxin is the **enzyme immunoassay** (EIA), a same-day test for **toxin A** and/or **toxin B** with sufficient specificity (94–100%) but less-than-ideal sensitivity (88–93%). Many laboratories use **nucleic acid amplification tests** (NAATs) to supplement or supplant **EIA** with the goal of improving sensitivity. The sensitivities of the real-time polymerase chain reaction (PCR) assay for **toxin A/B** are superior compared with **EIA** for **toxin A/B** (95% vs 35%, respectively), and the specificity is equal (100%). However, some have questioned the clinical significance of low copy number–positive tests. For example, positive *C. difficile* PCR results occur with similar frequency in patients with IBD with and without an IBD exacerbation. A positive result in a highly sensitive PCR assay that detects low copy numbers of a toxin gene in *C. difficile* may reflect colonization in a subset of patients (e.g., with IBD), confounding clinical decision-making in managing disease exacerbations. To address this, **NAAT**-positive tests may be "confirmed" by toxin assays. In addition, eliminating certain high carrier populations from testing (e.g., children under 1 year of age) will increase the positive predictive value of laboratory testing. Because sensitivity is so high with molecular tests, if the first test is negative, repeat testing during the same episode of diarrhea is discouraged, as repeat testing in this setting is more likely to result in another negative or a false-positive test than a true positive test. Because shedding of *C. difficile* in stool can persist for several months after symptom resolution, tests of cure are impractical and are not performed.

Culture for organism isolation is a sensitive test but is labor intensive, taking several days. Culture alone is not specific because it does not differentiate between toxin-producing and non–toxin-producing strains.

Pseudomembranous nodules and characteristic plaques may be seen in colonoscopy or sigmoidoscopy, but endoscopy is usually not performed to make the diagnosis.

TREATMENT

Initial treatment of **CDI** involves discontinuation of any nonvital antibiotic therapy and administration of fluid and electrolyte replacement. For mild cases, this treatment may be curative. Drugs that decrease intestinal motility should be avoided. Asymptomatic patients should not be treated. Persistent symptoms or moderate to severe disease warrant antimicrobial therapy directed against *C. difficile*.

Oral metronidazole or vancomycin is the first-line therapy for mild to moderate **CDI** in children (Table 258.2). In adults, vancomycin or fidaxomicin are the preferred first-line therapies. For more severe infection, oral vancomycin is approved by the U.S. Food and Drug Administration (FDA) for CDI. Vancomycin exhibits ideal pharmacologic properties for treatment of this enteric pathogen because it is not absorbed in the gut. Vancomycin is suggested as a first-line agent for severe disease, as manifested by hypotension, peripheral leukocytosis, or severe pseudomembranous colitis. Fidaxomicin is approved for use in children at least 6 months of age and is a narrow-spectrum macrolide antibiotic with noninferior efficacy to vancomycin but superior recurrence prevention. Because treatment of CDI continues to evolve, adult-based protocols (Table 258.3) may be relevant to older children and adolescents.

Table 258.2 Treatment Recommendations for *Clostridioides difficile* Infection in Children

CDI CLASSIFICATION	ANTIBIOTIC REGIMEN
First episode or first recurrence,* nonsevere	Metronidazole 7.5 mg/kg/dose (max 500 mg/dose) PO tid × 10 days; *OR* Vancomycin 10 mg/kg/dose (max 125 mg/dose) PO qid × 10 days
Second or subsequent† recurrence, nonsevere	Vancomycin in a tapered and pulsed regimen‡; *OR* Vancomycin (dosing and duration as above) followed by rifaximin 10 mg/kg/dose (max 400 mg/dose) PO tid × 20 days§; *OR* Fidaxomicin 16 mg/kg/dose (max 200 mg/dose) PO bid × 10 days; *OR* Fecal microbiota transplantation
Severe/fulminant‖ (first or recurrent¶ episode)	Vancomycin 10 mg/kg/dose (max 500 mg/dose) PO qid × 10 days If critically ill, consider adding metronidazole 7.5 mg/kg/dose (max 500 mg/dose) IV tid × 10 days

*For first recurrence, consider vancomycin if metronidazole was used to treat initial episode.
†Recommend tapered and pulsed regimen if vancomycin was used for the initial infection.
‡Tapered and pulsed regimen: vancomycin 10 mg/kg/dose (max 125 mg/dose) qid × 10-14 days, then 10 mg/kg/dose (max 125 mg/dose) bid × 1 wk, then 10 mg/kg/dose (max 125 mg/dose) qd × 1 wk, and then 10 mg/kg/dose (max 125 mg/dose) every 2-3 days for 2-8 wk.
§Pediatric rifaximin dosing is not available and not FDA-approved for children younger than 12 yr.
‖Definitions for severe and fulminant CDI are based on expert consensus for adult patients and have not been validated. Severe: leukocytosis with a white blood cell count of ≥15,000 cells/μL or a serum creatinine level >1.5 mg/dL. Fulminant: hypotension or shock, ileus, megacolon.
¶If treating a recurrent episode that is severe/fulminant, consider extending vancomycin in a pulsed, tapering fashion as indicated above§ or fecal microbiota transplantation when clinically improved.
Data from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018; 66(7):e1–e48.

PROGNOSIS AND RECURRENCE

The response rate to initial treatment of CDI can reach >95%. Studies have demonstrated a variation in response rates based on the severity of CDI and the treatment agent. Treatment failure and recurrence have been increasing; the risk of subsequent reappearance increases with each recurrence.

Recurrences occur in 5–20% of patients, are diagnosed clinically, and generally occur within 4 weeks of treatment. Some recurrences result from incomplete eradication of the original strain, and others are caused by reinfection with a different strain. Treatment for the initial recurrence involves retreatment with the original antibiotic course.

Table 258.3 Recommendations for the Treatment of *C. difficile* Infection in Adults

CLINICAL DEFINITION		SUPPORTIVE CLINICAL DATA	RECOMMENDED TREATMENT*	STRENGTH OF RECOMMENDATION/QUALITY OF EVIDENCE
Initial infection		Leukocytosis with white blood cell count of ≤15,000 cells/mL and serum creatinine level <1.5 mg/dL	Fidaxomicin 200 mg bid × 10 days	Strong/high
			Vancomycin 125 mg qid × 10 days	Strong/high
			Alternate if previous agents are unavailable: metronidazole 500 mg tid PO × 10-14 days	Weak/high
	Fulminant	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg qid PO or by nasogastric tube	Strong/moderate (oral vancomycin), weak/low (rectal vancomycin), strong/moderate (intravenous metronidazole)
			If ileus, consider adding rectal instillation of vancomycin; intravenous metronidazole (500 mg every 8 hr) should be administered with oral or rectal vancomycin, particularly if ileus is present	
Recurrence	First recurrence, nonsevere		Fidaxomicin 200 mg bid × 10 days, or bid × 5 days, then qod for 20 days *or*	Weak/low
			Use prolonged tapered and pulsed vancomycin regimen (if standard regimen was used for initial episode) 125 mg qid for 10-14 days, bid for 1 wk, qd for 1 wk, and then every 2 or 3 days for 2-8 wk, *or*	Weak/low
			Vancomycin 125 mg qid × 10 days (if metronidazole was used for the initial episode)	Weak/moderate
	Second or subsequent recurrence		Fidaxomicin 200 mg bid × 10 days, *or* bid × 5 days, then qod for 20 days	Weak/low
			Vancomycin in a tapered or pulsed regimen *or*	Weak/low
			Vancomycin 125 mg qid × 10 days, followed by rifaximin 400 mg tid × 20 days, *or*	Weak/low
			Fecal microbiota transplantation†	Strong/moderate

*All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment, and clinicians should consider extending treatment duration to 14 days in those circumstances.

†The opinion of the panel is that appropriate antibiotic treatments for at least two recurrences (i.e., three CDI episodes) should be tried before offering fecal microbiota transplantation. For adult patients with a recurrent CDI episode within the last 6 months, current guidelines suggest using bezlotoxumab in addition to appropriate antibiotics as the first approach.

PO, Orally (by mouth); qd, once daily; bid, twice daily; tid, 3 times daily; qid, 4 times daily; qod, every other day.

Adapted from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1–e48, Table 1; and Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021;73(5):e1029–e1044, Table 1.

Recurrences of CDI may be caused by a suboptimal immune response, failure to kill organisms that have sporulated, or failure of delivery of antibiotic to the site of infection in the case of ileus or toxic megacolon. Subsequent treatment with pulsed or tapered vancomycin decreases recurrence rates. In addition to this approach, other antibiotics (rifaximin or nitazoxanide), toxin-binding polymers (Tolevamer), and probiotics (*Saccharomyces boulardii* or *Lactobacillus* GG) have been used as adjunctive therapy. For adult patients with a recurrent CDI episode within the last 6 months, guidelines suggest using bezlotoxumab, a humanized monoclonal antibody against *C. difficile* toxin B, as a co-intervention. Because treatment of CDI continues to evolve, adult-based protocols (see Table 258.3) may be applicable for treatment of older children and adolescents.

Because failure to manifest an adequate antitoxin immune response is associated with a higher frequency of recurrent CDI, intravenous immune globulin has been used to treat recurrent disease. In the case of ileus or toxic megacolon, an enema of vancomycin may be used to place the antibiotic directly at the site of infection, although most often intravenous therapy is first attempted in this circumstance.

Fecal microbiota transplantation (FMT) has been used to address the disruption in normal gut flora thought to allow colonization with *C. difficile* (see Table 258.3). FMT involves the instillation of fecal material from a healthy donor into the patient's GI tract by nasoenteric tube, enema, capsules, or colonoscopy. Published FMT results in children with recurrent CDI are limited to case reports and small case series. There are few data to guide clinicians on the indications, route, efficacy, and safety of FMT in children. Initial reports indicate an overall success rate of approximately 90% in patients with recurrent CDI. Current approaches to FMT are not specific and involve complete reconstitution of the gut microbiome. The gut microbiota has been shown to influence susceptibility to genetic and environmentally acquired conditions. Transplantation of healthy donor fecal material to patients with CDI may reestablish the "normal" composition of the gut microbiota but has the theoretical concern of adding new, microbiome-based susceptibilities derived from the donor microbiome.

The FDA has approved an orally administered commercially available fecal microbiotic product for patients ≥18 years old, following antibiotic therapy for recurrent CDI. The goal is to prevent recurrence of CDI. Fecal-derived live bacteria from screened donors is administered once daily for 3 days.

It is important to recognize that postinfectious diarrhea may result from other causes, such as postinfectious irritable bowel syndrome, microscopic colitis, and IBD.

PREVENTION

The strategies for prevention of CDI include recognition of common sites of acquisition (hospitals, childcare settings, extended-care facilities); effective environmental cleaning (i.e., use of chlorinated cleaning solutions); appropriate antibiotic (antibiotic stewardship) and PPI prescription practices; cohorting of infected patients; contact precautions; and proper handwashing with soap and water. Probiotics may possibly reduce the incidence of *C. difficile*–associated diarrhea.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 259

Other Anaerobic Infections

Michael E. Russo

Anaerobic bacteria are among the most numerous organisms colonizing humans and are also present widely in the soil. **Obligate anaerobes** are markedly or entirely intolerant of exposure to oxygen. **Facultative anaerobes** can survive in the presence of environmental oxygen but grow better in settings of reduced oxygen tension. This chapter concentrates on obligate anaerobes and associated infections.

Infections with endogenous anaerobes usually occur adjacent to mucosal surfaces, often as polymicrobial infections with aerobes. In many of these polymicrobial infections, it is unclear how direct a role anaerobes are playing in illness versus just being present by virtue of breached mucosal barriers. Traumatized areas that have been devascularized with resultant low oxygen tension provide ideal sites for anaerobic infection. Abscess formation can evolve over days to weeks and generally involves both aerobes and anaerobes. An example of such an infection is ruptured appendicitis leading to secondary peritonitis and intrabdominal abscesses. Pure anaerobic infections from endogenous bacteria are much less common (although certain relevant clinical syndromes such as Lemierre syndrome are discussed later).

The most common and clinically relevant anaerobic bacteria in pediatrics are listed in Table 259.1 and discussed further later in the chapter. The taxonomy has undergone significant changes over the years, and many species that would not have been easily identifiable may now be identified in clinical specimens with the widespread use of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). Our understanding of anaerobic bacteria in infections is largely limited to easily culturable species. As many anaerobes of the human microbiota remain unculturable, our understanding of anaerobic infections will continue to evolve with culture-independent methods such as metagenomic sequencing.

Bacteroides fragilis and related species are the predominant anaerobes of the large intestine and thus are involved in complicated intraabdominal infections. *Prevotella* spp., *Porphyromonas* spp., and *Fusobacterium* spp. reside in the upper respiratory tract and intestine and are most frequently involved in complications of pharyngitis and sinusitis or in aspiration pneumonia. The gram-positive anaerobic cocci (GPAC) have undergone significant taxonomic changes in recent years, with most prior *Peptostreptococcus* spp. being reclassified into the genera of *Finegoldia, Parvimonas, Anaerococcus,* and *Peptoniphilus*. It is not clear yet how clinically relevant this reclassification is Collectively, the GPAC are normal flora of the skin and upper respiratory, intestinal, and genital mucosa. They may be involved in complications of infections of any of these areas, but they are relatively less virulent than other anaerobic bacteria, and their recovery in culture may or may not be clinically relevant. The gram-positive anaerobic bacilli can be divided into spore forming (*Clostridium* spp.) and non–spore-forming (*Cutibacterium acnes* [formerly *Propionibacterium acnes*] and *Actinomyces* spp.). *C. acnes* lives within hair follicles and sebaceous glands and is an important cause of prosthetic infections, particularly related to ventricular shunts. Some *Actinomyces* spp. are obligate or facultative anaerobes and are discussed in Chapter 235. *Clostridium* spp. cause disease by proliferation and often by production of toxins. Of the >60 species that have been identified, only a few cause infections in humans. The most frequently implicated *Clostridium* spp. are *C. difficile* (see Chapter 258), *C. perfringens* (discussed further later), *C. botulinum* (see Chapter 256), and *C. tetani* (see Chapter 257).

CLINICAL MANIFESTATIONS

Anaerobic infections occur in a variety of sites throughout the body, with examples including complications of pharyngitis such as peritonsillar abscess and Lemierre syndrome (see Chapter 432), dental abscesses (see Chapter 358), complications of sinusitis such as orbital cellulitis (see Chapter 674) and brain abscess (see Chapter 644), aspiration pneumonia (see Chapter 447) and lung abscess (see Chapter 453), secondary peritonitis (see Chapter 419), appendicitis (see Chapter 391), necrotizing enterocolitis (see Chapter 136), and pelvic inflammatory disease and tubo-ovarian abscesses (see Chapter 163).

Table 259.1 Clinically Relevant Anaerobic Bacteria in Common Pediatric Infections

Gram-positive cocci	*Peptostreptococcus, Finegoldia, Parvimonas, Anaerococcus,* and *Peptoniphilus* spp.
Gram-positive, spore-forming rods	*Clostridium* spp.
Gram-positive, non–spore-forming rods	*Cutibacterium acnes* Some *Actinomyces* spp.
Gram-negative bacilli	*Bacteroides fragilis* *Prevotella, Porphyromonas,* and *Fusobacterium* spp.

Anaerobic Bacteremia

Anaerobic bacteremia is relatively rare in children, and the yield of routine anaerobic blood cultures in various settings and patient populations continues to be debated. There is wide practice variation on the routine collection of anaerobic blood culture bottles, and multiple studies have failed to consistently identify predictive risk factors for anaerobic bacteremia in children. *B. fragilis* bacteremia has been seen most frequently (albeit uncommonly) in two settings: early-onset sepsis in premature infants and sepsis in those with compromised lower gastrointestinal tract mucosa (perforation, surgery, or chemotherapy-induced mucositis). *Fusobacterium* spp. bacteremia is typically seen in the setting of Lemierre syndrome: **septic thrombophlebitis** of the internal jugular vein as a complication of pharyngitis.

Myonecrosis (Gas Gangrene)

C. perfringens is the major etiologic cause of myonecrosis, a rapidly progressive anaerobic soft tissue infection. Gas gangrene usually affects muscles compromised by surgical or trauma sites that become contaminated with *C. perfringens* spores from soil or other foreign material. Infection progresses rapidly (within 24 hours) with swelling, edema, crepitus, and myonecrosis. Severe shock and multiorgan dysfunction are common. A clue to the diagnosis of gas gangrene is pain out of proportion to the clinical appearance of the wound. Exudate from surgical specimens reveals gram-positive bacilli but few leukocytes. Early and complete debridement with excision of necrotic tissue is key to controlling the infection. Repeated, frequent assessment of tissue viability in the operating room is required; however, the prognosis is poor, and morbidity and mortality are high. The role of adjunctive hyperbaric oxygen therapy is uncertain.

Food Poisoning

C. perfringens can also produce an enterotoxin that causes **food poisoning**. This intoxication results in the acute onset of watery diarrhea and crampy abdominal pain. Therapy is mainly supportive and consists of rehydration and electrolyte replacement if necessary. The illness resolves spontaneously within 24 hours of onset, and thus specific etiologic diagnosis is rarely made unless a large outbreak is investigated by public health authorities. Frequent sources of infection include meat and other animal products served in group settings during which food is allowed to sit for hours at temperatures warm enough to promote growth of *C. perfringens*.

DIAGNOSIS

The diagnosis of anaerobic infection requires a high index of suspicion and the collection of appropriate and adequate specimens for anaerobic culture (Table 259.2). Culture specimens should be obtained in a manner that protects them from contamination with mucosal bacteria. Aspirates of infected sites, abscess material, and biopsy specimens are appropriate for anaerobic culturing. Specimens should be protected from atmospheric oxygen and transported to the laboratory immediately. Anaerobic transport medium increases the likelihood of recovery of obligate anaerobes. Gram staining is useful, because even if the organisms do not grow in culture, they can be seen on the smear. Once growth has occurred, many clinically relevant anaerobes may now be identified by MALDI-TOF MS. 16S ribosomal RNA (rRNA) gene sequencing at a reference laboratory can identify less common bacteria.

Table 259.2 Clues to the Presumptive Diagnosis of Anaerobic Infections*

Infection contiguous to or near a mucosal surface colonized with anaerobic bacteria (oropharynx, intestinal-genitourinary tract)
Severe tissue necrosis, abscesses, gangrene, or fasciitis
Gas formation in tissues (crepitus on exam or gas visible on imaging)
Failure to culture organisms using conventional aerobic microbiologic methods, despite the presence of visible organisms on Gram stain
Toxin-mediated syndromes: botulism, tetanus, gas gangrene, food poisoning, pseudomembranous colitis

*Suspicion of anaerobic infection is critical before specimens are sampled for culture to ensure optimal microbiologic techniques.

Antimicrobial resistance among anaerobes has increased over time, and the susceptibility of anaerobes to certain antibiotics has become less predictable. A rapid and simple screening test for β-lactamase production and presumptive penicillin resistance can be performed on some anaerobic gram-negative bacilli. More detailed susceptibility testing is usually only available at reference laboratories and may be recommended for isolates recovered from sterile body sites that are deemed clinically important and are known to have variable or unique susceptibilities. Because anaerobic bacteria are less routinely submitted for susceptibility testing, local antibiogram data are frequently limited and extrapolated from larger national case series.

TREATMENT

Treatment of anaerobic infections usually requires adequate drainage and appropriate antimicrobial therapy. Anaerobes can be generally lumped into groups of predicted susceptibility, but because most anaerobic infections are polymicrobial, the choice of agents is frequently driven by the aerobic bacteria suspected or proven to be involved. The specific dose, frequency, and duration vary widely by the specific clinical syndrome.

ANAEROBIC GRAM-NEGATIVE BACILLI

Most *B. fragilis* produces a β-lactamase that hydrolyzes penicillins but is inhibited by most β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam but not avibactam). They also produce a cephalosporinase that hydrolyzes most cephalosporins but not cephamycins. Neither of the enzymes hydrolyzes carbapenems. Hence, most isolates are susceptible to ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, cefoxitin, and carbapenems (imipenem, meropenem, doripenem, and ertapenem). Notably, ceftazidime-avibactam is the exception to the reliability of β-lactamase inhibitors and does not have reliable *B. fragilis* activity. *Prevotella, Porphyromonas,* and *Fusobacterium* spp. are all generally less resistant than *Bacteroides*. They less frequently produce a β-lactamase, and many remain susceptible to penicillin. *Fusobacterium* spp. are usually susceptible to cephalosporins such as ceftriaxone, but *Prevotella* and *Porphyromonas* have more variable susceptibility.

Metronidazole is reliably active against nearly all anaerobic gram-negative bacilli. Clindamycin resistance in *B. fragilis* has increased over the years, and thus clindamycin is no longer recommended for empiric treatment, leading to the admonition against using clindamycin for infections "below the diaphragm." The other anaerobic gram-negative bacilli are usually still susceptible to clindamycin. Because of increasing resistance, moxifloxacin is no longer recommended as first-line therapy for infections involving anaerobic gram-negative bacilli.

ANAEROBIC GRAM-POSITIVE ORGANISMS

Most non–spore-forming, positive bacilli and some GPAC are resistant to metronidazole. Most are highly susceptible to penicillin but variably susceptible to clindamycin. Treatment of clostridial infections varies widely by the specific clinical syndrome and may or may not involve antibiotics and/or specific antitoxins.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 7

Mycobacterial Infections

Chapter 260

Principles of Antimycobacterial Therapy

Stacene R. Maroushek

The treatment of mycobacterial infection and disease can be challenging. Patients require therapy with multiple agents, the offending pathogens commonly exhibit complex drug resistance patterns, and patients often have underlying conditions that affect drug choice and monitoring. Several of the drugs have not been well studied in children, and current recommendations are extrapolated from the experience in adults.

Single-drug therapy of *Mycobacterium tuberculosis* and nontuberculous mycobacteria is not recommended because of the high likelihood of developing antimicrobial resistance. Susceptibility testing of mycobacterial isolates often can aid in therapeutic decision-making.

AGENTS USED AGAINST MYCOBACTERIUM TUBERCULOSIS

Commonly Used Agents

Isoniazid

Isoniazid **(INH)** is a hydrazide form of isonicotinic acid and is bactericidal for rapidly growing *M. tuberculosis.* The primary target of INH involves the *INHA* gene, which encodes the enoyl acyl carrier protein (ACP) reductase needed for the last step of the mycolic acid biosynthesis pathway of cell wall production. Resistance to INH occurs after pathogenic variants in the *INHA* gene or in other genes encoding enzymes that activate INH, such as *katG*.

INH is indicated for the treatment of *M. tuberculosis, M. kansasii,* and *M. bovis.* The pediatric dosage is 10-15 mg/kg/day orally (PO) in a single dose, not to exceed 300 mg/day. The adult dosage is 5 mg/kg/day PO in a single dose, not to exceed 300 mg/day. Alternative pediatric dosing is 20-30 mg/kg PO in a single dose, not to exceed 900 mg/dose, given twice weekly under **directly observed therapy (DOT)**, in which patients are observed to ingest each dose of antituberculosis medication to maximize the likelihood of completing therapy. The duration of treatment depends on the disease being treated (Table 260.1). INH needs to be taken 1 hour before or 2 hours after meals because food decreases absorption. It is available in liquid, tablet, intravenous (IV; not approved by the U.S. Food and Drug Administration [FDA]), and intramuscular (IM) preparations.

Major **adverse effects** include hepatotoxicity in 1% of children and approximately 3% of adults (increasing with age) and dose-related peripheral neuropathy. Pyridoxine can prevent the peripheral neuropathy and is indicated for breastfeeding infants and their mothers, children and youth on milk- or meat-deficient diets, pregnant adolescents, and symptomatic HIV-infected children. Minor adverse events include rash, worsening of acne, epigastric pain with occasional nausea and vomiting, decreased vitamin D levels, and dizziness. The liquid formulation of INH contains sorbitol, which often causes diarrhea and stomach upset.

INH is accompanied by significant drug-drug interactions (Table 260.2). The metabolism of INH is by acetylation. Acetylation rates have minimal effect on efficacy, but **slow acetylators** have an increased risk for hepatotoxicity, especially when INH is used in combination with rifampin. Routine baseline liver function testing or monthly monitoring is only indicated for persons with underlying hepatic disease or those receiving concomitant hepatotoxic drugs, including other antimycobacterial agents, acetaminophen, or alcohol. Monthly clinic visits while taking INH alone are encouraged to monitor adherence, adverse effects, and worsening of infection.

Rifamycins

The rifamycins (rifampin, rifabutin, rifapentine) are a class of macrolide antibiotics developed from *Streptomyces mediterranei.* Rifampin is a synthetic derivative of rifamycin B, and rifabutin is a derivative of rifamycin S. Rifapentine is a cyclopentyl derivative. The rifamycins inhibit the DNA-dependent RNA polymerase of mycobacteria, resulting in decreased RNA synthesis. These agents are generally bactericidal at treatment doses, but they may be bacteriostatic at lower doses. Resistance is from a pathogenic variant in the DNA-dependent RNA polymerase gene *(rpoB)* that is often induced by previous incomplete therapy. Cross-resistance between rifampin and rifabutin has been demonstrated.

Rifampin is active against *M. tuberculosis, M. leprae, M. kansasii,* and *M. avium* complex. Rifampin is an integral drug in standard combination treatment of active *M. tuberculosis* disease and can be used as an alternative to INH in the treatment of latent tuberculosis infection in children who cannot tolerate INH. **Rifabutin** has a similar spectrum, with increased activity against *M. avium* complex. **Rifapentine** is undergoing pediatric clinical trials and appears to have activity similar to the activity of rifampin. The pediatric dosage of rifampin is 10-15 mg/kg/day PO in a single dose, not to exceed 600 mg/day. The adult dosage of rifampin is 5-10 mg/kg/day PO in a single dose, not to exceed 600 mg/day. Commonly used rifampin preparations include 150- and 300-mg capsules and a suspension that is usually formulated at a concentration of 10 mg/mL. The shelf life of rifampin suspension is short (approximately 4 weeks), so it should not be compounded with other antimycobacterial agents. An IV form of rifampin is also available for initial treatment of patients who cannot take oral preparations. Dosage adjustment is needed for patients with liver failure. Other rifamycins (rifabutin and rifapentine) have been poorly studied in children and are not recommended for pediatric use.

Rifampin can be associated with **adverse effects** such as transient elevations of liver enzymes; gastrointestinal (GI) upset with cramps, nausea, vomiting, and anorexia; headache; dizziness; and immunologically mediated fever and flulike symptoms. Thrombocytopenia and hemolytic anemias can also occur. Rifabutin has a similar spectrum of toxicities, except for an increased incidence of rash (4%) and neutropenia (2%). Rifapentine has fewer adverse effects but is associated with hyperuricemia and cytopenias, especially lymphopenia and neutropenia. All rifamycins can turn urine and other secretions (tears, saliva, stool, sputum) *orange,* which can stain contact lenses. Patients and families should be warned about this common but otherwise innocuous adverse effect.

Rifamycins induce the hepatic cytochrome P450 (CYP) isoenzyme system and are associated with the increased metabolism and decreased level of several drugs when administered concomitantly. These drugs include digoxin, corticosteroids such as prednisone and dexamethasone, dapsone, fluconazole, phenytoin, oral contraceptives, warfarin, and many antiretroviral agents, especially protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifabutin has less of an effect on lowering protease inhibitor levels.

The use of pyrazinamide in combination with rifampin for short-course latent tuberculosis therapy has been associated with serious liver dysfunction and death. This combination has never been well studied or recommended for pediatric patients and should not be used.

Table 260.1 Recommended Usual Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

INFECTION/DISEASE CATEGORY	REGIMEN	COMMENTS
LATENT *MYCOBACTERIUM TUBERCULOSIS* INFECTION*		
Isoniazid susceptible	12 wk of isoniazid plus rifapentine once a wk *or*	
	4 mo of rifampin once a day *or*	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
	9 mo of isoniazid once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo.
Isoniazid resistant	4 mo of rifampin once a day	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
Isoniazid-rifampin resistant	Consult a tuberculosis specialist.	Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide.
PULMONARY AND EXTRAPULMONARY INFECTION		
Except meningitis†	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily or twice weekly, followed by 4 mo of isoniazid and rifampin‡ by DOT§ for drug-susceptible *M. tuberculosis*	Some experts recommend a three-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low. DOT is highly desirable. If hilar adenopathy only and the risk of drug resistance is low, 6-mo course of isoniazid and rifampin is sufficient. Drugs can be given 2 or 3 times/wk under DOT.
	9-12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide and an aminoglycoside‖ or ethionamide once daily, followed by 7-10 mo of isoniazid and rifampin once daily or twice weekly (9-12 mo total) for drug-susceptible *M. tuberculosis* At least 12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis*	For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin.

*Positive TST or IGRA result, no disease. See text for comments and additional acceptable/alternative regimens.
†Duration of therapy may be longer for human immunodeficiency virus (HIV)–infected people, and additional drugs and dosing intervals may be indicated
‡Medications should be administered daily for the first 2 wk to 2 mo of treatment and then can be administered 2-3 times/wk by DOT. (Twice-weekly therapy is not recommended for HIV-infected people.)
§If initial chest radiograph shows pulmonary cavities and sputum culture after 2 mo of therapy remains positive, the continuation phase is extended to 7 mo, for a total treatment duration of 9 mo.
‖Streptomycin, kanamycin, amikacin, or capreomycin.
DOT, Directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.
Adapted from American Academy of Pediatrics: *Red Book: 2018–2021 report of the Committee on Infectious Diseases*, 31st ed. Elk Grove Village, IL: AAP, 2018: Table 3.85.

Table 260.2 Isoniazid Drug-Drug Interactions

DRUG USED WITH ISONIAZID	EFFECTS
Acetaminophen, alcohol, rifampin	Increased hepatotoxicity of isoniazid or listed drugs
Aluminum salts (antacids)	Decreased absorption of isoniazid
Carbamazepine, phenytoin, theophylline, diazepam, warfarin	Increased level, effect, or toxicity of listed drugs due to decreased metabolism
Itraconazole, ketoconazole, oral hypoglycemic agents	Decreased level or effect of listed drugs due to increased metabolism
Cycloserine, ethionamide	Increased central nervous system adverse effects of cycloserine and ethionamide
Prednisolone	Increased isoniazid metabolism

No routine laboratory monitoring for rifamycins is indicated unless the patient is symptomatic. In patients with signs of toxicity, complete blood count (CBC) and kidney and liver function tests are indicated.

Pyrazinamide

Pyrazinamide **(PZA)** is a synthetic pyrazine analog of nicotinamide that is bactericidal against intracellular *M. tuberculosis* organisms in acidic environments, such as within macrophages or inflammatory lesions. A bacteria-specific enzyme (pyrazinamidase) converts PZA to pyrazinoic acid, which leads to low pH levels not tolerated by *M. tuberculosis*. Resistance is poorly understood but can arise from bacterial pyrazinamidase alterations.

PZA is indicated for the initial treatment phase of active tuberculosis in combination with other antimycobacterial agents. The pediatric dosage is 30-40 mg/kg/day PO in a single dose, not to exceed 2,000 mg/day. Twice-weekly dosing with DOT only is with 50 mg/kg/day PO in a single dose, not to exceed 4,000 mg/day. It is available in a 500-mg tablet and can be made into a suspension of 100 mg/mL.

Adverse effects include GI upset (e.g., nausea, vomiting, poor appetite) in approximately 4% of children, dosage-dependent hepatotoxicity, and elevated serum uric acid levels that can precipitate gout in susceptible adults. Approximately 10% of pediatric patients have elevated uric acid levels but with no associated clinical sequelae. Minor reactions include arthralgias, fatigue, and, rarely, fever.

Use of PZA in combination with rifampin for short-course treatment of latent tuberculosis is associated with serious liver dysfunction and death, and this combination should be avoided.

No routine laboratory monitoring for PZA is required, but monthly visits to reinforce the importance of therapy are desirable.

Ethambutol

Ethambutol is a synthetic form of ethylenedi-imino-di-1-butanol dihydrochloride that inhibits RNA synthesis needed for cell wall formation. At standard dosages, ethambutol is bacteriostatic, but at dosages >25 mg/kg, it has bactericidal activity. The mechanism of resistance to ethambutol is unknown, but resistance develops rapidly when ethambutol is used as a single agent against *M. tuberculosis.*

Ethambutol is indicated for the treatment of infections caused by *M. tuberculosis, M. kansasii, M. bovis,* and *M. avium* complex. Ethambutol should only be used as part of a combination treatment regimen for *M. tuberculosis.* Daily dosing is 15-25 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Twice-weekly dosing is with 50 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Dosage adjustment is needed in renal insufficiency. Ethambutol is available in 100- and 400-mg tablets.

The major adverse effect with ethambutol is **optic neuritis**, and thus ethambutol should generally be reserved for children old enough to have visual acuity and color discrimination reliably monitored. Visual changes are usually dosage dependent and reversible. Other adverse events include headache, dizziness, confusion, hyperuricemia, GI upset, peripheral neuropathy, hepatotoxicity, and cytopenias, especially neutropenia and thrombocytopenia.

Routine laboratory monitoring includes baseline and periodic visual acuity and color discrimination testing, CBC, serum uric acid levels, and kidney and liver function tests.

Less Commonly Used Agents

Aminoglycosides

The aminoglycosides used for mycobacterial infections include streptomycin, amikacin, kanamycin, and capreomycin. **Streptomycin** is isolated from *Streptomyces griseus* and was the first drug used to treat *M. tuberculosis.* **Capreomycin**, a cyclic polypeptide from *Streptomyces capreolus,* and **amikacin**, a semisynthetic derivative of kanamycin, are newer agents that are recommended when streptomycin is unavailable. Aminoglycosides act by binding irreversibly to the 30S subunit of ribosomes and inhibiting subsequent protein synthesis. Streptomycin exhibits concentration-dependent bactericidal activity, and capreomycin is bacteriostatic. Resistance results from a pathogenic variant in the binding site of the 30S ribosome, by decreased transport into cells, or by inactivation by bacterial enzymes. Cross-resistance between aminoglycosides has been demonstrated.

The aminoglycosides are indicated for the treatment of *M. tuberculosis* and *M. avium* complex. All are considered second-line drugs in the treatment of *M. tuberculosis* and should be used only when resistance patterns are known. Aminoglycosides are poorly absorbed orally and are administered by IM injection. Pediatric dosing ranges for streptomycin are 20 mg/kg/day if given daily and 20-40 mg/kg/day if given twice weekly; dosing is IM in a single daily dose. Capreomycin, amikacin, and kanamycin dosages are 15-30 mg/kg/day IM in a single dose, not to exceed 1 g/day. Dosage adjustment is necessary in renal insufficiency.

Aminoglycosides have **adverse effects** on proximal renal tubules, the cochlea, and the vestibular apparatus of the ear. Nephrotoxicity and ototoxicity account for most of the significant adverse events. Rarely, patients exhibit fever or rash with administration of aminoglycosides. Concomitant use of other nephrotoxic or ototoxic agents should be avoided, because adverse effects may be additive. An infrequent but serious synergistic, dosage-dependent aminoglycoside effect with nondepolarizing neuromuscular blockade agents can result in respiratory depression or paralysis.

Hearing and kidney function should be monitored at baseline and periodically. Early signs of ototoxicity include tinnitus, vertigo, and hearing loss. Ototoxicity appears to be irreversible, but early kidney damage may be reversible. As with other aminoglycosides, peak and trough drug levels are helpful in dosing and managing early toxicities.

Cycloserine

Cycloserine, derived from *Streptomyces orchidaceous* or *Streptomyces garyphalus,* is a synthetic analog of the amino acid D-alanine that interferes with bacterial cell wall synthesis through competitive inhibition of D-alanine components to be incorporated into the cell wall. It is bacteriostatic, and the mechanism of resistance is unknown.

Cycloserine is used to treat *M. tuberculosis* and *M. bovis*. The dosage is 10-20 mg/kg/day PO divided into two doses, not to exceed 1 g/day. It is available in a 250-mg capsule.

The major adverse effect is **neurotoxicity** with significant psychologic disturbance, including seizures, acute psychosis, headache, confusion, depression, and personality changes. The neurotoxic effects are additive with ethionamide and INH. Cycloserine has also been associated with megaloblastic anemia. It must be dosage-adjusted in patients with kidney impairment and should be used with caution in patients with underlying psychiatric illness.

Routine laboratory monitoring includes kidney and hepatic function, CBC, and cycloserine levels. Psychiatric symptoms are less common at blood levels <30 μg/mL.

Ethionamide

Ethionamide is structurally related to INH and is an ethyl derivative of thioisonicotinamide that inhibits peptide synthesis by an unclear mechanism thought to involve nicotinamide adenine dinucleotide (NAD) and NAD phosphate dehydrogenase disruptions. Ethionamide is bacteriostatic at most therapeutic levels. Resistance develops quickly if ethionamide is used as a single-agent therapy, although the mechanism is unknown.

Ethionamide is used as an alternative to streptomycin or ethambutol in the treatment of *M. tuberculosis* and has some activity against *M. kansasii* and *M. avium* complex. A metabolite, ethionamide sulfoxide, is bactericidal against *M. leprae.* Ethionamide has been shown to have good central nervous system (CNS) penetration and has been used as a fourth drug in combination with rifampin, INH, and PZA. The pediatric dosing is 15-20 mg/kg/day PO in two divided doses, not to exceed 1 g/day. It is available as a 250-mg tablet.

GI upset is common, and other **adverse effects** include neurologic disturbances (anxiety, dizziness, peripheral neuropathy, seizures, acute psychosis), hepatic enzyme elevations, hypothyroidism, hypoglycemia, and hypersensitivity reaction with rash and fever. Ethionamide should be used with caution in patients with underlying psychiatric or thyroid disease. The psychiatric adverse effects can be potentiated with concomitant use of cycloserine.

In addition to close assessment of mood, routine monitoring includes thyroid and liver function tests. In diabetic patients taking ethionamide, blood glucose levels should be monitored.

Fluoroquinolones

The fluoroquinolones are fluorinated derivatives of the quinolone class of antibiotics. Ciprofloxacin is a first-generation fluoroquinolone, and levofloxacin is the more active l-isomer of ofloxacin. **Moxifloxacin** and **gatifloxacin** are agents with emerging use in pediatric mycobacterial disease. Fluoroquinolones are not indicated for use in children <18 years old, but studies of their use in pediatric patients continue to indicate that they may be used in special circumstances. Fluoroquinolones are bactericidal and exert their effect by inhibition of DNA gyrase. The alterations in DNA gyrase result in relaxation of supercoiled DNA and breaks in double-stranded DNA. The mechanism of resistance is not well defined but likely involves pathogenic variants in the DNA gyrase.

Levofloxacin is an important second-line drug in the treatment of multidrug-resistant (MDR) *M. tuberculosis.* **Ciprofloxacin** has activity against *M. fortuitum* complex and against *M. tuberculosis.* The pediatric dosage of ciprofloxacin is 20-30 mg/kg/day PO or IV, not to exceed 1.5 mg/day PO or 800 mg/day IV. The adult dosage of ciprofloxacin is 500-750 mg/dose PO in two divided doses or 200-400 mg/dose IV every 12 hours. Ciprofloxacin is available in 100-, 250-, 500-, and 750-mg tablets and can be made in 5% (50 mg/mL) or 10% (100 mg/mL) suspensions. The dosage of levofloxacin for children is 5-10 mg/kg/day

given once daily either PO or IV, not to exceed 1,000 mg/day, and for adults, 500-1,000 mg/day PO or IV, not to exceed 1,000 mg/day. Levofloxacin is available in 250-, 500-, and 750-mg tablets, and a 50 mg/mL suspension can be extemporaneously compounded. The suspension has a shelf life of only 8 weeks.

The most common adverse effect of fluoroquinolones is **GI upset**, with nausea, vomiting, abdominal pain, and diarrhea, including pseudomembranous colitis. Other less common adverse effects include bone marrow depression, CNS effects (e.g., lowered seizure threshold, confusion, tremor, dizziness, headache), elevated liver transaminases, photosensitivity, and arthropathies. The potential for arthropathies (e.g., tendon ruptures, arthralgias, tendinitis) is the predominant reason that fluoroquinolones are not recommended for pediatric use. The mechanism of injury appears to involve the disruption of extracellular matrix of cartilage and depletion of collagen, a particular concern related to the bone and joint development of children.

Fluoroquinolones induce the CYP isoenzymes that can increase the concentrations of dually administered theophylline and warfarin. Nonsteroidal antiinflammatory drugs (NSAIDs) can potentiate the CNS effects of fluoroquinolones and should be avoided while taking a fluoroquinolone. Both ciprofloxacin and levofloxacin should be dosage-adjusted in patients with significant renal dysfunction.

While taking fluoroquinolones, patients should be monitored for hepatic and renal dysfunction, arthropathies, and hematologic abnormalities.

Linezolid

Linezolid is a synthetic oxazolidinone derivative. This drug is not currently approved for use against mycobacterial infection in pediatric or adult patients but has activity against some mycobacterial species. Studies on efficacy of treatment of mycobacterial infections are under way. Linezolid inhibits translation by binding to the 23S ribosomal component of the 50S ribosome subunit, preventing coupling with the 70S subunit. Resistance is thought to be from a point a pathogenic variant at the binding site but is poorly studied because only a few cases of resistance have been reported.

The approved indications for linezolid are for bacterial infections other than mycobacteria, but studies reveal in vitro activity against rapidly growing mycobacteria (*M. fortuitum* complex, *M. chelonae, M. abscessus*), *M. tuberculosis,* and *M. avium* complex. The dosage for 0- to 11-year-old children is 10 mg/kg/day PO or IV in divided doses every 8-12 hours. For persons >12 years old, the dosage is 600 mg PO or IV every 12 hours. Linezolid is available in 400- and 600-mg tablets and as a 20-mg/mL suspension.

Adverse effects of linezolid include GI upset (e.g., nausea, vomiting, diarrhea), CNS disturbances (e.g., dizziness, headache, insomnia, peripheral neuropathy), lactic acidosis, fever, myelosuppression, and pseudomembranous colitis. Linezolid is a weak inhibitor of monoamine oxidase A, and patients are advised to avoid foods with high tyramine content. Linezolid should be used cautiously in patients with preexisting myelosuppression.

In addition to monitoring for GI upset and CNS perturbations, routine laboratory monitoring includes CBC at least weekly.

Paraaminosalicylic Acid

Paraaminosalicylic acid **(PAS)** is a structural analog of paraaminobenzoic acid (PABA). It is bacteriostatic and acts by competitively inhibiting the synthesis of folic acid, similar to the action of sulfonamides. Resistance mechanisms are poorly understood.

PAS acts against *M. tuberculosis.* The dosage is 150 mg/kg/day PO in two or three divided doses. PAS is dispensed in 4-g packets, and the granules should be mixed with liquid and swallowed whole.

Common **adverse effects** include GI upset, and less common events include hypokalemia, hematuria, albuminuria, crystalluria, and elevations of hepatic transaminases. PAS can decrease the absorption of rifampin, and co-administration with ethionamide potentiates the adverse effects of PAS.

In addition to monitoring for weight loss, routine laboratory monitoring includes liver and kidney function tests.

Bedaquiline Fumarate

This oral diarylquinoline has been recommended for the treatment of MDR tuberculosis. Bedaquiline fumarate should be used as part of combination therapy and administered by direct observation. Although approved for patients ≥18 years old, bedaquiline may be considered for children on a case-by-case basis.

Serious **adverse effects** include hepatotoxicity and a prolonged QT interval.

Delamanid

Delamanid is a dihydro-nitroimidazooxazole derivative recently approved for use in the treatment of MDR tuberculosis. It acts by inhibiting the synthesis of mycobacterial cell wall compounds such as methoxymycolic acid and ketomycolic acid. Limited studies are available in the pediatric population, and delamanid should be used only in conjunction with a tuberculosis specialist.

Adverse effects include nausea, vomiting, dizziness, anxiety, shaking, and QT prolongation.

AGENTS USED AGAINST *MYCOBACTERIUM LEPRAE*

Dapsone

Dapsone is a sulfone antibiotic with characteristics similar to sulfonamides. Similar to other sulfonamides, dapsone acts as a competitive antagonist of PABA, which is needed for the bacterial synthesis of folic acid. Dapsone is bacteriostatic against *M. leprae.* Resistance is not well understood but is thought to occur after alterations at the PABA-binding site.

Dapsone is used in the treatment of *M. leprae* in combination with other antileprosy agents (rifampin, clofazimine, ethionamide). The pediatric dosage is 1-2 mg/kg/day PO as a single dose, not to exceed 100 mg/day, for a duration of 3-10 years. The adult dosage is 100 mg/day PO as a single dose. Dapsone is available in 25- and 100-mg scored tablets and as an oral suspension of 2 mg/mL. The dosage should be adjusted in renal insufficiency.

Dapsone has many reported **adverse effects**, including dosage-related hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, pancreatitis, renal complications (acute tubular necrosis, acute renal failure, albuminuria), increased liver enzymes, psychosis, tinnitus, peripheral neuropathy, photosensitivity, and a hypersensitivity syndrome with fever, rash, hepatic damage, and malaise. Treatment may produce a *lepra reaction,* which is a nontoxic, paradoxical worsening of lepromatous leprosy with the initiation of therapy. This hypersensitivity reaction is not an indication to discontinue therapy. Dapsone should be used with caution in patients with G6PD deficiency or taking other folic acid antagonists. Dapsone levels can decrease with concomitant rifampin use and can increase with concomitant clotrimazole use.

Routine laboratory monitoring includes CBC weekly during the first month of therapy, weekly through 6 months of therapy, and then every 6 months thereafter. Other periodic assessments include kidney function with creatine levels, urinalysis, and liver function tests.

Clofazimine

Clofazimine is a synthetic phendimetrazine tartrate derivative that acts by binding to the mycobacterial DNA at guanine sites. It has slow bactericidal activity against *M. leprae.* Mechanisms of resistance are not well studied. No cross-resistance between clofazimine and dapsone or rifampin has been shown.

Clofazimine is indicated as part of a combination therapy for the treatment of *M. leprae.* It appears there may be some activity against other mycobacteria such as *M. avium* complex, although treatment failures are common. The safety and efficacy of clofazimine are poorly studied in children. The pediatric dosage is 1 mg/kg/day PO as a single dose, not to exceed 100 mg/day, in combination with dapsone and rifampin for 2 years and then additionally as a single agent for >1 year. The adult dosage is 100 mg/day PO. Clofazimine should be taken with food to increase absorption.

The most common adverse effect is a dosage-related, reversible, pink to tan-brown discoloration of the skin and conjunctiva. Other **adverse**

effects include a dry, itchy skin rash, headache, dizziness, abdominal pain, diarrhea, vomiting, peripheral neuropathy, and elevated hepatic transaminases.

Routine laboratory monitoring includes periodic liver function tests.

AGENTS USED AGAINST NONTUBERCULOUS MYCOBACTERIA

Cefoxitin

Cefoxitin, a cephamycin derivative, is a second-generation cephalosporin that, like other cephalosporins, inhibits cell wall synthesis by linking with penicillin-binding proteins to create an unstable bacterial cell wall. Resistance develops by alterations in penicillin-binding proteins.

Cefoxitin is often used in combination therapy for mycobacterial disease (Table 260.3). Pediatric dosing is based on disease severity, with a range of 80-160 mg/kg/day divided every 4-8 hours, not to exceed 12 g/day. Adult dosages are 1-2 g/dose, not to exceed 12 g/day. Cefoxitin is available in IV and IM formulations. Increased dosing intervals are needed with renal insufficiency.

Adverse effects are primarily hematologic (eosinophilia, granulocytopenia, thrombocytopenia, hemolytic anemia), GI (nausea, vomiting,

Table 260.3 Treatment of Nontuberculous Mycobacteria Infections in Children

ORGANISM	DISEASE	INITIAL TREATMENT
SLOWLY GROWING SPECIES		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol and/or rifampin (or rifabutin).
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults with mild to moderate disease support that 3-times-weekly therapy is as effective as daily therapy, with less toxicity. For patients with advanced or cavitary disease, drugs should be given daily.
Mycobacterium chimaera	Prosthetic valve endocarditis	Valve removal, prolonged antimicrobial therapy based on susceptibility testing.
	Disseminated	See text.
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid daily. If rifampin resistance is detected, a three-drug regimen based on drug susceptibility testing should be used.
	Osteomyelitis	Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid.
Mycobacterium marinum	Cutaneous infection	None, if minor; rifampin, TMP-SMX, clarithromycin, or doxycycline* for moderate disease; extensive lesions may require surgical debridement. Susceptibility testing not routinely required.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin for 8 wk; excision to remove necrotic tissue, if present; potential response to thermotherapy.
RAPIDLY GROWING SPECIES		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus meropenem IV, followed by clarithromycin, doxycycline,* TMP-SMX, or ciprofloxacin PO on the basis of in vitro susceptibility testing; may require surgical excision. Up to 50% of isolates are resistant to cefoxitin.
	Catheter infection	Catheter removal and amikacin plus meropenem IV; clarithromycin, TMP-SMX, or ciprofloxacin orally on the basis of in vitro susceptibility testing.
Mycobacterium abscessus	Otitis media; cutaneous infection	There is no reliable antimicrobial regimen because of variability in drug susceptibility. Clarithromycin plus an initial course of amikacin plus cefoxitin or imipenem/meropenem; may require surgical debridement on the basis of in vitro susceptibility testing (50% are amikacin resistant).
	Pulmonary infection (in cystic fibrosis)	Serious disease; clarithromycin, amikacin, and cefoxitin or imipenem/meropenem on the basis of susceptibility testing; most isolates have very low MIC to tigecycline; may require surgical resection.
Mycobacterium chelonae	Catheter infection, prosthetic valve endocarditis	Catheter removal; debridement, removal of foreign material; valve replacement; and tobramycin (initially) plus clarithromycin, meropenem, and linezolid.
	Disseminated cutaneous infection	Tobramycin and meropenem or linezolid (initially) plus clarithromycin.

*Doxycycline can be used for short durations (i.e., ≤21 days) without regard to patient age but is not recommended for longer treatment durations in children <8 yr old. Only 50% of isolates of *M. marinum* are susceptible to doxycycline.

IV, Intravenously; MIC, minimum inhibitory concentration; PO, orally (by mouth); TMP-SMX, trimethoprim-sulfamethoxazole.

From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

diarrhea with possible pseudomembranous colitis), and CNS related (dizziness, vertigo). Potential additive adverse effects can occur when cefoxitin is used with aminoglycosides.

Routine laboratory monitoring with long-term use includes CBC and liver and renal function tests.

Doxycycline

Doxycycline is in the tetracycline family of antibiotics and has limited use in pediatrics. As with other tetracyclines, doxycycline acts to decrease protein synthesis by binding to the 30S ribosome and to transfer RNA. It can also cause alterations to the cytoplasmic membrane of susceptible bacteria.

Doxycycline is used to treat *M. fortuitum* (see Table 260.3). Although it can be used to treat *M. marinum,* adult treatment failures have occurred. Pediatric dosing is based on age and weight. For children >8 years old who weigh <45 kg, the dosage is 4.4 mg/kg/day divided twice daily. Dosing for larger children and adults is 100 mg twice daily. Doxycycline is available as 50- and 100-mg capsules or tablets and in 25-mg/5 mL and 50-mg/5 mL suspensions.

Doxycycline use in children is limited by a **permanent tooth discoloration**, which becomes worse with long-term use. Other **adverse effects** include photosensitivity, liver and kidney dysfunction, and esophagitis, which can be minimized by dosing with large volumes of liquid. Doxycycline can decrease the effectiveness of oral contraceptives. Rifampin, carbamazepine, and phenytoin can decrease the concentration of doxycycline.

Routine laboratory monitoring with long-term use includes kidney and liver function tests as well as CBC.

Macrolides

Clarithromycin and azithromycin belong to the macrolide family of antibiotics. Clarithromycin is a methoxy derivative of erythromycin. Macrolides act by binding the 50S subunit of ribosomes, subsequently inhibiting protein synthesis. Resistance mechanisms for mycobacteria are not well understood but might involve binding site alterations. Clarithromycin appears to have synergistic antimycobacterial activity when combined with rifamycins, ethambutol, or clofazimine.

Clarithromycin is widely used for the prophylaxis and treatment of *M. avium* complex disease and also has activity against *M. abscessus, M. fortuitum,* and *M. marinum.* Azithromycin has significantly different pharmacokinetics compared with other macrolide agents and has not been studied and is not indicated for mycobacterial infections. The pediatric dosage of clarithromycin for primary prophylaxis of *M. avium* complex infections is 7.5 mg/kg/dose PO given twice daily, not to exceed 500 mg/day. This dosage is used for recurrent *M. avium* complex disease in combination with ethambutol and rifampin. The adult dosage is 500 mg PO twice daily to be used as a single agent for primary prophylaxis or as part of combination therapy with ethambutol and rifampin. Dosage adjustment is needed for renal insufficiency but not liver failure. Clarithromycin is available in 250- and 500-mg tablets and suspensions of 125 mg/5 mL and 250 mg/5 mL.

The primary adverse effect of clarithromycin is **GI upset**, including vomiting (6%), diarrhea (6%), and abdominal pain (3%). Other **adverse effects** include taste disturbances, headache, and QT prolongation if used with inhaled anesthetics, clotrimazole, antiarrhythmic agents, or azoles. Clarithromycin should be used cautiously in patients with renal insufficiency or liver failure.

Routine laboratory monitoring with prolonged use of clarithromycin includes periodic liver enzyme tests. Diarrhea is an early sign of pseudomembranous colitis.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) is formulated in a fixed ratio of one part TMP to five parts SMX. SMX is a sulfonamide that inhibits synthesis of dihydrofolic acid by competitively inhibiting PABA, similar to dapsone. TMP blocks production of tetrahydrofolic acid and downstream biosynthesis of nucleic acids and protein by reversibly binding to dihydrofolate reductase. The combination of the two agents is synergistic and often bactericidal.

TMP-SMX is often used in combination therapy for mycobacterial disease (see Table 260.3). Oral or IV pediatric dosage for serious infections is TMP 15-20 mg/kg/day divided every 6-8 hours, and for mild infections, TMP 6-12 mg/kg/day divided every 12 hours. The adult dosage is 160 mg TMP and 800 mg SMX every 12 hours. Dosage reduction may be needed in renal insufficiency. TMP-SMX is available in single-strength tablets (80/400 mg TMP-SMX) and double-strength tablets (160/800 mg TMP-SMX) and in a suspension of 40 mg TMP and 200 mg SMX per 5 mL.

The most common adverse effect with TMP-SMX is **myelosuppression**. It must be used with caution in patients with G6PD deficiency. Other **adverse effects** include renal abnormalities, rash, aseptic meningitis, GI disturbances (e.g., pancreatitis, diarrhea), and prolonged QT interval if co-administered with inhaled anesthetics, azoles, or macrolides.

Routine laboratory monitoring includes monthly CBC and periodic electrolytes and creatinine to monitor renal function.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 261

Tuberculosis (*Mycobacterium tuberculosis*)

Lindsay H. Cameron and Jeffrey R. Starke

Mycobacterium tuberculosis has caused human disease for more than 4,000 years and is one of the most important infectious diseases worldwide. There are five closely related mycobacteria in the *Mycobacterium tuberculosis* complex: *M. tuberculosis, M. bovis, M. africanum, M. microti,* and *M. canetti. M. tuberculosis* is the most important cause of tuberculosis (TB) disease in humans. The tubercle bacilli are non–spore-forming, nonmotile, pleomorphic, weakly gram-positive curved rods 1-5 µm long, typically slender, and slightly bent. They can appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Löwenstein-Jensen culture media). These mycobacteria grow best at 37–41°C (98.6–105.8°F), produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is **acid fastness**—the capacity to form stable mycolate complexes with arylmethane dyes (crystal violet, carbolfuchsin, auramine, and rhodamine). They resist decoloration with ethanol and hydrochloric or other acids.

M. tuberculosis grows slowly, with a generation time of 12-24 hours. Isolation from clinical specimens on solid synthetic media usually takes 3-6 weeks, and drug susceptibility testing requires an additional 2-4 weeks. Growth can be detected in 1-3 weeks in selective liquid medium using radiolabeled nutrients (e.g., BACTEC radiometric system), and drug susceptibilities can be determined in an additional 3-5 days. Once mycobacterial growth is detected, the species of mycobacteria present can be determined within hours using high-pressure liquid chromatography analysis (identifying the mycolic acid fingerprint of each species) or DNA probes/nucleic amplification tests (NAATs).

NAATs are used to identify genes associated with *M. tuberculosis* drug resistance and complement phenotypic drug susceptibility testing. Results are available in hours, which expedites management decisions. Phenotypic drug susceptibility testing is necessary to confirm susceptibility to each drug. Restriction fragment length polymorphism genetic profiling of mycobacteria is a helpful tool to study the epidemiology of TB strain relatedness in both outbreaks and routine epidemiology of TB in a community.

CLINICAL STAGES

There are three major clinical stages of TB: exposure, infection, and disease. **Exposure** means a child has had recent significant contact (shared the air) with an adult or adolescent with infectious TB but lacks proof of infection. In this stage, the tuberculin skin test (TST) or interferon-γ release assay (IGRA) result is negative, the chest radiograph is normal, the physical examination is normal, and the child lacks signs or symptoms of disease. However, the child may be infected and develop TB disease rapidly, because there may not have been enough time for the TST or IGRA to turn positive. **Tuberculosis infection (TBI)** occurs when the individual inhales droplet nuclei containing *M. tuberculosis,* which survive intracellularly within the lung and associated lymphoid tissue. The hallmark of TBI is a positive TST or IGRA result. In this stage the child has no signs or symptoms and has a normal physical examination, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma. **Disease** occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated TBI has approximately a 5–10% lifetime risk of developing disease. In contrast, an infected child <1 year old has a 40% chance of developing TB disease within 9 months.

EPIDEMIOLOGY

TB remains a leading cause of death from an infectious disease worldwide. The global burden of TB is influenced by several factors, including the HIV pandemic; the development of **multidrug-resistant (MDR) tuberculosis**; the disproportionately low access of populations in low-resource settings worldwide to both diagnostic tests and effective medical therapy; and the COVID-19 pandemic.

The World Health Organization (WHO) 2020 Global Tuberculosis Report estimates that the COVID-19 pandemic could have a significant impact on access to essential TB services (human capital, financial), which may increase the rates of TB-associated morbidity and mortality. Many countries have had to allocate public health resources from TB prevention efforts toward COVID-19 prevention, including contact tracing and using GeneXpert machines for COVID-19 testing. The WHO predicts that this resource diversion from TB case-finding, testing, treatment, and prevention may result in an increase of global TB-associated deaths by 0.2-0.4 million per year.

Approximately 95% of TB cases occur in the developing world. In 2019, the 30 high-TB-burden countries accounted for 87% of incident cases (Fig. 261.1). Two thirds of cases occurred in eight countries, including India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. An estimated 10 million incident cases and 1.4 million TB-associated deaths occurred worldwide in 2019. The WHO 2020 Global Tuberculosis Report estimates that in 2019 there were 1.2 million childhood incident cases and 230,000 TB-associated deaths among children, including 32,000 TB-associated deaths among children living with HIV.

The incidence of drug-resistant TB has increased in some areas of the world in both adults and children. In 2019, the WHO reported a global total of 206,030 cases of multidrug- or rifampicin-resistant TB, a 10% increase from 2018 (Fig. 261.2). Isoniazid (INH)–monoresistant TB is resistance to INH alone, rifampicin-resistant TB (RR-TB) is resistance to at least rifampin, MDR-TB is defined as resistance to at least isoniazid and rifampin, and extensively drug-resistant tuberculosis TB (XDR-TB) includes MDR-TB plus resistance to any fluoroquinolone and at least one of three injectable drugs (kanamycin, capreomycin, or amikacin). In 2014, the worldwide estimate for MDR-TB in children was 2.9% of all cases and 0.1% for XDR-TB. The highest incidence of MDR-TB in children occurs in the Southeast Asian, African, and Western Pacific regions; however, the proportion of drug-resistant cases is highest in countries belonging to the Russian Federation, where over 30% of children with TB have a drug-resistant organism.

In the United States, TB case rates decreased steadily during the first half of the 20th century, long before the advent of antituberculosis drugs, as a result of improved living conditions and likely genetic selection favoring persons resistant to developing disease. A resurgence of TB in the late 1980s was associated primarily with the HIV epidemic, transmission of the organism in congregate settings including healthcare institutions, disease occurring in recent immigrants, and poor conduct of community TB control. Since 1992, the TB incidence in the

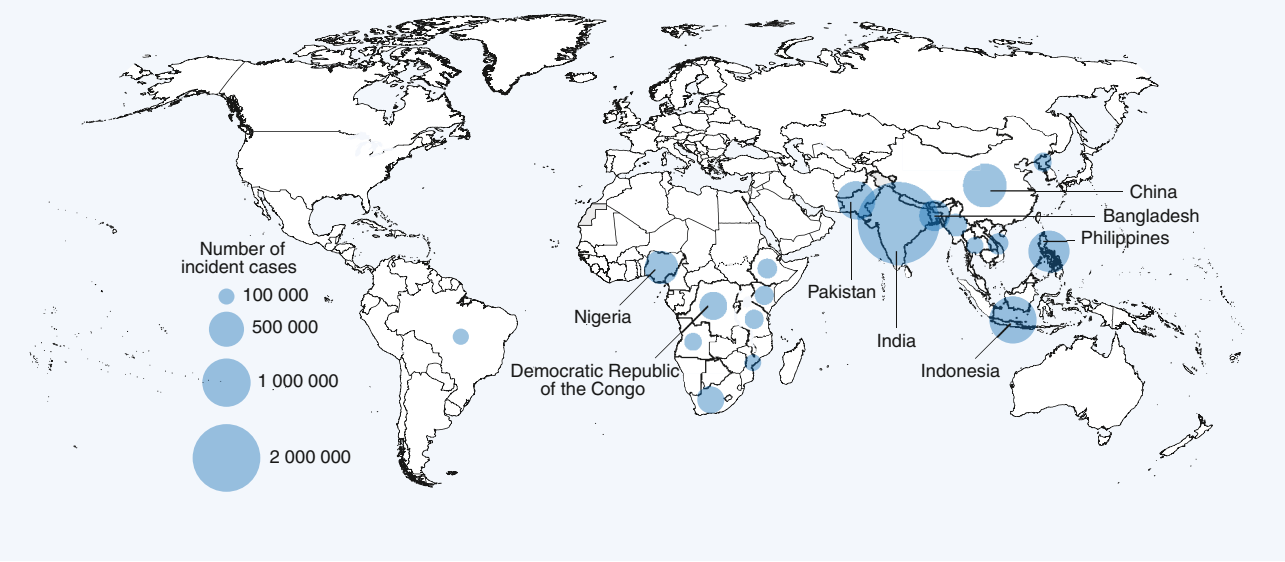

Fig. 261.1 Countries that had at least 100,000 incident cases of TB in 2021. The countries that rank first to eighth in terms of numbers of cases and that accounted for about two thirds of global cases in 2021 are labeled. *(From the World Health Organization: Global Tuberculosis Report 2022. Geneva: World Health Organization; 2022, Fig 12. License: CC BY-NC-SA 3.0 IGO.)*

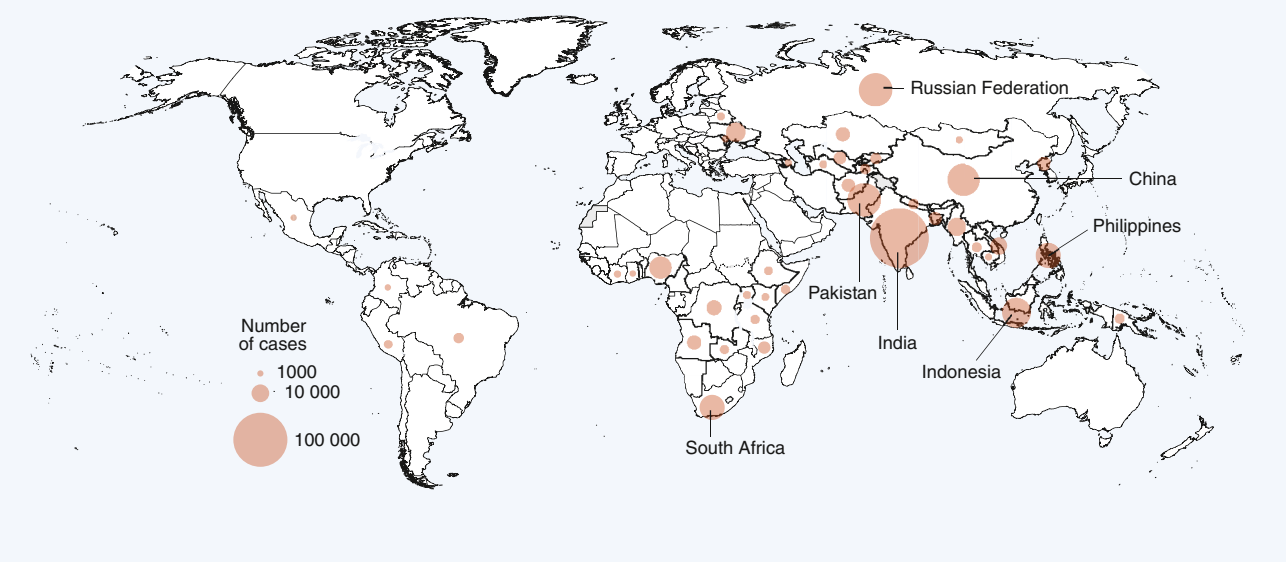

Fig. 261.2 Percentage of new TB cases with MDR-/RR-TB. The seven countries with the highest burden in terms of numbers of MDR/RR -TB cases and that accounted for two thirds of global MDR-/RR-TB cases in 2021 are labeled. *(From the World Health Organization: Global Tuberculosis Report 2022. Geneva: World Health Organization; 2022, Fig 17. License: CC BY-NC-SA 3.0 IGO.)*

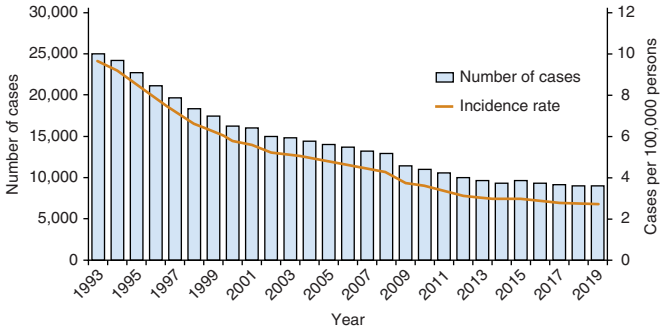

Fig. 261.3 Reported tuberculosis cases in the United States for 1993–2019 (as of October 29, 2020). *(From Centers for Disease Control and Prevention. Trends in Tuberculosis, 2019. Atlanta: U.S. Department of Health and Human Services; 2020.)*

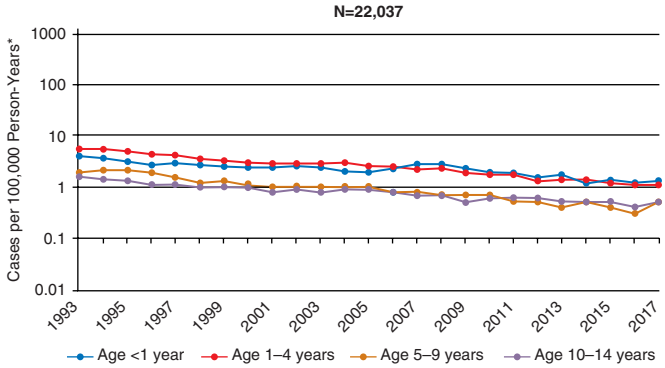

Fig. 261.4 Reported pediatric tuberculosis (TB) cases in the United States by age-group for the years 1993-2017. *Rates are presented on a logarithmic scale. *(From Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. Pediatric Tuberculosis in United States, 1993–2017. Atlanta: U.S. Department of Health and Human Services; 2018.)*

United States has decreased over time. In 2020, the case rate was at the all-time low of 2.2 per 100,000 persons (Fig. 261.3).

In 2017, the incidence rate of TB among children <15 years was 0.7 cases per 100,000 person-years, a decline of 41% from 1993. The TB incidence rates were highest in children less than 12 months of age (1.3 per 100,000 person-years), followed by children age 1-4 years (1.1 per 100,000 person-years), and were lowest among children age 5-14 years (0.5 per 100,000 person-years) (Fig. 261.4).

From 1993 to 2017, non-United States–born children, children born to non-United States–born parents, and children of racial or ethnic minority status were disproportionately affected by TB. Non-United States–born children accounted for approximately 25% of the total number of childhood TB cases, the majority being from Mexico, followed by the Philippines, Somalia, Vietnam, Ethiopia, and Haiti (Fig. 261.5).

According to data reported to the National TB Surveillance System from 2007 to 2017, among United States–born children, the incidence rates of TB if both parents were non-United States–born and if one parent was non-United States–born were eight and three times higher, respectively, compared to United States–born children with both parents being United States–born. This is supported by prior research that found that 75% of United States–born children with TB had some international connection through a family member or previous travel or residence in a TB-endemic country. Similar to adults in the United

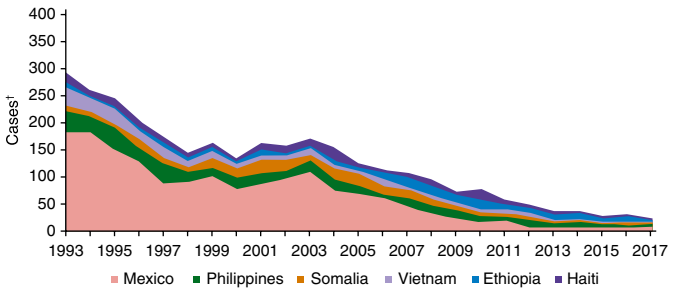

Fig. 261.5 Top six countries of birth for non–United States–born* pediatric TB cases for the years 1993-2017. *Non-United States–born refers to persons born outside the United States or its territories or not born to a US citizen. †Cases in United States–born children of non-United States–born parents are included in United States–born counts and thus not displayed in this figure. *(From Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. Pediatric Tuberculosis in United States, 1993–2017. Atlanta: U.S. Department of Health and Human Services; 2018.)*

States, TB among children of racial-ethnic minority status occurs disproportionately. The incidence rates of TB among children of Native Hawaiian or Pacific Islander, Asian, Native American or Native Alaskan, Black, and Hispanic children were 144, 44, 22, 19, and 18 times higher, respectively, than among non-Hispanic White children.

The rates of drug-resistant TB in children in the United States remain low. A total of 89 childhood cases of MDR-TB were reported in the United States in 2015; of those, 70.8% were non-United States–born. Among children with culture-confirmed TB in the United States in 2015, 15.2% had organisms with resistance to at least one first-line drug and 0.9% had MDR organisms.

Most children are infected with *M. tuberculosis* in their home by someone close to them, but outbreaks of childhood TB also have occurred in elementary and high schools, nursery schools, daycare centers and homes, churches, school buses, and sports teams. Adults living with HIV who have pulmonary TB can transmit *M. tuberculosis* to children, and children living with HIV are at increased risk for developing TB after infection. Other specific groups are at high risk for acquiring TBI and progressing to tuberculosis disease (Table 261.1).

Table 261.1 Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence

RISK FACTORS FOR TUBERCULOSIS INFECTION
Children exposed to high-risk adults
Foreign-born persons from high-prevalence countries
Homeless persons
Persons who inject drugs
Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes
Healthcare workers caring for high-risk patients (if infection control is not adequate)
RISK FACTORS FOR PROGRESSION OF TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Infants and children ≤4 yr old, especially those <2 yr old
Adolescents and young adults
Persons co-infected with human immunodeficiency virus
Persons with skin test conversion in the past 1-2 yr
Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition
RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS
Personal or contact history of treatment for tuberculosis
Contacts of patients with drug-resistant tuberculosis
Birth or residence in a country with a high rate of drug resistance
Poor response to standard therapy
Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy

TRANSMISSION

Transmission of *M. tuberculosis* is usually by inhalation of airborne mucus droplet nuclei, particles 1-5 μm in diameter that contain *M. tuberculosis.* Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough (although the absence of cough does not eliminate the risk of TBI). Environmental factors such as poor air circulation enhance transmission. Within several days to 2 weeks after beginning adequate chemotherapy, most adults no longer transmit the organism, but some patients remain infectious for many weeks. Young children with TB rarely infect other children or adults; tubercle bacilli are sparse in their endobronchial secretions, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. However, adolescents often present with adult-type cavity or endobronchial TB and can easily transmit the organism.

Airborne transmission of *M. bovis* and *M. africanum* also occurs rarely. *M. bovis* can penetrate the gastrointestinal (GI) mucosa or invade the lymphatic tissue of the oropharynx when large numbers of the organism are ingested. Human infection with *M. bovis* is rare in developed countries as a result of the pasteurization of milk and effective TB control programs for cattle. Approximately 46% of culture-proven childhood TB cases from the San Diego, California, region since 1994 were caused by *M. bovis,* likely acquired by children when visiting Mexico or another country or consuming dairy products from countries with suboptimal veterinary TB control programs.

Zoonotic transmission is an uncommon source of *M. tuberculosis* that has been reported in adults exposed to elephants and potentially cattle.

PATHOGENESIS

The **primary complex** (or **Ghon complex**) of TB includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts. Most of the bacilli are killed, but some survive within nonactivated macrophages, which carry them through lymphatic vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus can drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2-12 weeks as the organisms grow in number and **tissue hypersensitivity** develops. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation (Fig. 261.6). Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. If caseation is intense, the center of the lesion liquefies and empties into the associated bronchus, leaving a residual cavity.

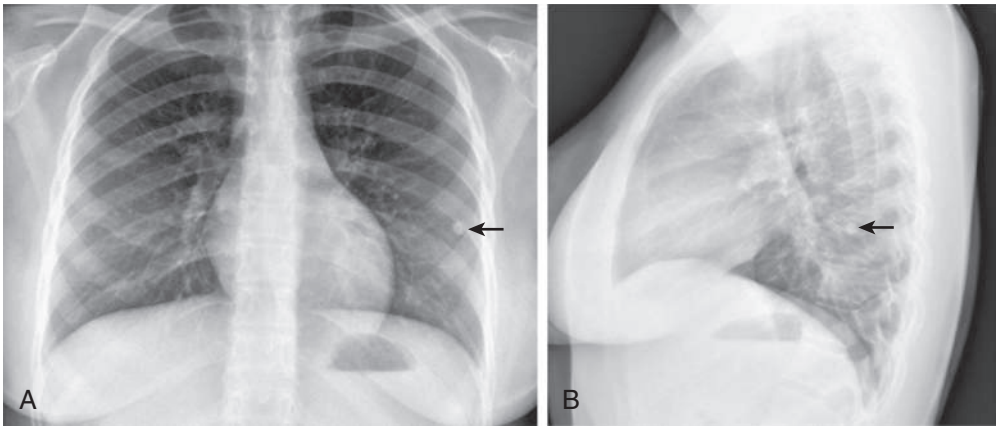

Fig. 261.6 Posteroanterior (A) and lateral (B) chest radiographs of an adolescent showing a 7-mm calcified granuloma in the left lower lobe *(arrows). (From Lighter J, Rigaud M. Diagnosing childhood tuberculosis: traditional and innovative modalities. Curr Probl Pediatr Adolesc Health Care. 2009;39:55–88.)*

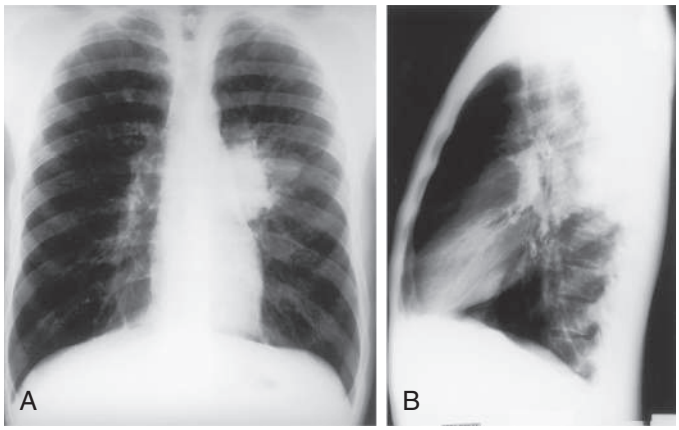

Fig. 261.7 A 14-yr-old child with proven primary tuberculosis. Frontal (**A**) and lateral (**B**) views of the chest show hyperinflation, prominent left hilar lymphadenopathy, and alveolar consolidation involving the posterior segment of the left upper lobe and the superior segment of the left lower lobe. *(From Hilton SVW, Edwards DK, eds. Practical Pediatric Radiology, 3rd ed. Philadelphia: Saunders; 2003:334.)*



Fig. 261.8 An 8-yr-old child with a history of cough. A single frontal view of the chest shows marked right hilar and paratracheal lymphadenopathy with alveolar disease involving the right middle and lower lung fields. This was also a case of primary tuberculosis. *(From Hilton SVW, Edwards DK, eds. Practical Pediatric Radiology, 3rd ed. Philadelphia: Saunders; 2003:335.)*

The foci of infection in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesion. Viable *M. tuberculosis* can persist for decades within these foci. In most cases of initial TBI, the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction can encroach on a regional bronchus (Figs. 261.7 and 261.8). Partial obstruction of the bronchus caused by external compression can cause hyperinflation in the distal lung segment. Complete obstruction results in atelectasis. Inflamed caseous nodes can attach to the bronchial wall and erode through it, causing endobronchial TB or a fistula tract. The caseum causes complete obstruction of the bronchus. The resulting lesion is a combination of pneumonitis and atelectasis and has been called a **collapse-consolidation lesion** or **segmental lesion** (Fig. 261.9).

During the development of the primary complex, tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels. Although seeding of the organs of the reticuloendothelial system is common, bacterial replication is more likely to occur in organs with conditions that favor their growth, such as the lung apices, brain, kidneys, and bones. **Disseminated tuberculosis** occurs if the number of circulating bacilli is large and the host's cellular immune response is inadequate. More often, the number of bacilli is small, leading to



Fig. 261.9 Right-sided hilar lymphadenopathy and collapse-consolidation lesions of primary tuberculosis in a 4-yr-old child. *(From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH (eds). Red Book: 2021-2024 Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics, 2021. p 805-806; with data from Furin J, Seddon J, Becerra M, et al. Management of Multi-drug-Resistant Tuberculosis Children: A Field Guide, 4th ed. Boston: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis, 2019. Available at:* http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf*)*

clinically inapparent metastatic foci in many organs. These remote foci usually become encapsulated, but they may be the origin of both **extrapulmonary tuberculosis** and **reactivation pulmonary tuberculosis**.

The time between initial infection and clinically apparent TB disease is variable. Disseminated and meningeal TB are early manifestations, often occurring within 2-6 months of acquisition. Significant lymph node or endobronchial TB usually appears within 3-9 months. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extrapulmonary manifestations are more common in children than in adults and develop in 25–35% of children with TB vs approximately 10% of immunocompetent adults.

Pulmonary TB that occurs >1 year after the primary infection is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions. This **reactivation TB** is rare in young children but is common among adolescents and young adults. The most common form is an infiltrate or cavity in the apex of the upper lobes, where oxygen tension and blood flow are highest.

The risk for dissemination of *M. tuberculosis* is very high in persons living with HIV. Reinfection also can occur in persons with advanced HIV or AIDS. In immunocompetent persons, the response to the initial infection with *M. tuberculosis* usually provides protection against reinfection when a new exposure occurs. However, exogenous reinfection has been reported to occur in adults and children without immune compromise in highly endemic areas.

Immunity

Conditions that adversely affect cell-mediated immunity predispose to progression from TBI to disease. Rare specific genetic defects (Mendelian susceptibility to mycobacterial disease [MSMD]) associated with deficient cell-mediated immunity in response to mycobacteria include interleukin (IL)-12 receptor B1 deficiency *TYK2* pathogenic gene variants; ~15 other genes associated with primary immunodeficiencies such as *NEMO, STAT1, JAK1,* and *RORC;* and complete and partial interferon (IFN)-γ receptor 1 chain deficiencies. TBI is associated with a humoral antibody response, which plays a little known role in host defense. Shortly after infection, tubercle bacilli replicate in both free alveolar spaces and inactivated alveolar macrophages. Sulfatides in the

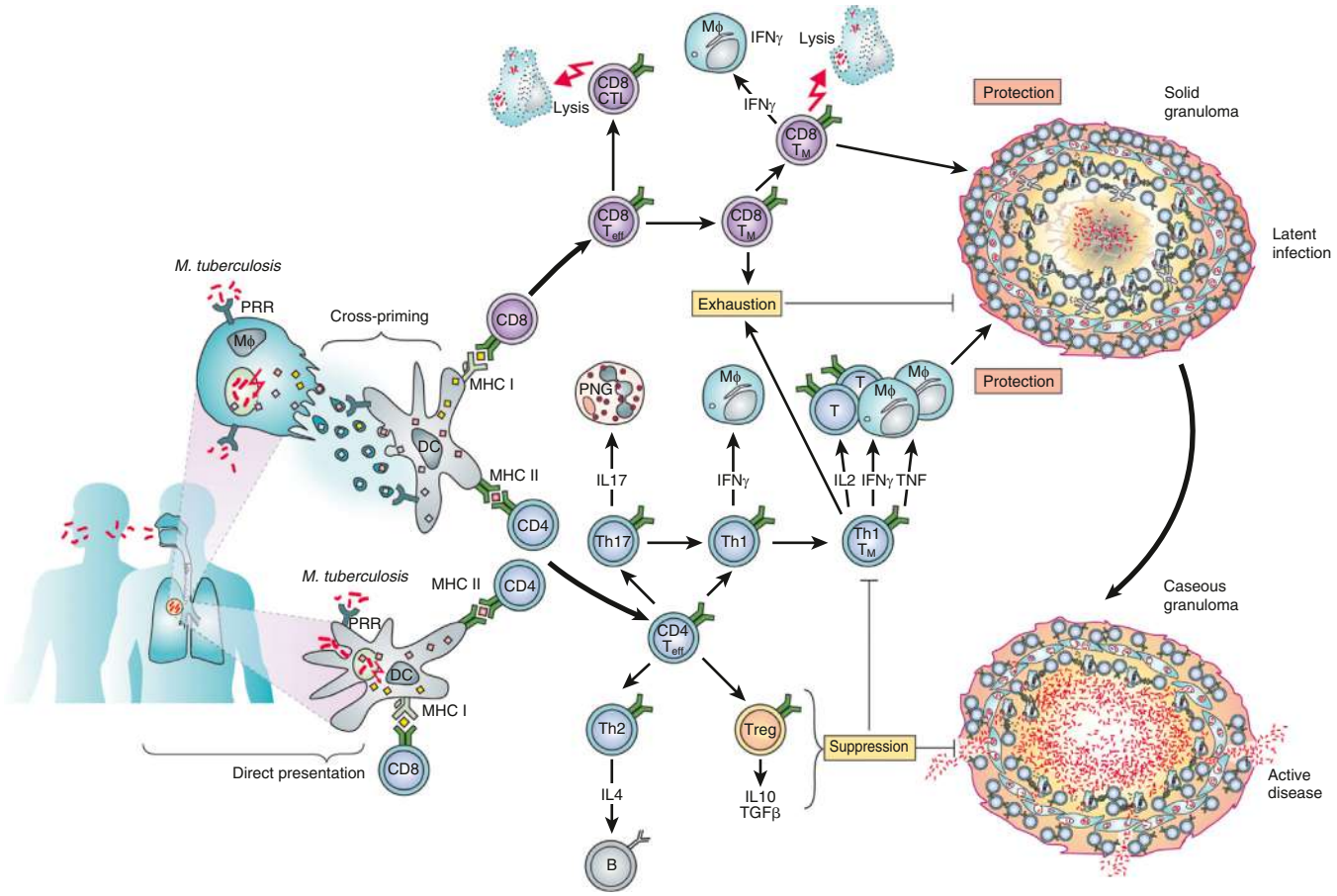

Fig. 261.10 Overview of the immune response in tuberculosis. Control of *Mycobacterium tuberculosis* is mainly the result of productive teamwork between T-cell populations and macrophages (Mø). *M. tuberculosis* survives within macrophages and dendritic cells (DCs) inside the phagosomal compartment. Gene products of major histocompatibility complex (MHC) class II are loaded with mycobacterial peptides that are presented to CD4 T cells. CD8 T-cell stimulation requires loading of MHC I molecules by mycobacterial peptides in the cytosol, either by egression of mycobacterial antigens into the cytosol or cross-priming, by which macrophages release apoptotic bodies carrying mycobacterial peptides. These vesicles are taken up by DCs and peptides presented. The CD4 T-helper (Th) cells polarize into different subsets. DCs and macrophages express pattern recognition receptors (PRRs), which sense molecular patterns on pathogens. Th1 cells produce interleukin (IL)-2 for T-cell activation, interferon-γ (IFN-γ), or tumor necrosis factor (TNF) for macrophage activation. Th17 cells, which activate polymorphonuclear granulocytes (PNGs), contribute to the early formation of protective immunity in the lung after vaccination. Th2 cells and regulatory T cells (Treg) counterregulate Th1-mediated protection via IL-4, transforming growth factor-β (TGF-β), or IL-10. CD8 T cells produce IFN-γ and TNF, which activate macrophages. They also act as cytolytic T lymphocytes (CTLs) by secreting perforin and granulysin, which lyse host cells and directly attack *M. tuberculosis*. These effector T cells (Teff) are succeeded by memory T cells (T_M). T_M cells produce multiple cytokines, notably IL2, IFN-γ, and TNF. During active containment in solid granuloma, *M. tuberculosis* recesses into a dormant stage and is immune to attack. Exhaustion of T cells is mediated by interactions between T cells and DCs through members of the programmed death 1 system. Treg cells secrete IL-10 and TGF-β, which suppress Th1. This process allows resuscitation of *M. tuberculosis,* which leads to granuloma caseation and active disease. B, B cell. *(From Kaufman SHE, Hussey G, Lambert PH. New vaccines for tuberculosis. Lancet. 2010;375:2110–2118.)*

mycobacterial cell wall inhibit fusion of the macrophage phagosome and lysosomes, allowing the organisms to escape destruction by intracellular enzymes. **Cell-mediated immunity** develops 2-12 weeks after infection, along with tissue hypersensitivity (Fig. 261.10). After bacilli enter macrophages, lymphocytes that recognize mycobacterial antigens proliferate and secrete lymphokines and other mediators that attract other lymphocytes and macrophages to the area. Certain lymphokines activate macrophages, causing them to develop high concentrations of lytic enzymes that enhance their mycobactericidal capacity. A discrete subset of regulator helper and suppressor lymphocytes modulates the immune response. Development of specific cellular immunity prevents progression of the initial infection in most persons.

The pathologic events in the initial TBI seem to depend on the balance among the mycobacterial antigen load; cell-mediated immunity (which enhances intracellular killing); and tissue hypersensitivity, which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, and fibroblasts. When both antigen load and degree of sensitivity are high, granuloma formation is less organized. Tissue necrosis is incomplete, resulting in formation of caseous material. When the degree of tissue sensitivity is low, as often occurs in infants or immunocompromised persons, the reaction is diffuse and the infection is not well contained, leading to dissemination and local tissue destruction. Tumor necrosis factor (TNF) and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible persons.

CLINICAL MANIFESTATIONS

Primary Pulmonary Disease

The **primary complex** includes the parenchymal pulmonary focus and the regional lymph nodes. Approximately 70% of lung foci are subpleural, and localized pleurisy is common. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. All lobar segments of the lung are at equal risk for initial infection. Two or more primary foci are present in 25% of cases. The hallmark of primary TB in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size

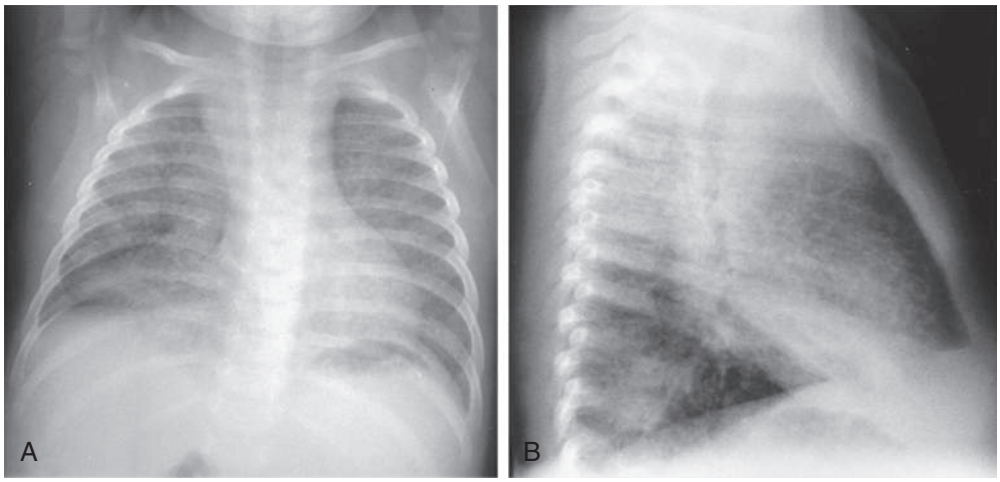

Fig. 261.11 Posteroanterior (A) and lateral (B) chest radiographs of an infant with miliary tuberculosis. The child's mother had failed to complete treatment for pulmonary tuberculosis twice within 3 years of this child's birth.

of the initial lung focus (see Figs. 261.7 and 261.8). As delayed-type hypersensitivity develops, the hilar lymph nodes continue to enlarge in some children, especially infants, compressing the regional bronchus and causing obstruction. The usual sequence is *hilar lymphadenopathy, focal hyperinflation,* and then *atelectasis.* The resulting radiographic shadows have been called **collapse-consolidation** or *segmental* TB (see Fig. 261.9). Rarely, inflamed caseous nodes attach to the endobronchial wall and erode through it, causing endobronchial TB or a fistula tract. The caseum causes complete obstruction of the bronchus, resulting in extensive infiltrate and collapse. Enlargement of the subcarinal lymph nodes can cause compression of the esophagus and, rarely, a bronchoesophageal fistula.

Most cases of tuberculous bronchial obstruction in children resolve fully with appropriate treatment. Occasionally, there is residual calcification of the primary focus or regional lymph nodes. The appearance of calcification implies that the lesion has been present for at least 6-12 months. Healing of the segment can be complicated by scarring or contraction associated with cylindrical bronchiectasis, but this is rare.

Children can have lobar TB pneumonia without impressive hilar lymphadenopathy. If the primary infection is progressively destructive, liquefaction of the lung parenchyma can lead to formation of a thin-walled primary TB cavity. Rarely, bullous tuberculous lesions occur in the lungs and lead to pneumothorax if they rupture. Erosion of a parenchymal focus of TB into a blood or lymphatic vessel can result in dissemination of the bacilli and a **miliary** pattern, with small nodules evenly distributed on the chest radiograph (Fig. 261.11).

The symptoms and physical signs of primary pulmonary TB in children are surprisingly meager considering the degree of radiographic changes often present. When active case finding is performed, up to 50% of infants and children with radiographically moderate to severe pulmonary TB have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive syndrome that often does not improve significantly until several months of effective treatment have been taken. Pulmonary signs are even less common. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds that may be accompanied by tachypnea or, rarely, respiratory distress. These pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial superinfection.

Progressive Primary Pulmonary Disease

A rare but serious complication of TB in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common. Physical signs include diminished breath sounds, rales, and dullness or egophony over the cavity. The prognosis for full recovery is excellent with appropriate therapy.

Reactivation Tuberculosis

Pulmonary TB in adults usually represents endogenous reactivation of a site of TBI established previously in the body. This form of TB is rare in childhood but can occur in adolescence. Children with a healed TBI acquired when they were <2 years old rarely develop chronic reactivation pulmonary disease, which is more common in those who acquire the initial infection when they are >7 years old. The most common pulmonary sites are the original parenchymal focus, lymph nodes, and the apical seedings **(Simon foci)** established during the hematogenous phase of the early infection. This form of TB disease usually remains localized in the lungs, because the established immune response prevents further extrapulmonary spread. The most common radiographic findings are extensive infiltrates and thick-walled cavities in the upper lobes.

Older children and adolescents with reactivation TB are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary TB. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months. This form of TB may be highly contagious if there is significant sputum production and cough. The prognosis for full recovery is excellent with appropriate therapy.

Pleural Effusion

Tuberculous pleural effusions, which can be local or general, originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated lymph node. Asymptomatic local pleural effusion is so common in primary TB that it is considered part of the primary complex. Larger and clinically significant effusions occur months to years after the primary infection. Tuberculous pleural effusion is uncommon in children <6 years old and rare in children <2 years old. Effusions are usually unilateral but can be bilateral. They are rarely associated with a segmental pulmonary lesion and are uncommon in disseminated TB. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms (Fig. 261.12).

Clinical onset of tuberculous pleurisy is often sudden and characterized by low to high fever, shortness of breath, chest pain on deep inspiration, and diminished breath sounds. The fever and other symptoms can last for several weeks after the start of antituberculosis chemotherapy. The TST is positive in 70–80% of cases. The prognosis is



Fig. 261.12 Pleural tuberculosis in 16-yr-old female.

excellent, but radiographic resolution often takes months. Scoliosis is a rare complication from a long-standing effusion.

Examination of pleural fluid and the pleural membrane is important to establish the diagnosis of tuberculous **pleurisy**. The pleural fluid is usually yellow and only occasionally tinged with blood. The specific gravity is usually 1.012-1.025, the protein level is usually 2-4 g/dL, and the glucose concentration may be low, although it is usually in the low-normal range (20-40 mg/dL). Typically, there are several hundred to several thousand white blood cells per microliter (WBCs/μL), with an early predominance of polymorphonuclear leukocytes (PMNs) followed by a high percentage of lymphocytes. Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Measurement of adenosine deaminase (ADA) levels may enhance the diagnosis of pleural TB. Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

Pericardial Disease

The most common form of cardiac TB is pericarditis. It is rare, occurring in 0.5–4% of TB cases in children. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30–70% of cases. ADA levels are elevated in TB pericarditis. The culture yield from pericardial biopsy may be higher, and the presence of granulomas often suggests the diagnosis. Partial or complete pericardiectomy may be required when constrictive pericarditis develops.

Lymphohematogenous (Disseminated) Disease

Tubercle bacilli are disseminated to distant sites, including the liver, spleen, skin, and lung apices, in all cases of TBI. Lymphohematogenous spread is usually asymptomatic. Rare patients experience protracted hematogenous TB caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of a blood vessel in the lung. The clinical picture subsequent to lymphohematogenous dissemination depends on the burden of organisms released from the primary focus to distant sites and the adequacy of the host's immune response. Although the clinical picture may be acute, more often it is indolent and prolonged, with spiking fever accompanying the release of organisms into the bloodstream. Multiple organ involvement is common, leading to hepatomegaly, splenomegaly, lymphadenitis in superficial or deep nodes, and papulonecrotic tuberculids appearing on the skin. Bones and joints or kidneys also can become involved. Meningitis occurs only late in the course of the disease. Early pulmonary involvement is surprisingly mild, but diffuse involvement becomes apparent with prolonged infection.

The most clinically significant form of disseminated TB is miliary disease, which occurs when massive numbers of tubercle bacilli are released into the bloodstream, causing disease in two or more organs. **Miliary tuberculosis** usually complicates the primary infection, occurring within 2-6 months of the initial infection. Although this form of disease is most common in infants and young children, it is also found in adolescents and older adults, resulting from the breakdown of a previously healed primary pulmonary lesion. The clinical manifestations of miliary TB are protean, depending on the number of organisms that disseminate and where they lodge. Lesions are often larger and more numerous in the lungs, spleen, liver, and bone marrow than in other tissues. Because this form of TB is most common in infants and malnourished or immunosuppressed patients, the host's immune incompetence likely plays a role in pathogenesis.

Rarely, the onset of miliary TB is explosive, and the patient can become gravely ill in several days. More often, the onset is insidious, with early systemic signs, including anorexia, weight loss, and low-grade fever. At this time, abnormal physical signs are usually absent. Generalized lymphadenopathy and hepatosplenomegaly develop within several weeks in approximately 50% of cases. The fever can then become higher and more sustained, although the chest radiograph usually is normal and respiratory symptoms are minor or absent. Within several more weeks, the lungs can become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. The lesions of miliary TB are usually <2-3 mm in diameter when first visible on chest radiograph (see Fig. 261.11). The smaller lesions coalesce to form larger lesions and sometimes extensive infiltrates. As the pulmonary disease progresses, an alveolar air block syndrome can result in frank respiratory distress, hypoxia, and pneumothorax or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20–40% of patients with advanced disease. Chronic or recurrent headache in a patient with miliary TB usually indicates the presence of meningitis, whereas the onset of abdominal pain or tenderness is a sign of tuberculous peritonitis. **Cutaneous lesions** include papulonecrotic tuberculids, nodules, or purpura. Choroid tubercles occur in 13–87% of patients and are highly specific for the diagnosis of miliary TB. Unfortunately, the TST is nonreactive in up to 40% of patients with disseminated TB.

Diagnosis of disseminated TB can be difficult, and a high index of suspicion by the clinician is required. Often the patient presents with fever of unknown origin (FUO). Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis. The most important clue is usually a history of recent exposure to an adult with infectious TB.

The resolution of miliary TB is slow, even with proper therapy. Fever usually declines within 2-3 weeks of starting chemotherapy, but the chest radiographic abnormalities might not resolve for many months. Occasionally, corticosteroids hasten symptomatic relief, especially when air block, peritonitis, or meningitis is present. The prognosis is excellent with early diagnosis and adequate chemotherapy.

Upper Respiratory Tract Disease

TB of the upper respiratory tract is rare in developed countries but is still observed in developing countries. Children with laryngeal TB have a crouplike cough, sore throat, hoarseness, and dysphagia. Most children with laryngeal TB have extensive upper lobe pulmonary disease, but occasional patients have primary laryngeal disease with a normal chest radiograph. TB of the middle ear results from aspiration of infected pulmonary secretions into the middle ear or from hematogenous dissemination in older children. The most common signs and symptoms are painless unilateral otorrhea, tinnitus, decreased hearing, facial paralysis, and a perforated tympanic membrane. Enlargement of



Fig. 261.13 Scrofula. Axial CT image of the neck in 8-yr-old male shows calcified right cervical lymphadenopathy *(black arrow)* and tonsillar swelling *(white arrow). (From Lighter J, Rigaud M. Diagnosing childhood tuberculosis: traditional and innovative modalities. Curr Probl Pediatr Adolesc Health Care. 2009;39:55–88.)*

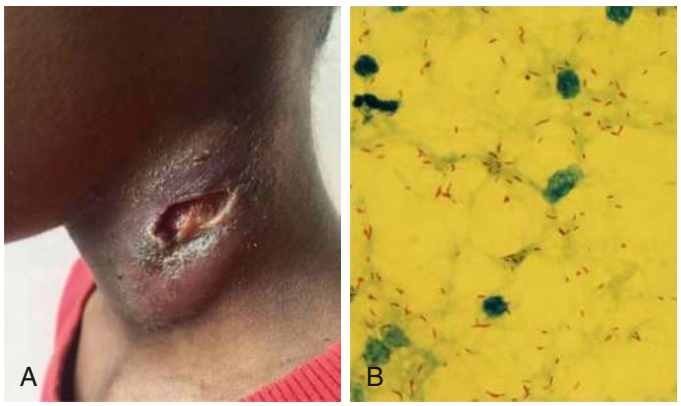

Fig. 261.14 Scrofula. A, Ulcerative lesion 3.2 × 2.1 cm with undermined edges and necrotic base with surrounding induration. B, Acid-fast bacilli. *(From Sharawat IK. Scrofula. J Pediatr. 2017;189:236.)*

lymph nodes in the preauricular or anterior cervical chains can accompany this infection. Diagnosis is difficult, because stains and cultures of ear fluid are often negative, and histology of the affected tissue often shows a nonspecific acute and chronic inflammation without granuloma formation.

Lymph Node Disease

TB of the superficial lymph nodes, often referred to as **scrofula**, is the most common form of extrapulmonary TB in children (Figs. 261.13-261.15). Historically, scrofula was usually caused by drinking unpasteurized cow's milk laden with *M. bovis*. Most current cases occur within 6-9 months of initial infection by *M. tuberculosis,* although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. Infected nodes in the inguinal, epitrochlear, or axillary regions result from regional



Fig. 261.15 Scrofula. Tuberculous lymphadenitis with fistula in 4-yr-old male associated with scrofuloderma *(arrows). (From Pereira C, Cascais M, Felix M, Salgado M. Scrofula in a child. J Pediatr. 2017;189:235.)*

lymphadenitis associated with TB of the skin or skeletal system. The nodes usually enlarge gradually in the early stages of lymph node disease. They are discrete, nontender, and firm but not hard. The nodes often feel fixed to underlying or overlying tissue. Disease is most often **unilateral**, but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. As infection progresses, multiple nodes are infected, resulting in a mass of matted nodes. Systemic signs and symptoms other than a low-grade fever are usually absent. The TST is usually reactive. The chest radiograph is often normal (in 70% of cases). The onset of illness is occasionally more acute, with rapid enlargement, tenderness, and fluctuance of lymph nodes and with high fever. The initial presentation is rarely a fluctuant mass with overlying cellulitis or skin discoloration.

Lymph node TB can resolve if left untreated but more often progresses to caseation and necrosis. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. Rupture of the node usually results in a draining sinus tract that can require surgical removal. **Tuberculous lymphadenitis** can usually be diagnosed by fine-needle aspiration (FNA) of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size for months or even years. Surgical removal is not usually necessary and must be combined with antituberculosis medication, because the lymph node disease is only one part of a systemic infection.

A definitive diagnosis of tuberculous adenitis usually requires histologic, bacteriologic, or molecular confirmation, which is best accomplished by FNA for culture, molecular testing, stain, and histology. If FNA is not successful in establishing a diagnosis, excisional biopsy of the involved node is indicated. Culture of lymph node tissue yields the organism in only approximately 50% of cases. Many other conditions can be confused with tuberculous adenitis, including infection caused by **nontuberculous mycobacteria (NTM)**, cat scratch disease *(Bartonella henselae),* tularemia, brucellosis, toxoplasmosis, pyogenic infection, or noninfectious causes, including tumor, branchial cleft cyst, and cystic hygroma. The most common problem is distinguishing infection caused by *M. tuberculosis* from lymphadenitis caused by NTM in geographic areas where NTM are common. Both conditions are usually associated with a normal chest radiograph and a reactive TST. An important clue to the diagnosis of tuberculous adenitis is an epidemiologic link to an adult with infectious TB. In areas where both diseases are common, culture or PCR testing of the involved tissue may be necessary to establish the exact cause of the disease.

Central Nervous System Disease

TB of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment. **Tuberculous meningitis** usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops

during the lymphohematogenous dissemination of the primary infection. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of the cerebral cortex. The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular system at the level of the basilar cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in the severe damage that can occur gradually or rapidly. Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis complicates approximately 0.3% of untreated TBIs in children. It is most common in children 6 months to 4 years old. Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of one or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More often, the signs and symptoms progress slowly over weeks and are divided into three stages.

The **first stage** typically lasts 1-2 weeks and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones. The **second stage** usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment. The **third stage** is marked by coma, hemiplegia or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the first stage have an excellent outcome, whereas most patients in the third stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children. It is imperative that antituberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology. Often the key to the correct diagnosis is identifying an adult who has infectious TB and is in contact with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in the adult in many cases.

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician. The TST is nonreactive in up to 50% of cases, and 20–50% of children have a normal chest radiograph. The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF. The CSF leukocyte count usually ranges from 10 to 500 cells/μL. PMNs may be present initially, but lymphocytes predominate in the majority of cases. The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL. The protein level is elevated and may be extremely high (400-5,000 mg/dL) secondary to hydrocephalus and spinal block. Although the lumbar CSF is grossly abnormal, ventricular CSF can have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction. During early stage one, the CSF can resemble that of viral aseptic meningitis, only to progress to the more severe CSF profile over several weeks. The success of the microscopic examination of acid-fast–stained CSF and mycobacterial culture is related directly to the volume of the CSF sample. Examinations or culture of small amounts of CSF are unlikely to demonstrate *M. tuberculosis.* It is recommended that serial collections of large-volume lumbar CSF (up to 15 mL) be obtained for acid-fast stain and culture. When 5-10 mL of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 30% of cases and the culture is positive in 50–70% of cases. Polymerase chain reaction (PCR) testing of the CSF and ADA levels can improve the diagnosis. Cultures of other body fluids can help confirm the diagnosis.

Radiographic studies can aid in the diagnosis of tuberculous meningitis. CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease. As the disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings (Fig. 261.16). Some young children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions.

Another manifestation of CNS TB is the **tuberculoma,** a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor. Tuberculomas account for up to 30% of brain tumors in some areas of the world but are rare in North America. In adults, tuberculomas are most often supratentorial, but in children, they are often infratentorial, located at the base of the brain near the cerebellum (Fig. 261.17). Lesions are most often singular but may be multiple. The most common symptoms are headache, fever, focal neurologic findings, and convulsions. The TST is usually reactive, but the chest radiograph is usually normal. Surgical excision is sometimes necessary to distinguish tuberculoma from other causes of brain tumor. However, surgical removal is not necessary because most tuberculomas resolve with medical management. Corticosteroids are administered during the first few weeks of treatment or in the immediate postoperative period to decrease cerebral edema. On CT or MRI of the brain, tuberculomas usually appear as discrete lesions with a significant amount of surrounding edema. Contrast medium enhancement is often impressive and can result in a ringlike lesion. Since the advent of CT, the paradoxical development of tuberculomas in patients with tuberculous meningitis who are receiving ultimately effective chemotherapy has been recognized. The cause and nature of these tuberculomas are poorly understood, but they do not represent failure of antimicrobial treatment. This phenomenon should be considered whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings during treatment. Corticosteroids

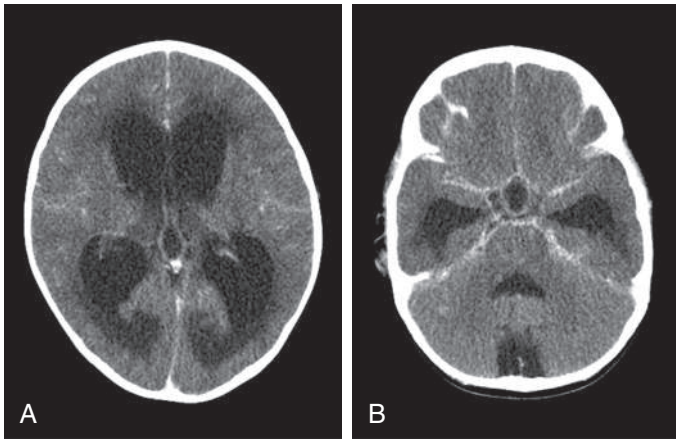

Fig. 261.16 Tuberculous meningitis in a child. **A** and **B**, Postcontrast CT images demonstrate intense enhancement in the suprasellar cistern, sylvian cistern, and prepontine cistern. Dilation of the ventricular system is seen, consistent with associated hydrocephalus. *(From Lerner A, Rajamohan A, Shiroishi MS, et al. Cerebral infections and inflammation. In Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig 10-20.)*

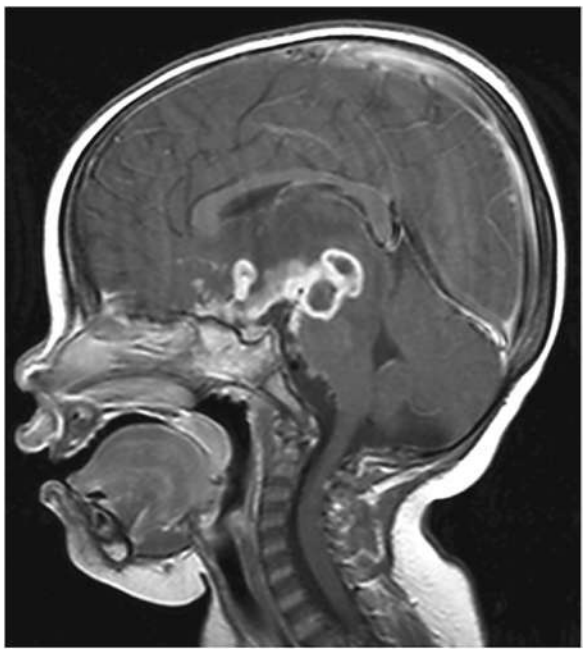

Fig. 261.17 MRI of brain of 3-yr-old child showing multiple pontine tuberculomas.

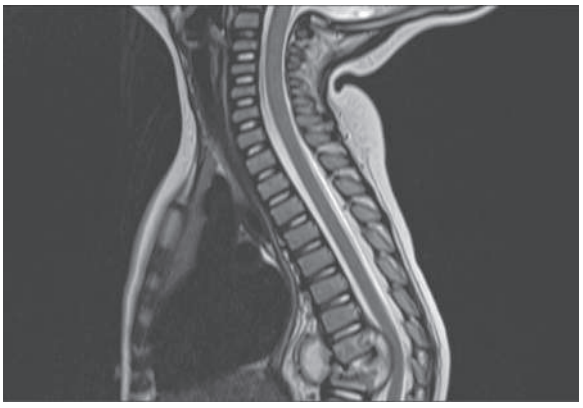

Fig. 261.18 Tuberculosis of the spine in a toddler. *(From Feder HM Jr, Rigos L, Teti K. Pott's disease in a Connecticut toddler. Lancet. 2016;388:504–505.)*

can alleviate the occasionally severe clinical signs and symptoms that occur. These lesions can persist for months or years.

Cutaneous Disease

Cutaneous TB is rare in the United States but occurs worldwide and accounts for 1–2% of tuberculosis (see Chapter 706).

Bone and Joint Disease

TB involving bone or joints is most likely to involve the vertebrae. The classic manifestation of **tuberculous spondylitis** is progression to **Pott disease**, in which destruction of the vertebral bodies leads to gibbus deformity and kyphosis (Fig. 261.18) (see Chapter 720.4). **Skeletal tuberculosis** is a late complication of TB and has become a rare entity since the availability of antituberculosis therapy but is more likely to occur in children than in adults. Tuberculous bone lesions can resemble pyogenic and fungal infections or bone tumors. *Multifocal bone involvement can occur.* A bone biopsy is essential to confirm the diagnosis. Surgical intervention is generally not necessary for cure, and the prognosis is excellent with adequate medical treatment. A sterile polyarticular (large joint) arthritis may also be noted in patients with active TB at another site.

Abdominal and Gastrointestinal Disease

TB of the oral cavity or pharynx is quite unusual. The most common lesion is a painless ulcer on the mucosa, palate, or tonsil with enlargement of the regional lymph nodes. TB of the parotid gland has been reported rarely in endemic countries. TB of the esophagus is rare in children but may be associated with a tracheoesophageal fistula in infants. These forms of TB are usually associated with extensive pulmonary disease and swallowing of infectious respiratory secretions. They can occur in the absence of pulmonary disease, by spread from mediastinal or peritoneal lymph nodes.

Tuberculous peritonitis occurs most often in young males and is uncommon in adolescents and rare in children. Generalized peritonitis can arise from subclinical or miliary hematogenous dissemination. Localized peritonitis is caused by direct extension from an abdominal lymph node, intestinal focus, or genitourinary TB. Rarely, the lymph nodes, omentum, and peritoneum become matted and can be palpated as a doughy, irregular, nontender mass. Abdominal pain or tenderness, ascites, anorexia, and low-grade fever are typical manifestations. The TST is usually reactive. The diagnosis can be confirmed by paracentesis with appropriate stains and cultures, but this procedure must be performed carefully to avoid entering a bowel that is adherent to the omentum.

Tuberculous enteritis is caused by hematogenous dissemination or by swallowing tubercle bacilli discharged from the patient's own lungs. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. The typical findings are shallow ulcers that cause pain, diarrhea or constipation, weight loss, and low-grade fever. Mesenteric adenitis usually complicates the infection. The enlarged nodes can cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. The clinical presentation of tuberculous enteritis is nonspecific, mimicking other infections and conditions that cause diarrhea. The disease should be suspected in any child with chronic GI complaints and a reactive TST or positive IGRA. Biopsy, acid-fast stain, and culture of the lesions are usually necessary to confirm the diagnosis.

Genitourinary Disease

Renal TB is rare in children because the incubation period is several years or longer. Tubercle bacilli usually reach the kidney during lymphohematogenous dissemination. The organisms often can be recovered from the urine in cases of miliary TB and in some patients with pulmonary TB in the absence of renal parenchymal disease. In true renal TB, small caseous foci develop in the renal parenchyma and release *M. tuberculosis* into the tubules. A large mass develops near the renal cortex that discharges bacteria through a fistula into the renal pelvis. Infection then spreads locally to the ureters, prostate, or epididymis. Renal TB is often clinically silent in its early stages, marked only by sterile pyuria and microscopic hematuria. Dysuria, flank or abdominal pain, and gross hematuria develop as the disease progresses. Superinfection by other bacteria is common and can delay recognition of the underlying TB. Hydronephrosis or ureteral strictures can complicate the disease. Urine cultures for *M. tuberculosis* are positive in 80–90% of cases, and acid-fast stains of large volumes of urine sediment are positive in 50–70% of cases. The TST is nonreactive in up to 20% of patients. A pyelogram or CT scan often reveals mass lesions, dilation of the proximal ureters, multiple small filling defects, and hydronephrosis if ureteral stricture is present. Disease is most often unilateral.

Genital tract TB is uncommon in prepubescent males and females. This condition usually originates from lymphohematogenous spread, although it can be caused by direct spread from the intestinal tract or bone. Adolescent females can develop genital tract TB during the primary infection. The fallopian tubes are most often involved (90–100% of cases), followed by the endometrium (50%), ovaries (25%), and cervix (5%). The most common symptoms are lower abdominal pain and dysmenorrhea or amenorrhea. Systemic manifestations are usually absent, and the chest radiograph is normal in the majority of cases. The TST is usually reactive. Genital TB in adolescent males causes epididymitis or orchitis. The condition usually manifests as a painless, unilateral nodular swelling of the scrotum. Involvement of the glans

penis is extremely rare. Genital abnormalities and a positive TST in an adolescent male or female suggest genital tract TB.

Pregnancy and the Newborn

Pulmonary and particularly extrapulmonary TB other than lymphadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight, and perinatal mortality. **Congenital TB** is rare because the most common result of female genital tract TB is infertility. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection. Congenital transmission usually occurs from a lesion in the placenta through the umbilical vein, when tubercle bacilli infect the fetal liver, where a primary focus with periportal lymph node involvement can occur. Organisms pass through the liver into the main fetal circulation and infect many organs. The bacilli in the lung usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital TB can also be caused by aspiration or ingestion of infected amniotic fluid. However, the most common route of infection for the neonate is postnatal airborne transmission from an adult with infectious pulmonary TB.

Perinatal Disease

Symptoms of congenital TB may be present at birth but usually begin by the second or third week of life. The most common signs and symptoms are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. The clinical manifestations vary in relation to the site and size of the caseous lesions. Many infants have an abnormal chest radiograph, most often with a miliary pattern. Some infants with no pulmonary findings early in the course of the disease later develop profound radiographic and clinical abnormalities. Hilar and mediastinal lymphadenopathy and lung infiltrates are common. Generalized lymphadenopathy and meningitis occur in 30–50% of infants.

The clinical presentation of TB in newborns is similar to that caused by bacterial sepsis and other congenital infections, such as syphilis, toxoplasmosis, and cytomegalovirus. The diagnosis should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and in whom evaluation for other infections is unrevealing. The most important clue for rapid diagnosis of congenital TB is a maternal or family history of TB. Often, the mother's disease is discovered only after the neonate's diagnosis is suspected. The infant's TST is negative initially but can become positive in 1-3 months. A positive acid-fast stain of an early morning gastric aspirate from a newborn usually indicates TB. Direct acid-fast stains on middle ear discharge, bone marrow, tracheal aspirate, or tissue biopsy (especially liver) can be useful. The CSF should be examined, cultured, and sent for PCR testing. The mortality rate of congenital TB remains very high because of delayed diagnosis. Many children have a complete recovery if the diagnosis is made promptly and adequate chemotherapy is started.

Tuberculosis Disease in Children Living with HIV

In the United States, the rate of TB disease in children living with untreated HIV is 30 times higher than in children without HIV. Establishing the diagnosis of TB in a child living with HIV may be difficult because TST reactivity can be absent (also with a negative IGRA), culture confirmation is difficult, and the clinical features of TB are similar to many other HIV-related opportunistic infections and conditions. TB in children living with HIV is often more severe, progressive, and likely to occur in extrapulmonary sites. Radiographic findings are similar to those in children with normal immune systems, but lobar disease and lung cavitation are more common. Nonspecific respiratory symptoms, fever, and weight loss are the most common complaints. Rates of drug-resistant TB tend to be higher in adults living with HIV and probably are also higher in children living with HIV. Recurrent TB disease and relapsed TB occur more frequently in children living with HIV. The prognosis generally is good if TB disease is not far advanced at diagnosis and appropriate antituberculosis drugs are available.

The mortality rate of children living with HIV with TB is high, especially as the CD4 lymphocyte numbers decrease. In adults, the host immune response to TBI appears to enhance HIV replication and accelerate the immune suppression caused by HIV. Increased mortality rates are attributed to progressive HIV infection rather than TB. Therefore children living with HIV with potential TB exposures and/or recent TBI should be promptly evaluated and treated for TB. Conversely, all children with TB disease should be tested for HIV infection.

Children living with HIV who are given highly active antiretroviral therapy (HAART) are at high risk of developing **immune reconstitution inflammatory syndrome (IRIS)**. IRIS should be suspected in patients who experience a worsening of TB symptoms while receiving antituberculosis therapy (*paradoxical* IRIS) or who develop new-onset TB symptoms and radiographic findings after initiation of HAART (*unmasking* IRIS). Factors suggesting IRIS are temporal association (within 3 months of starting HAART), unusual clinical manifestations, unexpected clinical course, exclusion of alternative explanations, evidence of preceding immune restoration (rise in CD4 lymphocyte count), and decrease in HIV viral load. The most common clinical manifestations of IRIS in children are fever, cough, new skin lesions, enlarging lymph nodes in the thorax or neck, and appearance or enlargement of tuberculomas in the brain, with or without accompanying meningitis. The treatment of TB-associated IRIS in children living with HIV often included steroids but should be undertaken by a clinician with specific expertise in TB treatment.

IMMUNE-BASED TESTING ("TESTS OF TUBERCULOSIS INFECTION")

Tuberculin Skin Testing

The development of delayed-type hypersensitivity in most persons infected with the *M. tuberculosis* complex organisms makes the TST a useful diagnostic tool. The **Mantoux TST** is the intradermal injection of 0.1 mL purified protein derivative stabilized with Tween 80. T cells sensitized by prior infection are recruited to the skin, where they release lymphokines that induce induration through local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. The amount of induration in response to the test should be measured by a trained person 48-72 hours after administration. In some patients, the onset of induration is >72 hours after placement; this is also a positive result. Immediate hypersensitivity reactions to tuberculin or other constituents of the preparation are short-lived (<24 hours) and not considered a positive result. Tuberculin sensitivity develops 3 weeks to 3 months (most often in 4-8 weeks) after inhalation of organisms.

Host-related factors, including very young age, malnutrition, immunosuppression by disease or drugs, viral infections (measles, mumps, varicella, influenza), vaccination with live-virus vaccines, and overwhelming TB, can depress the skin test reaction in a child infected with *M. tuberculosis*. Corticosteroid therapy can decrease the reaction to tuberculin, but the effect is variable; TST done at the time of initiating corticosteroid therapy is usually reliable. Approximately 10% of immunocompetent children with TB disease (up to 50% of those with meningitis or disseminated disease) do not react initially to purified protein derivative; most become reactive after several months of antituberculosis therapy. False-positive reactions to tuberculin can be caused by cross-sensitization to antigens of NTM, which generally are more prevalent in the geographic environment as one approaches the equator. These cross-reactions are usually transient over months to years and produce <10-12 mm of induration, but larger areas of induration can occur. Previous vaccination with bacille Calmette-Guérin (BCG) also can cause a reaction to a TST, especially if a person has received two or more BCG vaccinations. Approximately 50% of the infants who receive a BCG vaccine never develop a reactive TST, and the reactivity usually wanes in 2-3 years in those with initially positive skin test results. Older children and adults who receive a BCG vaccine are more likely to develop tuberculin reactivity, but most lose the reactivity by 5-10 years after vaccination. However,

Table 261.2 Tuberculin Skin Test (TST) or Interferon-γ Release Assay (IGRA): Recommendations for Infants, Children, and Adolescents*

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED†
Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
Children with radiographic or clinical findings suggesting tuberculosis disease
Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from former Soviet Union), including international adoptees
Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries‡
Children who should have annual TST or IGRA: Children infected with human immunodeficiency virus
CHILDREN AT INCREASED RISK FOR PROGRESSION OF TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease.
Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered.
An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged corticosteroid administration, organ transplantation, or use of TNF-α antagonists or blockers, or immunosuppressive therapy in any child requiring these treatments.

*Bacille Calmette-Guérin immunization is not a contraindication to a TST.
†Beginning as early as 3 mo of age.
‡If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:789.

Table 261.3 Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents*

INDURATION ≥5 MM
Children in close contact with known or suspected contagious people with tuberculosis disease
Children suspected to have tuberculosis disease: • Findings on chest radiograph consistent with active or previously tuberculosis disease • Clinical evidence of tuberculosis disease†
Children receiving immunosuppressive therapy‡ or with immunosuppressive conditions, including HIV infection
INDURATION ≥10 MM
Children at increased risk of disseminated tuberculosis disease: • Children <4 yr old • Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 261.2)
Children with increased exposure to tuberculosis disease: • Children born in high-prevalence regions of the world • Children often exposed to adults with HIV infection, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers • Children who travel to high-prevalence regions of the world
INDURATION ≥15 MM
Children ≥4 yr old without any risk factors

*These definitions apply regardless of previous BCG immunization; erythema at TST site does not indicate a positive test result. Tests should be read at 48-72 hr after placement.
†Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).
‡Including immunosuppressive doses of corticosteroids or tumor necrosis factor-α antagonists.
BCG, Bacille Calmette-Guérin; HIV, human immunodeficiency virus.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:788.

some individuals maintain tuberculin reactivity from BCG vaccine for many years. When present, skin test reactivity usually causes <10 mm of induration, although larger reactions occur in some persons.

The appropriate size of induration indicating a positive Mantoux TST result varies with related epidemiologic and risk factors. In children with no TB risk factors, skin test reactions are usually false-positive results. The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) discourage routine testing of all children and recommend targeted tuberculin testing of children at risk identified through periodic screening questionnaires (Table 261.2). Possible exposure to an adult with or at high risk for infectious pulmonary TB is the most crucial risk factor for children. Reaction size limits for determining a positive TST result vary with the person's risk for infection (Table 261.3). In those at highest risk of progression to TB disease, TST sensitivity is most important, whereas specificity is more important for persons at low risk of progression.

Interferon-γ Release Assay

Two blood tests—T-SPOT.*TB* (Oxford Immunotec; Marlborough, MA) and QuantiFERON-TB Gold/Gold Plus (QFT, Qiagen; Germantown, MD) detect IFN-γ generation by the patient's T cells in response to specific *M. tuberculosis* antigens (ESAT-6, CFP-10, and TB7.7). The QFT test measures whole blood concentrations of IFN-γ, and the T-SPOT.*TB* test measures the number of lymphocytes/monocytes producing IFN-γ. The test antigens are not present on *M. bovis*–BCG (vaccine) and *M. avium* complex, the major group of environmental mycobacteria, so one would expect higher specificity compared with the TST and fewer false-positive results. Both IGRAs have internal positive and negative controls. Internal positive controls allow for detection of an anergic test response, which is useful in children who are young and immunocompromised. Indeterminate (QFT)/invalid (T-SPOT.*TB*) responses occur when the test sample is negative but the positive control has insufficient activity or if the negative control has high background activity. Indeterminate/invalid results are also caused by technical factors (e.g., insufficient shaking of QFT tubes, delayed processing time). Most studies report indeterminate or invalid rates in children of 0–10%, which is influenced by a child's age and immune status. In children <2 years old, indeterminate rates can be as high as 8.1% vs 2.7% in older children, although more recent studies generally report much lower rates. *An indeterminate or invalid IGRA result is neither negative nor positive and cannot be used to guide treatment decisions.*

Some IGRAs cannot differentiate between TBI and TB disease. If available, certain IGRA tests will test CD4 and CD8 T-cell reactivity, which may help differentiate latent from active disease. Two clear advantages of the IGRAs are the need for only one patient encounter (vs two with TST) and the lack of cross-reaction with BCG vaccination and most other mycobacteria, thereby increasing test specificity for TBI. Studies comparing IGRA and TST performance in children have shown comparable sensitivity (85% in culture-confirmed children) between the two tests and superior IGRA specificity (95% vs 49%) in BCG-immunized, low-risk children.

Neither the TST nor the IGRAs perform well in infants and young children who are malnourished, severely immunocompromised, or have disseminated TB disease. It is now standard to use an IGRA in the evaluation of healthy young children ≥2 years of age, and most experts use IGRAs in younger children who are at low risk of TB infection, especially in those who have received a BCG vaccine. Both TST and

Table 261.4 Recommendations for Use of Tuberculin Skin Test (TST) and Interferon-γ Release Assay (IGRA) in Children

TST preferred, IGRA acceptable:
- Children <2 yr of age*

IGRA preferred, TST acceptable:
- Children ≥2 yr of age who have received BCG vaccine
- Children ≥2 yr of age who are unlikely to return for TST reading

TST and IGRA should be considered when:
- The initial and repeat IGRAs are indeterminate or invalid
- The initial test (TST or IGRA) is negative and:
  - Clinical suspicion for TB disease is moderate to high†
  - The child has a TB risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biologic agent, e.g., TNF-α antagonist)†
- The initial TST is *positive* and:
  - ≥2 yr old and history of BCG vaccination
  - Additional evidence needed to increase adherence with therapy

*Some experts do not use an IGRA for children younger than 2 yr because of a relative lack of data for this age-group and the high risk of progression to disease.
†Positive result of either test is considered significant in these groups.
BCG, Bacille Calmette-Guérin; TB, tuberculosis, TNF, tumor necrosis factor.
Adapted from Starke JR, AAP Committee of Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics.* 2014;134(6):e1763–1773.

IGRA testing should be considered in children whose initial TST or IGRA result is negative for whom the risk of TB is high (to enhance the sensitivity of the combination of the two tests).

Technical advantages of the IGRAs over the TST include the need for a single patient encounter (vs two spaced in time with the TST), the lack of cross-reaction with BCG vaccination and most environmental mycobacteria, and eliminating the need for experience in correctly interpreting the TST. IGRAs are also useful for those who are unlikely to return for TST interpretation, those whose family is reluctant to treat a child with TBI based on a TST result alone, and those with a positive TST result in whom NTM disease is suspected (Table 261.4).

Most studies have shown no consistent, significant difference between the two commercially available IGRAs, and the CDC recommends no preference. Because of cost constraints, the WHO does not endorse IGRA use in low- and middle-income countries, even in those with a high prevalence of tuberculosis.

MYCOBACTERIAL SAMPLING, SUSCEPTIBILITY, AND CULTURE

The most specific confirmation of pulmonary TB is isolation of *M. tuberculosis* from a clinical sample. Sputum specimens for culture should be collected from adolescents and older children who are able to expectorate. Induced sputum with a jet nebulizer, inhaled saline, and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 year. Sputum induction provides samples for both culture and acid-fast bacilli (AFB) staining. The traditional culture specimen in young children is the early morning gastric acid obtained before the child has arisen and peristalsis has emptied the stomach of the pooled respiratory secretions that have been swallowed overnight. However, even under optimal conditions, three consecutive morning gastric aspirates yield the organisms in <50% of cases. The culture yield from bronchoscopy is even lower, but this procedure can demonstrate the presence of endobronchial disease or a fistula. To improve the sensitivity of a diagnosis of TB in children, in high-burden TB settings, there is an increasing trend to collect nontraditional specimens, including stool, nasopharyngeal, and urine specimens. These specimens are easier to obtain than respiratory specimens but less sensitive in diagnosing TB in children compared to sputum or serial gastric aspirate specimens. Their diagnostic utility is increased when multiple specimens are collected in conjunction with traditional respiratory specimens. *Negative cultures never exclude the diagnosis of TB in a child.* The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with TB, and history of recent exposure to an adult with infectious TB is highly suggestive of the clinical diagnosis of TB disease. If a likely adult source case has been identified, drug susceptibility test results of the isolate from the adult source usually can be used to determine the best therapeutic regimen for the child, except in very high-incidence areas, where the apparent source case might not be the actual one. Cultures should be always obtained from the child whenever the source case is unknown, there are multiple possible source cases, or the source case has possible or confirmed drug-resistant TB.

Confirmation of extrapulmonary TB is best achieved with a positive culture or PCR testing. However, for many forms of TB, the culture yield is only 25–50%, and probable diagnosis is by a combination of clinical signs and symptoms, analysis of body fluids when possible, radiographic or histopathologic evidence of TB, PCR testing, and elimination of other possible diagnoses.

Nucleic Acid Amplification Tests

The main NAAT studied in children with TB is PCR, which uses specific DNA sequences as markers for microorganisms. Compared with a clinical diagnosis of pulmonary TB in children, the sensitivity of PCR has varied from 25% to 83%, and specificity has varied from 80% to 100%. A negative PCR result never eliminates the diagnosis of TB, and the diagnosis is not confirmed by a positive PCR result.

NAAT identifies genes associated with drug resistance and is used to supplement culture-based (phenotypic) methods for drug susceptibility testing. It also decreases the time to identification of drug resistance from weeks to hours, which expedites the initiation of optimal therapy. Culture-based, phenotypic, drug susceptibility testing is necessary to confirm susceptibility to each drug; the absence of resistance genes is not always predictive of drug susceptibility. The interpretation of molecular-based drug susceptibility testing is constantly evolving, and an expert in the management of pediatric TB should be involved when drug resistance is suspected.

Gene Xpert MTB/RIF cartridge and Xpert MTB Ultra cartridge (Xpert; Cepheid, Sunnyvale, CA) are real-time PCR assays for *M. tuberculosis* that simultaneously detect **rifampin resistance**, which is often used as a proxy for MDR-TB. These assays use a self-contained cartridge system, which yields results from direct specimens in 2 hours and is less operator dependent than traditional PCR detection methods. Sensitivity and specificity of Xpert MTB/RIF have averaged 72–77% and 99% in AFB sputum smear–negative adults and 98–99% and 99–100% in AFB sputum smear–positive adults, respectively. Pediatric studies reveal that, compared to culture, the sensitivity and specificity of Xpert MTB/RIF is 62% and 98% on induced or expectorated sputa and 66% and 98% on gastric aspirates, respectively. For other specimen types (nasopharyngeal aspirate and stool), Xpert MTB/RIF pooled sensitivity for pulmonary TB ranges between 46% and 73% with a pooled specificity of 98% and 100%. Compared with smear microscopy, Xpert improved the sensitivity of detecting pediatric TB cases by 36–44%. For lymph node aspirates or biopsies, Xpert MTB/RIF compared with culture had a sensitivity and specificity of 90%. Compared to culture, Xpert MTB/RIF's sensitivity and specificity to detect rifampin resistance in respiratory specimens collected from children with suspected pulmonary TB are 86% and 98%, respectively.

Xpert Ultra is a next-generation assay that has enhanced performance in children who often have paucibacillary or smear-negative TB. The pooled sensitivity of Ultra for detection of *M. tuberculosis* was 73% in sputum samples, 64% in gastric aspirate samples, 53% in stool specimens, and 46% in nasopharyngeal samples. The pooled specificity was 98% in sputum samples, 98% in nasopharyngeal aspirate specimens, 98% in stool samples, and 95% in gastric aspirate samples. The WHO recommends use of Xpert Ultra in sputum and nasopharyngeal specimens collected from children for the diagnosis of TB and rifampin resistance, in addition to the use of Xpert MTB/RIF in sputum, gastric aspirate, nasopharyngeal aspirate, and stool specimens. Although cartridges for the Xpert systems are expensive, they offer advantages in rapid detection of MDR-TB and are especially useful in settings lacking

laboratory infrastructure. In many low-resource settings, Xpert has replaced smear microscopy; however, it has not replaced mycobacterial cultures and drug susceptibility studies.

TREATMENT

The basic principles of management of TB disease in children and adolescents are the same as in adults. Several drugs are used to effect a relatively rapid cure and prevent the emergence of secondary drug resistance during therapy (Tables 261.5 to 261.8). The choice of regimen depends on the extent of TB disease, the host, and the likelihood of drug resistance (see Chapter 260, Table 260.1). As recommended by the WHO and AAP, *the standard therapy of intrathoracic, presumed or confirmed drug-susceptible TB (pulmonary disease and/or hilar lymphadenopathy) in children is a 4- to 6-month regimen of multidrug therapy. The initial treatment regimen includes isoniazid, rifampin, pyrazinamide, and ethambutol.* The ethambutol can be discontinued once the organism is known to be susceptible to the other first-line drugs. Pyrazinamide is discontinued after 2 months, and isoniazid and rifampin are continued for an additional 2-4 months. Several clinical trials have shown that a 6-month regimen yields a success rate approaching 100%, with an incidence of clinically significant adverse reactions of <2%. Data from the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children) found that a 4-month treatment regimen in children age 0-16 years (≥3 kg) with nonsevere, smear negative, presumed drug-susceptible TB was noninferior to a 6-month course. Based on the results of this trial, the WHO supports the use of a 4-month treatment regimen in eligible children. Most experts recommend that all drug administration be either directly observed or electronically observed, meaning that a healthcare worker watches when the medications are administered to/or taken by the patients. When in-person **directly observed therapy (DOT)** or video directly observed therapy (VDOT) is used, intermittent (twice or thrice weekly) administration of drugs after an initial period as short as 2 weeks of daily therapy is as effective for drug-susceptible TB in children as daily therapy for the entire course.

Table 261.5 Dosage Recommendations for the Treatment of TB in Adults and Children[1]

			DOSE IN MG/KG (MAXIMUM DOSAGE IN PARENTHESES)			
DRUG	**ADULTS/CHILDREN[2]**		**DAILY**	**1 TIME/WK[3]**	**2 TIMES/WK[3]**	**3 TIMES/WK[3]**
Isoniazid	Adults		5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
	Children		10– 15 mg/kg (300 mg)	—	20– 30 mg/kg (900 mg)	—
Rifampin	Adults		10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
	Children		10– 20 mg/kg (600 mg)	—		10– 20 mg/kg (600 mg)
Rifabutin	Adults		5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
	Children ≥12 yr		Appropriate dosing for children unknown			
Rifapentine	Adults		—	10 mg/kg (600 mg; continuation phase)	—	—
	Children					
Pyrazinamide	Adults (weight)	40– 55 kg	18.2– 25 mg/kg (1000 mg)	—	36.4– 50 mg/kg (2000 mg)	27.3– 37.5 mg/kg (1500 mg)
		56– 75 kg	20– 26.8 mg/kg (1500 mg)	—	40– 53.6 mg/kg (3000 mg)	33.3– 44.6 (2500 mg)
		76– 90 kg	22.2– 26.3 mg/kg (2000 mg)	—	44.4– 52.6 mg/kg (4000 mg)	33.3– 39.5 mg/kg (3000 mg)
	Children <40 kg		30– 40 mg/kg (2000 mg)	—		50 mg/kg (2000 kg)
Ethambutol[4]	Adults (weight)	40– 55 kg	14.5– 20 mg/kg (800 mg)	—	36.4– 50 mg/kg (2000 mg)	21.8– 30 mg/kg (1200 mg)
		56– 75 kg	16– 21.4 mg/kg (1200 mg)	—	37.3– 50 mg/kg (2800 mg)	26.7– 35.7 mg/kg (2000 mg)
		76– 90 kg	17.8– 21.1 mg/kg (1600 mg)	—	44.4– 52.6 mg/kg (4000 mg)	26.7– 31.6 mg/kg (2400 mg)
	Children		15– 20 mg/kg (1000 mg)	—	50 mg/kg (2500 mg)	—

[1]Although these regimens are broadly applicable, modifications may be needed for certain circumstances (patients on antiretroviral therapy [ART]). For more information, refer to treatment of tuberculosis guidelines. *MMWR* 2003; 52 (No.RR-11).
[2]For purposes of this document, adult dosing begins at age 15 years. Children weighing more than 40 kg should be dosed as adults. Adjust doses as the patient's weight changes.
[3]All patients prescribed an intermittent regimen should be given DOT.
[4]Ethambutol should be used with caution in young children since it is difficult to monitor their vision. However, if they have TB that is resistant to INH or RIF, a dose of 15 mg/kg per day can be used.
From Centers for Disease Control and Prevention. *Core Curriculum on Tuberculosis: What the Clinician Should Know*, 7th ed. Atlanta: CDC, 2021. Table 6.4. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf

Table 261.6 Common Adverse Reactions to TB Drugs

CAUSED BY	ADVERSE REACTION	SIGNS AND SYMPTOMS	SIGNIFICANCE OF REACTION*
Any drug	Allergic	• Skin rash	May be serious or minor
Ethambutol	Eye damage	• Blurred or changed vision • Changed color vision	Serious
Isoniazid Pyrazinamide Rifampin	Hepatic toxicity	• Abdominal pain • Abnormal liver function test results • Dark urine • Fatigue • Fever for 3 or more days • Flulike symptoms • Lack of appetite • Nausea • Vomiting • Yellowish skin or eyes	Serious
Isoniazid	Nervous system damage	• Dizziness; tingling or numbness around the mouth	Serious
	Peripheral neuropathy	• Tingling sensation in hands and feet	Serious
Pyrazinamide	Stomach upset	• Stomach upset • Vomiting • Lack of appetite	May be serious or minor
	Gout	• Abnormal uric acid level** • Joint aches	Serious
Rifampin	Bleeding problems	• Easy bruising • Slow blood clotting	Serious
	Discoloration of body fluids	• Orange urine, sweat, or tears • Permanently stained soft contact lenses	Minor
	Drug interactions	• Interferes with certain medications such as birth control pills, birth control implants, and methadone treatment	May be serious or minor
	Sensitivity to the sun	• Frequent sunburn	Minor

*Patients should stop medication for serious adverse reactions and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.
**Asymptomatic elevated uric acid levels are expected with PZA treatment. Acute gouty arthritis, which is rare without preexisting gout, is a contraindication to PZA use.
EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF,.
From Centers for Disease Control and Prevention. *Core Curriculum on Tuberculosis: What the Clinician Should Know*, 7th ed. Atlanta: CDC, 2021. Table 6.11. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf

Table 261.7 Commonly Used Drug Regimens and Dosages for Treatment in Pediatric Patients with TB Infection (TBI)

DRUGS	DOSAGE FORMS AND AGE GROUP	ADMINISTRATION	DURATION (MO)	AGE RESTRICTION	COMMENTS
Isoniazid + Rifapentine (3HP)	Age ≥12 yr INH: 15 mg/kg rounded up to the nearest 50 or 100 mg (max 900 mg) Rifapentine (by weight): 10-14 kg: 300 mg 14.1-25 kg: 450 mg 25.1-32 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50 kg: 900 mg Age 2-11 yr INH: 25 mg/kg, rounded up to the nearest 50 or 100 mg (max 900 mg) Rifapentine (see above)	Weekly (DOT)	3	Not for children <2 yr	Take with food, containing fat if possible, pyridoxine for selected patients RFP has drug-drug interactions
Rifampin (4R)	Adult: 10 mg/kg (max 600 mg) Child: 15-20 mg/kg (max 600 mg)	Daily (SAT)	4	None	Drug-drug interactions
INH + Rifampin	Same daily doses as when the drugs are used individually	Daily (SAT)	3	None	RIF has drug-drug interactions
INH	Adult: 5 mg/kg (max 300 mg) Child 10-15 mg/kg (max 300 mg) Adult: 15 mg/kg (max 900 mg) Child: 20-30 mg/kg (max 900 mg)	Daily (SAT) Twice weekly (DOT)	6 or 9	None	Seizures with overdose; pyridoxine for selected patients*

*Exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all asymptomatic children living with HIV infection; and pregnant adolescents and women.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:805–806; and Nolt D, Starke JR. Tuberculosis infection in children and adolescents: testing and treatment. *Pediatrics*. 2021;148(6):e2021054663.

Table 261.8 Drug Grouping for the Treatment of MDR-TB

GROUP	INSTRUCTIONS	DRUG
Group A	Include all three drugs (unless they cannot be used), add delamanid if age >3 yr	Levofloxacin OR moxifloxacin Bedaquiline Linezolid
Group B	Add both drugs (unless they cannot be used)	Clofazimine Cycloserine or terizidone
Group C	Add to complete regimen (of four to five agents) Add when drugs from groups A or B cannot be used	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin Meropenem Amikacin OR streptomycin Ethionamide OR prothionamide *p*-Aminosalicylic acid

Extrapulmonary tuberculosis is usually caused by small numbers of mycobacteria. In general, the treatment for most forms of extrapulmonary TB in children, including cervical lymphadenopathy, is the same as for pulmonary TB. *Exceptions are bone and joint, disseminated, and CNS TB, for which there are inadequate data to recommend 6 months of therapy; these conditions are usually treated for 9-12 months.* Surgical debridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

The optimal treatment of TB in children living with HIV has not been established. Adults living with HIV with TB disease can be treated successfully with standard regimens that include isoniazid, rifampin, pyrazinamide, and ethambutol. The total duration of therapy should be 6-9 months or 6 months after culture of sputum becomes sterile, whichever is longer. Data for children are limited to relatively small series. *Most experts believe that children living with inadequately controlled HIV who have drug-susceptible TB should receive the standard four-drug regimen for the first 2 months followed by isoniazid and rifampin for a total duration of at least 9 months. However, all treatment should be daily, not intermittent.* Children living with HIV appear to have more frequent adverse reactions to antituberculosis drugs and must be monitored closely during therapy. Co-administration of rifampin and some antiretroviral agents results in subtherapeutic blood levels of protease inhibitors and nonnucleoside reverse transcriptase inhibitors and toxic levels of rifampin. Concomitant administration of these drugs is not recommended. Treatment of children living with HIV with TB is often empirically based on epidemiologic and radiographic information because the radiographic appearance of other pulmonary complications of HIV in children, such as lymphoid interstitial pneumonitis and bacterial pneumonia, may be similar to that of TB. Therapy should be considered when TB cannot be excluded.

Drug-Resistant Tuberculosis

The incidence of drug-resistant TB is increasing in many areas of the world, including North America. There are two major types of drug resistance. **Primary resistance** occurs when a person is infected with *M. tuberculosis* that is already resistant to a particular drug. **Secondary resistance** occurs when drug-resistant organisms emerge as the dominant population during treatment. The major causes of secondary drug resistance are poor adherence to the medication by the patient or inadequate treatment regimens prescribed by the physician. Nonadherence to one drug is more likely to lead to secondary resistance than is failure to take all drugs. Secondary resistance is rare in children because of the small size of their mycobacterial population. Consequently, most drug resistance in children is primary, and patterns of drug resistance among children tend to mirror those found among adults in the same population. The main predictors of drug-resistant TB among adults are history of previous antituberculosis treatment, co-infection with HIV, and exposure to another adult with infectious drug-resistant TB.

Treatment of drug-resistant TB is successful only when at least two bactericidal drugs are given to which the infecting strain of M. tuberculosis is susceptible. When a child has possible drug-resistant TB, usually at least four or five drugs should be administered initially until the susceptibility pattern is determined and a more specific regimen can be designed. The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case. Treatment duration of 9 months with rifampin, pyrazinamide, and ethambutol is usually adequate for isoniazid-resistant TB in children. High-dose isoniazid is often added in those with low-level isoniazid-resistant TB. The recommendations for the treatment of MDR-TB have rapidly evolved in recent years. In 2019, the WHO advocated for the use of all-oral (injectable-free) regimens and reprioritized the order of the available oral drugs (Tables 261.8 and 261.9). Treatment regimens should prioritize administering group A and B drugs in addition to delamanid for children older than 3 years of age. Bedaquiline can be used in those older than 6 years of age. First-line treatment includes an all-oral regimen using three group A drugs and at least one group B drug. If only one or two group A medications are used, then group B drugs should be added to make a regimen of four drugs. Group C drugs are only used if the isolate is susceptible and when drugs from groups A and B cannot be used. The WHO recommends treatment of those with severe MDR-TB disease for 12-18 months; however, in children younger than 15 years with less severe MDR-TB disease, the treatment duration can be shortened to 9-12 months. The WHO defines severe MDR-TB disease as children with cavities or bilateral parenchymal disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy. Those with severe malnutrition; advanced immunosuppression; or positive smear, NAAT, or culture are also often treated with a longer course of therapy.

The second-line drugs require close monitoring for adverse effects and toxicity (see Table 261.9). The prognosis of single-drug–resistant or MDR-TB in children with nonsevere disease is good if the drug resistance is identified early in the treatment, if appropriate drugs are administered under DOT, if adverse reactions from the drugs are minor, and if the child and family are in a supportive environment. The treatment of drug-resistant TB in children always should be undertaken by a clinician with specific expertise in TB treatment.

Corticosteroids

Corticosteroids are useful in treating some children with TB disease. They are most beneficial when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. There is convincing evidence that corticosteroids decrease mortality rates and long-term neurologic sequelae in some patients with **tuberculous meningitis** by reducing vasculitis, inflammation, and ultimately intracranial pressure. Lowering the intracranial pressure limits tissue damage and favors circulation of antituberculosis drugs through

Table 261.9 Drugs Used for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*

DRUGS	DOSAGE, FORMS	DAILY DOSAGE (mg/kg)	MAXIMUM DOSE	ADVERSE REACTIONS
Amikacin†	Vials: 500 mg, 1 g	15-20 (IV or IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Amoxicllin-clavulanate	(Strength expressed in terms of amoxicillin component) Syrup: 50 mg/mL 80 mg/mL 120 mg/mL (ES 600) Tablets: 500 mg 875 mg 1000 mg (XR tablet)	40 (amoxicillin component), twice daily	4 g (amoxicillin) 500 mg (clavulanate)	Abdominal pain, diarrhea, rash
Bedaquiline	Tablets: 20 mg, 100 mg	Adults and children ≥5 yr, 15 to <30 kg weeks 1-2: 200 mg/day; weeks 3-24: 100 mg 3x/week > 30 kg weeks 1-2: 400 mg/day; weeks 3-24: 200 mg 3x/week	600 mg/week	QTc prolongation, reduced levels with efavirenz co-administration
Clofazimine	Gelcaps: 50 mg 100 mg	2-5 per day	100 mg	QTc prolongation, reversible skin pigmentation
Cycloserine or terizidone	Capsules: 250 mg	10-20, given in 2 divided doses	1 g	Psychosis, personality changes, seizures, rash
Delamanid	Tablets: 50 mg 100 mg	6–11 years: 50 mg 2x/day 12–17 years: 100 mg 2x/day	100 mg/dose	QTc prolongation, adverse events with hypoalbuminemia, avoid if metronidazole allergic
Ethambutol	Tablets: 100 mg 400 mg	Children <40 kg: 15–25 Children ≥40 kg: 40-55 kg: 800 mg/ day PO 56-75 kg: 1200 mg/ day PO 76-90 kg: 1600 mg/ day PO	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Ethionamide	Tablets: 125 mg 250 mg	15-20, given in 1–2 divided doses	1 g	GI tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism
Imipenem-cilastatin		60-100 per day, divided in 4 doses	4 g	Anemia, thrombocytopenia, eosinophilia, elevated liver enzymes
Levofloxacin	Tablets: 250 mg 500 mg 750 mg Oral solution: 25/mL Vials: 25 mg/mL	Adults: 750-1000 mg (daily) Children: 15-20 mg/kg daily	1 g	Theoretic effect on growing cartilage, joint pain, GI tract disturbances, rash, headache, restlessness, confusion
Linezolid	Tablets: 400 mg 600 mg Syrup: 20 mg/mL	Children <16 kg: 15 mg/kg once daily Children >16 kg: 10-12 mg/kg/day once daily	600 mg if ≥12 yr 300 mg if <12 yr	Bone marrow suppression, peripheral neuropathy, lactic acidosis, potential overlapping toxicity with nucleoside reverse transcriptase inhibitors
Moxifloxacin	Tablets: 400 mg IV solution: 400 mg/250 mL in 0.8% saline	Adults/adolescents: 400 mg Children: 10-15 mg/kg daily	400 mg; maximum doses of 600-800 mg per day are used for higher MIC or in malabsorption	Arthropathy, arthritis
p-Aminosalicylic acid (PAS)	Packets: 3 g	200-300 (2-4 times a day)	10 g	GI tract disturbances, hypersensitivity, hepatotoxic effects
Prothionamide	Tablets: 250 mg 500 mg	15-20 (divided twice daily)	1 g	GI tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism

Table 261.9 Drugs Used for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*—cont'd

DRUGS	DOSAGE, FORMS	DAILY DOSAGE (mg/kg)	MAXIMUM DOSE	ADVERSE REACTIONS
Pyrazinamide	Scored tablets: 500 mg	30-40	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Streptomycin†	Vials: 1 g 4 g	20-40 (IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects, rash

*These drugs should be used in consultation with a specialist in tuberculosis.
†Dose adjustment in renal insufficiency.
GI, Gastrointestinal; IM, intramuscular; IV, intravenous.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:805–806; and Furin J, Seddon J, Becerra M, et al. *Management of Multi-drug-Resistant Tuberculosis Children: A Field Guide*, 4th ed. Boston: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; 2019. Available at: http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf

the brain and meninges. Short courses of corticosteroids also may be effective for children with **endobronchial tuberculosis** that causes respiratory distress, localized emphysema, or segmental pulmonary lesions. Several randomized clinical trials have shown that corticosteroids can help relieve symptoms and constriction associated with acute tuberculous **pericardial effusion**. Corticosteroids can cause dramatic improvement in symptoms in some patients with tuberculous pleural effusion and shift of the mediastinum. However, the long-term course of the disease is probably unaffected. Some children with severe **miliary tuberculosis** have dramatic improvement with corticosteroid therapy if the inflammatory reaction is so severe that alveolocapillary block is present. There is no convincing evidence to support a specific corticosteroid preparation. The most common regimen is **prednisone** 1-2 mg/kg/day in one to two divided doses orally for 4-6 weeks followed by a taper.

Supportive Care

Children receiving TB treatment should be followed carefully to promote **adherence** to therapy, to monitor for toxic reactions to medications, and to ensure that the TB is being adequately treated. Adequate **nutrition** is important. Patients should be seen at monthly intervals and should be given just enough medication to last until the next visit. **Anticipatory guidance** with regard to the administration of medications to children is crucial. The physician should foresee difficulties that the family might have in introducing several new medications in inconvenient dosage forms to a young child. The clinician must report all cases of suspected TB in a child to the local health department to be sure that the child and family receive appropriate care and evaluation.

Nonadherence to TB treatment is the major problem. The patient and family must know what is expected of them through verbal and written instructions in their primary language. Approximately 30–50% of patients taking long-term treatment are significantly nonadherent with self-administered medications, and clinicians are usually not able to determine in advance which patients will be nonadherent. Preferably, DOT should be instituted by the local health department.

Mycobacterium tuberculosis Infection

The following aspects of the natural history and treatment of TBI, often referred to as *latent TB infection,* in children must be considered in the formulation of recommendations about therapy:

1. Infants and children <5 years old with TBI who have been infected recently.
2. The risk for progression to disease is high.
3. Untreated infants with TBI have up to a 40% chance of development of TB disease.
4. The risk for progression decreases gradually through childhood until adolescence, when the risk increases.
5. Infants and young children are more likely to have life-threatening forms of TB, including meningitis and disseminated disease.
6. Children with TBI have more years at risk for development of disease than adults.

Because of these factors and the excellent safety profile of isoniazid, rifampin, and rifapentine in children, there is a tendency to err on the side of overtreatment in infants, young children, and adolescents.

The main TBI treatment regimens used in children are summarized in Table 261.7. The regimens include 6-9 months of **isoniazid** (daily or twice weekly by DOT), 3 months of daily **rifampin** and isoniazid, 4 months of daily rifampin, and once-weekly isoniazid and **rifapentine** (3HP) for 12 total doses. Because of improved treatment completion rates and noninferiority, the rifamycin-based, shorter treatment regimens are often favored over isoniazid monotherapy. The main indication for the use of isoniazid is if the child is at risk of drug-drug interactions with rifamycins.

Isoniazid therapy for TBI appears to be more effective for children than for adults, with several large clinical trials demonstrating a risk reduction of 70–90%. The risk of isoniazid-related hepatitis is minimal in infants, children, and adolescents, who tolerate the drug better than adults. Analysis of data from several studies demonstrates that the efficacy decreased significantly if isoniazid was taken for <9 months. However, the international standard is 6 months of treatment with isoniazid because of resource considerations. Isoniazid given twice weekly has been used extensively to treat TBI in children, especially schoolchildren and close contacts of case patients. DOT or VDOT should be considered when it is unlikely that the child and family will adhere to daily self-administration or if the child is at increased risk for rapid development of disease (newborns and infants, recent contacts, immunocompromised children). For healthy children taking isoniazid but no other potentially hepatotoxic drugs, routine biochemical monitoring and supplementation with pyridoxine are not necessary. Rifampin alone for 4 months is now frequently used for the treatment of TBI in infants, children, and adolescents. This regimen is most often used when a shorter, self-administered treatment regimen is preferred, when isoniazid cannot be tolerated, or the child has had contact with a source case infected with an isoniazid-resistant but rifamycin-susceptible organism. If a child is identified with TBI during a contact investigation or if the cost of rifampin is prohibitive for families, administration of the medication through VDOT programs offered by health departments should be considered. Rifapentine is a rifamycin with a very long half-life, allowing for weekly administration in conjunction with high-dose isoniazid. Studies have demonstrated that 12 doses of once-weekly isoniazid and rifapentine (3HP) are as effective for treating TBI and as safe as 9 months of daily isoniazid in children as young as 2 years. This is becoming the preferred regimen for the treatment of TBI in age-eligible children who are exposed to a contact with presumed pan-susceptible TB. Given the risk of selecting for drug-resistant isolates by missing intermittent doses of rifamycins, this treatment regimen currently is recommended only with DOT under the supervision of local health departments. The main reason children or adolescents are unable to complete this regimen is the inability to crush the tablets and the high pill burden. In these situations, the children are often transitioned to an alternative treatment regimen. A 3-month daily regimen of rifampin and isoniazid has been used throughout

Europe. Although this regimen has not been used regularly in the United States, experts believe it is favorable in children less than 5 years of age in whom the pill burden of 3HP is difficult. Studies have revealed that the shorter treatment regimens for TBI in children are equally efficacious as 9 months of isoniazid and are associated with superior treatment completion rates.

For children with MDR-TB, the regimen will depend on the drug-susceptibility profile of the contract case's organism; an expert in TB should be consulted. There are data that support the use of levofloxacin or moxifloxacin for treatment of MDR-TBI.

Few controlled studies have been published regarding the efficacy of any form of treatment for TBI in children living with HIV. A 9-month course of daily isoniazid is recommended. Most experts recommend that routine monitoring of serum hepatic enzyme concentrations be performed and pyridoxine be given when children living with HIV are treated with isoniazid. The optimal duration of rifampin therapy in children living with HIV with TBI is not known, but many experts recommend at least a 6-month course.

Isoniazid or rifampin should be given to children <5 years old who have a negative TST or IGRA result but who have a known recent exposure to an adult with potentially contagious TB disease. This practice is often referred to as **window prophylaxis**. By the time delayed hypersensitivity develops (2-3 months), an untreated child already may have developed severe TB. For these children, TST or IGRA is repeated 8-10 weeks after contact with the source case for TB has been broken (*broken contact* is defined as physical separation or adequate initial treatment of the source case). If the second test result is positive, the child should complete a treatment course for TBI (either 9 months of isoniazid or 4 months of rifampin). There is a benefit to using rifampin over isoniazid for window prophylaxis (unless contraindicated because of drug-drug interactions or prohibitive because of cost). By the time of the second test result (8-10 weeks later), if positive, the child receiving rifampin has approximately 2 months of therapy to complete compared to 7 months of isoniazid. Alternatively, if a new, shorter TBI treatment course is started after the second test result becomes positive (either 4 months of rifampin [if isoniazid was given as window prophylaxis], 12 weekly doses of isoniazid and rifapentine, or 3 months of isoniazid and rifampin), the treatment start date is day 1 of the new regimen. If the second test result is negative, TBI treatment can be stopped.

PREVENTION

The highest priority of any TB control program should be case finding and treatment, which interrupt transmission of infection between close contacts. All children and adults with symptoms suggestive of TB disease and those in close contact with an adult with suspected infectious pulmonary TB should be tested for TBI (by TST or IGRA) and examined as soon as possible. On average, 30–50% of household contacts to infectious cases are also infected, and 1% of contacts already have overt disease. This scheme relies on effective and adequate public health response and resources. Children, particularly young infants, should receive high priority during contact investigations because their risk for infection is high and they are more likely to rapidly develop severe forms of TB.

Mass testing of large groups of children for TBI is an inefficient process. When large groups of children at low risk for TB are tested, the vast majority of TST reactions are actually false-positive reactions because of biologic variability or cross-sensitization with NTM. However, testing of high-risk groups of adults or children should be encouraged because most of these persons with positive TST or IGRA results have TBI. Testing should take place only if effective mechanisms are in place to ensure adequate evaluation, follow-up, and treatment of the persons who test positive.

Bacille Calmette-Guérin Vaccination

The only available vaccine against TB is the BCG vaccine. The original vaccine organism was a strain of *M. bovis* attenuated by subculture every 3 weeks for 13 years. This strain was distributed to dozens of laboratories that continued to subculture the organism on different media under various conditions. The result has been production of many BCG vaccines that differ widely in morphology, growth characteristics, sensitizing potency, and animal virulence.

The administration route and dosing schedule for the BCG vaccines are important variables for efficacy. The preferred route of administration is intradermal injection with a syringe and needle because it is the only method that permits accurate measurement of an individual dose.

The BCG vaccines are extremely safe in immunocompetent hosts. Local ulceration and regional suppurative adenitis occur in 0.1–1% of vaccine recipients. Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine. Most reactions are mild and usually resolve spontaneously, but chemotherapy is needed occasionally. Surgical excision of a suppurative draining node is rarely necessary and should be avoided if possible. **Osteitis** is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use. Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination. Profoundly immunocompromised patients can develop disseminated BCG infection after vaccination. Children living with HIV appear to have rates of local adverse reactions to BCG vaccines that are comparable with rates in immunocompetent children. However, the incidence in these children of disseminated infection months to years after vaccination is currently unknown.

Recommended vaccine schedules vary widely among countries. The official WHO recommendation is a single dose administered during infancy in populations where the risk for TB is high. However, *infants with known or suspected HIV infection should not receive a BCG vaccination.* In some countries, repeat vaccination is universal, although no clinical trials support this practice. In others, it is based on either TST or the absence of a typical scar. The optimal age for BCG administration and dosing schedule are unknown because adequate comparative trials have not been performed.

Although dozens of BCG trials have been reported in various human populations, the most useful data have come from several controlled trials. The results of these studies have been disparate. Some demonstrated substantial protection from BCG vaccines, but others showed no efficacy at all. A meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary TB in adults and children. The protective effect for disseminated and meningeal TB appears to be slightly higher, with BCG preventing 50–80% of cases. A variety of explanations for the varied responses to BCG vaccines have been proposed, including methodologic and statistical variations within the trials, interaction with NTM that either enhances or decreases the protection afforded by BCG, different potencies among the various BCG vaccines, and genetic factors for BCG response within the study populations. BCG vaccination administered during infancy has little effect on the ultimate incidence of TB in adults, suggesting waning protection with time.

BCG vaccination has worked well in some situations but poorly in others. Clearly, BCG vaccination has had little effect on the ultimate control of TB throughout the world, because >5 billion doses have been administered, but TB remains epidemic in most regions. BCG vaccination does not substantially influence the chain of transmission, because cases of contagious pulmonary TB in adults that can be prevented by BCG vaccination constitute a small fraction of the sources of infection in a population. The best use of BCG vaccination is to prevent life-threatening forms of TB in infants and young children.

BCG vaccination has never been adopted as part of the strategy for TB control in the United States. Widespread use of the vaccine would render subsequent TSTs less useful. However, BCG vaccination can contribute to TB control in select population groups. BCG is recommended for TST-negative, HIV-negative infants and children who are at high risk for intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious

pulmonary TB and who cannot be removed from the source of infection or placed on long-term preventive therapy. It also is recommended for those who are continuously exposed to persons with TB who have bacilli that are resistant to isoniazid and rifampin. Any child receiving BCG vaccination should have a documented negative TST before receiving the vaccine. After receiving the vaccine, the child should be separated from the possible sources of infection until it can be demonstrated that the child has had a vaccine response, as evidenced by tuberculin reactivity, which usually develops within 1-3 months.

Prevention of Perinatal Tuberculosis

The most effective way of preventing TB infection and disease in the neonate or young infant is through appropriate testing and treatment of the mother and other family members. High-risk pregnant women should be tested with TST or IGRA, and those with a positive test result should receive a chest radiograph with appropriate abdominal shielding. If the mother has a negative chest radiograph and is clinically well, no separation of the infant and mother is needed after delivery. The child needs no special evaluation or treatment if the child remains asymptomatic. Other household members should undergo testing for TBI and further evaluation as indicated.

If the mother has suspected TB at the time of delivery, the newborn should be separated from the mother until the chest radiograph is obtained. If the mother's chest radiograph is abnormal, separation should be maintained until the mother has been evaluated thoroughly, including examination of the sputum. If the mother's chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph show no evidence of current active TB, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate TB treatment, and she and her infant should receive careful follow-up care.

If the mother's chest radiograph or AFB sputum smear shows evidence of current TB disease, additional steps are necessary to protect the infant. Isoniazid therapy for newborns has been so effective that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become nonadherent to treatment, or has suspected drug-resistant TB. Isoniazid treatment for the infant should be continued until the mother is sputum culture negative for ≥3 months. At that time, a TST should be placed on the child. If the test is positive, isoniazid is continued for a total duration of 9-12 months; if the TST is negative, isoniazid can be discontinued. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, because the medications, although found in milk, are present in low concentrations. If isoniazid resistance is suspected or the mother's adherence to medication is in question, continued separation of the infant from the mother should be considered. The duration of separation must be at least as long as is necessary to render the mother noninfectious. A TB expert should be consulted if the young infant has potential exposure to the mother or another adult with TB disease caused by an isoniazid-resistant strain of *M. tuberculosis*.

Although isoniazid is not thought to be teratogenic, the treatment of pregnant women who have asymptomatic TBI is often deferred until after delivery. However, symptomatic pregnant women or those with radiographic evidence of TB disease should be appropriately evaluated. Because pulmonary TB is harmful to both the mother and the fetus and represents a great danger to the infant after delivery, TB in pregnant women always should be treated. The most common regimen for drug-susceptible TB is isoniazid, rifampin, and ethambutol. The aminoglycosides and ethionamide should be avoided because of their teratogenic effect. The safety of pyrazinamide in pregnancy has not been established.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 262

Hansen Disease (*Mycobacterium leprae*)

Cristina Tomatis Souverbielle and Asuncion Mejias

Leprosy (Hansen disease [**HD**]) is a heterogeneous, curable infection caused by *Mycobacterium leprae* that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are mainly determined by the host's immunologic response to infection, resulting in a wide clinical spectrum. The majority of exposed individuals never develop clinical disease. HD is currently the accepted designation of leprosy, and contrary to popular folklore, HD is *not* highly transmissible and *is* treatable. In addition, the associated morbidity and disability can be prevented with early diagnosis and appropriate treatment.

MICROBIOLOGY

M. leprae is an obligate, intracellular, acid-fast, gram-positive bacillus of the family Mycobacteriaceae measuring 1-8 μm in length. It grows optimally at 27–33°C (80.6–91.4°F) yet cannot be cultured in vitro. The bacillus multiplies slowly, with a doubling time of 11-13 days. It is the only bacterium known to infect **Schwann cells** of peripheral nerves. Identification of acid-fast bacilli (AFB) in peripheral nerves is pathognomonic of leprosy.

EPIDEMIOLOGY

The prevalence of leprosy is variable, with most cases being identified in tropical and subtropical areas. The World Health Organization (WHO) goal to eliminate leprosy as a public health problem, defined as a reduction in its prevalence to less than 1 case per 10,000 population, was achieved at the global level in 2000. Despite an overall decline in reported prevalence, HD continues to afflict more than 2 million people worldwide. In 2022, 174,059 new cases were reported globally, with most cases occurring in Southeast Asia (mostly India), Africa, and South America (mostly Brazil). Of those, 5.92% occurred in children <15 years. In 2018, the WHO reviewed the available evidence on key issues related to the elimination of leprosy and developed a guidance WHO Guidelines for the Diagnosis, Treatment and Prevention of Leprosy. More recently, the WHO released Towards Zero Leprosy – Global Leprosy (Hansen's Disease) Strategy 2021-2030, which was aligned with the 2021-2030 road map for neglected tropical diseases during the same period.

Since 1984, HD has been a *notifiable disease* in the United States, with about 14,000 cases recorded since then. Since the 1990s, an average of 175 new cases are reported annually. Of the 159 new U.S. cases reported in 2020, 69% were identified in Texas, Louisiana, Hawaii, California, Florida, and New York. Most new cases (~75%) in the United States were identified among immigrants from HD-endemic countries or in citizens who have worked abroad in endemic areas. However, over one third of U.S. cases are **autochthonous** and do not report contact with foreign countries or people with leprosy.

The likelihood of developing HD is determined by several variables: age (with two incidence peaks: 10-14 years and 30 years), gender (male/female ratio 2:1, with no differences observed in children), genetics, immune status, type of leprosy (with higher risk in those exposed to patients with multibacillary disease), and possibly through exposure to **armadillos**. Whole genome sequencing has allowed identification of genes and polymorphisms associated with increased susceptibility to leprosy and found that approximately 5% of people are genetically susceptible to *M. leprae* infection. HD in immunocompromised

hosts has been reported in solid organ and bone marrow transplant recipients and patients receiving tumor necrosis factor (TNF)–blocking monoclonal antibodies. Patients with HIV infection do not appear to be at increased risk of acquiring leprosy, increased disease severity, or poor response to treatment. However, clinicians should be aware that concomitant HIV infection and leprosy can result in worsening of symptoms of leprosy during HIV treatment as a result of an immune reconstitution inflammatory syndrome.

The exact mechanism of transmission is not fully understood but is thought to occur primarily by the respiratory route. Natural infection occurs in humans and armadillos, which are the only recognized nonhuman reservoir. The risk of transmission from armadillos to humans seems low, and again, the mechanism is not fully understood. The incubation period between natural infection and overt clinical disease in humans ranges from 3 months to 20 years, with a mean of 4 years for **tuberculoid** leprosy and 10 years for **lepromatous** leprosy. Up to 10^7 viable bacilli per day can be shed in respiratory secretions of patients with **multibacillary** leprosy. The relative risk for developing disease in household contacts is 8- to 10-fold for lepromatous disease and 2- to 4-fold for the tuberculoid form. Transmissions by breast milk, the transplacental route, and through broken skin have been reported. Environmental factors and subclinically infected humans may also play a role in disease transmission. The infectivity of patients with HD becomes negligible within 24 hours of the first administration of effective therapy.

PATHOGENESIS

In the skin, *M. leprae* shows affinity for keratinocytes, macrophages, and histiocytes, and in peripheral nerves, the organism can be found in the Schwann cells. The mechanism of mycobacterial dissemination from the respiratory tract to the skin and nerves is thought to occur hematogenously but has not been completely elucidated. *M. leprae* induces demyelination and binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves, where it replicates slowly over several years. Infection stimulates the dedifferentiation of Schwann cells to immature cells through the activation of the Erk1/2 pathway. This reprogramming of Schwann cells seems to be linked to disease dissemination. In addition to the direct nerve invasion, the immune response to infection also contributes to nerve damage. Schwann cells express human leukocyte antigen (HLA) class II molecules and present mycobacterial peptides to the HLA class II restricted $CD4^+$ T cells, which initiate an inflammatory response. These events explain the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually fibrosis and axonal death.

DISEASE CLASSIFICATION

Disease classification is important to determine potentially infectious cases and prognosis. Based on the cellular immune response and disease dissemination, two classification schemes for leprosy are frequently used: the Ridley-Jopling scale and the WHO classification:

A. The **Ridley-Jopling scale** is used in the United States and describes the five types of leprosy, according to clinical spectrum of disease, bacillary load, and findings on histopathology.
   1. *Tuberculoid form*: Patients usually have a vigorous and specific cellular immune response to *M. leprae* antigens and have a small number of skin lesions, generally one to three well-demarcated macules or plaques with elevated borders (Fig. 262.1) and reduced or absent sensation. The lesions are infiltrated by T-helper 1 (Th1) cells producing abundant interferon (IFN)-γ and TNF-α, forming well-demarcated granulomas, with few, if any, bacilli found within the lesions.
   2. *Borderline tuberculoid form*
   3. *Borderline form*
   4. *Borderline lepromatous*
   5. *Lepromatous form*: Patients have an absence of specific cellular immunity to *M. leprae* (but intact immunity to *Mycobacterium tuberculosis*) and present the most severe form of disease. They manifest clinically apparent infiltration of peripheral nerves and skin lesions (usually many lesions and not all hypoesthetic or anesthetic), with a high load of bacilli in the absence of an effective cell-mediated immune response. Skin biopsies reveal extensive infiltration of the skin and nerves, containing messenger RNA for Th2 cytokines such as interleukin (IL)-4 and IL-10, poorly formed granulomas, and uncontrolled proliferation of bacilli within foamy macrophages. A large amount of circulating antibody to *M. leprae* is present but does not confer protective immunity. Over time, patients with the lepromatous form develop a systemic disease with symmetric peripheral nerve involvement and a diffuse infiltrative dermopathy that includes thickening of the facial skin and hair loss of the eyelashes and eyebrows (madarosis), leading to the classic presentation of the *leonine facies*. They also have involvement of the nasal mucosa causing nasal congestion and epistaxis.
   6. The majority of patients will present with a borderline form. From borderline tuberculoid to borderline lepromatous forms, there is a progressive reduction in cellular immune responses, an increase in bacillary load, more frequent hypopigmented skin lesions and nerve involvement, and higher antibody titers (Fig. 262.2). Patients with the extreme forms of the disease (tuberculoid and lepromatous) are considered to have stable cell-mediated immunity, because their disease manifestations do not change much over time. In contrast, patients with borderline disease have unstable cell-mediated immunity and demonstrate changes in their clinical manifestations over time toward the polar forms (downgrade) or present sudden reversal reactions (upgrade). *Indeterminate leprosy* is the earliest form of the disease and is seen most frequently in young children. Patients usually have a single hypopigmented macule with poorly defined borders, without erythema or induration. Anesthesia is minimal or absent, especially if the lesion is on the face. The diagnosis is



Fig. 262.1 Tuberculous leprosy in a patient who has a single skin lesion with a raised border and flattened center.



Fig. 262.2 Borderline leprosy in a patient who has numerous hypopigmented lesions with poorly defined borders.

usually one of exclusion in the setting of a contact investigation. Tissue biopsies show diagnostic evidence of leprosy but do not meet sufficient criteria for classification. Up to 50–75% of these lesions will heal spontaneously, and the rest will progress to another form of leprosy.

B. The **WHO classification** can be used when histologic evaluation and confirmatory diagnosis is unavailable, a common scenario in the field. This simplified scheme is based on the number of skin lesions:
   1. Paucibacillary (1-5 patches)
   2. Multibacillary (>5 patches)

CLINICAL MANIFESTATIONS

The host immune response determines the clinical spectrum of leprosy. Skin and serologic studies suggest that up to 90% of infected people develop immunity after exposure, without manifesting clinical disease. In genetically susceptible individuals with sufficient exposure to become infected, the cellular host's immunologic response to infection and unique tropism for peripheral nerves determine the wide spectrum of clinical (and histologic) manifestations. Regardless of the disease subtype, HD affects the skin and peripheral nerves. Leprosy lesions usually do not itch or hurt. Polymorphisms in vitamin D and its receptor have been proposed to play a role in the manifestations of leprosy.

Skin Involvement

The most common skin lesions are **macules** or **plaques** with unclear outer limits, with or without neurologic symptoms. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin. Lesions may involve any area of the body, are more pronounced in cooler areas (e.g., earlobes, nose), and occur less frequently in the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion and the degree of Th1 immune response. Examination of the skin should ideally be performed in natural sunlight and include testing for hypoesthesia to light touch, pinprick, temperature, and anhidrosis. Studies in endemic areas in children <15 years old have shown a predominance of **paucibacillary** forms, with a predominance of single lesions.

Nerve Involvement

Peripheral nerves are most frequently affected early in the disease and should be palpated for thickness and tenderness (Fig. 262.3), as well as evaluated for both motor and sensory function, particularly temperature and light touch. The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist), lateral popliteal (fibular neck), and facial nerves. The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. There is a pure **neuritic** form of leprosy, usually occurring in India and Nepal, in which patients present with asymmetric neuropathy but lack skin lesions.

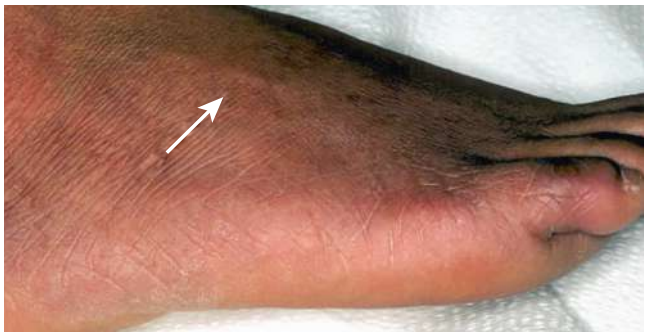

Fig. 262.3 Thickened, superficial peroneal nerve of leprosy.

Other Organ Involvement

Ocular involvement leading to vision loss results from both direct bacillary invasion of the eye and optic nerve damage. **Lagophthalmos** occurs when there is destruction of the facial nerve (cranial nerve VII), and trigeminal nerve (cranial nerve V) destruction causes anesthesia of the cornea and conjunctiva, leading to abrasions. Facial skin lesions are associated with a 10-fold higher risk of facial nerve damage. Systemic involvement of other organs is seen mainly in patients with lepromatous leprosy, where a high bacillary burden leads to infiltration of the nasal mucosa, bones, and testes. Renal involvement and amyloidosis are rare findings.

Immunologic Reactions

Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to *M. leprae* infection and occurring in 30–50% of all leprosy patients. These sudden changes occur in patients with borderline and lepromatous leprosy, typically during the initial years after infection (sometimes as the initial presentation), but can occur before, during, or after completion of treatment. There are two main types of leprosy reactions, which require immediate treatment to prevent long-term complications. In children <15 years old, leprosy reactions range from 1% to 30% and are mainly type 1 reactions.

Type 1 reactions (also known as **reversal reactions**) occur in one third of patients with borderline disease. These reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules, with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon and appear to be associated with an increase in Th1-mediated reactivity to mycobacterial antigens. Increased serum concentrations of CXCL10 have been found in type 1 reactions. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.

Type 2 reactions, or **erythema nodosum leprosum (ENL)**, occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of *M. leprae* antigens and antibodies, most often in the first 2 years after starting therapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-α. Patients develop high fever and signs

of systemic toxicity, and in severe cases, ENL can be life threatening, presenting with features similar to septic shock. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and, rarely, nephritis. Patients may present with a single acute episode, a relapsing form comprising multiple acute episodes, or a chronic continuous form. Management of type 2 reactions is usually more complicated because of recurrence and systemic involvement.

Lucio phenomenon (erythema necroticans) is an uncommon but potentially fatal reaction distinct from type 1 or 2 reactions and occurs in patients with untreated lepromatous leprosy and in patients whose ancestry is from Mexico. It is a necrotizing vasculitis caused by *M. leprae* directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.

DIAGNOSIS

The diagnosis of HD requires high clinical suspicion and should be considered in any patient with a **hypoesthetic or anesthetic skin lesion that does not respond to standard treatment**, especially if there is a history of travel or residence in an endemic region or a history of contact with leprosy patients or armadillos. There are no reliable tests to diagnose subclinical leprosy. Full-thickness skin biopsy and polymerase chain reaction (PCR) are the main laboratory tests to aid in the diagnosis. Patients are considered to have HD if they have **one or more of the three cardinal signs**: loss of sensation in a localized skin lesion (pale or erythematous), thickened peripheral nerve with loss of sensation and/or weakness of muscles enervated by that nerve, or the presence of AFB on biopsy. The positive predictive value for the diagnosis of leprosy in patients meeting all three criteria is 98%.

To confirm the diagnosis and determine the extent of nerve involvement and the type of infiltrate, a full-thickness skin biopsy from the most active lesion should be performed. *M. leprae* is best identified in tissue using the *Fite stain*. Lesions from patients with the lepromatous form reveal numerous AFB in clumps (globi), whereas patients with the tuberculoid form rarely have mycobacteria identified, but the diagnosis can be made by demonstration of well-formed noncaseating granulomas and nerve involvement. The presence of **neural inflammation** differentiates leprosy from other granulomatous disorders. Mycobacterial culture of lesions should be performed to exclude *M. tuberculosis* and nontuberculous cutaneous infections. If no resources are available, slit-skin (skin smear) biopsies represent an alternative. Slit-skin smears have high specificity but low sensitivity; only 30% of adults and 10–30% of children <15 years old are smear positive (usually patients with the lepromatous form). The bacterial index can range from 0 (no bacilli in 100 oil-immersion fields), as generally seen in paucibacillary disease, to 6+ (>1,000 bacilli/field), as can be seen in multibacillary disease.

Diagnostic and histopathologic consultation in the United States is available through the **National Hansen's Disease Program** (**NHDP**; http://www.hrsa.gov/hansens or 800-642-2477). Specimens (formalin or paraffin embedded) can be sent to the NHDP for pathologic analysis free of charge. A PCR test for *M. leprae* is not readily available in clinical practice but may be performed at the NHDP. In nonendemic areas, PCR may be useful for diagnosis when AFB are discernible in tissue but clinical and histopathologic features are not typical. *M. leprae* DNA is detectable by PCR in 95% of lepromatous disease and 55% of tuberculoid lepra. PCR has also allowed detection of the organism in nasal secretions from asymptomatic people. Molecular testing for mutations causing drug resistance is also available through the NHDP and is usually used in the setting of relapse.

Antibodies to *M. leprae* are present in 90% of patients with untreated lepromatous disease, 40–50% of patients with paucibacillary disease, and 1–5% of healthy controls. However, serologic testing is insensitive and is not used for diagnosis.

TREATMENT

The primary goal of treatment is early antimicrobial therapy to prevent permanent neuropathy. Leprosy is curable. Effective treatment requires multidrug therapy (MDT) with **dapsone**, **clofazimine**, and **rifampin**. Combination therapy is employed to prevent antimicrobial resistance. In the United States, clinical providers considering a diagnosis and treatment of a patient with HD should obtain **consultation from the NHDP**. The recommended combination MDT can be obtained free of charge from the NHDP (Table 262.1) and in other countries through the WHO (Table 262.2). Compared with the WHO, the NHDP advocates for a longer duration of treatment and daily rather than monthly administration of rifampin because shorter antimicrobial regimens have been associated with a greater risk of relapse. The recommended duration by the WHO for tuberculoid disease is 6 months and for lepromatous disease is 12 months. Since 2018, the WHO has advocated for a three-drug regimen for all leprosy forms; however, NHDP guidelines recommend two drugs (dapsone and rifampin) for the treatment of paucibacillary disease.

Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline

Table 262.1 NHDP-Recommended Multidrug Therapy Regimens for Hansen Disease in the United States

TYPE OF LEPROSY	PATIENT POPULATION	ANTIMICROBIAL THERAPY	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Dapsone 100 mg/day *and* rifampin* 600 mg/day *and* clofazimine 50 mg/day	24 mo
	Pediatric†	Dapsone 1 mg/kg/day *and* rifampin 10-20 mg/kg/day *and* clofazimine 1 mg/kg/day‡	
Paucibacillary (TT, BT)	Adult	Dapsone 100 mg/day *and* rifampin 600 mg/day	12 mo
	Pediatric†	Dapsone 1 mg/kg/day *and* rifampin 10-20 mg/kg/day	

*Rifampin is taken monthly if the patient is on prednisone.
†Daily pediatric mg/kg dose should not exceed the adult daily maximum.
‡Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg, and capsules should not be cut. Alternative dosing includes clofazimine 2 mg/kg every other day
NHDP, National Hansen's Disease Program; BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.
NHDP multidrug therapy is daily and of longer duration than WHO-recommended regimen. All drugs are administered orally. For immunologically compromised or elderly patients, these protocols may be modified. Consultation with the NHDP is advised.

Table 262.2 WHO-Recommended Multidrug Therapy (MDT) Regimens for Hansen Disease

TYPE OF LEPROSY	PATIENT POPULATION	ANTIMICROBIAL THERAPY	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Rifampicin 600 mg once monthly *and* dapsone 100 mg/day *and* clofazimine 300 mg once monthly and 50 mg/day	12 mo
	Pediatric*	Rifampicin 450 mg once monthly *and* dapsone 50 mg/day *and* clofazimine 150 mg once monthly and 50 mg every other day	
Paucibacillary (TT, BT)	Adult	Rifampicin 600 mg once monthly *and* dapsone 100 mg/day *and* clofazimine 300 mg once monthly and 50 mg/day	6 mo
	Pediatric*	Rifampicin 450 mg once monthly *and* dapsone 50 mg/day *and* clofazimine 150 mg once monthly and 50 mg every other day	

*In children <10 yr old, or <than 40Kg, MDT dosages should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, and clofazimine100 mg once a month, 50 mg twice weekly.
WHO, World Health Organization; BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

complete blood cell count and liver function testing, and be evaluated for evidence of active tuberculosis, in which monotherapy with rifampin should be avoided. Response to therapy is seen clinically as flattening or disappearance of skin lesions and improvement in nerve function, usually within 1-2 months after initiating MDT. Complete resolution or improvement may take 6-12 months, depending on the severity of infection. Most skin lesions heal without scarring. Identification of biomarkers for the optimal identification and management of leprosy continue to be under study. CXCL10 (IP-10) has been identified as a potential marker to help monitor treatment efficacy in patients with multibacillary disease, as higher levels of CXCL-10 are important for the control of bacillary load.

Alternative agents to treat HD include minocycline, clarithromycin, and some fluoroquinolones (levofloxacin, ofloxacin, moxifloxacin). Given limited data, these alternative antimicrobials are used in selected cases of intolerance to the routine combination MDT regimen or for documented resistance. It is important to note that some patients who have been adequately treated for HD may later show evidence of chronic reversal reactions and late neuropathies, but these are bacillus negative and thus should not be considered relapses. Neuritis must be treated promptly to minimize nerve injury and disability. Treatment with corticosteroids appears to improve nerve function in two thirds of patients.

Bone marrow suppression and hepatotoxicity have been reported and should be monitored every 3 months during therapy. A screening urinalysis should be performed annually. Other reactions, such as methemoglobinemia and hypersensitivity reactions to dapsone, are rare. An ophthalmologic evaluation should routinely be performed in all patients with HD because ocular complications can occur. Given the proclivity for testicular invasion in multibacillary leprosy with resultant testicular dysfunction and infertility, males should be screened for elevated follicle-stimulating hormone or luteinizing hormone concentrations and decreased testosterone levels.

After completion of MDT, annual follow-up for ≥5 years for paucibacillary and ≥10 years for multibacillary disease is warranted. Relapse of the disease after completion of MDT is rare (0.01–1.4%) and must be distinguished from the more common leprosy immunologic reactions. Patients who have a bacillary index of ≥4 pre-MDT or ≥3 at the completion of MDT have the highest risk of relapse (approximately 20%). When relapse occurs, it is usually within 5-10 years of MDT completion and a result of reactivation of drug-susceptible mycobacteria. Thus patients who are expected to relapse are generally treated with the same MDT regimen. Resistance to all three drugs has been documented, although it rarely occurs with combination therapy. There is no role for routine baseline resistance testing, but the NHDP can provide it if needed.

Leprosy Reactions

Immunologic reactions can occur before, during, and years after treatment and should be treated aggressively to prevent peripheral nerve damage. In general, antimycobacterial drugs should be continued. Fatigue, malaise, or fever can be present, and the inflammation associated with these reactions can cause severe nerve injury. Prompt therapy with corticosteroids with or without other antiinflammatory agents, adequate analgesia, and physical support are essential for patients with active neuritis to prevent nerve damage. **If corticosteroids are indicated for a prolonged time, the frequency of rifampicin administration should be decreased from daily to monthly** administration (to avoid drug interactions). In 2020, to aid with the management of leprosy reactions, the WHO published the technical guide: *Leprosy/Hansen Disease: Management of Reactions and Prevention of Disabilities*.

For severe **type 1 reactions**, **prednisone is recommended**, 1 mg/kg/day orally (40-60 mg) with a slow taper (decreasing by 5 mg every 2-4 weeks after evidence of improvement over 3-6 months) in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed. Nerve function improves after corticosteroid treatment in 30–80% of patients who did not have preexisting neuritis. In patients not responding to corticosteroids, cyclosporine may be used as a second-line agent.

For severe **type 2 reactions**, **prednisone is routinely used** at 1 mg/kg/day for 12 weeks. However, given the recurrence and chronicity of ENL, **corticosteroid-sparing agents should be considered** to avoid complications associated with their prolonged use. **Thalidomide** (100-400 mg/daily for 48-72 hours, tapering over 2 weeks to 100 mg/daily) is effective in treating these types of reactions. Given the teratogenicity of thalidomide (contraindicated for children <12 years old and women of childbearing age), the drug is only available through a restrictive distribution program approved by the U.S. Food and Drug Administration (FDA). **Clofazimine** (300 mg/day for several months, tapering to <100 mg/day, within a year) alone or in combination with corticosteroids, has also been useful in managing patients with chronic ENL and is generally used until all signs of the reaction have abated. Other immunosuppressive drugs have been used to treat type 2 reactions with inconsistent results, including cyclosporine, mycophenolate, and methotrexate. **Lucio phenomenon is managed similarly to ENL** and treatment of underlying infections.

LONG-TERM COMPLICATIONS

Leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. The major chronic complications and deformities of leprosy are caused by **nerve injury**. Nerve impairment may be purely sensory, motor, or autonomic or may be a combination. The prognosis for arresting progression of tissue and nerve damage is good if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve function impairment can occur before diagnosis, during MDT, or after MDT and can develop without overt signs of skin or nerve inflammation (silent neuropathy). Patients at highest risk of nerve impairment are those with multibacillary leprosy and preexisting nerve damage. These patients should undergo regular monthly surveillance during therapy and for at least 2 years from the time of diagnosis. In children, deformities can occur in 3–10% of cases and mainly in those with nerve enlargement. Other factors contributing to risk of deformities include increasing age in children, delay in accessing medical care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and leprosy reaction at presentation.

PREVENTION

In addition to treating active leprosy cases, control measures for HD include the management of **contacts** of index patients. In endemic countries, close monitoring of household contacts of HD patients, particularly HD patients with multibacillary disease, is warranted to ensure that early treatment can be implemented if evidence of early HD develops. These household contacts should be examined at baseline and then yearly for 5 years. In nonendemic areas, disease presenting in the contacts of patients with HD is rare. A single dose of bacille Calmette-Guérin (BCG) vaccine has variable protective efficacy against leprosy, ranging from 10% to 80%; an additional dose results in increased protection. Any suspected or newly diagnosed case of leprosy in the United States should be reported to local and state public health departments, the Centers for Disease Control and Prevention (CDC), and NHDP. There are no leprosy vaccines available or recommended for use in the United States. In the hospital setting, **standard precautions** should be implemented. Hand hygiene is recommended for all people in contact with a patient with lepromatous leprosy. The use of chemoprophylaxis with a single dose of rifampin (SDR) within endemic areas is recommended by the WHO, but not the NHDP, for adults and children ≥2 years in contact with leprosy patients. Because leprosy is a highly stigmatized disease, caution must be exercised when implementing SDR in contacts, particularly for those outside the patient's family.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 263

Nontuberculous Mycobacteria

Ericka V. Hayes

Nontuberculous mycobacteria **(NTM)**, also referred to as **atypical mycobacteria** and **mycobacteria other than tuberculosis** (MOTT), are all members of the genus *Mycobacterium* and include species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. The NTM constitute a highly diverse group of bacteria that differ from *M. tuberculosis* complex bacteria in their pathogenicity, interhuman transmissibility, nutritional requirements, ability to produce pigments, enzymatic activity, and drug susceptibility. In contrast to the *M. tuberculosis* complex, NTM are acquired from environmental sources and not by person-to-person spread, although the latter is under debate, especially in patients with cystic fibrosis (CF). Their omnipresence in the environment means that the clinical relevance of NTM isolation from clinical specimens is sometimes unclear; a positive culture might reflect occasional presence or contamination rather than true NTM disease. NTM are associated with pediatric lymphadenitis, otomastoiditis, serious lung infections, and, rarely, disseminated disease. Treatment is long-term and cumbersome and often requires adjunctive surgical intervention. Comprehensive guidelines on diagnosis and treatment are provided by the American Thoracic Society (ATS) and British Thoracic Society (BTS).

ETIOLOGY

NTM are ubiquitous in the environment all over the world, existing as saprophytes in soil and water (including municipal water supplies, tap water, hot tubs, and shower heads), environmental niches that are the supposed sources of human infections. With the introduction of molecular identification tools such as 16S recombinant DNA gene sequencing, the number of identified NTM species has grown to more than 150; the *clinical relevance* (i.e., percentage of isolates that are causative agents of true NTM disease, rather than occasional contaminants) differs significantly by species.

Mycobacterium avium complex (**MAC**; i.e., *M. avium, Mycobacterium intracellulare,* and several closely related but rarer species) and *Mycobacterium kansasii* are most often isolated from clinical samples, yet the isolation frequency of these species differs significantly by geographic area. MAC bacteria have been frequently isolated from natural and synthetic environments, and cases of MAC disease have been successfully linked to home exposure to shower and tap water. Although the designation *M. avium* suggests that human infections are acquired from birds (Latin *avium*), molecular typing has established that *M. avium* strains that cause pediatric lymphadenitis and adult pulmonary disease represent the *M. avium* hominis suis subgrouping, mainly found in humans and pigs and not in birds.

Some NTM have well-defined ecologic niches that help explain infection patterns. The natural reservoir for *Mycobacterium marinum* is fish and other cold-blooded animals, and the **fish tank granuloma**, a localized skin infection caused by *M. marinum,* follows skin injury in an aquatic environment. *Mycobacterium fortuitum* complex bacteria and *Mycobacterium chelonae* are ubiquitous in water and have caused clusters of nosocomial surgical wound and venous catheter–related infections. *Mycobacterium ulcerans* is associated with severe, chronic skin infections **(Buruli ulcer disease)** and is endemic mainly in West Africa and Australia, although other foci exist. Its incidence is highest in children <15 years old. *M. ulcerans* had been detected in environmental samples by polymerase chain reaction (PCR) and has been recovered by culture from a water strider (an insect of the *Gerris* genus) from Benin.

EPIDEMIOLOGY

Humans are exposed to NTM on a daily basis. In rural U.S. counties, where *M. avium* is common in swamps, the prevalence of asymptomatic infections with *M. avium* complex, as measured by skin test sensitization, approaches 70% by adulthood. Still, the incidence and prevalence of the various NTM disease types remain largely unknown, especially for pediatric NTM disease. In Australian children, the overall incidence of NTM infection is 0.84 per 100,000, with lymphadenitis accounting for two thirds of cases. The incidence of pediatric NTM disease in the Netherlands is estimated at 0.77 infections per 100,000 children per year, with lymphadenitis making up 92% of all infections.

In comparison, estimations of the prevalence of NTM from respiratory samples in adults are 5-15 per 100,000 persons per year, with important differences between countries or regions. Because pulmonary NTM disease progresses slowly, over years rather than months, and usually takes several years to cure, the prevalence of pulmonary NTM disease is much higher than incidence rates would suggest.

The paradigm that NTM disease is a rare entity limited to resource-rich countries is changing. In recent studies in African countries with a high prevalence of HIV infection, it has been found that NTM might play a much larger role as a cause of tuberculosis-like disease of children and adults than previously assumed and thus confuse the diagnosis of tuberculosis.

Although it is generally believed that NTM infections are contracted from environmental sources, whole genome sequence analysis of *Mycobacterium abscessus* strains of patients in a CF clinic in the United Kingdom supports the possibility of nosocomial horizontal transmission among CF patients.

PATHOGENESIS

The histologic appearances of lesions caused by *M. tuberculosis* and NTM are often indistinguishable. The classic pathologic lesion consists of caseating granulomas. Compared with *M. tuberculosis* infections, NTM infections are more likely to result in **granulomas that are non-caseating**, poorly defined (nonpalisading), irregular or serpiginous, or even absent, with only chronic inflammatory changes observed. The histology likely reflects the immune status of the patient.

In patients with AIDS and disseminated NTM infection, the inflammatory reaction is usually scant, and tissues are filled with large numbers of histiocytes packed with acid-fast bacilli (AFB). These disseminated NTM infections typically occur only after the number of CD4 T lymphocytes has fallen below 50/μL in children ≥6 years, below 75/μL in children 2 to <6 years, below 500/μL in children 1 to <2 years, and below 750/μL in children <1 year, suggesting that specific T-cell products or activities are required for immunity to mycobacteria.

The pivotal roles of interferon (IFN)-γ, interleukin (IL)-12, and tumor necrosis factor (TNF)-α in disease pathogenesis are demonstrated by the high incidence of mostly disseminated NTM disease in children with IFN-γ and IL-12 pathway deficiencies and in persons treated with agents that neutralize TNF-α.

Observed differences in pathogenicity, clinical relevance, and spectrum of clinical disease associated with the various NTM species emphasize the importance of bacterial factors in the pathogenesis of NTM disease, although exact virulence factors remain largely unknown.

CLINICAL MANIFESTATIONS

Lymphadenitis of the superior anterior cervical or submandibular lymph nodes is the most common manifestation of NTM infection in children (Table 263.1). Preauricular, posterior cervical, axillary, and inguinal nodes are involved occasionally. Lymphadenitis is most

Table 263.1 Major Clinical Syndromes Associated with Nontuberculous Mycobacterial Infection

SYNDROME	MOST COMMON CAUSES	LESS FREQUENT CAUSES*
Chronic nodular disease (adults with bronchiectasis; cystic fibrosis)	MAC (*M. intracellulare, M. avium*), *M. kansasii, M. abscessus*	*M. xenopi, M. malmoense, M. szulgai, M. smegmatis, M. celatum, M. simiae, M. goodii, M. asiaticum, M. heckeshornense, M. branderi, M. lentiflavum, M. triplex, M. fortuitum, M. arupense, M. abscessus* subsp. *bolletii, M. phocaicum, M. aubagnense, M. florentinum, M. abscessus* subsp. *massiliense, M. nebraskense, M. saskatchewanense, M. seoulense, M. senuense, M. paraseoulense, M. europaeum, M. sherrisii, M. kyorinense, M. noviomagense, M. mantenii, M. shinjukuense, M. koreense, M. heraklionense, M. parascrofulaceum, M. arosiense*
Cervical or other lymphadenitis (especially children)	MAC	*M. scrofulaceum, M. malmoense* (northern Europe), *M. abscessus, M. fortuitum, M. lentiflavum, M. tusciae, M. palustre, M. interjectum, M. elephantis, M. heidelbergense, M. parmense, M. bohemicum, M. haemophilum, M. europaeum, M. florentinum, M. triplex, M. asiaticum, M. kansasii, M. heckeshornense*
Skin and soft tissue disease	*M. fortuitum* group, *M. chelonae, M. abscessus, M. marinum, M. ulcerans* (Australia, tropical countries only)	*M. kansasii, M. haemophilum, M. porcinum, M. smegmatis, M. genavense, M. lacus, M. novocastrense, M. houstonense, M. goodii, M. immunogenum, M. mageritense, M. abscessus* subsp. *massiliense, M. arupense, M. monacense, M. bohemicum, M. branderi, M. shigaense, M. szulgai, M. asiaticum, M. xenopi, M. kumamotense, M. setense, M. montefiorense* (eels), *M. pseudoshottsii* (fish), *M. shottsii* (fish)
Skeletal (bone, joint, tendon) infection	*M. marinum*, MAC, *M. kansasii, M. fortuitum* group, *M. abscessus, M. chelonae*	*M. haemophilum, M. scrofulaceum, M. heckeshornense, M. smegmatis, M. terrae/chromogenicum* complex, *M. wolinskyi, M. goodii, M. arupense, M. xenopi, M. triplex, M. lacus, M. arosiense*
Disseminated infection		*M. genavense, M. haemophilum, M. xenopi*
HIV-seropositive host	*M. avium, M. kansasii*	*M. marinum, M. simiae, M. intracellulare, M. scrofulaceum, M. fortuitum, M. conspicuum, M. celatum, M. lentiflavum, M. triplex, M. colombiense, M. sherrisii, M. heckeshornense*
HIV-seronegative host	*M. abscessus, M. chelonae*	*M. marinum, M. kansasii, M. haemophilum, M. chimaera, M. conspicuum, M. shottsii* (fish), *M. pseudoshottsii* (fish)
Catheter-related infections	*M. fortuitum, M. abscessus, M. chelonae*	*M. mucogenicum, M. immunogenum, M. mageritense, M. septicum, M. porcinum, M. bacteremicum, M. brumae*
Hypersensitivity pneumonitis (metal workers; hot tub users)	*M. immunogenum, M. avium*	

*The available information is sparse for selected pathogens such as *M. xenopi, M. malmoense, M. szulgai, M. celatum*, and *M. asiaticum* and the newly described species.
HIV, Human immunodeficiency virus; MAC, *Mycobacterium avium* complex.
From Brown-Elliott BA, Wallace RJ Jr. Infections caused by nontuberculous mycobacteria other than *Mycobacterium avium* complex. In Bennett JF, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of* Infectious *Diseases*, 8th ed. Philadelphia: Elsevier; 2015: Table 254-1.



Fig. 263.1 Enlarging cervical lymph node infected with *Mycobacterium avium* complex infection. The node is firm, painless, freely movable, and not erythematous.



Fig. 263.2 Suppurating cervical lymph node infected with *Mycobacterium avium* complex.



Fig. 263.3 Ruptured cervical lymph node infected with *Mycobacterium avium* complex, which resembles the classic scrofula of tuberculosis.

common in children 1-5 years of age and has been related to soil exposure (e.g., playing in sandboxes) and teething, although exact predisposing conditions have not been identified. Given the constant environmental exposure to NTM, the occurrence of these infections might also reflect an atypical immune response of a subset of the infected children during or after their first contact with NTM. However, in healthy children with isolated NTM lymphadenitis, immunodeficiency is quite rare.

Affected children usually lack constitutional symptoms and present with a unilateral, subacute, and slowly enlarging lymph node or group of closely approximated nodes >1.5 cm in diameter that are firm, painless, freely movable, and not erythematous (Fig. 263.1). The involved nodes occasionally resolve without progression, but most undergo rapid suppuration after several weeks (Fig. 263.2). The center of the node becomes fluctuant, and the overlying skin thins and becomes erythematous and often even violaceous. Eventually, the nodes rupture and can form cutaneous sinus tracts that can drain persistently, reminiscent of scrofula from tuberculosis (Fig. 263.3).

In the United States and Western Europe, MAC accounts for approximately 80% of NTM lymphadenitis in children. *M. kansasii* accounts for most other cases of lymphadenitis in the United States. *M. malmoense* and *M. haemophilum* have also been described as causative agents of lymphadenitis. *M. malmoense* is most common in Northwestern Europe. For *M. haemophilum,* underestimation of its importance is likely because the bacteria require specific culture conditions (hemin-enriched media, low incubation temperatures). On the basis of PCR analysis of lymph node samples from lymphadenitis cases in The Netherlands, *M. haemophilum* is the second most common cause of this infection, after MAC. One study suggests that children with MAC lymphadenitis are significantly younger than those infected by *M. haemophilum,* possibly related to age-specific environmental exposures. *Mycobacterium lentiflavum* is also an emerging NTM associated with lymphadenitis.

Cutaneous disease caused by NTM is rare in children (see Table 263.1). Infection usually follows percutaneous inoculation with fresh or salt water contaminated by *M. marinum.* Within 2-6 weeks after exposure, an erythematous papule develops at the site of minor abrasions on the elbows, knees, or feet **(swimming pool granuloma)** and on the hands and fingers of fish tank owners, mostly inflicted during tank cleaning **(fish tank granuloma)**. These lesions are usually nontender and enlarge over 3-5 weeks to form violaceous plaques. Nodules or pustules can develop and occasionally will ulcerate, resulting in a serosanguineous discharge. The lesions sometimes resemble sporotrichosis, with satellite lesions near the site of entry, extending along the superficial lymphatics. Lymphadenopathy is usually absent. Although most infections remain localized to the skin, penetrating *M. marinum* infections can result in tenosynovitis, bursitis, osteomyelitis, or arthritis.

M. ulcerans infection is the third most common mycobacterial infection in immunocompetent patients, after *M. tuberculosis* and *M. leprae* infection, and causes cutaneous disease in children living in tropical regions of Africa, South America, Asia, and parts of Australia. In some communities in West Africa, up to 16% of people have been affected. Children <15 years old are particularly affected in rural tropical counties, accounting for 48% of infected individuals in Africa. Infection follows percutaneous inoculation from minor trauma, such as pricks and cuts from plants or insect bites. After an incubation period of approximately 3 months, lesions appear as an erythematous nodule, usually on the legs or arms. The lesion undergoes central necrosis and ulceration. The lesion, often called a **Buruli ulcer** after the region in Uganda where a large case series was reported, has a characteristic undermined edge, expands over several weeks, and can result in extensive, deep soft tissue destruction or bone involvement (Fig. 263.4). Lesions are typically painless, and constitutional symptoms are unusual. Lesions might heal slowly over 6-9 months or might continue to spread, leading to deformities, contractures, and disability. Depending on the location of the ulcer, these can be significantly disfiguring.

Skin and soft tissue infections caused by **rapidly growing mycobacteria**, such as *M. fortuitum, M. chelonae,* or *M. abscessus,* are rare in children and usually follow percutaneous inoculation from puncture or surgical wounds, minor abrasions, or tattooing. There has been a large outbreak of *M. fortuitum* furunculosis related to nail salon footbaths. Clinical disease usually arises after a 4- to 6-week incubation period and manifests as localized cellulitis, painful nodules, or a draining abscess. *M. haemophilum* can cause painful subcutaneous nodules, which often ulcerate and suppurate in immunocompromised patients, particularly after kidney transplantation.

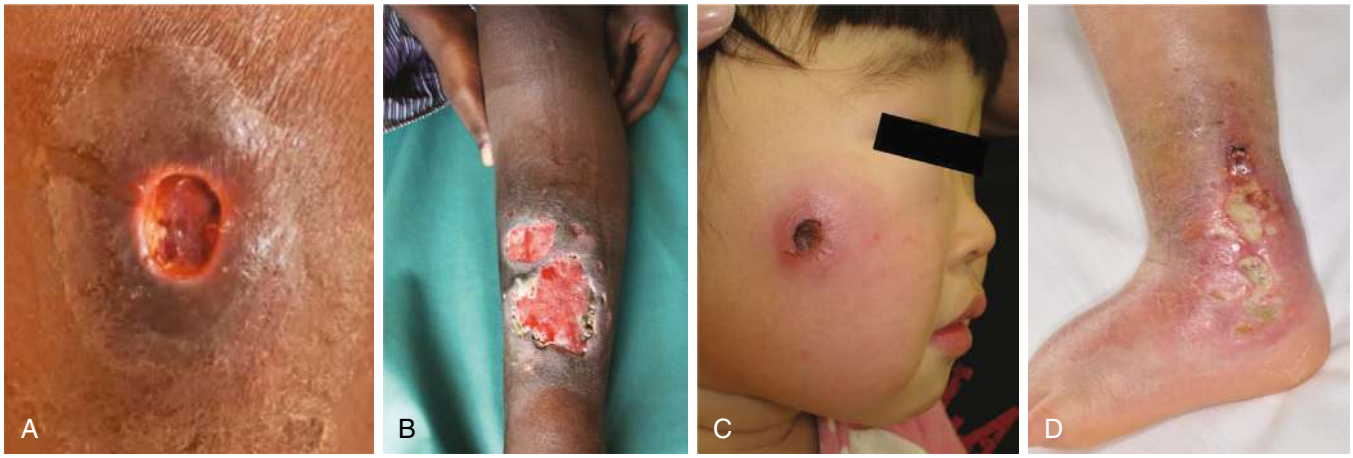

Fig. 263.4 Buruli ulcer lesions in patients from West Africa (**A** and **B**) and Japan (**C** and **D**). *(A, B from Röltgen K, Pluschke G. Buruli ulcer: history and disease burden. In: Pluschke G, Röltgen K, eds. Buruli Ulcer. Cham: Springer; 2019; C, D courtesy Dr Mikio Ohtsuka, Fukushima Medical University.)*

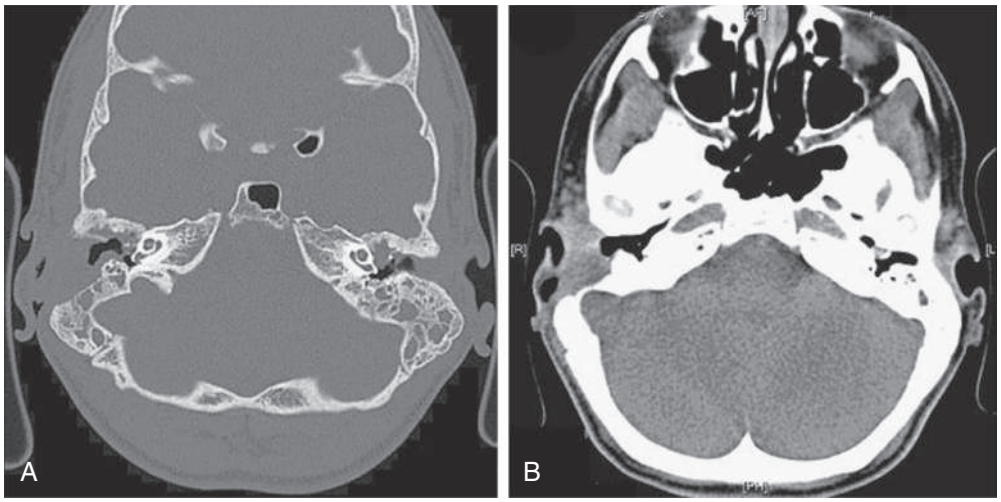

Fig. 263.5 CT images of the middle ear of 6-yr-old child infected with *Mycobacterium abscessus*, demonstrating extensive bone destruction in the right mastoid and associated right-sided mucosal swelling. **A,** Bone tissue window setting. **B,** Soft tissue window setting.

NTM are an uncommon cause of **catheter-associated infections** but are becoming increasingly recognized in this respect. Infections caused by *M. fortuitum, M. chelonae,* or *M. abscessus* can manifest as bacteremia or localized catheter tunnel infections.

Otomastoiditis, or chronic otitis media, is a rare extrapulmonary NTM disease type that specifically affects children with tympanostomy tubes and a history of topical antibiotic or steroid use. *M. abscessus* is the most common causative agent, followed by MAC (see Table 263.1). Patients present with painless, chronic otorrhea resistant to antibiotic therapy. CT can reveal destruction of the mastoid bone with mucosal swelling (Fig. 263.5).

Delayed or unsuccessful treatment can result in permanent hearing loss. In unusual circumstances, NTM cause other bone and joint infections that are indistinguishable from those produced by *M. tuberculosis* or other bacterial agents. Such infections usually result from operative incision or accidental puncture wounds. *M. fortuitum* infections from puncture wounds of the foot resemble infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Pulmonary infections are the most common form of NTM illness in adults but are rare in children. MAC bacteria, the most commonly identified organisms (see Table 263.1), are capable of causing acute pneumonitis, chronic cough, or wheezing associated with paratracheal or peribronchial lymphadenitis and airway compression in normal children. Associated constitutional symptoms such as fever, anorexia, and weight loss occur in 60% of these children. Chest radiographic findings are similar to those for primary tuberculosis, with unilateral infiltrates and hilar lymphadenopathy (Fig. 263.6). Pleural effusion is



Fig. 263.6 Chest radiograph of 2-yr-old child infected with *Mycobacterium avium* complex, demonstrating a left upper lobe infiltrate and left hilar lymphadenopathy.

uncommon. Rare cases of progression to endobronchial granulation tissue have been reported.

Pulmonary infections usually occur in adults with underlying chronic lung disease. The onset is insidious and consists of cough and fatigue, progressing to weight loss, night sweats, low-grade fever, and generalized malaise in severe cases. Thin-walled cavities with minimal surrounding parenchymal infiltrates are characteristic, but radiographic findings can resemble those of tuberculosis. A separate disease manifestation occurs typically in postmenopausal women and is radiologically characterized by bronchiectasis and nodular lesions, often affecting the middle lobe and lingula (Lady Windemere's syndrome).

Chronic pulmonary infections specifically affect children with CF and are generally caused by *M. abscessus* or MAC. *M. abscessus* primarily affects children, and MAC is most common among adults. The percentage of CF patients with at least one sputum culture positive for NTM is 6–8.1% overall and increases with age; in CF patients <12 years old, a prevalence of 3.9% has been reported. The strong representation of *M. abscessus* in these patients is remarkable, because this bacterium is an uncommon isolate in other categories of patients. There are indications that NTM infections in CF patients further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

Disseminated disease is usually associated with MAC infection and occurs in immunocompromised children. The first category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor or for IL-12 production. Patients with complete **IFNGR deficiency** have severe, difficult-to-treat disease. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to IFN-γ and antimycobacterial therapy. **Multifocal osteomyelitis** is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The second category of patients affected by disseminated disease is patients with **AIDS**. Disseminated NTM disease in patients with AIDS usually appears when CD4 cell counts are <50/μL for children ≥6 years , <75/μL in children 2 to <6 years, <500/μL in children 1 to <2 years, and <750/μL in children <1 year. The most recent estimate of the incidence of disseminated NTM disease is 0.14-0.2 episodes per 100 person-years, a 10-fold decrease from its incidence before combination antiretroviral therapy (cART) was available.

Colonization of the respiratory or gastrointestinal (GI) tract probably precedes disseminated MAC infections, but screening studies of respiratory secretions or stool samples are not useful to predict dissemination. Continuous high-grade bacteremia is common, and multiple organs are infected, typically including the lymph nodes, liver, spleen, bone marrow, and GI tract. The thyroid, pancreas, adrenal gland, kidney, muscle, and brain can also be involved. The most common signs and symptoms of disseminated MAC infections in patients with AIDS are fever, night sweats, chills, anorexia, marked weight loss, wasting, weakness, generalized lymphadenopathy, and hepatosplenomegaly. Jaundice, elevated alkaline phosphatase or lactate dehydrogenase levels, anemia, and neutropenia can occur. Imaging studies usually demonstrate massive lymphadenopathy of hilar, mediastinal, mesenteric, or retroperitoneal nodes. Successful treatment of disseminated infection in children with AIDS requires immune reconstitution and cART in addition to specific NTM therapy. The survival in children with AIDS has improved considerably with the availability of cART.

Disseminated disease in children without any apparent immunodeficiency is exceedingly rare.

DIAGNOSIS

For infections of lymph nodes, skin, bone, and soft tissues, isolation of the causative NTM bacteria by *Mycobacterium* culture, preferably with histologic confirmation of granulomatous inflammation, normally suffices for diagnosis. The differential diagnosis of NTM lymphadenitis includes acute bacterial lymphadenitis, tuberculosis, cat scratch disease *(Bartonella henselae* infection*)*, mononucleosis, toxoplasmosis, brucellosis, tularemia, and malignancies, especially lymphomas.

Table 263.2 American Thoracic Society Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacteria (NTM) Pulmonary Disease

CLINICAL*	PULMONARY OR SYSTEMIC SYMPTOMS
Radiologic*	Nodular or cavitary opacities on chest radiograph or a high-resolution computed tomography (HRCT) scan that shows bronchiectasis with multiple small nodules
AND	Appropriate exclusion of other diagnoses
Microbiologic	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures. or 2. Positive culture results from at least one bronchial wash or lavage. or 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM.

*Note: Both clinical and radiologic criteria are required.
AFB, Acid-fast bacilli.
From Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline [published correction appears in Clin Infect Dis. 2020 Dec 31;71(11):3023]. *Clin Infect Dis.* 2020;71(4):e1–e36.

Differentiation between NTM and *M. tuberculosis* may be difficult, but children with NTM lymphadenitis usually have a Mantoux tuberculin skin test reaction of <15 mm induration, unilateral anterior cervical node involvement, a normal chest radiograph, and no history of exposure to tuberculosis. Definitive diagnosis requires excision of the involved nodes for culture and histology. Fine-needle aspiration for PCR and culture can enable earlier diagnosis, before excisional biopsy.

The diagnosis of pulmonary NTM infection in children is difficult because many species of NTM, including MAC, are omnipresent in our environment and can contaminate clinical samples or be present but not causative of disease. As a result, isolation of these bacteria from nonsterile specimens (respiratory and digestive tract) does not necessarily reflect true disease. To determine the clinical relevance of isolation of NTM, the ATS/BTS diagnostic criteria are an important support (Table 263.2). These criteria take into consideration clinical features and radiologic, pathologic, and microbiologic findings. Their hallmark is the need for multiple positive cultures yielding the same NTM species to make a definitive diagnosis of pulmonary NTM disease, though a single culture from bronchoalveolar lavage (BAL)/bronchial lavage is acceptable in patients who meet clinical and radiologic criteria. In children, definitive diagnosis often requires invasive procedures such as bronchoscopy and pulmonary or endobronchial biopsy; in CF patients, more aggressive sample pretreatment in the clinical microbiology laboratory is necessary to prevent overgrowth by other species, especially *Pseudomonas*. The chance of NTM isolation being clinically relevant differs significantly by species; some species are more likely causative agents of true pulmonary disease *(M. avium, M. kansasii*, *M. abscessus, M. malmoense)*, whereas others are more likely contaminants (*M. gordonae, M. fortuitum, M. chelonae)*.

Blood cultures are 90–95% sensitive in AIDS patients with disseminated infection. MAC may be detected within 7-10 days of inoculation in almost all patients by automated blood culture systems. In adults, some studies have shown that liver biopsy cultures and stains are more sensitive than blood culture or bone marrow biopsy workup. Commercially available DNA probes differentiate NTM from *M.*

tuberculosis. If DNA probes cannot identify the causative mycobacteria, DNA sequencing of bacterial housekeeping genes can yield a clue to the identity of these NTM. Identification of histiocytes containing numerous AFB from bone marrow and other biopsy tissues provides a rapid presumptive diagnosis of disseminated mycobacterial infection.

TREATMENT

Therapy for NTM infections is long-term and cumbersome; expert consultation is advised. Therapy involves medical, surgical, or often combined treatment (see Chapter 260, Table 260.3). Isolation of the infecting strain followed by drug-susceptibility testing is ideal, because it provides a baseline for drug susceptibility. Important discrepancies exist between in vitro drug susceptibility and in vivo response to treatment, explained in part by synergism, mainly among first-line antituberculosis drugs. In vitro, **slow growers** *(M. kansasii, M. marinum, M. xenopi, M. ulcerans, M. malmoense)* are usually susceptible to the first-line antituberculosis drugs **rifampin** and **ethambutol**; MAC bacteria are often resistant to these drugs alone but susceptible to the combination and have variable susceptibility to other antibiotics, most importantly the macrolides. **Rapid growers** *(M. fortuitum, M. chelonae, M. abscessus)* are highly resistant to antituberculosis drugs and often have inducible macrolide-resistance mechanisms. Susceptibility to macrolides, aminoglycosides, carbapenems, tetracyclines, and glycylcyclines are most relevant for therapy guidance. In all NTM infections, multidrug therapy (MDT) is essential to avoid development of resistance.

The preferred treatment of NTM lymphadenitis is complete surgical excision. Clinical trials revealed that surgery is more effective than antibiotic treatment (see Table 260.3). Nodes should be removed while still firm and encapsulated. Excision is more difficult if extensive caseation with extension to surrounding tissue has occurred, and complications of facial nerve damage or relapse of infection are more likely in such cases. Incomplete surgical excision is not advised, because chronic drainage can develop. If there are concerns or risk factors for possible *M. tuberculosis* infection, therapy with isoniazid, rifampin, ethambutol, and pyrazinamide should be administered until cultures confirm the cause to be NTM (see Chapter 261). If surgery of NTM lymphadenitis cannot be performed, or removal of infected tissue is incomplete, or recurrence or chronic drainage develops, a 3-month trial of antibiotic therapy should be considered. **Clarithromycin or azithromycin combined with rifampin or ethambutol are the most common therapy regimens reported for MAC lymphadenitis** (see Table 260.3). Suppuration may still occur on appropriate antibiotic therapy. In immunocompetent patients, **an observational approach** to NTM lymphadenitis can be chosen without antibiotic therapy, although resolution will take up to 12 months.

Posttraumatic cutaneous NTM lesions in immunocompetent patients usually heal spontaneously after incision and drainage without other therapy. *M. marinum* is susceptible to rifampin, amikacin, ethambutol, sulfonamides, trimethoprim-sulfamethoxazole, and tetracycline. Therapy with a combination of these drugs, particularly clarithromycin and ethambutol, may be given until 1 month after the lesion has disappeared. Corticosteroid injections should not be used. Superficial infections with *M. fortuitum* or *M. chelonae* usually resolve after surgical incision and open drainage, but deep-seated or catheter-related infections require removal of infected central lines and therapy with parenteral amikacin plus cefoxitin, ciprofloxacin, or clarithromycin.

Some localized forms of *M. ulcerans* skin disease (Buruli ulcer) can heal spontaneously; for most forms, excisional surgery with primary closure or skin grafting is recommended. **The combination of rifampin (10 mg/kg once daily) and clarithromycin (7.5 mg/kg twice daily) for 8 weeks results in excellent outcomes and is now the recommended treatment for early limited Buruli ulcer.** Another agent that shows great promise is telacebec (also known as *Q203*), a novel first-in-class antituberculosis drug targeting cellular energy production through inhibition of the mycobacterial cytochrome bc1 complex; animal studies have demonstrated significant potency against *M. ulcerans,* possibly allowing for shorter courses of treatment. In January 2021, the U.S. Food and Drug Administration granted orphan drug designation (ODD) to telacebec for Buruli ulcer treatment. **Physiotherapy** after surgery is essential to prevent contractures and functional disabilities.

For patients who meet diagnostic criteria for pulmonary NTM infections (see Table 263.2), treatment rather than observation is recommended, particularly with persistently positive sputum smears and/or cavitary lung disease. Although treatment offers possibility of cure, there can be significant adverse effects of treatment and low cure rates for some forms of infection. Patients who require treatment for NTM pulmonary disease should have isolates sent for susceptibility testing, with the caveat that this testing is helpful for NTM for antibiotics where there is a well-documented correlation between in vitro activity and microbiologic response to therapy. Drugs for which this correlation exist include macrolides (azithromycin, clarithromycin) and amikacin for MAC and *M. abscessus* and rifampin for *M. kansasii*. **For macrolide-susceptible MAC pulmonary disease, treatment with three drugs for at least 12 months after culture conversion is recommended, generally azithromycin, rifampin, and ethambutol.** For macrolide-resistant isolates, parenteral amikacin is often used, as MAC isolates are usually susceptible in vitro to this agent.

Macrolides are a mainstay in the treatment of *M. abscessus* pulmonary disease. However, macrolide resistance can develop via chromosomal mutation or through induction of the erm(41) gene. **For *M. abscessus* disease caused by strains without inducible or chromosomal macrolide resistance, a macrolide-containing treatment regimen is recommended, typically with at least three active drugs. If macrolide resistance (chromosomal or inducible) is present, at least four active drugs are recommended. Treatment regimens for *M. abscessus* are complex, usually with oral plus parental drugs. Regimens typically include two to three oral agents, which may include azithromycin, clofazimine, or linezolid, and at least one parenteral agent, with options including amikacin, imipenem, and tigecycline.** In CF patients, inhaled agents may also have a role. Choice of treatment regimens and duration of therapy should be guided by expert consultation. For select patients, surgical resection of severely diseased lung in addition to medical therapy may be indicated.

For *M. kansasii* pulmonary disease, susceptibility-based treatment for rifampin is recommended over empirical therapy. The recommended treatment regimen for rifampin-susceptible *M. kansasii* infections is rifampin, ethambutol, and either isoniazid or a macrolide for at least 12 months. Fluoroquinolones also have good activity against *M. kanasasii* but are reserved for rifampin-resistant *M. kansasii* infection treatment and for patients who have intolerance to one of the first-line antibiotics.

Patients with disseminated MAC and IL-12 pathway defects or IFNGR deficiency should be treated for at least 12 months with clarithromycin or azithromycin combined with rifampin or rifabutin and ethambutol. In vitro susceptibility testing for macrolides is important to guide therapy. Once the clinical illness has resolved, lifelong daily prophylaxis with azithromycin or clarithromycin is advisable to prevent recurrent disease. The use of IFN adjunctive therapy is determined by the specific genetic defect.

In children with AIDS, prophylaxis with azithromycin or clarithromycin is indicated to prevent infection with MAC. Although few pediatric studies exist, the U.S. Public Health Service recommends either **azithromycin** (20 mg/kg once weekly PO, maximum 1,200 mg/dose *or* 5 mg/kg once daily PO, maximum 250 mg/dose in patients intolerant of the larger dose) or **clarithromycin** (7.5 mg/kg/dose twice daily PO; maximum 500 mg/dose) for HIV-infected children with significant immune deficiency, as defined by the CD4 count (children ≥6 years old, CD4 count <50 cells/μL; 2 to <6 years old, <75/μL; 1 to <2 years old, <500/μL; <1 year old, <750/μL). Rifabutin may also be used. Primary prophylaxis may be safely discontinued in children >2 years old receiving stable highly active antiretroviral therapy (HAART) for >6 months and experiencing sustained (>3 months) CD4 cell recovery well above the age-specific target for initiation of prophylaxis: >100 cells/μL for children ≥6 years old and >200/μL for children 2-5 years old. For children <2 years old, no specific recommendations for discontinuing MAC prophylaxis exist.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 8

Spirochetal Infections

Chapter 264

Syphilis (*Treponema pallidum*)

Alice I. Sato and H. Dele Davies

Syphilis is a chronic systemic sexually or vertically (mother to child) transmitted infection that can be easily treated if detected early but manifests with protean clinical symptoms and significant morbidity if left unchecked. (Please note that the terms *mother* and *maternal* are used to designate the birthing parent throughout this chapter and are not intended to exclude other birthing parents.)

ETIOLOGY

Syphilis is caused by *Treponema pallidum,* a delicate, tightly spiraled, motile spirochete with finely tapered ends belonging to the family Spirochaetaceae. The pathogenic members of this genus include *T. pallidum* subspecies *pallidum* (venereal syphilis), *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (bejel or endemic syphilis), and *T. pallidum* subspecies *carateum* (pinta). Because these microorganisms stain poorly and are below the detection limits of conventional light microscopy, detection in clinical specimens requires dark-field, phase-contrast microscopy or direct immunofluorescent or silver staining. *T. pallidum* has only recently been successfully grown in vitro via co-culture with mammalian tissue culture cells, and a method has now been described for inoculation of fresh and frozen needle aspirates from primary experimental syphilis lesions onto culture plates but remains to be developed for clinical use. Use of nucleic acid amplification testing by polymerase chain reaction (PCR) may have a role in diagnosis, particularly in seronegative patients or those with discrepant serology results.

EPIDEMIOLOGY

Acquired syphilis is transmitted almost exclusively by sexual contact, including vaginal, anal, and oral exposure. Less common modes of transmission include transfusion of contaminated blood or direct contact with infected tissues. Syphilis in men who have sex with men (MSM) may be acquired in the absence of visible lesions. DNA-based *T. pallidum* testing has identified organisms in oral rinse or swab samples and in anal canal swabs, urine, semen, and peripheral blood; the risk is highest in secondary and early latent syphilis. The incubation period for acquired primary syphilis is about 3 weeks (range 10-90 days). After an epidemic resurgence of primary and secondary syphilis in the United States that peaked in 1989, the annual rate declined 90% to the lowest-ever rate by 2000. The total number of cases of primary and secondary syphilis has subsequently rebounded since 2000 (Fig. 264.1). MSM have been disproportionately impacted: ~46% of cases in 2021. Rates of primary and secondary syphilis in women remain lower than in men yet still have increased 55% during 2021. Cases of congenital syphilis reached an historic low in 2005 but have subsequently increased annually since 2013, reflecting the rates among women. In 2021, the US national congenital syphilis rate was 77.9 cases per 100,000 live births, representing a 30.5% increase from 2020 and a 219.3% increase from 2017 (Fig. 264.2); syphilitic still births also increased over this period. The increase occurs across every region and all races and ethnicities, but marked disparities exist,

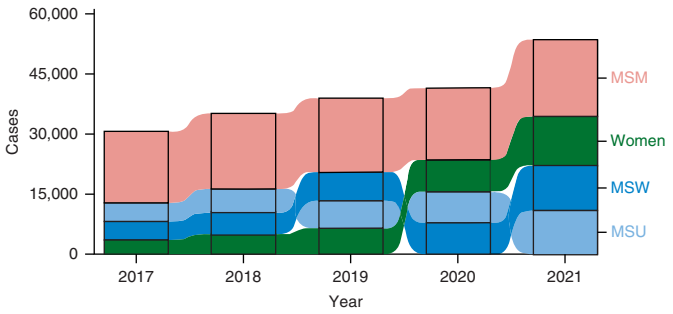

Fig 264.1 Primary and secondary syphilis – Reported cases by sex and sex of sex partners 2017–2021. Note: Over the 5-yr period, 0.2% of cases were missing sex and were not included. MSM, Gay, bisexual, and other men who have sex with men; MSU, Men with unknown sex of sex partners; MSW, men who have sex with women only. *(From Centers for Disease Control and Prevention. Sexually transmitted disease surveillance. National overview of STDs, 2021. https://www.cdc.gov/std/statistics/2021/overview.htm)*

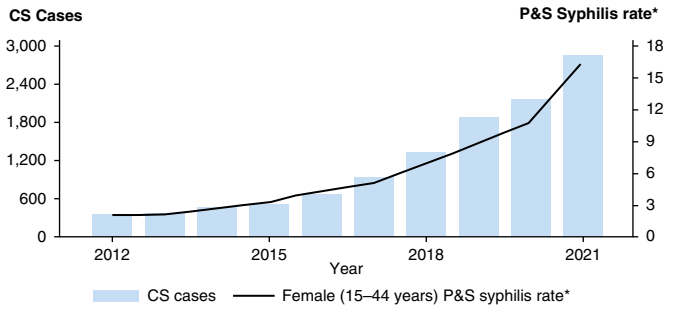

Fig. 264.2 Congenital syphilis — Reported cases by year of birth and rates of reported cases of primary and secondary syphilis among women age 15-44 years, United States, 2012–2021. *Per 100,000. CS, Congenital syphilis; P&S syphilis, Primary and secondary syphilis. *(From Centers for Disease Control and Prevention. Sexually transmitted disease surveillance. National overview of STDs, 2021. https://www.cdc.gov/std/statistics/2021/overview.htm)*

with minority groups, gay and bisexual men, and youth most affected. The COVID-19 pandemic disrupted screening programs and access to care, and increased cases are expected.

Congenital syphilis results from transplacental transmission of spirochetes or occasionally by intrapartum contact with infectious lesions or possibly involved mucosa without obvious lesions. Women with primary and secondary syphilis and spirochetemia are more likely to transmit infection to the fetus than are women with latent infection. Transmission can occur at any stage of pregnancy, resulting in early fetal loss, preterm or low birthweight infants, stillbirths, neonatal deaths, or infants born with congenital disease. The incidence of congenital infection in offspring of untreated or inadequately treated infected women remains highest during the first 4 years after acquisition of primary infection, secondary infection, and early latent disease. Maternal (parental) factors associated with congenital syphilis include limited access to healthcare, late or no prenatal care, drug use, multiple sex partners, unprotected sexual contact, incarceration, work in the sex trade, and inadequate treatment of syphilis during pregnancy. Congenital syphilis may be seen in the context of untreated, inadequately treated, or undocumented treatment before or during pregnancy. In addition, the mother may have been treated appropriately but did not have an adequate serologic response to therapy and the infant was inadequately evaluated, or the infant had documented congenital syphilis. Confirmed cases of both acquired and congenital syphilis must be reported to the local health department.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Many persons infected with syphilis are *asymptomatic for years,* or do not recognize the early signs of disease, or do not seek or have access

to treatment. The Centers for Disease Control and Prevention (CDC) recommends testing all pregnant persons and selective testing of adolescents, based on lesions or risk factors (those with other sexually transmitted diseases including HIV, MSM, incarcerated individuals, or persons who exchange sex for money or drugs). CDC/MMWR sexually transmitted infection (STI) guidelines should be consulted to ensure that all appropriate screening is performed. All 50 states and the District of Columbia explicitly allow minors to consent for STI services, though as of 2022, 18 states allow (but do not require) physicians to notify parents of STI services provided to a minor (https://www.cdc.gov/hiv/policies/law/states/minors.html). Periods of active clinical disease alternate with periods of latency (Fig. 264.3). **Primary syphilis** is characterized by a chancre and regional lymphadenitis. A **painless papule** (which may be overlooked) appears at the site of entry (usually the genitalia) 2-6 weeks after inoculation and develops into a clean, painless but highly contagious ulcer with raised borders **(chancre)** containing abundant *T. pallidum*. Extragenital chancres can occur at other sites of primary entry and pose a diagnostic challenge. Oral lesions can be mistaken for aphthous ulcers or herpes. Lesions on the nipple can be confused with cellulitis or eczema. Adjacent lymph nodes are generally enlarged and nontender. The chancre heals spontaneously within 4-6 weeks, leaving a thin scar.

Untreated patients develop manifestations of **secondary syphilis** related to spirochetemia 2-10 weeks after the chancre heals. Manifestations of secondary syphilis include a generalized nonpruritic maculopapular rash, notably involving the palms and soles (Fig. 264.4). Pustular lesions can also develop. **Condylomata lata**, gray-white to erythematous wartlike plaques, can occur in moist areas around the anus, scrotum, or vagina, and white plaques **(mucous patches)** may be found in mucous membranes. Secondary syphilis should be considered in the differential diagnosis of virtually any rash of unknown etiology. A **flulike illness** with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgias, arthralgias, and generalized lymphadenopathy is often present. Renal, hepatic, or ocular manifestations may be present. Meningitis occurs in about 30% of patients with untreated syphilis, occurring at any stage but most commonly in



Fig. 264.4 Secondary syphilis. Ham-colored palmar macules on an adolescent with secondary syphilis. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002.)*

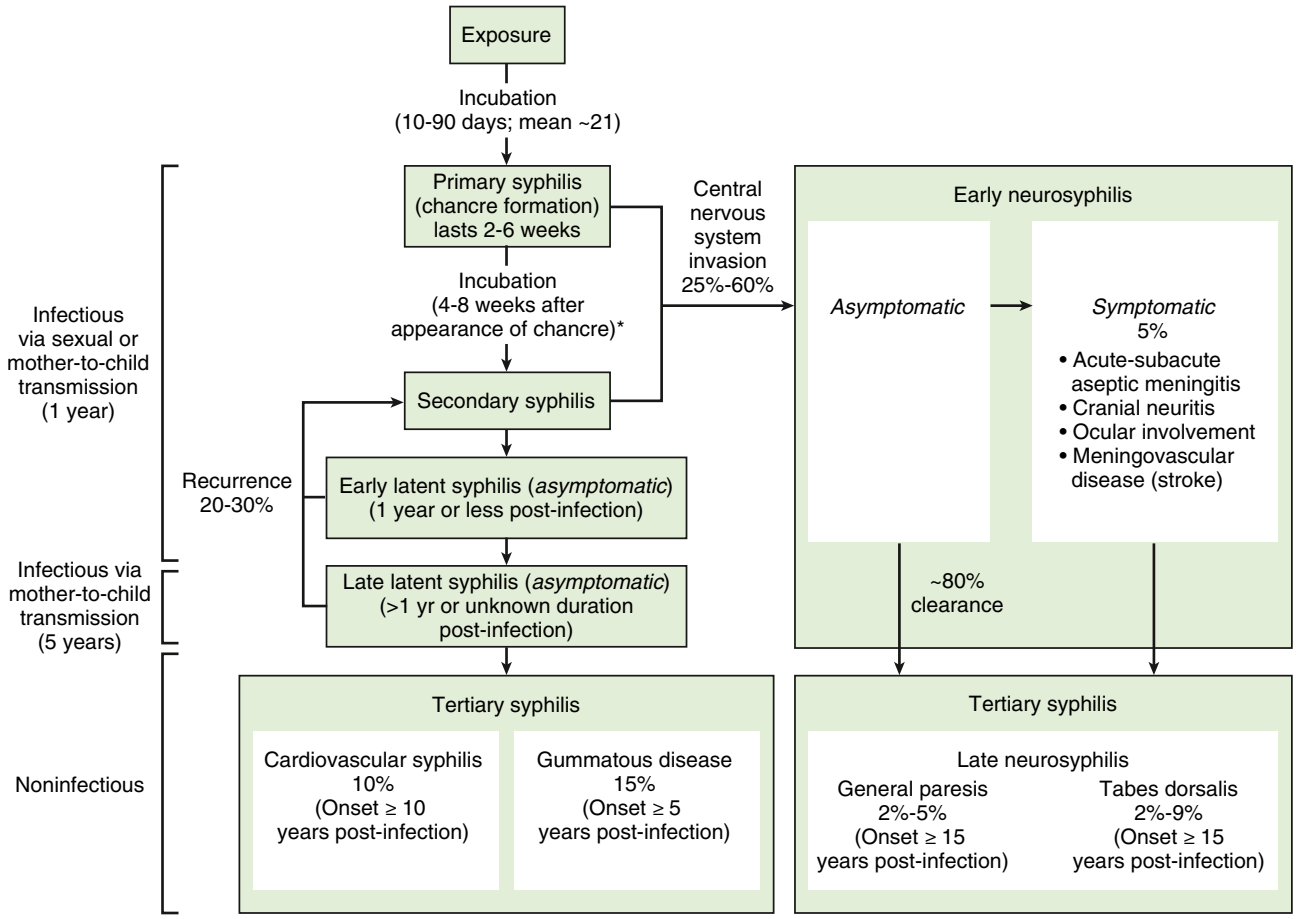

Fig. 264.3 Natural course of untreated syphilis. As of January 2018, the Centers for Disease Control and Prevention renamed early and late latent syphilis *early syphilis, nonprimary, nonsecondary* and *syphilis, unknown duration or late*, respectively. *HIV infection may modify the progression of syphilis; the chancre may coexist with the secondary syphilis stage, suggesting a more rapid progression to the secondary stage. *(Modified from Radolf JD, Tramont EC, Salazar JC. Syphilis [Treponema pallidum]. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Philadelphia: Elsevier; 2020: Fig. 237.5, p. 2874.)*

secondary syphilis (see Fig. 264.3). It is characterized by cerebrospinal fluid (CSF) pleocytosis and elevated protein level. Patients with meningitis might not show neurologic symptoms. Even without treatment, secondary infection becomes **latent** within 1-2 months after onset of rash. Relapses with secondary manifestations can occur during the first year of latency (the **early latent period**). **Late syphilis** follows and may be either asymptomatic **(late latent)** or symptomatic **(tertiary)**. Tertiary disease follows in about one-third of untreated cases and is marked by neurologic, cardiovascular, and **gummatous lesions** (nonsuppurative granulomas of the skin, bone, and liver resulting from the host cytotoxic T-cell response). In the preantibiotic era, neurologic manifestations of tertiary syphilis **(tabes dorsalis** and **paresis)** were common. The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses. A robust timeline of progression through the overlapping stages occurs in immunocompromised HIV patients

Congenital Infection

Untreated syphilis during pregnancy results in a vertical transmission rate approaching 100%, with profound effects on pregnancy outcome, reflecting obliterating endarteritis. Fetal or perinatal death occurs in 40% of affected infants. Premature delivery can also occur. Neonates can also be infected at delivery by contact with an active genital lesion. Most infected infants are asymptomatic at birth, including up to 40% with CSF seeding, and are identified only by routine prenatal screening. In the absence of treatment, symptoms develop within weeks or months. Among infants symptomatic at birth or in the first few months of life, manifestations have traditionally been divided into early and late stages. All stages of congenital syphilis are characterized by a vasculitis, with progression to necrosis and fibrosis. The **early signs** appear during the first 2 years of life, and the **late signs** appear gradually during the first 2 decades. Early manifestations vary and involve multiple organ systems, resulting from transplacental spirochetemia, and are analogous to the secondary stage of acquired syphilis. Hepatosplenomegaly, jaundice, and elevated liver enzymes are common. Histologically, liver involvement includes bile stasis, fibrosis, and extramedullary hematopoiesis. Lymphadenopathy tends to be diffuse and resolve spontaneously, although shotty nodes can persist.



Fig. 264.5 Osteochondritis and periostitis in a newborn with congenital syphilis.

Coombs-negative hemolytic anemia is characteristic. Thrombocytopenia is often associated with platelet trapping in an enlarged spleen. Characteristic **osteochondritis** and **periostitis** (Fig. 264.5) and a mucocutaneous rash (Fig. 264.6A and B) manifesting with erythematous maculopapular or vesiculobullous lesions followed by desquamation involving the hands and feet (see Fig. 264.6C) are common. Mucous patches, persistent rhinitis **(snuffles)**, and condylomatous lesions (Fig. 264.7) are highly characteristic features of mucous membrane involvement containing abundant spirochetes. Blood and moist, open lesions from infants with congenital syphilis and children with acquired primary or secondary syphilis are infectious until 24 hours of appropriate treatment.

Bone involvement is common. Roentgenographic abnormalities include **Wimberger lines** (demineralization of the medial proximal tibial metaphysis); multiple sites of osteochondritis at the wrists, elbows, ankles, and knees; and periostitis of the long bones and, rarely, the skull. The osteochondritis is painful, often resulting in irritability and refusal to move the involved extremity **(pseudoparalysis of Parrot)**.

Congenital neurosyphilis is often asymptomatic in the neonatal period, although CSF abnormalities can occur even in asymptomatic infants. Failure to thrive, chorioretinitis, nephritis, and nephrotic syndrome can also be seen. Manifestations of renal involvement include hypertension, hematuria, proteinuria, hypoproteinemia, hypercholesterolemia, and hypocomplementemia, probably related to glomerular deposition of circulating immune complexes. Less common clinical manifestations of early congenital syphilis include gastroenteritis, peritonitis, pancreatitis, pneumonia, eye involvement (glaucoma and chorioretinitis), nonimmune hydrops, and testicular masses.

Late manifestations (children >2 years of age) are rarely seen in developed countries. These result primarily from chronic granulomatous inflammation of bone, teeth, and the central nervous system and are summarized in Table 264.1. Skeletal changes are caused by persistent or recurrent periostitis and associated thickening of the involved



Fig. 264.6 A and B, Papulosquamous plaques in two infants with syphilis. C, Desquamation on the palm of a newborn's hand. *(A and B from Eichenfeld LF, Frieden IJ, Esterly NB, eds. Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2001: p. 196; courtesy Dr. Patricia Treadwell.)*



Fig. 264.7 Perianal condylomata lata. *(From Karthikeyan K, Thappa DM. Early congenital syphilis in the new millennium. Pediatr Dermatol. 2002;19:275–276.)*



Fig. 264.8 Hutchinson teeth as a late manifestation of congenital syphilis.

Table 264.1 Late Manifestations of Congenital Syphilis

SYMPTOM/SIGN	DESCRIPTION/COMMENTS
Olympian brow	Bony prominence of the forehead caused by persistent or recurrent periostitis
Clavicular or Higoumenakis sign	Unilateral or bilateral thickening of the sternoclavicular third of the clavicle
Saber shins	Anterior bowing of the midportion of the tibia
Scaphoid scapula	Convexity along the medial border of the scapula
Hutchinson teeth	Peg-shaped upper central incisors; they erupt during sixth yr of life with abnormal enamel, resulting in a notch along the biting surface
Mulberry molars	Abnormal first lower (6 yr) molars characterized by small biting surface and excessive number of cusps
Saddle nose*	Depression of the nasal root, a result of syphilitic rhinitis destroying adjacent bone and cartilage
Rhagades	Linear scars that extend in a spokelike pattern from previous mucocutaneous fissures of the mouth, anus, and genitalia
Juvenile paresis	Latent meningovascular infection; it is rare and typically occurs during adolescence with behavioral changes, focal seizures, or loss of intellectual function
Juvenile tabes	Rare spinal cord involvement and cardiovascular involvement with aortitis
Hutchinson triad	Hutchinson teeth, interstitial keratitis, and eighth cranial nerve deafness
Clutton joint	Unilateral or bilateral painless joint swelling (usually involving the knees) from synovitis with sterile synovial fluid; spontaneous remission usually occurs after several weeks
Interstitial keratitis	Manifests with intense photophobia and lacrimation, followed within weeks or months by corneal opacification and complete blindness
Eighth cranial nerve deafness	May be unilateral or bilateral, appears at any age, manifests initially as vertigo and high-tone hearing loss, and progresses to permanent deafness

*A perforated nasal septum may be an associated abnormality.



Fig. 264.9 Saddle nose in a newborn with congenital syphilis.

bone. Dental abnormalities, such as **Hutchinson teeth** (Fig. 264.8), are common. Defects in enamel formation lead to repeated caries and eventual tooth destruction. **Saddle nose** (Fig. 264.9) is a depression of the nasal root and may be associated with a perforated nasal septum.

Other late manifestations of congenital syphilis can manifest as hypersensitivity phenomena. These include unilateral or bilateral interstitial keratitis and the **Clutton joint** (see Table 264.1). Other common ocular manifestations include choroiditis, retinitis, vascular occlusion, and optic atrophy. Soft tissue gummas (identical to those of acquired disease) and paroxysmal cold hemoglobinuria are rare hypersensitivity phenomena.

DIAGNOSIS

Fundamental limitations of the currently available tests for syphilis are vexing, but results must always be interpreted in the context of patient history and physical examination. Physicians should remain aware of their local prevalence rates and treat presumptively when syphilis is suspected by clinical and epidemiologic data. The diagnosis of primary syphilis is confirmed when *T. pallidum* is demonstrated by dark-field microscopy or direct fluorescent antibody testing on specimens from skin lesions, placenta, or umbilical cord. Nucleic acid–based amplification assays, such as PCR, are also used in some specialized laboratories but are not commercially available. Despite the absence of a true

gold-standard serologic assay, serologic testing for syphilis remains the principal means for diagnosis and traditionally involves a two-step screening process with a nontreponemal test followed by a confirmatory treponemal test (Fig. 264.10A). Both test types are required for serologic-based diagnosis. False-negative tests may occur in early syphilis, and high-risk individuals may need repeat testing in 2-4 weeks if clinically indicated.

The **Venereal Disease Research Laboratory (VDRL)** and **rapid plasma reagin (RPR)** tests are sensitive **nontreponemal tests** that detect antibodies against phospholipid antigens on the treponeme surface that cross react with cardiolipin-lecithin-cholesterol antigens of damaged host cells. The quantitative results of these tests are helpful both in screening and in monitoring therapy. Titers increase with active disease, including treatment failure or reinfection, and decline with adequate treatment (Fig. 264.11). Nontreponemal tests usually become nonreactive within 1 year of adequate therapy for primary syphilis and within 2 years of adequate treatment for secondary disease. Fifteen to twenty percent of patients become **serofast** (nontreponemal titers persisting at low levels for long periods). In congenital infection, nontreponemal tests become nonreactive within a few months after adequate treatment. Certain conditions such as infectious mononucleosis and other viral infections, autoimmune diseases, and pregnancy can give false-positive VDRL results. False-positive results are less common with the use of purified cardiolipin-lecithin-cholesterol antigen. All pregnant women should be screened early in pregnancy and at delivery. All positive maternal (parental) serologic tests for syphilis, regardless of titer, necessitate thorough investigation. Antibody excess can give a false-negative reading unless the serum is diluted **(prozone effect) as the formation of the antigen-antibody lattice needed to visualize a positive flocculation test is disrupted.** False-negative results can also occur in early primary syphilis, in latent syphilis of long duration, and in late congenital syphilis.

Treponemal tests traditionally are used to confirm diagnosis and measure specific *T. pallidum* antibodies (immunoglobulin [Ig] G, IgM, and IgA), which appear earlier than nontreponemal antibodies. Treponemal tests include the *T. pallidum* particle agglutination test (TP-PA, which is the preferred treponemal test) and the fluorescent treponemal antibody absorption test (FTA-ABS). Treponemal antibody titers become positive soon after initial infection and usually remain positive for life, even with adequate therapy (see Fig. 264.11). These antibody titers do not correlate with disease activity. Traditionally they are useful for diagnosis of a first episode of syphilis and for distinguishing false-positive results of nontreponemal antibody tests but cannot accurately identify length of time of infection, response to therapy, or reinfection.

There is limited cross reactivity of treponemal antibody tests with other spirochetes, including the causative organisms of Lyme disease *(Borrelia burgdorferi),* yaws, endemic syphilis, and pinta. Only venereal syphilis and Lyme disease are found in the United States. Nontreponemal tests (VDRL, RPR) are uniformly nonreactive in Lyme disease.

Various enzyme-linked, chemiluminescence, and multiplex flow immunoassays to detect treponemal IgG and IgM have been developed. These assays have increased sensitivity and are amenable to automation and high-volume use. Rapid point-of-care tests are available to allow quality screening programs in resource-limited settings where the World Health Organization otherwise relies on syndromic management of STIs and patients are treated for all likely causes of their constellation of signs and symptoms. In the United States, use of immunoassays has confounded screening because it switches the traditional algorithm: the treponemal-specific testing is done before the nontreponemal testing. Because the former remain positive for life, clinical and epidemiologic data are required to provide guidelines to distinguish cured disease, early syphilis, untreated late latent disease, and true false-positive tests. Benefits of **reverse screening** are

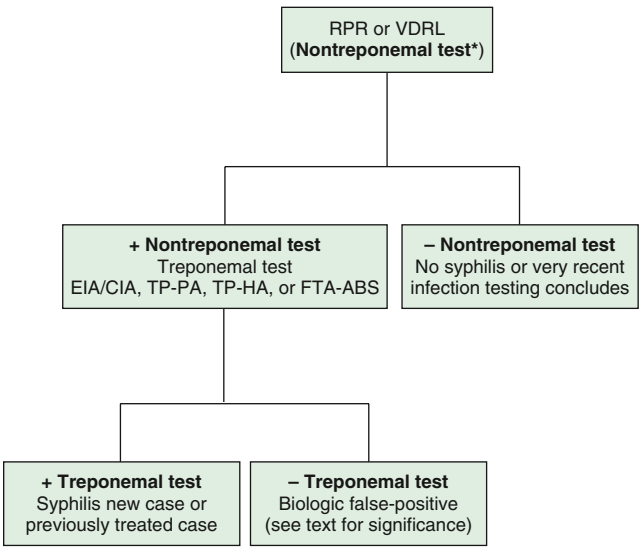

A

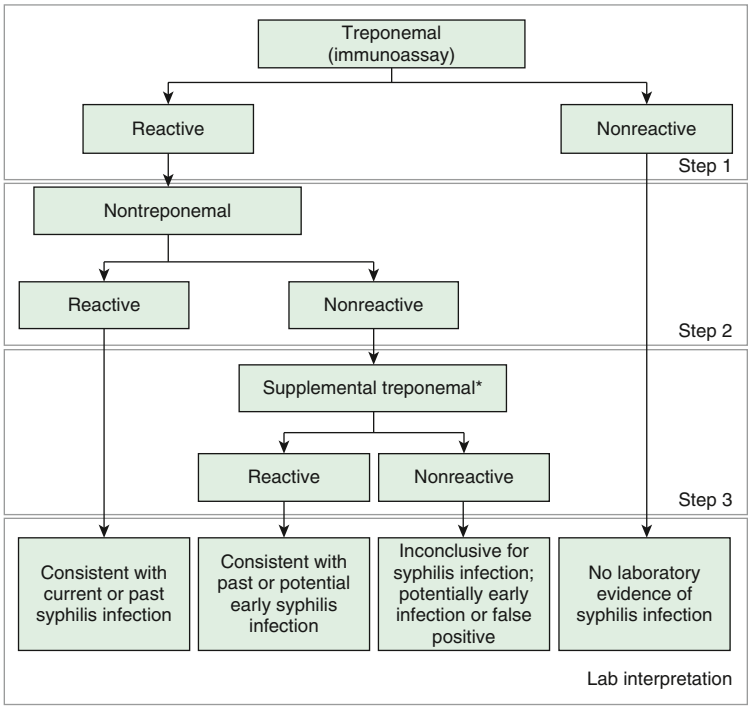

**The supplemental treponemal test should use a unique platform and/or antigen, different from the first treponemal test.*

B

Fig. 264.10 A, Traditional laboratory testing algorithm for syphilis. B, Suggested alternative testing algorithm. EIA/CIA, Enzyme immunoassay/chemiluminescence immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; *RPR*, rapid plasma reagin; TP-HA, *Treponema pallidum* hemagglutination; TP-PA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. *(A based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59[RR-12]:1–110. pp. 26–29.)*

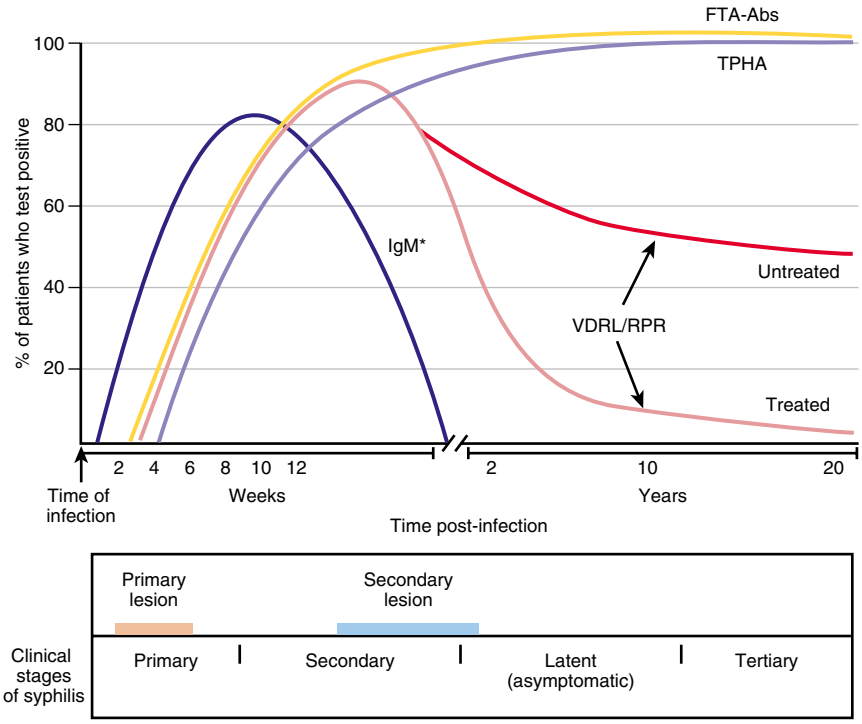

*IgM by ELISA or FTA-ABS 195 or immunoblot.

Fig. 264.11 Common patterns of serologic reactivity in syphilis patients. *FTA-Abs*, fluorescent treponemal antibody absorption (test); *RPR*, rapid plasma reagin (test); *TPHA*, *Treponema pallidum* hemagglutination assay; *VDRL*, Venereal Disease Research Laboratory (test). IgM by immunoassay. *(From Peeling R, Ye H. Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. Bull World Health Organ. 2004;82[6]:439–446.)*

increased detection of transmissible early syphilis and of late latent disease to afford monitoring for tertiary disease. Although the CDC and American Academy of Pediatrics (AAP) Red Book continue to recommend the traditional screen ("conventional diagnostic approach"; see Fig. 264.10A), they have provided guidelines for interpretation of the reverse screening algorithm (see Fig. 264.10B). Reverse screening may yield false-positive results, particularly in low-prevalence populations where testing results should be interpreted with caution, as false-positive testing in children may have serious adverse consequences. If reverse testing yields a positive treponemal result but a negative nontreponemal result, a second treponemal test targeting a different treponemal antigen is needed for confirmation. Interpretation of nontreponemal and treponemal serologic tests in the newborn can be confounded by maternal IgG antibodies transferred to the fetus. Passively acquired antibody is suggested by a neonatal titer at least fourfold (i.e., a two-tube dilution) less than the maternal (parental) titer. This conclusion can be verified by a gradual decline in antibody in the infant, usually becoming undetectable by 3-6 months of age. Conversely, an infant nontreponemal titer fourfold higher than the mother's at the time of delivery or a persistent or rising nontreponemal titer in the infant suggests congenital infection.

Neurologic involvement can occur at any stage of syphilis. The diagnosis of neurosyphilis remains difficult but is often established by demonstrating pleocytosis and increased protein in the CSF and a positive CSF VDRL test along with neurologic symptoms. The CSF VDRL test is specific but relatively insensitive (22–69%) for neurosyphilis. CSF PCR and IgM immunoblot tests are being studied but not currently recommended for use in making the diagnosis of neurosyphilis.

Dark-field or direct fluorescent antibody microscopy of scrapings from primary lesions or congenital or secondary lesions can reveal *T. pallidum,* often before serology becomes positive, but these modalities are usually not available in clinical practice. Since 2015 different methods of PCR, including routine PCR, nested PCR, reverse-transcriptase PCR, and quantitative PCR targeting different DNA gene sequences, have been used by many laboratories as methods to detect *T. pallidum* in primary disease. However, there are currently no commercially available test kits, and each test must be validated for use in each laboratory. Furthermore, these tests are not useful for asymptomatic patients, and interpretation may be complicated by the fact that they amplify both dead and living organisms. Placental examination by gross and microscopic techniques can be useful in the diagnosis of congenital syphilis. The disproportionately large placentas are characterized histologically by focal proliferative villitis, endovascular and perivascular arteritis, and focal or diffuse immaturity of placental villi.

Congenital Syphilis

A diagnosis of congenital syphilis requires a thorough review of maternal (parental) history of syphilis treatment preconception and the testing, treatment, and dynamics of response during the current pregnancy. Regardless of maternal (parental) treatment and the presence/absence of symptoms in the infant, proactive evaluation and treatment of exposed neonates is critical (Fig. 264.12 and Table 264.2). Symptomatic infants should be thoroughly evaluated and treated. Figure 264.12 and Table 264.3 describe the guidelines for evaluating and managing asymptomatic infants who are considered at risk for congenital syphilis because the maternal (parental) nontreponemal and treponemal serology is positive. Internationally adopted, refugee, and immigrant children should also be screened, regardless of history or report of treatment. Diagnostic testing risk-stratifies infants to probability of congenital infection: proven or highly probable congenital syphilis, possible congenital syphilis, congenital syphilis less likely, or congenital syphilis unlikely.

A diagnosis of neurosyphilis in the newborn with syphilitic infection is confounded by poor sensitivity of the CSF VDRL test in this age-group and lack of CSF abnormalities. A positive CSF VDRL test in a newborn warrants treatment for neurosyphilis, even though it might reflect passive transfer of antibodies from serum to CSF. It is now accepted that all infants with a presumptive diagnosis of congenital syphilis should be treated with regimens effective for neurosyphilis because central nervous system involvement cannot be reliably excluded. A diagnosis of syphilis beyond early infancy should lead to consideration of possible child abuse.

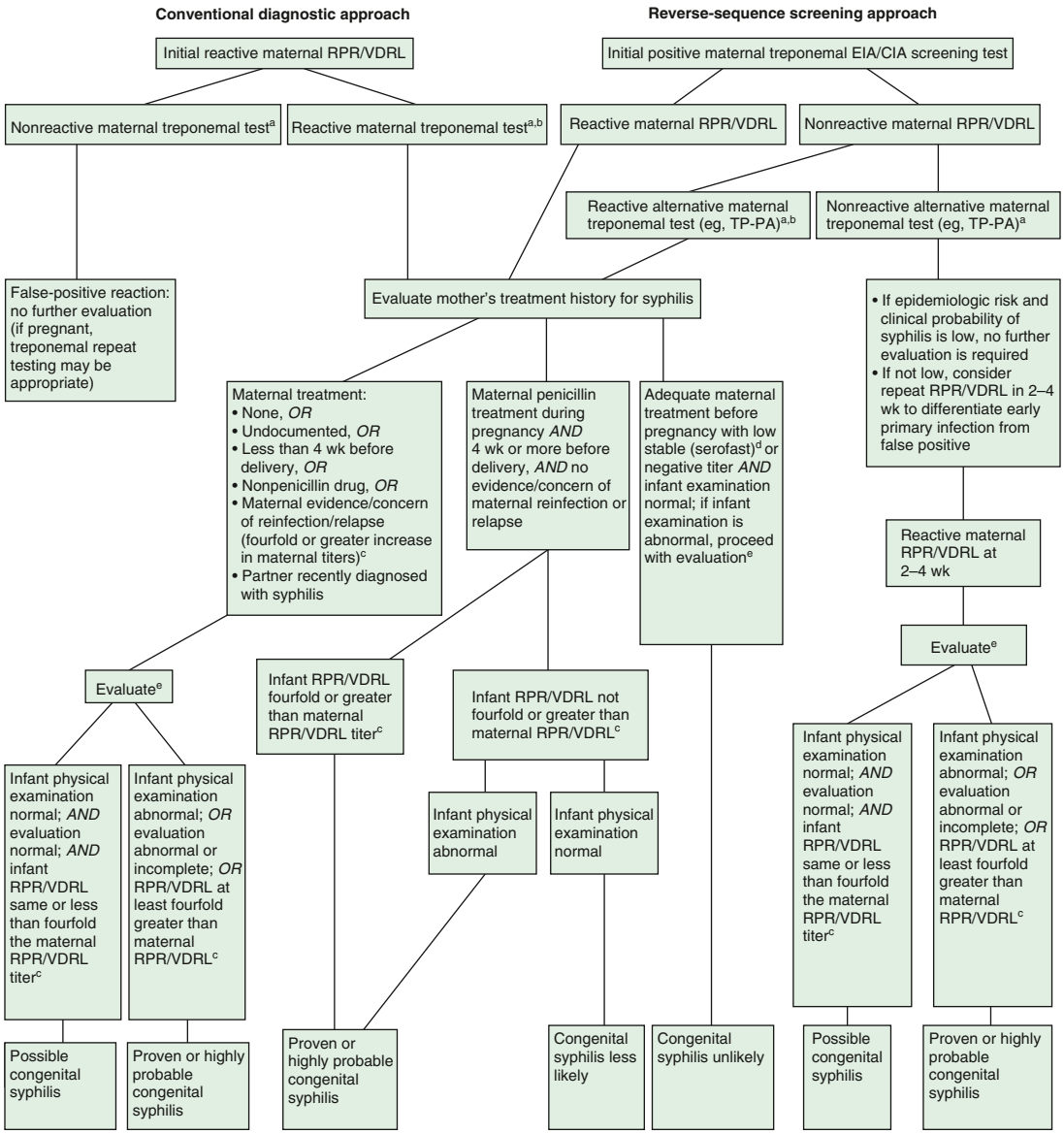

Fig. 264.12 Algorithm for the diagnostic approach of infants born to mothers (birthing parents) with reactive serologic tests for syphilis. [a]*Treponema pallidum* particle agglutination (TP-PA) (which is the preferred treponemal test) or fluorescent treponemal antibody absorption (FTA-ABS). [b]Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment for syphilis. [c]A fourfold change in titer is the same as a change of two dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16. When comparing titers, the same type of nontreponemal test should be used (e.g., if the initial test was an RPR, the follow-up test should also be an RPR). [d]Stable VDRL titers 1:2 or less or RPR 1:4 or less beyond 1 year after successful treatment are considered low serofast. [e]Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (e.g., chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response). For neonates, pathologic examination of the placenta or umbilical cord with specific fluorescent antitreponemal antibody staining, if possible. RPR, Rapid plasma regain; VDRL, Venereal Disease Research Laboratory. *(From American Academy of Pediatrics. Syphilis. In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021–2024 Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021: Fig. 3.15, p. 734.)*

For infants with proven or highly probable disease or abnormal physical findings, complete evaluation, including serologic tests (RPR or VDRL), complete blood count with differential and platelet count, liver function tests, long-bone radiographs, ophthalmology examination, auditory brainstem response, and other tests as indicated, should be performed. If possible, pathologic examination of the placenta and/or umbilical cord with specific fluorescent antitreponemal antibody staining is recommend by the AAP. For infants with a positive VDRL or RPR test result and normal physical examination whose mothers were inadequately treated, further evaluation is not necessary if 10 days of parenteral therapy are administered.

TREATMENT

The goals of early detection and treatment include treatment of current infection and prevention of both late-stage disease and sexual or vertical transmission. *T. pallidum* remains extremely sensitive to penicillin, with no evidence of emerging penicillin resistance, and thus penicillin remains the treatment drug of choice (additional information available in Table 264.4 and at http://www.cdc.gov/std/treatment for patients over 1 month old). Parenteral penicillin G is the only documented effective treatment for congenital syphilis, syphilis during pregnancy, and neurosyphilis and is recommended for treatment of syphilis in persons with HIV. Aqueous crystalline penicillin G is preferred over

Table 264.2 Clues that Suggest a Diagnosis of Congenital Syphilis

EPIDEMIOLOGIC BACKGROUND	CLINICAL FINDINGS
Untreated early syphilis in the mother	Osteochondritis, periostitis
Untreated latent syphilis in the mother	Snuffles, hemorrhagic or mucopurulent rhinitis
An untreated mother who has contact with a known patient with syphilis during pregnancy	Condylomata lata
Mother treated less than 30 days before delivery	Bullous lesions, palmar or plantar rash
Mother treated for syphilis during pregnancy with a drug other than penicillin	Mucous patches
Mother treated for syphilis during pregnancy without follow-up to demonstrate fourfold decrease in titer	Hepatomegaly, splenomegaly
Mother co-infected with HIV	Jaundice, hepatitis
	Nonimmune hydrops fetalis
	Generalized lymphadenopathy
	Central nervous system signs; elevated cell count or protein in cerebrospinal fluid
	Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia
	Pneumonitis
	Nephrotic syndrome
	Placental villitis or vasculitis (unexplained enlarged placenta)
	Intrauterine growth restriction

Arranged in decreasing order of confidence of diagnosis.
Modified from Remington JS, Klein JO, Wilson CB, et al., eds. *Infectious Diseases of the Fetus and Newborn Infant*, 6th ed. Philadelphia: WB Saunders; 2006:556.

Table 264.3 Confirmed Proven or Highly Probable Congenital Syphilis

DIAGNOSIS AND TREATMENT

Any neonate with:

- An abnormal physical examination that is consistent with congenital syphilis;
- A serum quantitative nontreponemal serologic titer that is fourfold (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32); or
- A positive dark-field test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.

Recommended evaluation:

- CSF analysis for VDRL, cell count, and protein
- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs
- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brainstem response)

Recommended regimens, confirmed or highly probable congenital syphilis:

Aqueous crystalline penicillin G 100,000-150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 hr during the first 7 days of life and every 8 hr thereafter for a total of 10 days*

OR

Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis. Using agents other than penicillin requires close serologic follow-up for assessing therapy adequacy.

*Preferred therapy per the 2021-2024 AAP Red Book
From Centers for Disease Control and Prevention. Congenital syphilis. Sexually Transmitted Diseases and Treatment Guidelines, 2021. Scenario 1. https://www.cdc.gov/std/treatment-guidelines/congenital-syphilis.htm.

procaine penicillin, because it better achieves and sustains the minimum concentration of 0.018 μg/mL (0.03 units/mL) needed for 7-10 days to achieve the prolonged treponemicidal levels required for the long dividing time of *T. pallidum*.

In 2023, due to manufacturing limitations and increased demand, the United States entered a period of penicillin G shortage, requiring prioritization of pregnant persons to receive this antibiotic, as no other medication is proven to prevent vertical transmission. Penicillin G is often preferred for IM injection in treatment of other syphilis infections as an approach to ensure adherence to therapy, and thus the shortage may lead to increased transmission.

For proven or highly probable congenital syphilis, procaine penicillin G (50,000 U/kg IM daily × 10 days) should only be used if access to IV penicillin G is limited (such as in a low-resource setting) or if IV access cannot be obtained. For infants with possible congenital syphilis, aqueous penicillin G (50,000 U/kg IV every 12 hours when 1 wk or younger, then every 8 hours for infants older than 1 wk, for a total of 10 days of therapy) is preferred, though procaine penicillin G (50,000 U/kg IM daily x 10 days) may be given. Benzathine penicillin G (50,000 U/kg IM) as a single dose can be considered but only if all components of the evaluation are normal and follow-up is certain. Infants in whom congenital syphilis is less likely may be treated with benzathine penicillin G (50,000 U/kg IM) as a single dose. If no treatment is given, infants must be closely followed until the nontreponemal test becomes nonreactive. If any portion of the assessment for congenital syphilis is abnormal or not obtained, or the CSF studies are uninterpretable, or outpatient follow-up cannot be assured, treatment with procaine penicillin G is preferred. Patients with persistent or increasing titers require repeat evaluation and treatment with a 10-day course of parenteral penicillin G, even if previously treated.

Although nonpenicillin regimens are available to the penicillin-allergic patient, desensitization followed by standard penicillin therapy is the most reliable strategy. Success of treatment also depends on the integrity of the host immune response. A transient acute systemic febrile reaction called the **Jarisch-Herxheimer reaction** (caused by massive release of endotoxin-like antigens during bacterial lysis) occurs in 15–20% of patients with acquired or congenital syphilis treated with penicillin. It is not an indication for discontinuing penicillin therapy. Use of other agents for congenital syphilis should only be done in consultation with a pediatric infectious diseases specialist and requires close clinical and serologic follow-up.

Acquired Syphilis

Primary, secondary, and early latent disease is treated with a single dose of benzathine penicillin G (50,000 units/kg IM, maximum 2.4 million units, in a single dose). Persons with late latent or tertiary disease require three doses at 1-week intervals. Nonpregnant penicillin-allergic patients without neurosyphilis may be treated with either doxycycline (4.4 mg/kg divided in 2 doses, max 200 mg per day, orally twice a day for 14 days) or tetracycline (25-50 mg/kg divided in 4 doses, max 2 g per day, orally for 14 days, for age ≥8 years). Emerging *azalide* and *macrolide resistance* has been documented throughout the United States (a 23S ribosomal NA [rRNA] point mutation at position 2058) and, more recently, worldwide (a 23S rRNA point mutation at position 2059), compromising the effective use of these antibiotics. Careful serologic follow-up is always necessary. Documentation of serologic cure is an essential part of syphilis treatment. Less than a fourfold decline in titer reflects treatment failure.

The CDC recommends that all persons with syphilis be tested for HIV and other STIs. Patients diagnosed with syphilis with a negative HIV test should undergo repeat testing 3 months later. Diagnosis of syphilis in high-risk individuals, particularly men or transgender women who have sex with men, is associated with increased risk of

Table 264.4 Recommended Treatment for Syphilis in People Older Than 1 Mo

STATUS	CHILDREN	ADULTS
Congenital syphilis in patients >1 mo old; OR children >2 mo with late and previously untreated congenital syphilis	Aqueous crystalline penicillin G 200,000-300,000 U/kg/day IV administered as 50,000 U/kg, every 4-6 hr for 10 days*	
Primary, secondary, and early latent syphilis†	Penicillin G benzathine‡ 50,000 U/kg IM, up to the adult dose of 2.4 million U in a single dose *If allergic to penicillin and not pregnant,* Doxycycline 4.4 mg/kg divided in 2 doses, max 200 mg per day, orally twice a day for 14 days (for ages ≥8 yr) *OR* Tetracycline 25-50 mg/kg divided in 4 doses, max 2 g per day, orally for 14 days (for ages ≥8 yr)	Penicillin G benzathine 2.4 million U IM in a single dose *OR* *If allergic to penicillin and not pregnant,* doxycycline 100 mg orally twice a day for 14 days *OR* Tetracycline 500 mg orally 4 times/day for 14 days
Late latent syphilis§	Penicillin G benzathine 50,000 U/kg IM, up to the adult dose of 2.4 million U, administered as 3 single doses at 1-wk intervals (total 150,000 U/kg, up to the adult dose of 7.2 million U) *If allergic to penicillin and not pregnant,* Doxycycline 4.4 mg/kg divided in 2 doses, max 200 mg per day, orally twice a day for 4 weeks (for ages ≥8 yr) *OR* Tetracycline 25-50 mg/kg divided in 4 doses, max 2 g per day, orally for 4 weeks (for ages ≥8 yr)	Penicillin G benzathine 7.2 million U total, administered as 3 doses of 2.4 million U IM, each at 1-wk intervals; pregnant women who have delays in any dose of therapy beyond 9 days between doses should repeat the full course of therapy *OR* *If allergic to penicillin and not pregnant,* Doxycycline 100 mg orally twice a day for 4 wk *OR* Tetracycline 500 mg orally, 4 times/day for 4 wk
Tertiary	—	Penicillin G benzathine 7.2 million U total, administered as 3 doses of 2.4 million U IM at 1-wk intervals *If allergic to penicillin and not pregnant, consult an infectious diseases expert*
Neurosyphilis‖	Aqueous crystalline penicillin G 200,000-300,000 U/kg/day IV every 4-6 hr for 10-14 days, in doses not to exceed the adult dose	Aqueous crystalline penicillin G 18-24 million U per day, administered as 3-4 million U IV every 4 hr for 10-14 days¶ *OR* Penicillin G procaine‡ 2.4 million U IM once daily PLUS probenecid 500 mg orally 4 times/day, both for 10-14 days¶

*If the patient has no clinical manifestations of disease, the cerebrospinal fluid (CSF) examination is normal, and the CSF Venereal Disease Research Laboratory (VDRL) test result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine 50,000 U/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 U/kg IM after the 10-day course of intravenous aqueous penicillin.
†Early latent syphilis is defined as being acquired within the preceding year.
‡Penicillin G benzathine and penicillin G procaine are approved for intramuscular administration only.
§Late latent syphilis is defined as syphilis beyond 1 year's duration.
‖Patients who are allergic to penicillin should be desensitized.
¶Some experts administer penicillin G benzathine 2.4 million U IM once per week for up to 3 weeks after completion of these neurosyphilis treatment regimens.
IV, Intravenously; *IM*, intramuscularly.
From American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021: Table 3.67, pp. 741–742.

subsequent HIV acquisition, and preexposure prophylaxis (PrEP) should be considered. Patients co-infected with HIV are at increased risk for neurologic complications and higher rates of treatment failure. CDC guidelines recommend the same treatment of primary and secondary syphilis as for patients who are not infected with HIV, but some experts recommend three weekly doses of benzathine penicillin G. HIV-infected patients with late latent syphilis or latent syphilis of unknown duration should have a CSF evaluation for neurosyphilis before treatment.

Sex partners of infected persons of any stage should be evaluated and treated. Persons exposed for 90 days or less preceding diagnosis in a sex partner should be treated presumptively even if seronegative. Persons exposed for more than 90 days before the diagnosis in a sex partner should be treated if seropositive or if serologic tests are not available. Follow-up serology should be performed on treated patients to establish adequacy of therapy, and all patients should be tested for other sexually transmitted diseases, including HIV. Children with acquired primary, secondary, or latent syphilis should undergo evaluation for possible sexual assault or abuse.

Syphilis in Pregnancy

When clinical or serologic findings suggest active infection or when the diagnosis of active syphilis cannot be excluded with certainty, treatment is indicated. The goals of treatment of the pregnant person include eradication of maternal (parental) disease, prevention of parent-to-child transmission, and treatment of fetal infection. Patients should be treated immediately with the penicillin regimen appropriate for the pregnant person's stage of syphilis. Those who have been

adequately treated in the past do not require additional therapy unless quantitative serology suggests evidence of reinfection **(fourfold elevation in titer)**.

Penicillin G is the only agent known to be effective for treating fetal infection and for prevention of congenital infection. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin. If doses for late latent syphilis are delayed beyond 9 days from the prior dose, the full course of therapy needs to be repeated. Additional therapy may be considered for pregnant persons with primary, secondary, or early latent syphilis or when syphilis is diagnosed during the second half of pregnancy and sonographic evidence of fetal or placental syphilis is noted. In these cases, a second dose of benzathine penicillin G (2.4 million units IM given 1 week after the initial dose) may decrease the risk of vertical transmission. Jarisch-Herxheimer reaction in the second half of pregnancy may induce premature labor or fetal distress, and patients with reactions should seek obstetric attention promptly.

Congenital Syphilis

Adequate maternal (parental) treatment at least 30 days before delivery is likely to prevent congenital syphilis. All infants born to pregnant persons with syphilis should be followed until nontreponemal serology is negative. The infant should be treated if there is any uncertainty about the adequacy of maternal (parental) treatment. The goal of infant treatment is prevention of organ damage, skeletal deformity, and developmental delay. Any infant at risk of congenital syphilis should be evaluated for HIV.

Congenital syphilis is treated in infants up to 1 month of age with aqueous penicillin G (100,000-150,000 units/kg/24 hr IV divided every 12 hours for the first week of life and every 8 hours thereafter) or procaine penicillin G (50,000 units/kg IM once daily) given for 10 days. Both penicillin regimens are recognized as adequate therapy for congenital syphilis, but higher concentrations of penicillin are achieved in the CSF of infants treated with intravenous aqueous penicillin G than in those treated with intramuscular procaine penicillin. Treated infants should be closely monitored at 2-, 4-, 6-, and 12-month well child care visits and serologic nontreponemal titers repeated every 2-3 months until nonreactive. Titers generally decrease by 3 months of age and become nonreactive by 6 months of age if adequately treated or if antibody was merely transplacentally acquired without infection. Infants diagnosed and treated for congenital syphilis after 1 month of age should be treated with aqueous crystalline penicillin G 200,000-300,000 U/kg/day IV administered as 50,000 U/kg, every 4-6 hr for 10 days (Table 264.4). Nontreponemal titers may resolve more slowly if the patient was treated after 1 month old. Increasing or persistent stable titers 6-12 months after initial treatment suggest possible ongoing infection, and repeat evaluation, including CSF, is indicated. Repeat treatment (penicillin G IV for 10 days) may be indicated. Infants with a negative nontreponemal test born to a person seroreactive at the time of delivery could have incubating congenital infection and so should be retested at 3 months. Infants with initial abnormal CSF studies only require repeat lumbar puncture if they have persistent nontreponemal serologic titers at 6-12 months old. If CSF has a persistent positive VDRL or abnormal indices not attributable to another ongoing illness, retreatment is indicated after 2 years of follow-up. At age 2 previously treated infants should receive a full developmental assessment. In a very low-risk neonate who is asymptomatic and whose mother was treated appropriately, without evidence of relapse or reinfection but with a low and stable VDRL titer (serofast), no evaluation is necessary. Some specialists, however, would treat such an infant with a single dose of benzathine penicillin G 50,000 units/kg IM.

PREVENTION

Syphilis, including congenital syphilis, is a reportable disease in all 50 states and the District of Columbia. Testing is indicated at any time for persons with suspicious lesions, a history of recent sexual exposure to a person with syphilis, or diagnosis of another sexually transmitted infection, including HIV infection. Screening for syphilis in asymptomatic, nonpregnant persons at increased risk for infection has received an A recommendation from the US Preventive Services Task Force (USPSTF) as providing significant benefit. Direct-to-consumer test services for STIs (or "home tests") have become more acceptable following consumer experience with similar testing during the COVID-19 pandemic, and best practices for implementation are an area of intense research. As of late 2023, the US CDC had posted request for comment on proposed guidelines for the use of doxycycline as post-exposure prophylaxis for bacterial STI prevention, including syphilis, to be offered to MSM and transgender women with a history of at least one bacterial STI in the last 12 months; insufficient evidence is currently available to give recommendations for other groups, including children, cisgender women or heterosexual men, transgender men, or other queer and nonbinary individuals. The resurgence of syphilis compels clinicians to remain cognizant of its protean manifestations to avoid missed or late diagnosis. Timely treatment lessens risk of community spread. Despite the genome sequencing of *T. pallidum* in 1998, vaccine development remains elusive, confounded by the treponeme's ability to evade the immune system.

Congenital Syphilis

Congenital syphilis is a preventable disease, a sentinel event indicating multiple missed opportunities. Primary prevention is tied to prevention of syphilis in women of childbearing age, and secondary prevention with early diagnosis and prompt treatment of women and their partners. Access to and use of comprehensive prenatal care is key, with careful history taking (including interim sexual partners) at each visit. Routine prenatal screening for syphilis remains the most important factor in identifying infants at risk for developing congenital syphilis. Screening all women at the beginning of prenatal care is an evidence-based standard of care and legally required in all states. In pregnant women without optimal prenatal care, serologic screening for syphilis should be performed at the time pregnancy is diagnosed. Any person who is delivered of a stillborn infant at 20 weeks or fewer of gestation should be tested for syphilis. In communities and populations with a high prevalence of syphilis and in patients at high risk (pregnant persons with a history of incarceration, drug use, or multiple or concurrent partners), testing should be performed at least two additional times: at the beginning of the third trimester (28 weeks) and at delivery. Some states mandate repeat testing at delivery for all pregnant persons, underscoring the importance of preventive screening. Those at high risk for syphilis should be screened even more frequently, either monthly or, pragmatically (in the case of inconsistent prenatal care), at every medical encounter because they can have repeat infections during pregnancy or reinfection late in pregnancy. Follow-up serologic testing of all treated pregnant persons should be done after treatment to document titer decline, relapse, or reinfection.

No newborn should leave the hospital without the mother's (parent's) syphilis status having been determined at least once during pregnancy or at delivery. In states conducting newborn screening for syphilis, both the parent's and infant's serologic results should be known before discharge. Appropriate follow-up for the treated or exposed infant should be arranged. In addition, all previously uninvestigated infants of an infected mother should be screened. Strong linkages between clinicians and public health practitioners remain essential for comprehensive prevention of acquired and congenital syphilis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 265

Nonvenereal Treponemal Infections

Stephen K. Obaro and H. Dele Davies

Nonvenereal treponemal infections—yaws, bejel (endemic syphilis), and pinta—are caused by different subspecies of *Treponema pallidum* and occur in tropical and subtropical areas. The causative agents of nonvenereal treponematoses—*T. pallidum pertenue, T. pallidum* subspecies *endemicum,* and *Treponema carateum*—cannot be distinguished from *T. pallidum* subspecies *pallidum* by morphologic or serologic tests.

In general, nonvenereal treponematoses have prominent cutaneous manifestations and relapsing courses, as in venereal syphilis, but they are not found in urban centers, they are not sexually transmitted, and they are not congenitally acquired. Transmission is primarily through body contact, poor hygiene, crowded conditions, and poor access to healthcare. Children also serve as the primary reservoirs for these organisms, spreading infection via skin-to-skin and skin–to–mucous membrane contact, and possibly via fomites as well.

Penicillin remains the treatment of choice for syphilis and nonvenereal treponemal infections.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

265.1 Yaws (*Treponema pertenue*)

Stephen K. Obaro and H. Dele Davies

Yaws is the most prevalent nonvenereal treponematosis. The causative agent, *Treponema pertenue,* bears very close genomic resemblance to *T. pallidum* subspecies *pallidum*. The overall sequence identity between the genomes of *T. pallidum pertenue* and *T. pallidum* subspecies *pallidum is* 99.8%. Yaws is a contagious, chronic, relapsing infection involving the skin and bony structures caused by the spirochete *T. pertenue,* which is identical to *T. pallidum* microscopically and serologically. This disease occurs in tropical regions with heavy rainfall and annual temperatures ≥27°C (80°F). Almost all cases occur in children in tropical and subtropical countries. It is also referred to as "framboesia," "pian," "parangi," and "bouba." A high percentage of the population is infected in endemic areas.

T. pertenue is transmitted by direct contact from an infected lesion through a skin abrasion or laceration. Transmission is facilitated by overcrowding and poor personal hygiene in the rainforest areas of the world. Yaws predominantly affects children, with approximately 75% of cases being reported in children younger than 15 years of age. This population also constitutes the reservoir for disease transmission. The initial papular lesion, which constitutes **primary yaws**, also described as the **mother yaw,** occurs 2-8 weeks after inoculation. This lesion typically involves the buttocks or lower extremities. The papule develops into a raised, raspberry-like papilloma and is often accompanied by regional lymphadenopathy. The skin pathology is similar to that of venereal syphilis, consisting of epidermal hyperplasia and papillomatosis (Fig. 265.1). Healing of the mother yaw leaves a hypopigmented scar. The **secondary-stage** lesions can erupt anywhere on the body before or after the healing of the mother yaw and may be accompanied by lymphadenopathy, anorexia, and malaise. Multiple cutaneous lesions (daughter yaws, pianomas, or framboesias) appear, spread diffusely, ulcerate, and are covered by exudates containing treponemes. Secondary lesions heal without scarring. Recurrent lesions are common within 5 years after the primary lesion.

The lesions are often associated with bone pain resulting from underlying periostitis or osteomyelitis, especially of the fingers, nose, and tibia. The initial period of clinical activity is followed by a 5- to 10-year period of latency. The appearance of tertiary-stage lesions develops in approximately 10% of infected patients, with onset typically at puberty, with solitary and destructive lesions. These lesions occur as painful papillomas on the hands and feet, gummatous skin ulcerations, or osteitis. Bony destruction and deformity, juxtaarticular nodules, depigmentation, and painful

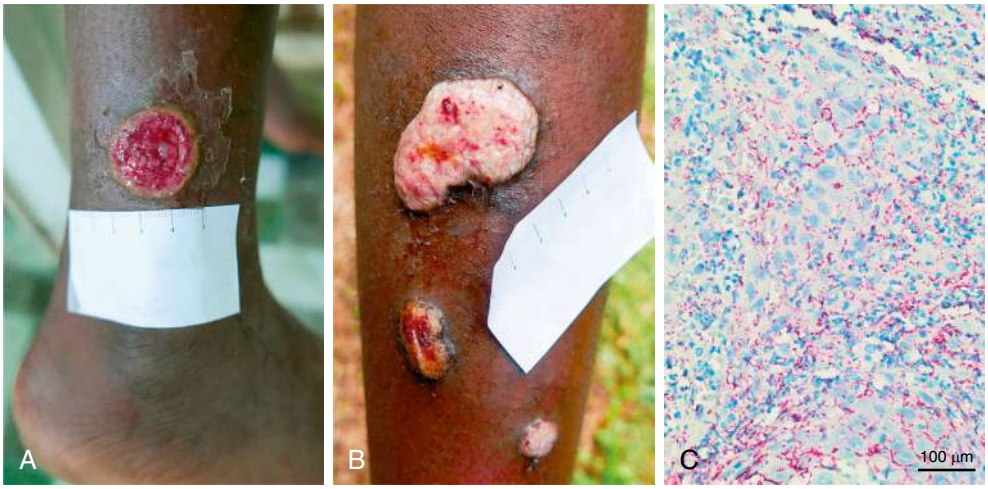

Fig. 265.1 Yaws lesions in a patient with treatment failure associated with macrolide-resistant *T p pertenue*. **A,** Primary lesion (red, moist 2.5-cm ulcer) on the left leg of an 11-yr-old patient with yaws observed at the 30-mo survey. Lesional swab PCR was positive for *T p pertenue* with wild-type 23S rRNA. **B,** Secondary yaws papillomas (multiple nodules with yellow granular surface) seen at 36-mo survey. These lesions were PCR positive for *T p pertenue* with A2059G mutation in 23S rRNA. **C,** Photomicrograph of skin biopsy of the larger papilloma lesion in panel **B** with abundant spirochete organisms stained bright red by the *Treponema pallidum* immunohistochemical stain (×400 magnification). *T p pertenue*, *Treponema pallidum* subspecies pertenue. *(From Mitja O, Godornes C, Houinei W, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. Lancet. 2018;391:1599–1606, Fig. 2.)*

hyperkeratosis **(dry crab yaws)** of the palms and soles are common. Approximately 10% of patients may progress and develop tertiary-stage lesions after 5 years or more of untreated infection, although this outcome is now rare.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis. The nontreponemal agglutination tests, such as the rapid plasma reagin and Venereal Diseases Research Laboratory tests, are positive in untreated cases, and these tests can be used for test of cure, because they revert to negative after treatment. However, the treponemal tests (*T. pallidum* hemagglutination assay, *T. pallidum* particle agglutination assay, and fluorescent treponemal antibody absorption) are more specific and remain positive for life. New immunochromatographic test strips that can be applied for testing both whole blood and serum are simple, cheap, and easy to use and do not require refrigeration. However, they have lower sensitivity compared with the antibody assays and appear to work best in persons with more active disease.

The differential diagnosis includes other conditions with similar cutaneous manifestations such as eczema, psoriasis, excoriated chronic scabies, tungiasis, leishmaniasis, tropical ulcer cutaneous mycoses, and verrucae. Involvement of the bone may mimic dactylitis that is commonly associated with sickle cell disease.

Treatment of yaws consists of a single dose of the long-acting benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 years) for index patients and all contacts. Patients allergic to penicillin may be treated with erythromycin, doxycycline, or tetracycline at appropriate doses for venereal syphilis (see Chapter 264). One oral dose of azithromycin (30 mg/kg; maximum: 2 g) is as effective as benzathine penicillin. Treatment cures the lesions of active yaws, renders them noninfectious, and prevents relapse. Family members, contacts, and patients with latent infection should receive the same dose as those with active disease. Eradication of yaws from some endemic areas has been accomplished by treating the entire population (mass treatment) with azithromycin, although reemergence has been reported in those who did not receive mass treatment. In 2023, due to manufacturing limitations and increased demand, the United States entered a period of penicillin G shortage, potentially causing treatment to shift to erythromycin, doxycycline, or tetracycline until the shortages are resolved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

265.2 Bejel (Endemic Syphilis; *Treponema pallidum endemicum*)

Stephen K. Obaro and H. Dele Davies

Bejel, or endemic syphilis, affects children in remote rural communities living in poor hygienic conditions. Unlike yaws, bejel can occur in temperate and dry, hot climates. Infection with *T. pallidum* subspecies *endemicum* follows penetration of the spirochete through traumatized skin or mucous membranes. In experimental infections, a primary papule forms at the inoculation site after an incubation period of 3 weeks. A primary lesion is almost never visualized in human infections; however, primary ulcers have been described surrounding the nipples of nursing mothers with infected children.

The clinical manifestations of the **secondary stage** typically occur 3-6 months after inoculation and are confined to the skin and mucous membranes. They consist of highly infectious mucous patches on the oral mucosa and condyloma-like lesions on the moist areas of the body, especially the axilla and anus. These mucocutaneous lesions resolve spontaneously over a period of several months, but recurrences are common. The secondary stage is followed by a variable latency period before the onset of late or tertiary bejel. The tertiary stage can occur as early as 6 months or as late as several years after resolution of initial symptoms. The lesions in the tertiary stage are identical to those of yaws and include gumma formation in skin, subcutaneous tissue, and bone, resulting in painful destructive ulcerations, swelling, and deformity.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

Differentiation from venereal syphilis is extremely difficult in an endemic area. Bejel is distinguished by the absence of a primary chancre and lack of involvement of the central nervous system and cardiovascular system during the late stage.

Treatment of early infection consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 years). Late infection is treated with three injections of the same dosage at intervals of 7 days. Patients allergic to penicillin may be treated with erythromycin or tetracycline. Similarly, when penicillin G is unavailable because of manufacturing limitations, treatment with erythromycin or tetracycline is appropriate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

265.3 Pinta (*Treponema carateum*)

Stephen K. Obaro and H. Dele Davies

Pinta is a chronic, nonvenereally transmitted infection caused by *T. pallidum* subsp. *carateum,* a spirochete morphologically and serologically indistinguishable from other human treponemes. This is perhaps the mildest of the nonvenereal treponematoses. The disease is endemic in Mexico, Central America, South America, and parts of the West Indies and largely affects children younger than 15 years of age.

Infection follows direct inoculation of the treponeme through abraded skin. After a variable incubation period of days, the **primary** lesion appears at the inoculation site as a small asymptomatic erythematous papule resembling localized psoriasis or eczema. The regional lymph nodes are often enlarged. Spirochetes can be visualized on dark-field examination of skin scrapings or from biopsy of the involved lymph nodes. After a period of enlargement, the primary lesion disappears. Unlike primary yaws, the lesion does not ulcerate but can expand with central depigmented resolution. **Secondary** lesions follow within 6-8 months and consist of small macules and papules on the face, scalp, and other sun-exposed portions of the body. These pigmented, highly infectious lesions are scaly and nonpruritic and can coalesce to form large plaquelike elevations resembling psoriasis. In the late or **tertiary** stage, atrophic and depigmented lesions develop on the hands, wrists, ankles, feet, face, and scalp. Hyperkeratosis of palms and soles is uncommon.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

Treatment consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 years). Tetracycline and erythromycin are alternatives for patients allergic to penicillin and during periods when penicillin G is unavailable because of manufacturing limitations. Treatment campaigns and improvement of standards of living are necessary for reduction and elimination of the disease.

Chapter 266

Leptospira

H. Dele Davies and Kari A. Simonsen

Leptospirosis is a common and widespread zoonosis caused by aerobic, motile spirochetes of the genus *Leptospira*.

ETIOLOGY

Leptospira spp. are thin, helix-shaped members of the phylum Spirochaetes. There are 22 species identified within the genus *Leptospira,* and these are further divided into over 300 serovars. There are at least 10 pathogenic *Leptospira* species, with serovars demonstrating preferential host specificity.

EPIDEMIOLOGY

Leptospirosis has a worldwide distribution, but most human cases occur in tropical and subtropical countries with disease burden disproportionately affecting resource-poor populations. Leptospires survive for days to weeks in warm and damp environmental conditions, including water and moist soil. In the United States, the CDC estimates 100-200 annual cases; Hawaii reports about 50% of U.S. cases, with Pacific Coast and Southern states having a higher incidence than the remainder of the country. Leptospires infect many species of animals, including rats, mice, and moles; livestock such as cattle, goats, sheep, horses, and pigs; wild mammals like raccoons or opossums; and domestic dogs. Infected animals excrete spirochetes in their urine for prolonged periods. Globally, most human cases result from exposure to water or soil contaminated with rat urine; however, the major animal reservoir in the United States is the dog. Groups at high risk for leptospirosis include persons exposed occupationally or recreationally to contaminated soil, water, or infected animals. High-risk occupations include agricultural workers, veterinarians, abattoir workers, meat inspectors, rodent control workers, laboratory workers, sewer workers, and military personnel. Cases are more frequent in the late summer and fall and often after heavy rainfalls. Exposure to contaminated floodwaters is also a documented source of infection. Transmission via animal bites and directly from person to person has been rarely reported.

PATHOLOGY AND PATHOGENESIS

Leptospires enter human hosts through mucous membranes (primarily the eyes, nose, and mouth), transdermally through abraded skin, or by ingestion of contaminated water. After penetration, they circulate in the bloodstream, causing endothelial damage of small blood vessels with secondary ischemic damage to end organs.

CLINICAL MANIFESTATIONS

The spectrum of human leptospirosis ranges from asymptomatic infection to severe disease (5–10% of infections) with multiorgan dysfunction and death. The onset is usually abrupt, and the illness may follow a monophasic or the classically described biphasic course (Fig. 266.1). The incubation period ranges from 2 to 30 days, after which there is an **initial** or **septicemic phase** lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic **immune** or **leptospiruric phase**. This phase is associated with the appearance of circulating IgM antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

Anicteric Leptospirosis

The **septicemic phase** of anicteric leptospirosis has an abrupt onset with flulike signs of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia most prominent in the lower extremities, lumbosacral spine, and abdomen. Bradycardia and hypotension can occur, but circulatory collapse is uncommon. Conjunctival suffusion with photophobia and orbital pain (in the absence of chemosis and purulent exudate),

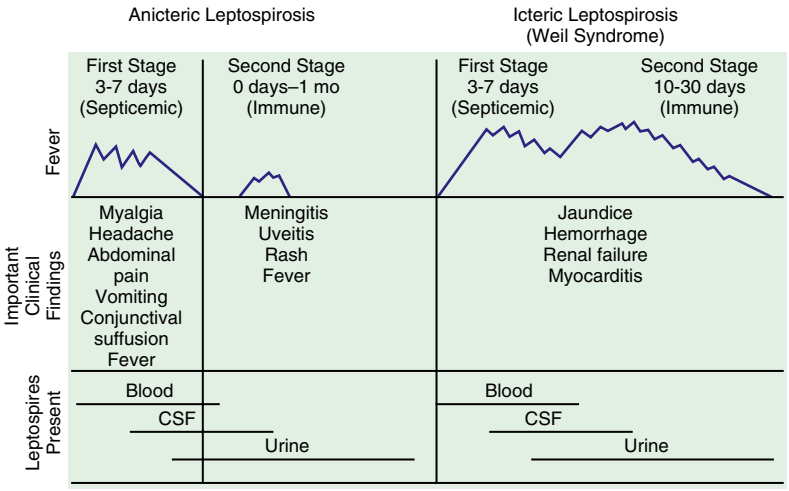

Fig. 266.1 Stages of anicteric and icteric leptospirosis. Correlation between clinical findings and presence of leptospires in body fluids. *CSF*, Cerebrospinal fluid. *(From Feigin RD, Anderson DC. Human leptospirosis. CRC Crit Rev Clin Lab Sci. 1975;5:413–467. Copyright CRC Press, Inc., Boca Raton, FL.)*

generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient (<24 hours) erythematous maculopapular, urticarial, petechial, purpuric, or desquamating rash occurs in 10% of cases. Rarer manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis, and orchitis. The **second** or **immune phase** can follow a brief asymptomatic interlude and is characterized by recurrence of fever and aseptic meningitis. Although 80% of infected children have abnormal CSF profiles, only 50% have clinical meningeal manifestations. CSF abnormalities include a modest elevation in pressure, pleocytosis with early polymorphonuclear leukocytosis followed by mononuclear predominance rarely exceeding 500 cells/mm^3, normal or slightly elevated protein levels, and normal glucose values. Encephalitis, cranial and peripheral neuropathies, papilledema, and paralysis are uncommon. A self-limited unilateral or bilateral uveitis can occur during this phase, rarely resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 week, with almost no mortality.

Icteric Leptospirosis (Weil Syndrome)

Weil syndrome is a severe form of leptospirosis seen more commonly in adults (>30 years) than in children. The initial manifestations are similar to those described for anicteric leptospirosis. However, the immune phase is characterized by jaundice, acute renal dysfunction, thrombocytopenia, and, in fulminant cases, pulmonary hemorrhage and cardiovascular collapse. Hepatic involvement leads to right upper quadrant pain, hepatomegaly, direct and indirect hyperbilirubinemia, and modestly elevated serum levels of hepatic enzymes. Liver function usually returns to normal after recovery. Patients have abnormal findings on urinalysis (hematuria, proteinuria, and casts), and azotemia is common, often associated with oliguria or anuria. Acute kidney failure occurs in 16–40% of cases. Abnormal electrocardiograms are present in 90% of cases, but congestive heart failure is uncommon. Transient thrombocytopenia occurs in >50% of cases. Rarely, hemorrhagic manifestations occur, including epistaxis, hemoptysis, and pulmonary, gastrointestinal, and adrenal hemorrhage. Patients with pulmonary hemorrhage syndrome may have >50% mortality rate, although the overall mortality rate for severe disease is lower, about 5–15%.

DIAGNOSIS

Leptospirosis should be considered in the differential diagnosis of acute flulike febrile illnesses with a history of direct contact with animals or with soil or water contaminated with animal urine. The disease may be difficult to distinguish clinically from dengue or malaria in endemic areas.

The diagnosis is most often confirmed by serologic testing and less often confirmed by isolation of the infecting organism from clinical specimens. The gold-standard diagnostic method is the microscopic agglutination test, a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination. A fourfold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins usually appear by the 12th day of illness and reach a maximum titer by the third week. Low titers can persist for years. Approximately 10% of infected persons do not have detectable agglutinins, presumably because available antisera do not identify all *Leptospira* serotypes. Additionally, enzyme-linked immunosorbent assay (ELISA) methods, latex agglutination, and immunochromatography are commercially available, and DNA PCR diagnostics have been developed. Phase-contrast and dark-field microscopy are insensitive for spirochete detection, but organisms may be identified using Warthin-Starry silver stain or fluorescent antibody staining of tissue or body fluids. Unlike other pathogenic spirochetes, leptospires can be recovered from the blood or CSF during the first 10 days of illness and from urine after the second week by repeated culture of small inoculum (i.e., one drop of blood or CSF in 5 mL of medium) on commercially available selective media. However, the inoculum in clinical specimens is small, and growth can take up to 16 weeks.

TREATMENT

Leptospira spp. demonstrate in vitro susceptibility to penicillin and tetracyclines, but in vivo effectiveness of these antibiotics in treating human leptospirosis is unclear because of the naturally high spontaneous recovery rates. Some studies suggest that initiation of treatment before the seventh day shortens the clinical course and decreases the severity of the infection; thus treatment with penicillin G, ceftriaxone, or doxycycline (in children ≥8 years of age) should be instituted early when the diagnosis is suspected. There is evidence that a short (<2 weeks) course of doxycycline may be safely used in children >2 years of age. Parenteral penicillin G (6-8 million U/m^2/day divided every 4 hours IV for 7 days) is recommended, with doxycycline 2 mg/kg/day divided in two doses with a maximum of 100 mg twice daily as an alternative for patients allergic to penicillin. Ceftriaxone, and azithromycin have been evaluated in clinical trials and have demonstrated equivalent effectiveness with doxycycline. These antibiotics can be used as alternatives in patients for whom doxycycline is contraindicated. In mild illness, oral doxycycline, amoxicillin, and ampicillin have been used successfully. In severe illness, supportive care with specific attention given to cardiopulmonary status, renal function, coagulopathy, and fluid and electrolyte balance is warranted.

PREVENTION

Prevention of human leptospirosis infection is facilitated through rodent control measures and avoidance of contaminated water and soil. Immunization of livestock and domestic dogs is recommended as a means of reducing animal reservoirs. Human vaccine development has been challenging because of the diversity of *Leptospira* serovars and their variable geographic distribution. Protective clothing (i.e., boots, gloves, and goggles) should be worn by persons at risk for occupational exposure. In hospital settings, in addition to standard precautions, contact precautions are recommended for potential exposures to infected urine. Leptospirosis was successfully prevented in American soldiers stationed in the tropics by administering prophylactic doxycycline (200 mg PO once a week). This approach may be similarly effective for travelers to highly endemic areas for short periods; however, there are no specific pediatric data to support any prophylaxis regimen.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 267

Relapsing Fever *(Borrelia)*

Stephen K. Obaro and H. Dele Davies

Relapsing fever is characterized by recurring fevers and flulike symptoms such as headaches, myalgia, arthralgia, and rigors.

ETIOLOGY

Relapsing fever is an arthropod (lice or tick)-transmitted infection caused by spirochetes of the genus *Borrelia*.

Louse-borne (epidemic) relapsing fever is caused by *Borrelia recurrentis* and is transmitted from person to person by *Pediculus humanus,* the human body louse. Human infection occurs as a result of crushing lice during scratching, facilitating entry of infected hemolymph through abraded or normal skin or mucous membranes.

Tick-borne (endemic) relapsing fever is caused by several species of *Borrelia* and is transmitted to humans by *Ornithodoros* ticks. *Borrelia hermsii* and *Borrelia turicatae* are the common species in the western United States, whereas *Borrelia dugesii* is the major cause of disease in Mexico and Central America. Human infection occurs when saliva, coxal fluid, or excrement is released by the tick during feeding, thereby permitting spirochetes to penetrate the skin and mucous membranes.

Borrelia miyamotoi has been identified in the Japanese *Ixodes persulcatus* tick and in the *Ixodes dammini* tick, the agent that transmits Lyme disease in the northeastern United States. This *Borrelia* species causes a Lyme disease–like illness rather than relapsing fever.

EPIDEMIOLOGY

Louse-borne relapsing fever tends to occur in epidemics associated with war, poverty, famine, and poor personal hygiene, often in association with typhus. This form of relapsing fever is no longer seen in the United States but is endemic in parts of East Africa. Using 16S ribosomal RNA (rRNA) polymerase chain reaction assays for molecular detection, up to 20.5% of all unexplained fever in the Horn of Africa, including northwestern Morocco where the population traditionally lives in mud huts, is caused by tick-borne relapsing fever, making this the most common cause of bacterial infections.

Ornithodoros ticks, which transmit endemic relapsing fever and are distributed worldwide, including in the western United States, prefer warm, humid environments and high altitudes and are found in rodent burrows, caves, and other nesting sites (Fig. 267.1). Rodents (e.g., squirrels and chipmunks) are the principal reservoirs. Infected ticks gain access to human dwellings on the rodent host. Human contact is often unnoticed because these soft ticks have a painless bite and detach immediately after a short blood meal.

PATHOLOGY AND PATHOGENESIS

Relapsing fever is cyclical because the *Borrelia* organisms undergo antigenic (phase) variation. Multiple variants evolve simultaneously during the first relapse, with one type becoming predominant. Spirochetes isolated during the primary febrile episode differ antigenically from those recovered during a subsequent relapse. During febrile episodes, spirochetes enter the bloodstream, induce the development of specific immunoglobulin M and G antibodies, and undergo agglutination, immobilization, lysis, and phagocytosis. During remission, *Borrelia* spirochetes may remain in the bloodstream, but spirochetemia is insufficient to produce symptoms. The number of relapses in untreated patients depends on the number of antigenic variants of the infecting strain.

CLINICAL MANIFESTATIONS

Relapsing fever is characterized by febrile episodes lasting 2-9 days, separated by afebrile intervals of 2-7 days. Louse-borne disease has an incubation period of 2-14 days, longer periods of pyrexia, fewer relapses, and longer remission periods than tick-borne disease. The incubation period of tick-borne disease is usually 7 days (range: 2-9 days). Each form of relapsing fever is characterized by sudden onset of high fever, lethargy, headache, photophobia, nausea, vomiting, myalgia, and arthralgia. Additional symptoms may appear later and include abdominal pain, a productive cough, mild respiratory distress, and bleeding manifestations, including epistaxis, hemoptysis, hematuria, and hematemesis. During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days may develop over the trunk and shoulders. There may also be lymphadenopathy, pneumonia, and splenomegaly. Hepatic tenderness associated with hepatomegaly is a common sign, with jaundice in half of affected children. Central nervous system manifestations include lethargy, stupor, meningismus, convulsions, peripheral neuritis, focal neurologic deficits, and cranial nerve paralysis and may be the principal feature of late relapses in tick-borne disease. Severe manifestations include myocarditis, hepatic failure, and disseminated intravascular coagulopathy.

The initial symptomatic period characteristically ends with a crisis in 2-9 days, marked by abrupt diaphoresis, hypothermia, hypotension, bradycardia, profound muscle weakness, and prostration. In untreated patients, the first relapse occurs within 1 week, followed by usually 3 but up to 10 relapses, with symptoms during each relapse becoming milder and shorter as the afebrile remission period lengthens.

DIAGNOSIS

Diagnosis depends on demonstration of spirochetes by dark-field microscopy or in thin or thick blood smears stained with Giemsa or Wright stain and by blood culture (Fig. 267.2). During afebrile remissions, spirochetes are not found in the blood. Serologic tests have not been standardized, are generally not available, and produce cross reactions with other spirochetes, including *Borrelia burgdorferi,* the agent of Lyme disease. Central nervous system involvement may be associated with lymphocytic pleocytosis. Molecular methods, including nested polymerase chain reaction or 16S rRNA polymerase chain reaction assays, have been used for detection of tick-borne and louse-borne recurrent fever and have been found to have improved sensitivity and specificity compared with blood smears. However, these assays are not yet routinely available for commercial use.

TREATMENT

Oral or parenteral tetracycline or doxycycline is the drug of choice for louse-borne and tick-borne relapsing fever. For children older than 8 years of age and young adults, tetracycline 500 mg PO every 6 hours or doxycycline 100 mg PO every 12 hours for 10 days is effective. Single-dose treatment with tetracycline (500 mg PO) or

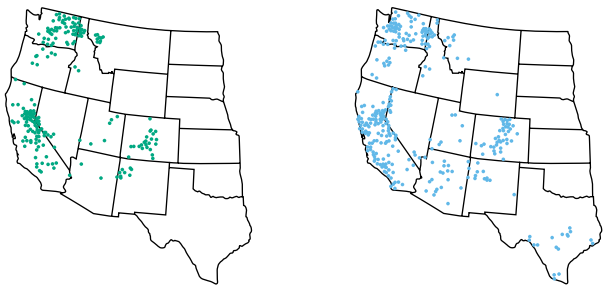

Fig. 267.1 Cases of tickborne relapsing fever–United States, 1990–2011. During the years 1990–2011, 483 cases of tickborne relapsing fever were reported in the western United States, with infections being transmitted most frequently in California, Washington, and Colorado. *(From Centers for Disease Control and Prevention [CDC]. Tick-borne relapsing fever: distribution. Available at:* http://www.cdc.gov/relapsing-fever/distribution*)*

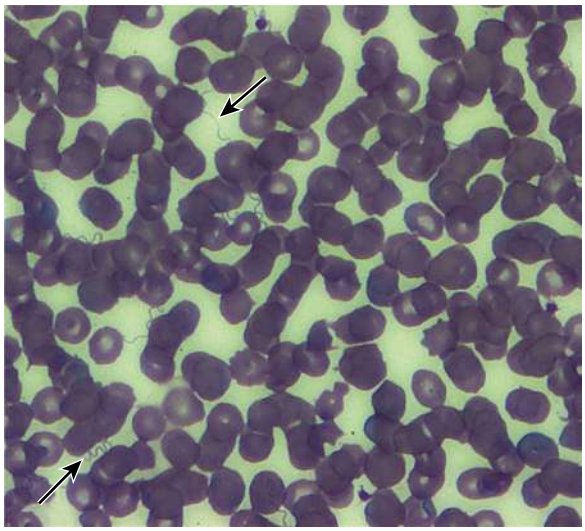

Fig. 267.2 Stained thin smear of a newborn's peripheral blood showing the presence of numerous spirochetes (indicated by *arrows*) at ×63 magnification—Colorado, 2011. *(From Centers for Disease Control and Prevention [CDC]. Tickborne relapsing fever in a mother and newborn child–Colorado, 2011. MMWR Morb Mortal Wkly Rep. 2012;61:174–176.)*

erythromycin is efficacious in adults, but experience in children is limited. In children younger than 8 years of age, erythromycin (50 mg/kg/day divided every 6 hours PO) for a total of 10 days is recommended, although there is evidence that doxycycline given for durations of less than 2 weeks is safe in children >2 years of age. Penicillin and chloramphenicol are also effective. Central nervous system involvement is usually responsive to intravenous ceftriaxone or penicillin.

Resolution of each febrile episode either by natural crisis or as a result of antimicrobial treatment is often accompanied by the Jarisch-Herxheimer reaction, which is caused by massive antigen release. Corticosteroid or antipyretic pretreatment does not prevent this reaction.

PROGNOSIS

With adequate therapy, the mortality rate for relapsing fever is <5%. A majority of patients recover from their illness with or without treatment after the appearance of anti-*Borrelia* antibodies, which agglutinate, kill, or opsonize the spirochete. However, pregnant women and their neonates are at increased risk for tick-borne recurrent fever-associated complications, including adult respiratory distress syndrome, Jarisch-Herxheimer reaction, and precipitous or premature delivery. Neonates have up to a 33% case fatality rate. The risk of Jarisch-Herxheimer reaction appears to be much higher in louse-borne relapsing fever (LBRF) (55.8%) compared to TBRF (19.3%). However, they have similar overall case fatality rates, TBRF (6.5%) and LBRF (4–10.2%).

PREVENTION

No vaccine is available. Disease control requires avoidance or elimination of the arthropod vectors. In epidemics of louse-borne disease, good personal hygiene and delousing of persons, dwellings, and clothing with commercially available insecticides can prevent dissemination. The risk for tick-borne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Giving prophylactic doxycycline for 4 days after a tick bite may prevent tick-borne relapsing fever caused by *Borrelia persica.*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 268

Lyme Disease *(Borrelia burgdorferi)*

Sanjeev K. Swami

Lyme disease is the most common vector-borne disease in the United States and is an important public health problem.

ETIOLOGY

Lyme disease is a zoonotic infection caused by the transmission of the spirochete *Borrelia burgdorferi* sensu lato (broad sense) to humans via the bite of an infected tick of the *Ixodes* genus. In North America, *B. burgdorferi* sensu stricto (strict sense) causes almost all cases; another species in the upper Midwestern United States, *Borrelia mayonii* (belonging to the group *B. burgdorferi* sensu lato), also causes Lyme disease, but the illness is slightly different, with more diffuse rashes and gastrointestinal symptoms. In Europe, the species *Borrelia afzelii* and *Borrelia garinii* also cause disease. The three major outer-surface proteins, called *OspA, OspB,* and *OspC* (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kDa, respectively), and the 41-kDa flagellar protein are important targets for the immune response. Differences in the molecular structure of the different species are associated with differences in the clinical manifestations of Lyme borreliosis in Europe and the United States. These differences include the higher incidence of radiculoneuritis in Europe.

TRANSMISSION

In the eastern and midwestern United States, the vector for Lyme disease is ***Ixodes scapularis***, the black-legged tick that is commonly known as the **deer tick**. It is responsible for most cases in the United States. The vector on the Pacific Coast is *Ixodes pacificus,* the western black-legged tick. *Ixodes* ticks have a 2-year, three-stage life cycle. The larvae hatch in the early summer and are usually uninfected with *B. burgdorferi.* The tick can become infected at any stage of its life cycle by feeding on a host, usually a small mammal such as the white-footed mouse *(Peromyscus leucopus)*, which is a natural reservoir for *B. burgdorferi.* The larvae overwinter and emerge the following spring in the nymphal stage, which is the stage of the tick most likely to transmit the infection. The nymphs molt to adults in the fall, and then adults spend the second winter attached to white-tailed deer *(Odocoileus virginianus)*. The females lay their eggs the following spring before they die, and the 2-year life cycle begins again.

Several factors are associated with increased risk for transmission of *B. burgdorferi* from ticks to humans. The proportion of infected ticks varies by geographic area and by the stage of the tick's life cycle. In endemic areas in the northeastern and midwestern United States, 15–25% of nymphal ticks and 35–50% of adult ticks are infected with *B. burgdorferi.* By contrast, *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi,* reducing the chance that these ticks will be infected. The risk for transmission of *B. burgdorferi* from infected *Ixodes* ticks is related to the duration of feeding. Experiments in animals show that infected nymphal ticks must feed for 36-48 hours and infected adults must feed for 48-72 hours before the risk for transmission of *B. burgdorferi* becomes substantial. If the tick is recognized and removed promptly, transmission of *B. burgdorferi* will not occur. *Most patients with Lyme disease do not remember the tick bite that transmitted the infection.*

The habitat of tick species that carry *B. burgdorferi* may be geographically expanding in the United States because of climate change. *I. scapularis* also transmits other microorganisms, namely *Anaplasma*

phagocytophilum and *Babesia microti,* as well as *Borrelia miyamotoi.* Simultaneous transmission can result in co-infections with these organisms and *B. burgdorferi.*

EPIDEMIOLOGY

Lyme disease has been reported in more than 50 countries, including forested areas of Asia; northwestern, central, and eastern Europe; and eastern and midwestern United States. In Europe, most cases occur in the Scandinavian countries and in central Europe, especially Germany, Austria, and Switzerland, whereas in the United States, 92% of cases occurred in 16 states in 2019: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and Wisconsin (Fig. 268.1).

In 2019, the most recent year for which U.S. data are available, more than 23,000 confirmed cases and more than 11,000 probable cases were reported. The 3-year averaged national incidence is estimated at 7.8 cases per 100,000 population, and in recent years the national incidence has ranged from a low of 7.0 cases per 100,000 (2012) to a high of 9.1 cases per 100,000 (2017). In endemic areas, the reported annual incidence ranges from 20 to 100 cases per 100,000 population, although this figure may be as high as 600 cases per 100,000 population in hyperendemic areas. The reported incidence of disease by age is bimodal. There is an initial peak among children age 5-14 followed by a second peak among adults 55-69. In the United States, Lyme disease is diagnosed in males slightly more often than in females. Early Lyme disease usually occurs from spring to early fall, corresponding to deer tick activity. Late disease (primarily arthritis) occurs year-round. Among adults, outdoor occupation and leisure activities are risk factors; for children, location of residence in an endemic area is the most important risk for infection.

Lyme disease is designated a nationally notifiable disease by the CDC and Council for State and Territorial Epidemiologists. Healthcare providers, hospitals, laboratories, and other parties are required by law to notify local health departments when a confirmed or probable case of Lyme disease occurs. The local health departments report cases to the state and territorial health departments; it is voluntary in turn for these authorities to report data to the CDC, and therefore the actual number of Lyme disease cases and incidence are likely underreported and underestimated. Lyme disease was the sixth most common notifiable disease reported to the CDC in 2019 (following *Chlamydia trachomatis,* gonorrhea, syphilis, campylobacteriosis, and salmonellosis).

PATHOLOGY AND PATHOGENESIS

Similar to other spirochetal infections, untreated Lyme disease is characterized by asymptomatic infection, clinical disease that can occur in stages, and a propensity for cutaneous and neurologic manifestations. The skin is the initial site of infection by *B. burgdorferi.* Disseminated Lyme disease results from the spread of spirochetes through the bloodstream to tissues throughout the body. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are the skin, central and peripheral nervous systems, joints, heart, and eyes. Because the organism can persist in tissues for prolonged periods, symptoms can appear very late after initial infection.

The symptoms of disseminated Lyme disease are a result of inflammation mediated by interleukin-1 and other lymphokines in response to the presence of the organism. It is likely that relatively few organisms actually invade the host, but cytokines serve to amplify the inflammatory response and lead to much tissue damage. Lyme disease is characterized by inflammatory lesions that contain both T and B lymphocytes, macrophages, plasma cells, and mast cells. The refractory symptoms of disseminated Lyme disease can have an immunogenetic basis. Persons with certain HLA-DR allotypes may be genetically predisposed to develop chronic Lyme arthritis. An autoinflammatory response in the synovium can result in clinical symptoms long after the bacteria have been killed by antibiotics.

CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease are divided into early and disseminated stages. Older nomenclature included early localized disease, early disseminated disease, and late disease; early disseminated and late disease have been combined into disseminated disease in the current nomenclature (Table 268.1). Untreated patients can progressively develop clinical symptoms of each stage of the disease, or they can present with disseminated disease without having had any symptoms of the early Lyme disease.

Early Disease

The first clinical manifestation of Lyme disease in many patients is **erythema migrans** (Fig. 268.2). Although it usually occurs 7-14 days after the bite, the onset of the rash has been reported from 3 to 30 days later. The initial lesion occurs at the site of the bite. The rash is generally either uniformly erythematous or a target lesion with central clearing; rarely, there are vesicular or necrotic areas

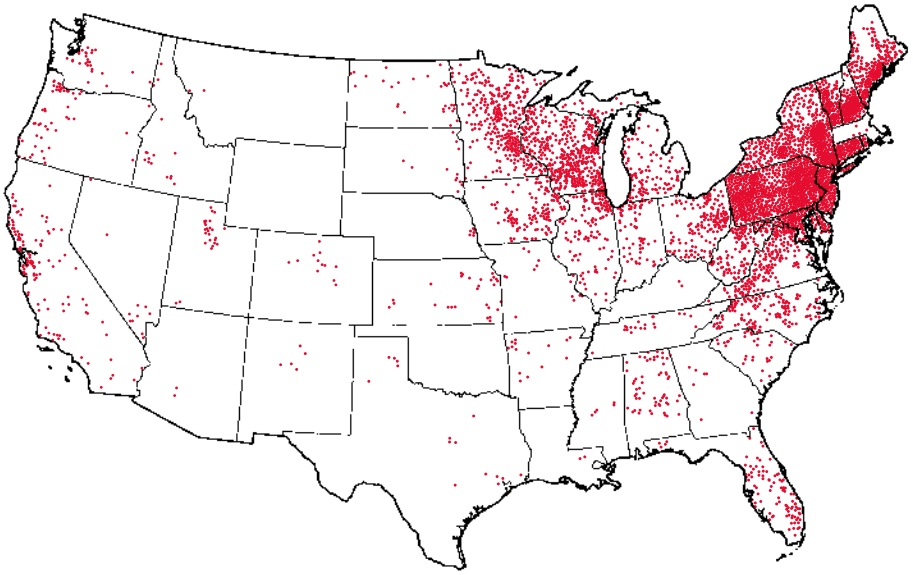

Fig. 268.1 The geographic distribution of Lyme disease cases in the United States. *(From the Centers for Disease Control and Prevention. Reported cases of Lyme disease—United States, 2019. Available at: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html)*

Table 268.1 Clinical Stages of Lyme Disease

DISEASE STAGE	TIMING AFTER TICK BITE	TYPICAL CLINICAL MANIFESTATIONS
Early localized	3-30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Disseminated	3-12 wk	Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease
Disseminated	>2 mo	Arthritis



Fig. 268.3 Multiple erythema migrans in early disseminated Lyme disease.



Fig. 268.2 Skin manifestations of Lyme borreliosis. **A,** Erythema migrans on the upper leg, showing central clearing. **B,** Erythema migrans of the arm showing "bull's-eye" appearance. *(A from Stanek G, Strle F. Lyme borreliosis. Lancet. 2003;362:1639–1647.)*

in the center of the rash. Occasionally the rash is itchy or painful, although usually it is asymptomatic. The lesion can occur anywhere on the body, but the most common locations are the axilla, periumbilical area, thigh, and groin. It is not unusual for the rash to occur on the neck, face, or hairline, especially in young children. Without treatment, the rash gradually expands (hence the name *migrans*) to an average diameter of 15 cm and typically remains present for 1-2 weeks. Erythema migrans may be associated with systemic features, including fever, myalgias, arthralgias, headache, or malaise; gastrointestinal symptoms are rare. Co-infection with *B. microti* or *A. phagocytophilum* during early infection with *B. burgdorferi* is associated with more severe systemic symptoms. **Co-infections** should be suspected with unusual features of Lyme disease, poor response to appropriate antibiotics, prolonged fever, or laboratory abnormalities that include anemia, leukopenia, thrombocytopenia, or elevated liver enzymes.

Disseminated Disease

In the United States, approximately 20% of patients with acute *B. burgdorferi* infection develop secondary (multiple) erythema migrans lesions, a common manifestation of disseminated Lyme disease, caused by hematogenous spread of the organisms to multiple skin sites (Fig. 268.3). The secondary lesions, which can develop several days or weeks after the first lesion, are usually smaller than the primary lesion and are often accompanied by more severe constitutional symptoms. The lesions may not have the classic appearance of erythema migrans; they may lack central clearing, appear oval in shape, or have irregular borders. The most common neurologic manifestations are **peripheral facial nerve palsy** and **meningitis**. Peripheral (or cranial) nerves other than the facial nerve may be affected, and patients can present with multiple concurrent nerve palsies. Lyme meningitis usually has an indolent onset with days to weeks of symptoms (longer than viral meningitis) that can include headache, neck pain and stiffness, and fatigue. Fever is variably present. Patients can present with both peripheral nerve palsy *and* meningitis, but typically they have either central nervous system or peripheral nervous system disease.

The clinical findings of papilledema, cranial neuropathy (especially cranial nerve VII), and erythema migrans, which are present individually or together in up to 90% of cases, help differentiate Lyme meningitis from viral meningitis, in which these findings are rarely present. The aseptic meningitis caused by Lyme disease can be accompanied by significant elevations of intracranial pressure, which can sometimes last weeks or even months. All the cranial nerves except the olfactory have been reported to be involved with Lyme disease, but the most common are VI and especially VII. In endemic areas, Lyme disease is the leading cause of peripheral facial nerve palsy. It is often the initial or the only manifestation of Lyme disease and is sometimes bilateral. The facial paralysis usually lasts 2-8 weeks and resolves completely in most cases. Radiculoneuritis and other peripheral neuropathies can occur but are more common in Europe.

Cardiac involvement occurs in 5–15% of disseminated Lyme disease (overall <1% of Lyme infections) and usually takes the form of **heart block**, which can be first, second, or third degree, and the rhythm can fluctuate rapidly. Rarely, myocardial dysfunction (myocarditis) can occur. Patients presenting with suspected or proven disseminated Lyme disease should have a careful cardiac examination, and electrocardiography should be strongly considered, especially if patients report chest pain, palpitations, or presyncopal symptoms. Lyme carditis is a treatable condition and is the only manifestation of Lyme disease that has been fatal.

Papilledema and uveitis are most common ocular conditions associated with Lyme disease; optic neuritis has also been reported.

Arthritis is the most common manifestation of disseminated Lyme disease and begins weeks to months (possibly years) after the initial infection. Lyme arthritis is classically a monoarticular, nonmigratory arthritis affecting the large joints. The knee is the

most commonly infected joint followed by the hip. Lyme arthritis can occasionally be oligoarticular or migratory. The hallmark of Lyme arthritis is joint swelling, which is a result of synovial effusion and sometimes synovial hypertrophy. The swollen joint may be only mildly symptomatic, or less often, it may be painful and tender, although patients usually do not experience the severe pain and systemic toxicity that are common with pyogenic arthritis. Micromotion tenderness is rare with Lyme arthritis. If untreated, the arthritis can last several weeks, resolve, and then be followed by recurrent attacks in the same or other joints.

Other manifestations of Lyme disease involving the central nervous system, sometimes termed *late neuroborreliosis,* are rarely reported in children. In adults, chronic encephalitis and polyneuritis have been attributed to Lyme disease. The term *Lyme encephalopathy* has been used to describe chronic encephalitis (demonstrable by objective measures), but other literature has also used this term in reference to memory loss and other cognitive sequelae after Lyme disease has been treated. At times, the vague and mistaken term *chronic Lyme disease* has been used to describe symptomatology in persons who might have never had well-documented infection with *B. burgdorferi* at all, have serologic evidence of prior infection but current symptoms not consistent with Lyme disease, or have persistent symptoms after having received appropriate antibiotic therapy. Prolonged treatment does not treat the chronic neuropsychiatric symptoms and at times has harmed the patient.

Some patients experience prolonged symptoms after treatment of early or disseminated Lyme disease; these symptoms frequently include fatigue, headaches, myalgias, arthralgias, and difficulty thinking. This phenomenon is termed **posttreatment Lyme disease syndrome**. The etiology for this process is unclear, but prolonged antibiotic treatment has not been shown to hasten recovery and has been associated with harm. Most patients have symptom resolution by 6 months without antibiotic therapy.

Congenital Lyme Disease

In endemic areas, infection can occur during pregnancy, and although congenital infection appears to be a rare event, there is no recognized congenital infection syndrome associated with Lyme disease. *B. burgdorferi* has been identified from several abortuses and from a few live-born children with congenital anomalies; however, the tissues in which the spirochete has been identified usually have not shown histologic evidence of inflammation. Severe skin and cardiac manifestations have been described in a few cases, but studies conducted in endemic areas have indicated that there is no difference in the prevalence of congenital malformations among the offspring of women with serum antibodies against *B. burgdorferi* and the offspring of those without such antibodies.

LABORATORY FINDINGS

Standard laboratory tests rarely are helpful in diagnosing Lyme disease because any associated laboratory abnormalities usually are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate (ESR) may be mildly elevated. Liver transaminases are occasionally mildly elevated. In Lyme arthritis, the white blood cell count in joint fluid can range from 25,000 to 100,000/mL, often with a preponderance of polymorphonuclear cells. A lower ESR (≤40) and C-reactive protein and a peripheral blood absolute neutrophil count of less than 10,000 may help to differentiate Lyme from septic arthritis. When meningitis is present, there usually is a low-grade pleocytosis with a lymphocytic and monocytic predominance. The cerebrospinal fluid (CSF) protein level may be elevated, but the glucose concentration usually is normal. Gram stain and routine bacterial cultures are negative. Imaging of the central nervous system (e.g., magnetic resonance imaging and single-photon emission computed tomography) occasionally reveals abnormalities, but there is no definitive pattern in Lyme disease. The main role of imaging is to exclude other diagnoses.

DIAGNOSIS

In the appropriate epidemiologic setting (endemic area, season), typical erythema migrans is pathognomonic. Occasionally, the diagnosis of erythema migrans may be difficult because the rash initially can be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite reaction, southern tick–associated rash illness, or cellulitis. The relatively rapid expansion of erythema migrans helps distinguish it from these other skin lesions. The other clinical manifestations of Lyme disease are less specific and may be confused with other conditions; the monoarticular or oligoarticular arthritis sometimes is confused with a septic joint or other causes of arthritis in children, such as juvenile idiopathic arthritis or rheumatic fever; the facial nerve palsy caused by Lyme disease is clinically indistinguishable from Bell palsy, although bilateral involvement is much more common with Lyme disease; Lyme meningitis generally occurs in the warmer months, the same period that enteroviral meningitis is prevalent. Therefore for all disease manifestations other than erythema migrans, it is recommended to have laboratory confirmation of infection with *B. burgdorferi.*

Although *B. burgdorferi* has been isolated from the blood, skin, CSF, myocardium, and synovium of patients with Lyme disease, the organism is difficult to isolate in culture (cultivation is largely relegated to research laboratories). Infection is usually identified by the detection of antibody in serum. Although some laboratories offer polymerase chain reaction as a diagnostic test for Lyme disease, its sensitivity is poor because of the low concentrations of bacteria in many sites, especially CSF. Other antigen-based tests, including a test for *B. burgdorferi* antigens in urine, are unreliable. Clinicians should be aware that some laboratories use alternative diagnostic tests and/or alternative interpretive criteria that are not evidence based, leading to a false diagnosis of Lyme disease. The CDC and the Food and Drug Administration recommend against using these tests.

Serology

After the transmission of *B. burgdorferi* from a tick bite, specific immunoglobulin (Ig) M antibodies appear first, usually within 2 weeks, peak at 6-8 weeks, and subsequently decline. Sometimes a prolonged or recurrent elevation of IgM antibodies occurs despite effective antimicrobial treatment. Elevated IgM levels after 6-8 weeks are often false positives. Specific IgG antibodies usually appear between 2 and 6 weeks, peak after 4-6 months, and can remain elevated for years, particularly in patients with arthritis. The antibody response to *B. burgdorferi* may be blunted in patients with early Lyme disease who are treated promptly with an effective antimicrobial agent. *Serodiagnosis during the first 4 weeks of infection is not sensitive and may need to be repeated.*

Historically, the most common method used to detect IgG and IgM antibodies has been the enzyme-linked immunosorbent assay **(ELISA)**. *This method is sensitive but not optimally specific*. The ELISA sometimes produces false-positive results because of antibodies that cross react with other spirochetal infections (e.g., *B. miyamotoi,* syphilis, leptospirosis, or relapsing fever), or certain viral infections (e.g., Epstein-Barr virus), or that occur in certain autoimmune diseases (e.g., systemic lupus erythematosus). The positive predictive value of the ELISA result depends primarily on the plausibility that the patient has Lyme disease based on the clinical and epidemiologic history and the physical examination **(the pretest probability)**. For patients who have been in endemic areas with opportunities for *Ixodes* tick exposure and who have typical clinical manifestations of Lyme disease, the pretest probability is high, and positive ELISA results are usually true positives. For patients who are from nonendemic areas and/or who have little risk for *Ixodes* tick exposures and/or have nonspecific symptoms (low pretest probability), rates of false-positive results are high. Infection with *B. miyamotoi* may cause false-positive ELISA tests for Lyme disease. This syndrome of relapsing fever, headache, and myalgia

but no rash with neutropenia or thrombocytopenia is uncommon in Lyme disease.

Western immunoblotting is well-standardized, and there are accepted criteria for interpretation. Five of 10 IgG bands and 2 of 3 IgM bands are considered reactive. The Western blot is not as sensitive as ELISA, especially in early infection, but is highly specific. Any positive or equivocal ELISA can be confirmed with Western blotting. The CDC recommends using IgM and IgG Western blot confirmation when symptoms have been present ≤30 days and IgG only when symptoms have been present longer than 30 days.

Two-tier testing is the recommended laboratory evaluation of most cases of Lyme disease and is associated with a high degree of sensitivity and specificity when used appropriately. Two-tier assays using serial ELISAs have been developed that have similar or better sensitivity and specificity when compared with ELISA followed by Western blot. The serial ELISA methodology can have improved turn-around time and has two quantitative tests rather than a quantitative test followed by a test that requires interpretation. Stand-alone ELISAs have also been developed that have similar sensitivity and specificity when compared with two-tier testing.

Clinicians should be aware that Lyme disease might not be the cause of a patient's symptoms despite the presence of antibodies to *B. burgdorferi*. The test result may be falsely positive (as described for ELISA), or the patient might have been infected previously. Antibodies to *B. burgdorferi* that develop with infection can persist for many years despite adequate treatment and clinical cure of the disease. In addition, because some people who become infected with *B. burgdorferi* are asymptomatic, the background rate of seropositivity among patients who have never had clinically apparent Lyme disease may be substantial in endemic areas. Finally, because antibodies against *B. burgdorferi* persist after successful treatment, there is no reason to obtain follow-up serologic tests.

TREATMENT

Table 268.2 provides treatment recommendations. Most patients can be treated with oral antibiotics. Young children are generally treated with amoxicillin. Doxycycline has the advantages of good central nervous system penetration and activity against *A. phagocytophilum,* which may be transmitted at the same time as *B. burgdorferi* in certain geographic areas. Historically, children <8 years were not treated with doxycycline because of the risk of staining of the permanent teeth. Data from the CDC have shown that this is not a concern for treatment courses <2 weeks. Doxycycline oral solution is still challenging to find, so most younger children are prescribed amoxicillin. There are no data that show a difference in efficacy between amoxicillin and doxycycline for the treatment of Lyme disease. Patients who are treated with doxycycline should be alerted to the risk for developing photosensitivity in sun-exposed areas while taking the medication; thus long sleeves, long pants, and a hat are recommended for activities in direct sunlight. The only oral cephalosporin proved to be effective for the treatment of Lyme disease is cefuroxime axetil, which is an alternative for persons who cannot take doxycycline or who are allergic to penicillin. There is no reported resistance of *B. burgdorferi* to these antibiotics. Macrolide antibiotics, including azithromycin, appear to have limited activity and are only recommended for patients allergic to all of the other active medications.

Parenteral therapy is usually recommended for patients with higher degrees of heart block or central nervous system involvement, although oral therapy for meningitis is also considered acceptable for ambulatory patients. Patients with arthritis that fails to resolve after an initial course of oral therapy can be retreated with an oral regimen or can receive intravenous antibiotic therapy. Ceftriaxone is favored because of its excellent anti-*Borrelia* activity, tolerability, and once-daily dosing regimen, which can usually be done on an outpatient basis.

Table 268.2 Recommended Treatment of Lyme Disease

DRUG	PEDIATRIC DOSING
Amoxicillin	50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)
Doxycycline	4.4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)
Cefuroxime axetil	30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)
Ceftriaxone (IV)*,†	50-75 mg/kg/day once daily (max: 2,000 mg/day)
Azithromycin‡	10 mg/kg/day once daily ×7 days
RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION	
Erythema migrans	Doxycycline ×10 days Amoxicillin ×14 days Cefuroxime ×14 days
Meningitis, radiculopathy	Doxycycline ×14-21 days or Ceftriaxone ×14 days (14-21 for hospitalized patients)
Cranial nerve palsy§	Doxycycline ×14-21 days
Cardiac disease	Oral regimen or ceftriaxone 14-21 days (see text for specifics)
Arthritis	Oral regimen 28 days
Persistent or recurrent arthritis after initial treatment	Oral regimen ×28 days or Ceftriaxone 14-28 days
Borrelial lymphocytoma	Doxycycline, amoxicillin, cefuroxime 14 days

*Penicillin G is an alternative parenteral agent but requires more frequent dosing.
†Doses of 100 mg/kg/day should be used for meningitis.
‡For those unable to take amoxicillin or doxycycline.
§Treatment is to prevent late disease, not to treat the cranial palsy; avoid corticosteroids.

Peripheral facial nerve palsy can be treated using an oral antibiotic. Experts are divided on whether every patient with Lyme-associated facial palsy needs a CSF analysis, but clinicians should consider lumbar puncture for patients with significant headache, neck pain or stiffness, or papilledema.

Patients with symptomatic cardiac disease, second- or third-degree heart block, or significantly prolonged PR interval should be hospitalized and monitored closely. These patients should receive a parenteral antibiotic for their initial treatment. Patients with first-degree heart block can be treated with an oral antibiotic, and patients with high degrees of heart block can be transitioned to oral treatment as their heart block resolves.

Some patients develop a Jarisch-Herxheimer reaction soon after treatment is initiated; this results from lysis of the *Borrelia*. The manifestations of this reaction are low-grade fever and achiness. These symptoms resolve spontaneously within 24-48 hours, and administration of nonsteroidal antiinflammatory drugs often is beneficial. Nonsteroidal antiinflammatory drugs also may be useful in treating symptoms of early Lyme disease and of Lyme arthritis. *Co-infections with other pathogens transmitted by Ixodes ticks should be treated according to standard recommendations.*

There is no clear evidence that posttreatment Lyme disease syndrome is related to persistence of the organism. Studies in adults have

Table 268.3 Personal Prevention Measures

BEFORE VENTURING OUTSIDE	DURING AND/OR AFTER EXPOSURE TO TICK HABITAT†
Personal prevention measures*	Conduct a thorough tick check of extremities, torso, and areas where ticks may be visually obscured (e.g., axilla, nape of neck, hairline, in and around ears, umbilicus, groin, popliteal fossa)
Avoid risky habitats	Bathe or shower within 2 hr
Wear light-colored clothing	Dry clothes on high heat for at least 10 min; if not possible, wash clothes in hot water
Wear long sleeves and pants	
Tuck pants into socks or footwear	
Wear permethrin-treated clothing	
Use an EPA-approved repellent or insecticide as per manufacturer's instructions	***If an attached tick is detected***
	Remove properly and clean bite area
DEET	https://www.cdc.gov/lyme/removal/index.html
Picaridin	Tip: Store tick (e.g., in sealed container/plastic bag, wrapped in clear tape, or taped to a piece of paper). Label with date and likely geographic location of exposure.
IR3535	See clinician and show tick if concerned that it is an *Ixodes* spp. and has fed at least 36 hr.
Oil of lemon eucalyptus (OLE)	Monitor health for symptoms of Lyme disease and other tick-borne diseases
p-Methane-3,8-diol (PMD)	
2-undecanone	
Permethrin (for application to clothing and gear only)	

*Tip: Have handy a fine-tipped tweezers, tick storage container, and hand sanitizer.
†Continue to conduct a tick check whenever possible to detect and remove feeding ticks as soon as possible.
DEET, N,N-Diethyl-meta-toluamide; EPA, Environmental Protection Agency.
From Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis.* 2021;72(1):e1–e48, Table 5, p. e13.

not shown benefit with prolonged or repeated treatment with oral or parenteral antibiotics.

PROGNOSIS

There is a widespread misconception that Lyme disease is difficult to cure and that chronic symptoms and clinical recurrences are common. The most likely reason for apparent treatment failure is an incorrect diagnosis of Lyme disease.

The prognosis for children treated for Lyme disease is excellent. Children treated for erythema migrans rarely develop symptoms of late Lyme disease. The long-term prognosis for patients who are treated beginning in the later stages of Lyme disease also is excellent. Although chronic and recurrent arthritis may occur, especially among patients with certain human leukocyte antigen allotypes (an autoimmune process), most children who are treated for Lyme arthritis are cured and have no sequelae. Although there are rare reports of adults who have developed late neuroborreliosis, usually among persons with Lyme disease in whom treatment was delayed for months or years, similar cases in children are rare.

Table 268.4 Management of a Suspected *Ixodes* Tick Bite in the United States

DO	DO NOT
1. Remove tick with clean fine-tipped tweezers (or other comparable device).	1. Do not use other nonmechanical methods for tick removal.
2. Identify tick. Send to a laboratory, refer to an online resource.	2. Do not test tick for pathogens (e.g., send for PCR).
3. Determine if tick meets high-risk criteria. a. Identified as *Ixodes* vector species b. Bite occurred in a highly endemic area c. Attached for ≥36 hr	3. Do not initiate prophylaxis in any other scenario.
Consider initiating prophylaxis if a, b, and c are met AND it is within 72 hr of tick removal. See dosing in the footnote*.	

*Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children.
PCR, Polymerase chain reaction.
From Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis.* 2021;72(1):e1–e48, Table 6, p. e13.

PREVENTION

The best way to avoid Lyme disease is to avoid tick-infested areas (Table 268.3). Children should be examined for deer ticks after known or potential exposure (although many people are not able to identify the species or the stage of the tick). If a tick attachment is noted, the tick should be grasped at the mouthparts with a forceps or tweezers; if these are not available, the tick should be covered with a tissue (Table 268.4). The recommended method of tick removal is to pull directly outward without twisting; infection is usually preventable if the tick is removed before 36 hours of attachment; at this time the ticks are flat and nonengorged (Fig. 268.4).

The overall risk for acquiring Lyme disease after a tick bite is low (1–3%) in most endemic areas. If the tick is engorged and present for >72 hours (a high-risk tick bite), the risk of infection may increase to 25% in *hyperendemic* areas. Patients and families should be advised to watch the area for development of erythema migrans and to seek medical attention if the rash or constitutional symptoms occur. If infection develops, early treatment of the infection is highly effective. Prophylaxis after a high-risk tick bite with a single dose of oral doxycycline in adults (200 mg) or 4.4 mg/kg in children is effective in reducing the risk of Lyme disease. The routine testing of ticks that have been removed from humans for evidence of *B. burgdorferi* is not recommended because the value of a positive test result for predicting infection in the human host is unknown.

Personal protective measures that may be effective in reducing the chance of tick bites include wearing protective clothing (long pants tucked into socks, long-sleeved shirts) when entering tick-infested areas, checking for and promptly removing ticks, and using tick repellents such as *N,N*-diethyl-3-methylbenzamide (DEET) (see Table 268.3). This chemical can safely be used on pants, socks, and shoes; care must be used with heavy or repeated application on skin,

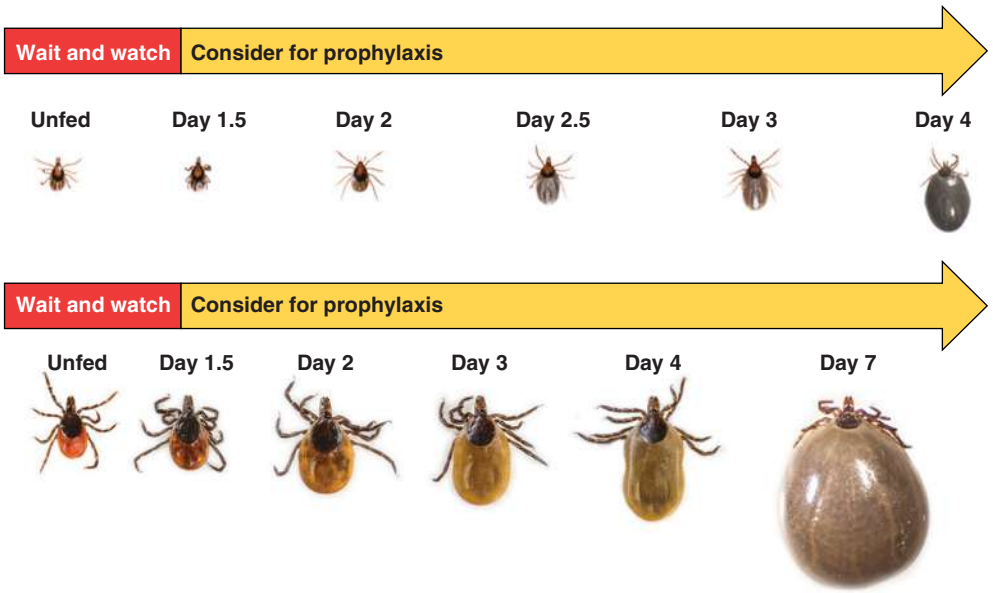

Fig. 268.4 Relative sizes of engorging nymphal and adult female *Ixodes scapularis* (black-legged = deer tick) as a function of time spent feeding (= attachment time). Transmission of *Borrelia burgdorferi* requires 36-48 hr of feeding, and therefore antibiotic prophylaxis is recommended only if the tick has been attached for at least 36 hr, or 1.5 days. By itself, duration of feeding is insufficient for recommending antibiotic prophylaxis. *(Top)* Nymphs (Feeding time: Unfed = 0 hr; Day 1.5 = 36 hr; Day 2 = 48 hr; Day 2.5 = 60 hr; Day 3 = 72 hr; Day 4 = 96 hr). *(Bottom)* Adult females over the same period. Unfed nymph and adult female are the sizes of poppy and sesame seeds, respectively. Not actual size. *(Courtesy of URI TickEncounter Resource Center, TickEncounter.org; From Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America [IDSA], American Academy of Neurology [AAN], and American College of Rheumatology [ACR]: 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. Clin Infect Dis. 2021;72[1]:e1–e48, Fig. 6.)*

particularly in infants, because of the risk of systemic absorption and toxicity. Permethrin treatment of clothing is also an effective prevention strategy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 9

Mycoplasmal Infections

Chapter 269

Mycoplasma pneumoniae

Asuncion Mejias and Octavio Ramilo

Among the few *Mycoplasma* species isolated from the human respiratory tract, *Mycoplasma pneumoniae* remains the most common species causing respiratory infections in school-age children and young adults and is associated with a variety of clinical manifestations.

THE ORGANISM

Mycoplasmas are the smallest self-replicating prokaryotes known to cause disease in humans. Their size of 150-250 nm is more on the order of viruses than bacteria. *M. pneumoniae* is a fastidious double-stranded DNA bacterium that is distinguished by a small genome (~800,000 base pairs) and a long doubling time, which makes culturing it a slow process (5-20 days) compared to other bacteria. *M. pneumoniae* isolates can be classified in two major genetic groups (subtypes 1 and 2) based on the P1 adhesion protein. Distinguishing these two subtypes is important for epidemiologic purposes. Like other mycoplasmas, *M. pneumoniae* is distinguished by the complete absence of a cell wall, resulting in (1) their dependence on host cells for obtaining essential nutrients, (2) their intrinsic resistance to β-lactam agents, and (3) their pleomorphic shape and lack of visibility on Gram staining.

EPIDEMIOLOGY

M. pneumoniae infections occur worldwide and throughout the year. This organism is a frequent cause of community-acquired pneumonia (CAP) in children >5 years of age and adults, accounting for ~20% of all CAP in middle school and high school children and up to 50% of CAP in college students and military recruits. The proportion of cases increases according to age, as recently shown in a large population-based study of CAP conducted in the United States (3% in <5 years, 17% in 5-9 years, and 24% in 10-17 years).

In contrast to the acute, short-lived epidemics associated with some respiratory viruses, *M. pneumoniae* infection occurs endemically worldwide. Epidemic outbreaks of variable intensity occur every few years and are likely related to the alternative circulation of the two *M. pneumoniae* subtypes. Transmission occurs through the respiratory route by large droplet spread during close contact with a symptomatic person. Community outbreaks have been described in closed settings (colleges, boarding schools, military bases) and can spread largely through school contacts. Attack rates within families are high, with transmission rates of 40–80% for household adult and children contacts, respectively. In contrast to many other respiratory infections, the incubation period is 2-3 weeks; hence, the course of infection in a specific population (family) may last several weeks.

The occurrence of mycoplasma illnesses is related, in part, to age and preexposure immunity. Overt illness is less common before 3 years of age but can occur. Children younger than 5 years of age appear to have milder illnesses associated with upper respiratory tract involvement, vomiting, and diarrhea. Immunity after infection is not long-lasting, as evidenced by the frequency of reinfections over time. Other pathogens

are frequently co-detected in children with *M. pneumoniae,* especially in those younger than 2 years of age, where viral co-infections have been identified in up to 30% of cases. *Asymptomatic carriage* after infection can last up to 4 months despite antibiotic therapy and may contribute to prolonged outbreaks. Children are often the reservoir from whom mycoplasma spreads. In the clinical setting, there are no available tools yet to differentiate carriage vs infection.

PATHOGENESIS

The pathogenicity of *M. pneumoniae* is dependent on its extracellular attachment and the initiation of the host cell immune response. The mechanisms by which *M. pneumoniae* causes disease include (1) direct bacterial invasion that initiates in the cells of the ciliated respiratory epithelium, the target cells of *M. pneumoniae* infection; (2) toxin mediated through the production of the adenosine diphosphate–ribosylating and vacuolating toxin termed *community-acquired respiratory distress syndrome* (CARDS), an exotoxin that may damage the respiratory tract and has been associated with more severe or even fatal disease; and (3) indirect immune-mediated effects, by altering antigens in the cell surface and inducing the production of autoantibodies.

The organism is an elongated snakelike structure with a one-end organelle, which mediates the attachment to sialic acid receptors in the cilia through a complex set of adhesion transmembrane proteins (P1, P30, proteins B and C, P116, and HMW1-3). Virulent organisms attach to ciliated respiratory epithelial cell surfaces located in the bronchi, bronchioles, alveoli, and possibly upper respiratory tract and burrow down between cells, resulting in ciliostasis and eventual sloughing of the cells. This bacterium is capable of forming biofilms, with strain-specific phenotypic differences, which hinder antibiotic penetration and recognition by the immune system.

Once *M. pneumoniae* reaches the lower respiratory tract, it promotes the polyclonal activation of B lymphocytes and $CD4^+$ T cells and amplifies the immune response with the production of various proinflammatory and antiinflammatory cytokines and chemokines, such as tumor necrosis factor-α, interleukin (IL)-8, IL-1β, Il-6, and IL-10.

Although it is well documented that specific cell-mediated immunity and antibody titers against *M. pneumoniae* increase with age (and therefore probably follow repeated infections), the immune mechanisms that protect against or clear the infection are not well defined. In humans, nasal IgA antibodies correlated with protection after experimental challenge. A distinct aspect of *M. pneumoniae* is its ability to induce the production of cold agglutinins (IgM antibodies) directed against the I antigen on the erythrocyte's surface. Even though antibody responses do not confer complete protection against reinfections, the importance of a robust humoral response is apparent, because patients with congenital antibody deficiencies, such as those with hypogammaglobulinemia, can develop severe and prolonged disease and have a higher risk of extrapulmonary manifestations. In children with sickle cell disease or sickle-related hemoglobinopathies, *M. pneumoniae* is a common infectious trigger of acute chest syndrome. These children and also children with Down syndrome can develop severe *Mycoplasma* pneumonia. On the other hand, *M. pneumoniae* does not seem to be a common infectious agent in patients with AIDS.

M. pneumoniae has been detected by polymerase chain reaction (PCR) in many nonrespiratory sites, including blood, pleural fluid, cerebrospinal fluid (CSF), and synovial fluid. The mechanisms of extrapulmonary disease associated with *M. pneumoniae* are unclear and appear to be different according to the duration of symptoms at the time of presentation: direct invasion vs immune-mediated.

CLINICAL MANIFESTATIONS

M. pneumoniae is a frequent cause of upper and lower respiratory tract infections in children and adolescents. The clinical manifestations of *M. pneumoniae* can be divided into respiratory (more common) and extrapulmonary (less common).

Respiratory Tract Disease

Tracheobronchitis and atypical pneumonia are the most commonly recognized clinical syndromes associated with *M. pneumoniae*. This agent is responsible for up to 20% of all cases of CAP. The clinical manifestations of *M. pneumoniae* pneumonia evolve according to the stage of the disease. The onset is usually characterized by gradual development of headache, malaise, fever, and sore throat, followed by progression of lower respiratory symptoms, including hoarseness and nonproductive cough. The gradual onset in children with atypical pneumonia is in contrast to the sudden onset of lobar pneumonia. Coryza and gastrointestinal manifestations are unusual and suggest a viral etiology, if present. Approximately 10% of children will develop a cutaneous maculopapular rash. Although the clinical course in untreated patients is variable, cough, the clinical hallmark of *M. pneumoniae* infection, usually worsens during the first week of illness. Symptoms generally resolve within 2 weeks, although cough can last up to 4 weeks and may be accompanied by wheezing.

Chest examination may be unrevealing, even in patients with severe cough. There may be no auscultative or percussive findings or only minimum dry rales. Clinical findings are often less severe than suggested by the chest radiograph, explaining why the term "walking pneumonia" is often used to describe CAP caused by *M. pneumoniae*. Radiographic findings are variable and nonspecific, not allowing differentiation from viral or bacterial pathogens. Bilateral diffuse infiltrates, lobar pneumonia, or hilar lymphadenopathy can occur in up to 30% of patients. Although unusual, large pleural effusions associated with lobar infiltrates and necrotizing pneumonia have been described in patients with immunodeficiency, Down syndrome, chronic cardiopulmonary disease, and sickle cell disease. The white blood cell and differential counts are usually normal, whereas the erythrocyte sedimentation rate and C-reactive protein are often elevated. Appropriate antibiotics shorten the duration of illness but do not reliably eradicate the organism from the respiratory tract.

Other respiratory illnesses occasionally caused by *M. pneumoniae* include undifferentiated upper respiratory tract infections; intractable, nonproductive cough; pharyngitis (usually without marked cervical lymphadenopathy); sinusitis; croup; and bronchiolitis. *M. pneumoniae* is a common trigger of wheezing in asthmatic children and can cause chronic colonization in the airways, resulting in lung dysfunction in adolescent and adult asthmatic patients. Otitis media and bullous myringitis, which also occur with other viral and bacterial infections, have been described but are rare, and their absence should not exclude the diagnosis of *M. pneumoniae*.

Extrapulmonary Disease

Despite the reportedly rare isolation of *M. pneumoniae* from nonrespiratory sites, the improved sensitivity of PCR for *M. pneumoniae* DNA detection has led to increasing identification of this bacterium in nonrespiratory sites, particularly the central nervous system (CNS). Patients with or without respiratory symptoms can have involvement of the skin, CNS, blood, heart, gastrointestinal tract, and joints. Extrapulmonary manifestations have been documented in 11–26% of children with *M. pneumoniae* infection and include:

1. ***CNS disease:*** Occurs in 0.1% of all patients with *M. pneumoniae* infection and in 7% of those requiring hospitalization. Manifestations include encephalitis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, cerebellar ataxia, aseptic meningitis, Guillain-Barré syndrome, Bell palsy, and peripheral neuropathy. CNS disease manifestations occur 3-23 days (mean: 10 days) after onset of respiratory illness but may not be preceded by any signs of respiratory infection in up to 20% of cases. Studies in children suggest that there are two pathogenic mechanisms for *M. pneumoniae*–associated neurologic disease: the first pattern is characterized by almost absent or no prodromal respiratory symptoms (<7 days) and nonreactive IgM responses. On the other hand, the second pattern is characterized by the presence of respiratory symptoms (most commonly cough) for ≥7 days and reactive IgM in acute serum. In the first group *M. pneumoniae* is usually identified in CSF by PCR but not in the respiratory tract, whereas in children presenting with ≥7 days of respiratory symptoms, the opposite is true. These studies suggest that encephalitis occurring more than 7 days after onset of prodromal symptoms is more likely to be caused by an autoimmune response to *M. pneumoniae,* whereas its occurrence early in the course of the disease may be associated with direct bacterial invasion of the CNS. Involvement of the brainstem can result in severe

dystonia and movement disorders. The CSF may be normal or have mild mononuclear pleocytosis and/or increased CSF protein concentrations with normal glucose. Diagnosis is confirmed with positive CSF PCR, positive PCR from a throat swab, or demonstration of seroconversion. Findings on MRI include focal ischemic changes, ventriculomegaly, diffuse edema, or multifocal white matter inflammatory lesions consistent with postinfectious ADEM. Long-term sequelae have been reported in 23–64% of cases.

2. ***Mucocutaneous disease:*** Up to 25% of children with *M. pneumoniae* infections can have associated skin and mucosal exanthems, most notably maculopapular rashes, urticaria, and *Mycoplasma*-induced rash and mucositis syndrome (MIRM) or Stevens-Johnson syndrome (SJS). Gianotti-Crosti syndrome and erythema nodosum are also associated with *M. pneumoniae* infections. Approximately 10% of children with *M. pneumoniae* CAP will exhibit a maculopapular rash. *Mycoplasma*-induced rash and mucositis usually develop 3-21 days after initial respiratory symptoms, last less than 14 days, and are rarely associated with severe complications (Figs. 269.1 and 269.2). *M. pneumoniae* may also produce an isolated oral mucositis in absence of a rash.
3. ***Hematologic abnormalities:*** Include mild degrees of hemolysis with a positive Coombs test and minor reticulocytosis 2-3 weeks after the onset of illness. Severe hemolysis is associated with high titers of cold hemagglutinins (≥1:512) and occurs rarely. Thrombocytopenia, aplastic anemia, hemophagocytic syndrome, and coagulation defects occur occasionally.



Fig. 269.1 Lip changes found in *Mycoplasma pneumoniae*–associated mucositis.



Fig. 269.2 Classic skin lesions found in *Mycoplasma pneumoniae*–associated rash.

4. ***Musculoskeletal:*** Arthritis appears to be less common in children than in adults, but monoarthritis, polyarthritis, and migratory arthritis have been described. Rhabdomyolysis has also been documented, often associated with other organ system manifestations.
5. ***Other conditions,*** such as mild hepatitis, gastroenteritis, pancreatitis, acute glomerulonephritis, iritis or uveitis, and cardiac complications (pericarditis, myocarditis, and rheumatic fever–like syndrome, most commonly seen in adults) are also described. Fatal *M. pneumoniae* infections are rare.

DIAGNOSIS

No specific clinical, epidemiologic, or laboratory parameters allow for a definite diagnosis of *M. pneumoniae* infection. Nevertheless, pneumonia in school-age children and young adults with a gradual onset and cough as prominent findings suggests *M. pneumoniae* infection. The best method for diagnosis is a combination of PCR from respiratory samples and serology (acute and convalescent), as *M. pneumoniae* colonizes the airway and has been identified in 17–25% of asymptomatic children.

Cultures on special media (SP4 agar media) of the throat or sputum might demonstrate the classic *M. pneumoniae* "mulberry" colonies, but growth generally requires incubation for more than 2-3 weeks. The fastidious nutritional requirements of *Mycoplasma* make cultures slow and impractical, and few laboratories maintain the capability of culturing *M. pneumoniae*.

Serologic tests (immunofluorescence tests, enzyme-linked immune assays [EIAs]) to detect serum immunoglobulin (Ig) M, IgA, and IgG antibodies against *M. pneumoniae* are commercially available. IgM antibodies have a high rate of false-positive and false-negative results. In most cases, IgM antibodies are not detected within the first week after symptom onset or in children with recurrent infections and may be positive for up to 6-12 months after infection, or even years, and thus may not indicate acute infection. A fourfold or greater increase in IgG antibody titers against *M. pneumoniae* between acute and convalescent sera obtained 2-4 weeks apart is diagnostic. Complement fixation assays are less sensitive and specific than EIA or immunofluorescent assays.

Cold hemagglutinins (cold-reacting antibodies [IgM] against red blood cells) can be detected in approximately 50% of patients with *M. pneumoniae* pneumonia. These antibodies are nonspecific, especially at titers <1:64, as modest increases in cold hemagglutinins can be observed in other viral infections. Cold agglutinin antibodies should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available.

Nucleic acid amplification test (NAATs) for *M. pneumoniae* have replaced other diagnostic tests. PCR of a nasopharyngeal or throat swab (the combination of both increases sensitivity) for *M. pneumoniae* genomic DNA carries a sensitivity and a specificity of 80% to >97%. Different primers have been used to identify gene sequences of the P1 cytoadhesion protein or the ribosomal (r) 16S RNA. PCR allows a more rapid diagnosis in acutely ill patients and can be positive earlier in the course of infection than serologic tests. Identification of *M. pneumoniae* by PCR (or culture) from a patient with compatible clinical manifestations suggests causation.

The diagnosis of extrapulmonary disease associated with *M. pneumoniae* is challenging. Although *M. pneumoniae* has been identified by PCR in the CSF of children with encephalitis, there are currently no reliable tests for the diagnosis of CNS or other nonrespiratory sites associated with *M. pneumoniae*. Because the extrapulmonary manifestations of *M. pneumoniae* may have an immunologic base, measuring acute and convalescent IgM and IgG antibody levels is advisable.

TREATMENT

M. pneumoniae illness is usually mild, and most cases of pneumonia can be managed without the need for hospitalization. Because mycoplasmas lack a cell wall, they are inherently resistant to β-lactam agents that act by inhibiting the cell wall synthesis. In addition, drugs from other classes, such as trimethoprim, rifampin, or linezolid, are inactive against *M. pneumoniae*. Studies regarding the effectiveness of antimicrobial therapy for *M. pneumoniae* infections in children are contradictory. Nevertheless, empiric treatment is often initiated in hospitalized children with CAP or severe extrapulmonary manifestations based on clinical suspicion because of the difficulty of a definitive diagnosis.

Antimicrobial Therapy

M. pneumoniae is typically sensitive to macrolides (erythromycin, clarithromycin, azithromycin), tetracyclines, and quinolones in vitro. Treatment of *Mycoplasma* does not assure eradication. Data from observational studies showed that macrolide treatment of children with *M. pneumoniae* CAP shortened the course of illness. Treatment may be more effective when started within 3-4 days of illness onset. Although macrolides do not have bactericidal activity, they are preferred in children younger than 8 years of age. Two multicenter studies of pediatric CAP demonstrated comparable clinical and bacteriologic success rates between erythromycin and clarithromycin or azithromycin. However, the newer macrolides were better tolerated. The recommended treatment is **clarithromycin (15 mg/kg/day divided into two doses PO for 10 days; maximum daily dose 1 g) or azithromycin (10 mg/kg PO once on day 1 [maximum dose 500 mg] and 5 mg/kg once daily [maximum dose 250 mg] PO on days 2-5)**. Doxycycline (2-4 mg/kg/day PO twice a day for 7 days, maximum daily dose 200 mg) in children of all ages and fluoroquinolones such as levofloxacin (10 mg/kg per dose twice a day in children <5 years; 10 mg/kg/day once a day in children ≥5 years—maximum daily dose 750 mg—for 7-10 days) are effective but have higher minimum inhibitory concentrations (MICs) compared with macrolides and currently are not recommended as a first-line therapy in children.

Macrolide-resistant *M. pneumoniae* infections should be suspected in patients with severe infections not responding to macrolide therapy within the first 48 hours of treatment, especially if they have a history of exposure to macrolides. Macrolide-resistant *M. pneumoniae* strains have been reported in Asia (70–90% in Japan and China), Europe (with great variability from country to country: 0% in the Netherlands vs 26% in Italy), and Israel. In the United States and Canada, the rates of resistance have varied from 2.8% to 13% of cases. The clinical significance of macrolide-resistant infections has not been completely elucidated. However, if macrolide-resistant *M. pneumoniae* is suspected, switching to a nonmacrolide antimicrobial regimen such as doxycycline or levofloxacin might be prudent.

Adjunctive Therapy

There is no evidence that treatment of upper respiratory tract or nonrespiratory tract disease with antimicrobial agents alters the course of illness. However, patients with severe manifestations of extrapulmonary disease may benefit from antimicrobial treatment because direct involvement of the bacterium cannot be excluded. Oftentimes antibiotics are administered in combination with immunomodulatory therapy. In this regard, corticosteroids with or without intravenous immunoglobulin are the most commonly used agents for managing severe *M. pneumoniae* extrapulmonary manifestations, particularly for patients with CNS involvement or rash and mucositis. Although definitive data are lacking, case studies suggest the associated clinical benefit of steroids in the management of severe lung disease, SJS, and hemolytic anemia.

PREVENTION

Trials with inactivated and live attenuated vaccines for *M. pneumoniae* have been conducted with disappointing results. In hospitalized patients, standard and droplet precautions are recommended for the duration of symptoms. It is important to emphasize that *Mycoplasma* infection remains contagious as long as cough persists and despite successful antibiotic therapy. Prophylaxis with tetracyclines or azithromycin substantially reduces the secondary attack rates in institutional outbreaks and family close contacts. Antimicrobial prophylaxis is not recommended routinely; however, it can be considered in patients at high risk for severe disease, such as children with sickle cell disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 270

Genital Mycoplasmas (*Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma urealyticum*)

María I. Sánchez Códez and Asuncion Mejias

ETIOLOGY

Mycoplasma species are small pleomorphic bacteria that typically lack a cell wall and are bound by a cell membrane. Many of the biologic properties of mycoplasmas are in fact the result of the absence of a rigid cell wall, including resistance to β-lactam antibiotics. These ubiquitous organisms are difficult to cultivate using routine media and belong to the family Mycoplasmataceae in the class Mollicutes and represent the smallest self-replicating organisms known to date. The entire genome of many of the *Mycoplasma* species is among the smallest of the prokaryotic genomes. The family Mycoplasmataceae is composed of two genera responsible for human infection: *Mycoplasma* and *Ureaplasma.* Of those, *Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma* spp., which include *Ureaplasma urealyticum* (biovar 2) and *Ureaplasma parvum* (biovar 1), are considered human urogenital pathogens and are reviewed in this chapter. The main feature that distinguishes *Ureaplasma* spp. from *Mycoplasma* spp. is the ability of the former to hydrolyze urea for energy production.

Genital mycoplasmas are often associated with sexually transmitted infections such as cervicitis and nongonococcal urethritis (NGU) or with puerperal infections such as endometritis. *M. hominis* and *Ureaplasma* spp. commonly colonize the female genital tract and can cause chorioamnionitis, colonization of neonates, and perinatal infections. The role of *M. genitalium* in pregnant women has not been well defined.

EPIDEMIOLOGY

Genital mycoplasmas are part of the normal flora and are commonly present in the genitourinary (GU) tract of postpubertal women and men and the upper respiratory tract. The prevalence of genital colonization with these bacteria has been directly associated with low socioeconomic status, hormonal changes, and ethnicity and increases proportionally according to sexual activity, being highest among individuals with multiple sexual partners. Female colonization is greatest in the vagina (and less in the endocervix, urethra, and endometrium), with rates varying from 40% to 80% for *Ureaplasma* spp. and 21–50% for *M. hominis* among sexually active asymptomatic women. *Ureaplasma* is isolated less often from urine than from the cervix, but *M. hominis* is present in the urine and in the cervix with approximately the same frequency. Male colonization is less common and occurs primarily in the urethra. Among prepubertal children and sexually inactive adults, colonization rates are <10%. *M. genitalium* is implicated in approximately 15–20% of NGU cases in men and in 10–30% of women with cervicitis and also plays a role in pelvic inflammatory disease in women. Studies using polymerase chain reaction (PCR) show that colonization of the female lower urogenital tract with *M. genitalium* is less common than with *M. hominis* or *Ureaplasma* spp.

TRANSMISSION

Genital mycoplasmas are transmitted by sexual contact or by vertical transmission from mother to infant. As with other perinatal infections, vertical transmission can occur through ascending intrauterine infection or hematogenous spread from placental infection but most often occurs through a colonized birth canal at the time of delivery. Transmission rates among neonates born to women colonized with *Ureaplasma* spp. range from 18% to 88%. Neonatal colonization rates are higher among infants who weigh <1,000 g, infants who are born in the presence of chorioamnionitis, and infants born to mothers who are heavily colonized and of lower socioeconomic status. Neonatal colonization is transient and decreases proportionally with age. Organisms may be recovered from the newborn's throat, vagina, rectum, and, occasionally, conjunctiva and respiratory tract.

PATHOGENESIS

Genital mycoplasmas can cause chronic inflammation of the GU tract and amniotic membranes. These bacteria usually live in a state of adherence to the respiratory or urogenital tract but can disseminate to other organs when there is a disruption of the mucosa or a weakened or immature immune system, such as in premature infants. *Ureaplasma* spp. can infect the amniotic sac early in gestation without rupturing the amniotic membranes, resulting in a clinically silent, chronic chorioamnionitis characterized by an intense inflammatory response. In addition, mycoplasmas and *Ureaplasma* spp. hydrolyze arginine or urea into ammonium for energy production. Ammonium causes an increase in the genital pH that leads to bacterial dysbiosis with a reduction in *Lactobacillus* and overgrowth of other genital bacteria that can promote preterm labor, premature rupture of membranes, and chorioamnionitis.

Attachment to fetal human tracheal epithelium can cause ciliary disarray, clumping, and loss of epithelial cells. In vitro studies show that *Ureaplasma* spp. stimulates macrophage production of interleukin (IL)-6 and tumor necrosis factor-α. In addition, high concentrations of proinflammatory cytokines possibly associated with development of bronchopulmonary dysplasia (BPD) of prematurity, such as monocyte chemoattractant protein-1 and IL-8, have been found in tracheal secretions from very low birthweight infants colonized with *Ureaplasma* spp. Immunity appears to require serotype-specific antibody. Thus lack of maternal antibodies might account for a higher disease risk in premature newborns.

CLINICAL MANIFESTATIONS

The main syndromes associated with *Ureaplasma* spp., *M. genitalium,* and *M. hominis* are displayed in Table 270.1.

Intrauterine and Neonatal Infections

Chorioamnionitis and Early Onset Infections

Genital mycoplasmas are associated with a variety of fetal and neonatal infections. *Ureaplasma* spp. have been associated with clinically inapparent chorioamnionitis, resulting in spontaneous abortion, increased fetal death, or premature delivery, although the causative role remains uncertain. Studies have shown that women with *Ureaplasma* spp. detected by PCR in amniotic fluid in the first or second trimester of gestation have an increased risk of preterm labor and delivery. In addition, *Ureaplasma* spp. are the microorganism most commonly identified by PCR in women with premature rupture of membranes, and data suggest that *U. parvum* plays a bigger role than *U. urealyticum* in prematurity.

Table 270.1 Clinical Syndromes and Antibiotic Therapy for Ureaplasmas and Mycoplasmas Infection

	UREAPLASMA SPP.	*M. HOMINIS*	*M. GENITALIUM*
INTRAUTERINE AND NEONATAL INFECTIONS			
Chorioamnionitis	++	++	–
Preterm delivery	++	+	++
Postpartum fever	++	+++	UK
BPD	+++	+	UK
CNS infections	+	+	UK
NEC	+	UK	UK
GENITOURINARY INFECTIONS			
NGU (acute/chronic)	++*	–	+++
Cervicitis	–	–	+++
PID	+	++	+++
NON-NEONATAL/NONGENITOURINARY INFECTIONS			
CNS disease†	+	++	–
Bacteremia	+	++	–
Surgical wound infections	++	++	–
Arthritis	+	++	–
TREATMENT			
Macrolides	++	–	++
Quinolones‡	+	++	+
Clindamycin	–	++	+
Tetracyclines (doxycycline)	++	+	+

*Only *Ureaplasma urealyticum* (not *parvum*).
†CNS disease include meningitis, hydrocephalus, brain abscess, subdural empyema, intraventricular hemorrhage, and nonfunctioning CNS shunts.
‡The most commonly used quinolones are ciprofloxacin, levofloxacin, and moxifloxacin.
BPD, Bronchopulmonary dysplasia; CNS, central nervous system; NEC, necrotizing enterocolitis; NGU, nongonococcal urethritis; PID, pelvic inflammatory disease; UK, unknown.

Ureaplasma spp. can also be recovered from tracheal, blood, cerebrospinal fluid (CSF), or lung biopsy specimens in up to 50% of sick infants younger than 34 weeks of gestation. In a study of 351 mother/infant dyads, isolation of *Ureaplasma* spp. or *M. hominis* from cord blood was documented in 23% of infants born between 23 and 32 weeks of gestation and correlated with the development of systemic inflammatory response syndrome.

Bronchopulmonary Dysplasia

The role of these organisms in causing severe respiratory insufficiency, the need for mechanical ventilation, the development of BPD, or death remains controversial. Nevertheless, meta-analyses of published studies have identified respiratory colonization with *Ureaplasma* spp. as an independent risk factor for the development of BPD. However, trials using erythromycin or azithromycin therapy in high-risk preterm infants with tracheobronchial colonization of *Ureaplasma* spp. have failed to show any difference in the development of BPD in treated vs. nontreated infants. Similarly, treatment with azithromycin in pregnant women colonized with *Ureaplasma* spp. did not show a reduction in the risk of BPD in neonates. To date there is not enough evidence to support the use of antibiotic therapy in preterm infants at risk for or with confirmed *Ureaplasma* spp. infection to prevent the development of BPD.

Central Nervous System Infections

M. hominis and *Ureaplasma* spp. have been isolated from the CSF of premature infants and, less commonly, full-term infants. These bacteria may represent true pathogens and may be associated with CNS disease based on the host susceptibility/gestational age and bacteria pathogenicity. However, the clinical significance of recovering *M. hominis* and *Ureaplasma* spp. from the CSF is uncertain, as most infants have no overt signs of CNS disease, CSF pleocytosis is not consistent, and spontaneous clearance of mycoplasmas has been documented without specific therapy.

Ureaplasma spp. have been associated with the development of subdural empyema and meningitis associated with intraventricular hemorrhage (IVH) and hydrocephalus. Limited data suggest that meningitis caused by *M. hominis* can also be associated with IVH, hydrocephalus, and brain abscess, particularly in low birthweight or preterm neonates and in infants with neural tube defects. In a review of 29 reported neonatal cases with *M. hominis* meningitis, 8 (28%) neonates died and 8 (28%) developed neurologic sequelae. The age of onset of meningitis ranges from 1 to 196 days of life, and organisms can persist in the CSF without therapy for days to weeks. Pachymeningitis may be evident on MRI.

Other: *M. hominis* and *Ureaplasma* spp. have also been associated with neonatal conjunctivitis, abscesses (mainly at the scalp electrode site and associated with *M. hominis*), pneumonia, bacteremia, and necrotizing enterocolitis (NEC).

Genitourinary Infections

In sexually active adolescents and adults, genital mycoplasmas are associated with sexually transmitted diseases and are rarely associated with focal infections outside the genital tract. *U. urealyticum* (not *U. parvum*) and *M. genitalium* are recognized etiologic agents of NGU, mainly in men, and represent the second most common cause of urethritis after *Chlamydia trachomatis*. *M. genitalium* has been identified in 30% of patients with persistent or recurrent NGU, because this bacterium is relatively resistant to the antibiotics recommended for the treatment of NGU. Rare complications of NGU include epididymitis and prostatitis. Salpingitis, cervicitis, pelvic inflammatory disease, and endometritis have been described in women associated with *M. genitalium* and, to a lesser extent, with *M. hominis*.

Nongenital Infections

Ureaplasma spp. and *M. hominis* infections are rarely described outside the neonatal period. These infections have been reported in both immunocompetent and immunocompromised children, including patients with hypogammaglobulinemia, lymphoma, or solid organ transplant recipients, who appear to be at higher risk of infection.

Cases of *Ureaplasma* spp. pneumonia, osteomyelitis, arthritis, meningitis, mediastinitis, bacteremia, infection of aortic grafts, and surgical site infections have been reported. Recent data suggest that *Ureaplasma* spp. is associated with posttransplant hyperammonemia syndrome, a rare but potentially fatal complication.

M. hominis is most commonly reported in systemic infections and has been associated with CNS disease (including meningitis, brain abscesses, subdural empyema, and nonfunctioning shunts), surgical wound infections, arthritis (associated in up to 50% of cases with prior manipulation of the GU tract), prosthetic and naïve endocarditis, osteomyelitis, and pneumonia. There are reports of life-threatening mediastinitis, sternal wound infections, pleuritis, peritonitis, and pericarditis, with high mortality rates in patients after organ transplantation. These infections should be suspected in culture-negative systemic or local infections, when samples have been properly collected and before initiation of antibiotic therapy.

DIAGNOSIS

All Mollicutes lack a cell wall and are therefore not visible on Gram stain. *M. hominis* and *Ureaplasma* spp. can grow in cell-free media and require sterols for growth, producing characteristic colonies on agar. Colonies of *M. hominis* are 200-300 μm in diameter with a fried-egg appearance, whereas colonies of *Ureaplasma* spp. are smaller (16-60 μm in diameter). *M. genitalium* is a fastidious organism and can be isolated with difficulty in cell culture systems, requiring up to 8 weeks to be detected. Most clinical microbiology laboratories do not routinely test for these pathogens, and nucleic acid–based tests are the preferred method for diagnosis. PCR-based assays have greater sensitivity than culture (90% vs 40%, respectively) and provide a more practical method for detection. Serologic assays for genital mycoplasmas have limited value in the clinical setting and are not commercially available for diagnostic purposes. In addition, serologic studies for *Ureaplasma* spp. are not useful because of the high prevalence of colonization in healthy children and adults.

Genital Tract Infection

Confirmation of genital tract infection is challenging because of the high colonization rates in the vagina and urethra. NGU is typically defined as new-onset urethral discharge or dysuria with Gram stain of urethral discharge showing ≥5 polymorphonuclear leukocytes per oil-immersion field in the absence of gram-negative diplococci (i.e., *Neisseria gonorrhoeae*). The lack of cell wall prevents the identification of these bacteria by routine Gram stain. Detection of *Ureaplasma* spp. or *M. hominis* by PCR is available for a variety of specimens, including urine and swabs of the cervix, urethra, and vagina. *M. genitalium* is often identified by nucleic acid amplification tests (NAATs) of first-void urine specimens in men and vaginal swabs in women.

Neonates

Ureaplasma spp. and *M. hominis* have been isolated from urine, blood, CSF, tracheal aspirates, pleural fluid, abscesses, and lung tissue. Premature neonates who are clinically ill with pneumonitis, focal abscesses, or CNS disease (particularly progressive hydrocephalus with or without pleocytosis) for whom bacterial cultures are negative or in whom there is no improvement with standard antibiotic therapy warrant further workup to rule out genital mycoplasmas. Isolation of *Ureaplasma* spp. and *M. hominis* requires special media using urea for the former and arginine for the latter, and clinical specimens must be cultured immediately or frozen at −70°C (−94°F) to prevent loss of organisms. *M. hominis* can also be detected sometimes using routine laboratory media such as blood agar or chocolate agar. When inoculated into broth containing arginine (for *M. hominis*) or urea (for *Ureaplasma* spp.), growth is indicated by an alkaline pH. Identification of

Ureaplasma spp. on agar requires 1-3 days of growth and visualization with the dissecting microscope, whereas *M. hominis* is apparent to the eye but can require 2-7 days to grow. PCR-based assays are available and will shed light on the causality of these pathogens when sterile sites are tested (e.g., CSF, joint fluid).

TREATMENT

These organisms lack a cell wall, and thus **β-lactam agents or glycopeptides are not effective**. These bacteria are also resistant to sulfonamides and trimethoprim because they do not synthesize folic acid. Rifamycins do not have activity against Mollicutes (see Table 270.1).

Unlike other mycoplasmas and ureaplasmas, ***M. hominis* is resistant to macrolides** but generally susceptible to clindamycin and quinolones. **Most *Ureaplasma* spp. are susceptible to macrolides and advanced-generation quinolones**, such as levofloxacin or moxifloxacin, but are intrinsically resistant to aminoglycosides and often resistant to ciprofloxacin and clindamycin. Susceptibility to tetracyclines is variable for both organisms, with increasing resistance being reported. ***M. genitalium* is typically susceptible to macrolides and moxifloxacin**, with variable resistance to tetracyclines and clindamycin.

Adolescents and Adults

Recommended treatment for NGU should include antibiotics with activity against *C. trachomatis* with either doxycycline (100 mg PO twice daily for 7 days) or azithromycin (1 g PO as a single dose). If adherence to a multiday regimen is not a concern, azithromycin administered over a 5-day course (500 mg on day 1 followed by 250 mg daily for 4 days) is an alternative and may limit the development of resistance. Recurrent NGU after completion of treatment suggests the presence of doxycycline or azithromycin-resistant *M. genitalium*. If the initial empiric regimen did not include macrolides, retreatment with an azithromycin-based regimen may be indicated. Azithromycin is also preferred in children younger than 8 years and in those with allergy to tetracyclines. On the other hand, if patients received azithromycin initially, retreatment with moxifloxacin may be most effective. Before the introduction of azithromycin, up to 60% of patients with *M. genitalium* NGU developed recurrent or chronic urethritis despite 1-2 weeks of treatment with doxycycline.

Sexual partners should also be treated to avoid recurrent disease in the index case. Nongenital mycoplasmal infections may require surgical drainage and prolonged antibiotic therapy.

Neonates

Treatment of these infections in neonates is challenging, and **no optimal treatment has been established**. Doxycycline and quinolones are generally avoided at this age because of their associated toxicities. In addition, attributing causality may be difficult. In general, therapy for neonates with genital mycoplasma infections is indicated if infections are associated with pure growth of the organism or if the organism is detected by PCR from a normally sterile site in conjunction with compatible disease manifestations to assure the treatment of an infectious process rather than merely colonization.

Treatment is usually based on predictable antimicrobial sensitivities because susceptibility testing is not readily available for individual isolates (see Table 270.1). The treatment of BPD with **azithromycin** for the treatment of ***Ureaplasma* spp.** remains controversial. For infants with symptomatic central nervous system (CNS) infection, cures have been described with chloramphenicol, doxycycline, and quinolones, as they have better penetration into the CSF than macrolides. The long-term consequences of asymptomatic CNS infection associated with genital mycoplasmas, especially in the absence of pleocytosis, are unknown. Because mycoplasmas can spontaneously clear from the CSF, therapy should involve minimal risks.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 10

Chlamydial Infections

Chapter 271

Chlamydia pneumoniae

Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia pneumoniae is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults. This organism was briefly known as *Chlamydophila pneumoniae,* and that name is still used as an alternative designation in some sources.

ETIOLOGY

Chlamydiae are obligate intracellular pathogens that have established a unique niche in host cells. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. The most significant human pathogens are *C. pneumoniae* and *C. trachomatis* (see Chapter 272). *C. psittaci* is the cause of psittacosis, an important zoonosis (see Chapter 273). There are now nine recognized chlamydial species.

Chlamydiae have a gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. pneumoniae* and *C. trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for three of four nucleoside triphosphates, they encode functional glucose-catabolizing enzymes that can be used to generate adenosine triphosphate. As with peptidoglycan synthesis, for some reason, these genes are turned off. All chlamydiae also encode an abundant surface-exposed protein called the *major outer membrane protein.* The major outer membrane protein is the major determinant of the serologic classification of *C. trachomatis* and *C. psittaci* isolates.

EPIDEMIOLOGY

C. pneumoniae is primarily a human respiratory pathogen. The organism has also been isolated from nonhuman species, including horses, koalas, reptiles, and amphibians, where it also causes respiratory infection, although the role that these infections might play in transmission to humans is unknown. *C. pneumoniae* appears to affect individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2–19%, varying with geographic location, the age-group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0–18% of patients based on serology or culture for diagnosis. In one study, almost 20% of the children with *C. pneumoniae* infection were co-infected with *Mycoplasma pneumoniae. C. pneumoniae* may also be responsible for 10–20% of episodes of acute chest syndrome in children with sickle cell disease, up to 10% of asthma exacerbations, 10% of episodes of bronchitis, and 5–10% of episodes of pharyngitis in children. Asymptomatic infection appears to be common based on epidemiologic studies.

Transmission probably occurs from person to person through respiratory droplets. Spread of the infection appears to be enhanced by close proximity, as is evident from localized outbreaks in enclosed populations, such as military recruits and in nursing homes.

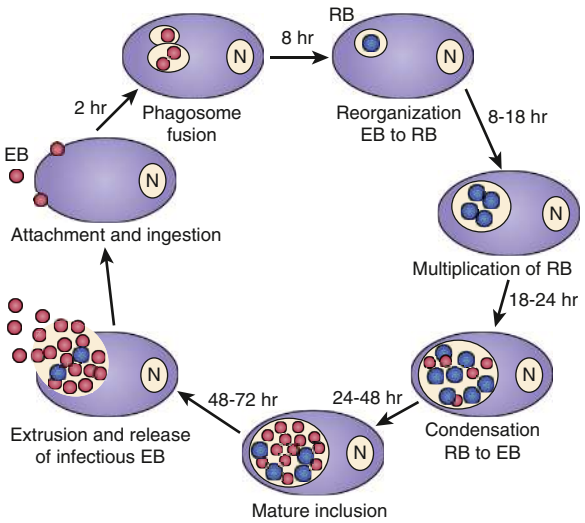

Fig. 271.1 Life cycle of chlamydiae in epithelial cells. *EB,* Elementary body; *RB,* reticulate body. *(From Hammerschlag MR. Infections due to Chlamydia trachomatis and Chlamydia pneumoniae in children and adolescents. Pediatr Rev. 2004;25:43–50.)*

PATHOGENESIS

Chlamydiae are characterized by a unique developmental cycle (Fig. 271.1) with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). After infection, the infectious EBs, which are 200-400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hours, the RBs differentiate into EBs. At approximately 48 hours, release can occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae can also enter a persistent state after treatment with certain cytokines such as interferon-γ, treatment with antibiotics, or restriction of certain nutrients. While chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of chlamydiae.

CLINICAL MANIFESTATIONS

Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae.* The pneumonia usually occurs as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms, including fever, malaise, headache, cough, and often pharyngitis. Severe pneumonia with pleural effusions and empyema has been described. Milder respiratory infections have been described, manifesting as a pertussis-like illness.

C. pneumoniae can serve as an infectious trigger for asthma, can cause pulmonary exacerbations in patients with cystic fibrosis, and can produce acute chest syndrome in patients with sickle cell anemia. *C. pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media, most of the time as co-infection with other bacteria. Asymptomatic respiratory infection has been documented in 2–5% of adults and children and can persist for 1 year or longer.

DIAGNOSIS

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and can show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection has been based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis.* The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. There are two U.S. Food and Drug Administration (FDA)–cleared multiplexed nucleic acid amplification testing assays available for detection of respiratory viruses; pneumonia pathogens; and *C. pneumoniae, M. pneumoniae,* and *Bordetella pertussis* on upper respiratory samples. These systems combine nucleic acid extraction, amplification, detection, and data analysis.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation tests. The complement fixation test is genus specific and is also used for diagnosis of lymphogranuloma venereum (see Chapter 272.4) and psittacosis (see Chapter 273). Its sensitivity in hospitalized patients with *C. pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a fourfold increase in immunoglobulin (Ig) G titer or an IgM titer of ≥16; use of a single elevated IgG titer was discouraged. An IgG titer of ≥16 was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. Because diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because of concern about the inconsistent correlation of these results with culture results. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that more than 50% of children with culture-documented infection have no detectable serum anti–*C. pneumoniae* antibody. Because of the availability of FDA-cleared nucleic acid test technology, diagnosis of acute infection should not be made using serology.

TREATMENT

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. Most treatment studies have used only serology for diagnosis, and thus microbiologic efficacy cannot be assessed. Prolonged therapy for 2 weeks or longer is required for some patients, because recrudescent symptoms and persistent positive cultures have been described after 2 weeks of erythromycin and 30 days of tetracycline or doxycycline.

Tetracyclines, macrolides (erythromycin, azithromycin, and clarithromycin), and quinolones show in vitro activity. Like *C. psittaci, C. pneumoniae* is resistant to sulfonamides. The results of treatment studies have shown that erythromycin (40 mg/kg/day PO divided twice a day for 10 days), clarithromycin (15 mg/kg/day PO divided twice a day for 10 days), and azithromycin (10 mg/kg PO on day 1 and then 5 mg/kg/day PO on days 2-5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases. Resistance to these commonly used drug classes has not been conclusively demonstrated. Persistent symptoms may, however, reflect persistent infection caused by the latent nature of the organism or another etiology and should prompt a thorough reevaluation.

PROGNOSIS

Clinical response to antibiotic therapy varies. Coughing often persists for several weeks even after therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 272

Chlamydia trachomatis

Margaret R. Hammerschlag

Chlamydia trachomatis is subdivided into two biovars, namely, lymphogranuloma venereum (LGV) and trachoma, which is the agent of human oculogenital diseases other than LGV. Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, *C. trachomatis* is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.

272.1 Trachoma

Margaret R. Hammerschlag

Trachoma is the most important preventable cause of blindness in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis.* It is endemic in the Middle East and Southeast Asia and among Navajo Indians in the southwestern United States. In areas that are endemic for trachoma, genital chlamydial infection is caused by the serotypes responsible for oculogenital disease: D, E, F, G, H, I, J, and K. The disease is spread from eye to eye. Flies are a common vector.

Trachoma begins as a **follicular conjunctivitis**, usually in early childhood. The follicles heal, leading to conjunctival scarring that can result in an entropion, with the eyelid turning inward so that the lashes abrade the cornea. It is the corneal ulceration secondary to the constant trauma that leads to scarring and blindness. Bacterial superinfection can also contribute to scarring. Blindness occurs years after the active disease.

Trachoma can be diagnosed clinically. The World Health Organization suggests that at least two of four criteria must be present for a diagnosis of trachoma: lymphoid follicles on the upper tarsal conjunctivae, typical conjunctival scarring, vascular pannus, and limbal follicles. The diagnosis is confirmed by culture or staining tests for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially. Endemic trachoma is managed by mass drug administration (MDA) with azithromycin in affected communities. Endemic communities should receive MDA until clinical signs of active disease in children 1-9 years of age falls below 5%. MDA with a single dose of azithromycin to all the residents of a village dramatically reduces the prevalence and intensity of infection. This effect continues for 2 years after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

272.2 Genital Tract Infections

Margaret R. Hammerschlag

EPIDEMIOLOGY

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States. *C. trachomatis* is a major cause of epididymitis and is the cause of 23–55% of all cases of nongonococcal urethritis. As many as 50% of men with gonorrhea may be co-infected with *C. trachomatis.* The prevalence of chlamydial cervicitis among sexually active women is 2–35%. Rates of infection among girls 15-19 years of age exceed 20% in many urban populations and can be as high as 15% in suburban populations.

Children who have been sexually abused can acquire anogenital *C. trachomatis* infection, which is usually asymptomatic. However, because perinatally acquired rectal and vaginal *C. trachomatis* infections can persist for 3 years or longer, the detection of *C. trachomatis* in the vagina or rectum of a young child is not absolute evidence of sexual abuse.

CLINICAL MANIFESTATIONS

The trachoma biovar of *C. trachomatis* causes a spectrum of disease in sexually active adolescents and adults. Up to 75% of women with *C. trachomatis* have no symptoms of infection. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent. Asymptomatic urethral infection is common in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

DIAGNOSIS

Diagnosis of genital chlamydial infection is now accomplished by nucleic acid amplification tests (NAATs). These tests have high sensitivity, detecting 10–20% more cases than culture, while retaining high specificity. Six FDA-approved NAATs are commercially available for detecting *C. trachomatis,* including polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (ProbeTec, BD Diagnostic Systems, Sparks, MD), transcription-mediated amplification (Amp CT, Hologic, San Diego, CA), and GeneXpert CT/NG assay (Cepheid, Sunnyvale, CA). PCR and strand displacement amplification are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that is present at approximately 10 copies in each infected cell. Transcription-mediated amplification is a ribosomal RNA amplification assay. GeneXpert is an on-demand, qualitative, real-time PCR. All these assays are also available as co-amplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae.*

The available commercial NAATs are FDA-approved for cervical and vaginal swabs from adolescent girls and women, urethral swabs from adolescent boys and men, and urine, pharyngeal, and rectal swabs from adolescents and adults. Use of urine avoids the necessity for a clinical pelvic examination and can greatly facilitate screening in certain populations, especially adolescents, although several studies have now demonstrated that endocervical specimens and vaginal swabs are superior to urine for NAAT. Self-collected vaginal specimens appear to be as reliable as specimens obtained by a healthcare professional.

Data on the use of NAATs for vaginal specimens or urine from children are very limited and are insufficient to allow making a recommendation for their use. NAATs can be used, but confirmatory testing must be done. Because of the low prevalence of infection in this population, the positive predictive values of a positive test can be less than 30%. Confirmatory testing should consist of testing the original sample with a second FDA-approved NAAT that targets a different gene sequence from the initial test or repeating the testing **before** treatment. Use of non-FDA-cleared assays is strongly discouraged.

The etiology of most cases of nonchlamydial nongonococcal urethritis is unknown, although *Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* are implicated in up to one third of cases (see Chapter 270). Proctocolitis may develop in individuals who have a rectal infection with an LGV strain (see Chapter 272.4).

TREATMENT

The first-line treatment regimen now recommended by the CDC for uncomplicated *C. trachomatis* genital and rectal infection in adult and adolescent men and nonpregnant women is doxycycline (100 mg PO twice a day for 7 days). Recent studies have documented that doxycycline is significantly more effective than single-dose azithromycin. Alternative regimens are azithromycin (1 g orally in a single dose) or levofloxacin (500 mg PO once daily for 7 days). Doxycycline and quinolones are contraindicated in pregnant women, and quinolones are contraindicated in persons younger than 18 years. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days).

Empirical treatment without microbiologic diagnosis is recommended only for patients at high risk for infection who are unlikely to return for follow-up evaluation, including adolescents with multiple sex partners. These patients should be treated empirically for both *C. trachomatis* and *N. gonorrhoeae*.

Sex partners of patients with nongonococcal urethritis should be treated if they have had sexual contact with the patient during the 60 days preceding the onset of symptoms. The most recent sexual partner should be treated even if the last sexual contact was more than 60 days from onset of symptoms.

COMPLICATIONS

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh–Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection (see Chapter 272.3). Women with *C. trachomatis* infection have a threefold to fivefold increased risk for acquiring HIV infection.

PREVENTION

Timely treatment of sex partners is essential for decreasing the risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was >60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose regimen or after completion of a 7-day regimen.

Annual routine screening for *C. trachomatis* is recommended for all sexually active female adolescents, for all women 20-25 years of age, and for older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment might indicate more frequent screening of some women.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

272.3 Conjunctivitis and Pneumonia in Newborns

Margaret R. Hammerschlag

EPIDEMIOLOGY

Chlamydial genital infection is reported in 5–30% of pregnant women, with a risk for vertical transmission at parturition to newborn infants of approximately 50%. The infant may become infected at one or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare after cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the United States. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for >60% of neonatal conjunctivitis.

Inclusion Conjunctivitis

Approximately 30–50% of infants born to mothers with active, untreated chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5-14 days after delivery, or earlier in infants born after prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and may bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight-threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia

Pneumonia caused by *C. trachomatis* can develop in 10–20% of infants born to women with active, untreated chlamydial infection. Only approximately 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a characteristic presentation. Onset usually occurs between 1 and 3 months of age and is often insidious, with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is occasionally present but is uncommon. The absence of fever and wheezing generally helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/μL). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infections at Other Sites

Infants born to mothers with *C. trachomatis* can develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it can cause confusion if it is identified later. Perinatally acquired rectal, vaginal, and nasopharyngeal infections can persist for 3 years or longer.

DIAGNOSIS

Definitive diagnosis is achieved by isolation of *C. trachomatis* in cultures of specimens obtained from the conjunctiva or nasopharynx. Data on the use of NAATs for diagnosis of *C. trachomatis* in children are limited but suggest that PCR may be equivalent to culture for detecting *C. trachomatis* in the conjunctiva of infants with conjunctivitis. However, NAATs are not currently FDA-cleared for use with conjunctival or nasopharyngeal specimens from infants. Laboratories can do internal validation delineated in the CDC 2014 *C. trachomatis* and *N. gonorrhoeae* laboratory guidelines.

TREATMENT

The recommended treatment regimens for *C. trachomatis* conjunctivitis or pneumonia in infants are erythromycin (base or ethylsuccinate, 50 mg/kg/day divided 4 times a day PO for 14 days) or azithromycin suspension (20 mg/kg/day once daily PO for 3 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies demonstrate that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10–20%, and some infants require a second

course of treatment. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin or oral azithromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 weeks of age.

PREVENTION

Neonatal gonococcal prophylaxis with topical erythromycin ointment does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia. *The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women.* In 2015, the Canadian Pediatric Society recommended that neonatal ocular prophylaxis be discontinued and that prenatal screening for chlamydia be enhanced. The program was implemented in 2016. In the United States, implementation of prenatal screening and treatment of pregnant women has resulted in a dramatic decrease in perinatal chlamydial infections. For treatment of *C. trachomatis* infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

272.4 Lymphogranuloma Venereum

Margaret R. Hammerschlag

LGV is a systemic sexually transmitted disease caused by the L_1, L_2, and L_3 serotypes of the LGV biovar of *C. trachomatis*. Unlike strains of the trachoma biovar, LGV strains have a predilection for lymphoid tissue. Fewer than 1,000 cases are reported in adults in the United States annually. There has been a resurgence of LGV infections among men who have sex with men in Europe and the United States. Many of the men were HIV infected and used illicit drugs, specifically methamphetamines. The only pediatric case that has been reported since the emergence of the new clusters of HIV-associated cases in 2003 was a 16-year-old boy who presented with LGV proctocolitis after having receptive unprotected anal intercourse with a 30-year-old man he met on the Internet. This history was obtained after the boy was found to be HIV-positive. The diagnosis of LGV, particularly when it presents with proctocolitis, relies on a high index of suspicion that would lead to emphasizing certain aspects of the history and ordering the pertinent diagnostic tests. Many pediatricians and pediatric gastroenterologists might not be familiar with the entity and might not entertain it as a diagnostic consideration in pediatric patients. The diagnosis can be further suggested by *C. trachomatis* testing: commonly by NAATs or culturing the organism if culture is available. Currently available NAATs will not differentiate LGV from other *C. trachomatis* serovars. NAATs for *C. trachomatis* are also not FDA-cleared for testing rectal specimens, but laboratories can do an internal validation as recommended in the CDC 2014 *C. trachomatis* and *N. gonorrhoeae* laboratory guidelines. NAATs have been found in several clinical studies to perform well with rectal specimens. Typing of the *C. trachomatis* specimen can be done by sequencing from the NAAT specimen by many state laboratories. Trying to ascertain the *C. trachomatis* serovar for confirmation of LGV has therapeutic implications, as LGV needs to be treated with a 3-week course of doxycycline; a single-dose of azithromycin will not eradicate the infection.

CLINICAL MANIFESTATIONS

The **first stage of LGV** is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The **second stage** is characterized by usually unilateral femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in men. In women, the vulvar lymph drains to the retroperitoneal nodes. Fever, myalgia, and headache are common. The **third stage** is a genitoanorectal syndrome with rectovaginal fistulas, rectal strictures, and urethral destruction. Among men who have sex with men, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

DIAGNOSIS

LGV can be diagnosed by serologic testing or by culture of *C. trachomatis* or molecular testing for *C. trachomatis* from a specimen aspirated from a bubo. Most patients with LGV have complement-fixing antibody titers of >1:16. Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, co-infections can occur.

TREATMENT

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. Alternative regimens are azithromycin (1 g PO once weekly for 3 weeks) or erythromycin base (500 mg PO 4 times a day for 21 days). As the azithromycin regimen has not been validated, it is recommended that a test of cure with a *C. trachomatis* NAAT 4 weeks after completion of therapy be performed. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 273

Psittacosis *(Chlamydia psittaci)*

Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia psittaci, the agent of psittacosis (also known as **parrot fever** and **ornithosis**), is primarily an animal pathogen and rarely causes human disease. In birds, *C. psittaci* infection is known as *avian chlamydiosis*.

ETIOLOGY

C. psittaci affects both psittacine birds (e.g., parrots, parakeets, macaws) and nonpsittacine birds (ducks, turkeys); the known host range includes 130 avian species. The life cycle of *C. psittaci* is the same as for *C. pneumoniae* (see Chapter 271). Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are seven avian serovars. The organism has also been found in nonavian domestic animals,

including cattle, sheep, pigs, goats, and cats. Nonavian *C. psittaci* has rarely caused disease in humans. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics. There are four other *Chlamydia* species that have birds as their primary hosts: *C. avium* (pigeons, parrots), *C. gallinacea* (chickens, turkeys, ducks), *C. ibdis* (ibis), and *C. buteonis* (hawks, buzzards). *C. gallinacea* may have the potential to cause outbreaks in poultry plants.

EPIDEMIOLOGY

On average, 11 cases of psittacosis per year in the United States were reported from 2000 to 2017. However, experts believe the disease is potentially underreported and underdiagnosed. In 2018, a multistate psittacosis outbreak among poultry plant workers had 13 laboratory-confirmed cases. The majority of cases were associated with exposure to birds, including 70% after exposure to caged pet birds, which were usually psittacine birds, including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most often in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include workers in poultry plants, bird fanciers, owners of pet birds, and pet shop employees. Reported cases most likely underestimate the number of actual infections owing to a lack of awareness and readily available diagnostic tests.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage.

CLINICAL MANIFESTATIONS

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe disease, including pneumonia and multiorgan involvement. The mean incubation period is 15 days after exposure, with a range of 5-21 days. Onset of disease is usually abrupt, with fever, cough, headache, myalgia, and malaise. The fever is high and is often associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastrointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal and are characterized by the presence of variable infiltrates, sometimes accompanied by pleural effusions. The white blood cell count is usually normal but is sometimes mildly elevated. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common. Nonpulmonary complications include pericarditis, endocarditis, and myocarditis. Mortality occurs in 5% of cases.

DIAGNOSIS

Psittacosis can be difficult to diagnose because of the varying clinical presentations. A history of exposure to birds or association with an active case can be important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include routine bacterial and viral respiratory infections as well as *Coxiella burnetii* infection (Q fever), *Mycoplasma pneumoniae* infection, *C. pneumoniae* infection, tularemia, tuberculosis, fungal infections, and Legionnaires' disease.

A patient is considered to have a confirmed case of psittacosis if clinical illness is compatible with psittacosis and the case is laboratory confirmed by identification of *C. psittaci* by polymerase chain reaction (PCR) from respiratory specimens (e.g., sputum, pleural fluid, or lung tissue), blood, or stool. Serologic methods are most available, but these tests have poor specificity and require testing of paired specimens collected weeks apart, delaying or preventing confirmation of the clinical diagnosis in a timely fashion. A patient is considered to have a probable case of psittacosis if the clinical illness is compatible with psittacosis and there is an epidemiologic exposure. Lower respiratory tract samples are the specimen of choice, although 5 of 13 (38%) of the patients in the 2018 multistate outbreak also had *C. psittaci* DNA detected in their stool specimens.

Although *C. psittaci* will grow in the same culture systems used for isolation of *C. trachomatis* and *C. pneumoniae,* very few laboratories culture for *C. psittaci,* mainly because of the potential biohazard. Real-time PCR assays can distinguish *C. psittaci* from other chlamydial species and identify different *C. psittaci* genotypes. Currently real-time PCR for *C. psittaci* is only available at the CDC.

TREATMENT

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO twice daily) or tetracycline (500 mg PO 4 times a day) for at least 10-14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 hours IV; maximum: 100 mg/dose). Erythromycin (500 mg PO 4 times a day) and azithromycin (10 mg/kg PO on day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2-5, not to exceed 250 mg) are alternative agents if tetracyclines are contraindicated (e.g., children <8 years of age and pregnant women) but may be less effective. Remission is usually evident within 48-72 hours. Reinfection and clinical disease can develop within 2 months of treatment, indicating that initial infection does not appear to be followed by long-term immunity.

PROGNOSIS

The mortality rate of psittacosis is 15–20% with no treatment but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

PREVENTION

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to heat and to most disinfectants and detergents but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30-45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should not be sold or purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 11

Rickettsial Infections

Chapter 274

Spotted Fever Group Rickettsioses

Megan E. Reller and J. Stephen Dumler

Rickettsia species were classically divided into *spotted fever* and *typhus* groups based on serologic reactions and the presence or absence of the outer membrane protein A gene *(ompA)*. Sequencing of over 150 complete genomes has refined distinctions. However, there is controversy regarding phylogeny, and some data suggest that diversity and pathogenicity are the result of gene loss and lateral gene transfer from other prokaryotes or even eukaryotes, which further obscures accurate taxonomic classification. One proposal is to divide existing species into spotted fever and *transitional* groups based on genetic relatedness; both include pathogenic species and species not now known to cause human disease (Table 274.1). Although increasingly more is understood about the molecular basis by which these bacteria cause human illness, an alternative classification system based on pathogenetic mechanisms has not been defined.

The list of pathogens and potential pathogens in the spotted fever group has expanded dramatically in recent years. Unfortunately, the most common diagnostic approach uses a serologic method that cannot distinguish among related species; thus the CDC classifies serologically defined cases as "spotted fever rickettsiosis" to reflect this uncertainty. Among the etiologic agents of spotted fever rickettsiosis are the tick-borne agents *Rickettsia rickettsii,* the cause of Rocky Mountain or Brazilian spotted fever (RMSF); *R. conorii,* the cause of Mediterranean spotted fever (MSF) or boutonneuse fever; *R. sibirica,* the cause of North Asian tick typhus; *R. japonica,* the cause of Oriental or Japanese spotted fever; *R. honei,* the cause of Flinders Island spotted fever or Thai tick typhus; *R. africae,* the cause of African tick bite fever; *R. akari,* the cause of mite-transmitted rickettsialpox; *R. felis*, the cause of cat flea–transmitted typhus; and *R. australis,* the cause of tick-transmitted Queensland tick typhus. The recognition that *R. parkeri* and "*R. philipii*" (*Rickettsia* 364D) both cause mild spotted fever in North America and the association of high seroprevalence for spotted fever group *Rickettsia* infections in humans where *Amblyomma* ticks frequently contain *R. amblyommatis* suggest that the full range of agents that can cause spotted fever is still to be discerned.

Infections with other members of the spotted fever and transitional groups are clinically similar to MSF, with fever, maculopapular rash, and eschar at the site of the tick bite. Israeli spotted fever (*R. conorii* infection) is generally associated with a more severe course in children, including death. African tick bite fever is relatively mild, can include a vesicular rash, and often manifests with multiple eschars. New potentially pathogenic rickettsial species have been identified, including *R. slovaca,* the cause of tick-borne lymphadenopathy or *Dermacentor*-borne necrosis and lymphadenopathy. *R. aeschlimannii, R. heilongjiangensis, R. helvetica, R. massiliae,* and *R. raoultii* are all reported to cause mild to moderate illnesses in humans, although few cases have been described. Fortunately, the vast majority of infections respond well to doxycycline treatment if instituted early in illness; however, this is a significant challenge.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

274.1 Rocky Mountain Spotted Fever *(Rickettsia rickettsii)*

Megan E. Reller and J. Stephen Dumler

RMSF is the most severe rickettsial disease in the United States and Western Hemisphere. Although spotted fever rickettsiosis is the most common vector-borne disease in the United States after Lyme disease, the proportion of these cases caused by *R. rickettsii* is not known. Although considered uncommon, RMSF is believed to be greatly underdiagnosed and underreported. RMSF should be considered in the differential diagnosis of fever, headache, and rash in the summer months, especially after tick exposure. Because fulminant disease and death are associated with delays in treatment, patients in whom the illness is clinically suspected should be treated promptly.

ETIOLOGY

RMSF results from systemic infection of endothelial cells by the obligate intracellular bacterium *R. rickettsii.*

EPIDEMIOLOGY

The term **Rocky Mountain spotted fever** is historical, because the agent was discovered in the Bitterroot Range of the Rocky Mountains of Montana. Few cases are reported from this region. Cases have been reported throughout the continental United States (except Vermont and Maine), southwestern Canada, Mexico, Central America, and South America, but not from outside of the Western Hemisphere. In 2010, the CDC reporting criteria for RMSF changed to **spotted fever group rickettsiosis**, because serology often does not distinguish *R. rickettsii* from infection by other spotted fever group *Rickettsia*. Additionally, cases detected by enzyme immunoassay were classified as probable. Thus in 2012, 2,802 confirmed and probable cases of spotted fever rickettsiosis were reported in *Morbidity and Mortality Weekly Reports* Summary of Notifiable Diseases. Unlike in prior years, most cases were reported from the west southcentral states, especially from Arkansas, Oklahoma, and Missouri; high numbers of cases were also reported from North Carolina, Tennessee, Virginia, New Jersey, Georgia, Alabama, and Arizona (Fig. 274.1). The incidence of RMSF cycles over 25- to 35-year intervals, but spotted fever rickettsioses have steadily increased since 1998 over which time approximately 14% occur in individuals younger than 19 years. Habitats favored by ticks, including wooded areas or coastal grassland and salt marshes, and, in the southwestern United States and Mexico, shaded areas where dogs congregate and acquire infected ticks are those that place children at increased risk for infection. Foci of intense risk for infection are found both in rural and urban areas, most recently in Mexico and South America. Clustering of cases within families likely reflects shared environmental exposures. In the United States, 90% of cases occur between April and September, months in which humans spend the most time outdoors. The highest age-specific incidence of RMSF among children is seen in those older than 10 years of age, with males outnumbering females; however, the highest case fatality rate for RMSF is observed in those less than 10 years of age.

TRANSMISSION

Ticks are the natural hosts, reservoirs, and vectors of *R. rickettsii* and maintain the infection in nature by transovarial transmission (passage of the organism from infected ticks to their progeny). Ticks harboring rickettsiae are substantially less fecund than uninfected ticks; thus horizontal transmission (acquisition of rickettsiae by taking a blood meal from transiently rickettsemic hosts such as small mammals or dogs) contributes to maintenance of rickettsial infections in ticks. Uninfected ticks that simultaneously feed (co-feed) with infected transmitting ticks easily become infected, even if feeding on an immune host, and are also likely to be major contributors to natural transmission and maintenance. Ticks transmit the infectious agent to mammalian hosts (including humans) via infected saliva during feeding. The pathogen *R. rickettsii* in ticks becomes virulent after exposure to blood or increased temperature; thus the longer the tick is attached, the greater the risk of transmission. The principal tick

Table 274.1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
SPOTTED FEVER GROUP								
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor* species (wood tick, dog tick) *Rhipicephalus sanguineus* (brown dog tick)	Dogs Rodents	Western hemisphere	Fever, headache, rash,* emesis, diarrhea, myalgias	AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol
Mediterranean spotted fever (boutonneuse fever)	*Rickettsia conorii*	Tick bite: *R. sanguineus* (brown dog tick)	Dogs Rodents	Africa, Mediterranean, India, Middle East	Painless eschar (tache noir) with regional lymphadenopathy, fever, headache, rash,* myalgias	AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol Azithromycin Clarithromycin Fluoroquinolones
African tick-bite fever	*Rickettsia africae*	Tick bite	Cattle Goats?	Sub-Saharan Africa, Caribbean	Fever, single or multiple eschars, regional lymphadenopathy, rash* (can be vesicular)	AST, ALT ↓Platelets	Early: IH, DFA After 1st wk: IFA	**Doxycycline**
Tickborne lymphadenopathy (TIBOLA); Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	*Rickettsia slovaca, Rickettsia raoultii, Rickettsia sibirica mongolotimonae*	Tick bite: *Dermacentor*	?	Europe	Eschar (scalp), painful lymphadenopathy	?	PCR	**Doxycycline**
Rickettsia spp., 364D genotype	"*Rickettsia philippii*"	*Dermacentor occidentalis* (Pacific coast tick)		California	Eschar, fever, headache, lymphadenopathy, malaise	Unremarkable	PCR	Doxycycline
Flea-borne spotted fever	*Rickettsia felis*	Flea bite	Opossums Cats Dogs	Western hemisphere, Europe	Fever, rash,* headache	?	Early: PCR After first wk: IFA	Doxycycline
TRANSITIONAL GROUP								
Rickettsialpox	*Rickettsia akari*	Mite bite	Mice	North America, Russia, Ukraine, Adriatic, Korea, South Africa	Painless eschar, ulcer or papule; tender regional lymphadenopathy, fever, headache, rash* (can be vesicular)	↓WBC	Early: IH, DFA After first wk: IFA	**Doxycycline** Chloramphenicol
Queensland tick typhus	*Rickettsia australis*	*Ixodes holocyclus, I. tasmani*	Bandicoots and Rodents	Australia, Tasmania	Fever, eschar, headache, myalgia, lymphadenopathy	↓WBC, ↓platelets	Early: PCR on eschar or eschar swab; After first wk: IFA	**Doxycycline**
TYPHUS GROUP								
Murine typhus	*Rickettsia typhi*	Flea feces	Rats Opossums	Worldwide	Fever, headache, rash,* myalgias, emesis, lymphadenopathy, hepatosplenomegaly	AST, ALT ↓Na (mild) ↓WBC ↓ Platelets	Early: DFA, PCR After first wk: IFA	**Doxycycline** Chloramphenicol

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 274.1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*—cont'd

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
Epidemic (louse-borne) typhus (recrudescent form: Brill-Zinsser disease)	*Rickettsia prowazekii*	Louse feces	Humans	South America, Central America, Mexico, Africa, Asia, Eastern Europe	Fever, headache, abdominal pain, rash,* CNS involvement	AST, ALT ↓Platelets	Early: none After first wk: IgG/IgM, IFA	**Doxycycline** Tetracycline Chloramphenicol
Flying squirrel (sylvatic) typhus	*Rickettsia prowazekii*	Louse feces? Flea feces or bite?	Flying squirrels	Eastern United States	Same as above (often milder)	AST, ALT ↓Platelets	Early: none After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol
SCRUB TYPHUS								
Scrub typhus	*Orientia tsutsugamushi, Orientia chuto "Orientia chiloensis"*	Chigger bite: *Leptotrombidium* spp.	Rodents?	South Asia, Japan, Indonesia, Korea, China, Russia, Australia, Africa, Middle East, Chile	Fever, rash,* headache, painless eschar, hepatosplenomegaly, gastrointestinal symptoms	↓Platelets AST, ALT	Early: none After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol **Rifampicin** Azithromycin
EHRLICHIOSIS AND ANAPLASMOSIS								
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum* (lone star tick)	Deer Dogs	United States, Mexico	Fever, headache, malaise, myalgias, rash*‡, hepatosplenomegaly,‡ swollen hands/feet‡	AST, ALT ↓WBC ↓Platelets ↓Na (mild)	Early: PCR After first wk: IFA	**Doxycycline** Tetracycline
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes* species *Haemaphysalis longicornis*	Rodents Deer Ruminants	United States, Europe, Asia	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓ANC ↓Platelets	Early: PCR, blood smear After first wk: IFA	**Doxycycline** Tetracycline Rifampin
Ewingii ehrlichiosis	*Ehrlichia ewingii*	Tick bite: *Amblyomma americanum* (lone star tick)	Dogs Deer	United States (south-central, southeast)	Fever, headache, malaise, myalgias	AST, ALT, ↓WBC ↓Platelets	Early: PCR serology not available	**Doxycycline** Tetracycline
Ehrlichia muris eauclairensis infection	*Ehrlichia muris* ssp. *eauclairensis*	*Ixodes scapularis*	?	Minnesota, Wisconsin	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓Platelets	Early: PCR specific serology not available	**Doxycycline**
Neoehrlichiosis	*Neoehrlichia mikurensis*	*Ixodes ricinus*	Small mammals?	Europe, Asia	Fever, headache, myalgias, thrombosis	Neutrophilia, anemia, elevated CRP, AST, ALT	PCR	**Doxycycline**
Sennetsu neorickettsiosis	*Neorickettsia sennetsu*	Ingestion of fish helminth?, ingestion of fermented fish	Fish, trematodes	Japan, Malaysia, Laos	Fever, "mononucleosis" symptoms, postauricular and posterior cervical lymphadenopathy	Atypical lymphocytosis	Early: none After first wk: IFA	**Doxycycline** Tetracycline

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 274.1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*—cont'd

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
Q FEVER								
Q Fever: acute (for chronic, see text)	*Coxiella burnetii*	Inhalation of infected aerosols: contact with parturient animals, abattoir, contaminated cheese and milk, ?ticks	Cattle Sheep Goats Cats Rabbits	Worldwide	Fever, headache, arthralgias, myalgias, gastrointestinal symptoms, cough, pneumonia, rash (children)	AST, ALT WBC ↓ Platelets Interstitial infiltrate	Early: PCR After first wk: IFA	**Doxycycline** Tetracycline Fluoroquinolones Trimethoprim-sulfamethoxazole

*Rash is infrequently present at initial presentation but appears during the first wk of illness.
†Preferred treatment is in **bold**.
‡Often present in children but not adults.
ALT, Alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IH, immunohistochemistry; PCR, polymerase chain reaction; WBC, white blood cell count.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

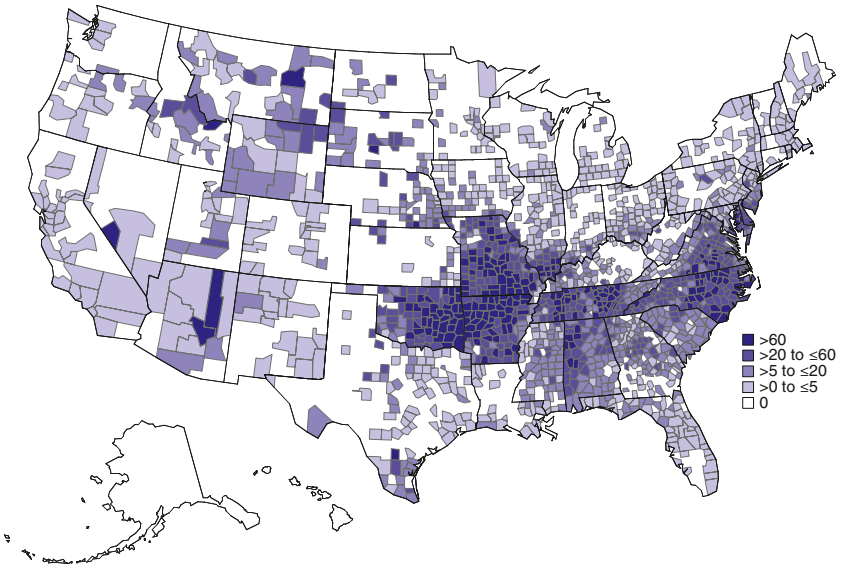

Fig. 274.1 Reported incidence rate* of spotted fever rickettsiosis,† by county—United States, 2000–2013. *As reported through national surveillance, per 1,000,000 persons per year. Cases are reported by county of residence, which is not always where the infection was acquired. †Includes Rocky Mountain spotted fever (RMSF) and other spotted fever group rickettsioses. In 2010, the name of the reporting category changed from RMSF to spotted fever rickettsiosis. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44. Fig. 1.)*

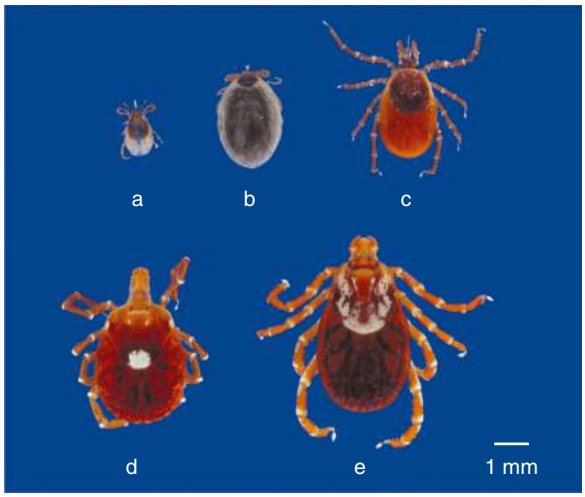

Fig. 274.2 Tick vectors of agents of human rickettsial diseases. An unengaged nymph *(a)*, engorged nymph *(b)*, and adult female *(c)* of *Ixodes scapularis* (deer tick), the vector of *Anaplasma phagocytophilum* and *Ehrlichia muris*–like agent (EMLA), the causes of human granulocytic anaplasmosis and EMLA ehrlichiosis, respectively. An adult female *(d)* of *Amblyomma americanum* (lone star tick), the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, the causes of human monocytic ehrlichiosis and ewingii ehrlichiosis, respectively. An adult female *(e)* of *Dermacentor variabilis* (American dog tick), the vector of *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever.

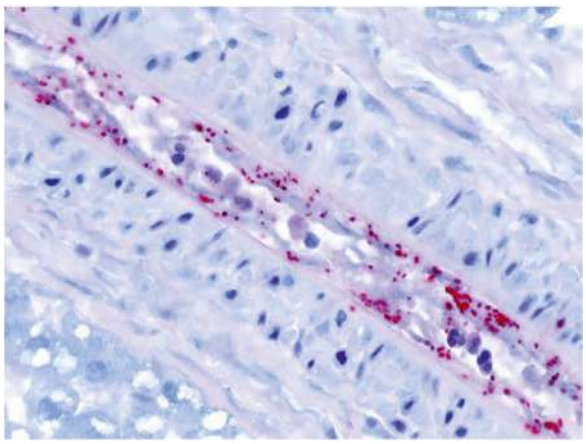

Fig. 274.3 Immunohistochemical stain demonstrating *Rickettsia (red)* in infection of blood vessel endothelial cells. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 20.)*

hosts of *R. rickettsii* are *Dermacentor variabilis* (the American dog tick) in the eastern United States and Canada, *Dermacentor andersoni* (the wood tick) in the western United States and Canada, *Rhipicephalus sanguineus* (the common brown dog tick) in the southwestern United States and in Mexico, and several *Amblyomma* spp. in Central and South America (Fig. 274.2).

Dogs can serve as reservoir hosts for *R. rickettsii*, can develop RMSF themselves, and can bring infected ticks into contact with humans. Serologic studies suggest that many patients with RMSF likely acquired the illness from ticks carried by the family dog.

Humans can also become infected when trying to remove an attached tick, because *R. rickettsii*–containing tick fluids or feces can be rubbed into the open wound at the bite site or into the conjunctivae by contaminated fingers. Inhalation of aerosolized rickettsiae has caused severe infections and deaths in laboratory workers, highlighting another mechanism of infection.

PATHOLOGY AND PATHOGENESIS

Systemic infection is most obvious on the skin (rash), but nearly all organs and tissues are affected. After inoculation of tick saliva into the dermis, rickettsial outer surface proteins bind to the vascular endothelial cell surface proteins, which signals focal cytoskeletal changes and endocytosis. Thereafter, rickettsia phospholipase-mediated dissolution of the endosomal membranes allows escape into the cytosol. Members of the spotted fever group actively nucleate actin polymerization on one pole to achieve directional movement, allowing some to propel into neighboring cells despite minimal initial host cell damage. The rickettsiae proliferate and injure host cells by oxidative membrane alterations, protease activation, or continued phospholipase activity. It is likely that some aspects of intracellular infection are mediated by rickettsial protein effectors delivered into the host cell by bacterial secretion systems.

The histologic correlate of the initial macular or maculopapular rash is perivascular infiltration of lymphoid and histiocytic cells with edema but without significant endothelial damage. Proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to endothelial injury and **lymphohistiocytic or leukocytoclastic vasculitis** of small venules and capillaries, which allows extravasation of intravascular erythrocytes into the dermis and manifests as a petechial rash (Fig. 274.3). This process is systemic and ultimately results in widespread microvascular leakage,

tissue hypoperfusion, and possibly septic shock or end-organ ischemic injury. Infrequently, inflammation leads to nonocclusive thrombi. Very rarely, small and large vessels become completely obliterated by thrombi, leading to tissue infarction or hemorrhagic necrosis. Interstitial pneumonitis and vascular leakage in the lungs can lead to noncardiogenic pulmonary edema, and meningoencephalitis can cause significant cerebral edema and herniation.

The presence of the infectious agent initiates an inflammatory cascade, including release of cytokines and chemokines such as tumor necrosis factor, interleukin-1β, interferon-γ, and regulated upon activation, normal T-cell expressed and secreted (RANTES). Infection of endothelial cells by *R. rickettsii* induces surface E-selectin expression and procoagulant activity followed by chemokine recruitment of lymphocytes, macrophages, and, occasionally, neutrophils. Local inflammatory and immune responses are suspected to contribute to the vascular injury; however, the benefits of effective innate immunity are greater. Blockade of tumor necrosis factor and interferon-γ in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ-producing natural killer cells, accompanied by rickettsia antibody, helps control the infection. The timing and balance between rickettsia-mediated increases in vascular permeability and the benefits of induction of innate and adaptive immunity are likely the major determinants of severity and outcome.

CLINICAL MANIFESTATIONS

The incubation period of RMSF in children varies from 2 to 14 days (median: 7 days). In 49% of cases, patients or their parents report a history of removing an attached tick, although the site of the tick bite is usually inapparent. Epidemiologic clues include living in or visiting an endemic area, playing or hiking in the woods, typical season, similar illness in family members, and close contact with a dog. In patients presenting for care, the illness is initially nonspecific, and most patients are not diagnosed during their first visit with a healthcare practitioner. Manifestations often (>50%) include fever, rash (frequently involving the palms or soles), nausea and vomiting, and headache and, less often (<50%), myalgias, abdominal pain, diarrhea, conjunctival injection, altered mental status, lymphadenopathy, and peripheral edema. Pain and tenderness of calf muscles are particularly common in children.

The typical **clinical triad of fever, headache, and rash** is observed in 58% of pediatric patients overall, and rash involving the soles and palms first appearing after day 3 is associated with significantly higher risk of death. Fever and headache persist if the illness is untreated. Fever can exceed 40°C (104°F) and can remain persistently elevated or can fluctuate dramatically. Headache is severe, unremitting, and unresponsive to analgesics.

Rash usually appears after only 1-2 days of illness, and an estimated 3–5% of children never develop a rash that is recognized. Initially, discrete, pale, rose-red blanching macules or maculopapules appear; characteristically, this initial rash is observed on the extremities, including the wrists, ankles, or lower legs (Fig. 274.4). In 65% of patients, the initial rash spreads rapidly to involve the entire body, including the soles and palms. The rash can become petechial or even hemorrhagic, sometimes with palpable purpura.

In severe disease, the petechiae can enlarge into ecchymoses, which can become necrotic (Fig. 274.5). Severe vascular obstruction secondary to the rickettsial vasculitis and thrombosis is uncommon but can result in gangrene of the digits, earlobes, scrotum, nose, or an entire limb.

Central nervous system infection usually manifests as changes in mental status (33%) or as photophobia (18%), seizure (17%), or meningismus (16%). Patients can also manifest ataxia, coma, or auditory deficits. Cerebrospinal fluid parameters are usually normal, but one third have pleocytosis (<10-300 cells/μL), either mononuclear or, less often, neutrophil-dominated. Some (20%) have elevated protein (<200 mg/dL) in the cerebrospinal fluid; hypoglycorrhachia is rare.



Fig. 274.4 Maculopapular rash with central petechiae associated with Rocky Mountain spotted fever. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 21.)*



Fig. 274.5 Late-stage petechial purpuric rash involving the sole of the foot in a patient with Rocky Mountain spotted fever. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 22.)*

Neuroimaging studies often reveal only subtle abnormalities. However, with advanced disease and neurologic signs, a unique but nonspecific "starry sky" appearance may be observed on brain MRI that reflects the same systemic vasculitis observed with skin lesions.

Other

Pulmonary disease occurs more often in adults than in children. However, 33% of children examined have a chest radiograph interpreted as an infiltrate or pneumonia. The clinical presentation in these cases can manifest as rales, infiltrates, and noncardiogenic pulmonary edema. Other findings can include conjunctival suffusion, periorbital edema, dorsal hand and foot edema, and hepatosplenomegaly. Severe disease can include myocarditis, acute renal failure, and vascular collapse.

Persons with glucose-6-phosphate dehydrogenase deficiency are at increased risk for fulminant RMSF, defined as death from *R. rickettsii* infection within 5 days. The clinical course of fulminant RMSF is characterized by profound coagulopathy and extensive thrombosis leading to kidney, liver, and respiratory failure. Features associated with increased risk of death include altered mental status, admission to an intensive care unit, need for inotropic support, coma, and need for rapidly administered intravenous fluid.

Occasionally, clinical signs and symptoms suggest a localized process such as appendicitis or cholecystitis. Thorough evaluation usually reveals evidence of a systemic process, and unnecessary surgical interventions are avoided.

LABORATORY FINDINGS

Laboratory abnormalities are common but nonspecific. Thrombocytopenia occurs in 60%, and the total white blood cell count is most often normal, with leukocytosis in 24% and leukopenia in 9%. Other characteristic abnormalities include a left-shifted leukocyte differential, anemia (33%), hyponatremia (<135 mEq/mL in 52%), and elevated serum aminotransferase levels (50%).

DIAGNOSIS

Delays in diagnosis and treatment are associated with severe disease and death. Because no reliable diagnostic test is readily available to confirm RMSF during illness, which lasts from 10 days to not more than 3 weeks, the decision to treat must be based on compatible epidemiologic, clinical, and laboratory features. RMSF should be considered in patients presenting spring through fall with an acute febrile illness accompanied by headache and myalgia (particularly if they report exposure to ticks or contact with a dog or have been in forested or tick-infested rural areas). A history of tick exposure, a rash (especially if on the palms or soles), a normal or low leukocyte count with a marked left shift, a relatively low or decreasing platelet count, and a low serum sodium concentration are all clues that can support a diagnosis of RMSF. In patients without a rash or in dark-skinned patients in whom a rash can be difficult to appreciate, the diagnosis can be exceptionally elusive and delayed. One half of pediatric deaths occur within 9 days of onset of symptoms. Thus treatment should not be withheld pending definitive laboratory results for a patient with clinically suspected illness. Further, prompt response to early treatment is diagnostically helpful.

If a rash is present, a vasculotropic rickettsial infection can be diagnosed as early as day 1 or 2 of illness with biopsy of a petechial lesion and immunohistochemical or immunofluorescent demonstration of a specific rickettsial antigen in the endothelium. Although highly specific, the sensitivity of this method is probably 70% at most. Furthermore, it can be adversely influenced by prior antimicrobial therapy, suboptimal selection of skin lesions for biopsy, and examination of insufficient tissue because of the focal nature of the infection. Tissue or blood can also be evaluated for *R. rickettsii* nucleic acids by polymerase chain reaction (PCR) at the CDC and selected public health or reference laboratories; PCR on blood is less sensitive than PCR on tissue and of similar sensitivity to tissue immunohistochemistry, probably because the level of rickettsemia is generally very low (<6 rickettsiae/mL). Because eschars are rare with RMSF, scab scrapings or skin swabs are not useful specimens for the detection of rickettsemia by PCR.

Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titer is not seen until after the first week of illness. The gold standard for the diagnosis of RMSF is a fourfold increase in immunoglobulin G antibody titer by indirect fluorescent antibody assay between paired acute and convalescent (at 2-4 weeks) sera, including in the case of seroconversion. A single IgG titer is neither sensitive (patients can die before seroconversion) nor specific (an elevated titer can represent prior infection). IgM is nonspecific and does not confirm acute infection. With current serologic methods, RMSF cannot be reliably distinguished from other spotted fever group rickettsiae infections, some of which are not known to be pathogenic. Therefore confirming acute spotted fever group rickettsia infection requires a compatible clinical illness. Cross reactions of spotted fever group rickettsiae with typhus group rickettsiae also occur, but titers may be lower for the typhus group. Cross reactions are not seen with *Ehrlichia* or *Anaplasma* infections. Currently, enzyme-linked immunosorbent assay (ELISA) serologic methods can only provide "probable" rather than confirmed evidence of infection. Weil-Felix antibody testing should not be performed because it lacks both sensitivity and specificity. RMSF and other spotted fever group rickettsioses are reportable diseases in the United States; however, few reported cases include paired IgG serology, PCR with sequencing, and epidemiologic and clinical metadata. Therefore little is known about the breadth, pathogenicity, and epidemiology of different spotted fever group rickettsiae in the United States or across the globe. Chronic infections by spotted fever group rickettsiae are not documented, such that positive serologic tests after 1 month or more do not reflect ongoing spotted fever group rickettsia infection.

DIFFERENTIAL DIAGNOSIS

Other rickettsial infections are easily confused with RMSF, especially all forms of human ehrlichiosis and murine typhus and novel spotted fever group rickettsioses that result from *R. parkeri* or "*R. philipii*" str. 364D infections. RMSF can also mimic a variety of other diseases, such as meningococcemia and enterovirus infections. Negative blood cultures can exclude meningococcemia. PCR can differentiate enterovirus from *R. rickettsii* in patients with aseptic meningitis and cerebrospinal fluid pleocytosis. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, Lyme disease, leptospirosis, rat-bite fever, scarlet fever, toxic shock syndrome, rheumatic fever, rubella, parvovirus infection, Kawasaki disease, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, hemolytic uremic syndrome, aseptic meningitis, acute gastrointestinal illness, acute abdomen, hepatitis, infectious mononucleosis, hemophagocytic and macrophage activation syndromes, dengue fever, and drug reactions.

TREATMENT

The time-proven effective therapies for RMSF are tetracyclines and chloramphenicol. The treatment of choice for suspected RMSF in patients of all ages, including children under 8 years of age, is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) is an alternative. Chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day) should be reserved for patients with doxycycline allergy and for pregnant women because chloramphenicol is an independent risk factor for increased mortality vs tetracyclines. If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Chloramphenicol is preferred for pregnant women because of potential adverse effects of doxycycline on fetal teeth and bone and maternal liver function. RMSF is a life-threatening illness for which prompt therapy is imperative, and multiple recent studies demonstrate a negligible risk for tooth discoloration in children younger than 8 years of age with the use of doxycycline. Chloramphenicol is rarely associated with aplastic anemia and is no longer available as an oral preparation in the United States. An additional benefit of doxycycline over chloramphenicol is its effectiveness against potential concomitant *Ehrlichia* or *Anaplasma* infection. Sulfonamides should not be used because they are associated with greater morbidity and mortality with all rickettsial infections. Other antibiotics, including penicillins, cephalosporins, and aminoglycosides, are not effective. The use of alternative antimicrobial agents, such as fluoroquinolones and the macrolides (azithromycin and clarithromycin), has not been evaluated.

Therapy should be continued for a minimum of 5-7 days and until the patient has been afebrile for at least 3 days. Treated patients usually defervesce within 48 hours, so the duration of therapy is usually <10 days. Spotted fever group rickettsia infection resolves within several weeks if treated appropriately; thus patients with remitting clinical manifestations after 1 month do not benefit from continued or additional treatment.

SUPPORTIVE CARE

Most infections resolve rapidly with appropriate antimicrobial therapy and do not require hospitalization or other supportive care. Among those hospitalized, 36% require intensive care. Particular attention to hemodynamic status is mandatory in severely ill children because iatrogenic pulmonary or cerebral edema could be easily precipitated owing to diffuse microvascular injury of the lungs, meninges, and

brain. Judicious use of corticosteroids for meningoencephalitis has been advocated by some, but no controlled trials have been conducted.

COMPLICATIONS

Complications of RMSF include noncardiogenic pulmonary edema from pulmonary microvascular leakage, cerebral edema from meningoencephalitis, and multiorgan damage (hepatitis, pancreatitis, cholecystitis, epidermal necrosis, and gangrene) mediated by rickettsial vasculitis and/or the accumulated effects of hypoperfusion and ischemia (acute renal failure). Long-term neurologic sequelae can occur in any child with RMSF but are more likely to occur in those hospitalized for ≥2 weeks. Examples of neurologic sequelae include speech or swallowing disorders; global encephalopathy; cerebellar, vestibular, and motor dysfunction; hearing loss; and cortical blindness. Learning disabilities and behavioral problems are the most common neurologic sequelae among children who have survived severe disease.

PROGNOSIS

Delays in diagnosis and therapy are significant factors associated with severe illness or death. Before the advent of effective antimicrobial therapy for RMSF, the case fatality rate was 10% for children and 30% for adults. The overall case fatality rate decreased to a historic low (0.3–0.4%) from 2003 to 2012; however, many experts attribute this decrease to detection and reporting of other less virulent emerging forms of spotted fever group rickettsioses that cannot be readily differentiated from RMSF using current serologic tests. The overall case fatality rate of children 0-9 years of age was 1.4%, but rates as high as 8.5% and 11.8% were documented in Texas (1986–1996) and in Arizona (1999–2007), respectively, and rates as high as 30–40% are now reported from outbreaks in Mexico, Brazil, and other parts of South America. Diagnosis based on serology alone underestimates the true mortality of RMSF, because death occurs at a median of 7 days (before developing a serologic response). Deaths occur despite the availability of effective therapeutic agents, indicating the need for clinical vigilance and a low threshold for early empiric therapy. Even with administration of appropriate antimicrobials, delayed therapy can lead to irreversible vascular or end-organ damage and long-term sequelae or death. Early therapy in uncomplicated cases usually leads to rapid defervescence within 1-3 days and recovery within 7-10 days. A slower response may be seen if therapy is delayed. In those who survive despite no treatment, fever subsides in 2-3 weeks.

PREVENTION

No vaccines are available. Prevention of RMSF is best accomplished by preventing or treating tick infestation in dogs, avoiding areas where ticks reside, using insect repellents containing N,*N*-diethyl-3-methylbenzamide (DEET) or new alternatives (https://www.epa.gov/insect-repellents/find-repellent-right-you), wearing protective clothing, and carefully inspecting children after play in areas where they are potentially exposed to ticks. Recovery from infection yields lifelong immunity.

Prompt and complete removal of attached ticks helps reduce the risk for transmission because rickettsiae in the ticks need to be reactivated to become virulent, and this requires at least several hours to days of exposure to body heat or blood. Contrary to popular belief, the application of petroleum jelly, 70% isopropyl alcohol, fingernail polish, or a hot match are not effective in removing ticks. A tick can be safely removed by grasping the mouth parts with a pair of forceps at the site of attachment to the skin and applying gentle and steady pressure to achieve retraction without twisting, thereby removing the entire tick and its mouth parts. The site of attachment should then be disinfected. Ticks should not be squeezed or crushed, because their fluids may be infectious. The removed tick should be soaked in alcohol or flushed down the toilet, and hands should be washed to avoid accidental inoculation into conjunctivae, mucous membranes, or breaks in skin. Typically, prophylactic antimicrobial therapy is not recommended because tetracyclines and chloramphenicol are only rickettsiastatic; however, the evidence to support this position is meager.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

274.2 Mediterranean Spotted Fever or Boutonneuse Fever (*Rickettsia conorii*)

Megan E. Reller and J. Stephen Dumler

MSF, or boutonneuse fever, is caused by *R. conorii;* it is also called by other names, such as *Kenya tick typhus, Indian tick typhus, Israeli spotted fever,* and *Astrakhan fever*. It is a moderately severe vasculotropic rickettsiosis in adults but comparatively milder in children, with more frequent lymphadenopathy; often, MSF is initially associated with an eschar at the site of the tick bite. Minor differences in clinical presentation could be associated with genetic diversity of this species.

ETIOLOGY

MSF is caused by systemic endothelial cell infection by the obligate intracellular bacterium *R. conorii*. Similar species are distributed globally, such as *R. sibirica, R. heilongjiangensis,* and *R. mongolotimonae* in Russia, China, Mongolia, and Pakistan; *R. australis* and *R. honei* in Australia; *R. japonica* in Japan; *R. africae* in South Africa; and *R. parkeri* and "*R. philippii*" str. 364D in the Americas (see Table 274.1). Analysis of antigens and related DNA sequences show that all are closely related within a broad genetic clade that includes spotted fever group *Rickettsia* species such as *R. rickettsii*, the cause of RMSF.

EPIDEMIOLOGY

R. conorii is distributed over a large geographic region, including India, Pakistan, Russia, Ukraine, Georgia, Israel, Morocco, southern Europe, Ethiopia, Kenya, and South Africa. Reported cases of MSF in southern Europe have steadily increased since 1980, and the seroprevalence is 11–26% in some areas. The peak in reported cases occurs during July and August in the Mediterranean basin; in other regions it occurs during warm months when ticks are active.

TRANSMISSION

Transmission occurs after the bite of the brown dog tick, *R. sanguineus,* or for other *Rickettsia* spp. tick genera such as *Dermacentor, Haemaphysalis, Amblyomma, Hyalomma,* and *Ixodes.* Clustering of human cases of boutonneuse fever, infected ticks, and infected dogs implicates the household dog as a potential vehicle for transmission.

PATHOLOGY AND PATHOGENESIS

The underlying pathology seen with MSF is nearly identical to that of RMSF, except that eschars are often present at the site of a tick bite where inoculation of rickettsiae occurs. The histopathology of the resultant lesion includes necrosis of dermal and epidermal tissues with a superficial crust; a dermis densely infiltrated by lymphocytes, histiocytes, and scattered neutrophils; and damaged capillaries and venules in the dermis. Immunohistochemical stains and nucleic acid amplification tests confirm that the lesions contain rickettsia-infected endothelial cells and potentially other cells such as macrophages. The necrosis results from both direct rickettsia-mediated vasculitis and resultant extensive local inflammation. Thus rickettsiae have ready access to lymphatics and venous blood and disseminate to cause systemic disease.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Typical findings in children include fever (37–100%), a maculopapular rash that appears 3-5 days after onset of fever (94–100%), hepatosplenomegaly (20–83%), myalgias and arthralgias (10–42%), headache (8–63%), nausea, vomiting, or diarrhea (5–28%), and lymphadenopathy (52–54%). In 60–90% of patients, a **painless eschar**, or **tache noire**, appears at the site of the tick bite, often on the scalp, with accompanying regional lymphadenopathy (50–60%) (Fig. 274.6). The infection can be severe, mimicking RMSF, although morbidity and fatalities in children

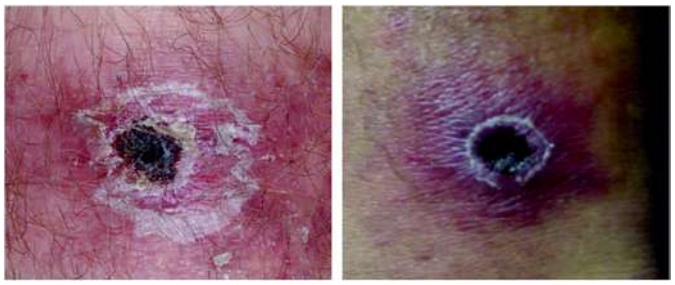

Fig. 274.6 Various appearances of eschars associated with *Rickettsia parkeri* rickettsiosis. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 24.)*

are less frequent than in adults. Findings can include seizures, purpuric skin lesions, meningitis and neurologic deficits, respiratory and/or acute renal failure, and severe thrombocytopenia. Even though the case fatality rate can be as high as 10% in adults and severe infections occur in approximately 9% of children, pediatric deaths are rare. As with RMSF, a particularly severe form occurs in patients with glucose-6-phosphate dehydrogenase deficiency and in patients with underlying conditions such as alcoholic liver disease or diabetes mellitus.

DIAGNOSIS

Laboratory diagnosis of MSF and related spotted fever group rickettsioses is the same as that for RMSF. Cases can be confirmed by immunohistologic or immunofluorescent demonstration of or amplification of nucleic acids from rickettsiae in eschar crust or skin biopsies, or demonstration of seroconversion, or accompanied by a fourfold rise in serum antibody titer to spotted fever group rickettsiae between acute and convalescent sera. Antibodies to spotted fever group antigens cross react, so RMSF or other spotted fever group rickettsiosis in the United States or MSF in Europe, Africa, and Asia cannot be distinguished by these methods. When eschars are present, biopsy of the eschar with submission of tissue or a swab of the base for PCR provides considerably higher sensitivity than PCR on blood and is advocated, if available. In vitro cultivation via centrifugation-assisted shell vial tissue culture is rarely used for clinical diagnosis. Treatment should not be withheld while waiting for diagnostic test results.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes conditions also associated with single eschars, such as anthrax, bacterial ecthyma, brown recluse spider bite, rat-bite fever (caused by *Spirillum minus*), and other rickettsioses (such as rickettsialpox, African tick-bite fever, *R. parkeri* or "*R. philipii*" str. 364D rickettsiosis, and scrub typhus). The spotted fever group rickettsia *R. africae* causes African tick-bite fever, a milder illness than MSF that is often associated with multiple eschars and occasionally a vesicular rash. African tick-bite fever can be contracted in North Africa, where MSF also occurs, and is a common infection of travelers to sub-Saharan Africa who encounter bush or high grasslands on safari. *R. parkeri* and "*R. philipii*" str. 364D rickettsiosis are emerging infections in North and South America and in the U.S. western states, respectively. Both often present with an eschar and milder clinical manifestations similar to those observed with African tick-bite fever.

TREATMENT AND SUPPORTIVE CARE

In adults, MSF is effectively treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, or clarithromycin. For children, the treatment of choice is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Tetracycline and chloramphenicol are alternatives, as for RMSF. Azithromycin (10 mg/kg/day once daily PO for 3 days) and clarithromycin (15 mg/kg/day divided twice daily PO for 7 days) are also used. Specific fluoroquinolone regimens effective for children have not been established, although recent reports suggest that the use of fluoroquinolones is associated with increased disease severity as compared with doxycycline. Intensive care may be required.

COMPLICATIONS

The complications of MSF are similar to those of RMSF. Overall, the case fatality rate is less than 2%, but fatalities are rare in children. Particularly severe infections have been noted in patients with underlying medical conditions, including glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus.

PREVENTION

MSF is transmitted by tick bites, and prevention is the same as recommended for RMSF. No vaccine is currently available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

274.3 Rickettsialpox *(Rickettsia akari)* and Flea-Borne Spotted Fever

Megan E. Reller and J. Stephen Dumler

Rickettsialpox is caused by *R. akari,* a transitional-group *Rickettsia* species that is transmitted by the mouse mite, *Allodermanyssus sanguineus.* The mouse host for this mite is widely distributed in cities in the United States, Europe, and Asia. Seroepidemiologic studies suggest a high prevalence of this infection in urban settings. The disease is uncommon and is usually mild. Unlike the situation with most forms of rickettsiosis, the macrophage is an important target cell for *R. akari.*

Rickettsialpox is best known because of its association with a varicelliform rash. In fact, this rash is a modified form of an antecedent typical macular or maculopapular rash like those seen in other vasculotropic rickettsioses and is occasionally seen with other rickettsioses such as African tick-bite fever. Clinical descriptions in children are infrequent. At presentation, most patients have fever, headache, and chills. In up to 90% of cases, there is a painless papular, ulcerative lesion, or eschar at the initial site of inoculation, which can be associated with tender regional lymphadenopathy. In some patients, the maculopapular rash becomes vesicular, involving the trunk, head, and extremities. The infection generally resolves spontaneously and does not require therapy. However, a short course of doxycycline hastens resolution and is sometimes used in patients older than 8 years of age and in young children with relatively severe illness. Complications and fatalities are rare; however, clear examples of severe disease in children like that observed with RMSF are described.

Flea-borne spotted fever, caused by *Rickettsia felis,* is often considered within the typhus group because of flea transmission; however, phylogenetic studies place it close to the *Rickettsia* genus spotted fever or within the "transitional" group. Similarly, a related cat flea–associated agent, *R. asembonensis,* was isolated from cat fleas; it and other related rickettsiae in fleas have been identified in environmental samples over broad geographic regions but are not known to cause human disease. Since the discovery of *R. felis* in a febrile patient from Texas by use of molecular amplification methods, and its subsequent isolation from infected cat fleas, molecular and cross reactive serologic tests have purported to identify human infections globally, some at high rates of prevalence. Clinical isolates have yet to be made from infected humans, and many patients identified by molecular methods lack serologic responses or even clinical signs. Its identification within mosquitoes and in conjunction with malaria further confound its role as a human pathogen. Until many of the discrepant findings observed with *R. felis* are resolved, its role as an important infectious agent in humans remains to be resolved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 275

Scrub Typhus (*Orientia tsutsugamushi*)

Megan E. Reller and J. Stephen Dumler

Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific and could be emerging in the Middle East, Africa, and South America. The causative agent is distinct from, but related to, *Rickettsia* species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi* or emerging *Orientia* spp. such as "*O. chuto*" and "*O. chiloensis,*" hampering vaccine development.

ETIOLOGY

The causative agent of scrub typhus, or tsutsugamushi fever, is *O. tsutsugamushi,* which is distinct from other spotted fever and typhus group rickettsiae (see Table 274.1 in Chapter 274). *O. tsutsugamushi* lacks both lipopolysaccharide and peptidoglycan in its cell wall. Like other vasculotropic rickettsiae, *O. tsutsugamushi* infects endothelial cells and causes vasculitis, the predominant clinicopathologic feature of the disease. However, the organism also infects macrophages and cardiac myocytes. A new *Candidatus* species, "*Orientia chuto,*" was isolated from a patient in the Middle East, and definitive evidence of infection based on serology and/or PCR amplification of *O. tsutsugamushi* genes from acute-phase blood suggests a wider range for scrub typhus and related infections. Similarly, a scrub typhus–like illness in southern Chile has been attributed to infection by a new species, "*Orientia chiloensis*."

EPIDEMIOLOGY

At least 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk. Scrub typhus is recognized mostly in Asia, including areas delimited by Korea, Pakistan, and northern Australia. Outside these tropical and subtropical regions, the disease occurs in Japan, the Primorsky of far eastern Russia, Tajikistan, Nepal, and nontropical China, including Tibet. Cases imported to the United States and other parts of the world are reported. Endemic scrub typhus has historically been confined to Asia and Oceania and the tsutsugamushi triangle; however, *Orientia* may be distributed more broadly, with confirmed cases in South America and possible cases in Africa. Most infections in children are acquired in rural areas. In Thailand and Sri Lanka, scrub typhus is the cause of 1–8% of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.

TRANSMISSION

O. tsutsugamushi is transmitted via the bite of the larval stage (chigger) of a trombiculid mite (*Leptotrombidium* in Asia, *Herpetacarus* in Chile, and *Microtrombicula* in Africa), which serves as both vector and reservoir. Vertical transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among co-feeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

PATHOLOGY AND PATHOGENESIS

The pathogenesis of scrub typhus is uncertain. The process may be stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions observed in histopathologic examinations. In autopsy series, the major result of the vascular injury appears to be hemorrhage. However, data support the concept that vascular injury initiated by the infection is sustained by immune-mediated inflammation that together cause significant vascular leakage. The net result is significant vascular compromise and ensuing end-organ injury, most often manifested in the brain and lungs, as with other vasculotropic rickettsioses.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Scrub typhus can be mild or severe in children and can affect almost every organ system. Most patients present with fever for 9-11 days (range: 1-30 days) before seeking medical care. Regional or generalized lymphadenopathy is reported in 23–93%, hepatomegaly in about two thirds, and splenomegaly in about one third of children with scrub typhus. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea, occur in up to 40% of children at presentation. A **single painless eschar** with an erythematous rim at the site of the chigger bite is seen in 7–68% of cases, and a maculopapular rash is present in less than half; both can be absent. Hemophagocytic lymphohistiocytosis has been described. Leukocyte and platelet counts are most commonly within normal ranges, although thrombocytopenia occurs in one quarter to one third of children, and leukocytosis is observed in approximately 40% of children. Clinical manifestations often respond dramatically to appropriate treatment. Adverse outcomes in fetuses and newborn infants of infected mothers have been described, resulting from vertical transmission.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Owing to the potential for severe complications, diagnosis and decision to initiate treatment should be based on clinical suspicion. The reference diagnostic standard for acute scrub typhus remains demonstration of a fourfold rise in IgG antibody titer by indirect fluorescent antibody testing of acute-phase and convalescent-phase (obtained at 2- to 4-week follow-up) sera. The IgG indirect fluorescent antibody assay is >90% sensitive with 11 days or more of fever but does not distinguish acute from past infection in those residing in endemic regions. A positive acute-phase IgM is also not definitive evidence of acute scrub typhus. Although the rickettsiae can be cultivated using tissue culture methods, polymerase chain reaction tests are not highly sensitive, and these diagnostic methods are not widely available. The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, and infectious mononucleosis.

TREATMENT AND SUPPORTIVE CARE

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hours; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hours; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/24 hr). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Alternatives now supported by data from randomized trials include azithromycin (10 mg/kg PO on day 1, then 5 mg/kg PO; maximum: 500 mg/day) or clarithromycin (15-30 mg/kg/day PO divided every 12 hours; maximum: 1 g/day). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid relapse. However, a single dose of oral doxycycline was reported effective for all 38 children treated with this regimen in a large series from Thailand. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range: 1-5 days). Strains of *O. tsutsugamushi* with modestly higher doxycycline minimal inhibitory concentrations are reported in some regions of Thailand. Clinical trials showed that azithromycin could be as effective and that rifampicin is superior to doxycycline in such cases and could have a role as an alternative therapy, especially for pregnant women. The use of ciprofloxacin in pregnant women resulted in an adverse outcome in

five of five pregnancies among Indian women. Intensive care may be required for hemodynamic management of severely affected patients.

COMPLICATIONS

Serious complications include pneumonitis in 20–35% and meningoencephalitis in approximately 10–25% of children. Acute renal failure, myocarditis, and septic shock occur less often. Cerebrospinal fluid examination shows a mild mononuclear pleocytosis with normal glucose levels. Chest radiographs reveal transient perihilar or peribronchial interstitial infiltrates in most children who are examined. The reported case fatality rate varies widely; among 883 patients <20 years of age in 18 published studies, the case fatality rate was 11%; the median for the studies was 1.6–1.8% and ranged as high as 33%. In a contemporary systematic review and meta-analysis of Indian children, the case fatality rate was 1.1%.

PREVENTION

Prevention is based on avoidance of the chiggers that transmit *O. tsutsugamushi.* Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, because natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. No vaccines are currently available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 276

Typhus Group Rickettsioses

Megan E. Reller and J. Stephen Dumler

Members of the typhus group of rickettsiae (see Table 274.1 in Chapter 274) include *Rickettsia typhi,* the cause of murine typhus, and *Rickettsia prowazekii,* the cause of louse-borne or epidemic typhus. *R. typhi* is transmitted to humans by fleas, and *R. prowazekii* is transmitted in the feces of body lice. Louse-borne or epidemic typhus is widely considered to be the most virulent of the rickettsial diseases, with a high case fatality rate even with treatment. Murine typhus is moderately severe and likely underreported worldwide; global warming and increased precipitation may increase cases and spread. The genomes of both *R. typhi* and *R. prowazekii* are similar.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

276.1 Murine (Endemic or Flea-Borne) Typhus *(Rickettsia typhi)*

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Murine typhus is caused by *R. typhi,* a rickettsia transmitted from infected fleas to rats, other rodents, or opossums and back to fleas. Transovarial transmission (passage of the organism from infected fleas to their progeny) in fleas is inefficient. Transmission depends on infection from the flea to uninfected mammals that then sustain transient rickettsemia and serve as sources of the bacterium for uninfected fleas that bite during the period of rickettsemia.

EPIDEMIOLOGY

Murine typhus has a worldwide distribution and occurs especially in warm coastal ports, where it is primarily maintained in a cycle involving rat fleas *(Xenopsylla cheopis)* and rats (*Rattus* species). Peak incidence occurs when rat populations are highest during spring, summer, and fall. Sentinel surveillance studies suggest that travel-acquired murine typhus occurs most often in those visiting Southeast Asia and Africa. In the United States, murine typhus was prevalent before eradication efforts using DDT in the 1940s and is now re-emerging. The disease is recognized most often in south Texas and Southern California. However, seroprevalence studies among children indicate that murine typhus is acquired across the southeast and southcentral United States, thus expanding the endemic areas in which pediatricians must be alert for this infection. In the coastal areas of south Texas and in Southern California, the disease is seen in all months, but predominantly from January through July, and is associated with a *sylvatic cycle* involving opossums and cat fleas *(Ctenocephalides felis)*. The marked increase in reported cases in the past decade likely relates to increased recognition, improved surveillance, and ecologic factors.

TRANSMISSION

R. typhi normally cycles between rodents or midsize animals such as opossums and their fleas. Human acquisition of murine typhus occurs when rickettsiae-infected flea feces contaminate flea bite wounds. Direct inoculation via flea bite is possible, but inefficient.

PATHOLOGY AND PATHOGENESIS

R. typhi is a vasculotropic rickettsia that causes disease in a manner similar to *Rickettsia rickettsii* (see Chapter 274.1). *R. typhi* organisms in flea feces deposited on the skin as part of the flea feeding reflex are inoculated into the pruritic flea bite wound. After an interval for local proliferation, the rickettsiae spread systemically via lymphatics to the blood, after which they infect the endothelium in many tissues. As with spotted fever group rickettsiae, typhus group rickettsiae infect endothelial cells, but unlike the spotted fever group rickettsiae, they polymerize intracellular actin poorly, have limited intracellular mobility, and probably cause cellular injury by either enzymatic membrane or mechanical lysis after accumulating in large numbers within the endothelial cell cytoplasm. Intracellular infection leads to endothelial cell damage, recruitment of inflammatory cells, and vasculitis. The inflammatory cell infiltrates bring in a number of effector cells, including macrophages that produce proinflammatory cytokines, and CD4, CD8, and natural killer lymphocytes, which can produce immune cytokines such as interferon-γ or participate in cell-mediated cytotoxic responses. Intracellular rickettsial proliferation of typhus group rickettsiae is inhibited by cytokine-mediated mechanisms and nitric oxide–dependent and –independent mechanisms.

Pathologic findings include systemic vasculitis in response to rickettsiae within endothelial cells. This vasculitis manifests as interstitial pneumonitis, meningoencephalitis, interstitial nephritis, myocarditis, and mild hepatitis with periportal lymphohistiocytic infiltrates. As vasculitis and inflammatory damage accumulate, multiorgan damage can ensue.

CLINICAL MANIFESTATIONS

In children, murine typhus is generally a self-limited infection, but can be severe, similar to other vasculotropic rickettsioses. The incubation period varies from 1 to 2 weeks. The initial presentation is often nonspecific and mimics typhoid fever; fever of undetermined origin is the most common presentation. Pediatric patients with murine typhus exhibit symptoms classically attributed to other vasculotropic rickettsioses, such as rash (48–80%), myalgias (29–57%), vomiting (29–45%), cough (15–40%), headache (19–77%), and diarrhea or abdominal pain (10–40%). A petechial rash is observed in <15% of children, and the usual appearance is that of macules or maculopapules distributed on the trunk and extremities. The rash can involve both the soles and palms. Among common clinical features, only abdominal pain, diarrhea, and sore throat are more common in children than in adults, underscoring

the mild nature of most cases in children. Murine typhus–associated hemophagocytic lymphohistiocytosis (HLH) is described. Although neurologic involvement is a common finding in adults with murine typhus, photophobia, confusion, stupor, coma, seizures, meningismus, and ataxia are seen in <20% of hospitalized children and <6% of infected children treated as outpatients. Poor neonatal outcomes are reported with infection during pregnancy; however, frequency and clinical spectrum are not well documented.

LABORATORY FINDINGS

Although nonspecific, laboratory findings are less severe than in adults. Helpful findings include mild leukopenia (28–40%) with a moderate left shift, mild to marked thrombocytopenia (30–60%), hyponatremia (20–66%), hypoalbuminemia (30–87%), and elevated aspartate aminotransferase (82%) and alanine aminotransferase (38%). Elevations in serum urea nitrogen are usually a result of prerenal mechanisms.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Delays in diagnosis and therapy are associated with increased morbidity and mortality; thus diagnosis must be based on clinical suspicion. Occasionally, patients present with findings suggesting pharyngitis, bronchitis, hepatitis, gastroenteritis, or sepsis; thus the differential diagnosis may be extensive. Murine typhus can also mimic SARS-CoV-2–associated multisystem inflammatory syndrome in children (MIS-C).

Confirmation of the diagnosis is usually accomplished by comparing acute- and convalescent-phase antibody titers obtained with the indirect fluorescent antibody assay (IFA) to demonstrate a fourfold rise in titer. Current objective studies of the diagnostic yield of *R. typhi* nucleic acid amplification from acute-phase whole blood show disappointingly low sensitivity, and rickettsial culture is not readily available. Thus paired (acute and convalescent) serology to demonstrate a fourfold rise in immunoglobulin (Ig) G antibody titer by IFA remains the standard for confirming acute infection. Use of IgM serologic tests is discouraged for diagnosis of rickettsial infections because of both limited sensitivity and specificity.

TREATMENT

A meta-analysis of murine typhus in children reviewed treatment in 261 children, including 54 who received no antimicrobial therapy. Although 15% had complications, there were no deaths. The standard therapy for murine typhus in children was similar to that for adults and focused on use of tetracyclines or chloramphenicol. Quinolones have been used in children, and limited clinical studies show that ciprofloxacin is as effective as doxycycline and chloramphenicol to treat murine typhus; however, treatment failures are reported. In vitro experiments suggest that minimal inhibitory concentrations of azithromycin and clarithromycin for *R. typhi* should be easily achieved. However, in adult patients, a prospective randomized clinical trial showed that either a 3- or 7-day course of doxycycline was superior to 3 days of azithromycin for fever clearance.

Therefore the time-honored recommended treatment for murine typhus remains doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day). Therapy should be for a minimum of 3 days and continued until the patient has been afebrile for at least 3 days.

SUPPORTIVE CARE

Although disease is usually mild, 15% of children have complications and 2–7% require intensive care for management of meningoencephalitis, a disseminated intravascular coagulation–like condition, or other conditions. As for other rickettsial infections with significant systemic vascular injury, careful hemodynamic management is mandatory to avoid pulmonary or cerebral edema.

COMPLICATIONS

Complications of murine typhus in pediatric patients are uncommon; however, relapse, stupor, facial edema, dehydration, splenic rupture, and meningoencephalitis are reported. Predominance of abdominal pain has led to surgical exploration to exclude a perforated viscus.

PREVENTION

Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this approach remains important. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban areas where close human exposures occur poses increasingly difficult control problems. It is not known with certainty if infection confers protective immunity; reinfection appears to be rare.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

276.2 Epidemic (Louse-Borne) Typhus (*Rickettsia prowazekii*)

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Humans are considered the principal reservoir of *R. prowazekii,* the causative agent of epidemic or louse-borne typhus and its recrudescent form, Brill-Zinsser disease. Another reservoir exists in flying squirrels, their ectoparasites, and potentially ticks in a sylvatic cycle with small rodents. *R. prowazekii* is the most pathogenic member of the genus *Rickettsia* and multiplies to very large intracellular quantities before rupture of infected endothelial cells.

EPIDEMIOLOGY

The infection is characteristically seen in winter or spring and especially during times of poor hygienic practices associated with crowding, war, famine, extreme poverty, and civil strife. As observed in a recent outbreak among youths at a rehabilitation center in Rwanda, infections in children under these conditions can lead to severe adverse outcomes. *R. prowazekii* has also been associated with sporadic cases of a mild, typhus-like illness in the United States; such cases are associated with exposure to flying squirrels harboring infected lice or fleas. *R. prowazekii* organisms isolated from these squirrels appear to be genetically similar to isolates obtained during typical outbreaks.

Most cases of louse-borne typhus in the developed world are sporadic, but outbreaks have been identified in Africa (Ethiopia, Nigeria, Rwanda, and Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, Russia, northern India, and China within the past 25 years. After the Burundi Civil War in 1993, 35,000-100,000 cases of epidemic typhus were diagnosed in displaced refugees, resulting in an estimated 6,000 deaths.

TRANSMISSION

Human body lice *(Pediculus humanus)* become infected by feeding on persons who have rickettsiae circulating in their blood owing to endothelial cell infection. The ingested rickettsiae infect the midgut epithelial cells of the lice and are passed into the feces, which, in turn, are introduced into a susceptible human host through abrasions or perforations in the skin, through the conjunctivae, or rarely, through inhalation as fomites in clothing, bedding, or furniture.

CLINICAL MANIFESTATIONS

Louse-borne typhus can be mild or severe in children. The incubation period is usually <14 days. The typical clinical manifestations include fever, severe headache, abdominal tenderness, and rash in most patients, as well as chills (82%), myalgias (70%), arthralgias (70%), anorexia (48%), nonproductive cough (38%), dizziness (35%),

photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%), meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.5% and 20% in outbreaks.

Brill-Zinsser disease is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.

TREATMENT

Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days. Evidence exists that doxycycline as a single 200-mg oral dose (4.4 mg/kg if <45 kg) is also efficacious.

PREVENTION

Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus searches for ectoparasites should include examination of clothing. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 277

Ehrlichiosis and Anaplasmosis

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Ehrlichiosis in humans was first described in 1987, when clusters of bacteria confined within cytoplasmic vacuoles of circulating leukocytes (morulae), particularly **mononuclear** leukocytes, were detected in the peripheral blood of a patient with suspected Rocky Mountain spotted fever (RMSF). The etiologic agent, *Ehrlichia chaffeensis,* was cultivated from blood of an infected patient in 1990 and identified as the predominant cause of human ehrlichiosis. Investigations showed that infection by *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks and occurs more often than RMSF in some geographic areas. By 1994, other cases in which morulae were found only in **neutrophils** and lacked serologic evidence for *E. chaffeensis* infection led to the recognition of the species classified as *Anaplasma phagocytophilum,* which encompasses several previously described veterinary pathogens on at least two different continents and causes **anaplasmosis**.

Since these discoveries, additional species in the Anaplasmataceae family were identified as human pathogens, including (1) *Ehrlichia ewingii* in 1996, a veterinary pathogen of canine neutrophils transmitted by *A. americanum* ticks; (2) the *Ixodes scapularis*–transmitted *Ehrlichia muris* subsp. *eauclairensis* in 2009, only present so far in patients from Minnesota and Wisconsin in the United States; (3) infections by *Candidatus* Neoehrlichia mikurensis, presumably *Ixodes* spp. or *Haemaphysalis concinna* tick-transmitted, recognized in 2010 as a cause of sepsis-like infections of immune-compromised patients in Europe, and later as a cause of mild febrile illness in healthy individuals in China; (4) Panola Mountain *Ehrlichia,* a bacterium rarely associated with infections in humans but present in *A. americanum* ticks in the United States and with genetic features of the ruminant pathogen *Ehrlichia ruminantium*; (5) *Ehrlichia canis,* the established canine pathogen that has infected humans in Venezuela and possibly Costa Rica; and (6) *Anaplasma capra,* the cause of mild fever after *Ixodes persulcatus* tick bites, so far only identified in China. The latter five have not yet been established as causes of infection in children.

Although the infections caused by these various genera have been called ehrlichiosis, further study has identified substantial differences in biology and diagnostic approaches such that the CDC now generally separates these into ehrlichiosis, anaplasmosis, or undetermined ehrlichiosis/anaplasmosis. **Human monocytic ehrlichiosis (HME)**, or simply ehrlichiosis, describes disease characterized by infection of predominantly monocytes and is caused by *E. chaffeensis;* **human granulocytic anaplasmosis (HGA)**, now "anaplasmosis," describes disease related to infection of circulating neutrophils by *Anaplasma phagocytophilum;* and **ewingii ehrlichiosis** is caused by infection of granulocytes by *E. ewingii* (see Table 274.1 in Chapter 274).

All of these organisms are tick-transmitted and are small, obligate intracellular bacteria with gram-negative-type cell walls. *Neorickettsia sennetsu* is another related bacterium that is rarely recognized as a cause of human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a **morula**, an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins that prevent normal endosomal trafficking and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris* subsp. *eauclairensis* grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or modulation of transcription of the host cell that diminishes host defenses toward the bacterium. Yet host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis, such as overlaps with macrophage activation syndrome or hemophagocytic lymphohistiocytosis.

EPIDEMIOLOGY

Infections with *E. chaffeensis* occur across the southeastern, south central, and Mid-Atlantic States of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Reported cases of ehrlichiosis have more than doubled since adoption of the current surveillance case definition in 2008. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in

photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%), meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.5% and 20% in outbreaks.

Brill-Zinsser disease is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.

TREATMENT

Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days. Evidence exists that doxycycline as a single 200-mg oral dose (4.4 mg/kg if <45 kg) is also efficacious.

PREVENTION

Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus searches for ectoparasites should include examination of clothing. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 277

Ehrlichiosis and Anaplasmosis

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Ehrlichiosis in humans was first described in 1987, when clusters of bacteria confined within cytoplasmic vacuoles of circulating leukocytes (morulae), particularly **mononuclear** leukocytes, were detected in the peripheral blood of a patient with suspected Rocky Mountain spotted fever (RMSF). The etiologic agent, *Ehrlichia chaffeensis,* was cultivated from blood of an infected patient in 1990 and identified as the predominant cause of human ehrlichiosis. Investigations showed that infection by *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks and occurs more often than RMSF in some geographic areas. By 1994, other cases in which morulae were found only in **neutrophils** and lacked serologic evidence for *E. chaffeensis* infection led to the recognition of the species classified as *Anaplasma phagocytophilum,* which encompasses several previously described veterinary pathogens on at least two different continents and causes **anaplasmosis**.

Since these discoveries, additional species in the Anaplasmataceae family were identified as human pathogens, including (1) *Ehrlichia ewingii* in 1996, a veterinary pathogen of canine neutrophils transmitted by *A. americanum* ticks; (2) the *Ixodes scapularis*–transmitted *Ehrlichia muris* subsp. *eauclairensis* in 2009, only present so far in patients from Minnesota and Wisconsin in the United States; (3) infections by *Candidatus* Neoehrlichia mikurensis, presumably *Ixodes* spp. or *Haemaphysalis concinna* tick-transmitted, recognized in 2010 as a cause of sepsis-like infections of immune-compromised patients in Europe, and later as a cause of mild febrile illness in healthy individuals in China; (4) Panola Mountain *Ehrlichia,* a bacterium rarely associated with infections in humans but present in *A. americanum* ticks in the United States and with genetic features of the ruminant pathogen *Ehrlichia ruminantium*; (5) *Ehrlichia canis,* the established canine pathogen that has infected humans in Venezuela and possibly Costa Rica; and (6) *Anaplasma capra,* the cause of mild fever after *Ixodes persulcatus* tick bites, so far only identified in China. The latter five have not yet been established as causes of infection in children.

Although the infections caused by these various genera have been called ehrlichiosis, further study has identified substantial differences in biology and diagnostic approaches such that the CDC now generally separates these into ehrlichiosis, anaplasmosis, or undetermined ehrlichiosis/anaplasmosis. **Human monocytic ehrlichiosis (HME)**, or simply ehrlichiosis, describes disease characterized by infection of predominantly monocytes and is caused by *E. chaffeensis;* **human granulocytic anaplasmosis (HGA)**, now "anaplasmosis," describes disease related to infection of circulating neutrophils by *Anaplasma phagocytophilum;* and **ewingii ehrlichiosis** is caused by infection of granulocytes by *E. ewingii* (see Table 274.1 in Chapter 274).

All of these organisms are tick-transmitted and are small, obligate intracellular bacteria with gram-negative-type cell walls. *Neorickettsia sennetsu* is another related bacterium that is rarely recognized as a cause of human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a **morula**, an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins that prevent normal endosomal trafficking and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris* subsp. *eauclairensis* grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or modulation of transcription of the host cell that diminishes host defenses toward the bacterium. Yet host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis, such as overlaps with macrophage activation syndrome or hemophagocytic lymphohistiocytosis.

EPIDEMIOLOGY

Infections with *E. chaffeensis* occur across the southeastern, south central, and Mid-Atlantic States of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Reported cases of ehrlichiosis have more than doubled since adoption of the current surveillance case definition in 2008. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in

areas where *E. chaffeensis* also exists, perhaps owing to the shared tick vector. Canine infections are documented in both sub-Saharan Africa and South America.

Although the median age of patients with ehrlichiosis and anaplasmosis is generally older (>51 years), many infected children have been identified, and for ehrlichiosis, the case fatality rate is 4% in those <5 years of age. Perinatal transmission of ehrlichiosis and anaplasmosis has been documented in case reports. Little is known about the epidemiology of *E. ewingii* infections; although infections in children occur, they are recognized at a rate 100-fold less than for *E. chaffeensis*. All infections are strongly associated with tick exposure and tick bites and are identified predominantly during May through September. Although both nymphal and adult ticks can transmit infection, nymphs are more likely to transmit disease because they are most active during the summer.

TRANSMISSION

The predominant tick species that harbors *E. chaffeensis* and *E. ewingii* is *A. americanum,* the lone star tick (see Fig. 274.2*d* in Chapter 274). The tick vectors of *A. phagocytophilum* are *Ixodes* spp., including *I. scapularis* (black-legged or deer tick) in the eastern United States (see Fig. 274.1 in Chapter 274), *Ixodes pacificus* (western black-legged tick) in the western United States, *Ixodes ricinus* (sheep tick) in Europe, *Ixodes persulcatus* in Eurasia, and *Haemaphysalis* spp. in China. The *Ixodes* spp. ticks also transmit *Borrelia burgdorferi, Borrelia miyamotoi, Borrelia mayonii, Babesia microti,* and tick-borne encephalitis-associated flaviviruses in Europe and Powassan viruses and *E. muris* subsp. *eauclairensis* in North America. Co-infections with these agents and *A. phagocytophilum* are documented in children and adults.

Ehrlichia and *Anaplasma* species are maintained in nature predominantly by horizontal transmission (tick to mammal to tick) because the organisms are not transmitted to the progeny of infected adult female ticks (transovarial transmission). The major reservoir for *E. chaffeensis* is the white-tailed deer *(Odocoileus virginianus)*, which is found abundantly in many parts of the United States. A reservoir for *A. phagocytophilum* in the eastern United States appears to be the white-footed mouse, *Peromyscus leucopus.* Deer or domestic ruminants can sustain persistent asymptomatic infections, but the genetic variants in these reservoirs might not be infectious for humans. Efficient transmission requires persistent infections of mammals. Although *E. chaffeensis* and *A. phagocytophilum* can cause persistent infections in animals, clear evidence of chronic infections in humans is exceedingly rare. Transmission of *Ehrlichia* can occur within hours of tick attachment, in contrast to the 1-2 days of attachment required for transmission of *B. burgdorferi* to occur. Transmission of *A. phagocytophilum* is via the bite of the small nymphal stage of *Ixodes* spp., including *I. scapularis* (see Fig. 274.2a in Chapter 274), and is effective only after 36 hours of attachment on laboratory mice.

PATHOLOGY AND PATHOGENESIS

Although ehrlichiosis and anaplasmosis often clinically mimic RMSF or typhus, vasculitis is rare. Pathologic findings include mild, diffuse perivascular lymphohistiocytic infiltrates; Kupffer cell hyperplasia and mild lobular hepatitis with infrequent apoptotic hepatocytes and, less frequently, centrilobular necrosis, cholestasis, and steatosis; infiltrates of mononuclear phagocytes in the spleen, lymph nodes, and bone marrow with occasional hemophagocytosis; granulomas of the liver and bone marrow in patients with *E. chaffeensis* infections; and hyperplasia of one or more bone marrow hematopoietic lineages.

The exact pathogenetic mechanisms are poorly understood, but histopathologic examinations suggest diffuse macrophage activation and poorly regulated host immune and inflammatory reactions. This activation results in moderate to profound leukopenia and thrombocytopenia despite a hypercellular bone marrow, and deaths often are related to hemorrhage or secondary opportunistic infections. Hepatic and other organ-specific injury occurs by a mechanism that appears to be triggered by the bacterium but is more closely related to induction of innate and adaptive immune effectors that are dysregulated in severely affected patients. Meningoencephalitis with a mononuclear cell pleocytosis in the cerebrospinal fluid (CSF) occurs with ehrlichiosis but is rare with anaplasmosis.

CLINICAL MANIFESTATIONS

The clinical manifestations of ehrlichiosis, anaplasmosis, and ewingii ehrlichiosis are similar. Many well-characterized infections of ehrlichiosis and anaplasmosis of variable severity have been reported in children, including deaths. Whereas anaplasmosis is more common in children, ehrlichiosis appears to be more severe. Children with ehrlichiosis are often ill for 4-12 days, shorter than in adults. Abdominal pain may occur disproportionately in children vs adults with anaplasmosis. In a series of children with ehrlichiosis, most required hospitalization and many (25%) required intensive care; these statistics might represent preferential reporting of severe cases. However, review of case reports and electronic surveillance of anaplasmosis to the CDC identified that 42% of patients 5-9 years of age required hospitalization, and the case fatality rate is 4% among children <5 years of age. Population-based studies document that seroconversion often occurs in children who are well or who have only a mild illness. Many fewer pediatric cases of *E. ewingii* infection are reported, so the clinical manifestations related to this infection are less well characterized. The incubation period (time from last tick bite or exposure) appears to range from 2 days to 3 weeks. Nearly 25% of patients do not report a tick bite.

Clinically, ehrlichiosis and anaplasmosis are undifferentiated febrile illnesses. In ehrlichiosis, fever (~100%), headache (77%), and myalgia (77%) are most common, but many patients also report abdominal pain, nausea, and vomiting. Altered mental status accompanied by other signs of central nervous system involvement is present in 36%. Rash is a common feature (~60%) in children. The rash is usually macular or maculopapular, but petechial lesions can occur. The triad of fever, headache, and rash is observed in ~50%. Photophobia, conjunctivitis, pharyngitis, and arthralgias can occur but are less consistently present. Lymphadenopathy, hepatomegaly, and splenomegaly are detected in nearly 50% of children with ehrlichiosis. Edema of the face, hands, and feet occurs more commonly in children than in adults, but arthritis is uncommon.

Similar but less severe manifestations occur with anaplasmosis in children, including fever (93%), headache (73%), myalgia (73%), and rigors (60%). Nausea, vomiting, abdominal pain, and anorexia occur in 30% or less of patients. Cough is present in 20%. Rash is infrequent in anaplasmosis and most often is erythema migrans that results from concurrent Lyme disease.

Meningoencephalitis with a lymphocyte-predominant CSF pleocytosis is an uncommon but potentially severe complication of ehrlichiosis that appears to be rare with anaplasmosis. CSF protein may be elevated, and glucose may be mildly depressed in adults with ehrlichiosis meningoencephalitis, but CSF protein and glucose in affected children are typically normal. In one series, 19% of adult patients with central nervous system symptoms and abnormal CSF died despite normal CTs of the brain.

Chronic or persistent disease with low or absent fever is very unlikely to be any form of ehrlichiosis.

LABORATORY FINDINGS

Characteristically, most children with ehrlichiosis and anaplasmosis present with leukopenia (57–80%) and thrombocytopenia (38–93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both ehrlichiosis and anaplasmosis. Leukocytosis can also occur, but usually after the first week of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with ehrlichiosis, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with anaplasmosis. Mild to markedly elevated serum hepatic transaminase levels are frequent in both ehrlichiosis (85–92%) and anaplasmosis (40–50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

DIAGNOSIS

Any delays in diagnosis or treatment are major contributors to increased morbidity or mortality in adults, where those not started on doxycycline at hospital admission are much more likely to require intensive care and undergo a significantly longer course of illness and hospitalization. Tick bites are not always reported; thus treatment must begin as early as possible based on epidemiologic (geographic) and clinical suspicion. Because both ehrlichiosis and anaplasmosis can be fatal, therapy should not be withheld while waiting for the results of confirmatory testing. In fact, prompt response to therapy supports the diagnosis.

Although several reports document pediatric patients with *E. chaffeensis* infection diagnosed based on typical *Ehrlichia* morulae in peripheral blood leukocytes (Fig. 277.1A), this finding is too infrequent to be considered a useful diagnostic approach. In contrast, anaplasmosis in adults presents with a small but significant percentage (1–40%) of circulating neutrophils (see Fig. 277.1B) containing typical morulae in 20–60% of patients.

E. chaffeensis and *A. phagocytophilum* infections are currently most frequently established by specific polymerase chain reaction assays used during the acute phase of illness when antibodies are often not detected. Both infections can be confirmed by demonstrating a fourfold change in immunoglobulin G titer by indirect immunofluorescence assay between paired sera. Serologic tests during the acute phase of infection are often negative; consequently, confirmation of acute infection requires demonstration of a fourfold rise in IgG titer in paired samples. A single specific titer of ≥128 is suggestive, but the use of IgM testing is discouraged owing to a lack of specificity. Identification of morulae in monocytes or macrophages for *E. chaffeensis* or in neutrophils or eosinophils for *A. phagocytophilum* by microscopy is suggestive. Demonstration of specific antigen in a tissue sample by immunohistochemistry and isolation of the organism in cell culture are not timely and are used infrequently. *E. ewingii* infection can only be confirmed by polymerase chain reaction because it has not been cultured and serologic antigens are not available. *E. ewingii* antibodies cross react with *E. chaffeensis* in routine serologic tests. Up to 15% of patients with anaplasmosis have serologic cross reactions with *E. chaffeensis;* thus serodiagnosis depends on testing with both *E. chaffeensis* and *A. phagocytophilum* antigens and demonstrating a fourfold or higher difference between titers.

DIFFERENTIAL DIAGNOSIS

Because of the nonspecific presentation, ehrlichiosis mimics other arthropod-borne infections such as RMSF, tularemia, babesiosis, Lyme disease, murine typhus, relapsing fever, and Colorado tick fever. Other potential diagnoses often considered include otitis media, streptococcal pharyngitis, infectious mononucleosis, Kawasaki disease, endocarditis, respiratory or gastrointestinal viral syndromes, hepatitis, leptospirosis, Q fever, collagen-vascular diseases, hemophagocytic syndromes, and leukemia. If rash and disseminated intravascular coagulopathy predominate, meningococcemia, bacterial sepsis, and toxic shock syndrome should also be suspected. Meningoencephalitis might suggest aseptic meningitis caused by enterovirus or herpes simplex virus, bacterial meningitis, or RMSF. Severe respiratory disease may be confused with bacterial, viral, and fungal causes of pneumonia. Mounting evidence suggests that ehrlichiosis and anaplasmosis may be precipitating factors for hemophagocytic lymphohistiocytosis.

TREATMENT

Both ehrlichiosis and anaplasmosis are effectively treated with tetracyclines, especially doxycycline, and the majority of patients improve within 48 hours. In vitro tests document that both *E. chaffeensis* and *A. phagocytophilum* have minimal inhibitory concentrations to chloramphenicol above blood levels that can be safely achieved. Therefore a short course of doxycycline is the recommended regimen. Doxycycline is used safely in children younger than 8 years of age because tooth discoloration is dose dependent and the need for multiple courses is unlikely; experience has demonstrated that adverse consequences of doxycycline use in children <8 years of age are extremely rare, in particular if courses are relatively short. Few data exist to recommend alternative therapies; however, both *E. chaffeensis* and *A. phagocytophilum* are susceptible in vitro to rifampin, which has been used successfully to treat anaplasmosis in pregnant women and children.

The recommended regimen for patients of all ages with severe or complicated ehrlichiosis and anaplasmosis is doxycycline (for those who weigh <45 kg, 4 mg/kg/day PO or IV divided every 12 hours; maximum 200 mg/day). An alternative regimen is tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum 2 g/day). For children who weigh more than 45 kg, the adult dose, 100 mg twice daily by oral or intravenous route, can be used. Therapy should be continued for ≥5 days and until the patient has been afebrile for ≥2-4 days.

Other broad-spectrum antibiotics, including penicillins, cephalosporins, aminoglycosides, and macrolides, are not effective. In vitro studies suggest that fluoroquinolones are active against *A. phagocytophilum,* although at least one patient relapsed when levofloxacin was discontinued. *E. chaffeensis* is naturally resistant to fluoroquinolones owing to a single nucleotide change in *gyrA,* which suggests that *A. phagocytophilum* could also become resistant to fluoroquinolones rapidly.

COMPLICATIONS AND PROGNOSIS

Fatal ehrlichiosis has been reported in occasional pediatric patients, where the findings included pulmonary involvement and respiratory failure in patients with or without immune compromise. The pattern of severe pulmonary involvement culminating in diffuse alveolar damage and acute respiratory distress syndrome and secondary nosocomial

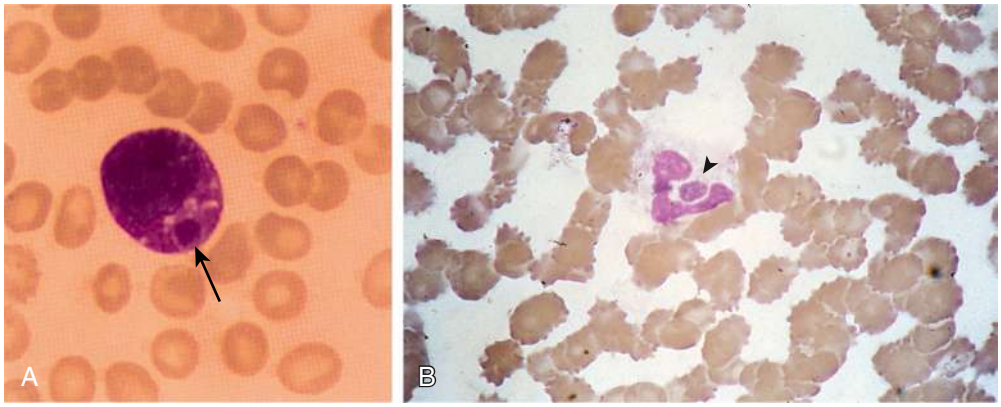

Fig. 277.1 Morulae in peripheral blood leukocytes in patients with human monocytic ehrlichiosis and human granulocytic anaplasmosis. **A,** A morula *(arrow)* containing *Ehrlichia chaffeensis* in a monocyte. **B,** A morula *(arrowhead)* containing *Anaplasma phagocytophilum* in a neutrophil. Wright stains, original magnifications ×1,200. *E. chaffeensis* and *A. phagocytophilum* have similar morphologies but are serologically and genetically distinct.

or opportunistic infections is now well-documented with ehrlichiosis and anaplasmosis in adults. Of greater concern is the frequency with which secondary hemophagocytic lymphohistiocytosis is diagnosed with ehrlichiosis and anaplasmosis in children. Children and adults who are immunocompromised (e.g., HIV infection, high-dose corticosteroid therapy, cancer chemotherapy, immunosuppression for organ transplantation) are at high risk for fulminant *E. chaffeensis* infection, for *E. ewingii* infection, and for severe anaplasmosis.

PREVENTION

Ehrlichiosis, anaplasmosis, and ewingii ehrlichiosis are tick-borne diseases, and any activity that increases exposure to ticks increases risk. Avoiding tick-infested areas, wearing appropriate light-colored clothing, spraying tick repellents on clothing, carefully inspecting for ticks after exposure, and promptly removing any attached ticks diminish the risk. The interval between tick attachment and transmission of the agents may be as short as 4 hours; thus attached ticks should be removed promptly. A role of prophylactic therapy for ehrlichiosis and anaplasmosis after tick bites has not been investigated. It is not known if infection confers protective immunity; however, reinfection appears to be rare.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 278

Q Fever (*Coxiella burnetii*)

Megan E. Reller and J. Stephen Dumler

Q fever (for query fever, the name given after an outbreak of febrile illness in an abattoir in Queensland, Australia) is rarely reported in children but is probably underdiagnosed. Symptomatic patients can have acute or chronic disease.

ETIOLOGY

Although previously classified within the order Rickettsiales, *Coxiella burnetii* (the causative agent of Q fever) is genetically distinct from the genera *Rickettsia, Orientia*, *Ehrlichia,* and *Anaplasma*. Hence, based on small genome analysis, it best aligns with the order Legionellales, family Coxiellaceae. *C. burnetii* is highly infectious for both humans and animals; even a single organism can cause infection. The agent has been nationally notifiable since 1999 and is listed as a Category B agent of bioterrorism by the Centers for Disease Control and Prevention (CDC). Unlike *Rickettsia,* the organism can enter a sporogenic differentiation cycle, which renders it highly resistant to chemical and physical treatments.

C. burnetii resides intracellularly within macrophages. In vitro, the organism undergoes a lipopolysaccharide phase variation similar to that described for smooth and rough strains of Enterobacteriaceae. Unlike *Ehrlichia, Anaplasma,* and *Chlamydia, C. burnetii* survives and proliferates within acidified phagosomes to form aggregates of >100 bacteria.

EPIDEMIOLOGY

The disease is reported worldwide, except in New Zealand. Although seroepidemiologic studies suggest that infection occurs just as often in children as in adults, children less often present with clinical disease than adults. During the large outbreak of Q fever in the Netherlands in 2007–2009, only 3.5% of those diagnosed with Q fever were age 19 years or younger. Infections are recognized more often in men than in women. Historically, reported cases in boys and girls have been equal, although a recent study reported male predominance. Approximately 60% of infections are asymptomatic, and only 5% of symptomatic patients require hospitalization. Seroprevalence surveys show that 6–70% of children in endemic European and African communities have evidence of past infection. In France, the overall incidence of Q fever is estimated to be 50 cases per 100,000 persons. A similar estimate is not available for Africa, where cases are likely misdiagnosed as malaria. The seroprevalence of Q fever in the United States is estimated to be 3.1%. Reported cases of Q fever in the United States have been received from every state, but 35% are reported from four states (California, Texas, Colorado, and Illinois). In the United States, reported Q fever cases increased by greater than ninefold from 17 cases in 2000 to 167 cases in 2008, reflecting an increase in incidence, increased reporting after September 11, 2001, improved diagnostic tools, or a combination of factors. Cases decreased significantly in 2008–2013 relative to 2007 but returned to previous high levels in 2014 (173 cases, including 147 acute and 39 chronic). Beginning in 2008, reported cases in the United States have been classified as acute or chronic. Between 2002 and 2014, more than 50% of recognized cases in the United States required hospitalization. Reported cases in Asia and Australia have also increased. Most infections in children are identified during the lamb birthing season in Europe (January through June), after farm visits, or after exposure to placentas of dogs, cats, and rabbits. The largest (~4,000 human cases) community outbreak ever described occurred in the Netherlands in 2007–2012 and was associated with intensive farming of dairy goats and dairy sheep. In 2011, the first multistate outbreak of Q fever in humans was linked to interstate sale of infected goats; an outbreak of unknown source was also reported. From 2000 to 2010, 60% of cases reported to the CDC occurred in individuals without reported exposure to livestock. More than 20% of cases of clinically recognized acute or chronic Q fever occur in immunosuppressed hosts or in persons with prosthetic valves or damaged native valves or vessels. These findings highlight the need for considering Q fever in those with clinically compatible illness, especially but not exclusively in those with likely exposures and in vulnerable hosts. Epidemiologic investigations and control efforts require a One Health approach, with consideration of the interactions between humans, animals, environment, and public health.

TRANSMISSION

In contrast to other rickettsial infections, humans usually acquire *C. burnetii* by inhaling infectious aerosols (e.g., contaminated barnyard dust) or ingesting (and likely aspirating) contaminated foods. Ticks are rarely implicated. Cattle, sheep, and goats are the primary reservoirs, but infection in other livestock and domestic pets is also described. Organisms are excreted in milk, urine, and feces of infected animals, but especially in amniotic fluids and the placenta. An increase in incidence is associated with the seasonal mistral winds in France that coincide with lamb birthing season and with consumption of cheese among children in Greece. In Nova Scotia and Maine, exposure to newborn animals, especially kittens, has been associated with small outbreaks of Q fever in families. Exposure to domestic ruminants is the major risk in Europe and Australia, although many urban dwellers in France also acquire Q fever without such an exposure. Person-to-person transmission is possible but rare. Clinical Q fever during pregnancy can result from primary infection or reactivation of latent infection and is associated with miscarriage, intrauterine growth retardation, and premature births. Obstetricians and other related healthcare workers are at risk for acquiring infection because of the quantity of *C. burnetii* sequestered in the placenta. Sexual transmission and cases attributable to blood transfusion or bone marrow transplantation are also reported. Transmission after *live cell therapy* (injected live animal cells) has also been reported.

PATHOLOGY AND PATHOGENESIS

The pathology of Q fever depends on the mode of transmission, route of dissemination, specific tissues involved, and course of the infection. When acquired via inhalation, a mild interstitial lymphocytic pneumonitis and macrophage- and organism-rich intraalveolar exudates are

often seen. When the liver is involved, a mild to moderate lymphocytic lobular hepatitis can be seen. Inflammatory pseudotumors can develop in the pulmonary parenchyma or other tissues. Classic fibrin-ring ("doughnut") granulomas, generally associated with acute, self-limited infections, are occasionally identified in liver, bone marrow, meninges, and other organs. Typically, infected tissues are also infiltrated by lymphocytes and histiocytes.

Recovery from symptomatic or asymptomatic acute infection can result in persistent subclinical infection, possibly maintained by dysregulated cytokine responses. The persistence of *C. burnetii* in tissue macrophages at sites of preexisting tissue damage elicits low-grade chronic inflammation and, depending on the site of involvement, can result in irreversible cardiac valve damage, persistent vascular injury, or osteomyelitis. Endocarditis of native or prosthetic valves is characterized by infiltrates of macrophages and lymphocytes in necrotic fibrinous valvular vegetations and an absence of granulomas.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Children are less likely to develop symptoms compared with adults. Only approximately 40–50% of people infected with *C. burnetii* develop symptoms. Historically, two forms of symptomatic disease have been thought to occur. **Acute Q fever**, now better characterized as **primary Q fever**, is more common and usually manifests as self-limited undifferentiated fever or an influenza-like illness with interstitial pneumonitis. Persistent localized infection with *C. burnetii* can cause what has historically been referred to as **chronic Q fever**. In adults, persistent localized infection usually involves the cardiovascular system—native heart valves, especially those with preexisting valvulopathy, prosthetic valves, or other endovascular prostheses. Q fever osteomyelitis is less common but proportionally more common as a manifestation of infection in children. Less common persistent localized *C. burnetii* infections include lymphadenitis, genital infection, and pericarditis.

Primary (Acute) Q Fever

Acute Q fever develops approximately 3 weeks (range: 14-39 days) after exposure to the causative agent. The severity of illness in children ranges from subclinical infection to a systemic illness of sudden onset characterized by high fever, severe frontal headache, nonproductive cough, chest pain, vomiting, diarrhea, abdominal pain, arthralgias, and myalgias. Approximately 40% of children with acute Q fever present with fever, 25% with pneumonia or an influenza-like illness, >10% with meningoencephalitis, and >10% with myocarditis. Other manifestations include pericarditis, hepatitis, hemophagocytic lymphohistiocytosis, rhabdomyolysis, and a hemolytic uremic–like syndrome. Rash, ranging from maculopapular to purpuric lesions, is an unusual finding in adults with Q fever but is observed in approximately 50% of pediatric patients. Rigors and night sweats are common in adults with Q fever and occur less often in children. Prominent clinical findings that can create diagnostic confusion include fatigue, vomiting, abdominal pain, and meningismus. Hepatomegaly and splenomegaly may be detected in some patients.

Routine laboratory investigations in pediatric acute Q fever are usually normal but can reveal mild leukocytosis and thrombocytopenia. Up to 85% of children have modestly elevated serum hepatic transaminase levels that usually normalize within 10 days. Hyperbilirubinemia is uncommon in the absence of complications. C-reactive protein may not be elevated in pediatric Q fever. Chest radiographs are abnormal in nearly 30% of all patients; in children, the most common findings include single or multiple bilateral infiltrates with reticular markings in the lower lobes.

Primary Q fever in children is usually a self-limited illness, with fever persisting for only 7-10 days compared with 2-3 weeks in adults. However, severe manifestations of acute illness, such as myocarditis requiring cardiac transplantation, meningoencephalitis, pericarditis, hemophagocytosis, thrombosis with antiphospholipid antibody syndrome, and a relapsing febrile illness lasting for several months, have been reported.

Persistent Localized Q Fever Infection

The risk for developing persistent localized Q fever infection, historically called *chronic Q fever,* is strongly correlated with advancing age and underlying conditions such as cardiac valve damage or immunosuppression; persistent localized Q fever infection is rarely diagnosed in children. A review identified only five cases of Q fever endocarditis and six cases of osteomyelitis among children, none of whom had known predisposing immune deficiencies. Four of the five cases of endocarditis occurred in children with underlying congenital heart abnormalities and involved the aortic, pulmonary, and tricuspid valves. Four of the six children with Q fever osteomyelitis had a prior diagnosis or clinical course consistent with idiopathic chronic recurrent multifocal osteomyelitis. A long interval before diagnosis and lack of high fever are common in pediatric cases of persistent localized Q fever infection—historically chronic Q fever.

Although Q fever endocarditis often results in death (23–65% of cases) in adults, mortality has not been reported for children. Endocarditis associated with persistent or chronic Q fever can occur months to years after acute infection and can occur in the absence of recognized acute Q fever and in the absence of clinically recognized valvulopathy. Chronic hepatitis has also been reported.

LABORATORY FINDINGS

Laboratory features in children with chronic Q fever are poorly documented; adult patients often have an erythrocyte sedimentation rate of >20 mm/hr (80% of cases), hypergammaglobulinemia (54%), and hyperfibrinogenemia (67%). In children, the presence of rheumatoid factor in >50% of cases and circulating immune complexes in nearly 90% suggest an autoimmune process. The presence of antiplatelet antibodies, anti–smooth muscle antibodies, antimitochondrial antibodies, circulating anticoagulants, positive direct Coombs tests, and antiphospholipid antibodies also suggest this possibility.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although uncommonly diagnosed, Q fever in children most often mimics other childhood respiratory infections. It should be considered in children who have an influenza-like illness, lower or upper respiratory tract infection, fever of unknown origin, myocarditis, meningoencephalitis, culture-negative endocarditis, or recurrent osteomyelitis and who live in rural areas or who are in close contact with domestic livestock, cats, or animal products.

The diagnosis of primary (acute) Q fever is most easily and commonly confirmed by testing acute and convalescent sera (3-6 weeks apart), which show a fourfold increase in indirect fluorescent immunoglobulin G antibody titers to phase II *C. burnetii* antigens. The phase II antibody response to *C. burnetii* appears first and is higher than the phase I antibody response. Phase II immunoglobulin G antibodies can remain elevated for months to years, regardless of initial symptoms or lack thereof. In contrast, persistent localized (chronic) Q fever is characterized by a phase I immunoglobulin G antibody titer greater than 800 that is sustained for 6 months or more, such as occurs with Q fever endocarditis in patients with valvular heart disease. Cross-reactions with antibodies to *Legionella* and *Bartonella* can occur.

Although culture has been considered the gold standard, sensitivity (compared with a composite standard including serology and polymerase chain reaction [PCR]) is low. *C. burnetii* has been cultivated in tissue culture cells, which can become positive within 48 hours, but isolation and antimicrobial susceptibility testing of *C. burnetii* should be attempted only in specialized biohazard facilities. Testing by PCR can be performed on blood, serum, and tissue samples and is available only in some public health, reference, or research laboratories. PCR has been helpful in patients with equivocal titers, as occurs with early infection. PCR usually remains positive for 7-10 days after acute infection. Sensitivity has been improved by real-time methods and the use

of repeated sequences as targets. Immunohistochemical staining has also been used but is not readily available. PCR should be performed either before or shortly after initiation of treatment. PCR can also confirm a serologic diagnosis of endocarditis in untreated patients. Genotyping has aided epidemiologic investigations to confirm the source of infection. The differential diagnosis depends on the clinical presentation. In patients with respiratory disease, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* legionellosis, psittacosis, and Epstein-Barr virus infection should be considered. In patients with granulomatous hepatitis, tuberculous and nontuberculous mycobacterial infections, salmonellosis, visceral leishmaniasis, toxoplasmosis, Hodgkin disease, monocytic ehrlichiosis, brucellosis, cat scratch disease *(Bartonella henselae)*, or autoimmune disorders such as sarcoidosis should be considered. **Culture-negative endocarditis** suggests infection with *Brucella, Bartonella,* HACEK organisms *(Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella)*, partially treated bacterial endocarditis, nonbacterial endocarditis, or potentially noninfectious inflammatory conditions, including chronic recurrent multifocal osteomyelitis and antiphospholipid syndrome.

TREATMENT

Selection of an appropriate antimicrobial regimen for children is difficult owing to the lack of rigorous studies, the limited therapeutic window for drugs that are known to be efficacious, and the potential length of therapy required to preclude relapse.

Most pediatric patients with Q fever have a self-limited illness that is identified only on retrospective serologic evaluation. However, to prevent potential complications, treatment should be considered for patients who present with suspected acute Q fever within 3 days of onset of symptoms, because therapy started more than 3 days after the onset of illness has little effect on the course of acute Q fever. Early treatment is effective in shortening illness duration and severity. Doxycycline (100 mg orally 2 times/day for children 8 years or older or 4 mg/kg/day orally divided 2 times/day for children younger than 8 years, maximum: 200 mg/day, for 14 days) is the drug of choice. Doxycycline may cause permanent tooth discoloration for children younger than 8 years if used repeatedly but is generally safe when used for short courses. Children younger than 8 years with mild illness, pregnant adolescents, and patients allergic to doxycycline can be treated with trimethoprim-sulfamethoxazole.

For persistent focal Q fever, especially endocarditis and mostly in adults, therapy for 18-36 months is mandatory, because treatment is more difficult and relapses can occur despite appropriate therapy. The current recommended regimen for Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for 18 months or longer. For patients with heart failure, valve replacement could be necessary.

PREVENTION

Recognition of the disease in livestock or other domestic animals should alert communities to the risk for human infection by aerosol exposures within 15 km. Milk from infected herds must be pasteurized at temperatures sufficient to destroy *C. burnetii. C. burnetii* is resistant to significant environmental conditions but can be inactivated with a solution of 1% Lysol, 1% formaldehyde, or 5% hydrogen peroxide. Special isolation measures are not required because person-to-person transmission is rare, except when others are exposed to the placenta of an infected patient. A vaccine is available and provides protection against Q fever for at least 5 years in abattoir workers; however, it is not licensed in the United States. Prospective studies of vaccination in children at high risk are needed. Clusters of cases resulting from intense natural exposures, such as in slaughterhouses or on farms, are well documented. Clusters of cases that occur in the absence of such an exposure should be investigated as potential sentinel events for bioterrorism.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 12

Fungal Infections

Chapter 279

Principles of Antifungal Therapy

William J. Steinbach

Invasive fungal infections are a major cause of morbidity and mortality in the growing number of immunocompromised children. The antifungal armamentarium has markedly increased in recent years (Tables 279.1 and 279.2).

POLYENES

Amphotericin B

The prototype of the oldest antifungal class, the polyene macrolides, is amphotericin B deoxycholate. Amphotericin B was once the preferred treatment for most invasive fungal infections and the standard of comparison for all newer antifungal agents. Amphotericin B is so named because it is amphoteric, forming soluble salts in both acidic and basic environments. However, because of its insolubility in water, amphotericin B for clinical use is actually amphotericin B mixed with the detergent deoxycholate. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, and acts by creating transmembrane channels. The fungicidal activity is the result of a damaged barrier and subsequent cell death through leakage of essential nutrients from the fungal cell.

Amphotericin B is released from its carrier and distributes efficiently with lipoproteins and is then taken up preferentially by organs of the reticuloendothelial system. After an initial 24- to 48-hour distributional half-life, there is very slow release and a subsequent terminal elimination half-life of up to 15 days. In addition to conventional amphotericin B deoxycholate, two fundamentally different lipid-associated formulations are currently available that offer the advantage of an increased daily dosage of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen), and reduced toxicity. Amphotericin B lipid complex (ABLC) is a tightly packed ribbon-like structure of a bilayered membrane, and liposomal amphotericin B (L-amphotericin B) consists of small uniformly sized vesicles of a lipid bilayer of amphotericin B. Lipid formulations of amphotericin B generally have a slower onset of action, presumably owing to the required disassociation of free amphotericin B from the lipid vehicle. The ability to safely administer higher daily doses of the parent drugs improves their efficacy, comparing favorably with amphotericin B deoxycholate but with less toxicity. Lipid formulations have the added benefit of increased tissue concentrations compared with conventional amphotericin B, specifically in the liver, lungs, and spleen. Tolerance to amphotericin B deoxycholate is limited by its acute and chronic toxicities. In addition to interacting with fungal ergosterol, the drug also interacts with cholesterol in human cell membranes, likely accounting for its toxicity. Up to 80% of patients receiving amphotericin B develop either infusion-related toxicity or nephrotoxicity, especially with concomitant therapy with nephrotoxic drugs such as aminoglycosides, vancomycin, cyclosporine, or tacrolimus. Renal function usually returns to normal after cessation of amphotericin B, although permanent renal impairment can occur after larger doses. Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely because of the more rapid clearance of the drug in children. Lipid formulations appear to stabilize

Table 279.1 Suggested Dosing of Antifungal Agents in Children and Neonates

DRUG	FORMULATIONS	SUGGESTED PEDIATRIC DOSAGE	COMMENTS
Amphotericin B deoxycholate	IV	1 mg/kg/day	Generally less toxicity in children than adults; do not start with smaller test doses
Lipid amphotericin B formulations	IV	5 mg/kg/day	Generally, all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy
Fluconazole	IV, PO	12 mg/kg/day	Loading dose (25 mg/kg) is recommended in neonates based on pharmacokinetic simulations and likely suggested in children, but insufficiently studied
Itraconazole	PO	2.5 mg/kg/dose bid	Divide dosage twice daily in children; follow trough levels
Voriconazole	IV, PO	8 mg/kg/dose bid IV maintenance; 9 mg/kg/dose bid oral maintenance	Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels carefully
Posaconazole	IV, PO	At least 18 mg/kg/day divided tid for oral suspension; IV and new powder for oral suspension 6 mg/kg/day once daily (given bid as a loading dose on first day)	Dosage unclear in children at present In adults, max dosage for oral suspension is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels; adult dosing for IV and extended-release tablet is 300 mg twice on first day, then 300 mg once daily
Isavuconazole	PO, IV	10 mg/kg (q8h on days 1 and 2 and then once daily thereafter)	Adult dosing for IV and tablet is 200 mg 3 times on first day, then 200 mg once daily
Micafungin	IV	2-10 mg/kg/day	Highest dosages in neonates (10 mg/kg/day) and lower dosages in children; >8 yr of age, use adult dosage
Anidulafungin	IV	1.5 mg/kg/day	Loading dose of 3 mg/kg/day
Caspofungin	IV	50 mg/m^2/day; neonates 25 mg/m^2/day	Load with 70 mg/m^2/day, then 50mg/m^2/day as maintenance dosage

amphotericin B in a self-associated state so that it is not available to interact with the cholesterol of human cellular membranes.

A clinical trial comparing L-amphotericin B at doses of 3 mg/kg/day versus 10 mg/kg/day found no efficacy benefit for the higher dose and only greater toxicity. Therefore it is generally not recommended to use any lipid amphotericin B preparations at very high dosages (>5 mg/kg/day), although some experts report using higher dosing in very difficult infections where a lipid amphotericin B formulation is the first-line therapy (e.g., mucormycosis).

PYRIMIDINE ANALOGS

5-Fluorocytosine

5-Fluorocytosine (5-FC) is a fluorinated analog of cytosine and has antifungal activity resulting from the rapid conversion into 5-fluorouracil (5-FU) within susceptible fungal cells. Clinical and microbiologic antifungal resistance develops quickly to 5-FC monotherapy, so clinicians have reserved it for combination approaches. Fungistatic 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is often suboptimal, such as cerebrospinal fluid (CSF). 5-FC penetrates well into most body sites because it is small, highly water-soluble, and not bound by serum proteins to any great extent. One explanation for the synergy detected with the combination of amphotericin B plus 5-FC is that the membrane-permeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC to the cell interior. 5-FC is only available as an oral formulation in the United States, and the dosage is 150 mg/kg/day in four divided doses.

5-FC can exacerbate myelosuppression in patients with neutropenia, and toxic levels can develop when used in combination with amphotericin B, owing to nephrotoxicity of the amphotericin B and decreased renal clearance of 5-FC. Routine serum 5-FC level monitoring is warranted in high-risk patients, and levels should be obtained after 3-5 days of therapy, with a goal to achieve a 2-hour postdose peak <100 µg/mL (and ideally 30-80 µg/mL). Levels >100 µg/mL are associated with bone marrow aplasia. Toxicities can include azotemia, renal tubular acidosis, leukopenia, thrombocytopenia, and others and appear in approximately 50% of patients in the first 2 weeks of therapy.

Nearly all clinical studies involving 5-FC for cryptococcal meningitis are combination antifungal protocols with amphotericin B. The use of 5-FC for *Candida* meningitis in premature neonates is discouraged. A study evaluating risk factors and mortality rates of neonatal candidiasis among extremely premature infants showed that infants with *Candida* meningitis who received amphotericin B in combination with 5-FC had a prolonged time to sterilization of the CSF compared with infants receiving amphotericin B monotherapy.

AZOLES

The azole antifungals inhibit the fungal cytochrome $P450_{14DM}$ (also known as *lanosterol 14α-demethylase*), which catalyzes a late step in fungal cell membrane ergosterol biosynthesis. Of the older first-generation, itraconazole has activity against *Aspergillus,* but fluconazole is ineffective against *Aspergillus* and other molds. Second-generation triazoles (voriconazole, posaconazole, and isavuconazole) have an expanded antifungal spectrum of activity, including activity against molds, and generally greater in vitro antifungal activity.

Fluconazole

Fluconazole is fungistatic, and this activity is not influenced by concentration once the maximal fungistatic concentration is surpassed (concentration independent), in contrast to the concentration-dependent

Table 279.2 Suggested Antifungals for Specific, More Common Fungal Pathogens

FUNGAL SPECIES	AMP	FLU	ITR	VOR	POS	ISA	FLUC	CMA
Aspergillus calidoustus	++	–	–	–	–	–	–	++
Aspergillus fumigatus	+	–	±	++	+	++	–	+
Aspergillus terreus	–	–	+	++	+	++	–	+
Blastomyces dermatitidis	++	+	++	+	+	+	–	–
Candida albicans	+	++	+	+	+	+	+	++
Candida glabrata	+	–	±	±	±	±	+	±
Candida krusei	+	–	–	+	+	+	+	++
Candida lusitaniae	–	++	+	+	+	+	+	+
Candida parapsilosis	++	++	+	+	+	+	+	±
Coccidioides immitis	++	+	++	+	++	+	–	–
Cryptococcus spp.	++	+	+	+	+	+	++	–
Fusarium spp.	±	–	–	++	+	+	–	–
Histoplasma capsulatum	++	+	++	+	+	+	–	–
Mucor spp.	++	–	±	–	+	+	–	–
Scedosporium apiospermum	–	–	±	+	+	+	–	±
Scedosporium prolificans	–	–	±	±	±	±	–	±

AMP, amphotericin B formulations; FLU, fluconazole; ITR, itraconazole; VOR, voriconazole; POS, posaconazole; ISA, isavuconazole; FLUC, flucytosine; CMA, caspofungin, micafungin, or anidulafungin.
++, preferred therapy(ies); +, usually active; ±, variably active; –, usually not active.

fungicidal activity of amphotericin B. Fluconazole is available as either an oral or intravenous form, and oral administration has a bioavailability of approximately 90% relative to intravenous administration. Fluconazole passes into tissues and fluids quite rapidly, probably because of its relatively low lipophilicity and limited degree of binding to plasma proteins. Concentrations of fluconazole are 10- to 20-fold higher in the urine than in blood, making it an ideal agent for treating fungal urinary tract infections. Concentrations in the CSF and vitreous humor of the eye are approximately 80% of those found simultaneously in blood.

Simple conversion of the corresponding adult dosage of fluconazole on a weight basis is inappropriate for pediatric patients. Fluconazole clearance is generally more rapid in children than in adults, with a mean plasma half-life of approximately 20 hours in children and approximately 30 hours in adult patients. Therefore to achieve comparable exposure in pediatric patients, the daily fluconazole dosage needs to be essentially doubled. Correct pediatric fluconazole dosages should be proportionately higher than adult dosages, generally 12 mg/kg/day. In neonates, the volume of distribution is significantly greater and more variable than in infants and children, and doubling the dosage for neonatal patients is necessary to achieve comparable plasma concentrations. The increased volume of distribution is thought to be the result of the larger amount of body water found in the total body volume of neonates. A pharmacokinetic study in premature infants suggests that maintenance fluconazole dosages of 12 mg/kg/day are necessary to achieve exposures similar to those in older children and adults. In addition, a loading dose of 25 mg/kg in neonates has achieved steady-state concentrations sooner. Although a fluconazole loading dose has been studied in adult and neonatal patients, this approach has never been formally studied in children, yet makes clinical sense. Side effects of fluconazole are uncommon but generally include gastrointestinal upset (vomiting, diarrhea, nausea) and skin rash.

Fluconazole plays an important role in the treatment of invasive candidiasis. Consensus guidelines suggest that use of the fungistatic fluconazole for invasive candidiasis is acceptable as step-down therapy after a good clinical response to initial therapy with an echinocandin. Other clinical scenarios for fluconazole include patients who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species. Although most isolates of *Candida albicans* remain susceptible to fluconazole, for certain *Candida* species, fluconazole is not an ideal agent: *C. krusei* is generally resistant, and *C. glabrata* is often resistant. There is no confirmed role for combination antifungal therapy with fluconazole and another antifungal against invasive candidiasis.

Prophylaxis with fluconazole to prevent neonatal candidiasis remains a controversial topic. In the first prospective, randomized double-blind trial of 100 infants with birthweights <1,000 g, infants who received fluconazole for 6 weeks had a decrease in fungal colonization and a decrease in the development of invasive fungal infection (0% vs 20%) compared with placebo. Other studies have yielded similarly encouraging results and have demonstrated that use of fluconazole prophylaxis for 4-6 weeks in high-risk infants does not increase the incidence of fungal colonization and infections caused by natively fluconazole-resistant *Candida* species. A more recent large trial studied fluconazole prophylaxis in extremely low birthweight infants in nurseries with a lower incidence of candidiasis and found that fluconazole

prophylaxis led to a decreased incidence of candidiasis but had no effect on mortality. The universal implementation of such a strategy across nurseries is discouraged, because the rate of *Candida* infections varies greatly among centers. Consensus guidelines now recommend fluconazole prophylaxis only in centers with high rates (>10%) of neonatal candidiasis.

Itraconazole

Compared to fluconazole, itraconazole has the benefit of antifungal activity against *Aspergillus* species but comes with several practical constraints, such as erratic oral absorption in high-risk patients and significant drug interactions. These pharmacokinetic concerns have been addressed with a better-absorbed oral solution to replace the unpredictable capsules used earlier. Itraconazole has a high volume of distribution and accumulates in tissues, and tissue-bound levels are probably more clinically relevant to infection treatment than serum levels. Dissolution and absorption of itraconazole are affected by gastric pH. Patients with achlorhydria or taking H_2-receptor antagonists might demonstrate impaired absorption, and co-administration of the capsule with acidic beverages such as colas or cranberry juice can enhance absorption. Administration with food significantly increases the absorption of the capsule formulation, but the oral suspension with a cyclodextrin base is better absorbed on an empty stomach.

Side effects are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. There have been reports in adults of development of cardiomyopathy. Because of important drug interactions, prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided.

Itraconazole has its largest role in treating less serious infections with endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis). The plethora of drug interactions make itraconazole a concern in complex patients receiving other medications. As with most azole antifungals, monitoring itraconazole serum levels is a key principle in management (generally itraconazole trough levels should be 1-2 μg/mL; trough levels >5 μg/mL may be associated with increased toxicity). Concentrations should be checked after 5 days of therapy to ensure adequate drug exposure. When measured by high-pressure liquid chromatography, both itraconazole and its bioactive hydroxyitraconazole metabolite are reported, the sum of which should be considered in assessing drug levels.

Voriconazole

Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole generally has the spectrum of activity of itraconazole and the high bioavailability of fluconazole. Importantly, it is fungicidal against *Aspergillus* and fungistatic against *Candida*. It is extensively metabolized by the liver and has approximately 90% oral bioavailability in adults but appears to be closer to 50–60% bioavailability in children. The cytochrome P450 2C19 (CYP2C19) enzyme appears to play a major role in the metabolism of voriconazole, and polymorphisms in CYP2C19 are associated with slow voriconazole metabolism. As many as 20% of non-Indian Asians have low CYP2C19 activity and develop voriconazole levels as much as fourfold higher than those in homozygous subjects, leading to potentially increased toxicity.

Voriconazole is available as an oral tablet, an oral suspension, and an intravenous solution. In adults, voriconazole exhibits nonlinear pharmacokinetics, has a variable half-life of approximately 6 hours with large interpatient variation in blood levels, and achieves good CSF penetration. In contrast to the situation in adults, elimination of voriconazole is linear in children. A multicenter safety, population pharmacokinetic study of intravenous voriconazole dosages in immunocompromised pediatric patients showed that body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics, and voriconazole needs to be dosed higher in pediatric patients than in adult patients. Adult patients load with 6 mg/kg/dose and then transition to a maintenance dosage of 4 mg/kg/dose, but children should begin and continue with 9 mg/kg/dose intravenously (see Table 279.1) and continue maintenance dosing at 8 mg/kg/dose. This need for an increased dosage in treating children is crucial to understand and is mandated by the fundamentally different pharmacokinetics of this drug in pediatric patients. Obtaining voriconazole serum levels (to achieve ≥2 μg/mL) is critical for therapeutic success. Oral voriconazole is best absorbed on an empty stomach. Generally a trough level greater than the minimum inhibitory concentration (MIC) of the infecting organism is preferred, and very high voriconazole levels have been associated with toxicity (generally >6 μg/mL). However, many studies have shown an inconsistent relationship between dosing and levels, highlighting the need for close monitoring after the initial dosing scheme and then dose adjustment as needed in the individual patient. Trough levels should be monitored approximately 5 days after initiation of therapy and repeated the following week to confirm the patient remains in the therapeutic range or repeated 4 days after change of dose. The main side effects of voriconazole include reversible dosage-dependent visual disturbances (increased brightness, blurred vision) in as many as one third of treated patients, elevated hepatic transaminases with increasing dosages, and occasional skin reactions likely caused by photosensitization. In some rare long-term (mean of 3 years of therapy) cases, this voriconazole phototoxicity has developed into cutaneous squamous cell carcinoma. Discontinuing voriconazole is recommended in patients experiencing chronic phototoxicity.

The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis compared initial randomized therapy with voriconazole versus amphotericin B and demonstrated improved response and survival with voriconazole over amphotericin B. **Voriconazole is guideline-recommended as the preferred primary therapy against invasive aspergillosis.** Voriconazole also has a role in treating candidiasis, but its fungistatic nature makes it often less than ideal for treating critically ill or neutropenic patients where the fungicidal echinocandin antifungals are preferred.

Posaconazole

Posaconazole is a second-generation triazole that is a derivative of itraconazole and is currently available as an oral suspension, an intravenous formulation, and a delayed-release tablet. The antimicrobial spectrum of posaconazole is similar to that of voriconazole; however, the former is active against mucormycosis, and voriconazole is not active against these particular mold infections.

Effective absorption of the less desirable oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one fourth of the absorption as in the fed state, emphasizing the importance of diet to increase serum levels of oral suspension posaconazole (the opposite of voriconazole). Posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors. The tablet formulation has much better absorption because of its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient can take the large-sized tablets, the delayed-release tablet is the preferred form because of the ability to easily obtain higher and more consistent drug levels. Importantly, the delayed-release tablet cannot be broken for use due to its chemical coating. As a result of the low pH (<5) of IV posaconazole, a central venous catheter is required for administration. The IV formulation contains only slightly lower amounts of the cyclodextrin vehicle than voriconazole, so similar theoretical renal accumulation concerns exist. Posaconazole causes transient hepatic reactions, including mild to moderate elevations in liver transaminases, alkaline phosphatase, and total bilirubin.

In adult patients, dosages of the oral suspension at >800 mg/day do not result in increased serum levels, and division of daily dosing into three or four doses/day results in greater serum levels than a once- or twice-daily dosing scheme when using the oral suspension. The pediatric oral suspension dose recommended by some experts for treating invasive disease is estimated to be at least 18 mg/kg/day divided 3 times daily, but even that dose did not achieve target levels when studied. A study with a new pediatric formulation for suspension, essentially the tablet form that is able to be suspended, showed a dose of 6 mg/

kg (given twice a day as a loading dose on the first day and then once daily) achieved target exposures necessary for antifungal prophylaxis, with a safety profile similar to adult patients. A subsequent study suggested that posaconazole dosing for the delayed-release tablets and IV formulation requires greater daily doses for children <13 years old. Pediatric dosing with the current IV or extended-release tablet dosing is not yet fully defined, but adolescents can likely follow the adult dosing schemes. Similar to itraconazole and voriconazole, posaconazole should be monitored with trough levels (to achieve ≥1 μg/mL for treatment and ≥0.07 μg/mL for prophylaxis).

In an international randomized, single-blinded study of posaconazole versus fluconazole or itraconazole in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections. Another multisite international randomized, double-blinded study in patients with allogeneic hematopoietic stem cell transplantation and graft versus host disease showed that posaconazole was not inferior to fluconazole in the prevention of invasive fungal infections. **Posaconazole is approved for prophylaxis against invasive fungal infections but has shown great efficacy in clinical experience with recalcitrant mold infections.**

In patients with chronic granulomatous disease (CGD) and proven invasive fungal infection refractory to standard therapy, posaconazole was proved to be well tolerated and quite effective and is the preferred agent against invasive aspergillosis in this patient population.

Isavuconazole

Isavuconazole is a triazole that was FDA approved in 2015 for treatment of invasive aspergillosis and invasive mucormycosis with oral (capsules only) and IV formulations. Isavuconazole has an antifungal spectrum similar to that of voriconazole and some activity against *Zygomycetes* such as mucormycosis (yet potentially not as potent against *Zygomycetes* as posaconazole). A phase 3 clinical trial in adult patients demonstrated noninferiority versus voriconazole against invasive aspergillosis and other mold infections, whereas another study showed good clinical activity against mucormycosis. Isavuconazole is dispensed as the prodrug isavuconazonium sulfate. Dosing in adult patients is loading with isavuconazole 200 mg (equivalent to 372-mg isavuconazonium sulfate) every 8 hours for 2 days (6 doses), followed by 200 mg once daily for maintenance dosing. The half-life is long (>5 days), there is 98% bioavailability in adults, and there is no reported food effect with oral isavuconazole. Unlike voriconazole, the IV formulation does not contain the vehicle cyclodextrin, possibly making it more attractive in patients with renal failure. Early experience suggests a much lower rate of photosensitivity and skin disorders as well as visual disturbances compared with voriconazole. A recently completed pediatric pharmacokinetic study reported that a dose of 10 mg/kg (q8h on days 1 and 2 and once daily thereafter) resulted in similar exposures and safety as seen in adults.

ECHINOCANDINS

The echinocandins are a class of antifungals that interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells. 1,3-β-glucan is an essential cell wall polysaccharide and provides structural integrity for the fungal cell wall. Echinocandins are generally fungicidal in vitro against *Candida* species, although not as rapidly as amphotericin B, and are fungistatic against *Aspergillus*. As a class, these agents are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azole class. The echinocandins appear to have a prolonged and dosage-dependent fungicidal antifungal effect on *C. albicans* compared with the fungistatic fluconazole. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA approved for use, but there are others (rezafungin) in late-stage clinical trials. Owing to the large size of the molecules, the current echinocandins are only available in an intravenous formulation. Because 1,3-β-glucan is a selective target present only in fungal cell walls and not in mammalian cells, drug-related toxicity is minimal, with no apparent myelotoxicity or nephrotoxicity with the agents. **The echinocandins are the preferred primary therapy for invasive candidiasis.**

Caspofungin

Caspofungin is administered to adults as a 70-mg loading dose followed by a daily maintenance 50-mg dosage. Caspofungin has been evaluated at double the recommended dosage (100 mg/day in adults) with no adverse effects, and it is unclear if higher dosage of this relatively safe agent results in greater clinical efficacy. At present there is no known maximum tolerated dosage and no toxicity-determined maximum length of therapy for caspofungin.

Pharmacokinetics are slightly different in children, with caspofungin levels lower in smaller children and with a reduced half-life. A study evaluated the pharmacokinetics of caspofungin in children with neutropenia and showed that in patients receiving 50 mg/m^2/day (maximum, 70 mg/day), the levels were similar to those in adults receiving 50 mg/day and were consistent across age ranges. In this study, weight-based dosing (1 mg/kg/day) was suboptimal when compared with body surface area regimens, so caspofungin should be appropriately dosed in children as a loading dose of 70 mg/m^2/day, followed by daily maintenance dosing of 50 mg/m^2/day.

Echinocandins like caspofungin are guideline-recommended initial therapy for invasive candidiasis but should be used against invasive aspergillosis only in the setting of potential combination therapy or for resistant or refractory disease. In a multicenter trial of patients with invasive candidiasis, 73% of patients who received caspofungin had a favorable response at the end of therapy compared with 62% in the amphotericin B group. Importantly, caspofungin treatment performed equally well to amphotericin B treatment for all the major *Candida* species. Earlier studies suggested that some infections with *C. parapsilosis* do not potentially clear as effectively with an echinocandin, but the echinocandins are still preferred empiric therapy against invasive candidiasis. Caspofungin was also evaluated against L-amphotericin B in the empirical treatment of patients with persistent fever and neutropenia and was not inferior to liposomal amphotericin B. A study in children with acute myeloid leukemia demonstrated that caspofungin prophylaxis resulted in a significantly lower incidence of invasive fungal disease compared with fluconazole prophylaxis. A study comparing caspofungin with triazole prophylaxis in pediatric allogeneic hematopoietic stem cell transplant recipients found no difference in the agents.

Caspofungin in newborns (25 mg/m^2/day) has been used for refractory cases of disseminated candidiasis. Neonates with invasive candidiasis are at high risk for central nervous system involvement; it is not known if the dosages of caspofungin studied provide sufficient exposure to penetrate the central nervous system at levels necessary to cure infection. Therefore caspofungin is not recommended as standard monotherapy in neonatal candidiasis.

Micafungin

The pharmacokinetics of micafungin have been evaluated in children and young infants. An inverse relation between age and clearance was observed, where mean systemic clearance was significantly greater and mean half-life was significantly shorter in patients 2-8 years of age compared to patients 9-17 years of age. Therefore dosing of micafungin in children is age-related and needs to be higher in children <8 years old. Doses in children are generally 2 mg/kg/day, with higher doses needed for neonates, infants, and younger patients, and with a dose of 10 mg/kg/day for preterm neonates. Several pharmacokinetic studies in term and preterm infants have shown that micafungin has a shorter half-life and a more rapid rate of clearance in infants compared with published data in older children and adults. Adult micafungin dosing (100 or 150 mg once daily) is to be used in patients who weigh more than 40 kg. Unlike the other echinocandins, a loading dose is not required for micafungin.

Clinical trials, including those of micafungin used for treatment of invasive candidiasis, as well as prophylaxis studies in patients after

stem cell transplantation, have demonstrated fewer adverse events compared with liposomal amphotericin B and fluconazole. The most common adverse events experienced by these patients are related to the gastrointestinal tract (nausea, diarrhea). Hypersensitivity reactions associated with micafungin have been reported, and liver enzymes are elevated in 5% of patients receiving this agent. Hyperbilirubinemia, renal impairment, and hemolytic anemia related to micafungin use have also been identified in postmarketing surveillance of the drug.

Micafungin at dosages of 100 and 150 mg daily was also noninferior to caspofungin in an international, randomized, double-blinded study of adults with candidemia or invasive candidiasis and was found to be superior to fluconazole in the prevention of invasive fungal infections in a randomized study of adults undergoing hematopoietic stem cell transplantation.

Of the three drugs within the echinocandin class, micafungin has been the one most extensively studied in children. A pediatric substudy as part of a double-blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as first-line treatment for invasive candidiasis showed similar success for micafungin and liposomal amphotericin B. In general, micafungin was better tolerated than liposomal amphotericin B, as evidenced by fewer adverse events leading to discontinuation of therapy.

Anidulafungin

Anidulafungin has the longest half-life of all the echinocandins (approximately 18 hours). In a study of 25 neutropenic children receiving anidulafungin as empirical therapy, four patients in the group receiving 0.75 mg/kg/day experienced adverse events such as facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension. In a pharmacokinetic study in neonates and young infants, anidulafungin exposures comparable to adults were achieved with doses of 1.5 mg/kg/day (3 mg/kg loading dose). One infant in this cohort supported by extracorporeal membrane oxygenation achieved the lowest exposure, which suggests that dose adjustments are required in this population. The adult dose for invasive candidiasis is a loading dose of 200 mg on the first day, followed by 100 mg daily. An open-label study of invasive candidiasis in children showed similar efficacy and minimal toxicity, comparable to the other echinocandins. An additional study showed similar and acceptable pharmacokinetics in patients 1 month to 2 years of age.

Ibrexafungerp

Ibrexafungerp was approved in 2021 for adults with vulvovaginal candidiasis after two phase 3 studies (VANISH203 and VANISH 306). This is the first new class of antifungals (also called "fungerps"). Similar to the echinocandins, ibrexafungerp noncompetitively inhibits β-1,3-glucan synthase and is also fungicidal against *Candida* spp. and *Aspergillus* spp. The binding site on the glucan synthase enzyme is not the same as the echinocandins. Resistance or reduced susceptibility to the echinocandins is largely through two hot-spot pathogenic variants in the *FKS1* gene, whereas many resistance mutations to ibrexafungerp are caused by the *FKS2* gene, and ibrexafungerp does have activity against some echinocandin-resistant isolates. Ibrexafungerp is the first orally available glucan synthase inhibitor and has a long half-life, suggesting once-daily dosing for clinical use. Similar to the echinocandins, initial studies show limited to no distribution to the central nervous system and variable distribution to the eye. In a phase 2 study, ibrexafungerp as step-down therapy after initial echinocandin therapy for invasive candidiasis was well-tolerated and achieved a favorable global response similar to the standard of care. There is an ongoing co-administration study with voriconazole in pulmonary invasive aspergillosis (SCYNERGIA) and an ongoing recurrent vulvovaginal candidiasis study (CANDLE), yet no completed pediatric studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 280
Candida

Jessica E. Ericson and Daniel K. Benjamin Jr.

Candidiasis encompasses many clinical syndromes that may be caused by several species of *Candida*. Invasive candidiasis (*Candida* infections of the blood and other sterile body fluids) is a leading cause of infection-related mortality in hospitalized immunocompromised patients.

C. albicans accounts for most human infections, but *C. parapsilosis, C. tropicalis, C. krusei, C. lusitaniae, C. glabrata,* and several other species are commonly isolated from hospitalized children. Species identification and susceptibility testing are important owing to increasing frequency of fluconazole resistance and increasing prevalence of non-*albicans Candida* species. *C. auris* is an emerging multiresistant invasive pathogen that has a global presence and affects immunocompromised patients; nosocomial spread has been reported.

Treatment of invasive *Candida* infections is complicated by the emergence of non-*albicans* strains. Amphotericin B deoxycholate is inactive against approximately 20% of strains of *C. lusitaniae.* Fluconazole is useful for many *Candida* infections but is inactive against all strains of *C. krusei* and 5–25% of strains of *C. glabrata.* Most *Candida* are susceptible to echinocandins, but resistance is occasionally seen, most often among *C. krusei* and *C. glabrata*. **Susceptibility testing of these clinical isolates is recommended.**

280.1 Neonatal Infections

Jessica E. Ericson and Daniel K. Benjamin Jr.

Candida is a common cause of oral mucous membrane infections **(thrush)** and perineal skin infections **(*Candida* diaper dermatitis)** in young infants. Rare presentations include **congenital cutaneous candidiasis**, caused by an ascending infection into the uterus during gestation, and **invasive fungal dermatitis**, a postnatal skin infection resulting in positive blood cultures. Invasive candidiasis is a common infectious complication in the neonatal intensive care unit (NICU) because of improved survival of extremely preterm infants.

EPIDEMIOLOGY

Candida species are a common cause of bloodstream infection in premature infants. The incidence varies greatly by individual NICU. Among centers in the National Institutes of Health–sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1,000 g birthweight ranges from 2% to 28%. Colonization is associated with a significantly increased risk of future invasive *Candida* infection. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in premature infants. Colonization rates increase to >50% among infants admitted to the NICU by 1 month of age. Histamine-2 blockers, corticosteroids, and broad-spectrum antibiotics facilitate *Candida* colonization and overgrowth.

Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotics, abdominal surgery, endotracheal intubation, and presence of a central venous catheter.

PATHOGENESIS

Immunologic immaturity along with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibiotics places preterm infants at great risk for invasive candidiasis. Premature infants are also at high risk for spontaneous intestinal perforations and

necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral nutrition administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis by decreasing the physiologic barriers that protect against invasive infection.

CLINICAL MANIFESTATIONS

The manifestations of neonatal candidiasis vary in severity from oral thrush and *Candida* diaper dermatitis (see Chapter 280.2) to invasive candidiasis that can manifest with overwhelming sepsis (see Chapter 280.3). Signs of invasive candidiasis among premature infants are often nonspecific and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distention, and thrombocytopenia.

Central nervous system involvement is common and is most accurately described as meningoencephalitis. *Candida* infections involving the central nervous system often result in abscesses, leading to unremarkable cerebrospinal fluid parameters (white blood cell count, glucose, protein) even though central nervous system infection is present. Endophthalmitis is an uncommon complication affecting <5% of infants with invasive candidiasis, but candidemia is associated with an increased risk of severe retinopathy of prematurity. Renal involvement commonly complicates neonatal invasive candidiasis. Renal involvement may be limited to candiduria or can manifest with diffuse infiltration of *Candida* throughout the renal parenchyma or the presence of *Candida* and debris within the collecting system. Because of the poor sensitivity of blood cultures for *Candida*, candiduria should be considered a surrogate marker of candidemia in premature infants. Other affected organs include the heart, bones, joints, liver, and spleen.

DIAGNOSIS

Mucocutaneous infections are most often diagnosed by direct clinical exam. Scrapings of skin lesions may be examined with a microscope after Gram staining or suspension in KOH. Definitive diagnosis of invasive disease requires histologic demonstration of the fungus in tissue specimens or recovery of the fungus from normally sterile body fluids. Hematologic parameters are sensitive but not specific. Thrombocytopenia occurs in more than 80% of premature infants with invasive candidiasis, but also occurs in 75% of premature infants with gram-negative bacterial sepsis and nearly 50% of infants with gram-positive bacterial sepsis. Blood cultures have very low sensitivity for invasive candidiasis. In a study of autopsy-proven candidiasis in adult patients, the sensitivity of multiple blood cultures for detecting single-organ disease was 28%. Blood culture volumes in infants are often only 0.5-1 mL, making the sensitivity in this population almost certainly lower. Blood culture volume should be maximized as much as possible to increase sensitivity.

Further assessment of infants in the presence of documented candidemia should include ultrasound or computerized tomography of the head to evaluate for abscesses; ultrasound of the liver, kidney, and spleen; cardiac echocardiography; ophthalmologic exam; lumbar puncture; and urine culture. These tests are necessary to determine if more than one body system is infected, which is commonly the case.

PROPHYLAXIS

NICUs with a high incidence of invasive candidiasis should consider prophylaxis with fluconazole in infants <1,000 g birthweight as a cost-effective method of reducing invasive candidiasis. Twice-weekly fluconazole at 3 or 6 mg/kg/dose decreases rates of both colonization with *Candida* species and invasive fungal infections. Use of this dosing strategy has not been shown to increase the frequency of infections caused by fluconazole-resistant strains, but use of an alternative antifungal class for cases of breakthrough infection is suggested.

TREATMENT

In the absence of systemic manifestations, **topical antifungal therapy is the treatment of choice for congenital cutaneous candidiasis in full-term infants**. Congenital cutaneous candidiasis in preterm infants can progress to systemic disease, and therefore systemic therapy is warranted in these patients.

Every attempt should be made to **remove or replace central venous catheters** once the diagnosis of candidemia is confirmed. Delayed removal has been consistently associated with increased mortality and morbidity, including poor neurodevelopmental outcomes.

Although no well-powered randomized controlled trials exist to guide the length and type of therapy**, 21 days of systemic antifungal therapy from the last positive *Candida* culture is recommended in infants**. Antifungal therapy should be targeted based on susceptibility testing. Amphotericin B deoxycholate has been the mainstay of therapy for systemic candidiasis and is active against both yeast and mycelial forms. Nephrotoxicity, hypokalemia, and hypomagnesemia are common, but amphotericin B deoxycholate is better tolerated in infants than in adult patients. *C. lusitaniae,* an uncommon pathogen in infants, is often resistant to amphotericin B deoxycholate. Liposomal amphotericin is associated with worse outcomes in infants and should be used only when urinary tract involvement can reliably be excluded. Fluconazole is often used instead of amphotericin B deoxycholate for treatment of invasive neonatal *Candida* infections because of its effectiveness and low incidence of side effects. It is particularly useful for urinary tract infections, obtaining high concentrations in the urine. A loading dose should be given to obtain therapeutic serum concentrations in a timely manner. Fluconazole is inactive against all strains of *C. krusei* and some isolates of *C. glabrata.* Additionally, in centers where fluconazole prophylaxis is used, another agent, such as amphotericin B deoxycholate, should be used for treatment. The echinocandins have excellent activity against most *Candida* species and have been used successfully in patients with resistant organisms or in whom other therapies have failed. Two trials comparing an echinocandin with amphotericin B deoxycholate were stopped early because of low recruitment but found similar efficacy for the two treatments among the included patients. Several studies have described the pharmacokinetics of antifungals in infants (Table 280.1).

PROGNOSIS

Mortality after invasive candidiasis in premature infants has been consistently reported to be around 20% in large studies but can be as high as 50% in infants <1,500 g birthweight. Candidiasis is also associated with poor neurodevelopmental outcomes, chronic lung disease, and severe retinopathy of prematurity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

280.2 Infections in Immunocompetent Children and Adolescents

Jessica E. Ericson and Daniel K. Benjamin Jr.

ORAL CANDIDIASIS

Oral thrush is a superficial mucous membrane infection that affects approximately 2–5% of normal neonates. *C. albicans* is the most commonly isolated species. Oral thrush can develop as early as 7-10 days of age. The use of antibiotics, especially in the first year of life, can lead to recurrent or persistent thrush. It is characterized by pearly white, curdish material visible on the tongue, palate, and buccal mucosa. Oral thrush may be asymptomatic or can cause pain, fussiness, and decreased feeding, leading to inadequate nutritional intake and dehydration. It is uncommon after 1 year of age but can occur in older children treated with antibiotics. Persistent or recurrent thrush with no obvious predisposing reason, such as recent antibiotic treatment, warrants investigation of an underlying immunodeficiency, especially vertically transmitted HIV infection or a primary congenital immune defect.

Treatment of mild cases might not be necessary. When treatment is warranted, the most commonly prescribed antifungal agent is topical

Table 280.1 Dosing of Antifungal Agents Studied in Infants* with Reported Pharmacokinetic (PK) Parameters

DRUG	PK STUDIED IN INFANTS	SUGGESTED DOSE
Amphotericin B deoxycholate	Yes (multiple)	1 mg/kg/day
Amphotericin B lipid complex	Yes (single)	5 mg/kg/day
Liposomal amphotericin B	Yes (single)	5 mg/kg/day
Amphotericin B colloidal dispersion	No	5 mg/kg/day
Fluconazole†	Yes (best studied with ~250 infant contributing PK samples)	12 mg/kg/day
Voriconazole	No – drug concentrations reported for a single infant with neonatal candidiasis	
Posaconazole	No – drug concentrations reported for a single infant with cutaneous rhizopus infection	
Micafungin‡	Yes (multiple)	10 mg/kg/day
Caspofungin§	Yes (single)	50 mg/m^2/day
Anidulafungin‡	Yes (single)	1.5 mg/kg/day

*Voriconazole and posaconazole dosing have not been investigated in the nursery. Doses are those suggested by experts.
†A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum and cerebrospinal fluid concentrations in the early days of therapy.
‡Micafungin has been studied in infants <120 days of life at this dosage.
§Caspofungin and anidulafungin should generally be avoided because dosing sufficient to penetrate brain tissue has not been studied.

nystatin. For recalcitrant or recurrent infections, a single dose of fluconazole may be useful. In breastfed infants, simultaneous treatment of infant and mother with topical nystatin or oral fluconazole may be indicated.

DIAPER DERMATITIS

Diaper dermatitis is the most common infection caused by *Candida* (see Chapter 707) and is characterized by a confluent erythematous rash with satellite pustules. *Candida* diaper dermatitis often complicates other noninfectious diaper dermatitides and often occurs after a course of oral antibiotics.

A common practice is to presumptively treat any diaper rash that has been present for longer than 3 days with topical antifungal therapy such as nystatin, clotrimazole, or miconazole. If significant inflammation is present, the addition of hydrocortisone 1% may be useful for the first 1-2 days, but topical corticosteroids should be used cautiously in infants because the relatively potent topical corticosteroid can lead to adverse effects. Frequent diaper changes and short periods without diapers are important adjunctive treatments.

UNGUAL AND PERIUNGUAL INFECTIONS

Paronychia and onychomycosis may be caused by *Candida,* although *Trichophyton* and *Epidermophyton* are more common causes. *Candida* onychomycosis differs from tinea infections by its propensity to involve the fingernails and not the toenails and by the associated paronychia. *Candida* paronychia often responds to treatment consisting of keeping the hands dry and using a topical antifungal agent. Psoriasis and immune dysfunction, including HIV and primary immunodeficiencies, predispose to *Candida* ungual infections. Ungual infections often require systemic antifungal therapy. **Once-weekly fluconazole for 4-12 months is an effective treatment strategy with fairly low toxicity.**

VULVOVAGINITIS

Vulvovaginitis is a common *Candida* infection of pubertal and postpubertal female patients. Predisposing factors include pregnancy, use of oral contraceptives, and use of oral antibiotics. Prepubertal children with *Candida* vulvovaginitis usually have a predisposing factor such as diabetes mellitus or prolonged antibiotic treatment. Clinical manifestations can include pain or itching, dysuria, vulvar or vaginal erythema, and an opaque white or cheesy exudate. More than 80% of cases are caused by *C. albicans.*

***Candida* vulvovaginitis can be effectively treated with either vaginal creams or troches of nystatin, clotrimazole, or miconazole. Oral therapy with a single dose of fluconazole is also effective.**

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

280.3 Infections in Immunocompromised Children and Adolescents

Jessica E. Ericson and Daniel K. Benjamin Jr.

ETIOLOGY

Candida albicans is the most common cause of invasive candidiasis among immunocompromised pediatric patients and is associated with higher rates of mortality and end-organ involvement than are non-*albicans* species.

CLINICAL MANIFESTATIONS

HIV-Infected Children

Oral thrush and diaper dermatitis are the most common *Candida* infections in HIV-infected children. Besides oral thrush, three other types of oral *Candida* infections can occur in HIV-infected children: atrophic candidiasis, which manifests as a fiery erythema of the mucosa or loss of papillae of the tongue; chronic hyperplastic candidiasis, which presents with oral symmetric white plaques; and angular cheilitis, in which there is erythema and fissuring of the angles of the mouth. Topical antifungal therapy may be effective, but **systemic treatment with fluconazole or itraconazole is usually necessary**. Symptoms of dysphagia or poor oral intake can indicate progression to *Candida* esophagitis, requiring systemic antifungal therapy. In HIV patients, esophagitis can also be caused by cytomegalovirus, herpes simplex virus, reflux, or lymphoma; *Candida* is the most common cause, and *Candida* esophagitis can occur in the absence of thrush.

Candida dermatitis and onychomycosis are more common in HIV-infected children. These infections are generally more severe than they are in immunocompetent children and can require systemic antifungal therapy.

Cancer and Transplant Patients

Fungal infections, especially *Candida* and *Aspergillus* infections, are a significant problem in oncology patients with chemotherapy-associated neutropenia (see Chapter 223). Greater than 5 days of fever during a neutropenic episode is associated with presence of an invasive fungal infection. Accordingly, empirical antifungal therapy should be started if fever and neutropenia persist for 5 or more days. **An echinocandin should be used until sensitivity testing results are available.** High-risk oncology patients warrant prophylaxis against invasive *Candida* infection. Both fluconazole and echinocandins are used for this indication, typically at lower doses than those used for treatment. If an echinocandin is used for prophylaxis, liposomal amphotericin B should be used if empirical treatment becomes warranted.

Bone marrow transplant recipients have a much higher risk of fungal infections because of the dramatically prolonged duration of neutropenia. Voriconazole prophylaxis decreases the incidence of candidemia in bone marrow transplant recipients with the additional benefit over fluconazole of mold prophylaxis. The use of granulocyte colony-stimulating factor reduces the duration of neutropenia after chemotherapy and is associated with decreased risk for candidemia. When *Candida* infection occurs in this population, the lung, spleen, kidney, and liver are involved in more than 50% of cases.

Solid organ transplant recipients are also at increased risk for superficial and invasive *Candida* infections. Studies in liver transplant recipients demonstrate the utility of antifungal prophylaxis with amphotericin B deoxycholate, fluconazole, voriconazole, or caspofungin in high-risk patients (those with prolonged surgical time, comorbidities, recent antibiotic exposure, or bile leak).

Catheter-Associated Infections

Central venous catheter infections occur most often in oncology patients but can affect any patient with a central catheter. Neutropenia, use of broad-spectrum antibiotics, and parenteral alimentation are associated with increased risk for *Candida* central catheter infection. Treatment typically requires removing or replacing the catheter followed by a 2- to 3-week course of systemic antifungal therapy. **Removal of the central catheter in place at the time of a positive blood culture and use of a peripheral IV or enteral support for at least 48 hours before obtaining central access is advocated.** Removal of the original catheter followed by immediate replacement with a new central catheter in a different anatomic location is acceptable if an interval without central access is not feasible. Delays in catheter removal are associated with increased risks of metastatic complications and death.

DIAGNOSIS

The diagnosis is often presumptive in neutropenic patients with prolonged fever because positive blood cultures for *Candida* occur only in a minority of patients who are later found to have disseminated infection. If isolated, *Candida* grows readily on routine blood culture media, with ≥90% of positive cultures identified within 72 hours. CT scan may demonstrate findings consistent with invasive fungal infection but also is limited by nonspecific findings and false negatives. The role of screening by CT scan has not been well defined. In high-risk patients, serial serum assays for (1,3)-β-D-glucan, a polysaccharide component of the fungal cell wall, may contribute to the diagnosis of invasive Candida infection. However, this test is not sensitive or specific enough to be used without a careful assessment of the limitations of the assay.

Table 280.2 Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease

DRUG	SUGGESTED DOSE
Amphotericin B deoxycholate	1 mg/kg/day
Amphotericin B lipid complex	5 mg/kg/day
Liposomal amphotericin B	5 mg/kg/day
Amphotericin B colloidal dispersion	5 mg/kg/day
Fluconazole†	12 mg/kg/day
Voriconazole*,‡	8 mg/kg every 12 hr
Micafungin	2-4 mg/kg/day
Caspofungin	50 mg/m²/day
Anidulafungin	1.5 mg/kg/day

*Use adult dosages in children older than 12 yr of age for voriconazole and older than 8 yr of age for micafungin.
†Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m²), and anidulafungin (3 mg/kg).
‡Dosing should be adjusted based on the results of therapeutic drug monitoring.

TREATMENT

Echinocandins are favored as empirical therapy for moderately or severely ill children and for those with neutropenia; fluconazole is acceptable for those who are infected with a susceptible organism and are less critically ill; amphotericin B products are also acceptable. Definitive antifungal selection should be made based on susceptibility testing results. Fluconazole is not effective against *C. krusei* and some isolates of *C. glabrata. C. parapsilosis* has occasional resistance to the echinocandins, but the overall rate is still low. Amphotericin B deoxycholate is inactive against approximately 20% of the strains of *C. lusitaniae,* and therefore susceptibility testing should be performed for all strains (Table 280.2). *C. auris,* a species first identified in 2009 that has caused nosocomial infections worldwide, is resistant to most antifungals. An echinocandin should be used until sensitivity results are available.

PRIMARY IMMUNE DEFECTS

Chronic mucocutaneous candidiasis involves *Candida* infections of the oral cavity, esophagus, and/or genital mucosa, as well as involvement of skin and nails, that is recurrent or persistent and difficult to treat. There is a broad spectrum of genetic immune defects associated with chronic mucocutaneous candidiasis mostly related to severe T-cell defects or disorders of interleukin-17 production. Genes or disorders associated with chronic mucocutaneous candidiasis include severe combined immunodeficiency syndrome, NEMO or IKBG deficiency, DOCK8 deficiency, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), autoimmune polyendocrinopathy type 1, CARD9 deficiency, *STAT1* gain-of-function mutations, and *IL17RA* mutations.

Primary immunodeficiencies associated with an increased risk of invasive *Candida* infections include severe congenital neutropenia, CARD9 deficiency, chronic granulomatous disease, and leukocyte adhesion deficiency type 1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 281

Cryptococcus neoformans and *Cryptococcus gattii*

David L. Goldman

ETIOLOGY

More than 30 cryptococcal species have been described; however, 2 species (*Cryptococcus neoformans* and *Cryptococcus gattii*) cause the vast majority of disease in children and adults. Both *C. neoformans* and *C. gattii* are encapsulated, facultative intracellular yeasts that are recognized for their tendency to cause central nervous system (CNS) infection, especially in immunocompromised patients. Although there is significant overlap in the disease caused by these pathogens, there are key differences in epidemiology and clinical presentation, which will be reviewed here. Cryptococcal disease may rarely be caused by other species (e.g., *C. laurentii* and *C. albidus*), especially in immunocompromised individuals (including neonates). These latter species will not be covered in this chapter.

EPIDEMIOLOGY

Cryptococcosis is primarily acquired from exposure to contaminated environments. *C. neoformans* is distributed in temperate climates predominantly in soil contaminated with droppings from certain avian species, including pigeons, canaries, and cockatoos. It may also be found on rotting wood, fruits, and vegetables and may be carried by cockroaches. Transmission from pet birds to their owners and via solid organ transplantation of infected organs are uncommon, but have also been described.

Disease secondary to *C. neoformans* occurs primarily in immunocompromised individuals and especially in those with defects in cellular immunity, though apparently normal individuals can also be affected. A large increase in the incidence of cryptococcosis was noted in association with the AIDS epidemic, with disease generally occurring with severe immunosuppression ($CD4^+$ T cells <100/μL). However, since the development of effective antiretroviral therapies (ART), the incidence of AIDS-associated cryptococcosis has decreased dramatically, except in resource-limited areas of the world such as sub-Saharan Africa, where ART is not readily available.

Other risk factors for cryptococcal infection include immunosuppression associated with organ transplantation, diabetes mellitus, renal failure, cirrhosis, corticosteroids, rheumatologic conditions, chemotherapeutics, and immune-modulating monoclonal antibodies (e.g., etanercept, infliximab, and alemtuzumab). In patients who have undergone organ transplantation, cryptococcosis is the third most common fungal infection after candidiasis and aspergillosis. Children with certain primary immunodeficiency diseases may also be at increased risk for cryptococcosis, including those with hyper-IgM syndrome, severe combined immunodeficiency, idiopathic $CD4^+$ lymphopenia, autoantibodies to granulocyte-macrophage colony-stimulating factor or interferon-γ, CD40 ligand deficiency, and monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia).

C. gattii was initially recognized for its tendency to cause disease in tropical regions, especially among the native peoples of Australasia, where the organism can be found in association with eucalyptus trees. In these regions, affected individuals are typically immunocompetent. *C. gattii* disease has also been observed outside these tropical regions. An outbreak of *C. gattii* disease involving British Columbia and extending into the Pacific Northwest region of the United States was first recognized in 1999. Affected individuals were typically adults, with disease occurring in both immunocompetent and immunocompromised individuals. However, comorbid conditions were often present, including chronic lung and heart disease. A disproportionate fraction of patients (relative to those infected with *C. neoformans*) presented with pulmonary disease. An incubation period ranging from 2 to 12 months is typical. Thus in the appropriate clinical context, cryptococcosis should be considered in the differential diagnosis of residents of the Pacific Northwest and returning travelers.

Overall, cryptococcosis (both caused by *C. neoformans* and *C. gattii*) is significantly less common in children than in adults. The basis for this discrepancy is poorly understood but could be related to differences in exposure or immune response. Serologic studies suggest that subclinical infection is common among children living in urban areas after age 2 years. Reactivation of latent infection is thought to be an important mechanism of cryptococcal pathogenesis. It is reasonable to postulate that children do not have enough exposures to establish latent infection. During the early AIDS epidemic, the incidence of cryptococcosis in the United States was reported to be on the order of 10% in adults and 1% in children. The largest series of pediatric cryptococcosis comes from South Africa and describes 361 cases, accounting for 2% of the cryptococcosis cases over a 2-year period.

PATHOGENESIS

Like many fungi, *C. neoformans* and *C. gattii* survive as saprophytes in the environment. Their virulence characteristics appear to have evolved as an adaptive response to environmental stressors and predators, such as amoeba. Several key factors have been identified, including the ability to grow at 37°C, encapsulation, and melanin production. These same traits allow the organisms to successfully replicate within the host cell. The polysaccharide capsule, which is readily recognized by India ink staining of cerebrospinal fluid (CSF), is an essential virulence factor. Disease secondary to acapsular strains is exceedingly rare. The capsular material exhibits a variety of biologic activities that are important in the pathogenesis of disease, including interference with opsonization, inhibition of chemotaxis, and enhancement of nonprotective type 2 helper T cells (TH2) inflammation. Capsular material is shed by the organism into body tissues and fluids during infection and has been implicated in the development of increased intracranial pressure (ICP), a hallmark of cryptococcal meningoencephalitis. Detection of shed capsular antigen in the serum and CSF is key to the diagnosis of cryptococcal disease. The organism also has the ability to undergo phenotypic variation in response to environmental changes through a variety of mechanisms and can form large giant cells (on the order 20 times its normal size), which are resistant to phagocytosis. Other recognized virulence factors include a secreted urease, which may promote intraphagolysosomal survival.

In most cases, infection is believed to be acquired by inhalation of desiccated forms of the organism, which upon deposition within the lungs are engulfed by alveolar macrophages. An additional portal of entry is the transplantation of infected organs. Furthermore, direct inoculation can lead to cutaneous or ophthalmic infection. After entry into the respiratory tract, infection can be latent and later progress (i.e., reactivate) in the context of immunodeficiency, in a manner similar to tuberculosis. Alternatively, infection can immediately progress and disseminate to produce symptomatic disease. Cell-mediated immunity that leads to macrophage activation is the most important host defense and is associated with granulomatous inflammation, which effectively contains infection. The precise mechanism of entry of this yeast into the CNS is not known, though several mechanisms have been hypothesized, including transit via infected macrophages (Trojan horse model), direct uptake by endothelial cells, and entry between the tight junctions of endothelial cells.

CLINICAL MANIFESTATIONS

The manifestations of cryptococcal infection reflect the route of inoculation, the infecting strain, and the immune status of the host. Sites of infection include the lung, CNS, blood, skin, bone, eyes, and lymph nodes.

Meningitis/Meningoencephalitis

CNS disease is the most commonly recognized manifestation of cryptococcosis. The disease is characteristically subacute or chronic (evolving over weeks to months). Although the term *meningitis* is commonly used to describe CNS involvement, some degree of encephalitis is also typically present, with occasional patients developing intracerebral masses, known as *cryptococcomas*. Importantly, meningeal signs and fever (typical of other forms of meningitis) may be lacking. In a review of pediatric cryptococcosis from Colombia, the most common symptoms were headache (78%), fever (69%), nausea and vomiting (66%), confusion (50%), and meningismus (38%). Other symptoms include decreased level of consciousness, changes in personality, ataxia, hearing deficits, and visual deficits. Increased intracranial pressure is thought to occur as a result of impaired absorption of CSF and has been reported to occur in more than 50% of adults with cryptococcal meningitis.

Despite antifungal therapy, the mortality rate for cryptococcosis remains high, ranging from 15–40%. Most deaths occur within several weeks of diagnosis. Factors associated with a poor prognosis reflect a high fungal burden and poor host response, including altered mentation, high CSF fungal burden, low CSF white blood cell (WBC) number (<10 cells/mm^3), and failure to rapidly sterilize the CSF. Increased ICP is a key factor in the morbidity and mortality of cryptococcal meningitis and is especially problematic for patients with *C. gattii* disease. Appropriate management of increased ICP is therefore essential to the appropriate management of cryptococcal meningitis (see later). Postinfectious sequelae are common and include hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures, and ataxia.

Pneumonia

Cryptococcosis is acquired via inhalation, and pneumonia is the most commonly recognized form of disease after meningitis. As with meningitis, pneumonia occurs in both immunocompetent and immunocompromised individuals. Pulmonary disease can present in isolation or in the context of disseminated disease/meningitis, which is typical among immunocompromised individuals. Among adults with AIDS-associated cryptococcal pneumonia, over 90% had concomitant CNS infection. Thus clinicians should have a high suspicion for cryptococcal meningitis/disseminated disease in patients with cryptococcal pneumonia, especially among immunocompromised individuals, and should pursue a workup to exclude dissemination.

Cryptococcal pneumonia is often asymptomatic and may be detected because of radiographs performed for other reasons. In this regard, asymptomatic pulmonary nodules secondary to *C. neoformans* can be found in children with sarcomas, who are being evaluated for metastatic disease. Among symptomatic patients, a wide array of symptoms has been reported, including fever, cough, pleuritic chest pain, and constitutional symptoms like weight loss. Severe disease may result in respiratory failure. Chest radiographic findings are variable and may demonstrate a poorly localized bronchopneumonia, nodules, masses, or lobar consolidations. Pulmonary cavities and pleural effusions are rare. Immunocompromised patients with disseminated disease can have alveolar and interstitial infiltrates that mimic the pattern of disease seen in some patients with *Pneumocystis* pneumonia.

Cutaneous Infection

Cutaneous disease occurs most commonly in the context of disseminated cryptococcosis but rarely can result from local inoculation. The appearance of cutaneous cryptococcosis is both nondistinct and variable and includes papules, ulcers, subcutaneous nodules, and rarely, cellulitis. The lesions are typically subacute, evolving over weeks to months. Early lesions are often erythematous, are variably indurated and tender, and may be single or multiple. Lesions often become ulcerated with central necrosis and raised borders. Cutaneous cryptococcosis in immunocompromised patients can also resemble molluscum contagiosum. Given the variable and nondistinct nature of this disease, a high suspicion of disease, especially in the appropriate clinical context (e.g., immunocompromised host), is needed to make the diagnosis.

Skeletal Infection

Skeletal infection occurs in approximately 5% of patients with disseminated infection but rarely in HIV-infected patients. Interestingly, chronic infection of the tibia was the first recognized manifestation of cryptococcal disease and was described in 1894. Like other forms of cryptococcosis, the onset of symptoms is insidious and chronic. Bone involvement is typified by soft tissue swelling and tenderness, and arthritis is characterized by effusion, erythema, and pain on motion. Skeletal disease is unifocal in approximately 75% of cases. The vertebrae are the most common site of infection, followed by the tibia, ileum, rib, femur, and humerus. Concomitant bone and joint disease can result from contiguous spread.

Sepsis Syndrome

Sepsis syndrome is a rare manifestation of cryptococcosis and occurs almost exclusively among HIV-infected patients. Fever is followed by respiratory distress and multiorgan system disease that is often fatal.

Immune Reconstitution Inflammatory Syndrome

Cryptococcal-associated immune reconstitution inflammatory syndrome (C-IRIS) occurs in the setting of AIDS and in solid organ transplantation. Improvement of immune function resulting from the administration of ART in AIDS patients (or the reduction of immunosuppression in transplant recipients) is thought to enhance and dysregulate inflammation, leading to an exacerbation of symptoms. This situation is similar to IRIS seen with other opportunistic pathogens. More commonly, C-IRIS presents as a worsening of symptoms in someone with a known diagnosis of cryptococcosis, often within 1-2 months of initiation of ART. Occasionally, C-IRIS, which presents as a meningitis or lymphadenitis, occurs in individuals who were never known to have cryptococcosis (unmasking-IRIS). IRIS is particularly problematic in CNS cryptococcosis and may result in worsening of increased ICP. Although cases of C-IRIS have been described in children, the incidence is not well defined.

DIAGNOSIS

The approach to the diagnosis of cryptococcosis depends on the organ system involved. Recovery of the fungus by culture or demonstration of the fungus in histologic sections of infected tissue or body fluids by India ink staining is definitive. Cryptococci readily grow on standard fungal and bacterial culture media. Colonies can be seen within 48-72 hours when grown aerobically at standard temperatures. The CSF profile in patients with cryptococcal meningitis typically reveals a mild lymphocytosis and elevated protein, but findings can also be normal.

Detection of cryptococcal polysaccharide in the CSF, which can be done by several different methods, is key to the diagnosis of CNS infection. One of the earliest detection tests to be developed is the latex agglutination test, which can detect cryptococcal antigen in serum and CSF. Titers of ≥1:4 in bodily fluid strongly suggest infection, and titers of >1:1,024 reflect high burden of yeast, poor host immune response, and greater likelihood of therapeutic failure. Serial monitoring of cryptococcal antigen levels is not useful in guiding

therapy, as the polysaccharide antigen is actively shed into the tissue and may persist for prolonged periods. Patients with localized pneumonia typically do not have elevated serum antigen levels (though occasionally low levels of antigen, <1:4, may be detected). Higher serum antigen levels in patients with pulmonary disease are indicative of dissemination outside the lungs. A point-of-care, lateral flow assay for polysaccharide detection has been developed and has comparable sensitivity to the latex-agglutination assay, with the advantage of being less labor intensive. This assay provides a qualitive positive/negative result, but can also be performed to provide a semiquantitative result. False negatives for both latex agglutination and lateral flow assays may occur in the context of antigen excess, so samples are typically run both undiluted and diluted. False-positive results can occur with other fungal infections, including infection with *Trichosporon* spp. and, rarely, by disinfectants. A commercially available ELISA also allows for the detection of cryptococcal polysaccharide in body fluids. Several PCR-based film arrays have also been developed for the diagnosis of cryptococcosis. These assays allow for the detection of *C. neoformans* DNA in the CSF as part of a panel of meningitis/encephalitis-associated pathogens. Nonetheless, both false positives and false negatives (especially in the context of low-burden disease) have been well documented.

TREATMENT

The choice of treatment for cryptococcosis depends on the sites of involvement and the host immune status. These regimens have not been rigorously studied in children and generally represent extrapolations from studies done in adults. Guidelines for the treatment of pediatric cryptococcosis have been developed by the Infectious Diseases Society of America (IDSA) and the World Health Organization (WHO).

Pulmonary Disease

The immunocompetent patient with asymptomatic or mild disease limited to the lungs should be treated with oral fluconazole (pediatric dose 6-12 mg/kg/day and adult dose 400 mg/day) for 6-12 months to prevent dissemination and progression of disease. Alternative treatments include itraconazole in solution form (pediatric dose 5-10 mg/kg/day divided every 12 hours and adult dose 400 mg/day), voriconazole, and posaconazole. Fluconazole therapy can also be used for immunocompromised individuals with isolated mild to moderate pulmonary disease in the absence of dissemination or CNS disease. Longer maintenance therapy with fluconazole to prevent recurrence should be considered in this cohort, especially among AIDS patients if the $CD4^+$ T cells remain less than 100/μL. Adjunctive surgical management of pulmonary lesions that are not responsive to surgical management should be considered. Patients with diffuse pulmonary disease or those with severe symptoms (e.g., acute respiratory distress syndrome) should be treated in the same manner as those with meningitis.

Disseminated Disease and Meningitis

For more severe forms of disease, including meningitis and any form of disseminated disease, an initial induction regimen to promote rapid decline in fungal burden is indicated. According to Infectious Diseases Society of America (IDSA) guidelines, induction therapy should consist of amphotericin B (1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hours, assuming normal kidney function) for a minimum of 2 weeks, keeping serum flucytosine concentrations between 40 and 60 μg/mL. Lipid amphotericin B has replaced standard amphotericin B for the treatment of severe cryptococcosis in adults, primarily based on its lower toxicity profile. Strong consideration should be given to the use of lipid complex amphotericin B (3-6 mg/kg/day) in all affected pediatric patients, especially those with underlying kidney disease or at risk for kidney disease. Alternative induction therapies as outlined by the WHO guidelines include (1) 1 week of amphotericin B in combination with flucytosine, followed by 1 week of high-dose fluconazole with amphotericin B; and (2) 2 weeks of amphotericin B in combination with high-dose fluconazole. Repeat lumbar puncture is generally recommend at the end of induction therapy to document sterilization of CSF. Longer periods of induction (4-6 weeks) should be considered in the following scenarios: (1) immunocompetent patients with cryptococcal meningitis, (2) meningitis secondary to *C. gattii,* (3) failure to sterilize CSF, and (4) neurologic complications (including cryptococcomas). After induction, consolidation therapy with oral fluconazole (pediatric dose 10-12 mg/kg/day, adult dose 400-800 mg/day) should be given for 8 weeks. In patients with ongoing immunosuppression, maintenance fluconazole should be used to prevent recurrence. In organ transplant recipients, current recommendations are for 6-12 months of maintenance therapy with fluconazole (pediatric dose 6 mg/kg/day, adult dose 200-400 mg/day). In patients with AIDS, prolonged maintenance therapy should be given. Studies in adults suggest that maintenance therapy can be discontinued once the patient has achieved immune reconstitution (as indicated by $CD4^+$ T cells >100/μL and an undetectable or very low HIV RNA level that is sustained for greater than 3 months). A minimum of 12 months of antifungal therapy is indicated. Use of adjuvant interferon gamma for patients with refractory cryptococcal meningitis has been described in adults, but not in pediatric patients.

Increased ICP. Increased ICP contributes greatly to the morbidity and mortality of cryptococcal meningitis, and aggressive management of this phenomenon is indicated. Current guidelines indicate that in patients with increased ICP (>25 cm H_2O), CSF should be removed to establish a pressure ≤20 cm H_2O or by 50% if ICP is extremely high. Serial lumbar punctures may be needed to ensure normalization of ICP, and ventriculoperitoneal shunts can be considered for patients with persistently elevated increased ICP. Corticosteroids, mannitol, and acetazolamide are generally not indicated in the treatment of increased ICP, though anecdotal reports describe use in association with cryptococcoma (in patients with *C. gattii* infection) and C-IRIS.

C-IRIS. To prevent the development of C-IRIS, most experts recommend delaying the institution of ART for 4-6 weeks after the initiation of antifungal therapy. Recurrence of disease and emergence of antifungal resistance should be excluded in the context of a diagnosis of C-IRIS. Treatment strategies have not been well studied but generally consist of antifungal therapy along with antiinflammatory agents (e.g., NSAIDs and corticosteroids). Reduction of increased ICP through therapeutic lumbar puncture may be necessary.

PREVENTION

Persons at high risk for cryptococcosis should be advised to avoid exposures to bird droppings. Effective ART for persons with HIV infection significantly reduces the risk of cryptococcal disease. For adolescent patients with AIDS, regular cryptococcal antigen testing with subsequent diagnostic evaluation and therapy should be considered for individuals with $CD4^+$ lymphocyte counts <100/μL. Cryptococcal antigen screening should also be done before the initiation of antiretroviral therapy in patients newly diagnosed with HIV infection. In the absence of ability to perform regular screening, fluconazole prophylaxis for all patients with $CD4^+$ lymphocyte counts <100/μL can be considered. However, in children for whom the incidence of cryptococcosis is relatively low, screening and prophylaxis are generally not needed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 282

Malassezia

Ashley M. Maranich

Members of the genus *Malassezia* are lipophilic yeasts that are a significant component of the skin microbiome. They have a predilection for the sebum-rich areas of the skin and are considered normal skin flora. Colonization is established just after birth and rises before puberty, with distribution (both in species and number) related to numerous factors, including age, body site, and geographic location.

The history of *Malassezia* nomenclature is complex and can be confusing. Yeast forms may appear oval or round, resulting in early designations of both *Pityrosporum ovale* and *Pityrosporum orbiculare*. Additionally, newer technologies, such as matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), are allowing for an improved classification system. The genus *Malassezia* has recently been assigned its own class, Malasseziomycetes, with 18 currently recognized species. Disease is facilitated by transformation of the yeast form to a hyphal form, with clusters of thick-walled blastospores with the hyphae producing the characteristic **spaghetti-and-meatballs** appearance of *Malassezia* spp. under light microscopy.

Malassezia can cause a number of dermatologic conditions, more commonly in tropical environments, to include **tinea versicolor** (also **pityriasis versicolor**) (Fig. 282.1; see Chapter 707), neonatal acne, seborrheic dermatitis, dandruff, *Malassezia* folliculitis, and onychomycosis and are linked with atopic dermatitis and psoriasis. *M. sympodialis, M. globosa,* and *M. furfur* are the major causes of tinea versicolor. *Malassezia* spp. may be isolated from sebum-rich skin areas of asymptomatic persons, emphasizing that demonstration of the fungus does not equate with infection.



Fig. 282.1 A young adult with tinea versicolor. Notice the characteristic hypopigmented scaling macules. *(Courtesy Ashley M. Maranich, MD.)*

Invasive infections, namely catheter-associated **fungemia**, can occur, with premature infants and immunocompromised individuals (especially those with malignancies) the most high-risk populations. *M. furfur* is the species most commonly causing fungemia, with *M. pachydermatis* implicated in neonatal intensive care unit outbreaks. The use of lipid emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* spp. and can prevent infection. Symptoms of catheter-associated fungemia are indistinguishable from other causes of catheter-associated infections but should be suspected in patients, especially neonates, receiving intravenous lipid infusions. Compared with other causes of fungal sepsis, it is unusual for catheter-related *Malassezia* fungemia to be associated with secondary focal infection.

Malassezia species do not grow readily on standard fungal media, and successful culture requires overlaying the agar with olive oil. Recovery of *Malassezia* from blood culture is optimized by supplementing the medium with olive oil or palmitic acid and allowing for prolonged incubation for at least 2 weeks.

Topical treatment of skin-related conditions is considered first-line to minimize the risk of side effects. **The traditional primary therapy for tinea versicolor is daily use of topical selenium sulfide 2.5% applied to affected areas for 10 minutes for a week. Additional regimens for skin disorders include topical azole creams, ketoconazole 2% shampoo applied daily for 3 days, and terbinafine 1% cream applied 1-2 times daily for 1-2 weeks. *Malassezia*-associated skin diseases limited to the head and neck can be managed with either 1% ciclopirox, ketoconazole, or zinc pyrithione shampoos.** Regardless of the agent chosen, recovery time can be prolonged, with repigmentation not occurring for several months. **Continued application of topical treatment on a weekly or monthly basis is frequently recommended to prevent relapse.** Recurrence is common and usually responds well to the original treatment regimen.

Oral therapy for tinea versicolor with fluconazole or itraconazole is easier to administer (especially with large areas of skin involved) but is more expensive, has higher side effect risks, and may be less effective than topical therapy. **Various dosing regimens have been used with success, including fluconazole 300 mg weekly for 2-4 weeks, fluconazole as a single 400-mg dose, and itraconazole 200 mg daily for 5-7 days or 100 mg daily for 2 weeks.** Recent studies have examined alternative therapies, with early data suggesting that essential oils might be a possible option for long-term therapy of *Malassezia* skin infections, with additional studies needed.

Treatment of *Malassezia* fungemia is complicated by the lack of standardized susceptibility testing references. **Recent consensus recommendations name liposomal amphotericin B as first-line treatment for systemic *Malassezia* infections, with amphotericin B deoxycholate as an alternative. Additionally, the involved catheter should be removed and any lipid infusion should be discontinued. Itraconazole, posaconazole, or voriconazole may be alternative agents, but fluconazole should be avoided, given that many patients with *Malassezia* bloodstream infections in existing clinical series were receiving fluconazole prophylaxis at the time of developing the infection.**

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 283
Aspergillus

William J. Steinbach

The genus *Aspergillus* contains approximately 250 species, but most human disease is caused by *Aspergillus fumigatus, A. flavus*, *A. niger*, *A. terreus,* and *A. nidulans*. Invasive disease is most commonly caused by *A. fumigatus*. Most cases of *Aspergillus* disease **(aspergillosis)** are caused by inhalation of airborne spores (conidia) that subsequently germinate into fungal hyphae and invade host tissue. When inhaled by an immunocompetent person, conidia are rarely deleterious, presumably because they are efficiently cleared by phagocytic cells. Macrophage- and neutrophil-mediated host defenses are required for resistance to invasive disease.

Aspergillus is a relatively unusual pathogen in that it can create very different disease states depending on the host characteristics, including allergic (hypersensitivity), saprophytic (noninvasive), chronic, or invasive disease. Immunodeficient hosts are at risk for invasive disease, whereas immunocompetent atopic hosts tend to develop allergic disease. Disease manifestations include primary allergic reactions; colonization of the lungs or sinuses; localized infection of the lung or skin; chronic infection of the lung; invasive pulmonary disease; or widely disseminated disease of the lungs, brain, skin, eye, bone, heart, and other organs. Clinically, these syndromes often manifest with mild, nonspecific, and late-onset symptoms, particularly in the immunosuppressed host, complicating accurate diagnosis and timely treatment.

283.1 Allergic Disease (Hypersensitivity Syndromes)

William J. Steinbach

ASTHMA

Attacks of atopic asthma can be triggered by inhalation of *Aspergillus* conidia, producing allergic responses and subsequent bronchospasm. Exposure to fungi, especially *Aspergillus,* needs to be considered as a trigger in a patient with an asthma flare, especially in those patients with severe or recalcitrant asthma.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease resulting from immunologic sensitization to *Aspergillus* antigens. It is primarily seen in patients with asthma or cystic fibrosis. Inhalation of conidia produces noninvasive colonization of the bronchial airways, resulting in persistent inflammation and development of hypersensitivity inflammatory responses. Disease manifestations are the result of abnormal immunologic responses to *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and even fibrosis.

There are eight primary diagnostic criteria for ABPA: episodic bronchial obstruction, peripheral eosinophilia, immediate cutaneous reactivity to ***Aspergillus*** antigens, precipitating IgE antibodies to *Aspergillus* antigen, elevated total IgE, serum precipitin (specific IgG) antibodies to *A. fumigatus,* pulmonary infiltrates, and central bronchiectasis. Secondary diagnostic criteria include repeated detection of *Aspergillus* from sputum by identification of morphologically consistent fungal elements or direct culture and coughing of brown plugs or specks. Radiologically, bronchial wall thickening, pulmonary infiltrates, and central bronchiectasis can be seen.

Treatment depends on relieving inflammation via an extended course of systemic corticosteroids. Addition of oral antifungal agents, such as itraconazole or voriconazole, is used to decrease the fungal burden and diminish the inciting stimulus for inflammation. Because disease activity is correlated with serum IgE levels, these levels are used as one marker to define duration of therapy. An area of research interest is the utility of anti-IgE antibody therapy in the management of ABPA.

ALLERGIC *ASPERGILLUS* SINUSITIS

Allergic *Aspergillus* sinusitis is thought to be similar in etiology to ABPA. It has been primarily described in young adult patients with asthma and may or may not be seen in combination with ABPA. Patients often present with symptoms of chronic sinusitis or recurrent acute sinusitis, such as congestion, headaches, and rhinitis, and are found to have nasal polyps and opacification of multiple sinuses on imaging. Laboratory findings can include elevated IgE levels, precipitating antibodies to *Aspergillus* antigen, and immediate cutaneous reactivity to *Aspergillus* antigens. Sinus tissue specimens might contain eosinophils, Charcot-Leyden crystals, and fungal elements consistent with *Aspergillus* species. **Surgical drainage is an important aspect of treatment, often accompanied by courses of either systemic or inhaled steroids. Use of an antifungal agent may also be considered.**

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

283.2 Saprophytic (Noninvasive) Syndromes

William J. Steinbach

PULMONARY ASPERGILLOMA

Aspergillomas are masses of fungal hyphae, cellular debris, and inflammatory cells that proliferate without vascular invasion, generally in the setting of preexisting cavitary lesions or ectatic bronchi. These cavitary lesions can occur as a result of infections such as tuberculosis, histoplasmosis, or resolved abscesses or secondary to congenital or acquired defects such as pulmonary cysts or bullous emphysema. Patients may be asymptomatic, with diagnosis made through imaging for other reasons, or may present with hemoptysis, cough, or fever. On imaging, initially there may be thickening of the walls of a cavity, and later on there is a solid round mass separated from the cavity wall as the fungal ball develops. Detection of *Aspergillus* antibody in the serum suggests this diagnosis. Treatment is indicated for control of complications, such as hemoptysis. **Surgical resection is the definitive treatment but has been associated with significant risks. Systemic antifungal treatment with azole-class agents is indicated in certain patients.**

CHRONIC PULMONARY ASPERGILLOSIS

Chronic aspergillosis can occur in patients with normal immune systems or mild degrees of immunosuppression, including intermittent corticosteroids. Three major categories, each with overlapping clinical features, have been proposed to describe different manifestations of chronic aspergillosis. The first is chronic **cavitary pulmonary aspergillosis** (CCPA), which is similar to aspergilloma, except that multiple cavities form and expand with occupying fungal balls. The second is **chronic fibrosing pulmonary aspergillosis**, where the multiple individual lesions progress to significant pulmonary fibrosis. The final is **subacute invasive aspergillosis** (IA), which was previously called *chronic necrotizing pulmonary aspergillosis,* a slowly progressive process found in patients with mild to moderate immune impairment.

Treatment based on consensus guidelines can sometimes involve surgical resection, although long-term antifungal therapy is often indicated. Management of semi-IA is similar to that of invasive pulmonary aspergillosis; however, the disease is more indolent, and thus there is a greater emphasis on oral therapy. Direct instillation of antifungals into the lesion cavity has been employed with some success.

OTOMYCOSIS

Aspergillus can colonize the external auditory canal, with possible extension to the middle ear and mastoid air spaces if the tympanic membrane is disrupted by concurrent bacterial infection. Symptoms include pain, itching, decreased unilateral hearing, or otorrhea.

Otomycosis is more often seen in patients with impaired mucosal immunity, such as patients with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV and those using chronic steroids. **Treatments have not been well studied, but topical treatment with acetic or boric acid instillations or oral azoles such as voriconazole, itraconazole, and posaconazole have been described.**

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

283.3 Invasive Disease

William J. Steinbach

IA is primarily a disease of immunocompromised hosts, and common risk factors in adults include cancer or chemotherapy-induced neutropenia, particularly if severe and/or prolonged; hematopoietic stem cell transplantation, especially during the initial preengraftment phase or if complicated by graft-versus-host disease; neutrophil or macrophage dysfunction, as occurs in severe combined immunodeficiency (SCID) or chronic granulomatous disease (CGD); prolonged high-dose steroid use; solid organ transplantation; and rarely, HIV. The most common site of primary infection is the lung, but primary invasive infection is also seen in the sinuses and skin and rarely elsewhere. Secondary infection can be seen after hematogenous spread, often to the skin, central nervous system (CNS), eye, bone, and heart.

INVASIVE PULMONARY ASPERGILLOSIS

Invasive pulmonary aspergillosis is the most common form of aspergillosis and plays a significant role in morbidity and mortality in the patient populations mentioned at increased risk for IA. Presenting symptoms can include fever despite initiation of empirical broad-spectrum antibacterial therapy, cough, chest pain, hemoptysis, and pulmonary infiltrates. Patients on high-dose steroids are less likely to present with fever. Symptoms in these immunocompromised patients can be very vague, and thus maintaining a high index of suspicion when confronted with a high-risk patient is essential.

Diagnosis

Imaging can be helpful, although no finding is pathognomonic for invasive pulmonary aspergillosis. Characteristically, multiple ill-defined nodules can be seen, though lobar or diffuse consolidation is not uncommon, and normal chest x-rays do not rule out disease. Classic radiologic signs on CT during neutropenia include the **halo sign**, when angioinvasion produces a hemorrhagic nodule surrounded by ischemia (Fig. 283.1). Early on there is a rim of ground-glass opacification surrounding a nodule. Over time, these lesions evolve into cavitary lesions or lesions with an **air crescent sign** when the lung necroses around the fungal mass, often seen during recovery from neutropenia. Unfortunately, these findings are not specific to invasive pulmonary aspergillosis and can also be seen in other pulmonary fungal infections, and in pulmonary hemorrhage and organizing pneumonia. In addition, several reviews of imaging results of pediatric aspergillosis cases suggest that cavitation and air crescent formation are less common among these patients than among adult patients. On MRI, the typical finding for pulmonary disease is the **target sign**, a nodule with a lower central signal compared with the rim-enhancing periphery.

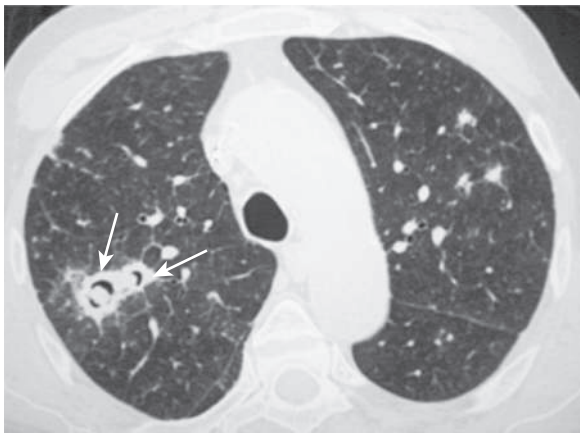

Fig. 283.1 Angioinvasive aspergillosis. CT section at the level of the lower trachea shows a consolidation with an eccentric cavitation and air crescent sign *(arrows)*. This finding in this neutropenic patient is highly diagnostic of angioinvasive aspergillosis. *(From Franquet T. Nonneoplastic parenchymal lung disease. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig. 36.14.)*

Conclusive diagnosis requires culture of *Aspergillus* from a normally sterile site and histologic identification of tissue invasion by fungal hyphae consistent with *Aspergillus* morphology. In addition, depending on the specimen type, a positive result from culture can represent colonization rather than infection; however, all positive cultures should be interpreted conservatively in high-risk patients. Serology can be useful in the diagnosis of allergic ***Aspergillus*** syndromes and in aspergilloma but is low yield for invasive disease, likely because of deficient immune responses in the high-risk immunocompromised population. Bronchoalveolar lavage (BAL) can be useful, but negative culture results cannot be used to rule out disease, owing to inadequate sensitivity. Proven disease requires histologic confirmation or microbiologic recovery of the organism, whereas probable disease diagnosis includes radiographic findings coupled with molecular biologic assays such as galactomannan antigen detection either in the serum or from the BAL. This galactomannan assay has been shown to be the most sensitive in detecting disease in cancer patients or hematopoietic stem cell transplant recipients, with less utility in solid organ transplant recipients. Earlier reports of increased false-positive reactions in children versus adults have been refuted, and the galactomannan assay is effective in diagnosing IA in children. This test does possess high rates of false negativity in patients with congenital immunodeficiency (e.g., CGD) and invasive ***Aspergillus*** infections. The beta-glucan assay is a nonspecific molecular fungal assay that detects the major component of the fungal cell wall. Unlike the galactomannan assay, which is specific for *Aspergillus*, the beta-glucan assay will not discriminate which fungal organism is infecting the patient. Polymerase chain reaction (PCR)–based assays are in development for the diagnosis of aspergillosis but are still being optimized.

Treatment

Successful treatment of IA hinges on the ability to reconstitute normal immune function and use of effective antifungal agents until immune recovery can be achieved. Therefore lowering overall immunosuppression, specifically via cessation of corticosteroid use, is vital to improve the ultimate outcome. **Multiple published guidelines recommend that primary therapy for all forms of IA is voriconazole**, based on several studies showing both improved response rates and improved survival in patients receiving voriconazole when compared with amphotericin B. Guideline-recommended alternative therapies include liposomal amphotericin B, isavuconazole, and other lipid formulations of amphotericin B. European guidelines recommend isavuconazole and voriconazole for treatment of pulmonary disease with a similar strength of recommendation, mentioning fewer adverse effects with isavuconazole than with voriconazole and use of liposomal amphotericin B as an alternative. Posaconazole is another triazole antifungal that is approved for antifungal prophylaxis and may be considered an alternative agent for first-line treatment of IA.

The echinocandin class of antifungals may also a play a role in treatment of IA, but to date, these agents are generally employed as second-line medications, particularly for salvage therapy. Combination antifungal therapy has revealed disparate results. The U.S. guidelines state that combination primary antifungal therapy with voriconazole plus an echinocandin may be considered in select patients with documented IA; however, this is not a recommendation. Importantly, primary therapy with an echinocandin is not recommended, but an echinocandin can be used in the settings in which azole or polyene antifungals are contraindicated. Unfortunately, even with newer

antifungals, complete or partial response rates for treatment of IA are only approximately 50%. To augment antifungal therapies, patients have been treated with growth factors to increase neutrophil counts, granulocyte transfusions, interferon-γ, and surgery. Treatment of IA should be continued for a minimum of 6-12 weeks; however, many experts feel that treatment should continue until complete clinical and radiographic resolution of disease.

Special Populations

Patients with CGD represent a pediatric population at particular risk for pulmonary aspergillosis. Invasive pulmonary aspergillosis can be the first serious infection identified in these patients, and the lifetime risk of developing pulmonary aspergillosis is estimated to be 33%. Unlike classical IA in cancer patients, the onset of symptoms is often gradual, with slow development of fever, fatigue, pneumonia, and elevated sedimentation rate. The neutrophils of patients with CGD surround the collections of fungal elements but cannot kill them, thereby permitting local invasion with extension of disease to the pleura, ribs, and vertebrae, though angioinvasion is not seen. Imaging in these patients is much less likely to reveal the halo sign, infarcts, or cavitary lesions and instead generally shows areas of tissue destruction caused by the ongoing inflammatory processes.

CUTANEOUS ASPERGILLOSIS

Cutaneous aspergillosis can occur as a primary disease or as a consequence of hematogenous dissemination or spread from underlying structures. Primary cutaneous disease classically occurs at sites of skin disruption, such as intravenous access device locations, adhesive dressings, or sites of injury or surgery. Premature infants are at particular risk, given their immature skin and need for multiple access devices. Cutaneous disease in transplant recipients tends to reflect hematogenous distribution from a primary site of infection, often the lungs. Lesions are erythematous, indurated papules that progress to painful, ulcerated, necrotic lesions. Treatment depends on the combination of surgical debridement and antifungal therapy, with systemic voriconazole recommended as primary therapy.

INVASIVE SINONASAL DISEASE

Invasive *Aspergillus* sinusitis represents a difficult diagnosis because the clinical presentation tends to be highly variable. Patients can present with congestion, rhinorrhea, epistaxis, headache, facial pain or swelling, orbital swelling, fever, or abnormal appearance of the nasal turbinates. Because noninvasive imaging can be normal, diagnosis rests on direct visualization via endoscopy and biopsy. Sinus mucosa may be pale, discolored, granulating, or necrotic, depending on the stage and extent of disease. The infection can invade adjacent structures, including the eye and brain. This syndrome is difficult to distinguish clinically from other types of invasive fungal disease of the sinuses such as mucormycosis, rendering obtaining specimens for culture and histology extremely important. If the diagnosis is confirmed, treatment should be with voriconazole similar to invasive pulmonary disease. Because voriconazole is not active against mucormycosis, amphotericin B formulations should be considered in invasive fungal sinusitis pending definitive identification.

CENTRAL NERVOUS SYSTEM

The primary site of *Aspergillus* infection tends to be the lungs, but as the hyphae invade into the vasculature, fungal elements can dislodge and travel through the bloodstream, permitting establishment of secondary infection sites. One of the sites commonly involved in disseminated disease is the CNS. Cerebral aspergillosis can also arise secondary to local extension of sinus disease. The presentation of cerebral aspergillosis is highly variable but can include changes in mental status, seizures, paralysis, coma, and ophthalmoplegia. As the hyphae invade the CNS vasculature, hemorrhagic infarcts develop that convert to abscesses. Biopsy is required for definitive diagnosis, but patients are often too ill to tolerate surgery. Imaging can be helpful for diagnosis, and MRI is preferred. In general, the prognosis for CNS aspergillosis is extremely poor, likely owing to the late onset at presentation. Reversal of immunosuppression is extremely important, when possible. Surgical resection of lesions may be useful. Voriconazole is the best therapy, usually at high doses.

EYE

Fungal endophthalmitis and keratitis may be seen in patients with disseminated *Aspergillus* infection. Pain, photophobia, and decreased visual acuity may be present, though many patients are asymptomatic. Emergent ophthalmologic evaluation is important when these entities are suspected. Endophthalmitis is treated with intravitreal injection of either amphotericin B or voriconazole along with surgical intervention and systemic antifungal therapy with voriconazole. Keratitis requires topical and systemic antifungal therapy.

BONE

Aspergillus osteomyelitis can occur, most commonly in the vertebrae. Rib involvement occurs as a result of extension of disease in patients with CGD and is most often caused by *A. nidulans*. Treatment depends on the combination of surgical debridement and systemic antifungals. Arthritis can develop after hematogenous dissemination or local extension, and treatment depends on joint drainage combined with antifungal therapy. Voriconazole is the preferred first-line therapy.

HEART

Cardiac infection can occur as a result of surgical contamination, secondary to disseminated infection, or after direct extension from a contiguous focus of infection and includes endocarditis, myocarditis, and pericarditis. Treatment requires surgical intervention in the case of endocarditis and pericarditis, along with systemic antifungals, sometimes lifelong because of the possibility of recurrent infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 284

Histoplasmosis (*Histoplasma capsulatum*)

Matthew C. Washam and Lara A. Danziger-Isakov

ETIOLOGY

Histoplasmosis is caused by *Histoplasma capsulatum,* a dimorphic fungus found in the environment as a saprobe in the mycelial (mold) form and in tissues in the parasitic form as yeast.

EPIDEMIOLOGY

Two varieties of *Histoplasma* cause human histoplasmosis. The most common variety, *H. capsulatum* var. *capsulatum,* is found in soil as the saprotrophic form throughout the midwestern United States, primarily along the Ohio and Mississippi rivers. In parts of Kentucky and Tennessee, almost 90% of the population older than 20 years of age have positive skin test results for histoplasmin. Sporadic cases have also been reported in nonendemic states in patients without a travel history. Worldwide, *H. capsulatum* var. *capsulatum* is endemic to parts of Central and South America, the Caribbean, China, India, Southeast Asia, and the Mediterranean. The less common variety, *H. capsulatum* var. *duboisii,* is endemic to certain areas of western and central sub-Saharan Africa.

H. capsulatum thrives in soil rich in nitrates such as areas that are heavily contaminated with bird or bat droppings or decayed wood. Fungal spores are often carried on the wings of birds. Focal outbreaks of histoplasmosis have been reported after aerosolization of microconidia

resulting from construction in areas previously occupied by starling roosts or chicken coops or by chopping decayed wood or burning bamboo exposed to a blackbird roost. Unlike birds, bats are actively infected with *Histoplasma.* Focal outbreaks of histoplasmosis have also been reported after intense exposure to bat guano in caves and along bridges frequented by bats. Horizontal person-to-person transmission does not occur, although transplacental transmission of *H. capsulatum* has been reported in immunocompromised mothers.

PATHOGENESIS

Inhalation of microconidia (fungal spores) is the initial stage of human infection. The conidia reach the alveoli, germinate, and proliferate as yeast. Alternatively, spores can remain as mold with the potential for activation. Most infections are asymptomatic or self-limited. When disseminated disease occurs, any organ system can be involved. The initial infection is a bronchopneumonia. As the initial pulmonary lesion ages, giant cells form, followed by formation of caseating or noncaseating granulomas and central necrosis. Granulomas contain viable yeast, and disease can relapse. At the time of spore germination, yeast cells are phagocytosed by alveolar macrophages, where they replicate and gain access to the reticuloendothelial system via the pulmonary lymphatic system and hilar lymph nodes. Dissemination with splenic involvement typically follows the primary pulmonary infection. In normal hosts, specific cell-mediated immunity follows in approximately 2 weeks, enabling sensitized T cells to activate macrophages and kill the organism. The initial pulmonary lesion resolves within 2-4 months but may undergo calcification resembling the Ghon complex of tuberculosis. Alternatively, buckshot calcifications involving the lung and spleen may be seen. Unlike tuberculosis, reinfection with *H. capsulatum* may occur and can lead to exaggerated host responses in some cases.

Children with immune deficiencies, specifically deficiencies involving cell-mediated immunity, are at increased risk for disseminated histoplasmosis. Primary immunodeficiencies involving pathogenic genetic variants in the interleukin (IL)-12/interferon (IFN)-γ pathway have been reported in children with disseminated histoplasmosis, including IL-12Rβ1 deficiency and IFN-γ R1 deficiency. Other primary immunodeficiencies identified in children with disseminated disease include *STAT1* gain-of-function pathogenic genetic variants, idiopathic CD4 lymphopenia, AR-DOCK8 deficiency, AD-GATA2 deficiency, and X-linked CD40L deficiency. Children with certain secondary immunodeficiencies (cancer patients, solid organ transplant recipients, children with HIV infection, and children receiving immunomodulatory therapy with tumor necrosis factor [TNF]-α inhibitors) are also at increased risk for disseminated disease.

CLINICAL MANIFESTATIONS

Exposure to *Histoplasma* is common in endemic areas, although most infections are subclinical. Less than 1% of those infected display the following clinical manifestations:

Acute pulmonary histoplasmosis follows initial or recurrent respiratory exposure to microconidia. Symptomatic disease occurs more often in young children; in older patients, symptoms follow exposure to large inocula in closed spaces (e.g., chicken coops or caves) or prolonged exposure (e.g., camping on contaminated soil, chopping decayed wood). The median incubation time is 14 days. The prodrome is not specific and usually consists of flulike symptoms, including headache, fever, chest pain, cough, and myalgias. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress and hypoxia and can require intubation, mechanical ventilation, and steroid therapy. Acute pulmonary disease can also manifest with a prolonged illness (10 days to 3 weeks) consisting of weight loss, dyspnea, high fever, asthenia, and fatigue. Children with symptomatic disease typically have a patchy bronchopneumonia; hilar lymphadenopathy is variably present (Fig. 284.1). In young children, the pneumonia can coalesce. Focal or buckshot calcifications are convalescent findings in patients after acute pulmonary infection.



Fig. 284.1 Radiograph of a 5-yr-old child with acute pulmonary histoplasmosis showing right perihilar lymphadenopathy.

Complications of pulmonary histoplasmosis occur secondary to exaggerated host responses to fungal antigens within the lung parenchyma or hilar lymph nodes. **Histoplasmomas** are of parenchymal origin and are usually asymptomatic. These fibroma-like lesions are often concentrically calcified and single. Rarely, these lesions produce broncholithiasis associated with "stone spitting," wheezing, and hemoptysis. In endemic regions, these lesions can mimic parenchymal tumors and are occasionally diagnosed at lung biopsy. **Mediastinal granulomas** form when reactive hilar lymph nodes coalesce and mat together. Although these lesions are usually asymptomatic, huge granulomas can compress the mediastinal structures, producing symptoms of esophageal, bronchial, or vena caval obstruction. Local extension and necrosis can produce pericarditis or pleural effusions. **Mediastinal fibrosis** is a rare complication of mediastinal granulomas and represents an uncontrolled fibrotic reaction arising from the hilar nodes. Structures within the mediastinum become encased within a fibrotic mass, producing obstructive symptomatology. Superior vena cava syndrome, pulmonary venous obstruction with a mitral stenosis–like syndrome, and pulmonary artery obstruction with congestive heart failure have been described. Dysphagia accompanies esophageal entrapment, and a syndrome of cough, wheeze, hemoptysis, and dyspnea accompanies bronchial obstruction. Rarely, children develop a sarcoid-like disease with arthritis or arthralgia, erythema nodosum, keratoconjunctivitis, iridocyclitis, and pericarditis. **Pericarditis**, with effusions both pericardial and pleural, is a self-limited benign condition that develops as a result of an inflammatory reaction to adjacent mediastinal disease. The effusions are exudative, and the organism is rarely culturable from fluid. **Progressive disseminated histoplasmosis** can occur in infants and in children with deficient cell-mediated immunity. Disseminated disease may occur either during the initial acute infection in children with primary or secondary immunodeficiencies affecting T-cell function (see "Pathogenesis"), in infants, or as a reactivation of a latent focus of infection within the reticuloendothelial system in children who acquire an immunosuppressive condition years after primary infection. Disseminated histoplasmosis in an HIV-infected patient is an AIDS-defining illness. Fever is the most common finding and can persist for weeks to months before the condition is diagnosed. The majority of patients have hepatosplenomegaly, lymphadenopathy, and interstitial pulmonary disease. Extrapulmonary infection is a characteristic of disseminated disease and can include destructive bony lesions, Addison

disease, meningitis, multifocal chorioretinitis, and endocarditis. Some patients develop mucous membrane ulcerations and skin findings such as nodules, ulcers, or molluscum-like papules. A sepsis-like syndrome has been identified in a small number of HIV-infected patients with disseminated histoplasmosis and is characterized by the rapid onset of shock, multiorgan failure, and coagulopathy. Reactive hemophagocytic syndrome has been described in immunocompromised patients with severe disseminated histoplasmosis. Many children with disseminated disease experience transient hyperglobulinemia. Elevated acute-phase reactants and hypercalcemia are typically seen but are nonspecific. Anemia, thrombocytopenia, and pancytopenia are variably present; elevated liver function tests and high serum concentrations of angiotensin-converting enzyme may be observed. Chest radiographs are normal in more than half of children with disseminated disease.

Chronic pulmonary histoplasmosis is an opportunistic infection in adult patients with centrilobular emphysema. **Chronic progressive disseminated histoplasmosis** is a slowly progressive infection caused by *Histoplasma* that occurs in older adults without obvious immunosuppression that is uniformly fatal if untreated. These entities are rare in children.

DIAGNOSIS

Optimal diagnosis of suspected histoplasmosis depends on the clinical presentation and underlying immune status of the patient. Using serum and urine antigen tests along with serum antibody tests via complement fixation and immunodiffusion yields a diagnostic sensitivity >90% for acute pulmonary and disseminated forms of histoplasmosis. Diagnostic testing options include the following:

Antigen detection is the most widely available diagnostic study for patients with suspected pulmonary histoplasmosis or progressive disseminated histoplasmosis. Current laboratory methodology uses enzyme immunoassay (EIA) to detect *H. capsulatum* polysaccharide antigen in urine, blood, bronchoalveolar lavage fluid, and cerebrospinal fluid. In patients at risk for disseminated disease, antigen can be demonstrated in the urine, blood, or bronchoalveolar lavage fluid in more than 90% of cases. Antigenuria has been shown to correlate with severity of disseminated histoplasmosis. Serum, urine, and bronchoalveolar lavage fluid from patients with acute or chronic pulmonary infections are variably antigen positive. In one study, antigenuria was present in 83% of patients with acute pulmonary disease and 30% of patients with subacute pulmonary disease. False-positive results on urinary antigen testing can occur in patients with *Blastomyces dermatitidis, Coccidioides immitis, Coccidioides posadasii, Paracoccidioides brasiliensis,* and *Penicillium marneffei*. Testing both urine and serum samples for histoplasma antigen increases the sensitivity compared with testing only the urine or serum alone. Sequential measurement of serum antigen levels in patients with disseminated disease is useful for monitoring response to therapy; persistent low-level antigenuria may occur in some patients who have completed therapy and have no evidence of active infection.

Antibody tests continue to be useful for the diagnosis of acute pulmonary histoplasmosis, its complications, and chronic pulmonary disease. Serum antibody to yeast and mycelium-associated antigens is classically measured by complement fixation. Although titers of >1:8 are found in more than 80% of patients with histoplasmosis, titers of ≥1:32 are most significant for the diagnosis of recent infection. Complement-fixation antibody titers are often not significant early in the infection and do not become positive until 4-6 weeks after exposure. A fourfold increase in either yeast or mycelial-phase titers or a single titer of ≥1:32 is presumptive evidence of active infection. Complement-fixation titers may be falsely positive in patients with other systemic mycoses such as *B. dermatitidis* and *C. immitis* and may be falsely negative in immunocompromised patients. Antibody detection by immunodiffusion is less sensitive but more specific than complement fixation and is used to confirm questionably positive complement-fixation titers. An EIA-based method that has improved sensitivity and specificity compared with other serologic methods has been developed. The highest sensitivity for antibody testing can be achieved by combining methodologies.

Culture sensitivity of tissue or body fluid samples is generally highest for children with progressive disseminated histoplasmosis or acute pulmonary histoplasmosis caused by a large inoculum of organisms. *Histoplasma* typically grows within 6 weeks on Sabouraud agar at 25°C (77°F). Identification of tuberculate macroconidia allows for only a presumptive diagnosis, because *Sepedonium* species form similar structures. A confirmatory test using a chemiluminescent DNA probe for *H. capsulatum* is necessary to establish a definitive identification. The yeast can be recovered from blood or bone marrow in >90% of patients with progressive disseminated histoplasmosis. Sputum cultures are rarely obtained and are variably positive in normal hosts with acute pulmonary histoplasmosis; cultures of bronchoalveolar lavage fluid appear to have a slightly higher yield than sputum cultures. Blood cultures are sterile in patients with acute pulmonary histoplasmosis, and cultures from any source are typically sterile in patients with the sarcoid form of the disease.

Histologic examination can identify yeast forms in tissue from patients with complicated forms of acute pulmonary disease (histoplasmoma and mediastinal granuloma). Tissue should be stained with methenamine silver or periodic acid–Schiff stains, and yeast can be found within or outside of macrophages. In children with disseminated disease, organisms can be identified from bone marrow, liver, and mucocutaneous lesions. In those who are severely ill, Wright stain of peripheral blood can demonstrate fungal elements within leukocytes. Examination of fibrotic tissue from children with mediastinal fibrosis usually demonstrates no organisms.

Real-time polymerase chain reaction has been used on formalin-fixed, paraffin-embedded biopsy tissue and has an analytical sensitivity of at least 6 pg/μL from tissue-extracted DNA and a clinical sensitivity and specificity of 88.9% and 100%, respectively. Although not widely available, molecular methods may ultimately provide a more timely and accurate diagnosis.

Skin testing is useful only for epidemiologic studies, as cutaneous reactivity is lifelong and intradermal injection can elicit an immune response in otherwise seronegative persons. Reagents are no longer commercially available.

TREATMENT

Acute pulmonary histoplasmosis does not require antifungal therapy for asymptomatic or mildly symptomatic children. Oral itraconazole (4-10 mg/kg/day in two divided doses, not to exceed 400 mg daily) for 6-12 weeks should be considered in patients with acute pulmonary infections who fail to improve clinically within 1 month. Although it appears to be less effective, fluconazole may be considered as an alternative therapy in children intolerant to itraconazole. Clinical experience in treating histoplasmosis with the newer azoles (voriconazole and posaconazole) is increasing, with posaconazole having increased in vitro activity. *Patients with pulmonary histoplasmosis who become hypoxemic or require ventilatory support* should receive amphotericin B deoxycholate (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (3-5 mg/kg/day) until improved, and adjunctive corticosteroids (intravenous methylprednisolone at a dose of 0.5-1 mg/kg/day) can be considered for 1-2 weeks; continued therapy with oral itraconazole for a minimum of 12 wk is also recommended. The lipid preparations of amphotericin are not preferentially recommended in children with pulmonary histoplasmosis, as the classic preparation is generally well tolerated in this patient population. Patients with severe obstructive symptoms caused by granulomatous mediastinal disease may be treated sequentially with amphotericin B followed by itraconazole for 6-12 months, and inclusion of adjunctive corticosteroids should be considered for the first 1-2 weeks. Patients with milder mediastinal disease may be treated with oral itraconazole alone. Some experts recommend that surgery be reserved for patients who fail to improve after 1 month of intensive amphotericin B therapy. Sarcoid-like disease with or without pericarditis may be treated with nonsteroidal antiinflammatory agents for 2-12 weeks.

Progressive disseminated histoplasmosis usually requires amphotericin B deoxycholate (1.0 mg/kg/day for 4-6 weeks) or amphotericin B lipid complex (3-5 mg/kg/day). Alternatively, amphotericin B may be given for 2-4 weeks followed by oral itraconazole (4-10 mg/kg/day in two divided doses) as maintenance therapy for 12 months,

depending on *Histoplasma* antigen status. Longer therapy may be needed in patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. It is recommended to monitor blood levels of itraconazole during treatment, aiming for a concentration of ≥1 μg/mL but <10 μg/mL to avoid potential drug toxicity. It is also recommended to monitor urine antigen levels during therapy and for 12 months after therapy has ended to ensure cure. Relapses in immunocompromised patients with progressive disseminated histoplasmosis are relatively common. Lifelong suppressive therapy with daily itraconazole (5 mg/kg/day up to adult dose of 200 mg/day) may be required if immunosuppression cannot be reversed. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (2-5 mg/kg every 12-24 hours) may be used prophylactically. Care must be taken to avoid interactions between antifungal azoles and protease inhibitors.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 285

Blastomycosis

Gregory M. Gauthier and Bruce S. Klein

ETIOLOGY

The etiologic agents of blastomycosis belong to a species complex and include *Blastomyces dermatitidis, B. gilchristii, B. helicus, B. emzantsi, B. percursus, B. parvus,* and *B. silverae*. The latter two species *(B. parvus, B. silverae)* rarely cause human infection. All *Blastomyces* species exhibit thermal dimorphism in which they grow as mold and produce spores in the soil at environmental temperature (22–25°C [71.6–77°F]) and as pathogenic yeast at core human body temperature (37°C [98.6°F]). Once in tissue, *Blastomyces* infection results in pyogranulomatous inflammation, which is characterized by neutrophil infiltration and granuloma formation. *Blastomyces* yeast can be differentiated from other fungi by the presence of a broad-based budding pattern between dividing yeast cells, which occurs in all *Blastomyces* species.

EPIDEMIOLOGY

Blastomyces species cause disease in immunocompetent and immunocompromised children. Approximately 2–13% of blastomycosis cases occur in the pediatric population (average age: 9.1-12.9 years; range: 19 days to 18 years). Blastomycosis of newborns and infants is rare. In North America, the traditional geographic range of blastomycosis cases is restricted to the Midwest, southcentral, and southeastern United States and parts of Canada bordering the Great Lakes and Saint Lawrence River Valley. In these geographic regions, several areas are hyperendemic for blastomycosis (e.g., Marathon and Vilas counties, Wisconsin; central and southcentral Mississippi; Kenora, Ontario). Outside of North America, autochthonous infections have been reported from Africa (~100 cases), India (<12 cases), and Israel. *B. dermatitidis* is not endemic to Central America, South America, Europe, Asia, or Australia.

In North America, *B. dermatitidis* and *B. gilchristii* grow in an ecologic niche characterized by forested, sandy soils with an acidic pH that have decaying vegetation and are near water. *B. dermatitidis* is located throughout the traditional geographic range, whereas *B. gilchristii* is restricted to Minnesota, Wisconsin, Canada, and areas along the St. Lawrence River. *B. helicus* is located in the western United States (California, Montana, Idaho, Colorado, Nebraska, Texas) and Canada (Saskatchewan, Alberta); however, its environmental niche remains to be determined. In Africa, there are multiple species of *Blastomyces,* including *B. dermatitidis, B. gilchristii, B. percursus,* and *B. emzantsi.* Knowledge about the ecological niche and geographic distribution of *Blastomyces* species in Africa is limited. *B. percursus* has been reported from Israel.

Most *Blastomyces* infections are sporadic, but at least 20 outbreaks have been reported, and most of these outbreaks have included pediatric patients. Outbreaks have been associated with construction or outdoor activities (camping, hiking, fishing, rafting on a river, using a community compost pile); however, some outbreaks have no identifiable risk factors other than geography. Although blastomycosis is often thought to be an infection that primarily affects persons residing in or visiting rural areas, outbreaks and sporadic cases of blastomycosis are well reported in urban areas. Blastomycosis outbreak investigations in Wisconsin suggested that persons of Hmong ethnicity are at increased risk for the disease, which may be the result of polymorphisms in the interleukin-6 (IL-6) gene. These polymorphisms result in reduced IL-6 cytokine production and $CD4^+$ T lymphocytes that produce IL-17, which in turn, impairs activation of neutrophils and macrophages against *Blastomyces*. Although persons of Hmong ethnicity are at increased risk for blastomycosis, they do not appear to be at risk for disseminated infection. Increased incidence of blastomycosis has also been reported in indigenous persons living in the United States and Canada.

The severity of infection is influenced by the size of the inhaled inoculum and the integrity of the patient's immune system. Solid organ transplant recipients are at risk for severe pulmonary blastomycosis, including acute respiratory distress syndrome (ARDS); however, they are not at higher risk for disseminated infection. Although blastomycosis is uncommon in persons immunosuppressed with AIDS, there is an increased risk for dissemination to the central nervous system (CNS). Persons receiving tumor necrosis factor-α inhibitors are at risk for blastomycosis, but rates of dissemination or severe disease are not well defined.

PATHOGENESIS

The ability of mycelial fragments and spores to convert to yeast in the lung is a crucial event in the pathogenesis of infection with *Blastomyces* and other dimorphic fungi. This temperature-dependent morphologic shift, which is known as the *phase transition,* enables *Blastomyces* to evade the host immune system and establish infection. In the yeast form, the essential virulence factor BAD1 (B*lastomyces* ad*hesin*-1; formerly WI-1) is secreted into the extracellular milieu and binds back to chitin on the fungal cell wall. BAD1 is a multifunctional protein that promotes binding of yeast to alveolar macrophages (via CR3 and CD14 receptors) and lung tissue (via heparan sulfate), blocks the deposition of complement on the yeast surface, binds calcium, suppresses the host's ability to produce cytokines (tumor necrosis factor-α, IL-17, interferon-gamma), and inhibits activation of $CD4^+$ T lymphocytes. Deletion of *BAD1* abolishes virulence of *Blastomyces* yeast in a murine model of pulmonary infection.

The phase transition between mold and yeast forms is a complex event that involves alteration in cell wall composition, metabolism, intracellular signaling, and gene expression. The morphologic shift to yeast is regulated in part by a histidine kinase known as DRK1 (*d*imorphism *r*egulating *k*inase-1). This sensor kinase controls not only the conversion of mold to yeast but also spore production, cell wall composition, and *BAD1* expression; the loss of *DRK1* gene expression through gene disruption renders *B. dermatitidis* avirulent in a murine model of pulmonary blastomycosis. The function of DRK1 is conserved in other thermally dimorphic fungi, including *Histoplasma capsulatum* and *Talaromyces marneffei* (formerly *Penicillium marneffei*).

The phase transition is reversible, and after a drop in temperature from 37°C (98.6°F) to 22°C (71.6°F), yeast convert to sporulating mold. Growth as mold promotes survival in the soil, allows for sexual reproduction to enhance genetic diversity, and facilitates transmission to new hosts (via spores and mycelial fragments). The transition from

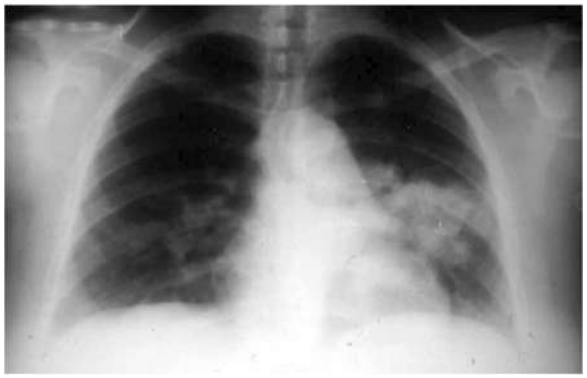

Fig. 285.1 Left lung infection in a patient with symptoms resembling acute bacterial pneumonia. Organisms of *Blastomyces* in the sputum seen with potassium hydroxide preparation, and subsequent culture confirmed the diagnosis. *(From Bradsher RW Jr. Blastomycoses. In: Bennett JE, Blaser MJ, Dolin R, et al, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed, Philadelphia: Saunders; 2015: Fig. 266-5.)*

yeast to mold is influenced by SREB (siderophore biosynthesis repressor in *Blastomyces*) and *N*-acetylglucosamine transporters (NGT1, NGT2). Deletion of *SREB,* which encodes a GATA transcription factor, results in the failure of *B. dermatitidis* yeast to complete the conversion to mold at 22°C. *N*-Acetylglucosamine, which polymerizes to form chitin, accelerates the transition to hyphae via NGT1 and NGT2 transporters.

Innate and adaptive immune systems are required to effectively control infection; humoral immunity is dispensable. Macrophages and neutrophils are capable of ingesting and killing *Blastomyces* conidia. In contrast, yeast are poorly killed by nonactivated macrophages, are resistant to reactive oxygen species, and suppress nitric oxide production. Adaptive immunity is mediated by T lymphocytes (Th1 and Th17), which activate macrophages and neutrophils to facilitate clearance of infection. After infection, cell-mediated immunity against *Blastomyces* can last for at least 2 years.

CLINICAL MANIFESTATIONS

The clinical manifestations of blastomycosis are diverse and include subclinical infection, symptomatic pneumonia, and disseminated disease. Clinical disease develops 3 weeks to 3 months after inhalation of spores or mycelial fragments. Asymptomatic or subclinical infections are estimated to occur in 50% of patients.

The most common clinical manifestation of blastomycosis is **pneumonia**, which can range from acute to chronic. Acute symptoms resemble community-acquired pneumonia and include fever, dyspnea, cough, chest pain, and malaise (Fig. 285.1). Respiratory failure, including ARDS, can occur in patients with an overwhelming burden of infection. The most common chest imaging pattern is air space consolidation with or without air bronchograms. Any lobe of the lung can be involved, and multiple lobe involvement is not uncommon. Other radiographic features include masslike consolidation, nodules with cavity formation, reticulonodular pattern, and miliary disease. Hilar adenopathy and pleural effusions occur in approximately 20% of cases. Because the clinical and radiographic features often mimic bacterial pneumonia, patients can be mistakenly treated with antibiotics, resulting in disease progression, which can result in disseminated disease or respiratory failure, including ARDS. Patients with subacute or chronic pneumonia experience fevers, chills, night sweats, cough, weight loss, hemoptysis, dyspnea, and chest pain. Mass lesions and cavitary disease on chest roentgenography can mimic malignancy and tuberculosis, respectively.

Extrapulmonary blastomycosis most often affects the skin or bone but can involve almost any organ. The incidence of **extrapulmonary blastomycosis** in children ranges from 38% to 50%, similar to rates in adult patients (15–48%). *B. dermatitidis* is more likely to cause disseminated infection, whereas *B. gilchristii* is more likely to remain localized to the lungs. The skin is the most common site for extrapulmonary blastomycosis, which is usually the result of hematogenous dissemination. Direct inoculation of *B. dermatitidis* into the skin from trauma or a laboratory accident can result in primary cutaneous blastomycosis. Skin manifestations include plaques, papules, ulcers, nodules, and verrucous lesions. Erythema nodosum is rare in blastomycosis. Dissemination of *B. dermatitidis* to the bone results in lytic destruction, pain, soft tissue swelling, sinus tract formation, and ulceration. The ribs, skull, spine, and long bones are most commonly affected. Patients with osteomyelitis often have pulmonary or cutaneous involvement. Vertebral osteomyelitis can be complicated by paraspinal abscess, psoas abscess, and vertebral body collapse. Extension of long bone osteomyelitis can result in pathologic fracture or septic arthritis. Genitourinary blastomycosis occurs in just under 10% of adults but is rare in children.

CNS blastomycosis (brain abscess, meningitis) occurs in <10% of immunocompetent patients but in up to 40% of persons with AIDS. The majority of patients with CNS blastomycosis have clinically apparent infection at non-CNS sites (e.g., lung, skin, mass lesion). Symptoms of CNS infection include headache, altered mental status, memory loss, seizure, cranial nerve deficits, and focal neurologic deficits. Complications include hydrocephalus, cerebral herniation, infarction, panhypopituitarism, residual weakness, and poor functioning in school. Lumbar puncture demonstrates leukocytosis with a neutrophil or lymphocyte predominance, elevated protein, and low glucose. Growth of *Blastomyces* in culture from cerebrospinal fluid occurs in less than 50% of affected patients.

Blastomycosis can complicate pregnancy, and clinical information is limited to case reports. Disseminated infection involving the lungs, skin, and bone is common. Spread of infection to the placenta has been documented by histopathology; however, the frequency of placental blastomycosis remains unknown. Transmission of *Blastomyces* to the fetus is uncommon and is postulated to occur through transplacental transmission or aspiration of infected vaginal secretions. Although clinical data are limited, blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

DIAGNOSIS

The diagnosis of blastomycosis requires a high index of suspicion because the clinical and radiographic manifestations can mimic other diseases, including community-acquired pneumonia, tuberculosis, and malignancy. The misdiagnosis of blastomycosis, most often as community-acquired pneumonia, results in a delay of therapy and progression of disease, including dissemination and respiratory failure. In addition, absence of exposure to traditional environmental risk factors for blastomycosis can lead to a delay in diagnosis. Blastomycosis should be included in the differential diagnosis for patients with pneumonia who (1) live in or visit areas in which this pathogen is endemic, (2) fail to respond to a treatment course of antibiotics, or (3) have concomitant skin lesions or osteomyelitis. A detailed medical history regarding exposure risks (e.g., canoeing, rafting, hiking, fishing, playing in outdoor forts, beaver dam exploration, home remodeling, nearby road or building construction, woodpile for a wood burning stove, and use of a community compost pile) should be obtained. In addition, the health of family pets such as dogs should be ascertained, as canine disease may be a harbinger of human infection. Studies from Wisconsin and Minnesota have demonstrated that 7.7–10% of persons with blastomycosis have a dog with concomitant or prior blastomycosis. The incidence of canine blastomycosis is 10-fold higher than human blastomycosis, and canine infection suggests a common source of environmental *Blastomyces* exposure.

Growth of *Blastomyces* in culture from sputum, skin, bone, or other clinical specimens provides a definitive diagnosis. Sputum specimens should be stained with 10% potassium hydroxide or calcofluor white. Histopathology shows neutrophilic infiltration with noncaseating

granulomas (pyogranulomas). *Blastomyces* yeast in tissue samples can be visualized using Gomori methenamine silver or periodic acid–Schiff stains. Yeasts are 4-29 μm in size, have a double refractile cell wall, and are characterized by broad-based budding between mother and daughter cells.

Nonculture diagnostic techniques should be used in conjunction with fungal smears and cultures to facilitate the diagnosis of blastomycosis. The development of a *Blastomyces* antigen test has supplanted insensitive serologic methods such as complement fixation and immunodiffusion. Urine, serum, cerebrospinal fluid, and bronchoalveolar fluid specimens can be collected for the *Blastomyces* antigen test. Sensitivity of the urine antigen test ranges from 85% to 93% and is influenced by the burden of infection. The antigen test has similar sensitivity for *B. dermatitidis* and *B. gilchristii,* but ability to detect other species is poorly characterized. The antigen test can cross react with other dimorphic fungi, including *Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Penicillium marneffei,* decreasing the specificity to 76.9–79%. An antibody test against the BAD1 protein has been developed and has a sensitivity of 87.8% and a specificity of 94–99%; however, this test is not yet commercially available. Combination antigen and BAD1 antibody testing can increase diagnostic sensitivity to 97.6%.

TREATMENT

Antifungal therapy is influenced by the severity of the infection, involvement of the CNS, the integrity of the host's immune system, and pregnancy. All persons diagnosed with blastomycosis should receive antifungal therapy. **Newborns** with blastomycosis should be treated with amphotericin B deoxycholate 1 mg/kg/day. **Children with mild to moderately severe infection** can be treated with itraconazole 10 mg/kg/day (maximum: 400 mg/day) for 6-12 months. **Children with severe disease, immunodeficiency, or immunosuppression** should be treated with amphotericin B deoxycholate 0.7-1.0 mg/kg/day or lipid amphotericin B 3-5 mg/kg/day until there is clinical improvement, generally 7-14 days, and then itraconazole 10 mg/kg/day (maximum: 400 mg/day) for a total of 12 months. **Central nervous system blastomycosis** requires therapy with lipid amphotericin B 5 mg/kg/day for 4-6 weeks, followed by itraconazole, fluconazole, or voriconazole for ≥12 months.

All pediatric patients of childbearing age should undergo pregnancy testing before initiation of azole antifungals. Itraconazole can increase the risk for spontaneous abortion, and fluconazole can cause craniofacial defects resembling Antley-Bixler syndrome. Voriconazole and posaconazole cause skeletal abnormalities in animal models. Treatment of blastomycosis in **pregnant patients** consists of lipid amphotericin B 3-5 mg/kg/day for 6-8 weeks.

For patients receiving itraconazole, the oral antifungal of choice, therapeutic drug monitoring should be performed 14 days into therapy (goal total itraconazole level 1-5 μg/mL), and liver function tests should be monitored periodically. Because of the long half-life of itraconazole, serum drug levels can be obtained at any time of the day, irrespective of when the drug was administered. Total itraconazole level is determined by adding itraconazole and hydroxyitraconazole concentrations; hydroxyitraconazole is a metabolite that possesses antifungal activity. Voriconazole, posaconazole, and isavuconazonium sulfate have activity against *B. dermatitidis*. Clinical experience with these drugs is growing, and treatment outcomes are promising. Therapeutic drug monitoring is recommended for voriconazole and posaconazole (goal trough levels 1-5 μg/mL) and can be considered with isavuconazonium sulfate. The echinocandins (caspofungin, micafungin, and anidulafungin) should not be used to treat blastomycosis. Serial measurement of urine antigen levels to assess response to therapy can be a helpful adjunct in monitoring response to antifungal therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 286

Coccidioidomycosis (*Coccidioides* Species)

Felicia A. Scaggs Huang and Rebecca C. Brady

ETIOLOGY

Coccidioidomycosis (valley fever, San Joaquin fever, desert rheumatism, coccidioidal granuloma) is caused by *Coccidioides* spp., a soil-dwelling dimorphic fungus. *Coccidioides* spp. grow in the environment as spore-bearing (arthroconidia-bearing) mycelial forms. In their parasitic form, they appear as unique, endosporulating spherules in infected tissue. The two recognized species, *C. immitis* and *C. posadasii,* cause clinically indistinguishable illnesses.

EPIDEMIOLOGY

Coccidioides spp. inhabit soil in arid regions. *C. immitis* is primarily found in California's San Joaquin Valley. *C. posadasii* is endemic to southern regions of Arizona, Utah, Nevada, New Mexico, western Texas, and regions of Mexico and Central and South America. The risk of infection among long-term residents in endemic regions is 3% per year.

Population migrations into endemic areas and increasing numbers of immunosuppressed persons have caused coccidioidomycosis to become an important health problem. From 2000 to 2012 in California, 4,582 cases, 1,301 hospitalizations, and 11 deaths associated with coccidioidomycosis were reported in children, who accounted for 9.2% of total cases. From 2015 to 2016, the rate of coccidioidomycosis cases among California children increased from 2.1 per 100,000 to 5.2 per 100,000. Case and hospitalization rates were highest in males and those 12-17 years. Another recent California study showed that 55% of children were hospitalized, with a median length of stay of 44 days.

Infection results from inhalation of aerosolized spores. Incidence increases during windy, dry periods that follow rainy seasons. Seismic events, archaeologic excavations, and other activities that disturb contaminated sites have caused outbreaks. Person-to-person transmission does not occur. Rarely, infections result from spores that contaminate fomites or grow beneath casts or wound dressings of infected patients. Infection has also resulted from transplantation of organs from infected donors and from mother to fetus. Visitors to endemic areas can acquire infections, and diagnosis may be delayed when they are evaluated in nonendemic areas. Spores are highly virulent, and *Coccidioides* spp. are potential agents of bioterrorism (see Chapter 763).

PATHOGENESIS

Inhaled spores reach terminal bronchioles, where they transform into septated spherules that resist phagocytosis and within which many endospores develop. Released endospores transform into new spherules, and the process results in an acute focus of infection. Endospores can also disseminate lymphohematogenously. Eventually, a granulomatous reaction predominates. Both recovery and protection upon reexposure depend on effective cellular immunity.

Children with congenital primary immunodeficiency disorders may be at increased risk for infection; these disorders include interleukin-12Rβ1 deficiency, interferon-γR1 deficiency, and *STAT1* gain-of-function mutations.

CLINICAL MANIFESTATIONS

The clinical spectrum (Fig. 286.1) encompasses pulmonary and extrapulmonary disease. Pulmonary infection occurs in 95% of cases and can be divided into primary, complicated, and residual

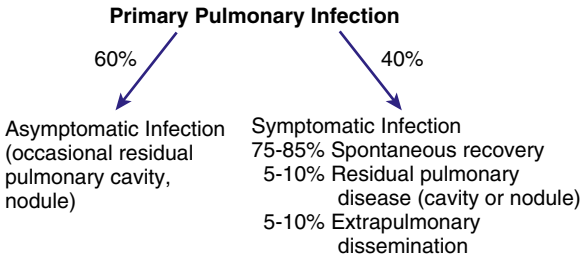

Fig. 286.1 Natural history of coccidioidomycosis.

infections. Approximately 60% of infections are asymptomatic. Symptoms in children are often milder than those in adults. The incidence of extrapulmonary dissemination in children approaches that of adults.

Primary Coccidioidomycosis

The incubation period is 1-4 weeks, with an average of 10-16 days. Early symptoms include malaise, chills, fever, and night sweats. Chest discomfort occurs in 50–70% of patients and varies from mild tightness to severe pain. Headache and/or backache are sometimes reported. Evanescent, generalized, fine macular, erythematous or urticarial eruptions may be seen within the first few days of infection. Erythema nodosum can occur (more often in females) and is sometimes accompanied by erythema multiforme, usually 3-21 days after the onset of symptoms. The clinical constellation of erythema nodosum, fever, chest pain, and arthralgias (especially knees and ankles) is called *desert rheumatism* and *valley fever.* Profound fatigue can occur and lasts weeks to months. Of note, extrapulmonary manifestations of a primary pulmonary infection do not necessarily represent disseminated disease. In hospitalized children, pulmonary symptoms are most common. The chest examination is often normal even if radiographic findings are present. Dullness to percussion, friction rub, or fine rales may be present. Pleural effusions can occur and can become large enough to compromise respiratory status. Hilar and mediastinal lymphadenopathy are common (Fig. 286.2).

Complicated Pulmonary Infection

Complicated infections include severe and persistent pneumonia, progressive primary coccidioidomycosis, progressive fibrocavitary disease, transient cavities that develop in areas of pulmonary consolidation, and empyema that follows rupture of a cavity into the pleural space. Some cavities persist, are thin walled and peripheral, and cause no symptoms; occasionally there is mild hemoptysis, and rarely there is serious hemorrhage. Rarely, acute respiratory insufficiency occurs after intense exposure; this condition is associated with high mortality rates.

Residual Pulmonary Coccidioidomycosis

Residual pulmonary coccidioidomycosis includes fibrosis and persisting pulmonary nodules. Nodules are present in 5–7% of infections and sometimes require differentiation from malignancy in adults.

Disseminated (Extrapulmonary) Infection

Clinically apparent dissemination occurs in 0.5% of patients. Its incidence is increased in infants; men; pregnant women who become infected during the second and third trimesters; persons of Filipino, African, and Latin American ancestry; and persons from other Asian backgrounds. Primary or acquired disorders of cellular immunity (Table 286.1) markedly increase the risk of dissemination. A convenience sample of 108 children in California reported that diagnosis occurred a median of 57 days after symptom onset in those with disseminated infection (compared to 16 days in those with acute or pulmonary coccidioidomycosis).

Symptoms usually occur within 6 months of primary infection. Prolonged fever, toxicity, skin lesions, subcutaneous and/or osseous cold abscesses, and laryngeal lesions can herald the onset. Skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. **Basilar meningitis** is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Hydrocephalus is the most common complication in surviving patients. Bone infections account for 20–50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.



Fig. 286.2 Chest radiograph of a 19-yr-old male with acute primary coccidioidomycosis. There is prominent hilar lymphadenopathy and mediastinal widening.

Table 286.1 Risk Factors for Poor Outcome in Patients with Active Coccidioidomycosis

PRIMARY INFECTIONS
Severe, prolonged (≥6 wk), or progressive infection
RISK FACTORS FOR EXTRAPULMONARY DISSEMINATION
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors or high-dose glucocorticoids)
Neonates, infants, the elderly
Male sex (adult)
Filipino, African, Native American, or Latin American ethnicity
Late-stage pregnancy and early postpartum period
Standardized complement fixation antibody titer >1:16 or increasing titer with persisting symptoms
Blood group B
Human leukocyte antigen class II allele-DRBI*1301
Diabetes mellitus

DIAGNOSIS

Nonspecific tests have limited usefulness. Most routine laboratory evaluations are unremarkable. Complete blood count might show an elevated eosinophil count; marked eosinophilia can accompany dissemination. As a result, a high index of suspicion is required to direct an appropriate workup, especially in patients who have visited or reside in an endemic area.

Culture, Histopathologic Findings, and Antigen Detection

Any isolation of *Coccidioides* spp. from a patient specimen is considered definitive evidence of infection because the fungus is not part of the normal human microbiome. However, although diagnostic, culture is positive in only 8.3% of respiratory tract specimens and in 3.2% of all other sites. It may take several days for a specimen to grow. *Coccidioides* spp. is isolated from clinical specimens as the spore-bearing mold form, and thus the laboratory should be informed and use special precautions when the diagnosis is suspected. Inappropriate biocontainment procedures can lead to infection of exposed laboratory staff. The observation of endosporulating spherules in histopathologic specimens using potassium hydroxide (KOH) preparations, calcofluor white, or hematoxylin and eosin (H&E) stains is diagnostic. Periodic acid Schiff–or Gomori–methenamine silver stains also may be used to demonstrate the fungus.

A quantitative enzyme immunoassay (EIA) (MiraVista Diagnostics, Indianapolis, IN) that detects coccidioidal galactomannan in urine, serum, plasma, cerebrospinal fluid (CSF), or bronchoalveolar lavage fluid has excellent specificity and is positive in 70% of patients with severe infections. Although the EIA can cross react with other endemic mycoses, interpretation is often straightforward because there is negligible geographic overlap with areas endemic for other mycoses. In addition, a real-time polymerase chain reaction (PCR) assay has been developed to directly detect the fungus in tissue samples. The specificity is high, but sensitivity is not greater than that of routine cultures. Presently, *Coccidioides* spp. PCR is available through reference laboratories.

CSF analysis should be performed in patients with suspected dissemination. Findings in meningitis are similar to those seen with tuberculous meningitis (see Chapter 261). Eosinophilic pleocytosis may be present. Fungal stains and culture are usually negative. Volumes of 10 mL in adults have improved the yield of culture.

Serology

Serologic tests provide valuable diagnostic information but may be falsely negative early in self-limited infections and in immunocompromised patients. Three major methods are used, including EIA, complement fixation (CF), and immunodiffusion. EIA and CF tests are best done in experienced reference laboratories because false-positive results may be reported.

Immunoglobulin (Ig) M–specific antibody becomes measurable in 50% of infected patients 1 week after onset and in 90% of infected patients by 3 weeks. EIA is sensitive and can detect IgM and IgG antibody. It is less specific than other methods; confirmation with immunodiffusion or CF may be needed. IgG antibodies measured by CF appear between the second and third week but can take several months; follow-up testing is needed if tests are negative and clinical suspicion persists. In the presence of CF titers of 1:2 or 1:4, a positive immunodiffusion test can help corroborate significance because it is less sensitive but more specific than EIA. IgG-specific antibody can persist for months, with titers elevated in proportion to the severity of illness. CF titers >1:16 are suggestive of dissemination. Direct comparison of the results of CF (IgG) antibody tests measured by different methodologies should be interpreted with caution. IgG antibody titers used to monitor disease activity should be tested concurrently with serum samples taken earlier in the illness using the same methodology.

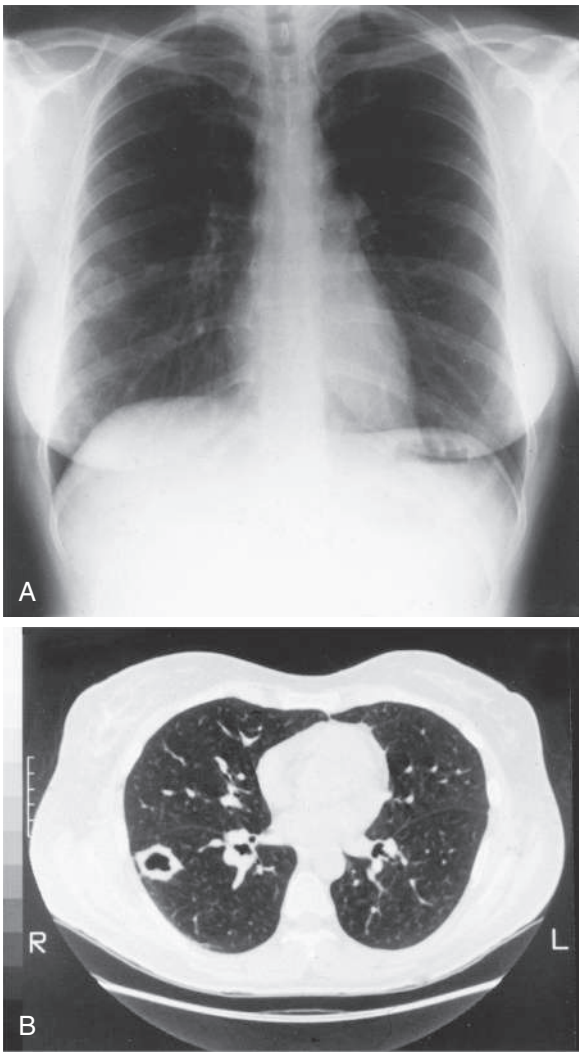

Fig. 286.3 A, Chest radiograph revealing a chronic cavitary lesion in the right lung of a female with coccidioidomycosis. B, CT showing the same cavity in the right lung.

C. immitis antibody is present in CSF in 95% of patients with meningitis and is usually diagnostic. Rarely, "spillover" in patients without meningitis but with high IgG titers in serum can be present in CSF. Isolation of *Coccidioides* spp. from CSF culture of patients with meningitis is uncommon, although culture of large volumes of CSF may improve sensitivity.

Imaging Procedures

During primary infection, chest radiography may be normal or demonstrate consolidation, single or multiple circumscribed lesions, or soft pulmonary densities. Pulmonary infiltrates in the upper lobes are more common in coccidioidal infection than in classic bacterial pneumonia. Hilar and subcarinal lymphadenopathy is often present (see Fig. 286.2). Cavities tend to be thin walled (Fig. 286.3). Pleural effusions vary in size. The presence of miliary or reticulonodular lesions is prognostically unfavorable. Isolated or multiple osseous lesions are usually lytic and affect cancellous bone. Lesions can affect adjacent structures, and vertebral lesions can affect the spinal cord.

TREATMENT

Based on the few rigorous clinical trials performed in adults and the opinions of experts in the management of coccidioidomycosis, consensus treatment guidelines have been developed (Table 286.2).

Table 286.2 Indications for Treatment of Coccidioidomycosis in Adults

INDICATION	TREATMENT
Acute pneumonia, mild	Observe without antifungal treatment at 1- to 3-mo intervals for 2 yr; some experts recommend antifungal treatment
Weight loss >10%; night sweats >3 wk; infiltrates at least half of one lung or parts of both lungs; prominent or persistent hilar lymphadenopathy; complement fixation titers >1:16; inability to work, symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1- to 3-mo intervals for 2 yr
Uncomplicated acute pneumonia, special circumstances: immunosuppression, late pregnancy, Filipino or African ancestry, age >55 yr, other chronic diseases (diabetes, cardiopulmonary disease), symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1- to 3-mo intervals for 2 yr Treat with amphotericin B if in late pregnancy
Diffuse pneumonia: reticulonodular or miliary infiltrates suggest underlying immunodeficiency and possible fungemia	Treat initially with amphotericin B if significant hypoxia or rapid deterioration, followed by an azole for ≥1 yr In mild cases, an azole for ≥1 yr
Chronic pneumonia	Treat with an azole for ≥1 yr
Disseminated disease, nonmeningeal	Treat with an azole for ≥1 yr except in severe or rapidly worsening cases, for which amphotericin B is recommended
Disseminated disease, meningeal	Treat with fluconazole (some add intrathecal amphotericin B) and treat indefinitely

Consultation with experts in an area of endemicity should be considered when formulating a management plan. Many patients with mild primary coccidioidomycosis do not require antifungal therapy. However, those at risk of severe or complicated disease should receive treatment.

Treatment is recommended for HIV-infected patients with active coccidioidomycosis and CD4 counts <250/μL. After successful treatment, antifungals may be stopped if the CD4 count exceeds 250/μL. Treatment should be continued if the CD4 count remains less than 250/μL and should be given indefinitely in all HIV-infected patients with coccidioidal meningitis. Patients with other forms of chronic immunosuppression (e.g., solid organ transplant recipients) may also require lifelong therapy.

First-line agents include oral and intravenous preparations of **fluconazole** (6-12 mg/kg; max 400-1200 mg/day) and itraconazole (2-5 mg/kg PO twice daily; max 400 mg/day). Fluconazole is often the first-line therapy because it has high bioavailability and few side effects. Serum concentrations of itraconazole should be monitored.

Amphotericin B is preferred for initial treatment of severe infections. Amphotericin B deoxycholate is less costly than lipid formulations and is often well tolerated in children. Once a daily dose of amphotericin B deoxycholate of 0.5-1.5 mg/kg/day is achieved, the frequency of administration can be reduced to 3 times weekly. The recommended total dosage ranges from 15-45 mg/kg and is determined by the clinical response. Lipid formulations of amphotericin are recommended for patients with impaired renal function, for patients receiving other nephrotoxic agents, or if amphotericin B deoxycholate is not tolerated. Some experts prefer liposomal amphotericin to treat central nervous system infections because it achieves higher levels in brain parenchyma. Amphotericin B preparations do not cross the blood-brain barrier to effectively treat *Coccidioides* spp., but they can mask the signs of meningitis. Infections during pregnancy should be treated with amphotericin B, because the azoles are potentially teratogenic. Isavuconazole, voriconazole, and posaconazole have been used successfully as salvage therapy.

Primary Pulmonary Infection

Primary pulmonary coccidioidomycosis resolves in 95% of patients without risk factors for dissemination; antifungal therapy does not lessen the frequency of dissemination or pulmonary residua. When it is elected to defer antifungal therapy, visits are recommended at 1- to 3-month intervals for 2 years and as needed.

Patients with significant or prolonged symptoms are more likely to incur benefit from antifungal agents, but there are no established criteria upon which to base the decision. Table 286.2 summarizes commonly used indicators in adults. A treatment trial in adults with primary respiratory infections examined outcomes of antifungal therapy prescribed on the basis of severity and compared them with an untreated group with less severe symptoms; complications occurred only in patients in the treatment group and only in those in whom treatment was stopped. If treatment is elected, a 3- to 6-month course of fluconazole (12 mg/kg/day) or itraconazole (10 mg/kg/day) is recommended.

Diffuse Pneumonia

Diffuse reticulonodular densities or miliary infiltrates, sometimes accompanied by severe illness, can occur in dissemination or after exposure to a large fungal inoculum. In this setting, amphotericin B is recommended for initial treatment, followed thereafter by extended treatment with high-dose fluconazole (see Table 286.2).

Disseminated (Extrapulmonary) Infection

For nonmeningeal infection (see Table 286.2), oral fluconazole and itraconazole are effective for treating disseminated coccidioidomycosis that is not extensive, is not progressing rapidly, and has not affected the central nervous system. Some experts recommend higher doses for adults than were used in clinical trials. A subgroup analysis showed a tendency for improved response of skeletal infections that were treated with itraconazole. Amphotericin B deoxycholate is used as an alternative, especially if there is rapid worsening and lesions are in critical locations. Voriconazole has been used successfully as salvage therapy. The optimal duration of therapy with the azoles has not been clearly defined. Late relapses have occurred after lengthy treatment and favorable clinical response.

Meningitis

Therapy with oral or IV fluconazole is currently preferred for coccidioidal meningitis. In adults, a dosage of 400-1,200 mg/day is recommended. For children, the dose is 12 mg/kg/day. Some experts use intrathecal, intraventricular, or intracisternally administered amphotericin B in addition to an azole, believing that the clinical response may be faster. Patients who respond to the azole should continue treatment indefinitely. Hydrocephalus is common and not necessarily a marker of treatment failure. In the event of treatment failure with azoles, intrathecal amphotericin B deoxycholate is indicated, with or without the azole. Cerebral vasculitis can occur and may predispose to cerebral ischemia, infarction, or hemorrhage. The efficacy of high-dose steroids is unresolved. Salvage therapy with isavuconazole or voriconazole has been effective.

Surgical Management

If a pulmonary cavity is located peripherally or there is recurrent bleeding or pleural extension, excision may be needed. Infrequently, bronchopleural fistula or recurrent cavitation occurs as a surgical

complication; rarely, dissemination can result. Perioperative intravenous amphotericin B may be considered. Drainage of cold abscesses, synovectomy, and curettage or excision of osseous lesions are sometimes needed. Surgical consultation is appropriate if vertebral involvement is identified to evaluate for spinal cord involvement. Local and systemic administration of amphotericin B can be used to treat coccidioidal articular disease.

Monitoring

Patients should be followed closely because late relapses can occur despite treatment, especially in those who are immunosuppressed or have severe manifestations. Testing for CF antibodies should be obtained every 12 weeks during treatment. Most titers decline as the patient improves and ultimately become undetectable. However, titers may remain positive in recovered patients. Progressive or disseminated disease should be considered when titers are persistently elevated (>1:32). These individuals may need thorough physical examinations and imaging studies. After completion of therapy, patients should be evaluated yearly for at least 2 years because some patients relapse (28% of adults who completed 12 months of fluconazole, 18% for itraconazole).

Refractory Disease

In patients who do not improve clinically on appropriate therapy, develop new symptoms, or have persistently elevated CF titers, investigations are indicated for complicated and disseminated disease. Evaluations should assess for joint effusions, skin lesions, and neurologic dysfunction. Consultation with a physician experienced in the management of coccidioidal infections should be considered.

PREVENTION

Prevention relies on education about ways to reduce exposure. Physicians practicing in nonendemic regions should incorporate careful travel histories when evaluating patients with symptoms compatible with coccidioidomycosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 287

Paracoccidioides brasiliensis

Andrew P. Steenhoff

ETIOLOGY

Paracoccidioidomycosis (South American or Brazilian blastomycosis, Lutz-Splendore-Almeida disease) is the most common systemic mycosis in Latin America. It is a fungal infection that is endemic in South America, with cases also reported in Mexico and Central America. Brazil accounts for more than 80% of all reported cases. The etiologic agent, *Paracoccidioides brasiliensis,* is a thermally dimorphic fungus found in the environment in the mycelial (mold) form and in tissues as yeast.

EPIDEMIOLOGY

P. brasiliensis is a soil-inhabiting microorganism and is ecologically unique to Central and South America. Endemic outbreaks occur mainly in the tropical rainforests of Brazil, with cases scattered in Argentina, Colombia, and Venezuela. There is an increased incidence in areas with moderately high altitude, with high humidity and rainfall, and where coffee and tobacco are grown. Armadillos appear to be a natural reservoir for *P. brasiliensis.* The most common route of infection is by inhalation of conidia. The disease is not usually thought to be contagious, and person-to-person transmission has not been confirmed. Paracoccidioidomycosis is more common among boys after puberty because of the role of estrogen in preventing the transition of conidia to the yeast form. Children account for <10% of the total number of cases.

PATHOGENESIS

Invasion of *P. brasiliensis* into the human body is based on a myriad of fungal components and strategies to bypass host defense mechanisms. With the emergence of CRISPR technology and full access to diverse databanks (such as genomes, transcriptomes, proteomes, metabolomes, lipidomes), investigators are poised to better understand the virulence processes of *P. brasiliensis,* hopefully allowing translation into benefits for patients.

The entry route into the body is via the respiratory tract, and the lungs are the site of primary infection, although not all patients have respiratory symptoms. Once the conidia or hyphal fragments reach the alveoli, yeast transformation takes place. The infection then spreads to the mucous membranes of the nose, mouth, and gastrointestinal tract. Cell-mediated immunity, mainly through lymphocytes and the production of Th-1 cytokines, is crucial to containing the infection. Tumor necrosis factor-α and interferon-γ activated macrophages are responsible for intracellular killing of *P. brasiliensis*. If the initial immune response is not successful, the response may shift toward a Th-2 pattern, which is unable to contain the infection, resulting in clinical progression. The yeast can disseminate by the lymphohematogenous route to skin, lymph nodes, and other organs and remain dormant in lymph nodes, producing a latent infection with reactivation occurring later in life. There are cases of patients who developed disease 30 or more years after leaving an endemic region.

Histopathologically, the yeastlike cells are round, with the parent cell being quite large and surrounded by small buds, giving it the appearance of a ship's wheel. A mixed suppurative and granulomatous inflammatory reaction with areas of necrosis is seen in pulmonary infections. In chronic infections, fibrosis and calcification may be seen. Mucocutaneous infections are typified by ulceration and pseudoepitheliomatous hyperplasia.

CLINICAL MANIFESTATIONS

There are two clinical forms of disease. The **acute** form (juvenile paracoccidioidomycosis) is rare, occurs almost exclusively in children and persons with impaired immunity, and targets the reticuloendothelial system. Pulmonary symptoms may be absent, although chest radiographs often show patchy, confluent, or nodular densities. Patients typically present acutely with fever, malaise, wasting, lymphadenopathy, and abdominal enlargement from intraabdominal lymphadenopathy. Hepatomegaly and splenomegaly are nearly constant. Localized bony lesions have been reported in children and can progress to systemic disease. Multifocal osteomyelitis, arthritis, and pericardial effusions can also occur. Nonspecific laboratory findings include anemia, eosinophilia, and hypergammaglobulinemia. Acute paracoccidioidomycosis has a 25% mortality rate. Hepatic involvement associated with jaundice and hypoalbuminemia may confer a worse prognosis.

Adults develop a **chronic** progressive illness that manifests initially with flulike symptoms, fever, and weight loss (adult paracoccidioidomycosis). Pulmonary infection develops with dyspnea, cough, chest pain, and hemoptysis. Findings on physical examination are scant, although chest radiographs can show infiltrates that are disproportionate with mild clinical findings. Mucositis involving the mouth and its structures as well as the nose can manifest as localized pain, change in voice, or dysphagia. Lesions can extend beyond the oral cavity onto the skin. Generalized lymphadenopathy, hepatosplenomegaly, and

adrenal involvement (seen in 15–50% of cases) can lead to Addison disease. Meningoencephalitis and central nervous system granulomas can occur as presenting or secondary symptoms. Adults with extensive exposure to soil, such as farmers, are most likely to develop the chronic form of the disease.

DIAGNOSIS

Demonstration of the fungus by direct wet mount (potassium hydroxide) preparation of sputum, exudate, or pus supports the diagnosis in many cases. Histopathologic examination of biopsy specimens using special fungal staining techniques is also diagnostic. Immunohistochemistry using monoclonal antibodies to specific glycoproteins can also be done on tissue sections. Culture of the fungus on Sabouraud dextrose or yeast extract agar confirms the diagnosis. Antibodies to *P. brasiliensis* can be demonstrated in most patients. Serial antibody titers and lymphocyte proliferative responses to fungal antigens are useful for monitoring the response to therapy. The 43-kDa glycoprotein (gp43) is present in sera of more than 90% of patients with paracoccidioidomycosis by immunodiffusion (the most commonly used diagnostic test) and in 100% of patients by immunoblotting. A latex particle agglutination test using pooled crude fungal exoantigens is being developed for the detection of anti–*P. brasiliensis* antibodies and has shown 92% agreement with the immunodiffusion test. Newer diagnostic methods that might prove to be very useful in the future include polymerase chain reaction, detection of gp43, and capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in patient sera. Skin testing with paracoccidioidin is not reliable, because 30–50% of patients with active disease are nonreactive initially, and a positive test indicates previous exposure but not necessarily active disease.

TREATMENT

Itraconazole (5-10 mg/kg/day with a maximum dose of 200 mg/day) orally for 6 months is the treatment of choice for paracoccidioidomycosis. **Fluconazole has also been used**, but high doses (≥600 mg/day) and longer treatment periods are required. A small number of patients have been treated with other azoles, including **voriconazole, posaconazole, and isavuconazole**. These drugs are potential substitutes for itraconazole but are more costly and can have interactions with other drugs. **Terbinafine** is an allylamine that has potent in vitro activity against *P. brasiliensis* and has been used for successful treatment of paracoccidioidomycosis. **Amphotericin B** is recommended for disseminated disease and if other therapies fail. Therapy with sulfonamide compounds, including sulfadiazine, TMP-SMX (trimethoprim 8-10 mg/kg/day to maximum of 160 mg, sulfamethoxazole 40-50 mg/kg/day to maximum of 800 mg), and dapsone, have been used historically and are generally less expensive than the newer azoles and allylamines. The primary disadvantage is that the treatment course is very long, lasting months to years, depending on the agent selected. Relapse can occur after any form of therapy, including with amphotericin B. In selected patients with intense inflammation in sites such as the central nervous system or with lung lesions causing respiratory insufficiency, there is some evidence that use of prednisone for 1-2 weeks concomitantly with antifungal therapy reduces inflammation more effectively and may be of benefit. Occasionally children develop paradoxical clinical worsening during treatment, including new lymph node enlargement, fistula formation, fever, and weight loss. In this circumstance, steroids are also recommended.

Two therapies currently under investigation include the use of **curcumin**, an antioxidant found in the Indian spice turmeric, and the calcineurin inhibitor **cyclosporine**. Curcumin was found to have more antifungal activity than fluconazole against *P. brasiliensis* when studied in vitro using human buccal epithelial cells. Cyclosporine blocks the thermodimorphism of *P. brasiliensis*. Animal models demonstrate that fungal whole cells, purified antigens, peptides, and DNA vaccines have great potential toward the development of a vaccine for use in humans.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 288

Sporotrichosis (*Sporothrix schenckii*)

Andrew P. Steenhoff

ETIOLOGY

Sporotrichosis is a rare fungal infection that occurs worldwide, both sporadically and in outbreaks, and is caused by *Sporothrix schenckii,* which exhibits temperature dimorphism, existing as a mold at environmental temperatures (25–30°C [77–86°F]) and as a yeast in vivo (37°C [98.6°F]). *S. schenckii* comprises a group of cryptic, phylogenetically related species, including *S. brasiliensis, S. chilensis, S. globosa, S. luriei, S. mexicana,* and *S. pallida*. *S brasiliensis* is the most virulent species.

EPIDEMIOLOGY

S. schenckii is found throughout the world, but most cases of sporotrichosis are reported from South America, Central America, and Asia, including Japan, India, and China. In the United States, the majority of cases have occurred in the Midwest, particularly in areas along the Mississippi and Missouri rivers. The fungus is found in decaying vegetation and has been isolated most commonly from sphagnum moss, rosebushes, barberry, straw, and some types of hay. Sporotrichosis can occur as an occupational disease among farmers, gardeners, veterinarians, and laboratory workers. Transmission from bites and scratches of animals, most commonly cats and armadillos, has occurred. Reports of human-to-human transmission are rare. Sporotrichosis has rarely been reported in infants. The mechanism of transmission in children may be zoonotic but usually is unclear. In one endemic area of Peru, the incidence of infection is greater in children than in adults; risk factors for infection in these children are playing in crop fields, living in houses with dirt floors, and owning a cat.

PATHOGENESIS

Disease in humans usually follows cutaneous inoculation of the fungus into a minor wound. Pulmonary infection can result from the inhalation of large numbers of spores. Disseminated infection is unusual but can occur in immunocompromised patients after ingestion or inhalation of spores. The cellular immune response to *S. schenckii* infection is both neutrophilic and monocytic. Histologically, the coexistence of noncaseating granulomas and microabscess formation is characteristic. T-cell–mediated immunity appears to be important in limiting infection, and antibody does not protect against infection. As a result of the paucity of organisms, it is usually difficult to demonstrate the fungi in biopsy specimens.

CLINICAL MANIFESTATIONS

Cutaneous sporotrichosis is the most common form of disease in all age-groups. Cutaneous disease may either be lymphocutaneous or fixed cutaneous, the former being much more common (Fig. 288.1). Lymphocutaneous sporotrichosis accounts for more than 75% of reported cases in children and occurs after traumatic subcutaneous inoculation. After a variable and often prolonged incubation period (1-12 weeks), an isolated, painless erythematous papule develops at the inoculation site. The initial lesion is usually on an extremity in adults but is often on the face in children. The original papule enlarges and ulcerates. Although the infection might remain limited to the inoculation site (fixed cutaneous form), satellite lesions follow lymphangitic spread and appear as multiple tender subcutaneous nodules tracking along the lymphatic channels that drain the lesion. These secondary nodules are subcutaneous granulomas that adhere to the overlying skin and subsequently ulcerate. Sporotrichosis does not heal spontaneously, and these ulcerative lesions can persist for years if untreated. Systemic signs and symptoms are uncommon.



Fig. 288.1 Sporotrichosis. Erythematous papules and nodules on the plantar surface with early lymphangitic (sporotrichoid) spread. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2016: Fig. 17.48.)*

Extracutaneous sporotrichosis is rare in children, and most cases are reported in adults with underlying medical conditions, including AIDS and other immunosuppressing diseases. The most common form of extracutaneous sporotrichosis involves infection of the bones and joints. Pulmonary sporotrichosis usually manifests as a chronic pneumonitis similar to the presentation of pulmonary tuberculosis. Erythema nodosum is an immunoreactive manifestation.

DIAGNOSIS

Cutaneous and lymphocutaneous sporotrichosis must be differentiated from other causes of nodular lymphangitis, including atypical mycobacterial infection, nocardiosis, leishmaniasis, tularemia, melioidosis, cutaneous anthrax, and other systemic mycoses, including coccidioidomycosis. Definitive diagnosis requires isolation of the fungus from the site of infection by culture. Special histologic staining such as periodic acid–Schiff and methenamine silver is required to identify yeast forms in tissues, which are typically oval or cigar-shaped. In spite of special staining techniques, diagnostic yield from biopsy specimens is low because of the small number of organisms present in the tissues. In cases of disseminated disease, demonstration of serum antibody against *S. schenckii*–related antigens can be diagnostically useful. Serologic testing is not commercially available but is offered by specialized laboratories, including the Centers for Disease Control and Prevention in the United States.

TREATMENT

Although comparative trials and extensive experience in children are not available, **itraconazole is the recommended treatment of choice for infections outside the central nervous system**. The recommended dosage for children is 5-10 mg/kg/day orally, with an initial maximum dose of 200 mg daily, which may be increased up to 400 mg daily if there is no initial response. Alternatively, **younger children with cutaneous disease only may be treated with a saturated solution of potassium iodide** (1 drop, 3 times daily by mouth, increasing as tolerated to a maximum of 1 drop/kg of body weight or 40-50 drops, 3 times daily, whichever is lowest). Adverse reactions, usually in the form of nausea and vomiting, should be managed with temporary cessation of therapy and reinstitution at a lower dosage. Therapy is continued 2-4 weeks after cutaneous lesions have resolved, which usually takes at least 6-12 weeks. **Terbinafine has been used successfully to treat cutaneous sporotrichosis but is reported to have lower cure rates and higher relapse rates than itraconazole.** Further clinical efficacy data are needed to routinely recommend its use. **Amphotericin B is the treatment of choice for pulmonary infections, disseminated infections, central nervous system disease, and infections in immunocompromised persons.** Oral **fluconazole** 12 mg/kg daily (maximum dose, 400-800 mg daily) can be used if other agents are not tolerated. **Posaconazole** shows promise, but further data are needed.

Therapy with azoles or a saturated solution of potassium iodide should not be used in pregnant women. **Amphotericin B can be used safely for cases of pulmonary or disseminated disease in pregnancy.** Pregnant patients with cutaneous disease can be treated with local hyperthermia or can have therapy delayed until the pregnancy is completed. Hyperthermia involves heating the affected area to 42–45°C (107.6–113°F) using water baths or heating pads and works by inhibiting growth of the fungus. Dissemination to the fetus does not occur, and the disease is not worsened by pregnancy. **Surgical debridement has a role in the treatment of some cases of sporotrichosis, particularly in osteoarticular disease.**

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 289

Mucormycosis

Rachel L. Wattier and William J. Steinbach

ETIOLOGY

Mucormycosis refers to opportunistic invasive fungal infections caused by fungi of the order Mucorales. These organisms are found commonly in soil and decaying organic matter and are distributed worldwide. Mucormycosis was previously called *zygomycosis,* but this terminology has been abandoned because of reclassification of organisms using molecular phylogenetic analysis. The most common disease-causing genera of Mucorales are *Rhizopus, Mucor,* and *Lichtheimia* (formerly *Absidia*). Infections caused by organisms of the genera *Rhizomucor, Cunninghamella, Saksenaea*, *Apophysomyces,* and others are less common. Mucormycosis in humans is characterized by a rapidly evolving course, tissue necrosis, and blood vessel invasion.

EPIDEMIOLOGY

Mucormycosis is primarily a disease of persons with underlying conditions that impair host immunity, though it can sometimes manifest with cutaneous and soft tissue infections at sites of trauma in immunocompetent hosts. Predisposing factors include poorly controlled diabetes, especially if complicated by ketoacidosis, and profound immunocompromise resulting from therapy for hematologic malignancies (especially with prolonged neutropenia), stem cell or organ transplantation, and/or high-dose corticosteroid therapy. Other risk factors include iron overload and prematurity. Mucormycosis may develop as a breakthrough infection in patients receiving voriconazole antifungal prophylaxis; voriconazole lacks activity against the Mucorales. Therefore breakthrough infections or nonresponse to voriconazole should prompt increased consideration of mucormycosis.

Mucormycosis is the second most common invasive mold infection in immunocompromised hosts after aspergillosis, and its incidence is increasing because of an increase in the number and improved survival of immunocompromised persons at risk. A contemporary review of reported pediatric cases from 2008 to 2017 found a 32% case fatality rate across all included cases. Mortality rates vary depending on disease manifestations of mucormycosis and underlying patient conditions, with worse outcomes observed in patients with more extensive disease manifestations and those with irreversible predisposing risk factors. However, observational studies suggest that pediatric patients with mucormycosis generally have more favorable outcomes compared to adults and that outcomes may be improving over time with contemporary therapeutic approaches.

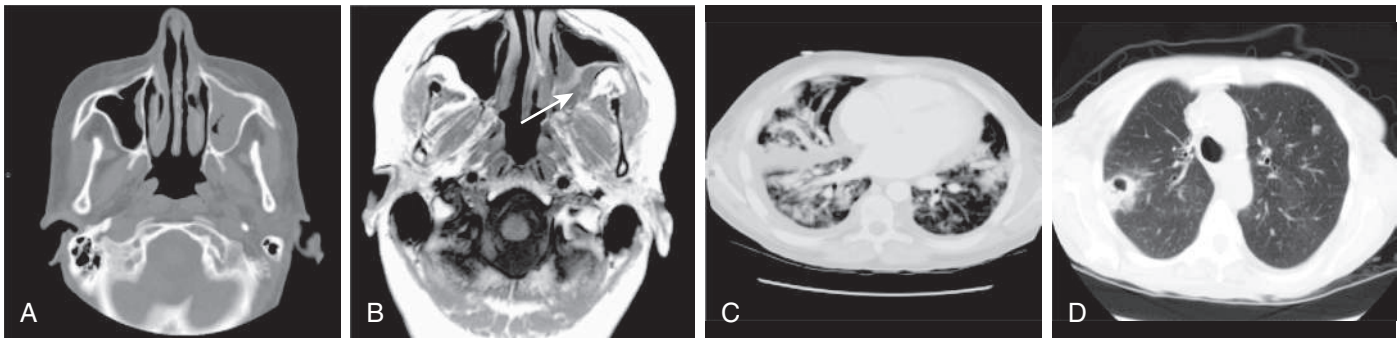

Fig. 289.1 Radiographic findings in mucormycosis. **A,** CT scan shows left maxillary sinus air-fluid level, similar to bacterial sinusitis. **B,** Magnetic resonance image reveals T2 signal hyperintensity in the left pterygoid musculature *(arrow)* in conjunction with a left maxillary sinus air-fluid level. **C,** Multiple heterogeneous nodular and consolidative lesions with a large pulmonary vessel infarct and modest pleural effusions are shown in a patient with cancer and pulmonary mucormycosis. **D,** Contrast-enhanced CT scan demonstrates a cavity within a dense infiltrate in a patient with acute myelogenous leukemia and pulmonary mucormycosis. *(Courtesy Dr. Edith Marom, University of Texas, MD Anderson Cancer Center, Houston, Texas.)*

PATHOGENESIS

Spores can be inhaled from the environment into the upper and/or lower airways, inoculated at sites of cutaneous trauma, or, less commonly, ingested. If, because of impaired immune response, spores are not cleared by macrophages and neutrophils, they germinate into hyphae, resulting in local invasion and tissue destruction. Mucormycosis is characterized by extensive angioinvasion, resulting in thrombosis, infarction, and tissue necrosis, which can limit the delivery of antifungal agents and leukocytes to the site of infection and contribute to dissemination of the infection to other organs.

Many of the Mucorales can scavenge iron, an element essential for cell growth, from the host. The iron chelator deferoxamine paradoxically increases iron availability and uptake by members of the Mucorales. Acidosis diminishes the phagocytic and chemotactic ability of neutrophils while increasing the availability of unbound iron, likely explaining the susceptibility to mucormycosis among individuals with uncontrolled acidosis.

CLINICAL MANIFESTATIONS

Mucormycosis can occur as any of several clinical syndromes, including rhinocerebral, pulmonary, cutaneous or subcutaneous, gastrointestinal, or disseminated disease. The initial symptoms and signs of each may be subtle and not easily distinguishable from other infections, so it is important to have a high index of suspicion for the disease in patients at risk.

Rhinocerebral mucormycosis is the most common form and can involve the palate, sinuses, orbit, and/or adjacent structures with potential progression to the brain. Initial symptoms are similar to sinusitis and include headache, retroorbital pain, fever, and nasal discharge. Infection can evolve rapidly or be slowly progressive. Orbital involvement manifests as periorbital edema, proptosis, ptosis, and/or ophthalmoplegia. The nasal discharge may be dark and bloody; involved tissues become red, then violaceous, and then black as vessel thrombosis and tissue necrosis occur. Extension beyond the nasal cavity into the mouth is common and may be apparent as palatal lesion(s). Destructive paranasal sinusitis with bone involvement and possible intracranial extension can be demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 289.1). Rhinocerebral mucormycosis can be complicated by cavernous sinus thrombosis or thrombosis of the internal carotid artery. Intracranial extension can occur directly from the nasal cavity and sinuses, usually to the frontal or frontotemporal lobes, or hematogenously, commonly involving the occipital lobe or brainstem.

Pulmonary mucormycosis usually occurs in profoundly neutropenic patients and presents similarly to other pulmonary invasive mold infections. Manifestations can include fever, tachypnea, productive cough, pleuritic chest pain, and hemoptysis; however, initial symptoms may be minimal. A wide range of pulmonary radiographic findings, including pulmonary nodules, consolidation, cavitary lesion(s), and lung infarct(s), are recognized (see Fig. 289.1). Although the radiographic findings overlap with other pulmonary invasive fungal infections, the presence of multiple nodules (≥10), pleural effusion(s), or the **reverse halo sign**, a focal area of ground-glass opacity surrounded by a ring of consolidation, is more suggestive of mucormycosis.



Fig. 289.2 Cutaneous presentation of mucormycosis. Chronic, nonhealing ulcer with necrosis after traumatic inoculation. *(From Kontoyiannis DP, Lewis RE. Agents of mucormycosis and entomophthoramycosis. In Bennett JF, Dolin R, Blaser MJ (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier, 2015. Fig. 260-6A; Courtesy Drs. Gerald Bodey and Saud Ahmed, University of Texas, MD Anderson Cancer Center, Houston, TX.)*

Cutaneous and soft tissue mucormycosis can be primary, resulting from direct inoculation at sites of trauma, including burns, surgical sites, or vascular access sites, or secondary, resulting from hematogenous dissemination to the skin from another primary site. Primary cutaneous lesions manifest initially as painful erythematous papules that ulcerate, leaving a black necrotic center. In contrast, secondary cutaneous lesions from hematogenous seeding tend to be nodular, with minimal destruction of the epidermis. Either may be invasive locally, progressing through multiple tissue layers, including muscle, fascia, and bone (Fig. 289.2), with accompanying tissue necrosis.

Gastrointestinal mucormycosis is the least common form of disease except in preterm neonates, in whom it is the most commonly reported form of mucormycosis. Manifestations include abdominal pain, nausea, vomiting, gastrointestinal bleeding, obstruction, and perforation. Any part of the gastrointestinal tract can be involved, with the stomach followed by colon and ileum being the most commonly

affected. The clinical presentation in neonates mimics necrotizing enterocolitis, sometimes with a palpable abdominal mass. Recognition of gastrointestinal mucormycosis is challenging given its rarity and overlap in presentation with other gastrointestinal diseases. It is associated with particularly high mortality and commonly not diagnosed until postmortem examination.

Disseminated mucormycosis can develop from any site of primary disease but is more commonly associated with initial pulmonary disease. It carries the highest mortality rates seen with mucormycosis, especially among immunocompromised persons. The clinical presentation varies based on the involved sites. Dissemination of mucormycosis to the brain is of particular concern and alters management and prognosis, so many experts recommend brain imaging routinely, even in the absence of neurologic symptoms.

DIAGNOSIS

All forms of mucormycosis are considered medically emergent, and some (e.g., rhinocerebral) are also surgical emergencies. Diagnostic evaluation and initiation of treatment should be pursued simultaneously with a coordinated multidisciplinary approach. The diagnosis depends on early recognition of compatible clinical findings in a patient with predisposing risk factors. Once mucormycosis is suspected, cross-sectional imaging should be performed to define the site(s) of disease as indicated based on the clinical presentation, and tissue from the site of disease should be obtained for diagnostic evaluation, along with initial surgical debridement for rhinocerebral or cutaneous mucormycosis. The diagnosis relies on direct morphologic identification of mycotic elements from culture or tissue biopsy specimens. Mucorales appear as broad (5-25 μm in diameter), infrequently septate (denoted as aseptate or pauci-septate on pathology), thin-walled hyphae, branching irregularly at right angles when stained with Gomori methenamine silver (GMS) or hematoxylin and eosin. Organisms may be challenging to identify reliably by morphology from tissue specimens; immunohistochemistry or molecular diagnostic tests can provide more reliable identification to the species level.

Mucorales can be cultured on standard laboratory media; however, cultures from nontissue specimens, such as bronchoalveolar lavage fluid, have poor sensitivity. Mucorales hyphae can also be easily disrupted, decreasing the yield of cultures. Submitting fresh tissue with careful handling to avoid disruption (e.g., grinding) can improve yield. When an organism is visualized by histopathology but not recovered in culture, molecular methods may improve detection. Though Mucorales can be culture contaminants, isolation in a susceptible host should prompt consideration of clinical disease. Noninvasive fungal biomarkers, such as galactomannan and 1,3-β-D-glucan, do not detect the causative agents of mucormycosis. Though molecular tests are available to detect Mucorales and other fungal pathogens directly from blood samples, these have not yet been sufficiently validated to replace tissue-based diagnosis.

TREATMENT

Though mucormycosis can be aggressive and difficult to treat, with high mortality rates, more favorable outcomes can be achieved via early recognition and prompt institution of medical therapy combined with extensive surgical debridement of devitalized tissue to the extent possible. It is essential to reverse predisposing factors, such as neutropenia, hyperglycemia, and/or acidosis, and to withdraw immunosuppression or deferoxamine therapy, if applicable.

Given the rarity of mucormycosis, there are few clinical trials to guide optimal therapy. Based on clinical experience, observational data, and small clinical trials, the European Confederation of Medical Microbiology and the Mycoses Study Group published "global guidelines" for mucormycosis in 2019. **Lipid formulations of amphotericin B, with preference for liposomal amphotericin B, are strongly recommended as first-line therapy for all forms of mucormycosis in all age-groups.** It is recommended to initiate therapy with the full dose of liposomal amphotericin B of at least 5 mg/kg/day, with consideration up to 10 mg/kg/day, and 10 mg/kg/day is recommended for treatment of central nervous system infection. Other antifungals with activity against the Mucorales include isavuconazole (administered as the prodrug isavuconazonium sulfate) and posaconazole; however, there is less experience with these antifungals for initial or "primary therapy" of mucormycosis, and their activity can vary based on causative species and specific antifungal susceptibility patterns. Guidelines moderately recommend primary therapy with IV formulations of either posaconazole or isavuconazole in patients with significant preexisting renal impairment, because of potential nephrotoxicity with amphotericin B formulations. However, some experts prefer liposomal amphotericin B for patients with severe or progressive mucormycosis even in the setting of renal impairment.

There is increasing pharmacokinetic and safety data supporting the use of isavuconazole and posaconazole in pediatric patients, though posaconazole pharmacokinetics vary by formulation, and the immediate-release oral suspension does not reliably achieve optimal target concentrations. Therefore IV or delayed-release formulations of posaconazole are preferred. **Isavuconazole or posaconazole is recommended for specific roles in the treatment of mucormycosis, the most established role being for "salvage therapy" in patients who either do not respond adequately to initial amphotericin B–based therapy or who develop intolerance precluding continuation of amphotericin B-based therapy.** In the case of inadequate response, many experts recommend combination therapy, including liposomal amphotericin B with either isavuconazole or posaconazole, so that the "backbone" therapy with liposomal amphotericin B can also be continued. Given the rapidly progressive course and severe outcomes associated with mucormycosis, primary combination therapy (a regimen with multiple antifungal agents from the beginning) is also frequently used in practice. However, there is currently insufficient evidence to determine whether initial combination therapy is beneficial over monotherapy with liposomal amphotericin B. The results of animal model studies and observational clinical studies have varied, and some of the better-quality observational studies have not shown a clear benefit. **Combination therapy with liposomal amphotericin B and isavuconazole or posaconazole is therefore marginally recommended in the global mucormycosis guidelines.** Some clinicians have given combination therapy with an echinocandin antifungal (e.g., caspofungin) added to amphotericin B–based therapy based on animal model data and limited clinical studies showing potential benefit with this combination. However, this combination has been less preferred recently, partly because echinocandins lack intrinsic activity against the Mucorales and because increasing data favor isavuconazole or posaconazole for salvage therapy.

Given the complex considerations when selecting and monitoring antifungal therapy for mucormycosis, and also considering surgical approaches, which are well-established for rhinocerebral and cutaneous mucormycosis and favored when possible for localized pulmonary mucormycosis, a multidisciplinary approach with expert guidance is necessary. Patients with mucormycosis should be monitored with frequent repeat imaging to evaluate their response to therapy, and multiple surgical procedures are often necessary to achieve stabilization of disease.

The duration of antifungal therapy is individualized but is usually continued until all clinical and radiographic findings have resolved and the patient shows reconstitution or significant improvement of their immune response. Patients with a good response to initial IV antifungal therapy may be converted to maintenance therapy with enteral isavuconazole or posaconazole.

Various adjunctive therapies have been reported for mucormycosis; the most commonly used are treatments such as hematopoietic growth factors to reverse neutropenia as a predisposing factor. Hyperbaric oxygen has been used anecdotally as an adjunctive therapy but is not well established and not routinely recommended. Iron chelation with deferasirox has been tried as salvage therapy in refractory mucormycosis but is currently not recommended because of adverse outcomes in a small clinical trial. The overall emphasis of disease management should remain on optimizing the antifungal and surgical therapies and reversing any modifiable predisposing conditions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 290

Pneumocystis jirovecii

Francis Gigliotti and Terry W. Wright

Pneumocystis jirovecii pneumonia (interstitial plasma cell pneumonitis) in an immunocompromised person is a life-threatening infection. Primary infection in the immunocompetent individual is usually subclinical and goes unrecognized. The disease most likely results from new or repeat acquisition of the organism rather than reactivation of latent organisms. Even in the most severe cases, with rare exceptions, the pathogen remains localized to the lungs.

ETIOLOGY

The genus ***Pneumocystis*** contains a group of common extracellular **fungal pathogens,** which are found worldwide and exist exclusively in the lungs of mammalian hosts as **obligate biotrophs**. The initial taxonomic placement of *Pneumocystis* was ambiguous. However, comparative genomics definitively positioned *Pneumocystis* among the ascomycetous fungi, despite sharing certain morphologic features and drug susceptibility profiles with protozoa. Detailed information on the basic biology and life cycle of *Pneumocystis* is incomplete because of the inability to grow these organisms in culture. However, phenotypic and genotypic analyses show that the *Pneumocystis* organisms infecting each individual mammalian host are unique and restricted to that host. Current knowledge suggests that a distinct *Pneumocystis* evolved in each host species and ultimately adapted to its specific host in a manner that prevented transmission and replication in heterologous host species.

The clear biological distinction of *Pneumocystis* from different mammalian hosts led to the **division of *Pneumocystis* into multiple species** that are named according to the host from which they are derived. Current convention uses the name ***P. jirovecii*** to refer to the *Pneumocystis* species infecting humans, whereas those infecting rats and mice are designated *P. carinii* and *P. murina*, respectively. Clinicians should be aware that the term *P. carinii* was originally used for all *Pneumocystis* regardless of host species of origin and may sometimes refer to human-derived *Pneumocystis* in older medical literature.

EPIDEMIOLOGY

P. jirovecii is found worldwide, but a natural habitat outside of the human host has not been identified. Serologic surveys show that most humans are exposed to *P. jirovecii* before 4 years of age, and polymerase chain reaction (PCR) analyses has confirmed the prevalence of *P. jirovecii* in both children and adults. Full genome sequencing of three *Pneumocystis* species, including *P. jirovecii*, revealed that ***Pneumocystis* has lost critical genes required for autonomous survival and growth**. Thus currently available evidence suggests that *P. jirovecii* only lives in the lungs of humans and that it persists in the human population through repeat subclinical or mild infection of immunocompetent adults and children. Gene loss helps to explain the inability to either culture *Pneumocystis* or identify a natural reservoir outside the host. The universal prevalence of *P. jirovecii* in the human population likely explains why *P. jirovecii* is a common opportunistic infection in immunocompromised people not receiving prophylaxis.

The mode of *Pneumocystis* transmission to humans is undefined, but animal-to-animal airborne transmission has been clearly demonstrated. Animal-to-human transmission is unlikely because of the stringent host-species restriction of *Pneumocystis* species. Person-to-person transmission is likely but has not been directly proven. However, the appearance of geographically clustered *Pneumocystis* cases caused by genetically similar *P. jirovecii* strains supports the occurrence of community spread among immunocompromised patients. In addition, *P. jirovecii* has been detected in air samples collected in close proximity to patients with *Pneumocystis* pneumonia. **Thus it seems likely that *P. jirovecii* is passed from human to human through an airborne route**.

Most humans are infected with *P. jirovecii* during early childhood. In the immunocompetent child, these infections are usually asymptomatic or mild and indistinguishable from other common childhood respiratory infections. Pneumonia caused by *P. jirovecii* occurs almost exclusively in severely immunocompromised hosts, including those with congenital or acquired immunodeficiency disorders, malignancies, or transplanted organs. Patients with primary immunodeficiency diseases at risk for infection include severe combined immunodeficiency disease, X-linked CD40 ligand deficiency, major histocompatibility complex class II deficiency, nuclear factor kappa B essential modulator (NEMO) deficiency, dedicator of cytokinesis 8 (DOCK8) deficiency, Wiskott-Aldrich syndrome, and caspase recruitment domain 11 (CARD11) deficiency. *P. jirovecii* can be found in the lungs of infants who have died with the diagnosis of sudden infant death syndrome (SIDS). However, further study concluded that *P. jirovecii* is likely not the cause of SIDS but instead that there is overlap in the timing of the primary *P. jirovecii* infection and the onset of SIDS. Recent studies have described pathologic changes in the lungs of infants during primary infection and have suggested a possible association of *P. jirovecii* with respiratory distress syndrome in preterm infants.

Without chemoprophylaxis, approximately 40% of infants and children with AIDS, 70% of adults with AIDS, 12% of children with leukemia, and 10% of patients with organ transplants develop *P. jirovecii* pneumonia. Epidemics that occurred among debilitated infants in Europe during and after World War II are attributed to malnutrition. Currently, **the use of novel immunosuppressive agents for the treatment of inflammatory syndromes, autoimmune disease, and malignancy has expanded the at-risk population**. For example, the addition of anti–tumor necrosis factor (TNF) therapy to the management of patients with inflammatory bowel disease or rheumatoid arthritis has resulted in a demonstrable increase in *P. jirovecii* pneumonia in these patient populations. The use of rituximab or ibrutinib in patients with hematologic malignancies also increases the risk of *Pneumocystis* pneumonia.

PATHOGENESIS

Two forms of *P. jirovecii* are found in the alveolar spaces: the cyst form (or ascus), which are 5-8 μm in diameter and contain up to eight pleomorphic intracystic bodies (sporozoites or ascospores); and trophic forms (or trophozoites), which are 2-5 μm cells derived from excysted sporozoites. The names sporozoite and trophozoite were based on the morphologic similarities to protozoa. However, the inclusion of *Pneumocystis* among the fungi led to the adoption of names such as ascus and ascospore, which are derived from fungal terminology. The cyst form accounts for 5–10% of the *Pneumocystis* in the lung. The cyst has a thick wall composed of β-glucan, which is thought to be a major driver of pulmonary inflammation during *Pneumocystis* pneumonia. *P. jirovecii* trophic forms typically constitute approximately 90% of the *Pneumocystis* in the lungs and have the ability to suppress inflammation induced by the cyst form. Trophic forms attach firmly to the type 1 pneumocytes lining the alveoli, possibly by adhesive bridging proteins such as fibronectin or mannose-dependent ligands. The consequences of this interaction are unclear, but it may provide signals or nutrients to *Pneumocystis* to stimulate growth. As the infection progresses, this interaction may contribute to the characteristic alveolar damage.

Control of *P. jirovecii* infection in immunocompetent people requires functional cell-mediated immunity, and patients with AIDS show an increased incidence of *Pneumocystis* pneumonia as $CD4^+$ T-lymphocyte counts decrease. Before widespread prophylaxis of AIDS patients, life-threatening *Pneumocystis* pneumonia occurred in a high percentage of these patients when $CD4^+$ T cell counts dropped below 200 cells/mm^3. **$CD4^+$ T cell counts provide a useful indicator in both older children and adults of the need for prophylaxis against *Pneumocystis* pneumonia**. Although normally functioning $CD4^+$ T cells are central to controlling *P. jirovecii* infection, the final effector pathway for destruction of *P. jirovecii* is poorly understood but likely requires macrophages. $CD4^+$ T cells may activate macrophages for phagocytosis and clearance of *Pneumocystis* through local cytokine secretion, and also provide help for the production of specific antibody.

Anti-*Pneumocystis* antibody has the potential to facilitate fungal clearance through opsonization, complement activation, or interfering with *Pneumocystis* binding to lung epithelial cells.

Clinical investigation as well as work in animal models has revealed that the host's immune response to *Pneumocystis* infection is a major contributor to the pathogenesis of *Pneumocystis* pneumonia. Human studies found that the severity of disease correlates with the degree of lung inflammation but not with fungal burden. Furthermore, patients with profound AIDS-related immunosuppression present with higher *P. jirovecii* burdens but better lung function than non-AIDS patients with *Pneumocystis* pneumonia and with greater retained immune function. A classic AIDS-related presentation of *Pneumocystis* pneumonia can be modeled in $CD4^+$ T cell–depleted rodents and simian immune virus–infected nonhuman primates. In the absence of $CD4^+$ T cells a progressive accumulation of $CD8^+$ T cells occurs in a likely attempt to fight the infection. These cells do not provide effective host defense against *Pneumocystis*, but instead directly contribute to *Pneumocystis* pneumonia–related immunopathogenesis and lung injury. Similar to humans with *Pneumocystis* pneumonia, polymorphonuclear leukocytes (PMNs) also accumulate in the lungs of animals as *Pneumocystis* pneumonia progresses. These phagocytes do not contribute meaningfully to either *Pneumocystis* eradication or immunopathogenesis. However, as is the case in human patients, there is a strong correlation between the number of PMNs in the lung and the severity of disease.

In the complete absence of an adaptive immune response, as can be modeled in severe combined immunodeficient (SCID) mice, *Pneumocystis* infection produces little alteration in lung histology or function until late in the course of the disease. However, if congenic lymphocytes are transferred to *Pneumocystis*-infected SCID mice, an acute $CD4^+$ T cell–dependent immune response is mounted against the *Pneumocystis*. There is rapid onset of pulmonary inflammation, surfactant dysfunction, severe respiratory impairment, and significant hypoxia, mimicking the characteristic changes of *Pneumocystis* pneumonia in humans. The functional $CD4^+$ T cells generate an effective immune response against the existing infection, but also cause inflammation and lung injury. $CD8^+$ T cells are typically ineffective in the eradication of *Pneumocystis* but may modulate the $CD4^+$ T cell response to lessen the immune-mediated damage. **The functional interactions of T cell subsets in patients with differing and often fluctuating immune status are likely responsible for the variations in presentation and outcome of *Pneumocystis* pneumonia**.

PATHOLOGY

The histopathologic features of *P. jirovecii* pneumonia are of two types. The first type is infantile interstitial plasma cell pneumonitis, which was observed in epidemic outbreaks in debilitated infants 3-6 months of age. Extensive infiltration with thickening of the alveolar septum occurs, and plasma cells are prominent. The second type is a diffuse desquamative alveolar pneumonitis found in immunocompromised children and adults. The alveoli contain large numbers of *P. jirovecii* in a foamy exudate with alveolar macrophages active in the phagocytosis of organisms. The alveolar septum is not infiltrated to the extent it is in the infantile type, and plasma cells are usually absent.

CLINICAL MANIFESTATIONS

There are at least three distinct clinical presentations of *P. jirovecii* pneumonia. In patients with profound congenital immunodeficiency or in AIDS patients with very few $CD4^+$ T cells, the onset of hypoxia and symptoms is subtle and often without fever, with tachypnea progressing to nasal flaring; intercostal, suprasternal, and infrasternal retractions; and cyanosis in severe cases. In children and adults with immunodeficiency resulting from immunosuppressive medications, the onset of hypoxia and symptoms is often more abrupt, with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This type accounts for the majority of cases, although the severity of clinical expression can vary. *Rales are usually not detected on physical examination.* The third pattern of *Pneumocystis* pneumonia is reported in severely immunocompromised patients who appear to be responding to therapy but then have an acute and seemingly paradoxical deterioration thought to be associated with the restoration of immune function. This condition is referred to as *immune reconstitution inflammatory syndrome* and is most commonly seen in patients with newly diagnosed AIDS who present with *P. jirovecii* pneumonia and who have a rapid response to antiretroviral therapy that is instituted at the same time as anti-*Pneumocystis* therapy. It can also occur in stem cell transplant recipients who engraft while infected with *P. jirovecii*.

LABORATORY FINDINGS AND DIAGNOSIS

The chest radiograph reveals bilateral diffuse interstitial or alveolar ground glass infiltrates (Fig. 290.1). The earliest densities are perihilar, and progression proceeds peripherally, sparing the apical areas until last. The arterial oxygen tension (Pao_2) is invariably decreased. The major role of the laboratory in establishing a diagnosis of *P. jirovecii* pneumonia is to identify organisms in lung specimens by a variety of methods. **Definitive diagnosis requires visualization of *P. jirovecii* in the lung in the presence of clinical signs and symptoms of the infection**. Organisms can be detected in specimens collected by bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, and open lung biopsy. Hypertonic saline–induced sputum samples are helpful if *P. jirovecii* is found, but the absence of the organisms in induced sputum does not exclude the infection and BAL should be performed. Open lung biopsy is the most reliable method, although BAL is more practical in most cases. Estimates of the diagnostic yield of the various specimens are 20–40% for induced sputum, 50–60% for tracheal aspirate, 75–95% for BAL, 75–85% for transbronchial biopsy, and 90–100% for open lung biopsy.

Once obtained, the specimens are typically stained with one of four commonly used stains: Grocott-Gomori silver stain and toluidine blue stain for the cyst form, polychrome stains such as Giemsa stain for the trophic forms and ascospores, and the fluorescein-labeled monoclonal antibody stains for both trophic forms and cysts. **Many clinical laboratories have adopted polymerase chain reaction analysis of respiratory specimens for the diagnosis of *Pneumocystis* pneumonia**. Serum lactate dehydrogenase (LDH) levels are often elevated during *Pneumocystis* pneumonia, and although elevated LDH is not a specific or definitive diagnosis, high levels should raise suspicion.

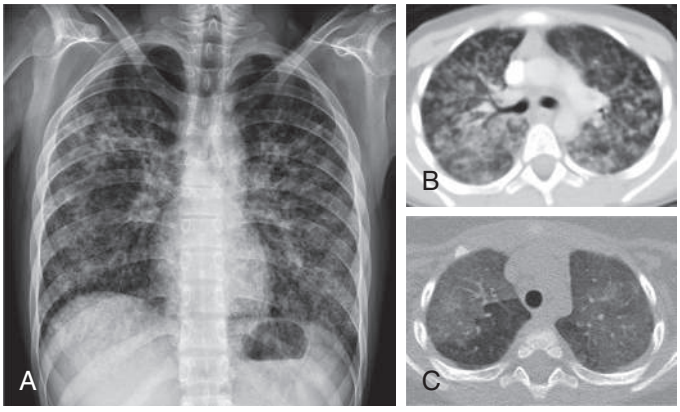

Fig. 290.1 *Pneumocystis jirovecii* infection in a 17-yr-old male with acute lymphoblastic leukemia and immunodeficiency, who presented with dyspnea, fever, nonproductive cough, and decreased white blood cell counts. A, Radiograph shows diffuse bilateral interstitial opacity throughout the lungs. B, Contrast-enhanced computed tomography confirms the bilateral patchy and ground-glass opacities in both lungs. The diagnosis was confirmed by a positive polymerase chain reaction test from bronchial lavage fluid. C, CT in a different patient demonstrates a typical "crazy paving" pattern in both upper lobes. *(From Westra SJ, Yikilmaz A, Lee EY. Pulmonary infection. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 54.30.)*

TREATMENT

The recommended therapy for *P. jirovecii* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg TMP and 75-100 mg SMX/kg/day in four divided doses) administered intravenously or orally if there is mild disease and no malabsorption or diarrhea. The duration of treatment is 3 weeks for patients with AIDS and 2 weeks for other patients. Unfortunately, adverse reactions often occur with TMP-SMX, especially rash and neutropenia in patients with AIDS. For patients who cannot tolerate or who fail to respond to TMP-SMX after 5-7 days, pentamidine isethionate (4 mg/kg/day as a single dose IV) may be used. Adverse reactions are frequent and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone (750 mg twice daily with food, for patients >13 years of age) is an alternative treatment that has been used primarily in adults with mild to moderate disease. Limited experience is available for younger children. Pharmacokinetic studies of atovaquone show that a dose of 30 mg/kg/day PO in two divided doses for children 0-3 months of age and older than 2 years of age is adequate and safe; a dose of 45 mg/kg/day PO in two divided doses is needed for children between 4 months and 2 years of age. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine. The combination of caspofungin and TMP-SMX is also being assessed as a treatment for *Pneumocystis* pneumonia and may help control inflammation in some patients.

Some studies in adults suggest that administration of **corticosteroids as adjunctive therapy to suppress the inflammatory response** increases the chances for survival in moderate and severe cases of *P. jirovecii* pneumonia. The recommended regimen of corticosteroids for adolescents older than 13 years of age and for adults is oral prednisone, 80 mg/day PO in two divided doses on days 1-5, 40 mg/day PO once daily on days 6-10, and 20 mg/day PO once daily on days 11-21. A reasonable regimen for children is oral prednisone, 2 mg/kg/day for the first 7-10 days, followed by a tapering regimen for the next 10-14 days.

SUPPORTIVE CARE

Basic supportive care is dictated by the condition of the patient, with careful attention to maintain appropriate hydration and oxygenation. Only 5–10% of patients with AIDS require mechanical ventilation compared with 50–60% of patients without AIDS, consistent with the hypothesis that the patient's ability to mount an immune/inflammatory response correlates with severity and outcome of *Pneumocystis* pneumonia. There are anecdotal reports of giving surfactant to children with severe *P. jirovecii* pneumonia, although the use of surfactant to treat adult-type respiratory distress syndrome is controversial.

COMPLICATIONS

Most complications occur as adverse events associated with the treatment drugs or as a consequence of mechanical ventilation. The most severe pulmonary complication of *P. jirovecii* pneumonia is adult-type respiratory distress syndrome. Rarely, *P. jirovecii* infection affects extrapulmonary sites (e.g., retina, spleen, and bone marrow), but such infections are usually not symptomatic and also respond to treatment.

PROGNOSIS

Without treatment, *P. jirovecii* pneumonitis is fatal in almost all immunocompromised hosts within 3-4 weeks of onset. The mortality rate varies with patient population and is related to inflammatory response rather than organism burden. Patients with AIDS have a mortality rate of 5–10%, and patients with other diseases such as malignancies have mortality rates as high as 20–25%. Patients who require mechanical ventilation have mortality rates of 60–90%. Patients remain at risk for *P. jirovecii* pneumonia as long as they are immunocompromised. Continuous prophylaxis should be initiated or reinstituted at the end of therapy for patients with AIDS (see Chapter 322).

PREVENTION

Patients at high risk for *P. jirovecii* pneumonia should be placed on chemoprophylaxis. Prophylaxis in infants born to HIV-infected mothers and for HIV-infected infants and children is based on age and CD4 cell counts (see Chapter 322). Because CD4 counts fluctuate rapidly during the first year of life, infants born to HIV-infected mothers should be placed on prophylaxis during the first year of life until HIV infection is ruled out. Patients with severe combined immunodeficiency disease, patients receiving intensive immunosuppressive therapy for cancer or other diseases, and organ transplant recipients are also candidates for prophylaxis. **TMP-SMX (5 mg/kg TMP and 25 mg SMX/kg PO once daily or divided into two doses daily) is the drug of choice and may be given for 3 consecutive days each week or, alternatively, each day**. Alternatives for prophylaxis include **dapsone** (2 mg/kg/day PO, maximum: 100 mg/dose; or 4 mg/kg PO once weekly, maximum: 200 mg/dose), **atovaquone** (30 mg/kg/day PO for infants 1-3 months and ≥24 months of age; 45 mg/kg/day for infants and toddlers 4-23 months of age), and **aerosolized pentamidine** (300 mg/mo by Respirgard II nebulizer), but all of these agents are inferior to TMP-SMX. Finally, limited clinical experience suggests that pentamidine can be given intravenously once monthly to prevent *P. jirovecii* pneumonia. Prophylaxis must be continued as long as the patient remains immunocompromised. Some patients with AIDS who reconstitute adequate immunity during highly active antiretroviral therapy may have prophylaxis withdrawn. Recent animal studies suggest that vaccines may be effective at preventing *Pneumocystis* pneumonia in immunocompromised hosts, but to date none have been tested in humans.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 291

Other Pathogenic Fungi

William J. Steinbach

Less common fungi that were once innocent or only contaminants are now emerging as lethal pathogens in a world of increasingly immunocompromised patients. Although there are reports of countless previously considered nonpathogenic fungi infecting severely immunocompromised patients, this chapter focuses on the most common and relevant miscellaneous fungi causing disease.

PHAEOHYPHOMYCOSIS: *CLADOPHIALOPHORA BANTIANA, BIPOLARIS* SPP., AND OTHERS

Phaeohyphomycosis is a heterogeneous group of fungal species commonly found in the soil and characterized by dematiaceous (darkly pigmented brown or black) hyphal forms in tissue. This staining can help distinguish between *Aspergillus* infections, and hyphae often appear more fragmented that seen with *Aspergillus* infections. The characteristic color of the hyphae is related to the presence of melanin in the fungal cell wall, which likely plays a role in fungal pathogenesis. *Phaeo* comes from Greek, meaning "dark," and has been commonly used to describe infections with these fungi as phaeohyphomycosis. It has been suggested that the term *dematiaceous* is not appropriate given its etymologic derivation from the Greek *deme*, meaning "bundle," although it has become fairly entrenched in medical mycologic literature. The term *melanized* is also used, given its specific meaning.

Phaeohyphomycosis has been attributed to more than 150 species of fungi. Among the most prevalent causes of human infection are *Alternaria alternata*, *Acrophialophora fusispora*, *Aureobasidium pullulans*, *Bipolaris* spp., *Curvularia* spp., *Chaetomium* spp., *Cladophialophora*

bantiana, *Exserohilum*, *Fonsecaea*, *Hortaea werneckii*, *Neoscytalidium dimidiatum*, *Verruconis gallopava* (previously *Ochroconis gallopava*), *Phaeoacremonium*, *Phoma*, *Pyrenochaeta*, *Rhinocladiella*, *Veronaea botryosa*, *Wangiella dermatitidis* (previously *Exophiala dermatitidis*), and *Phialophora* spp.

In the multicenter CDC-funded epidemiologic TRANSNET study, 26 cases of phaeohyphomycosis were identified in hematopoietic stem cell transplant (HSCT) recipients analyzed, representing 2.6% of all reported invasive fungal disease in the HSCT cohort. The median time from transplant to diagnosis was 100 days, and 92% of cases were seen in allogeneic HSCT recipients. The mortality rate was 42% at 90 days after diagnosis. There was a higher incidence of phaeohyphomycosis noted from transplant centers in the southern United States versus other regions of the country. Phaeohyphomycosis also represented 2.5% of the overall number of invasive fungal disease in solid organ transplant (SOT) recipients in the TRANSNET study. The median time from transplant to diagnosis was much longer at 18 months, and 53% of cases were specifically diagnosed in lung transplant recipients. There was a 10% mortality rate at 90 days after diagnosis. Overall, cutaneous disease was more common in SOT recipients, whereas pulmonary disease was more common in hematopoietic stem cell transplant recipients. In this series, bloodstream and central nervous system (CNS) infections were seen only in hematopoietic stem cell transplant recipients.

Historically, organisms causing phaeohyphomycosis have been largely associated with cutaneous and subcutaneous infections occurring mostly in immunocompetent persons in tropical and subtropical regions. However, they have emerged with increasing frequency as causes of invasive disease in immunocompromised persons worldwide. Infections can manifest as a range of clinical entities, including localized cutaneous infection and subcutaneous nodules, mycetomas (localized infections involving the cutaneous and subcutaneous tissue, fascia, and bone, often of the lower extremities, and characterized by mycotic granules), chromoblastomycosis (sclerotic bodies in tissues usually seen in tropical regions), keratitis, pulmonary infections, localized deep infections, cerebral abscesses, disseminated infection, allergic fungal sinusitis, and allergic bronchopulmonary mycosis.

C. bantiana is the etiology for the majority of CNS phaeohyphomycosis, including patients that may have no apparent immunosuppression. CNS disease commonly presents with a headache and a focal neurologic deficit, frequently a hemiparesis, or seizures. The most common CNS manifestation is a solitary brain abscess. Though the pathophysiology is not well understood, these are thought to originate via hematogenous dissemination from occult pulmonary or cutaneous foci.

Diagnosis of phaeohyphomycosis relies on pathologic examination of cultures and biopsies, often with expert gross and microscopic examination required. There are no serologic or antigen tests to detect these fungi in blood or tissue, and PCR is in its infancy for this group of organisms. Almost all allergic disease and eosinophilia is caused by either *Bipolaris* spp. or *Curvularia* spp.

Treatment

Treatment recommendations for the rare molds causing phaeohyphomycosis are unfortunately primarily based on in vitro susceptibility data, case reports, and expert opinion. Recommendations can be found in European and Australian guidelines and the American Transplant Society Infectious Diseases Community of Practice Guidelines. European antifungal treatment guidelines highlight the sparse data on preferred therapy, including in vitro data, limited animal model studies, and expert opinion. **There are no clearly defined standard therapies, but the guideline panel generally recommended voriconazole, posaconazole, or itraconazole, because those agents demonstrate the most consistent in vitro antifungal activity against this group of fungi. Specifically, voriconazole is likely the best for CNS infections because of its excellent CNS penetration. For invasive infections, surgery is crucial to the overall treatment.** For phaeohyphomycosis, there is substantial variability in susceptibility both between and within species of a given genus, making correct species identification and susceptibility testing especially critical in guiding therapy for these infections. Combination therapy is suggested in some circumstances for disseminated or CNS infection and for organisms for which no single agent has predictably favorable activity.

Therapy for CNS infections with *C. bantiana* is often unsuccessful despite susceptibility of this organism to several antifungal agents, and it is unclear whether antifungal therapy alters outcome, because survival without complete abscess resection is exceedingly rare. Some experts recommend combination therapy, particularly for cases in which the abscess cannot be completely resected. Surgery is particularly important for brain abscesses secondary to *C. bantiana* infection; regardless of host immune status and antifungal therapy, survival is extremely poor if the abscess is not completely resected. If an invasive mold infection is associated with an intravenous catheter or a peritoneal dialysis catheter, removal of the catheter is recommended.

Including only culture-positive cases of CNS phaeohyphomycosis, the survival rate for this infection is only 35%. A series of 30 cases revealed those patients with single, encapsulated CNS lesions did much better than those with multifocal disease. However, no patient who did not undergo surgery survived. Whether patients underwent neurosurgery alone or with antifungal therapy, the most important factor for cure was resectability of the lesion; antifungal therapy itself was not associated with improved survival.

HYALOHYPHOMYCOSIS: *FUSARIUM* AND *SCEDOSPORIUM* SPP. AND OTHERS

In contrast to phaeohyphomycosis, hyalohyphomycosis refers to infections caused by hyaline (colorless, nonpigmented, nonmelanized) septate fungal hyphae. The major hyalohyphomycotic pathogens are *Fusarium* spp., *Scedosporium* spp., *Paecilomyces* spp., *Trichoderma* spp., *Acremonium* spp., *Scopulariopsis* spp., and *Purpureocillium* spp. These species are often misidentified as *Aspergillus* spp., but they can be differentiated by their conidia and phialide morphologies. This section focuses on *Fusarium* and *Scedosporium* spp., which are usually the third and fourth most common invasive mold diseases in immunocompromised hosts, after invasive aspergillosis and mucormycosis.

The majority of human cases of fusariosis are caused by members of the *Fusarium solani, Fusarium oxysporum,* and *Fusarium fujikuroi* spp. complexes, with the *F. solani* spp. complex demonstrating greater pathogenicity. Nomenclature of organisms causing scedosporiosis can be confusing and has undergone recent changes. The genus name *Pseudallescheria* applies to the sexual state (teleomorph) whereas *Scedosporium* applies to the asexual state (anamorph) of these organisms. *Scedosporium apiospermum* was once thought to be the anamorph of *Pseudallescheria boydii*, but these organisms are now known to be distinct species. The *S. apiospermum* spp. complex encompasses *S. apiospermum*, *Scedosporium boydii*, *Scedosporium aurantiacum*, *Scedosporium dehoogii*, and *Scedosporium minutispora*. The organism formerly known as *Scedosporium prolificans* is now renamed *Lomentospora prolificans* and is phylogenetically distinct from the *Scedosporium* spp.

In addition to the usual airborne and cutaneous inoculation routes of acquisition common to other invasive molds, *Fusarium* can be transmitted via contaminated water sources (e.g., shower heads) and can cause infection associated with intravenous catheters. Both *Fusarium* and *Scedosporium/Lomentospora* spp. can cause infection in immunocompetent hosts, primarily localized infections such as keratitis or onychomycosis. In immunocompromised patients, *Fusarium* can disseminate from initially localized infections such as onychomycosis or intertrigo. The major predisposing factors for invasive disease are profound and prolonged neutropenia and severe cell-mediated immunodeficiency.

Among HSCT recipients in the TRANSNET study, fusariosis accounted for 3% of invasive fungal disease. Identified risk factors for fusariosis in HSCT recipients include history of cytomegalovirus infection, receipt of an umbilical cord blood transplant (compared with other stem cell sources), receipt of antithymocyte globulin, and

hyperglycemia. Risk factors specific to development of fusariosis beyond day 40 after transplant include graft-versus-host disease and prior invasive mold disease. Scedosporiosis is less common among HSCT recipients compared with fusariosis, with only 16 cases identified in the TRANSNET study compared with 31 cases of fusariosis and 77 cases of mucormycosis. Among 1208 invasive fungal infections in the TRANSNET study of SOT recipients, there were 6 cases of fusariosis and 11 cases of scedosporiasis, compared with 28 cases of mucormycosis. In a literature review of *L. prolificans* cases, SOT recipients constituted 8.6% of cases. Scedosporiasis is most common among lung transplant recipients, in whom colonization of the airways can occur pretransplantation (particularly in patients with cystic fibrosis), or posttransplantation, and may progress to invasive infection. Among patients undergoing therapy for cancer, fusariosis primarily occurs in those with hematologic malignancy, especially acute myelogenous leukemia. In a single center study of 44 cases, the most commonly identified risk factors for fusariosis in patients with hematologic malignancy were active leukemia, prolonged and profound neutropenia, and high-dose corticosteroid exposure.

Clinical Presentations

The most common sites of invasive fusariosis in immunocompromised persons are the skin (60–80% of cases), lungs (50–80% of cases), and sinuses (20–30% of cases). *Fusarium* can develop yeastlike adventitious sporulation within infected tissue, which facilitates dissemination, seen in 70% of cases. Unlike other molds that infrequently cause detectable fungemia and are difficult to recover in standard blood culture media, blood cultures are positive for *Fusarium* in 40–50% of cases.

Radiographic series comparing findings of pulmonary fusariosis to those of invasive aspergillosis and mucormycosis note that the halo sign (a nodule surrounded by ground glass opacity) is frequently absent in cases of fusariosis. Cutaneous lesions of invasive fusariosis are distinctive, consisting of painful, circular macules or papules, usually with central necrosis and surrounding erythema. Appearance of cutaneous lesions in invasive fusariosis is usually secondary to hematogenous dissemination to the skin, rather than direct inoculation into the skin.

Invasive disease caused by *S. apiospermum* spp. complex most frequently involves the skin, lungs, and CNS. CNS disease develops in the context of hematogenous dissemination and can manifest as brain abscess(es) or meningoencephalitis. Other manifestations include sinusitis and endogenous endophthalmitis. Skin lesions of *S. apiospermum* spp. complex can manifest as nodules, erythematous or violaceous papules, or bullae, which may develop necrosis. They are usually secondary to hematogenous dissemination rather than primary cutaneous lesions from direct inoculation of the skin. Lymphangitic or sporotrichoid spreading patterns have been described. Blood cultures are positive in approximately 30% of cases of invasive infection with *S. apiospermum* spp. complex. Similar manifestations are seen in invasive *L. prolificans* infections, but the propensity to disseminate is higher and positive blood cultures are reported in over 50% of cases. Hematogenous dissemination of *L. prolificans* to the CNS is common.

Diagnosis

Diagnosis of fusariosis or scedosporiasis requires isolation and identification of the causative organism from the affected site(s). The causative organisms have thin septate hyphae with acute angle branching; they are not morphologically distinguishable from *Aspergillus* when examined in tissue. Culture is necessary for definitive identification of these organisms, though distinguishing between *Fusarium* spp. complexes may be difficult using conventional methods. Organisms causing fusariosis and scedosporiosis can be detected in conventional blood cultures; however, they may be initially reported out as "yeast" because of the appearance of conidia produced by adventitious sporulation.

The *Aspergillus* serum galactomannan assay is positive in approximately half of patients with invasive fusariosis and detection of serum galactomannan above threshold has been shown to precede diagnosis of invasive fusariosis in a high prevalence setting.

Treatment

Treatment recommendations for fusariosis and scedosporiasis are provided in European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) joint guidelines, and in Australian consensus guidelines. The optimal therapy is unknown; recommendations are primarily based on case reports, clinical experience, and in vitro data, given a lack of clinical trials for these rare diseases. **The ESCMID/ECMM guidelines recommend voriconazole or a lipid-based amphotericin B formulation for treatment of fusariosis, with preference for voriconazole.** Australian guidelines do not state a preference for either agent on the basis of inadequate data. Voriconazole treatment has been associated with higher treatment responses and improved survival, though these should be interpreted with caution because of potential confounding by earlier diagnosis or other interventions.

Because in vitro susceptibility of *Fusarium* isolates to both voriconazole and amphotericin B varies widely, some experts routinely use combination therapy with voriconazole and lipid-based amphotericin B to ensure that at least one agent is active. Some reports describe successful combination therapy with terbinafine and either liposomal amphotericin B or voriconazole, and in vitro data show synergy between terbinafine and voriconazole. Isavuconazole has been studied in few adult cases; based on in vitro susceptibilities it appears to be less active than voriconazole. *Fusarium* spp. are resistant to the echinocandins and to itraconazole.

The activity of antifungal agents against members of the *S. apiospermum* spp. complex is variable, and there are species-based differences in susceptibility pattern. Amphotericin B–based therapy is not recommended due to in vitro resistance and poor clinical responses. Voriconazole is the most active agent and the recommended first-line therapy. In a large observational study, the response rate to voriconazole therapy for *S. apiospermum* infections was 66%. The echinocandins, itraconazole, and posaconazole have variable activity. Isavuconazole is active in vitro but so far has been studied in only a handful of adults with scedosporiasis, limiting conclusions about its utility.

L. prolificans is highly resistant to all antifungal agents currently available. Successful treatment of infections caused by this organism depends on reversal of predisposing conditions and aggressive surgical debridement. Voriconazole is the antifungal with best demonstrated activity, but minimum inhibitory concentrations tend to be high and clinical responses to voriconazole therapy are suboptimal. Combination therapy is typically used, including voriconazole and other agents; successful outcomes have been reported with voriconazole or posaconazole and terbinafine or voriconazole with an echinocandin. Australian guidelines recommend the combination of voriconazole with terbinafine. However, terbinafine is highly protein-bound with distribution primarily to skin and adipose tissue, leading some experts to doubt its utility in treating systemic fungal infections. There have been reports of combination therapy including miltefosine, which is typically used in the treatment of leishmaniasis but demonstrates some in vitro antifungal activity against *L. prolificans*. It is important to recognize that publication bias likely has an impact on reporting of outcomes and no particular antifungal regimen has convincing evidence to support efficacy against *L. prolificans*.

Surgical debridement of infected and necrotic tissue is recommended to facilitate cure, particularly in *L. prolificans* infection, for which surgery and immune reconstitution are the primary effective therapies. Removal of intravenous catheters is recommended for catheter-associated fusariosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 13
Viral Infections

Chapter 292
Principles of Antiviral Therapy
Mark R. Schleiss

Antiviral chemotherapy typically requires a delicate balance between targeting critical steps in viral replication without interfering with host cellular function. Because viruses require cellular functions to complete replication, many antiviral agents exert significant host cellular toxicity, a limitation that has hindered antiviral drug development. In spite of this limitation, a number of agents are licensed for use against viruses, particularly herpesviruses, respiratory viruses, and hepatitis viruses (Table 292.1).

In making the decision to commence antiviral drugs, it is important for the clinician to obtain appropriate diagnostic specimens, which can help clarify the antiviral of choice. The choice of a specific antiviral is based on the recommended agent of choice for a particular clinical condition, pharmacokinetics, toxicities, cost, and the potential for development of resistance (Table 292.2). Intercurrent conditions in the patient, such as renal insufficiency, should also be considered. Clinicians must monitor antiviral therapy closely for adverse events or toxicities, both anticipated and unanticipated.

In vitro sensitivity testing of virus isolates to antiviral compounds usually involves a complex tissue culture system. The potency of an antiviral is determined by the **50% inhibitory dose (ID_{50}),** which is the antiviral concentration required to inhibit the growth in cell culture of a standardized viral inoculum by 50%. Because of the complexity of these assays, the results vary widely, and the actual relationship between antiviral sensitivity testing and antiviral therapy outcomes is sometimes unclear. Because these assays are often not readily available and take considerable time to complete, **genotypic analysis** for antiviral susceptibility is increasingly being offered. Such assays may be useful for patients on long-term antiviral therapy.

Clinical context is essential in making decisions about antiviral treatment, along with knowledge of a patient's immune status. For example, antiviral treatment is rarely if ever indicated in an immunocompetent child shedding cytomegalovirus (CMV) but may be lifesaving when administered to an immunocompromised solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) patient. Antivirals can be used with a variety of clinical goals in mind. Antivirals can be used for **treatment** of active end-organ disease, as **prophylaxis** to prevent viral infection or disease, or as **preemptive therapy** aimed at reducing risk of progression to disease (i.e., a positive signal indicating viral replication but in the absence of clinical evidence of end-organ disease). In preemptive therapy, a patient will usually have a positive signal for polymerase chain reaction–based identification of viral nucleic acids in a clinical sample (blood or body fluid) but have no symptoms. However, SOT and HSCT patients are at high risk of developing disease in this setting (particularly due to CMV infection), a scenario that warrants preemptive treatment with an antiviral agent. In contrast, prophylaxis is administered to seropositive patients who are at risk to reactivate latent viral infection but do not yet have evidence of active viral replication or shedding.

A fundamental concept important in the understanding of the mechanism of action of most antivirals is that viruses must use host cell components to replicate. Thus mechanisms of action for antiviral compounds must be selective to virus-specific functions whenever possible, and antiviral agents may have significant toxicities to the host if these compounds impact cellular physiology. Some of the more commonly targeted sites of action for antiviral agents include viral entry, absorption, penetration, and uncoating (amantadine, rimantadine); transcription or replication of the viral genome (acyclovir, valacyclovir, cidofovir, famciclovir, letermovir, maribavir, penciclovir, foscarnet, ganciclovir, valganciclovir, ribavirin, trifluridine); viral protein synthesis (interferons [IFNs]) or protein modification (protease inhibitors); and viral assembly, release, or deaggregation (baloxavir, oseltamivir, peramivir, zanamivir, IFNs).

An understudied and underappreciated issue in antiviral therapy is emergence of resistance, particularly in the setting of high viral load, high intrinsic viral mutation rate, and prolonged or repeated courses of antiviral therapy. Resistant viruses are more likely to develop or be selected for in immunocompromised patients because these patients are more likely to have multiple or long-term exposures to an antiviral agent.

ANTIVIRALS USED FOR HERPESVIRUSES

The herpesviruses are important pediatric pathogens, particularly in newborns and immunocompromised children. Most of the licensed antivirals are nucleoside analogs that inhibit viral DNA polymerase, inducing premature chain termination during viral DNA synthesis in infected cells.

Acyclovir

Acyclovir is a safe and effective therapy for herpes simplex virus (HSV) infections. The favorable safety profile of acyclovir derives from its requirement for activation to its active form via phosphorylation by a viral enzyme, thymidine kinase (TK). Thus acyclovir can be activated only in cells already infected with HSV that express the viral TK enzyme, a strategy that maximizes selectivity and reduces the potential for cellular toxicity in uninfected cells. Acyclovir is most active against HSV and is also active against varicella-zoster virus (VZV); therapy is indicated for infections with these viruses in a variety of clinical settings. Activity of acyclovir against CMV is less pronounced, and activity against Epstein-Barr virus is minimal, both in vitro and clinically. Therefore, under most circumstances, acyclovir should not be used to treat CMV or Epstein-Barr virus infections.

The biggest impact of acyclovir in clinical practice is in the treatment of primary and recurrent genital HSV infections. Oral nucleoside therapy plays an important role in the management of acute primary genital herpes, treatment of episodic symptomatic reactivations, and prophylaxis against reactivation. Acyclovir is also indicated in the management of suspected or proven HSV encephalitis in patients of all ages and for treatment of neonatal HSV infection, with or without central nervous system (CNS) involvement. With respect to neonatal HSV infection, the routine empirical use of acyclovir against presumptive or possible HSV infection in infants admitted with fever and no focus in the first 4 weeks of life is controversial. Acyclovir should be used routinely in infants born to women with risk factors for primary genital herpes or infants presenting with any combination of vesicular lesions, seizures, meningoencephalitis, hepatitis, pneumonia, or disseminated intravascular coagulation. Some experts advocate the initiation of acyclovir in all febrile neonates. Other experts have argued that a selective approach based on the history and physical examination is more appropriate when making decisions about the use of acyclovir in febrile infants. Given the safety of the drug, prudence would dictate the use of acyclovir in such patients if HSV infection cannot be excluded.

Acyclovir is indicated for the treatment of primary HSV gingivostomatitis and for primary genital HSV infection. Long-term suppressive therapy for genital HSV and for recurrent oropharyngeal infections (herpes labialis) is also effective. Acyclovir is also recommended for

Table 292.1 Currently Licensed Antiviral Drugs

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION/COMMENTS
Acyclovir	Zovirax	Inhibits viral DNA polymerase
Adefovir	Hepsera	Nucleotide reverse transcriptase inhibitor
Amantadine*	Symmetrel	Blocks M2 protein ion channel
Baloxavir	Xofluza	Inhibits polymerase acidic endonuclease, blocking viral replication
BMS-791325	Beclabuvir	Inhibitor of HCV NS5B Evaluated in combination with asunaprevir and daclatasvir; active against HCV genotype 1
Boceprevir†	Victrelis	Inhibitor of HCV NS3 serine protease Active against HCV genotype 1
Cidofovir	Vistide	Inhibits viral DNA polymerase
Daclatasvir	Daklinza	Inhibitor of HCV NS5A Used in varying combinations with sofosbuvir, ribavirin, and interferon
Dasabuvir	Exviera	Inhibitor of HCV NS5B Used together with the combination medication ombitasvir/paritaprevir/ritonavir (Viekira Pak) Activity limited to HCV genotype 1
Elbasvir	(Zepatier)	Inhibitor of HCV NS5A Used in combination with the NS3/4A protease inhibitor grazoprevir under the trade name Zepatier, either with or without ribavirin
Entecavir	Baraclude	Nucleoside reverse transcriptase inhibitor Active against HBV
Famciclovir†	Generic	Inhibits viral DNA polymerase
Fomivirsen‡	Vitravene	Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism
Foscarnet	Foscavir	Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site
Ganciclovir	Cytovene	Inhibits viral DNA polymerase
Grazoprevir	Zepatier	Inhibitor of HCV NS3-4A serine protease Used in combination with elbasvir under the trade name Zepatier, either with or without ribavirin
Idoxuridine Ophthalmic†	Herplex	Inhibits viral DNA polymerase
Interferon-α	Intron-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1)	Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components
Interferon-α2b plus ribavirin	Rebetron	Not established
Lamivudine (3TC)	Epivir	Inhibits viral DNA polymerase and reverse transcriptase; active against HBV With dolutegravir, Dovato; with tenofovir, Delstrigo; with zidovudine, Combivir; with abacavir and dolutegravir, Triumeq.
Ledipasvir	(with Sofosbuvir: Harvoni)	Inhibitor of HCV NS5A
Letermovir	Prevymis	Prophylaxis against CMV following HSCT
Maribavir	Livtencity	Treatment of refractory CMV disease when treated with conventional antiviral therapy
Molnupiravir	Lagevrio	Treatment of SARS-CoV-2 Induces viral RNA mutations during replication
Nirmatrelvir/ritonavir	Paxlovid	Treatment of SARS-CoV-2 Protease inhibitor
Ombitasvir	(Viekira Pak)	Inhibitor of HCV NS5A Used in combination with paritaprevir, ritonavir and dasabuvir in Viekira Pak Active against HCV genotype 1

Continued

Table 292.1 Currently Licensed Antiviral Drugs—cont'd

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION/COMMENTS
Oseltamivir	Tamiflu	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
Paritaprevir	(Viekira Pak) (Technivie†/Viekirax)	Inhibitor of HCV NS3-4A serine protease Used in combination with ombitasvir, ritonavir and dasabuvir (Viekira Pak), or in combination with ombitasvir and ritonavir (Technivie†/Viekirax)
Pegylated interferon	PEG-Intron (α2b), Pegasys (α2a)	Same as interferon
Penciclovir (topical)	Denavir	Inhibits viral DNA polymerase
Peramivir	Rapivab	Neuraminidase inhibitor
Remdesivir	Veklury	Treatment of SARS-CoV-2 Inhibits viral RNA polymerase
Ribavirin	Virazole, Rebetol, Copegus	Interference with viral messenger RNA
Rimantadine*	Flumadine	Blocks M2 protein ion channel
Simeprevir†	Olysio	Inhibitor of HCV NS3-4A serine protease Active against genotype 1 ± genotype 4 Used in combinations with sofosbuvir or ribavirin and pegylated interferon-alfa†
Sofosbuvir	(Harvoni)	Inhibitor of HCV NS5B Used in combination with ledipasvir (Harvoni) Approved in children >6 years of age and >17 kg
Telaprevir†	Incivek Incivo VX-950	Inhibitor of HCV NS3-4A serine protease Active against HCV genotype 1 No longer available in United States
Telbivudine†	Tyzeka	Interferes with HBV DNA replication No longer available in United States
Tenofovir	Viread Vemlidy	Nucleoside reverse transcriptase inhibitor Active against HBV
Trifluridine	Viroptic	Inhibits viral DNA polymerase
Valacyclovir	Valtrex	Same as acyclovir
Valganciclovir	Valcyte	Same as ganciclovir
Velpatasvir	(Epclusa, Sofosvel, Velpanat)	Inhibitor of HCV NS5A Used in combination with sofosbuvir (Epclusa, Sofosvel, Velpanat) Active against all 6 HCV genotypes
Vidarabine	Ara-A	Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)
Zanamivir	Relenza	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
FDA-APPROVED COMBINATION THERAPIES WITH INTERFERONS		
Interferon-α2b + ribavirin	Rebetron (Intron-A plus Rebetol† [ribavirin])	Discontinuation of Rebetol announced by FDA in 2019
Interferon-α2a + ribavirin	Roferon-A† + ribavirin	Discontinuation of Roferon announced by manufacturer in 2020
Pegylated interferon-α2b + ribavirin (3 yr and older)	PEG-Intron PegIntron Sylatron ViraferonPeg PEG-Intron/Rebetol (with ribavirin)	Indicated for chronic hepatitis C
Pegylated interferon-α2a ± ribavirin (5 yr and older)	Pegasys + Copegus	Approved for the treatment of chronic hepatitis C (in combination with ribavirin) and treatment of chronic hepatitis B (can be used alone) Has been used in the treatment of mycosis fungoides (a T-cell lymphoma)

*No longer recommended by Centers for Disease Control and Prevention for treatment of influenza.
†No longer marketed in United States.
‡No longer available.

Table 292.2 Antiviral Therapies for Non-HIV Clinical Conditions*

*VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Influenza A and B	Treatment	Oseltamivir (>2 wk old)	Zanamivir (>7 yr old) Peramivir (>2 yr old) Baloxavir (>12 yr old)
	Prophylaxis	Oseltamivir (>3 mo old)	Zanamivir (>5 yr old)
Respiratory syncytial virus	Bronchiolitis or pneumonia in high-risk host	Ribavirin aerosol	
COVID-19	Pneumonia MIS-C†	Remdesivir	Nirmatrelvir-ritonavir Molnupiravir
Adenovirus	In immunocompromised patients: Pneumonia Viremia Nephritis Hemorrhagic cystitis	Cidofovir	
CMV	Congenital CMV infection (symptomatic disease)	Valganciclovir (long-term oral valganciclovir may improve developmental and hearing outcomes)	Ganciclovir
	Retinitis in AIDS patients	Valganciclovir	Ganciclovir Cidofovir Foscarnet Ganciclovir ocular insert
	Pneumonitis, colitis; esophagitis in immunocompromised patients	Ganciclovir (IV)	Foscarnet Cidofovir Valganciclovir Maribavir
	Prophylaxis for HSCT or SOT	Acyclovir (high-dose; oral)	Valganciclovir Letermovir
HSV	Neonatal herpes	Acyclovir (IV)	
	Suppressive therapy following neonatal herpes	Acyclovir (PO)	
	HSV encephalitis	Acyclovir (IV)	
	HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV) Valacyclovir (PO)
	First episode genital infection	Acyclovir (PO)	Valacyclovir
			Acyclovir (IV) (severe disease)
	Recurrent genital herpes	Acyclovir (PO)	Valacyclovir
	Suppression of genital herpes	Acyclovir (PO)	Valacyclovir
	Cutaneous HSV (whitlow, herpes gladiatorum)	Acyclovir (PO)	Penciclovir (topical)
	Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
	Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
	Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
	HSV prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir
	Acyclovir-resistant HSV	Foscarnet	Cidofovir
	Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine

Continued

Table 292.2 Antiviral Therapies for Non-HIV Clinical Conditions*—cont'd

*VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Varicella-zoster virus	Chickenpox, healthy child	Supportive care	Acyclovir (PO)
	Chickenpox, immunocompromised child	Acyclovir (IV)	
	Zoster (not ophthalmic branch of trigeminal nerve), healthy child	Supportive care	Acyclovir (PO)
	Zoster (ophthalmic branch of trigeminal nerve), healthy child	Acyclovir (IV)	
	Zoster, immunocompromised child	Acyclovir (IV)	Valacyclovir

*For antiviral agents for hepatitis B and hepatitis C, see Table 292.1.
†For MIS-C, adjunctive therapies also include steroids, immunomodulatory therapy; see Chapter 449.1.
CMV, Cytomegalovirus; HSV, herpes simplex virus.

less commonly encountered HSV infections, including herpetic whitlow, eczema herpeticum, and herpes gladiatorum. In addition, acyclovir is commonly used for prophylaxis against HSV reactivation in SOT and HSCT patients. Severe end-organ HSV disease, including disseminated infection, is occasionally encountered in immunocompromised or pregnant patients, representing another clinical scenario in which acyclovir therapy is warranted.

Acyclovir modifies the course of primary VZV infection, although the effect is modest. Acyclovir or another nucleoside analog should always be used in localized or disseminated VZV infections in immunocompromised patients. Primary VZV infection in pregnancy is another setting in which acyclovir is indicated; this is a high-risk scenario and can be associated with a substantial risk of maternal mortality, particularly if pneumonia is present.

Acyclovir is available in topical (5% ointment), parenteral, and oral formulations, including an oral suspension formulation for pediatric use. Topical therapy has little role in pediatric practice and should be avoided in favor of alternative modes of delivery, particularly in infants with vesicular lesions compatible with herpetic infection, where topical therapy should never be used. The bioavailability of oral formulations is modest, with only 15–30% of the oral dose being absorbed. There is widespread tissue distribution after systemic administration, and high concentrations of drug are achieved in the kidneys, lungs, liver, myocardium, and skin vesicles. Cerebrospinal fluid concentrations are approximately 50% of plasma concentrations. Acyclovir crosses the placenta, and breast milk concentrations are approximately 3 times plasma concentrations, although there are no data on efficacy of in utero therapy or impact of acyclovir therapy on nursing infants. Acyclovir therapy in a nursing mother is not a contraindication to breastfeeding. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Hemodialysis also eliminates acyclovir.

Acyclovir has an exceptional safety profile. Toxicity is observed typically only in exceptional circumstances: for example, if administered by rapid infusion to a dehydrated patient or a patient with underlying renal insufficiency, acyclovir can crystallize in renal tubules and produce a reversible obstructive uropathy. High doses of acyclovir are associated with neurotoxicity, and prolonged use can cause neutropenia. The favorable safety profile of acyclovir is underscored by recent studies of its safe use during pregnancy, and suppressive therapy in pregnant women with histories of recurrent genital HSV infection, typically with valacyclovir (see later), has become standard of care among many obstetricians. One uncommon but important complication of long-term use of acyclovir is the selection for acyclovir-resistant HSV strains, which usually occurs from pathogenic variants in the HSV *TK* gene. Resistance is rarely observed in pediatric practice but should be considered in any patient who has been on long-term antiviral therapy and who has an HSV or VZV infection that fails to clinically respond to acyclovir therapy.

Valacyclovir

Valacyclovir is the L-valyl ester of acyclovir and is rapidly converted to acyclovir after oral administration. This agent has a safety and activity profile similar to that of acyclovir but has a bioavailability of >50%, 3-5–fold greater than that of acyclovir. Plasma concentrations approach those observed with intravenous acyclovir. Valacyclovir is available only for oral administration. A suspension formulation is not commercially available, but an oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500-mg caplets for use in pediatric patients for whom a solid dosage form is not appropriate. Suppressive therapy with valacyclovir is commonly prescribed in the second and third trimesters of pregnancy in women who have a clinical history of recurrent genital herpes. *It is important to be aware that perinatal transmission of HSV can occur, leading to symptomatic disease in spite of maternal antenatal antiviral prophylaxis.* In such settings, the possibility of emergence of acyclovir-resistant virus should be considered.

Penciclovir and Famciclovir

Penciclovir is an acyclic nucleoside analog that, like acyclovir, inhibits the viral DNA polymerase after phosphorylation to its active form. Compared with acyclovir, penciclovir has a substantially longer intracellular half-life, which in theory can confer superior antiviral activity at the intracellular level; however, there is no evidence that this effect confers clinical superiority. Penciclovir is licensed only as a topical formulation (1% penciclovir cream), and this formulation is indicated for therapy of cutaneous HSV infections. Topical therapy for primary or recurrent herpes labialis or cutaneous HSV infection is an appropriate use of penciclovir in children older than 2 years of age.

Famciclovir is the prodrug formulation (diacetyl ester) of penciclovir. After oral administration, famciclovir is deacetylated to the parent drug, penciclovir. The efficacy of famciclovir for HSV and VZV infections appeared equivalent to that of acyclovir, although the pharmacokinetic profile was more favorable. As of 2016, the drug has been discontinued.

Ganciclovir and Valganciclovir

Ganciclovir is a nucleoside analog with structural similarity to that of acyclovir. Like acyclovir, ganciclovir must be phosphorylated for antiviral activity, which is targeted against the viral polymerase. The gene responsible for ganciclovir phosphorylation is not TK but rather the virally encoded UL97 phosphotransferase gene. Antiviral resistance in CMV can be observed with prolonged use of nucleoside antivirals, and resistance should be considered in patients on long-term therapy who appear to fail to respond clinically and virologically. Ganciclovir is broadly active against many herpesviruses, including HSV and VZV, but is most valuable for its activity against CMV. Ganciclovir was

the first antiviral agent licensed specifically to treat and prevent CMV infection. It is indicated for prophylaxis against and therapy of CMV infections in high-risk patients, including HIV-infected patients and SOT or HSCT recipients. Of particular importance is the use of ganciclovir in the management of CMV retinitis, a sight-threatening complication of HIV infection. Ganciclovir is also of benefit for newborns with symptomatic congenital CMV infection and may be of value in partially ameliorating the sensorineural hearing loss and developmental disabilities that are common complications of congenital CMV infection.

Ganciclovir is supplied in parenteral and oral (as the prodrug, valganciclovir) formulations. Ganciclovir ocular implants are also available for the management of CMV retinitis. The bioavailability of oral ganciclovir is poor, <10%, and therefore oral ganciclovir therapy has been supplanted by the oral prodrug valganciclovir, which is well absorbed from the gastrointestinal tract and quickly converted to ganciclovir by intestinal or hepatic metabolism. Bioavailability of ganciclovir (from valganciclovir) is approximately 60% from tablet and solution formulations. Significant concentrations are found in the aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue (enough to inhibit susceptible strains of CMV). Subretinal concentrations are comparable with plasma concentrations, but intravitreal concentrations are lower. Drug concentrations in the CNS range from 24% to 70% of plasma concentrations. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Dose reduction is proportional to the creatinine clearance. Hemodialysis efficiently eliminates ganciclovir, so administration of additional doses after dialysis is necessary.

Ganciclovir has several important toxicities. Reversible myelosuppression is the most important toxicity and commonly requires either discontinuation of therapy or the intercurrent administration of granulocyte colony–stimulating factor. There are also the theoretical risks of carcinogenicity and gonadal toxicity; although these effects have been observed in some animal models, they have never been observed in patients. The decision to administer ganciclovir to a pediatric patient is complex and should be made in consultation with a pediatric infectious disease specialist.

Foscarnet

Foscarnet has a unique profile, insofar as it is not a nucleoside analog but rather a pyrophosphate analog. The drug has broad activity against most herpesviruses. Like the nucleoside analogs, foscarnet inhibits viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase to exert its antiviral effect and therefore retains activity against strains of HSV and CMV that are resistant to nucleoside analogs. Its clinical utility is as a second-line agent for management of CMV infections in high-risk patients who cannot tolerate ganciclovir and as an alternative for patients with persistent or refractory HSV, CMV, or VZV disease with suspected or documented antiviral drug resistance.

Foscarnet is available only as a parenteral formulation and is a toxic agent that must be administered cautiously. Nephrotoxicity is common, and reversible renal insufficiency is often observed, as evidenced by an increase in serum creatinine. Abnormalities in calcium and phosphorus homeostasis are common, and electrolytes and renal function must be monitored carefully during treatment.

Cidofovir

Cidofovir is an acyclic nucleotide analog that requires phosphorylation to its active form, cidofovir diphosphate, to exert its antiviral effect. Analogous to penciclovir, it has an extended intracellular half-life that contributes to its prolonged antiviral activity. Cidofovir is active against HSV, VZV, and CMV. In contrast to most of the other agents with activity against herpesviruses, cidofovir also exhibits broad-spectrum activity against other DNA viruses, most notably the poxviruses. Cidofovir has activity against the BK virus, a polyomavirus, and therapy may be warranted in some settings of BK reactivation after HSCT and SOT. Cidofovir is useful in the management of adenovirus infections in the immunocompromised host. Cidofovir is also useful in the management of CMV disease caused by strains with documented ganciclovir resistance.

Cidofovir is administered intravenously and is cleared renally by tubular secretion. Extensive prehydration and co-administration of probenecid are recommended. Nephrotoxicity is commonly encountered, even with appropriate prehydration; cidofovir must be co-administered with care with other nephrotoxic medications. Other potential toxicities include reproductive toxicity and carcinogenesis.

Trifluridine

Trifluridine is a pyrimidine nucleoside analog with activity against HSV, CMV, and adenovirus. It is formulated as a 1% ophthalmic solution and approved for topical use in the treatment of HSV keratitis and keratoconjunctivitis. Trifluridine is the treatment of choice for HSV keratitis, a disease that should always be managed in consultation with an ophthalmologist.

Vidarabine

Vidarabine is a nucleoside analog that has activity against HSV. It was the first parenteral antiviral agent for HSV infection, although it is no longer available for intravenous administration. A topical preparation remains available to treat HSV keratitis and is considered a second-line agent for this indication.

Fomivirsen

Fomivirsen is an anti-CMV compound that was used as a second-line agent for CMV retinitis by direct injection into the vitreous space. It is an antisense 21-mer DNA oligonucleotide that binds directly to complementary messenger RNA. This agent is of interest because it was the first antisense antiviral agent approved by the U.S. Food and Drug Administration (FDA). The drug is no longer marketed.

Letermovir

Letermovir is a highly orally bioavailable agent with a novel mechanism of antiviral action, functioning through interference with the viral terminase complex. This agent demonstrates substantial promise as an alternative to more toxic antivirals in patients at high risk for CMV disease, particularly in the transplantation setting. It is licensed for prophylaxis for CMV infection and disease in adult CMV-seropositive recipients of allogeneic HSCT.

Maribavir

Maribavir is a licensed orally bioavailable agent that targets the CMV gene product UL97, in the process blocking viral replication. The drug is indicated to treat patients >12 years of age who weigh >35 kg and have evidence of posttransplant CMV infection and/or disease that does not respond to other antiviral agents.

ANTIVIRALS USED FOR RESPIRATORY VIRAL INFECTIONS

Antiviral therapies are available for many respiratory pathogens, including respiratory syncytial virus (RSV), influenza A, and influenza B. Antiviral therapy for respiratory viral infections is of particular value for infants, children with chronic lung disease, and immunocompromised children.

Ribavirin

Ribavirin is a guanosine analog that has broad-spectrum activity against a variety of viruses, particularly RNA viruses. Its precise mechanism of action is incompletely understood but is probably related to interference with viral messenger RNA processing and translation. Ribavirin is available in oral, parenteral, and aerosolized formulations. Although intravenous ribavirin is highly effective in

the management of Lassa fever and other hemorrhagic fevers, this formulation is not licensed for use in the United States. The only licensed formulations in the United States are an aqueous formulation for aerosol administration (indicated for RSV infection) and an oral formulation that is combined with IFN-α for the treatment of hepatitis C. (For more information about antivirals for hepatitis, see Chapter 406.) Administration of ribavirin by aerosol should be considered for serious RSV lower respiratory tract disease in immunocompromised children, young infants with serious RSV-associated illness, and high-risk infants and children (children with chronic lung disease or cyanotic congenital heart disease). In vitro testing and uncontrolled clinical studies also suggest efficacy of aerosolized ribavirin for parainfluenza, influenza, and measles infections.

Ribavirin is generally nontoxic, particularly when administered by aerosol. Oral ribavirin is used in combination with other agents for therapy of hepatitis C (discussed later). There is no role for the use of oral ribavirin in the treatment of community-acquired viral respiratory tract infections. Ribavirin and its metabolites concentrate in red blood cells and can persist for several weeks and, in rare instances, may be associated with anemia. Conjunctivitis and bronchospasm have been reported after exposure to aerosolized drug. Care must be taken when using aerosolized ribavirin in children undergoing mechanical ventilation to avoid precipitation of particles in ventilator tubing; the drug is not formally approved for use in the mechanically ventilated patient, although there is published experience with this approach, which can be considered for mechanically ventilated patients, particularly in a "high-dose, short-duration" regimen (6 g/100 mL water given for a period of 2 hours 3 times a day). Concerns regarding potential teratogenicity from animal studies have not been borne out in clinical practice, although care should be taken to prevent inadvertent exposure to aerosolized drug in pregnant healthcare providers.

Amantadine and Rimantadine

Amantadine and rimantadine are tricyclic amines (adamantanes) that share structural similarity. Both were indicated for prophylaxis and therapy of influenza A. The mechanism of action of the tricyclic amines against influenza A virus was unclear, but they appeared to exert their antiviral effect at the level of uncoating of the virus. Both agents are extremely well absorbed after oral administration and are eliminated via the kidneys (90% of the dose is unchanged), necessitating dosage adjustments for renal insufficiency. The toxicities of the tricyclic amines are modest and include CNS adverse effects such as anxiety, difficulty concentrating, and lightheadedness and gastrointestinal adverse effects such as nausea and loss of appetite.

Although these agents are still manufactured and available, the Centers for Disease Control and Prevention (CDC) no longer recommends the use of the adamantane agents in treatment or prophylaxis against influenza, because of the emergence of widespread resistance.

Oseltamivir, Peramivir, Zanamivir (Neuraminidase Inhibitors)

These agents are active against both influenza A and B, although the importance of this broader spectrum of antiinfluenza activity in disease control is modest because influenza B infection is typically a much milder illness. Emerging strains of influenza, including H5N1 and the 2009 to 2010 pandemic strain, H1N1 (swine flu), are susceptible to oseltamivir and zanamivir but resistant to amantadine. Therefore these agents have emerged as the antivirals of choice for influenza infection. These agents have no appreciable activity against other respiratory viruses. The mechanism of antiviral activity of oseltamivir, zanamivir, and peramivir is via inhibition of the influenza neuraminidase. Unfortunately, oseltamivir resistance may occur as a result of a mutation in 2009 H1N1 viruses, resulting in treatment failure.

Zanamivir has poor oral bioavailability and is licensed only for inhalational administration. With inhaled administration, >75% of the dose is deposited in the oropharynx and much of it is swallowed. The actual amount distributed to the airways and lungs depends on factors such as the patient's inspiratory flow. Approximately 13% of the dose appears to be distributed to the airways and lungs, with approximately 10% of the inhaled dose distributed systemically. Local respiratory mucosal drug concentrations greatly exceed the drug concentration needed to inhibit influenza A and B viruses. Elimination is via the kidneys, and no dosage adjustment is necessary with renal insufficiency, because the amount systemically absorbed is low.

Oseltamivir is administered as an esterified prodrug that has high oral bioavailability. It is eliminated by tubular secretion, and dosage adjustment is required for patients with renal insufficiency. Gastrointestinal adverse effects, including nausea and vomiting, are occasionally observed. The drug is indicated for both treatment and prophylaxis. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days. Treatment should be initiated within 2 days of the appearance of symptoms. Recommended treatment dosages for children vary by age and weight. The recommended dose for children younger than 1 year of age is 3 mg/kg/dose twice a day. For children older than 1 year of age, doses are 30 mg twice a day for children weighing ≤15 kg, 45 mg twice a day for children weighing 15-23 kg, 60 mg twice a day for those weighing 23-40 kg, and 75 mg twice a day for children weighing ≥40 kg. Dosages for chemoprophylaxis are the same for each weight group in children older than 1 year, but the drug should be administered only once daily rather than twice daily. Oseltamivir is FDA approved for therapy of influenza A and B treatment in children 2 weeks of age and older, whereas zanamivir is recommended for treatment of children 7 years of age and older. Current treatment and dosage recommendations for treatment of influenza in children and for chemoprophylaxis are available at https://www.cdc.gov/flu/highrisk/children-antiviral.htm. Oseltamivir has been described to produce neuropsychiatric (narcolepsy) and psychologic (suicidal events) side effects in some patient populations; the drug should be discontinued if behavioral or psychiatric side effects are observed. In late 2014 the FDA approved the neuraminidase inhibitor peramivir for treatment of influenza in pediatrics. It is available as a single-dose, intravenous option. The drug is currently approved for use in children >2 years. The dose is 12 mg/kg dose, up to 600 mg maximum, by intravenous infusion for a minimum of 15 minutes in children from 2 to 12 years. Children 13 and older should receive the adult dose (600 mg IV in a single, one-time dose).

Baloxavir

Baloxavir is dosed as baloxavir marboxil, a prodrug that is converted by hydrolysis to baloxavir, the active agent. It is active against influenza A and B. Baloxavir inhibits the endonuclease activity of the influenza polymerase acidic (PA) protein, in the process inhibiting virus replication. It is administered as a single dose of 40 mg in individuals 40-80 kg, and 80 mg in those >80 kg.

Oral baloxavir marboxil (Xofluza) is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people ≥12 years. The safety and efficacy of baloxavir for the treatment of influenza have been established in pediatric patients ≥12 years and older weighing at least 40 kg. Safety and efficacy in patients <12 years or weighing less than 40 kg have not been established. Baloxavir efficacy is based on clinical trials in outpatients 12 to 64 years of age; people with underlying medical conditions and adults >65 years were not included in the initial published clinical trials. There are no available data for baloxavir treatment of hospitalized patients with influenza.

ANTIVIRALS USED FOR COVID-19

The advent of the COVID-19 pandemic has necessitated the urgent development of antivirals active against the SARS-CoV-2 virus. **Remdesivir** is an adenosine analog that was originally developed as a therapeutic option for Ebola virus. It is metabolized to its active metabolite, remdesivir triphosphate, which is a structural analog of adenosine triphosphate and results in delayed chain termination during viral replication. It reduces early-stage COVID-19 mortality and the need for mechanical

ventilation among hospitalized COVID-19 patients. The dose for pediatric patients less than 12 years of age and weighing at least 3 kg (and <40 kg) is a single loading dose of 5 mg/kg on day 1 followed by 2.5 mg/kg once daily for up to 5 days; for hospitalized patients requiring invasive mechanical ventilation and/or ECMO, up to 10 days total therapy can be administered. **Paxlovid** (also variably referred to as ritonavir-boosted nirmatrelvir) is a therapeutic combination consisting of two compounds: nirmatrelvir, an oral inhibitor of SARS-CoV-2 protease, and ritonavir, an inhibitor of the HIV-1 protease. Ritonavir is also a potent inhibitor of cytochrome P-450 (CYP) 3A; thus its inclusion results in higher levels of PF-07321332. In patients with SARS-CoV-2 infection who were treated with Paxlovid within 3 days of symptom onset, hospitalization and mortality rates were statistically significantly lower compared with placebo. The FDA Emergency Use Authorization (EUA) includes treatment of children over 12 years of age with a body weight of >40 kg, with a suggested dose of 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet), with all three tablets taken together, twice daily, by oral administration, for 5 days. **Molnupiravir** (Lagevrio) was originally developed as an influenza antiviral agent. It is a prodrug of a synthetic nucleoside hydroxycytidine derivative. Its antiviral effect is mediated by the introduction of copying errors during the SARS-CoV-2 RNA replication cycle. The reported efficacy against hospitalization or death in an adult study of mild or moderate COVID-19 disease was approximately 30%. The drug is not authorized for patients <18 years of age because of concerns that it may affect cartilage and bone growth.

ANTIVIRALS USED FOR HEPATITIS

Seven antiviral agents have been approved by the FDA for treatment of adults with chronic hepatitis B in the United States. These agents are categorized as either IFN-α2b and peginterferon-α2a) or nucleoside or nucleotide analogs (lamivudine, adefovir, entecavir, tenofovir, telbivudine). Lamivudine is currently considered the first-line therapy in adult patients, but experience in children is limited. In 2012 tenofovir was FDA approved for children with chronic hepatitis B age ≥12 years weighing >35 kg. Entecavir was approved in the United States for use in children 2 years and older with chronic HBV and evidence of active viral replication and disease activity and, with IFN-α, is emerging as a first-line antiviral regimen for children with hepatitis B who are candidates for antiviral therapy.

Adefovir demonstrates a favorable safety profile and is less likely to select for resistance than lamivudine, but virologic response was limited to adolescent patients and was lower than that of lamivudine. Most experts recommend watchful waiting of children with chronic hepatitis B infection, because current therapies are only modestly effective at best and evidence of long-term benefit is scant. Young children are often thought to be immune tolerant of hepatitis B infection (i.e., they have viral DNA present in serum but normal transaminase levels and no evidence of active hepatitis). These children should have transaminases and viral load monitored but are not typically considered to be candidates for antiviral therapy.

Various formulations of IFNs and ribavirin have been approved by the FDA to treat adults and children with chronic hepatitis C (see Tables 292.1 and 292.2). The impact of hepatitis C genotype had formerly been a major issue in treatment response. Previous studies using ribavirin and pegylated IFNs demonstrated significant genotype-dependent differences in responsiveness to antiviral therapy; patients with genotype 1 had the lowest levels of sustained virologic response, and patients with genotype 2 or 3 had the highest response. The development of novel and highly effective antivirals for HCV has revolutionized the care of hepatitis C patients. Novel drugs include ledipasvir, sofosbuvir, daclatasvir, elbasvir, beclabuvir, grazoprevir, paritaprevir, ombitasvir, velpatasvir, and dasabuvir. Ledipasvir, ombitasvir, daclatasvir, elbasvir, and velpatasvir inhibit the virally encoded phosphoprotein NS5A, which is involved in viral replication, assembly, and secretion, whereas sofosbuvir is metabolized to a uridine triphosphate mimic, which functions as an RNA chain terminator when incorporated into the nascent RNA by the NS5B polymerase enzyme. Dasabuvir and beclabuvir are also NS5B inhibitors. Paritaprevir and grazoprevir inhibit the nonstructural protein 3 (NS3/4) serine protease, a viral nonstructural protein that is the 70-kDa cleavage product of the hepatitis C virus polyprotein.

Sofosbuvir in a fixed-dose combination was originally licensed for treatment of hepatitis C in adults. It is highly effective (>90%) for hepatitis C genotypes 1 through 6. In 2020, it was licensed for treatment in children ages 6 years and older and weighing at least 17 kilograms for any of the six HCV genotypes in patients without cirrhosis or with mild cirrhosis. Epclusa in combination with ribavirin is indicated for the treatment of pediatric patients 6 years and older or weighing at least 17 kilograms with severe cirrhosis.

ANTIVIRAL IMMUNE GLOBULINS

Immune globulins are useful adjuncts in the management of viral disease. However, they are most valuable when administered as prophylaxis against infection and disease in high-risk patients; their value as therapeutic agents in the setting of established infection is less clear. **Varicella-zoster immune globulin (human)** is valuable for prophylaxis against VZV in high-risk children, particularly newborns and immunocompromised children (see Chapter 300). **CMV immune globulin** is warranted for children at high risk for CMV disease, particularly SOT and HSCT patients, and can play a role in preventing injury to the infected fetus when administered to the pregnant patient (see Chapter 302). **Palivizumab,** a monoclonal antibody with anti-RSV activity, is effective for preventing severe RSV lower respiratory tract disease in high-risk premature infants and has replaced **RSV immune globulin** (see Chapter 307). **Hepatitis B immune globulin** is indicated in infants born to hepatitis B surface antigen–positive mothers (see Chapter 406). A variety of monoclonal antibodies had received FDA EUA clearance for prophylaxis and/or therapy of SARS-CoV-2 infection, including **bamlanivimab** (LY-CoV555; administered alone or in combination with **etesevimab**), the combination of **casirivimab** and **imdevimab** (REGEN-COV), and the combination of **tixagevimab** (AZD8895) and **cilgavimab** (AZD1061), also known as Evusheld. As of late 2023, these products are no longer available due to their lack of effectiveness against emerging circulating variants of the SARS-CoV-2 virus. The US Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices has also recently recommended the routine use of **nirsevimab**, a monoclonal antibody targeting the prefusion conformation of the RSV F protein, for the prevention of RSV lower respiratory tract disease (see Chapter 307). Treatment is recommended for newborns and infants younger than 8 months of age during, or entering, their first RSV season, as well as for children up to 24 months of age at increased risk of developing RSV disease entering their second RSV season. A single dose of 50 mg administered intramuscularly is recommended for infants <5 kg, and 100 mg is recommended for infants ≥5 kg. Nirsevimab should not be given to children ≥8 months and older who are not at increased risk of severe RSV disease. For the 2023-24 respiratory virus season, and in light of shortage and distribution issues with nirsevimab, the CDC has recommended (https://emergency.cdc.gov/han/2023/han00499.asp) assigning the highest priority for nirsevimab 100 mg doses for infants at the highest risk for severe RSV disease: young infants (age <6 months and >5 kg) and infants with underlying conditions that place them at highest risk for severe RSV disease. The CDC also recommended that providers not use nirsevimab in palivizumab-eligible children ages 8–19 months for the 2023–24 RSV season; instead, they should receive palivizumab per American Academy of Pediatrics (AAP) recommendations https://publications.aap.org/pediatrics/article/152/1/e2023061803/192153/Palivizumab-Prophylaxis-in-Infants-and-Young?autologincheck=redirected).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 293

Measles

Hayley A. Gans

Measles is highly contagious, but endemic transmission has been interrupted in the United States as a result of widespread vaccination; imported cases have resulted in epidemics in the United States in unimmunized or partially immunized individuals. In some areas of the world, measles remains a major cause of morbidity and mortality in children (Fig. 293.1).

ETIOLOGY

Measles virus is a negative sense single-stranded, lipid-enveloped RNA virus in the family Paramyxoviridae and genus *Morbillivirus.* Other members of the genus *Morbillivirus* affect a variety of mammals, such as rinderpest virus in cattle and distemper virus in dogs, but humans are the only host of measles virus. Of the six major structural proteins of measles virus, the two most important in terms of induction of immunity are the hemagglutinin (H) protein and the fusion (F) protein. The neutralizing antibodies are directed against the H protein, and antibodies to the F protein limit proliferation of the virus during infection. Small variations in genetic composition have also been identified that result in no effect on protective immunity but provide molecular markers that can distinguish between viral types. Related genotypes have been grouped by clades, and the World Health Organization (WHO) recognizes 8 clades, A-H, and 23 genotypes. These markers have been useful in the evaluation of endemic and epidemic spread of measles.

EPIDEMIOLOGY

The measles vaccine has changed the epidemiology of measles dramatically. Once worldwide in distribution, endemic transmission of measles has been interrupted in many countries where there is widespread vaccine coverage. Historically, measles caused universal infection in childhood in the United States, with 90% of children acquiring the infection before 15 years of age. Morbidity and mortality associated with measles decreased before the introduction of the vaccine as a result of improvements in healthcare and nutrition. However, the incidence declined dramatically following the introduction of the measles vaccine in 1963. The attack rate fell from 313 cases per 100,000 population in 1956–1960 to 1.3 cases per 100,000 in 1982–1988.

A nationwide indigenous measles outbreak occurred in the United States in 1989–1991, resulting in more than 55,000 cases, 11,000 hospitalizations, and 123 deaths, demonstrating that the infection had not yet been controlled. This resurgence was attributed to vaccine failure in a small number of school-age children, low coverage of preschool-age children, and more rapid waning of maternal antibodies in infants born to mothers who had never experienced wild-type measles infection. Implementation of the two-dose vaccine policy and more intensive immunization strategies resulted in interruption of endemic transmission, and in 2000 measles was declared eliminated from the United States.

Measles continues to be imported into the United States; therefore continued maintenance of >90% immunity through vaccination is necessary to prevent widespread outbreaks from occurring (see Fig. 293.1).

Since elimination in 2000, there have been several measles epidemics, with the two largest occurring in 2014 with 667 cases and in 2019 with 1,282 cases. In 2014 there were 23 outbreaks reported, compared with a median of 4 outbreaks reported annually during 2001–2010. The majority of cases were associated with importations from other countries (returning tourists, adoptees, refugees), particularly from the Philippines, with prior year epidemics associated with epidemics in the WHO European Region. Measles cases were largely restricted to unvaccinated individuals. The epidemic in 2019 resulted in the highest number of cases since 1992, with 89% of cases in unvaccinated or unknown vaccination status, and 10% of cases requiring hospitalization. There were 22 outbreaks in 17 states (7 were multistate outbreaks), and 85% of cases were in close-knit, isolated communities where standard control measures that generally quickly contain outbreaks were difficult to implement.

Population levels of measles immunity of ~95% are required to interrupt the endemic spread of measles. In the United States this can be achieved through the current two-dose immunization strategies when coverage rates are high (>90% one-dose coverage at 12-15 months and >95% two-dose coverage in school-age children). Although measles-mumps-rubella coverage remains high (~95% for 2011–2020), pockets of lower coverage rates exist because of reluctance of parents to vaccinate their children. This variability in vaccination has contributed to outbreaks among children in recent years.

TRANSMISSION

The portal of entry of measles virus is through the respiratory tract or conjunctivae following contact with large droplets or small-droplet aerosols in which the virus is suspended. Individuals are infectious from 3 days before to up to 4-6 days after the onset of rash. Approximately 90% of exposed susceptible individuals experience measles. Face-to-face contact is not necessary, because viable virus may be suspended in air for as long as 2 hours after the source case leaves a room. Secondary cases from spread of aerosolized virus have been reported in airplanes, physicians' offices, and hospitals.

PATHOLOGY

Measles infection causes necrosis of the respiratory tract epithelium and an accompanying lymphocytic infiltrate. Measles produces a small-vessel vasculitis on the skin and on the oral mucous membranes. Histology of the rash and exanthem reveals intracellular edema and dyskeratosis associated with formation of epidermal syncytial giant cells with up to 26 nuclei. Viral particles have been identified within these giant cells. In lymphoreticular tissue, lymphoid hyperplasia is prominent. Fusion of infected cells results in multinucleated giant cells, the **Warthin-Finkeldey giant cells** that are pathognomonic for measles, with up to 100 nuclei and intracytoplasmic and intranuclear inclusions.

PATHOGENESIS

Measles infection consists of four phases: incubation period, prodromal illness, exanthematous phase, and recovery. During incubation, measles virus migrates to regional lymph nodes. A primary viremia ensues that disseminates the virus to the reticuloendothelial system. A secondary viremia spreads virus to body surfaces. The prodromal illness begins after the secondary viremia and is associated with epithelial necrosis and giant cell formation in body tissues. Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside. Measles virus also infects $CD4^+$ T cells, resulting in suppression of the Th1 immune response and a multitude of other immunosuppressive effects.

Measles virus attaches to specific cell receptors to infect host cells. Studies in primates show that the initial targets for measles virus are alveolar macrophages, dendritic cells, and lymphocytes. The cell receptor in these cells appears to be the signaling lymphocyte-activating molecule CD150. Subsequently, respiratory epithelial cells become infected by attachment to the PVRL4 receptor (Nectin4), which is expressed on cells in the trachea, oral mucosa, nasopharynx, and lungs.

CLINICAL MANIFESTATIONS

Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent exanthem (Fig. 293.2). After an incubation period of 8-12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. **Koplik spots**

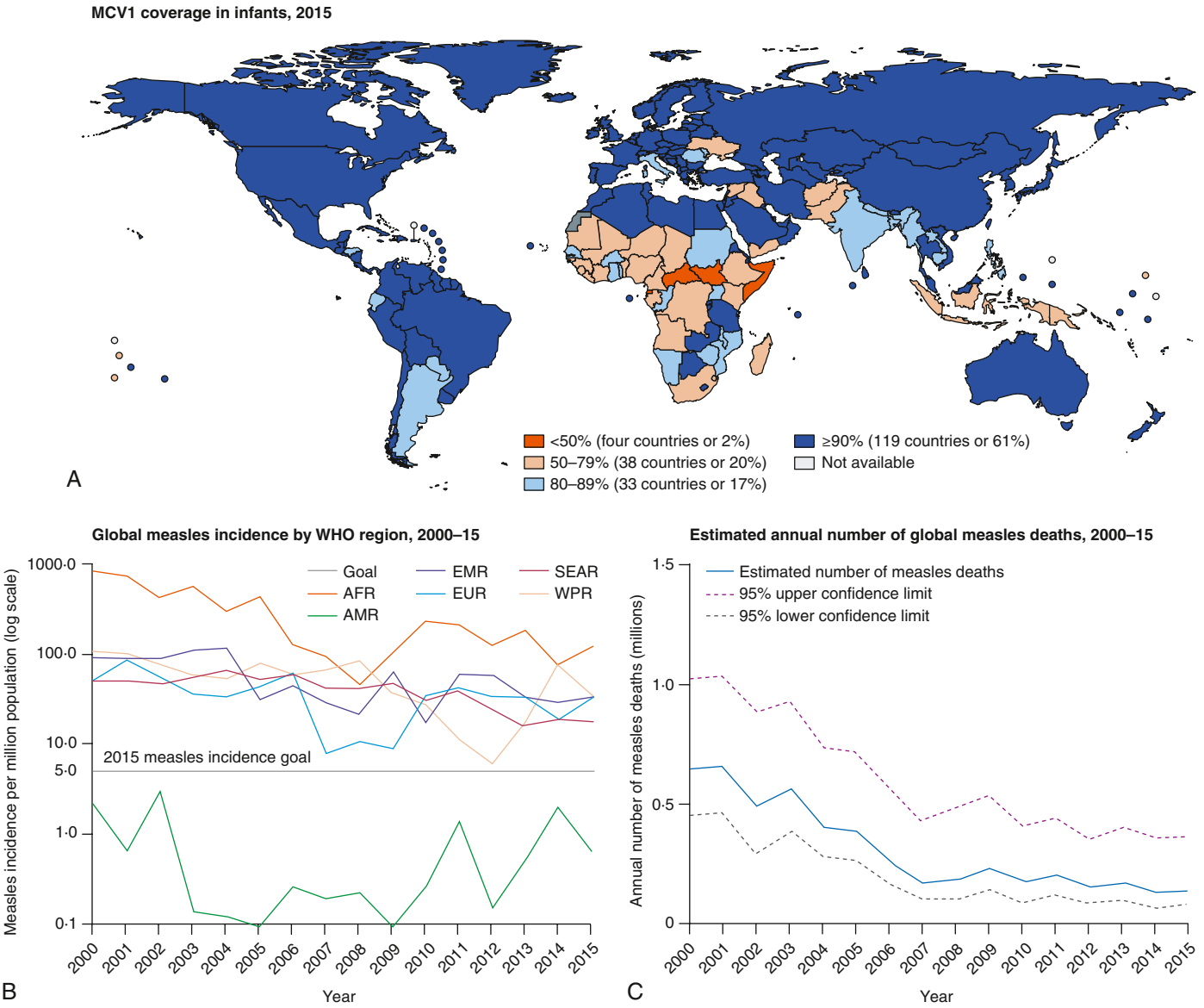

Fig. 293.1 Progress toward achieving global measles milestones for measles vaccine coverage (A), measles incidence (B), and measles mortality (C). A, Milestone 1: increase routine coverage with the first dose of measles-containing vaccine (MCV1) for children age 1 yr to ≥90% nationally and ≥80% in every district. Progress: The number of countries with ≥90% MCV1 coverage increased from 84 (44%) in 2000 to 119 (61%) in 2015. Among countries with ≥90% MCV1 coverage nationally, the percentage with ≥80% coverage in every district was only 39% of 119 countries in 2015. B, Milestone 2: reduce global measles incidence to <5 cases/1 million population. Progress: reported global annual measles incidence decreased 75% from 2000 to 2015, but only the Region of the Americas achieved the milestone of <5 cases/1 million population. C, Milestone 3: reduce global measles mortality by 95% from the 2000 estimate. Progress: the number of estimated global annual measles deaths decreased 79% from 2000 to 2015. AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region. *(From Moss WJ. Measles. Lancet. 2017;390:2490–2502. Fig. 2; with data from Patel MK, Gacic-Dobo M, Strebel PM, et al. Progress toward regional measles elimination—worldwide, 2000–2015. MMWR Morb Mortal Wkly Rep. 2016;65:1228–1233.)*

represent the enanthem and are the pathognomonic sign of measles, appearing 1-4 days before the onset of the rash (Fig. 293.3). They first appear as discrete red lesions with bluish-white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik spots have been reported in 50–70% of measles cases but probably occur in the great majority.

Symptoms increase in intensity for 2-4 days until the first day of the rash. The rash begins on the forehead (around the hairline), behind the ears, and on the upper neck as a red maculopapular eruption. It then spreads downward to the torso and extremities, reaching the palms and soles in up to 50% of cases. The exanthem frequently becomes confluent on the face and upper trunk (Fig. 293.4).

With the onset of the rash, symptoms begin to subside. The rash fades over about 7 days in the same progression as it evolved, often leaving a fine desquamation of skin in its wake. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.

MODIFIED MEASLES INFECTION

In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Similarly, some individuals who have been vaccinated may have a rash but few other symptoms after exposure to measles. Persons with modified measles are not considered highly contagious.

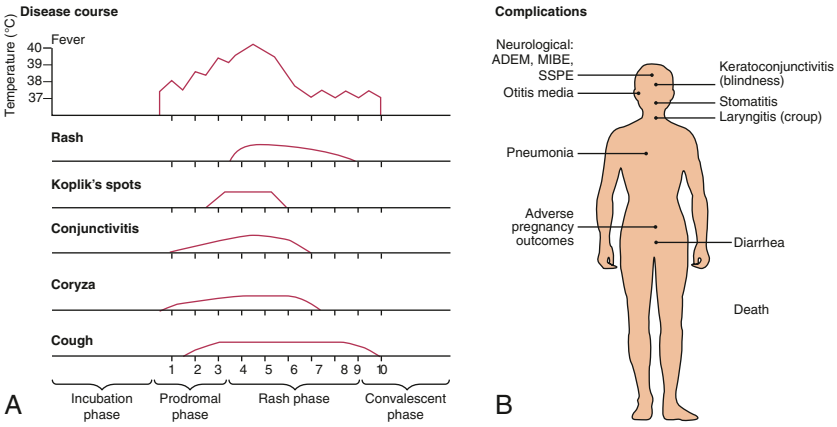

Fig. 293.2 Measles disease course (A) and complications (B). ADEM, Acute demyelinating encephalomyelitis; MIBE, measles inclusion body encephalitis; SSPE, subacute sclerosing panencephalitis. *(Modified from Moss WJ. Measles. Lancet. 2017;390:2490–2502. Fig. 4.)*



Fig. 293.3 Koplik spots on the buccal mucosa during the third day of rash. *(From Centers for Disease Control and Prevention [CDC]. Public health image library, image 4500. https://phil.cdc.gov/Details.aspx?pid=4500.)*



Fig. 293.4 A child with measles displaying the characteristic red blotchy pattern on his face and body. *(From Kremer JR, Muller CP. Measles in Europe—there is room for improvement. Lancet. 2009;373:356–358.)*

LABORATORY FINDINGS

The diagnosis of measles is almost always based on clinical and epidemiologic findings. Laboratory findings in the acute phase include reduction in the total white blood cell count, with lymphocytes decreased more than neutrophils. However, absolute neutropenia has been known to occur. In measles not complicated by bacterial infection, the erythrocyte sedimentation rate and C-reactive protein level are usually normal.

DIAGNOSIS

Isolation of measles from blood, urine, or respiratory secretions can be accomplished by culture at the CDC or local or state laboratories. Molecular detection by polymerase chain reaction (PCR) can be performed on specimens from nasopharyngeal aspirates, throat swabs, or urine. Serologic confirmation is most conveniently made by identification of immunoglobulin (Ig) M antibody in serum. IgM antibody appears 1-2 days after the onset of the rash and remains detectable for about 1 month. If a serum specimen is collected <72 hours after onset of rash and is negative for measles antibody, a second specimen should be obtained. Serologic confirmation may also be made by demonstration of a fourfold rise in IgG antibodies in acute and convalescent specimens collected 2-4 weeks apart. Collection of both a throat swab specimen for PCR and a serum specimen for IgM detection is recommended from all patients with clinical features compatible with measles. In addition, samples should be sent to local state public health laboratories or the CDC for genotyping.

DIFFERENTIAL DIAGNOSIS

Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed. Measles in the later stages or modified or atypical infections may be confused with a number of other exanthematous immune-mediated illnesses and infections, including rubella, adenovirus infection, enterovirus infection, and Epstein-Barr virus infection. Exanthem subitum (in infants) and erythema infectiosum (in older children) may also be confused with measles. *Mycoplasma pneumoniae* and group A *Streptococcus* may also produce rashes similar to that of measles. Kawasaki syndrome can cause many of the same findings as measles but lacks discrete intraoral lesions (Koplik spots) and a severe prodromal cough and typically leads to elevations of neutrophils and acute-phase reactants. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles (see Chapter 208). Drug eruptions may occasionally be mistaken for measles.

TABLE 293.1 Complications by Age for Reported Measles Cases, United States, 1987–2000

COMPLICATION	OVERALL (67,032 CASES WITH AGE INFORMATION)	NO. (%) OF PERSONS WITH COMPLICATION BY AGE GROUP				
		<5 YR (*N* = 28,730)	5-9 YR (*N* = 6,492)	10-19 YR (*N* = 18,580)	20-29 YR (*N* = 9,161)	<30 YR (*N* = 4,069)
Any	19,480 (29.1)	11,883 (41.4)	1,173 (18.1)	2,369 (12.8)	2,656 (29.0)	1,399 (34.4)
Death	177 (0.3)	97 (0.3)	9 (0.1)	18 (0.1)	26 (0.3)	27 (0.7)
Diarrhea	5,482 (8.2)	3,294 (11.5)	408 (6.3)	627 (3.4)	767 (8.4)	386 (9.5)
Encephalitis	97 (0.1)	43 (0.2)	9 (0.1)	13 (0.1)	21 (0.2)	11 (0.3)
Hospitalization	12,876 (19.2)	7,470 (26.0)	612 (9.4)	1,612 (8.7)	2,075 (22.7)	1,107 (27.2)
Otitis media	4,879 (7.3)	4,009 (14.0)	305 (4.7)	338 (1.8)	157 (1.7)	70 (1.7)
Pneumonia	3,959 (5.9)	2,480 (8.6)	183 (2.8)	363 (2.0)	554 (6.1)	379 (9.3)

From Perry RT, Halsey NA. The clinical significance of measles: a review. *Clin Infect Dis.* 2004;189(Suppl. 1):S4–S16.

COMPLICATIONS

Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Table 293.1, see Fig. 293.2). Several factors make complications more likely. Morbidity and mortality from measles are greatest in individuals younger than 5 years of age (especially <1 year of age) and older than 20 years of age. In resource poor countries, higher case fatality rates have been associated with crowding, possibly attributable to larger inoculum doses after household exposure. Severe malnutrition in children results in a suboptimal immune response and higher morbidity and mortality with measles infection. Low serum retinol levels in children with measles are associated with higher measles morbidity and mortality in developing countries and in the United States. Measles infection lowers serum retinol concentrations, so subclinical cases of hyporetinolemia may be made symptomatic during measles. Measles infection in immunocompromised persons is associated with increased morbidity and mortality. Among patients with malignancy in whom measles develops, pneumonitis occurs in 58% and encephalitis occurs in 20%.

Pneumonia is the most common cause of death in measles. It may manifest as **giant cell pneumonia** caused directly by the viral infection or as superimposed bacterial infection. The most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*. Following severe measles pneumonia, the final common pathway to a fatal outcome is often the development of bronchiolitis obliterans.

Croup, tracheitis, and bronchiolitis are common complications in infants and toddlers with measles. The clinical severity of these complications frequently requires intubation and ventilatory support until the infection resolves.

Acute otitis media is the most common complication of measles and was of particularly high incidence during the epidemic of the late 1980s and early 1990s because of the relatively young age of affected children. Sinusitis and mastoiditis also occur as complications. Viral and/or bacterial tracheitis is seen and can be life-threatening. Retropharyngeal abscess has also been reported.

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tuberculosis in populations of individuals infected with *Mycobacterium tuberculosis* who are then exposed to measles.

Diarrhea and vomiting are common symptoms associated with acute measles, and diffuse giant cell formation is found in the epithelium in the gastrointestinal tract. Dehydration is a common consequence, especially in young infants and children. Appendicitis or abdominal pain may occur from obstruction of the appendiceal lumen by lymphoid hyperplasia.

Febrile seizures occur in <3% of children with measles. Encephalitis following measles is a long-associated complication, often with an unfavorable outcome. Rates of 1-3 in 1,000 cases of measles have been reported, with greater numbers occurring in adolescents and adults than in preschool- or school-age children. Encephalitis is a postinfectious, immunologically mediated process and is not the result of a direct effect by the virus. Clinical onset begins during the exanthem and manifests as seizures (56%), lethargy (46%), coma (28%), and irritability (26%). Findings in cerebrospinal fluid include lymphocytic pleocytosis in 85% of cases and elevated protein concentrations. Approximately 15% of patients with measles encephalitis die. Another 20–40% of patients suffer long-term sequelae, including cognitive impairment, motor disabilities, and deafness.

Measles encephalitis in immunocompromised patients results from direct damage to the brain by the virus. Subacute measles encephalitis manifests 1-10 months after measles in immunocompromised patients, particularly those with AIDS, lymphoreticular malignancies, and immunosuppressive therapy. Signs and symptoms include seizures, myoclonus, stupor, and coma. In addition to intracellular inclusions, abundant viral nucleocapsids and viral antigen are seen in brain tissue. Progressive disease and death almost always occur. A severe form of encephalitis called measles inclusion-body encephalitis (MIBE) is being increasingly recognized in immunocompromised hosts, typically occurring within a year of infection or vaccination and almost universally resulting in death. Although the pathophysiology is incompletely understood, the measles viruses implicated in MIBE are usually replication-defective, with their genomes possessing numerous mutations. Diagnosis is confirmed by detection of virus via immunohistochemistry of brain tissue.

A severe form of measles rarely seen nowadays is **hemorrhagic measles** or **black measles.** It manifested as a hemorrhagic skin eruption and was often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection.

Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy is associated with high rates of maternal morbidity, fetal wastage, and stillbirths, with congenital malformations in 3% of liveborn infants.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system for several years. After 7-10 years the virus apparently regains virulence and attacks the cells in the central nervous system that offered the virus protection. This "slow virus infection" results in inflammation and cell death, leading to an inexorable neurodegenerative process.

SSPE is a rare disease and generally follows the prevalence of measles in a population. The incidence in the United States in 1960 was 0.61 cases per million persons younger than age 20 years. By 1980 the rate had fallen to 0.06 cases per million. Between 1956 and 1982 a total of 634 cases of SSPE had been reported to the national SSPE registry. After 1982 ~5 cases/year were reported annually in the United States, and only 2-3 cases/year were reported in the early 1990s. However, between 1995 and 2000, reported cases in the United States increased and 13 cases were reported in 2000. Of the 13 cases, 9 occurred in foreign-born individuals. This "resurgence" may be the result of an increased incidence of measles between 1989 and 1991. Although the age of onset ranges from <1 year to <30 years, the illness is primarily one of children and adolescents. Measles at an early age favors the development of SSPE: 50% of patients with SSPE have had primary measles before 2 years of age, and 75% have had measles before 4 years of age. Males are affected twice as often as females, and there appear to be more cases reported from rural than urban populations. Recent observations from the registry indicate a higher prevalence among children of Hispanic origin.

The pathogenesis of SSPE remains enigmatic. Factors that seem to be involved include defective measles virus and interaction with a defective or immature immune system. The virus isolated from brain tissue of patients with SSPE is missing one of the six structural proteins, the matrix or M protein. This protein is responsible for assembly, orientation, and alignment of the virus in preparation for budding during viral replication. Immature virus may be able to reside, and possibly propagate, within neuronal cells for long periods. The fact that most patients with SSPE were exposed at a young age suggests that immune immaturity is involved in pathogenesis.

Clinical manifestations of SSPE begin insidiously 7-13 years after primary measles infection. Subtle changes in behavior or school performance appear, including irritability, reduced attention span, and temper outbursts. This initial phase **(stage I)** may at times be missed because of brevity or mildness of the symptoms. Fever, headache, and other signs of encephalitis are absent. The hallmark of the **second stage** is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia. Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained. In the **third stage**, involuntary movements disappear and are replaced by choreoathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia. The sensorium deteriorates into dementia, stupor, and then coma. The **fourth stage** is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.

The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least one of the following supporting findings: (1) measles antibody detected in cerebrospinal fluid, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

Cerebrospinal fluid analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1:8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of, but not pathognomonic for, SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

Management of SSPE is primarily supportive and similar to care provided to patients with other neurodegenerative diseases. Clinical trials using isoprinosine with or without interferon suggest significant benefit (30–34% remission rate) compared with patients without treatment (5–10% with spontaneous remissions).

It is recognized that carbamazepine is of significant benefit in the control of myoclonic jerks in the early stages of the illness.

Virtually all patients eventually succumb to SSPE. Most die within 1-3 years of onset from infection or loss of autonomic control mechanisms. Prevention of SSPE depends on prevention of primary measles infection through vaccination. SSPE has been described in patients who have no history of measles infection and exposure only to the vaccine virus. However, wild-type virus, not vaccine virus, has been found in brain tissue of at least some of these patients, suggesting that they had subclinical measles previously.

TREATMENT

Management of measles is supportive because there is no specific antiviral therapy approved for treatment of measles. Maintenance of hydration, oxygenation, and comfort are goals of therapy. Antipyretics for comfort and fever control are useful. For patients with respiratory tract involvement, airway humidification and supplemental oxygen may be of benefit. Respiratory failure from croup or pneumonia may require ventilatory support. Oral rehydration is effective in most cases, but severe dehydration may require intravenous therapy. Prophylactic antimicrobial therapy to prevent bacterial infection is not indicated.

Measles infection in immunocompromised patients is highly lethal. Ribavirin is active in vitro against measles virus. Anecdotal reports of ribavirin therapy with or without intravenous gamma globulin suggest some benefit in individual patients. Although no controlled trials have been performed, many experts favor use of ribavirin for treatment of measles pneumonia in patients <12 months, patients ≥12 months with pneumonia requiring ventilatory support, and patients with severe immunosuppression. Ribavirin dosing is 15-20 mg/kg/day orally in two divided doses. The optimal duration of therapy is not known; a duration of 5-7 days may be reasonable, guided by the patient's clinical status (respiratory symptoms and chest radiograph findings). Several investigational treatments have been used in individuals with SSPE with the goal of stabilization and delay of progression, including Isoprinosine (inosine pranobex) and interferon-α and interferon-β.

Vitamin A

Vitamin A deficiency in children in resource poor countries has long been known to be associated with increased mortality from a variety of infectious diseases, including measles. In the United States, studies in the early 1990s documented that 22–72% of children with measles had low retinol levels. In addition, one study demonstrated an inverse correlation between the level of retinol and severity of illness. Several randomized controlled trials of vitamin A therapy in the developing world have demonstrated reduced morbidity and mortality from measles. Use of vitamin A for treatment of measles in developed countries has not been evaluated in a large clinical trial, but a small study showed no effect on morbidity. Given the potential for benefit, the WHO and the CDC recommend that vitamin A be administered to all children with acute measles, even in countries where measles is not usually severe. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 months of age or older; 100,000 IU for infants 6-11 months of age; and 50,000 IU for infants younger than 6 months of age. In children with signs and symptoms of vitamin A deficiency, a third age-appropriate dose is recommended 2-4 weeks after the second dose.

PROGNOSIS

In the early 20th century, deaths from measles in the United States varied between 2,000 and 10,000 per year, or about 10 deaths per 1,000 cases of measles. With improvements in healthcare and antimicrobial therapy, better nutrition, and decreased crowding, the death-to-case ratio fell to 1 per 1,000 cases. Between 1982 and 2002, the CDC estimated that there were 259 deaths caused by measles in the United States, with a death-to-case ratio of 2.5-2.8 per 1,000 cases of measles. Pneumonia and encephalitis were complications in most of the fatal cases, and immunodeficiency conditions were identified in 14–16% of deaths. In 2011, of the 222 cases reported in the United States, 70

(32%) were hospitalized, including 17 (24%) with diarrhea, 15 (21%) with dehydration, and 12 (17%) with pneumonia. No cases of encephalitis or deaths were reported. In 2019, 10% of cases were hospitalized, 5% had pneumonia, and one (0.1%) had encephalitis, but no deaths were reported.

PREVENTION

Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash. Exposure of susceptible individuals to those with measles should be avoided during this period. In hospitals, standard and airborne precautions should be observed for this period. Immunocompromised individuals with measles will shed virus for the duration of the illness, so isolation should be maintained throughout the disease.

Vaccine

Vaccination against measles is the most effective and safe prevention strategy. Measles vaccine in the United States is available as a combined vaccine with measles-mumps-rubella vaccine (Table 293.2). After the measles resurgence of 1989–1991, a second dose of measles vaccine was added to the schedule. The current recommendations include a first dose at 12-15 months of age and a second dose at 4-6 years of age. However, the second dose can be given any time after 30 days following the first dose, and the current schedule is a convenience schedule. Seroconversion is slightly lower in children who receive the first dose before or at 12 months of age (87% at 9 months, 95% at 12 months, and 98% at 15 months) because of persisting maternal antibody; however, this is an evolving situation, with children currently as young as 6 months unprotected from maternal antibodies and susceptible to measles infection. For children who have not received two doses by 11-12 years of age, a second dose should be provided. Infants who receive a dose before 12 months of age should be given two additional doses, one at 12-15 months and another at 4-6 years of age. Children who are traveling should be offered either primary measles immunization even as young as 6 months or a second dose even if <4 years.

Adverse events from the measles-mumps-rubella vaccine include fever (usually 6-12 days after vaccination), rash in approximately 5% of vaccinated persons, and, rarely, transient thrombocytopenia. Children prone to febrile seizures may experience an event following vaccination, so the risks and benefits of vaccination should be discussed with parents. Encephalopathy and autism have not been shown to be causally associated with the measles-mumps-rubella vaccine or vaccine constituents.

A review of the effect of measles vaccination on the epidemiology of SSPE has demonstrated that measles vaccination protects against SSPE

TABLE 293.2 Recommendations for Measles Immunization

CATEGORY	RECOMMENDATIONS
Unimmunized, no history of measles (12-15 mo of age)	MMR or MMRV vaccine is recommended at 12-15 mo of age; a second dose is recommended at least 28 days after the first dose (or 90 days for MMRV) and usually is administered at 4 through 6 yr of age
Children 6-11 mo of age in epidemic situations or before international travel	Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the first birthday are required. The first valid dose should be administered at 12-15 mo of age; the second valid dose is recommended at least 28 days later and usually is administered at 4 through 6 yr of age. MMRV should not be administered to children <12 mo of age.
Students in kindergarten, elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the second dose
Students in college and other postsecondary institutions who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the second dose
History of immunization before the first birthday	Dose not considered valid; immunize (2 doses)
History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963–1967	Dose not considered valid; immunize (2 doses)
Further attenuated or unknown vaccine administered with immunoglobulin	Dose not considered valid; immunize (2 doses)
Allergy to eggs	Immunize; no reactions likely
Neomycin allergy, nonanaphylactic	Immunize; no reactions likely
Severe hypersensitivity (anaphylaxis) to neomycin or gelatin	Avoid immunization
Tuberculosis	Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing
Measles exposure	Immunize or give immunoglobulin, depending on circumstances
HIV infected	Immunize (2 doses) unless severely immunocompromised; administration of immunoglobulin if exposed to measles is based on degree of immunosuppression and measles vaccine history
Personal or family history of seizures	Immunize; advise parents of slightly increased risk of seizures
Immunoglobulin or blood recipient	Immunize at the appropriate interval

MMR, Measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine.
From American Academy of Pediatrics. Measles. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book 2018 Report of the Committee on Infectious Diseases,* 31st ed. Itasca, IL: American Academy of Pediatrics, 2018: Table 3.39, p. 543.

TABLE 293.3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*

INDICATION FOR IMMUNOGLOBULIN	ROUTE	DOSE		
		UNITS (U) OR MILLILITERS (ML)	MG IgG/KG	INTERVAL (MO)†
Tetanus (as tetanus Ig)	IM	250 U	10	3
Hepatitis A prophylaxis (as Ig):				
Contact prophylaxis	IM	0.02 mL/kg	3.3	3
International travel	IM	0.06 mL/kg	10	3
Hepatitis B prophylaxis (as hepatitis B Ig)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as rabies Ig)	IM	20 IU/kg	22	4
Varicella prophylaxis (as VariZIG)	IM	125 U/10 kg (maximum 625 U)	20-40	5
Measles prophylaxis (as Ig):				
Standard	IM	0.50 mL/kg	80	6
Immunocompromised host	IV		400 mg/kg	8
Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)‡	IM	—	15 mg/kg (monoclonal)	None
Cytomegalovirus immune globulin	IV	3 mL/kg	150	6
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20-60	6
Whole blood	IV	10 mL/kg	80-100	6
Plasma or platelet products	IV	10 mL/kg	160	7
Replacement (or therapy) of immune deficiencies (as IVIG)	IV	—	300-400	8
ITP (as IVIG)	IV	—	400	8
ITP	IV	—	1,000	10
ITP or Kawasaki disease	IV	—	1,600-2,000	11

*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.
†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles.
‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.
Ig, Immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed "idiopathic") thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.
From American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: Table 1.10, p. 39.

and does not accelerate the course of SSPE or trigger the disease in those already infected with wild measles virus.

Passively administered immune globulin may inhibit the immune response to live measles vaccine, and administration should be delayed for variable amounts of time based on the dose of Ig (Table 293.3).

Live vaccines should not be administered to pregnant women or to immunodeficient or immunosuppressed patients. However, patients with HIV who are not severely immunocompromised should be immunized. Because measles virus may suppress the cutaneous response to tuberculosis antigen, skin testing for tuberculosis should be performed before or at the same time as administration of the vaccine. Individuals infected with *M. tuberculosis* should be receiving appropriate treatment at the time of administration of measles vaccine.

Postexposure Prophylaxis

Susceptible individuals exposed to measles may be protected from infection either by vaccine administration or with Ig. The vaccine is effective in prevention or modification of measles if given within 72 hours of exposure. Ig may be given up to 6 days after exposure to prevent or modify infection. Immunocompetent children should receive 0.5 mL/kg (maximum dose in both cases is 15 mL/kg) intramuscularly. For severely immunocompromised children and pregnant woman without evidence of measles immunity, immunoglobulin intravenously (IGIV) is the recommended Ig at 400 mg/kg. Ig is indicated for susceptible household contacts of patients with measles, especially infants <6 months of age, pregnant women, and immunocompromised persons.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 294

Rubella

Hayley A. Gans

Rubella (**German measles** or **3-day measles**) is a mild, often exanthematous disease of childhood that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the **congenital rubella syndrome (CRS)**.

ETIOLOGY

Rubella virus is a member of the family Togaviridae and is the only species of the genus *Rubivirus.* It is a positive-sense single-stranded RNA virus with a lipid envelope and three structural proteins, including a nucleocapsid protein (C) that is associated with the nucleus and two glycoproteins, E1 and E2, that are associated with the envelope, carry the main epitopes, and therefore are the major antigenic sites of the virus. The virus is sensitive to heat, ultraviolet light, and extremes of pH but is relatively stable at cold temperatures. Humans are the only known reservoir.

EPIDEMIOLOGY

Rubella is found worldwide and circulates predominantly in late winter and early spring. In the United States, in the prevaccine era, rubella appeared to occur in major epidemics every 6-9 years, with smaller peaks interspersed every 3-4 years, and was most common in preschool-age and school-age children. During the rubella epidemic of 1964–1965 there were an estimated 12.5 million cases of rubella associated with 2,000 cases of encephalitis, more than 13,000 abortions or perinatal deaths, and 20,000 cases of CRS. After introduction of the rubella vaccine in 1969 in the United States, the incidence of rubella fell 78% and CRS cases fell 69% by 1976 (Fig. 294.1). Further decline in rubella and CRS cases occurred when certain at-risk populations were added to those for whom rubella immunization is indicated, including adolescents and college students. After years of decline, a resurgence of rubella and CRS cases occurred during 1989–1991 in association with the epidemic of measles during that period (see Fig. 294.1). Subsequently, a two-dose recommendation for rubella vaccine was implemented and resulted in a decrease in incidence of rubella from 0.45 per 100,000 population in 1990 to 0.1 per 100,000 population in 1999 and a corresponding decrease of CRS, with an average of six infants with CRS reported annually from 1992 to 2004. Mothers of these infants tended to be young, Hispanic, or foreign born. The number of reported cases of rubella continued to decline through the 1990s and the first decade of this century.

The endemic spread of rubella was declared eliminated in the United States in 2004 and eliminated in the Americas in 2015. However, cases of rubella continue to be imported into the United States from countries where it remains endemic. Accelerated global vaccine efforts have resulted in declines of rubella cases worldwide from 94,277 in 2012 to 10,194 in 2020. Rubella elimination has been verified in 93 (48%) of 194 countries, with 70% of infants globally receiving a rubella vaccine in 2020. From 2004 to 2016 there were 101 cases of rubella and 11 cases of CRS reported in the United States, all of which were imported cases of unknown source. Three of the CRS cases were acquired in Africa. This information highlights the need for continued maintenance of high levels of immunity in the United States.

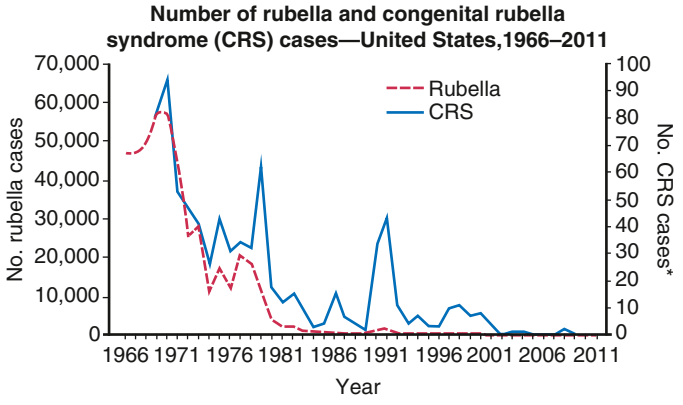

Fig. 294.1 Number of rubella and congenital rubella syndrome cases—United States, 1966–2011. Rubella and CRS data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, et al. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013. MMWR Recomm Rep. 2013;62[RR-04]:1–34.)*

PATHOLOGY

Little information is available on the pathologic findings in rubella occurring postnatally. The few reported studies of biopsy or autopsy material from cases of rubella revealed only nonspecific findings of lymphoreticular inflammation and mononuclear perivascular and meningeal infiltration. The pathologic findings for CRS are often severe and may involve nearly every organ system (Table 294.1).

PATHOGENESIS

The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well delineated. The main mechanisms of transmission is respiratory for postnatal infection and transplacental in CRS. The incubation period following respiratory exposure averages 14 days, with a range from 12 to 23 days. After infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes (Fig. 294.2). Viremia ensues and is most intense from 10 to 17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 weeks after onset of the rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

Congenital infection occurs during maternal viremia. After infecting the placenta, the virus spreads through the vascular system of the developing fetus and may infect any fetal organ. The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the first 8 weeks of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 weeks of gestation, 33% at 11-12 weeks, 11% at 13-14 weeks, and 24% at 15-16 weeks. Defects occurring after 16 weeks of gestation are uncommon, even if fetal infection occurs.

Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

CLINICAL MANIFESTATIONS

Postnatal infection with rubella is typically a mild disease not easily discernible from other viral infections, especially in children. After an incubation period of 12-23 days, a prodrome consisting of low-grade fever, sore throat, red eyes with or without eye pain, headache, malaise, anorexia, and lymphadenopathy begins. Suboccipital, postauricular, and anterior cervical lymph nodes are most prominent. In children, the first manifestation of rubella is usually the rash, which is variable and not distinctive, often more prominent with heat. It begins on the face and neck as small, irregular pink macules that coalesce, and it spreads centrifugally to involve the torso and extremities, where

it tends to occur as discrete macules (Fig. 294.3). About the time of onset of the rash, examination of the oropharynx may reveal tiny, rose-colored lesions **(Forchheimer spots)** or petechial hemorrhages on the soft palate. The rash fades from the face as it extends to the rest of the body so that the whole body may not be involved at any one time. The duration of the rash is generally 3 days, and it usually resolves without desquamation. Subclinical infections are common, and 25–40% of children may not have a rash. Teenagers and adults tend to be more symptomatic and have systemic manifestations, with up to 70% of females demonstrating arthralgias and arthritis.

TABLE 294.1 Pathologic Findings in Congenital Rubella Syndrome

SYSTEM	PATHOLOGIC FINDINGS
Cardiovascular	Patent ductus arteriosus Pulmonary artery stenosis Ventriculoseptal defect Myocarditis
Central nervous system	Chronic meningitis Parenchymal necrosis Vasculitis with calcification
Eye	Microphthalmia Cataract Iridocyclitis Ciliary body necrosis Glaucoma Retinopathy
Ear	Cochlear hemorrhage Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation Fibrosis Lobular disarray Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid Poor mineralization of osteoid Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction Absence of germinal centers
Skin	Erythropoiesis in dermis

LABORATORY FINDINGS

Leukopenia, neutropenia, and mild thrombocytopenia have been described during postnatal rubella.

DIAGNOSES

A specific diagnosis of rubella is important for epidemiologic reasons, for diagnosis of infection in pregnant women, and for confirmation of the diagnosis of congenital rubella. The most common diagnostic test is rubella immunoglobulin (Ig) M enzyme immunosorbent assay, which is typically present ~4 days after the appearance of the rash. As with any serologic test, the positive predictive value of testing decreases in populations with low prevalence of disease and in immunized individuals. Tests should be performed in the context of a supportive history of exposure or consistent clinical findings. The relative sensitivity and specificity of commercial kits used in most laboratories range from 96–99% and 86–97%, respectively. A caveat for testing of congenitally infected infants early in infancy is that false-negative results may occur owing to competing IgG antibodies circulating in these patients. In



Fig. 294.3 Rash of rubella.

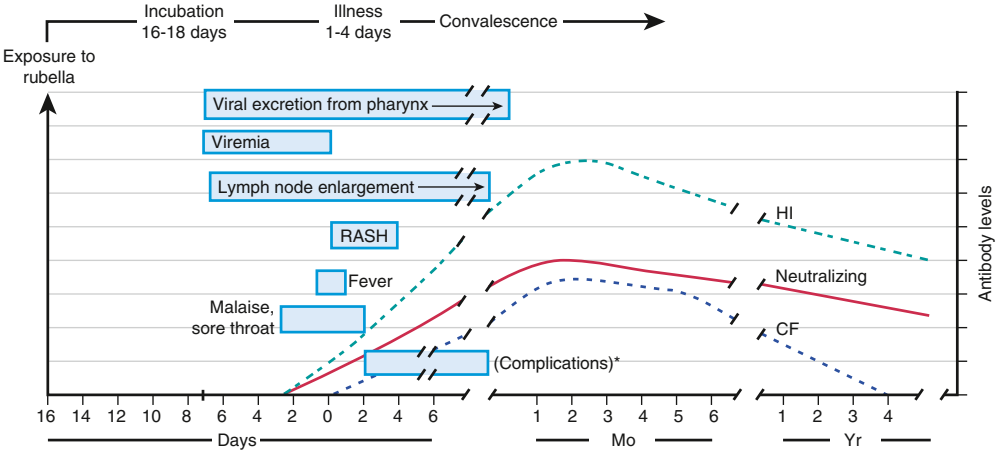

Fig. 294.2 Pathophysiologic events in postnatally acquired rubella virus infection. *Possible complications include arthralgia and/or arthritis, thrombocytopenic purpura, and encephalitis. CF, Complement fixation titer; HI, hemagglutination-inhibition titer. *(From Lamprecht CL. Rubella virus. In: Beshe RB, ed. Textbook of Human Virology, 2nd ed. Littleton, MA: PSG Publishing; 1990:685.)*

such patients, an IgM capture assay, reverse transcriptase polymerase chain reaction (PCR) test, or viral culture should be performed for confirmation. Virus can be detected by PCR in nasal, throat, urine, blood, and cerebrospinal fluid (CSF) specimens up to 10 days after rash onset (with highest yield within 3 days). Viral isolation by culture or PCR of nasopharyngeal secretions, urine in the newborn (as close to birth as possible), or cord blood or placenta can be used to diagnose congenital infection. PCR testing of amniotic fluid during pregnancy is also an appropriate approach to diagnose congenital infection. If CRS is confirmed, infants should be screened for viral shedding monthly after the age of 3 months until two consecutive negative tests are obtained. Viral shedding may be detected for up to 1 year.

DIFFERENTIAL DIAGNOSES

Rubella may manifest as distinctive features suggesting the diagnosis. It is frequently confused with other infections because it is uncommon, is similar to other viral exanthematous diseases, and demonstrates variability in the presence of typical findings. In severe cases, it may resemble measles. The absence of Koplik spots, a severe prodrome, and a shorter course, allow for differentiation from measles. Other diseases frequently confused with rubella include infections caused by adenoviruses, parvovirus B19 (erythema infectiosum), Epstein-Barr virus, enteroviruses, roseola, and *Mycoplasma pneumoniae*.

COMPLICATIONS

Complications following postnatal infection with rubella are infrequent and generally not life threatening.

Postinfectious **thrombocytopenia** occurs in approximately 1 in 3,000 cases of rubella and occurs more frequently among children and in girls. It manifests about 2 weeks after the onset of the rash as petechiae, epistaxis, gastrointestinal bleeding, and hematuria and is usually self-limited.

Arthritis following rubella occurs more commonly among adults, especially women. It begins within 1 week of onset of the exanthem and classically involves the small joints of the hands. It is self-limited and resolves within weeks without sequelae. There are anecdotal reports and some serologic evidence linking rubella with rheumatoid arthritis, but a true causal association remains speculative.

Encephalitis is the most serious complication of postnatal rubella. It occurs in two forms: a postinfectious syndrome following acute rubella and a rare progressive panencephalitis manifesting as a neurodegenerative disorder years after rubella.

Postinfectious encephalitis is uncommon, occurring in 1 in 5,000 cases of rubella. It appears within 7 days after onset of the rash, consisting of headache, seizures, confusion, coma, focal neurologic signs, and ataxia. Fever may recrudesce with the onset of neurologic symptoms. CSF may be normal or have a mild mononuclear pleocytosis and/or elevated protein concentration. Virus is rarely, if ever, isolated from CSF or brain, suggesting a noninfectious pathogenesis. Most patients recover completely, but mortality rates of 20% and long-term neurologic sequelae have been reported.

Progressive rubella panencephalitis (PRP) is an extremely rare complication of either acquired rubella or CRS. It has an onset and course similar to those of the subacute sclerosing panencephalitis associated with measles (see Chapter 293). However, unlike in the postinfectious form of rubella encephalitis, rubella virus may be isolated from brain tissue of the patient with PRP, suggesting an infectious pathogenesis, albeit a slow one. The clinical findings and course are indistinguishable from those of subacute sclerosing panencephalitis and transmissible spongiform encephalopathies (see Chapter 324). Death occurs 2-5 years after onset.

Other neurologic syndromes rarely reported with rubella include Guillain-Barré syndrome and peripheral neuritis. Myocarditis is a rare complication.

Congenital Rubella Syndrome

In 1941 an ophthalmologist first described a syndrome of cataracts and congenital heart disease that he correctly associated with rubella infections in the mothers during early pregnancy (Table 294.2). Shortly after the first description, hearing loss was recognized as a common finding often associated with microcephaly. In 1964 to 1965 a pandemic of rubella occurred, with 20,000 cases reported in the United States, leading to more than 11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths. From this experience emerged the expanded definition of CRS that includes numerous other transient or permanent abnormalities.

TABLE 294.2 Clinical Manifestations of Congenital Rubella Syndrome in 376 Children After Maternal Rubella*

MANIFESTATION	RATE (%)
Deafness	67
Ocular	71
Cataracts	29
Retinopathy	39
Heart disease†	48
Patent ductus arteriosus	78
Right pulmonary artery stenosis	70
Left pulmonary artery stenosis	56
Valvular pulmonic stenosis	40
Low birthweight	60
Psychomotor delay	45
Neonatal purpura	23
Death	35

*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.
†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.
From Cooper LZ, Ziring PR, Ockerse AB, et al. Rubella: clinical manifestations and management. *Am J Dis Child.* 1969;118:18–29.

Nerve deafness is the single most common finding among infants with CRS. Most infants have some degree of intrauterine growth restriction. Retinal findings described as **salt-and-pepper retinopathy** are the most common ocular abnormality but have little early effect on vision. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants (Fig. 294.4). Cardiac abnormalities occur in half of the children infected during the first 8 weeks of gestation. Patent ductus arteriosus is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease. Interstitial pneumonitis leading to death in some cases has been reported. Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10–20% of infants with CRS and may persist for up to 12 months. Longitudinal follow-up through 9-12 years of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. PRP has also been recognized rarely after CRS. Subsequent postnatal growth retardation and ultimate short stature have been reported in a minority of cases. Rare reports of immunologic deficiency syndromes have also been described.

A variety of late-onset manifestations of CRS have been recognized. In addition to PRP, they include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated with the retinopathy, which had previously been considered benign.

TREATMENT

There is no specific treatment available for either acquired rubella or CRS.



Fig. 294.4 Bilateral cataracts in infant with congenital rubella syndrome.

SUPPORTIVE CARE

Postnatal rubella is generally a mild illness that requires no care beyond antipyretics and analgesics. Intravenous immunoglobulin or corticosteroids can be considered for severe, nonremitting thrombocytopenia.

Management of children with CRS is more complex and requires pediatric, cardiac, audiologic, ophthalmologic, and neurologic evaluation and follow-up because many manifestations may not be readily apparent initially or may worsen with time. Hearing screening is of special importance because early intervention may improve outcomes in children with hearing problems caused by CRS.

PROGNOSIS

Postnatal infection with rubella has an excellent prognosis. Long-term outcomes of CRS are less favorable and somewhat variable. In an Australian cohort evaluated 50 years after infection, many had chronic conditions but most were married and had made good social adjustments. A cohort from New York from the mid-1960s epidemic had less-favorable outcomes, with 30% leading normal lives, 30% in dependent situations but functional, and 30% requiring institutionalization and continuous care.

Reinfection with wild virus occurs postnatally in both individuals who were previously infected with wild-virus rubella and vaccinated individuals. Reinfection is defined serologically as a significant increase in IgG antibody level and/or an IgM response in an individual who has a documented preexisting rubella-specific IgG above an accepted cutoff. Reinfection may result in an anamnestic IgG response, an IgM and IgG response, or clinical rubella. There are 29 reports in the literature of CRS following maternal reinfection. Reinfection with serious adverse outcomes to adults or children is rare and of unknown significance.

PREVENTION

Patients with postnatal infection should be isolated from susceptible individuals for 7 days after onset of the rash. Standard plus droplet precautions are recommended for hospitalized patients. Children with CRS may excrete the virus in respiratory secretions up to 1 year of age, so contact precautions should be maintained for them until 1 year of age, unless repeated cultures of urine and pharyngeal secretions are negative. Similar precautions apply to patients with CRS with regard to attendance in school and out-of-home childcare.

Exposure of susceptible pregnant women poses a potential risk to the fetus. For pregnant women exposed to rubella, a blood specimen should be obtained as soon as possible for rubella IgG-specific antibody testing; a frozen aliquot also should be saved for later testing. If the rubella antibody test result is positive, the mother is likely immune. If the rubella antibody test is negative, a second specimen should be obtained 2-3 weeks later and tested concurrently with the saved specimen. If both of these samples test negative, a third specimen should be obtained 6 weeks after exposure and tested concurrently with the saved specimen. If both the second and third specimens test negative, infection has not occurred. A negative first specimen and a positive test result in either the second or third specimen indicate that seroconversion has occurred in the mother, suggesting recent infection. Counseling should be provided about the risks and benefits of termination of pregnancy. The routine use of immunoglobulin for susceptible pregnant women exposed to rubella is not recommended and is considered only if termination of pregnancy is not an option because of maternal preferences. In such circumstances, immunoglobulin 0.55 mL/kg intramuscularly may be given with the understanding that prophylaxis may reduce the risk for clinically apparent infection but does not guarantee prevention of fetal infection.

VACCINATION

Rubella vaccine in the United States consists of the attenuated Wistar RA 27/3 strain that is usually administered in combination with measles and mumps (MMR) or also with varicella (MMRV) in a two-dose regimen at 12-15 months and 4-6 years of age. It theoretically may be effective as postexposure prophylaxis if administered within 3 days of exposure. Vaccine should not be administered to severely immunocompromised patients. Patients with HIV infection who are not severely immunocompromised may benefit from vaccination. Fever is not a contraindication, but if a more serious illness is suspected, immunization should be delayed. Immunoglobulin preparations may inhibit the serologic response to the vaccine (see Chapter 215). Vaccine should not be administered during pregnancy. If pregnancy occurs within 28 days of immunization, the patient should be counseled on the theoretical risks to the fetus. Studies of more than 200 women who had been inadvertently immunized with rubella vaccine during pregnancy showed that none of their offspring developed CRS. Therefore interruption of pregnancy is probably not warranted.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons 12 months of age and older develop serologic immunity, and after two doses 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective, because 97% of those vaccinated are protected from clinical disease after one dose. Detectable antibodies remain for 15 years in most individuals vaccinated after one dose, and 91–100% had antibodies after 12-15 years after two doses. Although antibody levels may wane, especially after one dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. MMR administration is associated with fever in 5–15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common after rubella vaccination in adults. Approximately 25% of postpubertal women experience arthralgia, and 10% of postpubertal women experience arthritis. Peripheral neuropathies and transient thrombocytopenia may also occur.

As part of the worldwide effort to eliminate endemic rubella virus transmission and occurrence of CRS, maintaining high population immunity through vaccination coverage and high-quality integrated measles-rubella surveillance have been emphasized as being vital to its success.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for a Bibliography.

Chapter 295

Mumps

Hayley A. Gans

Mumps is an acute self-limited infection that was once commonplace but is now uncommon in countries with widespread use of vaccination. It is characterized by fever, bilateral or unilateral parotid swelling and tenderness, and the frequent occurrence of meningoencephalitis and orchitis. Although infrequent in countries with extensive vaccination programs, mumps remains endemic in the rest of the world, warranting continued vaccine protection. Nonetheless, outbreaks of mumps have been reported in highly vaccinated populations in the United States, particularly among students.

ETIOLOGY

Mumps virus is in the family Paramyxoviridae and the genus *Rubulavirus*. It is a negative-sense single-stranded nonsegmented RNA virus encapsulated in a lipoprotein envelope possessing seven structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both proteins stimulate production of protective antibodies. Mumps virus exists as a single serotype with up to 12 known genotypes, and humans are the only natural host.

EPIDEMIOLOGY

In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 years and in epidemics about every 4 years. Mumps infection occurred more often in the winter and spring months. In 1968, just after the introduction of the mumps vaccine, 185,691 cases were reported in the United States. Following the recommendation for routine use of mumps vaccine in 1977, the incidence of mumps fell dramatically in young children (Fig. 295.1) and shifted instead to older children, adolescents, and young adults. Outbreaks continued to occur *even in highly vaccinated* populations as a result of primary vaccine failure with one dose of vaccine and because of undervaccination of susceptible persons. After implementation of the two-dose recommendation for the measles-mumps-rubella (MMR) vaccine for measles control in 1989, the number of mumps cases declined further. During 2001–2003, fewer than 300 mumps cases were reported each year. In 2006 the largest mumps epidemic in the past 20 years occurred in the United States. A total of 6,584 cases occurred, 85% of them in 8 midwestern states. Twenty-nine percent of the cases occurred in patients 18-24 years old, most of whom were attending college. An analysis of 4,039 patients with mumps seen in the first 7 months of the epidemic indicated that 63% had received more than two doses of the MMR vaccine. Subsequently, several outbreaks of mumps have been documented in highly vaccinated populations in the United States, several in school settings including universities and in Guam. This phenomenon is reported globally as well. The majority of cases in vaccinated persons represent close contact thought to provide intense exposure that may overcome vaccine immunity and perhaps genotype mismatch between circulating mumps genotypes and those in the vaccine. Through 2020, mumps outbreaks have continued to occur, with a peak in 2016 with 6,366 cases, which dropped to 154 in 2021.

Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1-2 days before to 5 days after onset of parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations. The risk of spreading the virus increases the longer and the closer the contact a person has with someone who has mumps. The U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Health Infection Control Practices Advisory Committee recommend an isolation period of 5 days after onset of parotitis for patients with mumps in both community and healthcare settings.

PATHOLOGY AND PATHOGENESIS

Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

After infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues, including the meninges, salivary glands, pancreas, testes, and ovaries. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

CLINICAL MANIFESTATIONS

The incubation period for mumps ranges from 12-25 days but is usually 16-18 days. Mumps virus infection may result in clinical presentation

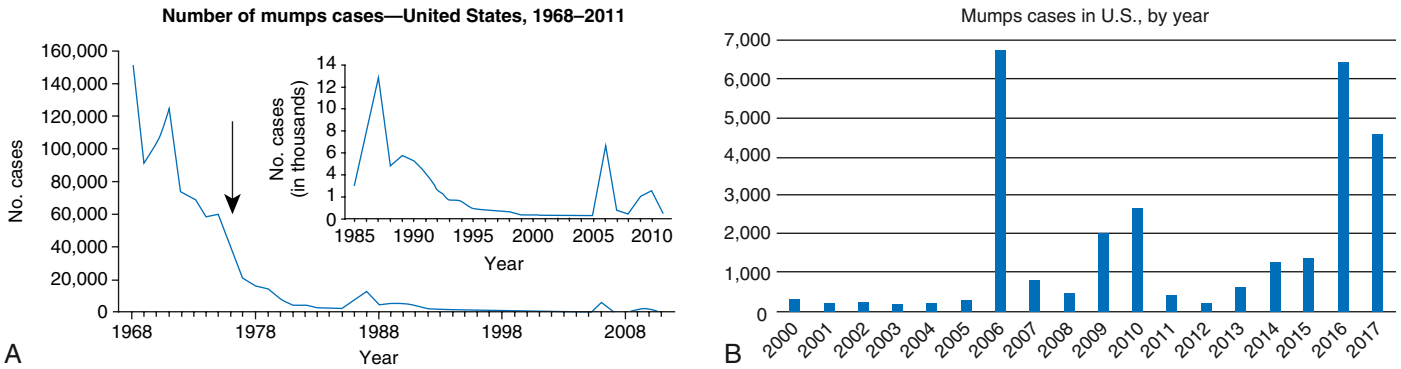

Fig. 295.1 **A,** Mumps cases in the United States from 1968, right after the live mumps vaccine was introduced in 1967, to 2011. There was a steady decline following introduction of the vaccine and recommendation for routine vaccination in 1977 *(arrow)*. Note national increases in activity in 1986–1987, 2006. Mumps data provided were reported voluntarily to the Centers for Disease Control and Prevention (CDC) from state health departments. **B,** Mumps cases in the United States from 2000–2017 showing the increased activity in 2006, 2009, 2010, and 2014–2017. Mumps data provided were reported voluntarily to CDC from state health departments. *(**A,** From McLean HQ, Fiebelkorn AP, Temte JL, et al. Prevention of measles, rubella, congenital rubella syndrome and mumps. MMWR Recomm Rep. 2013;62[RR-04]:1–34; **B,** From Morbidity and Mortality Weekly Report (MMWR): Notifiable Diseases and Mortality Tables. https://www.cdc.gov/mumps/outbreaks.html.)*

ranging from asymptomatic (in the prevaccine era 15–24% of infections were asymptomatic; accurate estimates in the postvaccination era are difficult to measure) or nonspecific symptoms to the typical illness associated with parotitis with or without complications involving several body systems. The typical patient presents with a prodrome lasting 1-2 days consisting of fever, headache, vomiting, malaise, and myalgias. Parotitis follows and may be unilateral initially but becomes bilateral in approximately 70% of cases (Fig. 295.2). The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured, and the ear lobe may be lifted upward and outward (see Figs. 295.2 and 295.3). The opening of the Stensen duct may be red and edematous. The parotid swelling peaks in approximately 3 days and then gradually subsides over 7 days. Fever and the other systemic symptoms resolve in 3-5 days. A morbilliform rash is rarely seen. Submandibular salivary glands may also be involved or may be enlarged without parotid swelling. Edema over the sternum as a result of lymphatic obstruction may also occur. Symptoms in immunized individuals are the same but tend to be less severe, and parotitis may be absent.

DIAGNOSIS

When mumps was highly prevalent, the diagnosis could be made on the basis of a history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings. Confirmation of the presence of parotitis could be made with demonstration of an elevated serum amylase value. Leukopenia with a relative lymphocytosis was a common finding. Currently, in highly immunized populations patients with parotitis lasting longer than 2 days and of unknown cause, a specific diagnosis of mumps should be confirmed or ruled out by virologic or serologic examination. This step may be accomplished by isolation of the virus in cell culture, detection of viral antigen by direct immunofluorescence, or identification of nucleic acid by reverse transcriptase polymerase chain reaction (PCR). Virus can be isolated from upper respiratory tract secretions (buccal and oropharyngeal mucosa), CSF, or urine during the acute illness; however, PCR from the oropharyngeal secretions becomes negative quickly, especially in immunized individuals, and thus should be run within 3 days of parotid swelling. Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G (IgG) antibody between acute and convalescent serum specimens as detected by complement fixation, neutralization hemagglutination, or enzyme immunoassay tests establishes the diagnosis. Mumps IgG antibodies may cross react with antibodies to parainfluenza virus in serologic testing. More commonly, an enzyme immunoassay for mumps IgM antibody is used to identify recent infection. All serologic tests are difficult to interpret in immunized individuals, and negative test results do not rule out mumps infection. Skin testing for mumps is neither sensitive nor specific and should not be used.

DIFFERENTIAL DIAGNOSIS

Parotid swelling may be caused by many other infectious and noninfectious conditions, especially in sporadic cases. Viruses that cause parotitis include parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV. Purulent parotitis, usually caused by *Staphylococcus aureus,* is unilateral, is extremely tender, is associated with an elevated white blood cell count, and may involve purulent drainage from the Stensen duct. Submandibular or anterior cervical adenitis from a variety of pathogens may also be confused with parotitis. Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, immunologic diseases, tumor, and drugs.

COMPLICATIONS

The most common complications of mumps are meningitis, with or without encephalitis, and gonadal (orchitis, oophoritis) involvement. Uncommon complications include conjunctivitis, optic neuritis, pneumonia, nephritis, pancreatitis, mastitis, and thrombocytopenia. Complications can occur in the absence of parotitis, especially in immunized individuals, and overall complication rates in immunized individuals are lower than in unimmunized and are shifted toward the adult populations.

Maternal infection with mumps during the first trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Meningitis and Meningoencephalitis

Mumps virus is neurotropic and is thought to enter the CNS via the choroid plexus and infect the choroidal epithelium and ependymal cells, both of which can be found in CSF along with mononuclear leukocytes. In the prevaccine era mumps represented one of the most common causes of aseptic meningitis and hearing loss among children. Symptomatic CNS involvement occurs in 10–30% of infected individuals, but CSF pleocytosis has been found in 40–60% of patients with mumps parotitis. The meningoencephalitis may occur before, along with, or following the parotitis. It most commonly manifests 5 days after the parotitis. Clinical findings vary with age. Infants and young children have fever, malaise, and lethargy, whereas older children, adolescents, and adults complain of headache and demonstrate

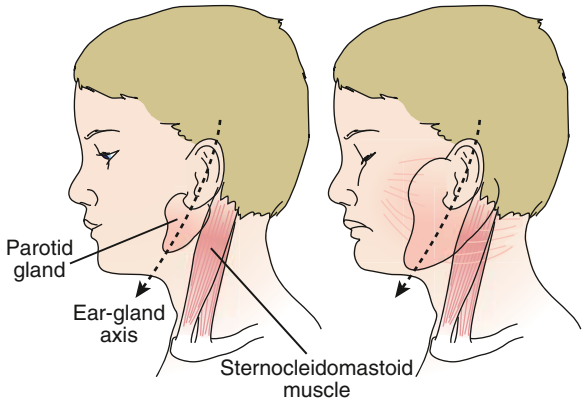

Fig. 295.2 Schematic of a parotid gland infected with mumps *(right)* compared with a normal gland *(left)*. An imaginary line bisecting the long axis of the ear divides the parotid gland into two equal parts. These anatomic relationships are not altered in the enlarged gland. An enlarged cervical lymph node is usually posterior to the imaginary line. *(From Mumps [epidemic parotitis]. In Krugman S, Ward R, Katz SL, eds. Infectious Diseases in Children, 6th ed. St. Louis: Mosby; 1977:182.)*



Fig. 295.3 A child with mumps showing parotid swelling. *(From the Centers for Disease Control and Prevention. Public Health Image Library [PHIL], Image 4491. https://phil.cdc.gov/Details.aspx?pid=4491.)*

meningeal signs. In a series of children with mumps and meningeal involvement, findings were fever in 94%, vomiting in 84%, headache in 47%, parotitis in 47%, neck stiffness in 71%, lethargy in 69%, and seizures in 18%. In typical cases, symptoms resolve in 7-10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200-600 μL with a predominance of lymphocytes. The CSF glucose content is normal in most patients, but a moderate hypoglycorrhachia (glucose content 20-40 mg/dL) may be seen in 10–20% of patients. The CSF protein content is normal or mildly elevated.

Less-common CNS complications of mumps include transverse myelitis, acute disseminated encephalomyelitis **(ADEM)**, aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare and has been estimated to occur in 0.5-5.0 in 100,000 cases of mumps. The hearing loss can be transient. There is some evidence that hearing loss is more likely in patients with meningoencephalitis.

Orchitis and Oophoritis

In adolescent and adult males, orchitis is second only to parotitis as a common finding in mumps. Involvement in prepubescent boys is extremely rare, but after puberty, orchitis occurs in 30–40% of males. It begins within days following onset of parotitis in most cases and is associated with moderate to high fever, chills, and exquisite pain and swelling of the testes. In 30% or less of cases, the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement.

Oophoritis is uncommon in postpubertal females but may cause severe pain and may be confused with appendicitis when located on the right side.

Pancreatitis

Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

Cardiac Involvement

Myocarditis has been reported in mumps, and molecular studies have identified mumps virus in heart tissue taken from patients with endocardial fibroelastosis.

Arthritis

Arthralgia, monoarthritis, and migratory polyarthritis have been reported in mumps. Arthritis is seen with or without parotitis and usually occurs within 3 weeks of onset of parotid swelling. It is generally mild and self-limited.

Thyroiditis

Thyroiditis is rare following mumps. It has not been reported without parotitis and may occur weeks after the acute infection. Most cases resolve, but some become relapsing and result in hypothyroidism.

TREATMENT

No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintaining adequate hydration. Antipyretics may be given for fever.

PROGNOSIS

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported. No mumps deaths have occurred in the recent outbreaks in the United States.

PREVENTION

Immunization with the live mumps vaccine is the primary mode of prevention used in the United States. It is given as part of the MMR two-dose vaccine schedule, at 12-15 months of age for the first dose and 4-6 years of age for the second dose. If not given at 4-6 years, the second dose should be given before children enter puberty. In those traveling, two doses are recommended in individuals older than 12 months administered at least 28 days apart. Antibody develops in 94% (range: 89–97%) after one dose. Antibody levels achieved after vaccination are lower than after natural infection.

The median vaccine effectiveness of mumps vaccine after one dose of vaccine is 78% (range: 49–92%) and after two doses is 88% (range: 66–95%). Duration of effectiveness is ≥10 years after one dose and ≥15 years after two doses.

During outbreaks, *a third MMR dose* administered to the at-risk population was associated with improved outbreak control with significantly fewer cases in those receiving the third dose compared with those not receiving it. Despite these results, modeling supports the current two-dose schedule without a routine third booster dose because the current regimen significantly controls size of outbreaks, severity of disease, and number of hospitalizations, whereas the third dose appears to be a possible strategy during an outbreak.

As a live-virus vaccine, MMR should not be administered to pregnant women or to severely immunodeficient or immunosuppressed individuals. HIV-infected patients who are not severely immunocompromised may receive the vaccine, because the risk for severe infection with mumps outweighs the risk for serious reaction to the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Persons with other types of reactions to egg or reactions to other components of the vaccine are not restricted from receiving the vaccine.

In 2006, in response to the multistate outbreak in the United States, evidence of immunity to mumps through vaccination was redefined. Acceptable presumptive evidence of immunity to mumps now consists of one of the following: (1) documentation of adequate vaccination at age 12 months or older, (2) laboratory evidence of immunity, (3) birth before 1957, and (4) documentation of physician-diagnosed mumps. Evidence of immunity through documentation of adequate vaccination is defined as one dose of a live mumps virus vaccine for preschool-age children and adults not at high risk and two doses for school-age children (i.e., grades K-12) and for adults at high risk (e.g., healthcare workers, international travelers, and students at post–high school educational institutions).

All persons who work in healthcare facilities should be immune to mumps. Adequate mumps vaccination for healthcare workers born during or after 1957 consists of two doses of a live mumps virus vaccine. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive two doses, with >28 days between doses. Healthcare workers who have received only one dose previously should receive a second dose. Because birth before 1957 is only presumptive evidence of immunity, healthcare facilities should consider recommending one dose of a live mumps virus vaccine for unvaccinated workers born before 1957 who do not have a history of physician-diagnosed mumps or laboratory evidence of mumps immunity. During an outbreak, healthcare facilities should strongly consider recommending two doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity.

Adverse reactions to mumps virus vaccine are rare. Parotitis and orchitis have been reported rarely. There is inadequate information to make a causal relationship to other reactions, such as febrile seizures, deafness, rash, purpura, encephalitis, and meningitis with the strain of mumps vaccine virus used for immunization in the United States. Higher rates of aseptic meningitis following vaccination for mumps are associated with vaccine strains used elsewhere in the world, including the Leningrad 3 and Urabe Am 9 strains. Transient suppression of reactivity to tuberculin skin testing has been reported after mumps vaccination.

In 2005 the quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine was made available. However, in 2010, studies showed a greater risk of febrile seizures in children 12-23 months of age 5-12 days after administration of the vaccine. No increased risk of seizures was seen in children receiving the first dose of the MMRV at older than 48 months of age. As a result, the American Academy of Pediatrics currently recommends either the MMR vaccine and separate varicella vaccine or the MMRV vaccine in children 12-47 months of age. After 48 months of age, the MMRV is generally preferred.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 296

Polioviruses

Eric A.F. Simões

ETIOLOGY

The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae family, in the genus *Enterovirus,* species enterovirus C and consist of three antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to the central nervous system (CNS), where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature.

EPIDEMIOLOGY

The most devastating result of poliovirus infection is paralysis, although 90–95% of infections are inapparent. Despite the absence of symptoms, clinically inapparent infections induce protective immunity. Clinically apparent but nonparalytic illness occurs in approximately 5% of all infections, with paralytic polio occurring in approximately 1 in 1,000 infections among infants to approximately 1 in 100 infections among adolescents. In industrialized countries before universal vaccination, epidemics of paralytic poliomyelitis occurred primarily in adolescents. Conversely, in developing countries with poor sanitation, infection early in life results in infantile paralysis. Improved sanitation explains the virtual eradication of polio from the United States in the early 1960s, when only approximately 65% of the population was immunized with the Salk vaccine, which contributed to the disappearance of circulating wild-type poliovirus in the United States and Europe.

TRANSMISSION

Humans are the only known reservoir for the polioviruses, which are spread by the fecal-oral route. Poliovirus has been isolated from feces for longer than 2 weeks before paralysis to several weeks after the onset of symptoms.

PATHOGENESIS

Polioviruses infect cells by adsorbing to the genetically determined **poliovirus receptor (CD155)**. The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shutoff of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6-8 hours and are released into the environment by disruption of the cell.

In the contact host, wild-type and vaccine strains of polioviruses gain host entry via the gastrointestinal tract. Recent studies in nonhuman primates demonstrate that the primary sites of replication are in the $CD155^+$ epithelial cells lining the mucosa of the tonsil follicle and small intestine, as well as in the macrophages/dendritic cells in the tonsil follicle and Peyer patches. Regional lymph nodes are infected, and primary viremia occurs after 2-3 days. The virus seeds multiple sites, including the reticuloendothelial system, brown fat deposits, and skeletal muscle. Wild-type poliovirus probably accesses the CNS along peripheral nerves. Vaccine strains of polioviruses do not replicate in the CNS, a feature that accounts for the safety of the live-attenuated vaccine. Occasional **revertants** (by nucleotide substitution) of these vaccine strains develop a neurovirulent phenotype and cause **vaccine-associated paralytic poliomyelitis (VAPP)**. Reversion occurs in the small intestine and probably accesses the CNS via the peripheral nerves. Poliovirus has almost never been cultured from the cerebrospinal fluid (CSF) of patients with paralytic disease, and patients with aseptic meningitis caused by poliovirus never have paralytic disease. With the first appearance of non-CNS symptoms, a secondary viremia probably occurs as a result of enormous viral replication in the reticuloendothelial system.

The exact mechanism of entry into the CNS is not known. However, once entry is gained, the virus may traverse neural pathways, and multiple sites within the CNS are often affected. The effect on motor and autonomic neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection. The poliovirus primarily infects motor neuron cells in the spinal cord **(the anterior horn cells)** and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by two to three adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis. Other neurons affected are the nuclei in the roof and vermis of the cerebellum, the substantia nigra, and, occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the first 4-6 months of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus-neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the tonsils and in the intestinal tract and deep lymphatic tissues. This early production of circulating immunoglobulin (Ig) G antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

CLINICAL MANIFESTATIONS

The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8-12 days, with a range of 5-35 days. Poliovirus infections with wild-type virus may follow one of several courses: **inapparent infection**, which occurs in 90–95% of cases and causes no disease and no sequelae; abortive poliomyelitis; nonparalytic poliomyelitis; or paralytic poliomyelitis. Paralysis, if it occurs, appears 3-8 days after the initial symptoms. The clinical manifestations of paralytic polio caused by wild or vaccine strains are comparable, although the incidence of abortive and nonparalytic paralysis with vaccine-associated poliomyelitis is unknown.

Abortive Poliomyelitis

In approximately 5% of patients, a nonspecific influenza-like syndrome occurs 1-2 weeks after infection, which is termed *abortive poliomyelitis*. Fever, malaise, anorexia, and headache are prominent features, and there may be sore throat and abdominal or muscular pain. Vomiting occurs irregularly. The illness is short lived, lasting up to 2-3 days. The physical examination may be normal or may reveal nonspecific pharyngitis, abdominal or muscular tenderness, and weakness. Recovery is complete, and no neurologic signs or sequelae develop.

Nonparalytic Poliomyelitis

In approximately 1% of patients infected with wild-type poliovirus, signs of abortive poliomyelitis are present, as are more intense headache, nausea, and vomiting, as well as soreness and stiffness of the posterior muscles of the neck, trunk, and limbs. Fleeting paralysis of the bladder and constipation are frequent. Approximately two thirds

of these children have a short symptom-free interlude between the first phase **(minor illness)** and the second phase (CNS disease or **major illness**). Nuchal rigidity and spinal rigidity are the basis for the diagnosis of nonparalytic poliomyelitis during the second phase.

Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes. Gentle forward flexion of the occiput and neck elicits nuchal rigidity. The examiner can demonstrate head drop by placing the hands under the patient's shoulders and raising the patient's trunk. Although normally the head follows the plane of the trunk, in poliomyelitis it often falls backward limply, but this response is not attributable to true paresis of the neck flexors. In struggling infants, it may be difficult to distinguish voluntary resistance from clinically important true nuchal rigidity. The examiner may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand, and then flex the head anteriorly. True nuchal rigidity persists during this maneuver. When open, the anterior fontanel may be tense or bulging.

In the early stages the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or decreased, may precede weakness by 12-24 hours. The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. The spinal and gluteal reflexes may disappear before the abdominal and cremasteric reflexes. Changes in the deep tendon reflexes generally occur 8-24 hours after the superficial reflexes are depressed and indicate impending paresis of the extremities. Tendon reflexes are absent with paralysis. Sensory defects do not occur in poliomyelitis.

Paralytic Poliomyelitis

Paralytic poliomyelitis develops in approximately 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes that represent a continuum of infection differentiated only by the portions of the CNS most severely affected. These are (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) polioencephalitis.

Spinal paralytic poliomyelitis may occur as the second phase of a biphasic illness, the first phase of which corresponds to abortive poliomyelitis. The patient then appears to recover and feels better for 2-5 days, after which severe headache and fever occur with exacerbation of the previous systemic symptoms. Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop. On physical examination the distribution of paralysis is characteristically spotty. Single muscles, multiple muscles, or groups of muscles may be involved in any pattern. Within 1-2 days, *asymmetric flaccid paralysis or paresis occurs*. Involvement of one leg is most common, followed by involvement of one arm. The proximal areas of the extremities tend to be involved to a greater extent than the distal areas. To detect mild muscular weakness, it is often necessary to apply gentle resistance in opposition to the muscle group being tested. Examination at this point may reveal nuchal stiffness or rigidity, muscle tenderness, initially hyperactive deep tendon reflexes (for a short period) followed by absence or diminution of reflexes, and paresis or flaccid paralysis. In the spinal form, there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities. *Sensation is intact; sensory disturbances, if present, suggest a disease other than poliomyelitis.*

The paralytic phase of poliomyelitis is extremely variable; some patients progress during observation from paresis to paralysis, whereas others recover, either slowly or rapidly. The extent of paresis or paralysis is directly related to the extent of neuronal involvement; paralysis occurs if >50% of the neurons supplying the muscles are destroyed. The extent of involvement is usually obvious within 2-3 days; only rarely does progression occur beyond this interval. Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention often accompany paralysis of the lower limbs.

The onset and course of paralysis are variable in developing countries. The biphasic course is rare; typically the disease manifests in a single phase in which prodromal symptoms and paralysis occur in a continuous fashion. In developing countries, where a history of intramuscular injections precedes paralytic poliomyelitis in approximately 50–60% of patients, patients may present initially with fever and paralysis **(provocation paralysis)**. The degree and duration of muscle pain are also variable, ranging from a few days usually to a week. Occasionally, spasm and increased muscle tone with a transient increase in deep tendon reflexes occur in some patients, whereas in most patients, flaccid paralysis occurs abruptly. Once the temperature returns to normal, progression of paralytic manifestations stops. Little recovery from paralysis is noted in the first days or weeks, but, if it is to occur, it is usually evident within 6 months. The return of strength and reflexes is slow and may continue to improve for as long as 18 months after the acute disease. Lack of improvement from paralysis within the first several weeks or months after onset is usually evidence of permanent paralysis. Atrophy of the limb, failure of growth, and deformity are common and are especially evident in the growing child.

Bulbar poliomyelitis may occur as a clinical entity without apparent involvement of the spinal cord. Infection is a continuum, and designation of the disease as bulbar implies only dominance of the clinical manifestations by dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extraocular, facial, and masticatory muscles) include (1) nasal twang to the voice or cry caused by palatal and pharyngeal weakness (hard-consonant words such as cookie and candy bring this feature out best); (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx, indicating partial immobility (holding the larynx lightly and asking the patient to swallow will confirm such immobility); (3) accumulated pharyngeal secretions, which may cause irregular respirations that appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness; (4) absence of effective coughing, shown by constant fatiguing efforts to clear the throat; (5) nasal regurgitation of saliva and fluids as a result of palatal paralysis, with inability to separate the oropharynx from the nasopharynx during swallowing; (6) deviation of the palate, uvula, or tongue; (7) involvement of vital centers in the medulla, which manifest as irregularities in rate, depth, and rhythm of respiration and as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature; (8) paralysis of one or both vocal cords, causing hoarseness, aphonia, and, ultimately, asphyxia unless the problem is recognized on laryngoscopy and managed by immediate tracheostomy; and (9) the **rope sign**, an acute angulation between the chin and larynx caused by weakness of the hyoid muscles (the hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet).

Uncommonly, bulbar disease may culminate in an ascending paralysis (Landry type), in which there is progression cephalad from initial involvement of the lower extremities. Hypertension and other autonomic disturbances are common in bulbar involvement and may persist for a week or more or may be transient. Occasionally, hypertension is followed by hypotension and shock and is associated with irregular or failed respiratory effort, delirium, or coma. This kind of bulbar disease may be rapidly fatal.

The course of bulbar disease is variable; some patients die as a result of extensive, severe involvement of the various centers in the medulla; others recover partially but require ongoing respiratory support, and others recover completely. Cranial nerve involvement is seldom permanent. Atrophy of muscles may be evident, patients immobilized for long periods may experience pneumonia, and renal stones may form as a result of hypercalcemia and hypercalciuria secondary to bone resorption.

Polioencephalitis is a rare form of the disease in which higher centers of the brain are severely involved. Seizures, coma, and spastic paralysis with increased reflexes may be observed. Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis that coexists or ensues. Hypoxia and hypercapnia caused by inadequate ventilation due to respiratory insufficiency may produce disorientation without true encephalitis. The manifestations are common to encephalitis of any cause and can be

attributed to polioviruses only with specific viral diagnosis or if accompanied by flaccid paralysis.

Paralytic poliomyelitis with ventilatory insufficiency results from several components acting together to produce ventilatory insufficiency resulting in hypoxia and hypercapnia. It may have profound effects on many other systems. Because respiratory insufficiency may develop rapidly, close continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort associated with anxiety and fear that overventilation may occur at the outset, resulting in respiratory alkalosis. Such effort is fatiguing and contributes to respiratory failure.

There are certain characteristic patterns of disease. Pure spinal poliomyelitis with respiratory insufficiency involves tightness, weakness, or paralysis of the respiratory muscles (chiefly the diaphragm and intercostals) without discernible clinical involvement of the cranial nerves or vital centers that control respiration, circulation, and body temperature. The cervical and thoracic spinal cord segments are chiefly affected. Pure bulbar poliomyelitis involves paralysis of the motor cranial nerve nuclei with or without involvement of the vital centers. Involvement of the 9th, 10th, and 12th cranial nerves results in paralysis of the pharynx, tongue, and larynx with consequent airway obstruction. Bulbospinal poliomyelitis with respiratory insufficiency affects the respiratory muscles and results in coexisting bulbar paralysis.

The clinical findings associated with involvement of the respiratory muscles include (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, breathless sentences; (3) increased respiratory rate; (4) movement of the alae nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements caused by diaphragmatic immobility caused by spasm or weakness of one or both leaves; and (7) relative immobility of the intercostal spaces, which may be segmental, unilateral, or bilateral. When the arms are weak, and especially when deltoid paralysis occurs, there may be impending respiratory paralysis because the phrenic nerve nuclei are in adjacent areas of the spinal cord. Observation of the patient's capacity for thoracic breathing while the abdominal muscles are splinted manually indicates minor degrees of paresis. Light manual splinting of the thoracic cage helps to assess the effectiveness of diaphragmatic movement.

DIAGNOSIS

Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease. Although this guideline is most applicable in poliomyelitis endemic countries (Afghanistan, and Pakistan in 2023), the spread of polio in 2013 from endemic countries to many nonendemic countries (Niger, Chad, Cameroon, Ethiopia, Kenya, Somalia, and Syria) and the isolation of wild poliovirus type 1 in Israel in 2014 and circulating type 1 vaccine-associated paralytic polio in Ukraine in 2015 suggest that the diagnosis of polio should be entertained in all countries. VAPP should be considered in any child with paralytic disease occurring 7-14 days after receiving the orally administered polio vaccine (OPV). VAPP can occur at later times after administration and should be considered in any child with paralytic disease in countries or regions where wild-type poliovirus has been eradicated and the OPV has been administered to the child or a contact. The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory loss, and pleocytosis does not regularly occur in any other illness.

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, two stool specimens should be collected 24-48 hours apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the first week after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80–90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus at 3-4 weeks after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal straws may be used to obtain specimens; ideally a minimum of 8-10 g of stool should be collected. In laboratories that can isolate poliovirus, isolates should be sent to either the U.S. Centers for Disease Control and Prevention (CDC) or to one of the WHO-certified poliomyelitis laboratories where DNA sequence analysis can be performed to distinguish between wild poliovirus and neurovirulent, revertant OPV strains. With the current WHO plan for global eradication of poliomyelitis, most regions of the world (the Americas, Europe, and Australia) have been certified wild-poliovirus free; in these areas, poliomyelitis is most often caused by vaccine strains. Hence it is critical to differentiate between wild-type and revertant vaccine-type strains.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20-300 cells/μL with CNS involvement. The cells in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells soon afterward. By the second week of major illness, the CSF cell count falls to near-normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50-100 mg/dL by the second week of illness. In polioencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a fourfold or greater increase in antibody titers from the acute phase of illness to 3-6 weeks later.

DIFFERENTIAL DIAGNOSIS

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis and is only one of many causes of acute flaccid paralysis (AFP) in children and adults. There are numerous other causes of acute flaccid paralysis (Table 296.1). As evidence of this point, in 2022 of the 57,983 cases of AFP reported to WHO, there were 30 cases of WPV1, 173 of cVDPV1, and 648 cases of cVDPV2. In most conditions, the clinical features are sufficient to differentiate between these various causes, but in some cases nerve conduction studies and electromyograms, in addition to muscle biopsies, may be required.

The possibility of polio should be considered in any case of acute flaccid paralysis, even in countries where polio has been eradicated. The diagnoses most often confused with polio are VAPP, West Nile virus infection, and infections caused by other enteroviruses (including EV-A71 and EV-D68), as well as Guillain-Barré syndrome, transverse myelitis, and traumatic paralysis. In **Guillain-Barré syndrome**, which is the most difficult to distinguish from poliomyelitis, the paralysis is characteristically symmetric, and sensory changes and pyramidal tract signs are common, contrasting with poliomyelitis. Fever, headache, and meningeal signs are less notable, and the CSF has few cells but an elevated protein content. **Transverse myelitis** progresses rapidly over hours to days, causing an acute symmetric paralysis of the lower limbs with concomitant anesthesia and diminished sensory perception. Autonomic signs of hypothermia in the affected limbs are common, and there is bladder dysfunction. The CSF is usually normal. **Traumatic neuritis** occurs from a few hours to a few days after the traumatic event, is asymmetric, is acute, and affects only one limb. Muscle tone and deep tendon reflexes are reduced or absent in the affected limb with pain in the gluteus. The CSF is normal.

Conditions causing pseudoparalysis do not present with nuchal-spinal rigidity or pleocytosis. These causes include unrecognized trauma, transient (toxic) synovitis, acute osteomyelitis, acute rheumatic fever, scurvy, and congenital syphilis (pseudoparalysis of Parrot).

TREATMENT

There is no specific antiviral treatment for poliomyelitis. However, pocapavir (a capsid inhibitor) and V-7404 (an enterovirus 3C protease inhibitor) are being developed potentially for use in combination for treatment of poliovirus and other enteroviral infections. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the

Table 296.1 Differential Diagnosis of Acute Flaccid Paralysis

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ANTERIOR HORN CELLS OF SPINAL CORD							
Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)	Paralysis	Incubation period 7-14 days (range: 4-35 days)	24-48 hr to onset of full paralysis; proximal → distal, asymmetric	No	Yes	Yes	Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)
Nonpolio enteroviruses (including EV-A71, EV D68)	Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	As in poliomyelitis
West Nile virus	Meningitis encephalitis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	Yes
OTHER NEUROTROPIC VIRUSES							
Rabies virus		Mo to yr	Acute, symmetric, ascending	Yes	Yes	No	±
Varicella-zoster virus	Exanthematous vesicular eruptions	Incubation period 10-21 days	Acute, symmetric, ascending	Yes	±	±	Yes
Japanese encephalitis virus		Incubation period 5-15 days	Acute, proximal, asymmetric	±	±	±	Yes
GUILLAIN-BARRÉ SYNDROME							
Acute inflammatory polyradiculo-neuropathy	Preceding infection, bilateral facial weakness	Hr to 10 days	Acute, symmetric, ascending (days to 4 wk)	Yes	Yes	±	No
Acute motor axonal neuropathy	Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement	Hr to 10 days	1-6 days	No	Yes	±	No

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 296.1 Differential Diagnosis of Acute Flaccid Paralysis—cont'd

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ACUTE TRAUMATIC SCIATIC NEURITIS							
Intramuscular gluteal injection	Acute, asymmetric	Hr to 4 days	Complete, affected limb	Yes	Yes	±	No
Acute transverse myelitis	Preceding *Mycoplasma pneumoniae*, *Schistosoma*, other parasitic or viral infection	Acute, symmetric hypotonia of lower limbs	Hr to days	Yes	Yes, early	Yes	Yes
Epidural abscess	Headache, back pain, local spinal tenderness, meningismus	Complete		Yes	Yes	±	Yes
Spinal cord compression; trauma		Complete	Hr to days	Yes	Yes	±	±
NEUROPATHIES							
Exotoxin of *Corynebacterium diphtheriae*	In severe cases, palatal paralysis, blurred vision	Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)		Yes	Yes		±
Toxin of *Clostridium botulinum*	Abdominal pain, diplopia, loss of accommodation, mydriasis	Incubation period 18-36 hr	Rapid, descending, symmetric	±	No		No
Tick bite paralysis	Ocular symptoms	Latency period 5-10 days	Acute, symmetric, ascending	No	Yes		No
DISEASES OF THE NEUROMUSCULAR JUNCTION							
Myasthenia gravis	Weakness, fatigability, diplopia, ptosis, dysarthria		Multifocal	No	No	No	No
DISORDERS OF MUSCLE							
Polymyositis	Neoplasm, autoimmune disease	Subacute, proximal → distal	Wk to mo	No	Yes		No
Viral myositis		Pseudoparalysis	Hr to days	No	No		No
METABOLIC DISORDERS							
Hypokalemic periodic paralysis		Proximal limb, respiratory muscles	Sudden postprandial	No	Yes	±	No
INTENSIVE CARE UNIT WEAKNESS							
Critical illness polyneuropathy	Flaccid limbs and respiratory weakness	Acute, following systemic inflammatory response syndrome/sepsis	Hr to days	±	Yes	±	No

Modified from Marx A, Glass JD, Sutter RW. Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance. *Epidemiol Rev*. 2000;22:298–316.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

acute phase of the illness, especially in the first week of illness, because they might result in progression of disease.

Abortive Poliomyelitis

Supportive treatment with analgesics, sedatives, an appetizing diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 weeks is desirable, and careful neurologic and musculoskeletal examinations should be performed 2 months later to detect any minor involvement.

Nonparalytic Poliomyelitis

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15-30 minutes every 2-4 hours. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some weeks, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 months after apparent recovery to detect minor residual effects that might cause postural problems in later years.

Paralytic Poliomyelitis

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the first 2-3 weeks. **Suitable body alignment** is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells. The position should be changed every 3-6 hours. **Active and passive movements** are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented. When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15-30 minutes; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychologic effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections. An appealing diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central venous catheter. An orthopedist and a physiatrist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20-25 degrees) prone position with the face to one side. Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte equilibrium is best maintained by intravenous infusion because tube or oral feeding in the first few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measured at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for preemptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

COMPLICATIONS

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation. In the later stages, because of immobilization, hypertension may occur along with hypercalcemia, nephrocalcinosis, and vascular lesions. Dimness of vision, headache, and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Cardiac irregularities are uncommon, but electrocardiographic abnormalities suggesting myocarditis occur with some frequency. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalciuria, which in turn predisposes the patient to urinary calculi, especially when urinary stasis and infection are present. High fluid intake is the only effective prophylactic measure.

PROGNOSIS

The outcome of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae. The outcome of paralytic disease is determined primarily by degree and severity of CNS involvement. In severe bulbar poliomyelitis, the mortality rate may be as high as 60%, whereas in less-severe bulbar involvement and/or spinal poliomyelitis, the mortality rate varies from 5–10%, death generally occurring from causes other than the poliovirus infection.

Maximum paralysis usually occurs 2-3 days after the onset of the paralytic phase of the illness, with stabilization followed by gradual return of muscle function. The recovery phase usually lasts about 6 months, beyond which persisting paralysis is permanent. In general, paralysis is more likely to develop in male children and female adults. Mortality and the degree of disability are greater after the age of puberty. Pregnancy is associated with an increased risk for paralytic disease. Tonsillectomy and intramuscular injections may enhance the risk for acquisition of bulbar and localized disease, respectively. Increased physical activity, exercise, and fatigue during the early phase of illness have been cited as factors leading to a higher risk for paralytic disease. Finally, it has been clearly demonstrated that type 1 poliovirus has the greatest propensity for natural poliomyelitis and type 3 poliovirus has a predilection for producing VAPP.

Postpolio Syndrome

After an interval of 30-40 years, as many as 30–40% of persons who survived paralytic poliomyelitis in childhood may experience muscle pain and exacerbation of existing weakness or development of new weakness or paralysis. This entity, referred to as postpolio syndrome, has been reported only in persons who were infected in the era of wild-type poliovirus circulation. Risk factors for postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from acute illness, and female sex.

PREVENTION

Vaccination is the only effective method of preventing poliomyelitis. Hygienic measures help to limit the spread of the infection among

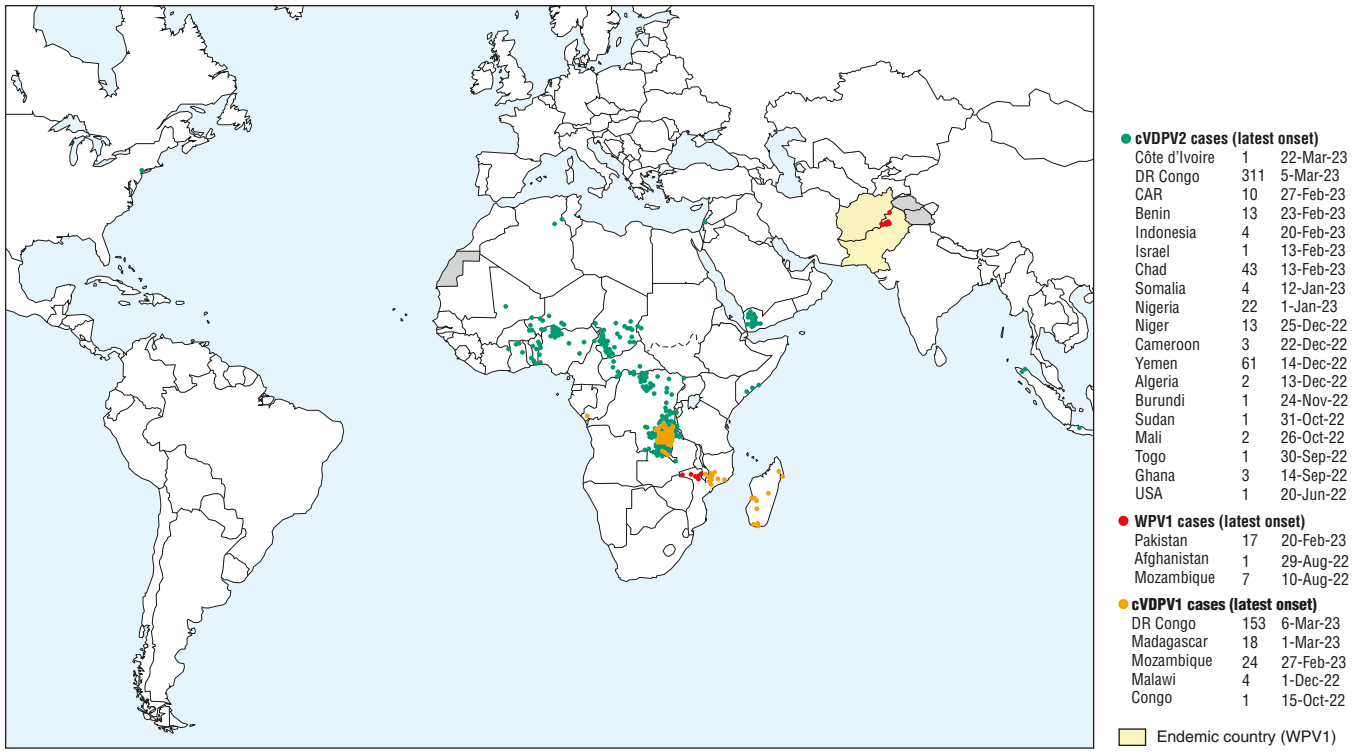

Fig. 296.1 Global WPV1 and cVDPV cases, previous 12 months. Excludes viruses detected from environmental surveillance. Onset of paralysis: 3 May 2022 to 2 May 2023; data in WHO HQ as of 2 May 2023. *(Courtesy Global Polio Eradication Initiative. https://polioeradication.org/polio-today/polio-now/. Accessed Jan 26, 2022.)*

young children, but immunization is necessary to control transmission among all age groups. Both the inactivated polio vaccine (IPV), which is currently produced using better methods than those for the original vaccine and is sometimes referred to as enhanced IPV, and the live-attenuated OPV have established efficacy in preventing poliovirus infection and paralytic poliomyelitis. Both vaccines induce production of antibodies against the three strains of poliovirus. IPV elicits higher serum IgG antibody titers, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites. Transmission of wild poliovirus by fecal spread is limited in OPV recipients. The immunogenicity of IPV is not affected by the presence of maternal antibodies, and IPV has no adverse effects. Live vaccine may undergo reversion to neurovirulence as it multiplies in the human intestinal tract and may cause VAPP in vaccinees or in their contacts. The overall risk for recipients varies from 1 case per 750,000 immunized infants in the United States to 1 in 143,000 immunized infants in India. The risk for paralysis in the B-cell–immunodeficient recipient may be as much as 6,800 times that in normal persons. HIV infection has not been found to result in long-term excretion of virus. *As of January 2000, the IPV-only schedule is recommended for routine polio vaccination in the United States.* All children should receive four doses of IPV, at 2 months, 4 months, 6-18 months, and 4-6 years of age. Five combination vaccines (DTaP-HepB-IPV-Pediarix; DTaP-IPV/Hib—Pentacel; DTaP-IPV-Hib-HepB—Vaxelis, and DTaP-IPV—Kinrix and Quadracel) and a single antigen IPV (IPOL; distributed in 10 dose vials) are approved in the United States with different schedules and ages for use. Given the rapid spread of cVPDV (Fig. 296.1) in many countries of the world, the reader is advised to refer to CDC or WHO websites to determine the necessity for accelerated vaccination of children going to identified countries. IPV can be given at a minimum of 6, 10, or 14 weeks of age with a booster at 6 months.

In 1988 the World Health Assembly resolved to eradicate poliomyelitis globally by 2000, and remarkable progress had been made toward reaching this target. To achieve this goal, the WHO used four basic strategies: routine immunization, National Immunization Days, acute flaccid paralysis surveillance, and mop-up immunization. This strategy has resulted in a >99% decline in poliomyelitis cases; in early 2002, there were only 10 countries in the world endemic for poliomyelitis. In 2012 there were the fewest cases of poliomyelitis ever and the virus was endemic in only three countries (Afghanistan, Pakistan, and Nigeria). The last case of WPV 3 infection occurred in Nigeria in November 2012, leading to certification of global WPV3 eradication. The last case of wild poliovirus type 2 infection occurred in India in October 1999. Polioviruses remain endemic in Pakistan and Afghanistan. The rejection of poliovirus vaccine initiatives and campaign quality in security-compromised areas in parts of these countries are still the main factors interfering with efforts to eradicate polio.

In May 2013 the WHO assembly recommended the development of a *Polio Eradication and Endgame Strategic Plan*. This plan included the replacement of trivalent OPV (tOPV) with bivalent OPV (bOPV) containing only Sabin types 1 and 3 in all countries by 2016 and the introduction of initially one dose of IPV followed by the replacement of bOPV with IPV in all countries of the world by 2019. As long as the OPV is being used, there is the potential that vaccine-derived poliovirus (VDPV) will acquire the neurovirulent phenotype and transmission characteristics of the wild-type polioviruses. VDPV emerges from the OPV because of continuous replication in immunodeficient persons (iVDPV) or by circulation in populations with low vaccine coverage (cVDPVs). The risk was highest with the type 2 strain. Since the world switched from the use of tOPV to bOPV, tOPV is no longer used globally in any routine or supplemental immunization activities.

Recommendations for international travelers to certain countries were made by the WHO and endorsed by the CDC. Continuing spread due to poor herd immunity and now international spread pose a significant threat to the eradication effort. The committee recommended that for countries with WPV1, cVDPV1, or cVDPV2 with potential risk of international spread, all residents and long-term visitors (i.e., >4 weeks) of all ages receive a dose of bOPV or IPV between 4 weeks and 12 months before travel to these countries. Such travelers should

be provided with an International Certificate of Vaccination of Prophylaxis to record their polio vaccination and service proof of vaccination. These countries have been advised to restrict at the point of departure the international travel of any resident lacking documentation of full vaccination, whether by air, sea, or land. For countries infected with cVDPV2 with potential risk of international spread (see Fig. 296.1 and WHO website), visitors should be encouraged to follow these recommendations (not mandated).

The WHO has mandated that infants in all countries still using bOPV should receive a dose of IPV, to offer protection against polio virus type 2. These efforts have been stymied because of the global inability to produce IPV in a large enough volume to cover all the 128 million babies born annually in the world. This problem was a crisis during the global synchronized introduction of bOPV, when several countries (e.g., India) had to use two fractional doses of IPV (1/5 dose) administered intradermally. To enhance scale-up of IPV production in countries such as India, Brazil, and China, IPV using Sabin strains of poliovirus (sIPV) were developed in Japan and China. These mitigate the stringent requirements for wild-type poliovirus culture that are normally required for IPV production. Other strategies include developing adjuvants for IPV (approved by the Danish Medicines Agency in 2019) and other novel *E.coli*–based adjuvants that could potentially lower the antigen quantities needed for each dose.

Given the ongoing spread of cVDPVs, alternative stable novel Sabin vaccine strains that do not revert to neurovirulence (nOPVs) were developed for all three strains (Bio Farma, Indonesia) and have been shown to be immunogenic, stable, and safe.

In countries where bOPV is included in routine immunization, it is best if it follows at least one dose of IPV or two doses of fractional intradermal IPV.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 297

Nonpolio Enteroviruses

Kevin B. Messacar and Mark J. Abzug

The genus *Enterovirus* contains a large number of viruses spread via the gastrointestinal and respiratory routes that produce a broad range of illnesses in patients of all ages. Many of the manifestations predominantly affect infants and young children.

ETIOLOGY

Enteroviruses are nonenveloped, single-stranded, positive-sense viruses in the Picornaviridae (small RNA virus) family, which also includes the rhinoviruses, hepatitis A virus, and parechoviruses. The original human enterovirus subgroups—polioviruses (see Chapter 296), coxsackieviruses, and echoviruses—were differentiated by their replication patterns in tissue culture and animals (Table 297.1). Enteroviruses have been reclassified on the basis of genetic similarity into four species, human enteroviruses A-D. Specific enterovirus types are distinguished by antigenic and genetic sequence differences, with enteroviruses discovered after 1970 classified by species and number (e.g., enterovirus D68 and A71). Although more than 100 types have been described, 10-15 account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are associated with specific serotypes. *The closely related human parechoviruses can cause clinical presentations similar to those associated with enteroviruses.*

Table 297.1 Classification of Human Enteroviruses

Family	Picornaviridae
Genus	*Enterovirus*
Subgroups*	Poliovirus serotypes 1-3 Coxsackie A virus serotypes 1-22, 24 (23 reclassified as echovirus 9) Coxsackie B virus serotypes 1-6 Echovirus serotypes 1-9, 11-27, 29-33 (echoviruses 10 and 28 reclassified as nonenteroviruses; echovirus 34 reclassified as a variant of coxsackie A virus 24; echoviruses 22 and 23 reclassified within the genus *Parechovirus*) Numbered enterovirus serotypes (enterovirus 72 reclassified as hepatitis A virus)

*The human enteroviruses have been alternatively classified on the basis of nucleotide and amino acid sequences into four species (human enteroviruses A-D).

Epidemiology

Enterovirus infections are common, with a worldwide distribution. In temperate climates, annual epidemic peaks occur in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33–65% of acute febrile illnesses and 55–65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States. In tropical and semitropical areas, enteroviruses typically circulate year-round. In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status. More than 25% of symptomatic infections occur in children younger than 1 year of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies.

Humans are the only known natural reservoir for human enteroviruses. Virus is primarily spread person to person, by the fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission. Virus can be transmitted vertically prenatally or in the peripartum period or possibly via breastfeeding. Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources, sewage, and wet soil. Although contamination of drinking water, swimming pools and ponds, and hospital water reservoirs may occasionally be responsible for transmission, such contamination is often considered the result rather than the cause of human infection. Transmission is common within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing. Tickborne transmission has been suggested by some authors but is not a predominant route of transmission.

Large enterovirus outbreaks have included meningitis epidemics (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus A71 in Asia and Australia; outbreaks of atypical, severe hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus D68 respiratory illness associated with acute flaccid myelitis in the Americas, Europe, and Asia; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus D70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR) and genomic sequencing help identify outbreaks and demonstrate commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, co-infections with different enterovirus serotypes, and associations between specific genogroups and/or

be provided with an International Certificate of Vaccination of Prophylaxis to record their polio vaccination and service proof of vaccination. These countries have been advised to restrict at the point of departure the international travel of any resident lacking documentation of full vaccination, whether by air, sea, or land. For countries infected with cVDPV2 with potential risk of international spread (see Fig. 296.1 and WHO website), visitors should be encouraged to follow these recommendations (not mandated).

The WHO has mandated that infants in all countries still using bOPV should receive a dose of IPV, to offer protection against polio virus type 2. These efforts have been stymied because of the global inability to produce IPV in a large enough volume to cover all the 128 million babies born annually in the world. This problem was a crisis during the global synchronized introduction of bOPV, when several countries (e.g., India) had to use two fractional doses of IPV (1/5 dose) administered intradermally. To enhance scale-up of IPV production in countries such as India, Brazil, and China, IPV using Sabin strains of poliovirus (sIPV) were developed in Japan and China. These mitigate the stringent requirements for wild-type poliovirus culture that are normally required for IPV production. Other strategies include developing adjuvants for IPV (approved by the Danish Medicines Agency in 2019) and other novel *E.coli*–based adjuvants that could potentially lower the antigen quantities needed for each dose.

Given the ongoing spread of cVDPVs, alternative stable novel Sabin vaccine strains that do not revert to neurovirulence (nOPVs) were developed for all three strains (Bio Farma, Indonesia) and have been shown to be immunogenic, stable, and safe.

In countries where bOPV is included in routine immunization, it is best if it follows at least one dose of IPV or two doses of fractional intradermal IPV.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 297

Nonpolio Enteroviruses

Kevin B. Messacar and Mark J. Abzug

The genus *Enterovirus* contains a large number of viruses spread via the gastrointestinal and respiratory routes that produce a broad range of illnesses in patients of all ages. Many of the manifestations predominantly affect infants and young children.

ETIOLOGY

Enteroviruses are nonenveloped, single-stranded, positive-sense viruses in the Picornaviridae (small RNA virus) family, which also includes the rhinoviruses, hepatitis A virus, and parechoviruses. The original human enterovirus subgroups—polioviruses (see Chapter 296), coxsackieviruses, and echoviruses—were differentiated by their replication patterns in tissue culture and animals (Table 297.1). Enteroviruses have been reclassified on the basis of genetic similarity into four species, human enteroviruses A-D. Specific enterovirus types are distinguished by antigenic and genetic sequence differences, with enteroviruses discovered after 1970 classified by species and number (e.g., enterovirus D68 and A71). Although more than 100 types have been described, 10-15 account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are associated with specific serotypes. *The closely related human parechoviruses can cause clinical presentations similar to those associated with enteroviruses.*

Table 297.1 Classification of Human Enteroviruses

Family	Picornaviridae
Genus	*Enterovirus*
Subgroups*	Poliovirus serotypes 1-3 Coxsackie A virus serotypes 1-22, 24 (23 reclassified as echovirus 9) Coxsackie B virus serotypes 1-6 Echovirus serotypes 1-9, 11-27, 29-33 (echoviruses 10 and 28 reclassified as nonenteroviruses; echovirus 34 reclassified as a variant of coxsackie A virus 24; echoviruses 22 and 23 reclassified within the genus *Parechovirus*) Numbered enterovirus serotypes (enterovirus 72 reclassified as hepatitis A virus)

*The human enteroviruses have been alternatively classified on the basis of nucleotide and amino acid sequences into four species (human enteroviruses A-D).

Epidemiology

Enterovirus infections are common, with a worldwide distribution. In temperate climates, annual epidemic peaks occur in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33–65% of acute febrile illnesses and 55–65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States. In tropical and semitropical areas, enteroviruses typically circulate year-round. In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status. More than 25% of symptomatic infections occur in children younger than 1 year of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies.

Humans are the only known natural reservoir for human enteroviruses. Virus is primarily spread person to person, by the fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission. Virus can be transmitted vertically prenatally or in the peripartum period or possibly via breastfeeding. Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources, sewage, and wet soil. Although contamination of drinking water, swimming pools and ponds, and hospital water reservoirs may occasionally be responsible for transmission, such contamination is often considered the result rather than the cause of human infection. Transmission is common within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing. Tickborne transmission has been suggested by some authors but is not a predominant route of transmission.

Large enterovirus outbreaks have included meningitis epidemics (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus A71 in Asia and Australia; outbreaks of atypical, severe hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus D68 respiratory illness associated with acute flaccid myelitis in the Americas, Europe, and Asia; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus D70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR) and genomic sequencing help identify outbreaks and demonstrate commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, co-infections with different enterovirus serotypes, and associations between specific genogroups and/or

genetic substitutions and epidemiologic and clinical characteristics. Genetic analyses have demonstrated recombination and genetic drift that lead to evolutionary changes in genomic sequence and antigenicity and extensive genetic diversity. For example, emergence of new subgenotypes and genetic lineages of enterovirus A71 may contribute to sequential outbreaks and increases in circulation.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Symptomatic and asymptomatic infected children typically shed cultivable virus from the respiratory tract for <1-3 weeks. In contrast, fecal shedding of cultivatable virus continues for as long as 7-11 weeks for acid stabile strains (e.g., poliovirus, enterovirus A71). Enterovirus RNA can be shed from mucosal sites for comparable and possibly longer periods.

PATHOGENESIS

Cell surface macromolecules, including poliovirus receptor, integrin very-late-activation antigen (VLA)-2, decay-accelerating factor/complement regulatory protein (DAF/CD55), intercellular adhesion molecule-1 (ICAM-1), ICAM-5, and coxsackievirus-adenovirus receptor, serve as viral receptors. In addition, respiratory epithelial cell sialic acids serve as receptors for enterovirus D68, enterovirus D70, and coxsackievirus A24 variants, and human scavenger receptor class B2 (SCARB2), human P-selectin glycoprotein ligand-1, and DC-SIGN are receptors for enterovirus A71. After virus attaches to a cell surface receptor, a conformational change in surface capsid proteins expels a hydrophobic pocket factor, facilitating penetration and uncoating with release of viral RNA in the cytoplasm. Translation of the positive-sense RNA produces a polyprotein that undergoes cleavage by proteases encoded in the polyprotein. Several proteins resulting from cleavage of the polyprotein guide synthesis of negative-sense RNA that serves as a template for replication of new positive-sense RNA. The genome is approximately 7,500 nucleotides long and includes a highly conserved 5′ noncoding region important for replication efficiency and a highly conserved 3′ polyA region; these regions flank a continuous region encoding viral proteins. The 5′ end is covalently linked to a small viral protein (VPg) necessary for initiation of RNA synthesis. There is significant variation within genomic regions encoding the structural proteins, leading to variability in antigenicity. Replication is followed by further cleavage of proteins and assembly into 30-nm icosahedral virions. Of the four structural proteins (VP1-VP4) in the capsid, VP1 is the most important determinant of serotype specificity. Additional regulatory proteins such as an RNA-dependent RNA polymerase and proteases are also present in the virion. Approximately 10^4-10^5 virions are released from an infected cell by lysis within 5-10 hours of infection.

Following oral or respiratory acquisition, initial replication for most enteroviruses occurs in the pharynx and intestine, possibly within mucosal M cells. The acid stability of most enteroviruses favors survival in the gastrointestinal tract. Two or more enteroviruses may invade and replicate in the gastrointestinal tract simultaneously, but interference due to replication of one type often hinders growth of the heterologous type. Initial replication of most enteroviruses in the pharynx and intestine is followed within days by multiplication in lymphoid tissue, such as tonsils, Peyer patches, and regional lymph nodes. A primary, transient viremia **(minor viremia)** results in spread to distant parts of the reticuloendothelial system, including the liver, spleen, bone marrow, and distant lymph nodes. Host immune responses may limit replication and progression beyond the reticuloendothelial system, resulting in subclinical infection. Clinical infection occurs if replication proceeds in the reticuloendothelial system and virus spreads via a secondary, sustained viremia **(major viremia)** to target organs such as the CNS, heart, and skin. *Tropism to target organs is determined in part by the infecting serotype.* Some enteroviruses, such as enterovirus D68, can be acid-labile and bind sialic acid receptors on respiratory epithelial cells in the upper and lower respiratory tract and primarily produce respiratory illness. Cytokine responses may contribute to development of respiratory disease by these viruses. Enterovirus D68 RNA has also been transiently detected by PCR in the blood of young children with enterovirus D68 pneumonia when drawn soon after illness onset.

Enteroviruses can damage a wide variety of organs and systems, including the CNS, heart, liver, lungs, pancreas, kidneys, muscle, and skin. Damage is mediated by necrosis and the inflammatory response. **CNS infections** are often associated with pleocytosis in the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. **Encephalitis** during enterovirus A71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and can be complicated by pulmonary edema, pulmonary hemorrhage, and/or interstitial pneumonitis, presumed secondary to brainstem damage; sympathetic hyperactivity; myoclonus; ataxia; autonomic dysfunction; and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression). Immunologic cross-reactivity with brain tissue has been postulated as one mechanism responsible for neurologic damage and sequelae following enterovirus A71 infection.

Enterovirus **myocarditis** is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocyte damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

The potential for enteroviruses to cause persistent infection is controversial. Persistent infection in dilated cardiomyopathy and in myocardial infarction has been suggested, but enterovirus RNA sequences and/or antigens have been demonstrated in cardiac tissues in some, but not other, series. Infections with enteroviruses such as coxsackievirus B4, during gestation or subsequently, have been implicated as a trigger for development of β-cell autoantibodies and/or type 1 diabetes in genetically susceptible hosts. Persistent infection in the pancreas, intestine, or peripheral blood mononuclear cells, with downstream immunomodulatory effects, has been suggested, but data are inconsistent. Similarly, persistent infection has been implicated in a variety of conditions, including amyotrophic lateral sclerosis, Sjögren syndrome, chronic fatigue syndrome, and gastrointestinal tumors. Early enterovirus infection was associated with reduced risk of developing lymphocytic and myeloid leukemia in a large retrospective Taiwanese cohort study.

Severe **neonatal infections** can produce hepatic necrosis, hemorrhage, inflammation, endotheliitis, and venoocclusive disease; myocardial mixed inflammatory infiltrates, edema, and necrosis; meningeal and brain inflammation, hemorrhage, gliosis, necrosis, and white matter damage; inflammation, hemorrhage, thrombosis, and necrosis in the lungs, pancreas, and adrenal glands; and disseminated intravascular coagulation. In utero infections are characterized by placentitis and infection of multiple fetal organs such as heart, lung, and brain.

Development of type-specific neutralizing antibodies appears to be the most important immune defense, mediating prevention against and recovery from infection. Immunoglobulin (Ig) M antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Although local reinfection of the gastrointestinal tract can occur, replication is usually limited and not associated with disease. In vitro and animal experiments suggest that heterotypic antibody may enhance disease caused by a different serotype. Evidence also suggests that subneutralizing concentrations of serotype-specific antibody may lead to antibody-dependent enhancement of enterovirus A71 infection. Innate and cellular defenses (macrophages and cytotoxic T lymphocytes) may play important roles in recovery from infection. Altered cellular responses to enterovirus A71, including T lymphocyte and natural killer cell depletion, have been associated with severe meningoencephalitis and pulmonary edema.

Hypogammaglobulinemia and *agammaglobulinemia predispose to severe, often chronic enterovirus infections.* Similarly, perinatally infected neonates lacking maternal type-specific antibody to the infecting virus are at risk for severe disease. Enterovirus A71 disease increases after 6 months of age, when maternal serotype-specific antibody levels have



Fig. 297.1 A, Oval blisters of the palms in a child with hand-foot-and-mouth disease (coxsackievirus A16 infection). B, Oval blisters on the feet of a child with hand-foot-and-mouth disease. C, Erosion of the tongue in a child with hand-foot-and-mouth disease. *(From Weston WL, Lane AT, Morelli JG. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002:109.)*

declined. Other risk factors for significant illness include young age, immune suppression (posttransplantation and lymphoid malignancy), and, according to animal models and/or epidemiologic observations, exercise, cold exposure, malnutrition, and pregnancy. Specific human leukocyte antigen genes, immune response gene (e.g., interleukin-10 and interferon-γ) polymorphisms, and low vitamin A levels have been linked to enterovirus A71 susceptibility and severe disease.

CLINICAL MANIFESTATIONS

Manifestations are protean, ranging from asymptomatic infection to undifferentiated febrile or respiratory illnesses, often in association with exanthems and/or enanthems, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as important sources for spread of infection. Symptomatic disease is generally more common in young children.

Nonspecific Febrile Illness

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to differentiate clinically from serious infections such as urinary tract infection, bacteremia, and bacterial meningitis, often necessitating hospitalization with diagnostic testing and presumptive antibiotic therapy for suspected bacterial infection in young infants.

Illness usually begins abruptly with fever of 38.5–40°C (101.3–104°F), malaise, and irritability. Associated symptoms may include lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms. Older children may have headaches and myalgias. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal injection, and cervical lymphadenopathy. Meningitis may be present, but specific clinical features such as meningeal findings or bulging anterior fontanelle distinguishing those with meningitis are often lacking in infants. Fever lasts a mean of 3 days and occasionally is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 week. White blood cell (WBC) count, inflammatory biomarkers (e.g., C-reactive protein, erythrocyte sedimentation rate), and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection is rare but has been observed in a small number of infants, most commonly with urinary tract infections.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in cases of pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Serotypes commonly associated with rashes are echoviruses 9, 11, 16, and 25; coxsackie A viruses 2, 4, 6, 9, and 16; coxsackie B viruses 3-5; and enterovirus A71. Virus can occasionally be recovered from vesicular skin lesions.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by enterovirus A71; coxsackie A viruses 5, 6, 7, 9, and 10; coxsackie B viruses 2 and 5; and some echoviruses. It is usually a mild illness, with or without low-grade fever. When the mouth is involved, the oropharynx is inflamed and often contains scattered, painful vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips (Fig. 297.1). These lesions may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin (see Figs. 297.1 and 297.2). Skin lesions occur more commonly on the hands than feet and are more common on dorsal surfaces, but frequently also affect palms and soles. Hand and foot lesions are usually tender, 3-7–mm vesicles that resolve in about 1 week. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes described as **eczema coxsackium** may complicate preexisting eczema. Coxsackievirus A6, in particular, is responsible for relatively severe, atypical hand-foot-and-mouth disease (and herpangina) affecting adults and children that is characterized by fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles (see Fig. 297.2). **Onychomadesis** (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections. Hand-foot-and-mouth disease caused by enterovirus A71 can be associated with neurologic and cardiopulmonary involvement, especially in young children (see "Neurologic Manifestations," later). Hand-foot-and-mouth disease caused by coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and painful lesions in the posterior pharynx. Temperatures range from normal to 41°C (105.8°F); fever tends to be higher in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2–mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. The number of lesions can range from 1 to >15 but is most commonly around 5. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications. However, dehydration as a result of decreased oral intake may occur with more severe illness; meningitis can also sometimes occur. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. A variety of enteroviruses cause herpangina, including enterovirus A71, but coxsackie A viruses are implicated most often.



Fig. 297.2 Atypical hand-foot-and-mouth disease. Vesiculobullous rash on the right buttock and posterior thigh. *(From Waldman A, Thomas L, Thacker S, et al. Vesiculobullous eruption as an atypical hand, foot, and mouth presentation. J Pediatr. 2016;179:273. Fig. B.)*

Respiratory Manifestations

Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients. Clusters and outbreaks of cases of severe respiratory disease, including pneumonia and wheezing (both in children with a history of asthma and those unaffected by asthma), have been increasingly recognized in association with multiple lineages of enterovirus D68.

Pleurodynia (Bornholm disease), caused most frequently by coxsackie B viruses 3, 5, 1, and 2 and echoviruses 1 and 6, is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, as a result of myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, which occur every 10-20 years, children and adults are affected, but most cases occur in persons younger than age 30 years. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe, and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub is noted during pain episodes in <10% of patients. Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Pain usually subsides within 3-6 days but may persist for up to weeks. Symptoms may occur in a biphasic or, rarely, recurrent pattern, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis.

Life-threatening noncardiogenic pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus A71 brainstem encephalitis.

Ocular Manifestations

Epidemics of **acute hemorrhagic conjunctivitis**, primarily caused by enterovirus D70 and coxsackievirus A24/A24 variant, are explosive and marked by high contagiousness, with spread mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 years of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Subconjunctival hemorrhage is the hallmark of enterovirus D70 cases (>70%) but is more rare with coxsackievirus infections. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms, including fever and headache, occur in up to 20% of cases; manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 weeks. Polyradiculoneuropathy or acute flaccid paralysis following enterovirus D70 infection occurs occasionally. Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis.

Epidemic and sporadic uveitis in infants caused by subtypes of enteroviruses 11 and 19 can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Myocarditis and Pericarditis

Enteroviruses account for approximately 25–35% of cases of myocarditis and pericarditis of proven etiology (see Chapters 488 and 489). Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults (especially physically active males) are disproportionately affected. Myopericarditis may be the dominant feature, or it may be one manifestation of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory tract symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement, and echocardiography may confirm ventricular dilation, reduced contractility, and/or pericardial effusion. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and serum myocardial enzyme concentrations are often elevated. The acute mortality of enterovirus myocarditis is 0–4%. Recovery is complete without residual disability in the majority of patients. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result. The role of persistent infection in chronic dilated cardiomyopathy is controversial. Enteroviruses have also been implicated in late adverse cardiac events following heart transplantation and in acute cardiac events such as myocardial infarction, endocarditis, and peripartum cardiomyopathy. Cardiopulmonary dysfunction observed in enterovirus A71 epidemics most commonly occurs without evidence of myocarditis and may be of neurogenic origin; however, true myocarditis has also been described.

Gastrointestinal and Genitourinary Manifestations

Gastrointestinal symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis, most commonly presenting in adolescents. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed approximately 2 weeks later by orchitis, often with epididymitis. Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

Neurologic Manifestations

Enteroviruses are the most common cause of viral **meningitis** in mumps-immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 months of age, often during community epidemics. Frequently implicated serotypes include coxsackie B viruses 2-5; echoviruses 4, 6, 7, 9, 11, 13, 16, and 30; and enteroviruses D70 and A71. Most cases in infants and young children are mild and lack specific meningeal signs, whereas nuchal rigidity is apparent in more than half of children older than 1-2 years of age. Fever is present in 50–100% and may be accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Some cases are biphasic, with fever and nonspecific symptoms lasting a few days and followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 week. In adults, symptoms tend to be more severe and of longer duration. CSF findings include pleocytosis (generally <500 but occasionally as high as 1,000-8,000 WBCs/μL; often predominantly polymorphonuclear cells in the first 48 hours before becoming mostly mononuclear); normal or slightly low glucose content (10% <40 mg/dL); and normal or mildly increased protein content (generally <100 mg/dL). *CSF parameters are normal in up to half of young infants despite detection of enterovirus in CSF and may also be normal in older children early after illness onset.* Acute complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The long-term prognosis for most children, even in those with acute complications, is good.

Enteroviruses are also responsible for ≥10–20% of cases of **encephalitis** with an identified cause. Frequently implicated serotypes include echoviruses 3, 4, 6, 9, and 11; coxsackie B viruses 2, 4, and 5; coxsackie A virus 9; and enterovirus A71. After initial nonspecific symptoms, there is progression to encephalopathy characterized by confusion, weakness, lethargy, and/or irritability. Symptoms are most commonly generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Meningeal signs and CSF indices similar to those of enteroviral meningitis are commonly present, leading to characterization of most cases as **meningoencephalitis**. Severity ranges from mild alteration in mental status to coma and decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsy, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been observed rarely.

Neurologic manifestations have been prominent in epidemics in Asia and Australia of enterovirus A71, and, to a lesser extent, coxsackievirus A16 disease. Many affected children have had hand-foot-and-mouth disease, some have had herpangina, and others have had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children have included meningitis, meningoencephalomyelitis, **acute flaccid paralysis**, Guillain-Barré syndrome, transverse myelitis, acute disseminated encephalomyelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and **brainstem encephalitis** (**rhombencephalitis** involving the midbrain, pons, and medulla). Enterovirus A71 rhombencephalitis is characterized by altered consciousness, myoclonus, vomiting, ataxia, nystagmus, tremor, cranial nerve abnormalities, autonomic dysfunction, and MRI demonstrating lesions in the brainstem, thalamus, and cerebellum. Although the disease has been mild and reversible in some children, others have had rapid progression to noncardiogenic (presumed neurogenic) pulmonary edema and hemorrhage, cardiopulmonary failure, shock, and coma. High mortality rates have been reported in children younger than 5 years of age, especially in those younger than 1 year of age. Deficits such as central hypoventilation, bulbar dysfunction, neurodevelopmental delay, cerebellar defects, attention deficit/hyperactivity–related symptoms, persistent limb weakness, and muscle atrophy have been observed among survivors, especially those who experienced cardiopulmonary failure or acute flaccid paralysis during their acute illness. Although the most severe cases have been associated with enterovirus A71, similar clinical pictures have been produced by other enterovirus serotypes (e.g., coxsackieviruses A16 and B5, echovirus 7).

Patients with **antibody or combined immunodeficiencies** (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, **chronic enterovirus meningoencephalitis**. The latter is characterized by persistent CSF abnormalities, viral detection in CSF or brain tissue for years, and recurrent encephalitis and/or progressive neurologic deterioration, including insidious intellectual or personality deterioration, altered mental status, seizures, motor weakness, and increased intracranial pressure. Although disease may wax and wane, deficits generally become progressive and ultimately are frequently fatal or lead to long-term sequelae. A **dermatomyositis-like syndrome**, hepatitis, arthritis, myocarditis, or disseminated infection may also occur. Chronic enterovirus meningoencephalitis has become less common with prophylactic high-dose intravenous immunoglobulin replacement in agammaglobulinemic patients.

A variety of nonpoliovirus enteroviruses, including enteroviruses D68, D70, A71, coxsackie A viruses 7 and 24, coxsackie B viruses, and several echoviruses, have been associated with acute flaccid paralysis with motor weakness as a result of spinal cord anterior horn cell involvement. **Acute flaccid myelitis** is used to designate the clinical syndrome of acute flaccid limb weakness with longitudinal MRI abnormalities in the spinal cord gray matter. Neurologic abnormalities are commonly preceded by a febrile respiratory or gastrointestinal prodromal illness around 1 week before onset. Limb involvement tends to be asymmetric and varies from one to all four limbs, with severity ranging from mild weakness to complete paralysis. Cranial nerve dysfunction, including bulbar paralysis, and respiratory failure requiring ventilator support, similar to poliovirus poliomyelitis, have been described in acute flaccid myelitis cases associated with enterovirus D68 and enterovirus A71. Sensory involvement, encephalopathy, seizures, and supratentorial imaging changes are uncommon with enterovirus D68 infection. Functional improvements may be seen over time, but muscle atrophy with limb weakness and some degree of disability persist in the vast majority of cases. A proportion of children with acute flaccid myelitis will have a need for long-term tracheostomy, ventilation, and enteral feeding tubes as a result of persistent bulbar or respiratory paralysis, and scoliosis requiring spinal fusion, limb deformity requiring orthotics and assistive devices, and low bone density predisposing to fractures are common. Nerve transfer surgical procedures that involve splitting and moving functioning nerves to completely denervated muscles have been used to improve functional outcomes in select cases.

Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome (including Miller Fisher variant) and axonal polyneuropathy; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and polymyositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected patients with hypogammaglobulinemia. Enteroviruses are a rare cause of arthritis in normal hosts.

Neonatal Infections

Neonatal infections are relatively common, with a disease incidence comparable to or greater than that of symptomatic neonatal herpes simplex virus, cytomegalovirus, and group B streptococcus infections. Infection frequently is caused by coxsackie B viruses 2-5 and

echoviruses 6, 9, 11, and 19, although many serotypes have been implicated, including coxsackie B virus 1 and echovirus 30 in more recent years. Enteroviruses may be acquired vertically before, during, or after delivery, including possibly via breast milk; horizontally from family members; or by sporadic or epidemic transmission in nurseries. In utero infection can lead to fetal demise, nonimmune hydrops fetalis, or neonatal illness. Additionally, maternal and intrauterine infections have been speculatively linked to congenital anomalies; prematurity, low birthweight, and intrauterine growth restriction; neurodevelopmental sequelae; unexplained neonatal illness and death; and increased risk of type 1 diabetes and schizophrenia.

The majority of neonatal infections are asymptomatic, and symptomatic presentations range from benign febrile illness to severe multisystem disease. Most affected newborns are full term and previously well. Maternal history often reveals a recent viral illness preceding or immediately following delivery, which may include fever and abdominal pain. Neonatal symptoms may occur as early as day 1 of life, with onset of severe disease generally within the first 2 weeks of life. Frequent findings include fever or hypothermia, irritability, lethargy, anorexia, rash (usually maculopapular, occasionally petechial or papulovesicular), jaundice, respiratory symptoms, apnea, hepatomegaly, abdominal distention, emesis, diarrhea, and decreased perfusion. Most patients have benign courses, with resolution of fever in an average of 3 days and of other symptoms in about 1 week. A biphasic course may occur occasionally. A minority have severe disease dominated by any combination of sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and/or pneumonitis. Meningoencephalitis may be manifested by focal or complex seizures, bulging fontanelle, nuchal rigidity, and/or reduced level of consciousness. Myocarditis, most often associated with coxsackie B virus infection, may be suggested by tachycardia, dyspnea, cyanosis, and cardiomegaly. Hepatitis and pneumonitis are most often associated with echovirus infection, although they may also occur with coxsackie B viruses. Gastrointestinal manifestations may be prominent in premature neonates. Laboratory and radiographic evaluation may reveal leukocytosis, thrombocytopenia, CSF pleocytosis, CNS white matter damage, elevations of serum transaminases and bilirubin, coagulopathy, pulmonary infiltrates, and electrocardiographic changes.

Complications of severe neonatal disease include CNS necrosis and generalized or focal neurologic compromise; arrhythmias, congestive heart failure, myocardial infarction, and pericarditis; hepatic necrosis and failure; coagulopathy with intracranial or other bleeding; adrenal necrosis and hemorrhage; and rapidly progressive pneumonitis and pulmonary hypertension. Myositis, arthritis, necrotizing enterocolitis, inappropriate antidiuretic hormone secretion, hemophagocytic lymphohistiocytosis-like presentation, bone marrow failure, and sudden death are rare events. Mortality with severe disease is significant and is most often associated with hepatitis and bleeding complications, myocarditis, and/or pneumonitis.

Survivors of severe neonatal disease may have gradual resolution of hepatic and cardiac dysfunction, although persistent hepatic dysfunction and residual cardiac impairment, chronic calcific myocarditis, and ventricular aneurysm may occur. Meningoencephalitis may be associated with speech and language impairment; cognitive deficits; spasticity, hypotonicity, or weakness; seizure disorders; microcephaly or hydrocephaly; and ocular abnormalities. However, many survivors appear to have no long-term sequelae. Risk factors for severe disease include illness onset in the first few days of life; maternal illness just before or after delivery; prematurity; male sex; infection by echovirus 11 or a coxsackie B virus; positive serum viral culture; absence of neutralizing antibody to the infecting virus; and evidence of severe hepatitis, myocarditis, and/or multisystem disease.

Transplant Recipients and Patients with Malignancies

Enterovirus infections in stem cell and solid organ transplant recipients may be severe and/or prolonged, causing progressive pneumonia, severe diarrhea, pericarditis, heart failure, meningoencephalitis, and disseminated disease. Enterovirus-associated hemophagocytic lymphohistiocytosis, meningitis, encephalitis, acute flaccid myelitis, and myocarditis have been reported in children with malignancies and patients treated with anti-CD20 monoclonal antibody. Infections in these groups are associated with high fatality rates.

DIAGNOSIS

Clues to enterovirus infection include characteristic findings such as hand-foot-and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. Acute flaccid myelitis due to enterovirus should be considered in the differential diagnosis of any child presenting with acute-onset limb weakness, particularly in the summer to fall during enterovirus outbreaks and when following a febrile illness. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive.

Traditionally, enterovirus infection has been confirmed with viral culture using a combination of cell lines. Sensitivity of culture ranges from 50% to 75% and can be increased by sampling of multiple sites (e.g., CSF plus oropharynx and rectum in children with meningitis). In neonates, yields of 30–70% are achieved when blood, urine, CSF, and mucosal swabs are cultured. A major limitation is the inability of most coxsackie A viruses to grow in culture. Yield may also be limited by neutralizing antibody in patient specimens, improper specimen handling, or insensitivity of the cell lines used. Culture is relatively slow, with 3-8 days usually required to detect growth. Although cultivation of an enterovirus from any site can generally be considered evidence of recent infection, isolation from the rectum or stool can reflect more remote shedding. Similarly, recovery from a mucosal site may suggest an association with an illness, whereas recovery from a normally sterile site (e.g., CSF, blood, or tissue) is more conclusive evidence of causation. Serotype identification by type-specific antibody staining or neutralization of a viral isolate is generally required only for investigation of an outbreak or an unusual disease manifestation, for surveillance, or to distinguish nonpoliovirus enteroviruses from vaccine or wild-type polioviruses.

Direct testing for nucleic acid has replaced culture because of increased sensitivity and more rapid turnaround. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses in CSF; serum; urine; conjunctival, nasopharyngeal, oropharyngeal, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. However, the closely related parechoviruses are not detected by most enterovirus RT-PCR primers. Sensitivity and specificity of RT-PCR are high, with results available in as short as 1 hour. Real-time, quantitative PCR assays and nested PCR assays with enhanced sensitivity have been developed, as have enterovirus-containing multiplex PCR assays, nucleic acid sequence–based amplification assays, reverse transcription loop-mediated isothermal amplification, culture-enhanced PCR assays, and PCR-based microarray assays. PCR testing of CSF from children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Routine PCR testing of CSF in infants and young children with suspected meningitis during enterovirus season decreases the number of diagnostic tests, duration of hospital stay, antibiotic use, and overall costs. Enterovirus RNA may not be detected in CSF by the time of clinical presentation with neurologic syndromes associated with certain enteroviruses (e.g., enterovirus A71 and D68), but shedding may still be detectable in nonsterile sites (stool/rectal for enterovirus A71; respiratory for enterovirus D68). PCR testing of tracheal aspirates of children with myocarditis has good concordance with testing of myocardial specimens. In ill neonates and young infants, PCR testing of serum and urine has higher yields than culture. Viral load in blood of neonates is correlated with disease severity; viral nucleic acid may persist in blood of severely ill newborns for up to 2 months.

Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases. Serotype-specific (e.g., enterovirus A71, enterovirus D68, and coxsackievirus A16) PCR assays have been developed. For enterovirus A71, the yield of specimens other than CSF and blood (oropharyngeal, nasopharyngeal, rectal, vesicle swabs, and CNS tissue) is greater than the yield of CSF and blood, which are infrequently

positive. Enterovirus D68 is more readily detected in respiratory specimens (i.e., nasal wash or nasopharyngeal swab) compared to stool/rectal or CSF specimens. Routine collection and testing of respiratory and stool/rectal specimens, in addition to CSF, is warranted in neurologic presentations potentially associated with these viruses. Of note, commercially available multiplex respiratory PCR assays generally are unable to distinguish enteroviruses (including enterovirus D68) from rhinoviruses. Antigen detection assays that target specific serotypes such as enterovirus A71 with monoclonal antibodies have also been developed.

Enterovirus infections can be detected serologically by a rise in serum or CSF of neutralizing, complement fixation, enzyme-linked immunosorbent assay, or other type-specific antibody or by detection of serotype-specific IgM antibody. However, serologic testing requires presumptive knowledge of the infecting serotype or an assay with sufficiently broad cross-reactivity. Sensitivity and specificity may be limiting, and cross-reactivity among serotypes may occur. Except for epidemiologic studies or cases characteristic of specific serotypes (e.g., enterovirus A71 or enterovirus D68), serology is generally less useful than culture or nucleic acid detection. Enterovirus antibodies have been detected in CSF of children with acute flaccid myelitis when viral RNA was not detectable.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of enterovirus infections varies with the clinical presentation (Table 297.2).

Human parechoviruses, members of the Picornaviridae family, produce many manifestations similar to the nonpolio enteroviruses. They are small RNA viruses that were originally classified as echoviruses. Nineteen parechoviruses have been identified that infect humans; serotypes 1 and 3 are the most common causes of symptomatic infection. Parechovirus epidemics occur in the same season as enterovirus infections, with a biennial pattern of circulation noted in Europe. Outbreaks have been described in the nursery setting. In young infants, parechoviruses can cause a sepsis-like illness similar to enterovirus illness and are a common, underrecognized cause of viral meningoencephalitis. More frequently than with enteroviruses, infants with parechovirus CNS infection often have no CSF pleocytosis. There is also a higher incidence of white matter MRI abnormalities and long-term neurodevelopmental deficits with parechovirus encephalitis compared with enterovirus encephalitis. Rarely, parechoviruses have been identified in cases of hepatitis or myocarditis. Infections in older children are often unrecognized or cause acute, benign febrile, respiratory, or gastrointestinal illnesses with few specific findings.

Infants suspected of having an enterovirus infection should also be considered as possibly having a parechovirus infection, because the two may be indistinguishable. A distinctive rash involving the extremities with palm and sole erythema or peripheral leukopenia in the setting of high fever during the summer-fall season are clinical findings that should also prompt consideration of parechovirus infection. The diagnosis of parechovirus infection is confirmed by human parechovirus-specific PCR on CSF, blood, stool, and oropharyngeal or nasopharyngeal specimens.

TREATMENT

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluation and hospitalization for presumptive treatment of bacterial and herpes simplex virus infection. Neonates with severe disease and infants and children with concerning disease manifestations (e.g., myocarditis, enterovirus A71 neurologic and cardiopulmonary disease, enterovirus D68 respiratory failure, and acute flaccid myelitis) may require intensive cardiorespiratory support.

Table 297.2 Differential Diagnosis of Nonpolio Enterovirus Infections

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS	NONINFECTIOUS
Nonspecific febrile illness	*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*	Influenza viruses, human herpesviruses 6 and 7, human parechoviruses	Rheumatologic disorders, oncologic diseases, drug reaction
Exanthems/enanthems	Group A *Streptococcus, Staphylococcus aureus, N. meningitidis, T. pallidum, M. pneumoniae*	Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses	Drug reaction, Stevens Johnson syndrome, toxic epidermal necrolysis, Kawasaki syndrome, vasculitis
Respiratory illness/ conjunctivitis	*S. pneumoniae, H. influenzae* (nontypeable and type b), *N. meningitidis, Mycoplasma pneumoniae, Chlamydophila pneumoniae*	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses	Asthma exacerbation, rheumatologic uveitis, Kawasaki syndrome
Myocarditis/pericarditis	*S. aureus, H. influenzae* type b, *M. pneumoniae*	Adenoviruses, influenza virus, parvovirus, cytomegalovirus	Drugs, Kawasaki syndrome, rheumatic fever
Meningitis/encephalitis	*S. pneumoniae, H. influenzae* type b, *N. meningitidis, Mycobacterium tuberculosis, Borrelia burgdorferi, M. pneumoniae, Bartonella henselae, Listeria monocytogenes*	Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses	Drugs, intravenous immunoglobulin, Kawasaki syndrome, autoimmune encephalitis (e.g., anti-NMDA receptor), acute disseminated encephalomyelitis (ADEM), demyelinating disorders
Acute flaccid myelitis	*C. botulinum*	Poliovirus, West Nile virus, Japanese encephalitis virus, rabies virus, adenovirus	Spinal cord infarction, antimyelin oligodendrocyte glycoprotein (MOG) myelitis, neuromyelitis optica (NMO), Guillain-Barré syndrome, ADEM, transverse myelitis, lupus, tick paralysis
Neonatal infections	Group B *Streptococcus*, gram-negative enteric bacilli, *L. monocytogenes, Enterococcus*	Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses	Neonatal lupus, Aicardi-Goutières syndrome

Milrinone has been suggested as a useful agent in severe enterovirus A71 cardiopulmonary disease. Liver and cardiac transplantation have been performed for neonates with progressive end-organ failure.

Immunoglobulin has been used to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Anecdotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. The one randomized controlled trial was too small to demonstrate significant clinical benefits, although neonates who received immunoglobulin containing high neutralizing titers to their own isolates had shorter periods of viremia and viruria. Immunoglobulin has been administered intravenously and intraventricularly to treat hypogammaglobulinemia in patients with chronic enterovirus meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enterovirus A71, enterovirus D68, and other enteroviruses. Modulation of cytokine profiles after administration of intravenous immunoglobulin for enterovirus A71–associated brainstem encephalitis has been demonstrated. High-titer enterovirus A71 immunoglobulin appeared promising in animal models, and clinical trials in regions with epidemic enterovirus A71 disease are ongoing. Anti–enterovirus A71 and D68 monoclonal antibodies have also been generated and evaluated in vitro and in animal models. A retrospective study suggested that treatment of presumed viral myocarditis with immunoglobulin was associated with improved outcome; however, virologic diagnoses were not made. Evaluation of corticosteroids and cyclosporine and other immunosuppressive therapy for myocarditis has been inconclusive. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Activity of interferon-α against enterovirus A71 has been demonstrated with in vitro and animal models, but potency varies with interferon-α type.

Antiviral agents that act at various steps in the enterovirus life cycle—attachment, penetration, uncoating, translation, polyprotein processing, protease activity, replication, and assembly—are being evaluated. Candidates include pharmacologically active chemical compounds, small interfering RNAs and DNA-like antisense agents, purine nucleoside analogs, synthetic peptides, enzyme inhibitors of signal transduction pathways, interferon-inducers, and herbal compounds. Pleconaril, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections. A randomized controlled trial of pleconaril in neonates with severe hepatitis, coagulopathy, and/or myocarditis suggested possible virologic and clinical benefits of treatment. Pocapavir, an agent with a similar mechanism of action that is in development for treatment of poliovirus infections, has been used in a small number of cases of severe neonatal enterovirus sepsis. Vapendavir is another attachment inhibitor that is in clinical trials for rhinovirus infections and has in vitro activity against enteroviruses (including enterovirus A71) but has not entered clinical trials for enterovirus infections. Pleconaril, pocapavir, and vapendavir are not currently available for clinical use.

Design and evaluation of candidate agents active against enterovirus A71 and enterovirus D68 are high priorities. Challenges for therapies of enterovirus A71 include limited cross-genotypic activity of candidate compounds and high viral mutagenicity that favors emergence of resistance. Lactoferrin and ribavirin have demonstrated activity with in vitro and/or animal models. The investigational agents rupintrivir and V-7404, which inhibit the 3C-protease conserved among many enteroviruses and essential for infectivity, have broad activity in vitro, including against both enterovirus A71 and enterovirus D68. DAS181 is an investigational, inhaled drug with sialidase activity that has in vitro activity against recently circulating strains of enterovirus D68. The antidepressant fluoxetine interacts with the enterovirus 2C protein and has in vitro activity against group B and D enteroviruses; it has been used anecdotally for chronic enterovirus encephalitis associated with agammaglobulinemia and enterovirus D68-associated acute flaccid myelitis. A retrospective study did not demonstrate a signal of efficacy in the latter condition.

COMPLICATIONS AND PROGNOSIS

The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immunocompromised hosts.

Prevention

The first line of defense is prevention of transmission through good hygiene, such as handwashing, avoidance of sharing utensils and drinking containers and other potential fomites, disinfection of contaminated surfaces, and avoiding community settings where exposures are likely to occur. The paucity of enterovirus circulation and associated hand-foot-mouth disease and respiratory and neurologic disease in 2020 during the COVID-19 pandemic provides indirect evidence of the efficacy of nonpharmaceutical interventions targeted to decrease SARS-CoV-2 spread (masking, distancing, school mitigation strategies) against enteroviruses. Chlorination of drinking water and swimming pools also may be an important preventative strategy. Contact precautions should be used for all patients with enterovirus infections in the hospital setting; droplet precautions should also be included for patients with respiratory syndromes and, possibly, enterovirus A71 and D68 infection. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy.

Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. If a pregnant woman experiences a suggestive illness, it is advisable not to proceed with emergency delivery unless there is concern for fetal compromise or obstetric emergencies cannot be excluded. Rather, it may be advantageous to extend pregnancy, allowing the fetus to passively acquire protective antibodies. A strategy of prophylactically administering immunoglobulin (or maternal convalescent plasma) to neonates born to mothers with enterovirus infections is untested.

Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Inactivated vaccines to prevent enterovirus A71 infections, given to children 6-35 months of age, have been demonstrated to be safe and effective (>90% against enterovirus A71 hand-foot-and-mouth disease and >80% against enterovirus A71 serious disease) in phase 3 clinical trials. Three inactivated enterovirus A71 vaccines have been licensed and approved for prevention of severe hand-foot-and-mouth disease in China and are being studied in other Asian countries. Other vaccine strategies for enterovirus A71, including VP1 capsid protein–based subunit, DNA, and vector vaccines; combined peptide vaccines; live-attenuated vaccines; virus-like particles; breast milk enriched with VP1 capsid protein or lactoferrin; and interferon-γ–expressing recombinant viral vectors, are also under investigation. Circulation of multiple enterovirus A71 types, antigenic drift, viral recombination, and potential immunologic cross-reactivity with brain tissue may pose challenges to development of enterovirus A71 vaccines. Vaccine candidates against EV-D68, including virus-like particle vaccines and inactivated whole virus vaccines, are in development, but have not progressed beyond animal studies. Most enterovirus vaccines do not provide cross-protection against other serotypes; however, the potential to create multivalent enterovirus vaccines targeting several common strains with severe manifestations is under investigation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 298

Parvoviruses

William C. Koch

The parvoviruses are small, single-stranded DNA viruses. They are common infectious agents of a wide variety of animal species, including mammals, birds, and insects. Parvoviruses as a group include a number of important animal pathogens. There are five different types of parvoviruses known to infect humans: the dependoviruses, also called adeno-associated viruses (AAVs), parvovirus B19 (B19V), human bocaviruses (HBoVs), parvovirus 4 (PARV4), and human bufavirus (HBuV). B19V and HBoV are the only two parvoviruses proven to be pathogenic in humans. B19V is the most well studied and clinically important of the human parvoviruses and the cause of **erythema infectiosum** or **fifth disease**. *Human bocavirus is an emerging human pathogen.*

ETIOLOGY

The five human parvoviruses are distinct enough from each other to represent five different genera within the Parvoviridae family. B19V is a member of the genus *Erythroparvovirus*, is composed of an icosahedral protein capsid without an envelope, and contains a single-stranded DNA genome of approximately 5.5 kb. It is relatively heat and solvent resistant. It is antigenically distinct from other mammalian parvoviruses and has only one known serotype, with three distinct genotypes described. The relatively short genome in parvoviruses does not encode a DNA polymerase, so all parvoviruses require either host cell factors present in late S phase or co-infection with another virus to replicate their DNA. B19V can be propagated effectively in vitro only in $CD36^+$ erythroid progenitor cells derived from human bone marrow, umbilical cord blood, or peripheral blood.

HBoV is a member of the genus *Bocaparvovirus*. HBoV was first isolated from nasopharyngeal specimens from children with respiratory tract infection in 2005. It was identified using random polymerase chain reaction (PCR) amplification and sequencing methods specifically designed to detect previously unknown viral sequences. Analysis of the gene sequences showed similarities to both *bo*vine and *ca*nine parvoviruses, and thus the virus was named human bocavirus. Later, three other HBoVs were identified in stool samples and designated as HBoV types 2, 3, and 4, with the initial respiratory isolate called HBoV1. The HBoV capsid structure and genome size are similar to those of B19V, but the genomic organization and replication are different (though not fully characterized to date). HBoVs cannot be propagated in conventional cell culture but have been grown in a pseudostratified human airway epithelial cell culture system.

The **AAVs** are members of the genus Dependoparvovirus and were the first parvoviruses to be found in humans. They were originally identified as contaminants in laboratory preparations of adenovirus, resulting in the designation "adeno-associated viruses." They were later isolated directly from human tissue samples, and now several AAV serotypes are known to commonly infect humans. AAVs have a unique life cycle that can take one of two paths: (1) a lytic infection with replication of viral DNA and production of new virus, or (2) viral integration into the host cell DNA. In the presence of a "helper" virus, usually an adenovirus or a herpesvirus, AAV can replicate its DNA, produce capsids, and release new virions by cell lysis. In the absence of a helper virus infection, the AAV genome becomes integrated into the host cell DNA. This feature has drawn interest in AAVs as potential vectors for gene therapy. Although human infection with AAVs is common, there is only one possible disease association (idiopathic hepatitis) (see Chapter 406).

PARV4 was initially identified in 2005 from the blood of an adult patient with acute viral syndrome, who was also an intravenous drug user co-infected with hepatitis C. Subsequently, this virus has been found in blood donors and donated plasma pools in many different countries. It appears to be present in approximately 3% of blood donors in the United States and 4% of plasma pools. There is currently no known disease association or clinical symptomology associated with infection. Likewise, BuV is a parvovirus that was first identified in 2012 in the feces from children <5 years of age with acute diarrhea but has an unclear role as a pathogen. PARV4 has been assigned to the genus *Tetraparvovirus*, and BuV is a member of the genus *Protoparvovirus*. The full epidemiology and clinical relevance of these viruses await further study.

EPIDEMIOLOGY

Parvovirus B19

Infections with B19V are common and occur worldwide. Clinically apparent infections, such as the rash illness of erythema infectiosum and transient aplastic crisis, are most prevalent in school-age children (70% of cases occur in patients between 5 and 15 years of age). Seasonal peaks occur in the late winter and spring, with sporadic infections throughout the year. Seroprevalence increases with age, with 40–60% of adults having evidence of prior infection.

Transmission of B19V is by the respiratory route, presumably via large-droplet spread from nasopharyngeal viral shedding. The transmission rate is 15–30% among susceptible household contacts, and mothers are more commonly infected than fathers. In outbreaks of erythema infectiosum in elementary schools, the secondary attack rates range from 10–60%. Nosocomial outbreaks also occur, with secondary attack rates of 30% among susceptible healthcare workers.

Although respiratory spread is the primary mode of transmission, B19V is also transmissible in blood and blood products, as documented among children with hemophilia receiving pooled-donor clotting factor. Given the resistance of the virus to solvents, fomite transmission could be important in childcare centers and other group settings, but this mode of transmission has not been definitively established.

Human Bocaviruses

The majority of published studies have used molecular methods to detect HBoV DNA in respiratory secretions, fecal samples, blood, and other tissues. HBoV DNA (HBoV1) can be found commonly in respiratory secretions from children hospitalized with acute lower respiratory tract infections (LRTIs). It is more prevalent in children younger than 2 years of age and seems to be associated with wheezing respiratory illness. However, it can be isolated from respiratory secretions from asymptomatic children and can often be found as a co-infection with other common respiratory pathogens of children this age, including respiratory syncytial virus, human metapneumovirus, and rhinoviruses. This has caused some confusion as to the pathogenic role of HBoV in acute LRTI, including whether it can persist in secretions long after a subclinical infection or requires a helper virus. A limited number of seroepidemiologic studies have been performed, and these suggest that infection is common in children younger than 5 years of age. The most recent studies provide evidence that the virus is in fact pathogenic, especially in children younger than 2 years with wheezing and LRTI, because HBoV1 is more likely to be the only virus isolated in these patients and more likely to have an acute antibody response when coupled with specific antibody testing. When quantitative PCR is used, the virus is found to be much higher in titer in these symptomatic cases.

HBoV DNA (HBoV2, HBoV3, and HBoV4) has also been found in fecal samples in studies from various countries, but its role as a cause of viral gastroenteritis is still undetermined.

PATHOGENESIS

Parvovirus B19

The primary target of B19V infection is the erythroid cell line, specifically erythroid precursors near the pronormoblast stage. Viral infection produces cell lysis, leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis. The virus has no apparent effect on the myeloid cell line. The tropism for erythroid cells is related to the erythrocyte P blood group antigen, which is the primary cell receptor for the virus and is also found on endothelial cells, placental cells, and fetal myocardial cells. Thrombocytopenia and

neutropenia are often observed clinically, but the pathogenesis of these abnormalities is not completely understood.

Experimental infection of normal volunteers with B19V revealed a biphasic illness. From 7-11 days after inoculation, subjects had viremia and nasopharyngeal viral shedding with fever, malaise, and rhinorrhea. Reticulocyte counts dropped to undetectable levels but resulted in only a mild, clinically insignificant fall in serum hemoglobin. With the appearance of specific antibodies, symptoms resolved and serum hemoglobin returned to normal. Several subjects experienced a rash associated with arthralgia 17-18 days after inoculation. Some manifestations of B19 infection, such as transient aplastic crisis, appear to be a direct result of viral infection, whereas others, including the exanthem and arthritis, appear to be *postinfectious phenomena* related to the immune response. Skin biopsy of patients with erythema infectiosum reveals edema in the epidermis and a perivascular mononuclear infiltrate compatible with an immune-mediated process.

Individuals with **chronic hemolytic anemia** and increased red blood cell (RBC) turnover are very sensitive to minor perturbations in erythropoiesis. Infection with B19V leads to a transient arrest in RBC production and a precipitous fall in serum hemoglobin, often requiring transfusion. The reticulocyte count drops to undetectable levels, reflecting the lysis of infected erythroid precursors. Humoral immunity is crucial in controlling infection. Specific immunoglobulin (Ig) M appears within 1-2 days of infection and is followed by anti-B19 IgG, which leads to control of the infection, restoration of reticulocytosis, and a rise in serum hemoglobin.

Individuals with **impaired humoral immunity** are at increased risk for more serious or persistent infection with B19V, which usually manifests as chronic RBC aplasia, although neutropenia, thrombocytopenia, and marrow failure are also described. Children undergoing chemotherapy for leukemia or other forms of cancer, transplant recipients, and patients with congenital or acquired immunodeficiency states (including AIDS) are at risk for chronic B19V infections.

Infections in the **fetus** and **neonate** are somewhat analogous to infections in immunocompromised persons. B19V is associated with nonimmune fetal hydrops and stillbirth in women experiencing a primary infection but does not appear to be teratogenic. Like most mammalian parvoviruses, B19V can cross the placenta and cause fetal infection during primary maternal infection. Parvovirus cytopathic effects are seen primarily in erythroblasts of the bone marrow and sites of extramedullary hematopoiesis in the liver and spleen. Fetal infection can presumably occur as early as 6 weeks of gestation, when erythroblasts are first found in the fetal liver; after the fourth month of gestation, hematopoiesis switches to the bone marrow. In some cases, fetal infection leads to profound fetal anemia and subsequent high-output cardiac failure (see Chapter 138). **Fetal hydrops** ensues and is often associated with fetal death. There may also be a direct effect of the virus on myocardial tissue that contributes to the cardiac failure. However, most infections during pregnancy result in normal deliveries at term. Some of the asymptomatic infants from these deliveries have been reported to have chronic postnatal infection with B19V that is of unknown significance.

Human Bocaviruses

Mechanisms of HBoV replication and pathogenesis are poorly characterized to date. Growth of HBoV1 in tissue culture is difficult, though the virus has been cultured in primary respiratory epithelial cells as noted above. The primary site of viral replication appears to be the respiratory tract, because the virus has been detected most frequently and in highest copy numbers here. HBoV1 has also been found occasionally in the serum, suggesting the potential for systemic spread. HBoV1 has also been detected in stool, but copy numbers are very low. In contrast, HBoV types 2-4 are found predominantly in the stool, but host cell types are not known.

CLINICAL MANIFESTATIONS

Parvovirus B19

Many infections are clinically inapparent (Table 298.1). Infected children characteristically demonstrate the rash illness of erythema infectiosum. Adults, especially women, frequently experience acute polyarthropathy with or without a rash.

TABLE 298.1 Clinical Associations with Parvovirus B19 Infection

Asymptomatic infection
Exanthematous disorders
Erythema infectiosum (fifth disease)
Papular-purpuric gloves-and-socks syndrome
Asymmetric periflexural exanthem
"Bathing trunk" exanthem
Petechial exanthems
Other disorders
Arthritis
Transient aplastic crises
Chronic anemia
Refractory anemia after solid organ or stem cell transplantation
Hemophagocytic lymphohistiocytosis
Myelodysplastic syndrome
Fetal hydrops
Vasculitis
Neurologic disease, including arterial ischemic stroke, encephalopathy, encephalitis
Rheumatologic disease
Liver failure
Myocarditis

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Box 16.2, p. 452.

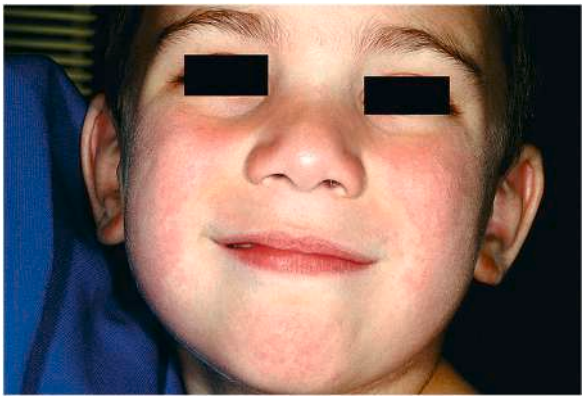

Fig. 298.1 Erythema infectiosum. Erythema of the bilateral cheeks, which has been likened to a "slapped-cheek" appearance. *(From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: WB Saunders; 2006:431.)*

Erythema Infectiosum (Fifth Disease)

The most common manifestation of B19V is erythema infectiosum, also known as *fifth disease*, which is a benign, self-limited exanthematous illness of childhood.

The incubation period for erythema infectiosum is 4-28 days (average: 16-17 days). The prodromal phase is mild and consists of low-grade fever in 15–30% of cases, headache, and symptoms of mild upper respiratory tract infection. The hallmark of erythema infectiosum is the characteristic rash, which occurs in three stages that are not always distinguishable. The initial stage is an erythematous facial flushing, often described as a **slapped-cheek appearance** (Fig. 298.1). The rash spreads rapidly or concurrently to the trunk and proximal extremities as a diffuse macular erythema in the second stage. Central clearing of macular lesions occurs promptly, giving the rash a **lacy**, **reticulated appearance** (Fig. 298.2). The rash tends to be more prominent on extensor surfaces, sparing the palms and soles. Affected children are afebrile and do not appear ill. Some have petechiae. Older children and adults often complain of mild pruritus. The rash resolves spontaneously without desquamation but tends to wax and wane over 1-3 weeks. It can recur with exposure to sunlight, heat, exercise, and stress.



Fig. 298.2 Erythema infectiosum. Reticulate erythema on the upper arm of a patient with erythema infectiosum. *(From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: WB Saunders; 2006:431.)*



Fig. 298.3 Papular-purpuric gloves-and-socks syndrome. Petechial purpura of the palms in a patient with parvovirus B19 infection. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 16.18, p. 453.)*

Lymphadenopathy and atypical papular, purpuric and vesicular rashes are also described.

Arthropathy

Arthritis and arthralgia may occur in isolation or with other symptoms. Joint symptoms are much more common among adults and older adolescents with B19V infection. Females are affected more frequently than males. In one large outbreak of fifth disease, 60% of adults and 80% of adult women reported joint symptoms. Joint symptoms range from diffuse polyarthralgia with morning stiffness to frank arthritis. The joints most often affected are the hands, wrists, knees, and ankles, but practically any joint may be affected. The joint symptoms are self-limited and, in the majority of patients, resolve within 2-4 weeks. Some patients may have a prolonged course of many months, suggesting rheumatoid arthritis. Transient rheumatoid factor positivity is reported in some of these patients but with no joint destruction.

Transient Aplastic Crisis

The transient arrest of erythropoiesis and absolute reticulocytopenia induced by B19V infection leads to a sudden fall in serum hemoglobin in individuals with chronic hemolytic conditions. This B19V-induced RBC aplasia or transient aplastic crisis occurs in patients with all types of chronic hemolysis and/or rapid RBC turnover, including sickle cell disease, thalassemia, hereditary spherocytosis, and pyruvate kinase deficiency, among others. In contrast to children with erythema infectiosum only, patients with aplastic crisis are ill at presentation with fever, malaise, and lethargy and have signs and symptoms of profound anemia, including pallor, tachycardia, and tachypnea. Rash is rarely present. The incubation period for transient aplastic crisis is shorter than that for erythema infectiosum because the crisis occurs coincident with the viremia. Children with sickle cell hemoglobinopathies may also have a concurrent vasoocclusive pain crisis, further confusing the clinical presentation.

Immunocompromised Persons

Individuals with impaired humoral immunity are at risk for chronic B19V infection. Chronic anemia is the most common manifestation, sometimes accompanied by neutropenia, thrombocytopenia, or complete marrow suppression. Chronic infections occur in persons receiving cancer chemotherapy or immunosuppressive therapy for transplantation and persons with congenital immunodeficiencies, AIDS, and functional defects in IgG production who are thereby unable to generate neutralizing antibodies.

Fetal Infection

Primary maternal infection is associated with nonimmune fetal hydrops and intrauterine fetal demise, with the risk for fetal loss when infection occurs in pregnancy estimated at 2–5%. The mechanism of fetal disease appears to be a viral-induced RBC aplasia at a time when the fetal erythroid fraction is rapidly expanding, leading to profound anemia, high-output cardiac failure, and fetal hydrops. Viral DNA has been detected in infected abortuses. The second trimester seems to be the most sensitive period, but fetal losses are reported at every stage of gestation. If maternal B19V infection is suspected, fetal ultrasonography and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive, noninvasive procedures to diagnose fetal anemia and hydrops. Most infants infected in utero are born normal at term, including some who have had ultrasonographic evidence of hydrops. A small subset of infants infected in utero may acquire a chronic or persistent postnatal infection with B19V that is of unknown significance. Congenital anemia associated with intrauterine B19V infection has been reported in a few cases, sometimes following intrauterine hydrops. This process may mimic other forms of congenital hypoplastic anemia (e.g., Diamond-Blackfan syndrome). Fetal infection with B19V has been associated with bone lesions but has not been associated with other birth defects. B19V is only one of many causes of hydrops fetalis (see Chapter 140).

Myocarditis

B19V infection has been associated with myocarditis in fetuses, infants, children, and a limited number of adults. Diagnosis has often been based on serologic findings suggestive of a concurrent B19V infection, but in many cases B19V DNA has been demonstrated in cardiac tissue. B19-related myocarditis is plausible because fetal myocardial cells are known to express P antigen, the cell receptor for the virus. In the few cases in which histology is reported, a predominantly lymphocytic infiltrate is described. Outcomes have varied from complete recovery to chronic cardiomyopathy to fatal cardiac arrest. Although B19-associated myocarditis seems to be a rare occurrence, there appears to be enough evidence to consider B19V as a potential cause of lymphocytic myocarditis, especially in infants and immunocompromised persons.

Other Cutaneous Manifestations

A variety of atypical skin eruptions have been reported with B19V infection. Most of these are petechial or purpuric, often with evidence of vasculitis on biopsy. Among these rashes, the **papular-purpuric gloves-and-socks syndrome (PPGSS)** is well established in the dermatologic literature as distinctly associated with B19V infection (Figs. 298.3 and 298.4). PPGSS is characterized by fever, pruritus, and painful edema and erythema localized to the distal extremities in a distinct gloves-and-socks distribution, followed by acral petechiae and oral lesions. The syndrome is self-limited and resolves within a few weeks. Although PPGSS was initially described in young adults, a number of reports of the disease in

children have since been published. In those cases linked to B19V infection, the eruption is accompanied by serologic evidence of acute infection. Generalized petechial rash has also been reported.

Human Bocaviruses

Many studies have reported an association between respiratory tract infection and HBoV1 infection as detected by PCR of respiratory secretions, primarily nasopharyngeal secretions. Clinical manifestations in these studies have ranged from mild upper respiratory symptoms to pneumonia. However, the role of HBoV1 as a pathogen has been challenged by the detection of the virus in asymptomatic children and by the frequent detection of other respiratory viruses in the same samples. Nonetheless, studies that have included some combination of quantitative PCR, serum PCR, and serology have been more convincing about HBoV1 as a human pathogen. The use of a quantitative PCR method also seems to differentiate between HBoV1 infection (and wheezing) and prolonged viral shedding, because patients with higher viral titers were more likely to be symptomatic, to be viremic, and to have HBoV1 isolated without other viruses.

HBoV type 2 DNA has been found in the stool of 3–25% of children with gastroenteritis, but often with another enteric virus. DNA of HBoV types 2, 3, and 4 has also been found in the stool of healthy, asymptomatic individuals. At present, there are few data linking HBoV2, HBoV3, or HBoV4 to gastroenteritis or any clinical illness. Further studies are required to determine if any of the HBoVs are associated with some cases of childhood gastroenteritis.



Fig. 298.4 Papular-purpuric gloves-and-socks syndrome. Erythema and petechiae of the plantar feet were accompanied by pruritus and sore throat in this young girl with parvovirus B19 infection. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 16.19, p. 454.)*

DIAGNOSIS

Parvovirus B19 Infection

The diagnosis of erythema infectiosum is usually based on clinical presentation of the typical rash and rarely requires virologic confirmation. Similarly, the diagnosis of a typical transient aplastic crisis in a child with sickle cell disease is generally made on clinical grounds without specific virologic testing.

Serologic tests for the diagnosis of B19V infection are available. B19-specific IgM develops within 2-3 days after infection and persists up to 6 months (Fig. 298.5). Anti-B19 IgG serves as a marker of current or past infection. Seroconversion of anti-B19 IgG antibodies in paired sera can also be used to confirm recent infection.

Serologic diagnosis is unreliable in immunocompromised persons; diagnosis in these patients requires methods to detect viral DNA. Because the virus cannot be isolated by standard cell culture, methods to detect viral particles or viral DNA, such as PCR are necessary to establish the diagnosis. Viral DNA may be detectable for ~1 month after infection in immunocompetent patients but longer in immune compromised patients. Some reports suggest that prolonged detection of viral DNA (months) may represent DNA but not the complete virus. Prenatal diagnosis of B19V-induced fetal hydrops can be accomplished by detection of viral DNA in fetal blood or amniotic fluid by these methods.

Human Bocavirus Infections

HBoV1 infections cannot be differentiated from other viral respiratory infections on clinical grounds. HBoV DNA can be readily detected by PCR methods and is now included in several commercially available multiplex respiratory virus PCR assays. Quantitative PCR is useful to differentiate acute infection from persistent viral shedding, because higher viral copy numbers (>10^4 HBoV1 genomes/mL) correlate with acute illness, but this test is not widely available. Likewise, serologic methods to detect specific IgM and IgG antibodies have been developed, but these too are not routinely available and there are problems with cross-reactivity among antibodies to the various HBoV types. The most reliable method to diagnose HBoV1 infection would include detection of viral DNA in serum by PCR and in respiratory tract samples by quantitative PCR, with concurrent detection of IgM or a diagnostic IgG response in paired samples.

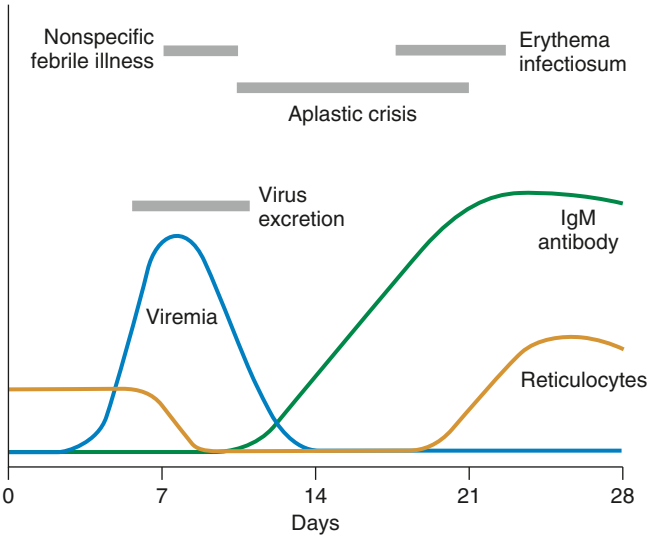

Fig. 298.5 Selected virologic, immunologic, hematologic, and clinical events in parvovirus B19 virus infection. *(From Schulte DJ. Human parvovirus B19. In Kaplan SL, Harrison GJ, Steinbach WJ, Cherry JD, Hotez PJ, eds. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 8th ed. Philadelphia: Elsevier, 2019. Fig 152.1.)*

DIFFERENTIAL DIAGNOSIS

Parvovirus B19

The rash of erythema infectiosum must be differentiated from roseola, rubella, measles, enteroviral infections, and drug reactions. Rash and arthritis in older children should prompt consideration of juvenile idiopathic arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue disorders.

Human Bocavirus

Respiratory illness and wheezing caused by HBoV1 cannot be differentiated clinically from other common viral respiratory infections, especially respiratory syncytial virus, human metapneumovirus, rhinoviruses, enterovirus D68, and parainfluenza viruses. HBoV1 infection in young children seems to most closely resemble that of respiratory syncytial virus and human metapneumovirus, because the clinical symptoms and age ranges will overlap.

TREATMENT

Parvovirus B19

There is no specific antiviral therapy approved for B19V infection. The acyclic nucleoside phosphonates cidofovir and brincidofovir have been shown to inhibit B19V replication in vitro, but no clinical studies have been performed and thus antiviral therapy cannot be recommended. Commercial lots of intravenous immunoglobulin (IVIG) have been used with some success to treat B19V-related episodes of anemia and bone marrow failure in immunocompromised children. Specific antibody may facilitate clearance of the virus but is not always necessary, because cessation of cytotoxic chemotherapy with subsequent restoration of immune function often suffices. In patients whose immune function is not likely to recover, such as patients with AIDS, administration of IVIG may give only a temporary remission, and periodic reinfusions may be required. In patients with AIDS, clearance of B19V infection has been reported after initiation of highly active antiretroviral therapy (HAART) without the use of IVIG.

No controlled studies have been published regarding dosing of IVIG for B19V-induced RBC aplasia. Multiple case reports and limited clinical series have reported successful treatment of severe anemia secondary to chronic B19V infection using several different IVIG dosing regimens. Initial reports recommended a starting dose of 400 mg/kg/day for up to 5 days. Other reports have used higher doses ranging from 1-2 g/kg split into one to three infusions. The dose and duration of IVIG may be adjusted based on the response to therapy. The optimal schedule of IVIG treatment is not known.

B19V-infected fetuses with anemia and hydrops have been managed successfully with intrauterine RBC transfusions, but this procedure has significant attendant risks. Once fetal hydrops is diagnosed, regardless of the suspected cause, the mother should be referred to a fetal therapy center for further evaluation because of the high risk for serious complications (see Chapter 140).

Human Bocavirus

There is no specific antiviral therapy available. Appropriate supportive treatment for viral LRTI and pneumonia is recommended, as directed by clinical severity. For children with wheezing illness specifically caused by HBoV1 infection, there are no data examining their response to bronchodilator therapy.

COMPLICATIONS

Parvovirus B19

Erythema infectiosum is often accompanied by arthralgias or arthritis in adolescents and adults that may persist after resolution of the rash (see Table 298.1). B19V may rarely cause thrombocytopenic purpura. Neurologic conditions, including aseptic meningitis, encephalitis, and peripheral neuropathy, have been reported in both immunocompromised and healthy individuals in association with B19V infection. The incidence of stroke may be increased in children with sickle cell disease following B19V-induced transient aplastic crisis. B19V is also a cause of infection-associated hemophagocytic lymphohistiocytosis, usually in immunocompromised persons.

Human Bocavirus

There are no studies reporting on complications of HBoV1 infection. Complications of wheezing and viral pneumonia would be possible, including hypoxemia and secondary bacterial infection, among others.

PREVENTION

Parvovirus B19

Children with erythema infectiosum are not likely to be infectious at presentation because the rash and arthropathy represent immune-mediated, postinfectious phenomena. Isolation and exclusion from school or childcare are unnecessary and ineffective after diagnosis.

Children with B19V-induced RBC aplasia, including the transient aplastic crisis, are infectious upon presentation and demonstrate a more intense viremia. Most of these children require transfusions and supportive care until their hematologic status stabilizes. They should be isolated in the hospital to prevent spread to susceptible patients and staff. Isolation should continue for at least 1 week and until fever has resolved. Pregnant caregivers should not be assigned to these patients. Exclusion of pregnant women from workplaces where children with erythema infectiosum may be present (e.g., primary and secondary schools) is not recommended as a general policy because it is unlikely to reduce their risk. There are no data to support the use of IVIG for postexposure prophylaxis in pregnant caregivers or immunocompromised children. No vaccine is currently available, though this is a topic of ongoing research.

Human Bocavirus

There are no studies that have addressed the prevention of transmission of this infection. In the hospital setting, standard precautions should be observed to limit spread of the virus. Because HBoV1 causes respiratory infection and can be detected in respiratory secretions sometimes in very high titer, measures to limit contact with respiratory secretions should be considered, including contact and droplet isolation for severely symptomatic young children. No vaccine is available, and no other preventive measures have been reported.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 299

Herpes Simplex Virus

Lawrence R. Stanberry and Philip Zachariah

The two closely related herpes simplex viruses (HSVs), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses, depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection. Common infections involve the skin, eye, oral cavity, and genital tract. Infections tend to be mild and self-limiting, except in the immunocompromised patient and newborn infants, in whom they may be severe and life-threatening.

Primary infection occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no preexisting immunity to HSV, primary infections can be severe. **Nonprimary first infection** occurs in individuals previously infected with one type of HSV (e.g., HSV-1) who

have become infected for the first time with the other type of HSV (HSV-2). Because immunity to one HSV type provides some cross-protection against disease caused by the other HSV type, nonprimary first infections tend to be less severe than true primary infections. During primary and nonprimary initial infections, HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause **recurrent infection**. Symptomatic recurrent infections tend to be less severe and of shorter duration than first infections. Asymptomatic recurrent infections are extremely common and cause no physical distress, although patients with these infections are contagious and can transmit the virus to susceptible individuals. Reinfection with a new strain of either HSV-1 or HSV-2 at a previously infected anatomic site (e.g., the genital tract) can occur but is relatively uncommon, suggesting that host immunity, perhaps site-specific local immunity, resulting from the initial infection affords protection against exogenous reinfection.

ETIOLOGY

HSVs contain a double-stranded DNA genome of approximately 152 kb that encodes at least 84 proteins. The DNA is contained within an icosadeltahedral capsid, which is surrounded by an outer envelope composed of a lipid bilayer containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, whereas other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs. HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the two viruses is their glycoprotein G proteins, which have been exploited to develop a new generation of commercially available, accurate, type-specific serologic tests that can be used to discriminate whether a patient has been infected with HSV-1 or HSV-2 or both.

EPIDEMIOLOGY

HSV infections are ubiquitous, and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. There are no documented incidental transmissions from inanimate objects such as toilet seats.

All infected individuals harbor latent infection and experience recurrent infections, which may be symptomatic or may go unrecognized and thus are periodically contagious. This information helps explain the widespread prevalence of HSV.

HSV-1 and HSV-2 are equally capable of causing initial infection at any anatomic site but differ in their capacity to cause recurrent infections. HSV-1 has a greater propensity to cause recurrent oral infections, whereas HSV-2 has a greater proclivity to cause recurrent genital infections. For this reason, HSV-1 infection typically results from contact with contaminated oral secretions, whereas HSV-2 infection most commonly results from anogenital contact.

HSV seroprevalence rates are highest in developing countries and among lower socioeconomic groups, although high rates of HSV-1 and HSV-2 infections are found in developed nations and among persons of the highest socioeconomic strata. Incident HSV-1 infections are more common during childhood and adolescence but are also found throughout later life. Data on HSV-1 and HSV-2 antibody prevalence from the National Health and Nutrition Examination Survey (NHANES) among persons age 14-49 years showed the prevalence of HSV-1 and HSV-2 to be 47.8% and 11.9%, respectively. Prevalence of both HSV-1 and HSV-2 increased linearly with age and was higher among females than males.

Modifiable factors that predict HSV-2 seropositivity include less education, poverty, cocaine use, and a greater lifetime number of sexual partners. Studies show that only approximately 10–20% of HSV-2–seropositive subjects report a history of genital herpes, emphasizing the asymptomatic nature of most HSV infections.

A 3-year longitudinal study of Midwestern adolescent females 12-15 years of age found that 44% were seropositive for HSV-1 and 7% for HSV-2 at enrollment. At the end of the study, 49% were seropositive for HSV-1 and 14% for HSV-2. The attack rates, based on the number of cases per 100 person-years, were 3.2 for HSV-1 infection among all females and 4.4 for HSV-2 infection among females who reported being sexually experienced. Findings of this study indicate that sexually active young women have a high attack rate for genital herpes and suggest that genital herpes should be considered in the differential diagnosis of any young woman who reports recurrent genitourinary complaints. In this study, participants with preexisting HSV-1 antibodies had a significantly lower attack rate for HSV-2 infection, and those who became infected were less likely to have symptomatic disease than females who were HSV seronegative when they entered the study. Prior HSV-1 infection appears to afford adolescent females some protection against becoming infected with HSV-2; in adolescent females infected with HSV-2, the preexisting HSV-1 immunity appears to protect against development of symptomatic genital herpes.

Neonatal herpes is an uncommon but potentially fatal infection of the fetus or more likely the newborn. It is not a reportable disease in most states, and therefore there are no solid epidemiologic data regarding its frequency in the general population. The overall U.S. incidence of neonatal HSV was estimated to be 9.6 per 100,000 births in 2006, which is higher than reported for the reportable perinatally acquired sexually transmitted infections such as congenital syphilis and gonococcal ophthalmia neonatorum. More than 90% of the cases are the result of maternal-child transmission. The risk for transmission is greatest during a primary or nonprimary first infection (30–50%) and much lower when the exposure is during a recurrent infection (<2%). HSV viral suppression therapy in mothers does not consistently eliminate the possibility of neonatal infection. Infants born to mothers dually infected with HIV and HSV-2 are also at higher risk for acquiring HIV than infants born to HIV-positive mothers who are not HSV-2 infected. It is estimated that approximately 25% of pregnant women are HSV-2 infected and that approximately 2% of pregnant women acquire HSV-2 infection during pregnancy.

HSV is a leading cause of sporadic, fatal encephalitis in children and adults. In the United States the annual hospitalization rate for HSV encephalitis has been calculated to be 10.3 ± 2.2 cases/million in neonates, 2.4 ± 0.3 cases/million in children, and 6.4 ± 0.4 cases/million in adults.

PATHOGENESIS

In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a cutaneous portal of entry such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. The virus enters the cell through attachment and fusion, a multistep process mediated by interaction of viral envelope glycoproteins (e.g., gB and gH-gL) with host surface receptors (e.g., Nectin-1). Virus replicates locally, resulting in the death of the cell, and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons, and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery, where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions, although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease. Although many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication. It is in these neurons that the virus establishes a latent infection, a condition in which the viral genome persists within the neuronal nucleus in a largely metabolically inactive state. Intermittently throughout the

life of the host, undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate. This replication occurs despite the host's having established a variety of humoral and cellular immune responses that successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection, where further replication occurs and causes recurrent infections. Recurrent infections may be symptomatic (with typical or atypical herpetic lesions) or asymptomatic. In either case, virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals who come in contact with the site or with contaminated secretions. Latency and reactivation are the mechanisms by which the virus is successfully maintained in the human population.

Viremia, or hematogenous spread of the virus, does not appear to play an important role in HSV infections in the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity, as occurs with HIV infection, malignancy, or immunosuppressive therapies. Viremia can result in dissemination of the virus to visceral organs, including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates.

The pathogenesis of HSV infection in newborns is complicated by their relative immunologic immaturity. The source of virus in neonatal infections is typically but not exclusively the mother. Transmission generally occurs during delivery, although it is well documented to rarely occur with cesarean delivery with intact fetal membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abrasions in the skin that occur with scalp electrode use or forceps delivery. With prompt antiviral therapy, virus replication may be restricted to the site of inoculation (the skin, eye, or mouth). However, virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain. Factors that may influence neonatal HSV infection include the virus type, portal of entry, inoculum of virus to which the infant is exposed, gestational age of the infant, and presence of maternally derived antibodies specific to the virus causing infection. Latent infection is established during neonatal infection, and survivors may experience recurrent cutaneous and neural infections. Persistent central nervous system infection may affect the neurodevelopment of the infant.

CLINICAL MANIFESTATIONS

The hallmarks of common HSV infections are skin vesicles and shallow ulcers. Classic infections manifest as small, 2- to 4-mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and is generally brief and sometimes just fleeting when moist mucous membranes are the site of infection. Because HSV infections are common, and their natural history is influenced by many factors, including portal of entry, immune status of the host, and whether it is an initial or recurrent infection, the typical manifestations are seldom classic. Most infections are asymptomatic or unrecognized, and nonclassic presentations, such as small skin fissures and small erythematous nonvesicular lesions, are common.

Acute Oropharyngeal Infections

Herpes gingivostomatitis most often affects children 6 months to 5 years of age but is seen across the age spectrum. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever of up to 40.0–40.6°C (104–105.1°F). The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including the gums, lips, tongue, palate, tonsils, pharynx, and perioral skin (Fig. 299.1). The vesicles may be more extensively distributed than typically seen with enteroviral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally present only a few days before progressing to form shallow indurated ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy is common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.



Fig. 299.1 Clustered perioral vesicles and erosions in an infant with primary herpetic gingivostomatitis. *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 1988:1078.)*

In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a healthcare provider, and signs and symptoms may be indistinguishable from those of streptococcal pharyngitis, consisting of fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

Herpes Labialis

Fever blisters (cold sores) are the most common manifestation of *recurrent* HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa. Older patients report experiencing burning, tingling, itching, or pain 3-6 hours (rarely as long as 24-48 hours) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that progress over a few hours to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6-10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

Cutaneous Infections

In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macroabrasions or microabrasions and exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling **(herpes gladiatorum)** and rugby **(scrum pox)**. An initial cutaneous infection establishes a latent infection that can subsequently result in recurrent infections at or near the site of the initial infection. Pain, burning, itching, or tingling often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then heal without scarring in 6-10 days. Although herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions



Fig. 299.2 Herpes simplex infection of finger (whitlow). *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 1988:1079.)*

and involves a larger surface area. Regional lymphadenopathy may occur, but systemic symptoms are uncommon. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Herpes whitlow is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. Among children, this condition is most commonly seen in infants and toddlers who suck the thumb or fingers and who are experiencing either a symptomatic or a subclinical oral HSV-1 infection (Fig. 299.2). An HSV-2 herpes whitlow occasionally develops in an adolescent as a result of exposure to infectious genital secretions. The onset of the infection is heralded by itching, pain, and erythema 2-7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if it is incised, little fluid is present. Incising the lesion is discouraged, because this maneuver typically prolongs recovery and increases the risk for secondary bacterial infection. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18-20 days. Regional lymphadenopathy is common, and lymphangitis and neuralgia may occur. Unlike other recurrent herpes infections, recurrent herpetic whitlows are often as painful as the primary infection but are generally shorter in duration.

Cutaneous HSV infections can be severe or life-threatening in patients with disorders of the skin such as eczema (eczema herpeticum), pemphigus, burns, and Darier disease and following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin (Fig. 299.3). If untreated, these lesions can progress to disseminated infection and death. Recurrent infections are common but generally less severe than the initial infection.

Genital Herpes

Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90% of infected individuals are *unaware* they are infected. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatic and asymptomatic individuals periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of pregnant women, to their newborns. Classic primary genital herpes may be preceded by a short period of local burning and tenderness before vesicles develop on genital mucosal surfaces or keratinized skin and sometimes around the anus or on the buttocks and thighs. Vesicles on mucosal surfaces are short lived and rupture to produce shallow, tender ulcers covered with a yellowish gray exudate and surrounded by an erythematous border. Vesicles on keratinized epithelium persist for a few days before progressing to the pustular stage and then crusting.

Patients may experience urethritis and dysuria severe enough to cause urinary retention and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge,



Fig. 299.3 Widespread cutaneous herpes infection in a child with underlying eczema (eczema herpeticum).

and men may have a clear mucoid urethral discharge. Significant local pain and systemic symptoms such as fever, headache, and myalgia are common. Aseptic meningitis develops in an estimated 15% of cases. The course of classic primary genital herpes from onset to complete healing is 2-3 weeks.

Most patients with symptomatic primary genital herpes experience at least one recurrent infection in the following year. Recurrent genital herpes is usually less severe and of shorter duration than the primary infection. Some patients experience a sensory prodrome with pain, burning, and tingling at the site where vesicles subsequently develop. Asymptomatic recurrent anogenital HSV infections are common, and all HSV-2–seropositive individuals appear to periodically shed virus from anogenital sites. *Most sexual transmissions and maternal-neonatal transmissions of virus result from asymptomatic shedding episodes.*

Genital infections caused by HSV-1 and HSV-2 are indistinguishable, but HSV-1 causes significantly fewer subsequent episodes of recurrent infection; hence, knowing which virus is causing the infection has important prognostic value. Genital HSV infection increases the risk for acquiring HIV infection.

Rarely, genital HSV infections are identified in young children and preadolescents. Although genital disease in children should raise concerns about possible sexual abuse, there are documented cases of autoinoculation, in which a child has inadvertently transmitted virus from contaminated oral secretions to his or her own genitalia.

Ocular Infections

HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and is often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically

have fever. Untreated infection generally resolves in 2-3 weeks. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic. Extension to the stroma is uncommon although more likely to occur in patients inadvertently treated with corticosteroids. When it occurs, it may be associated with corneal edema, scarring, and corneal perforation. Recurrent infections tend to involve the underlying stroma and can cause progressive corneal scarring and injury that can lead to blindness.

Retinal infections are rare and are more likely among infants with neonatal herpes and immunocompromised persons with disseminated HSV infections.

Central Nervous System Infections

HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults in the United States. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may manifest as nonspecific findings, including fever, headache, nuchal rigidity, nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid (CSF) typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration, and often a moderate number of erythrocytes. HSV has also been associated with autoimmune (NMDA receptor) encephalitis (see Chapter 638.4). Genetic factors that increase the susceptibility to HSV encephalitis include pathogenic variants in toll-like receptor-3 *(TLR3)*-dependent interferon immunity, *DBR1*, RNA5SP141, *TRAF3*, and other genes involved in *TLR3* sensing or downstream signaling.

HSV is also a cause of aseptic meningitis and is the most common cause of recurrent aseptic meningitis **(Mollaret meningitis)**.

Infections in Immunocompromised Persons

Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neonates, the severely malnourished, those with primary or secondary immunodeficiency diseases (including AIDS), and those receiving some immunosuppressive regimens, particularly for cancer and organ transplantation. Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues. Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

Perinatal Infections

HSV infection may be acquired in utero, during the birth process, or during the neonatal period. Intrauterine (prenatal) and postpartum (cutaneous lesions in caretakers) infections are well described but occur infrequently. Postpartum transmission may be from the mother or another adult with a nongenital (typically HSV-1) infection such as herpes labialis. Most cases of neonatal herpes result from maternal infection and transmission, usually during passage through an infected birth canal of a mother with asymptomatic genital herpes. Transmission is well documented in infants delivered by cesarean section. *Fewer than 30% of mothers of an infant with neonatal herpes have a history of genital herpes.* The risk for infection is higher in infants born to mothers with primary genital infection (>30%) than with recurrent genital infection (<2%). Use of scalp electrodes may also increase risk. There also have been rare cases of neonatal herpes associated with Jewish ritual circumcisions, but only with ritual oral contact with the circumcision site.

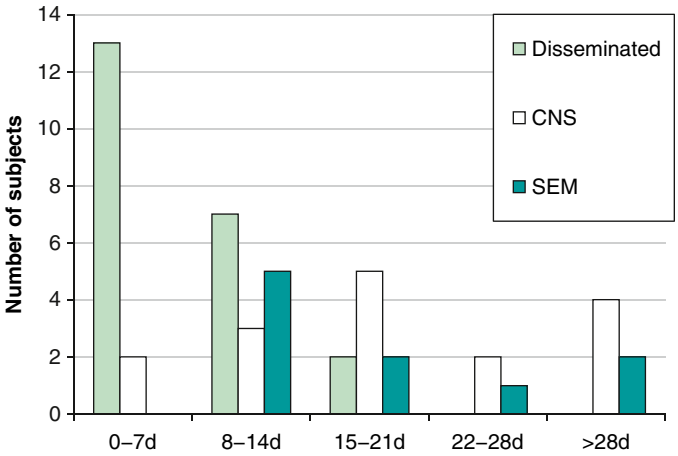

Fig. 299.4 Herpes simplex virus (HSV). Age at presentation by HSV disease type. SEM, skin, eye, mouth. *(From Curfman AL, Glissmeyer EW, Ahmad FA, et al. Initial presentation of neonatal herpes simplex virus infection. J Pediatr. 2016;172:121–126, p. 124.)*

Neonatal HSV infection is thought to never be asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with the rare onset of **intrauterine infection** typically have skin vesicles or scarring; eye findings, including chorioretinitis and keratoconjunctivitis; and microcephaly or hydranencephaly that are present at delivery.

Few infants survive without therapy, and those who do generally have severe sequelae. Infants infected during delivery or the postpartum period present with one of the following three patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, and mouth disease; and (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin (Fig. 299.4). Most present in the first 28 days of life. Approximately 20% present between 5 and 9 weeks of age.

Infants with **skin**, **eye**, **and mouth disease** generally present at 5-11 days of life and typically demonstrate a few clustered small vesicles, particularly on the presenting part or at sites of trauma such as sites of scalp electrode placement. If untreated, skin, eye, and mouth disease in infants may progress to encephalitis or disseminated disease.

Infants with encephalitis typically present at 8-17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever or hypothermia may occur but is not universal; skin vesicles occur in only approximately 60% of cases (Fig. 299.5). If untreated, 50% of infants with HSV encephalitis die and most survivors have severe neurologic sequelae.

Infants with disseminated HSV infections generally become ill at 5-11 days of life. Their clinical picture is similar to that of infants with bacterial sepsis, consisting of hyperthermia or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles are seen in approximately 75% of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90% of these infants die, and most survivors have severe neurologic sequelae.

Infants with neonatal herpes whose mothers received antiherpes antiviral drugs in the weeks before delivery may present later than their untreated counterparts; whether the natural history of the infection in these infants is different is an unanswered question.



Fig. 299.5 Vesicular-pustular lesions on the face of a neonate with herpes simplex virus infection. *(From Kohl S. Neonatal herpes simplex virus infection. Clin Perinatol. 1997;24:129–150.)*

DIAGNOSIS

The clinical diagnosis of HSV infections, particularly life-threatening infections and genital herpes, should be confirmed by laboratory test, preferably isolation of virus or detection of viral DNA by polymerase chain reaction (PCR). Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests. HSV immunoglobulin M tests are notoriously unreliable, and the demonstration of a fourfold or greater rise in HSV-specific immunoglobulin G titers between acute and convalescent serum samples is useful only in retrospect.

The highest yield for virus cultures comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells. Culturing dried, crusted lesions is generally of low yield. Although not as sensitive as viral culture, direct detection of HSV antigens in clinical specimens can be done rapidly and has very good specificity. The use of DNA amplification methods such as PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be performed rapidly. It is the test of choice in examining CSF in cases of suspected HSV encephalitis.

Evaluation of the neonate with suspected HSV infection should include cultures and/or PCR of suspicious lesions as well nasopharynx, mouth, conjunctivae, rectum, umbilicus, and scalp electrode site (if applicable), and PCR of *both* CSF and blood. In neonates testing for elevation of liver enzymes may provide indirect evidence of HSV dissemination to visceral organs. Efforts to develop clinical scoring systems for invasive HSV in infants have identified younger age, prematurity, seizure at home, ill appearance, abnormal triage temperature (fever or hypothermia), vesicular rash, thrombocytopenia, and CSF fluid pleocytosis as predictors.

Culture or antigen detection should be used in evaluating lesions associated with suspected acute genital herpes. HSV-2 type-specific antibody tests are useful for evaluating sexually experienced adolescents or young adults who have a history of unexplained recurrent nonspecific urogenital signs and symptoms, but these tests are less useful for general screening in populations in which HSV-2 infections are of low prevalence.

Because most HSV diagnostic tests take at least a few days to complete, treatment should not be withheld but rather initiated promptly so as to ensure the maximum therapeutic benefit.

LABORATORY FINDINGS

Most self-limited HSV infections cause few changes in routine laboratory parameters. Mucocutaneous infections may cause a moderate polymorphonuclear leukocytosis. In HSV meningoencephalitis there can be an increase in mononuclear cells and protein in CSF, the glucose content may be normal or reduced, and red blood cells may be present. The electroencephalogram and MRI of the brain may show temporal lobe abnormalities in HSV encephalitis beyond the neonatal period. Encephalitis in the neonatal period tends to be more global and not limited to the temporal lobe (Fig. 299.6). Disseminated infection may cause elevated liver enzymes, thrombocytopenia, and abnormal coagulation.

TREATMENT AND PREVENTION

See Chapter 292 for more information about principles of antiviral therapy.

Three antiviral drugs are available in the United States for the management of HSV infections, namely acyclovir, valacyclovir, and famciclovir. All three are available in oral form, but only acyclovir is available in a suspension form. Acyclovir has the poorest bioavailability and hence requires more frequent dosing. Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, both have very good oral bioavailability and are dosed once or twice daily. Acyclovir and penciclovir are also available in a topical form, but these preparations provide limited or no benefit to patients with recurrent mucocutaneous HSV infections. Only acyclovir has an intravenous formulation. Early initiation of therapy results in the maximal therapeutic benefit. All three drugs have exceptional safety profiles and are safe to use in pediatric patients. *Doses should be modified in patients with renal impairment.*

Resistance to acyclovir and penciclovir is rare in immunocompetent persons but does occur in immunocompromised persons and is usually mediated by mutations within the thymidine kinase and DNA polymerase genes. Virus isolates from immunocompromised persons whose HSV infection is not responding or is worsening with acyclovir therapy should be tested for drug sensitivities. Foscarnet and cidofovir have been used in the treatment of HSV infections caused by acyclovir-resistant mutants.

Topical trifluridine and topical ganciclovir are used in the treatment of herpes keratitis.

Patients with genital herpes also require counseling to address psychosocial issues, including possible stigma, and to help them understand the natural history and management of this chronic infection.

Acute Mucocutaneous Infections

For gingivostomatitis, limited evidence suggests that oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days; maximum: 1 g/day) started within 72 hours of onset reduces the severity and duration of the illness. Pain associated with swallowing may limit oral intake of infants and children, putting them at risk for dehydration. Intake should be encouraged through the use of cold beverages, ice cream, and yogurt.

For **herpes labialis**, oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (400 mg 5 times daily PO for 5 days), or famciclovir (1,500 mg once daily PO for 1 day) shortens the duration of the episode. Long-term daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

Anecdotal reports suggest that treatment of adolescents with **herpes gladiatorum** with valacyclovir (500 mg bid PO for 7-10 days) at the

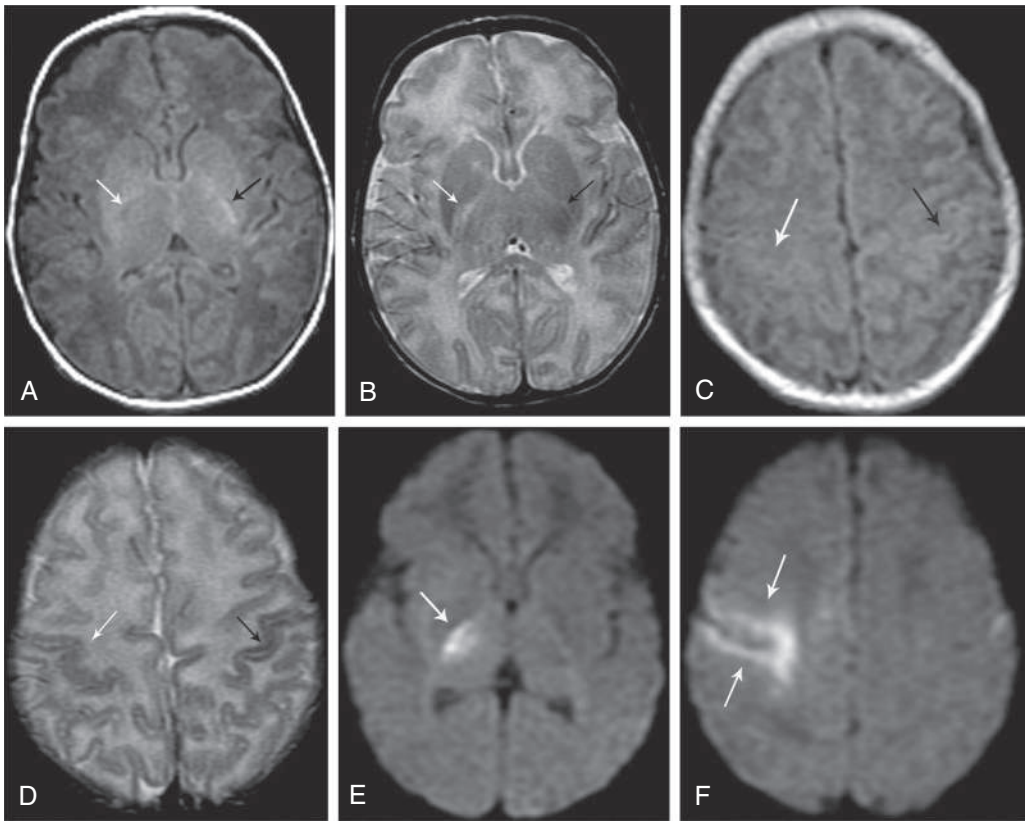

Fig. 299.6 Involvement of corticospinal tract and thalamus in a 2-wk old infant. **A,** Axial T1-weighted MRI demonstrating subtle loss of T1 hyperintensity corresponding to myelination in the posterior limb of the right internal capsule *(white arrow)*. T1 hyperintensity in the left posterior limb of the internal capsule is maintained *(black arrow)*. **B,** T2 weighted image showing findings similar to those seen on T1-weighted imaging. **C,** Axial T1- and **(D)** T2-weighted images through the vertex demonstrating subtle indistinct margins of the cortex around the right central sulcus *(white arrow)* compared to the normal appearance on the left side *(black arrow)*. **E** and **F,** Diffusion-weighted images with more extensive diffusion restriction in the posterior limb of the right internal capsule and lateral thalamus *(arrows)*, and in the right precentral and postcentral gyrus *(arrows)*. *(From Bajaj M, Mody S, Natarajan G. Clinical and neuroimaging findings in neonatal herpes simplex virus infection. J Pediatr. 2014;165:404–407. Fig. 1.)*

first signs of the outbreak can shorten the course of the recurrence with accompanying guidance on the importance of good hydration. For patients with a history of recurrent herpes gladiatorum, chronic daily prophylaxis with valacyclovir (500-1,000 mg/day) has been reported to prevent recurrences.

There are no clinical trials assessing the benefit of antiviral treatment for **herpetic whitlow**. High-dose oral acyclovir (1,600-2,000 mg/day divided in two or three doses PO for 10 days) started at the first signs of illness has been reported to abort some recurrences and reduce the duration of others in adults.

Children with mild cases of **eczema herpeticum** can be treated with oral acyclovir (10-20 mg/kg three times daily) or valacyclovir (20 mg/kg per day in three divided doses) for 7-21 days. However, serious infections should be treated with intravenous acyclovir. Oral-facial HSV infections can reactivate after cosmetic facial laser resurfacing, causing extensive disease and scarring. Treatment of adults beginning the day before the procedure with either valacyclovir (500 mg twice daily PO for 10-14 days) or famciclovir (250-500 mg bid PO for 10 days) has been reported to be effective in preventing the infections. HSV infections in **burn patients** can be severe or life-threatening and have been treated with intravenous acyclovir (10-20 mg/kg/day divided every 8 hours).

Antiviral drugs are not effective in the treatment of HSV-associated **erythema multiforme**, but their daily use as for herpes labialis prophylaxis prevents *reoccurrences* of erythema multiforme.

Genital Herpes

Pediatric patients, usually adolescents or young adults, with suspected first-episode genital herpes should be treated with antiviral therapy. Treatment of the initial infection reduces the severity and duration of the illness but has no effect on the frequency of subsequent recurrent infections. Treatment options for adolescents include acyclovir (400 mg tid PO for 7-10 days), famciclovir (250 mg tid PO for 7-10 days), or valacyclovir (1,000 mg bid PO for 7-10 days). The twice-daily valacyclovir option avoids treatment during school hours. For smaller children, acyclovir suspension can be used at a dose of 10-20 mg/kg/dose 4 times daily, not to exceed the adult dose. The first episode of genital herpes can be extremely painful, and use of analgesics is generally indicated. Intravenous acyclovir is indicated for those with severe or complicated primary infections that may require hospitalization. All patients with genital herpes should be offered counseling to help them deal with psychosocial issues and understand the chronic nature of the illness.

There are three strategic options regarding the management of recurrent infections. The choice should be guided by several factors, including the frequency and severity of the recurrent infections, the psychologic impact of the illness on the patient, and concerns regarding transmission to a susceptible sexual partner. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is long-term suppressive therapy. For **episodic therapy,** treatment should be initiated at the first signs of an outbreak. Recommended choices for episodic therapy in adolescents include famciclovir (1,000 mg bid PO for 1 day), acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days.) Long-term suppressive therapy offers the advantage that it prevents most outbreaks, improves patient quality of life in terms of the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for **long-term suppressive therapy** are acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500 or 1,000 mg qd PO).

Ocular Infections

HSV ocular infections can result in blindness. Management should involve consultation with an ophthalmologist.

Central Nervous System Infections

Patients older than neonates who have herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hours given as a 1-hour infusion for 21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

Infections in Immunocompromised Persons

Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (30 mg/kg per day, in three divided doses for 7-14 days) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less-severe HSV infections and for suppression of recurrences during periods of significant immunosuppression. Drug resistance does occur occasionally in immunocompromised patients, and in individuals whose HSV infection does not respond to antiviral drug therapy, viral isolates should be tested to determine sensitivity. Acyclovir-resistant viruses are often also resistant to famciclovir but may be sensitive to foscarnet or cidofovir.

Perinatal Infections

All infants with proven or suspected neonatal HSV infection should be treated immediately with high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hours). Treatment may be discontinued in infants shown by laboratory testing not to be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, whereas those with disseminated or central nervous system disease should receive a minimum of 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Suppressive oral acyclovir therapy for 6 months after completion of the intravenous therapy has been shown to improve the neurodevelopment of infants with central nervous system infection and to prevent cutaneous recurrences in infants regardless of disease pattern. Infants surviving neonatal HSV disease of any classification should receive 300 mg/m^2 per dose 3 times daily for 6 months. The absolute neutrophil count should be measured at weeks 2 and 4 after initiation of treatment and then monthly.

PROGNOSIS

Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2-3 weeks (for primary infections) and heal without scarring. Recurrent oral-facial herpes in a patient who has undergone dermabrasion or laser resurfacing can be severe and lead to scarring. Because genital herpes is a sexually transmitted infection, it can be stigmatizing, and its psychologic consequences may be much greater than its physiologic effects. Some HSV infections can be severe and may have grave consequences without prompt antiviral therapy. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children. Recurrent ocular herpes can lead to corneal scarring and blindness.

PREVENTION

Transmission of infection occurs through exposure to virus either as the result of skin-to-skin contact or from contact with contaminated secretions. Good handwashing and, when appropriate, the use of gloves provide healthcare workers with excellent protection against HSV infection in the workplace. Healthcare workers with active oral-facial herpes or herpetic whitlow should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions. Patients and parents should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions, during active herpes outbreaks. Schools and daycare centers should clean shared toys and athletic equipment such as wrestling mats at least daily after use. Athletes with active herpes infections who participate in contact sports such as wrestling and rugby should be excluded from practice or games until the lesions are completely healed. Genital herpes can be prevented by avoiding genital-genital and oral-genital contact. The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. Male circumcision is associated with a reduced risk of acquiring genital HSV infection. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.

For **pregnant women** with **active genital herpes** at the time of delivery, the risk for mother-to-child transmission can be reduced but not eliminated by delivering the baby via a cesarean section. The risk for recurrent genital herpes, and therefore the need for cesarean delivery, can be reduced but not eliminated in pregnant women with a history of genital herpes by the daily use of oral acyclovir, valacyclovir, or famciclovir during the last 4 weeks of gestation, which is recommended by the American College of Obstetrics and Gynecology. There are documented cases of neonatal herpes occurring in infants delivered by cesarean section, as well as in infants born to mothers who have been appropriately treated with antiherpes antiviral drugs for the last month of gestation. Therefore a history of cesarean delivery or antiviral treatment at term does not rule out consideration of neonatal herpes.

Asymptomatic infants delivered vaginally to women with *first-episode* genital herpes are at *very high risk* for acquiring HSV infection. The nasopharynx, mouth, conjunctivae, rectum, umbilicus, and scalp electrode site (if applicable) should be cultured (with PCR surface testing if available) at approximately 24 hours after birth for all infants born to mothers with primary genital herpes. Some also recommend HSV-PCR on blood and CSF. Some authorities recommend that these infants receive anticipatory acyclovir therapy for at least 10 days, and others treat such infants if signs develop or if there is evidence of HSV infection. Infants delivered to women with a history of *recurrent genital herpes* are at low risk for development of neonatal herpes. In this setting, while surface cultures and PCRs are done, empirical acyclovir is not started. Parents should be educated about the signs and symptoms of neonatal HSV infection and should be instructed to seek care without delay at the first suggestion of infection. When the situation is in doubt, infants should be evaluated and tested with surface culture (and PCR) for neonatal herpes as well as with PCR on blood *and* CSF; intravenous acyclovir is begun until culture and PCR results are negative or until another explanation can be found for the signs and symptoms.

Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir also have been used to prevent recurrent HSV infections in immunocompromised patients. Use of sun blockers is reported to be effective in preventing recurrent oral-facial herpes in patients with a history of sun-induced recurrent disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 300

Varicella-Zoster Virus*

Shivang S. Shah, Mona Marin, Philip S. LaRussa, and Anne A. Gershon

Varicella-zoster virus (VZV) causes primary, latent, and reactivation infections. The primary infection manifests as varicella (chickenpox) and results in establishment of a lifelong latent infection of sensory ganglionic neurons. Reactivation of the latent infection causes herpes zoster (shingles). Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults, as well as in immunocompromised persons. Varicella predisposes to severe group A streptococcus and staphylococcus infections. Primary clinical disease can be prevented by immunization with live-attenuated varicella vaccine. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs. Vaccines are also available to prevent herpes zoster in older adults.

ETIOLOGY

VZV is a neurotropic human herpesvirus with similarities to herpes simplex virus. VZV enveloped viruses contain double-stranded DNA genomes that encode 71 proteins, including proteins that are targets of cellular and humoral immunity.

EPIDEMIOLOGY

Before the introduction of the varicella vaccine in 1995, varicella was an almost universal communicable infection of childhood in the United States. Annual varicella epidemics occurred in winter and spring, and there were about 4 million cases of varicella, 11,000-13,500 hospitalizations, and 100-150 deaths every year in the United States. Most children were infected by 10 years of age, with fewer than 5% of adults remaining susceptible. This pattern of infection at younger ages remains characteristic in all countries in temperate climates. By contrast, in tropical areas, children acquire varicella at older ages and a higher proportion of young adults remain susceptible, leading to a higher proportion of cases occurring among adults. Varicella is a more serious disease in young infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children. Primary varicella is highly transmissible. Within households, transmission of VZV to susceptible individuals occurs at a rate of 65–86%; more casual contact, such as occurs in a school classroom, is associated with lower attack rates among susceptible children. Persons with varicella may be contagious 24-48 hours before the rash is evident and until vesicles are crusted, usually 4-7 days after onset of rash, consistent with evidence that VZV is spread by aerosolization of virus in cutaneous lesions; spread from oropharyngeal secretions may occur but to a much lesser extent. Susceptible persons may also acquire varicella after close, direct contact with adults or children who have herpes zoster, again via aerosolization of virus in skin lesions.

Since implementation of the varicella vaccination program in 1995, there have been substantial declines in varicella morbidity and mortality in the United States. By 2006, before implementation of the two-dose program, one-dose vaccination coverage had reached 90% and varicella incidence had declined 90% since 1995 in sites where active surveillance was being conducted; varicella-related hospitalizations had declined 84% from prevaccine years. Varicella-related deaths decreased by 88% from 1990–1994 to 2005–2007; in persons younger than 20 years of age there was a 97% decline in deaths. Declines in morbidity and mortality were seen in all age groups, including infants younger than 12 months of age who were not eligible for vaccination, indicating protection from exposure by indirect vaccination effects. The continued occurrence of breakthrough infections and of outbreaks in settings with high one-dose varicella vaccine coverage, together with the evidence that one dose is only 82% effective against all varicella, prompted adoption in 2007 of a routine two-dose childhood varicella vaccination program with catch-up vaccination of all individuals without evidence of immunity. Further declines in morbidity and mortality occurred during the two-dose program so that by 2019, declines reached more than 97% for incidence and 90% for hospitalizations and deaths. The greatest decline occurred in persons younger than 20 years of age, born during the varicella vaccination program, with 99%, 97%, and >99% reduction in incidence, hospitalizations, and deaths, respectively. Additionally, the two-dose program led to a reduction in the number, size, and duration of varicella outbreaks. Although the age-specific incidence has declined in all age groups, the median age at infection has increased, with cases occurring predominantly in children in ages 7-10 years rather than in the preschool years. This change in varicella epidemiology highlights the importance of offering vaccine to every susceptible child, adolescent, and adult.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus. The lifetime risk for herpes zoster for individuals with a history of varicella is at least 30%, with 75% of cases occurring after 45 years of age. Herpes zoster is unusual in healthy children younger than 10 years of age, with the exception of those infected with VZV in utero or in the first year of life, who have an increased risk for development of zoster in the first few years of life. Herpes zoster in otherwise healthy children tends to be milder than herpes zoster in adults, is less frequently associated with acute pain, and is generally not associated with postherpetic neuralgia. In children receiving immunosuppressive therapy for malignancy or other diseases and in those who have HIV infection, herpes zoster occurs more frequently, occasionally multiple times, and may be severe. The attenuated VZV in the varicella vaccine can establish latent infection and reactivate as herpes zoster. However, the risk for development of subsequent herpes zoster is much lower after vaccination than after natural VZV infection among both healthy and immunocompromised children. Although the Oka vaccine type VZV is attenuated, in children the severity of zoster caused by the Oka strain seems to be similar to or slightly milder than that caused by the natural or wild-type VZV. Vaccinated children who do develop zoster may have disease resulting from either vaccine or wild-type VZV, due to breakthrough varicella or subclinical infection of some vaccinees with wild-type VZV occurring at some point after immunization.

PATHOGENESIS

Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10- to 21-day incubation period, virus replicates in the local lymphoid tissue and spreads to T lymphocytes, causing a viremia that delivers the virus to skin where innate immunity controls VZV replication for several days. After innate immunity is overcome in skin, widespread cutaneous lesions develop as the incubation period ends. Adaptive host immune responses, especially cellular immunity, limit viral replication and lead to recovery from infection. In the immunocompromised child, the failure of adaptive immunity, especially cellular immune responses, results in continued viral replication that may lead to prolonged and/or disseminated infection with resultant complications of infection in the lungs, liver, brain, and other organs.

Latent infection develops during the incubation period or the disease itself. VZV is transported in a retrograde manner through sensory axons to the dorsal root ganglia in the spinal cord and to cranial nerve ganglia. Latency may also develop from viremia, infecting spinal and cranial nerve ganglia as well as autonomic ganglia that do not project to

*The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.

the skin, including the enteric nervous system of the intestine. Latency of VZV occurs only in ganglionic neurons. Subsequent **reactivation** of latent VZV causes **herpes zoster**, usually manifested by a vesicular rash that is unilateral and dermatomal in distribution. Reactivation of VZV may also occur without a rash; examples are unilateral dermatomal pain without rash **(zoster sine herpete)**, aseptic meningitis, and gastrointestinal illness (enteric zoster). During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells in associated ganglia. The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

CLINICAL MANIFESTATIONS

Varicella is an acute febrile rash illness that was common in children in the United States before the universal childhood vaccination program. It has variable severity but is usually self-limited. It may be associated with severe complications, including bacterial superinfection, especially with staphylococci and group A streptococci, pneumonia, encephalitis, bleeding disorders, congenital infection, and life-threatening perinatal infection. Herpes zoster is not common in children and typically causes localized cutaneous symptoms, but may disseminate in immunocompromised patients.

Varicella in Unvaccinated Individuals

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10-21 days. Subclinical varicella is rare; almost all exposed, susceptible persons experience a rash, albeit so mild in some cases that it may go unnoticed. Prodromal symptoms may be present, particularly in older children and adults. Fever, malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hours before the rash appears. Temperature elevation is usually 37.8–38.9°C (100–102°F) but may be as high as 41.1°C (106°F); fever and other systemic symptoms usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk. The initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24-48 hours. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella (Fig. 300.1). The distribution of the rash is predominantly central or centripetal, with the greatest concentration on the trunk and proximally on the extremities. Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common; many children have vesicular lesions on the eyelids and conjunctivae, but corneal involvement and serious ocular disease are rare. The average number of varicella lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older children, more lesions usually occur, and new crops of lesions may continue to develop for more than 7 days. The exanthem may be much more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.



Fig. 300.1 A, Varicella lesions in unvaccinated persons display the characteristic "cropping" distribution, or manifest themselves in clusters; the simultaneous presence of lesions in various stages of evolution is characteristic. B, Breakthrough varicella lesions are predominantly maculopapular, and vesicles are less common; the illness is most commonly mild with <50 lesions. *(Courtesy Centers for Disease Control and Prevention and Dr. John Noble, Jr.)*

The differential diagnosis of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox (mpox), rickettsial pox, and *Staphylococcus aureus;* drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

Varicelliform Rashes in Vaccinated Individuals

Varicelliform rashes that occur after vaccination could be a result of wild-type VZV, vaccine strain VZV, or other causes (e.g., insect bites, coxsackievirus). During days 0-42 after vaccination, the likelihood of rash from wild-type or vaccine strain VZV varies depending on the stage of a country's vaccination program. In the early stages of a vaccination program, rash within 1-2 weeks is still most commonly caused by wild-type VZV, reflecting exposure to varicella before vaccination could provide protection. Rash occurring 14-42 days after vaccination is a result of either wild-type or vaccine strains, reflecting exposure and infection before protection from vaccination or an adverse event of vaccination (vaccine-associated rash), respectively. As wild-type varicella continues to decline as a consequence of the vaccination program, wild-type VZV circulation will also decline and rashes in the interval 0-42 days after vaccination will be less commonly caused by wild-type VZV, as is the case in the United States. Spread of vaccine type VZV from a vaccinee with skin lesions has occurred but is rare. The resulting illness in contacts is commonly mild with only a few vesicular lesions. Clinical reversion of the vaccine virus to virulence has not been described.

Breakthrough varicella is disease caused by **wild-type** virus in a vaccinated person, occurring after 42 days past vaccination. One dose of varicella vaccine is 98% effective in preventing moderate and severe varicella and is 82% effective in preventing all disease after exposure to wild-type VZV. This means that after close exposure to VZV, as may occur in a household or an outbreak setting in a school or daycare center, about 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella. Exposure to VZV may also result in asymptomatic infection in the previously immunized child. The rash in breakthrough disease is frequently atypical and predominantly maculopapular, and vesicles are seen less commonly. The illness is most commonly mild with fewer than 50 lesions, shorter duration of rash, fewer complications, and little or no fever. However, approximately 25–30% of breakthrough cases in vaccinees who received one dose are not mild, with clinical features more similar to those of wild-type infection. Breakthrough cases are overall **less contagious** than wild-type infections within household settings, but contagiousness varies proportionally with the number of lesions; typical breakthrough cases (<50 lesions) are about one-third as contagious as disease in unvaccinated cases, whereas breakthrough cases with ≥50 lesions are as contagious as wild-type cases. Consequently, children with breakthrough disease should be considered potentially infectious and excluded from school until lesions have crusted or, if there are no vesicles present, until no new lesions are occurring. Transmission has been documented to occur from breakthrough cases in household, childcare, and school settings.

Two doses of varicella vaccine provide better protection than a one-dose schedule. One clinical trial estimated the two-dose vaccine efficacy for preventing all disease at 98%; the estimate is 92% in conditions of everyday clinical practice. Institution of two doses routinely in the United States substantially reduced the school outbreaks that were occurring among children who had received only one dose.

Breakthrough cases have been reported among two-dose vaccinees; however, recipients of two doses of varicella vaccine are less likely to have breakthrough disease than those who received one dose. Additionally, data suggest that breakthrough varicella may be further attenuated among two-dose vaccine recipients.

Neonatal Varicella

Mortality is particularly high in neonates born to susceptible mothers who contract varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period from 5 days before delivery to 2 days afterward are at high risk for severe varicella. These infants acquire the infection transplacentally as a result of maternal viremia, which may occur up to 48 hours before onset of maternal rash. The infant's rash usually occurs toward the end of the first week to the early part of the second week of life (although it may be as soon as 2 days). Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody. If the mother demonstrates varicella more than 5 days before delivery, she still may pass virus to the soon-to-be-born child, but infection is attenuated because of transmission of maternal VZV-specific antibody across the placenta. This moderating effect of maternal antibody is present if delivery occurs after about 30 weeks of gestation, when maternal immunoglobulin (Ig) G (IgG) is able to cross the placenta in significant amounts. *The recommendations for use of human varicella-zoster immunoglobulin (VZIG) differ based on when the infant is exposed to varicella.* Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive VZIG as soon as possible after birth. Although neonatal varicella may occur in about half of these infants despite administration of VZIG, it is milder than in the absence of VZIG administration. All premature infants born <28 weeks of gestation to a mother with active varicella at delivery (even if the maternal rash has been present for >1 week) should receive VZIG. If VZIG is not available, intravenous immunoglobulin (IVIG) may provide some protection, although varicella-specific antibody titers may vary from lot to lot. Because perinatally acquired varicella may be life threatening, the infant should usually be treated with acyclovir (10-15 mg/kg every 8 hours IV) when lesions develop. Neonatal varicella can also follow a postpartum exposure of an infant delivered to a mother who was susceptible to VZV, although the frequency of complications declines rapidly in the weeks after birth. Recommendations for VZIG administration for these infants are presented in the postexposure prophylaxis section. Neonates with community-acquired varicella who experience severe varicella, especially those who have a complication such as pneumonia, hepatitis, or encephalitis, should also receive treatment with intravenous acyclovir (10 mg/kg every 8 hours). Infants with neonatal varicella who receive prompt antiviral therapy have an excellent prognosis.

Congenital Varicella Syndrome

In utero transmission of VZV can occur; however, because most adults in temperate climates are immune, pregnancy complicated by varicella is unusual in these settings. When pregnant women do contract varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. Fortunately, clinically apparent disease in the infant is uncommon: the congenital varicella syndrome occurs in approximately 0.4% of infants born to women who have varicella during pregnancy before 13 weeks of gestation and in approximately 2% of infants born to women with varicella between 13 and 20 weeks of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 weeks of pregnancy, the latest occurring at 28 weeks of gestation. Before availability of varicella vaccine in the United States, 44 cases of congenital varicella syndrome were estimated to occur each year. The congenital varicella syndrome is characterized by cicatricial skin scarring in a zoster-like distribution; limb hypoplasia; and abnormalities of the neurologic system (e.g., microcephaly, cortical atrophy, seizures, and intellectual disability), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal system (e.g., hydroureter and hydronephrosis), and autonomic nervous system



Fig. 300.2 Newborn with congenital varicella syndrome. The infant had severe malformations of both lower extremities and cicatricial scarring over his left abdomen.

(e.g., neurogenic bladder, swallowing dysfunction, and aspiration pneumonia). Low birthweight is common among infants with congenital varicella syndrome. Most of the manifestations can be attributed to virus-induced injury to the nervous system, although there is no obvious explanation why certain regions of the body are preferentially infected during fetal VZV infection. The characteristic cutaneous lesion has been called a cicatrix, a zigzag scarring, in a *dermatomal* distribution, often associated with atrophy of the affected limb (Fig. 300.2). Many infants with severe manifestations of congenital varicella syndrome (atrophy and scarring of a limb) have significant neurologic deficiencies. Alternatively, there may be neither skin nor limb abnormalities, but the infant may show cataracts or even extensive aplasia of the entire brain.

There are rare case reports of fetal abnormalities after the development of herpes zoster in the mother; whether these cases truly represent the congenital varicella syndrome is unclear. If it does occur, the congenital syndrome acquired as a result of maternal herpes zoster is exceedingly rare. Maternal herpes zoster was associated with typical congenital varicella syndrome in one case, but the mother had disseminated herpes zoster (at 12 weeks of gestation).

The diagnosis of VZV fetopathy is based mainly on the history of gestational varicella combined with the presence of characteristic abnormalities in the newborn infant. Virus cannot be cultured from the affected newborn, but viral DNA may be detected in tissue samples by polymerase chain reaction (PCR). Because many infants with congenital varicella syndrome develop zoster before a year of age, it may be possible to isolate VZV from that rash. Alternatively, use of PCR to identify VZV DNA in vesicular fluid or scabs from zoster lesions in such an infant may be diagnostic. VZV-specific IgM antibody is detectable in the cord blood sample in some infants, although the IgM titer drops quickly in the postpartum period and can be nonspecifically positive. Chorionic villus sampling and fetal blood collection for the detection of viral DNA, virus, or antibody have been used in an attempt to diagnose fetal infection and embryopathy. The usefulness of these tests for patient management and counseling has not been defined. Because these tests may not distinguish between infection and disease, their utility may primarily be that of reassurance when the result is negative. Ultrasound may be useful to try to identify limb atrophy, which is common in congenital varicella syndrome. A persistently positive VZV IgG antibody titer at 12-18 months of age is a reliable indicator of prenatal

infection in the asymptomatic child, as is the development of zoster in the first year of life without evidence of postnatal infection.

VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity; it is uncertain whether this step modifies infection in the fetus, although some evidence suggests that it may be beneficial for the fetus too. Similarly, acyclovir treatment may be given to the mother with severe varicella. A prospective registry of acyclovir use in the first trimester demonstrated that the occurrence of birth defects approximates that found in the general population. Acyclovir is a class B drug for pregnancy and should be considered when the benefit to the mother outweighs the potential risk to the fetus. The efficacy of acyclovir treatment of the pregnant woman in preventing or modifying the severity of congenital varicella is not known, but its use should be considered to protect the mother from severe disease. Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral treatment of infants with congenital VZV syndrome is not indicated.

COMPLICATIONS

The complications of VZV infection (varicella or zoster) occur more commonly in immunocompromised patients. In the otherwise healthy child, asymptomatic transient varicella hepatitis is relatively common. Mild thrombocytopenia occurs in 1–2% of children with varicella and may be associated with petechiae. Purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding are rare complications that may have serious consequences. Other complications of varicella, some of them rare, include acute cerebellar ataxia, encephalitis, pneumonia, nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis. A reduction in the number and rates of varicella-related complications is seen in vaccinated populations. Reports of serious varicella-related complications in vaccinated persons (breakthrough) are rare (meningitis, pneumonia, acute transverse myelitis, encephalitis [one fatal case in an apparently immunocompetent child], and sepsis). Severe breakthrough varicella can occur among healthy persons, but cases appear to be more common among immunocompromised persons who are usually not recommended to receive varicella vaccine.

Declines in varicella-related hospitalizations and deaths in the United States since implementation of the varicella vaccination program provide supporting evidence that varicella vaccine reduces severe complications from varicella. Approximately 105 deaths (with varicella listed as the underlying cause of death) occurred in the United States annually before the introduction of the varicella vaccine; during 2017–2019 the annual average number of varicella deaths was 18. In both the pre- and postvaccine eras, the majority of deaths (>80%) have been among persons without high-risk preexisting conditions.

Bacterial Infections

Secondary bacterial infections of the skin, usually caused by group A streptococcus or *S. aureus,* may occur in children with varicella. These range from impetigo to cellulitis, lymphadenitis, and subcutaneous abscesses. An early manifestation of secondary bacterial infection is erythema of the base of a new vesicle. Recrudescence of fever 3-4 days after the initial exanthem may also herald a secondary bacterial infection. Varicella is a well-described risk factor for serious invasive infections caused by group A streptococcus, which can have a fatal outcome. The more invasive infections, such as varicella gangrenosa, bacterial sepsis, pneumonia, arthritis, osteomyelitis, cellulitis, and necrotizing fasciitis, account for much of the morbidity and mortality of varicella in otherwise healthy children. Bacterial toxin–mediated diseases (e.g., toxic shock syndrome) also may complicate varicella. A substantial decline in varicella-related invasive bacterial infections is associated with the use of the varicella vaccine.

Encephalitis and Cerebellar Ataxia

Encephalitis (1 per 50,000 cases of varicella in unvaccinated children) and acute cerebellar ataxia (1 per 4,000 cases of varicella in unvaccinated children) are well-described neurologic complications of varicella; morbidity from central nervous system complications is highest among patients younger than 5 years and older than 20 years. Nuchal rigidity, altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hours, and is usually complete. Although severe hemorrhagic encephalitis, analogous to that caused by herpes simplex virus, is very rare in children with varicella, the consequences are similar to those of herpes simplex virus encephalitis. Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses such as influenza is rare now that salicylates are no longer used as antipyretics in these situations (see Chapter 405).

Pneumonia

Varicella pneumonia (viral, due to VZV) is a severe complication that accounts for most of the increased morbidity and mortality from varicella in adults and other high-risk populations, but viral pneumonia may also complicate varicella in young children. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1-6 days after the onset of the rash. Smoking has been described as a risk factor for severe pneumonia complicating varicella. The frequency of varicella pneumonia may be greater in the parturient.

Progressive Varicella

Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days, is a severe complication of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver, or the appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease. Although rare in healthy children, the risk for progressive varicella is highest in children with congenital cellular immune deficiency disorders and those with malignancy, particularly if chemotherapy, and especially corticosteroids, had been given during the incubation period and the absolute lymphocyte count is <500 cells/μL. The mortality rate for children who acquired varicella while undergoing treatment for malignancy and who were not treated with antiviral therapy approached 7%; varicella-related deaths usually occurred within 3 days after the diagnosis of varicella pneumonia. Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children undergoing long-term, low-dose systemic or inhaled corticosteroid therapy are not considered to be at higher risk for severe varicella, but progressive varicella does occur in patients receiving high-dose corticosteroids. There are case reports in patients receiving inhaled corticosteroids as well as in asthmatic patients receiving multiple short courses of systemic corticosteroid therapy. Unusual clinical findings of varicella, including lesions that develop a hyperkeratotic appearance and continued new lesion formation for weeks or months, have been described in children with untreated, late-stage HIV infection. Immunization of HIV-infected children who have a $CD4^+$ T-lymphocyte percent ≥15%, as well as children with leukemia and solid organ tumors who are in remission and whose chemotherapy can be interrupted for 2 weeks around the time of immunization or has been terminated, have reduced frequency of severe disease. Moreover, since the advent of the universal immunization program in the United States, many children who would become immunocompromised later in life because of disease or treatment are protected before the immunosuppression occurs; also, as a result of reductions in varicella incidence, immunocompromised children are less likely to be exposed to varicella.

Herpes Zoster

Herpes zoster manifests as vesicular lesions clustered within one or, less commonly, two adjacent dermatomes (Fig. 300.3). In the elderly,



Fig. 300.3 Herpes zoster involving the lumbar dermatome. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2005:1783.)*



Fig. 300.4 Many groups of blisters occurring over the arm in a child with herpes zoster. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002: Fig. 8-28.)*

herpes zoster typically begins with burning pain or itching followed by clusters of skin lesions in a dermatomal pattern. Almost half of the elderly with herpes zoster experience complications; the most frequent complication is postherpetic neuralgia, a painful condition that affects the nerves despite resolution of the skin lesions. Approximately 4% of patients suffer a second episode of herpes zoster; three or more episodes are rare. Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few days (Fig. 300.4); symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1-2 weeks. Unlike in adults, postherpetic neuralgia is unusual in children. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the first year of life.

Immunocompromised children may have more severe herpes zoster, similar to the situation in adults, including postherpetic neuralgia. Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease, retinitis, or central nervous system disease without rash. The finding of a lower risk for herpes zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV. A study of HIV-infected vaccinated children found no cases of zoster 4.4 years after immunization, which was significantly different from the rate in children who had experienced varicella. Studies to date indicate that the risk for herpes zoster in healthy children who have received one or more doses of vaccine is 78% lower than in children who had wild-type varicella, with two-dose vaccination providing 50% greater protection than one-dose. Many more years of follow-up are needed to determine whether this lower risk is maintained among older persons who are at greatest risk for herpes zoster.

DIAGNOSIS

Varicella and herpes zoster are usually diagnosed primarily by their clinical appearance. Laboratory evaluation has not been considered necessary for diagnosis or management. However, as varicella disease has declined to low levels, laboratory confirmation has become increasingly necessary. The atypical nature of breakthrough varicella, with a higher proportion of papular rather than vesicular rashes, poses both clinical and laboratory diagnostic challenges.

Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be important for infection control, especially for breakthrough cases that have mild or atypical presentations. Confirmation of VZV infections can be accomplished by many referral hospital laboratories and all state health laboratories. VZV can be identified quickly by either PCR amplification testing (vesicular fluid, crusts) or direct fluorescence assay of cells from cutaneous lesions (vesicular fluid). In the absence of vesicles or scabs, scrapings of maculopapular lesions can be collected for PCR or direct fluorescence assay testing. Infectious virus may be recovered by means of tissue culture methods; such methods require specific expertise, and virus may take days to weeks to grow. Of available tests, PCR is the most sensitive and also allows for differentiation of wild-type and vaccine strains. Direct fluorescence assay is specific and less sensitive than PCR but when available allows for rapid diagnosis. Although multinucleated giant cells can be detected with nonspecific stains (Tzanck smear), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections. Strain identification (genotyping) can distinguish wild-type VZV from the vaccine strain in a vaccinated child; however, genotyping is available only at specialized reference laboratories. Laboratory tests of lesions cannot be used to distinguish between varicella and disseminated herpes zoster. VZV IgG antibodies can be detected by several methods, and a fourfold or greater rise in IgG antibodies is confirmatory of acute infection (although this requires a 2- to 3-week delay to collect a convalescent specimen). In vaccinated persons, commercially available tests are not sufficiently sensitive to always detect antibodies following immunization, and a fourfold rise in IgG antibodies may not occur. Testing for VZV IgM antibodies is not useful for routine confirmation or ruling out of varicella because commercially available methods are unreliable and the kinetics of the IgM response have not been well defined. IgM is inconsistently detected, even among patients with PCR-confirmed disease. Furthermore, IgM detection does not confirm a primary infection because specific IgM antibodies are transiently produced on each exposure to VZV, whether through primary infection, reinfection, or reactivation from latency, even subclinical. Serologic tests are not useful for the initial diagnosis of herpes zoster, but a significant rise in IgG titer in convalescent titer in the presence of an atypical zoster rash is confirmatory. As with any laboratory test, a negative varicella test should be considered in the context of the clinical presentation. Clinicians should use clinical judgment to decide on the best course of therapy. VZV IgG antibody can be useful to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal. However, caution must be taken in interpreting tests for immunity to VZV, especially in immunocompromised patients after a close exposure to VZV. Due to the possibility of false-positive results, it is preferable to rely on clinical rather than laboratory information, and if in doubt, assume the individual is susceptible to varicella and proceed accordingly.

TREATMENT

Antiviral treatment with acyclovir or valacyclovir modifies the course of both varicella and herpes zoster. Antiviral drug resistance is rare for VZV but has occurred, primarily in children with HIV infection and other immunocompromising conditions in which frequent relapse of VZV infections has resulted in multiple courses of antiviral therapy. Foscarnet and cidofovir may be useful for the treatment of acyclovir-resistant VZV infections, but consultation of an infectious diseases specialist is recommended.

Varicella

Given the safety profile of acyclovir and valacyclovir, and their demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. Oral therapy with acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) given as four doses/day for 5 days can be used to treat uncomplicated varicella. Therapy is particularly important for individuals at increased risk for moderate to severe varicella: individuals older than 12 years of age; individuals older than 12 months of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hours of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hours after onset of the exanthem. Acyclovir therapy does not interfere with the induction of VZV immunity. Acyclovir has been successfully used to treat varicella in pregnant women. Valacyclovir or famciclovir may be given to older children who can swallow tablets. These drugs are highly active against VZV by the same mechanism as acyclovir and are better absorbed by the oral route than acyclovir. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose, administered 3 times daily for 5 days) is licensed for treatment of varicella in children 2 to <18 years of age, and both valacyclovir and famciclovir are approved for treatment of herpes zoster in adults. Patients receiving these antivirals should be well hydrated, and for prolonged use, renal function and white blood cell counts (especially neutrophils) should be monitored frequently. Common adverse symptoms during valacyclovir treatment are neurologic (headache, agitation, dizziness) and gastrointestinal (nausea, abdominal pain).

Intravenous therapy is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hours after onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. Intravenous acyclovir therapy (10 mg/kg or 500 mg/m^2 every 8 hours) initiated within 72 hours of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients. Treatment is continued for 7-10 days or until no new lesions have appeared for 48 hours. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not recommended because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV. These children may be treated with intravenous foscarnet (120 mg/kg/day divided every 8 hours). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these two drugs should be initiated in collaboration with an infectious diseases specialist.

Herpes Zoster

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5-7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness but do not prevent development of postherpetic neuralgia. In otherwise healthy children, herpes zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore treatment of uncomplicated herpes zoster in the child with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hours from onset of rash limits its effectiveness.

In contrast, herpes zoster in immunocompromised children can be severe, and disseminated disease may be life-threatening. Patients at high risk for disseminated disease should receive intravenous acyclovir (500 mg/m^2 or 10 mg/kg every 8 hours). Oral acyclovir, famciclovir, and valacyclovir are options for immunocompromised patients with uncomplicated herpes zoster, who are considered at low risk for visceral dissemination. Neuritis with herpes zoster should be managed with appropriate analgesics.

Use of corticosteroids in the treatment of herpes zoster in children is not recommended.

PROGNOSIS

Primary varicella in unvaccinated persons has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 years of age (~1 deaths/100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic conditions. The mortality rate of untreated primary infection was 7% in immunocompromised children in the 1960s. In the era of antiviral therapy and improved supportive care, the prognosis has improved with treatment administered early in the course of illness, but deaths have continued to occur. Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

PREVENTION

VZV transmission is difficult to prevent, especially from persons with varicella, because a person with varicella may be contagious for 24-48 hours before the rash is apparent. Herpes zoster is less infectious than varicella; nonetheless, transmission has been reported even in the absence of direct contact with the patient. Infection control practices, including caring for patients with varicella in isolation rooms with filtered air systems, are essential. All healthcare workers should have evidence of varicella immunity (Table 300.1). Unvaccinated healthcare workers without other evidence of immunity who have had a close exposure to VZV should be furloughed for days 8-21 after exposure because they are potentially infectious during this period. Routine testing for VZV antibodies after vaccination is not useful for identifying individuals who are immune to varicella because the tests are insensitive for this purpose.

Vaccine

Varicella is a vaccine-preventable disease. Varicella vaccine contains live, attenuated VZV (Oka strain) and is indicated for subcutaneous or intramuscular administration. In the United States, varicella vaccine is recommended for routine administration as a two-dose regimen to healthy children at ages 12-15 months and 4-6 years. Administration of the second dose earlier than 4-6 years of age is acceptable, but it must be at least 3 months after the first dose. Catch-up vaccination with the second dose is recommended for children and adolescents who received only one dose. Vaccination with two doses is recommended for all persons without evidence of immunity. The minimum interval between the two doses is 3 months for persons 12 years of age or younger and 4 weeks for older children, adolescents, and adults. Administration of varicella vaccine within 4 weeks of measles-mumps-rubella (MMR) vaccination is associated with a

Table 300.1 Evidence of Immunity to Varicella

Evidence of immunity to varicella consists of any of the following:

- Documentation of age-appropriate vaccination with a varicella vaccine:
  - Preschool-age children (i.e., age ≥12 mo): one dose
  - School-age children, adolescents, and adults: two doses*
- Laboratory evidence of immunity† or laboratory confirmation of disease
- Birth in the United States before 1980‡
- Diagnosis or verification of a history of varicella disease by a healthcare provider§
- Diagnosis or verification of a history of herpes zoster by a healthcare provider

*For children who received their first dose at younger than age 13 years and for whom the interval between the two doses was 28 or more days, the second dose is considered valid.

†Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).

‡For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.

§Verification of history or diagnosis of typical disease can be provided by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or his/her designee is recommended, and one of the following should be sought: (1) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or (2) evidence of laboratory confirmation if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases might mimic mild atypical varicella.

higher risk for breakthrough disease; therefore it is recommended that the varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 weeks apart. Varicella vaccine can be administered as a monovalent vaccine (for all healthy persons ≥12 months of age) or as the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine (for children age 12 months through 12 years only).

Varicella vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine; pregnant women; persons with cell-mediated immune deficiencies, including those with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems; persons receiving immunosuppressive therapy; and persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives unless the immune competence of the potential vaccine recipient is demonstrated. Children with isolated humoral immunodeficiencies may receive varicella vaccine. The monovalent varicella vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia and certain solid tumors who were in remission, but this practice is not recommended except in a research setting. Varicella vaccine can be administered to patients with leukemia, lymphoma, or other malignancies whose disease is in remission, who have restored immunocompetence, and whose chemotherapy has been terminated for at least 3 months.

The vaccine should be considered for HIV-infected children with a $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 or percentage ≥15%. These children should receive two doses of the monovalent vaccine, 3 months apart. Specific guidelines for immunizing these children should be reviewed before vaccination. Data indicate that varicella vaccine is highly effective in preventing herpes zoster among children infected with HIV. MMRV should not be administered as a substitute for the component vaccines in HIV-infected children.

A recombinant subunit (non-live) adjuvanted vaccine is available in the United States for use for prevention of herpes zoster and its related complications among individuals 50 years and older and among those 19 years and older who are or will be immunodeficient or immunosuppressed because of disease or therapy. The zoster vaccine is not indicated for primary prevention of varicella, or for the treatment of zoster or postherpetic neuralgia.

Vaccine-Associated Adverse Events

Varicella vaccine is safe and well tolerated. The incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (22%). A mild vaccine-associated varicelliform rash was reported in approximately 1–5% of healthy vaccinees, consisting of 6-10 papular-vesicular, erythematous lesions with peak occurrence 8-21 days after vaccination. Serious adverse reactions confirmed to be caused by the vaccine strain are rare and include pneumonia, hepatitis, meningitis, recurrent herpes zoster, severe rash, and seven deaths (all deaths occurred in persons with immunocompromising conditions). Transmission of vaccine virus to susceptible contacts is a very rare event from healthy vaccine recipients (13 instances from 11 immunocompetent varicella vaccine recipients, all in the presence of a rash in the vaccinee, 6 varicella-like and 5 herpes zoster). MMRV vaccine is associated with a greater risk for febrile seizures 5-12 days after the first dose among children 12-23 months of age compared with simultaneous MMR and varicella vaccines (one extra febrile seizure for every 2,500 children vaccinated).

Postexposure Prophylaxis

Vaccine given to healthy children within 3 and up to 5 days after exposure (as soon as possible is preferred) is effective in preventing or modifying varicella. Varicella vaccine is recommended for postexposure use and for outbreak control. Oral acyclovir administered late in the incubation period may modify subsequent varicella in the healthy child; however, its use in this manner is not recommended until it can be further evaluated.

High-titer anti-VZV immune globulin as postexposure prophylaxis is recommended for immunocompromised children, pregnant women, and newborns exposed to varicella. Since 2012 the product licensed for use in the United States is VariZIG. VariZIG is commercially available from a broad network of specialty distributors in the United States (list available at https://www.varizig.com). The recommended dose is 1 vial (125 units) for each 10-kg increment of body weight (maximum: 625 units), except for infants weighing ≤2 kg who should receive 0.5 vial. VariZIG should be given intramuscularly as soon as possible but may be efficacious up to 10 days after exposure.

Newborns whose mothers have varicella 5 days before to 2 days after delivery should receive VariZIG (0.5 vial for those weighing ≤2 kg and 1 vial for those weighing >2 kg). VariZIG is also indicated for pregnant women and immunocompromised persons without evidence of varicella immunity; hospitalized premature infants born at <28 weeks of gestation (or weight <1,000 g) who were exposed to varicella, regardless of maternal varicella immunity; and hospitalized premature infants born at ≥28 weeks of gestation who were exposed to varicella and whose mothers have no evidence of varicella immunity. Patients given VariZIG should be monitored closely and treated with acyclovir if necessary once lesions develop.

Close contact between a susceptible high-risk patient and a patient with herpes zoster is also an indication for VariZIG prophylaxis. Passive antibody administration or treatment does not reduce the risk for herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

Although licensed pooled IVIG preparations contain anti-VZV antibodies, the titer varies from lot to lot. In situations in which administration of VariZIG is not possible, IVIG can be administered (400 mg/kg administered once within 10 days of exposure). Immunocompromised patients who have received high-dose IVIG (>400 mg/kg) for other indications within 3 weeks before VZV exposure can be expected to have serum antibodies to VZV.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 301

Epstein-Barr Virus

Terri L. Stillwell and Jason B. Weinberg

Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness.

ETIOLOGY

EBV is a double-stranded DNA virus that is a member of the gammaherpesviruses and causes >90% of cases of infectious mononucleosis. Two distinct types of EBV, type 1 and type 2 (also called type A and type B), have been characterized and have 70–85% sequence homology. EBV-1 is more prevalent worldwide, although EBV-2 is more common in Africa than in the United States and Europe. Both types lead to *persistent*, *lifelong*, *latent infection*. Dual infections with both types have been documented among immunocompromised persons. EBV-1 induces in vitro growth transformation of B lymphocytes more efficiently than does EBV-2, but no type-specific disease manifestations or clinical differences have been identified.

As many as 5–10% of infectious mononucleosis–like illnesses are caused by other types of primary infections, particularly cytomegalovirus but also pathogens such as *Toxoplasma gondii*, adenovirus, hepatitis viruses, and HIV. In the majority of EBV-negative cases of infectious mononucleosis, the exact cause remains unknown.

EPIDEMIOLOGY

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. EBV is shed in oral secretions consistently for more than 6 months after acute infection and then intermittently for life. As many as 20–30% of healthy EBV-infected persons shed virus at any particular time. EBV is also found in male and female genital secretions, and some studies suggest the possibility of spread through sexual contact. Nonintimate contact, environmental sources, and fomites do not contribute to transmission of EBV.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations in developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 years of age. Among more affluent populations in industrialized countries, half of the population is infected by 6-8 years of age, with approximately 30% of infections occurring during adolescence and young adulthood. In the United States, seroprevalence increases with age, from approximately 54% for children 6-8 years to 83% for patients 18-19 years. Seroprevalence at each age is substantially higher for Mexican-Americans and non-Hispanic Blacks than for non-Hispanic Whites. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income.

The epidemiology of the disease manifestations of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from other childhood infections. Primary EBV infection in adolescents and adults manifests in 30–50% of cases as the **classic triad of fatigue**, **pharyngitis**, **and generalized lymphadenopathy**, which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 years of age, when most EBV infections are asymptomatic, or in adults older than 40 years of age, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20-70 per 100,000 person-years. In young adults, the incidence increases to approximately 100 per 100,000 person-years. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

EBV infection has been implicated in other diseases, including both nonmalignant and malignant disorders such as lymphoproliferative diseases and lymphomas (Table 301.1). In addition, various monogenic immune susceptibility defects predispose to EBV-associated hemophagocytic lymphohistiocytosis, lymphoproliferative disorders, or lymphoma (Fig. 301.1; see also Chapter 174.3).

PATHOGENESIS

After transmission by saliva to the oral cavity, EBV infects both oral epithelial cells and tonsillar B lymphocytes, although it is unclear which cells are the primary initial targets. Ongoing viral replication leads to viremia and dissemination of infected B lymphocytes into peripheral blood and the lymphoreticular system, including the liver and spleen. Clinical manifestations of infectious mononucleosis, which are due to the host immune response to EBV infection, occur after a 6-week incubation period following acute infection. The atypical lymphocytes that are frequently detected in patients with infectious mononucleosis are primarily CD8 T lymphocytes. Polyclonal CD8 T lymphocyte activation occurs early during the incubation period following infection, whereas expansion of EBV-specific CD8 T lymphocytes is detected closer to the time of symptom onset. Natural killer (NK) cells also

Table 301.1 Diseases Caused by Epstein-Barr Virus Infection

INFECTED CELL TYPE	NONMALIGNANT DISEASES	MALIGNANT DISEASES
B lymphocytes	• B-lymphoproliferations (B-LPD) • Posttransplant B-LPD • Hemophagocytic lymphohistiocytosis (HLH)	• Hodgkin lymphoma (HL) • Diffuse large B cell lymphoma (DLBCL) • Burkitt lymphoma (BL)

T/NK lymphocytes	• Systemic T/NK-cell type chronic active EBV (CAEBV)
	• Cutaneous CAEBV
	  • Hydroa vacciniforme–like lymphoproliferation (HVL)
	  • Severe mosquito bite allergy (SMBA)
	• HLH
		• Systemic EBV+ T-cell lymphoma of childhood (STLC)
		• Extranodal NK/T-cell lymphoma (ENKTL)
		• Aggressive NK cell leukemia (ANKL)

Smooth muscle cells	• Smooth muscle tumor/leiomyoma (SMT)	
Epithelial cells	• Hairy leukoplakia*	• Nasopharyngeal carcinoma (NPC) • Gastric carcinoma

*Hairy leukoplakia is a benign epithelial/mucosal disease caused by uncontrolled lytic infection that occurs in immunocompromised patients. It is characterized by white patches with hairy appearance on the tongue.

From Fournier B, Latour S. Immunity to EBV as revealed by immunodeficiencies. *Curr Opin Immunol*. 2021;72:107–115. Table 1.

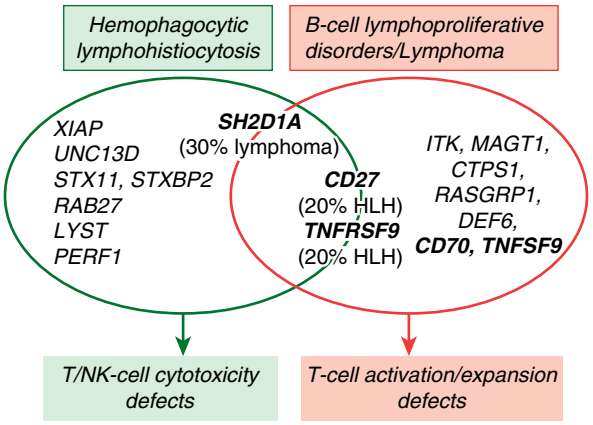

Fig. 301.1 Classification of gene defects predisposing to Epstein-Barr virus (EBV)-driven hemophagocytic lymphohistiocytosis (HLH) or B-cell lymphoproliferative disorders. *Red circle*, Gene defects associated with impaired cell-cytotoxicity causing HLH. *Green circle*, Gene defects associated with impaired T-cell activation/expansion causing B cell lymphoproliferative disorder (B-LPD)/lymphoma. Gene defects with a highly selective predisposition to EBV are in **bold**. In *parentheses* is the percentage of patients having developed HLH or B lymphoma for defects associated with both HLH and B-LPD/lymphoma. *(From Fournier B, Latour S. Immunity to EBV as revealed by immunodeficiencies. Curr Opin Immunol. 2021;72:107–115. Fig.1.)*

expand in frequency and number following infection, particularly a $CD56^{dim}$ $CD16^{-}$ NK cell subset that is more effective than other NK cell subsets at recognizing infected cells. The host immune response is effective in rapidly reducing the EBV viral load, although persistent shedding of high levels of virus can be detected in the oropharynx for up to 6 months. Intermittent shedding from the oropharynx occurs for many years following primary infection.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary infection. Latent virus persists primarily in memory B lymphocytes. The EBV genome persists as an episome in the nucleus of an infected cell and replicates with cell division. Viral integration into the cell genome is not typical. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Reactivation and new viral replication occur at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. *Reactivation is unlikely to be accompanied by distinctive clinical symptoms*.

CLINICAL MANIFESTATIONS

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 week) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 weeks. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The **classic physical examination findings** are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Although liver enzymes are usually elevated, symptomatic hepatitis or jaundice is uncommon. Splenomegaly to 2-3 cm below the costal margin is typical (15–65% of cases); massive enlargement is uncommon.



Fig. 301.2 Tonsillitis with membrane formation in infectious mononucleosis. *(Courtesy Alex J. Steigman, MD.)*



Fig. 301.3 Amoxicillin-induced rash in Epstein-Barr virus infection. Morbilliform maculopapular rash on the leg, which appeared shortly after starting amoxicillin. The rash is typical of that seen in the context of Epstein-Barr virus infection in patients treated with amoxicillin or ampicillin. *(From Norman SD, Murray IA, Shetty D, et al. Jaundice, abdominal pain, and fever in a young woman. Lancet. 2017;390:1713–1714. Fig. A.)*

The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig. 301.2). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis is similar to that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids. Rashes are usually maculopapular and have been reported in 3–15% of patients. Patients with infectious mononucleosis who are treated with ampicillin or amoxicillin may experience an **ampicillin rash**, which may also occur with other β-lactam antibiotics (Fig. 301.3). This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment. EBV can also be associated with Gianotti-Crosti syndrome, a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may also appear on the extremities and buttocks.

DIAGNOSIS

A presumptive diagnosis of infectious mononucleosis may be made by the presence of classic clinical symptoms with atypical lymphocytosis in the peripheral blood. The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Differential Diagnosis

EBV is the most common cause of infectious mononucleosis. Infectious mononucleosis–like illnesses may also be caused by primary infection with other pathogens, such as cytomegalovirus, *T. gondii*, adenovirus, and HIV. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of

infectious mononucleosis, but it is not typically associated with hepatosplenomegaly. Approximately 5% of cases of EBV-associated infectious mononucleosis have throat cultures positive for group A *Streptococcus*, representing pharyngeal streptococcal carriage. Failure of a patient with presumed streptococcal pharyngitis to improve within 48-72 hours should evoke suspicion of infectious mononucleosis. Hematologic malignancies should also be considered in a patient with an infectious mononucleosis–like illness, particularly when lymphadenopathy and hepatosplenomegaly are appreciated and the results of an initial laboratory evaluation are not consistent with an infectious etiology.

Laboratory Diagnosis

The majority of patients (>90%) have a leukocytosis of 10,000-20,000 cells/μL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, **atypical lymphocytes** are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many other infections associated with lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Mild thrombocytopenia to 50,000-200,000 platelets/μL occurs in more than 50% of patients but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 75% of uncomplicated cases, but it is usually asymptomatic and without jaundice.

Detection of Heterophile Antibodies

Heterophile antibodies are cross-reactive immunoglobulin (Ig) M antibodies that agglutinate mammalian erythrocytes but are not EBV-specific. Heterophile antibody tests, such as the **monospot** test, are positive in 90% of cases of EBV-associated infectious mononucleosis in adolescents and adults during the second week of illness, but in only up to 50% of cases in children younger than 4 years of age. Test results can remain positive for up to 12 months. The false-positive rate is low, generally <10%. A positive heterophile antibody test in a patient with classic clinical manifestations of mononucleosis strongly supports that diagnosis. However, because of the nonspecific nature of heterophile antibody testing, EBV-specific antibody testing should be performed when a precise diagnosis is necessary.

Detection of Epstein-Barr Virus–Specific Antibodies

If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated. Measurement of antibodies to EBV proteins, including viral capsid antigen (VCA), Epstein-Barr nuclear antigen (EBNA), and early antigen (EA), are used most frequently (Fig. 301.4 and Table 301.2). The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 weeks and occasionally up to 3 months; in rare cases, anti-VCA IgM can persist even longer. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EA IgG antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA (EA-D) are found transiently in 80% of patients during the acute phase of infectious mononucleosis. Antibodies to the cytoplasmic-restricted component of EA (EA-R) emerge transiently in the convalescence from infectious mononucleosis. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV replication.

Anti-EBNA IgG antibodies are the last to develop in infectious mononucleosis and gradually appear 3-4 months after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3-4 months previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is generally sufficient to confirm the diagnosis of acute EBV infection, although false positive results can still occasionally occur.

Detection of Viral DNA

EBV DNA can be detected and viral genome copy number quantified in whole blood, peripheral blood mononuclear cells (PBMCs), and plasma using real-time polymerase chain reaction. EBV DNA can be detected in PBMCs and plasma of patients with infectious mononucleosis for a brief period after the onset of symptoms and in PBMCs for an extended period. However, detection of EBV DNA is usually not necessary to diagnose infectious mononucleosis in immunocompetent patients with typical manifestations of disease. In contrast, serial measurements of EBV genome copy number are often used following solid organ or hematopoietic stem cell transplantation as surveillance for posttransplant lymphoproliferative disease (PTLD). Very high or consistently increasing EBV genome copy number suggests an increased risk for PTLD, although definitive diagnosis is typically based on tissue biopsy. The frequency and duration of monitoring EBV genome copy number is determined by the time after transplant and risk factors such as the type of transplant and the degree of immunosuppression. Serial measurement of EBV genome copy number can be useful in monitoring response to therapy for PTLD. Measurement of EBV genome copy number can also be used for screening and to determine prognosis for some EBV-associated malignancies, such as nasopharyngeal carcinoma and Hodgkin lymphoma.

COMPLICATIONS

Severe complications are unusual in patients with infectious mononucleosis. Splenic rupture, either spontaneous or following mild trauma, may occur in approximately 0.1% of cases but is rarely fatal. Airway obstruction due to swelling of oropharyngeal lymphoid tissue occurs in <5% of cases. A variety of neurologic conditions have been associated with EBV infectious mononucleosis. Headache is a common symptom, but symptomatic meningitis or encephalitis is uncommon. More severe neurologic manifestations, such as seizures and ataxia, may occur in 1–5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the **Alice in Wonderland syndrome (metamorphopsia)**, may be a presenting symptom. Some reports suggest an association between infectious mononucleosis and the possible development of multiple sclerosis. Hematologic abnormalities such as mild hemolytic anemia, thrombocytopenia, and neutropenia are relatively common, but aplastic anemia, severe thrombocytopenia, and severe neutropenia are rare. Other rare complications include myocarditis, interstitial pneumonia, pancreatitis, parotitis, and orchitis.

Patients with dysregulated immune responses to primary infection, such as individuals with primary or secondary **hemophagocytic lymphohistiocytosis (HLH)**, can develop severe, life-threatening complications with primary EBV infection (see Fig. 301.1). Patients with other primary immunodeficiencies that result in failure to control EBV infection and/or abnormal inflammatory responses to infection are at risk for severe manifestations of EBV infection, often with fulminant infectious mononucleosis, chronic viremia, dysgammaglobulinemia, and lymphoproliferation. Immunodeficiencies most commonly linked to severe EBV infection tend to be those affecting aspects of NK cell, T lymphocyte, and NKT lymphocyte function. Examples include X-linked lymphoproliferative (XLP) syndrome, which is caused by variants in genes encoding the signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) or X-linked inhibitor of apoptosis (XIAP); X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (XMEN), caused by mutations in *MAGT1*, which encodes a magnesium transporter protein; and deficiencies in interleukin-2–inducible T-cell kinase (ITK), CD27, or CD70 (see Fig. 301.1; Chapter 174.3).

ONCOGENESIS

Infection with EBV, the first human virus to be associated with malignancy, accounts for up to 2% of cancers worldwide (see Table 301.1).

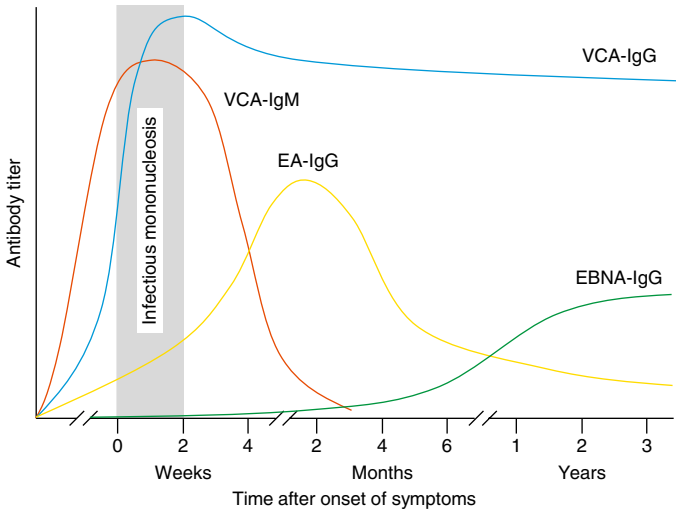

Fig. 301.4 Kinetics of antibody responses to Epstein-Barr virus (EBV) antigens in infectious mononucleosis. EA, Early antigen; EBNA, EBV-determined nuclear antigens; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Table 301.2 Correlation of Clinical Status and Antibody Responses to Epstein-Barr Virus Infection

CLINICAL STATUS	VCA IgM	VCA IgG	EA IgG	EBNA IgG
Susceptible	–	–	–	–
Acute primary infection	+	+	±	–
Recent primary infection	±	+	±	±
Past infection	–	+	±	+

EA, Early antigen (typically the diffuse staining component, or EA-D); EBNA, EBV-determined nuclear antigens; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Manipulation of infected cells by EBV can lead to transformation and oncogenesis. EBV is associated with lymphoid malignancies, such as Burkitt lymphoma, Hodgkin lymphoma, aggressive NK cell leukemia, T- and NK-cell lymphoproliferative disorder, and epithelial cell malignancies such as nasopharyngeal carcinoma and gastric carcinoma.

Endemic Burkitt lymphoma is the most common childhood cancer in equatorial East Africa and Papua New Guinea. These regions are holoendemic for *Plasmodium falciparum* malaria and have a high rate of EBV infection early in life. Constant exposure to malaria is thought to act as a B lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection, impairs T lymphocyte surveillance of EBV-infected B lymphocytes, and increases the risk for developing Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic) Burkitt lymphoma cases in other areas of the world.

The incidence of **Hodgkin lymphoma** peaks in childhood in developing countries and in young adulthood in developed countries. Infection with EBV increases the risk for Hodgkin lymphoma by a factor of 2-4, with the risk of developing Hodgkin lymphoma peaking at 2.4 years following infectious mononucleosis. EBV is associated with more than half of cases of mixed-cellularity Hodgkin lymphoma and approximately one quarter of cases of the nodular sclerosing subtype, but it is rarely associated with lymphocyte-predominant Hodgkin lymphoma. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin lymphoma.

Numerous congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, especially central nervous system lymphoma and leiomyosarcoma (see Fig. 301.1). Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferation include XLP syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or hematopoietic cell transplantation, or HIV infection have a significantly increased risk for EBV-associated lymphoproliferation. The lymphomas may be focal or diffuse and are usually histologically polyclonal but may become monoclonal. EBV-associated PTLD can occur following solid organ transplantation and, less commonly, allogeneic hematopoietic cell transplantation. The most important risk factors for PTLD are the degree of T lymphocyte immunosuppression and recipient EBV serostatus.

TREATMENT

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, adequate fluid and nutrition intake, and symptomatic treatment to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be encouraged to resume normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during the first 2-3 weeks of illness or while splenomegaly is present.

Antiviral therapy is not recommended. Although nucleoside analogs such as acyclovir and ganciclovir inhibit viral replication in vitro and decrease the duration of oropharyngeal viral shedding in patients with infectious mononucleosis, they have not been shown to provide consistent clinical benefit for patients with infectious mononucleosis or EBV-associated malignancies. Short courses of corticosteroids may be helpful for selected complications of infectious mononucleosis, such as airway obstruction, but there are insufficient data to support the use of corticosteroids to control typical symptoms in patients with infectious mononucleosis. Adoptive immunotherapy involving the infusion of EBV-specific cytotoxic T lymphocytes has shown some promise in early trials for transplant recipients with PTLD and for other patients with EBV-associated malignancies.

PROGNOSIS

The prognosis for complete recovery is excellent. The major symptoms typically last 2-4 weeks, followed by gradual recovery within 2 months of symptom onset. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue and malaise may wax and wane for several weeks to 6 months and are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. There is no convincing evidence linking EBV infection or EBV reactivation to chronic fatigue syndrome.

PREVENTION

Vaccination against EBV would be an appealing strategy to prevent acute disease (infectious mononucleosis) and complications such as EBV-associated malignancies. Early clinical trials using strategies targeting the EBV gp350 envelope glycoprotein demonstrated some protection against symptomatic infectious mononucleosis, although vaccination did not prevent EBV infection. No EBV vaccine is currently approved for clinical use.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 302

Cytomegalovirus

Suresh B. Boppana and William J. Britt

Human cytomegalovirus (CMV) is ubiquitous in the population, with serologic evidence of infection in >50% of adults in the United States and >96% in many populations in South America, Africa, and Asia. Individuals who become infected remain persistently infected for life and shed infectious virus intermittently from mucosal surfaces, thus serving as a source of infectious virus for transmission within populations. Although CMV infection rarely causes symptoms in immunocompetent individuals, it is an important cause of morbidity and sometimes death in immunocompromised hosts. CMV remains a well-recognized cause of disease in the newborn infant following intrauterine infection (congenital CMV) and in allograft recipients undergoing posttransplantation immunosuppression. CMV emerged as the most common opportunistic infection in HIV/AIDS patients before the advent of effective antiretroviral therapy. Invasive CMV infections can also be observed in patients treated with immunosuppressive biologics such as anti–tumor necrosis factor (TNF) antibodies. In each of these clinical settings that share some degree of immunosuppression, the association of disease with CMV infection has been linked to high levels of virus replication and end organ disease, usually associated with virus dissemination. In contrast, there is likely another group of disease states associated with chronic effects of persistent CMV infection that reflects the robust inflammatory response induced by this virus during persistent infection. Such associations have been proposed to include coronary artery disease, transplant vasculopathy and cardiac allograft loss, renal tubular sclerosis and renal allograft loss, exacerbations of inflammatory bowel disease, and possibly even some cancers such as glioblastoma. Whether definitive evidence will eventually directly link CMV to these disease states is uncertain.

THE VIRUS AND ITS HOST INTERACTIONS

CMV is the largest of the human herpesviruses, with an estimated size of 190 nm. The 230-kb double-stranded DNA genome is about 50% larger than the herpes simplex virus genome and encodes over 200 open reading frames, which conservatively estimated includes >100 unique virion proteins and an unknown number of nonstructural proteins. Viral DNA replication takes place in the nucleus of the infected cell followed by virus assembly in both the nucleus and cytoplasm. The structure of the virus is typical of herpesviruses and includes a complex envelope composed of host cell–derived membrane studded with virion glycoproteins, a less well-structured area between the envelope and the capsid called the tegument layer, and an icosahedral capsid that contains the virion DNA. The tegument layer is highly immunogenic and induces strong adaptive immune responses, including CMV specific $CD8^+$ cytotoxic T lymphocytes that are thought to play a pivotal role in controlling CMV replication in the infected host. Likewise, the protein components of the viral envelope are also immunogenic and induce antibody responses that have been correlated with virus neutralization, antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and other potential protective effector functions. In vivo, CMV appears to replicate in nearly all tissue and cell types, whereas in vitro productive virus replication (production of infectious progeny) occurs in primary fibroblasts and cells derived from epithelial tissue. Human CMV is species specific and productively infects only cells of human origin. Each strain of CMV that is isolated from epidemiologically unrelated individuals is genetically unique, a finding that suggests an extraordinarily large and undefined number of genetically unique viruses exist in the human population. Furthermore, studies using next-generation sequencing technologies have provided evidence that CMV can exist as genetically diverse populations of viruses within an individual. This finding has argued that during replication, CMV DNA synthesis is error prone, resulting in sequence error rates in its genome that are much higher than previous studies would predict and/or a high likelihood of recombination events between viral genomes if permissive cells are infected with genetically diverse populations of viruses. Thus repeated exposures to CMV over time could result in an individual acquiring a library of CMVs as reinfection of previously infected individuals with new strains of CMV also appears commonplace. These observations have led many investigators to argue that CMV must express an armamentarium of immune evasion functions that allow it to persist even in the presence of robust host immunity. This relationship between host and virus is best illustrated by the finding that over years a persistently infected individual can maintain a stable virus load in sites of persistence, unwavering antiviral antibody responses, and, in some individuals, up to 15% of total peripheral blood $CD8^+$ cytotoxic T lymphocyte activity can be directed at CMV antigens derived from a diverse number of virus-encoded proteins. These observations have resulted in a central paradigm of CMV biology in which, following infection, a detente is established between virus replication and host innate and adaptive antiviral immunity. Thus CMV can efficiently persist in an infected host for a lifetime while inducing chronic immune activation. This latter characteristic of the biology of CMV infection has supported a linkage between CMV and chronic inflammation, a link that could provide a common mechanism for many of the chronic diseases that have been associated with this ubiquitous virus.

EPIDEMIOLOGY

CMV infections can be acquired through several settings: (1) community exposure, (2) nosocomial transmission, and (3) intrauterine infection leading to congenital infection.

Community acquisition of CMV occurs throughout life and is linked by exposure to CMV shed from mucosal surfaces such as saliva, genital secretions, and urine. Peaks in exposure to infectious virus occur during childhood and in adolescents and young adults, presumably secondary to initiation of sexual activity in the latter age group. In addition, differences in age-specific and overall rates of virus infection in the United States are observed in different racial, ethnic, and socioeconomic groups. Common routes of infection of the very young infant include perinatal exposure to infected genital secretions during birth and ingestion of CMV-containing breast milk. Breastfeeding is the most common route of CMV infection in infancy. Ingestion of breast milk from seropositive women results in a rate of infection of about 60% in infants. Infection is most common during the first several months of breastfeeding, but the risk continues for the duration of breastfeeding. Infants infected through breast milk can shed large amounts of virus in the saliva and urine for prolonged periods measured in months to years, thus serving as a reservoir of virus for transmission to other infants, children, and adults. After this period of intense exposure to CMV during the first year of life, infection in the remainder of childhood and early teenage years depends on specific exposures such as enrollment in group childcare facilities and/or exposure to infected, similarly aged siblings. Up to 50% of young infants and children attending group care facilities can be excreting CMV, a source of virus that can result in infection of children enrolled in the facility and in some cases the adult workers within the facility. Furthermore, infants and children who acquire CMV in a group care setting can then transmit virus to their parents and siblings, thus providing a mechanism for spread of CMV within the community. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. However, in adolescence and early adulthood there is a spike in infection presumably associated with sexual exposure. CMV is considered a sexually transmitted infection (STI); data have shown an increased rate of CMV infection in sexually active populations and high rates of virus transmission in CMV-discordant couples.

Nosocomial infections with CMV are well described and can be associated with exposure to blood products containing CMV or to an allograft following transplantation of an organ from a CMV-infected donor. Before improvements in blood banking that limited the number of leukocytes in red cell transfusions and that more efficiently identified

CMV infected donors, transmission of CMV by blood transfusion was not uncommon and was closely related to the volume of blood that was transfused. **Transfusion-acquired CMV** infections often resulted in symptomatic illness, with laboratory findings including hepatitis and thrombocytopenia in children and adults. Severe and sometimes fatal infections can develop following exposure to CMV-infected blood products in newborn infants who lack transplacentally transferred antibodies to CMV either as a result of being born to women without seroimmunity to CMV or secondary to extreme prematurity. Similarly, immunocompromised patients who receive CMV-containing blood can also develop severe infection, regardless of their prior exposure to CMV. Methodologies that efficiently deplete contaminating leukocytes and the use of blood products from CMV seronegative donors have greatly decreased the incidence of transfusion-associated CMV infections. CMV transmission through **infected allografts** is well described; infections arising from CMV transferred in an infected allograft are a major cause of morbidity in both the early and late period after transplantation. Severe infections and graft loss following solid organ transplantation (SOT) are more often associated with mismatches between the donor and recipient, such as that following transplantation of an organ from a donor with a history of CMV infection (donor, CMV positive) into a recipient who has not been exposed to CMV (recipient, CMV negative; D+/R− mismatch). However, clinically significant CMV infections can occur even in moderate-risk allograft recipients (D+/R+). In contrast to the risk stratification for CMV infection and disease in SOT recipients, the highest risk of posttransplant CMV infection and disease occurs follows reactivation of CMV in hematopoietic stem cell transplant (HSCT) recipients with prior CMV infection (D+/−/R+) presumably because the risk of transmission in the graft is considerably lower than reactivation of persistent infection in the previously infected recipient. Even with effective antiviral therapy to modify CMV infections in the early posttransplant period during intense immunosuppression, CMV infection is linked to long-term graft dysfunction and graft loss and in specific patient groups such as cardiac and lung transplant recipients, can represent a barrier to long-term graft survival.

Congenital CMV infection (present at birth) occurs following intrauterine transmission of CMV and infection of the fetus. Rates of congenital infection between 0.4% and 1.0% have been reported in the United States, with perhaps the best estimate being about 0.4% based on a large multicenter study of nearly 100,000 births. Rates as high as 2% in some areas in Asia and Africa have been described. CMV is thought to be transferred to the developing fetus following hematogenous spread of CMV to the placenta, infection of resident cells of the placenta followed by cell-free transfer of virus to the fetal blood system. The rate of transmission to the fetus is about 30% in nonimmune women with primary infection during pregnancy; in utero infections also occur in previously immune women (nonprimary infection), albeit at a reduced rate that has been suggested to be ~1–2%. The rate of transmission of CMV is more frequent following primary maternal infection; the absolute number of congenitally infected infants born to women with nonprimary infections in most populations outnumber those resulting from primary maternal infection by threefold to fourfold. This is particularly true in Africa, South America, and Asia, where maternal seroimmunity to CMV often exceeds 95%. Interestingly, many of these highly CMV seroimmune maternal populations also have the highest prevalence of congenital CMV infections and almost certainly account for overall burden of congenital CMV infections in most regions of the world. In fact, recent estimates based on the prevalence of congenital CMV infections in sub-Saharan Africa, Asia, and South America suggest that 90% of all cases of congenital CMV infections followed nonprimary material infections. The source of nonprimary maternal infection remains less well defined. Reinfection by genetically distinct strains of CMV is frequent in previously infected women and viruses acquired by maternal reinfection can be transmitted to the developing fetus. The reinfection rates are ~15–20%, with annualized rates as high as 25%. Thus immunity to CMV is far from protective, although it can modify the risk of transmission to the developing fetus.

In addition to the impact of maternal to fetal transmission, the type of maternal infection (primary versus nonprimary) has also been shown to be a major determinant in the outcome of the intrauterine infection. The existing paradigm is that maternal immunity can modify the severity of the intrauterine infection, thus maternal infections in women with preexisting CMV immunity (nonprimary maternal infections) that result in intrauterine transmission are less likely to result in a severe infection in the fetus. Nonetheless, severe CMV infections may occur in fetuses infected following a nonprimary maternal infection, suggesting that the characteristics of the fetal infection such as timing of infection during gestation could be as important to the outcome of a fetal infection as the maternal immune status during pregnancy. Studies have documented a higher frequency of severe infections in fetuses that were infected in the first and early second trimester of gestation, findings that parallel similar risk stratifications for other intrauterine infections, including those caused by Zika virus, rubella virus, and *Toxoplasma gondii*.

Mechanisms of Disease Associated with Cytomegalovirus Infections

The mechanism(s) of disease associated with CMV infections remains either undefined or incompletely defined for many of the clinical syndromes that follow CMV infection. Several reasons have contributed to the overall lack of understanding of the pathogenesis of CMV infections and include (1) the asymptomatic nature of infections in almost all immunocompetent individuals; (2) the complexity of the multiple disease processes in immunocompromised hosts that can confound the assignment of specific manifestations of CMV infection; (3) the species-specific tropism of human CMV; and, perhaps most importantly, (4) limitations inherent in observational studies in humans. Although CMV replicates in a limited number of cell types in vitro, CMV inclusions, antigens, and nucleic acids can be demonstrated in almost all organ systems and most cell types in individuals with severe, disseminated infections. Thus CMV does not exhibit strict cellular or organ system tropism in vivo. Hematogenous dissemination has been argued to be associated primarily with cell-associated virus, and significant levels of plasma virus are usually detected only in severely immunocompromised hosts with high levels of total-blood viral loads. Virus and viral DNA can be recovered from neutrophils, monocytes, and endothelial cells present in peripheral blood, thus providing evidence for the significance of cell-associated spread of this virus. High levels of virus replication can result in end-organ disease secondary to direct virus-mediated cellular damage. These manifestations of CMV infections are thought to result from uncontrolled virus replication, dissemination, and virus-induced cytopathology secondary to deficits in innate and adaptive immune responses to CMV. In some cases, clinical disease has also been observed in patients without significant levels of virus replication, a finding suggesting indirect mechanisms of disease such as immunopathologic responses to CMV. Such a mechanism of disease was shown to be operative in patients with immune recovery vitritis, a pathologic T-lymphocyte–mediated response to CMV in HIV/AIDS patients with CMV retinitis that developed after successful active retroviral therapy and reconstitution of their CMV-specific T lymphocyte responses. Likewise, the level of virus replication has not been closely correlated with several chronic diseases thought to be linked to CMV, an observation that is consistent with indirect mechanisms of disease such as immunopathologic responses to a persistent infection.

From early observations in allograft recipients with invasive CMV infections it was apparent that immunosuppressive therapies that resulted in altered T lymphocyte function predisposed these patients to severe infections. Definitive evidence consistent with the critical role of CMV-specific T lymphocyte immunity in protection from disease in these patients was provided by a clinical study in which in vitro expanded, CMV-specific cytotoxic T lymphocytes limited invasive infection in hematopoietic cell transplant recipients. Invasive infections associated with end-organ disease, such as retinitis and colitis in HIV/AIDS patients with very low $CD4^+$ T-lymphocyte counts, also clearly demonstrated the importance of T lymphocyte response

control of invasive CMV infections, as the risk for these manifestations of CMV infections could be predicted in models that were based on $CD4^+$ T-lymphocyte counts in these patients. However, a role of anti-CMV antibodies in limiting the early events of CMV infection was also shown in studies in SOT recipients. These early studies demonstrated the transfer of immune globulins containing high titers of anti-CMV antibodies when used in a prophylaxis protocol could provide some degree of protection from CMV infections and end-organ disease. This important finding was consistent with the proposed role of antiviral antibodies in limiting CMV dissemination and disease in animal models of invasive CMV infections. The importance of innate immune responses such as natural killer (NK) cells and γδ T lymphocytes in limiting invasive infections have been well documented in animal models. Similarly, NK cells have been associated with both control of CMV reactivation and limiting the severity of CMV end-organ disease in human HCST and SOT recipients. Effector molecules such as interferon-γ appear to contribute to the control of local CMV infections in animal models, but evidence of a similar role in humans has not been demonstrated.

Studies in immunocompromised human hosts have shown that the control of acute CMV infection depends on an effective adaptive immune response; however, even a vigorous T lymphocyte response is not sufficient to eliminate CMV from the infected host, because CMV persists for the lifetime of the host either as a low-level chronic infection and/or as a latent infection with limited transcription from multiple regions of its genome. The inability of the host to completely clear CMV remains incompletely understood, but the large array of immune evasion functions encoded by this virus likely contributes to the blunted innate and adaptive immune response. Examples of these functions include (1) inhibition of cell death functions of infected cells, including apoptosis, necroptosis, and pyroptosis, (2) inhibition of interferon-regulated responses, (3) inhibition of NK cell activation, (4) downregulation of class I major histocompatibility complex (MHC) expression and inhibition of class II MHC function, and (5) mechanisms to limit antibody recognition of envelope proteins, including carbohydrate masking of antibody recognition sites and variation in amino acid sequences in virion envelope proteins targeted by antiviral antibodies. Although each of these functions by itself could potentially have only limited effects on virus clearance, the redundancy of these viral immune evasion functions when acting in concert likely provide the virus a sufficient advantage to favor persistence.

CLINICAL MANIFESTATIONS

The clinical manifestations of CMV infection reflect two parameters of the infection that are often linked: (1) the level of virus replication and (2) the degree of end-organ involvement. The manifestations of CMV infections that have been most well described in clinical studies are those that are present in acutely infected individuals without existing immunity to the virus. Such infections are termed acute or primary infections to distinguish these infections from persistent infections that are established after an acute infection. Similar clinical findings can be observed in patients with significant underlying deficits in innate and adaptive immune responses, regardless if infection follows an acute infection or recurrence/reactivation of persistent infection and reflect loss of immune control of virus replication. In contrast, the clinical manifestations of persistent or chronic CMV infections are frequently overlaid on underlying disease syndromes such as cardiovascular disease, thus confounding the contribution of CMV to the primary disease process and clinical findings in these patients.

Normal Host

In the overwhelming majority of patients with acute CMV infections, there are no specific symptoms or clinical findings. In patients with symptomatic, acute CMV infection, clinical findings have been most commonly reported to resemble a mononucleosis-like syndrome, with fatigue and occasionally cervical adenopathy. Up to 20% of heterophile antibody-negative mononucleosis may be attributed to CMV. Laboratory findings can include mild elevation of hepatic transaminases and decreased platelet counts.

Immunocompromised Host

The clinical presentation of CMV infection in immunocompromised hosts often reflects the magnitude of the immunodeficiency. Profoundly immunocompromised hosts such as HSCT recipients can present with disseminated infection and clinical manifestations of disease in multiple organ systems, including liver, lung, gastrointestinal tract, and, less frequently, the CNS. Organ-threatening and life-threatening disease is not infrequent in these patients. In less immunocompromised patients such as the case of most SOT recipients, CMV infection can present with fever, fatigue, hematologic abnormalities, including leukopenia and thrombocytopenia, and mild hepatocellular dysfunction, a collection of laboratory findings and symptoms described as the CMV syndrome (Table 302.1). In contrast to renal and liver SOT recipients, heart-lung and lung transplant recipients are at high risk for severe manifestations from CMV infection, presumably because the transplanted organ is a site of virus replication, disease, and virus-induced life-threatening organ dysfunction (see Table 302.1). Before the widespread use of antivirals for prophylaxis of allograft recipients, clinical disease usually developed between 30 and 60 days after transplantation. Prolonged antiviral *prophylaxis* has greatly reduced the frequency of CMV disease in the early posttransplant period in most SOT and HCST recipients; late manifestations of CMV infection often become apparent after discontinuation of antiviral prophylaxis. These late manifestations are most worrisome in HSCT recipients, because they may signal deficits in graft function that in turn predispose these patients to invasive CMV infections. Long-term graft function has been reported to be influenced by CMV infection. This has been most well studied in renal allograft recipients and is thought by many investigators to represent a significant cause of chronic graft dysfunction and eventual loss of the graft. Perhaps the most dramatic impact of CMV infection late in the posttransplant period can be seen in heart transplant recipients, in whom CMV is thought to play a major role in transplant vascular sclerosis, a vasculopathy of the coronary arteries in the allograft leading to loss of the transplanted heart allograft.

Congenital Infection

Congenital infection with CMV can present with clinically apparent (symptomatic) infection (Table 302.2) in about 10% of infected newborns, whereas 90% of infected infants will have *no clinical manifestations* of infection in the newborn period (asymptomatic infection) and can be identified only by screening newborns for the presence

Table 302.1 Findings in Cytomegalovirus Infections in Solid Organ Transplant Recipients

CLINICAL FINDINGS	LABORATORY FINDINGS
CMV SYNDROME	
Fever, nonspecific findings, fatigue	Leukopenia, thrombocytopenia, reactive lymphocytosis, hepatitis, CMV DNA in blood
END-ORGAN DISEASE	
Gastrointestinal disease, including esophagitis, colitis, and hepatitis	Detection of CMV DNA in blood; detection of CMV in tissue biopsy; hepatitis, including elevated bilirubin
Lung disease; hypoxemia	Abnormalities in lung imaging CMV in bronchoalveolar lavage fluid
Encephalitis	CSF pleocytosis, elevated CSF protein Abnormalities in CNS imaging
Allograft dysfunction	Evidence of graft rejection

Table 302.2 Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection

FINDINGS	% OF INFANTS
CLINICAL FINDINGS	
Prematurity (<37 wk)	24
Jaundice (direct bilirubin >2 mg/dL)	42
Petechiae	54
Hepatosplenomegaly	19
Purpura	3
Microcephaly	35
IUGR	28
1 clinical finding	41
2 clinical findings	59
LABORATORY FINDINGS	
Elevated ALT (>80 IU/mL)	71
Thrombocytopenia (<100,000 k/mm^3)	43
Direct hyperbilirubinemia (>2 mg/dL)	54
Head CT abnormalities	42

Findings in 70 infants with symptomatic congenital CMV infection identified during newborn screening program for infants with congenital CMV infection at the University of Alabama Hospitals over an approximate 20-yr interval.
CMV, Cytomegalovirus; *IUGR*, in utero growth restriction; ALT, alanine aminotransferase.



Fig. 302.1 Cytomegalovirus (CMV). One-day-old with congenital CMV infection. Noncontrast CT of the head demonstrates multiple areas of confluent calcifications within the periventricular regions bilaterally *(arrows)*, typical of the expected distribution of calcification secondary to CMV. Note the abnormal sulcal pattern of the right hemisphere, indicating associated polymicrogyria *(arrowheads)*. *(From Rothenberg Maddocks AB, Pollok AN. Infection and inflammation. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 34.31, p. 342.)*

of CMV in saliva, urine, or, less commonly, blood. **Severe multiorgan disease** is infrequent and occurs in approximately 30% of infants with symptomatic congenital CMV infections. The clinical findings in infants with symptomatic congenital CMV infections can include hepatosplenomegaly, petechial rashes, jaundice, and microcephaly. Intrauterine growth restriction is also a finding of symptomatic congenital CMV infection. Laboratory findings are consistent with the clinical findings and include direct hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, and abnormal findings on cranial ultrasonography/computed tomography/MRI (Fig. 302.1). If cerebrospinal fluid is obtained, there can be evidence of encephalitis, with elevation of mononuclear cell number and, in some cases, elevation of protein. A small number of symptomatically infected infants (<10%) will have chorioretinitis. Because **hearing loss** is the most common long-term sequela associated with congenital CMV infection, the failure of an infant to pass a newborn hearing screening exam should alert caregivers to the possibility of congenital CMV infection. Hearing loss in the older infant and young child should also alert the clinician to the possibility of congenital CMV infection, because about 50% of infants with hearing loss associated with congenital CMV infection will pass an initial hearing screening exam but will exhibit hearing loss in later infancy and early childhood. Importantly, hearing loss can be progressive in infants with congenital CMV infections and late-onset hearing loss and/or progression of hearing loss can only be identified by follow-up testing of hearing in congenitally infected infants (see later). Finally, the diagnosis of congenital CMV infection must be made within the first 2-3 weeks of life, and congenital CMV infection cannot be assumed to be the cause of hearing loss in older infants without evidence of CMV infection in the newborn period.

An organized plan for follow-up is an important component of the clinical management of infants with congenital CMV infection. Because permanent sequelae are limited to disorders of the central nervous system (CNS), long-term follow-up should include appropriate assessment of development and neuromuscular function in infected infants, with referral to specialized care if necessary. This is particularly important for infected infants who present with evidence of CNS damage such as microcephaly, seizures, or obvious motor deficits. Overall, about 11% of infected infants will exhibit some degree of hearing loss; hearing loss in some infants will progress during infancy or less frequently, develop later in infancy. Thus comprehensive audiologic testing and follow-up are mandatory in these patients. Other sequelae such as vision loss are infrequent, but vision testing and comprehensive eye examinations should be included in the care plan of infants with congenital CMV infection.

Perinatal Infection

Perinatal infections can be acquired during birth or following ingestion of CMV-containing breast milk. In almost all cases perinatal infections have not been associated with clinical manifestations of the infection and have not been associated with long-term sequelae that have been described in infants with congenital CMV infections. In rare cases such as is seen in breast milk transmission of CMV to extremely premature infants or infants born to nonimmune women, perinatal infection can result in severe, disseminated infections associated with end-organ disease and death. These more severe infections are thought to develop in infants that lack transplacentally acquired antiviral antibodies, either secondary to extreme prematurity or as the product of a mother lacking anti-CMV antibodies.

DIAGNOSIS

In the nonimmunocompromised individual, diagnosis of CMV infection has required evidence of a primary or acute infection. Serologic reactivity for CMV is lifelong following primary infection; therefore the presence of immunoglobulin (Ig) G antibody to CMV does not provide evidence of acute infection unless the absence of CMV-specific IgG reactivity in a prior serum specimen can be demonstrated, thus providing evidence of IgG seroconversion. In addition, IgM reactivity for CMV can be detected for prolonged periods after acute infection and cannot be used to reliably estimate the duration of a primary infection. Furthermore, recovery of virus from body fluids such as saliva or urine does not in itself permit diagnosis of

CMV infection, because persistently infected individuals can intermittently shed virus. In contrast, in the immunocompromised host, CMV can frequently be recovered from patients in the absence of evidence of invasive CMV infection. Thus assignment of CMV as a cause of disease in immunocompromised patients must be made carefully, and other potential causes of symptoms and clinical findings in these patients must also be considered. Serologic assays are of limited value in the transplant recipient secondary to the impact of immunosuppression on antibody responses in the allograft recipient. Moreover, IgM antibodies can be produced following a nonprimary infection in these patients. Sequential viral load measurements by nucleic acid amplification testing (NAAT) such as polymerase chain reaction (PCR) in relevant body fluids such as blood and detection of CMV DNA in biopsy tissue can be of great value in establishing CMV as a cause of disease in allograft recipients because increasing viral loads can provide evidence of the lack of host control of CMV replication (Table 302.3). Detection of CMV in urine, saliva, blood, and tissue specimens obtained at biopsy can most reliably be accomplished by NAAT, and because findings can be quantified, treatment responses can be monitored. However, conventional culture of CMV using human dermal fibroblasts often combined with immunofluorescence detection of CMV-encoded immediate early antigens also remains standard in many institutions. Histopathologic studies of tissue specimens that permit detection of CMV-infected cells containing characteristic nuclear inclusions (owl's-eye inclusions) are relatively insensitive but can aid in the diagnosis of an invasive CMV infection. The addition of immunohistochemistry for the detection of CMV-encoded proteins and/or in situ hybridization for the detection of CMV nucleic acids has greatly improved the sensitivity of histologic detection of CMV in tissue and/or biopsy specimens (see Table 302.3).

In practice, in nonimmunocompromised patients the demonstration of CMV-specific IgG seroconversion or the presence of CMV-specific IgM antibodies is considered evidence of a recently acquired CMV infection. However, in the case of pregnant women the timing of a primary infection often requires a more precise estimate of when the infection was acquired because CMV infections before conception carry significantly less risk to the developing fetus than infections acquired after conception. Furthermore, as noted in previous sections, maternal infections acquired in the first and early second trimester are more frequently associated with severe intrauterine infections and result in more significant long-term sequelae in infants with congenital CMV infections. Because IgM anti-CMV antibody reactivity can persist for months depending on the sensitivity of the particular assay, the use of IgM detection to precisely time the acquisition of CMV is of limited value. However, when combined with IgG avidity assays in which CMV-specific binding antibodies are eluted with increasing concentrations of chaotropic agents such as urea, IgG serology can provide a more accurate estimate of the duration of infection. Thus the IgG avidity assay has been used almost exclusively in the management of CMV infections during pregnancy to aid in identifying primary maternal infections in women who present at the first prenatal visits with CMV-specific IgM antibodies. The presence of CMV-specific IgG antibodies with high avidity argues for an infection that occurred in the distant past, whereas low-avidity CMV-specific IgG antibodies argues for a more proximal timing of infection. The presence of anti-CMV IgG antibodies with intermediate avidity is considered uninterpretable (see Table 302.3).

Congenital Infections

The diagnosis of congenital CMV infections requires the recovery of replicating virus and/or viral nucleic acids within the first 2-3 weeks of life. Sources of virus and viral nucleic acids include urine, saliva, and blood. Methods of detection include routine virus culture combined with immunofluorescence and NAAT. Although quantification of virus in various specimens can suggest the likelihood of long-term sequelae such as hearing loss for a population of infected newborns, the predictive value for the individual patient remains limited. A considerable amount of effort has been devoted to identifying screening assays that would be suitable for populations of newborn infants. Initial interest centered on dried blood spots, because these samples are routinely collected as a component of newborn screening programs. Unfortunately, studies have indicated that the sensitivity of detection of congenitally infected infants using dried blood spots is too low to be considered

Table 302.3 Laboratory Detection of Cytomegalovirus Infection

ASSAY	APPLICATION	CHARACTERISTICS OF ASSAY
TISSUE CULTURE		
Virus isolation	Detection of virus in clinical material	Requires prolonged culture periods; low sensitivity compared with molecular techniques; expensive
HISTOPATHOLOGY		
Histopathology	Identification of CMV infected cells (owl's eye inclusions)	Routine for most laboratories; low sensitivity is improved with IHC (see below)
Viral antigen detection (immunohistochemistry)	Sensitive and allows detection of CMV-infected cells in variety of specimens	Rapid and can be quantitative
MOLECULAR METHODOLOGIES		
Nucleic acid amplification (NAAT), including quantitative PCR, transcription-mediated amplification (TMA)	Quantitation of CMV DNA and viral RNA	Rapid, sensitive, and quantitative; can be applied to variety of clinical specimens (blood, saliva, urine, biopsy specimens, etc.)
DNA/RNA in-situ hybridization	Sensitive detection of CMV DNA or RNA transcripts in tissue specimens	Technically more difficult than NAAT, long turnaround times, can identify specific cells infected with CMV
SEROLOGIC TESTING		
CMV-specific IgM serology	Screening for recent infections	Variability in duration of response and low levels of IgM antibodies decrease sensitivity and specificity
CMV-specific IgG serology	Detection of infection with HCMV, useful for seroprevalence studies	Rapid, specific, and quantitative; gold standard for CMV infection (acute and past)
CMV-specific IgG avidity	Estimate of duration of HCMV infection	Interpretation limited to high and low values of avidity; useful for timing of recent CMV infections in pregnancy; not useful in allograft recipients

useful for screening. In contrast, newborn screening using saliva has proven sensitive and specific and is used for newborn screening in many institutions. The identification of an infected infant by screening of saliva requires confirmation, preferably by assaying urine for the presence of CMV.

TREATMENT

Treatment of *immunocompromised hosts* with invasive CMV disease limits both the morbidity and the mortality in the patient with disseminated CMV infections with end-organ disease. This has been shown in allograft transplant recipients and patients with HIV/AIDS. Similarly, antiviral prophylaxis can limit the development of clinically important CMV disease in allograft recipients and is the standard of care in most transplant centers, with the remaining centers using *preemptive* treatment in which antivirals are given once a predetermined level of CMV viremia is detected during routine monitoring in the posttransplant period. Several agents are licensed for CMV infections, including ganciclovir, foscarnet, and cidofovir; all have appreciable toxicity. Letermovir is another agent that has been licensed for use in adults; it is expected that indications for this agent will extend into pediatrics in the future. The antiviral agent, maribavir, has been licensed to treat refractory CMV infections in adult transplant recipients. In some transplant centers, high-titer CMV immunoglobulins have been included as a component of prophylaxis, most commonly in heart and lung SOT recipients. Early on, when the treatment of CMV infections with antiviral agents was in its infancy, treatment with CMV immunoglobulins was shown to alter the natural history of CMV infection in renal and liver allograft recipients. However, the efficacy of antiviral agents when used as prophylaxis in the immediate posttransplant period has resulted in less frequent use of these biologics.

Treatment of **congenitally infected infants** with ganciclovir has been studied in several clinical trials, and a significant number of infected infants with symptomatic congenital CMV infections have been treated off-label with this agent. In addition, infants with severe perinatal CMV infection following breast milk ingestion with documented end-organ disease have been successfully treated with ganciclovir. Two studies have suggested that 6 weeks of intravenously administered ganciclovir or 6 months of valganciclovir, an oral preparation of ganciclovir, could limit hearing loss and possibly improve developmental outcome of infected infants followed for approximately 2 years. In contrast to the apparent efficacy of valganciclovir treatment in congenitally CMV infected infants in these studies with relatively short-term follow-up, another study reported that valganciclovir failed to provide evidence of efficacy in altering the long-term outcomes of congenitally infected infants when followed over a longer time. Currently, there are no recommendations for the treatment of infants with congenital CMV infection.

PREVENTION

Passive Immunoprophylaxis

Passive transfer of anti-CMV antibodies has been used to limit disease but not infection in allograft recipients. A similar approach has also been considered for prevention of intrauterine transmission of CMV; disease based on studies from limited observational data suggests that antiviral antibodies could limit disease following CMV infections in the perinatal period. An uncontrolled trial of human immune globulin provided provocative evidence that passive transfer of anti-CMV antibodies to pregnant women undergoing primary CMV infection could limit intrauterine transmission and disease. A second study using the same immune globulin preparation failed to demonstrate that immune globulins provided protection from intrauterine transmission or disease. Another multicenter trial sponsored by the NIH was terminated secondary to the lack of any efficacy of the treatment. It remains to be determined if passively transferred anti-CMV antibodies can modulate infection and disease following intrauterine exposure to CMV.

Active Immunoprophylaxis

Active immunization for the prevention of congenital CMV infection (and in transplant recipients) has been a goal of biomedical research for over 3 decades. A number of different vaccine platforms have been explored, including replicating attenuated CMV vaccines, protein-based vaccines, heterologous virus-vectored CMV vaccines, DNA vaccines, and mRNA-based vaccines. In all cases, some level of immunity has been induced by each of these candidate vaccines. Larger scale trials have been carried out using replication competent, attenuated CMV vaccines and adjuvanted recombinant protein vaccines. Current approaches are directed toward development of an adequately attenuated replicating CMV strain that retains sufficient immunogenicity to induce protective responses. In contrast to programs testing candidate attenuated CMV vaccines, considerable progress has been made in the testing of adjuvanted recombinant viral proteins. An adjuvanted recombinant glycoprotein B, a major protein component of the envelope and target of neutralizing antibodies, has been shown to induce virus neutralizing antibodies and $CD4^+$ T lymphocyte proliferative responses. Moreover, this vaccine reduced virus acquisition by about 50% in a trial carried out in young women. Closer examination of this particular trial revealed that protection was very short-lived and that the effectiveness of the vaccine was not convincingly demonstrated because of the small numbers of subjects in the trial, despite attaining minimal statistical significance. A follow-up trial in adolescent women using the same vaccine preparation failed to show any statistically significant difference between vaccine and placebo recipients. A major question that will face all vaccine programs is whether existing immunity in seropositive women can be augmented to a level to prevent damaging infection in their offspring. The maternal population with existing immunity to CMV before childbearing age is responsible for the vast majority of congenitally infected infants in almost all regions of the world; thus merely recapitulating naturally acquired adaptive immunity to CMV with a vaccine may not be sufficient to prevent congenital CMV infection and/or limit disease.

Counseling

Studies of the natural history of CMV have repeatedly demonstrated that transmission requires repeated close, often direct contact with infected material such as secretions from the oral or genitourinary tract. Although limited data suggest that CMV can be transmitted on fomites, infectivity can persist for hours on surfaces such as toys. Limiting exposure to such secretions and attention to hygiene such as handwashing can drastically limit acquisition of CMV. Counseling has been shown to be very effective in the prevention of CMV infection in women of childbearing age. In fact, counseling programs have been shown to be more effective in limiting CMV infection during pregnancy than any vaccine that has been tested to date. Sexual transmission is an important route of infection, because CMV is considered to be an STI. Limiting sexual transmission through education and counseling should be considered in sexually active individuals. The acquisition of CMV by hospital workers and other healthcare providers has been shown to be less than in age-matched individuals in the general public. Importantly, these early studies in healthcare workers were carried out before universal precautions that are in place in most hospitals today. Thus patient education with an emphasis on describing the sources of infectious virus in communities and attention to general hygiene could dramatically reduce community-acquired CMV, particularly in women of childbearing age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 303

Roseola (Human Herpesviruses 6 and 7)

Brenda L. Tesini

Human herpesvirus 6 (HHV-6A and HHV-6B) and human herpesvirus 7 (HHV-7) cause ubiquitous infection in infancy and early childhood. HHV-6B is responsible for the majority of cases of **roseola infantum** (**exanthem subitum** or **sixth disease**) and is associated with other diseases, including encephalitis, especially in immunocompromised hosts. A small percentage of children with roseola have primary infection with HHV-7.

ETIOLOGY

HHV-6A, HHV-6B, and HHV-7 are the sole members of the Roseolovirus genus in the Betaherpesvirinae subfamily of human herpesviruses. Human cytomegalovirus, the only other β-herpesvirus, shares limited sequence homology with HHV-6 and HHV-7. Morphologically all human herpesviruses are composed of an icosahedral nucleocapsid, protein-dense tegument, and lipid envelope. Within the nucleocapsid, HHV-6 and HHV-7 both contain large, linear, double-stranded DNA genomes that encode more than 80 unique proteins.

Initially, two strain groups of HHV-6 were recognized: HHV-6 variant A and HHV-6 variant B. Despite sharing highly conserved genomes with approximately 90% sequence identity, the two variants could be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential cell tropism, and epidemiology. Because of these differences, the two were reclassified as separate species in the genus Roseolovirus by the International Committee on the Taxonomy of Viruses in 2012. HHV-6A detection is quite rare, and HHV-6B is the overwhelmingly predominant virus found in both immunocompetent and immunocompromised hosts. Previous reports of HHV-6A detection in children in Africa have not been substantiated in a large cohort using a more specific PCR target.

EPIDEMIOLOGY

Primary infection with HHV-6B is acquired rapidly by essentially all children after the loss of maternal antibodies in the first few months of infancy, with 95% of children being infected by 2 years of age. The peak age of primary HHV-6B infection is 6-9 months of life, with infections occurring sporadically and without seasonal predilection or contact with other ill individuals. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 years of age. Seroprevalence reaches 75% by 6 years of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 months, significantly older than that of children with primary HHV-6 infection.

Preliminary data suggest that the majority of children acquire primary infection with HHV-6 from the saliva or respiratory droplets of asymptomatic adults or older children. However, congenital infection with HHV-6 occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified: transplacental infection and chromosomal integration. HHV-6 is unique among the human herpesviruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2–2.2% of the population and is passed from parent to child via the germline. Chromosomal integration of HHV-7 has been suggested in only a single case report thus far. Chromosomal integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third resulting from HHV-6A, a percentage much higher than in primary infection in the United States. The clinical consequences of chromosomal integration or transplacental infection with HHV-6 have yet to be determined. In one series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. However, reactivation of chromosomally integrated HHV-6 virus has been demonstrated following hematopoietic stem cell transplantation (HSCT). Primary infection with HHV-7 is presumed to be spread by the saliva of asymptomatic individuals. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play a role in transmission of either HHV-6 or HHV-7.

PATHOLOGY AND PATHOGENESIS

Primary HHV-6B infection causes a viremia that can be demonstrated by co-culture of the patient's peripheral blood mononuclear cells with mitogen-stimulated cord blood mononuclear cells. HHV-6 has a recognizable cytopathic effect, consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intranuclear inclusions. Infected cells exhibit a slightly prolonged life span in culture; however, lytic infection predominates. HHV-6 infection also induces apoptosis of T cells. In vitro, HHV-6 can infect a broad range of cell types, including primary T cells, monocytes, natural killer cells, dendritic cells, and astrocytes. HHV-6 has also been documented to infect B-cell, megakaryocytic, endothelial, and epithelial cell lines. Human astrocytes, oligodendrocytes, and microglia have been infected with HHV-6 ex vivo. The broad tropism of HHV-6 is consistent with the recognition that CD46, present on the surface of all nucleated cells, is a cellular receptor for HHV-6, HHV-6A in particular. CD134, a member of the TNFR superfamily, is the main entry receptor for HHV-6B and may explain some of the differences in tissue tropism noted between HHV-6A and HHV-6B. The CD4 molecule has been identified as a receptor for HHV-7. HHV-7 has been demonstrated to reactivate HHV-6 from latency in vitro, but whether this phenomenon occurs in vivo is not clear.

Primary infection with HHV-6 and HHV-7 is followed by **lifelong latency** or persistence of virus at multiple sites. HHV-6 exists in a true state of viral latency in monocytes and macrophages. The detection of replicating HHV-6 in cultures of primary $CD34^+$ hematopoietic stem cells has also been described, suggesting that cellular differentiation is a trigger of viral reactivation. This observation is clinically significant because HHV-6 may cause either primary or reactivated infection during HSCT. Additionally, HHV-6 and HHV-7 infection may be persistent in salivary glands, and DNA of both HHV-6 and HHV-7 can be routinely detected in the saliva of both adults and children. HHV-7 can also be isolated in tissue culture from saliva, but HHV-6 cannot. HHV-6 DNA has been identified in the cerebrospinal fluid (CSF) of children, both during and subsequent to primary infection, as well as in brain tissue from immunocompetent adults at autopsy, implicating the central nervous system (CNS) as an additional important site of either viral latency or persistence. HHV-7 DNA has also been found in adult brain tissue but at a significantly lower frequency.

CLINICAL MANIFESTATIONS

Roseola infantum (**exanthem subitum**, or **sixth disease**) is an acute, self-limited disease of infancy and early childhood. It is characterized by the abrupt onset of high fever, which may be accompanied by fussiness. The fever usually resolves acutely after 72 hours (crisis) but may gradually fade over a day (lysis) coincident with the appearance of a faint pink or rose-colored, nonpruritic, 2- to 3-mm morbilliform rash on the trunk (Fig. 303.1). The rash usually lasts 1-3 days but is often described as evanescent and may be visible only for hours, spreading from the trunk to the face and extremities. Because the rash is variable in appearance, location, and duration, it is not distinctive and may be missed. Associated signs are few but can include mild injection of the pharynx, palpebral conjunctivae, or tympanic membranes and



Fig. 303.1 Roseola infantum. **A,** Erythematous, blanching macules and papules in an infant who had high fever for 3 days preceding development of the rash. **B,** On closer inspection some lesions reveal a subtle peripheral halo of vasoconstriction. *(From Paller AS, Mancinin AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Elsevier; 2006: p. 434)*

enlarged suboccipital nodes. In Asian countries, ulcers at the uvulopalatoglossal junction **(Nagayama spots)** are commonly reported in infants with roseola.

High fever (mean: 39.7°C [103.5°F]) is the most consistent finding associated with primary HHV-6B infection. Rash detected either during the illness or following defervescence has been reported in approximately 20% of infected children in the United States. Additional symptoms and signs include irritability, inflamed tympanic membranes, rhinorrhea and congestion, gastrointestinal complaints, and encephalopathy. Symptoms of lower respiratory tract involvement such as cough are identified significantly less frequently in children with primary HHV-6B infection than in children with other febrile illnesses. The mean duration of illness caused by primary HHV-6B infection is 6 days, with 15% of children having fever for 6 or more days. Primary infection with HHV-6B accounts for a significant burden of illness on the healthcare system; one study found that 24% of visits to emergency departments by infants between 6 and 9 months of age were because of primary HHV-6B infection. A population-based study of primary HHV-6B infection confirmed that 93% of infants had symptoms and were more likely to visit a physician than noninfected infants. Fever was less likely to be present with HHV-6B infection in children younger than 6 months of age but was significantly more common in older infants and children.

Much less is known about the clinical manifestations of HHV-7 infection. Primary infection with HHV-7 has been identified in a small number of children with roseola in whom the illness is indistinguishable from that caused by HHV-6B. Secondary cases of roseola caused by infection with HHV-7 have also been reported. Additionally, primary infection with HHV-7 may be asymptomatic or may cause a nonspecific febrile illness lasting approximately 3 days.

LABORATORY FINDINGS

The most characteristic laboratory findings noted in children with primary HHV-6B infection are lower mean numbers of total white blood cells (8,900/μL), lymphocytes (3,400/μL), and neutrophils (4,500/μL) than in febrile children without primary HHV-6B infection. Similar hematologic findings have been reported during primary infection with HHV-7. Thrombocytopenia, elevated serum transaminase values, and atypical lymphocytes have also been noted sporadically in children with primary HHV-6B infection.

Results of CSF analyses reported in patients with encephalitis thought to be caused by HHV-6 have been normal or demonstrated only minimal CSF pleocytosis with mild elevations of protein, especially early in the course of the disease, which may progress with time. Areas of hyperintense signal on T2 weighted and fluid attenuation inversion recovery images of the hippocampus, uncus, and amygdala have been found on MRI, and increased metabolism within the hippocampus has been observed on positron emission tomography scanning.

DIAGNOSIS

Although roseola is generally a benign self-limited disease, its diagnosis can exclude other, more serious disorders that cause fever and rash. A history of 3 days of high fever in an otherwise nontoxic 10-month-old infant with a blanching maculopapular rash on the trunk suggests a diagnosis of roseola. **A specific diagnosis of HHV-6 is not usually necessary except in situations in which the manifestations of the infection are severe or unusual and might benefit from antiviral therapy.**

The diagnosis of primary infection with either HHV-6 or HHV-7 is confirmed by demonstrating the presence of actively replicating virus in the patient's blood sample coupled with seroconversion. Viral culture is the gold standard method to document active viral replication. Unfortunately, culture is expensive, time consuming, and available only in research laboratories. Two other methods used to identify active HHV-6 replication are the detection of viral DNA by PCR on acellular fluids such as plasma or reverse transcriptase PCR on peripheral blood mononuclear cell samples designed to detect viral transcription and protein production. Quantitative PCR for HHV-6 genome copy numbers on various specimens is also frequently reported and is commercially available. However, the role of this methodology is not clear, as a specific value of DNA that can discriminate between patients with viremia and those who are culture negative has not been determined. Complicating the use of molecular assays for the detection of active replication of HHV-6 is the recognition that individuals with chromosomally integrated HHV-6 have persistent HHV-6 DNA in plasma, peripheral blood mononuclear cells, and CSF in the absence of disease and replicating virus.

Serologic methods such as indirect immunofluorescence assays, enzyme-linked immunosorbent assays, neutralization assays, and immunoblot have been described for the measurement of concentrations of antibodies to HHV-6 and HHV-7 in serum or plasma and are commercially available. Although immunoglobulin M antibody is produced early in infection with HHV-6, assays designed to measure this response have not proved useful in the diagnosis of primary or reactivated infection. The absence of immunoglobulin G antibody in an infant older than 6 months of age combined with the presence of replicating virus is strong evidence of primary infection with either HHV-6 or HHV-7. Alternatively, the demonstration of seroconversion between acute and convalescent samples also confirms primary infection but is not clinically useful in the acute care setting. Unfortunately, serologic assays have not been found reliable in the detection of HHV-6 reactivation and cannot be used to differentiate between infection with HHV-6A and infection with HHV-6B. Additionally, limited antibody cross-reactivity has been demonstrated between HHV-6 and HHV-7, complicating the interpretation of serologic assays, especially if low titers are reported.

Differential Diagnosis

Primary infection with either HHV-6B or HHV-7 usually causes an undifferentiated febrile illness that may be very difficult to distinguish from other common viral infections of childhood. This difficulty also applies to the early stages of roseola, before the development of rash. Once the rash is present, roseola may be confused with other exanthematous diseases of childhood, especially measles and rubella. Children with **rubella** often have a prodrome characterized by mild illness with low-grade fever, sore throat, arthralgia,

and gastrointestinal complaints, unlike those with roseola. On physical examination, suboccipital and posterior auricular lymph nodes are prominent up to 1 week before the rash of rubella is evident and persist during the exanthematous phase. Additionally, the rash of rubella usually begins on the face and spreads to the chest, like that in measles. The associated symptoms of **measles** virus infection include cough, coryza, and conjunctivitis, with high fever coincident with the development of rash, unlike in roseola. Roseola may also be confused with scarlet fever, though the latter is rare in children younger than 2 years of age and causes a characteristic sandpaper-like rash concurrent with fever.

Roseola may be confused with illness caused by **enterovirus infections**, especially in the summer and fall months. Drug hypersensitivity reactions may also be difficult to distinguish from roseola. Antibiotics are frequently prescribed for children with fever from roseola before the appearance of rash. A child who then demonstrates rash after the resolution of fever may erroneously be labeled as being drug allergic.

COMPLICATIONS

Convulsions are the most common complication of roseola and are recognized in up to one third of patients. Seizures are also the most common complication of children with documented primary HHV-6B infection, occurring in approximately 15%, with a peak age of 12-15 months. Children with primary HHV-6B infection are also reported to have a higher frequency of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures than are children with febrile seizures not associated with HHV-6. In a study limited to children with primary HHV-6B infection and seizures, 30% of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures. A prospective study of children 2-35 months of age with suspected encephalitis or severe febrile illness with convulsions found that 17% had primary infection with either HHV-6 or HHV-7, and status epilepticus was the most common presentation. Among children with febrile status epilepticus (FSE), primary or reactivated infection with HHV-6B or HHV-7 has been identified in approximately one third.

An association between recurrent seizures and reactivated or persistent infection of the CNS by HHV-6 has also been suggested. Studies evaluating brain tissue specimens implicate HHV-6 in as many as 60% of patients with temporal lobe epilepsy (TLE), high viral loads being found in the hippocampus or lateral temporal lobe regions. HHV-6 is postulated to induce neuroinflammation and potential injury via innate and adaptive immune system activation as a result of the broad tissue tropism of the virus. Subsequent neuronal hyperexcitability through the loss of glutamate regulatory control and increased blood-brain barrier permeability have been proposed as possible mechanisms for the development of recurrent seizures based on animal models and clinical data of patients with TLE and HHV-6 DNA detected in CNS specimens. Contrary to these findings, limited clinical data suggest that there may be a decreased risk of recurrent seizures after primary infection with HHV-6 and febrile seizures than of febrile seizures from other causes. Additionally, children with FSE associated with HHV-6B and HHV-7 had similar seizure characteristics and a similar proportion of electroencephalography and MRI hippocampal abnormalities as children with FSE not associated with HHV-6B or HHV-7, suggesting a shared pathogenesis to other etiologies of FSE.

Case reports and small-patient series have described additional complications in children with primary HHV-6B infection, including encephalitis, acute disseminated demyelination, autoimmune encephalitis, acute cerebellitis, hepatitis, and myocarditis. Late-developing long-term sequelae, including developmental disabilities and autistic-like features, are reported rarely in children who have CNS symptoms during primary HHV-6B infection.

Reactivation of HHV-6 has been reported in several different populations with and without disease with the use of various methods of detection. The best documentation of HHV-6 reactivation has been in immunocompromised hosts, especially those patients who have undergone HSCT. Such reactivation occurs in approximately 50% of patients, typically at 2-4 weeks after transplantation, and the risk of reactivation is associated with a lack of donor-derived HHV-6–specific T-cell immunity. Many of the clinical complications seen following HSCT have been associated with HHV-6B reactivation, including fever, rash, delayed engraftment of platelets or monocytes, and graft-versus-host disease, with variable degrees of support in the literature for each. HHV-6 reactivation has been associated with worse overall survival compared with HSCT recipients who did not experience reactivation.

HHV-6B reactivation has also been reported as a cause of encephalitis in both immunocompetent and immunocompromised hosts. A distinct syndrome of **posttransplant acute limbic encephalitis (PALE)** has been described primarily in patients following HSCT, especially cord blood stem cell transplantation; it is characterized by short-term memory dysfunction, confusion, and insomnia, with seizures noted either clinically or on prolonged electroencephalography monitoring. HHV-6B DNA has been identified in the CSF in the majority of these patients, with additional evidence of reactivation by detection of HHV-6B DNA in plasma. HHV-6 proteins were identified in the astrocytes of the hippocampus in one postmortem specimen, consistent with active HHV-6B infection at the time of death. The development of PALE is associated with increased mortality and long-term neurocognitive sequelae.

TREATMENT

Supportive care is usually all that is needed for infants with roseola. Parents should be advised to maintain hydration and may use antipyretics if the child is especially uncomfortable with the fever. Specific antiviral therapy is not recommended for routine cases of primary HHV-6B or HHV-7 infection. Unusual or severe manifestations of primary or presumed reactivated HHV-6B infection such as encephalitis/PALE, especially in immunocompromised patients, may benefit from treatment. Ganciclovir, foscarnet, and cidofovir all demonstrate inhibitory activity against HHV-6 in vitro, similar to their activity against cytomegalovirus. Case reports suggest that all three drugs, alone or in combination, can decrease HHV-6 viral replication, as evidenced by decreased viral loads in plasma and CSF. However, clinical data regarding efficacy are sparse and contradictory, with no randomized trials to guide use. Additionally, in vitro resistance of HHV-6 to all three drugs has been described. Despite these drawbacks, treatment with ganciclovir or foscarnet as first-line agents has been recommended for a minimum of 3 weeks in patients with PALE. Foscarnet appears to be most likely to have activity against HHV-7 on the basis of in vitro testing, but no clinical data are available.

PROGNOSIS

Roseola is generally a self-limited illness associated with complete recovery. The majority of children with primary infections with HHV-6B and HHV-7 also recover uneventfully without sequelae. Although seizures are a common complication of primary infection with HHV-6B and HHV-7, the risk of recurrent seizures does not appear to be higher than that associated with other causes of simple febrile seizures.

PREVENTION

Primary infections with HHV-6 and HHV-7 are widespread throughout the human population with no current means of interrupting transmission.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 304

Human Herpesvirus 8

Brenda L. Tesini

Human herpesvirus 8 (HHV-8) is an oncogenic virus identified in tissue specimens from patients with Kaposi sarcoma (KS). Because of this association, it is also known as **Kaposi sarcoma–associated herpesvirus**. HHV-8 is the etiologic agent of two additional lymphoproliferative disorders: **primary effusion–based lymphoma (PEL)** and **multicentric Castleman disease (MCD)**.

ETIOLOGY

HHV-8 is a γ_2-human herpesvirus similar to Epstein-Barr virus. The virus contains a large DNA genome encoding 85-95 unique proteins. Infection is followed by both lytic and latent viral states, with different degrees of viral replication associated with distinct disease manifestations.

EPIDEMIOLOGY

The prevalence of infection with HHV-8 varies both geographically and by population and roughly matches the epidemiology of KS. HHV-8 infection is endemic in Africa and parts of South America, with infection rates of up to 30–60% by adolescence. Seroprevalence >20% has also been found in regions bordering the Mediterranean. In contrast, infection rates <5% are noted in North America, Central Europe, and Asia. However, within geographic regions, the prevalence of infection varies with risk behaviors, with rates of 30–75% being found among men who have sex with men in North America and Europe. HHV-8 DNA can be detected in saliva, blood, semen, and tissues. Based on large-scale epidemiologic studies and the high prevalence of viral shedding in oral secretions, saliva is believed to be the major mode of transmission. Other less common routes of HHV-8 transmission include blood transfusion, bone marrow transplantation, and solid organ transplantation. Vertical transmission and transmission via breast milk may occur in regions where HHV-8 is highly endemic, but the risk appears low.

PATHOLOGY AND PATHOGENESIS

HHV-8 contains multiple genes that affect cell-cycle regulation and the host immune response. Viral proteins interfere with the function of the tumor suppressor molecules, induce the expression of proangiogenesis factors, and lead to upregulation of the rapamycin pathway target, which is instrumental in the control of cell growth and metabolism. HHV-8 also encodes a homolog of human interleukin-6, which can bind and activate cytokine receptors and serve as a host cell autocrine growth factor. Additionally, viral proteins are associated with the constitutive expression of the transcription factor nuclear factor-κB. All of these proteins may be potential targets for therapeutic intervention.

CLINICAL MANIFESTATIONS

Although subclinical infection appears to be common, symptomatic primary HHV-8 infection has been described in immunocompetent children. Patients commonly have fever and a maculopapular rash or a mononucleosis-like syndrome, with full recovery the rule. In immunocompromised patients, primary infection has been associated with fever, rash, splenomegaly, pancytopenia, and lymphoid hyperplasia and may be quite severe. Additionally, preliminary data suggest that transfusion-associated primary infection with HHV-8 is associated with an increased risk of mortality.

Even in regions with high rates of seroprevalence, the development of KS is uncommon. KS has several different clinical forms; each includes multifocal, angiogenic lesions arising from vascular endothelial cells infected with HHV-8. Classic KS is an indolent disorder seen in elderly men with limited involvement of the skin of the lower extremities. Endemic KS is more aggressive, occurring in children and young people, primarily in Africa, and can include visceral involvement as well as widespread cutaneous lesions (patches, plaques, or nodules). Posttransplantation KS and AIDS-related KS are the most severe forms, with disseminated lesions, often in the gastrointestinal tract and lungs, with or without cutaneous findings.

Primary effusion–based lymphoma is a rare disease caused by HHV-8 that is seen most commonly in HIV-infected individuals. It consists of lymphomatous invasion of the serosal surfaces of the pleura, pericardium, and peritoneum. Similarly, **multicentric Castleman disease** is an unusual lymphoproliferative disorder characterized by anemia, thrombocytopenia, generalized lymphadenopathy, and constitutional symptoms and is frequently associated with HHV-8 infection and a high degree of viral replication.

DIAGNOSIS

Serologic assays, including immunofluorescence and enzyme-linked immunosorbent assays, are the primary methods of diagnosing infection with HHV-8. However, testing has limited sensitivity, specificity, and reproducibility and is primarily a research tool with no universally recognized standard assays. Additionally, the loss of antibodies over time, referred to as *seroreversion,* has been described, further complicating serodiagnosis. Immunohistochemistry and molecular methods are available for the detection of HHV-8 in tissue samples and are used in the diagnosis of KS, PEL, and MCD, alongside their disease-specific clinical manifestations. Nucleic acid testing of blood and other body fluids is also available but has a limited diagnostic role.

TREATMENT

Treatment for KS, PEL, and MCD is multifaceted and includes attempts to control malignant proliferations with traditional chemotherapeutic regimens and biologic agents as well as agents aimed at specific cellular pathways targeted by HHV-8 proteins. Combined antiretroviral therapy (ART) is a mainstay of both prevention and therapy for HHV-8–related disease in HIV-infected patients. In HIV-associated KS, treatment with ART alone is often used for the control of mild (i.e., cutaneous) disease, whereas ART plus chemotherapy is used for more severe disease. In transplantation-associated KS, the first line of treatment includes decreasing immunosuppression, often in association with a switch from calcineurin inhibitors to sirolimus (rapamycin) to block the mammalian target of rapamycin pathway. Severe disease frequently requires the use of traditional chemotherapy as well. The role of specific antiherpesvirus antiviral treatment is unclear. Valganciclovir and ganciclovir treatment have been associated with decreased viral replication and rates of development of KS in HIV-infected individuals. However, results of using antivirals in the treatment of established disease have been generally disappointing. The prognosis for PEL tends to be poor despite the use of traditional chemotherapy, whereas rituximab (anti-CD20)–based therapy has been highly successful for MCD treatment. However, relapse and the development of lymphoma after treatment can still occur. Rituximab treatment may also worsen concurrent KS without additional agents.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 305

Influenza Viruses

Flor M. Munoz

Influenza viral infections cause a broad array of respiratory illnesses that are responsible for significant morbidity and mortality in children during **seasonal epidemics**. Influenza A viruses also have the potential to cause **global pandemics**, which can happen when a **new (novel) influenza A virus** emerges and transmits efficiently from person to person.

ETIOLOGY

Influenza viruses are large, single-stranded RNA viruses belonging to the family Orthomyxoviridae, which includes three genera (or types): A, B, and C. Influenza A and B viruses are the primary human pathogens causing seasonal epidemics, whereas influenza virus type C is a sporadic cause of predominantly mild upper respiratory tract illness. Influenza A viruses are further divided into subtypes based on two surface proteins that project as spikes from the lipid envelope, the hemagglutinin (HA) and neuraminidase (NA) proteins (Fig. 305.1). Strain variants are identified by antigenic differences in their HA and NA and are designated by the geographic area from which they were originally isolated, isolate number, and year of isolation—for example, influenza A/Victoria/361/2011(H3N2). The HA and NA antigens from influenza B and C viruses do not receive subtype designations, because there is less variation among influenza B and C antigens. However, influenza B viruses can be further broken down into lineages, with recent examples including the B/Yamagata and B/Victoria lineages.

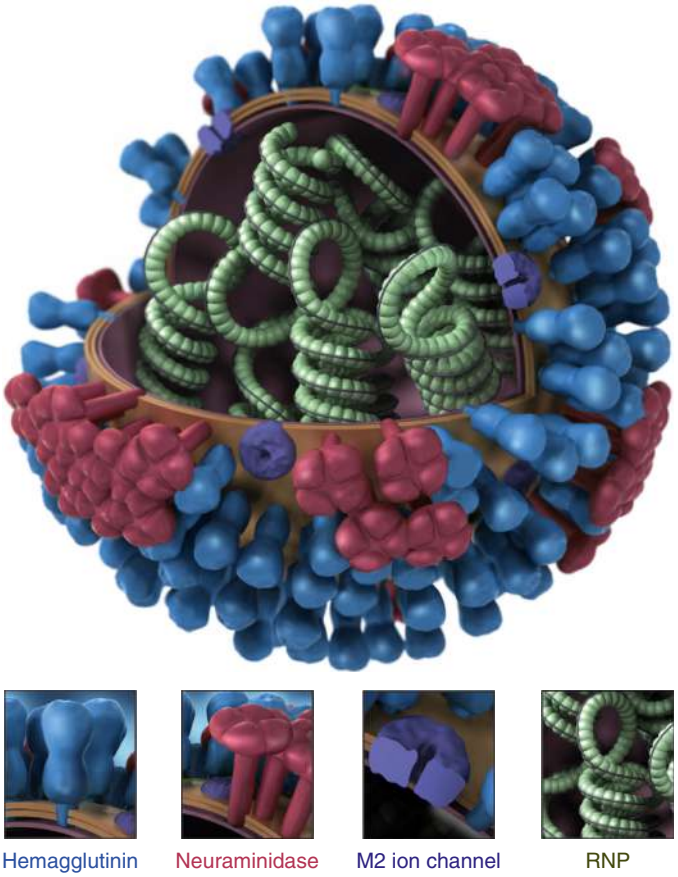

Fig. 305.1 Graphical representation of influenza virus. The key at bottom identifies the surface protein constituents: the hemagglutinin, neuraminidase, matrix protein 2 *(M2)* ion channel, and ribonucleoprotein *(RNP)*. *(From Centers for Disease Control and Prevention Public Health Image Library, Image ID#11822. https://phil.cdc.gov/Details.aspx?pid=11822; courtesy CDC/Douglas Jordan and Dan Higgins, 2009.)*

EPIDEMIOLOGY

Influenza has generally been thought to be transmitted primarily via respiratory droplets, but transmission through contact with secretions and small-particle aerosols may also occur. The typical incubation period ranges from 1 to 4 days, with an average of 2 days. Healthy adults are generally considered potentially infectious from a day before symptoms develop until 5-7 days after becoming ill. Children with primary influenza infection have higher influenza viral loads and more prolonged viral shedding than adults; therefore children may be able to infect others for a longer time. Influenza outbreaks occur commonly in schools and childcare settings. Healthcare-associated influenza infections can also occur in healthcare settings, and outbreaks in long-term care facilities and hospitals may cause significant morbidity.

In the United States, seasonal influenza viruses can be detected year-round, but circulating viruses are most common during the fall and winter. Transmission through a community is rapid, with the highest incidence of illness occurring within 2-3 weeks of introduction.

Antigenic Variation

Influenza A and B viruses contain a genome consisting of 8 single-stranded RNA segments. Minor changes within a subtype continually occur through point mutations during viral replication, particularly in the HA gene, and result in new influenza strains of the same HA type. This phenomenon, termed **antigenic drift**, occurs in both influenza A and B viruses. Variation in antigenic composition of influenza virus surface proteins occurs almost yearly, which confers a selective advantage to a new strain and contributes to annual epidemics. For this reason, the formulation of the influenza vaccine is reviewed each year and updated as needed.

Less frequent but more dramatic major changes in virus subtype can occur, resulting in a new influenza A subtype to which most people have little to no immunity. This process is called *antigenic shift* and can occur through reassortment of viral gene segments when there is simultaneous infection by more than one strain of influenza in a single host, or by direct adaptation of an animal virus to a human host. Antigenic shift occurs in influenza A viruses, which have multiple avian and mammalian hosts acting as reservoirs for diverse strains.

Through the process of **reassortment**, potentially any of 18 HA and 11 NA proteins currently known to reside in influenza A viruses of nonhuman hosts could be introduced into humans, who may have little existing immunologic cross protection to emerging viruses. A global pandemic can result if an influenza A virus with a novel HA or NA enters a nonimmune human population and acquires the capacity for sustained and efficient transmission between people. Four major **global pandemics** have occurred since 1900: in 1918 caused by an influenza A(H1N1) virus, 1957 caused by an influenza A(H2N2) virus, 1968 caused by an influenza A(H3N2) virus, and 2009 caused by an influenza A virus designated A(H1N1)pdm09. The most severe influenza pandemic in recorded history occurred in 1918, when the virus was estimated to have killed at least 50 million people. The 1918 pandemic virus was likely the result of direct adaptation of an avian influenza virus to the human host, rather than from reassortment. The 2009 pandemic virus stemmed from reassortment of genes from swine, avian, and human viruses (Fig. 305.2). This resulted in the emergence of a novel influenza A(H1N1)pdm09 virus that spread quickly from North America across the globe and replaced the previously circulating seasonal H1N1 viruses.

Several novel influenza viruses, all originating in animals, have also caused outbreaks of human infections. Avian influenza A(H5N1), a virulent avian influenza virus that was first identified in 1997, has caused more than 880 documented cases in 19 countries, with a mortality rate over 50%. A novel avian influenza A(H5N6) with a case fatality rate of >40%, emerged in China in 2014, causing infection in at least

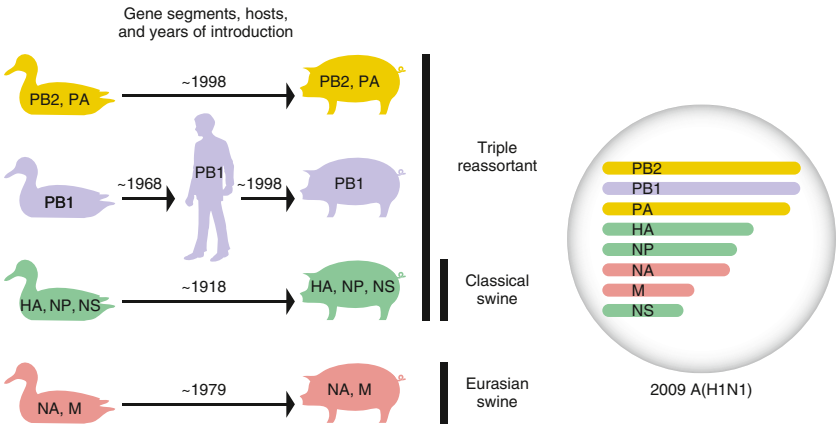

Fig. 305.2 Host and lineage origins for the gene segments of the 2009 A(H1N1) virus. HA, Hemagglutinin; M, matrix gene; NA, neuraminidase; NP, nucleoprotein; NS, nonstructural gene; PA, polymerase acidic; PB1, polymerase basic 1; PB2, polymerase basic 2. Color of gene segment in circle indicates host. *(From Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science. 2009;325[5937]:197–201.)*

Table 305.1 Subtypes of Novel Influenza A Viruses and Clinical Syndromes in Human Infections

	LPAI VIRUSES	HPAI VIRUSES	VARIANT VIRUSES*
Conjunctivitis	H7N2, H7N3, H7N7, H10N7	H7N3, H7N7	H1N1v, H3N2v
Upper respiratory tract illness	H6N1, H7N2, H7N3, H7N9, H9N2, H10N7	H5N1, H5N6, H7N7	H1N1v, H1N2v, H3N2v
Lower respiratory tract disease, pneumonia	H7N2, H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Respiratory failure, acute respiratory distress syndrome	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Multiorgan failure	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	—
Encephalopathy or encephalitis	H7N9	H5N1	—
Fatal outcomes†	H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v

*Variant viruses of swine origin.
†High mortality in reported cases: about 40% for LPAI H7N9, about 50% for HPAI H5N1, and about 70% for HPAI H5N6.
HPAI, Highly pathogenic avian influenza; LPAI, low-pathogenic avian influenza.
From Uyeki TM, Katz JM, Jernigan DB. Novel influenza A viruses and pandemic threats. *Lancet.* 2017;389:2172–2174.

60 people. Another avian influenza, A(H7N9) virus, has caused more than 1,500 documented cases and is also highly virulent. This virus first caused an outbreak of human infections in China during the spring of 2013, with annual epidemics in China occurring in subsequent years. During the first four yearly epidemics, infection was fatal in approximately 40% of documented cases.

In addition, novel influenza A variant viruses have caused human infections (Table 305.1). These include H3N2v viruses, which caused 372 confirmed human infections in the United States from 2011 to 2016 and were primarily transmitted through swine contact at agricultural fairs. Influenza viruses that normally circulate in swine are designated variant ("v") viruses when detected in humans, and H3N2v and other variant viruses, including H1N1v and H1N2v, continue to be detected and sporadically infect humans with prolonged exposure to infected pigs. In contrast to avian influenza A(H5N1), A(H5N6), and A(H7N9) viruses, variant viruses generally cause mild illness and have been primarily detected in children. However, none of these viruses has exhibited sustained, efficient human-to-human transmission.

Seasonal Influenza

An estimated 11,000-45,000 children younger than 18 years of age are hospitalized annually in the United States as a result of seasonal influenza-associated complications, with approximately 6,000-26,000 hospitalizations in children younger than 5 years of age. Since 2004, the annual number of reported influenza-associated pediatric deaths in the United States has ranged from 37 to 199 during regular influenza seasons (358 were reported to have occurred during the 2009 H1N1 pandemic). Influenza disproportionately affects children with specific chronic conditions, such as underlying pulmonary, cardiac, or neurologic and neuromuscular disorders. Very young children, especially those younger than 2 years of age, and children with chronic medical conditions are more likely to develop severe influenza-related complications, including viral and bacterial pneumonia, hospitalization, respiratory failure, and death. However, although children with underlying medical conditions are at higher risk of complications, many healthy children are hospitalized with influenza, and nearly half of pediatric influenza-associated deaths are in children that have no known underlying medical condition.

Influenza also causes a substantial burden of disease in outpatient settings. It contributes to an estimated 600,000 to 2,500,000 outpatient medical visits annually in children younger than 5 years of age and has been identified in 10–25% of outpatient visits among all children with respiratory symptoms during influenza season. Influenza may also be underdiagnosed. Many who seek medical care for influenza do not have laboratory testing performed and do not receive a diagnosis of influenza. Every year, three or four influenza virus types or subtypes typically co-circulate, including influenza A(H3N2), influenza A(H1N1), and two types of B viruses. Although one subtype usually predominates in any given season, it is difficult to predict which will be predominant. Thus the influenza vaccine varies annually and contains three or four antigens representing the expected circulating types.

PATHOGENESIS

Influenza viruses infect the respiratory tract epithelium, primarily the ciliated columnar epithelial cells, by using the HA to attach to sialic acid residues. After viral entry into cells, virus replication occurs usually within 4-6 hours, and new virus particles are assembled and released to infect neighboring cells. With primary infection, virus replication continues for 10-14 days. Influenza virus causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus

production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion, either directly through the epithelium or, in the case of the middle ear space, through obstruction of the normal drainage through the eustachian tube.

The exact immune mechanisms involved in termination of primary infection and protection against reinfection are complex. Induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor, as well as other host defenses, such as cell-mediated immune responses and local and humoral antibody defenses, all likely play a role. Secretory immunoglobulin A antibodies produced by the respiratory mucosa are thought to be an effective and immediate response generated during influenza infection. Serum antibody levels inhibiting HA activity can usually be detected by the second week after infection. These antibodies are also generated by vaccines, and high HA inhibition antibody titers correlate with protection.

CLINICAL MANIFESTATIONS

The onset of influenza illness is *often abrupt,* with a predominance of systemic symptoms, including fever, myalgias, chills, headache, malaise, and anorexia. Coryza, pharyngitis, and dry cough are also usually present at the onset of illness but may be less prominent than systemic symptoms. Respiratory manifestations can include isolated upper respiratory tract illness, including croup, or progression to lower tract disease, such as bronchiolitis or pneumonia. More than other respiratory viruses, influenza virus typically causes systemic manifestations such as high temperature, myalgia, malaise, and headache. Less common clinical manifestations can include parotitis and rash.

Abdominal pain, vomiting, and diarrhea may also occur in children; in some studies, diarrhea was reported to be more often associated with influenza A(H1N1)pdm09 compared with influenza A(H3N2) or influenza B viruses. Influenza is a less distinct illness in younger children and infants. The infected young infant or child may be highly febrile and toxic in appearance, prompting a full diagnostic workup. The typical duration of the febrile illness is 2-4 days. Cough may persist for longer periods, and evidence of small airway dysfunction is often found weeks later. Owing to the high transmissibility of influenza, other family members or close contacts of an infected person often experience a similar illness.

COMPLICATIONS

Otitis media and pneumonia are common complications of influenza in young children. Acute otitis media may be seen in up to 25% of cases of documented influenza. Pneumonia accompanying influenza may be a primary viral process or a secondary bacterial infection (such as with *Staphylococcus aureus*) facilitated through damaged respiratory epithelium. Influenza may cause acute myositis or rhabdomyolysis marked by muscle weakness and pain, particularly in the calf muscles, and myoglobinuria. Other extrapulmonary complications include acute renal failure, myocarditis, and sepsis. Central nervous system complications, such as encephalitis, myelitis, and Guillain-Barré syndrome, can occur and are seen more commonly in children than adults. Although it has essentially disappeared in the United States, Reye syndrome can result with the use of salicylates during influenza infection (see Chapter 409). Bacterial co-infection may also exacerbate respiratory complications of influenza and lead to sepsis, bacteremia, toxic shock syndrome, and other manifestations.

Influenza is particularly severe in some children, including those with underlying cardiopulmonary disease, including congenital and acquired valvular disease, cardiomyopathy, bronchopulmonary dysplasia, asthma, cystic fibrosis, and neurologic conditions. Pregnant women and adolescent females are also at high risk for severe influenza. Children receiving cancer chemotherapy and children with immunodeficiency also have a higher risk of complications and may shed virus for longer periods than immunocompetent children.

LABORATORY FINDINGS

The clinical laboratory abnormalities associated with influenza are nonspecific. Chest radiographs may show evidence of atelectasis or infiltrate.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of influenza depends on epidemiologic, clinical, and laboratory considerations. In the context of an epidemic, the clinical diagnosis of influenza in a child who has fever, malaise, and respiratory symptoms may be made based on clinical discretion; however, clinical presentation is often indistinguishable from infection with other respiratory viruses, including SARS-CoV-2, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, and even rhinovirus. Confirmation of influenza virus infection by diagnostic testing might be helpful in certain circumstances when other viruses are co-circulating, but it is not required for clinical decisions to prescribe antiviral medications, and prompt suspicion or diagnosis of influenza may allow for early antiviral therapy to be initiated and may reduce inappropriate use of antibiotics.

A number of diagnostic tests may be used for laboratory confirmation of influenza (Table 305.2). Although rapid influenza diagnostic tests based on antigen detection are often employed because of their ease of use and fast results, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid antigen diagnostic tests are generally 50–70% compared to viral culture or reverse-transcription polymerase chain reaction (RT-PCR). Specificities are higher, approximately 95–100%. Therefore false-negative results occur more often than false-positive results, particularly when the prevalence of influenza is high (i.e., during peak influenza activity in the community). The interpretation of negative results should consider the clinical characteristics and the patient's risk for complications. If there is clinical suspicion for influenza in a patient at high risk for complications (Table 305.3), early empirical treatment should be given regardless of a negative rapid antigen diagnostic test result, and another type of test may be performed for confirmation. RT-PCR or other rapid molecular assays are now preferred for influenza diagnosis in both outpatients and hospitalized patients.

TREATMENT

Antiviral medications are an important adjunct to influenza vaccination. Three classes of antiviral drugs are licensed for treatment of influenza in children. The neuraminidase inhibitors (NAIs), oral oseltamivir and inhaled zanamivir, may be used for treatment of children from birth and 7 years, respectively (Table 305.4). In December 2012, the U.S. Food and Drug Administration (FDA) approved the use of oseltamivir for the treatment of influenza in infants as young as 2 wk of age, and the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, and the Infectious Diseases Society of America recommend its use in infants of any age. A third NAI, peramivir, is given as an intravenous infusion and is approved for treatment in persons 2 years of age and older.

The second class of drugs is represented by a new orally administered influenza antiviral called baloxavir marboxil, which was approved by the FDA in October 2018. Baloxavir is active against both influenza A and B viruses and is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication. It is approved for treatment of acute uncomplicated influenza in people 12 years and older.

The third class of drugs is the adamantanes, including oral amantadine and oral rimantadine, which are effective only against influenza A viruses. Genetic variants have conferred widespread adamantane resistance among circulating influenza A viruses, including seasonal influenza viruses and many H5N1 and H7N9 avian influenza viruses; *therefore this class of antivirals is not currently recommended for use.*

When initiated early in the course of uncomplicated influenza illness, antiviral agents can reduce the duration of symptoms and the likelihood of complications. Among hospitalized patients, observational studies suggest that early treatment reduces disease severity and mortality. Although most data regarding potential benefit are for adults, a few studies support the use of antiviral agents in children. Antiviral treatment within 2 days of illness onset has been reported to reduce illness duration, the risk of otitis media, and the likelihood of hospitalization in children. Clinical benefit is greatest when antiviral

Table 305.2 Influenza Virus Testing Methods

METHOD	ACCEPTABLE SPECIMENS	TEST TIME	COMMENTS
Rapid influenza diagnostic tests (antigen detection)	Nasopharyngeal (NP) swab, aspirate or wash, nasal swab, aspirate, or wash, throat swab	<15 min	Rapid turnaround; suboptimal sensitivity
Rapid molecular assay (influenza nucleic acid amplification)	NP swab, nasal swab	15-30 min	Rapid turnaround; high sensitivity
Immunofluorescence, direct (DFA) or indirect (IFA) fluorescent antibody staining (antigen detection)	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hr	Relatively rapid turnaround; requires laboratory expertise and experience
RT-PCR (singleplex and multiplex; real-time and other RNA-based) and other molecular assays (influenza nucleic acid amplification)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varies by assay (generally 1-8 hr)	Excellent sensitivity, relatively rapid turnaround compared with conventional methods
Rapid cell culture (shell vials, cell mixtures; yields live virus)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-3 day	Culture isolates important for strain information and antiviral resistance monitoring
Viral tissue cell culture (conventional; yields live virus)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 day	Not recommended for routine patient diagnosis
Serologic tests (antibody detection)	Paired (appropriately timed) acute and convalescent serum specimens	N/A (not performed during acute infection)	Not recommended for routine patient diagnosis; useful for research studies

N/A, Not applicable; RT-PCR, reverse transcription-polymerase chain reaction.
Modified from Centers for Disease Control and Prevention (CDC): *Influenza virus testing methods*. Available at https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm in Information for Health Professionals (https://www.cdc.gov/flu/professionals/index.htm); and from 2018 IDSA Clinical Practice Guidelines.

Table 305.3 Children and Adolescents Who Are at Higher Risk for Influenza Complications for Whom Antiviral Treatment is Recommended*

- Children younger than 2 yr of age†
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), and metabolic disorders (including diabetes mellitus); or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Persons with immunosuppression, including that caused by medications or by HIV infection
- Adolescents who are pregnant, or postpartum (within 2 wk after delivery)
- Persons younger than 19 yr of age who are receiving long-term aspirin- or salicylate-containing medications therapy
- Indigenous/Alaska Natives
- Persons who are extremely obese (body mass index ≥40)
- Residents of long-term care facilities
- Hospitalized patients at high risk for influenza complications

*Antiviral treatment is recommended for children at high risk with confirmed or suspected influenza; antivirals are also recommended for children who are hospitalized or have severe or progressive disease.
†Although all children younger than 5 yr of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 yr of age, with the highest hospitalization and death rates among infants younger than 6 mo of age.
Current for 2021–2022 influenza season.
Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; and from American Academy of Pediatrics Policy Statement: Recommendations for Prevention and Control of Influenza in Children, 2021-2022. For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm.

treatment is administered early, especially within 48 hours of influenza illness onset.

The CDC recommends treatment as early as possible for (1) hospitalized patients, (2) patients with severe, complicated, or progressive illness, and (3) patients at high risk for influenza complications (see Table 305.3). Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza. Although early treatment is desired, treatment more than 48 hours from onset may be beneficial and is recommended for these three categories of patients.

The recommended treatment course for uncomplicated influenza is twice daily oral oseltamivir for 5 days, twice daily inhaled zanamivir for 5 days, or a single dose of intravenous peramivir or oral baloxavir. Currently, for hospitalized patients and patients with severe or complicated illness, treatment with oral or enterically administered oseltamivir is recommended. The optimal duration and dose are uncertain for severe or complicated influenza, and longer courses of treatment (e.g., 10 days of treatment) may be considered.

Clinical judgment considering a patient's disease severity, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms is important when making antiviral treatment decisions for outpatients at high risk for complications. Antiviral treatment can also be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza, if treatment can be initiated within 48 hours of illness onset.

Some influenza viruses may become resistant during antiviral treatment, an occurrence that has been reported most often for oseltamivir resistance in influenza A(H1N1) viruses. Following treatment with baloxavir, emergence of viruses with molecular markers associated with reduced susceptibility to baloxavir has been observed in clinical trials. Antiviral resistance and reduced susceptibility can also occasionally occur spontaneously with no known exposure to antiviral drugs. It is important to review annual recommendations and updates published by CDC before prescribing influenza antiviral medications (see https://www.cdc.gov/flu/professionals/antivirals/index.htm).

Table 305.4 Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis in Children for the 2021–2022 Influenza Season: United States

MEDICATION	TREATMENT DOSING*	CHEMOPROPHYLAXIS DOSING*
ORAL OSELTAMIVIR†		
Adults	75 mg twice daily	75 mg once daily
Children ≥12 mo		
≤15 kg (≤33 lb)	30 mg twice daily	30 mg once daily
>15-23 kg (33-51 lb)	45 mg twice daily	45 mg once daily
>23-40 kg (>51-88 lb)	60 mg twice daily	60 mg once daily
>40 kg (>88 lb)	75 mg twice daily	75 mg once daily
Infants 9-11 mo‡	3 mg/kg per dose twice daily	3 mg/kg per dose once daily
Term infants ages 0-8 mo‡	3 mg/kg per dose twice daily	3 mg/kg per dose once daily for infants 3-8 mo old; not recommended for infants <3 mo old unless situation judged critical because of limited safety and efficacy data in this age group
Preterm infants	See details in footnote§	Not recommended
INHALED ZANAMIVIR¶		
Adults	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
Children (≥7 yr old for treatment; ≥5 yr old for chemoprophylaxis)	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
INTRAVENOUS PERAMIVIR		
Adults	600 mg intravenous infusion once given over 15-30 min	Not recommended
Children (2-12 yr old)	One 12 mg/kg dose, up to 600 mg maximum, once via intravenous infusion for 15-30 min	Not recommended
Children (13-17 yr old)	One 600 mg dose once via intravenous infusion for 15-30 min	Not recommended
ORAL BALOXAVIR#		
Adults		
40 to <80 kg	One 40-mg dose	One 40-mg dose
>80 kg	One 80-mg dose	One 80-mg dose
Children		
2-11 yr	Not recommended	Not recommended
12-17 yr, 40 to <80 kg	One 40-mg dose	One 40-mg dose
12-17 yr, >80 kg	One 80-mg dose	One 80-mg dose

*Antiviral treatment duration for uncomplicated influenza is 5 days for oral oseltamivir or inhaled zanamivir, and a single dose for intravenous peramivir or oral baloxavir. Recommended postexposure chemoprophylaxis with oseltamivir or zanamivir in a nonoutbreak setting is 7 days after last known exposure.

†Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu or as a generic formulation as capsules and as a powder for oral suspension that is reconstituted to provide a final concentration of 6 mg/mL.

‡Approved by the FDA for children as young as 2 wk of age. Given preliminary pharmacokinetic data and limited safety data, oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment. CDC and U.S. Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children age 9-11 mo; the American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily. The dose of 3 mg/kg provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in two studies of oseltamivir pharmacokinetics in children. The AAP has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants 9-11 mo, on the basis of data that indicated that a higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the CASG 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5-mg/kg dose is harmful or causes more adverse events to infants in this age group.

§Oseltamivir dosing for preterm infants. The weight-based dosing recommendation for preterm infants is lower than for term infants. Preterm infants may have lower clearance of oseltamivir because of immature renal function, and doses recommended for term infants may lead to high drug concentrations in this age group. Limited data from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group provide the basis for dosing preterm infants by using their postmenstrual age (gestational age plus chronological age): 1 mg/kg per dose orally twice daily for those <38 wk postmenstrual age; 1.5 mg/kg per dose orally twice daily for those 38-40 wk postmenstrual age; and 3 mg/kg per dose orally twice daily for those >40 wk postmenstrual age. For extremely preterm infants (<28 wk), please consult a pediatric infectious diseases physician.

¶Zanamivir is administered by inhalation by using a proprietary Diskhaler device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered by using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for people with chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease, which increase the risk of bronchospasm.

#Oral baloxavir marboxil is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people 12 yr and older. The safety and efficacy of baloxavir for the treatment of influenza have been established in pediatric patients 12 yr and older weighing at least 40 kg. Safety and efficacy in patients <12 yr of age or weighing <40 kg have not been established. Baloxavir efficacy is based on clinical trials in outpatients 12 to 64 yr of age; people with underlying medical conditions and adults >65 yr were not included in the initial published clinical trials (Hayden F et al; *Clin Infect Dis* 2018). There are no available data for baloxavir treatment of hospitalized patients with influenza.

Adapted from Centers for Disease Control and Prevention (CDC): *Influenza antiviral medications: summary for clinicians*. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm; 2018 IDSA Clinical Practice Guidelines; and from Kimberlin DW, Acosta EP, Prichard MN, et al. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Oseltamivir pharmacokinetics, dosing, and resistance among children aged <2 yr with influenza. *J Infect Dis*. 2013;207(5):709–720.

SUPPORTIVE CARE

Adequate fluid intake and rest are important in the management of influenza. Bacterial superinfections are relatively common and should be appropriately treated with antibiotic therapy. Bacterial superinfection should be suspected with recrudescence of fever, prolonged fever, or deterioration in clinical status. With uncomplicated influenza, people should usually start to feel better after the first 48-72 hours of symptoms.

PROGNOSIS

The prognosis for recovery from uncomplicated influenza is generally excellent, although full return to normal level of activity and freedom from cough may require weeks rather than days. Fatigue may also persist for weeks. However, severe influenza disease can be associated with hospitalizations and death, even among previously healthy children.

PREVENTION

Influenza vaccination is the best means of preventing influenza illness. In studies of children who are fully vaccinated, influenza vaccine is 40–60% effective in reducing the risk of laboratory-confirmed influenza illness. Vaccine effectiveness can vary from year to year and among different age and risk groups. Recommendations for use of the influenza vaccine have broadened as the impact of influenza is appreciated in such groups as pregnant women and young infants. Starting in the 2008–2009 influenza season, the United States Advisory Committee on Immunization Practices (ACIP) recommended that all children from 6 months to 18 years of age be vaccinated against influenza unless they have a specific contraindication to receiving the vaccine. Since the 2010–2011 season, annual flu vaccination is recommended for everyone 6 months and older, with rare exception. In 2012, the Department of Health in the United Kingdom extended their influenza vaccination program to include all children between the ages of 2 and 17 years. To protect infants younger than 6 months who are too young to receive a vaccine, pregnant women, household contacts, and out-of-home caregivers are groups for whom additional vaccination efforts should be made. Chemoprophylaxis with antiviral medications is a secondary means of prevention and is not a substitute for vaccination.

Vaccines

There are two main categories of seasonal influenza vaccines available for children: inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). Previously referred to as the trivalent inactivated vaccine, IIV is given intramuscularly; it uses killed virus components. The LAIV vaccine uses weakened influenza virus and is administered as an intranasal spray. Neither IIV nor LAIV can cause influenza. Although in 2014–2015 ACIP and CDC recommended the use of the LAIV nasal spray vaccine for healthy children 2 through 8 years of age, this preferential recommendation was removed for the 2015–2016 season, and for the 2016–2017 and 2017–2018 seasons, ACIP and CDC made the interim recommendation that LAIV should not be used. This decision was based on concerns regarding low effectiveness against influenza A(H1N1)pdm09 in the United States noted during the 2013–2014 and 2015–2016 seasons. After review of additional data, LAIV containing an updated influenza A(H1N1)pdm09-like vaccine virus, was again recommended by CDC and ACIP as an option for vaccination for the 2018–2019 season. Since the 2018–2019 season, ACIP and CDC have recommend that LAIV4 may be used.

Special vaccination instructions for children 6 months to 8 years of age should be followed: children in this age group who have not previously received a total of at least two previous doses of trivalent or quadrivalent vaccine require two doses (at least 4 weeks apart) of the current season's influenza vaccine to optimize immune response (Fig. 305.3). Influenza vaccines have an excellent safety profile, with the most common side effects being soreness, redness, tenderness, or swelling from the injection, and nasal congestion after the nasal spray. Seasonal influenza vaccines may be co-administered with other vaccines, including SARS-CoV-2 vaccines.

Seasonal influenza vaccines become available in the late summer and early fall each year. The formulation reflects the strains of influenza viruses that are expected to circulate in the coming influenza season. Beginning in the 2013–2014 season, IIVs were available in both trivalent and quadrivalent formulations. The trivalent vaccine (IIV3) contains two influenza A strains and one influenza B strain; the quadrivalent vaccine (IIV4) contains a second influenza B strain of an antigenically distinct lineage. In addition to IIV and LAIV, a third vaccine category, recombinant HA influenza vaccine, became available in the 2013–2014 season. Since the 2020–2021 influenza season, all influenza vaccines used in the United States are quadrivalent.

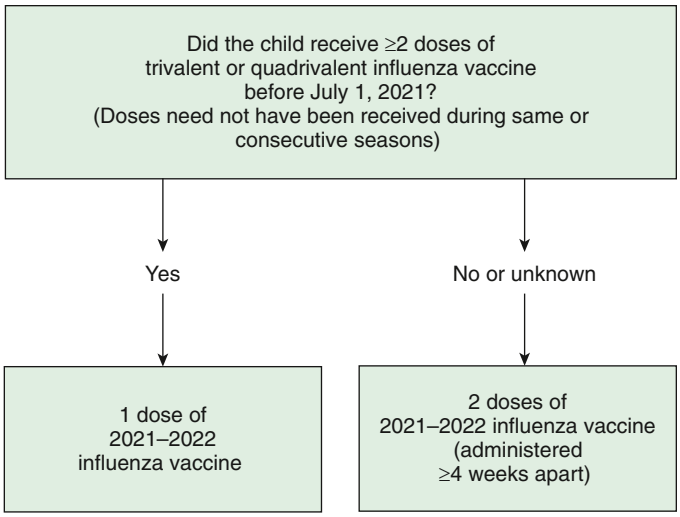

Fig. 305.3 Influenza vaccine dosing algorithm for children age 6 mo through 8 yr*—Advisory Committee on Immunization Practices, United States, 2021–2022 influenza season. *For children age 8 years who require two doses of vaccine, both dosages should be administered even if the child turns age 9 yr between receipt of dose 1 and dose 2. *(From Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices—United States, 2021-22 Influenza Season. MMWR Recomm Rep. 2021;70[No. RR-5]:1–28.)*

Ideally, vaccination should be given before the onset of influenza circulation in the community, so that there is time for antibodies to reach protective levels. Healthcare providers should offer vaccination by the end of October, if possible. The ACIP publishes guidelines for vaccine use each year when the vaccines are formulated and released; these guidelines should be referred to each season. The ACIP guidelines are widely publicized but appear initially in the *Morbidity and Mortality Weekly Report* published by CDC (https://www.cdc.gov/flu/index.htm).

Chemoprophylaxis

Routine use of antiviral medications for chemoprophylaxis is not recommended. Examples for which the use of chemoprophylaxis may be considered to prevent influenza after exposure to an infectious person include (1) unvaccinated persons at high risk of influenza complications, (2) persons for whom vaccine is contraindicated or expected to have low effectiveness, and (3) residents/patients in care facilities during institutional influenza outbreaks. Oral oseltamivir or inhaled zanamivir may be used for chemoprophylaxis of influenza; baloxavir is approved for postexposure prophylaxis in persons 12 years of age and older. Peramivir is not recommended for chemoprophylaxis because of a lack of data, and adamantanes are not currently recommended because of widespread adamantane resistance. Table 305.4 shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2021–2022 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (https://www.cdc.gov/flu/professionals/antivirals/index.htm).

In general, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 305.3) should be started within 48 hours of exposure to an infectious person and should be continued for 7 days after the last known exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop.

For control of influenza outbreaks among high-risk persons living in institutional settings, such as long-term care facilities, antiviral chemoprophylaxis is recommended for all vaccinated and unvaccinated residents and for unvaccinated healthcare providers. In these circumstances, CDC and the Infectious Diseases Society of America recommend antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the last known case is identified, whichever is longer.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 306

Parainfluenza Viruses

Fiona P. Havers and Angela J.P. Campbell

Human parainfluenza viruses (HPIVs) are common causes of acute respiratory illness in infants and children and are important causes of lower respiratory tract disease in young children and immunocompromised persons. These viruses cause a spectrum of upper and lower respiratory tract illnesses but are particularly associated with **croup** (laryngotracheitis or laryngotracheobronchitis), **bronchiolitis**, and **pneumonia**.

ETIOLOGY

HPIVs are members of the **Paramyxoviridae** family. Four HPIVs cause illness in humans, classified as types 1-4, with diverse manifestations of infection. Type 4 is divided into two antigenic subtypes: 4a and 4b. HPIVs have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope derived from budding through the host cell membrane. The major antigenic moieties are the hemagglutinin neuraminidase (HN) and fusion (F) surface glycoproteins.

EPIDEMIOLOGY

By 5 years of age, most children have experienced primary infection with HPIV types 1, 2, and 3. HPIV-3 infections generally occur earliest, with half of infants infected by age 1 year and over 90% by age 5 years. HPIV-1 and HPIV-2 are more common after infancy, with approximately 75% infected by age 5 years. With increased use of multiplex molecular testing and more frequent addition of HPIV-4 as a panel target, HPIV-4 is more frequently recognized and appears to occur earlier in life than HPIV-1 and -2. In the United States and temperate climates, HPIV-1 has typically been reported to have biennial epidemics in the fall in odd-numbered years, whereas HPIV-2 has biennial outbreaks in the fall of even-numbered years, with peaks that are not as high as HPIV-1 or HPIV-3 (Fig. 306.1). HPIV-3 can be endemic throughout the year but typically peaks yearly in late spring or early summer. In years with less HPIV-1 activity, the HPIV-3 season has been observed to extend longer or to have a second peak in the fall (see Fig. 306.1). The epidemiology of HPIV-4 was historically less well defined, but with an increase in molecular detection, it has been found to have yearly peaks starting in the fall and peaking in winter (see Fig. 306.1).

Similar to what has been observed for other non–SARS-CoV-2 respiratory viruses, during the COVID-19 pandemic in 2020 and early 2021, HPIVs circulated at levels lower than prior years. However, HPIVs began increasing in the United States in spring of 2021 and, for HPIV types 1, 3, and 4, circulation patterns in 2022 and through fall 2023 were similar to pre-pandemic seasons; HPIV-2 continued to circulate at lower levels during that period. National HPIV trends are created from weekly laboratory test result data that are reported on a voluntary basis and are available at the Centers for Disease Control and Prevention (CDC) National Respiratory and Enteric Virus Surveillance System (NREVSS) website (https://www.cdc.gov/surveillance/nrevss).

HPIVs are spread primarily from the respiratory tract of an infected person by inhalation of large respiratory droplets or contact with infected nasopharyngeal secretions. HPIVs are notable for causing **outbreaks** of respiratory illness in hospital wards, clinics, neonatal nurseries, and other institutional settings. The incubation period from exposure to symptom onset may range from 2 to 6 days. Children are likely to excrete virus from the oropharynx for 2-3 weeks, but shedding can be more prolonged, especially in immunocompromised children, and may persist for months. Primary infection does not confer permanent immunity, and reinfections are common throughout life. Reinfections are usually mild and self-limited but can cause serious lower respiratory tract illness, particularly in children with compromised immune systems.

PATHOGENESIS

HPIVs replicate in the respiratory epithelium. The propensity to cause illness in the upper large airways is presumably related to preferential replication in the larynx, trachea, and bronchi in comparison with other viruses. Some HPIVs induce cell-to-cell fusion. During the budding process, cell membrane integrity is lost, and viruses can induce cell death through the process of apoptosis. In children, the most severe illness generally coincides with the time of maximal viral shedding. However, disease severity is likely related to the host immune response to infection as much as to direct cytopathic effects of the virus. Virus-specific immunoglobulin A antibody levels and serum antibodies to the surface HN and F glycoproteins are able to neutralize HPIV, and both likely contribute to host immunity. Cell-mediated cytotoxicity is also important for controlling and terminating HPIV infection.

CLINICAL MANIFESTATIONS

The most common type of illness caused by HPIV infection consists of some combination of low-grade fever, rhinorrhea, cough, pharyngitis, and hoarseness and may be associated with vomiting or diarrhea. Rarely, HPIV infection is associated with parotitis. HPIVs have also been associated with a variety of skin manifestations, including typical maculopapular viral exanthems, erythema multiforme, and papular acrodermatitis, or Gianotti-Crosti syndrome (see Chapter 708). Although often mild, more serious HPIV illness may result in hospitalization, with common discharge diagnoses of bronchiolitis, fever/possible sepsis, and apnea among younger children and croup, pneumonia, and asthma among older children (Fig. 306.2). HPIVs account for 50% of hospitalizations for croup and at least 15% of cases of bronchiolitis and pneumonia. HPIV-1 and HPIV-2 cause more cases of croup, whereas HPIV-3 is more likely to infect the small air passages of the lower respiratory tract and cause pneumonia, bronchiolitis, or bronchitis. HPIV-4 causes a similar range of illness as the other types, and with advancements in molecular diagnosis, there is evidence that HPIV-4 may be comparable to HPIV-3 and frequently associated with acute lower respiratory infection (ALRI).

In fact, any HPIV can cause lower respiratory tract disease, particularly during primary infection or in patients with compromised immune systems. In children and adult patients with hematologic malignancies and undergoing hematopoietic stem cell transplantation, lymphopenia has repeatedly been shown to be an independent risk factor for progression from upper to lower respiratory tract disease. Recently, the first global burden estimates of HPIV-associated and HPIV-attributable ALRI were generated, with approximately 13% of ALRI cases, 4–14% of ALRI hospital admissions, and 4% of childhood ALRI mortality attributable to HPIV.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of HPIV infection in children is often based solely on clinical and epidemiologic criteria. Croup is a clinical diagnosis and must be distinguished from other diagnoses, including foreign body aspiration, epiglottitis, retropharyngeal abscess, angioedema, and subglottic stenosis or hemangioma. Although the radiographic "**steeple sign**," consisting of progressive narrowing of the subglottic region of the trachea, is characteristic of croup, differential considerations include acute epiglottitis, thermal injury, angioedema, and bacterial tracheitis. Manifestation of HPIV lower respiratory tract disease may be similar to that of a number of other respiratory viral infections; therefore virus identification should be sought by the most sensitive diagnostic means available for certain severe illnesses, such as pneumonia in immunocompromised children.

Sensitive, specific, and rapid molecular assays such as multiplex polymerase chain reaction assays have become more widely available

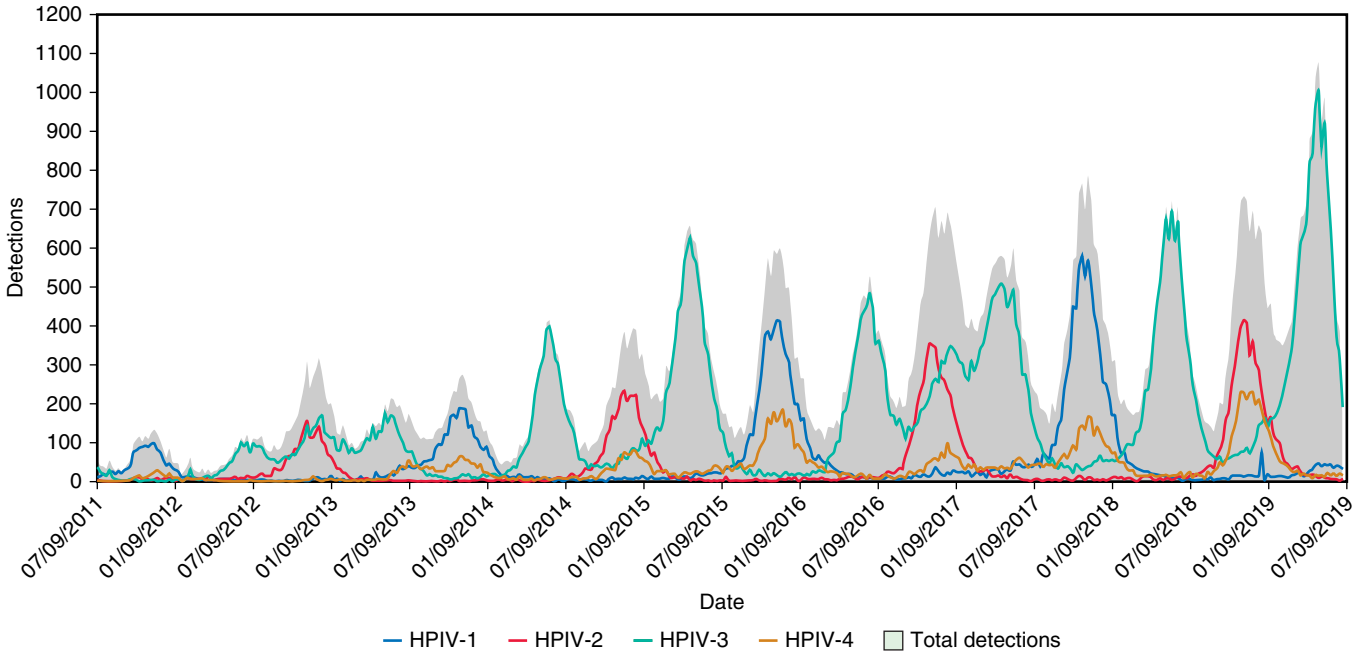

Fig. 306.1 Human parainfluenza virus (HPIV) circulation, National Enteric and Respiratory Virus Surveillance System, United States Census Regions, 2011–2019. *(From DeGroote NP, Haynes AK, Taylor C, et al. Human parainfluenza virus circulation, United States, 2011–2019. J Clin Virol. 2020;124:104261. Fig. 1.)*

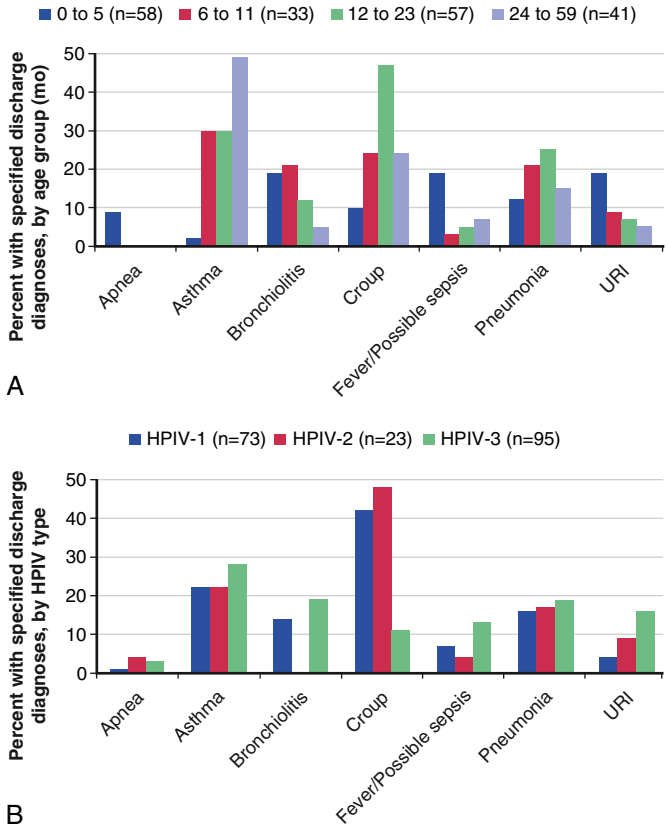

Fig. 306.2 Selected discharge diagnoses of hospitalized children with parainfluenza (HPIV) infection, by age in months (A) and virus type (B). *(Data from Weinberg GA, Hall CB, Iwane MK, et al. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization. J Pediatr. 2009;154:694–699, Table II)*

and greatly increase sensitivity of HPIV detection. For immunocompromised patients, these highly sensitive platforms provide the critical ability to make a prompt diagnosis by detecting a wide range of viral pathogens, including HPIVs, thus allowing for early implementation of infection prevention measures and potential treatment. Other laboratory diagnosis methods are available, such as isolation in tissue culture and direct immunofluorescent staining for identification of virus antigens in respiratory secretions, but these have been used less frequently given the increasing availability of molecular assays.

TREATMENT

There are no specific antiviral medications approved for the treatment of HPIV infections. For croup, the possibility of rapid respiratory compromise should influence the level of care and treatment given (see Chapter 433). The **severity assessment** of croup generally incorporates a number of clinical features, which include the presence and degree of chest wall retractions, whether stridor is present at rest, and evaluation of the child's mental status (e.g., for agitation, anxiety, lethargy).

Humidified air has not been shown to be significantly effective in reducing symptom severity. **Glucocorticoids** improve symptoms at 2 hours after treatment, lessen the need for other medications, and shorten hospital stays. **In general, because of its safety, efficacy, and cost-effectiveness, a single dose of oral dexamethasone (0.15 to 0.6 mg/kg) is the primary treatment for mild croup in the office or emergency room setting.** Oral prednisolone (1 mg/kg) is an acceptable alternative in this setting, particularly if dexamethasone is not available; however, in a meta-analysis, dexamethasone significantly reduced the rate of return visits and/or (re)admissions.

For obstructive airway symptoms associated with moderate to severe croup, corticosteroid therapy is recommended: oral dexamethasone (0.6 mg/kg) should be given if oral intake is tolerated. A single dose of intramuscular dexamethasone or budesonide (2 mg [2 mL solution] via nebulizer) may provide an alternative to oral dexamethasone for children with severe respiratory distress or vomiting. Alternatively, intravenous (IV) dexamethasone can be administered if IV access has been established. **Nebulized epinephrine (either racemic epinephrine 2.25% solution, 0.05 mL/kg/dose [up to maximum of 0.5 mL/dose] diluted to 3 mL with normal**

saline, or L-epinephrine using parenteral 1 mg/ml [1:1000] solution, 0.5 mL/kg/dose [up to maximum 5 mL/dose]) is also recommended and may provide temporary symptomatic improvement. Children should be observed for at least 2 hours after receiving epinephrine treatment for return of obstructive symptoms. Repeated treatments may be provided, depending on the duration of symptoms. The dexamethasone dose may be repeated, but this should not be necessary on a routine basis, and there are no guidelines to compare outcomes of single- and multiple-dose treatment schedules. Moderate to severe symptoms that persist for more than a few days should prompt investigation for other causes of airway obstruction. Oxygen should be administered for hypoxia, and supportive care with analgesics and antipyretics is reasonable for fever and discomfort associated with HPIV infections. The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

Ribavirin has some antiviral activity against HPIVs in vitro and in animal models. Inhaled ribavirin has been given to severely immunocompromised children with HPIV pneumonia; however, the majority of data have not shown improved outcomes, and randomized controlled studies are lacking. Some institutions use intravenous immunoglobulin for HPIV pneumonia in children with hematologic malignancies or who have undergone hematopoietic stem cell transplantation; the impact of this treatment strategy on clinical outcomes is also limited by lack of controlled studies. Use of DAS181, a novel sialidase fusion protein inhibitor, has shown clinical potential in a phase 2 clinical trial when used for treatment of HPIV lower respiratory tract disease among solid organ and hematopoietic stem cell transplant recipients, and a phase 3 trial is ongoing. Other potential strategies for drug development include hemagglutinin-neuraminidase inhibitors, transcription inhibitors, and synthetic small interfering RNAs.

COMPLICATIONS

Eustachian tube obstruction can lead to secondary bacterial invasion of the middle ear space and acute otitis media in 30–50% of HPIV infections. Similarly, obstruction of the paranasal sinuses can lead to sinusitis. The destruction of cells in the upper airways can lead to secondary bacterial invasion and resultant bacterial tracheitis, and antecedent HPIV infection of lower airways may predispose to bacterial pneumonia. Nonrespiratory complications of HPIV are rare but include aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, rhabdomyolysis, myocarditis, and pericarditis.

PROGNOSIS

The prognosis for full recovery from HPIV infection in the immunocompetent child is generally excellent, with no long-term pulmonary sequelae. Deaths may rarely occur, particularly in immunocompromised children with lower respiratory tract infection.

PREVENTION

Vaccine development has focused largely on live-attenuated intranasal HPIV-3 vaccines. Candidates include a recombinant human HPIV-3 virus (rcp45) derived from complementary DNA, as well as a complementary DNA–derived chimeric bovine/human HPIV-3 virus; these candidates are well tolerated and immunogenic in infants and young children. Constructs using chimeric bovine/human HPIV-3 virus in addition to the F or both F and G proteins of respiratory syncytial virus (RSV) have been investigated. A combined messenger RNA (mRNA) vaccine against HPIV-3 and human metapneumovirus has completed phase 1 clinical trials. Live attenuated candidate HPIV-1 and HPIV-2 vaccines have also undergone phase 1 clinical studies (www.clinicaltrials.gov). The measure of protection afforded by vaccines will be difficult to assess, because symptomatic reinfection occurs and the frequency of serious infection in the general population is low. Nonetheless, it is clear that prevention of acute respiratory illness caused by HPIVs, particularly lower respiratory tract infections among infants and young children, is a worthwhile goal.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 307

Respiratory Syncytial Virus

James E. Crowe Jr.

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 439) and viral pneumonia in children younger than 1 year of age and is the most important respiratory tract pathogen of early childhood.

ETIOLOGY

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Pneumoviridae, which comprises large enveloped, negative-sense RNA viruses. This taxon was formerly a subfamily within the Paramyxoviridae but was reclassified in 2016 as a family with two genera, *Orthopneumovirus* (which includes RSV) and *Metapneumovirus* (which includes human metapneumovirus; see Chapter 308). There are two antigenic subgroups of RSV (subgroups A and B), distinguished based primarily on sequence and antigenic variation in one of the two surface proteins, the G glycoprotein that is responsible for attachment to host cells. Sequence analysis of cDNAs of the full G glycoprotein ectodomain region allows clustering of sequence patterns and identification of molecular markers that can be used to assign genotypes, subgenotypes, and lineages. There is no unified classification scheme for genotypes, so reports differ in the number of genotypes in circulation. The observed genotypic variation, which also can alter antigenic properties at the protein level, is caused by point mutations from infidelity of the viral RNA polymerase and may contribute to some degree to the frequency with which RSV reinfects children and adults. However, adult human challenge experiments have shown that the same RSV strain can reinfect in the upper respiratory tract repetitively, suggesting that mucosal immunity in that site is incomplete or short-lived.

RSV replicates in a wide variety of cell line monolayer cultures in the laboratory. In HeLa and HEp-2 cell monolayers, the virus causes cell-to-cell fusion that produces characteristic cytopathology called syncytia (multinucleate enlarged cells), from which the virus derives its name. Identification of syncytia in diagnostic cultures of respiratory secretions is helpful in identifying RSV, but it is not clear whether syncytium formation occurs to any significant degree in the airway epithelium in patients.

EPIDEMIOLOGY

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over a 4- to 5-month period. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during the winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza virus or human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 months of age. In the tropics, the epidemic pattern is less clear. The pattern of widespread annual outbreaks and the high incidence of infection during the first 3-4 months of life are unique among human viruses. The conventional seasonality of RSV outbreaks was altered in 2020–2021 by events associated with the COVID-19 pandemic. Delayed and out-of-season RSV epidemics occurred during the COVID-19 pandemic when reopening activities

occurred after a long period of reduced transmission due to nonpharmaceutical interventions such as masking, distancing, and daycare and school closure reduced transmission.

Transplacentally acquired anti-RSV maternal immunoglobulin G (IgG) serum antibodies, if present in high concentration, appear to provide partial protection for the neonate. The age of peak incidence of severe lower respiratory tract disease and hospitalization is about 6 weeks. Maternal IgGs may account for the lower severity and incidence of RSV infections during the first 4-6 weeks of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides some protection against severe disease, an effect that may pertain only to female and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their second birthday. Reinfection occurs at a rate of at least 10–20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60–80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower than that in first infection and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree, with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5–4%, depending on region, sex, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the two processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 weeks to 7 months of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the first birthday. The terminology used for the diagnosis of virus-associated wheezing illnesses in toddlers can be confusing, because these illnesses are variably termed *wheezing-associated respiratory infection, wheezy bronchitis, exacerbation of reactive airways disease,* or *asthma attack*. Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term *asthma* only later in life. It is still uncertain if RSV-associated wheezing illness in infancy causes asthma in later life. On the whole, prevention of severe RSV illness in high-risk infants using RSV monoclonal antibody prophylaxis does not seem to reduce the incidence of asthma in those populations significantly. Whether a vaccine will have such an effect in the future is still to be determined.

Acute viral pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the first year. RSV plays a causative role in an estimated 40–75% of cases of hospitalized bronchiolitis, 15–40% of cases of childhood pneumonia, and 6–15% of cases of croup. Bronchiolitis and pneumonia resulting from RSV are more common in males than in females by a ratio of approximately 1.5:1. Other risk factors with a similar impact in the United States include one or more siblings in the home, White race, rural residence, maternal smoking, and maternal education <12 years. The medical factors in infants associated with the highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on the severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious viruses for 1-2 weeks after hospital admission. Excretion for 3 weeks and even longer has been documented. Spread of infection occurs when large infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren experiencing reinfection. Typically, in the space of a few days, 25–50% of older siblings and one or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults experiencing reinfection also have been implicated in the spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, because the virus is not spread by small particle aerosol to an appreciable degree, and a distance of about 6 ft is likely sufficient to avoid aerosol transmission. During the COVID-19 pandemic, widespread social measures, including masking and distancing, appeared to prevent transmission of RSV on a world-wide basis. However, in normal circumstances, adherence to isolation procedures by caregivers often is not complete.

PATHOGENESIS

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchioles; airway resistance is proportional to $1/\text{radius}^4$. There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in the formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells (mostly containing cytolytic T cells) is a double-edged sword, reducing the cells producing virus but also causing host cell death in the process. Many soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that co-infection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

CLINICAL MANIFESTATIONS

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with an increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual, and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently, and the chest radiographs may show air trapping.

Fever is an inconsistent sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion but rather appears to be a consequence of alterations in the central control of breathing.

RSV infections in profoundly immunocompromised hosts or those with chronic lung disease or pulmonary hypertension may be severe at any age of life. The mortality rates associated with RSV pneumonia in the first few weeks after hematopoietic stem cell or solid-organ transplantation in both children and adults are high. RSV infection does not appear to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus in respiratory secretions for prolonged periods.

Secondary (associated) bacterial infections are uncommon in most previously healthy patients with RSV bronchiolitis. However, otitis media may be present because of either RSV or bacterial middle ear infection.

DIAGNOSIS

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty based on the season of the year and the presence of the virus in the community. Other epidemiologic features that may be helpful are the presence of common colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the first few months of life are human metapneumovirus, influenza viruses, parainfluenza virus type 3, rhinoviruses, enteroviruses, and coronaviruses.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood carbon dioxide value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to differentiate viral infection from bacterial or chlamydial infection. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 months of age, interstitial pneumonitis may be caused by *Chlamydia trachomatis* (see Chapter 272). With *C. trachomatis* pneumonia, there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

The definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. Molecular diagnostic tests are more available, however. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than virus culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but are acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. RSV is thermolabile, so it degrades over relatively short periods of time unless it is frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

TREATMENT

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea. Humidified oxygen and suctioning usually are indicated for hospitalized infants who are hypoxic. High-flow nasal cannula (HFNC) therapy is used for respiratory distress either before or after admission to an intensive care unit. HFNC is often started based on the subjective assessment of work of breathing; despite HFNC use, it remains uncertain if the outcome of RSV bronchiolitis has been improved with HFNC. Nasal continuous positive airway pressure is used in the intensive care unit for infants who have increased work of breathing, and mechanical ventilation is used for respiratory failure.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, epinephrine, or β_2-agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit. The 2014 American Academy of Pediatrics bronchiolitis clinical practice guideline suggests limitations on the use of α- and β-adrenergic agents and corticosteroids.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to the development of antibiotic resistance. Interstitial pneumonia in infants 1-4 months old may be caused by *C. trachomatis,* and macrolide therapy may be indicated for that infection if identified by specific testing.

PROGNOSIS

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. However, it is estimated that more than 160,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

There is recurrent wheezing in 30–50% of children who have severe RSV bronchiolitis in infancy, and many older children who are diagnosed with asthma have a history of severe bronchiolitis in infancy. The likelihood of the recurrence of wheezing is increased in the presence

of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 year of age, there is an increasing probability that, although the episode may be virus-induced, the event is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the first year of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether persons destined to have asthma present with symptoms first when provoked by RSV infection during infancy. Results from a long-term follow-up study of infants who received palivizumab prophylaxis suggested that the prevention of severe RSV infection may reduce the incidence of reactive airways disease later in life.

PREVENTION

Prevention of Nosocomial Spread

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing (contact isolation) should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for the duration of hospitalization for most patients admitted for acute disease. Rapid antigen tests should not be used to determine whether a patient still requires isolation, because low concentrations of virus may be present in respiratory secretions that are infectious for humans but below the lower limit of detection for such assays. Ideally, patients with RSV or metapneumovirus infections are housed separately because co-infection with the two viruses may be associated with more severe disease.

Protection of Infants Against Infection or Severe Disease

Antibodies that neutralize RSV are the principal mechanism of protection against infection or reinfection. Antibodies are induced by natural infection but can also be provided to infants prior to a first infection in several ways. *First*, all mothers pass along their own naturally occurring IgG antibodies across the placenta beginning at about 28-32 weeks' gestation. *Second*, breastfeeding may transfer maternal antibodies (including IgA antibodies) to infant mucosal surfaces, providing benefit in some infants. *Third*, antibodies manufactured as biologic drugs can be administered directly to infants after birth. *Fourth*, maternal immunization with an approved RSV vaccine can increase the level of antibodies in the mother's serum and thus also the level of antibodies transferred across the placenta. The Advisory Committee on Immunization Practices (ACIP) in the United States recommends that either antibody administration to the infant or maternal vaccination during pregnancy should be used to prevent RSV-associated lower respiratory tract illness among all infants, but *both* exogenous antibodies and maternal vaccination are not needed for most infants.

Passive Immunoprophylaxis

A neutralizing humanized murine monoclonal antibody against RSV given IM once a month (palivizumab) has been approved for protecting high-risk children against serious complications from RSV disease. A next-generation monoclonal antibody (nirsevimab, Beyfortus, Sanofi and AstraZeneca) was subsequently approved for the prevention of lower respiratory tract infection caused by RSV in the European Union, United Kingdom, United States, and Canada. Nirsevimab is an RSV fusion-protein-specific monoclonal antibody with an extended half-life because of engineered changes in the antibody Fc region. Since the antibody is long-acting (with a half-life of about 3 months instead of 3 weeks as for conventional IgG), only a single dose is necessary to protect term, preterm, and high-risk infants for an entire RSV season. In the United States, nirsevimab is indicated for the prevention of RSV lower respiratory tract disease in neonates and infants <8 months born during or entering their first RSV season and in children 8–19 months of age at increased risk for severe RSV disease entering their second RSV season.

Nirsevimab is dispensed in prefill syringes of either 50 or 100 mg; the dose is 50 mg IM for infants < 5 kg, and 100 mg IM for infants < 8 months old and ≥ 5 kg. The first dose for infants <8 months of age may be given in the first week of life. For infants 8-19 months of age entering their second RSV season and at increased risk for severe RSV infection, the dose is 200 mg.

Because of a projected shortage of the 100 mg dose, it is recommended that only infants ≥ 5kg who are at high risk for severe RSV infection receive the 100 mg dose. High risk patients are defined as:

- Infants < 6 months
- American Indian and Alaska Natives < 8 months
- Infants age 6 to < 8 months with prematurity (< 29 weeks), chronic lung disease of prematurity, hemodynamically significant congenital heart disease, severe immunocompromise, cystic fibrosis, neuromuscular disease, or congenital pulmonary abnormalities that impair the ability to clear secretions

Palivizumab should be administered only to high risk infants (8-19 months old) and to eligible infants <8 months old if nirsevimab is not available.

Administration of palivizumab (15 mg/kg intramuscularly once a month) is recommended for protecting high-risk children against serious complications from RSV disease. Palivizumab is administered from the beginning to the end of the RSV season. Palivizumab prophylaxis may be considered for the following infants and children:

- Infants born before 29 wk of gestation in the first year of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required > 21% Fio_2 [fraction of inspired oxygen] for ≥ 28 days after birth), in the first year of life and in the second RSV season if continued medical support (oxygen, diuretics, steroids) is needed
- Infants younger than 1 yr of age with hemodynamically *significant* acyanotic congenital heart disease or those with moderate to severe pulmonary hypertension and those patients following cardiac transplantation (children < 2 yr of age)
- Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
- Infants in the first year of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises the handling of respiratory secretions

Vaccine

There are two licensed subunit protein vaccines against RSV for older adults (Abrysvo, Pfizer; Arexvy, GSK) based on a prefusion conformation of the RSV fusion (F) protein (RSVpreF). The bivalent RSVpreF Abrysvo vaccine has subunit proteins for both the type A and type B RSV antigenic subgroups, while the Arexvy vaccine contains only subgroup A antigen combined with an adjuvant. Neither vaccine is approved for use in infants or children, but Abrysvo is used in pregnant mothers 32-36 weeks pregnant during RSV season with the goal to protect infants. The mechanism of protection is that the resulting increased serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of those maternal RSV antibodies to the fetus. In efficacy trials, this vaccination reduced the incidence of medically attended RSV lower respiratory tract infections and hospitalization within 90 days after birth. The Abrysvo vaccine is recommended during September through January for most of the United States. since RSV typically peaks in fall and winter. The seasonality of RSV season varies depending on location, and thus state, local, or territorial health departments may recommend different timing for administration in diverse areas. The risk of severe RSV is even greater in infants born at <32 weeks' gestation. When Abrysvo was compared to placebo in clinical trials, infants born to pregnant individuals experienced low birth weight (5.1% Abrysvo compared to 4.4% placebo, a difference that was not statistically significant). The European Medicines Agency chose to approve maternal immunization with Abrysvo between weeks 24 and 36 of gestation, while the US FDA chose to approve the vaccine between weeks 32 and 36 of gestation while awaiting additional safety information from ongoing studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 308

Human Metapneumovirus

James E. Crowe Jr.

ETIOLOGY

Human metapneumovirus (HMPV) is a respiratory virus that is one of the most common causes of serious lower respiratory tract illness in children throughout the world.

ETIOLOGY

HMPV is an enveloped, single-stranded, nonsegmented, negative-sense RNA genome of the family Pneumoviridae, which comprises large enveloped negative-sense RNA viruses. This taxon was formerly a subfamily within the Paramyxoviridae but was reclassified in 2016 as a family with two genera: *Metapneumovirus* (which includes HMPV) and *Orthopneumovirus* (which includes respiratory syncytial virus [RSV]; see Chapter 307). HMPV and the avian pneumoviruses are highly related and are separated into the separate genus *Metapneumovirus* because the gene order in the nonsegmented genome is slightly altered and because avian pneumoviruses/HMPVs lack the genes for two nonstructural proteins, NS1 and NS2, which are encoded at the 3′ end of RSV genomes. These proteins are thought to counteract host type I interferons. The absence of NS1/NS2 in the metapneumoviruses (compared with RSV) may contribute to an overall slightly reduced pathogenicity relative to wild-type RSV strains.

The HMPV genome encodes nine proteins in the order 3′-N-P-M-F-M2-(orf1 and 2)-SH-G-L-5′. The genome also contains noncoding 3′ leader, 5′ trailer, and intergenic regions, consistent with the organization of most paramyxoviruses, with a viral promoter contained in the 3′ end of the genome. The F (fusion), G (glycosylated), and SH (short hydrophobic) proteins are integral membrane proteins on the surfaces of infected cells and virion particles. The F protein is a classic type I integral membrane viral fusion protein that contains two heptad repeats in the extracellular domain that facilitate membrane fusion. There is a predicted protein cleavage site near a hydrophobic fusion peptide that likely is cleaved by an extracellular protease, activating the F protein for fusion. The predicted attachment (G) protein of HMPV exhibits the basic features of a glycosylated type II mucin-like protein. The HMPV G protein differs from the RSV G protein that inhibits innate immune responses in that the HMPV G lacks a cysteine noose structure. The internal proteins of the virus appear similar in function to those of other paramyxoviruses.

EPIDEMIOLOGY

HMPV outbreaks occur in annual epidemics during late winter and early spring in temperate climates, often overlapping with the second half of the annual RSV epidemic (Fig. 308.1). Sporadic infections occur year-round. A near-total decline of HMPV infections occurred in the 2020–2021 winter associated with COVID-19 public health measures, followed by a delayed or interseasonal outbreak in 2021. The usual period of viral shedding is likely to be many days or even several weeks after primary infection in infants. The incubation period is approximately 3-5 days. Humans are the only source of the virus; there is no known animal or environmental reservoir. Transmission occurs by close or direct contact with contaminated secretions involving large-particle aerosols, droplets, or contaminated surfaces. Nosocomial infections have been reported, and contact isolation with excellent handwashing for healthcare providers is critical in medical settings. This virus also affects the elderly, immunocompromised patients, and patients with reactive airways disease more severely than otherwise healthy individuals.

PATHOLOGY

Infection is usually limited to the superficial layer of airway epithelial cells and is associated with a local inflammatory infiltrate consisting of lymphocytes and macrophages. Immunocompromised individuals have evidence of both acute and organizing injuries during prolonged infection.

PATHOGENESIS

Infection occurs via inoculation of the upper respiratory tract. Infection can spread rapidly to the lower respiratory tract, but it is not clear whether the dissemination is mediated by cell-to-cell spread or by aspiration of infected materials from the upper tract. Severe lower respiratory tract illness, especially wheezing, occurs mainly during the first year of life, at a time when the airways are of a very small diameter and thus a high resistance. Maternal serum-neutralizing antibodies that cross the placenta may afford a relative protection against severe disease for several weeks or months after birth. Once infection is established, it is likely that cytotoxic T cells recognize and eliminate virus-infected cells, thus terminating the infection but also causing some cytopathology. The virus appears to have specific mechanisms for inhibiting T-cell responses during acute infection. Individuals with an underlying predisposition for reactive airways disease (including adults) are susceptible to severe wheezing during reinfection later in life, suggesting that HMPV may cause smooth muscle hyperactivity, inflammation, or increased mucus production in such individuals. Infection in otherwise healthy individuals resolves without apparent long-term consequences in most cases. HMPV infection is associated with exacerbations of asthma later in life.

CLINICAL MANIFESTATIONS

HMPV is associated with the common cold (complicated by otitis media in approximately 30% of cases) and with lower respiratory tract illnesses such as bronchiolitis, pneumonia, croup, and exacerbation of reactive airways disease. The profile of signs and symptoms caused by HMPV is similar to that caused by RSV (Table 308.1). Approximately 5–10% of outpatient lower respiratory tract illnesses in otherwise healthy young children are associated with HMPV infection, which is second in incidence only to RSV. Children with RSV or HMPV infection require supplemental oxygen and medical intensive care at similar frequencies.

About half of the cases of HMPV lower respiratory tract illness in children occur in the first 6 months of life, suggesting that young age is a major risk factor for severe disease. Both young adults and the elderly can have HMPV infection that requires medical care, including hospitalization, but severe disease occurs at much lower frequencies in adults than in young children. Severe disease in pediatric and older subjects is most common in immunocompromised patients or those with complications of preterm birth, congenital heart disease, and neuromuscular disease and can be fatal. A significant number of both adult and pediatric patients with asthma exacerbations have HMPV infection; it is not clear whether the virus causes long-term wheezing. RSV and HMPV co-infections have been reported; co-infections may be more severe than infection with a single virus, resulting in pediatric intensive care unit admissions. It is difficult to define true co-infections because these viral RNA genomes can be detected by a reverse transcriptase polymerase chain reaction (PCR) in respiratory secretions for at least several weeks after illness, even when virus shedding has terminated.

LABORATORY FINDINGS

The virus can be visualized only with electron microscopy. The virus grows in primary monkey kidney cells or LLC-MK2 cell-line or Vero cell-line monolayer cultures in reference or research laboratories, but efficient isolation of the virus requires an experienced laboratory technician. Conventional bright-field microscopy of infected cell monolayer cultures often reveals a cytopathic effect only after multiple passages in the cell culture. The characteristics of the cytopathic effect are not sufficiently distinct to allow identification of the virus on this basis alone, even by a trained observer. The most sensitive test for identification of HMPV in clinical samples is reverse transcriptase PCR, usually performed with primers directed to conserved viral genes. Detection by this modality is also available in some multiplex PCR tests for panels of respiratory viruses. Real-time reverse transcriptase PCR tests offer enhanced sensitivity and specificity, including assays designed to detect viruses from the four known genetic lineages. Direct

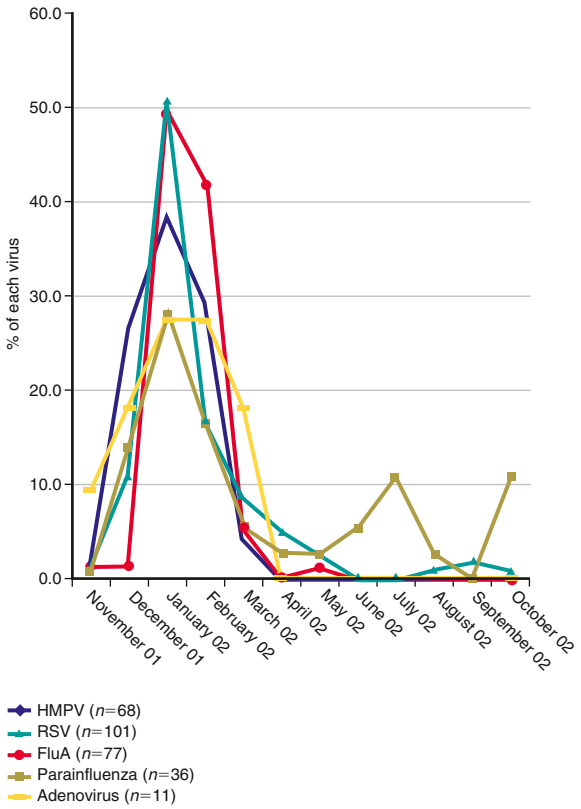

Fig. 308.1 Temporal distribution of respiratory viruses among children hospitalized with lower respiratory tract infections from November 2001 through October 2002. Data are displayed as the proportion of each virus detected monthly. FluA, influenza A; HMPV, human metapneumovirus; RSV, respiratory syncytial virus. *(From Wolf DG, Greenberg D, Kalkstein D, et al. Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. Pediatr Infect Dis J. 2006;25:320–324.)*

Table 308.1 Clinical Manifestations of Human Metapneumovirus in Children

COMMON (>50%)
Fever >38°C (100.4°F)
Cough
Rhinitis, coryza
Wheezing
Tachypnea, retractions
Hypoxia (O_2 saturation <94%)
Chest radiograph demonstration of infiltrates or hyperinflation
LESS COMMON
Otitis media
Pharyngitis
Rales
RARE
Conjunctivitis
Hoarseness
Encephalitis
Fatal respiratory failure in immunocompromised children

antigen tests for identification of HMPV antigens in nasopharyngeal secretions are available but are less efficient than nucleic acid–based detection. Some laboratories have success with the use of immunofluorescence staining with monoclonal or polyclonal antibodies to detect HMPV in nasopharyngeal secretions and shell vial cultures or in monolayer cultures in which virus has been cultivated, with reported sensitivities varying from about 65% to 90%. A fourfold rise in serum antibody titer to HMPV from the acute to convalescent time point can be used in research settings to confirm infection.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In temperate areas, the diagnosis should be suspected during the late winter in infants or young children with wheezing or pneumonia and a negative RSV diagnostic test result. The diseases caused by RSV and HMPV cannot be distinguished clinically. Many other common respiratory viruses, such as parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses, can cause similar disease in young children. Some of these viruses can be identified by PCR genetic testing or conventional cell culture means. Chest radiographs are not very specific, mostly showing parahilar opacities, hyperinflation, atelectasis, and, occasionally, consolidation but not pleural effusion or pneumothorax.

COMPLICATIONS

Bacterial superinfection of the lower airways is unusual but does occur. The local complication of otitis media is common, likely a result of eustachian tube dysfunction caused by the virus.

TREATMENT

There is no specific treatment currently for HMPV infection. A single small-molecule drug inhibitor for HMPV is in clinical trials as of early 2022. Management consists of supportive care like that used for RSV (see Chapter 307). The rate of bacterial lung infection or bacteremia associated with HMPV infection is not fully defined but is suspected to be low. Antibiotics are usually not indicated in the treatment of infants hospitalized for HMPV bronchiolitis or pneumonia.

Supportive Care

Treatment is supportive and includes careful attention to hydration; monitoring of respiratory status by physical examination and measurement of oxygen saturation; the use of supplemental oxygen, high-flow nasal cannula therapy, and nasal continuous positive airway pressure in an intensive care unit for increased work of breathing; and, in the case of respiratory failure, mechanical ventilation.

PROGNOSIS

Most infants and children recover from acute HMPV infection without apparent long-term consequences. Many experts believe an association exists between severe HMPV infections in infancy and the risk for recurrent wheezing or the development of asthma; however, it is not clear whether the virus causes these conditions or precipitates their first manifestations.

PREVENTION

The only method of prevention of HMPV infection is reduction of exposure. Contact precautions are recommended for the duration of HMPV-associated illness among hospitalized infants and young children. The near-total absence of HMPV infections during the first year of the COVID-19 pandemic suggests that nonpharmacologic interventions (such as masking and distancing) are effective when compliance is high. Patients known to have HMPV infection should be housed in single rooms or with a cohort of HMPV-infected patients. When feasible, it is wise to care for patients with RSV infection in a separate cohort from HMPV-infected patients to prevent co-infection, which may be associated with more severe disease. Preventive measures include limiting exposure to contagious settings during annual epidemics (such as daycare centers) as much as possible and an emphasis on hand hygiene in all settings, including the home, especially during periods when the contacts of high-risk children have respiratory infections. However, providers should keep in mind that infection is universal in the first several years of life. Therefore reduction of exposure makes the most sense during the first 6 months of life, when infants are at the highest risk for severe disease. Experimental HMPV vaccine candidates using live attenuated viruses or a messenger RNA (mRNA)–encoded HMPV fusion protein gene are under study.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 309

Adenoviruses

Terri L. Stillwell and Jason B. Weinberg

Human adenoviruses (HAdVs) are a common cause of human disease. Conjunctivitis is a familiar illness associated with the HAdVs, but these viruses also cause upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. HAdVs can cause severe disease in immunocompromised hosts. Outbreaks of HAdV infection occur in communities and closed populations, notably the military. No currently approved antiviral drugs are highly effective against HAdVs. Vaccines are available for HAdV types 4 and 7 but are used only in military populations.

ETIOLOGY

Adenoviruses are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA viral genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion and genomic sequencing define over 100 types, grouped into seven species. HAdV species differ in their tissue tropism and target organs, causing distinct clinical infections (Table 309.1). HAdVs can be shed from the gastrointestinal and respiratory tracts for prolonged periods and can establish persistent infection in mucosal lymphoid tissue.

EPIDEMIOLOGY

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease can occur, especially in schools, congregate living arrangements, and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are major sources of morbidity in military barracks, with attack rates ranging from 25% to over 90%. HAdV spread occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

PATHOGENESIS

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Progeny virion particles assemble in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by those cells of numerous cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but the strict species specificity of the adenoviruses has hindered detailed studies of HAdV pathogenesis in animal models. Studies using HAdV in Syrian hamsters, which are permissive for HAdV replication, and in a humanized mouse model have provided some insight. Mouse adenoviruses have also been used to study adenovirus pathogenesis using a murine model.

CLINICAL MANIFESTATIONS

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to reliably distinguish from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A *Streptococcus*, and other common viral and bacterial pathogens.

Acute Respiratory Disease

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5–10% of all childhood respiratory diseases. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may present with features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV infection typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15–20% of children with isolated pharyngitis, mostly in preschool children and infants.

Ocular Infections

The common follicular conjunctivitis caused by HAdV infection is self-limiting and requires no specific treatment. A more severe form called **epidemic keratoconjunctivitis** involves the cornea and conjunctiva. **Pharyngoconjunctival fever** is a distinct syndrome that includes a high temperature, pharyngitis, nonpurulent conjunctivitis, and preauricular and cervical lymphadenopathy.

Gastrointestinal Infections

HAdV can be detected in the stools of 5–10% of children with acute diarrhea. Most cases of acute diarrhea are self-limiting, although severe disease can occur. Enteric infection with HAdV is often asymptomatic, and shedding of virus after acute infection can be prolonged, so the causative role in these episodes is frequently uncertain. HAdV infection may also cause mesenteric adenitis.

Hemorrhagic Cystitis

Hemorrhagic cystitis consists of a sudden onset of hematuria, dysuria, frequency, and urgency with negative urine bacterial culture results. Urinalysis may show sterile pyuria in addition to hematuria. This illness occurs more frequently in young males and typically resolves on its own in 1-2 weeks.

Other Complications

Less frequently, HAdVs are associated with myocarditis, hepatitis, or meningoencephalitis in immunocompetent individuals.

Adenoviruses in Immunocompromised Patients

Immunocompromised persons, particularly recipients of hematopoietic stem cell transplants (HSCTs) and solid organ transplants, are at high risk for severe and fatal disease caused by HAdV. These patients may experience primary HAdV infection, but reactivation of persistent virus in a transplant recipient or transmission of virus from a donor organ may also occur. Organ failure as a consequence of pneumonia, hepatitis, gastroenteritis, and/or disseminated infection can occur in these immunocompromised patients. HAdV infection in HSCT recipients commonly manifests as pulmonary or disseminated disease and is most likely to occur in the first 100 days after transplantation. Hemorrhagic cystitis caused by HAdV can be severe in HSCT recipients. Infections caused by HAdV in solid organ transplant recipients usually involve the transplanted organ. Immunocompromised children are at greater risk than immunocompromised adults for complicated HAdV infection, presumably because of a lack of preexisting immunity. Additional risk factors include T-cell–depleted grafts, high-level immunosuppression, and the presence of graft-versus-host disease. Some experts advocate a preemptive screening approach to detect and treat HAdV infection early in immunocompromised patients, with the intent to prevent dissemination and severe illness in this vulnerable population, though no highly effective antiviral therapy exists.

DIAGNOSIS

HAdV may be suspected as the etiology of an illness on the basis of epidemiologic or clinical features, but neither of these categories is specific enough to firmly establish the diagnosis. The **frequency of asymptomatic shedding of HAdV** makes assigning causality to this pathogen

Table 309.1 Examples of Human Adenovirus Types and Common Manifestations of Disease

SPECIES	TYPE	COMMON DISEASE ASSOCIATIONS
A	12, 18, 31, 61	Gastroenteritis
B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66	Pharyngitis, pharyngoconjunctival fever, acute respiratory disease, pneumonia, hemorrhagic cystitis
C	1, 2, 5, 6, 57	Pharyngitis
D	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, 56, 58-60, 63-67, 69, 70-75	Epidemic keratoconjunctivitis
E	4	Acute respiratory disease
F	40, 41	Gastroenteritis
G	52	Gastroenteritis

difficult. Although most HAdV serotypes grow well in culture, culture-based identification requires several days and thus is not helpful for early identification, and most clinical microbiology laboratories no longer perform viral cultures on a routine basis. Cells from respiratory or ocular specimens can be tested using immunofluorescent staining with antibodies to detect HAdV protein. Commercially available enzyme-linked immunoassays can be used to rapidly detect HAdV in patient specimens, usually in stool. Multiplex molecular assays capable of identifying HAdV, in addition to other pathogens, are increasingly available and useful for rapid diagnosis. Specific diagnosis of HAdV infections are most clinically useful in immunocompromised hosts. In these patients, measurement of the **HAdV genome copy number (viral load)** using quantitative real-time polymerase chain reaction can facilitate diagnosis, and repeated measurements can aid in assessing a patient's response to treatment. Serology is generally useful only in epidemiologic investigations.

COMPLICATIONS

HAdV pneumonia can lead to respiratory failure requiring mechanical ventilation, especially in immunocompromised patients. Secondary bacterial pneumonia does not appear to be as common after HAdV infection as it is after influenza infection, but data that address this issue are limited. Severe HAdV pneumonia has been linked to chronic lung disease and bronchiolitis obliterans in a minority of cases. Epidemic keratoconjunctivitis is a vision-threatening form of HAdV infection. Nearly any form of HAdV infection can be fatal in an HSCT or solid organ transplant recipient. Refractory severe anemia requiring repeated blood transfusions can develop in HSCT recipients with hemorrhagic cystitis. Mortality rates of up to 60–80% have been reported in transplant recipients with disseminated HAdV or HAdV pneumonia.

TREATMENT

Supportive care is the mainstay of treatment for HAdV infections. Patients with severe HAdV conjunctivitis should be referred for ophthalmologic consultation. The nucleoside analog cidofovir has in vitro activity against most HAdV serotypes. Cidofovir is used topically to treat epidemic keratoconjunctivitis, often in conjunction with topical steroids or other immunosuppressive agents to limit the inflammatory component of the disease process. Cidofovir may be used intravenously for HAdV infections in immunocompromised patients. Cidofovir is highly nephrotoxic, but prehydration, concomitant administration of probenecid, and weekly dosing may reduce nephrotoxicity. Clinical studies suggest some benefit from cidofovir, but there are no prospective randomized controlled trials of cidofovir for HAdV infection. In addition, no formal guidelines or recommendations for treatment exist. The cidofovir derivative brincidofovir is better tolerated than cidofovir and has been evaluated as treatment of HAdV disease in immunocompromised patients, but it is not currently available for clinical use. Adoptive immunotherapy involving the infusion of HAdV-specific T cells may also provide some benefit for immunocompromised patients with life-threatening HAdV infections.

PREVENTION

Environmental and fomite transmission of HAdV occurs readily; therefore simple measures such as handwashing and cleaning are likely to reduce spread. Live-attenuated HAdV-4 and HAdV-7 vaccines were used effectively in the U.S. military from the 1970s until 1999. Cessation of their use led to widespread outbreaks in barracks, and those vaccines were subsequently reintroduced into military use. However, no HAdV-specific vaccines are available for routine use. HAdVs are highly immunogenic and have been used as gene therapy vectors and vaccine vectors for other pathogens, including malaria, HIV, and SARS-CoV-2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 310
Rhinoviruses

Katherine M. Richardson and Jennifer E. Schuster

Human rhinoviruses (HRVs) are the most frequent cause of the **common cold** in both adults and children. Although HRVs were once thought to cause only the common cold, it is now known that they are also associated with lower respiratory infections in adults and children. Many HRVs do not grow in culture. Recent studies using molecular diagnostic tools such as the polymerase chain reaction (PCR) have revealed that HRVs are leading causes of both mild and serious respiratory illnesses in children.

ETIOLOGY

HRVs are members of the Picornaviridae family ("pico" = small; "rna" = RNA genome). Traditional methods of virus typing using immune antiserum have identified approximately 100 serotypes, classified into HRVA, HRVB, and, recently, HRVC species based on the genetic sequence similarity. HRVCs can be detected by reverse transcriptase PCR but have been cultured only using highly specialized methods. Virus gene sequence analysis demonstrates that HRVCs are a genetically distinct and diverse species. The increased proportions of HRV reported in recent PCR-based studies are likely the result of detection of these previously unknown HRVC viruses in addition to improved detection of known HRVA and HRVB strains.

EPIDEMIOLOGY

Rhinoviruses are distributed worldwide. There is no consistent correlation between serotypes and epidemiologic or clinical characteristics. Several studies suggest that HRVCs may be more strongly associated with lower respiratory infection and asthma, and HRVC has been associated with children admitted to intensive care units with asthma exacerbations, bronchiolitis, and pneumonia. However, more studies are needed to determine severity compared with other HRVs. Multiple types circulate in a community simultaneously, and HRV strains may be isolated during consecutive epidemic seasons, suggesting persistence in a community over an extended period. In temperate climates, the incidence of HRV infection peaks in the fall, with another peak in the spring, but HRV infections occur year-round. HRVC appears to circulate with seasonal variation, exchanging dominance with HRVA. HRVs are the major infectious trigger for asthma among young children, and numerous studies have described a sharp increase in asthma attacks in this age-group when school opens in the fall. The peak HRV incidence in the tropics occurs during the rainy season, from June to October.

HRVs are present in high concentrations in nasal secretions and can be detected in the lower airways. HRV particles are nonenveloped and quite hardy, persisting for hours to days in secretions on hands or other surfaces such as telephones, light switches, doorknobs, and stethoscopes. Sneezing and coughing are inefficient methods of transfer. Transmission occurs when infected secretions carried on contaminated fingers are rubbed onto the nasal or conjunctival mucosa. HRVs are present in aerosols produced by talking, coughing, and sneezing. Children are the most important reservoir of these viruses.

PATHOGENESIS

The majority of HRVs infect respiratory epithelial cells via intercellular adhesion molecule-1, but some HRV strains utilize the low-density lipoprotein receptor. The receptor for HRVC is cadherin-related family member 3 (CDHR3); however, distinct genetic alleles encoding this protein confer different susceptibility to HRVC infection. Infection begins in the nasopharynx and spreads to the nasal mucosa and, in some cases, to bronchial epithelial cells in the lower airways. There is no direct cellular damage from the virus, and it is thought that many of the pathogenic effects are produced by the host immune response. Infected epithelial cells release a number of cytokines and chemokines, which induce an influx of neutrophils to the upper airway. Both innate and adaptive immune mechanisms are important in HRV pathogenesis and clearance. HRV-specific nasal immunoglobulin (Ig) A can be detected on day 3 after infection, followed by the production of serum IgM and IgG after 7-8 days. Neutralizing IgG to HRVs may prevent or limit the severity of illness after reinfection. However, cross protection by antibodies to different HRV serotypes is limited in breadth and duration, allowing recurrent infection. Both allergen exposure and elevated IgE values predispose patients with asthma to more severe respiratory symptoms in response to HRV infection. Abnormalities in the host cellular response to HRV infection that result in impaired apoptosis and increased viral replication may be responsible for the severe and prolonged symptoms in individuals with asthma.

CLINICAL MANIFESTATIONS

Most HRV infections produce clinical symptoms, but many are asymptomatic. Symptomatic HRV infection induces a much more robust host immune response in the blood than asymptomatic infection. After an incubation period of 1-4 days, typical symptoms of sneezing, nasal congestion, rhinorrhea, and sore throat develop. Cough and hoarseness are present in one third of cases. Fever is less common with HRV than with other common respiratory viruses, including influenza virus, respiratory syncytial virus (RSV), and human metapneumovirus. However, HRV was detected in 35% of febrile infants less than 90 days of age. Symptoms are frequently more severe and last longer in children, with 70% of children compared with 20% of adults still reporting symptoms by day 10. Virus can be shed for as long as 3 weeks. When HRV is detected >30 days from the initial illness, it is more likely to be a genotypically different strain of HRV. HRVA and HRVC are more commonly associated with symptomatic HRV infection compared with HRVB.

HRVs are the most prevalent agents associated with acute wheezing, otitis media, and hospitalization for respiratory illness in children and are an important cause of severe pneumonia and exacerbation of asthma or chronic obstructive pulmonary disease in adults. HRV-associated hospitalizations are more frequent in young infants than in older children and in children with a history of wheezing or asthma. Children hospitalized with HRV bronchiolitis are more likely to be older and have a history of wheezing than children with bronchiolitis caused by RSV. HRV infection in immunocompromised hosts may be life threatening. Certain strains or species of HRV, namely HRVC, may be more pathogenic than others.

DIAGNOSIS

Culturing HRVs is labor intensive and of relatively low yield. Sensitive and specific diagnostic methods based on reverse transcriptase PCR are commercially available. However, because commercially available reverse transcriptase PCR tests do not identify the HRV types, it can be difficult to distinguish prolonged shedding from newly acquired infection. An important caveat of HRV detection is the fact that HRV infection can be asymptomatic, and thus the presence of the virus does not prove causality in all cases. Serology is impractical because of the great number of HRV serotypes. A presumptive clinical diagnosis based on symptoms and seasonality is not specific, because many other viruses cause similar clinical illnesses. Rapid detection techniques for HRV might lessen the use of unnecessary antibiotics or procedures.

COMPLICATIONS

Possible complications of HRV infection include sinusitis, otitis media, asthma exacerbation, bronchiolitis, pneumonia, and, rarely, death. HRV-associated wheezing during infancy is a significant risk factor for the development of childhood asthma. In particular, this association has been noted with HRVA and HRVC, which have been associated with greater risk for recurrence of both wheezing and new infection with HRV. This effect appears to remain until adulthood, but the mechanisms have not been elucidated. One large study determined that genetic variants at the 17q21 locus were associated with asthma in children who had experienced HRV wheezing illnesses during infancy. A prospective study on a preterm cohort showed that a single nucleotide polymorphism on the gene coding for the vitamin D receptor was associated with development of lower respiratory infection with HRV. Further studies are required to determine the likely multiple genetic and environmental factors that contribute to HRV-related asthma.

TREATMENT

Supportive care is the mainstay of HRV treatment. The symptoms of HRV infection are commonly treated with analgesics, decongestants, antihistamines, or antitussives. Data are limited on the effectiveness of such nonprescription cold medications for children. If bacterial superinfections are highly suspected or diagnosed, antibiotics may be appropriate. Antibiotics are not indicated for uncomplicated viral upper respiratory infection. There are no licensed antivirals.

PREVENTION

Good handwashing remains the mainstay of the prevention of HRV infection and should be reinforced frequently, especially in young children, the predominant "vectors" for disease. Vaccines have not been successfully developed because of the numerous HRV serotypes and limited cross protection between serotypes. However, a polyvalent inactivated vaccine showed promise in a nonhuman primate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 311

Coronaviruses

Samuel R. Dominguez and Roberta L. DeBiasi

Coronaviruses are increasingly recognized as important human pathogens. Currently there are seven known coronaviruses that have been found to infect humans. Four coronaviruses are endemic in humans: human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. These CoVs cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis and might also be agents of meningitis or encephalitis. The fifth identified HCoV, SARS-associated coronavirus (SARS-CoV), the etiologic agent of severe acute respiratory syndrome (SARS), emerged in 2003 and caused a world-wide pandemic resulting in over 8,000 cases with an estimated case fatality rate of 10% before circulation ceased because of implementation of world-wide public health measures. Similarly, Middle East respiratory syndrome coronavirus (MERS-CoV), the sixth identified HCoV, first emerged in 2012 causing significant respiratory distress with very high mortality rates. MERS-CoV continues to cause local cases and outbreaks likely as a result of continued emergent events from its animal reservoir. Likely because of their high mortality, lower transmissibility, and lack of asymptomatic or presymptomatic spread, neither SARS-CoV nor MERS-CoV became endemic viruses.

In 2019 a seventh human coronavirus, SARS-CoV-2, emerged as the etiologic agent of novel coronavirus disease 2019 (COVID-19), resulting in a multiyear and ongoing global pandemic with multiple waves of circulating variants and disease burden exceeding any prior respiratory virus pandemic, including the 1918 influenza pandemic. The ultimate trajectory of SARS-CoV-2 global circulation is unclear, but it is likely that this virus will evolve to become the fifth endemic human coronavirus. The emergence of three distinct human coronaviruses resulting in world-wide pandemics in the past 2 decades emphasizes the potential for coronaviruses to emerge from animal hosts and become important human pathogens.

ETIOLOGY

Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of the spike protein, giving a corona or crownlike appearance on negative-stain electron microscopy. The human coronaviruses are all part of the order Nidovirales, suborder Cornidovirineae, family Coronaviridae, and subfamily Orthocoronavirinae. The subfamily Orthocoronavirinae is further subdivided into four genera based on genomic phylogenetic relationships. The genus alphacoronavirus includes HCoV-229E and HCoV-NL63. The remaining 5 HCoVs fall within the genus betacoronavirus. HCoV-OC43 and HCoV-HKU1 are in the subgenus Embecovirus, MERS-CoV is in the subgenus Merbecovirus, and SARS-CoV-1 and SARS-CoV-2 are in the subgenus Sarbecovirus (species severe acute respiratory syndrome-related coronavirus). Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

Coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related to SARS-CoV and are capable of infecting human cells. Thus SARS-CoV likely originated in bats and was transmitted to humans via an intermediary animal host such as the palm civet.

Another novel coronavirus, **MERS-CoV**, was first isolated from a man with acute pneumonia and renal failure in Saudi Arabia. As of late 2023, the World Health Organization (WHO) had recorded 2,605 confirmed cases of MERS in 27 countries, with 937 deaths worldwide (~36% mortality rate). MERS-CoV differs from SARS in that it seems to be less communicable, although human-to-human transmission has been documented. MERS-CoV uses dipeptidyl peptidase 4 and carcinoembryonic antigen–like cell-adhesion molecule 5 as its cellular receptor and co-receptor, respectively, whereas SARS-CoV and SARS-CoV-2 use the angiotensin-converting enzyme-2 receptor. With this receptor specificity, MERS-CoV can infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

EPIDEMIOLOGY

Endemic Coronaviruses

Seroprevalence studies have demonstrated that antibodies against endemic coronaviruses 229E and OC43 increase rapidly during early childhood, so that by adulthood 90–100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Seroprevalence studies have also suggested that prevalence rates may differ by geographic region. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age-groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-year alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often appear in coinfections with other respiratory viruses. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

SARS-CoV

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious,

with generally only two to four secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, "superspreaders," transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 years of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3-4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients.

MERS-CoV

As of late 2023, the WHO had recorded cases of MERS-CoV in 27 countries, all of which were linked to exposures in the Arabian Peninsula (~80% in Saudi Arabia). Though the route of transmission between animals and humans is not fully understood, MERS-CoV is proposed to have repeatedly entered the human population through contact with respiratory secretions of dromedary camels and possibly with raw camel products (e.g., unpasteurized milk). Antibodies to MERS-CoV are found in dromedaries throughout the Middle East, and strains identical to human MERS-CoV isolates have been found in camels in Egypt, Oman, Qatar, and Saudi Arabia. These strains do not appear to be highly pathogenic or virulent in camels and have likely circulated within dromedaries for >30 years. Despite well-documented zoonotic transmission, most reported cases occur through linked human-to-human transmission in healthcare settings, including outbreaks in Jordan, South Korea, and Saudi Arabia in 2015 and 2016. Risk factors for nosocomial MERS-CoV outbreaks include overcrowded emergency departments, delayed diagnosis or isolation, and poor infection control practices. Transmission most likely occurs through respiratory droplets and is thus a greater risk during aerosol-generating procedures. Outside of healthcare settings, human-to-human transmission has been infrequently documented and is primarily associated with close contact within households.

CLINICAL MANIFESTATIONS

Endemic Coronaviruses: Respiratory Manifestations

Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds and can cause fatal disease. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2-4 days, with symptoms typically lasting 4-7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 years of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency and severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Endemic Coronaviruses: Nonrespiratory Manifestations

There is prior evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units (ICUs) of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Additionally, more recent studies using PCR assays of stool from children with gastroenteritis have infrequently found HCoVs. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. Several studies have found an association of HCoVs, particularly HCoV-HKU1, with febrile seizures in young children. HCoVs have been detected by culture, in situ hybridization, and reverse-transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. HCoV-OC43 has been detected by RT-PCR in the spinal fluid, nasopharynx, or brain biopsy specimens of two children with acute encephalomyelitis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease.

Severe Acute Respiratory Syndrome–Associated Coronavirus

During the 2002–2003 global outbreak of SARS, the incubation period for SARS-CoV ranged from 1-14 days, with a median of 4-6 days. SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase, there was a progressive increase in viral load that reached its peak during the second week of illness. The appearance of specific antibodies coincided with peak viral replication. Clinical symptoms were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical deterioration that typified the second and third week of illness was characterized by a decline in the viral load and evidence of tissue injury, likely from cytokine-mediated immunity.

Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, myalgia, malaise, and headache. Following an initial improvement at the end of the first week, fever recurred, and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10–20% of patients, one third of whom required ventilator support. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients overall, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10–17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from <1% for those younger than 20 years of age to >50% for those older than 65 years of age.

In contrast, children younger than 12 years of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. Some young children had no respiratory symptoms. Coryza was more common in children younger than 12 years of age, whereas systemic symptoms were seen more often in teenagers. There were no deaths or cases of acute respiratory distress syndrome in children younger than 12 years of age from SARS-CoV infection.

Middle East Respiratory Syndrome Coronavirus

The incubation period of MERS-CoV is 2-14 days. The syndrome usually presents with nonspecific clinical features typical of acute febrile respiratory illnesses, including low-grade fever, rhinorrhea, sore throat, and myalgia. In mildly symptomatic cases, radiographic findings are typically normal. Severe disease is characterized by the acute respiratory distress syndrome with multilobular airspace disease, ground-glass opacities, and occasional pleural effusions on radiography. The median time between hospitalization and ICU transfer for critical illness is 2 days. Risk factors for severe disease include age >50 years and comorbidities such as obesity, diabetes, chronic obstructive pulmonary disease (COPD), end-stage renal disease, cancer, and immunosuppression. Specific host genetic risk factors have not been identified. Variation in clinical outcomes does not appear to be explained by viral strain-specific sequence variability. As with SARS, extrapulmonary manifestations are common in severe MERS disease. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea occur in one third of patients, and acute kidney injury has been documented in half of critically ill patients. Encephalitis-like neurologic manifestations have been observed in three cases. Laboratory analyses typically detect leukopenia and lymphopenia, with occasional thrombocytopenia, anemia, and aminotransferase elevations. The case fatality rate remains at 35%, though the true incidence of MERS-CoV infection is likely underestimated by existing data. Most patients have been adults, although children as young as 9 months of age have been infected. It is not known whether children are less susceptible to MERS-CoV or present with a different clinical picture.

DIAGNOSIS

With the advent of commercially available, syndromic, multiplex PCR respiratory panels, respiratory infections due to the four endemic HCoVs are now easily diagnosed and widely available in most clinical settings. These panels have rapid turnaround times, excellent sensitivity and specificity, and most commonly use upper respiratory tract specimens. Virus culture of primary clinical specimens remains a challenge for HCoVs HKU1, OC43, 229E, and NL63, even though the epidemic coronaviruses can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though the serology for SARS-CoV has a sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin (Ig) G seroconversion may be delayed for up to 4 weeks. The diagnosis of MERS-CoV should be guided by clinical features and an epidemiologic link. The mainstay for laboratory confirmation of MERS-CoV infection is real-time RT-PCR. The best diagnostic sensitivity is achieved from lower respiratory tract samples collected within the first week of infection, though MERS-CoV RNA can be detected in upper respiratory and blood samples. Alternatively, seroconversion can be documented by screening enzyme-linked immunosorbent assays followed by immunofluorescence microscopy. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, saliva, serum, or stool may also be positive.

TREATMENT AND PREVENTION

Several antiviral agents are available for clinical use against coronaviruses targeting the conserved coronavirus protease and polymerase. Ribavirin was extensively used during the 2003 SARS-CoV outbreak but is of questionable benefit given its poor in vitro activity against SARS-CoV at clinically relevant concentrations.

Challenges for the development of effective vaccines targeted against OC43, 229E, HKU1, and NL63 include the fact that infections are rarely life-threatening and reinfection is the rule, even in the presence of natural immunity from previous infections. The durability of immunity to SARS-CoV and MERS-CoV is poorly understood. Nevertheless, effective vaccines for SARS-CoV and MERS-CoV are highly desirable but not yet available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com Bibliography.

311.1 COVID-19

Samuel Dominguez and Roberta L. DeBiasi

New variants may evolve: recommendations for treatment and prevention may change. See Centers for Disease Control and Prevention for updates.

SARS-CoV-2 first emerged in Wuhan China in December 2019 as the etiologic agent of a severe respiratory illness termed COVID-19. Despite measures to contain transmission, SARS-CoV-2 rapidly spread globally, resulting in declaration of a worldwide pandemic by March 2020. As of late 2023, over 770 million cases and nearly 7 million deaths have occurred globally due to SARS-CoV-2. Ongoing transmission has led to the emergence of sequential variants (e.g., Delta, Omicron, BA.2, BA.5, BQ, XBB1.5 variants) with progressively unique gene variants in the receptor binding domain of the spike protein, conferring increased transmissibility compared to the parent strain (Alpha variant). Gene changes in some variants have been associated with reduced susceptibility to monoclonal antibody therapeutics and/or reduced neutralization by convalescent and vaccine-induced antibodies, promoting immune escape and breakthrough infections in previously infected and/or immunized individuals and ongoing community transmission.

EPIDEMIOLOGY

SARS-CoV-2 transmission occurs from human to human primarily by respiratory droplet, as well as by aerosol transmission, with the highest rates of transmission occurring from 2 days prior to 2-3 days after symptom onset. Transmission is quite common among asymptomatic or presymptomatic infected patients. Close contact (conversation distance) increases the risk; normal conversation as well as coughing, sneezing, singing, or just breathing are mechanisms. Immunocompromised hosts may shed infectious virus for longer periods of time, up to 21 days or more after symptom onset. Spread within households and close communal settings is common; transmission has been confirmed from infants, toddlers, and school-age children (who may have very high viral loads in the anterior nares even with asymptomatic or mild infection) and from adolescents to adult household members as well as from adults to children. A metanalysis of household secondary transmission has identified household secondary attack rates of nearly 17%, which exceeds that for SARS-CoV (7.5%) and MERS-CoV (4.7%). Secondary attack rates within households are increased from symptomatic compared to asymptomatic index cases, in adults compared to children, in spouses compared to other household members, and in households with three or more contacts. Throughout the pandemic, it has been noted that transmission is increased in unvaccinated compared to vaccinated individuals.

Young children were initially reported to be less likely to be infected or more likely to be asymptomatic with SARS CoV-2 (alpha, delta strains) than adults and unlikely to develop severe disease. However, despite overall lower rates of hospitalization and death, children are efficiently infected and can develop severe disease (usually older children and adolescents) that results in hospitalization, ICU admission, and occasional death (mortality <0.5%); the majority of young children experience mild to moderate illness.

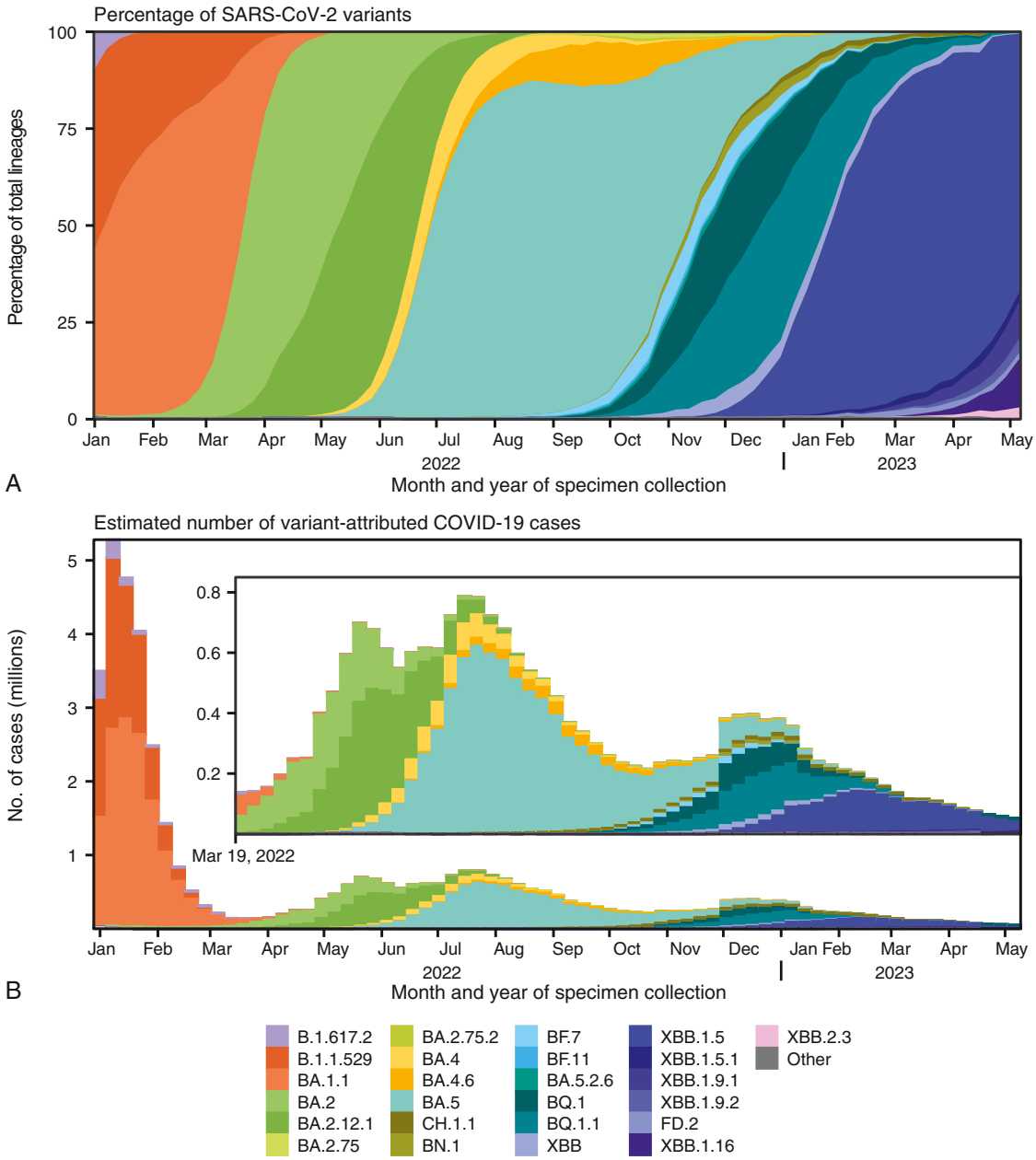

Fig. 311.1 National weekly proportion estimates* of SARS-CoV-2 variants† (A) and estimated number of variant-attributed cases‡ (B) United States, January 2, 2022–May 13, 2023. *Sequences are reported to CDC through NS3, contract laboratories, public health laboratories, and other U.S. institutions. Variant proportion estimation methods use a complex survey design and statistical weights to account for the probability that a specimen is sequenced. †Lineages reaching a prevalence of 1≥% with spike protein substitutions of potential therapeutic relevance and separated out on the COVID Data Tracker website. ‡Estimated numbers of COVID-19 cases attributable to variants were calculated by multiplying weekly numbers of reported positive nucleic acid amplification tests from CELR with estimated variant proportions. *(From Ma KC, Shirk P, Lambrou AS, et al: Genomic surveillance for SARS-CoV-2 variants: circulation of omicron lineages—United States, January 2002–May 2023. MMWR 2023;72,:651–656. Fig. 1, p. 653.)*

As of spring 2023, over 15 million laboratory-confirmed infections and nearly 40,000 hospitalizations have occurred cumulatively in U.S. children ≤18 years of age, representing ~13% of overall infections and up to 4.5% of hospitalizations in the United States. Young children under 5 years of age have made up a relatively increased proportion of cases and hospitalizations during later stages of the pandemic (late variants) presenting more with upper respiratory infection, croup, or bronchiolitis (Fig. 311.1). Milder illness may be due to less virulent variants or prior immunity from vaccination or infection; morbidity and mortality have remained low compared to adults, despite the increased transmissibility of more recent variants.

Early in the pandemic, a post-infectious hyperinflammatory complication of SARS-CoV-2 infection termed multisystem inflammatory syndrome of children (MIS-C; also referred to as pediatric inflammatory multisystem syndrome temporally associated with COVID-19, PIMS-TS) was recognized. MIS-C is associated with higher acuity in older children and initially was associated with higher rates of mortality due to hemodynamic instability, myocardial dysfunction, and cardiovascular collapse. With better recognition of this syndrome, key

Table 311.1 Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

Any illness in a person < 21 years that meets:
- The clinical AND the laboratory criteria (*Confirmed*), OR
- The clinical criteria AND epidemiologic linkage criteria (*Probable*), OR
- The vital records criteria (*Suspect*)

CLINICAL CRITERIA	LABORATORY CRITERIA FOR SARS-COV-2 INFECTION	EPIDEMIOLOGIC LINKAGE CRITERIA	VITAL RECORDS CRITERIA
An illness characterized by *all of the following*, in the absence of a more likely alternative diagnosis* • Subjective or documented fever (temperature ≥38.0°C) • Clinical severity requiring hospitalization or resulting in death • Evidence of systemic inflammation indicated by C-reactive protein ≥3.0 mg/dL (30 mg/L) • New-onset manifestations in *at least two* of the following categories: 1. **Cardiac** involvement indicated by: • Left ventricular ejection fraction <55% *OR* • Coronary artery dilatation, aneurysm, or ectasia, *OR* • Troponin elevated above laboratory normal range, or indicated as elevated in a clinical note 2. **Mucocutaneous** involvement indicated by: • Rash, *OR* • Inflammation of the oral mucosa (e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue), *OR* • Conjunctivitis or conjunctival injection (redness of the eyes), *OR* • Extremity findings (e.g., erythema [redness] or edema [swelling] of the hands or feet) 3. **Shock**§ 4. **Gastrointestinal** involvement indicated by: • Abdominal pain, *OR* • Vomiting, *OR* • Diarrhea 5. **Hematologic** involvement indicated by: • Platelet count <150,000 cells/μL *OR* • Absolute lymphocyte count (ALC) <1,000 cells/μL	• Detection of SARS-CoV-2 RNA in a clinical specimen† up to 60 days before or during hospitalization, or in a postmortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction [PCR]), OR • Detection of SARS-CoV-2– specific antigen in a clinical specimen† up to 60 days before or during hospitalization, or in a postmortem specimen, OR • Detection of SARS-CoV-2–specific antibodies‖ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization	Close contact‡ with a confirmed or probable case of COVID-19 disease in the 60 days before hospitalization	A person whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death

*If documented by the clinical treatment team, a final diagnosis of Kawasaki Disease should be considered an alternative diagnosis. These cases should not be reported to national multisystem inflammatory syndrome in children (MIS-C) surveillance.
†Positive molecular or antigen results from self-administered testing using over-the-counter test kits meet laboratory criteria.
‡Includes a positive serology test regardless of COVID-19 vaccination status. Detection of anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, and antispike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection.
§Clinician documentation of shock meets this criterion.
‖Close contact is generally defined as being within 6 feet for at least 15 min (cumulative over a 24-hr period). However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration.
From Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html

discriminatory diagnostic criteria, and institution of rapid immunomodulatory treatment, outcomes have improved (Table 311.1; Table 208.4 in Chapter 208). As of late 2023, there have been >9500 cases and 79 deaths due to MIS-C in the United States. The incidence of MIS-C has substantially decreased with the appearance of the late pandemic viral variants.

Pathogenesis of COVID-19

Severe disease in COVID-19 likely results from both direct virologic damage and subsequent immunopathology (Fig. 311.2). Postmortem exams have demonstrated COVID-19 virus in almost all tissues (lung, blood vessels, brain, gastrointestinal tract, heart, etc.). Substantial viral loads can be detected in the upper and lower respiratory tracts, stool, and blood. Late progression to severe disease appears *independent* of the quantity and timing of viremia; excessive host immune responses likely play an important role in the progression to lower respiratory disease, acute respiratory distress syndrome, and MIS-C (see Fig. 311.2). COVID-19 is associated with massive elaboration of inflammatory cytokines and recruitment of inflammatory cells. The roles for inflammatory cells are controversial, with cytotoxic T cells and macrophages implicated in both immune protection and immunopathology.

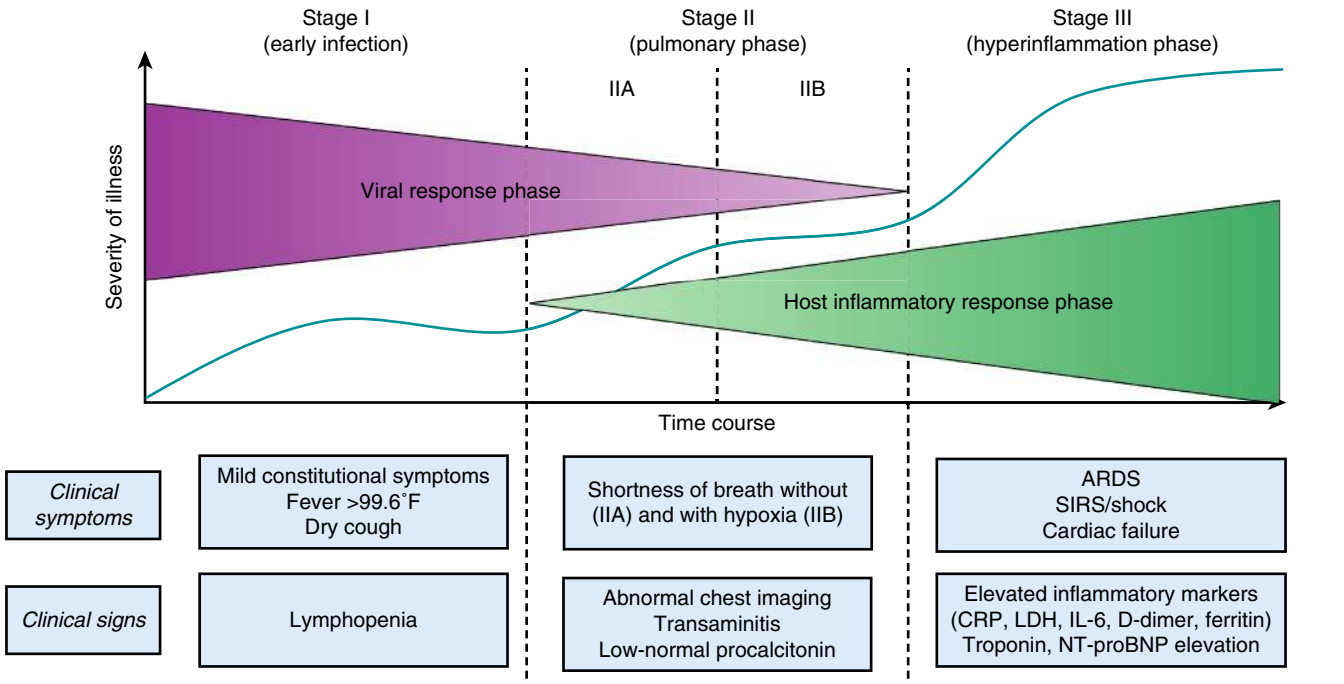

Fig. 311.2 Staging of acute COVID-19 infection. Classification of COVID-19 disease states and potential therapeutic targets. The figure illustrates three escalating phases of COVID-19 disease progression, with associated signs, symptoms. ARDS, Acute respiratory distress syndrome; JAK, Janus kinase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide; SIRS, systemic inflammatory response syndrome. *(Modified from Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transpl. 2020;39[5]:405–407. Fig. 1.)*

Table 311.2 Clinical Spectrum of SARS-CoV-2 Infection

- *Asymptomatic or presymptomatic infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but have no symptoms consistent with COVID-19.
- *Mild illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO_2) ≥94% on room air at sea level.
- *Severe illness:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (Pao_2/Fio_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- *Critical illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Spo_2 is a key parameter for defining the listed illness categories. However, pulse oximetry has important limitations. Clinicians who use Spo_2 when assessing a patient must be aware of those limitations and conduct the assessment in the context of that patient's clinical status.

Underlying conditions associated with a higher risk of severe COVID-19 include asthma, cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking, and being a recipient of immunosuppressive therapy or a transplant.

The initial evaluation for patients may include chest imaging (e.g., x-ray, ultrasound or computed tomography scan) and an electrocardiogram. Laboratory testing should include a complete blood count with differential and a metabolic profile, including liver and renal function tests. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements may have prognostic value.

In children with COVID-19, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; therefore hypoxemia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small subset of children and young adults, SARS-CoV-2 infection may be followed by the severe inflammatory condition multisystem inflammatory syndrome in children (MIS-C).

From Centers for Disease Control and Prevention. Clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

CLINICAL MANIFESTATIONS

In both children and adults, the spectrum of clinical manifestations of SARS-CoV-2 infection ranges from asymptomatic infection to mild, moderate, or severe, life-threatening pulmonary and extrapulmonary manifestations (Table 311.2). Children are more likely than adults to experience asymptomatic (up to 40%) or mild disease (all variants) but can also experience moderate and severe illness, including need for critical care support (MIS-C or early variants in older children or adolescents). Mild, moderate, or severe illness can include nonspecific symptoms such as fever, headache, myalgias, and fatigue (Table 311.3). Respiratory manifestations of COVID-19 in children are similar to those in adults and may include mild upper respiratory tract symptoms such as rhinorrhea, congestion, cough, and sore throat and lower respiratory symptoms such as shortness of breath and chest pain. Patients with severe or critical pulmonary and systemic features are at risk for venous thrombosis;

Table 311.3 Clinical Criteria for COVID-19

In the absence of a more likely diagnosis:

- At least two of the following symptoms:
  - Fever (measured or subjective)
  - Chills
  - Rigors
  - Myalgia
  - Headache
  - Sore throat
  - Nausea or vomiting
  - Diarrhea
  - Fatigue
  - Congestion or runny nose

OR

- Any one of the following symptoms:
  - Cough
  - Shortness of breath
  - Difficulty breathing
  - New olfactory disorder
  - New taste disorder

OR

- Severe respiratory illness with at least one of the following:
  - Clinical or radiographic evidence of pneumonia
  - Acute respiratory distress syndrome (ARDS)

LABORATORY CRITERIA (SEE TABLE 311.10)

EPIDEMIOLOGIC LINKAGE

- One or more of the following exposures in the prior 14 days:
  1. Close contact* with a confirmed or probable case of COVID-19 disease
  2. Member of a risk cohort as defined by public health authorities during an outbreak

CASE CLASSIFICATION†

Suspect

- Meets supportive laboratory evidence‡ with no prior history of being a confirmed or probable case.

Probable

- Meets clinical criteria AND epidemiologic linkage with no confirmatory laboratory testing performed for SARS-CoV-2
- Meets presumptive laboratory evidence
- Meets vital records criteria with no confirmatory laboratory evidence for SARS-CoV-2

Confirmed

- Meets confirmatory laboratory evidence

VITAL RECORDS CRITERIA

- A death certificate that lists COVID-19 disease or SARS-CoV-2 as an underlying cause of death or a significant condition contributing to death.

*Close contact is generally defined as being within 6 feet for at least 15 min. However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration. Data are insufficient to precisely define the duration of exposure that constitutes prolonged exposure and thus a close contact.

†The terms *confirmatory, presumptive,* and *supportive* are categorical labels used here to standardize case classifications for public health surveillance. The terms should not be used to interpret the utility or validity of any laboratory test methodology.

‡For suspect cases (positive serology only), jurisdictions may opt to place them in a registry for other epidemiologic analyses or investigate to determine probable or confirmed status.

From Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): 2020 interim case definition. Approved August 5, 2020. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-covid-19/

prophylactic doses of enoxaparin are recommended. Chest imaging is essential in those with respiratory symptoms (Fig. 311.3). Croup and bronchiolitis presentations have been observed in association with the Omicron and later variants. Anosmia and ageusia have been reported in 10–15% of cases in children as well as adults. Gastrointestinal symptoms such as abdominal pain (pseudoappendicitis), diarrhea, and vomiting may be more prominent in pediatric patients (COVID-19 and/or MIS-C) compared to adults (Fig. 311.4). Although children with and without underlying medical conditions may be infected, up to 60% of hospitalized children have one or more underlying medical conditions and up to 80% of children with severe disease requiring critical care support have an underlying condition.

Cutaneous lesions have often been reported in pediatric patients with COVID-19 and pediatric patients with MIS-C (Table 311.4 and Fig. 311.5).

SARS-CoV-2 is a neurotropic virus; 10–20% of pediatric patients with COVID-19 and/or MIS-C have central or peripheral nervous system manifestations during the acute illness. The most common neurologic manifestations include seizures (including status epilepticus), headaches, behavioral changes, myalgias, and encephalopathy (~30% with reversible splenial lesions). Other identifiable syndromes include stroke, acute disseminated encephalomyelitis (ADEM) (~50% are myelin oligodendrocyte glycoprotein [MOG] antibody positive), Guillain-Barré syndrome (also reported with the vaccine), optic neuritis, psychosis, and cerebellar or brainstem lesions.

Neuroimaging findings associated with neurologic complications in children with COVID-19 are shown in Fig. 311.6. Cerebrospinal fluid (CSF) findings include a pleocytosis.

Neonates are often hospitalized because of SARS-CoV-2 infection due to febrile illness with less prominent respiratory complaints, primarily to exclude neonatal bacterial sepsis or neonatal herpes simplex virus (HSV) infection. Although nearly 15% of women presenting in labor during the early phase of the COVID-19 pandemic were found to be SARS-CoV-2 PCR positive (majority are asymptomatic), very few infants born to these women are PCR positive at birth or become infected perinatally. Preterm birth and stillbirth due to effects on the placenta, placental inflammation, and other specific abnormalities have been reported in pregnant women with symptomatic SARS-CoV-2 infection. Congenital abnormalities or intrauterine growth restriction have not been observed in live-born infants with in-utero SARS-CoV-2 exposure; potential long-term neurodevelopmental effects are not yet known.

Over the course of the pandemic, extrapulmonary manifestations and complications of SARS-CoV-2 infection have increasingly been appreciated, including new onset or exacerbation of type 1 and type 2 diabetes, intestinal inflammation (pseudo-appendicitis) and mesenteric lymphadenitis (see Fig. 311.4), and vascular complications such as thrombosis of vessels in the extremities as well as cerebral vasculature. SARS-CoV-2 infection has been associated with sickle cell vasoocclusive crises and acute chest syndrome in patients with sickle cell disease and increased seizures in children with seizure disorders.

MIS-C

The primary clinical manifestations of MIS-C occur 2-6 weeks *after* SARS-CoV-2 infection and consist of unremitting fever, involvement of two or more organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), clinical severity requiring hospitalization, and laboratory evidence of inflammation (see Table 311.1). In addition, there is evidence for recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before the onset of symptoms.

The median age for children with MIS-C is 8-10 years (range 4-14 years), but MIS-C can affect any age group, including adolescents and rarely infants. A similar syndrome, MIS-A, has been reported in adults (≥21 years). The vast majority of cases of MIS-C have occurred in children with no underlying medical conditions or immunodeficiency. Cardiac manifestations including myocardial dysfunction, coronary artery dilatation, and aneurysm formations (Fig. 311.7), valvular dysfunction, reduced left ventricular ejection fraction, shock, cardiac arrhythmias, and pericardial effusion are present in up to 50% of children at presentation. With institution of rapid

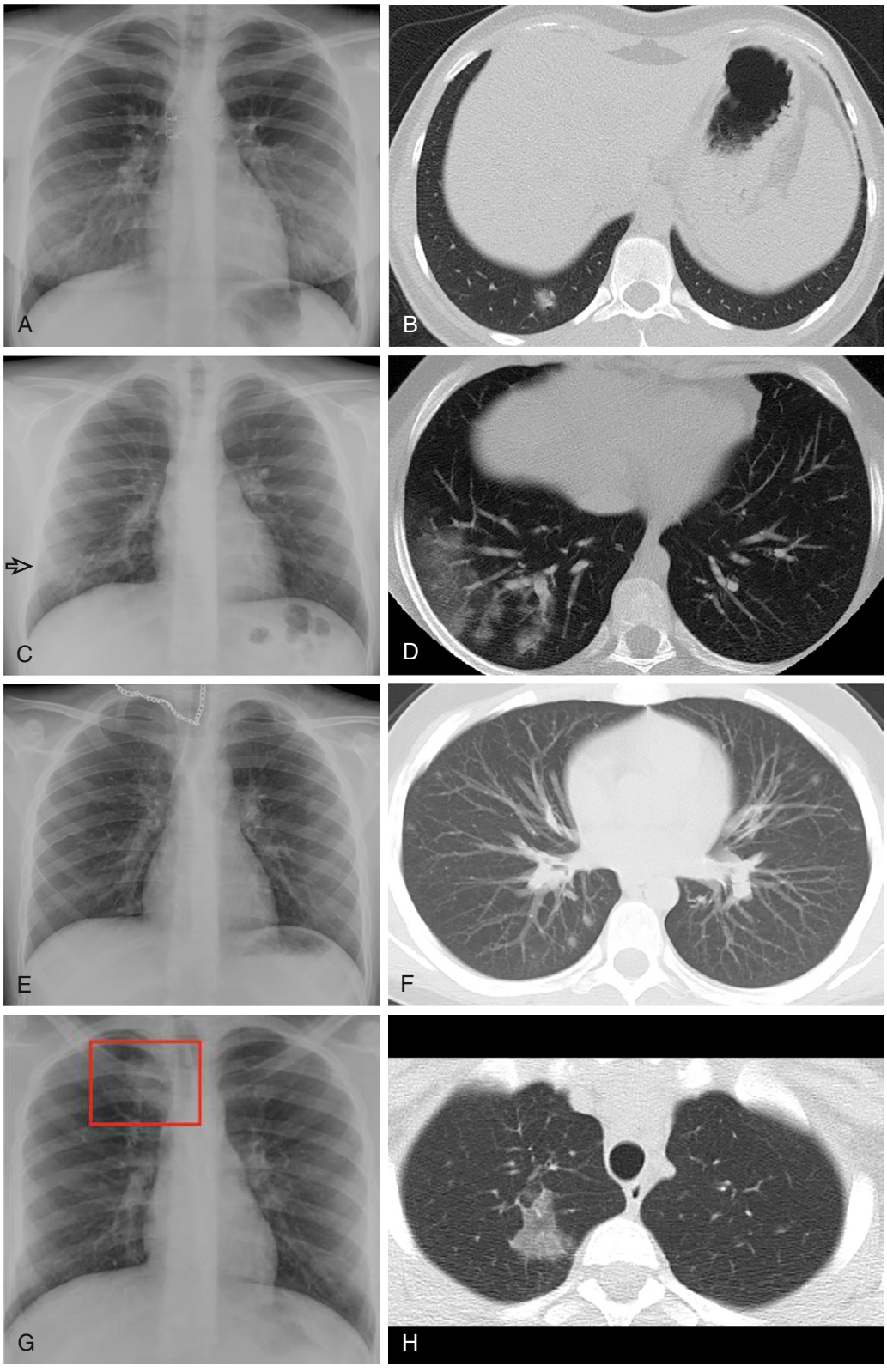

Fig. 311.3 Chest radiography and chest CT findings of children with COVID-19 in conjunction with symptom and time interval between imaging studies. **A,** Posteroanterior chest radiograph of a 13-yr-old patient who presented with fever for 2 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph was normal. **B,** Chest CT image in the axial plan revealed a single, peripheral located, ground-glass opacity (GGO) at the posterobasal segment of the right lower lobe. The opacity was obscured with the right liver lobe and diaphragm on chest radiography. **C,** Posteroanterior chest radiograph of a 10-yr-old patient who presented with cough and fever for 2 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph revealed peripheral GGO *(arrow)* at the basal segments of the right liver lobe. **D,** Axial section chest CT examination revealed bronchovascular distributed GGOs at the periphery of the basal segments of the right lower lobe. **E,** Posteroanterior chest radiograph of a 13-yr-old patient who presented with cough and fever for 2 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph was interpreted as normal. **F,** Axial chest CT image without contrast demonstrates bilateral, multifocal, peripheral, and perivascular distributed millimetric nodular-shaped GGOs. The opacities were not detected on chest radiography due to the smaller size and lower density. **G,** Posteroanterior chest radiograph of a 16-yr-old patient who presented with cough and fever for 3 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph demonstrates paramediastinal GGO at the right upper lobe *(red box)*. **H,** Axial chest CT image without contrast demonstrates peripherally distributed GGO at the right upper lobe with an interlobular interstitial thickening. *(From Bayramoglu Z, Canıpek E, Comert RG, et al. Imaging features of pediatric COVID-19 on chest radiography and chest CT: a retrospective, single-center study. Acad Radiol. 2021;28:18–27. Fig. 1.)*

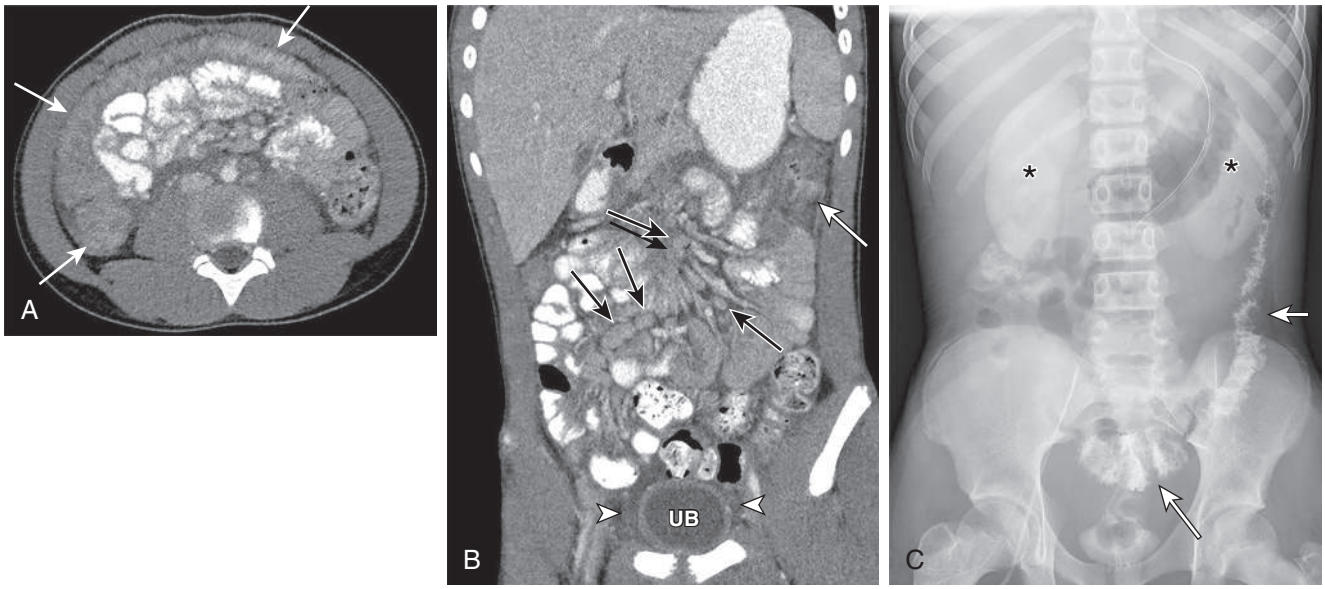

Fig. 311.4 A 14-yr-old with multisystem inflammatory syndrome in children (MIS-C). Imaging findings showed bowel wall thickening, acute kidney injury, ascites, and mesenteric adenopathy. **A,** Axial contrast-enhanced CT image shows diffuse mural thickening and mild mucosal hyperenhancement of colon *(arrows).* **B,** Coronal image from same CT examination as **A** shows mesenteric lymphadenopathy *(black arrows)* and pelvic ascites *(arrowheads).* Wall of urinary bladder *(UB)* is thickened, and thickening of colon *(white arrow)* is again noted. **C,** Supine anteroposterior abdominal radiograph obtained 15 hours after CT (**A** and **B**) shows retention of IV contrast material in kidneys *(asterisks)* (termed *delayed nephrogram*) in setting of acute kidney injury. Residual oral contrast material is present in descending colon and sigmoid *(arrows)* and shows wall thickening and irregularity. *(From Blumfield E, Levin TL, Kurian J, et al. Imaging findings in multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease (COVID-19). AJR. 2021;216:507–518. Fig. 7.)*

Table 311.4 Rashes Reported in COVID-19 Infected Patients

- Morbilliform*
- Chilblain-like/pernio*
- Urticarial
- Macular papular erythema*
- Vesicular
- Acrocyanosis
- Acral desquamation
- Papulosquamous
- Livedo reticularis–like*
- Erythema multiforme-like*
- Erythroderma
- Grover-like
- Retiform purpura*
- Petechial
- Bullous
- Palpable purpura/vasculitis (leukocytoclastic)*
- Dengue-like
- Pressure injury
- Erythema nodosum
- Livedo racemose*
- Miliaria rubra
- Acneiform
- Enanthem
- Anagen effluvium
- Erythema elevatum diutinum
- Photo-distributed

*Common.
Modified from Dinulos JE, Dinulos JG. Cutaneous coronavirus disease 2019 in children: a clinical primer for diagnosis and treatment. *Curr Opin Pediatr.* 2021;33:691–703. Table 1.

immunomodulation, short-term outcomes appear to be favorable, including resolution of coronary abnormalities in the majority of cases. Studies to evaluate the long-term prognosis for cardiac function are in progress, including studies using sensitive measures such as cardiac MRI. Patients with severe cardiac dysfunction must be followed by a pediatric cardiologist and abstain from sports for 3-6 months or until cleared by the cardiologist.

Sub-phenotypes of MIS-C include cases that appear very similar to Kawasaki disease (marked conjunctival injection, adenopathy, and/or prominent rash [Table 208.4 in Chapter 208]) and cases lacking Kawasaki disease features but with prominent abdominal symptoms mimicking an acute abdomen. Analysis of cytokine responses in children with MIS-C has identified elevation of a variety of biomarkers, confirming the hyperinflammatory nature of this illness (Table 311.5). Rapid institution of immunomodulatory therapy has been shown to be lifesaving in the setting of MIS-C and has included intravenous immunoglobulin (IGIV) with methylprednisolone and/or other biologics such as anakinra, tocilizumab, or infliximab (Table 311.6). The incidence of MIS-C has dramatically decreased with the appearance of newer variants.

Infectious complications are uncommon and are noted in Table 311.7. Another complication is rebound (recurrence) of COVID-19 symptoms after an initial episode (Table 311.8).

Post-Acute Sequelae of SARS-CoV-2 Infection (Long COVID)

An estimated 10–40% of adults and a much lower percentage of children who have recovered from recognized or unrecognized SARS-CoV-2 infection may develop long-standing and in some cases severe symptoms that are not specifically related to their original symptoms (Table 311.9). These may include ill-defined pain syndromes, headaches, abdominal pain, fatigue and postexertional malaise, shortness of breath, chronic cough, palpitations, dizziness/syncope, among others, as well as anxiety, depression, and posttraumatic stress disorder. The pathogenesis of long COVID is not yet known but may include genetic determinants related to immune dysregulation, autonomic instability, or persistent indolent viral effects. Long COVID may occur in individuals with mild symptoms, as well as those with moderate or severe infection. Affected individuals may benefit from multidisciplinary and coordinated evaluation in centers that can coordinate subspecialty evaluations



Fig. 311.5 Dermatologic manifestations of COVID-19. **A,** Petechial rash. **B,** Chilblains of the foot. **C,** Livedo reticularis of the lower extremity. *(A and B from Gottlieb M, Long B. Dermatologic manifestations and complications of COVID-19. Am J Emerg Med. 2020;38:1715–1721. Figs. 4 and 5; C from Nantsupawat T, Mankongpaisarnrung C, Soontrapa S, et al. Obscure severe infrarenal aortoiliac stenosis with severe transient lactic acidosis. J Investig Med High Impact Case Rep. 2013;1(1):2324709613479940. Fig. 2.)*

at a single visit, with focus on the symptoms that are most disruptive to quality of life and function.

DIAGNOSIS

Numerous diagnostic assays have been developed for the diagnosis of SARS-CoV-2, including laboratory-based and rapid/point-of-care nucleic acid amplification tests, rapid antigen tests, and serologic assays (Table 311.10). Multiple platforms targeting different aspects of the viral spike and nucleocapsid genes or proteins have been used for direct viral detection. Antibody to the spike protein may develop with either natural infection or vaccination, but presence of nucleocapsid antibody indicates natural infection. Virus may be detected by PCR or antigen-based methods for many days after the onset of symptoms, but immunocompetent individuals are generally not contagious after 10 days and immunocompromised patients are generally not contagious after 21 days, with late viral detection representing nonviable, replication incompetent remnants. Cycle time (Ct) in nonquantitative PCR assays cannot directly correlate with disease or likelihood of disease severity or progression but can be used as a rough estimate of viral load and shedding over time within a single patient, with lower Ct representing high viral loads and high Ct more likely representing shedding of nonviable virus.

Antibodies usually develop within 2 weeks of infection, but there is great variability in antibody responses to natural infection. Some infected individuals mount high antibody responses that are durable over many months, but others may not mount an effective or long-lived response after natural infection, highlighting the importance of vaccination for reliable immunity. Antibody responses have been documented to wane over time in both naturally infected and vaccinated individuals, leading to the recommendation for booster doses of vaccine. Vaccination has continued to be highly effective in prevention of severe disease, hospitalization, and death and in reducing the likelihood of MIS-C.

TREATMENT AND PREVENTION

Therapeutic agents for SARS-CoV-2 include antivirals that inhibit viral replication such as intravenous remdesivir, oral nirmatrelvir/ritonavir combination therapy, and oral molnupiravir. These antivirals reduce morbidity and mortality in hospitalized patients (5-10 day courses of intravenous remdesivir) as well as nonhospitalized high-risk children and adults (oral agents and shorter 3-day courses of intravenous remdesivir). High-risk conditions associated with severe disease include obesity, diabetes, chronic lung disease, neurologic disorders, cardiovascular disease, sickle cell disease, or immunosuppression because of underlying conditions or medications. Systemic corticosteroid therapy (dexamethasone) has been shown to significantly reduce morbidity and mortality in the treatment of hospitalized patients with COVID-19 pulmonary disease. Several monoclonal antibodies were developed and found to be effective during the early phase of the pandemic in preventing progression to severe disease in individuals with high-risk conditions. However, these antibodies have not retained activity against more recent variants of SARS-CoV-2. High-titer immune plasma has demonstrated variable efficacy with the original variant and is not recommended. Other biologics, such as the interleukin-6 inhibitor tocilizumab, have been used in critically ill adults unresponsive to first-line therapies but are used less commonly in children.

Multiple vaccines have been developed to combat spread of SARS-CoV-2, including novel platforms such as mRNA-based vaccines and adenovirus vector-based vaccines (see Chapter 215). For the majority of these SARS-CoV-2 vaccines, the primary target is the viral spike protein. The FDA had granted EUA approval for SARS-CoV-2 vaccines in the United States in children >6 months of age and adults.

Guidelines in late 2023 regarding isolation and precautions for people with COVID-19 are summarized in Table 311.11. However, guidelines continue to evolve and are available at the Centers for Disease Control and Prevention website (https://www.cdc.gov/coronavirus/2019-ncov/your-health/isolation.html).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

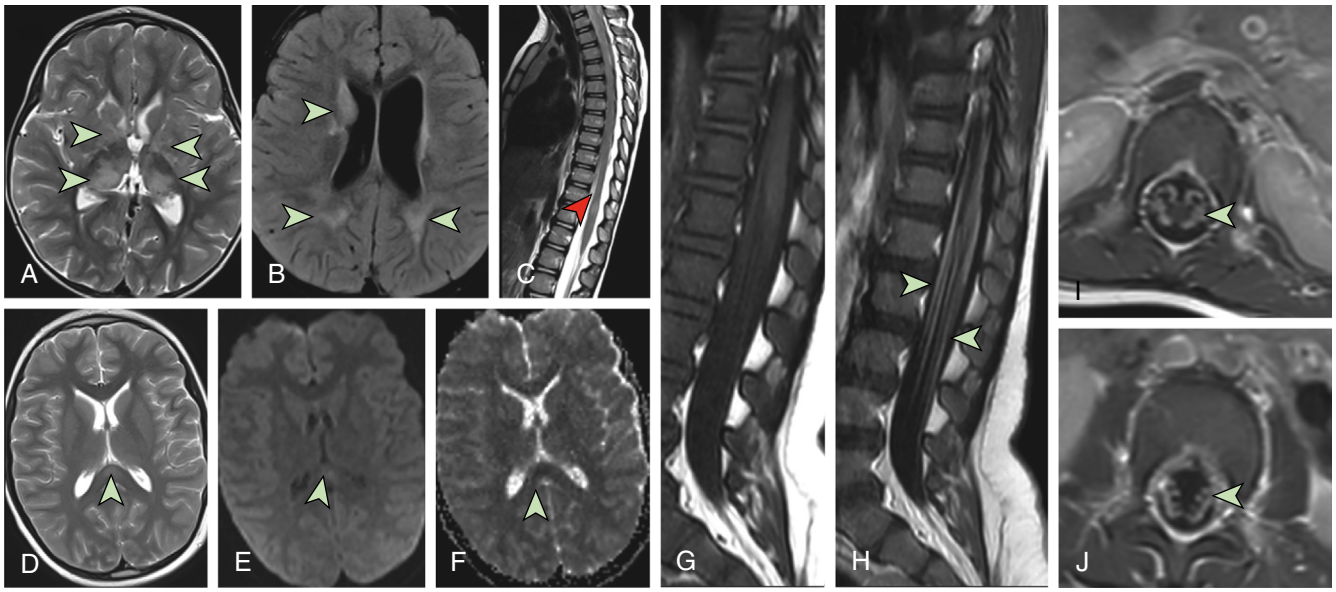

Fig. 311.6 MRI scans showing a range of neurologic complications. **A-C,** MRI brain and spine scans from 2-yr-old child with acute disseminated encephalomyelitis. Multiple hyperintense foci on axial T2-weighted (**A**) and T2 FLAIR (**B**) images involve both cerebral hemispheres, including the basal ganglia, thalami, and subcortical and periventricular white matter *(arrowheads)*. **C,** Sagittal T2-weighted image of the spine shows a focus of hyperintensity within the cord close to the conus *(arrowhead)*. **D-F,** MRI brain scans from 11-yr-old child who presented with MIS-C, encephalopathy, and MERS. **D,** Axial T2-weighted image shows a focus of hyperintensity involving the splenium of the corpus callosum along the midline *(arrowhead)*. The B1000 (**E**) and the ADC maps (**F**) from diffusion-weighted imaging show subtle diffusion restriction involving the lesion. **G-J,** MRI spine scans from a 16-mo-old infant who presented with Guillain-Barré syndrome. Sagittal T1-weighted images before (**G**) and after contrast (**H**) show enhancement of the lumbosacral nerve roots *(arrowheads)*. **I, J,** Axial T1-weighted postcontrast images show bilateral enhancement of the nerve roots. ADC, Apparent diffusion coefficient;; FLAIR, fluid-attenuated inversion recovery; MERS, mild encephalopathy with reversible splenial lesion; MIS-C, multisystem inflammatory syndrome in children. *(Modified from Ray ST, Abdel-Mannon O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc. 2021;5:631–641. Fig. 2.)*

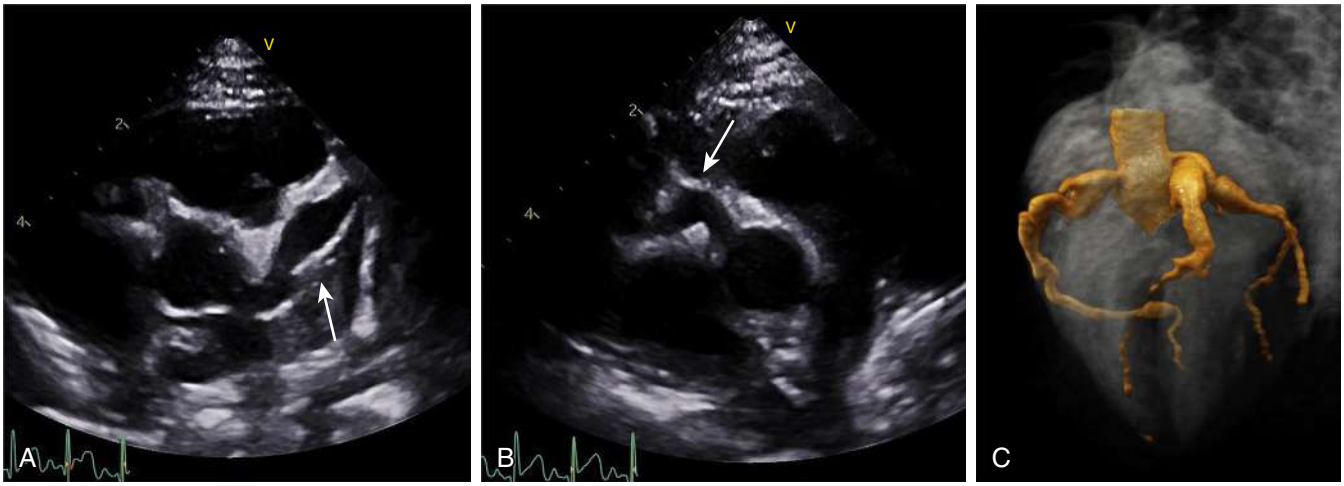

Fig. 311.7 Early cardiac imaging. Echocardiography (day 21) showing a giant (*z* score +26) left anterior descending artery aneurysm (**A**) and a large (*z* score +8.5) right coronary artery aneurysm (**B,** *arrow*). **C,** Three-dimensional reconstruction of coronary architecture. *(Modified from Villacis-Nunez DS, Hashemi S, Nelson MC, et al. Giant coronary aneurysms in multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. JACC Case Rep. 2021;3[13]:1499–1508. Fig. 2.)*

Table 311.5 Evaluation of MIS-C

LABORATORY TESTING

- A C-reactive protein ≥3.0 mg/dL (30 mg/L) is required for the CSTE/CDC MIS-C surveillance case definition; other laboratory tests may also indicate evidence of inflammation (e.g., erythrocyte sedimentation rate, fibrinogen, procalcitonin, and ferritin).
- Similarly, SARS-CoV-2 laboratory testing is indicated. Although detection of anti-nucleocapsid antibody or anti-spike protein antibody fulfill criteria for the case definition, when feasible SARS-CoV-2 anti-nucleocapsid antibody testing is recommended, particularly in children with a history of COVID-19 vaccination because anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, whereas antispike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection. Serology testing should be obtained before administering intravenous immunoglobulin or any other exogenous antibody treatments whenever possible.

IMAGING

Given the frequent association of MIS-C with cardiac involvement, the following tests are usually performed:

- Echocardiogram
- Electrocardiogram

Other imaging should be directed by patient signs or symptoms but could include:

- Imaging to evaluate for acute appendicitis
- Imaging to evaluate for pharyngeal space infection

OTHER EVALUATIONS

It is important to evaluate children with suspected MIS-C for alternative diagnoses, particularly because MIS-C clinical manifestations overlap with those of other etiologies. Testing to evaluate for other potential diagnoses should be directed by patient signs or symptoms. Alternative diagnoses to consider include:

- Acute viral infection (e.g., SARS-CoV-2, influenza, adenovirus)
- Acute viral infection myocarditis (e.g., influenza, enteroviruses)
- Kawasaki disease
- Rickettsial disease (e.g., typhus)

CSTE/CDC, Council of State and Territorial Epidemiologists/Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children.

From Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html

Table 311.6 Treatment of MIS-C

Initial treatment is tailored according to the patient's presenting signs and symptoms and may include:

- Fluid resuscitation
- Inotropic support
- Respiratory support

Antiinflammatory measures have included the frequent use of intravenous immunoglobulin and steroids. There is some evidence that multisystem inflammatory syndrome in children (MIS-C) with milder manifestations can be treated with steroid monotherapy and that prolonged duration of outpatient steroids should be avoided. The use of other antiinflammatory medications (e.g., anakinra) and the use of anticoagulation treatments have been variable. Aspirin has commonly been used because of concerns for coronary artery involvement, and antibiotics are routinely used to treat potential sepsis while awaiting bacterial cultures. Thrombotic prophylaxis is often used given the hypercoagulable state typically associated with MIS-C.

From Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html

Table 311.7 Infectious Complications in Patients with COVID-19

- *Co-infections at presentation:* Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported. Community-acquired bacterial pneumonia also has been reported, but it is uncommon, with a prevalence that ranges from 0% to 6% of people with SARS-CoV-2 infection. Antibacterial therapy is generally not recommended unless additional evidence for bacterial pneumonia is present (e.g., leukocytosis, the presence of a focal infiltrate on imaging).
- *Reactivation of latent infections:* There are case reports of underlying chronic hepatitis B virus and latent tuberculosis infections reactivating in patients with COVID-19 who receive immunomodulators as treatment, although the data are currently limited. Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported. Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Many clinicians would initiate empirical treatment (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients who require immunomodulators for the treatment of COVID-19 and have come from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).
- *Nosocomial infections:* Hospitalized patients with COVID-19 may acquire common nosocomial infections, such as hospital-acquired pneumonia (including ventilator-associated pneumonia), line-related bacteremia or fungemia, catheter-associated urinary tract infection, and *Clostridioides difficile*–associated diarrhea. Early diagnosis and treatment of these infections are important for improving outcomes in these patients.
- *Opportunistic fungal infections:* Invasive fungal infections, including aspergillosis and mucormycosis, have been reported in hospitalized patients with COVID-19. Although these infections are relatively rare, they can be fatal, and they may be seen more commonly in patients who are immunocompromised or receiving mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus or the use of corticosteroids.

From Centers for Disease Control and Prevention. Clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

Table 311.8 Viral or Symptom Rebound Soon After COVID-19

- Observational studies and results from clinical trials of therapeutic agents have described SARS-CoV-2 viral or COVID-19 symptom rebound in patients who have completed treatment for COVID-19.
- Viral and symptom rebounds have also occurred when anti–SARS-CoV-2 therapies were not used.
- Typically, this phenomenon has not been associated with progression to severe COVID-19.

From Centers for Disease Control and Prevention. Clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

Table 311.9 Adjusted Hazard Ratios of Selected Potential Post–COVID-19 Symptoms and Conditions Among Children and Adolescents Age 2-17 Years With and Without COVID-19, by Age Group: HealthVerity Medical Claims Database, United States, March 1, 2020–January 31, 2022

	ADJUSTED HAZARD RATIO (95% CI)*		
OUTCOME	**2-4 YR**	**5-11 YR**	**12-17 YR**
SYMPTOM			
Smell and taste disturbances	1.22 (0.70-2.15)	0.94 (0.83-1.07)	1.23 (1.16-1.31)†
Circulatory signs and symptoms	1.17 (1.12-1.23)†	1.11 (1.08-1.13)†	1.04 (1.02-1.06)†
Malaise and fatigue	1.13 (1.05-1.22)†	1.08 (1.05-1.12)†	1.03 (1.01-1.04)†
Musculoskeletal pain	1.16 (1.10-1.21)†	1.06 (1.04-1.07)†	1.00 (0.99-1.01)
Dizziness and syncope	1.08 (0.90-1.29)	1.03 (0.99-1.08)	1.00 (0.98-1.02)
GI and esophageal disorders	1.15 (1.10-1.20)†	1.02 (1.00-1.04)†	0.97 (0.95-0.99)†
Sleeping disorders	0.99 (0.93-1.06)	0.89 (0.86-0.92)†	0.91 (0.89-0.94)†
Respiratory signs and symptoms	1.07 (1.04-1.10)†	0.93 (0.92-0.94)†	0.88 (0.87-0.89)†
Symptoms of mental conditions	1.03 (0.97-1.10)	0.92 (0.90-0.95)†	0.89 (0.86-0.91)†
CONDITION			
Acute pulmonary embolism	—‡	—‡	2.03 (1.61-2.56)†
Myocarditis and cardiomyopathy	2.39 (1.57–3.65)†	2.84 (2.39-3.37)†	1.66 (1.48-1.88)†
Venous thromboembolic event	—‡	2.69 (1.73-4.19)†	1.52 (1.22-1.91)†
Acute and unspecified renal failure	1.52 (1.07–2.14)†	1.38 (1.16–1.63)†	1.27 (1.15–1.40)†
Type 1 diabetes	1.01 (0.57-1.78)	1.31 (1.13-1.53)†	1.20 (1.09–1.33)†
Coagulation and hemorrhagic disorders	1.47 (1.20-1.80)†	1.28 (1.15-1.43)†	1.10 (1.03–1.19)†
Type 2 diabetes	1.24 (0.85-1.81)	1.14 (1.02-1.28)†	1.18 (1.11-1.24)†
Cardiac dysrhythmias	1.44 (1.22-1.70)†	1.23 (1.14-1.32)†	1.12 (1.08-1.17)†
Cerebrovascular disease	1.66 (0.85-3.23)	1.14 (0.79-1.64)	1.18 (0.93-1.48)
Chronic kidney disease	0.86 (0.54-1.36)	1.04 (0.83-1.31)	1.12 (0.96-1.31)
Asthma	1.12 (1.07-1.18)†	1.02 (1.00-1.05)†	0.96 (0.94-0.98)†
Muscle disorders	0.87 (0.77-0.98)†	0.86 (0.82-0.91)†	0.96 (0.93-0.99)†
Neurologic conditions	0.98 (0.93-1.04)	0.96 (0.93-0.98)†	0.91 (0.89-0.93)†
Anxiety and fear-related disorders	0.91 (0.83-1.00)	0.86 (0.83-0.88)†	0.84 (0.82-0.85)†
Mood disorders	0.82 (0.62-1.08)	0.73 (0.69-0.77)†	0.80 (0.77-0.83)†

*Each adjusted hazard ratio was obtained from a single Cox proportional hazards model stratified by age group, with the specific symptom or condition as the outcome and the following covariates: presence of COVID-19, age (continuous variable), sex, race, U.S. Census Bureau region, payor type, previous medical complexity, and previous hospitalization.
†P-value < 0.05.
‡Age-stratified analyses were performed only when there were at least 10 patients with COVID-19 and at least 10 patients without COVID-19 in that age group with the specific symptom or condition.
From Kompaniyets L, Bull-Otterson L, Boehmer TK, et al. Post-COVID-19 symptoms and conditions among children and adolescents–United States, March 1, 2020-January 21, 2022. *Morb Mortal Wkly Rep*. 2022;71(31):993–998. Table 3.

Table 311.10 Laboratory Evidence for COVID-19 Infection

Laboratory evidence using a method approved or authorized by the U.S. Food and Drug Administration (FDA) or designated authority:

CONFIRMATORY* LABORATORY EVIDENCE
- Detection of SARS-CoV-2 ribonucleic acid (RNA) in a clinical or postmortem specimen using a diagnostic molecular amplification test performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified provider† OR
- Detection of SARS-CoV-2 RNA in a clinical or postmortem specimen by genomic sequencing‡

PRESUMPTIVE* LABORATORY EVIDENCE
- Detection of SARS-CoV-2–specific antigen in a clinical or postmortem specimen using a diagnostic test performed by a CLIA-certified provider.†

SUPPORTIVE* LABORATORY EVIDENCE
- Detection of SARS-CoV-2 specific antigen by immunocytochemistry, OR
- Detection of SARS-CoV-2 RNA or specific antigen using a test performed without CLIA oversight.

*The terms *confirmatory, presumptive,* and *supportive* are categorical labels used here to standardize case classifications for public health surveillance. The terms should not be used to interpret the utility or validity of any laboratory test methodology.
†Includes those tests performed under a CLIA certificate of waiver.
‡Some genomic sequencing tests that have been authorized for emergency use by the FDA do not require an initial polymerase chain reaction (PCR) result to be generated. Genomic sequencing results may be all the public health agency receives.
Modified from Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) 2023 Case Definition. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-covid-19/

Table 311.11 Isolation and Precautions for People with COVID-19

WHEN TO ISOLATE

- If you test negative: You can end your isolation.
- If you test positive: Follow the full isolation recommendations below.
- When you have COVID-19, isolation is counted in days, as follows.

If You Had No Symptoms

- Day 0 is the day you were tested (not the day you received your positive test result).
- Day 1 is the first full day following the day you were tested.
- If you develop symptoms within 10 days of when you were tested, the clock restarts at day 0 on the day of symptom onset.

If You Had Symptoms

- Day 0 of isolation is the day of symptom onset, regardless of when you tested positive.
- Day 1 is the first full day after the day your symptoms started.

Isolation

- If you test positive for COVID-19, stay home for at least 5 days and isolate from others in your home.
- You are likely most infectious during these first 5 days.
- Wear a high-quality mask if you must be around others at home and in public.
- Do not go places where you are unable to wear a mask. For travel guidance, see CDC's Travel webpage.
- Do not travel.
- Stay home and separate from others as much as possible.
- Use a separate bathroom, if possible.
- Take steps to improve ventilation at home, if possible.
- Do not share personal household items, such as cups, towels, and utensils.
- Monitor your symptoms. If you have an emergency warning sign (like trouble breathing), seek emergency medical care immediately.
- Learn more about what to do if you have COVID-19.

ENDING ISOLATION

- End isolation based on how serious your COVID-19 symptoms were.
- Loss of taste and smell may persist for weeks or months after recovery and need not delay the end of isolation.

If You Had No Symptoms

- You may end isolation after day 5.

If You Had Symptoms and Your Symptoms Are Improving

- You may end isolation after day 5 if you are fever free for 24 hr (without the use of fever-reducing medication).

Your Symptoms Are Not Improving

Continue to isolate until:

- You are fever free for 24 hr (without the use of fever-reducing medication).
- Your symptoms are improving.*

If You Had Symptoms and Had Moderate illness (you experienced shortness of breath or had difficulty breathing)

- You need to isolate through day 10.

Severe Illness (You Were Hospitalized) or Have a Weakened Immune System

- You need to isolate through day 10.
- Consult your doctor before ending isolation.
- Ending isolation without a viral test may not be an option for you.
- If you are unsure if your symptoms are moderate or severe or if you have a weakened immune system, talk to a healthcare provider for further guidance.

Regardless of When You End Isolation

Until at least day 11:

- Avoid being around people who are more likely to get very sick from COVID-19.
- Remember to wear a high-quality mask when indoors around others at home and in public.
- Do not go places where you are unable to wear a mask until you are able to discontinue masking (see below).
- For travel guidance, see CDC's Travel webpage.

Removing Your Mask

After you have ended isolation, when you are feeling better (no fever without the use of fever-reducing medications and symptoms improving):

- Wear your mask through day 10.

OR

- If you have access to antigen tests, you should consider using them. With two sequential negative tests 48 hr apart, you may remove your mask sooner than day 10.

NOTE: If your antigen test results* are positive, you may still be infectious. You should continue wearing a mask and wait at least 48 hours before taking another test. Continue taking antigen tests at least 48 hr apart until you have two sequential negative results. This may mean you need to continue wearing a mask and testing beyond day 10.

After you have ended isolation, if your COVID-19 symptoms recur or worsen, restart your isolation at day 0. Talk to a healthcare provider if you have questions about your symptoms or when to end isolation.

*As noted in the U.S. Food and Drug Administration labeling for authorized over-the-counter antigen tests, negative test results do not rule out SARS-CoV-2 infection and should not be used as the sole basis for treatment or patient management decisions, including infection control decisions.

From Centers for Disease Control and Prevention. Isolation and precautions for people with COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/your-health/isolation.html

Chapter 312

Rotaviruses, Caliciviruses, and Astroviruses

Dorsey M. Bass

Diarrhea is a leading cause of childhood death in the world, accounting for 5-10 million deaths per year. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteric viruses are not only major causes of pediatric deaths but also lead to significant morbidity. Before rotavirus vaccines were available, children in the United States were estimated to have a risk of hospitalization for rotavirus diarrhea of 1:43, corresponding to 80,000 hospitalizations annually.

ETIOLOGY

Rotaviruses, astroviruses, caliciviruses such as the Norwalk agent, and enteric adenoviruses are the medically important pathogens of human viral gastroenteritis (see Chapter 387).

Rotaviruses are in the Reoviridae family and cause disease in virtually all mammals and birds. These viruses are wheel-like, triple-shelled icosahedrons containing 11 segments of double-stranded RNA. The diameter of the particles on electron microscopy is approximately 80 nm. Rotaviruses are classified by serogroup (A, B, C, D, E, F, and G) and subgroup (I or II). Rotavirus strains are species specific and do not cause disease in heterologous hosts. Group A includes the common human pathogens and a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China

only. Occasional human outbreaks of group C rotavirus are reported. The other serogroups infect only nonhumans.

Subgrouping of rotaviruses is determined by the antigenic structure of the inner capsid protein, VP6. Serotyping of rotaviruses, described for group A only, is determined by classic cross-neutralization testing and depends on the outer capsid glycoproteins, VP7 and VP4. The VP7 serotype is referred to as the *G type* (for glycoprotein). There are 10 G serotypes, of which 4 cause most illness and vary in occurrence from year to year and region to region. The VP4 serotype is referred to as the P type. There are 11 P serotypes. Although both VP4 and VP7 elicit neutralizing immunoglobulin (Ig) G antibodies, the relative role of these systemic antibodies compared with mucosal IgA antibodies and cellular responses in protective immunity remains unclear.

Caliciviruses, which constitute the Caliciviridae family, are small, 27- to 35-nm viruses and are the most common cause of gastroenteritis outbreaks in older children and adults. Caliciviruses also cause a rotavirus-like illness in young infants. They are positive-sense, single-stranded RNA viruses with a single structural protein. Human caliciviruses are divided into two genera, the noroviruses and sapoviruses. Caliciviruses have been named for locations of initial outbreaks: Norwalk, Snow Mountain, Montgomery County, Sapporo, and others. Caliciviruses and astroviruses are sometimes referred to as **small, round viruses** on the basis of their appearance on electron microscopy.

Astroviruses constitute the Astroviridae family and are important agents of viral gastroenteritis in young children, with a high incidence in both the developing and developed worlds. Astroviruses are positive-sense, single-stranded RNA viruses. They are small particles, approximately 30 nm in diameter, with a characteristic central five- or six-pointed star when viewed on electron microscopy. The capsid consists of three structural proteins. There are eight known human serotypes.

Enteric adenoviruses are a common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in human stool, especially during and after typical upper respiratory tract infections (see Chapter 309), only serotypes 40 and 41 cause gastroenteritis. These strains are very difficult to grow in tissue culture. The virus consists of an 80-nm–diameter icosahedral particle with a relatively complex double-stranded DNA genome.

Aichi virus is a picornavirus that is associated with gastroenteritis and was initially described in Asia. Several other viruses that may cause diarrheal disease in animals have been postulated but are not well established as human gastroenteritis viruses. These include coronaviruses, toroviruses, and pestiviruses. The **picobirnaviruses** are an unclassified group of small (30-nm), single-stranded RNA viruses that have been found in 10% of patients with HIV-associated diarrhea.

EPIDEMIOLOGY

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children <5 years. Of these, 18 million cases are considered at least moderately severe, with approximately 200,000 deaths per year. Rotavirus caused 3 million cases of diarrhea, 80,000 hospitalizations, and 20-40 deaths annually in the United States before widespread vaccine use.

Rotavirus infection is most common in winter months in temperate climates. In the United States, the annual winter peak historically spread from west to east. Unlike the spread of other winter viruses, such as influenza, this wave of increased incidence was not caused by a single prevalent strain or serotype. Since widespread adoption of rotavirus vaccines, this geographic phenomenon has vanished and peaks have decreased. Typically, several serotypes predominate in a given community for one or two seasons, but nearby locations may harbor unrelated strains. Disease tends to be most severe in patients 3-24 months of age, although 25% of the cases of severe disease occur in children older than 2 years of age, with serologic evidence of infection developing in virtually all children by 4-5 years of age. Infants younger than 3 months are relatively protected by transplacental antibody and possibly breastfeeding. Infections in neonates and in adults in close contact with infected children are generally asymptomatic. Some rotavirus strains have stably colonized newborn nurseries for years, infecting virtually all newborns without causing any overt illness.

Rotavirus and the other gastrointestinal viruses spread efficiently by the fecal-oral route, and outbreaks are common in children's hospitals and childcare centers. The virus is shed in stool at a very high concentration before and for days after the clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

The epidemiology of **astroviruses** is not as thoroughly studied as that of rotavirus, but these viruses are a common cause of mild to moderate watery winter diarrhea in children and infants and are an uncommon pathogen in adults. Hospital outbreaks are common. **Enteric adenovirus** gastroenteritis occurs year-round, mostly in children younger than 2 years. Nosocomial outbreaks occur but are less common than with rotavirus and astrovirus. **Calicivirus** is best known for causing large, explosive outbreaks among older children and adults, particularly in settings such as schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source. Like astrovirus and rotavirus, caliciviruses are also commonly found in winter infantile gastroenteritis and are now the leading cause of significant pediatric viral diarrhea in communities with high rates of rotavirus vaccination.

PATHOGENESIS

Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the clinical resolution of diarrhea. The gastric mucosa is not affected despite the commonly used term *gastroenteritis,* although delayed gastric emptying has been documented during Norwalk virus infection.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions, such as hydrolysis of disaccharides, and absorptive functions, such as the transport of water and electrolytes via glucose and amino acid cotransporters. Crypt enterocytes are undifferentiated cells that lack the brush-border hydrolytic enzymes and are net secretors of water and electrolytes. Selective viral infection of intestinal villus tip cells thus leads to (1) decreased absorption of salt and water and an imbalance in the ratio of intestinal fluid absorption to secretion and (2) diminished disaccharidase activity and malabsorption of complex carbohydrates, particularly lactose. Most evidence supports altered absorption as the more important factor in the genesis of viral diarrhea. It has been proposed that a rotavirus nonstructural protein (NSP4) functions as an enterotoxin.

Viremia may occur in severe, primary infections, but symptomatic **extraintestinal infection** is extremely rare in immunocompetent persons. In contrast, immunocompromised patients may occasionally experience central nervous system, hepatic, or renal involvement. The increased vulnerability of infants (compared with older children and adults) to severe morbidity and mortality from gastroenteritis viruses may relate to a number of factors, including decreased intestinal reserve function, lack of specific immunity, and decreased nonspecific host defense mechanisms such as gastric acid and mucus. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk for food allergies and celiac disease.

CLINICAL MANIFESTATIONS

Rotavirus infection typically begins after an incubation period of <48 hours (range: 1-7 days) with mild to moderate fever as well as vomiting, followed by the onset of frequent, watery stools. All three symptoms are present in about 50–60% of cases. Vomiting and fever typically abate during the second day of illness, but diarrhea often continues for 5-7 days. The stool is without gross blood or white blood cells. Dehydration may develop and progress rapidly, particularly in infants. The most severe disease typically occurs among children 4-36 months of age. Malnourished children and children with underlying intestinal disease, such as short-bowel syndrome, are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children experience severe and prolonged illness. Rotavirus has rarely been associated with mild encephalopathy that may progress to cerebellitis and with reversible splenium lesions. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of **astrovirus** infection appears to be similar to that of rotavirus gastroenteritis, with the notable exception that the disease tends to be milder, with less significant dehydration. **Adenovirus enteritis** tends to cause diarrhea of longer duration, often 10-14 days. The **Norwalk virus** has a short (12-hour) incubation period. Vomiting and nausea tend to predominate in an illness associated with the Norwalk virus, and the duration is brief, usually consisting of 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as *Staphylococcus aureus* and *Bacillus cereus.*

DIAGNOSIS

In most cases, a satisfactory diagnosis of acute viral gastroenteritis can be made on the basis of the clinical and epidemiologic features. Many hospitals now offer multiplex PCR stool testing for multiple diarrheal pathogens, including a variety of bacterial and protozoan and all five common viral agents in one test. Enzyme-linked immunosorbent assays, which offer >90% specificity and sensitivity, are available for the detection of group A rotaviruses, caliciviruses, and enteric adenoviruses in stool samples. Research tools include electron microscopy of stools, RNA polymerase chain reaction analysis to identify G and P antigens, and culture. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent or high fever, blood or white blood cells in the stool, or persistent severe or bilious vomiting, especially in the absence of diarrhea.

LABORATORY FINDINGS

Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white blood cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other infectious causes of enteritis, such as bacteria and protozoa. Occasionally, surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis.

TREATMENT

Avoiding and treating dehydration are the main goals in the treatment of viral enteritis. A secondary goal is maintenance of the nutritional status of the patient (see Chapters 74 and 387).

There is no routine role for antiviral drug treatment of viral gastroenteritis. Controlled studies show limited benefits for antidiarrheal drugs, and there is a significant risk for serious side effects with these types of agents. Antibiotics are similarly of no benefit. Antiemetics such as ondansetron may help alleviate vomiting in children older than 2 years. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus and norovirus gastroenteritis, but this treatment is currently considered experimental. Therapy with probiotic organisms such as *Lactobacillus* spp. has been shown to be helpful only in mild cases and not in dehydrating disease.

Supportive Treatment

Rehydration via the oral route can be accomplished in most patients with mild to moderate dehydration (see Chapters 74 and 387). Severe dehydration requires immediate intravenous therapy followed by oral rehydration. Modern oral rehydration solutions containing appropriate quantities of sodium and glucose promote the optimum absorption of fluid from the intestine. There is no evidence that a particular carbohydrate source (rice) or the addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids, such as flat soda, fruit juice, and sports drinks, are inappropriate for the rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric) route should be done over 6-8 hours, and feedings should be initiated immediately thereafter. Providing the rehydration fluid at a slow, steady rate, typically 5 mL/min, reduces vomiting and improves the success of oral therapy. Rehydration solution should be continued as a supplement to make up for ongoing excessive stool loss. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hours) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breastfeeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (e.g., soy formula and lactose-free cow's milk) for several days, although this step is not necessary for most children. Hypocaloric diets low in protein and fat such as BRAT (*b*ananas, *r*ice, cereal, *a*pplesauce, and *t*oast) have not been shown to be superior to a regular diet.

PROGNOSIS

Most fatalities occur in infants with poor access to medical care and are attributed to dehydration. Children may be infected with rotavirus each year during the first 5 years of life, but each subsequent infection decreases in severity. Primary infection results in a predominantly serotype-specific immune response, whereas reinfection, which is usually with a different serotype, induces a broad immune response with cross-reactive heterotypic antibody. After the initial natural infection, children have limited protection against subsequent asymptomatic infection (38%) and greater protection against mild diarrhea (73%) and moderate to severe diarrhea (87%). After the second natural infection, protection increases against subsequent asymptomatic infection (62%) and mild diarrhea (75%) and is complete (100%) against moderate to severe diarrhea. After the third natural infection, there is even more protection against subsequent asymptomatic infection (74%) and near-complete protection against even mild diarrhea (99%).

PREVENTION

Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies, virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses. Good handwashing and isolation procedures can help control nosocomial outbreaks. The role of breastfeeding in prevention or amelioration of rotavirus infection may be slight, given the variable protection observed in a number of studies. Vaccines offer the best hope for control of these ubiquitous infections.

Vaccines

A trivalent rotavirus vaccine was licensed in the United States in 1998 and was subsequently linked to an increased risk for intussusception, especially during the 3- to 14-day period after the first dose and the 3- to 7-day period after the second dose. The vaccine was withdrawn from the market in 1999. Subsequently, two new live, oral rotavirus vaccines have been approved in the United States after extensive safety and efficacy testing.

A live, oral, pentavalent rotavirus vaccine was approved in 2006 for use in the United States. The vaccine contains five reassortant rotaviruses isolated from human and bovine hosts. Four of the reassortant rotaviruses express one serotype of the outer protein VP7 (G1, G2, G3, or G4), and the fifth expresses the protein P1A (genotype P[8]) from the human rotavirus parent strain. The pentavalent vaccine protects against rotavirus gastroenteritis when administered as a three-dose series at 2, 4, and 6 months of age. The first dose should be administered between 6 and 12 wk of age, with all three doses completed by 32 weeks of age. The vaccine provides substantial protection against rotavirus gastroenteritis, with a primary efficacy of 98% against severe rotavirus gastroenteritis caused by G1-G4 serotypes and 74% efficacy against rotavirus gastroenteritis of any severity through the first rotavirus season after vaccination. It provides a 96% reduction in hospitalizations for rotavirus gastroenteritis through the first 2 years after the third dose. In a study of more than 70,000 infants, the pentavalent vaccine did not increase the risk for intussusception, although other studies suggest a slight increased risk.

Another monovalent rotavirus vaccine was licensed in the United States and also appears to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as two oral doses at 2 and 4 months of age. The vaccine has 85% efficacy against severe gastroenteritis and was found to reduce hospital admissions for all diarrhea by

42%. Despite being monovalent, the vaccine is effective in prevention of all four common serotypes of human rotavirus.

Preliminary surveillance data on the rotavirus incidence from the U.S. Centers for Disease Control and Prevention suggest that rotavirus vaccination greatly reduced the disease burden in the United States during the 2007–2008 rotavirus season and thereafter. Given the incomplete vaccine coverage during this period, the results suggest a degree of "herd immunity" from rotavirus immunization. Studies from several developed countries show greater than 90% protection against severe rotavirus disease. Studies from developing countries show 50–60% protection from severe disease. Vaccine-associated disease has been reported in vaccine recipients who have severe combined immunodeficiency disease (a contraindication). In addition, vaccine-derived virus may undergo reassortment and become more virulent, producing diarrhea in unvaccinated siblings.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 313

Human Papillomaviruses

Kristen A. Feemster

See also Chapter 708.

Human papillomaviruses (HPVs) cause a variety of proliferative cutaneous and mucosal lesions, including common skin warts, benign and malignant anogenital tract lesions, oral pharyngeal cancers, and life-threatening respiratory papillomas. Most HPV-related infections in children and adolescents are benign (see also Chapter 708).

ETIOLOGY

The papillomaviruses are small (55 nm), DNA-containing viruses that are ubiquitous in nature, infecting most mammalian and many nonmammalian animal species. Strains are almost always species specific. Viral DNA is divided into an early region, which encodes proteins associated with viral replication and transcription, and a late region, which encodes capsid proteins necessary for virion assembly. These structural proteins are also the immunodominant antigens leading to type-specific immune responses. More than 100 different types of HPVs have been identified through the comparison of sequence homologies. The different HPV types typically cause disease in specific anatomic sites; more than 30 HPV types have been identified from genital tract specimens.

EPIDEMIOLOGY

HPV infections of the skin are common, and most individuals are probably infected with one or more HPV types at some time. There are no animal reservoirs for HPV; all transmission is presumably from person to person. There is little evidence to suggest that HPV is transmitted by fomites. Common warts, including palmar and plantar warts, are frequently seen in children and adolescents and typically infect the hands and feet, common areas of frequent minor trauma.

HPV is also the most prevalent viral sexually transmitted infection in the United States. Up to 80% of sexually active women will acquire HPV through sexual transmission; most have their first infection within 3 years of beginning sexual intercourse. Thus HPV disproportionately affects youth, with 75% of new infections occurring in 15- to 24-year-olds. The greatest risk for HPV in sexually active adolescents is exposure to new sexual partners, but HPV can still be acquired even with a history of one partner, underscoring the ease of transmission of this virus through sexual contact. It is estimated that after 11 acts of sexual intercourse, 100% of all HPV types infecting an individual will be transmitted to the other sexual partner. Couple studies show that there is high concordance in the genital area as well as between the hand and the genital area in the other partner. Whether the DNA detected in HPV on the hand is capable of transmitting infectious particles is unknown. Unlike other sexually transmitted infections, female-to-male transmission appears greater than male-to-female transmission. This may be because males in general have superficial transient infections or deposition. In turn, males do not develop an adequate immune response, so reinfections are quite common. The prevalence of HPV in women decreases with time, suggesting immune protection, whereas in men, the prevalence of HPV remains high across all ages.

As with many other genital pathogens, perinatal transmission to newborns can occur. Transmission from caregiver to child during the early childhood years has also been documented. However, both perinatal and early childhood infections appear transient. It remains unclear whether these HPV DNA detections are simply a deposition of caregiver DNA or a true infection. Detection of HPV DNA in older preadolescent children is rare. HPV DNA detection in non–sexually active adolescents has been reported, but a history of sexual activity in adolescents is not always disclosed and is therefore difficult to confirm. Although caregivers can spread HPV to young children, if lesions are detected in a child older than 3 years of age, the possibility of sexual transmission should be raised.

In adolescents, HPV DNA is most commonly detected without evidence of any lesion. Some of these detections are thought to be the result of partner deposition and hence do not represent a true infection. In older women, detection of HPV DNA is more commonly associated with a lesion. This is because the HPV DNA detected in older women reflects those HPV infections that became established persistent infections. Persistence is now the known necessary prerequisite for the development of significant precancerous lesions and cervical cancer.

Approximately 15–20% of sexually active adolescents have detectable HPV at any given time and have normal cytologic findings. The most common clinically detected lesion in adolescent women is the cervical lesion termed **low-grade squamous intraepithelial lesion (LSIL)** (Table 313.1). LSILs can be found in 25–30% of adolescents infected with HPV. External genital warts are much less common, occurring in <1% of adolescents; the incidence has decreased since introduction of HPV vaccines, but approximately 10% of individuals will develop genital warts in their lifetime. LSIL is a cytologic and histologic term to reflect the benign changes caused by an active viral infection and is likely present in most, if not all, women with HPV infection. However, the majority of women have very minute or subtle lesions not easily detected by cytology. As with HPV DNA detection, most LSILs regress spontaneously in young women and do not require any intervention or therapy. Less commonly, HPV can induce more severe cellular changes, termed **high-grade squamous intraepithelial lesions (HSILs)** (see Chapter 590).

Although HSILs are considered precancerous lesions, they rarely progress to invasive cancer. HSILs occur in approximately 0.4–3% of sexually active women, whereas invasive cervical cancer occurs in 8 cases per 100,000 adult women. In the United States, there are approximately 12,000 new cases (~7 cases/100,000) and 4,000 deaths from cervical cancer each year. Worldwide, cervical cancer is the fourth most common cause of cancer deaths among women. HPV is also associated with a range of other anogenital cancers, including an estimated 9,000 cases of anal cancer and 44,000 cases of oropharyngeal cancers in men and women.

Some infants may acquire papillomaviruses during passage through an infected birth canal, leading to recurrent **juvenile laryngeal papillomatosis** (JLP; also referred to as *respiratory papillomatosis*). Cases also have been reported after cesarean section. The incubation period for emergence of clinically apparent lesions (genital warts or laryngeal papillomas) after perinatally acquired infection is unknown but is estimated to be around 3-6 months (see Chapter 438.2). It may be that infections can also occur during hygienic care from an infected parent.

Genital warts may represent a sexually transmitted infection even in some very young children. Therefore genital warts appearing in childhood should raise suspicion for possible sexual abuse with HPV

Table 313.1 Terminology for Reporting Cervical Cytology and Histology

DESCRIPTIVE DIAGNOSIS OF EPITHELIAL CELL ABNORMALITIES	EQUIVALENT TERMINOLOGY
SQUAMOUS CELL	
Atypical squamous cells of undetermined significance (ASC-US)	Squamous atypia
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low-grade squamous intraepithelial lesion (LSIL)	Mild dysplasia, condylomatous atypia, HPV-related changes, koilocytic atypia, cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia, CIN 2, severe dysplasia, CIN 3, carcinoma in situ
GLANDULAR CELL	
Endometrial cells, cytologically benign, in a postmenopausal woman	
Atypical	
Endocervical cells, NOS	
Endometrial cells, NOS	
Glandular cells, NOS	
Endocervical cells, favor neoplastic	
Glandular cells, favor neoplastic	
ENDOCERVICAL ADENOCARCINOMA IN SITU	
Adenocarcinoma	
Endocervical	
Endometrial	
Extrauterine	
NOS	

NOS, Not otherwise specified.

transmission during the abusive contact. A child with genital warts should thus be provided with a complete evaluation for evidence of possible abuse (see Chapter 17.1), including the presence of other sexually transmitted infections (see Chapter 163). However, the presence of genital warts in a child does not confirm sexual abuse, because perinatally transmitted genital warts may go undetected until the child is older. Typing for specific genital HPV types in children is not helpful in diagnosis or to confirm sexual abuse status, because the same genital types occur in both perinatal transmission and abuse. In true virginal populations, including children who are not sexually abused, rates of clinical disease are close to zero.

PATHOGENESIS

Initial HPV infection of the cervix or other anogenital surfaces is thought to begin by viral invasion of the basal cells of the epithelium, a process that is enhanced by disruption of the epithelium caused by trauma or inflammation. It is thought that the virus initially remains relatively dormant because virus is present without any evidence of clinical disease. The life cycle of HPV depends on the differentiation program of keratinocytes. The pattern of HPV transcription varies throughout the epithelial layer and through different stages of disease (LSIL, HSIL, invasive cancer). Understanding of HPV transcription enhances understanding of its ability to behave as an oncovirus. Early region proteins, E6 and E7, function as transactivating factors that regulate cellular transformation. Complex interactions between E6- and E7-transcribed proteins and host proteins result in the perturbation of normal processes that regulate cellular DNA synthesis. The perturbations caused by E6 and E7 are primarily disruption of the anti-oncoprotein p53 and retinoblastoma protein (Rb), respectively, contributing to the development of anogenital cancers. Disruption of these proteins results in continued cell proliferation, even under the circumstances of DNA damage, which leads to basal cell proliferation, chromosomal abnormalities, and aneuploidy, hallmarks of squamous intraepithelial lesion (SIL) development.

Evidence of productive viral infection occurs in benign lesions such as external genital warts and LSILs, with the abundant expression of viral capsid proteins in the superficial keratinocytes. The appearance of the HPV-associated koilocyte is a result of the expression of E4, a structural protein that causes collapse of the cytoskeleton. Low-level expression of E6 and E7 proteins results in cell proliferation seen in the basal cell layer of LSILs. LSILs are a manifestation of active viral replication and protein expression. In HSILs, expression of E6 and E7 predominates throughout the epithelium, with little expression of the structural proteins L1 and L2. This results in the chromosomal abnormalities and aneuploidy characteristic of the higher-grade lesions. The critical events that lead to cancer have not been verified; however, several mechanisms are thought to be critical, including viral integration into the host chromosome and activation of telomerase to lengthen chromosomes and avoid physiologic cell senescence. Over 150 HPV types have been documented and are classified by extent of their DNA homology into 5 genera, with the different types having different life cycle and disease characteristics. The predominant group is α HPV types, which are associated with cutaneous and mucosal anogenital infections and cancers. β, γ, μ, and ν cause predominantly benign cutaneous lesions but can be difficult to manage in severely immunocompromised individuals. B types are commonly detected on the skin without any apparent lesions but are associated with the development of skin cancers in those with epidermodysplasia verruciformis or other forms of immunodeficiencies. Genital lesions caused by the α HPV types may be broadly grouped into those with little to no malignant potential (low risk) and those with greater malignant potential (high risk). Low-risk HPV types 6 and 11 are most commonly found in genital warts and are rarely found isolated in malignant lesions. High-risk HPV types are those types that are associated with anogenital cancers, specifically cervical cancer. HPV 16 and 18 are thought to be more oncogenic than other HPV types because they comprise 70% of cervical cancers, whereas each of the other 12 high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) contribute less than 1–9%. HPV 16 appears to be even more important in anal and HPV-associated oropharyngeal cancers, comprising close to 90% of these cancers. HPV 16 is also commonly found in women without lesions or in those with LSILs, making the connection with cancer confusing. Genital warts and SIL are commonly associated with the detection of multiple HPV types, including a combination of low- and high-risk HPV types. Data show that it is likely that a single lesion arises from a single HPV type. Detection of multiple HPV types reflects the presence of cervical and anal coexisting lesions. Almost all (95%) incident low-risk and high-risk HPV DNA detections, with or without detectable SIL, will spontaneously resolve within 1-3 years. Although HPV 16 has a slower rate of regression than some of the other high-risk types, the majority of incident HPV 16 detections also will resolve. Data suggest that clearance of an HPV type results in natural immune protection against reinfection with that same type. Redetections of the same type are not common and when found are often associated with a history of a new sexual partner, suggesting that these are not reactivated infections but are due to new exposures. These redetections rarely result in high-grade disease. Persistent high-risk–type infections are associated with increased risk for development of HSILs and invasive cancer. Progression of HSIL to invasive cancer is still rare, with only 5–15% showing progression. Approximately 50% of HPV 16–associated HSILs and 80% of non–HPV 16 HSILs will spontaneously regress in young women. Genital and common warts in general also resolve without therapy but may take years to do so. Genital warts in only extremely rare conditions can become malignant.

Most infants with recognized genital warts are infected with the low-risk types. In contrast, children with a history of sexual abuse have a clinical picture more like that of adult genital warts, consisting of mixed low- and high-risk types. There are rare reports of HPV-associated genital malignancies occurring in preadolescent children and adolescents. On the other hand, precancerous HSILs do occur in sexually active adolescents. There is a concern that younger age of sexual debut has contributed to the increase in invasive cervical cancers seen in women younger than 50 years of age in the United States, specifically cervical adenocarcinomas. Persistent HPV infections are considered necessary but not sufficient for the development of invasive



Fig. 313.1 Common warts of the left hand and the chest wall. *(From Meneghini CL, Bonifaz E. An Atlas of Pediatric Dermatology, Chicago: Year Book; 1986:45.)*



Fig. 313.2 Common warts of the hand in a mother and perianal condylomata acuminata in her son. *(From Meneghini CL, Bonifaz E. An Atlas of Pediatric Dermatology, Chicago: Year Book; 1986:44.)*

cancers. Other risk factors for which there is relatively strong suggestive evidence of association include smoking cigarettes, prolonged oral contraceptive use, greater parity, and *Chlamydia trachomatis* and herpes simplex virus infections.

CLINICAL MANIFESTATIONS

The clinical findings in HPV infection depend on the site of epithelial infection.

Skin Lesions

The typical HPV-induced lesions of the skin are proliferative, papular, and hyperkeratotic. Common warts are raised circinate lesions with a keratinized surface (Fig. 313.1). Plantar and palmar warts are practically flat. Multiple warts are common and may create a mosaic pattern. Flat warts appear as small (1- to 5-mm), flat, flesh-colored papules.

Genital Warts

Genital warts may be found throughout the perineum around the anus, vagina, and urethra, as well as in the cervical, intravaginal, and intraanal areas (Fig. 313.2). Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex. Although rare, lesions caused by genital genotypes can also be found on other mucosal surfaces, such as the conjunctivae, tongue, gingivae, and nasal mucosa. They may be single or multiple lesions and are frequently found in multiple anatomic sites, including the cervix. External genital warts can be flat, dome shaped, keratotic, pedunculated, and cauliflower shaped and may occur singly, in clusters, or as plaques. On mucosal epithelium, the lesions are softer. Depending on the size and anatomic location, lesions may be pruritic and painful, may cause burning with urination, may be friable and bleed, or may become superinfected. Adolescents are frequently disturbed by the development of genital lesions. Other rarer lesions caused by HPV of the external genital area include Bowen disease, bowenoid papulosis, squamous cell carcinomas, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Squamous Intraepithelial Lesions and Cancers

SILs detected with cytology are usually invisible to the naked eye and require the aid of colposcopic magnification and acetic acid. With aid, the lesions appear white and show evidence of neovascularity. SILs can occur on the cervix, vagina, vulva, penis, and intraanus. HPV-associated squamous cell lesions can also be found in the oropharynx. Invasive cancers tend to be more exophytic, with aberrant-appearing vasculature. These lesions are rarely found in non–sexually active individuals.

Laryngeal Papillomatosis

The median age at diagnosis of recurrent laryngeal papillomatosis is 3 years. Children present with hoarseness, an altered cry, and sometimes stridor. Rapid growth of respiratory papillomas can occlude the upper airway, causing respiratory compromise. These lesions may recur within weeks of removal, requiring frequent surgery. The lesions do not become malignant unless treated with irradiation.

DIAGNOSIS

The diagnosis of external genital warts and common warts may be reliably determined by visual inspection of a lesion by an experienced observer and does not require additional tests for confirmation. A biopsy should be considered if the diagnosis is uncertain, the lesions do not respond to therapy, or the lesions worsen during therapy.

Screening for cervical cancer in young women begins with cytology, which is performed by either Papanicolaou smear or liquid-based cytology and may also include high-risk HPV DNA testing for women age 30-65 years. Screening guidelines were updated in 2018 by the U.S. Preventive Services Task Force (USPSTF) and recommend starting screening at age 21 years. Screening earlier is more likely to result in unnecessary referrals for colposcopy, because most lesions, including both LSILs and HSILs in this age-group, are likely to regress. Guidelines recommend screening with cytology every 3 years through 29 years of age. For women age 30-65 years of age, USPSTF recommends screening every 3 years with cervical cytology alone, or every 5 years with high-risk HPV testing alone or high-risk HPV testing with cytology (co-testing). High-risk HPV testing is not recommended earlier than age 30 years, because HPV infections are extremely common in young women, resulting in a very low positive predictive value in this age-group. These recommendations apply to all persons who have a cervix, regardless of sexual history of HPV vaccination history.

The recommended terminology used for cytologic evaluation is based on the Bethesda system (see Table 313.1). Recent updates to the terminology used for histology uses similar terms. Many clinicians still prefer the World Health Organization terminology using cervical intraepithelial neoplasia (CIN) 1, 2, and 3 (see Table 313.1). Although the purpose of screening is to identify CIN 3+ lesions, the majority of CIN lesions are found in women who were referred for **atypical squamous cells of undetermined significance (ASC-US)** or LSILs on cytology. On the other hand, few CIN 3 or cancers exist in women younger than 24 years of age. Thus, for women 21-24 years of age, ASC-US and LSILs are treated the same.

Consensus guidelines from the American Society of Colposcopy and Cervical Pathology for the management of cervical cancer screening abnormalities were updated in 2019 and used a risk-based (related to

a patient's risk of CIN 3) rather than test-based algorithm. Treatment guidelines are also dichotomized by age group, 21-24 years and 25 years or older. Women age 21-24 years with ASC-US or LSIL should have repeat cytology at 12 months and 24 months after the initial abnormal result. For persistent ASC-US or LSILs at 2 years of follow-up or for HSIL at any point, referral for colposcopy is recommended. If colposcopy results show LSIL, cytology should be repeated in 1 year. If there are two negative cytology results, routine age-based screening can be resumed. If repeat cytology shows HSIL with CIN2+, observation with repeat colposcopy every 6 months should be performed. If HSIL persists for 2 years or if CIN 3+ is identified, treatment with an excisional procedure is recommended. In women 25 years of age and older, HSIL can be treated without histologic confirmation. However, this approach should be avoided in those 21-24 years of age, because HSIL is often misdiagnosed in this group or will resolve spontaneously.

In all women age 21 years and older, high-risk HPV testing is acceptable to assist in ASC-US triage. This recommendation is based on the observations that adult women with ASC-US and a positive HPV test result for high-risk types are more likely to have CIN 2/3 than women with a negative HPV test result. However, in women with ASC-US and a positive HPV test for high-risk types, repeat cytology is recommended for confirmation. In women 21-24 years of age referred for colposcopy and found to have no lesion or biopsy-confirmed LSIL after ASC-US or LSIL cytology, repeat cytology is recommended at 12-month intervals as described previously. In women with biopsy-confirmed LSIL after atypical squamous cells of high grade (ASC-H) or HSIL, observation with cytology and colposcopy is recommended at 6-month intervals for up to 2 years. For persistent ASC-H or HSIL at 2 years or progression at any time, treatment is recommended. These guidelines and updates can be found at http://www.asccp.org.

Very sensitive tests for the presence of HPV DNA, RNA, and proteins are becoming generally available, although they are not required for the diagnosis of external genital warts or related conditions. There are no indications for HPV DNA testing in women younger than 21 years of age or children. HPV DNA testing is also not recommended in women 21-29 years of age but is acceptable for ASC-US triage. Diagnosis of JLP is made based on laryngeal examination. There are no routine screening recommendations for noncervical or oropharyngeal lesions.

DIFFERENTIAL DIAGNOSIS

A number of other conditions should be considered in the differential diagnosis of genital warts, including condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, neoplasms, Bowen disease, bowenoid papulosis, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Condyloma latum is caused by secondary syphilis and can be diagnosed with darkfield microscopy and standard serologic tests for syphilis. Seborrheic keratoses are common, localized, hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, is highly infectious, and is often umbilicated. Pearly penile papules occur at the penile corona and are normal variants that require no treatment.

TREATMENT

Most common (plantar, palmar, skin) warts eventually resolve spontaneously (see Chapter 708). Symptomatic lesions should be removed. Removal includes a variety of self-applied therapies, including salicylic acid preparations and provider-applied therapies (cryotherapy, laser therapy, electrosurgery). Genital warts are benign and usually remit, but only over an extended period. It is recommended that genital lesions be treated if the patient or the parent requests therapy. Treatments for genital warts are categorized into self-applied and provider-applied. No one therapy has been shown to be more efficacious than any other. Recommended patient-applied treatment regimens for external genital warts include topical podofilox, imiquimod, and sinecatechins. Podofilox 0.5% solution (using a cotton swab) or gel (using a finger) is applied to visible warts in a cycle of applications twice per day for 3 days followed by 4 days of no therapy, repeated for up to a total of four cycles as needed. The total volume of podofilox used per day should not exceed 0.5 mL, and patients should wash hands before and after each application. Imiquimod 5% cream is applied at bedtime, 3 times per week, every other day, for up to 16 weeks. Imiquimod 3.75% cream is applied at bedtime every night for up to 8 weeks. For both formulations, the treated area should be washed with mild soap and water 6-10 hours after treatment. Sinecatechins (15% ointment) is a topical product from green tea extract used for external genital wart treatment that is applied 3 times daily until warts have completely resolved but no longer than 16 weeks. A 0.5-cm strand of ointment should be applied to each wart as a thin layer.

Provider-applied therapies include surgical treatments (electrosurgery, tangential scissor or shave excision, curettage, laser surgery), cryotherapy with liquid nitrogen or a cryoprobe and office-based application of bichloroacetic (BCA) or trichloroacetic acid (TCA) 80–90% solution. Surgical treatments require appropriate training and equipment but can be most beneficial for patients with large or extensive warts. Surgical removal or cryotherapy are also recommended for urethral meatus warts, while surgical removal, cryotherapy or BCA / TCA is recommended for vaginal, cervical, and intraanal warts. BCA or TCA treatment should be applied only to warts and can be repeated once per week for 3-6 weeks.

Alternative regimens include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir, but there are few available data regarding their efficacy. Intralesional interferon is associated with significant adverse effects and is reserved for treatment of recalcitrant cases. Podophyllin resin is no longer recommended because of the availability of other, safer regimens but may be considered for provider-administered treatment if there can be strict adherence to recommendations to prevent complications from systemic absorption.

Many therapies are painful, and children should not undergo painful genital treatments unless adequate pain control is provided. Parents and patients should not be expected to apply painful therapies themselves. None of the patient-applied therapies are approved for use during pregnancy, and podofilox is contraindicated in pregnancy. For any of the nonsurgical treatments, prescription is contraindicated in a patient with any history of hypersensitivity to any product constituents.

If HPV exposure as a result of sexual abuse is suspected or known, the clinician should ensure that the child's safety has been achieved and is maintained.

When indicated, the most common treatments for CIN 2/3 are ablative and excisional treatments, including cryotherapy, laser, and loop electrosurgical excisional procedures. Once confirmed by histology with CIN 1, LSILs can be observed as described previously. The decision to treat a persistent CIN 1 rests between the provider and patient. Risks of treatment, including premature delivery in a future pregnancy, should be discussed before any treatment decision. Treatment in pregnancy is not recommended unless invasive cancer is present.

JLP is commonly treated with surgical removal of lesions, but laser and microdebriders are also used. However, because of the incidence of scar formation after repeat debridement procedures, medical therapies have been increasingly investigated. Adjunctive treatments have included interferon-α, antivirals such as cidofovir administered locally or systemically, photodynamic therapy, antiinflammatory drugs (celecoxib), heat shock protein, human monoclonal antibodies (bevacizumab), and HPV vaccination. However, the effectiveness of adjunctive therapies is not consistent.

COMPLICATIONS

The presence of HPV lesions in the genital area may be a cause of profound embarrassment to a child or parent. Complications of therapy are uncommon; chronic pain (vulvodynia) or hypoesthesia may occur at the treatment site. Lesions may heal with hypopigmentation or hyperpigmentation and less commonly with depressed or hypertrophic scars. Surgical therapies can lead to infection and scarring. Premature delivery and low birthweight in future pregnancies are complications of excisional therapy for CIN.

It is estimated that 5–15% of untreated CIN 3 lesions will progress to cervical cancer. Most cancer is prevented by early detection and treatment of these lesions. Despite screening, cervical cancer develops rapidly in a few adolescents and young women. The reason for the rapid

development of cancer in these rare cases remains unknown, but host genetic defects are likely underlying causes. JLPs rarely become malignant, unless they have been treated with irradiation. Vulvar condylomas rarely become cancerous. HPV-associated cancers of the vagina, vulva, anus, penis, and oral cavity are much rarer than cervical tumors, and therefore screening for noncervical lesions is not currently recommended. However, anal, vaginal, and vulvar cancers are more common in women with cervical cancer; thus it is recommended to screen women with cervical cancer for other anogenital or oropharyngeal tumors with visual and/or digital inspection

PROGNOSIS

With all forms of therapy, genital warts commonly recur, and approximately half of children and adolescents require a second or third treatment. Recurrence is also evident in patients with JLP. Patients and parents should be warned of this likelihood. Combination therapy for genital warts (imiquimod and podofilox) does not improve response and may increase complications. Prognosis of cervical disease is better, with 85–90% cure rates after a single treatment with the loop electrosurgical excision procedure. Cryotherapy has a slightly lower cure rate. Recalcitrant disease should prompt an evaluation and is common in immunocompromised individuals, specifically men and women infected with HIV.

PREVENTION

The only means of preventing all types of HPV infection is to avoid direct contact with lesions. Condoms may reduce the risk for HPV transmission; condoms also prevent other sexually transmitted infections, which are risk factors associated with SIL development. In addition, condoms appear to hasten the regression of LSILs in women. Avoiding smoking cigarettes is important in preventing cervical cancer. Prolonged oral contraceptive use and parity have been shown to be risks for cervical cancer. However, the mechanisms associated with these factors have not been identified, and consequently no change in counseling is recommended.

HPV vaccines show efficacy against type-specific persistence and development of type-specific disease, including the cervix, vagina, vulva, and anus. A quadrivalent HPV vaccine containing types 6, 11, 16, and 18 was licensed in the United States in 2006, and a bivalent HPV vaccine containing types 16 and 18 was licensed in the United States in 2009. A 9-valent vaccine containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was approved in 2014. Initial licensure was for vaccination of persons age 9-26 years. In 2018, the FDA expanded licensure to include men and women age 27-45 years based on quadrivalent HPV vaccine clinical trial results in women age 27-45 years and bridging immunogenicity and safety data in women and men. The bivalent vaccine is indicated for the prevention of cervical precancer and cancer in females. The 4- and 9-valent HPV vaccines are indicated for the prevention of anal, cervical, vaginal, and vulvar precancers/cancers, as well as genital warts in females and anal precancer cancer and genital warts in males. The indication for the 9-valent HPV vaccine was expanded to include oropharyngeal and other head and neck cancers in 2021.

The types targeted by the nonavalent vaccine account for up to 85% of cervical cancer cases. The efficacy of these vaccines is mediated by the development of neutralizing antibodies. Prelicensure studies demonstrate 90–100% efficacy in the prevention of persistent HPV infection, CIN 2/3, adenocarcinoma in situ, anogenital warts, and precancerous vaginal and vulvar lesions. Since vaccine introduction, data from Sweden and Australia show a decrease in national rates of genital warts within 4 years of implementing vaccination programs. Data from the United States show significant reductions in the prevalence of the HPV types contained in the quadrivalent vaccine among adolescent and young adult females in the years 2009–2012 (postvaccine) compared with 2003–2006 (prevaccine). Additionally, the HPV vaccine–type prevalence was 2.1% in vaccinated compared with 16.9% in unvaccinated 14- to 24-year-old sexually active females. A systematic review of 20 studies conducted in nine high-income countries showed reductions of at least 68% in the prevalence of HPV 16 and 18 among 13- to 19-year-olds in countries with HPV vaccination rates >50%. Recent data also demonstrate significant reductions in cervical cancer rates and CIN 3 with the highest reductions among women who were vaccinated at age 12-13 years after implementation of a national HPV vaccination program in the United Kingdom. A 29% reduction in cervical cancer annual incidence rates from 2003–2006 to 2011–2014 was observed among females age 15-24 years in the United States. Additionally, an analysis of data from a population-based cancer registry showed a decline in the incidence of squamous cell carcinoma and adenocarcinoma among young women age 15-29 years, with the largest reductions in the 15- to 20-year age group. Available effectiveness data suggest that HPV vaccination confers herd immunity in addition to individual protection.

Vaccination in the United States is recommended routinely for all adolescents at 11-12 years of age and is administered intramuscularly in the deltoid region in a two-dose series at 0 and 6-12 months. A two-dose series was approved and recommended in 2016 for younger adolescents who initiate the HPV vaccine series before age 15 years based on immunogenicity data showing a comparable immune response among younger adolescents who receive a two-dose series compared with older adolescents, who receive a three-dose series. The effectiveness of one dose has also been evaluated in observational and post-hoc analyses from clinical trials.

It is important that vaccination take place in children before they become sexually active, because the rate of HPV acquisition is high shortly after the onset of sexual activity. Vaccine can be given to adolescents as young as 9 years of age, and catch-up vaccination is now recommended in all persons through 26 years of age. Vaccination is also recommended for adults 27-45 years using shared clinical decision making if they have not been previously vaccinated. For any adolescent who receives his or her first HPV vaccine dose at age 15 years or older, a three-dose series at 0, 1-2, and 6 months is recommended. The three-dose series is also recommended for adolescents and young adults 9-26 years of age who have an immunocompromising condition. Individuals who are already infected with one or more vaccine-related HPV types before vaccination are protected from clinical disease caused by the remaining vaccine HPV types. Therefore a history of prior HPV infection is not a contraindication to vaccine receipt. Currently licensed HPV vaccines are not therapeutic. However, there are therapeutic HPV vaccines under development that are primarily designed to generate a cell-mediated immune response to target infected cells.

Post-licensure vaccine safety surveillance has not identified any serious adverse events attributable to HPV vaccine receipt. Three large observational studies and safety monitoring through active and passive surveillance networks among more than 1 million individuals have not identified any association between HPV vaccination and outcomes such as autoimmune disorders, stroke, or venous thrombotic emboli. Vaccination can cause fever in approximately 1 in 60 and discomfort at the injection site in 1 in 30 vaccine recipients. Syncope has also been found to be correlated with vaccine administration in 0.1% of vaccine recipients. Therefore it is advised that adolescents remain seated for 15 minutes after vaccination.

Despite an excellent safety and efficacy profile, HPV vaccine uptake has been slow. Immunization rates have consistently lagged behind rates for the other vaccines included in the adolescent immunization platform. In 2020, 75% of 13- to 17-year-olds had received at least one HPV vaccine dose compared with 89% who received at least one dose of the quadrivalent meningococcal vaccine and 92% who received tetanus-diphtheria-acellular pertussis (Tdap) vaccine. Reasons for the slow uptake include inconsistent provider recommendation, lack of knowledge about HPV, parental belief that vaccination is not necessary for younger adolescents, and misconceptions about vaccine safety, among others. There is a growing body of literature evaluating interventions to improve HPV vaccine uptake. One important strategy is a strong, consistent recommendation in which HPV vaccines are presented in the same way as Tdap and meningococcal vaccines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 314

Arboviral Infections

Scott B. Halstead

The arthropod-borne viral infections are caused by a group of mosquito- or tick-transmitted viral pathogens of several taxa and manifest clinically mostly as neurologic infections, influenza-like illnesses, or acute viral exanthems. In temperate countries, arboviruses are transmitted during warmer weather; however, in tropical and subtropical countries, arboviruses may be transmitted year-round either in an urban cycle (human to mosquito to human) or by arthropods that feed on other vertebrate species and then feed on humans.

ETIOLOGY

The principal arthropod-borne viral infections in North America are West Nile encephalitis (WNE), St. Louis encephalitis (SLE), Powassan (POW) encephalitis, a complex of California encephalitis group viruses, and, less frequently, western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Colorado tick fever (Fig. 314.1). In 2013, chikungunya virus (CHIK) emerged from its original African zoonosis via Asia into the tropical and subtropical Western Hemisphere, exposing indigenes and many visitors who were traveling in the region. A few cases occurred in southern United States. In 2015, Zika virus (ZIKV), a flavivirus also maintained in Africa zoonoses, was introduced into the Americas, again from endemic areas in Asia. Limited transmission occurred within the continental United States. The major source of infection among Americans for each of these viruses has been travel to tropical and subtropical countries. CHIK appears to be endemic now, whereas ZIKV illnesses have decreased dramatically.

Throughout the world outside North America, there are many arboviruses that pose major health problems (Fig. 314.2). In descending order, these are the dengue viruses (DENV; Chapter 315), transmitted in all subtropical and tropical countries; Japanese encephalitis (JE), transmitted in northern, southern, and Southeast Asia; tick-borne encephalitis (TBE), transmitted across Europe and into northern and eastern Asia; yellow fever (YF; Chapter 316), transmitted from zoonotic cycles in Africa and South America; and Venezuelan equine encephalitis (VEE), transmitted in parts of South and Central America.

The etiologic agents belong to different viral taxa: *alphaviruses* of the family Togaviridae (CHIK, EEE, VEE, WEE), *flaviviruses* of the family Flaviviridae (DENV, JE, POW, SLE, TBE, WNE, YF, ZIKV), the California complex of the family Bunyaviridae (California encephalitis), and Reoviridae (Colorado tick fever virus). *Alphaviruses* are 69-nm, enveloped, positive-sense RNA viruses. Studies suggest that this group of viruses had a marine origin (specifically the southern ocean) and has subsequently spread to both the Old and New Worlds. VEE circulates in nature in six subtypes. Virus types I and III have multiple antigenic variants. Types IAB and IC have caused epizootics and human epidemics. Flaviviruses are 40- to 50-nm, enveloped, positive-sense RNA viruses that evolved from a common ancestor. They are mosquito-borne (WNE, SLE, JE, YF, DENV, ZIKV) and tick-borne (POW, TBE) agents, globally distributed, and responsible for many important human viral diseases. The California serogroup, 1 of 16 Bunyavirus groups, are 75- to 115-nm enveloped viruses possessing a three-segment, negative-sense RNA genome. Reoviruses are 60- to 80-nm double-stranded RNA viruses.

DIAGNOSIS

For arboviral infections not described separately, the etiologic diagnosis is established by testing either an acute-phase serum to detect the virus, viral antigen, or viral RNA (influenza-like illnesses or viral exanthems) or by recovery of virus from central nervous system (CNS) tissue or cerebrospinal fluid (CSF). More commonly, the diagnosis is established serologically. Serum obtained ≥5 days after the onset of illness is tested for the presence of virus-specific immunoglobulin (Ig) M antibodies using an enzyme-linked immunosorbent assay IgM capture test, an indirect immunofluorescence test, or a precipitin test. Alternatively, acute and convalescent sera can be tested for a fourfold or greater increase in enzyme-linked immunosorbent assay, hemagglutination inhibition, or neutralizing antibody titers. Commercial serologic diagnostic kits are marketed for DENV, CHIK, JE, TBE, WNE, YF, and ZIKV viral infections. The serum and CSF should be tested for JE or WNE virus–specific IgM. However, IgM may reflect past infection, because it may be present up to 12 months after infection. For suspected flavivirus infections, including ZIKV, it may be possible to establish infection using a serologic test, calling on the specificity of neutralizing antibodies. The most common of these is the plaque or focus-reduction neutralizing antibody test. Reference laboratories offer tests for all of the pathogenic flaviviruses. The diagnosis may also be established by the isolation of virus in cell cultures, by identification of viral RNA, or by detection of viral proteins (e.g., dengue NS1) from blood, brain tissue obtained by brain biopsy, or tissues obtained at autopsy.

PREVENTION

Several vaccines for JE and TBE are licensed in endemic and nonendemic countries. An experimental vaccine for VEE is available to protect laboratory workers. Travelers who plan to be in rural areas of Asia during the expected period of seasonal transmission should receive JE vaccine. Similarly, travelers who plan to travel, camp, or picnic in rural areas of Europe and East Asia should consult local health authorities concerning the need to be vaccinated against TBE. An inactivated JE vaccine manufactured in Japan by intracerebral injection of young mice once available throughout the world was taken off the market owing to a high incidence of adverse events. In 2008–2009, tissue culture–based JE vaccine (Ixiaro) was licensed in Europe, Australia, and the United States. In the United States, this vaccine, licensed for use in children and adults, distributed by Novartis (Basel), is administered intramuscularly as two doses of 0.5 mL each, 28 days apart. The final dose should be completed at least 1 week before the patient's expected arrival in a JE endemic area. This vaccine contains alum and protamine sulfate and has exhibited only mild adverse events. Chimerivax-JE, marketed by Sanofi Pasteur and licensed in Australia and several Asian countries, is a live-attenuated two-dose vaccine composed of the structural gene of JE inserted into the YF 17D vaccine backbone. A highly efficacious live-attenuated single-dose JE vaccine, SA 14-14-2, developed in China for children is licensed and marketed in Asian countries. This vaccine can be co-administered with live-attenuated measles vaccine without altering the immune responses to either vaccine. In humans, prior DENV infection provides partial protection against clinical JE.

No TBE vaccines are licensed or available in the United States. Two inactivated cell culture–derived TBE vaccines are available in Europe, in adult and pediatric formulations: FSME-IMMUN (Baxter, Austria) and Encepur (Novartis, Germany). The adult formulation of FSME-IMMUN is also licensed in Canada. Two other inactivated TBE vaccines are available in Russia: TBE-Moscow (Chumakov Institute, Russia) and EnceVir (Microgen, Russia). Immunogenicity studies suggest that the European and Russian vaccines should provide cross-protection against all three TBE virus subtypes. For both FSME-IMMUN and Encepur, the primary vaccination series consists of three doses. The specific recommended

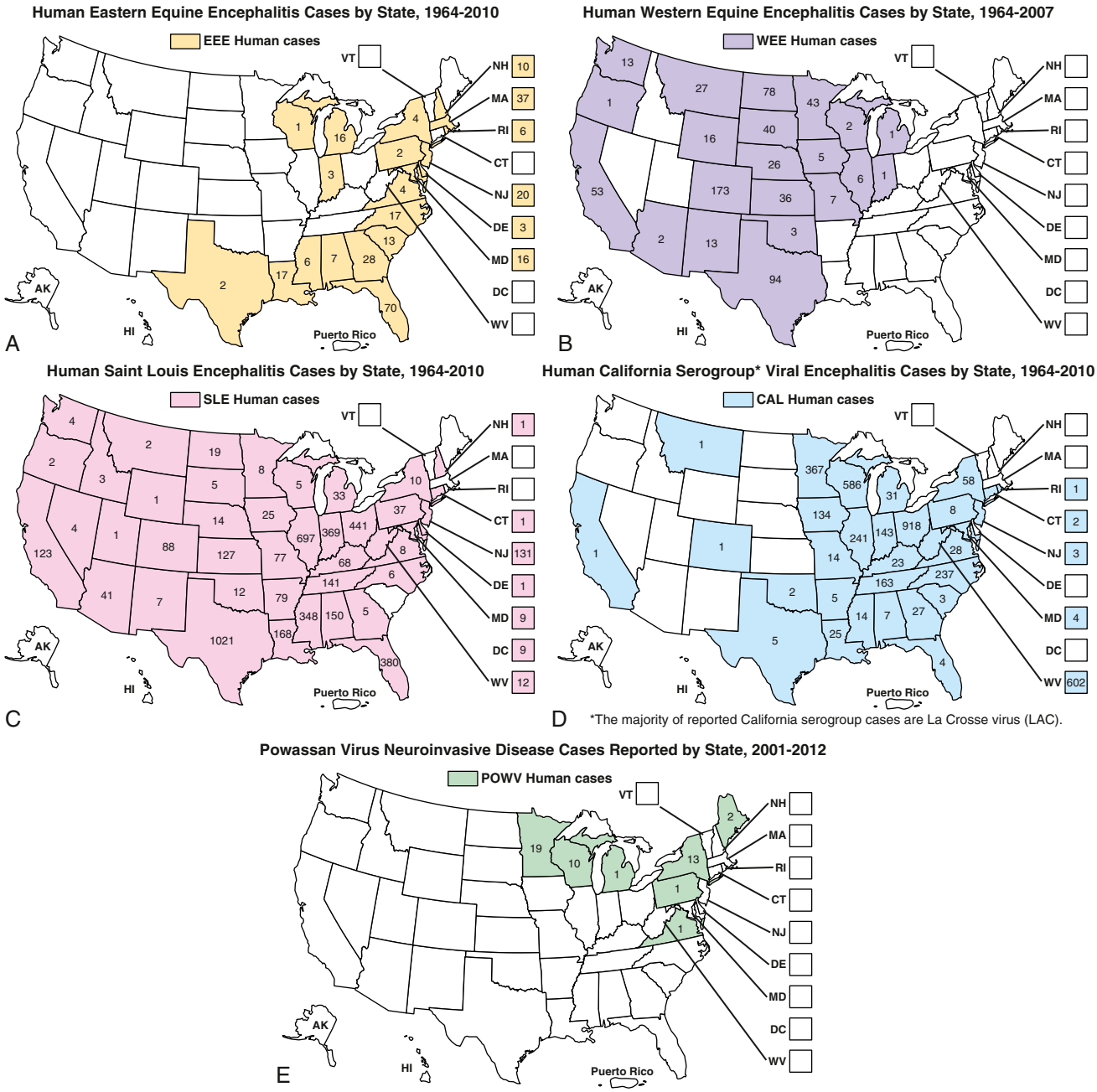

Fig. 314.1 The distribution and incidence of reported cases of eastern equine encephalitis (A), western equine encephalitis (B), St. Louis encephalitis (C), California serogroup encephalitis (D), and Powassan encephalitis; (E), reported by state to the Centers for Disease Control and Prevention, 1964 to 2010. *(From Division of Vector-Borne Diseases, Centers for Disease Control and Prevention. http://www.cdc.gov/ncidod/dvbid/arbor/arbocase/htm)*

intervals between doses vary by country and vaccine. Because the routine primary vaccination series requires ≥6 months for completion, most travelers to TBE-endemic areas will find avoiding tick bites to be more practical than vaccination.

For all viral diseases discussed in this chapter, personal measures should be taken to reduce exposure to mosquito or tick bites, especially for short-term residents in endemic areas. These measures include avoiding evening outdoor exposure, using insect repellents, covering the body with clothing, and using bed nets or house screening. Commercial pesticides, widely used by rice farmers, may be useful in reducing populations of vector mosquitoes or ticks. Fenthion, fenitrothion, and phenthoate are effectively adulticidal and larvicidal. Insecticides may be applied from portable sprayers or from helicopters or light aircraft.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

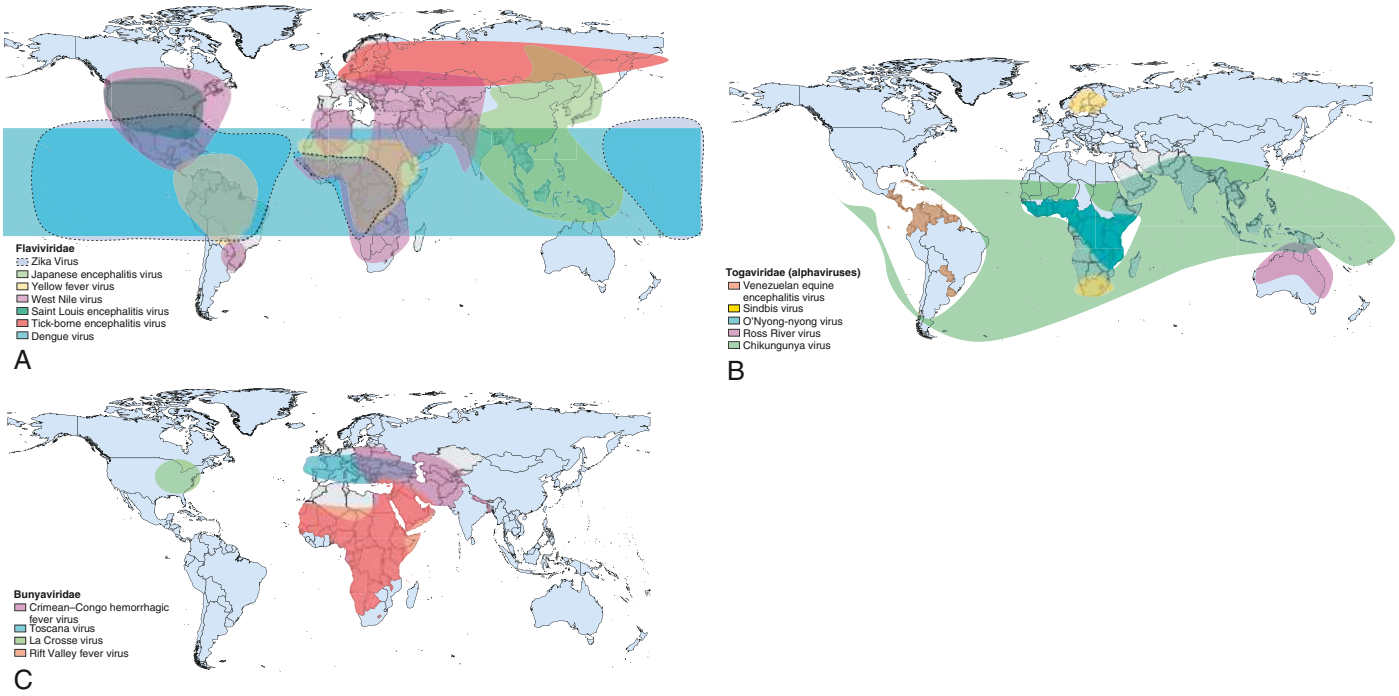

Fig. 314.2 World distribution of major arbovirus infections. *(From Charlier C, Beaudoin MC, Couderc T, et al. Arboviruses and pregnancy: maternal, fetal, and neonatal effects. Lancet Child Adolesc. 2017;1:134–146. Fig. 1.)*

314.1 Eastern Equine Encephalitis

Scott B. Halstead

In the United States, EEE is a disease with a very low incidence, with a median of eight cases occurring annually in the Atlantic and Gulf states from 1964 to 2007. A severe outbreak in 2019 resulted in 19 fatalities among 38 cases (see Fig. 314.1). Transmission occurs often in focal endemic areas of the coast of Massachusetts, the six southern counties of New Jersey, and northeastern Florida. In North America, the virus is maintained in freshwater swamps in a zoonotic cycle involving the *Culiseta melanura* mosquito and birds. Various other mosquito species obtain viremic meals from birds and transmit the virus to horses and humans. Virus activity varies markedly from year to year in response to still unknown ecologic factors. Most infections in birds are silent, but infections in pheasants are often fatal, and epizootics in these species are used as sentinels for periods of increased viral activity. Cases have been recognized on Caribbean islands. The case:infection ratio is lowest in children (1:8) and somewhat higher in adults (1:29).

EEE virus infections result in fulminant encephalitis with a rapid progression to coma and death in one third of cases. In infants and children, abrupt onset of fever, irritability, and headache are followed by lethargy, confusion, seizures, and coma. High temperature, bulging fontanel, stiff neck, and generalized flaccid or spastic paralysis are observed. There may be a brief prodrome of fever, headache, and dizziness. Unlike most other viral encephalitides, the peripheral white blood cell count usually demonstrates a marked leukocytosis and the CSF may show marked pleocytosis. Pathologic changes are found in the cortical and gray matter, with viral antigens localized to neurons. There is necrosis of neurons, neutrophilic infiltration, and perivascular cuffing by lymphocytes.

The prognosis in EEE is better for patients with a prolonged prodrome; the occurrence of convulsions conveys a poor prognosis. Patient fatality rates are 33–75% and are highest in the elderly. Residual neurologic defects are common, especially in children.

The diagnosis of encephalitis may be aided by CT or MRI and by electroencephalography. Focal seizures or focal findings on CT or MRI or electroencephalography should suggest the possibility of herpes simplex encephalitis, which should be treated with acyclovir (see Chapter 299).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.2 Western Equine Encephalitis

Scott B. Halstead

WEE infections occur principally in the United States and Canada west of the Mississippi River (see Fig. 314.1). Cases occur mainly in rural areas where water impoundments, irrigated farmland, and naturally flooded land provide breeding sites for the *Culex tarsalis* mosquito. The virus is transmitted in a cycle involving mosquitoes, birds, and other vertebrate hosts. Humans and horses are susceptible to encephalitis. The case:infection ratio varies by age, having been estimated at 1:58 in children younger than 4 years of age and 1:1,150 in adults. Infections are most severe at the extremes of life; one third of cases occur in children younger than 1 year of age. Recurrent human epidemics have been reported from the Yakima Valley in Washington State and the Central Valley of California; the largest outbreak on record resulted in 3,400 cases and occurred in Minnesota, North and South Dakota, Nebraska, and Montana, as well as Alberta, Manitoba, and Saskatchewan, Canada. Epizootics in horses precede human epidemics by several weeks. For the past 20 years, only three cases of WEE have been reported, presumably reflecting successful mosquito abatement.

In WEE, there may be a prodrome with symptoms of an upper respiratory tract infection. The onset is usually sudden with chills, fever, dizziness, drowsiness, increasing headache, malaise, nausea and vomiting,

stiff neck, and disorientation. Infants typically present with the sudden cessation of feeding, fussiness, fever, and protracted vomiting. Convulsions and lethargy develop rapidly. On physical examination, patients are somnolent, exhibit meningeal signs, and have generalized motor weakness and reduced deep tendon reflexes. In infants, a bulging fontanel, spastic paralysis, and generalized convulsions may be observed. On pathologic examination, disseminated small focal abscesses, small focal hemorrhages, and patchy areas of demyelination are distinctive.

Patient fatality rates in WEE are 3–9% and are highest in the elderly. Major neurologic sequelae have been reported in up to 13% of cases and may be as high as 30% in infants. Parkinsonian syndrome has been reported as a residual in adult survivors.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.3 St. Louis Encephalitis

Scott B. Halstead

Cases of SLE are reported from nearly all states; the highest attack rates occur in the gulf and central states (see Fig. 314.1). Epidemics frequently occur in urban and suburban areas; the largest occurred in 1975 and involved 1,800 persons living in Houston, Chicago, Memphis, and Denver. Cases often cluster in areas where there is ground water or septic systems, which support mosquito breeding. The principal vectors are *Culex pipiens* and *Culex quinquefasciatus* mosquitoes in the central gulf states, *Culex nigripalpus* in Florida, and *Culex tarsalis* in California. SLE virus is maintained in nature in a bird-mosquito cycle. Viral amplification occurs in bird species abundant in residential areas (e.g., sparrows, blue jays, and doves). Virus is transmitted in the late summer and early fall. The case:infection ratio may be as high as 1:300. Age-specific attack rates are lowest in children and highest in individuals older than 60 years. The most recent small outbreaks were in Florida in 1990 and Louisiana in 2001. For the past 15 years, there have been a mean of 18 cases annually.

Clinical manifestations of SLE vary from a mild flulike illness to fatal encephalitis. There may be a prodrome of nonspecific symptoms with subtle changes in coordination or mentation of several days to 1 week in duration. Early signs and symptoms include fever, photophobia, headache, malaise, nausea, vomiting, and neck stiffness. About half of patients exhibit an abrupt onset of weakness, incoordination, disturbed sensorium, restlessness, confusion, lethargy, and delirium or coma. The peripheral white blood cell count is modestly elevated, with 100-200 white blood cells/μL found in the CSF. On autopsy, the brain shows scattered foci of neuronal damage and perivascular inflammation.

The principal risk factor for fatal outcome of SLE is advanced age, with patient fatality rates being as high as 80% in early outbreaks. In children, mortality rates are 2–5%. In adults, underlying hypertensive cardiovascular disease has been a risk factor for fatal outcome. Recovery from SLE is usually complete, but the rate of serious neurologic sequelae has been reported to be as high as 10% in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

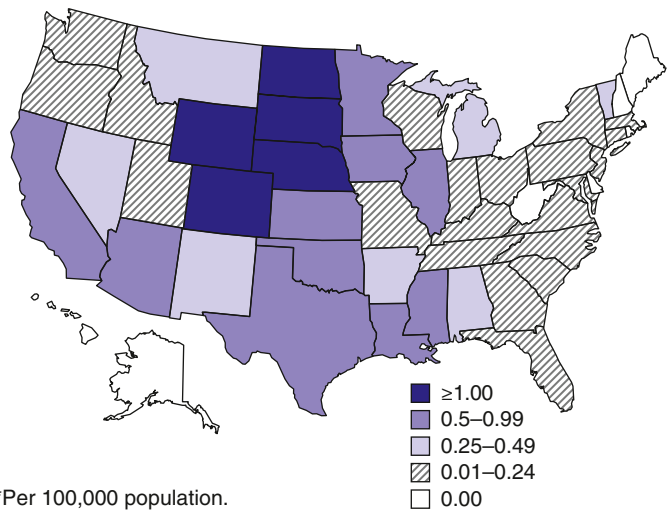

Fig. 314.3 Rate (per 100,000 population) of reported cases of West Nile virus neuroinvasive disease, United States, 2016. *(From Burakoff A, Lehman J, Fischer M, et al. West Nile virus and other nationally notifiable arboviral diseases, United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67[1]L13–17.)*

314.4 West Nile Encephalitis

Scott B. Halstead

West Nile virus (WNV) was imported into the United States in 1999 and survives in a broad enzootic cycle across the United States and Canada. Every state in the continental United States plus nine provinces in Canada have reported mosquito, bird, mammalian, or human WN virus infection, most frequently during the summer or fall months. Through the end of 2015, a total of 43,937 cases had been reported in the United States, 40–50% of which were neuroinvasive, with 1,911 deaths (Fig. 314.3). In 2020, there were 505 WNV cases, 159 of which were neuroinvasive, resulting in 52 deaths. WNV transmission cycles have come to resemble JE with large epizootics and human cases occurring every 5-10 years. WNV has entered the blood supply through asymptomatic viremic potential blood donors. Since 2003, blood banks screen for WNV RNA. During the major outbreak of 2012, 597 viremic potential blood donors were identified and the donation was rejected. WNV has also been transmitted to humans via the placenta, breast milk, and organ transplantation. Throughout its range, the virus is maintained in nature by transmission between mosquitoes of the *Culex* genus and various species of birds. In the United States, human infections are largely acquired from *C. pipiens*. Horses are the nonavian vertebrates most likely to exhibit disease with WNV infection. During the 2002 transmission season, 14,000 equine cases were reported, with a mortality rate of 30%. Disease occurs predominantly in individuals >50 years of age. WNV has been implicated as the cause of sporadic summertime cases of human encephalitis and meningitis in Israel, India, Pakistan, Romania, Russia, Canada, the United States, and parts of Central and South America. All North and South American WNVs are genetically similar and are related to a virus recovered from a goose in Israel in 1998.

West Nile encephalitis (WNE) may be asymptomatic, but when clinical features appear, they include an abrupt onset of high fever, headache, myalgias, and nonspecific signs of emesis, rash, abdominal pain, or diarrhea. Most infections manifest as a flulike febrile illness, whereas a minority of patients demonstrate meningitis or encephalitis or both. Rarely there may be cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, retinitis, orchitis, pancreatitis, or hepatitis. WNV disease in the United States has been accompanied by prolonged lymphopenia and an acute asymmetric polio-like paralytic illness with CSF pleocytosis involving the anterior horn cells of the spinal cord. A striking but uncommon feature has been parkinsonism and movement disorders (with tremor and myoclonus). WNV infections have been shown to lead to chronic kidney disease in a small group of patients.

Cases of WNE and deaths due to the disease occur mainly in the elderly, although many serologic surveys show that persons of all ages are infected. In 2015, among a total of 2,175 human cases, 1,455 were neuroinvasive disease with 146 deaths, a 10% mortality rate (see Fig. 314.2). Paralysis may result in permanent weakness.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.5 Powassan Encephalitis

Scott B. Halstead

POW virus is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States; it has been responsible for 39 deaths in the United States since 2008 (see Fig. 314.1). Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes scapularis* (also called *Ixodes dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States.

In a limited experience, POW encephalitis has occurred mainly in adults with vocational or recreational exposure and has a high fatality rate.

POW encephalitis has occurred mostly in adults living in enzootic areas with vocational or recreational exposure; it is associated with significant long-term morbidity and has a case fatality rate of 10–15%.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.6 La Crosse and California Encephalitis

Scott B. Halstead

La Crosse viral infections are endemic in the United States, occurring annually from July to September, principally in the north-central and central states (see Fig. 314.1). Infections occur in peridomestic environments as the result of bites from *Aedes triseriatus* mosquitoes, which often breed in tree holes. The virus is maintained vertically in nature by transovarial transmission and can be spread between mosquitoes by copulation and amplified in mosquito populations by viremic infections in various vertebrate hosts. Amplifying hosts include chipmunks, squirrels, foxes, and woodchucks. A case:infection ratio of 1:22-300 has been surmised. La Crosse encephalitis is principally a disease of children, who may account for up to 75% of cases. A mean of 100 cases has been reported annually for the past 10 years.

The clinical spectrum includes a mild febrile illness, aseptic meningitis, and fatal encephalitis. Children typically present with a prodrome of 2-3 days of fever, headache, malaise, and vomiting. The disease evolves with clouding of the sensorium, lethargy, and, in severe cases, focal or generalized seizures. On physical examination, children are lethargic but not disoriented. Focal neurologic signs, including weakness, aphasia, and focal or generalized seizures, have been reported in 16–25% of cases. CSF shows low to moderate leukocyte counts. On autopsy, the brain shows focal areas of neuronal degeneration, inflammation, and perivascular cuffing.

Recovery from California encephalitis is usually complete. The case fatality rate is approximately 1%.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.7 Colorado Tick Fever

Scott B. Halstead

Colorado tick fever virus is transmitted by the wood tick *Dermacentor andersoni,* which inhabits high-elevation areas of states extending from the central plains to the Pacific coast. The tick is infected with the virus at the larval stage and remains infected for life. Squirrels and chipmunks serve as primary reservoirs. Human infections typically occur in hikers and campers in indigenous areas during the spring and early summer.

Colorado tick fever begins with the abrupt onset of a flulike illness, including high temperature, malaise, arthralgia and myalgia, vomiting, headache, and decreased sensorium. Rash is uncommon. The symptoms rapidly disappear after 3 days of illness. However, in approximately half of patients, a second identical episode reoccurs 24-72 hours after the first one, producing the typical saddleback temperature curve of Colorado tick fever. Complications, including encephalitis, meningoencephalitis, and a bleeding diathesis, develop in 3–7% of infected persons and may be more common in children younger than 12 years of age.

Recovery from Colorado tick fever is usually complete. Three deaths have been reported, all in persons with hemorrhagic signs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.8 Chikungunya Fever

Scott B. Halstead

Chikungunya virus is enzootic in several species of African subhuman primates but also is endemic in urban *Aedes aegypti* or *Aedes albopictus* transmission cycles in Africa, Asia, and the Americas. From the 18th century, chikungunya exited Africa eastward, producing Asian pandemics in 1790, 1824, 1872, 1924, 1963, and 2005. In 1827, chikungunya went the other direction via the slave trade, reaching the Western

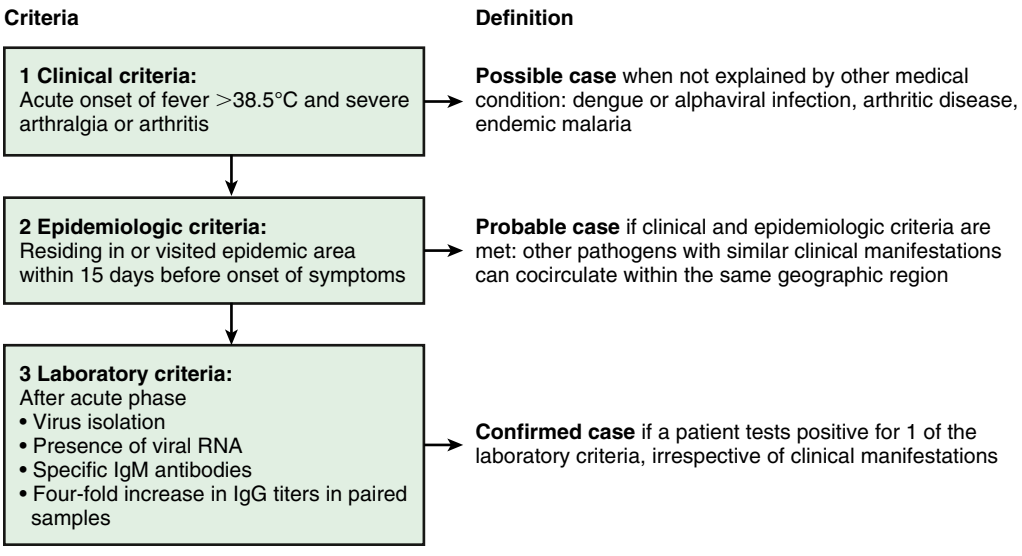

Fig. 314.4 Algorithm showing diagnostic criteria for chikungunya virus fever. *(From Burt FJ, Rolph MS, Rulli NE, et al. Chikungunya: a re-emerging virus. Lancet. 2012;379:662–668. Fig. 6.)*

Hemisphere predominantly in the Caribbean. In 2005, proceeding again in an easterly direction, virus appeared on Reunion Island and then traveled to Asia across the Indian Ocean. In 2013, chikungunya virus from this epidemic was introduced into the Americas, where it is now endemic.

Clinical manifestations begin 3-7 days after a mosquito bite; the onset is abrupt, with high fever and often severe joint symptoms (hands, feet, ankles, wrists) that include symmetric bilateral polyarthralgia or arthritis. Infections in children are often asymptomatic, but all ages are vulnerable to classic disease. There may be headache, myalgias, conjunctivitis, weakness, lymphopenia, and a maculopapular rash. Mortality is rare; some individuals develop prolonged joint symptoms (tenosynovitis, arthritis) lasting over a year. The acute episode lasts 7-10 days. The differential diagnosis includes dengue, West Nile, enterovirus diseases, leptospirosis, rickettsial disease, measles, parvovirus disease, rheumatologic diseases, and other alphavirus diseases (e.g., Ross River virus) in endemic areas. Figure 314.4 lists the diagnostic criteria.

The incidence of febrile convulsions is high in infants. The prognosis is generally good, although in large outbreaks in Africa and India, severe disease and deaths have been attributed to chikungunya infections, predominantly in adults.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.9 Venezuelan Equine Encephalitis

Scott B. Halstead

VEE virus was isolated from an epizootic in Venezuelan horses in 1938. Human cases were first identified in 1943. Hundreds of thousands of equine and human cases have occurred over the past 70 years. During 1971, epizootics moved through Central America and Mexico to southern Texas. After 3 decades of quiescence, epizootic disease emerged again in Venezuela and Colombia in 1995. Between December 1992 and January 1993, the Venezuelan state of Trujillo experienced an outbreak of this virus. Overall, 28 cases of the disease were reported, along with 12 deaths. A bigger outbreak occurred in June 1993, resulting in the death of 55 humans and 66 horses. A much larger outbreak in Venezuela and Colombia occurred in 1995. On May 23, 1995, equine encephalitis-like cases were reported in the northwest portion of the country. Eventually, the outbreak spread toward the north, as well as to the south. The outbreak caused about 11,390 febrile cases in humans, as well as 16 deaths. About 500 equine cases were reported with 475 deaths.

The incubation period is 2-5 days, followed by the abrupt onset of fever, chills, headache, sore throat, myalgia, malaise, prostration, photophobia, nausea, vomiting, and diarrhea. In 5–10% of cases, there is a biphasic illness; the second phase is heralded by seizures, projectile vomiting, ataxia, confusion, agitation, and mild disturbances in consciousness. There is cervical lymphadenopathy and conjunctival suffusion. Cases of meningoencephalitis may demonstrate cranial nerve palsy, motor weakness, paralysis, seizures, and coma. Microscopic examination of tissues reveals inflammatory infiltrates in lymph nodes, spleen, lung, liver, and brain. Lymph nodes show cellular depletion, necrosis of germinal centers, and lymphophagocytosis. The liver shows patchy hepatocellular degeneration, the lungs demonstrate a diffuse interstitial pneumonia with intraalveolar hemorrhages, and the brain shows patchy cellular infiltrates. Vertical transmission from mother to fetus has been documented. Ten fetal autopsies performed during an outbreak demonstrated VEE virus in the brains of aborted fetuses. https://www.ncbi.nlm.nih.gov/books/NBK559332/. Infants born to mothers with VEE may have neurologic sequelae or fatal cerebral lesions.

There is no specific treatment for VEE. The treatment is intensive supportive care (see Chapter 82), including control of seizures (see Chapter 633).

In patients with VEE meningoencephalitis, the fatality rate ranges from 10–25%. Sequelae include nervousness, forgetfulness, recurrent headache, and easy fatigability.

Several veterinary vaccines are available to protect equine animals. VEE virus is highly infectious in laboratory settings, and biosafety level 3 containment should be used. An experimental vaccine is available for use in laboratory workers. Several vaccine constructs are in the pipeline for potential use in humans.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.10 Japanese Encephalitis

Scott B. Halstead

JE is a mosquito-borne viral disease of humans, as well as horses, swine, and other domestic animals. The virus causes human infections and acute disease in a vast area of Asia, from Indochina through the Indian subcontinent, northern Japan, Korea, China, Taiwan, the Philippines, and the Indonesian archipelago. *Culex tritaeniorhynchus summarosus,* a night-biting mosquito that feeds preferentially on large domestic animals and birds but only infrequently on humans, is the principal vector of zoonotic and human JE in northern Asia. A more complex ecology prevails in southern Asia. From Taiwan to India, *C. tritaeniorhynchus* and members of the closely related *Culex vishnui* group are vectors. Before the introduction of JE vaccine, summer outbreaks of JE occurred regularly in Japan, Korea, China, Okinawa, and Taiwan. Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia. Seasonal rains are accompanied by increases in mosquito populations and JE transmission. Pigs serve as an amplifying host.

The annual incidence in endemic areas ranges from 1-10 per 10,000 population. Children younger than 15 years of age are principally affected, with nearly universal exposure by adulthood. The case:infection ratio for JE virus has been variously estimated at 1:25 to 1:1,000. Higher ratios have been estimated for populations indigenous to enzootic areas. JE occurs in travelers visiting Asia; therefore a travel history in the diagnosis of encephalitis is critical.

After a 4- to 14-day incubation period, cases typically progress through the following four stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days), and convalescence (4-7 weeks). The onset may be characterized by an abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting, and sensory changes, including psychotic episodes. Grand mal seizures are seen in 10–24% of children with JE; parkinsonian-like nonintention tremor and cogwheel rigidity are seen less frequently. Particularly characteristic are rapidly changing central nervous system signs (e.g., hyperreflexia followed by hyporeflexia or plantar responses that change). The sensory status of the patient may vary from confusion through disorientation and delirium to somnolence, progressing to coma. There is usually a mild pleocytosis (100-1,000 leukocytes/μL) in the cerebrospinal fluid, initially polymorphonuclear but in a few days predominantly lymphocytic. Albuminuria is common. Fatal cases usually progress rapidly to coma, and the patient dies within 10 days.

JE should be suspected in patients reporting exposure to night-biting mosquitoes in endemic areas during the transmission season. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a fourfold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction (PCR).

There is no specific treatment for JE. The treatment is intensive supportive care (see Chapter 82), including control of seizures (see Chapter 633).

Patient fatality rates for JE are 24–42% and are highest in children 5-9 years of age and in adults older than 65 years of age. The frequency

of sequelae is 5–70% and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 years at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

314.11 Tick-Borne Encephalitis

Scott B. Halstead

TBE refers to neurotropic tick-transmitted flaviviral infections occurring across the Eurasian land mass. In the Far East, the disease is called *Russian spring-summer encephalitis*; the milder, often biphasic form in Europe is simply called TBE. TBE is found in all countries of Europe except Portugal and the Benelux countries. The incidence is particularly high in Austria, Poland, Hungary, Czech Republic, Slovakia, former Yugoslavia, and Russia. The incidence tends to be very focal. Seroprevalence is as high as 50% in farm and forestry workers. The majority of cases occur in adults, but even young children may be infected while playing in the woods or on picnics or camping trips. The seasonal distribution of cases is midsummer in southern Europe, with a longer season in Scandinavia and the Russian Far East. TBE can be excreted in the milk of goats, sheep, or cows. Before World War II, when unpasteurized milk was consumed, milk-borne cases of TBE were common.

Viruses are transmitted principally by hard ticks, *Ixodes ricinus* in Europe and *Ixodes persulcatus* in the Far East. Viral circulation is maintained by a combination of transmission from ticks to birds, rodents, and larger mammals and transstadial transmission from larval to nymphal and adult stages. In some parts of Europe and Russia, ticks feed actively during the spring and early fall, giving rise to the name *spring-summer encephalitis.*

After an incubation period of 7-14 days, the European form begins as an acute nonspecific febrile illness that is followed in 5–30% of cases by meningoencephalitis. The Far Eastern variety more often results in encephalitis with higher case fatality and sequelae rates. The first phase of illness is characterized by fever, headache, myalgia, malaise, nausea, and vomiting for 2-7 days. Fever disappears but after 2-8 days may return, accompanied by vomiting, photophobia, and signs of meningeal irritation in children and more severe encephalitic signs in adults. This phase rarely lasts more than 1 week.

There is no specific treatment for TBE. The treatment is intensive supportive care (see Chapter 82), including control of seizures (see Chapter 633).

The main risk for a fatal outcome is advanced age; the fatality rate in adults is approximately 1%, but sequelae in children are rare. Transient unilateral paralysis of an upper extremity is a common finding in adults. Common sequelae include chronic fatigue, headache, sleep disorders, and emotional disturbances.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

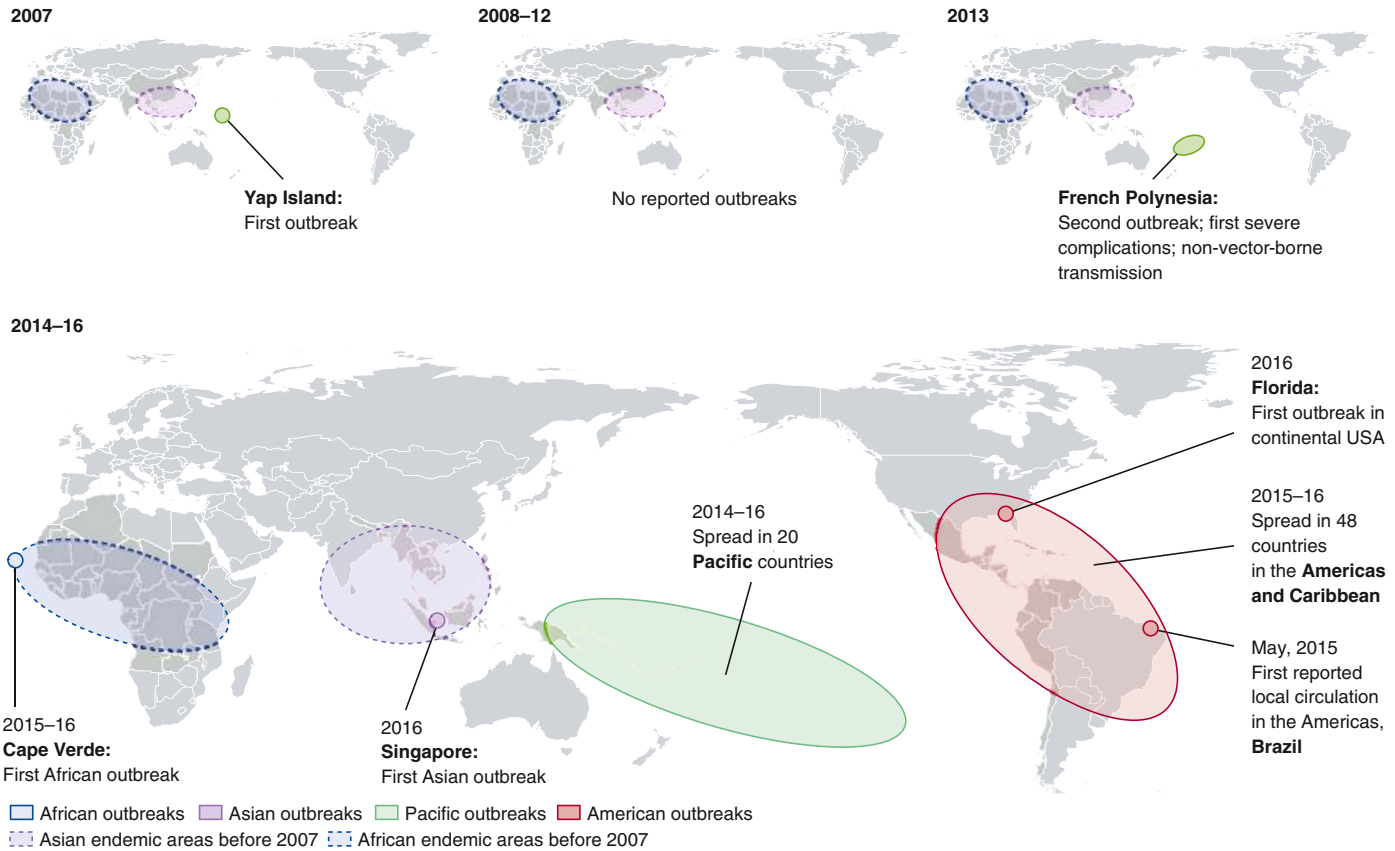

Fig. 314.5 Zika virus outbreaks from 2007 to 2016. *(From Baud D, Gubler DJ, Schaub B, et al. An update on Zika virus infection. Lancet. 2017;390:2099–2109. Fig. 2.)*

Table 314.1 Surveillance Case Classification: Children, Neonate to 2 Years of Age, Born to Mothers with Any Evidence of Zika Virus Infection During Pregnancy

ZIKA-ASSOCIATED BIRTH DEFECTS

Selected structural anomalies of the brain or eyes present at birth (congenital) and detected from birth to age 2 yr. Microcephaly at birth, with or without low birthweight, was included as a structural anomaly.

- **Selected congenital brain anomalies:** intracranial calcifications; cerebral atrophy; abnormal cortical formation (e.g., polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia); corpus callosum abnormalities; cerebellar abnormalities; porencephaly; hydranencephaly; ventriculomegaly/hydrocephaly.
- **Selected congenital eye anomalies:** microphthalmia or anophthalmia; coloboma; cataract; intraocular calcifications; chorioretinal anomalies involving the macula (e.g., chorioretinal atrophy and scarring, macular pallor, and gross pigmentary mottling), excluding retinopathy of prematurity; optic nerve atrophy, pallor, and other optic nerve abnormalities.
- **Microcephaly at birth:** birth head circumference <3rd percentile for infant sex and gestational age based on INTERGROWTH-21st online percentile calculator (http://intergrowth21.ndog.ox.ac.uk/).

NEURODEVELOPMENTAL ABNORMALITIES POSSIBLY ASSOCIATED WITH CONGENITAL ZIKA VIRUS INFECTION

Consequences of neurologic dysfunction detected from birth (congenital) to age 2 yr. Postnatal-onset microcephaly was included as a neurodevelopmental abnormality.

- **Hearing abnormalities:** Hearing loss or deafness documented by testing, most frequently auditory brainstem response (ABR). Includes sensorineural hearing loss, mixed hearing loss, and hearing loss not otherwise specified. Failed newborn hearing screening is not sufficient for diagnosis.
- **Congenital contractures:** Multiple contractures (arthrogryposis) and isolated clubfoot documented at birth. Brain anomalies must be documented for isolated clubfoot but not for arthrogryposis.
- **Seizures:** Documented by electroencephalogram or physician report. Includes epilepsy or seizures not otherwise specified; excludes febrile seizures.
- **Body tone abnormalities:** Hypertonia or hypotonia documented at any age in conjunction with (1) a failed screen or assessment for gross motor function; (2) suspicion or diagnosis of cerebral palsy from age 1-2 yr; or (3) assessment by a physician or other medical professional, such as a physical therapist.
- **Movement abnormalities:** Dyskinesia or dystonia at any age; suspicion or diagnosis of cerebral palsy from age 1-2 yr.
- **Swallowing abnormalities:** Documented by instrumented or noninstrumented evaluation, presence of a gastrostomy tube, or physician report.
- **Possible developmental delay:** Abnormal result from most recent developmental screening (i.e., failed screen for gross motor domain or failed screen for two or more developmental domains at the same time point or age); developmental evaluation; or assessment review by developmental pediatrician. Results from developmental evaluation are considered the gold standard if available.
- **Possible visual impairment:** Includes strabismus (esotropia or exotropia), nystagmus, failure to fix and follow at age <1 yr; diagnosis of visual impairment at age ≥1 yr.
- **Postnatal-onset microcephaly:** Two most recent head circumference measurements reported from follow-up care <3rd percentile for child's sex and age based on World Health Organization child growth standards; downward trajectory of head circumference percentiles with most recent measurement <3rd percentile. Age at measurement was adjusted for gestational age in infants born at <40 wk of gestational age through age 24 mo chronological age.

From Rice ME, Galang RR, Roth NM, et al. Vital signs: Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection—US territories and freely associated states, 2018. *MMWR Morb Mortal Wkly Rep.* 2018;67(31):858–866.

314.12 Zika Virus

Scott B. Halstead

EPIDEMIOLOGY

ZIKV, a member of the *Flavivirus* genus, is maintained in complex African zoonotic cycles, spilling over from time to time into the *Aedes aegypti/A. albopictus* urban transmission cycles, possibly over a period of many years (Fig. 314.5). After the virus was discovered in Africa in 1947, human antibodies were found widely dispersed throughout tropical Asia. However, in all these locations, human ZIKV disease was mild and rare until 2007, when there was an outbreak of a mild febrile exanthem on the Yap Islands in the western Pacific. Soon thereafter an outbreak on Tahiti in 2013–2014 was followed in 4 weeks by a small outbreak of Guillain-Barré syndrome (GBS). In 2015 a massive epidemic in South America was accompanied by focal reports, particularly in Brazil, of ZIKV infections of pregnant women that produced infected and damaged fetuses or newborns. The epidemiology of ZIKV infections is essentially identical to that of the DENV and CHIK. Residents of urban areas, particularly those without adequate sources of piped water, are at highest risk. *A. aegypti,* the principal vector mosquito, is very abundant and widespread throughout South and Central America, Mexico, and the Caribbean region. During the North, Central, and South American pandemic, ZIKV was found to infect the male reproductive tract, be secreted in urine and saliva, and be sexually transmitted. By 2017, the ZIKV epidemic in the American tropics appeared to wane, with few cases reported since then. During 2015–2016, large numbers of imported ZIKV infections, some in pregnant women, were reported in the United States and other temperate-zone developed countries. Small outbreaks of endogenous human ZIKV infections were reported in South Florida during the summer of 2016.

From the pediatric perspective, the most important outcome of human ZIKV infection is termed the *congenital Zika syndrome (CZS),* which consists of microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, irritability, seizures, arthrogryposis, ocular abnormalities, and sensorineural hearing loss (Table 314.1). A comprehensive understanding of the precise antecedents to CZS is not known. It appears that the earlier during pregnancy that ZIKV infections occur, the greater the likelihood of and the more severe is the CZS. Vertical transmission appears to follow viremia with ZIKV, transiting the uterus to infect the placenta and then the fetus. However, factors that affect the occurrence or severity of CZS, such as age, ethnicity, or prior immune status of the mother, are not known. In vitro studies have demonstrated that DENV antibodies can enhance ZIKV infection in vitro, in Fc-receptor–bearing cells. In Nicaraguan children, a prior DENV infection did not enhance Zika disease, and, as yet, there is no evidence that a prior DENV infection alters the chance of ZIKV crossing the placenta or increases the risk of CZS. Maternal–fetal transmission of ZIKV can occur during labor and delivery. There are no reports of ZIKV infection acquired by an infant at the time of delivery leading to microcephaly. There are no data to contraindicate breastfeeding, although the virus has been identified in breast milk. Maternal and newborn laboratory testing is indicated during the first 2 weeks of life if the mother had relevant epidemiologic exposure within 2 weeks of delivery and had clinical manifestations of ZIKV infection (e.g., rash, conjunctivitis, arthralgia, or fever). Infants and children who acquire ZIKV infection postnatally appear to have a mild course, similar to that seen in adults.

CLINICAL FEATURES

Congenital Zika syndrome may be defined in a fetus with diagnostic evidence of ZIKV infection, including (1) severe microcephaly (>3 SD below the mean), partially collapsed skull, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment; (2) brain anomalies, including cerebral cortex thinning, abnormal gyral patterns, increased fluid spaces, subcortical calcifications, corpus callosum anomalies, reduced white matter, and cerebellar vermis hypoplasia; (3) ocular findings, such as macular scarring, focal pigmentary retinal mottling, structural anomalies (microphthalmia,

Table 314.2 CDC Recommendations for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus Among Persons with Possible Zika Virus Exposure: United States, August 2018

EXPOSURE SCENARIO	RECOMMENDATIONS (UPDATE STATUS)
Only the male partner travels to an area with risk for ZIKV transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 3 mo after the male partner's symptom onset (if symptomatic) or last possible ZIKV exposure (if asymptomatic). **(Updated recommendation)**
Only the female partner travels to an area with risk for ZIKV transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 2 mo after the female partner's symptom onset (if symptomatic) or last possible ZIKV exposure (if asymptomatic). **(No change in recommendation)***
Both partners travel to an area with risk for ZIKV transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 3 mo from the male partner's symptom onset (if symptomatic) or last possible ZIKV exposure (if asymptomatic). **(Updated recommendation)**
One or both partners have ongoing exposure (i.e., live in or frequently travel to an area with risk for ZIKV transmission) and couple is planning to conceive	The couple should talk with their healthcare provider about their plans for pregnancy, their risk for ZIKV infection, the possible health effects of ZIKV infection on a baby, and ways to protect themselves from ZIKV. If either partner develops symptoms of ZIKV infection or tests positive for ZIKV infection, the couple should follow the suggested time frames listed previously before trying to conceive. **(No change in recommendation)***
Men with possible ZIKV exposure whose partner is pregnant	The couple should use condoms or abstain from sex for the duration of the pregnancy. **(No change in recommendation)***

*Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure—United States, September 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:1077–1081.
From Polen KD, Gilboa SM, Hills S, et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for men with possible Zika virus exposure: United States, August 2018. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):868–870.

coloboma, cataracts, and posterior anomalies), chorioretinal atrophy, or optic nerve hypoplasia/atrophy; (4) congenital contractures, including unilateral or bilateral clubfoot and arthrogryposis multiplex congenita; and (5) neurologic impairment, such as pronounced early hypertonia/spasticity with extrapyramidal symptoms, motor disabilities, cognitive disabilities, hypotonia, irritability/excessive crying, tremors, swallowing dysfunction, vision impairment, hearing impairment, and epilepsy (see Table 314.1).

Acquired ZIKV infection may present with nonspecific viral syndrome–like features. Nonetheless, patients are at increased risk of myelitis and GBS. In addition, the virus may remain present in the blood and body fluids for months after resolution of clinical symptoms.

MANAGEMENT

For infants with confirmed ZIKV infection, close follow-up is necessary. The appropriate follow-up evaluation depends on whether the infant has clinical signs and symptoms of congenital ZIKV syndrome. All infants should have close monitoring of growth and development, repeat ophthalmologic examinations, and auditory brainstem response testing (see Table 314.1).

LABORATORY DIAGNOSIS

Laboratory testing for ZIKV infection in the neonate includes the following: serum and urine for ZIKV RNA by real-time reverse transcription polymerase chain reaction (rRT-PCR) and serum ZIKV IgM enzyme-linked immunosorbent assay. If the IgM is positive, the plaque reduction neutralization test is used to confirm the specificity of the IgM antibodies against ZIKV and to exclude a false-positive IgM result. If CSF is available, it should be tested for ZIKV RNA (via rRT-PCR), as well as ZIKV IgM. CSF specimens need not be collected for the sole purpose of ZIKV testing but may be reasonable for the evaluation of infants with microcephaly or intracranial calcifications. A definitive diagnosis of congenital ZIKV infection is confirmed by the presence of ZIKV RNA in samples of serum, urine, or CSF collected within the first 2 days of life; IgM antibodies may be positive or negative. A negative rRT-PCR result with a positive ZIKV IgM test result indicates probable congenital ZIKV infection.

Fetuses or infants born to mothers who test positive for ZIKV infection should be studied sonographically or for clinical evidence of congenital Zika syndrome; a comprehensive evaluation (including ophthalmologic examination, laboratory tests, and specialist consultation) should be performed before hospital discharge.

PROGNOSIS

The prognosis of newborns with congenital Zika syndrome is unclear. Reported acute mortality rates among live-born infants range from 4–6%. The combination of ZIKV-related microcephaly and severe cerebral abnormalities generally has a poor prognosis, but little is known about the prognosis for congenitally infected infants with less severe or no apparent abnormalities at birth.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for congenital ZIKV infection includes other congenital infections and other causes of microcephaly.

PREVENTION

The prevention of the congenital Zika syndrome includes avoidance of travel to endemic regions, if possible; if travel to endemic regions cannot be avoided, careful contraception (male and female) is essential, especially with the knowledge that ZIKV can persist in semen for months after a primary infection (Table 314.2).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 315

Dengue Fever, Dengue Hemorrhagic Fever, and Severe Dengue

Scott B. Halstead

Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia, and lymphadenopathy. **Dengue hemorrhagic fever** (Philippine, Thai, or Singapore hemorrhagic fever; hemorrhagic dengue; acute infectious thrombocytopenic purpura) is a severe, often fatal, febrile disease caused by one of four dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome **(dengue shock syndrome),** which is thought to have an immunopathologic basis.

A revised case definition adopted by the World Health Organization (WHO) in 2009 includes as **severe dengue** those cases accompanied by fluid loss leading to shock, fluid loss with respiratory distress, liver damage evidenced by elevations of ALT or AST to >1000 U/L, severe bleeding, and altered consciousness or significant heart abnormalities.

ETIOLOGY

There are at least four distinct antigenic types of dengue virus (dengue 1, 2, 3, and 4), members of the family Flaviviridae. In addition, three other arthropod-borne viruses (arboviruses) cause similar dengue fever syndromes with rash (Table 315.1; see also Chapter 314).

EPIDEMIOLOGY

Dengue viruses are transmitted by mosquitoes of the Stegomyia family. *Aedes aegypti,* a daytime biting mosquito, is the principal vector, and all four virus types have been recovered from it. Transmission occurs from viremic humans by bite of the vector mosquito in which virus multiplies during an extrinsic incubation period and then by bite is passed on to a susceptible human in what is called the urban transmission cycle. In most tropical areas, *A. aegypti* is highly urbanized, breeding in water stored for drinking or bathing and in rainwater collected in any container. Dengue viruses have also been recovered from *A. albopictus,* as in the 2001 and 2015 Hawaiian epidemics, whereas outbreaks in the Pacific area have been attributed to several other *Aedes* species. These species breed in water trapped in vegetation. In Southeast Asia and West Africa, dengue virus may be maintained in a cycle involving canopy-feeding jungle monkeys and *Aedes* spp, which feed on monkeys.

In the 19th and early 20th centuries, epidemics were common in temperate areas of the Americas, Europe, Australia, and Asia. After several decades of virus control in the Americas, dengue fever and dengue-like disease are now endemic in tropical Asia, the South Pacific Islands, northern Australia, tropical Africa, the Arabian Peninsula, the Caribbean, and Central and South America (Fig. 315.1). The wide distribution of *A. aegypti* is frequently attributed to global warming, but this view is mistaken. This mosquito was widely dispersed during the "little ice age" in the 1700s, supporting yellow fever epidemics in New York and continental Europe. Mosquito breeding depends on access to stored fresh water, not temperature. Dengue fever occurs frequently among travelers to endemic areas. Locally acquired disease has been reported in Florida, Arizona, and Texas, and imported cases in the United States occur in travelers to endemic areas. More than 390 million dengue infections occur annually; approximately 96 million have clinical disease.

Dengue outbreaks in urban areas infested with *A. aegypti* may be explosive; in virgin soil epidemics, up to 70–80% of the population may be involved. Most overt disease occurs in older children and adults. Because *A. aegypti* has a limited flight range, spread of an epidemic occurs mainly through viremic human beings and follows the main lines of transportation. Sentinel cases may infect household mosquitoes; a large number of nearly simultaneous secondary infections give the appearance of a contagious disease. Where dengue is highly endemic, indigenous children and susceptible foreigners may be the only persons to acquire overt disease, because adults have become immune.

Table 315.1 Vectors and Geographic Distribution of Dengue-Like Diseases

VIRUS	GEOGRAPHIC GENUS AND DISEASE	VECTOR	DISTRIBUTION
Togavirus	Chikungunya	*Aedes aegypti* *Aedes africanus* *Aedes albopictus*	Africa, India, Southeast Asia, Latin America, United States
Togavirus	O'nyong-nyong	*Anopheles funestus*	East Africa
Flavivirus	West Nile fever	*Culex molestus* *Culex univittatus*	Europe, Africa, Middle East, India

Dengue-Like Diseases

Dengue-like diseases may occur in epidemics. Epidemiologic features depend on the vectors and their geographic distribution (see Chapter 314). Chikungunya virus is enzootic in subhuman primates throughout much of West, Central, and South Africa. Periodic introductions of virus into the urban transmission cycle have led to pandemics, resulting in widespread endemicity in the most populous areas of Asia. In Asia, *A. aegypti* is the principal vector; in Africa, other Stegomyia spp. may be important vectors. In Southeast Asia, dengue and chikungunya outbreaks occur concurrently in the urban cycle. Outbreaks of o'nyong-nyong fever usually involve villages or small towns, in contrast to the urban outbreaks of dengue and chikungunya. West Nile virus is enzootic in Africa. Chikungunya is now endemic in urban cycles in tropical countries throughout the world. Intense transmission in Caribbean and Central and South American countries beginning in 2013 results in the emergence of limited chikungunya transmission in the United States.

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is endemic in tropical America, Asia, the Pacific Islands, and parts of Africa, where warm temperatures and the practices of water storage in homes plus outdoor breeding sites result in large, permanent populations of *A. aegypti.* Under these conditions, infections with dengue viruses of all types are common. A first infection, referred to as a primary infection, may be followed by infection with a different dengue virus, referred to as a secondary infection. In areas of high endemicity, secondary infections are frequent.

Secondary dengue infections are relatively mild in the majority of instances, ranging from an inapparent infection through an undifferentiated upper respiratory tract or dengue-like disease, but may also progress to dengue hemorrhagic fever. Nonimmune foreigners, both adults and children, who are exposed to dengue virus during outbreaks of hemorrhagic fever have classic dengue fever or even milder disease. The differences in clinical manifestations of dengue infections between natives and foreigners in Southeast Asia are related to immunologic status. Dengue hemorrhagic fever is unusual in patients with primary dengue infection, with the exception of infants whose mothers

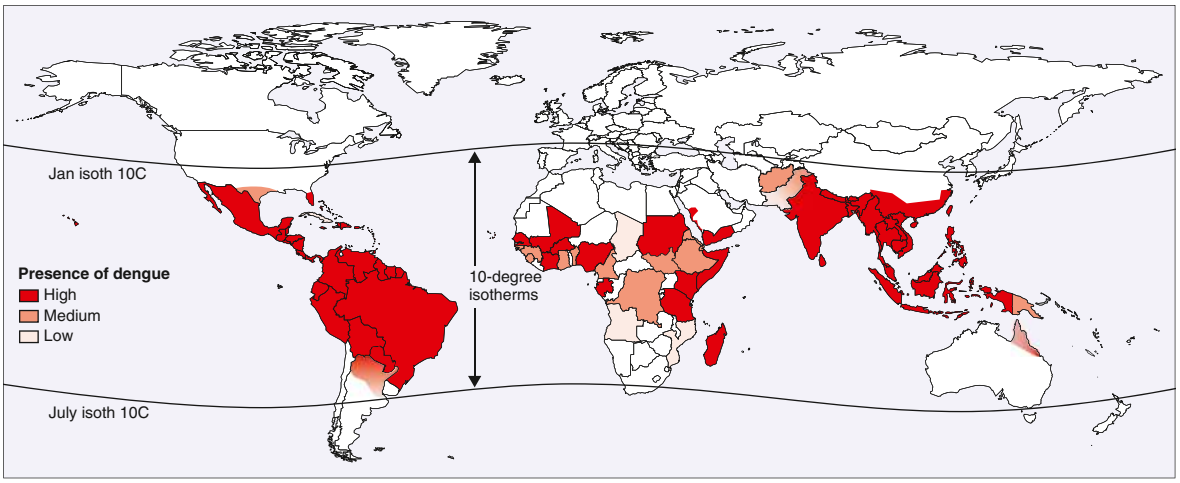

Fig. 315.1 Global dengue burden, 2014. *(From Guzman MG, Harris E. Dengue. Lancet. 2015;385:453–462. Fig. 1.)*

are immune to dengue. Dengue hemorrhagic fever or severe dengue occurs rarely in individuals of African ancestry because of an as yet incompletely described resistance gene. This gene is thought to have originated in populations with long-standing exposure to yellow fever and explains the low incidence of severe dengue throughout much of Africa and among African populations in the American tropics despite high rates of dengue infection.

PATHOGENESIS

The pathogenesis of dengue hemorrhagic fever is incompletely understood, but epidemiologic studies strongly associate this syndrome with second heterotypic infections with dengue types 1-4 or in infants born to mothers who have had two or more lifetime dengue infections. Retrospective studies of sera from human mothers whose infants acquired dengue hemorrhagic fever and prospective studies in children acquiring sequential dengue infections have shown that the circulation of infection-enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease. The absence of dengue neutralizing antibodies in the presence of enhancing antibodies from passive transfer or active production is the best correlate of risk for dengue hemorrhagic fever. Monkeys that are infected sequentially or have received enhancing antibodies experience enhanced viremias. In humans studied early during the course of secondary dengue infections, viremia levels directly predicted disease severity. When dengue virus immune complexes attach to monocyte/macrophage Fc receptors, a signal is sent that suppresses innate immunity, resulting in enhanced viral production. In the Americas, dengue hemorrhagic fever and dengue shock syndrome have been associated with dengue types 1-4 strains of recent Southeast Asian origin. Outbreaks of dengue hemorrhagic fever in all areas of the world are correlated with secondary dengue infections.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon-γ, and interleukin-2 are elevated, C1q, C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. All of these outcomes are attributed to circulating viral nonstructural protein 1 (NS1), a viral toxin that activates myeloid cells to release cytokines by attaching to toll-like receptor 4. NS1 also contributes to increased vascular permeability by activating complement and, most importantly, interacting with and damaging endothelial cells and interacting with blood clotting factors and platelets. The mechanism of bleeding in dengue hemorrhagic fever is not fully understood, but a mild degree of disseminated intravascular coagulopathy, liver damage, and thrombocytopenia may operate synergistically. NS1-mediated capillary damage allows fluid, electrolytes, small proteins, and, in some instances, red blood cells to leak into extravascular spaces. This internal redistribution of fluid, together with deficits caused by fasting, thirsting, and vomiting, results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis, and hyponatremia.

Usually no pathologic lesions are found to account for death. In rare instances, death may be a result of gastrointestinal or intracranial hemorrhages. Minimal to moderate hemorrhages are seen in the upper gastrointestinal tract, and petechial hemorrhages are common in the interventricular septum of the heart, on the pericardium, and on the subserosal surfaces of major viscera. Focal hemorrhages are occasionally seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged, often with fatty changes. Yellow, watery, and at times blood-tinged effusions are present in serous cavities in approximately 75% of patients at autopsy.

Dengue virus is frequently absent in tissues at the time of death; viral antigens or RNA have been localized to hepatocytes and macrophages in the liver, spleen, lung, and lymphatic tissues.

CLINICAL MANIFESTATIONS

Dengue Fever

The incubation period is 1-7 days. The clinical manifestations are variable and are influenced by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1-5 days, pharyngeal inflammation, rhinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4–41.1°C (103–106°F), usually accompanied by frontal or retroorbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever). A transient, macular, generalized rash that blanches under pressure may be seen during the first 24-48 hours of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. From the second to sixth day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately 1-2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days; desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

The differentiation between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild first phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough may be followed after 2-5 days by rapid clinical deterioration and collapse. In this second phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, mid-epigastric pain, and decreased urinary output. There may be scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The liver may enlarge to 4-6 cm below the costal margin and is usually firm and somewhat tender. Approximately 20–30% of cases of dengue hemorrhagic fever are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, the diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24- to 36-hour period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

Dengue with Warning Signs and Severe Dengue

In hyperendemic areas, dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) is the life-threatening event during a dengue infection that challenges the identifying physician. When the four dengue viruses spread to the American hemisphere and to South Asia, there were millions of primary and secondary dengue infections in individuals of all ages. Dengue disease in these areas presented a wider clinical spectrum resulting in a new diagnostic algorithm and case definitions (see later).

DIAGNOSIS

A clinical diagnosis of dengue fever derives from a high index of suspicion and knowledge of the geographic distribution and environmental cycles of causal viruses (for nondengue causes see Chapter 314). Because clinical findings vary and there are many possible causative agents, the term *dengue-like disease* should be used until a specific diagnosis is established. A case is confirmed by virologic diagnosis, which can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. A probable case is a typical acute febrile illness with supportive serology and occurrence at a location where there are confirmed cases.

The WHO criteria for **dengue hemorrhagic fever** are fever (2-7 days in duration or biphasic); minor or major hemorrhagic manifestations, including a positive tourniquet test, thrombocytopenia (≤100,000/μL), and objective evidence of increased capillary permeability (hematocrit increased by ≥20%); pleural effusion or ascites (by chest radiography or ultrasonography); or hypoalbuminemia. **Dengue shock syndrome** criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (≤20 mm Hg), and signs of poor perfusion (cold extremities).

In 2009, the WHO promulgated guidelines for the diagnosis of probable dengue, dengue with warning signs, and a category called severe dengue (Fig. 315.2). The presence of warning signs in an individual with probable dengue alerts the physician to the possible need for hospitalization. Severe dengue is a mixture of the syndromes that are associated with dengue infection, including classic DHF/DSS, but also rare instances of encephalitis or encephalopathy, liver damage, or myocardial damage. Severe dengue also includes respiratory distress, a harbinger of pulmonary edema caused by overhydration, an all-too-common outcome of inexpert treatment (see "Treatment" and "Complications" sections).

After primary and secondary dengue infections, there is an appearance of anti-dengue (immunoglobulin [Ig] M) antibodies. These disappear after 6-12 weeks, a feature that can be used to date a dengue infection. In secondary dengue infections, most dengue antibody is of the IgG class. Serologic diagnosis depends on a fourfold or greater increase in IgG antibody titer in paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Carefully standardized IgM and IgG capture enzyme commercial immunoassays are now widely used to identify acute-phase antibodies from patients with primary or secondary dengue infections in single-serum samples. Usually such samples should be collected not earlier than 5 days and not later than 6 weeks after onset. It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been prior infection with another member of the same arbovirus group. Virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquitoes. Viral RNA can be

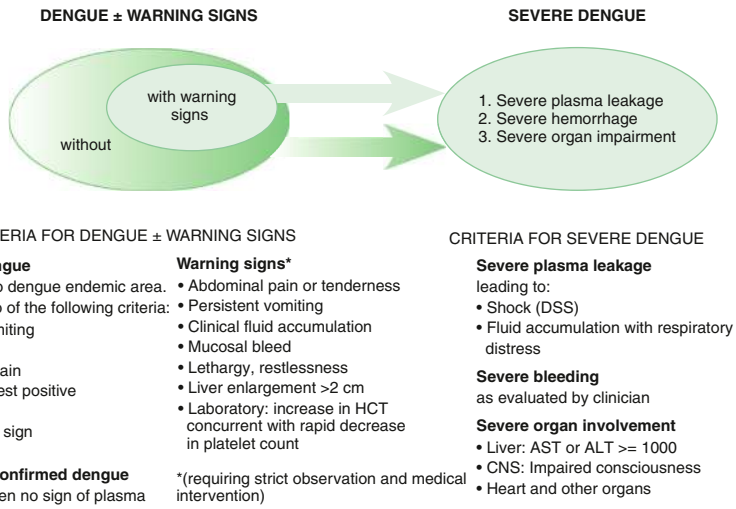

Fig. 315.2 Suggested dengue case classification and levels of severity. *(From World Health Organization [WHO] and Special Programme for Research and Training in Tropical Diseases [TDR]. Dengue: guidelines for diagnosis, treatment, prevention and control, 2009. Fig. 1.4, http://apps.who.int/iris/bitstream/handle/10665/44188/9789241547871_eng.pdf?sequence=1)*

detected in blood or tissues by specific complementary RNA probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction. A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid lateral flow tests. These tests offer a reliable point-of-care diagnosis of acute dengue infection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dengue fever includes dengue-like diseases, viral respiratory and influenza-like diseases, including COVID-19, the early stages of malaria, mild yellow fever, scrub typhus, viral hepatitis, and leptospirosis.

Four arboviral diseases have dengue-like courses but without rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever (see Chapter 314). Colorado tick fever occurs sporadically among campers and hunters in the western United States; sandfly fever in the Mediterranean region, the Middle East, southern Russia, and parts of the Indian subcontinent; and Rift Valley fever in North, East, Central, and South Africa. Ross River fever is endemic in much of eastern Australia, with epidemic extension to Fiji. In adults, Ross River fever often produces protracted and crippling arthralgia involving weight-bearing joints.

Because meningococcemia, yellow fever (see Chapter 316), other viral hemorrhagic fevers (see Chapter 317), many rickettsial diseases, and other severe illnesses caused by a variety of agents may produce a clinical picture similar to that of dengue hemorrhagic fever, the etiologic diagnosis should be made only when epidemiologic or serologic evidence suggests the possibility of a dengue infection.

LABORATORY FINDINGS

In patients with dengue fever, pancytopenia may develop after the 3-4 days of illness. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts <2,000/μL. Platelet counts rarely fall below 100,000/μL. Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive. Mild acidosis, hemoconcentration, increased transaminase values, and hypoproteinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci, flattened T waves, and prolongation of the P-R interval.

In dengue hemorrhagic fever, dengue shock syndrome, and severe dengue, the most common hematologic abnormalities are hemoconcentration with an increase of >20% in the hematocrit, thrombocytopenia, a prolonged bleeding time, and a moderately decreased prothrombin time that is seldom <40% of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated. Other abnormalities include moderate elevations of serum transaminase levels, depressed complement levels, mild metabolic acidosis with hyponatremia, occasional hypochloremia, slight elevation of blood urea nitrogen, and hypoalbuminemia. Chest x-ray reveals pleural effusions (right > left) in nearly all patients with dengue shock syndrome. Ultrasonography can be used to detect serosal effusions of the thorax or abdomen. Thickening of the gallbladder wall and the presence of perivesicular fluid, ascites, or pleural effusions are characteristic signs of increased vascular permeability.

TREATMENT

Dengue

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during the febrile period. Antipyretics should be used to keep the body temperature <40°C (104°F). Analgesics or mild sedation may be required to control pain. Aspirin is contraindicated and should not be used because of its effects on hemostasis. Fluid and electrolyte replacement is required for deficits caused by sweating, fasting, thirsting, vomiting, and diarrhea.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Shock syndrome is a medical emergency that may occur in any child who lives in or has a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often accompanies defervescence. Detailed instructions for case management are available at the Centers for Disease Control and Prevention web site: https://www.cdc.gov/dengue/healthcare-providers/index.html. Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hours because shock may occur or recur precipitously, usually several days after the onset of fever. Patients who are cyanotic or have labored breathing should be given oxygen. Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactated saline in treating shock. When the pulse pressure is ≤10 mm Hg or when elevation of the hematocrit persists after the replacement of fluids, plasma or colloid preparations are indicated. Oral rehydration of children who are being monitored is useful. Prophylactic platelet transfusions have not been shown to reduce the risk of hemorrhaging or improve low platelet counts and may be associated with adverse effects.

Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusions of fresh blood may be required to control bleeding but should not be given during hemoconcentration and should be administered only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

Sedation may be required for children who are markedly agitated. Use of vasopressors has not resulted in a significant reduction of mortality rates over that observed with simple supportive therapy. Disseminated intravascular coagulation may require treatment (see Chapter 532). Corticosteroids do not shorten the duration of disease or improve the prognosis in children receiving careful supportive therapy.

COMPLICATIONS

Hypervolemia during the fluid reabsorptive phase may be life-threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epistaxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding. Convulsions may occur during a high temperature. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

In endemic areas, dengue hemorrhagic fever should be suspected in children with a febrile illness suggestive of dengue fever who experience hemoconcentration and thrombocytopenia.

PROGNOSIS

Dengue Fever

The prognosis for dengue fever is good. Care should be taken to avoid the use of drugs that suppress platelet activity.

Dengue Hemorrhagic Fever

The prognosis of dengue hemorrhagic fever is adversely affected by a late diagnosis and delayed or improper treatment. Death has occurred in 40–50% of patients with shock, but with adequate intensive care, deaths should occur in <1% of cases. Infrequently, there

is residual brain damage as a consequence of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

PREVENTION

Dengue vaccines have been under development continuously since the 1970s. One such vaccine, Dengvaxia, developed by Sanofi Pasteur, is a mixture of four chimeras, dengue virus structural genes coupled with nonstructural genes of yellow fever 17D. Dengvaxia completed phase III per protocol analyses on 32,568 children, vaccinated and controls, age 2-16 years. These studies revealed poor protection and sensitization of seronegative vaccinated children to severe breakthrough dengue but moderate protection of children vaccinated when seropositive, who experienced a reduction of hospitalization and severe disease. Based on these data, the vaccine was endorsed by the WHO, United States, and European regulatory agencies for targeted use in individuals 9 years of age and older who have laboratory-based evidence of a prior dengue infection. The vaccine has been licensed for use in 20 countries. Other dengue type 1-4 vaccines are under development. The Takeda dengue 2 chimeric tetravalent vaccine has completed phase III testing with follow-up data for 2 years demonstrating strong protection against dengue 2 infection but modest protection against the other three viruses. A tetravalent dengue vaccine composed of mutagenized dengue 1, 3, and 4 and a chimeric dengue 2 virus developed by the U.S. National Institutes of Allergy and Infectious Diseases and Instituto Butantan in São Paulo, Brazil, is in the fourth year of phase III testing. Phase IIb live dengue virus human challenge data suggest this vaccine will provide solid protective immunity.

Prophylaxis in the absence of vaccine consists of avoiding daytime household-based mosquito bites through the use of insecticides, repellents, body covering with clothing, screening of houses, and destruction of *A. aegypti* breeding sites. If water storage is mandatory, a tight-fitting lid or a thin layer of oil may prevent egg laying or hatching. A larvicide, such as Abate (O,O′-[thiodi-*p*-phenylene] O,O,O,O′-tetramethyl phosphorothioate), available as a 1% sand-granule formation and effective at a concentration of 1 ppm, may be added safely to drinking water. Ultra-low-volume spray equipment effectively dispenses the adulticide malathion from trucks or airplanes for rapid intervention during an epidemic. Mosquito repellants and other personal anti-mosquito measures are effective in preventing mosquito bites in the field, forest, or jungle.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 316

Yellow Fever

Scott B. Halstead

Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria, and hemorrhage. The virus is mosquito-borne and occurs as urban epidemic, endemic, or jungle enzootic forms in South America and Africa. Until 1900, seasonal urban epidemics occurred in cities in temperate areas of Europe and the Americas. Urban and jungle yellow fever continues to be active in West, Central, and East Africa.

ETIOLOGY

Yellow fever is the prototype of the *Flavivirus* genus of the family Flaviviridae, which are enveloped, single-stranded RNA viruses 35-50 nm in diameter.

Yellow fever circulates zoonotically as five genotypes: type IA in West Central Africa, type IB in South America, type II in West Africa, type III in East Central Africa, and type IV in East Africa. Types IA and IB are capable of urban transmission between human beings by *Aedes aegypti.* Sometime in the 1600s, *A. aegypti,* together with yellow fever virus, were brought to the American tropics through the African slave trade. Subsequently, yellow fever caused enormous coastal and riverine epidemics in the Atlantic and Caribbean basins until the 20th century, when the virus and its urban and sylvan mosquito cycles were identified, mosquito control methods were perfected, and a vaccine was developed. The East and East/Central African genotypes have not fully entered the urban cycle and have not spread to the east coast of Africa or to the countries of Asia.

EPIDEMIOLOGY

Human and nonhuman primate hosts acquire the yellow fever infection by the bite of infected mosquitoes. After an incubation period of 3-6 days, virus appears in the blood and may serve as a source of infection for other mosquitoes. The virus must replicate in the gut of the mosquito and pass to the salivary gland before the mosquito can transmit the virus. Yellow fever virus is transmitted in an urban cycle—human to *A. aegypti* to human—and a jungle cycle—monkey to jungle mosquitoes to monkey. Classic yellow fever epidemics in the United States, South America, the Caribbean, and parts of Europe were of the urban variety. Since 2000, West Africa has experienced five urban epidemics, including in the capital cities of Abidjan (Cote d'Ivoire), Conakry (Guinea), and Dakar (Senegal). In 2012–2013, large outbreaks of East and East/Central yellow fever occurred across a large, predominantly rural area of war-ravaged Darfur in southwestern Sudan and in adjacent areas of northern Uganda. Beginning in 2015 and continuing to mid-2016, there were sharp outbreaks of yellow fever in and around Rwanda, Angola, and the bordering Democratic Republic of Congo, where there were 7,000 reported cases and 500 deaths. Eleven cases were imported into China by workers in Angola. In South America, all of the approximately 200 cases reported each year are jungle yellow fever. In late 2016 and continuing through 2019, a widespread zoonosis resulted in an estimated 2,237 yellow fever cases in natives and visitors to Brazil. In colonial times, urban yellow fever attack rates in White adults were very high, suggesting that subclinical infections are uncommon in this age-group. Yellow fever may be less severe in children, with subclinical infection:clinical case ratios ≥2:1. In areas where outbreaks of urban yellow fever are common, most cases involve children because many adults are immune. Transmission in West Africa is highest during the rainy season, from July to November.

In tropical forests, yellow fever virus is maintained in a transmission cycle involving monkeys and tree hole–breeding mosquitoes (*Haemagogus* in Central and South America; the *Aedes africanus* complex in Africa). In the Americas, most cases involve tourists, campers, those who work in forested areas, and vacationers exposed to infected mosquitoes. In Africa, enzootic virus is prevalent in moist savanna and savanna transition areas, where other tree hole–breeding *Aedes* vectors transmit the virus between monkeys and humans and between humans.

PATHOGENESIS

Pathologic changes seen in the liver include (1) coagulative necrosis of hepatocytes in the midzone of the liver lobule, with sparing of cells around the portal areas and central veins, (2) eosinophilic degeneration of hepatocytes **(Councilman bodies)**, (3) microvacuolar fatty change, and (4) minimal inflammation. The kidneys show acute tubular necrosis. In the heart, myocardial fiber degeneration and fatty infiltration are seen. The brain may show edema and petechial hemorrhages. Direct viral injury to the liver results in impaired ability to perform functions of biosynthesis and detoxification; this is the central pathogenic event of yellow fever. Hemorrhage is postulated to result from decreased synthesis of vitamin K–dependent

clotting factors and, in some cases, disseminated intravascular clotting. The shock that occurs in patients with yellow fever appears similar to the shock associated with dengue shock syndrome and other viral hemorrhagic fevers and results at least in part from viral damage to endothelial cells. Death and severe disease rates are lower in susceptible sub-Saharan African Black people than in other racial groups, suggesting existence of a resistance gene.

Renal dysfunction has been attributed to hemodynamic factors (prerenal failure progressing to acute tubular necrosis).

CLINICAL MANIFESTATIONS

In Africa, inapparent, abortive, or clinically mild infections are frequent. Some studies suggest that children experience a milder disease than do adults. Abortive infections, characterized by fever and headache, may be unrecognized except during epidemics.

In its classic form, yellow fever begins with a sudden onset of fever, headache, myalgia, lumbosacral pain, anorexia, nausea, and vomiting. Physical findings during the early phase of illness, when virus is present in the blood, include prostration, conjunctival injection, flushing of the face and neck, reddening of the tongue at the tip and edges, and relative bradycardia. After 2-3 days, there may be a brief period of remission, followed in 6-24 hours by the reappearance of fever with vomiting, epigastric pain, jaundice, dehydration, gastrointestinal and other hemorrhages, albuminuria, hypotension, renal failure, delirium, convulsions, and coma. Death may occur after 7-10 days, with a fatality rate in severe cases approaching 50%. Some patients who survive the acute phase of illness later succumb to renal failure or myocardial damage. Laboratory abnormalities include leukopenia; prolonged clotting, prothrombin, and partial thromboplastin times; thrombocytopenia; hyperbilirubinemia; elevated serum transaminase values; albuminuria; and azotemia. Hypoglycemia may be present in severe cases. Electrocardiogram abnormalities such as bradycardia and ST-T changes are described.

DIAGNOSIS

Yellow fever should be suspected when fever, headache, vomiting, myalgia, and jaundice appear in residents of enzootic areas or in unimmunized visitors who have recently traveled (within 2 weeks before the onset of symptoms) to endemic areas. There are clinical similarities between yellow fever and dengue hemorrhagic fever. In contrast to the gradual onset of acute viral hepatitis resulting from hepatitis A, B, C, D, or E virus, jaundice in yellow fever appears after 3-5 days of high temperature and is often accompanied by severe prostration. Mild yellow fever is dengue-like and cannot be distinguished from a wide variety of other infections. Jaundice and fever may occur in any of several other tropical diseases, including malaria, viral hepatitis, louse-borne relapsing fever, leptospirosis, typhoid fever, rickettsial infections, certain systemic bacterial infections, sickle cell crisis, Rift Valley fever, Crimean-Congo hemorrhagic fever, and other viral hemorrhagic fevers. Outbreaks of yellow fever always include cases with severe gastrointestinal hemorrhage.

The specific diagnosis depends on the detection of the virus or viral antigen in acute-phase blood samples or antibody assays. The immunoglobulin M enzyme immunoassay is particularly useful. Sera obtained during the first 10 days after the onset of symptoms should be kept in an ultra-low-temperature freezer (−70°C [−94°F]) and shipped on dry ice for virus testing. Convalescent-phase samples for antibody tests are managed by conventional means. In handling acute-phase blood specimens, medical personnel must take care to avoid contaminating themselves or others on the evacuation trail (laboratory personnel and others). The postmortem diagnosis is based on virus isolation from liver or blood, identification of Councilman bodies in liver tissue, or detection of antigen or viral genome in liver tissue.

TREATMENT

It is customary to keep patients with yellow fever in a mosquito-free area, with use of mosquito nets if necessary. Patients are viremic during the febrile phase of the illness. Although there is no specific treatment for yellow fever, medical care is directed at maintaining the physiologic status with the following measures: (1) sponging and acetaminophen to reduce a high temperature, (2) vigorous fluid replacement of losses resulting from fasting, thirsting, vomiting, or plasma leakage, (3) correcting an acid-base imbalance, (4) maintaining nutritional intake to lessen the severity of hypoglycemia, and (5) avoiding drugs that are either metabolized by the liver or toxic to the liver, kidney, or central nervous system.

COMPLICATIONS

Complications of acute yellow fever include severe hemorrhage, liver failure, and acute renal failure. Bleeding should be managed by transfusion of fresh whole blood or fresh plasma with platelet concentrates if necessary. Renal failure may require peritoneal dialysis or hemodialysis.

PREVENTION

Yellow fever 17D is a live-attenuated vaccine with a long record of safety and efficacy. It is administered as a single 0.5-mL subcutaneous injection at least 10 days before arrival in a yellow fever–endemic area. YF-VAX, manufactured by Sanofi Pasteur, is licensed for use in the United States. With the exceptions noted later, individuals traveling to endemic areas in South America and Africa should be considered for vaccination, but the length of stay, exact locations to be visited, and environmental or occupational exposure may determine the specific risk and individual need for vaccination. Persons traveling from yellow fever–endemic to yellow fever–receptive countries may be required by national authorities to obtain a yellow fever vaccine (e.g., from South America or Africa to India). Usually, countries that require travelers to obtain a yellow fever immunization do not issue a visa without a valid immunization certificate. Vaccination is valid for 10 years for international travel certification, although immunity lasts at least 40 years and probably for life. Immunoglobulin M antibodies circulate for years after administration of yellow fever vaccine.

Since 1996, there have been a number of reports of *yellow fever vaccine–associated viscerotropic disease* with a higher risk in elderly vaccine recipients and a few cases in persons with previous thymectomies. Yellow fever vaccine should not be administered to persons who have symptomatic immunodeficiency diseases, are taking immunosuppressant drugs, have HIV, or have a history of thymectomy. A recent study has shown that individuals taking maintenance corticosteroids may be successfully vaccinated. Although the vaccine is not known to harm fetuses, its administration during pregnancy is not advised. The vaccine virus may be rarely transmitted through breastfeeding. In very young children, there is a small risk of encephalitis and death after yellow fever 17D vaccination. The 17D vaccine should not be administered to infants younger than 6 months. Residence in or travel to areas of known or anticipated yellow fever activity (e.g., forested areas in the Amazon basin), which puts an individual at high risk, warrants immunization of infants 6-8 months of age. Immunization of children 9 months of age and older is routinely recommended before entry into endemic areas. Immunization of persons older than 60 years of age should be weighed against their risk for sylvatic yellow fever in the American tropics and for urban or sylvatic yellow fever in Africa. Vaccination should be avoided in persons with a history of egg allergy. Alternatively, a skin test can be performed to determine whether a serious allergy exists that would preclude vaccination.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 317

Ebola and Other Viral Hemorrhagic Fevers

Scott B. Halstead

Viral hemorrhagic fevers are a loosely defined group of clinical syndromes in which hemorrhagic manifestations are either common or especially notable during severe illness. Both the etiologic agents and the clinical features of the syndromes differ, but coagulopathy may be a common pathogenetic feature.

ETIOLOGY

Six of the viral hemorrhagic fevers are caused by arthropod-borne viruses (arboviruses) (Table 317.1). Four are caused by togaviruses of the family **Flaviviridae**: Kyasanur Forest disease, Omsk hemorrhagic fever, dengue (see Chapter 315), and yellow fever (see Chapter 316) viruses. Three are caused by viruses of the family **Bunyaviridae**: Congo fever, Hantaan fever, and Rift Valley fever (RVF) viruses. Four are caused by viruses of the family **Arenaviridae**: Junin fever, Machupo fever, Guanarito fever, and Lassa fever. Two are caused by viruses in the family **Filoviridae**: Ebola virus and Marburg virus, enveloped, filamentous RNA viruses that are sometimes branched, unlike any other known virus.

EPIDEMIOLOGY

With some exceptions, the viruses causing viral hemorrhagic fevers are transmitted to humans via a nonhuman entity. The specific ecosystem required for viral survival determines the geographic distribution of disease. Although it is commonly thought that all viral hemorrhagic fevers are arthropod borne, seven may be contracted from environmental contamination caused by animals or animal cells or from infected humans (see Table 317.1). Laboratory and hospital infections have occurred with many of these agents. Lassa fever and Argentine and Bolivian hemorrhagic fevers are reportedly milder in children than in adults.

Table 317.1 Viral Hemorrhagic Fevers

MODE OF TRANSMISSION	DISEASE	VIRUS
Tick-borne	Crimean-Congo hemorrhagic fever (HF)*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk
Mosquito-borne†	Dengue HF	Dengue (4 types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever*	Lassa
	Marburg disease*	Marburg
	Ebola HF*	Ebola
	HF with renal syndrome	Hantaan

*Patients may be contagious; nosocomial infections are common.
†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

Crimean-Congo Hemorrhagic Fever

Sporadic human infection with Crimean-Congo hemorrhagic fever in Africa provided the original virus isolation. Natural foci are recognized in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan regions; disease occurs in Central Asia from Kazakhstan to Pakistan. Index cases were followed by nosocomial transmission in Pakistan and Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South Africa in 1984. In the Russian Federation, the vectors are ticks of the species *Hyalomma marginatum* and *Hyalomma anatolicum*, which, along with hares and birds, may serve as viral reservoirs. Disease occurs from June to September, largely among farmers and dairy workers.

Kyasanur Forest Disease

Human cases of Kyasanur Forest disease occur chiefly in adults in an area of Mysore State, India. The main vectors are two Ixodidae ticks, *Haemaphysalis turturis* and *Haemaphysalis spinigera.* Monkeys and forest rodents may be amplifying hosts. Laboratory infections are common.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever occurs throughout south-central Russia and northern Romania. Vectors may include *Dermacentor pictus* and *Dermacentor marginatus,* but direct transmission from moles and muskrats to humans seems well established. Human disease occurs in a spring–summer–autumn pattern, paralleling the activity of the vectors. This infection occurs most frequently in persons with outdoor occupational exposure. Laboratory infections are common.

Rift Valley Fever

The virus causing RVF is responsible for epizootics involving sheep, cattle, buffalo, certain antelopes, and rodents in North, Central, East, and South Africa. The virus is transmitted to domestic animals by *Culex theileri* and several *Aedes* species. Mosquitoes may serve as reservoirs by transovarial transmission. An epizootic in Egypt in 1977–1978 was accompanied by thousands of human infections, principally among veterinarians, farmers, and farm laborers. Smaller outbreaks occurred in Senegal in 1987, Madagascar in 1990, and Saudi Arabia and Yemen in 2000–2001. Humans are most often infected during the slaughter or skinning of sick or dead animals. Laboratory infection is common.

Argentine Hemorrhagic Fever

Before the introduction of vaccine, hundreds to thousands of cases of Argentine hemorrhagic fever occurred annually from April through July in the maize-producing area northwest of Buenos Aires that reaches to the eastern margin of the Province of Cordoba. Junin virus has been isolated from the rodents *Mus musculus*, *Akodon arenicola*, and *Calomys laucha*. It infects migrant laborers who harvest the maize and who inhabit rodent-contaminated shelters.

Bolivian Hemorrhagic Fever

The recognized endemic area of Bolivian hemorrhagic fever consists of the sparsely populated province of Beni in Amazonian Bolivia. Sporadic cases occur in farm families who raise maize, rice, yucca, and beans. In the town of San Joaquin, a disturbance in the domestic rodent ecosystem may have led to an outbreak of household infection caused by Machupo virus transmitted by chronically infected *Calomys callosus,* ordinarily a field rodent. Mortality rates are high in young children.

Venezuelan Hemorrhagic Fever

In 1989, an outbreak of hemorrhagic illness occurred in the farming community of Guanarito, Venezuela, 200 miles south of Caracas. Subsequently, in 1990–1991, there were 104 cases reported with 26 deaths caused by Guanarito virus. Cotton rats *(Sigmodon alstoni)* and cane rats *(Zygodontomys brevicauda)* have been implicated as likely reservoirs of Venezuelan hemorrhagic fever.

Lassa Fever

Lassa virus has an unusual potential for human-to-human spread, resulting in many small epidemics in Nigeria, Sierra Leone, and Liberia. In 2012, an outbreak of more than 1,000 cases of Lassa fever occurred in east-central Nigeria. Medical workers in Africa and the United States have also contracted the disease. Patients with acute Lassa fever have been transported by international aircraft, necessitating extensive surveillance among passengers and crews. The virus is probably maintained in nature in a species of African peridomestic rodent, *Mastomys natalensis*. Rodent-to-rodent transmission and infection of humans probably operate via mechanisms established for other arenaviruses.

Marburg Disease

Previously, the world experience of human infections caused by Marburgvirus had been limited to 26 primary and 5 secondary laboratory-based cases in Germany and Yugoslavia in 1967 and to small outbreaks in Zimbabwe in 1975, Kenya in 1980 and 1988, and South Africa in 1983. However, in 1999 a large outbreak occurred in the Republic of Congo, and in 2005 a still larger outbreak occurred in Uige Province, Angola, with 252 cases and 227 deaths. In laboratory and clinical settings, transmission occurs by direct contact with tissues of the African green monkey or with infected human blood or semen. A reservoir in the African fruit bat, *Rousettus aegyptiacus*, has been demonstrated. Fruit bats infected with Marburg virus do not show obvious signs of illness. It appears that the virus is transmitted by close contact with fructivorous bats and by aerosol from bats.

Ebola Hemorrhagic Fever

Ebola virus was isolated in 1976 from a devastating epidemic involving small villages in northern Zaire and southern Sudan; smaller outbreaks have occurred subsequently. Outbreaks have initially been nosocomial. Attack rates have been highest in children from birth to 1 year of age and in persons from 15-50 years of age. The virus is in the *Filovirus* family and closely related to viruses in the genus Marburg virus. An Ebola virus epidemic occurred in Kikwit, Zaire, in 1995, followed by scattered outbreaks in Uganda and Central and West Africa. The virus has been recovered from chimpanzees, and antibodies have been found in other subhuman primates, which apparently acquire infection from a zoonotic reservoir in bats. The natural reservoir of Ebola is thought to be fruit bats. Reston virus, related to Ebola virus, has been recovered from Philippine monkeys and pigs and has caused subclinical infections in humans working in monkey colonies in the United States.

In 2014, West Africa experienced the largest outbreak of Ebola virus disease (EVD) in history and the first transmission in a large urban area (Fig. 317.1). Countries primarily affected were Liberia, Sierra Leone, and Guinea, with imported cases reported in Nigeria, Mali, and Senegal, as well as Europe and the United States. The outbreak was caused by the Zaire Ebola virus (species of Ebola virus include the Zaire, Sudan, Bundibugyo, Reston, and Tai Forest species), which has a mortality rate of approximately 55–65%. As of 8 May 2016, the World Health Organization (WHO) and respective governments reported a total of 28,616 suspected cases and 11,310 deaths (39.5%), though the WHO thinks that this substantially understates the magnitude of the outbreak. The outbreak had largely subsided by the end of 2015. In 2018–2020, an outbreak occurred in the Democratic Republic of the Congo, affecting more than 500 people (age 8-80 years), with a case fatality of approximately 50% (Fig. 317.2). In 2021 the Ministry of Health (MOH) in the Democratic Republic of the Congo (DRC) announced that a case of EVD had been confirmed in Biena Health Zone, North Kivu Province. Sequencing of samples suggests that this outbreak was linked to the 2018–2020 outbreak, likely caused by a persistent infection in a survivor that led to either a relapse or sexual transmission of the virus.

EVD may occur after exposure to fruit bats or bushmeat but most often occurs through exposure to body fluids of infected individuals (blood, sweat, saliva, vomitus, diarrhea, and less often human milk or semen) (Table 317.2). Persistent infection after recovery from acute EVD has been well documented, with virus particles present in body fluids such as semen for many months in apparently healthy survivors. Patients are infectious once they are symptomatic; the incubation period is 2-21 days (mean: 11 days). The age range in the West African epidemic was broad, but most patients were between 15 and 44 years old.

Hemorrhagic Fever with Renal Syndrome

The endemic area of hemorrhagic fever with renal syndrome (HFRS), also known as *epidemic hemorrhagic fever* and *Korean hemorrhagic fever*, includes Japan, Korea, far eastern Siberia, north and central China, European and Asian Russia, Scandinavia, Czechoslovakia, Romania, Bulgaria, Yugoslavia, and Greece. Although the incidence and severity of hemorrhagic manifestations and the mortality rates are lower in Europe than in northeastern Asia, the renal lesions are the same. Disease in Scandinavia, **nephropathia epidemica**, is caused by a different although antigenically related virus, Puumala virus, associated with the bank vole, *Clethrionomys glareolus*. Cases occur predominantly in the spring and summer. There appears to be no age factor in susceptibility, but because of occupational hazards, young adult men are most frequently attacked. Rodent plagues and evidence of rodent infestation have accompanied endemic and epidemic occurrences. Hantaan virus has been detected in the lung tissue and excreta

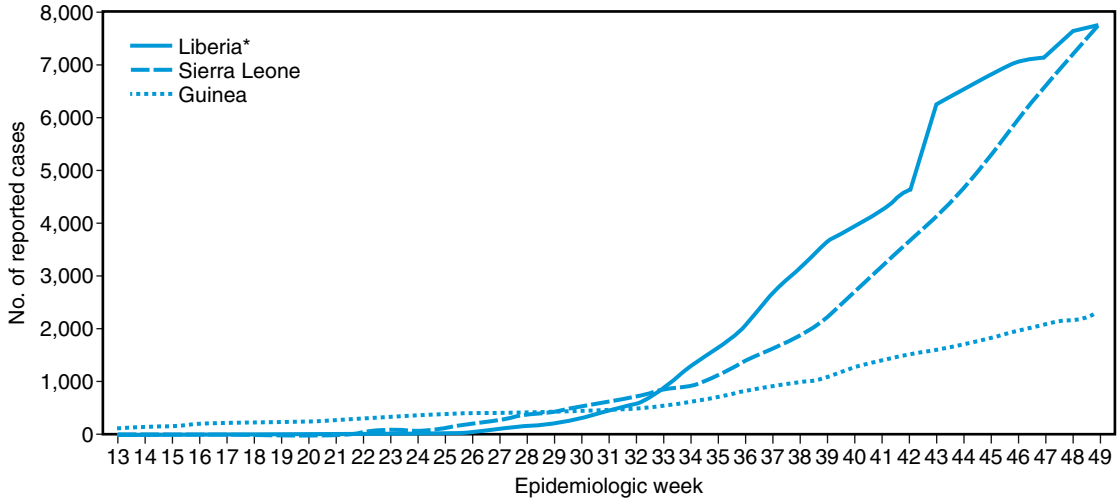

Fig. 317.1 Cumulative number of Ebola virus disease cases reported—three countries, West Africa, April 13, 2016. Reported from Sierra Leone (14,124 cases) and Liberia (10,678), followed by Guinea (3,814). *(Data from the number of cases and deaths in Guinea, Liberia, and Sierra Leone during the 2014–2016 West Africa Ebola Outbreak.* https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html*)*

of *Apodemus agrarius coreae*. Antigenically related agents have been detected in laboratory rats and in urban rat populations around the world, including Prospect Hill virus in the wild rodent *Microtus pennsylvanicus* in North America and *sin nombre* virus in the deer mouse in the southern and southwestern United States; these viruses are causes of hantavirus pulmonary syndrome (see Chapter 319). Rodent-to-rodent and rodent-to-human transmission presumably occurs via the respiratory route.

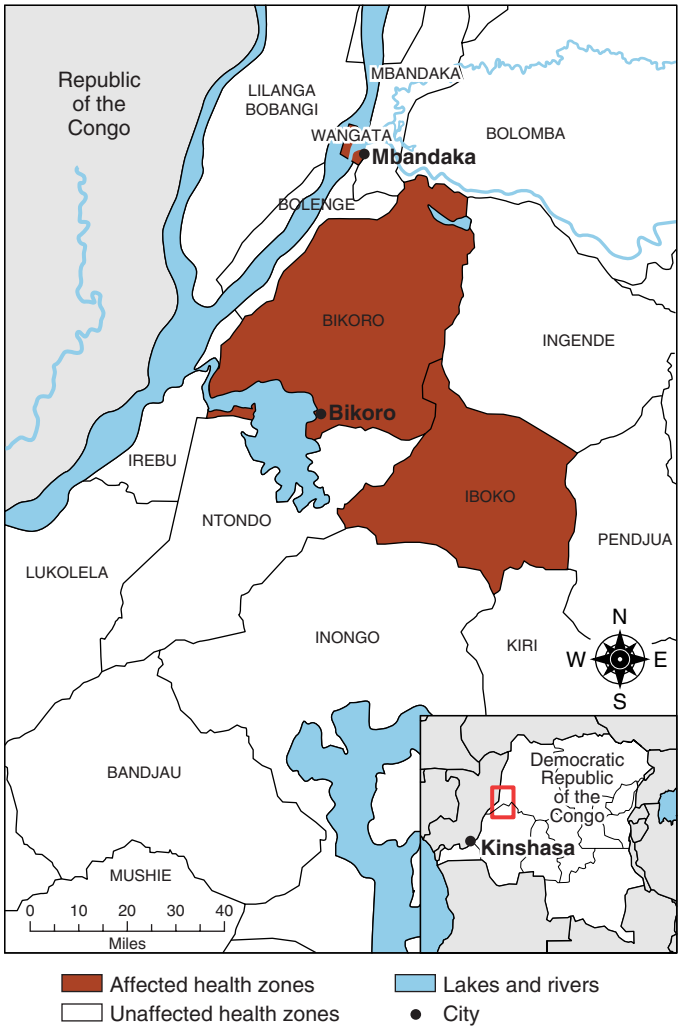

Fig. 317.2 Map of Ebola-affected health zones in the Democratic Republic of the Congo (DRC), 2018. *(Courtesy the Centers for Disease Control and Prevention, 2018.* https://www.cdc.gov/vhf/ebola/outbreaks/drc/drc-map.html*)*

CLINICAL MANIFESTATIONS

Dengue hemorrhagic fever (see Chapter 315) and yellow fever (see Chapter 316) cause similar syndromes in children in endemic areas.

Crimean-Congo Hemorrhagic Fever

The incubation period of 3-12 days is followed by a febrile period of 5-12 days and a prolonged convalescence. Illness begins suddenly with fever, severe headache, myalgia, abdominal pain, anorexia, nausea, and vomiting. After 1-2 days, the fever may subside until the patient experiences an erythematous facial or truncal flush and injected conjunctivae. A second febrile period of 2-6 days then develops, with a hemorrhagic enanthem on the soft palate and a fine petechial rash on the chest and abdomen. Less frequently, there are large areas of purpura and bleeding from the gums, nose, intestines, lungs, or uterus. Hematuria and proteinuria are relatively rare. During the hemorrhagic stage, there is usually tachycardia with diminished heart sounds and occasionally hypotension. The liver is usually enlarged, but there is no icterus. In protracted cases, central nervous system signs include delirium, somnolence, and progressive clouding of the consciousness. Early in the disease, leukopenia with relative lymphocytosis, progressively worsening thrombocytopenia, and gradually increasing anemia occur. In convalescence there may be hearing and memory loss. The mortality rate is 2–50%.

Kyasanur Forest Disease and Omsk Hemorrhagic Fever

After an incubation period of 3-8 days, both Kyasanur Forest disease and Omsk hemorrhagic fever begin with the sudden onset of fever and headache. Kyasanur Forest disease is characterized by severe myalgia, prostration, and bronchiolar involvement; it often manifests without hemorrhage but occasionally involves severe gastrointestinal bleeding. In Omsk hemorrhagic fever, there is moderate epistaxis, hematemesis, and a hemorrhagic enanthem but no profuse hemorrhage; bronchopneumonia is common. In both diseases, severe leukopenia and thrombocytopenia, vascular dilation, increased vascular permeability, gastrointestinal hemorrhages, and subserosal and interstitial petechial hemorrhages occur. Kyasanur Forest disease may be complicated by acute degeneration of the renal tubules and focal liver damage. In many patients, recurrent febrile illness may follow an

Table 317.2 Clinical Recommendations for Ebola Virus Infection

RECOMMENDATION	POPULATION	INTERVENTION
1	Patients with suspected, probable, or confirmed Ebola virus disease	Oral rehydration
2	Patients with suspected, probable, or confirmed Ebola virus disease who are unable to drink or who have inadequate oral intake	Parenteral administration of fluids
3	Patients with suspected, probable, or confirmed Ebola virus disease	Systematic monitoring and charting of vital signs and volume status
4	Patients with suspected, probable, or confirmed Ebola virus disease	Serum biochemistry
5	Patients with suspected, probable, or confirmed Ebola virus disease	Staffing ratio
6	Patients with suspected, probable, or confirmed Ebola virus disease	Communication with family and friends
7	Patients with suspected, probable, or confirmed Ebola virus disease who are in pain	Analgesic therapy
8	Patients with suspected, probable, or confirmed Ebola virus disease with high severity of illness	Antibiotics

Modified from Lamontagne F, Fowler RA, Adhikari NK, et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet*. 2018;391:700–708. Table 2.

Table 317.3 Clinical Stages of Lassa Fever

STAGE	SYMPTOMS
1 (days 1-3)	General weakness and malaise; high fever >39°C (102.2°F), constant with peaks of 40–41°C (104–105.8°F)
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side, or abdominal pain; conjunctivitis; nausea and vomiting; diarrhea; productive cough; proteinuria; low blood pressure (systolic <100 mm Hg); anemia
3 (after 7 days)	Facial edema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

From Richmond JK, Baglole DJ. Lassa fever: epidemiology, clinical features, and social consequences. *BMJ*. 2003;327:1271–1275.

afebrile period of 7-15 days. This second phase takes the form of a meningoencephalitis.

Rift Valley Fever

Most RVF infections have occurred in adults with signs and symptoms resembling those of dengue fever (see Chapter 315). The onset is acute, with fever, headache, prostration, myalgia, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy. The fever lasts 3-6 days and is often biphasic. The convalescence is often prolonged. In the 1977–1978 outbreak, many patients died after showing signs that included purpura, epistaxis, hematemesis, and melena. RVF affects the uvea and posterior chorioretina; macular scarring, vascular occlusion, and optic atrophy occur, resulting in permanent visual loss in a high proportion of patients with mild to severe RVF. At autopsy, extensive eosinophilic degeneration of the parenchymal cells of the liver has been observed.

Argentine, Venezuelan, and Bolivian Hemorrhagic Fevers and Lassa Fever

The incubation period in Argentine, Venezuelan, and Bolivian hemorrhagic fevers and Lassa fever is commonly 7-14 days; the acute illness lasts for 2-4 weeks. Clinical illnesses range from undifferentiated fever to the characteristic severe illness. **Lassa fever** is most often clinically severe in White persons. The onset is usually gradual, with increasing fever, headache, diffuse myalgia, and anorexia (Table 317.3). During the first week, signs frequently include a sore throat, dysphagia, cough, oropharyngeal ulcers, nausea, vomiting, diarrhea, and pains in the chest and abdomen. Pleuritic chest pain may persist for 2-3 weeks. In Argentine and Bolivian hemorrhagic fevers and less frequently in Lassa fever, a petechial enanthem appears on the soft palate 3-5 days after onset and at about the same time on the trunk. The tourniquet test may be positive. The clinical course of Venezuelan hemorrhagic fever has not been well described.

In 35–50% of patients, these diseases may become severe, with persistent high temperature, increasing toxicity, swelling of the face or neck, microscopic hematuria, and frank hemorrhages from the stomach, intestines, nose, gums, and uterus. A syndrome of **hypovolemic shock** is accompanied by pleural effusion and renal failure. **Respiratory distress** resulting from airway obstruction, pleural effusion, or congestive heart failure may occur. A total of 10–20% of patients experience late neurologic involvement, characterized by intention tremor of the tongue and associated speech abnormalities. In severe cases, there may be intention tremors of the extremities, seizures, and delirium. The cerebrospinal fluid is normal. In Lassa fever, nerve deafness occurs in early convalescence in 25% of cases. Prolonged convalescence is accompanied by alopecia and, in Argentine and Bolivian hemorrhagic fevers, by signs of autonomic nervous system lability, such as postural hypotension, spontaneous flushing or blanching of the skin, and intermittent diaphoresis.

Laboratory studies reveal marked leukopenia, mild to moderate thrombocytopenia, proteinuria, and, in Argentine hemorrhagic fever, moderate abnormalities in blood clotting, decreased fibrinogen, increased fibrinogen split products, and elevated serum transaminases. There is focal, often extensive eosinophilic necrosis of the liver parenchyma, focal interstitial pneumonitis, focal necrosis of the distal and collecting tubules, and partial replacement of splenic follicles by amorphous eosinophilic material. Usually, bleeding occurs by diapedesis with little inflammatory reaction. The mortality rate is 10–40%.

Marburg Disease and Ebola Hemorrhagic Fever

After an incubation period of 4-7 days, the illness begins abruptly, with severe frontal headache, malaise, drowsiness, lumbar myalgia, vomiting, nausea, and diarrhea. A **maculopapular** eruption begins 5-7 days later on the trunk and upper arms. It becomes generalized and often hemorrhagic and exfoliates during convalescence. The exanthem is accompanied by a dark red enanthem on the hard palate, conjunctivitis, and scrotal or labial edema. Gastrointestinal hemorrhage occurs as the severity of illness increases. Late in the illness, the patient may become tearfully depressed, with marked hyperalgesia to tactile stimuli. In fatal cases, patients become hypotensive, restless, and confused and lapse into coma. Convalescent patients may experience alopecia and may have paresthesias of the back and trunk. There is a marked leukopenia with necrosis of granulocytes. Dysfunction in bleeding and clotting and thrombocytopenia are universal and correlated with the severity of disease; there are moderate abnormalities in concentrations of clotting proteins and elevations of serum transaminases and amylase. Pregnant women and young children are at high risk of severe disease with a fatal outcome. The mortality rate of Marburg disease is 25–85%, and the mortality rate of Ebola hemorrhagic fever 50–90%. High viral loads in acute-phase blood samples convey a poor prognosis. Viral RNA persists in tissues long after symptoms subside, and the virus has been excreted in semen more than 1 year after recovery.

Manifestations of EVD may come in stages, but most EVD begins with the sudden onset of fever accompanied by fatigue, weakness, myalgias, headache, and sore throat. This is followed by gastrointestinal involvement, including anorexia, nausea, abdominal pain, vomiting, and diarrhea. Hemorrhage (defined by any evidence of bleeding) is seen in more than 50% and is a serious later phase, often accompanied by vascular leakage, multiorgan failure, and death. Those who survive improve on approximately days 6-11 of EVD. One late relapse producing meningoencephalitis has been reported.

Hemorrhagic Fever with Renal Syndrome

In most cases, HFRS is characterized by fever, petechiae, mild hemorrhagic phenomena, and mild proteinuria, followed by a relatively uneventful recovery. In 20% of recognized cases, the disease may progress through four distinct phases. The febrile phase is ushered in with fever, malaise, and facial and truncal flushing. It lasts 3-8 days and ends with thrombocytopenia, petechiae, and proteinuria. The hypotensive phase of 1-3 days follows defervescence. Loss of fluid from the intravascular compartment may result in marked hemoconcentration. Proteinuria and ecchymoses increase. The oliguric phase, usually 3-5 days in duration, is characterized by a low output of protein-rich urine, increasing nitrogen retention, nausea, vomiting, and dehydration. Confusion, extreme restlessness, and hypertension are common. The diuretic phase, which may last for days or weeks, usually initiates clinical improvement. The kidneys show little concentrating ability, and rapid loss of fluid may result in severe dehydration and shock. Potassium and sodium depletion may be severe. Fatal cases manifest as abundant protein-rich retroperitoneal edema and marked hemorrhagic necrosis of the renal medulla. The mortality rate is 5–10%.

DIAGNOSIS

The diagnosis of these viral hemorrhagic fevers depends on a high index of suspicion in endemic areas. In nonendemic areas, histories of recent travel, recent laboratory exposure, or exposure to an earlier case should evoke suspicion of a viral hemorrhagic fever.

In all viral hemorrhagic fevers, the viral agent circulates in the blood at least transiently during the early febrile stage. Togaviruses and bunyaviruses can be recovered from acute-phase serum samples by inoculation into a tissue culture or living mosquitoes. Argentine, Bolivian, and Venezuelan hemorrhagic fever viruses can be isolated from acute-phase blood or throat washings by intracerebral inoculation into guinea pigs, infant hamsters, or infant mice. Lassa virus may be isolated from acute-phase blood or throat washings by inoculation into tissue cultures. For Marburg disease and Ebola hemorrhagic fever, acute-phase throat washings, blood, and urine may be inoculated into a tissue culture, guinea pigs, or monkeys. The viruses are readily identified on electron microscopy, with a filamentous structure differentiating them from all other known agents. Specific complement-fixing and immunofluorescent antibodies appear during convalescence. The virus of HFRS is recovered from acute-phase serum or urine by inoculation into a tissue culture. A variety of antibody tests using viral subunits is becoming available. The serologic diagnosis depends on the demonstration of seroconversion or a fourfold or greater increase in immunoglobulin G antibody titer in acute and convalescent serum specimens collected 3-4 weeks apart. Viral RNA may also be detected in blood or tissues with the use of reverse transcriptase polymerase chain reaction analysis.

The diagnosis of EVD is confirmed by enzyme-linked immunosorbent assay immunoglobulin M and polymerase chain reaction (which may need to be repeated if initially negative) testing. Criteria to aid in the diagnosis of EVD include temperature >38.6°C (101.5°F) plus symptoms; contact with an affected patient, the patient's body fluids, or the funeral; residence in or travel to an endemic region; or a history of handling bats, rodents, or primates from an endemic area.

Handling blood and other biologic specimens is hazardous and must be performed by specially trained personnel. Blood and autopsy specimens should be placed in tightly sealed metal containers, wrapped in absorbent material inside a sealed plastic bag, and shipped on dry ice to laboratories with biocontainment safety level 4 facilities. Even routine hematologic and biochemical tests should be done with extreme caution.

Differential Diagnosis

Mild cases of hemorrhagic fever may be confused with almost any self-limited systemic bacterial or viral infection. More severe cases may suggest typhoid fever; epidemic, murine, or scrub typhus; leptospirosis; or a rickettsial spotted fever, for which effective chemotherapeutic agents are available. Many of these disorders may be acquired in geographic or ecologic locations endemic for a viral hemorrhagic fever.

The differential diagnosis of EVD includes malaria, typhoid, Lassa fever, influenza infection, and meningococcemia.

TREATMENT

Ribavirin administered intravenously is effective in reducing mortality rates in Lassa fever and HFRS. Further information and advice about the management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral Special Pathogens Branch, Atlanta, Georgia 30333 (470-312-0094).

The therapeutic principle involved in all of these diseases, especially HFRS, is the reversal of dehydration, hemoconcentration, renal failure, and protein, electrolyte, or blood losses (see Table 317.2). The contribution of disseminated intravascular coagulopathy to the hemorrhagic manifestations is unknown, and the management of hemorrhage should be individualized. Transfusions of fresh blood and platelets are frequently given. Good results have been reported in a few patients after the administration of clotting factor concentrates. The efficacy of corticosteroids, ε-aminocaproic acid, pressor amines, and α-adrenergic blocking agents has not been established. Sedatives should be selected with regard to the possibility of kidney or liver damage. The successful management of HFRS may require renal dialysis.

Whole-blood transfusions from Ebola virus–immune donors and administration of Ebola monoclonal antibodies have been shown to be effective in lowering case fatality rates.

Patients suspected of having Lassa fever, Ebola fever, Marburg fever, or Congo-Crimean hemorrhagic fever should be placed in a private room on standard contact and droplet precautions. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure. All persons entering the patient's room should wear gloves, gowns, and face shields. Before exiting the patient's room, caretakers should safely remove and dispose of all protective gear and should clean and disinfect shoes. Protocols require two-person clinical care teams, one observer and one caregiver (see Centers for Disease Control and Prevention [CDC] website: https://www.cdc.gov/vhf/ebola).

Treatment of EVD often requires an intensive care unit and management of multiorgan system dysfunction, including correction of hypovolemia, hyponatremia, hypokalemia, hypoalbuminemia, hypocalcemia, and hypoxia, often with renal replacement therapy as well as ventilation support (see Table 317.2). Convalescent serum and monoclonal antibodies have been employed on an experimental basis. Strict isolation and appropriate barrier protection of healthcare workers is mandatory. Several vaccines have been shown to be immunogenic, and one used late in the epidemic was protective. Epidemic control measures, isolation, and quarantine have been used to attempt to decrease the spread of the West African epidemic.

PREVENTION

A live-attenuated vaccine (Candid-I) for Argentine hemorrhagic fever (Junin virus) is highly efficacious. A form of inactivated mouse brain vaccine is reported to be effective in preventing Omsk hemorrhagic fever. Inactivated RVF vaccines are widely used to protect domestic animals and laboratory workers. HFRS inactivated vaccine is licensed in Korea, and killed and live-attenuated vaccines are widely used in China. A vaccinia-vector glycoprotein vaccine provides protection against Lassa fever in monkeys. Single doses of recombinant vesicular stomatitis virus or adenovirus type 3 vaccines containing surface glycoproteins from Ebola and Marburg viruses have been shown to protect monkeys against Ebola virus and Marburg virus disease. The vesicular stomatitis-vectored Ebola vaccine was shown to be effective in preventing Ebola cases in a ring vaccination trial in Guinea and has been used widely in outbreaks since 2018.

Prevention of mosquito-borne and tick-borne infections includes use of repellents, wearing of tight-fitting clothing that fully covers the extremities, and careful examination of the skin after exposure, with removal of any vectors found. Diseases transmitted from a rodent-infected environment can be prevented through methods of rodent control; elimination of refuse and breeding sites is particularly successful in urban and suburban areas.

Patients should be isolated until they are virus-free or for 3 weeks after illness. Patient urine, sputum, blood, clothing, and bedding should be disinfected. Disposable syringes and needles should be used. Prompt and strict enforcement of barrier nursing may be lifesaving. The mortality rate among medical workers contracting these diseases is 50%. A few entirely asymptomatic Ebola infections result in strong antibody production.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 318

Lymphocytic Choriomeningitis Virus

Daniel J. Bonthius

Lymphocytic choriomeningitis virus (LCMV) is a prevalent human pathogen and an important cause of meningitis in children and adults. Capable of crossing the placenta and infecting the fetus, LCMV is also an important cause of neurologic birth defects and encephalopathy in the newborn.

ETIOLOGY

LCMV is a member of the family Arenaviridae, which are enveloped, negative-sense, single-stranded RNA viruses. The name of the arenaviruses is derived from *arenosus,* the Latin word for "sandy," because of the fine granularities observed within the virion on ultra-thin electron microscopic sections.

EPIDEMIOLOGY

Like all arenaviruses, LCMV uses rodents as its reservoir. The common house mouse, *Mus musculus,* is both the natural host and primary reservoir for the virus, which is transferred vertically from one generation of mice to the next via intrauterine infection. Hamsters and guinea pigs are also potential reservoirs. Although heavily infected with LCMV, rodents that acquire the virus transplacentally often remain asymptomatic because congenital infection provides rodents with immunologic tolerance for the virus. Infected rodents shed the virus in large quantities in nasal secretions, urine, feces, saliva, and milk throughout their lives.

Humans typically acquire LCMV by contacting fomites contaminated with infectious virus or by inhaling aerosolized virus. Most human infections occur during the fall and early winter, when mice move into human habitations. Humans can also acquire the virus via organ transplantation. Congenital LCMV infection occurs when a woman acquires a primary LCMV infection during pregnancy. The virus passes through the placenta to the fetus during maternal viremia. The fetus may also acquire the virus during passage through the birth canal from exposure to infected vaginal secretions. Outside of organ transplantation and vertical transmission during pregnancy, there have been no cases of human-to-human transmission of LCMV.

LCMV is prevalent in the environment, has a great geographic range, and infects large numbers of humans. The virus is found throughout the world's temperate regions and probably occurs wherever the genus *Mus* has been introduced (which is every continent but Antarctica). An epidemiologic study found that 9% of house mice are infected and that substantial clustering occurs, where the prevalence is higher. Serologic studies demonstrate that approximately 5% of adult humans possess antibodies to LCMV, indicating prior exposure and infection.

PATHOGENESIS

LCMV is not a cytolytic virus. Thus unlike many other nervous system pathogens that directly damage the brain by killing host brain cells, LCMV pathogenesis involves other underlying mechanisms. Furthermore, the pathogenic mechanisms are different in postnatal (acquired) infection compared with prenatal (congenital) infection. A critical difference in the pathogenesis of postnatal versus prenatal infection is that the virus infects brain parenchyma in the case of prenatal infection but is restricted to the meninges and choroid plexus in postnatal cases.

In postnatal infections, LCMV replicates to high titers in the choroid plexus and meninges. Viral antigen within these tissues becomes the target of an acute mononuclear cell infiltration driven by $CD8^+$ T lymphocytes. The presence of lymphocytes in large numbers within the meninges and cerebrospinal fluid (CSF) leads to the symptoms of meningitis that mark acquired LCMV infection. As the lymphocytes clear the virus from the meninges and CSF, the density of lymphocytes declines and the symptoms of meningitis resolve. Thus symptoms of acquired (postnatal) LCMV infection are immune mediated and are a result of the presence of large numbers of lymphocytes.

Prenatal infection likewise inflames the tissues surrounding the brain parenchyma, and this inflammation leads to some of the signs of congenital LCMV. In particular, within the ventricular system, congenital LCMV infection often leads to ependymal inflammation, which may block the egress of CSF at the cerebral aqueduct and lead to hydrocephalus. However, unlike postnatal cases, prenatal infection with LCMV includes infection of the substance of the brain rather than just the meninges or ependyma. This infection of brain parenchyma leads to the substantial neuropathologic changes typically accompanying congenital LCMV infection. In particular, LCMV infects the mitotically active neuroblasts, located at periventricular sites. Through an unknown mechanism, the presence of the virus kills these periventricular cells, leading to periventricular calcifications, a radiographic hallmark of this disorder. Within the fetal brain, LCMV infection of neurons and glial cells also disrupts neuronal migration, leading to abnormal gyral patterns, and interferes with neuronal mitosis, leading to microcephaly and cerebellar hypoplasia.

CLINICAL MANIFESTATIONS

The clinical manifestations of LCMV infection depend on whether the infection occurs prenatally or postnatally. Congenital infection with LCMV is unique, as it involves both the postnatal infection of a pregnant woman and the prenatal infection of a fetus.

Acquired (Postnatal) Lymphocytic Choriomeningitis Virus Infection

LCMV infection during postnatal life (during childhood or adulthood) typically consists of a brief febrile illness from which the patient fully recovers. The illness classically consists of two clinical phases. In the first phase, the symptoms are those of a nonspecific viral syndrome and include fever, myalgia, malaise, nausea, anorexia, and vomiting. These symptoms usually resolve after several days but are followed by a second phase, consisting of central nervous system disease. The symptoms of this second phase are those of aseptic meningitis, including headache, fever, nuchal rigidity, photophobia, and vomiting. The entire course of the biphasic disease is typically 1-3 weeks.

The clinical spectrum of LCMV infection is broad. One third of postnatal infections are asymptomatic. Other patients develop extraneural disease that extends beyond the usual symptoms and may include orchitis, pneumonitis, myocarditis, parotitis, dermatitis, alopecia, and pharyngitis. In others, the neurologic disease may be considerably more severe than usual and may include transverse myelitis, Guillain-Barré syndrome, hydrocephalus, and encephalitis. Recovery from acquired LCMV infection is usually complete, but fatalities occasionally occur.

LCMV infections acquired via solid organ transplantation always induce severe disease. Several weeks after the transplantation, recipients of infected organs develop fever, leukopenia, and lethargy. After these nonspecific symptoms, the course of the disease rapidly progresses to multiorgan system failure and shock. These cases are almost always fatal.

Congenital Lymphocytic Choriomeningitis Virus Infection

LCMV infection during pregnancy can kill the fetus and induce spontaneous abortion. Among surviving fetuses, the two clinical hallmarks of congenital LCMV infection are vision impairment and brain dysfunction.

The vision impairment in congenital LCMV infection is a result of **chorioretinitis** and the formation of chorioretinal scars. The scarring is usually bilateral and most commonly located in the periphery of the fundus, but involvement of the macula also occurs.

Although the retinal injuries from congenital LCMV infection are often severe, it is the *brain* effects that cause the greatest disability. Prenatal infection with LCMV commonly induces either macrocephaly or microcephaly. **Macrocephaly** after LCMV infection is almost invariably caused by noncommunicating hydrocephalus, stemming from inflammation within the ventricular system. **Microcephaly** is a result of the virus-induced failure of brain growth. In addition to disturbances of head size, periventricular calcifications are also cardinal features of congenital LCMV infection.

Although hydrocephalus, microencephaly, and periventricular calcifications are by far the most commonly observed abnormalities of the brain in congenital LCMV, other forms of neuropathology, alone or in combination, can also occur. These include periventricular cysts, porencephalic cysts, encephalomalacia, intraparenchymal calcifications, cerebellar hypoplasia, and neuronal migration disturbances.

Infants with congenital LCMV infection typically present during the newborn period with evidence of brain dysfunction. The most common signs are lethargy, seizures, irritability, and jitteriness.

Within the fetus, LCMV has a specific tropism for the brain. Thus unlike many other congenital infections, LCMV usually does not induce systemic manifestations. Birthweight is typically appropriate for gestational age. Skin rashes and thrombocytopenia, which are common in several other prominent congenital infections, are unusual in congenital LCMV infection. Hepatosplenomegaly is only rarely observed, and serum liver enzyme levels are usually normal. Auditory deficits are unusual.

LABORATORY FINDINGS

In acquired (postnatal) LCMV infection, the hallmark laboratory abnormality occurs during the second (central nervous system) phase of the disease and is CSF pleocytosis. The CSF typically contains hundreds to thousands of white blood cells, almost all of which are lymphocytes. However, CSF eosinophilia may also occur. Mild elevations of CSF protein and hypoglycorrhachia are common.

In congenital LCMV infection, laboratory findings in the newborn depend on whether the infant is still infected or not. If the infant still harbors the infection, then examination of the CSF may reveal a lymphocytic pleocytosis. Unlike many other congenital infections, LCMV does not typically induce elevations in liver enzymes, thrombocytopenia, or anemia. In many cases, the most reliably abnormal test is the head CT scan, which typically reveals a combination of microencephaly, hydrocephalus, and periventricular calcifications (Fig. 318.1).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute LCMV infections can be diagnosed by isolating the virus from CSF. Polymerase chain reaction has also been used to detect LCMV RNA in patients with active infections. However, by the time of birth, a baby prenatally infected with LCMV may no longer harbor the virus. Thus congenital LCMV infection is more commonly diagnosed by serologic testing. The immunofluorescent antibody test detects both immunoglobulin (Ig) M and IgG and has greater sensitivity than the more widely available complement fixation method. The immunofluorescent antibody test is commercially available, and its specificity and sensitivity make it an acceptable diagnostic tool. A more sensitive test for detecting congenital LCMV infection is the enzyme-linked immunosorbent assay, which measures titers of LCMV IgG and IgM and is performed at the Centers for Disease Control and Prevention.

For acquired (postnatal) LCMV infection, the principal items in the differential diagnosis are the other infectious agents that can induce meningitis. These include bacteria, fungi, viruses, and some other forms of pathogens. The most common viral causes of meningitis are the enteroviruses, including coxsackieviruses and echoviruses, and the arboviruses, including La Crosse encephalitis virus and equine encephalitis virus. Unlike LCMV, which is most common in winter, the enteroviruses and arboviruses are most commonly acquired in summer and early fall.

The principal items in the differential diagnosis of congenital LCMV infection are the other infectious pathogens that can cross the placenta and damage the developing fetus. These infectious agents are linked by the acronym TORCHS and include *Toxoplasma gondii,* rubella virus, cytomegalovirus, herpes simplex virus, and syphilis. Toxoplasmosis, Zika virus infection, and cytomegalovirus infection are particularly difficult to differentiate from LCMV, because all of these infectious agents can produce microcephaly, intracerebral calcifications, and chorioretinitis. Although clinical clues may aid in distinguishing one congenital infection from another, definitive identification of the causative infectious agent usually requires laboratory data, including cultures and serologic studies.

COMPLICATIONS

Complications in children with congenital LCMV infection are nonspecific and include the medical problems that commonly arise in scenarios involving ventriculoperitoneal shunts, severe seizure disorders, and static encephalopathy. These complications include shunt failure or infection, aspiration pneumonia, injuries from falls, and joint contractures.

TREATMENT

There is no specific treatment for acquired or congenital LCMV infection. An effective antiviral therapy for LCMV infection has not yet been developed. Ribavirin is active against LCMV and other arenaviruses in vitro, but its utility in vivo is unproven. Immunosuppressive therapy, if present, should be reduced.

Supportive Care

Children with hydrocephalus from congenital LCMV infection often require placement of a ventriculoperitoneal shunt during infancy for treatment of hydrocephalus. Seizures often begin during early postnatal life, are often difficult to control, and require administration of multiple antiepileptic medications. The mental retardation induced by congenital LCMV infection is often profound. In most cases, affected children should be referred for educational intervention during early life. The spasticity accompanying congenital LCMV infection is often severe. Although physical therapy can help to maintain the range of motion and minimize painful spasms and contractures, implantation of a baclofen pump is often helpful.

PROGNOSIS

The great majority of patients with postnatally acquired LCMV infection have a full recovery with no permanent sequelae. Rarely, postnatal infections induce hydrocephalus and require shunting. Rarer yet, postnatal LCMV infection is fatal.

In contrast to the usual benign outcome of postnatal infections, prenatal infections typically lead to severe and permanent disability.



Fig. 318.1 Head CT scan from a 2-mo-old microcephalic baby with congenital lymphocytic choriomeningitis virus infection. The scan reveals enlargement of the lateral ventricles *(LV)* and periventricular calcifications *(arrows)*.

In children with congenital LCMV infection, brain function is nearly always impaired and chorioretinitis is invariably present. Mental retardation, cerebral palsy, ataxia, epilepsy, and blindness are common neurologic sequelae. However, children with congenital LCMV infection have diverse outcomes. All children with the combination of microencephaly and periventricular calcifications are profoundly neurologically impaired. Blindness, medically refractory epilepsy, spastic quadriparesis, and mental retardation are typical of this group. However, other children with congenital LCMV infection who do not have the combination of microencephaly and periventricular calcifications often have a more favorable outcome, with less severe motor, mental, and vision impairments. Children with isolated cerebellar hypoplasia may be ataxic but have only mild or moderate mental retardation and vision loss.

PREVENTION

No vaccine exists to prevent LCMV infection. However, measures can be taken to reduce the risk of infection. Because rodents, especially house mice, are the principal reservoir of LCMV, people can reduce their risk of contracting the virus by minimizing their exposure to the secretions and excretions of mice. This can be accomplished most effectively by eliminating cohabitation with mice. Congenital LCMV infection will not occur unless a woman contracts a primary infection with LCMV during pregnancy. Thus women should be especially careful to avoid contact or cohabitation with mice during pregnancy. Pregnant women should also avoid contact with pet rodents, especially mice and hamsters. These facts should be stressed during prenatal visits.

Acquisition of LCMV from solid organ transplantation represents a substantial risk to organ recipients. Prospective donors with LCMV meningitis or encephalitis pose a clear risk for transmitting a fatal infection to recipients. Healthcare providers, transplantation centers, and organ procurement organizations should be aware of the risks posed by LCMV and should consider LCMV in any potential donor with signs of aseptic meningitis but no identified infectious agent. The risks and benefits of offering and receiving organs from donors with possible LCMV infection should be carefully considered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 319

Hantavirus Pulmonary Syndrome

Scott B. Halstead

Hantavirus pulmonary syndrome (HPS) is caused by multiple closely related hantaviruses that have been identified from the western United States, with sporadic cases reported from the eastern United States (Fig. 319.1) and Canada and important foci of disease in several countries in South America. HPS is characterized by a febrile prodrome followed by the rapid onset of noncardiogenic pulmonary edema and hypotension or shock. Sporadic cases in the United States caused by related viruses may manifest with renal involvement. Cases in Argentina and Chile sometimes include severe gastrointestinal hemorrhaging; nosocomial transmission has been documented in this geographic region only.

ETIOLOGY

Hantaviruses are a genus in the family Bunyaviridae, which are lipid-enveloped viruses with a negative-sense RNA genome composed of three unique segments. Several pathogenic viruses that have been recognized within the genus include Hantaan virus, which causes the severe disease; hemorrhagic fever with renal syndrome (HFRS), seen primarily in mainland Asia (see Chapter 317); Dobrava virus, the cause of a form of HFRS seen primarily in the Balkans; Puumala virus, which causes a milder disease with a high proportion of subclinical infections prevalent in northern Europe; and Seoul virus, which results in moderate HFRS and is transmitted predominantly in Asia by urban rats or worldwide by laboratory rats. Prospect Hill virus, a hantavirus that is widely disseminated in meadow voles in the United States, is not known to cause human disease. There are an increasing number of case reports of European hantaviruses causing HPS.

HPS is associated with *sin nombre* virus, isolated from deer mice, *Peromyscus maniculatus,* in New Mexico. The multiple HPS-like agents in the Northern Hemisphere isolated to date belong to a single genetic group of hantaviruses and are associated with rodents of the family Muridae, subfamily Sigmodontinae. These rodent species are restricted to the Americas, suggesting that HPS may be a Western Hemisphere disease.

EPIDEMIOLOGY

Persons acquiring HPS generally have a history of recent outdoor exposure or live in an area with large populations of deer mice. Clusters of cases have occurred among individuals who have cleaned houses that were rodent infested. *P. maniculatus* is one of the most common North American mammals and, where found, is frequently the dominant member of the rodent community. About half of the average of 30+ cases seen annually occurs between the months of May and July. Patients are almost exclusively 12-70 years of age; 60% of patients are 20-39 years of age. Rare cases are reported in children younger than 12 years of age. Two thirds of patients are male, probably reflecting their greater outdoor activities. It is not known whether almost complete absence of disease in young children is a reflection of innate resistance or simply lack of exposure. Evidence of human-to-human transmission has been reported in Argentine outbreaks. As of January 2017, 728 cases of hantavirus disease have been reported in the United States since surveillance began in 1993.

Hantaviruses do not cause apparent illness in their reservoir hosts, which remain asymptomatically infected for life. Infected rodents shed virus in saliva, urine, and feces for many weeks, but the duration of shedding and the period of maximum infectivity are unknown. The presence of infectious virus in saliva, the sensitivity of these animals to parenteral inoculation with hantaviruses, and field observations of infected rodents indicate that biting is important for rodent-to-rodent transmission. Aerosols from infective saliva or excreta of rodents are implicated in the transmission of hantaviruses to humans. Persons visiting animal care areas housing infected rodents have been infected

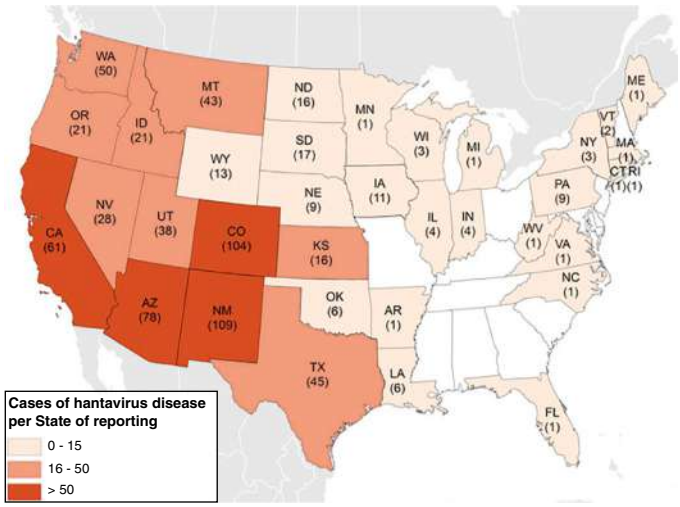

Fig. 319.1 Total number of confirmed cases of hantavirus pulmonary syndrome, by state reporting, United States, 1993-2016. N = 728 as of January 2017. *(From Viral Special Pathogens Branch, Centers for Disease Control and Prevention. http://www.cdc.gov/hantavirus/surveillance/reporting-state.html)*

after exposure for as little as 5 minutes. It is possible that hantaviruses are spread through contaminated food and breaks in skin or mucous membranes; transmission to humans has occurred by rodent bites. Person-to-person transmission is distinctly uncommon but has been documented in Argentina.

PATHOGENESIS

HPS is characterized by sudden and catastrophic pulmonary edema, resulting in anoxia and acute heart failure. The virus is detected in pulmonary capillaries, suggesting that pulmonary edema is the consequence of a T-cell attack on virus-infected capillaries. The disease severity is predicted by the level of acute-phase viremia titer. A useful hamster model of HPS is available.

CLINICAL MANIFESTATIONS

HPS is characterized by a prodrome and a cardiopulmonary phase. The mean duration after the onset of prodromal symptoms to hospitalization is 5.4 days. The mean duration of symptoms to death is 8 days (median: 7 days; range: 2-16 days). The most common **prodromal symptoms** are fever and myalgia (100%); cough or dyspnea (76%); gastrointestinal symptoms, including vomiting, diarrhea, and midabdominal pain (76%); and headache (71%). The **cardiopulmonary phase** is heralded by progressive cough and shortness of breath. The most common initial physical findings are tachypnea (100%), tachycardia (94%), and hypotension (50%). Rapidly progressive acute pulmonary edema, hypoxia, and shock develop in most severely ill patients. Pulmonary vascular permeability is complicated by cardiogenic shock associated with increased vascular resistance. The clinical course of the illness in patients who die is characterized by pulmonary edema accompanied by severe hypotension, frequently terminating in sinus bradycardia, electromechanical dissociation, ventricular tachycardia, or fibrillation. Hypotension may be progressive even with adequate oxygenation. HPS virus is excreted in the urine during the acute illness phase, and survivors may demonstrate evidence of chronic renal damage.

DIAGNOSIS

The diagnosis of HPS should be considered in a previously healthy patient presenting with a febrile prodrome, acute respiratory distress, and thrombocytopenia who has had outdoor exposure in the spring and summer months. A specific diagnosis of HPS is made by serologic tests that detect hantavirus immunoglobulin M antibodies. The early appearance of immunoglobulin G antibodies signals probable recovery. Hantavirus antigen can be detected in tissue by immunohistochemistry and amplification of hantavirus nucleotide sequences detected by reverse transcriptase polymerase chain reaction. The state health department or the Centers for Disease Control and Prevention should be consulted to assist in the diagnosis, epidemiologic investigations, and outbreak control.

Laboratory Findings

Laboratory findings include leukocytosis (median: 26,000 cells/μL), an elevated hematocrit resulting from hemoconcentration, thrombocytopenia (median: 64,000 cells/μL), prolonged prothrombin and partial thromboplastin times, elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, proteinuria, and microscopic hematuria. Patients who die often experience disseminated intravascular coagulopathy, including frank hemorrhage and exceptionally high leukocyte counts.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes adult respiratory distress syndrome, pneumonic plague, psittacosis, severe mycoplasmal pneumonia, influenza, leptospirosis, inhalation anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral pneumonia, legionellosis, meningococcemia, and other sepsis syndromes. The key determinant in the diagnosis of HPS is thrombocytopenia.

TREATMENT

Management of patients with hantavirus infection requires maintenance of adequate oxygenation and careful monitoring and support of cardiovascular function. The pathophysiology of HPS somewhat resembles that of dengue shock syndrome (see Chapter 315). Pressor or inotropic agents, such as dobutamine, should be administered in combination with judicious volume replacement to treat symptomatic hypotension or shock while avoiding exacerbation of the pulmonary edema. Intravenous ribavirin, which is lifesaving if given early in the course of HFRS and is effective in preventing death in the hamster model, has not yet been demonstrated to be of value in HPS.

Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral Special Pathogens Branch, Atlanta, Georgia 30333 (470-312-0094).

PROGNOSIS

In some geographic areas, fatality rates for HPS have been 50%. Severe abnormalities in hematocrit, white blood cell count, lactate dehydrogenase value, and partial thromboplastin time and a high viral load predict death with high specificity and sensitivity. The early appearance of immunoglobulin G antibodies may signal a hopeful prognosis.

PREVENTION

Avoiding contact with rodents is the only preventive strategy against HPS. Rodent control in and around the home is important. Barrier nursing is advised, and biosafety level 3 facilities and practices are recommended for laboratory handling of blood, body fluids, and tissues from suspect patients or rodents, because the virus may be aerosolized. However, to date, there are no cases of person-to-person transmission of HPS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 320

Rabies

Rodney E. Willoughby Jr.

Rabies virus is a bullet-shaped, negative-sense, single-stranded, enveloped RNA virus from the family Rhabdoviridae, genus *Lyssavirus.* There are 17 species of *Lyssavirus,* divided into three antigenic phylogroups. Rabies vaccines and immunoglobulins are active against phylogroup I viruses. The classic rabies virus (phylogroup I, genotype 1) is distributed worldwide and naturally infects a large variety of animals. The other genotypes are more geographically confined, with none found in the Americas. Six *Lyssavirus* genotypes are associated with rabies in humans, although genotype 1 accounts for the great majority of cases. Within genotype 1, different lineages are specific to animal reservoirs, although cross-species transmission can occur. Cosmopolitan dog, vampire bat, and insectivorous bat lineages in the Americas cause overlapping but distinct clinical syndromes and vary in immunogenicity, affecting survival.

EPIDEMIOLOGY

Rabies is present on all continents except Antarctica. Rabies predominantly afflicts underaged, poor, and geographically isolated populations. Approximately 59,000 cases of human rabies occur in Africa and Asia annually. Rabies virus can infect any mammal or bird, but true animal reservoirs that maintain the presence of rabies virus in the population are limited to terrestrial carnivores and bats. Worldwide, transmission from dogs accounts for >90% of human cases. In Africa and Asia, other animals serve as prominent reservoirs, such as jackals, mongooses, and raccoon dogs. In the United States, raccoons are the most infected wild animal along the eastern seaboard. Three lineages

of skunk rabies are endemic in the Midwest (north and south) and California, gray foxes harbor rabies in Arizona and Texas, red foxes and arctic foxes harbor rabies in Alaska, and mongooses carry rabies in Puerto Rico. Rabies occurs infrequently in livestock. Among American domestic pets, infected cats outnumber infected dogs, probably because cats frequently prowl unsupervised and are not uniformly subject to vaccine laws. Rabies is rare in small mammals, including mice, squirrels, and rabbits; to date, no animal-to-human transmission from these animals has been documented.

The epidemiology of human rabies in the United States is dominated by cryptogenic bat rabies. Bats are migratory in the spring and fall; rabid bats are identified in every state of the union except Hawaii. In almost all cases of bat-associated human rabies in the United States, there was no history of a bat bite. Among inhabitants of the Peruvian Amazon region who have exposure to rabies-infected vampire bats, there are some who have rabies virus–neutralizing antibodies. Antibody-positive patients remember bat bites but do not recall symptoms of rabies.

In the United States, 30,000 episodes of rabies postexposure prophylaxis (PEP) occur annually. Between one and three endemic human cases are diagnosed annually, half postmortem. There have been five outbreaks of rabies associated with solid organ and corneal transplantation.

TRANSMISSION

Rabies virus is found in large quantities in the saliva of infected animals, and transmission occurs almost exclusively through inoculation of the infected saliva through a bite or scratch from a rabid mammal. Approximately 35–50% of people who are bitten by a known rabies-infected animal and receive no PEP contract rabies. The transmission rate is increased if the victim has suffered multiple bites and if the inoculation occurs in highly innervated parts of the body such as the face and the hands. Infection does not occur after exposure of intact skin to infected secretions, but virus may enter the body through intact mucous membranes. Claims that spelunkers may experience rabies after inhaling bat excreta have come under doubt, although inhalational exposure can occur during laboratory accidents.

No case of nosocomial transmission to a healthcare worker has been documented to date, but caregivers of a patient with rabies are advised to use full barrier precautions. The virus is rapidly inactivated in the environment, and contamination of fomites is not a mechanism of spread.

PATHOGENESIS

After inoculation, rabies virus replicates slowly and at low levels in muscle or skin. This slow initial step likely accounts for the disease's long incubation period. The virus then enters the peripheral motor nerve, using the nicotinic acetylcholine receptor and possibly other receptors for entry. Once in the nerve, the virus travels by fast axonal transport, crossing synapses roughly every 12 hours. Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear. Infection of the dorsal root ganglia is apparently futile but causes characteristic radiculitis. Infection concentrates in the brainstem, accounting for autonomic dysfunction and relative sparing of cognition. Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis. The pathologic hallmark of rabies, the Negri body, is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies can be absent in documented rabies virus infection. Rabies may be a metabolic disorder of neurotransmission; tetrahydrobiopterin deficiency in human rabies causes severe deficiencies in dopamine, norepinephrine, and serotonin.

After infection of the central nervous system, the virus travels anterograde through the peripheral nervous system to virtually all innervated organs, further exacerbating dysautonomia. It is through this route that the virus infects the salivary glands. Many victims of rabies die from uncontrolled cardiac dysrhythmia in the first week of objective signs of rabies.

Deficiency of tetrahydrobiopterin, an essential cofactor for neuronal nitric oxide synthase, is predicted to lead to spasm of the basilar arteries. Onset of vasospasm has been confirmed in a few patients within 5-8 days of the first hospitalization, at about the time coma supervenes in the natural history. Metabolites in cerebrospinal fluid (CSF) consistent with ketogenesis are associated with demise. Immune response to rabies is delayed, usually evident 4-14 days after onset of clinical signs. Immune response to rabies varies by lineage; antibody responses in CSF are often inferior to those in serum. Common complications include complete heart block in dog rabies and cerebral edema in bat rabies.

CLINICAL MANIFESTATIONS

The incubation period for rabies is 1-3 months. In severe wounds to the head, symptoms may occur within 5 days after exposure, and occasionally the incubation period can extend to 8 years. Rabies has two principal clinical forms, but these overlap in practice. **Encephalitic** or **furious rabies** is extrapolated from carnivores and begins with nonspecific symptoms, including fever, sore throat, malaise, headache, nausea and vomiting, and weakness. Symptoms are often accompanied by paresthesia and pruritus at or near the site of the bite. The patient begins to demonstrate symptoms of encephalitis, with agitation, sleep disturbance, or depressed mentation. Characteristically, patients with rabies encephalitis initially have periods of lucidity alternating with periods of profound encephalopathy. Hydrophobia and aerophobia are the cardinal signs of rabies; they are unique to humans and are not universal or specific. Phobic spasms are manifested by agitation and fear created by being offered a drink or fanning of air in the face, which in turn produce choking and aspiration through spasms of the pharynx, neck, and diaphragm. Seizures are rare and should point to an alternative diagnosis; orofacial dyskinesias and myoclonus may be confused with seizures. Severe dysautonomia is common, and cardiac arrests occur in 25% of patients in the first week of hospitalization. The illness is relentlessly progressive. There is a dissociation of brain electrical activity with findings of brainstem coma caused by anterograde denervation. Death almost always occurs within 1-2 days of hospitalization in developing countries and by 18 days of hospitalization with intensive care.

Paralytic or **dumb rabies**, extrapolated from herbivores, is seen much less frequently and is characterized principally by fevers and ascending motor weakness affecting both the limbs and the cranial nerves. Most patients with paralytic rabies also have some element of encephalopathy as the disease progresses subacutely.

Case reports suggest that milder forms of rabies encephalitis may exist, and 45 rabies survivors are known. Rabies should be considered earlier and more frequently than current practice to improve outcomes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rabies encephalitis includes all forms of severe cerebral infections, tetanus, and some intoxications and envenomations. Rabies can be confused with autoimmune (anti–*N*-methyl-D-aspartate receptor, NMDAR) encephalitis, other infectious forms of encephalitis, psychiatric illness, drug abuse, and conversion disorders. Paralytic rabies is frequently confused with Guillain-Barré syndrome. The diagnosis of rabies is frequently delayed in Western countries because of the unfamiliarity of the medical staff with the infection. These considerations highlight the need to pursue a history of contact with an animal belonging to one of the known reservoirs for rabies or to establish a travel history to a rabies-endemic region.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) require complementary tests to confirm a clinically suspected case of rabies. The virus can be grown both in cell culture and after animal injection, but these methods are slow. Pan-lyssavirus reverse transcription polymerase chain reaction is 90% sensitive for the diagnosis of rabies when done on skin and iteratively in saliva. Rabies antigen is detected

through immunofluorescence of saliva or biopsies of hairy skin or brain. Corneal impressions are not recommended. Rabies-specific antibody can be detected in serum or CSF samples, but most patients die while seronegative. Antirabies antibodies are present in the sera of patients who have received an incomplete course of the rabies vaccine, precluding a meaningful interpretation in this setting. Recent treatment with intravenous immunoglobulin may result in a false-positive antibody test. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status. CSF abnormalities in cell count, glucose, and protein content are minimal and not diagnostic. MRI findings in the brain are late.

TREATMENT AND PROGNOSIS

Rabies is generally fatal. Conventional critical care yielded 6 survivors from 79 attempts since 1990. Seventeen of 103 patients survived with use of the Milwaukee Protocol (MP) (http://www.mcw.edu/rabies); neurologic outcomes are poor in half of patients. Neither rabies immunoglobulin (RIG) nor rabies vaccine provides benefit once symptoms have appeared. Among 10 survivors of rabies after use of rabies vaccine, 7 had poor neurologic outcomes. Among seven vaccine-naïve survivors, two had poor outcomes. Antiviral treatments have not been effective; favipiravir has been administered to eight patients with modest clinical effect. Ribavirin and RIG delay the immune response and should be avoided. In contrast, appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.

PREVENTION

Primary prevention of rabies infection includes vaccination of domestic animals and education to avoid wild animals, stray animals, and animals with unusual behavior.

Immunization and Fertility Control of Animal Reservoirs

The introduction of routine rabies immunization for domestic pets in the United States and Europe during the middle of the 20th century virtually eliminated infection in dogs. Dog rabies has now been almost eliminated from the Americas; residual cases concentrate in the Caribbean and Bolivia. In the 1990s, control efforts in Europe and North America shifted to immunization of wildlife reservoirs of rabies, where rabies was newly emerging. These programs employed bait laced with either an attenuated rabies vaccine or a recombinant rabies surface glycoprotein inserted into vaccinia, distributed by air or hand into areas inhabited by rabid animals. Human contact with vaccine-laden bait has been infrequent. Adverse events after such contact have been rare, but the vaccinia vector poses a threat to the same population at risk for vaccinia itself, namely, pregnant women, immunocompromised patients, and people with atopic dermatitis. Mass culling of endemic reservoirs has never worked; vaccination and fertility control stop outbreaks. Bats are ubiquitous and very important for insect control. Less than 1% of free-flying bats but >8% of downed bats and bats found in dwellings are rabid.

Postexposure Prophylaxis

Only one case of rabies has been documented in a person in the United States receiving the recommended schedule of PEP since introduction of modern cellular vaccines in the 1970s.

Given the incubation period for rabies, PEP is a medical urgency, not emergency. The relevance of rabies for most pediatricians centers on evaluating whether an animal exposure warrants PEP (Fig. 320.1). The decision to proceed ultimately depends on the local epidemiology of animal rabies as determined by active surveillance programs, information that can be obtained from local and state health departments. In general, bats, raccoons, skunks, coyotes, and foxes should be considered rabid unless proven otherwise through euthanasia and testing of brain tissue, whereas bites from small herbivorous animals (squirrels, hamsters, gerbils, chipmunks, rats, mice, and rabbits) can be discounted. The response to bites from a pet, particularly a dog, cat, or ferret, depends on local surveillance statistics and on whether the animal is vaccinated and available for observation. Areas free of canine lineage of rabies virus may still have rabid dogs and cats through wildlife transmission.

The approach to nonbite bat exposures is controversial. In response to the observation that most cases of rabies in the United States have been caused by bat variants and that most affected patients had no recollection of a bat bite, the CDC has recommended that **rabies PEP be considered after any physical contact with bats and when a bat is found in the same room as persons who may not be able to accurately report a bite**, assuming that the animal is unavailable for testing. Such people include young children, the mentally disabled, and intoxicated individuals. Other nonbite contacts (e.g., handling a carcass, exposure to an animal playing with a carcass, or coming into contact with blood or excreta from a potentially rabid animal) usually do not require PEP.

In all instances of a legitimate exposure, effort should be made to recover the animal for quarantine and observation or brain examination after euthanasia. Testing obviates the need for PEP more than half the time. In most instances, PEP can be deferred until the results of observation or brain histology are known. In dogs, cats, and ferrets, symptoms of rabies always occur within several days of viral shedding; therefore in these animals a 10-day observation period is sufficient to eliminate the possibility of rabies.

No duration of time between exposure and onset of symptoms should preclude rabies prophylaxis. Rabies PEP is most effective when applied expeditiously. Nevertheless, the series should be initiated in the asymptomatic person as soon as possible, regardless of the length of time since the bite. Rabies vaccine and RIG are contraindicated once symptoms develop.

The first step in rabies PEP is to cleanse the wound thoroughly. Soapy water is sufficient to inactivate an enveloped virus, and its effectiveness is supported by broad experience. Other commonly used disinfectants, such as iodine-containing preparations, are virucidal and should be used in addition to soap when available. Probably the most important aspect of this component is that the wound is cleansed with copious volumes of disinfectant. Primary closure is avoided; wounds may be bacterially infected as well, so cosmetic repair should follow. Antibiotics and tetanus prophylaxis (see Chapter 257) should be applied with the use of usual wound care criteria.

Schedules and indications for administration of rabies vaccine and human-derived rabies immunoglobulin (HRIG) are available at the CDC website (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/rabies.html). These do not harmonize fully with international recommendations by the World Health Organization that seek greater efficiencies in PEP and use of RIG after dog bites.

The second component of rabies PEP consists of passive immunization with RIG. Most failures of PEP are attributed to not using RIG. HRIG, the formulation used in industrialized countries, is administered at a dose of 20 IU/kg. Globally, the World Health Organization recommends that as much of the dose is infused around the wound as possible. In the United States, where bat rabies dominates, the remainder is injected intramuscularly in a limb distant from the one injected with the killed vaccine. Like other immunoglobulin preparations, RIG interferes with the take of live viral vaccines for at least 4 months after administration of the RIG dose. A more concentrated formulation of HRIG is available, which may be more suitable for bites on the face and digits to minimize risk of compartment syndrome after injection. HRIG is not available in many parts of the developing world. Modern preparations of equine RIG are associated with fewer side effects than prior products composed of crude horse serum. Regrettably, for a large segment of the world's population, no passive immunization product is available at all, so preexposure prophylaxis (PreRP) should be considered. Monoclonal antibody products are in clinical trials and may alleviate this deficiency.

The third component of rabies PEP is immunization with inactivated vaccine. In most of the world, cell-based vaccines have replaced previous preparations. Two formulations currently are available in the United States, namely, RabAvert (Chiron Behring Vaccines, Maharashtra, India), a purified chick embryo cell–cultivated vaccine, and Imovax

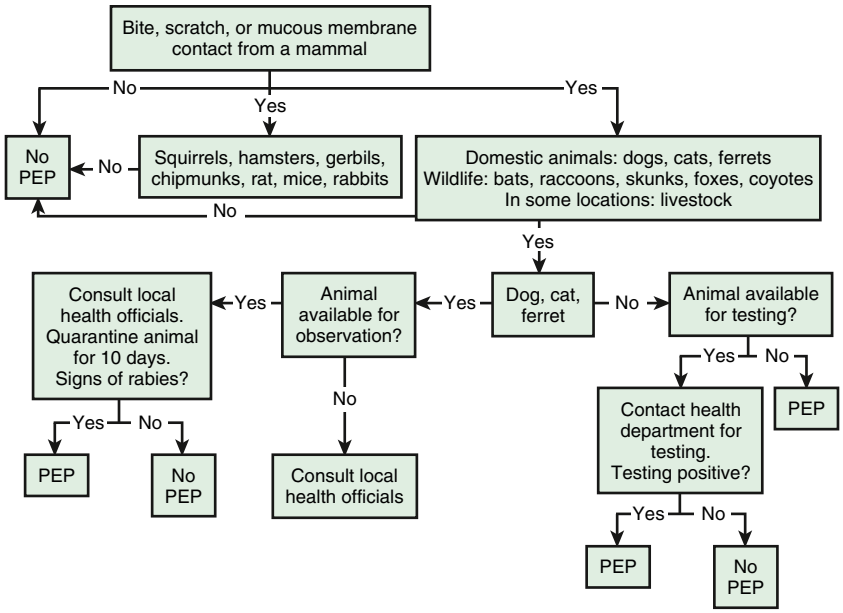

Fig. 320.1 Algorithm for evaluating a child for rabies postexposure prophylaxis. This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

Rabies (Aventis Pasteur, Bridgewater, NJ), cultivated in human diploid cell cultures. In both children and adults, both vaccines are administered intramuscularly in a 1-mL volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a blunted antibody response, so this area should not be used. The rabies vaccines can be safely administered during pregnancy. In most persons the vaccine is well tolerated; most adverse effects are related to booster doses. Pain and erythema at the injection site occur commonly, and local adenopathy, headache, and myalgias occur in 10–20% of patients. Approximately 5% of patients who receive the human diploid cell vaccine experience an immune complex–mediated allergic reaction, including rash, edema, and arthralgias, several days after a booster dose. The World Health Organization has approved schedules using smaller amounts of vaccine, administered intradermally, that are immunogenic and protective, but none is approved for use in the United States. Other cell culture–derived rabies virus vaccines are available in the developing world. A few countries still produce nerve tissue–derived vaccines; these preparations are poorly immunogenic, and cross reactivity with human nervous tissue may occur, producing severe neurologic symptoms even in the absence of rabies infection. Prompt travel to a clinic or country to obtain modern rabies vaccine is advised instead.

Preexposure Prophylaxis

The killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to wild-type virus, including laboratory personnel working with rabies virus, veterinarians, and others likely to be exposed to rabid animals as part of their occupation. PreEP should be considered for persons traveling to a rabies-endemic region where there is a credible risk for a bite or scratch from a rabies-infected animal, particularly if there is likely to be a shortage of RIG or cell culture–based vaccine. Rabies vaccine as part of the routine vaccine series is under investigation in some countries. The schedule for PreEP consists of two intramuscular injections on days 0, and 7; other schedules are available globally. PEP in the patient who has received PreEP or a prior three doses of PEP consists of two doses of vaccine (one each on days 0 and 3) and does not require RIG. Immunity from PreEP wanes after several years and requires boosting if the potential for exposure to rabid animals recurs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 321
Polyomaviruses

Bijal A. Parikh

Human polyomaviruses (PyV) comprise a unique group of viruses that cause disease in immunocompromised individuals but not in the healthy immune-competent host. The two best-studied human PyV, BK PyV and JC PyV, are acquired relatively early in life and generally cause no clinical disease, despite occasional bouts of asymptomatic viral shedding. PyV-associated sequelae become especially relevant in the setting of **posttransplant renal graft failure** and **hemorrhagic cystitis** in the case of BK PyV and **neurologic disease** for JC PyV reactivation. The number of human PyV has expanded dramatically, with discovery of up to 12 additional viruses. Two PyV, designated KI virus and WU virus, can be detected in respiratory samples from children; however, their disease associations are not as well established outside of a few case reports. Exceptions include **Merkel cell** or **MC PyV** and **trichodysplasia spinulosa-associated** or **TS PyV**, yet their relevance in the pediatric population is limited. Current knowledge regarding BK PyV and JC PyV epidemiology and disease associations with special emphasis on diagnostic and clinical management of pediatric populations is summarized next.

GENOMIC ORGANIZATION

PyV are nonenveloped, icosahedral virions of 40-45 nm in diameter. The genomes are circular double-stranded DNA composed of approximately 5,000 base pairs. The type member of the parent family, *Polyomaviridae*, is **simian virus 40** (SV40). Translation of proteins occurs from both early and late transcripts, transcribed in opposite directions from the noncoding control region (NCCR). The host range of PyV is very broad, having been isolated from a variety of mammals, birds, and even fish. However, PyV are strictly species specific; thus human PyV only infect humans.

PyV EPIDEMIOLOGY

Almost 90% of adults have been infected with BK PyV by their third decade; only 20% of children are seropositive for BK PyV by age 3,

climbing to 80% by age 7. Approximately 50–70% of adults are seropositive for JC PyV, and children show even lower seroprevalence rates, with less than 30% positive by age 7. Both BK PyV and JC PyV are primarily respiratory tract infections with subsequent spread to the kidneys and the central nervous system (CNS), respectively. **Tropism** for BK PyV has been demonstrated to be the bladder urothelium and renal tubular cells, where lifelong latency is likely established. In contrast, the primary tropism for JC PyV includes the CNS and lymphoid and renal tissue. MC PyV is found and shed from skin, although little is known about its acquisition.

BK PyV

BK PyV was first detected in the urine from a renal allograft recipient suffering from ureteral stenosis with the initials "BK." In the immunocompetent host, BK PyV may never result in any observable clinical disease. However, in the immunocompromised, BK PyV reactivation can lead to serious consequences. Immune suppression can either be iatrogenic after transplantation or constitutional, such as with inherited immune-deficiency syndromes. In renal transplant recipients, interstitial nephritis, renal dysfunction, and ultimately graft failure can develop. In **hematopoietic stem cell transplant** (HSCT) recipients, reactivation can lead to hemorrhagic cystitis. Although the incidence of such symptomatic complications is rare, **BK PyV must be proactively managed through careful monitoring and alteration of immunosuppressive regimens**.

Although the most common complication after pediatric kidney transplantation continues to be graft failure caused by chronic rejection, infections of the transplanted organ can also promote graft dysfunction. Common infectious complications placing pediatric recipients at risk for graft failure include EBV, CMV, BK PyV, and JC PyV. Fortunately, with current monitoring and interventions, the incidence of pediatric transplants that will fail as a result of nephropathy correlating with BK PyV infection is very low.

Nearly two thirds of pediatric renal transplant recipients show evidence of BK **viruria** (virus in the urine), with one fifth showing **viremia** (virus in the blood). **BK virus–associated nephropathy (BKVAN)** can **initially manifest as rising creatinine and is diagnosed definitively through core renal biopsies**. However, because the nephropathy can be focal, a single unaffected core specimen does not exclude disease. In the core biopsy, **BKVAN is characterized by tubular injury with cellular enlargement, epithelial necrosis, erosion of tubular basement membranes, and intranuclear inclusion bodies in epithelial cells**. If untreated, tubular necrosis and sclerosing allograft nephropathy can lead to irreversible renal impairment and rejection. Importantly, reduction of immunosuppression in viremic patients has been highly effective in limiting rejection caused by BKVAN. Rates of BKVAN in the pediatric population have been estimated at around 5%, and approximately 0.5% of renal transplant recipients will lose their graft because of BKVAN.

Laboratory evidence of BK PyV infection is best achieved through a **microscopic urine examination, followed by molecular (polymerase chain reaction [PCR]–based) quantitative analysis of urine and plasma** (Table 321.1). Depending on the method and analyte, a wide range of sensitivity and specificity has been reported. **Detection of "haufen,"** which are viral aggregates that can be detected only by electron microscopy, is nearly 100% sensitive and specific but requires special equipment. An alternative diagnostic approach includes microscopic examination for the **presence of decoy cells** (urothelial cells containing abundant viral particles) in the urine; however, sensitivity is poor, and thus examination for decoy cells is not the preferred screening method. More commonly, **PCR testing for BK genomic DNA from urine and plasma** is employed. Although highly sensitive for BK PyV, the specificity of single-time-point molecular tests for predicting renal nephropathy is low, as asymptomatic individuals can intermittently shed virus without progression to renal disease. Therefore the presence of **isolated BK viruria is not sufficient to diagnose infection** leading to renal impairment.

Accurate quantification of BK PyV in plasma and urine is essential for standardized care across transplant centers with broadly applied thresholds for intervention. The first WHO international standard for BK PyV was made available to enable interassay comparisons in 2016. In 2020, the first molecular platform to obtain FDA clearance for quantitative BK PyV testing included plasma and urine for monitoring renal transplant recipients based on the use of the WHO standard.

No single guideline exists for routine monitoring for BKVAN in either pediatric or adult populations, and thus transplant centers need to design strategies that best fit their local prevalence rates. One proposed guideline suggests **urine screening monthly in the first months after transplant, then every 3 months for 2 years, and then annually in years 3, 4, and 5. If viruria exceeds 1×10^7 copies/mL, then biopsy should be performed with a concomitant reduction in immunosuppression.** In addition, plasma levels exceeding 1×10^4 copies/mL should also prompt a biopsy and reduction in immunosuppression. Centers may include routine renal biopsies to monitor for overall graft health, and these may also be used to evaluate for BKVAN.

Although **there are no direct antiviral treatments for BK PyV**, the primary clinical parameter shown to have the greatest effect on preventing long-term kidney damage and rejection is **careful adjustment of the dose of immunosuppression**. This adjustment allows the body's natural immunity, specifically the T-cell compartment, to effectively reduce the viral burden. However, decreasing immunosuppression comes at a risk of graft rejection if not cautiously approached. A growing body of literature is beginning to emerge that reevaluates the anecdotal successes of specific treatments, including **cidofovir** (CDV) and **leflunomide**. These two drugs have shown efficacy in culture conditions, yet clinical utility remains unproven. The antibiotic class of fluoroquinolones has also demonstrated in vitro activity without a subsequent sustained clinical effect. Finally, both intravenous **immunoglobulin** (IVIG) and **cyclosporine A** have shown equally limited effects in clinical trials. In summary, **the current treatment options rely heavily on early and accurate detection of infection followed by an appropriately titered dose reduction in immunosuppressive drugs**.

In pediatric HSCT recipients, a common association between BK PyV shedding and hemorrhagic cystitis (HC) has been clinically observed. HC can occur in one fifth to one third of pediatric patients after HSCT; however, it rarely results in death. Unfortunately, the long-term sequelae of fibrosis and bladder contracture can lead to significant morbidity. After HSCT, either **early-onset (within 1 week) or late-onset (2-8 weeks) HC** may occur, with the timing providing insight into the pathogenic process. Early-onset HC appears to be a result of direct urothelial damage from conditioning agents (cyclophosphamide,

Table 321.1 Recommendations for Patients with BK PyV–Associated Nephropathy

	SCREENING	DIAGNOSIS	MONITORING
Cytology	Poor sensitivity	Decoy cells, Haufen	Poor sensitivity
Molecular	Routine BK PyV PCR after renal transplant	BK viremia >10,000 copies/mL	Follow until viral loads trend lower
Pathology	Institution specific for the frequency of kidney biopsy	Kidney allograft biopsy with characteristic changes and positive immunohistochemistry (IHC) demonstrating viral antigen	Institution specific for the frequency of kidney biopsy

busulfan, radiation) before transplant, independent of any infectious process, whereas the more commonly observed late-onset HC occurs around the time of engraftment. Although primarily associated with BK PyV, the differential diagnosis for late-onset HC also includes JC PyV, CMV, and adenovirus. **All causes of HC must be carefully considered for effective clinical management.**

Diagnosis of HC requires a triad of findings: cystitis, gross hematuria, and urine BK PyV loads >7 log10 copies/mL (Table 321.2). Current guidelines do not recommend screening for BK PyV after HSCT, citing a lack of effective prophylactic treatment. However, long-term sequelae of renal impairment greater than 2 years after transplant have been described, and therefore routine monitoring may need to eventually be considered.

The presence of BK PyV in the urine occurs in the majority of HSCT recipients and is therefore neither specific nor predictive of BK PyV-HC. Although not as sensitive, the presence of virus in plasma of >3 log10 copies/mL is seen in two thirds of recipients with BK PyV-HC, and diminution of viremia correlates strongly with resolution of HC.

For individuals with **severe HC, standard treatment includes hyperhydration and diuretics**. **Bladder irrigation may be necessary** to avoid renal damage and clotting. Less severe cases will spontaneously resolve in a few weeks. Unlike with renal transplantation, reduction of immunosuppression carries a large risk for potentially life-threatening **graft-versus-host disease (GVHD)** and so is not considered to be the initial treatment approach. Additionally, if thrombocytopenia and anemia are present**, appropriate transfusions should be initiated to maintain adequate blood counts**. The role of CDV in treating or preventing HC in the context of HSCT remains controversial, and thus professional society guidelines currently do not recommend its routine use.

JC PyV

JC PyV was first detected in the brain of a patient with Hodgkin lymphoma with the initials "JC." JC PyV can be acquired by the respiratory route and through ingestion from contaminated surfaces, food, and water and ultimately establishes latency in the kidneys, brain, and various lymphoid organs. In renal transplant recipients, JC PyV can be shed in the urine but only rarely causes nephropathy. After HSCT, HC from BK PyV is far more likely than from JC PyV. Conversely, only JC PyV infects the oligodendrocytes of the CNS and is responsible for **progressive multifocal leukoencephalopathy (PML)**. PML is a fatal demyelinating disease that results from the lysis of specific glial cells in afflicted immunocompromised individuals. In patients with hematologic malignancy, autoimmune disorders, or HIV infection leading to decreased cellular immunity, JC PyV reactivation can lead to PML. In immunocompetent adults, PML is a feared consequence of monoclonal antibody treatments for multiple sclerosis. However, the literature for JC PyV infection in the pediatric population is sparse, with the majority of studies provided as case reports. As a result, many of the clinical guidelines for screening, diagnosis, and therapy must be extended from the adult literature.

The more common clinical manifestations of PML in children are similar to what has been observed in adults and includes hemiparesis, ataxia, dysarthria, and seizures. Evaluation for PML is primarily through radiologic imaging, with primary findings consistent with characteristic asymmetric white matter lesions. The diagnosis of PML is established through molecular detection of viral DNA in the cerebrospinal fluid (CSF) or viral proteins on a brain biopsy (Table 321.3). Unlike with BK PyV, there are no quantitative thresholds because any amount of virus in the CSF is considered abnormal. Although the sensitivity for detection in pediatric cases is under 60%, the specificity is near 100%; therefore a positive PCR result can be considered diagnostic. Remarkably, the CSF cell counts and protein and glucose levels are typically normal. Cases without molecular evidence may still be termed "possible PML" based on neurologic and radiologic findings.

Treatment for PML is primarily through reversing the underlying cause of immune dysfunction. Adults with advanced HIV infection should be treated with antiretroviral therapy (ART), but the efficacy of ART for resolution of PML in children is not well-documented. It is important for the clinician to be aware of a rare but serious complication after HIV suppression promoting a paradoxical increase in JC PyV–mediated damage. This phenomenon has been termed PML-immune reconstitution inflammatory syndrome and can often be treated with steroids. Unfortunately, the prognosis for PML in children is grim, with most patients succumbing to the disease within 6 months. It remains to be seen if absolute viral load or specific radiologic and clinical findings might be used to better predict outcomes in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 321.2 Recommendations for Patients with BK PyV–Associated Hemorrhagic Cystitis

	SCREENING	DIAGNOSIS	MONITORING
Clinical	Suspect with anemia, thrombocytopenia, dysuria, or urinary obstruction after HSCT	Cystitis/lower abdominal pain	Follow clinical resolution
Cytology	Gross hematuria	Gross hematuria	No recommendations
Molecular	No recommendations	BK viruria >10,000,000 copies/mL	

Table 321.3 Recommendations for Patients with JCV PyV/Progressive Multifocal Leukoencephalopathy

	SCREENING	DIAGNOSIS	MONITORING
Clinical	Suspect in an immunosuppressed patient with subacute neurologic findings		
Imaging	No recommendations	Characteristic MRI findings	No recommendations
Molecular	No recommendations	Positive CSF PCR for JC PyV	
Pathology	No recommendations	Brain biopsy with characteristic lesions and positive IHC demonstrating viral antigen	

Chapter 322

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Ericka V. Hayes

Advances in research and major improvements in the treatment and management of HIV infection have brought about a substantial decrease in the incidence of new HIV infections and AIDS in children. Globally, from 2000–2015, there has been an estimated 70% decline in new infections in children age 0-14 years, largely the result of antiretroviral treatment (ART) of HIV-infected pregnant individuals for the prevention of vertical transmission. Of adults and children with HIV infection, 70% live in sub-Saharan Africa, where the disease continues to have a devastating impact (Fig. 322.1). Children experience more rapid disease progression than adults, with up to half of untreated children dying within the first 2 years of life. This rapid progression is correlated with a higher viral burden and faster depletion of infected CD4 lymphocytes in infants and children than in adults. Accurate diagnostic tests and the early initiation of potent drugs to inhibit HIV replication have dramatically increased the ability to prevent progression and control this disease.

ETIOLOGY

HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus, which includes cytopathic viruses causing diverse diseases in several animal species. The HIV-1 genome contains two copies of single-stranded RNA that is 9.2 kb in size. At both ends of the genome there are identical regions, called long terminal repeats, which contain the regulation and expression genes of HIV. The remainder of the genome includes three major sections: the GAG region, which encodes the viral core proteins (p24 [capsid protein: CA], p17 [matrix protein: MA], p9, and p6, which are derived from the precursor p55); the POL region, which encodes the viral enzymes (i.e., reverse transcriptase [p51], protease [p10], and integrase [p32]); and the ENV region, which encodes the viral envelope proteins (gp120 and gp41, which are derived from the precursor gp160). Other regulatory proteins, such as transactivator of transcription (tat: p14), regulator of virion (rev: p19), negative regulatory factor (nef: p27), viral protein r (vpr: p15), viral infectivity factor (vif: p23), viral protein u (vpu in HIV-1: P16), and viral protein x (vpx in HIV-2: P15), are involved in transactivation, viral messenger RNA expression, viral replication, induction of cell cycle arrest, promotion of nuclear import of viral reverse transcription complexes, downregulation of the CD4 receptors and class I major histocompatibility complex (MHC), proviral DNA synthesis, and virus release and infectivity (Fig. 322.2).

The HIV tropism to the target cell is determined by its envelope glycoprotein (Env). Env consists of two components: the surface, heavily glycosylated subunit, gp120 protein and the associated transmembrane subunit glycoprotein gp41. Both gp120 and gp41 are produced from the precursor protein gp160. The glycoprotein gp41 is very immunogenic and is used to detect HIV-1 antibodies in diagnostic assays; gp120 is a complex molecule that includes the highly variable V3 loop. This region is immunodominant for neutralizing antibodies. The heterogeneity of gp120 presents major obstacles in establishing an

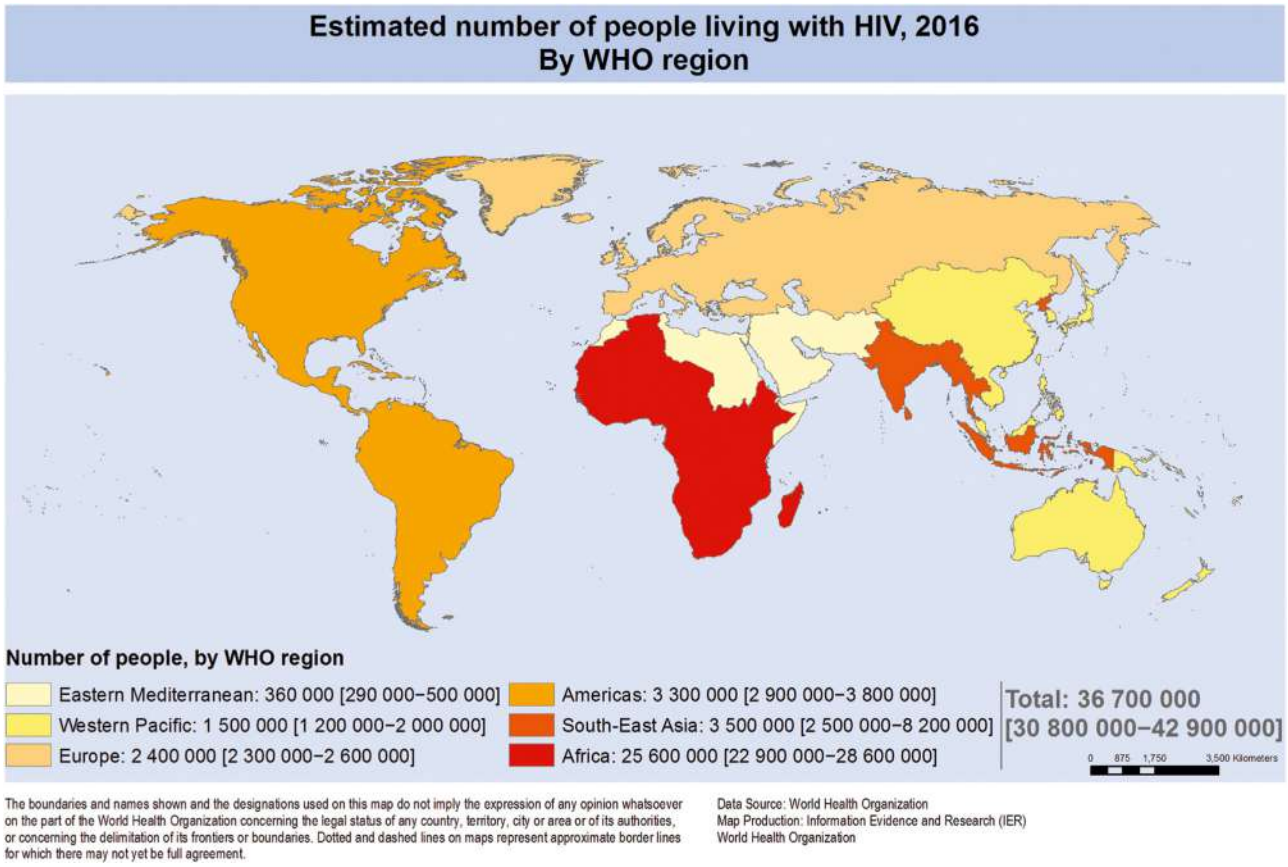

Fig. 322.1 Estimated number of people living with HIV in 2016 by WHO region. Data from WHO 2017 report. *(Courtesy World Health Organization, 2017. Global Health Observatory (GHO) data. http://www.who.int/gho/hiv/epidemic_status/cases_all/en/)*

effective HIV vaccine. The gp120 glycoprotein also carries the binding site for the CD4 molecule, the most common host cell surface receptor of T lymphocytes. This tropism for $CD4^+$ T cells is beneficial to the virus because of the resulting reduction in the effectiveness of the host immune system. Other CD4-bearing cells include macrophages and microglial cells. The observations that $CD4^-$ cells are also infected by HIV and that some $CD4^+$ T cells are resistant to such infections suggests that other cellular attachment sites are needed for the interaction between HIV and human cells. Several chemokines serve as co-receptors for the envelope glycoproteins, permitting membrane fusion and entry into the cell. Most HIV strains have a specific tropism for one of the chemokines, including the fusion-inducing molecule **CXCR-4**, which acts as a co-receptor for HIV attachment to lymphocytes, and **CCR-5**, a β chemokine receptor that facilitates HIV entry into macrophages. Several other chemokine receptors (CCR-3) have also been shown in vitro to serve as virus co-receptors. Other mechanisms of attachment of HIV to cells use nonneutralizing antiviral antibodies and complement receptors. The Fab portion of these antibodies attaches to the virus surface, and the Fc portion binds to cells that express Fc receptors (macrophages, fibroblasts), thus facilitating virus transfer into the cell. Other cell-surface receptors, such as the mannose-binding protein on macrophages or the DC-specific, C-type lectin (DC-SIGN) on dendritic cells, also bind to the HIV-1 envelope glycoprotein and increase the efficiency of viral infectivity. Cell-to-cell transfer of HIV without formation of fully formed particles is a more rapid mechanism of spreading the infection to new cells than is direct infection by the virus.

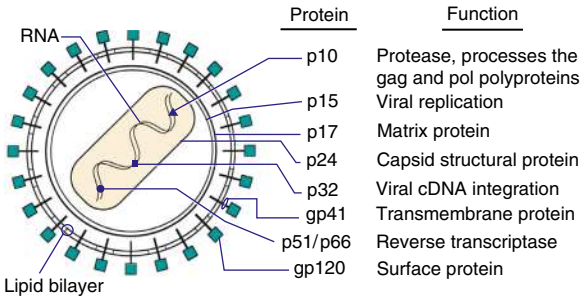

Fig. 322.2 The human immunodeficiency virus and associated proteins and their functions.

After viral attachment, gp120 and the CD4 molecule undergo conformational changes, and gp41 interacts with the fusion receptor on the cell surface (Fig. 322.3). Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. This process involves accessory viral proteins (nef, vif) and binding of cyclophilin A (a host cellular protein) to the capsid protein (p24). A number of HIV drugs that target the viral fusion/cell entry of the virus have been developed. The p24 protein is involved in virus uncoating, recognition by restriction factors, and nuclear importation and integration of the newly created viral DNA. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, which builds the first DNA strand from the viral RNA and then destroys the viral RNA and builds a second DNA strand to produce double-stranded circular DNA (see Fig. 322.3). The HIV-1 reverse transcriptase is error prone and lacks error-correcting mechanisms. Thus many mutations arise, creating a wide genetic variation in HIV-1 isolates even within an individual patient. Many of the drugs used to fight HIV infection were designed to block the reverse transcriptase action. The circular DNA is transported into the cell nucleus, using viral accessory proteins such as vpr, where it is integrated (with the help of the virus integrase) into the host chromosomal DNA and referred to as the *provirus* (see Fig. 322.3). Drugs have been developed that block this integration step. The provirus has the advantage of latency, because it can remain dormant for extended periods, making it extremely difficult to eradicate. The infected $CD4^+$ T cells that survive long enough to revert to resting memory state become the HIV latent reservoir where the virus persists

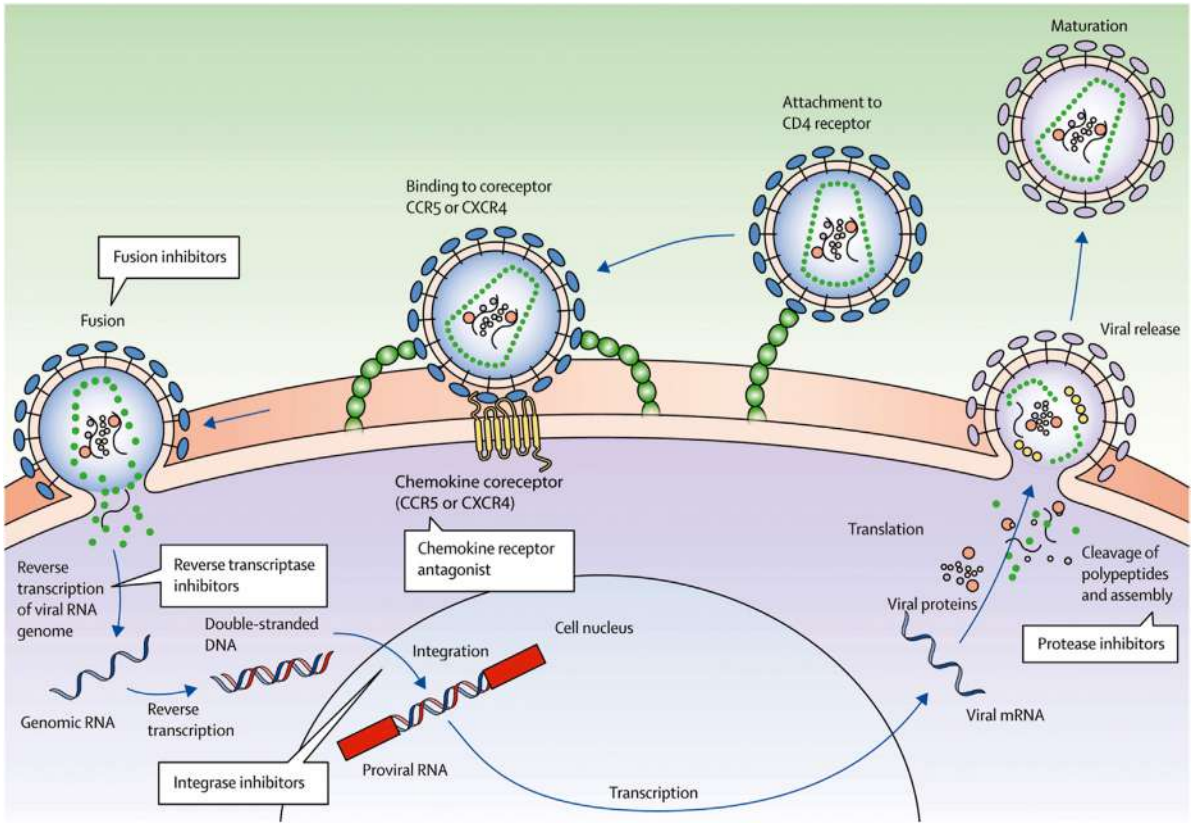

Fig. 322.3 HIV life cycle showing the sites of action and different classes of antiretroviral drugs. *(Adapted from Ralston SH, Penman ID, Strachan MWJ, Hobson R, eds. Davidson's Principles and Practice of Medicine, 23rd ed. London: Elsevier, 2018.)*

indefinitely even in patients who respond favorably to potent ART. The molecular mechanisms of this latency are complex and involve unique biologic properties of the latent provirus (e.g., absence of tat, epigenetic changes inhibiting HIV gene expression) and the nature of the cellular host (e.g., absence of transcription factors such as nuclear factor κB). Integration usually occurs near active genes, which allow a high level of viral production in response to various external factors such as an increase in inflammatory cytokines (by infection with other pathogens) and cellular activation. Depending on the relative expression of the viral regulatory genes (tat, rev, nef), the proviral DNA may encode production of the viral RNA genome, which, in turn, leads to production of viral proteins necessary for viral assembly.

HIV-1 transcription is followed by translation (see Fig. 322.3). A capsid polyprotein is cleaved to produce the virus-specific protease (p10), among other products. This enzyme is critical for HIV-1 assembly because it cleaves the long polyproteins into the proper functional pieces. Several HIV-1 antiprotease drugs have been developed, targeting the increased sensitivity of the viral protease, which differs from the cellular proteases. The regulatory protein vif is active in virus assembly and Gag processing. The RNA genome is then incorporated into the newly formed viral capsid that requires zinc finger domains (p7) and the matrix protein (MA: p17). The matrix protein forms a coat on the inner surface of the viral membrane, which is essential for the budding of the new virus from the host cell's surface. As new virus is formed, it buds through specialized membrane areas, known as lipid rafts, and is released. The virus release is facilitated by the viroporin vpu, which induces rapid degradation of newly synthesized CD4 molecules that impede viral budding. In addition, vpu counteracts host innate immunity (e.g., hampering natural killer T-cell activity).

Full-length sequencing of the HIV-1 genome demonstrated three different groups (M [main], O [outlier], and N [non-M, non-O]), probably occurring from multiple zoonotic infections from primates in different geographic regions. The same technique identified eight groups of HIV-2 isolates. Group M diversified to nine subtypes (or clades A to D, F to H, J, and K). In each region of the world, certain clades predominate, for example, clade A in Central Africa, clade B in the United States and South America, clade C in South Africa, clade E in Thailand, and clade F in Brazil. Although some subtypes were identified within group O, none was found in any of the HIV-2 groups. Clades are mixed in some patients as a result of HIV recombination, and some crossing between groups (i.e., M and O) has been reported.

HIV-2 has a similar life cycle to HIV-1 and is known to cause infection in several monkey species. Subtypes A and B are the major causes of infection in humans, but rarely cause infection in children. HIV-2 differs from HIV-1 in its accessory genes (e.g., it has no *vpu* gene but contains the *vpx* gene, which is not found in HIV-1). It is most prevalent in western Africa, but increasing numbers of cases are reported from Europe and southern Asia. The diagnosis of HIV-2 infection is more difficult because of major differences in the genetic sequences between HIV-1 and HIV-2. Thus several of the standard confirmatory assays (immunoblot), which are HIV-1 specific, may give indeterminate results with HIV-2 infection. If HIV-2 infection is suspected, a combination screening test that detects antibody to HIV-1 and HIV-2 peptides should be used. In addition, the rapid HIV detection tests have been less reliable in patients suspected to be dually infected with HIV-1 and HIV-2, because of lower antibody concentrations against HIV-2. HIV-2 viral loads also have limited availability. Notably, HIV-2 infection demonstrates a longer asymptomatic stage of infection and slower declines of $CD4^+$ T-cell counts and is less efficiently transmitted vertically than HIV-1, likely related to lower levels of viremia with HIV-2.

EPIDEMIOLOGY

In 2022, the World Health Organization (WHO) estimated that 2.6 million children younger than 19 years of age worldwide were living with HIV-1 infection, with 270,000 new infections annually. Nearly 90% of these children 0-9 years of age live in sub-Saharan Africa. From 2010-2022, there has been a 58% reduction in infection in children 0-9 years of age, reflecting steady expansion of services to prevent perinatal transmission of HIV to infants globally. Over the same period there has been a 46% reduction in new cases 10-19 years of age. Notably, there were still 100,000 deaths worldwide of children <19 years of age with HIV in 2020. As of 2022, an estimated 13.9 million children have been orphaned by AIDS (i.e., having at least one parent die from AIDS).

Globally, the vast majority of HIV infections in early childhood are the result of **vertical transmission**. In the United States, approximately 11,700 children, adolescents, or young adults were reported to be living with perinatally acquired HIV infection in 2014. The number of U.S. children with AIDS diagnosed each year increased from 1984–1992 but then declined by more than 95% to <100 cases annually by 2003, largely from the success of prenatal screening and perinatal **combination antiretroviral treatment (cART)** of HIV-infected pregnant individuals and infants. From 2014–2018, there were 507 infants born with perinatally acquired HIV in the United States and Puerto Rico, declining 54% over that interval, with 65 infants being born infected in 2018. As of 2019, the overall rate of perinatally acquired HIV infection in the United States was 0.8 per 100,000 births. Children of racial and ethnic minority groups are overrepresented, particularly non-Hispanic Blacks, who had a rate of 2.9 per 100,000 births in 2019. Race and ethnicity are not risk factors for HIV infection but more likely reflect other social determinants of health that may be predictive of an increased risk for HIV infection, such as lack of educational and economic opportunities as well as decreased access and barriers to healthcare. As of 2017, Florida, Illinois, Texas, Virginia, California, Tennessee, and Maryland are the states with the highest numbers of perinatally acquired cases of HIV in the United States.

Adolescents (13-24 years of age) constitute an important growing population of newly infected individuals; in 2018, 21% of all new HIV infections in the United States occurred in this age-group, with 81% of youth cases occurring in young males who have sex with males (MSM). It is estimated that 50% of HIV-positive youth, the highest rate of any age group, are unaware of their diagnosis. Considering the long latency period between the time of infection and the development of clinical symptoms, reliance on AIDS case definition surveillance data significantly underrepresents the impact of the disease in adolescents. Based on a median incubation period of 8-12 years, it is estimated that 15–20% of all patients with AIDS acquired HIV infection between 13 and 19 years of age.

Risk factors for HIV infection vary by sex in adolescents. Whereas 91–93% of males between the ages of 13 and 24 years with HIV acquire infection through sex with other males, 91–93% of adolescent females with HIV are infected through heterosexual contact. Adolescent racial and ethnic minority populations are overrepresented, especially among females. Another important group are **transgender** individuals. Transgender women in the United States have 49 times the odds of contracting HIV compared to the general population; transgender men have rates that are lower than in transgender women but still significantly higher than the rate in the general population. Transgender individuals unfortunately have many barriers to accessing and receiving appropriate transgender sensitive care and HIV testing and treatment that must be addressed.

Transmission

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from pregnant individual to child via exposure to vaginal secretions during birth or via breast milk. The primary route of infection in the pediatric population (<15 years) is vertical transmission. Rates of vertical transmission of HIV have varied in high- and low-resource countries; the United States and Europe have documented transmission rates in untreated pregnant individuals of 12–30%, whereas transmission rates in Africa and Haiti have been higher (25–52%), likely because of more advanced disease and the presence of co-infections. Perinatal treatment of HIV-infected pregnant persons with antiretroviral drugs has dramatically decreased the transmission rate to <2%.

Vertical transmission of HIV can occur before delivery **(intrauterine)**, during delivery **(intrapartum)**, or after delivery **(postpartum** through **breastfeeding)**. Although intrauterine transmission

has been suggested by identification of HIV by culture or polymerase chain reaction (PCR) in fetal tissue as early as 10 weeks, statistical modeling data suggest that the majority of in utero transmissions likely occur in late gestation, when the vascular integrity of the placenta weakens and microtransfusions across the maternal–fetal circulation occur. It is generally accepted that 20–30% of infected newborns are infected in utero, because this percentage of infants has laboratory evidence of infection (positive viral culture or PCR) within the first week of life. Some studies have found that viral detection soon after birth is also correlated with an early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation.

A higher percentage of HIV-infected children acquire the virus intrapartum, evidenced by the fact that 70–80% of infected infants do not demonstrate detectable virus until after 1 week of age. The mechanism of transmission appears to be mucosal exposure to infected blood and cervicovaginal secretions in the birth canal, and intrauterine contractions during active labor/delivery may also increase the risk of late microtransfusions. Breastfeeding is the least-common route of vertical transmission in resource-rich nations but is responsible for as much as 40% of perinatal infections in resource-limited countries. The risk of an infant acquiring HIV through breastfeeding is 15–20% over 2 years without parental cART or infant prophylaxis. Both free and cell-associated viruses have been detected in breast milk from HIV-infected individuals. The risk for transmission through breastfeeding for individuals not on suppressive cART is approximately 9–16% in individuals with established infection but is 29–53% in those who acquire HIV postnatally, suggesting that the viremia experienced by the breastfeeding individual during primary infection at least triples the risk for transmission. Where replacement feeding is readily available and safe, it is recommended that the parent substitute infant formula for breast milk if they are known to be HIV infected and not on suppressive cART or are at risk for ongoing sexual or parenteral exposure to HIV. However, the WHO recommends that in resource-limited countries where other diseases (diarrhea, pneumonia, malnutrition) substantially contribute to a high infant mortality rate, the benefit of breastfeeding outweighs the risk for HIV transmission, and HIV-infected persons in developing countries should exclusively breastfeed their infants for at least the first 6 months of life, ideally with parent on suppressive cART. Recently, infant feeding recommendations for breastfeeding (or chestfeeding) persons with HIV in resource-rich settings have evolved as well, given that the risk of transmission via breastfeeding from an individual on suppressive cART is very low (<1%) (see "Prevention" for more discussion).

Several risk factors influence the rate of vertical transmission: pregnant parent viral load at delivery, preterm delivery (<34 weeks' gestation), and low antenatal CD4 count. The most important variable is the level of viremia; the odds of transmission may be increased more than twofold for every $\log_{10}$ increase in viral load at delivery. Elective cesarean delivery has been shown to decrease transmission by 87% if used in conjunction with zidovudine therapy in the pregnant individual and infant. However, because these data predated the advent of **cART** (also called **highly active antiretroviral therapy** [**HAART**]), the additional benefit of cesarean section is negligible if the viral load is <1,000 copies/mL. It should be noted that rarely (≤0.1%), transmission may occur with viral loads <50 copies/mL.

Transfusions of infected blood or blood products have historically accounted for 3–6% of all pediatric AIDS cases. The period of highest risk was between 1978 and 1985, before the availability of HIV antibody–screened blood products. Whereas the prevalence of HIV infection in individuals with hemophilia treated before 1985 was as high as 70%, heat treatment of factor VIII concentrate and HIV antibody screening of donors has virtually eliminated HIV transmission in this population. Donor screening has dramatically reduced, but not eliminated, the risk for blood transfusion–associated HIV infection: nucleic acid amplification testing of minipools (pools of 16-24 donations) performed on antibody-nonreactive blood donations (to identify donations made during the window period before seroconversion) reduced the residual risk of transfusion-transmitted HIV-1 to approximately 1 in 2 million blood units. However, in many resource-limited countries, screening of blood is not uniform, and the risk for transmitting HIV infection via transfusion remains in these settings.

Although HIV can be isolated rarely from saliva, it is in very low titers (<1 infectious particle/mL) and saliva has not been implicated as a transmission vehicle. Studies of hundreds of household contacts of HIV-infected individuals have found that the risk for household HIV transmission is essentially nonexistent. Only a few cases have been reported in which urine or feces (possibly devoid of visible blood) have been proposed as a possible vehicle of HIV transmission, though these cases have not been fully verified.

In the pediatric population, sexual transmission is infrequent, but a small number of cases resulting from sexual abuse have been reported. Sexual contact is the major route of transmission in the adolescent population (≥13 years), accounting for the vast majority of cases. Infection via shared needles with IV drug use is seen in this population, but much less frequently.

PATHOGENESIS

HIV infection affects most of the immune system and disrupts its homeostasis (see Fig. 322.3). In most cases, the initial infection is caused by low amounts of a single founder virus. Therefore disease may be prevented by drug prophylaxis or vaccine. When the mucosa serves as the portal of entry for HIV, the first cells to be affected are the dendritic cells. These cells collect and process antigens introduced from the periphery and transport them to the lymphoid tissue. HIV does not infect the dendritic cell but binds to its DC-SIGN surface molecule, allowing the virus to survive until it reaches the lymphatic tissue. In the lymphatic tissue (e.g., lamina propria, lymph nodes), the virus selectively binds to cells expressing CD4 molecules on their surface, primarily helper T lymphocytes ($CD4^+$ T cells) and cells of the monocyte-macrophage lineage. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissue containing villous Hofbauer cells, may also be infected by HIV. Additional factors (co-receptors) are necessary for HIV fusion and entry into cells. These factors include the chemokines **CXCR-4** (fusion) and **CCR-5**. Other chemokines (CCR1, CCR3) may be necessary for the fusion of certain HIV strains. Several host genetic determinants affect the susceptibility to HIV infection, the progression of disease, and the response to treatment. These genetic variants vary in different populations. A deletion in the **CCR-5** gene that is protective against HIV infection (CCR-5Δ32) is relatively common in individuals of European descent but is rare in individuals of African descent. Several other genes that regulate chemokine receptors, ligands, the MHC, and cytokines also influence the outcome of HIV infection. Usually, $CD4^+$ lymphocytes migrate to the lymphatic tissue in response to viral antigens and then become activated and proliferate, making them highly susceptible to HIV infection. This antigen-driven migration and accumulation of CD4 cells within the lymphoid tissue may contribute to the generalized lymphadenopathy characteristic of acute HIV infection in adults and adolescents. HIV preferentially infects the very cells that respond to it (HIV-specific memory CD4 cells), accounting for the progressive loss of these cells and the subsequent loss of control of HIV replication. The continued destruction of memory $CD4^+$ cells in the gastrointestinal tract (in the gut-associated lymphoid tissue or GALT) leads to reduced integrity of the gastrointestinal epithelium followed by leakage of bacterial particles into the blood and increased inflammatory response, which cause further $CD4^+$ cell loss. When HIV replication reaches a threshold (usually within 3-6 weeks from the time of infection), a burst of plasma viremia occurs. This intense viremia causes **acute HIV infection**, formerly known as **acute retroviral syndrome** which can present similar to **influenza or mononucleosis** (fever, rash, pharyngitis, lymphadenopathy, malaise, arthralgia, fatigue, cytopenias, elevated liver enzymes) in 50–70% of infected adolescents and adults; this syndrome is not typically seen in infants. With establishment of a cellular and humoral immune response within 2-4 months, the viral load in the blood declines substantially, and patients enter a phase characterized by a lack of symptoms and a return of CD4 cells to only moderately decreased levels. Typically, adult patients who are not treated eventually progress to achieve a virologic set point (steady state), usually ranging from 10,000-100,000 during this clinical latency.

This is in contrast to untreated infants with vertically acquired HIV who have viral loads that are much higher, resulting in faster CD4 count declines and earlier onset of significant immunodeficiency. HIV rapidly responds to the immune system pressure by developing a genetically complex population (quasi-species) that successfully evades the immune system. In addition, inappropriate use of ART increases the ability of the virus to diverge even further by selecting for mutants with fitness or resistance advantages in the presence of subtherapeutic drug levels. Early HIV-1 replication in children has no apparent clinical manifestations. Whether tested by virus isolation or by PCR for viral nucleic acid sequences, fewer than 40% of HIV-1–infected infants demonstrate evidence of the virus at birth. The viral load increases by 1-4 months, and essentially all perinatally HIV-infected infants have detectable HIV-1 in peripheral blood by 4 months of age, except for those who may acquire infection via ongoing breastfeeding.

In adults, the long period of clinical latency (typically 8-12 years) is not indicative of viral latency. In fact, there is a very high turnover of virus and CD4 lymphocytes (more than a billion cells per day), gradually causing deterioration of the immune system, marked by depletion of CD4 cells. Several mechanisms for the depletion of CD4 cells in adults and children have been proposed, including HIV-mediated single cell killing, formation of multinucleated giant cells of infected and uninfected CD4 cells (syncytia formation), virus-specific immune responses (natural killer cells, antibody-dependent cellular cytotoxicity), superantigen-mediated activation of T cells (rendering them more susceptible to infection with HIV), autoimmunity, and programmed cell death (apoptosis). The viral burden is greater in the lymphoid organs than in the peripheral blood during the asymptomatic period. As the virions and their immune complexes migrate through the lymph nodes, they are trapped in the network of dendritic follicular cells. Because the ability of HIV to replicate in T cells depends on the state of activation of the cells, the immune activation that takes place within the microenvironment of the lymph nodes in HIV disease serves to promote infection of new CD4 cells, as well as subsequent viral replication within these cells. Monocytes and macrophages can be productively infected by HIV yet resist the cytopathic effect of the virus and, with their long lifespan, explain their role as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. In addition, they reside in anatomic viral sanctuaries where current treatment agents are less effective.

The innate immune system responds almost immediately after HIV-1 infection by recognizing the viral nucleic acids, once the virus fuses to the infected cell, by the toll-like receptor 7. This engagement leads to activation of pro-inflammatory cytokines and interferon (IFN-α), which blocks virus replication and spread. The virus uses its Nef protein to downregulate the expression of MHC and non-MHC ligands to reduce the natural killer (NK) cell–mediated anti-HIV activity. It also modulates NK cell differentiation and maturation, dysregulates cytokine production, and increases apoptosis. Although the mechanism by which the innate system triggers the adaptive immune responses is not yet fully understood, cell-mediated and humoral responses occur early in the infection. CD8 T cells play an important role in containing the infection. These cells produce various ligands (macrophage inflammatory proteins 1α and 1β, RANTES), which suppress HIV replication by blocking the binding of the virus to the co-receptors (CCR-5). HIV-specific cytotoxic T lymphocytes (CTLs) develop against both the structural (ENV, POL, GAG) and regulatory (tat) viral proteins. The CTLs appear at the end of the acute infection, as viral replication is controlled by killing HIV-infected cells before new viruses are produced and by secreting potent antiviral factors that compete with the virus for its receptors (CCR-5). Neutralizing antibodies appear later in the infection and seem to help in the continued suppression of viral replication during clinical latency. There are at least two possible mechanisms that control the steady-state viral load level during the chronic clinical latency. One mechanism may be the limited availability of activated CD4 cells, which prevent a further increase in the viral load. The other mechanism is the development of an active immune response, which is influenced by the amount of viral antigen and limits viral replication at a steady state. There is no general consensus about which of these two mechanisms is more important. The CD4 cell limitation mechanism accounts for the effect of ART, whereas the immune response mechanism emphasizes the importance of immune modulation treatment (cytokines, vaccines) to increase the efficiency of immune-mediated control. A group of cytokines that includes tumor necrosis factor-α (TNF-α), TNF-β, interleukin-1 (IL-1), IL-2, IL-3, IL-6, IL-8, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor plays an integral role in upregulating HIV expression from a state of quiescent infection to active viral replication. Other cytokines such as IFN-γ, IFN-β, and IL-13 exert a suppressive effect on HIV replication. Certain cytokines (IL-4, IL-10, IFN-γ, transforming growth factor-β) reduce or enhance viral replication depending on the infected cell type. The interactions among these cytokines influence the concentration of viral particles in the tissues. Plasma concentrations of cytokines need not be elevated for them to exert their effect, because they are produced and act locally in the tissues. The activation of virtually all the cellular components of the immune system (i.e., T and B cells, NK cells, and monocytes) plays a significant role in the pathologic aspects of HIV infection. Further understanding of their interactions during the infection will expand our treatment options. Commonly, HIV isolated during the clinical latency period grows slowly in culture and produces low titers of reverse transcriptase. These isolates from earlier in clinical latency use CCR-5 as their co-receptor. By the late stages of clinical latency, the isolated virus is phenotypically different. It grows rapidly and to high titers in culture and uses CXCR-4 as its co-receptor. The switch from CCR-5 receptor to CXCR-4 receptor increases the capacity of the virus to replicate, to infect a broader range of target cells (CXCR-4 is more widely expressed on resting and activated immune cells), and to kill T cells more rapidly and efficiently. As a result, the clinical latency phase is over and progression toward AIDS is noted. The **progression of disease** is related temporally to the gradual disruption of lymph node architecture and degeneration of the follicular dendritic cell network with loss of its ability to trap HIV particles. The virus is freed to recirculate, producing high levels of viremia and an increased disappearance of CD4 T cells during the later stages of disease.

The clinical course of HIV infection shows substantial heterogeneity. This variation is determined by both viral and host factors. HIV viruses that use co-receptor CXCR-4 in the course of the infection are associated with an accelerated deterioration of the immune system and more rapid progression to AIDS. In addition, several known host genetic determinants (e.g., variants in the human leukocyte antigen region, polymorphisms in the CCR-5 region such as CCR-5Δ32) affect disease course. There are likely additional host and viral factors yet to be identified that contribute to the variable course of HIV infection in individuals, as well. **Three distinct patterns of disease** are described in children. Approximately 15–25% of HIV-infected newborns in high resource settings present with a **rapid progression** course, with onset of AIDS and symptoms during the first few months of life and a median survival time of 6-9 months if untreated. In resource-limited settings, the majority of HIV-infected newborns will have this rapidly progressing disease course. It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, the virus could effectively infect the majority of the body's immunocompetent cells. The normal migration of these cells to the marrow, spleen, and thymus would result in efficient systemic delivery of HIV, unchecked by the immature immune system of the fetus. Thus infection would be established before the normal ontogenic development of the immune system, causing more-severe impairment of immunity. Most children in this group have detectable virus in the plasma (median level: 11,000 copies/mL) in the first 48 hours of life. This early evidence of viral presence suggests that the newborn was infected in utero. The viral load rapidly increases, peaking by 2-3 months of age (median: 750,000 copies/mL) and staying high for at least the first 2 years of life.

Sixty percent to 80% of perinatally infected newborns in high-resource settings present with a **slower progression** of disease, with a median survival time of 6 years representing the second pattern of disease. Many patients in this group have a negative PCR result in the first week of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases, peaking by 2-3 months of age (median: 100,000 copies/mL) and then slowly declines

Table 322.1 HIV Infection Stage* Based on Age-Specific CD4⁺ T-Lymphocyte Count or CD4⁺ T-Lymphocyte Percentage of Total Lymphocytes

	AGE ON DATE OF CD4⁺ T-LYMPHOCYTE TEST					
	<1 Yr		1-5 Yr		≥6 Yr	
STAGE	CELLS/μL	%	CELLS/μL	%	CELLS/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3	<750	<26	<500	<22	<200	<14

*Stage is based primarily on the CD4⁺ T-lymphocyte count. The CD4⁺ T-lymphocyte count takes precedence over the CD4⁺ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63(No RR-3):1–10.

over a period of 24 months. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained only partially by the immaturity of the immune system in newborns and infants.

The third pattern of disease occurs in <5% of perinatally infected children, referred to as **long-term survivors** or **long-term nonprogressors**, who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 years. Mechanisms for the delay in disease progression include effective humoral immunity and/or CTL responses, host genetic factors (e.g., human leukocyte antigen profile), and infection with an attenuated (defective-gene) virus. A subgroup of the long-term survivors called elite survivors or elite suppressors has no detectable virus in the blood and may reflect different or greater mechanisms of protection from disease progression. Note that both groups warrant long-term close follow-up because later in their course they may begin to progress with their disease.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. Absolute CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. A value of 750 CD4 cells/μL in children younger than 1 year of age is indicative of severe CD4 depletion and is comparable to <200 CD4 cells/μL in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease. Although cutaneous anergy is common during HIV infection, it is also frequent in healthy children younger than 1 year of age, and thus its interpretation is difficult in infected infants. The depletion of CD4 cells also decreases the response to soluble antigens such as in vitro mitogens phytohemagglutinin and concanavalin A.

Polyclonal activation of B cells occurs in most children early in the infection, as evidenced by elevation of immunoglobulins IgA, IgM, IgE, and, particularly, IgG **(hypergammaglobulinemia)**, with high levels of anti–HIV-1 antibody. This response may reflect both dysregulation of the T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of the B-lymphocyte humoral response. As a result, the antibody response to routine childhood vaccinations may be abnormal. The B-cell dysregulation precedes the CD4 depletion in many children and may serve as a surrogate marker of HIV infection in symptomatic children in whom specific diagnostic tests (PCR, culture) are not available or are too expensive. Despite the increased levels of immunoglobulins, some children lack specific antibodies or protective antibodies. Hypogammaglobulinemia is very rare (<1%).

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macrophages and microglia play an important role in HIV neuropathogenesis, and data show that astrocytes may also be involved. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain in young infants is affected by at least two mechanisms. The virus itself may directly infect various brain cells or cause indirect damage to the nervous system by the release of cytokines (IL-1α, IL-1β, TNF-α, IL-2) or reactive oxygen damage from HIV-infected lymphocytes or macrophages.

CLINICAL MANIFESTATIONS

The clinical manifestations of HIV infection vary widely among infants, children, and adolescents. In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, respiratory symptoms, or oral thrush, and may be distinguishable only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, pneumonia, wasting, and severe malnutrition predominate in Africa. Clinical manifestations found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration; note that chronic parotid swelling and LIP are associated with a slower progression of disease.

The Centers for Disease Control and Prevention (CDC) Surveillance Case Definition for HIV infection is based on the age-specific CD4⁺ T-lymphocyte count or the CD4⁺ T-lymphocyte percentage of total lymphocytes (Table 322.1), except when a stage 3–defining opportunistic illness (Table 322.2) supersedes the CD4 data. Age adjustment of the absolute CD4 count is necessary because counts that are relatively high in normal infants decline steadily until age 6 years, when they reach adult norms. The CD4 count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is unavailable.

Infections

Approximately 20% of AIDS-defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumoniae* and *Salmonella* as a result of disturbances in humoral immunity. Other pathogens, including *Staphylococcus*, *Enterococcus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*, and other gram-positive and gram-negative organisms may also be seen. The most common serious infections in HIV-infected children are bacteremia, sepsis, and bacterial pneumonia, accounting for more than 50% of infections in these patients. Meningitis, urinary tract infections, deep-seated abscesses, and bone/joint infections occur less frequently. Milder recurrent infections, such as otitis media, sinusitis, and skin and soft tissue infections, are very common and may be chronic with atypical presentations.

Opportunistic infections are generally seen in children with severe depression of the CD4 count. In adults, these infections often represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infection and often have a more fulminant course of disease reflecting the lack of prior immunity. In addition, infants <1 year of age have a higher incidence of developing stage 3–defining opportunistic infections and mortality rates compared with older children and adults even at higher CD4 counts, reflecting that the CD4 count may overpredict the immune competence in young infants. This principle is best illustrated by ***Pneumocystis jirovecii* pneumonia** (formerly *Pneumocystis carinii*), the most common opportunistic infection in the pediatric population (see Chapter 290). The peak incidence of *Pneumocystis* pneumonia occurs at age 3-6

Table 322.2 Stage 3–Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive†
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 mo duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV‡
- Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 mo duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary,† disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) pneumonia
- Pneumonia, recurrent†
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 mo
- Wasting syndrome attributed to HIV‡

*Only among children age <6 yr.
†Only among adults, adolescents, and children age ≥6 yr.
‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Recomm Rep*. 1994;43(No. RR-12); Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(No. RR-17).
From Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(No RR-3):1–10.

months in the setting of undiagnosed perinatally acquired HIV infection, with the highest mortality rate in children younger than 1 year of age regardless of CD4 count. Aggressive approaches to treatment have improved the outcome substantially. Although the overall incidence of opportunistic infections has markedly declined since the era of combination ART, opportunistic infections still occur in patients with severe immunodepletion as the result of unchecked viral replication, which often accompanies poor ART adherence.

The classic clinical presentation of *Pneumocystis* pneumonia includes an acute onset of fever, tachypnea, dyspnea, and marked hypoxemia; in some children, more indolent development of hypoxemia may precede other clinical or x-ray manifestations. In some cases, fever may be absent or low grade, particularly in more indolent cases. Chest x-ray findings most commonly consist of interstitial infiltrates or diffuse alveolar disease, which rapidly progresses. Chest x-ray in some cases can have very subtle findings and can mimic the radiologic appearance of viral bronchiolitis. Nodular lesions, streaky or lobar infiltrates, or pleural effusions may occasionally be seen. The diagnosis is established by demonstration of *P. jiroveci* with appropriate staining of induced sputum or bronchoalveolar fluid lavage; rarely, an open lung biopsy is necessary. Bronchoalveolar lavage and open lung biopsy have significantly improved sensitivity (75–95%) for *Pneumocystis* testing than induced sputum (20–40%), such that if an induced sputum is negative, it does not exclude the diagnosis. PCR testing on respiratory specimens is also available and is more sensitive than microscopy but also has less specificity; it is also not widely available.

The first-line therapy for *Pneumocystis* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg/kg/day of the TMP component divided every 6 hours intravenously) with adjunctive corticosteroids for moderate to severe disease, usually defined as if the Pao_2 is <70 mm Hg while breathing room air. After improvement, therapy with oral TMP-SMX should continue for a total of 21 days while the corticosteroids are weaned. An alternative therapy for *Pneumocystis* pneumonia includes intravenous administration of pentamidine (4 mg/kg/day). Other regimens such as TMP plus dapsone, clindamycin plus primaquine, or atovaquone are used as alternatives in adults but have not been widely used in children to date.

Nontuberculous mycobacteria (NTM), with *Mycobacterium avium-intracellulare* complex (MAC) being most common, may cause disseminated disease in HIV-infected children who are severely immunosuppressed. The incidence of MAC infection in ART–naïve children >6 years with <100 CD4 cells/μL is estimated to be as high as 10%, but effective cART that results in viral suppression makes MAC infections rare. Disseminated MAC infection is characterized by fever, malaise, weight loss, and night sweats; diarrhea, abdominal pain, and, rarely, intestinal perforation or jaundice (a result of biliary tract obstruction by lymphadenopathy) may also be present. Labs may be notable for significant anemia. The diagnosis is made by the isolation of MAC from blood, bone marrow, or tissue; the isolated presence of MAC in the stool does not confirm a diagnosis of disseminated MAC. Treatment can reduce symptoms and prolong life but is at best only capable of suppressing the infection if severe CD4 depletion persists. Therapy should include at least two drugs: clarithromycin or azithromycin and ethambutol. A third drug (rifabutin, rifampin, ciprofloxacin, levofloxacin, or amikacin) may be added to decrease the emergence of drug-resistant isolates. Careful consideration of possible drug interactions with antiretroviral agents is necessary before initiation of disseminated MAC therapy. Drug susceptibilities should be ascertained, and the treatment regimen should be adjusted accordingly in the event of an inadequate clinical response to therapy. Because of the great potential for toxicity with most of these medications, surveillance for adverse effects should be ongoing. Less commonly, NTM infections, including lymphadenitis, osteomyelitis, tenosynovitis, and pulmonary disease, can also be seen.

Oral candidiasis is the most common **fungal infection** seen in HIV-infected children. Oral nystatin suspension (2-5 mL qid) is often effective. Clotrimazole troches or fluconazole (3-6 mg/kg orally qd) are effective alternatives. Oral thrush progresses to involve the esophagus in as many as 20% of children with severe CD4 depletion, presenting with symptoms such as anorexia, dysphagia, vomiting, and fever. Treatment with oral fluconazole for 7-14 days generally results in rapid improvement in symptoms. Fungemia rarely occurs, usually in the setting of indwelling venous catheters, and up to 50% of cases may be caused by non-*albicans* species. Disseminated histoplasmosis, coccidioidomycosis, and cryptococcosis are rare in pediatric patients but may occur in endemic areas.

Parasitic infections such as intestinal cryptosporidiosis and microsporidiosis and rarely isosporiasis or giardiasis are other opportunistic infections that cause significant morbidity. Although these intestinal infections are usually self-limited in healthy hosts, they cause severe chronic diarrhea in HIV-infected children with low CD4 counts, often leading to malnutrition. Nitazoxanide therapy is partially effective at improving cryptosporidia diarrhea, but immune reconstitution with cART is the most important factor for clearance of the infection. Albendazole has been reported to be effective against most microsporidia (excluding *Enterocytozoon bieneusi* and *Vittaforma corneae*), and TMP-SMX appears to be effective for isosporiasis. Systemic fumagillin can be used to treat *Enterocytozoon* and *Vittaforma*.

Viral infections, especially with the herpesvirus group, pose significant problems for HIV-infected children. HSV causes recurrent gingivostomatitis, which may be complicated by local and distant cutaneous dissemination. Primary varicella-zoster virus infection (chickenpox) may be prolonged and complicated by bacterial superinfections or

visceral dissemination, including pneumonitis. Recurrent, atypical, or chronic episodes of herpes zoster are often debilitating and require prolonged therapy with acyclovir; in rare instances, varicella-zoster virus has developed a resistance to acyclovir, requiring the use of foscarnet. Disseminated cytomegalovirus infection occurs in the setting of severe CD4 depletion (<50 CD4 cells/μL for ≥6 years) and may involve single or multiple organs. Retinitis, pneumonitis, esophagitis, gastritis with pyloric obstruction, hepatitis, colitis, and encephalitis have been reported, but these complications are rarely seen if cART is given. Ganciclovir and foscarnet are the drugs of choice and are often given together in children with sight-threatening cytomegalovirus retinitis. Intraocular injections of foscarnet or intraocular ganciclovir implants plus oral valganciclovir have also been efficacious in adults and older children with cytomegalovirus retinitis. Measles may occur despite immunization and may present without the typical rash. It often disseminates to the lung or brain with a high mortality rate in these patients. HIV-infected children with low CD4 counts can also develop extensive cutaneous molluscum contagiosum infection. Respiratory viruses such as respiratory syncytial virus and adenovirus may present with prolonged symptoms and persistent viral shedding. In parallel with the increased prevalence of genital tract human papillomavirus infection, cervical intraepithelial neoplasia and anal intraepithelial neoplasia also occur with increased frequency among HIV-1–infected adult females compared with HIV-seronegative females. The relative risk for cervical intraepithelial neoplasia is 5-10 times higher for HIV-1 seropositive females. Multiple modalities are used to treat human papillomavirus (HPV) infection (see Chapter 313), although none is uniformly effective and the recurrence rate is high among HIV-1–infected persons. Prevention with appropriate vaccinations in patients whose CD4 counts are above threshold is recommended, including mumps-measles-rubella (MMR), varicella vaccine, and HPV vaccine (see "Supportive Care" section).

Appropriate therapy with antiretroviral agents may result in **immune reconstitution inflammatory syndrome (IRIS)**, which is characterized by an increased inflammatory response from the recovered immune system to subclinical opportunistic infections (e.g., *Mycobacterium* infection, herpes simplex virus (HSV) infection, toxoplasmosis, cytomegalovirus (CMV) infection, *Pneumocystis* infection, cryptococcal infection). This condition is more commonly observed in patients with progressive disease and severe $CD4^+$ T-lymphocyte depletion. Patients with IRIS develop fever and worsening of the clinical manifestations of the opportunistic infection or new manifestations (e.g., enlargement of lymph nodes, pulmonary infiltrates), typically within the first few weeks after initiation of ART. Determining whether the symptoms represent IRIS, worsening of a current infection, a new opportunistic infection, or drug toxicity can be challenging. If the syndrome does represent IRIS, adding nonsteroidal antiinflammatory agents or corticosteroids may alleviate the inflammatory reaction, although the use of corticosteroids is usually reserved for severe cases. The inflammation may take weeks or months to subside. In most cases, continuation of cART while treating the opportunistic infection (with or without antiinflammatory agents) is sufficient. If opportunistic infection is suspected before the initiation of ART, appropriate antimicrobial treatment should be started before starting cART, particularly in the case of cryptococcal meningitis.

Central Nervous System

The incidence of CNS involvement in perinatally infected children is as high as 50–90% in resource-limited settings but significantly lower in resource-rich settings, with a median onset at 19 months of age. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. **Encephalopathy** may be the initial manifestation of the disease or may present much later when severe immune suppression occurs. With progression, marked apathy, spasticity, hyperreflexia, and gait disturbance may occur, as well as loss of language and oral, fine, and/or gross motor skills. The encephalopathy may progress intermittently, with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioral problems and learning disabilities. Associated abnormalities identified by neuroimaging techniques include cerebral atrophy in up to 85% of children with neurologic symptoms, increased ventricular size, basal ganglia calcifications, and, less frequently, leukomalacia.

Fortunately, since the advent of cART, the incidence rate of encephalopathy has dramatically declined to as low as 0.08% in 2006. However, as HIV-infected children progress through adolescence and young adulthood, other subtle manifestations of CNS disease are evident, such as cognitive deficits, attention problems, and psychiatric disorders. Living with a chronic, often stigmatizing, disease; parental loss; and the requirement for lifelong pristine medication adherence compounds these issues, making it challenging for these youth as they inherit responsibility for managing their disease as adults.

Focal neurologic signs and seizures are unusual and may imply a comorbid pathologic process such as a CNS tumor, opportunistic infection, or stroke. **CNS lymphoma** may present with new-onset focal neurologic findings, headache, seizures, and mental status changes. Characteristic findings on neuroimaging studies include a hyperdense or isodense mass with variable contrast enhancement or a diffusely infiltrating contrast-enhancing mass. **CNS toxoplasmosis** is exceedingly rare in young infants but may occur in vertically HIV-infected adolescents and is typically associated with serum antitoxoplasma IgG as a marker of infection. Other opportunistic infections of the CNS are rare and include infection with CMV, JC virus **(progressive multifocal leukoencephalopathy)**, HSV, *Cryptococcus neoformans,* and *Coccidioides immitis.* Although the true incidence of cerebrovascular disorders (both hemorrhagic and nonhemorrhagic strokes) is unclear, 6–10% of children from large clinical series have been affected.

Respiratory Tract

Recurrent upper respiratory tract infections such as otitis media and sinusitis are very common. Although the typical pathogens *(S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis)* are most common, unusual pathogens such as *P. aeruginosa*, yeast, and anaerobes may be present in chronic infections and result in complications such as invasive sinusitis and mastoiditis.

LIP is the most common chronic lower respiratory tract abnormality reported to the CDC for HIV-infected children; historically this occurred in approximately 25% of HIV-infected children, although the incidence has declined in the cART era. LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial and bronchiolar epithelium, often leading to progressive alveolar capillary block over months to years. It has a characteristic chronic diffuse reticulonodular pattern on chest radiography rarely accompanied by hilar lymphadenopathy, allowing a presumptive diagnosis to be made radiographically before the onset of symptoms. There is an insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales. Progressive disease presents with symptomatic hypoxemia, which usually resolves with oral corticosteroid therapy, accompanied by digital clubbing. Several studies suggest that LIP is a lymphoproliferative response to a primary Epstein-Barr virus infection in the setting of HIV infection. It is also associated with a slower immunologic decline.

Most symptomatic HIV-infected children experience at least one episode of pneumonia during their disease. *S. pneumoniae* is the most common bacterial pathogen, but *P. aeruginosa* and other gram-negative bacterial pneumonias may occur in end-stage disease and may produce acute respiratory failure and death. Rarely, severe recurrent bacterial pneumonia results in bronchiectasis. *Pneumocystis* pneumonia is the most common opportunistic infection, but other pathogens, including CMV, *Aspergillus*, *Histoplasma*, and *Cryptococcus*, can cause pulmonary disease. Infection with common respiratory viruses, including respiratory syncytial virus, parainfluenza, influenza, and adenovirus, may occur simultaneously and have a protracted course and prolonged period of viral shedding from the respiratory tract. Infection with SARS-CoV-2 may also occur, without clear evidence of increased morbidity relative to children without HIV infection.

Pulmonary and extrapulmonary tuberculosis (TB) has been reported with increasing frequency in HIV-infected children in low-resource countries, although it is considerably more common in HIV-infected adults. Because of drug interactions between rifampin and ritonavir-based ART and poor tolerability of the combination of multiple drugs required, treatment of TB/HIV co-infection is particularly challenging in children.

Cardiovascular System

Cardiac dysfunction, including left ventricular hypertrophy, left ventricular dilation, reduced left ventricular fractional shortening, and/or heart failure occurred in 18–39% of HIV-infected children in the pre-cART era; among those affected, a lower nadir CD4 percentage and a higher viral load were associated with lower cardiac function. However, a more current evaluation of HIV-infected children taking long-term cART found that echocardiographic findings were closer to normal and none had symptomatic heart disease, suggesting that cART has a cardioprotective effect. What is still unclear is whether an increased rate of premature cardiovascular disease that has been seen in adults will be seen in children who have disease- or treatment-related hyperlipidemia, and prospective studies are needed to assess this risk. Because of this risk, regular monitoring of cholesterol and lipids, as well as education regarding a heart-healthy lifestyle and diet, is an important part of pediatric HIV care.

Gastrointestinal and Hepatobiliary Tract

Oral manifestations of HIV disease include erythematous or pseudomembranous candidiasis, periodontal disease (e.g., ulcerative gingivitis or periodontitis), salivary gland disease (i.e., swelling, xerostomia), and, rarely, ulcerations or oral hairy leukoplakia. Gastrointestinal tract involvement is common in HIV-infected children. A variety of pathogens can cause gastrointestinal disease, including bacteria (*Salmonella*, *Campylobacter*, *Shigella*, MAC), protozoa (*Giardia*, *Cryptosporidium*, *Isospora*, microsporidia), viruses (CMV, HSV, rotavirus), and fungi *(Candida)*. MAC and the protozoal infections are most severe and protracted in patients with severe CD4 cell depletion. Infections may be localized or disseminated and affect any part of the gastrointestinal tract from the oropharynx to the rectum. Oral or esophageal ulcerations, either viral in origin or idiopathic, are painful and often interfere with eating. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, has been postulated to be a result of direct HIV infection of the gut. Disaccharide intolerance is common in HIV-infected children with chronic diarrhea.

The most common symptoms of gastrointestinal disease are chronic or recurrent diarrhea with malabsorption, abdominal pain, dysphagia, and failure to thrive. Prompt recognition of weight loss or poor growth velocity in the absence of diarrhea is critical. Linear growth impairment is often correlated with the level of HIV viremia. Supplemental enteral feedings should be instituted, either by mouth or with nighttime nasogastric tube feedings in cases associated with more severe chronic growth problems; placement of a gastrostomy tube for nutritional supplementation may be necessary in severe cases. The wasting syndrome, defined as a loss of >10% of body weight, is not as common as failure to thrive in pediatric patients, but the resulting malnutrition is associated with a grave prognosis. Chronic liver inflammation evidenced by fluctuating serum levels of transaminases with or without cholestasis is relatively common, often without identification of an etiologic agent. Cryptosporidial cholecystitis is associated with abdominal pain, jaundice, and elevated γ-glutamyltransferase. In some patients, chronic hepatitis caused by CMV, hepatitis B, hepatitis C, or MAC may lead to portal hypertension and liver failure. Several of the antiretroviral drugs or other drugs such as didanosine, protease inhibitors (PIs), nevirapine, and dapsone may also cause reversible elevation of transaminases.

Pancreatitis with increased pancreatic enzymes with or without abdominal pain, vomiting, and fever may be the result of drug therapy (e.g., with pentamidine, didanosine, or stavudine) or, rarely, opportunistic infections such as MAC or CMV.

Renal Disease

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. A direct effect of HIV on renal epithelial cells has been suggested as the cause, but immune complexes, hyperviscosity of the blood (secondary to hyperglobulinemia), and nephrotoxic drugs are other possible factors. A wide range of histologic abnormalities has been reported, including focal glomerulosclerosis, mesangial hyperplasia, segmental necrotizing glomerulonephritis, and minimal change disease. Focal glomerulosclerosis generally progresses to renal failure within 6-12 months, but other histologic abnormalities in children may remain stable without significant renal insufficiency for prolonged periods. **Nephrotic syndrome** is the most common manifestation of pediatric renal disease, with edema, hypoalbuminemia, proteinuria, and azotemia with normal blood pressure. Cases resistant to steroid therapy may benefit from cyclosporine therapy. Polyuria, oliguria, and hematuria have also been observed in some patients.

Skin Manifestations

Many cutaneous manifestations seen in HIV-infected children are inflammatory or infectious disorders that are not unique to HIV infection. These disorders tend to be more disseminated and respond less consistently to conventional therapy than in the uninfected child. Seborrheic dermatitis or eczema that is severe and unresponsive to treatment may be an early nonspecific sign of HIV infection. Recurrent or chronic episodes of HSV, herpes zoster, molluscum contagiosum, flat warts, anogenital warts, and candidal infections are common and may be difficult to control.

Allergic drug eruptions are also common, in particular related to nonnucleoside reverse transcriptase inhibitors; they generally respond to withdrawal of the drug but also may resolve spontaneously without drug interruption; rarely, progression to Stevens-Johnson syndrome has been reported. Epidermal hyperkeratosis with dry, scaling skin is frequently observed, and sparse hair or hair loss may be seen in the later stages of the disease.

Hematologic and Malignant Diseases

Anemia occurs in 20–70% of HIV-infected children, more commonly in children with AIDS. The anemia may be a result of chronic infection, poor nutrition, autoimmune factors, virus-associated conditions (hemophagocytic syndrome, parvovirus B19 red cell aplasia), or the adverse effect of drugs (zidovudine).

Leukopenia occurs in almost 30% of untreated HIV-infected children, and neutropenia often occurs. Multiple drugs used for treatment or prophylaxis for opportunistic infections, such as *Pneumocystis* pneumonia (TMP-SMX), MAC, and CMV (ganciclovir), or antiretroviral drugs (zidovudine) may also cause leukopenia and/or neutropenia. In cases in which therapy cannot be changed, treatment with subcutaneous granulocyte colony-stimulating factor may be necessary.

Thrombocytopenia has been reported in 10–20% of patients. The etiology may be immunologic (i.e., circulating immune complexes or antiplatelet antibodies) or, less commonly, from drug toxicity, or idiopathic. cART may also reverse thrombocytopenia in ART-naïve patients. In the event of sustained severe thrombocytopenia (<10,000 platelets/μL), treatment with intravenous immunoglobulin or anti-D immune globulin offers temporary improvement in most patients already taking cART. If ineffective, a course of steroids may be an alternative, but consultation with a hematologist should be sought. Deficiency of clotting factors (factors II, VII, IX) is not rare in children with advanced HIV disease and corrects with vitamin K.

A novel disease of the thymus has been observed in a few HIV-infected children. These patients were found to have characteristic anterior mediastinal multilocular thymic cysts without clinical symptoms. Histologic examination shows focal cystic changes, follicular hyperplasia, and diffuse plasmacytosis and multinucleated giant cells. Treatment with cART may result in resolution, and spontaneous involution occurs in some cases.

Malignant diseases have been reported infrequently in HIV-infected children, representing only 2% of AIDS-defining illnesses. Non-Hodgkin lymphoma (including Burkitt lymphoma), primary CNS lymphoma, and

leiomyosarcoma are the most commonly reported neoplasms among HIV-infected children. Epstein-Barr virus is associated with most lymphomas and with all leiomyosarcomas (see Chapter 301). Kaposi sarcoma, which is caused by human herpesvirus 8, occurs frequently among HIV-infected adults but is exceedingly uncommon among HIV-infected children in resource-rich settings (see Chapter 304).

DIAGNOSIS AND TESTING

All infants born to HIV-infected individuals test antibody-positive at birth because of passive transfer of HIV antibody across the placenta during gestation; therefore antibody should not be used to establish the diagnosis of HIV in an infant. Most uninfected infants without ongoing exposure (i.e., who are not breastfed) lose antibodies against HIV between 6 and 18 months of age and are known as **seroreverters**. Because a small proportion of uninfected infants continue to test HIV antibody-positive for up to 24 months of age, positive IgG antibody tests, including the rapid tests, cannot be used to make a definitive diagnosis of HIV infection in infants younger than 24 months. The presence of IgA or IgM anti-HIV in the infant's circulation can indicate HIV infection, because these immunoglobulin classes do not cross the placenta; however, IgA and IgM anti-HIV assays have been both insensitive and nonspecific and therefore are not valuable for clinical use. In any child older than 24 months of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay and confirmatory HIV PCR establishes the diagnosis of HIV infection. Certain diseases (e.g., syphilis and autoimmune diseases) may cause false-positive or indeterminate results in antibody testing. In such cases, specific viral diagnostic tests must be done.

Several rapid HIV tests are currently available with sensitivity and specificity better than those of the standard enzyme immunoassay. Many of these tests require only a single step that allows test results to be reported within less than 30 minutes. Performing rapid HIV testing on individuals during delivery or immediately after birth is crucial for the care of HIV-exposed newborns whose birth parent's HIV status was unknown during pregnancy. A positive rapid test must be confirmed by a second different rapid test (testing different HIV-associated antibodies) or by HIV RNA PCR (viral load). Given the earlier detection of fourth-generation HIV enzyme-linked immunosorbent assay (ELISA) testing (p24 antigen + HIV-1, HIV-2 IgG and IgM antibodies), Western blots are not appropriate to confirm testing because the fourth-generation assays can be positive before the Western blot becomes positive (i.e., in acute infection). In acute infection, patients may have only a positive p24 antigen with negative antibodies on confirmatory testing; these patients should have HIV RNA PCR performed to confirm acute infection (or establish that the p24 antigen result was a false positive test). In infants who are at risk of exposure to HIV-2 infection (e.g., born to an HIV-infected person from West Africa or who has a partner with HIV from West Africa), a rapid test that can detect both HIV-1 and HIV-2 should be used. However, if the HIV testing is negative or the Western blot test reveals an unusual pattern, further diagnostic tests should be considered. In addition, they should be tested with an HIV-2–specific DNA PCR assay.

Viral diagnostic assays, such as HIV DNA or RNA PCR, are more useful in young infants, allowing a definitive diagnosis in most infected infants by 1-4 months of age. By 4 months of age, HIV PCR testing identifies all infected nonbreastfed infants. Historically, HIV DNA PCR testing was the preferred virologic assay over HIV RNA PCR testing in high-resource settings for young infants because of what was thought to be a modest advantage in detecting intrapartum acquired infection for DNA PCR in the first month of life. An FDA-approved HIV DNA PCR test is no longer commercially available in the United States, but other assays exist; however, the sensitivity and specificity of noncommercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the prior FDA-approved commercial test. HIV RNA PCR is recommended for non-subtype B viruses or group O infections, which are not common in the United States. It should be noted that PCR results can be affected by ART in both the birthing parent and the infant, serving as the rationale for the recommendation for testing 2-6 weeks after completing prophylaxis in high-risk newborns (Fig. 322.4) Almost 40% of infected newborns have positive DNA PCR test results in the first 2 days of life, with >90% testing positive by 2 weeks of age. The commercially available HIV-1 assays are not designed for quantification of HIV-2 RNA and thus should not be used to monitor patients with this infection.

Viral diagnostic testing should be performed within the first 12-24 hours of life for high-risk infants (i.e., those born to individuals without sustained virologic suppression, a late cART start, or a diagnosis with acute or primary HIV during the pregnancy); the tests can identify almost 40% of intrauterine HIV-infected children. Birth testing is optional in low-risk infants. Additional testing should be done at 2-3 weeks of age, 4-8 weeks of age, and 4-6 months of age. For higher-risk infants, additional virologic diagnostic testing should be done at 2 to 6 weeks after cessation of ARV prophylaxis (i.e., at 8-12 weeks of life) (see Fig. 322.4). Breastfed infants should have PCR testing performed per testing schedule based on their risk through 4 months of age; an additional test should be done between the 4- to 8-week test and the 4- to 6-month test if the gap between tests is more than 3 months. Breastfed infants should then be tested every 3 months while breastfeeding continues and then at 4-6 weeks, 3 months, and 6 months after cessation of breastfeeding regardless of age to identify those who may become infected at the end of lactation by the HIV-infected individual (see Fig. 322.4).

A positive virologic assay (i.e., detection of HIV by PCR) suggests HIV infection and should be confirmed by a repeat test on a second specimen as soon as possible because false-positive tests can occur. A confirmed diagnosis of HIV infection can be made with two positive virologic test results obtained from different blood samples. HIV infection can be presumptively excluded in nonbreastfed infants with two or more negative virologic tests (one at age ≥14 days and one at age ≥4 weeks), one negative virologic test (i.e., negative RNA or DNA) at age ≥8 weeks done at least 2 weeks after discontinuation of multidrug

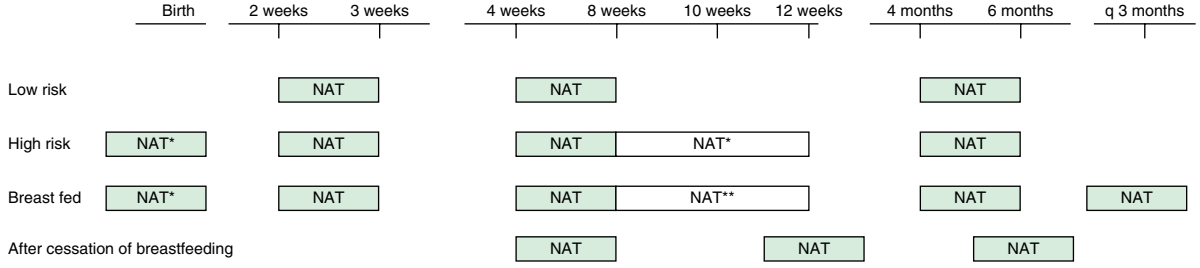

Fig. 322.4 Recommended virologic testing schedules for infants exposed to HIV by perinatal HIV transmission risk and breastfed infants. See Table 322.7 for definitions of low and high risk. *For higher-risk infants, additional virologic diagnostic testing should be done at birth and 2-6 wk after cessation of ARV prophylaxis (i.e., at 8-10 wk of life). **For breastfed infants, an additional virologic test should be performed between the 1- to 2-mo and 4- to 6-mo time points if the gap between tests is >3 mo. NAT, Nucleic acid test. *(Content adapted from Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf)*

empirical therapy or prophylaxis, or one negative HIV antibody test at age ≥6 months. Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at age ≥1 month (done 2-6 weeks after the cessation of multidrug empirical therapy or prophylaxis) and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months. Documentation of seroreversion (loss of antibody) at 12-18 month of age is no longer routinely recommended for nonbreastfed infants meeting definitive exclusion criteria who have had no known or suspected postnatal HIV exposure. Infants <18 months who have postnatal HIV exposure, including new HIV infection of breastfeeding parent, premasticated feedings, sexual abuse, contaminated blood product, or percutaneous exposure, should have HIV PCR-based testing to determine infection status. Children ≥18 months of age with no HIV perinatal exposure history with these postnatal exposures should be tested with HIV antibody/antigen testing. Note that HIV antibody/antigen testing should not be used for diagnosis in the perinatally exposed child until age ≥24 months. Any child or adolescent suspected of HIV infection should be tested with age-appropriate testing with the caveat that if acute infection is suspected, additional HIV PCR testing may be required to establish the diagnosis.

TREATMENT

The currently available therapies do not eradicate the virus and cure the patient; instead they suppress the virus for extended periods and change the course of the disease to a chronic process. It is now recommended that all children be started on cART, regardless of viral load, CD4 count, or clinical status at diagnosis. Treatment should be initiated within 7 days of diagnosis, with counseling and support for adherence. Because cART therapy changes as new drugs become available, decisions regarding therapy should be made in consultation with an expert in pediatric HIV infection. The following principles form the basis for cART:

1. Uninterrupted HIV replication causes destruction of the immune system and progression to AIDS.
2. The magnitude of the viral load predicts the rate of disease progression, and the CD4 cell count reflects the risk of opportunistic infections and HIV infection complications.
3. cART, which includes at least three drugs with at least two different mechanisms of action, should be the initial treatment. Potent combination therapy that suppresses HIV replication to an undetectable level restricts the selection of ART-resistant mutants; drug-resistant strains are the major factor limiting successful viral suppression and delay of disease progression.
4. The goal of sustainable suppression of HIV replication is best achieved by the simultaneous initiation of combinations of antiretroviral drugs to which the patient has not been exposed previously and to which the patient's virus does not have cross resistance.
5. Drug-related interactions and toxicities should be minimized as much as possible.
6. Adherence to the complex drug regimens is crucial for a successful outcome.

Very rarely, treatment may need to be deferred on a case-by-case basis based on clinical or psychosocial factors that may affect adherence with the caregivers and child. In these children, virologic, immunologic, and clinical status should be closely monitored at least every 3-4 months.

Combination Therapy

As of February 2023, 21 individual ART drugs, 22 co-formulated combination tablets, one injectable long-acting combination regimen, as well as two pharmacokinetic boosters were approved by the FDA for use in HIV-infected adults and adolescents. Of the 21 individual drugs, 19 were approved for at least some portion of the pediatric population (0-12 years of age), with many but not all of them available as a liquid, powder, or small tablet/capsule (Table 322.3). ART drugs are categorized by their mechanism of action, such as preventing viral entrance into $CD4^+$ T cells, inhibiting the HIV reverse-transcriptase or protease enzymes, or inhibiting integration of the virus into the human DNA (see Fig. 322.3). Within the reverse-transcriptase inhibitors, a further subdivision can be made: **nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs)** and **nonnucleoside reverse transcriptase inhibitors (NNRTIs)** (see Fig. 322.3). The **NRTIs** have a structure similar to that of the building blocks of DNA (e.g., thymidine, cytosine). When incorporated into DNA, they act as chain terminators and block further incorporation of nucleosides, preventing viral DNA synthesis. Among the NRTIs, thymidine analogs (e.g., zidovudine) are found in higher concentrations in activated or dividing cells, producing >99% of the HIV virion population, and nonthymidine analogs (e.g., lamivudine and emtricitabine) have more activity in resting cells, which account for <1% of the HIV virions but may serve as a reservoir for HIV. Suppression of replication in both populations is important for long-term viral control. **NNRTIs** (i.e., nevirapine, efavirenz, etravirine, rilpivirine, doravirine) act differently than NRTIs. They attach to the reverse transcriptase and cause a conformational change, reducing the activity of the enzyme (see Fig. 322.3). The **PIs** are potent agents that act farther along the viral replicative cycle. They bind to the site where the viral long polypeptides are cut into individual, mature, and functional core proteins that produce the infectious virions before they leave the cell (see Fig. 322.3). The virus entry into the cell is a complex process that involves several cellular receptors and fusion. Several drugs have been developed to prevent this process (see Fig. 322.3). The **fusion inhibitor** enfuvirtide (T-20), which binds to viral gp41, causes conformational changes that prevent fusion of the virus with the $CD4^+$ cell and entry into the cell; with the common use of integrase inhibitors, this medication is now used very rarely. Two entry inhibiting drugs are now approved for use only in treatment-experienced adult patients with multidrug-resistant HIV infection. Fostemsavir is an **attachment inhibitor** prodrug of temsavir that works by blocking CD4 binding to gp120; ibalizumab is a humanized monoclonal antibody (mAb) that acts as a postattachment inhibitor and prevents the HIV connection to co-receptors CCR-5 or CXCR-4. Maraviroc is an example of a selective **CCR-5 co-receptor antagonist** that blocks the attachment of the virus to this chemokine (an essential process in the viral binding and fusion to the $CD4^+$ cells). **Integrase inhibitors (INSTIs)** (i.e., raltegravir, dolutegravir, elvitegravir, bictegravir) block the enzyme that catalyzes the incorporation of the viral genome into the host's DNA (see Fig. 322.3).

By targeting different points in the viral life cycle and stages of cell activation and by delivering drug to all tissue sites, maximal viral suppression is achievable. **Combinations of three drugs consisting of a two-NRTI backbone of (1) a guanosine or thymidine analog NRTI (abacavir or zidovudine) or tenofovir and (2) a nonthymidine analog NRTI (lamivudine or emtricitabine) to suppress replication in both active and resting cells added to (3) a ritonavir-boosted PI (lopinavir, atazanavir, or darunavir), an NNRTI (efavirenz, nevirapine, rilpivirine, or etravirine), or an INSTI (raltegravir, dolutegravir, elvitegravir, or bictegravir) can produce prolonged suppression of the virus.** The use of three drugs from three different classes generally should be avoided but may be necessary in children with highly resistant viruses; these regimens should be chosen only by an HIV specialist with expert pharmacist input. For adult patients with established virologic suppression, some combination therapies pare down to just two drugs. Combination treatment increases the rate of toxicities (see Table 322.3), and complex drug-drug interactions occur among many of the antiretroviral drugs, particularly with the pharmacokinetic boosters ritonavir and cobicistat. Many PIs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes, including nonsedating antihistamines and psychotropic, vasoconstrictor, antimycobacterial, cardiovascular, anesthetic, analgesic, and gastrointestinal drugs (cisapride). Whenever new medications are added to an ART regimen, especially a PI- or cobicistat-containing regimen, a pharmacist and/or HIV specialist should be consulted to address possible drug interactions. The inhibitory effect of ritonavir (a PI) on the cytochrome P450 system is exploited, and small doses of the drug are added to several other PIs (e.g., lopinavir, atazanavir, darunavir) to slow their metabolism by the P450 system and to

Table 322.3 Summary of Antiretroviral Therapies Available in 2023

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Lactic acidosis with hepatic steatosis, particularly for older members of the class	
Abacavir (Ziagen, ABC): tablet: 300 mg; oral solution: 20 mg/mL Epzicom: combination of lamivudine, ABC (300, 600 mg) Triumeq: combination of ABC, lamivudine, dolutegravir (600, 300, 50 mg) Triumeq PD: combination of ABC, lamivudine, dolutegravir (60, 30, 5 mg)	Children: Full term <1 mo: 2 mg/kg/dose bid Full term ≥1 mo to <3 mo: 4 mg/kg/dose bid ≥3 mo to 13 yr: 8 mg/kg/dose bid (max: 300 mg bid) >25 kg: 300 mg bid Children with stable CD4 counts and undetectable viral load >6 mo while taking ABC can transition to 16 mg/kg once daily (max: 600 mg) Children ≥25 kg, adolescents and adults: 300 mg bid or 600 mg qd Epzicom (>25 kg): 1 tablet qd Triumeq: 1 tablet qd Triumeq PD (≥10 kg to <25 kg): Must be dispersed in 20 mL of water, not swallowed whole, cut, or chewed 10 kg to <14 kg: 4 tablets qd 14 kg to <20 kg: 5 tablets qd 20 kg to <25 kg: 6 tablets qd	Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash Less common: hypersensitivity reactions, which can be fatal Rare: lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction	Genetic screening for HLAB*5701 must be done before initiation of ABC-containing treatment. If test is positive, avoid ABC. Once-daily dosing is not preferred with liquid formulations. Can be given with or without food Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flulike symptoms). Oral solution does not require refrigeration. Abacavir should never be used for postexposure prophylaxis (PEP).
Emtricitabine (Emtriva, FTC): capsule: 200 mg; oral solution: 10 mg/mL Truvada: combination of FTC, tenofovir disoproxil fumarate (TDF) (200, 300 mg) Truvada Low Strength: combinations of FTC/TDF (100, 150 mg); (133, 200 mg); (167, 250 mg) Descovy: combinations of FTC, tenofovir alafenamide (TAF) (200, 25 mg); (120, 15 mg) Atripla: combination of FTC, TDF, efavirenz (EFV) (200, 300, 600 mg) Biktarvy: combinations of FTC, TAF, bictegravir (BIC) (200, 25, 50 mg); (120, 15, 30 mg) Complera: combination of FTC, TDF, rilpivirine (RPV) (200, 300, 25 mg) Odefsey: combination of FTC, TAF, RPV (200, 25, 25 mg) Stribild: combination of FTC, TDF, elvitegravir (EVG), cobicistat (COBI) (200, 300, 150, 150 mg) Genvoya: combination of FTC, TAF, EVG, COBI (200, 10, 150, 150 mg) Symtuza: combination of FTC, TAF, darunavir (DRV), COBI (200, 10, 800, 150 mg)	Infants: 0-<3 mo: 3 mg/kg qd Children ≥3 mo to 17 yr, oral solution: 6 mg/kg (max: 240 mg) qd >33 kg, adolescents and adults: 200 mg capsule or 240 mg solution qd ≥14 to <25 kg: Biktarvy (120, 15, 30 mg), Descovy (120, 15 mg): 1 tablet qd ≥25 kg: Biktarvy (200, 25, 50 mg), Genvoya: 1 tablet qd >25 kg to 35 kg: Descovy (200 mg, 25 mg) but cannot pair with boosted PI or COBI: 1 tablet qd ≥35 kg: Complera, Odefsey, Descovy (200, 25 mg): 1 tablet qd ≥35 kg, SMR* 4 or 5: Stribild: 1 tablet qd ≥40 kg Atripla, Symtuza: 1 tablet qd *SMR = Sexual maturity rating	Common: headache, insomnia, diarrhea, nausea, skin discoloration (hyperpigmentation of palms, soles) Less common: lactic acidosis with hepatic steatosis, neutropenia	Patient should be tested for hepatitis B virus (HBV) before starting because HBV exacerbation can occur when emtricitabine is discontinued. Some combination drugs may have food requirements. Oral solution should be refrigerated if temperature above 25°C (77°F) and for long-term storage. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR. Note FTC oral solution is less bioavailable and has a max dose of 240 mg, whereas the max dose for capsules is 200 mg.

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Lamivudine (Epivir, Epivir HBV, 3TC): tablet: 150 (scored), 300 mg (Epivir, generic), 100 mg (Epivir HBV); Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir) Combivir: combination of ZDV, lamivudine (300, 150 mg) Cimduo: combination of 3TC, TDF (300 mg, 300 mg) Delstrigo: combination of 3TC, TDF, doravirine (DOR) (300, 300, 100 mg) Dovato: combination of 3TC, DTG (300, 50 mg) Symfi: combination of 3TC, TDF, EFV (300, 300, 600 mg) Symfi Lo: combination of 3TC, TDF, EFV (300, 300, 400 mg) Temixys: combination of 3TC, TDF (300, 300 mg) Epzicom and Triumeq, Triumeq PD combination (see abacavir)	Neonates (≥32 wk gestational age through 4 wk of age for term infants): 2 mg/kg/dose bid ≥4 wk to <3 mo: 4 mg/kg/dose bid ≥3 mo to <3 yr: 5 mg/kg/dose bid (max: 150 mg) ≥3 yr: 5 mg/kg/dose bid (max: 150 mg) or 10 mg/kg/dose qd (max: 300 mg) For ≥14 kg with scored tablet (150 mg) 14 to <20 kg: 75 mg bid or 150 mg qd (if >3 yr) ≥20 to <25 kg: 75 mg qAM and 150 mg qPM or 225 mg qd (if >3 yr) ≥25 kg: 150 mg bid or 300 mg qd Children should be switched to once-daily dosing of lamivudine (oral solution or tablets) from twice-daily dosing at ≥3 yr if clinically stable for 36 wk with an undetectable viral load and stable CD4 count Adolescents and adults: Combivir, (≥30 kg): 1 tablet bid Cimduo (>35 kg): 1 tablet qd Epzicom (≥25 kg): 1 tablet qd Triumeq (≥25 kg): 1 tablet qd Triumeq PD: see abacavir Symfi (≥40 kg), Symfi Lo (≥35 kg and SMR* 4 or 5): 1 tablet qd on empty stomach Temixys (≥35 kg): 1 tablet qd Dovato: 1 tablet qd in children who meet minimum body weight as part of a three-drug regimen Child and adolescent ≥35 kg and virologically suppressed: Delstrigo: 1 tablet qd* SMR = Sexual maturity rating	Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy	No food restrictions for lamivudine alone but some restrictions with combination drugs Patient should be tested for hepatitis B virus (HBV) before starting because HBV exacerbation can occur when lamivudine is discontinued. M184V mutation for this drug decreases viral fitness and can be advantageous to maintain including inducing AZT hypersusceptibility.
Tenofovir alafenamide (Vemlidy, TAF) Descovy: combinations of TAF, FTC (25, 200 mg); (15, 120 mg) Genvoya: combination of TAF, FTC, EVG, COBI (10, 200, 150, 150 mg) Odefsey: combination of TAF, FTC, RPV (25, 200, 25 mg) Biktarvy: combinations of TAF, FTC, BIC (25, 200, 50 mg); (15, 120, 30 mg) Symtuza: combination of TAF, FTC, DRV, COBI (10, 200, 800, 150 mg)	≥ 2 yr ≥14 kg to <25 kg: Biktarvy (15, 120, 30 mg): 1 tablet qd Descovy (15, 120 mg): 1 tablet qd ≥25 kg: Biktarvy (25, 200, 50 mg), Descovy (25, 200 mg), Genvoya: 1 tablet qd ≥25 kg but <35 kg: Descovy but cannot pair with boosted PI: 1 tablet qd ≥35 kg: Descovy: 1 tablet qd ≥35 kg and ≥12 yr: Odefsey: 1 tablet qd ≥40 kg (adult dose) Symtuza: 1 tablet qd	Common: headache, diarrhea, nausea, asthenia, increased serum lipids	Newer version of TDF that has less renal and bone toxicity. Baseline serum creatinine still recommended before starting. Screen for HBV before TAF is started, because exacerbation of hepatitis may occur when TAF is discontinued. Concentrates in cells more so than TDF

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Tenofovir disoproxil fumarate (Viread, TDF): tablet: 150, 200, 250, 300 mg; powder: 40 mg/1 g powder Truvada: combination of FTC, TDF (200, 300 mg) Truvada Low Strength: combinations of FTC/TDF (100, 150 mg); (133, 200 mg); (167, 250 mg) Cimduo: combination of 3TC, TDF (300 mg, 300 mg) Atripla: combination of FTC, TDF, EFV (200, 300, 600 mg) Complera: combination of FTC, TDF, RPV (200, 300, 25 mg) Delstrigo: combination of 3TC, TDF, DOR (300, 300, 100 mg) Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg) Symfi: combination of 3TC, TDF, EFV (300, 300, 600 mg) Symfi Lo: combination of 3TC, TDF, EFV (300, 300, 400 mg) Temixys: combination of 3TC, TDF (300, 300 mg)	≥2 yr to <12 yr and ≥10 kg: 8 mg/kg/dose qd Weight probands for ≥2 yr and ≥17 kg: 17 to <22 kg: 150 mg qd 22 to <28 kg: 200 mg qd 28 to <35 kg: 250 mg qd ≥35 kg: 300 mg qd (max dose) Atripla (≥40 kg): 1 tablet qd Cimduo (≥35 kg): 1 tablet qd Complera (≥35 kg): 1 tablet qd Symfi (≥40 kg), Symfi Lo ≥ 12 yr (≥35 kg and SMR* 4 or 5): 1 tablet qd on empty stomach Stribild (≥35 kg, SMR* 4 or 5): 1 tablet qd Temixys (≥35 kg): 1 tablet qd Delstrigo: Child and adolescent ≥35 kg and virologically suppressed: 1 tablet qd *SMR = Sexual maturity rating	Common: nausea, vomiting, diarrhea, asthenia, flatulence Less common: lactic acidosis with hepatic steatosis, hepatomegaly, decreased bone density, renal toxicity (glomerular and proximal tubule dysfunction)	Baseline creatinine, urinalysis for protein and glucose should be obtained before starting. Screen for HBV before TDF is given, because exacerbation of hepatitis may occur when TDF is discontinued. Cautious use in SMR 1 and 2 patients with regard to bone mineral density.
Zidovudine (Retrovir, AZT, ZDV): capsule: 100 mg; tablet: 300 mg; syrup: 10 mg/mL; intravenous injection: 10 mg/mL (all available generic) Combivir: combination of ZDV, lamivudine (300, 150 mg)	**Low Risk Prophylaxis:** *≥35 wk gestation at birth:* *Birth to age 4 wk*: 4 mg/kg/dose PO bid (or 3 mg/kg/dose IV q12h) ≥30 to <35 wk gestation at birth: *Birth to age 2 wk*: 2 mg/kg/dose PO bid (or 1.5 mg/kg/dose IV q12h) THEN *Age 2 wk to 6 wk*: 3 mg/kg/dose PO bid (or 2.3 mg/kg/dose IV q12h) <30 wk gestation at birth *Birth to age 4 wk*: 2 mg/kg/dose PO bid (or 1.5 mg/kg/dose IV q12h) THEN *Age 4 wk to 6 wk*: 3 mg/kg/dose bid (or 2.3 mg/kg/dose IV q12h) (See text and Table 322.7 for recommended duration for low risk prophylaxis.)	Common: bone marrow suppression (e.g., anemia, neutropenia), headache, nausea, vomiting, asthenia Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution, myopathy/myositis	No food restrictions Drug interactions: should not be given with d4T or doxorubicin. Only antiretroviral with an IV formulation.
	Presumptive HIV therapy for high-risk exposed infants and treatment: *≥35 wk gestation at birth:* Birth to age 4 wk: 4 mg/kg/dose PO bid THEN Age >4 wk: 12 mg/kg/dose PO bid *≥30 to <35 wk gestation at birth:* Birth to age 2 wk: 2 mg/kg/dose PO bid THEN Age 2 wk to 6 wk: 3 mg/kg/dose PO bid THEN Age >6 wk: 12 mg/kg/dose PO bid <30 wk gestation at birth: Birth to age 4 wk: 2 mg/kg/dose PO bid THEN Age 4 wk to 8 wk: 3 mg/kg/dose PO bid THEN Age >8 wk: 12 mg/kg/dose PO bid *Infants >4 kg, ≥35 wk post conception and ≥4 wk post delivery and children:* 4 kg to <9 kg: 12 mg/kg/dose PO bid 9 kg to <30 kg: 9 mg/kg/dose PO bid >30 kg: 300 mg bid (max dose) Alternative body surface area dosing: 180-240 mg/m^2/dose PO bid Combivir (≥30 kg): 1 tablet bid IV dose is 75% of PO dose, same interval		

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: rash is mild to severe, usually within first 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever)	
Doravirine (Pifeltro, DOR) Tablet: 100 mg Delstrigo: combination of 3TC, TDF, DOR (300, 300, 100 mg)	Child and adolescent ≥35 kg and virologically suppressed: Doravirine: 1 tablet qd Delstrigo: 1 tablet qd	Common: nausea, abdominal pain, diarrhea, vivid dreams, insomnia	Not approved for use in <18 yr Can have multiple drug interactions; metabolized by cytochrome P450 3A. If co-administered with rifabutin, dose DOR bid
Efavirenz (Sustiva, EFV): capsule: 50, 200 mg; tablet: 600 mg Atripla: combination of EFV, FTC, TDF (600, 200, 300 mg) Symfi Lo: combination of 3TC, TDF, EFV (300, 300, 400 mg) Symfi: combination of 3TC, TDF, EFV (300, 300, 600 mg)	Children <3 yr: Consult with expert; not recommended for children <3 yr Children ≥3 yr: 10 to <15 kg: 200 mg qd 15 to <20 kg: 250 mg qd 20 to <25 kg: 300 mg qd 25 to <32.5 kg: 350 mg qd 32.5 to <40 kg: 400 mg qd ≥40 kg: 600 mg qd or 367 mg/m^2 body surface area (max: dose 600 mg) Atripla (≥40 kg): 1 tablet qd on empty stomach Symfi Lo (≤35 kg and SMR* 4 or 5): 1 tablet qd on empty stomach *SMR = Sexual maturity rating For Symfi Lo consider use of therapeutic drug monitoring for pediatric patients ≥40 kg Symfi (≥40 kg): 1 tablet qd	Common: transient skin rashes, CNS symptoms (e.g., vivid dreams, impaired concentration, insomnia, depression, hallucinations, depression, suicidal ideation esp. in adolescents and young adults), gynecomastia Less common: increased liver enzymes; potentially teratogenic, QTc prolongation (be careful with other QT-prolonging medications), false positives on some cannabinoid and benzodiazepine tests	Capsules can be opened for mixing in food. Administer at bedtime on empty stomach to minimize CNS side effects. Taking with food, especially fatty meal, can increase absorption and worsen CNS side effects. Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. For some individuals with certain CYP450 polymorphisms, Symfi Lo is appropriate (lower EFV dose). Increased clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV, and azithromycin should be considered. Avoid using in individuals with a history of past or active psychiatric issues and use with caution in adolescents and young adults owing to possible affective side effects, including increased suicidality.
Etravirine (ETR, Intelence): tablet: 25, 100, 200 mg	Not approved for <2 yr 10 to <20 kg: 100 mg bid 20 to <25 kg: 125 mg bid 25 to <30 kg: 150 mg bid ≥30 kg: 200 mg bid	Common: nausea, rash, diarrhea Less common: hypersensitivity reactions with rash, including Stevens-Johnson syndrome, multiorgan dysfunction including hepatic failure	Always administer with a meal for absorption; taking on empty stomach decreases absorption by 50%. Tablets can be dispersed in water but swallowing is preferred because consumption of dispersed tablets results in lower levels. Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Cobicistat-boosted PIs, nonnucleoside reverse transcriptase inhibitors, bictegravir, and elvitegravir/cobicistat should not be used with ETR. Raltegravir and dolutegravir should only be used with ETR with ritonavir (RTV)-boosted atazanavir, darunavir, or lopinavir.

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Nevirapine (Viramune, NVP): tablet: 200 mg; extended-release (XR) tablet: 100, 400 mg; suspension: 10 mg/mL	**Presumptive HIV therapy for high-risk exposed infants and treatment:** 32 to <34 wk gestation at birth: Birth to age 2 wk: 2 mg/kg/dose bid 2 wk to 4 wk: 4 mg/kg/dose bid 4 wk to 6 wk: 6 mg/kg bid >6 wk with confirmed infection: NVP 200 mg/m^2/dose bid 34 wk to <37 wk gestation at birth: Birth to 1 wk: 4 mg/kg/dose bid 1 wk to 4 wk: 6 mg/kg/dose bid >4 wk and confirmed infection: 200 mg/m^2/dose bid ≥37 wk gestation at birth: Birth to age 4 wk: 6 mg/kg/dose bid Age >4 wk and confirmed infection: 200 mg/m^2/dose bid ≥1 mo to <8 yr: 200 mg/m^2 once daily for 14 days; then same dose bid (max: 200 mg/dose for immediate-release tablets) ≥8 yr: 120-150 mg/m^2 once daily for 14 days; then bid (max: 200 mg/dose for immediate-release tablets) Adolescents and adults: 200 mg once daily for 14 days; then 200 mg bid Or XR 400 mg qd (after 14-day lead in) Extended-release tablets: ≥6 yr by BSA: 0.58 m^2 to 0.83 m^2: 200 mg 0.84 m^2 to 1.16 m^2: 300 mg ≥1.17 m^2: 400 mg Patients already on immediate-release formulation can transition to qd XR dosing without lead-in Note doses are never adjusted down if patient is tolerating. 3-dose series for high-risk infants (less commonly used) ≥32 wk gestation at birth: NOTE: DOSES ARE A FLAT DOSE, NOT PER KG Dosing intervals: Within 48 hr of birth, 48 hr after first dose, 96 hr after second dose Birth weight 1.5-2 kg: 8 mg/dose PO Birth weight >2 kg: 12 mg/dose PO	Common: skin rash (usually in first 6 wk of therapy), headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening hepatic necrosis), hypersensitivity reactions, Stevens Johnson syndrome (1.4–7.1% of pediatric patients in large series) that can have multiorgan involvement	No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations. Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives also may be affected. XR formulation must be swallowed whole. For children ≤2 yr, some experts start with bid dosing without the 14 day lead-in of qd dosing. Lead-in dosing decreases occurrence of rash by allowing induction of cytochrome p450 metabolizing enzymes. If rash develops during initial 14 days of therapy, do not increase dose until rash resolves. If therapy is interrupted for >14 days, restart using lead-in dosing. Nevirapine should never be used for postexposure prophylaxis (PEP).

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Rilpivirine (Edurant, RPV): tablet: 25 mg Complera: combination of RPV, FTC, TDF (25, 200, 300 mg) Odefsey: combination of FTC, TAF, RPV (25, 200, 25 mg) Juluca: combination of RPV, Dolutegravir (DTG) (25, 50 mg) Co-packaged formulation (Cabenuva): combinations injectable of RPV, cabotegravir: (900, 600 mg); (600, 400 mg)	≥12 yr and ≥35 kg: 25 mg PO qd Complera or Odefsey: 1 tablet qd Juluca (>18 yr): 1 tablet qd; only for use in adults with ≥6 mo virologic suppression with no resistance to replace current regimen ≥12 years and ≥35 kg with virologic suppression and no history of treatment failure starting on last day of 28 day oral lead in therapy: Cabenuva (900, 600 mg) IM, then Cabenuva (600, 400 mg) IM monthly Alternate every 2 mo dosing also available	Headache, insomnia, rash, depression, mood changes Less common: hepatotoxicity	Given with food only, 500-kcal meal (not just liquid). Do not use with proton pump inhibitors; antacids have to be spaced from dose by 2 hr before or 4 hr after. H_2 antagonists should be administered 12 hr before or 4 hr after RPV. Should not be used if viral load >100,000 copies/μL or drugs that induce CYP3A. Injectables can give local site reaction, soreness. Administration window is ±7 days for injectable regimens. It is critical that injectable regimens are received on schedule, as prolonged subtherapeutic drug levels will lead to emergence of resistance.
PROTEASE INHIBITORS		Class adverse effects: GI side effects, hyperglycemia, hyperlipidemia (except atazanavir and darunavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can induce metabolism of ethinyl estradiol; use alternative contraception (other than estrogen-containing oral contraceptives). All of these drugs undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions. Treatment note: always administer with boosting agent (RTV or COBI).	
Atazanavir (Reyataz, ATV): powder packet: 50 mg/packet; capsule: 150, 200, 300 mg (*Note:* capsules and packets are *not* interchangeable) Evotaz: combination of ATV, COBI (300, 150 mg)	Infants and children ≥3 mo and ≥5 kg: 5 to <15 kg: ATV 200 mg (4 packets) + RTV 80 mg qd 15 to <25 kg: ATV 250 mg (5 packets) + RTV 80 mg qd *Note:* Capsules are not approved for <6 yr or <15 kg Children ≥6 yr and ≥15 kg capsule dosing: 15 to <35 kg: 200 mg + RTV qd 100 mg ≥35 kg: 300 mg + RTV 100 mg qd OR Evotaz: 1 tablet qd	Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis	Administer ATV with food to increase absorption and decrease GI side effects. Do not open capsules. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2, CYP2C9, and UGT1A1 enzymes. Use with caution with cardiac conduction disease or liver impairment. TDF, antacids, H_2-receptor antagonists, and proton-pump inhibitors decrease ATV concentrations. PPIs should be taken 12 hr before boosted ATV and not coadministered. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Darunavir (Prezista, DRV): tablets: 75, 150, 600, 800 mg; suspension: 100 mg/mL Prezcobix: combination DRV, COBI (800, 150 mg) Symtuza: combination DRV, TAF, FTC, COBI (800, 10, 200, 150 mg)	<3 yr or <10 kg: Do not use 3 yr to <12 yr: 10 to <11 kg: DRV 200 mg + RTV 32 mg bid 11 to <12 kg: DRV 220 mg + RTV 32 mg bid 12 to <13 kg: DRV 240 mg + RTV 40 mg bid 13 to <14 kg: DRV 260 mg + RTV 40 mg bid 14 to <15 kg: DRV 280 mg + RTV 48 mg bid 15 to <30 kg: DRV 375 mg + RTV 48 mg bid 30 to <40 kg: DRV 450 mg + RTV 100 mg bid >12 yr and ≥30 to <40 kg: DRV 450 mg + RTV 100 mg bid ≥40 kg: DRV 600 mg + RTV 100 mg bid ≥12 yr and ≥40 kg and *no* DRV mutations: DRV 800 mg + RTV 100 mg qd OR Prezcobix: 1 tablet qd ≥40 kg *with* DRV mutation(s): DRV 600 mg + RTV 100 mg bid >40 kg with *no* DRV or TDF/TAF resistance: Symtuza: 1 tablet qd	Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations and hepatotoxicity, hyperglycemia, fat maldistribution	DRV should always be given with food for absorption and to decrease GI side effects. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class DRV should not be administered once daily to individuals <12 yr or <40 kg. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.
Lopinavir/Ritonavir (Kaletra, LPV/r): tablet: 100/25 mg, 200/50 mg; solution: 80/20 mg per/mL (contains 42% alcohol, 15% propylene glycol)	<14 days: Not approved 14 days to 18 yr: LPV 300 mg/m^2/dose + RTV 75 mg/m^2/dose bid In treatment naïve children >1 yr a dose of 230 mg/m^2/dose bid can be used. >18 yr: LPV 400 mg + RTV 100 mg bid *Or* 800 mg LPV + 200 mg RTV qd >45 kg: If taken with NVP, EFV, fosamprenavir, or nelfinavir: LPV 600 mg + RTV 150 mg bid	Common: diarrhea, headache, nausea and vomiting, lipid elevation, alteration of taste, hyperlipidemia (hypertriglyceridemia) Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, QT interval prolongation and torsades de pointes. Life threatening cardiotoxicity risk in neonates.	**Do not administer before postmenstrual age of 42 wk and postnatal age of 14 days due to potential severe toxicities.** If patient on concomitant NVP or EFV, dosing must be adjusted and it must be given bid. No food restrictions for tablets but has better GI tolerability when given with or after a meal. Oral solution should be administered with high-fat meal to increase absorption. Pills must be swallowed whole. Poor palatability of oral solution is difficult to mask with flavorings or foods. Once-daily dosing is poorly tolerated in most children, and plasma concentration variability makes qd dosing contraindicated in children and adolescents. Interacts with drugs using CYP3A4, which can cause multiple drug interactions.
Ritonavir (Norvir, RTV): capsule: 100 mg; tablet: 100 mg; solution: 80 mg/mL (contains 43% alcohol)	Only use is to enhance other PIs; dose varies (see information for specific PI)	Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions	Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated (store at 20–25°C). RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids (Cushing syndrome has been reported specifically with coadministration with fluticasone).

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
ENTRY AND FUSION INHIBITORS			
Fostemsavir (Rukobia, FTR): Extended-release tablet 600 mg	Safety and efficacy data not established for <18 yr Adults >18 yr: 1 tablet twice daily	QTc prolongation with higher than recommended doses, increased transaminases in Hep B or Hep C co-infection	Reserved for treatment in experienced patients with significant resistance. Tablet must be swallowed whole. Do not co-administer with strong P450 CYP 3A4 inducers. Potential drug interactions.
Ibalizumab (Trogarzo, IBA) IV: single-dose vial 200 mg/1.33 mL	Safety and efficacy data for <18 yr olds not established Adults >18 yr: Loading dose 2000 mg IV, maintenance dose 800 mg q2 wk	Diarrhea, nausea, rash, dizziness, IRIS, possible development of anti-IBA antibodies	Reserved for treatment in experienced patients with significant resistance. Used in combination with optimized cART regimen.
Maraviroc (Selzentry, MVC): oral solution: 20 mg/mL; tablet: 25, 75, 150, 300 mg	Given with potent CYP3A inhibitors (all PIs): 2 to <10 kg: Not recommended 10 to <20 kg: 50 mg bid 20 to <30 kg: 75-80 mg bid 30 to <40 kg: 100 mg bid ≤40 kg: 150 mg bid Given with noninteracting drugs such as NRTIs, T-20, NVP, RAL, or other drugs not affecting CYP3A: 2 to <4 kg: 30 mg bid 4 to <6 kg: 40 mg bid 6 to <10 kg: 100 mg bid 10 to <14 kg: 150 mg bid 14 to <30 kg: 200 mg bid 30 to <40 kg: 300 mg bid ≥40 kg: 300 mg bid Insufficient data for all children and adolescents for dosing with potent CYP3A inducer, including EFV, ETR Adults: Given with noninteracting medications: 300 mg bid Given with potent CYP3A inhibitors (including all PIs): 150 mg bid Given with potent CYP3A inducers including EFV and ETR 600 mg bid	Common: fever, upper respiratory infection–like symptoms including cough, nausea, vomiting, rash, abdominal pain, musculoskeletal symptoms, dizziness	Testing for CCR-5-tropic virus required; virus must not have mixed tropism (i.e., CCR-5/CXC4) to have efficacy. No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or P-glycoprotein-modulating drugs.
INTEGRASE INHIBITORS (INSTI)		Class side effects: headache, mild GI symptoms, potential significant weight gain for some INSTIs	
Bictegravir (BIC) Only available as Biktarvy: combinations of BIC, TAF, FTC (50, 25, 200 mg); (30, 15, 120 mg)	≥2 y and ≥14 kg to <25 kg: 1 tablet (30, 15, 120 mg) qd ≥25 kg: 1 tablet (50, 25, 200 mg) qd	Diarrhea, nausea, headache,	No food restrictions. Metabolized by UGT1A1 and CYP450 (CYP) 3A. For children unable to swallow tablet whole, tablet can be split and all parts swallowed separately within 10 min. All patients should be screened for HBV before using FTC or TAF. Avoid in severe hepatic impairment.

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Cabotegravir (Vocabria, CAB): Tablet: 30 mg Single-dose vial for IM injection (Apretude): 600 mg (PrEP only) Co-packaged formulation (Cabenuva): combinations injectable of RPV, CAB: (900, 600 mg); (600, 400 mg)	**PrEP (CAB only)** Adolescents and adults ≥35 kg confirmed HIV negative who meet criteria: Optional oral lead-in for 1 mo (dosing below) then on last day oral lead-in, patient receives IM 600 mg CAB monthly for 2 mo then every 2 mo **For treatment of HIV (CAB/RPV):** ≥12 y and ≥35 kg and adults with suppressed viral load and no history of treatment failure: Optional oral lead in with oral RPV and CAB for 1 mo: CAB 30 mg, RPV 25 mg PO qd Monthly administration: Starting on last day of oral lead in IM CAB/RPV (600/900 mg) first month then CAB/RPV (400/600 mg) monthly Every 2 mo administration: Starting on last day of oral lead in IM CAB/RPV (600/900 mg) monthly for 2 mo then CAB/RPV (600/900 mg) every 2 mo.	Injection site reactions, depression, insomnia, headache, rash (can be severe with systemic symptoms), hepatotoxicity, weight gain, CPK elevation, ACTH stimulation test alteration of unclear significance	**Close monitoring and strong engagement in care needed for injectable therapies as missing doses with prolonged subtherapeutic levels can lead to emergence of resistance and for PrEP acquisition of resistant HIV infection.** There is a ±7 day dose administration window for the monthly dose. CAB and RPV are injected separately into separate ventrogluteal sites.
Dolutegravir (Tivicay, DTG): film-coated tablet: 10, 25, 50 mg Dispersible tablets for oral suspension (Tivicay PD): 5 mg Triumeq: combination of ABC, 3TC, DTG (600, 300, 50 mg) Juluca: combination of RPV, DTG (25, 50 mg) Dovato: combination of DTG, 3TC (50, 300 mg) Triumeq PD: combination of ABC, lamivudine, dolutegravir (60, 30, 5 mg)	Neonates: not approved ≥4 wk, ≥3 kg, dispersible tablets: 3 kg to <6 kg: 5 mg qd 6 kg to <10 kg: 15 mg qd 10 kg to <14 kg: 20 mg qd 14 to <20 kg: 25 mg qd ≥20 kg 30 mg qd ≥14 kg film coated tablets: 14 kg to <20 kg: 40 mg qd ≥20 kg: 50 mg qd ≥25 kg: Triumeq: 1 tablet qd Juluca: 1 tablet qd; only for use in patients with ≥6 mo virologic suppression with no resistance to replace current regimen. Can be used in adolescents meeting weight requirements for treatment simplification Dovato: 1 tablet qd; can be used in adolescents meeting weight requirements for treatment simplification Triumeq PD (≥10 kg to <25 kg): Must be dispersed, not swallowed whole, cut or chewed 10 kg to <14 kg: 4 tablets 14 kg to <20 kg: 5 tablets 20 kg to <25 kg: 6 tablets	Insomnia, headache, neuropsychiatric illness Rare: rash, hepatotoxicity, hypersensitivity reactions	**Film-coated tablets and dispersible tablets are not bioequivalent and are not interchangeable.** Film-coated tablets should not be used in <14 kg patients. Juluca and Dovato are not recommended as first-line regimens for children and adolescents but if child meets weight criteria and viral load criteria could be used to reduce pill burden).
Elvitegravir (EVG): only found in 2 co-formulated fixed-dose combination (FDC) tablets Stribild: combination of EVG, FTC, TDF, COBI (150, 200, 300, 150 mg) Genvoya: combination of FTC, TAF, EVG, COBI (200, 10, 150, 150 mg)	≥25 kg: Genvoya 1 tablet qd >35 kg and SMR* 4 or 5: Stribild 1 tablet qd *SMR = Sexual Maturity Rating	Nausea, diarrhea, headache, fatigue	Administer with food. EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Use cautiously with nephrotoxic drugs. Administer 4 hr before or after antacids, multivitamins or supplements that contain iron, calcium, aluminum, or magnesium. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Raltegravir (Isentress, RAL): film-coated tablet: 400 mg; film-coated high dose (HD) tablet: 600 mg; chewable tablet: 25, 100 mg (scored); granules for oral suspension: 100 mg suspended in 10 mL of water for final concentration of 10 mg/mL	**Presumptive therapy for high-risk exposed neonates and treatment:** ≥37 wk gestation at birth and ≥2 kg (oral suspension): *Birth to age 1 wk:* approximately 1.5 mg/kg/dose qd 2 to <3 kg: 4 mg qd 3 to <4 kg: 5 mg qd 4 to <5 kg: 7 mg qd If parent on raltegravir in 2-24 hr before delivery, delay first dose 24-48 hr after birth. Start other ART ASAP. *Age 1-4 wk:* approximately 3 mg/kg/dose bid 2 to <3 kg: 8 mg bid 3 to <4 kg: 10 mg bid 4 to <5 kg: 15 mg bid **Infant and Pediatrics dosing** Oral suspension: Children age ≥4 wk and ≥3 kg to <20 kg: approximately 6 mg/kg/dose bid 3 to <4 kg: 25 mg bid 4 to <6 kg: 30 mg bid 6 to <8 kg: 40 mg bid 8 to <10 kg: 60 mg bid 10 to <14 kg: 80 mg bid 14 to <20 kg: 100 mg bid Chewable tablet: 3 kg to <6 kg: 25 mg bid 6 to <10 kg: 50 mg bid 10 to <14 kg: 75 mg bid 14 to <20 kg: 100 mg bid 20 to <28 kg: 150 mg bid 28 to <40 kg: 200 mg bid ≥40 kg: 300 mg bid Film-coated tablet: ≥25 kg: 400 mg bid HD tablet: ≥40 kg HD tablet: 1200 mg qd for treatment naïve patients or patients virologically suppressed on RAL 400 mg bid	Common: nausea, headache, dizziness, diarrhea, fatigue Less common: itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity, insomnia, fever Rare: rash including Stevens-Johnson, TEN, hypersensitivity reaction	**Oral suspension, film-coated tablet and chewable tablet are not interchangeable; chewable tablets and suspension have better oral bioavailability than film-coated tablet; hence, higher-dose for film-coated tablets.** The chewable tablet can be crushed. Place tablet in small clean cup, add 5 mL (1 tsp) of liquid (water, breast milk, juice) and let stand for 2 min while pill absorbs liquid. Use spoon to crush remaining intact pill. Administer immediately. Add 5 mL of liquid to cup, swirl, and administer that liquid as well to ensure full dose consumed. Film-coated tablets must be swallowed whole. RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin) will reduce RAL levels, whereas inhibitors of this system (e.g., ATV) will increase RAL levels. Do not administer rifampin, ETR, or calcium carbonate with once-daily raltegravir (HD). Aluminum and magnesium containing antacids should not be taken while on RAL. UGT1A1 metabolism is low at birth and increases rapidly over first 4-6 wk of life. No data for preterm infants.

Antiretroviral drugs often have significant drug-drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

The information in this table is not all-inclusive. Updated and additional information on dosages, drug-drug interactions, and toxicities is available and regularly updated on the AIDSinfo website at https://www.nih.gov/research-training/hiv/aids-info-center

Modified from the Guidelines for use of antiretroviral agents in pediatric HIV infection. http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf.

improve their pharmacokinetic profile. This strategy provides more effective drug levels with less toxicity and less-frequent dosing. Cobicistat provides an alternative to ritonavir as a pharmacokinetic booster but does not have antiviral activity against HIV. Although cobicistat is a potent inhibitor of cytochrome P450 3A, it is a weak inhibitor of CYP2D6 and other CYP isoforms (e.g., CYP1A2), making pharmacologic interactions with many drugs more predictable than for ritonavir, which is also active against these isoforms. Studies with cobicistat show a good tolerability profile and less effect on adipocytes (resulting in lesser accumulations of lipid and a milder response to insulin). The better solubility of cobicistat compared with ritonavir has helped the development of more single-tablet combination regimens with cobicistat. Cobicistat is used for boosting both PIs and INSTIs. However, cobicistat is currently approved only for children ≥25 kg; it is not recommended for use in pregnancy because of a paucity of data and concern for pharmacokinetics.

Adherence

Adherence to the medication schedules and dosages is fundamental to cART success. Therefore assessment of the likelihood of adherence to treatment is an important factor in initiating therapy and choice of regimen. Numerous studies show that compliance of <90% results in less-successful suppression of the viral load. In addition, several studies document that almost half of the pediatric patients surveyed were nonadherent to their regimen. Poor adherence to prescribed medication regimens results in subtherapeutic drug concentrations and enhances the development of resistant viruses, leading to limited treatment options. Several barriers to adherence are unique to children with HIV infection. Combination antiretroviral regimens in liquid form are often unpalatable and require extreme dedication on the part of the caregiver and child; a reluctance to disclose the child's disease to others reduces social support; there may be a tendency to skip doses if the caregiver is not around or when the child is in school. Adolescents have other issues

that reduce adherence. Denial of the diagnosis, an unstructured lifestyle, feelings of invincibility, desires for "normalcy," adherence fatigue to lifelong medications, affective disorders, and substance use are just a few of the many factors that may interfere with long-term adherence in this growing population. These and other barriers make involving the family in optimizing adherence essential when possible. Intensive education on the relationship of drug adherence to viral suppression, training on drug administration, frequent follow-up visits, peer support, ongoing support including text messaging and other platforms from medical team and case managers, and commitment of the caregiver and the patient are critical for successful antiviral treatment. Multiple methods such as the viral load response, self-reporting of missed doses during the last 3-7 days, and pharmacy/pill counting should be used to assess adherence. Assessing for emergence of resistant virus on sequencing (genotype) can also be a helpful tool in patients not achieving virologic suppression as expected. For older children and adults, long-acting injectable regimens also now exist and have the potential for enormous benefit for adherence, though currently are only FDA approved for individuals with virologic suppression and no history of treatment failure.

Initiation of Therapy

The decision of when to initiate cART has evolved significantly over the years in both adults and children. When cART was first introduced, medication regimens had significant side effects, leading to decisions to delay therapy until it was thought to be most beneficial, usually after advanced immunologic suppression had developed. The Strategic Timing of Antiretroviral Treatment (START) trial demonstrated a strong benefit in starting therapy earlier in adults, even before CD4 counts fell into an immunosuppressed range; this became more feasible with the development of safer, better-tolerated medications. In adults, it has also been found that receiving suppressive cART eliminates the risk of the sexual transmission of HIV to others. Current adult guidelines recommend the initiation of cART in all adults with HIV. **In line with the adult guidelines, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV now also recommends starting treatment for all children with HIV as soon as possible**. For children <1 year of age, the Children with HIV Early Antiretroviral Therapy (CHER) trial has clearly demonstrated the benefit of early immediate ART. Children younger than 1 year of age are at high risk for disease progression, and immunologic and virologic tests to identify those likely to develop rapidly progressive disease are less predictive than in older children. Therefore all HIV-infected infants younger than 1 year of age should be treated with cART as soon as the diagnosis of HIV infection has been confirmed, regardless of their clinical or immunologic status or viral load. Data suggest that HIV-infected infants who are treated before the age of 3 months control their HIV infection better than infants whose cART started later than 3 months of age. Among older children, mortality rates are lower and growth is more normal in children who are started on immediate cART. Initiation of cART therapy should be deferred in children with active cryptococcal meningitis, tuberculosis infection, or disseminated MAC infection in collaboration with an HIV expert.

The pediatric HIV guidelines are updated twice yearly, and care providers should check for revisions regularly at https://www.nih.gov/research-training/hiv/aids-info-center.

Dosages

Children are usually treated with higher doses (per kilogram weight) than adults because of reduced absorption or increased drug metabolism. Data on ART drug dosages for neonates, especially premature infants, are often limited. Because of the immaturity of the neonatal liver, there often must be an increase in the dosing interval of drugs primarily cleared through hepatic glucuronidation.

For some medications in older children, ART dosages/selections need to factor in sexual maturity rating (SMR) (formerly known as Tanner staging). Fortunately thanks to evolving pediatric pharmacokinetic data, many simpler regimens are now available to children ≥25 kg, including once-daily, single-pill (fixed-dose combination) regimens (see Table 322.3 for comprehensive dosing information for current HIV drugs used in children as of February 2023). Because some ART agents may alter the metabolism of some hormonal contraceptives and decrease their effectiveness, interactions should be considered when choosing contraceptive agents for adolescents. A comprehensive table of interactions of HIV medications with hormonal contraceptives can be found in the perinatal HIV guidelines that are updated twice yearly at https://www.nih.gov/research-training/hiv/aids-info-center. Medroxyprogesterone (DMPA) is a reasonable choice for most cART regimens. Alternative long-acting contraception options, such as use of an intrauterine device, should also be considered.

Changing Antiretroviral Therapy

A change in therapy should be strongly considered when the current regimen is judged ineffective as evidenced by an increase in viral load, deterioration of the CD4 cell count, or clinical progression. Development of toxicity or intolerance to drugs is another reason to consider a change in therapy. When a change is considered, the patient and family should be reassessed for adherence concerns. Because adherence is a major issue in this population, resistance testing (while the patient is taking antiretroviral medications) is important in identifying adherence issues (e.g., detectable virus sensitive to current drug regimen is consistent with a lack of adherence) or the development of resistance (e.g., evidence of resistance mutations to current drug regimen). In both situations, other contributing factors, such as poor absorption, an incorrect dose, or drug-drug interactions, should be carefully reviewed. While considering possible new drug choices, the potential for cross-resistance should be addressed. In starting a new regimen in a patient with virologic failure, the new regimen should include at least two, but preferably three, fully active antiretroviral medications, with assessment of the anticipated activity based on the treatment history and resistance testing (genotype or less commonly phenotype). The goal is to achieve and maintain virologic suppression. If virologic suppression cannot be achieved, the goals of therapy should focus on preserving immunologic function and preventing further disease progression, as well as preventing the emergence of additional drug resistance (which could limit future treatment options).

Monitoring Antiretroviral Therapy

To ensure proper monitoring, the CD4 cell count, viral load, complete blood count, chemistries, urinalysis, and serum lipids should be obtained before an initiation of or change in cART to have a baseline for comparisons during treatment. At entry into care, genotypic resistance testing should be done as well. Children must be seen within 1-4 weeks after initiation of new cART to reinforce and counsel regarding adherence and to screen for potential side effects. Ideally, telephone or text follow-up by the medical team for adherence and side effects also occurs in the interval between cART start and the follow-up visit. Virologic and immunologic surveillance (using the quantitative HIV RNA PCR and CD4 lymphocyte count), as well as clinical assessment, should be performed regularly while on cART. The initial virologic response (i.e., at least a fivefold [0.7 $\log_{10}$] reduction in viral load) should be achieved within 4-8 weeks of initiating ART. The maximum response to therapy usually occurs within 12-16 weeks but may be later (24 weeks) in very young infants. Thus HIV RNA levels should be measured at 4-8 weeks and 12-24 weeks after therapy initiation. Once an optimal response has occurred, the viral load should then be measured at least every 3-6 months. If the response is unsatisfactory, another viral load should be determined as soon as possible to verify the results before a change in therapy is considered. Virologic failure is defined as a repeated plasma viral load ≥200 copies/mL after 6 months of therapy. The CD4 cells respond more slowly to successful treatment, particularly in patients with long-standing infection and CD4 suppression. CD4 counts should be monitored every 3-4 months and potentially can be done less frequently in adolescents and adults with documented virologic suppression. Potential toxicity should be monitored closely for the first ~8 weeks (including complete blood count, serum chemistries), and if no clinical or laboratory toxicity is documented, follow-up visits are recommended every 1-2 months for children <18 months to allow increases in medication doses in

association with weight gain) and every 3-4 months for older children and adolescents. Monitoring for potential toxicity should be tailored to the patient's medication regimen. Toxicities include but are not limited to hematologic complications (e.g., zidovudine); hypersensitivity rash (e.g., efavirenz); lipodystrophy (e.g., redistribution of body fat seen with NRTIs and PIs, which can take several years to emerge); hyperlipidemia (elevation of cholesterol and triglyceride concentrations); hyperglycemia and insulin resistance (e.g., PIs); mitochondrial toxicity leading to severe lactic acidosis; electrocardiogram abnormalities (e.g., atazanavir, lopinavir); abnormal bone mineral metabolism (e.g., tenofovir disoproxil fumarate but not tenofovir alafenamide); and hepatic toxicity, including severe hepatomegaly with steatosis. After a patient is on a stable regimen, labs outside of CD4 count and viral load can be done every 6-12 months. An important part of every visit is ongoing adherence counseling given the need for excellent adherence to cART to avoid the emergence of resistance. *Detailed current guidelines for monitoring HIV-infected children during therapy can be found at* https://www.nih.gov/research-training/hiv/aids-info-center.

Resistance to Antiretroviral Therapy

Young children usually are at greater risk than adults for developing resistance because they have higher viral loads and fewer ART options than adults (reflecting the fact that only some agents are available in a liquid formulation and have pharmacokinetic dosing data for children). The high mutation rate of HIV (mainly as a result of the absence of error-correcting mechanisms in the reverse-transcriptase enzyme) results in the generation of viruses with multiple mutations every day in the absence of cART. Failure to reduce the viral load to <50 copies/mL on cART because of nonadherence resulting in subtherapeutic drug levels increases the risk for developing resistance by selecting those mutant viruses with a competitive advantage (i.e., drug resistance mutations). Even effectively treated patients do not completely suppress all viral replication, and persistence of HIV transcription and evolution of envelope sequences continues in the latent cellular reservoirs, though data show that this evolution does not appear to affect the emergence of resistance to cART in virologically suppressed patients. Accumulation of resistance mutations, particularly in nonadherent patients, progressively diminishes the potency of the cART and challenges the physician to find new regimens. For some drugs (e.g., nevirapine, lamivudine), a single mutation is associated with resistance, whereas for other drugs (e.g., zidovudine, lopinavir, darunavir, etravirine, etc.), several mutations are needed before significant resistance develops. Testing for drug resistance, especially when devising a new regimen, is standard of care. Two types of tests are available; genotype is most commonly used, but the phenotype may be helpful in select patients with complex viral resistance as a result of exposure to multiple cART regimens.

The **phenotype** measures the virus susceptibility in various concentrations of the drug. This allows calculation of the drug concentration that will inhibit the viral replication by 50% (IC_{50}). The ratio of the IC_{50} and a reference virus IC_{50} is reported as the fold resistance change. Note that this test is usually combined with a genotype when used but is largely reserved for patients with extremely complex mutations. The **genotype** predicts the virus susceptibility from mutations identified in the HIV genome isolated from the patient and is the more commonly used test. Several online sites (e.g., http://hivdb.stanford.edu) can assist in interpreting the test's results. Several studies show that the treatment success is higher in patients whose cART was guided by genotype or phenotype testing.

Neither method may detect drug resistance if the amount of the resistant virus is <10% of the circulating population or if it is present only in the latent reservoir. Note that if a patient has not been taking cART for several weeks, the absence of selective drug pressure will make the dominant population of circulating viruses revert to the wild type, and resistance mutations can be missed.

It is recommended to test for drug resistance before initiating therapy and before changing treatment because of virologic failure. When changing therapy, the resistance test results should be considered in the context of previous resistance tests results, if done, and drugs used in previous regimens.

Supportive Care

Even before cART drugs were available, a significant impact on the quality of life and survival of HIV-infected children was achieved when supportive care was given. A multidisciplinary team approach is desirable for successful management. After the initiation or change of cART, more frequent visits or contacts with the patient/caregivers for support and education will help in their acceptance and adjustment to the new regimen and will contribute to a better adherence. Close attention should be paid to the nutritional status, which is often delicately balanced and may require aggressive supplementation, especially in children with advanced disease. Painful oropharyngeal lesions and dental caries may interfere with eating, and thus routine dental evaluations and careful attention to oral hygiene are important. Paradoxically, an increasing number of adolescents with perinatally acquired or behavioral risk–acquired disease are obese. Some teens experience cART-related central lipoaccumulation (usually related to older agents), but others have poor dietary habits and inactivity as the cause of their obesity, just as others do who are obese in epidemic numbers in the United States. Their development should be evaluated regularly, with the provision of necessary physical, occupational, and/or speech therapy. Recognition of pain in the young child may be difficult, and effective nonpharmacologic and pharmacologic protocols for pain management should be instituted when indicated.

All HIV-exposed and HIV-infected children should receive standard pediatric immunizations (Table 322.4). Live oral polio vaccine should not be given because of poor immunologic response in HIV-infected children and concern for live vaccination in potentially immunocompromised children. The risk and benefits of rotavirus vaccination should be considered in HIV-exposed infants. Because <1% of these infants in resource-rich settings will develop HIV infection, the vaccine should be given in infants with negative testing at 2-3 weeks and 6-8 weeks of age. In other situations, the considerable attenuation of the vaccine's strains should be considered, and unless the infant has clinical symptoms of AIDS or a CD4 count <750, vaccination is likely appropriate; consultation with an HIV expert is recommended. Other live bacterial vaccines (e.g., bacillus Calmette-Guérin) should be avoided because of the high incidence of bacillus Calmette-Guérin–related disease in HIV-infected infants. Varicella and measles-mumps-rubella vaccines are recommended for children who are not severely immunosuppressed (i.e., CD4 cell percentage ≥15%, absolute CD4 count >500 cells/μL for ages 1-5 years), but these vaccines should not be given to severely immunocompromised children (i.e., CD4 cell percentage <15%, absolute CD4 count <500 cells/μL for age 1-5 year). Of note, prior immunizations do not always provide protection, as evidenced by outbreaks of measles and pertussis in immunized HIV-infected children. The durability of vaccine-induced titers is often short, especially if vaccines are administered when the child's CD4 cell count is low, and reimmunization when the CD4 count has increased may be indicated. It is recommended that children with HIV receive quadrivalent meningococcal conjugate vaccine at a younger age than the routine schedule. Adolescent vaccines are also important, including the Tdap booster and HPV vaccine. The current recommended annotated vaccine schedule for HIV-infected children is found here (updated annually): https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.

Prophylactic regimens are integral for the care of HIV-infected children. All infants 4-6 weeks to 1 year of age who are proved to be HIV-infected should receive prophylaxis to prevent *P. jiroveci* pneumonia regardless of the CD4 count or percentage (Tables 322.5 and 322.6). Infants exposed to HIV-infected individuals should receive the same prophylaxis until they are proved to be noninfected; however, prophylaxis does not have to be initiated if there is strong presumptive evidence of noninfection (i.e., nonbreastfed infant with two negative HIV PCR tests at >14 days and 4 weeks of age, respectively). When the HIV-infected child is >1 year of age, prophylaxis should be given according to the CD4 lymphocyte count (see Table 322.5). The best prophylactic regimen is 150 mg/m^2/day of TMP and 750 mg/

Table 322.4 Routine Childhood Immunization Schedule for HIV-Infected Children

VACCINE	BIRTH	1 MO	2 MO	4 MO	6 MO	12-15 MO	2 YR	4-6 YR	11-12 YR
Hepatitis B	HepB		HepB			HepB			
Measles, mumps, and rubella* Varicella vaccines*						MMR* Varicella* If CD4 >500		MMR* Varicella* If CD4 >200	
Influenza†					Annual				
COVID-19‡					Regular schedule‡				
Pneumococcal conjugate vaccine§			PCV	PCV	PCV	PCV			
Pneumococcal polysaccharide vaccine							PPSV23‖		
Haemophilus influenzae B vaccine			Hib	Hib	Hib	Hib			
Diphtheria, tetanus and pertussis			DTaP	DTaP	DTaP	DTaP		DTaP	Tdap
Inactivated polio vaccine			IPV	IPV		IPV		IPV	
Hepatitis A vaccine						HepA	HepA		
Meningococcal conjugate vaccine							MCV4¶ (2-shot series)		
HPV vaccine									HPV** (3-shot series)
Rotavirus vaccine			RV†† (2- to 3-shot series)						
Dengue‡‡									Dengue‡‡ (3-shot series) If CD4 >200

Note some combination vaccines may allow for fewer doses to be administered (such as for combination vaccines containing DTaP and Hib; followed recommended schedule of product)
*MMR vaccine and varicella vaccine should only be administered to children age 1-5 yr with absolute CD4 count >500 sustained for 6 mo and children >5 yr with CD4 count >200 sustained for 6 mo (or CD4% >15% if absolute count unavailable). MMRV is contraindicated in HIV-infected children. For immune-reconstituted children can consider giving second MMR and varicella vaccines 1-3 mo after first dose as long as criteria are met.
†Inactivated influenza vaccine should be used in ages ≥6 mo.
‡COVID-19 vaccination is recommended for HIV-infected children and should be given per the pediatric recommendations, including boosters starting at 6 mo of age.
§PCV15 or PCV20 can be used.
‖PPSV23 is given and boosted at 5 years; If PCV20 is given, PPSV23 optional. PPSV23 must be given 8 weeks after PCV given.
¶MCV4 (quadrivalent conjugate vaccine) should be administered starting 24 mo with 2-dose series 8 wk apart. Must be given at least 4 wk after completion of PCV13 series. Booster recommended at 5 years. Meningococcal B conjugate vaccine also should be considered.
**HPV vaccine should be given in a 3-shot series at 0, 1-2 mo, 6 mo (minimum intervals 4 wk from dose 1 to 2, 12 wk from dose 2 to 3 with minimum of 5 mo between doses 1 and 3). HIV patients require 3 shots regardless of age series is started.
††Rotavirus vaccine has not been well studied in infants with HIV infection. It should be given to low-risk exposed infants. For infected infants, use caution particularly in those with significant immunosuppression. If given, series must be started before 15 wk of age and completed by 8 mo of age.
‡‡Dengue vaccination is recommended for children 9-16 yr living in endemic areas of dengue who have laboratory confirmed dengue at 0, 6 mo, 12 mo. It should not be given if CD4 <200. It is not recommended for children traveling to dengue-endemic areas.
Current vaccine schedule with recommendations for immunocompromised populations can be found here (updated annually): https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

m^2/day of SMX (maximum: 320/1,600 mg) given as 1-2 daily doses 3 days (consecutively or every other day) per week or daily if preferred for ease of adherence. For severe adverse reactions to TMP-SMX, alternative therapies include dapsone, atovaquone, and aerosolized pentamidine.

Prophylaxis against MAC should be offered to HIV-infected children with advanced immunosuppression (i.e., CD4 lymphocyte count <750 cells/μL in children <1 year of age, <500 cells/μL in children 1-2 year of age, <75 cells/μL in children 2-5 years of age, and <50 cells/μL in children >6 years of age) (see Table 322.6). The drugs of choice are azithromycin (20 mg/kg [maximum: 1,200 mg] once a week orally *or* 5 mg/kg [maximum: 250 mg] once daily orally) *or* clarithromycin (7.5 mg/kg twice daily orally). In rare situations, rifabutin 300 mg daily can be an alternative for children >6 years of age, though efficacy data in children is very limited.

Based on data for adults, primary prophylaxis against most opportunistic infections may be discontinued if patients have experienced sustained (>6 months' duration) immune reconstitution with cART, even if they had previous opportunistic infections such as *Pneumocystis* pneumonia or disseminated MAC. HIV-infected children are at higher risk for TB and thus should have tuberculin skin testing (5 tuberculin units purified protein derivation [PPD]) or IFN-γ release assay (IGRA) testing for TB annually; an induration of ≥5 mm should be considered positive for the PPD. IGRA is preferred in children with history of BCG

Table 322.5 Recommendations for *Pneumocystis jiroveci* Pneumonia Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

AGE/HIV INFECTION STATUS	PJP PROPHYLAXIS	CD4 MONITORING
Birth to 4-6 wk, HIV-exposed	No prophylaxis	None
HIV infection reasonably excluded*	No prophylaxis	None
<1 yr, HIV-infected or HIV-indeterminate	Prophylaxis regardless of CD4 count or percentage	According to local practice for initiation or follow-up of cART
1-5 yr, HIV-infected	Prophylaxis if CD4 <500 cells/μL or <15%†	According to local practice for initiation or follow-up of cART
>6 yr, HIV-infected	Prophylaxis if CD4 <200 cells/μL or <15%†,‡	According to local practice for initiation or follow-up of cART

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.
*See text.
†More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.
‡Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PJP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PJP should receive PJP prophylaxis until their CD4 count is ≥200 cells/mm^3 for patients age ≥6 yr, CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients age 1 to <6 yr for >3 consecutive mo after receiving cART for ≥6 mo.
cART, Combined antiretroviral therapy; PJP, *Pneumocystis jiroveci* pneumonia.

Table 322.6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*

		PREVENTIVE REGIMEN	
PATHOGEN	INDICATION	FIRST CHOICE	ALTERNATIVE
STRONGLY RECOMMENDED AS STANDARD OF CARE			
Pneumocystis pneumonia†	HIV-infected or HIV-indeterminate infants age 1-12 mo; HIV-infected children age 1-5 yr with CD4 count of <500 cells/μL or CD4 percentage of <15%; HIV-infected children age 6-12 yr with CD4 count of <200 cells/μL or CD4 percentage of <15%; >13 yr with CD4 count <200 or <15%	**TMP-SMX**, 150/750 mg/m^2 body surface area per day or 5-10 mg/kg/day (TMP)/25-50 mg/kg/day (SMX) (max: 320/1,600 mg) orally qd or bid 3 times weekly on consecutive days *Or* qd or bid orally 3 times weekly on alternate days	**Dapsone:** age ≥ 1 mo: 2 mg/kg (max: 100 mg) orally qd; or 4 mg/kg (max: 200 mg) orally once a week **Atovaquone:** age 1-3 mo and >24 mo-12 yr: 30 mg/kg orally qd with food Age 4-24 mo: 45 mg/kg orally qd with food; ≥13 yr 1,500 mg orally qd with food **Aerosolized pentamidine:** age ≥5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer
Malaria	Living or traveling to area in which malaria is endemic	Same for HIV-infected and HIV-uninfected children. Refer to http://www.cdc.gov/malaria/ for the most recent recommendations. **Mefloquine**, 5 mg/kg orally 1 time weekly (max: 250 mg) **Atovaquone/proguanil** (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets >40 kg: 1 adult tablet (250 mg/100 mg)	**Doxycycline**, 2.2 mg/kg body weight (maximum 100 mg) orally qd for children >8 yr **Chloroquine**, 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive)

Continued

Table 322.6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*—cont'd

PATHOGEN	PREVENTIVE REGIMEN		
	INDICATION	FIRST CHOICE	ALTERNATIVE
Mycobacterium tuberculosis			
Isoniazid-sensitive	TST reaction ≥5 mm Or Prior positive TST result without treatment Or Positive interferon-γ release assay (IGRA) result Or Close contact with any person who has contagious TB. TB disease must be excluded before start of prophylaxis	Age ≥12 yr: 12 doses of weekly isoniazid (15 mg/kg rounded up to the nearest 50 or 100 mg; max 900 mg) and rifapentine: 10–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: max 900 mg 12 weekly doses of isoniazid (25 mg/kg for children age 2–12 yr) and rifapentine: 10–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: max 900 mg *Or* 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo; DOT highly recommended	**Rifampin**, 15-20 mg/kg body weight (max: 600 mg) orally daily for 4 mo Isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 10–20 mg/kg (max 300 mg/day) for 3 mo Isoniazid 10-15 mg/kg body weight (max 300 mg) daily for 6-9 mo
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	**Rifampin**, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4 mo	Consult TB expert
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient	
Mycobacterium avium complex‡	For children age ≥6 yr with CD4 count of <50 cells/μL; age 2 to <6 yr with CD4 count of <75 cells/μL; age 1 to <2 yr with CD4 count of <500 cells/μL; age <1 yr with CD4 count of <750 cells/μL	**Clarithromycin,** 7.5 mg/kg (max: 500 mg) orally bid *Or* **Azithromycin,** 20 mg/kg (max: 1,200 mg) orally once a week	**Azithromycin,** 5 mg/kg body weight (max: 250 mg) orally qd *Or* Children age ≥5 yr **Rifabutin**, 300 mg orally qd
Varicella-zoster virus§	Exposure to varicella or shingles with no history of varicella Or Zoster or seronegative status for VZV Or Lack of evidence for age-appropriate vaccination	Varicella-zoster immunoglobulin (VariZIG), 125 IU/10 kg (max: 625 IU) IM, administered ideally within 96 hr after exposure; potential benefit up to 10 days after exposure	If VariZIG is not available and <96 hr from exposure, **acyclovir** 20 mg/kg (max: 800 mg) 4 times a day for 7 days starting 7-10 days postexposure *Or* IVIG, 400 mg/kg, administered once
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see Table 322.4)	
USUALLY RECOMMENDED			
Toxoplasma gondii¶	Seropositive IgG to *Toxoplasma* and severe immunosuppression: age <6 yr with CD4 percentage <15%; age ≥6 yr with CD4 count <100 cells/μL	TMP-SMX, 150/750 mg/m^2 orally qd or divided bid	**Dapsone**, age ≥1 mo: 2 mg/kg or 15 mg/m^2 (max: 25 mg) orally qd Plus **Pyrimethamine**, 1 mg/kg (max: 25 mg) orally qd Plus **Leucovorin**, 5 mg orally every 3 days *Or* Atovaquone per PJP dosing
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400 mg/dL)	IVIG 400 mg/kg body weight every 2-4 wk	

Table 322.6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*—cont'd

		PREVENTIVE REGIMEN	
PATHOGEN	**INDICATION**	**FIRST CHOICE**	**ALTERNATIVE**
Cytomegalovirus	CMV antibody positivity and severe immunosuppression (CD4 count <50 cells/μL for >6 yr; CD4 percentage <5% for ≤6 yr)	**Valganciclovir**, 900 mg orally qd with food for older children who can receive adult dosing For children age 4 mo to 16 yr, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 × BSA × CrCl (up to maximum CrCl of 150 mL/min/1.73 m^2) orally qd with food (maximum dose 900 mg/day)	N/A

*Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval.
†Daily trimethoprim-sulfamethoxazole (TMP-SMX) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with a lower incidence of PCP but higher hematologic toxicity and mortality rates. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMX. TMP-SMX, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine), protect against toxoplasmosis; however, data have not been prospectively collected.
‡Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.
§Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.
¶Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and likely by atovaquone.
CMV, Cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole; TST, tuberculin skin test; VZV, varicella-zoster virus.
From Panel on Opportunistic Infections in Children with and Exposed to HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection. Table 1: Primary Prophylaxis. Accessed 11/5/23.

vaccination. If the child is living in close contact with a person with TB, the child should be tested more frequently. Of note, the sensitivity of PPD and IGRA are reduced in severely immunocompromised patients. The Guidelines for Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children (https://www.nih.gov/research-training/hiv/aids-info-center) should be consulted for these and other opportunistic infections that may occur in these populations. To reduce the incidence of opportunistic infections, parents should be counseled about (1) the importance of good handwashing; (2) avoiding raw or undercooked food *(Salmonella)*; (3) avoiding drinking or swimming in lake or river water or being in contact with young farm animals *(Cryptosporidium)*; and (4) the risk of playing with or having certain pets (*Toxoplasma* and *Bartonella* from cats, *Salmonella* from reptiles).

PROGNOSIS

The improved understanding of the pathogenesis of HIV infection in children and the availability of more effective antiretroviral drugs has changed the prognosis considerably for children with HIV infection. The earlier cART is started, the better the prognosis. In settings with ready access to early diagnosis and ART, progression of the disease to AIDS has significantly diminished. Since the advent of cART in the mid-1990s, mortality rates in perinatally infected children have declined more than 90% and most children in high-income settings survive to adolescence and adulthood. Even with only partial reduction of the viral load, children may have significant immunologic and clinical benefits. In general, the best prognostic indicators are the sustained suppression of the plasma viral load and the restoration of a normal $CD4^+$ lymphocyte count. If determinations of the viral load and CD4 lymphocytes are available, the results can be used to evaluate prognosis. It is unusual to see rapid progression in an infant with a viral load <100,000 copies/mL. In contrast, a high viral load (>100,000 copies/mL) over time is associated with a greater risk for disease progression and death. CD4 count is also another prognostic indicator with mortality rate significantly higher in profoundly immunosuppressed individuals. To define the prognosis more accurately, the use of changes in both markers (CD4 lymphocyte percentage and plasma viral load) is recommended.

Even in resource-limited settings where cART and molecular diagnostic tests are less available, the use of cART has had a substantial benefit on the survival of HIV-infected children and has reduced the likelihood of mortality by >75%. Children with opportunistic infections (e.g., *Pneumocystis* pneumonia, MAC), encephalopathy and regressing developmental milestones, or wasting syndrome, which are all AIDS-defining conditions, have the worst prognosis, with 75% dying before 3 years of age. A higher risk of death was documented in children who did not receive TMP-SMX preventive therapy. Persistent fever and/or oral thrush, serious bacterial infections (meningitis, pneumonia, sepsis), hepatitis, persistent anemia (<8 g/dL), and/or thrombocytopenia (<100,000/μL) also suggest a poor outcome, with >30% of such children dying before 3 years of age. In contrast, lymphadenopathy, splenomegaly, hepatomegaly, lymphoid interstitial pneumonitis, and parotitis are associated with a slower progression of disease and a better prognosis. With sustained virologic suppression and maintained immunologic function, life expectancy is quite good. Unfortunately, access to cART for children in resource-limited settings lags greatly behind access for adults even today. For adults and adolescents acquiring HIV, effective cART can restore life expectancy to near normal.

PREVENTION

Parental Treatment and Infant Prophylaxis

Use of ART for interruption of perinatal transmission has been one of the greatest achievements of HIV research. cART is documented to decrease the rate of perinatal HIV-1 transmission to <2%, and to <1% if the person with HIV has a viral RNA level <1,000 copies/mL at delivery. **Therefore it is recommended that all pregnant individuals be tested for HIV, and if they are positive, be treated with a cART regimen, irrespective of the viral load or CD4 count during pregnancy. All infants born to HIV-infected individuals should receive zidovudine prophylaxis; duration is determined by risk status, with 2-4 weeks for low-risk infants and 6 weeks for high-risk infants** (Table 322.7). Additional antiretroviral drugs should be added to zidovudine if the risk of acquiring HIV by the newborn is high. High-risk scenarios include infants born to individuals who received neither antepartum nor intrapartum antiretroviral drugs or only intrapartum antiretroviral drugs, who do not achieve a suppressed viral load near delivery despite cART (defined as at least two consecutive tests with HIV RNA <50 copies/mL obtained at least 4 weeks apart), who have acute or primary HIV infection during the pregnancy, who have unknown HIV status who test positive at delivery or postpartum, or infants who have a positive

Table 322.7 Intrapartum and Neonatal Management for HIV Exposed Infants by Risk Category

RISK OF PERINATAL HIV TRANSMISSION	DEFINITION	INTRAPARTUM AND NEONATAL ART MANAGEMENT
Low risk (3 defined groups)	Infants ≥37 weeks gestation who are born to a person with HIV who meets **ALL** of the following criteria: • Is currently receiving and has received at least 10 consecutive weeks of ART during pregnancy • Has achieved and maintained or maintained viral suppression† for the remainder of the pregnancy • Has a viral load <50 copies/mL at or after 36 wk • Did not have acute HIV infection during pregnancy • Has reported good ART adherence, and adherence concerns have not been identified	No IV AZT* required in labor Vaginal delivery Prophylaxis with zidovudine × 2 wk
	Infants born to a person with HIV who do not meet the criteria above but who have a HIV RNA <50 copies/mL at or after 36 wk gestation	No IV AZT* required in labor Vaginal delivery ZDV for 4-6 wk
	Premature infants (<37 wk gestation) who are not at high risk of perinatal acquisition of HIV	No IV AZT* required in labor Vaginal delivery ZDV for 4-6 wk
High risk	Infants who are born to a person with HIV who meet **ANY** of the following criteria: • Did not receive cART antepartum or received only intrapartum therapy • Did not achieve viral suppression* within 4 wk before delivery • Had acute or primary HIV infection during the pregnancy or breastfeeding (in the case of the latter, breastfeeding should be immediately discontinued [see text])	Parent should get IV AZT in labor if viral load >1000 or unknown C-section if viral load >1000 or unknown Presumptive HIV therapy regimen × 6 wk with either • Zidovudine, lamivudine, and nevirapine* • Zidovudine, lamivudine and raltegravir* for up to 6 wk Alternate regimen: • Zidovudine × 6 wk + 3-dose nevirapine protocol In all cases, duration of zidovudine should be for 6 wk if other 2 medications are discontinued before that time point.
Presumed newborn HIV exposure	Infants born to a person with HIV who: • Have unconfirmed HIV status with at least one positive HIV test in labor or during delivery/postpartum period • Have a newborn with positive HIV antibody test at delivery	Same as for high risk If supplemental testing confirms person giving birth does not have HIV, infant ARV drugs should be discontinued immediately.

*Due to resistance of HIV-2 to NNRTIs, raltegravir regimen should be considered for high-risk infants born to individuals with HIV-2.
†See Table 322.3 for dosing.
Adapted from Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV transmission in the United States. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

HIV antibody test on screening after delivery. In these scenarios, three regimen options can be considered: (1) a presumptive HIV therapy regimen of zidovudine, lamivudine, and nevirapine at treatment doses; (2) a presumptive HIV therapy regimen of zidovudine, lamivudine, and raltegravir at treatment doses; or (3) zidovudine plus the addition of three doses of nevirapine (at birth, 48 hours, and 144 hours of life) (see Table 322.7). Note that treatment doses of raltegravir for neonates are different than for older children, with an escalating dose over the 6 weeks of therapy because of evolving liver metabolism in neonates. For infants at high risk, options 1 and 2 are now preferred, though option 3 has excellent data supporting it for select patient scenarios. Enthusiasm and support for treatment regimens (particularly option 1) have been driven by a case of an apparent functional cure in an infant in 2013 who went 2 years without cART with virologic suppression before rebound of the infection occurred (the Mississippi baby), as well as a large cohort of high-risk, exposed infants in Canada. For neonates, experience is greatest with zidovudine, which can cause transient anemia or neutropenia in exposed infants. There is also a strong pool of data supporting the safety of lamivudine in neonates, including neonates born as early as 32 weeks' gestational age (GA). For the remaining drugs for treatment of infants at high risk, data are most robust for nevirapine, with dosing recommendations down to 32 weeks' GA. Data for raltegravir are more limited, supporting use only in newborns 37 weeks' GA and up. *In infants at high risk, consultation with an experienced HIV specialist is highly recommended. The National Perinatal HIV Hotline (1-888-448-8765) provides 24/7 support from experienced HIV specialists to help in managing high-risk infants. Guidelines and current recommended doses for prophylaxis in newborns are updated at least yearly and can be accessed at* https://www.nih.gov/research-training/hiv/aids-info-center. A complete blood count, differential leukocyte count, and platelet count should be performed at 4-8 weeks of age to monitor zidovudine toxicity. If the child is found to be HIV infected, baseline laboratory assessment (e.g., CD4 count, HIV RNA, complete blood count, chemistries, lipids, and genotype) should be obtained and cART should be started as soon as possible. Cesarean section as a prevention strategy was examined in a multinational meta-analysis, which showed that the combination of elective C-section and parental zidovudine treatment reduced transmission by 87%. However, these data were obtained before the advent of cART, and the additional benefit of elective C-section to the cART-treated individual whose viral load is <1,000 copies/mL is negligible. Thus elective C-section at 38 weeks of gestation should be considered only for pregnant individuals whose viral load is >1,000 copies/mL in late gestation, to further reduce the risk of vertical transmission.

Because perinatal transmission can be reduced dramatically by treating pregnant individuals, prenatal testing and identification of HIV-1 infection as early as possible is extremely important. The benefit of therapy both for the individual's health and to prevent transmission

to the infant cannot be overemphasized. The recommended universal prenatal HIV counseling and testing for all pregnant individuals has reduced the number of new infections dramatically in many areas of the United States and Europe. For those not tested during pregnancy, the use of rapid HIV antibody testing during labor or shortly after the infant's birth is a way to provide perinatal prophylaxis to an additional group of at-risk infants. Perinatal recommendations also now endorse the testing of pregnant individuals' partners to identify partners with HIV who may transmit HIV infection to them, leading to acute HIV infection, which carries an extremely high risk of vertical transmission both intrapartum and postpartum if the individual is breastfeeding and seroconverts.

Feeding of the HIV-Exposed Infant: Breastfeeding Recommendations and Prophylaxis

It is universally recommended that all pregnant individuals receive a cART regimen appropriate for their own health, which should be continued for the remainder of their lives. This approach improves parental survival, lowers the transmission risk to sexual partners, promotes simplified universal treatment regimens, and reduces transmission during breastfeeding and future pregnancies.

Breastfeeding has been recommended for infants born to individuals with HIV in resource-limited settings by the WHO and other authorities for nearly 2 decades. This recommendation was based on strong evidence that early weaning is not safe in resource-limited settings because of the high risk of death from malnutrition and diarrhea in formula-fed infants without a consistent source of clean water and formula. Furthermore, exclusive breastfeeding (no additional solids or fluids other than water) resulted in less transmission than mixed feeding. Guidelines evolved to recommend that HIV-infected persons living in resource-limited settings should breastfeed their infants until at least 12 months of age, with exclusive breastfeeding for the first 6 months, and cART should continue to be provided to the breastfeeding parent. **Data from multiple large studies of this practice in low- and middle-income countries have shown suppressive parental cART is extremely effective in preventing transmission of HIV via breastfeeding to <1%. Additionally, there have been a series of smaller case series in resource-rich settings with individuals on suppressive cART breastfeeding with no transmission documented. However, it is important to stress that the rate of transmission even for fully suppressed HIV-infected breastfeeding individuals is not zero.** Because of this data, in January 2023, the guidelines in the U.S. for recommended infant feeding have significantly changed for feeding of the HIV-exposed infant. These recommendations were made for several reasons:

- Recognition of the very low risk of transmission from virologically suppressed individuals.
- Recognition of the benefits of breastfeeding to both the infant (improved immune status, lower risk of developing asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome, gastrointestinal infections, and necrotizing enterocolitis) and breastfeeding parent (decreased risk of hypertension; type 2 diabetes; breast, endometrial, and ovarian cancers; bonding with infant; decreased monetary costs of feeding).
- Recognition that pregnant individuals living with HIV in the United States are disproportionately Black, a group that has significantly higher prevalence of many of these negative health outcomes as well and that prohibiting breastfeeding in this group denies them potential benefit.
- Recognition of important cultural pressures that may affect the desire to breastfeed and fear that by not breastfeeding, HIV status may be inadvertently disclosed to family and friends.
- Recognition that some individuals living with HIV in the past who were prohibited from breastfeeding did so surreptitiously without support that could have decreased risk to infant.

It is now recommended that expectant individuals with HIV should receive evidence-based, patient-centered counseling regarding infant feeding starting early, ideally before conception or in early pregnancy. The provider should engage in open-minded shared decision making in discussing the decision to breastfeed or formula feed the infant throughout the pregnancy. Key points of counseling should include:

- Achieving and maintaining viral suppression through ART during pregnancy and postpartum decreases breastfeeding transmission risk to less than 1%, but not zero.
- Replacement feeding with properly prepared formula or pasteurized donor human milk from a milk bank eliminates the risk of postnatal HIV transmission to the infant. This is the recommended feeding choice for individuals living with HIV who do not have suppressed viral load through the third trimester and at delivery given the significantly increased risk of HIV transmission to the infant.
- Individuals with HIV who are on cART with a sustained undetectable viral load and who choose to breastfeed will be supported in this decision.
- Individuals with HIV who choose to formula feed should also be supported in their decision, and potential barriers should be addressed.

It is important to stress that engaging Child Protective Services or similar agencies is not an appropriate response to infant feeding choices of an individual living with HIV. This puts an important therapeutic relationship at risk for both the individual and the infant, can result in harm to families, and can further exacerbate the stigma and discrimination that individuals living with HIV face.

The risk of HIV transmission via breastmilk for individuals on suppressive cART (<50) is <1%. There are ways to make risk of transmission as low as possible in this scenario, including providing excellent parental support such as addressing resource needs, mental health, and helping promote cART adherence. The postpartum period is a time of high risk for developing nonadherence to cART because of the stress of child-raising, lack of sleep, potential postpartum depression (PPD) and other factors. Individuals living with HIV who give birth have significantly higher rates of PPD that is associated with significant rise in cART nonadherence, so early screening and treatment of PPD is critical. Support of a lactation specialist is also important to help establish and maintain good milk supply so that mixed feeding can be minimized and to promote good breast health and avoidance of milk stasis, bleeding nipples, and mastitis. In the pre cART era, mixed feeding (i.e., introduction of breast milk plus other liquid or solid foods, including formula) was associated with increased risk of transmission of HIV, particularly in the first 2 months of life; no data are available in this area (including just formula supplementation) in the context of cART and virologic suppression. Because of this historical data, the goal is exclusive breastfeeding for 6 months to minimize risk.

It is recommended that individuals with HIV who are breastfeeding/chestfeeding have HIV RNA testing every 1-2 months to monitor virologic suppression closely. For the breastfed infant, the initial testing schedule is dictated by risk of infant at birth. Additionally, the breastfed infant should receive testing at 1-2 months and 4-6 months to avoid an interval of >3 months between tests, and every 3 months after the 4- to 6-month test for as long as breastfeeding continues. It is recommended to avoid rapid weaning, with a goal of weaning over 2-4 weeks because of pre-cART data associating rapid weaning with increased risk of HIV transmission to the infant. Infants should be tested 4-6 weeks, 3 months, and 6 months after weaning is complete (see Fig. 322.4).

Several studies demonstrate the efficacy of ART prophylaxis of the breastfed infant in preventing transmission of HIV during breastfeeding in the era before cART being recommended for all pregnant individuals and in some studies in which pregnant individuals received cART but did not have viral load routinely monitored. Successful regimens have included daily single-dose nevirapine (NVP), lamivudine (3TC), lopinavir/ritonavir (LPV/r), and a combined NVP + ADV regimen. For infants at low risk, it is not clear whether additional prophylaxis during breastfeeding after the initial prophylaxis of 2-6 weeks adds additional benefit; that said, some experts choose to provide prophylaxis for infants at low risk. In the scenario in which an individual with HIV who is not virologically suppressed elects to breastfeed after counseling despite recommendations not to do so because of increased risk, it is recommended that the infant receive 6 weeks of three-drug presumptive HIV therapy (high risk), and then daily NVP throughout

Table 322.8 Infant Antiretroviral Prophylaxis for Newborns of Individuals Who Breastfeed

NEWBORNS AT LOW RISK OF HIV ACQUISITION DURING BREASTFEEDING*	
RECOMMENDED REGIMEN	**DURATION**
ZDV	2 wk
EXTENDED POSTNATAL PROPHYLAXIS FOR NEWBORNS AT HIGH RISK OF HIV TRANSMISSION DURING BREASTFEEDING*	
RECOMMENDED REGIMEN	**DURATION**
ZDV	4-6 wk*
NVP†	SIMPLIFIED AGE-BASED DOSING FOR NEWBORNS ≥32 WK GESTATION RECEIVING EXTENDED NVP PROPHYLAXIS DURING BREASTFEEDING‡
AGE	**VOLUME NVP MG/ML ORAL SYRUP DAILY**
6 wk to 6 mo	2 mL
6 mo to 9 mo	3 mL
9 mo to 1-4 wk post weaning	4 mL

*This extended neonatal prophylaxis regimen is optional for low-risk infants, though recommended by some experts. For high-risk breastfed infants (parent not virologically suppressed), 6 wk of ZDV (plus additional agents as recommended in Table 322.7) followed by extended neonatal NVP prophylaxis is recommended.

†For breastfeeding parents with viral resistance to NVP, alternative regimens for infant prophylaxis after completion of the 4-6 wk of presumptive HIV therapy include daily 3TC or LPV/r; see Table 322.3 Antiretroviral Drug Dosing Recommendations for Newborns for dosing information.

‡Extended NVP prophylaxis during breastfeeding recommendations are adapted from the Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. If prescribed, these simplified doses should start following confirmation of a negative infant NAT test and completion of a presumptive HIV therapy regimen in infants at high risk of HIV acquisition. For infants at low risk of transmission, these doses can be given from birth. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization, 2021. Table A1.7. Available at https://www.who.int/publications/i/item/9789240031593. (Accessed 5 Nov 2023)

breastfeeding and for 1-4 weeks after weaning to further mitigate risk of HIV transmission (Table 322.8).

HIV-negative breastfeeding individuals with a sexual partner with HIV should also be monitored closely for developing HIV infection, because acute infection during breastfeeding carries a high risk of transmission to the infant (29–53%). It is recommended that these individuals consider preexposure prevention (PrEP) (see later) and practice barrier protection consistently to decrease risk of acute HIV infection during the breastfeeding period and educated on the signs and symptoms of acute HIV infection. They should also be tested every 1-2 months for seroconversion; if they become positive, breastfeeding should cease, and the infant should be placed on a high-risk three-drug presumptive HIV therapy regimen for 28 days and tested per the high-risk schedule with start point at time of cessation of breastfeeding.

Risk of transmission of HIV goes up considerably if virologic suppression in the breastfeeding parent is compromised. Therefore frequent HIV RNA (viral load) monitoring is recommended so that if there is virologic rebound, risk can be mitigated. In the scenario that viral load becomes detectable in the breastfeeding parent, it is recommended that the parent stop breastfeeding the infant immediately; milk can be pumped and discarded to maintain supply. The individual should be provided counseling regarding adherence, support, and resources, and discussion of whether to cease breastfeeding altogether or continue given the risk of HIV transmission to the infant should occur. Other scenarios that would require either modifying or stopping breastfeeding (in some cases temporarily) include cracked or bleeding nipples and mastitis. In these conditions, breastfeeding can continue on the unaffected side, and milk from the affected side should be pumped and discarded until the breast is fully healed and recovered. Again, having an experienced lactation consultant involved in the care of these individuals is critical. *Clinicians are strongly encouraged to consult the national Perinatal HIV/AIDS hotline (1-888-448-8765) with questions about infant feeding by individuals with HIV; the hotline provides 24/7 support from experienced HIV specialists to help in managing infants at high risk. U.S. guidelines for prevention of vertical transmission are regularly updated at https://www.nih.gov/research-training/hiv/aids-info-center/ and the international guidelines are regularly updated at the WHO website (https://www.who.int/health-topics/hiv-aids#tab=tab_1).*

Prevention of Sexual Transmission: Preexposure Prophylaxis and Postexposure Prevention

Prevention of sexual transmission involves avoiding the exchange of bodily fluids. In sexually active adolescents, barrier protection (male and female condoms) should be an integral part of programs to reduce sexually transmitted diseases, including HIV-1. Unprotected sex with older partners, multiple partners, transactional sex, and the use of recreational drugs can be associated with acquisition of HIV-1 infection in adolescents and young adults. Educational efforts about avoidance of risk factors and safer sex practices are essential for older school-age children and adolescents and should begin well before the onset of sexual activity. In addition, promising research for sexually active adults may translate to increased prevention for adolescents. Three African trials demonstrated that male circumcision was associated with a 50–60% reduction in the risk of HIV acquisition in young men. For females, use of a 1% vaginal gel formulation of tenofovir during intercourse was found to reduce HIV acquisition by nearly 40% in one study, though subsequent trials have had variable efficacy; other topical microbicides are being investigated. An increasingly important tool for HIV prevention is **PrEP** using once-daily dosing of co-formulated tenofovir and emtricitabine, approved for adolescents and adults weighing at least 35 kg (77 lb). The efficacy of PrEP in preventing sexual acquisition of HIV in MSM, heterosexual couples, and individuals in noncommitted relationships ranges from 70–92%. A depo injectable PrEP option (cabotegravir) dosed every 8 weeks is now approved for adults and adolescents ≥12 years weighing at least 35 kg (77 lb). large randomized multinational clinical trials of HIV serodiscordant adults have demonstrated that effective cART therapy in the HIV-infected partner essentially eliminates secondary sexual transmission to an uninfected sexual partner, creating the catchphrase "U = U" or "undetectable = untransmittable." The data from these trials can likely be extrapolated for youth with long-standing virologic suppression.

Postexposure prevention (PEP) is another important tool in HIV prevention and has been used in healthcare workers after needlesticks and body substance exposures. It can also be effective after a single high-risk event (including unprotected sexual activity, high-risk sexual assault, and intravenous drug use/needle sharing). PEP should be given as soon as possible after the high-risk exposure, ideally within 24 hours and at the latest within 72 hours of the exposure to have efficacy. Efficacy is higher the sooner it is given. Baseline testing should be performed at the time PEP is started, but initial doses should not be delayed for laboratory test results. Baseline testing includes HIV antigen/antibody testing (fourth-generation HIV ELISA), hepatitis B and C testing (because most high-risk exposures have risk of transmission of these as well), serum creatinine, and alanine aminotransferase (ALT). If a patient is hepatitis B immune (including having completed a full hepatitis B vaccine series), hepatitis B testing does not need to be performed. For sexual exposures, gonorrhea, chlamydia, and syphilis, testing should be done. After completion of a PEP course, follow-up testing should be done at 4-6 weeks and 3 months after exposure. If hepatitis C was transmitted, HIV testing should be repeated at 6 months as well, because HIV seroconversion can be delayed in patients with co-infection with hepatitis C. PEP regimens are three-drug treatment regimens for 28 days. For

individuals ≥12 years old, generally the preferred regimen consists of tenofovir DF + emtricitabine with either dolutegravir or raltegravir (note that dolutegravir allows for a once-daily regimen). For individuals 2 years old to <12 years old, the preferred regimen is tenofovir DF + emtricitabine + raltegravir. For those <2 years old the preferred regimen is zidovudine + lamivudine + raltegravir. In the rare cases in which the source patient is known to have HIV infection and is in care, selection can be guided by the source patient's genotype and/or treatment history. Abacavir and nevirapine are both contraindicated for use in PEP.

SUMMARY

The course and prognosis of HIV infection has improved dramatically as a consequence of cART for all ages, particularly with newer agents with fewer side effects. With good adherence, patients can achieve prolonged virologic suppression and immune function can be preserved or reconstituted. However, lifelong adherence and side effects of medications are important challenges to recognize that can prevent patients from achieving good outcomes. Globally, great strides have been made in preventing vertical transmission and increasing access to cART for children and adults, which is important for maintaining health as well as driving down sexual and vertical transmission with virologic suppression. However, there is still much work to be done to ensure the end of the global HIV epidemic, including continued advancement of our understanding of the immunology of HIV latency and reservoirs, HIV vaccines, and continued increases in access to cART worldwide, particularly in children.

Visit Elsevier Ebooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 323

Human T-Cell Leukemia Viruses (1 and 2)

Paul Spearman and Lee Ratner

ETIOLOGY

Human T-cell leukemia viruses 1 (HTLV-1) and 2 (HTLV-2) are members of the *Deltaretrovirus* genus of the Retroviridae family, which are single-stranded RNA viruses that encode reverse transcriptase, an RNA-dependent DNA polymerase that transcribes the single-stranded viral RNA into a double-stranded DNA copy. HTLV-1 was the first human retrovirus discovered, isolated in 1979 from a cutaneous T-cell lymphoma. The closely related virus HTLV-2 was subsequently identified in 1981. HTLV-1 is associated with adult T-cell leukemia/lymphoma (ATL) and HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), whereas HTLV-2 is less pathogenic and rarely is associated with neurologic diseases.

HTLV-1 and -2 share a genome homology of approximately 65%. The genome contains *gag, pr, pol,* and *env* genes and several nonstructural genes. The nonstructural proteins include the Tax and Rex regulatory proteins, the novel proteins essential for virus spread (p30, p12, and p13), and the antisense-encoded HTLV-1 basic leucine zipper factor, HBZ. HTLV-1 and -2 infect cells via the ubiquitous glucose transporter type or via neuropilin-1, both of which serve as virus receptors. HTLV-1 and -2 can infect a variety of cells, with HTLV-1 most often found in $CD4^+$ T cells and HTLV-2 showing preference for $CD8^+$ T cells. After viral entry, reverse transcription produces a double-stranded DNA copy of the RNA genome that is transported into the nucleus and integrated into chromosomal DNA (the provirus), evading the typical mechanisms of immune surveillance and facilitating lifelong infection.

EPIDEMIOLOGY AND MODES OF TRANSMISSION

HTLV-1 has infected 15-20 million persons globally. It is endemic in southwestern Japan (where >10% of adults are seropositive); areas of the Caribbean, including Jamaica and Trinidad (up to 6%); and in parts of sub-Saharan Africa (up to 5%). Lower seroprevalence rates are found in South America (up to 2%) and Taiwan (0.1–1%). There is microclustering with marked variability within geographic regions.

The seroprevalence of HTLV-1 and HTLV-2 in the general population in the United States is 0.01–0.03% for each virus, with higher rates with increasing age. The prevalence of HTLV-1 infection is highest in babies born in endemic areas or in persons who have had sexual contact with persons from endemic areas. The prevalence of HTLV-2 infection is highest in intravenous drug users, with a seroprevalence of 8.8–17.6% in this population.

HTLV-1 and -2 are transmitted as cell-associated viruses from mother to child and **transmission** through genital secretions, contaminated blood products, and intravenous drug use. Mother-to-child transmission during the intrauterine period or peripartum period is estimated to occur in less than 5% of cases but increases to approximately 20% with breastfeeding. Higher maternal HTLV-1 proviral load and prolonged breastfeeding are associated with greater risk of mother-to-child transmission. In Japan, approximately 20–25% of children born to HTLV-1–infected mothers became infected before recommendations that seropositive mothers should avoid breastfeeding, with a marked reduction to 2.5% transmission after restriction of breastfeeding. HTLV-2 may also be transmitted via breastfeeding, but it has a slightly lower reported transmission rate via breast milk of approximately 14%.

DIAGNOSIS

HTLV-1 and HTLV-2 infections are diagnosed by screening using a second-generation enzyme immunoassay with confirmation by immunoblot, indirect immunofluorescence, or line immunoassays. Polymerase chain reaction can also be used to distinguish HTLV-1 from HTLV-2 infection.

CLINICAL MANIFESTATIONS

The lifetime risk of disease associated with HTLV-1 infection is estimated at 5–10% and is highest after vertical transmission. HTLV-1 is associated with ATL and several nonmalignant conditions, including the neurodegenerative disorder HAM, also known as tropical spastic paraparesis (TSP) and sometimes termed HAM/TSP. The geographic epidemiologic characteristics of ATL and HAM are similar. **HTLV-1–associated arthropathy** mimics rheumatoid arthritis, including a positive rheumatoid factor. Treatment is with antiinflammatory agents. **HTLV-1–associated uveitis** may be unilateral or bilateral, is more common among women, and resolves spontaneously, although it often recurs within 1-3 years. Topical corticosteroids hasten recovery. **HTLV-1–associated infective dermatitis** is a chronic and recurrent eczematous disease occurring during childhood and adolescence that predisposes to staphylococcal infection. HTLV-1 infection predisposes to disseminated and recurrent *Strongyloides stercoralis* infection, increased risk of developing tuberculosis disease after latent infection, and severe scabies.

ADULT T-CELL LEUKEMIA/LYMPHOMA

The age distribution of ATL peaks at approximately 50 years, underscoring the long latent period of HTLV-1 infection. HTLV-1–infected persons remain at risk for ATL even if they move to an area of low HTLV-1 prevalence, with a lifetime risk for ATL of 2–4%. Most cases of ATL are associated with monoclonal integration of HTLV-1 provirus into the cellular genome of $CD4^+$ T lymphocytes, resulting in unchecked proliferation of CD4 T cells. There is a spectrum of disease that is categorized into different forms: acute, lymphomatous, chronic, primary cutaneous smoldering, and primary cutaneous tumoral. The acute form of ATL comprises 55–75% of all cases. Smoldering subclinical lymphoproliferation may spontaneously resolve in approximately

half of cases or progress to chronic leukemia or lymphomatous, or even acute ATL. **Chronic, low-grade, HTLV-1–associated lymphoproliferation (pre-ATL)** may persist for years with abnormal lymphocytes with or without peripheral lymphadenopathy before progressing to the acute form. Acute ATL is characterized by hypercalcemia, lytic bone lesions, lymphadenopathy that spares the mediastinum, hepatomegaly, splenomegaly, cutaneous lymphomas, and opportunistic infections. Leukemia may develop with circulating polylobulated malignant lymphocytes, called **flower cells**, possessing mature T-cell markers. Antiviral therapy with zidovudine and interferon-α is the standard therapy for leukemic-type ATL in the United States and Europe. In lymphoma-type ATL, **response rates may be improved using the anti-CCR4 monoclonal antibody mogamulizumab with chemotherapy**. Allogeneic hematopoietic stem cell transplantation is sometimes employed.

HUMAN T-CELL LYMPHOTROPIC VIRUS-1–ASSOCIATED MYELOPATHY

HAM is more common in women than in men and has a relatively short incubation period of 1-4 years after HTLV-1 infection, compared with 40-60 years for ATL. HAM occurs in up to 4% of persons with HTLV-1 infection, usually developing during middle age. It is characterized by infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, leading to severe white matter degeneration and fibrosis. HTLV-1 is found near but not directly within the lesions, suggesting that reactive inflammation is a major mechanism of disease. The cerebrospinal fluid typically shows a mildly elevated protein and a modest monocytic pleocytosis, along with anti–HTLV-1 antibodies. Neuroimaging studies are normal or show periventricular lesions in the white matter. Clinical manifestations include gradual onset of slowly progressive, symmetric neurologic degeneration of the corticospinal tracts and, to a lesser extent, the sensory system that leads to lower-extremity spasticity or weakness, lower back pain, and hyperreflexia of the lower extremities with an extensor plantar response. The bladder and intestines may become dysfunctional, and men may become impotent. Some patients develop dysesthesias of the lower extremities with diminished sensation to vibration and pain. Upper-extremity function and sensation, cranial nerves, and cognitive function are usually preserved. **Treatment regimens have included corticosteroids, danazol, interferon, plasmapheresis, high-dose vitamin C, and antivirals, all with minimal effects.** Recent studies examined the effects of mogamulizumab (anti-CCR4 antibody) on HAM, but results are not yet conclusive.

HUMAN T-CELL LYMPHOTROPIC VIRUS-2

HTLV-2 was originally identified in patients with hairy cell leukemia, although most patients with hairy cell leukemia are seronegative for HTLV-2 infection. HTLV-2 has been rarely isolated from patients with leukemias or with myelopathies resembling HAM, and there is limited evidence of disease specifically associated with HTLV-2 infection.

PREVENTION

Routine antibody testing of all blood products for HTLV-1 and -2 is performed in many developed countries and is effective in preventing blood transfusion–associated infections. Unfortunately, this testing is not always available in low- and middle-income countries with higher endemicity. Prenatal screening and avoidance of breastfeeding by HTLV-1–infected mothers is an effective means of reducing mother-to-child transmission of HTLV-1. Safe sexual practices to avoid sexually transmitted infections, such as condom use and avoiding multiple sexual partners, may reduce transmission of both HTLV-I and HTLV-2. No vaccine is available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 324

Transmissible Spongiform Encephalopathies

David M. Asher and Brian S. Appleby

The transmissible spongiform encephalopathies (**TSEs, prion diseases**) are slow infections of the human nervous system, consisting of at least four diseases of humans (Table 324.1): kuru; **Creutzfeldt-Jakob disease (CJD)** with its variants—sporadic CJD (sCJD), familial CJD (fCJD—some authorities prefer "genetic" CJD), iatrogenic CJD (iCJD), and new-variant or **variant CJD** (vCJD); Gerstmann-Sträussler-Scheinker syndrome (GSS); and fatal familial insomnia (FFI), or the even more rare sporadic fatal insomnia syndrome. sCJD can also be further subdivided based on clinical features—e.g., Heidenhain variant in which early onset of occipital blindness is prominent—or differences in characteristics of abnormal prion protein—e.g., variably protease-sensitive prionopathy (VPSPr). TSEs also affect animals. The most common and best-known TSEs of animals are scrapie in sheep, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, and a chronic wasting disease (CWD) of deer, elk, reindeer, and moose found in parts of the United States, Canada and, more recently, in Norway, Sweden, and Finland. A TSE of camels has recently been described in North Africa, and others might be anticipated. So far, of all the TSEs of animals, only BSE has proven zoonotic (i.e., transmissible to humans).

All TSEs have similar clinical manifestations and histopathology, and all are "slow" infections with very long asymptomatic incubation periods (often years), durations of several months or more, and overt disease affecting only the nervous system. TSEs are relentlessly progressive after illness begins and invariably fatal. The most striking neuropathologic change that occurs in each TSE, to a greater or lesser extent, is vacuolation, sometimes leading to spongy degeneration of the cerebral cortical gray matter.

ETIOLOGY

The TSEs are transmissible to susceptible animals by inoculation of suspensions of brain and some other tissues from affected subjects. Although the infectious agents replicate in a few cell cultures, they do not achieve the high titers of infectivity found in brain tissues or cause recognizable cytopathic effects in cultures. Most studies of TSE agents, before discovery of the prion proteins, used in vivo bioassays, relying on the transmission of typical neurologic disease to animals as evidence that the agent was present. Inoculation of susceptible recipient animals with small amounts of infectious TSE agents results, months or years later, in the accumulation in tissues of large amounts of agent having the same physical and biologic properties as the original agent. The TSE agents display a spectrum of extreme resistance to inactivation by a variety of chemical and physical treatments that is unknown among conventional pathogens. This characteristic, as well as their partial resistance to protein-disrupting treatments and their consistent association with abnormal isoforms of the normal host-encoded "prion" protein (PrP), stimulated the hypothesis that the TSE agents are probably subviral in size, composed of protein, and devoid of nucleic acid.

The term **prion** (for proteinaceous infectious agent), coined by S. B. Prusiner, is now widely used for such agents. The prion hypothesis proposes that the molecular mechanism by which the pathogen-specific information of TSE agents is propagated involves a self-replicating change in the folding of host-encoded PrP associated with a transition

Table 324.1 Clinical and Epidemiologic Features of Human Transmissible Spongiform Encephalopathies (Prion Diseases)

DISEASE	CLINICAL FEATURES	SOURCE OF INFECTION	GEOGRAPHIC DISTRIBUTION AND PREVALENCE	USEFUL ANCILLARY TESTS	DURATION OF ILLNESS
sCJD	Dementia, myoclonus, ataxia	Unknown	Worldwide; ~1-2/1 million/yr; 85–95% of all CJD cases in the United States	EEG-PSWCs; CSF 14-3-3; RT-QuIC, MRI/DWI	1-24 mo (mean: 4-6 mo)
fCJD	Dementia, myoclonus, ataxia	Genetic association (*PRNP* pathogenic variants)	Worldwide; geographic clusters; >100 known families; 5–15% of CJD cases	Gene testing; EEG-PSWC; CSF 14-3-3, RT-QuIC, MRI/DWI	Mean ~15 mo
iCJD	Incoordination, dementia (late)	Cadaveric dural grafts, human pituitary hormones, corneal transplantation, neurosurgical instruments, EEG depth electrodes	~1% of CJD cases in toto (cadaveric dural grafts); human pituitary hormones, >100 cases; corneal transplantation, three cases; neurosurgical instruments, six cases, including two from cortical depth electrodes; RBC transfusions, four cases of vCJD infection, three clinical, one preclinical (United Kingdom); human plasma–derived factor VIII, one preclinical case of vCJD (United Kingdom)	EEG-PSCW, CSF 14-3-3, RT-QuIC, MRI/DWI	18 mo - >30 yr
vCJD	Mood and behavioral abnormalities, paresthesias, dementia	Linked to BSE in cattle, transfusion plasma products	>230 clinical cases (see iatrogenic vCJD): none living, May 2017	Tonsil biopsy may show PrP^{TSE} MRI/FLAIR	8-36 mo (mean 14 mo)
Kuru	Incoordination, ataxia, tremors, dementia (late)	Linked to cannibalism	Fore tribe of Papua New Guinea (~2,600 known cases)	EEG-no PSWCs; CSF 14-3-3 often negative; MRI (?)	3-24 mo
GSS	Incoordination, chronic progressive ataxia, corticospinal tract signs, dementia (late), myoclonus (rare)	90% genetic (*PRNP* pathogenic variants)	Worldwide; >50 families; ~1-10/100 million/yr	*PRNP* gene sequencing	2-12 yr (mean ~ 57 mo)
FFI	Disrupted sleep, intractable insomnia; autonomic hyperactivation; myoclonus, ataxia; corticospinal tract signs; dementia	*PRNP* gene pathogenic variant (D 178L); very rare sporadic cases	~27 families in Europe, United Kingdom, United States, Finland, Australia, China, Japan	PRNP testing; EEG-PSWCs only rarely positive; MRI-no DWI abnormalities; CSF 14-3-3 positive in ~50%	8 mo to 6 yr (mean: *PRNP* 129 MM 12 ± 4 mo 129 MV 21 ± 15 mo)

BSE, Bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; *PRNP*, prion protein–encoding gene; PrP^{TSE}, abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; RT-QuIC, real-time quaking-induced conversion; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

NOTE: PRNP 129 MM, homozygous, encoding the amino acid methionine at both codons 129 of the prion protein–encoding (*PRNP*) gene on chromosome 20; 129 MV, heterozygous at PRNP codon 129, encoding methionine on one chromosome 20 and valine on the other.

Modified from Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Elsevier; 2005: p. 2222; Love S, Louis DN, Ellison DW, eds. *Greenfield's Neuropathology*. 8th ed. London: Hodder Arnold; 2008: p. 1239.

from an α-helix-rich structure in the native protease-sensitive conformation ("cellular" PrP or PrP^{C}) to a β-sheet-rich structure in the protease-resistant conformation associated with infectivity. The existence of a second host-encoded protein—termed *protein X*—that participates in the transformation was once postulated to explain certain otherwise puzzling findings but was never identified.

The prion hypothesis is still not universally accepted; it relies on the postulated existence of a genome-like coding mechanism based on differences in protein folding that have not yet been satisfactorily elucidated at a molecular level. In addition, it has yet to account convincingly for the many biologic strains of TSE agent that have been observed, although strain-specific differences in glycosylation patterns

of abnormal PrP have been proposed as providing a plausible molecular basis for the coding. It fails to explain why pure PrP uncontaminated with nucleic acid from an infected host has not consistently transmitted a typical spongiform encephalopathy associated with a serially self-propagating agent. Also troubling is the fact that abnormal PrP and infectivity were not consistently associated in several experimental models and human illnesses. Particularly problematic is the finding that some illnesses associated with pathogenic variants in the *PRNP* gene and accompanied by abnormal PrP failed to transmit infection to animals. If the TSE agents ultimately prove to consist of protein and only protein, with no obligatory nucleic acid component, then proponents of the prion hypothesis will have been prescient. If the agents are ultimately found to contain small nucleic acid genomes, then they might better be considered atypical viruses, for which the term *virino* was once suggested. Until the actual molecular structure of the infectious TSE pathogens and the presence or absence of a nucleic acid genome are rigorously established, it seems acceptable to continue calling them TSE agents (a term that remains popular among some European authorities). Most U.S. authorities now prefer the term *prion* (sometimes referring to the infectious agents of TSEs and sometimes to abnormal PrP, even when not transmissible).

The earliest evidence that abnormal proteins are associated with the TSE was morphologic: scrapie-associated fibrils (SAFs) were found by negative-stain electron microscopy in detergent-treated extracts of brain tissues from patients and animals with TSEs but not in brain tissues of unaffected persons. SAFs resemble but are distinguishable from the amyloid fibrils that accumulate in the brains of patients with Alzheimer disease. Antigenically related protease-resistant PrPs (PrP-res) proved to be components of SAFs and to be present in the amyloid plaques found in the brains of patients and animals with TSEs. The abnormal forms of PrP have been variously designated PrP^{Sc} (scrapie-type PrP), PrP-res, PrP^{TSE} (TSE-associated PrP), or PrP^{D} (also PrP^{Dis}, for "disease-associated" PrP) by different authorities.

It remains unclear whether abnormal PrP constitutes the complete infectious particle of spongiform encephalopathies, is a component of those particles, or is a pathologic host protein not usually separated from the actual infectious entity by current techniques. The demonstration that PrP is encoded by a normal host gene seemed to favor the last possibility. (A possible model for mammalian prions was provided by several studies. The model suggested that agent-specific pathogenic information can be transmitted and replicated by different conformations of fungal proteins having the same primary amino acid sequence without participation of any agent-specific nucleic acids, although those transmissions required microinjections and misfolded proteins were apparently not naturally transmitted to recipient fungi as infectious elements.)

Whatever its relationship to the actual infectious TSE particles, PrP clearly plays a central role in susceptibility to infection, because the normal PrP must be expressed in mice and cattle to infect them. Furthermore, inherited normal variations (genetic polymorphisms) in PrP genotype are associated with increased susceptibility to vCJD and, to a lesser extent, to sCJD and with occurrence of two familial TSEs (fCJD and GSS). PrPs are glycoproteins that have the physical properties of amyloid proteins when misfolded and aggregated into protease-resistant PrP^{TSE}. The PrPs of different species of animals are very similar in their amino acid sequences and antigenicity but are not identical in structure. The primary structure of PrP is encoded by the host and is not altered by the source of the infectious agent provoking its formation. The function of the normal ubiquitous protease-sensitive PrP precursor (designated either PrP^{C} or PrP-sen, for protease-sensitive PrP, by different authorities) in normal cells is unknown; it binds copper and may play some role in normal synaptic transmission but is not required to sustain life or for relatively normal cerebral function in mice and cattle. As noted, animals must express PrP to develop overt TSE as well as to support replication of the TSE agents. The degree of homology between amino acid sequences of PrPs in different animal species may correlate with a "species barrier" that affects susceptibility of animals of one species to infection with a TSE agent adapted to grow in another species, although the degree of sequence homology does not always predict susceptibility to the same TSE agent.

Attempts to find particles resembling those of known viruses or virus-like agents in brain tissues of humans or animals with spongiform encephalopathies have been unsuccessful. Peculiar tubulovesicular structures reminiscent of some viruses have been seen repeatedly in thin sections of TSE-infected brain tissues and cultured cells but not in normal brain cells; it has never been established that those structures are associated with infectivity.

EPIDEMIOLOGY

Kuru once affected many children of both sexes ≥4 years of age, adolescents, and young adults (mainly women) living only in a limited area of Papua New Guinea. The complete disappearance of kuru among people born after 1957 suggests that the practice of ritual cannibalism (thought to have ended that year) was probably the only mechanism by which the infection spread in Papua New Guinea. The probable incubation periods of some cases of kuru have exceeded 50 years. Kuru has not been diagnosed since 2005.

sCJD is the most common human spongiform encephalopathy. Most countries with surveillance for CJD have identified between one and two cases of sCJD per million total population per year (0.25-2 cases per million population, not age-adjusted). That figure is somewhat misleading in that the Centers for Disease Control and Prevention (CDC) has estimated the lifetime risk of sCJD in the United States to be as many as 1 in 6,000 persons, taking into account the number of recognized iCJD cases attributed to use of cadaveric pituitary hormones, typical advanced age of CJD cases at onset, and probable incubation periods of decades. sCJD was formerly thought to occur only in older adults; however, sCJD and sporadic fatal insomnia have also affected a few young people (to date, seven cases reported in adolescents, one in a 14-year-old girl). vCJD, however, has a peculiar predilection for younger people. Of 174 cases of vCJD reported through 2010 in the United Kingdom, all except 23 were in people younger than 40 years of age and 22 were younger than 20 years of age; the youngest age at onset was 12 years.

Proponents of the prion hypothesis are convinced that PrP can spontaneously misfold, becoming self-replicating and causing sCJD; skeptics favor the hypothesis of infection with some ubiquitous TSE agent that, fortunately, has a very low attack rate except in persons with certain pathogenic variants in the *PRNP* gene or possibly non-*PRNP* genetic risk factors. Neither possible etiology has been proven. fCJD, the second most common human TSE, accounts for only 10% or 15% of total cases of CJD. fCJD occurs in a foci of considerably higher incidence in Israel (among Libyan Jews), in isolated villages of Slovakia, and in other limited areas.

sCJD has not been convincingly linked to any prior exposure to other cases and the source of infection remains unknown. Person-to-person spread has been confirmed only for iatrogenic cases. Spouses and household contacts of patients are not at increased risk of acquiring CJD, although two instances of conjugal CJD have been reported. However, medical personnel exposed to brains of patients with CJD may be at some increased risk; at least 20 healthcare workers have been recognized with the disease. In 2019 a young laboratory worker in France died after a 2-year illness confirmed at autopsy to be vCJD; her infection was plausibly attributed to an accidental penetrating wound 7.5 years before onset by a forceps contaminated with brain tissue from a mouse experimentally infected with BSE agent.

The striking resemblance of CJD to scrapie prompted a concern that infected sheep tissues might be a source of spongiform encephalopathy in humans. No reliable epidemiologic evidence suggests that exposure to potentially scrapie-contaminated animals, meat, meat

products, or experimental preparations of the scrapie agent have transmitted a TSE to humans. The potential of the CWD agent to infect human beings has also not been demonstrated but remains under investigation by the CDC and Canadian authorities. Consumption of contaminated venison from animals infected with the CWD agent has not been implicated as a risk factor for human TSE by epidemiologic studies. However, a Canadian study reported that CWD had been experimentally transmitted to monkeys fed venison from overtly healthy infected deer, prompting a health advisory from Canadian authorities (https://www.thetyee.ca/Documents/2017/06/24/Risk-Advisory-Opinion-CWD-2017.pdf).

The same thing is not true for vCJD, which is clearly a zoonosis acquired by humans after dietary exposure to the BSE agent. The outbreak of BSE among cattle (possibly infected by eating scrapie agent–contaminated meat-and-bone meal and later bovine-contaminated meal added to feed) was first recognized in the United Kingdom in 1986 and later reported in cattle of 27 other countries, including Canada and the United States. More than 190,000 cases of BSE have been reported to the World Organization for Animal Health (OIE), almost 97% of those from the United Kingdom. Cases of BSE progressively declined in the United Kingdom after 1992 and somewhat later in other countries; in 2016 only two cases worldwide were reported to the OIE (from France and Spain) and none from the United Kingdom. A single case of BSE was recognized in the United States in 2018. Rare sporadic cases of BSE in old cows, associated with an "atypical" PrP^{TSE} having somewhat different electrophoretic properties from those of the PrP^{TSE} in younger cattle with "classic" cases of BSE during the epidemic, stimulated the hypothesis that atypical BSE was caused by spontaneous generation of a PrP^{TSE} rather than by a feed-borne infection; that hypothesis, however intriguing and appealing to some agricultural authorities, remains unconfirmed though little investigated.

The finding of a new TSE in ungulate and feline animals in British zoos and later in domestic cats first raised a fear that the BSE agent might have acquired a range of susceptible hosts broader than that of scrapie, posing a potential danger for humans. A broadening of the host range of BSE agent remains the most plausible explanation for the later appearance of human vCJD, first described in adolescents in Britain in 1996 and, as of August 2021, eventually affecting at least 178 people potentially exposed to a BSE agent in the United Kingdom (not counting a disturbing number of people with evidence of possible asymptomatic or "preclinical" vCJD infection) and more than 50 in 11 other countries (total 231 cases worldwide): 28 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 3 in Italy, 2 in Portugal, and single cases in Japan and Saudi Arabia. vCJD has also occurred in former residents in the United Kingdom (for more than 6 months) later living in Ireland (two cases), France (one case), Canada (one case), Taiwan (one case), and the United States (two cases). Two cases of vCJD, one in the United States and one in Canada, have been reported in former long-time residents of the Kingdom of Saudi Arabia, a country that has not recognized BSE but might have imported infected cattle or contaminated halal beef products from Britain. A third case of vCJD was previously confirmed in a Saudi citizen residing in the Kingdom of Saudi Arabia. The most recent case of vCJD diagnosed in the United States occurred in an immigrant deemed by the CDC to have been infected during years spent in Kuwait or, less likely, Russia.

No case of vCJD has been confirmed in anyone born in the United Kingdom after 1989. However, examination by immunohistochemistry of resected appendices in the United Kingdom for evidence of subclinical vCJD infection suggested that about 1 in 2,000 tissues tested had detectable accumulations of PrP^{TSE} in lymphoid follicles. It remains controversial whether those accumulations result from subclinical vCJD or other TSE (https://app.box.com/s/hhhhg857fjpu2bnxhv6e/1/2936396377/91796156506/1); none of the PrP^{TSE}-positive subjects to date has been reported with overt TSE.

Iatrogenic transmissions of CJD (iCJD) have been recognized for more than 30 years (Table 324.2). Such accidental medical transmissions of CJD have been attributed to use of contaminated neurosurgical instruments (no case reported since 1980), cortical electrodes contaminated during epilepsy surgery, injections of human cadaveric pituitary growth hormone and gonadotropin (neither currently marketed in the United States), transplantation of human dura mater allografts formerly used as a surgical patching material (especially in Japan), and, rarely, contaminated corneal transplants. Pharmaceuticals and tissue grafts derived from or contaminated with human neural tissues, particularly if obtained from unselected donors and large pools of donors, pose special risks.

Studies of animals experimentally infected with TSE agents first suggested that blood and blood components from humans with preclinical CJD infections might pose a risk of transmitting disease to recipients. Since the 1980s such blood components have been withdrawn as a precaution in the United States when a donor was later found to have CJD and blood products were still in-date. A surveillance program in the United Kingdom reported vCJD in three recipients of nonleukoreduced red blood cells from donors later diagnosed with vCJD; there was autopsy evidence of a preclinical vCJD infection in a fourth red cell recipient who died of another disease. (vCJD has not occurred in anyone exclusively transfused with leukoreduced red blood cells from a donor who later developed vCJD.) A study initiated more than 20 years ago by the American Red Cross and CDC found no recipient of blood components obtained from donors later diagnosed with sCJD (and from one donor with fCJD) had ever developed a TSE.

Evidence of a preclinical vCJD infection was found at autopsy in a British patient with hemophilia A treated with a human plasma–derived coagulation factor VIII to which at least one vCJD-infected donor contributed; the coagulation factor involved was never licensed or marketed in the United States. Authorities in the United Kingdom described two recipients of plasma-derived coagulation factors (both having history of transfusion with blood components as well) who later developed sCJD, concluding that the finding, while of concern, might be coincidental.

PATHOGENESIS AND PATHOLOGY

The probable portal of entry for the TSE agent in kuru is thought to have been either through the gastrointestinal tract or lesions in the mouth or integument incidentally exposed to the agent during cannibalism. Patients with vCJD (and animals with BSE and BSE-related TSEs) are thought to have been similarly infected with the BSE agent by consuming contaminated beef products. Except after direct introduction into the nervous system, the first site of replication of TSE agents appears to be in tissues of the reticuloendothelial system. TSE agents have been detected in low titers in blood of experimentally infected animals (mice, hamsters, cervids, sheep, and monkeys) and in the blood of persons with vCJD; infectivity was mainly associated with nucleated cells, although plasma contained a substantial portion of total infectivity in blood. Mice must have circulating lymphoid cells to be infected by peripheral routes. Limited evidence suggests that TSE agents can also spread to the central nervous system (CNS) by ascending peripheral nerves.

In kuru, it seems probable that the only portal of exit of the agent from the body, at least in quantities sufficient to infect others, was through infected tissues exposed during cannibalism. In iatrogenically transmitted CJD, the brains and eyes of patients with sCJD have been the probable sources of contamination. Experimental transmission of the agent to animals from kidney, liver, lung, lymph node, and spleen sampled at autopsies of patients with sCJD showed that those tissues as well as cerebrospinal fluid (CSF) sometimes contained the CJD agent; none of those sources has been implicated in accidental transmissions of CJD to humans. At no time during the course of any TSE have antibodies or cell-mediated immunity

Table 324.2 Iatrogenic Transmission of Creutzfeldt-Jakob Disease by Products of Human Origin

PRODUCT	PATIENTS (NO.)	INCUBATION TIME	
		MEAN	RANGE
Cornea	3	17 mo	16-18 mo
Dura mater allograft	>100	7.4 yr	1.3-16 yr
Pituitary extracts			
Growth hormone	>100*	12 yr	5-38.5 yr
Gonadotropin	4	13 yr	12-16 yr
Red blood cells	4	? 6 yr	6.3-8.5 yr†
Plasma-derived coagulation factor VIII	1	? >11 yr‡	

*There have been 28 cases reported among approximately 8,000 recipients of human cadaveric growth hormone in the United States; the remaining cases have been reported in other countries.

†The second transfusion-transmitted case of vCJD (Peden AH, Head MW, Ritchie DL, et al. Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient. *Lancet.* 2004;364:527–529) died of unrelated causes about 5 years after transfusion but was found to have accumulations of abnormal PrP in spleen and cervical lymph node, a finding unique to vCJD and interpreted as probable preclinical infection.

‡The diagnosis of vCJD infection attributed to treatment with human plasma–derived coagulation factor VIII (UK Health Protection Agency vCJD abnormal prion protein found in a patient with haemophilia at post mortem. Press release 17 February 2009. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C-/1234859690542?p=1231252394302) was also supported by immunohistochemical testing for abnormal PrP in the spleen of a person who died of other causes. Both patients with "preclinical" infections are thought to have died during the asymptomatic incubation period of vCJD.

to the infectious agents been convincingly demonstrated in either patients or animals. However, mice must be immunologically competent to be infected with the scrapie agent by peripheral routes of inoculation.

Typical changes in TSE include vacuolation and loss of neurons with hypertrophy and proliferation of glial cells, most pronounced in the cerebral cortex in patients with CJD and in the cerebellum in those with kuru. The lesions are usually most severe in or even confined to gray matter, at least early in the disease. Loss of myelin appears to be secondary to degeneration of neurons. There generally is no inflammation, but a marked increase in the number and size of astrocytes is usual. Spongiform changes are not a striking autopsy finding in patients with FFI, and neuronal degeneration and gliosis are largely restricted to thalamic nuclei.

Amyloid plaques are found in the brains of all patients with GSS and in at least 70% of those with kuru. These plaques are less common in patients with CJD. Amyloid plaques are most common in the cerebellum but occur elsewhere in the brain as well. In brains of patients with vCJD, plaques surrounded by halos of vacuoles (described as flower-like or "florid" plaques) have been a consistent finding. TSE amyloid plaques react with antiserum prepared against PrP. Even in the absence of plaques, extracellular PrP^{TSE} can be detected in the brain parenchyma by immunostaining, Western blotting, and enzyme-linked immunosorbent assay (ELISA).

CLINICAL MANIFESTATIONS

Kuru was a progressive degenerative disease of the cerebellum and brainstem with less obvious involvement of the cerebral cortex. The first sign of kuru was usually cerebellar ataxia followed by progressive incoordination. Coarse, shivering tremors were characteristic. Variable abnormalities in cranial nerve function appeared, frequently with impairment in conjugate gaze and swallowing. Patients died of inanition and pneumonia or of burns from cooking fires, usually within 1 year after onset. Although changes in mentation were common, there was no frank dementia or progression to coma, as seen in CJD. There were also no signs of acute encephalitis such as fever, headaches, and convulsions.

Patients with sCJD initially have either sensory disturbances (most often visual) or confusion and inappropriate behavior, progressing over weeks or months to frank dementia, akinetic mutism, and ultimately coma. Some patients have cerebellar ataxia early in disease, and most patients experience myoclonic jerking movements. Mean survival of patients with sCJD has been 4-6 months from the earliest signs of illness, although approximately 10% live for 2 years. vCJD (Table 324.3) differs from the more common sCJD: patients with vCJD are much younger at onset (as young as 12 years) and more often present with complaints of dysesthesia and subtle behavioral changes, often mistaken for psychiatric illness. Severe mental deterioration occurs later in the course of vCJD. Patients with vCJD have survived substantially longer than those with sCJD. (Attempts have been made to subclassify cases of CJD based on electrophoretic differences in PrP^{TSE} and variation in its sensitivity to digestion with the proteolytic enzyme proteinase [PK]; the different variants are said to have somewhat different clinical features, including duration of illness, though all are ultimately fatal.)

GSS is a familial disease somewhat resembling CJD but with more prominent cerebellar ataxia or parkinsonian syndrome and amyloid plaques. Dementia may appear only late in the course of GSS, and the average duration of illness is longer than that of typical sCJD (~5 years). Progressively severe insomnia and dysautonomia as well as ataxia, myoclonus, and other signs resembling those of CJD and GSS characterize FFI and sporadic fatal insomnia. GSS has not been diagnosed in children or adolescents. A case of sporadic fatal insomnia has been described in a young adolescent.

DIAGNOSIS

Diagnosis of spongiform encephalopathies is most often determined on clinical grounds after excluding other diseases. The presence of the 14-3-3 protein (see the section "Laboratory Findings") in CSF may aid in distinguishing between CJD and Alzheimer disease, which is not a consideration in children. Elevations of 14-3-3 protein levels in CSF are not specific to TSEs and are common in viral encephalitis and other conditions causing rapid necrosis of brain tissue. A research-use PrP peptide amplification test (real-time quaking-induced conversion [RT-QuIC]) appears to be sensitive and specific for antemortem diagnosis of sCJD when applied to CSF or nasal brushings but may be less sensitive in younger patients compared with older individuals with TSEs. Brain MRI has proven clinically useful (see later). Brain biopsy may be diagnostic for all forms of CJD but can be recommended only if a potentially treatable disease remains to be excluded or some other reason compels an antemortem diagnosis and may result in a false negative result depending on tissue quality, type, and TSE. Definitive diagnosis usually requires microscopic examination of brain tissue obtained at autopsy. The demonstration of PrP^{TSE} in brain extracts augments histopathologic diagnosis. Accumulation of the abnormal PrP in lymphoid tissues, even before the onset of neurologic signs, is typical of vCJD. Tonsil biopsy may avoid the need for brain biopsy when antemortem histologic diagnosis of vCJD is indicated. To date no blood-based test has been validated for antemortem testing of either humans or animals, though one cumbersome PrP^{TSE} research-use test (protein misfolding cyclic amplification [PMCA]) shows promise. Transmission of disease to susceptible animals by inoculation of brain suspension, while sensitive, specific, and reliable, must be reserved for cases of special research interest. Diagnosis usually rests on recognizing the typical constellation of clinical findings, course of illness, and

Table 324.3 Clinical and Histopathologic Features of Patients with Variant and Typical Sporadic Creutzfeldt-Jakob Disease

FEATURE	VARIANT CJD (FIRST 10 PATIENTS)	SPORADIC CJD (185 PATIENTS)
Years of age at death* (range)	29 (19-74)	65
Duration of illness, mo (range)	12 (8-23)	4-6
Presenting signs	Abnormal behavior, dysesthesia	Dementia, ataxia
Later signs	Dementia, ataxia, myoclonus	Ataxia, myoclonus
Periodic complexes on EEG	Rare	Most
PRNP 129 Met/Met	All tested (except one transfusion-transmitted case, one plasma-derivative transmitted case; one possible clinical case in United Kingdom where no tissue was available to confirm)	83%
Histopathologic changes	Vacuolation, neuronal loss, astrocytosis, plaques (100%)	Vacuolation, neuronal loss, astrocytosis, plaques (≤15%)
Florid PrP plaques†	100%	0
PrP^{TSE} glycosylation pattern	BSE-like‡	Not BSE-like

*Median age and duration for variant CJD; averages for typical sporadic CJD.
†Dense plaques with a pale periphery of surrounding vacuolated cells.
‡Characterized by an excess of high molecular mass band (diglycosylated) and 19-kDa nonglycosylated band glycoform of PrP-res (Collinge J, Sidle KC, Meads J, et al. Molecular analysis of prion strain variation and the aetiology of "new variant" CJD. *Nature.* 1996;383:685–690).
BSE, Bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; Met, codon 129 of one *PRNP* gene encoding for methionine; *PRNP*, prion protein–encoding gene; PrP, prion protein.
Modified from Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet.* 1996;347:921–925.

testing (CSF examination, MRI, EEG), confirmed by histopathology and detection of PrP^{TSE} in brain tissues at autopsy (or, less often, by tonsil or brain biopsy).

LABORATORY FINDINGS

Virtually all patients with typical sporadic, iatrogenic, and familial forms of CJD have abnormal EEGs as the disease progresses; the background becomes slow and irregular with diminished amplitude. A variety of paroxysmal discharges such as slow waves, sharp waves, and spike-and-wave complexes may also appear, and these may be unilateral or focal or bilaterally synchronous. Paroxysmal discharges may be precipitated by loud noise. Many patients have typical periodic suppression-burst complexes of high-voltage slow activity on EEG at some time during the illness. Patients with vCJD have only generalized slowing, without periodic bursts of high-voltage discharges on EEG. CT or MRI may show cortical atrophy and large ventricles late in the course of CJD. Most cases of sCJD and many cases of familial TSE demonstrate hyperintensity in cortex or basal ganglia diffusion by weighted imaging (DWI). Many patients with vCJD have an increase in density of the pulvinar on fluid attenuated inversion recovery (FLAIR) MRI sequences. Reliable interpretation of the images is best left to experienced radiologists.

There may be modest elevation of CSF protein content in patients with TSE. Unusual protein spots were observed in CSF specimens from sCJD patients separated by two-dimensional gel electrophoresis and silver staining; the spots were later identified as 14-3-3 proteins, normal proteins not related to PrP that are abundant in neurons but not ordinarily detected in CSF. However, 14-3-3 protein, as noted previously, has also been detected in CSF specimens from some patients with acute viral encephalitides and recent cerebral infarctions, and is not specific to CJD. Finding the 14-3-3 protein in CSF is neither sensitive nor specific but can help confirm the diagnosis of sCJD, especially when accompanied by increases in other cellular proteins. Tests for 14-3-3 in CSF are often negative in patients with vCJD.

TREATMENT

No treatment has proven effective for any TSE, and it seems unlikely that treatment can reverse the severe brain damage found in late disease. Studies of cell cultures and rodents experimentally infected with TSE agents suggested that treatments with chlorpromazine, quinacrine, and tetracyclines might be of benefit, especially during the incubation period; however, results of clinical trials based on those studies have been discouraging. Infusions with pentosan polysulfate directly into the cerebral ventricles may have delayed the progression of vCJD in at least one patient but did not reverse earlier brain damage. On the basis of experimental studies in animals, several prophylactic postexposure treatment regimens have been suggested, but none has been validated or widely accepted. Results of some preliminary studies suggested that treatments with antisense oligonucleotides or other molecular genetic therapies might impair translation of the prion protein gene, potentially ameliorating the degenerative process of TSE if initiated before CNS damage has appeared; such early treatment would have to be directed to otherwise healthy persons bearing a pathogenic variant known to occur in familial TSE, because those destined to develop the more common sCJD cannot be identified before brain damage appears. Appropriate compassionate supportive care should be provided to all CJD patients as for those with other progressive fatal neurologic diseases.

GENETIC COUNSELING

TSEs occur in some families in a pattern consistent with an autosomal dominant mode of inheritance. In patients with a family history of CJD, the clinical and histopathologic findings are similar to those seen in sporadic cases. In the United States, only approximately 10% of cases of CJD are familial. GSS and FFI are always familial. In some affected families, approximately 50% of siblings and children of a patient with a familial TSE eventually acquire the disease; in other families, the "penetrance" of illness is lower.

The gene encoding PrP is closely linked if not identical to that controlling the incubation periods of scrapie in sheep and both scrapie and CJD in mice. The same gene in humans is designated the *PRNP*

gene, located on the short arm of chromosome 20. It has an open reading frame of about 759 nucleotides (253 codons), in which more than 20 different point pathogenic variants and a variety of inserted sequences encoding extra tandem-repeated octapeptides have been linked to the occurrence of spongiform encephalopathy in families, a disease expressed in a pattern consistent with autosomal dominance of variable penetrance. The E200K point pathogenic variant has been the most common worldwide.

The same nucleotide substitution at codon 178 of the *PRNP* gene (D178N) associated with CJD in some families has also been found in all patients with FFI but associated with linkage to a different polymorphic amino acid at codon 129 of the *PRNP* gene on the same chromosome (fCJD with 129V and FFI with 129M). Homozygosity for valine (V) and especially for methionine (M) at codon 129 seems to increase susceptibility to both iCJD and sCJD. All but three patients with vCJD to be genotyped have been homozygous for methionine at codon 129 of the *PRNP* gene. A few probable preclinical vCJD infections and two clinically typical cases of vCJD (one confirmed and another not completely evaluated) occurred in persons with the 129 MV heterozygous genotype. It is of interest that when the *PRNP* genes from appendices containing accumulations of what appears to be PrP^{TSE} in the United Kingdom were sequenced, a surprising number were homozygous for 129V—the genotype of only approximately 10% of British subjects—and never found in a case of overt vCJD. The significance of this finding is not clear. Authorities in the United Kingdom adopted the precautionary assumption that some persons with PrP^{TSE} in lymphoid tissues may have latent infections; as time goes by without detecting any overt cases of vCJD in those persons, that assumption becomes less likely. Whether the blood or tissues of such persons are infectious remains unknown.

Although the interpretation of these findings in regard to the prion hypothesis remains controversial, persons from families with CJD or GSS who have the associated pathogenic variants in the *PRNP* gene clearly have a high probability of eventually developing TSE. Bearers of TSE-associated pathogenic variants have successfully employed preimplantation genetic diagnosis and in vitro selection of embryos to avoid passing the mutant gene to offspring. The significance of pathogenic variants in the *PRNP* genes of individuals from families with no history of spongiform encephalopathy is not known. It seems wise to avoid alarming those from unaffected families who have miscellaneous pathogenic variants in the *PRNP* gene, because the implications are not yet clear. In the United States, persons are currently deferred from donating blood if a blood relative has been diagnosed with a familial TSE unless the donor (the relative or implicated parent) has no TSE-related mutation.

PROGNOSIS

The prognosis of all spongiform encephalopathies is uniformly poor. Approximately 10% of patients may survive for longer than 2 years but the quality of life is poor.

FAMILY SUPPORT

The CJD Foundation (http://www.cjdfoundation.org), organized and maintained by family members and friends of patients with CJD and related disorders, working closely with the CDC (www.cdc.gov/prions/index.html) and with the National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, Ohio (http://www.cjdsurveillance.com), is a support and educational group and a useful source of information regarding available resources for those dealing with the diseases.

PREVENTION

Exposure to the BSE agent in meat products clearly poses a special danger, which is now greatly reduced. Authorities in Canada, the United States, and other countries responded by implementing progressively more stringent agricultural and public health measures during the past 25 years, with prohibition of most bovine-derived materials from feeds for ruminants probably the most effective measure. Three cases of BSE in native cattle were recognized in the United States from 2004 through 2012; a case was also found in a Canadian cow imported into the United States in 2003. Canada found 20 native cattle with BSE between 2003 and 2015 (and imported a case from the United Kingdom in 1993). In spite of encouraging epidemiologic studies that failed to implicate exposure to scrapie or CWD agents in human TSEs, it seems prudent to avoid exposing children to meat and other products likely to be contaminated with any TSE agent.

The safety of human blood, blood components, and plasma derivatives in the United States and Canada is protected by deferring, as a precaution, some donors with histories suggesting an increased risk of exposure to TSE agents: persons treated with human cadaveric pituitary hormones or dura mater allografts (neither currently marketed in the United States) and donors who voluntarily disclose history of familial TSE (fCJD, GSS, FFI) unless sequencing shows that the TSE-affected relative or the donor has no TSE-related mutation in either *PRNP* gene (https://www.fda.gov/vaccines-blood-biologics/guidancecompliance-regulatory-information-biologics/biologicsguidances).

In principle, it would be better to identify the very few blood and tissue donors actually infected with a TSE rather than deferring all those at increased risk of exposure, because most of them are unlikely to have been infected. Antemortem screening tests that might eventually identify donors with preclinical TSE infections are currently under development though not clinically validated. It seems unlikely that any test would be adopted to screen blood donors without simultaneously implementing a highly specific validated confirmatory test to avoid the serious adverse implications resulting from the inevitable false-positive screening results. In any case, the current risk of transfusion-transmitted TSE in the United States appears to be extremely low. Postmortem testing of brain tissue from cadaveric tissue donors would be feasible and more justifiable in view of the surprisingly high lifetime risk of sCJD; tissue transplantation–associated TSE has not been recognized since donors with history of dementia and other neurologic disease have been excluded.

Standard universal precautions should be used to handle all human tissues, blood, and body fluids. Materials and surfaces contaminated with tissues and CSF from patients suspected of having CJD must be treated with great care, paying special attention to preventing injuries with needles and other sharp instruments. Whenever possible, discard contaminated instruments as "medical-pathological waste" by careful packaging and incineration. Contaminated tissues and biologic products probably cannot be completely freed of infectivity without destroying their structural integrity and biologic activity; therefore the medical and family histories of individual tissue donors should be carefully reviewed to exclude a diagnosis of TSE or other neurologic disease. Histopathologic examination of brain tissues of cadaveric donors and rapid testing for abnormal PrP might eventually be performed where feasible (no rapid diagnostic test is currently marketed for use with human tissues, though commercial animal TSE tests detect PrP^{TSE} in human CJD brains) to provide some additional assurance of safety. Although no method of sterilization can be relied on to remove all infectivity from contaminated surfaces, exposures to moist heat, sodium hydroxide, chlorine bleach, concentrated formic acid, acidified detergent, and guanidine salts markedly reduced infectivity in experimental studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 14

Antiparasitic Therapy

Chapter 325

Principles of Antiparasitic Therapy

Beth K. Thielen

Parasites are divided into three main groups taxonomically: **protozoans,** which are unicellular, and **helminths** and **ectoparasites,** which are multicellular. Chemotherapeutic agents appropriate for one group may not be appropriate for the others, and not all drugs are readily available (Table 325.1). Some drugs are not available in the United States, and some are available only from the manufacturer, specialized compounding pharmacies, or the Centers for Disease Control and Prevention (CDC). Information on the availability of drugs and expert guidance in management can be obtained by contacting the CDC Parasitic Diseases Branch (1-404-718-4745; e-mail parasites@cdc.gov (M-F, 8 AM-4 PM, Eastern time). For assistance in the management of malaria, healthcare providers should call the CDC Malaria Hotline: 1-770-488-7788 or 1-855-856-4713 toll-free, e-mail malaria@cdc.gov (M-F, 9 AM-5 PM, Eastern time). For all emergency consultations after hours, clinicians can contact the CDC Emergency Operations Center at 1-770-488-7100 and request to speak with a CDC Malaria Branch clinician or on-call parasitic diseases physician. Some antiparasitic drugs are not licensed for use in the United States but can be obtained as investigational new drugs (INDs) from the CDC; providers should call the CDC Drug Service, Division of Scientific Resources and Division of Global Migration and Quarantine, at 1-404-639-3670.

SELECTED ANTIPARASITIC DRUGS FOR PROTOZOANS

Nitazoxanide (Alinia)

Nitazoxanide is a nitrothiazole benzamide, initially developed as a veterinary anthelmintic. Nitazoxanide inhibits pyruvate: ferredoxin oxidoreductase, which is an enzyme necessary for anaerobic energy metabolism. In humans, nitazoxanide is effective against many **protozoans** and **helminths.** Nitazoxanide is approved for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia intestinalis* in patients ≥1 year of age.

Nitazoxanide is available as a tablet (500 mg) and an oral suspension (100 mg/5 mL), which has a pink color and strawberry flavor. The bioavailability of the suspension is ~70% compared with the tablet. The drug is well absorbed from the gastrointestinal tract but should be taken with food due to approximately twofold higher absorption. One third is excreted in urine, and two thirds is excreted in feces as the active metabolite, tizoxanide. Although in vitro metabolism studies have not demonstrated cytochrome P450 enzyme effects, no pharmacokinetic studies have been performed in patients with compromised renal or hepatic function. In addition, limited studies have been performed in pregnant or lactating women; nevertheless, CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend nitazoxanide for the treatment of severe cryptosporidiosis after the first trimester. Tizoxanide is known to be excreted in breast milk, but decisions to breastfeed during therapy can be individualized. Common adverse effects include abdominal pain, diarrhea, nausea, and urine discoloration. Rare side effects include anorexia, flatulence, increased appetite, fever, pruritus, and dizziness. Intriguingly, nitazoxanide has in vitro activity against multiple other pathogens, including influenza virus, rotavirus, hepatitis C virus, and SARS-CoV-2, although the clinical use of the agent against these viruses remains investigational.

Tinidazole (Tindamax)

Tinidazole is a synthetic nitroimidazole with a chemical structure similar to metronidazole. It is approved by the Food and Drug Administration (FDA) for patients 3 years of age and older and for treatment of trichomoniasis, giardiasis, and amebiasis. In the treatment of giardiasis, it has the advantages of very few side effects and only requiring a single dose. It is available as a tablet, which can be crushed and administered with food. Its mechanism of action against *Trichomonas* may be secondary to the generation of free nitro radicals by the **protozoan.** The mechanism of action against *Giardia lamblia* and *Entamoeba histolytica* is unknown. Like metronidazole, it can cause a disulfiram-like reaction if combined with alcohol. After oral administration, tinidazole is rapidly and completely absorbed and is distributed into almost all tissues and body fluids; it can cross the blood-brain barrier and placental barrier. It is excreted via urine and feces. Hemodialysis increases clearance of the drug. No studies have been performed for patients undergoing peritoneal dialysis or for patients with compromised hepatic function. Tinidazole is known to cross the placenta and enter fetal circulation; the safety in pregnancy has not been well evaluated, and alternative agents are preferred. It can also be detected in breast milk, and breastfeeding should be interrupted during treatment and for 3 days after treatment.

Atovaquone/Proguanil (Malarone)

Atovaquone is a hydroxynaphthoquinone and has been used in the past predominantly against *Pneumocystis* pneumonia in AIDS patients. Its mechanism of action is via disruption of the mitochondria membrane potential through interaction with cytochrome b. However, atovaquone can also effectively inhibit liver stages of all *Plasmodium* species, and in 2000 the FDA approved atovaquone/proguanil for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults and children ≥11 kg. Atovaquone alone and in combination with proguanil is the only drug to completely inhibit the liver stage, providing the advantage of only needing to use the drug for 7 days after departing a malaria-endemic area (compared with several weeks).

Proguanil inhibits the parasite dihydrofolate reductase enzyme by the active form, cycloguanil. When used alone, it has poor efficacy for prophylaxis, but when administered with atovaquone, it acts in synergy on the cytochrome b enzyme in *Plasmodia* mitochondria, though the exact mechanism of synergy is unknown.

Two double-blind, randomized clinical trials assessing malaria prophylaxis demonstrated that atovaquone/proguanil was at least comparable to (and perhaps better than) chloroquine plus proguanil, and that atovaquone/proguanil was comparable to mefloquine. Atovaquone/proguanil was better tolerated than chloroquine plus proguanil and mefloquine. Atovaquone/proguanil treatment of acute uncomplicated *P. falciparum* infection has demonstrated higher or comparable cure rates when compared with other *P. falciparum* treatment drugs. Compared with other antimalarial therapies, atovaquone/proguanil has the highest cost. There are limited data on use during pregnancy, and pharmacokinetics may be altered during pregnancy so alternative regimens are preferred for malaria in pregnancy if available.

ARTEMISININ DERIVATIVES (ARTEMETHER, ARTESUNATE) AND COMBINATION THERAPIES (ARTEMETHER/LUMEFANTRINE OR COARTEM)

Artemisinin is a sesquiterpene lactone isolated from the weed *Artemisia annua.* It was developed in China, where it is known as qinghaosu. Artemisinin and its derivatives act very rapidly against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant *P. falciparum.* Artemisinins are also rapidly eliminated. Resistance to artemisinins has been documented in Cambodia, Laos, Myanmar, Thailand, and Vietnam. Coartem is the first artemisinin-containing

Table 325.1 Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of HIV, physicians anywhere may see infections caused by previously unfamiliar parasites. This table lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ACANTHAMOEBA KERATITIS			
Drug of choice:	See footnote[1]		
AMEBIASIS (ENTAMOEBA HISTOLYTICA)			
Asymptomatic			
Drug of choice:	Iodoquinol (Yodoxin)[2]	650 mg PO tid × 20 days	30-40 mg/kg/day (max 1950 mg) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 5-10 days	25-35 mg/kg/day PO in 3 doses × 5-10 days
Alternative:	Diloxanide furoate[3]	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease			
Drug of choice:	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[4]	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol[2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 5-10 days
Alternative:	Nitazoxanide[5]	500 mg bid × 3 days	1-3 yr: 100 mg bid × 3 days 4-11 yr: 200 mg bid × 3 days ≥12 yr: use adult dosing
Severe intestinal and extraintestinal disease			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[4]	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol[2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 5-10 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
NAEGLERIA FOWLERI			
Drug of choice:	Amphotericin B deoxycholate[6,7]	1.5 mg/kg/day IV in 2 divided doses × 3 days, then 1 mg/kg daily IV × 11 days	1.5 mg/kg/day IV in 2 divided doses × 3 days, then 1 mg/kg daily IV × 11 days
	plus Amphotericin B deoxycholate[6,7]	1.5 mg/kg intrathecally daily × 2 days, then 1 mg/kg intrathecally every other day × 8 days	1.5 mg/kg intrathecally daily × 2 days, then 1 mg/kg intrathecally every other day × 8 days
	plus Rifampin[7]	10 mg/kg (max 600 mg) IV or PO daily × 28 days	10 mg/kg (max 600 mg) IV or PO daily × 28 days
	plus Fluconazole[7]	10 mg/kg (max 600 mg) IV or PO daily × 28 days	10 mg/kg (max 600 mg) IV or PO daily × 28 days
	plus Azithromycin[7]	500 mg IV or PO daily × 28 days	10 mg/kg (max 500 mg) IV or PO daily × 28 days

[1]For treatment of keratitis caused by *Acanthamoeba*, 0.02% topical polyhexamethylene biguanide (PHMB) and 0.02% chlorhexidine have been successfully used individually and in combination in a large number of patients (Tabin G, et al. *Cornea.* 2001;20:757; Wysenbeek YS, et al. *Cornea.* 2000;19:464). The expected treatment course is 6-12 mo. PHMB is no longer available from Leiter's Park Avenue Pharmacy but is available from the O'Brien Pharmacy (1-800-627-4360; distributes in many states) and the Greenpark Pharmacy (1-713-432-9855; Texas only). Combinations with either 0.1% propamidine isethionate (Brolene) or hexamidine (Desomedine) have been used (Seal DV. *Eye.* 2003;17:893) successfully, but these are not available in the United States. Neomycin is not recommended due to high levels of resistance (*Acanthamoeba* keratitis: Treatment guidelines from *The Medical Letter,* 143, 8/1/2013). In addition, the combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al. *Jpn J Ophthalmol.* 2003;47:616).

[2]The drug is not available commercially but can be compounded by Expert Compounding Pharmacy, 6744 Balboa Blvd, Lake Balboa, CA 91406 (1-800-247-9767 or 1-818-988-7979 or info@expertpharmacy.org).

[3]This drug is not available commercially in the United States.

[4]A nitroimidazole similar to metronidazole, tinidazole was approved by the FDA in 2004 and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (HUMCO, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

[5]Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in immunocompetent children ≥1 yr of age. It has also been used in some small studies for *Balantidium coli* infection. It may also be effective for mild to moderate amebiasis (Diaz E, et al. *Am J Trop Med Hyg.* 2003;68:384; Rossignol JF, et al. *Trans R Soc Trop Med Hyg.* 2007;101:1025) and as an alternative therapy for microsporidiosis (published dosing for microsporidiosis: Bicart-See A, et al. *Antimicrob Agents Chemother.* 2000;44:167), 2020 CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

[6]*Naegleria* infection has been treated successfully with IV and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al. *N Engl J Med.* 1982;306:346; Jain R, et al. *Neurol India.* 2002;50:470). Other reports of successful therapy are less well documented.

[7]An approved drug, but usage is considered off-label for this condition by the FDA.

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
	plus Miltefosine[6–8]	50 mg PO tid × 28 days	<45 kg: 50 mg bid (max 2.5 mg/kg) × 28 days
			≥45 kg: use adult dosing
	plus dexamethasone	0.6 mg/kg/day IV in 4 divided doses × 4 days	0.6 mg/kg/day IV in 4 divided doses × 4 days
ACANTHAMOEBA			
Drug of choice:	See footnote[7,8]		
BALAMUTHIA MANDRILLARIS			
Drug of choice:	See footnote[7,9,10]		
SAPPINIA DIPLOIDEA			
Drug of choice:	See footnote[11]		
ANCYLOSTOMA CANINUM (EOSINOPHILIC ENTEROCOLITIS)			
Drug of choice:	Albendazole[7]	400 mg PO once	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days[13]
or	Pyrantel pamoate (OTC)[7]	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
ANCYLOSTOMA DUODENALE, (see Hookworm infection)			
ANGIOSTRONGYLIASIS (*ANGIOSTRONGYLUS CANTONENSIS, ANGIOSTRONGYLUS COSTARICENSIS*)			
Drug of choice:	See footnote[14]		
ANISAKIASIS (*ANISAKIS* SPP.)			
Treatment of choice:	Surgical or endoscopic removal		
Alternative:	Albendazole[7,15]	400 mg PO bid × 6-21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
ASCARIASIS (*ASCARIS LUMBRICOIDES*, ROUNDWORM)			
Drug of choice:	Albendazole[7]	400 mg PO once	<10 kg/2 yr: see adult dosing[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once[13]
or	Ivermectin[7]	150-200 µg/kg PO once	<15 kg: not indicated
			≥15 kg: see adult dosing

[8]If you have a patient with suspected free-living amoeba infection, please contact the CDC Emergency Operations Center at 1-800-CDC-INFO to consult with a CDC expert regarding the use of this drug. Miltefosine has been reported to successfully treat primary amebic meningoencephalitis due to *Naegleria fowleri,* although controlled trials have not been conducted (Linam WM, et al. *Pediatrics.* 2015;135:e744).

[9]Strains of *Acanthamoeba* isolated from fatal granulomatous amebic encephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in two children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al. *Pediatr Infect Dis.* 2001;*J* 20:623), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al. *J Clin Microbiol.* 2000;38:3892). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al. *N Engl J Med.* 1994;331:85).

[10]A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al. *Clin Infect Dis.* 2003;37:1304; Jung S, et al. *Arch Pathol Lab Med.* 2004;128:466). Case reports and in vitro data suggest miltefosine may have some antiamebic activity (Aichelburg AC, et al. *Emerg Infect Dis.* 2008;14:1743; Martínez DY, et al. *Clin Infect Dis.* 2010;51:e7; Schuster FL, et al. *J Eukaryot Microbiol.* 2006;53:121). Miltefosine (Impavido) is now commercially available. Contact the Centers for Disease Control/Agency for Toxic Substances Disease Registry at 1-770-488-7100 or 1-800-232-4636 (main number) for guidance on treatment.

[11]A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al. *J Neuropathol Exp Neurol.* 2003;62:990).

[12]Limited data in children <2 yr but has been used successfully for treatment of cutaneous larva migrans in children as young as 8 mo at a dose of 200 mg daily × 3 days (Black MD, et al. *Australas J Dermatol.* 2010;51:281). The WHO also recommends albendazole in children <2 yr for treatment of taeniasis, strongyloidiasis, filariasis, hookworms, roundworms, pinworms, and threadworms.

[13]Limited safety data in children <2 yr of age.

[14]Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ. *Am J Med.* 2003;114:217). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al. *N Engl J Med.* 2002;346:668). Mebendazole or albendazole and a corticosteroid appeared to shorten the course of infection (Sawanyawisuth K, et al. *Trans R Soc Trop Med Hyg.* 2008;102:990; Chotmongkol V, et al. *Am J Trop Med Hyg.* 2009;81:443).

[15](Repiso Ortega A, et al. *Gastroenterol Hepatol.* 2003;26:341.) Successful treatment of a patient with anisakiasis with albendazole has been reported (Moore DA, et al. *Lancet.* 2002;360:54).

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
BABESIOSIS (*BABESIA MICROTI*)			
Drugs of choice:[16]	Atovaquone[7]	750 mg PO bid × 7-10 days	20 mg/kg (max 750 mg) PO bid × 7-10 days
	plus azithromycin[7]	500-1,000 mg once, then 250 mg daily × 7-10 days. Higher doses (600-1,000 mg) and/or prolonged therapy (6 wk or longer) may be required for immunocompromised patients	10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/day (max 250 mg/dose) PO days 2-10
or	Clindamycin[7]	300-600 mg IV qid or 600 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose)
	plus quinine[7]	542 mg base (650 mg salt) tid PO × 7-10 days	6 mg base/kg (8 mg salt/kg) (max 542 mg base or 650 mg salt/ dose), PO tid × 7-10 days
Balamuthia mandrillaris, *see Amebic meningoencephalitis, primary*			
BALANTIDIASIS (*BALANTIDIUM COLI*)			
Drug of choice:	Tetracycline[7,17]	500 mg PO qid × 10 days	<8 yr: not indicated
			≥8 yr: 10 mg/kg (max 500 mg) PO qid × 10 days
Alternatives:	Metronidazole[7]	750 mg PO tid × 5 days	35-50 mg/kg/day PO in 3 divided doses × 5 days
or	Iodoquinol[2,7]	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) PO in 3 divided doses × 20 days
or	Nitazoxanide[5,7]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
			≥12 yr: see adult dosing
BAYLISASCARIASIS (*BAYLISASCARIS PROCYONIS*)			
Drug of choice:	Albendazole[7,18]	400 mg PO bid × 10-20 days	<10 kg/2 yr: 25-50 mg/kg/day PO in 1-2 divided doses × 10-20 days[12]
			≥2 yr: 25-50 mg/kg/day PO in 1-2 divided doses × 10-20 days
BLASTOCYSTIS HOMINIS INFECTION			
Drug of choice:	See footnote[19]		
CAPILLARIASIS (*CAPILLARIA PHILIPPINENSIS*)			
Drug of choice:	Mebendazole[7]	200 mg PO bid × 20 days	200 mg PO bid × 20 days[13]
Alternative:	Albendazole[7]	400 mg PO daily × 10 days	<10 kg/2 yr [12]
			≥15 kg/2 yr: see adult dosing
CHAGAS DISEASE, SEE TRYPANOSOMIASIS			
CLONORCHIS SINENSIS, SEE FLUKE INFECTION			
CRYPTOSPORIDIOSIS (*CRYPTOSPORIDIUM PARVUM*)			
Immunocompetent			
Drug of choice:	Nitazoxanide[5]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
			≥12 yr: see adult dosing

[16]Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al. *Clin Infect Dis.* 2001;32:1117). Clindamycin and quinine is the preferred therapy for severely ill patients. In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al. *N Engl J Med.* 2000;343:1454). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (Krause PJ, et al. *Clin Infect Dis.* 2008;46:370). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (Weiss LM, et al. *N Engl J Med.* 2001;344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (Wormser GP, et al. *Clin Infect Dis.* 2010;50:381). Most asymptomatic patients do not require treatment unless parasitemia persists >3 mo (Wormser GP, et al. *Clin Infect Dis.* 2006;43:1089).

[17]Use of tetracyclines has historically been contraindicated in pregnancy and in children younger than 8 yr. The American Academy of Pediatrics now recommends that doxycycline can be administered for short durations (i.e., 21 days or less) without regard to the patient's age (Kimberlin DW, et al. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases.* 32nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2021. p 866).

[18]No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/day PO and high-dose steroids has been used successfully (Peters JM, et al. *Pediatrics.* 2012;129:e806; Haider S. *Emerg Infect Dis.* 2012;18:347). Albendazole 25 mg/kg/day PO × 20 days started as soon as possible (up to 3 days after possible infection) might prevent clinical disease and is recommended for children with known exposure, as in the setting of ingestion of raccoon stool or contaminated soil (Murray WJ, et al. *Clin Infect Dis.* 2004;39:1484). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

[19]Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days, or trimethoprim-sulfamethoxazole 1 DS tablet bid × 7 days has been reported to be effective (Stenzel DJ, et al. *Clin Microbiol Rev.* 1996;9:563; Ok UZ, et al. *Am J Gastroenterol.* 1999;94:3245). Metronidazole resistance may be common (Haresh K, et al. *Trop Med Int Health.* 1999;4:274). Nitazoxanide has been effective in children (Diaz E, et al. *Am J Trop Med Hyg.* 2003;68:384).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
HIV infected			
Drug of choice:	See footnote[20]		
CUTANEOUS LARVA MIGRANS (*ANCYLOSTOMA BRAZILIENSE, ANCYLOSTOMA CANINUM*, DOG AND CAT HOOKWORM, CREEPING ERUPTION)			
Drug of choice:	Albendazole[7,21]	400 mg PO daily × 3-7 days	<10 kg/2 yr: 200 mg PO daily × 3 days[12]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg PO daily × 1-2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Alternative:	Thiabendazole	Apply topically tid × 7 days	Apply topically tid × 7 days
CYCLOSPORIASIS (*CYCLOSPORA CAYETANENSIS*)			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7,22]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	4-5 mg/kg TMP component (max 160 mg) PO bid × 7-10 days
CYSTICERCOSIS, SEE TAPEWORM INFECTION			
CYSTOISOSPORIASIS (*CYSTOISOSPORA BELLI*, FORMERLY KNOWN AS *ISOSPORA BELLI*)			
Drug of choice:	TMP-SMX[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	4-5 mg/kg TMP component (max 160 mg) PO bid × 10 days
Alternative:	Pyrimethamine	50-75 mg PO divided bid x 10 days	—
	plus leucovorin	10-25 mg PO daily × 10 days	—
or	Ciprofloxacin[7]	500 mg PO bid × 7-10 days	—
Dientamoeba fragilis infection[23]			
	Paromomycin[7]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 divided doses × 7 days
or	Iodoquinol[2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 divided doses × 20 days
or	Metronidazole[7]	500-750 mg tid × 10 days	35-50 mg/kg/day in 3 divided doses × 10 days
DIPHYLLOBOTHRIUM LATUM, SEE TAPEWORM INFECTION			
DRACUNCULUS MEDINENSIS (GUINEA WORM) INFECTION			
Treatment of choice:	Slow mechanical extraction of worm[24]		
ECHINOCOCCUS, SEE TAPEWORM INFECTION			
ENTAMOEBA HISTOLYTICA, SEE AMEBIASIS			
ENTEROBIUS VERMICULARIS (PINWORM) INFECTION[25]			
Drug of choice:	Albendazole[7]	400 mg PO once; repeat in 2 wk	<10 kg/2 yr: 200 mg PO once; repeat in 2 wk[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO once; repeat in 3 wk	100 mg PO once; repeat in 3 wk[13]
or	Pyrantel pamoate (OTC)	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk

[20]Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al. *Lancet*. 2002;360;1375). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide 500-1,000 mg for 14 days, paromomycin 500 mg 4 times daily × 14-21 days, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (Pantenburg B, et al. *Expert Rev Anti Infect Ther*. 2009;7:385).

[21]Albanese G, et al. *Int J Dermatol*. 2001;40:67.

[22]HIV-infected patients may need a higher dosage and long-term maintenance (Kansouzidou A, et al. *J Trav Med*. 2004;11:61).

[23]Norberg A, et al. *Clin Microbiol Infect*. 2003;9:65.

[24]Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morbid Mortal Wkly Rep*. 2011;60:1450). Instructions for this can be found at https://www.cdc.gov/parasites/guineaworm/treatment.html. Ten days of treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but it decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

[25]Because all family members are usually infected, treatment of the entire household is recommended.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
FASCIOLA HEPATICA, SEE FLUKE INFECTION			
FILARIASIS[26]			
Lymphatic filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)			
Drug of choice:[27]	Diethylcarbamazine[28,29]	6 mg/kg once or 6 mg/kg PO in 3 divided doses × 12 days[30]	<18 mo: no indication
			≥18 mo: see adult dosing
LOA LOA			
<8,000 microfilaria/mL[29]			
Drug of choice:	Diethylcarbamazine[28,29]	9 mg/kg PO in 3 doses × 14 days[30]	<18 mo: no indication
			≥18 mo: see adult dosing
Alternatives:	Albendazole[28]	200 mg PO bid × 21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
8,000 microfilaria/mL[29,31]			
Treatment of choice:	Apheresis		
or	Albendazole[28]	200 mg PO bid × 21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Either followed by:	Diethylcarbamazine[28,29]	8-10 mg/kg PO in 3 doses × 21 days[30]	<18 mo: no indication
			≥18 mo: see adult dosing
MANSONELLA OZZARDI			
Drug of choice:	See footnote[32]		
MANSONELLA PERSTANS			
Drug of choice:	Doxycycline[7,17,33]	100 mg bid PO × 6 wk	4 mg/kg/day in 2 doses PO × 6 wk
MANSONELLA STREPTOCERCA[34]			
Drug of choice:	Diethylcarbamazine[28]	6 mg/kg/day PO × 14 days	6 mg/kg/day PO × 14 days
or	Ivermectin[7]	150 µg/kg PO once	<15 kg: not indicated
			≥15 kg: see adult dosing
TROPICAL PULMONARY EOSINOPHILIA (TPE)[35]			
Drug of choice:	Diethylcarbamazine[28]	6 mg/kg once or 6 mg/kg PO in 3 divided doses × 14-21 days[27]	<18 mo: no indication
			≥18 mo: see adult dosing

[26]Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent blocking of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al. *Med Microbiol Immunol*. 2003;192:211; Hoerauf A, et al. *BMJ*. 2003;326:207).

[27]Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al. *Cochrane Database Syst Rev*. 2004;(1):CD003753).

[28]This drug is not FDA approved and not commercially available but is available under IND application through the CDC Drug Service (CDC Drug Service, Division of Scientific Resources, telephone at 1-404-639-3670).

[29]Diethylcarbamazine is contraindicated in patients co-infected with *Onchocerca volvulus* due to risk of a life-threatening Mazzotti reaction and in patients with *Loa loa* infection and microfilaria levels ≥8,000 mm^3 due to risk of encephalopathy and renal failure. Some experts use a cutoff of ≥2,500 mm^3.

[30]For patients with microfilaria in the blood, *Medical Letter* consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa*, day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al. *Trans R Soc Trop Med Hyg*. 1995;89:319; Simonsen PE, et al. *Am J Trop Med Hyg*. 1995;53:267). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueredo-Silva J, et al. *Trans R Soc Trop Med Hyg*. 1996;90:192; Noroes J, et al. *Trans R Soc Trop Med Hyg*. 1997;91:78).

[31]In heavy infections with *Loa loa*, rapid killing of microfilariae can provoke encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottesen EA. *Infect Dis Clin North Am*. 1993;7:619). Albendazole or ivermectin has also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al. *J Infect Dis*. 1993;168:202; Kombila M, et al. *Am J Trop Med Hyg*. 1998;58:458). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al. *Clin Infect Dis*. 1999;29:680). Diethylcarbamazine, 300 mg once a week, has been recommended for prevention of loiasis (Nutman TB, et al. *N Engl J Med*. 1988;319:752).

[32]Diethylcarbamazine has no effect. Ivermectin 200 µg/kg once has been effective.

[33]Doxycycline is preferred for strains that carry *Wolbachia* bacteria. Combination therapy with diethylcarbamazine and mebendazole and monotherapy with mebendazole have been used successfully in strains that do not carry *Wolbachia*. Evidence is limited, and optimal therapy is uncertain. Ivermectin and albendazole appear to be ineffective.

[34]Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (*The Medical Letter:* Drugs for parasitic infections, vol 11, 2013.)

[35]Relapse occurs and can be treated with diethylcarbamazine.

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ONCHOCERCA VOLVULUS (RIVER BLINDNESS)			
Drug of choice:	Ivermectin[36]	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic	<15 kg: not indicated
			≥15 kg: see adult dosing
FLUKE, HERMAPHRODITIC, INFECTION			
Clonorchis sinensis (Chinese liver fluke)			
Drug of choice:	Praziquantel	25 mg/kg PO tid × 2 day	25 mg/kg PO tid × 2 day[37]
or	Albendazole[7]	10 mg/kg PO × 7 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Fasciola hepatica (sheep liver fluke)			
Drug of choice:	Triclabendazole[7,38,39]	10 mg/kg PO once or twice	10 mg/kg PO once or twice
Alternative:	Nitazoxanide[7]	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid
			4-11 yr: 200 mg PO bid
			≥2 yr: see adult dosing
or	Bithionol[3,7]	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai (intestinal flukes)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 1 day	25 mg/kg PO tid × 1 day[37]
Metorchis conjunctus (North American liver fluke)[40]			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 1 day	25 mg/kg PO tid × 1 day[37]
Nanophyetus salmincola			
Drug of choice:	Praziquantel[7]	20 mg/kg PO tid × 1 day	20 mg/kg PO tid × 1 day[37]
Opisthorchis viverrini (Southeast Asian liver fluke), Opisthorchis felineus (cat liver fluke)			
Drug of choice:	Praziquantel	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[37]
or	Albendazole[7]	10 mg/kg PO × 7 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Paragonimus westermani (lung fluke)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[37]
or	Triclabendazole[7,41]	10 mg/kg PO bid × 1 day or 5 mg/kg daily × 3 days	10 mg/kg PO bid × 1 day or 5 mg/kg daily × 3 days
or	Bithionol[3,7]	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
GIARDIASIS (*GIARDIA INTESTINALIS*, ALSO KNOWN AS *GIARDIA DUODENALIS* OR *GIARDIA LAMBLIA*)			
Drugs of choice:	Metronidazole[7]	250 mg PO tid × 5 days	5 mg/kg (max 250 mg) PO tid × 5 days
or	Nitazoxanide[5]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO every 12 hr × 3 days
			4-11 yr: 200 mg PO every 12 hr × 3 days
			≥12 yr: see adult dosing

[36]Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al. *Ophthalmology.* 1996;103:1001). Ivermectin kills only the microfilaria but not the adult worms; emerging evidence suggests doxycycline is effective in killing adult worms and sterilizing females. The recommended regimen from the CDC is doxycycline 100-200 mg PO daily for 6 wk begun 1 wk after a dose of ivermectin is given to reduce the microfilaria burden. Diethylcarbamazine and suramin were formerly used for treatment of this disease but should no longer be used because of the availability of less toxic therapies.

[37]Limited safety data in children <4 yr of age but has been used in mass prevention campaigns with no reported adverse effects.

[38]Unlike infections with other flukes, *Fasciola hepatica* infections do not respond to praziquantel. Triclabendazole may be safe and effective, but data are limited (Graham CS, et al. *Clin Infect Dis.* 2001;33:1). In the United States, the drug is not approved by the FDA and is not yet commercially available. However, it is available to physicians licensed in the United States through the CDC Drug Service, under a special protocol, which requires that both the CDC and FDA agree that the drug is indicated for treatment of a particular patient. Providers should contact the CDC Drug Service, Division of Scientific Resources, at 1-404-639-3670. It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com). The drug should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al. *Aliment Pharmacol Ther.* 2003;17:265).

[39]Richter J, et al. *Curr Treat Options Infect Dis.* 2002;4:313.

[40]MacLean JD, et al. *Lancet.* 1996;347:154.

[41]Triclabendazole may be effective in a dosage of 5 mg/kg once a day × 3 days or 10 mg/kg bid × 1 day (Calvopiña M, et al. *Trans R Soc Trop Med Hyg.* 1998;92:566). In the United States, it is not approved by the FDA and is not yet commercially available. However, it is available to physicians licensed in the United States through the CDC Drug Service, under a special protocol, which requires both the CDC and FDA to agree that the drug is indicated for treatment of a particular patient. Providers should contact the CDC Drug Service, Division of Scientific Resources, at 1-404-639-3670. The drug is available from Victoria Pharmacy, Zurich, Switzerland; Phone, 41 43 344 60 60; FAX, 41 43 344 60 69; http://www.pharmaworld.com; e-mail, info@pharmaworld.com.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
GIARDIASIS (*GIARDIA INTESTINALIS*, ALSO KNOWN AS *GIARDIA DUODENALIS* OR *GIARDIA LAMBLIA*)			
Drugs of choice:	Metronidazole[7]	250 mg PO tid × 5 days	5 mg/kg (max 250 mg) PO tid × 5 days
or	Tinidazole[4]	2 g PO once	50 mg/kg PO once (max 2 g)
Alternatives[42]	Paromomycin[7,43]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Furazolidone[3]	100 mg PO qid × 7-10 days	6 mg/kg/day PO in 4 doses × 7-10 days
or	Quinacrine[2]	100 mg PO tid × 5 days	2 mg/kg tid PO × 5 days (max 300 mg/day)
GNATHOSTOMIASIS (*GNATHOSTOMA SPINIGERUM*)			
Treatment of choice:[44]	Albendazole[7]	400 mg PO bid × 21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg/day PO × 2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
±	Surgical removal		
GONGYLONEMIASIS (*GONGYLONEMA* SP.)[45]			
Treatment of choice:	Surgical removal		
or	Albendazole[7]	400 mg PO daily × 3 days	10 mg/kg/day PO × 3 days
HOOKWORM INFECTION (*ANCYLOSTOMA DUODENALE, NECATOR AMERICANUS*)			
Drug of choice:	Albendazole[7]	400 mg PO once	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once[13]
or	Pyrantel pamoate (OTC)[7]	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
HYDATID CYST, SEE TAPEWORM INFECTION			
HYMENOLEPIS NANA, SEE TAPEWORM INFECTION			
LEISHMANIA INFECTION[46]			
Visceral[47]			
Drugs of choice:	Liposomal amphotericin B (AmBisome)[48,49]	3 mg/kg/day IV on days 1-5, 14, and 21 (total dose 21 mg/kg)	3 mg/kg/day IV on days 1-5, 14, and 21 (total dose 21 mg/kg)
or	Miltefosine[50]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5mg/kg daily × 28 days[7]
		45 kg: 50 mg PO tid × 28 days	≥12 yr: see adult dosing
or	Sodium stibogluconate (Pentostam)[28,51]	20 mg Sb/kg/day IV or IM × 28 days	20 mg Sb/kg/day IV or IM × 28 days
or	Amphotericin B deoxycholate[7]	1 mg/kg IV daily or every 2 days for 15-20 doses	1 mg/kg IV daily or every 2 days for 15-20 doses

[42]Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, et al. *Trans R Soc Trop Med Hyg*. 1993;87:84; Dutta AK, et al. *Indian J Pediatr*. 1994;61:689; Cacopardo B, et al. *Clin Ter*. 1995;146:761). Combination treatment with standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al. *Clin Infect Dis*. 2001;33:22). In one study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* infection resistant to metronidazole and albendazole (Abboud P, et al. *Clin Infect Dis*. 2001;32:1792).

[43]Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[44]de Gorgolas M, et al. *J Travel Med*. 2003;10:358. All patients should be treated with a medication regardless of whether surgery is attempted.

[45]Eberhard ML, et al. *Am J Trop Med Hyg*. 1999;61:51; Wilson ME, et al. *Clin Infect Dis*. 2001;32:1378.

[46]Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage, and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (Murray HW. *Lancet*. 2005;366:1561; Aronson N, et al. *Clin Infect Dis*. 2016;63:e202). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (Sundar S, et al. *Expert Opin Pharmacother*. 2013;14:53).

[47]Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species *Leishmania chagasi*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world in which the infection was acquired. Liposomal amphotericin B is the treatment of choice in the IDSA leishmaniasis guidelines (Aronson N, et al. *Clin Infect Dis*. 2016;63:e202).

[48]Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum*, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A. *Clin Infect Dis*. 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

[49]The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day on days 1-5 and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, et al. *J Infect*. 1996;32:133).

[50]For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (~205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al. *N Engl J Med*. 1999;341:1795; Sangraula H, et al. *J Assoc Physicians India*. 2003;51:686). GI adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al. *Clin Infect Dis*. 2004;38:217). Miltefosine (Impavido) has been approved by the FDA for treatment of leishmaniasis due to *Leishmania donovani;* cutaneous leishmaniasis due to *L. braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*, and mucosal leishmaniasis due to *L. braziliensis* since 2014 and is now commercially available.

[51]May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL. *Lancet*. 1999;354:1191).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Alternative:	Meglumine antimonate[3,51]	20 mg pentavalent antimony/kg/day IV or IM × 28 days	20 mg pentavalent antimony/kg/day IV or IM × 28 days
or	Pentamidine[7]	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous[52,53]			
Drugs of choice:	Sodium stibogluconate[28,51]	20 mg Sb/kg/day IV or IM × 20 days	20 mg Sb/kg/day IV or IM × 20 days
or	Liposomal amphotericin B (AmBisome)[7]	3 mg/kg/day IV on days 1-5 and 10 or 1-7 (total dose 18-21 mg/kg)	3 mg/kg/day IV on days 1-5 and 10 or 1-7 (total dose 18-21 mg/kg)
or	Amphotericin B deoxycholate[7]	0.5-1 mg/kg IV daily or every 2 days (total dose 15-30 mg/kg)	0.5-1 mg/kg IV daily or every 2 days (total dose 15-30 mg/kg)
or	Miltefosine[50]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5mg/kg daily × 28 days[7]
		³ 45 kg: 50 mg PO tid x 28 days	≥12 yr: see adult dosing
Alternatives:	Meglumine antimonate[3,51]	20 mg pentavalent antimony/kg/day IV or IM × 20 days	20 mg pentavalent antimony/kg/day IV or IM × 20 days
or	Pentamidine[7,54]	3-4 mg/kg IV or IM every 2 days × 3-4 doses	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses
or	Paromomycin[7,55]	Topically 2×/day × 10-20 days	Topically 2×/day × 10-20 days
or	Ketoconazole[7]	600 mg daily × 28 days	
or	Fluconazole[7]	200 mg daily × 6 wk	
or	Local therapy including cryotherapy, thermotherapy, intralesional Sb^V, topical paromomycin, photodynamic or laser therapy		
Mucosal[56]			
Drugs of choice:	Sodium stibogluconate[28,51]	20 mg Sb/kg/day IV or IM × 28 days	20 mg Sb/kg/day IV or IM × 28 days
or	Liposomal amphotericin B (AmBisome)[7]	3 mg/kg/day IV × 10 days or 4 mg/kg days 1-5, 10, 17, 24, 31, and 38 (total dose 20-60 mg/kg)	2-4 mg/kg/day IV × 10 days or 4 mg/kg days 1-5, 10, 17, 24, 31, and 38 (total dose 20-60 mg/kg)
or	Amphotericin B deoxycholate[7]	0.5-1 mg/kg IV daily or every 2 days (total dose 20-45 mg/kg)	0.5-1 mg/kg IV daily or every 2 days (total dose 20-45 mg/kg)
or	Miltefosine[50]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5 mg/kg daily × 28 days[7]
		45 kg: 50 mg PO tid × 28 days	≥12 yr: see adult dosing
Alternative:	Meglumine antimonate[3,51]	20 mg pentavalent antimony/kg/day IV or IM × 28 days	20 mg pentavalent antimony/kg/day IV or IM × 28 days
LICE (HEAD AND BODY) INFESTATION (*PEDICULUS HUMANUS CAPITIS, PEDICULUS HUMANUS HUMANUS*)			
Drugs of choice:	0.5% Malathion (Ovide)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for 6 yr
or	1% Permethrin (Nix) (OTC)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for 2 mo
or	Pyrethrins with piperonyl butoxide (A-200, Proto, R&C, Rid, Triple X) (OTC)[58]	Topically 2×, 1 wk apart	Topically 2×, 1 wk, approved for ≥2 yr

[52]Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana, Leishmania (Viannia) braziliensis,* and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[53]In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *Leishmania (Viannia) braziliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. "Motion sickness," nausea, headache, and increased creatinine were the most frequent adverse effects (Soto J, et al. *Clin Infect Dis.* 2004;38:1266). For treatment of *Leishmania major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al. *N Engl J Med.* 2002;346:891).

[54]At this dosage, pentamidine has been effective against leishmaniasis in Colombia, where the likely organism was *Leishmania (Viannia) panamensis* (Soto-Mancipe J, et al. *Clin Infect Dis.* 1993;16:417; Soto J, et al. *Am J Trop Med Hyg.* 1994;50:107); its effect against other species is not well established. Updated based on *Leishmania* practice guidelines (Aronson N, et al. *Clin Infect Dis.* 2016;63:e202).

[55]Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *Leishmania major* in Israel and against *Leishmania mexicana* and *Leishmania (Viannia) braziliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al. *Am J Trop Med Hyg.* 2001;65:466). Methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

[56]Mucosal infection is most commonly due to the New World species *Leishmania (Viannia) braziliensis, Leishmania (Viannia) panamensis,* or *Leishmania (Viannia) guyanensis.* Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[57]Yoon KS, et al. *Arch Dermatol.* 2003;139:994.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	0.5% Ivermectin lotion (Sklice)	Topically, once	Topically once, approved for ≥6 mo
or	0.9% Spinosad suspension (Natroba)	Topically once, second dose in 1 wk if live adult lice seen	Topically once, second dose in 1 wk if live adult lice seen, approved for ≥6 mo
or	Ivermectin[7,59]	200-400 µg/kg PO 2×, 1 wk apart	<15 kg: not indicated
			15 kg: see adult dosing
or	5% Benzyl alcohol lotion (Ulesfia)	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart
LICE (PUBIC) INFESTATION *(PHTHIRUS PUBIS)*[60]			
Drugs of choice:	1% Permethrin (Nix) (OTC)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for ≥2 mo
or	Pyrethrins with piperonyl butoxide (A-200, Proto, R&C, Rid, Triple X) (OTC)[53]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for ≥2 yr
or	0.5% Malathion (Ovide)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for ≥6 yr
or	0.5% Ivermectin lotion (Sklice)	Topically, once	Topically once, approved for ≥6 mo
or	Ivermectin[7,59]	200-400 µg/kg PO 2×, 1 wk apart	<15 kg: not indicated
			≥15 kg: see adult dosing
LOA LOA, SEE FILARIASIS			
MALARIA (*PLASMODIUM FALCIPARUM, PLASMODIUM OVALE, PLASMODIUM VIVAX*, AND *PLASMODIUM MALARIAE*) – TREATMENT			
Uncomplicated infection due to P. falciparum or species not identified acquired in areas of chloroquine resistance or unknown resistance[61]			
Drugs of choice:[62]	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily or 2 adult tabs PO bid × 3 days[64]	<5 kg: not indicated
			5-8 kg: 2 pediatric tabs PO daily × 3 days
			9-10 kg: 3 pediatric tabs PO daily × 3 days
			11-20 kg: 1 adult tab PO daily × 3 days
			21-30 kg: 2 adult tabs PO daily × 3 days
			31-40 kg: 3 adult tabs PO daily × 3 days
			>40 kg: 4 adult tabs PO daily × 3 days
or	Coartem (artemether/lumefantrine) Fixed dose of 20 mg artemether and 120 mg lumefantrine per tablet	4 tablets per dose. A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. These 6 doses should be administered over 3 days at 0, 8, 24, 36, 48, and 60 hr	5 to <15 kg: 1 tablet PO per dose
			15 to <25 kg: 2 tablets PO per dose
			25 to <35 kg: 3 tablets per dose
			≥35 kg: 4 tablets PO per dose

[58]A second application is recommended 1 wk later to kill hatching progeny. Lice are increasingly demonstrating resistance to pyrethrins and permethrin (Meinking TL, et al. *Arch Dermatol.* 2002;138:220). Ivermectin lotion 0.5% was approved by the FDA in 2012 for treatment of head lice in persons 6 mo of age and older. It is not ovicidal, but it appears to prevent nymphs from surviving. It is effective in most patients when given as a single application on dry hair without nit combing (www.cdc.gov/parasites/lice/head/treatment.html).

[59]Ivermectin is effective against adult lice but has no effect on nits (Jones KN, et al. *Clin Infect Dis.* 2003;36:1355).

[60]For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; Trimethoprim-sulfamethoxazole (TMP-SMX) has also been used (Meinking TL. *Curr Probl Dermatol.* 1996;24:157). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective, together with permethrin for head lice (Hipolito RB, et al. *Pediatrics.* 2001;107:E30).

[61]Chloroquine-resistant *Plasmodium falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger C, et al. *Trans R Soc Trop Med Hyg.* 1994;88:213; Karbwang J, et al. *Trans R Soc Trop Med Hyg.* 1995;89:296).

[62]Uncomplicated or mild malaria may be treated with oral drugs.

[63]To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown, and use is generally not recommended. In a few small studies, outcomes were normal in women treated with the combination in the second and third trimesters (Paternak B, et al. *Arch Intern Med.* 2011;171:259; Boggild AK, et al. *Am J Trop Med Hyg.* 2007;76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in *Plasmodium falciparum* in Africa, but *Medical Letter* consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (Schwartz E, et al. *Clin Infect Dis.* 2003;37:450; Farnert A, et al. *BMJ.* 2003;326:628; Kuhn S, et al. *Am J Trop Med Hyg.* 2005;72:407; Happi C, et al. *Malar J.* 2006;5:82).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate	542 mg base (650 mg salt) PO tid × 3-7 days[64]	8.3 mg base/kg (10 mg salt/kg) PO tid × 3-7 days[65]
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,17]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,66]	20 mg/kg/day PO in 3 divided doses × 7 days[67]	20 mg/kg/day PO in 3 doses × 7 days
Alternative:	Mefloquine[68,69]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
Uncomplicated infection due to P. falciparum or species not identified acquired in areas of chloroquine sensitivity or uncomplicated P. malariae or P. knowlesi			
Drug of choice:	Chloroquine phosphate (Aralen)	600 mg base (1,000 mg salt) PO, then 300 mg base (500 mg salt) PO at 6, 24, and 48 hr	10 mg base/kg (16.7 mg salt/kg) PO, then 5 mg base/kg (8.3 mg salt/kg) PO at 6, 24, and 48 hr
or	Hydroxychloroquine (Plaquenil)[70]	620 mg base (800 mg salt) PO, then 310 mg base (400 mg salt) PO at 6, 24, and 48 hr	10 mg base/kg (12.9 mg salt/kg) PO, then 5 5 mg base/kg (6.5 mg salt/kg) PO at 6, 24, and 48 hr
or	Artemether-lumefantrine (Coartem)10 (1 tab: 20 mg artemether / 120 mg lumefantrine)	Adults: 4 tabs PO per dose Three-day course: day 1: initial dose and second dose 8 hr later; days 2 and 3: 1 dose bid	5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: day 1: initial dose and second dose 8 hr later; days 2 and 3: 1 dose bid
Uncomplicated infection with P. vivax acquired in areas of chloroquine resistance[71]			
Drugs of choice:	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily × 3 days	<5 kg: not indicated
			5-8 kg: 2 pediatric tabs PO daily × 3 days
			9-10 kg: 3 pediatric tabs PO daily × 3 days
			11-20 kg: 1 adult tab PO daily × 3 days
			21-30 kg: 2 adult tabs PO daily × 3 days
			31-40 kg: 3 adult tabs PO daily × 3 days
			>40 kg: 4 adult tabs PO daily × 3 days
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Quinine sulfate	542 mg base (650 mg salt) PO tid × 3-7 days[64]	8.3 mg base/kg (10 mg salt/kg) PO tid × 3-7 days[58]
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,17]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,66]	20 mg/kg/day PO in 3 divided doses × 7 days[67]	20 mg/kg/day PO in 3 doses × 7 days
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days

[64]Although approved for once-daily dosing, *Medical Letter* consultants usually divide the dose into 2 doses to decrease nausea and vomiting.

[65]In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

[66]For use in pregnancy.

[67]Lell B, et al. *Antimicrob Agents Chemother*. 2002;46:2315.

[68]At this dosage, adverse effects, including nausea, vomiting, diarrhea, dizziness, a disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option, because of an increased risk for stillbirth (Nosten F, et al. *Clin Infect Dis*. 1999;28:808). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β-blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[69]*Plasmodium falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[70]If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

[71]*Plasmodium vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

[72]Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy. For those with intermediate G6PD deficiency, weekly primaquine may be used (45 mg/wk) for 8 wk with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) PO weekly for 1 yr for acute infection to prevent relapses.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Artemether-lumefantrine (1 tab: 20 mg artemether/120 mg lumefantrine) Weight-based treatment schedule for both adult and pediatric patients. Patients take initial dose, followed by a second dose 8 hr later, then 1 dose twice a day for the next 2 days (total of 6 oral doses over 3 days)		5 kg to <15 kg: 1 tablet per dose 15 kg to <25 kg: 2 tablets per dose 25 kg to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose Not recommended for people taking mefloquine prophylaxis or for children weighing <5 kg, or people breastfeeding infants weighing <5 kg
or	Mefloquine[68]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
Uncomplicated infection with P. ovale and P. vivax acquired in areas without chloroquine resistance[71]			
Drug of choice:	Chloroquine phosphate (Aralen)	600 mg base (1,000 mg salt) PO, then 300 mg base (500 mg salt) PO at 6, 24, and 48 hr	10 mg base/kg (16.7 mg salt/kg) PO, then 5 mg base/kg (8.3 mg salt/kg) PO at 6, 24, and 48 hr
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Hydroxychloroquine (Plaquenil)[70]	620 mg base PO, then 310 mg base PO at 6, 24, and 48 hr	10 mg/kg base PO, then 5 mg/kg base PO at 6, 24, and 48 hr
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Tafenoquine (Krintafel)[73]	300 mg PO × 1 dose	>16 yr: see adult dosing
Severe malaria due to all Plasmodium spp.			
Drugs of choice:[74]	Artesunate[28,75]	2.4 mg/kg/dose IV × 3 days, at 0, 12, and 24 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, and 24 hr
	Followed by: • Artemether/lumefantrine (preferred), *or* • Atovaquone-proguanil, *or* • Quinine *plus* doxycycline *or* clindamycin, *or* • Mefloquine (only if no other options available)	Dosing as above	Dosing as above
Alternative:	Coartem (Artemether/lumefantrine) Fixed dose of 20 mg artemether and 120 mg lumefantrine per tablet (preferred)	4 tablets per dose. A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. These 6 doses should be administered over 3 days at 0, 8, 24, 36, 48, and 60 hr	5 to <15 kg: 1 tablet PO per dose 15 to <25 kg: 2 tablets PO per dose 25 to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
or	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO daily × 3 days 9-10 kg: 3 pediatric tabs PO daily × 3 days 11-20 kg: 1 adult tab PO daily × 3 days 21-30 kg: 2 adult tabs PO daily × 3 days 31-40 kg: 3 adult tabs PO daily × 3 days >40 kg: 4 adult tabs PO daily × 3 days

[73]Tafenoquine received regulatory approval in the United States in 2018 for prophylaxis of malaria and radical cure of *Plasmodium vivax*. Tafenoquine is associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Prior to use, quantitative G6PD testing is needed to confirm normal activity.

[74]Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al. *N Engl J Med*. 1989;321:65).

[75]Artesnuate is considered first-line therapy for severe malaria. If not available within 24 hours, contact CDC's Malaria Hotline. To avoid the development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (Nosten F, et al. *Lancet*. 2000;356:297; van Vugt M. *Clin Infect Dis*. 2002;35:1498; Smithuis F, et al. *Trans R Soc Trop Med Hyg*. 2004;98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group. *Lancet*. 2005;366:717; Duffy PE, et al. *Lancet*. 2005;366:1908). If oral therapy is not tolerated, consider administration via nasogastric (NG) tube or after an antiemetic. If parasitemia >1%, continue IV artesunate at the same dose daily up to 6 more days until parasite density ≤1%. When parasite density ≤1%, give complete follow-up on oral regimen as listed earlier. Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (Rogers WO, et al. *Malar J*. 2009;8:10; Dundorp AM, et al. *N Engl J Med*. 2009;361:455).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate	648 mg salt PO tid × 3-7 days[64]	10 mg salt/kg PO tid × 3-7 days[58]
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,17]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,66]	20 mg/kg/day PO in 3 divided doses × 7 days[67]	20 mg/kg/day PO in 3 doses × 7 days
or	Artemether-lumefantrine (1 tab: 20 mg artemether/120 mg lumefantrine) Weight-based treatment schedule for both adult and pediatric patients. Patients take initial dose, followed by a second dose 8 hr later, then 1 dose twice a day for the next 2 days (total of 6 oral doses over 3 days)		5 kg to <15 kg: 1 tablet per dose 15 kg to <25 kg: 2 tablets per dose 25 kg to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose Not recommended for people taking mefloquine prophylaxis or for children weighing <5 kg, or people breastfeeding infants weighing <5 kg
or	Mefloquine[68]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
Prevention of relapses: P. vivax and P. ovale only			
Drug of choice:	Primaquine phosphate[72]	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
or	Tafenoquine (Krintafel)[73]	300 mg PO × 1 dose	>16 yr: see adult dosing
MALARIA – PREVENTION[76]			
Chloroquine-sensitive areas[61]			
Drug of choice	Chloroquine phosphate[77–79]	500 mg salt (300 mg base), PO once/wk beginning 1-2 wk before travel to malarious area and 4 wk after leaving	5 mg/kg base once/wk, up to adult dose of 300 mg base beginning 1-2 wk before travel to malarious area and 4 wk after leaving
or	Hydroxychloroquine (Plaquenil)[70]	400 mg (310 mg base) PO once/wk beginning 1-2 wk before travel to malarious area and 4 wk after leaving	5 mg/kg base once/wk, up to adult dose of 310 mg base beginning 1-2 wk before travel to malarious area and 4 wk after leaving
Chloroquine-resistant areas[61]			
Drug of choice:	Atovaquone/ proguanil[63,78,80]	1 adult tab PO per day beginning 1-2 days before travel to malarious area and 7 days after leaving	11-20 kg: 1 pediatric tab PO/day
			21-30 kg: 2 pediatric tabs PO/day
			31-40 kg: 3 pediatric tabs PO/day
			>40 kg: 1 adult tab PO/day
or	Mefloquine[48,78,79,81]	1 adult tab PO per day beginning 1-2 wk before travel to malarious area and 4 wk after leaving	<9 kg: 5 mg/kg salt once/wk
			9-19 kg: 1/4 tab once/wk
			19-30 kg: 1/2 tab once/wk
			31-45 kg: 3/4 tab once/wk
			>45 kg: 1 tab once/wk

[76]No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett.* 2003;45:41). Malaria in pregnancy is particularly serious for both the pregnant individual and the fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

[77]In pregnancy, chloroquine prophylaxis has been used extensively and safely.

[78]For prevention of attack after departure from areas where *Plasmodium vivax* and *Plasmodium ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote[71].

[79]Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within three doses. Some *Medical Letter* consultants favor starting mefloquine 3 wk before travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than ½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

[80]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In one study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al. *Clin Infect Dis.* 2001;33:1015). The protective efficacy of Malarone against *Plasmodium vivax* is variable, ranging from 84% in Indonesian New Guinea (Ling J, et al. *Clin Infect Dis.* 2002;35:825) to 100% in Colombia (Soto J, et al. *Am J Trop Med Hyg.* 2006;75:430). Some *Medical Letter* consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

[81]Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the second or third trimester of pregnancy and possibly during early pregnancy, as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Doxycycline[7,82]	100 mg PO daily	≥8 yr: 2 mg/kg/day, up to 100 mg/day
or	Tafenoquine (Arakoda)	200 mg once daily for 3 days before travel to a malarious area, then 200 mg weekly while in the malarious area, then 200 mg as a single dose, 7 days after leaving malarious area	No dosing data for children
Alternatives for areas with primarily *P. vivax:*	Primaquine[7,83]	30 mg base PO daily beginning 1-2 days before travel to malarious area and 7-14 days after leaving	0.5 mg/kg base (max 30 mg) daily beginning 1-2 days before travel to malarious area and 7-14 days after leaving
MALARIA – PRESUMPTIVE SELF-TREATMENT[84]			
Drugs of choice:	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily × 3 days	<5 kg: not indicated
			5-8 kg: 2 pediatric tabs PO daily × 3 days
			9-10 kg: 3 pediatric tabs PO daily × 3 days
			11-20 kg: 1 adult tab PO daily × 3 days
			21-30 kg: 2 adult tabs PO daily × 3 days
			31-40 kg: 3 adult tabs PO daily × 3 days
			>40 kg: 4 adult tabs PO daily × 3 days
or	Quinine sulfate[64]	648 mg salt PO tid × 3-7 days	10 mg salt/kg PO tid × 3-7 days
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 divided doses × 7 days
or	Mefloquine[68,69]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
MICROSPORIDIOSIS			
Ocular (Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])			
Drug of choice:	Albendazole[7,85]	400 mg PO bid	<10 kg/2 yr: 15 mg/kg/day in 2 doses[12] ≥2 yr: see adult dosing
	plus fumagillin[86]	Topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve concentration of 70 mg/mL of fumagillin) 2 drops per eye every 2 hr for 4 days, then 2 drops qid	
Intestinal (Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)			
E. bieneusi[87]			
Drug of choice:	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
Alternatives:	Nitazoxanide[5,7]	1000 mg PO bid × 3 days	
E. intestinalis			
Drug of choice	Albendazole[7,85]	400 mg PO bid × 21 days	<10 kg/2 yr 15 mg/kg/day in 2 doses:[12]
			≥2 yr: see adult dosing
Disseminated (E. hellem, E. cuniculi, E. intestinalis, Pleistophora sp., Trachipleistophora sp., and Brachiola vesicularum)			
Drug of choice[88]	Albendazole[7,85]	400 mg PO bid	<10 kg/2 yr[12]
			≥2 yr: see adult dosing

[82]Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause GI disturbances, vaginal moniliasis, and photosensitivity reactions.

[83]Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malarious area provides effective prophylaxis against chloroquine-resistant *Plasmodium falciparum* (Baird JK, et al. *Clin Infect Dis.* 2003;37:1659). Some studies have shown less efficacy against *Plasmodium vivax.* Nausea and abdominal pain can be diminished by taking with food.

[84]A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

[85]For HIV-infected patients, continue until resolution of ocular symptoms and until CD4 count >200 cells/μL for >6 mo after initiation of antiretroviral therapy.

[86]Ocular lesions caused by *Encephalitozoon hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC. *Am J Ophthalmol.* 1993;115:293), available from Leiter's Park Avenue Pharmacy (San Jose, CA; 1-800-292-6773; www.leiterrx.com). For lesions caused by *Vittaforma corneae,* topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al. *Ophthalmology.* 1990;97:953).

[87]Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *Enterocytozoon. bieneusi* (Molina J-M, et al. *N Engl J Med.* 2002;346:1963), but it has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, et al. *MMWR Recomm Rep.* 2004;53([RR-15]:1). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

[88]Molina J-M, et al. *J Infect Dis.* 1995;171:245. There is no established treatment for *Pleistophora.* For disseminated disease caused by *Trachipleistophora* or *Brachiola,* itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al. *N Engl J Med.* 2004;351:42).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
MITES, SEE SCABIES			
MONILIFORMIS MONILIFORMIS INFECTION			
Drug of choice:	Pyrantel pamoate (OTC)[7]	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
NAEGLERIA SPECIES, SEE AMEBIC MENINGOENCEPHALITIS, PRIMARY			
NECATOR AMERICANUS, SEE HOOKWORM INFECTION			
OESOPHAGOSTOMUM BIFURCUM			
Drug of choice:	See footnote[89]		
ONCHOCERCA VOLVULUS, SEE FILARIASIS			
OPISTHORCHIS VIVERRINI, SEE FLUKE INFECTION			
PARAGONIMUS WESTERMANI, SEE FLUKE INFECTION			
PEDICULUS CAPITIS, PEDICULUS HUMANUS, PHTHIRUS PUBIS, SEE LICE			
PINWORM, SEE ENTEROBIUS			
PNEUMOCYSTIS JIROVECII (FORMERLY *PNEUMOCYSTIS CARINII*) PNEUMONIA (PCP)[90]			
Moderate to severe disease			
Drug of choice:	TMP-SMX	15-20 mg/kg/day TMP component IV in 3-4 divided doses × 21 days (change to PO after clinical improvement)	15-20 mg/kg/day TMP component IV in 3-4 divided doses × 21 days (change to PO after clinical improvement)
Alternatives:	Pentamidine	3-4 mg IV daily × 21 days	3-4 mg IV daily × 21 days
or	Primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO (max 30 mg) daily × 21 days
	plus clindamycin[7]	600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)
Mild to moderate disease			
Drug of choice:	TMP-SMX	320 mg/1600 mg (2 DS tablets) PO tid × 21 days	TMP 15-20 mg/kg/day PO in 3 or 4 doses × 21 days
Alternative:	Dapsone	100 mg PO daily × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days
	plus trimethoprim	15 mg/kg/day PO in 3 doses	15 mg/kg/day PO in 3 doses
or	primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO daily (max 30 mg) × 21 days
	plus clindamycin	300-450 mg PO tid or qid × 21 days	10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days
or	atovaquone	750 mg PO bid × 21 days	1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis[91]			
Drug of choice:	TMP-SMX	1 tab (single strength or greater) PO daily or 1 DS tab PO 3 days/wk	TMP 150 mg/m^2 in 1-2 doses daily or on 3 consecutive days/wk
Alternatives:[91]	Dapsone[7]	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone[7]	50 mg PO daily or 200 mg PO each wk	
	plus pyrimethamine[92]	50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via Respirgard II nebulizer	≥5 yr: 300 mg inhaled monthly via Respirgard II nebulizer
or	Atovaquone[7]	1,500 mg/day PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO
			4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days
			>24 mo: 30 mg/kg/day PO in 2 doses × 21 days

[89]Albendazole or pyrantel pamoate may be effective (Ziem JB, et al. *Ann Trop Med Parasitol*. 2004;98:385).
[90]*Pneumocystis* has been reclassified as a fungus. In severe disease with room air P_{O_2} ≤70 mm Hg or A-a O_2 gradient ≥35 mm Hg, prednisone should also be used (Gagnon S, et al. *N Engl J Med*. 1990;323:1444; Caumes E, et al. *Clin Infect Dis*. 1994;18:319).
[91]Primary/secondary prophylaxis in patients with HIV can be discontinued after the CD4 count increases to >200 × 10^6/L for longer than 3 mo.
[92]Plus leucovorin 25 mg with each dose of pyrimethamine.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ROUNDWORM, SEE ASCARIASIS			
SAPPINIA DIPLOIDEA, SEE AMEBIC MENINGOENCEPHALITIS, PRIMARY			
SCABIES (*SARCOPTES SCABIEI*)			
Drug of choice:	5% Permethrin[93]	Topically, 2× at least 1 wk apart	Topically 2×, 1 wk apart, approved for ≥ 2 mo
Alternatives:[93]	Ivermectin[7,93,94]	200 µg/kg PO × 2 at least 1 wk apart	<15 kg: not indicated
			≥15 kg: see adult dosing
	10% Crotamiton	Topically overnight on days 1, 2, 3, and 8	Topically overnight on days 1, 2, 3, and 8
SCHISTOSOMIASIS (BILHARZIASIS)			
Schistosoma haematobium or Schistosoma intercalatum			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day[37]
Schistosoma japonicum or Schistosoma mekongi			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day[37]
Schistosoma mansoni			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day[37]
Alternative:	Oxamniquine[95,96]	15 mg/kg PO once	20 mg/kg/day PO in 2 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
Strongyloidiasis (Strongyloides stercoralis)			
Drug of choice:[97]	Ivermectin	200 µg/kg/day PO × 2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Alternative:	Albendazole[7,98]	400 mg PO bid × 7 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
TAPEWORM INFECTION			
Adult (intestinal stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)			
Drug of choice:	Praziquantel[7]	5-10 mg/kg PO once	5-10 mg/kg PO once[37]
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
Hymenolepis nana (dwarf tapeworm)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO once	25 mg/kg PO once[37]
Alternative:	Niclosamide[99]	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1 then 500 mg/day PO × 6 days
			>34 kg: 1.5 g PO on day 1 then 1 g/day PO × 6 days
Larval (tissue stage)			
Echinococcus granulosus (hydatid disease cystic echinococcosis)			
Drug of choice:[100]	Albendazole[7]	400 mg PO bid × 1-6 mo	<10 kg/2 yr: 10-15 mg/kg/day (max 800 mg/day) PO, in 2 doses[12]
			≥2 yr: 15 mg/kg/day PO (max 400 mg) × 1-6 mo

[93]In some cases, treatment may need to be repeated in 10-14 days (Currie BJ, et al. *N Engl J Med*. 2010;362:717). A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (Usha V, et al. *J Am Acad Dermatol*. 2000;42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P. *Curr Opin Infect Dis*. 2004;15:123).

[94]Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P. *Curr Opin Infect Dis*. 2004;15:123). The safety of oral ivermectin in pregnancy and young children has not been well studied. Ivermectin is included on the KIDS list (Meyers RS, et al. *J Pediatr Pharmacol Ther*. 2020;25:175) due to concerns about encephalopathy, but more recent studies suggest that it may be used safely (Levy M, et al. *Br J Dermatol*. 2020;182:1003).

[95]Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al. *J Infect Dis*. 1997;176:304). Oxamniquine is contraindicated in pregnancy.

[96]In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC. *Drugs*. 1991;42:379).

[97]In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al. *Lancet*. 2000;355:43; Orem J, et al. *Clin Infect Dis*. 2003;37:152; Tarr PE. *Am J Trop Med Hyg*. 2003;68:453).

[98]Albendazole must be taken with food; a fatty meal increases oral bioavailability.

[99]Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (Juan JO, et al. *Trans R Soc Trop Med Hyg*. 2002;96:193; Chero JC, et al. *Trans R Soc Trop Med Hyg*. 2007;101:203; Diaz E, et al. *Am J Trop Med Hyg*. 2003;68:384).

[100]Optimal treatment depends on multiple factors, including size, location, and number of cysts and presence of complications. In some patients, medical therapy alone is preferred, but some patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Puncture aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al. *Clin Infect Dis*. 2003;37:1073).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Echinococcus multilocularis (alveolar echinococcosis)			
Treatment of choice:	See footnote[101]		
Neurocysticerosis			
Taenia solium (pork)			
		1-2 viable parenchymal cysticerci[115]	
Treatment of choice:[102,115]	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	<10 kg/2 yr: 15 mg/kg/day PO in 2 doses (max dose 1200 mg/day) for 10-14 days with food
			≥2 yr: 15 mg/kg/day PO in 2 doses (max 1200 mg/day) for 10-14 days with food
		>2 viable parenchymal cysticerci[115]	
	Albendazole plus praziquantel	—	15 mg/kg/day for 10-14 days 50 mg/kg/day for 10-14 days
		Single enhancing lesions (SELs) from cysticercosis[115]	
	Albendazole	—	15 mg/kg/day bid with meals for 1–2 weeks
		Single enhancing lesions (SELs) from cysticercosis[115]	
	Albendazole	—	15 mg/kg/day bid with meals for 1–2 weeks
		Calcified parenchymal lesions[115]	
		Symptomatic therapy alone	
	plus steroids		
or	Surgical removal		

[101]Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases, the use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P. *Curr Opin Infect Dis.* 2003;16:437). Medical treatment is prolonged up to 2 yr or more.

[102]Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JH. *N Engl J Med.* 2004;350:215). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al. *N Engl J Med.* 2004;350:249). Some recent studies have shown improved outcomes with combination albendazole and praziquantel (Garcia HH, et al. *Lancet Infect Dis.* 2014;14:687). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al. *N Engl J Med.* 2001;345:879). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White AC Jr. *Annu Rev Med.* 2000;51:187). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

[115]For patients with *1-2 viable parenchymal cysticerci*, albendazole monotherapy for 10-14 days compared to either no antiparasitic therapy (strong, high) or combination antiparasitic therapy (weak, moderate). We recommend albendazole (15 mg/kg/day) combined with praziquantel (50 mg/kg/day) for 10–14 days rather than albendazole monotherapy for patients with *>2 viable parenchymal cysticerci* (strong, moderate). We suggest retreatment with antiparasitic therapy for parenchymal cystic lesions persisting for 6 months after the end of the initial course of therapy (weak, low). We suggest albendazole therapy rather than no antiparasitic therapy for all patients with SELs (weak, moderate). Remarks: albendazole (15 mg/kg/day in twice-daily doses up for 1–2 weeks) should be given with meals. We recommend symptomatic therapy alone instead of antiparasitic drugs in patients with calcified parenchymal lesions (strong, moderate). (Infectious Diseases Society of America [IDSA] and the American Society of Tropical Medicine and Hygiene [ASTMH]. Diagnosis and treatment of neurocysticercosis: 2017 Clinical Practice Guidelines by the CID. Published 2/22/2018. *Clin Infect Dis* 2018;66(8):e49–e75.)

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
TOXOCARIASIS, SEE VISCERAL LARVA MIGRANS			
TOXOPLASMOSIS (*TOXOPLASMA GONDII*)[103] (ACQUIRED OR OCULAR INFECTION)			
Drugs of choice:[104,105]	Pyrimethamine[106]	Dosage is adjusted for weight, but 50 mg PO bid on days 1 and 2, then 50 mg qd is maximum. Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336	1 mg/kg (max 50 mg) bid × 2 days, then 1 mg/kg qd (max 50 mg). Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336[107] Calcium leucovorin is always given with pyrimethamine and in the week after discontinuing Please see formulation and instructions for infants in Chapter 336 In the United States pyrimethamine serum levels can be measured at NMS Laboratories in Philadelphia Pyrimethamine cannot be given in the first trimester of pregnancy
	plus sulfadiazine	1.5 g PO bid is a standard dose for a 100-lb person, maximum 2 g PO bid. Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336.	1.5 g PO bid is a standard dose for a 100-lb person, maximum 2 g PO bid. Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336 This is used with pyrimethamine for synergy
Alternative for sulfadiazine or for suppression/ prophylaxis	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 double-strength tablet daily. *Alternative dosing*: one double-strength tablet 3 times weekly. *Adult alternative regimen:* Trimethoprim-sulfamethoxazole (TMP-SMX) – 5 mg/kg trimethoprim and 25 mg/kg sulfamethoxazole given PO or IV bid Clindamycin (600 mg IV or PO 4 times daily) plus oral pyrimethamine (200 mg loading dose followed by 50 mg daily among patients <60 kg or 75 mg daily among patients ≥60 kg) plus oral leucovorin (10 to 25 mg daily).	TMP-SMX 150/750 mg/m^2 body surface area once daily PO
TRICHINELLOSIS (*TRICHINELLA SPIRALIS*)			
Drugs of choice:	Steroids for severe symptoms	Prednisone 30-60 mg PO daily × 10-15 days	
	plus Albendazole[7]	400 mg PO bid × 8-14 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Alternative:	Mebendazole[7]	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days[13]
TRICHOMONIASIS (*TRICHOMONAS VAGINALIS*)			
Drug of choice:[108]	Metronidazole	2 g PO once or 500 mg PO bid × 7 days	15 mg/kg/day PO in 3 doses × 7 days
or	Tinidazole[4]	2 g PO once	50 mg/kg PO once (max 2 g)
TRICHOSTRONGYLUS INFECTION			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole[7]	100 mg PO bid × 3 days	100 mg PO bid × 3 days[13]
or	Albendazole[7]	400 mg PO once	<10 kg/2 yr[12]
			≥2 yr: 15 mg/kg/day PO (max 800 mg) × 1-6 mo

[103]In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

[104]To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al. *Clin Infect Dis.* 2002;34:1243). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with <100 × 10^6/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to >200 × 10^6/L for more than 3 mo (Benson CA, et al. *MMWR Recomm Rep.* 2004;53([RR-15]:1).

[105]Women who develop toxoplasmosis during the first trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the first trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, et al. *Lancet.* 2004;363:1965). Pyrimethamine is a potential teratogen and should be used only after the first trimester.

[106]Plus leucovorin 10-25 mg with each dose of pyrimethamine.

[107]Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, et al., eds. *Infectious Disease of the Fetus and Newborn Infant.* 5th ed. Philadelphia: WB Saunders; 2001: p. 290).

[108]Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD. *Sex Transm Dis.* 2004;31:343).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
TRICHURIASIS (*TRICHURIS TRICHIURA*, WHIPWORM)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days[13]
Alternative:	Albendazole[7]	400 mg PO × 3 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg PO daily × 3 days	<15 kg: not indicated
			≥15 kg: see adult dosing
TRYPANOSOMIASIS[109]			
Trypanosoma cruzi (American trypanosomiasis, Chagas disease)			
Drug of choice:	Benznidazole[28]	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 5-7.5 mg/kg/day PO in 2 divided doses × 60 days
			>12 yr: see adult dosing
Alternative:	Nifurtimox[28,110]	8-10 mg/kg/day PO in 3-4 doses × 90 days	≤10 yr: 15-20 mg/kg/day PO in 3-4 doses × 90 days
			11-16 yr: 12.5-15 mg/kg/day in 3-4 doses × 90 days
			>16 yr: see adult dosing
Trypanosoma brucei gambiense (West African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice[111]	Pentamidine isethionate[7]	4 mg/kg/day IM × 7-10 days	4 mg/kg/day IM or IV × 7-10 days
Alternative:	Suramin[28]	100 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 7, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Eflornithine[28,112]	100 mg/kg IV qid × 14 days	100 mg/kg IV qid × 14 days
Alternative:	Melarsoprol[28,113]	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days.	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days
Trypanosoma brucei rhodesiense (East African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice:	Suramin[28]	100 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 7, 14, and 21
Late disease with CNS involvement			

[109]Barrett MP, et al. *Lancet*. 2003;362:1469.

[110]The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al. *J Infect Dis*. 1991;163:912).

[111]For treatment of *Trypanosoma brucei gambiense*, pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

[112]Eflornithine is highly effective in *Trypanosoma brucei gambiense* but not against *Trypanosoma brucei rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 days when used in conjunction with nifurtimox at a dose of 5 mg/kg PO tid × 10 days (Priotto G, et al. *Lancet*. 2009;374:56).

[113]In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pépin J, et al. *Trans R Soc Trop Med Hyg*. 1995;89:92). Up to 20% of patients with *Trypanosoma brucei gambiense* fail to respond to melarsoprol (Barrett MP. *Lancet*. 1999;353:1113). Consultation with experts at the CDC is recommended.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Drug of choice:	Melarsoprol[28,112]	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days
VISCERAL LARVA MIGRANS (TOXOCARIASIS)[114]			
Drugs of choice:	Albendazole[7]	400 mg PO bid × 5 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Mebendazole[7]	100-200 mg PO bid × 5 days	100-200 mg PO bid × 5 days[13]
WHIPWORM, SEE TRICHURIASIS			
WUCHERERIA BANCROFTI, SEE FILARIASIS			

[114]Optimum duration of therapy is not known; some consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.
bid, Twice a day; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DEC, diethylcarbamazine; DS, double strength; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; IDSA, Infectious Disease Society of America; IM, intramuscularly; IND, investigational new drugs; IV, intravenously; OTC, over the counter; PO, by mouth; qd, once a day; qid, four times a day; tid, three times a day; WHO, World Health Organization.
Adapted from Drugs for parasitic infection. *Med Lett.* 2013;11(Suppl):e1–e23. Available at http://www.medicalletter.org

drug approved for use by the FDA for patients ≥5 kg. It is a fixed-dose combination of two novel antimalarials, artemether (20 mg) and lumefantrine (120 mg). It is a highly effective 3-day malaria treatment, with cure rates of >96%, even in areas of multidrug resistance. It can be used to treat chloroquine-resistant uncomplicated malaria during the second and third trimesters of pregnancy and as an alternative agent in the first trimester. Artesunate was approved by the FDA for intravenous (IV) treatment for severe malaria in 2020.

SELECTED ANTIPARASITIC DRUGS FOR HELMINTHS AND ECTOPARASITES

Albendazole (Albenza)

Albendazole is a benzimidazole carbamate structurally related to mebendazole and has similar anthelmintic activity. Its absorption from the gastrointestinal tract is poor but improved with a concomitant high-fat meal. Albendazole sulfoxide, the principal metabolite with anthelmintic activity, has a plasma half-life of 8.5 hours. It is widely distributed in the body, including the bile and cerebrospinal fluid. It is eliminated in bile. Albendazole is FDA approved for treatment of two cestode (tapeworm) infections: neurocysticercosis and hydatid diseases *(Echinococcus granulosus).* It is used off-label for numerous other **helminth** infections, including cutaneous larva migrans *(Ancylostoma caninum* and *Ancylostoma braziliense),* ascariasis *(Ascaris lumbricoides),* liver flukes *(Clonorchis sinensis* and *Opisthorchis viverrini),* pinworm *(Enterobius vermicularis),* lymphatic filariasis *(Wuchereria bancrofti, Brugia malayi, Brugia timori),* gnathostomiasis (*Gnathostoma* spp.), hookworms *(Ancylostoma duodenale* and *Necator americanus),* microsporidiosis, trichinellosis *(Trichinella spiralis),* and visceral larva migrans *(Toxocara canis* and *Toxocara cati).* Albendazole is generally well tolerated. Common adverse effects include headache, nausea, vomiting, and abdominal pain. Serious adverse effects include elevated liver enzymes and leukopenia, which have occurred in a few patients with treatment of hydatid disease. Rare adverse effects include acute renal failure, pancytopenia, granulocytopenia, and thrombocytopenia. Despite the fact that albendazole and other antiparasitic drugs, including mebendazole, praziquantel, and pyrimethamine, have been in use for decades, the number of manufacturers is small and costs have risen in recent years. Data are limited in pregnancy, and treatment during pregnancy generally deferred if possible. Albendazole is excreted in breast milk but is generally considered compatible with breastfeeding by the WHO.

Ivermectin (Stromectol, Mectizan)

Ivermectin is a semisynthetic derivative of one of the avermectins, which is a group of macrocyclic lactones produced by *Streptomyces avermitilis.* After oral administration, ivermectin has peak plasma concentrations after approximately 4 hours and a plasma elimination half-life of approximately 12 hours. It is excreted as metabolites over a 2-week period via feces. It is FDA approved for treatment of two nematode (roundworm) infections: onchocerciasis (*Onchocerca volvulus)* and strongyloidiasis *(Strongyloides stercoralis).* It may have some effect in treating a broad range of other **helminths** and **ectoparasites,** including cutaneous larva migrans *(Ancylostoma braziliense),* ascariasis *(Ascaris lumbricoides),* loiasis, pinworm *(Enterobius vermicularis),* whipworm *(Trichuris trichiura),* gnathostomiasis *(Gnathostoma spinigerum), Mansonella* infections, lice *(Pediculus humanus* and *Phthirus pubis),* mites (*Demodex* spp.), and scabies *(Sarcoptes scabiei).* Combination therapies of ivermectin with albendazole or diethylcarbamazine are being used to treat lymphatic filariasis. Combination therapy with albendazole and the off-label use of veterinary injectable formulations have been used to treat complicated *Strongyloides* infections, including disseminated disease and hyperinfection syndrome. Though there has been significant public interest in ivermectin as a treatment for SARS-CoV-2, clinical studies have not shown efficacy. Common adverse events include dizziness, headache, pruritus, and gastrointestinal effects. Serious adverse events include encephalopathy due to pathogenic variants in the *ABCB1* transporter and **Mazzotti reactions** in patients with onchocerciasis, including arthralgia, synovitis, enlarged lymph nodes, rash, and fever secondary to microfilaria death. A topical formulation is available for treatment of head lice, which are increasingly becoming very resistant to over-the-counter medications such as permethrins. Data are limited in pregnancy, and other agents are preferred if available for a given condition. Ivermectin is excreted in breast milk, and decisions to use this medication while breastfeeding should consider the risks and benefits of therapy based on the specific indication.

Praziquantel (Biltricide)

Praziquantel achieves its antiparasitic activity via the pyrazino isoquinoline ring system and was originally synthesized as a potential tranquilizer. After oral administration, praziquantel is rapidly absorbed, with peak levels in 1-2 hours and a plasma half-life of about 1-3 hours. Elimination via the urine and feces is >80% complete after 24 hours. Praziquantel is metabolized in the liver by the microsomal cytochrome P450 (especially 2B1 and 3A). Bioavailability of praziquantel is increased with concomitant administration of agents that inhibit cytochrome P450. Praziquantel is FDA approved for treatment of several species of trematodes (flatworms) including the Chinese liver fluke *(Clonorchis sinensis),* Southeast Asian liver fluke *(Opisthorchis viverrini),* and schistosomiasis (*Schistosoma* spp.). It is used off-label for treatment of additional trematode pathogens, including the North American liver fluke *(Metorchis conjunctus), Nanophyetus salmincola,* intestinal flukes *(Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai),* and lung flukes *(Paragonimus westermani, Paragonimus kellicotti).* It is also used off-label for multiple cestode (tapeworm) infections. Adverse effects can be seen in 30–60% of patients, although most are mild and disappear within 24 hours. Common adverse effects include headache, abdominal pain, dizziness, and malaise. Serious but rare adverse effects include arrhythmias, heart block, and convulsions.

Section 15

Protozoan Diseases

Chapter 326

Primary Amebic Meningoencephalitis

Matthew D. Eberly

Naegleria, Acanthamoeba, Balamuthia, and *Sappinia* are small, free-living amebae that cause human amebic meningoencephalitis, which has two distinct clinical presentations. The more common is an acute, fulminant, and usually fatal **primary amebic meningoencephalitis** caused by *Naegleria fowleri* that occurs in previously healthy children and young adults. **Granulomatous amebic meningoencephalitis,** which is caused by *Acanthamoeba, Balamuthia,* and *Sappinia,* is a more indolent infection that typically occurs in immunocompromised hosts and may also present with a disseminated form of the disease.

ETIOLOGY

Naegleria is an ameboflagellate that can exist as cyst, trophozoite, and transient flagellate forms. Temperature and environmental nutrient and ion concentrations are the major factors that determine the stage of the ameba. Trophozoites are the only stages that are invasive, although cysts are potentially infective because they can convert to the vegetative form very quickly under the proper environmental stimuli. Although there are over 40 species of *Naegleria,* only *Naegleria fowleri* has been shown to be pathogenic for humans.

Acanthamoeba exists in cyst and motile trophozoite forms; only the trophozoite form is invasive. Cases of *Acanthamoeba* **keratitis** usually follow incidents of trivial corneal trauma followed by flushing with contaminated tap water. Infections can also occur among contact lens wearers who come into contact with contaminated water during swimming or use contact lenses cleaned or stored in contaminated tap water. Granulomatous amebic encephalitis from *Acanthamoeba* occurs worldwide and is associated with an immunocompromising condition such as HIV infection, diabetes mellitus, chronic liver disease, renal failure, immunosuppressive therapy, or radiation therapy.

Balamuthia mandrillaris has been implicated as an etiology of granulomatous amebic encephalitis. Although the clinical presentation is similar to infection with *Acanthamoeba,* most patients are not immunocompromised.

Other free-living amebae can also cause infection, as illustrated by a case report of *Sappinia pedata* granulomatous encephalitis.

EPIDEMIOLOGY

The free-living amebae have a worldwide distribution. *Naegleria* species have been isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies, hot springs and spas, thermal discharge of power plants, groundwater, and, occasionally, from the nasal passages of healthy children. *Acanthamoeba* species have been isolated from soil, mushrooms, vegetables, brackish water, and seawater, as well as most of the freshwater sources for *Naegleria.* It can also be found in tap water because chlorination does not kill *Acanthamoeba. Balamuthia* is present in soil and may be transmitted by inhalation or contamination of preexisting skin lesions.

Naegleria meningoencephalitis has been reported from every continent except Antarctica. Most of the cases occur during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater lakes and rivers before their illness. Between 1962 and 2022, 157 cases of primary amebic meningoencephalitis (PAM) were reported in the United States. Most of the reports have come from the southern and southwestern states, particularly Florida and Texas, but infections have occurred in Kansas, Indiana, and Minnesota. Of note, cases have been linked to sinus irrigation with neti pots containing contaminated tap water; exposure to a lawn water slide, which derived its tap water from a treated public drinking water system; a chlorinated recreational splash pad; a swimming pool supplied by an overland water pipe; and rafting on an artificial whitewater river.

PATHOGENESIS

The free-living amebae enter the nasal cavity by inhalation or aspiration of dust or water contaminated with trophozoites or cysts. *Naegleria* gains access to the central nervous system through the olfactory epithelium and migrates via the olfactory nerve to the olfactory bulbs located in the subarachnoid space and bathed by the cerebrospinal fluid (CSF). This space is richly vascularized and is the route of spread to other areas of the central nervous system. Grossly, there is widespread cerebral edema and hyperemia of the meninges. The olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate. Microscopically, the gray matter is the most severely affected, with severe involvement in all cases. Fibrinopurulent exudate may be found throughout the cerebral hemispheres, brainstem, cerebellum, and upper portions of the spinal cord. Pockets of trophozoites may be seen in necrotic neural tissue, usually in the perivascular spaces of arteries and arterioles.

The route of invasion and penetration in cases of granulomatous amebic meningoencephalitis caused by *Acanthamoeba* and *Balamuthia* may be by direct spread through olfactory epithelium or hematogenous spread from a primary focus in the skin or lungs. Pathologic examination reveals granulomatous encephalitis, with multinucleated giant cells mainly in the posterior fossa structures, basal ganglia, bases of the cerebral hemispheres, and cerebellum. Both trophozoites and cysts may be found in the central nervous system lesions, primarily located in the perivascular spaces and invading blood vessel walls. The olfactory bulbs and spinal cord are usually spared. The single case of *Sappinia* encephalitis followed a sinus infection, and evaluation revealed a solitary 2 cm temporal lobe mass with mild ring enhancement.

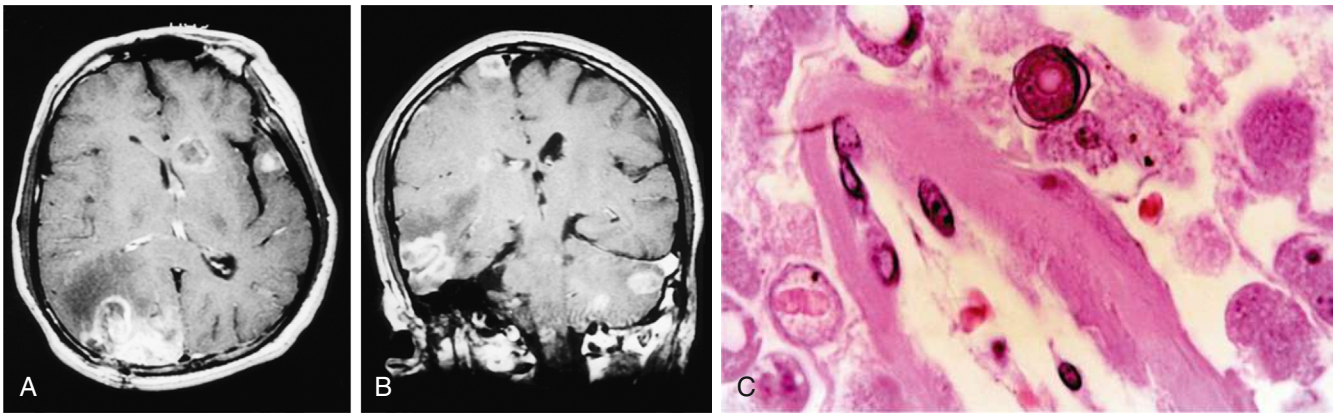

Fig. 326.1 A and B, MRIs of the brain of a patient with *Balamuthia mandrillaris* granulomatous amebic encephalitis. Multiple enhancing lesions are seen in the right hemisphere, left cerebellum, midbrain, and brainstem. C, Photomicrograph of the brain lesion from the same patient showing perivascular amebic trophozoites. A round amebic cyst with a characteristic double wall is seen in the top center (hematoxylin and eosin, original magnification ×100). *(From Deol I, Robledo L, Meza A, et al. Encephalitis due to a free-living amoeba [Balamuthia mandrillaris]: case report with literature review. Surg Neurol. 2000;53:611–616.)*

CLINICAL MANIFESTATIONS

The incubation period of ***Naegleria* infection** may be as short as 2 days or as long as 15 days. Symptoms have an acute onset and progress rapidly. Infection is characterized by a sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, followed by altered mental status, nuchal rigidity, photophobia, confusion, somnolence, seizures, and ultimately coma. Most cases end in death within 3-10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis may occur weeks to months after the initial infection. The presenting signs and symptoms are often those of single or multiple central nervous system space-occupying lesions and include hemiparesis, ataxia, personality changes, seizures, and drowsiness. Altered mental status is often a prominent symptom. Headache and fever occur only sporadically, but stiff neck is seen in a majority of cases. Cranial nerve palsies, especially of cranial nerves III and VI, may be present. There is also one report of acute hydrocephalus and fever with *Balamuthia.* Granulomatous amebic meningoencephalitis is usually fatal after 4-6 weeks of illness. Results of neuroimaging studies of the brain usually demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas (Fig. 326.1).

DIAGNOSIS

The CSF in *Naegleria* infection may mimic that of herpes simplex encephalitis early in the disease and that of acute bacterial meningitis later in the disease, with a neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia. *Motile amebae may be visualized on a wet mount of freshly drawn CSF using Wright or Giemsa stains*, but they are often mistaken for lymphocytes or macrophages. Because *Naegleria* are the only amebae that differentiate into the flagellate state in a hypotonic environment, placing a drop of fresh CSF in 1 mL of distilled water and watching for the development of swimming flagellates after 1-2 hours can confirm the diagnosis of *Naegleria. Naegleria* can also be grown on a non-nutrient agar plate coated with *Escherichia coli,* on which they feed. Polymerase chain reaction (PCR) and immunofluorescence assays for *Naegleria* performed on CSF and biopsy material are available through the U.S. Centers for Disease Control and Prevention (CDC).

The diagnosis of granulomatous amebic meningoencephalitis relies on the isolation or histologic identification of *Acanthamoeba* trophozoites or cysts from brain tissue specimens. The CSF findings of granulomatous meningoencephalitis reveal lymphocytic pleocytosis, moderately elevated protein, and low glucose concentrations. However, motile trophozoites of *Acanthamoeba* are more difficult to isolate than *Naegleria,* and the CSF is typically sterile. *Acanthamoeba* may be cultured from the same agar used for growing *Naegleria,* but *Balamuthia* must be grown on mammalian cell cultures. Pediatric cases of *Balamuthia* meningoencephalitis have been diagnosed antemortem by brain biopsy as well as postmortem. PCR and immunofluorescence assays can be used on specimens to identify *Acanthamoeba* and *Balamuthia* species, and are also available from the CDC.

TREATMENT

Naegleria infection is nearly always fatal, but early recognition and treatment are crucial to survival. Until 2013, there had been only two known survivors in North America, with treatment regimens of amphotericin B, either alone or in combination with other agents such as rifampin, chloramphenicol, fluconazole, ketoconazole, and dexamethasone. In 2013, however, the CDC made available the antileishmanial drug **miltefosine** for the treatment of primary amebic meningoencephalitis. That summer, two children who contracted *Naegleria* both survived; both patients received oral miltefosine as part of their treatment, and one underwent external ventricular drain placement and therapeutic hypothermia. Miltefosine is now commercially available in the United States (www.impavido.com). **The recommended drug treatment for primary amebic meningoencephalitis by the CDC includes intravenous and intrathecal amphotericin B, oral miltefosine, along with azithromycin, fluconazole, rifampin, and dexamethasone**. Early identification, early initiation of combination therapy, and aggressive management of increased intracranial pressure remain key elements for a successful outcome. For suspected cases, clinicians should contact the CDC Emergency Operations Center at (770) 488-7100 for assistance.

The optimal therapy for granulomatous amebic meningoencephalitis is uncertain. However, miltefosine has likewise been used to successfully treat patients with *Balamuthia* and disseminated *Acanthamoeba* infections. Strains of *Acanthamoeba* isolated from fatal cases are usually susceptible in vitro to pentamidine, ketoconazole, and flucytosine and less so to amphotericin B. One patient was successfully treated with sulfadiazine and fluconazole, and another was successfully treated with intravenous pentamidine followed by oral itraconazole. *Acanthamoeba* keratitis responds to long courses of topical propamidine–polymyxin B sulfate or topical polyhexamethylene biguanide or chlorhexidine gluconate, and antifungal azoles plus topical steroids. Limited success has been demonstrated in *Balamuthia* infection with systemic azole therapy combined with flucytosine. More recently, the combination of flucytosine, pentamidine, fluconazole, sulfadiazine, azithromycin, and phenothiazines resulted in the survival of two patients with *Balamuthia* meningoencephalitis, although both were left with mild neuromotor and cognitive impairment. Corticosteroids before initiating effective therapy appear to have a detrimental effect, contributing to rapid progression of disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 327

Amebiasis

Edsel Maurice T. Salvana and Robert A. Salata

Entamoeba species infect or colonize up to 10% of the world's population, with a disproportionate burden of illness in resource-limited settings. In most infected individuals, *Entamoeba histolytica* or a related species infects the lumen of the gastrointestinal tract and causes few symptoms or sequelae. Although *E. histolytica* is the only confirmed invasive species, other *Entamoeba* species have been implicated in human disease. Molecular epidemiology is helping detail the role that these diverse protozoans play in human health. Invasive *E. histolytica* infection can lead to **amebic colitis, amebic liver abscess,** and, less commonly, abscesses in other extraintestinal sites.

ETIOLOGY

Four morphologically identical but genetically distinct species of *Entamoeba* are known to infect humans. *Entamoeba histolytica*, the main pathogenic species, causes a spectrum of disease and can become invasive in 4–10% of infected patients. *Entamoeba dispar,* the most prevalent species, does not cause symptomatic disease. *Entamoeba moshkovskii,* can cause diarrhea in infants and children, and asymptomatic infection with *E. moshkovskii* may be as common as *E. dispar* infection in some communities. Patients previously described as asymptomatic carriers of *E. histolytica* based on microscopy findings were likely harboring *E. dispar* or *E. moshkovskii.* A fourth species, *E. bangladeshi,* was discovered in Bangladesh in 2012 and has recently been found in South Africa. The potential for *E. bangladeshi* to cause human disease remains unclear. Four other species of nonpathogenic *Entamoeba* are known to colonize the human gastrointestinal tract: *Entamoeba coli, E. hartmanni, E. gingivalis,* and *E. polecki.* A fifth species, *E. nuttalli,* typically infects nonhuman primates such as macaques, but a case of asymptomatic infection has been described in a zookeeper.

Infection is usually acquired through the ingestion of parasite cysts, which measure 10-18 μm in diameter and contain four nuclei. Cysts are resistant to harsh environmental conditions, including chlorine concentrations commonly used in water purification, but can be killed by heating them to 55°C (131°F). Cysts are resistant to gastric acidity and digestive enzymes and germinate in the small intestine to form trophozoites. These large, actively motile organisms colonize the lumen of the large intestine and may invade the mucosal lining. Some eventually transform to cysts and are passed out in the stool to infect other hosts anew.

EPIDEMIOLOGY

The prevalence of infection with *E. histolytica* varies greatly by region and socioeconomic status. Early prevalence studies did not distinguish between *E. histolytica* and *E. dispar,* but more recent estimates show that infection with *E. histolytica* causes 100 million cases of symptomatic disease and 2,000 to 17,000 deaths annually. Molecular studies have put the global prevalence of *E. histolytica* at 3.55%, ranging from 1.72% to 21.58% in different regions of the world.

Prospective studies have shown that 4–10% of individuals infected with *E. histolytica* develop amebic colitis and that <1% of infected individuals develop disseminated disease, including amebic liver abscess. These numbers vary by region; for example, in South Africa and Vietnam, liver abscesses form a disproportionately large number of the cases of invasive disease due to *E. histolytica.* Amebic liver abscesses occur equally in male and female children but are generally rare in childhood. Peak abscess formation occurs in individuals between 30-60 years old and is 10-12 times more prevalent in adult males than females.

Amebiasis causes its largest burden of disease in Africa, Southeast Asia, and the Eastern Mediterranean. In the United States, amebiasis is seen most frequently in travelers to and immigrants from developing countries. Residents of mental health institutions and men who have sex with men are at increased risk for invasive amebiasis. Food or drink contaminated with *Entamoeba* cysts and oral-anogenital sex are the most common means of infection. Untreated water and night soil (human feces used as fertilizer) are important sources of infection in resource-limited settings. Food handlers shedding amebic cysts play a role in spreading infection.

PATHOGENESIS

Trophozoites are responsible for tissue invasion and destruction. *E. histolytica* secretes many proteases, the best described of which is amebic cysteine protease 5 (EhCP5). EhCP5 cleaves MUC2 mucin, degrading the intestinal mucus layer and exposing colonic epithelial cells. MUC2 is also involved in regulating antimicrobial peptide production by Paneth cells during *E. histolytica* infection. Amebae then attach using a galactose and *N*-acetyl-D-galactosamine–specific lectin. This lectin also provides resistance to complement-mediated lysis, and its intermediate subunit has been found to have hemagglutinating, hemolytic, and cytolytic activity.

Once attached to the colonic mucosa, trophozoites penetrate the epithelial layer, destroying host cells by cytolysis and induction of apoptosis. Cytolysis is mediated by trophozoite release of amebapores (pore-forming proteins), phospholipases, and hemolysins. Once host cells are partially digested by amebic proteases, the degraded material is internalized through phagocytosis. Trogocytosis is another mechanism that amebae use to kill host cells. This involves ingesting pieces of living cells, inducing intracellular calcium elevation leading to apoptosis.

Early invasive amebiasis produces significant inflammation, owing in part to parasite-mediated activation of nuclear factor-κB. Once *E. histolytica* trophozoites invade the intestinal mucosa, the organisms multiply and spread laterally underneath the intestinal epithelium to produce the characteristic *flask-shaped ulcers.* Amebae produce similar lytic lesions if they reach the liver. These lesions are commonly called *abscesses,* although they contain no granulocytes. Well-established ulcers and amebic liver abscesses demonstrate little local inflammatory response.

Immunity to infection is associated with a mucosal secretory IgA response against the galactose/*N*-acetyl-D-galactosamine lectin.

Macrophages are among the earliest responders, mediating phagocytosis and secreting cytokines to recruit other inflammatory cells. Eosinophilia is common in parasitic infections and may play a role in IgA regulation. Neutrophils are generally protective and exert amebicidal activity by phagocytosis, degranulation, and formation of neutrophil extracellular traps (NETs). The disparity between the extent of tissue destruction by amebae and the absence of a local host inflammatory response in the presence of systemic humoral and cell-mediated responses may reflect both parasite-mediated apoptosis and the ability of the trophozoite to kill not only epithelial cells but also neutrophils, monocytes, and macrophages.

The *E. histolytica* genome is functionally tetraploid, and there is evidence of lateral gene transfer from bacteria. The amebapore-A *(Ap-A)* gene, along with other important genes, can be epigenetically silenced using plasmids with specifically engineered sequences or short hairpin RNAs. Transcriptional profiling using proteomics and microarrays has identified multiple virulence factors, including cysteine proteases, which modulate lysosome and phagosome function, as well as excretory-secretory proteins. Many calcium-binding proteins are encoded and are involved in motility, adhesion, cytolysis, and phagocytosis. Some of these proteins bind directly to actin to modulate pseudopod formation and phagocytosis. The bacterial microbiome has also been shown to influence *E. histolytica* pathogenicity by affecting lectin expression, with increased *Prevotella copri* populations associated with higher rates of diarrhea in infected children. Enteropathogenic *Escherichia coli* have been linked to increased *E. histolytica* virulence through upregulation of amebic proteolytic activity. Enteric bacteria improve survival of these anaerobic amebae during times of oxidative stress. Decreased bacterial diversity has been linked to an increase in symptomatic amebic infections in children.

CLINICAL MANIFESTATIONS

Clinical presentations range from asymptomatic cyst passage to amebic colitis, amebic dysentery, ameboma, and extraintestinal disease. Up to 10% of infected persons develop invasive disease within a year, and asymptomatic carriers should be treated. Severe disease is more common in young children, pregnant women, malnourished individuals, and persons taking corticosteroids. Invasive disease is more common in men. Extraintestinal disease usually involves the liver, but less common extraintestinal manifestations include amebic brain abscess, pleuropulmonary disease, skin ulcers, and genitourinary lesions.

Amebic Colitis

Amebic colitis may occur within 2 weeks of infection or may be delayed for months. The onset is usually gradual, with colicky abdominal pain and frequent bowel movements (6-8/day). Diarrhea is frequently associated with tenesmus. Almost all stool is heme-positive, but most patients do not present with grossly bloody stools. Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients. Amebic colitis affects all age groups but is strikingly common in children 1-5 years of age. Severe amebic colitis in infants and young children tends to be rapidly progressive, with more frequent extraintestinal involvement and high mortality rates, particularly in tropical countries. Amebic dysentery can result in dehydration and electrolyte disturbances.

Amebic Liver Abscess

Amebic liver abscess, a serious manifestation of disseminated infection, is uncommon in children. Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscesses occur in <1% of infected individuals and may appear in patients with no clear history of intestinal disease. Amebic liver abscess may occur months to years after exposure, so obtaining a careful travel history is critical. In children, fever is the hallmark of amebic liver abscess and is frequently associated with abdominal pain, abdominal distention, and enlargement and tenderness of the liver. Changes at the base of the right lung may also occur, including elevation of the diaphragm and atelectasis or effusion.

LABORATORY FINDINGS

Laboratory examination findings are often unremarkable in uncomplicated amebic colitis. Laboratory findings in amebic liver abscess are a slight leukocytosis, moderate anemia, high erythrocyte sedimentation rate, and elevations of hepatic enzyme (particularly alkaline phosphatase) levels. Stool examination for amebae is negative in more than half of patients with documented amebic liver abscess. Ultrasonography, CT, or MRI can localize and delineate the size of the abscess cavity (Fig. 327.1). The most common finding is a single abscess in the right hepatic lobe.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A diagnosis of amebic colitis is made in the presence of compatible symptoms with detection of *E. histolytica* either by stool antigen testing or PCR. This approach has a greater than 95% sensitivity and specificity, and when it is coupled with a positive serology test, it is the most accurate means of diagnosis in developed countries. Several approved stool antigen kits are commercially available in the United States, but most cannot distinguish between *E. histolytica* and *E. dispar.* Microscopic examination of stool samples has a sensitivity of 60%. Sensitivity can be increased to 85–95% by examining three stools. Microscopy cannot differentiate between *E. histolytica*, *E. dispar*, *E. moshkovskii,* and *E. bangladeshi* unless phagocytosed erythrocytes (specific for *E. histolytica*) are seen. Endoscopy and biopsies of suspicious areas should be performed when stool sample results are negative and suspicion remains high. Various serum antibody tests are available. Serologic results are positive in 70–80% of patients with invasive disease (colitis or liver abscess) at presentation and in >90% of patients after 7 days. Indirect hemagglutination is the most sensitive serologic test and yields a positive result even years after invasive infection. Therefore many uninfected adults and children in highly endemic areas demonstrate antibodies to *E. histolytica.*

Conventional and real-time multiplex PCR performed on stool is the most sensitive and preferred method for distinguishing *E. histolytica* from nonpathogenic *E. dispar*, *E. moshkovskii,* and *E. bangladeshi.*

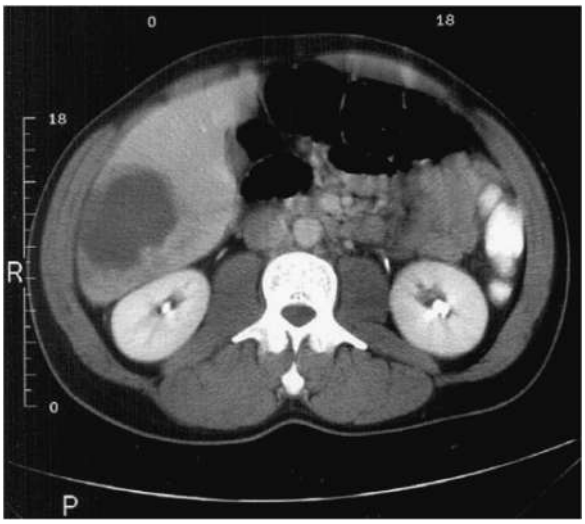

Fig. 327.1 Abdominal CT scan of a patient with an amebic liver abscess. *(From Miller Q, Kenney JM, Cotlar AM. Amebic abscess of the liver presenting as acute cholecystitis. Curr Surg. 2000;57:476–479. Fig. 1.)*

Different multiplex formats have also been developed, including enteric pathogen panels with varying sensitivities and specificities. Tetraplex assays that can distinguish between all four morphologically identical isolates have also been developed. Isothermal nucleic acid methods using recombinase and loop-mediated amplification (LAMP) in point-of-care diagnostics are promising and will greatly facilitate treatment, especially in developing countries. A small study using quantitative PCR detected *E. histolytica* DNA in the serum of patients with amebic liver abscess with a sensitivity of 89.5% and a specificity of 100%.

The **differential diagnosis** for amebic colitis includes colitis due to bacterial, mycobacterial, and viral pathogens, as well as noninfectious causes such as inflammatory bowel disease. Pyogenic liver abscess due to bacterial infection, hepatoma, and echinococcal cysts are in the differential diagnosis for amebic liver abscess. However, echinococcal cysts are rarely associated with systemic symptoms such as fever, unless there is cyst rupture or leakage.

COMPLICATIONS

Complications of amebic colitis include acute necrotizing colitis, ameboma, toxic megacolon, extraintestinal extension, and local perforation and peritonitis. Less commonly, a chronic form of amebic colitis develops, often recurring over several years. Amebomas are nodular foci of proliferative inflammation that sometimes develop in the wall of the colon. Amebiasis should be excluded before initiating corticosteroid treatment for inflammatory bowel disease because steroid treatment of *E. histolytica* is associated with high mortality rates.

An amebic liver abscess may rupture into the peritoneum, pleural cavity, skin, and pericardium. Cases of amebic abscesses in extrahepatic sites, including the lung and brain, have been reported.

TREATMENT

Invasive amebiasis is treated with a nitroimidazole such as **metronidazole** or **tinidazole** and then a luminal amebicide (Table 327.1). Tinidazole may have better clinical efficacy than metronidazole, with shorter and simpler dosing, and is better tolerated. Adverse effects include nausea, abdominal discomfort, and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol. Diloxanide furoate can also be used in children >2 years of age but is no longer available in the United States. Paromomycin should not be given concurrently with metronidazole or tinidazole because diarrhea is a common side effect of paromomycin and may confuse the clinical picture. Asymptomatic intestinal infection with *E. histolytica* should be treated, preferably with paromomycin or alternatively with either iodoquinol or diloxanide furoate. For fulminant cases of amebic colitis, some experts suggest adding dehydroemetine (1 mg/kg/

Table 327.1 Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 500 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
Or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
Or		
Diloxanide furoate†	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
Or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred) *Or* Diloxanide furoate† *Or* Iodoquinol	As for invasive disease	As for invasive disease

*All pediatric dosages are up to a maximum of the adult dose.
†Not available in the United States.

day subcutaneously or intramuscularly, never intravenously), available only through the Centers for Disease Control and Prevention (CDC). Patients should be hospitalized for monitoring if dehydroemetine is administered. Dehydroemetine should be discontinued if tachycardia, T-wave depression, arrhythmia, or proteinuria develops. Nitazoxanide has been shown to be amebicidal in several clinical trials, but more studies are needed to define optimal dosing and duration of treatment.

Broad-spectrum antibiotic therapy may be indicated in fulminant colitis to cover possible spillage of intestinal bacteria into the peritoneum and translocation into the bloodstream. Intestinal perforation and toxic megacolon are indications for surgery. In amebic liver abscess, image-guided aspiration of large lesions or left lobe abscesses may be necessary if rupture is imminent or if the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs. A Cochrane meta-analysis comparing metronidazole and metronidazole plus aspiration in uncomplicated amebic liver abscess showed that there is insufficient evidence to make any recommendation for or against this approach. Chloroquine, which concentrates in the liver, may also be a useful adjunct to nitroimidazoles in the treatment of amebic liver abscess or in cases of treatment failure or intolerance. To confirm cure, stool examination should be repeated every 2 weeks after completion of therapy until clear.

PROGNOSIS

Most infections evolve to either an asymptomatic carrier state or eradication. Extraintestinal infection carries about a 5% mortality rate.

PREVENTION

Control of amebiasis can be achieved by exercising proper sanitation and hygiene. Regular examination of food handlers and thorough investigation of diarrheal episodes may help identify the source of infection. No prophylactic drug or vaccine is available.

Immunization with different *E. histolytica* antigens has shown promising protective responses in animal models. Amebic surface protein LecA, galactose/*N*-acetyl-D-galactosamine lectin, serine-rich *E. histolytica* protein (SREHP), heparan sulfate binding proteins, and other antigens have elicited protective immune responses, especially in combination with different adjuvants. Acquired immune response can be protective as evidenced by anti-lectin IgA in stool among Bangladeshi children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 328 Giardiasis and Balantidiasis

328.1 *Giardia duodenalis*

Chandy C. John

Giardia duodenalis is a flagellated protozoan that infects the duodenum and jejunum. Infection results in clinical manifestations that range from asymptomatic colonization to acute or chronic diarrhea and malabsorption. Infection is more prevalent in children than in adults. *Giardia* is endemic in areas of the world with poor levels of sanitation. It is also an important cause of morbidity in developed countries, where it is associated with urban childcare centers, residential institutions for the developmentally delayed, and waterborne and foodborne outbreaks. *Giardia* is a particularly significant pathogen in children with malnutrition and certain immunodeficiencies (IgA deficiency, common variable immunodeficiency, X-linked hypogammaglobulinemia).

ETIOLOGY

The life cycle of *G. duodenalis* (also known as *Giardia lamblia* or *Giardia intestinalis*) is composed of two stages: trophozoites and cysts. *Giardia* infects humans after ingestion of as few as 10-100 cysts, which measure 8-10 μm in diameter. Each ingested cyst produces two trophozoites in the duodenum. After excystation, trophozoites colonize the lumen of the duodenum and proximal jejunum, where they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. The body of the trophozoite is teardrop shaped, measuring 10-20 μm in length and 5-15 μm in width. *Giardia* trophozoites contain two oval nuclei anteriorly, a large ventral disk, a curved median body posteriorly, and four pairs of flagella. As detached trophozoites pass down the intestinal tract, they encyst to form oval cysts that contain four nuclei. Cysts are passed in stools of infected individuals and may remain viable in water for as long as 2 months. Their viability often is not affected by the usual concentrations of chlorine used to purify water for drinking.

Giardia strains that infect humans are diverse biologically, as shown by differences in antigens, restriction endonuclease patterns, DNA fingerprinting, isoenzyme patterns, and pulsed-field gel electrophoresis. Studies suggest that different *Giardia* genotypes may cause unique clinical manifestations, but these findings appear to vary according to the geographic region tested.

EPIDEMIOLOGY

Giardia occurs worldwide and is the most common intestinal parasite identified in public health laboratories in the United States, where it is estimated that up to 2 million cases of giardiasis occur annually. *Giardia* infection usually occurs sporadically, but *Giardia* is a frequently identified etiologic agent of outbreaks associated with drinking water. The age-specific prevalence of giardiasis is high during childhood and begins to decline after adolescence. The asymptomatic carrier rate of *G.*

lamblia in the United States is as high as 20–30% in children younger than 36 months of age attending childcare centers. Asymptomatic carriage may persist for several months.

Risk of acquiring and transmitting *Giardia* is increased in children and employees in childcare centers, individuals who drink contaminated water, international travelers, men who have sex with men, immunodeficient individuals, and individuals exposed to farm animals. Children visiting friends and relatives are at increased risk for *Giardia* infections during international travel. The major reservoir and vehicle for spread of *Giardia* appears to be water contaminated with *Giardia* cysts, but foodborne transmission also occurs. The seasonal peak in age-specific case reports coincides with the summer recreational water season and may be a result of the extensive use of communal swimming venues by young children, the low infectious dose, and the extended periods of cyst shedding that can occur. In addition, *Giardia* cysts are relatively resistant to chlorination and to ultraviolet light irradiation. Boiling is effective for inactivating cysts.

Person-to-person spread also occurs, particularly in areas of low hygiene standards, frequent fecal-oral contact, and crowding. Individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all predispose to transmission of enteropathogens, including *Giardia,* in childcare centers. Childcare centers play an important role in transmission of urban giardiasis, with secondary attack rates in families as high as 17–30%. Children in childcare centers may pass cysts for several months. Campers who drink untreated stream or river water, particularly in the western United States, and residents of institutions for the developmentally delayed are also at increased risk for infection.

Humoral immunodeficiencies, including common variable immunodeficiency and X-linked agammaglobulinemia, predispose humans to chronic symptomatic *Giardia* infection, suggesting the importance of humoral immunity in controlling giardiasis. Selective immunoglobulin A deficiency is also associated with *Giardia* infection. Although many individuals with AIDS have relatively mild *Giardia* infections, *Giardia* infection refractory to treatment may occur in a subset of individuals with AIDS. Human milk contains glycoconjugates and secretory immunoglobulin A antibodies that may provide protection to nursing infants against *Giardia*.

CLINICAL MANIFESTATIONS

The incubation period of *Giardia* infection usually is 1-2 weeks but may be longer. A broad spectrum of clinical manifestations occurs, depending on the interaction between *G. lamblia* and the host. Children who are exposed to *G. lamblia* may experience asymptomatic excretion of the organism, acute infectious diarrhea, or chronic diarrhea with persistent gastrointestinal tract signs and symptoms, including failure to thrive and abdominal pain or cramping. *Giardia* was the cause of 15% of nondysenteric diarrheal illnesses in children examined in U.S. outpatient clinics in one study. Most infections in children and adults are asymptomatic. There is usually no extraintestinal spread, but occasionally trophozoites may migrate into bile or pancreatic ducts.

Symptomatic infections occur more frequently in children than in adults. Most symptomatic patients usually have a limited period of acute diarrheal disease with or without low-grade fever, nausea, and anorexia; in a small proportion of patients, an intermittent or more protracted course characterized by diarrhea, abdominal distention and cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss develops (Table 328.1). Stools initially may be profuse and watery and later become greasy and foul smelling and may float. Stools do not contain blood, mucus, or fecal leukocytes. Varying degrees of malabsorption may occur. Abnormal stool patterns may alternate with periods of constipation and normal bowel movements. Malabsorption of sugars, fats, and fat-soluble vitamins is well documented and may be responsible for substantial weight loss. *Giardia* has been associated with iron deficiency in internationally adopted children. Extraintestinal manifestations of *Giardia* appear to be more common in adults than children and include arthritis and, in one report after an outbreak, chronic fatigue syndrome. Giardiasis in children has been associated with growth stunting, and repeated *Giardia* infections correlate with a decrease in cognitive function in children in endemic areas.

Table 328.1 Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64–100
Malaise, weakness	72–97
Abdominal distention	42–97
Flatulence	35–97
Abdominal cramps	44–81
Nausea	14–79
Foul-smelling, greasy stools	15–79
Anorexia	41–73
Weight loss	53–73
Vomiting	14–35
Fever	0–28
Constipation	0–27

DIAGNOSIS

Giardiasis should be considered in children who have acute nondysenteric diarrhea, persistent diarrhea, intermittent diarrhea and constipation, malabsorption, chronic crampy abdominal pain and bloating, failure to thrive, or weight loss. It should be particularly high in the differential diagnosis of children in childcare centers, children in contact with an index case, children with a history of recent travel to an endemic area, and children with humoral immunodeficiencies. Testing for giardiasis should be standard for internationally adopted children from *Giardia*-endemic areas, and screening for iron deficiency should be considered in internationally adopted children with giardiasis.

Stool enzyme immunoassay (EIA) or direct fluorescent antibody tests for *Giardia* antigens are the tests of choice for giardiasis. EIA is less reader dependent and more sensitive for detection of *Giardia* than microscopy. Some studies report that a single stool is sufficiently sensitive for detection of *Giardia* by EIA, whereas others suggest that sensitivity is increased with testing of two samples. A diagnosis of giardiasis was traditionally established by microscopy documentation of trophozoites or cysts in stool specimens, but three stool specimens are required to achieve a sensitivity of >90% using this approach. In patients in whom other parasitic intestinal infections are in the differential diagnosis, microscopy examination of stool allows evaluation for these infections in addition to *Giardia.*

Polymerase chain reaction and gene probe–based detection systems specific for *Giardia* have been used in environmental monitoring and clinical testing. Multiplex polymerase chain reaction testing for multiple parasitic pathogens is a viable option for testing.

In patients with chronic symptoms in whom giardiasis is suspected but in whom testing of stool specimens for *Giardia* yields a negative result, aspiration or biopsy of the duodenum or upper jejunum should be considered. In a fresh specimen, trophozoites usually can be visualized by direct wet mount. An alternate method of directly obtaining duodenal fluid is the commercially available Entero-Test (Hedeco Corp, Mountain View, CA), but this method is less sensitive than aspiration or biopsy. The biopsy can be used to make touch preparations and tissue sections for identification of *Giardia* and other enteric pathogens and also to visualize changes in histology. Biopsy of the small intestine should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimen findings, and one or more of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine); an abnormal lactose tolerance test result; an absent secretory immunoglobulin A level; hypogammaglobulinemia; or achlorhydria. Duodenal biopsy may show findings consistent with chronic inflammation, including eosinophilic infiltration of the lamina propria.

Radiographic contrast studies of the small intestine may show nonspecific findings such as irregular thickening of the mucosal folds. Blood cell counts usually are normal. Giardiasis is not tissue invasive and is not associated with peripheral blood eosinophilia.

TREATMENT

Children with acute diarrhea in whom *Giardia* organisms are identified should receive therapy. In addition, children who manifest failure to thrive or exhibit malabsorption or gastrointestinal tract symptoms such as chronic diarrhea should be treated.

Asymptomatic excreters generally are not treated, except in specific instances such as outbreak control, prevention of household transmission by toddlers to pregnant women and patients with hypogammaglobulinemia or cystic fibrosis, and situations requiring oral antibiotic treatment where *Giardia* may produce malabsorption of the antibiotic.

The FDA has approved tinidazole and nitazoxanide for the treatment of *Giardia* in the United States. Both medications have been used to treat *Giardia* in thousands of patients in other countries and have excellent safety and efficacy records against *Giardia* (Table 328.2). Tinidazole has the advantage of single-dose treatment and very high efficacy (>90%), while nitazoxanide has the advantage of a suspension form, high efficacy (80–90%), and very few adverse effects. Metronidazole, although never approved by the FDA for treatment of *Giardia,* is also highly effective (80–90% cure rate), and the generic form is considerably less expensive than tinidazole or nitazoxanide. For children ≥3 year of age, tinidazole is the preferred treatment, with nitazoxanide as alternative, while for children 1-2 years, nitazoxanide is the preferred treatment, since tinidazole is approved only for children ≥3 years of age. Metronidazole is the drug of choice for children <12 months and an alternative to tinidazole and nitazoxanide for children ≥12 months. Recent reports on travelers to South Asia document resistance rates as high as 30% to metronidazole, so nitazoxanide or tinidazole may be preferred for children who have traveled to or are from this area. Frequent adverse effects are seen with metronidazole therapy, and it requires 3-times-a-day dosing for 5-7 days. Suspension forms of tinidazole and metronidazole must be compounded by a pharmacy; neither drug is sold in suspension form.

Second-line alternatives for the treatment of patients with giardiasis include albendazole, paromomycin, and quinacrine (see Table 328.2). Albendazole may be of similar efficacy to metronidazole. Albendazole has few adverse effects and is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected. Paromomycin is a nonabsorbable aminoglycoside and is less effective than other agents but is recommended for treatment of pregnant women with giardiasis because of the potential teratogenic effects of other agents. Quinacrine is effective and inexpensive but is not available commercially and must be obtained from compounding pharmacies (see Table 328.2). Quinacrine can also rarely have serious side effects, including hallucinations and psychosis. Refractory cases of giardiasis have been successfully treated with a number of regimens, including nitazoxanide, prolonged courses of tinidazole, or combination therapy, most commonly a 3-week course of metronidazole and quinacrine.

Table 328.2 Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days 4-11 yr: 200 mg (10 mL) bid for 3 days >12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	500 mg tid for 5-10 days	Not recommended
Quinacrine†	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

*All pediatric dosages are up to a maximum of the adult dose.
†Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-8970) or Panorama Compounding Pharmacy in Van Nuys, CA (818-988-7979).

PROGNOSIS

Symptoms recur in some patients in whom reinfection cannot be documented and in whom an immune deficiency such as an immunoglobulin abnormality is not present, despite use of appropriate therapy. Several studies have demonstrated that variability in antimicrobial susceptibility exists among strains of *Giardia,* and in some instances resistant strains have been demonstrated. Combined therapy may be useful for infection that persists after single-drug therapy, assuming reinfection has not occurred and the medication was taken as prescribed.

PREVENTION

Infected persons and persons at risk should practice strict handwashing after any contact with feces. This point is especially important for caregivers of diapered infants in childcare centers, where diarrhea is common and *Giardia* organism carriage rates are high.

Methods to purify public water supplies adequately include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires the coordination of multiple variables such as chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be appropriately controlled in all municipalities and are difficult to control in swimming pools. Individuals, especially children in diapers, should avoid swimming if they have diarrhea. Individuals should also avoid swallowing recreational water and drinking untreated water from shallow wells, lakes, springs, ponds, streams, and rivers.

Travelers to endemic areas are advised to avoid uncooked foods that might have been grown, washed, or prepared with water that was potentially contaminated. Purification of drinking water can be achieved by a filter with a pore size of <1 μm or that has been rated by the National Sanitation Foundation for cyst removal, or by brisk boiling of water for at least 1 minute. Treatment of water with chlorine or iodine is less effective but may be used as an alternate method when boiling or filtration is not possible.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

328.2 Balantidiasis

Chandy C. John

Balantidium coli is a ciliated protozoan and is the largest protozoan that parasitizes humans. Both trophozoites and cysts may be identified in feces. Disease caused by this organism is uncommon in the United States and generally is reported where there is a close association of humans with pigs, which are the natural hosts of *B. coli.* Because the organism infects the large intestine, symptoms are consistent with large bowel disease, similar to those associated with amebiasis and trichuriasis, and include nausea, vomiting, lower abdominal pain, tenesmus, and bloody diarrhea. Symptoms associated with chronic infection include abdominal cramps, watery diarrhea with mucus, occasionally bloody diarrhea, and colonic ulcers similar to those associated with *Entamoeba histolytica.* Extraintestinal spread of *B. coli* is rare and usually occurs only in immunocompromised patients. Most infections are asymptomatic.

Diagnosis using direct saline mounts is established by identification of trophozoites (50-100 μm long) or spherical or oval cysts (50-70 μm in diameter) in stool specimens. Trophozoites usually are more numerous than cysts.

The recommended treatment regimen is metronidazole (25-50 mg/kg/day divided tid PO; maximum: 750 mg/dose) for 5 days, or tetracycline (40 mg/kg/day divided qid PO; maximum: 500 mg/dose) for 10 days for persons older than 8 years of age. An alternative is iodoquinol (40 mg/kg/day divided tid PO; maximum: 650 mg/dose) for 20 days.

Prevention of contamination of the environment by pig feces is the most important means for control.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 329

Cryptosporidium, Cystoisospora, Cyclospora, and *Microsporidia*

Sarah M. Heston and Patricia M. Flynn

The spore-forming intestinal protozoa *Cryptosporidium, Cystoisospora* (formerly *Isospora*), and *Cyclospora* are important intestinal pathogens in both immunocompetent and immunocompromised hosts. *Cryptosporidium, Cystoisospora,* and *Cyclospora* are coccidian parasites that predominantly infect the epithelial cells lining the digestive tract, and all are transmitted by the fecal-oral route. Microsporidia were formerly considered spore-forming protozoa but have been reclassified as fungi. Microsporidia are ubiquitous, obligate intracellular organisms that infect many other organ systems in addition to the gastrointestinal tract and cause a broader spectrum of disease.

CRYPTOSPORIDIUM

Cryptosporidium is recognized as a leading protozoal cause of diarrhea in children worldwide and is a **common cause of outbreaks in childcare centers**; it is also a significant pathogen in immunocompromised patients.

Etiology

Cryptosporidium hominis and *Cryptosporidium parvum* cause most cases of cryptosporidiosis in humans. Disease is initiated by ingestion of infectious oocysts that were excreted in the feces of infected humans and animals. The oocysts are immediately infectious to other hosts or can reinfect the same host. The ingested oocysts release sporozoites that attach to and invade the intestinal epithelial cells.

Epidemiology

Cryptosporidiosis is associated with diarrheal illness worldwide and is more prevalent in developing countries and among children younger than 2 years of age. It has been implicated as an etiologic agent of persistent diarrhea in the developing world and as a cause of significant morbidity and mortality from malnutrition, including permanent effects on growth. Risk factors for infection include animal contact, diarrhea in a household member, open defecation/lack of toilet facilities, and poor drinking water quality.

Transmission of *Cryptosporidium* to humans can occur by close association with infected animals, via person-to-person transmission, or from environmentally contaminated water and food. Although zoonotic transmission, especially from cows, occurs in persons in close association with animals, person-to-person transmission is probably responsible for cryptosporidiosis outbreaks within hospitals and childcare centers, where transmission rates as high as 67% have been reported. Recommendations to prevent outbreaks in childcare centers include exclusion of children with diarrhea from attending, strict handwashing, elimination of water play or swimming activities, use of protective clothes or diapers capable of retaining liquid diarrhea, and separation of diapering and food-handling areas and responsibilities.

Outbreaks of cryptosporidial infection are associated with contaminated community water supplies and recreational waters, including lakes and chlorinated swimming pools. Wastewater in the form of raw sewage and runoff from dairies and grazing lands can contaminate both drinking and recreational water sources. It is estimated that *Cryptosporidium* oocysts are present in 65–97% of the surface water in the United States. The organism's small size (4-6 μm in diameter), resistance to chlorination, and ability to survive for long periods outside a host create problems in public water supplies.

Clinical Manifestations

The **incubation period is 2-10 days** (average, 7 days) after infection. *Cryptosporidium* infection is associated with **profuse, watery, nonbloody diarrhea** that can be accompanied by diffuse crampy abdominal pain, nausea, vomiting, and anorexia. Although less common in adults, vomiting occurs in more than 80% of children with cryptosporidiosis. Nonspecific symptoms such as myalgia, weakness, and headache also may occur. Fever occurs in 30–50% of cases. Malabsorption, lactose intolerance, dehydration, weight loss, and malnutrition often occur in severe cases. The clinical spectrum and disease severity have been linked with both the infecting species and host human leukocyte antigen class I and class II alleles.

In **immunocompetent persons, the disease is usually self-limiting**, typically 5-10 days, although diarrhea may persist for several weeks and oocyst shedding may persist for many weeks after symptoms resolve. Chronic diarrhea is common in young infants and individuals with immunodeficiency, such as congenital hypogammaglobulinemia or HIV infection. Symptoms and oocyst shedding can continue indefinitely and may lead to severe malnutrition, wasting, anorexia, and even death.

Cryptosporidiosis in immunocompromised hosts is often associated with biliary tract disease, characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. It also is associated with pancreatitis. Respiratory tract disease is rare.

Diagnosis

Infection can be diagnosed by microscopy using modified acid-fast stain or polymerase chain reaction (PCR), but immunodetection of antigens on the surface of the organism in stool samples using monoclonal antibody–based assays is the current diagnostic method of choice because of the high sensitivity and specificity. Multiplex molecular test panels for gastrointestinal pathogens that include *Cryptosporidium* are available and are a standard test.

In stool, oocysts appear as small, spherical bodies (2-6 μm) and stain red with modified acid-fast staining. Because *Cryptosporidium* does not invade below the epithelial layer of the mucosa, fecal leukocytes are not found in stool specimens. Oocyst shedding in feces can be intermittent, and several fecal specimens (at least three for an immunocompetent host) should be collected for microscopic examination. Serologic diagnosis is not helpful in acute cryptosporidiosis.

In tissue sections, *Cryptosporidium* organisms can be found along the microvillus region of the epithelia that line the gastrointestinal tract. The highest concentration usually is detected in the jejunum. Histologic section results reveal villus atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

Treatment

Often the diarrheal illness attributable to cryptosporidiosis is self-limited in *immunocompetent* patients and requires no specific antimicrobial therapy. Treatment should focus on supportive care, including rehydration orally or, if fluid losses are severe, intravenously. A 3-day course of nitazoxanide (100 mg bid PO for 3 days for children 1-3 years of age; 200 mg bid PO for children 4-11 years of age; 500 mg bid PO for children ≥12 years of age) is approved for treatment of diarrhea caused by *Cryptosporidium.* A recent meta-analysis revealed a favorable clinical response to treatment with nitazoxanide compared with placebo, although the parasitologic response was no different than the response to placebo. Clinical studies have not definitively demonstrated that nitazoxanide is superior to placebo in trials of HIV-infected (with low CD4 counts) or immunocompromised patients. However, given the severity of the infection in these populations, nitazoxanide treatment

is usually initiated. Immune function should be optimized in immunocompromised patients, with combination antiretroviral therapy in patients living with HIV and decreased immunosuppression in transplant recipients, if possible. Other agents that have been suggested for treatment in clinical reports or small studies include orally administered human serum immunoglobulin or bovine colostrum, paromomycin, spiramycin, azithromycin, and roxithromycin or a combination of antibiotics. Clofazimine was recently investigated as a potential therapy among adults living with HIV; however, it failed to show efficacy based on clinical and parasitologic outcomes. Prevention measures include adequate hand hygiene, avoiding untreated ice or water, especially in areas with poor sanitation, and exclusion of children with diarrhea from public pools.

CYSTOISOSPORA

Like *Cryptosporidium, Cystoisospora belli* is implicated as a cause of diarrhea in institutional outbreaks and in travelers and has also been linked with **contaminated water and food**. *Cystoisospora* appears to be more common in tropical and subtropical climates and in developing areas, including South America, Africa, and Southeast Asia. *Cystoisospora* has not been associated with animal contact. It is also an infrequent cause of diarrhea in patients with AIDS in the United States but may infect up to 15% of AIDS patients in Haiti.

The life cycle and pathogenesis of infection with *Cystoisospora* species are similar to those of *Cryptosporidium* organisms except that oocysts excreted in the stool are not immediately infectious and must undergo further maturation at temperatures below 37°C (98.6°F). Thus **direct person-to-person transmission is unlikely**. The **incubation period averages approximately one week.** The most common clinical manifestation is **watery, nonbloody diarrhea**. Symptoms of infection are indistinguishable from those of cryptosporidiosis, although fever may be a more common finding. Eosinophilia may be present in up to 50% of cases, contrasting with other enteric protozoan infections. The diagnosis is established by detecting the oval, 22- to 33-μm long by 10- to 19-μm wide oocysts by using modified acid-fast staining of the stool. Fecal leukocytes are not detected. Oocysts are shed in low numbers, underscoring the need for repeated stool examinations. The presence of oocysts in the gastrointestinal tract is almost always associated with clinical symptoms. The histologic appearance of the gastrointestinal epithelium reveals blunting and atrophy of the villi, acute and chronic inflammation, and crypt hyperplasia.

Cystoisosporiasis responds promptly to treatment with oral **trimethoprim-sulfamethoxazole** (TMP-SMX: 5 mg TMP and 25 mg SMX/kg/dose [maximum: 160 mg TMP and 800 mg SMX/dose] bid for 10 days). In patients with AIDS, relapses are common and often necessitate higher doses of TMP/SMX and/or maintenance therapy. Combination antiretroviral therapy associated with immune recovery may also result in improved symptoms. **Ciprofloxacin** or a regimen of **pyrimethamine** alone or with **folinic acid** is effective in patients intolerant of sulfonamide drugs. In endemic areas, *Cystoisospora* can be avoided by ensuring water used for drinking, food preparation, and washing fresh produce has been filtered or boiled.

CYCLOSPORA

Cyclospora cayetanensis is a coccidian parasite similar to but larger than *Cryptosporidium.* The organism infects both immunocompromised and immunocompetent individuals and is more common in children younger than 18 months of age. The pathogenesis and pathologic findings of cyclosporiasis are similar to those of cystoisosporiasis. Asymptomatic carriage of the organism has been found, but travelers who harbor the organism almost always have diarrhea. Most cases of cyclosporiasis in the United States are domestically acquired. Outbreaks of cyclosporiasis are linked with **contaminated food and water** and occur most frequently during spring and summer months. Implicated foods include raspberries, lettuce, snow peas, basil, cilantro, and other fresh food items. After fecal excretion, the oocysts must sporulate outside the host to become infectious. This finding explains the lack of person-to-person transmission.

The clinical manifestations of cyclosporiasis are similar to those of cryptosporidiosis and cystoisosporiasis and follow an **incubation period of approximately 7 days**. Moderate *Cyclospora* illness is characterized by a median of 6 stools/day with a median duration of 10 days (range: 3-25 days). The duration of diarrhea in immunocompetent persons is characteristically longer in cyclosporiasis than in the other intestinal protozoan illnesses. Associated symptoms frequently include anorexia; fatigue; abdominal bloating or gas; abdominal cramps or pain; nausea; muscle, joint, or body aches; low-grade fever; chills; headache; and weight loss. Vomiting may occur. Bloody stools are uncommon. Biliary disease has been reported. Intestinal pathology includes inflammation with villus blunting.

The diagnosis is established by identification of oocysts in the stool or molecular diagnostic testing. Oocysts are wrinkled spheres, measure 8-10 μm in diameter, and resemble large *Cryptosporidium* organisms. The organisms can be seen by using modified acid-fast, auramine-phenol, or modified trichrome staining, but stain less consistently than *Cryptosporidium.* They can also be detected with phenosafranin stain and by autofluorescence using strong green or intense blue under ultraviolet epifluorescence. Multiple stool samples enhance identification of the pathogen. Fecal leukocytes are not present. Commercially available multiplex molecular test panels for gastrointestinal pathogens that include *Cyclospora* are now available and may become the new standard. The sensitivity of molecular testing and the inclusion of *Cyclospora* on multiplex molecular testing may be partly responsible for the increased number of reported cases in the United States in recent years.

The treatment of choice for cyclosporiasis is **TMP-SMX** (5 mg TMP and 25 mg SMX/kg/dose bid [maximum 160 mg TMP and 800 mg SMX/dose] for 10 days.) **Ciprofloxacin** or **nitazoxanide** is effective in patients intolerant of sulfonamide drugs.

MICROSPORIDIA

Microsporidia are ubiquitous and infect most animal groups, including humans. They are classified as fungi, and multiple species of the phylum Microsporidia have been linked with human disease in both immunocompetent and immunocompromised hosts. The species most commonly associated with gastrointestinal disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis.* The global prevalence of microsporidial infections among children is 7.5%, although prevalence is likely higher among pediatric patients living with HIV, oncology patients, and transplant recipients.

Although still not definitive, the source of human infections is likely zoonotic. Like *Cryptosporidium,* there is concern for waterborne transmission through occupational and recreational contact with contaminated water sources. There is also the potential for foodborne outbreaks; the organisms have been identified on vegetables as a consequence of contaminated irrigation water. Vector-borne transmission is hypothesized because one species, *Brachiola algerae,* typically infects mosquitoes. Finally, transplacental transmission has been reported in animals but not in humans. Once infected, intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment via feces. Spores also have been detected in urine and respiratory epithelium, suggesting that some body fluids may also be infectious. Once in the environment, microsporidial spores remain infectious for up to 4 months.

Initially, microsporidial intestinal infection had been almost exclusively reported in patients with AIDS, but there are increasing reports of microsporidial infections in transplant recipients, including donor-derived infections in solid organ transplant recipients. There is increasing evidence that immunocompetent individuals are also commonly infected. Microsporidia-associated **diarrhea is intermittent, watery, copious, and nonbloody**. Abdominal cramping and weight loss may be present; fever is unusual. Stromal keratitis and encephalitis may

also be associated with microsporidia infections. Disseminated disease involving most organs, including liver, heart, kidney, bladder, biliary tract, lung, bone, skeletal muscle, central nervous system, skin, and sinuses, has been reported.

Microsporidia stain with modified trichrome, hematoxylin-eosin, Giemsa, Gram, periodic acid–Schiff, and acid-fast stains but are often overlooked because of their small size (1-5 μm) and the absence of associated inflammation in surrounding tissues. Electron microscopy remains the reference method of detection. An immunofluorescence assay is available. The Centers for Disease Control and Prevention (CDC) offer a molecular identification of *Enterocytozoon bieneusi, Encephalitozoon intestinalis, Encephalitozoon hellem,* and *Encephalitozoon cuniculi* using species-specific PCR assays.

There is no proven therapy for microsporidial intestinal infections. **Albendazole** (adult dose 400 mg bid PO for 3 weeks; for children, 7.5 mg/kg body weight [maximum 400 mg/dose] bid PO) is usually effective against *E. intestinalis* infection but is ineffective against infection caused by some microsporidial species. Fumagillin (adult dose 20 mg tid PO for 2 weeks) was effective in a small controlled study of adults with *E. bieneusi* infection, and topical therapy with this agent was also demonstrated to be effective in HIV-infected adults with keratoconjunctivitis. Fumagillin is not currently available in the United States. Supportive care with hydration, correction of electrolyte imbalances, and nutrition should be used in gastrointestinal infection when clinically indicated. Improvement in underlying HIV infection with combination antiretroviral therapy also improves microsporidiosis symptoms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 330

Trichomoniasis (*Trichomonas vaginalis*)

Edsel Maurice T. Salvana and Robert A. Salata

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. It is the second most common sexually transmitted infection worldwide. Vulvovaginitis is the symptomatic disease form, but *T. vaginalis* has been implicated in pelvic inflammatory disease, pregnancy loss, chronic prostatitis, and an increased risk of HIV transmission.

EPIDEMIOLOGY

Over 156 million new cases of trichomoniasis occur annually around the world. Most men and up to 30% of women are asymptomatic. Although the disease is easily treated, sequelae of untreated infection remain a significant cause of morbidity because of high reinfection rates from untreated partners, underrecognition of asymptomatic cases, and insensitive diagnostics.

Trichomoniasis is the most common parasitic infection in the United States, with a prevalence of 2.6 million cases and 6.9 million incident infections per year. Among the factors associated with a higher prevalence of infection are female sex, belonging to underrepresented minorities, poverty, lower educational attainment, younger age at first sex, multiple sexual partners, and a recent *Chlamydia* infection. Vaginal trichomoniasis is rare until menarche, and its presence in a younger child should raise the possibility of **sexual abuse.**

Trichomoniasis may be transmitted to neonates during passage through an infected birth canal. Infection in this setting is usually self-limited, but rare cases of neonatal vaginitis and respiratory infection have been reported.

PATHOGENESIS

T. vaginalis is an anaerobic, flagellated protozoan parasite. Infected vaginal secretions contain 10^1 to 10^5 or more protozoa/mL. *T. vaginalis* is pear shaped and exhibits characteristic twitching motility in wet mount (Fig. 330.1). Reproduction is by binary fission. It exists only as vegetative cells; cyst forms have not been described. *T. vaginalis* has hydrogenosomes, which are organelles that produce energy in anaerobic environments and have hydrogen as a waste product. Hydrogenosomes are derived from mitochondria, suggesting that *T. vaginalis* may have had an aerobic ancestor.

Many types of adhesion molecules allow attachment of *T. vaginalis* to host cells. Tv lipoglycan is a surface glycoconjugate that binds human galectin-1 and galectin-3 and plays a major role in adhesion, pathogenicity, and immune modulation. In addition, hundreds of putative membrane proteins, BspA proteins, and tetraspanins are involved in cellular attachment. Adhesion is a prerequisite for cytolysis and, once attached, the parasite secretes hydrolases, proteases, and cytotoxic molecules that destroy or impair the integrity of host cells.

Trichomonas is highly dependent on iron for its growth and metabolism. Cysteine proteinase mRNAs have been shown to interact with other parasite proteins for posttranscriptional regulation in the absence of iron-regulatory proteins. The *T. vaginalis* genome is very large at 160 Mbps, with multiple repetitive sequences and transposable elements making up over 60,000 genes and with apparently nonfunctional but transcribed pseudogenes.

Macrophage migration and cytokine production have been shown to be downregulated by the parasite in successful infection. Parasite-specific antibodies and lymphocyte priming occur in response to infection, but durable protective immunity does not occur, possibly also owing to degradation of antibodies by parasitic cysteine proteases. *Trichomonas* infection has been linked to dysregulation of the vagina microbiota and is frequently associated with concomitant bacterial vaginosis. *Trichomonas* can host *Mycoplasma genitalium* as a symbiont, and the presence of both microorganisms can significantly increase the risk of bacterial vaginosis, pelvic inflammatory disease, and adverse pregnancy outcomes.

CLINICAL MANIFESTATIONS

The incubation period in females is 5-28 days. Symptoms may begin or worsen with menses. Most infected women eventually develop symptoms, although up to one third remain asymptomatic. Common signs and symptoms include a copious malodorous gray, frothy vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Physical examination may reveal a frothy discharge with vaginal erythema and

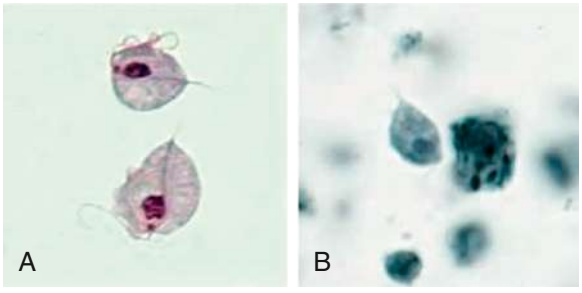

Fig. 330.1 *Trichomonas vaginalis* trophozoites stained with Giemsa (A) and iron hematoxylin (B). *(From the Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trichomoniasis [website].* https://www.cdc.gov/dpdx/trichomoniasis/index.html*)*

cervical hemorrhages (strawberry cervix). The discharge usually has a pH of >4.5. Abdominal discomfort is unusual and should prompt evaluation for pelvic inflammatory disease (see Chapter 163).

Most infections in males are asymptomatic. Symptomatic males usually have dysuria and scant urethral discharge. Trichomonads occasionally cause epididymitis, prostatic involvement, and superficial penile ulceration. Infection is often self-limited, spontaneously resolving in about one third of men. *Trichomonas* has been implicated as a cause of recurrent or relapsing urethritis and can be isolated in 3–20% of men with nongonococcal urethritis. Treatment failures with standard therapy for gonorrhea and *Chlamydia* are frequently treated with antitrichomonal therapy.

DIAGNOSIS

Trichomonads may be recognized in vaginal secretions by wet mount microscopy, which has a sensitivity of 51–65% in vaginal specimens and a lower sensitivity in specimens from men. Although *Trichomonas* is sometimes seen on Pap smears and urine microscopy, these methods are not considered reliable tests for disease. Culture of the organism used to be the gold standard for detection, but this is increasingly being replaced by nucleic acid amplification tests, which are more sensitive. The APTIMA TV (Hologic/Gen-Probe, Inc., Marlborough, MA) assay and the BD Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson, Franklin Lakes, NJ) are U.S. Food and Drug Administration (FDA) cleared commercial NAATs for testing of samples from women. Xpert TV (Cepheid Inc., Sunnyvale, CA) is a cartridge-based near-point-of-care nucleic acid test that is FDA-cleared for men and women, with a sensitivity of 95% for self-collected vaginal swabs and up to 100% for symptomatic endocervical swabs. Three point-of-care kits for rapid testing, Affirm VP III (BD Diagnostic Systems, Sparks, MD), OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), and Solana Trichomonas Assay (Quidel, San Diego, CA) are FDA cleared for women and can yield results in 45 minutes or less. Patients with *T. vaginalis* should be screened for other sexually transmitted infections.

COMPLICATIONS

Untreated trichomoniasis has been associated with pelvic inflammatory disease, premature delivery, low birthweight, endometritis, salpingitis, and vaginal cuff cellulitis. The association between trichomoniasis and infertility is relatively weak, but there is some evidence that coinfection with other sexually transmitted infections increases the overall risk of pelvic inflammatory disease. *T. vaginalis* infection increases the risk of acquisition and transmission of HIV. In HIV-infected individuals, trichomoniasis is associated with higher viral loads in cervical secretions and semen, as well as higher levels of infected lymphocytes in urogenital fluids.

TREATMENT

In the United States, metronidazole and tinidazole are used; in other countries, secnidazole, azanidazole, and ornidazole are also used. Both **metronidazole** (single-dose regimen of 2 g orally as a single dose for adolescents and adults; alternative regimen, 500 mg orally bid for 7 days) and **tinidazole** (single 2 g dose orally in adolescents and adults) are used as first-line treatments. For children infected before adolescence, the recommended regimen is metronidazole 15 mg/kg/day divided in three doses orally for 7 days; tinidazole is not approved for dosing in younger children. For HIV-infected patients, the 7-day course of metronidazole is superior to and recommended over the single-dose regimen. Sexual partners should be treated simultaneously to prevent reinfection. Recent studies have shown that single-dose metronidazole is less effective than a multidose regimen in women. A small number of patients with severe nitroimidazole hypersensitivity have been treated with intravaginal suppositories of boric acid, nitazoxanide, and paromomycin with varying degrees of success. Desensitization to metronidazole with a validated protocol under an allergy specialist is recommended if possible.

Treatment failures have been reported with metronidazole and tinidazole. Metronidazole resistance in *Trichomonas* is estimated to be 4.3–9.6%, and tinidazole resistance is about 1%. Second-line treatment is a 7-day course of metronidazole 500 mg twice daily. If this approach fails, either metronidazole or tinidazole at 2 g daily for 7 days is recommended. Further treatment failure should be referred to an infectious diseases specialist. Susceptibility testing is available from the Centers for Disease Control and Prevention (CDC). Higher dose tinidazole (2-3 g for 14 days) in combination with intravaginal tinidazole or paromomycin have been used in nitroimidazole-resistant infections. Metronidazole has not been shown to be teratogenic but is currently classified as a category C drug. Treatment of trichomoniasis in pregnancy should always be considered, especially in symptomatic patients, and may decrease the risk of perinatal transmission.

PREVENTION

Prevention of *T. vaginalis* infection is best accomplished by treatment of all sexual partners of an infected person, and by programs aimed at prevention of all sexually transmitted infections (see Chapter 163). No vaccine is available, and drug prophylaxis is not recommended. A recent randomized controlled trial showed that *T. vaginalis* infection with concurrent bacterial vaginosis responded better to metronidazole treatment when intravaginal probiotics were co-administered, consistent with findings that altered vaginal microflora plays a significant role in *T. vaginalis* pathogenesis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 331

Leishmaniasis *(Leishmania)*

Peter C. Melby

The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus *Leishmania,* which are transmitted by phlebotomine sand flies. Multiple species of *Leishmania* are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs (Table 331.1). Cutaneous disease is usually localized and mild but may cause cosmetic disfigurement. Rarely, cutaneous infection can disseminate or involve the skin diffusely. Mucosal and visceral forms of leishmaniasis are associated with significant morbidity and mortality.

ETIOLOGY

Leishmania organisms are members of the Trypanosomatidae family and include two subgenera, *Leishmania (Leishmania)* and *Leishmania (Viannia)*. The parasite is dimorphic, existing as a flagellate promastigote in the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host. Within the **sand fly** vector, the promastigote changes from a noninfective procyclic form to an infective metacyclic stage (Fig. 331.1). Amplification of the number of metacyclic promastigotes in the infected sand fly occurs following a second blood meal. Fundamental to metacyclogenesis are changes that take place in the terminal polysaccharides of the surface **lipophosphoglycan,** which allow forward migration of the infective parasites to be inoculated in the host skin during a blood meal. Metacyclic lipophosphoglycan also plays an important role in the entry and survival of *Leishmania* in the vertebrate host cells. Once within the macrophage, the promastigote transforms to an amastigote and resides and replicates within a phagolysosome. The parasite is resistant to the acidic, hostile environment of the macrophage and eventually ruptures the cell and goes on to infect other macrophages. Infected macrophages have a diminished capacity to initiate and respond to an inflammatory response, thus providing a safe haven for the intracellular parasite.

Table 331.1 Clinical and Epidemiologic Characteristics of Main *Leishmania* Species

	SUBGENUS	CLINICAL FORM	MAIN CLINICAL FEATURES	NATURAL PROGRESSION	RISK GROUPS	MAIN RESERVOIR	HIGH-BURDEN COUNTRIES OR REGIONS	ESTIMATED ANNUAL WORLDWIDE INCIDENCE
*Leishmania donovani**	*Leishmania*	VL, PKDL	Persistent fever, splenomegaly, weight loss, and anemia in VL; multiple painless macular, papular, or nodular lesions in PKDL	VL is fatal within 2 yr; PKDL lesions self-heal in up to 85% of cases in Africa but rarely in Asia	Predominantly adolescents and young adults for VL; young children in Sudan and no clearly established risk factors for PKDL	Humans	India, Bangladesh, Ethiopia, Sudan, and South Sudan	50,000-90,000 VL cases; unknown number of PKDL cases
*Leishmania tropica**	Leishmania	CL, LR, rarely VL	Ulcerating dry lesions, painless, and frequently multiple	CL lesions often self-heal within 1 yr	No well-defined risk groups	Humans, but zoonotic foci exist	Eastern Mediterranean, Middle East, northeastern and southern Africa	200,000-400,000 CL
*Leishmania aethiopica**	*Leishmania*	CL, DCL, DsCL, oronasal CL	Localized cutaneous nodular lesions; occasionally oronasal; rarely ulcerates	Self-healing, except for DCL, within 2-5 yr	Limited evidence; adolescents	Hyraxes	Ethiopia, Kenya	20,000-40,000 CL
*Leishmania major**	*Leishmania*	CL	Rapid necrosis, multiple wet sores, severe inflammation	Self-healing in >50% of cases within 2-8 mo; multiple lesions slow to heal, and severe scarring	No well-defined risk groups	Rodents	Iran, Saudi Arabia, North Africa, Middle East, Central Asia, West Africa	230,000-430,000 CL
*Leishmania infantum**	*Leishmania*	VL, CL	Persistent fever and splenomegaly in VL; typically single nodules and minimal inflammation in CL	VL is fatal within 2 yr; CL lesions self-heal within 1 yr and confers individual immunity	Children <5 yr old and immunocompromised adults for VL; older children and young adults for CL	Dogs, hares, humans	China, Southern Europe, Brazil, and South America for VL and CL; Central America for CL	6,200-12,000 cases of Old World VL and 4,500-6,800 cases of New World VL; unknown number of CL cases
Leishmania mexicana†	*Leishmania*	CL, DCL, DsCL	Ulcerating lesions, single or multiple	Often self-healing in 3-4 mo	No well-defined risk groups	Rodents, marsupials	South America	Limited number of cases, included in the 187, 200-300,000 total cases of New World CL‡
Leishmania amazonensis†	*Leishmania*	CL, DCL, DsCL	Ulcerating lesions, single or multiple	Not well described	No well-defined risk groups	Possums, rodents	South America	Limited number of cases, included in the 187, 200-300,000 total cases of New World CL‡
Leishmania braziliensis†	*Viannia*	CL, MCL, DCL, LR	Ulcerating lesions can progress to mucocutaneous form; local lymph nodes are palpable before and early on in the onset of the lesions	Might self-heal in 6 mo; 2.5% of cases progress to MCL	No well-defined risk groups	Dogs, humans, rodents, horses	South America	Majority of the 187, 200-300,000 total cases of New World CL‡
Leishmania guyanensis†	*Viannia*	CL, DsCL, MCL	Ulcerating lesions, single or multiple that can progress to mucocutaneous form; palpable lymph nodes	Might self-heal within 6 mo	No well-defined risk groups	Possums, sloths, anteaters	South America	Limited number of cases, included in the 187, 200-300,000 total cases of New World CL‡

*Old World leishmaniasis.
†New World leishmaniasis.
‡Estimates are of all New World leishmaniases, with *Leishmania braziliensis* comprising the vast majority of these cases.
CL, Cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; DsCL, disseminated cutaneous leishmaniasis; LR, leishmaniasis recidivans; MCL, mucocutaneous leishmaniasis; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.
Adapted from Burza S, Croft SL, Boelaert ML. Leishmaniasis. *Lancet*. 2018;392:951–966. Table 1.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

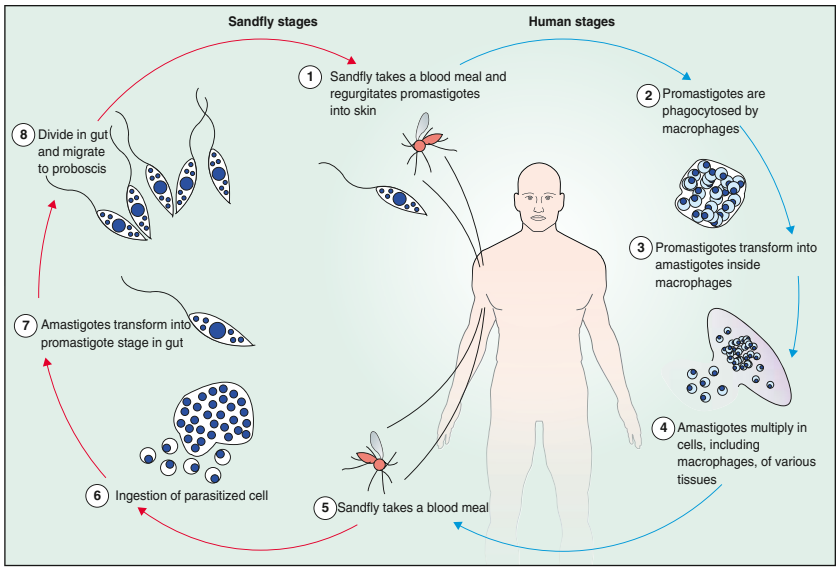

Fig. 331.1 *Leishmania* life cycle. *(From Reithinger R, Dujardin JC, Louzir H, et al. Cutaneous leishmaniasis. Lancet Infect Dis. 2007;7:581–596. Fig. 5.)*

EPIDEMIOLOGY

The leishmaniases are estimated to affect 10-20 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica (Fig. 331.2). The different forms of the disease are distinct in their causes, epidemiologic characteristics, transmission, and geographic distribution. The leishmaniases may occur sporadically throughout an endemic region or may occur in epidemic waves. With only rare exceptions, the *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.

Localized cutaneous leishmaniasis (LCL) in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, Central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and **diffuse cutaneous leishmaniasis (DCL)** in Kenya and Ethiopia. In the New World, *L. (L.) mexicana* causes LCL in a region stretching from Texas through Central America. *L. (L.) amazonensis, L. (L.) pifanoi, L. (L.) garnhami,* and *L. (L.) venezuelensis* cause LCL in South America, the Amazon basin, and northward. These parasites can also cause DCL. Members of the *Viannia* subgenus (*L. [Viannia] braziliensis, L. [V.] panamensis, L. [V.] guyanensis,* and *L. [V.] peruviana*) cause LCL and **mucosal leishmaniasis (ML)** from the northern highlands of Argentina northward to Central America. Some species, particularly *L. (V.) braziliensis,* rarely cause **disseminated leishmaniasis (DL)**. **Visceral leishmaniasis (VL)** in the Old World is caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. VL in the New World is caused by *L. (L.) infantum* (formerly also called *L. chagasi*), which is distributed from Mexico (rare) through Central and South America. *L. infantum* can also cause LCL in the absence of visceral disease in this same geographic distribution.

The maintenance of *Leishmania* in most endemic areas is through a **zoonotic** transmission cycle. In general, the dermotropic strains in both the Old and the New World are maintained in rodent reservoirs, and the domestic dog is the usual reservoir for *L. infantum*. The transmission between reservoir and sand fly is highly adapted to the specific ecologic characteristics of the endemic region. Human infections occur when activities bring them in contact with the zoonotic cycle. **Anthroponotic** transmission, in which humans are the presumed reservoir for vector-borne transmission, occurs with *L. tropica* in some urban areas of the Middle East and Central Asia, and with *L. donovani* in India and Sudan. Congenital transmission of *L. donovani* or *L. infantum* has been reported.

There is a resurgence of leishmaniasis in long-standing endemic areas as well as in new foci. Tens of thousands of cases of LCL occurred in outbreaks in Syria and Kabul, Afghanistan; severe epidemics with >100,000 deaths from VL have occurred in India and Sudan. VL is most prevalent among the poorest of the poor, with substandard housing contributing to the vector-borne transmission and undernutrition leading to increased host susceptibility. The emergence of the leishmaniases in new areas is the result of (1) movement of a susceptible population into existing endemic areas, usually because of agricultural or industrial development or timber harvesting; (2) increase in vector and/or reservoir populations as a result of agriculture development projects and/or climate change; (3) increase in anthroponotic transmission resulting from rapid urbanization in some focuses; and (4) increase in sand fly density resulting from a reduction in vector control programs.

PATHOLOGY

Histopathologic analysis of the skin lesions of LCL and DL show intense chronic granulomatous inflammation involving the epidermis and dermis with relatively few amastigotes. Occasionally, neutrophils and even microabscesses can be seen. The lesions of DCL are characterized by dense infiltration with vacuolated macrophages containing abundant amastigotes. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Amastigotes are abundant in the histiocytes and Kupffer cells. Late in the course of disease, splenic infarcts are common, centrilobular necrosis and fatty infiltration of the liver occur, the normal marrow elements are replaced by parasitized histiocytes, and erythrophagocytosis is present.

PATHOGENESIS

Cellular immune mechanisms determine resistance or susceptibility to infection with *Leishmania*. Resistance is mediated by interleukin (IL)-12–driven generation of a T helper 1 (Th1) cell response, with interferon (IFN)-γ inducing classic macrophage (M1) activation and parasite killing. Susceptibility is associated with expansion of IL-4–producing Th2 cells and/or the production of IL-10 and transforming growth factor (TGF)-β, which are inhibitors of macrophage-mediated parasite killing, and the generation of regulatory T cells and arginase-producing (M2) macrophages. An exuberant innate inflammatory response involving inflammasome activation and IL-1β production in lesions is associated with greater local pathology and delayed healing. Patients with ML exhibit a hyperresponsive cellular immune reaction that contributes to the prominent tissue destruction seen in this form of the disease. Patients with DCL or active VL demonstrate reduced or altered *Leishmania*-specific cellular immune responses, with prominent generation of IL-10, but these responses recover after successful therapy.

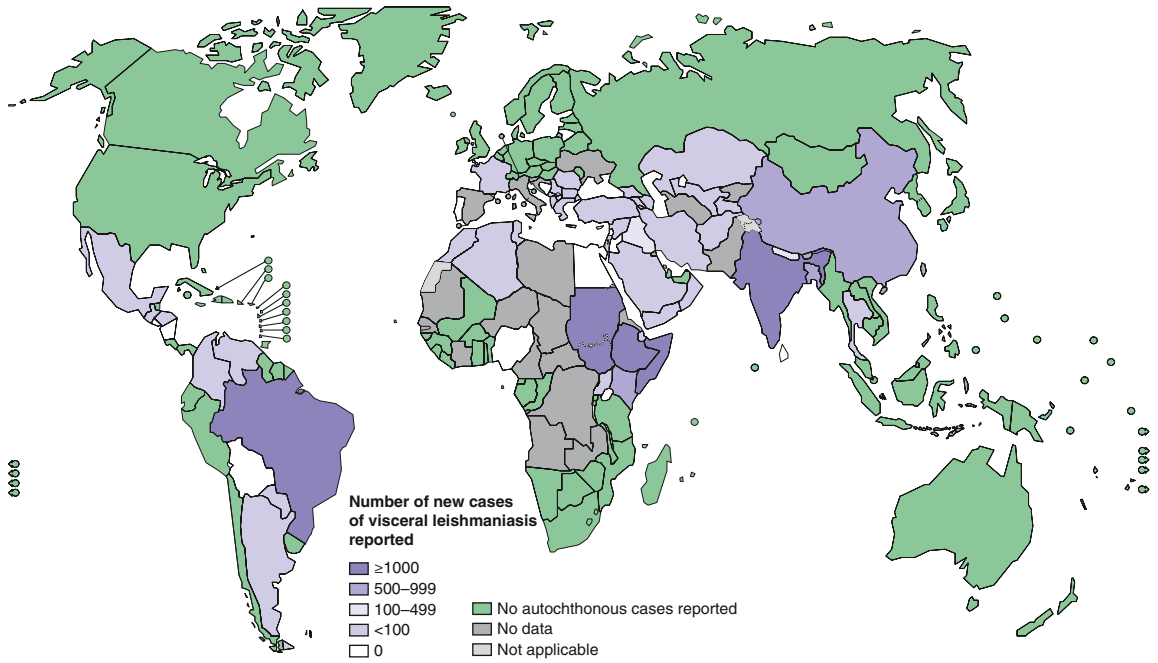

Fig. 331.2 Status of endemicity of visceral leishmaniasis worldwide in 2016. *(From World Health Organization. Recognizing Neglected Tropical Diseases Through Changes on the Skin: A Training Guide for Front-Line Health Workers. Geneva: WHO; 2018.)*

Within endemic areas, people who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens (**Montenegro skin test**) or by antigen-induced production of IFN-γ in a whole blood assay. Subclinical infection occurs considerably more frequently than does active cutaneous or visceral disease. **Host** factors (genetic background, concomitant disease, nutritional status), **parasite** factors (virulence, size of the inoculum), and possibly **vector**-specific factors (vector genotype, immunomodulatory salivary constituents) influence the expression as either subclinical infection or active disease. Within endemic areas, the prevalence of skin test positivity increases with age, and the incidence of clinical disease decreases with age, indicating that immunity is acquired in the population over time. Individuals with prior active disease or subclinical infection are usually immune to a subsequent clinical infection; however, latent infection can lead to active disease if the patient is immunosuppressed.

CLINICAL MANIFESTATIONS

The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized Cutaneous Leishmaniasis

LCL (**Oriental sore**) can affect individuals of any age, but children are the primary victims in many endemic regions. It may present as one or a few papular, nodular, plaque-like, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 331.3). Rarely, >100 lesions have been recorded. The lesions typically begin as a small papule at the site of the sand fly bite, which enlarges to 1-3 cm in diameter and may ulcerate over the course of several weeks to months. The shallow ulcer is usually nontender and surrounded by a sharp, indurated, erythematous margin. There is no drainage unless a bacterial superinfection develops. Lesions caused by *L. major* and *L. mexicana* usually heal spontaneously after 3-6 months, leaving a depressed scar. Lesions on the ear pinna caused by *L. mexicana,* called **chiclero ulcer** because they were common in chicle harvesters in Mexico and Central America, often follow a chronic, destructive course. In general, lesions caused by *L. (Viannia)* species tend to be larger and more chronic. Regional lymphadenopathy and palpable subcutaneous nodules or lymphatic cords, the so-called sporotrichoid appearance, are also more common when the patient is infected with organisms of the *Viannia* subgenus. If lesions do not become secondarily infected, there are usually no complications aside from the residual cutaneous scar.

Diffuse Cutaneous Leishmaniasis

DCL is a rare form of leishmaniasis caused by organisms of the *L. mexicana* complex in the New World and *L. aethiopica* in the Old World. DCL manifests as large, non-ulcerating macules, papules, nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most often involved. Dissemination from the initial lesion usually takes place over several years. These patients are anergic to the Montenegro skin test, and it is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis.

Disseminated Leishmaniasis

In rare cases, parasites can spread (likely by the hematogenous route) in an immunocompetent host from a primary lesion to cause DL. This is defined as >10 lesions (usually in the hundreds) involving at least two noncontiguous areas of the skin. DL has been most often attributed to *L. (V.) braziliensis*. The lesions are typically inflammatory papules or ulcers, in contrast to the nodular and plaque-like lesions of DCL, and about one-third of patients have mucosal involvement.

Mucosal Leishmaniasis

ML (**espundia**) is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous spread of parasites to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the *L. (Viannia)* complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 years, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have, or have had, LCL caused by *L. (V.) braziliensis.* Patients with ML typically have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible

deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

Visceral Leishmaniasis

VL **(kala-azar)** typically affects children <5 years old in the New World and Mediterranean region *(L. infantum)* and older children and young adults in Africa and Asia *(L. donovani)*. After inoculation of the organism into the skin by the sand fly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active kala-azar. Children with **asymptomatic** infection are transiently seropositive but show no clinical evidence of disease. Children who are **oligosymptomatic** have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kala-azar within 2-8 months. Extreme incubation periods of several years have rarely been described. During the first few weeks to months of disease evolution, the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop 3-6 months after the onset of the illness, but a rapid clinical course over 1 month has been noted in up to 20% of patients in some series (Fig. 331.4). At the terminal stages of kala-azar, the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection, HIV coinfection, and underlying malnutrition are risk factors for the development, rapid evolution, and severe disease of active VL. Death occurs in >90% of patients without specific antileishmanial treatment and in 4–10% of treated patients. VL is a known cause of **hemophagocytic lymphohistiocytosis** in endemic areas.

VL is an opportunistic infection associated with **HIV infection**. Most cases have occurred in southern Europe and Brazil, often as a result of needle sharing associated with illicit drug use, with the potential for many more cases as the endemic regions for HIV and VL converge. Leishmaniasis may also result from reactivation of a long-standing subclinical infection. Frequently there is an atypical clinical presentation of VL in HIV-infected individuals with prominent involvement of the gastrointestinal tract and absence of the typical hepatosplenomegaly.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as **post–kala-azar dermal leishmaniasis.** These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of post–kala-azar dermal leishmaniasis are hypopigmented, erythematous, or nodular and usually involve the face and torso. They may persist for several months or for many years.

LABORATORY FINDINGS

Patients with cutaneous leishmaniasis or ML generally do not have abnormal laboratory results unless the lesions are secondarily infected with bacteria. Laboratory findings associated with classic kala-azar include anemia (hemoglobin, 5-8 mg/dL), thrombocytopenia, leukopenia (2,000-3,000 cells/μL), elevated hepatic transaminase levels, and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

DIFFERENTIAL DIAGNOSIS

Diseases that should be considered in the differential diagnosis of LCL include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, ecthyma, syphilis, yaws, and neoplasms. Infections such as syphilis, tertiary yaws, histoplasmosis, and paracoccidioidomycosis, as well as sarcoidosis, granulomatosis with polyangiitis, midline granuloma, and carcinoma, may have clinical features similar to those of ML. VL should be strongly suspected in the patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential exposure in an endemic area. The clinical picture may also be consistent with that of malaria, typhoid fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

DIAGNOSIS

The development of one or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient who had potential exposure in an endemic area should raise suspicion of LCL.

Serologic tests for diagnosis of cutaneous or mucosal disease generally have low sensitivity and specificity and offer little for diagnosis. Serologic testing by enzyme immunoassay, indirect fluorescence assay, or direct agglutination is very useful in VL because of the very high level of antileishmanial antibodies. An immunochromatographic strip test using a recombinant antigen (K39) has a diagnostic sensitivity and specificity for VL of 80–90% and 95%, respectively. Serodiagnostic tests have positive findings in only about half the patients co-infected with HIV.

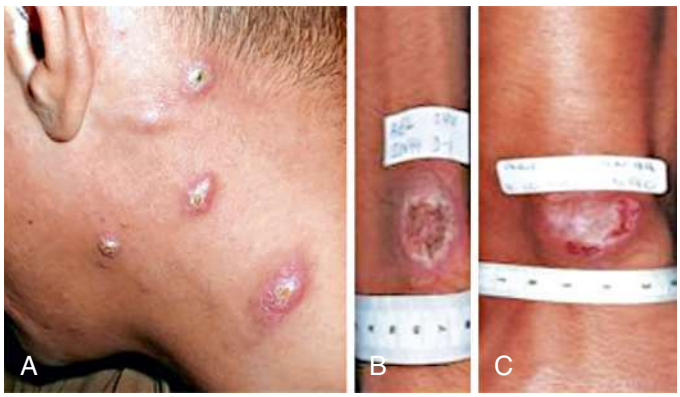

Fig. 331.3 Cutaneous disease. **A**, Old World infection *(Leishmania major)* acquired in Iraq; note five papular and nodular lesions on neck. **B**, New World infection *(Leishmania panamensis)* in Colombia; purely ulcerative lesion is characteristic of New World disease. **C**, Healed infection in patient shown in **B** 70 days after 20 days of meglumine antimonate treatment; note paper-thin scar tissue over flat reepithelialized skin. *(**A**, Courtesy P. Weina; **B**, Courtesy J. Soto. **A-C**, Modified from Murray HW, Berman JD, Davies CR, et al. Advances in leishmaniasis. Lancet. 2005;366:1561–1577.)*



Fig. 331.4 Visceral leishmaniasis *(Leishmania donovani)* in Bihar State, India. **A**, Hepatosplenomegaly and wasting in a young man. **B**, Children with burn marks over enlarged spleen or liver evidence of a local shaman's unsuccessful remedy. *(**A**, Courtesy D. Sacks; **B**, Courtesy R. Kenney; **A** and **B**, Adapted from Murray HW, Berman JD, Davies CR, et al. Advances in leishmaniasis. Lancet. 2005;366:1561–1577.)*

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. **Amastigotes** can be identified in Giemsa-stained tissue sections, aspirates, or impression smears in about half the cases of LCL but only rarely in the lesions of ML. **Culture** of a tissue biopsy or aspirate, best performed by using Novy-MacNeal-Nicolle biphasic blood agar medium, yields a positive finding in only approximately 65% of cases of cutaneous leishmaniasis. Identification of parasites in impression smears, histopathologic sections, or culture medium is more readily accomplished in DCL than in LCL. In patients with VL, smears or cultures of material from splenic, bone marrow, or lymph node aspirations are usually diagnostic. In experienced hands, **splenic aspiration** has a higher diagnostic sensitivity, but it is rarely performed in the United States because of the risk for bleeding complications. A positive culture result allows speciation of the parasite, usually by isoenzyme analysis by a reference laboratory, which may have therapeutic and prognostic significance.

TREATMENT

Specific antileishmanial therapy should be individualized for each patient. It is not routinely indicated for immunocompetent persons having uncomplicated simple LCL (single or few lesions, lesion diameter <1 cm, no mucosal involvement) caused by strains that have a high rate of spontaneous resolution and self-healing *(L. major, L. mexicana).* Lesions that are extensive, severely inflamed, or located where a scar would result in disability (near a joint) or cosmetic disfigurement (face or ear), that involve the lymphatics, or that do not begin healing within 3-4 months should be treated. Cutaneous lesions suspected or known to be caused by members of the *Viannia* subgenus (New World) should be treated because of the low rate of spontaneous healing and the potential risk for development of mucosal or disseminated disease. Similarly, patients with lesions caused by *L. tropica* (Old World), which are typically chronic and nonhealing, should be treated. All patients with VL or ML should receive therapy.

The pentavalent **antimony compounds** (sodium stibogluconate [Pentostam, GlaxoSmithKline, Uxbridge, UK] and **meglumine antimoniate** [Glucantime, Aventis, Strasbourg, France]) have been the mainstay of antileishmanial chemotherapy for >40 years. These drugs have similar efficacies, toxicities, and treatment regimens. Currently, for **sodium stibogluconate** (available in the United States from the Centers for Disease Control and Prevention, Atlanta, GA), the recommended regimen is 20 mg/kg/day intravenously (IV) or intramuscularly (IM) for 20 days (for LCL and DCL) or 28 days (for ML and VL). Repeated courses of therapy may be necessary in patients with severe cutaneous lesions, ML, DCL, DL, or VL. An initial clinical response to therapy usually occurs in the first week of therapy, but complete clinical healing (reepithelialization and scarring for LCL and ML, and regression of splenomegaly and normalization of cytopenias for VL) is usually not evident for weeks to a few months after completion of therapy. Cure rates with this regimen of 90–100% for LCL, 50–70% for ML, and 80–100% for VL were common in the 1990s, but treatment failures, especially in children, have become common in parts of India, East Africa, and Latin America.

Relapses are common in patients who do not have an effective antileishmanial cellular immune response (DCL or HIV co-infection). Adverse effects of antimony therapy are dose and duration dependent and include fatigue, arthralgias, and myalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30–80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10–30%), and nonspecific T-wave changes on electrocardiography (30%). Sudden death from cardiac toxicity has rarely been reported with use of very high doses of pentavalent antimony.

Amphotericin B desoxycholate and **liposomal amphotericin B** are very useful in the treatment of VL, ML, or DL, and in some regions have replaced antimony as first-line therapy, especially in HIV-infected patients. However, the prohibitively high cost of these drugs precludes their use in many resource-poor regions of the world. Amphotericin B desoxycholate at doses of 0.5-1.0 mg/kg every day or every other day for 14-20 doses achieved a cure rate for VL of close to 100%, but renal toxicity associated with amphotericin B was common. **Liposomal amphotericin B** (AmBisome, Gilead Sciences, Foster City, CA) is especially attractive for treatment of leishmaniasis because the drug is concentrated in the reticuloendothelial system and is less nephrotoxic. It is approved by the U.S. Food and Drug Administration (FDA) for treatment of VL at a recommended dose for *immunocompetent patients* of 3 mg/kg on days 1-5, 14, and 21 (total dose 21 mg/kg) and should be considered for first-line therapy in the United States. It is highly effective, with a 90–100% cure rate for VL in immunocompetent children, including those who were refractory to antimony therapy. Therapy for *immunocompromised patients* should be prolonged (recommended total dose 40 mg/kg). A single high dose of liposomal amphotericin B (10 mg/kg) was found to be effective in India (approximately 95% efficacy) but was less effective in East Africa (58% efficacy).

Parenteral treatment of VL with the aminoglycoside **paromomycin** (aminosidine) has efficacy (95%) similar to that of amphotericin B in India. A dose-sparing regimen of the combination of sodium stibogluconate and paromomycin is effective and used in East Africa. **Miltefosine**, a membrane-activating alkyl phospholipid, has been approved as the first oral treatment for VL and has a cure rate of 80–90% in Indian patients with VL when administered orally at 50-100 mg/day (or 2.5 mg/kg for children <12 years old) for 28 days. Miltefosine is indicated for cutaneous infection caused by *L. braziliensis*, *L. guyanensis,* and *L. panamensis*; ML caused by *L. braziliensis*; and VL caused by *L. donovani*. Gastrointestinal adverse effects were frequent but did not require discontinuation of the drug. An increased rate of relapse (up to 20%) has been seen in children treated with miltefosine. Dose-sparing combination regimens are being actively investigated for treatment of VL. Treatment of LCL with oral drugs has had only modest success. Ketoconazole has been effective in treating adults with LCL caused by *L. major, L. mexicana,* and *L. panamensis,* but not *L. tropica* or *L. braziliensis*. Fluconazole in high doses (up to 8 mg/kg/day) for 4-8 weeks was demonstrated to be effective in treating LCL in studies in both the Old and New World; however, the experience in young children is limited. Miltefosine, 2.5 mg/kg/day orally for 20-28 days, was effective in 70–90% of patients with LCL in the Americas. Local therapy, including heat, cryotherapy, and topical 15% paromomycin ointment has been effective treatment for LCL in selected areas in both the Old and the New World. Enhanced drug development efforts and clinical trials of new drugs are clearly needed, especially in children.

PREVENTION

Personal protective measures should include avoidance of exposure to the nocturnal sand flies and, when necessary, the use of insect repellent and permethrin-impregnated mosquito netting. Where peridomiciliary transmission is present, community-based residual insecticide spraying has had some success in reducing the prevalence of leishmaniasis, but long-term effects are difficult to maintain. Control or elimination of infected reservoir hosts (e.g., seropositive domestic dogs) has had limited success. Where anthroponotic transmission is thought to occur, as in south Asia, early recognition, diagnosis, and treatment of cases and vector control measures are essential for progress toward elimination. Several vaccines have been demonstrated to have efficacy in experimental models, and vaccination of humans or domestic dogs may have a role in the control of the leishmaniases in the future.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 332

African Trypanosomiasis (Sleeping Sickness; *Trypanosoma brucei* Complex)

Edsel Maurice T. Salvana and Robert A. Salata

Sixty-five million people in 36 countries are at risk for infection with *Trypanosoma brucei* complex, the causative agent of sleeping sickness. Also known as **human African trypanosomiasis (HAT)**, this disease is restricted to sub-Saharan Africa, the range of the tsetse fly vector. It is a disease of extreme poverty, with the highest disease burden observed in remote rural areas. HAT comes in two geographically and clinically distinct forms. *Trypanosoma brucei gambiense* causes a chronic infection and affects people who live in western and central Africa **(West African sleeping sickness, Gambian trypanosomiasis)**. *Trypanosoma brucei rhodesiense* is a zoonosis that presents as an acute illness lasting several weeks and usually occurs in residents or travelers from eastern and southern Africa **(East African sleeping sickness, Rhodesian trypanosomiasis)**.

ETIOLOGY

HAT is a vector-borne disease caused by parasitic, extracellular, flagellated kinetoplastid protozoans of two subspecies of *T. brucei*. It is transmitted to humans through the bite of *Glossina,* commonly known as the **tsetse fly**.

Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, making it difficult to eradicate. Animal reservoirs occur, but the main source of infection remains chronically infected human hosts.

LIFE CYCLE

T. brucei undergoes several stages of development in the insect and mammalian host. On ingestion with a blood meal, nonproliferative **short stumpy (SS)** forms of the parasite transform into procyclic forms in the insect's midgut. These procyclic forms proliferate and undergo further development into epimastigotes, which then become infective metacyclic forms that migrate to the insect's salivary glands. The life cycle within the tsetse fly takes 15-35 days. On inoculation into the mammalian host, the metacyclic stage transforms into proliferative **long slender (LS)** forms in the bloodstream and the lymphatics, eventually penetrating the central nervous system (CNS). LS forms appear in waves in the peripheral blood, with each wave followed by a febrile crisis and heralding the formation of a new antigenic variant. Once a critical density of LS forms is reached, a quorum-sensing mechanism causes most of these to transform into nonproliferative SS forms that are ingested by *Glossina* and start the cycle anew. Quorum sensing controls peak parasitemia to ensure that the host survives infection long enough for the parasite to complete its life cycle.

Direct transmission to humans has been reported, either vertically to infants or mechanically through contact with tsetse flies with viable LS forms on their mouthparts from a recent blood meal from an infected host.

EPIDEMIOLOGY

HAT occurs mainly in sub-Saharan Africa between latitudes 14 degrees north and 29 degrees south, where the annual rainfall creates optimal climatic conditions for *Glossina*. In 2009, new HAT cases annually fell below 10,000 as a result of intensive control efforts. In 2018, new cases fell to 977, the lowest level in 80 years since the start of systematic data collection. In the last 10 years, 70% of cases were reported from the Democratic Republic of Congo. Gambian trypanosomiasis is targeted for sustainable elimination as a public health problem by 2030.

T. brucei rhodesiense infection is restricted to the eastern third of the endemic area in tropical Africa, stretching from Ethiopia to the northern boundaries of South Africa. *T. brucei gambiense,* which accounts for 95% of HAT cases, occurs mainly in the western half of the continent's endemic region. Rhodesian HAT, which has an acute and often fatal course, greatly reduces chances of transmission to tsetse flies. The ability of *T. brucei rhodesiense* to multiply rapidly in the bloodstream and infect other species of mammals helps maintain its life cycle. HAT is infrequently reported in non-endemic countries, usually in returning travelers or migrants.

PATHOGENESIS

At the site of the *Glossina* bite, tsetse fly salivary antigens, peptides, and proteins promote an immune-tolerant microenvironment that facilitates parasite invasion. Injected metacyclic parasites transform into LS forms, which rapidly divide by binary fission. The parasites, along with the attendant inflammation, cellular debris, and metabolic products, may give rise to a hard, painful, red nodule known as a **trypanosomal chancre** within 5-15 days postinoculation. Parasites directionally migrate from the skin to the lymphatics via an unknown mechanism and pass into the draining lymph node and onward into the main lymphatic ducts. Dissemination into the blood and lymphatic systems follows, with subsequent localization to the CNS. Histopathologic findings in the brain are consistent with meningoencephalitis. The appearance of **morula** cells of Mott (large, strawberry-like cells, supposedly derived from plasma cells) is a characteristic finding in chronic disease.

Mechanisms underlying virulence in HAT are still incompletely understood but seem to be mediated by a complex interplay of trypanosomal, human, and *Glossina* factors. *T. brucei gambiense* utilizes at least three mechanisms to evade lysis by human sera. These include reduced binding to trypanolytic factor 1 (TLF1) via reduced expression and mutation of a haptoglobin-hemoglobin receptor; expression of a specific glycoprotein TgsGP, which reduces trypanosomal membrane fluidity; and a cysteine protease-mediated reduction of sensitivity to apolipoprotein L-1 (APOL1). *T. brucei rhodesiense,* on the other hand, expresses a protein known as serum resistance–associated protein (SRA), which counteracts trypanolytic APOL1 in human serum. APOL1 and the hemoglobin binding protein haptoglobin-related protein (HPR) are major components of two high-density lipoprotein complexes called TLF1 and TLF2, which protect humans against non-human trypanosomes. Trypanosomes also secrete a host of biologically active molecules that can dampen immune responses.

Antigenic variation of **variant surface glycoprotein (VSG)** on the trypanosome surface has long been recognized as a major factor in evading acquired immunity during infection. This antigenic diversity is generated by a tightly controlled system of DNA double-stranded breaks with associated homologous recombination. VSG also inhibits complement activation and antibody-mediated aggregation, facilitating establishment and maintenance of infection. Soluble VSG is hypersecreted, especially at the peak of parasitemia, and may serve as a decoy for antibodies and complement factor, diverting immune responses away from trypanosomes.

CLINICAL MANIFESTATIONS

Clinical presentations vary not only because of the two subspecies of organisms but also because of differences in host response in the

indigenous population of endemic areas and in newcomers or visitors. Visitors usually suffer more from the acute symptoms, but if untreated, death usually follows for natives and visitors alike. Symptoms usually occur within 2-3 weeks of infection. The clinical syndromes of HAT are trypanosomal chancre, hemolymphatic stage, and meningoencephalitic stage.

Trypanosomal Chancre

The site of the tsetse fly bite may be the first presenting feature. A nodule or chancre (3-4 cm) develops in 2-3 days and becomes a painful, hard, red nodule surrounded by an area of erythema and swelling within 1 week. Nodules are typically seen on the lower limbs and sometimes also on the head. They subside spontaneously in about 2 weeks, leaving no permanent scar.

Hemolymphatic Stage (Stage 1)

The most common presenting features of acute HAT occur at the time of invasion of the bloodstream by the parasites, 2-3 weeks after infection. Patients usually present with irregular episodes of fever, each lasting up to 7 days, accompanied by headache, sweating, and generalized lymphadenopathy. Attacks may be separated by symptom-free intervals of days or even weeks. Painless, nonmatted **lymphadenopathy**, most often of the posterior cervical and supraclavicular nodes, is one of the most constant signs, particularly in the Gambian form. A common feature of trypanosomiasis is the presence of blotchy, irregular, nonpruritic, erythematous **macules**, which may appear any time after the first febrile episode, usually within 6-8 weeks. The majority of macules have a normal central area, giving the rash a circinate outline. This **rash** is seen mainly on the trunk and is evanescent, fading in one place only to appear at another site. Examination of the blood during this stage may show anemia, leukopenia with relative monocytosis, and elevated levels of immunoglobulin M (IgM). Cardiac manifestations of HAT have also been reported but are generally limited to nonspecific ST-T wave electrocardiographic abnormalities. Histopathologic characterization shows a lymphomonohistiocytic infiltrate in the interstitium, with no penetration of the myocardial cells, unlike that for American trypanosomiasis (see Chapter 333). The perimyocarditis is usually self-limited and does not typically progress to congestive heart failure.

Meningoencephalitic Stage (Stage 2)

Neurologic symptoms and signs are nonspecific, including irritability, insomnia, and irrational and inexplicable anxieties with frequent changes in mood and personality. Neurologic symptoms may precede invasion of the CNS by the organisms. In untreated *T. brucei rhodesiense* infections, CNS invasion occurs within 3-6 weeks and is associated with recurrent bouts of headache, fever, weakness, and signs of acute toxemia. Death occurs in 6-9 months as a result of secondary infection or cardiac failure.

In Gambian HAT, cerebral symptoms appear within 2 years after the acute symptoms. An increase in drowsiness during the day and insomnia at night reflect the continuous progression of infection and may be accompanied by anemia, leukopenia, and muscle wasting. The chronic, diffuse meningoencephalitis without localizing symptoms is the form referred to as **sleeping sickness**. Drowsiness and an uncontrollable urge to sleep are the major features of this stage and become almost continuous in the terminal stages. Tremor or rigidity with stiff and ataxic gait suggest involvement of the basal ganglia. Psychotic changes occur in one third of untreated patients. Although most untreated disease is fatal, in rare cases, individuals remain asymptomatic, clear parasitemia, and become seronegative.

DIAGNOSIS

Definitive diagnosis can be established during the early stages by examination of a fresh, thick blood smear, which permits visualization of the motile active forms (Fig. 332.1). HAT can also be detected from blood using a variety of sensitive techniques, such as quantitative buffy coat smears and mini anion exchange resins. Dried, Giemsa-stained smears should be examined for the detailed morphologic features of the organisms. If a thick blood or buffy coat smear is negative, concentration techniques may help. Aspiration of an enlarged lymph node can also be used to obtain material for parasitologic examination. If positive, cerebrospinal fluid (CSF) should also be examined for the organisms. The presence of trypanosomes, or ≥5 white blood cells (WBCs)/μL, or both, is indicative of stage 2 disease. If trypanosomes are absent in the CSF, some authorities use a count of 10-20 WBCs/μL as a cutoff for diagnosing late-stage disease.

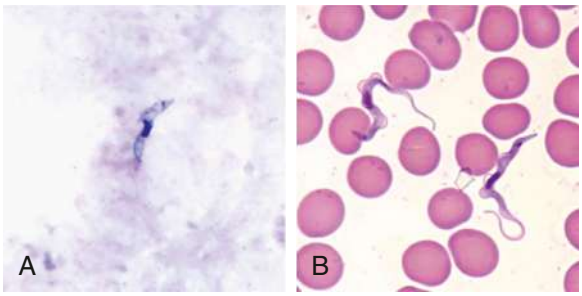

Fig. 332.1 *Trypanosoma brucei* sp. trypomastigotes in thick blood smear stained with Giemsa (A) and thin blood smear stained with Wright-Giemsa (B). *(From Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trypanosomiasis, African [website], 2018. https://www.cdc.gov/dpdx/trypanosomiasisafrican/index.html)*

The card agglutination trypanosomiasis test (CATT) is of value for epidemiologic purposes and for screening for *T. brucei gambiense*. Lateral flow formats of CATT have enabled point-of-care testing. Because CATT detects antibodies against particular VSG molecules, it cannot distinguish present from past infection.

Polymerase chain reaction–based tests have been shown to be highly sensitive and specific, but these tests require laboratory facilities. Field-based loop-mediated isothermal amplification tests have been developed and validated. Other areas of active research for diagnostics include new biomarkers, cytokine profiles, proteomics, and polysomnography, which are being used not only to identify disease but to differentiate disease stages.

TREATMENT

The choice of chemotherapeutic agents for treatment depends on the stage of the infection and the causative organisms.

Stage 1 Treatment

Hematogenous forms of both Rhodesian and Gambian HAT have been traditionally treated with either suramin or pentamidine. **Suramin** is a polysulfonated symmetric naphthalene derivative given as a 10% solution for intravenous (IV) administration. A **test dose** (10 mg for children; 100-200 mg for adults) is initially administered to detect rare idiosyncratic reactions of shock and collapse. The dose for subsequent IV injections is 20 mg/kg (maximum 1 g) administered on days 1, 3, 7, 14, and 21. Suramin is nephrotoxic; thus a urinalysis should be performed before each dose. Marked proteinuria, blood, or casts is a contraindication to continuation of suramin. Resistance is rare but has been reported.

Pentamidine isethionate (4 mg/kg/day intramuscularly [IM] daily or on alternate days for 7-10 days) concentrates to high levels in trypanosomes and is highly trypanocidal. It is better tolerated than suramin but carries significant risk of hypoglycemia, nephrotoxicity, hypotension, leukopenia, and liver enzyme elevation. Because of its

potency, long half-life, and toxicity, short-course treatment is desirable and is being investigated.

Fexinidazole has recently been approved for oral treatment of stage 1 and 2 Gambian HAT in 6 years of age and older and weighing at least 20 kg. Dosing is weight based over 10 days. For 35 kg and above, a loading dose of 1,800 mg for 4 days followed by a maintenance dose of 1,200 mg over 6 days is recommended. For 20 kg to <35 kg, the loading dose is 1,200 mg over 4 days and 600 mg maintenance over 6 days. Common side effects include gastrointestinal upset, asthenia, headache, tremors, and dizziness. Some patients may develop neutropenia.

Stage 2 Treatment

Combination **eflornithine and nifurtimox** (NECT) is the current treatment of choice for *T. brucei gambiense* CNS infection. Eflornithine is given at 400 mg/kg/day IV divided every 12 hours for 7 days, along with nifurtimox, 15 mg/kg/day orally divided every 8 hour for 10 days. If nifurtimox is unavailable, eflornithine monotherapy can be given at 400 mg/kg/day IV divided every 6 hours for 14 days. Adverse reactions to these regimens include fever, hypertension, and seizures, with NECT having less frequent events.

Fexinidazole is a safe and effective, all oral alternative to NECT for stage 2 Gambian HAT. However, it is associated with lower efficacy in severe disease (86.9% with fexinidazole vs 98.7% for NECT). Dosing and duration are the same as for stage 1 disease.

Melarsoprol is an arsenical compound and is the only effective treatment for late *T. brucei rhodesiense* disease. Treatment of children is initiated at 0.36 mg/kg IV once daily, with gradually escalating doses every 1-5 days to 3.6 mg/kg once daily; treatment is usually 10 doses (18-25 mg/kg total dose). Treatment of adults is with melarsoprol 2-3.6 mg/kg IV once daily for 3 days; and after 1 week, 3.6 mg/kg once daily for 3 days, which is repeated after 10-21 days. An alternative regimen is 2.2 mg/kg once daily for 10 days. Guidelines recommend 18-25 mg/kg total over 1 month. Reactions such as fever, abdominal pain, and chest pain are rare but may occur during or shortly after administration. Serious toxic effects include encephalopathy and exfoliative dermatitis.

Following on the success of fexinidazole, other candidate oral drugs for HAT are being studied. This includes acoziborole, which is currently in clinical trials as a single-dose oral treatment for stage 2 HAT.

PREVENTION

A vaccine or consistently effective prophylactic therapy is not available and is particularly challenging because of the antigenic variation caused by VSGs. Virus-like particles are being explored as an adjuvant to hurdle the complexities of the immunologic response. A single injection of pentamidine (3-4 mg/kg IM) provides protection against Gambian trypanosomiasis for at least 6 months, but the effectiveness against the Rhodesian form is uncertain.

Vector control programs against *Glossina* have been essential in controlling disease, coupled with the use of screens, traps, insecticides, and sanitary measures. Neutral-colored clothing may reduce tsetse fly bites. Control of infection in animal reservoirs with mass administration of trypanocidal drugs in cattle has met with some success.

The full genome of *T. brucei* with about 9,000 genes has been sequenced. Approximately 10% of these genes encode VSGs. CRISPR-Cas9-based gene editing has helped identify genes relevant to the disease and its possible prevention, as well as the design of new antitrypanosomal drugs, including those that target specific metabolic pathways.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 333

American Trypanosomiasis (Chagas Disease; *Trypanosoma cruzi*)

Edsel Maurice T. Salvana and Robert A. Salata

American trypanosomiasis or Chagas disease is caused by the protozoan *Trypanosoma cruzi*. Its natural vectors are the reduviid insects, specifically **triatomines**, variably known as wild bedbugs, assassin bugs, or kissing bugs. It can also be transmitted orally from contaminated food, vertically from mother to child, and through blood transfusion or organ transplantation. Signs and symptoms of acute Chagas disease are usually nonspecific, whereas chronic disease may manifest as cardiomyopathy or severe gastrointestinal (GI) dilation and dysfunction.

ETIOLOGY

American trypanosomiasis is caused by *T. cruzi*, a parasitic, flagellated kinetoplastid protozoan. The main vectors for *T. cruzi* are insects of the family Reduviidae, subfamily Triatominae, which includes *Triatoma infestans, Rhodnius prolixus,* and *Panstrongylus megistus.*

LIFE CYCLE

T. cruzi has three recognizable morphogenetic phases: amastigotes, trypomastigotes, and epimastigotes (Figs. 333.1 and 333.2). **Amastigotes** are intracellular forms found in mammalian tissues that are spherical and have a short flagellum but form clusters of oval shapes (pseudocysts) within infected tissues. **Trypomastigotes** are spindle-shaped, extracellular, nondividing forms that are found in blood and are responsible for both transmission of infection to the insect vector and cell-to-cell spread of infection. **Epimastigotes** are found in the midgut of the vector insect and multiply in the midgut and rectum of arthropods, differentiating into metacyclic forms. **Metacyclic trypomastigotes** are the infectious form for humans and are released onto the skin of a human when the insect defecates close to the site of a bite, entering through the damaged skin or mucous membranes. Once in the host, these multiply intracellularly as amastigotes, which then differentiate into bloodstream trypomastigotes and are released into the circulation when the host cell ruptures. Blood-borne trypomastigotes circulate until they enter another host cell or are taken up by the bite of another insect, completing the life cycle. There is some variability in these stages. Reverse transitions can occur; epimastigote-like forms have been found in the mammalian hosts, and trypomastigotes have been observed to replicate. Amastigotes can also quickly transform into quiescent forms upon drug exposure and can maintain persistent infection despite treatment.

EPIDEMIOLOGY

Natural transmission of Chagas disease occurs in North and South America, most frequently in continental Latin America. The disease may arise elsewhere because of migration and transmission through contaminated blood. World Health Organization (WHO) and Pan-American Health Organization–led efforts in large-scale vector control, blood donor screening to prevent transmission through transfusion and case finding, and treatment of chronically infected

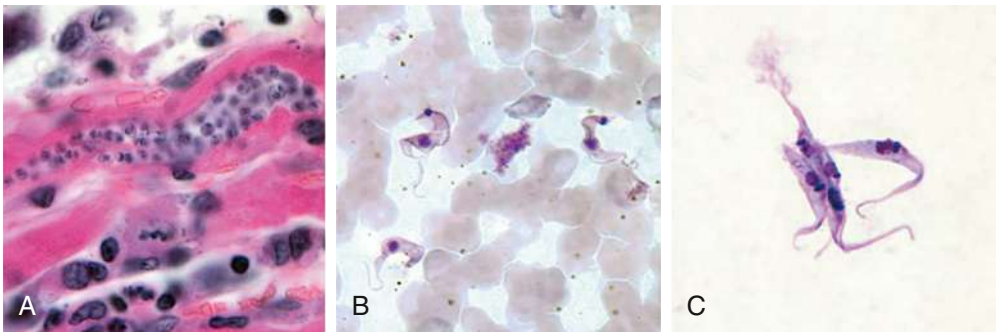

Fig. 333.1 Stages of *Trypanosoma cruzi*. **A,** Amastigote. **B,** Trypomastigote. **C,** Epimastigotes. *(From Centers for Disease Control and Prevention. Laboratory identification of parasites of public health concern. Trypanosomiasis, American [website], 2018. https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html)*

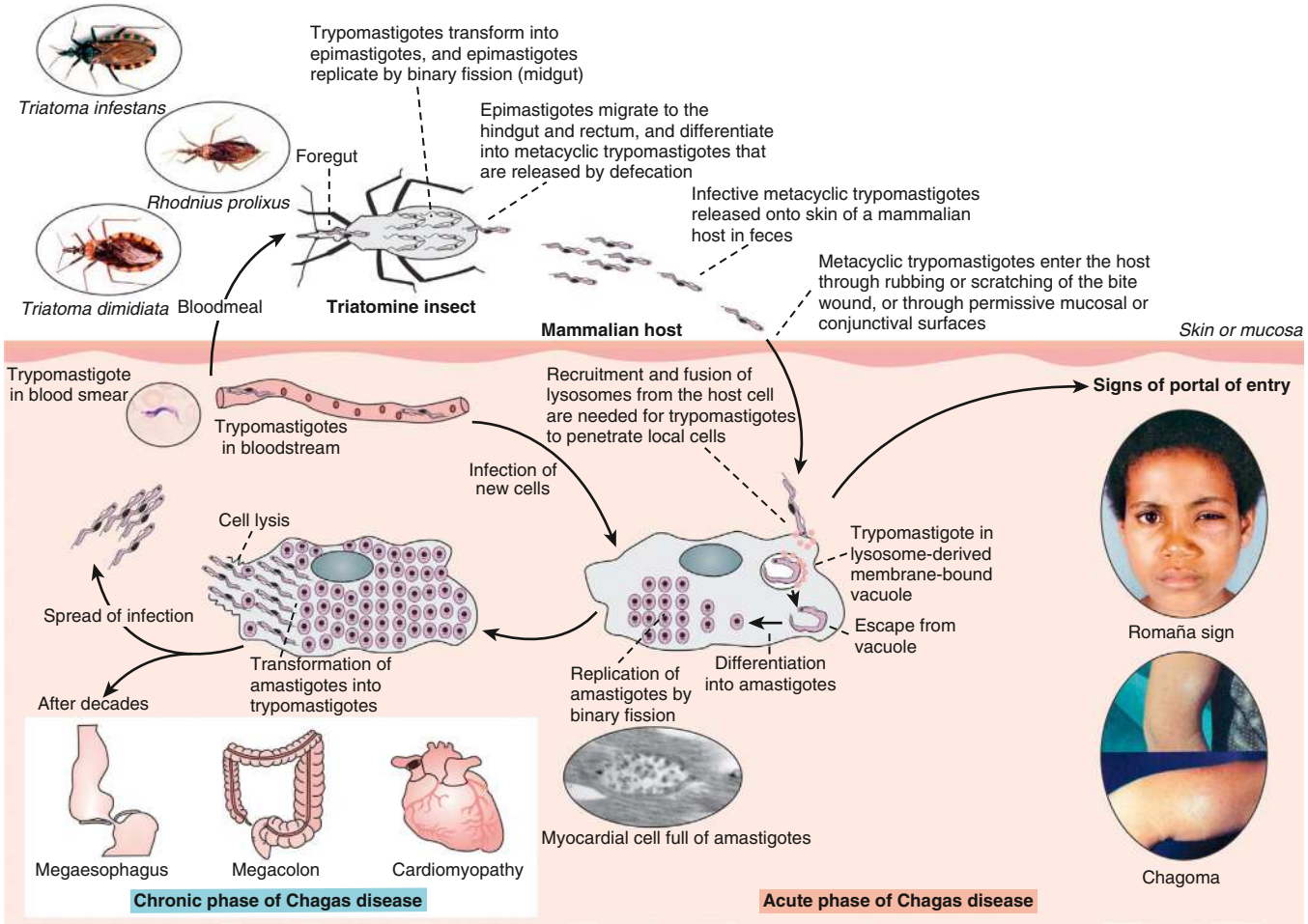

Fig. 333.2 Vector-borne transmission and life cycle of *Trypanosoma cruzi*. *(From Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010;375:1388–1400. Fig. 1.)*

mothers and newborn infants have effectively halted transmission in a number of areas of South America. The number of cases has dropped from a peak of 24 million in 1984 to a current estimate of 6-7 million. Incident cases are estimated at 30,000 infections per year, including 8,000 newborns from vertical transmission. Chagas disease causes 10,000-12,000 deaths annually. This is likely an underestimate as long-term complications of Chagas disease as a cause of death may not be properly attributed to undiagnosed, chronically infected persons.

Infection is divided into two main phases: acute and chronic (Table 333.1). **Acute infection** can manifest as fever, lymphadenopathy, organomegaly, myocarditis, and meningoencephalitis but is otherwise asymptomatic in up to 95% of infected individuals. **Chronic infection** in 60–70% of patients is *indeterminate,* meaning the patient is asymptomatic but has a positive antibody titer. Approximately 30% of infected persons proceed to chronic determinate or symptomatic *T. cruzi* infection.

The *T. cruzi* genome has been fully sequenced and contains 12,000 genes, the most widely expanded among trypanosomatids, and may reflect its ability to invade virtually any nucleated cell type within reach. Significant variability is present, along with extensive epigenetic modification of surface proteins, which may contribute to immune evasion. Seven genetic lineages, known as *discrete typing units* (DTUs) are recognized. These are referred to as TcI through TcVI, and Tcbat for

Table 333.1 Clinical Features and Diagnosis of Chagas Disease

	GEOGRAPHIC DISTRIBUTION	CLINICAL SIGNS/SYMPTOMS	DIAGNOSIS
ACUTE FORMS*			
Vectorial	Endemic countries	• Incubation period: 1-2 wk • Signs of portal of entry: indurated cutaneous lesion (chagoma) or palpebral edema (Romaña sign) • Most cases are mild disease (95–99%) and unrecognized • Persistent fever, fatigue, lymphadenopathy, hepatomegaly, splenomegaly, morbilliform rash, edema • In rare cases, myocarditis or meningoencephalitis • Anemia, lymphocytosis, elevated AST/ALT concentrations • Risk of mortality: 0.2–0.5%	• Direct parasitologic methods: patent parasitemia up to 90 days • Microscopic examination of fresh blood, Giemsa-stained thin and thick blood films, or buffy coat • Concentration methods: microhematocrit and Strout method PCR techniques • Serology is not useful
Congenital	Endemic and nonendemic countries	• Incubation period: birth to several weeks • Most are asymptomatic or have mild disease • Prematurity, low birthweight, abortion, neonatal death • Fever, jaundice, edema, hepatomegaly, splenomegaly, respiratory distress syndrome, myocarditis, meningoencephalitis • Anemia and thrombocytopenia • Risk of mortality: <2%	• Direct parasitologic methods • Concentration methods: microhematocrit, Strout method • Direct microscopy also useful • PCR: most sensitive technique • Serology: after 9 mo or later
Oral	Restricted areas of endemic countries (Amazon basin) and local outbreaks	• Incubation period: 3-22 days • Fever, vomiting, periocular edema, dyspnea, fever, myalgia, prostration, cough, splenomegaly, hepatomegaly, chest pain, abdominal pain, digestive hemorrhage • Risk of mortality: 1–35%	Same as for vectorial
Transfusion and transplant	Endemic and nonendemic countries	• Incubation period: 8-160 days; persistent fever • Clinical characteristics similar to those of vectorial cases (excluding portal of entry signs) • Risk of mortality is variable and depends on the severity of baseline disease	• Same as for vectorial • PCR techniques usually yield positive results days to weeks before trypomastigotes are detectable in blood • Tissue samples are needed in some circumstances
Reactivation in HIV-infected patients	Endemic and nonendemic countries	• Behaves as other opportunistic infections • Reactivation with <200 CD4 cells/μL (mostly with <100) • Affects CNS (75–90%) as single or multiple space-occupying lesions or as severe necrohemorrhagic meningoencephalitis • Cardiac involvement (10–55%): myocarditis, pericardial effusion or worsening of previous cardiomyopathy • Risk of mortality: 20%	• Direct parasitologic methods, as in vectorial cases • Parasite can be found in CSF, other body fluids, and tissue samples • PCR: not useful for diagnosis of reactivation • Serology: indicative of chronic infection and helpful in cases of suspected disease
Reactivation in other immunosuppressed patients	Endemic and nonendemic countries	• Reactivation after transplantation or in patients with hematologic malignancies • Clinical characteristics similar to those of patients who undergo transfusion and those with panniculitis and other skin disorders • Risk of mortality is variable and depends on severity of baseline disease and prompt diagnosis	• Direct parasitologic methods, as in vectorial cases • Parasite can be found in tissue samples • PCR: increasing parasite load detected with real-time PCR in serial specimens could be indicative of a high risk of reactivation
CHRONIC FORMS			
Indeterminate	Endemic and nonendemic countries	• Asymptomatic • Normal chest radiograph and 12-lead ECG	• Serology: detection of IgG • PCR: low sensitivity

Table 333.1 Clinical Features and Diagnosis of Chagas Disease—cont'd

	GEOGRAPHIC DISTRIBUTION	CLINICAL SIGNS/SYMPTOMS	DIAGNOSIS
Cardiac and gastrointestinal	Endemic and nonendemic countries	• Cardiac manifestations: fatigue, syncope, palpitations, dizziness, stroke; late manifestations: chest pain (atypical), dyspnea, edema, left ventricular dysfunction, congestive heart failure; alterations in 12-lead ECG, echocardiography, or other heart function tests • Gastrointestinal: dysphagia, regurgitation, severe constipation (dilated esophagus or colon); alterations in esophageal manometry, barium swallow, or barium enema	• Serology: detection of IgG • PCR: low sensitivity

*Including reactivation in immunosuppressed patients.
ALT, Alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.
From Pérez-Molina J, Molina I. Chagas disease. *Lancet*. 2018;391:82–92. Table 2.

the seventh DTU. DTUs may differ in geographic distribution and predominant vector and hosts and may also vary in disease manifestations and response to treatment. A recent meta-analysis showed that TcI, the most widespread DTU, may be less susceptible to benznidazole.

T. cruzi infection is primarily a zoonosis, and humans are incidental hosts. *T. cruzi* has a large sylvan reservoir and has been isolated from numerous animal species. The presence of reservoirs and vectors of *T. cruzi* and the socioeconomic and educational levels of the population are the most important risk factors for vector-borne transmission to humans. Insect vectors are found in rural, wooded areas and acquire infection through ingestion of blood from humans or animals with circulating trypomastigotes.

Housing conditions are very important in the transmission chain. Incidence and prevalence of infection depend on the adaptation of the triatomines to human dwellings, as well as the vector capacity of the species. Animal reservoirs of reduviid bugs include dogs, cats, rats, opossum, guinea pigs, monkeys, bats, and raccoons. Humans often become infected when land in enzootic areas is developed for agricultural or commercial purposes. An estimated 240,000 to 350,000 immigrants from endemic countries living in the United States are likely infected with *T. cruzi*. Seventy-six cases of **autochthonous** transmission in the United States have also been reported from 2000 to 2018; more than half of the cases were described in Texas.

The risk of congenital Chagas disease transmission is 1–5%. Heavy parasite loads are associated with higher risk of vertical transmission. Transplacental infection is associated with premature birth, fetal wastage, hepatomegaly, and anemia. Infected infants are mostly asymptomatic at birth, although 10–40% may have signs suggestive of congenital infection. Untreated infected infants are at risk for developing Chagas cardiomyopathy later in life.

Disease transmission can occur through blood transfusions in endemic areas from asymptomatic blood donors. The risk for transmission through a single blood transfusion from a chagasic donor is 13–23%. Blood screening for Chagas disease in the United States has detected 2,462 confirmed cases between 2007 and 2019 (www.aabb.org).

Percutaneous injection from laboratory accidents is a documented mode of transmission. Oral transmission through **contaminated food** can occur. Although transmission from breastfeeding is uncommon, women with acute infections should not nurse until they have been treated.

PATHOGENESIS

Acute Disease

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages, and monocytes infiltrate. *T. cruzi* organisms are engulfed by macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, and replicate. A local tissue reaction, the **chagoma**, develops and the process extends to a local lymph node (see Fig. 333.2). Blood forms appear, and the process disseminates. A multitude of innate response mechanisms are deployed at the beginning of infection but are largely ineffective for controlling invasion. However, this initial response is essential for setting up the more potent subsequent adaptive response. Peak parasite numbers are seen after 2-3 weeks and drop quickly when the adaptive immune response comes into play. This response, while efficient at clearing up to 95% of the parasites, is not sterilizing and parasites can persist in more susceptible tissues such as muscle and ganglion cells.

Chronic Disease

The pathophysiology of chronic Chagas disease involves several mechanisms and most significantly affects two main target organs: the heart and the GI tract. Development of pathology in these organs is linked to parasite tropism and persistence in susceptible tissue types against the background of an otherwise effective *T. cruzi*–specific systemic immune response.

In the case of cardiac pathology, parasite-dependent myocardial damage plays some role because of invasion of myocardial cells. The extent of injury seems to be less severe compared to acute disease, and its actual proportional contribution to overall tissue destruction is unclear. Additional damage comes from chronic immune-mediated myocardial injury as a result of delayed type IV hypersensitivity to parasite persistence in myocardial cells. This causes mononuclear myocarditis and myocytolysis, leading to fibrosis and contributing to the development of cardiomyopathy. Dysautonomia due to direct damage to ganglion cells and antineuronal autoimmune reactions leads to the development of cardiomyopathy as an effect of excess catecholamine stimulation. This phenomenon in turn increases myocardial irritability resulting in a higher risk of malignant arrhythmias and sudden cardiac death. Microvascular disturbances also further exacerbate cardiac damage from intimal proliferation and fibrosis due to parasite-induced perivascular inflammation and cell necrosis.

In patients with GI tract involvement, myenteric plexus destruction leads to pathologic organ dilation. There is a diminution in the Auerbach and the Meissner plexus, as well as preganglionic lesions and a reduction in the number of dorsal motor nuclear cells of the vagus nerve. Loss of ganglia in the esophagus results in abnormal dilation.

Antibodies involved in resistance to *T. cruzi* invasion are related to the phase of infection. IgG antibodies to several major surface antigens mediate immunophagocytosis of *T. cruzi* by macrophages. Activation

of autoreactive T- and B-cell clones (with B-cell clones resulting in the production of autoantibodies) is a well-described phenomenon during *T. cruzi* infection. However, the contribution of this activation to pathology seems to be dependent on persistence of infection. Conditions that depress cell-mediated immunity increase the severity of *T. cruzi* infection. There is evidence that host genetic factors play a significant role in progression and severity of chronic disease.

CLINICAL MANIFESTATIONS

Acute Chagas disease in children is usually asymptomatic or is associated with mild febrile illness characterized by malaise, facial edema, and lymphadenopathy (see Table 333.1). Infants often demonstrate local signs of inflammation at the site of parasite entry, which is then referred to as a **chagoma**. Approximately 50% of children come to medical attention with the **Romaña sign** (unilateral, painless eye swelling), conjunctivitis, and preauricular lymphadenitis. Patients complain of fatigue and headache. Fever can persist for 4-5 weeks. More severe systemic presentations can occur in children <2 years old and may include lymphadenopathy, hepatosplenomegaly, and meningoencephalitis. A cutaneous morbilliform eruption can accompany the acute syndrome. Anemia, lymphocytosis, hepatitis, and thrombocytopenia have also been described.

The heart, central nervous system (CNS), peripheral nerve ganglia, and reticuloendothelial system are often heavily parasitized. The heart is the primary target organ. The intense parasitism can result in acute inflammation and in four-chamber cardiac dilation.

Intrauterine infection in pregnant women can cause spontaneous abortion or premature birth. In children with congenital infection, severe anemia, hepatosplenomegaly, jaundice, and seizures can mimic congenital cytomegalovirus infection, toxoplasmosis, and erythroblastosis fetalis. *T. cruzi* can be visualized in the cerebrospinal fluid in cases of meningoencephalitis. Children usually undergo spontaneous remission in 8-12 weeks and enter the indeterminate chronic phase with lifelong low-grade parasitemia and development of antibodies to many *T. cruzi* cell surface antigens. In acute disease, mortality is 5–10%, with deaths caused by acute myocarditis, with resultant heart failure, or meningoencephalitis. Acute Chagas disease should be differentiated from malaria, schistosomiasis, visceral leishmaniasis, brucellosis, typhoid fever, and infectious mononucleosis.

Autonomic dysfunction and peripheral neuropathy can occur. CNS involvement in Chagas disease is uncommon. If granulomatous encephalitis occurs during acute infection, it is usually fatal.

Chronic Chagas disease may be asymptomatic or symptomatic. The most common presentation of chronic *T. cruzi* infection is **cardiomyopathy,** manifested by congestive heart failure, arrhythmia, and thromboembolic events. ECG abnormalities include partial or complete atrioventricular block and right bundle branch block. Left bundle branch block is unusual. Myocardial infarction has been reported and may be secondary to left apical aneurysm embolization or necrotizing arteriolitis of the microvasculature. Left ventricular apical aneurysms are pathognomonic of chronic chagasic cardiomyopathy.

GI manifestations of chronic Chagas disease occur in 8–10% of patients. Characteristically, this involvement presents clinically as megaesophagus and megacolon. Sigmoid dilation, volvulus, and fecalomas are often found in **megacolon**. **Megaesophagus** presents as dysphagia, odynophagia, and cough. The esophagus can reach up to 26 times its normal weight and hold up to 2 L of excess fluid. Esophageal body abnormalities occur independently of lower esophageal dysfunction. Megaesophagus can lead to esophagitis and cancer of the esophagus. Aspiration pneumonia and pulmonary tuberculosis are also more common in patients with megaesophagus.

Immunocompromised Persons

T. cruzi infections in immunocompromised persons may be caused by **transmission** from an asymptomatic donor of blood products or **reactivation** of prior infection. Organ donation to allograft recipients can result in a devastating form of the illness. Cardiac transplantation for Chagas cardiomyopathy has resulted in reactivation, despite prophylaxis and postoperative treatment with benznidazole. HIV infection also leads to reactivation in about 20% of cases; cerebral lesions are more common in these patients and can mimic *Toxoplasma* encephalitis. Myocarditis is also frequently observed, and secondary prophylaxis may be of benefit in some HIV–co-infected patients. In immunocompromised patients at risk for reactivation, serologic testing and close monitoring are necessary.

DIAGNOSIS

A careful history with attention to geographic origin and travel is important. A peripheral blood smear or a Giemsa-stained smear during the acute phase of illness may show motile trypanosomes, which is diagnostic for Chagas disease (see Fig. 333.1). These are only seen in the first 6-12 weeks of illness. Buffy coat smears may improve yield.

Most persons seek medical attention during the chronic phase of the disease, when parasites are not found in the bloodstream and clinical symptoms are not diagnostic. Serologic testing is used for diagnosis, most commonly enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination, and indirect fluorescent antibody testing. No single serology test is sufficiently reliable to make the diagnosis, so repeat or parallel testing using a different method or antigen is required to confirm the result of an initial positive serologic test, and in the case of discordant results, a third test may be employed. Two tests, the Ortho *T. cruzi* ELISA Test System and the Abbott Prism Chagas Assay, are approved by the U.S. Food and Drug Administration (FDA) for screening of blood donors but not for clinical samples. For clinical samples in suspected Chagas cases in the United States, contact the Centers for Disease Control and Prevention (CDC) for further guidance. Confirmatory tests include the radiologic immunoprecipitation assay (Chagas RIPA, currently for research or limited clinical testing only) and Western blot assays based on trypomastigote excreted-secreted antigens (TESA-WB). The Abbott Enzyme Strip Assay Chagas (ESA-Chagas) using recombinant *T. cruzi* antigens is the only FDA-approved confirmatory test in the United States.

Nonimmunologic methods of diagnosis are available. Mouse inoculation and **xenodiagnosis** (allowing uninfected reduviid bugs to feed on a patient's blood and examining the intestinal contents of those bugs 30 days after the meal) are cumbersome and not routinely performed. Parasites can be cultured in Novy-MacNeal-Nicolle (NNN) media. Polymerase chain reaction (PCR) tests of nuclear and kinetoplast DNA sequences have been developed and can be highly sensitive in acute disease but are less reliable in chronic disease. PCR has been used as an early indicator of treatment failure in therapeutic clinical trials, and to detect reactivation in chronically infected patients at risk because of immunosuppression. PCR is not sufficiently sensitive for blood screening. Moreover, there is significant variability among methods and parasite strains. Diagnosis of congenital transmission in newborns cannot be made at birth with serology because of the presence of maternal antibodies in the first 6 months of life. Microscopic examination, parasite culture, or PCR can be used. However, a serologic test at 6-12 months is recommended to exclude infection definitively.

TREATMENT

Biochemical differences between the metabolism of American trypanosomes and that of mammalian hosts have been exploited for chemotherapy. Trypanosomes are very sensitive to oxidative radicals and do not possess catalase or glutathione reductase/glutathione peroxidase, which are key enzymes in scavenging free radicals. All trypanosomes also have an unusual, reduced nicotinamide adenine dinucleotide phosphate (NADPH)–dependent disulfide reductase. Drugs that stimulate hydrogen peroxide (H_2O_2) generation or prevent its utilization are potential trypanosomicidal agents. Other biochemical pathways

that have been targeted include ergosterol synthesis using azole compounds and the hypoxanthine-guanine phosphoribosyltransferase pathway using allopurinol.

Drug treatment for *T. cruzi* infection is currently limited to nifurtimox and benznidazole. Both are effective against trypomastigotes and amastigotes and have been used to eradicate parasites in the acute stages of infection. Treatment responses vary according to the phase of Chagas disease, duration of treatment, dose, age of the patient, and geographic origin of the patient. For acute disease, the average cure rate is about 60–80%. Cure of chronic disease is difficult to assess due to the different definitions of cure, whether with a negative serology or quantitative PCR. Other drugs that have been tried include posaconazole, ravuconazole, and fexinidazole but have not been as successful as traditional treatment.

Benznidazole, a nitroimidazole derivative, is the most effective treatment for Chagas disease. Benznidazole's primary mechanism of action involves covalent binding with trypanosomal protein thiols and low molecular weight thiols, resulting in depletion of these molecules and disruption of the parasite metabolism. The recommended treatment regimen for children 2-12 years old is 5-8 mg/kg/day orally (PO), which can be divided twice daily (bid) for 60 days. For those >12 years old, 5-7 mg/kg/day for 60 days is recommended. The tablets can be administered as a slurry for children who have difficulty swallowing. A recent meta-analysis suggests a 30-day regimen may be noninferior to a 60-day regimen. Cure rates for chronic disease as assessed by PCR is 66–91% at the end of treatment, but this drops to 82% at 1 year, 55% at 2 years, and 47% at 5 years. This drug is associated with significant toxicity, including rash, photosensitivity, peripheral neuritis, granulocytopenia, and thrombocytopenia.

Nifurtimox generates highly toxic oxygen metabolites through the action of nitroreductases, which produce unstable nitroanion radicals, which in turn react with oxygen to produce peroxide and superoxide free radicals. The FDA recently approved nifurtimox for the treatment of Chagas disease in pediatric patients from birth to <18 years of age and weighing at least 2.5 kg. The recommended total daily dose in pediatric patients is 10-20 mg/kg/day orally divided into three doses for 60 days for children <40 kg, and 8-10 mg/kg/day orally divided into three doses for children >40 kg. Nifurtimox has been associated with weakness, anorexia, GI disturbances, toxic hepatitis, tremors, seizures, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

With the adoption by WHO of control and elimination strategies for Chagas disease, both acute and chronic disease should be treated. Serologic conversion is seen as an appropriate treatment response for chronic disease, although some patients who achieve this still eventually develop symptoms. One study reported cure rates as high as 97% for chronic disease in patients <16 years old and supports early and aggressive case findings and treatment. Infants suspected of congenitally acquired Chagas disease should be properly evaluated and treated immediately upon confirmation of the diagnosis. Women who give birth to infants with congenital Chagas disease should be offered treatment to prevent congenital transmission in subsequent pregnancies. Continuing efforts for elimination will necessitate development of more accurate diagnostics and more effective drugs, particularly for chronic disease.

Treatment of congestive heart failure is generally in line with recommendations for management of dilated cardiomyopathy from other causes. β-Adrenergic blockers have been validated in the management of these patients. Digitalis toxicity occurs frequently in patients with Chagas cardiomyopathy. Pacemakers may be necessary in cases of severe heart block. Although cardiac transplantation has been used successfully in chagasic patients, it is reserved for those with the most severe disease manifestations. Plasmapheresis to remove antibodies with adrenergic activity has been proposed for refractory patients; this approach has worked in patients with dilated cardiomyopathy from other causes, but its application to Chagas disease is unproved.

A light, balanced diet is recommended for **megaesophagus**. Surgery or dilation of the lower esophageal sphincter treats megaesophagus; pneumatic dilation is the superior mode of therapy. Nitrates and nifedipine have been used to reduce lower esophageal sphincter pressure in patients with megaesophagus. Treatment of **megacolon** is surgical and symptomatic.

In accidental infection when parasitic penetration is certain, treatment should be immediately initiated and continued for 10-15 days. Blood is usually collected and serologic samples tested for seroconversion at 15, 30, and 60 days.

PREVENTION

Massive coordinated vector control programs under the auspices of WHO and the Pan-American Health Organization and the institution of widespread blood donor screening and targeted surveillance of chronically infected mothers and infants at risk have effectively eliminated or at least drastically reduced transmission in most endemic countries. Chagas disease remains linked to poverty; thus improvement of living conditions is likewise essential to successful control and eradication. Education of residents in endemic areas, use of bed nets, use of insecticides, and destruction of adobe houses that harbor reduviid bugs are effective methods to control the bug population. Synthetic pyrethroid insecticides help keep houses free of vectors for up to 2 years and have low toxicity for humans. Paints incorporating insecticides have also been used.

Because immigrants can carry this disease to nonendemic areas, serologic testing should be performed in blood and organ donors from endemic areas. Potential seropositive donors can be identified by determining whether they have been or have spent extensive time in an endemic area. Questionnaire-based screening of potentially infected blood and organ donors from areas endemic for infection can reduce the risk for transmission. Seropositivity should be considered a contraindication to organ donation, particularly for heart transplantation.

Prophylactic and therapeutic vaccine development is being pursued but is hampered by the ability of the parasite to evade immune mechanisms and persist in different body compartments. Nucleic acid–based techniques and viral vectors are being explored, along with novel adjuvants and strategies for addressing significant genetic variability among the DTUs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 334

Malaria *(Plasmodium)*

Chandy C. John and Robert O. Opoka

Malaria is a vector-borne disease caused by intraerythrocytic protozoa of the genus *Plasmodium* and transmitted by an infective female *Anopheles* mosquito. Malaria is an acute illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly. It has played a major role in human history, causing harm to more people than perhaps any other infectious disease. Although substantial progress has been made in combating malaria in endemic areas, with a 22% reduction in malaria incidence since 2010, malaria remains one of the leading causes of morbidity and mortality worldwide, with an estimated 229 million cases and 409,000 deaths in 2019. Malarial deaths in areas of high malaria transmission occur primarily in children <5 years of age, but in areas of low transmission, a large percentage of

deaths may occur in older children and adults. Although malaria is not endemic in the United States, 1,500-2,000 imported cases are seen in the United States each year. Physicians practicing in non-endemic areas should consider the diagnosis of malaria in any febrile child who has returned from a malaria-endemic area within the previous year, because delay in diagnosis and treatment can result in severe illness or death.

ETIOLOGY

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Before 2004, only four species of *Plasmodium* were known to cause malaria in humans: *P. falciparum, P. malariae, P. ovale,* and *P. vivax*. In 2004, *P. knowlesi* (a primate malaria species) was also shown to cause human malaria, and cases of *P. knowlesi* infection have been documented in Malaysia, Indonesia, Singapore, and the Philippines. Malaria also can be transmitted through blood transfusion and use of contaminated needles and transplacentally from a pregnant woman to her fetus. The risk for blood transmission is low in the United States, but may occur through transfusion of whole blood, packed red blood cells (RBCs), platelets, and leukocytes and through organ transplantation.

EPIDEMIOLOGY

Malaria is a major worldwide problem, occurring in 87 countries that comprise approximately half the world's population (Fig. 334.1). Worldwide malaria cases decreased from an estimated 238 million cases in 2010 to 229 million cases of in 2019. The principal areas of transmission are Africa, Asia, and South America. *P. falciparum* and *P. malariae* are found in most malarious areas. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. *P. vivax* predominates in Bangladesh, Central America, India, Pakistan, and Sri Lanka. *P. vivax* and *P. falciparum* predominate in Southeast Asia, South America, and Oceania. *P. ovale* is the least common species and is transmitted primarily in Africa. Transmission of malaria has been eliminated in most of North America (including the United States), Europe, and most of the Caribbean, as well as Australia, Chile, Israel, Japan, Lebanon, and Taiwan. In 2021, the World Health Organization (WHO) certified that China had eliminated malaria, a landmark achievement for this area of >1 billion people.

P. falciparum is the parasite most commonly associated with severe illness and death, typically among young children. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. Over 99% of cases in Africa are caused by *P. falciparum*, and 94% of all malaria deaths occur in Africa. Previously malarial deaths were predominantly in children under 5 years of age but over the years more older children are being affected, with the percentage of total malaria deaths among children age under 5 years dropping from 84% in 2000 to 67% in 2019. *P. vivax,* contributes to about 3.3% of global malaria. *P. vivax* is responsible for 75% of malaria cases in central America and 50% of cases in Southeast Asia (World Malaria Report 2019).

Most cases of malaria in the United States occur among previously infected visitors to the United States from endemic areas and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis. Due to the increase in global travel, the number of imported malaria cases has been increasing over the last 40 years, with 2,161 cases reported in 2017. Most cases were acquired in Africa (87%), with Asia (8%), South America (1.9%), and Central America (1.5%) contributing most remaining cases. Among all cases, *P. falciparum* accounted for the majority of infections (1,523; 70.5%), followed by *P. vivax* (216; 10.0%), *P. ovale* (119; 5.5%), and *P. malariae* (55; 2.6%). Among all reported cases of malaria in 2017, a total of 312 (14.4%) were classified as severe malaria, and 6 of these 312 persons (1.9%) died. Cases peak during the summer travel months. Children comprised 18% of all malaria cases in the United States in 2017, and 39% of pediatric cases occurred in U.S. resident children, 70% of whom were visiting friends or relatives. Severe malaria was more slightly common in children (18.4%) than adults (13.6%).

Local transmission of malaria can rarely occur in the United States, as demonstrated in 2003, when eight cases were diagnosed among non-travelers in Palm Beach, Florida, and as demonstrated again in 2023 in Florida, Texas, and Maryland. These cases may result from transmission from untreated and often asymptomatic infected individuals from malaria-endemic countries who travel to the United States and infect local mosquitoes or from infected mosquitoes from malaria-endemic areas that are transported to the United States on airplanes. Transfusion-transmitted malaria can also occur in the United States.

PATHOGENESIS

Plasmodium species exist in a variety of forms and have a complex life cycle that enables them to survive in different cellular environments in the human host (asexual phase) and the mosquito (sexual phase) (Fig. 334.2). A marked amplification of *Plasmodium,* from approximately 10^2 to as many as 10^{14} organisms, occurs during a two-step process in humans, with the first phase in hepatic cells (pre-erythrocytic phase) and the second phase in the RBCs (erythrocytic phase). The **pre-erythrocytic phase** begins with inoculation of sporozoites into the bloodstream by a female *Anopheles* mosquito. Within minutes the

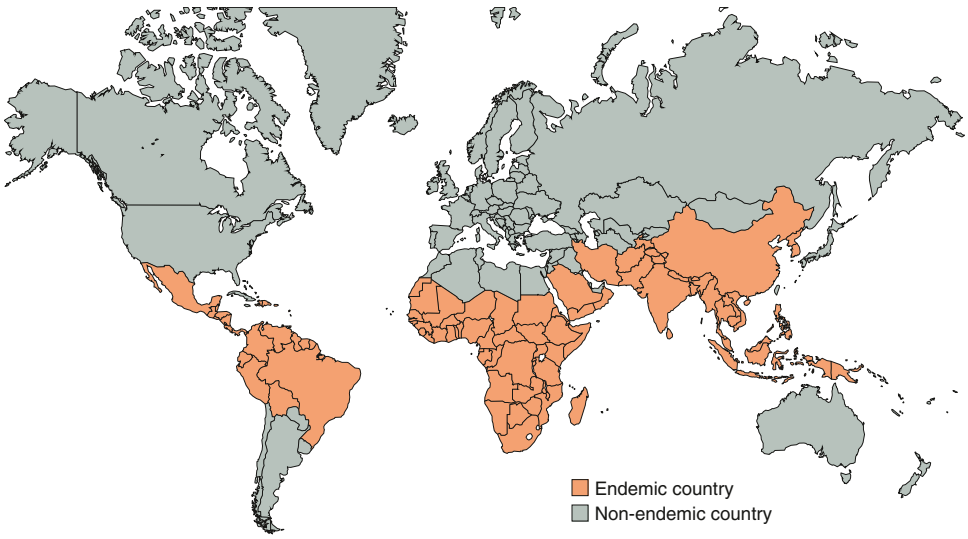

Fig. 334.1 Spatial distribution of malaria in the Eastern and Western hemispheres. In this map, countries with areas endemic for malaria are shaded completely even if transmission occurs only in a small part of the country. For more specific within-country malaria transmission information, see the Yellow Fever & Malaria Information, by Country section in in the Centers for Disease Control and Prevention (CDC) link in this caption. *(From Tan RK, Arguin PM. Malaria. In Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. Maps 4.8 and 9* https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#5217*)*

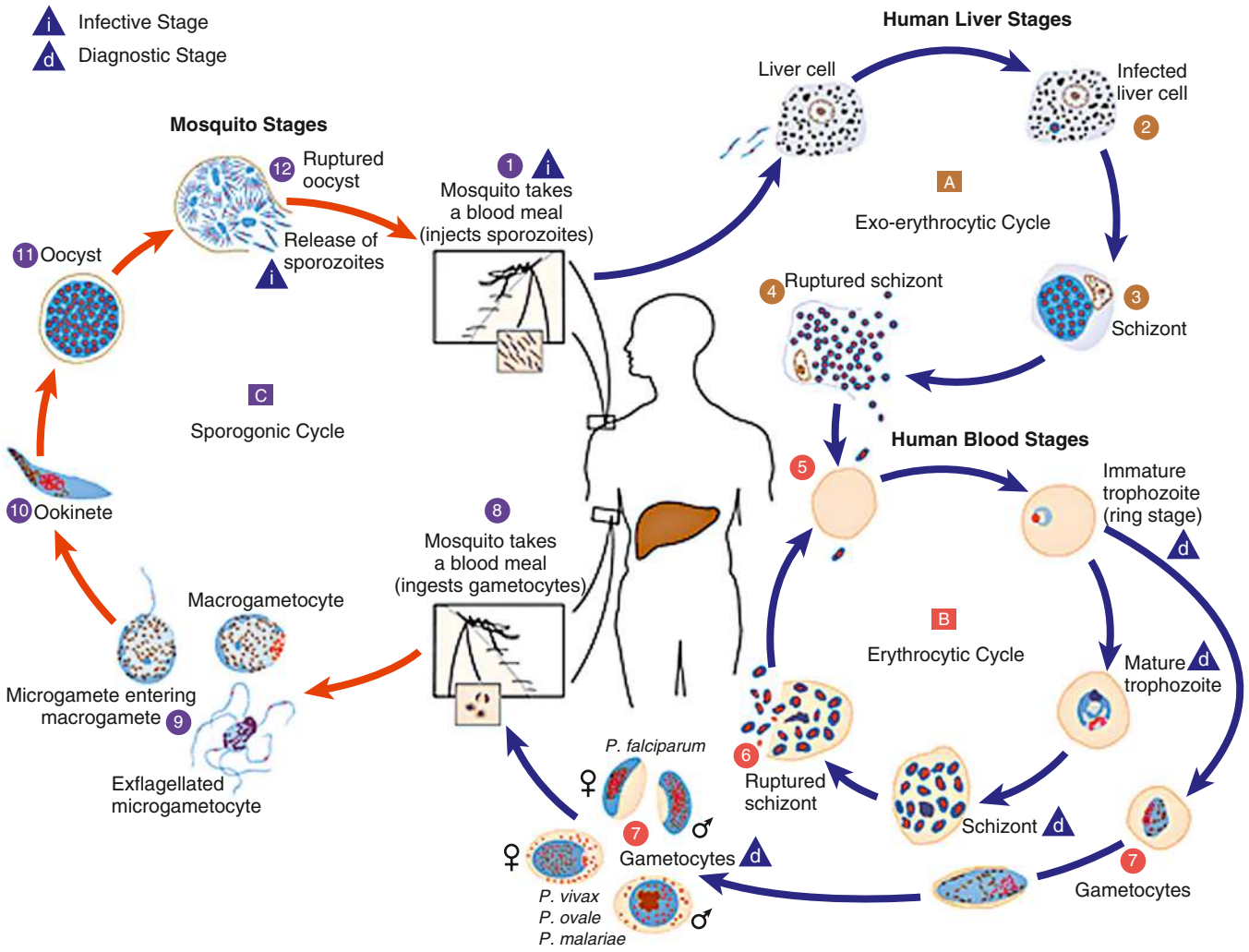

Fig. 334.2 Life cycle of *Plasmodium* spp. *(From Centers for Disease Control and Prevention. Laboratory diagnosis of malaria: Plasmodium spp. https://www.cdc.gov/dpdx/malaria/index.html)*

sporozoites enter the hepatocytes of the liver, where they develop and multiply asexually as a **schizont.** After 1-2 weeks, the hepatocytes rupture and release thousands of merozoites into the circulation. The tissue schizonts of *P. falciparum, P. malariae,* and apparently *P. knowlesi* rupture once and do not persist in the liver. There are two types of tissue schizonts for *P. ovale* and *P. vivax.* The primary type ruptures in 6-9 days, and the secondary type remains dormant in the liver cell for weeks, months, or as long as 5 years before releasing merozoites and causing relapse of infection. The **erythrocytic phase** of *Plasmodium* asexual development begins when the merozoites from the liver penetrate erythrocytes. Once inside the erythrocyte, the parasite transforms into the **ring form**, which then enlarges to become a **trophozoite.** These latter two forms can be identified with Giemsa stain on blood smear, the primary means of confirming the diagnosis of malaria (Fig. 334.3). The trophozoite multiplies asexually to produce a number of small erythrocytic **merozoites** that are released into the bloodstream when the erythrocyte membrane ruptures, which is associated with fever. Over time, some of the merozoites develop into male and female gametocytes that complete the *Plasmodium* life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a **zygote** in the stomach cavity of the mosquito. After a series of further transformations, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

Pathophysiology and pathogenesis in malaria differ according to species. Infection with all species leads to **fever,** caused by the host immune response when erythrocytes rupture and release merozoites into the circulation, and **anemia,** caused by hemolysis and bone marrow suppression. Severe malaria is more common in *P. falciparum* because of several processes, including higher-density parasitemia, which may lead to excessive production of proinflammatory cytokines; cytoadherence of *P. falciparum*-infected erythrocytes to the vascular endothelium; and polyclonal activation, resulting in both hypergammaglobulinemia and the formation of immune complexes. **Cytoadherence** of infected erythrocytes to vascular endothelium can lead to obstruction of blood flow and capillary damage, with resultant vascular leakage of blood, protein, and fluid and tissue anoxia. Parasite anaerobic metabolism may also lead to hypoglycemia and metabolic acidosis. The cumulative effects of these pathologic processes may lead to cerebral, cardiac, pulmonary, renal, and hepatic failure.

Immunity after *Plasmodium* sp. infection is incomplete, preventing severe disease but still allowing future infection. In some cases, parasites circulate in small numbers for a long time but are prevented from rapidly multiplying and causing severe illness. Repeated episodes

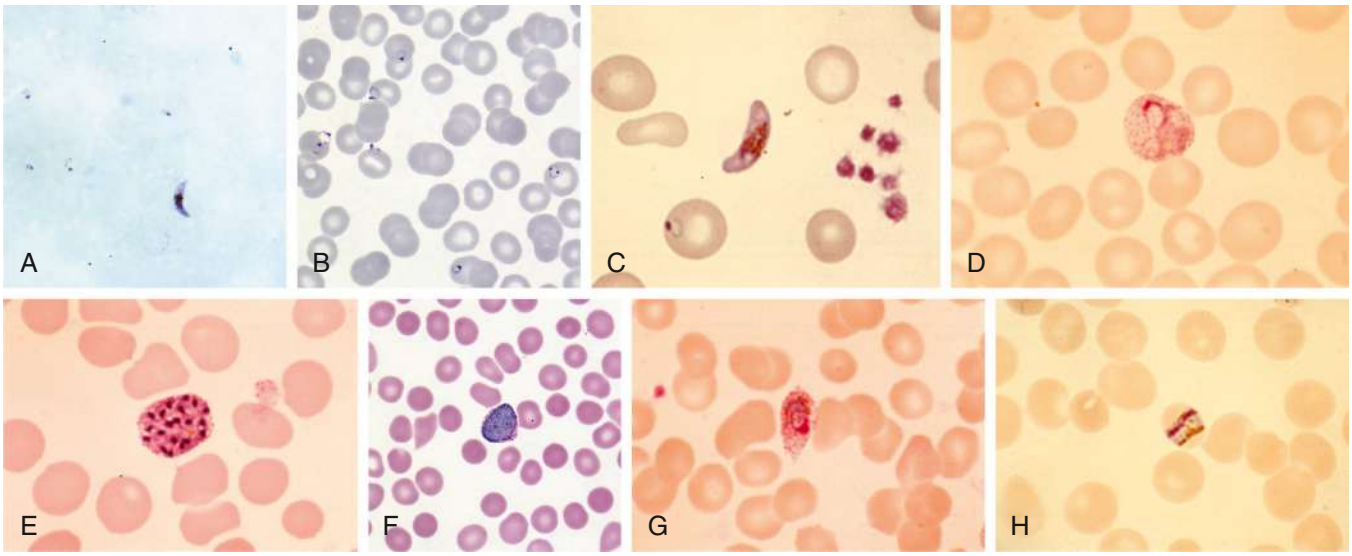

Fig. 334.3 Giemsa-stained thick (A) and thin (B-H) smears used for the diagnosis of malaria and the speciation of *Plasmodium* parasites. A, Multiple signet-ring *Plasmodium falciparum* trophozoites that are visualized outside erythrocytes. B, A multiply infected erythrocyte containing signet-ring *P. falciparum* trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane. C, Banana-shaped gametocyte unique to *P. falciparum*. D, Ameboid trophozoite characteristic of *P. vivax*. Both *P. vivax*– and *P. ovale*–infected erythrocytes exhibit Schüffner dots and tend to be enlarged compared with uninfected erythrocytes. E, *P. vivax* schizont. Mature *P. falciparum* parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. F, *P. vivax* spherical gametocyte. G, *P. ovale* trophozoite. Note Schüffner dots and ovoid shapes of the infected erythrocyte. H, Characteristic band-form trophozoite of *P. malariae*, containing intracellular pigment hemozoin. *(A, B, and F, from Centers for Disease Control and Prevention. DPDx: Laboratory identification of parasites of public health concern.* https://www.cdc.gov/dpdx/malaria/index.html*; C, D, E, G, and H, courtesy David Wyler, Newton Centre, MA.)*

of infection occur because the parasite has developed a number of immune-evasive strategies, such as intracellular replication, vascular cytoadherence that prevents infected erythrocytes from circulating through the spleen, rapid antigenic variation, and alteration of the host immune system resulting in partial immune suppression. The human host response to *Plasmodium* infection includes natural immune mechanisms that prevent infection by other *Plasmodium* spp., such as those of birds or rodents, as well as several alterations in erythrocyte physiology that prevent or modify malarial infection. Erythrocytes containing **hemoglobin S** (sickle erythrocytes) resist malaria parasite growth, erythrocytes lacking Duffy blood group antigen are relatively resistant to *P. vivax*, and erythrocytes containing **hemoglobin F** (fetal hemoglobin) and ovalocytes are resistant to *P. falciparum*. In hyperendemic areas, newborns rarely become ill with malaria, in part because of passive maternal antibody and high levels of fetal hemoglobin. Children 3 months to 2-5 years of age have little specific immunity to malaria species and therefore suffer yearly attacks of debilitating and potentially fatal disease. Immunity is subsequently acquired, and severe cases of malaria become less common. Severe disease may occur during pregnancy, particularly first pregnancies or after extended residence outside the endemic region. Both T-cell and antibody responses are important in development of biologic and clinical immunity to *Plasmodium* spp.

CLINICAL MANIFESTATIONS

Children and adults are asymptomatic during the initial phase of infection, the incubation period of malaria infection. The usual incubation periods are 9-14 days for *P. falciparum,* 12-17 days for *P. vivax,* 16-18 days for *P. ovale,* and 18-40 days for *P. malariae*. The incubation period can be as long as 6-12 months for *P. vivax* and can also be prolonged for patients with partial immunity or incomplete chemoprophylaxis. A prodrome lasting 2-3 days is noted in some patients before parasites are detected in the blood. Prodromal symptoms include headache, fatigue, anorexia, myalgia, slight fever, and pain in the chest, abdomen, and joints.

Children with malaria often lack the typical paroxysms seen in adults (high fever, followed by shaking chills and then diaphoresis) and may have nonspecific symptoms, including fever (may be low grade but is often >40°C [104°F]), headache, drowsiness, anorexia, nausea, vomiting, and diarrhea. Although the rupture of schizonts that occurs every 48 hours with *P. vivax* and *P. ovale* and every 72 hours with *P. malariae* can result in a classic pattern of fevers every other day (*P. vivax* and *P. ovale*) or every third day *(P. malariae),* periodicity is less apparent with *P. falciparum* and mixed infections and may not be apparent early on in infection, when parasite broods have not yet synchronized. Patients with primary infection, such as travelers from non-endemic regions, also may have irregular symptomatic episodes for 2-3 days before regular paroxysms begin, so most travelers presenting with malaria lack a classic malaria fever pattern. Distinctive physical signs may include fever, pallor as a consequence of anemia, and splenomegaly or hepatomegaly. Typical laboratory findings include anemia, thrombocytopenia, and a normal or raised leukocyte count.

P. falciparum is the most severe form of malaria and is associated with higher-density parasitemia and a number of complications (Fig. 334.4). The most common serious complication is severe **anemia**, which also is associated with other malaria species. Serious complications that appear unique to *P. falciparum* include cerebral malaria, respiratory distress from metabolic acidosis, acute renal failure, hypotension, and bleeding diatheses (Table 334.1) (see "Severe Malaria").

The diagnosis of *P. falciparum* malaria in a nonimmune individual constitutes a medical emergency. Severe complications and death can occur if appropriate therapy is not instituted promptly. In contrast to malaria caused by *P. ovale, P. vivax,* and *P. malariae,* which usually result in parasitemias of <2%, malaria caused by *P. falciparum* can be associated with parasitemia levels as high as 60%. The differences in parasitemia reflect that *P. falciparum* infects both immature and mature erythrocytes, whereas *P. ovale* and *P. vivax* primarily infect immature erythrocytes and *P. malariae* infects only mature erythrocytes. Like *P.*

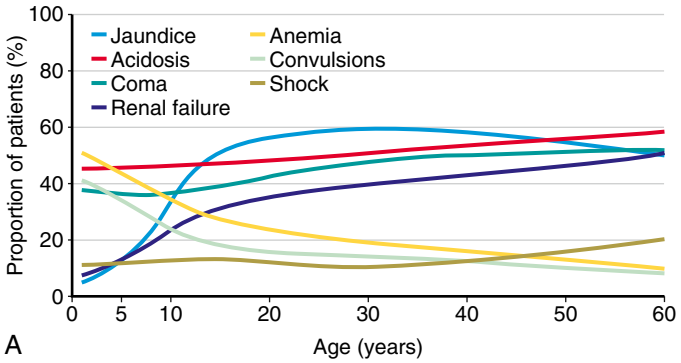

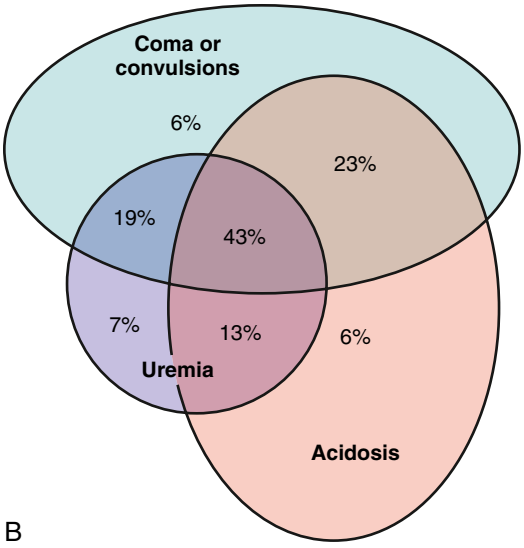

Fig. 334.4 Manifestations of severe falciparum malaria by age (A) and mortality in children associated with central nervous system involvement, acidosis, and uremia (B). Data from 3,228 prospectively studied African children with severe falciparum malaria. *Uremia* here is defined as a blood urea nitrogen >7.14 mmol/L. Surface areas denote the relative prevalence of the different severity signs, which frequently coexist. The percentages denote the observed mortality associated with the presenting signs. *(From White NJ, Pukrittayakamee S, Hien TT, et al. Malaria. Lancet. 2014;383:723–735.)*

Table 334.1 World Health Organization Criteria for Severe Malaria, 2021

SEVERE MALARIA CRITERION	DEFINITION
Impaired consciousness	Glasgow Coma Scale score <11 in adults or Blantyre coma score <3 in children
Prostration	Generalized weakness so that a person is unable to sit, stand, or walk without assistance
Multiple convulsions	More than two episodes of convulsions within 24 hr
Acidosis	A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, labored breathing)
Hypoglycemia	Blood or plasma glucose <40 mg/dL (<2.2 mmol/L)
Severe malarial anemia	Hemoglobin concentration ≤5 g/dL or hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in those ≥12 years) with parasite count >10,000/μL
Renal impairment (acute kidney injury)	Plasma or serum creatinine >3 mg/dL (265 μmol/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 μmol/L (3 mg/dL) with a parasite count >100,000/μL (approximately 2%).
Pulmonary edema	Radiographically confirmed or oxygen saturation <92% on room air with respiratory rate >30/min, often with chest indrawing and crepitation on auscultation
Significant bleeding	Includes recurrent or prolonged bleeding from the nose, gums, or venipuncture sites; hematemesis, or melena
Shock	Compensated shock is defined as capillary refill ≥3 sec or temperature gradient on leg (mid to proximal limb) but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia	*P. falciparum* parasitemia >10% (>500,000/μL)

falciparum, *P. knowlesi* has a 24-hour replication cycle and can also lead to very high density parasitemia.

P. vivax malaria has long been considered less severe than *P. falciparum* malaria, but recent reports suggest that in some areas it is as frequent a cause of severe disease and death as *P. falciparum*. Severe disease and death from *P. vivax* are usually caused by severe anemia and sometimes splenic rupture. *P. ovale* malaria is the least common type of malaria. It is similar to *P. vivax* malaria and usually is found in conjunction with *P. falciparum* malaria. Case reports of worsening *P. ovale* disease with respiratory symptoms and pulmonary infiltrates and/or effusions after antimalarial treatment have been reported, but all resolved with completion of treatment. *P. malariae* is the mildest and most chronic of all malaria infections. **Nephrotic syndrome** is a rare complication of *P. malariae* infection that is not observed with any other human malaria species. Nephrotic syndrome associated with *P. malariae* infection is poorly responsive to corticosteroids. Low-level, undetected *P. malariae* infection may be present for years and is sometimes unmasked by immunosuppression or physiologic stress such as splenectomy or corticosteroid treatment. *P. knowlesi* malaria is most often uncomplicated but can lead to severe malaria and death if high-density parasitemia is present.

The definition of severe *P. vivax* or *P. ovale* malaria is the same as that of severe falciparum malaria except that there are no parasite density thresholds. The definition of severe malaria due to *P. knowlesi* differs from that of severe falciparum malaria; the threshold parasite density is >100,000/μL (alone) or >20,000/μL in patients with jaundice.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from a pre-erythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale*, or from persistence within the erythrocyte, which occurs with *P. malariae* and rarely with *P. falciparum*. A history of typical symptoms in a person >4 weeks after return from an endemic area is therefore more likely to be *P. vivax*, *P. ovale*, or *P. malariae* infection than *P. falciparum* infection. In the most recent survey of malaria in the United States (2013) by the CDC, among individuals in whom a malaria species was identified, 61% of cases were caused by *P. falciparum*,14% by *P. vivax*, 2% by *P. malariae*, 4% by *P. ovale*, and 2% by mixed-species infection; 94% of *P. falciparum* infections were diagnosed within 30 days of arrival in the United States,

and 99% within 90 days of arrival. In contrast, 54% of *P. vivax* cases occurred >30 days after arrival in the United States.

Congenital malaria is acquired from the mother prenatally or perinatally but is rarely reported in the United States. Congenital malaria usually occurs in the offspring of a nonimmune mother with *P. vivax* or *P. malariae* infection, although it can be observed with any of the human malaria species. The first sign or symptom typically occurs between 10 and 30 days of age (range: 14 hours to several months of age). Signs and symptoms include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly. **Malaria in pregnancy** is a major health problem in malaria-endemic countries, can be severe, and is associated with adverse outcomes in the fetus or neonate, including intrauterine growth restriction and low birthweight, even in the absence of transmission from mother to child.

Severe Malaria

WHO has identified 12 complications of *P. falciparum* malaria that define severe malaria (see Table 334.1 and Fig. 334.4). The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), acute kidney injury, multiple seizures, prostration, and jaundice. A more complete discussion of severe malaria is provided in the treatment section (see "Treatment of Severe Malaria"), where treatment for these complications is also described.

DIAGNOSIS

Any child who presents with fever or unexplained systemic illness and has traveled or resided in a malaria-endemic area within the previous year should be evaluated for malaria. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring <1 month after return from an endemic area, >2% parasitemia, ring forms with double-chromatin dots, and erythrocytes infected with greater than one parasite.

The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood (see Fig. 334.3) or by rapid immunochromatographic assay (rapid diagnostic test). Giemsa stain is superior to Wright stain or Leishman stain. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a **thick smear** is 20-40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The **thin smear** allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes and is useful in following the response to therapy. Identification of the species is best made by an experienced microscopist and checked against color plates of the various *Plasmodium* spp. (see Fig. 334.3). Morphologically, it is impossible to distinguish *P. knowlesi* from *P. malariae,* so polymerase chain reaction (PCR) detection by a reference laboratory or the CDC is required. Although *P. falciparum* is most likely to be identified from blood just after a febrile paroxysm, most children with malaria will have a positive blood smear regardless of the time the smear is obtained. Most guidelines recommend at least three negative blood smears to rule out malaria in children in whom malaria is strongly suspected, because low-level parasitemia could potentially go undetected early in the illness. However, few data are available on the utility of repeated blood smears for malaria detection, and most case reports and series document a positive initial smear.

The BinaxNOW Malaria test is approved by the U.S. Food and Drug Administration (FDA) for rapid diagnosis of malaria. This immunochromatographic test for *P. falciparum* histidine-rich protein (HRP2) and aldolase is approved for testing for *P. falciparum* and *P. vivax*. **Aldolase** is present in all five of the malaria species that infect humans; thus a positive result for *P. vivax* could be because of *P. ovale* or *P. malariae* infection. Sensitivity and specificity for *P. falciparum* (94–99% and 94–99%, respectively) and *P. vivax* (87–93% and 99%, respectively) are good, but sensitivity for *P. ovale* and *P. malariae* is lower. Sensitivity for *P. falciparum* decreases at lower levels of parasitemia, so microscopy is still advised in areas where expert microscopy is available. The test is simple to perform and can be done in the field or laboratory in 10 minutes. PCR is more sensitive than microscopy but is technically more complex. It is available in some reference laboratories and can be useful for confirmation and for diagnosis of multiple species of malaria. The time delay in availability of results typically precludes its use for acute diagnosis of malaria, but it is useful to send where available, as it can confirm the diagnosis, allow for detection of multiple infections, and detect malaria not detected by standard microscopy because of low levels of parasitemia (particularly nonfalciparum malaria). PCR detection may detect asymptomatic parasitemia in children with very low level parasitemia (e.g., internationally adopted children from malaria-endemic areas), with greater sensitivity than microscopy, and may be the preferred method of detection in these children, who, because they are asymptomatic, do not require immediate treatment.

Differential Diagnosis

The differential diagnosis of malaria is broad. In a child traveler returning to or arriving in the United States from an endemic area, diseases that may mimic malaria include viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, encephalitis, endocarditis, gastroenteritis, pyelonephritis, babesiosis, brucellosis, leptospirosis, tuberculosis, relapsing fever, typhoid fever, yellow fever, viral hemorrhagic fevers, amebic liver abscess, neoplasm, and collagen vascular disease. There is also considerable clinical overlap between features of malaria (uncomplicated or severe) and other common bacterial and viral infections. Malaria in child travelers returning to or arriving in the United States is typically the sole reason for the clinical symptoms the child presents with, but the relatively nonspecific presentation may require a larger workup and empiric treatment for other conditions while awaiting testing results.

TREATMENT

Physicians caring for patients with malaria or traveling to endemic areas need to be aware of current information regarding malaria because resistance to antimalarial drugs has complicated therapy and prophylaxis. The CDC website provides excellent guidance on diagnosis and treatment of malaria in individuals in the United States (https://www.cdc.gov/malaria/diagnosis_treatment/diagnosis.html). Specific pages provide general guidelines (https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html), a treatment algorithm (https://www.cdc.gov/malaria/resources/pdf/Malaria_Management_Algorithm.pdf, Fig. 334.5), a treatment table for all forms of uncomplicated and severe malaria (https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf, Tables 334.2-334.6), and specific guidance on obtaining artesunate, which is now available commercially in the United States as an FDA-approved drug (https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html) and must be ordered emergently by hospitals that do not have in it stock. Severe malaria care requires infectious diseases consultation. In cases where treatment is unclear or complex, calling the CDC Malaria Hotline is strongly recommended. CDC expert malaria guidance is available to physicians 24 hours a day (844-856-4713, from 9 AM to 5 PM Eastern Time Monday-Friday, and 770-488-7100 at all other times and on holidays; request to speak to the CDC Malaria Branch Expert).

General Principles

Treatment for malaria should be based on laboratory confirmation of the diagnosis. "Presumptive treatment," i.e., without laboratory confirmation, may be required in children with severe disease in a setting where prompt laboratory diagnosis is not available. Once the diagnosis of malaria has been made, appropriate antimalarial treatment should be initiated immediately. Treatment is influenced by multiple factors, including infecting *Plasmodium* species; clinical status of the patient; expected drug susceptibility of the infecting parasite as determined by the geographic area where the infection was acquired; and previous use of antimalarials, including those taken for malaria chemoprophylaxis.

Fever without an obvious cause in any patient who has left a *P. falciparum*–endemic area within 30 days and is nonimmune should be

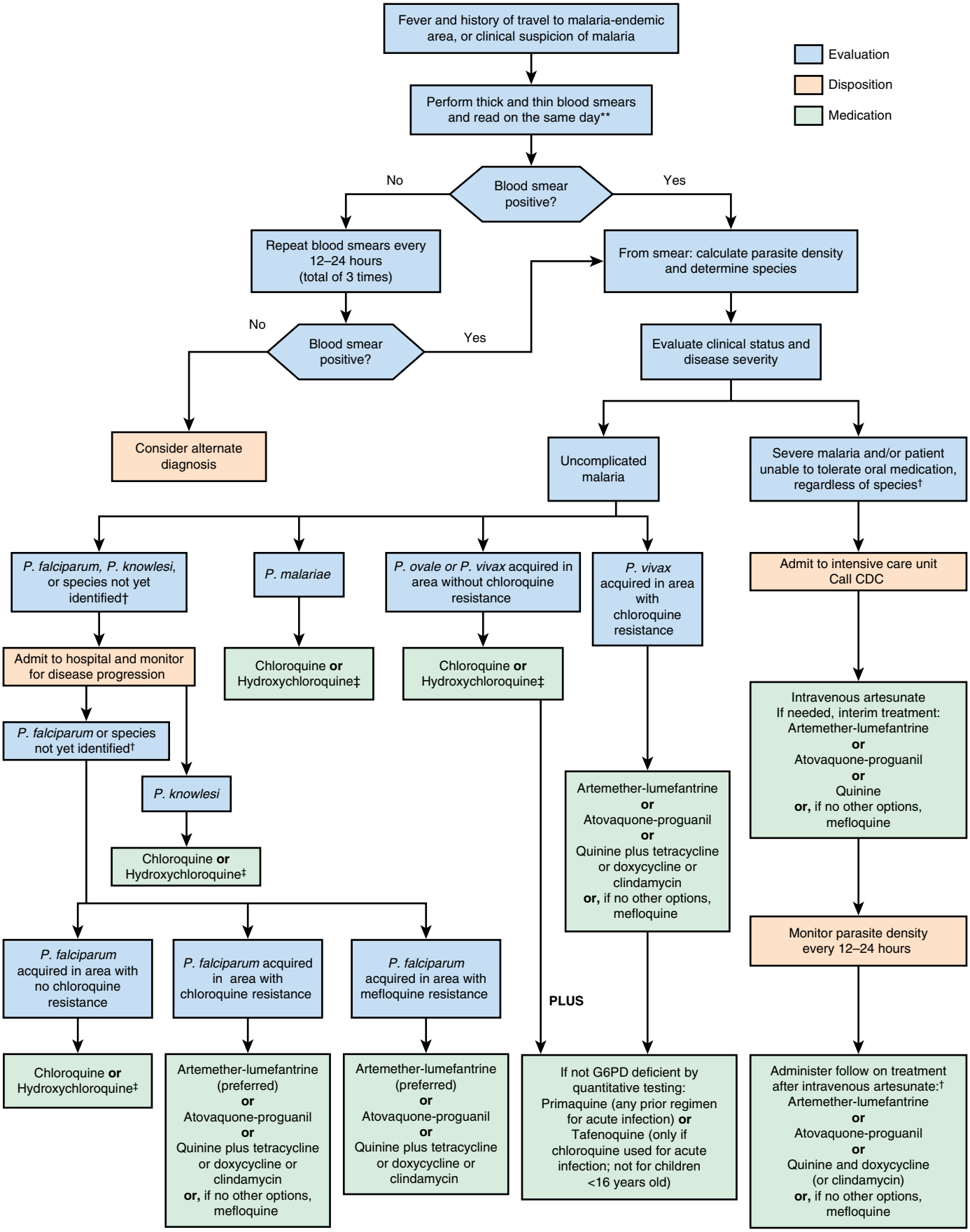

Fig. 334.5 Algorithm for approach to patient with malaria in the United States. Treatment for special populations (children and pregnant women) can be found in the Centers for Disease Control and Prevention (CDC) Treatment Guidelines and Treatment Table at https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf. **If rapid diagnostic test performed, smear should also be performed with results available as soon as possible. †If species later identified as *P. vivax* or *P. ovale*, add primaquine if not glucose-6-phosphate (G6PD) deficient by quantitative testing. Tafenoquine can only be used if chloroquine or hydroxychloroquine used for acute infection. ‡Drug options for chloroquine-resistant *P. falciparum* may be used. *(From Centers for Disease Control and Prevention.* http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf*)*

considered a medical emergency. Thick and thin blood smears should be obtained immediately, and all children with symptoms of severe disease should be hospitalized. If negative, blood films should be repeated every 12 hours until three smears are documented as negative. If the patient is severely ill, antimalarial therapy should be initiated immediately. Outpatient therapy generally is not given to nonimmune children but may be considered in immune or semi-immune children who have low-level parasitemia (<1%), no evidence of complications defined by WHO, no vomiting, and a lack of toxic appearance; who are able to contact the physician or emergency department at any time; and in whom follow-up within 24 hours is ensured.

TREATMENT OF UNCOMPLICATED MALARIA

P. falciparum or Species Not Identified: Acquired in Areas with Chloroquine Resistance

Treatment regimens for children with uncomplicated malaria in the United States are summarized in Tables 334.2-334.5. For *P. falciparum* infections acquired in areas with chloroquine resistance, four treatment options are available. These include artemether-lumefantrine (Coartem), which is the preferred option if readily available, and atovaquone-proguanil (Malarone). These are fixed-dose combination therapies that can be used for pediatric patients >5 kg. Quinine sulfate plus doxycycline, tetracycline, or clindamycin is the next treatment option. For the quinine sulfate combination options, quinine sulfate plus either doxycycline or tetracycline is generally preferred to quinine sulfate plus clindamycin because there are more data on the efficacy of quinine plus doxycycline or tetracycline. Quinine should be given for 3 days, except for infections acquired in Southeast Asia where 7 days of treatment is required. The fourth option, mefloquine, is associated with rare but potentially severe neuropsychiatric reactions when used at treatment dose, and it is recommended only if the other options cannot be used.

For infections attributed to "species not identified" in areas with chloroquine resistance that are subsequently diagnosed as being due to *P. vivax* or *P. ovale,* additional treatment with primaquine or tafenoquine should be administered, as described in the section on *P. vivax* and *P. ovale* treatment.

P. falciparum or Species Not Identified: Acquired in Areas Without Chloroquine Resistance

For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include Central America west of the Panama Canal, Haiti, and the Dominican Republic, patients can be treated with oral chloroquine. Alternatively, hydroxychloroquine may be used at recommended doses. In addition, any of the regimens listed for the treatment of chloroquine-resistant malaria may be used for the treatment of chloroquine-sensitive *P. falciparum* malaria. Prompt initiation of an effective regimen is vitally important as delay of initiation of treatment may increase the risk of progression to severe disease in patients with *P. falciparum* infection. If infections initially attributed to "species not identified" are subsequently diagnosed as being due to *P. vivax* or *P. ovale,* additional treatment with primaquine or tafenoquine should be administered, as outlined in the sections on *P. vivax* and *P. ovale*.

P. vivax and *P. ovale*

Chloroquine (or hydroxychloroquine) remains an effective choice for *P. vivax* and *P. ovale* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia, as there is high prevalence of chloroquine-resistant *P. vivax* in these countries. Rare cases of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine. If chloroquine is not available, or if the infection was acquired in an area with a high frequency of chloroquine resistance (Indonesia or Papua New Guinea), artemether-lumefantrine, atovaquone-proguanil, quinine sulfate plus doxycycline or tetracycline or clindamycin, or mefloquine should be used (mefloquine should be used only if the other drugs are not available or contraindicated). If chloroquine is given and the patient has an inadequate response including persistence or worsening of clinical symptoms or no decrease in parasite density, treatment should be changed to one of the regimens recommended for chloroquine-resistant *P. vivax* infections.

In addition to requiring the acute phase treatment of blood-stage parasites, *P. vivax* and *P. ovale* infections can relapse due to hypnozoites, which are dormant forms that remain in the liver. To eradicate the hypnozoites, patients should be treated with either tafenoquine (Krintafel) or primaquine phosphate. If primaquine phosphate is used, the CDC recommends a dose of 30 mg (base) by mouth daily for 14 days for adults, and a dose of 0.5 mg/kg (base) by mouth, to a maximum of 30 mg (base) daily for children.

P. malariae and *P. knowlesi*

There has been no widespread evidence of chloroquine resistance in *P. malariae* and *P. knowlesi* species; therefore chloroquine (or hydroxychloroquine) may still be used for both of these species. In addition, any of the regimens listed previously for the treatment of chloroquine-resistant *P. falciparum* may be used for the treatment of *P. malariae* and *P. knowlesi* infections. Due to the risk of complications among patients with *P. knowlesi,* clinicians should consider hospitalization to monitor clinical response and check parasite density every 12-24 hours until clinical presentation improves and a decrease in parasite density becomes apparent.

TREATMENT OF SEVERE MALARIA

General Principles

Death due to severe malaria can occur within hours of presentation, so prompt assessment and initiation of effective antimalarial therapy is essential. Equally important is the concurrent administration of supportive therapy to manage life-threatening complications of the disease. Supportive measures such as oxygen therapy, blood transfusion, rehydration, control of convulsions, correction of metabolic derangements like hypoglycemia, and institution of antibiotics in children with features of sepsis should be instituted as indicated by clinical findings. Children with severe malaria should be managed in an intensive care unit (ICU).

The risk of death due to severe malaria is greatest in the first 24 hours after clinical presentation. Independent predictors for fatality among African children with severe malaria include acidosis, impaired consciousness, elevated blood urea nitrogen, and acute kidney injury. Early diagnosis and prompt initiation of antimalarial medication and appropriate supportive care can reduce mortality.

Drug treatment guidelines in this chapter are based on treatment for children in the United States (Table 334.6). Children in other areas have other drugs and treatments available, and local or WHO guidelines for malaria treatment are available at https://www.who.int/publications/i/item/guidelines-for-malaria.

Intravenous Antimalarial Therapy for Severe Malaria

Treatment of severe malaria involves initial treatment with intravenous (IV) artesunate, followed by a full dose of effective artemisinin combination therapy (ACT). In the United States, the only FDA-approved treatment for severe malaria is IV artesunate. Quinidine, which was previously approved for treatment of severe malaria, ceased to be manufactured in 2019. Artesunate dosing need not be adjusted for hepatic or renal failure, nor for concomitant or previous therapy with other medications. Artesunate is well tolerated with few side effects. Adverse effects include nausea, vomiting, anorexia, and dizziness, although these may be due to malaria rather than drug toxicity. In nonimmune patients, delayed onset of anemia has been noted in some cases, so patients treated with IV artesunate should be monitored for delayed hemolytic anemia, and repeat hemoglobin testing at 7, 14, and 30 days should be considered.

In the United States, IV artesunate was approved by the FDA through the CDC as part of an expanded-use investigational new drug (IND) protocol in May 2020. As of June 2021, the drug can be obtained through major drug distributors. Healthcare providers treating patients meeting the following criteria and who are unable to obtain

Table 334.2 Treatment of Uncomplicated Malaria: *Plasmodium falciparum* or Unknown Species[1–3] (If Later Diagnosed as *P. vivax* or *P. ovale*, See Table 334.3 for Antirelapse Treatment)

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS	RECOMMENDED PEDIATRIC REGIMENS[4]
Chloroquine resistant or unknown resistance (All malaria-endemic regions except those in Central America west of Panama Canal, Haiti, and Dominican Republic)	A. **Artemether-lumefantrine (Coartem)**[5] (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[6] (Adult tab: 250 mg atovaquone and 100 mg proguanil) 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[7] **plus doxycycline,**[8] **tetracycline,**[8] **or clindamycin**[9] Quinine sulfate: 542 mg base (650 mg salt) PO tid × 3 or 7 days[7] Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days D. **Mefloquine**[10] Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO	A. **Artemether-lumefantrine (Coartem)**[5] (1 tab: 20 mg artemether and 120 mg lumefantrine) 5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[6] (Adult tab: 250 mg atovaquone and 100 mg proguanil; Peds tab: 62.5 mg atovaquone and 25 mg proguanil) 5 to <8 kg: 2 peds tabs PO qd × 3 days 8 to <10 kg: 3 peds tabs PO qd × 3 days 10 to <20 kg: 1 adult tab PO qd × 3 days 20 to <30 kg: 2 adult tabs PO qd × 3 days 30 to <40 kg: 3 adult tabs PO qd × 3 days ≥40 kg: 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[7] **plus doxycycline,**[8] **tetracycline,**[8] **or clindamycin**[9] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) PO tid × 3 or 7 days[7] Doxycycline: 2.2 mg/kg PO bid × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg /kg/day PO divided tid × 7 days D. **Mefloquine**[10] Dose 1: 13.7 mg base/kg (15 mg salt/kg) PO Dose 2 at 6-12 hr: 9.1 mg base/kg (10 mg salt/kg) PO
Chloroquine sensitive[11] (Central America west of Panama Canal, Haiti, and Dominican Republic)	**Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose	**Chloroquine phosphate (Aralen and generics)** Dose 1: 10 mg base/kg (16.7 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (8.3 mg salt/kg) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 10 mg base/kg (12.9 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (6.5 mg salt/kg) PO per dose

[1]qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Option A preferred, Options B and C adequate alternatives and should be used if more readily available than Option A. Option D should be used only if other options not available.
[4]Not to exceed adult dose.
[5]Artemether-lumefantrine can be used in second and third trimesters of pregnancy and, if no other options available, in first trimester as well. Not for infants <5 kg or women breastfeeding infants <5 kg.
[6]Atovaquone-proguanil not recommended during pregnancy, in infants <5 kg, or in women breastfeeding infants <5 kg. May be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[7]Quinine to be given for 3 days, except for infections acquired in Southeast Asia, where 7 days of treatment are required. Quinine available in the United States has 324 mg (salt) per capsule, therefore two capsules for adult dosing. Pediatric dosing may need compounding pharmacy.
[8]Doxycycline or tetracycline combined with quinine preferred due to more efficacy data, but not recommended during pregnancy or in children <8 yr old unless no other options and benefits outweigh risks.
[9]Clindamycin with quinine preferred option for pregnant women and children <8 yr old.
[10]Mefloquine not recommended for infections acquired in Southeast Asia due to drug resistance. Not recommended if other options available or in patients with neuropsychiatric history.
[11]Regimens used to treat chloroquine-resistant *P. falciparum* infections may be used if chloroquine and hydroxychloroquine not available.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

commercially available artesunate within 24 hours should call the CDC Malaria Hotline to obtain IV artesunate.

If artesunate is not immediately available, oral antimalarials can be given while waiting to obtain IV artesunate. Choices include artemether-lumefantrine (preferred), atovaquone-proguanil, quinine sulfate, and mefloquine (Table 334.2).

FOLLOW-UP ORAL ANTIMALARIAL THERAPY FOR SEVERE MALARIA

Parenteral artesunate should be given for three doses over 24 hours at 0, 12, and 24 hours. If parasite density is <1% at 20 hours and the patient can take oral medication, treatment should be completed with an effective oral medication, such as artemether-lumefantrine (preferred),

Table 334.3 Treatment of Uncomplicated Malaria: *P. vivax* or *P. ovale*[1,2]

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS (BOTH ACUTE AND ANTIRELAPSE TREATMENTS RECOMMENDED)	RECOMMENDED PEDIATRIC REGIMENS[3] (BOTH ACUTE AND ANTIRELAPSE TREATMENTS RECOMMENDED)
Chloroquine sensitive (All malaria-endemic regions except Papua New Guinea and Indonesia)	Acute treatment[4]: **Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose **AND** **Antirelapse treatment[5]:** Primaquine phosphate[6–8] 30 mg base PO qd × 14 days *OR* **Tafenoquine (Krintafel)**[6,7,9] 300 mg PO × 1 dose	Acute treatment[4]: **Chloroquine phosphate (Aralen and generics)** Dose 1: 10 mg base/kg (16.7 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (8.3 mg salt/kg) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 10 mg base/kg (12.9 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (6.5 mg salt/kg) PO per dose **AND** **Antirelapse treatment[5]:** Primaquine phosphate[6–8] 0.5 mg base/kg PO qd × 14 days *OR* **Tafenoquine (Krintafel)**[6,7,9] 300 mg PO × 1 dose, only for patients ≥16 yr old
Chloroquine resistant (Papua New Guinea and Indonesia)	Acute treatment: A. **Artemether-lumefantrine (Coartem)**[10] (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[11] (Adult tab: 250 mg atovaquone and 100 mg proguanil) 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[12] **plus doxycycline,**[13] **tetracycline,**[13] **or clindamycin**[14] Quinine sulfate: 542 mg base (650 mg salt) PO tid × 3 days Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days D. **Mefloquine**[15] Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO **AND** **Antirelapse treatment**[16]**:** **Primaquine phosphate**[17,18,19] 30 mg base PO qd × 14 days	Acute treatment: A. **Artemether-lumefantrine (Coartem)**[10] (1 tab: 20 mg artemether and 120 mg lumefantrine) 5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[11] (Adult tab: 250 mg atovaquone and 100 mg proguanil; peds tab: 62.5 mg atovaquone and 25 mg proguanil) 5 to <8 kg: 2 peds tabs PO qd × 3 days 8 to <10 kg: 3 peds tabs PO qd × 3 days 10 to <20 kg: 1 adult tab PO qd × 3 days 20 to <30 kg: 2 adult tabs PO qd × 3 days 30 to <40 kg: 3 adult tabs PO qd × 3 days ≥40 kg: 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[12] **plus doxycycline,**[13] **tetracycline,**[13] **or clindamycin**[14] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) PO tid × 3 days Doxycycline: 2.2 mg/kg PO q12h × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days D. **Mefloquine**[10] Dose 1: 13.7 mg base/kg (15 mg salt/kg) PO Dose 2 at 6-12 hr: 9.1 mg base/kg (10 mg salt/kg) PO **AND** **Antirelapse treatment**[16]**:** **Primaquine phosphate**[17–19] 0.5 mg base/kg PO qd × 14 days

[1]qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Not to exceed adult dose.
[4]Regimens used to treat chloroquine-resistant *P. vivax* infections may be used if chloroquine and hydroxychloroquine not available.
[5]Either option for antirelapse treatment recommended if chloroquine or hydroxychloroquine used for acute treatment. If regimens other than either chloroquine or hydroxychloroquine are used for acute treatment, primaquine is the only option for antirelapse treatment.
[6]Primaquine and tafenoquine associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before use, quantitative G6PD testing needed to confirm normal activity. For those with intermediate G6PD deficiency, weekly primaquine may be used (45 mg/wk) for 8 wk with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) PO weekly for 1 yr from acute infection to prevent relapses.
[7]Primaquine and tafenoquine must not be used during pregnancy; pregnant patients with *P. vivax* and *P. ovale* infections should receive chloroquine 300 mg (base) PO weekly after acute treatment for the remainder of pregnancy. After delivery, patients with normal G6PD activity can be given primaquine or tafenoquine depending on breastfeeding, or continue with chloroquine prophylaxis for a total of 1 yr from acute infection. Primaquine can be used during breastfeeding if infant found to also have normal G6PD activity; tafenoquine not recommended during breastfeeding.
[8]Dose of primaquine in patients ≥70 kg should be adjusted to a total dose of 6 mg/kg, divided into doses of 30 mg per day.
[9]Tafenoquine can only be used if chloroquine or hydroxychloroquine administered for acute treatment due to limited data on efficacy when used in combination with other regimens.
[10]Artemether-lumefantrine can be used in second and third trimesters of pregnancy and, if no other options available, in first trimester as well. Not for infants <5 kg or women breastfeeding infants <5 kg.
[11]Atovaquone-proguanil not recommended during pregnancy, in infants <5 kg, or in women breastfeeding infants <5 kg. May be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[12]Quinine available in the United States has 324 mg (salt) per capsule, therefore, two capsules for adult dosing. Pediatric dosing may need compounding pharmacy.

Table 334.3 Treatment of Uncomplicated Malaria: *P. vivax* or *P. ovale*[1,2]—cont'd

[13]Doxycycline or tetracycline combined with quinine preferred due to more efficacy data, but not recommended during pregnancy or in children <8 yr old unless no other options and benefits outweigh risks.
[14]Clindamycin with quinine preferred option for pregnant women and children <8 yr old.
[15]Use only if no other options available. Not for use in patients with neuropsychiatric history.
[16]Primaquine is the only option if regimens other than either chloroquine or hydroxychloroquine are used for treatment of acute infection.
[17]Primaquine associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before use, quantitative G6PD testing needed to confirm normal activity. For those with intermediate G6PD deficiency, weekly primaquine may be considered (45 mg/wk) for 8 wk with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) PO weekly for 1 yr from acute infection to prevent relapses.
[18]Primaquine must not be used during pregnancy; pregnant patients with *P. vivax* and *P. ovale* infections should receive chloroquine 300 mg (base) PO weekly after acute treatment for the remainder of pregnancy. After delivery, patients with normal G6PD activity can be given primaquine depending on breastfeeding or continue with chloroquine prophylaxis for a total of 1 yr from acute infection. Primaquine can be used during breastfeeding if infant found to also have normal G6PD activity.
[19]Dose of primaquine in patients ≥70 kg should be adjusted to a total dose of 6 mg/kg, divided into doses of 30 mg/day.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

Table 334.4 Treatment of Uncomplicated Malaria: *P. malariae* or *P. knowlesi*[1,2]

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS	RECOMMENDED PEDIATRIC REGIMENS[3]
Chloroquine sensitive (All malaria-endemic regions, no known resistance)	A. **Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose B. **Artemether-lumefantrine (Coartem)**[4] (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid C. **Atovaquone-proguanil (Malarone)**[5] (Adult tab: 250 mg atovaquone and 100 mg proguanil) 4 adult tabs PO qd × 3 days D. **Quinine sulfate**[6] **plus doxycycline,**[7] **tetracycline,**[7] **or clindamycin**[8] Quinine sulfate: 542 mg base (648 mg salt) PO tid × 3 days Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days E. **Mefloquine**[9] Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO	A. **Chloroquine phosphate (Aralen and generics)** Dose 1: 10 mg base/kg (16.7 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (8.3 mg salt/kg) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 10 mg base/kg (12.9 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (6.5 mg salt/kg) PO per dose B. **Artemether-lumefantrine (Coartem)**[4] (1 tab: 20 mg artemether and 120 mg lumefantrine) 5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid C. **Atovaquone-proguanil (Malarone)**[5] (Adult tab: 250 mg atovaquone and 100 mg proguanil; peds tab: 62.5 mg atovaquone and 25 mg proguanil) 5 to <8 kg: 2 peds tabs PO qd × 3 days 8 to <10 kg: 3 peds tabs PO qd × 3 days 10 to <20 kg: 1 adult tab PO qd × 3 days 20 to <30 kg: 2 adult tabs PO qd × 3 days 30 to <40 kg: 3 adult tabs PO qd × 3 days ≥40 kg: 4 adult tabs PO qd × 3 days D. **Quinine sulfate**[6] **plus doxycycline,**[7] **tetracycline,**[7] **or clindamycin**[8] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) PO tid × 3 days Doxycycline: 2.2 mg/kg PO bid × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg /kg/day PO divided tid × 7 days E. **Mefloquine**[9] Dose 1: 13.7 mg base/kg (15 mg salt/kg) PO Dose 2 at 6-12 hr: 9.1 mg base/kg (10 mg salt/kg) PO

[1]qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Not to exceed adult dose.
[4]Artemether-lumefantrine can be used in second and third trimesters of pregnancy and, if no other options available, in first trimester as well. Not for infants <5 kg or women breastfeeding infants <5 kg.
[5]Atovaquone-proguanil not recommended during pregnancy, in infants <5 kg, or in women breastfeeding infants <5 kg. May be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[6]Quinine available in the United States has 324 mg (salt) per capsule, therefore, two capsules for adult dosing. Pediatric dosing may need compounding pharmacy.
[7]Doxycycline or tetracycline combined with quinine preferred due to more efficacy data, but not recommended during pregnancy or in children <8 yr old unless no other options and benefits outweigh risks.
[8]Clindamycin with quinine preferred option for pregnant women and children <8 yr old.
[9]Use only if no other options available. Not for use in patients with neuropsychiatric history.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

Table 334.5 Treatment of Uncomplicated Malaria in Pregnant Women[1,2]

SPECIES AND DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS
Chloroquine resistant[3] *P. falciparum* (All malaria-endemic regions except Central America west of Panama Canal, Haiti, and Dominican Republic) *P. vivax* or *P. ovale* (Papua New Guinea and Indonesia)	Preferred for second and third trimesters: **Artemether-lumefantrine (Coartem)[4]** (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid **All trimesters: Quinine sulfate plus clindamycin** Quinine sulfate: 542 mg base (650 mg salt) PO tid × 3 or 7 days[5] Clindamycin: 20 mg/kg/day PO divided tid × 7 days **If no other options, all trimesters: Mefloquine** Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO **AND if *P. vivax* or *P. ovale*:** **Chloroquine** 500 mg salt (300 mg base) weekly until delivery, then consider antirelapse treatment (Table 334.3 for options and dosing) Antirelapse treatment with either primaquine or tafenoquine contraindicated during pregnancy
Chloroquine sensitive *P. falciparum* (Central America west of Panama Canal, Haiti, and Dominican Republic) *P. vivax* or *P. ovale* (All malaria-endemic regions except Papua New Guinea and Indonesia) *P. malariae* or *P. knowlesi*	**Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose OR **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose **Options above for chloroquine-resistant malaria parasites** **AND if *P. vivax* or *P. ovale*:** **Chloroquine** 500 mg salt (300 mg base) weekly until delivery, then consider antirelapse treatment (Table 334.3 for options and dosing) Antirelapse treatment with either primaquine or tafenoquine contraindicated during pregnancy

[1]bid, twice a day; tid, three times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Atovaquone-proguanil not listed due to insufficient data on its safety during pregnancy but may be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[4]Artemether-lumefantrine may be considered during first trimester if other treatment options not available or not tolerated, and benefits outweigh risks.
[5]Quinine to be given for 3 days for *P. falciparum* and *P. vivax* infections, except for *P. falciparum* infections acquired in Southeast Asia where 7 days of treatment is required.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

atovaquone-proguanil, quinine sulfate, or mefloquine (mefloquine only if the other options are not available) (Table 334.6). If parasite density is >1%, continue IV artesunate daily up to 6 more days until the parasite density is <1%. After this, the oral regimen can be completed (Table 334.6).

Supportive Care for Severe Malaria

It is the malaria-associated complications that might kill the patient, so intensive nursing care, preferably in an ICU where possible, is required. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score, and urine output. Blood glucose should be monitored every 4 hours, if possible, particularly in unconscious patients.

Severe malarial anemia (SMA) is defined as the presence of *P. falciparum* parasitemia in an individual with a hemoglobin of <5 g/dL. In endemic areas, WHO includes a parasitemia cutoff of >10,000 parasites per microliter for this definition. SMA is the most common severe complication of malaria in children and is the leading cause of anemia leading to hospital admission in African children. The etiology of SMA is complex, involving increased destruction and removal of infected and uninfected RBCs and reduced RBC production due to bone marrow dyserythropoiesis. Timely blood transfusion is critical, and mortality in this condition is low with timely transfusion. However, SMA is not benign; it contributes to significant long-term morbidity, including impaired neurocognitive function, repeated hospitalizations, and postdischarge mortality.

Cerebral malaria is defined as the presence of coma in a child with *P. falciparum* parasitemia and an absence of other reasons for coma. Children with altered mental status who are not in a coma fall into the larger category of *impaired consciousness*. Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15–40% and is associated with long-term cognitive impairment in children. Repeated seizures are frequent in children with cerebral malaria. Hypoglycemia is common, but children with true cerebral malaria fail to arouse from coma even after receiving a dextrose infusion that normalizes their glucose level. Physical findings may include high fever, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and mildly increased cerebrospinal fluid protein, typically with no cerebrospinal fluid (CSF) pleocytosis. and a normal CSF glucose. Studies suggest that funduscopic findings of **malaria retinopathy** (retinal hemorrhages, peripheral whitening, macular whitening, vessel changes) are relatively specific for cerebral malaria, so children with cerebral malaria who do not have malaria retinopathy should be carefully assessed for other causes of coma. However, they should still be treated for cerebral malaria because a growing body of evidence suggests that even in these children, *P. falciparum* is a contributor to their comatose state. Beyond antimalarial medications, treatment of cerebral malaria is largely supportive and includes evaluation and treatment of seizures and hypoglycemia. A study using MRI to assess children with cerebral malaria documented that cerebral edema with increased intracranial pressure is the leading cause of death in children with cerebral malaria, and treatment with mannitol and corticosteroids has not improved outcomes in these children.

Respiratory distress syndrome (RDS) is best characterized by signs of acute respiratory distress and deep acidotic breathing. The acidosis is partly due to impaired tissue perfusion secondary to RBC sequestration and reduced oxygen-carrying capacity. RDS is a poor prognostic indicator in severe malaria and in children it appears to be caused by **metabolic acidosis** rather than intrinsic pulmonary disease. The kidney is important in acid metabolism and excretion and is believed to contribute to the acidosis seen in severe malaria. To date, no successful interventions for treatment of metabolic acidosis in children with severe malaria have been described, and primary therapy of malaria appears to be the most effective way to address acidosis.

Table 334.6 Treatment of Severe Malaria[1–5]

SPECIES AND DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMEN	RECOMMENDED PEDIATRIC REGIMEN
All species, drug susceptibility not relevant for acute treatment of severe malaria If *P. vivax* or *P. ovale* infections, in addition to acute treatment listed here, antirelapse treatment needed (Table 334.3)	**IV artesunate:** Commercially available. If not in stock or available within 24 hr, contact CDC Malaria Hotline: (770) 488-7100 or (855) 856-4713 (toll free) Mon–Fri, 9 am–5 pm EST; (770) 488-7100 after hours, weekends, and holidays. 1 dose = 2.4 mg/kg IV doses (3 in total) at 0, 12, and 24 hr **PLUS reassessment and follow-on the following treatment**	
	If IV artesunate not readily available, give oral antimalarials while obtaining IV artesunate. When IV artesunate arrives, discontinue oral antimalarial and initiate IV treatment. Interim treatment options (Table 334.2 for dosing): • Artemether-lumefantrine (Coartem) (preferred), or • Atovaquone-proguanil (Malarone), or • Quinine sulfate, or • Mefloquine (only if no other options available) If oral therapy not tolerated, consider administration via nasogastric (NG) tube or after an antiemetic	
	Reassessment and follow-on treatment: **Reassess parasite density at least 4 hr after the third dose** **Parasite density ≤1% and patient able to tolerate oral medications:** Give a complete follow-on oral regimen. Options include (Table 334.2 for dosing): • Artemether-lumefantrine (Coartem) (preferred), or • Atovaquone-proguanil (Malarone), or • Quinine plus doxycycline or, in children <8 yr old and pregnant women, clindamycin, or • Mefloquine (only if no other options available) **Parasite density >1%:** Continue IV artesunate, same dose, qd up to 6 more dys until parasite density ≤1%. When parasite density ≤1%, give complete follow-on oral regimen as listed previously (Table 334.2 for dosing) **Parasite density ≤1% but patient unable to take oral medication:** Continue IV artesunate, same dose, qd up to 6 more days until patient able to take oral therapy	

[1]qd, once a day; IV, intravenous.
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Laboratory-confirmed or suspected malaria cases with ≥1 clinical criteria for severe disease (impaired consciousness/convulsions/coma, severe anemia [hemoglobin <7 mg/dL], acute kidney injury, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, acidosis, jaundice [plus at least one other sign]); and/or parasite density ≥5%. Information on how to estimate parasite density available at www.cdc.gov/dpdx.
[4]Parasite density should be repeated every 12-24 hr until negative.
[5]Exchange transfusion no longer recommended based on a systematic review of the literature and analysis of US malaria surveillance data showing no added benefit.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

Seizures are a common complication of severe malaria, occurring in up to 70% of children with severe malaria; subclinical seizures occur in 15–20% of cases. Most of the seizures are associated with cerebral malaria, but it is important to evaluate for other common causes of seizure such as hypoglycemia and fever and to treat accordingly. Benzodiazepines are first-line therapy for seizures. Diazepam (0.4 mg/kg) can be administered IV or per rectum; lorazepam (0.1 mg/kg) can be administered IV or intraosseously. These doses can be repeated once if seizures do not cease within 5 minutes of the initial dose. Benzodiazepines should not be combined due to risk of respiratory depression. For persistent seizures, phenobarbital or phenytoin are the standard medications used. Phenobarbitone is given at dose of 15-20 mg/kg, slow IV push) while phenytoin is given at a dose of 18 mg/kg diluted in 100 mL normal saline, infused over 20 minutes. Phenytoin may be preferred for seizure treatment, particularly in hospitals or clinics where ventilatory support is not available. However, no comparative trials of the two drugs have been performed. Routine seizure prophylaxis should not be given in children with rapid resolution of seizures during their hospital course. There are currently no drugs recommended for seizure prophylaxis in children with severe malaria. Phenobarbital prophylaxis decreased seizure activity but increased mortality in one major study of children with severe malaria, probably because the respiratory depression associated with phenobarbital may have been exacerbated by benzodiazepine therapy.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Any child with impaired consciousness and malaria should have a glucose level checked, and if glucometers are not immediately available, an empirical bolus of dextrose should be given. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Shock is a rare complication that manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. It is most likely caused by bacterial superinfection, because up to 15% of children in endemic areas with severe malaria may have concurrent bacteremia. Death may occur within hours. Any child with severe malaria and hypotension or hypoperfusion should have a blood culture obtained and should be treated empirically for bacterial sepsis.

Acute kidney injury (AKI) is increasingly being recognized as an important complication of severe malaria and an independent predictor of mortality, occurring in >40% of children with severe malaria in one study of Ugandan children. The WHO 2023 definition of renal impairment in children with severe malaria (creatinine of ≥3.0 mg/dL) uses almost certainly too high a creatinine cutoff value, as severe AKI associated with increased mortality has been seen in children with much lower creatinine levels. Ongoing work seeks to use Kidney Disease: Improving Global Outcomes (KDIGO) criteria to establish better creatinine values to define AKI and renal impairment in children with severe malaria. Although data suggest AKI is related to reduced kidney perfusion, additional studies are needed to evaluate the spectrum of AKI over hospitalization to define the etiology and pathophysiology of AKI in pediatric severe malaria. In adults, use of acetaminophen has been associated with decreased AKI, and studies are investigating this possibility in children. Other urinary tract complications in children include **blackwater fever (or dark urine syndrome)**, which has reemerged as a clinical problem in some areas of Africa. The syndrome is thought to be associated in part with increased use of artemisinin derivatives and is associated with increased risk of readmission or death.

Prostration is defined as the inability to sit, stand, or eat without support, in the absence of impaired consciousness. Prostration has also been associated with increased mortality in some studies, but the pathophysiology of this process is not well understood.

In children, **abnormal bleeding** and **pulmonary edema** are uncommon, though the latter may sometimes be seen after treatment in *P. vivax* or *P. ovale* malaria.

Long-Term Complications of Malaria

Neurocognitive impairment and behavioral and mental health problems occur in children after episodes of cerebral malaria and severe malarial anemia. **Epilepsy** also occurs in a subset of children after severe malaria. The mechanisms leading to brain injury and subsequent neurocognitive complications due to severe malaria are still being investigated. Clinical predictors of neurocognitive impairment in children with cerebral malaria include duration of coma, number of seizures, acute kidney injury, and severe malarial anemia. CSF cytokines and metabolites like tumor necrosis factor (TNF)-α and kynurenic acid, as well as plasma and CSF levels of tau, a marker of neuronal injury, are elevated acutely in children with cerebral malaria who subsequently develop cognitive impairment. Additional studies are needed to delineate the mechanisms leading to neurocognitive complications in severe malaria, particularly in children without overt clinical signs suggestive of brain injury. Interventions to rehabilitate children with cognitive impairment have provided only short-term improvement in specific areas of function, and further studies in this area are needed.

Hyperreactive malarial splenomegaly (HMS) is a chronic complication of *P. falciparum* malaria in which massive splenomegaly persists after treatment of acute infection. Major criteria include splenomegaly (>10 cm), IgM >2 SD above local mean, high levels of antibodies to a blood-stage *P. falciparum* antigen, and a clinical response to an antimalarial drug. HMS occurs exclusively in children in endemic areas with repeated exposure to malaria and is thought to be caused by an impaired immune response to *P. falciparum* antigens. Prolonged antimalarial prophylaxis (for at least 1 year, typically with chloroquine, quinine, or mefloquine) is required to treat this syndrome if the child remains in a malaria-endemic area. Spleen size gradually regresses on antimalarial prophylaxis but often increases again if prophylaxis is stopped.

PREVENTION

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis. The most accurate and current information on areas in the world where malaria risk and drug resistance exist can be obtained by contacting local and state health departments or the CDC or consulting *Health Information for International Travel,* which is published by the U.S. Public Health Service.

Travelers to endemic areas should remain in well-screened areas from dusk to dawn, when the risk for transmission is highest. They should sleep under permethrin-treated mosquito netting and spray insecticides indoors at sundown. During the day, travelers should wear clothing that covers the arms and legs, with trousers tucked into shoes or boots. Mosquito repellent should be applied to thin clothing and exposed areas of the skin, with applications repeated as noted on the repellent instructions, and at least every 4 hours. A child should not be taken outside from dusk to dawn, but if at risk for exposure, a solution with 25–35% *N,N*-diethyltoluamide (DEET) (not >40%) should be applied to exposed areas, except for the eyes, mouth, or hands. Hands are excluded because they are often placed in the mouth. DEET should then be washed off as soon as the child comes back inside. The American Academy of Pediatrics recommends that DEET solutions be avoided in children <2 months old. Adverse reactions to DEET include rashes, toxic encephalopathy, and seizures, but these reactions occur almost exclusively with inappropriate application of high concentrations of DEET. **Picaridin** is an alternative and sometimes better tolerated repellent. Even with these precautions, a child should be taken to a physician immediately if the child develops illness when traveling to a malarious area.

Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy, including children of all ages (Tables 334.7 and 334.8). Healthcare providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients. Chloroquine is given in the few remaining areas of the world free of chloroquine-resistant malaria strains. In areas where chloroquine-resistant *P. falciparum* exists, atovaquone-proguanil, mefloquine, or doxycycline may be given as chemoprophylaxis. **Atovaquone-proguanil** is generally recommended for shorter trips (up to 2 weeks) because it must be taken daily. Pediatric tablets are available and are generally well tolerated, although the taste is

Table 334.7 Drugs Used in the Prophylaxis of Malaria

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Atovaquone-proguanil	Prophylaxis in all areas	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride. 1 adult tablet orally, daily	Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride. 5-8 kg: ½ pediatric tablet daily >8-10 kg: ¾ pediatric tablet daily >10-20 kg: 1 pediatric tablet daily >20-30 kg: 2 pediatric tablets daily >30-40 kg: 3 pediatric tablets daily >40 kg: 1 adult tablet daily	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in people with severe renal impairment (creatinine clearance <30 mL/min). Atovaquone-proguanil should be taken with food or a milky drink. Not recommended for prophylaxis for children weighing <5 kg, pregnant women, and women breastfeeding infants weighing <5 kg. Partial tablet doses may need to be prepared by a pharmacist and dispensed in individual capsules
Chloroquine	Prophylaxis only in areas with chloroquine-sensitive malaria	300 mg base (500 mg salt) orally, once/wk	5 mg/kg base (8.3 mg/kg salt) orally, once/wk, up to maximum adult dose of 300 mg base	Begin 1-2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. May exacerbate psoriasis
Doxycycline	Prophylaxis in all areas	100 mg orally, daily	≥8 yr of age: 2.2 mg/kg up to adult dose of 100 mg/day	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 wk after leaving such areas. Contraindicated in children <8 yr of age and pregnant women

Continued

Table 334.7 Drugs Used in the Prophylaxis of Malaria—cont'd

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Hydroxychloroquine	An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive malaria	310 mg base (400 mg salt) orally, once/wk	5 mg/kg base (6.5 mg/kg salt) orally, once/wk, up to a maximum adult dose of 310 mg base	Begin 1-2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas
Mefloquine	Prophylaxis in areas with mefloquine-sensitive malaria	228 mg base (250 mg salt) orally, once/wk	≤9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/wk >9-19 kg: ¼ tablet once/wk >19-30 kg: ½ tablet once/wk >30-45 kg: ¾ tablet once/wk >45 kg: 1 tablet once/wk	Begin ≥2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. Contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine) and in people with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in people with psychiatric disturbances or a previous history of depression. Not recommended for people with cardiac conduction abnormalities
Primaquine[1]	Prophylaxis for short-duration travel to areas with principally *P. vivax*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas
	Presumptive antirelapse therapy (PART or terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	PART indicated for people with prolonged exposure to *P. vivax, P. ovale,* or both: daily for 14 days after departure from the malarious area Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation, unless the infant being breastfed has a documented normal G6PD level
Tafenoquine[1]	Prophylaxis in all areas	200 mg orally	Not indicated in children <16 yr old	Begin taking daily for 3 days before travel to malarious areas. Then, take weekly while at the malarious area, and for 1 wk after leaving the malarious area
	Presumptive antirelapse therapy (PART or terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale*	300 mg orally once	300 mg orally once for children ≥16 yr old	PART indicated for people who had prolonged exposure to *P. vivax, P. ovale,* or both: Administered as a single dose Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level

[1]All people who take primaquine or tafenoquine should have a documented normal G6PD level before starting the medication.
PART, presumptive antirelapse therapy; G6PD, glucose-6-phosphate dehydrogenase.
From Tan KR, Arguin PM: Malaria. In Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. Table 4.10. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#5217

Table 334.8 Considerations When Choosing a Drug for Malaria Prophylaxis

DRUG	REASONS TO CONSIDER USE OF THIS DRUG	REASONS TO CONSIDER AVOIDING USE OF THIS DRUG
Atovaquone-proguanil	• Good for last-minute travelers because the drug is started 1-2 days before travel • Some people prefer to take a daily medicine • Good choice for shorter trips because the traveler takes the medicine for only 7 days after traveling rather than 4 wk. • Well tolerated; side effects uncommon • Pediatric tablets are available and may be more convenient	• Cannot be used by women who are pregnant or breastfeeding a child that weighs <5 kg • Cannot be taken by people with severe renal impairment • Tends to be more expensive than some of the other options (especially for long trips) • Some people (including children) would rather not take a medicine every day
Chloroquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Some people are already taking hydroxychloroquine chronically for rheumatologic conditions; in those instances, they may not have to take an additional medicine • Can be used in all trimesters of pregnancy	• Cannot be used in areas with chloroquine or mefloquine resistance • May exacerbate psoriasis • Some people would rather not take a weekly medication • For short trips, some people would rather not take medication for 4 wk after travel • Not a good choice for last-minute travelers, because drug needs to be started 1-2 wk before travel
Doxycycline	• Some people prefer to take a daily medicine • Good for last-minute travelers because the drug is started 1-2 days before travel • Tends to be the least expensive antimalarial • People who are already taking doxycycline chronically to prevent acne do not have to take an additional medicine • Doxycycline also can prevent some additional infections (such as rickettsial infections and leptospirosis), so it may be preferred by people planning to hike, camp, and swim in fresh water	• Cannot be used by pregnant women and children age <8 yr • Some people would rather not take a medicine every day • For short trips, some people would rather not take medication for 4 wk after travel • Women prone to getting vaginal yeast infections when taking antibiotics may prefer taking a different medicine • People may want to avoid the increased risk of sun sensitivity • Some people are concerned about the potential of getting an upset stomach from doxycycline
Mefloquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Can be used in all trimesters of pregnancy	• Cannot be used in areas with mefloquine resistance • Cannot be used in patients with certain psychiatric conditions • Cannot be used in patients with a seizure disorder • Not recommended for people with cardiac conduction abnormalities • Not a good choice for last-minute travelers because drug needs to be started ≥2 wk before travel • Some people would rather not take a weekly medication • For short trips, some people would rather not take medication for 4 wk after travel
Primaquine	• It is the most effective medicine for preventing *P. vivax,* so it is a good choice for travel to places with >90% *P. vivax* • Good choice for shorter trips because you only have to take the medicine for 7 days after traveling rather than 4 wk • Good for last-minute travelers because the drug is started 1-2 days before travel • Some people prefer to take a daily medicine	• Cannot be used in patients with G6PD deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time primaquine is considered • Cannot be used by pregnant women • Cannot be used by women who are breastfeeding, unless the infant has also been tested for G6PD deficiency • Some people (including children) would rather not take a medicine every day • Some people are concerned about the potential of getting an upset stomach from primaquine
Tafenoquine	• One of the most effective drugs for prevention of *P. vivax* malaria but also prevents *P. falciparum* • Good choice for shorter trips because the traveler takes the medicine once, 1 wk after traveling rather than 4 wk • Good for last-minute travelers because the drug is started 3 days before travel	• Cannot be used in people with G6PD deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time tafenoquine or primaquine is considered • Cannot be used by children • Cannot be used by pregnant women • Cannot be used by women who are breastfeeding • Not recommended in those with psychotic disorders

From Tan KR, Arguin PM: Malaria. In Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. Table 4.9. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#5217

sometimes unpleasant to very young children. For longer trips, **mefloquine** is preferred, because it is given only once a week. Mefloquine does not have a pediatric formulation and has an unpleasant taste that usually requires that the cut tablet be disguised in another food, such as chocolate syrup. Mefloquine should not be given to children if they have a known hypersensitivity to mefloquine, are receiving cardiotropic drugs, have a history of convulsive or certain psychiatric disorders, or travel to an area where mefloquine resistance exists (the borders of Thailand with Myanmar and Cambodia, western provinces of Cambodia, and eastern states of Myanmar). Atovaquone-proguanil is started 1-2 days before travel, and mefloquine is started 2 weeks before travel. It is important that these doses are given, both to allow therapeutic levels of the drugs to be achieved and to be sure that the drugs are tolerated. **Doxycycline** is an alternative for children >8 years old. It must be given daily and should be given with food. Side effects of doxycycline include photosensitivity and vaginal yeast infections. **Primaquine** is a daily prophylaxis option for children who cannot tolerate any of the other options, but it should be provided in consultation with a travel medicine specialist if needed, and all children should be checked for glucose-6-phosphate dehydrogenase (G6PD) deficiency before prescribing this medication, because it is contraindicated in children with G6PD deficiency. Provision of medication can be considered in individuals who refuse to take prophylaxis or will be in very remote areas without accessible medical care. Provision of medication for self-treatment of malaria should be done in consultation with a travel medicine specialist, and the medication provided should be different than that used for prophylaxis.

A number of other efforts are currently underway to prevent malaria in malaria-endemic countries. Some have been highly successful, leading to a significant decrease in malaria incidence in many countries in Africa, Asia, and South America in the past decade. These interventions include the use of **insecticide-treated bed nets** (which have decreased all-cause mortality in children <5 years old in several highly malaria-endemic areas by approximately 20%), indoor residual spraying with long-lasting insecticides, and the use of **artemisinin-combination therapy** for first-line malaria treatment.

Intermittent prevention treatment is successfully used in many African countries for seasonal chemoprevention treatment in areas with seasonal malaria transmission. **Sulfadoxine-pyrimethamine** given to infants at the second and third doses of the diphtheria, tetanus toxoid, and pertussis vaccine is safe and relatively effective. Intermittent prevention treatment has also been given to pregnant women; three doses of sulfadoxine-pyrimethamine have resulted in a reduction of low birthweight infants. Treatment of African children in malaria-endemic areas who have severe anemia with **dihydroartemisinin-piperaquine** reduces their risk of readmission and death, and this intervention is under consideration for standard treatment of severe anemia in children in several African countries.

The first malaria vaccine to have any degree of efficacy is the **RTS,S vaccine,** which is based on the circumsporozoite protein of *P. falciparum*. The RTS,S vaccine was approved by WHO in 2021 for use in children <2 years of age in malaria-endemic regions, in combination with other malaria prevention strategies. WHO approval was based on the results of phase IV studies showing a 30% reduction in severe malaria in children who received the four-dose vaccine series. WHO also approved the R21/Matrix-M vaccine in 2023 for use in children <2 years of age in malaria-endemic regions. Numerous other vaccines are also in current clinical trials. There is currently no vaccine with sufficient efficacy to be considered for prevention of malaria in travelers. A trial of monoclonal antibodies showed short-term efficacy in prevention of malaria, and this intervention could potentially be useful in malaria prevention in travelers and the military if efficacy is reproduced in larger studies. Trials of monoclonal antibodies for prevention of seasonal malaria in African children are also ongoing. If monoclonal antibodies can be produced at low cost, they may have a role in prevention in areas of seasonal malaria transmission.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 335

Babesiosis *(Babesia)*

Peter J. Krause

Babesiosis is a malaria-like disease caused by intraerythrocytic protozoa that are transmitted by hard body **(ixodid)** ticks. The clinical manifestations of babesiosis range from subclinical illness to fulminant disease resulting in death.

ETIOLOGY

More than 100 species of *Babesia* infect a wide variety of wild and domestic animals throughout the world. Only a few of these species have been reported to infect humans, including *Babesia crassa*-like agent, *Babesia divergens, Babesia duncani, Babesia microti, Babesia motosi,* and *Babesia venatorum*.

EPIDEMIOLOGY

Babesia organisms are transmitted to humans from vertebrate reservoir hosts by the *Ixodes ricinus* family of ticks. *B. microti* is the most common cause of babesiosis in humans. The primary reservoir for *B. microti* in the United States is the white-footed mouse, *Peromyscus leucopus*, and the primary vector is *Ixodes scapularis*, the black-legged tick. *I. scapularis* ticks also transmit the causative agents of **Lyme disease**, human granulocytic anaplasmosis, *Borrelia mayonii, Borrelia miyamotoi* infection, *Ehrlichia muris eauclairensis*, and Powassan virus encephalitis and may simultaneously transmit two or more microorganisms. White-tailed deer *(Odocoileus virginianus)* serve as the host on which adult ticks most abundantly feed but are incompetent reservoirs of *B. microti*. Babesiosis may be transmitted through blood transfusion, and *B. microti* has been one of the most frequently reported transfusion-transmitted microbial agents in the United States. Rarely, babesiosis is acquired by transplacental transmission or organ transplantation.

In the United States, human *B. microti* infection is endemic in the Northeast and Upper Midwest with more than 2,000 reported cases a year, although the actual number of cases is probably much greater (Fig. 335.1). Most cases occur in June, July, and August. *B. duncani* infects humans along the Pacific coast and is reported sporadically, with less than 50 cases having been described to date. *B. divergens*–like infections have been described in Arkansas, Kentucky, Missouri, and Washington State. In Europe, human babesiosis caused by *B. divergens, B. microti,* and *B. venatorum* occurs sporadically. In Asia, *B. venatorum* and *Babesia crassa*–like agent are endemic in northeastern China. Cases of *B. microti* infection are endemic in southwestern China and also have been described in Taiwan and Japan. Infection due to *Babesia motosi* has been reported in Korea. Human babesiosis also has been documented in Africa, Australia, Canada, Cuba, Egypt, India, Mexico, South America, and Turkey.

In certain sites and in certain years of high transmission, babesiosis constitutes a significant public health burden. On Nantucket Island, case rates as high as 280 per 100,000 population have been recorded, placing the community burden of disease in a category with gonorrhea as "moderately common." Comparable incidence rates have been described elsewhere on the southern New England coast.

PATHOGENESIS

The pathogenesis of human babesiosis is not well understood. Lysis of infected erythrocytes with resultant anemia and the excessive production of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 may account for most of the clinical manifestations and complications of the disease. Cytoadherence of *Babesia*-infected red blood cells to vascular epithelium with subsequent vascular obstruction and tissue anoxia might also cause complications. The spleen has an important role in clearing parasitemia, as do T and B cells, macrophages, polymorphonuclear leukocytes, cytokines, antibody, and complement.

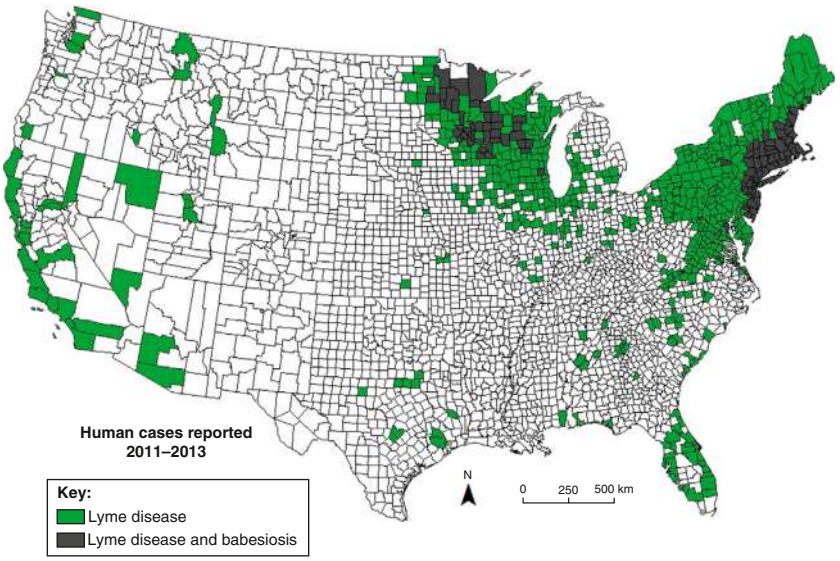

Fig. 335.1 Human babesiosis emerging in areas endemic for Lyme disease. This U.S. map is based on data obtained from the Centers for Disease Control and Prevention that recorded the names of counties that reported cases of Lyme disease and/or babesiosis from 2011 to 2013. Counties with ≥3 cases of Lyme disease but <3 cases of babesiosis are depicted in *green*. Counties with ≥3 cases of Lyme disease and ≥3 cases of babesiosis are depicted in *gray*. No county reported ≥3 cases of babesiosis but <3 cases of Lyme disease. *(Adapted from Diuk-Wasser M, Vannier E, Krause PJ. Coinfection by Ixodes tick-borne pathogens: ecological, epidemiological, and clinical consequences. Trends Parasitol. 2016;32:30–42.)*

CLINICAL MANIFESTATIONS

The clinical severity of babesiosis ranges from subclinical infection to fulminant disease and death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1-9 weeks from the beginning of tick feeding or 1 week to 6 months after transfusion. Typical symptoms in moderate to severe infection include intermittent fever to as high as 40°C (104°F) accompanied by any combination of chills, sweats, headache, and myalgias. Less common are arthralgias, sore throat, abdominal pain, nausea, vomiting, emotional lability, hyperesthesia, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally, but rash is seldom reported. Abnormal laboratory findings include moderately severe hemolytic anemia, elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated bilirubin, BUN, and creatinine levels. The leukocyte count is normal to slightly decreased, often with neutropenia. Complications include respiratory failure, disseminated intravascular coagulation, congestive heart failure, renal failure, liver failure, coma, and death. Babesiosis symptoms usually last for 1-2 weeks, although prolonged recovery of over 1 year may occur in highly immunocompromised hosts who experience relapsing infection despite multiple courses of antibabesial therapy. Such patients include those with cancer and asplenia, those receiving immunosuppressive therapy, and those with HIV/AIDS. In one study, more than 20% of these patients died, while the remainder were cured after an average of 3 months (range: 1-24 months) of antibabesial therapy.

Risk factors for severe disease include aging, neonatal prematurity, anatomic or functional asplenia, malignancy, HIV/AIDS, immunosuppressive drugs, acquisition of infection through blood transfusion, or organ transplantation. Concurrent babesiosis and Lyme disease has been reported in 3–11% of patients experiencing Lyme disease, depending on location in the United States. Such co-infection results in more severe Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection generally is less severe than in adults. About half of infected children are asymptomatic or experience minimal symptoms. Neonates may develop severe illness and usually are infected from blood transfusion.

DIAGNOSIS

Diagnosis of *B. microti* infection in human hosts is confirmed by microscopic demonstration of the organism using Giemsa-stained thin blood films. Parasitemia may be exceedingly low, especially early in the course of illness. Thick blood smears may be examined, but the organisms may be mistaken for stain precipitate or iron inclusion bodies. Polymerase chain reaction (PCR) is a sensitive and specific test for detection of *Babesia* DNA and can be used in addition to or instead of blood smear to confirm the diagnosis. Serologic testing can be useful in supporting the diagnosis of *Babesia* infection. The indirect immunofluorescence serologic assay for both IgG and IgM antibodies is sensitive and specific, although it may reflect past infection rather than acute disease. The diagnosis of babesiosis is most reliably made in patients who have lived or traveled in an area where babesiosis is endemic, who experience viral infection–like symptoms, and who have identifiable parasites on blood smear or amplifiable *Babesia* DNA in blood. The diagnosis of active babesial infection based on seropositivity alone is suspect.

TREATMENT

The combination of **clindamycin** (7-10 mg/kg given intravenously [IV] or orally [PO] every 6-8 hr, up to maximum of 600 mg/dose) and **quinine sulfate** (8 mg/kg PO every 8 hr, up to maximum of 650 mg/dose) for 7-10 days was the first effective therapeutic combination for the treatment of babesiosis; however, adverse reactions associated with this regimen are common, especially tinnitus and abdominal distress. The combination of **atovaquone** (20 mg/kg PO every 12 hr, up to maximum of 750 mg/dose) and **azithromycin** (10 mg/kg/day PO once on day 1, up to maximum of 500 mg/dose, and 5 mg/kg once daily thereafter, up to maximum of 250 mg/dose) for 7-10 days is as effective as clindamycin and quinine but has far fewer adverse effects. Atovaquone with azithromycin has been used successfully to treat babesiosis in infants and should be used initially in all children experiencing babesiosis. Clindamycin with quinine is an alternative choice. Treatment failure with atovaquone-azithromycin and clindamycin-quinine may occur in highly immunocompromised hosts. Consultation with an infectious diseases expert is recommended in these cases. Exchange blood transfusion can decrease parasitemia rapidly and remove toxic by-products of infection. Partial or complete exchange transfusion is recommended for children with high-grade parasitemia (>10%), severe anemia (hemoglobin <10 g/dL), or severe pulmonary, renal, or hepatic compromise.

PROGNOSIS

Moderate to severe disease is frequently observed in some highly endemic areas but mostly in adults. The babesiosis case fatality rate was estimated at 5% in a retrospective study of 136 New York cases but may be as high as 21% in immunocompromised hosts and those who acquire babesiosis through blood transfusion. Clearance of infection is sometimes delayed, with low-level asymptomatic parasitemia persisting for as long as 26 months after symptoms have resolved, or with relapsing symptomatic disease in immunocompromised hosts.

PREVENTION

Prevention of babesiosis can be accomplished by avoiding areas where ticks, deer, and mice are known to thrive. Use of clothing that covers the

lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. DEET can be applied directly to the skin. A search for ticks should be carried out and the ticks removed using tweezers. Prospective blood donors with a history of babesiosis are excluded from giving blood to prevent transfusion-related cases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 336

Toxoplasmosis *(Toxoplasma gondii)*

Rima McLeod and Kenneth M. Boyer

Toxoplasma gondii, an obligate, intracellular, apicomplexan protozoan, is acquired perorally, transplacentally, or rarely parenterally in laboratory accidents, transfusions, or from a transplanted organ. In immunologically normal children, acute acquired infection most often is asymptomatic or unrecognized but may cause lymphadenopathy or affect almost any organ. *Once acquired, latent encysted organisms persist in the host throughout life.* In immunocompromised persons, initial acquisition or recrudescence of latent organisms can cause signs or symptoms related to the central nervous system (CNS) or result in systemic disease, as in bone marrow transplant recipients. If untreated, congenital infection causes disease that manifests either perinatally or later in life, most frequently chorioretinitis and CNS lesions. Other manifestations include intrauterine growth restriction, prematurity, cognitive and motor deficits, fever, lymphadenopathy, rash, hearing loss, pneumonitis, hepatitis, thrombocytopenia, and cerebrospinal fluid (CSF) inflammatory changes. Unrecognized congenital toxoplasmosis in infants with HIV infection may be fulminant.

ETIOLOGY

T. gondii is a coccidian protozoan that multiplies only in living cells. It is descended from an ancient, free-living, single-celled extracellular parasite called *Colpodella,* which shares some ultrastructural features with *T. gondii* (Fig. 336.1A). Tachyzoites are the pathogenic form of the parasite in active infections and are oval or crescent-like, measuring 2-4 × 4-7 μm (see Fig. 336.1B). Tissue cysts are 10-100 μm in diameter, may contain thousands of latent parasites called **bradyzoites** (see Fig. 336.1C), and will remain in tissues, especially the CNS and skeletal and heart muscle, for the life of the host. *Toxoplasma* can multiply in all tissues of mammals and birds. There is also a dormant "stressed persister" form of the parasite that arrests and does not progress through the G1 phase of the cell cycle, unable to pass a checkpoint into the tachyzoite replicative phase of the cell cycle. In recent years critical transcription factors that can distinguish *Toxoplasma* bradyzoites from **tachyzoites** and **merozoites** have been identified.

Oocysts are another form of the parasite and are formed in the cat intestine (see Fig. 336.1D). Newly infected, nonimmune cats and other Felidae species are the definitive hosts of *T. gondii* and represent the location where genetic exchange occurs during a sexual cycle. *Toxoplasma* organisms are transmitted to cats when the cat ingests infected meat containing encysted bradyzoites or ingests oocysts containing **sporozoites** excreted by other recently infected cats. The parasites then multiply through schizogonic merozoite and other gametogonic cycles in the distal ileal epithelium of the cat intestine. Intestinal delta-6-desaturase activity and linoleic acid determine the host range of oocyst formation in cats. Genes in the parasite that promote fusion of the female and male gamete to form a zygote and are critical for conception have been identified. Oocysts containing two sporocysts are excreted, and under the proper temperature and moisture conditions each sporocyst matures into four sporozoites. For approximately 2 weeks the cat excretes 10^5-10^7 oocysts daily, which may retain their viability for >1 year in a suitable environment. Oocysts sporulate 1-5 days after excretion and are then infectious. They are killed by drying or boiling but are resistant to bleach. Oocysts have been isolated from soil and sand frequented by cats, and outbreaks associated with contaminated food and water have been reported. Oocysts and tissue cysts are sources of animal and human infections (see Fig. 336.1D).

There are genetically distinct types of *T. gondii* that differ in virulence for mice, form different numbers of cysts in the brain of outbred mice, and cause different clinical manifestations for humans. In the United States, there are four predominant clonal lineages called **types I**, **II**, **III**, and **IV** (haplogroup XII) in addition to atypical, recombinant types. There is one predominant clonal type (type II) in France, Austria, and Poland, and nonarchetypal parasites are prevalent in Brazil, Guyana, French Guiana, and Central America. Hypervirulent parasites containing a single stranded RNA virus appear to cause epidemics of disease in Guiana and Victoria Canada.

EPIDEMIOLOGY

Toxoplasma infection is ubiquitous in animals and is one of the most common latent infections of humans throughout the world, infecting and persisting in approximately 2 billion people. Prevalence varies considerably among people and animals in different geographic areas. In different areas of the world, approximately 3–35% of pork, 7–60% of lamb, and 0–9% of beef contain *T. gondii* organisms. Significant antibody titers are detected in 50–80% of residents of some localities, such as France, Brazil, and Central America, and in <5% of populations in other areas. The current overall prevalence estimate in the United States is 10%, but prevalence varies among different demographic groups and in different geographic locations. For example, in a study of pregnant women in an Amish community in Lancaster County, Pennsylvania, prevalence was 50%. There appears to be a higher prevalence of infection in some warmer, more humid climates. Non–type II parasites are more common in mothers of congenitally infected infants in warm, moist southern climates, in rural areas, in those with lower socioeconomic status and with Hispanic ethnicity in the United States. Non–type II parasites are more often associated with prematurity and severe congenital infection in the United States.

Human infection in older children and adults is usually acquired orally by eating undercooked or raw meat that contains cysts or food or other material contaminated with oocysts from acutely infected cats. Fruits and vegetables that have not been properly washed may carry oocysts, consistent with the high overall prevalence of *Toxoplasma* oocysts in the soil and water in many regions of the globe. Freezing meat to −20°C (−4°F) or heating meat to 66°C (150.8°F) renders the tissue cysts noninfectious. Outbreaks of acute acquired infection have occurred in families, at social gatherings, and in restaurants where people have consumed the same infected food or water. It was previously thought that *T. gondii* could not be transmitted from person to person except for transplacental infection from mother to fetus and, rarely, by organ transplantation or transfusion. However, there is now increasing evidence of the ability of both humans and animals to pass *T. gondii* from male to female via sperm.

Seronegative transplant recipients who receive an organ, bone marrow, or stem cells from seropositive donors have experienced life-threatening illness requiring immediate therapy. Seropositive recipients who receive an infected donor organ may have increased serologic titers without recognized, associated disease. Laboratory accidents have resulted in infections, including fatalities.

Transmission to the fetus usually follows acquisition of primary infection by an immunologically normal pregnant woman during gestation. Congenital transmission from mothers infected before pregnancy is extremely rare except for immunocompromised women who are chronically infected. The estimated incidence of congenital infection in the United States ranges from 1 in 1,000 to 1 in 8,000 live births. An estimated 15 million people are living with congenital toxoplasmosis worldwide. The incidence of infection among pregnant women depends on the general risk for infection in the specific locale and the proportion of the population that has not been infected previously.

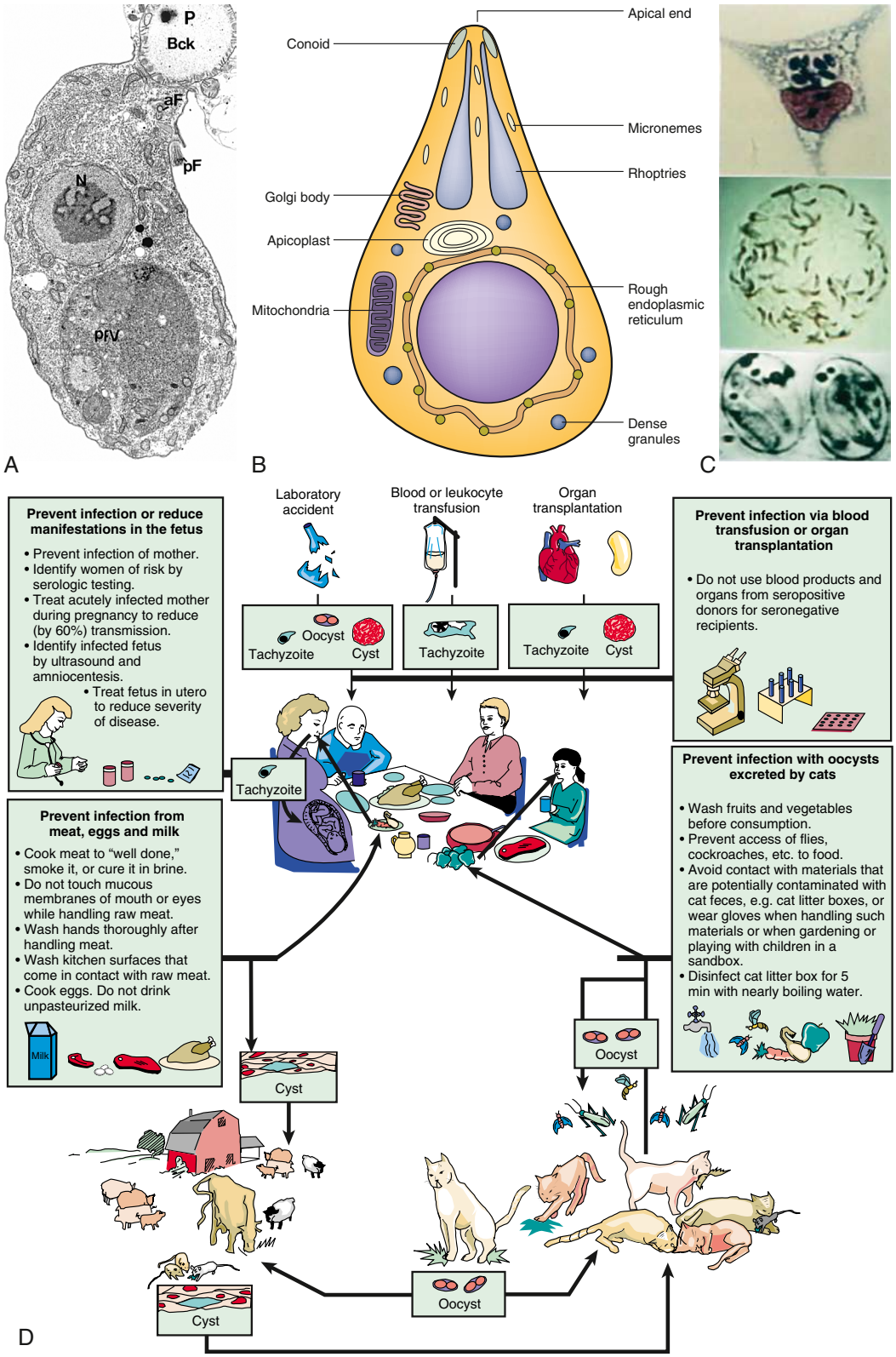

Fig. 336.1 The parasite: *Toxoplasma* ancient ancestor, ultrastructure, and life cycle stages affecting humans. **A,** *Colpodella vorax,* an ancient progenitor to the apicomplexans. **B,** Ultrastructure of *T. gondii* tachyzoite. **C,** Light micrographs of, *top to bottom,* tachyzoite, bradyzoite, and sporozoite stages of *T. gondii*. **D,** Life cycle of *Toxoplasma gondii* and prevention of toxoplasmosis by interruption of transmission to humans. N, nucleus; PBck, prey being ingested; aF, anterior flagellum; pF, posterior flagellum; pFV, posterior food vacuole. (*A from Brugerolle G. Colpodella vorax: Ultrastructure, predation, life-cycle, mitosis, and phylogenetic relationships. Eur J Protistol. 2002;38[2]:113–125; B from Wheeler K. Characterization of Toxoplasma gondii dense granule protein 1: Genetic, functional, and mechanistic analyses (Undergraduate Honors thesis), Kelsey Wheeler; C, bottom panel, from Dubey JP, Miller N, Frenkel JK. The Toxoplasma gondii oocyst from cat feces. J Exp Med. 1970;132[4]:636–662.)*

PATHOGENESIS

T. gondii is acquired by children and adults from ingesting food that contains cysts or that is contaminated with oocysts from acutely infected cats. Oocysts also may be transported to food by flies and cockroaches and may be carried to people on the fur of dogs. When the organism is ingested, bradyzoites are released from cysts or sporozoites are produced from oocysts. The organisms enter gastrointestinal (GI) cells, where they multiply, rupture cells, infect contiguous cells, enter the lymphatics and blood, and disseminate lymphohematogenously throughout the body. **Tachyzoites** proliferate, producing necrotic foci surrounded by a cellular reaction. With development of a normal immune response that is both humoral and cell mediated, tachyzoites disappear from tissues. In immunocompromised individuals and also in some apparently immunocompetent people, acute infection progresses and may cause pneumonitis, myocarditis, or encephalitis, sometimes resulting in lethal disease.

Alterations of T-lymphocyte populations during acute *T. gondii* infection are common and include lymphocytosis, increased $CD8^+$ T-cell count, and decreased $CD4^+/CD8^+$ ratio. Characteristic histopathologic changes in lymph nodes during acute infection include (1) reactive follicular hyperplasia with irregular clusters of epithelioid histiocytes that encroach on and blur margins of germinal centers, and (2) focal distention of sinuses with monocytoid cells. Depletion of $CD4^+$ T cells in patients with AIDS predisposes to severe manifestations of toxoplasmosis.

Cysts form as early as 7 days after infection and remain in the host for life. During latent infection they produce little or no inflammatory response but can cause recrudescent disease in immunocompromised persons. **Recrudescent chorioretinitis** can occur in children and adults with postnatally acquired infection and in older children and adults with congenitally acquired infection. Host and parasite genetics influence outcomes.

When a mother acquires infection during gestation, organisms may disseminate hematogenously to the placenta. Infection may be transmitted to the fetus transplacentally or to the infant during vaginal delivery. Of untreated maternal infections acquired in the first trimester, approximately 17% of fetuses are infected, usually with severe disease. Of untreated maternal infection acquired in the third trimester, approximately 65% of fetuses are infected, usually with disease that is milder and sometimes inapparent at birth (Fig. 336.2). These different rates of transmission and outcomes are most likely related to placental blood flow, virulence, inoculum of *T. gondii,* and immunologic capacity of the mother and fetus to limit parasitemia.

Examination of the placenta of infected newborns may reveal chronic inflammation and cysts. Tachyzoites can be seen with Wright or Giemsa stains but are best demonstrated with the immunoperoxidase technique. Tissue cysts stain well with periodic acid–Schiff and silver stains as well as with the immunoperoxidase technique. Gross or microscopic areas of necrosis may be present in many tissues, especially the CNS, choroid and retina, heart, lungs, skeletal muscle, liver, and spleen. Areas of calcification occur in the brain.

Almost all congenitally infected individuals who are not treated develop signs or symptoms of infection by adolescence. Some severely affected infants with congenital infection appear to have *Toxoplasma* antigen–specific cell-mediated hyporesponsiveness, which may be important in the pathogenesis of disease.

CLINICAL MANIFESTATIONS

Manifestations of primary infection with *T. gondii* are highly variable and are influenced primarily by host immunocompetence. Clinical features range from no signs or symptoms to severe disease. Reactivation of previously asymptomatic congenital toxoplasmosis usually manifests as ocular toxoplasmosis.

Acquired Toxoplasmosis

Immunocompetent children who acquire infection postnatally generally do not have clinically recognizable symptoms. When clinical

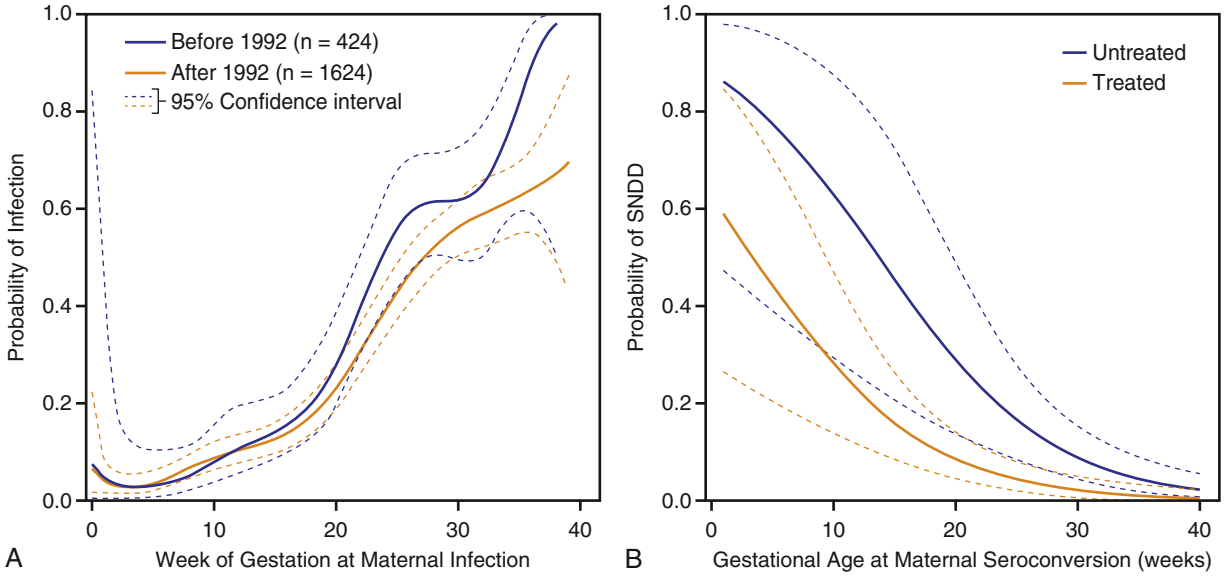

Fig. 336.2 Probability and severity of congenital toxoplasmosis and relationship to gestational age. **A,** Probability of fetal infection according to gestational age at the time of maternal infection before (n = 451) and after (n = 1624) mid-1992, Lyon cohort (1987–2008). **B,** Risk of severe neurologic disease or death (SNDD) in children with congenital toxoplasmosis (CT) according to antepartum treatment. Probability of SNDD according to imputed gestational age at seroconversion and 95% Bayesian credible limits. *Gold* lines denote treated pregnancies; *purple lines* denote untreated pregnancies. (SNDD is a composite outcome comprising a pediatric report at any age of microcephaly; insertion of an intraventricular shunt; an abnormal or suspicious neurodevelopmental examination that resulted in referral to a specialist; seizures during infancy or at an older age that required anticonvulsant therapy; severe bilateral visual impairment [visual acuity of Snellen ≤6/60 in both eyes assessed after 3 yr]; cerebral palsy; or death from any cause before age 2 years, including termination of pregnancy [consistency of SSND findings was checked through multiple assessments].) Severe neurologic sequelae were assessed at a median of 4 years' follow-up, death was assessed by age 2 yr, and severe bilateral visual impairment was included in the composite outcome of severe neurologic sequelae. *(A from Wallon M, Peyron F, Cornu C, et al. Congenital toxoplasmosis infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. Clin Infect Dis. 2013;56:1229; B from Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment of serious neurologic sequelae of congenital toxoplasmosis: an observational prospective cohort study. PLoS Med. 2010;7:e1000351.)*

manifestations are apparent, they may include almost any combination of fever, stiff neck, myalgia, arthralgia, maculopapular rash that spares the palms and soles, localized or generalized lymphadenopathy, hepatomegaly, hepatitis, reactive lymphocytosis, meningitis, brain abscess, encephalitis, confusion, malaise, pneumonia, polymyositis, pericarditis, pericardial effusion, and myocarditis. **Chorioretinitis** occurs in approximately 1% of U.S. cases and in 20% of cases in epidemics in Brazil at 2 years after infection. Approximately 10% of mothers of congenitally infected infants have eye lesions on dilated indirect ophthalmoscopic examinations. Postnatally acquired chorioretinal lesions cannot be distinguished from congenitally acquired lesions based on appearance. In some areas of Brazil, 80% of the population is infected, with 50% of infected individuals >50 years old and 20% of infected individuals having retinal involvement. Symptoms and signs of active ocular infection may be present for a few weeks only or may persist for many months.

The most common manifestation of acute acquired toxoplasmosis is enlargement of one or a few cervical lymph nodes. Cases of *Toxoplasma* **lymphadenopathy** can resemble infectious mononucleosis, lymphoma, or other lymphadenopathies (see Chapter 539). Pectoral, mediastinal, mesenteric, and retroperitoneal lymph nodes may be involved. Involvement of intraabdominal lymph nodes may be associated with fever, mimicking appendicitis. Nodes may be tender but do not suppurate. Lymphadenopathy may wax and wane for as long as 1-2 years. However, almost all patients with lymphadenopathy recover spontaneously without antimicrobial therapy. Significant organ involvement in immunologically normal persons is uncommon, although some individuals have significant morbidity, including rare cases of encephalitis, brain abscesses, hepatitis, myocarditis, pericarditis, and polymyositis. In persons acquiring *T. gondii* in Guyana near the Maroni River and along Amazon tributaries, a severe form of life-threatening, multi-visceral involvement with fever has occurred. The causative parasites in these cases are genetically different from the parasites in others.

Ocular Toxoplasmosis

In the United States and Western Europe, *T. gondii* is estimated to cause 35% of cases of **chorioretinitis** (Fig. 336.3). In Brazil, *T. gondii* retinal lesions are common. Clinical manifestations include blurred vision, visual floaters, photophobia, epiphora, and, with macular involvement, loss of central vision. Ocular findings of **congenital toxoplasmosis** also include strabismus, microphthalmia, microcornea, cataracts, anisometropia, nystagmus, glaucoma, optic neuritis, and optic atrophy. Episodic recurrences are common, but precipitating factors have not been defined. Recurrent, active disease usually occurs at school-entry age and during adolescence. Anecdotally, stress or trauma seems to precipitate symptoms. Recurrences are most common closest to the time of acquisition of infection, and treatment leads to resolution of activity. PD-L1 may contribute to susceptibility to recurrent active retinal disease.

Immunocompromised Persons

Host factors play a prominent role in susceptibility to disease due to *T. gondii* and in the outcome of toxoplasmosis. Disseminated *T. gondii* infection among older children who are **immunocompromised** by AIDS, malignancy, cytotoxic therapy, corticosteroids, or immunosuppressive drugs given for organ transplantation involves the CNS in 50% of cases and may also involve the heart, lungs, and GI tract. Stem cell transplant recipients present a special problem, because active infection is difficult to diagnose serologically. After transplantation, *T. gondii*–specific antibody levels may remain the same, increase, or decrease, and can even become undetectable. Toxoplasmosis in transplantation patients results from reactivation of latent organisms or transplantation from a seropositive donor to a seronegative recipient; thus knowledge of the serologic status of the donor and recipient is essential. Prompt diagnosis is of utmost importance, as active infection is often fulminant and rapidly fatal without treatment.

Congenital *T. gondii* infection in infants with HIV infection is rare in the United States but can be a severe and fulminant disease with substantial CNS involvement. Alternatively, it may be more indolent in presentation, with focal neurologic deficits or systemic manifestations such as pneumonitis occurring with progressive CD4 depletion in infants who are not receiving highly active antiretroviral therapy (HAART).

Up to 50% of persons with *T. gondii* antibodies and HIV infection who are not on antiretroviral treatment eventually experience **toxoplasmic encephalitis**, which is fatal if not treated. HAART and trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis to prevent *Pneumocystis jirovecii* have reduced the incidence of toxoplasmosis in patients with HIV infection, but toxoplasmic encephalitis remains a presenting manifestation in some adult patients with AIDS. Typical findings include fever, headache, altered mental status, psychosis, cognitive impairment, seizures, and focal neurologic defects such as hemiparesis, aphasia, ataxia, visual field loss, cranial nerve palsies, dysmetria, and movement disorders. In adult patients with AIDS, toxoplasmic retinal lesions are often large with diffuse necrosis and contain many organisms but little inflammatory cellular infiltrate. Diagnosis of presumptive toxoplasmic encephalitis based on neuroradiologic studies in patients with AIDS necessitates a prompt therapeutic trial of medications effective against *T. gondii*. Clear clinical improvement within 7-14 days and improvement of neuroradiologic findings within 3 weeks make the presumptive diagnosis almost certain.

Congenital Toxoplasmosis

Congenital toxoplasmosis usually occurs when a woman acquires primary infection while pregnant. Most often, maternal infection is asymptomatic or without specific symptoms or signs. As with other adults with acute toxoplasmosis, lymphadenopathy is the most commonly identified physical finding.

In monozygotic twins the clinical pattern of involvement is most often similar, whereas in dizygotic twins the manifestations often differ, including cases of congenital infection in only one twin. The major histocompatibility complex class II gene DQ3 appears to be more common than DQ1 among HIV-infected persons seropositive for *T. gondii* who develop toxoplasmic encephalitis, as well as in children with congenital toxoplasmosis who develop hydrocephalus. These findings suggest that the presence of HLA-DQ3 is a risk factor for severity of toxoplasmosis. Other allelic variants of genes, including *COL2A, ABC4R, P2X7R, NALP1, ALOX12, TLR9, TIRAP MAL,* and *ERAAP,* are also associated with increased susceptibility.

Congenital infection may present as a mild or severe neonatal disease (Table 336.1). It may also present with sequelae or relapse of a previously undiagnosed and untreated infection later in infancy or even later in life (see Table 336.1). There is a wide variety of manifestations of congenital infection, ranging from hydrops fetalis and perinatal death to small size for gestational age, prematurity, peripheral or central retinal scars, persistent jaundice, mild thrombocytopenia, CSF pleocytosis, and the characteristic triad of chorioretinitis, hydrocephalus, and cerebral calcifications (Figs. 336.4 and 336.5). More than 50% of congenitally infected infants are considered normal in the perinatal period, but almost all such children will develop ocular involvement later in life if they are not treated during infancy. Neurologic signs such as convulsions, setting-sun sign with downward gaze, and increased head circumference due to ventricular dilatation or hydrocephalus caused by relatively mild involvement with inflammation or marked destruction of tissue obstructing the aqueduct of Sylvius or foramen of Monroe or inflammation resulting in stiff ventricles may be associated with substantial cerebral damage. If affected infants are treated promptly with antimicrobial therapy and placement of a ventriculoperitoneal shunt, signs and symptoms may resolve and development may be normal, making evidence of hydrocephalus a medical emergency. Early signs of potential congenital toxoplasmosis, such as ventricular dilatation or hydrocephalus, should be treated as a pediatric emergency. Outcomes are better with prompt placement of a ventriculoperitoneal shunt when indicated than when shunt placement is delayed. Head circumference crossing percentiles and obviously dilated ventricles with increased intracranial pressure require shunt placement, and ventricular dilatation without obvious increased pressure can also benefit from shunt placement.

The spectrum and frequency of neonatal manifestations of 210 newborns with congenital *Toxoplasma* infection identified by a serologic screening program of pregnant women in France were described in 1984. In this study, 10% had severe congenital toxoplasmosis with CNS involvement, eye lesions, and general systemic manifestations; 34% had mild

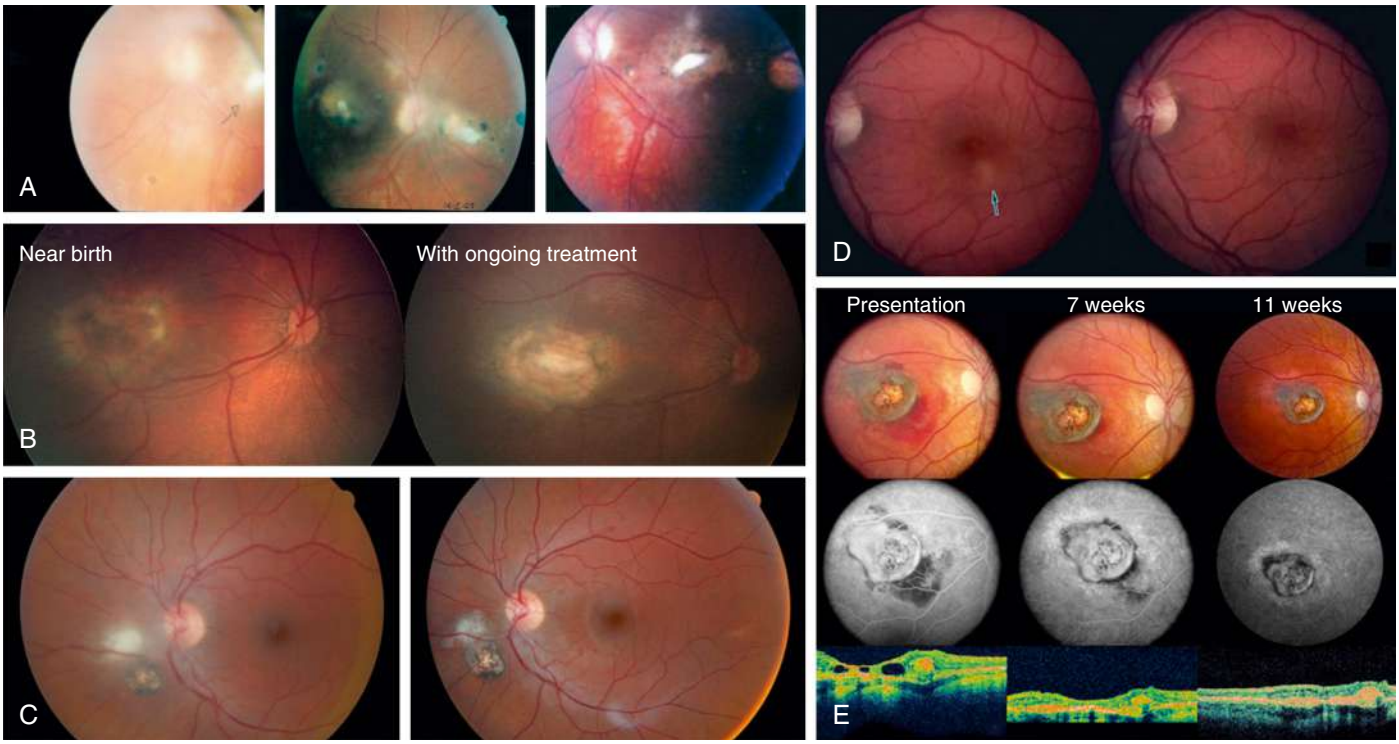

Fig. 336.3 Toxoplasmic chorioretinitis. **A,** Retinal photographs of a child with severe vitreitis that is less intense than the classic "headlight in fog" appearance *(left).* Resolving vitreitis caused by underlying active lesion *(middle).* Resolved healed lesion without vitreitis *(right).* **B,** Retina photographs for a newborn infant with active vitreitis (*left,* "near birth") with clearing of vitreitis and marked, but not complete, resolution of activity of the lesion 3 wk later (*right,* "with ongoing treatment"). **C,** Retinal photographs of a child showing an active lesion at presentation *(left),* and scarred lesion *(right).* **D,** Retinal photographs showing an active retinal lesion before treatment *(left)* and a completely resolved normal appearing retina within 1 mo of initiating treatment *(right).* **E,** Active choroidal neovascular membranes in a child. Fundus photographs *(top row),* fluorescein angiogram *(middle row),* and ocular coherence tomography *(bottom row)* of a child at presentation *(first column),* 7 wk after first ranibizumab (Lucentis, antibody to vascular endothelial growth factor [VEGF]) injection *(second column),* and 11 wk after first ranibizumab injection *(third column).* (**A-D,** *Adapted from Delair E, Latkany P, Noble AG, et al. Clinical manifestations of ocular toxoplasmosis. Ocul Immunol Inflamm. 2011;19:91–102;* **E,** *Adapted from Benevento JD, Jager RD, Noble AG, et al. Toxoplasmosis-associated neovascular lesions treated successfully with ranibizumab and antiparasitic therapy. Arch Ophthalmol. 2008;126:1152–1156.)*

involvement with normal clinical examination results other than retinal scars on dilated indirect exams or isolated intracranial calcifications in brain CT scans; and 55% had no detectable manifestations. These numbers represent an *underestimation* of the incidence of severe congenital infection for several reasons: the most severe cases, including most who died, were not referred; therapeutic abortion sometimes was performed when acute acquired infection of the mother was diagnosed early during pregnancy; in utero **spiramycin** therapy prevented or diminished the severity of infection; and only 13 of 210 congenitally infected newborns had brain CT, and only 77% of these 210 infants had a CSF examination. Routine newborn examinations often yield normal findings for congenitally infected infants, but more careful evaluations may reveal significant abnormalities. A 2012 analysis of the **National Collaborative Chicago-Based Congenital Toxoplasmosis Study** (NCCCTS, 1981–2009) data found that 72% of children at or near birth had chorioretinal scars, 70% had CNS calcifications, 12% had microcephaly, 37% had hydrocephalus, 41% had thrombocytopenia, 39% had hepatomegaly, 32% had splenomegaly, and 41% were born prematurely. In a study of 28 infants in New England identified by a universal state-mandated serologic screening program for *T. gondii*–specific immunoglobulin (Ig) M, 26 (93%) had normal findings on routine newborn examination, but 14 (50%) had significant abnormalities detected with more careful evaluation. The abnormalities included retinal scars (seven infants), active chorioretinitis (three infants), and CNS abnormalities (eight infants). In Fiocruz, Belo Horizonte, Brazil, infection is common, affecting 1 in 600 live births. Half of these infected infants have active chorioretinitis at birth.

There is also a wide spectrum of symptoms of untreated congenital toxoplasmosis that presents later in the first year of life. These children may have IQ scores of <70, convulsions, and severely impaired vision. When the infection is acquired in utero and the fetus is treated by drug therapy of the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin, ocular and neurologic sequelae in the infant may be prevented.

SYSTEMIC SIGNS

From 25–50% of infants with clinically apparent disease at birth are born prematurely. Parasite clonal types other than type II are more often associated with prematurity and more severe disease. Intrauterine growth restriction, low Apgar scores, and temperature instability are common. Other manifestations may include lymphadenopathy, hepatosplenomegaly, myocarditis, pneumonitis, nephrotic syndrome, vomiting, diarrhea, and feeding problems. Bands of metaphyseal lucency and irregularity of the line of provisional calcification at the epiphyseal plate may occur without periosteal reaction in the ribs, femurs, and vertebrae. Congenital toxoplasmosis may be confused with erythroblastosis fetalis resulting from isosensitization, although the Coombs test result is usually negative with congenital *T. gondii* infection.

Prematurity, growth restriction, signs suggesting sepsis, thrombocytopenia, and abnormal CSF cells, protein, and glucose in the perinatal period should suggest congenital toxoplasmosis.

Skin

Cutaneous manifestations among newborn infants with congenital toxoplasmosis include rashes and jaundice and/or petechiae secondary to thrombocytopenia, but ecchymoses and large hemorrhages secondary to thrombocytopenia also occur. Rashes may be fine punctate, diffuse maculopapular, lenticular, deep blue-red, sharply defined macular, or diffuse blue and papular. Macular rashes involving the entire body including the palms and soles, exfoliative dermatitis, and cutaneous calcifications have been described. **Jaundice** with hepatic involvement and/or hemolysis, cyanosis due to interstitial pneumonitis from congenital infection, and edema

Table 336.1 Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed ≥4 Years (B)

	FREQUENCY OF OCCURRENCE IN PATIENTS WITH	
SIGNS AND SYMPTOMS	**"NEUROLOGIC" DISEASE***	**"GENERALIZED" DISEASE†**
A. Infants	**108 Patients (%)**	**44 Patients (%)**
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephaly	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. Children ≥4 Yr Old	**70 Patients (%)**	**31 Patients (%)**
Intellectual impairment	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)
Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephaly	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

*Patients with otherwise undiagnosed central nervous system disease in the first year of life.
†Patients with otherwise undiagnosed nonneurologic diseases during the first 2 mo of life.
Adapted from Eichenwald H. A study of congenital toxoplasmosis. In: Slim JC, ed. *Human Toxoplasmosis*. Copenhagen: Munksgaard; 1960: pp 41–49. Study performed in 1947. The most severely involved institutionalized patients were not included in the later study of 101 children.

secondary to myocarditis or nephrotic syndrome may be present. Jaundice and conjugated hyperbilirubinemia may persist for months.

Endocrine Abnormalities

Endocrine abnormalities may occur secondary to hypothalamic or pituitary involvement or end-organ involvement but are not common. Occasionally reported endocrine manifestations include myxedema, persistent hypernatremia with vasopressin-sensitive diabetes insipidus, sexual precocity, and partial anterior hypopituitarism.

Central Nervous System

Neurologic manifestations of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurologic syndromes. Toxoplasmosis should be considered as a potential cause of any undiagnosed neurologic disease in children <1 year old, especially if retinal lesions are present.

Hydrocephalus may be the sole neurologic manifestation of congenital toxoplasmosis and almost always requires shunt placement (see Fig. 336.5). Hydrocephalus may present prenatally and progress during the perinatal period or, much less often, may present later in life. Patterns of seizures

are protean and have included focal motor seizures, petit and grand mal seizures, muscular twitching, opisthotonos, and hypsarrhythmia. Spinal or bulbar involvement may be manifested by paralysis of the extremities, difficulty swallowing, and respiratory distress. **Microcephaly** usually reflects severe brain damage, but some children with microcephaly caused by congenital toxoplasmosis who have been treated promptly have normal or even superior cognitive function. Seizures, focal motor defects, and intellectual impairment may become apparent after the newborn period, even when infection is subclinical at birth.

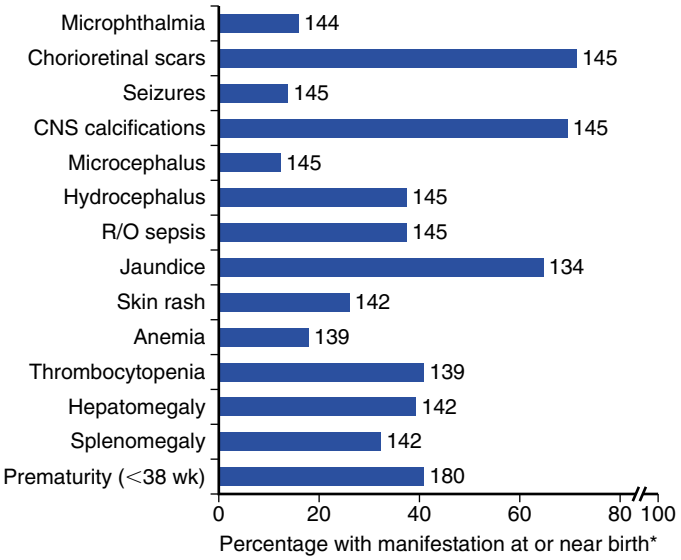

Fig. 336.4 Congenital toxoplasmosis: manifestations at presentation. National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS, 1981–2009). *Infants diagnosed with congenital toxoplasmosis in the newborn period and referred to the NCCCTS during the first year of life. Numbers adjacent to histogram bars represent number of infants with this manifestation and are based on information in birth records. Sample size dependent on available birth records/diagnoses at birth. R/O, Rule out; CNS, central nervous system. *(Adapted from McLeod R, Boyer KM, Lee D, et al. Prematurity and severity are associated with Toxoplasma gondii alleles [NCCCTS, 1981–2009]. Clin Infect Dis. 2012;54:1595–1605.)*

Other Neurologic Disease

T. gondii infection is a cause of epilepsy and other neurologic disorders that improve with medical treatment. Ketogenic diet has led to resolution of seizures refractory to other treatments due to *T. gondii*. Symptomatic spinal cord lesions may be evident as T2-weighted abnormalities and can also resolve with medical treatment.

Symptomatic spinal cord lesions may be evident as T2 weighted abnormalities on MRI and can resolve with medical treatment.

CSF abnormalities occur in at least 50% of infants with congenital toxoplasmosis. A CSF protein level >1 g/dL is characteristic of severe CNS toxoplasmosis and is usually accompanied by hydrocephalus. Local production of *T. gondii*–specific IgG and IgM antibodies may be demonstrated. CT of the brain is useful to detect calcifications, determine ventricular size, and demonstrate porencephalic cystic structures (see Fig. 336.5). MRI is used to assess ventricular size and configuration and can detect T2-weighted abnormalities associated with active disease. **Calcifications** occur throughout the brain, but there is a propensity for development of calcifications in the caudate nucleus and basal ganglia, choroid plexus, and subependyma. MRI and contrast-enhanced CT brain scans are useful for detecting active inflammatory lesions. Rapid MRI or ultrasonography may be useful for following ventricular size. Medical treatment in utero and in the first year of life results in improved neurologic outcomes and oftentimes diminution or disappearance of calcifications.

Eyes

Almost all untreated congenitally infected infants develop **chorioretinal lesions** by adulthood and may have severe visual impairment. *T. gondii* causes a **focal necrotizing retinitis** in congenitally infected individuals (see Fig. 336.3). Retinal detachment may occur. Any part of the retina may be involved, either unilaterally or bilaterally, including the maculae. The optic nerve may be involved, and toxoplasmic lesions that involve projections of the visual pathways in the brain or the visual cortex also may lead to visual impairment. In association with severe retinal lesions and vitritis, secondary anterior uveitis may develop and occasionally lead to erythema of the external eye.

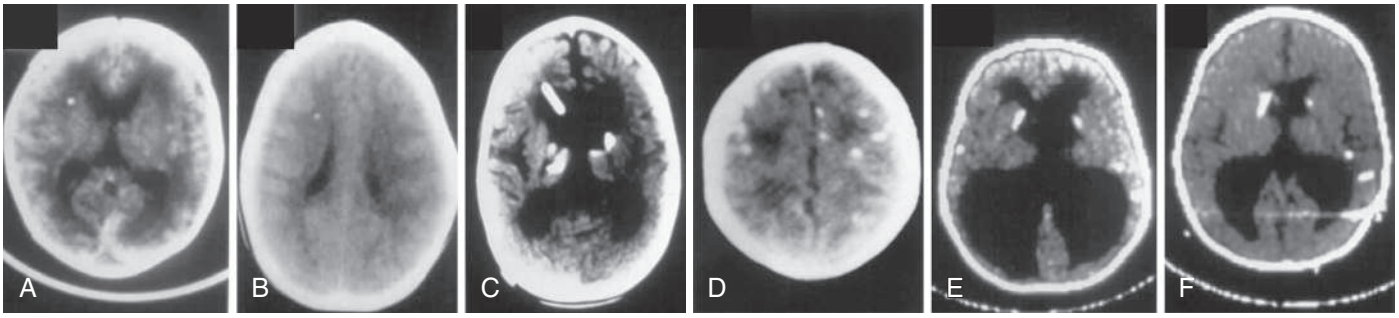

Fig. 336.5 Head CT scans of infants with congenital toxoplasmosis. **A,** CT scan at birth that shows areas of hypolucency, mildly dilated ventricles, and small calcifications. **B,** CT scan of the same child at 1 yr of age (after antimicrobial therapy for 1 yr). This scan is normal, with the exception of two small calcifications. This child's Mental Development Index (MDI) at 1 yr old was 140 by the Bayley Scale of Infant Development. **C,** CT scan from a 1-yr-old infant who was normal at birth. His meningoencephalitis became symptomatic in the first few weeks of life but was not diagnosed correctly and remained untreated during his first 3 mo of life. At 3 mo old, development of hydrocephalus and bilateral macular chorioretinitis led to the diagnosis of congenital toxoplasmosis, and antimicrobial therapy was initiated. This scan shows significant residual atrophy and calcifications. This child had substantial motor dysfunction, development delays, and visual impairment. **D,** CT scan obtained during the first month of life of a microcephalic child. Note the numerous calcifications. This child's IQ scores using the Stanford-Binet Intelligence Scale for children when she was 3 yr old and Wechsler Preschool and Primary Scale Intelligence when she was 5 yr old were 100 and 102, respectively. She received antimicrobial therapy during her first year of life. **E,** CT scan with hydrocephalus caused by aqueductal obstruction, before placement of a ventricular shunt. **F,** Scan from the same patient as the scan in **E,** after shunt placement. This child's IQ scores using the Stanford-Binet Intelligence Scale for children were approximately 100 when she was 3 yr old and 6 yr old. *(**A-F** adapted from McAuley J, Boyer K, Patel D, et al. Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial. Clin Infect Dis. 1994;18:38–72.)*

Other ocular findings include cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and neovascular formation on the surface of the iris, sometimes with increased intraocular pressure and glaucoma. Rarely, the extraocular musculature may also be involved directly. Other manifestations include strabismus, nystagmus, visual impairment, and microphthalmia. Enucleation has been required for a blind, phthisic, painful eye. The **differential diagnosis** of ocular toxoplasmosis includes congenital coloboma and inflammatory lesions caused by cytomegalovirus (CMV), lymphocytic choriomeningitis virus, *Bartonella henselae, Toxocara canis*, *Treponema pallidum, Mycobacterium tuberculosis,* varicella-zoster virus, Zika virus, or vasculitis. Ocular toxoplasmosis may be a recurrent and progressive disease that requires multiple courses of therapy. Limited data suggest that occurrence of lesions in the early years of life may be prevented by instituting **antimicrobial treatment** with pyrimethamine and sulfadiazine during the first year of life. Initiation of treatment of the infected fetus in utero followed by treatment in the first year of life further reduces the incidence and the severity of retinal disease.

Ears

Both mild and severe sensorineural hearing loss may occur. It is not known whether this hearing loss is a static or progressive disorder. Treatment in the first year of life is associated with decreased frequency of hearing loss.

DIAGNOSIS

Diagnosis of acute *T. gondii* infection can be established by a number of methods (Table 336.2): isolation of *T. gondii* from blood or body fluids; identification of tachyzoites in sections or preparations of tissues and body fluids, amniotic fluid, or placenta; identification of cysts in the placenta or tissues of a fetus or newborn; and characteristic lymph node histologic features. Serologic tests are very useful for diagnosis. Polymerase chain reaction (PCR) is useful to identify *T. gondii* DNA in CSF and amniotic fluid and has been reported to be useful with infant peripheral blood and urine to establish the diagnosis definitively and in immunocompromised patients for diagnosis and monitoring treatment.

Isolation or Identification of *T. gondii*

Organisms can be isolated by inoculation of body fluids, leukocytes, or tissue specimens into mice or tissue culture cells. Body fluids should be processed and inoculated immediately, but *T. gondii* has been isolated from tissues and blood that have been stored overnight or even for 4-5 days at 4°C (39.2°F). Freezing or treatment of specimens with formalin kills *T. gondii*. From 6-10 days after inoculation into mice, or earlier if mice die, peritoneal fluids should be examined for tachyzoites. If inoculated mice survive for 6 weeks and seroconvert, definitive diagnosis is made by visualization of *Toxoplasma* cysts in mouse brain. If cysts are not seen, **subinoculation** of mouse tissue into other mice is performed. Treatment of subinoculated mice with corticosteroids appears to enhance ability to isolate the parasite.

Microscopic examination of tissue culture cells inoculated with *T. gondii* shows necrotic, heavily infected cells with numerous extracellular tachyzoites. Isolation of *T. gondii* from blood or body fluids reflects acute infection. Except in the fetus or neonate, it is usually not possible to distinguish acute from past infection by isolation of *T. gondii* from tissues (e.g., skeletal muscle, lung, brain, eye) obtained by biopsy or at autopsy.

Diagnosis of acute infection can be established by visualization of tachyzoites in biopsy tissue sections, bone marrow aspirates, or body fluids (e.g., CSF, amniotic fluid). Immunofluorescent antibody and immunoperoxidase staining techniques may be necessary, because it is often difficult to distinguish the tachyzoite using ordinary stains. Tissue cysts are diagnostic of infection but do not differentiate between acute and chronic infection, although the presence of many cysts suggests recent acute infection. Cysts in the placenta or tissues of the newborn infant establish the diagnosis of congenital infection. Characteristic histologic features strongly suggest the diagnosis of toxoplasmic lymphadenitis.

Serologic Testing

Serologic tests are useful in establishing the diagnosis of congenital or acutely acquired *T. gondii* infection. Each laboratory that reports serologic test results must have established values for their tests that diagnose infection in specific clinical settings, provide interpretation of their results, and ensure appropriate quality control before therapy is based on serologic test results. Serologic test results used as the basis for therapy should ideally be confirmed in a reference laboratory.

The **Sabin-Feldman dye test** is sensitive and specific. This test measures primarily IgG antibodies. Results should be expressed in international units (IU/mL), based on international standard reference sera available from the World Health Organization (WHO).

The **IgG indirect fluorescent antibody (IgG-IFA) test** measures the same antibodies as the Sabin-Feldman dye test, and the titers tend to be parallel. These antibodies usually appear 1-2 weeks after infection, reach high titers (≥1:1,000) after 6-8 weeks, and then decline over months to years. Low titers (1:4 to 1:64) usually persist for life. Antibody titer does not correlate with severity of illness.

An **agglutination test** (bioMérieux, Lyon, France) available commercially in Europe uses formalin-preserved whole parasites to detect IgG antibodies. This test is accurate, simple to perform, and inexpensive.

The **IgM-IFA test** is useful for the diagnosis of acute acquired infection with *T. gondii* in the older child because IgM antibodies appear earlier, often by 3-5 days after infection, and diminish more quickly than IgG antibodies. In most instances, IgM antibodies rise rapidly (1:50 to ≥1:1,000) and then fall to low levels (1:10 or 1:20) or disappear after weeks or months. However, some patients continue to have positive IgM levels with low titers for several years. The IgM-IFA test detects *Toxoplasma*-specific IgM in only approximately 25% of congenitally infected infants at birth. IgM antibodies may not be present in sera of immunocompromised patients with acute toxoplasmosis or in patients with reactivation of ocular toxoplasmosis. The IgM-IFA test may yield false-positive results as a result of rheumatoid factor (RF).

The **double-sandwich IgM enzyme-linked immunosorbent assay (IgM-ELISA)** is also useful for detection of *Toxoplasma* IgM antibodies. In the older child, serum IgM-ELISA *Toxoplasma* antibodies of >2 (a value of one reference laboratory; each laboratory must establish its own value for positive results) indicates that *Toxoplasma* infection most likely has been acquired recently. The IgM-ELISA identifies approximately 50–75% of infants with congenital infection. IgM-ELISA avoids both the false-positive results from RF and the false-negative results from high levels of passively transferred maternal IgG antibody in fetal serum, as may occur with the IgM-IFA test. Results obtained with commercial kits must be interpreted with caution, because false-positive reactions can occur. Care must also be taken to determine whether kits have been standardized for diagnosis of infection in specific clinical settings, such as in the newborn infant. The **IgA-ELISA** also is a sensitive test for detection of maternal and congenital infection, and results may be positive when those of the IgM-ELISA are not.

The **immunosorbent agglutination assay (ISAGA)** combines trapping of a patient's IgM to a solid surface and use of formalin-fixed organisms or antigen-coated latex particles. It is read as an agglutination test. There are no false-positive results from RF or antinuclear antibodies (ANAs). **IgM-ISAGA** is more sensitive and may detect specific IgM antibodies before and for longer periods than IgM-ELISA.

At present, IgM-ISAGA and IgA-ELISA are the most useful tests for diagnosis of congenital infection in the newborn but are not positive in all infected infants. The IgE-ELISA and IgE-ISAGA are also sometimes useful in establishing the diagnosis of congenital toxoplasmosis or acute acquired *T. gondii* infection. The presence of IgM antibodies in the older child or adult can never be used alone to diagnose acute acquired infection. The lateral immunochromatographic test (ICT) can identify IgG and/or IgM in serum or whole blood from fingerstick precisely and rapidly. Western blot II is highly accurate for identifying *T. gondii*-specific IgG and for IgM.

Table 336.2 Generalizations Concerning Clinical Presentations, *Toxoplasma*-Specific Diagnostic Tests, and Treatment

CLINICAL SETTING AND MANIFESTATION	SAMPLE SOURCE	*TOXOPLASMA*-SPECIFIC DIAGNOSTIC TESTS								TREATMENT				
		G	M	A	E	AV	AC/HS	PCR KARIUS	SUBINOCULATION	SP	PSL*	CO	LU	NONE
PRENATAL														
Acute infection in pregnant woman ≤15 wk amenorrhea in gestation *and* no clinical evidence of fetal infection	Mother	+	+	+	+	L	Acute	AF (17-18 wk)	NS	+	+ †No P first trimester			
Acute infection in pregnant woman ≤15 wk amenorrhea in gestation *and* signs of fetal infection	Mother	+	+	+	+	L	Acute	AF (may not be necessary)	NS		+ †No P first trimester			
Acute infection in pregnant woman at >18 wk gestation	Mother	+	+	+	+	L	Acute	AF	NS		+			
Congenital infection in infant	Infant	+	+	+	+	L	Acute	Placenta/buffy coat	Placenta/buffy coat		+	‡		
POSTNATAL														
Acute, symptomatic Acute, self-limited symptoms	Child	+	+	+	+	L	Acute	NS	NS		+			+
Chronic, asymptomatic	Child	+	–	–	–	H	Chronic	NS	NS					
Acute, severely symptomatic	Child	+	+	+	+	L	Acute	§	Body fluids/buffy coat		+			
Immune compromised¶	Child	+/–	+/–	+/–	+/–	+/–	+/–	§	Body fluids/buffy coat					
Laboratory accident#	Child	+/–	+/–	+/–	+/–	+/–	+/–	NS	NS		+			
Eye Disease														
Quiescent scar**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS					+
Active chorioretinitis**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS		+			
Active CNVM**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS		+		††	

*Pyrimethamine and leucovorin should be adjusted for granulocytopenia; complete blood counts, including platelets, should be monitored each Monday and Thursday. If there is sulfonamide allergy, alternative medicines include azithromycin (first choice), clarithromycin, or clindamycin in place of sulfadiazine.

†*Do not* use pyrimethamine in the first 14 weeks of gestation.

‡Occasionally, corticosteroids (prednisone) have been used when CSF protein is ≥1 g/dL or when active chorioretinitis threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

§Utility of PCR depends on clinical setting. For example, the following may be useful to establish the diagnosis: PCR of body fluids such as amniotic fluid or CSF; cells from bronchoalveolar lavage from a patient with pneumonia; or tissue such as placenta where the presence of parasites or parasite DNA would support a diagnosis of infection.

¶In some cases, in immunocompromised persons, there is no detectable serologic response to *T. gondii*. However, if clinical presentation is indicative of infection in the absence of positive serologic results, CSF, buffy coat of peripheral blood, histopathology of tissue samples, or body fluids tested with PCR or subinoculation may be useful. If PCR demonstrates the presence of *T. gondii* DNA in the sample, it is useful for diagnosis. However, the sensitivity of PCR has been variable in this setting. In some circumstances, presumptive treatment may be warranted.

#Whether a person should be treated for a laboratory accident depends on the nature of the accident, the serology of the person before the accident, and other factors. When there is risk of infection, prompt treatment is given, considering the possible genetic manipulation of the laboratory strain.

**Serologic results depend on whether infection is acute (recently acquired) or chronic. When testing serum from persons with ocular toxoplasmosis, *T. gondii*–specific IgG may be demonstrable only in an undiluted serum sample.

††Corticosteroids (prednisone) are used if inflammation or edema caused by infection threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

+, Positive; –, negative; +/–, equivocal; A, *T. gondii*–specific IgA; AC/HS, differential agglutination test where A represents acetone fixed parasites and H represents formalin fixed antigen; AF, amniotic fluid; Av, *T. gondii*–specific IgG avidity; CNVM, choroidal neovascular membrane; Co, corticosteroids (prednisone); CSF, cerebrospinal fluid; E, *T. gondii*–specific IgE; G, *T. gondii*–specific IgG; L, leucovorin; Lu, Lucentis (antibody to vascular endothelial growth factor); M, *T. gondii*–specific IgM; NS, not standard to obtain; P, pyrimethamine; PCR, polymerase chain reaction; PSL, pyrimethamine (P), sulfadiazine (S), leucovorin (L) (folinic acid); Sp, spiramycin.

Adapted from Remington JS, McLeod R, et al. Toxoplasmosis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia: Saunders; 2006.

The **differential agglutination test (HS/AC)** compares antibody titers obtained with formalin-fixed tachyzoites (**HS antigen**) with titers obtained using acetone-fixed tachyzoites (**AC antigen**) to differentiate recent and remote infections in adults and older children. This method may be particularly useful in differentiating remote infection in pregnant women, because levels of IgM and IgA antibodies detectable by ELISA or ISAGA may remain elevated for months to years in adults and older children.

The **avidity test** can be helpful to establish time of acquisition of infection. A high-avidity test result indicates that infection began >12-16 weeks earlier, which is especially useful in determining time of acquisition of infection in the first or final 16 weeks of gestation. A low-avidity test result may be present for many months or even years and does not definitively identify recent acquisition of infection.

A relatively higher level of *Toxoplasma* antibody in the aqueous humor or in CSF demonstrates local production of antibody during active ocular or CNS toxoplasmosis. This comparison yields a coefficient [C], which is calculated as follows:

$$C = \frac{\text{Antibody titer in body fluid}}{\text{Antibody titer in serum}} \times \frac{\text{Concentration of IgG in serum}}{\text{Concentration of IgG in body fluid}}$$

Significant coefficients [C] are >8 for ocular infection, >4 for congenital CNS infection, and >1 for CNS infection in patients with AIDS. If the serum dye test titer is >300 IU/mL, it is not possible to demonstrate significant local antibody production using this formula with either the dye test or the IgM-IFA test titer. IgM antibody may be detectable in CSF.

Comparative **Western immunoblot** tests of sera from a mother and infant may detect congenital infection. Infection is suspected when the mother's serum and her infant's serum contain antibodies that react with different *Toxoplasma* antigens.

The **enzyme-linked immunofiltration assay** using micropore membranes permits simultaneous study of antibody specificity by immunoprecipitation and characterization of antibody isotypes by immunofiltration with enzyme-labeled antibodies. This method is able to detect 85% of cases of congenital infection in the first few days of life.

Serologic tests in development include multiplex antibody tests for IgG-, IgM-, and IgA-specific antibodies and point-of-care tests designed to provide accurate and rapid identification of recent infection or seroconversion in pregnant women. The ICT point-of-care IgG-IgM test (LDBIO Diagnostic, Lyon, France) has shown very high diagnostic sensitivity and specificity and has been CE marked for use in Europe.

Nucleic Acid Detection

PCR on amniotic fluid is used to detect a repetitive *T. gondii* gene such as the 529 bp multi-copy gene or the 20 copy B1 gene and is the method of choice for establishing the diagnosis of congenital *Toxoplasma* infection in the fetus. Sensitivity and specificity of PCR on amniotic fluid obtained between 17 and 21 weeks of gestation are approximately 95% for diagnosing congenital infection. PCR of peripheral white blood cells, CSF, and urine has been used to detect congenital infection at birth or postnatally. PCR of vitreous or aqueous fluids has been used to diagnose ocular toxoplasmosis. Karius test also detects nucleic acid. Abnormalities in MRI studies of brain and spinal cord may demonstrate activity of infection and are indicative (see Fig. 336.4). Both patient and parasite genetics contribute to severity and manifestations of illness (see Figs. 336.3 to 336.5).

Other Tests

Lymphocyte blastogenesis to *T. gondii* antigens has been used to diagnose congenital toxoplasmosis when the diagnosis is uncertain and other test results are negative. However, a negative result does not exclude the diagnosis, as immune tolerance sometimes interferes with response of neonatal peripheral blood lymphocytes to *T. gondii* antigens. Novel biomarkers such as microRNAs and certain proteins may indicate active infection.

Acquired Toxoplasmosis

Recent infection is diagnosed by seroconversion from a negative to a positive IgG antibody titer (in the absence of transfusion), a two-tube increase in *Toxoplasma*-specific IgG titer when serial sera are obtained 3 weeks apart and tested in parallel, or the detection of *Toxoplasma*-specific IgM antibody in conjunction with other tests, but never alone.

Ocular Toxoplasmosis

IgG antibody titers of 1:4 to 1:64 are typical in older children with active *Toxoplasma* chorioretinitis. The presence of antibodies measurable only when serum is tested undiluted is also helpful in establishing the diagnosis. The diagnosis of ocular infection is likely with characteristic retinal lesions and positive serologic tests. PCR of aqueous or vitreous fluid has been used to diagnose ocular toxoplasmosis but is performed infrequently because of the risks associated with obtaining intraocular fluid and because the diagnosis can be made based on clinical appearance and history.

Immunocompromised Persons

Toxoplasma IgG antibody titers may be low and *Toxoplasma* IgM is often absent in immunocompromised stem cell transplant recipients but not in kidney or heart transplant recipients with toxoplasmosis. Demonstration of *Toxoplasma* DNA by PCR in serum, blood, and CSF may identify disseminated *Toxoplasma* infection in immunocompromised persons. Resolution of CNS lesions during a therapeutic trial of pyrimethamine and sulfadiazine has been useful to diagnose toxoplasmic encephalitis in patients with AIDS. Brain biopsy has been used to establish the diagnosis if there is no response to a therapeutic trial and to exclude other possible diagnoses such as CNS lymphoma.

Congenital Toxoplasmosis

Fetal ultrasound examination performed every 2 weeks during gestation beginning at diagnosis of acute acquired infection in a pregnant woman and PCR analysis of amniotic fluid are used for prenatal diagnosis. Examination of the placenta at delivery by histology and by PCR may facilitate diagnosis of congenital infection but is not sufficiently sensitive or specific for routine diagnosis.

Newborns suspected of having congenital toxoplasmosis should be evaluated by general, ophthalmologic, and neurologic examinations; head CT scan; and ideally all of the following tests: an attempt to detect *T. gondii* in the placenta and the infant's leukocytes from peripheral blood buffy coat; measurement of serum *Toxoplasma*-specific IgG, IgM, IgA, and IgE antibodies and the levels of total serum IgM and IgG; lumbar puncture, including analysis of CSF for cells, glucose, protein, *Toxoplasma*-specific IgG and IgM antibodies, and level of total IgG; and testing of CSF for *T. gondii* by PCR and inoculation into mice. Presence of *Toxoplasma*-specific IgM in CSF that is not contaminated with blood or confirmation of local antibody production of *Toxoplasma*-specific IgG antibody in CSF establishes the diagnosis of congenital *Toxoplasma* infection.

Serologic tests are also useful in establishing a diagnosis of congenital toxoplasmosis. Either persistent or rising titers in the Sabin-Feldman dye test or the IgG-IFA test or a positive IgM-ELISA or IgM-ISAGA result is diagnostic of congenital toxoplasmosis. The half-life of IgM is approximately 2 days, so presence of detectable IgM antibodies in the infant's serum decreases relatively quickly, usually within 1 week. Passively transferred maternal IgG antibodies may require many months to a year to disappear from the infant's serum, depending on the magnitude of the original titer. The half-life of passively transferred maternal IgG is approximately 30 days, so the titer diminishes by half each 30 days. Synthesis of *Toxoplasma* antibody is usually demonstrable by the third month of life if the infant is untreated, although the rate of IgG synthesis varies considerably in infants <1 year old. If the infant is treated, synthesis may be delayed for as long as the ninth month of life and occasionally does not occur at all. When an infant begins to synthesize IgG antibody, infection may be documented serologically even without demonstration of IgM antibodies by an increase in the ratio of specific serum IgG antibody titer to the total IgG. In contrast, the ratio of specific serum IgG to the total IgG will decrease if the specific IgG antibody has been passively transferred from the mother.

Many manifestations of congenital toxoplasmosis are similar to findings that occur in other perinatal infections, especially congenital CMV infection. Because neither cerebral calcification nor chorioretinitis is pathognomonic, a negative urine culture or PCR for CMV soon after birth is a useful adjunctive test. The clinical picture in the newborn infant may also be compatible with sepsis, aseptic meningitis, syphilis,

or hemolytic disease. Some children <5 years old with chorioretinitis have postnatally acquired *T. gondii* infection.

TREATMENT

Currently available treatments are effective against the active tachyzoite form of the parasite. No commercially available medicines to date eliminate the latent encysted form of the parasite, although promising preclinical data suggest that such treatments will be possible in the future. Table 336.1 summarizes treatments in each clinical category.

A number of therapeutic agents, including pyrimethamine, sulfonamides, and macrolides, have been used to treat toxoplasmosis in its various clinical manifestations. In general, they have activity that is limited to the pathogenic tachyzoite stage of the parasite's life cycle. No clinically available antimicrobial agent has yet been found capable of eliminating the encysted bradyzoite stage. Thus, active disease may be effectively treated, but not ultimately cured, by current therapies. In a person with normal cell-mediated immunity, a single course of therapy may be sufficient. In immune-compromised patients and congenital infection, recurrences may be a long-term management problem. Curative therapies remain an area of continuing active research, with several promising candidates. Table 336.2 summarizes treatment according to clinical category of disease.

Pyrimethamine and **sulfadiazine** act synergistically against *Toxoplasma,* and combination therapy is **considered the treatment of choice** and is indicated for all clinical presentations of toxoplasmosis that require treatment, except for acute *Toxoplasma* infection acquired during the first trimester of pregnancy (see Table 336.2). Pyrimethamine is contraindicated during the first trimester of pregnancy because of teratogenic effects. Pyrimethamine and sulfadiazine are used in Austria and Germany and now sometimes in France and the United States for treatment of newly seropositive mothers after 15 weeks of gestation.

In contrast to mammals, *Toxoplasma* cannot take up folinic acid, a precursor for folate synthesis. Thus folinic acid protects the human bone marrow from toxicity due to pyrimethamine, which inhibits the enzyme dihydrofolate reductase (DHFR), blocking synthesis of folic acid. By correcting an enzymatic pathway accessible in human cells but not in *Toxoplasma,* leucovorin (folinic acid) renders pyrimethamine/sulfadiazine a safer and more selective antiparasitic combination. Leucovorin is always given in conjunction with pyrimethamine and in the week after discontinuing pyrimethamine because of pyrimethamine's long half-life.

Pyrimethamine levels can be measured to make certain that they are in a therapeutic, nontoxic range of less than approximately 2.3 mg/dL and more than approximately 0.5 mg/dL for pyrimethamine when older children are treated for retinal disease or in other circumstances when medicines may be continued for longer times and reach high levels. Therapeutic endpoint is until resolution of the active retinal lesion and then at least 1 month beyond that, with no immune compromise, immune deficiency, or immune immaturity (for infants).

For treatment of those with primary, acute acquired toxoplasma in gestation to prevent or treat infection in the fetus, pyrimethamine is contraindicated during the first trimester of pregnancy. Pyrimethamine sulfadiazine is used in Austria and Germany, and now sometimes in France and the United States for treatment of those newly seropositive mothers after 15 weeks amenorrhea during gestation.

Spiramycin is used to attempt to prevent vertical transmission of infection to the fetus of acutely infected pregnant women in the first trimester. A recent meta-analysis adds to the evidence of significant reduction in mother-to-child transmission rates following spiramycin treatment of diagnosed gestational *T. gondii* infection. In 2018, Mandelbrot et al. reported results of a randomized controlled trial that compared treatment with pyrimethamine sulfadiazine promptly following seroconversion after 15 weeks rather than using spiramycin until 17 weeks' gestation with pyrimethamine sulfadiazine initiated only for PCR-positive amniotic fluid. Hypersensitivity for the mother is a greater risk in the group that receives pyrimethamine sulfadiazine earlier and may make diagnosis more difficult by obscuring evidence of infection in the fetus and infant. There was a very small increase in the number of infants with severe findings in the group that received pyrimethamine sulfadiazine initiated at the later time.

The merits of this gestational treatment approach have been examined in cost-benefit analyses examining both the United States and Austria, and the first direct cost-benefit comparison of prenatal and neonatal in the context of France (not yet published) all indicate better outcomes for affected infants and the healthcare system if treatment is started in utero, rapidly following seroconversion. Toxoplasma cannot take up folinic acid, a precursor for folate synthesis, whereas mammalian cells can take up folinic acid. Thus, folinic acid protects the human bone marrow from toxicity due to pyrimethamine. Use of pyrimethamine is contraindicated in the first trimester of pregnancy; it inhibits the enzyme dihydrofolate reductases and thus synthesis of folic acid.

Spiramycin is a macrolide antibiotic that is active against *Toxoplasma* in the placenta but does not reach sufficient levels in other tissues to treat a fetus or to be used postnatally. Hence, it has been used successfully to prevent congenital toxoplasmosis in pregnant women who have documented seroconversion in the first trimester when pyrimethamine is contraindicated.

Azithromycin is a macrolide that is used in severe or recurrent disease when sulfonamide allergy precludes the use of sulfadiazine. Azithromycin has been used to suppress infection and prevent recurrences of retinochoroiditis.

TMP-SMX is less active than pyrimethamine/sulfadiazine, with a suboptimal ratio of the DHFR and para-amino benzoic acid synthase inhibitors and with a shorter half-life of trimethoprim relative to pyrimethamine. Treatment failures have occurred with TMP-SMX, underscoring the importance of treating with pyrimethamine and sulfadiazine if at all possible. Clindamycin and atovaquone have also been used as second line agents but not as single antimicrobial agents.

Reversible neutropenia is the most common adverse effect in pyrimethamine-treated infants and typically responds to temporary holding of doses. All patients treated with pyrimethamine should have leukocyte counts twice weekly. Medicines may be held temporarily. GCSF treatment is rarely needed. Improper preparation of medicine, not making it fresh each week, is a cause of increased difficulties with neutropenia. Seizures may occur with overdose of pyrimethamine. Potential toxic effects of sulfonamides include crystalluria, hematuria, and rash. Profound neutropenia is a risk with sulfonamide overdosage, which has occurred when pharmacies make large quantities of the suspension and there is settling of the medication with the starch binder. The protocol for preparation for infants should be followed carefully, with fresh medicine prepared weekly and the bottle shaken well. Hypersensitivity reactions occur, especially in patients with AIDS. For older children and adults, eight glasses of a nonacidic beverage should be consumed each day while taking the medicine. Hypersensitivity reactions occur, especially frequently in patients with AIDS. As mentioned above, folinic acid, as calcium leucovorin, should always be administered concomitantly and for 1 week after treatment with pyrimethamine is discontinued to prevent bone marrow suppression.

Acquired Toxoplasmosis

Patients with acquired toxoplasmosis and lymphadenopathy usually do not need specific treatment unless they have severe and persistent symptoms or evidence of damage to vital organs (see Table 336.2). If such signs and symptoms occur, treatment with pyrimethamine, sulfadiazine, and leucovorin should be initiated. Patients who appear to be immunocompetent but have severe and persistent symptoms or damage to vital organs (e.g., chorioretinitis, myocarditis) need specific therapy until these specific symptoms resolve, followed by therapy for an additional 2 weeks. Therapy often is administered for at least 4-6 weeks, though the optimal duration of therapy has not been defined. A loading dose of pyrimethamine for older children is 2 mg/kg/day divided twice daily (maximum 50 mg bid), given for the first 1-2 days of treatment. The maintenance dose begins on the third day and is 1 mg/kg/day (maximum 50 mg/day). Sulfadiazine is administered at 100 mg/kg/day bid (maximum 4 g/day). Leucovorin is administered orally at 5-20 mg 3 times weekly (or 10 mg daily depending on the leukocyte count).

Ocular Toxoplasmosis

Patients with active ocular toxoplasmosis are treated with pyrimethamine, sulfadiazine, and leucovorin (see Table 336.2). They are treated while disease is active and then for at least several weeks after the lesion has developed a quiescent appearance (i.e., sharp borders, pigmentation at margins of the lesion, and resolution of associated inflammatory cells in the vitreous), which usually occurs in 2-4 weeks when treatment is initiated promptly. Within 7-10 days, the borders of the retinal lesions sharpen, and visual acuity usually returns to the level before development of the acute lesion. Systemic corticosteroids have been administered concomitantly with antimicrobial treatment when lesions involve the macula, optic nerve head, or papillomacular bundle. Corticosteroids must never be given alone but may be initiated after loading doses of pyrimethamine and sulfadiazine have been administered (2 days). With recurrences, new lesions often appear contiguous to old ones. Very rarely, vitrectomy and removal of the lens are needed to restore visual acuity. Active choroidal neovascular membranes as a result of toxoplasmic chorioretinitis have been treated successfully in children with intravitreal injection of antibody to vascular endothelial growth factor in addition to oral anti-*Toxoplasma* medicines. Suppressive treatment has prevented frequent recurrences of vision-threatening lesions.

Immunocompromised Persons

Serologic evidence of acute infection in an immunocompromised patient, regardless of whether signs and symptoms of infection are present or tachyzoites are demonstrated in tissue, is indication for therapy similar to that described for immunocompetent persons with symptoms of organ injury (see Table 336.2). It is important to establish the diagnosis as rapidly as possible and institute treatment early. In immunocompromised patients other than those with AIDS, therapy should be continued for at least 4-6 weeks beyond complete resolution of all signs and symptoms of active disease and resolution of immune compromise. Careful follow-up of these patients is imperative because relapse may occur, requiring prompt reinstitution of therapy. Relapse was once common in AIDS patients without antiretroviral treatment, and suppressive therapy with pyrimethamine and sulfadiazine, or TMP-SMX, was continued for life. Now it is possible to discontinue maintenance therapy when the CD4 count remains at >200 cells/μL for 4 months and all lesions have resolved. Therapy usually induces a beneficial response clinically but does not eradicate cysts. Treatment of *T. gondii*–seropositive patients with AIDS should be continued as long as CD4 counts remain at <200/μL. Prophylactic TMP-SMX therapy for *P. jirovecii* pneumonia significantly reduces the incidence of toxoplasmosis in AIDS patients.

Congenital Toxoplasmosis

All fetuses and newborns infected with *T. gondii* should be treated regardless of whether they have clinical manifestations of infection, because treatment may be effective in interrupting acute disease that damages vital organs (see Table 336.2). The fetus is treated by treating the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin after the first trimester. Infants should be treated for 1 year with pyrimethamine (2 mg/kg/day orally [PO] bid for 2 days, then 1 mg/kg/day for 2-6 months, and then 1 mg/kg given on Monday, Wednesday, and Friday), sulfadiazine (100 mg/kg/day PO bid), and leucovorin (5-10 mg PO given on Monday, Wednesday, and Friday, or more often depending on neutrophil count). The relative efficacy in reducing sequelae of infection and the safety of treatment with 2 months vs 6 months of the higher dosage of pyrimethamine are being compared in the U.S. National Collaborative Study. (Updated information about this study and these regimens is available from Dr. Rima McLeod, 773-834-4131.) Pyrimethamine and sulfadiazine are available only in tablet form but can be prepared as suspensions. **Prednisone** (1 mg/kg/day PO bid) has been used in addition when active chorioretinitis involves the macula or otherwise threatens vision or when the CSF protein is >1,000 mg/dL at birth, but the efficacy of this adjunctive therapy is not established. Prednisone is continued only for as long as the active inflammatory process in the posterior pole of the eye is vision-threatening or the CSF protein is >1,000 mg/dL and is then tapered rapidly if the duration of treatment has been brief.

Pregnant Women with *Toxoplasma gondii* Infection

The immunologically normal pregnant woman who acquires *T. gondii* >6 months before conception does not need treatment to prevent congenital infection of her fetus. Although data are not available to allow for a definitive time interval, if infection occurs during or shortly before the pregnancy, it is reasonable to evaluate the fetus by PCR on amniotic fluid and ultrasonography and to treat to prevent congenital infection in the fetus (see Table 336.2).

Treatment of a pregnant woman who acquires infection at any time during pregnancy reduces the chance of congenital infection in her infant. If the mother develops acute toxoplasmosis during the first trimester of pregnancy, **spiramycin** (1 g PO every 8 hours without food) or sulfadiazine is recommended for prevention of fetal infection. Spiramycin is available in the United States on an "emergency use" request by a physician through the FDA Division of Anti-Infective Drugs (301-796-1400) after the diagnosis of acute infection is confirmed in a reference laboratory (Palo Alto Medical Facility Toxoplasma Serology Lab, 650-853-4828). With this approval, the physician can then contact the spiramycin manufacturer, Sanofi Pasteur (1-800-822-2463), to obtain spiramycin for the patient. Adverse reactions to spiramycin are infrequent and include paresthesia, rash, nausea, vomiting, and diarrhea.

For treatment of the pregnant woman whose fetus has a confirmed or probable infection in the second or third trimester, the combination of pyrimethamine, sulfadiazine, and leucovorin is recommended. Following a loading dose of pyrimethamine (50 mg bid) for 2 days, then pyrimethamine is administered at 50 mg once daily beginning on the third day. Sulfadiazine (1.5-2.0 g PO bid) and leucovorin (10 mg PO once daily) are initiated on the first day of treatment with pyrimethamine and continued for the full course of treatment. Delay in maternal treatment during gestation results in greater brain and eye disease in the infant. Diagnostic amniocentesis should be performed at >17-18 weeks of gestation in pregnancies when there is high suspicion of fetal infection. After 24 weeks of gestation, incidence of transmission is relatively high, and all pregnant women who are infected acutely after that time are treated with pyrimethamine, sulfadiazine, and leucovorin to treat the fetus.

The approach in France to congenital toxoplasmosis includes systematic serologic screening of all pregnant women beginning at ≤11 weeks of gestational age. For women who are seronegative, testing is performed again each month during gestation, at birth, and 1 month after birth. Mothers with acute infection early in gestation and without evidence of involvement of the fetus are treated with spiramycin to prevent transmission and sulfadiazine and pyrimethamine to treat possible fetal infection. Ultrasonography and amniocentesis for PCR at approximately week 17-18 of gestation are used for fetal diagnosis and have 97% sensitivity and 100% specificity. Confidence intervals for sensitivity are larger early and late in gestation. Fetal infection is treated with pyrimethamine, sulfadiazine, and leucovorin after 14 weeks of gestation, and termination of pregnancy is very rare at present. Prompt initiation of treatment with pyrimethamine, sulfadiazine, and leucovorin during pregnancy usually results in an excellent outcome, with normal development of children in most cases. Only 19% of infants have findings of congenital infection, including intracranial calcifications (13%) and chorioretinal scars (6%), although the prevalence of chorioretinal scars is 39% at follow-up later in childhood. Several studies have demonstrated improved outcomes with shorter times between diagnosis and initiation of treatment. In Germany, for seroconverting women who are between 15 and 17 weeks' gestation and before amniocentesis, administration of pyrimethamine, sulfadiazine, and leucovorin results in good outcomes for infants but is sometimes associated with sulfadiazine hypersensitivity in mothers.

Chronically infected pregnant women who are immunocompromised have transmitted *T. gondii* to their fetuses. Such women should be treated with spiramycin throughout gestation. The optimal

management for prevention of congenital toxoplasmosis in the fetus of a pregnant woman with HIV infection, a CD4 count <200 cells/μL, and inactive *T. gondii* infection is unknown. Fortunately, this situation now is rarely encountered in the United States. If the pregnancy is not terminated, some experts suggest that the mother should be treated with spiramycin or sulfadiazine alone during the first 14 weeks of gestation and thereafter with pyrimethamine, sulfadiazine, and leucovorin until term. There are no universally accepted guidelines at present.

In a study of adult patients with AIDS and toxoplasmic encephalitis, pyrimethamine (75 mg PO once daily) combined with high dosages of intravenous clindamycin (1,200 mg every 6 hr) appeared equal in efficacy to pyrimethamine and sulfadiazine in the treatment of toxoplasmic encephalitis. Other experimental agents include the macrolides clarithromycin and azithromycin.

Future Treatments

Many potential future treatments are currently being studied, including tetrahydroquinolones and another cytochrome b/c inhibitor as a prodrug, calcium kinase inhibitors, DHFR inhibitors, and nanoparticle technology. Research is ongoing regarding the molecular targets of a toxoplasmosis vaccine that could be administered to mothers, children, or the general population. One group has developed an effective, porous, nanoparticle-based, intranasally administered vaccine against latent and congenital toxoplasmosis that protects nonhuman primates.

PROGNOSIS

Early institution of specific treatment for congenitally infected infants usually rapidly controls the active manifestations of toxoplasmosis, including active chorioretinitis, meningitis, encephalitis, hepatitis, splenomegaly, and thrombocytopenia. Rarely, hydrocephalus resulting from aqueductal obstruction may develop or become worse during therapy. Treatment appears to reduce the incidence of diminished cognitive and abnormal motor function. Chorioretinitis often recurs in untreated patients and sometimes recurs in treated patients. Treated children with extensive involvement at birth may function normally later in life or have mild to severe impairment of vision, hearing, cognitive function, and other neurologic functions. Delays in diagnosis and therapy, perinatal hypoglycemia, hypoxia, hypotension, repeated shunt infections, and severe visual impairment are associated with a poorer prognosis. The prognosis is not necessarily poor for infected babies. Currently available treatments do not eradicate encysted parasites.

Studies in France have demonstrated that outcome of treated fetal toxoplasmosis, even when infection is acquired early in gestation, is usually favorable if no hydrocephalus is detected on ultrasound and treatment with pyrimethamine, sulfadiazine, or leucovorin is initiated promptly. The **Systematic Review on Congenital Toxoplasmosis** (SYROCOT) study in Europe indicated that neurologic outcome is improved with shorter times between diagnosis and initiation of treatment of fetal toxoplasmosis. Work in Lyon, France, has indicated a low incidence of recurrent eye disease in children with congenital toxoplasmosis who had been treated in utero and in their first year of life. The NCCCTS (1981–2004) in the United States found that neurologic, developmental, audiologic, and ophthalmologic outcomes are considerably better for most children who were treated in the first year of life with pyrimethamine, sulfadiazine, and leucovorin compared with children who had not been treated or were treated for only 1 month in earlier decades described in the literature.

PREVENTION

Counseling pregnant women about the methods of preventing transmission of *T. gondii* (see Fig. 336.1) during pregnancy can reduce acquisition of infection during gestation. Women who do not have specific antibody to *T. gondii* before pregnancy should only eat well-cooked meat during pregnancy and should avoid contact with materials contaminated with oocysts excreted by cats, when possible. Cats that are kept indoors, maintained on prepared food, and not fed fresh, uncooked meat should not contact encysted *T. gondii* or shed oocysts. Serologic screening, ultrasound monitoring, and treatment of pregnant women during gestation can also reduce the incidence and manifestations of congenital toxoplasmosis.

Point-of-care testing to facilitate gestational screening, recent developments in medicines for treatment of active and chronic infections, and progress toward vaccines to prevent infections in humans and oocyst shedding by cats are all recent advances with promise to prevent or improve outcomes for *Toxoplasma gondii* infections. There is a point-of-care test that has been CE marked for use in Europe and is currently moving toward completion of feasibility studies in the United States with consideration of FDA clearance, potentially marking the beginning of more widespread testing for optimal obstetrical care to prevent congenital toxoplasmosis and for public health initiatives to identify prevalence of toxoplasmosis in specific high-risk areas of the globe.

ACKNOWLEDGMENT

We gratefully acknowledge the participant families, physicians, and other personnel of the National Collaborative Congenital Toxoplasmosis Study (NCCTS), and colleagues, for helping to create the understanding and knowledge in this chapter; and the Cornwell Mann, Rodriguez, and Morel families. Taking out Toxo (TOT), TRI, and NIH, NIAID/DMID ROI AI27530 and RO1 AI071319-01 for support. We also thank Andrew Grose for his assistance in preparing this chapter.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 16
Helminthic Diseases

Chapter 337
Ascariasis (*Ascaris lumbricoides*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Ascariasis is caused by the nematode, or **roundworm**, *Ascaris lumbricoides.* Adult worms of *A. lumbricoides* inhabit the lumen of the small intestine. The reproductive potential of *Ascaris* is prodigious; a gravid female worm produces 200,000 eggs per day. The fertile ova are oval in shape with a thick, mamillated covering measuring 45-70 μm in length and 35-50 μm in breadth (Fig. 337.1). After passage in the feces, the eggs embryonate and become infective in 5-10 days under favorable environmental conditions. Adult worms can live for 12-18 months (Fig. 337.2).

EPIDEMIOLOGY

Ascariasis occurs globally and is the most prevalent human **helminthiasis** in the world. It is most common in tropical areas (South America, Africa, Asia) where environmental conditions are optimal for maturation of ova in the soil. Approximately 1 billion persons are estimated to be infected. Although the number of cases in the United States is not known precisely, the highest prevalence is thought to be in high-poverty areas of the South and Appalachia. Pig farming is also associated with *Ascaris* species. Key factors linked with a higher prevalence of infection include poor socioeconomic conditions, use of human feces as fertilizer, and geophagia. Even though infection can occur at any age, the highest rate is in preschool or early school-age children. Transmission is primarily hand to mouth but may also involve ingestion of

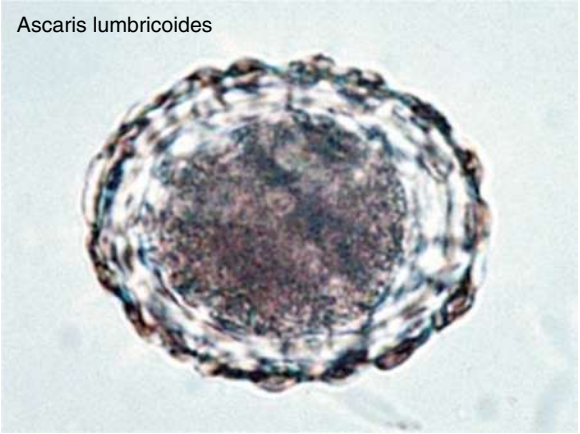

Fig. 337.1 Soil-transmitted helminth eggs (*Ascaris lumbricoides*). *(From Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521–1532.)*

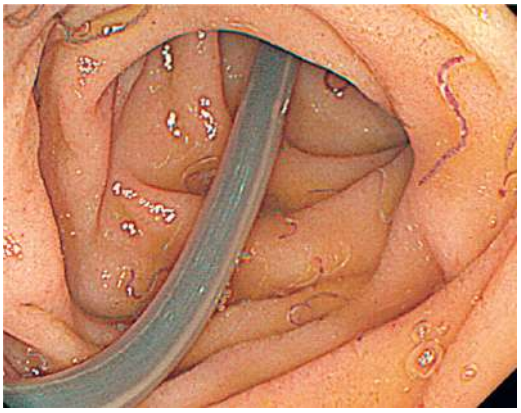

Fig. 337.2 Endoscopic image of intestinal *Ascaris lumbricoides* and hookworm co-infection. The ascaris worm is large in relation to the lumen and multiple blood-filled hookworms. *(Courtesy Dr. Kunimitsu Inoue, Nakamura Hospital, Oita, Japan.)*

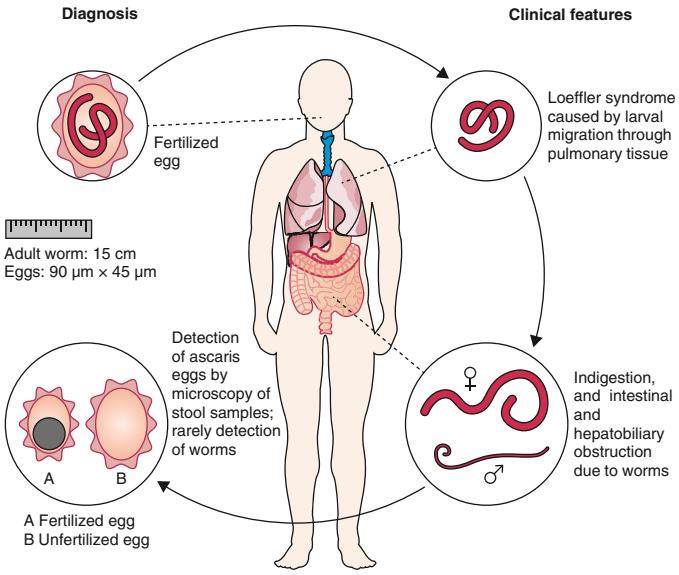

Fig. 337.3 Transmission of *Ascaris lumbricoides*: diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2A.)*

contaminated raw fruits and vegetables. Transmission is enhanced by the high output of eggs by fecund female worms and resistance of ova to the outside environment. *Ascaris* eggs can remain viable at 5–10°C (41–50°F) for as long as 2 years.

PATHOGENESIS

Ascaris ova hatch in the small intestine after ingestion by the human host. Larvae are released, penetrate the intestinal wall, and migrate to the lungs by way of the venous circulation. The parasites then cause **pulmonary ascariasis** as they enter into the alveoli and migrate through the bronchi and trachea (Fig. 337.3). They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female *Ascaris* begin depositing eggs in 8-10 weeks.

CLINICAL MANIFESTATIONS

The clinical presentation depends on the intensity of infection and the organs involved. Most individuals have low to moderate worm burdens and have no symptoms or signs. The most common clinical problems are from **pulmonary disease** and **obstruction of the intestinal or biliary tract**. Larvae migrating through these tissues may cause allergic symptoms, fever, urticaria, and granulomatous disease. The pulmonary manifestations resemble Loeffler syndrome and include transient respiratory symptoms such as cough and dyspnea, pulmonary infiltrates, and blood eosinophilia. Larvae may be observed in the sputum. Vague abdominal complaints have been attributed to the presence of adult worms in the small intestine, although the precise contribution of the parasite to these symptoms is difficult to ascertain. A more serious complication occurs when a large mass of worms leads to acute bowel obstruction. Children with heavy infections may present with vomiting, abdominal distention, and cramps. In some cases, worms may be passed in the vomitus or stools. *Ascaris* worms occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Worm migration through the intestinal wall can lead to peritonitis. Dead worms can serve as a nidus for stone formation. Studies show that chronic infection with *A. lumbricoides* (often coincident with other helminth infections) impairs growth, physical fitness, and cognitive development.

DIAGNOSIS

Microscopic examination of fecal smears can be used for diagnosis because of the high number of eggs excreted by adult female worms (see Fig. 337.1). A high index of suspicion in the appropriate clinical context is needed to diagnose pulmonary ascariasis or obstruction of the gastrointestinal tract. Ultrasound examination of the abdomen is capable of visualizing intraluminal adult worms.

TREATMENT

Although several chemotherapeutic agents are effective against ascariasis, none has documented utility during the pulmonary phase of infection. Treatment options for gastrointestinal ascariasis include **albendazole** (400 mg orally once, for all ages), **mebendazole** (100 mg orally twice daily for 3 days or 500 mg once, for all ages), **pyrantel pamoate** (11 mg/kg orally once; maximum dose: 1g), or **ivermectin** (200 μg/kg orally once). **Nitazoxanide** (100 mg orally twice per day for 3 days for children 1-3 years old; 200 mg twice per day for 3 days for children 4-11 years; 500 mg twice per day for 3 days for adolescents and adults) produces cure rates comparable to single-dose albendazole. **Piperazine citrate** (75 mg/kg/day for 2 days; maximum dose: 3.5 g/day), which causes neuromuscular paralysis of the parasite and rapid expulsion of the worms, is a good treatment for intestinal or biliary obstruction but has been withdrawn from the market in many regions due to toxicity and good alternatives. Surgery may be required for cases with severe obstruction. Drug resistance has not been reported, but repeated treatment for ascariasis may be necessary because reinfection is common.

PREVENTION

Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control (Table 337.1). **Anthelmintic**

Table 337.1 Clinical and Public Health Control of Soil-Transmitted Helminthiasis

	CLINICAL DIAGNOSIS AND MANAGEMENT	PUBLIC HEALTH CONTROL
Diagnosis	Individual	Community level (e.g., in select schools)
Diagnostic criteria	Parasitologic	Residence in an area with soil-transmitted helminthiasis prevalence >20%
Treatment approach	Single dose or multiple dose	Single-dose periodic mass treatment
Threshold for treatment	Travel history, symptoms and signs, positive laboratory test	Estimated prevalence of infection in target population
Treatment objective	Parasitologic cure	Decreased worm burden; reduction in transmission
Ancillary treatment	Based on clinical signs and symptoms	Typically, only if included in mass treatment (e.g., vitamin A supplementation)
Follow-up	Parasitologic test of cure; improvement in associated health conditions	Not usually done
Health education (sanitation/hygiene)	Recommended	Recommended

From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. *Lancet*. 2018;391:252–262. Table 1.

chemotherapy programs can be implemented in one of three ways: (1) offering universal treatment to all individuals in an area of high endemicity; (2) offering treatment targeted to groups with high frequency of infection, such as children attending primary school; or (3) offering individual treatment based on intensity of current or past infection. Improving education about and practices of sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and education are the most effective long-term preventive measures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 338

Hookworms (*Necator americanus* and *Ancylostoma* spp.)

Peter J. Hotez

ETIOLOGY

Two major genera of hookworms, which are nematodes, or roundworms, infect humans. *Necator americanus,* the only representative of its genus, is a major **anthropophilic** hookworm and is the most common cause of human hookworm infection. Hookworms of the genus *Ancylostoma* include the anthropophilic hookworm *Ancylostoma duodenale,* which also causes classic hookworm infection, and the less common **zoonotic** species *Ancylostoma ceylanicum* (restricted mostly to Southeast Asia). Human zoonotic infection with the dog hookworm *Ancylostoma caninum* is associated with an eosinophilic enteritis syndrome. The larval stage of *Ancylostoma braziliense,* whose definitive hosts include dogs and cats, is the principal cause of cutaneous larva migrans.

The infective larval stages of the anthropophilic hookworms live in a developmentally arrested state in warm, moist soil. Larvae infect humans either by penetrating through the skin (*N. americanus* and *A. duodenale*) or when they are ingested *(A. duodenale).* Larvae entering the human host by skin penetration undergo **extraintestinal migration** through the venous circulation and lungs before they are swallowed, whereas orally ingested larvae may undergo extraintestinal migration or remain in the gastrointestinal (GI) tract (Figs. 338.1 and 338.2). Larvae returning to the small intestine undergo two molts to become adult, sexually mature, male and female worms ranging in length from 5-13 mm. The buccal capsule of the adult hookworm is armed with cutting plates *(N. americanus)* or teeth *(A. duodenale)* to facilitate attachment to the mucosa and submucosa of the small intestine. Hookworms can remain in the intestine for 1-5 years, where they mate and produce eggs. Although up to 2 months is required for the larval stages of hookworms to undergo extraintestinal migration and develop into mature adults, *A. duodenale* larvae may remain developmentally arrested for many months before resuming development in the intestine. Mature *A. duodenale* female worms produce about 30,000 eggs per day; daily egg production by *N. americanus* is <10,000/day (Fig. 338.3). The eggs are thin shelled and ovoid, measuring approximately 40-60 μm. Eggs that are deposited on soil with adequate moisture and shade develop into first-stage larvae and hatch. Over the ensuing several days and under appropriate conditions, the larvae molt twice to the **infective** stage. Infective larvae are developmentally arrested and nonfeeding. They migrate vertically in the soil until they either infect a new host or exhaust their lipid metabolic reserves and die.

EPIDEMIOLOGY

Hookworm infection is one of the most prevalent infectious diseases of humans. The Global Burden of Disease Study 2015 reported that approximately 428 million people are infected with hookworms, with further estimates indicating that hookworm infection globally results in 4.1 million disability-adjusted life-years, possibly leading all **neglected tropical diseases** in years lost through disability. In the case of hookworm infection, all the years lost through disability are attributed to anemia from intestinal blood loss. There is also a massive socioeconomic impact from hookworm infection, with estimates that hookworm can cause up to $139 billion in losses from diminished productivity.

Because of the requirement for adequate soil moisture, shade, and warmth, hookworm infection is usually confined to rural areas, especially where human feces are used for fertilizer or where sanitation is inadequate. Hookworm is an infection associated with *economic underdevelopment and poverty* throughout the tropics and subtropics. Sub-Saharan Africa, East Asia, and tropical regions of the Americas have the highest prevalence of hookworm infection. High rates of infection are often associated with cultivation of certain agricultural products, such as tea in India; sweet potato, corn, cotton, and mulberry trees in China; coffee in Central and South America; and rubber in Africa. It is not uncommon to find dual *N. americanus* and *A. duodenale* infections. *N. americanus* predominates in Central and South America as well as in southern China and Southeast Asia, whereas *A. duodenale* predominates in North Africa, in northern India, in China north of the Yangtze River,

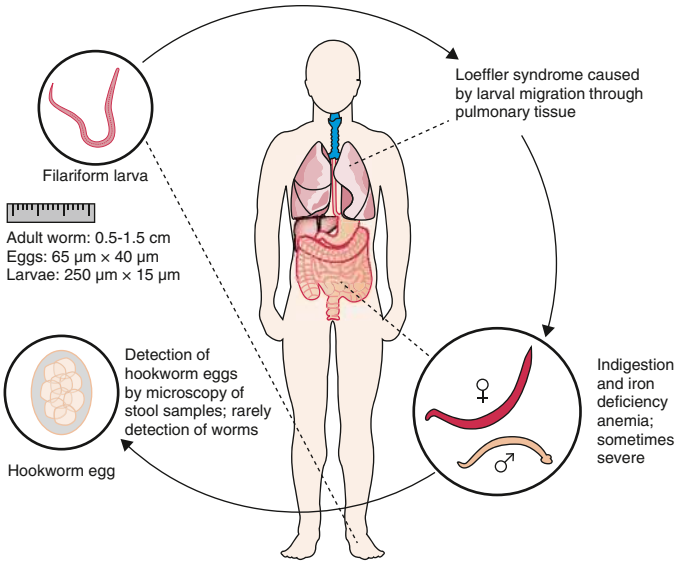

Fig. 338.1 Transmission of hookworm (*Ancylostoma duodenale* and *Necator americanus*): diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2C.)*

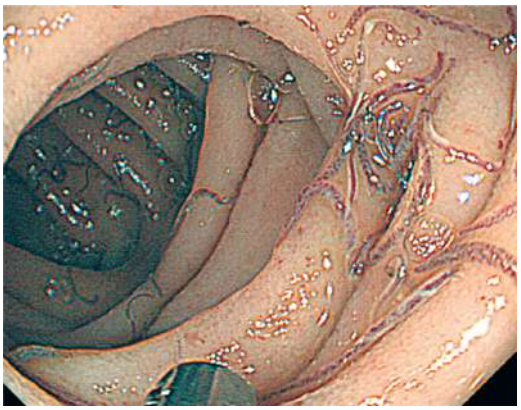

Fig. 338.2 Endoscopic images of intestinal hookworm infection. *(Courtesy Dr. Kunimitsu Inoue, Nakamura Hospital, Oita, Japan.)*



Fig. 338.3 Soil-transmitted hookworm helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521–1532.)*

and among aboriginal people in Australia. The ability of *A. duodenale* to withstand somewhat harsher environmental and climatic conditions may reflect its ability to undergo arrested development in human tissues. *A. ceylanicum* infection occurs in India and Southeast Asia.

Eosinophilic enteritis caused by *A. caninum* was first described in Queensland, Australia, with two reported cases in the United States. Because of its global distribution in dogs, it was initially anticipated that human *A. caninum* infections would be identified in many locales, but this has not been found.

PATHOGENESIS

The major morbidity of human hookworm infection is a direct result of **intestinal blood loss**. Adult hookworms adhere tenaciously to the mucosa and submucosa of the proximal small intestine by using their cutting plates or teeth and a muscular esophagus that creates negative pressure in their buccal capsules. At the attachment site, host inflammation is downregulated by the release of antiinflammatory polypeptides by the hookworm. Rupture of capillaries in the lamina propria is followed by blood extravasation, with some of the blood ingested directly by the hookworm. After ingestion, the blood is anticoagulated, the red blood cells are lysed, and the hemoglobin is released and digested. Each adult *A. duodenale* hookworm causes loss of an estimated 0.2 mL of blood/day; blood loss is less for *N. americanus*. Individuals with light infections have minimal blood loss and thus may have hookworm infection but not hookworm disease. There is a direct correlation between the number of adult hookworms in the gut and the volume of fecal blood loss. Hookworm disease results only when individuals with moderate and heavy infections experience sufficient blood loss to develop iron deficiency and anemia. Hypoalbuminemia and consequent edema and anasarca from the loss of intravascular oncotic pressure can also occur. These features depend heavily on the dietary reserves of the host.

CLINICAL MANIFESTATIONS

Chronically infected children with moderate and heavy hookworm infections suffer from intestinal blood loss that results in **iron deficiency** and can lead to anemia as well as protein malnutrition. Prolonged iron deficiency associated with hookworms in childhood can lead to physical growth retardation and cognitive and intellectual deficits.

Anthropophilic hookworm larvae elicit dermatitis sometimes referred to as **ground itch** when they penetrate human skin. The vesiculation and edema of ground itch are exacerbated by repeated infection. Infection with a zoonotic hookworm, especially *A. braziliense,* can result in lateral migration of the larvae to cause the characteristic cutaneous tracts of **cutaneous larva migrans** (see Chapter 338.1). Cough subsequently occurs in *A. duodenale* and *N. americanus* hookworm infection when larvae migrate through the lungs to cause laryngotracheobronchitis, usually about 1 week after exposure. Pharyngitis also can occur. The onset of eosinophilia coincides with the entry of hookworm larvae into the GI tract. Upper abdominal pain can occur during this period, but it eventually subsides.

Chronic intestinal hookworm infection is not typically associated with specific GI complaints, although pain, anorexia, and diarrhea have been attributed to the presence of hookworms. The major clinical manifestations are related to intestinal blood loss. Heavily infected children exhibit all the signs and symptoms of **iron-deficiency anemia** and **protein malnutrition**. In some cases, children with chronic hookworm disease acquire a yellow-green pallor known as **chlorosis.**

An infantile form of **ancylostomiasis** resulting from heavy *A. duodenale* infection has been described. Affected infants experience diarrhea, melena, failure to thrive, and profound anemia. Infantile ancylostomiasis has significant mortality.

Eosinophilic enteritis caused by *A. caninum* is associated with colicky abdominal pain that begins in the epigastrium and radiates outward and is usually exacerbated by food. Extreme cases may mimic acute appendicitis.

DIAGNOSIS

Children with hookworm release eggs that can be detected by direct fecal examination (see Fig. 338.3). Quantitative methods are available

to determine whether a child has a heavy **worm burden** that can cause hookworm disease. The eggs of *N. americanus* and *A. duodenale* are morphologically indistinguishable. Species identification typically requires egg hatching and differentiation of third-stage infective larvae; methods using polymerase chain reaction (PCR) have been developed but are not generally used in clinical practice.

In contrast, eggs are generally not present in the feces of patients with eosinophilic enteritis caused by *A. caninum*. Eosinophilic enteritis is often diagnosed by demonstrating ileal and colonic ulcerations by colonoscopy in the presence of significant blood eosinophilia. An adult canine hookworm may occasionally be recovered during colonoscopic biopsy. Patients with this syndrome develop IgG and IgE serologic responses.

TREATMENT

The goal of **deworming** is removal of the adult hookworms with an **anthelmintic** drug. The **benzimidazole** anthelmintics, mebendazole and albendazole, are effective at eliminating hookworms from the intestine, although multiple doses are sometimes required. **Albendazole** (400 mg orally [PO] once, for all ages) often results in cure, although *N. americanus* adult hookworms are sometimes more refractory and require additional doses. **Mebendazole** (100 mg PO twice daily [bid] for 3 days, for all ages) is also effective. In many developing countries, mebendazole is administered as a single dose of 500 mg; however, the cure rates with this regimen can be as low as 10% or less. According to the World Health Organization (WHO), children should be encouraged to chew tablets of albendazole or mebendazole, because forcing very young children to swallow large tablets may cause choking or asphyxiation. Mebendazole is recommended for *A. caninum*–associated eosinophilic enteritis, although recurrences are common. Because the benzimidazoles have been reported to be embryotoxic and teratogenic in laboratory animals, their safety during pregnancy and in young children is a potential concern, and the risks vs benefits must be carefully considered. WHO currently supports the use of benzimidazoles in infected children ≥1 year old but at a reduced dose (200 mg for albendazole) in the youngest age-group (1-2 years old). The most up to date guidelines for treating these populations are available from the US Centers for Disease Control and Prevention https://www.cdc.gov/parasites/hookworm/health_professionals/index.html#tx. In some countries, **pyrantel pamoate** (11 mg/kg PO once daily for 3 days; maximum dose: 1 g) is available in liquid form and is an effective alternative to the benzimidazoles. A newer drug known as **tribendimidine** is still under clinical development and may be available in the future. Replacement therapy with oral iron is not usually required to correct hookworm-associated iron deficiency in children.

PREVENTION

In 2001, the World Health Assembly urged its member states to implement programs of periodic deworming so as to control the morbidity of hookworm and other soil-transmitted helminth infections (see Table 337.1 in Chapter 337). Although anthelmintic drugs are effective at eliminating hookworms from the intestine, the high rates of drug failure from single-dose mebendazole or albendazole and post-treatment reinfection among children suggest that mass drug administration alone is not effective for controlling hookworm in highly endemic areas. Moreover, data suggest that the efficacy of mebendazole decreases with frequent, periodic use, leading to concerns about the possible emergence of **anthelminthic drug resistance**. To reduce the reliance exclusively on anthelminthic drugs, a recombinant human hookworm vaccine has been developed and is undergoing clinical testing. Economic development and associated improvements in sanitation, health education, and avoidance of human feces as fertilizer remain critical for reducing hookworm transmission and endemicity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

338.1 Cutaneous Larva Migrans

Peter J. Hotez

ETIOLOGY

Cutaneous larva migrans **(creeping eruption)** is caused by the larvae of several nematodes, primarily hookworms, which are not usually parasitic for humans. *A. braziliense,* a hookworm of dogs and cats, is the most common cause, but other animal hookworms may also produce the disease.



Fig. 338.4 Creeping eruption of cutaneous larva migrans. *(From Korting GW. Hautkrankheitenbeikindern und jugendlichen. Stuttgart, Germany: FK Schattauer Verlag, 1969.)*

EPIDEMIOLOGY

Cutaneous larva migrans is usually caused by *A. braziliense,* which is endemic to the southeastern United States and Puerto Rico. Travelers account for a significant percentage of the cases. Recently, autochthonous cases have been reported from Europe.

CLINICAL MANIFESTATIONS

After penetrating the skin, larvae localize at the epidermal-dermal junction and migrate in this plane, moving at a rate of 1-2 cm/day. The response to the parasite is characterized by raised, erythematous, serpiginous tracks, which occasionally form bullae (Fig. 338.4). These lesions may be single or numerous and are usually localized to an extremity, although any area of the body may be affected. As the organism migrates, new areas of involvement may appear every few days. Intense localized pruritus, without any systemic symptoms, may be associated with the lesions. Bacterial superinfection can occur.

DIAGNOSIS

Cutaneous larva migrans is diagnosed by clinical examination of the skin. Patients are often able to recall the exact time and location of exposure because the larvae produce intense itching at the site of penetration. Eosinophilia may occur but is uncommon.

TREATMENT

If left untreated, the larvae die, and the syndrome resolves within a few weeks to several months. Treatment with **ivermectin** (200 μg/kg PO in a single dose for children over 15 kg; considered drug of choice by some investigators), **albendazole** (400 mg PO daily for 3 days, for children over the age of 2 years), or topical **thiabendazole** hastens resolution, if symptoms warrant treatment. The U.S. Food and Drug Administration has not approved these drugs for cutaneous larva migrans. The safety of ivermectin in young children (weighing <15 kg) and pregnant women remains to be established. Albendazole should be taken with a fatty meal. The latest guidelines from the US Centers for Disease Control and Prevention can be found at https://www.cdc.gov/parasites/zoonotichookworm/health_professionals/index.html#tx.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 339

Trichuriasis (*Trichuris trichiura*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Trichuriasis is caused by the **whipworm**, *Trichuris trichiura,* a nematode, or roundworm, that inhabits the cecum and ascending colon. The principal hosts of *T. trichiura* are humans, who acquire infection by ingesting embryonated, barrel-shaped eggs (Fig. 339.1). The larvae escape from the shell in the upper small intestine and penetrate the intestinal villi. The worms slowly move toward the cecum, where the anterior three-quarters whiplike portion remains within the superficial mucosa and the short posterior end is free in the lumen (Fig. 339.2). In 1-3 months, the adult female worm begins producing 5,000-20,000 eggs per day. After excretion in the feces, embryonic development occurs in 2-4 weeks with optimal temperature and soil conditions. The adult worm life span is approximately 2 years.

EPIDEMIOLOGY

Trichuriasis occurs throughout the world and is especially common in poor rural communities with inadequate sanitary facilities and soil contaminated with human or animal feces. Trichuriasis is one of the most prevalent human helminthiases, with an estimated 1 billion infected individuals worldwide. In many parts of the world, where protein-energy malnutrition and anemia are common, the prevalence of *T. trichiura* infection can be as high as 95%. Although trichuriasis occurs in the rural southeastern United States, its prevalence has not been reported. The highest rate of infection occurs among children 5-15 years old. Infection develops after ingesting embryonated ova by direct contamination of hands, food (raw fruits and vegetables fertilized with human feces), or drink (Fig. 339.3). Transmission can also occur indirectly through flies or other insects.

CLINICAL MANIFESTATIONS

Most persons harbor low worm burdens and do not have symptoms. Some individuals may have a history of right lower quadrant or vague periumbilical pain. Adult *Trichuris* ingest approximately 0.005 mL of blood per worm per day. Children, who are most likely to be heavily infected, frequently suffer from disease. Clinical manifestations include chronic dysentery, rectal prolapse, anemia, poor growth, as well as developmental and cognitive deficits. There is no significant eosinophilia, even though a portion of the worm is embedded in the mucosa of the large bowel.

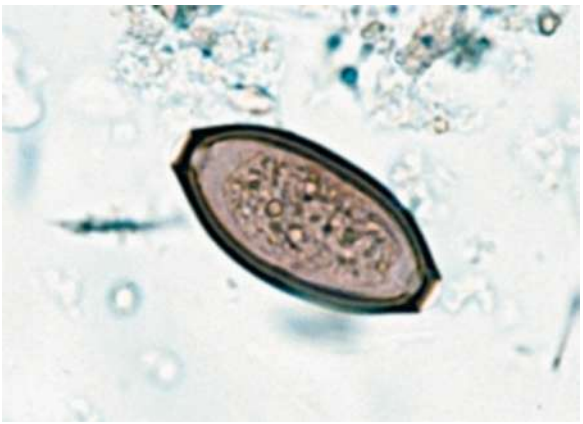

Fig. 339.1 *Trichuris trichiura.* Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521–1532.)*



Fig. 339.2 *Trichuris trichiura* infection. *(Courtesy Dr. Kunimitsu Inoue, Nakamura Hospital, Oita, Japan.)*

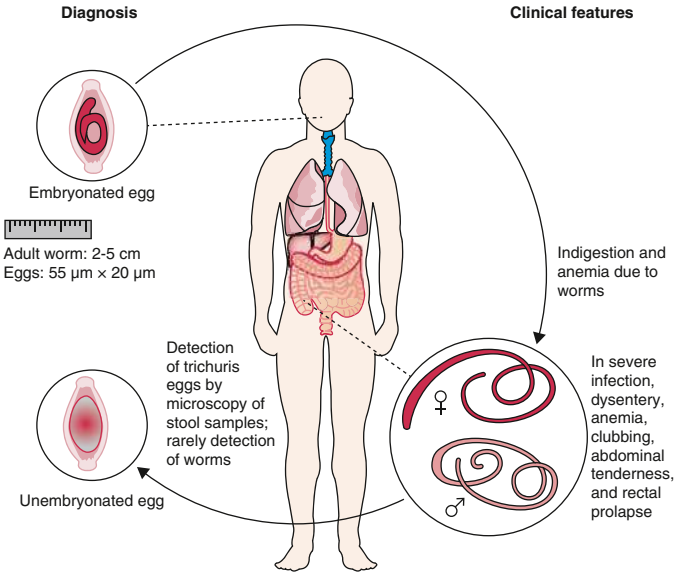

Fig. 339.3 Transmission of *Trichuris trichiura*: diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2B.)*

DIAGNOSIS

Because egg output is so high, fecal smears frequently reveal the characteristic barrel-shaped ova of *T. trichiura.*

TREATMENT

Albendazole (400 mg orally for 3 days, for all ages) is the drug of choice and is safe and effective, in part because it is poorly absorbed from the gastrointestinal tract. It reduces egg output by 90–99% and has cure rates of 70–90%, although reinfection and resumption of egg production by live worms that presumably survive after treatment may occur. Alternatives include **mebendazole** (100 mg orally twice daily for 3 days) and **ivermectin** (600 µg/kg orally for 3 days). Single-day treatment with albendazole, nitazoxanide, or albendazole plus nitazoxanide leads to cure rates that are low and short-lived. Combination treatment with **oxantel pamoate** (20 mg/kg) plus 400 mg albendazole on consecutive days may have the highest cure rate.

PREVENTION

Disease can be prevented by personal hygiene, improved sanitary conditions, and eliminating the use of human feces as fertilizer (see Table 337.1 in Chapter 337).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 340

Enterobiasis *(Enterobius vermicularis)*

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

The cause of enterobiasis, or **pinworm** infection, is *Enterobius vermicularis,* which is a small (1 cm in length), white, threadlike nematode, or roundworm that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15,000 eggs. Ova are convex on one side and flattened on the other and have diameters of approximately 30 × 60 µm. Eggs embryonate within 6 hours and remain viable for 20 days. Human infection occurs by the fecal-oral route typically by ingestion of embryonated eggs that are carried on fingernails, clothing, bedding, or house dust. After ingestion, the larvae mature to form adult worms in 36-53 days.

EPIDEMIOLOGY

Enterobiasis infection occurs in individuals of all ages and socioeconomic levels. It is prevalent in regions with temperate climates and is the most common helminth infection in the United States. It infects 30% of children worldwide, and humans are the only known host. Infection occurs primarily in institutional or family settings that include children. The prevalence of pinworm infection is highest in children 5-14 years of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission. Because the life span of the adult worm is short, chronic parasitism is likely caused by repeated cycles of reinfection. **Autoinoculation** can occur in individuals who habitually put their fingers in their mouth.

PATHOGENESIS

Enterobius infection may cause symptoms by mechanical stimulation and irritation, allergic reactions, and migration of the worms to anatomic sites where they become pathogenic. *Enterobius* infection has been associated with concomitant *Dientamoeba fragilis* infection, which causes diarrhea.

CLINICAL MANIFESTATIONS

Pinworm infection is innocuous and rarely causes serious medical problems. The most common complaints include itching and restless sleep secondary to nocturnal perianal or **perineal pruritus**. The precise cause and incidence of pruritus are unknown but may be related to the intensity of infection, psychologic profile of the infected individual and the family, or allergic reactions to the parasite. Eosinophilia is not observed in most cases, because tissue invasion does not occur. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

DIAGNOSIS

A history of nocturnal **perianal pruritus** in children strongly suggests enterobiasis. Definitive diagnosis is established by identification of parasite eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs (Fig. 340.1). Repeated examinations increase the chance of detecting ova; one examination detects 50% of infections, three examinations 90%, and five examinations 99%. Worms seen in the perianal region should be removed and preserved in 75% ethyl alcohol until microscopic examination can be performed. Digital rectal examination may also be used to obtain samples for a wet mount. Routine stool samples rarely demonstrate *Enterobius* ova.



Fig. 340.1 Eggs of *Enterobius vermicularis. (From Guerrant RL, Walker DH, Weller PF, et al. Tropical Infectious Diseases. Philadelphia: Churchill Livingstone, 2006. p. 1248.)*

TREATMENT

Anthelmintic drugs should be administered to infected individuals and their family members. **Albendazole** (400 mg orally with a repeat dose 2 week later for all age-groups) is the treatment of choice and results in cure rates exceeding 90%. Alternatives include **mebendazole** (100 mg orally with a repeat dose 2 weeks later) and **pyrantel pamoate** (11 mg/kg base orally 3 times a day up to a maximum of 1 g; repeat at 2 weeks). Morning bathing removes a large portion of eggs. Frequent changing of underclothes, bedclothes, and bedsheets decreases environmental egg contamination and may decrease the risk for autoinfection.

PREVENTION

Household contacts can be treated at the same time as the infected individual. Repeated treatments every 3-4 months may be required in circumstances with repeated exposure, such as with institutionalized children. Good hand hygiene is the most effective method of prevention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 341

Strongyloidiasis *(Strongyloides stercoralis)*

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Strongyloidiasis is caused by the nematode, or roundworm, *Strongyloides stercoralis.* Only adult female worms inhabit the small intestine. The nematode reproduces in the human host by parthenogenesis and releases eggs containing mature larvae into the intestinal lumen. **Rhabditiform** larvae immediately emerge from the ova and are passed in feces, where they can be visualized by stool examination. Rhabditiform larvae either differentiate into free-living adult male and female worms or metamorphose into the infectious **filariform** larvae. Sexual reproduction occurs only in the free-living stage. Humans are usually infected through skin contact with soil contaminated with infectious larvae (Fig. 341.1). Larvae penetrate the skin, enter the venous circulation, and then pass to the lungs, break into alveolar spaces, and migrate up the bronchial tree. They are then swallowed and pass through the stomach, and adult female worms develop in the small intestine. Egg deposition begins approximately 28 days after initial infection.

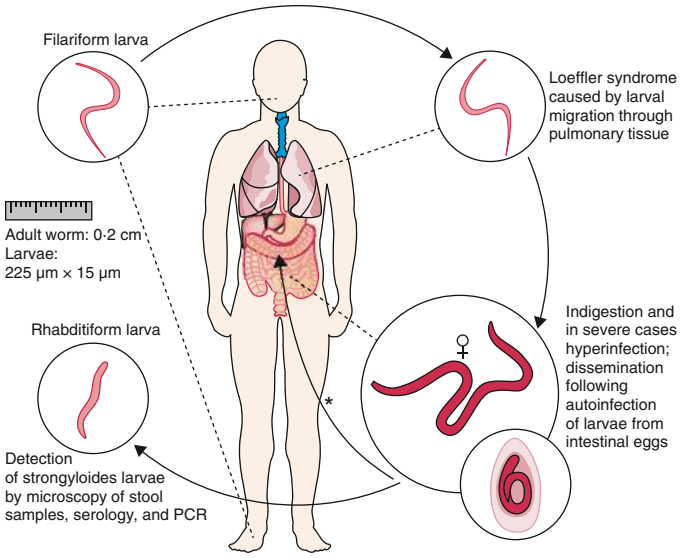

Fig. 341.1 Transmission of *Strongyloides stercoralis*: diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, et al. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2D.)*

The **hyperinfection syndrome** occurs when large numbers of larvae transform into infective organisms during their passage in feces and then reinfect **(autoinfect)** the host by way of the lower gastrointestinal (GI) tract or perianal region. This cycle may be accelerated in immunocompromised persons, particularly those with depressed T-cell function.

EPIDEMIOLOGY

S. stercoralis infection is prevalent in tropical and subtropical regions of the world and is endemic in several areas of Europe, the southern United States, and Puerto Rico. Transmission requires appropriate environmental conditions, particularly warm, moist soil. Poor sanitation and crowded living conditions are conducive to high levels of transmission. Dogs and cats can act as reservoirs. The highest prevalence of infection in the United States occurs in impoverished areas and among socially marginalized groups, such as immigrants, refugees, and indigenous or ethnic minority groups. Infection may be especially common among residents of mental institutions, veterans who were prisoners of war in areas of high endemicity, and refugees and immigrants. Because of internal autoinfection, individuals may remain infected for decades. Infection may be transmitted by organ transplantation. Individuals with hematologic malignancies, autoimmune diseases, malnutrition, and drug-induced immunosuppression (especially corticosteroids) are at high risk for the hyperinfection syndrome. Patients with AIDS may experience a rapid course of disseminated strongyloidiasis with a fatal outcome.

PATHOGENESIS

The initial host immune response to infection is production of immunoglobulin E and eosinophilia in blood and tissues, which presumably prevents dissemination and hyperinfection in the immunocompetent host. Adult female worms in otherwise healthy and asymptomatic individuals may persist in the GI tract for years. If infected persons become immunocompromised, the reduction in cellular and humoral immunity may lead to an abrupt and dramatic increase in parasite load with systemic dissemination.

CLINICAL MANIFESTATIONS

Approximately 30% of infected individuals are asymptomatic. The remaining patients have symptoms that correlate with the three stages of infection: invasion of the skin, migration of larvae through the lungs, and parasitism of the small intestine by adult worms. **Larva currens** is the manifestation of an allergic reaction to filariform larvae that migrate through the skin, where they leave pruritic, tortuous, urticarial tracks. The lesions may recur and are typically found over the lower abdominal wall, buttocks, or thighs, resulting from larval migration from defecated stool. Pulmonary disease secondary to larval migration through the lung rarely occurs and may resemble **Loeffler syndrome** (cough, wheezing, shortness of breath, transient pulmonary infiltrates accompanied by eosinophilia). GI strongyloidiasis is characterized by indigestion, crampy abdominal pain, vomiting, diarrhea, steatorrhea, protein-losing enteropathy, protein-caloric malnutrition, and weight loss. Edema of the duodenum with irregular mucosal folds, ulcerations, and strictures can be seen radiographically. Infection may be chronic in nature and is associated with **eosinophilia**.

Strongyloidiasis is potentially lethal because of the ability of the parasite to replicate within the host and cause overwhelming hyperinfection in immunocompromised persons. The **hyperinfection syndrome** is characterized by an exaggeration of the clinical features that develop in symptomatic immunocompetent individuals. The onset is usually sudden, with generalized abdominal pain, distention, and fever. Multiple organs can be affected as massive numbers of larvae disseminate throughout the body and introduce bowel flora. The latter may result in bacteremia and septicemia. Cutaneous manifestations may include petechiae and purpura. Cough, wheezing, and hemoptysis are indicative of pulmonary involvement. Whereas eosinophilia is a prominent feature of strongyloidiasis in immunocompetent persons, this sign may be absent in immunocompromised persons. Because of the low incidence of strongyloidiasis in industrialized countries, it is often misdiagnosed, resulting in a significant delay in treatment.

DIAGNOSIS

Intestinal strongyloidiasis is diagnosed by examining feces or duodenal fluid for the characteristic larvae (Fig. 341.2). Several stool samples should be examined by direct smear, the Koga agar plate method, or the Baermann test. Alternatively, duodenal fluid can be sampled by the **enteric string test** (Entero-Test) or aspiration via endoscopy. In children with the hyperinfection syndrome, larvae may be found in sputum, gastric aspirates, and rarely in small intestinal biopsy specimens. An enzyme-linked immunosorbent assay for IgG antibody to *Strongyloides* may be more sensitive than parasitologic methods for diagnosing intestinal infection in the immunocompetent host. The utility of the assay in diagnosing infection in immunocompromised patients with the hyperinfection syndrome has not been determined. Eosinophilia is common.

TREATMENT

Treatment is directed at eradication of infection. **Ivermectin** (200 µg/kg/day once daily orally for 2 days) is the drug of choice for uncomplicated strongyloidiasis. Alternatively, **albendazole** (400 mg orally twice daily for 7 days) may be used. Patients with the hyperinfection syndrome should be treated with ivermectin for 7-14 days and may require repeated courses. Reducing the dose of immunosuppressive therapy and treatment of concomitant bacterial infections are essential in the management of the **hyperinfection syndrome**. Close follow-up with repeated stool examination is necessary to ensure complete elimination of the parasite. *Strongyloides* antibodies decrease within 6 months after successful treatment.

PREVENTION

Sanitary practices designed to prevent soil and person-to-person transmission are the most effective control measures (see Table 337.1). Wearing **shoes** is a main preventive strategy. Reducing transmission in institutional settings can be achieved by decreasing fecal contamination of the environment, such as by the use of clean bedding. Because infection is uncommon in most settings, case detection and treatment are advisable. Individuals who will be given prolonged high-dose corticosteroids, immunosuppressive drugs before organ transplantation, or cancer chemotherapy should have a screening examination for *S. stercoralis*. If infected, they should be treated before immunosuppression is initiated.



Fig. 341.2 Larvae of intestinal strongyloidiasis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 342

Lymphatic Filariasis (*Brugia malayi*, *Brugia timori*, and *Wuchereria bancrofti*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

The filarial worms *Brugia malayi* **(Malayan filariasis)**, *Brugia timori,* and *Wuchereria bancrofti* **(bancroftian filariasis)** are threadlike nematodes that cause similar infections. Infective larvae are introduced into humans during blood feeding by the **mosquito** vector. Over 4-6 months, the larval forms develop into sexually mature adult worms. Once an adequate number of male and female worms accumulate in the afferent lymphatic vessels, adult female worms release large numbers of microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when mosquitoes ingest microfilariae in a blood meal, which molt to form infective larvae over 10-14 days. Adult worms have a 5–7-year life span.

EPIDEMIOLOGY

More than 120 million people living in tropical Africa, Asia, and Latin America are infected; approximately 10–20% of these individuals have clinically significant morbidity attributable to filariasis. *W. bancrofti* is transmitted in Africa, Asia, and Latin America and accounts for 90% of lymphatic filariasis. *B. malayi* is restricted to the South Pacific and Southeast Asia, and *B. timori* is restricted to several islands of Indonesia. Travelers from nonendemic areas of the world who spend brief periods in endemic areas are rarely infected. Global programs have targeted elimination in >80% of endemic countries by 2030.

CLINICAL MANIFESTATIONS

The clinical manifestations of *B. malayi, B. timori,* and *W. bancrofti* infection are similar; manifestations of acute infection include transient, recurrent lymphadenitis and lymphangitis. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headaches, and myalgias that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms. Initial damage to lymphatic vessels may remain subclinical for years. The syndrome is most frequently observed in persons 10-20 years old. Manifestations of chronic lymphatic filariasis occur mostly in adults ≥30 years old and result from anatomic and functional obstruction to lymph flow. This obstruction results in lymphedema of the legs, arms, breasts, and/or genitalia. Male genital involvement, such as hydrocele, is very common in *W. bancrofti* infection, but uncommon in *Brugia* spp. infection. Chronic lymphedema predisposes affected extremities to bacterial superinfections, sclerosis, and verrucous skin changes, resulting in **elephantiasis**, which may involve one or more limbs, the breasts, or genitalia. It is uncommon for children to have overt signs of chronic filariasis.

Tropical Pulmonary Eosinophilia

The presence of microfilariae in the body has no apparent pathologic consequences except in persons with tropical pulmonary eosinophilia, a syndrome of filarial etiology in which microfilariae are found in the lungs and lymph nodes but not the bloodstream. It occurs only in individuals who have lived for years in endemic areas. Men 20-30 years old are most likely to be affected, although the syndrome occasionally occurs in children. The presentation includes paroxysmal nocturnal cough with dyspnea, fever, weight loss, and fatigue. Rales and rhonchi are found on auscultation of the chest. The x-ray findings may occasionally be normal, but increased bronchovascular markings, discrete opacities in the middle and basal regions of the lung, or diffuse miliary lesions are usually present (Fig. 342.1). Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Hepatosplenomegaly and generalized lymphadenopathy are often seen in children. The **diagnosis** is suggested by residence in a filarial endemic area, eosinophilia (>2,000/µL), compatible clinical symptoms, increased serum IgE (>1,000 IU/mL), and high titers of antimicrofilarial antibodies in the absence of microfilaremia. Although microfilariae may be found in sections of lung or lymph node, biopsy of these tissues is unwarranted in most situations. The clinical response to **diethylcarbamazine** (2 mg/kg/dose orally 3 times daily for 12-21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy. If symptoms recur, a second anthelmintic course should be administered. Patients with chronic symptoms are less likely to show improvement than those who have been ill for a short time.

DIAGNOSIS

Demonstration of microfilariae in the blood is the primary means for confirming the diagnosis of lymphatic filariasis. Because microfilaremia is **nocturnal** in most cases, blood samples should be obtained between 10 PM and 2 AM. Anticoagulated blood is passed through a Nuclepore filter that is stained and examined microscopically for microfilariae. Adult worms or microfilariae can be identified in tissue specimens obtained at biopsy. Infection with *W. bancrofti* in the absence of bloodborne microfilariae may be diagnosed by detection of parasite antigen in the serum. Adult worms in lymphatic vessels can be visualized by ultrasonography.

TREATMENT

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypotension, and even death may occur, especially with high microfilarial levels, the dose of **diethylcarbamazine** should be increased gradually (*children*: 1 mg/kg orally as a single dose on day 1,



Fig. 342.1 Chest radiograph of tropical pulmonary eosinophilia. Reticulonodular opacities are scattered throughout both lungs. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier, 2006. p. 3274.)*

1 mg/kg 3 times daily on day 2, 1-2 mg/kg 3 times daily on day 3, and 2 mg/kg 3 times daily on days 4-14; *adults*: 50 mg orally on day 1, 50 mg 3 times daily on day 2, 100 mg 3 times daily on day 3, and 2 mg/kg 3 times daily on days 4-14). For patients with no microfilaria in the blood, the full dose (2 mg/kg/day orally divided 3 times daily) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilaremia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine.

Global programs to control and ultimately eradicate lymphatic filariasis from endemic populations outside of sub-Saharan Africa currently recommend triple drug treatment with one or two annual doses of **diethylcarbamazine** (6 mg/kg orally once), **albendazole** (400 mg orally once), and **ivermectin** (150 µg/kg orally once) (mass drug administration). In co-endemic areas of filariasis and **onchocerciasis**, mass drug applications with single-dose ivermectin and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 343

Other Tissue Nematodes

Katherine R. Dobbs and Arlene E. Dent

ONCHOCERCIASIS (*ONCHOCERCA VOLVULUS*)

Infection with *Onchocerca volvulus* leads to onchocerciasis or **river blindness**. Onchocerciasis occurs primarily in West Africa but also in Central and East Africa and is the world's second leading infectious cause of blindness. There have been scattered foci in South America and Yemen. *O. volvulus* larvae are transmitted to humans by the bite of *Simulium* black flies that breed in fast-flowing streams. The larvae penetrate the skin and migrate through the connective tissue and eventually develop into adult worms that can be found tangled in fibrous tissue. Adult worms can live in the human body for up to 14 years. Female worms produce large numbers of microfilariae that migrate through the skin, connective tissue, and eye. Most infected individuals are asymptomatic. In heavily infected individuals, clinical manifestations are a result of localized host inflammatory reactions to dead or dying microfilariae and subcutaneous adult worms surrounded by a palpable fibrous capsule. Cutaneous and ocular reactions to microfilariae produce pruritic dermatitis, punctate keratitis, corneal pannus formation, and chorioretinitis. Adult worms in subcutaneous nodules are not painful and tend to occur over bony prominences of the hip. The **diagnosis** can be established by obtaining snips of skin covering the scapulae, iliac crests, buttocks, or calves. The snips are immersed in saline for several hours and examined microscopically for microfilariae that have emerged into the fluid. The diagnosis can also be established by demonstrating microfilariae in the cornea or anterior chamber on slit-lamp examination or finding adult worms on a nodule biopsy specimen. Ophthalmology consultation should be obtained before treatment of eye lesions.

A single dose of **ivermectin** (150 µg/kg orally) is the drug of choice and clears *O. volvulus* microfilariae from the skin for several months but has no effect on the adult worm. Treatment with ivermectin should be repeated every 6-12 months until the patient is asymptomatic or has no evidence of eye infection. Adverse effects of ivermectin therapy include fever, urticaria, and pruritus, which are more frequent in individuals not born in endemic areas who acquired the infection after periods of intense exposure, such as Peace Corps volunteers. Patients with concurrent high-density microfilaremia from loiasis may develop potentially fatal encephalopathy with ivermectin therapy. Treatment with ivermectin should be withheld until *Loa loa* microfilaremia can be reduced. **Moxidectin** is a promising new agent. Personal protection includes avoiding areas where biting flies are numerous, wearing protective clothing, and using insect repellent. Programs of mass treatment with ivermectin have been implemented in Africa and South America in an effort to reduce the prevalence of onchocerciasis.

The World Health Organization (WHO) set goals for onchocerciasis elimination by 2025 using mass drug administration with ivermectin. Elimination can be declared only after 3 years of posttreatment surveillance without microfilaria detection in skin biopsies.

Nodding syndrome, a form of epilepsy in African children living in focal areas of Uganda and South Sudan, was epidemiologically associated with onchocerciasis, but an etiologic link was not established. Recently, researchers identified neurotoxic autoantibodies that cross-react with *O. volvulus* proteins, which were found more frequently in people with nodding syndrome than in those in the same village without the syndrome. Nodding syndrome may be an autoimmune epileptic disorder triggered by *O. volvulus* infection.

LOIASIS (*LOA LOA*)

Loiasis is caused by infection with the tissue nematode *Loa loa*. The parasite is transmitted to humans by diurnally biting flies *(Chrysops)* that live in the rain forests of West and Central Africa. Migration of adult worms through skin, subcutaneous tissue, and subconjunctival area can lead to transient episodes of pruritus, erythema, and localized edema known as **Calabar swellings**, which are nonerythematous areas of subcutaneous edema 10-20 cm in diameter typically found around joints such as the wrist or the knee (Fig. 343.1). They resolve over several days to weeks and may recur at the same or different sites. Lifelong residents of *L. loa*–endemic regions may have microfilaremia and eosinophilia but are often asymptomatic. In contrast, travelers to endemic regions may have a hyperreactive response to *L. loa* infection characterized by frequent recurrences of swelling, high level eosinophilia, debilitation, and serious complications such as glomerulonephritis and encephalitis. **Diagnosis** is usually established on clinical grounds, often assisted by the infected individual reporting a worm being seen crossing the conjunctivae. Microfilariae may be detected in blood smears collected between 10 AM and 2 PM. Adult worms should be surgically excised when possible.

Diethylcarbamazine is the treatment of choice for loiasis, as there is evidence that it kills both microfilariae and adult worms and results in a sustained decrease in microfilarial intensity after treatment. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur, especially



Fig. 343.1 Calabar swelling of the right hand. *(From Guerrant RL, Walker DH, Weller PF, et al. Tropical Infectious Diseases. Philadelphia: Churchill Livingstone, 2006: p. 1165.)*

with high microfilaria levels, the dose of diethylcarbamazine should be increased gradually in such cases (*children*: 1 mg/kg orally on day 1, 1 mg/kg three times daily on day 2, 1-2 mg/kg three times daily on day 3, 3 mg/kg three times daily on days 4-21; *adults*: 50 mg orally on day 1, 50 mg three times daily on day 2, 100 mg three times daily on day 3, 3 mg/kg three times daily on days 4-21). Full doses can be instituted on day 1 in persons without microfilaremia (3 mg/kg orally times daily for 21 days). A 3-week course of **albendazole** can also be used to slowly reduce *L. loa* microfilarial levels as a result of embryotoxic effects on the adult worms. Antihistamines or corticosteroids may be used to limit allergic reactions secondary to killing of microfilariae. Personal protective measures include avoiding areas where biting flies are present, wearing protective clothing, and using insect repellents. Diethylcarbamazine (300 mg orally once weekly) prevents infection in travelers who spend prolonged periods in endemic areas. *L. loa* do not harbor *Wolbachia* endosymbionts, and therefore doxycycline has no effect on infection.

INFECTION WITH ANIMAL FILARIAE

The most commonly recognized zoonotic filarial infections are caused by members of the genus *Dirofilaria*. The worms are introduced into humans by the bites of mosquitoes containing third-stage larvae. The most common filarial zoonosis in the United States is *Dirofilaria tenuis,* a parasite of raccoons. In Europe, Africa, and Southeast Asia, infections are usually caused by the dog parasite *Dirofilaria repens.* The **dog heartworm**, *Dirofilaria immitis,* is the second most frequently encountered filarial zoonosis worldwide. Other genera, including *Dipetalonema*-like worms, *Onchocerca,* and *Brugia,* are rare causes of zoonotic filarial infections.

Animal filariae do not undergo normal development in the human host. The clinical manifestations and pathologic findings correspond to the anatomic site of infection and can be categorized into four major groups: subcutaneous, lung, eye, and lymphatic. Pathologic examination of affected tissue reveals a localized foreign body reaction around a dead or dying parasite. The lesion consists of granulomas with eosinophils, neutrophils, and tissue necrosis. *D. tenuis* does not leave the subcutaneous tissues, whereas *Brugia beaveri* eventually localizes to superficial lymph nodes. Infections may be present for up to several months. *D. immitis* larvae migrate for several months in subcutaneous tissues and most frequently result in a well-circumscribed, coinlike lesion in a single lobe of the lung. The chest radiograph typically reveals a solitary pulmonary nodule 1-3 cm in diameter. Definitive **diagnosis** and cure depend on surgical excision and identification of the nematode within the surrounding granulomatous response. *D. tenuis* and *B. beaveri* infections present as painful, rubbery, 1-5 cm nodules in the skin of the trunk, of the extremities, and around the orbit. Patients often report having been engaged in activities predisposing to exposure to infected mosquitoes, such as working or hunting in swampy areas. Management is by **surgical excision**.

ANGIOSTRONGYLUS CANTONENSIS

Angiostrongylus cantonensis, the **rat lungworm,** is the most common cause of **eosinophilic meningitis** worldwide. Rats are the definitive host. Human infection follows ingestion of third-stage larvae in raw or undercooked intermediate hosts such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and fish. Most cases are sporadic, but clusters have been reported, including clusters related to consumption of lettuce contaminated with intermediate or transport hosts. Even though most infections have been described in Southeast Asia, the South Pacific, and Taiwan, shipboard travel of infected rats has spread the parasite to Madagascar, Africa, the Caribbean, and most recently Australia and North America. Larvae penetrate the vasculature of the intestinal tract and migrate to the meninges, where they usually die but induce eosinophilic aseptic meningitis. Patients present 2-35 days after ingestion of larvae with severe headache, neck pain or nuchal rigidity, hyperesthesias and paresthesias (often migrating), fatigue, fever, rash, pruritus, nausea, and vomiting. Neurologic involvement varies from asymptomatic to paresthesias, severe pain, weakness, and focal neurologic findings such as cranial nerve palsies. Symptoms can last for several weeks to months, especially headache. Coma and death from hydrocephalus occur rarely in heavy infections. Peripheral blood eosinophilia is not always present on initial examination but peaks about 5 weeks after exposure, often when symptoms are improving. Cerebrospinal fluid (CSF) analysis reveals pleocytosis with >10% eosinophils in more than half of patients, with mildly elevated protein, a normal glucose level, and an elevated opening pressure. Head CT or MRI is usually unremarkable. The **diagnosis** is established clinically with supporting travel and diet history. A sensitive and specific enzyme-linked immunosorbent assay (ELISA) is available on a limited basis from the Centers for Disease Control and Prevention (CDC) for testing CSF or serum.

Treatment is primarily supportive because the majority of infections are mild, and most patients recover within 2 months without neurologic sequelae. Analgesics should be given for headache. Careful, repeated lumbar punctures should be performed to relieve hydrocephalus. Anthelmintic drugs have not been shown to influence the outcome and may exacerbate neurologic symptoms. The use of corticosteroids may shorten the duration of persistent and severe headaches. There is a higher incidence of permanent neurologic sequelae and mortality among children than among adults. Infection can be avoided by not eating raw or undercooked crabs, prawns, or snails.

ANGIOSTRONGYLUS COSTARICENSIS

Angiostrongylus costaricensis is a nematode that infects several species of rodents and causes abdominal **angiostrongyliasis**, which has been described predominantly in Latin America and the Caribbean. The mode of transmission to humans, who are accidental hosts, is unknown. It is speculated that infectious larvae from a molluscan intermediate host, such as the slug *Vaginulus plebeius,* contaminate water or vegetation that is inadvertently consumed (chopped up in salads or on vegetation contaminated with the slug's mucous secretions). Although this slug is not indigenous to the continental United States, it has been found on imported flowers and produce. The incubation period for abdominal angiostrongyliasis is unknown, but limited data suggest that it ranges from 2 weeks to several months after ingestion of larvae. Third-stage larvae migrate from the gastrointestinal tract to the mesenteric arteries, where they mature into adults. These eggs degenerate and elicit an eosinophilic granulomatous reaction. The clinical findings of abdominal angiostrongyliasis mimic **appendicitis,** although the former is typically more indolent. Children can have fever, right lower quadrant pain, a tumor-like mass, abdominal rigidity, and a painful rectal examination. Most patients have leukocytosis with eosinophilia. Radiologic examination may show bowel wall edema, spasticity, or filling defects in the ileocecal region and the ascending colon. Examination of stool for ova and parasites is not useful for *A. costaricensis* but is useful for evaluating the presence of other intestinal parasites. An

ELISA is available for **diagnosis** on a limited basis from the CDC, but the test has a low specificity and is known to cross react with *Toxocara, Strongyloides,* and *Paragonimus.*

Many patients undergo laparotomy for suspected appendicitis and are found to have a mass in the terminal ileum to the ascending colon. *No specific treatment is known for abdominal angiostrongyliasis.* Even though the use of anthelmintic therapy has not been studied systematically, thiabendazole or diethylcarbamazine has been suggested. The prognosis is generally good. Most cases are self-limited, although surgery may be required in some patients. Cornerstones of **prevention** include avoidance of slugs and not ingesting raw food and water that may be contaminated with imperceptible slugs or slime from slugs. Rat control is also important in preventing the spread of infection.

DRACUNCULIASIS *(DRACUNCULUS MEDINENSIS)*

Dracunculiasis is caused by the guinea worm, *Dracunculus medinensis.* WHO has targeted dracunculiasis for eradication in 2030. Eradication efforts have been hampered by conflicts as well as increasing rates of infections in animals such as dogs. As of 2021, transmission of the infection was occurring in Chad, Ethiopia, Mali, South Sudan, Angola, and Cameroon. Humans become infected by drinking contaminated stagnant water that contains immature forms of the parasite in the gut of tiny crustaceans (copepods or water fleas). Larvae are released in the stomach, penetrate the mucosa, mature, and mate. Approximately 1 year later, the adult female worm (1-2 mm in diameter and up to 1 m long) migrates and partially emerges through the human host skin, usually of the legs. Thousands of immature larvae are released when the affected body part is immersed in the water. The cycle is completed when larval forms are ingested by the crustaceans. Infected humans have no symptoms until the worm reaches the subcutaneous tissue, causing a **stinging papule** that may be accompanied by urticaria, nausea, vomiting, diarrhea, and dyspnea. The lesion vesiculates, ruptures, and forms a painful ulcer in which a portion of the worm is visible. **Diagnosis** is established clinically. Larvae can be identified by microscopic examination of the discharge fluid.

Metronidazole (25 mg/kg/day orally divided into three doses for 10 days; maximum dose: 750 mg) decreases local inflammation. Although the drug does not kill the worm, it facilitates its removal. The worm must be physically removed by rolling the slowly emerging 1 m–long parasite onto a thin stick over a week. Topical corticosteroids shorten the time to complete healing, while topical antibiotics decrease the risk of secondary bacterial infection. Dracunculiasis can be prevented by boiling or chlorinating drinking water or passing the water through a cloth sieve before consumption. Eradication is dependent on behavior modification and education.

GNATHOSTOMA SPINIGERUM

Gnathostoma spinigerum is a dog and cat nematode endemic to Southeast Asia, Japan, China, Bangladesh, and India, but it has been sporadically reported in numerous countries worldwide. Infection is acquired by ingesting intermediate hosts containing larvae of the parasite, such as raw or undercooked freshwater fish, chickens, pigs, snails, or frogs. Penetration of the skin by larval forms and prenatal transmission has also been described. Nonspecific signs and symptoms such as generalized malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain develop 24-48 hours after ingestion of *G. spinigerum.* Ingested larvae penetrate the gastric wall and migrate through soft tissue for up to 10 years. Moderate to severe eosinophilia can develop. Cutaneous **gnathostomiasis** manifests as intermittent episodes of localized, migratory nonpitting edema associated with pain, pruritus, or erythema. Central nervous system involvement in gnathostomiasis is suggested by focal neurologic findings, initially neuralgia followed within a few days by paralysis or changes in mental status. Multiple cranial nerves may be involved, and CSF may be xanthochromic but typically shows an eosinophilic pleocytosis. **Diagnosis** of gnathostomiasis is based on clinical presentation and epidemiologic background. Brain and spinal cord lesions may be seen on CT or MRI. Serologic testing varies in sensitivity and specificity and is available through the CDC.

There is no well-documented effective chemotherapy, although **albendazole** (400 mg orally twice daily for 21 days) as first-line therapy or **ivermectin** (200 μg/kg for 2 days) as an alternative is recommended without or with surgical removal. Multiple courses may be needed. Corticosteroids have been used to relieve focal neurologic deficits. **Surgical resection** of the *Gnathostoma* is the major mode of therapy and the treatment of choice. Blind surgical resection of subcutaneous areas of diffuse swelling is not recommended because the worm can rarely be located. **Prevention** through the avoidance of ingestion of poorly cooked or raw fish, poultry, or pork should be emphasized for individuals living in or visiting endemic areas.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 344

Toxocariasis (Visceral and Ocular Larva Migrans)

Katherine R. Dobbs and Arlene E. Dent

Most cases of human toxocariasis are caused by the **dog roundworm**, *Toxocara canis.* Adult female *T. canis* worms live in the intestinal tracts of young puppies and their lactating mothers. Large numbers of eggs are passed in the feces of dogs and embryonate under optimal soil conditions. *Toxocara* eggs can survive relatively harsh environmental conditions and are resistant to freezing and extremes of moisture and pH. Humans ingest embryonated eggs contaminating soil, hands, or fomites. The larvae hatch and penetrate the intestinal wall and travel via the circulation to the liver, lung, and other tissues. Humans do not excrete *T. canis* eggs because the larvae are unable to complete their maturation to adult worms in the intestine. The **cat roundworm**, *Toxocara cati,* is responsible for far fewer cases of **visceral larva migrans (VLM)** than *T. canis.* Ingestion of infective larvae of the raccoon ascarid *Baylisascaris procyonis* rarely leads to VLM but can cause **neural larva migrans**, resulting in fatal eosinophilic meningitis. Ingestion of larvae from the opossum ascarid *Lagochilascaris minor* leads to VLM rarely.

EPIDEMIOLOGY

Human *T. canis* infections have been reported in almost all parts of the world, primarily in temperate and tropical areas where dogs are popular household pets. Young children are at highest risk because of their unsanitary play habits and tendency to place fingers in the mouth. Other behavioral risk factors include **pica**, contact with puppy litters, and institutionalization. In North America, the highest prevalence of infection is in the southeastern United States and Puerto Rico, particularly among socially disadvantaged Black and Hispanic children. In the United States, serosurveys show that 3–3.9% of children are infected. Assuming an unrestrained and untreated dog population, toxocariasis is prevalent in settings where other **geohelminth infections**, such as ascariasis, trichuriasis, and hookworm infections, are common.

PATHOGENESIS

T. canis larvae secrete large amounts of immunogenic glycosylated proteins. These antigens induce immune responses that lead to eosinophilia and polyclonal and antigen-specific immunoglobulin E production. The characteristic histopathologic lesions are granulomas containing eosinophils, multinucleated giant cells (histiocytes), and collagen. Granulomas are typically found in the liver but may also

Table 344.1 Clinical Syndromes of Human Toxocariasis

SYNDROME	CLINICAL FINDINGS	AVERAGE AGE	INFECTIOUS DOSE	INCUBATION PERIOD	LABORATORY FINDINGS	ELISA
Visceral larva migrans	Fevers, hepatomegaly, asthma	5 yr	Moderate to high	Weeks to months	Eosinophilia, leukocytosis, elevated IgE	High (≥1:16)
Ocular larva migrans	Visual disturbances, retinal granulomas, endophthalmitis, peripheral granulomas	12 yr	Low	Months to years	Usually none	Low
Covert toxocariasis	Abdominal pain, gastrointestinal symptoms, weakness, hepatomegaly, pruritus, rash	School-age to adult	Low to moderate	Weeks to years	± Eosinophilia ± Elevated IgE	Low to moderate

ELISA, Enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ±, with or without.
Adapted from Glickman LT, Schantz PM. Epidemiology and pathogenesis of zoonotic toxocariasis. *Epidemiol Rev.* 1981;3:230–250.

occur in the lungs, central nervous system (CNS), and ocular tissues. Clinical manifestations reflect the intensity and chronicity of infection, anatomic localization of larvae, and host granulomatous responses.

CLINICAL MANIFESTATIONS

Three major clinical syndromes are associated with human toxocariasis: VLM, **ocular larva migrans (OLM)**, and **covert toxocariasis** (Table 344.1). The classic presentation of VLM includes eosinophilia, fever, and hepatomegaly and occurs most often in toddlers with a history of pica and exposure to puppies. The findings include fever, cough, wheezing, bronchopneumonia, anemia, hepatomegaly, leukocytosis, eosinophilia, and positive *Toxocara* serology. Cutaneous manifestations such as pruritus, eczema, and urticaria can be present. OLM tends to occur in older children without signs or symptoms of VLM. Presenting symptoms include unilateral visual loss, eye pain, white pupil, or strabismus that develops over weeks. Granulomas occur on the posterior pole of the retina and may be mistaken for retinoblastoma. Serologic testing for *Toxocara* has allowed the identification of individuals with less obvious or covert symptoms of infection. These children may have nonspecific complaints that do not constitute a recognizable syndrome. Common findings include hepatomegaly, abdominal pain, cough, sleep disturbance, failure to thrive, and headache with elevated *Toxocara* antibody titers. Eosinophilia may be present in 50–75% of cases. The prevalence of positive *Toxocara* serology in the general population supports that most children with *T. canis* infection are asymptomatic and will not develop overt clinical sequelae over time. A correlation between positive *Toxocara* serology and allergic asthma has also been described.

DIAGNOSIS

A presumptive diagnosis of toxocariasis can be established in a young child with **eosinophilia** (>20%), leukocytosis, hepatomegaly, fevers, wheezing, and a history of geophagia and exposure to puppies or unrestrained dogs. Supportive laboratory findings include hypergammaglobulinemia and elevated isohemagglutinin titers to A and B blood group antigens. Most patients with VLM have an absolute eosinophil count >500/μL. Eosinophilia is less common in patients with OLM. Biopsy confirms the diagnosis. When biopsies cannot be obtained, an enzyme-linked immunosorbent assay using excretory-secretory proteins harvested from *T. canis* larvae maintained in vitro is the standard serologic test used to confirm toxocariasis. A titer of 1:32 is associated with a sensitivity of approximately 78% and a specificity of approximately 92%. The sensitivity for OLM is significantly less. The diagnosis of OLM can be established in patients with typical clinical findings of a retinal or peripheral pole granuloma or endophthalmitis with elevated antibody titers. Vitreous and aqueous humor fluid anti-*Toxocara* titers are usually greater than serum titers. The diagnosis of covert toxocariasis should be considered in individuals with chronic weakness, abdominal pain, or allergic signs with eosinophilia and increased IgE. In temperate regions of the world, nonparasitic causes of eosinophilia that should be considered in the differential diagnosis include allergies, drug hypersensitivity, lymphoma, vasculitis, and idiopathic hypereosinophilic syndrome (see Chapter 169).

TREATMENT

Most patients do not require treatment because signs and symptoms are mild and subside over weeks to months. Several anthelmintic drugs have been used for symptomatic cases, often with adjunctive corticosteroids to limit inflammatory responses that presumably result from release of *Toxocara* antigens by dying parasites. **Albendazole** (400 mg orally twice daily for 5 days for all ages) has demonstrated efficacy in both children and adults. **Mebendazole** (100-200 mg PO twice daily for 5 days for all ages) is also useful. Anthelmintic treatment of CNS and ocular disease should be extended (3-4 weeks). Even with no clinical trials on OLM therapy, a course of oral corticosteroids such as **prednisone** (1 mg/kg/day PO for 2-4 weeks) has been recommended to suppress local inflammation while treatment with anthelmintic agents is initiated.

PREVENTION

Transmission can be minimized by public health measures that prevent dog feces from contaminating the environment. These include keeping dogs on leashes and excluding pets from playgrounds and sandboxes that toddlers use. Children should be discouraged from putting dirty fingers in their mouth and eating dirt. Vinyl covering of sandboxes reduces the viability of *T. canis* eggs. Widespread veterinary use of broad-spectrum anthelmintics effective against *Toxocara* may lead to a decline in parasite transmission to humans.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 345

Trichinellosis (*Trichinella spiralis*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Human trichinellosis (also called **trichinosis**) is caused by consumption of meat containing encysted larvae of *Trichinella spiralis,* a tissue-dwelling nematode with a worldwide distribution. After ingestion of raw or inadequately cooked meat from pigs (or other commercial meat sources such as horses) containing viable *Trichinella* larvae, the organisms are released from the cyst by acid-pepsin digestion of the cyst walls in the stomach and then pass into the small intestine. The larvae invade the small intestine columnar epithelium at the villi base and develop into adult worms. The adult female worm produces about 500 larvae over 2 weeks and is then expelled in the feces. The larvae enter the bloodstream and seed striated muscle by burrowing into individual muscle fibers. Over a period of 3 weeks, they coil as they increase about 10 times in length and become capable of infecting a new host if ingested. The larvae eventually become encysted and can remain viable for years. **Sylvatic** *Trichinella* spp. (*T. britovi, T. nativa, T. pseudospiralis,* and *T. murrelli*) are present in traditional native foods, such as walrus meat, and **game meat** may also cause disease similar to that caused by *T. spiralis*.

EPIDEMIOLOGY

Despite public health efforts to control trichinellosis by eliminating the practice of feeding garbage to domestic swine, epidemics and isolated cases of *Trichinella* spp. infection continue to be a health problem in many areas of the world. It is most common in Asia, Latin America, and Central Europe. Swine fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. Prevalence rates of *T. spiralis* in domestic swine range from 0.001% in the United States to ≥25% in China. The resurgence of this disease can be attributed to translocations of animal populations, human travel, and export of food as well as ingestion of sylvatic *Trichinella* through game meat. In the United States from 2008 to 2012, wild game meat (especially bear or wild boar meat) was the most common source of infection. Most outbreaks occur from the consumption of *T. spiralis*–infected pork (or horse meat in areas of the world where horse is eaten) obtained from a single source.

PATHOGENESIS

During the first 2-3 weeks after infection, pathologic reactions to infection are limited to the gastrointestinal (GI) tract and include a mild, partial villous atrophy with an inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Larvae are released by female worms and disseminate over the next several weeks. Skeletal muscle fibers show the most striking changes with edema and basophilic degeneration. The muscle fiber may contain the typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate.

CLINICAL MANIFESTATIONS

The development of symptoms depends on the number of viable larvae ingested. Most infections are asymptomatic or mild, and children often show milder symptoms than adults who consumed the same amount of infected meat. Watery diarrhea is the most common symptom corresponding to maturation of the adult worms in the GI tract, which occurs during the first 1-2 weeks after ingestion. Patients may also complain of abdominal discomfort and vomiting. Fulminant **enteritis** may develop in individuals with extremely high worm burdens. The classic symptoms of facial and periorbital edema, fever, weakness, malaise, and myalgia peak approximately 2-3 weeks after the infected meat is ingested, as the larvae migrate and then encyst in the muscle. Headache, cough, dyspnea, dysphagia, subconjunctival and splinter hemorrhages, and a macular or petechial rash may occur. Patients with high-intensity infection may die from myocarditis, encephalitis, or pneumonia. In symptomatic patients, **eosinophilia** is common and may be dramatic.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) diagnostic criteria for trichinellosis require positive serology or muscle biopsy for *Trichinella* with one or more compatible clinical symptoms (eosinophilia, fever, myalgia, facial or periorbital edema). To declare a discrete outbreak, at least one person must have positive serology or muscle biopsy. Antibodies to *Trichinella* are detectable approximately 3 weeks after infection. Severe muscle involvement results in elevated serum creatine phosphokinase and lactic dehydrogenase levels. Muscle biopsy is not usually necessary, but if needed, a sample should be obtained from a tender swollen muscle. A history of eating undercooked meat supports the diagnosis. The cysts may calcify and may be visible on radiograph.

TREATMENT

Recommended treatment of trichinellosis diagnosed at the GI phase is **albendazole** (400 mg orally twice daily for 8-14 days for all ages) to eradicate the adult worms if a patient has ingested contaminated meat within the previous 1 week. An alternative regimen is mebendazole (200-400 mg PO 3 times daily for 3 days followed by 400-500 mg 3 times daily for 10 days). There is no consensus for treatment of muscle-stage trichinellosis. Corticosteroids may be used, although evidence for efficacy is anecdotal.

PREVENTION

Trichinella larvae can be killed by cooking meat (≥55°C [131°F]) until there is no trace of pink fluid or flesh, or by storage in a freezer (−15°C [5°F]) for ≥3 wk. Freezing to kill larvae should only be applied to pork meat, because larvae in horse, wild boar, or game meat can remain viable even after 4 weeks of freezing. Smoking, salting, and drying meat are unreliable methods of killing *Trichinella.* Strict adherence to public health measures, including garbage feeding regulations, stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses, constructing barriers between livestock, wild animals, and domestic pets, and proper handling of wild animal carcasses by hunters, can reduce infection with *Trichinella.* Current meat inspection for trichinellosis is by direct digestion and visualization of encysted larvae in meat samples. Serologic testing does not have a role in meat inspection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 346

Schistosomiasis *(Schistosoma)*

Amaya L. Bustinduy, Sophie Pach, and Katja Doerholt

The term **schistosomiasis** (also known as **bilharzia**) encompasses the acute and chronic inflammatory disorders caused by human infection with *Schistosoma* spp. parasites. Disease is related to both the systemic and the focal effects of schistosome infection and its consequent host immune responses triggered by parasite eggs deposited in the tissues. For the affected individuals, this frequently manifests as disabling chronic morbidity.

ETIOLOGY

Schistosoma organisms are trematodes, or **flukes**, that parasitize the bloodstream. Five schistosome species are known to infect humans: *Schistosoma haematobium, S. mansoni, S. japonicum, S. intercalatum,* and *S. mekongi*. Humans are infected through contact with water contaminated with *cercariae*, the free-living infective stage of the parasite. These motile, forked-tail organisms emerge from infected snails and are capable of penetrating intact human skin. As they reach maturity, adult worms migrate to specific anatomic sites characteristic of each schistosome species: *S. haematobium* adults are found in the perivesical and periureteral venous plexus, *S. mansoni* in the inferior mesenteric veins, and *S. japonicum* in the superior mesenteric veins. The less common *S. intercalatum* and *S. mekongi* are usually found in the mesenteric vessels. Adult schistosome worms (1-2 cm long) are clearly adapted for an intravascular existence. The female accompanies the male in a groove formed by the lateral edges of its body. On fertilization, female worms begin oviposition in the small venous tributaries. The eggs of the three main schistosome species have characteristic morphologic features: *S. haematobium* has a terminal spine, *S. mansoni* has a lateral spine, and *S. japonicum* has a smaller size with a short, curved spine (Fig. 346.1). Parasite eggs provoke a significant granulomatous inflammatory response that allows them to ulcerate through host tissues to reach the lumen of the urinary tract or the intestines. They are carried to the outside environment in urine or feces (depending on the species), where they will hatch if deposited in freshwater. Motile miracidia emerge, infect specific freshwater snail intermediate hosts, and divide asexually. After 4-12 weeks, the infective cercariae are released by the snails into the contaminated water.

EPIDEMIOLOGY

Schistosomiasis affects more than 300 million people worldwide with more than 700 million people at risk, primarily children and young adults. There are 1.8 million disability-adjusted life-years (DALYs) attributed to schistosomiasis, making it the second most disabling parasitic disease after malaria. Prevalence is increasing in many areas as population density increases and new irrigation projects provide broader habitats for the intermediate **snail** hosts. Humans are the main definitive hosts for the five clinically important species of schistosomes, although *S. japonicum* is also a zoonosis, infecting animals such as dogs, rats, pigs, and cattle. *S. haematobium* is prevalent in Africa and the Middle East with cases reported in the Mediterranean (Corsica in France); *S. mansoni* is prevalent in Africa, the Middle East, the Caribbean, and South America; and *S. japonicum* is prevalent in China, the Philippines, and Indonesia, with some sporadic foci in parts of Southeast Asia. The other two species are less prevalent. *S. intercalatum* is found in West and Central Africa, and *S. mekongi* is found only along the upper Mekong River in Asia.

Transmission depends on water contamination by human excreta (urine and stool), the presence of specific intermediate snail hosts, and the patterns of water contact and social habits of the population (Fig. 346.2). The distribution of infection in endemic areas shows that prevalence increases with age, to a peak at 10-20 years old. Exposure to infected water starts early in life for children living in endemic areas. Passive water contact by infants (accompanying mothers in their daily household activities) evolves to more active water contact as preschool and school-age children pursue recreational activities such as swimming and wading.

Measuring intensity of infection (by quantitative egg count in urine or feces) demonstrates that the heaviest worm loads are found in school-age and adolescent children. Even though schistosomiasis is most prevalent and most severe in older children and young adults, who are at maximal risk for suffering from its acute and chronic sequelae, preschool children can also exhibit significant disease manifestations.

PATHOGENESIS

Both early and late manifestations of schistosomiasis are immunologically mediated. *Acute* schistosomiasis, known as **snail fever** or **Katayama syndrome**, is a febrile illness that represents an immune complex disease associated with early infection and oviposition 4-8 weeks after cercarial skin penetration. The major pathology of infection occurs later, with *chronic* schistosomiasis, in which retention of eggs in the host tissues is associated with chronic granulomatous injury. Eggs may be trapped at sites of deposition (urinary bladder, ureters, cervix, intestine) or may be carried by the bloodstream to ectopic sites, most frequently the liver and less often the lungs and central nervous system (CNS). The host response to these eggs involves local as well as systemic manifestations. The cell-mediated immune response leads to granulomas composed of lymphocytes, macrophages, and eosinophils that surround the entrapped eggs and add significantly to the degree of tissue destruction. Granuloma formation in the bladder wall and at the ureterovesical junction results in the major disease manifestations of *S. haematobium* infection: hematuria, dysuria, and obstructive uropathy. Granulomata in the genital tissues also contributes to reproductive organ obstruction and local inflammation. Intestinal as well as hepatic granulomas underlie the pathologic sequelae of the other schistosome infections: ulcerations and fibrosis of intestinal wall, hepatosplenomegaly, and portal hypertension caused by presinusoidal obstruction of blood flow. In terms of systemic disease, antischistosome inflammation increases circulating levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, associated with elevated levels of C-reactive protein. These responses are associated with hepcidin-mediated inhibition of iron uptake and use, leading to anemia of chronic inflammation. Schistosomiasis-related undernutrition and decreased cognition may be the result of similar pathways of chronic inflammation. Acquired partial protective immunity against schistosomiasis has been demonstrated in some animal species and may occur in humans.

CLINICAL MANIFESTATIONS

Two main chronic clinical syndromes arise from *Schistosoma* spp. infection: **urogenital schistosomiasis** caused by *S. haematobium* and **intestinal schistosomiasis** caused by *S. mansoni* or *S. japonicum*. Most chronically infected individuals experience mild symptoms and may not seek medical attention; the more severe symptoms of schistosomiasis occur mainly in those who are heavily infected or who have been infected over longer periods. In addition to organ-specific morbidities, infected patients frequently demonstrate anemia (often complicated by malaria in endemic regions), chronic pain, diarrhea, exercise intolerance, and chronic undernutrition manifesting as growth stunting. Cercarial penetration of human skin may result in a pruritic papular rash known as **schistosomal dermatitis** or **swimmer's itch**. Skin manifestations are more pronounced in previously exposed individuals and are characterized by edema and intense cellular infiltrates in the dermis and epidermis.

Acute schistosomiasis (Katayama syndrome) may occur 4-8 weeks after exposure and is most commonly seen in *S. japonicum* endemic

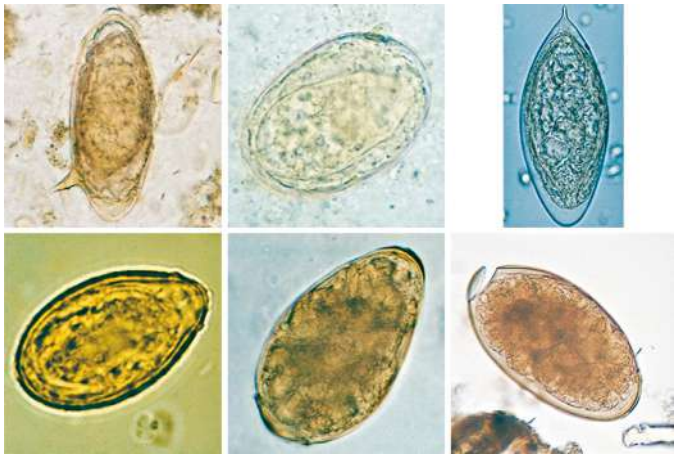

Fig. 346.1 Eggs of common human trematodes. Clockwise from upper left: *Schistosoma mansoni, S. japonicum, S. haematobium, Clonorchis sinensis, Paragonimus westermani,* and *Fasciola hepatica* (note the partially open operculum). *(From Centers for Disease Control and Prevention. DPDx: laboratory identification of parasites of public health concern.* http://www.cdc.gov/dpdx/az.html*)*

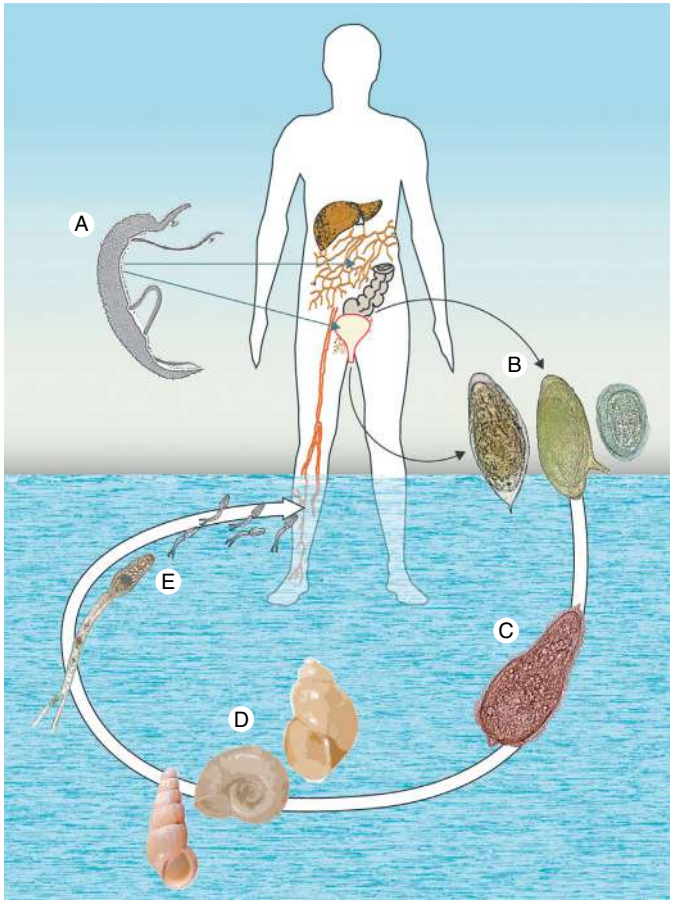

Fig. 346.2 Life cycle of *Schistosoma mansoni, S. haematobium,* and *S. japonicum*. *A,* Paired adult worms (larger male enfolding slender female). *B,* Eggs (left to right, *S. haematobium, S. mansoni, S. japonicum). C,* Ciliated miracidium. *D,* Intermediate host snails (left to right, *Oncomelania, Biomphalaria, Bulinus). E,* Cercariae. *(From Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014;383:2253–2264. Fig 1.)*

areas, though it can occur with all species. This is a serum sickness–like syndrome manifested by the acute onset of fever, cough, chills, sweating, abdominal pain, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Acute schistosomiasis typically presents in first-time visitors to endemic areas who experience primary infection at an older age.

Chronic schistosomiasis occurs after granuloma formation in the organs where eggs have entrapped. In urogenital schistosomiasis, caused by *S. haematobium*, symptomatic children usually complain of frequency, dysuria, and macro- and micro-hematuria. Urine examination shows erythrocytes, parasite eggs, and occasional eosinophiluria. In endemic areas, moderate to severe pathologic lesions have been demonstrated in the urinary tract of >20% of infected children. The extent of disease correlates with the intensity of infection, but significant morbidity can occur even in lightly infected children, including children under 5 years of age. The advanced stages of urogenital schistosomiasis are associated with chronic renal failure, secondary infections, and squamous cell carcinoma of the bladder.

An important complication of *S. haematobium* infection to consider, particularly in adolescent females, is **female genital schistosomiasis (FGS)**. Eggs migrate from the vesical plexus to lodge in the female genital tract, where they induce a granulomatous inflammatory response that can manifest as contact bleeding, pain after sex, ectopic pregnancies, and infertility. Symptoms start before sexual debut and get later confused with those of sexually transmitted infections. There is a threefold to fourfold greater risk of HIV transmission. Pathognomonic lesions can be visualized in the cervix by colposcopy. **Male genital schistosomiasis (MGS)** can present in adolescent males with hematospermia, pain, erectile dysfunction, and infertility and is likely to contribute to increased male-to-female HIV transmission.

Children with **chronic intestinal schistosomiasis** due to *S. mansoni, S. japonicum,* and, less commonly, *S. intercalatum* or *S. mekongi* can present with intestinal symptoms; colicky abdominal pain and bloody diarrhea are the most common. However, the intestinal phase may remain subclinical, and the late syndrome of hepatosplenomegaly, portal hypertension, ascites, and hematemesis may then be the first clinical presentation in later years. Liver disease is caused by granuloma formation and subsequent **periportal fibrosis**; no appreciable liver cell injury occurs, and hepatic function may be preserved for a long time. Schistosome eggs can escape into the lungs, causing **pulmonary hypertension** and cor pulmonale. *S. japonicum* worms may migrate to the brain vasculature and produce localized lesions that cause seizures. **Transverse myelitis**, spinal compression, and other CNS involvement (meningoencephalitis) are rare but well-known complications in children or young adults with either acute or chronic *S. haematobium* or *S. mansoni* infection.

Although end-organ scarring is pathognomonic, affected children may also have persistent long-term systemic effects of infection, including poor growth, anemia, decreased aerobic capacity, and cognitive impairment and poor school performance.

DIAGNOSIS

Parasitologic diagnosis entails finding schistosome eggs in the excreta of infected individuals; quantitative methods should be used to provide an indication of the burden of infection. For the diagnosis of *S. haematobium* infection, a volume of 10 mL of urine should be collected around midday, the time of maximal egg excretion, and filtered for microscopic examination. Stool examination by the Kato-Katz thick smear procedure and detection of parasite antigen in patient serum or urine are the methods of choice for diagnosis and quantification of other schistosome infections (*S. mansoni* and *S. japonicum*). More sensitive **antigenic diagnosis** includes the unique schistosome antigens in urine or plasma: *circulating anodic antigen* (CAA), which is not yet commercially available, and *circulating cathodic antigen* (CCA) from stool for the detection only of *S. mansoni* and *S. japonicum*.

Morbidity diagnosis can be ascertained by abdominal ultrasonography; in urogenital schistosomiasis, by the detection of **bladder polyps** and derived renal complications, and in intestinal schistosomiasis, by the detection of **periportal fibrosis** in the liver. **Colposcopy** and **semen** analysis are useful in adolescent children suspected of having FGS and MGS.

TREATMENT

Treatment of children with schistosomiasis should be based on an appreciation of the intensity of infection and the extent of disease. The World Health Organization (WHO)–recommended treatment for schistosomiasis is **praziquantel.** For infection due to *S. mansoni, S. haematobium*, or *S. intercalatum*, the dose of praziquantel is 40 mg/kg/day PO divided into two doses for 1 day. For infection due to *S. japonicum* or *S. mekongi*, the dose of praziquantel is 60 mg/kg/day PO divided into three doses for 1 day. A second treatment 4-6 weeks after the first course is advised by some experts, allowing for maturation of immature forms not cleared initially. Praziquantel is well tolerated but can give side effects that correlate with intensity of infection, including abdominal pain and cramps, sweating, and somnolence. Pregnant and lactating women with schistosomiasis can safely be treated with praziquantel at usual doses starting at the second trimester of pregnancy.

PREVENTION

Transmission in endemic areas may be decreased by reducing the parasite load in the human population. WHO recommends praziquantel to be given as a single dose to school-age children through mass drug administration programs once or twice a year depending on parasite endemicity levels. Recently, preschool children 2 years and older have also been included in control strategies. When added to national drug-based control programs, other measures such as improved sanitation, antiparasitic treatment given at well child visits, focal application of molluscicidals, and animal vaccination may prove useful in breaking the cycle of transmission. Ultimately, control of schistosomiasis is closely linked to economic and social development.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 347

Flukes (Liver, Lung, and Intestinal)

Amaya L. Bustinduy, Sophie Pach, and Katja Doerholt

Several different **trematodes**, or flukes, can parasitize humans and cause disease. Flukes are endemic worldwide but are more prevalent in the less developed parts of the world. They include *Schistosoma,* or the blood flukes (see Chapter 346), as well as fluke species that cause infection in the human biliary tree, lung tissue, and intestinal tract. These latter trematodes are characterized by complex life cycles (Fig. 347.1). Sexual reproduction of adult worms in the definitive host produces eggs that are passed in the stool. Larvae, called **miracidia**, develop in freshwater. These, in turn, infect certain species of mollusks (aquatic snails or clams), in which asexual multiplication by parasite larvae produces cercariae. Cercariae then seek a second intermediate host, such as an insect, crustacean, or fish, or attach to vegetation to produce infectious **metacercariae**. Humans acquire liver, lung, and intestinal fluke infections by eating uncooked, lightly cooked, pickled, or smoked foods containing these infectious parasite cysts. The "alternation of generations" requires that flukes parasitize more than one host (often three) to complete their life cycle. Because parasitic flukes are dependent on these nonhuman species for transmission, the distribution of human fluke infection closely matches the ecologic range of the flukes' intermediate hosts. As a group, these parasites are commonly referred to as **food-borne trematodes**.

LIVER FLUKES

Fascioliasis (*Fasciola hepatica*)

Fasciola hepatica, the sheep liver fluke, infects cattle, other ungulates, and occasionally humans. This infection affects approximately 17 million people worldwide and has been reported in many different parts of the world, particularly South America, Europe, Africa, China, Australia, and Cuba. Although *F. hepatica* is enzootic in North America, reported cases are extremely rare. Humans are infected by ingestion of metacercariae attached to vegetation, especially wild watercress, lettuce, and alfalfa. In the duodenum, the parasites excyst and penetrate the intestinal wall, liver capsule, and parenchyma. They wander for a few weeks before entering the bile ducts, where they mature. Adult *F. hepatica* (1-2.5 cm) commence oviposition approximately 12 weeks after infection; the eggs are large (75-140 μm) and operculated. They pass to the intestines with bile and exit the body in the feces (see Fig. 347.1). On reaching freshwater, the eggs mature and hatch into miracidia, which infect specific snail intermediate hosts to multiply into many cercariae. These then emerge from infected snails and encyst on aquatic grasses and plants.

Clinical manifestations usually occur either during the liver migratory phase of the parasites or after their arrival at their final habitat in upper bile ducts. Fever, right upper quadrant pain, and hepatosplenomegaly characterize the first phase of illness. Peripheral blood eosinophilia is usually marked. As the worms enter bile ducts, most of the acute symptoms subside. On rare occasions, patients may have obstructive jaundice or biliary cirrhosis, with signs of cholestasis, ascending cholangitis, cholelithiasis and jaundice and increased liver enzymes, direct bilirubin, and γ-glutamyl transpeptidase. *F. hepatica* infection is diagnosed by identifying the characteristic eggs in fecal smears or duodenal aspirates. **Diagnosis** can be suggested by positive serology and imaging that reveals acute, hypodense liver lesions that change over time. Presentation can be dramatic in children, with features including generalized edema, hepatic cirrhosis with esophageal varices, and in severe cases, death from generalized organ failure.

The recommended **treatment** of fascioliasis is triclabendazole (10 mg/kg orally [PO] once or twice) or bithionol (30-50 mg/kg PO once daily on alternate days for a total of 10-15 doses). In the United States, bithionol is not generally available, but it may be available from compounding pharmacies.

Clonorchiasis (*Clonorchis sinensis*)

Infection of bile passages with *Clonorchis sinensis,* the Chinese or oriental liver fluke, is endemic in China, South Korea, northern Vietnam,

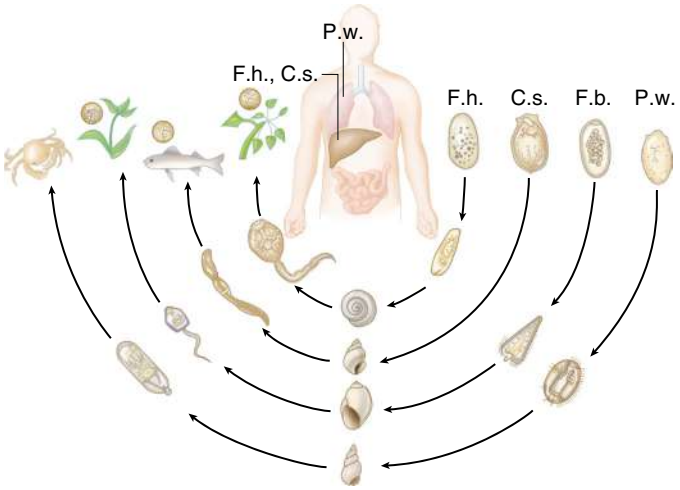

Fig. 347.1 Life cycle of parasitic liver, lung, and intestinal flukes. C.s., *Clonorchis sinensis*; F.b., *Fasciolopsis buski*; F.h., *Fasciola hepatica*; P.w., *Paragonimus westermani. (Adapted from Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 7th ed. Philadelphia: Elsevier, 2010: Fig 289-2.)*

and parts of Russia and Japan, affecting more than 15 million people. Humans acquire infection by ingestion of raw or inadequately cooked **freshwater fish** carrying the encysted metacercariae of the parasite under their scales or skin. Metacercariae excyst in the duodenum and pass through the ampulla of Vater to the common bile duct and bile capillaries, where they mature into hermaphroditic adult worms (3-15 mm). *C. sinensis* worms deposit small operculated eggs (14-30 μm), which are discharged through the bile duct to the intestine and feces (see Fig. 347.1). The eggs mature and hatch outside the body, releasing motile miracidia into local freshwater streams, rivers, or ponds. If these are taken up by the appropriate snails, they develop into cercariae, which are, in turn, released from the snail to encyst under the skin or scales of freshwater fish.

Clinical manifestations are minimal in most individuals with *C. sinensis* infection, particularly those with few organisms. Among heavily infected individuals, who tend to be older (>30 years), localized obstruction of a bile duct results from repeated local trauma and inflammation. In these patients, **cholangitis and cholangiohepatitis** may lead to liver enlargement and jaundice. In Hong Kong, Korea, and other parts of Asia, **cholangiocarcinoma** is associated with chronic *C. sinensis* infection.

Diagnosis of clonorchiasis is made by examination of feces or duodenal aspirates for the parasite eggs and serology. Radiologic imaging (CT scan) can detect fibrosis in the biliary tract and cholangiocarcinoma. The recommended **treatment** of clonorchiasis is praziquantel (75 mg/kg/day PO divided 3 times daily [tid] for 2 days). An alternative, used in adults, is albendazole (10 mg/kg once daily PO for 7 days). Tribendimidine (400 mg PO for 3 days) has been used in China with good cure rates.

Opisthorchiasis (*Opisthorchis* spp.)

Infections with species of *Opisthorchis* are clinically similar to those caused by *C. sinensis. Opisthorchis felineus* and *Opisthorchis viverrini* are liver flukes of cats and dogs that infect humans through ingestion of metacercariae in freshwater fish. Infection with *O. felineus* is endemic in Eastern Europe and Southeast Asia, and *O. viverrini* is found mainly in Thailand, affecting an estimated 10 million people. Most individuals are minimally symptomatic; liver enlargement, relapsing cholangitis, and jaundice may occur in heavily infected individuals. *O. viverrini* is a known carcinogen, much like *Clonorchis* spp. responsible for **cholangiocarcinoma.** Diagnosis is based on recovering eggs from stools or duodenal aspirates and serology. The recommended **treatment** of opisthorchiasis is praziquantel (75 mg/kg/day PO tid for 2 days).

LUNG FLUKES

Paragonimiasis (*Paragonimus* spp.)

Human infection by the lung fluke *Paragonimus westermani,* and less frequently other species of *Paragonimus,* occurs throughout the Far East, in localized areas of West Africa, and in several parts of Central and South America, affecting approximately 20 million people. The highest incidence of paragonimiasis occurs in older children and adolescents 11-15 years of age. Although *P. westermani* is found in many carnivores, human cases are relatively rare and seem to be associated with specific dietary habits, such as eating raw **freshwater crayfish or crabs**. These crustaceans contain the infective metacercariae in their tissues. After ingestion, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate to their final habitat in the lungs. Adult worms (5-10 mm) encapsulate within the lung parenchyma and deposit brown operculated eggs (60-100 μm) that pass into the bronchioles and are expectorated by coughing (see Fig. 347.1). Ova can be detected in the sputum of infected individuals or in their feces. If eggs reach freshwater, they hatch and undergo asexual multiplication in specific snails. The cercariae encyst in the muscles and viscera of crayfish and freshwater crabs.

Clinical Manifestations

Most individuals infected with *P. westermani* harbor low or moderate worm loads and are minimally symptomatic. The clinical manifestations include cough, production of rust-colored sputum, and **hemoptysis** *(mimicking tuberculosis),* which is the principal manifestation and occurs in 98% of symptomatic children. In addition, children with paragonimiasis have pleural effusions, hepatomegaly, and subcutaneous nodules. For the **diagnosis**, there are no characteristic physical findings, but laboratory examination usually demonstrates marked **eosinophilia.** Chest radiographs often reveal small, **patchy infiltrates** or radiolucencies in the middle lung fields; however, radiographs may appear normal in one fifth of infected individuals. In rare circumstances, lung abscess, pleural or pericardial effusion, or bronchiectasis may develop. Extrapulmonary localization of *P. westermani* in the brain, peritoneum, intestines, or pericardium may rarely occur. **Cerebral paragonimiasis** occurs primarily in heavily infected individuals living in highly endemic areas of the Far East. The clinical presentation resembles jacksonian epilepsy or the symptoms of cerebral tumors. Definitive diagnosis of paragonimiasis is established by identification of eggs in fecal or sputum smears and serology. The recommended **treatment** of paragonimiasis is praziquantel (75 mg/kg/day PO tid for 2 days). Triclabendazole can also be used (10 mg/kg PO daily for 1-2 days).

INTESTINAL FLUKES

Several wild and domestic animal intestinal flukes, including *Fasciolopsis buski, Nanophyetus salmincola,* and *Heterophyes heterophyes,* may accidently infect humans who eat uncooked or undercooked fish or water plants. For example, *F. buski* is endemic in the Far East, where humans who ingest metacercariae encysted on aquatic plants become infected. These develop into large flukes (1-5 cm) that inhabit the duodenum and jejunum. Mature worms produce operculated eggs that pass with feces; the organism completes its life cycle through specific snail intermediate hosts. Individuals with *F. buski* infection are usually asymptomatic; heavily infected patients complain of **abdominal pain and diarrhea** and show signs of malabsorption. **Diagnosis** of fasciolopsiasis and other intestinal fluke infections is established by fecal examination and identification of the eggs (see Fig. 347.1). As for other fluke infections, praziquantel (75 mg/kg/day PO tid for 2 days) is the drug of choice.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 348

Adult Tapeworm Infections

Philip R. Fischer and A. Clinton White Jr.

Tapeworms are adult forms of **cestodes**, multicellular helminth parasites, that live in human intestines and cause non–life-threatening illness. Invasive larval forms of cestodes are associated with cysts that lead to severe human disease such as neurocysticercosis (*Taenia solium*; see Chapter 349) and echinococcosis (mostly *Echinococcus granulosa* and *E. multilocularis*; Chapter 350). The adult worms themselves are flat and multisegmented, varying in length from 8 mm to 10 meters (m). Table 348.1 summarizes the key features of tapeworms that affect children.

ETIOLOGY

The **beef tapeworm** *(Taenia saginata)*, the **pork tapeworm** *(T. solium),* and the Asian tapeworm *(Taenia asiatica)* are long worms (4-10 m) named for their intermediate hosts *(T. saginata, T. solium)* or geographic distribution (*T. asiatica*; larval host is the pig). The adult worms are found only in the human intestine. As with the adult stage of all

Table 348.1 Key Features of Common Tapeworms in Children

PARASITE SPECIES	GEOGRAPHY	SOURCE	SYMPTOMS	TREATMENT
Taenia saginata	Asia, Africa, Latin America	Cysts in beef	Abdominal discomfort, motile proglottid migration, passing segments	Praziquantel or niclosamide, possibly nitazoxanide
Taenia solium	Asia, Africa, Latin America	Cysticerci in pork	Minimal, proglottids in stool	Praziquantel or niclosamide
Taenia asiatica	Asia	Pigs	Minimal	Praziquantel or niclosamide
Dibothriocephalus latus	Europe, North America	Plerocercoid cysts in freshwater fish	Usually minimal; with prolonged or heavy infection with D. latus, vitamin B_{12} deficiency	Praziquantel or niclosamide
Dibothriocephalus nihonkaiense	Northeast Asia, North Pacific coast of North America	Plerocercoid cysts in saltwater fish	Usually minimal; passing proglottids	Praziquantel or niclosamide
Adenocephalus pacificus	Pacific Coast of South America	Infected fish	Usually none or mild	Praziquantel or niclosamide
Hymenolepis	Worldwide, often northern areas	Infected humans, rodents	Mild abdominal discomfort	Praziquantel, niclosamide, or nitazoxanide
Dipylidium caninum	Worldwide	Domestic dogs and cats	Proglottids in stool, anal pruritus confused with pinworm	Praziquantel or niclosamide

tapeworms, their body is a series of hundreds or thousands of flattened segments **(proglottids)** with an anterior attachment organ **(scolex)** that anchors the parasite to the bowel wall. New segments arise from the distal aspect of the scolex with progressively more mature segments attached distally. The gravid terminal segments contain 50,000-100,000 eggs, and the eggs or even detached intact proglottids pass out of the child through the anus (with or separate from defecation). These tapeworms differ most significantly in that the intermediate stage of the pork tapeworm **(cysticercus)** can also infect humans and cause significant morbidity (see Chapter 349), whereas the larval stage of *T. saginata* does not cause human disease. *T. asiatica* is similar to and often confused with the beef tapeworm.

EPIDEMIOLOGY

The pork and beef tapeworms are distributed worldwide, with the highest risk for infection in Latin America, Africa, India, Southeast Asia, and China, where the relevant intermediate host is raised domestically. The prevalence in adults may not reflect the prevalence in young children, because cultural practices may dictate how well meat is cooked and how much is served to children.

PATHOGENESIS

When children ingest raw or undercooked meat containing larval cysts, gastric acid and bile facilitate release of immature scolices that attach to the lumen of the small intestine. The parasite grows, adding new segments at the base of the scolex. The terminal segments mature and after 2-3 months produce eggs that are released in stool. The surface of proglottids serves as an absorptive organ to "steal" nutritional elements from the child's small bowel for use by the parasite. There is sometimes a transient eosinophilia before the parasite matures enough to release eggs.

CLINICAL MANIFESTATIONS

Nonspecific abdominal symptoms have been reported with beef and pork tapeworm infections, but the most bothersome symptom is the psychologic distress caused by seeing proglottids in the stool or undergarments. The released segments of the worms are motile (especially those of *T. saginata*) and sometimes lead to anal pruritus. The adult beef and pork tapeworms are only rarely associated with other symptoms.

DIAGNOSIS

Identification of the infecting tapeworm species facilitates understanding of risk for invasive disease. Carriers of adult pork tapeworms are at increased risk for transmitting eggs with the pathogenic intermediate stage (cysticercus) to themselves or others, whereas children infected with the beef tapeworm or *T. asiatica* are a risk only to livestock. Because proglottids are generally passed intact, visual examination for gravid proglottids in the stool is a sensitive test; these segments may be used to identify species. Eggs, by contrast, are often absent from stool and cannot distinguish between *T. saginata* and *T. solium* (Fig. 348.1). If the parasite is completely expelled, the scolex of each species is diagnostic. The scolex of *T. saginata* has only a set of four anteriorly oriented suckers, whereas *T. solium* is armed with a double row of hooks in addition to suckers. The proglottids of *T. saginata* have >20 branches from a central uterine structure, and the proglottids of *T. solium* have ≤10 branches. Expelled proglottid segments are usually approximately 0.5 × 1-2 × 0.1 cm in size. Molecular methods can distinguish *T. saginata* from *T. asiatica*. Antigen detection tests are increasingly available.

DIFFERENTIAL DIAGNOSIS

Anal pruritus may mimic symptoms of pinworm *(Enterobius vermicularis)* infection. Broad tapeworms such as *Dibothriocephalus latus* (formerly *Diphyllobothrium latum*) and *Ascaris lumbricoides* (a long round worm) may be mistaken for *T. saginata* or *T. solium* in stools.

TREATMENT

Infections with all adult tapeworms respond to praziquantel (25 mg/kg orally [PO] once). When available, an alternative treatment for **taeniasis** is niclosamide (50 mg/kg PO once for children; 2 g PO once for adults). Nitazoxanide is sometimes effective as well. The parasite is usually expelled on the day of administration. Treatment with electrolyte–polyethylene glycol bowel preparations can increase the yield of passage of scolices.

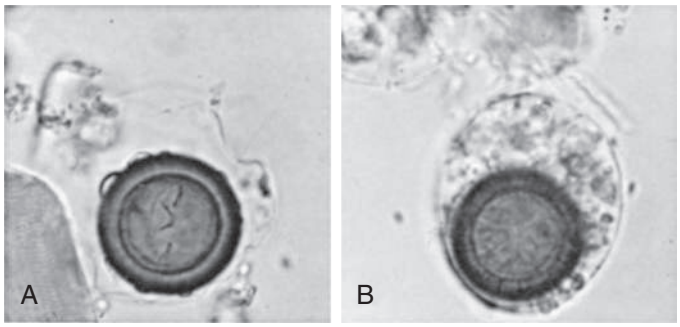

Fig. 348.1 Eggs of *Taenia saginata* recovered from feces (original magnification ×400). **A** and **B,** The eggs are generally bile-stained, dark, and prismatic. There is occasionally some surrounding cellular material from the proglottid in which the egg develops, which is more evident in **B** than in **A.** The larva within the egg shows three pairs of hooklets (**A**), which may occasionally be observed in motion.

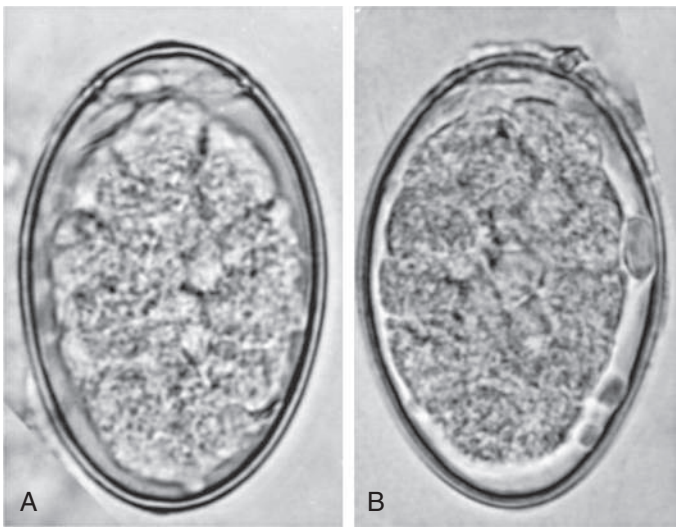

Fig. 348.2 Eggs of *Dibothriocephalus latus* as seen in feces (original magnification ×400). **A** and **B,** The caplike operculum is at the upper end of the eggs here.

PREVENTION

Prolonged freezing or thorough cooking of beef and pork kills the larval cystic forms of the parasite. Appropriate human sanitation can interrupt transmission by preventing infection in livestock. Mass treatment does not lead to lasting reductions in prevalence.

DIPHYLLOBOTHRIASIS (*DIBOTHRIOCEPHALUS* SPP.)

Etiology

The **broad tapeworms** of the order Diphyllobothriidea are the longest human tapeworms, reaching >10 m in length, and have an anatomic organization similar to that of other adult cestodes. An elongated scolex, equipped with slits **(bothria)** along each side but no suckers or hooks, is followed by thousands of segments looped in the small bowel. Gravid terminal proglottids detach periodically but tend to disintegrate before expulsion, thus releasing eggs rather than intact worm segments in the feces. In contrast to taeniids, the life cycle of Diphyllobothriid spp. requires two intermediate hosts. Small, freshwater crustaceans (copepods) take up the larvae that hatch from parasite eggs. The parasite passes up the food chain as small fish eat the copepods and are, in turn, eaten by larger fish. In this way, the juvenile parasite becomes concentrated in pike, walleye, perch, burbot, and salmon. Consumption of raw or undercooked fish leads to human infection with adult fish tapeworms. Recent molecular studies have led to marked revision in the taxonomy with regional differences in the predominant species (*Dibothriocephalus latus* in Europe, North America; *Dibothriocephalus nihonkaiense* in Japan, Northeast Asia, and the northern Pacific coast of North America, and *Adenocephalus pacificus* in coastal South America).

Epidemiology

The fish tapeworms are most prevalent in the temperate climates of Europe, North America, and northeastern Asia and along the Pacific coast of South America and in Africa. In North America the prevalence is highest in Alaska, Canada, and northern areas of the continental United States. The tapeworm is found in fish from those areas that are then taken to market. Persons who prepare raw fish for home or commercial use or who sample fish before cooking are particularly at risk for infection.

Pathogenesis

The adult worm of *Dibothriocephalus latus* (found in northern Europe) has high-affinity receptors and efficiently scavenges vitamin B_{12} for its own use in the constant production of large numbers of segments and as many as 1 million eggs per day. As a result, diphyllobothriasis causes **megaloblastic anemia** in 2–9% of infections. Interestingly, other Diphyllobothriid spp. do not out-compete the host for vitamin B_{12}. Children with other causes of vitamin B_{12} or folate deficiency, such as chronic infectious diarrhea, celiac disease, or congenital malabsorption, are more likely to develop symptomatic infection.

Clinical Manifestations

Infection is largely asymptomatic. Segments may be noted in stool. Those who develop vitamin B_{12} or folate deficiency present with megaloblastic anemia with leukopenia, thrombocytopenia, glossitis, and/or signs of spinal cord posterior column dysfunction (loss of vibratory sense, proprioception, and coordination).

Diagnosis

Parasitologic examination of the stool is useful because eggs are abundant in the feces and have morphology distinct from that of all other tapeworms. The eggs are ovoid and have an **operculum**, which is a cap structure at one end that opens to release the embryo (Fig. 348.2). The worm itself has a distinct scolex and proglottid morphology; however, these are not likely to be passed spontaneously.

Differential Diagnosis

A segment or a whole section of the worm might be confused with *Taenia* or *Ascaris* after it is passed. Pernicious anemia, bone marrow toxicity, and dietary restriction may contribute to or mimic the nutritional deficiencies associated with diphyllobothriasis.

Treatment

As with all adult tapeworms, *D. latus* infections respond to praziquantel (5-10 mg/kg PO once). Niclosamide (50 mg/kg PO in a single dose) is also effective.

Prevention

The intermediate stage is easily killed by brief cooking or prolonged freezing of fish before ingestion. Because humans are the major reservoir for adult worms, health education is one of the most important tools for preventing transmission, together with improved human sanitation.

HYMENOLEPIASIS (*HYMENOLEPIS*)

Infection with *Hymenolepis nana,* the **dwarf tapeworm,** is very common in developing countries. Most cases are asymptomatic. However, heavy infection has been associated with diarrhea, weight loss, fever, anemia, and eosinophilia. The intermediate stage of *Hymenolepis diminuta* develops in various hosts (e.g., rodents, ticks, fleas), but the entire life cycle of *H. nana* is completed in humans. Therefore hyperinfection with thousands of small adult worms in a single child may occur. A similar infection may occur less often with *H. diminuta.* Eggs

but not segments may be found in the stool. *H. nana* infection responds to praziquantel (25 mg/kg PO once). Nitazoxanide is effective in about three fourths of children (100 mg PO twice daily [bid] for 3 days for children 1-3 years old, 200 mg bid for 3 days for children 4-11 years old, and 500 mg bid for 3 days for older children).

DIPYLIDIASIS (*DIPYLIDIUM CANINUM*)

Dipylidium caninum is a common tapeworm of domestic dogs and cats. Human infection is relatively rare. Direct transmission between pets and humans does not occur; human infection requires ingestion of the parasite's intermediate host, the dog or cat flea. Infants and small children are particularly susceptible because of their level of hygiene, generally more intimate contact with pets, and activities in areas where fleas can be encountered. Thus children are most at risk of inadvertent ingestion of fleas infected with the larvae. The most common symptom is passage of proglottids in stool. The proglottids are similar in size and shape to white rice grains. Anal pruritus, vague abdominal pain, and diarrhea have at times been associated with dipylidiasis, which is thus sometimes confused with pinworm *(E. vermicularis)*. Dipylidiasis responds to treatment with praziquantel (5-10 mg/kg PO once) and niclosamide (50 mg/kg PO as a single dose). **Deworming** of pets and **flea control** are the best preventive measures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 349

Cysticercosis

A. Clinton White Jr., Miguel M. Cabada, and Philip R. Fischer

Taenia solium, also known as the **pork tapeworm**, causes two different infections in children. In its normal life cycle, children can acquire the tapeworm form by ingestion of undercooked pork containing the larval cysts (see Chapter 348). In the intestines, the cyst converts into the tapeworm form. Children are also susceptible to infection by the eggs shed by tapeworm carriers. After the eggs are ingested, the larvae are released from the eggs, invade through the intestines, and migrate through the bloodstream to the muscles (and other organs), where they form tissue cysts (0.2-2.0 cm fluid-filled bladders containing a single invaginated **scolex**). Infection with the cystic form is termed **cysticercosis**, and involvement of the central nervous system (CNS) is termed **neurocysticercosis.** The tapeworm form only develops after ingestion of undercooked pork. Ingestion of pork is not necessary to develop cysticercosis, but individuals harboring an adult worm may infect themselves with the eggs by the fecal-oral route.

EPIDEMIOLOGY

The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs in Central and South America, southern and Southeast Asia, and much of sub-Saharan Africa. In these areas, approximately 30% of cases of seizures may be a result of cysticercosis. Most cases of cysticercosis in the United States are imported; however, local transmission has been documented.

PATHOGENESIS

Living, intact cystic stages usually suppress the host immune and inflammatory responses. Intact cysts can be associated with disease when they obstruct the flow of cerebrospinal fluid. Most cysts remain asymptomatic for a few years. Symptoms typically develop as the cysticerci begin to degenerate, associated with a host inflammatory response. The natural history of cysts is eventually to resolve by complete resorption or calcification, but this process may take years. Cysticerci can also present as subcutaneous nodules, ocular infection, or spinal lesions with myelopathy or radiculopathy.

CLINICAL MANIFESTATIONS

Seizures and headache are the presenting findings in the vast majority of children with neurocysticercosis. Less common manifestations include hydrocephalus, diffuse cerebral edema, or focal neurologic findings. It is important to classify neurocysticercosis as parenchymal, intraventricular, subarachnoid, spinal, or ocular on the basis of anatomic location, clinical presentation, and radiologic appearance because the prognosis and management vary with location.

Parenchymal neurocysticercosis typically presents with seizures. The seizures are usually focal, but often generalize. Children may present with a single seizure or recurrent epilepsy. Mild neurocognitive defects have been documented from cysticerci alone but are more commonly associated with poorly controlled seizures. A fulminant encephalitis-like presentation may rarely occur after a massive initial infection associated with cerebral edema. **Intraventricular** neurocysticercosis (up to 20% of cases) is associated with obstructive hydrocephalus and acute, subacute, or intermittent signs of increased intracranial pressure, usually without localizing signs. **Subarachnoid** neurocysticercosis is rare in children. It can be associated with basilar arachnoiditis that can present with signs of meningeal irritation, communicating hydrocephalus, cerebral infarction, or **spinal** disease with radiculitis or transverse myelitis. Cysticerci in the tissues may present with focal findings from mass effect. **Ocular** neurocysticercosis causes decreased visual acuity because of cysticerci in the retina or vitreous, retinal detachment, or iridocyclitis.

DIAGNOSIS

Neurocysticercosis should be suspected in a child with onset of seizures or hydrocephalus and who also has a history of residence in an endemic area and/or a care provider from an endemic area. The most useful diagnostic study for parenchymal disease is MRI of the head. MRI provides the most information about cyst location, cyst viability, and associated inflammation. The scolex can appear as a 1-2 mm nodule attached to the cyst wall, and, when identified, is diagnostic for cysticercosis (Fig. 349.1A). The MRI also better detects basilar arachnoiditis (Fig. 349.1B), intraventricular cysts (Fig. 349.1C), and cysts in the spinal cord. CT is best for identifying calcifications. A solitary parenchymal cyst, with or without contrast enhancement, or CNS calcifications are the most common findings in children (Fig. 349.2). Plain films may reveal calcifications in muscle or brain consistent with cysticercosis. In children from endemic regions, the presentation with a single enhancing lesion that is round and <2 cm in diameter, absence of symptoms or signs of other diseases (e.g., no fever or lymph nodes), no focal findings, and no evidence of increased intracranial pressure is highly specific for neurocysticercosis.

Serologic diagnosis using the enzyme-linked immunotransfer blot is available commercially in the United States and through the Centers for Disease Control and Prevention (CDC). Serum antibody testing is highly specific but is frequently negative in children with single lesions or just calcifications. Antigen-detection assays and polymerase chain reaction assays show promise for diagnosis of ventricular and subarachnoid disease and are available from the Laboratory for Parasitic Diseases, National Institutes of Health (NIH). They are not commercially available in the United States.

Differential Diagnosis

Neurocysticercosis is often confused clinically with other seizure disorders. Clinical suspicion is based on travel history, a history of contact with an individual who might carry an adult tapeworm, or suggestive

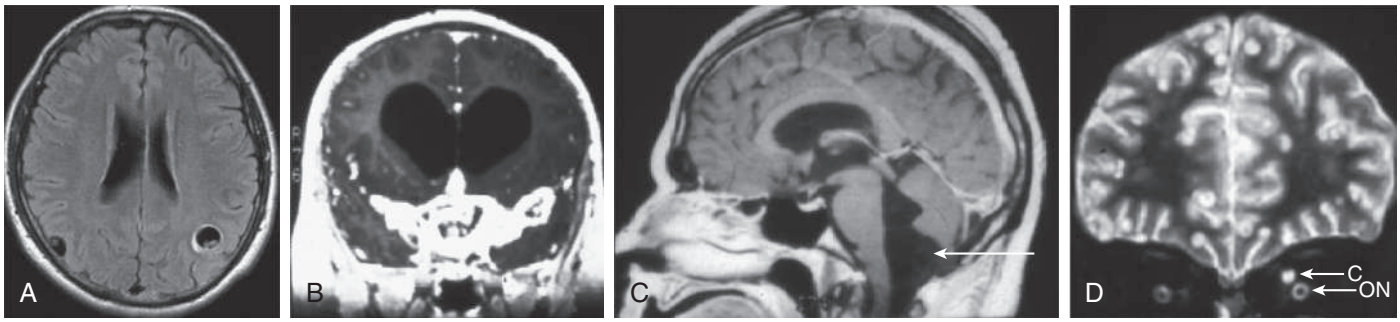

Fig. 349.1 Neurocysticercosis. **A,** T1-weighted MRI demonstrating two parenchymal cysts with scolices. **B,** T1-weighted MRI of cysticercal basilar arachnoiditis. **C,** T1-weighted MRI showing a cyst below the fourth ventricle *(arrow)*. **D,** T2-weighted MRI showing a cysticercus *(C)* above the optic nerve *(ON)*.

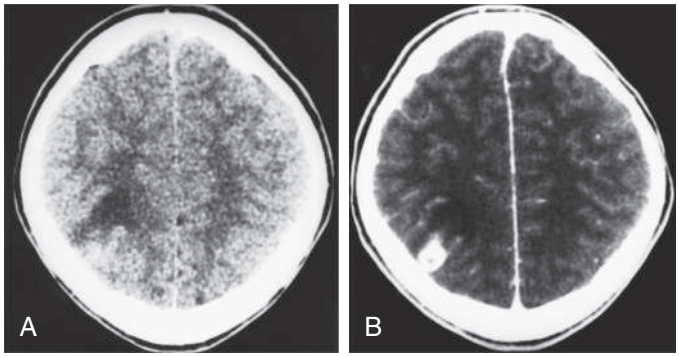

Fig. 349.2 Neurocysticercosis. CT image of a solitary lesion with **(A)** and without **(B)** contrast, showing contrast enhancement. *(Courtesy Dr. Wendy G. Mitchell and Dr. Marvin D. Nelson, Children's Hospital, Los Angeles.)*

imaging studies. The imaging appearance can be confused with brain abscess, granulomas (including tuberculomas, fungal infections, Langerhans histiocytosis, and toxoplasmosis), and tumors.

TREATMENT

The initial management of cysticercosis should focus on symptomatic therapy for seizures and/or hydrocephalus. Seizures can usually be controlled using standard antiepileptic drugs. If the lesions resolve, antiepileptic drugs can often be tapered and stopped. Frequent seizures or the development of calcified lesions are risk factors for recurrent seizures and indications for prolonged or lifelong antiepileptic therapy.

The natural history of **parenchymal** lesions is to resolve spontaneously, with or without antiparasitic drugs, but this process is often prolonged (months to years). Solitary parenchymal cysts resolve slightly more rapidly with antiparasitic therapy. Antiparasitic drugs also decrease the frequency of recurrent seizures. Other forms of the disease are less common in children. In adults with cystic lesions, randomized controlled trials suggested an overall 50% decrease in recurrence of generalized seizures with albendazole treatment. The benefit to children was significantly less, perhaps because most of these infections were with only one to two cysts. Corticosteroids likely also decrease seizure frequency.

The most commonly used antiparasitic is **albendazole** (15 mg/kg/day orally [PO] divided twice daily [bid]). It should be taken with a fatty meal to improve absorption. The most common duration of therapy is 7 days for single parenchymal lesions. However, longer duration (months), higher doses (up to 30 mg/kg/day), or combination therapy with praziquantel is often required for multiple lesions or subarachnoid disease. For example, in adults with more than two cysticerci, trials note improved resolution with combination therapy with corticosteroids, albendazole, and praziquantel (50 mg/kg/day PO divided three times daily for 14 days). **Praziquantel** (50-100 mg/kg/day for 28 days) may be used as an alternative to albendazole. First-pass metabolism is common with corticosteroids or antiepileptic drugs. **Cimetidine** can be used in conjunction with praziquantel to blunt the first-pass metabolism. A worsening of symptoms can follow the use of either drug based on the host's inflammatory response to the dying parasite. Patients should be medicated with prednisone (1-2 mg/kg/day) or oral dexamethasone (0.15 mg/kg/day) beginning before the first dose of antiparasitic drugs and continuing for at least 2 weeks.

Most patients with hydrocephalus require neurosurgical interventions. Some cases require emergent placement of a ventriculostomy, but most can be managed by cystectomy alone. For obstructive hydrocephalus caused by ventricular cysticercosis, many patients can be cured by minimally invasive surgery. **Neuroendoscopy** is the preferred approach to cysticerci in the lateral or third ventricle. Cysticerci in the fourth ventricle can be removed by a suboccipital craniotomy. There are also reports of endoscopic removal of fourth ventricular cysticerci using flexible neuroendoscopy. Adherent cysticerci that cannot be removed can be treated by placement of a ventriculoperitoneal shunt (VPS). However, there is a high rate of shunt failure, which can be minimized somewhat by treatment with antiparasitic drugs plus corticosteroids.

Subarachnoid disease has a poor prognosis. The prognosis is much improved by aggressive therapy, including antiparasitic drugs, antiinflammatory treatment, and neurosurgical procedures for hydrocephalus (e.g., VPS placement). However, the duration of antiparasitic and antiinflammatory therapy often needs to be prolonged. **Methotrexate** and/or tumor necrosis factor inhibitors can be used as a steroid-sparing agent in patients requiring prolonged anti-inflammatory therapy. **Ocular** cysticercosis is usually treated surgically, although there are reports of cure using medical therapy alone.

PREVENTION

In areas with evolved public health systems, cysticercosis can largely be eliminated by meat inspection, condemnation of infected meat, thorough cooking of pork, and improved sanitation. This approach has not worked in countries where most meat is butchered informally. Mass chemotherapy for tapeworm carriers, mass treatment of pigs, and improved personal hygiene have decreased or eliminated transmission in some areas. Screening family members and those preparing food for index cases for cysticercosis has a very low yield, in part because of the poor sensitivity of current tests. Those who have noted passing material consistent with taeniasis should be treated with praziquantel regardless of the results of stool studies. Veterinary vaccines for several cestode infections have a high degree of efficacy and have a potential role in decreasing parasite transmission.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 350

Echinococcosis (*Echinococcus granulosus sensu lato* and *Echinococcus multilocularis*)

Miguel M. Cabada, Philip R. Fischer, and A. Clinton White Jr.

ETIOLOGY

Echinococcosis (**hydatid disease** or **hydatidosis**) is a widespread, serious human cestode infection (Fig. 350.1). Two major *Echinococcus* groups of species are responsible for distinct clinical presentations. *Echinococcus granulosus sensu lato* causes **cystic echinococcosis, and** *Echinococcus multilocularis* causes **alveolar echinococcosis**. The adult parasites are small (2-7 mm) tapeworms with only two to six segments that inhabit the intestines of canines such as dogs, wolves, dingoes, jackals, coyotes, and foxes. Canines are infected by ingesting contaminated viscera from ungulates *(E. granulosus sensu lato)* or mice *(E. multilocularis)*. These carnivores pass the eggs in their stool, which contaminate the soil, pasture, and water, as well as their own fur. Domestic animals, such as sheep, goats, cattle, and camels, ingest *E. granulosus* complex eggs while grazing. Some species of *E. granulosus sensu lato* have a **sylvatic** cycle involving wild cervids such as moose, elk, and deer. For *E. multilocularis*, the main intermediate hosts are small rodents. Humans are infected by consuming eggs by direct contact with infected canines or from ova in the environment. In Europe, contamination of gardens by fox excrement is a major risk factor for transmission. The larvae hatch, penetrate the gut, and are carried by the vascular or lymphatic systems to the liver, lungs, and less frequently, bones, kidney, brain, or heart in *E. granulosus* infection. *E. multilocularis* larvae infect the liver almost exclusively.

Echinococcus granulosus sensu lato comprises several recognized species, including *E. granulosus sensu stricto*, *E. equinus*, *E. ortleppi*, and *E. canadensis*. The species within *E. granulosus sensu lato* show significant variation not only in genetics but also in ecology. While *E. granulosus sensu stricto* is mainly found in domesticated ovines and dogs around the world, *E. canadensis* is found in a sylvatic wolf/moose cycle in North America and Siberia and has been identified in bovines and swine in South America.

EPIDEMIOLOGY

There is potential for transmission of *E. granulosus* to humans wherever dogs are allowed to ingest the entrails of herd animals. Disease is highly endemic in the Middle East and Central Asia. Cysts have been detected in up to 10% of the human population in northern Kenya and western China. In South America, the disease is prevalent in sheep-herding areas of the Andes, the beef-herding areas of the Brazilian/Argentine Pampas, and Uruguay. Among developed countries, the disease is recognized in Italy, Greece, Portugal, Spain, and Australia and is reemergent in dogs in Great Britain. In North America, transmission occurs rarely through a sylvatic cycle in the Artic regions and in sheep-raising areas of the western United States.

Transmission of *E. multilocularis* occurs primarily in Western China, Central Europe, Siberia, and Turkey. Transmission is now rare in western Canada and the Arctic regions of North America. Ingestion of infected rodents by dogs or foxes facilitates transmission to children. Separate species, *E. vogeli* and *E. oligarthrus*, have mainly a sylvatic cycle involving canines and felines causing polycystic disease in northern South America.

PATHOGENESIS

E. granulosus sensu lato parasites are often acquired in childhood, and cysts require many years to become large enough to be detected or cause symptoms. In children the lung is a common site of infection, whereas in adults up to 70% of cysts develop in the liver. Cysts can also develop in bone, the genitourinary system, spleen, subcutaneous tissues, and brain. The host surrounds the primary cyst with a tough, fibrous capsule. Inside this capsule, the parasite produces a thick lamellar layer with the consistency of a soft-boiled egg white. Inside the lamellar layer is the thin germinal layer of cells responsible for production of 1000s of protoscoleces that remain attached to the wall or float free in the cyst fluid (Video 350.1). Smaller internal daughter cysts may develop within the primary cyst capsule. The fluid in a healthy cyst is clear, colorless, and watery. Rupture of the cyst, which can occur

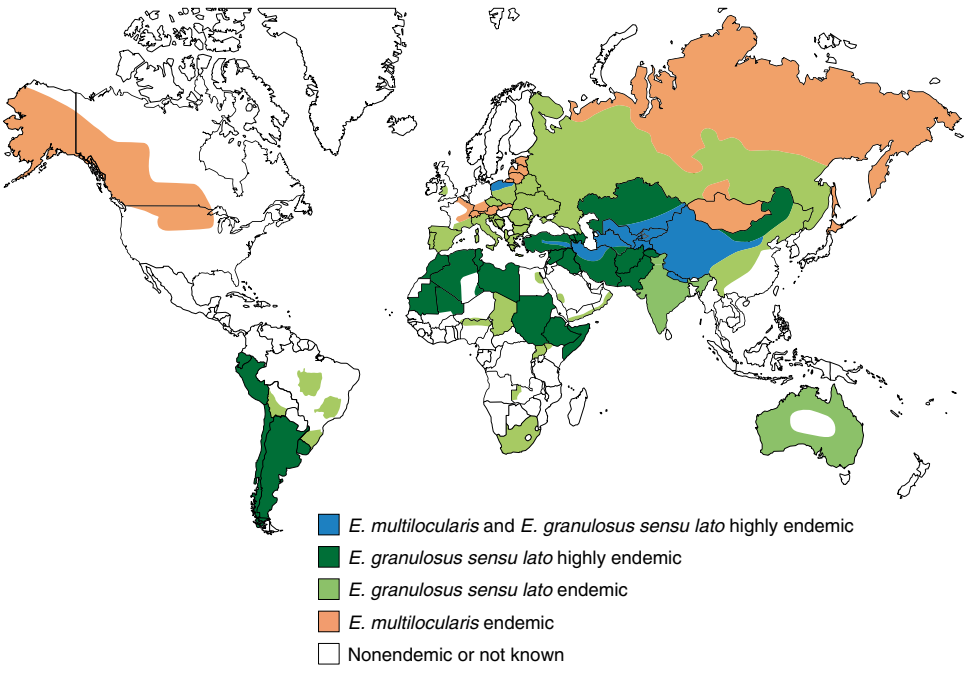

Fig. 350.1 Global distribution of cystic echinococcosis and alveolar echinococcosis. *(From Wen H, Vuitton L, Tuxun T, et al. Echinococcosis: advances in the 21st century. Clin Microbiol Rev. 2019;32[2]:e00075–18. Fig 3.)*

spontaneously, with trauma, or during surgery, can be associated with immediate hypersensitivity reactions, including anaphylaxis. Protoscoleces released into the tissues can also develop into new cysts.

E. multilocularis almost always involves the liver. The lesions grow very slowly and rarely present in children. The secondary reproductive units bud externally and are not confined within a single, well-defined structure. Thus the lesions are invasive and often confused with a malignancy. Furthermore, the cyst tissues are poorly demarcated from those of the host, making surgical removal difficult. The secondary cysts are also capable of distant metastatic spread. The growing cyst mass eventually replaces a significant portion of the liver and compromises adjacent tissues and structures.

CLINICAL MANIFESTATIONS

In the liver, cysts may remain asymptomatic, may regress spontaneously, or may produce nonspecific symptoms. Symptomatic cysts can cause increased abdominal girth, hepatomegaly, a palpable mass, vomiting, or abdominal pain. In the lung, cysts produce chest pain, chronic cough, or hemoptysis. Expectorated fluid from ruptured lung cysts is often described as "salty." Mass effects can be noted in the brain and bone. Serious complications result from compression of adjacent structures or spillage of cyst contents. Type I hypersensitivity reactions, including **anaphylaxis,** can occur with spontaneous spillage or with cyst rupture from trauma or during surgery. Fluid from ruptured lung cysts can cause hypersensitivity pneumonitis. Spillage of fluid from a viable cyst can cause catastrophic long-term complications. Each protoscolex can form a new cyst and fill up the abdominal cavity or other spaces, including the pleura, biliary tree, and pelvis. Jaundice from cystic hydatid disease is rare.

Alveolar hydatid disease is sometimes diagnosed incidentally, but often the proliferating mass compromises the biliary system and/or hepatic tissue, causing progressive obstructive jaundice and hepatic failure. Symptoms also occur from expansion of extrahepatic foci.

DIAGNOSIS

Ultrasonography is the most valuable tool for both the diagnosis and treatment of cystic echinococcosis of the liver. The World Health Organization (WHO) standardized ultrasound criteria for classification of liver cystic echinococcosis have been shown to be reliable with excellent inter/intraobserver reliability. Ultrasonography staging has a direct use in defining optimal therapy with cystic echinococcosis types 1 and type 2 (CE1 and CE2) cysts considered fully active, CE3a and CE3b transitional, and CE4 and CE5 inactive (Fig. 350.2). Chest radiographs frequently reveal characteristic rounded masses in lung cystic echinococcosis (Fig. 350.3). Alveolar disease resembles a diffuse solid tumor. CT findings are similar to those of ultrasonography and may at times be useful in distinguishing alveolar from cystic echinococcosis in geographic regions where both occur (Fig. 350.4). CT or MRI is also important in planning a surgical intervention.

Serologic studies are used to confirm the diagnosis of cystic echinococcosis, although some children with active cystic echinococcosis do not have detectable levels of specific antibody. Cross-reaction with other helminths is possible when using crude hydatid fluid antigens for the serology. The sensitivity and specificity of serologic assays to diagnose cystic echinococcosis vary significantly by location of the cyst, stage, and treatment status. The enzyme-linked immunosorbent assay performs better than Western blot and indirect hemagglutination with the highest sensitivity for CE2, CE3, and CE1 cysts (64–99%) compared to CE4 and CE5 (51–91%). The sensitivity is higher for hepatic or bone disease, but the false-negative rate may be >50% with pulmonary or central nervous system (CNS) infection.

Differential Diagnosis

Benign hepatic cysts are common but can be distinguished from cystic echinococcosis by the absence of a distinct three-layer wall, internal membranes, and hydatid sand. The density of bacterial hepatic abscesses is distinct from the watery cystic fluid characteristic of *E. granulosus* infection, but *Echinococcus* cysts may also be complicated

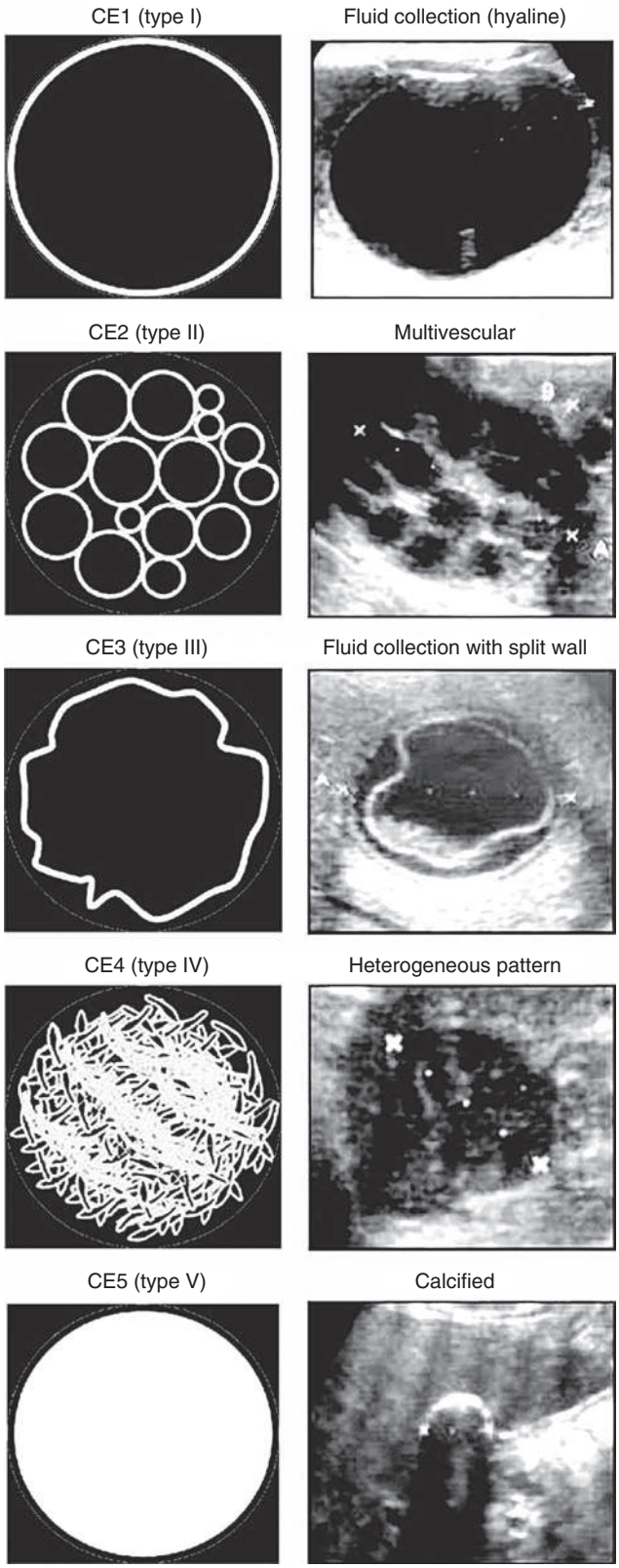

Fig. 350.2 Ultrasound classification of cystic echinococcosis (CE) cysts. The WHO informal working group on echinococcosis classification differs from that of Gharbi and colleagues by the addition of a "cystic lesion" (CL) stage (undifferentiated) *(not shown)* and by reversing the order of CE types 2 and 3. CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). CE1 and CE3a are early-stage cysts and CE4 and CE5 late-stage cysts. *(From McManus DP, Gray DJ, Zhang W, Yang Y. Diagnosis, treatment, and management of echinococcosis. BMJ. 2012;344:e3866. Fig 4.)*

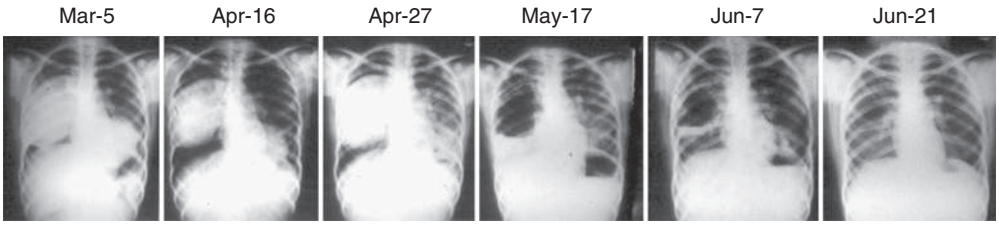

Fig. 350.3 Serial chest radiographs of bilateral hydatid cysts. After 2 months of albendazole therapy, sudden rupture of the right cyst was associated with massive aspiration and acute respiratory distress.

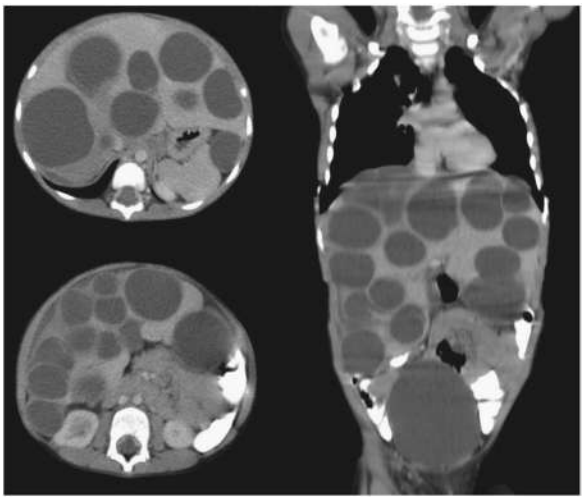

Fig. 350.4 Liver cystic echinococcosis (hydatid disease). Abdominal CT revealed hepatomegaly and multiple (>20) liver cysts. *(From Ben-Shimol S, Zelcer I. Liver hydatid cysts. J Pediatr. 2013;163:1792.)*

by secondary bacterial infection. Alveolar echinococcosis is often confused with hepatoma or metastatic tumor.

TREATMENT

Management of cystic echinococcosis should be individualized and guided by disease stage and location. Approaches range from surgical resection for disease that tends to respond poorly to drugs and complicated cysts to watchful waiting for cysts that have already degenerated. For CE1 or CE3a cysts (see Fig. 350.2) that are <5 cm in diameter, **albendazole** chemotherapy alone (15 mg/kg/day orally divided twice daily for 1-6 months; maximum 800 mg/day) may result in a high rate of cure. Adverse effects include occasional alopecia, mild gastrointestinal disturbance, and elevated transaminases on prolonged use. Because of leukopenia, the U.S. Food and Drug Administration (FDA) recommends that blood counts be monitored at the beginning and every 2 weeks during the first 3 months of therapy and monthly afterward. Medical treatment with albendazole may also be used for cysts that are not suitable for interventions such as **PAIR** (percutaneous, aspiration, instillation, and reaspiration) or surgery, but response rates are low.

For larger CE1 and CE3a lesions, ultrasound- or CT-guided PAIR is the preferred therapy. Compared with surgical treatment alone, PAIR plus albendazole results in similar cyst disappearance with fewer adverse events and fewer days in the hospital. Spillage with PAIR is uncommon, but prophylactic albendazole therapy is routinely administered at least 1 week before PAIR and 1 month afterward. PAIR is contraindicated in pregnancy and for bile-stained cysts, which may indicate the presence of a biliary fistula. The scolicidal agents instilled during PAIR may increase risk for biliary complications in these patients. Surgery with albendazole treatment is the recommended approach for CE2 and CE3b cysts of the liver. In experienced centers, cysts with thick internal septation (CE2) can be managed using a trocar to break up the membranes and external drainage. CE4 and CE5 cysts do not require immediate interventions and are followed ultrasonographically for signs of reactivation.

Surgery is the treatment of choice for complicated **cysts**, including ruptured cysts, cysts communicating with the biliary tract, large pulmonary cysts, or cysts of the CNS or bones. Small thoracic cysts may resolve with albendazole, but most cysts require operative removal.

For conventional surgery, the inner cyst wall (only laminate and germinal layers are of parasite origin) can be easily peeled from the fibrous layer, although some studies suggest that removal of the whole capsule has a better outcome in terms of recurrent disease. Considerable care must be taken to avoid spillage of cyst contents, and surgical drapes should be soaked in hypertonic saline because cyst fluid contains viable protoscoleces, each capable of producing secondary cysts. An additional risk is anaphylaxis because of spilled cyst fluid, making it useful to employ a surgeon experienced in this surgery. For hepatic cysts, patients should begin therapy with albendazole (ideally in combination with praziquantel) for several days to weeks preoperatively. Antiparasitic drugs should be continued for 4-12 weeks postoperatively.

Alveolar hydatidosis frequently requires radical surgery, including partial hepatectomy, lobectomy, or liver transplantation. Medical therapy with albendazole should be continued for at least 2 years after presumably curative surgery. In patients who are not operative candidates or whose lesions are not amenable to surgical cure, albendazole long-term suppressive therapy should be used to slow the progression, but the infection generally recurs if albendazole is stopped.

PROGNOSIS

Factors predictive of success with chemotherapy are age of the cyst (<2 years), low internal complexity of the cyst, and small size. The site of the cyst is not important, although cysts in bone respond poorly. For alveolar echinococcosis, if surgical removal is unsuccessful, the average mortality is 92% by 10 years after diagnosis.

PREVENTION

Important measures to interrupt transmission include thorough **handwashing**, avoiding contact with dogs in endemic areas, and boiling or filtering water when camping. Strict procedures for proper disposal of refuse from slaughterhouses must be instituted and followed so that dogs and wild carnivores do not have access to entrails. Other useful measures are control or treatment of the feral dog population and regular praziquantel treatment of pets and working dogs in endemic areas. Vaccines have been developed to prevent infection in grazing animals but are not widely used.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

The Digestive System

PART XVI

Section 1

Clinical Manifestations of Gastrointestinal Disease

Chapter 351

Normal Digestive Tract Phenomena

Asim Maqbool and Chris A. Liacouras

Gastrointestinal function varies with maturity; what is a physiologic event in a newborn or infant might be a pathologic symptom at an older age. A fetus can swallow amniotic fluid as early as 12 weeks of gestation, but nutritive sucking in neonates first develops at about 34 weeks of gestation. The coordinated oral and pharyngeal movements necessary for swallowing solids develop within the first few months of life. Before this time, the tongue thrust is upward and outward to express milk from the nipple, instead of a backward motion, which propels solids toward the esophageal inlet. By 1 month of age, infants appear to show preferences for sweet and salty foods. Infants' interest in solids increases at approximately 4 months of age. The recommendation to begin solids at 6 months of age is based on nutritional and cultural concepts rather than maturation of the swallowing process (see Chapter 61). Infants swallow air during feeding, and burping is encouraged to prevent gaseous distention of the stomach.

A number of normal anatomic variations may be noted in the mouth. A **short lingual frenulum** ("tongue-tie") may be worrisome to parents but only rarely interferes with nursing, bottle feeding, eating, or speech, generally requiring no treatment. **Surface furrowing** of the tongue (a geographic or scrotal tongue) is usually a normal finding. A **bifid uvula** may be isolated or associated with a submucous cleft of the soft palate (Fig. 351.1).

Regurgitation, the result of gastroesophageal reflux, occurs commonly in the first year of life. Effortless regurgitation can dribble out of an infant's mouth but also may be forceful. In an otherwise healthy infant with regurgitation; volumes of emesis are commonly approximately 15-30 mL but occasionally are larger. Most often, the infant remains happy, although possibly hungry, after an episode of regurgitation. Episodes can occur from one to several times per day. Regurgitation gradually resolves in 80% of infants by 6 months of age and in 90% by 12 months. If complications develop or regurgitation persists, gastroesophageal reflux is considered pathologic rather than merely developmental and deserves further evaluation and treatment. Complications of gastroesophageal reflux include failure to thrive, pulmonary disease (apnea or aspiration pneumonitis), and esophagitis with its sequelae (see Chapters 369 and 370).

Infants and young children may be erratic eaters; this may be a worry to parents. A toddler might eat insatiably or refuse to consume food during a meal. Toddlers and young children also tend to eat only a limited variety of foods. Parents should be encouraged to view nutritional intake over several days and not be overly concerned about individual meals. Infancy and adolescence are periods of rapid growth; high nutrient requirements for growth may be associated with voracious appetites. The reduced appetite of toddlers and preschool children is often a worry to parents who are used to the relatively greater dietary intake during infancy. Demonstration of age-appropriate growth on a growth curve is reassuring.

The number, color, and consistency of stools can vary greatly in the same infant and between infants of similar age, without apparent explanation. The earliest stools after birth consist of meconium, a dark, viscous material that is normally passed within the first 48 hours of life. With the onset of feeding, meconium is replaced by green-brown transition stools, often containing curds, and, after 4-5 days, by yellow-brown milk stools. **Stool frequency** is extremely variable in normal infants and can vary from none to seven per day. Breastfed infants can have frequent small, loose stools early (transition stools), and then after 2-3 weeks can have very infrequent soft stools. Some nursing infants might not pass any stool for 1-2 weeks and then have a normal soft bowel movement. The color of stool has little significance except for the presence of blood or absence of bilirubin products (white-gray rather than yellow-brown). The presence of vegetable matter, such as peas or corn, in the stool of an older infant or toddler ingesting solids is normal and suggests poor chewing and not malabsorption. A pattern of intermittent loose stools, known as **toddler's diarrhea,** occurs commonly between 1 and 3 years of age. These otherwise healthy growing children often drink excessive carbohydrate-containing beverages. The stools typically occur during the day and not overnight. The volume of fluid intake is often excessive; limiting sugar and unabsorbable carbohydrate-containing beverages and increasing fat in the diet often lead to resolution of the pattern of loose stools.

A protuberant abdomen is often noted in infants and toddlers, especially after large feedings. This can result from the combination of weak abdominal musculature, relatively large abdominal organs, and lordotic stance. In the first year of life, it is common to palpate the liver 1-2 cm



Fig. 351.1 Classic submucous cleft palate with triad of bifid uvula *(large arrow)*, furrow along the midline of the soft palate *(arrowheads)*, and a notch in the posterior margin of the hard palate *(small arrow)*. The midline furrow is sometimes referred to as the zona pellucida, reflecting the translucent nature of this area in some patients. *(From Hasan A, Gardner A, Devlin M, Russell C. Submucous cleft palate with bifid uvula. J Pediatr. 2014;165:872.)*

below the right costal margin. The normal liver is soft in consistency and percusses to normal size for age. A Riedel lobe is a thin projection of the right lobe of the liver that may be palpated low in the right lateral abdomen. A soft spleen tip might also be palpable as a normal finding. In thin young children, the vertebral column is easily palpable, and an overlying structure may be mistaken for a mass. Pulsation of the aorta can be appreciated. Normal stool can often be palpated in the left lower quadrant in the descending or sigmoid colon.

Blood loss from the gastrointestinal tract is never normal, but swallowed blood may be misinterpreted as gastrointestinal bleeding. Maternal blood may be ingested at the time of birth or later by a nursing infant if there is bleeding near the mother's nipple. Nasal or oropharyngeal bleeding is occasionally mistaken for gastrointestinal bleeding (see Chapter 142). Red dyes in foods or drinks can turn the stool red but do not produce a positive test result for occult blood.

Jaundice is common in neonates, especially among premature infants, and usually results from the inability of an immature liver to conjugate bilirubin, leading to an elevated indirect component (see Chapter 137). Persistent elevation of indirect bilirubin levels in nursing infants may be a result of breast milk jaundice, which is usually a benign entity in full-term infants. An elevated direct bilirubin is not normal and suggests liver disease, although in infants it may be a result of extrahepatic infection (urinary tract infection). The direct bilirubin fraction should account for no more than 15–20% of the total serum bilirubin. Elevations in direct bilirubin levels can follow indirect hyperbilirubinemia as the liver converts excessive indirect to direct bilirubin and the rate-limiting step in bilirubin excretion shifts from the glucuronidation of bilirubin to excretion of direct bilirubin into the bile canaliculus. Indirect hyperbilirubinemia, which occurs commonly in normal newborns, tends to tint the sclerae and skin golden yellow, whereas direct hyperbilirubinemia produces a greenish yellow hue. The degree of jaundice does not always directly correlate with serum bilirubin levels. An elevated total serum bilirubin warrants closer examination, fractionation of bilirubin (direct and indirect), and ongoing surveillance. Atypical elevations of unconjugated bilirubin are associated with risk for kernicterus (see Chapter 140). Elevations in conjugated bilirubin are reviewed in the chapter on cholestasis (see Chapter 404.1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 352

Major Symptoms and Signs of Digestive Tract Disorders

Asim Maqbool and Chris A. Liacouras

Disorders of organs outside the gastrointestinal (GI) tract can produce symptoms and signs that mimic digestive tract disorders and should be considered in the differential diagnosis (Table 352.1). In children with normal growth and development, treatment may be initiated without a formal evaluation based on a presumptive diagnosis after taking a history and performing a physical examination. Poor weight gain or weight loss is often associated with a significant pathologic process and usually necessitates a more formal evaluation.

Table 352.1 Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children

ANOREXIA
Systemic disease: inflammatory, neoplastic
Cardiorespiratory compromise
Iatrogenic: drug therapy, unpalatable therapeutic diets
Depression
Anorexia nervosa
VOMITING
Inborn errors of metabolism
Medications: erythromycin, chemotherapy, nonsteroidal antiinflammatory drugs, marijuana
Increased intracranial pressure
Brain tumor
Infection of the urinary tract
Labyrinthitis
Adrenal insufficiency
Pregnancy
Psychogenic
Abdominal migraine
Poisoning/toxins
Renal disease
DIARRHEA
Infection: otitis media, urinary tract infection
Uremia
Medications: antibiotics, cisapride
Tumors: neuroblastoma
Pericarditis
Adrenal insufficiency
CONSTIPATION
Hypothyroidism
Spina bifida
Developmental delay
Dehydration: diabetes insipidus, renal tubular lesions
Medications: narcotics
Lead poisoning
Infant botulism
ABDOMINAL PAIN
Pyelonephritis, hydronephrosis, renal colic
Pneumonia (lower lobe)
Pelvic inflammatory disease
Porphyria
Fabry disease
Angioedema
Endocarditis
Abdominal migraine
Familial Mediterranean fever
Sexual or physical abuse
Systemic lupus erythematosus
School phobia
Sickle cell crisis
Vertebral disk inflammation
Psoas abscess
Pelvic osteomyelitis or myositis
Medications
Anterior (abdominal) cutaneous nerve entrapment syndrome (ACNES)
ABDOMINAL DISTENTION OR MASS
Ascites: nephrotic syndrome, neoplasm, heart failure
Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma
Pregnancy
JAUNDICE
Hemolytic disease
Urinary tract infection
Sepsis
Hypothyroidism
Panhypopituitarism

DYSPHAGIA

Difficulty in swallowing is termed *dysphagia*. Painful swallowing is termed **odynophagia**. **Globus** is the sensation of something stuck in the throat without a clear etiology. Swallowing is a complex process that starts in the mouth with mastication and lubrication of food that is formed into a bolus. The bolus is pushed into the pharynx by the tongue. The pharyngeal phase of swallowing is rapid and involves protective mechanisms to prevent food from entering the airway. The epiglottis is lowered over the larynx while the soft palate is elevated against the nasopharyngeal wall; respiration is temporarily arrested while the upper esophageal sphincter opens to allow the bolus to enter the esophagus. In the esophagus, peristaltic coordinated muscular contractions push the food bolus toward the stomach. The lower esophageal sphincter relaxes shortly after the upper esophageal sphincter, so liquids that rapidly clear the esophagus enter the stomach without resistance.

Dysphagia is classified as oropharyngeal dysphagia and esophageal dysphagia. **Oropharyngeal dysphagia** occurs when the transfer of the food bolus from the mouth to the esophagus is impaired (also termed *transfer dysphagia*). The striated muscles of the mouth, pharynx, and upper esophageal sphincter are affected in oropharyngeal dysphagia. Neurologic and muscular disorders can give rise to oropharyngeal dysphagia (Table 352.2). Chiari malformations, Russell-Silver syndrome, and cri du chat may present with upper esophageal sphincter dysfunction, manifest by dysphagia with solids. The most serious complication of oropharyngeal dysphagia is life-threatening aspiration.

A complex sequence of neuromuscular events is involved in the transfer of foods to the upper esophagus. Abnormalities of the muscles involved in the ingestion process and their innervation, strength, or coordination are associated with transfer dysphagia in infants and children. In such cases, an oropharyngeal problem is usually part of a more generalized neurologic or muscular problem (botulism, diphtheria, neuromuscular disease). Painful oral lesions, such as acute viral stomatitis or trauma, occasionally interfere with ingestion. If the nasal air passage is seriously obstructed, the need for respiration causes severe distress when suckling. Although severe structural, dental, and salivary abnormalities would be expected to create difficulties, ingestion proceeds relatively well in most affected children if they are hungry.

Esophageal dysphagia occurs when there is difficulty in transporting the food bolus down the esophagus. Esophageal dysphagia can result from neuromuscular disorders or mechanical obstruction (Table 352.3). Primary motility disorders causing impaired peristaltic function and dysphagia are rare in children. Eosinophilic esophagitis can present with esophageal dysphagia. Achalasia is an esophageal motility disorder with associated inability of relaxation of the lower esophageal sphincter; it rarely occurs in children. Motility of the distal esophagus is disordered after surgical repair of tracheoesophageal fistula or achalasia. Abnormal motility can accompany collagen vascular disorders. Mechanical obstruction can be intrinsic or extrinsic. Intrinsic structural defects cause a fixed impediment to the passage of food bolus because of a narrowing within the esophagus, as in a stricture, web, or tumor. Extrinsic obstruction is caused by compression from vascular rings, mediastinal lesions, or vertebral abnormalities. Structural defects typically cause more problems in swallowing solids than liquids. In infants, esophageal web, tracheobronchial remnant, or vascular ring can cause dysphagia. An esophageal stricture secondary to esophagitis (chronic gastroesophageal reflux, eosinophilic esophagitis, chronic infections) occasionally has dysphagia as the first manifestation. An esophageal foreign body or a stricture secondary to a caustic ingestion also causes dysphagia. A Schatzki ring, a thin ring of mucosal tissue near the lower esophageal sphincter, is another mechanical cause of recurrent dysphagia, and again is rare in children.

When dysphagia is associated with a delay in passage through the esophagus, the patient may be able to point to the level of the chest where the delay occurs, but esophageal symptoms are usually referred

Table 352.2 Causes of Oropharyngeal Dysphagia

NEUROMUSCULAR DISORDERS
Cerebral palsy
Brain tumors
Cerebrovascular disease/stroke
Chiari malformation
Polio and postpolio syndromes
Multiple sclerosis
Myositis
Dermatomyositis
Myasthenia gravis
Muscular dystrophies
Acquired or inherited dystonia syndrome
Dysautonomia
METABOLIC AND AUTOIMMUNE DISORDERS
Hyperthyroidism
Systemic lupus erythematosus
Sarcoidosis
Amyloidosis
INFECTIOUS DISEASE
Meningitis
Botulism
Diphtheria
Lyme disease
Neurosyphilis
Viral infection: polio, coxsackievirus, herpes, cytomegalovirus
STRUCTURAL LESIONS
Inflammatory: abscess, pharyngitis
Congenital web
Cricopharyngeal bar
Dental problems
Bullous skin lesions
Plummer-Vinson syndrome
Zenker diverticulum
Extrinsic compression: osteophytes, lymph nodes, thyroid swelling, aberrant right subclavian artery (dysphagia lusoria)
OTHER
Corrosive injury
Side effects of medications
After surgery
After radiation therapy

Adapted from Gasiorowska A, Faas R. Current approach to dysphagia. *Gastroenterol Hepatol*. 2009;5(4):269–279.

Table 352.3 Causes of Esophageal Dysphagia

NEUROMUSCULAR
Eosinophilic esophagitis
Achalasia cardia
Diffuse esophageal spasm
Scleroderma
GERD
INTRINSIC LESIONS
Foreign bodies including pills
Esophagitis: GERD, eosinophilic esophagitis, infections
Stricture: corrosive injury, pill induced, peptic
Esophageal webs
Esophageal rings
Esophageal diverticula
Neoplasm
Chagas disease
EXTRINSIC LESIONS
Vascular compression
Mediastinal lesion
Cervical osteochondritis
Vertebral abnormalities

GERD, Gastroesophageal reflux disease.
Adapted from Gasiorowska A, Faas R. Current approach to dysphagia. *Gastroenterol Hepatol*. 2009;5(4):269–279.

to the suprasternal notch. When a patient points to the suprasternal notch, the impaction can be found anywhere in the esophagus.

REGURGITATION

Regurgitation is the effortless movement of stomach contents into the esophagus and mouth. It is not associated with distress, and infants with regurgitation are often hungry immediately after an episode. The lower esophageal sphincter prevents reflux of gastric contents into the esophagus. Regurgitation is a result of gastroesophageal reflux through an incompetent or, in infants, immature lower esophageal sphincter. This is often a developmental process, and regurgitation or "spitting" resolves with maturity. Regurgitation should be differentiated from vomiting, which denotes an active reflex process with an extensive differential diagnosis (Table 352.4).

NAUSEA

Nausea has been described as an unpleasant, subjective sensation of impending/imminent vomiting, often with epigastric sensation that may be painless. Nausea is frequently associated with typical autonomic signs that accompany vomiting. Not all nausea is a prodrome to vomiting. There are multiple potential triggers to nausea, including environmental exposures (toxins, odors), unpleasant visual stimuli, visceral pain, anxiety, stress, and a variety of additional etiologies (Table 352.5).

The central nervous system (CNS) is frequently implicated for nausea. Receptors and neural pathways at the chemoreceptor trigger zone (CTZ) are most often implicated by chemical stimuli with chemotherapy a prime example. Visceral stimuli can include ingestions, gastric hyperacidity, physical stress, psychologic stressors, mechanical distention of the stomach, and impaired GI motility; vagal and sympathetic nerves are involved in this process. Vestibular pathways are most often implicated in nausea related to motion sickness. Increased intracranial pressure can also present with nausea plus or minus vomiting.

Chronic nausea is more common in adolescents and may be coincidental with other functional GI disorders, including functional dyspepsia, delayed gastric emptying/gastroparesis, and constipation. There are gender and ethnic differences with respect to chronic nausea in adolescence, with adolescent White females with anxiety more at risk than other groups; there may be alterations in the brain gut axis coupled with increased visceral hypersensitivity and hyperalgesia at play in the setting (see Chapter 212). Dehydration and autonomic dysfunction may also present with nausea as one facet of GI manifestations.

Nausea is often a clinical diagnosis, and while the differential diagnosis is extensive, negative findings do not equate to the patient not having nausea. Nausea is often distressing, disruptive, and may be disabling with respect to normal function. Table 352.5 reviews common medical conditions associated with nausea, as well as treatment strategies. Hydration is important in many of these conditions. Many of the medications used employ antihistamine, serotonergic, dopaminergic, and potentially even opioid pathways (although these are still controversial). These agents are active at both the CNS and GI level, with significant brain-gut axis interplay. Complementary and

Table 352.4 Differential Diagnosis of Emesis During Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Gastroenteritis	Gastroenteritis	Gastroenteritis
Gastroesophageal reflux	Systemic infection	GERD
Overfeeding	Gastritis	Systemic infection
Anatomic obstruction*	Toxic ingestion/poisoning	Toxic ingestion/poisoning/marijuana
Systemic infection†	Pertussis syndrome	Gastritis
Pertussis syndrome	Medication	Sinusitis
Otitis media	Reflux (GERD)	Inflammatory bowel disease
	Sinusitis	Appendicitis
	Otitis media	Migraine
	Anatomic obstruction*	Pregnancy
	Eosinophilic esophagitis	Medications
		Ipecac abuse, bulimia
		Concussion
RARE		
Adrenogenital syndrome	Reye syndrome	Reye syndrome
Inborn errors of metabolism	Hepatitis	Hepatitis
Brain tumor (increased intracranial pressure)	Peptic ulcer	Peptic ulcer
Subdural hemorrhage	Pancreatitis	Pancreatitis
Food poisoning	Brain tumor	Cholecystitis
Rumination	Increased intracranial pressure	Brain tumor
Renal tubular acidosis	Middle ear disease/labyrinthitis	Increased intracranial pressure
Ureteropelvic junction obstruction	Chemotherapy	Concussion
Pseudoobstruction	Achalasia	Middle ear disease/labyrinthitis
	Cyclic vomiting (migraine)	Chemotherapy
	Esophageal stricture	Cyclic vomiting (migraine)
	Duodenal hematoma	Biliary colic
	Inborn error of metabolism	Renal colic
	Pseudoobstruction	Porphyria
	Gastroparesis	Diabetic ketoacidosis
		Adrenal insufficiency
		Pseudoobstruction
		Intestinal tumor
		Gastroparesis
		Achalasia
		Superior mesentery artery syndrome
		Distal intestinal obstruction syndrome

*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease, adhesions, and hernias.
†Meningitis, sepsis.
GERD, Gastroesophageal reflux disease.

Table 352.5 Examples of Causes and Management of Nausea

FUNCTIONAL GASTROINTESTINAL DISORDERS	TREATMENT APPROACHES
Gastroesophageal reflux	Diet and lifestyle; acid reduction, refluxate management
Esophagitis (reflux related, eosinophilic, etc.)	Acid reduction, identifying and restricting environmental/dietary triggers
Dyspepsia	Dietary and lifestyle modification; acid reduction; cyproheptadine
Gastroparesis	Smaller, more frequent meals; dietary modification; prokinetic agents (D_2 antagonists such as metoclopramide and domperidone*; low-dose erythromycin or azithromycin)
Constipation	Adequate hydration, diet and lifestyle modification, stool softeners, stimulant laxatives, additional adjunct measures if/as indicated
Visceral hyperalgesia	Tricyclic antidepressants (e.g., amitriptyline), cognitive behavioral therapy, hypnotherapy, biofeedback, physical therapy for desensitization; biofeedback; stress reduction
OTHER GASTROINTESTINAL DISORDERS	
Gastritis (medication/NSAID induced; *Helicobacter pylori*)	Reduce/remove medications involved; treat the underlying cause
Gastrointestinal dysmotility	Adequate hydration; diet/feeding or eating modification; promotility agents
Biliary dysfunction (cholelithiasis, cholecystitis, biliary dyskinesia)	Treat the underlying cause
Fundoplication	Smaller, more frequent meals; cyproheptadine to improve gastric accommodation
CENTRAL NERVOUS SYSTEM	
Increased intracranial pressure	Treat underlying cause
Migraines, headaches	Migraine prophylactic agents, including cyproheptadine. Abortive medications including triptans.
Motion sickness/vestibular dysfunction	Antihistamines (e.g., diphenhydramine, hydroxyzine) anticholinergics (e.g., scopolamine)
Autonomic dysfunction	Adequate hydration, increased salt intake, diet and lifestyle modification
Chemotherapy-induced nausea and vomiting	5-HT_3 receptor antagonists; D_2 antagonists; NK-1 antagonists; butyrophenones; benzodiazepines; dexamethasone; synthetic cannabinoids
Postoperative nausea and vomiting	5-HT_3 receptor antagonists
NON-GI AND NON-CNS ETIOLOGIES OF NAUSEA	
Uremia	Treat the underlying disorder
Endocrine disorders [e.g., hypothyroidism]	Treat the underlying disorder

*D_2 receptor antagonists such as metoclopramide and domperidone have a significant side effect profile, and have a U.S. Food and Drug Administration black box warning, and should be used with caution.
NK-1, Neurokinin 1.

alternative medicine approaches including using ginger, peppermint, aromatherapy, and biofeedback may be helpful. Behavior psychology and social work may be helpful in decreasing disability and enhancing functionality.

VOMITING

Vomiting is a highly coordinated reflex process that may be preceded by increased salivation and begins with involuntary retching. Violent descent of the diaphragm and constriction of the abdominal muscles with relaxation of the gastric cardia actively force gastric contents back up the esophagus. This process is coordinated in the medullary vomiting center, which is influenced directly by afferent innervation and indirectly by the CTZ and higher CNS centers. Many acute or chronic processes can cause vomiting (see Tables 352.1 and 352.4).

Vomiting caused by obstruction of the GI tract is probably mediated by intestinal visceral afferent nerves stimulating the vomiting center (Table 352.6). If obstruction occurs below the second part of the duodenum, vomitus is usually bile stained. Emesis can also become bile stained with repeated vomiting in the absence of obstruction when duodenal contents are refluxed into the stomach. Nonobstructive lesions of the digestive tract can also cause vomiting; this includes diseases of the upper bowel, pancreas, liver, or biliary tree. CNS or metabolic derangements and cyclic vomiting syndrome (see Chapter 390) can lead to severe, persistent emesis. Marijuana use among teens has also led to cannabis hyperemesis syndrome (see Chapter 157.3)

Potential complications of emesis are noted in Table 352.7. Broad management strategies for vomiting in general and specific causes of emesis are noted in Tables 352.8 and 352.9.

DIARRHEA

Diarrhea is best defined as excessive loss of fluid and electrolyte in the stool. Acute diarrhea is defined as sudden onset of excessively loose stools of >10 mL/kg/day in infants and >200 g/24 hr in older children, which lasts <14 days. When the episode lasts longer than 14 days, it is called *chronic* or *persistent diarrhea*.

Normally, a young infant has approximately 5 mL/kg/day of stool output; the volume increases to 200 g/24 hr in an adult. The greatest volume of intestinal water is absorbed in the small bowel; the colon concentrates intestinal contents against a high osmotic gradient. The small intestine of an adult can absorb 10-11 L/day of a combination of ingested and secreted fluid, whereas the colon absorbs approximately 0.5 L. Disorders that interfere with absorption in the small bowel tend to produce voluminous diarrhea, whereas disorders compromising colonic absorption produce lower-volume diarrhea. **Dysentery** (small-volume, frequent bloody stools with mucus, tenesmus, and urgency) is the predominant symptom of colitis.

The basis of all diarrheas is disturbed intestinal solute transport and water absorption. Water movement across intestinal membranes is passive and is determined by both active and passive fluxes of solutes, particularly sodium, chloride, and glucose. The pathogenesis of most episodes of diarrhea can be explained by secretory, osmotic, or motility abnormalities or a combination of these (Table 352.10).

Secretory diarrhea occurs when the intestinal epithelial cell solute transport system is in an active state of secretion. It is often caused by a secretagogue, such as cholera toxin, binding to a receptor on the surface epithelium of the bowel and thereby stimulating intracellular accumulation of cyclic adenosine monophosphate or cyclic guanosine monophosphate. Some intraluminal fatty acids and bile salts cause the colonic mucosa to secrete through this

Table 352.6 Causes of Gastrointestinal Obstruction

ESOPHAGUS

Congenital

Esophageal atresia
Vascular rings
Schatzki ring
Tracheobronchial remnant

Acquired

Esophageal stricture
Foreign body
Achalasia
Chagas disease
Collagen vascular disease

STOMACH

Congenital

Antral webs
Pyloric stenosis

Acquired

Bezoar, foreign body
Pyloric stricture (ulcer)
Chronic granulomatous disease of childhood
Eosinophilic gastroenteritis
Crohn disease
Epidermolysis bullosa

SMALL INTESTINE

Congenital

Duodenal atresia
Annular pancreas
Malrotation/volvulus
Malrotation/Ladd bands
Ileal atresia
Meconium ileus
Meckel diverticulum with volvulus or intussusception
Inguinal hernia
Internal hernia
Intestinal duplication
Pseudoobstruction

Acquired

Postsurgical adhesions
Crohn disease
Intussusception
Distal ileal obstruction syndrome (cystic fibrosis)
Duodenal hematoma
Superior mesenteric artery syndrome

COLON

Congenital

Meconium plug
Hirschsprung disease
Colonic atresia, stenosis
Imperforate anus
Rectal stenosis
Pseudoobstruction
Volvulus
Colonic duplication

Acquired

Ulcerative colitis (toxic megacolon)
Chagas disease
Crohn disease
Fibrosing colonopathy (cystic fibrosis)

Table 352.7 Complications of Vomiting

COMPLICATION	PATHOPHYSIOLOGY	HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES
Metabolic	Fluid loss in emesis	Dehydration
	HCl loss in emesis	Alkalosis; hypochloremia
	Na, K loss in emesis	Hyponatremia; hypokalemia
	Acidosis	Dehydration
Nutritional	Emesis of calories and nutrients Anorexia for calories and nutrients	Malnutrition; "failure to thrive"
Mallory-Weiss tear	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock	Severe fluid loss in emesis or in accompanying diarrhea	Dehydration (accompanying diarrhea can explain acidosis?)
	Severe blood loss in hematemesis	Blood volume depletion
Pneumomediastinum, pneumothorax	Increased intrathoracic pressure	Chest x-ray
Petechiae, retinal hemorrhages	Increased intrathoracic pressure	Normal platelet count

From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004: p. 318.

Table 352.8 Pharmacologic Therapies for Vomiting Episodes

DISORDER – THERAPEUTIC CLASS	DRUG	DOSAGE	COMMENTS
REFLUX – ANTACIDS			
Histamine-2 receptor antagonist	Famotidine (Pepcid)	<3 months: 0.5 mg/kg/dose PO daily ≥ 3 months: 0.5 mg/kg/dose PO twice daily Children >40 kg: 20 mg twice daily, max: 40 mg/dose	• H2RAs are associated with tachyphylaxis • Ranitidine was withdrawn in 2020 • Cimetidine has antiandrogenic potential, can stimulate prolactin secretion, and may be subject to drug interactions due to enzyme inhibition
	Nizatidine (Axid)	<12 years: 5 mg/kg/dose PO twice daily* ≥12 years: 150 mg PO twice daily, max 300 mg/day	
	Cimetidine	<16 years: 30-40 mg/kg/day PO divided 2-3x daily,* max: 400 mg/dose ≥16 years: 400 mg PO 4 times daily or 800 mg PO twice daily	
Proton pump inhibitors	Omeprazole (Prilosec) Lansoprazole (Prevacid) Esomeprazole (Nexium) Pantoprazole (Protonix)	1-2 mg/kg/day PO in 1-2 divided doses Maximum dose: omeprazole, esomeprazole, pantoprazole: 40 mg/dose; lansoprazole: 30 mg/dose	• Administer 30 minutes before first meal of the day for optimal effect • Long-term side effects include increased risk of infections, bone health abnormalities, hypomagnesemia, vitamin B12 deficiency • Consider weaning in patients on prolonged course (>6 months) to avoid rebound symptoms
GASTROPARESIS – PROKINETICS			
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg/dose PO/IV every 6 to 8 hours, max: 10 mg/dose	• Use minimum effective dose and limit duration due to increased risk of extrapyramidal symptoms (EPS) with cumulative exposure • Although some clinicians use diphenhydramine to limit EPS, anticholinergic effects of diphenhydramine may negate prokinetic benefit
Motilin agonist	Erythromycin	5 mg/kg/dose PO 3-4 times daily, titrate up to 10 mg/kg/dose, max: 250 mg/dose	• Prescribe suspension for optimal pharmacokinetic profile in patients with hypomotility • Cycling or drug-holidays may mitigate tachyphylaxis • Subject to drug interactions due to CYP3A4 inhibition • Associated with QTc prolongation, consider baseline EKG and/or periodic monitoring in patients with risk factors (underlying cardiac disorder, concomitant QT prolonging medications, electrolyte derangements) • Routine use of other macrolides (azithromycin, clarithromycin) is not recommended due to limited data to support use, unknown optimal dose/frequency, and concerns for antibiotic resistance

Continued

Table 352.8 Pharmacologic Therapies for Vomiting Episodes—cont'd

DISORDER – THERAPEUTIC CLASS	DRUG	DOSAGE	COMMENTS
Serotonin (5HT-4) agonist	Cisapride	Consult GI specialist	• Withdrawn from the market in most countries due to QTc prolongation risk • Use restricted to regulated/limited-access programs with specialist supervision
	Prucalopride* (Motegrity)	>4 years: 0.04 mg/kg/dose PO once daily, max: 2 mg/dose Dosing range 0.02-0.06 mg/kg/dose to accommodate tablets	• Approved for constipation in adults, but a single-center retrospective study showed improvement in children with refractory upper GI symptoms
Cholinergic agonist	Bethanechol*	0.1-0.2 mg/kg/dose PO 3 to 4 times daily, max: 10 mg/dose	• Administer before feeds/meals • Stimulates antral contractions but does not impact gastric emptying • Caution when using with anticholinergic agents (e.g., glycopyrrolate) due to potential for reduced efficacy/negating effect
CHEMOTHERAPY-INDUCED NAUSEA/VOMITING (CINV), POSTOPERATIVE, GENERAL			
Serotonin 5HT3 antagonist	Ondansetron (Zofran)	0.1-0.15 mg/kg/dose PO/IV q8h, max: 24 mg/day Single dose regimen: 0.3 mg/kg/dose PO/IV, max: 16 mg/dose	• Adverse effects: constipation, headache, QTc prolongation • Dose varies based on chemotherapy emetogenicity
	Granisetron (Kytril)	≥2 years: 0.01 mg/kg/dose PO/IV q12h, max: 2 mg/dose *Single daily dose: 0.02-0.04 mg/kg PO/IV	
Phenothiazine	Prochlorperazine (Compazine)	≥2 years: 0.1 mg/kg/dose PO/IV q6-8h PRN, max: 10 mg/dose	• Due to safety concerns (EPS, sedation, respiratory depression), routine use of phenothiazines is not recommended • Consider concomitant diphenhydramine to decrease risk of dystonic reactions • Promethazine is associated with extravasation; IV/IM administration is generally avoided
	Promethazine (Phenergan)	≥2 years: 0.25 to 0.5 mg/kg/dose PO/rectal q4-6h PRN, max: 25 mg/dose	
	Chlorpromazine (Thorazine)	≥6 months: 0.5 to 1 mg/kg/dose PO/IM/IV q6-8h PRN	
Substance P / neurokinin 1 antagonist	Aprepitant (Emend), for CINV	≥6 months and children <30 kg: 3 mg/kg PO on day 1, then 2 mg/kg once daily on days 2 and 3 Children >30 kg: 125 mg PO daily on day 1, then 80 mg PO daily on days 2 and 3	• Subject to drug interactions due to enzyme inhibition
Steroids	Dexamethasone, for CINV	0.1 mg/kg/dose or 3 mg/m2/dose PO/IV q12h-24h	• Reported regimens vary, dose depends on chemotherapy emetogenicity • May require dose reduction with concomitant aprepitant

Table 352.8 Pharmacologic Therapies for Vomiting Episodes—cont'd

DISORDER – THERAPEUTIC CLASS	DRUG	DOSAGE	COMMENTS
MOTION SICKNESS, VESTIBULAR DISORDERS			
Antihistamine	Diphenhydramine (Benadryl)	0.5-1 mg/kg/dose PO/IV/IM q6-8h, max: 50 mg/dose	• Anticholinergic effects may contribute to decreased motility • Dimenhydrinate is available as 50 mg tablets, prescribe in 12.5 mg increments • Do not cut or manipulate scopolamine transdermal patches • Withdrawal (cholinergic rebound) symptoms reported with long-term use, limit duration or consider weaning with extended use
	Dimenhydrinate (Dramamine)	>2 years: 1 to 1.5 mg/kg/dose PO q6-8h, max: 25 mg/dose	
	Meclizine (Antivert)	>2 to <12 years: 6.25 mg to 12.5 mg PO three times daily PRN >12 years: 25 mg to 50 mg PO 1 to 4 times daily, max: 100 mg/day	
	Scopolamine (Transderm-Scop)	>15 kg: 1 transdermal patch applied behind the ear every 3 days	
MISCELLANEOUS			
Visceral Hypersensitivity, Feeding Intolerance Antihistamine/serotonin antagonist	Cyproheptadine*	0.25 mg/kg/day PO in 1-3 divided doses, usual max: 4 mg/dose	• Consider starting with bedtime dose and titrating up to prevent daytime sedation • Associated with tachyphylaxis • Benefit reported in patients with visceral hypersensitivity • Anticholinergic effects may decrease motility
Pseudo-obstruction Somatostatin analog	Octreotide*	0.5 to 1 mcg/kg subQ once daily, max: 100 mcg/dose	• May cause bradycardia, hypoglycemia
Adrenal Crisis	Hydrocortisone	100 mg/m^2 IV/IM x1, followed by 25 mg/m^2/dose IV/IM q6h, max: 100 mg/day Taper as clinically indicated	• Reported regimens vary, refer to individual protocols

*Limited data available

Table 352.9 Supportive and Nonpharmacologic Therapies for Vomiting Episodes

DISEASE	THERAPY
All	Treat cause • Obstruction: operate • Allergy: change diet (±steroids) • Metabolic error: Rx defect • Acid peptic disease: H_2Ras, PPIs, etc.
COMPLICATIONS	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H_2Ras, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS, Distal intestinal obstruction syndrome; GI, gastrointestinal; H_2RA, H_2-receptor antagonist; NG, nasogastric; NJ, nasojejunal; PPIs, proton pump inhibitors; tbs, tablespoon.
From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004: p. 319.

Table 352.10 Mechanisms of Diarrhea

PRIMARY MECHANISM	DEFECT	STOOL EXAMINATION	EXAMPLES	COMMENT
Secretory	Decreased absorption, increased secretion, electrolyte transport	Watery, normal osmolality with ion gap <100 mOsm/kg	Cholera, toxigenic *Escherichia coli*; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, *Clostridium difficile*, cryptosporidiosis (AIDS)	Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes
Osmotic	Maldigestion, transport defects ingestion of unabsorbable substances	Watery, acidic, and reducing substances; increased osmolality with ion gap >100 mOsm/kg	Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse	Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes
Increased motility	Decreased transit time	Loose to normal-appearing stool, stimulated by gastrocolic reflex	Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome	Infection can also contribute to increased motility
Decreased motility	Defect in neuromuscular unit(s) stasis (bacterial overgrowth)	Loose to normal-appearing stool	Pseudoobstruction, blind loop	Possible bacterial overgrowth
Decreased surface area (osmotic, motility)	Decreased functional capacity	Watery	Short bowel syndrome, celiac disease, rotavirus enteritis	Might require elemental diet plus parenteral alimentation
Mucosal invasion	Inflammation, decreased colonic reabsorption, increased motility	Blood and increased WBCs in stool	*Salmonella, Shigella* infection; amebiasis; *Yersinia, Campylobacter* infection	Dysentery evident in blood, mucus, and WBCs

VIP, Vasoactive intestinal peptide; WBC, white blood cell.
From Kliegman RM, Greenbaum LA, Lye PS. eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004: p 274.

mechanism. Diarrhea not associated with an exogenous secretagogue can also have a secretory component (congenital microvillus inclusion disease). Secretory diarrhea is usually of large volume and persists even with fasting. The stool osmolality is predominantly indicated by the electrolytes, and the ion gap is 100 mOsm/kg or less. The ion gap is calculated by subtracting the concentration of electrolytes from total osmolality:

$$\text{Ion gap} = \text{Stool osmolality} - [(\text{Stool Na} + \text{stool K})\,2]$$

Osmotic diarrhea occurs after ingestion of a poorly absorbed solute. The solute may be one that is normally not well absorbed (magnesium, phosphate, lactulose, or sorbitol) or one that is not well absorbed because of a disorder of the small bowel (lactose with lactase deficiency or glucose with rotavirus diarrhea). Malabsorbed carbohydrate is fermented in the colon, and short-chain fatty acids are produced. Although short-chain fatty acids can be absorbed in the colon and used as an energy source, the net effect is increase in the osmotic solute load. This form of diarrhea is usually of lesser volume than a secretory diarrhea and stops with fasting. The osmolality of the stool will not be explained by the electrolyte content, because another osmotic component is present and so the anion gap is >100 mOsm.

Motility disorders can be associated with rapid or delayed transit and are not generally associated with large-volume diarrhea. Slow motility can be associated with bacterial overgrowth leading to diarrhea. The differential diagnosis of common causes of acute and chronic diarrhea is noted in Table 352.11.

CONSTIPATION

Any definition of constipation is relative and depends on stool consistency, stool frequency, and difficulty in passing the stool. A normal child might have a soft stool only every second or third day without difficulty; this is not constipation. A hard stool passed with difficulty every third day should be treated as constipation. Constipation can arise from defects either in filling or emptying the rectum (Table 352.12).

A nursing infant might have very infrequent stools of normal consistency, which is usually a normal pattern. True constipation in the neonatal period is most likely secondary to Hirschsprung disease, intestinal pseudoobstruction, or hypothyroidism.

Defective rectal filling occurs when colonic peristalsis is ineffective (in cases of hypothyroidism or opiate use and when bowel obstruction is caused either by a structural anomaly or by Hirschsprung disease). The resultant colonic stasis leads to excessive drying of stool and a failure to initiate reflexes from the rectum that normally trigger evacuation. Emptying the rectum by spontaneous evacuation depends on a defecation reflex initiated by pressure receptors in the rectal muscle. Therefore stool retention can also result from lesions involving these rectal muscles, the sacral spinal cord afferent and efferent fibers, or the muscles of the abdomen and pelvic floor. Disorders of anal sphincter relaxation can also contribute to fecal retention.

Constipation tends to be self-perpetuating, whatever its cause. Hard, large stools in the rectum become difficult and even painful to evacuate; thus more retention occurs and a vicious circle ensues. Distention of the rectum and colon lessens the sensitivity of the defecation reflex and the effectiveness of peristalsis. Fecal impaction is common and leads to other problems. Eventually, watery content from the proximal colon might percolate around hard retained stool and pass per rectum unperceived by the child. This involuntary **encopresis** may be mistaken for diarrhea. Constipation itself does not have deleterious systemic organic effects, but urinary tract stasis with increased risk of urinary tract infections can accompany severe long-standing cases and constipation can generate anxiety, having a marked emotional impact on the patient and family.

Table 352.11 Differential Diagnosis of Diarrhea

INFANT	CHILD	ADOLESCENT
ACUTE		
Common		
Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)
Systemic infection	Food poisoning	Food poisoning
Antibiotic associated	Systemic infection	Antibiotic associated
Overfeeding	Antibiotic associated	
Rare		
Primary disaccharidase deficiency	Toxic ingestion	Hyperthyroidism
Hirschsprung toxic colitis	Hemolytic uremic syndrome	Appendicitis
Adrenogenital syndrome	Intussusception	
Neonatal opiate withdrawal		
CHRONIC		
Common		
Postinfectious secondary lactase deficiency	Postinfectious secondary lactase deficiency	Irritable bowel syndrome
Cow's milk or soy protein intolerance (allergy)	Irritable bowel syndrome	Inflammatory bowel disease
Chronic nonspecific diarrhea of infancy	Celiac disease	Lactose intolerance
Excessive fruit juice (sorbitol) ingestion	Cystic fibrosis	Giardiasis
Celiac disease	Lactose intolerance	Laxative abuse (anorexia nervosa)
Cystic fibrosis	Excessive fruit juice (sorbitol) ingestion	Constipation with encopresis
AIDS enteropathy	Giardiasis	
	Inflammatory bowel disease	
	AIDS enteropathy	
Rare		
Primary immune defects	Primary and acquired immune defects	Secretory tumor
Autoimmune enteropathy	Secretory tumors	Primary bowel tumor
IPEX and IPEX-like syndromes	Pseudoobstruction	Parasitic infections and venereal diseases
Glucose-galactose malabsorption	Sucrase-isomaltase deficiency	Appendiceal abscess
Microvillus inclusion disease (microvillus atrophy)	Eosinophilic gastroenteritis	Addison disease
Congenital transport defects (chloride, sodium)	Secretory tumors	
Primary bile acid malabsorption		
Factitious syndrome by proxy		
Hirschsprung disease		
Shwachman syndrome		
Secretory tumors		
Acrodermatitis enteropathica		
Lymphangiectasia		
Abetalipoproteinemia		
Eosinophilic gastroenteritis		
Short bowel syndrome		

IPEX, Immunodysregulation polyendocrinopathy enteropathy X-linked.
From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004: p. 272.

Table 352.12 Causes of Constipation

NONORGANIC (FUNCTIONAL): RETENTIVE

Anatomic
Anal stenosis, atresia with fistula
Imperforate anus
Anteriorly displaced anus
Intestinal stricture (postnecrotizing enterocolitis)
Anal stricture

Abnormal Musculature
Prune-belly syndrome
Gastroschisis
Down syndrome
Muscular dystrophy

Intestinal Nerve or Muscle Abnormalities
Hirschsprung disease
Pseudoobstruction (visceral myopathy or neuropathy)
Intestinal neuronal dysplasia
Spinal cord lesions
Tethered cord
Autonomic neuropathy
Spinal cord trauma
Spina bifida
Chagas disease

Drugs
Anticholinergics
Narcotics
Methylphenidate
Phenytoin
Antidepressants
Chemotherapeutic agents (vincristine)
Pancreatic enzymes (fibrosing colonopathy)
Lead, arsenic, mercury
Vitamin D intoxication
Calcium channel blocking agents

Metabolic Disorders
Hypokalemia
Hypercalcemia
Hypothyroidism
Diabetes mellitus, diabetes insipidus
Porphyria

Intestinal Disorders
Celiac disease
Cow's milk protein intolerance
Cystic fibrosis (meconium ileus equivalent)
Inflammatory bowel disease (stricture)
Tumor
Connective tissue disorders
Systemic lupus erythematosus
Scleroderma

Psychiatric Diagnosis
Anorexia nervosa

ANOREXIA

Anorexia means prolonged lack of appetite. Hunger and satiety centers are located in the hypothalamus; it seems likely that afferent nerves from the GI tract to these brain centers are important determinants of the anorexia that characterizes many diseases of the stomach and intestine. Satiety is stimulated by distention of the stomach or upper small bowel, the signal being transmitted by sensory afferents, which are especially dense in the upper gut. Chemoreceptors in the intestine, influenced by the assimilation of nutrients, also affect afferent flow to the appetite centers. Impulses reach the hypothalamus from higher centers, possibly influenced by pain or the emotional disturbance of an intestinal disease. Other regulatory factors include hormones, ghrelin, leptin, and plasma glucose, which, in turn, reflect intestinal function.

ABDOMINAL PAIN

There is considerable variation among children in their perception and tolerance for abdominal pain. This is one reason the evaluation of chronic abdominal pain is difficult. A child with **functional abdominal pain** (also known as centrally mediated abdominal pain syndrome or brain-gut axis dysfunction) may be as uncomfortable as one with an organic cause. It is very important to distinguish between organic and nonorganic (functional) abdominal pain because the approach for the management is based on this (Table 352.13). Normal growth and physical examination (including a rectal examination) and the absence of anemia or hematochezia are reassuring in a child who is suspected of having functional pain.

A specific cause may be difficult to find, but the nature and location of a pain-provoking lesion can usually be determined from the clinical description. Two types of nerve fibers transmit painful stimuli in the abdomen. In skin and muscle, A fibers mediate sharp localized pain; C fibers from viscera, peritoneum, and muscle transmit poorly localized, dull pain. These afferent fibers have cell bodies in the dorsal root ganglia, and some axons cross the midline and ascend to the medulla, midbrain, and thalamus. Pain is perceived in the cortex of the postcentral gyrus, which can receive impulses arising from both sides of the body. In the gut, the usual stimulus provoking pain is tension or stretching. Inflammatory lesions can lower the pain threshold, but the mechanisms producing pain or inflammation are not clear. Tissue metabolites released near nerve endings probably account for the pain caused by ischemia. Perception of these painful stimuli can be modulated by input from both cerebral and peripheral sources. Psychologic factors are particularly important. Tables 352.14 and 352.15 list features of abdominal pain. Pain that suggests a potentially serious organic etiology is associated with age younger than 5 years; fever; weight loss; bile- or blood-stained emesis; jaundice; hepatosplenomegaly; back or flank pain or pain in a location other than the umbilicus; awakening from sleep in pain; referred pain to shoulder, groin, or back; elevated erythrocyte sedimentation rate, white blood cell count, or CRP; anemia; edema; hematochezia; or a strong family history of inflammatory bowel disease or celiac disease (see Table 352.13).

Table 352.13 Red Flags and Clues to an Organic Cause of Abdominal Pain

Age <5 yr old
Localized pain in nonperiumbilical site
Referred pain
Sudden onset of excruciating pain
Crescendo nature of pain
Sudden worsening of pain
Fever (high fever >39.4°C suggests pneumonia, pyelonephritis, dysentery, cholangitis, more than perforation or abscess)
Jaundice
Distention*
Dysphagia
Dysuria
Emesis (especially bilious)
Anorexia
Weight loss, failure to thrive
Positive family history (metabolic disorders, peptic ulcer disease)†
Change in urine or stool color (blood, acholic) or frequency
Vaginal discharge
Menstrual abnormalities (amenorrhea)
Sexual activity
Delayed sexual development (chronic pain)
Anemia
Elevated erythrocyte sedimentation rate
Elevated stool calprotectin
Specific physical findings (hepatomegaly, splenomegaly, absent bowel sounds, adnexal tenderness, palpable mass, involuntary guarding, focal or diffuse tenderness, positive rectal examination results, perianal disease, joint swelling, rashes)

*Consider 5 Fs: fat, feces, flatus (aerophagia, obstruction), fluid (ascites, hydronephrosis, cysts), and fetus (pregnancy or fetal-like abnormal growth [e.g., tumors]).
†Family history is also positive for chronic pain syndromes (constipation, irritable bowel, dysmenorrhea, and lactase or sucrase deficiency).
Modified from Miranda A. Abdominal pain. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis.* 2nd ed. Philadelphia: Elsevier; 2023: Table 13.8, p. 229.

Visceral pain tends to be dull and aching and is experienced in the dermatome from which the affected organ receives innervations. So, most often, the pain and tenderness are not felt over the site of the disease process. Painful stimuli originating in the liver, pancreas, biliary tree, stomach, or upper bowel are felt in the epigastrium; pain from the distal small bowel, cecum, appendix, or proximal colon is felt at the umbilicus; and pain from the distal large bowel, urinary tract, or pelvic organs is usually suprapubic. The pain from the cecum, ascending colon, and descending colon sometimes is felt at the site of the lesion because of the short mesocecum and corresponding mesocolon. The pain caused by appendicitis is initially felt in the periumbilical region, and pain from the transverse colon is usually felt in the suprapubic region. The shifting (localization) of pain is a pointer toward diagnosis; for example, periumbilical pain of a few hours localizing to the right lower quadrant suggests appendicitis. Radiation of pain can be helpful in diagnosis; in biliary colic the radiation of pain is toward the inferior angle of the right scapula, pancreatic pain is radiated to the back, and the renal colic pain is radiated to the inguinal region on the same side.

Differentiating abdominal wall pain from visceral pain is important and can prevent unnecessary testing. Nerve entrapment is one of the more common causes in adults. **Costochondritis** can be differentiated from underlying pain by palpating the rib margins, which should reproduce the pain. Treatment with topical anesthetics and NSAIDs if needed usually resolve pain within a few days. **Slipped rib syndrome** can follow overuse or even minor trauma to the ribs on either side. The name originates from a popping/slipping sensation that is often reported. Slipped rib syndrome may be mistaken for hepatobiliary, splenic, pancreatic, esophageal, or gastric etiologies, among others. Rib fractures, costochondritis, perichondritis [Tietze syndrome], and pleuritic pain may also present as an etiology. **Anterior (abdominal) cutaneous nerve entrapment syndrome (ACNES)** may produce acute, recurrent, or chronic unilateral localized abdominal pain. Nerve entrapment is most common at the lateral border of the rectus muscle.

Somatic pain is intense and usually well localized. When the inflamed viscus comes in contact with a somatic organ such as the parietal peritoneum or the abdominal wall, pain is localized to that site. Peritonitis gives rise to generalized abdominal pain with rigidity, involuntary guarding, rebound tenderness, and cutaneous hyperesthesia on physical examination.

Referred pain from extraintestinal locations, from shared central projections with the sensory pathway from the abdominal wall, can give rise to abdominal pain, as in pneumonia when the parietal pleural pain is referred to the abdomen (Fig. 352.1).

GASTROINTESTINAL HEMORRHAGE

Bleeding can occur anywhere along the GI tract, and identification of the site may be challenging (Table 352.16). Bleeding that originates in the esophagus, stomach, or duodenum can cause **hematemesis.** When exposed to gastric or intestinal juices, blood quickly darkens to

Table 352.14 Chronic Abdominal Pain in Children

DISORDER	CHARACTERISTICS	KEY EVALUATIONS
NONORGANIC		
Functional abdominal pain	Nonspecific pain, often periumbilical	Hx and PE; tests as indicated
Irritable bowel syndrome	Intermittent cramps, diarrhea, and constipation	Hx and PE
Nonulcer dyspepsia	Peptic ulcer–like symptoms without abnormalities on evaluation of the upper GI tract	Hx; esophagogastroduodenoscopy
GASTROINTESTINAL TRACT		
Chronic constipation	Hx of stool retention, evidence of constipation on examination	Hx and PE; plain x-ray of abdomen
Lactose intolerance	Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea	Trial of lactose-free diet; lactose breath hydrogen test
Parasite infection (especially *Giardia*)	Bloating, gas, cramps, and diarrhea	Stool evaluation for O&P; specific immunoassays for *Giardia*
Excess fructose or sorbitol ingestion	Nonspecific abdominal pain, bloating, gas, and diarrhea	Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol
Crohn disease	See Chapter 382.2	
Peptic ulcer	Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids	Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy
Esophagitis	Epigastric pain with substernal burning	Esophagogastroduodenoscopy
Meckel diverticulum	Periumbilical or lower abdominal pain; may have blood in stool (usually painless)	Meckel scan or enteroclysis
Recurrent intussusception	Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode	Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract
Internal, inguinal, or abdominal wall hernia	Dull abdomen or abdominal wall pain	PE, CT of abdominal wall
Chronic appendicitis or appendiceal mucocele	Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain	Barium enema, CT
GALLBLADDER AND PANCREAS		
Cholelithiasis	RUQ pain, might worsen with meals	Ultrasound of gallbladder
Choledochal cyst	RUQ pain, mass ± elevated bilirubin	Ultrasound or CT of RUQ
Recurrent pancreatitis	Persistent boring pain, might radiate to back, vomiting	Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas
GENITOURINARY TRACT		
Urinary tract infection	Dull suprapubic pain, flank pain	Urinalysis and urine culture; renal scan
Hydronephrosis	Unilateral abdominal or flank pain	Ultrasound of kidneys
Urolithiasis	Progressive, severe pain; flank to inguinal region to testicle	Urinalysis, ultrasound, IVP, CT
Other genitourinary disorders	Suprapubic or lower abdominal pain; genitourinary symptoms	Ultrasound of kidneys and pelvis; gynecologic evaluation
MISCELLANEOUS CAUSES		
Abdominal migraine	See text; nausea, family Hx migraine	Hx
Abdominal epilepsy	Might have seizure prodrome	EEG (can require >1 study, including sleep-deprived EEG)
Gilbert syndrome	Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin	Serum bilirubin
Familial Mediterranean fever	Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis	Hx and PE during an episode, DNA diagnosis
Sickle cell crisis	Anemia	Hematologic evaluation
Lead poisoning	Vague abdominal pain ± constipation	Serum lead level
IgA vasculitis (Henoch-Schönlein purpura)	Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis	Hx, PE, urinalysis
Angioneurotic edema	Swelling of face or airway, crampy pain	Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor
Acute intermittent porphyria	Severe pain precipitated by drugs, fasting, or infections	Spot urine for porphyrins
Anterior cutaneous nerve entrapment syndrome (ACNES)	Exquisite localized (~2 × 2 cm) tenderness that is replicable, most often RLQ	Pain relief within 15 min of abdominal wall injection of local anesthetic; may need surgery

ERCP, Endoscopic retrograde cholangiopancreatography; EEG, electroencephalogram; GI, gastrointestinal; Hx, history; IVP, intravenous pyelography; O&P, ova and parasites; PE, physical exam; RLQ, right lower quadrant; RUQ, right upper quadrant.

Table 352.15 Distinguishing Features of Acute Abdominal Pain in Children

DISEASE	ONSET	LOCATION	REFERRAL	QUALITY	COMMENTS
Pancreatitis	Acute	Epigastric, left upper quadrant	Back	Constant, sharp, boring	Nausea, emesis, tenderness
Intestinal obstruction	Acute or gradual	Periumbilical-lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, emesis, increased bowel sounds
Appendicitis	Acute (1-3 days)	Periumbilical, then localized to lower right quadrant; generalized with peritonitis	Back or pelvis if retrocecal	Sharp, steady	Anorexia, nausea, emesis, local tenderness, fever with peritonitis
Intussusception	Acute	Periumbilical-lower abdomen	None	Cramping, with painless periods	Hematochezia, knees in pulled-up position
Urolithiasis	Acute, sudden	Back (unilateral)	Groin	Sharp, intermittent, cramping	Hematuria
Urinary tract infection	Acute	Back	Bladder	Dull to sharp	Fever, costovertebral angle tenderness, dysuria, urinary frequency
Pelvic inflammatory disease	Acute	Pelvis, lower quadrant	Upper thigh	Aching, peritoneal signs	Vaginal discharge, fever
Small bowel obstruction	Acute to subacute	Periumbilical	None	Cramping diffuse	Emesis and obstipation
Ruptured ectopic pregnancy	Acute sudden	Pelvis, lower quadrant	None	Sharp, intense, localized	Vaginal bleeding, shock

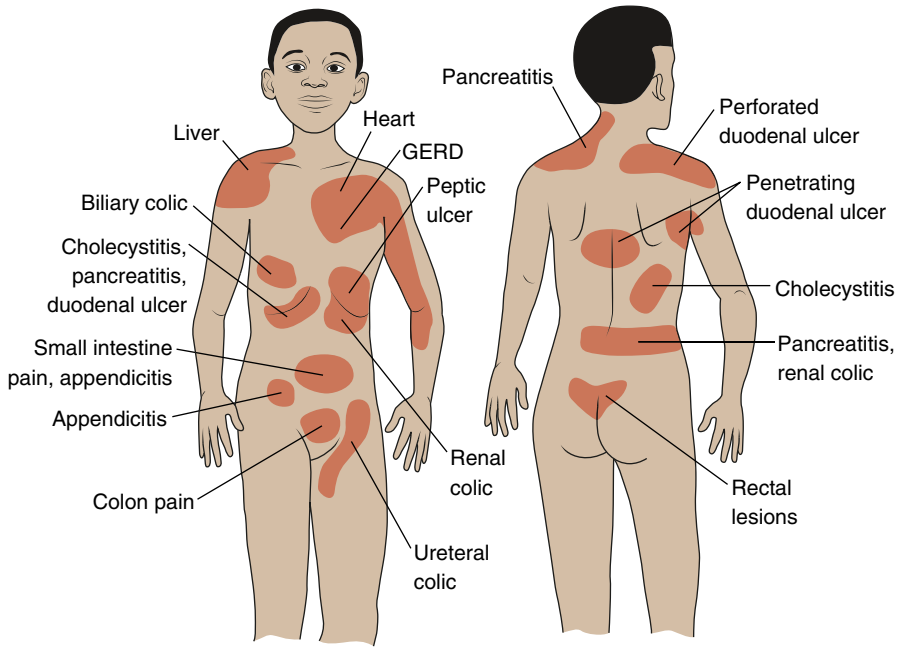

Fig. 352.1 Common sites of referred pain from the abdominal viscera. When a patient gives a history of referred pain from the viscera, the pain's location may not be directly over the impaired organ. Visceral embryologic development is the mechanism of the referred pain pattern. Pain is referred to the site where the organ was located in fetal development.

resemble coffee grounds; massive bleeding is likely to be red. Red or maroon blood in stools, **hematochezia,** signifies either a distal bleeding site or massive hemorrhage above the distal ileum. Moderate to mild bleeding from sites above the distal ileum tends to cause blackened stools of tarry consistency **(melena);** major hemorrhages in the duodenum or above can also cause melena.

Erosive damage to the mucosa of the GI tract is the most common cause of bleeding, although variceal bleeding secondary to portal hypertension occurs often enough to require consideration. Prolapse gastropathy producing subepithelial hemorrhage and Mallory-Weiss lesions secondary to mucosal tears associated with emesis are causes of upper intestinal bleeds. Vascular malformations are a rare cause in children; they are difficult to identify (Figs. 352.2 and 352.3). Upper intestinal bleeding is evaluated with esophagogastroduodenoscopy. Evaluation of the small intestine is facilitated by capsule endoscopy. The capsule-sized imaging device is swallowed in older children or placed endoscopically in younger children. Lower GI bleeding is investigated with a colonoscopy. In brisk intestinal bleeding of unknown location, a tagged red blood cell scan is helpful in locating the site of the bleeding, although CT angiography is usually diagnostic. Occult blood

Table 352.16 Differential Diagnosis of Gastrointestinal Bleeding in Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Bacterial enteritis	Bacterial enteritis	Bacterial enteritis
Milk protein allergy intolerance	Anal fissure	Inflammatory bowel disease
Intussusception	Colonic polyps	Peptic ulcer/gastritis
Swallowed maternal blood	Intussusception	Prolapse (traumatic) gastropathy secondary to emesis
Anal fissure	Peptic ulcer/gastritis	Mallory-Weiss syndrome
Lymphonodular hyperplasia	Swallowed epistaxis	Colonic polyps
	Prolapse (traumatic) gastropathy secondary to emesis	Anal fissure
	Mallory-Weiss syndrome	
RARE		
Volvulus	Esophageal varices	Hemorrhoids
Necrotizing enterocolitis	Esophagitis	Esophageal varices
Meckel diverticulum	Meckel diverticulum	Esophagitis
Stress ulcer, gastritis	Lymphonodular hyperplasia	Pill ulcer
Coagulation disorder (hemorrhagic disease of newborn)	IgA vasculitis (Henoch-Schönlein purpura)	Telangiectasia-angiodysplasia
Esophagitis	Foreign body	Graft versus host disease
	Hemangioma, arteriovenous malformation	Duplication cyst
	Sexual abuse	Angiodysplasia
	Hemolytic-uremic syndrome	Angiodysplasia with von Willebrand disease
	Inflammatory bowel disease	Blue rubber bleb nevus syndrome
	Coagulopathy	
	Duplication cyst	
	Angiodysplasia	
	Angiodysplasia with von Willebrand disease	
	Blue rubber bleb nevus syndrome	

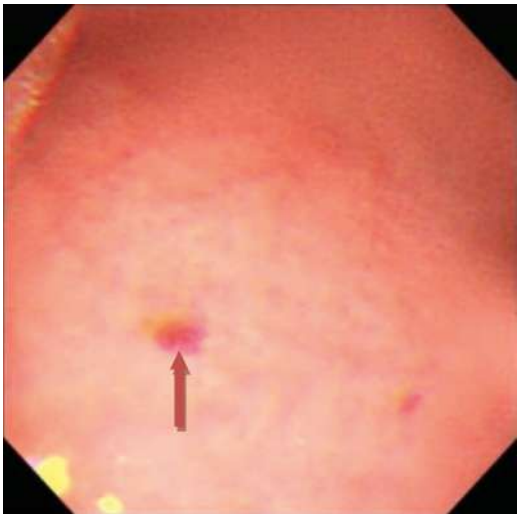

Fig. 352.2 Intestinal angiodysplasia. A 7-year-old boy had tarry stool for days. Panendoscopy showed multiple cherry red flat spots in the gastric mucosa, compatible with the findings of angiodysplasia in CT angiography. *(From Chuang F, Lin JS, Yeung C, et al. Intestinal angiodysplasia: an uncommon cause of gastrointestinal bleeding in children. Pediatr Neonatol. 2011;52:214–218, Fig. 2.)*

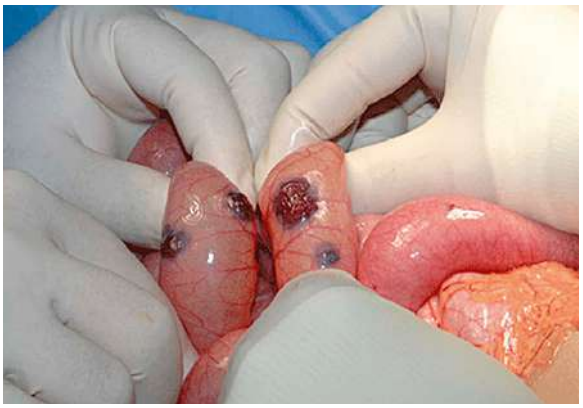

Fig. 352.3 Operative features of blue rubber bleb nevus syndrome. These lesions are similar to cutaneous lesions. *(From Hasosah MY, Abdul-Wahab AA, Bin-Yahab SA, et al. Blue rubber bled nevus syndrome: extensive small bowel vascular lesions responsible for gastrointestinal bleeding. J Pediatr Child Health. 2010;46:63–65. Fig. 3.)*

in stool is usually detected by using commercially available fecal occult blood testing cards, which are based on a chemical reaction between the chemical guaiac and oxidizing action of a substrate (hemoglobin), giving a blue color. The guaiac test is very sensitive, but random testing can miss chronic blood loss, which can lead to iron-deficiency anemia. GI hemorrhage can produce hypotension and tachycardia but rarely causes GI symptoms; brisk duodenal or gastric bleeding can lead to nausea, vomiting, or diarrhea. The breakdown products of intraluminal blood might tip patients into hepatic coma if liver function is already compromised and can lead to elevation of serum bilirubin.

ABDOMINAL DISTENTION AND ABDOMINAL MASSES

Enlargement of the abdomen can result from diminished tone of the wall musculature or from increased content: fluid, gas, or solid. Ascites, the accumulation of fluid in the peritoneal cavity, distends the abdomen both in the flanks and anteriorly when it is large in volume. This fluid shifts with movement of the patient and conducts a percussion wave. Ascitic fluid is usually a transudate with a low protein concentration resulting from reduced plasma colloid osmotic pressure of hypoalbuminemia and/or from raised portal venous pressure. In cases of portal hypertension, the fluid leak probably occurs from lymphatics on the liver surface and from visceral peritoneal capillaries, but ascites does not usually develop until the serum albumin level falls. Sodium excretion in the urine decreases greatly as the ascitic fluid accumulates, and thus additional dietary sodium goes directly to the peritoneal

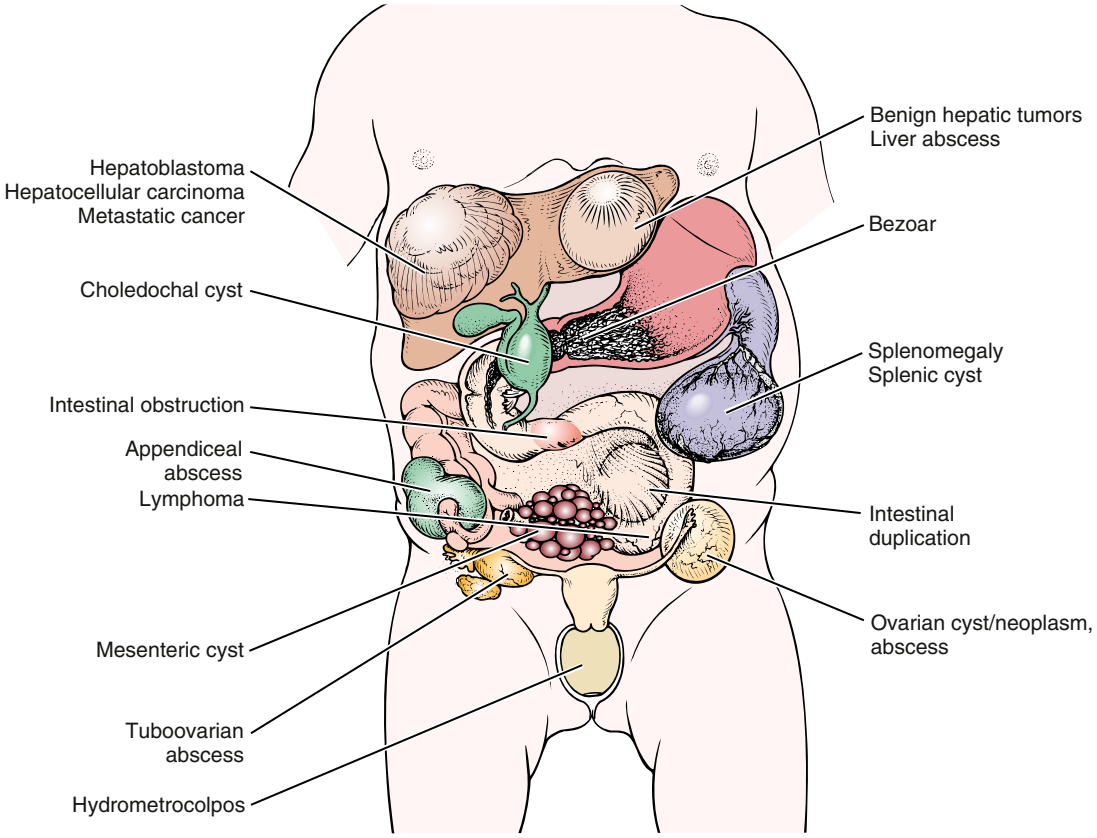

Fig. 352.4 Location of select intrabdominal tumors and masses. *(From Densmore JC, Densmore EM. Abdominal masses. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Fig. 20.1, p. 354.)*

space, taking with it more water. When ascitic fluid contains a high protein concentration, it is usually an exudate caused by an inflammatory or neoplastic lesion.

When fluid distends the gut, either obstruction or imbalance between absorption and secretion should be suspected. The factors causing fluid accumulation in the bowel lumen often cause gas to accumulate too. The result may be audible gurgling noises. The source of gas is usually swallowed air, but endogenous flora can increase considerably in malabsorptive states and produce excessive gas when substrate reaches the lower intestine. Gas in the peritoneal cavity (pneumoperitoneum) is usually caused by a perforated viscus and can cause abdominal distention depending on the amount of gas leak. A tympanitic percussion note, even over solid organs such as the liver, indicates a large collection of gas in the peritoneum.

An abdominal organ can enlarge diffusely or be affected by a discrete mass (Fig. 352.4). In the digestive tract, such discrete masses can occur in the lumen, wall, omentum, or mesentery. In a constipated child, mobile, nontender fecal masses are often found. Congenital anomalies, cysts, or inflammatory processes can affect the wall of the gut. Gut wall neoplasms are extremely rare in children. The pathologic enlargement of liver, spleen, bladder, and kidneys can give rise to abdominal distention.

ACKNOWLEDGMENT

Thanks to Astrela Moore, PharmD, Clinical Pharmacy Specialist at Children's Hospital of Philadelphia, for reviewing, verifying, and updating the pharmacotherapy table.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2
The Oral Cavity

Chapter 353
Development and Developmental Anomalies of the Teeth

Vineet K. Dhar

Newborn infants do not have teeth for about first 6 months after birth (predentate period). At this stage, the upper and lower alveolar ridges in the mouth, also known as gum pads, house the primary (deciduous) and some permanent tooth buds. The primary dentition period starts with eruption of the first primary tooth; all 20 primary teeth erupt by 3 years of age. The permanent teeth start erupting around 6 years of age, and the transition to full permanent dentition is completed by 13 years of age. The transition time between primary and permanent dentition, when a mix of primary and permanent teeth are present, is referred to as mixed dentition.

DEVELOPMENT OF TEETH

Initiation

The primary teeth form in dental crypts that arise from a band of epithelial cells incorporated into each developing jaw. By 12 weeks of fetal life, each of these epithelial bands **(dental laminae)** has five areas of rapid growth on each side of the maxilla and the mandible, seen as rounded, budlike enlargements. Organization of adjacent mesenchyme takes place in each area of epithelial growth, and the two elements together are the beginning of a tooth.

After the formation of these crypts for the 20 primary teeth, another generation of tooth buds forms lingually (toward the tongue); these will develop into the succeeding permanent incisors, canines, and premolars that eventually replace the primary teeth. This process takes place from approximately 3-4 months of gestation for the central incisors to approximately 24-30 months of age for the second premolars. On the other hand, the permanent first, second, and third molars arise from extension of the dental laminae distal to the second primary molars; buds for these teeth develop approximately at birth, 3 years of age, and 7-10 years of age, respectively.

Histodifferentiation–Morphodifferentiation

As the epithelial bud proliferates, the deeper surface invaginates and a mass of mesenchyme becomes partially enclosed. The epithelial cells differentiate into the ameloblasts that lay down an organic matrix that forms enamel; the mesenchyme forms the dentin and dental pulp.

Calcification

After the organic matrix has been laid down, the deposition of the inorganic mineral crystals takes place from several sites of calcification that later coalesce. The characteristics of the inorganic portions of a tooth can be altered by disturbances in formation of the matrix, decreased availability of minerals, or the incorporation of foreign materials. Such disturbances can affect the color, texture, or thickness of the tooth surface. Calcification of primary teeth begins at 3-4 months in utero and concludes postnatally at approximately 12 months, with mineralization of the second primary molars (Table 353.1).

Eruption

At the time of tooth bud formation, each tooth begins a continuous movement toward the oral cavity. Table 353.1 lists the times of eruption of the primary and permanent teeth. Occasionally the permanent teeth may erupt behind the primary teeth ("shark tooth"); this usually causes no problems.

Table 353.1 Calcification, Crown Completion, and Eruption

TOOTH	FIRST EVIDENCE OF CALCIFICATION	CROWN COMPLETED	ERUPTION
PRIMARY DENTITION			
Maxillary			
Central incisor	3-4 mo in utero	4 mo	7.5 mo
Lateral incisor	4.5 mo in utero	5 mo	8 mo
Canine	5.5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
Mandibular			
Central incisor	4.5 mo in utero	4 mo	6.5 mo
Lateral incisor	4.5 mo in utero	4½ mo	7 mo
Canine	5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
PERMANENT DENTITION			
Maxillary			
Central incisor	3-4 mo	4-5 yr	7-8 yr
Lateral incisor	10 mo	4-5 yr	8-9 yr
Canine	4-5 mo	6-7 yr	11-12 yr
First premolar	1½ -1¾ yr	5-6 yr	10-11 yr
Second premolar	2-2¼ yr	6-7 yr	10-12 yr
First molar	At birth	2½ -3 yr	6-7 yr
Second molar	2½ -3 yr	7-8 yr	12-13 yr
Third molar	7-9 yr	12-16 yr	17-21 yr
Mandibular			
Central incisor	3-4 mo	4-5 yr	6-7 yr
Lateral incisor	3-4 mo	4-5 yr	7-8 yr
Canine	4-5 mo	6-7 yr	9-10 yr
First premolar	1¾-2 yr	5-6 yr	10-12 yr
Second premolar	2¼- 2 ½ yr	6-7 yr	11-12 yr
First molar	At birth	2½ -3 yr	6-7 yr
Second molar	2½-3 yr	7-8 yr	11-13 yr
Third molar	8-10 yr	12-16 yr	17-21 yr

Modified from Logan WHG, Kronfeld R. Development of the human jaws and surrounding structures from birth to age 15 years. *J Am Dent Assoc.* 1993;20:379.

Anomalies Associated with Eruption Pattern

Delayed eruption of the 20 primary teeth can be familial or indicate systemic or nutritional disturbances such as hypopituitarism, hypothyroidism, cleidocranial dysplasia, trisomy 21, and multiple other syndromes. Failure of eruption of single or small groups of teeth can arise from local causes such as malpositioned teeth, supernumerary teeth, cysts, or retained primary teeth. Premature *loss* of primary teeth is commonly caused by premature *eruption* of the permanent teeth. If the entire dentition is advanced for age and gender, precocious puberty or hyperthyroidism should be considered.

Natal teeth are observed in approximately 1 in 2,000 newborn infants, usually in the position of the mandibular central incisors. Natal teeth are present at birth, whereas **neonatal teeth** erupt in the first month of life. Attachment of natal and neonatal teeth is generally limited to the gingival margin, with little root formation or bony support. They may be a supernumerary or a prematurely erupted primary tooth. A radiograph can easily differentiate between the two conditions. Natal teeth are associated with cleft palate, Pierre Robin syndrome, mesoectodermal dysplasia syndrome (Ellis-van Creveld), oculomandibulofacial syndrome (Hallermann-Streiff), pachyonychia

Table 353.2 Syndromes with Natal Teeth

SYNDROME	ASSOCIATED ANOMALIES	INHERITANCE/GENE ABNORMALITY/ PREVALENCE
Ellis-van Creveld (chondroectodermal dysplasia)	Bilateral postaxial polydactyly of hands, chondrodysplasia of long bones resulting in dwarfism, ectodermal dysplasia affecting nails/teeth, congenital heart malformation	Autosomal-recessive *EVC, EVC2* $7/1 \times 10^6$
Hallermann-Streiff	Dyscephaly, hypotrichosis, micro-ophthalmia, cataracts, beaked nose, micrognathia, proportionate short stature	Sporadic Not known >150 cases to date
Pachyonychia congenita (1: Jadassohn-Lewandowsky) (2: Jackson-Lawler)	Dystrophic nails, palmoplantar keratosis, hyperhidrosis, follicular keratosis, oral leukokeratosis, cutaneous cysts	Autosomal-dominant Keratin gene variants: type I: 6a/16, type 2:6b/17 $0.071/1 \times 10^6$ 9:5 male to female
Pallister-Hall (hypothalamic hamartoblastoma)	Hypothalamic hamartoblastoma, craniofacial abnormalities, postaxial polydactyly, cardiac and renal defects	Autosomal-dominant *GLI3* >13 cases to date 8:5 male to female
Wiedemann-Rautenstrauch	Endocrine dysfunction, aged facies, frontal and biparietal bossing, small facial bones, sparse scalp hair, prominent scalp veins, small beaked nose, low-set ears	Autosomal-recessive *POLR3A* >30 cases to date
Natal teeth, patent ductus arteriosus, intestinal pseudoobstruction	Dilatation/hypermobility of small bowel, short or microcolon without obstruction, incomplete rotation of midgut, patent ductus arteriosus	X-linked recessive Not known 2 cases to date, brothers

Modified from Hebert AA. Mucous membrane disorders. In Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2011: Table 9.2, p. 654.

congenita, and other anomalies (Table 353.2). A family history of natal teeth or premature eruption is present in 15–20% of affected children.

Natal or neonatal teeth occasionally result in pain and refusal to feed and can produce maternal discomfort because of abrasion or biting of the nipple during nursing. If the tooth is mobile, there is a danger of detachment, with aspiration of the tooth. Because the tongue lies between the alveolar processes during birth, it can become lacerated **(Riga-Fede disease)**. Decisions regarding extraction of prematurely erupted primary teeth must be made on an individual basis.

Exfoliation failure occurs when a primary tooth is not shed before the eruption of its permanent successor. Most often the primary tooth exfoliates eventually, but in some cases the primary tooth needs to be extracted. This occurs most commonly in the mandibular incisor region.

Anomalies Associated with Tooth Development

Both failures and excesses of tooth initiation are observed. Developmentally missing teeth can result from environmental insult, a genetic defect involving only teeth, or the manifestation of a syndrome.

Anomalies of Number

Anodontia, or absence of teeth, occurs when no tooth buds form (ectodermal dysplasia, or familial missing teeth) or when there is a disturbance of a normal site of initiation (the area of a palatal cleft). The teeth that are most commonly absent are the third molars, the maxillary lateral incisors, and the mandibular second premolars.

If the dental lamina produces more than the normal number of buds, **supernumerary teeth** occur, most often in the area between the maxillary central incisors. Because they tend to disrupt the position and eruption of the adjacent normal teeth, their identification by radiographic examination is important. Supernumerary teeth also occur with cleidocranial dysplasia (see Chapter 356) and in the area of cleft palates.

Anomalies of Size

Twinning, in which two teeth are joined together, is most often observed in the mandibular incisors of the primary dentition. It can result from gemination, fusion, or concrescence. **Gemination** is the result of the division of one tooth germ to form a bifid crown on a single root with a common pulp canal; an extra tooth appears to be present in the dental arch. **Fusion** is the joining of incompletely developed teeth that, due to pressure, trauma, or crowding, continue to develop as one tooth. Fused teeth are sometimes joined along their entire length; in other cases, a single wide crown is supported on two roots. **Concrescence** is the attachment of the roots of closely approximated adjacent teeth by an excessive deposit of cementum. This type of twinning, unlike the others, is found most often in the maxillary molar region.

Disturbances during differentiation can result in alterations in dental morphology, such as **macrodontia** (large teeth) or **microdontia** (small teeth). The maxillary lateral incisors can assume a slender, tapering shape **(peg-shaped laterals).**

Anomalies of Shape

Dens in dente or **dens invaginatus** presents as *tooth within tooth* appearance, which results from invagination of inner enamel epithelium caused by disruption during morphodifferentiation. Dens evaginatus presents as an extra cusp on anterior or posterior teeth, which contains enamel, dentin, and sometimes even pulp tissue. In the anterior teeth the cusp is talon shaped and presents in the cingulum area.

Taurodontism is more common in permanent molars and is characterized by elongated pulp chamber with short-stunted roots due to failure or late invagination of Hertwig epithelial root sheath. It may be associated with several syndromic conditions such as Down syndrome, tricho-dento-osseous syndrome, ectodermal dysplasia (hypohidrotic), and amelogenesis imperfecta (hypomaturation-hypoplastic type).

Dilaceration is an abnormal bend or curve in root possibly due to trauma. It may be subsequent to injury to the primary predecessor tooth.



Fig. 353.1 Amelogenesis imperfecta, hypoplastic type. The enamel defect results in areas of missing or thin enamel, as well as grooves and pits.



Fig. 353.2 Dentinogenesis imperfecta. The bluish, opalescent sheen on several of these teeth results from genetically defective dentin. This condition may be associated with osteogenesis imperfecta. *(From Nazif MM, Martin BS, McKibben DH, et al. Oral disorders. In Zitelli BJ, Davis HW, eds. Atlas of Pediatric Physical Diagnosis. 4th ed. Philadelphia: Mosby; 2002: p. 703.)*

Anomalies of Structure

Amelogenesis imperfecta represents a group of hereditary conditions that manifest in enamel defects of the primary and permanent teeth without evidence of systemic disorders (Fig. 353.1). There are four subtypes: hypoplastic (type I), hypomaturation (type II), hypocalcified (type III), and hypomaturation-hypoplastic-taurodontism (type IV). Of the multiple subtypes, there are 19 genes inherited predominantly as autosomal dominant or recessive traits. The teeth are covered by only a thin layer of abnormally formed enamel through which the yellow underlying dentin is seen. The primary teeth are generally affected more than the permanent teeth. Susceptibility to caries is low, but the enamel is subject to destruction from abrasion. Complete coverage of the crown may be indicated for dentin protection, to reduce tooth sensitivity, and for improved appearance.

Dentinogenesis imperfecta, or hereditary opalescent dentin, is a condition analogous to amelogenesis imperfecta in which the odontoblasts fail to differentiate normally, resulting in poorly calcified dentin (Fig. 353.2). This autosomal dominant disorder can also occur in patients with **osteogenesis imperfecta.** The enamel-dentin junction is altered, causing enamel to break away. The exposed dentin is then susceptible to abrasion, in some cases worn to the gingiva. The teeth are opaque and pearly, and the pulp chambers are generally obliterated by calcification. Both primary and permanent teeth are usually involved. If there is excessive wear of the teeth, selected complete coverage of the teeth may be indicated to prevent further tooth loss and improve appearance.

Localized disturbances of calcification that correlate with periods of illness, malnutrition, premature birth, or birth trauma are common. **Hypocalcification** appears as opaque white patches or horizontal lines on the tooth; **hypoplasia** is more severe and manifests as pitting or areas devoid of enamel. Systemic conditions, such as renal failure and cystic fibrosis, are associated with enamel defects. Local trauma to the primary incisors can also affect calcification of permanent incisors.

Fluorosis (mottled enamel) can result from systemic fluoride consumption >0.05 mg/kg/day during enamel formation. This high fluoride consumption can be caused by residing in an area of high fluoride content of the drinking water (>2.0 ppm), swallowing excessive fluoridated toothpaste, or inappropriate fluoride prescriptions. Excessive fluoride during enamel formation affects ameloblastic function, resulting in inconspicuous white, lacy patches on the enamel to severe brownish discoloration and hypoplasia. The latter changes are usually seen with fluoride concentrations in the drinking water >5.0 ppm.

Anomalies of Color

Discolored teeth can result from incorporation of foreign substances into developing enamel. Neonatal hyperbilirubinemia can produce blue to black discoloration of the primary teeth. Porphyria produces a red-brown discoloration. Tetracyclines are extensively incorporated into bones and teeth and, if administered during the period of formation of enamel, can result in brown-yellow discoloration and hypoplasia of the enamel. Such teeth fluoresce under ultraviolet light. The period at risk extends from approximately 4 months of gestation to 7 years of age. Repeated or prolonged therapy with tetracycline carries the highest risk.

Teething is associated with primary tooth eruption and may manifest with benign symptoms such as gingival hyperemia, irritability, sucking fingers, and drooling; some infants have no symptoms or symptoms not identified by their parents. Low-grade fever is an inconsistent finding. The treatment of symptoms of teething is often unnecessary but could include oral analgesics and iced teething rings. Teething remedies containing benzocaine may cause methemoglobinemia and are not recommended. "Natural" (homeopathic) teething remedies may contain toxic additives and should be avoided. In addition, teething necklaces and bracelets are a risk for foreign body aspiration and choking.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 354

Disorders of the Oral Cavity Associated with Other Conditions

Vineet K. Dhar

Disorders of the teeth and surrounding structures can occur in isolation or in combination with other systemic conditions (Table 354.1). Most commonly, medical conditions that occur during tooth development can affect tooth formation or appearance. Damage to teeth during their development is permanent.

Table 354.1 Dental Problems Associated with Selected Medical Conditions

MEDICAL CONDITION	COMMON ASSOCIATED DENTAL OR ORAL FINDINGS
Cleft lip and palate	Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems
Kidney failure	Mottled enamel (permanent teeth), facial dysmorphology
Cystic fibrosis	Stained teeth with extensive medication, mottled enamel
Immunosuppression	Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia
Low birthweight	Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth
Heart defects with susceptibility to bacterial endocarditis	Bacteremia from dental procedures or trauma
Neutrophil chemotactic deficiency	Aggressive periodontitis (loss of supporting bone around teeth)
Diabetes mellitus type 1 (uncontrolled)	Aggressive periodontitis
Neuromotor dysfunction	Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene
Prolonged illness (generalized) during tooth formation	Enamel hypoplasia of crown portions forming during illness
Seizures	Gingival enlargement if phenytoin is used
Maternal infections	Syphilis: abnormally shaped teeth
Vitamin D–dependent rickets	Enamel hypoplasia

Chapter 355

Malocclusion

Vineet K. Dhar

The oral cavity is essentially a masticatory instrument. The purpose of the anterior teeth is to bite off large portions of food. The posterior teeth reduce foodstuff to a soft, moist bolus. The cheeks and tongue force the food onto the areas of tooth contact. Establishing a proper relationship between the mandibular and maxillary teeth is important for both physiologic and cosmetic reasons.

VARIATIONS IN GROWTH PATTERNS

Growth patterns are classified into three main types of occlusion, determined when the jaws are closed and the teeth are held together (Fig. 355.1). According to the Angle classification of malocclusion, in **class I occlusion** (normal), the cusps of the posterior mandibular teeth interdigitate ahead of and inside of the corresponding cusps of the opposing maxillary teeth. This relationship provides a normal facial profile.

In **class II malocclusion,** *buck teeth*, the cusps of the posterior mandibular teeth are behind and inside the corresponding cusps of the maxillary teeth. This common occlusal disharmony is found in approximately 45% of the population. The facial profile can give the appearance of a *receding chin* (retrognathia) (mandibular deficiency) or protruding front teeth. The resultant increased space between upper and lower anterior teeth encourage finger sucking and tongue-thrust habits. In addition, children with pronounced class II malocclusions are at greater risks of damage to the incisors as a consequence of trauma. Treatment includes orthodontic retraction of the maxilla or stimulation of the mandible.

In **class III malocclusion,** *underbite*, the cusps of the posterior mandibular teeth interdigitate a tooth or more ahead of their opposing maxillary counterparts. The anterior teeth appear in crossbite with the mandibular incisors protruding beyond the maxillary incisors. The facial profile gives the appearance of a *protruding chin* **(prognathia)** with or without an appearance of maxillary deficiency. If necessary,

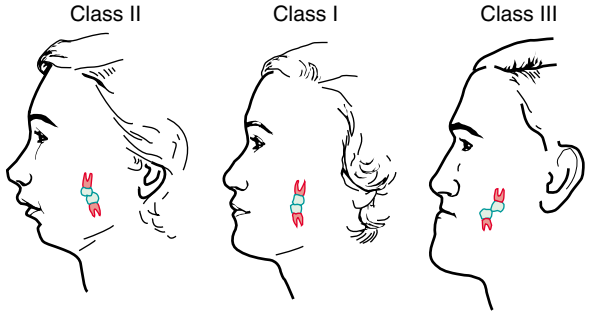

Fig. 355.1 Angle classification of occlusion. The typical correspondence between the facial-jaw profile and molar relationship is shown. *(Data from Borrie FR, Bearn DR, Innes NP, et al. Interventions for the cessation of non-nutritive sucking habits in children. Cochrane Database Syst Rev. 2015;31:CD008694.)*

treatment includes mandibular excess reduction osteotomy or orthodontic maxillary facial protrusion.

The molar relationship in primary dentition/baby teeth also has three main types. The **flush terminal plane** relationship, where the distal surface of mandibular second primary molar is flush with the distal surface of maxillary second primary molar, is most common and can translate into class I occlusion or class II malocclusion in permanent dentition. The **mesial step** relationship, where the distal surface of mandibular second primary molar lies mesial to the distal surface of maxillary second primary molar, is the second most common and often translates into class I occlusion or sometimes into class III malocclusion in permanent dentition. Lastly, the **distal step** relationship, where the distal surface of the mandibular second primary molar lies distal to the distal surface of maxillary second primary molar, almost always translates into class II occlusion in permanent dentition.

CROSSBITE

Normally, the mandibular teeth are in a position just inside the maxillary teeth so that the outside mandibular cusps or incisal edges meet the central portion of the opposing maxillary teeth. A reversal of this relation is referred to as a crossbite. Crossbites can be anterior, involving the incisors; can be posterior, involving the molars; or can involve single or multiple teeth; or can be unilateral or bilateral. Functional posterior crossbites that involve lateral shift of the mandible during closure may result in dental, skeletal adjustments, and even asymmetric condylar positioning; therefore an early diagnosis and correction is recommended.

OPEN AND CLOSED BITES

If the posterior mandibular and maxillary teeth make contact with each other, but the anterior teeth are still apart, the condition is called an *open bite*. Open bites can result from skeletal growth pattern or digit sucking. If digit sucking is terminated before skeletal and dental growth is complete, the open bite might resolve naturally. If mandibular anterior teeth occlude inside the maxillary anterior teeth in an overclosed position, the condition is referred to as a *closed* or *deep bite*.

Treatment of open and closed bites consists of orthodontic correction, generally performed in the preteen or teenage years. Some severe cases require orthognathic surgery to position the jaws optimally in a vertical direction.

DENTAL CROWDING

Overlap of incisors can result when the jaws are too small, or the teeth are too large for adequate alignment of the teeth. Growth of the jaws is mostly in the posterior aspects of the mandible and maxilla; therefore inadequate space for the teeth at 7 or 8 years of age will not resolve with growth of the jaws. Spacing in the primary dentition is normal and favorable for adequate alignment of successor teeth.

DIGIT SUCKING

Various and conflicting etiologic theories and recommendations for correction have been proposed for digit sucking in children. Prolonged digit sucking can cause flaring of the maxillary incisor teeth, an open bite, and a posterior crossbite. The prevalence of digit sucking decreases steadily from the age of 2 years to approximately 10% by the age of 5 years. The earlier the habit is discontinued after the eruption of the permanent maxillary incisors (age 7-8 years), the greater the likelihood that there will be lessening effects on the dentition.

A variety of treatments have been suggested, from behavioral modification to insertion of an appliance with extensions that serves as a reminder when the child attempts to insert the digit. Unfortunately, a systematic review has found only low-quality evidence of the effectiveness of interventions such as orthodontic appliances and psychologic interventions. The greatest likelihood of success occurs in cases in which the child desires to stop. Stopping of the habit will not rectify a malocclusion caused by a prior deviant growth pattern.

Chapter 356
Cleft Lip and Palate

Vineet K. Dhar

Clefts of the lip and palate are distinct entities that are closely related embryologically, functionally, and genetically. It is thought that cleft of the lip appears because of hypoplasia of the mesenchymal layer, resulting in a failure of the medial nasal and maxillary processes to join. Cleft of the palate results from failure of palatal shelves to approximate or fuse.

INCIDENCE AND EPIDEMIOLOGY

The incidence of cleft lip with or without cleft palate is approximately 1 in 1,000 births. The reported incidence of cleft palate alone in the United States is 1 in 1,687 births. Clefts of the lip are more common in males. Possible causes include maternal drug exposure, a syndrome-malformation complex, or genetic factors. Although clefts of lips and palates appear to occur sporadically, the presence of susceptible genes appears important. There are approximately 400 syndromes associated with cleft lip and palates. There are families in which a cleft lip or palate, or both, is inherited in a dominant fashion (**van der Woude syndrome**), and careful examination of parents is important to distinguish this type from others, because the recurrence risk is 50%. Ethnic factors also affect the incidence of cleft lip and palate; the incidence varies by race, with Asian children most likely to be affected. Cleft lip may be associated with other cranial facial anomalies, whereas cleft palate may be associated with central nervous system anomalies.

CLINICAL MANIFESTATIONS

Cleft lip can vary from a small notch in the vermilion border to a complete separation involving skin, muscle, mucosa, tooth, and bone. Clefts of the lip may be unilateral (more often on the left side) or bilateral and can involve the alveolar ridge (Fig. 356.1).

Isolated cleft palate occurs in the midline and might involve only the uvula or can extend into or through the soft and hard palates to the incisive foramen. When associated with cleft lip, the defect can involve the midline of the soft palate and extend into the hard palate on one or both sides, exposing one or both of the nasal cavities as a unilateral or bilateral cleft palate. The palate can also have a **submucosal cleft** indicated by a bifid uvula, partial separation of muscle with intact mucosa, or a palpable notch at the posterior of the palate (see Fig. 356.1).

TREATMENT

A complete program of habilitation for the child with a cleft lip or palate can require years of special treatment by a team consisting of a pediatrician, plastic surgeon, otolaryngologist, oral and maxillofacial surgeon, pediatric dentist, prosthodontist, orthodontist, speech therapist, geneticist, medical social worker, psychologist, and public health nurse.

The immediate problem in an infant born with a cleft lip or palate is feeding. Although some advocate the construction of a plastic obturator to assist in feedings, most believe that, with the use of soft artificial nipples with large openings, a squeezable bottle, and proper instruction, feeding of infants with clefts can be achieved.

Surgical closure of a cleft lip is usually performed by 3 months of age, when the infant has shown satisfactory weight gain and is free of any oral, respiratory, or systemic infection. Modification of the Millard rotation–advancement technique is the most commonly used technique; a staggered suture line minimizes notching of the lip from retraction of scar tissue. The initial repair may be revised at 4 or 5 years of age. Corrective surgery on the nose may be delayed until adolescence. Nasal surgery can also be performed at the time of the lip repair. Cosmetic results depend on the extent of the original deformity,

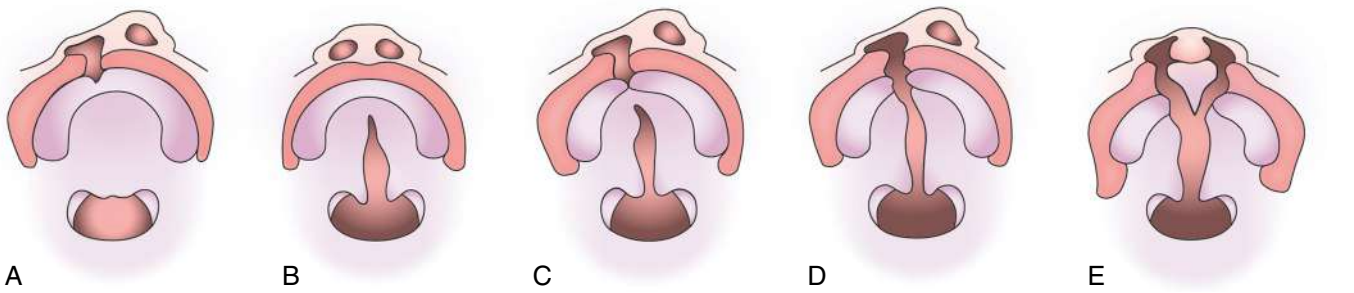

Fig. 356.1 Nonsyndromic orofacial clefts. **A,** Cleft lip and alveolus. **B,** Cleft palate. **C,** Incomplete unilateral cleft lip and palate. **D,** Complete unilateral cleft lip and palate. **E,** Complete bilateral cleft lip and palate. *(From Shaw WC. Orthodontics and Occlusal Management. Oxford, UK: Butterworth-Heinemann; 1993.)*

healing potential of the individual patient, absence of infection, and the skill of the surgeon.

Because clefts of the palate vary considerably in size, shape, and degree of deformity, the timing of surgical correction should be individualized. Criteria such as width of the cleft, adequacy of the existing palatal segments, morphology of the surrounding areas (width of the oropharynx), and neuromuscular function of the soft palate and pharyngeal walls affect the decision. The goals of surgery are the union of the cleft segments, intelligible and pleasant speech, reduction of nasal regurgitation, and avoidance of injury to the growing maxilla.

In an otherwise healthy child, closure of the palate is usually done before 1 year of age to enhance normal speech development. When surgical correction is delayed beyond the third year, a contoured speech bulb can be attached to the posterior of a maxillary denture so that contraction of the pharyngeal and velopharyngeal muscles can bring tissues into contact with the bulb to accomplish occlusion of the nasopharynx and help the child to develop intelligible speech.

A cleft palate usually crosses the alveolar ridge and interferes with the formation of teeth in the maxillary anterior region. Teeth in the cleft area may be displaced, malformed, or missing. Missing teeth or teeth that are nonfunctional are replaced by prosthetic devices.

POSTOPERATIVE MANAGEMENT

During the immediate postoperative period, special nursing care is essential. Gentle aspiration of the nasopharynx minimizes the chances of the common complications of atelectasis or pneumonia. The primary considerations in postoperative care are maintenance of a clean suture line and avoidance of tension on the sutures. The infant is fed with a specially designed bottle, and the arms are restrained with elbow cuffs. A fluid or semifluid diet is maintained for 3 weeks. The patient's hands, toys, and other foreign bodies must be kept away from the surgical site.

SEQUELAE

Recurrent otitis media and subsequent hearing loss are frequent with cleft palate. Displacement of the maxillary arches and malposition of the teeth usually require orthodontic correction. Misarticulations and velopharyngeal dysfunction are often associated with cleft lip and palate and may be present or persist because of physiologic dysfunction, anatomic insufficiency, malocclusion, or inadequate surgical closure of the palate. Such speech is characterized by the emission of air from the nose and by a hypernasal quality with certain sounds, or by compensatory misarticulations (glottal stops). Before and sometimes after palatal surgery, the speech defect is caused by inadequacies in function of the palatal and pharyngeal muscles. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve that separates the nasopharynx from the oropharynx during swallowing and in the production of certain sounds. If the valve does not function adequately, it is difficult to build up enough pressure in the mouth to make such explosive sounds as p, b, d, t, h, y, or the sibilants s, sh, and ch, and such words as "cats," "boats," and "sisters" are not intelligible. After operation or the insertion of a speech appliance, speech therapy is necessary.

VELOPHARYNGEAL DYSFUNCTION

The speech disturbance characteristic of the child with a cleft palate can also be produced by other osseous or neuromuscular abnormalities where there is an inability to form an effective seal between oropharynx and nasopharynx during swallowing or phonation. In a child who has the potential for abnormal speech, adenoidectomy can precipitate overt hypernasality. If the neuromuscular function is adequate, compensation in palatopharyngeal movement might take place and the speech defect might improve, although speech therapy is necessary. In other cases, slow involution of the adenoids can allow gradual compensation in palatal and pharyngeal muscular function. This might explain why a speech defect does not become apparent in some children who have a submucous cleft palate or similar anomaly predisposing to palatopharyngeal incompetence.

Clinical Manifestations

Although clinical signs vary, the symptoms of velopharyngeal dysfunction are similar to those of a cleft palate. There may be hypernasal speech (especially noted in the articulation of pressure consonants such as p, b, d, t, h, v, f, and s); conspicuous constricting movement of the nares during speech; inability to whistle, gargle, blow out a candle, or inflate a balloon; loss of liquid through the nose when drinking with the head down; otitis media; and hearing loss. Oral inspection might reveal a cleft palate or a relatively short palate with a large oropharynx; absent, grossly asymmetric, or minimal muscular activity of the soft palate and pharynx during phonation or gagging; or a submucous cleft.

Velopharyngeal dysfunction may also be demonstrated radiographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel u as in "boom." The soft palate contacts the posterior pharyngeal wall in normal function, whereas in velopharyngeal dysfunction such contact is absent.

In selected cases of velopharyngeal dysfunction, the palate may be retropositioned or pharyngoplasty may be performed using a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. The type of surgery used is best tailored to the findings on nasoendoscopy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 357

Syndromes with Oral Manifestations

Vineet K. Dhar

Many syndromes have distinct or accompanying facial, oral, and dental manifestations (see Apert syndrome, Chapter 631.9; Crouzon disease, Chapter 631.9; Down syndrome, Chapter 99.2).

Osteogenesis imperfecta is often accompanied by effects on the teeth, termed **dentinogenesis imperfecta** (see Chapter 353, Fig. 353.2). Depending on the severity of presentation, treatment of the dentition varies from routine preventive and restorative monitoring to covering affected posterior teeth with stainless steel crowns to prevent further tooth loss and improve appearance. Dentinogenesis imperfecta can also occur in isolation without the bony effects.

Another syndrome, **cleidocranial dysplasia,** has orofacial features such as frontal bossing, hypoplastic maxilla, and supernumerary teeth. The primary teeth can be overretained, and the permanent teeth remain unerupted. Supernumerary teeth are common, especially in the premolar area. Extensive dental rehabilitation may be needed to correct severe tooth crowding and unerupted and supernumerary teeth.

Ectodermal dysplasias are a heterogeneous group of conditions in which oral manifestations range from little or no involvement (the dentition is completely normal) to cases in which the teeth can be totally or partially absent or malformed (see Chapter 690). Because alveolar bone does not develop in the absence of teeth, the alveolar processes can be either totally or partially absent, and the resultant overclosure of the mandible causes the lips to protrude. Facial development is otherwise not disturbed. Teeth, when present, can range from normal to small and conical. If aplasia of the buccal and labial salivary glands is present, dryness and irritation of the oral mucosa can occur. People with ectodermal dysplasia might need partial or full dentures, even at a very young age. The vertical height between the jaws is thus restored, improving the position of the lips and facial contours, as well as restoring masticatory function.

Pierre Robin syndrome consists of micrognathia and is usually accompanied by a high arched or cleft palate (Fig. 357.1). The tongue is usually of normal size, but the floor of the mouth is foreshortened. The air passages can become obstructed, particularly on inspiration, usually requiring treatment to prevent suffocation. The infant should be maintained in a prone or partially prone position so that the tongue falls forward to relieve respiratory obstruction. Some patients require tracheostomy. Mandibular distraction procedures in the neonate can improve mandibular size, enhance respiration, and facilitate oral feedings.

Sufficient spontaneous mandibular growth can take place within a few months to relieve the potential airway obstruction. Often the growth of the mandible achieves a normal profile in 4-6 years. Of children with Pierre Robin syndrome, 30–50% have **Stickler syndrome** (types I-VI), an autosomal dominant condition that includes other findings such as prominent joints, arthritis, hypotonia, hypermobile joints, mitral valve prolapse, hearing loss, spine problems (scoliosis, kyphosis, platyspondyly), and ocular problems (high myopia, glaucoma, cataracts, retinal detachment). Symptoms may vary greatly even within a family. Pathogenic variants are noted in the genes that produce collagen (*COL2A1* in most; *COL11A1* in others) in many, but not all, patients with Stickler syndrome. Other syndromes are associated with Pierre Robin syndrome, including 22Q11.2 deletion syndrome (velocardiofacial syndrome).

Mandibulofacial dysostosis (Treacher Collins syndrome or Franceschetti syndrome) is an autosomal dominant syndrome that primarily affects the face. The facial appearance varies but is characterized by downward-sloping palpebral fissures, colobomas of the lower eyelids, sunken cheekbones, blind fistulas opening between the angles of the mouth and the ears, malformed pinnae, atypical hair growth extending toward the cheeks, receding chin, and large mouth. Facial clefts, abnormalities of the ears, and deafness are common. The mandible is usually hypoplastic; the ramus may be deficient, and the coronoid and condylar processes are flat or even aplastic. The palatal vault may be either high or cleft. Dental malocclusions are common. The teeth may be missing, hypoplastic, or displaced or be in an open bite position. Initially, the primary concern is breathing and feeding problems. Surgery to restore normal structure of the face can be performed, which may include repair of cleft palate, zygomatic and orbit reconstruction, reconstruction of the lower eyelid, external ear reconstruction, and orthognathic surgery.

Hemifacial microsomia presentation can be quite variable but is usually characterized by unilateral hypoplasia of the mandible and can be associated with partial paralysis of the facial nerve, underdeveloped ear, and blind fistulas between the angles of the mouth and the ears. Severe facial asymmetry and malocclusion can develop because of the absence or hypoplasia of the mandibular condyle on the affected side. Congenital condylar deformity tends to increase with age. Early craniofacial surgery may be indicated to minimize the deformity. This disorder can be associated with ocular and vertebral anomalies (oculoauriculovertebral spectrum, including Goldenhar syndrome); therefore radiographs of the vertebrae and ribs should be considered to determine the extent of skeletal involvement.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 357.1 Pierre Robin syndrome. *(From Clark DA. Atlas of Neonatology. 7th ed. Philadelphia: Saunders; 2000. p. 144.)*

Chapter 358

Dental Caries

Vineet K. Dhar

ETIOLOGY

The development of dental caries depends on interrelationships among the tooth surface, dietary carbohydrates, and specific oral bacteria. Organic acids produced by bacterial fermentation of dietary carbohydrates reduce the pH of dental plaque adjacent to the tooth to a point where demineralization occurs. The initial demineralization appears as an opaque **white spot lesion** on the enamel, and with progressive loss of tooth mineral, cavitation of the tooth occurs (Fig. 358.1).

The group of microorganisms, *Streptococcus mutans*, is the main bacteria associated with the development of dental caries. These bacteria have the ability to adhere to enamel, produce abundant acid, and survive at low pH. Once the enamel surface cavitates, other oral bacteria (lactobacilli) can colonize the tooth, produce acid, and foster further tooth demineralization. Demineralization from bacterial acid production is determined by the frequency of carbohydrate consumption and by the type of carbohydrate. Sucrose is the most cariogenic sugar because one of its by-products during bacterial metabolism is glucan, a polymer that enables bacteria to adhere more readily to tooth structures. Dietary behaviors, such as consuming sweetened beverages in a nursing bottle or frequently consuming sticky candies, increase the cariogenic potential of foods because of the long retention of sugar in the mouth.

EPIDEMIOLOGY

As per the 2011–2012 National Health and Nutrition Examination Survey (NHANES), approximately 15% of children ranging from 2 to 8 years of age had one or more primary teeth affected by dental caries (Fig. 358.2). In the permanent dentition, over 10% of children age 12-15 years had dental caries and one fourth of children were affected by age 16-19 years (Fig. 358.3).

CLINICAL MANIFESTATIONS

Dental caries of the primary dentition usually begins in the pits and fissures. Small lesions may be difficult to diagnose by visual inspection, but larger lesions are evident as darkened or cavitated lesions on the tooth surfaces (Fig. 358.4). Rampant dental caries in infants and toddlers, referred to as **early childhood caries**, is the result of early colonization of the child with cariogenic bacteria and the frequent ingestion of sugar, either in the bottle or in solid foods. The carious process in this situation is initiated earlier and consequently can affect the maxillary incisors first and then progress to the molars as they erupt.

The prevalence of untreated caries was significantly higher in children between 3 and 9 years of age living at or below 100% of federal poverty level compared with those above the poverty level. Along with

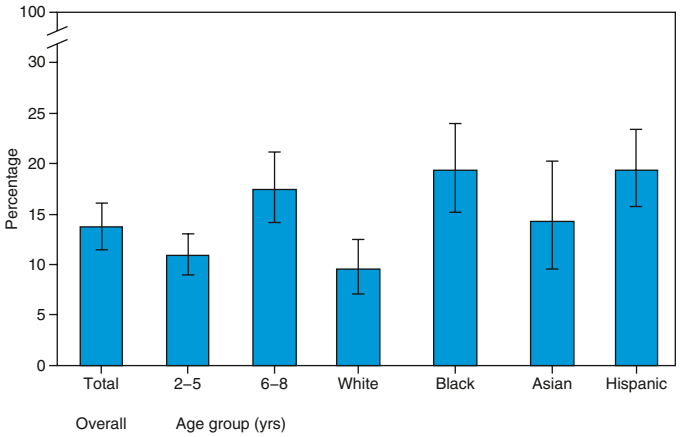

Fig. 358.2 Prevalence* of untreated dental caries† in primary teeth‡ among children age 2-8 yr, by age group, and race/Hispanic origin—National Health and Nutrition Examination Survey, 2011–2014. *With 95% confidence intervals indicated with error bars. †Untreated dental caries is defined as tooth decay (dental cavities) that has not received appropriate treatment. Data were collected by dentists in the mobile examination center as part of the oral health component of the National Health and Nutrition Examination Survey. ‡Primary teeth are the first teeth (baby teeth), that are shed and replaced by permanent teeth. *(From Centers for Disease Control and Prevention: Prevalence of untreated dental caries in primary teeth among children aged 2-8 years, by age group and race/Hispanic origin—National Health and Nutrition Examination Survey, 2011–2014. MMWR. 2017;66[9]:261.)*

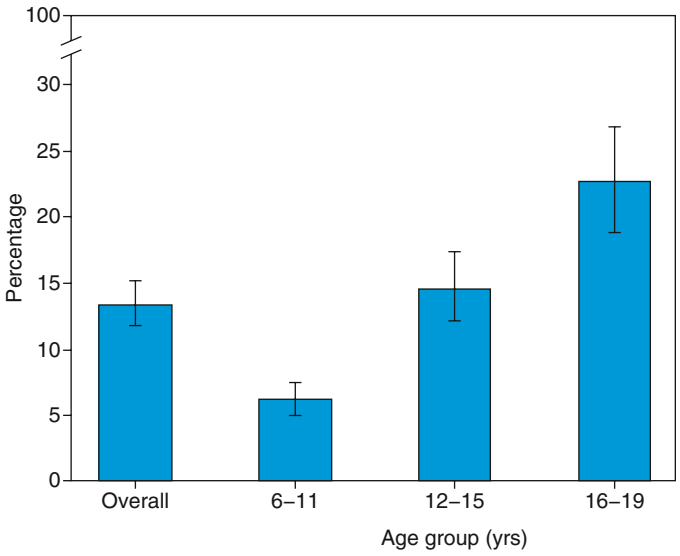

Fig. 358.3 Prevalence* of untreated dental caries† in permanent teeth among children and adolescents age 6-19 yr, by age group—National Health and Nutrition Examination Survey, United States, 2011-2014. *With 95% confidence intervals indicated with error bars. †Untreated dental caries (i.e., dental cavities) are defined as tooth decay that has not received appropriate treatment. Data were collected by dentists in the mobile examination center as part of the oral health component of the National Health and Nutrition Examination Survey. *(From Centers for Disease Control and Prevention: Prevalence of untreated dental caries in permanent teeth among children and adolescents aged 6-19 years, by age group—National Health and Nutrition Examination Survey, United States, 2011–2014. MMWR. 2017;66[1]:36.)*



Fig. 358.1 Initial carious lesions (white spot lesions) around the necks of the maxillary central incisors.



Fig. 358.4 Rampant caries in a 3-yr-old child. Note darkened and cavitated lesions on the fissure surfaces of mandibular molars.

high frequency of sugar consumption and colonization with cariogenic bacteria, other enabling factors include low socioeconomic status of the family, other family members with carious teeth, recent immigrant status of the child, and the visual presence of dental plaque on the child's teeth. Children who develop caries at a young age are known to be at high risk for developing further caries as they get older. Therefore the appropriate prevention of early childhood caries can result in the elimination of major dental problems in toddlers and less decay in later childhood.

Among adolescents, the prevalence of dental caries was higher in age group 16-19 years (67%) compared with age group 12-15 years (50%). Overall, the caries experience did not significantly differ by race, Hispanic origin, and poverty levels.

COMPLICATIONS

Left untreated, dental caries usually destroy most of the tooth and invade the dental pulp (Fig. 358.5), leading to an inflammation of the pulp **(pulpitis)** and significant pain. Pulpitis can progress to pulp necrosis, with bacterial invasion of the alveolar bone causing a **dental abscess** (Fig. 358.6). Red flags for serious spreading of dental infection are noted in Table 358.1. Infection of a primary tooth can disrupt normal development of the successor permanent tooth. In some cases, this process leads to spread of infection to other facial spaces (Fig. 358.7; Table 358.2).

TREATMENT

The age at which dental caries occurs is important in dental management. Children younger than 3 years of age lack the developmental ability to cooperate with dental treatment and often require sedation or general anesthesia to repair carious teeth. After 4 years of age, children can generally cope with dental restorative care with the use of local anesthesia. Children with neurologic impairment or developmental delay may require general anesthesia for dental procedures at older ages.

Current evidence supports the use of a chronic disease management model to modify risk factors and manage dental caries. The disease management includes at-home strategies and in-office preventive, minimally invasive, and invasive interventions for treating dental caries. Minimally invasive strategies such as interim therapeutic restorations and silver diamine fluoride application can be used to arrest active carious lesions. Conventional dental treatment, using silver amalgam, plastic composite, or stainless steel crowns, can restore most teeth affected with dental caries. If caries involves the dental pulp, a partial removal of the pulp (pulpotomy) or complete removal of the pulp (pulpectomy) may be required. If a tooth requires extraction, a space maintainer may be indicated to prevent migration of teeth, which subsequently leads to malposition of permanent successor teeth.

Clinical management of the pain and infection associated with untreated dental caries varies with the extent of involvement and the medical status of the patient. Dental infection localized to the dentoalveolar unit can be managed by local measures (extraction, pulpectomy).

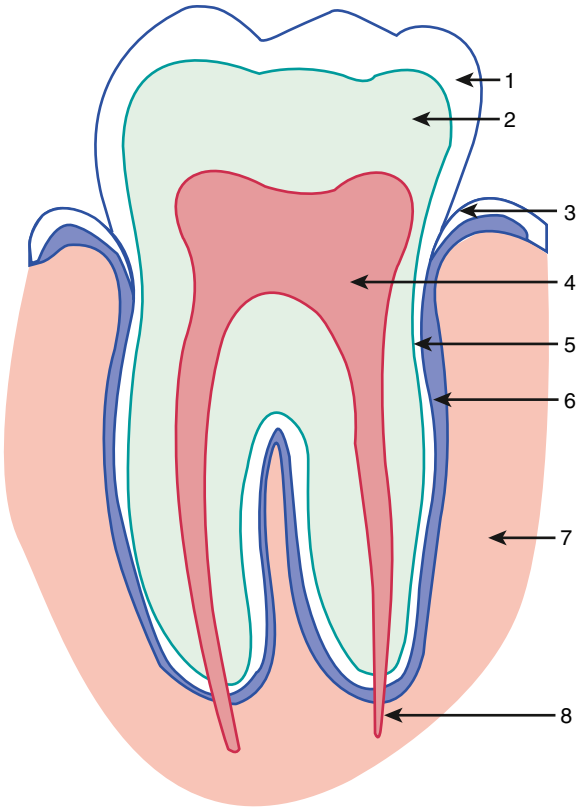

Fig. 358.5 Basic dental anatomy: *1*, enamel; *2*, dentin; *3*, gingival margin; *4*, pulp; *5*, cementum; *6*, periodontal ligament; *7*, alveolar bone; *8*, neurovascular bundle.



Fig. 358.6 Facial swelling from an abscessed primary molar. Resolution of the inflammation can be achieved by a course of antibiotics, followed by either extraction or root canal of the offending tooth.

Table 358.1 Red Flags Suggestive of a Spreading Dental Infection

- Pyrexia
- Tachycardia or tachypnea
- Trismus; may be relative due to pain or absolute due to a collection within the muscle causing muscle spasm in cases of masticator space involvement
- Raised tongue and floor of mouth, drooling
- Periorbital cellulitis
- Difficulty with speaking, swallowing, and breathing
- Hypotension
- Increased white blood cell count
- Lymphadenopathy
- Dehydration

From Robertson DP, Keys W, Rautemaa-Richardson R, et al. Management of severe acute dental infections. *BMJ*. 2015;350:h1300. Box 3, p. 151.

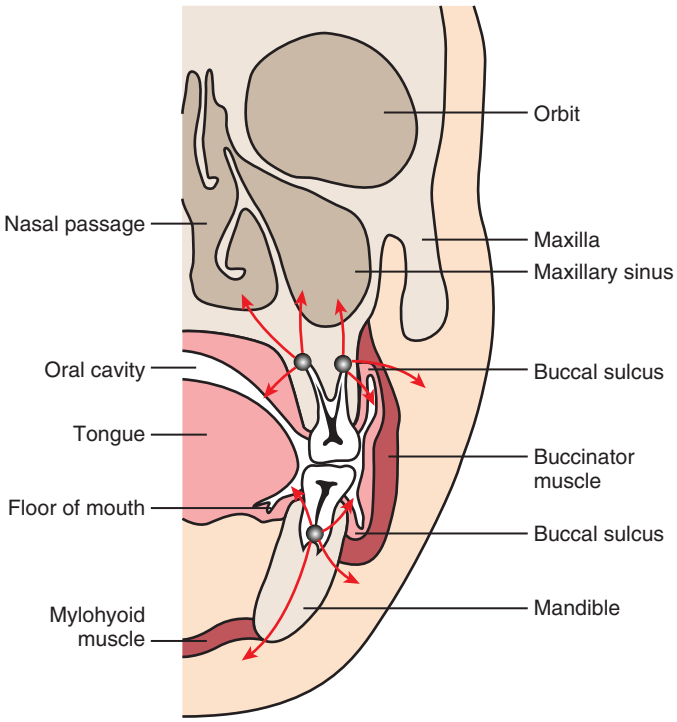

Fig. 358.7 Spread of infection in the maxillofacial region is complicated by the variety of vital structures. Routes of spread are determined by fascial planes and this affects the presentation and management of each subdivision of cervicofacial infection. *(From Robertson DP, Keys W, Rautemaa-Richardson R, et al. Management of severe acute dental infections. BMJ. 2015;350:h1300. Fig. 3, p. 151.)*

Oral antibiotics are indicated for dental infections associated with fever, cellulitis, and facial swelling or if it is difficult to anesthetize the tooth in the presence of inflammation. Penicillin is the antibiotic of choice, except in patients with a history of allergy to this agent. Clindamycin and erythromycin are suitable alternatives. Oral analgesics, such as ibuprofen, are usually adequate for pain control.

Table 358.2 Clinical Presentation of Odontogenic Infections by Location

TYPE OF INFECTION	CLINICAL PRESENTATION
Dentoalveolar	Swelling of the alveolar ridge with periodontal, periapical, and subperiosteal abscess
Submental space	Firm midline swelling beneath the chin; caused by infection from the mandibular incisors
Submandibular space	Swelling of the submandibular triangle of the neck around the angle of the mandible; caused by mandibular molar infections; trismus typical
Sublingual space	Swelling of the floor of the mouth with possible elevation of the tongue and dysphagia
Retropharyngeal space	Stiff neck, sore throat, dysphagia, raspy voice; caused by infections of the molars; infection of retropharyngeal space has a high potential to spread to the mediastinum
Buccal space	Swelling of the cheek; caused by infection of premolar or molar tooth
Masticator space	Swelling on either side of the mandibular ramus; caused by infection of the mandibular third molar; trismus present
Canine space	Swelling of the anterior cheek with loss of the nasolabial fold and possible extension to the infraorbital region

From Ogle OE. Odontogenic infections. *Dent Clin North Am*. 2017;61:235–252. Table 1.

PREVENTION

Dental caries screening, risk assessment, and preventive management in young children need to be part of the scope of medical providers because children younger than 3 years of age often are not under the care of a dentist. Prevention of early childhood caries is critical because, if primary dental care is not initiated or does not succeed, teeth may develop dental caries requiring restorative care. Dental restorative care to treat caries in young children may require the use of sedation or general anesthesia with its associated high costs and possible health risks, and there is high recurrence of carious lesions once they develop.

Because they are seeing infants and toddlers on a periodicity schedule, physicians have an important role in screening children younger than 3 years of age for dental caries; providing preventive instructions; applying preventive measures, such as fluoride varnish; and referring the child to a dentist if problems exist.

Fluoride

The most effective preventive measure against dental caries is communal water supplies with optimal fluoride content. Water fluoridation at the level of 0.7-1.2 mg fluoride per liter (ppm F) was introduced in the United States in the 1940s. Because fluoride from water supplies is now one of several sources of fluoride, the Department of Health and Human Services proposes to not have a fluoride range, but instead to limit the recommendation to the lower limit of 0.7 ppm F. The rationale is to balance the benefits of preventing dental caries with reducing the chance of fluorosis. Children who reside in areas with fluoride-deficient water supplies or who consume primarily bottled water, and are at risk for caries, benefit from dietary fluoride supplements (Table 358.3). If the patient

Table 358.3 Supplemental Fluoride Dosage Schedule

	FLUORIDE IN HOME WATER		
AGE	<0.3 (PPM)	0.3-0.6 (PPM)	>0.6 (PPM)
6mo-3yr	0.25*	0	0
3-6yr	0.50	0.25	0
6-16yr	1.00	0.50	0

*Milligrams of fluoride per day.

uses a private water supply, it is necessary to get the water tested for fluoride levels before prescribing fluoride supplements. To avoid potential overdoses, no fluoride prescription should be written for more than a total of 1 mg/day of fluoride. However, because of confusion regarding fluoride supplements among practitioners and parents, association of supplements with fluorosis, and lack of parent compliance with the daily administration, supplements may no longer be the first-line approach for preventing caries in preschool-age children.

Topical fluoride on a daily basis can be achieved by using fluoridated toothpaste. Supervised use of less than a *pea-sized* amount of toothpaste (approximately 0.25 g) on the toothbrush in children between 3 and 6 years of age reduces the risk of fluorosis. Children younger than 3 years of age should brush with less than a *smear* or *grain-sized* amount of fluoridated toothpaste. Professional topical fluoride applications performed semiannually reportedly reduce caries by approximately 30%. Fluoride varnish is ideal for professional applications in preschool children because of ease of use, even with non–dental health providers, and its safety because of single-dose dispensers. Products that are available come in containers of 0.25, 0.4, or 0.6 mL of varnish, corresponding to 5.6, 9.0, and 13.6 mg fluoride, respectively. Fluoride varnish should be administered twice a year for preschool children at moderate caries risk and 4 times a year for children at high caries risk.

Oral Hygiene

Daily brushing, especially with fluoridated toothpaste, helps prevent dental caries. Most children younger than 8 years of age do not have the coordination required for adequate tooth brushing. Accordingly, parents should assume responsibility for the child's oral hygiene, with the degree of parental involvement appropriate to the child's changing abilities.

Diet

Frequent consumption of sweetened fruit drinks is not generally recognized by parents for its high cariogenic potential. Consuming sweetened beverages in a nursing bottle or sippy cup should be discouraged and special efforts made to instruct parents that their child should consume sweetened beverages only at meal times and not exceed 6 oz/day.

Dental Sealant

Plastic dental sealants have been shown to be effective in preventing caries on the pit and fissure of the primary and permanent molars. Sealants are most effective when placed soon after teeth erupt and used in children with deep grooves and fissures in the molar teeth. Sealants have been shown to reduce the incidence of caries by 85% over 7 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 359
Periodontal Diseases

Vineet K. Dhar

The periodontium includes the gingiva, alveolar bone, cementum, and periodontal ligament (see Fig. 358.5).

GINGIVITIS

Poor oral hygiene results in the accumulation of dental plaque at the tooth-gingival interface that activates an inflammatory response, expressed as localized or generalized reddening and swelling of the gingiva. More than half of American school children experience gingivitis. In severe cases, the gingiva spontaneously bleeds and there is oral malodor. With proper oral hygiene (careful tooth brushing and flossing) complete resolution can be expected. Fluctuations in hormonal levels during the onset of puberty can increase inflammatory responses to plaque. Gingivitis in healthy children is unlikely to progress to periodontitis (inflammation of the periodontal ligament resulting in loss of alveolar bone).

AGGRESSIVE PERIODONTITIS IN CHILDREN (PREPUBERTAL PERIODONTITIS)

Periodontitis in children before puberty is a rare disease that often begins between the time of eruption of the primary teeth and the age of 4 or 5 years. The disease occurs in localized and generalized forms. There is rapid bone loss, often leading to premature loss of primary teeth. It is often associated with systemic problems, including neutropenia, leukocyte adhesion or migration defects, hypophosphatasia, Papillon-Lefèvre syndrome, leukemia, and Langerhans cell histiocytosis. However, in many cases, there is no apparent underlying medical problem. Nonetheless, diagnostic workups are necessary to rule out underlying systemic disease.

Treatment includes aggressive professional teeth cleaning, strategic extraction of affected teeth, and antibiotic therapy. There are few reports of long-term successful treatment to reverse bone loss surrounding primary teeth.

AGGRESSIVE PERIODONTITIS IN ADOLESCENTS

Localized aggressive periodontitis (LAgP) in adolescents is characterized by rapid attachment and alveolar bone loss, on at least two first molars and incisors. Overall prevalence in the United States is <1%, but the prevalence among Black people is reportedly 2.5%. This form of periodontitis is associated with a strain of *Aggregatibacter (Actinobacillus)* bacteria. In addition, the neutrophils of patients with aggressive periodontitis can have chemotactic or phagocytic defects. If left untreated, affected teeth lose their attachment and can exfoliate. Treatment varies with the degree of involvement. Patients whose disease is diagnosed at onset are usually managed by surgical or nonsurgical debridement in conjunction with antibiotic therapy. Prognosis depends on the degree of initial involvement and compliance with therapy.

Generalized aggressive periodontitis (GAgP) occurs more in adolescents and young adults and is characterized by generalized interproximal attachment loss and bone loss, including three teeth that are not first molars and incisors.

CYCLOSPORINE- OR PHENYTOIN-INDUCED GINGIVAL OVERGROWTH

The use of cyclosporine to suppress organ rejection or phenytoin for anticonvulsant therapy, and in some cases calcium channel blockers, is associated with generalized enlargement of the gingiva.

Phenytoin and its metabolites have a direct stimulatory action on gingival fibroblasts, resulting in accelerated synthesis of collagen. Phenytoin induces less gingival hyperplasia in patients who maintain meticulous oral hygiene.

Gingival hyperplasia occurs in 10–30% of patients treated with phenytoin. Severe manifestations can include gross enlargement of the gingiva, sometimes covering the teeth; edema and erythema of the gingiva; secondary infection, resulting in abscess formation; migration of teeth; and inhibition of exfoliation of primary teeth and subsequent impaction of permanent teeth. Treatment should be directed toward prevention and, if possible, discontinuation of cyclosporine or phenytoin. Patients undergoing long-term treatment with these drugs should receive frequent dental examinations and oral hygiene care. Severe forms of gingival overgrowth are treated by gingivectomy, but the lesion recurs if drug use is continued.

ACUTE PERICORONITIS

Acute inflammation of the flap of gingiva that partially covers the crown of an incompletely erupted tooth is common in mandibular permanent molars. Accumulation of debris and bacteria between the gingival flap and tooth precipitates the inflammatory response. A variant of this condition is a gingival abscess caused by entrapment of bacteria because of orthodontic bands or crowns. Trismus and severe pain may be associated with the inflammation. Untreated cases can result in facial space infections and facial cellulitis.

Treatment includes local debridement and irrigation, warm saline rinses, and antibiotic therapy. When the acute phase has subsided, resection of the gingival flap prevents recurrence. Early recognition of the partial impaction of mandibular third molars and their subsequent extraction prevents these areas from developing pericoronitis.

NECROTIZING PERIODONTAL DISEASE (ACUTE NECROTIZING ULCERATIVE GINGIVITIS)

Necrotizing periodontal disease, in the past sometimes referred to as "trench mouth," is a distinct periodontal disease associated with oral spirochetes and fusobacteria. However, it is not clear whether bacteria initiate the disease or are secondary. It rarely develops in healthy children in developed countries, with a prevalence in the United States of <1%, but is seen more often in children and adolescents from developing areas of Africa, Asia, and South America. In certain African countries, where affected children usually have protein malnutrition, the lesion can extend into adjacent tissues, causing necrosis of facial structures (cancrum oris, or noma).

Clinical manifestations of necrotizing periodontal disease include necrosis and ulceration of gingiva between the teeth, an adherent grayish pseudomembrane over the affected gingiva, oral malodor, cervical lymphadenopathy, malaise, and fever. The condition may be mistaken for acute herpetic gingivostomatitis. Dark-field microscopy of debris obtained from necrotizing lesions demonstrates dense spirochete populations.

Treatment of necrotizing periodontal disease is divided into an acute management with local debridement, oxygenating agents (direct application of 10% carbamide peroxide in anhydrous glycerol qid), and analgesics. Dramatic resolution usually occurs within 48 hours. If a patient is febrile, antibiotics (penicillin or metronidazole) may be an important adjunctive therapy. A second phase of treatment may be necessary if the acute phase of the disease has caused irreversible morphologic damage to the periodontium. The disease is not contagious.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 360

Dental Trauma

Vineet K. Dhar

Traumatic oral injuries may be categorized into three groups: injuries to teeth, injuries to soft tissue (contusions, abrasions, lacerations, punctures, avulsions, and burns), and injuries to jaw (mandibular and/or maxillary fractures).

INJURIES TO TEETH

Approximately 10% of children between 18 months and 18 years of age sustain significant tooth trauma. Oral injuries are second most common, covering 18% of all somatic injuries in the age-group 0-6 years. Among oral injuries, injuries to teeth are most common, followed by soft tissue injuries. There appear to be three age periods of greatest predilection: toddlers (1-3 years), usually from falls or child abuse; school-age children (7-10 years), usually from bicycle and playground accidents; and adolescents (16-18 years), often the result of fights, athletic injuries, and automobile accidents. Injuries to teeth are more common among children with protruding front teeth. Children with craniofacial abnormalities or neuromuscular deficits are also at increased risk for dental injury. Injuries to teeth can involve the hard dental tissues, the dental pulp (nerve), and injuries to the periodontal structure (surrounding bone and attachment apparatus) (Fig. 360.1; Table 360.1).

Fractures of teeth may be uncomplicated (confined to the hard dental tissues) or complicated (involving the pulp). Exposure of the pulp results in its bacterial contamination, which can lead to infection and pulp necrosis. Such pulp exposure complicates therapy and can lower the likelihood of a favorable outcome.

The teeth most often affected are the maxillary incisors. Uncomplicated crown fractures are treated by covering exposed dentin and by

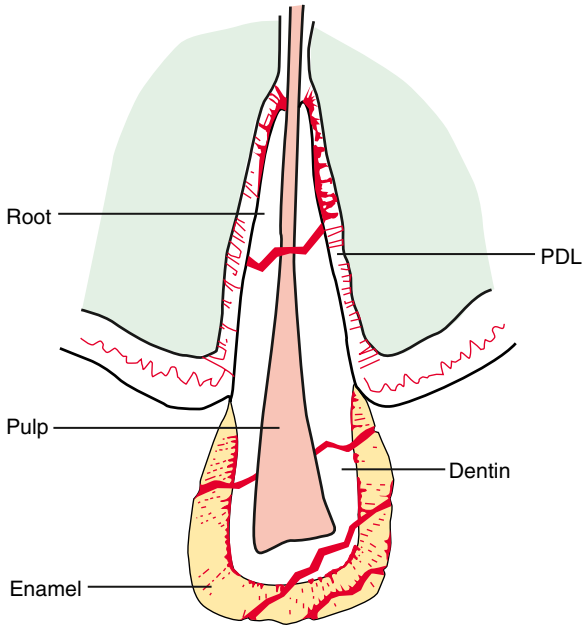

Fig. 360.1 Tooth fractures can involve enamel, dentin, or pulp and can occur in the crown or root of a tooth. PDL, Periodontal ligament. *(From Pinkham JR. Pediatric Dentistry: Infancy Through Adolescence. Philadelphia: Saunders; 1988. p. 172.)*

Phenytoin and its metabolites have a direct stimulatory action on gingival fibroblasts, resulting in accelerated synthesis of collagen. Phenytoin induces less gingival hyperplasia in patients who maintain meticulous oral hygiene.

Gingival hyperplasia occurs in 10–30% of patients treated with phenytoin. Severe manifestations can include gross enlargement of the gingiva, sometimes covering the teeth; edema and erythema of the gingiva; secondary infection, resulting in abscess formation; migration of teeth; and inhibition of exfoliation of primary teeth and subsequent impaction of permanent teeth. Treatment should be directed toward prevention and, if possible, discontinuation of cyclosporine or phenytoin. Patients undergoing long-term treatment with these drugs should receive frequent dental examinations and oral hygiene care. Severe forms of gingival overgrowth are treated by gingivectomy, but the lesion recurs if drug use is continued.

ACUTE PERICORONITIS

Acute inflammation of the flap of gingiva that partially covers the crown of an incompletely erupted tooth is common in mandibular permanent molars. Accumulation of debris and bacteria between the gingival flap and tooth precipitates the inflammatory response. A variant of this condition is a gingival abscess caused by entrapment of bacteria because of orthodontic bands or crowns. Trismus and severe pain may be associated with the inflammation. Untreated cases can result in facial space infections and facial cellulitis.

Treatment includes local debridement and irrigation, warm saline rinses, and antibiotic therapy. When the acute phase has subsided, resection of the gingival flap prevents recurrence. Early recognition of the partial impaction of mandibular third molars and their subsequent extraction prevents these areas from developing pericoronitis.

NECROTIZING PERIODONTAL DISEASE (ACUTE NECROTIZING ULCERATIVE GINGIVITIS)

Necrotizing periodontal disease, in the past sometimes referred to as "trench mouth," is a distinct periodontal disease associated with oral spirochetes and fusobacteria. However, it is not clear whether bacteria initiate the disease or are secondary. It rarely develops in healthy children in developed countries, with a prevalence in the United States of <1%, but is seen more often in children and adolescents from developing areas of Africa, Asia, and South America. In certain African countries, where affected children usually have protein malnutrition, the lesion can extend into adjacent tissues, causing necrosis of facial structures (cancrum oris, or noma).

Clinical manifestations of necrotizing periodontal disease include necrosis and ulceration of gingiva between the teeth, an adherent grayish pseudomembrane over the affected gingiva, oral malodor, cervical lymphadenopathy, malaise, and fever. The condition may be mistaken for acute herpetic gingivostomatitis. Dark-field microscopy of debris obtained from necrotizing lesions demonstrates dense spirochete populations.

Treatment of necrotizing periodontal disease is divided into an acute management with local debridement, oxygenating agents (direct application of 10% carbamide peroxide in anhydrous glycerol qid), and analgesics. Dramatic resolution usually occurs within 48 hours. If a patient is febrile, antibiotics (penicillin or metronidazole) may be an important adjunctive therapy. A second phase of treatment may be necessary if the acute phase of the disease has caused irreversible morphologic damage to the periodontium. The disease is not contagious.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 360

Dental Trauma

Vineet K. Dhar

Traumatic oral injuries may be categorized into three groups: injuries to teeth, injuries to soft tissue (contusions, abrasions, lacerations, punctures, avulsions, and burns), and injuries to jaw (mandibular and/or maxillary fractures).

INJURIES TO TEETH

Approximately 10% of children between 18 months and 18 years of age sustain significant tooth trauma. Oral injuries are second most common, covering 18% of all somatic injuries in the age-group 0-6 years. Among oral injuries, injuries to teeth are most common, followed by soft tissue injuries. There appear to be three age periods of greatest predilection: toddlers (1-3 years), usually from falls or child abuse; school-age children (7-10 years), usually from bicycle and playground accidents; and adolescents (16-18 years), often the result of fights, athletic injuries, and automobile accidents. Injuries to teeth are more common among children with protruding front teeth. Children with craniofacial abnormalities or neuromuscular deficits are also at increased risk for dental injury. Injuries to teeth can involve the hard dental tissues, the dental pulp (nerve), and injuries to the periodontal structure (surrounding bone and attachment apparatus) (Fig. 360.1; Table 360.1).

Fractures of teeth may be uncomplicated (confined to the hard dental tissues) or complicated (involving the pulp). Exposure of the pulp results in its bacterial contamination, which can lead to infection and pulp necrosis. Such pulp exposure complicates therapy and can lower the likelihood of a favorable outcome.

The teeth most often affected are the maxillary incisors. Uncomplicated crown fractures are treated by covering exposed dentin and by

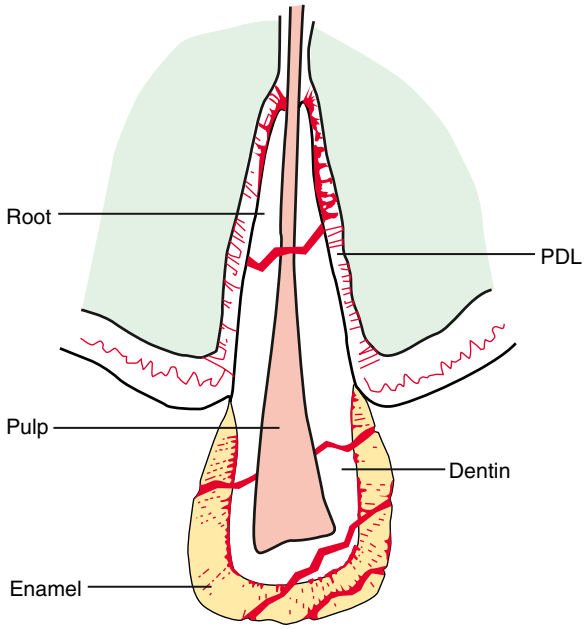

Fig. 360.1 Tooth fractures can involve enamel, dentin, or pulp and can occur in the crown or root of a tooth. PDL, Periodontal ligament. *(From Pinkham JR. Pediatric Dentistry: Infancy Through Adolescence. Philadelphia: Saunders; 1988. p. 172.)*

Table 360.1 Injuries to Crowns of Teeth

TYPE OF TRAUMA	DESCRIPTION	TREATMENT AND REFERRAL
Enamel infraction (crazing)	Incomplete fracture of enamel without loss of tooth structure	Initially might not require therapy but should be assessed periodically by dentist
Enamel fractures	Fracture of only the tooth enamel	Tooth may be smoothed or treated to replace fragment
Enamel and dentin fracture	Fracture of enamel and dentinal layer of the tooth. Tooth may be sensitive to cold or air. Pulp may become necrotic, leading to periapical abscess	Refer as soon as possible. Area should be treated to preserve the integrity of the underlying pulp
Enamel, dentin fracture involving the pulp	Bacterial contamination can lead to pulpal necrosis and periapical abscess. The tooth might have the appearance of bleeding or might display a small red spot	Refer immediately. The dental therapy of choice depends on the extent of injury, the condition of the pulp, the development of the tooth, time elapsed from injury, and any other injuries to the supporting structures. Therapy is directed toward minimizing contamination in an effort to improve the prognosis

From Josell SD, Abrams RG. Managing common dental problems and emergencies. *Pediatr Clin North Am.* 1991;38:1325–1342.

placing an aesthetic restoration. Complicated crown fractures involving the tooth pulp usually require **endodontic therapy** (root canal). Crown-root fractures and root fractures usually require extensive dental therapy. Such injuries in the primary dentition can interfere with normal development of the permanent dentition; therefore significant injuries of the primary incisor teeth are usually managed by extraction.

Traumatic oral injuries should be referred to a dentist as soon as possible. Even when the teeth appear intact, a dentist should promptly evaluate the patient. Baseline data (radiographs, mobility patterns, responses to specific stimuli) enable the dentist to assess the likelihood of future complications.

INJURIES TO PERIODONTAL STRUCTURES

Trauma to teeth with associated injury to periodontal structures that hold the teeth usually manifests as mobile or displaced teeth. Categories of trauma to the periodontium include concussion, subluxation, intrusive luxation, extrusive luxation, and avulsion.

Concussion

Injuries that produce minor damage to the periodontal ligament are termed *concussions*. Teeth sustaining such injuries are not mobile or displaced but react markedly to percussion (gentle hitting of the tooth with an instrument). This type of injury usually requires no therapy and resolves without complication. Primary incisors that sustain concussion can change color, which may indicate pulpal degeneration and should be evaluated by a dentist.

Subluxation

Subluxated teeth exhibit mild to moderate horizontal mobility and/or vertical mobility. Hemorrhage is usually evident around the neck of the tooth at the gingival margin. There is no displacement of the tooth. Many subluxated teeth need to be immobilized by splints to ensure adequate repair of the periodontal ligament. Some of these teeth develop pulp necrosis.

Intrusion

Intruded teeth are pushed up into their socket, sometimes to the point where they are not clinically visible. Intruded primary incisors can give the false appearance of being avulsed (knocked out). To rule out avulsion, a dental radiograph is indicated (Figs. 360.2 and 360.3). Intruded primary teeth are usually monitored for spontaneous repositioning or re-eruption. Depending on the severity, the intruded permanent teeth may be monitored for re-eruption or repositioned surgically or orthodontically. Some of these teeth develop pulp necrosis and infection requiring further management.

Extrusion

Extrusion injury is characterized by displacement of the tooth from its socket. The tooth is usually displaced to the lingual (tongue) side, with fracture of the wall of the alveolar socket. These teeth need immediate treatment; the longer the delay, the more likely the tooth will be fixed in its displaced position. Therapy is directed at reduction (repositioning the tooth) and fixation (splinting). The pulp of such teeth often becomes necrotic and requires endodontic therapy. Extrusive luxation in the primary dentition is usually managed by extraction because complications of reduction and fixation can result in problems with development of permanent teeth.

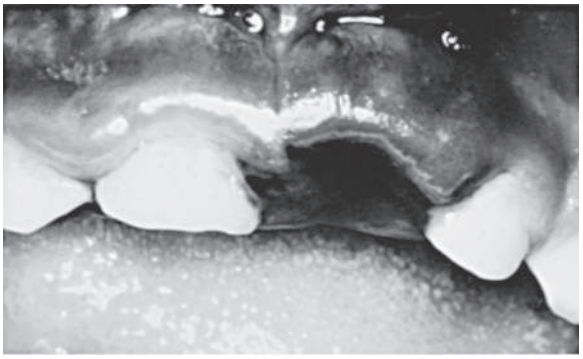

Fig. 360.2 Intruded primary incisor that appears avulsed (knocked out).

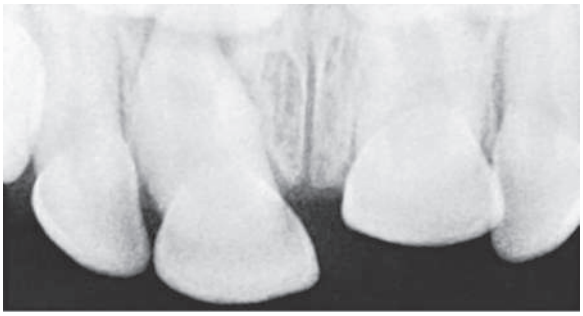

Fig. 360.3 Occlusal radiograph documents intrusion of "missing tooth" presented in Figure 360.2.

Avulsion

If avulsed permanent teeth are replanted as soon as possible after injury, there is a good chance that normal reattachment will follow and the tooth will have a good prognosis. However, if the tooth is in a dry environment for longer than 1 hour, the ligament that holds the tooth in place has little chance for survival and failure (root resorption, ankylosis) is common. Parents confronted with this emergency situation can be instructed to do the following:

- Find the tooth.
- Briefly rinse the tooth. (Do not scrub the tooth. Do not touch the root. After plugging the sink drain, hold the tooth by the crown and rinse it under running tap water.)
- Insert the tooth into the socket. (Gently place it back into its normal position. Do not be concerned if the tooth extrudes slightly. If the parent or child is too apprehensive for replantation of the tooth, the tooth should be placed in cold cow's milk or other cold isotonic solution.)
- Go directly to the dentist. (In transit, the child should hold the tooth in its socket with a finger. The parent should place the child in an age-appropriate child seat, buckle a seatbelt around the child, and drive safely.)

After the tooth is replanted, it must be immobilized to facilitate reattachment; endodontic therapy is always required. The initial signs of complications associated with replantation can appear as early as 1 week after trauma or as late as several years later. Close dental follow-up is indicated for at least 1 year.

PREVENTION

To minimize the likelihood of dental injuries:

- Every child or adolescent who engages in contact sports should wear a **mouth guard**, which may be constructed by a dentist or purchased at any athletic goods store.
- Helmets with face guards should be worn by children or adolescents with neuromuscular problems or seizure disorders to protect the head and face during falls.
- Helmets should also be used during biking, skiing, skating, and skateboarding.
- All children or adolescents with protruding incisors should be evaluated by a pediatric dentist or orthodontist.

ADDITIONAL CONSIDERATIONS

Children who experience dental trauma might also have sustained head or neck trauma, and therefore, neurologic assessment is warranted. Tetanus prophylaxis should be considered with any injury that disrupts the integrity of the oral tissues. The possibility of child abuse should always be considered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 361

Common Lesions of the Oral Soft Tissues

Vineet K. Dhar

OROPHARYNGEAL CANDIDIASIS

Oropharyngeal infection with *Candida albicans* (thrush, moniliasis) (see Chapter 280.1) is common in neonates from contact with the organism in the birth canal or contact with the breast during breastfeeding. The lesions of oropharyngeal candidiasis (OPC) appear as white plaques covering all or part of the oropharyngeal mucosa. These plaques are removable from the underlying surface, which is characteristically inflamed and has pinpoint hemorrhages. The diagnosis is confirmed by direct microscopic examination on potassium hydroxide smears and culture of scrapings from lesions. OPC is usually self-limited in the healthy newborn infant, but topical application of nystatin to the oral cavity of the baby and to the nipples of breastfeeding mothers will hasten recovery.

OPC is also a major problem during myelosuppressive therapy. **Systemic candidiasis**, a major cause of morbidity and mortality during myelosuppressive therapy, develops almost exclusively in patients who have had prior oropharyngeal, esophageal, or intestinal candidiasis. This observation implies that prevention of OPC should reduce the incidence of systemic candidiasis. The use of oral rinses of 0.2% chlorhexidine gluconate solution along with systemic antifungals may be effective in preventing OPC, systemic candidiasis, or candidal esophagitis.

APHTHOUS ULCERS

The aphthous ulcer (canker sore) is a distinct oral lesion (Fig. 361.1), prone to recurrence; Table 361.1 notes the differential diagnosis. Aphthous ulcers are reported to develop in 20% of the population. Their etiology is unclear, but allergic or immunologic reactions, emotional stress, genetics, and injury to the soft tissues in the mouth have been implicated. Aphthous-like lesions may be associated with inflammatory bowel disease, Behçet disease, gluten-sensitive enteropathy, periodic fever-aphthae-pharyngitis-adenitis syndrome, Sweet syndrome, HIV infection (especially if ulcers are large and slow to heal), and cyclic neutropenia (see Table 361.1). Clinically, these ulcers are characterized by well-circumscribed, ulcerative lesions with a white necrotic base surrounded by a red halo. The lesions generally last 10-14 days and heal without scarring. Nonprescription palliative therapies, such as benzocaine and topical lidocaine, are effective, as are topical steroids. Use of soft tissue dental lasers may help manage aphthous ulcers by accelerating wound healing and reducing pain. Tetracycline is beneficial with severe outbreaks, but caution is necessary in pregnant women, because it is classified as U.S. Food and Drug Administration (FDA) pregnancy category D. In younger children (≤8 years), tetracycline can affect developing teeth and cause permanent staining of the teeth.

HERPETIC GINGIVOSTOMATITIS

After an initial incubation period of approximately 1 week, the primary infection with herpes simplex virus manifests as fever and malaise, usually in a child younger than 5 years (see Chapter 299). The oral cavity can show various expressions, including the gingiva becoming erythematous, mucosal hemorrhages, and clusters of small vesicles erupting throughout the mouth. There is often involvement of the mucocutaneous margin and perioral skin (Fig. 361.2). The oral symptoms generally are accompanied by fever, lymphadenopathy, and difficulty eating and drinking. The symptoms usually regress within 2 weeks without scarring. Fluids should be encouraged because the child may become dehydrated. Analgesics and anesthetic rinses can make



Fig. 361.1 Major aphthous in a child. *(From Gürkan A, Özlü SG, Altiaylik-Özer P, et al. Recurrent aphthous stomatitis in childhood and adolescence: a single-center experience. Pediatr Dermatol. 2015;32[4]:476–480. Fig. 1.)*

Table 361.1 Differential Diagnosis of Oral Ulceration

CONDITION	COMMENT
COMMON	
Aphthous ulcers (canker sores)	Painful circumscribed lesions; recurrences
Traumatic ulcers	Accidents, chronic cheek biter, after dental local anesthesia
Hand, foot, and mouth disease	Painful; lesions on tongue, anterior oral cavity, hands, and feet
Herpangina	Painful; lesions confined to soft palate and oropharynx
Herpetic gingivostomatitis	Vesicles on mucocutaneous borders; painful, febrile
Recurrent herpes labialis	Vesicles on lips; painful
Chemical burns	Alkali, acid, aspirin; painful
Heat burns	Hot food, electrical
Medicine effect	NSAIDs, methotrexate, azathioprine, enalapril, losartan, fluoxetine, antiretroviral agents
RIME	Mycoplasma and other agents; predominant oral ulcerations with scattered cutaneous lesions
UNCOMMON	
Neutrophil defects	Agranulocytosis, leukemia, cyclic neutropenia; painful
Systemic lupus erythematosus	Recurrent; may be painless
Behçet syndrome	Resembles aphthous lesions; associated with genital ulcers, uveitis
Necrotizing ulcerative gingivostomatitis	Vincent stomatitis; painful
Syphilis	Chancre or gumma; painless
Oral Crohn disease	Aphthous-like; painful
Histoplasmosis	Lingual
Pemphigus	May be isolated to the oral cavity
Stevens-Johnson syndrome	May be isolated to or appear initially in the oral cavity

NSAIDs, Nonsteroidal antiinflammatory drugs; RIME, reactive infectious mucotaneous eruption.



Fig. 361.2 Herpetic gingivostomatitis. Lip erosions with multiple perioral herpetic lesions involving the mucocutaneous borders. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology. 3rd ed. Philadelphia: Saunders; 2006. p. 398.)*

the child more comfortable. Oral valacyclovir, if taken within the first 3 days of symptoms in immunocompetent patients, is beneficial in shortening the duration of symptoms. Caution should be exercised to prevent autoinoculation, especially of the eyes.

RECURRENT HERPES LABIALIS

Approximately 90% of the worldwide population develops antibodies to herpes simplex virus. In periods of quiescence, the virus is thought to remain latent in sensory neurons. Unlike primary herpetic gingivostomatitis, which manifests as multiple painful vesicles on the lips, tongue, palate, gingiva, and mucosa, recurrent herpes is generally limited to the lips. Other than the annoyance of causing pain and being a cosmetic issue, recurrent episodes generally do not involve systemic symptoms. Reactivation of the virus is thought to be the result of exposure to ultraviolet light, tissue trauma, stress, or fevers. There is little advantage of antiviral therapy over palliative therapies in an otherwise healthy patient affected by recurrent herpes.

PARULIS

The parulis (gum boil) is a soft reddish papule located adjacent to the root of a chronically abscessed tooth. It occurs at the end-point of a draining dental sinus tract. Treatment consists of diagnosing which tooth is abscessed and extracting it or performing root canal treatment on the offending tooth.

CHEILITIS

Cheilitis, dryness of the lips followed by scaling and cracking and accompanied by a characteristic burning sensation, is common in children. Cheilitis may be caused by sensitivity to contact substances, lip licking, vitamin deficiency, weakened immune system, or fungal or bacterial infections, and often occurs in association with fever. Treatment may include antifungal or antibacterial agents and frequent application of petroleum jelly.

ANKYLOGLOSSIA

Ankyloglossia, or tongue-tie, is characterized by an abnormally short lingual frenum that can hinder the tongue movement, but rarely interferes with feeding or speech. It is possible that the frenum could spontaneously lengthen as the child gets older. If, in the rare event that the extent of the ankyloglossia is severe, speech may be affected and surgical correction may be indicated.

GEOGRAPHIC TONGUE

Geographic tongue (migratory glossitis) is a benign and asymptomatic lesion that is characterized by one or more smooth bright red patches, often showing a yellow, gray, or white membranous margin on the dorsum of an otherwise normally roughened tongue. The condition has no known cause, and no treatment is indicated (see Chapter 705).

FISSURED TONGUE

The fissured tongue (scrotal tongue) is a malformation manifested clinically by numerous small furrows or grooves on the dorsal surface (see Chapter 705). If the tongue is painful, brushing the tongue or irrigating with water can reduce the bacteria in the fissures.

DEVELOPMENTAL (NORMAL) VARIATIONS

Bohn Nodules

Bohn nodules are small developmental anomalies located along the buccal and lingual aspects of the mandibular and maxillary ridges and in the hard palate of the neonate. These lesions arise from remnants of mucous gland tissue. Treatment is not necessary as the nodules usually disappear within a few weeks.

Dental Lamina Cysts

Dental lamina cysts are small cystic lesions located along the crest of the mandibular and maxillary ridges of the neonate. These lesions arise from epithelial remnants of the dental lamina. Treatment is not necessary; they disappear within a few weeks.

Epstein Pearls
Epstein pearls are small developmental lesions located in the median palatal raphe region due to entrapment of epithelial remnants along the line of fusion of the palatal halves. Treatment is not necessary, as these slough off on their own within a few weeks.

Fordyce Granules
Fordyce granules are common and almost 80% of adults have these yellow-white granules in clusters or plaquelike areas on the oral mucosa, most commonly on the buccal mucosa or lips. They are aberrant sebaceous glands. The glands are present at birth, but they can undergo hypertrophy and first appear as discrete yellowish papules during the preadolescent period in approximately 50% of children. No treatment is necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 362

Diseases of the Salivary Glands and Jaws

Vineet K. Dhar

With the exception of mumps (see Chapter 295), diseases of the salivary glands are rare in children. Bilateral enlargement of the submaxillary glands can occur in HIV/AIDS, cystic fibrosis, Epstein-Barr virus infection, malnutrition, COVID-19, and transiently during acute asthmatic attacks. Chronic vomiting can be accompanied by enlargement of the parotid glands. Benign salivary gland hypertrophy has been associated with endocrinopathies: thyroid disease, diabetes, and Cushing syndrome. Infiltrative disease or tumors are uncommon; red flags include facial nerve palsy, rapid growth, fixed skin, paresthesias, ulceration, or a history of radiation to the head or neck region.

PAROTITIS
Acute parotitis is often caused by blockage, with further inflammation due to bacterial infection. The blockage may be due to a salivary stone or mucus plug. Stones can be removed by physical manipulation, surgery, or lithotripsy. **Recurrent parotitis** is an idiopathic swelling of the parotid gland that can occur in otherwise healthy children. The swelling is usually unilateral, but both glands can be involved simultaneously or alternately. There is little pain; the swelling is limited to the gland and usually lasts 2-3 weeks. Treatment may include local heat, massaging the gland, and antibiotics. **Suppurative parotitis** is usually caused by *Staphylococcus aureus*. It is usually unilateral and may be accompanied by fever. The gland becomes swollen, tender, and painful. Suppurative parotitis responds to antibacterial therapy based on culture obtained from the Stensen duct or by surgical drainage. Viral causes of parotitis include mumps (often in epidemics), Epstein-Barr virus, human herpesvirus 6, enteroviruses, COVID-19, and HIV.

RANULA
A ranula is a cyst associated with a major salivary gland in the sublingual area. It is a large, soft, mucus-containing swelling in the floor of the mouth. It occurs at any age, including infancy. The cyst should be excised, and the severed duct should be exteriorized.

MUCOCELE
Mucocele is a salivary gland lesion caused by a blockage of a salivary gland duct. It is most common on the lower lip and has the appearance of a fluid-filled vesicle, or a fluctuant nodule with the overlying mucosa being normal in color. Treatment is surgical excision, with removal of the involved accessory salivary gland.

CONGENITAL LIP PITS
Congenital lip pits are caused by fistulous tracts that lead to embedded mucous glands in the lower lip. They leak saliva, especially with salivary stimulation. Lip pits can be isolated anomalies, or they can be found in patients with cleft lip or palate. Treatment is surgical excision of the glandular tissue.

ERUPTION CYST
Eruption cyst is a smooth painless swelling over the erupting tooth. If bleeding occurs in the cyst space, it may appear blue or blue-black. In most cases, no treatment is indicated, and the cyst resolves with the full eruption of the tooth.

XEROSTOMIA
Also known as *dry mouth*, xerostomia may be associated with fever, dehydration, anticholinergic drugs, chronic graft-versus-host disease, Mikulicz disease (leukemic infiltrates), Sjögren syndrome, or tumoricidal doses of radiation when the salivary glands are within the field. Long-term xerostomia is a high-risk factor for dental caries.

SALIVARY GLAND TUMORS
See Chapter 549.

HISTIOCYTIC DISORDERS
See Chapter 556.

TUMORS OF THE JAW
Ossifying fibroma is a common benign tumor of the jaw. It is often asymptomatic and is usually discovered on routine radiographic examinations. Treatment is resection due to the possibility of recurrence. **Central giant cell granuloma** is another common lesion thought to be reactive, rather than neoplastic. Although usually asymptomatic, it can be expansile, with or without resorption of the roots of teeth and perforation of the cortical plate. Treatment is complete curettage or surgical excision. **Dentigerous cysts** are common lesions associated with the crown of an impacted or unerupted tooth. Although usually asymptomatic, they can become large and destructive. Treatment is surgical removal.

The malignant primary tumors of the jaw in children include Burkitt lymphoma, osteogenic sarcoma, lymphosarcoma, ameloblastoma, and, more rarely, fibrosarcoma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 363

Diagnostic Radiology in Dental Assessment

Vineet K. Dhar

Diagnostic dental radiology in children follows the as low as reasonably achievable (ALARA) principle. In children, intraoral radiographs such as bitewings and select periapical radiographs are taken during routine dental visits and repeated every 6 months to 2 years based on the caries risk assessment. Additional radiographs such as panoramic views, cephalometric radiographs, and dental cone beam computed tomography (CBCT) are taken when indicated. In general, the cumulative radiation exposure due to routine dental radiographs is minimal. In addition, precautions such as use of high-speed film, collimated beam, protective aprons and thyroid collars, proper technique, and minimizing number of exposures are all taken to keep radiation exposure minimal.

Intraoral dental radiographs are highly detailed, direct-exposure films that demonstrate sections of the child's teeth and supporting bone structures. The film or image receptor is placed lingual to the teeth, and the x-ray beam is directed through the teeth and supporting structures. The resulting images are used to detect dental caries, loss of alveolar bone (periodontal disease), abscesses at the roots of the teeth, and trauma to the teeth and alveolar bone. These radiographs are also used to demonstrate the developmental status of permanent teeth within the bone.

The **panoramic radiograph** provides a single tomographic image of the upper and lower jaw, including all teeth and supporting structures. The x-ray tube rotates about the patient's head with reciprocal movement of the film or image receptor during the exposure. The panoramic image shows the teeth, mandibular bodies, rami, and condyles; maxillary sinuses; and a majority of the facial buttresses. Such images are used to show abnormalities of tooth number, development and eruption pattern, cystic and neoplastic lesions, bone infections, and fracture, as well as dental caries and periodontal disease (Fig. 363.1).

Cephalometric radiographs are posteroanterior and lateral skull films that are taken using a **cephalostat** (head positioner) and employ techniques that clearly demonstrate the facial skeleton and soft facial tissues. Similar protocols for positioning children are used throughout the world. From these images, cranial and facial points and planes can be determined and compared with standards derived from thousands of images. A child's facial growth can be assessed serially when cephalometric radiographs are taken sequentially. Relationships among the maxilla, mandible, cranial base, and facial skeleton can be determined in a quantitative manner. Additionally, the alignment of the teeth and the relation of the teeth to the supporting bone can be serially measured.

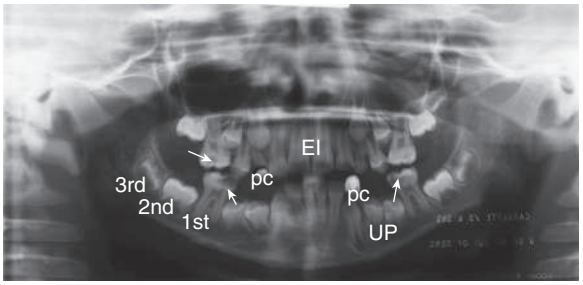

Fig. 363.1 A panoramic radiograph of a 10-yr-old child showing extensive dental caries of the first permanent molars *(arrows)*, as well as normal structures: erupted first permanent molar, unerupted second molar, and unerupted third molar. EI, Erupted incisors, UP, unerupted premolars, pc, erupted primary canines.

Dental CBCT is a variation of traditional CT, used mainly to evaluate oral and maxillofacial regions and teeth. Dental CBCT generally delivers lower radiation exposure than traditional CT, but higher than conventional dental radiography. There are several indications for CBCT, such as evaluation of oral-maxillofacial pathologies, diagnosis of dental trauma, endodontic treatment, visualization of abnormal teeth, orthodontic assessment, or cleft palate assessment, among others.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

The Esophagus

Chapter 364

Embryology, Anatomy, and Function of the Esophagus

Seema Khan and Sravan Kumar Reddy Matta

The esophagus is a hollow muscular tube, separated from the pharynx above and the stomach below by two tonically closed sphincters. Its primary function is to convey ingested material from the mouth to the stomach. Largely lacking digestive glands and enzymes, and exposed only briefly to nutrients, it has no active role in digestion.

EMBRYOLOGY

The esophagus develops from the postpharyngeal foregut and can be distinguished from the stomach in the 4-week-old embryo. At the same time, the trachea begins to bud just anterior to the developing esophagus; the resulting laryngotracheal groove extends and becomes the lung. Disturbance of this stage can result in congenital anomalies such as **tracheoesophageal fistula** (see Chapter 365). The length of the esophagus is 8-10 cm at birth and doubles in the first 2-3 years of life, reaching approximately 25 cm in the adult. The abdominal portion of the esophagus is as large as the stomach in an 8-week-old fetus but gradually shortens to a few millimeters at birth, attaining a final length of approximately 3 cm by a few years of age. This intraabdominal location of both the distal esophagus and the **lower esophageal sphincter** (LES) is an important antireflux mechanism because an increase in intraabdominal pressure is also transmitted to the sphincter, augmenting its defense. Swallowing can be seen in utero as early as 16-20 weeks of gestation, helping to circulate the amniotic fluid; **polyhydramnios** is a hallmark of lack of normal swallowing or of esophageal or upper gastrointestinal tract obstruction. Sucking and swallowing are not fully coordinated before 34 weeks of gestation, a contributing factor for feeding difficulties in premature infants.

ANATOMY

The luminal aspect of the esophagus is covered by thick, protective, nonkeratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach's upper margin at the **gastroesophageal junction (GEJ).** This squamous epithelium is relatively

Chapter 363

Diagnostic Radiology in Dental Assessment

Vineet K. Dhar

Diagnostic dental radiology in children follows the as low as reasonably achievable (ALARA) principle. In children, intraoral radiographs such as bitewings and select periapical radiographs are taken during routine dental visits and repeated every 6 months to 2 years based on the caries risk assessment. Additional radiographs such as panoramic views, cephalometric radiographs, and dental cone beam computed tomography (CBCT) are taken when indicated. In general, the cumulative radiation exposure due to routine dental radiographs is minimal. In addition, precautions such as use of high-speed film, collimated beam, protective aprons and thyroid collars, proper technique, and minimizing number of exposures are all taken to keep radiation exposure minimal.

Intraoral dental radiographs are highly detailed, direct-exposure films that demonstrate sections of the child's teeth and supporting bone structures. The film or image receptor is placed lingual to the teeth, and the x-ray beam is directed through the teeth and supporting structures. The resulting images are used to detect dental caries, loss of alveolar bone (periodontal disease), abscesses at the roots of the teeth, and trauma to the teeth and alveolar bone. These radiographs are also used to demonstrate the developmental status of permanent teeth within the bone.

The **panoramic radiograph** provides a single tomographic image of the upper and lower jaw, including all teeth and supporting structures. The x-ray tube rotates about the patient's head with reciprocal movement of the film or image receptor during the exposure. The panoramic image shows the teeth, mandibular bodies, rami, and condyles; maxillary sinuses; and a majority of the facial buttresses. Such images are used to show abnormalities of tooth number, development and eruption pattern, cystic and neoplastic lesions, bone infections, and fracture, as well as dental caries and periodontal disease (Fig. 363.1).

Cephalometric radiographs are posteroanterior and lateral skull films that are taken using a **cephalostat** (head positioner) and employ techniques that clearly demonstrate the facial skeleton and soft facial tissues. Similar protocols for positioning children are used throughout the world. From these images, cranial and facial points and planes can be determined and compared with standards derived from thousands of images. A child's facial growth can be assessed serially when cephalometric radiographs are taken sequentially. Relationships among the maxilla, mandible, cranial base, and facial skeleton can be determined in a quantitative manner. Additionally, the alignment of the teeth and the relation of the teeth to the supporting bone can be serially measured.

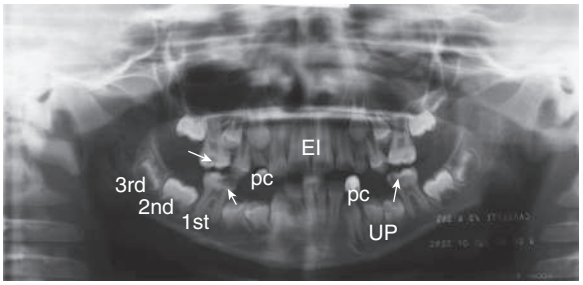

Fig. 363.1 A panoramic radiograph of a 10-yr-old child showing extensive dental caries of the first permanent molars *(arrows)*, as well as normal structures: erupted first permanent molar, unerupted second molar, and unerupted third molar. EI, Erupted incisors, UP, unerupted premolars, pc, erupted primary canines.

Dental CBCT is a variation of traditional CT, used mainly to evaluate oral and maxillofacial regions and teeth. Dental CBCT generally delivers lower radiation exposure than traditional CT, but higher than conventional dental radiography. There are several indications for CBCT, such as evaluation of oral-maxillofacial pathologies, diagnosis of dental trauma, endodontic treatment, visualization of abnormal teeth, orthodontic assessment, or cleft palate assessment, among others.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

The Esophagus

Chapter 364

Embryology, Anatomy, and Function of the Esophagus

Seema Khan and Sravan Kumar Reddy Matta

The esophagus is a hollow muscular tube, separated from the pharynx above and the stomach below by two tonically closed sphincters. Its primary function is to convey ingested material from the mouth to the stomach. Largely lacking digestive glands and enzymes, and exposed only briefly to nutrients, it has no active role in digestion.

EMBRYOLOGY

The esophagus develops from the postpharyngeal foregut and can be distinguished from the stomach in the 4-week-old embryo. At the same time, the trachea begins to bud just anterior to the developing esophagus; the resulting laryngotracheal groove extends and becomes the lung. Disturbance of this stage can result in congenital anomalies such as **tracheoesophageal fistula** (see Chapter 365). The length of the esophagus is 8-10 cm at birth and doubles in the first 2-3 years of life, reaching approximately 25 cm in the adult. The abdominal portion of the esophagus is as large as the stomach in an 8-week-old fetus but gradually shortens to a few millimeters at birth, attaining a final length of approximately 3 cm by a few years of age. This intraabdominal location of both the distal esophagus and the **lower esophageal sphincter** (LES) is an important antireflux mechanism because an increase in intraabdominal pressure is also transmitted to the sphincter, augmenting its defense. Swallowing can be seen in utero as early as 16-20 weeks of gestation, helping to circulate the amniotic fluid; **polyhydramnios** is a hallmark of lack of normal swallowing or of esophageal or upper gastrointestinal tract obstruction. Sucking and swallowing are not fully coordinated before 34 weeks of gestation, a contributing factor for feeding difficulties in premature infants.

ANATOMY

The luminal aspect of the esophagus is covered by thick, protective, nonkeratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach's upper margin at the **gastroesophageal junction (GEJ).** This squamous epithelium is relatively

resistant to damage by gastric secretions, in contrast to the ciliated columnar epithelium of the respiratory tract. However, chronic irritation by gastric contents can result in morphometric changes such as thickening of the basal cell layer and lengthening of papillary ingrowth into the epithelium, and subsequent metaplasia of the cells lining the lower esophagus from squamous to columnar. Deeper layers of the esophageal wall are composed successively of lamina propria, muscularis mucosae, submucosa, and the two layers of muscularis propria (circular surrounded by longitudinal). The two delimiting sphincters of the esophagus, the **upper esophageal sphincter (UES)** at the cricopharyngeus muscle and the **LES** at the **GEJ,** constrict the esophageal lumen at its proximal and distal boundaries. The muscularis propria of the upper third of the esophagus is predominantly striated, and that of the lower two-thirds is smooth muscle. Clinical conditions involving striated muscle (cricopharyngeal dysfunction, cerebral palsy) affect the upper esophagus, whereas those involving smooth muscle (achalasia, reflux esophagitis) affect the lower esophagus. The muscular LES and the mucosal "Z-line" of the GEJ may be discrepant up to several centimeters.

FUNCTION

The esophagus can be divided into three areas: the UES, the esophageal body, and the LES. At rest, the tonic LES pressure is normally approximately 20 mm Hg; values <10 mm Hg are usually considered abnormal, although it seems that competence against retrograde flow of gastric material is maintained if the LES pressure is >5 mm Hg. The LES pressure rises during intragastric pressure amplifications, whether caused by gastric contractions, abdominal wall muscle contractions ("straining"), or external pressure applied to the abdominal wall. It also rises in response to cholinergic stimuli, gastrin, gastric alkalization, and certain drugs (bethanechol, metoclopramide, cisapride). The UES pressure is more variable and often higher than that of the LES; it decreases almost to zero during deep sleep and it increases markedly during stress and straining. The UES and LES relax briefly to allow material to pass through during swallowing, belching, reflux, and vomiting. They can contract in response to subthreshold levels of reflux (esophagoglottal closure reflex).

Swallowing is initiated by elevation of the tongue, propelling the bolus into the pharynx. The larynx elevates and moves anteriorly, pulling open the relaxing UES, while the opposed aryepiglottic folds close. The epiglottis drops back to cover the larynx and direct the bolus over the larynx and into the UES. The soft palate occludes the nasopharynx. The primary peristalsis thus initiated is a contraction originating in the oropharynx that clears the esophagus aborally (Fig. 364.1). Oropharyngeal swallowing related dysfunction may occur at multiple levels (Table 364.1). The LES, tonically contracted as a barrier against gastroesophageal reflux (GER), relaxes as swallowing is initiated, at nearly the same time as the UES relaxation. The LES relaxation persists considerably longer, until the peristaltic wave traverses it and closes it. The normal esophageal peristaltic speed is approximately 3 cm/sec; the wave takes 4 sec or longer to traverse the 12-cm esophagus of a young infant and considerably longer in a larger child. Facial stimulation by a puff of air can induce swallowing and esophageal peristalsis in healthy young infants, a reflex termed the **Santmyer swallow.**

In addition to relaxing to move swallowed material past the GEJ into the stomach, the LES normally relaxes to vent swallowed air or to allow retrograde expulsion of material from the stomach. Perhaps as an extension of these functions, the normal LES also permits physiologic reflux episodes, brief events that occur approximately five times in the first postprandial hour, particularly in the awake state, but are otherwise uncommon. **Transient LES relaxation,** not associated with swallowing, is the major mechanism underlying **pathologic reflux** (see Fig. 364.1).

The close linkage of the anatomy of the upper digestive and respiratory tracts has mandated intricate functional protections of the respiratory tract during retrograde movement of gastric contents as well as during swallowing. The protective functions include the LES tone, the bolstering of the LES by the surrounding diaphragmatic crura, and the *backup protection* of the UES tone. Secondary peristalsis, akin to primary peristalsis but without an oral component, originates in the upper esophagus, triggered mainly by GER, thereby also clearing refluxed gastric contents from the esophagus. Another protective reflex is the *pharyngeal swallow* (initiated above the esophagus, but without lingual participation). There are multiple levels of protection against aspiration, including the rhythmic coordination of swallowing and breathing and a series of protective reflexes with

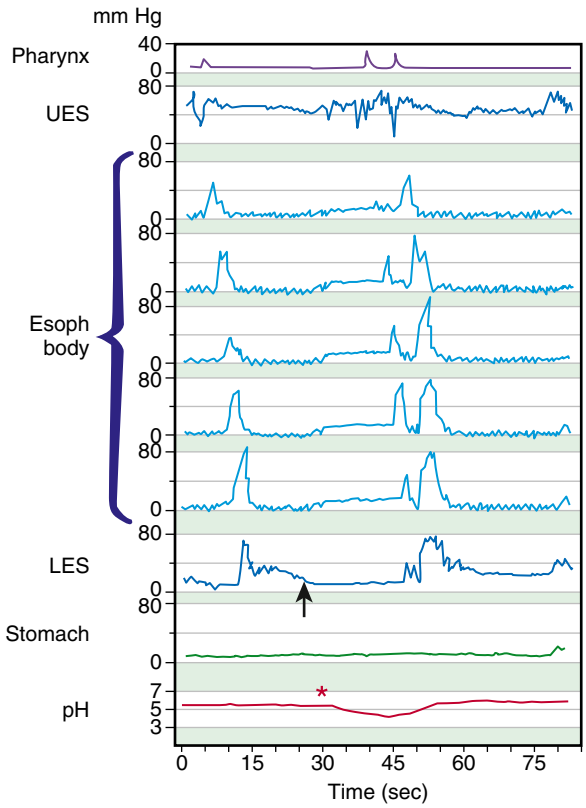

Fig. 364.1 Continuous tracing of esophageal motility showing two swallows, as indicated by the pharyngeal contraction associated with relaxation of the upper esophageal sphincter *(UES)* and followed by peristalsis in the body of the esophagus. The lower esophageal sphincter *(LES)* also displays a transient relaxation *(arrow)* unassociated with a swallow. There is an episode of gastroesophageal reflux *(asterisk)* recorded by a *pH* probe at the time of the transient *LES* relaxation. *(Courtesy John Dent, FRACP, PhD and Geoffrey Davidson, MD.)*

Table 364.1 Mechanical Events of the Oropharyngeal Swallow and Evidence of Dysfunction

MECHANICAL EVENT	EVIDENCE OF DYSFUNCTION
Nasopharyngeal closure	Nasopharyngeal regurgitation Nasal voice
Laryngeal closure	Aspiration during bolus transit
Upper esophageal sphincter opening	Dysphagia Post-swallow residue/aspiration Diverticulum formation
Tongue loading and bolus propulsion	Sluggish misdirected bolus
Pharyngeal clearance	Post-swallow residue in hypopharynx/aspiration

Modified from Pandolfino JE, Kahrilas PJ. Esophageal neuromuscular function and motility disorders. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 10th ed. Philadelphia: Elsevier; 2016: Table 43.1.

esophagopharyngeal afferents and efferents that close the UES or larynx. These reflexes include the esophago-UES contractile reflex, the pharyngo-UES contractile reflex, the esophagoglottal closure reflex, and two pharyngoglottal adduction reflexes. The last two reflexes have chemoreceptors on the laryngeal surface of the epiglottis and mechanoreceptors on the aryepiglottic folds as their sites of stimulus. It is likely that interactions between the esophagus and the respiratory tract, which cause extraesophageal manifestations of gastroesophageal reflux disease (GERD), will be explained by subtle abnormalities in these protective reflexes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

364.1 Common Clinical Manifestations and Diagnostic Aids

Seema Khan and Sravan Kumar Reddy Matta

Manifestations of esophageal disorders include pain, obstruction or difficulty swallowing, abnormal retrograde movement of gastric contents (reflux, regurgitation, or vomiting), or bleeding; esophageal disease can also cause respiratory symptoms. Pain in the chest unrelated to swallowing **(heartburn)** can be a sign of esophagitis, but similar pain might also represent cardiac, pulmonary, or musculoskeletal disease or visceral hyperalgesia. Pain during swallowing **(odynophagia)** localizes the disease more discretely to the pharynx and esophagus and often represents inflammatory mucosal disease. Complete esophageal obstruction can be produced acutely by esophageal foreign bodies, including food impactions; can be congenital, as in esophageal atresia; or can evolve over time as a peptic stricture occludes the esophagus. Difficulty swallowing **(dysphagia)** can be produced by incompletely occlusive esophageal obstruction (by extrinsic compression, intrinsic narrowing, or foreign bodies) but can also result from dysmotility of the esophagus (whether primary/idiopathic or secondary to systemic disease). Inflammatory lesions of the esophagus without obstruction or dysmotility are a third cause of dysphagia; eosinophilic esophagitis (EoE) is also relatively common.

The most common esophageal disorder in children is **GERD** (see Chapter 369)**,** which is from retrograde return of gastric contents into the esophagus. **Esophagitis** can be caused by GERD, by eosinophilic disease, by infection, or by caustic substances. Esophageal **bleeding** can result from severe esophagitis that produces erosions or ulcerations and can manifest as anemia or hemoccult-positive stools. More acute or severe bleeding can be from ruptured **esophageal varices.** The resulting hematemesis must be differentiated from more distal bleeding (gastric ulcer) and from more proximal bleeding (a nosebleed or hemoptysis). Respiratory symptoms of esophageal disease can result from luminal contents incorrectly being directed into the respiratory tract or to reflexive respiratory responses to esophageal stimuli.

DIAGNOSTIC AIDS

The esophagus can be evaluated by radiography, endoscopy, histology, scintigraphy, manometry, pH-metry (linked as indicated with other polysomnography), and multichannel intraluminal impedance. Contrast (usually barium) radiographic study of the esophagus usually incorporates fluoroscopic imaging over time so that motility and anatomy can be assessed. Although most often requested to evaluate for GERD, it is neither sensitive nor specific for this purpose; it can detect complications of GERD (stricture) or conditions mimicking GERD (pyloric stenosis or malrotation with intermittent volvulus), or concurrent hiatal hernia complicating GERD.

Barium fluoroscopy is optimal for evaluating for structural anomalies, such as duplications; strictures; hiatal hernia; congenital esophageal stenosis or external esophageal compression by an aberrant blood vessel; or for causes of dysmotility, such as achalasia. Modifications of the routine barium fluoroscopic study are used in special situations. When an *H-type* tracheoesophageal fistula is suspected, the test is most sensitive if the radiologist, with the patient prone, distends the esophagus with barium via a nasogastric tube. The videofluoroscopic evaluation of swallowing performed with varying consistencies of barium (modified barium swallow, oropharyngeal videoesophagram, or cookie swallow) optimally evaluates children with dysphagia by demonstrating incoordination of the pharyngeal and esophageal phases of swallowing and any associated aspiration.

In some centers, fiberoptic endoscopic evaluation of swallowing uses nasopharyngeal endoscopy to visualize the pharynx and larynx during swallowing of dye-enhanced foods when dysphagia, laryngeal penetration, or aspiration is suspected. This is often combined with sensory testing of the laryngeal adductor reflex in response to a calibrated puff of air through the endoscope to the arytenoids, generating the composite fiberoptic endoscopic evaluation of swallowing sensory testing that examines the mechanisms of any aspiration that is present. Endoscopy allows direct visualization of esophageal mucosa and helps therapeutically in the removal of foreign bodies and treatment of esophageal varices. Endoscopy also allows biopsy samples to be taken, thus improving the diagnosis of **endoscopy-negative GERD**, differentiating GERD from EoE, and identifying viral or fungal causes of esophagitis.

Radionuclide scintigraphy scans are helpful in evaluating the efficiency of peristalsis and demonstrating reflux episodes. They can be specific, although not very sensitive, for aspiration and can quantify gastric emptying, thus hinting at a cause for GERD. The related radionuclide salivagram can demonstrate aspiration of even minute amounts of saliva.

Esophageal manometry evaluates for dysmotility from the pharynx to the stomach; by synchronized quantitative pressure measurements along the esophagus, it detects and characterizes dysfunctions sometimes missed radiographically. Manometry is often challenging in young infants, and sphincters are optimally evaluated with special Dent sleeves, rather than the simple ports available for the esophageal body. High-resolution esophageal manometry (HRM) along with video fluoroscopic swallowing study (VFSS) to evaluate UES relaxation and pharyngeal and peristaltic pressures is now available at a few centers of expertise.

Extended pH monitoring of the distal esophagus is a sensitive test for acidic GER episodes that can quantify duration and degree of acidity, but not volume, of the reflux episodes. It is linked with polysomnography (a pneumogram) when GER is suspected to cause apnea or similar symptoms. Multichannel intraluminal impedance is a method for pH-independent detection of bolus movements in the esophagus; with a pH probe incorporated, it can distinguish between acid and nonacid liquid and gaseous reflux, the proximal extent of reflux, and several aspects of esophageal function, such as direction of bolus flow, duration of bolus presence, and bolus clearance.

The functional luminal imaging probe (FLIP) is another testing modality available in few pediatric motility centers; it is used as a diagnostic tool to guide and measure therapeutic success. FLIP is indicated in patients with EoE to assess esophageal compliance and esophagogastric junction (EGJ) distensibility in patients with achalasia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 365

Congenital Anomalies

365.1 Esophageal Atresia and Tracheoesophageal Fistula

Seema Khan and Sravan Kumar Reddy Matta

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus, with a prevalence of 1.7 per 10,000 live births. Of these, >90% have an associated tracheoesophageal fistula (TEF). In the most common form of EA, the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus (type C). Figure 365.1 shows the types of EA and TEF and their relative frequencies. The exact cause is still unknown; associated features include advanced maternal age, European ethnicity, maternal obesity, low socioeconomic status, and tobacco smoking. This defect has survival rates of >90%, due largely to improved neonatal intensive care, earlier recognition, and appropriate intervention. Infants weighing <1,500 g at birth and those with severe associated cardiac anomalies have the highest risk for mortality. Fifty percent of infants are *nonsyndromic* without other anomalies; the rest have syndromes with associated anomalies, most often associated with the vertebral, anorectal, (cardiac), tracheal, esophageal, renal, radial (limb) (VACTERL) syndrome. Cardiac and vertebral anomalies are seen in 32% and 24%, respectively. VACTERL is a sporadic disorder and is generally associated with normal intelligence. Genetic factors have a role in the pathogenesis of TEF in patients with other non-VACTERL syndromes as suggested by discrete pathogenic variants in syndromic cases: **Feingold syndrome** *(N-MYC),* CHARGE syndrome (*c*oloboma of the eye; *c*entral nervous system anomalies; *h*eart defects; *a*tresia of the choanae; *r*etardation of growth and/or development; *g*enital and/or urinary defects [hypogonadism]; *e*ar anomalies and/or deafness) *(CHD7),* and anophthalmia-esophageal-genital syndrome *(SOX2).*

PRESENTATION

The neonate with EA typically has frothing and bubbling at the mouth and nose after birth as well as episodes of coughing, cyanosis, and respiratory distress. Polyhydramnios is common. Feeding exacerbates these symptoms, causes regurgitation, and can precipitate aspiration. Aspiration of gastric contents via a distal fistula causes more damaging pneumonitis than aspiration of pharyngeal secretions from the blind upper pouch. The infant with an isolated TEF in the absence of EA ("H-type" fistula) might come to medical attention later in life with chronic respiratory problems, including refractory bronchospasm and recurrent aspiration pneumonias.

DIAGNOSIS

In the setting of polyhydramnios, early-onset respiratory distress and the inability to pass a nasogastric or orogastric tube in the newborn suggests EA. Imaging findings of absence of the fetal stomach bubble and maternal polyhydramnios might alert the physician to EA before birth. Plain radiography in the evaluation of respiratory distress might reveal a coiled feeding tube in the esophageal pouch and/or an air-distended stomach, indicating the presence of a coexisting TEF (Fig. 365.2). Conversely, pure EA can manifest as an airless scaphoid abdomen. In isolated TEF (H type), an esophagogram with contrast medium injected under pressure can demonstrate the defect (Fig. 365.3). Alternatively, the orifice may be detected at bronchoscopy or when methylene blue dye injected into the endotracheal tube during endoscopy is observed in the esophagus during forced inspiration. The differential diagnosis of congenital esophageal lesions is noted in Table 365.1.

MANAGEMENT

Initially, maintaining a patent airway, preoperative proximal pouch decompression to prevent aspiration of oral secretions, and use of antibiotics to prevent consequent pneumonia are paramount. Prone positioning minimizes movement of gastric secretions into a distal fistula, and esophageal suctioning minimizes aspiration from a

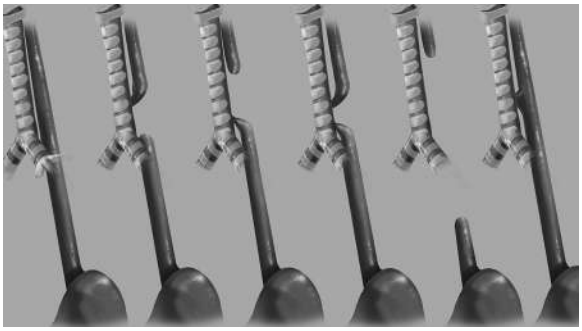

Fig. 365.1 Gross type classification and esophageal atresia (EA) and trachea-esophageal fistulas (TEF). Left to right: normal anatomy, gross type B (EA with proximal TEF; 2%), gross type C (EA with distal TEF; 86%), gross type D (EA with proximal and distal TEF; 1%), gross type A (pure EA, 7%), and gross type E (TEF without EA; 4%). *(From Harrington AW, Riebold J, Hernandez K, et al. Feeding and growth outcomes in infants with type C esophageal atresia who undergo early primary repair. J Pediatr. 2022;241:77–82, Fig. 1.)*

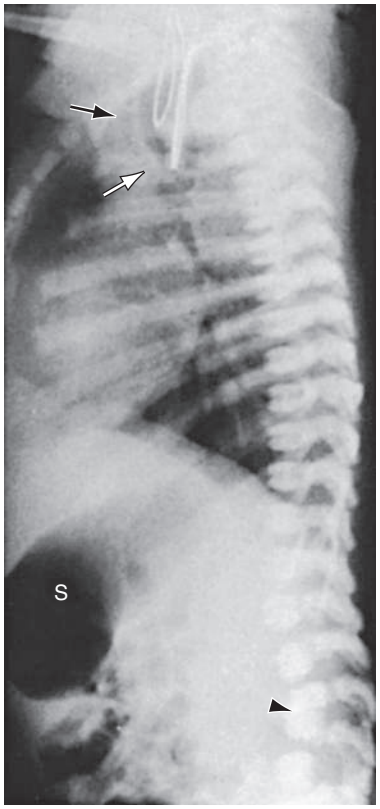

Fig. 365.2 Tracheoesophageal fistula. Lateral radiograph demonstrating a nasogastric tube coiled *(arrows)* in the proximal segment of an atretic esophagus. The distal fistula is suggested by gaseous dilation of the stomach *(S)* and small intestine. The *arrowhead* depicts vertebral fusion, whereas a heart murmur and cardiomegaly suggest the presence of a ventricular septal defect. This patient demonstrated elements of the vertebral, anorectal, tracheal, esophageal, renal, and radial anomalad. *(From Balfe D, Ling D, Siegel M. The esophagus. In Putman CE, Ravin CE, eds. Textbook of Diagnostic Imaging. Philadelphia: WB Saunders; 1988.)*

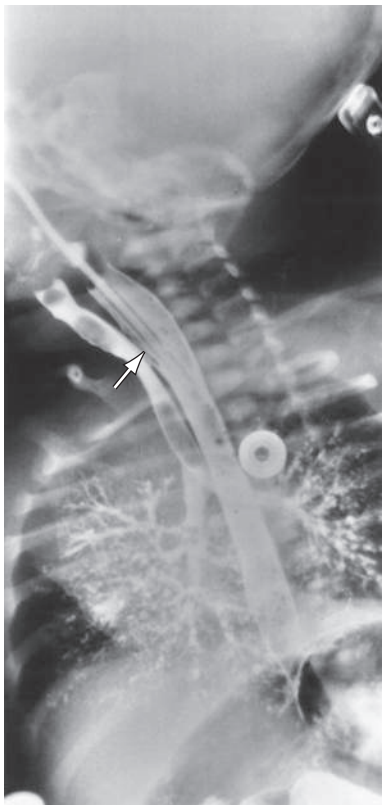

Fig. 365.3 H-type fistula *(arrow)* demonstrated in an infant after barium swallow on frontal-oblique chest x-ray. The tracheal aspect of the fistula is characteristically superior to the esophageal aspect. Barium is seen to outline the tracheobronchial tree. *(From Wyllie R, Hyams JS, eds. Pediatric Gastrointestinal and Liver Disease. 3rd ed. Philadelphia: Saunders; 2006: p. 299.)*

blind pouch. Endotracheal intubation with mechanical ventilation is to be avoided if possible because it can worsen distention of the stomach. Surgical ligation of the TEF and primary end-to-end anastomosis of the esophagus via right-sided thoracotomy constitute the standard surgical approach. In the premature or otherwise complicated infant, a primary closure may be delayed by temporizing with fistula ligation and gastrostomy tube placement. If the gap between the atretic ends of the esophagus is >3-4 cm (>3 vertebral bodies), primary repair cannot be done; options include using gastric, jejunal, or colonic segments interposed as a neoesophagus. Careful search must be undertaken for the common associated cardiac, renal, and other anomalies. *Thoracoscopic surgical repair is feasible and associated with favorable long-term outcomes.*

OUTCOME

Most children with nonsyndromic EA and TEF grow up to lead normal lives, but complications are often challenging, particularly during the first 5 years of life. Complications of surgery include anastomotic leak, refistulization, and anastomotic stricture formation, necessitating endoscopic dilations. Some recurrent and refractory strictures may need esophageal stent placement or surgical stricture resection. Gastroesophageal reflux disease, resulting from intrinsic abnormalities of esophageal function, often combined with delayed gastric emptying, contributes to management challenges in many cases. Gastroesophageal reflux disease contributes significantly to the respiratory disease **(reactive airway disease)** that often complicates EA and TEF and also worsens the frequent anastomotic strictures after repair of EA.

Many patients have an associated tracheomalacia that improves as the child grows. Hence, it is important to target on prevention of long-term complications using appropriate surveillance techniques such as endoscopy or pH-Impedance.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 365.1 Clinical Aspects of Esophageal Developmental Anomalies

ANOMALY	AGE AT PRESENTATION	PREDOMINANT SYMPTOMS	DIAGNOSIS	TREATMENT
Isolated atresia	Newborns	Regurgitation of feedings Aspiration	Esophagogram* Plain film: gasless abdomen	Surgery
Atresia + distal TEF	Newborns	Regurgitation of feedings Aspiration	Esophagogram* Plain film: gas-filled abdomen	Surgery
H-type TEF	Infants to adults	Recurrent pneumonia Bronchiectasis	Esophagogram* Bronchoscopy†	Surgery
Esophageal stenosis	Infants to adults	Dysphagia Food impaction	Esophagogram* Endoscopy†	Dilation‡ Surgery§
Duplication cyst	Infants to adults	Dyspnea, stridor, cough (infants) Dysphagia, chest pain (adults)	EUS* MRI/CT†	Surgery
Vascular anomaly	Infants to adults	Dyspnea, stridor, cough (infants) Dysphagia (adults)	Esophagogram* Angiography† MRI/CT/EUS	Dietary modification‡ Surgery§
Esophageal ring	Children to adults	Dysphagia	Esophagogram* Endoscopy†	Dilation‡ Endoscopic incision§
Esophageal web	Children to adults	Dysphagia	Esophagogram* Endoscopy†	Bougienage

*Diagnostic test of choice.
†Confirmatory test.
‡Primary therapeutic approach.
§Secondary therapeutic approach.
TEF, Tracheoesophageal fistula; EUS, endoscopic ultrasound.
From Madanick R, Orlando RC. Anatomy, histology, embryology, and developmental anomalies of the esophagus. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 42.2.

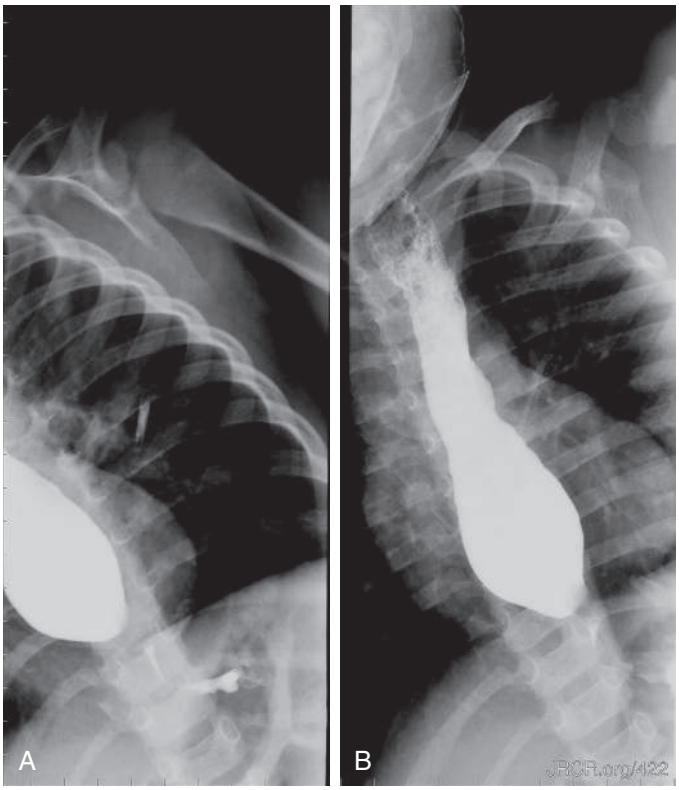

Fig. 365.4 An 18-month-old male with congenital esophageal stenosis. Esophagogram using barium as contrast media shows an anteroposterior (AP) projection (**A**) and an unsuccessful attempt to obtain a lateral projection (**B**) due to poor collaboration of the patient. An asymmetric short narrowing of the distal esophagus is observed as well as proximal dilatation of the esophagus. Gastroesophageal reflux was not identified. *(From Serrao E, Santos, A, Gaivao A. Congenital esophageal stenosis: a rare case of dysphagia. J Radiol Case Rep. 2010;4:8–14. Fig. 2.)*

365.2 Laryngotracheoesophageal Clefts

Seema Khan and Sravan Kumar Reddy Matta

Laryngotracheoesophageal clefts are uncommon anomalies that result when the septum between the esophagus and trachea fails to develop fully, leading to a common channel defect between the pharyngoesophagus and laryngotracheal lumen, thus making the laryngeal closure incompetent during swallowing or reflux. Other developmental anomalies, such as EA and TEF, are seen in 20% of patients with clefts. The severity of presenting symptoms depends on the type of cleft; they are commonly classified as one of four types (I-IV) according to the inferior extent of the cleft. Early in life, the infant presents with stridor, choking, cyanosis, aspiration of feedings, and recurrent chest infections. The diagnosis is difficult and usually requires direct endoscopic visualization of the larynx and esophagus. When contrast radiography is used, material is often seen in the esophagus and trachea. Treatment is surgical repair, which can be complex if the defects are long.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 365.5 An 18-month-old male with congenital esophageal stenosis. Esophagoscopy showed a circumferential, slightly noncentral narrowing at the distal esophagus, 2 cm proximal to the esophagogastric junction. *(From Serrao E, Santos, A, Gaivao A. Congenital esophageal stenosis: a rare case of dysphagia. J Radiol Case Rep. 2010;4:8–14. Fig. 3.)*

365.3 Congenital Esophageal Stenosis

Seema Khan and Sravan Kumar Reddy Matta

Congenital esophageal stenosis (CES) is a rare anomaly of the esophagus with clinical significance. Though the original incidence is not known, it is estimated to affect 1:25,000 to 50,000 live births. The defect results from incomplete separation of respiratory tract from the primitive foregut at the 25th day of fetal life. CES is differentiated by histology into three types: esophageal membrane/web, total bronchial remnants (TBR), and fibromuscular remnants (FMR). Symptoms vary depending on the location and severity of the defect. Higher lesions present with respiratory symptoms and lower lesions present with dysphagia and vomiting. Esophagogram (Fig. 365.4), MRI, CT, and endoscopic ultrasound are used for diagnosis. Endoscopy (Fig. 365.5) is done to evaluate mucosal abnormalities like strictures, foreign bodies, and esophagitis. Treatment option (surgical correction, bougie dilation) is chosen based on the location, severity, and type of stenosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 366

Obstructing Disorders of the Esophagus

Seema Khan and Sravan Kumar Reddy Matta

Obstructing lesions classically produce **dysphagia** to *solids* earlier and more noticeably than to liquids and can manifest when the infant liquid diet begins to incorporate solids; this is in contrast to **dysphagia** from **dysmotility,** in which swallowing of *liquids* is affected as early as, or earlier than, solids. In most instances of dysphagia, evaluation begins with fluoroscopy, which may include videofluoroscopic evaluation of swallowing, particularly if aspiration is a primary symptom. Secondary studies are often endoscopic if intrinsic obstruction is suspected or manometric if dysmotility is suspected; other imaging studies may be used in particular cases. Congenital lesions can require surgery, whereas webs and peptic strictures might respond adequately to endoscopic (or bougie) dilation. Peptic strictures, once dilated, should prompt consideration of fundoplication for ongoing prophylaxis.

EXTRINSIC

Esophageal duplication cysts are the most commonly encountered foregut duplications (see Table 365.1). These cysts are lined by intestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract. Duplication cysts are described as either communicating or noncommunicating with the lumen of the alimentary tract. Most of these affect the distal half of the esophagus on the right side. The most common presentation is respiratory distress caused by compression of the adjacent airways. Dysphagia is a common symptom in older children. Upper gastrointestinal bleeding can occur as a result of acid-secreting gastric mucosa in the duplication wall. **Neuroenteric cysts** might contain glial elements and are associated with **vertebral anomalies.** Diagnosis is made using modalities, such as barium swallow, chest CT, and MRI, or endosonography. Treatment is surgical; laparoscopic approach to excision is also possible.

Enlarged mediastinal or subcarinal **lymph nodes,** caused by infection (tuberculosis, histoplasmosis) or neoplasm (lymphoma), are the most common external masses that compress the esophagus and produce obstructive symptoms. **Vascular anomalies** can also compress the esophagus; *dysphagia lusoria* is a term denoting the dysphagia produced by a developmental vascular anomaly, which is often an aberrant right subclavian artery or right-sided or double aortic arch (see Chapter 481.1).

INTRINSIC

Intrinsic narrowing of the esophageal lumen can be congenital or acquired. The etiology is suggested by the location, the character of the lesion, and the clinical situation. The lower esophagus is the most common location for peptic strictures, which are generally somewhat ragged and several centimeters long. Thin membranous rings, including the **Schatzki ring** at the squamocolumnar junction, can also occlude this area. In the midesophagus, congenital narrowing may be associated with the esophageal atresia–tracheoesophageal fistula complex, in which some of the lesions might incorporate cartilage and might be impossible to dilate safely; alternatively, reflux esophagitis can induce a ragged and extensive narrowing that appears more proximal than the usual peptic stricture, often because of an associated hiatal hernia. Congenital webs or rings can narrow the upper esophagus. The upper esophagus can also be narrowed by an inflammatory stricture occurring after a caustic ingestion or due to epidermolysis bullosa. Cricopharyngeal achalasia can appear radiographically as a cricopharyngeal bar posteriorly in the upper esophagus. **Eosinophilic esophagitis** is one of the most common causes for esophageal obstructive symptoms (see Chapter 370). Although the pathogenesis of obstructive eosinophilic esophagitis is not yet completely explained and seems to vary among individual patients, endoscopy or radiology demonstrates stricture formation in some children with eosinophilic esophagitis, and in others a noncompliant esophagus is evident, with thickened wall layers demonstrable by ultrasonography.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 367

Dysmotility

Seema Khan and Sravan Kumar Reddy Matta

UPPER ESOPHAGEAL AND UPPER ESOPHAGEAL SPHINCTER DYSMOTILITY (STRIATED MUSCLE)

Cricopharyngeal **achalasia** signifies a failure of complete relaxation of the upper esophageal sphincter (UES), whereas cricopharyngeal **incoordination** implies full relaxation of the UES but incoordination of the relaxation with the pharyngeal contraction. These entities are usually detected on videofluoroscopic evaluation of swallowing (sometimes accompanied by visible cricopharyngeal prominence, termed a *bar*), but often the most precise definition of the dysfunction is obtained with manometry. A self-limited form of cricopharyngeal incoordination occurs in infancy and remits spontaneously in the first year of life if nutrition is maintained despite the dysphagia. In children, treatment options for non–self-limited cricopharyngeal achalasia consist of dilation, Botox injection, and transcervical myotomy. It is important to evaluate such children thoroughly, including cranial MRI to detect **Arnold-Chiari malformations,** which can manifest in this way but are best treated by cranial decompression rather than esophageal surgery. Cricopharyngeal spasm may be severe enough to produce posterior pharyngeal (**Zenker**) **diverticulum** above the obstructive sphincter; this entity occurs rarely in children.

Systemic causes of swallowing dysfunction that can affect the oropharynx, UES, and upper esophagus include cerebral palsy, Arnold-Chiari malformations, syringomyelia, bulbar palsy or cranial nerve defects (Möbius syndrome, transient infantile paralysis of the superior laryngeal nerve), transient pharyngeal muscle dysfunction, spinal muscular atrophy, muscular dystrophy, multiple sclerosis, infections (botulism, tetanus, poliomyelitis, diphtheria), inflammatory and autoimmune diseases (dermatomyositis, myasthenia gravis, polyneuritis, scleroderma), and familial dysautonomia. All of these can produce dysphagia. Medications (nitrazepam, benzodiazepines) and tracheostomy can adversely affect the function of the UES and thereby produce dysphagia.

LOWER ESOPHAGEAL AND LOWER ESOPHAGEAL SPHINCTER DYSFUNCTION (SMOOTH MUSCLE)

Causes of dysphagia resulting from more distal primary esophageal dysmotility include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES); all but achalasia are rare in children. Secondary causes include Hirschsprung disease, pseudoobstruction syndromes, inflammatory myopathies, scleroderma, and diabetes.

Achalasia is a primary esophageal motor disorder of unknown etiology characterized by loss of LES relaxation and loss of esophageal peristalsis, both contributing to a functional obstruction of the distal esophagus. Degenerative, autoimmune (antibodies to Auerbach

plexus), and infectious (Chagas disease caused by *Trypanosoma cruzi*) factors are possible causes in select cases. In rare cases, achalasia is familial or part of the achalasia, alacrima, and adrenal insufficiency, known as triple A syndrome or **Allgrove syndrome**. *Pseudoachalasia* refers to achalasia caused by various forms of cancer via obstruction of the gastroesophageal junction, infiltration of the submucosa and muscularis of the LES, or as part of the paraneoplastic syndrome with formation of anti-Hu antibodies. Pathologically, in achalasia, inflammation surrounds ganglion cells, which are decreased in number. There is selective loss of postganglionic inhibitory neurons that normally lead to sphincter relaxation, leaving postganglionic cholinergic neurons unopposed. This imbalance produces high basal LES pressures and insufficient LES relaxation. The loss of esophageal peristalsis can be a secondary phenomenon.

Achalasia manifests with regurgitation and dysphagia for solids and liquids and may be accompanied by undernutrition or chronic cough; retained esophageal food can produce esophagitis. *The presentations of chronic regurgitation/vomiting with weight loss, and chronic cough have led to misdiagnoses of anorexia nervosa and asthma, respectively.* The mean age in children is 8.8 years, with a mean duration of symptoms before diagnosis of 23 months; it is uncommon before school age. Chest radiograph shows an air-fluid level in a dilated esophagus. **Barium fluoroscopy** reveals a smooth tapering of the lower esophagus leading to the closed LES, resembling a bird's beak (Fig. 367.1). Loss of primary peristalsis in the distal esophagus with retained food and poor emptying are often present. **Manometry** is the most sensitive diagnostic test and helps differentiate the three types of achalasia; it reveals the defining features of aperistalsis in the distal esophageal body and incomplete or absent LES relaxation, often accompanied by high-pressure LES and low-amplitude esophageal body contractions (Fig. 367.2).

The goals of achalasia therapy are relief of symptoms, improvement of esophageal emptying, and prevention of megaesophagus. The two most effective treatment options are sequential repeated pneumatic dilation and laparoscopic or surgical (Heller) myotomy. Pneumatic dilation is the initial treatment of choice and does not preclude a future myotomy. Surgeons often supplement a myotomy with an antireflux procedure (fundoplication) to prevent the gastroesophageal reflux disease that otherwise often ensues when the sphincter is rendered less competent. Laparoscopic myotomy is a particularly effective procedure in adolescent and young adult males. Peroral endoscopic myotomy (POEM) is a feasible, safe, and effective alternative to the laparoscopic method. Calcium channel blockers (nifedipine) and phosphodiesterase inhibitors offer temporary relief of dysphagia. Endoscopic injection of the LES with **botulinum toxin** counterbalances the selective loss of inhibitory neurotransmitters by inhibiting the release of acetylcholine from nerve terminals and may be an effective initial therapy before a definitive procedure. Botulinum toxin is effective in 50–65% of patients and is expensive; half the patients might require a repeat injection within 1 year. Most eventually require dilation or surgery.

Diffuse esophageal spasm causes chest pain and dysphagia and affects adolescents and adults. It is diagnosed **manometrically** and can be treated with nitrates or calcium-channel-blocking agents.

Gastroesophageal reflux disease (see Chapter 369) constitutes the most common cause of nonspecific abnormalities of esophageal motor function, probably through the effect of the esophageal inflammation on the musculature.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 367.1 Barium esophagogram of a patient with achalasia demonstrating dilated esophagus and narrowing at the lower esophageal sphincter. Note retained secretions layered on top of barium in the esophagus.

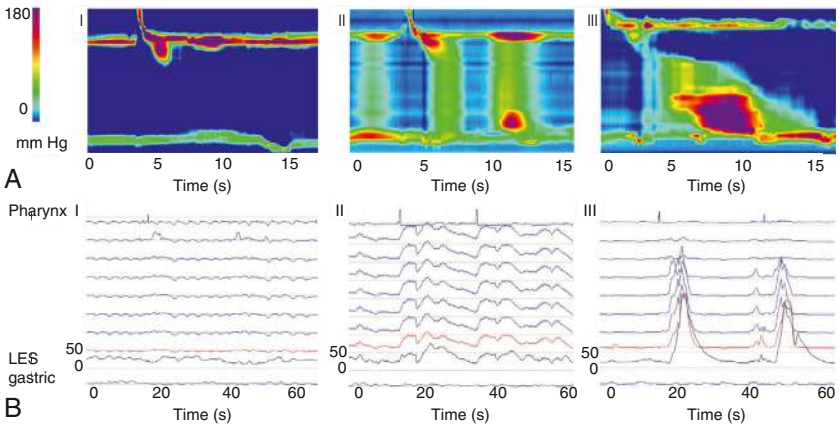

Fig. 367.2 Based on the residual wave type on high-resolution esophageal manometry (HRM), three subtypes of achalasia can be determined. **A,** No distal pressurization is observed in type I (AI), whereas panesophageal pressurizations and spastic contractions are observed in type II (AII) and type III (AIII), respectively. **B,** A similar classification can be made when conventional manometry is used. Note that pressure recordings in type II achalasia are similar in every line tracing, compatible with panesophageal pressurization. LES, Lower esophageal sphincter. *(From Rohof WO, Salvador R, Annese V. Outcomes of treatment for achalasia depend on manometric subtype. Gastroenterology. 2013;144:718–725. Fig. 1.)*

Chapter 368

Hiatal Hernia

Seema Khan and Sravan Kumar Reddy Matta

Herniation of the stomach through the esophageal hiatus can occur as a common sliding hernia (type 1), in which the gastroesophageal junction slides into the thorax, or it can be paraesophageal (type 2), in which a portion of the stomach (usually the fundus) is insinuated next to the esophagus inside the gastroesophageal junction in the hiatus (Figs. 368.1 and 368.2). A combination of sliding and paraesophageal types (type 3) is present in some patients. Sliding hernias are often associated with gastroesophageal reflux disease (see Chapter 369), especially in developmentally delayed children. The relationship to hiatal hernias in adults is unclear. Diagnosis is usually made by an upper gastrointestinal series and upper endoscopy. Medical treatment is not directed at the hernia but at the gastroesophageal reflux, unless failure of medical therapy prompts correction of the hernia at the time of fundoplication.

A paraesophageal hernia can be an isolated congenital anomaly or associated with gastric volvulus, or it may be encountered after fundoplication for gastroesophageal reflux, especially if the edges of a dilated esophageal diaphragmatic hiatus have not been approximated. Fullness after eating and upper abdominal pain are the usual symptoms. Infarction of the herniated stomach is rare.

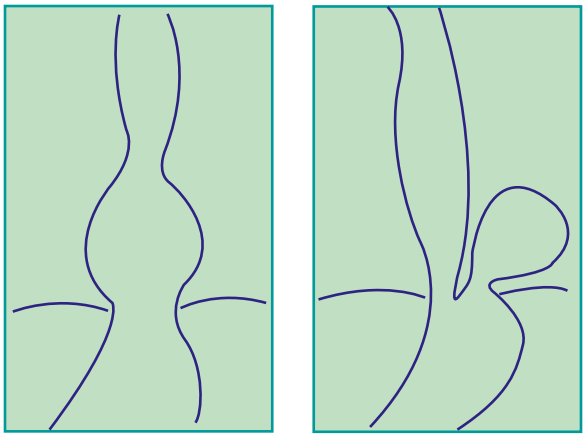

Fig. 368.1 Types of esophageal hiatal hernia. **A,** Sliding hiatal hernia, the most common type. **B,** Paraesophageal hiatal hernia.

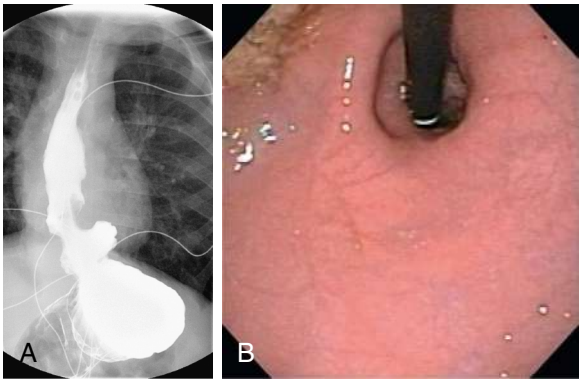

Fig. 368.2 **A,** An upper gastrointestinal series shows a large hiatal hernia that extends above the diaphragm and impedes the exit of contrast from the esophagus into the stomach. Contrast is also noted to reflux to the upper esophagus. **B,** A retroflexed view of the hernia from the stomach during an upper endoscopy.

Chapter 369

Gastroesophageal Reflux Disease

Seema Khan and Sravan Kumar Reddy Matta

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus, which occurs physiologically every day in all infants, older children, and adults. Physiologic GER is exemplified by the effortless regurgitation of normal infants and runs an uncomplicated course. Natural history studies observe that it is uncommon for physiologic GER to have onset before 1 week and to persist beyond 6 months of age, and usually peaks between 3 and 4 months. The phenomenon becomes **pathologic GERD** in infants and children who manifest or report bothersome symptoms because of frequent or persistent GER, producing esophagitis-related symptoms, or extraesophageal presentations, such as respiratory (cough, wheezing, hoarse voice) symptoms, nutritional effects, or growth failure. However, the clinical differentiation between GER and GERD is not straightforward in nonverbal infants who may present with excess crying, fussiness, and intermittent feeding and sleep problems while thriving well, due to non-GERD causes or even to variations of normal infant behavior. Pediatricians may try multiple therapeutic options as they try to diagnose and treat these behaviors. Concerned parents and caregivers may also influence the management through requests for interventions they may have heard about through the internet, or from other parents. As a consequence, we are seeing widespread prescriptions of histamine 2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) to treat neonates and infants with physiologic GER. It is profoundly important for pediatricians and pediatric gastroenterologists to instead address this challenge and curb the trend for over investigation and over treatment through more effective educational campaigns, reassurance of parents, and emphasizing the benign nature of the diagnosis that is best handled with a conservative approach.

PATHOPHYSIOLOGY

Factors determining the esophageal manifestations of reflux include the duration of esophageal exposure (a product of the frequency and duration of reflux episodes), the causticity of the refluxate, and the susceptibility of the esophagus to damage. The LES, defined as a high-pressure zone by manometry, is supported by the crura of the diaphragm at the gastroesophageal junction and, together with valvelike functions of the esophagogastric junction anatomy, form the antireflux barrier. In the context of even the normal intraabdominal pressure augmentations that occur during daily life, the frequency of reflux episodes is increased by insufficient LES tone, by abnormal frequency of LES relaxations, and by hiatal herniation that prevents the LES pressure from being proportionately augmented by the crura during abdominal straining. Normal intraabdominal pressure augmentations may be further exacerbated by straining or respiratory efforts. The duration of reflux episodes is increased by lack of swallowing (e.g., during sleep) and by defective esophageal peristalsis. Vicious cycles ensue because chronic esophagitis produces esophageal peristaltic dysfunction (low-amplitude waves, propagation disturbances), decreased LES tone, and inflammatory esophageal shortening that induces hiatal herniation, all worsening reflux.

Transient LES relaxation (TLESR) is the primary mechanism allowing reflux to occur and is defined as simultaneous relaxation of both LES and the surrounding crura. TLESRs occur independent of swallowing, reduce LES pressure to 0-2 mm Hg (above gastric), and last 10-60 seconds; they appear by 26 weeks of gestation. A vagovagal reflex, composed of afferent mechanoreceptors in the proximal stomach, a brainstem pattern generator, and efferents in the LES, regulates TLESRs. Gastric distention (postprandially, or from abnormal gastric emptying or air swallowing) is the main stimulus for TLESRs. Whether GERD is caused by a higher frequency of TLESRs or by a greater incidence of reflux during TLESRs is debated; each is likely in different persons. Straining during a TLESR makes reflux more likely, as do positions that place the gastroesophageal junction below the air-fluid interface in the stomach. Other factors influencing gastric pressure–volume dynamics, such as increased movement, straining, obesity, large-volume or hyperosmolar meals, gastroparesis, a large sliding hiatal hernia, and increased respiratory effort (coughing, wheezing), can have the same effect.

EPIDEMIOLOGY AND NATURAL HISTORY

Infant reflux becomes evident in the first few months of life, peaks at 4 months, and resolves in up to 88% by 12 months and in nearly all by 24 months. *Happy spitters* are infants who have recurrent regurgitation *without* exhibiting discomfort or refusal to eat and failure to gain weight. Symptoms of GERD in **older children** tend to be chronic, waxing and waning, but completely resolving in no more than half, which resembles adult patterns (Table 369.1). The histologic findings of esophagitis persist in infants who have naturally resolving symptoms of reflux. GERD likely has genetic predispositions: family clustering of GERD symptoms, endoscopic esophagitis, hiatal hernia, Barrett esophagus, and adenocarcinoma have been identified. As a continuously variable and common disorder, complex inheritance involving multiple genes and environmental factors is likely. Genetic linkage is indicated by the strong evidence of GERD in studies with monozygotic twins. A pediatric autosomal dominant form with otolaryngologic and respiratory manifestations has been located to chromosome 13q14, and the locus is termed GERD1.

CLINICAL MANIFESTATIONS

Most of the common clinical manifestations of esophageal disease can signify the presence of GERD and are generally thought to be mediated by the pathogenesis involving acid GER (Table 369.2). Although less noxious for the esophageal mucosa, non–acid-reflux events are recognized to play an important role in extraesophageal disease manifestations. **Infantile reflux** manifests more often with regurgitation (especially postprandially), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion), and resulting failure to thrive; symptoms resolve spontaneously in the majority of infants by 12-24 months. **Older children** can have regurgitation during the preschool years; this complaint diminishes somewhat as children age, and complaints of abdominal and chest pain supervene in later childhood and adolescence. Occasional children present with food refusal or neck contortions (arching, turning of head) that is termed **Sandifer syndrome.** The respiratory presentations are also age dependent: GERD in infants may manifest as obstructive apnea or as stridor or lower airway disease in which reflux complicates primary airway disease such as laryngomalacia or bronchopulmonary dysplasia. Otitis media, sinusitis, lymphoid hyperplasia, hoarseness, vocal cord nodules, and laryngeal edema have all been associated with GERD. Airway manifestations in older children are more commonly related to asthma or to otolaryngologic disease such as laryngitis or sinusitis. Despite the high prevalence of GERD symptoms in asthmatic children, data showing direction of causality are conflicting.

Neurologically challenged children are at an increased risk for GERD. It is not well established if the greater risk is conferred due to inadequate defensive mechanisms and/or inability to express symptoms. A low clinical threshold is important in the early identification and prompt treatment of GERD symptoms in these individuals.

DIAGNOSIS

For most of the typical GERD presentations, particularly in older children, a thorough history and physical examination suffice initially to reach the diagnosis. This initial evaluation aims to identify the pertinent positives in support of GERD and its complications and the negatives that make other diagnoses unlikely. The history may be facilitated and standardized by questionnaires (e.g., the Infant Gastroesophageal Reflux Questionnaire [I-GERQ], and its derivative, the I-GERQ-R), which also permit quantitative scores to be evaluated for their diagnostic discrimination and for evaluative assessment of improvement or worsening of symptoms. The clinician should be alerted to the

Table 369.1 Symptoms According to Age

MANIFESTATIONS	INFANTS	CHILDREN	ADOLESCENTS AND ADULTS
Impaired quality of life	+++	+++	+++
Regurgitation	++++	+	+
Excessive crying/irritability	+++	+	–
Vomiting	++	++	+
Food refusal/feeding disturbances/anorexia	++	+	+
Persisting hiccups	++	+	+
Failure to thrive	++	+	–
Abnormal posturing/Sandifer syndrome	++	+	–
Esophagitis	+	++	+++
Persistent cough/aspiration pneumonia	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor/croup	+	++	–
Sleeping disturbances	+	+	+
Anemia/melena/hematemesis	+	+	+
Apnea/BRUE/desaturation	+	–	–
Bradycardia	+	?	?
Heartburn/pyrosis	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Dental erosions/water brush	?	+	+
Hoarseness/globus pharyngeus	?	+	+
Chronic asthma/sinusitis	–	++	+
Laryngostenosis/vocal nodule problems	–	+	+
Stenosis	–	(+)	+
Barrett/esophageal adenocarcinoma	–	(+)	+

+++, Very common; ++ common; + possible; (+) rare; – absent; ? unknown; BRUE, brief resolved unexplained event; previously called ALTE, or apparent life-threatening event.
From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia: WB Saunders; 2011: Table 22.3, p. 235.

possibility of other important diagnoses in the presence of any *alarm or warning signs*: bilious emesis, frequent projectile emesis, gastrointestinal bleeding, lethargy, organomegaly, abdominal distention, dysphagia, odynophagia, micro- or macrocephaly, hepatosplenomegaly, anorexia, failure to thrive, diarrhea, fever, bulging fontanelle, and seizures. The important differential diagnoses to consider in the evaluation of an infant or a child with chronic vomiting are milk and other food allergies, eosinophilic esophagitis, pyloric stenosis, intestinal obstruction (especially malrotation with intermittent volvulus), nonesophageal inflammatory diseases, infections, inborn errors of metabolism, hydronephrosis, increased intracranial pressure, rumination, and bulimia. Focused diagnostic testing, depending on the presentation and the differential diagnosis, can then supplement the initial examination.

Most of the esophageal tests are of some use in particular patients with suspected GERD. **Contrast (usually barium) radiographic** study of the esophagus and upper gastrointestinal tract is performed in children with vomiting and dysphagia to evaluate for achalasia, esophageal strictures and stenosis, hiatal hernia, and gastric outlet or intestinal obstruction (Fig. 369.1). It has poor sensitivity and specificity in the diagnosis of GERD as a result of its limited duration and the inability to differentiate physiologic GER from GERD. Furthermore, contrast radiography neither accurately assesses mucosal inflammation nor correlates with severity of GERD.

Extended esophageal pH monitoring of the distal esophagus, no longer considered the sine qua non of a GERD diagnosis, provides a quantitative and sensitive documentation of acidic reflux episodes, the most important type of reflux episodes for pathologic reflux. The distal esophageal pH probe is placed at a level corresponding to 87% of the nares-LES distance, based on regression equations using the patient's height, on fluoroscopic visualization, or on manometric identification of the LES. Normal values of distal esophageal acid exposure (pH <4) are generally established as <5–8% of the total monitored time, but these quantitative normals are insufficient to establish or disprove a diagnosis of pathologic GERD. The most important indications for esophageal pH monitoring are for assessing efficacy of acid suppression during treatment, evaluating apneic episodes in conjunction with a pneumogram and perhaps impedance, and evaluating atypical GERD presentations such as chronic cough, stridor, and asthma. Dual pH probes, adding a proximal esophageal probe to the standard distal one, are used in the diagnosis of extraesophageal GERD, identifying upper esophageal acid exposure times of 1% of the total time as threshold values for abnormality.

Endoscopy allows diagnosis of erosive esophagitis (Fig. 369.2) and complications such as strictures or Barrett esophagus; esophageal biopsies can diagnose histologic reflux esophagitis in the absence of erosions while eliminating allergic and infectious causes. Endoscopy is also used therapeutically to dilate reflux-induced strictures. Radionucleotide scintigraphy using technetium can demonstrate aspiration and delayed gastric emptying when these are suspected.

Table 369.2 Symptoms and Signs That May Be Associated with Gastroesophageal Reflux

SYMPTOMS	SIGNS
Recurrent regurgitation with or without vomiting	Esophagitis
Weight loss or poor weight gain	Esophageal stricture
Irritability in infants	Barrett esophagus
Ruminative behavior	Laryngeal/pharyngeal inflammation
Heartburn or chest pain	Recurrent pneumonia
Hematemesis	Anemia
Dysphagia, odynophagia	Dental erosion
Wheezing	Feeding refusal
Stridor	Dystonic neck posturing (Sandifer syndrome)
Cough	Apnea spells
Hoarseness	Apparent life-threatening events

From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia: Saunders; 2011: Table 22.1, p. 235.

The multichannel **intraluminal impedance** is a cumbersome test, but with potential applications both for diagnosing GERD and for understanding esophageal function in terms of bolus flow, volume clearance, and (in conjunction with manometry) motor patterns associated with GERD. Because of the multiple sensors and a distal pH sensor, it is possible to document acidic reflux (pH <4), weakly acidic reflux (pH 4-7), and weakly alkaline reflux (pH >7) with multichannel intraluminal impedance. It is an important tool in those with respiratory symptoms, particularly for the determination of nonacid reflux, but must be cautiously applied in routine clinical evaluation because of limited evidence-based parameters for GERD diagnosis and symptom association.

Esophageal manometry is not useful in demonstrating gastroesophageal reflux but might be of use to evaluate TLESR.

Laryngotracheobronchoscopy evaluates for visible airway signs that are associated with extraesophageal GERD, such as posterior laryngeal inflammation and vocal cord nodules; it can permit diagnosis of silent aspiration (during swallowing or during reflux) by bronchoalveolar lavage with subsequent quantification of lipid-laden macrophages in airway secretions. Detection of pepsin in tracheal fluid is a marker of reflux-associated aspiration of gastric contents. Esophageal manometry permits evaluation for dysmotility, particularly in preparation for antireflux surgery.

Empirical antireflux therapy, using a time-limited trial of high-dose PPI, is a cost-effective strategy for diagnosis in adults; although not formally evaluated in older children, it has also been applied to this age group (Fig. 369.3). Failure to respond to such empirical treatment, or a requirement for the treatment for prolonged periods, mandates formal diagnostic evaluation.

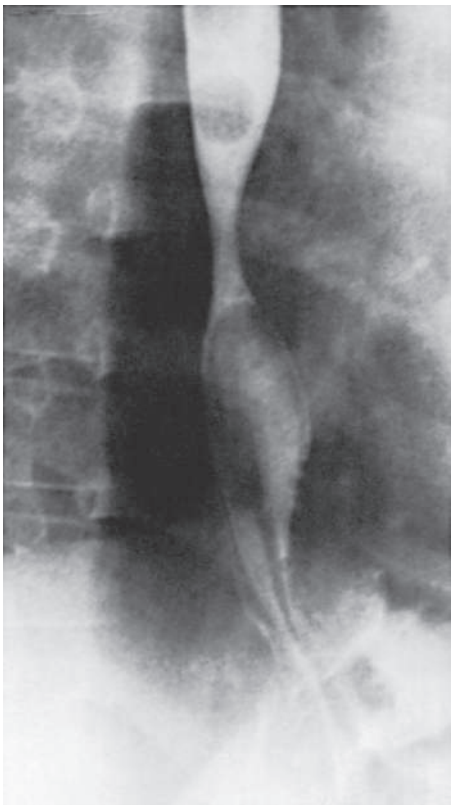

Fig. 369.1 Barium esophagogram demonstrating free gastroesophageal reflux. Note stricture caused by peptic esophagitis. Longitudinal gastric folds above the diaphragm indicate the unusual presence of an associated hiatal hernia.

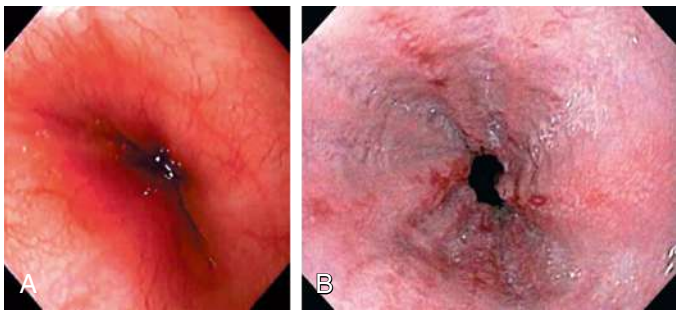

Fig. 369.2 Endoscopic image of a normal esophagus (A) and erosive peptic esophagitis (B).

MANAGEMENT

The conservative therapy and lifestyle modifications that form the foundation of GERD therapy can be effectively implemented through education and reassurance for parents. Dietary measures for infants include normalization of any abnormal feeding techniques, volumes, and frequencies. Thickening of feeds or use of commercially prethickened formulas increases the percentage of infants with no regurgitation, decreases the frequency of daily regurgitation and emesis, and increases the infant's weight gain. However, caution should be exercised when managing preterm infants because of the possible association between xanthan gum-based thickened feeds and necrotizing enterocolitis. The evidence does not clearly favor one type of thickener over another; the addition of a tablespoon of rice or oat cereal per ounce of formula results in a greater caloric density (30 kcal/oz) and reduced crying time, although it might not modify the number of nonregurgitant reflux episodes. Caution must be exercised while using rice cereal, as studies show increased risk of arsenic exposure in children with excessive rice and rice product consumption. A short trial (2 weeks) of a hypoallergenic diet in infants may be used to exclude milk or soy protein allergy before pharmacotherapy. A combination of modified feeding volumes, hydrolyzed infant formulas, proper positioning, and avoidance of tobacco smoke exposure satisfactorily improve GERD symptoms in 24–59% of infants with GERD. Older children should be counseled to avoid acidic or reflux-inducing foods, particularly if these trigger symptoms (tomatoes, chocolate, mint), and beverages (juices, carbonated and caffeinated drinks, alcohol). Weight reduction for obese patients and elimination of smoke exposure are other crucial measures at all ages.

Positioning measures are particularly important for infants who cannot control their positions independently. Seated position worsens infant reflux and should be avoided in infants with GERD. Esophageal pH monitoring demonstrates more reflux episodes in infants in supine and side positions compared with the prone position, but evidence that the supine position reduces the risk of sudden infant death syndrome (SIDS) has led the American Academy of Pediatrics and the North American Society of Pediatric Gastroenterology and Nutrition to recommend supine positioning during sleep. When the infant is awake and observed, prone position and upright carried position can be used to minimize

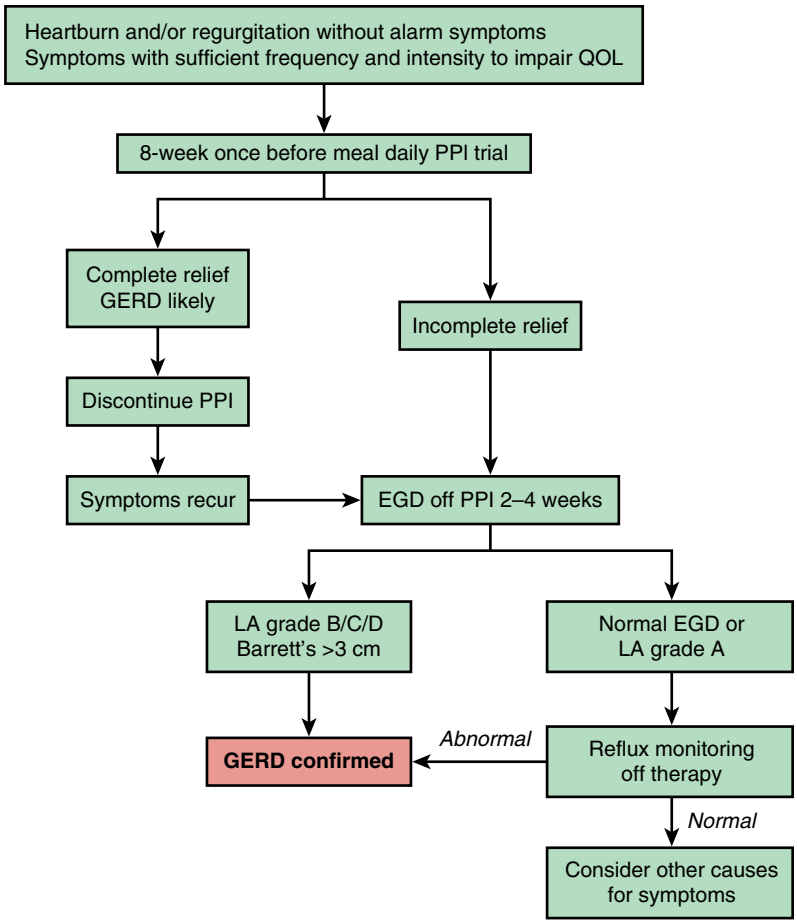

Fig. 369.3 Diagnostic algorithm for GERD. EGD, Esophagogastroduodenoscopy; LA, Los Angeles; PPI, proton pump inhibitor; QOL, quality of life. *(From Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022;117:27–56. Fig. 1, p. 33.)*

reflux. Lying in the flat supine position and semi-seated positions (e.g., car seats, infant carriers) in the postprandial period are considered provocative positions for GER and therefore should be avoided. The efficacy of positioning for older children is unclear, but some evidence suggests a benefit to left side position and head elevation during sleep. The head should be elevated by elevating the head of the bed, rather than using excess pillows, to avoid abdominal flexion and compression that might worsen reflux, and increases the risk of SIDS (see Chapter 423).

Pharmacotherapy is directed at ameliorating the acidity of the gastric contents or at promoting their aboral movement and should be considered for those symptomatic infants and children who are either highly suspected or proven to have GERD. Antacids are the most commonly used antireflux therapy and are readily available over the counter. They provide rapid but transient relief of symptoms by acid neutralization. The long-term regular use of antacids cannot be recommended because of side effects of diarrhea (magnesium antacids) and constipation (aluminum antacids) and rare reports of more serious side effects of chronic use.

H_2RAs (cimetidine, famotidine, and nizatidine) have been used as antisecretory agents that act by selective inhibition of histamine receptors on gastric parietal cells. It is important to note that ranitidine, one of the most popular H_2RAs was recalled by the FDA in 2020 due to the discovery that it contained concerning amounts of a potential carcinogen called N-nitrosodimethylamine (NDMA). H_2RAs were beneficial in the treatment of mild to moderate reflux esophagitis. They have been recommended because of their excellent overall safety profile, *but they are superseded by PPIs in this role.*

PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) provide the most potent acid blockade effect by blocking the hydrogen–potassium adenosine triphosphatase channels of the final common pathway in gastric acid secretion. PPIs are superior to H_2RAs in the treatment of severe and erosive esophagitis. Pharmacodynamic studies indicate that children require higher doses of PPIs than adults on a per-weight basis. The use of PPIs to treat infants and children deemed to have GERD on the basis of symptoms is common; however, an important systematic review of the efficacy and safety of PPI therapy in pediatric GERD reveals no clear benefit for PPI over placebo use in *suspected infantile GERD* (crying, arching behavior). Limited pediatric data are available to draw definitive conclusions about potential complications implicated with PPI use, such as respiratory infections, *Clostridium difficile* infection, osteopenic bone fractures (noted in adults), hypomagnesemia, and kidney damage; most randomized controlled studies have not confirmed these side effects.

Prokinetic agents available in the United States include metoclopramide (dopamine-2 and 5-HT_3 antagonist), bethanechol (cholinergic agonist), and erythromycin (motilin receptor agonist). Most of these increase LES pressure, some improve gastric emptying or esophageal clearance, but none affects the frequency of TLESRs. The available controlled trials *have not* demonstrated much efficacy for GERD. The FDA announced a black box warning for metoclopramide, linking its chronic use (longer than 3 months) with tardive dyskinesia, the rarely reversible movement disorder. Baclofen is a centrally acting γ-aminobutyric acid agonist that decreases reflux by decreasing TLESRs in healthy adults and in a small number of neurologically impaired children with GERD. Other agents of interest include peripherally acting γ-aminobutyric acid agonists devoid of central side effects, and metabotropic glutamate receptor 5 antagonists that are reported to reduce TLESRs but are as yet inadequately studied for this indication in children.

Cisapride is a serotonergic-receptor agonist with a prokinetic effect that is only available in the United States through a limited access program because of its cardiac side effects (QT prolongation, dysrhythmias).

Surgery, usually **fundoplication,** is effective therapy for intractable GERD in children, particularly those with refractory esophagitis or strictures and those at risk for significant morbidity from chronic pulmonary disease. It may be combined with a gastrostomy for feeding or venting. The availability of potent acid-suppressing medication mandates more-rigorous analysis of the relative risks (or costs) and benefits of this

relatively irreversible therapy compared with long-term pharmacotherapy. Some of the risks of fundoplication include a wrap that is *too tight* (producing dysphagia or gas-bloat) or *too loose* (and thus incompetent). Surgeons may choose to perform a *tight* (360 degrees, Nissen) or variations of a *loose* (<360 degrees, Thal, Toupet, Boix-Ochoa) wrap, or to add a gastric drainage procedure (pyloroplasty) to improve gastric emptying, based on their experience and the patient's disease. Preoperative accuracy of the diagnosis of GERD and the skill of the surgeon are two of the most important predictors of successful outcome. Long-term studies suggest that fundoplications often become incompetent in children, as in adults, with reflux recurrence rates of up to 14% for Nissen and up to 20% for loose wraps (the rates may be highest with laparoscopic procedures); this fact currently combines with the potency of PPI therapy that is available to shift practice toward long-term pharmacotherapy in many cases. Fundoplication procedures may be performed as open operations, by laparoscopy, or by endoluminal (gastroplication) techniques. Pediatric experience is limited with endoscopic application of radiofrequency therapy (Stretta procedure) to a 2-3 cm area of the LES and cardia to create a high-pressure zone to reduce reflux.

Total esophagogastric dissociation is performed in selective neurologically impaired children with repeated failed fundoplications and with severe life-threatening GERD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

369.1 Complications of Gastroesophageal Reflux Disease

Seema Khan and Sravan Kumar Reddy Matta

ESOPHAGEAL: ESOPHAGITIS AND SEQUELAE—STRICTURE, BARRETT ESOPHAGUS, ADENOCARCINOMA

Esophagitis can manifest as irritability, arching, and feeding aversion in infants; chest or epigastric pain in older children; and, rarely, as hematemesis, anemia, or Sandifer syndrome at any age. Erosive esophagitis is found in approximately 12% of children with GERD symptoms and is more common in boys, older children, neurologically challenged children, children with severe chronic respiratory disease, and in those with hiatal hernia. Prolonged and severe esophagitis leads to formation of strictures, generally located in the distal esophagus, producing dysphagia, and requiring repeated esophageal dilations and often fundoplication. Long-standing esophagitis predisposes to metaplastic transformation of the normal esophageal squamous epithelium into intestinal columnar epithelium, termed **Barrett esophagus,** a precursor of esophageal adenocarcinoma. A large multicenter prospective study of 840 consecutive children who underwent elective endoscopies reported a 25.7% prevalence for reflux esophagitis, and a mere 0.12% for Barrett esophagus in children without neurologic disorders or tracheoesophageal anomalies. Both Barrett esophagus and adenocarcinoma occur more in White males and in those with increased duration, frequency, and severity of reflux symptoms. This transformation increases with age to plateau in the fifth decade; adenocarcinoma is rare in childhood. Barrett esophagus, uncommon in children, warrants periodic surveillance biopsies, aggressive pharmacotherapy, and fundoplication for progressive lesions.

NUTRITIONAL

Esophagitis and regurgitation may be severe enough to induce failure to thrive because of caloric deficits. Enteral (nasogastric or nasojejunal, or percutaneous gastric or jejunal) or parenteral feedings are sometimes required to treat such deficits.

EXTRAESOPHAGEAL: RESPIRATORY ("ATYPICAL") PRESENTATIONS

GERD should be included in the differential diagnosis of children with unexplained or refractory otolaryngologic and respiratory complaints. GERD can produce respiratory symptoms by direct contact of the refluxed gastric contents with the respiratory tract (aspiration, laryngeal penetration, or microaspiration) or by reflexive interactions between the esophagus and respiratory tract (inducing laryngeal closure or bronchospasm). Often, GERD and a primary respiratory disorder, such as asthma, interact and a vicious cycle between them worsens both diseases. Many children with these extraesophageal presentations do not have typical GERD symptoms, making the diagnosis difficult. These atypical GERD presentations require a thoughtful approach to the differential diagnosis that considers a multitude of primary otolaryngologic (infections, allergies, postnasal drip, voice overuse) and pulmonary (asthma, cystic fibrosis) disorders. Therapy for the GERD must be more intense (usually incorporating a PPI) and prolonged (usually at least 3-6 months). In these cases a multidisciplinary approach involving otolaryngology, pulmonary for airway disease, and gastroenterology for reflux disease is often warranted for specialized diagnostic testing and for optimizing intensive management.

APNEA AND STRIDOR

These upper airway presentations have been linked with GERD in case reports and epidemiologic studies; temporal relationships between them and reflux episodes have been demonstrated in some but not all patients by esophageal pH–multichannel intraluminal impedance studies, and a beneficial response to therapy for GERD provides further support in a number of case series. An evaluation of 1,400 infants with apnea attributed the apnea to GERD in 50%, but other studies have failed to find an association. Apnea and brief resolved unexplained event (BRUE)-like presentation (previously called an "apparent life-threatening event"; see Chapter 424) caused by reflux is generally obstructive due to laryngospasm that may be conceived as an abnormally intense protective reflex. At the time of such apnea, infants have often been provocatively positioned (supine or flexed seated), have been recently fed, and have shown signs of obstructive apnea, with unproductive respiratory efforts. *The evidence suggests that for the large majority of infants presenting with apnea and BRUE, GERD is not causal.* Stridor triggered by reflux generally occurs in infants anatomically predisposed toward stridor (laryngomalacia, micrognathia). Spasmodic croup, an episodic frightening upper airway obstruction, can be an analogous condition in older children. Esophageal pH probe studies might fail to demonstrate linkage of these manifestations with reflux because of the buffering of gastric contents by infant formula and the episodic nature of the conditions. Pneumograms can fail to identify apnea if they are not designed to identify obstructive apnea by measuring nasal airflow.

Reflux laryngitis and other otolaryngologic manifestations (also known as laryngopharyngeal reflux) can be attributed to GERD. **Hoarseness,** voice fatigue, throat clearing, chronic cough, pharyngitis, sinusitis, otitis media, and a sensation of globus have been cited. Laryngopharyngeal signs of GERD include edema and hyperemia (of the posterior surface), contact ulcers, granulomas, polyps, subglottic stenosis, and interarytenoid edema. The paucity of well-controlled evaluations of the association contributes to the skepticism with which these associations may be considered. Other risk factors irritating the upper respiratory passages can predispose some patients with GERD to present predominantly with these complaints.

Many studies have reported a strong association between asthma and reflux as determined by history, pH–multichannel intraluminal impedance, endoscopy, and esophageal histology. GERD symptoms are present in ~23% (19–80%) of children with asthma; abnormal pH results are noted in ~63%, and esophagitis in ~35% of asthmatic children. However, this association does not clarify the direction of causality in individual cases and thus does not indicate which patients with asthma are likely to benefit from anti-GERD therapy. Children with asthma who are particularly likely to have GERD as a provocative factor are those with symptoms of reflux disease, those with refractory or steroid-dependent asthma, and those with nocturnal worsening of asthma. Endoscopic evaluation that discloses esophageal sequelae of GERD provides an impetus to embark on the aggressive (high dose and many months' duration) therapy of GERD.

Dental erosions constitute the most common oral lesion of GERD, the lesions being distinguished by their location on the lingual surface of the teeth. The severity seems to correlate with the presence of reflux symptoms and the presence of an acidic milieu as the result of reflux in the proximal esophagus and oral cavity. The other common factors that can produce similar dental erosions are juice consumption and bulimia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 370

Eosinophilic Esophagitis, Pill Esophagitis, and Infective Esophagitis

Seema Khan

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EoE) is a chronic esophageal disorder characterized by esophageal dysfunction and infiltration of the esophageal epithelium by ≥15 eosinophils per high-power field (hpf). The proposed diagnostic criteria are the clinical presentation of esophageal dysfunction in association with esophageal epithelial infiltration of at least 15 eosinophils per hpf or ~60 eosinophils per mm^2; a careful evaluation of non-EoE disorders was warranted. Proton pump inhibitors (PPIs) should be considered as another treatment option rather than a diagnostic criterion to differentiate from gastroesophageal reflux disease (GERD). EoE is a global disease, with incidence and prevalence rates in children of 5 and 29.5 per 100,000. Although infants and toddlers present commonly with vomiting, feeding problems, and poor weight gain, older children and adolescents usually experience solid food dysphagia with occasional food impactions (Figs. 370.1 and 370.2) or strictures and may complain of heartburn and chest or epigastric pain. Many patients are male. The mean age at diagnosis is 7 years (range: 1-17 years), and the duration of symptoms is 3 years. Many patients have other atopic diseases (or a positive family history) and associated food allergies; laboratory abnormalities can include peripheral eosinophilia and elevated immunoglobulin E (IgE) levels. The pathogenesis involves mainly T-helper type 2 (Th2) cytokine-mediated (interleukin [IL]-5 and -13) pathways leading to production of a potent eosinophil chemoattractant, eotaxin-3, by esophageal epithelium.

The eosinophilic esophagitis endoscopic reference score **(EREFS)**, based on commonly observed features of edema (E), rings (R; Fig. 370.3), exudates (E; see Fig. 370.3), furrows (F; Fig. 370.4), and strictures (S), has utility in diagnosis and monitoring response to treatment. Esophageal histology reveals profound eosinophilia, with a currently acceptable cutoff for diagnosis chosen at ≥15-20 eosinophils per hpf. Up to 30% children with EoE have grossly visible normal esophageal mucosa or endoscopy.

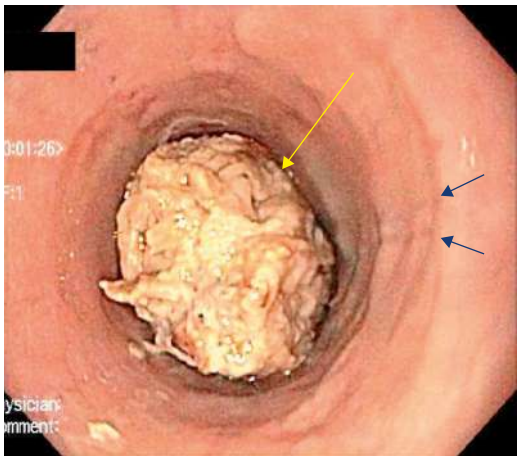

Fig. 370.1 Endoscopic visualization of esophageal food impaction *(yellow arrow)* and mucosal rings *(blue arrows)*.

The role of acid in the pathogenesis and treatment of EoE has been the subject of intense research with studies arguing for and against acid suppression. It is important to highlight that gastric acid, among other functions, activates important digestive enzymes and thereby facilitates digestion of food. Acid suppression is postulated to promote absorption of relatively larger intact proteins with allergenic potential as a consequence of reduced food digestion. Dilated esophageal epithelial intercellular spaces that have been described secondary to proton pump inhibition may increase mucosal permeability of food antigens and further provoke allergic pathways. Retrospective studies have shown that infants treated with histamine receptor antagonists and PPIs are at risk for developing EoE at an earlier age compared to matched control infants. EoE is differentiated from GERD by concurrent atopic diseases, its general lack of erosive esophagitis, its greater eosinophil density, and its normal esophageal pH–multichannel intraluminal impedance results. *A favorable response to PPI therapy should not be considered diagnostic of GERD, as approximately 50% of children with EoE also demonstrate histologic response.* Observations in children and adults with EoE are notable for striking similarities between PPI responders and PPI nonresponders with regard to symptoms, histology, molecular signature, and mechanistic features. This response may be because of an acid suppressive action or downregulation of Th2 allergic cell pathway, an antieosinophil effect of the PPI class that is mediated by inhibition of eotaxin-3 secretion. Evaluation of EoE should include a search for food (aerodigestive) and environmental allergies via skin prick (IgE mediated) and patch (non–IgE mediated) tests to guide decisions regarding dietary elimination and future food challenges.

Initial treatment involves dietary restrictions that take one of three forms: elimination diets guided by circumstantial evidence and food allergy test results, "6-food elimination diet" removing the major food allergens (milk, soy, wheat, egg, peanuts and tree nuts, seafood), and trial of an elemental diet composed exclusively of an amino acid-based formula. Elimination diets are generally successful, with highest histologic response observed in nearly 91% on the elemental diet, in 73% who undergo empiric dietary elimination, and 48% with a targeted elimination diet. The major drawbacks of these dietary therapies lie in their cost, difficult access, and lower quality of life, any or all of which influence adherence and outcome.

Topically acting swallowed corticosteroids (fluticasone without spacer, viscous budesonide suspension) are the only therapy strongly recommended based on moderate quality evidence as first-line therapy, as well as for those who refuse, fail to adhere, or have a poor response to restricted diets. Histologic remission is observed in 68–77% children and adults treated with fluticasone for 3 months. Histologic recurrence after discontinuation of fluticasone is common, and emphasizes the need for maintenance therapy. Ideal approaches carefully balance the risks of adrenocortical insufficiency as well as bone demineralization and fungal infections against the risk of EoE evolving from an inflammatory to fibrostenotic disease, which can produce esophageal stenosis and strictures. Therapies under investigation include esophageal-specific delivery formulation of topical corticosteroids and monoclonal antibodies against IL-13 (RPC4046) and IL-5 (mepolizumab, reslizumab). Dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, administered by subcutaneous injection, is approved for patients ≥12 years of age with EoE. Histologic remission and improvement of dysphagia symptoms has occurred during dupilumab therapy with minor side effects (injection site reactions, upper respiratory tract infections, arthralgias, herpes viral infections). Patients require periodic endoscopy and histologic reassessment to accurately monitor response to treatment, particularly given that there can be a significant disconnect between symptoms and histology in the evolution of the disease. Expert clinical guidelines stress the need for long-term studies to develop systematic treatment and best follow-up protocols.

INFECTIVE ESOPHAGITIS

Uncommon, and most often affecting immunocompromised children, infective esophagitis is caused by fungal agents, such as

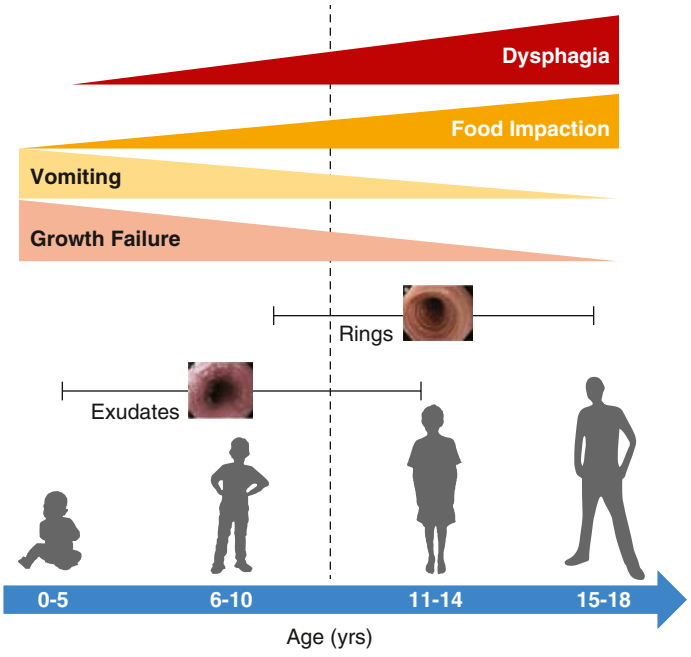

Fig. 370.2 Eosinophilic esophagitis. Graphical representation of symptoms and endoscopic findings by age. *(Modified from Oliva S, Dias JA, Rea F, et al. Characterization of eosinophilic esophagitis from the European pediatric eosinophilic esophagitis registry [pEEr] or ESPGHAN. J Pediatr Gastroenterol Nutr. 2022;75[3]:325–333. Fig. 2.)*



Fig. 370.3 Endoscopic image of eosinophilic esophagitis with characteristic mucosal appearance of furrowing and white specks.

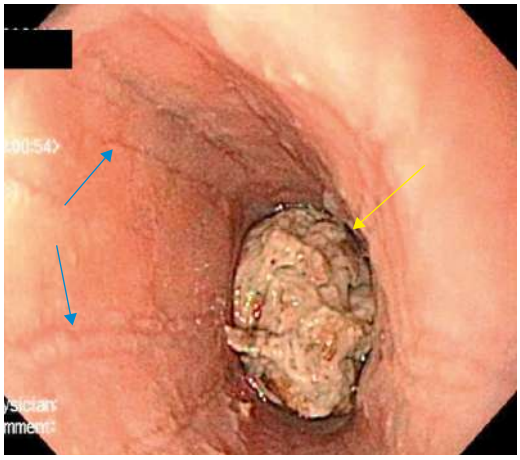

Fig. 370.4 Endoscopy photograph showing mucosal furrowing *(blue arrows)* characteristic of eosinophilic esophagitis in a patient with food impaction *(yellow arrow)*.

Candida albicans and *Torulopsis glabrata;* viral agents, such as herpes simplex (HSV), cytomegalovirus (CMV), HIV, and varicella zoster; and, rarely, bacterial infections, including diphtheria and tuberculosis, or parasites. The typical presenting signs and symptoms are odynophagia, dysphagia, and retrosternal or chest pain; there may also be fever, nausea, and vomiting. *Candida* is the leading cause of infective esophagitis in immunocompetent and immunocompromised children and presents with concurrent oropharyngeal infection in the majority of immunocompromised patients. It may also be an incidental finding in asymptomatic patients, notably in those with EoE receiving topical swallowed corticosteroids. Esophageal viral infections can also manifest in immunocompetent hosts as an acute febrile illness. Infectious esophagitis, like other forms of esophageal inflammation, occasionally progresses to esophageal stricture. Diagnosis of infectious esophagitis is made by endoscopy, usually notable for white plaques in *Candida,* multiple superficial ulcers or *volcano ulcers* in HSV, and single deep ulcer in CMV. Histopathologic examination solidifies the diagnosis with the detection of yeast and pseudohyphae in *Candida;* tissue invasion distinguishes esophagitis from mere colonization. Multinucleated giant cells with intranuclear Cowdry type A (eosinophilic) and type B (ground glass appearance) inclusions in HSV, and both intranuclear and intracytoplasmic inclusions producing an *owl's eye* appearance in CMV are typically described. Adding polymerase chain reaction, tissue-viral culture, and immunocytochemistry enhances the

diagnostic sensitivity and precision. Treatment is with appropriate antimicrobial agents: azole therapy, particularly oral fluconazole for *Candida;* oral acyclovir for HSV; and oral valganciclovir for CMV, or alternatively intravenous ganciclovir in severe CMV disease.

PILL ESOPHAGITIS

This acute injury is produced by contact with a damaging agent. Medications implicated in pill esophagitis include tetracycline, doxycycline, potassium chloride, ferrous sulfate, nonsteroidal antiinflammatory medications, cloxacillin, and alendronate (Table 370.1). Most often the offending tablet is ingested at bedtime with inadequate water. This practice often produces acute discomfort followed by progressive retrosternal pain, odynophagia, and dysphagia. Endoscopy shows a focal lesion often localized to one of the anatomic narrowed regions of the esophagus or to an unsuspected pathologic narrowing (Fig. 370.5). Treatment is supportive; lacking much evidence, sucralfate, antacids, topical anesthetics, and bland or liquid diets are often used. The offending pill may be restarted after complete resolution of symptoms, if deemed necessary, though with clear emphasis on ingestion with an adequate volume of water, usually at least 4 oz.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

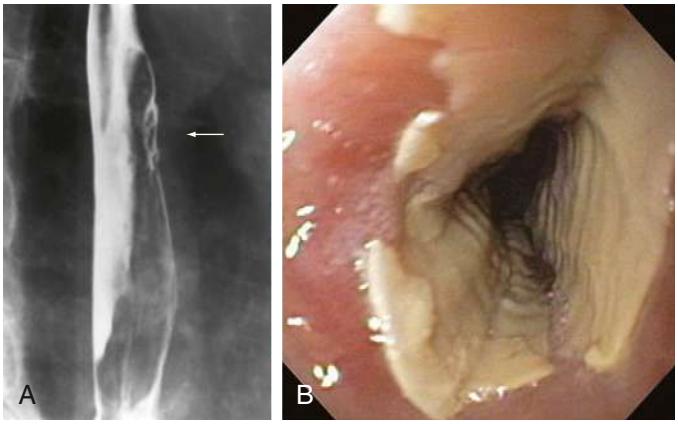

Fig. 370.5 A, Barium esophagogram showing esophageal ulceration secondary to tetracycline, with the *arrow* pointing to an area of ulcerations. B, Endoscopic image of a tetracycline-induced esophageal burn. *(From Katzka DA. Esophageal disorders caused by medications, trauma, and infection. In Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th ed. Philadelphia: Elsevier; 2016: Fig. 46.1).*

Table 370.1 Medications Commonly Associated with Esophagitis or Esophageal Injury

ANTIBIOTICS
Clindamycin
Doxycycline
Penicillin
Rifampin
Tetracycline
ANTIVIRAL AGENTS
Nelfinavir
Zalcitabine
Zidovudine
BISPHOSPHONATES
Alendronate
Etidronate
Pamidronate
CHEMOTHERAPEUTIC AGENTS
Bleomycin
Cytarabine
Dactinomycin
Daunorubicin
5-Fluorouracil
Methotrexate
Vincristine
NSAIDs
Aspirin
Ibuprofen
Naproxen
OTHER MEDICATIONS
Ascorbic acid
Ferrous sulfate
Lansoprazole
Multivitamins
Potassium chloride
Quinidine
Theophylline

NSAIDs, Nonsteroidal antiinflammatory drugs.
From Katzka DA. Esophageal disorders caused by medications, trauma, and infection. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 10th ed. Philadelphia: Elsevier; 2016: Box 46.1.

Chapter 371
Esophageal Perforation

Seema Khan

The majority of esophageal perforations in children are from blunt trauma (automobile injury, gunshot wounds, child abuse) or are iatrogenic. Cardiac massage, the Heimlich maneuver, nasogastric tube placement, traumatic laryngoscopy or endotracheal intubation, excessively vigorous postpartum suctioning of the airway during neonatal resuscitation, difficult upper endoscopy, sclerotherapy of esophageal varices, esophageal compression by a cuffed endotracheal tube, and dilation for therapy of achalasia and strictures have all been implicated. Esophageal rupture has followed forceful vomiting in patients with anorexia and has followed esophageal injury due to caustic ingestion, foreign body ingestion, food impactions, pill esophagitis, or eosinophilic esophagitis. Drinking cold, carbonated beverages rapidly is also known to cause esophageal perforation.

Spontaneous esophageal rupture **(Boerhaave syndrome)** is less common and is associated with sudden increases in intraesophageal pressure brought on by situations such as vomiting, coughing, or straining to stool. Children and adults with eosinophilic esophagitis have also been described with Boerhaave syndrome in the setting of forceful emesis in the aftermath of esophageal food impaction. The prevalence of esophageal perforation in a large retrospective analysis was reported to be 0.05%, the majority of whom were low birthweight (<1,000 g) and ≤28 weeks' gestational age. Importantly, esophageal perforation was not associated with an increased mortality in this pediatric cohort. In older children, as in adults, the tear occurs on the distal left lateral esophageal wall, because the smooth muscle layer here is weakest; in neonates (neonatal Boerhaave syndrome), spontaneous rupture is on the right.

Symptoms of esophageal perforation include pain, neck tenderness, dysphagia, subcutaneous crepitus, fever, and tachycardia; several patients with cervical-level esophageal perforations have displayed cold water polydipsia in an attempt to soothe pain in the throat.

Imaging studies are important for a rapid and accurate diagnosis. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Plain radiography (posteroanterior and lateral views) and CT of the neck and chest are often used, with the latter as more sensitive and accurate in diagnosis. Signs of perforation include pneumomediastinum, mediastinal widening, subcutaneous emphysema, pneumothorax, hydrothorax, pleural effusion, and lung collapse. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, although it has a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Endoscopic techniques, considered less invasive and morbid, are now being used more frequently and include clips for defects <2 cm, and placement of stents and suturing for larger defects. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 372

Esophageal Varices

Seema Khan

Esophageal varices form in adults and children with portal hypertension with hepatic venous pressure gradient >10 mm Hg and pose a risk for bleeding at >12 mm Hg (see Chapter 415). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are *uphill varices;* less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are *downhill varices*. Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with extrahepatic portal venous obstruction (EHPVO) might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise. The leading causes of pediatric portal hypertension, biliary atresia, and EHPVO are uniquely distinct from diseases encountered in adults. Hence, children tend to tolerate variceal bleeding better because they have generally well compensated liver disease, with studies reporting mortality risk <1% after initial variceal bleed. The likelihood of esophageal varices in children with EHPVO increases from 1% to 22%, and small (13%) to large (54%) at 1 year and 5 years of age, respectively. Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report comprising a large series of children with biliary atresia and portal hypertension described endoscopic findings of large varices, red marks, and the presence of gastric varices as predictive of bleeding. Noninvasive methods of evaluating varices include barium contrast studies, ultrasound, computerized tomography, magnetic resonance, and elastography, but they are not recommended for routine diagnostic evaluation because of suboptimal accuracy compared to endoscopy.

Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective β-blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. Variceal band ligation is regarded as the preferred endotherapy and can be feasibly performed in children weighing more than 10 kg. Meso-Rex bypass surgery should be offered to children with EHPVO as both primary and secondary prophylaxis in the appropriate context (Fig. 372.1). Due to insufficient evidence, the same cannot be recommended regarding endoscopic therapies and nonselective β blockers for primary prophylaxis in children. In contrast, adults do have a reduced risk of first-time variceal bleeding with endoscopic variceal ligation when compared with untreated controls as well as patients treated with β-blockade; a decrease in mortality is only noted compared with the control group (see Chapter 415). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses nonselective β-blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

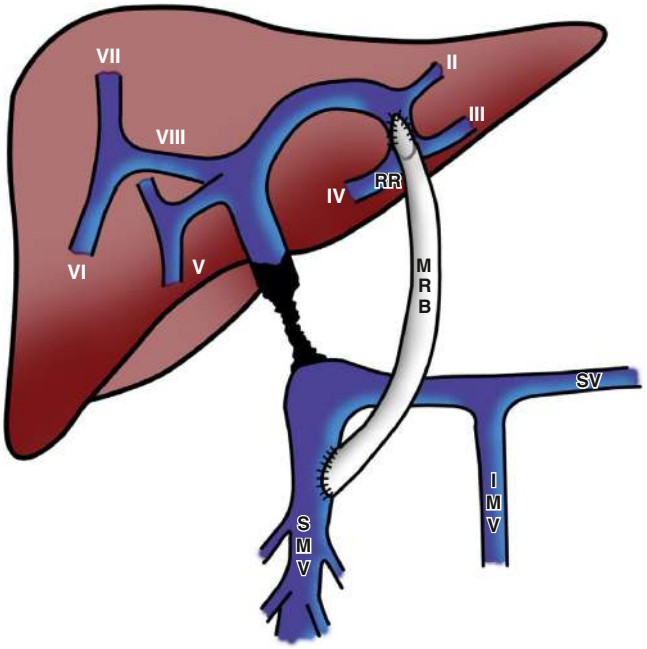

Fig. 372.1 Meso-Rex bypass between the superior mesenteric vein *(SMV)* and the Rex recess *(RR)* of the left portal vein. IMV, Inferior mesenteric vein; MRB, Meso-Rex bypass; SV, splenic vein. *(From Brichard M, Iesari S, Lerut J, et al. Meso-Rex bypass for the management of extrahepatic portal vein obstruction in adults. Hepatobiliary Pancreat Dis Int. 2022;21:25–32. Fig. 3.)*

Imaging studies are important for a rapid and accurate diagnosis. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Plain radiography (posteroanterior and lateral views) and CT of the neck and chest are often used, with the latter as more sensitive and accurate in diagnosis. Signs of perforation include pneumomediastinum, mediastinal widening, subcutaneous emphysema, pneumothorax, hydrothorax, pleural effusion, and lung collapse. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, although it has a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Endoscopic techniques, considered less invasive and morbid, are now being used more frequently and include clips for defects <2 cm, and placement of stents and suturing for larger defects. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 372

Esophageal Varices

Seema Khan

Esophageal varices form in adults and children with portal hypertension with hepatic venous pressure gradient >10 mm Hg and pose a risk for bleeding at >12 mm Hg (see Chapter 415). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are *uphill varices;* less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are *downhill varices*. Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with extrahepatic portal venous obstruction (EHPVO) might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise. The leading causes of pediatric portal hypertension, biliary atresia, and EHPVO are uniquely distinct from diseases encountered in adults. Hence, children tend to tolerate variceal bleeding better because they have generally well compensated liver disease, with studies reporting mortality risk <1% after initial variceal bleed. The likelihood of esophageal varices in children with EHPVO increases from 1% to 22%, and small (13%) to large (54%) at 1 year and 5 years of age, respectively. Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report comprising a large series of children with biliary atresia and portal hypertension described endoscopic findings of large varices, red marks, and the presence of gastric varices as predictive of bleeding. Noninvasive methods of evaluating varices include barium contrast studies, ultrasound, computerized tomography, magnetic resonance, and elastography, but they are not recommended for routine diagnostic evaluation because of suboptimal accuracy compared to endoscopy.

Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective β-blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. Variceal band ligation is regarded as the preferred endotherapy and can be feasibly performed in children weighing more than 10 kg. Meso-Rex bypass surgery should be offered to children with EHPVO as both primary and secondary prophylaxis in the appropriate context (Fig. 372.1). Due to insufficient evidence, the same cannot be recommended regarding endoscopic therapies and nonselective β blockers for primary prophylaxis in children. In contrast, adults do have a reduced risk of first-time variceal bleeding with endoscopic variceal ligation when compared with untreated controls as well as patients treated with β-blockade; a decrease in mortality is only noted compared with the control group (see Chapter 415). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses nonselective β-blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

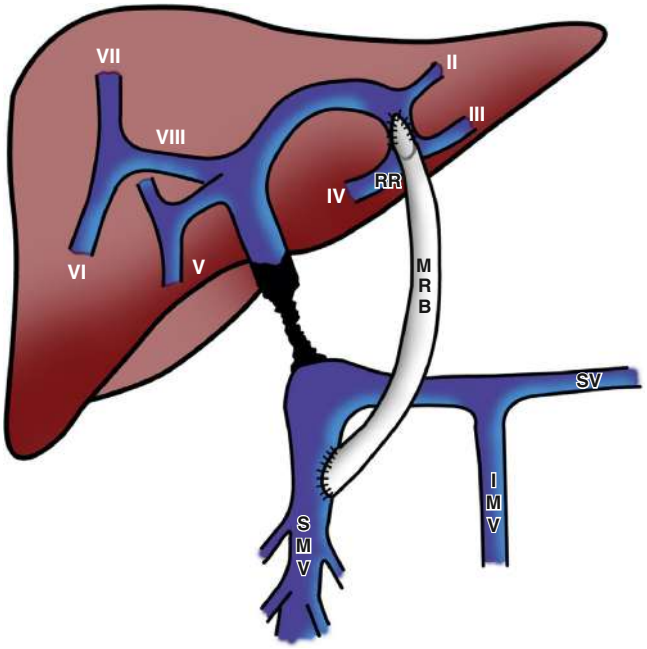

Fig. 372.1 Meso-Rex bypass between the superior mesenteric vein *(SMV)* and the Rex recess *(RR)* of the left portal vein. IMV, Inferior mesenteric vein; MRB, Meso-Rex bypass; SV, splenic vein. *(From Brichard M, Iesari S, Lerut J, et al. Meso-Rex bypass for the management of extrahepatic portal vein obstruction in adults. Hepatobiliary Pancreat Dis Int. 2022;21:25–32. Fig. 3.)*

Chapter 373 Ingestions

373.1 Foreign Bodies in the Esophagus

Seema Khan

The majority (80%) of accidental foreign-body ingestions occur in children, most of whom are 5 years of age or younger. Older children and adolescents with developmental delays and those with psychiatric disorders are also at increased risk. Most ingested foreign bodies are associated with a good outcome as they pass spontaneously through an anatomically normal digestive tract. The presentation of a foreign body lodged in the esophagus constitutes an emergency and is associated with significant morbidity and mortality because of the potential for perforation and sepsis. Although coins are by far the most commonly ingested foreign body, followed by small toy items, it is the ingestion of batteries and multiple magnets that could lead to life-threatening complications. Food impactions are less common in children than in adults and usually occur in children in association with eosinophilic esophagitis (diagnosed in 92% of those presenting with food impactions and dysphagia), repair of esophageal atresia, and Nissen fundoplication. Most esophageal foreign bodies lodge at the level of the cricopharyngeus (upper esophageal sphincter), the aortic arch, or just superior to the diaphragm at the gastroesophageal junction (lower esophageal sphincter).

At least 30% of children with esophageal foreign bodies may be totally asymptomatic, so any history of foreign-body ingestion should be taken seriously and investigated. An initial bout of choking, gagging, and coughing may be followed by excessive salivation, dysphagia, food refusal, emesis, or pain in the neck, throat, or sternal notch regions. Respiratory symptoms such as stridor, wheezing, cyanosis, or dyspnea may be encountered if the esophageal foreign body impinges on the larynx or membranous posterior tracheal wall. Cervical swelling, erythema, or subcutaneous crepitations suggest perforation of the oropharynx or proximal esophagus.

Evaluation of the child with a history of foreign-body ingestion starts with plain anteroposterior radiographs of the neck, chest, and abdomen, along with lateral views of the neck and chest. The flat surface of a coin in the esophagus is seen on the anteroposterior view and the edge on the lateral view (Fig. 373.1). The reverse is true for coins lodged in the trachea; here, the edge is seen anteroposteriorly and the flat side is seen laterally. Disk-shaped button batteries can look like coins and can be differentiated on close examination by the double halo (not obvious in the new slimmer batteries) and step-off (indicating the negative pole) on anteroposterior and lateral views, respectively (Fig. 373.2). The use of button batteries has been increasingly popular, leading to a sharp rise in accidental ingestions, and an increase in morbidity and mortality. The latter is thought to be due to both an increase in diameter and a change to lithium cells. Children younger than 5 years of age with ingestion of batteries ≥20 mm are considered to have the highest risk for catastrophic events such as necrosis, tracheoesophageal fistula, perforation, stricture, vocal cord paralysis, mediastinitis, and aortoenteric fistula (Fig. 373.3). Materials such as plastic, wood, glass, aluminum, and bones may be radiolucent; failure to visualize the object with plain films in a symptomatic patient warrants urgent endoscopy. CT scan with three-dimensional reconstruction may increase the sensitivity of imaging a foreign body. Although barium contrast studies may be helpful in the occasional asymptomatic patient with negative plain films, their use is to be discouraged because of the potential of aspiration, as well as making subsequent visualization and object removal more difficult.

In managing the child with an esophageal foreign body, it is important to assess risk for airway compromise and to obtain a chest CT scan and surgical consultation in cases of suspected airway perforation. Treatment of esophageal foreign bodies usually merits endoscopic visualization of the object and underlying mucosa and removal of the object using an appropriately designed foreign body–retrieving accessory instrument through the endoscope and with an endotracheal tube protecting the airway. Sharp objects in the esophagus, multiple magnets or a single magnet with a metallic object, or foreign bodies associated with respiratory symptoms mandate urgent removal within 12 hours of presentation. Button batteries, in particular, must be emergently removed within 2 hours of presentation regardless of the timing of the patient's last oral intake, because they can induce mucosal injury in as little as 1 hour of contact time and involve all esophageal layers within 4 hours (see Fig. 373.3; Fig. 373.4). In cases of delayed endoscopic intervention, frequent ingestion of honey and sucralfate are recommended as mitigation measures to reduce injury. Asymptomatic blunt objects and coins lodged in the esophagus can be observed for up to 24 hours in anticipation of passage into the stomach. If there are no problems in handling secretions, meat impactions can be observed for up to 24 hours. In patients without prior esophageal surgeries, glucagon (0.05 mg/kg intravenously; maximum pediatric dose, 0.5 mg; adult dose, 1-2 mg) can sometimes be useful in facilitating passage of distal esophageal food boluses by decreasing the lower esophageal sphincter pressure. The use of meat tenderizers or gas-forming agents can lead to perforation and are not recommended. An alternative technique for removing esophageal coins impacted for <24 hours, performed most safely by experienced radiology personnel, consists of passage of a Foley catheter beyond the coin at fluoroscopy, inflating the balloon, and then pulling the catheter and coin back simultaneously with the patient in a prone oblique position. Concerns about the lack of direct mucosal visualization and, when tracheal intubation is not used, the lack of airway protection prompt caution in the use of this technique. Bougienage of esophageal coins toward the stomach in selected uncomplicated pediatric cases has been suggested to be an effective, safe, and economical modality where endoscopy might not be routinely available.

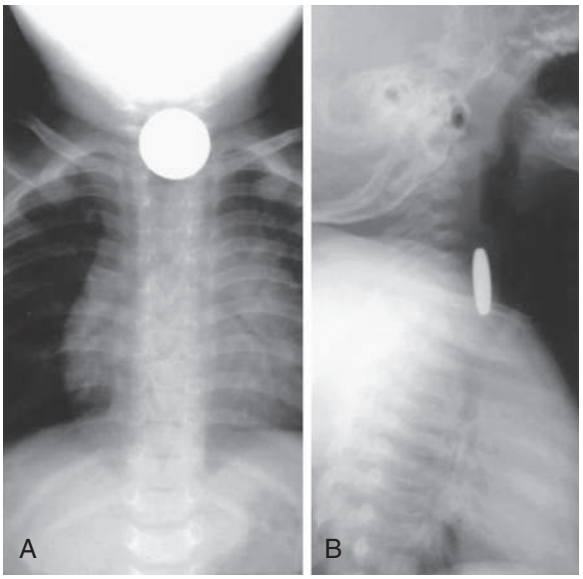

Fig. 373.1 Radiographs of a coin in the esophagus. When foreign bodies lodge in the esophagus, the flat surface of the object is seen in the anteroposterior view (A) and the edge is seen in the lateral view (B). The reverse is true for objects in the trachea. *(Courtesy Beverley Newman, MD.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

373.2 Caustic Ingestions

Seema Khan

Ingestion of caustic substances is a worldwide public health problem accounting for a significant burden on healthcare resources. According

to an inpatient database of U.S. pediatric hospital discharges in 2009, the estimated number of caustic ingestions was 807 (95% confidence interval [CI], 731-882) cases, amounting to $22.9 million in total hospital charges. The medical sequelae of caustic ingestions are esophagitis, necrosis, perforation, and stricture formation (see Chapter 94). Most cases (70%) are accidental ingestions of liquid alkali substances that produce severe, deep liquefaction necrosis; drain decloggers are

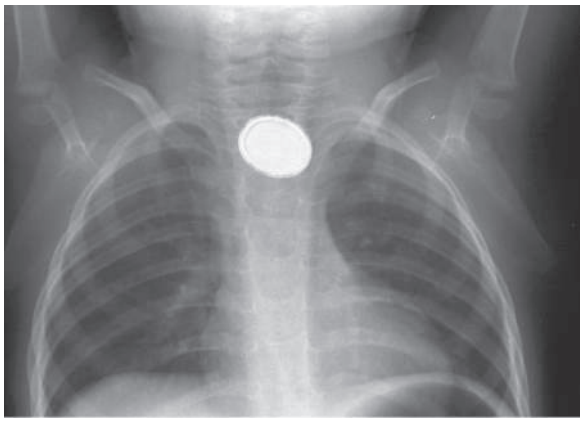

Fig. 373.2 Disk battery impacted in esophagus. Note the double rim. *(From Wyllie R, Hyams JS, eds. Pediatric Gastrointestinal and Liver Disease, 3rd ed. Philadelphia: Saunders; 2006.)*

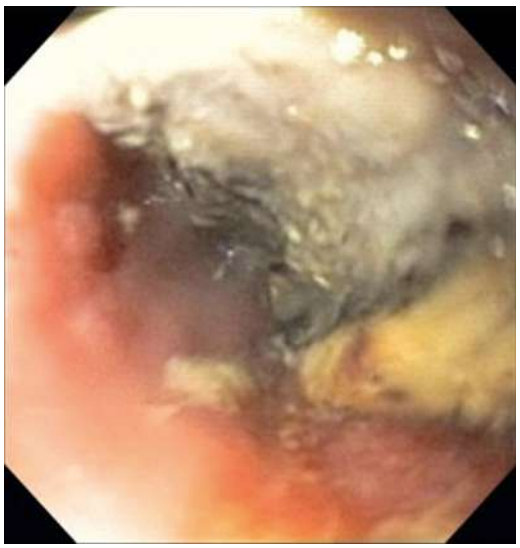

Fig. 373.3 Severe esophageal injury at site of button battery (BB) removal, with necrosis and eschar. *(From Leinwand K, Brumbaugh DE, Kramer RE. Button battery ingestion in children—a paradigm for management of severe pediatric foreign-body ingestions. Gastrointest Endosc Clin North Am. 2016;26:99–118. Fig. 1.)*

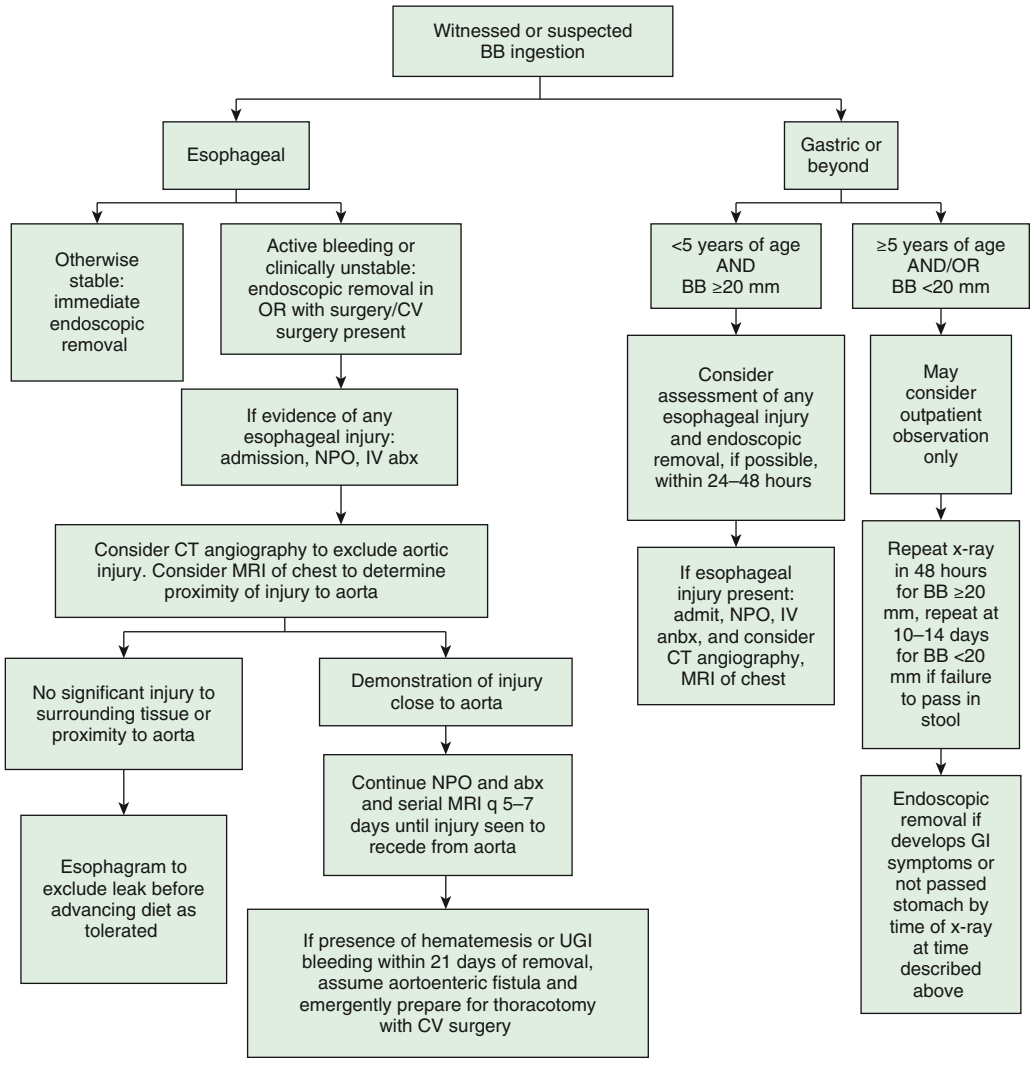

Fig. 373.4 Proposed management algorithm for ingestion of button battery *(BB)* in children. Abx, Antibiotics; CV, cardiovascular; GI, gastrointestinal; IV, intravenous; NPO, nil per os; OR, operating room; q, every; UGI, upper gastrointestinal series. *(From Kramer RE, Lerner DG, Lin T, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN endoscopy committee. J Pediatr Gastroenterol Nutr. 2015;60[4]:562–574. Fig. 1.)*

Table 373.1 Ingestible Caustic Materials Around the House

CATEGORY	MOST DAMAGING AGENTS	OTHER AGENTS
Alkaline drain cleaners, milking machine pipe cleaners	Sodium or potassium hydroxide	Ammonia, sodium hypochlorite, aluminum particles
Acidic drain openers	Hydrochloric acid, sulfuric acid	
Toilet cleaners	Hydrochloric acid, sulfuric acid, phosphoric acid, other acids	Ammonium chloride, sodium hypochlorite
Oven and grill cleaners	Sodium hydroxide, perborate (borax)	
Denture cleaners	Persulfate (sulfur), hypochlorite (bleach)	
Dishwasher detergent		
Liquid	Sodium hydroxide	
Powdered	Sodium hypochlorite	
Packaged	Sodium carbonate	
Bleach	Sodium hypochlorite	Ammonia salt
Swimming pool chemicals	Acids, alkalis, chlorine	
Battery acid (liquid)	Sulfuric acid	
Disk batteries	Electric current	Zinc or other metal salts
Rust remover	Hydrofluoric, phosphoric, oxalic, and other acids	
Household delimers	Phosphoric acid, hydroxyacetic acid, hydrochloric acid	
Barbeque cleaners	Sodium and potassium hydroxide	
Glyphosate surfactant (RoundUp) acid	Glyphosate herbicide	Surfactants
Hair relaxer	Sodium hydroxide	
Weed killer	Dichlorophenoxyacetate, ammonium phosphate, propionic acid	

Source: National Library of Medicine: *Health and Safety Information on Household Products* (website). http://householdproducts.nlm.nih.gov/
From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 4th ed. Philadelphia: Saunders; 2011: Table 19.1, p. 198.

most common, and because they are tasteless, more is ingested (Table 373.1). **Acidic agents** (20% of cases) are bitter, so less may be consumed; they produce coagulation necrosis and a somewhat protective thick eschar. They can produce severe gastritis, and volatile acids can result in respiratory symptoms. Children younger than 5 years of age account for half of the cases of caustic ingestions, and boys are far more often involved than girls.

Caustic ingestions produce signs and symptoms such as vomiting, drooling, refusal to drink, oral burns, dysphagia, dyspnea, abdominal pain, hematemesis, and stridor. Twenty percent of patients develop esophageal strictures. Absence of oropharyngeal lesions does not exclude the possibility of significant esophagogastric injury, which can lead to perforation or stricture. The absence of symptoms is usually associated with no or minimal lesions; hematemesis, respiratory distress, or presence of at least three symptoms predicts severe lesions. An upper endoscopy is recommended as the most efficient means of rapid identification of tissue damage and must be undertaken in all symptomatic children within the first 24-48 hours of ingestion. In select situations when endoscopy may not be possible, CT of the chest and abdomen should be considered in the evaluation of transmural and extraesophageal injury, as well as in anticipation of emergent surgical planning.

Dilution by water or milk is recommended as acute treatment, but neutralization, induced emesis, and gastric lavage are contraindicated. Treatment depends on the severity and extent of damage (Table 373.2, Fig. 373.5). Stricture risk is increased by circumferential ulcerations, white plaques, and sloughing of the mucosa and is reported to occur in 70–100% of grade 2b and grade 3 caustic esophagitis. Strictures can require treatment with dilation, and in some severe cases, surgical resection and colon or small bowel interposition are needed. Silicone stents (self-expanding) placed endoscopically after a dilation procedure can be an alternative and conservative approach to the management of strictures. Rare late cases of superimposed esophageal carcinoma are reported. The role of corticosteroids is controversial; they are not recommended in grade 1 burns, but they can reduce the risk of strictures in more-advanced caustic esophagitis. Many centers also use proton pump inhibitors as well as antibiotics in the initial treatment of caustic esophagitis on the premise that reducing superinfection in the necrotic tissue bed will, in turn, lower the risk of stricture formation. Studies examining the role of antibiotics in caustic esophagitis have not reported a clinically significant benefit even in those with grade 2 or greater severity of esophagitis.

There may be an increase of esophageal (not gastric) carcinoma following a caustic ingestion.

Table 373.2 Classification of Caustic Injury

GRADE	VISIBLE APPEARANCE	CLINICAL SIGNIFICANCE
Grade 0	History of ingestion but no visible damage or symptoms	Able to take fluids immediately
Grade 1	Edema, loss of normal vascular pattern, hyperemia, no transmucosal injury	Temporary dysphagia, able to swallow within 0-2 days, no long-term sequelae
Grade 2a	Transmucosal injury with friability, hemorrhage, blistering, exudate, scattered superficial ulceration	Scarring, no circumferential damage (no stenosis), no long-term sequelae
Grade 2b	Grade 2a plus discrete ulceration and/or circumferential ulceration	Small risk of perforation, scarring that may result in later stenosis
Grade 3a	Scattered deep ulceration with necrosis of the tissue	Risk of perforation, high risk of later stenosis
Grade 3b	Extensive necrotic tissue	High risk of perforation and death, high risk of stenosis

From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease,* 4th ed. Philadelphia: Saunders; 2011: Table 19.2, p. 199.

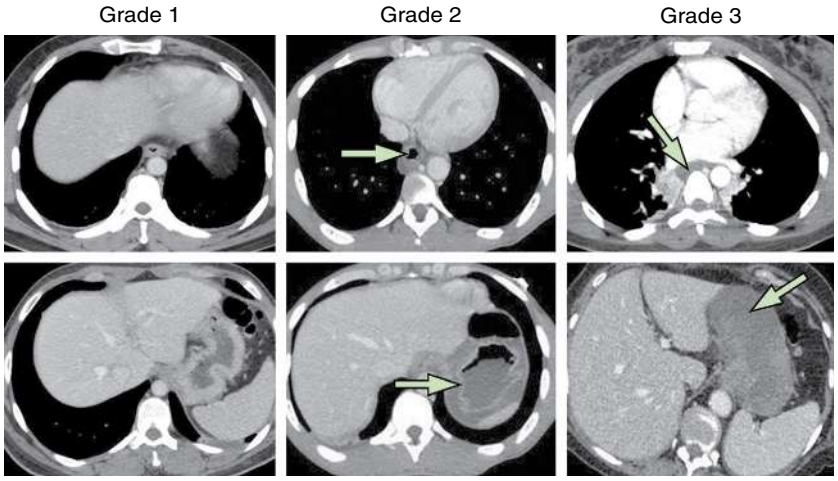

Fig. 373.5 CT grading of corrosive injuries of the esophagus and the stomach. Grade 1, normal appearance; grade 2, wall and soft tissue edema, increased wall enhancement *(arrow)*; grade 3, transmural necrosis with absent wall enhancement *(arrow)*. *(From Chirica M, Bonavina L, Kelly MD, et al. Caustic ingestion. Lancet. 2017;389:2041–2050. Fig. 1.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Stomach and Intestines

Chapter 374

Normal Development, Structure, and Function of the Stomach and Intestines

Asim Maqbool and Chris A. Liacouras

DEVELOPMENT

The primitive gut is recognizable by the fourth week of gestation and is composed of the foregut, midgut, and hindgut. The **foregut** gives rise to the upper gastrointestinal tract, which includes the esophagus, stomach, and duodenum to the level of the insertion of the common bile duct. The **midgut** gives rise to the rest of the small bowel and the large bowel to the level of the midtransverse colon. The **hindgut** forms the remainder of the colon and upper anal canal. The rapid growth of the midgut causes it to protrude out of the abdominal cavity through the umbilical ring during fetal development. The midgut subsequently returns to the peritoneal cavity and rotates counterclockwise until the cecum lies in the right lower quadrant. The process is normally complete by the eighth week of gestation.

The liver derives from the hepatic diverticulum that evolves into parenchymal cells, bile ducts, vascular structures, and hematopoietic and Kupffer cells. The extrahepatic bile ducts and gallbladder develop first as solid cords that canalize by the third month of gestation. The dorsal and ventral pancreatic buds grow from the foregut by the fourth week of gestation. The two buds fuse by the sixth week. Exocrine secretory capacity is present by the fifth month.

Cis-regulatory genomic sequences govern gene expression during development. Modules of *cis* sequences are linked and allow a cascade of gene regulation that controls functional development. Extrinsic factors have the capacity to influence gene expression. In the gut, several growth factors, including growth factor-β, insulin-like growth factor, and growth factors found in human colostrum (human growth factor and epidermal growth factor), influence gene expression.

Propulsion of food down the gastrointestinal tract relies on the coordinated action of muscles in the bowel wall. The contractions are regulated by the enteric nervous system under the influence of a variety of peptides and hormones. The enteric nervous system is derived from neural crest cells that migrate in a cranial to caudal fashion. Migration of the neural crest tissue is complete by the 24th week of gestation.

Interruption of the migration results in **Hirschsprung disease**. Newborn bowel motor patterns are different from adults. Normal fasting upper gastrointestinal motility is characterized by a triphasic pattern known as the migrating motor complex. Migrating motor complexes occur less often in neonates, and they have more nonmigrating phasic activity. This leads to ineffective propulsion, particularly in premature infants. Motility in the fed state consists of a series of ring contractions that spread caudad over variable distances.

DIGESTION AND ABSORPTION

The wall of the stomach, small bowel, and colon consists of four layers: mucosa, submucosa, muscularis, and serosa. Eighty-five percent of the gastric mucosa is lined by oxyntic glands containing cells that secrete hydrochloric acid, pepsinogen, and intrinsic factor, and mucous and endocrine cells that secrete peptides having paracrine and endocrine effects. Pepsinogen is a precursor of the proteolytic enzyme pepsin, and intrinsic factor is required for the absorption of vitamin B_{12}. Pyloric glands are located in the antrum and contain gastrin-secreting cells. Acid production and gastrin levels are inversely related to each other except in pathologic secretory states. Acid secretion is low at birth but increases dramatically by 24 hours. Acid and pepsin secretions peak in the first 10 days and decrease from 10 to 30 days after birth. Intrinsic factor secretion rises slowly in the first 2 weeks of life.

The small bowel is approximately 270 cm long at birth in a term neonate and grows to an adult length of 450-550 cm by 4 years of age. The mucosa of the small intestine is composed of villi, which are finger-like projections of the mucosa into the bowel lumen that significantly expand the absorptive surface area. The mucosal surface is further expanded by a brush border containing digestive enzymes and transport mechanisms for monosaccharides, amino acids, dipeptides and tripeptides, and fats. The cells of the villi originate in adjacent crypts and become functional as they migrate from the crypt up the villus. The small bowel mucosa is completely renewed in 4-5 days, providing a mechanism for rapid repair after injury, but in young infants or malnourished children, the process may be delayed. Crypt cells also secrete fluid and electrolytes. The villi are present by 8 weeks of gestation in the duodenum and by 11 weeks in the ileum.

Disaccharidase activities are measurable at 12 weeks, but lactase activity does not reach maximal levels until 36 weeks. Even premature infants usually tolerate lactose-containing formulas because of carbohydrate salvage by colonic bacteria. In children of African and Asian ethnicity, lactase levels may begin to fall at 4 years of age, leading to intolerance to mammalian milk. Mechanisms to digest and absorb protein, including pancreatic enzymes and mucosal mechanisms to transport amino acids, dipeptides, and tripeptides, are in place by the 20th week of gestation.

Carbohydrates, protein, and fat are normally absorbed by the upper half of the small intestine; the distal segments represent a vast reserve of absorptive capacity. Most of the sodium, potassium, chloride, and water are absorbed in the small bowel. Bile salts and vitamin B_{12} are selectively absorbed in the distal ileum, and iron is absorbed in the duodenum and proximal jejunum. Intraluminal digestion depends on the exocrine pancreas. Secretin and cholecystokinin stimulate synthesis and secretion of bicarbonate and digestive enzymes, which are released by the upper intestinal mucosa in response to various intraluminal stimuli, among them components of the diet.

Carbohydrate digestion is normally an efficient process that is completed in the distal duodenum. Starches are broken down to glucose, oligosaccharides, and disaccharides by pancreatic amylase. Residual glucose polymers are broken down at the mucosal level by glucoamylase. Lactose is broken down at the brush border by lactase, forming glucose and galactose; sucrose is broken down by sucrase-isomaltase to fructose and glucose. Galactose and glucose are primarily transported into the cell by a sodium- and energy-dependent process, whereas fructose is transported by facilitated diffusion.

Proteins are hydrolyzed by pancreatic enzymes, including trypsin, chymotrypsin, elastase, and carboxypeptidases, into individual amino acids and oligopeptides. The pancreatic enzymes are secreted as proenzymes, which are activated by release of the mucosal enzyme enterokinase. Oligopeptides are further broken down at the brush border by peptidases into dipeptides, tripeptides, and amino acids. Protein can enter the cell by separate noncompetitive carriers that can transport individual amino acids or dipeptides and tripeptides similar to those in the renal tubule. The human gut is capable of absorbing antigenic intact proteins in the first few weeks of life because of *leaky* junctions between enterocytes. Entry of potential protein antigens through the mucosal barrier might have a role in later food- and microbe-induced symptoms.

Fat absorption occurs in two phases. Dietary triglycerides are broken down into monoglycerides and free fatty acids by pancreatic lipase and colipase. The free fatty acids are subsequently emulsified by bile acids, forming micelles with phospholipids and other fat-soluble substances, and are transported to the cell membrane, where they are absorbed. The fats are reesterified in the enterocyte, forming chylomicrons that are transported through the intestinal lymphatics to the thoracic duct. Medium-chain fats are absorbed more efficiently and can directly enter the cell. They are subsequently transported to the liver via the portal system. Fat absorption can be affected at any stage of the digestion and absorption process. Decreased pancreatic enzymes occur in cystic fibrosis, cholestatic liver disease leads to poor bile salt production and micelle formation, celiac disease affects mucosal surface area, abnormal chylomicron formation occurs in abetalipoproteinemia, and intestinal lymphangiectasia affects transport of the chylomicrons.

Fat absorption is less efficient in the neonate compared with adults. Premature infants can lose up to 20% of their fat calories compared with up to 6% in the adult. Decreased synthesis of bile acids and pancreatic lipase and decreased efficiency of ileal absorption are contributing factors. Fat digestion in the neonate is facilitated by lingual and gastric lipases. Bile salt–stimulated lipase in human milk augments the action of pancreatic lipase. Infants with malabsorption of fat are usually fed with formulas that have a greater percentage of medium-chain triglycerides, which are absorbed independently of bile salts.

The colon is a 75- to 100-cm sacculated tube formed by three strips of longitudinal muscle called *taenia coli* that traverse its length and fold the mucosa into haustra. Haustra and taenia appear by the 12th week of gestation. The most common motor activity in the colon is nonpropulsive rhythmic segmentation that acts to mix the chyme and expose the contents to the colonic mucosa. Mass movement within the colon typically occurs after a meal. The colon extracts additional water and electrolytes from the luminal contents to render the stools partially or completely solid. The colon also acts to scavenge by-products of bacterial degradation of carbohydrates. Stool is stored in the rectum until distention triggers a defecation reflex that, when assisted by voluntary relaxation of the external sphincter, permits evacuation.

THE GASTROINTESTINAL MICROBIOTA

The term "microbiome" refers to organisms and their genomes/functions, whereas "microbiota" refers to the organisms themselves. The difference is very subtle, and sometimes they are used interchangeably.

The gastrointestinal microbiota composition develops early in life; it is influenced by environmental exposures, including specifically exposure to maternal flora (via vaginal delivery vs C-section), birth location (hospital vs at home, suburban vs rural), antibiotic use, and prominently are related to diet and infant feeding practices (breastfed vs formula fed, food supplementation). The richness and diversity of gastrointestinal microbiota developed early, as does gastrointestinal immunotolerance to it. Microbiota concentration and complexity increase from proximal to distal throughout the gastrointestinal tract.

This microflora has implications on human health and disease. There is a symbiotic relationship between the host of the gastrointestinal tract and the commiserate microflora. These microorganisms are involved in the fermentation of undigestible carbohydrates (in particular, fiber), resulting in short-chain fatty acids, the preferred fuel for colonic tissues. Additionally, the microbiota is involved in the metabolism of intraluminal conjugated bile acids, and the synthesis of vitamins (vitamin K), and in the degradation of other compounds. The metabolome specifically refers to the collection of metabolites that organisms produce.

The composition of the intestinal microbiota may render individuals at risk for noncommunicable diseases, including obesity. The intestinal microbiota may have implications for vaccine efficacy. Perturbations in the intestinal microbiota composition may increase risk for gastrointestinal inflammatory conditions and disorders, including inflammatory bowel disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 375

Pyloric Stenosis and Other Congenital Anomalies of the Stomach

375.1 Hypertrophic Pyloric Stenosis

Arunjot Singh and Chris A. Liacouras

Hypertrophic pyloric stenosis occurs in 2-5/1,000 infants in the United States. It is common in White people, particularly of northern European ancestry, and less frequent in Black and Asian populations. Males (especially firstborns) are affected approximately 4 times as often as females. There is a familial link with an increased risk in offspring of parent(s) with pyloric stenosis. Pyloric stenosis develops in approximately 20% of the male and 10% of the female descendants of a mother who had pyloric stenosis. Pyloric stenosis has also been associated with other congenital defects, including tracheoesophageal fistula and hypoplasia or agenesis of the inferior labial frenulum.

ETIOLOGY

The etiology of infantile hypertrophic pyloric stenosis is unknown, although many genetic and environmental factors have been implicated. Development of pyloric stenosis is likely postnatal, given that it is unusual in stillbirths. Genetic predisposition, a well-established risk of pyloric stenosis, is more concordant in monozygotic than dizygotic twins. Pyloric stenosis has been associated with eosinophilic gastroenteritis, Apert syndrome, Zellweger syndrome, trisomy 18, Smith-Lemli-Opitz syndrome, and Cornelia de Lange syndrome (Table 375.1). An association has been seen with the use of macrolide antibiotics, particularly erythromycin in neonates, if given within the first 2 weeks of life. There have also been reports of a higher incidence of pyloric stenosis among mostly female infants of mothers treated with macrolide antibiotics during pregnancy and breastfeeding. Other risk factors may include formula feeding and a maternal history of smoking during pregnancy. Abnormal muscle innervation, elevated serum levels of prostaglandins, and infant hypergastrinemia have also been implicated. Multiple genetic susceptibility loci have been identified including *IHPS* genes on chromosomes 12q, 16p13 and 11q14, and Xq23. The etiologic role of nitric oxide synthase gene *(NOS1)* is also apparent with reduced levels of neuronal nitric oxide found via altered expression of the neuronal nitric oxide synthase exon 1c regulatory region.

Table 375.1 Etiology of Gastric Outlet Obstruction

CONGENITAL
Aplasia
Atresia
Diaphragms, webs, valves
Ectopic pancreatic rests
Gastric duplication
Associated with epidermolysis bullosa
IDIOPATHIC HYPERTROPHIC PYLORIC STENOSIS
Infantile-onset pyloric stenosis
Late onset
Associated with medications: erythromycin, prostaglandin E1
ACQUIRED
Peptic ulcer disease
Caustic chemical injury
Bezoars: lacto-, phyto-, tricho-, medications
Associated with Crohn disease
Associated with chronic granulomatous disease
Associated with eosinophilic gastroenteritis
Tumor
Gastric volvulus

CLINICAL MANIFESTATIONS

Nonbilious vomiting is the initial symptom of pyloric stenosis. The vomiting may or may not be projectile initially but is usually progressive, occurring immediately after a feeding. Emesis might follow each feeding, or it may be intermittent. The vomiting usually starts after 3 weeks of age, but symptoms can develop as early as the first week of life and as late as 5 months of age. On rare occasions, late-onset pyloric stenosis may develop between 2 and 8 years of life. Approximately 20% have intermittent emesis from birth that then progresses to the classic picture. After vomiting, the infant is hungry and wants to feed again. As vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to *hypochloremic metabolic alkalosis*. Awareness of pyloric stenosis has led to earlier identification of patients with fewer instances of chronic malnutrition and severe dehydration and at times a subclinical self-resolving hypertrophy.

Hyperbilirubinemia is the most common clinical *association* of pyloric stenosis, also known as *icteropyloric syndrome*. Unconjugated hyperbilirubinemia is more common than the conjugated type and usually resolves with surgical correction of the pyloric stenosis. It may be associated with a decreased level of glucuronyl transferase as seen in approximately 5% of affected infants. Pathogenic gene variants in the bilirubin uridine diphosphate glucuronosyltransferase gene *(UGT1A1)* have also been implicated, supporting the notion that Gilbert syndrome may be linked in pathogenesis. If conjugated hyperbilirubinemia is a part of the presentation, other etiologies need to be investigated including eosinophilic gastroenteritis, hiatal hernia, peptic ulcer, congenital nephrotic syndrome, congenital heart disease, and congenital hypothyroidism.

The diagnosis has clinically been established by palpating a pyloric mass. The mass is firm, movable, approximately 2 cm in length, olive shaped, and best palpated when the patient is lying on the left side. The mass is located above and to the right of the umbilicus in the midepigastrium beneath the liver edge. The olive is easiest palpated after an episode of vomiting. After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen (Fig. 375.1). *Earlier imaging diagnosis has made the palpable olive a less common physical finding.*

Two imaging studies are used to establish the diagnosis. Ultrasound examination confirms the diagnosis in the majority of cases. Criteria for diagnosis include pyloric thickness 3-4 mm, an overall pyloric



Fig. 375.1 Gastric peristaltic wave in an infant with pyloric stenosis.

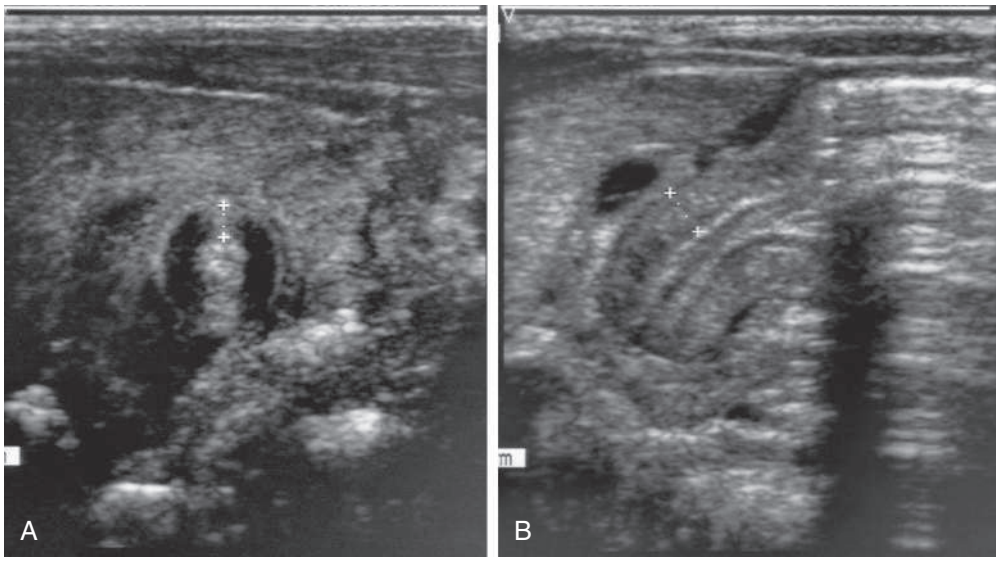

Fig. 375.2 A, Transverse sonogram demonstrating a pyloric muscle wall thickness of >4 mm (distance between *crosses*). B, Horizontal image demonstrating a pyloric channel length >14 mm (wall thickness outlined between *crosses*) in an infant with pyloric stenosis.



Fig. 375.3 Barium in the stomach of an infant with projectile vomiting. The attenuated pyloric canal is typical of congenital hypertrophic pyloric stenosis.

length 15-19 mm, and pyloric diameter of 10-14 mm (Fig. 375.2). Ultrasonography has a sensitivity of approximately 95%. Less commonly, an upper gastrointestinal (GI) contrast study is used. Contrast studies demonstrate an elongated pyloric channel (string sign), a bulge of the pyloric muscle into the antrum (shoulder sign), and parallel streaks of barium seen in the narrowed channel, producing a "double tract sign" (Fig. 375.3).

DIFFERENTIAL DIAGNOSIS

Pyloric stenosis must be differentiated from other causes that present with vomiting, irritability, and dehydration in the infant. Gastroesophageal reflux is one of the most common etiologies of vomiting. In contrast to pyloric stenosis, reflux is typically a self-limiting condition that manifests with frequent effortless regurgitation and vomiting and usually does not cause abnormal chemistries. If symptoms are significant, reflux can be differentiated from pyloric stenosis by radiographic studies. Adrenogenital syndrome can also simulate pyloric stenosis; however, abnormalities including metabolic acidosis and elevated serum potassium and urinary sodium concentrations of adrenal insufficiency aid in differentiation. Inborn errors of metabolism can also cause recurrent emesis and are manifested by alkalosis (urea cycle) or acidosis (organic acidemia) with lethargy, coma, or seizures. Metabolic disorders and adrenogenital syndrome may first be identified on the newborn screening test. Vomiting may also be a presentation of an infection such as urinary tract infection or gastroenteritis, although these are usually accompanied by fever or diarrhea. Rarely, a pyloric membrane or pyloric duplication results in projectile vomiting, visible peristalsis, and, in the case of a duplication, a palpable mass (Table 375.2). Duodenal stenosis proximal to the ampulla of Vater results in the clinical features of pyloric stenosis but can be differentiated by the presence of a pyloric mass on physical examination or ultrasonography.

TREATMENT

The treatment of pyloric stenosis requires surgery in most patients. The preoperative treatment is directed toward **correcting the fluid and electrolyte losses, as well as the acid-base disturbance**. Correction of the alkalosis is essential to prevent postoperative apnea, which may be associated with anesthesia. Most infants can be successfully rehydrated within 24 hours. Vomiting usually stops when the stomach is empty, and only an occasional infant requires nasogastric suction.

Surgical treatment of pyloric stenosis is by open or laparoscopic pyloromyotomy. This procedure is safe and cost-effective. Treatment is curative, with an operative mortality of 0–0.5%. The traditional Ramstedt procedure had been performed through a short transverse skin incision in the right upper quadrant of the abdomen followed by a longitudinal cut of the pyloric mass to the layer of the submucosa. Laparoscopic pyloromyotomy has become the procedure of choice given improved laparoscopic instrumentation and potential of shorter recovery times.

Postoperative vomiting occurs in half the infants and is thought to be secondary to edema of the pylorus at the incision site. In most infants, feedings can be initiated within 12-24 hours after surgery and advanced to maintenance oral feedings within 36-48 hours. Persistent vomiting suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction. Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.

Conservative management with nasoduodenal feedings is a rare treatment choice, advisable only in rare patients who are not good surgical candidates. Oral and intravenous atropine sulfate (pyloric muscle relaxant) has also been described when surgical expertise is

Table 375.2 Anomalies of the Stomach

ANOMALY	INCIDENCE	AGE AT PRESENTATION	SYMPTOMS AND SIGNS	TREATMENT
Gastric, antral, or pyloric atresia	3/100,000, when combined with webs	Infancy	Nonbilious emesis	Gastroduodenostomy, gastrojejunostomy
Pyloric or antral membrane (web)	As above	Any age	Failure to thrive, emesis	Incision or excision, pyloroplasty
Microgastria	Rare	Infancy	Emesis, malnutrition	Continuous-drip feedings or jejunal reservoir pouch
Gastric diverticulum	Rare	Any age	Usually asymptomatic	Usually unnecessary
Gastric duplication	Rare; male:female, 1:2	Any age	Abdominal mass, emesis, hematemesis; peritonitis if ruptured	Excision or partial gastrectomy
Gastric teratoma	Rare	Any age	Upper abdominal mass	Resection
Gastric volvulus	Rare	Any age	Emesis, refusal to feed	Reduction of volvulus, anterior gastropexy
Pyloric stenosis (infantile hypertrophic and adult forms)	United States, 3/1,000 (range, 1-8/1,000 in various regions); male:female, 4:1	Infancy	Nonbilious emesis	Pyloromyotomy
Congenital absence of the pylorus	Rare	Childhood, adulthood	Dyspepsia, if symptomatic	Usually unnecessary

Modified from Semrin MG, Russo MA. Anatomy, histology, and developmental anomalies of the stomach and duodenum. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016; Table 48.1.

not available with 80% success rate described in some studies. Because conservative management takes longer and oral feedings may not be well tolerated, worsening of the nutritional status can occur in these patients and total parenteral nutrition may be required.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

375.2 Congenital Gastric Outlet Obstruction

Arunjot Singh and Chris A. Liacouras

Gastric outlet obstruction resulting from pyloric atresia and antral webs is uncommon and accounts for <1% of all GI atresias of the alimentary tract (see Tables 375.1 and 375.2). The exact cause of the defect is unknown but is hypothesized to be secondary to incomplete recanalization of the foregut or an intrauterine vascular accident. Pyloric atresia has been associated with **epidermolysis bullosa** and usually presents in early infancy. The gender distribution is equal.

CLINICAL MANIFESTATIONS

Infants with pyloric atresia present with nonbilious vomiting, feeding difficulties, and abdominal distention during the first day of life. Low birthweight is also common. **Polyhydramnios** is a feature seen on prenatal ultrasonography in most cases. The gastric aspirate at birth is large (>20 mL fluid) and should be removed to prevent aspiration. Rupture of the stomach may occur as early as the first 12 hours of life. Infants with an antral web may present with less dramatic symptoms, depending on the degree of obstruction. Older children with antral webs present with nausea, vomiting, abdominal pain, and weight loss.

DIAGNOSIS

The diagnosis of congenital gastric outlet obstruction is suggested by the finding of a large, dilated stomach on abdominal plain radiographs or in utero ultrasonography. Upper GI contrast series is usually diagnostic and demonstrates a pyloric dimple. When contrast studies are performed, care must be taken to avoid possible aspiration. An antral web may appear as a thin septum near the pyloric channel. In older children, endoscopy has been helpful in identifying antral webs.

TREATMENT

The treatment of all causes of gastric outlet obstruction in neonates starts with the correction of dehydration and hypochloremic alkalosis. Persistent vomiting should be relieved with nasogastric decompression. Surgical or endoscopic repair is then required when the patient is medically stable.

375.3 Gastric Duplication

Arunjot Singh and Chris A. Liacouras

Gastric duplications are rare cystic or tubular malformations that usually occur within the wall of the stomach. With an incidence of 1.7 per 100,000, gastric duplications account for 2–9% of all congenital duplications in the alimentary tract. The cystic type is most common and involves the greater curvature of the stomach (see Table 375.2). Most are less than 12 cm in diameter and do not usually communicate with the stomach lumen; however, they do have a common blood supply. Associated anomalies occur in as many as 35% of patients. Several hypotheses for the etiology of gastric duplication have been developed including the splitting notochord theory, diverticulation, canalization defects, and caudal twinning.

CLINICAL MANIFESTATIONS

The most common clinical manifestations are associated with partial or complete gastric outlet obstruction. Presentation can also be complicated by intussusception, volvulus of the small bowel, and bleeding secondary to ulceration of ectopic mucosa. In 33% of patients, the duplication cyst may be palpable. Communicating duplications can cause gastric ulceration and be associated with hematemesis or melena.

DIAGNOSIS
Radiographic studies usually show a paragastric mass displacing the stomach. Ultrasound can show the inner hyperechoic mucosal and outer hypoechoic muscle layers that are typical of gastric duplications. CT and MRI are diagnostic in cases where ultrasound remains unclear, although these should be used judiciously given risk associated with radiation and sedation.

TREATMENT
Surgical treatment for symptomatic gastric duplications with complete resection of the duplication cyst is the gold standard. Avoiding incision into the gastric lumen is preferred whenever possible. Recently laparoscopic resection has shown successful outcomes. For communicating types of duplication, the marsupialization and drainage procedure may also be used.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

375.4 Gastric Volvulus
Arunjot Singh and Chris A. Liacouras

The stomach is tethered longitudinally by the gastrohepatic, gastrosplenic, and gastrocolic ligaments. In the transverse axis, it is tethered by the gastrophrenic ligament and the retroperitoneal attachment of the duodenum. A volvulus occurs when one of these attachments is absent or elongated, allowing the stomach to rotate around itself. In some children, other associated defects are present, including intestinal malrotation, diaphragmatic defects, hiatal hernia, or adjacent organ abnormalities such as asplenia. Volvulus can occur along the longitudinal axis, producing organo-axial volvulus, or along the transverse axis, producing mesentero-axial volvulus. Combined volvulus occurs if the stomach rotates around both organo-axial and mesentero-axial axes.

CLINICAL MANIFESTATIONS
Gastric volvulus in infancy is usually associated with nonbilious vomiting and abdominal distention. It has also been associated with episodes of dyspnea and apnea in this age group. Acute volvulus can advance rapidly to strangulation and perforation. Chronic gastric volvulus is more common in older children who present with a history of emesis, abdominal pain, distention, early satiety, and failure to thrive.

DIAGNOSIS
The diagnosis is suggested in plain abdominal radiographs by the presence of a dilated stomach. Erect abdominal films demonstrate a double fluid level with a characteristic "beak" near the lower esophageal junction in mesentero-axial volvulus. The stomach tends to lie in a vertical plane. In organo-axial volvulus, a single air-fluid level is seen without the characteristic beak with stomach lying in a horizontal plane. Upper GI series is the more definitive test as it reveals gastric rotation and estimates the degree of obstruction.

TREATMENT
Treatment of acute gastric volvulus requires prompt management given the increased mortality risk. Following immediate stabilization, emergent surgery via laparoscopic gastropexy is the most common surgical approach. Open thoracotomies are also a treatment modality with gastropexy, gastrostomy, and partial/total gastric resection potentially being required. Endoscopic reduction has also been reported in select cases, although gastropexy may ultimately be needed. Chronic gastric volvulus may be treated with conservative measures, including dietary modification, positioning, prokinetics, and antisecretory agents.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

375.5 Hypertrophic Gastropathy
Arunjot Singh and Chris A. Liacouras

Hypertrophic gastropathy in children is uncommon and usually a transient, benign, and self-limited condition. The mean age at diagnosis is 5 years (range: 2 days to 17 years).

PATHOGENESIS
The condition is often secondary to cytomegalovirus (CMV) infection, but other agents, including herpes simplex virus, *Giardia,* and *Helicobacter pylori* have also been implicated. The pathophysiologic mechanisms underlying the clinical picture are not completely understood but might involve widening of gap junctions between gastric epithelial cells with resultant fluid and protein losses. There is an association with increased expression of transforming growth factor-α in gastric mucosal tissue shown in CMV-induced gastropathy. *H. pylori* infection can cause the elevation of serum glucagon-like peptide-2 levels, a mucosal growth-inducing gut hormone.

CLINICAL MANIFESTATIONS
Clinical manifestations include epigastric abdominal pain, fatigue, vomiting, anorexia, and edema (protein-losing enteropathy). Other symptoms of nausea, diarrhea, and GI bleeding via hematemesis may arise due to gastric erosion or ulceration. In children, disease is typically of acute onset and spontaneously resolves within a few weeks (range: 2-14 weeks).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
Diagnostic imaging such as upper GI series and ultrasound show thickened gastric mucosa, although endoscopy and biopsy is essential for diagnosis. Endoscopy visualizes the enlargement of gastric folds and rugae typically in the fundus or body of the stomach. Histopathology shows characteristic foveolar hyperplasia, reduction in parietal cells, and hyperplasia of smooth muscle, whereas *H. pylori* staining and tissue CMV polymerase chain reaction can identify infectious etiology. The differential diagnosis includes different forms of hyperplastic and nonhyperplastic gastropathy such as Menetrier disease, Zollinger-Ellison syndrome, eosinophilic gastroenteritis, gastric lymphoma, Crohn disease, and inflammatory pseudotumor.

TREATMENT
Therapy is supportive and should include adequate hydration, antisecretory agents (H_2-receptor blockade, proton pump inhibitors), and albumin replacement if hypoalbuminemia is symptomatic. When *H. pylori* are detected, appropriate treatment is recommended. Ganciclovir in CMV-positive gastropathy is indicated only in severe cases. There are no official guidelines as far as the length of treatment. In practice, IV therapy is initiated for the first 24-48 hours. Treatment is continued with oral valganciclovir for a total of 3 weeks. Octreotide therapy has been of benefit in some case reports. Complete recovery is the rule.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 376

Intestinal Atresia, Stenosis, and Malrotation

Christina B. Bales and Chris A. Liacouras

Approximately 1 in 2,000 children is born with intestinal obstruction. Obstruction may be partial or complete, and it may be characterized as simple or strangulating. Luminal contents fail to progress in an aboral direction in simple obstruction, whereas blood flow to the intestine is also impaired in strangulating obstruction. If strangulating obstruction is not promptly relieved, it can lead to bowel infarction and perforation.

Intestinal obstruction can be further classified as either intrinsic or extrinsic based on underlying etiology. Intrinsic causes include inherent abnormalities of intestinal innervation, mucus production, or tubular anatomy. Among these, congenital disruption of the tubular structure is most common and can manifest as obliteration (atresia) or narrowing (stenosis) of the intestinal lumen. More than 90% of intestinal stenosis and atresia occurs in the duodenum, jejunum, and ileum. Rare cases occur in the colon, and these may be associated with more proximal atresias.

Extrinsic causes of congenital intestinal obstruction involve compression of the bowel by vessels (e.g., preduodenal portal vein), organs (e.g., annular pancreas), and cysts (e.g., duplication, mesenteric). Abnormalities in intestinal rotation during fetal development also represent a unique extrinsic cause of congenital intestinal obstruction. Malrotation is associated with inadequate mesenteric attachment of the intestine to the posterior abdominal wall, which leaves the bowel vulnerable to auto obstruction as a result of intestinal twisting or volvulus. Malrotation is commonly accompanied by congenital adhesions that can compress and obstruct the duodenum as they extend from the cecum to the right upper quadrant.

Obstruction is typically associated with bowel distention, which is caused by an accumulation of ingested food, gas, and intestinal secretions proximal to the point of obstruction. As the bowel dilates, absorption of intestinal fluid is decreased and secretion of fluid and electrolytes is increased. This shift results in isotonic intravascular depletion, which is usually associated with hypokalemia. Bowel distention also results in a decrease in blood flow to the obstructed bowel. As blood flow is shifted away from the intestinal mucosa, there is loss of mucosal integrity. Bacteria proliferate in the stagnant bowel, with a predominance of coliforms and anaerobes. This rapid proliferation of bacteria, coupled with the loss of mucosal integrity, allows bacteria to translocate across the bowel wall and potentially lead to endotoxemia, bacteremia, and sepsis.

The clinical presentation of intestinal obstruction varies with the cause, level of obstruction, vascular compromise, and time between the obstructing event and the patient's evaluation. Classic symptoms of obstruction in the neonate include vomiting, abdominal distention, and obstipation. Obstruction high in the intestinal tract results in large-volume, frequent, bilious emesis with little or no abdominal distention. Pain is intermittent and is usually relieved by vomiting. Obstruction in the distal small bowel leads to moderate or marked abdominal distention with emesis that is progressively feculent. Both proximal and distal obstructions are eventually associated with obstipation. However, meconium stools can be passed initially if the obstruction is in the upper part of the intestinal tract or if the obstruction developed late in intrauterine life.

The diagnosis of congenital bowel obstruction relies on a combination of history, physical examination, and radiologic findings. In certain cases, the diagnosis is suggested in the prenatal period. Routine prenatal ultrasound can detect polyhydramnios, which often accompanies high intestinal obstruction. The presence of polyhydramnios should prompt aspiration of the infant's stomach immediately after birth. Aspiration of more than 15-20 mL of fluid, particularly if it is bile stained, is highly indicative of intestinal obstruction.

In the postnatal period, a plain radiograph is the initial diagnostic study and can provide valuable information about potential associated complications. With completely obstructing lesions, plain radiographs reveal bowel distention proximal to the point of obstruction. Upright or cross-table lateral views typically demonstrate a series of air-fluid levels in the distended loops. Caution must be exercised in using plain films to determine the location of intestinal obstruction. Because colonic haustra are not fully developed in the neonate, small and large bowel obstructions may be difficult to distinguish with plain films. In these cases, contrast studies of the bowel or computed tomography images may be indicated. Oral or nasogastric contrast medium may be used to identify obstructing lesions in the proximal bowel, and contrast enemas may be used to diagnose more-distal entities. Indeed, enemas may also play a therapeutic role in relieving distal obstruction caused by meconium ileus or meconium plug syndrome.

Initial treatment of infants and children with bowel obstruction must be directed at fluid resuscitation and stabilizing the patient. Nasogastric decompression usually relieves pain and vomiting. After appropriate cultures, broad-spectrum antibiotics are usually started in ill-appearing neonates with bowel obstruction and those with suspected strangulating infarction. Patients with strangulation must have immediate surgical relief before the bowel infarcts, resulting in gangrene and intestinal perforation. Extensive intestinal necrosis results in short bowel syndrome (see Chapter 385.6). Nonoperative conservative management is usually limited to children with suspected adhesions or inflammatory strictures that might resolve with nasogastric decompression or antiinflammatory medications. If clinical signs of improvement are not evident within 12-24 hours, then operative intervention is usually indicated.

376.1 Duodenal Obstruction

Christina B. Bales and Chris A. Liacouras

Congenital duodenal obstruction occurs in 2.5-10/100,000 live births. In most cases, it is caused by atresia, an intrinsic defect of bowel formation. It can also result from extrinsic compression by abnormal neighboring structures (e.g., annular pancreas, preduodenal portal vein), duplication cysts, or congenital bands associated with malrotation. Although intrinsic and extrinsic causes of duodenal obstruction occur independently, they can also coexist. Thus a high index of suspicion for more than one underlying etiology may be critical to avoiding unnecessary reoperations in these infants.

Duodenal atresia complicates 1/5-10,000 live births and accounts for up to 60% of all intestinal atresias. In contrast to more distal atresias, which likely arise from prenatal vascular accidents, duodenal atresia results from failed recanalization of the intestinal lumen during gestation. Throughout the fourth and fifth week of normal fetal development, the duodenal mucosa exhibits rapid proliferation of epithelial cells. Persistence of these cells, which should degenerate after the seventh week of gestation, leads to occlusion of the lumen (atresia) in approximately two thirds of cases and narrowing (stenosis) in the remaining one third. Duodenal atresia can take several forms, including a thin membrane that occludes the lumen, a short fibrous cord that connects two blind duodenal pouches, or a gap that spans two nonconnecting ends of the duodenum. The membranous form is most common, and it almost invariably occurs near the ampulla of Vater. In rare cases, the membrane is distensible and is referred to as a *windsock web*. This unusual form of duodenal atresia causes obstruction several centimeters distal to the origin of the membrane.

Approximately 50% of infants with duodenal atresia are premature. Concomitant congenital anomalies are common and include congenital heart disease (30%), malrotation (10–30%), annular pancreas (30%), renal anomalies (5–15%), esophageal atresia with or without tracheoesophageal fistula (5–10%), skeletal malformations (5%), and

anorectal anomalies (5%). Of these anomalies, only complex congenital heart disease is associated with increased mortality. Annular pancreas is associated with increased late complications, including gastroesophageal reflux disease, peptic ulcer disease, pancreatitis, gastric outlet and recurrent duodenal obstruction, and gastric cancer. Thus long-term follow-up of these patients into adulthood is warranted. Nearly half of patients with duodenal atresia have chromosome abnormalities; trisomy 21 is identified in up to 40% of patients.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The hallmark of duodenal obstruction is bilious vomiting without abdominal distention, which is usually noted on the first day of life. Peristaltic waves may be visualized early in the disease process. A history of polyhydramnios is present in up to 80% of pregnancies and is caused by inadequate absorption of amniotic fluid in the distal intestine. This fluid may be bile stained because of intrauterine vomiting. Jaundice is present in one third of the infants.

The diagnosis is suggested by the presence of a *double-bubble* sign on a plain abdominal radiograph (Fig. 376.1). The appearance is caused by a distended and gas-filled stomach and proximal duodenum, which are invariably connected. Contrast studies are occasionally needed to exclude malrotation and volvulus because intestinal infarction can occur within 6-12 hours if the volvulus is not relieved. Contrast studies are generally not necessary and may be associated with aspiration. Prenatal diagnosis of duodenal atresia is readily made by fetal ultrasonography, which reveals a sonographic double-bubble. Prenatal identification of duodenal atresia is associated with decreased morbidity and fewer hospitalization days.

TREATMENT

The initial treatment of infants with duodenal atresia includes nasogastric or orogastric decompression and intravenous fluid replacement. Echocardiography, renal ultrasound, and radiology of the chest and spine should be performed to evaluate for associated anomalies. Definitive correction of the atresia is usually postponed until life-threatening anomalies are evaluated and treated.

The typical surgical repair for duodenal atresia is duodenoduodenostomy. This procedure is also preferred in cases of concomitant or isolated annular pancreas. In these instances, the duodenoduodenostomy is performed without dividing the pancreas. The dilated proximal bowel might have to be tapered to improve peristalsis. Postoperatively, a gastrostomy tube can be placed to drain the stomach and protect the airway. Intravenous nutritional support or a transanastomotic jejunal tube is needed until the infant starts to feed orally. Long-term prognosis is excellent, approaching 90% survival in most series.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

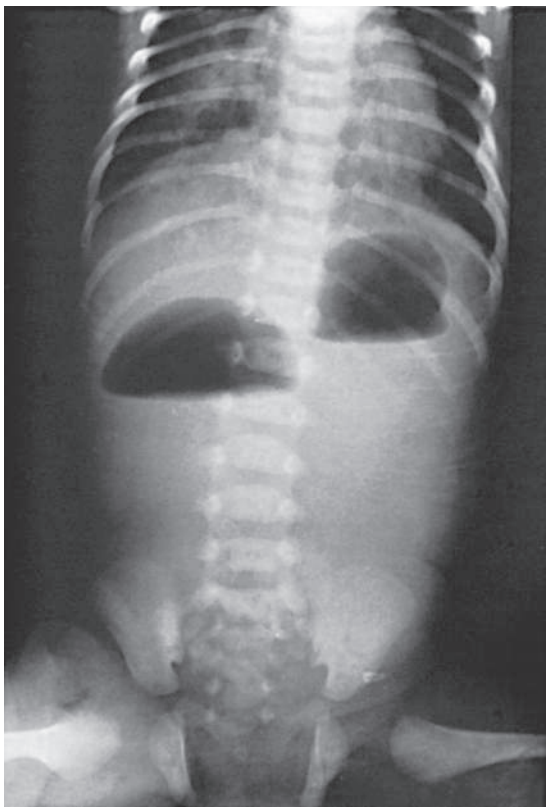

Fig. 376.1 Abdominal radiograph of a newborn infant held upright. Note the "double-bubble" gas shadow and the absence of gas in the distal bowel in this case of congenital duodenal atresia.

376.2 Jejunal and Ileal Atresia and Obstruction

Christina B. Bales and Chris A. Liacouras

The primary etiologies of congenital small bowel obstruction involve intrinsic abnormalities in anatomic development (jejunoileal stenosis and atresia), mucus secretion (meconium ileus), and bowel wall innervation (long-segment Hirschsprung disease).

Jejunoileal atresias are generally attributed to intrauterine vascular accidents, which result in segmental infarction and resorption of the fetal intestine. Underlying events that potentiate vascular compromise include intestinal volvulus, intussusception, meconium ileus, and strangulating herniation through an abdominal wall defect associated with gastroschisis or omphalocele. Maternal behaviors that promote vasoconstriction, such as cigarette smoking and cocaine use, can also have a role. Only a few cases of familial inheritance have been reported. In these families, multiple intestinal atresias have occurred in an autosomal recessive pattern. Jejunoileal atresias have been linked with multiparity, low birthweight, and prematurity. Unlike atresia in the duodenum, they are not commonly associated with extraintestinal anomalies.

Five types of jejunal and ileal atresias are encountered (Fig. 376.2), with a relatively even distribution among the five types. In type I, a mucosal web occludes the lumen, but continuity is maintained between the proximal and distal bowel. Type II involves a small-diameter solid cord that connects the proximal and distal bowel. Type III is divided into two subtypes. Type IIIa occurs when both ends of the bowel end in blind loops, accompanied by a small mesenteric defect. Type IIIb is similar, but it is associated with an extensive mesenteric defect and a loss of the normal blood supply to the distal bowel. The distal ileum coils around the ileocolic artery, from which it derives its entire blood supply, producing an "apple-peel" appearance. This anomaly is

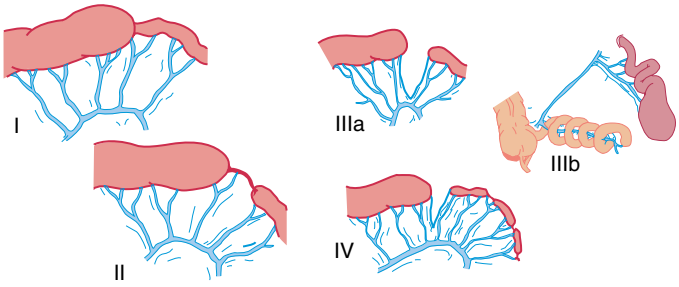

Fig. 376.2 Classification of intestinal atresia. *Type I:* Mucosal obstruction caused by an intraluminal membrane with intact bowel wall and mesentery. *Type II:* Blind ends are separated by a fibrous cord. *Type IIIa:* Blind ends are separated by a V-shaped mesenteric defect. *Type IIIb:* "Apple-peel" appearance. *Type IV:* Multiple atresias. *(From Grosfeld J. Jejunoileal atresia and stenosis. In Welch KJ, Randolph JG, Ravitch MM, eds. Pediatric Surgery, 4th ed. Chicago: Year Book Medical Publishers; 1986.)*

associated with prematurity, an unusually short distal ileum, and significant foreshortening of the bowel. Type IV involves multiple intestinal atresias. In rare cases, Type IV atresia may be associated with pathogenic variants in the *TTC7A* gene, which disrupt normal development of the thymus and intestinal epithelial lining of the intestine. This subset of patients may present with stricturing inflammatory bowel disease, severe combined immune deficiency (SCID), and associated recurrent sepsis. Thus type IV atresia uniquely warrants genetic and immunologic screening.

Meconium ileus occurs primarily in newborn infants with cystic fibrosis, an exocrine gland defect of chloride transport that results in abnormally viscous secretions (see Chapter 454). Approximately 80–90% of infants with meconium ileus have cystic fibrosis, but only 10–15% of infants with cystic fibrosis present with meconium ileus. Pathogenic variants in *GUCY2C* also produce meconium ileus. In simple cases of meconium ileus, the distal 20-30 cm of ileum is collapsed and filled with pellets of pale stool. The proximal bowel is dilated and filled with thick meconium that resembles sticky syrup or glue. Peristalsis fails to propel this viscid material forward, and it becomes impacted in the ileum. In complicated cases, a volvulus of the dilated proximal bowel can occur, resulting in intestinal ischemia, atresia, and/or perforation. Perforation in utero results in **meconium peritonitis**, which can lead to potentially obstructing adhesions and calcifications.

Both intestinal atresia and meconium ileus must be distinguished from long-segment Hirschsprung disease. This condition involves congenital absence of ganglion cells in the myenteric and submucosal plexuses of the bowel wall. In a small subset (5%) of patients, the aganglionic segment includes the terminal ileum in addition to the entire length of the colon. Infants with long-segment Hirschsprung disease present with a dilated small intestine that is ganglionated but has hypertrophied walls, a funnel-shaped transitional hypoganglionic zone, and a collapsed distal aganglionic bowel. Congenital pseudoobstruction syndromes may mimic long-segment Hirschsprung disease and other etiologies of intestinal obstruction (see Chapter 378).

CLINICAL MANIFESTATION AND DIAGNOSIS

Distal intestinal obstruction is less likely than proximal obstruction to be detected in utero. Polyhydramnios is identified in 20–35% of jejunoileal atresias, and it may be the first sign of intestinal obstruction. Abdominal distention is rarely present at birth, but it develops rapidly after initiation of feeds in the first 12-24 hours. Distention is often accompanied by vomiting, which is often bilious. Up to 80% of infants fail to pass meconium in the first 24 hours of life. Jaundice is reported in 20–30% of patients.

In patients with obstruction caused by jejunoileal atresia or long-segment Hirschsprung disease, plain radiographs typically demonstrate multiple air-fluid levels proximal to the obstruction in the upright or lateral decubitus positions (Fig. 376.3). These levels may be absent in patients with meconium ileus because the viscosity of the secretions in the proximal bowel prevents layering. Instead, a typical hazy or ground-glass appearance may be appreciated in the right lower quadrant. This haziness is caused by small bubbles of gas that become trapped in inspissated meconium in the terminal ileal region. If there is meconium peritonitis, patchy calcification may also be noted, particularly in the flanks. Plain films can reveal evidence of pneumoperitoneum due to intestinal perforation. Air may be seen in the subphrenic regions on the upright view and over the liver in the left lateral decubitus position.

Because plain radiographs do not reliably distinguish between small and large bowel in neonates, contrast studies are often required to localize the obstruction. Water-soluble enemas (Gastrografin, Hypaque) are particularly useful in differentiating atresia from meconium ileus and Hirschsprung disease. A small *microcolon* suggests disuse due to in utero obstruction proximal to the ileocecal valve. Abdominal ultrasound may be an important adjunctive study, which can help to distinguish meconium ileus from ileal atresia and identify concomitant intestinal malrotation.

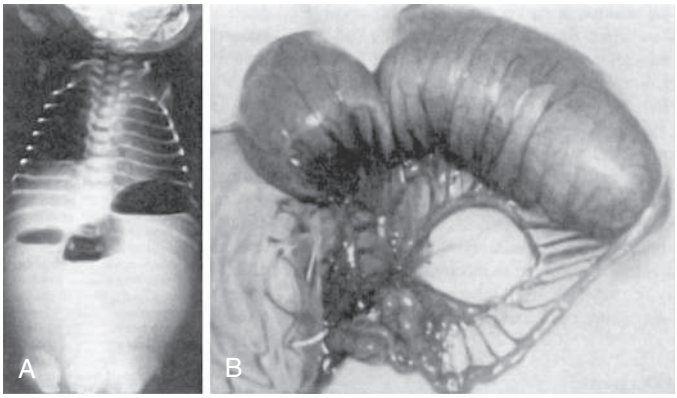

Fig. 376.3 A, Abdominal radiograph in a neonate with bilious vomiting shows a few loops of dilated intestine with air-fluid levels. B, At laparotomy, a type I (mucosal) jejunal atresia was observed. *(From O'Neill JA Jr, Grosfeld JL, Fonkalsrud EW, et al., eds. Principles of Pediatric Surgery, 2nd ed. St. Louis: Mosby; 2003: p 493.)*

TREATMENT

Patients with small bowel obstruction should be stable and in adequate fluid and electrolyte balance before operation or radiographic attempts at disimpaction unless volvulus is suspected. Documented infections should be treated with appropriate antibiotics. Prophylactic antibiotics are usually given before surgery.

Ileal or jejunal atresia requires resection of the atretic portion of the bowel followed by end-to-end anastomosis. In select cases, proximal bowel dilation necessitates initial decompressing ostomy creation and/or bowel tapering before bowel anastomosis. If a simple mucosal diaphragm is present, jejunoplasty or ileoplasty with partial excision of the web is an acceptable alternative to resection. In uncomplicated meconium ileus, Gastrografin enemas diagnose the obstruction and wash out the inspissated material. Gastrografin is hypertonic, and care must be taken to avoid dehydration, shock, and bowel perforation. The enema may have to be repeated after 8-12 hours. Resection after reduction is not needed if there have been no ischemic complications.

Approximately 50% of patients with simple meconium ileus do not adequately respond to water-soluble enemas and need laparotomy. Operative management is indicated when the obstruction cannot be relieved by repeated attempts at nonoperative management and for infants with complicated meconium ileus. The extent of surgical intervention depends on the degree of pathology. In simple meconium ileus, the plug can be relieved by manipulation or direct enteral irrigation with *N*-acetylcysteine following an enterotomy. In complicated cases, bowel resection, peritoneal lavage, abdominal drainage, and stoma formation may be necessary. Total parenteral nutrition is generally required.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

376.3 Malrotation

Christina B. Bales and Chris A. Liacouras

Disruptions in the normal sequential herniation, rotation, and fixation of the midgut during development give rise to a spectrum of rotational abnormalities. The gut starts as a straight tube from stomach to rectum. Intestinal rotation and attachment begin in the fifth week of gestation when the mid-bowel (distal duodenum to mid-transverse colon) elongates, gradually herniates through the umbilical ring, and then rotates in stages in a counterclockwise direction, using the superior mesenteric artery (SMA) as a rotational axis. As a 270-degree counterclockwise rotation is accomplished, the third portion of the duodenum passes posterior to the SMA and the duodenal-jejunal junction moves to the left upper quadrant and becomes suspended in the ligament of Treitz (LOT), while the cecum settles in the right lower quadrant. The ascending and descending colon subsequently become fixed in the right and

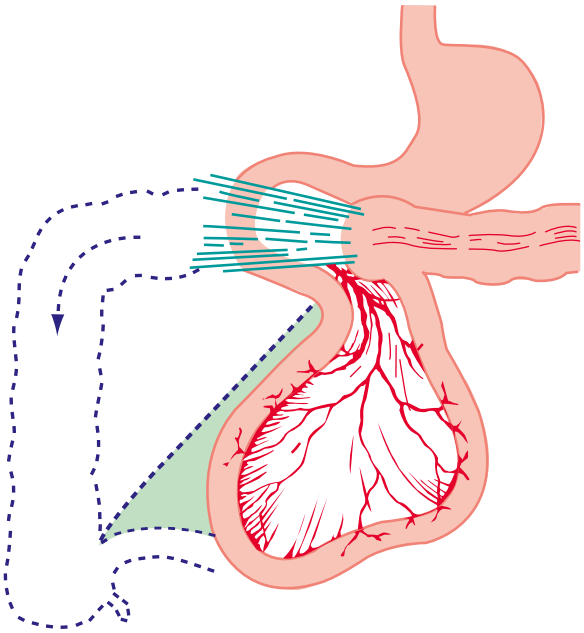

Fig. 376.4 Mechanism of intestinal obstruction with incomplete rotation of the midgut (malrotation). The *dashed lines* show the course the cecum should have taken. Failure to rotate has left obstructing bands across the duodenum and a narrow pedicle for the midgut loop, making it susceptible to volvulus. *(From Nixon HH, O'Donnell B. The Essentials of Pediatric Surgery. Philadelphia: JB Lippincott; 1961.)*

left retroperitoneum, respectively. Fixation of the bowel at the LOT and in the retroperitoneum provides a broad-based support to the mesentery, thus preventing twisting of the mesenteric root and kinking of the vascular supply. Intestinal rotation and attachment are completed by the 12th week of gestation.

Nonrotation occurs when the bowel fails to rotate after it returns to the abdominal cavity. The first and second portions of the duodenum assume their normal position, but the residual small bowel remains on the right side of the abdomen and the colon resides on the left. In contrast, typical malrotation involves failure of the cecum to fully rotate into the right lower quadrant (Fig. 376.4) and form the normal broad-based adherence to the posterior abdominal wall. As a consequence of this incomplete rotation, the mesentery, including the SMA, is tethered by a narrow stalk. This configuration leaves patients with malrotation vulnerable to midgut volvulus, a life-threatening complication that occurs when the small bowel twists around the SMA, leading to vascular compromise and ischemia of the bowel. Bowel obstruction may also be caused by congenital bands of tissue (Ladd bands), which can extend from the cecum to the right upper quadrant, compress, and possibly obstruct the duodenum.

Rotational abnormalities are commonly associated with other congenital anomalies, including intestinal atresia, Hirschsprung disease and other congenital motility disorders, diaphragmatic hernia, gastroschisis, and omphalocele. Malrotation may also be associated with heterotaxy syndrome, which is a complex of congenital anomalies including heart malformations, malrotation, biliary atresia, and asplenia or polysplenia (see Chapter 480.11).

CLINICAL MANIFESTATIONS

Symptomatic malrotation occurs in 1 in 6,000 live births, whereas asymptomatic cases may be as frequent as 1 in 200 live births. Most symptomatic patients present in the first year of life, with approximately 50% presenting in the first week and 75% in the first month of life. Symptomatic infants typically present with bilious emesis due to bowel obstruction caused by volvulus or duodenal compression by Ladd bands or other adhesive bands that constrict the small and large bowel. Infants with volvulus may experience irritability, bloody stools, and rapid clinical deterioration with signs of sepsis. Older children with midgut volvulus may manifest similar features, though symptoms may be more subtle. Sporadic colicky pain and bilious emesis due to intermittent volvulus mandates a high level of suspicion for this entity.

DIAGNOSIS

Upper GI series is considered the gold standard for diagnosis (≥93%) and reveals displacement of duodenojejunal junction (DJJ) from its normal position to the left of the spine, generally posterior and level or superior to the duodenal bulb. DJJ displacement may be appreciated in other conditions, including spleen or left kidney enlargement/tumor, gastric or colonic distention, and enteric feeding tubes. As fixation of the DJJ increases with age (>4 years), the specificity of these findings for malrotation improves. In equivocal cases, a follow-through series or contrast enema may demonstrate malposition of the cecum, though this finding may be absent in up to 20% of patients. Ultrasonography can demonstrate the inversion of the SMA and vein, with the vein located to the left rather than to the right of the artery. In cases of midgut volvulus, the upper GI series may reveal a corkscrew appearance of the small bowel or a *bird's beak* narrowing of the duodenum, consistent with obstruction, and Doppler ultrasound may show a *whirlpool* sign.

TREATMENT

Surgical intervention is recommended for any symptomatic patient with malrotation, regardless of age. Treatment of asymptomatic malrotation appreciated incidentally on imaging is more controversial, particularly in patients with congenital heterotaxy syndrome, who may be at higher risk for surgical complications. In asymptomatic patients careful assessment of imaging, supplemented in some cases by exploratory laparoscopy, guides selection for surgical intervention. Those patients who are older and have a broad-based mesentery may be appropriate for nonsurgical observation with careful parental counseling. If a volvulus is present, surgery is done immediately as an acute emergency. The volvulus is reduced, and a Ladd procedure is typically performed. In the Ladd procedure, the duodenum and upper jejunum are freed of any bands and remain in the right abdominal cavity. The colon is freed of adhesions and placed in the right abdomen with the cecum in the left lower quadrant, usually accompanied by incidental appendectomy. The Ladd procedure may be performed laparoscopically for malrotation without volvulus, but it is generally done as an open procedure if volvulus is present. The purpose of surgical intervention is to minimize the risk of subsequent volvulus rather than to return the bowel to a normal anatomic configuration. Extensive intestinal ischemia from volvulus can result in short bowel syndrome (see Chapter 385.6).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 377

Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

377.1 Intestinal Duplication

Máire A. Conrad and Chris A. Liacouras

Duplications of the intestinal tract are rare anomalies that consist of well-formed tubular or spherical structures firmly attached to the intestine with a common blood supply. The lining of the duplications resembles that of the gastrointestinal (GI) tract. Duplications are located on the mesenteric border and can communicate with the intestinal lumen. Duplications can be classified into three categories: (1) localized duplications, (2) duplications associated with spinal cord defects and vertebral malformations, and (3) duplications of the colon. Occasionally (10–15% of cases), multiple duplications are found.

Localized duplications can occur in any area of the GI tract but are most common in the ileum and jejunum. They are usually cystic or tubular structures within the wall of the bowel. The cause is unknown, but their development has been attributed to defects in recanalization of the intestinal lumen after the solid stage of embryologic development. Duplication of the intestine occurring in association with **vertebral and spinal cord anomalies** (hemivertebra, anterior spina bifida, band connection between lesion and cervical or thoracic spine) is thought to arise from splitting of the notochord in the developing embryo. **Duplication of the colon** is usually associated with anomalies of the urinary tract and genitals. Duplication of the entire colon, rectum, anus, and terminal ileum rarely occur. The defects are thought to be secondary to caudal twinning, with duplication of the hindgut, genital, and lower urinary tracts.

CLINICAL MANIFESTATIONS

Symptoms depend on the size, location, and type of mucosal lining. Duplications can cause bowel obstruction by compressing the adjacent intestinal lumen, or they can act as the lead point of an intussusception or a site for a volvulus. If they are lined by acid-secreting mucosa, they can cause ulceration, perforation, and hemorrhage of or into the adjacent bowel. Patients can present with abdominal pain, vomiting, palpable mass, or acute GI hemorrhage. Intestinal duplications in the thorax **(neuroenteric cysts)** can manifest as respiratory distress. Duplications of the lower bowel can cause constipation or diarrhea or be associated with recurrent prolapse of the rectum.

The diagnosis is suspected based on the history and physical examination. Radiologic studies such as barium studies, ultrasonography, CT, and MRI are helpful but usually nonspecific, demonstrating cystic structures or mass effects. Radioisotope technetium scanning can localize ectopic gastric mucosa. The treatment of duplications is surgical resection and management of associated defects.

377.2 Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct

Máire A. Conrad and Chris A. Liacouras

Meckel diverticulum is the most common congenital anomaly of the GI tract and is caused by the incomplete obliteration of the omphalomesenteric duct (also known as the *vitelline duct*) during the seventh week of gestation. The omphalomesenteric duct connects the yolk sac to the gut in a developing embryo and provides nutrition until the placenta is established. Between the fifth and seventh week of gestation, the duct attenuates and separates from the intestine. Just before this involution, the epithelium of the yolk sac develops a lining similar to that of the stomach. Partial or complete failure of involution of the omphalomesenteric duct results in various residual structures. Meckel diverticulum is the most common of these structures, occurring in 2–3% of all infants. A typical Meckel diverticulum is a true diverticulum containing all layers of the small intestinal wall and is a 3- to 6-cm outpouching of the ileum along the antimesenteric border 50-75 cm (approximately 2 feet) from the ileocecal valve (Fig. 377.1). The distance from the ileocecal valve depends on the age of the patient. Meckel diverticulum has been conveniently characterized by the "rule of 2s," which explains the classic presentation of this congenital anomaly. Meckel diverticula are found in approximately 2% of the general population, are usually located 2 feet proximal to the ileocecal valve, are approximately 2 inches in length, can contain two types of ectopic tissue (pancreatic or gastric), generally present before the age of 2 years, and are found twice as often in females. Although intraabdominal in location, a rare presentation of a Meckel diverticulum is entrapment in an inguinal, umbilical, or femoral hernia (known as a *Littre hernia*). Other omphalomesenteric duct remnants occur infrequently, including a persistently patent duct, a solid cord, or a cord with a central cyst or a diverticulum associated with a persistent cord between the diverticulum and the umbilicus.

CLINICAL MANIFESTATIONS

Symptoms of a Meckel diverticulum usually arise in the first or second year of life (average: 2.5 years), but initial symptoms may occur in the first decade. The majority of symptomatic Meckel diverticula are lined by an ectopic mucosa, including an acid-secreting mucosa that causes intermittent painless rectal bleeding by ulceration of the adjacent normal ileal mucosa. This ectopic mucosa is most commonly of gastric origin, but it can also be pancreatic, jejunal, or a combination of these tissues. Unlike in the duodenum, the secreted acid is not neutralized by pancreatic bicarbonate.

The stool is typically described as brick colored or currant jelly colored. Bleeding can cause significant anemia but is usually self-limited because of contraction of the splanchnic vessels, as patients become



Fig. 377.1 Typical Meckel diverticulum located on the antimesenteric border.

hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

Less often, a Meckel diverticulum is associated with partial or complete bowel obstruction. The most common mechanism of obstruction occurs when the diverticulum acts as the lead point of an intussusception. The mean age of onset of obstruction is younger than that for patients presenting with bleeding. Obstruction can also result from intraperitoneal bands connecting residual omphalomesenteric duct remnants to the ileum and umbilicus. These bands cause obstruction by internal herniation or volvulus of the small bowel around the band. A Meckel diverticulum occasionally becomes inflamed **(diverticulitis)** and manifests similarly to acute appendicitis. These children are older, with a mean of 8 years of age. Diverticulitis can lead to perforation and peritonitis.

DIAGNOSIS

The diagnosis of omphalomesenteric duct remnants depends on the clinical presentation. If an infant or child presents with significant painless rectal bleeding, the presence of a Meckel diverticulum should be suspected because Meckel diverticulum accounts for 50% of all lower GI bleeds in children younger than 2 years of age.

Confirmation of a Meckel diverticulum can be difficult. Plain abdominal radiographs are of no value, and routine barium studies rarely fill the diverticulum. The most sensitive study is a Meckel radionuclide scan, which is performed after intravenous infusion of technetium-99m pertechnetate. The mucus-secreting cells of the ectopic gastric mucosa take up pertechnetate, permitting visualization of the Meckel diverticulum (Fig. 377.2). The uptake can be enhanced with various agents, including histamine H_2-blockers such as famotidine or cimetidine, glucagon, and pentagastrin. The sensitivity of the enhanced scan is approximately 85%, with a specificity of approximately 95%. A false-negative scan may be seen in anemic patients; although false-positive results are uncommon, they have been reported with intussusception, appendicitis, duplication cysts, arteriovenous malformations, and tumors. Other methods of detection include radiolabeled tagged red blood cell scan (the patient must be actively bleeding), abdominal ultrasound, superior mesenteric angiography, abdominal CT scan, or exploratory laparoscopy. In patients with omphalomesenteric duct remnants who present with intestinal obstruction or symptoms most similar to appendicitis, the diagnosis is rarely made before surgery.

The treatment of a symptomatic Meckel diverticulum is surgical excision. A diverticulectomy can be performed safely as either a laparoscopic or open procedure. There is significant debate regarding the proper management of an asymptomatic Meckel diverticulum and whether excision versus observation is appropriate. However, the risk of serious complications does seem to exceed the operative risk in children younger than 8 years old.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

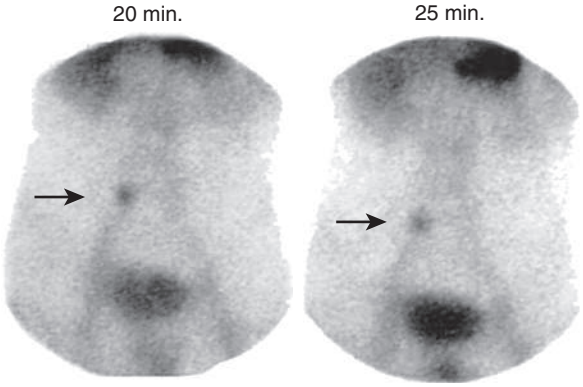

Fig. 377.2 Meckel scan demonstrating accumulation of technetium in the stomach (superior), bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum (arrows).

Chapter 378
Motility Disorders and Hirschsprung Disease

378.1 Chronic Intestinal Pseudoobstruction

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Chronic intestinal pseudoobstruction (CIPO) comprises a group of primary and secondary disorders characterized as a motility disorder with the dominant defect of impaired peristalsis; symptoms are consistent with intestinal obstruction in the absence of mechanical obstruction (Tables 378.1 and 378.2). It has been suggested that pseudoobstruction in the pediatric population should be referred to as pediatric intestinal pseudoobstruction (PIPO) as it is a distinct entity from adult CIPO (Table 378.3). The natural history of primary pseudoobstruction is that of a progressive disorder, although there are occasional cases of secondary pseudoobstruction caused by conditions that can transiently or permanently alter bowel motility. The most common cause of acute

Table 378.1 Classification of Pediatric Intestinal Pseudoobstruction

PRIMARY PIPO
- Sporadic or familial forms of myopathy and/or neuropathy and/or mesenchymopathy (abnormal ICC development) that relate to disordered development, degeneration, or inflammation. Inflammatory (including autoimmune) conditions include lymphocytic and eosinophilic ganglionitis and/or leiomyositis
- Mitochondrial neuro-gastrointestinal-encephalomyopathy (MNGIE) and other mitochondrial diseases
- Neuropathy associated with multiple endocrine neoplasia type IIB
- Hirschsprung disease, for example, total intestinal aganglionosis*
- MMIHS

SECONDARY PIPO
- Conditions affecting GI smooth muscle:
  - Rheumatologic conditions (dermatomyositis/polymyositis, scleroderma, systematic lupus erythematosus, Ehlers-Danlos syndrome)
  - Other (Duchenne muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome)
- Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, postviral-related inflammatory neuropathy, e.g., cytomegalovirus, Epstein-Barr virus, varicella zoster virus, JC virus)
- Endocrinologic disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma)
- Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium)
- Gastroschisis
- Neuropathy post neonatal necrotizing enterocolitis
- Other: celiac disease, eosinophilic gastroenteritis, Crohn disease, radiation injury, Chagas disease, Kawasaki disease, angioedema, drugs (e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants, antineoplastic agents like vinca alkaloids), paraneoplastic CIPO, major trauma/surgery, chromosome abnormalities

Idiopathic (i.e., where forms of primary or secondary PIPO classified earlier do not, as yet, have a defined etiopathogenesis)

*Needs to be excluded in all cases of PIPO

PIPO, Pediatric intestinal pseudoobstruction; ICC, interstitial cells of Cajal; GI, gastrointestinal; MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome.

From Thapar N, Saliakellis E, Benninga M, et al. Paediatric Intestinal Pseudo-obstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. *J Pediatr Gastroenterol Nutr*. 2018;66(6):991–1019. Table 3.

hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

Less often, a Meckel diverticulum is associated with partial or complete bowel obstruction. The most common mechanism of obstruction occurs when the diverticulum acts as the lead point of an intussusception. The mean age of onset of obstruction is younger than that for patients presenting with bleeding. Obstruction can also result from intraperitoneal bands connecting residual omphalomesenteric duct remnants to the ileum and umbilicus. These bands cause obstruction by internal herniation or volvulus of the small bowel around the band. A Meckel diverticulum occasionally becomes inflamed **(diverticulitis)** and manifests similarly to acute appendicitis. These children are older, with a mean of 8 years of age. Diverticulitis can lead to perforation and peritonitis.

DIAGNOSIS

The diagnosis of omphalomesenteric duct remnants depends on the clinical presentation. If an infant or child presents with significant painless rectal bleeding, the presence of a Meckel diverticulum should be suspected because Meckel diverticulum accounts for 50% of all lower GI bleeds in children younger than 2 years of age.

Confirmation of a Meckel diverticulum can be difficult. Plain abdominal radiographs are of no value, and routine barium studies rarely fill the diverticulum. The most sensitive study is a Meckel radionuclide scan, which is performed after intravenous infusion of technetium-99m pertechnetate. The mucus-secreting cells of the ectopic gastric mucosa take up pertechnetate, permitting visualization of the Meckel diverticulum (Fig. 377.2). The uptake can be enhanced with various agents, including histamine H_2-blockers such as famotidine or cimetidine, glucagon, and pentagastrin. The sensitivity of the enhanced scan is approximately 85%, with a specificity of approximately 95%. A false-negative scan may be seen in anemic patients; although false-positive results are uncommon, they have been reported with intussusception, appendicitis, duplication cysts, arteriovenous malformations, and tumors. Other methods of detection include radiolabeled tagged red blood cell scan (the patient must be actively bleeding), abdominal ultrasound, superior mesenteric angiography, abdominal CT scan, or exploratory laparoscopy. In patients with omphalomesenteric duct remnants who present with intestinal obstruction or symptoms most similar to appendicitis, the diagnosis is rarely made before surgery.

The treatment of a symptomatic Meckel diverticulum is surgical excision. A diverticulectomy can be performed safely as either a laparoscopic or open procedure. There is significant debate regarding the proper management of an asymptomatic Meckel diverticulum and whether excision versus observation is appropriate. However, the risk of serious complications does seem to exceed the operative risk in children younger than 8 years old.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

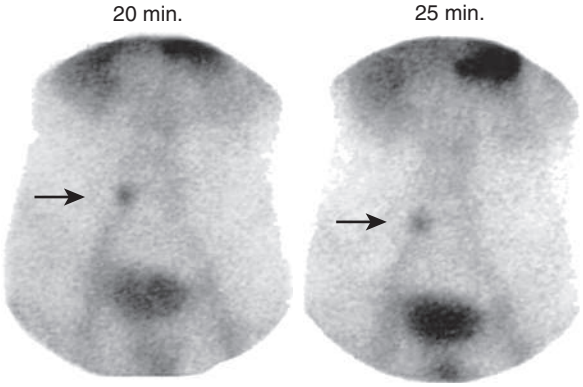

Fig. 377.2 Meckel scan demonstrating accumulation of technetium in the stomach (superior), bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum (arrows).

Chapter 378
Motility Disorders and Hirschsprung Disease

378.1 Chronic Intestinal Pseudoobstruction

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Chronic intestinal pseudoobstruction (CIPO) comprises a group of primary and secondary disorders characterized as a motility disorder with the dominant defect of impaired peristalsis; symptoms are consistent with intestinal obstruction in the absence of mechanical obstruction (Tables 378.1 and 378.2). It has been suggested that pseudoobstruction in the pediatric population should be referred to as pediatric intestinal pseudoobstruction (PIPO) as it is a distinct entity from adult CIPO (Table 378.3). The natural history of primary pseudoobstruction is that of a progressive disorder, although there are occasional cases of secondary pseudoobstruction caused by conditions that can transiently or permanently alter bowel motility. The most common cause of acute

Table 378.1 Classification of Pediatric Intestinal Pseudoobstruction

PRIMARY PIPO
- Sporadic or familial forms of myopathy and/or neuropathy and/or mesenchymopathy (abnormal ICC development) that relate to disordered development, degeneration, or inflammation. Inflammatory (including autoimmune) conditions include lymphocytic and eosinophilic ganglionitis and/or leiomyositis
- Mitochondrial neuro-gastrointestinal-encephalomyopathy (MNGIE) and other mitochondrial diseases
- Neuropathy associated with multiple endocrine neoplasia type IIB
- Hirschsprung disease, for example, total intestinal aganglionosis*
- MMIHS

SECONDARY PIPO
- Conditions affecting GI smooth muscle:
  - Rheumatologic conditions (dermatomyositis/polymyositis, scleroderma, systematic lupus erythematosus, Ehlers-Danlos syndrome)
  - Other (Duchenne muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome)
- Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, postviral-related inflammatory neuropathy, e.g., cytomegalovirus, Epstein-Barr virus, varicella zoster virus, JC virus)
- Endocrinologic disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma)
- Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium)
- Gastroschisis
- Neuropathy post neonatal necrotizing enterocolitis
- Other: celiac disease, eosinophilic gastroenteritis, Crohn disease, radiation injury, Chagas disease, Kawasaki disease, angioedema, drugs (e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants, antineoplastic agents like vinca alkaloids), paraneoplastic CIPO, major trauma/surgery, chromosome abnormalities

Idiopathic (i.e., where forms of primary or secondary PIPO classified earlier do not, as yet, have a defined etiopathogenesis)

*Needs to be excluded in all cases of PIPO

PIPO, Pediatric intestinal pseudoobstruction; ICC, interstitial cells of Cajal; GI, gastrointestinal; MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome.

From Thapar N, Saliakellis E, Benninga M, et al. Paediatric Intestinal Pseudo-obstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. *J Pediatr Gastroenterol Nutr*. 2018;66(6):991–1019. Table 3.

Table 378.2 Primary Pediatric Intestinal Pseudoobstruction with Identified Genetic Pathogenic Variants

GENE	SYNDROME	INHERITANCE	PHENOTYPE	AGE OF ONSET
Sox 10	Type IV Waardenburg syndrome	Autosomal dominant	Peripheral neuropathy with hypomyelination, sensorineural deafness and pseudoobstruction	Neonatal period
POLG1 (DNA-polymerase gamma)	Congenital myopathy and gastrointestinal pseudoobstruction	Autosomal recessive	Associated with mitochondrial depletion and deletions. Severe hypotonia and generalized muscle weakness, severe abdominal distension and hypoactive bowel	Neonatal period
FLNA (filamin A)	Chronic idiopathic intestinal pseudoobstruction (CIIPX)	X-linked recessive	Abnormal filamin A leads to cytoskeletal abnormalities and potentially disrupts enteric-neuron structure and function. Seizures and progressive abdominal distension and obstruction	Neonatal period
L1CAM (L1 cell adhesion molecule)	Hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) and congenital idiopathic intestinal pseudoobstruction	Autosomal recessive	Defect in the differentiation of the interstitial cells of Cajal leading to progressive distension and intermittent episodes of obstruction	Neonatal period
ACTG2 (enteric smooth muscle actin–gamma 2)	Familial visceral myopathy; megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal dominant, sporadic	Altered ACTG2 protein in the muscularis propria leads to impaired contractility	Neonatal to third decade in life
MYH11 (myosin heavy chain 11)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal recessive	Abnormal MYH11 in smooth muscle myosin leads to impaired contractility	Neonatal to third decade in life
MYLK (myosin light chain kinase)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal recessive	Abnormal MYLK leads to impaired smooth muscle cell contraction	Neonatal to third decade in life
LMOD1 (leiomodin 1)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Sporadic	Abnormal LMOD1 leads to impaired intestinal smooth muscle contractility	Neonatal to third decade in life
MYL9 (myosin regulatory light chain 9)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal recessive	Abnormal MYL9 leads to impaired intestinal smooth muscle contractility	Neonatal to third decade in life
RET protooncogene (receptor tyrosine kinase)	MEN2B	Autosomal dominant	Gain-in-function mutation associated with intestinal ganglioneuromas leading to increased cell number in the myenteric plexus and dysmotility	Infancy to third decade of life
TYMP (thymidine phosphorylase)	Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Autosomal recessive	Accumulation of thymidine in mitochondrial DNA leads to impaired function. Multisystem mitochondrial disease with progressive gastrointestinal dysmotility	Infancy to third decade of life
RAD21	Mungan syndrome	Autosomal recessive	Pseudoobstruction, megaduodenum, long segment Barrett esophagus and cardiac abnormalities	First to second decade of life
SGOL1	Chronic atrial and intestinal dysrhythmia (CAID)	Autosomal recessive	Accelerated cell cycle progression and enhanced activation of transforming growth factor-β signaling leading to changes in both the enteric nervous system and smooth muscle	First to fourth decade of life
ACTA2	Megacystitis-microcolon-intestinal hypoperistalsis	Autosomal dominant	Smooth muscle dysfunction, congenital mydriasis	Neonatal period

Modified from Gamboa H, Sood M. Pediatric intestinal pseudo-obstruction in the era of genetic sequencing. *Curr Gastroenterol Rep.* 2019;21:1–12. Table 1.

Table 378.3 Common and Distinctive Features of Pediatric Chronic Intestinal Pseudoobstruction

	CHILDREN	ADOLESCENTS AND YOUNG ADULTS
Etiology	Majority of cases appear to be congenital (up to 80%) and primary. Secondary forms rare (<10%)	Secondary forms (mostly to systemic disease) common and account for up to 50% of cases
Disease subtype	Neuropathies more common (~70%) with myopathic forms seen in ~30%	Predominantly neuropathies (majority inflammatory) (~45%) with myopathies accounting for (~30%)
Symptom onset	In utero, from birth or early infancy (65–80% of patients by 12 mo of age)	Median age of onset is 20-40 yr
Clinical features	Recurrent or continuous episodes of intestinal pseudoobstruction with symptoms present from birth/early life Pain infrequently seen (approximately 30%) Urologic involvement common (36–100%) Intestinal malrotation in about 30% of cases High risk of colonic and small bowel volvulus	Chronic abdominal pain and distension with superimposed acute episodes of pseudoobstruction Pain is a cardinal symptom present in at least 80% of patients Urologic involvement rare Intestinal malrotation rarely seen Low risk of colonic and small bowel volvulus
Natural history	Poor outcome predicted by myopathic forms of PIPO; urinary involvement; concurrent intestinal malrotation; and inability to tolerate enteral feeds Risk of mortality in approximately 20% of cases	Low mortality if ability to restore oral feeding and the presence of symptoms <20 yr of age High mortality if systemic sclerosis or paraneoplasia and severe/diffuse esophageal and intestinal dysmotility
Diagnostic approach	Diagnosis relies on clinical picture and radiology together with specialized tests (e.g., intestinal manometry, histopathology) Dilated bowel loops with fluid levels commonly absent (~40%) in patients presenting in the neonatal period Histopathology yield high and used to inform management, for example, use of parenteral nutrition in intestinal myopathies and prokinetics in intestinal neuropathies Apart from specific indications little yield from investigating for secondary PIPO Need to differentiate from feeding problems and fabricated or induced illness.	Diagnosis made on clinical picture and radiology with variable use of intestinal manometry On radiology defined by the presence of dilated loops of bowel with fluid levels Histopathology has a positive yield in the majority of patients but guides treatment only in minority May help support a diagnosis of secondary CIPO with other clinical findings/investigations
Nutritional therapy	Significant number (~80%) require parenteral nutrition to maintain normal growth and development. Specialized feeds (e.g., hydrolyzed protein feeds) and feeding routes (e.g., jejunal) used to promote enteral feed tolerance	Approximately 20–50% need home parenteral nutrition to prevent malnutrition
Pharmacologic therapy	Virtually no evidence base from controlled trials. Use of medication mostly anecdotal, case reports or drawn from adult literature	Few controlled trials, often small studies; few conclusions can be drawn
Surgical therapy	Venting ostomies very commonly used to decompress and reduce pseudoobstructive events; Surgery as a "bridge" to transplantation may be indicated in highly selected cases	Venting or defunctioning ostomies may help some patients. Little role for surgical resection

PIPO, Pediatric intestinal pseudoobstruction.
Modified from Thapar N, Saliakellis E, Benninga M, et al. Paediatric Intestinal Pseudo-obstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. *J Pediatr Gastroenterol Nutr.* 2018;66(6):991–1019. Table 2.

pseudoobstruction is Ogilvie syndrome (acute pseudoobstruction of the colon). Pseudoobstruction represents a wide spectrum of pathologic disorders from abnormal myoelectric activity to abnormalities of the nerves (intestinal neuropathy) or musculature (intestinal myopathy) of the gut. The organs involved can include the entire gastrointestinal tract or be limited to certain components, although almost always include the small bowel. The distinctive pathologic abnormalities are considered together because of their clinical similarities. For these reasons, CIPO may be thought of more as a clinical syndrome at times.

Most congenital forms of primary pseudoobstruction occur sporadically, although autosomal dominant *(SOX10, ACTG2, RET),* autosomal recessive *(RAD2I, SGOL1, TYMP, POLG),* X-linked *(FLNA, L1CAM),* and familial patterns of inheritance have been identified (see Table 378.2). Patients with autosomal dominant forms of pseudoobstruction have variable expressions of the disease. Patients with pathogenic variants in *TYMP* and *POLG* genes present with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is another mitochondrial disorder associated with CIPO. MNGIE is characterized by intestinal dysmotility, abdominal pain and distention, emesis, cachexia, ptosis, leukoencephalopathy, peripheral neuropathy (paresthesia, pain), and myopathy. Sixty percent have symptoms (often subtle) before age 20 years (see Chapter 378.2). Megacystis microcolon intestinal hypoperistalsis (MMIHS) syndrome includes pseudoobstruction plus bladder dysfunction and is due to pathogenic variants in *ACTG2* and other genes (Table 378.2). *Acquired* pseudoobstruction can follow episodes of acute gastroenteritis, presumably resulting in injury to the myenteric plexus.

In *congenital* pseudoobstruction, abnormalities of the muscle or nerves can be demonstrated in most cases. In myopathies, the smooth muscle is involved, in which the outer longitudinal muscle layer is replaced by fibrous material. These manifestations of visceral myopathies may be a primary or secondary phenomenon. The enteric nervous system is usually altered in neuropathies and may involve disorganized ganglia, hypoganglionosis, or hyperganglionosis. Abnormalities in the interstitial cells of Cajal, the intestinal pacemaker, are classified as mesenchymopathies. In others, mitochondrial defects have been identified.

CLINICAL MANIFESTATIONS

More than half the children with congenital pseudoobstruction experience symptoms in the neonatal period (see Table 378.3). Two thirds of the

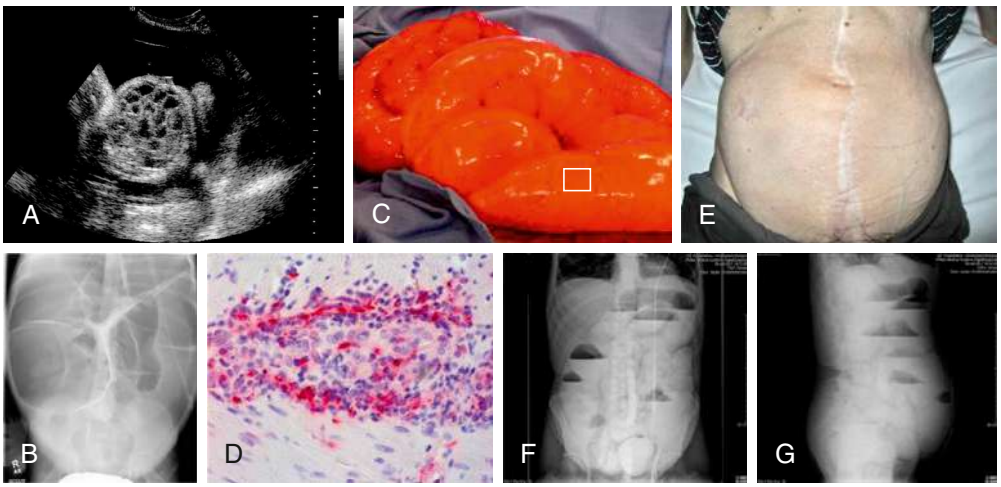

Fig. 378.1 Synoptic view of the chronic intestinal pseudoobstruction (CIPO) spectrum. **A** and **B,** The most severe pediatric cases with antenatal (in utero) evidence of multivisceral dilation, often gut (**B**) and urinary system, commonly associated with an extremely poor prognosis. **C** and **D,** CIPO phenotype with rapid progression to intestinal dilation (± ureter/bladder) and failure, often occurring as a result of an anamnestically reported gastroenteritis. Massive bowel dilation (**C**) and associated histopathology (**D;** corresponds to white squared area in **C**) revealed an intense inflammatory (mainly lymphocytic) neuropathy (hence, myenteric ganglionitis). Alkaline phosphatase anti-alkaline phosphatase immunohistochemical technique using specific anti-CD8 monoclonal antibodies was used to identify a subset of T lymphocytes. **E** and **G,** Examples of another phenotype of the syndrome that may be seen in patients who have more insidious mild and nonspecific symptoms progressing to a classic CIPO over time. **E,** Markedly distended abdomen of a 32-yr-old man who presented with subocclusive episodes after years of unspecific (dyspeptic-like/irritable bowel syndrome–like) symptoms. Note the evident air-fluid levels detectable in upright position in anteroposterior (**F**) and laterolateral (**G**) plain abdominal radiographs. *(**A** from Shen O, Schimmel MS, Eitan R, et al. Prenatal diagnosis of intestinal pseudo-obstruction. Ultrasound Obstet Gynecol. 2007;29:229–231; **B–G** from Di Nardo G, Di Lorenzo C, Lauro A, et al. Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options. Neurogastroenterol Motil. 2017;29:e12945.)*

infants presenting in the first few days of life are born prematurely, and approximately 40% have malrotation of the intestine. In 75% of all affected children, symptoms occur in the first year of life, whereas the remainder are usually symptomatic within the next several years. Females present with CIPO more than males during the first year of life, with equal sex distribution in older children. The most common symptoms are abdominal distention (85–95% of patients) and vomiting (55–90%). Constipation, growth failure, and abdominal pain occur in approximately 60% of patients and diarrhea in 25–30%. The symptoms wax and wane in most patients; poor nutrition, psychologic stress, and intercurrent illness tend to exacerbate symptoms. Urinary tract and bladder involvement occurs in 80% of children with myopathic pseudoobstruction and in 20% of those with neuropathic disease. Symptoms can manifest as recurrent urinary tract infection, megacystis, or obstructive symptoms. Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is a prenatal or neonatal manifestation of CIPO.

The clinical manifestations depend in large part on the areas of the gastrointestinal tract that are involved, with milder forms more common in older children. Although counterintuitive, older children with CIPO may present with both abdominal distention and diarrhea, related to *small bowel bacterial overgrowth* because of altered motility. Other presentations may include constipation and bilious emesis, as well as failure to thrive, as a consequence of decreased enteral feeding tolerance.

DIAGNOSIS

The diagnosis of pseudoobstruction is based on the presence of compatible symptoms in the absence of mechanical obstruction (Fig. 378.1). If CIPO is considered, diagnosis should start with exclusion of mechanical obstruction, exclusion of alternative diagnoses, and confirmation of impaired motility. Plain abdominal radiographs demonstrate air-fluid levels in the intestine. Contrast studies are integral to rule out mechanical obstruction and often demonstrate slow passage of barium; water-soluble agents should be considered. Gastric emptying scintigraphy can be used to evaluate upper GI dysmotility. Antroduodenal (small intestinal) manometry is integral to

Table 378.4 Findings in Pseudoobstruction

GI SEGMENT	FINDINGS*
Esophageal motility	Abnormalities in approximately half of CIPO, although in some series up to 85% demonstrate abnormalities Decreased LES pressure Failure of LES relaxation Esophageal body: low-amplitude waves, poor propagation, tertiary waves, retrograde peristalsis, occasionally aperistalsis
Gastric emptying	May be delayed
EGG	Tachygastria or bradygastria may be seen
ADM	Postprandial antral hypomotility is seen and correlates with delayed gastric emptying Myopathic subtype: low-amplitude contractions, <10-20 mm Hg Neuropathic subtype: contractions are uncoordinated, disorganized Absence of fed response Fasting MMC is absent, or MMC is abnormally propagated
Colonic	Absence of gastrocolic reflex because there is no increased motility in response to a meal
ARM	Normal rectoanal inhibitory reflex

*Findings can vary according to the segment(s) of the GI tract that are involved.
ADM, Antroduodenal manometry; ARM, anorectal manometry; CIPO, chronic intestinal pseudoobstruction; EGG, electrogastrography; GI, gastrointestinal; LES, lower esophageal sphincter; MMC, migrating motor complex.
From Steffen R: Gastrointestinal motility. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease,* 3rd ed. Philadelphia: WB Saunders; 2006: p 66.

diagnosis with a normal study conclusively ruling out a diagnosis of CIPO (Table 378.4). Manometric evidence of a normal migrating motor complex and postprandial activity should redirect the diagnostic evaluation. CIPO due to an intestinal myopathy may demonstrate manometry evidence of low-amplitude contractions, whereas CIPO due to enteric neuropathy demonstrates normal amplitude but poorly organized contractions (nonperistaltic or tonic). Anorectal motility is normal and differentiates pseudoobstruction from Hirschsprung disease. Full-thickness intestinal biopsy might show involvement of the muscle layers or abnormalities of the intrinsic intestinal nervous system. *Gene panels or whole exome sequencing helps define the genetic etiology of CIPO.*

The differential diagnosis is broad and includes such etiologies as Hirschsprung disease, MNGIE, mechanical obstruction, psychogenic constipation, neurogenic bladder, and superior mesenteric artery syndrome. Secondary causes of ileus or pseudoobstruction that should be considered include medication side effects, infectious etiologies, metabolic disturbances, immunologic disorders, oncologic processes, vasculitides, neuropathies, and myopathies (see Table 378.1). Examples include use of opiates, hypokalemia, hypothyroidism, hypokalemia, diabetic neuropathy, porphyria, amyloidosis, Chagas disease, scleroderma, hereditary angioedema, mitochondrial disorders, and radiation, and these must be excluded. Other causes of abdominal distention such as small bowel bacterial overgrowth and aerophagia may present similarly and should be considered. *Small bowel bacterial overgrowth is a complication of CIPO.*

TREATMENT

Nutritional support is the mainstay of treatment for pseudoobstruction. Thirty to 50% of patients require partial or complete parenteral nutrition. Some patients can be treated with intermittent enteral supplementation, whereas others can maintain themselves on selective oral diets. Prokinetic drugs are generally used, although studies have not shown definitive evidence of their efficacy. Isolated gastroparesis can follow episodes of viral gastroenteritis and spontaneously resolves, usually in 6-24 months. Erythromycin, a motilin receptor agonist, and cisapride, a serotonin 5-HT_4 receptor agonist, may enhance gastric emptying and proximal small bowel motility and may be useful in this select group of patients. Metoclopramide, a prokinetic and antinausea agent, is effective in gastroparesis, although side effects, such as tardive dyskinesia, limit its use. Domperidone, an antidopaminergic agent, is a prokinetic agent that can be considered. Pain management is difficult and requires a multidisciplinary approach. Intravenous immunoglobulin (IVIG) may be beneficial in immune mediated CIPO.

Symptomatic small bowel bacterial overgrowth is usually treated with rotated nonabsorbable oral antibiotics and/or probiotics. Bacterial overgrowth can be associated with steatorrhea and malabsorption. Octreotide, a long-acting somatostatin analog, has been used in low doses to treat small bowel bacterial overgrowth. Patients with acid peptic symptoms are generally treated with acid suppression. Many patients with CIPO benefit from a gastrostomy for decompression, and some benefit from decompressive enterostomies (Fig. 378.2). Colectomy with ileorectal anastomosis is beneficial if the large bowel is the primary site of the motility abnormality. Bowel transplantation may benefit selected patients with CIPO. The prognosis is better for patients without urinary tract involvement and for those with neuropathic etiologies over myopathic disorders.



Fig. 378.2 Photograph of a child with chronic intestinal pseudoobstruction who improved clinically after ileostomy creation. He receives enteral feeding through his jejunal feeding tube, whereas his gastrostomy tube remains to straight drain. *(From Bitton S, Markowitz JF. Ulcerative colitis in children and adolescents. In: Wyllie R, Hyams JS, Kay M, eds. Pediatric Gastrointestinal and Liver Disease, 5th ed. Philadelphia: Elsevier; 2016: Fig. 44.3.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

378.2 Mitochondrial Neurogastrointestinal Encephalomyopathy

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a multisystem autosomal recessive disease that initially presents with severe gastrointestinal disturbances; the neurologic manifestations usually occur later in the illness and may initially be subtle or asymptomatic.

MNGIE is caused by a pathogenic variant in the nuclear DNA *TYMP* gene encoding thymidine phosphorylase that results in abnormalities in intergenomic communication with resulting instability of mitochondrial DNA (some patients have pathogenic variants in *POLG1*). There are at least 50 individual variants with a poor genotype-phenotype correlation and varying manifestations within each family. Consanguinity is present in 30% of families.

MNGIE affects both males and females and is usually diagnosed in the second and third decade (average age: 18 years; range: 5 months to 35 years). Onset is usually around age 12 years, but there is often a 5- to 10-year delay in the diagnosis. The disease is progressive with an overall survival of <5% after 50 years of age.

MNGIE *initially* presents with gastrointestinal symptoms. Severe intestinal dysmotility and gastroparesis are associated with early satiety, postprandial emesis, episodic pseudoobstruction, diarrhea, constipation, and abdominal pain and cramping, which leads to significant cachexia. Because of the age of onset, emesis, early satiety, and cachexia

patients are often misdiagnosed with an eating disorder. Radiologic studies may find small bowel diverticulosis or GI dilation.

Most often, neurologic symptoms follow the onset of gastrointestinal manifestations, which include ptosis, progressive external ophthalmoplegia, hearing loss, myopathy, and peripheral neuropathy. The neuropathy is either demyelinating or a mixed axonal demyelinating type and manifests as weakness, decreased or absent deep tendon reflexes, and paresthesias. Leukoencephalopathy is initially asymptomatic and noted on MRI as patchy lesions predominantly in the cortex but also in the basal ganglia and brainstem. Eventually the central nervous system lesions become diffuse and confluent. A small number of patients develop cognitive impairment or dementia.

The diagnosis is suggested by the constellation of gastrointestinal and neurologic symptoms, lactic acidosis, ragged red fibers, and cytochrome C oxidase–deficient fibers seen in most patients on muscle biopsy. Reduced activity of thymidine phosphorylase enzyme and elevated plasma levels of thymidine and deoxyuridine are often diagnostic; genetic testing for the *TYMP* pathogenic variant or other genes *(POLG1)* is recommended.

Treatment is focused on providing sufficient nutritional support and avoidance of infectious complications and of nutritional deficiencies. Hemodialysis, continuous ambulatory peritoneal dialysis, and platelet infusions have been effective in achieving temporary improvement and can be used while waiting for a permanent treatment option or as compassionate care. Domperidone has been used for nausea and emesis, antibiotics for small bowel bacterial overgrowth, amitriptyline or gabapentin for neuropathic pain, and parenteral alimentation for nutritional support. Opiates and any medications that affect intestinal motility or mitochondrial function must be avoided. Stem cell transplantation and liver transplantation have been successful in a small number of patients, although they are limited by posttreatment mortality rates.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

378.3 Encopresis and Functional Constipation

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Constipation is defined as a delay or difficulty in defecation present for >1 month and significant enough to cause distress to the patient. Another approach to the definition is the Rome criteria, outlined in Tables 378.5 and 378.6. Functional constipation, also known as idiopathic constipation or fecal withholding, can usually be differentiated from constipation secondary to organic causes based on a history and physical examination. Unlike anorectal malformations and Hirschsprung disease, functional constipation typically starts *after* the neonatal period. Usually there is an intentional or subconscious withholding of stool. An acute episode usually precedes the chronic course. This acute event could include changes in diet such as transition to formula or addition of pureed/solid foods and can also include a social stressor such as initiation of toilet training, birth of a sibling, starting daycare/school, or abuse. The stool becomes firm, smaller, and difficult to pass, resulting in anal irritation and often an anal fissure. In toddlers, coercive or inappropriately early toilet training is a factor that can initiate a pattern of stool retention. In older children, retentive constipation can develop after entering a situation that makes stooling inconvenient, such as school. Because the passage of bowel movements is painful, voluntary or subconscious withholding of feces to avoid the painful stimulus develops.

CLINICAL MANIFESTATIONS

When children have the urge to defecate, typical behaviors include contracting the gluteal muscles by stiffening the legs while lying down,

Table 378.5 Rome IV Diagnostic Criteria for Defecatory Disorders in Neonates and Toddlers

FGID	AGE RANGE	CRITERIA REQUIREMENTS	CRITERIA ELEMENTS
Functional constipation	All pediatric age groups	Must include 1 month of ≥2 of the criteria elements in infants up to 4 mo of age	• 2 or fewer defecations weekly • History of excessive stool retention • History of hard/painful bowel movements • History of large-diameter stools • Presence of a large fecal mass in the rectum
		In toilet-trained children, the following additional criteria elements may be used	• At least 1 weekly episode of incontinence after being toilet trained • History of large-diameter stools that may clog the toilet

FGID, Functional gastrointestinal disorders.
Modified from Benninga MA, Faure C, Hyman PE, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150:1443–1455.

Table 378.6 Rome IV Diagnostic Criteria for Defecatory Disorders in Children and Adolescents

	AGE RANGE	CRITERIA REQUIREMENTS	CRITERIA ELEMENTS
Functional constipation	Developmental age ≥4 yr	Must include ≥2 of the criteria elements for ≥2 months with insufficient criteria to diagnose irritable bowel syndrome	• ≤2 defecations in the toilet per week • ≥1 episode of fecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of large-diameter stools that can obstruct the toilet
Nonretentive fecal Incontinence	Developmental age ≥4 yr	History of symptoms (criteria elements) for ≥1 month	• Defecation into places inappropriate to the sociocultural context • No evidence of fecal retention • After appropriate evaluation, symptoms cannot be fully explained by another medical condition

Modified from Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150:1456–1468.

holding onto furniture while standing, or squatting quietly in corners, waiting for the urge to stool to pass. The urge to defecate passes as the rectum accommodates to its contents. A vicious cycle of retention develops, as increasingly larger volumes of stool need to be expelled. Caregivers may misinterpret these withholding behaviors as straining or pain. There is often a history of blood in the stool noted with the passage of a large bowel movement. Findings suggestive of underlying pathology include failure to thrive, weight loss, abdominal pain, significant abdominal distention, vomiting, or persistent anal fissure or fistula.

In functional constipation, encopresis is common. **Encopresis** is defined as voluntary or involuntary passage of feces into inappropriate places at least once a month for 3 consecutive months once a chronological or developmental age of 4 year has been reached. Encopresis is not diagnosed when the behavior is exclusively the result of the direct effects of a substance (e.g., laxatives) or a general medical condition (except through a mechanism involving constipation). Subtypes include retentive encopresis (with constipation and overflow incontinence), representing 65–95% of cases, and nonretentive encopresis (without constipation and overflow incontinence). **Nonretentive fecal incontinence** is defined as no evidence of fecal retention (impaction), ≥1 episodes per week in the previous 1 month, or defecation in places inappropriate to the social context in a child who has been previously toilet trained and without evidence of anatomic, inflammatory, metabolic, endocrine, or neoplastic process that could explain the symptoms. Encopresis can persist from infancy onward (primary) or can appear after successful toilet training (secondary). The updated Rome criteria (IV) differentiate between infants/toddlers and older children who have been toilet trained versus not toilet trained, for practical assessment purposes.

DIAGNOSIS

The physical examination often demonstrates a large volume of stool palpated in the suprapubic area; rectal examination demonstrates a dilated rectal vault filled with guaiac-negative stool. Children with encopresis often present with reports of underwear soiling, and many parents initially presume that diarrhea, rather than constipation, is the cause. In **retentive encopresis**, associated complaints of difficulty with defecation, abdominal or rectal pain, impaired appetite with poor growth, and urinary (day and/or night) incontinence are common. Children often have large bowel movements that obstruct the toilet. There may also be retentive posturing or recurrent urinary tract infections. **Nonretentive encopresis** is more likely to occur as a solitary symptom and have an associated primary underlying psychologic etiology. Children with encopresis can present with poor school performance and attendance that is triggered by the scorn and derision from schoolmates because of the child's offensive odor.

The location of the anus relative to perineal anatomic landmarks by sex also needs to be considered. This is expressed as the **anogenital index**, and it can be calculated when necessary. This is determined by the distance in centimeters from the vagina or scrotum to the anus, divided by the distance from the vagina or scrotum to the coccyx. The normal anogenital index in females is 0.39 ± 0.09, whereas 0.56 ± 0.2 is normal for males.

The presence of a hair tuft over the spine or spinal dimple, or failure to elicit a cremasteric reflex or anal wink suggests spinal pathology. A tethered cord is suggested by decreased or absent lower leg reflexes. **Spinal cord lesions** can occur with overlying skin anomalies. Urinary tract symptoms include recurrent urinary tract infection and enuresis. Children with no evidence of abnormalities on physical examination rarely require radiologic evaluation.

In refractory patients (intractable constipation), specialized testing should be considered to rule out conditions such as hypothyroidism, hypocalcemia, lead toxicity, celiac disease, and disorders of neuromuscular gastrointestinal pathology (Table 378.7). Colonic transit studies using radiopaque markers or scintigraphy techniques may be useful. Selected children can benefit from MRI of the spine to identify an intraspinal process, motility studies to identify underlying myopathic or neuropathic bowel abnormalities, or a contrast enema to identify structural abnormalities. In patients with severe functional constipation, water-soluble contrast enema reveals the presence of a mega rectosigmoid (Fig. 378.3). Anorectal motility studies can demonstrate a pattern of paradoxical contraction of the external anal sphincter during defecation, which can be treated by behavior modification, biofeedback, and pelvic floor physical therapy. Colonic motility can guide therapy in refractory cases, demonstrating segmental problems that might require surgical intervention.

Table 378.7 London Classification of Gastrointestinal Neuromuscular Pathology

1. Neuropathies
   - 1.1 Absent neurons
     - 1.1.1 Aganglionosis*
   - 1.2 Decreased numbers of neurons
     - 1.2.1 Hypoganglionosis
   - 1.3 Increased numbers of neurons
     - 1.3.1 Ganglioneuromatosis†
     - 1.3.2 IND, type B‡
   - 1.4 Degenerative neuropathy§
   - 1.5 Inflammatory neuropathies
     - 1.5.1 Lymphocytic ganglionitis¶
     - 1.5.2 Eosinophilic ganglionitis
   - 1.6 Abnormal content in neurons
     - 1.6.1 Intraneuronal nuclear inclusions
     - 1.6.2 Megamitochondria
   - 1.7 Abnormal neurochemical coding**
   - 1.8 Relative immaturity of neurons
   - 1.9 Abnormal enteric glia
     - 1.9.1 Increased numbers of enteric glia
2. Myopathies
   - 2.1 Muscularis propria malformations††
   - 2.2 Muscle cell degeneration
     - 2.2.1 Degenerative leiomyopathy/‡‡
     - 2.2.2 Inflammatory leiomyopathy
       - 2.2.2.1 Lymphocytic leiomyositis
       - 2.2.2.2 Eosinophilic leiomyositis
   - 2.3 Muscle hyperplasia/hypertrophy
     - 2.3.1 Muscularis mucosae hyperplasia
   - 2.4 Abnormal content in myocytes
     - 2.4.1 Filament protein abnormalities
       - 2.4.1.1 Alpha-actin myopathy§§
       - 2.4.1.2 Desmin myopathy
     - 2.4.2 Inclusion bodies
       - 2.4.2.1 Polyglucosan bodies
       - 2.4.2.2 Amphophilic
       - 2.4.2.3 Megamitochondria¶¶
   - 2.5 Abnormal supportive tissue
     - 2.5.1 Atrophic desmosis***
3. ICC abnormalities (enteric mesenchymopathy)
   - 3.1 Abnormal ICC networks†††

*Can include rare cases of non-Hirschsprung disease severe hypoplastic hypoganglionosis with long interganglionic intervals (zonal aganglionosis).
†Although neurons have not been formally quantified, gross increases of disorganized neurons are evident.
‡Can include retarded neuronal maturation.
§May occur with or without neuronal loss but is best regarded as a separate entity.
¶May occur with neuronal degeneration and/or loss; lymphocytic epithelioganglionitis is a variant.
**Includes neurotransmitter loss (e.g., reduced or absent expression) or loss of a neurochemically defined functional subset of nerves (see text).
††Includes absence, fusion, or additional muscle coats.
‡‡Hollow visceral myopathy may be diagnosed in familial cases with other characteristic phenotypic features; myopathy with autophagic activity and pink blush myopathy with nuclear crowding are rare variants in which degenerative findings are less overt.
§§Smooth muscle alpha-actin deficiency is best described, although deficiencies of other proteins related to the contractile apparatus of myocytes have been reported.
¶¶Mitochondrial neurogastrointestinal encephalomyopathy causes a degenerative appearance predominantly in the longitudinal muscle.
***Absent connective tissue scaffold has been almost exclusively described in the colon.
†††Generally reduced or absent ICC, although abnormal morphology also reported.
ICC, Interstitial cells of Cajal; IND, intestinal neuronal dysplasia.
From Knowles CH, De Giorgio R, Kapur RP, et al. The London classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group. *Gut.* 2010;59:882–887. Table 1.

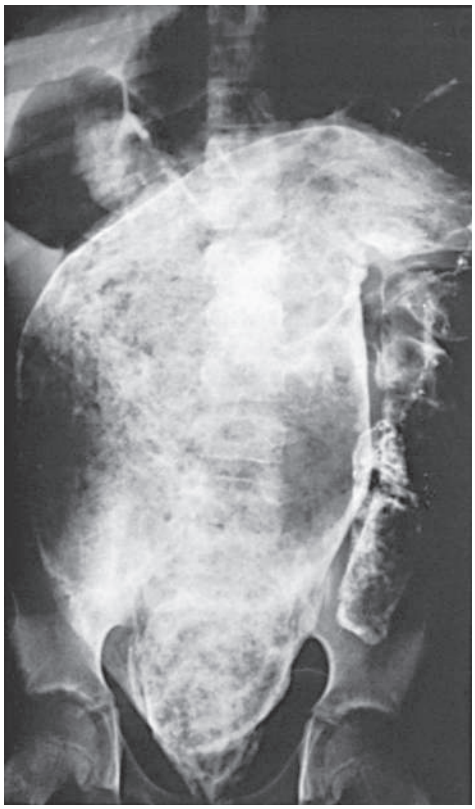

Fig. 378.3 Barium enema in a 14-yr-old boy with severe constipation. The enormous dilation of the rectum and distal colon is typical of acquired functional megacolon.

Complications of retentive encopresis include day and night urinary incontinence, urinary retention, urinary tract infection, megacystis, and rarely toxic megacolon.

TREATMENT

Therapy for functional constipation and encopresis includes patient education, behavioral interventions, relief of impaction, and softening of the stool. Caregivers must understand that soiling associated with overflow incontinence is associated with loss of normal sensation and not a willful act. There needs to be a focus on adherence with regular postprandial toilet sitting and adoption of a balanced diet. In addition, caregivers should be instructed not to respond to soiling with retaliatory or punitive measures, because children are likely to become angry, ashamed, and resistant to intervention. From the outset, parents should be actively encouraged to reward the child for adherence to a healthy bowel regimen and to avoid power struggles.

If an impaction is present on the initial physical examination, an enema is usually required to clear the impaction while stool softeners are started as maintenance medications. Typical regimens include the use of polyethylene glycol preparations, lactulose, magnesium, or mineral oil (Tables 378.8 and 378.9). Stimulant laxatives such as senna and bisacodyl can also be helpful.

Compliance can wane, and failure of this standard treatment approach sometimes requires more intensive intervention. In cases where behavioral or psychiatric problems are evident, involvement of a psychologist or behavioral management (e.g., behavior programs and/or biofeedback) is recommended. Maintenance therapy is generally continued until a regular bowel pattern has been established and the association of pain with the passage of stool is abolished.

For children with chronic diarrhea and/or irritable bowel syndrome where stress and anxiety play a major role, stress reduction and learning effective coping strategies can play an important role in responding to the encopresis. Relaxation training, stress inoculation, assertiveness training, and/or general stress management procedures can be helpful, and the participation of behavioral health specialists is valuable.

Neurostimulation (transcutaneous or sacral implantation) and pelvic physiotherapy are novel approaches used in patients with medication refractory constipation. Surgical interventions such as rectal Botox, cecostomy, and colostomy may be considered for severe cases.

Table 378.8 Suggested Medications and Dosages for Disimpaction

MEDICATION	AGE	DOSAGE
RAPID RECTAL DISIMPACTION		
Glycerin suppositories	Infants and toddlers	
Phosphate enema	6 mo-2 yr	66 mL
	≥3 yr	133 mL
SLOW ORAL DISIMPACTION IN OLDER CHILDREN		
Over 2-3 Days		
Polyethylene glycol with electrolytes		25 mL/kg body weight/hr, up to 1,000 mL/hr until clear fluid comes from the anus
Over 5-7 Days		
Polyethylene without electrolytes		1.5 g/kg body weight/day for 3 days
Milk of magnesia		2 mL/kg body weight twice/day for 7 days
Mineral oil		3 mL/kg body weight twice/day for 7 days
Lactulose or sorbitol		2 mL/kg body weight twice/day for 7 days

From Loening-Baucke V. Functional constipation with encopresis. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: WB Saunders; 2006: p 183.

Table 378.9 Suggested Medications and Dosages for Maintenance Therapy of Constipation

MEDICATION	AGE	DOSE
TYPICAL DOSES FOR LONG-TERM TREATMENT (YR)		
Milk of magnesia	>1 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Mineral oil	>12 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Lactulose or sorbitol	>1 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Polyethylene glycol 3350 (MiraLAX)	>1 yr	0.7 g/kg body weight/day
FOR SHORT-TERM TREATMENT (MO)		
Senna (Senokot) syrup, tablets	1-5 yr	5 mL (1 tablet) with breakfast, max 15 mL daily
	5-15 yr	2 tablets with breakfast, maximum 3 tablets daily

From Loening-Baucke V. Functional constipation with encopresis. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: WB Saunders; 2006: p 185.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

378.4 Congenital Aganglionic Megacolon (Hirschsprung Disease)

Prasanna K. Kapavarapu, Kristin N. Fiorino, and Chris A. Liacouras

Hirschsprung disease, or congenital aganglionic megacolon, is a developmental disorder (neurocristopathy) of the enteric nervous system, characterized by the absence of ganglion cells in the submucosal and myenteric plexus. It is the most common cause of lower intestinal obstruction in neonates, with an overall incidence of 1 in 5,000 live births. The male:female ratio for Hirschsprung disease is 4:1 for short-segment disease and approximately 2:1 with total colonic aganglionosis. Prematurity is uncommon.

There is an increased familial incidence in long-segment disease. Hirschsprung disease may be associated with other congenital defects, including trisomy 21, Joubert syndrome, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, Shah-Waardenburg syndrome, cartilage-hair hypoplasia, multiple endocrine neoplasm 2 syndrome, neurofibromatosis, neuroblastoma, congenital hypoventilation (Ondine's curse), and urogenital or cardiovascular abnormalities. Hirschsprung disease has been seen in association with microcephaly, intellectual disability, abnormal facies, autism, cleft palate, hydrocephalus, and micrognathia.

PATHOLOGY

Hirschsprung disease is the result of an absence of ganglion cells in the bowel wall, extending proximally from the anus for a variable distance. The absence of neural innervation is a consequence of an arrest of neuroblast migration from the proximal to distal bowel. Without the myenteric and submucosal plexus, there is inadequate relaxation of the bowel wall and bowel wall hypertonicity, which can lead to intestinal obstruction.

Hirschsprung disease is usually sporadic, although dominant and recessive patterns of inheritance have been demonstrated in family groups. Genetic variants have been identified in multiple genes that encode proteins of the RET signaling pathway (*RET, GDNF, NTN, ARTN,* and *PSPN*) and involved in the endothelin (EDN) type B receptor pathway (*EDNRB, EDN3,* and *ECE-1*). **Syndromic forms** of Hirschsprung disease have been associated with the *L1CAM, SOX10, PHOX2B, KIAA1279,* and *ZFHX1B* (formerly *SIP1*) genes.

The aganglionic segment is limited to the rectosigmoid in 80% of patients. Approximately 10–15% of patients have long-segment disease, defined as disease proximal to the sigmoid colon. Total bowel aganglionosis is rare and accounts for approximately 5% of cases. Observed histologically is an absence of Meissner's and Auerbach's plexuses and hypertrophied nerve bundles with high concentrations of acetylcholinesterase between the muscular layers and in the submucosa.

CLINICAL MANIFESTATIONS

Hirschsprung disease is usually diagnosed in the neonatal period secondary to a distended abdomen, failure to pass meconium, and/or bilious emesis or aspirates with feeding intolerance. In 99% of healthy full-term infants, meconium is passed within 48 hours of birth. Hirschsprung disease should be suspected in any full-term infant (the disease is unusual in preterm infants) with delayed passage of stool. Some neonates pass meconium normally but subsequently present with a history of chronic constipation. Failure to thrive with hypoproteinemia from protein-losing enteropathy is a less common presentation because Hirschsprung disease is usually recognized early in the course of the illness but has been known to occur. Breastfed infants might not present as severely as formula-fed infants.

Failure to pass stool leads to dilation of the proximal bowel and abdominal distention. As the bowel dilates, intraluminal pressure increases, resulting in decreased blood flow and deterioration of the mucosal barrier. Stasis allows proliferation of bacteria, which can lead to **enterocolitis** (*Clostridium difficile, Staphylococcus aureus,* anaerobes, coliforms) with associated diarrhea, abdominal tenderness, sepsis, and signs of bowel obstruction. *Red flags* in the neonatal period then include neonatal intestinal obstruction, bowel perforation, delayed passage of meconium, abdominal distention relieved by digital rectal stimulation or enemas, chronic severe constipation, and enterocolitis. Early recognition of Hirschsprung disease before the onset of enterocolitis is essential in reducing morbidity and mortality.

Hirschsprung disease in older patients must be distinguished from other causes of abdominal distention and chronic constipation (see Tables 378.7; Table 378.10 and Figs. 378.4 and 378.5). The history often reveals constipation starting in infancy that has responded poorly to medical management. Failure to thrive is not uncommon. Fecal incontinence, fecal urgency, and stool-withholding behaviors are usually not present. Significant abdominal distention is unusual in non–Hirschsprung-related constipation, as is emesis. The abdomen is tympanitic and distended, with a large fecal mass palpable in the left lower abdomen. Rectal examination demonstrates a normally placed anus that easily allows entry of the finger but feels snug. The rectum is usually empty of feces, and when the finger is removed, there may be an explosive discharge of foul-smelling feces and gas. The stools, when passed, can consist of small pellets, be ribbon-like, or have a fluid consistency, unlike the large stools seen in patients with functional constipation. Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever. Urinary retention with enlarged bladder or hydronephrosis can occur secondary to urinary compression.

In neonates, Hirschsprung disease must be differentiated from meconium plug syndrome, meconium ileus, and intestinal atresia. In older patients, the **Currarino triad** must be considered, which includes anorectal malformations (ectopic anus, anal stenosis, imperforate anus), sacral bone anomalies (hypoplasia, poor segmentation), and presacral anomaly (anterior meningoceles, teratoma, cyst). Mimics of Hirschsprung disease include intestinal neuronal dysplasia (IND), hypoganglionosis, absence of argyrophil plexus, and **megacystis**

Table 378.10 Distinguishing Features of Hirschsprung Disease and Functional Constipation

VARIABLE	FUNCTIONAL	HIRSCHSPRUNG DISEASE
HISTORY		
Onset of constipation	After 2yr of age	At birth
Encopresis	Common	Very rare
Failure to thrive	Uncommon	Possible
Enterocolitis	None	Possible
Forced bowel training	Usual	None
EXAMINATION		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Malnutrition	None	Possible
INVESTIGATIONS		
Anorectal manometry	Relaxation of internal anal sphincter	Failure of internal anal sphincter relaxation
Rectal biopsy	Normal	No ganglion cells, increased acetylcholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24hr)

From Imseis E, Gariepy C. Hirschsprung disease. In: Walker WA, Goulet OJ, Kleinman RE, et al., eds. *Pediatric Gastrointestinal Disease*, 4th ed. Hamilton, ON: BC Decker; 2004: p 1035.



Fig. 378.4 Lateral view of a barium enema in a 3-yr-old with Hirschsprung disease. The aganglionic distal segment is narrow, with distended normal ganglionic bowel above it.

microcolon intestinal hypoperistalsis syndrome (MMIHS). MMIH demonstrates an enlarged bladder and intestinal obstruction with microcolon (Fig. 378.6 and Fig. 378.7); involved genes are noted in Table 378.11.

DIAGNOSIS

Rectal suction biopsy is the "gold standard" for diagnosing Hirschsprung disease (see Fig. 378.5). The biopsy material should contain an adequate amount of submucosa to evaluate for the presence of ganglion cells. To avoid obtaining biopsies in the normal area of hypoganglionosis, which ranges from 3 to 17 mm in length, the suction rectal biopsy should be obtained no closer than 2 cm above the dentate line. The biopsy specimen should be stained for acetylcholinesterase to facilitate interpretation. Patients with aganglionosis demonstrate a large number of hypertrophied nerve bundles that stain positively for acetylcholinesterase with an absence of ganglion cells. Calretinin is a calcium binding protein expressed in ganglion cells in submucosa and myenteric plexus; hence, calretinin staining may provide a diagnosis of Hirschsprung disease when acetylcholinesterase staining may not be sufficient. In Hirschsprung disease, on the hematoxylin and eosin staining there is absence of ganglion cells in the submucosa with abundance of hypertrophic nerves; on acetylcholinesterase staining there is abnormal accumulation of acetylcholinesterase-positive hypertrophied nerve bundles in muscularis mucosa and lamina propria; and on calretinin staining there is paucity of calretinin-immunoreactive nerves in muscularis mucosa and lamina propria.

Anorectal manometry evaluates the internal anal sphincter while a balloon is distended in the rectum. In healthy individuals, rectal distention initiates relaxation of the internal anal sphincter in response to rectal distention (known as the rectoanal inhibitory reflux [RAIR]). In patients with Hirschsprung disease, the internal

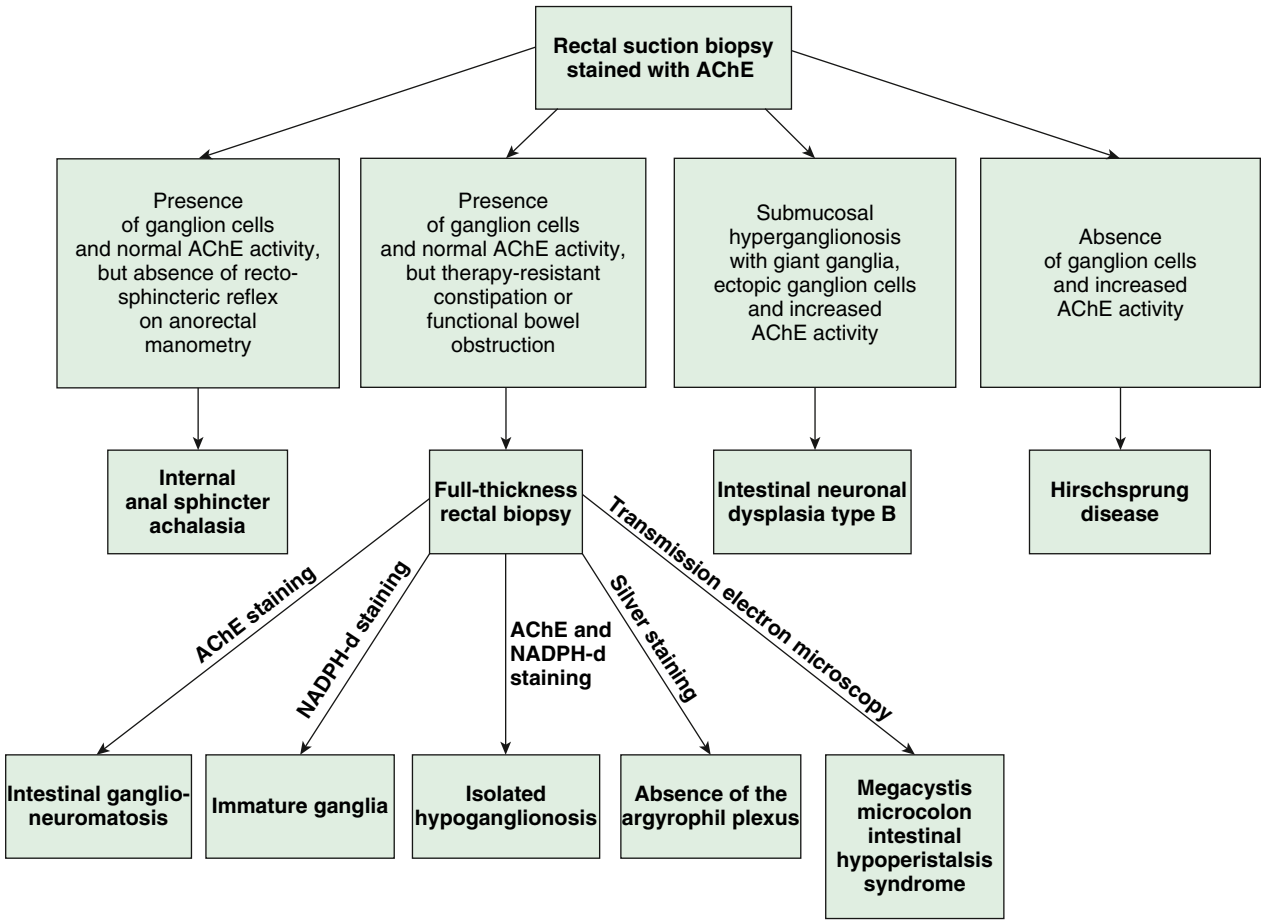

Fig. 378.5 Diagnostic algorithm for investigating chronic constipation and functional bowel obstruction in newborn infants and young children. AChE, Acetylcholinesterase; NADPH-d, nicotinamide adenine dinucleotide phosphate diaphorase. *(From Friedmacher F, Puri P. Classification and diagnostic criteria of variants of Hirschsprung's disease. Pediatr Surg Int. 2013;29:855–872. Fig. 1.)*

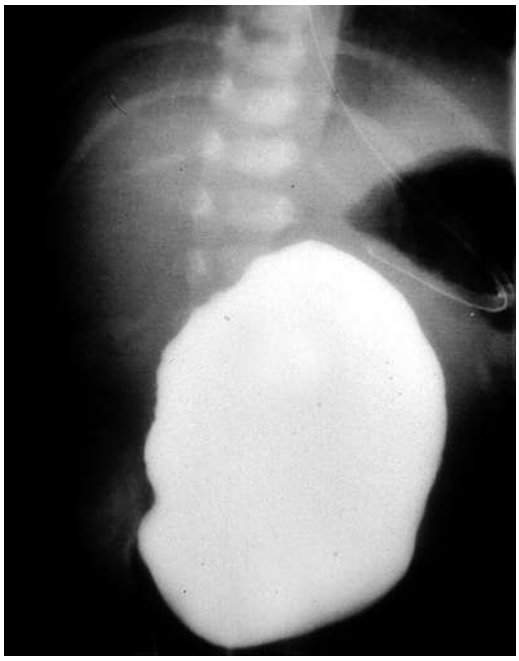

Fig. 378.6 Voiding cystourethrogram showing massively enlarged bladder in an MMIHS patient. *(Modified from Puri P, Gosemann JH. Variants of Hirschsprung disease. Semin Pediatr Surg. 2012;21:310–318. Fig. 5A.)*

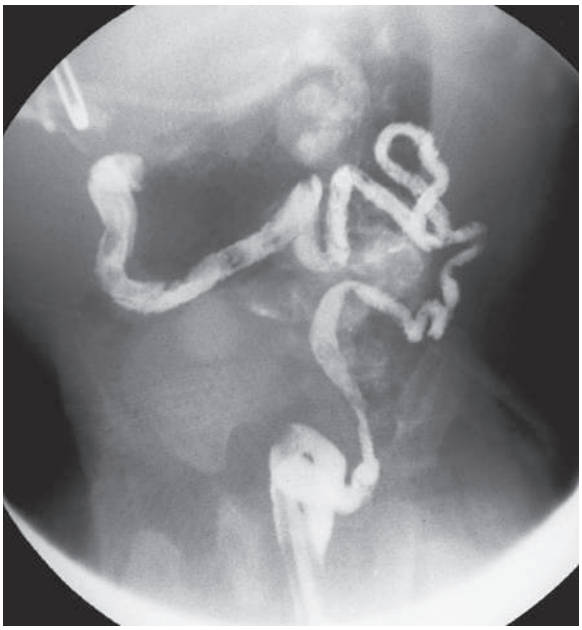

Fig. 378.7 Megacystis-microcolon-intestinal hypoperistalsis syndrome. Single frontal view of newborn female reveals the microcolon characteristic of this entity. Note the malposition of the cecum, consistent with the malrotation that is common in these patients. Soft tissue density in the pelvis is consistent with a distended urinary bladder. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 105.16, p. 1019.)*

anal sphincter fails to relax in response to rectal distention, and there is absence of the RAIR. Although the sensitivity and specificity can vary widely, in experienced hands, the test can be quite sensitive. However, the test can be technically difficult to perform in young infants. A normal response in the course of manometric evaluation precludes a diagnosis of Hirschsprung disease; an equivocal or paradoxical response requires a repeat anorectal manometry or rectal suction biopsy. The sensitivity and specificity of anorectal manometry are both >90%.

An unprepared contrast enema is most likely to aid in the diagnosis in children older than 1 month of age because the proximal ganglionic segment might not be significantly dilated in the first few weeks of life. Classic findings are based on the presence of an abrupt narrow transition zone between the normal dilated proximal colon and a smaller-caliber obstructed distal aganglionic segment. In the absence of this finding, it is imperative to compare the diameter of the rectum with that of the sigmoid colon, because a rectal diameter that is the same as or smaller than the sigmoid colon suggests Hirschsprung disease. Radiologic evaluation should be performed without prior preparation (i.e., *unprepped contrast enema study*) to prevent transient dilation of the aganglionic segment. As many as 10% of newborns with Hirschsprung disease have a normal contrast study. This diagnostic test is most valuable in the disease that involves the distal colon, and specifically, the rectosigmoid. A transition zone may not be readily identifiable in total bowel aganglionosis. The 24-hour delayed films are helpful in showing retained contrast (see Fig. 378.4). If significant barium is still present in the colon, it increases the suspicion of Hirschsprung disease even if a transition zone is not identified. Barium enema examination is useful in determining the extent of aganglionosis before surgery and in evaluating other diseases that manifest as lower bowel obstruction in a neonate. The sensitivity (~70%) and specificity (50–80%) of barium enema studies diagnosing Hirschsprung disease is lower than other methodologies. Full-thickness rectal biopsies can be performed at the time of surgery to confirm the diagnosis, level of involvement, and to differentiate other disorders (see Fig. 378.5).

TREATMENT

Once the diagnosis is established, the definitive treatment is operative intervention. Previously, a temporary ostomy was placed, and definitive surgery was delayed until the child was older. Currently, many infants undergo a primary pull-through procedure unless there is associated enterocolitis or other complications, when a decompressing ostomy is usually required.

There are essentially two surgical options. One procedure creates a neorectum, bringing down normally innervated bowel behind the aganglionic rectum. The neorectum created in this procedure has an anterior aganglionic segment with normal sensation and a posterior ganglionic segment with normal propulsion. The **endorectal pull-through procedure** involves stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within. Advances in techniques have led to successful laparoscopic single-stage endorectal pull-through procedures, which are the treatment of choice.

In **ultrashort-segment Hirschsprung disease**, also known as **anal achalasia**, the aganglionic segment is limited to the internal sphincter. The clinical symptoms are similar to those of children with functional constipation. Ganglion cells are present on rectal suction biopsy, but the anorectal manometry is abnormal, with failure of relaxation of the internal anal sphincter in response to rectal distention. Current treatment, although controversial, includes anal botulism injection to relax the anal sphincter and anorectal myectomy if indicated.

Long-segment Hirschsprung disease involving the entire colon and, at times, part of the small bowel presents a difficult problem. Anorectal manometry and rectal suction biopsy demonstrate findings of Hirschsprung disease, but radiologic studies are difficult to interpret because a colonic transition zone cannot be identified. The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy. When the entire colon is aganglionic, often together with a length of terminal ileum, ileal-anal anastomosis is the treatment of choice, preserving part of the aganglionic colon to facilitate water absorption, which helps the stools to become firm.

Table 378.11 Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome: Genes and Distinguishing Clinical Features

GENE*	% OF ALL MMIHS	MOI	DISTINGUISHING CLINICAL FEATURES	OTHER
ACTG2	44.1%	AD	Classic features of MMIHS (e.g., megacystis, microcolon, intestinal dysmotility)	Greater disease severity reported in probands with a de novo (vs inherited) pathogenic variant Parental somatic and germline mosaicism reported
LMOD1	1 person	AR	Classic features of MMIHS	Large deletions/duplications not reported to date
MYH11	2 persons	AR	Overlapping features of MMIHS and prune-belly sequence (one person) Overlapping features of MMIHS and MSMDS (1 person)	Large del/dups not associated with MMIHS to date
MYL9	1 person	AR	Mydriasis No vascular smooth muscle dysfunction†	Homozygous partial-gene deletion reported
MYLK	2 families	AR	No vascular smooth muscle dysfunction†	Large deletions/duplications not associated with MMIHS to date
Unknown	~55%			

*Genes are listed alphabetically.
†Vascular smooth muscle dysfunction including aortic aneurysms or dissection has not been reported.
AD, Autosomal dominant; AR, autosomal recessive; MMIHS, megacystis-microcolon-intestinal hypoperistalsis syndrome; MOI, mode of inheritance; MSMDS, multisystemic smooth muscle dysfunction syndrome.
Modified from Ambartsumyan L. Megacystis-microcolon-intestinal hypoperistalsis syndrome overview. NIH National Library of Medicine. *GeneRev*. 2019.

The prognosis of surgically treated Hirschsprung disease is generally satisfactory independent of the kind of surgical procedure, about 15–60% experience bowel problems ranging from constipation and/or fecal incontinence and enterocolitis episodes, but these symptoms diminish with age. Children presenting with persistent bowel problems after surgery often need additional diagnostics (contrast enema, three-dimensional [3D] high-definition anorectal manometry, rectal suction biopsy, and colon manometry), advanced bowel regimen (stool softeners, stimulant laxatives, medicated enemas, pelvic floor therapy), and additional surgical procedures (anal dilation, anal myectomy, re-do pull-through corrective surgery, appendicostomy or cecostomy, colostomy, ileostomy). Recent advances in the field of motility include usage of 3D high-definition anorectal manometry to assess the anorectal function of the post-surgical anal sphincter and high-resolution colon manometry to assess and characterize the motility function of the residual colon after Hirschsprung surgery.

Hirschsprung disease–associated **enterocolitis** can occur at any time before or after surgery and is the leading cause of death in these patients. Dysmotility related to partial obstruction, underlying disease, impaired immune function, and the intestinal microbiome may all contribute to this pathophysiologic process. Explosive, foul-smelling and/or bloody diarrhea, abdominal distention, explosive discharge of rectal contents on digital examination, diminished peripheral perfusion, lethargy, and fever are all ominous signs. Management principles include hydration, decompression from above and below (nasogastric Salem Sump, rectal tube, rectal irrigation), and the use of broad-spectrum antibiotics.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

378.5 Intestinal Neuronal Dysplasia

Prasanna K. Kapavarapu, Kristin N. Fiorino, and Chris A. Liacouras

IND describes different quantitative (hypoganglionosis or hyperganglionosis) and qualitative (immature or heterotropic ganglion cells) abnormalities of the submucosal plexus. The typical histology is that of hyperganglionosis and giant ganglia. **Type A** occurs very rarely and is characterized by congenital aplasia or hypoplasia of the sympathetic innervation. Patients present early in the neonatal period with episodes of intestinal obstruction, diarrhea, and bloody stools. **Type B** accounts for more than 95% of cases. Biopsies for diagnosis of IND type B have to be taken 8 cm proximal to the dentate line with sufficient submucosa and should be cut rectangular to the surface mucosa to avoid false-positive results. Qualitative criteria include hypoganglionosis and hypertrophy of nerve trunks. Quantitative criteria include presence of at least 20% submucosal giant ganglia in 30 serial sections examined, 8 (10 ± 2) nerve cells per ganglion, and children >1 year of age. IND type B mimics Hirschsprung disease, and patients present with chronic constipation (see Table 378.7 and Fig. 378.5). Clinical manifestations include abdominal distention, constipation, and enterocolitis. Various lengths of bowel may be affected from segmental to the entire intestinal tract. IND has been observed in an isolated form and proximal to an aganglionic segment. Other intraintestinal and extraintestinal manifestations are present in patients with IND. It has been reported in all age groups, most commonly in infancy, but is also seen in adults who have had constipation not dating back to childhood.

Associated diseases and conditions include Hirschsprung disease, prematurity, small left colon syndrome, and meconium plug syndrome. Studies have identified a deficiency in substance P in patients with IND. Type A IND may be inherited in a familial, autosomal recessive pattern. Most cases of IND type B are sporadic, with few familial clusters, suggesting autosomal dominant inheritance.

Management includes that for functional constipation, and, if unsuccessful, surgery is indicated including emergency surgeries for acute obstruction.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

378.6 Superior Mesenteric Artery Syndrome (Wilkie Syndrome, Cast Syndrome, Arteriomesenteric Duodenal Compression Syndrome)

Prasanna K. Kapavarapu, Kristin N. Fiorino, and Chris A. Liacouras

Superior mesenteric artery syndrome results from compression of the third duodenal segment by the superior mesenteric artery against the aorta. Malnutrition or catabolic states may cause mesenteric fat depletion, which collapses the duodenum within a narrowed aortomesenteric angle. Other etiologies include extraabdominal compression (e.g., body cast) and mesenteric tension, as can occur from ileoanal pouch anastomosis. Rapid weight loss and immobilization are risk factors.

Symptoms include intermittent epigastric pain, anorexia, nausea, and vomiting. Risk factors include thin body habitus, prolonged bed rest, abdominal surgery, and exaggerated lumbar lordosis. Onset can be within weeks of a trigger, but some patients have chronic symptoms that evade diagnosis. A classic example is an underweight adolescent who begins vomiting 1-2 weeks after scoliosis surgery or spinal fusion. Recognition may be delayed in the context of an eating disorder. Superior mesenteric artery syndrome can not only simulate anorexia nervosa, but also precipitate and sometimes even complicate anorexia nervosa.

The diagnosis is established radiologically by demonstrating a duodenal cutoff just right of midline along with proximal duodenal dilation, with or without gastric dilation. Although the upper gastrointestinal series remains a mainstay, modalities including abdominal CT or CT/MR angiography, or ultrasound may be more appropriate if there is concern for other etiologies such as malignancy. Upper endoscopy should be considered to rule out intraluminal pathology.

Treatment focuses on obstructive relief, nutritional rehabilitation, and correction of associated fluid and electrolyte abnormalities. Lateral or prone positioning can shift the duodenum away from obstructing structures and allow resumption of oral intake. If repositioning is unsuccessful, patients require nasojejunal enteral nutrition past the obstruction or parenteral nutrition if this is not tolerated. This management is successful in the vast majority of cases, with eventual withdrawal of tube feeding once weight has been regained and enteral feeding tolerance orally has been gradually and fully restored. Patients with refractory courses may require surgery to bypass the obstruction.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 379 Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

379.1 Ileus

Elizabeth C. Maxwell and Chris A. Liacouras

Ileus is the failure of intestinal peristalsis caused by loss of coordinated gut motility without evidence of mechanical obstruction. In children, it is most often associated with abdominal surgery or infection (gastroenteritis, pneumonia, peritonitis). Ileus also accompanies metabolic abnormalities (e.g., uremia, hypokalemia, hypercalcemia, hypermagnesemia, acidosis) or administration of certain drugs, such as opiates, vincristine, and antimotility agents such as loperamide when given during gastroenteritis.

Ileus manifests with nausea, vomiting, feeding intolerance, abdominal distention with associated pain, and delayed passage of stool and bowel gas. Bowel sounds are minimal or absent, in contrast to early mechanical obstruction, when they are hyperactive. Abdominal radiographs demonstrate multiple air-fluid levels throughout the abdomen. Serial radiographs usually do not show progressive distention as they do in mechanical obstruction. Contrast radiographs, if performed, demonstrate slow movement of barium through a patent lumen. Ileus after abdominal surgery generally resolves within 72 hours.

Treatment involves correcting the underlying abnormality, supportive care of comorbidities, and mitigation of iatrogenic contributions. Electrolyte abnormalities should be identified and corrected, and narcotic agents, when used, should be weaned as tolerated. Nasogastric decompression can relieve recurrent vomiting or abdominal distention associated with pain; resultant fluid losses should be corrected with isotonic crystalloid solution. Prokinetic agents such as erythromycin are not routinely recommended. Selective peripheral opioid antagonists such as methylnaltrexone hold promise in decreasing postoperative ileus, but pediatric data are lacking.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

379.2 Adhesions

Elizabeth C. Maxwell and Chris A. Liacouras

Adhesions are fibrous tissue bands that result from peritoneal injury. Their formation is a complex process involving inflammation, hypoxia, and the extracellular matrix. They can constrict hollow organs and are a major cause of postoperative small bowel obstruction. Most remain asymptomatic, but problems can arise any time after the second postoperative week to years after abdominal surgery, regardless of surgical extent. In one large meta-analysis, the incidence of bowel obstruction

secondary to adhesive formation (ASBO) was between 1 and 12.6% in children. ASBO is an important cause of pediatric surgical emergency.

The diagnosis is suspected in patients with colicky abdominal pain, constipation, anorexia, emesis, and a history of intraperitoneal surgery. Nausea and vomiting quickly follow onset of pain. Initially, bowel sounds are hyperactive, and the abdomen is flat. Subsequently, bowel sounds disappear, and bowel dilation can cause abdominal distention. Fever and leukocytosis suggest bowel necrosis and peritonitis. Plain radiographs demonstrate obstructive features, and a CT scan or contrast studies may be needed to define the etiology.

Management includes nasogastric decompression, intravenous fluid resuscitation, and broad-spectrum antibiotics in preparation for surgery. The laparoscopic approach is used with increased frequency now compared to open laparotomy. Nonoperative intervention is contraindicated unless a patient is stable with obvious clinical improvement. Gastrografin (diatrizoate meglumine), typically used as an oral contrast agent for radiologic studies, may be a useful nonoperative management tool. A few small pediatric studies have shown promise, including decreased surgical requirement, decreased time to feed after admission, decreased hospital length of stay, and decreased healthcare costs with its use. Long-term complications include formation of new adhesions from surgery to relieve the obstruction, female infertility, failure to thrive, and chronic abdominal and/or pelvic pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

379.3 Intussusception

Elizabeth C. Maxwell and Chris A. Liacouras

Intussusception occurs when a portion of the alimentary tract is telescoped into an adjacent segment. It is the most common cause of intestinal obstruction between 5 months and 3 years of age and the most common abdominal emergency in children younger than 2 years of age. Sixty percent of patients are younger than 1 year of age and 80% of the cases occur before age 24 months; it is rare in neonates. The incidence varies from 1 to 4 per 1,000 live births. The male:female ratio is 3:1. Many small bowel–small bowel and a few small bowel–colonic intussusceptions reduce spontaneously; *if left untreated, ileal-colonic intussusception may lead to intestinal infarction, perforation, peritonitis, and death.*

ETIOLOGY AND EPIDEMIOLOGY

Approximately 90% of cases of intussusception in children are idiopathic. The seasonal incidence has peaks in fall and winter. Correlation with prior or concurrent respiratory adenovirus (type C) infection has been noted, and the condition can complicate otitis media, gastroenteritis, Henoch-Schönlein purpura, COVID-19, or upper respiratory tract infections. A slight increase in intussusception has been noted to occur within 3 weeks of the rotavirus vaccine (especially after the first dose), but this is a very rare side effect.

It is postulated that gastrointestinal infection or the introduction of new food proteins results in swollen Peyer patches in the terminal ileum. Lymphoid nodular hyperplasia is another related risk factor. Prominent mounds of lymph tissue lead to mucosal prolapse of the ileum into the colon, thus causing an intussusception. In 2–8% of patients, **recognizable lead points** for the intussusception are found, such as a Meckel diverticulum, intestinal polyp, neurofibroma, intestinal duplication cysts, inverted appendix stump, leiomyomas, hamartomas, ectopic pancreatic tissue, anastomotic suture line, enterostomy tube, posttransplant lymphoproliferative disease, hemangioma, or malignant conditions such as lymphoma or Kaposi sarcoma. Gastrojejunal and jejunostomy tubes can also serve as lead points for intussusception. Lead points are more common in children older than 2 years of age; the older the child, the higher the risk of a lead point. In adults, lead points are present in 90%. Intussusception can complicate mucosal hemorrhage, as in Henoch-Schönlein purpura, idiopathic thrombocytopenic purpura, or hemophilia. Cystic fibrosis, celiac disease, and Crohn disease are other risk factors. Postoperative intussusception is ileoileal and usually occurs within several days of an abdominal operation. Anterograde intussusception may occur rarely following bariatric surgery with a Roux-en-Y gastric bypass and is noteworthy that there does not seem to be a lead point in these cases. Intussusception occurring during development in utero may be associated with the development of intestinal atresia. Intussusception in premature infants is rare.



Fig. 379.1 Transverse image of an ileocolic intussusception. Note the loops within the loops of bowel.

Ileo-ileal (as compared to ileo-colonic) intussusception may be more common than previously believed, is often idiopathic or associated with Henoch-Schönlein purpura, and usually resolves spontaneously.

PATHOLOGY

Symptomatic intussusceptions are most often ileocolic, less commonly cecocolic, and occasionally ileal. Very rarely, the appendix forms the apex of an intussusception. The upper portion of bowel, the **intussusceptum,** invaginates into the lower, the **intussuscipiens,** pulling its mesentery along with it into the enveloping loop. Constriction of the mesentery obstructs venous return; engorgement of the intussusceptum follows, with edema, and bleeding from the mucosa leads to a bloody stool, sometimes containing mucus. The apex of the intussusception can extend into the transverse, descending, or sigmoid colon, even to and through the anus in neglected cases. This presentation must be distinguished from rectal prolapse. Most intussusceptions do not strangulate the bowel within the first 24 hours but can eventuate in intestinal gangrene and shock.



Fig. 379.2 Intussusception in an infant. The obstruction is evident in the proximal transverse colon. Contrast material between the intussusceptum and the intussuscipiens *(arrows)* is responsible for the coiled-spring appearance.

CLINICAL MANIFESTATIONS

In typical cases, there is sudden onset, in a previously well child, of severe paroxysmal colicky pain that recurs at frequent intervals and is accompanied by straining efforts with legs and knees flexed and loud cries. The child may initially be comfortable and play normally between the paroxysms of pain, but if the intussusception is not reduced, the child becomes progressively weaker and lethargic. At times, the **lethargy** is often disproportionate to the abdominal signs. With progression, a shocklike state, with fever and peritonitis, can develop. The pulse becomes weak and thready, the respirations become shallow and grunting, and the pain may be manifested only by moaning sounds. Vomiting occurs in most cases and is usually more frequent in the early phase. In the later phase, the vomitus becomes bile stained. Stools of normal appearance may be evacuated in the first few hours of symptoms. After this time, fecal excretions are small or more often do not occur, and little or no flatus is passed. Blood is generally passed in the first 12 hours but at times not for 1-2 days and infrequently not at all; 60% of infants pass a stool containing red blood and mucus, the commonly described **currant jelly stool**. Some patients have only irritability and alternating or progressive lethargy. *The classic triad of pain, a palpable sausage-shaped abdominal mass, and bloody or currant jelly stool is seen in <30% of patients with intussusception.* The combination of paroxysmal pain, vomiting, and a palpable abdominal mass has a positive predictive value of >90%; the presence of rectal bleeding increases this to approximately 100%.

Palpation of the abdomen usually reveals a slightly tender sausage-shaped mass, sometimes ill defined, which might increase in size and firmness during a paroxysm of pain and is most often in the right upper abdomen, with its long axis cephalocaudal. If it is felt in the epigastrium, the long axis is transverse. Approximately 30% of patients do not have a palpable mass. The presence of bloody mucus on rectal examination supports the diagnosis of intussusception. Abdominal distention and tenderness develop as intestinal obstruction becomes more acute. On rare occasions, the advancing intestine prolapses through the anus. *This prolapse can be distinguished from prolapse of the rectum by the separation between the protruding intestine and the rectal wall, which does not exist in prolapse of the rectum.*

Ileoileal intussusception in children younger than 2 years can have a less typical clinical picture, and the symptoms and signs are chiefly those of small intestinal obstruction. These often resolve without treatment. **Recurrent intussusception** is noted in 5–8% and is more common after hydrostatic than surgical reduction. Chronic intussusception, in which the symptoms exist in milder form at recurrent intervals, is more likely to occur with or after acute enteritis and can arise in older children as well as in infants.

DIAGNOSIS

When the clinical history and physical findings suggest intussusception, an abdominal ultrasound is typically performed. A plain abdominal radiograph might show a density in the area of the intussusception. Screening ultrasounds for suspected intussusception increases the yield of diagnostic or therapeutic enemas and reduces unnecessary radiation exposure in children with negative ultrasound examinations. The diagnostic findings of intussusception on ultrasound include a tubular mass in longitudinal views and a doughnut or target appearance in transverse images (Fig. 379.1). Ultrasound has a sensitivity of approximately 98–100% and a specificity of approximately 98% in diagnosing intussusception. Air, hydrostatic (saline), and, less often, water-soluble contrast enemas have replaced barium examinations. Contrast enemas demonstrate a filling defect or cupping in the head of the contrast media where its advance is obstructed by the intussusceptum (Fig. 379.2). A central linear column of contrast media may be visible in the compressed lumen of the intussusceptum, and a thin rim of contrast may be seen trapped around the invaginating intestine in the folds of mucosa within the intussuscipiens (coiled-spring sign), especially after evacuation. Retrogression of the intussusceptum under pressure and visualized on x-ray or ultrasound documents successful reduction. Air reduction is associated with fewer complications and lower radiation exposure than traditional contrast hydrostatic techniques.

DIFFERENTIAL DIAGNOSIS

It may be particularly difficult to diagnose intussusception in a child who already has gastroenteritis; a change in the pattern of illness, in the character of pain, or in the nature of vomiting or the onset of rectal bleeding should alert the physician. The bloody stools and abdominal cramps that accompany enterocolitis can usually be differentiated from intussusception because in enterocolitis the pain is less severe and less regular, there is diarrhea, and the infant is recognizably ill between painful episodes. Bleeding from a Meckel diverticulum is usually painless. Joint symptoms, purpura, or hematuria usually but not invariably accompany the intestinal hemorrhage of Henoch-Schönlein purpura. Because intussusception can be a complication of this disorder, ultrasonography may be needed to distinguish the conditions.

It is important in patients with cystic fibrosis to distinguish intussusception from distal intestinal obstruction syndrome. Distal intestinal obstruction syndrome requires antegrade treatment, which would be harmful if there was an intussusception.

TREATMENT

Reduction of an acute intussusception is an emergency procedure and should be performed immediately after diagnosis in preparation for possible surgery. In patients with prolonged intussusception and signs of shock, peritoneal irritation, intestinal perforation, or pneumatosis intestinalis, hydrostatic reduction should not be attempted.

The success rate of radiologic hydrostatic reduction under fluoroscopic or ultrasonic guidance is approximately 80–95% in patients with ileocolic intussusception. Spontaneous reduction of

intussusception occurs in approximately 4–10% of patients. Bowel perforations occur in 0.5–2.5% of attempted barium and hydrostatic (saline) reductions. The perforation rate with air reduction is 0.1–0.2%. Surgical reduction is indicated in the presence of refractory shock, suspected bowel necrosis or perforation, peritonitis, and multiple recurrences (suspected lead point).

An *ileoileal intussusception* is best demonstrated by abdominal ultrasonography. Reduction by instillation of contrast agents, saline, or air might not be possible. Such intussusceptions can develop insidiously after bowel surgery and require reoperation if they do not spontaneously reduce. Ileoileal disease is common with Henoch-Schönlein purpura and other unidentifiable disorders and usually resolves without the need for any specific treatment. If manual operative reduction is impossible or the bowel is not viable, resection of the intussusception is necessary, with end-to-end anastomosis.

PROGNOSIS

Untreated ileal-colonic intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the first 24 hours, but the mortality rate rises rapidly after this time, especially after the second day. Spontaneous reduction during preparation for operation is not uncommon.

The **recurrence rate** after nonsurgical reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2–5%; none has recurred after surgical resection. Most recurrences occur within 72 hours of reduction. Corticosteroids may reduce the frequency of recurrent intussusception but are rarely used for this purpose. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies if present. A single recurrence of intussusception can usually be reduced radiologically. In patients with multiple ileal-colonic recurrences, a lead point should be suspected and laparoscopic surgery considered. It is unlikely that an intussusception caused by a lesion such as lymphosarcoma, polyp, or Meckel diverticulum will be successfully reduced by radiologic intervention. With adequate surgical management, laparoscopic reduction carries a very low mortality.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

379.4 Closed-Loop Obstructions

Elizabeth C. Maxwell and Chris A. Liacouras

Closed-loop obstructions (i.e., **internal hernia**) result from bowel loops that enter windows created by mesenteric defects or adhesions and become trapped, with the entrapped segment of bowel becoming obstructed at two points. Vascular engorgement of the strangulated bowel results in intestinal ischemia and necrosis unless promptly relieved. Prior abdominal surgery is an important risk factor. Symptoms include abdominal pain, distention, and bilious emesis. Symptoms can be intermittent if the herniated bowel slides in and out of the defect. Peritoneal signs suggest ischemic bowel. Plain radiographs demonstrate signs of small bowel obstruction or free air if the bowel has perforated. CT scan can identify and delineate internal hernias. Supportive management includes intravenous fluids, antibiotics, and nasogastric decompression. Prompt surgical relief of the obstruction is indicated to prevent bowel necrosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com Bibliography.

Chapter 380 Foreign Bodies and Bezoars

380.1 Foreign Bodies in the Stomach and Intestine

Trusha Patel, Petar Mamula, and Chris A. Liacouras

Foreign body (FB) ingestions are common in children, with most ingestions occurring between 6 months and 3 years of age. Generally, FB ingestions in young children are unintentional and involve small household objects (coins, toys, jewelry, magnets, batteries, etc.). Although children may present with symptoms of abdominal pain or chest pain, stridor, drooling, respiratory distress, fever, dysphagia, or inability to tolerate oral intake after FB ingestions, up to 50% of children may be asymptomatic at the time of presentation. A thorough history and clinical examination is required, including evaluation for respiratory distress, oropharyngeal injury, and signs of perforation such as subcutaneous emphysema or peritoneal signs. When determining the appropriate management of a child after FB ingestion, clinicians must consider patient age and anatomy; object type, location, and size; timing of ingestion; presence or absence of symptoms; nil per os (NPO) status; and logistical factors (availability of necessary staff, social factors that may impact timely follow-up). In addition to history and clinical examination, anteroposterior and lateral radiographs of the neck, chest, and/or abdomen are useful to confirm the presence and determine the location of radiopaque foreign bodies. Object location is particularly important to consider in the context of the most common sites of potential FB impaction, obstruction, or retention, which include multiple locations in the esophagus, pylorus, duodenal sweep, ligament of Treitz, ileocecal valve, rectosigmoid colon, and anus.

Otolaryngologists, gastroenterologists, and general surgeons are all trained in the management of FB ingestions and center-specific availability and expertise should guide consultation with the appropriate specialist. The management of esophageal foreign bodies is reviewed elsewhere (Chapter 373.1). Considerations for management of gastrointestinal foreign bodies in the stomach and intestine are based on object type, along with recommendations regarding timing of potential endoscopic removal as being emergent (<2 hours, regardless of NPO status), urgent (<24 hours, following usual NPO guidelines), or elective (>24 hours from presentation, following usual NPO guidelines). It should be noted, however, that given the great variability in patient and object size, the management of pediatric FB ingestions is case dependent, and clinicians must use their judgment when determining appropriate management.

BUTTON BATTERIES

Button battery ingestion in a child of any age requires emergent evaluation, given the potential for rapid, severe caustic injury and associated complications. For children ≥1 year of age with suspected lithium button battery ingestion in the prior 12 hours or confirmed location in the esophagus, current recommendations are to administer honey 10 mL every 10 minutes (or sucralfate if available) and proceed to the emergency department as soon as possible.

intussusception occurs in approximately 4–10% of patients. Bowel perforations occur in 0.5–2.5% of attempted barium and hydrostatic (saline) reductions. The perforation rate with air reduction is 0.1–0.2%. Surgical reduction is indicated in the presence of refractory shock, suspected bowel necrosis or perforation, peritonitis, and multiple recurrences (suspected lead point).

An *ileoileal intussusception* is best demonstrated by abdominal ultrasonography. Reduction by instillation of contrast agents, saline, or air might not be possible. Such intussusceptions can develop insidiously after bowel surgery and require reoperation if they do not spontaneously reduce. Ileoileal disease is common with Henoch-Schönlein purpura and other unidentifiable disorders and usually resolves without the need for any specific treatment. If manual operative reduction is impossible or the bowel is not viable, resection of the intussusception is necessary, with end-to-end anastomosis.

PROGNOSIS

Untreated ileal-colonic intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the first 24 hours, but the mortality rate rises rapidly after this time, especially after the second day. Spontaneous reduction during preparation for operation is not uncommon.

The **recurrence rate** after nonsurgical reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2–5%; none has recurred after surgical resection. Most recurrences occur within 72 hours of reduction. Corticosteroids may reduce the frequency of recurrent intussusception but are rarely used for this purpose. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies if present. A single recurrence of intussusception can usually be reduced radiologically. In patients with multiple ileal-colonic recurrences, a lead point should be suspected and laparoscopic surgery considered. It is unlikely that an intussusception caused by a lesion such as lymphosarcoma, polyp, or Meckel diverticulum will be successfully reduced by radiologic intervention. With adequate surgical management, laparoscopic reduction carries a very low mortality.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

379.4 Closed-Loop Obstructions

Elizabeth C. Maxwell and Chris A. Liacouras

Closed-loop obstructions (i.e., **internal hernia**) result from bowel loops that enter windows created by mesenteric defects or adhesions and become trapped, with the entrapped segment of bowel becoming obstructed at two points. Vascular engorgement of the strangulated bowel results in intestinal ischemia and necrosis unless promptly relieved. Prior abdominal surgery is an important risk factor. Symptoms include abdominal pain, distention, and bilious emesis. Symptoms can be intermittent if the herniated bowel slides in and out of the defect. Peritoneal signs suggest ischemic bowel. Plain radiographs demonstrate signs of small bowel obstruction or free air if the bowel has perforated. CT scan can identify and delineate internal hernias. Supportive management includes intravenous fluids, antibiotics, and nasogastric decompression. Prompt surgical relief of the obstruction is indicated to prevent bowel necrosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com Bibliography.

Chapter 380 Foreign Bodies and Bezoars

380.1 Foreign Bodies in the Stomach and Intestine

Trusha Patel, Petar Mamula, and Chris A. Liacouras

Foreign body (FB) ingestions are common in children, with most ingestions occurring between 6 months and 3 years of age. Generally, FB ingestions in young children are unintentional and involve small household objects (coins, toys, jewelry, magnets, batteries, etc.). Although children may present with symptoms of abdominal pain or chest pain, stridor, drooling, respiratory distress, fever, dysphagia, or inability to tolerate oral intake after FB ingestions, up to 50% of children may be asymptomatic at the time of presentation. A thorough history and clinical examination is required, including evaluation for respiratory distress, oropharyngeal injury, and signs of perforation such as subcutaneous emphysema or peritoneal signs. When determining the appropriate management of a child after FB ingestion, clinicians must consider patient age and anatomy; object type, location, and size; timing of ingestion; presence or absence of symptoms; nil per os (NPO) status; and logistical factors (availability of necessary staff, social factors that may impact timely follow-up). In addition to history and clinical examination, anteroposterior and lateral radiographs of the neck, chest, and/or abdomen are useful to confirm the presence and determine the location of radiopaque foreign bodies. Object location is particularly important to consider in the context of the most common sites of potential FB impaction, obstruction, or retention, which include multiple locations in the esophagus, pylorus, duodenal sweep, ligament of Treitz, ileocecal valve, rectosigmoid colon, and anus.

Otolaryngologists, gastroenterologists, and general surgeons are all trained in the management of FB ingestions and center-specific availability and expertise should guide consultation with the appropriate specialist. The management of esophageal foreign bodies is reviewed elsewhere (Chapter 373.1). Considerations for management of gastrointestinal foreign bodies in the stomach and intestine are based on object type, along with recommendations regarding timing of potential endoscopic removal as being emergent (<2 hours, regardless of NPO status), urgent (<24 hours, following usual NPO guidelines), or elective (>24 hours from presentation, following usual NPO guidelines). It should be noted, however, that given the great variability in patient and object size, the management of pediatric FB ingestions is case dependent, and clinicians must use their judgment when determining appropriate management.

BUTTON BATTERIES

Button battery ingestion in a child of any age requires emergent evaluation, given the potential for rapid, severe caustic injury and associated complications. For children ≥1 year of age with suspected lithium button battery ingestion in the prior 12 hours or confirmed location in the esophagus, current recommendations are to administer honey 10 mL every 10 minutes (or sucralfate if available) and proceed to the emergency department as soon as possible.

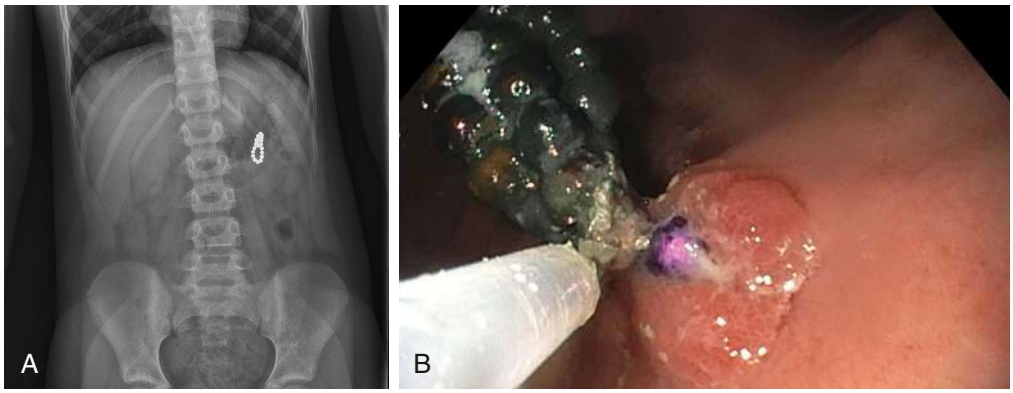

Fig. 380.1 A, Supine abdominal radiograph of 8-yr-old girl with history of ingestion of 23 Buckyball-type magnets over preceding 3-mo period demonstrating loop of magnets. B, Endoscopic image of magnets during retrieval from lesser curvature of the stomach, with additional finding of magnet penetrating the wall of stomach. Subsequent surgical exploration demonstrated fistula between stomach and jejunum, which was repaired.

Immediate two-view radiograph is indicated to determine battery location and negative pole orientation; direct notification of otolaryngology, gastroenterology, and/or general surgery is indicated pending results of this radiograph. Although removal of esophageal button batteries is emergent, management of button batteries in the stomach and more distally depends on the presence of symptoms and whether a single battery or multiple objects have been ingested. If symptoms of anorexia, vomiting, abdominal pain, or fever are present or if there is co-ingestion of a magnet, then urgent endoscopic removal is indicated if the button battery is in the stomach or proximal small intestine. If the patient is asymptomatic after the ingestion of a single button battery ≥15 mm that has passed beyond the esophagus, esophagram should still be considered (particularly in children <6 years of age) to evaluate for esophageal injury. If esophagram is normal, observant management may be appropriate, with repeat abdominal x-ray (AXR) in 2-3 days and consideration of button battery removal if it still has not passed the stomach within 4 days. However, if the esophagram is abnormal or if patient size or other factors make it unlikely that the battery will pass spontaneously, hospital admission for observation, endoscopic evaluation, and potential battery removal is indicated. If the patient is asymptomatic and only a single button battery <15 mm has been ingested and is in the stomach or more distal, observant management is appropriate. AXR should be considered if an ingested button battery has not passed in the stool within 10-14 days.

COINS/BLUNT OBJECTS

Although coins are the most frequently ingested FB, when coin ingestion is reported or identified on imaging, it is important to confirm that the ingested object could not potentially be a button battery (on imaging, it is important to make sure there is no "step-off" sign on lateral view or "double halo" sign on anteroposterior views). Generally, endoscopic removal of coins and other small, blunt objects in the stomach and more distally is only necessary if the patient is symptomatic or if the object is unlikely to pass (child <2 years old and object dimensions of width >2 cm or length >5 cm). Repeat abdominal radiography may be considered in 2-3 weeks if a child under 2 years of age swallowed a quarter or another object that may not pass in a timely fashion.

MAGNETS

In the case of a suspected or confirmed magnet ingestion, two-view radiographs should be obtained to confirm whether a single magnet or multiple magnets have been ingested, as multiple magnet ingestion places the patient at risk for entero-enteric fistula formation between magnets in adjacent loops of bowel, which can lead to perforation, peritonitis, and bowel ischemia/necrosis. If a single magnet has been ingested and is in the stomach or intestine and the patient is asymptomatic, with low risk for ingestion of additional magnets and with good follow-up, allowing spontaneous passage is appropriate. In that case, precautions that should be taken include removing all magnets and metallic objects from the patient's environment (including patient's clothing) and preventing any risk of additional magnet ingestion until the magnet has passed. In the case of multiple magnet ingestion, urgent endoscopic removal is indicated if the magnets are in the stomach to prevent further passage or complications (Fig. 380.1). If multiple magnets are beyond the stomach, consultation with a general surgeon is recommended and magnet removal should be pursued if the patient is symptomatic (either with enteroscopy, laparoscopy or laparotomy, depending on center expertise) (Fig. 380.2). If the patient is asymptomatic, hospital admission for laxative therapy, serial abdominal exams and x-rays (every 4-6 hours) and consideration of later removal if not passing is appropriate.

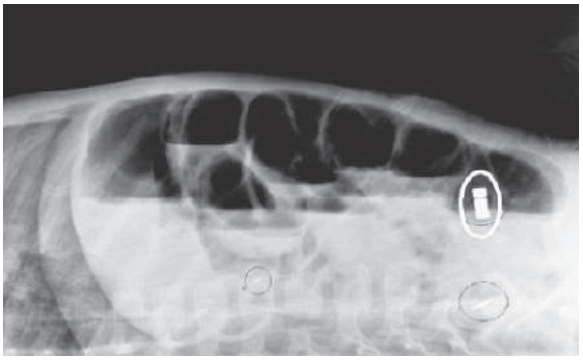

Fig. 380.2 Abdominal radiograph of a 3-yr-old boy, noting three attached magnets that resulted in volvulus (i.e., twisting of the bowel) and multiple bowel perforations. *(Courtesy U.S. Consumer Product Safety Commission. From Centers for Disease Control and Prevention: Gastrointestinal injuries from magnet ingestion in children—United States, 2003–2006. MMWR Morb Mortal Wkly Rep. 2006;55:1296–1300.)*

SHARP OBJECTS

The management of ingested sharp objects depends on size and shape of the object. Radiographic evaluation is key in identifying size, location, and orientation of radiopaque sharp objects, although it will not be beneficial for radiolucent objects. Generally, urgent endoscopic removal is indicated for sharp objects in the stomach or duodenum if the patient is symptomatic, the object is likely to cause perforation if allowed to pass spontaneously, or if the object is unlikely to pass due to large size (>5-6 cm long in teenagers/adults or ≥2-3 cm long in a younger child). If a large, sharp object is beyond the duodenum, consultation with general surgery is recommended, as removal is indicated if the patient is symptomatic. Even if the patient is asymptomatic, serial radiographs are indicated and removal with enteroscopy or surgery may be needed if symptoms develop or if the object does not pass after 3 days. Otherwise, if the patient is asymptomatic and the object is smaller than the aforementioned dimensions, particularly with the sharp end of the object trailing behind a heavier blunt end, allowing spontaneous passage is reasonable. For reported ingestion of sharp, radiolucent objects, urgent endoscopic evaluation and potential removal is indicated if the patient is asymptomatic. If the patient is symptomatic, alternate imaging (CT, ultrasound, MRI, fluoroscopy) may be utilized for assessment and removal may be considered if the object is identified.

SPECIAL CONSIDERATIONS

Other foreign bodies that may require special considerations include those with the potential to cause obstruction or toxicity based on object characteristics. Super-absorbent objects (including expanding children's spongelike toys, tampons) may expand rapidly within the GI tract and cause gastric outlet or bowel obstruction. If not yet expanded and accessible via endoscope, removal should be considered. Lead-containing foreign bodies should be removed promptly if endoscopically accessible, as they have the potential to cause lead toxicity. Consultation with toxicology is recommended and obtaining baseline serum lead level is suggested. If the lead-containing FB is beyond the stomach, bowel irrigation and monitoring of blood lead levels may be appropriate to minimize and monitor toxicity. In the case of ingestion of narcotic packets, endoscopic removal should be avoided to prevent packet rupture and severe toxicity and consultation with Poison Control Center is recommended.

Children occasionally place objects in their rectum. Small blunt objects usually pass spontaneously, but large or sharp objects typically need to be retrieved. Adequate sedation is essential to relax the anal sphincter before attempting endoscopic or speculum removal. If the object is proximal to the rectum, observation for 12-24 hours usually allows the object to descend into the rectum.

IMPORTANT NUMBERS

National Battery Ingestion Hotline: 800-498-8666
Poison Control: 800-222-1222

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

380.2 Bezoars

Trusha Patel, Petar Mamula, and Chris A. Liacouras

A bezoar is an accumulation of exogenous matter in the stomach or intestine. Risk factors for development of a bezoar include anatomic abnormalities (congenital or due to prior gastrointestinal surgery), gastric dysmotility, and medical and psychiatric conditions that lead to consumption of nonfood materials. Bezoars are often incidental findings on imaging or endoscopy in an asymptomatic patient. When they cause symptoms, abdominal pain, nausea, vomiting, decreased appetite, and halitosis are most common. An abdominal plain film can suggest the presence of a bezoar, which can be confirmed on ultrasound, fluoroscopy, or CT examination. On fluoroscopy or CT scan, a bezoar appears as a nonhomogeneous, nonenhancing mass within the lumen of the stomach or intestine. Oral contrast circumscribes the mass.



Fig. 380.3 Large trichobezoar in the shape of the stomach, duodenum, and proximal jejunum after surgical removal. *(Courtesy Dr. Michael L. Nance, Division of Pediatric General, Thoracic and Fetal Surgery, Children's Hospital of Philadelphia.)*

Bezoars are classified on the basis of their composition. **Phytobezoars** are the most common type of bezoar and are composed of undigestible vegetable/fruit matter. Carbonated soda has been demonstrated to help dissolve phytobezoars and should be considered as a first-line option for management. When available, cellulase can also be used for chemical dissolution. Given the risk of gastric ulcer or perforation, the use of papain (meat tenderizer) is not recommended. If endoscopic removal is needed, endotracheal intubation is required and use of an overtube may be considered. In addition to chemical dissolution and endoscopic or removal, prokinetic agents may be used for adjuvant medical therapy as well. **Trichobezoars** are composed of hair and are most frequently a complication of the psychiatric disorder trichotillomania, and the most severe form is known as Rapunzel syndrome (hair bezoar extending beyond the stomach to the small intestine). Large trichobezoars require surgical removal; endoscopic removal is not recommended (Fig. 380.3). **Lactobezoars** are uncommon and are most frequently seen in premature infants and can be attributed to the high casein or calcium content of some premature formulas. These bezoars generally resolve when feedings are withheld for 24-48 hours. **Pharmacobezoars** (composed of ingested medications) and other bezoars composed of various other objects (vinyl gloves, cement, Styrofoam, etc.) may also be seen and management is case-dependent.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 381

Peptic Ulcer Disease in Children

Samra S. Blanchard and Steven J. Czinn

Peptic ulcer disease, the end result of inflammation caused by an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum, manifests with varying degrees of gastritis or frank ulceration. The pathogenesis of peptic ulcer disease is multifactorial, but the final common pathway for the development of ulcers is the action of acid and pepsin-laden contents of the stomach on the gastric and duodenal mucosa and the inability of mucosal defense mechanisms to allay those effects. Abnormalities in the gastric and duodenal mucosa can be visualized on endoscopy, with or without histologic changes. Deep mucosal lesions that disrupt the muscularis mucosa of the gastric or duodenal wall define **peptic ulcers.** Gastric ulcers are generally located on the lesser curvature of the stomach, and 90% of duodenal ulcers are found in the duodenal bulb. Rates of peptic ulcer disease in childhood appear to be low. Large pediatric centers anecdotally report an incidence of 5-7 children with gastric or duodenal ulcers per 2,500 hospital admissions each year.

Ulcers in children can be classified as **primary** peptic ulcers, which are chronic and more often duodenal, or **secondary,** which are usually more acute in onset and are more often gastric (Table 381.1). Primary ulcers are most often associated with *Helicobacter pylori* infection. Secondary peptic ulcers can result from stress caused by sepsis, shock, or an intracranial lesion (Cushing ulcer), or in response to a severe burn injury (Curling ulcer). Secondary ulcers can also occur as the result of using drugs (nonsteroidal antiinflammatory drugs [NSAIDs], corticosteroids, sodium valproate, iron, potassium supplements, theophylline), hypersecretory states like Zollinger-Ellison syndrome (see Chapter 381.1), G-cell hyperplasia, short bowel syndrome, and hyperparathyroidism. Infections with cytomegalovirus, herpes simplex virus, and tuberculosis and systemic inflammatory diseases like Crohn disease, sarcoidosis, mastocytosis, and eosinophilic gastroenteritis can also cause ulcers.

PATHOGENESIS

Acid Secretion

By 3-4 years of age, gastric acid secretion approximates adult values. Acid initially secreted by the oxyntic cells of the stomach has a pH of approximately 0.8, whereas the pH of the stomach contents is 1-2. Excessive acid secretion is associated with a large parietal cell mass, hypersecretion by antral G cells, and increased vagal tone, resulting in increased or sustained acid secretion in response to meals and increased secretion during the night. The secretagogues that promote gastric acid production include acetylcholine released by the vagus nerve, histamine secreted by enterochromaffin cells, and gastrin released by the G cells of the antrum. Mediators that decrease gastric acid secretion and enhance protective mucin production include prostaglandins.

Table 381.1 Etiologic Classification of Peptic Ulcers

Positive for *Helicobacter pylori* infection
Drug (NSAID)-induced
H. pylori and NSAID-positive
H. pylori and NSAID-negative*
Acid hypersecretory state (Zollinger-Ellison syndrome)
Anastomosis ulcer after subtotal gastric resection
Tumors (cancer, lymphoma, carcinoid syndrome)
Crohn disease of the stomach or duodenum
Eosinophilic gastroduodenitis
Systemic mastocytosis
Radiation damage
Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients)
Colonization of stomach with *Helicobacter heilmannii*
Severe systemic disease
Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)
True idiopathic ulcer

*Requires search for other specific causes.
NSAID, Nonsteroidal antiinflammatory drug.
From Vakil N, Megraud F. Eradication therapy for *Helicobacter pylori. Gastroenterology.* 2007;133:985–1001.

Mucosal Defense

A continuous layer of mucous gel that serves as a diffusion barrier to hydrogen ions and other chemicals covers the gastrointestinal (GI) mucosa. Mucus production and secretion are stimulated by prostaglandin E_2. Underlying the mucous coat, the epithelium forms a second-line barrier, the characteristics of which are determined by the biology of the epithelial cells and their tight junctions. Another important function of epithelial cells is to secrete chemokines when threatened by microbial attack. Secretion of bicarbonate into the mucous coat, which is regulated by prostaglandins, is important for neutralization of hydrogen ions. If mucosal injury occurs, active proliferation and migration of mucosal cells occurs rapidly, driven by epithelial growth factor, transforming growth factor-α, insulin-like growth factor, gastrin, and bombesin, and covers the area of epithelial damage.

CLINICAL MANIFESTATIONS

The presenting symptoms of peptic ulcer disease vary with the age of the patient. Hematemesis or melena is reported in up to half of the patients with peptic ulcer disease. School-age children and adolescents more commonly present with epigastric pain and nausea, presentations generally seen in adults. Dyspepsia, epigastric abdominal pain or fullness, is seen in older children. Infants and younger children usually present with feeding difficulty, vomiting, crying episodes, hematemesis, or melena. In the neonatal period, gastric perforation can be the initial presentation.

The classic symptom of peptic ulceration, epigastric pain alleviated by the ingestion of food, is present only in a minority of children. Many pediatric patients present with poorly localized abdominal pain, which may be periumbilical. The vast majority of patients with periumbilical or epigastric pain or discomfort do not have a peptic ulcer, but rather a functional GI disorder, such as irritable bowel syndrome or nonulcer (functional) dyspepsia (see Chapter 389). Patients with peptic ulceration rarely present with acute abdominal pain from perforation or symptoms and signs of pancreatitis from a posterior penetrating ulcer. Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short. Vomiting can be a sign of gastric outlet obstruction.

The pain is often described as dull or aching, rather than sharp or burning, as in adults. It can last from minutes to hours; patients have frequent exacerbations and remissions lasting from weeks to months. Nocturnal pain waking the child is common in older children. A history of typical ulcer pain with prompt relief after taking antacids is found in <33% of children. Rarely, in patients with acute or chronic blood loss, penetration of the ulcer into the abdominal cavity or adjacent organs produces shock, anemia, peritonitis, or pancreatitis. If inflammation and edema are extensive, acute or chronic gastric outlet obstruction can occur.

DIAGNOSIS

Esophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease. Endoscopy allows the direct visualization of esophagus, stomach, and duodenum, identifying the specific lesions. Biopsy specimens must be obtained from the esophagus, stomach, and duodenum for histologic assessment as well as to screen for the presence of *H. pylori* infection. Endoscopy also provides the opportunity for hemostatic therapy including clipping, injection, and the use of thermal coagulation.

PRIMARY ULCERS

Helicobacter pylori Gastritis

H. pylori is among the most common bacterial infections in humans. It is a gram-negative, S-shaped rod that produces urease, catalase, and oxidase; these enzymes might play a role in the pathogenesis of peptic ulcer disease. The mechanism of acquisition and transmission of *H. pylori* is unclear, although the most likely mode of transmission is fecal-oral or oral-oral. Viable *H. pylori* organisms can be cultured from the stool or vomitus of infected patients. Risk factors such as low socioeconomic status in childhood or affected family members also influence the prevalence. All children infected with *H. pylori* develop histologic chronic active gastritis but are often asymptomatic. In children, *H. pylori* infection can manifest with abdominal pain or vomiting and, less often, refractory iron-deficiency anemia or poor growth. *H. pylori* can be associated, though rarely, with chronic autoimmune thrombocytopenia. Chronic colonization with *H. pylori* can predispose children to a significantly increased risk of developing a duodenal ulcer, gastric cancer such as adenocarcinoma, or mucosa-associated lymphoid tissue lymphomas. The relative risk of gastric carcinoma is 2.3-8.7 times greater in infected adults compared with uninfected subjects. *H. pylori* is classified by the World Health Organization as a group I carcinogen.

Anemia, idiopathic thrombocytopenic purpura, short stature, and sudden unexplained infant death (SUID) have also been reported as extragastric manifestations of *H. pylori* infection. In one published study, *H. pylori* infection has been correlated with cases of SUID, but there is no evidence to suggest that *H. pylori* plays a role in the pathogenesis of SUID.

The **diagnosis** of *H. pylori* infection is made histologically by demonstrating the organism in the biopsy specimens. The current consensus report does not recommend using antibody-based tests (IgG, IgA) for *H pylori* in serum, whole blood, urine, and saliva in the clinical setting. ^{13}C-urea breath tests and stool antigen tests are reliable noninvasive methods of detecting *H. pylori* infection in patients who do not require endoscopic evaluation. Patients should stop proton pump inhibitor (PPI) therapy 2 weeks before testing as they can cause false-negative results. Nonetheless, for symptomatic children with suspected *H. pylori* infection, an initial upper endoscopy is recommended to evaluate and confirm *H. pylori* disease. The range of endoscopic findings in children with *H. pylori* infection varies from being grossly normal to the presence of nonspecific gastritis with prominent rugal folds, nodularity (Fig. 381.1), or ulcers. Because the antral mucosa appears to be *endoscopically normal* in a significant number of children with primary *H. pylori* gastritis, gastric biopsies should always be obtained from the body and antrum of the stomach regardless of the endoscopic appearance. If *H. pylori* is identified, even in a child with no symptoms, eradication therapy should be offered (Tables 381.2 and 381.3). Successful *H. pylori* eradication is associated with cure of peptic ulcer disease and very low risk of relapse. Therefore monitoring the success of therapy is mandatory in these patients 4-6 weeks after stopping antibiotics and at least 2 weeks after stopping PPI therapy. Eradication must be tested with the ^{13}C-urea breath test or stool antigen test. If there is an eradication failure, the patient should receive *rescue* therapy.

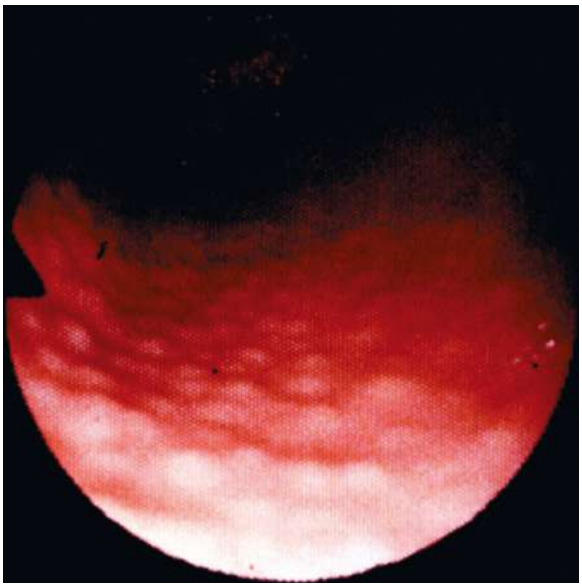

Fig. 381.1 Endoscopic view of lymphoid modular hyperplasia of the gastric antrum. Endoscopic hemostatic therapy is indicated for ulcers with active spurting, active oozing, and nonbleeding but visible vessels. Hemostatic therapy may include bipolar electrocoagulation or heater probe, or injectable soluble alcohol. *(From Campbell DI, Thomas JE. Helicobacter pylori infection in paediatric practice. Arch Dis Child Educ Pract Ed. 2005;90:ep25–ep30.)*

IDIOPATHIC ULCERS

H. pylori–negative peptic ulcers in children who have no history of taking NSAIDs represent 15–20% of pediatric peptic ulcers. The pathogenesis of idiopathic ulcer remains uncertain. These patients do not have nodularity in the gastric antrum or histologic evidence of gastritis. In idiopathic ulcers, acid suppression alone is the preferred effective treatment. Either PPIs or H_2-receptor antagonists may be used. Idiopathic ulcers have a high recurrence rate after discontinuing antisecretory therapy. These children should be followed closely, and if symptoms recur, antisecretory therapy should be restarted. It is also important to consider uncommon but possible conditions like Crohn disease, cytomegalovirus, and Zollinger-Ellison syndrome.

SECONDARY ULCERS

Aspirin and Other Nonsteroidal Antiinflammatory Drugs

NSAIDs produce mucosal injury by direct local irritation and by inhibiting cyclooxygenase (COX) and prostaglandin formation. Prostaglandins enhance mucosal resistance to injury; therefore a decrease in prostaglandin production increases the risk of mucosal injury. The severe erosive gastropathy produced by NSAIDs can ultimately result in bleeding ulcers or gastric perforations. The location of these ulcers is more common in the stomach than in the duodenum, and usually in the antrum. The discovery of two isoforms of COX-1 and COX-2 has led to the development of COX-2-selective NSAIDs, but they can still cause ulcerations in the GI tract.

STRESS ULCERATION

Stress ulceration usually occurs within 24 hours of onset of a critical illness in which physiologic stress is present. In many cases, the patients bleed from gastric erosions, rather than ulcers. Approximately 25% of the critically ill children in a pediatric intensive care unit have macroscopic evidence of gastric bleeding. Preterm and term infants in the neonatal intensive care unit can also develop gastric mucosal lesions and can present with upper GI bleeding or perforated ulcers. Although prophylactic measures to prevent stress ulcers in children are not standardized, drugs that inhibit gastric acid production (PPIs) are often used in the pediatric intensive care unit to reduce the rate of gastric erosions or ulcers. There is a concern that prophylactic PPI therapy increases the risk of ventilator-associated pneumonia and possibly *Clostridium difficile*–associated disease.

TREATMENT

The management of acute hemorrhage includes serial monitoring of pulse, blood pressure, and hematocrit to ensure hemodynamic stability and avoid significant hypovolemia and anemia. Normal saline can be used to resuscitate a patient who has poor intravascular volume status. This can be followed by packed red blood cell transfusions for significant symptomatic anemia. The patient's blood should be typed and cross matched, and a large-bore catheter should be placed for fluid or blood replacement. A nasogastric tube should be placed to determine whether the bleeding has stopped. Significant anemia can occur after fluid resuscitation as a consequence of equilibration or continued blood loss (which can also cause shock). In adults, a conservative threshold for transfusion (<7 g/dL vs 9 g hemoglobin) resulted in improved survival and fewer episodes of rebleeding. Fortunately, most acute peptic ulcer bleeding stops spontaneously.

Table 381.2 Recommended Eradication Therapies for *Helicobacter pylori*–Associated Disease in Children

MEDICATIONS	DOSE		DURATION OF TREATMENT
Proton pump inhibitor	1 mg/kg/dose twice a day		1 mo
ANTIBIOTICS	**WEIGHT**	**DOSE**	**DURATION OF TREATMENT**
Amoxicillin	15-24 kg	500 mg twice a day	14 days
	25-34 kg	750 mg twice a day	
	>35 kg	1,000 mg twice a day	
Clarithromycin	15-24 kg	250 mg twice a day	14 days
	25-34 kg	500 mg in a.m., 250 mg in p.m.	
	>35 kg	500 mg twice a day	
Metronidazole	15-24 kg	250 mg twice a day	14 days
	25-34 kg	500 mg in a.m., 250 mg in p.m.	
	>35 kg	500 mg twice a day	

Depending on previous antibiotic use history, recommended combinations are amoxicillin + clarithromycin + PPI OR amoxicillin + metronidazole + PPI OR clarithromycin + metronidazole + PPI. Adapted from Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents. *J Pediatr Gastroenterol Nutr.* 2017;64(6):991–1003.

Table 381.3 Antisecretory Therapy with Pediatric Dosages

MEDICATION	PEDIATRIC DOSE	HOW SUPPLIED
H_2-RECEPTOR ANTAGONISTS		
Ranitidine	4-10 mg/kg/day divided 2 or 3 × a day	Pulled from market
Famotidine	1-2 mg/kg/day divided twice a day	Syrup: 40 mg/5 mL. Tablets: 20, 40 mg
Nizatidine	5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day	Pulled from market
PROTON PUMP INHIBITORS		
Omeprazole	1.0-3.3 mg/kg/day weigh <20 kg: 10 mg/day weigh >20 kg: 20 mg/day Approved for use in those older than 1 month	Capsules: 10, 20, 40 mg
Lansoprazole	0.8-4 mg/kg/day weigh <30 kg: 15 mg/day weigh >30 kg: 30 mg/day Approved for use in those older than 1 yr	Capsules: 15, 30 mg Powder packet: 15, 30 mg SoluTab: 15, 30 mg
Rabeprazole	1-11 yr (weigh <15 kg): 5 mg/day 1-11 yr (weigh >15 kg): 10 mg/day >12 yr: 20 mg tablet Approved for use in those older than 1 yr	Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg
Pantoprazole	1-5 yr: 0.3-1.2 mg/kg/day (limited data) >5 yr of age: weigh >15 kg to <40 kg: 20 mg/day weigh >40 kg: 40 mg/day Approved for use in those older than 1 yr	Tablet: 20, 40 mg Powder pack: 40 mg
Esomeprazole	1 mo - < 1 yr old weigh 3 kg to 5 kg: 2.5 mg weigh >5 kg to 7.5 kg: 5 mg weigh >7.5 kg to 12 kg: 10 mg 1-11 yr old weigh <20 kg: 10 mg weigh >20 kg: 20 mg Approved for use 1 mo and older	Capsules: 20, 40 Delayed-release single-dose packs: 2.5, 5, 10, 20 mg
Dexlansoprazole	12-17 yr: 30-60 mg Approved for use in those older than 12 yr	Capsules: 30, 60
Omeprazole sodium bicarbonate	Safety and efficacy have not been established for those under 18 yr	Capsules: 20, 40 Powder for oral suspension: 20 mg, 40 mg
CYTOPROTECTIVE AGENTS		
Sucralfate	40-80 mg/kg/day	Suspension: 1,000 mg/5 mL Tablet: 1,000 mg

Patients with suspected peptic ulcer hemorrhage should receive high-dose intravenous (IV) PPI therapy, which lowers the risk of rebleeding. Some centers also use octreotide, which lowers splanchnic blood flow and gastric acid production.

Once the patient is hemodynamically stable, endoscopy is indicated to identify the source of bleeding and to treat a potential bleeding site (Fig. 381.2). Methods used to achieve hemostasis include mechanical devices (clipping), injection therapy (diluted epinephrine 1:100,00), and thermal therapy (heater probe). Ulcer therapy has two goals, ulcer healing and elimination of the primary cause. Other important considerations are relief of symptoms and prevention of complications. The **first-line drugs** for the treatment of gastritis and peptic ulcer disease in children are PPIs and H_2-receptor antagonists (see Table 381.3). PPIs are more potent in ulcer healing. Cytoprotective agents can also be used as adjunct therapy if mucosal lesions are present. Antibiotics in combination with a PPI must be used for the treatment of *H. pylori*–associated ulcers (see Table 381.2).

H_2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) competitively inhibit the binding of histamine at the H_2 subtype receptor of the gastric parietal cell. PPIs block the gastric parietal cell H^+/K^+-adenosine triphosphatase pump in a dose-dependent fashion, reducing basal and stimulated gastric acid secretion. Ranitidine and nizatidine were pulled out of the market in April 2020 due to unacceptable levels of N-nitrosodimethylamine (NDMA), a probable human carcinogen. NDMA impurities have been introduced during the manufacturing processes and as the result of product degradation during storage. Currently, seven PPIs are available in the United States: omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole, and omeprazole/sodium bicarbonate. Apart from the last two, they are all approved in children and adolescents. They are well tolerated with only minor adverse effects, such as diarrhea (1–4%), headache (1–3%), and nausea (1%). When one considers therapeutic efficacy, the evidence suggests that all PPIs have comparable efficacy in treatment of peptic ulcer disease using standard doses and are superior to H_2-receptor antagonists. PPIs have their greatest effect when given before a meal. Pantoprazole and esomeprazole are the only PPI available in IV form in United States. IV PPI should be used in acute upper GI bleeding. Studies in adults have demonstrated that twice a day IV PPI is as effective as continuous infusion, and the current recommendation is to start with IV PPI and change to the oral form after evaluating their rebleeding risk at the time of endoscopy.

Treatment of *Helicobacter pylori*–Related Peptic Ulcer Disease

In pediatrics, antibiotics and bismuth salts have been used in combination with PPIs to treat *H. pylori* infection (see Table 381.2). Eradication rates in children range from 68–92% when the dual or triple therapy is used for 14 days. The ulcer healing rate ranges from 91–100%. Triple therapy yields a higher cure rate than dual therapy. The optimal regimen for the eradication of *H. pylori* infection in children has yet to be established, but the use of a PPI in combination with clarithromycin and amoxicillin or metronidazole for 2 weeks is a well-tolerated and recommended triple therapy (see Table 381.2). Although children younger than 5 years of age can become reinfected, the most common reason for treatment failure is poor compliance or antibiotic resistance. *H. pylori* has become more resistant to clarithromycin or metronidazole as a consequence of the extensive use of these antibiotics for other infections. In the case of resistant *H. pylori* infection, *bismuth-based quadruple therapy* or *sequential treatment* with different antibiotics or rescue therapy are acceptable options. The sequential treatment regimen is a 10-day treatment consisting of a PPI and amoxicillin (both twice daily) administered for the first 5 days followed by triple therapy consisting of a PPI, clarithromycin, and metronidazole for the remaining 5 days. Levofloxacin, rifabutin, or furazolidone can be used with amoxicillin and bismuth as a rescue therapy depending on the age of the patient. Fidaxomicin has equivalent efficacy to vancomycin in adults. Knowledge of the community's *H. pylori* resistance pattern to clarithromycin or metronidazole might help choose the initial or rescue therapy. In adults with persistent *H. pylori* infection, a combination of rifabutin with amoxicillin and esomperazole was effective in eradicating *H. pylori*.

Surgical Therapy

Since the discovery of *H. pylori* and the availability of modern medical management, peptic ulcer disease requiring surgical treatment has become extremely rare. The indications for surgery remain uncontrolled bleeding, perforation, and obstruction.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

381.1 Zollinger-Ellison Syndrome

Samra S. Blanchard and Steven J. Czinn

Zollinger-Ellison syndrome is a rare syndrome characterized by refractory, severe peptic ulcer disease caused by gastric hypersecretion due to the autonomous secretion of gastrin by a neuroendocrine tumor (gastrinoma). Clinical presentations are similar to those of peptic ulcer disease with the addition of diarrhea. The diagnosis is suspected by the presence of recurrent, multiple, or atypically located ulcers. More than 98% of patients have elevated fasting gastrin levels. Zollinger-Ellison syndrome is common in patients with **multiple endocrine neoplasia 1** and rare with **neurofibromatosis** and **tuberous sclerosis**. Prompt and effective management of increased gastric acid secretion is essential in the management. PPIs are the drug of choice due to their long duration of action and potency. H_2-receptor antagonists are also effective, but higher doses are required than those used in peptic ulcer disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

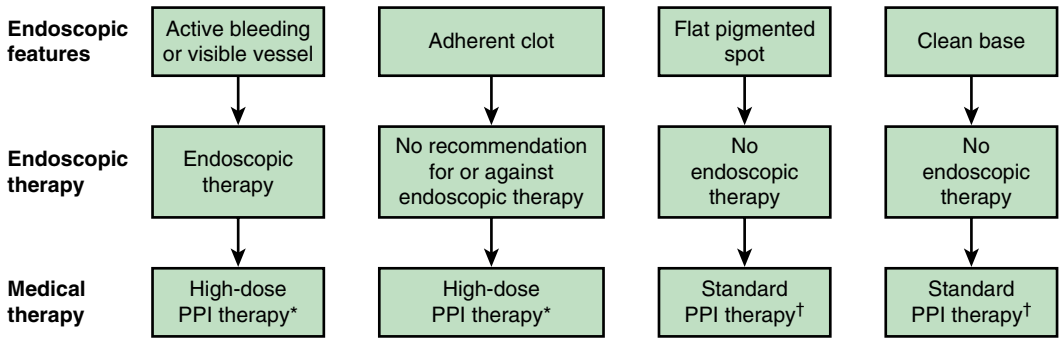

Fig. 381.2 Endoscopic and medical therapy algorithm for ulcer bleeding based on endoscopic features of ulcer. *For continuous regimen, 80-mg bolus followed by 8-mg/min infusion for 3 days is recommended. For intermittent regimens, doses of 40 mg 2 to 4 times daily for 3 days are suggested, given orally if feasible, and an initial bolus of 80 mg may be appropriate. †Standard PPI therapy (e.g., oral PPI once daily) has been recommended by previous guidelines. PPI, Proton pump inhibitor. *(From Laine L, Barkun AN, Saltzman JR, et al. ACG clinical guideline: upper gastrointestinal and ulcer bleeding. Am J Gastrointerol. 2021;116:899–917. Fig. 3.)*

Chapter 382

Inflammatory Bowel Disease

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

The term *inflammatory bowel disease* (IBD) is used to represent two distinctive disorders of idiopathic chronic intestinal inflammation: Crohn disease and ulcerative colitis. Their respective etiologies are poorly understood, and both disorders are characterized by unpredictable exacerbations and remissions. The most common time of onset of IBD is during the preadolescent/adolescent era and young adulthood. A bimodal distribution has been shown with an early onset at 10-20 years of age and a second, smaller peak at 50-80 years of age. Approximately 25% of patients present before 20 years of age. IBD may begin as early as the first year of life, and an increased incidence among young children has been observed since the turn of the 20th century. Children with *early-onset* IBD are more likely to have colonic involvement. In developed countries, these disorders are the major causes of chronic intestinal inflammation in children beyond the first few years of life. A third, less-common category, *indeterminate colitis*, represents approximately 10% of pediatric patients.

Genetic and environmental influences are involved in the pathogenesis of IBD. The risk of IBD in family members of an affected person has been reported in the range of 7–30%; a child whose parents both have IBD has a >35% chance of acquiring the disorder. Relatives of a patient with ulcerative colitis have a greater risk of acquiring ulcerative colitis than Crohn disease, whereas relatives of a patient with Crohn disease have a greater risk of acquiring this disorder; the two diseases can occur in the same family. The risk of occurrence of IBD among relatives of patients with Crohn disease is somewhat greater than for patients with ulcerative colitis.

The importance of genetic factors in the development of IBD is noted by a higher chance that both twins will be affected if they are monozygotic rather than dizygotic. The concordance rate in twins is higher in Crohn disease (36%) than in ulcerative colitis (16%). Genetic disorders that have been associated with IBD include Turner syndrome, Hermansky-Pudlak syndrome, glycogen storage disease type Ib, and various immunodeficiency disorders. The first IBD gene, *NOD2,* was identified through association mapping; an IBD5 risk haplotype was also identified. There has been an exponential growth in the set of validated genetic risk factors for IBD (Table 382.1).

A perinuclear antineutrophil cytoplasmic antibody is found in approximately 70% of patients with ulcerative colitis compared with <20% of those with Crohn disease and is believed to represent a marker of genetically controlled immunoregulatory disturbance. Approximately 55% of those with Crohn disease are positive for anti–*Saccharomyces cerevisiae* antibody. Since the importance of these were first described, multiple other serologic and immune markers of Crohn disease and ulcerative colitis have been recognized.

IBD is caused by dysregulated or inappropriate immune response to environmental factors in a genetically susceptible host. An abnormality in intestinal mucosal immunoregulation may be of primary importance in the pathogenesis of IBD, involving activation of cytokines, triggering a cascade of reactions that results in bowel inflammation. These cytokines are recognized as known or potential targets for IBD therapies.

Multiple environmental factors are recognized to be involved in the pathogenesis of IBD, none more critical than the gut microbiota. The increasing incidence of IBD over time is likely in part attributable to alterations in the microbiome. Evidence includes association between IBD and residence in or immigration to industrialized nations, a *Western diet*, increased use of antibiotics at a younger age, high rates of vaccination, and less exposure to microbes at a young age. Although gut microbes likely play an important role in the pathogenesis of IBD, the exact mechanism needs to be elucidated further. Some environmental factors are disease specific; for example, cigarette smoking is a risk factor for Crohn disease but paradoxically protects against ulcerative colitis.

It is usually possible to distinguish between ulcerative colitis and Crohn disease by the clinical presentation and radiologic, endoscopic, and histopathologic findings (Table 382.2). It is not possible to make a definitive diagnosis in approximately 10% of patients with chronic colitis; this disorder is called *indeterminate colitis*. Occasionally, a child initially believed to have ulcerative colitis on the basis of clinical findings is subsequently found to have Crohn colitis. This is particularly true for the youngest patients, because Crohn disease in this patient population can more often manifest as exclusively colonic inflammation, mimicking ulcerative colitis. The medical treatments of Crohn disease and ulcerative colitis overlap.

Extraintestinal manifestations occur slightly more commonly with Crohn disease than with ulcerative colitis (Table 382.3). Poor growth is seen in 15–40% of children with Crohn disease at diagnosis. Decrease in height velocity occurs in nearly 90% of patients with Crohn disease diagnosed in childhood or adolescence. Of the extraintestinal manifestations that occur with IBD, joint, skin, eye, mouth, and hepatobiliary involvement tend to be associated with colitis, whether ulcerative or Crohn. The presence of some manifestations, such as peripheral arthritis, erythema nodosum, and anemia, correlates with activity of the bowel disease. Activity of pyoderma gangrenosum correlates less well with activity of the bowel disease, whereas sclerosing cholangitis, ankylosing spondylitis, and sacroiliitis do not correlate with intestinal disease. Arthritis occurs in three patterns: migratory peripheral arthritis involving primarily large joints, ankylosing spondylitis, and sacroiliitis. The peripheral arthritis of IBD tends to be nondestructive. Ankylosing spondylitis begins in the third decade and occurs most commonly in patients with ulcerative colitis who have the human leukocyte antigen B27 phenotype. Symptoms include low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints are typically affected. Isolated sacroiliitis is usually asymptomatic but is common when a careful search is performed. Among the skin manifestations, erythema nodosum is most common. Patients with erythema nodosum or pyoderma gangrenosum have a high likelihood of having arthritis as well. Glomerulonephritis, uveitis, and a hypercoagulable state are other rare manifestations that occur in childhood. Cerebral thromboembolic disease has been described in children with IBD.

382.1 Chronic Ulcerative Colitis

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

Ulcerative colitis, an idiopathic chronic inflammatory disorder, is localized to the colon and spares the upper gastrointestinal (GI) tract. Disease usually begins in the rectum and extends proximally for a variable distance. When it is localized to the rectum, the disease is ulcerative proctitis, whereas disease involving the entire colon is pancolitis. Approximately 50–80% of pediatric patients have extensive colitis; adults more commonly have distal disease. Ulcerative *proctitis* is less likely to be associated with systemic manifestations, although it may be less responsive to treatment than more diffuse disease. Approximately 30% of children who present with ulcerative proctitis experience proximal spread of the disease. Ulcerative colitis has rarely been noted to present in infancy. Dietary protein intolerance can easily be misdiagnosed as ulcerative colitis in this age-group. Dietary protein intolerance (cow's milk protein) is a transient disorder; symptoms are directly associated with the intake of the offending antigen.

The incidence of ulcerative colitis has increased but not to the extent of the increase in Crohn disease; incidence varies with country of origin. The age-specific incidence rates of pediatric ulcerative colitis in

Table 382.1 Selection of Most Important Genes Associated with Inflammatory Bowel Disease and the Most Commonly Associated Physiologic Functions and Pathways

	GENE NAME	ASSOCIATED DISEASE	GENE FUNCTION AND ASSOCIATED PATHWAYS	PHYSIOLOGIC FUNCTION
NOD2	Nucleotide-binding oligomerization domain- containing protein 2	Crohn disease	Bacterial recognition and response, NFκB activation and autophagy and apoptosis	Innate mucosal defense
IL10	IL-10	Crohn disease	Antiinflammatory cytokine, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RA	IL-10 receptor A	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RB	IL-10 receptor B	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL23R	IL-23 receptor	Crohn disease and ulcerative colitis	Immune regulation, proinflammatory pathways—JAK-STAT regulation	IL-23/T helper 17
TKY2	Tyrosine kinase 2	Crohn disease and ulcerative colitis	Inflammatory pathway signaling (IL-10 and -6, etc.) through intracellular activity	IL-23/T helper 17
IRGM	Immunity-related GTPase M	Crohn disease	Autophagy and apoptosis in cells infected with bacteria	Autophagy
ATG16L1	Autophagy-related 16 like 1	Crohn disease	Autophagy and apoptotic pathways	Autophagy
SLC22A4	Solute carrier family 22 member 4	Crohn disease	Cellular antioxidant transporter	Solute transporters
CCL2	C-C motif chemokine ligand 2	Crohn disease	Cytokine involved in chemotaxis for monocytes	Immune cell recruitment
CARD9	Caspase recruitment domain family member 9	Crohn disease and ulcerative colitis	Apoptosis regulation and NFκB pathway activation	Oxidative stress
IL2	IL-2	Ulcerative colitis	Cytokine involved in immune cell activation	T-cell regulation
MUC19	Mucin 19	Crohn disease and ulcerative colitis	Gel-forming mucin protein	Epithelial barrier

IL, Interleukin; JAK-STAT, Janus kinase-signal transducers and activators of transcription; NFκB, nuclear factor κ-light chain enhancer of activated B cells.
From Ashton JJ, Ennis S, Beattie RM. Early-onset paediatric inflammatory bowel disease. *Lancet.* 2017;1:147–158. Table 1.

Table 382.2 Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS	FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common	Strictures	Common	Rare
Diarrhea, mucus, pus	Variable	Common	Fissures	Common	Rare
Abdominal pain	Common	Variable	Fistulas	Common	Rare
Abdominal mass	Common	Not present	Toxic megacolon	None	Present
Growth failure	Common	Variable	Sclerosing cholangitis	Less common	Present
Perianal disease	Common	Rare	Risk for intestinal cancers	Increased	Greatly increased
Rectal involvement	Occasional	Universal	Discontinuous (skip) lesions	Common	Not present
Pyoderma gangrenosum	Rare	Present	Transmural involvement	Common	Unusual
Erythema nodosum	Common	Less common	Crypt abscesses	Less common	Common
Mouth ulceration	Common	Rare	Granulomas	Common	None
Thrombosis	Less common	Present	Linear ulcerations	Uncommon	Common
Colonic disease	50–75%	100%	Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%
Ileal disease	Common	None except backwash ileitis			
Stomach–esophageal disease	More common	Chronic gastritis can be seen			

Table 382.3 Extraintestinal Complications of Inflammatory Bowel Disease

MUSCULOSKELETAL
Peripheral arthritis
Granulomatous monoarthritis
Granulomatous synovitis
Rheumatoid arthritis
Sacroiliitis
Ankylosing spondylitis
Digital clubbing and hypertrophic osteoarthropathy
Periostitis
Osteoporosis, osteomalacia
Rhabdomyolysis
Pelvic osteomyelitis
Chronic recurrent multifocal osteomyelitis (CRMO)
Relapsing polychondritis

SKIN AND MUCOUS MEMBRANES
Oral lesions
Orofacial granulomatosis
Cheilitis
Aphthous stomatitis, glossitis
Granulomatous oral Crohn disease
Inflammatory hyperplasia fissures and cobblestone mucosa
Peristomatitis vegetans

DERMATOLOGIC
Erythema nodosum
Pyoderma gangrenosum
Sweet syndrome
Metastatic Crohn disease
Psoriasis
Epidermolysis bullosa acquisita
Perianal skin tags
Polyarteritis nodosa
Melanoma and nonmelanoma skin cancers

OCULAR
Conjunctivitis
Uveitis, iritis
Episcleritis
Scleritis
Retrobulbar neuritis
Chorioretinitis with retinal detachment
Crohn keratopathy
Posterior segment abnormalities
Retinal vascular disease
Idiopathic orbital inflammation (orbital pseudotumor)

BRONCHOPULMONARY
Chronic bronchitis with bronchiectasis
Chronic bronchitis with neutrophilic infiltrates
Fibrosing alveolitis
Pulmonary vasculitis
Small airway disease and bronchiolitis obliterans
Eosinophilic lung disease
Granulomatous lung disease
Tracheal obstruction

CARDIAC
Pleuropericarditis
Cardiomyopathy
Endocarditis
Myocarditis

MALNUTRITION
Decreased intake of food
- Inflammatory bowel disease
- Dietary restriction

Malabsorption
- Inflammatory bowel disease
- Bowel resection
- Bile salt depletion
- Bacterial overgrowth

Intestinal losses
- Electrolytes
- Minerals
- Nutrients

Increased caloric needs
- Inflammation
- Fever

HEMATOLOGIC/ONCOLOGIC
Anemia: iron deficiency (blood loss)
Vitamin B_{12} (ileal disease or resection, bacterial overgrowth, folate deficiency)
Anemia of chronic inflammation
Anaphylactoid purpura (Crohn disease)
Hyposplenism
Autoimmune hemolytic anemia
Coagulation abnormalities
Increased activation of coagulation factors
Activated fibrinolysis
Anticardiolipin antibody
Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions and pulmonary embolism
Systemic lymphoma (nonenteric)

RENAL AND GENITOURINARY
Metabolic
- Urinary crystal formation (nephrolithiasis, uric acid, oxalate)

Hypokalemic nephropathy
Inflammation
- Retroperitoneal abscess
- Fibrosis with ureteral obstruction
- Fistula formation

Glomerulitis
Membrane nephritis
Renal amyloidosis, nephrotic syndrome

PANCREATITIS
Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)
Ampullary Crohn disease
Granulomatous pancreatitis
Decreased pancreatic exocrine function
Sclerosing cholangitis with pancreatitis

HEPATOBILIARY
Primary sclerosing cholangitis
Small duct primary sclerosing cholangitis (pericholangitis)
Carcinoma of the bile ducts
Fatty infiltration of the liver
Cholelithiasis
Autoimmune hepatitis

ENDOCRINE AND METABOLIC
Growth failure, delayed sexual maturation
Thyroiditis
Osteoporosis, osteomalacia

NEUROLOGIC
Peripheral neuropathy
Meningitis
Vestibular dysfunction
Idiopathic intracranial hypertension (Pseudotumor cerebri)
Cerebral vasculitis
Migraine

Modified from Kugathasan S. Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004.p. 285.

North America is 2/100,000 population. The prevalence of ulcerative colitis in northern European countries and the United States varies from 100 to 200/100,000 population. Men are slightly more likely to acquire ulcerative colitis than are women; the reverse is true for Crohn disease.

CLINICAL MANIFESTATIONS

Blood, mucus, and pus in the stool as well as diarrhea are the typical presentation of ulcerative colitis. Constipation may be observed in those with proctitis. Symptoms such as tenesmus, urgency, cramping abdominal pain (especially with bowel movements), and nocturnal bowel movements are common. The mode of onset ranges from insidious with gradual progression of symptoms to acute and fulminant (Table 382.4; Figs. 382.1 and 382.2). Fever, severe anemia, hypoalbuminemia, leukocytosis, and more than five bloody stools per day for 5 days define **fulminant colitis**. Chronicity is an important part of the diagnosis; it is difficult to know if a patient has a subacute, transient infectious colitis or ulcerative colitis when a child has had 1-2 weeks of symptoms. Symptoms beyond this duration often prove to be secondary to IBD. Anorexia, weight loss, and growth failure may be present, although these complications are more typical of Crohn disease.

Extraintestinal manifestations that tend to occur more commonly with ulcerative colitis than with Crohn disease include pyoderma gangrenosum, sclerosing cholangitis, chronic active hepatitis, and ankylosing spondylitis. Iron deficiency can result from chronic blood loss as well as decreased intake. Folate deficiency is unusual but may be accentuated in children treated with sulfasalazine, which interferes with folate absorption. Chronic inflammation and the elaboration of a variety of inflammatory cytokines can interfere with erythropoiesis and result in the anemia of chronic disease. Secondary amenorrhea is common during periods of active disease.

Table 382.4 Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): four or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): four stools per day, minimum signs of systemic symptoms
- S3 (severe): six or more bloody stools per day, pulse rate of ≥90 beats/min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr

E, Extent; S, severity.
From Ordàs I, Eckmann L, Talamini M, et al. Ulcerative colitis. *Lancet.* 2012;380: 1606–1616. Panel 2.

The clinical course of ulcerative colitis is marked by remission and relapse, often without apparent explanation. After treatment of initial symptoms, approximately 5% of children with ulcerative colitis have a prolonged remission (longer than 3 years). Approximately 25% of children presenting with severe ulcerative colitis require colectomy within 5 years of diagnosis, compared with only 5% of those presenting with mild disease. It is important to consider the possibility of enteric infection with recurrent symptoms, specifically *Clostridium difficile;* these infections can mimic a flare-up or actually provoke a recurrence. The use of nonsteroidal antiinflammatory drugs is considered by some to predispose to exacerbation.

It is generally believed that the risk of colon cancer begins to increase after 8-10 years of disease and can then increase by 0.5–1% per year. The risk is delayed by approximately 10 years in patients with colitis limited to the descending colon. Proctitis alone is associated with virtually no increase in risk over the general population. Because colon cancer is usually preceded by changes of mucosal dysplasia, it is recommended that patients who have had ulcerative colitis for longer than 8-10 years be screened with colonoscopy and biopsies every 1-2 years. Although this is the current standard of practice, it is not clear if morbidity and mortality are changed by this approach. Two competing concerns about this plan of management remain unresolved. The original studies may have overestimated the risk of colon cancer; therefore the need for surveillance has been overemphasized, and screening for dysplasia might not be adequate for preventing colon cancer in ulcerative colitis if some cancers are not preceded by dysplasia.

DIFFERENTIAL DIAGNOSIS

The major conditions to exclude are infectious colitis, allergic colitis, and Crohn colitis. Every child with a new diagnosis of ulcerative colitis should have stool cultured for enteric pathogens, stool evaluation for *C. difficile,* ova and parasites, and perhaps serologic studies for amebae (Table 382.5). Cytomegalovirus infection can mimic ulcerative colitis or be associated with an exacerbation of existing disease, usually in immunocompromised patients. The most difficult distinction is from Crohn disease because the colitis of Crohn disease can initially appear identical to that of ulcerative colitis, particularly in younger children. The gross appearance of the colitis or development of small bowel disease eventually leads to the correct diagnosis; this can occur years after the initial presentation.

At the onset, the colitis of hemolytic uremic syndrome may be identical to that of early ulcerative colitis. Ultimately, signs of microangiopathic hemolysis (the presence of schistocytes on blood smear), thrombocytopenia, and subsequent renal failure should confirm the diagnosis of hemolytic-uremic syndrome. Although IgA vasculitis (Henoch-Schönlein purpura) can manifest as abdominal pain and bloody stools, it is not usually associated with colitis. Behçet disease can be distinguished by its typical features (see Chapter 202). Other considerations are radiation proctitis, viral colitis in immunocompromised patients, and ischemic colitis (Table 382.6). In infancy, dietary protein intolerance can be confused with ulcerative colitis, although the former is a transient problem that resolves on removal of the offending

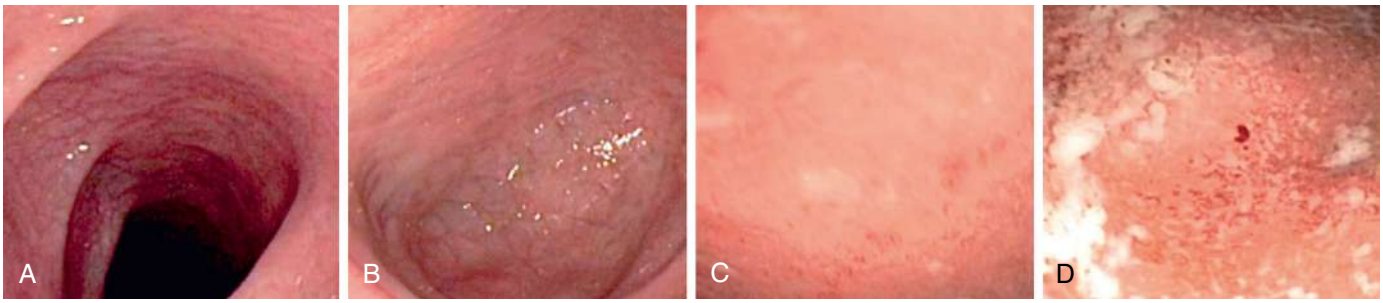

Fig. 382.1 Mayo endoscopic score for ulcerative colitis. **A,** Score 0 = normal; endoscopic remission. **B,** Score 1 = mild; erythema, decreased vascular pattern, mild friability. **C,** Score 2 = moderate; marked erythema, absent vascular pattern, friability, erosions. **D,** Score 3 = severe; spontaneous bleeding, ulceration. *(Images courtesy Elena Ricart. From Ordàs I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet. 2012;380:1606–1616. Fig. 2, p. 1610.)*

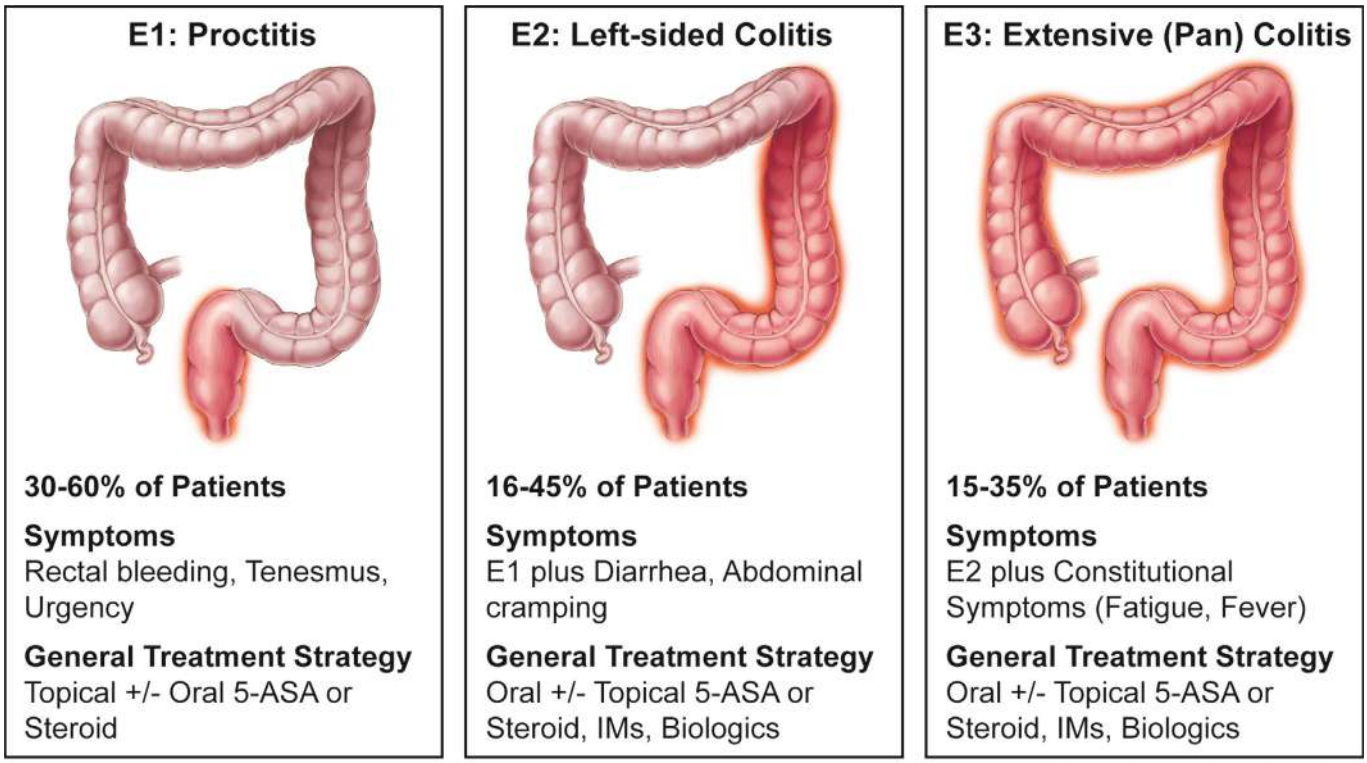

Fig. 382.2 Ulcerative colitis phenotypes by Montreal Classification. Symptoms and treatment strategy can differ based on extent of disease. 5-ASA, 5-Aminosalicylate; IM, immunomodulator. *(Illustration by Jill Gregory. Printed with permission of Mount Sinai Health System.)*

protein, and ulcerative colitis is extremely rare in this age-group. Very early onset monogenic disorders should be considered in infants (see Chapter 382.3 and Table 382.6). Hirschsprung disease can produce an enterocolitis before or within months after surgical correction; this is unlikely to be confused with ulcerative colitis.

DIAGNOSIS

The diagnosis of ulcerative colitis or ulcerative proctitis requires a typical presentation in the absence of an identifiable specific cause (see Tables 382.5 and 382.6) and typical endoscopic and histologic findings (see Tables 382.2 and 382.4). One should be hesitant to make a diagnosis of ulcerative colitis in a child who has experienced symptoms for <2-3 weeks until infection has been excluded. When the diagnosis is suspected in a child with subacute symptoms, the physician should make a firm diagnosis only when there is evidence of chronicity on colonic biopsy. Laboratory studies can demonstrate evidence of anemia (either iron deficiency or the anemia of chronic disease) or hypoalbuminemia. Although the sedimentation rate and C-reactive protein are often elevated, they may be normal even with fulminant colitis. An elevated white blood cell count is usually seen only with more severe colitis. Fecal calprotectin levels are usually elevated and are increasingly recognized to be a more sensitive and specific marker of GI inflammation than typical laboratory parameters. Barium enema is suggestive but not diagnostic of acute (Fig. 382.3) or chronic burned-out disease (Fig. 382.4).

The diagnosis of ulcerative colitis must be confirmed by endoscopic and histologic examination of the colon (see Fig. 382.1). Classically, disease starts in the rectum with a gross appearance characterized by erythema, edema, loss of vascular pattern, granularity, and friability. There may be a *cutoff* demarcating the margin between inflammation and normal colon, or the entire colon may be involved. There may be some variability in the intensity of inflammation even in those areas involved. Flexible sigmoidoscopy can confirm the diagnosis; colonoscopy can evaluate the extent of disease and rule out Crohn colitis. A colonoscopy should not be performed when fulminant colitis is suspected because of the risk of provoking *toxic megacolon* or causing a perforation during the procedure. The degree of colitis can be evaluated by the gross appearance of the mucosa. One does not generally see discrete ulcers, which would be more suggestive of Crohn colitis. The endoscopic findings of ulcerative colitis result from microulcers, which give the appearance of a diffuse abnormality. With very severe chronic colitis, pseudopolyps may be seen. Biopsy of involved bowel demonstrates evidence of acute and chronic mucosal inflammation. Typical histologic findings are cryptitis, crypt abscesses, separation of crypts by inflammatory cells, foci of acute inflammatory cells, edema, mucus depletion, and branching of crypts. The last finding is not seen in infectious colitis. Granulomas, fissures, or full-thickness involvement of the bowel wall (usually on surgical rather than endoscopic biopsy) suggest Crohn disease.

Perianal disease, except for mild local irritation or anal fissures associated with diarrhea, should make the clinician think of Crohn disease. Plain radiographs of the abdomen might demonstrate loss of haustral markings in an air-filled colon or marked dilation with toxic megacolon. With severe colitis, the colon may become dilated; a diameter of >6 cm, determined radiographically, in an adult suggests toxic megacolon. If it is necessary to examine the colon radiologically in a child with severe colitis (to evaluate the extent of involvement or to try to rule out Crohn disease), it is sometimes helpful to perform an upper GI contrast series with small bowel follow-through and then look at delayed films of the colon. Small bowel ultrasonography is another option for evaluation of small intestinal inflammation. CT and MR enterography allow for even higher resolution images of the small intestine. A barium enema is contraindicated in the setting of a potential toxic megacolon.

TREATMENT

Medical

A medical *cure* for ulcerative colitis is not available; treatment is aimed at controlling symptoms and reducing the risk of recurrence, with a secondary goal of minimizing steroid exposure. The intensity of treatment varies with the severity of the symptoms.

The first drug class to be used with mild or mild to moderate colitis is an aminosalicylate. Sulfasalazine is composed of a sulfur moiety linked

Table 382.5 Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
BACTERIAL			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
Yersinia enterocolitica	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
Salmonella	Watery → bloody diarrhea, food-borne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
Plesiomonas shigelloides	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now *Mycobacterium* tuberculosis Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
PARASITES			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-ASSOCIATED ENTEROPATHY			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
Isospora belli	As in *Cryptosporidium*		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

to the active ingredient 5-aminosalicylate (5-ASA). This linkage prevents the absorption of the medication in the upper GI tract, allowing it to reach the colon, where the two components are separated by bacterial cleavage. The dose of sulfasalazine is 30-100 mg/kg/24 hr (divided into two to four doses). Generally, the dose is not more than 2-4 g/24 hr. Hypersensitivity to the sulfa component is the major side effect of sulfasalazine and occurs in 10–20% of patients. Because of poor tolerance, sulfasalazine is used less commonly than other, better tolerated 5-ASA preparations (mesalamine, 50-100 mg/kg/day; balsalazide 2.25-6.75 g/day). Sulfasalazine and the 5-ASA preparations effectively treat active ulcerative colitis and prevent recurrence. It is recommended that the medication be continued even when the disorder is in remission. These medications might also modestly decrease the lifetime risk of colon cancer.

Approximately 5% of patients have an *allergic reaction* to 5-ASA, manifesting as rash, fever, and bloody diarrhea, which can be difficult to distinguish from symptoms of a flare of ulcerative colitis. 5-ASA can also be given in enema or suppository form and is especially useful for proctitis. Hydrocortisone enemas are used to treat proctitis as well, but they are probably not as effective. A combination of oral and rectal 5-ASA as well as monotherapy with rectal preparation has been shown to be more effective than just oral 5-ASA for distal colitis. Extended release budesonide may also induce remission in patients with mild to moderate ulcerative colitis. Rectal preparations of budesonide are also available.

Probiotics are effective in adults for maintenance of remission for ulcerative colitis, although they do not induce remission during an active flare. The most promising role for probiotics has been to prevent *pouchitis*, a common complication following colectomy and ileal-pouch anal anastomosis surgery.

Children with moderate to severe pancolitis or colitis that is unresponsive to 5-ASA therapy should be treated with corticosteroids, most commonly oral prednisone. The usual starting dose of prednisone is 1-2 mg/kg/24 hr (40-60 mg maximum dose). This medication can be given once daily. With severe colitis, the dose can be divided twice daily and can be given intravenously. Steroids are considered an effective medication for acute flares, but they are not appropriate maintenance medications because of loss of effect and side effects, including poor growth, adrenal suppression, cataracts, osteopenia, aseptic necrosis of the head of the femur, glucose intolerance, risk of infection, mood disturbance, and cosmetic effects.

For a hospitalized patient with persistence of symptoms despite intravenous steroid treatment for 3-5 days, escalation of therapy or surgical options should be considered. The validated pediatric ulcerative colitis activity index can be used to help determine current disease severity based on clinical factors and help determine who is more likely to respond to steroids and those who will likely require escalation of therapy (Table 382.7).

With medical management, most children are in remission within 3 months; however, 5–10% continue to have symptoms unresponsive

Table 382.6 Chronic Inflammatory Bowel–Like Intestinal Disorders Including Monogenic Diseases

INFECTION (SEE TABLE 382.5)
AIDS-Associated
Toxin
Immune–Inflammatory
Severe combined immunodeficiency diseases
Agammaglobulinemia
Chronic granulomatous disease
Wiskott-Aldrich syndrome
Common variable immunodeficiency diseases
Acquired immunodeficiency states
Dietary protein enterocolitis
Autoimmune polyendocrine syndrome type 1
Behçet disease
Lymphoid nodular hyperplasia
Eosinophilic gastroenteritis
Omenn syndrome
Graft-versus-host disease
IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes
Interleukin-10 signaling defects
Autoimmune enteropathy*
Microscopic colitis
Hyperimmunoglobulin M syndrome
Hyperimmunoglobulin E syndromes
Mevalonate kinase deficiency
Familial Mediterranean fever
Phospholipase Cγ_2 defects
IL10RA pathogenic variant
Familial hemophagocytic lymphohistiocytosis type 5
X-linked lymphoproliferative syndromes types 1, 2 (*XIAP* gene)
Congenital neutropenias
TRIM22 pathogenic variant
Leukocyte adhesion deficiency 1
NLRC4 pathogenic variants
VASCULAR–ISCHEMIC DISORDERS
Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Granulomatosis with angiitis
OTHER
Glycogen storage disease type 1b
Dystrophic epidermolysis bullosa
X-linked ectodermal dysplasia and immunodeficiency
Dyskeratosis congenita
ADAM-17 deficiency
Prestenotic colitis
Diversion colitis
Kindler syndrome
Radiation colitis
Neonatal necrotizing enterocolitis
Typhlitis
Sarcoidosis
Hirschsprung colitis
Intestinal lymphoma
Laxative abuse
Endometriosis
Hermansky-Pudlak syndrome
Trichohepatoenteric syndrome
Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome

*May be the same as IPEX.

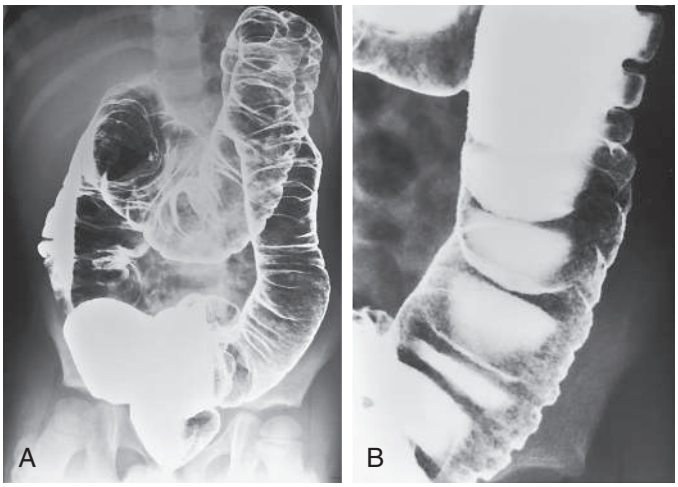

Fig. 382.3 Ulcerative colitis. Double-contrast barium enema in a 5-yr-old child who had had intermittent intestinal and extraintestinal symptoms since the age of 3 yr. **A,** Small ulcerations are distributed uniformly about the colonic circumference and continuously from the rectum to the proximal transverse colon. This pattern of involvement is typical of ulcerative colitis. **B,** In this coned view of the sigmoid in the same patient, small ulcerations are represented by fine spiculation of the colonic contour in tangent and by fine stippling of the colon surface en face. *(From Hoffman AD. The child with diarrhea. In Hilton SW, Edwards DK, eds. Practical Pediatric Radiology, 2nd ed. Philadelphia: WB Saunders; 1994. p. 260.)*



Fig. 382.4 Ulcerative colitis: late changes. This single-contrast barium enema shows the late changes of ulcerative colitis in a 15-yr-old child. The colon is featureless, reduced in caliber, and shortened. Dilation of the terminal ileum (backwash ileitis) is present. *(From Hoffman AD. The child with diarrhea. In Hilton SW, Edwards DK, eds. Practical Pediatric Radiology, 2nd ed. Philadelphia: WB Saunders; 1994. p. 262.)*

to treatment beyond 6 months. Many children with disease requiring frequent corticosteroid therapy are started on immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1-1.5 mg/kg/day). Uncontrolled data suggest a corticosteroid-sparing effect in many treated patients. This is not an appropriate choice in a patient who is nonresponsive to steroids with acute severe colitis because of longer onset of action. Lymphoproliferative disorders are associated with thiopurine use. Infliximab and adalimumab, which are a fully human monoclonal antibody to tumor necrosis factor (TNF)-α, are effective for induction and maintenance therapy in children and adults with moderate to severe disease. TNF blocking agents are associated with an increased risk of infection (particularly tuberculosis) and malignancies (lymphoma, leukemia). There are a number of other agents that are approved for treatment of refractory ulcerative colitis in adults, but are often used

Table 382.7 Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS
(1) ABDOMINAL PAIN	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) RECTAL BLEEDING	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) STOOL CONSISTENCY OF MOST STOOLS	
Formed	0
Partially formed	5
Completely unformed	10
(4) NUMBER OF STOOLS PER 24 HR	
0-2	0
3-5	5
6-8	10
>8	15
(5) NOCTURNAL STOOLS (ANY EPISODE CAUSING WAKENING)	
No	0
Yes	10
(6) ACTIVITY LEVEL	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

off-label in children, including vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, and ustekinumab, a monoclonal antibody against interleukins (ILs) 12 and 23. Small molecule agents are another class of medications to be approved for adults with moderate to severe ulcerative colitis in adults, including tofacitinib and upadacitinib; oral Janus kinase inhibitors; and ozanimod, a sphingosine 1-phosphate receptor modulator that leads to peripheral lymphocyte sequestration. A specific combination of three to four broad-spectrum oral antibiotics given over 2-3 weeks may be effective in treating severe pediatric ulcerative colitis refractory to other therapies, but it is being further studied in children.

Surgical

Colectomy is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management. No clear benefit of the use of total parenteral nutrition or a continuous enteral elemental diet in the treatment of severe ulcerative colitis has been noted. Nevertheless, parenteral nutrition is used if oral intake is insufficient so that the patient will be nutritionally ready for surgery if medical management fails. With any medical treatment for ulcerative colitis, the clinician should always weigh the risk of the medication or therapy against the fact that colitis can be successfully treated surgically.

Surgical treatment for intractable or fulminant colitis is total colectomy. The optimal approach is to combine colectomy with an endorectal pull-through, where a segment of distal rectum is retained and the mucosa is stripped from this region. The distal ileum is pulled down and sutured at the internal anus with a J pouch created from ileum immediately above the rectal cuff. This procedure allows the child to maintain continence. Commonly, a temporary ileostomy is created to protect the delicate anastomosis between the sleeve of the pouch and the rectum. The ileostomy is usually closed within several months, restoring bowel continuity. At that time, stool frequency is often increased but may be improved with loperamide. The major complication of this operation is *pouchitis,* which is a chronic inflammatory reaction in the pouch, leading to bloody diarrhea, abdominal pain, and, occasionally, low-grade fever. The cause of this complication is unknown, although it is more common when the ileal pouch has been constructed for ulcerative colitis than for other indications (e.g., familial polyposis coli). Pouchitis is seen in 30–40% of patients who had ulcerative colitis. It commonly responds to treatment with oral metronidazole or ciprofloxacin. Probiotics have also been shown to decrease the rate of pouchitis as well as the recurrence of pouchitis following antibiotic therapy.

Support

Psychosocial support is an important part of therapy for this disorder. This may include adequate discussion of the disease manifestations and management between patient and physician, psychologic counseling for the child when necessary, and family support from a social worker or family counselor. Patient support groups have proved helpful for some families. Children with ulcerative colitis should be encouraged to participate fully in age-appropriate activities; however, activity may need to be reduced during periods of disease exacerbation.

PROGNOSIS

The course of ulcerative colitis is marked by remissions and exacerbations. Most children with this disorder respond initially to medical management. Many children with mild manifestations continue to respond well to medical management and may stay in remission on a prophylactic 5-ASA preparation for long periods. An occasional child with mild onset, however, experiences intractable symptoms later. Beyond the first decade of disease, the risk of development of colon cancer begins to increase rapidly. The risk of colon cancer may be diminished with surveillance colonoscopies beginning after 8-10 years of disease. Detection of significant dysplasia on biopsy would prompt colectomy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

382.2 Crohn Disease (Regional Enteritis, Regional Ileitis, Granulomatous Colitis)

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

Crohn disease, an idiopathic, chronic inflammatory disorder of the bowel, involves any region of the alimentary tract from the mouth to the anus. Although there are many similarities between ulcerative colitis and Crohn disease, there are also major differences in the clinical course and distribution of the disease in the GI tract (see Table 382.2). The inflammatory process tends to be eccentric and segmental, often with skip areas (normal regions of bowel between inflamed areas). Although inflammation in ulcerative colitis is limited to the mucosa (except in toxic megacolon), GI involvement in Crohn disease is often *transmural*.

Compared to adult-onset disease, pediatric Crohn disease is more likely to have extensive anatomic involvement. At initial presentation, more than 50% of patients have disease that involves ileum and colon (ileocolitis), 20% have exclusively colonic disease, and upper GI involvement (esophagus, stomach, duodenum) is seen in up to 30% of children. Isolated small bowel disease is much less common in the pediatric population compared to adults. Isolated colonic disease is common in children younger than 8 years of age and may be indistinguishable from ulcerative colitis. Anatomic location of disease tends to extend over time in children.

Crohn disease tends to have a bimodal age distribution, with the first peak beginning in the teenage years. The incidence of Crohn disease has been increasing. In the United States, the reported incidence of

pediatric Crohn disease is 4.56/100,000 and the pediatric prevalence is 43/100,000 children.

CLINICAL MANIFESTATIONS

Crohn disease can be characterized as inflammatory, stricturing, or penetrating. Patients with small bowel disease are more likely to have an obstructive pattern (most commonly with right lower quadrant pain) characterized by fibrostenosis, and those with colonic disease are more likely to have symptoms resulting from inflammation (diarrhea, bleeding, cramping). Disease phenotypes often change as duration of disease lengthens (inflammatory becomes structuring and/or penetrating) (Figs. 382.5 and 382.6).

Systemic signs and symptoms are more common in Crohn disease than in ulcerative colitis. Fever, malaise, and easy fatigability are common. Growth failure with delayed bone maturation and delayed sexual development can precede other symptoms by 1 or 2 years and is at least twice as likely to occur with Crohn disease as with ulcerative colitis. Children can present with growth failure as the only manifestation of Crohn disease. Decreased height velocity occurs in about 88% of prepubertal patients diagnosed with Crohn disease, and this often precedes GI symptoms. Causes of growth failure include inadequate caloric intake (anorexia, partial obstruction–related pain), suboptimal absorption or excessive loss of nutrients, the effects of chronic inflammation on bone metabolism and appetite, and the use of corticosteroids during treatment. Primary or secondary amenorrhea and pubertal delay are common. In contrast to ulcerative colitis, perianal disease is common (tag, fistula, deep fissure, abscess). Gastric or duodenal involvement may be associated with recurrent vomiting and epigastric pain. **Partial small bowel obstruction**, usually secondary to narrowing of the bowel lumen from *inflammation* or *stricture*, can cause symptoms of cramping abdominal pain (especially with meals), borborygmus, and intermittent abdominal distention (Fig. 382.7). Stricture should be suspected if the child notes relief of symptoms in association with a sudden sensation of gurgling of intestinal contents through a localized region of the abdomen.

Penetrating disease is demonstrated by fistula formation. Enteroenteric or enterocolonic fistulas (between segments of bowel) are often asymptomatic but can contribute to malabsorption if they have high output or result in bacterial overgrowth. Enterovesical fistulas (between bowel and urinary bladder) originate from ileum or sigmoid colon and appear as signs of urinary infection, pneumaturia, or fecaluria. Enterovaginal fistulas originate from the rectum, cause feculent vaginal drainage, and are difficult to manage. Enterocutaneous fistulas (between bowel and abdominal skin) often are caused by prior surgical anastomoses with leakage. Intraabdominal abscess may be associated with fever and pain but might have relatively few symptoms. Hepatic or splenic abscess can occur with or without a local fistula. Anorectal abscesses often originate immediately above the anus at the crypts of Morgagni. The patterns of perianal fistulas are complex because of the different tissue planes. Perianal abscess is usually painful, but perianal fistulas tend to produce fewer symptoms than anticipated. Purulent drainage is commonly associated with perianal fistulas. Psoas abscess secondary to intestinal fistula can present as hip pain, decreased hip extension (psoas sign), and fever.

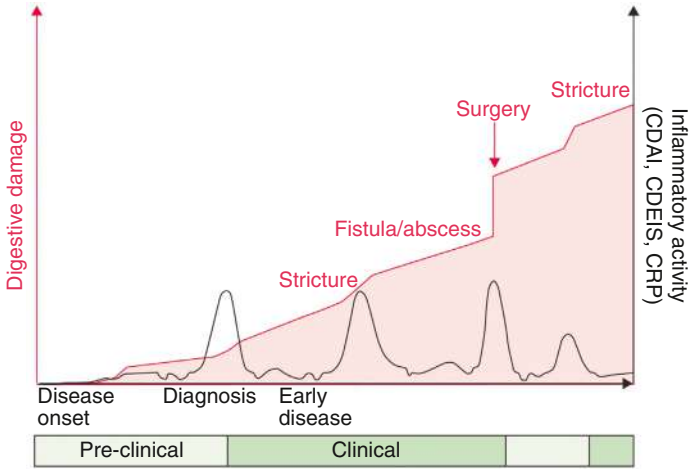

Fig. 382.5 The Lémann Score. Exemplary visualization of the Lémann score, a new technique to score and study intestinal damage in Crohn disease. CDAI, Crohn disease activity index; CDEIS, Crohn disease of endoscopic severity; CRP, C-reactive protein. *(From Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–1602. Fig. 5, p. 1596.)*

Extraintestinal manifestations occur more commonly with Crohn disease than with ulcerative colitis; those that are especially associated with Crohn disease include oral aphthous ulcers, peripheral arthritis, erythema nodosum, digital clubbing, episcleritis, venous thrombosis, pulmonary disease, renal stones (uric acid, oxalate), and gallstones. Any of the extraintestinal disorders described in the section on IBD can occur with Crohn disease (see Table 382.3). The peripheral arthritis is nondeforming. The occurrence of extraintestinal manifestations usually correlates with the presence of colitis. Metastatic Crohn disease is most often cutaneous, presenting with noncaseating granulomas in a location that is not contiguous with an active penetrating lesion; it may resemble erythema nodosum.

Extensive involvement of small bowel, especially in association with surgical resection, can lead to short bowel syndrome, which is rare in children. Complications of terminal ileal dysfunction or resection include bile acid malabsorption with secondary diarrhea and vitamin B_{12} malabsorption, with possible resultant deficiency. Chronic steatorrhea can lead to oxaluria with secondary renal stones. Increasing calcium intake can actually decrease the risk of renal stones secondary to ileal inflammation. The risk of cholelithiasis is also increased secondary to bile acid depletion.

A disorder with this diversity of manifestations can have a major impact on an affected child's lifestyle. Fortunately, the majority of children with Crohn disease are able to continue with their normal activities, having to limit activity only during periods of increased symptoms.

DIFFERENTIAL DIAGNOSIS

The most common diagnoses to be distinguished from Crohn disease are the infectious enteropathies (in the case of Crohn disease: acute terminal ileitis, infectious colitis, enteric parasites, and periappendiceal abscess) (see Tables 382.5 and 382.6; Table 382.8). *Yersinia* can cause many of the radiologic and endoscopic findings in the distal small bowel that are seen in Crohn disease. The symptoms of bacterial dysentery are more likely to be mistaken for ulcerative colitis than for Crohn disease. Celiac disease and *Giardia* infection have been noted to produce a Crohn-like presentation including diarrhea, weight loss, and protein-losing enteropathy. GI tuberculosis is rare but can mimic Crohn disease. Foreign-body perforation of the bowel (toothpick) can mimic a localized region with Crohn disease. Small bowel lymphoma can mimic Crohn disease but tends to be associated with nodular filling defects of the bowel without ulceration or narrowing of the lumen. Bowel lymphoma is much less common in children than is Crohn disease. Recurrent functional abdominal pain can mimic the pain of small bowel Crohn disease. *Lymphoid nodular hyperplasia* of the terminal ileum (a normal finding) may be mistaken for Crohn ileitis. Right lower quadrant pain or mass with fever can be the result of periappendiceal abscess. This entity is occasionally associated with diarrhea as well.

Growth failure may be the only manifestation of Crohn disease; other disorders such as growth hormone deficiency, gluten-sensitive enteropathy (celiac disease), Turner syndrome, or anorexia nervosa must be considered. If arthritis precedes the bowel manifestations, an initial diagnosis of juvenile idiopathic arthritis may be made. Refractory anemia may be the presenting feature and may be mistaken for a primary hematologic disorder. Chronic granulomatous disease of childhood can cause inflammatory changes in the bowel as well as perianal disease. Antral narrowing in this disorder may be mistaken for a stricture secondary to Crohn disease. Other immunodeficiencies or autoinflammatory conditions and monogenetic disorders may

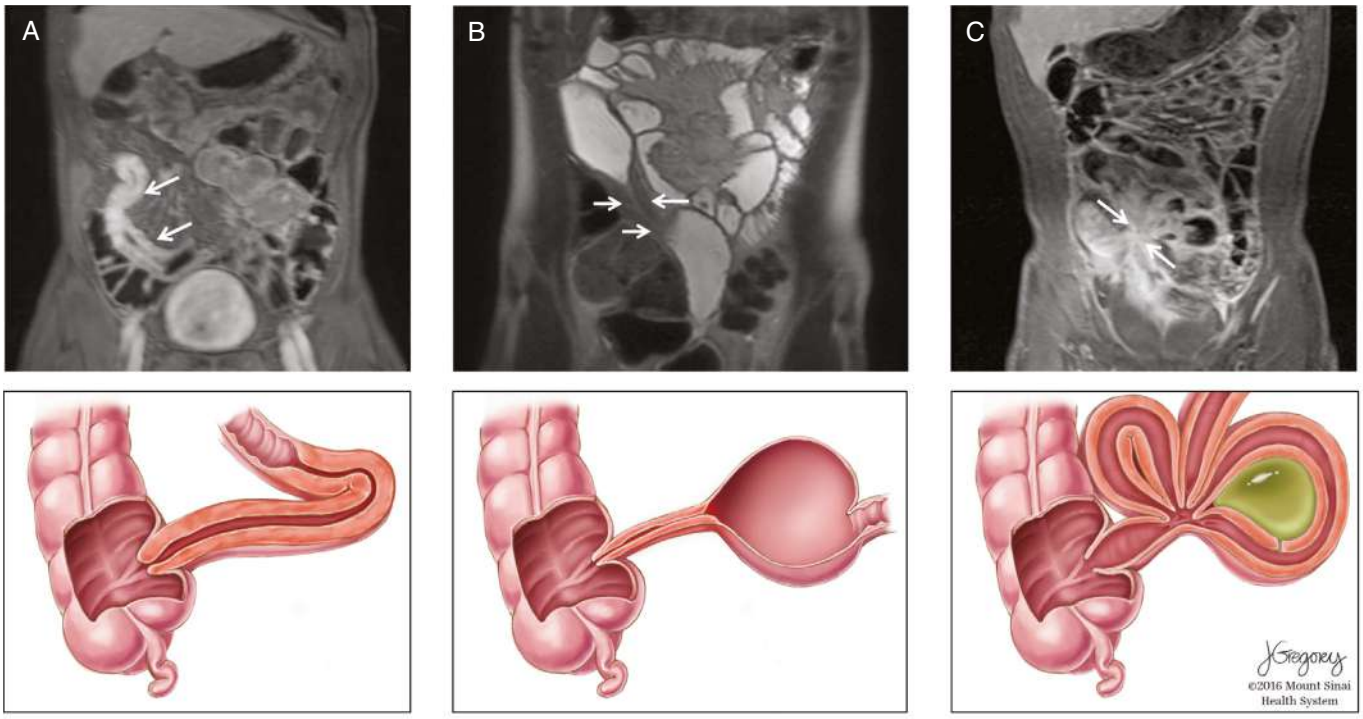

- Diarrhea
- Abdominal pain
- Weight loss
- Low-grade fever
- Fatigue
- Growth retardation
- Malnourishment

- Postprandial pain
- Bloating
- Nausea and vomiting
- Occlusion/subocclusion

- Symptoms depend on the location of fistulae
- Enterourinary fistula: fecaluria, pneumaturia, recurrent UTI
- Rectovaginal fistula: dispareunia, stool discharge through the vagina
- Enteroenteric fistula: asymptomatic, abdominal abscesses

Fig. 382.6 Behavior of Crohn disease (CD) as per Montreal classification represented in MR enterography (MRE) and illustrated with typical symptoms. **A,** T1 weighted MRE imaging with fat saturation after injection of gadolinium chelates shows mural thickening and enhancement in the distal ileum *(arrows)* in a patient with active CD. **B,** T2 weighted MRE imaging shows a narrowed luminal segment with thickened wall and upstream dilation *(arrows),* suggesting the presence of a stricture. **C,** T1 weighted MRE imaging with fat saturation after injection of gadolinium chelates shows multiple converging enhancing loops of small bowel suggestive of enteroenteric fistulas *(arrows).* Lower illustration shows a deep and transmural fissure or ulcer leading to the formation of an abscess. UTI, Urinary tract infection. *(Illustration by Jill Gregory. Printed with permission of Mount Sinai Health System.)*

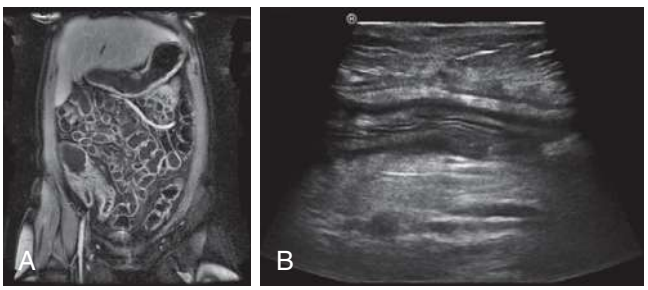

Fig. 382.7 Stenosis in Crohn disease. **A,** MR enterography of Crohn disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. **B,** Ultrasound image of an intestinal stenosis in Crohn disease. *(From Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–1602. Fig. 4.)*

present with GI symptoms suggestive of IBD, particularly in very early or infant/toddler onset of disease (see Table 382.6).

DIAGNOSIS

Crohn disease can manifest as a variety of symptom combinations (see Fig. 382.6). At the onset, symptoms may be subtle (growth failure, abdominal pain alone); this explains why the diagnosis might not be made until 1 or 2 years after the start of symptoms. The diagnosis of Crohn disease depends on finding typical clinical features of the disorder (history, physical examination, laboratory studies, and endoscopic or radiologic findings), ruling out specific entities that mimic Crohn disease, and demonstrating chronicity. The history can include any combination of abdominal pain (especially right lower quadrant), diarrhea, vomiting, anorexia, weight loss, growth retardation, and extraintestinal manifestations. Only 25% initially have the triad of diarrhea, weight loss, and abdominal pain. Most do not have diarrhea, and only 25% have GI bleeding.

Children with Crohn disease often appear chronically ill. They commonly have weight loss and growth failure, and they are often malnourished. The earliest sign of growth failure is decreased height velocity, which can be present in up to 88% of prepubertal patients with Crohn disease and typically precedes symptoms. Children with Crohn disease often appear pale, with decreased energy level and poor appetite; the latter finding sometimes results from an association between meals and abdominal pain or diarrhea. There may be abdominal tenderness that is either diffuse or localized to the right lower quadrant. A tender mass or fullness may be palpable in the right lower quadrant. Perianal disease, when present, may be characteristic. Large anal skin tags (1-3 cm in diameter) or perianal fistulas with purulent drainage suggest Crohn disease. Digital clubbing, findings of arthritis, and skin manifestations may be present.

A complete blood cell count commonly demonstrates anemia, often with a component of iron deficiency, as well as thrombocytosis. Although the erythrocyte sedimentation rate and C-reactive protein are often elevated, they may be unremarkable. The serum albumin level may be low, indicating small bowel inflammation or protein-losing enteropathy. Fecal calprotectin and lactoferrin are more sensitive and specific markers of bowel inflammation as compared to serologic parameters, and these are often elevated. Multiple serologic, immune, and genetic markers can also be abnormal, although the best utilization of these remains to be determined.

The small and large bowel and the upper GI tract should be examined by both endoscopic and radiologic studies in the child with suspected Crohn disease. Esophagogastroduodenoscopy and ileocolonoscopy should be performed to properly assess the upper GI tract, terminal ileum, and entire colon. Findings on colonoscopy can include patchy, nonspecific inflammatory changes (erythema, friability, loss of vascular pattern), aphthous ulcers, linear ulcers, nodularity, and strictures. Findings on biopsy may be only nonspecific chronic inflammatory changes. Noncaseating granulomas, similar to those of sarcoidosis, are the most characteristic histologic findings, although often they are not present. Transmural inflammation is also characteristic but can be identified only in surgical specimens.

Radiologic studies are necessary to assess the entire small bowel and investigate for evidence of structuring or penetrating disease. A variety of findings may be apparent on radiologic studies. Plain films of the abdomen may be normal or might demonstrate findings of partial small bowel obstruction or thumbprinting of the colon wall (Fig. 382.8). An upper GI contrast study with small bowel follow-through might show aphthous ulceration and thickened, nodular folds as well as narrowing or stricturing of the lumen. Linear ulcers can give a cobblestone appearance to the mucosal surface. Bowel loops are often separated as a result of thickening of bowel wall and mesentery (Fig. 382.9). Other manifestations on radiographic studies that suggest more severe Crohn disease are fistulas between bowel (enteroenteric or enterocolonic), sinus tracts, and strictures (see Fig. 382.7).

An upper GI contrast examination with small bowel follow-through has typically been the study of choice for imaging of the small bowel, but CT and MR enterography as well as small bowel ultrasonography are more often performed (Fig. 382.10). MR and ultrasound have the advantage of not exposing the patient to ionizing radiation. CT and MR enterography can also assess for extraluminal findings such as intraabdominal abscess. MR of the pelvis is also useful for delineating the extent of perianal involvement. PET/MRI studies are also helpful in identifying areas of active intestinal and extraintestinal inflammation (Fig. 382.11).

Video capsule endoscopy is another modality that allows for evaluation of the small bowel. This study can uncover mucosal inflammation or ulceration that might not have been detected by traditional imaging. However, video capsule endoscopy is contraindicated in the presence of stricturing disease, as surgical intervention would be required to remove a video capsule that is unable to pass through the bowel because a stricture. If there is concern for stricturing disease, a patency capsule can be swallowed before video capsule endoscopy to assess for passage through the GI tract.



Fig. 382.8 A 19-yr-old patient who presented with bloody stools and later diagnosed with inflammatory bowel disease. Abdominal radiograph at presentation showed classic thumbprinting involving the distal transverse colon, splenic flexure, and descending colon *(arrows)* representing submucosal edema seen in colitis. *(Images from Department of Radiology, Children's Hospital of Philadelphia.)*

Table 382.8 Differential Diagnosis of Presenting Symptoms of Crohn Disease

PRIMARY PRESENTING SYMPTOM	DIAGNOSTIC CONSIDERATIONS
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., *Campylobacter, Yersinia* spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst
Chronic periumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic disease
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome
Bloody diarrhea	Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, *Cryptosporidium* infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis

From Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004. p. 287.

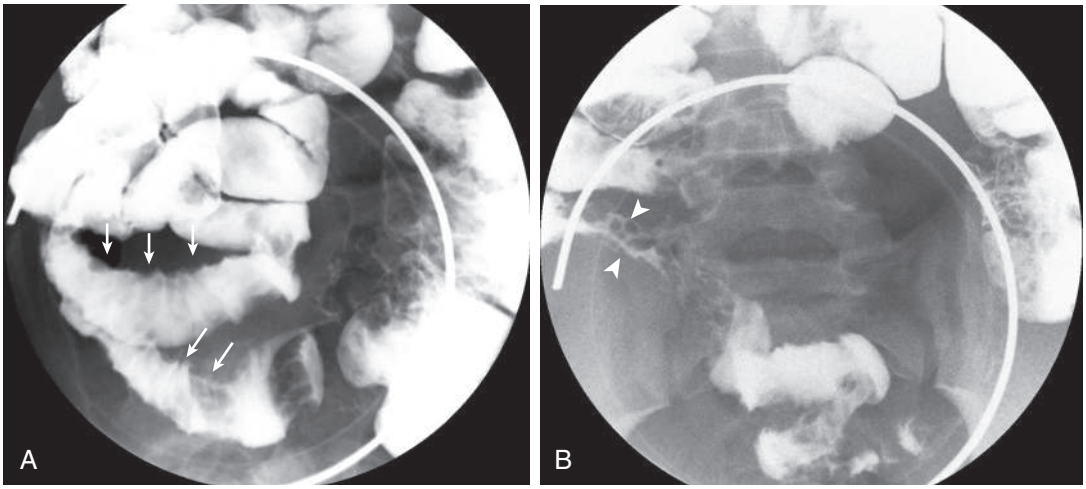

Fig. 382.9 A 12-yr-old child with weight loss and bloody stools diagnosed with Crohn disease. Small bowel follow-through barium examination showed the classic features of Crohn disease. **A,** Mucosal thickening, irregularity *(arrows).* **B,** Nodularity, "cobblestoning" *(arrowheads)* of the terminal ileum and distal ileal loops. There was also separation of the bowel loops due to fatty proliferation of the mesentery. *(Images from Department of Radiology, Children's Hospital of Philadelphia.)*

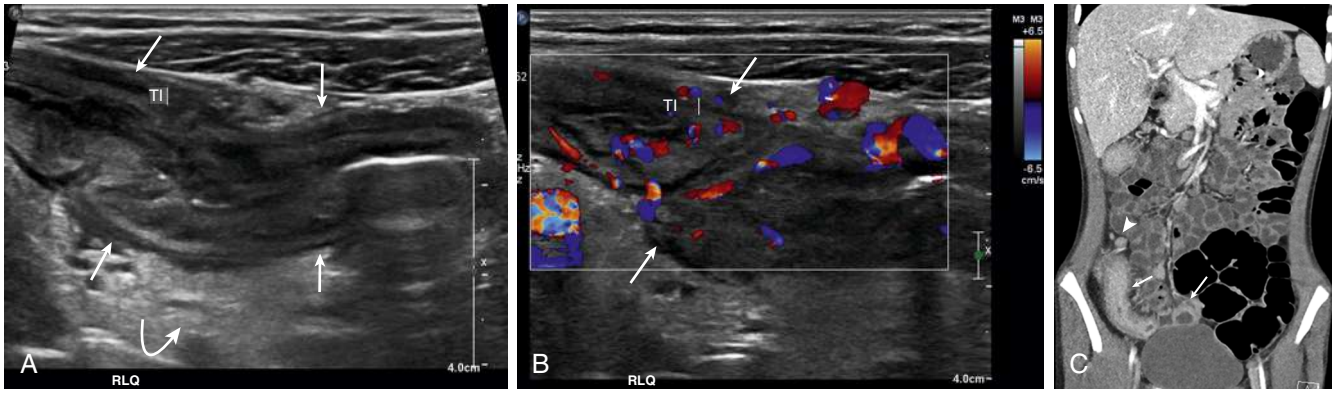

Fig. 382.10 An 11-yr-old child who presented with abdominal pain, weight loss, leukocytosis, and elevated erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP). The patient underwent an initial bowel ultrasound and then CT enterography with assistance from Child Life mitigating use of sedation. Sagittal **(A)** grayscale and color Doppler **(B)** ultrasound images showed markedly thickened abnormal hyperemic terminal ileum *(straight arrows)* and surrounding thickened echogenic mesentery *(curved arrow)* indicative of active inflammation, **C,** Coronal image from a contrast-enhanced CT enterography showed correlating abnormal enhancing and thickened distal and terminal ileum *(arrows)* with enlarged reactive adjacent lymph nodes *(arrowhead). (Images from Department of Radiology, Children's Hospital of Philadelphia.)*

TREATMENT

Crohn disease cannot be *cured* by medical or surgical therapy. The aim of treatment is to relieve symptoms and prevent complications of chronic inflammation (anemia, growth failure), prevent relapse, minimize corticosteroid exposure, and, if possible, effect mucosal healing.

Medical

The specific therapeutic modalities used depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess). Traditionally, a *step-up* treatment paradigm has been used in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medications, or for steroid dependence. A *top-down* approach has also been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease-modifying agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course. This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. Improvements in remission and growth have been shown using a top-down approach in pediatrics, and this treatment approach is being increasingly used among children.

5-Aminosalicylates

For mild terminal ileal disease or mild Crohn disease of the colon, an initial trial of mesalamine (50-100 mg/kg/day, maximum 3-4 g) may be attempted. Specific pharmaceutical preparations have been formulated to release the active 5-ASA compound throughout the small bowel, in the ileum and colon, or exclusively in the colon. Rectal preparations are used for distal colonic inflammation.

Antibiotics/Probiotics

Antibiotics such as metronidazole (5 mg/kg/dose three times per day, up to 250 mg three times per day) are used for infectious complications and are first-line therapy for perianal disease (although perianal disease usually recurs when antibiotic is discontinued). Additionally, at low doses antibiotics may be effective for treatment of mild to moderate Crohn disease. To date, probiotics have not been shown to be effective in induction or maintenance of remission for pediatric Crohn disease.

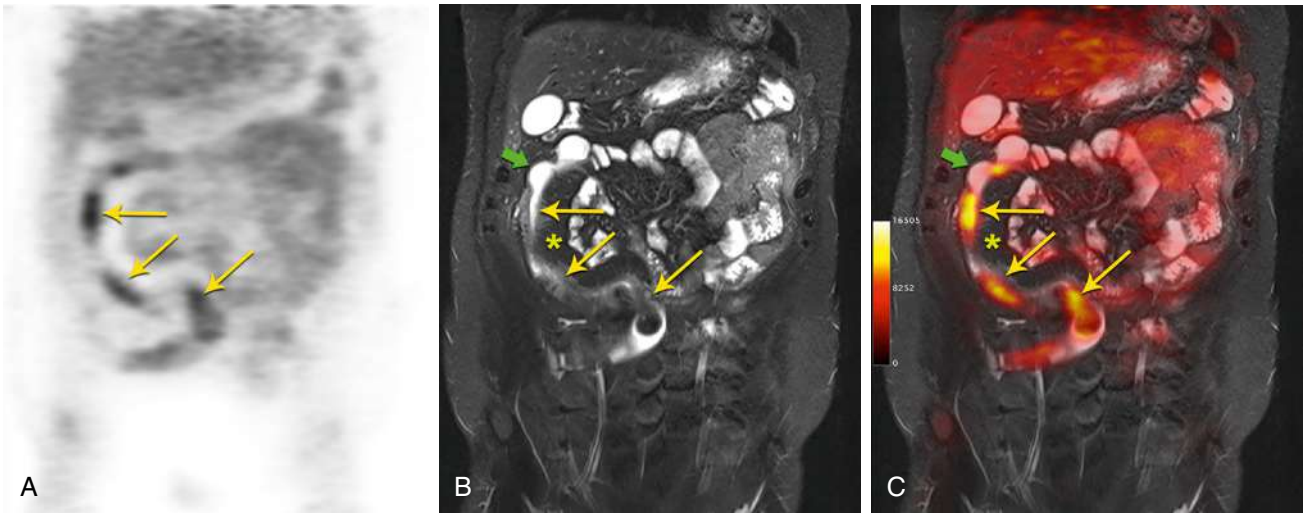

Fig. 382.11 Crohn disease, coexistence of active and chronic changes. Coronal PET (**A**), coronal STIR MRI (**B**), and fused PET/MRI (**C**). Discontinuous areas of active inflammation *(arrows)* demonstrate increased focal FDG uptake, bowel wall thickening, and edema. Note adjacent fibrofatty proliferation *(asterisk)* and pseudosacculations indicative of the chronicity of the process. *(From Furtado FS, Suarez-Weiss KE, Amorim BJ, et al. Gastrointestinal imaging. In Catalano A (ed). Clinical PET/MRI. London: Elsevier, 2023. Fig 14.15.)*

Corticosteroids

Corticosteroids are used for acute exacerbations of pediatric Crohn disease because they effectively suppress acute inflammation, rapidly relieving symptoms (prednisone, 1-2 mg/kg/day, by mouth [PO], maximum 40-60 mg). The goal is to taper dosing as soon as the disease becomes quiescent. Clinicians vary in their tapering schedules, and the disease can flare during this process. There is no role for continuing corticosteroids as maintenance therapy because, in addition to their side effects, tolerance develops, and steroids do not change disease course or promote healing of mucosa. A special controlled ileal-release formulation of budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and high hepatic first-pass metabolism, is also used for mild to moderate ileal or ileocecal disease (adult dose: 9 mg daily). Ileal-release budesonide appears to be more effective than mesalamine in the treatment of active ileocolonic disease but is less effective than prednisone. Although less effective than traditional corticosteroids, budesonide does cause fewer steroid-related side effects.

Immunomodulators

Approximately 70% of patients require escalation of medical therapy within the first year of pediatric Crohn disease diagnosis. Immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1.0-1.5 mg/kg/day) may be effective in some children who have a poor response to prednisone or who are steroid dependent. Because a beneficial effect of these drugs can be delayed for 3-4 months after starting therapy, they are not helpful acutely. The early use of these agents can decrease cumulative prednisone dosages over the first 1-2 years of therapy. Genetic variations in an enzyme system responsible for metabolism of these agents (thiopurine *S*-methyltransferase) can affect response rates and potential toxicity. Lymphoproliferative disorders have developed from thiopurine use in patients with IBD. Other common toxicities include hepatitis, pancreatitis, increased risk of skin cancer, increased risk of infection, and slightly increased risk of lymphoma.

Methotrexate is another immunomodulator that is effective in the treatment of Crohn disease and has been shown to improve height velocity in the first year of administration. The advantages of this medication include once-weekly dosing by either a subcutaneous or oral route (15 mg/m^2, adult dose 25 mg weekly) and a more rapid onset of action (6-8 weeks) than azathioprine or 6-mercaptopurine. Folic acid is usually administered concomitantly to decrease medication side effects. Administration of ondansetron before methotrexate has been shown to diminish the risk of the most common side effect of nausea. The most common toxicity is hepatitis. The immunomodulators are effective for the treatment of perianal fistulas.

Biologic Therapy

Therapy with antibodies directed against mediators of inflammation is used for patients with Crohn disease. Infliximab, a chimeric monoclonal antibody to TNF-α, is effective for the induction and maintenance of remission and mucosal healing in chronically active moderate to severe Crohn disease, healing of perianal fistulas, steroid sparing, and preventing postoperative recurrence. Pediatric data additionally support improved growth with the administration of this medication. The onset of action of infliximab is quite rapid, and it is initially given as three infusions over a 6-week period (0, 2, and 6 weeks), followed by maintenance dosing beginning every 8 weeks. The durability of response to infliximab is variable, and dose escalation (higher dose and/or decreased interval) is often necessary. Measurement of serum trough infliximab level before an infusion can help guide dosing decisions. Side effects include infusion reactions, increased incidence of infections (especially reactivation of latent tuberculosis), increased risk of lymphoma, and the development of autoantibodies. The development of antibodies to infliximab is associated with an increased incidence of infusion reactions and decreased durability of response. Regularly scheduled dosing of infliximab, as opposed to episodic dosing on an as-needed basis, is associated with decreased levels of antibodies to infliximab. A purified protein derivative test or gamma interferon test for tuberculosis should be done before starting infliximab.

Adalimumab, a subcutaneously administered, fully humanized monoclonal antibody against TNF-α, is effective for the treatment of chronically active moderate to severe Crohn disease in adults and children. After a loading dose, this is typically administered once every 2 weeks, although dose escalation is sometimes required with this medication. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, is approved for

the treatment of Crohn disease in adults. Like infliximab, vedolizumab is initially given as three infusions over a 6-week period followed by maintenance dosing beginning every 8 weeks. However, the onset of action for vedolizumab is slower compared to infliximab and adalimumab. Therefore concomitant therapies may be needed until response is demonstrated. Dose escalation to every 4 weeks may be necessary in some patients with loss of response, but it is being further studied. Ustekinumab, a monoclonal antibody against both IL-12 and IL-23, is also approved for treatment of chronically active moderate to severe Crohn disease in adults. A loading dose is given intravenously followed by maintenance dosing administered subcutaneously every 8 weeks. Risankizumab, a monoclonal antibody against IL-23A, has demonstrated efficacy for induction and remission maintenance in adults.

Enteral Nutritional Therapy

Exclusive enteral nutritional therapy, whereby all of a patient's calories are delivered via formula, is an effective primary as well as adjunctive treatment. The enteral nutritional approach is as rapid in onset and as effective as the other treatments. Pediatric studies have suggested similar efficacy to prednisone for improvement in clinical symptoms, but enteral nutritional therapy is superior to steroids for actual healing of mucosa. Because affected patients have poor appetite and these formulas are relatively unpalatable, they are often administered via a nasogastric or gastrostomy infusion, usually overnight. The advantages are that it is relatively free of side effects, avoids the problems associated with corticosteroid therapy, and simultaneously addresses the nutritional rehabilitation. Children can participate in normal daytime activities. A major disadvantage of this approach is that patients are not able to eat a regular diet because they are receiving all of their calories from formula. A novel approach where 80–90% of caloric needs are provided by formula, allowing children to have some food intake, has been successful. For children with growth failure, this approach may be ideal.

High-calorie oral supplements, although effective, are often not tolerated because of early satiety or exacerbation of symptoms (abdominal pain, vomiting, or diarrhea). Nonetheless, they should be offered to children whose weight gain is suboptimal even if they are not candidates for exclusive enteral nutritional therapy. The continuous administration of nocturnal nasogastric feedings for chronic malnutrition and growth failure has been effective with a much lower risk of complications than parenteral hyperalimentation.

Surgical

Surgical therapy should be reserved for very specific indications. Recurrence rate after bowel resection is high (>50% by 5 years); the risk of requiring additional surgery increases with each operation. Potential complications of surgery include development of fistula or stricture, anastomotic leak, postoperative partial small bowel obstruction secondary to adhesions, and short bowel syndrome. Surgery is the treatment of choice for localized disease of small bowel or colon that is unresponsive to medical treatment, bowel perforation, fibrosed stricture with symptomatic partial small bowel obstruction, and intractable bleeding. Intraabdominal or liver abscess sometimes is successfully treated by ultrasonographic or CT-guided catheter drainage and concomitant intravenous antibiotic treatment. Open surgical drainage is necessary if this approach is not successful.

Perianal abscess often requires drainage unless it drains spontaneously. In general, perianal fistulas should be managed by a combined medical and surgical approach. Often, the surgeon places a seton through the fistula to keep the tract open and actively draining while medical therapy is administered, to help prevent the formation of a perianal abscess. A severely symptomatic perianal fistula can require fistulotomy, but this procedure should be considered only if the location allows the sphincter to remain undamaged.

The surgical approach for Crohn disease is to remove as limited a length of bowel as possible. There is no evidence that removing bowel up to margins that are free of histologic disease has a better outcome than removing only grossly involved areas. The latter approach reduces the risk of short bowel syndrome. Laparoscopic approach is increasingly being used, with decreased postoperative recovery time. One approach to symptomatic small bowel stricture has been to perform a strictureplasty rather than resection. The surgeon makes a longitudinal incision across the stricture but then closes the incision with sutures in a transverse fashion. This is ideal for short strictures without active disease. The reoperation rate is no higher with this approach than with resection, whereas bowel length is preserved. Postoperative medical therapy with agents, such as mesalamine, metronidazole, azathioprine, and, more recently, infliximab, is often given to decrease the likelihood of postoperative recurrence.

Severe perianal disease can be incapacitating and difficult to treat if unresponsive to medical management. Diversion of fecal stream can allow the area to be less active, but on reconnection of the colon, disease activity usually recurs.

Support

Psychosocial issues for the child with Crohn disease include a sense of being different, concerns about body image, difficulty in not participating fully in age-appropriate activities, and family conflict brought on by the added stress of this disease. Social support is an important component of the management of Crohn disease. Parents are often interested in learning about other children with similar problems, but children may be hesitant to participate. Social support and individual psychologic counseling are important in the adjustment to a difficult problem at an age that by itself often has difficult adjustment issues. Patients who are socially "connected" fare better. Ongoing education about the disease is an important aspect of management because children generally fare better if they understand and anticipate problems. The Crohn and Colitis Foundation has local chapters throughout the United States and supports several regional camps for children with Crohn disease.

PROGNOSIS

Crohn disease is a chronic disorder that is associated with high morbidity but low mortality. Symptoms tend to recur despite treatment and often without apparent explanation. Weight loss and growth failure can usually be improved with treatment and attention to nutritional needs. Up to 15% of patients with early growth retardation secondary to Crohn disease have a permanent decrease in linear growth. Osteopenia is particularly common in those with chronic poor nutrition and frequent exposure to high doses of corticosteroids. Dual-energy x-ray absorptiometry can help identify patients at risk for developing osteopenia. Steroid-sparing agents, weight-bearing exercise, and improved nutrition, including supplementation with vitamin D and calcium, can improve bone mineralization. Some of the extraintestinal manifestations can, in themselves, be major causes of morbidity, including sclerosing cholangitis, chronic active hepatitis, pyoderma gangrenosum, and ankylosing spondylitis.

The region of bowel involved and complications of the inflammatory process tend to increase with time and include bowel strictures, fistulas, perianal disease, and intraabdominal or retroperitoneal abscess. Most patients with Crohn disease eventually require surgery for one of its many complications; the rate of reoperation is high. Surgery is unlikely to be curative and should be avoided except for the specific indications noted previously. An earlier, most aggressive medical treatment approach, with the goal of exacting mucosal healing may improve long-term prognosis, and this is an active area of investigation. The risk of colon cancer in patients with long-standing Crohn colitis approaches that associated with ulcerative colitis, and screening colonoscopy after 8-10 years of colonic disease is indicated.

Despite these complications, most children with Crohn disease lead active, full lives with intermittent flare-up in symptoms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

382.3 Very Early Onset Inflammatory Bowel Disease

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

IBD may be classified according to age at onset: pediatric onset (<17 years), early onset (<10 years), very early onset (<6 years), infant/toddler onset (0-2 years), and neonatal onset IBD (<28 days). The incidence of pediatric IBD is rising with the greatest rates of increase occurring among young children. Very early onset IBD (VEO-IBD) accounts for up to 15% of pediatric-onset IBD with an estimated prevalence of 14/100,000 children. Approximately 1% of children with IBD are diagnosed before the age of 2 years.

Although IBD is a complex disorder with genetics, the immune system, the microbiome, and environmental factors each contributing to its development, children with VEO-IBD are more likely to have a *monogenic* cause for their disease. Genetic testing has led to the identification of novel genetic pathways linked to the development of VEO-IBD. Many of these pathways contain genes associated with primary immunodeficiencies (see Tables 382.1 and 382.6; Table 382.9). Family history of IBD among first-degree relatives occurs more frequently in children diagnosed at a younger age. Approximately 44% of children diagnosed with ulcerative colitis under the age of 2 years will have a first-degree relative with IBD compared with 19% of older children with IBD.

VEO-IBD has a distinct clinical phenotype characterized by a higher likelihood for extensive colonic involvement and a greater tendency for a more aggressive disease course that is refractory to conventional therapies. However, there is a spectrum of clinical presentations within this population, including patients with milder forms of the disease and a more traditional disease course. Younger patients with IBD can present with any combination of diarrhea, abdominal pain, vomiting, and growth failure. Severe perirectal disease can be present and is often associated with monogenic forms of VEO-IBD, including those caused by IL-10 receptor pathogenic variants. In addition to intestinal symptoms, there may be associated manifestations of the specific monogenetic disorder (Fig. 382.12).

Table 382.9 Known Defects Associated with Very Early Onset Inflammatory Bowel Disease and Its Associated Extraintestinal Manifestations and Laboratory Findings

DEFECTS	GENE DEFECT	EXTRAINTESTINAL IMMUNE, HEMATOLOGIC, OR SOMATIC MANIFESTATIONS	LABORATORY FINDINGS AND FUNCTIONAL EVALUATION
IPEX AND IPEX-LIKE DISORDERS			
IPEX	*FOXP3*	Autoimmune endocrinopathy, cytopenia, hepatitis and kidney disease, eczema, food allergy, eosinophilia	Decrease in Treg cells number and function Decreased Foxp3 expression
CD25 deficiency	*CD25*	Autoimmune endocrinopathy, cytopenia, eczema, gingivitis, alopecia universalis, bullous pemphigoid, CMV, EBV disease	Absent CD25 expression
STAT5b deficiency	*STAT5B*	Autoimmune endocrinopathy, eczema, short stature, interstitial pneumonitis, alopecia universalis, bullous pemphigoid, varicella and herpes zoster infections	Variable immune abnormality Normal to low T, B, and NK cells
STAT1 GOF mutation	*STAT1*	Mucocutaneous candidiasis, short stature, eczema, autoimmune endocrinopathy, sinopulmonary infection, hypertension, aneurysm	Most have normal Treg cell number and Foxp3 expression, abnormal STAT1 phosphorylation studies
STAT3 GOF mutation	*STAT3*	Multisystem autoimmunity, variable short stature, lymphoproliferation	Hypogammaglobulinemia Decreased class switched memory B cells
LRBA deficiency	*LRBA*	Multisystem autoimmunity, cytopenia, arthritis, recurrent sinopulmonary infection, granuloma, hypogammaglobulinemia	Hypogammaglobulinemia Decreased class switched memory B cells
CTLA4 haploinsufficiency	*CTLA4*	Diarrhea, enteropathy, hypogammaglobulinemia, granulomatous lymphocytic interstitial lung disease, multisystem autoimmunity	Hypogammaglobulinemia Decreased class switched memory B cells
DEFECTS IN IL-10 SIGNALING			
Defects in IL-10 and IL-10R	*IL-10RA* *IL-10RB* *IL-10*	Perianal fistula, folliculitis, arthritis, abscess, lymphoma	STAT3 phosphorylation by IL-6 and IL-10 studies*
DEFECTS IN NEUTROPHIL FUNCTION			
CGD	*CYBB* *CYBA* *NCF1* *NCF2* *NCF4*	Perianal fistula, recurrent cold abscess from catalase positive organisms,† gastric outlet obstruction	Decreased neutrophil oxidative burst study Elevated IgG
Glycogen storage disease 1b	*SLC37A4*	Recurrent bacterial infections, hypoglycemic seizures, hepatomegaly	Neutropenia, hypoglycemia, hyperuricemia, hyperlipidemia
Leukocyte adhesion defect	*ITGB2*	Neutrophilia, recurrent bacterial infections, delayed separation of umbilical cord, poor wound healing	Leukocytosis Absent CD18 expression
Congenital neutropenia	*G6PC3*	Cutaneous vascular malformation and cardiac defect	Severe neutropenia

Continued

Table 382.9 Known Defects Associated with Very Early Onset Inflammatory Bowel Disease and Its Associated Extraintestinal Manifestations and Laboratory Findings—cont'd

DEFECTS	GENE DEFECT	EXTRAINTESTINAL IMMUNE, HEMATOLOGIC, OR SOMATIC MANIFESTATIONS	LABORATORY FINDINGS AND FUNCTIONAL EVALUATION
HYPERINFLAMMATORY DISORDERS			
XIAP	*BIRC4*	Perianal fistula, recurrent HLH, EBV, and CMV infections, hypogammaglobinemia	Markedly elevated IL-18 Decreased or absent XIAP protein expression by flow
NLRC4 GOF variant	*NLRC4*	Recurrent macrophage activation, rash	Markedly elevated IL-18
Mevalonate kinase deficiency	*MVK*	Recurrent fever, rash, abdominal pain and emesis	Elevated inflammatory markers Elevated IgD Elevated urine mevalonate
Familial Mediterranean fever	*MEFV*	Recurrent fever, abdominal pain, arthralgia, peritonitis	Elevated inflammatory markers
Familial HLH type 5	*STXBP2*	HLH, hypogammaglobinemia, sensorineural hearing loss	Marked elevated ferritin and sIL-2R Decreased CD107a degranulation
Hermansky-Pudlak syndrome	*HPS1* *HPS4* *HPS6*	Partial albinism, bleeding tendency, recurrent infection and immunodeficiency	Decreased CD107a degranulation
DEFECTS IN EPITHELIAL BARRIER FUNCTION			
TTC7A deficiency	*TTC7A*	Varying degree of intestinal atresia, T-cell immune defect and recurrent infections	Mild to severe T-cell immune deficiency Hypogammaglobinemia
X-linked ectodermal immunodeficiency (NEMO deficiency)	*IKBKG*	Varying degree of ectodermal dysplasia, conical teeth, sparse and brittle hair, recurrent bacterial, viral and mycobacterial infections	Hypogammaglobinemia Decreased class switched memory B cells
ADAM17 deficiency	*ADAM17*	Neonatal inflammatory skin and bowel disease, generalized pustular rash	Normal T-cell and B-cell numbers
Dystrophic epidermolysis bullosa	*COL7A1*	Blistering disorder primarily affect the hands, feet, knees, and elbows	Unremarkable immune findings
Kindler syndrome	*FERMT1*	Acral skin blistering, photosensitivity, progressive poikiloderma, and diffuse cutaneous atrophy	Eosinophilia
ISOLATED OR COMBINED T-CELL AND B-CELL IMMUNE DEFECTS			
X-linked agammaglobulinemia	*BTK*	Recurrent sinopulmonary infection	Absent B cells in peripheral blood Absent plasma cells in tissue Decreased class switched memory B cells
Common variable immune defect (CVID)		Heterogeneous group of defects with sinopulmonary infections, autoimmunity, lymphoproliferation, and variable T-cell immune defect	Hypogammaglobinemia Variable T-cell lymphopenia
X-linked hyper IgM (CD40L)	*CD40L*	Sclerosing cholangitis, Cryptosporidium diarrhea and Pneumocystis infection	Elevated or normal IgM, neutropenia Absent class switched memory B cells
Wiskott-Aldrich syndrome	*WAS*	Eczema, recurrent infection, autoimmunity, vasculitis	Microthrombocytopenia Variable lymphopenia, low IgM Decreased WAS protein
Leaky SCID or Omenn	*RAG1, RAG2* *IL-7Ra* *IL-2RG*	Generalized erythroderma, hepatosplenomegaly, lymphadenopathy	Eosinophilia T-cell lymphopenia Decreased naïve T cells

*STAT3 signaling following IL-6 and IL-10 will only identify IL-10R A and B defects; it will not identify IL-10 deficiency.
†*Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia, Aspergillus,* and *Candida.*
IPEX, Immune dysfunction, polyendocrinopathy, enteropathy, X-linked; Treg, regulatory T cell; CMV, cytomegalovirus; EBV, Epstein-Barr virus; NK, natural killer; GOF, gain of function; IL, interleukin; CGD, chronic granulomatous disease; HLH, hemophagocytic lymphohistiocytosis; SCID, severe combined immune deficiency.
From Chandrakasan S, Venkateswaran S, Kugathasan S. Nonclassic inflammatory bowel disease in young infants – immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, and other disorders. *Pediatr Clin N Am.* 2017;64:139–160. Table 2.

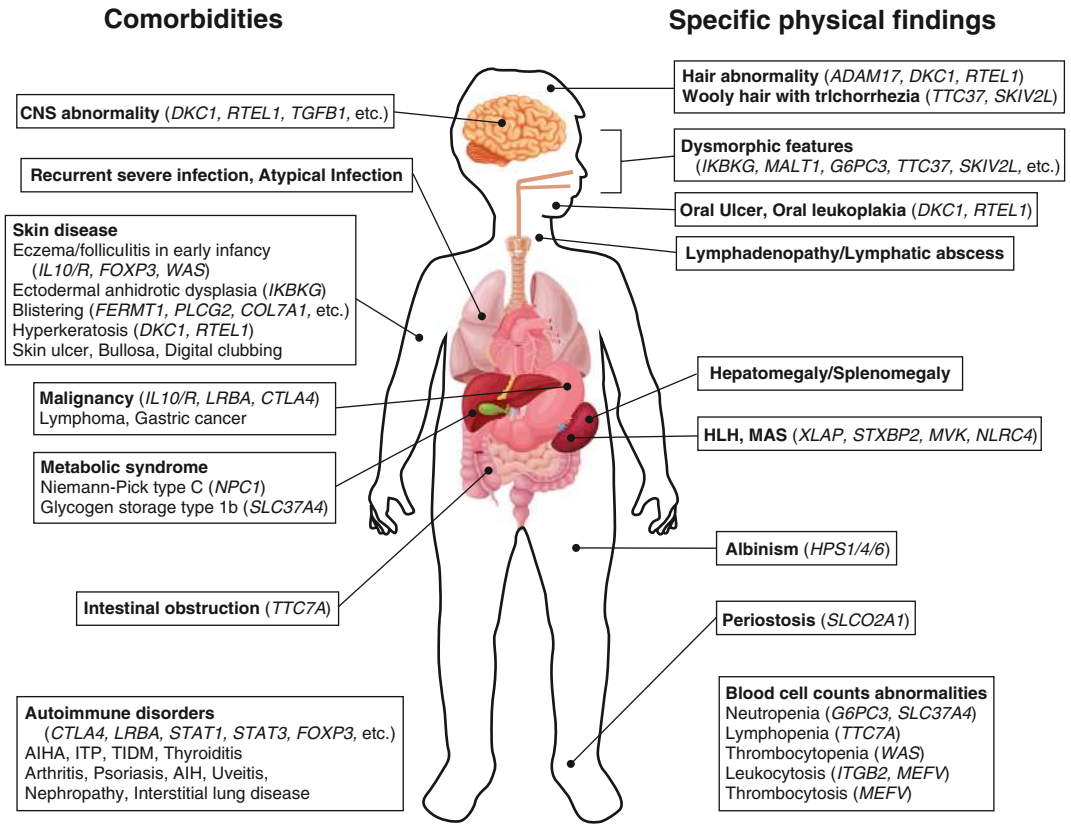

Fig. 382.12 Key indicators of monogenic IBD in clinical practice. Showing physical findings and comorbidities of which physicians should be aware at the initial physical examination and during follow-up. *(Modified from Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. Front Pediatr. 2021;8:Article 618918. Fig. 1C.)*

Diagnosis of IBD is ultimately confirmed by upper endoscopy and ileocolonoscopy. Classic histologic findings of IBD can be seen, although atypical findings, such as the presence of extensive epithelial apoptosis, could indicate the presence of monogenic disease. Most children with VEO-IBD will have isolated colonic inflammation on ileocolonoscopy. However, the inflammation can be extensive and involve the entire colon making it challenging to differentiate between Crohn disease and ulcerative colitis; 11–22% of patients with VEO-IBD are diagnosed with *indeterminate colitis* at diagnosis. Additionally, an initial diagnosis of ulcerative colitis occurs in approximately 60% of VEO-IBD patients. However, because children with VEO-IBD are more likely to have disease extension over time, a number of patients felt to have indeterminate colitis or ulcerative colitis at diagnosis may eventually be reclassified as having Crohn disease later in life. As small bowel imaging using CT or MR enterography may not be tolerated in a young child, small bowel ultrasonography is an alternative imaging modality in VEO-IBD.

The differential diagnosis of VEO-IBD is similar to older children and adults including infectious and allergic colitis (see Table 382.5). However, primary immunodeficiencies, such as chronic granulomatous disease, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome and immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, are higher on the differential (see Tables 382.6 and 382.9). Therefore immunologic evaluation is a critical component of diagnosis and management (Table 382.10). History of autoimmunity, atypical infections, recurrent infections, skin disorders, and/or hair abnormalities could indicate an underlying immunodeficiency. Laboratory evaluation could include dihydrorhodamine cytometric testing, quantitative immunoglobulins, vaccine titers, as well as testing of B- and T-cell function. More targeted immunologic testing is guided by clinical history. Genetic testing modalities, such as whole exome sequencing, are helpful in identifying rare monogenic pathways responsible for development of the disease.

A multidisciplinary team approach at a center experienced in VEO-IBD can be helpful in formulating an individualized treatment plan. Younger children are more likely to fail conventional therapies, such as 5-ASA, immunomodulators, and biologics, and require surgical intervention. Surgical decisions must be made with caution in very young children as disease extension from the colon to the small intestine can occur with time. More extensive and severe disease at presentation could explain the higher rates of treatment failure among younger children. However, other children may fail conventional therapies if the inflammation is being driven by a monogenic disease process that is not targeted by conventional therapies. Therefore for children with an underlying primary immunodeficiency or a novel monogenic disease process, the specific disease pathway involved may influence treatment choices. In some cases, bone marrow transplantation may be a necessary treatment for the underlying disease process.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 382.10 Functional Analysis

FUNCTIONAL SCREENING CONSIDERED	
• Immunoglobulins (IgG, IgM, IgA, IgD, IgE) • Lymphocyte subsets by flow • Antibody to vaccines • TRECs • DHR-123 • Cytokine assay (serum cytokine level during flare)	
TARGETED FUNCTIONAL ANALYSIS *(RECOMMENDED)*	
GENE	FUNCTIONAL ANALYSIS
IL10RA	IL-10-induced STAT3 phosphorylation by flow cytometry or immunoblotting
IL10RB	
NCF1	Neutrophil oxidative burst study, DHR-123 test
NCF2	
CYBA	
CYBB	
*NCF4**	Neutrophil oxidative burst study
CYBC1	
TTC7A	Immunohistochemistry-TTC7A, apoptosis
WAS	WASP expression by flow cytometry
XIAP	XIAP expression by flow cytometry TNF, IL-8, and MCP-1 expression in response to MDP stimulation
SLCO2A1	Immunohistochemistry-SLCO2A1
NPC1	Filipin staining of cultured skin fibroblasts
SLC37A4	G6Pase enzyme activity in Liver tissue (non-frozen)
MVK	Increased urine mevalonic acid when fever
TNFAIP3	A20 expression by immunoblotting RT-PCR using total RNA
CTLA4	CTLA-4 expression within stimulated Treg cells by flow cytometry
LRBA	LRBA expression in response to PHA stimulation by flow cytometry
FOXP3	FOXP3 expression by flow cytometry
STAT1(GOF)	CD25 expression by flow cytometry
STAT3(GOF)	STAT3 reporter luciferase assay under basal or stimulated condition (IL-6/growth hormone) in cell lines SOCS3 expression levels under basal or stimulated condition (IL-21) in EBV-transformed patient cell lines

*The production of ROS in phagocyte is normal and need to examine the bacterial killing activity.

TREC, T-cell receptor excision circles; DHR-123, dihydrorhodamine 123; WASP, Wiskott-Aldrich syndrome protein; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein; MDP, muramyl dipeptide; RT-PCR, real-time reverse transcription polymerase chain reaction, TNF, tumor necrosis factor; Treg, regulatory T cell; PHA, phytohemagglutinin; SOCS3, suppressor of cytokine signaling 3; EBV, Epstein-Barr virus; ROS, reactive oxygen species.

From Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. *Front Pediatr*. 2021;8:Article 618918. Table 1A.

Chapter 383

Eosinophilic Gastroenteritis

Ronen E. Stein and Robert N. Baldassano

Eosinophilic gastroenteritis consists of a group of rare and poorly understood disorders that have in common gastric and small intestine infiltration with eosinophils and peripheral eosinophilia. The esophagus and large intestine may also be involved. Tissue eosinophilic infiltration can be seen in mucosa, muscularis, or serosa. The mucosal form is most common and is diagnosed by identifying large numbers of eosinophils in biopsy specimens of gastric antrum or small bowel. Endoscopy may reveal gastritis or colitis, ulceration, and thickened mucosal folds, as well as nodules. This condition clinically overlaps the dietary protein hypersensitivity disorders of the small bowel and colon. Peripheral eosinophilia may be absent. The differential diagnosis also includes celiac disease, chronic granulomatous disease, connective tissue disorders and vasculitides (eosinophilic granulomatosis with polyangiitis), multiple infections (particularly parasites), hypereosinophilic syndrome, early inflammatory bowel disease, medications (tacrolimus, enalapril, naproxen, interferon, rifampicin, azathioprine), and rarely malignancy. Many patients have allergies to multiple foods, seasonal allergies, atopy, eczema, and asthma. Serum immunoglobulin E is commonly elevated. Laboratory abnormalities may include hypoalbuminemia, iron-deficiency anemia, and elevated liver enzymes. Medications have been associated with eosinophilic gastroenteritis including gold, enalapril, and carbamazepine.

The presentation of eosinophilic gastroenteritis is nonspecific. Clinical symptoms often correlate with which layers of the gastrointestinal tract are affected. Mucosal involvement can produce nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, protein-losing enteropathy, or malabsorption. Involvement of the muscularis can produce obstruction (especially of the pylorus) or intussusception, whereas serosal activity produces abdominal distention and eosinophilic ascites. Presentation in infants can be similar to pyloric stenosis. Laboratory testing often reveals peripheral eosinophilia, elevated serum immunoglobulin E levels, hypoalbuminemia, and anemia.

The disease usually runs a chronic, debilitating course with sporadic severe exacerbations. Although usually effective for the treatment of isolated eosinophilic esophagitis (see Chapter 370), elemental diets are not always successful for the treatment of eosinophilic gastroenteritis. Orally administered cromolyn sodium and montelukast are sometimes successful. There have been case reports of clinical improvement using ketotifen, an antihistamine and mast cell stabilizer. Many patients require treatment for acute disease exacerbations with systemic corticosteroids, which are often effective. Systemic corticosteroids may also be needed long term. Oral budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and limited systemic absorption due to high hepatic first-pass metabolism, can be attempted for long-term therapy. In adults, biologic agents (e.g., omalizumab) have been used.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com Bibliography.

Chapter 384
Celiac Disease

Ankur A. Chugh

ETIOLOGY AND EPIDEMIOLOGY

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten in wheat and related prolamins from rye and barley in genetically susceptible individuals, and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leukocyte antigen (HLA)-DQ2 or DQ8 haplotypes, and enteropathy. CD-specific antibodies comprise autoantibodies against tissue transglutaminase (TG2) including endomysial antibodies (EMAs), and antibodies against forms of deamidated gliadin peptides (DGPs).

CD is a common disorder with 1.4% global prevalence of positive serologies and 0.7% of biopsy-proven disease, with variability across countries. CD affects both children and adults (second to third decade of life). Although CD develops in genetically susceptible individuals, environmental factors might affect the risk of developing CD or the timing of its presentation. Neither breastfeeding during gluten introduction nor any breastfeeding has been shown to reduce the risk of CD. The impact of *early* gluten introduction (age 4 months) on the risk of developing CD is contradictory. *Large* amounts of gluten at a young age (6 months) may convey risk of earlier development of CD autoimmunity (positive serology) and CD, whereas *lower* amounts of gluten in the first 2 years of life may convey lower risk of CD. Infectious agents have been hypothesized to play a causative role, as frequent rotavirus infections were shown to be associated with an increased risk of developing CD. It is plausible that the contact with gliadin at a time when there is an ongoing intestinal inflammation alters intestinal permeability, and the enhanced antigen presentation can increase the risk of developing CD, at least in a subset of persons. The mode of delivery, socioeconomic status, season of birth, and the use of drugs have been associated with the risk of developing CD, but the evidence is contradictory.

GENETICS AND PATHOGENESIS

A genetic predisposition is suggested by the family aggregation and the concordance in monozygotic twins, which approaches 100%. The strongest association is with HLA-DQ2.5 (one or two copies encoded by DQA1*05 [for the alpha] and DQB1*02 genes [for the beta chain]). Such a DQ molecule has been found to be present in more than 90% of CD patients. The highly homologous DQ2.2 molecule confers a much lower risk, whereas the data available on DQ2-negative CD patients indicate that they almost invariably are HLA-DQ8 positive (DQA1*0301/DQB1*0302). A gene dosage effect has been proved in prospective studies, and a molecular hypothesis for such a phenomenon has been proposed, based on the impact of the number and quality of the HLA-DQ2 molecules on gluten peptide presentation to T cells. The HLA locus is the most significant and dominant gene associated with CD; however, other loci known to contribute to CD have been documented. Most have been found to be associated with other autoimmune diseases such as type 1 diabetes. Interestingly, very few polymorphisms associated with CD are in coding regions, as they often are in binding sites for transcription factors, where they then affect gene expression.

CD is a T-cell–mediated chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability, and activation of innate immunity mechanisms precede the activation of the adaptive immune response. Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favors the immunostimulatory and toxic effects of these sequences. Some gliadin peptides activate innate immunity, in particular they induce interleukin (IL)-15. The latter, but also type 1 interferons, may alter the tolerogenic phenotype of dendritic cells, resulting in lamina propria T-cell activation by other peptides presented in the context of HLA-DQ2 or HLA-DQ8 molecules. Gliadin-specific T-cell responses are enhanced by the action of TG2: the enzyme converts particular glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLA-DQ2 or HLA-DQ8. The pattern of cytokines produced following gliadin activation is dominated by interferon-γ (T-helper type 1 skewed); IL-21 is also upregulated. In downstream T-cell activation a complex remodeling of the mucosa takes place involving increased levels of metalloproteinases and growth factors, which leads to the classical histologic finding of a flat mucosa. A severe impairment of intraepithelial lymphocyte (IEL) homeostasis is present in CD. IL-15 is implicated in the expression of natural killer receptors CD94 and NKG2D, as well as in epithelial expression of stress molecules, thus enhancing cytotoxicity, cell apoptosis, and villous atrophy. The most evident expression of autoimmunity is the presence of serum antibodies to TG2. However, the mechanisms leading to autoimmunity are largely unknown, as well as their pathogenetic significance. *Potential* CD, in which TG2 antibodies can be detected in situ without any histologic abnormality, shows that the production of antibodies does not necessarily lead to intestinal damage. The finding that IgA deposits on extracellular TG2 are not limited to the intestine but can be found in the liver, lymph nodes, and muscles indicates that TG2 is accessible to the gut-derived autoantibodies, turning CD into a systemic disease.

CLINICAL PRESENTATION AND ASSOCIATED DISORDERS

Clinical features of CD vary considerably. Intestinal symptoms are more common in children whose disease is diagnosed *within the first 2 years of life*; failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle wasting, anorexia, and irritability are present in most cases (Fig. 384.1). Occasionally there is constipation, with cases presenting with intussusception. As the age at presentation of the disease shifts to later in childhood, and with the more extensive use of serologic screening tests, extraintestinal manifestations, without any accompanying digestive symptoms, have increasingly become recognized, affecting

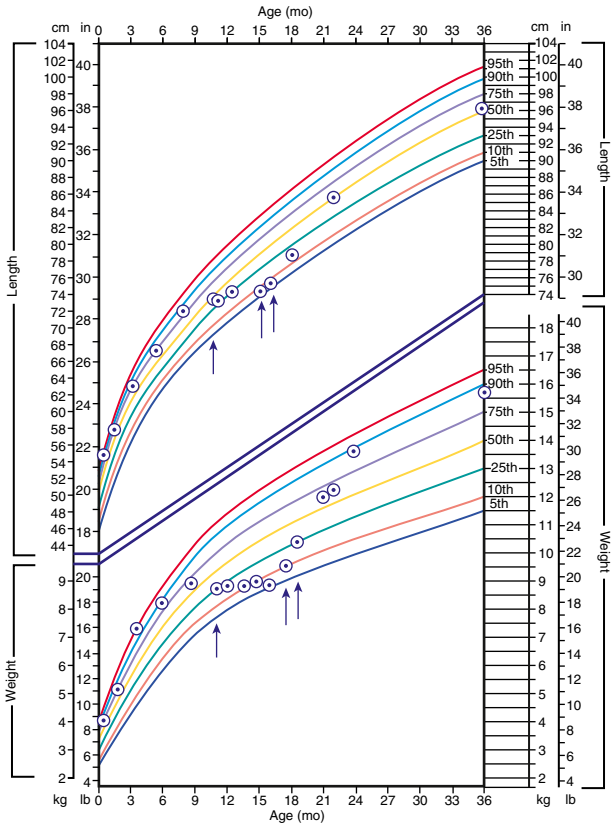

Fig. 384.1 Gluten-sensitive enteropathy. Growth curve demonstrates initial normal growth from 0 to 9 mo, followed by onset of poor appetite with intermittent vomiting and diarrhea after initiation of gluten-containing diet *(single arrow)*. After biopsy confirmed diagnosis and treatment with gluten-free diet *(double arrow)*, growth improves.

almost all organs (Table 384.1). One of the most common extraintestinal manifestation of CD is iron-deficiency anemia, which is usually unresponsive to iron therapy. Osteoporosis may be present; in contrast to adults, it can be reversed by a gluten-free diet in children, with restoration of normal peak bone densitometric values. Other extraintestinal manifestations include short stature, delayed puberty, arthritis and arthralgia, epilepsy with bilateral occipital calcifications, peripheral neuropathies, isolated hypertransaminasemia, dental enamel hypoplasia, and aphthous stomatitis. The mechanisms responsible for the severity and the variety of clinical presentations remain obscure. Nutritional deficiencies or abnormal immune responses have been suggested. Silent CD is recognized, mainly in asymptomatic first-degree relatives of CD patients and in subjects affected by diseases associated with CD (Table 384.2). Small bowel biopsy in silent/subclinical CD reveals severe mucosal damage consistent with CD. Potential CD is defined when patients have positive CD-specific antibodies, but without documented small bowel damage (Table 384.3).

Some diseases, many with an autoimmune pathogenesis, are found with a higher than normal incidence in CD patients. Among these are type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjögren syndrome, rheumatoid arthritis, autoimmune cholangitis, autoimmune hepatitis, primary biliary cholangitis, and juvenile idiopathic arthritis. Such associations have been interpreted as a consequence of the sharing of identical HLA haplotypes, but a direct role of

Table 384.1 Extraintestinal Manifestations of Celiac Disease

MANIFESTATION	PROBABLE CAUSE(S)
CUTANEOUS	
Ecchymoses and petechiae	Vitamin K deficiency; rarely, thrombocytopenia
Edema	Hypoproteinemia
Dermatitis herpetiformis	Epidermal (type 3) tTG autoimmunity
Follicular hyperkeratosis and dermatitis	Vitamin A malabsorption, vitamin B complex malabsorption
ENDOCRINOLOGIC	
Amenorrhea, infertility, impotence, delayed puberty, short stature, type 1 diabetes, thyroiditis, Addison disease, Graves disease	Malnutrition, hypothalamic-pituitary dysfunction, immune dysfunction
Secondary hyperparathyroidism	Calcium and/or vitamin D malabsorption with hypocalcemia
HEMATOLOGIC	
Anemia	Iron, folate, vitamin B_{12}, or pyridoxine deficiency
Hemorrhage	Vitamin K deficiency; rarely, thrombocytopenia due to folate deficiency
Thrombocytosis, Howell-Jolly bodies	Hyposplenism; splenic atrophy; autoantibodies
Pancytopenia	Vitamin B_{12} deficiency; immune medicated
Thrombosis	Venous and arterial, including portal vein
Malignancies	Enteropathy-type T-cell lymphoma, B-cell gut lymphoma, adenocarcinoma of small intestine
HEPATIC	
Elevated liver biochemical test levels	Lymphocytic celiac hepatitis, NAFLD
Autoimmune hepatitis	Associated autoimmune hepatitis
MUSCULAR	
Atrophy	Malnutrition due to malabsorption
Tetany	Calcium, vitamin D, and/or magnesium malabsorption
Weakness	Generalized muscle atrophy, hypokalemia
NEUROLOGIC	
Peripheral neuropathy	Deficiencies of vitamin B_{12} and thiamine; immune-based neurologic dysfunction
Ataxia	Cerebellar and/or posterior column damage
Demyelinating central nervous system lesions	Immune-based neurologic dysfunction
Seizures (difficult to treat)	Unknown; associated occipital calcifications
SKELETAL	
Osteopenia, osteomalacia, and osteoporosis	Malabsorption of calcium and vitamin D, secondary hyperparathyroidism, chronic inflammation
Osteoarthropathy	Unknown
Pathologic fractures	Osteopenia and osteoporosis
OTHER	
Enamel hypoplasia	Vitamin D, calcium malabsorption
Anxiety, schizophrenia	Unknown, uncertain
Pulmonary hemosiderosis	Unknown, uncertain
Aphthous stomatitis	Unknown
Benign inflammatory mass	Granulomatous self-resolving process with treatment

tTG, Tissue transglutaminase; NAFLD, nonalcoholic fatty liver disease.
Modified from Kelly CP. Celiac disease. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 107.1.

Table 384.2 National Institute for Health and Care Excellence Guidelines on the Indications That Should Prompt Testing for Celiac Disease

CELIAC TESTING RECOMMENDED
• Persistent unexplained abdominal or gastrointestinal symptoms
• Faltering growth
• Prolonged fatigue
• Unexpected weight loss
• Severe or persistent mouth ulcers
• Unexplained iron, vitamin B_{12}, or folate deficiency
• Type 1 diabetes
• Autoimmune thyroid disease
• Irritable bowel syndrome
• First degree relatives of people with coeliac disease
• Dermatitis herpetiformis
CELIAC TESTING SHOULD BE CONSIDERED
• Metabolic bone disorders (reduced bone mineral density or osteomalacia)
• Unexplained neurologic symptoms (particularly peripheral neuropathy or ataxia)
• Unexplained subfertility or recurrent miscarriage
• Persistently increased concentrations of liver enzymes with unknown cause
• Dental enamel defects
• Down syndrome
• Turner syndrome
• William syndrome
• Selective IgA deficiency

IgA, Immunoglobulin A.
From Downey L, Houten R, Murch S, Longson D for the Guideline Development Group. Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance. *BMJ*. 2015;351:h4513.

Table 384.3 Clinical Spectrum of Celiac Disease

SYMPTOMATIC
Frank malabsorption symptoms and signs (e.g., chronic diarrhea, failure to thrive, weight loss)
Extraintestinal symptoms and signs (e.g., anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis)
SILENT
No apparent symptoms in spite of histologic evidence of villous atrophy
In most cases identified by serologic screening in at-risk groups (see Table 384.1)
LATENT
Subjects who have a normal intestinal histology, but at some other time have shown a gluten-dependent enteropathy
POTENTIAL
Subjects with positive celiac disease serology but without evidence of altered intestinal histology. Patients may or may not have symptoms and signs of disease and may or may not develop a gluten-dependent enteropathy later

gluten in promoting autoimmunity cannot be excluded. The relation between CD and other autoimmune diseases is poorly defined; once those diseases are established, they are not influenced by a gluten-free diet. Other associated conditions include selective IgA deficiency and Down, Turner, and Williams syndromes (see Table 384.2).

DIAGNOSIS

The diagnosis of CD is based on a combination of symptoms, antibodies, and duodenal histology. The initial approach to symptomatic patients is to test for anti-TG2 IgA antibodies and for total IgA in serum to exclude IgA deficiency. If IgA anti-TG2 antibodies are negative, and serum total IgA is normal for age, CD is unlikely to be the cause of the symptoms. If anti-TG2 antibody testing is positive, the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels.

In patients with selective IgA deficiency, testing is recommended with IgG antibodies to TG2. Patients with positive anti-TG2 antibody levels <10 times the upper limit of normal should undergo upper endoscopy with multiple biopsies. In patients with positive anti-TG2 antibody levels at or >10 times the upper limit of normal, EMA titers should be obtained in a second blood draw (to prevent mislabeling). If the patient has positive antibodies, the diagnosis of CD is essentially confirmed, a lifelong gluten-free diet is started, and the patient is followed for the improvement of symptoms and the decline of antibodies. In the rare case of negative anti-EMA in a child with TG2 antibody titers >10 times the upper limits of normal, the diagnostic workup should be extended, and duodenal biopsies obtained (Fig. 384.2). In asymptomatic persons belonging to high-risk groups with anti-TG2 levels >10 times the upper limit of normal, the decision to utilize the nonbiopsy approach should be a shared decision with the patient/family. When biopsies are indicated, at least four fragments should be obtained from the descending part of the duodenum and at least one from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. CD is not the only cause for lymphocytic infiltration or villous atrophy (Table 384.4). HLA testing is helpful for diagnostic uncertainty, patients already on a gluten free diet, and in screening of high-risk individuals. The benefit of obtaining additional DGP antibodies in patients <2 years of age is no longer favored.

TREATMENT

The only treatment for CD is lifelong, strict adherence to a gluten-free diet. This requires a wheat-, barley-, and rye-free diet (Tables 384.5 and 384.6). Despite evidence that oats are safe for most patients with CD, there is concern regarding the possibility of contamination of oats with gluten during harvesting, milling, and shipping. Nevertheless, it seems wise to add oats to the gluten-free diet only when the latter is well established, so that possible adverse reactions can be readily identified. There is a consensus that all CD patients should be treated with a gluten-free diet regardless of the presence of symptoms. However, whereas it is relatively easy to assess the health improvement after treatment of CD in patients with clinical symptoms of the disease, it proves difficult in persons with *asymptomatic* CD. The nutritional risks, particularly osteopenia and increased risk for other autoimmune disorders, along with the increased but rare risk of intestinal lymphoma, are those mainly feared for subjects who have silent CD and continue on a gluten-containing diet. Little is known about the health risks in untreated patients with potential CD. For these patients, adequate gluten intake should be confirmed, the biopsy orientation should be checked, and monitoring should occur at a tertiary medical center, given the potential for serologies to both normalize or progress to villous atrophy.

Some older patients do not respond to a gluten free diet; *refractory or nonresponsive CD* requires a systematic approach to determine the correct diagnosis, compliance, and therapeutic options (Fig. 384.3).

The Codex Alimentarius Guidelines define gluten-free food item for food containing <20 parts per million (ppm; equivalent to 20 mg gluten in 1 kg of product). However, despite analytical methods for gluten detection reaching a satisfactory degree of sensitivity, more information is needed on the daily gluten amount that may be tolerated by CD patients. The data available so far seem to suggest that the threshold should be set to <50 mg/day, although individual variability makes it difficult to set a universal threshold.

It is important that an experienced dietitian with specific expertise in CD counseling educates the family and the child about dietary restriction. Compliance with a gluten-free diet can be difficult, especially in adolescents, and patients should be monitored for signs of depression and referred to psychology or adolescent medicine as appropriate. It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination, and adherence to the gluten-free diet. Bloodwork, such as complete blood count, hepatic panel, thyroid function, calcium, vitamin D, iron, and ferritin have been suggested at diagnosis, with abnormal values followed until normalized. Periodic measurements of TG2 antibody levels to document reduction in antibody titers are recommended as indirect evidence of adherence to a

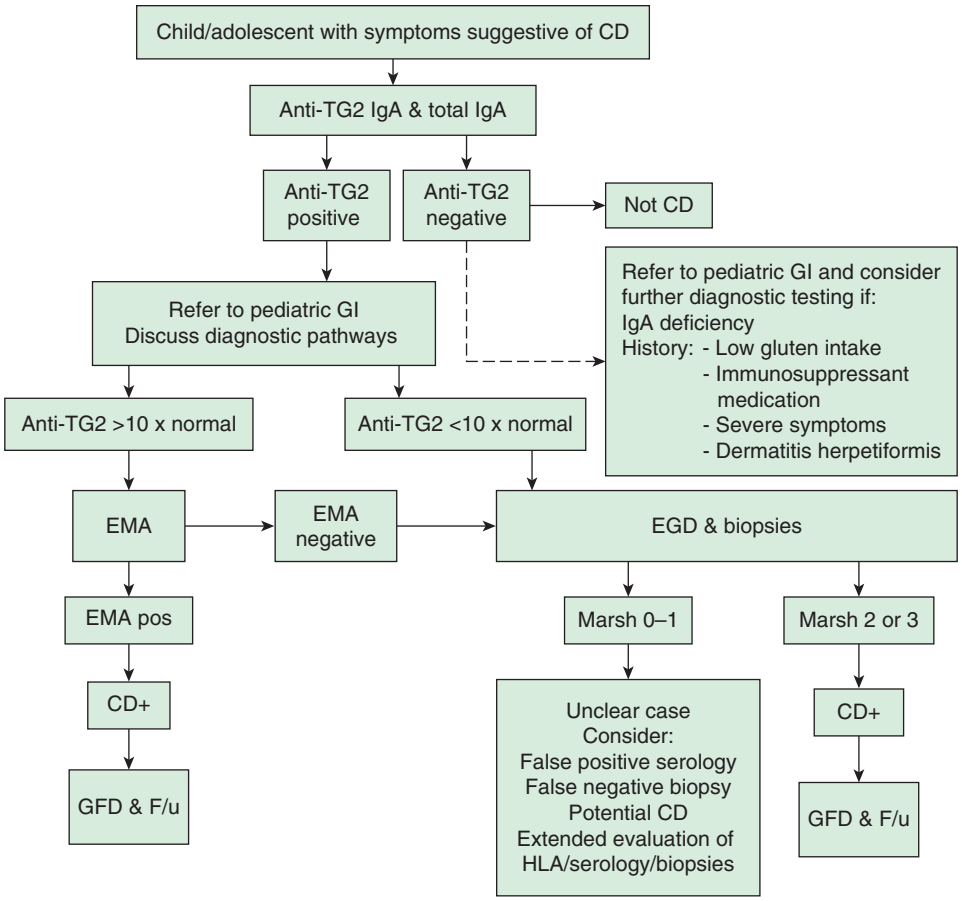

Fig. 384.2 Diagnostic algorithm for celiac disease according to European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). CD, Celiac disease; EMA, endomysial antibodies; EGD, esophagogastroduodenoscopy; F/u, follow-up; GFD, gluten-free diet; GI, gastrointestinal; HLA, human leukocyte antigen; Ig, immunoglobulin; neg, negative; pos, positive; TG2, transglutaminase. *(Modified from Husby S, Koletzko S, Korponay-Szabò IR, et al. European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease. J Pediatr Gastroenterol Nutr. 2020;70:13841–14157. Fig. 4.)*

Table 384.4 Conditions Other Than Celiac Disease That Can Cause Duodenal Lymphocytosis or Villous Atrophy

DUODENAL LYMPHOCYTOSIS
• Food allergy, non-celiac gluten sensitivity
• Infection (e.g., *Helicobacter pylori* or giardiasis)
• Drugs (e.g., nonsteroidal antiinflammatory drugs)
• Postenteritis syndrome
• Immune deficiency (e.g., selective IgA deficiency, common variable immune deficiency)
• Immune dysregulation (e.g., autoimmune thyroiditis)
• Crohn disease
• Preinfiltrative intestinal T-cell lymphoma
VILLOUS ATROPHY
• Environmental enteropathy (tropical sprue)
• Common variable immune deficiency
• Autoimmune enteropathy
• Drugs (e.g., olmesartan or azathioprine)
• Food allergy
• Giardiasis
• Crohn disease
• Eosinophilic enteritis
• Radiation enteritis
• Intestinal lymphoma
• HIV enteropathy
• Bacterial overgrowth
• Graft-versus-host disease
• Protein energy malnutrition

Modified from Catassi C, Verdu EF, Bai JC, Lionette E. Coeliac disease. *Lancet.* 2022;399:2413–2424.

Table 384.5 Principles of Initial Dietary Therapy for Patients with Celiac Disease

Avoid all foods containing wheat, rye, and barley gluten (pure oats usually safe).
Avoid malt unless clearly labeled as derived from corn.
Use only rice, corn, maize, buckwheat, millet, amaranth, quinoa, sorghum, potato or potato starch, soybean, tapioca, and teff, bean, and nut flours.
Wheat starch and products containing wheat starch should only be used if they contain <20 ppm gluten and are marked "gluten free."
Read all labels and study ingredients of processed foods.
Beware of gluten in medications, supplements, food additives, emulsifiers, or stabilizers.
Limit milk and milk products initially if there is evidence of lactose intolerance.
Avoid all beers, lagers, ales, and stouts (unless labeled gluten free).
Wine, most liqueurs, ciders, and spirits, including whiskey and brandy, are allowed.

ppm, Parts per million.

gluten-free diet, although they are insensitive to slight dietary transgressions and can take up to 2-3 years to normalize. The TG2 antibody levels can be checked every 1-2 years after they normalize, or sooner if symptoms or concerns for compliance arise. Commercial tests are available to monitor for compliance and transgressions via the detection of gluten peptides in the urine and stool, but remain under investigation for validation. If compliance is uncertain or body mass index (BMI) *z* scores are low, bone health should be assessed. Therapeutic treatments, such as those that target IL-15, IL-21, and gluten degradation, remain in clinical trials.

Table 384.6 Some Potential Sources of Hidden Gluten

Beers, ales, other fermented beverages (distilled beverages acceptable)
Bouillon and soups
Candy
Communion wafers
Drink mixes
Gravy and sauces
Herbal tea
Imitation meat and seafood
Nutritional supplements
Play-Doh
Salad dressings and marinades
Self-basting turkeys
Soy sauce

From Kelly CP. Celiac disease. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier, 2016: Box 107.3.

THE SPECTRUM OF GLUTEN-RELATED DISORDERS

CD is not the only disorder related to gluten ingestion. Symptoms in IgE-mediated wheat allergy are usually immediate (urticaria, angioedema, asthma, exercise-induced anaphylaxis). Diagnosis is based on dietary challenge, in vitro assay for specific IgE, and skin testing.

Nonceliac gluten sensitivity (NCGS) is a poorly understood condition. Diagnosis is suspected in patients who do not have CD or wheat allergy, and yet show GI and non-GI symptoms upon ingestion of gluten- or wheat-containing food. In the general population, the incidence of self-reported gluten avoidance varies from 0.5% to 13%. Similar symptoms are often experienced by patients with irritable bowel syndrome (IBS), and some patients with IBS respond positively to a gluten-free diet or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP diet).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

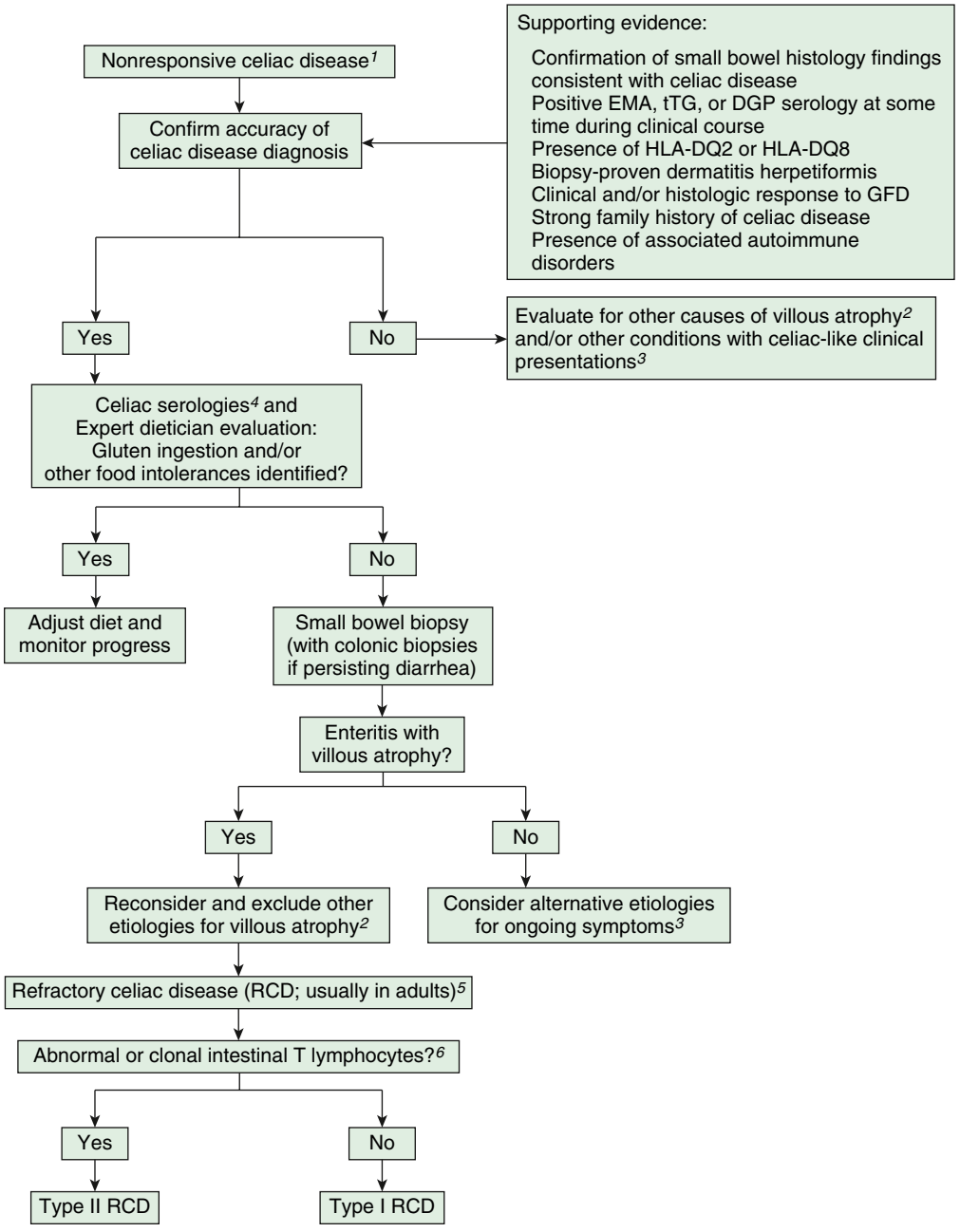

Fig. 384.3 Diagnostic algorithm for the approach to patients with nonresponsive celiac disease. [1]*Nonresponsive celiac disease* may be defined as persistent symptoms and signs despite 6-12 mo of dietary gluten avoidance. Abnormal tissue transglutaminase (tTG) can last even 2-3 yr. [2]Causes of nonceliac small intestinal villous atrophy that may be misdiagnosed as celiac disease include autoimmune enteropathy, tropical sprue, medication induced enteropathy, hypogammaglobulinemia, combined variable immunodeficiency, collagenous sprue, Crohn disease, and peptic duodenitis. [3]Conditions that present clinically in a fashion similar to celiac disease but where villous atrophy is not evident include irritable bowel syndrome (IBS), carbohydrate malabsorption, small intestinal bacterial overgrowth, Crohn's disease, and microscopic colitis. [4]Positive serologic testing for celiac disease despite 12 mo of treatment with a gluten-free diet (GFD) suggest that there may be ongoing gluten ingestion.[5]*Refractory celiac disease (RCD)* is defined as persistent or recurrent malabsorptive symptoms and signs, with small intestinal villous atrophy despite a strict GFD for more than 12 mo and in the absence of other disorders including overt lymphoma. [6]Abnormal intestinal lymphocytes may be identified by immunohistochemistry of intraepithelial lymphocytes or by flow cytometry showing an increased number of CD3-positive cells that lack CD8 or by the identification of clonal T-cell receptor gene rearrangement by molecular analysis. EMA, Endomysial antibody; DGP, deamidated gliadin peptide; HLA, human leukocyte antigen. *(Adapted from Green PHR, Paski S, Ko CW, Rubio-Tapia A. AGA clinical practice update on management of refractory celiac disease: expert review. Gastroenterology 2022;163(5):1461–1469.)*

Chapter 385

Disorders of Malabsorption

Abdul-Aziz K. Elkadri

Malabsorption is defined as a decreased intestinal absorption of one or more dietary elements. The intestinal tract requires several components to properly absorb the required elements from our diet, and the absence or improper **digestion** within the lumen or diminished or dysfunctional mucosal **absorption** is due to the lack of presence or function of these components. Due to the change in composition or volume of luminal contents, many if not all malabsorptive disorders result in diarrhea. Chronic ongoing losses further worsen the malabsorption, resulting in chronic diarrhea (see Chapter 388). Malabsorption can be categorized based on mucosal defects resulting in a more generalized malabsorption with multiple nutrient defects (Table 385.1), or due to the malabsorption of specific components such as carbohydrates, proteins, lipids, vitamins, minerals, and trace elements (Table 385.2).

CLINICAL APPROACH

Because malnutrition leads to the loss of typically absorbed components in stool, the presentation of a patient will differ depending upon the length of time with malabsorption, the extent of losses, and the phase of growth and magnitude of required nutrients. With proper follow-up, the clinical features tend to be growth related, with failure to gain weight and a stagnation of linear growth percentiles. Physical exam findings tend to be subtle, with abdominal distension, diarrhea, and even constipation as presenting features depending on the malabsorbed component. With more extensive losses or delay in presentation, the clinical features become more pronounced. Findings can include muscle wasting, loss of subcutaneous fat, and loose skinfolds (Fig. 385.1). Because toddlers have increased energy requirements, presentation in this age-group can be dramatic and more acute. In older children and adolescents, the presentation may be more subtle, with suboptimal weight gain or weight loss as a more common presentation. Height stunting tends to lag behind weight parameters. In developing areas of the world where access to health resources including enteral and parenteral nutrition (PN) continues to be limited, prolonged malabsorption may lead to death (see Chapter 64). This outcome is uncommon in the developed world, where access to healthcare leads to improved outcomes. Nonetheless, monogenetic causes of malabsorption often produce failure to thrive in any region of the world. Specific findings on examination can guide toward a specific disorder; edema is usually associated with protein-losing enteropathy (PLE), digital clubbing with conditions including cystic fibrosis and celiac disease, perianal excoriation and gaseous abdominal distention with carbohydrate malabsorption, perianal and circumoral rash with acrodermatitis enteropathica, abnormal hair with Menkes syndrome (ATP7A defects), tricho-hepato-enteric syndrome (THE), and the typical facial features diagnostic of the Johanson-Blizzard syndrome.

To compensate for the fecal losses of nutrients and calories, many children present with a history of a good appetite. In exocrine pancreatic insufficiency, fecal losses of up to 40% of ingested protein and energy do not lead to malnutrition, as long as they are compensated by an increased appetite. In conditions associated with villous atrophy or inflammation (Celiac disease, postinfectious enteropathy or Crohn disease), fecal protein and energy losses are usually modest, but associated anorexia and thus reduced food intake results in malnutrition.

The nutritional assessment is an important part of clinical evaluation in children with malabsorptive disorders (see Chapter 60). Long-term calcium and vitamin D malabsorption can lead to reduced bone mineral density and metabolic bone disease (often resistant to oral vitamin D), with increased risk of bone fractures. Vitamin K malabsorption, irrespective of the underlying mechanism (fat malabsorption, mucosal atrophy), can result in coagulopathy. Severe PLE is often associated with malabsorption syndromes (celiac disease, Crohn disease, congenital disorders of glycosylation, intestinal lymphangiectasia [IL]) and causes hypoalbuminemia and edema. Other nutrient deficiencies include iron malabsorption causing microcytic anemia and low reticulocyte count, low serum folate levels in conditions associated with mucosal atrophy, especially in the proximal part of the small intestinal tract, and low serum vitamin A and vitamin E concentrations in fat malabsorption.

Diarrhea is the main clinical expression of malabsorption. Early presentation of diarrhea in early infancy suggests a congenital defect (Table 385.3). In congenital disorders of diarrhea such as microvillus inclusion disease (MVID) and congenital sodium or chloride diarrhea, higher volume fluid losses within the stool lead to watery like diarrhea, often mistaken for urine (see Chapter 388). The onset of symptoms after the introduction of a particular food into a child's diet can provide diagnostic clues, such as with sucrose in sucrase-isomaltase (SI) deficiency. The nature of the diarrhea may be helpful: explosive watery diarrhea suggests carbohydrate malabsorption; loose, bulky stools are associated with celiac disease; and pasty, yellowish, and offensive smelling stools suggest fat malabsorption and an exocrine pancreatic insufficiency. Stool color is usually not helpful, though it may suggest blood loss if red or melena. Green stool with undigested foods can suggest rapid intestinal transit in toddler's diarrhea, which by itself is a self-limiting condition unassociated with failure to thrive.

Following medical history, physical examination, and laboratory testing (see Chapter 385.1), intestinal biopsies may assist in the diagnosis. This is usually done for chronic rather than acute diseases which are typically self-limited. Generalized mucosal villous atrophy (flat mucosa) may be associated with malabsorption of multiple *macronutrients* and *micronutrients* and has a wide range of differential diagnoses (see Chapters 384 and 385.2).

385.1 Evaluation of Children with Suspected Intestinal Malabsorption

Abdul-Aziz K. Elkadri

In a child presenting with chronic or recurrent diarrhea, the initial workup should include nucleic acid amplification tests (NAATs) (viruses, bacteria) and, when not available, by stool cultures and antibody (or antigen testing) tests for parasites. Stool microscopy for ova and parasites can look for parasites such as *Giardia*. Fecal leukocytes and calprotectin and/or lactoferrin may suggest inflammatory disorders. Acidic stool pH and positive reducing substances suggest a component of carbohydrate malabsorption. Stool osmolality helps differentiate between osmotic and secretory diarrhea. Along with a careful diet history focusing on fat intake, quantitative stool fat examination helps determine whether there is fat malabsorption. Elevated fecal α_1-antitrypsin and a low serum albumin (in the absence of hepatic or renal disease) can suggest enteral protein loss. Fecal stool elastase-1 can assess for exocrine pancreatic insufficiency.

A complete blood count, including peripheral smear for microcytic anemia, lymphopenia (lymphangiectasia), neutropenia (Shwachman-Diamond syndrome), and acanthocytosis (abetalipoproteinemia), is useful. If celiac disease is suspected, serum immunoglobulin IgA and anti-tissue transglutaminase IgA (anti-TTG IgA) antibody levels should be determined (see Chapter 384). If inflammation is suspected, CRP and ESR can be drawn. Depending on the initial test results, more specific investigations can be planned.

INVESTIGATIONS FOR CARBOHYDRATE MALABSORPTION

The measurement of acidic stool pH and the amount of reducing substances are simple screening tests for carbohydrate malabsorption. An acidic stool with a pH <5 and >2+ reducing substance suggests carbohydrate malabsorption. Sucrose or starch in the stool is not recognized

Table 385.1 Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect

ACQUIRED AUTOIMMUNITY
Celiac disease (Gluten sensitive enteropathy)
Cow's milk and other protein intolerance enteropathy
Eosinophilic enteropathy
Crohn disease
Immune Dysregulation
Congenital immunodeficiency disorders
Selective immunoglobulin A deficiency (associated with celiac disease)
Severe combined immunodeficiency
Agammaglobulinemia
X-linked hypogammaglobulinemia
Wiskott-Aldrich syndrome
Common variable immunodeficiency disease
Chronic granulomatous disease
IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked inheritance) and IPEX-like syndromes (tregopathies)
Autoimmune polyendocrine candidiasis ectodermal dystrophy syndrome type 1 (APECED)
CONGENITAL BOWEL MUCOSAL DEFECTS
Microvillus inclusion disease
Tufting enteropathy
Carbohydrate-deficient glycoprotein syndrome
Enterocyte heparan sulfate deficiency
Tricho-hepatic-enteric syndrome
Enteroendocrine Cell Dysfunction
Enteric anendocrinosis *(NEUROG3)*
Proprotein convertase 1/3 deficiency *(PCSK1)*
ACQUIRED IMMUNE DEFICIENCY
HIV infection
Immunosuppressive therapy and post bone marrow transplantation
Mechanical Defects
Short bowel syndrome
Blind loop syndrome
Pseudoobstruction
MISCELLANEOUS
Lymphangiectasia
Immunoproliferative small intestinal disease
Radiation enteritis
Protein-calorie malnutrition

Table 385.2 Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed

CARBOHYDRATE MALABSORPTION
Lactose malabsorption
Congenital lactase deficiency
Hypolactasia (adult type)
Secondary lactase deficiency
Congenital sucrase isomaltase deficiency
Glucose galactose malabsorption
FAT MALABSORPTION
Exocrine pancreatic insufficiency
Cystic fibrosis
Shwachman-Diamond syndrome
Johanson-Blizzard syndrome
Pearson syndrome
Secondary exocrine pancreatic insufficiency
Chronic pancreatitis
Severe protein-calorie malnutrition
Decreased pancreozymin/cholecystokinin secretion
Isolated enzyme deficiency
Enterokinase deficiency
Trypsinogen deficiency
Lipase/colipase deficiency
Disrupted enterohepatic circulation of bile salts
Cholestatic liver disease
Bile acid synthetic defects
Deconjugation of bile acids (bacterial overgrowth)
Bile acid malabsorption (terminal ileal disease or resection)
Intestinal brush border disorders
Allergic enteropathy
Autoimmune enteropathy
Disorders in formation and transport of chylomicrons by enterocytes to the lymphatics
Abetalipoproteinemia
Homozygous hypobetalipoproteinemia
Chylomicron retention disease (Anderson disease)
Disorders of lymph flow
Primary or secondary lymphangiectasia
PROTEIN/AMINO ACID MALABSORPTION
Lysinuric protein intolerance (defect in dibasic amino acid transport)
Hartnup disease (defect in free neutral amino acids)
Blue diaper syndrome (isolated tryptophan malabsorption)
Oasthouse urine disease (defect in methionine absorption)
Lowe syndrome (lysine and arginine malabsorption)
Enterokinase deficiency
Protein-losing enteropathy
Congenital disorders of glycosylation
CD55 deficiency
MINERAL AND VITAMIN MALABSORPTION
Congenital chloride diarrhea
Congenital sodium diarrhea
Acrodermatitis enteropathica (zinc malabsorption)
Menkes disease (copper malabsorption)
Vitamin D–dependent rickets
Folate malabsorption
Secondary to chronic mucosal damage
Vitamin B_{12} malabsorption
Autoimmune pernicious anemia
Decreased gastric acid (H_2 blockers or proton pump inhibitors)
Terminal ileal disease (e.g., Crohn disease) or resection
Inborn errors of vitamin B_{12} transport and metabolism
Primary hypomagnesemia
DRUG INDUCED
Sulfasalazine: folic acid malabsorption
Cholestyramine: calcium and fat malabsorption
Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)
Gastric acid suppression: vitamin B_{12}
Methotrexate: mucosal injury

as a reducing sugar until after hydrolysis with hydrochloric acid, which converts them to reducing sugars.

Breath hydrogen test is used to identify the specific carbohydrate that is malabsorbed. After an overnight fast, the suspected sugar (lactose, sucrose, fructose, or glucose) is administered as an oral solution (carbohydrate load up to 2 g/kg, maximum total of 25 g, depending on the specific carbohydrate type). In malabsorption, the sugar is not digested or absorbed in the small bowel; it passes on to the colon and is metabolized by the normal gut microflora. One of the products of this process is hydrogen gas, which is absorbed through the colon mucosa and excreted in the breath. Because human cells are incapable of producing hydrogen, increased hydrogen concentration in the breath samples suggests carbohydrate malabsorption. A rise in breath hydrogen of 20 parts per million (ppm) above the baseline, preferably with associated symptoms, is considered a positive test. The child should not be on antibiotics at the time of the test because antibiotics may suppress the colonic flora, which is essential for fermenting the sugar. Care should be taken in the interpretation of these results as small intestinal bacterial overgrowth can lead to an early elevation of hydrogen.

Small bowel mucosal biopsies can directly measure mucosal disaccharidase (lactase, sucrase, maltase, palatinase) concentrations. In primary enzyme deficiencies the mucosal enzyme levels are low and small bowel

mucosal morphology is normal. Primary enzymatic deficiencies can also be diagnosed by genetic testing (see Chapters 385.8-385.10 and 388). Partial or total villous atrophy due to autoimmune disorders such as celiac disease or Crohn disease or following acute rotavirus gastroenteritis can result in secondary disaccharidase deficiency and transient lactose intolerance (see Chapters 384 and 385.2 for differential diagnosis of villous atrophy). The disaccharidase levels revert to normal after mucosal healing.



Fig. 385.1 An 18-month-old male with active celiac disease. Note the ill appearance with loose skinfolds, marked proximal muscle wasting, and distended abdomen.

INVESTIGATIONS FOR FAT MALABSORPTION

The presence of fat globules in the stool suggests fat malabsorption. The ability to absorb fat varies with age. While on a typical diet, a premature infant can absorb only 65–75% of dietary fat, a full-term infant absorbs almost 90%, and an older child absorbs more than 95% of fat. Quantitative determination of fat malabsorption requires a 3-day stool collection and dietary fat intake recall for evaluation of fat excretion and determination of the coefficient of fat absorption:

$$\text{Coefficient of fat absorption \%} = (\text{fat intake} - \text{fecal fat losses/fat intake}) \times 100$$

where fat intake and fat losses are in grams. Because fecal fat balance studies are cumbersome, expensive, and unpleasant to perform, simpler tests are often preferred. Among these stool tests, the acid steatocrit test is the most reliable. When bile acid (BA) deficiency is suspected of being the cause of fat malabsorption, the evaluation of BA levels in duodenal fluid aspirate may be useful. Intestinal mucosal abnormalities may not affect only fat absorption, but shorter intestinal transit time may also result in steatorrhea. Steatorrhea from intestinal mucosal disorders such as celiac disease or cow's milk protein enteropathy are usually far less severe in than in exocrine pancreatic insufficiency.

Exocrine pancreatic insufficiency and other fat malabsorption disorders (see Table 385.2) are usually associated with deficiencies of fat-soluble vitamins A, D, E, and K. Serum concentrations of vitamins A, D, and E can be measured. A prolonged prothrombin time is an indirect test to assess vitamin K malabsorption and subsequent deficiency.

INVESTIGATIONS FOR PROTEIN-LOSING ENTEROPATHY

Dietary and endogenous proteins secreted into the bowel are usually completely absorbed; minimal amounts of protein from these sources pass into the colon. The majority of stool nitrogen is derived from gut bacterial proteins. Excessive bowel protein loss usually manifests as

Table 385.3 Disorders Leading to Early-Onset Diarrhea

CATEGORY	DISORDER	GENE(S) INVOLVED	INHERITANCE	FEATURES
Defects in epithelial nutrient and electrolyte transport	Congenital chloride diarrhea	*SLC26A3*	AR	• High chloride in stools • Founder effect from Saudi Arabia (Taif region) and Finland • Premature with IUGR • Absence of meconium • Polyhydramnios and dilated loops of bowel on prenatal imaging, abdominal distension after birth • 24% had renal involvement (chronic kidney disease) • Dental carries • Some overlap with Bartter and Gitelman syndrome
	Congenital sodium diarrhea	*SLC9A3* *GUCY2C*	AR AD	• Increased risk of development of IBD • Polyhydramnios and dilated loops of bowel on prenatal imaging • High sodium in stools • Diarrhea may improve with time
	Glucose-galactose malabsorption	*SLC5A1*	AR	• Treatment requires avoidance of all sugars other than fructose
	Primary bile acid diarrhea	*SLC10A2* *SLC51B*	AR AR	• Associated with cholestasis, increased gamma-glutamyl transferase level, and fat-soluble vitamin deficiency
	Acrodermatitis enteropathica	*SLC39A4*	AR	• Perioral and extremity lesions, alopecia, and diarrhea • Recurrent infection from immune dysfunction

Table 385.3 Disorders Leading to Early-Onset Diarrhea—cont'd

CATEGORY	DISORDER	GENE(S) INVOLVED	INHERITANCE	FEATURES
Defects in epithelial enzymes and metabolism	Congenital lactase deficiency	*LCT*	AR	• Rare form of inherited diarrhea
	Congenital sucrase-isomaltase deficiency	*SI*	AR	• Bloating, diarrhea, and rarely associated with failure to thrive • High prevalence in Greenland and Inuit (5%), with 0.2% prevalence in Europeans • Variable phenotype
	Trehalase deficiency	*TREH*	AR	• Up to 8% of Greenland population • Similar to lactase deficiency
	Enterokinase deficiency	*TMPRSS15*	AR	• Deficiency of activator of pancreatic enzymes
	DGAT1 deficiency	*DGAT1*	AR	• Fat-soluble vitamin deficiency • Avoidance of enteral lipids seems to help
	Sieving protein-losing enteropathy	*PLVAP*	AR	• Protein loss of specific sizes • Syndromic with hydrops, dysmorphic facies, cardiac and renal abnormalities
	Abetalipoproteinemia	*MTTP*	AR	• Enterocytes show lipid-filled vacuoles • Steatorrhea and failure to thrive • Later noted to have fat-soluble vitamin deficiency and bleeding issues
	Hypobetalipoproteinemia	*APOB*	AR	
	Chylomicron retention disease	*SAR1B*	AR	
	Dyskeratosis congenita	*DKC1* *RTEL1*	X AR	• Nail pitting, leukoplakia, and immune defects
	Kabuki syndrome	*KMT2D*	AD	• Multiple congenital anomalies with varying phenotype
Defects in epithelial trafficking and polarity	Microvillus inclusion disease	*MYO5B*	AR	• Microvilli seen on electron microscopy are periodic acid–Schiff positive • May be associated with Fanconi syndrome
		STX3	AR	• Rare form; may be associated with neurologic findings
	Tufting enteropathy	*EPCAM*	AR	• Teardrop-shaped tufts of enterocytes throughout the intestine
	Syndromic sodium-losing diarrhea	*SPINT2*	AR	• Phenotype similar to tufting enteropathy, but with sodium-losing diarrhea
	Trichohepatoenteric syndrome	*TTC37*	AR	• Woolly hair, SCID-like phenotype and hepatic defects
		SKIV2L	AR	
	Familial hemophagocytic lymphohistiocytosis type 5	*STXBP2*	AR	• Recurrence after HSCT, villous blunting
	Multiple intestinal atresia	*TTC7A*	AR	• Variable phenotype with multiple intestinal atresia, SCID-like phenotype, and enterocolitis
Enteroendocrine cell dysfunction	Enteric anendocrinosis	*NEUROG3*	AR	• Severe malabsorptive diarrhea, neonatal-onset diabetes mellitus, and normal intestinal biopsies
	Proprotein convertase 1/3 deficiency	*PCSK1*	AR	• Age-dependent phenotype. Infants have TPN-dependent diarrhea and failure to thrive; later appear to lose intestinal phenotype and develop multiple endocrine abnormalities
	X-linked lissencephaly with abnormal genitalia	*ARX*	X	• Seizures, abnormal genitalia, survival between 6 days and 6 yr
	Mitchell-Riley syndrome	*RFX6*	AR	• Lack of enteroendocrine cells
	Intractable congenital diarrhea in infants	*ICR*	AR	• Secretory diarrhea caused by a noncoding variant with wide-ranging effects on multiple intestinal genes

Continued

Table 385.3 Disorders Leading to Early-Onset Diarrhea—cont'd

CATEGORY	DISORDER	GENE(S) INVOLVED	INHERITANCE	FEATURES
Immune dysregulation–associated enteropathy	Immune dysregulation, polyendocrinopathy, enteropathy X-linked	*FOXP3*	X	• Polyendocrinopathy
	Common variable immune deficiency (CVID) type 1	*ICOS*	AR	• Variable presentation; may have dietary-induced diarrhea
	CVID type 8	*LRBA*	AR	
	ADAM17 deficiency	*ADAM17*	AR	• Fatal in most patients
	EGFR deficiency	*EGFR*	AR	• Described in three patients
	CTLA-4	*CTLA-4*	AD	• Similar to LRBA; may respond to abatacept
	CD55 deficiency	*CD55*	AR	• Protein-losing enteropathy and thrombosis
	X-linked inhibitor of apoptosis	*XIAP*	X	• Responsive to HSCT

AD, Autosomal dominant; AR, autosomal recessive; EGFR, epidermal growth factor receptor; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; IUGR intrauterine growth restriction; SCID, severe combined immunodeficiency; TPN, total parenteral nutrition; X, X-linked.
From Elkadri AA. Congenital diarrheal syndrome. *Clin Perinatol.* 2020;47:87–104. Table 2.

hypoalbuminemia. Because the most common cause of hypoalbuminemia in children is a renal disorder, urinary protein excretion must be determined. Other potential causes of hypoalbuminemia include acute infection, liver disease (reduced production), and inadequate protein intake. Very rarely hypoalbuminemia can result from an extensive skin disorder (burns) causing protein loss via the skin. Measurement of stool α_1-antitrypsin is a useful screening test for PLE. This serum protein has a molecular weight similar to albumin; however, unlike albumin it is resistant to digestion in the gastrointestinal (GI) tract. Excessive α_1-antitrypsin excretion in the stool should prompt further investigations to identify the specific cause of intestinal or stomach (Ménétrier disease) protein loss (Table 385.4).

INVESTIGATIONS FOR EXOCRINE PANCREATIC FUNCTION

Cystic fibrosis (see Chapter 454) is the most common cause of exocrine pancreatic insufficiency in children; therefore a sweat chloride test must be performed before embarking on invasive tests to investigate possible exocrine pancreatic insufficiency (Fig. 385.2). Many cases of cystic fibrosis are detected by neonatal genetic screening programs; occasional rare pathogenic variants are undetected. Other etiologies are noted in Table 385.5.

Fecal elastase-1 estimation is a sensitive test to assess exocrine pancreatic function in chronic cystic fibrosis and pancreatitis. Elastase-1 is a stable endoprotease unaffected by exogenous pancreatic enzymes. One disadvantage of the fecal elastase-1 test is the lack of full differentiation between primary exocrine pancreatic insufficiency and exocrine pancreatic dysfunction secondary to intestinal villous atrophy. The proximal small bowel is the site for pancreozymin/cholecystokinin production; the latter is the hormone that stimulates enzyme secretion from the exocrine pancreas. Mucosal atrophy can lead to diminished pancreozymin/cholecystokinin secretion and subsequently to exocrine pancreatic insufficiency. Fecal elastase-1 can also give a false-positive result during acute episodes of diarrhea.

Serum trypsinogen concentration can also be used as a screening test for exocrine pancreatic insufficiency. In cystic fibrosis, the levels are greatly elevated early in life, and then they gradually fall, so that by 5-7 years of age, most patients with cystic fibrosis with pancreatic insufficiency have subnormal levels. Patients with cystic fibrosis and adequate exocrine pancreatic function tend to have normal or elevated levels. In such patients, observing the trend in serial serum trypsinogen estimation may be useful in monitoring exocrine pancreatic function. In Shwachman-Diamond syndrome, another condition associated with exocrine pancreatic insufficiency, the serum trypsinogen level is low.

Other tests for pancreatic insufficiency (nitroblue tetrazolium–para-aminobenzoic acid test and pancreolauryl test) measure urine or breath concentrations of substances released and absorbed across the mucosal surface following pancreatic digestion. These tests lack specificity and are rarely used in clinical practice.

The gold standard test for exocrine pancreatic function is direct analysis of duodenal aspirate for volume, bicarbonate, trypsin, and lipase upon secretin and pancreozymin/cholecystokinin stimulation. This involves duodenal intubation (see Chapter 396) and is technically difficult.

INVESTIGATIONS FOR INTESTINAL MUCOSAL DISORDERS

Establishing a specific diagnosis for malabsorption often requires histologic examination of small bowel mucosal biopsies. These are obtained during endoscopy, allowing multiple biopsies to be performed. Mucosal involvement can often be patchy, especially in milder forms of celiac disease or Crohn disease. Periodic acid–Schiff (PAS) staining of mucosal biopsies collected in formalin and electron microscopy biopsies collected in fixatives such as glutaraldehyde are necessary in congenital diarrhea to assess cellular ultrastructure and diagnose disorders such as congenital microvillus inclusion disease. Bowel mucosal lesions can also be segmental in cases of intestinal lymphangiectasia. In these situations, radiographic small bowel series, repeated ultrasonographies, lymphoscintigraphy, and/or MRI lymphangiography can identify a region of thickened bowel responsible for protein loss. Intestinal biopsies can also detect infectious agents such as *Giardia lamblia*. During endoscopy, mucosal biopsies can be obtained to measure mucosal disaccharidase activities. Duodenal aspirates can be performed to measure pancreatic enzyme concentration as well as quantitative bacterial cultures.

IMAGING PROCEDURES

Plain radiographs and barium contrast studies might suggest a site and cause of intestinal motility disorders. Although flocculations of barium and dilated bowel with thickened mucosal folds have been attributed to diffuse malabsorptive lesions such as celiac disease, these abnormalities are nonspecific. Diffuse fluid-filled bowel loops during sonography also suggest malabsorption. MRI enterography, though technically difficult in younger children due to the prolonged image acquisition time, provides information about small bowel inflammation and the extent of involvement.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 385.4 Etiology of Protein-Losing Enteropathy

CATEGORIES		AGENT, DISEASES (*GENE*)
Gastrointestinal infections		CMV, rotavirus, HIV enteropathy *Salmonella, Shigella, Campylobacter, Clostridium difficile, Helicobacter pylori* Whipple disease Small bowel bacterial overgrowth Giardiasis *Strongyloides stercoralis* Tuberculosis
Gastrointestinal inflammatory disorders		Ménétrier disease Eosinophilic gastroenteropathy Food (milk, others)-induced enteropathy Celiac disease Crohn disease Ulcerative colitis Tropical sprue Radiation enteritis GVHD NEC Malrotation/volvulus Lymphoproliferative disorder (posttransplant)
Malignancies		Adenocarcinomas Lymphomas Kaposi sarcoma Neuroblastoma Langerhan cell histiocytosis
Vasculitic disorders		IgA vasculitis (Henoch-Schönlein purpura) Systemic lupus erythematosus
Drugs		NSAID-induced enteropathy
Metabolic/genetic		Congenital disorders of glycosylation (CDG) Variants in *DGAT1* gene Variants in CD55 Congenital enterocyte heparan sulfate deficiency *(ALG6)* *PVLAP* -associated diarrhea Infantile systemic hyalinosis *(ANTRX2)* Familial polyposis *(SMAD4)*
Intestinal lymphangiectasia	Congenital/primary IL Syndromal/genetic/metabolic	Turner, Noonan, Klippel–Trenaunay–Weber Hennekam *(CCBE1, FAT4)* syndromes PLE with skeletal dysplasia *(FGFR3)* Generalized lymphatic dysplasia *(PIEZO1)*
	Secondary	
	Inflammation	Sarcoidosis
	Radiotherapy	Retroperitoneal fibrosis
	Neoplastic disorders	Retroperitoneal malignancies, lymphoma
	Cardiac disorders	Constrictive pericarditis, after Fontan operation, CHF
	Other	Budd-Chiari syndrome, lymphatic-enteric fistula

CHF, Congestive heart failure; CMV, cytomegalovirus; GVHD, graft-versus-host disease; IL, intestinal lymphangiectasia; NEC, necrotizing enterocolitis, NSAID, nonsteroidal antiinflammatory drug; PLE, protein-losing enteropathy.
From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 12.10, p. 221.

385.2 Other Malabsorptive Syndromes

Abdul-Aziz K. Elkadri

DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION

This group mainly includes two conditions characterized by typical histologic and ultrastructural lesions in the intestinal biopsies, microvillus inclusion disease (MVID) and congenital tufting enteropathy (CTE). Tricho-hepato-enteric syndrome (THE) or syndromic/phenotypic diarrhea is also usually classified in this group.

MICROVILLUS INCLUSION DISEASE (CONGENITAL MICROVILLUS ATROPHY)

MVID is an autosomal recessive disorder that manifests at birth with profuse watery *secretory diarrhea*. A late-onset variant, with onset 2-3 months postnatally, has also been described. It is the most severe cause of congenital diarrhea involving the development of the intestinal mucosa. Light microscopy of the small bowel mucosa demonstrates diffuse thinning of the mucosa, with hypoplastic villous atrophy and no inflammatory infiltrate. If MVID is suspected, electron microscopy should be performed as it shows enterocytes with electron-dense secretory granules as well as vesicles containing microvilli (Fig. 385.3). Using PAS and CD10 staining, light microscopy may show an absent or thin brush border with PAS-positive intracellular inclusions. Polyhydramnios is observed on prenatal sonography, and neonates usually present with very early onset severe watery diarrhea (up to 200-330 mL/kg/day) causing dehydration and failure to thrive. Despite parenteral nutrition, diarrhea continues; fluid management is difficult. Fanconi syndrome has been described in two unrelated patients with MVID, leading to increased renal fluid losses, aminoaciduria, renal tubular acidosis, and resulting phosphaturia with hypophosphatemic rickets. Disease causing variations of the *MYO5B* gene coding for a nonconventional motor

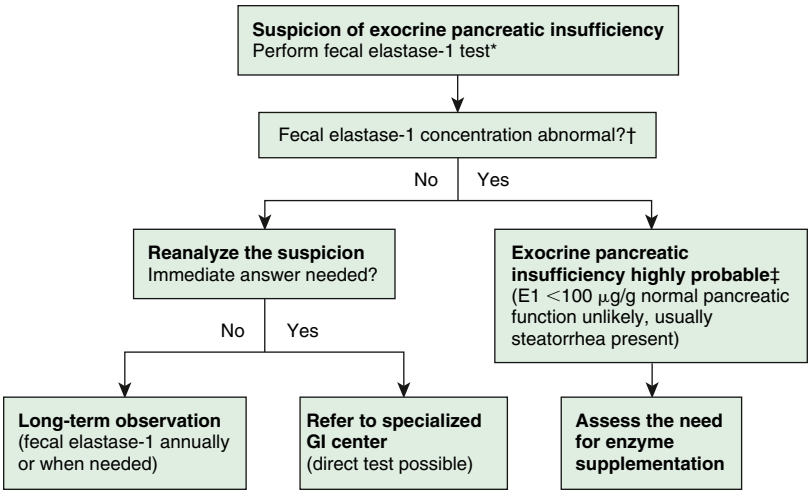

Fig. 385.2 Algorithm for assessment of exocrine pancreatic function. *If not available, use another test. Perform appropriate imaging studies of the pancreas. †In case of borderline values, consider repeating the test with three independent samples. ‡Consider differential diagnosis (especially consider mucosal villous atrophy and dilution effect of watery stool). GI, Gastrointestinal. *(Modified from Walkowiak J, Nousia-Arvanitakis S, Henker J, et al. Indirect pancreatic function tests in children. J Pediatr Gastroenterol Nutr. 2005;40:107–114.)*

Table 385.5 Pancreatic Disorders Leading to Early-Onset Chronic Diarrhea

DISEASE	GENETICS	SYMPTOMS	DIAGNOSIS
Cystic fibrosis	• AR • Pathogenic genetic variants involving CFTR • More than 1,300 pathogenic genetic variants have been described • Most common is pathogenic genetic variant ΔF508	• Meconium ileus in neonate • Megacolon • Chronic diarrhea from pancreatic insufficiency starting from 1 mo of age • Failure to thrive • Conjugated hyperbilirubinemia	• Low stool elastase • High sweat chloride (>60 mEq/L) • Newborn screening • Molecular genetic testing
Shwachman-Diamond syndrome	• AR • *SBDS* gene in over 90%	• Chronic diarrhea from pancreatic insufficiency • Bone marrow failure • Skeletal changes • Pancreatic lipomatosis on diagnostic imaging (ultrasound or computed tomography)	• Clinical features • Molecular genetic testing
Johanson-Blizzard syndrome	• AR • *UBR1* gene	• Chronic diarrhea from pancreatic insufficiency • Dysmorphic features: aplastic alae nasi, extension of the hairline to the forehead with upswept frontal hair, low-set ears, large anterior fontanel, micrognathia, thin lips, microcephaly, aplasia cutis (patchy distribution of hair with areas of alopecia), dental anomalies, poor growth, and anorectal anomalies (mainly imperforate anus)	• Clinical features • Molecular genetic testing
Pearson syndrome	Sporadic: caused by de novo single, large deletions of mtDNA, which can range from 1,000 to 10,000 nucleotides	• Chronic diarrhea from pancreatic insufficiency • Sideroblastic anemia, variable neutropenia, thrombocytopenia, and vacuolization of bone marrow precursors • Lactic acidosis and liver failure	• Clinical features • Molecular genetic testing

AR, Autosomal recessive; CFTR, cystic fibrosis transmembrane conductance regulator; mtDNA, mitochondrial DNA.
From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 14.12, p. 253.

protein, myosin Vb, results in MVID as is described in a cohort of patients suffering from early-onset MVID.

MYO5B disease causing variants result in mislocalization of apical proteins and disrupted enterocyte polarization, leading to the visualized inclusions in MVID. Another gene, the t-SNARE syntaxin3 *(STX3)*, has been described in patients with a milder form of MVID. Patients with pathologic variants in the STX3 binding protein *STXBP2/Munc18-2,* causing **familial hemophagocytic lymphohistiocytosis type 5**, also demonstrates microvillous atrophy and histologic findings reminiscent of MVID. Loss of STX3 or Munc18-2 inhibits the fusion of vesicles with the apical membrane, resulting in the intracellular retention of apical proteins. *MYO5B* disease causal variants have also been identified in several patients with **progressive familial intrahepatic cholestasis (PFIC)**-like phenotype with normal serum gamma-glutamyl transferase activity and without intestinal disease. Variants in MYO5B have been identified in children of Navajo descent presenting with severe infantile diarrhea.

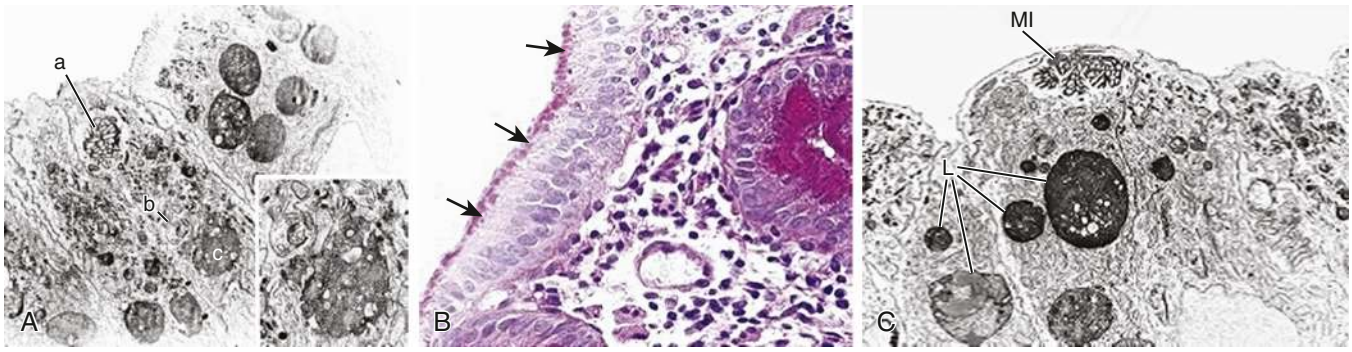

Fig. 385.3 Microvillus inclusion disease. **A**, From top to bottom: microvillus inclusion *(a)*, a granule with few microvilli *(b)*, and a lysosome *(c)* detected in the same enterocyte. *Inset:* Higher magnification of *b* and *c* ×11,000, inset ×21,500. **B**, Microvillus inclusion disease. Periodic acid–Schiff (PAS) staining highlights abundant PAS-positive material *(arrows)* in the apical part of the enterocyte cytoplasm. **C**, Microvillus inclusion disease. The villous enterocytes lack brush border microvilli, whereas their apical cytoplasm contains a microvillus inclusion *(MI)* and numerous lysosomes *(L)* ×5,500. *(A from Morroni M, Cangiotti AM, Guarino A, et al. Unusual ultrastructural features in microvillous inclusion disease: a report of two cases. Virchows Arch. 2006;448:805–810.)*

Management includes parenteral nutrition and, depending upon the severity of the diarrhea, intestinal transplantation (see Chapter 386).

TUFTING ENTEROPATHY (CONGENITAL TUFTING ENTEROPATHY)

CTE (intestinal epithelial dysplasia) manifests in the first few weeks of life with persistent watery diarrhea; it accounts for a small fraction of infants with *intractable diarrhea of infancy*. The distinctive feature on small intestinal mucosal biopsy is focal epithelial tufts (teardrop-shaped groups of closely packed enterocytes with apical rounding of the plasma membrane) involving 80–90% of the epithelial surface. The typical pathology does not appear immediately after birth; other enteropathies may show tufts on the epithelial surface.

CTE is a phenotypic and genetic heterogenous condition. Genetic studies identified causal variants in the epithelial cell adhesion molecule *(EPCAM)* gene in 73% of patients and causal variants in the serine protease inhibitor Kunitz type 2/hepatocyte growth factor activator inhibitor type 2 *SPINT2/HAI2* gene in 21%. A minority of patients do not carry any identifiable variants in either gene. The phenotype associated with pathologic variants of *EPCAM* is usually an isolated congenital diarrhea without associated extra digestive symptoms, except late-onset arthritis or superficial punctuate keratitis. In the **syndromic** form of CTE, diarrhea is associated with one or more of these same anomalies: superficial punctate keratitis (100%), choanal atresia (50%), esophageal or intestinal atresia, anal imperforation, hair dysplasia, skin hyperlaxity, bone abnormalities, hexadactylia, and facial dysmorphism.

No specific treatment exists, and as for MVID, management requires permanent parenteral nutrition with possible intestinal transplantation (see Chapter 386).

TRICHO-HEPATO-ENTERIC SYNDROME (SYNDROMIC DIARRHEA)

THE, also known as *syndromic diarrhea* (SD), is a congenital enteropathy manifesting with early onset of severe diarrhea. Patients are born small for gestational age and present with diarrhea starting in the first 6 months of life. They are noted to have facial dysmorphism with a prominent forehead, broad nose, and hypertelorism. Their hair is noted to have a poor pigmentation, with hair follicles showing **trichorrhexis nodosa,** a distinctly woolly, fragile, and uncombable presentation. Abnormal cutaneous lesions including café-au-lait on the lower limbs have been observed. Liver disease affects about half of the patients, with extensive fibrosis or cirrhosis observed. Cardiac abnormalities and colitis have been reported sporadically, as well as one case involving polyhydramnios, placental abnormalities, and congenital hemochromatosis. The immune phenotype is characterized by defective antibody responses to vaccination, with some patients with hypogammaglobulinemia that improves over time. Antigen-specific skin tests are defective despite positive proliferative responses in vitro. Patients with THE can also present as very early onset inflammatory bowel disease (VEO-IBD; see Chapter 382.3) with involvement of any portion of the GI tract. Small bowel biopsies show nonspecific villous atrophy with or without mononuclear cell infiltration of the lamina propria, and without specific histologic abnormalities involving the epithelium. Causal variants in either tetratricopeptide repeat domain 37 *(TTC37)* gene (60%) or *SKIV2L* (40%) have been identified as a cause of THE syndrome. Enterocytes with *TTC37* variants show reduced expression of brush border–associated NHE-2 and -3, aquaporin-7, the Na^+/I- symporter, and the H^+/K^+-ATPase or mislocalization relative to their normal pattern. Prognosis of this type of intractable diarrhea of infancy is noted to be poor. The long-term follow-up of these children reported that at 15 years about 50% of patients were alive or have been weaned off PN. The main complications are liver disease and infections. Most of the children achieve short final stature, and half are slightly developmentally delayed.

DEFECTS IN ENTEROENDOCRINE CELLS DIFFERENTIATION

This class of congenital diarrhea is characterized by abnormal enteroendocrine cell development, function, or complete absence. The genes causing these disorders encode either transcription factors essential for the development of all or a subset of enteroendocrine cells, or cellular proteins/endopeptidases that are required for the production of active hormones from prohormones. These conditions manifest with *osmotic* diarrhea and may be associated with additional systemic endocrine disorders. The treatment is nutritional support and hormonal replacement if needed. Defects in four genes have been associated with the diseases classified in this group: *NEUROG3, RFX6, ARX,* and *PCSK1*.

ENTERIC ANENDOCRINOSIS

NEUROG3 is a key transcription factor that controls the fate of endocrine cells in both the pancreas and intestine. Variants of the *NEUROG3* gene produce generalized mucosal malabsorption, vomiting, diarrhea, failure to thrive, dehydration, and a hyperchloremic metabolic acidosis. Oral alimentation with anything other than water produces diarrhea. Villus-crypt architecture in small bowel biopsies is normal, but staining for neuroendocrine cells using immunohistochemistry staining for chromogranin A demonstrates a complete absence of this secretory cell lineage with the preservation of goblet cells and Paneth cells.

PROPROTEIN CONVERTASE 1/3 DEFICIENCY

Autosomal recessive proprotein convertase 1/3 (PC1/3) deficiency, caused by variants in the *PCSK1* gene, is characterized by severe congenital malabsorptive diarrhea requiring parenteral nutrition, childhood-onset obesity, and other endocrine abnormalities. All functional hormones produced by endocrine cells, including those in the gut, are processed by a specific Ca^{2+}-dependent serine endoprotease named proprotein convertase 1/3 (also known as neuroendocrine convertase 1). Chronic watery, neonatal-onset diarrhea is described in infants with hyperinsulinism, hypoglycemia, hypogonadism, and hypoadrenalism. A small bowel biopsy reveals a nonspecific

enteropathy. Growth hormone deficiency, adrenal insufficiency, central diabetes insipidus, and hypogonadism are commonly observed.

MITCHELL-RILEY SYNDROME

Mitchell-Riley syndrome is a complex clinical phenotype that includes severe intrauterine growth restriction, neonatal diabetes, multiple GI anomalies including duodenal atresia, intestinal malrotation, gallbladder agenesis, abnormal biliary tract, and an annular pancreas. They also have chronic *osmotic* diarrhea. Several probands previously reported with Mitchell-Riley syndrome were found to carry pathologic variants in *RFX6*. DNA-binding protein RFX6 (regulatory factor X6; encoded by *RFX6*) is a winged helix transcription factor downstream of the neurogenin-3 signal required for islet cell development and enteroendocrine cell function. Immunofluorescence staining in RFX6 knockout mice shows that pancreatic endocrine cells are present, but do not express the islet cell hormones including insulin, glucagon, somatostatin, and ghrelin.

ARISTALESS-RELATED HOMEOBOX GENE VARIANTS

Aristaless-related homeobox (*ARX*) gene encodes a homeodomain containing a transcription factor required for the normal development of mouse and human enteroendocrine cells. ARX expression is detected in a subset of neurogenin-3-positive endocrine progenitors and is also found in a subset of hormone-producing cells. In mice, removal of *Arx* from the developing endoderm results in a decrease of some enteroendocrine cell types, such as gastrin, glucagon/GLP-1, CCK, secretin secreting cells, and an increase of somatostatin-expressing cells. Disease causal variants in the *ARX* gene are associated with a complex X-linked disorder with a clinical phenotype of intellectual disability, seizures, lissencephaly, loss of pancreatic alpha cells, abnormal genitalia, and in approximately half of the patients, congenital malabsorptive diarrhea.

AUTOIMMUNE ENTEROPATHY

The term autoimmune enteropathy describes a subgroup of infants with severe, protracted diarrhea, no response to dietary restriction, the presence of circulating gut autoantibodies and/or associated autoimmune diseases, and the lack of another cause of severe immunodeficiency. Symptoms of autoimmune enteropathy usually occur within the first 6 months of life, presenting with chronic diarrhea, PLE, malabsorption, and failure to thrive. The diagnosis is based on the endoscopic and histologic identification of inflammation of the GI tract, more pronounced in the small bowel. Histologic findings in the small bowel include partial or complete villous atrophy, crypt hyperplasia, and an increase in chronic inflammatory cells in the lamina propria. Marked intraepithelial lymphocytosis reminiscent of celiac disease can be present in a subset of patients. Cryptitis and crypt abscesses can also be seen and may obscure the presence of apoptosis. Immunologic analyses indicate the presence of autoantibodies including *anti–enterocyte antibodies (present in ~85% of patients)*, as well as *anti–autoimmune enteropathy-related 75-kDa antigen*.

Genetic testing in patients with autoimmune enteropathy identified that the majority of patients with autoimmune enteropathy carried disease causal variants in the forkhead box P3 *(FOXP3)* gene on the X chromosome. The term *immune dysregulation*, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is used to describe these patients. Patients not found to have a causal variant in FOXP3 had what were termed IPEX-like disorders and were found to have a variable phenotype and presented in females as well. Disease causing variants within other genes include interleukin-2 receptor A (IL2RA), LPS responsive beige-like anchor protein (LRBA), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and signal transducer and activator of transcription 1 and 3 (STAT1 and STAT3), along with others.

The differential diagnosis of pediatric autoimmune enteropathy includes other immune-mediated disorders, such as food sensitivity enteropathies (e.g., cow's milk protein intolerance and celiac disease), severe Crohn disease, and graft-versus-host disease.

Treatment options are limited and are based on nutritional support, including parenteral nutrition and glucocorticoids followed by immunosuppressive drugs. Hematopoietic stem cell transplantation is indicated in patients with a known molecular defect.

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1

See Chapter 165.

Defects in Lipids Transport and Metabolism

See Chapter 106.3.

After uptake from the lumen, fatty acids and monoacylglycerol are transported to the endoplasmic reticulum (ER). In the ER they are converted to triglycerides in several metabolic steps, the last of which is dependent on acyl CoA:diacylglycerol acyltransferase 1 (DGAT1). Apolipoprotein B (ApoB) and microsomal triglycerides transfer protein (MTTP) act in concert to incorporate triglycerides into chylomicrons. The newly formed chylomicrons bud from the ER in a prechylomicron transport vesicle (PCTV), which subsequently fuses with the Golgi, a process that is dependent on Sar1b. The chylomicron is then transported in a vesicle to the basal membrane, where it exits the cell.

ABETALIPOPROTEINEMIA

Abetalipoproteinemia (Bassen-Kornzweig syndrome) is a rare autosomal recessive disorder of lipoprotein metabolism associated with severe fat malabsorption and steatorrhea from birth (see Chapter 106.3). Children fail to thrive during the first year of life and have stools that are pale, foul smelling, and bulky. The abdomen is distended, and deep tendon reflexes are absent because of peripheral neuropathy secondary to vitamin E deficiency. Intellectual development tends to be delayed. After 10 years of age, intestinal symptoms are less severe, ataxia may develop, with loss of position and vibration sensation, and the onset of intention tremors. These latter symptoms reflect involvement of the posterior columns, cerebellum, and basal ganglia. In adolescence, in the absence of adequate supplement of vitamin E, atypical retinitis pigmentosa develops.

The diagnosis is suggested by the presence of acanthocytes in the peripheral blood smear and extremely low plasma levels of cholesterol (<50 mg/dL); triglycerides are also very low (<20 mg/dL). Chylomicrons and very low density lipoproteins are not detectable, and the low-density lipoprotein (LDL) fraction is virtually absent from the circulation. Marked triglyceride accumulation in villous enterocytes occurs in the duodenal mucosa. Patients with abetalipoproteinemia have pathogenic variants of the *MTTP* gene. MTTP catalyzes the transfer of triglycerides to nascent ApoB particles in the ER.

Specific treatment is not available. Nutritional support and large supplements of the fat-soluble vitamins A, D, E, and K should be given. High doses of vitamin E (100-300 mg/kg/24 hr) appears to arrest neurologic and retinal degeneration, with some children requiring higher doses based on serum levels. Limiting long-chain fat intake can alleviate intestinal symptoms; medium-chain triglycerides (MCTs) can be used to supplement fat intake.

HOMOZYGOUS HYPOBETALIPOPROTEINEMIA

Homozygous hypobetalipoproteinemia (see Chapter 106.3) is a dominantly inherited condition associated with pathogenic variants in the *APOB* gene, encoding ApoB, the apolipoprotein of the nascent chylomicron. The homozygous form is indistinguishable from abetalipoproteinemia. The parents of these patients, as heterozygotes, have reduced plasma LDL and ApoB concentrations, whereas the parents of patients with abetalipoproteinemia have normal levels. On transmission electron microscopy of small bowel biopsies, the size of lipid vacuoles in enterocytes differentiates between abetalipoproteinemia and hypobetalipoproteinemia: many small vacuoles are present in hypobetalipoproteinemia, and larger vacuoles are seen in abetalipoproteinemia.

CHYLOMICRON RETENTION DISEASE (ANDERSON DISEASE)

Chylomicron retention disease (CRD) is a rare autosomal recessive disorder caused by pathogenic variants in the *SAR1B* gene. *SAR1B* variants result in defective trafficking of nascent chylomicrons in PCTVs between the ER and the Golgi apparatus, interfering with the successful

assembly of chylomicrons and their delivery to the lamina propria. The patients with CRD have steatorrhea, chronic diarrhea, and failure to thrive. Acanthocytosis is rare, and neurologic manifestations are less severe than those observed in abetalipoproteinemia. Plasma cholesterol levels are moderately reduced (<75 mg/dL), and fasting triglycerides are normal, but the fat-soluble vitamins, particularly A and E, are very low. Treatment is early aggressive therapy with fat-soluble vitamins and modification of dietary fat intake, as in the treatment of abetalipoproteinemia.

DGAT1 VARIANTS

DGAT1 encodes for DGAT that converts diacylglycerides to triglycerides by adding an acyl CoA moiety. In the small intestine, DGAT1 helps to reassemble the triglycerides, whereas in the liver it produces triglycerides from fatty acids synthesized de novo or taken up from the circulation. The mechanism by which *DGAT1* disease causal variants causes diarrhea is unclear but is likely to involve the buildup of DGAT1 lipid substrates in the enterocytes or in the gut lumen. Pathogenic variants in *DGAT1* gene have been reported in patients presenting with failure to thrive, PLE, hypoalbuminemia, early-onset diarrhea, and oral vitamin D refractory rickets.

WOLMAN DISEASE

Wolman disease is a rare, lethal lipid storage disease that leads to lipid accumulation in multiple organs, including the small intestine and liver. In addition to vomiting, severe diarrhea, and hepatosplenomegaly, patients have steatorrhea as a result of lymphatic obstruction. Insufficient free cholesterol available for steroidogenesis in adrenal glands results in adrenal insufficiency; a characteristic pattern of subcapsular adrenal calcification represents a distinctive marker of disease. Deficiency of lysosomal acid lipase (LAL) is the underlying cause of disease (see Chapter 106.4). LAL is a lysosomal enzyme that hydrolyzes cholesteryl esters and triglycerides within endolysosomes. Loss-of-function variants in the *LIPA* gene are associated with variable phenotypes. Homozygous and compound heterozygous pathogenic variations, resulting in complete LAL deficiency, cause Wolman disease. Variants associated with residual LAL activity cause cholesteryl ester storage disease, an attenuated form of Wolman disease exhibiting a variable phenotype. Common features in infants, children, and adults include elevated serum aminotransferase levels, dyslipidemia, hepatomegaly, liver fibrosis, and cirrhosis. Wolman disease may also present with neonatal cholestasis and severe liver disease as its main feature already in infancy. Hemophagocytic lymphohistiocytosis has been reported in few infants with Wolman disease. The hallmark of the disease is the presence of *adrenal calcification* seen on imaging, and definite diagnosis is done genetically.

Hematopoietic stem cell transplantation has been reported in few patients with variable outcome. A recombinant human enzyme-replacement therapy for LAL deficiency is approved for use in patients suffering from LAL deficiency. This treatment has allowed a small number of infants with Wolman disease to achieve a relatively normal growth rate and to improve survival. In older children and adults, the enzyme has corrected their dyslipidemia and produced significant improvement in markers of hepatic function.

TANGIER DISEASE

See Chapter 106.

Cellular free cholesterol is mobilized, along with phospholipid, through the export pump ABCA1, resulting in the transfer to an extracellular ApoA-I acceptor and the formation of discoidal high-density lipoprotein (HDL) cholesterol. Loss-of-function variants in *ABCA1*genes in patients with Tangier disease cause cholesterol accumulation in the intestine, spleen, tonsils, relapsing neuropathy, orange-brown spots on the colon and ileum, and diarrhea in association with decreased plasma cholesterol levels (ApoA-I and A-II), with virtually no detectable plasma HDL. Heterozygosity of ABCA1 variants leads to low HDL levels (below the 10th percentile). Specific therapy for Tangier disease has not yet been established.

SITOSTEROLEMIA

See Chapter 106.4.

Sitosterol and other sterols are preferentially secreted back into the intestinal lumen through the sterol pump, paired half-transporters ABCG5/G8. Pathogenic variants of the *ABCG5* (sterolin-1) and *ABCG8* (sterolin-2) transporters result in the defective efflux of sterol and leads to the increased absorption of dietary sterols. The disorder is associated with tendon xanthomas, increased atherosclerosis, and hemolytic anemia. Plasma levels of phytosterols (mainly sitosterol) are typically >10 mg/dL.

BILE ACID MALABSORPTION

Bile acids (BAs) are detergent compounds secreted by and excreted from the liver, and are responsible for the solubilization of the dietary lipids, aiding in their digestion and absorption. Approximately 95% of BAs are reabsorbed in the terminal ileum and transported back to the liver, the enterohepatic circulation. The apical Na^+-dependent bile salt transporter (ASBT) or ileal BA transporter (IBAT) is responsible for the active reuptake of BAs in the terminal ileum. Pathogenic variants in the *ASBT/SLC10A2* gene are very rare and are responsible for *primary* BA malabsorption, a disease associated with congenital diarrhea, steatorrhea, and reduced plasma cholesterol levels. Unabsorbed BAs stimulate chloride excretion in the colon, resulting in diarrhea. *Secondary* BA malabsorption can result from ileal disease, such as in Crohn disease, and following ileal resection. The diagnosis of BA malabsorption is typically based on reduced BA retention of radiolabeled ^{75}selenium-homocholic acid taurine (^{75}SeHCAT), increased BA synthesis (serum C4), or increased fecal BA loss (measured by serum FGF-19 levels). In clinical practice, diagnosis is often based on the response to BA sequestrants (e.g., cholestyramine or colesevelam), which are also the treatment of choice for this disorder.

Chronic neonatal-onset diarrhea has also been described in autosomal recessive **cerebrotendinous xanthomatosis**, which is caused by pathogenic variants in CYP27A1 and results in an inborn error of BA synthesis due to 27-hydroxylase deficiency. These children also present with juvenile-onset cataracts and developmental delay. Neonatal cholestasis has also been described as a presenting feature. Tendon xanthomas develop in the second and third decades of life. The diagnosis is important to establish at a younger age, as treatment with oral chenodeoxycholic acid is effective at preventing irreversible neurologic damage.

PROTEIN-LOSING ENTEROPATHY

PLE is a rare entity caused by a variety of intestinal and extraintestinal disorders and characterized by excessive enteric loss of plasma proteins. The clinical presentation of patients with PLE is variable and depends upon the underlying cause, but generally includes edema and hypoproteinemia. Impaired synthesis (malnutrition, liver disease), protein loss through other organs (kidney or skin), or redistribution (septic states) must be excluded before considering PLE. The disorders causing PLE can be divided into those due to protein loss from an inflamed or abnormal mucosal surface or from derangements in intestinal lymphatics, such as in primary or secondary IL (see Table 385.4).

Intestinal lymphangectasia is characterized by diffuse or local dilatation of the enteric lymphatics and is located in the mucosa, submucosa, or subserosa. Lymph rich in proteins, lipids, and lymphocytes leaks into the bowel lumen, resulting in PLE, steatorrhea, and lymphocyte depletion. Hypoalbuminemia, hypogammaglobulinemia, edema, lymphopenia, malabsorption of fat and fat-soluble vitamins, and chylous ascites often occur. IL can also manifest with ascites, peripheral edema, and a low serum albumin. The etiology of *primary* IL is unknown. Several genes, including vascular endothelial growth factor receptor 3 *(VEGFR3)*, prospero-related homeobox-transcriptional factor *(PROX1)*, forkhead transcriptional factor *(FOXC2)*, and SRY (sex determining region Y)-box 18 *(SOX18)*, are involved in the development of the lymphatic system and have been shown to have altered expression in the duodenal mucosa in patients with IL. A pathogenic variant in CD55, a regulator of complement activation, has also been described as a cause for primary PLE. The diagnosis of PLE is suggested

by the typical clinical and laboratory findings in association with an elevated fecal α_1-antitrypsin clearance. Radiologic findings of uniform, symmetric thickening of mucosal folds throughout the small intestine are characteristic but nonspecific. Small bowel mucosal biopsy in patients with IL can show dilated lacteals with distortion of villi and no inflammatory infiltrate. A patchy distribution and deeper mucosal involvement on occasion causes false-negative results on small bowel histology. Video capsule endoscopy may reveal similar lesions (Figs. 385.4 and 385.5). Magnetic resonance lymphangiography may identify lymphatic abnormalities (Fig. 385.6).

Treatment of PLE is generally supportive and consists of a low-fat, high-protein diet. In patients with IL, a low-fat, high-protein diet supplemented with MCTs is recommended. Along with dietary adjustments, appropriate treatment for the underlying etiology is necessary, as well as supportive care to avoid complications of edema. Rarely, PN is required. If only a portion of the intestine is involved, surgical resection may be considered. A few patients with lymphatic malformation and generalized lymphatic anomalies were successfully treated with propranolol. Sirolimus, an mTOR inhibitor, has been used for primary IL and is thought to decrease lymphatic sprouting and proliferation. Everolimus use has been described in a patient with primary IL. Prognosis depends upon the severity and treatment options of the underlying disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.3 Intestinal Infections and Infestations Associated with Malabsorption

Abdul-Aziz K. Elkadri

Malabsorption is a rare consequence of primary intestinal infection and infestation in immunocompetent children but is relatively common in previously malnourished or immunocompromised children and is associated with significant mortality. Often malabsorption is associated with diarrhea and triggers a vicious cycle of further weight loss and growth failure. For children living in developing countries, malabsorption is associated with long-term growth failure leading to stunting within a peculiar condition defined as environmental enteropathy, in which diarrhea is not always present. Generally, malabsorption is associated with a duration of an intestinal infection longer than expected. *Prolonged* diarrhea is an acute-onset diarrhea that lasts >7 days, whereas *chronic* diarrhea lasts >14 days, with some using 30 days as a more definitive cutoff.

POSTINFECTIOUS DIARRHEA

Chronic diarrhea can appear following infectious enteritis, regardless of the nature of the pathogen. The pathogenesis of the diarrhea is not always clear and may be related to persistent infection or reinfection, secondary lactase deficiency, food protein allergy, antibiotic-associated diarrhea, or a combination of these. In some cases, postinfectious diarrhea may be the initial manifestation of functional diarrhea, in which case it is not associated with malabsorption.

Treatment of postinfectious diarrhea is supportive and may include a lactose-free diet in the presence of secondary lactase deficiency. Some infants might require a semi-elemental diet. The beneficial effect of specific probiotic products may be indicated in selected conditions.

PROXIMAL INTESTINAL BACTERIAL OVERGROWTH

Bacteria are normally present in large numbers in the colon (10^{11}-10^{13} colony-forming units [CFU]/g of feces) and have a symbiotic relationship with the host, providing nutrients and protecting the host from pathogenic organisms. Within the stomach and small bowel, bacteria are usually present in much smaller numbers. Excessive numbers of bacteria in the stomach or small bowel are noted to be harmful. Bacterial overgrowth can result from clinical conditions that alter the gastric pH or small bowel motility, such as partial bowel obstruction, diverticula, intestinal failure, intestinal duplications, diabetes mellitus, idiopathic intestinal pseudoobstruction syndrome, and scleroderma, as well as proton pump inhibitor use. Prematurity, immunodeficiency, and malnutrition are other factors associated with bacterial overgrowth of the small bowel.

The diagnosis of bacterial overgrowth is often difficult and can be made by culturing small bowel aspirate (>10^5 CFU/mL) or by a lactulose hydrogen breath test. Lactulose is a synthetic disaccharide not digested by mucosal brush border enzymes but is fermented by bacteria producing hydrogen and methane. High baseline breath hydrogen and a quick rise in hydrogen in expired breath samples support the diagnosis of bacterial overgrowth. Some individuals (up to 30%) produce methane as a predominant by-product of carbohydrate digestion. False-positive tests are common and may be due to rapid GI transit time and colonic fermentation.



Fig. 385.4 Swollen villi detected by video capsule endoscopy in the proximal ileum. *(From Gortani G, Maschio M, Ventura A. A child with edema, lower limb deformity, and recurrent diarrhea. J Pediatr. 2012;161:1177. Fig. 1.)*

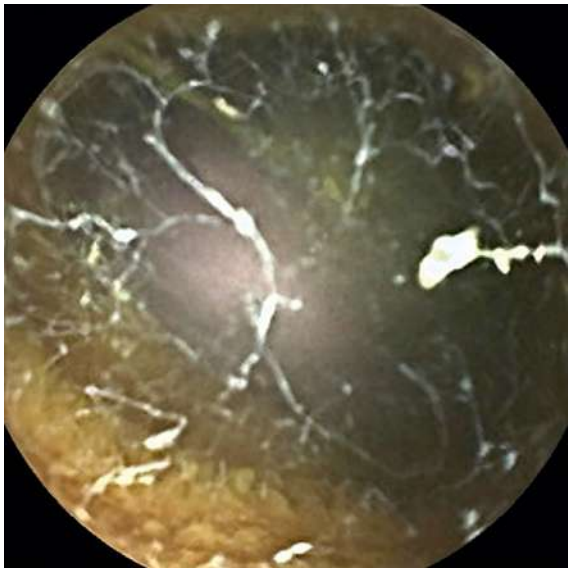

Fig. 385.5 Protein-rich lymphatic fluid aggregates detected by video capsule endoscopy in the intestinal lumen. *(From Gortani G, Maschio M, Ventura A. A child with edema, lower limb deformity, and recurrent diarrhea. J Pediatr. 2012;161:1177. Fig. 2.)*

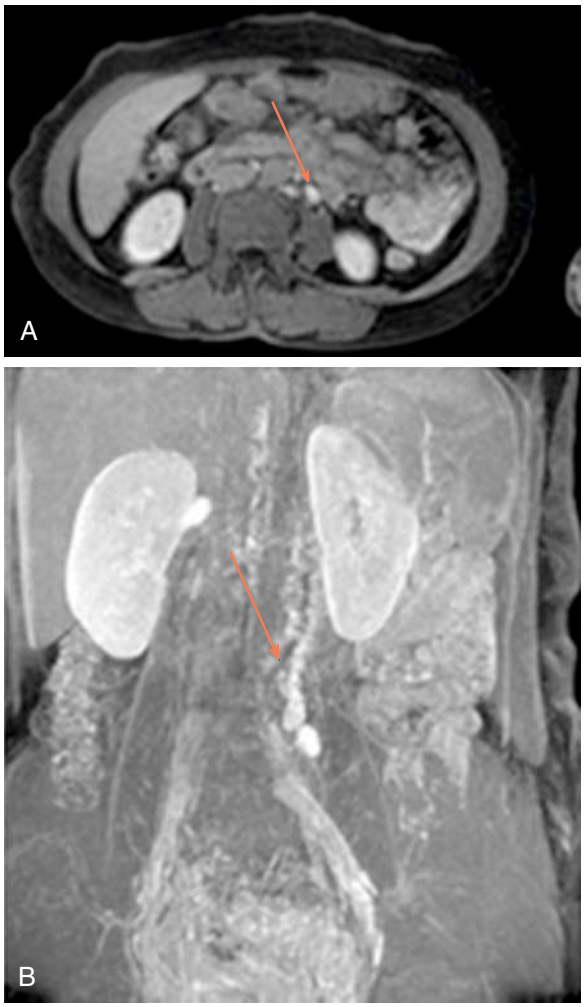

Fig. 385.6 MR lymphangiogram. **A,** Axial T1-weighted fat-saturated MR image showing contrasted-filled dilated retroperitoneal tubular channels *(arrow).* **B,** Thick maximum intensity projection of MR lymphangiogram (T1-weighted) image showing dilated retroperitoneal channels with contrast refluxing into bowel wall *(arrow)* suggestive of associated intestinal lymphangiectasia. *(From Valakada J, Madhusudhan KS, Ranjan G, et al. Abdominal lymphangiomatosis with intestinal lymphangiectasia diagnosed by magnetic resonance lymphangiography: a case study. Curr Prob Diag Radiol. 2018;47:200–202.)*

Bacterial overgrowth leads to inefficient intraluminal processing of dietary fat with steatorrhea due to bacterial deconjugation of bile salts, vitamin B_{12} malabsorption, and microvillus brush border injury with further malabsorption. Bacterial consumption of vitamin B_{12} and enhanced synthesis of folate result in decreased vitamin B_{12} and increased folate serum levels. Overproduction of *D-lactate* (the stereoisomer of L-lactate) can cause stupor, neurologic dysfunction, and shock from D-lactic acidosis. Lactic acidosis should be suspected in children at risk of bacterial overgrowth who show signs of neurologic deterioration and a high anion gap metabolic acidosis not explained by measurable acids such as L-lactate. Measurement of D-lactate is required because standard lactate assay only measures the L-isomer.

The treatment of bacterial overgrowth focuses on the correction of underlying causes such as partial obstruction. Oral metronidazole can provide relief for many months but is not always effective. The cycling of antibiotics, including azithromycin, trimethoprim-sulfamethoxazole, ciprofloxacin, and metronidazole, may be required. Other alternatives are oral nonabsorbable antibiotics such as aminoglycosides, nitazoxanide, or rifaximin. Occasionally, antifungal therapy is required to control fungal overgrowth of the bowel.

ENVIRONMENTAL ENTEROPATHY (TROPICAL SPRUE)

In developing regions of the world, an atypical subclinical form of enteropathy has been described termed environmental enteropathy (tropical sprue). Theorized to be due to chronic fecal-oral exposure, it is thought to be the result of interactions between enteric pathogens, enteropathy, and malnutrition. There is resulting malabsorption, which may be clinically evident or subclinical, at times with or without diarrhea. It is a frequent cause of death in childhood in endemic regions, particularly in South Asian areas, African countries, and other developing regions. Selected pathogens including rotavirus, *Shigella, Cryptosporidium,* and enterotoxigenic *Escherichia coli* cause the majority of intestinal infections leading to moderate to severe diarrhea and often triggers a vicious circle with malnutrition. This tends to progress to wasting and stunting with or without a clear association with diarrhea.

In addition to a high risk of death, environmental enteropathy impairs normal growth and brain development and impacts productivity. There is evidence of oral vaccine failure, pointing to an alteration of the intestinal mucosal immune system. The etiology of this disorder is unclear because it follows outbreaks of acute diarrheal disease and improves with antibiotic therapy. Individuals traveling in endemic regions have developed enteropathy similar to native residents, which improves with return to nonendemic regions. Immigrants with malabsorptive diarrhea were shown to have improved absorption and jejunal biopsies with increasing periods of residence in nonendemic countries. Therefore an infectious etiology within the endemic environment is suspected. Nevertheless, environmental enteropathy includes interrelated mechanisms such as intestinal malabsorption, increased permeability, loss of intestinal mass, inflammation, increased bacterial translocation, and impairment of immune response. The incidence is decreasing worldwide, largely because of an improvement in hygiene and access to nutrients. Clinical symptoms include fever and malaise followed by diarrhea. After about a week the acute features subside, and anorexia, intermittent diarrhea, and chronic malabsorption result in severe malnutrition characterized by glossitis, stomatitis, cheilosis, night blindness, hyperpigmentation, and edema, reflecting the various nutrient deficiencies. Muscle wasting is often marked, and the abdomen is often distended. Megaloblastic anemia results from folate and vitamin B_{12} deficiencies.

Diagnosis is made by small bowel biopsy, which shows villous flattening with crypt hyperplasia and mild intestinal inflammation, with lipid accumulation in the surface epithelium.

Treatment response with nutritional and antimicrobial interventions may be poor, with no clear improvement in weight gain. Nutritional supplementation, including supplementation of folate and vitamin B_{12} as well as glutamine, is recommended. To prevent recurrence, 6 months of therapy with oral folic acid (5-10 mg) and antibiotics are recommended. Relapses occur in 10–20% of patients who continue to reside in an endemic tropical region. This suggests a persistent environmental factor causing recurrence, and that improved overall hygiene is key to treatment and prevention. Improvements in public health infrastructure and educational interventions are the key to prevention rather than medical interventions in individual cases.

WHIPPLE DISEASE

Whipple disease is a rare childhood chronic systemic infectious disorder. It is caused by *Tropheryma whipplei,* which can be cultured from a lymph node in the involved tissue.

The most common symptoms in Whipple disease are diarrhea, abdominal pain, weight loss, and joint pains. Malabsorption, lymphadenopathy, skin hyperpigmentation, and neurologic symptoms are also common. Involvement of other organs, such as eyes, heart, and kidneys, has been reported.

Diagnosis requires a high index of suspicion and is made upon demonstration of PAS-positive macrophage inclusions in the biopsy material, usually a duodenal biopsy. Positive identification using polymerase chain reaction for *T. whipplei* confirms the diagnosis.

Treatment requires antibiotics, such as trimethoprim-sulfamethoxazole, for 1-2 years. A 2-week course of intravenous ceftriaxone or meropenem, followed by trimethoprim-sulfamethoxazole for 1 year, is recommended.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.4 Immunodeficiency Disorders

Abdul-Aziz K. Elkadri

Malabsorption and diarrhea are a common presentation of patients with underlying primary immune deficiencies. It is not surprising that more than half of the primary immunodeficiencies present with GI manifestations because the gut is the largest lymphoid organ in the body and represents an interface between our environment, microbiome, and immune system. Malabsorption can be due to either intestinal inflammation or infection, with chronic diarrhea and failure to thrive one of the main modes of presentation. Multiple defects of humoral and or cellular immunity have been described, including selective IgA deficiency, agammaglobulinemia, common variable immunodeficiency disease (CVID), severe combined immunodeficiency (SCID), hyper-IgM syndrome, Wiskott-Aldrich syndrome, and chronic granulomatous disease. The most common primary immunodeficiency is selective IgA deficiency, with the majority of patients being asymptomatic. Recurrent infections with *Giardia* or nonspecific enteropathy with bacterial overgrowth can occur; celiac disease is noted to be more common in selective IgA deficiency. In CVID and X-linked agammaglobulinemia, lymphoid hyperplasia, villous atrophy, granulomas, and increased intraepithelial lymphocytes have been reported in up to 60% of children these disorders, with relative paucity of plasma cells. Pathology is reminiscent of acute graft-versus-host disease, with the presence of apoptotic bodies in the intestinal epithelia. Malabsorption has also been reported in approximately 10% of patients with CVID or X-linked agammaglobulinemia, often secondary to noroviral infection, giardiasis, *Campylobacter, Salmonella, Cryptosporidium,* enteroviruses, or cytomegalovirus (CMV) infections, and can be hard to eradicate. *Cryptosporidium* is the most common pathogen causing diarrhea and malabsorption in hyper-IgM syndrome patients, though other infections have also been described. SCID-affected children develop severe diarrhea and malabsorption early in life involving viral and opportunistic infections, especially chronic rotavirus infection, CMV, and adenovirus. Malabsorption associated with immunodeficiency is exacerbated by villous atrophy and secondary disaccharidase deficiency. In chronic granulomatous disease, phagocytic function is impaired and granulomas develop throughout the GI tract, mimicking Crohn disease. In addition to failure to thrive, it is important to consider that malabsorption associated with immunodeficiency is often complicated by micronutrient deficiencies, including vitamins A, E, and B_{12}, and calcium, zinc, and iron.

Acquired immunodeficiencies in children are more often secondary to other conditions such as cancer and chemotherapy. Malnutrition, diarrhea, and failure to thrive are common in untreated children with HIV infection. The risk of GI infection is related to the depression of the CD4 count. Opportunistic infections include *Cryptosporidium parvum,* CMV, *Mycobacterium avium-intracellulare, Isospora belli, Enterocytozoon bieneusi, Candida albicans,* astrovirus, calicivirus, adenovirus, and the usual bacterial enteropathogens. In these patients, *Cryptosporidium* can cause a chronic secretory diarrhea.

Chemotherapeutic agents can damage the bowel mucosa, leading to secondary malabsorption of disaccharides such as lactose. After bone marrow transplantation, mucosal damage from conditioning agents and graft-versus-host disease can cause diarrhea and malabsorption. Small bowel biopsies show nonspecific villous atrophy, mixed inflammatory cell infiltrates, and increased apoptosis. Cancer chemotherapy and bone marrow transplantation are associated with pancreatic damage, which may lead to exocrine pancreatic insufficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.5 Immunoproliferative Small Intestinal Disease

Abdul-Aziz K. Elkadri

Lymphoma (see Chapter 545) is the most common small bowel malignancy in the pediatric age-group. Malignant lymphomas of the small intestine are categorized into three subtypes: Burkitt lymphoma, non-Hodgkin lymphomas, and immunoproliferative small intestinal disease (IPSID) (originally termed as Mediterranean lymphoma or α-heavy chain disease but found worldwide). Burkitt lymphoma, the most common form in children, characteristically involves the terminal ileum with extensive abdominal involvement. The relatively uncommon non-Hodgkin lymphomas (usually large B-cell type) can involve various regions of the small intestine. Inflammatory bowel disease and primary immunodeficiencies are risk factors for the development of lymphoproliferative disorders of the intestinal tract. IPSID is a rare extranodal marginal zone B-cell lymphoma occurring primarily in the proximal small intestine. It is a variant of **mucosa-associated lymphoid-tissue (MALT) lymphoma** described in young adults from the developing world and is characterized by lymphoplasmacytic intestinal infiltrates with monotypic α-heavy chain expression.

IPSID occurs most often in the proximal small intestine in older children and young adults in the Mediterranean basin, Middle East, Asia, and Africa. Poverty and frequent episodes of gastroenteritis during infancy are risk factors. The initial clinical presentation is intermittent diarrhea and abdominal pain. Later, chronic diarrhea with malabsorption, PLE, weight loss, digital clubbing, and growth failure ensue. Intestinal obstruction, abdominal masses, and ascites are common in advanced stages.

In contrast to primary nonimmunoproliferative small intestinal lymphomas, in which the pathology in the intestine is usually focal, IPSID involves specific segments of the intestine and leaves the segments between the involved areas free of disease. The pathology in IPSID is diffuse, with a mucosal cellular infiltrate involving large segments of the intestine and sometimes the entire length of the intestine, thus producing malabsorption. Molecular and immunohistochemical studies demonstrated an association with *Campylobacter jejuni* infection. The differential diagnosis includes chronic enteric infections (parasites, tropical sprue), celiac disease, and other lymphomas. Radiologic findings include multiple filling defects, ulcerations, strictures, and enlarged mesenteric lymph nodes on CT scan.

The diagnosis is usually established by endoscopic biopsies and/or laparotomy. Upper endoscopy shows thickening, erythema, and nodularity of the mucosal folds in the duodenum and proximal jejunum. Capsule endoscopy may be helpful in the diagnosis. When the disease progresses, tumors usually appear in the proximal small intestine and rarely in the stomach. The diagnosis requires multiple duodenal and jejunal mucosal biopsies showing dense mucosal infiltrates, consisting of centrocyte-like and plasma cells. Progression to higher grade large cell lymphoplasmacytic and immunoblastic lymphoma is characterized by increased plasmocytic atypia with formation of aggregates and later sheets of dystrophic plasma cells and immunoblasts invading the submucosa and muscularis propria. A serum marker of IgA, a heavy-chain paraprotein, is present in most cases.

Treatment of early-stage IPSID with antibiotics results in complete remission in 30–70% of cases (tetracycline, ampicillin, or metronidazole). Some patients achieve durable remission lasting several years but should be monitored closely for relapse. The majority of untreated IPSID cases progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall and mesenteric lymph nodes, resulting in metastasis to distant organs, and requiring aggressive treatment with surgery and/or chemotherapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.6 Short Bowel Syndrome

Abdul-Aziz K. Elkadri

Short bowel (or short gut) syndrome is defined as a state of reduced functional intestinal mass that is lower than the required amount for the digestion and absorption of nutrients and fluids required for normal growth and survival. It results from congenital malformations or the resection of the small bowel (Table 385.6). Its incidence increases with low birthweight and earlier gestational age and is estimated at 7/1,000 live births in U.S. infants with birthweight <1,500 mg. Depending upon the area of the bowel resected or absent, loss of >50% of the small bowel, with or without a portion of the large intestine, can result in symptoms of generalized malabsorptive disorder or in specific nutrient deficiencies. At birth, the length of small bowel is 200-250 cm; by adulthood, it grows to 300-800 cm. Bowel resection is better tolerated in infants with an improved prognosis relative to adults due to the potential for intestinal growth and adaptation. An infant with as little as 15 cm of bowel with an ileocecal valve, or 20 cm without an ileocecal valve, has the potential to survive and be eventually weaned from PN.

In addition to the length of the bowel, the anatomic location of the resection is also important. The proximal 100-200 cm of jejunum is the main site for carbohydrate, protein, iron, and water-soluble vitamin absorption, whereas fat absorption occurs over a longer length of the small bowel. Depending on the region of the bowel resected, specific nutrient malabsorption can result. Vitamin B_{12} and bile salts are only absorbed in the distal ileum (Fig. 385.7). Jejunal resections are generally tolerated better than ileal resections because the ileum, unlike the jejunum, is better able to adapt to absorb nutrients and fluids. Net sodium and water absorption is relatively higher in the ileum. Ileal resection has a profound effect on fluid and electrolyte absorption due to malabsorption of sodium and water by the remaining ileum. Ileal malabsorption of bile salts stimulates increased colonic secretion of fluid and electrolytes. The presence of a colon in continuity is better tolerated and improves absorption and enteral autonomy.

TREATMENT

After bowel resection, treatment of short bowel syndrome is initially focused on repletion of the massive fluid and electrolyte losses while the bowel initially accommodates to absorb these losses. Proton pump inhibitors are usually added to reduce gastric secretions due to hypersecretion of gastric acids of up to 4 L per day compared to 750 mL in healthy individuals. Nutritional support is often provided via parenteral nutrition. A central venous catheter should be inserted to provide optimized and durable parenteral fluid and nutrition support. The ostomy or stool output should be measured, and fluid and electrolyte losses adequately replaced. Measurement of urinary Na^+ to assess whole body Na^+ stores is useful to prevent Na^+ depletion. Maintaining urinary Na^+ higher than 20 mmol/L ensures that Na^+ intake is adequate. Early introduction of even a small amount of enteral feeding by mouth or tube feeding is essential and enhances bowel adaptation.

Table 385.6 Causes of Short Bowel Syndrome

CONGENITAL
Congenital short bowel syndrome
Intestinal atresia
Gastroschisis
BOWEL RESECTION
Necrotizing enterocolitis
Volvulus with or without malrotation
Long segment Hirschsprung disease
Meconium peritonitis
Crohn disease
Trauma

After the initial few weeks following resection, fluid and electrolyte losses begin to stabilize, and the focus of therapy shifts to bowel rehabilitation with a gradual increase in the volume of enteral feeds. Continuous or bolus small-volume enteral feeding should be promoted with an extensively or partially hydrolyzed protein with MCT-enriched formula if the colon is in continuity. Breast milk is preferable over formula, and its use should be encouraged as it stimulates gut hormones and promotes mucosal growth. Enteral feeding also increases pancreatobiliary flow and reduces parenteral nutrition-induced hepatotoxicity. To maintain interest in oral feeds and minimize oral aversion, infants should be given a small amount of formula or mother's milk by mouth as early as possible. As intestinal adaptation occurs, enteral feeding increases, and parenteral supplementation decreases. The bowel mucosa surface area proliferates, and the bowel lengthens with growth.

Approximately 60% of patients with short bowel syndrome achieve **enteral autonomy** within 5 years of bowel resection, and the majority do so in the first 2-3 years after resection. In addition to bowel length, factors increasing the likelihood of achieving enteral autonomy include the presence of the ileocecal valve, a diagnosis of necrotizing enterocolitis, and care by an intestinal rehabilitation program.

Patients may require repeat surgeries for obstruction or bowel lengthening procedures (longitudinal lengthening, serial transverse enteroplasties or both) to optimize the bowel absorptive capacity. Bowel lengthening procedures are indicated in patients with dilated bowel who are unable to progress toward enteral autonomy or in those with refractory small intestinal bacterial overgrowth.

Vitamin and micronutrient deficiencies are common and increase over time. The management of specific micronutrient and vitamin deficiencies and the treatment of transient problems such as postinfectious mucosal malabsorption are required. GI infections or small bowel bacterial overgrowth can cause setbacks in the progression to full enteral feeding in patients with marginal absorptive function. Marked increase in stool output or evidence of carbohydrate malabsorption (stool pH <5.5 and positive test for reducing substances) is a contraindication for further increases in enteral feeds. Slow advancement of continuous or bolus enteral feeding rates continues until all nutrients are provided enterally.

In patients with large stool output, the addition of soluble fiber and antidiarrheal agents, such as loperamide and anticholinergics, can be beneficial, although these drugs can increase the risk of bacterial

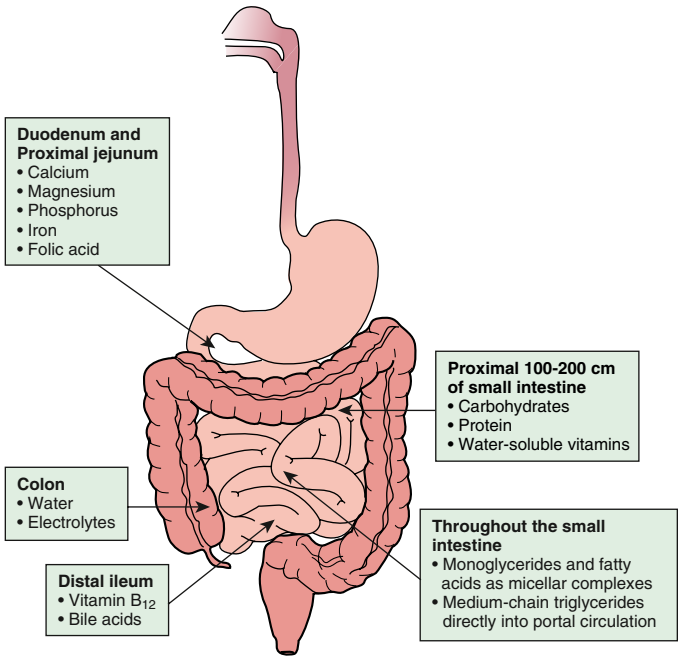

Fig. 385.7 Absorption of nutrients in the small bowel varies with the region.

overgrowth. Cholestyramine can be beneficial for patients with distal ileal resection, but its potential depletion of the BA pool can increase steatorrhea. Bacterial overgrowth is common in infants with a short bowel and can delay progression of enteral feedings. Empirical treatment with metronidazole or other antibiotics (nitazoxanide, rifaximin) is often useful. Diets high in fat and without simple sugars may be helpful in reducing bacterial overgrowth as well as in enhancing adaptation.

COMPLICATIONS

Long-term complications of short bowel syndrome include those of parenteral nutrition: central catheter infection, thrombosis, intestinal failure associated liver disease (IFALD), and gallstones. Appropriate care of the central line to prevent infection and catheter-related thrombosis is extremely important. Sepsis is a leading cause of death and can occur any time after treatment is initiated (months to years later), and is most often bacterial (single organism more common than polymicrobial), although fungal infection may be noted in 20–25% of septic episodes. The use of an ethanol, sodium bicarbonate, or taurolidine lock can reduce the incidence of central catheter infections and prevent infections.

Some patients will continue to require long-term parenteral nutritional support, and lack of central line access is potentially life-threatening. Inappropriate removal or frequent changes of central lines in the neonatal period should be avoided. **IFALD** can lead to cholestasis, cirrhosis, and liver failure and is a common reason for death or need the for transplantation. The incidence and severity of IFALD has significantly reduced over the past decade, probably due to the reduced use of soy-based lipid emulsions and the positive effect of omega-3-based lipid emulsions on cholestasis, as well as the collaboration of specialized intestinal failure teams to prevent recurrent septic episodes. Other complications of terminal ileal resection include vitamin B_{12} deficiency, which might not appear until 1-2 years after parenteral nutrition is withdrawn. Long-term monitoring for deficiencies of vitamin B_{12}, folate, iron, fat-soluble vitamins, and trace minerals, such as zinc and copper, is important. Renal stones can occur as a result of hyperoxaluria secondary to steatorrhea as calcium preferentially binds to the excess fat compared to oxalate, resulting in increased oxalate absorption and excretion in the urine. Venous thrombosis and vitamin deficiency have been associated with hyperhomocysteinemia in short bowel syndrome. Bloody diarrhea secondary to patchy, mild colitis can rarely develop during the progression of enteral feedings. The pathogenesis of this *feeding colitis* is unknown, but it is usually benign and can improve with a hypoallergenic diet or treatment with mesalamine.

In some children with life-threatening complications of parenteral nutrition, especially progressive liver failure and loss of vascular access, small intestine and liver transplantation becomes the preferred therapy (see Chapter 386).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.7 Chronic Malnutrition

Abdul-Aziz K. Elkadri

Malnutrition can be divided into primary malnutrition, which is more common in developing countries and due to the socioeconomic factors leading to inadequate access to an appropriate caloric intake, and secondary malnutrition, which is due to decreased food intake, disease processes that cause abnormal nutrient loss, or an increased expenditure of energy (see Chapter 64). The American Society for Parenteral and Enteral Nutrition (ASPEN) defined pediatric malnutrition in developed countries as an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes. Malnutrition can also be classified into *illness related* (caused by disease/trauma) or *non-illness related* (caused by environmental/behavioral factors). Based upon duration, it can also be further classified into *acute* malnutrition (<3 months; short duration, weight loss without stunting) or *chronic* malnutrition (>3 months; weight loss and stunting) that may differ in their etiology, growth patterns, and outcome. Chronic malnutrition is usually due to decreased food intake, malabsorption syndromes, or increased nutritional needs in children with chronic diseases. Malnutrition is diagnosed in 11–50% of hospitalized children and reports from Europe suggest a prevalence of close to 20% in chronically ill children. Child neglect and improper formula preparation can result in severe malnutrition. A detailed medical history should assess for symptoms that may lead to decreased oral intake, including decreased appetite, vomiting, dysphagia, abdominal pain, diarrhea, and tenesmus, as well as mood and behavioral changes. Obtaining a dietary history to determine caloric intake as well as obtaining anthropometric measurements will help determine nutritional status. Anthropometric measures to assess include reduced weight per age and weight per height, body mass index <5th percentile, and mid upper arm circumference <−1 *z* score. Physical exam findings suggestive of nutrient deficiencies include an atrophic tongue in iron deficiency, decreased subcutaneous fat, and alopecia in zinc deficiency. Laboratory testing can be used to assess vitamin and micronutrient deficiencies, including CBC and iron studies for anemia and serum albumin for protein losing enteropathy. Though screening tools for malnutrition are available in adults to provide a simple and fast way of diagnosing those patients at risk for malnutrition, few such screening tools for the pediatric population have been developed to assess children at risk, and their use in clinical practice is still questionable.

Malnourished children suffer from impaired immunity, chronic enteropathy, poor wound healing, muscle weakness, and diminished psychologic drive. Malnutrition has short-term consequences (increased disability, morbidity, and mortality) and long-term consequences (final adult size, developmental deficiencies, economic productivity). Undernutrition in hospitalized children is associated with increased infectious complications, delayed recovery, increased length of stay and costs, increased readmission rate, and increased mortality.

Nutritional rehabilitation in malnourished children is discussed in Chapter 64.

Chronic malnutrition complicated by diarrheal dehydration is a commonly observed phenomenon. Infectious diarrhea is common in tropical and subtropical countries, in the setting of poor hygiene practices and water quality, in immunocompromised hosts (e.g., HIV, congenital immunodeficiency), and when impairment of the immune response is due to chronic malnutrition itself. In children with chronic disorders, diarrhea may be related to the underlying disease, such as noncompliance with a gluten-free diet in celiac disease, noncompliance with pancreatic enzyme treatment in cystic fibrosis, and cholestatic liver disease with fat malabsorption. Malnutrition per se can lead to exocrine pancreatic insufficiency, which, in turn, aggravates malabsorption and diarrhea.

In infants and children with severe malnutrition, many of the signs normally used to assess the state of hydration or shock are unreliable. Severe malnutrition might be accompanied by sepsis; thus children with septic shock might not have diarrhea, thirst, or sunken eyes but may be hypothermic, hypoglycemic, or febrile. Cardiac reserve is lowered, and heart failure is a common complication.

Despite clinical signs of dehydration, urinary osmolality may be low in the chronically malnourished child. Renal acidifying ability is also limited in patients with malnutrition.

Management of diarrhea in chronically malnourished children is based on three principles: oral rehydration to correct dehydration, prompt resumption of feeds with avoidance of periods of nothing by mouth, and treating the underlying etiology behind the diarrhea.

When treating dehydration in malnutrition, the extracellular space appears to be overexpanded and intra- and extracellular spaces are hypo-osmolar. In this setting, reduced or hypotonic osmolarity oral rehydration solutions are indicated. When oral rehydration is not possible due to etiologies such as feeding aversion, the route of choice is nasogastric, and parenteral rehydration and nutrition should be avoided when possible.

Initial intravenous therapy in profound dehydration is designed to improve the circulation and expand extracellular volume. For patients with edema, the quality of fluid and the rate of administration might

require readjustment from recommended levels to avoid overhydration and pulmonary edema. Blood should be given if the patient is in shock and severely anemic. Potassium salts can be initiated early if urine output is good. Clinical improvement may be more rapid with magnesium therapy.

Children with chronic malnutrition are at risk for refeeding syndrome (see Chapter 63). Therefore initial calorie provision should not exceed the previous daily intake and is usually begun at 50–75% of estimated resting energy expenditure, with rapid increase to caloric goals once there are no severe abnormalities in sodium, potassium, phosphorus, calcium, or magnesium. Correction of malnutrition and catch-up growth are not part of the primary treatment of these children, but a nutrition rehabilitation plan is necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.8 Enzyme Deficiencies

Abdul-Aziz K. Elkadri

CARBOHYDRATE MALABSORPTION

Symptoms of carbohydrate malabsorption include loose watery diarrhea, flatulence, abdominal distention, and pain. Unless consumed in large amounts, children may remain asymptomatic. Disaccharidases are present on the brush border membrane of the small bowel. **Disaccharidase deficiency** can be caused by a genetic defect or secondary to damage to the small bowel epithelium, as occurs with infection or inflammatory disorders.

Nonabsorbed carbohydrates enter the large bowel and are fermented by intestinal bacteria, producing organic acids and gases such as methane and hydrogen. The gases can cause abdominal distension and discomfort, whereas the unabsorbed carbohydrates and the organic acids result in osmotic diarrhea characterized by an acidic pH and the presence of either reducing or nonreducing sugars in the stool. Hydrogen and methane gas can be detected in the breath as a sign of fermentation of unabsorbed carbohydrates **(hydrogen breath test).**

LACTASE DEFICIENCY

Congenital lactase deficiency is rare and is associated with symptoms occurring on exposure to lactose in milk. Fewer than 50 cases have been reported worldwide. In patients with congenital lactase deficiency, five distinct disease causal variants in the coding region of the *LCT* gene were found. In most patients (84%), homozygosity for a nonsense variant, 4170T-A (Y1390X; OMIM 223000), designated Fin (major), was found.

Primary adult-type hypolactasia is caused by a physiologic decline in lactase activity that occurs following weaning in most mammals. The brush border lactase enzyme is expressed at low levels during fetal life; activity increases in late fetal life and peaks from term to 3 years, after which levels gradually decrease with age. This decline in lactase levels varies between ethnic groups. Lactase deficiency occurs in approximately 15% of White adults, 40% of Asian adults, and 85% of Black adults in the United States. Lactase is encoded by a single gene *(LCT)* of approximately 50 kb located on chromosome 2q21. C/T (−13910) polymorphisms of the *MCM6* gene were found to be related to adult-type hypolactasia in most European populations. In three African populations—Tanzanians, Kenyans, and Sudanese—three single-nucleotide polymorphisms, G/C(−14010), T/G(−13915), and C/G(−13907), were identified with lactase persistence and have derived alleles that significantly enhance transcription from the lactase gene promoter in vitro.

Secondary lactose intolerance follows small bowel mucosal damage (celiac disease, acute severe gastroenteritis) and is usually transient, improving with mucosal healing. Lactase deficiency can be diagnosed by the hydrogen breath test (2 g/kg up to 25 g) or by measurement of lactase activity in mucosal tissue retrieved by small bowel biopsy. Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.

Treatment of lactase deficiency consists of a milk-free diet. A lactose-free formula (based on either soy or cow's milk) can be used in infants. In older children, low-lactose milk can be consumed. The addition of lactase to dairy products usually improves the symptoms.

Live-culture yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency. Hard cheeses and cottage cheeses have a small amount of lactose and are generally well tolerated.

FRUCTOSE MALABSORPTION

Children consuming a large quantity of juice rich in fructose, corn syrup, or natural fructose in fruit juices can present with diarrhea, abdominal distention, and slow weight gain. Identification by history followed by the restriction of the amount of juice in the diet resolves the symptoms and helps avoid unnecessary investigations. A fructose hydrogen breath test can be helpful in the diagnosis of fructose malabsorption. The reason for fructose malabsorption is a reduced abundance of GLUT-5 transporter on the surface of the intestinal brush border membrane, which occurs in approximately 5% of the population.

SUCRASE-ISOMALTASE DEFICIENCY

Sucrase-isomaltase (SI) deficiency is a rare autosomal recessive disorder with a complete absence of sucrase and reduced maltase digestive activity. The SI complex is composed of 1,927 amino acids encoded by a 3,385 bp messenger RNA. The gene locus on chromosome 3 has 30 exons spanning 106.6 kb. Most SI pathogenic variants result in a lack of enzyme protein synthesis (null variant). Posttranslational processing defects have also been identified.

Approximately 2% of Europeans and Americans are heterozygous for a causal variant. Sucrase deficiency is especially common in indigenous Greenlanders (estimated 5%) in whom it is often accompanied by lactase deficiency. Gene variants of the SI are found to have some implications in irritable bowel syndrome (IBS), as they were found more often in patients with IBS than in controls.

Symptoms of SI deficiency usually begin when the infant is exposed to sucrose or a glucose polymer diet. This can occur with ingestion of non–lactose-based infant formula or on the introduction of pureed food, especially fruits and sweets. Diarrhea, abdominal pain, and poor growth are observed. Occasionally, patients present with symptoms in late childhood or even adult life, but careful history often indicates that symptoms appeared earlier. Diagnosis of SI malabsorption requires acid hydrolysis of stool for reducing substances due to the fact that sucrase is a nonreducing sugar. Alternatively, hydrogen breath testing can be used, as well as direct enzyme assay of small bowel biopsy or genetic testing.

The mainstay of treatment is lifelong dietary restriction of sucrose-containing foods, although symptoms may diminish with age. Enzyme replacement with a purified yeast enzyme sacrosidase is a highly effective adjunct to dietary restriction.

GLUCOSE-GALACTOSE MALABSORPTION

More than 30 different pathogenic variants of the sodium/glucose co-transporter gene *(SGLT1)* have been identified. These variants cause a rare autosomal recessive disorder of intestinal glucose and galactose/Na^+ co-transport system that leads to osmotic diarrhea. Because most dietary sugars are polysaccharides or disaccharides with glucose or galactose moieties, diarrhea follows the ingestion of glucose, breast milk, or conventional lactose-containing formulas. Dehydration and acidosis can be severe, resulting in death.

Stools are noted to be acidic and contain sugar. Patients with the defect have normal absorption of fructose, and their small bowel function and structure are normal in all other aspects. Intermittent or permanent glycosuria after fasting, or after a glucose load, is a common finding due to the transport defect also being present in the kidney. The presence of reducing substances in watery stools and slight glycosuria despite low blood sugar levels is highly suggestive of glucose-galactose malabsorption. Malabsorption of glucose and galactose is easily identified using the breath hydrogen test. It is safe to perform the first test with a dose of

0.5 g/kg of glucose or galactose; if necessary, a second test can be performed using 2 g/kg. Breath hydrogen will rise more than 20 ppm. Biopsy of the small intestine is useful to document a normal villous architecture and normal disaccharidase activities and to rule out other etiologies. The identification of causal variants of *SGLT1* make it possible to perform prenatal screening in families at risk for the disease.

Treatment consists of rigorous restriction of glucose and galactose. Fructose, the only carbohydrate that can be given safely, should be added to a carbohydrate-free formula at a concentration of 6–8%. This formula results in almost immediate cessation of diarrhea. Although the defect is permanent and lifelong, limited amounts of glucose, starches, or sucrose may be tolerated later in life.

EXOCRINE PANCREATIC INSUFFICIENCY

Chapter 397 discusses disorders of exocrine pancreatic insufficiency (see Table 385.5). **Cystic fibrosis** is the most common congenital disorder associated with exocrine pancreatic insufficiency. Although rare, the next most common cause of pancreatic insufficiency in children is **Shwachman-Diamond syndrome**. Other rare disorders with exocrine pancreatic insufficiency include **Johanson-Blizzard syndrome** (severe steatorrhea, aplasia of alae nasi, deafness, hypothyroidism, scalp defects), **Pearson bone marrow syndrome** (sideroblastic anemia, variable degree of neutropenia, thrombocytopenia), and isolated pancreatic enzyme deficiency (lipase, colipase, trypsinogen, amylase). Enterokinase deficiency, a key enzyme produced in the proximal small bowel and responsible for the activation of trypsinogen to trypsin, manifests clinically as exocrine pancreatic insufficiency.

Autoimmune polyendocrinopathy syndrome type 1, a rare autosomal recessive disorder, is caused by pathogenic variants in the autoimmune regulator gene (*AIRE*). Patients develop chronic mucocutaneous candidiasis along with failure of the parathyroid gland, adrenal cortex, pancreatic β cells, gonads, gastric parietal cells, and thyroid gland. Pancreatic insufficiency and steatorrhea are associated with this condition.

ENTEROKINASE (ENTEROPEPTIDASE) DEFICIENCY

Enterokinase (enteropeptidase) is a brush border serine protease enzyme of the small intestine responsible for the cleavage of trypsinogen to trypsin. This in turn results in the cascade activation of a number of other pancreatic enzymes. Deficiency of this enzyme results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema shortly after birth.

The diagnosis can be established by measuring the enzyme level in intestinal tissue or by genetic testing, as enterokinase deficiency is caused by pathogenic variants in the serine protease-7 gene *(PRSS7)* on chromosome 21q21. Treatment of this rare autosomal recessive disorder consists of replacement with pancreatic enzymes and administration of a protein hydrolyzed formula with added MCT oil in infancy.

TREHALASE DEFICIENCY

The disaccharide trehalose is mainly present in mushrooms and has been approved to add to dried food. It is hydrolyzed by the intestinal trehalase into two molecules of glucose. Trehalase deficiency has been reported in 8% of Greenlanders; only three cases of this deficiency have been reported elsewhere. In untreated celiac disease, the intestinal trehalase activity is reduced as those of other disaccharidases and recovers after introduction of a gluten-free diet.

TRYPSINOGEN DEFICIENCY

Trypsinogen deficiency is a rare syndrome with symptomatology similar to that of enterokinase deficiency. Enterokinase catalyzes the conversion of trypsinogen to trypsin, which, in turn, activates the various pancreatic proenzymes, such as chymotrypsin, procarboxypeptidase, and proelastase, for their active forms. Deficiency of trypsinogen results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema soon after birth.

The trypsinogen gene is encoded on chromosome 7q35. Treatment is the same as for enterokinase deficiency, with pancreatic enzymes and protein hydrolysate formula with added MCT oil in infancy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

385.9 Liver and Biliary Disorders Causing Malabsorption

Abdul-Aziz K. Elkadri

Absorption of lipids and lipid-soluble vitamins depends to a great extent on an adequate bile flow delivering BA to the small intestine, which helps mixed micelle formation of lipid droplets. Most liver and biliary disorders lead to impairment of the bile flow, contributing to malabsorption of long-chain fatty acids and fat-soluble vitamins such as A, D, E, and K. Liver disorders associated with significant malabsorption and failure to thrive are mainly due to these categories:

In **PFIC syndromes and BA synthesis defects**, PFIC type 1 is associated with chronic diarrhea caused by a bile acid transport defect in the gut. It is not uncommon for these children to have symptomatic fat-soluble vitamin deficiencies and suffer from pathologic fractures and peripheral neuropathy.

Children with lipid storage disorders (e.g., **Wolman disease**) also manifest with severe failure to thrive and multiple vitamin deficiencies.

Children with biliary disorders such as biliary atresia after portoenterostomy surgery (Kasai portoenterostomy), cystic fibrosis, neonatal sclerosing cholangitis, Alagille syndrome, and sclerosing cholangitis constitute another major group of disorders with reduced bile flow where malabsorption could be a significant challenge.

Chronic liver disease of any etiology could also lead to lipid malabsorption mechanisms. In addition, severe portal hypertension can lead to portal hypertensive enteropathy, resulting in poor absorption of nutrients.

Decompensated liver disease leads to anorexia and increased energy expenditures, further widening the gap between calorie intake and net absorption and leading to severe malnutrition. Adequate management of nutrition is essential to improve the outcome with or without liver transplantation. This is usually achieved by using MCT-rich milk formula, supplemental vitamins, and continuous or bolus enteral feed where oral intake is poor.

Vitamin D deficiency is commonly observed on biochemical tests, and children can present with pathologic fractures. Simultaneous administration of vitamin D with the water-soluble vitamin E preparation (TPGS 1,000 succinate) enhances absorption of vitamin D as well. In young infants with cholestasis, oral vitamin D_3 is given at a dose of 1,000 IU/kg/24 hr. After 1 month, if the serum 25-hydroxyvitamin D level continues to be low, intramuscular administration of 10,000 units/kg or maximum of 60,000 is recommend. Monitoring of 25-hydroxy vitamin D serum levels every 1-2 months is recommended in children with severe cholestasis.

Vitamin E deficiency in patients with chronic cholestasis is not usually symptomatic but can manifest as a progressive neurologic syndrome, including peripheral neuropathy (manifesting as loss of deep tendon reflexes and ophthalmoplegia), cerebellar ataxia, and posterior column dysfunction. Early in the course, findings are partially reversible with treatment; late features may not be reversible. It may be difficult to identify vitamin E deficiency because the elevated blood lipid levels in cholestatic liver disease can falsely elevate the serum vitamin E level. Therefore it is important to also obtain serum lipid levels to measure the ratio of serum vitamin E to total serum lipids. A normal level for patients younger than 12 years of age is >0.6, and for patients older than 12 years is >0.8. Neurologic sequelae can be prevented with the use of an oral water-soluble vitamin E preparation (TPGS, Liqui-E) at a dose of 25-50 IU/day in neonates and 15-25 IU/kg/day in children.

Vitamin K deficiency can occur because of cholestasis and poor fat absorption. In children with liver disease, it is very important to differentiate between the coagulopathy related to vitamin K malabsorption and one secondary to the synthetic failure of coagulation factors from the liver. A single dose of vitamin K administered intravenously does not correct the prolonged prothrombin time in liver failure but will help correct the deficiency state within a few hours. Easy bruising may be the first sign. In neonatal cholestasis, coagulopathy because of vitamin K deficiency can manifest with intracranial bleeding with devastating consequences, and prothrombin time should be routinely measured to monitor for deficiency in children with cholestasis. All children with cholestasis should receive regular vitamin K supplementation.

Vitamin A deficiency is rare and is associated with night blindness, xerophthalmia, and increased mortality if patients contract measles. Serum vitamin A levels should be monitored, and adequate supplementation considered. Caution should be observed with supplementation, as high levels of vitamin A can cause liver damage.

385.10 Rare Inborn Defects Causing Malabsorption

Abdul-Aziz K. Elkadri

Congenital (primary) malabsorption disorders originate from a multitude of defects, which includes structural or functional defects of enterocytes or disorders involving other cellular lineages of the GI tract such as enteroendocrine or immune cells (see Chapters 385.3 and 388). Integral membrane proteins are another class of primary disorders of malabsorption as they fulfill the function of transporter of nutrients as a receptor or channel across the apical or basolateral membrane of enterocytes. Histologic examination of the mucosa of the small and large bowel is typically normal. Most of these disorders are rare and inherited in an autosomal recessive pattern as they are typically a loss of function of a protein. With increased access to genetic sequencing, patients are being discovered to carry pathologic variants in genes traditionally thought to carry a traditional phenotype. This broader phenotype is thought to be possibly due to modifier genes and variable penetrance and may provide us with a better understanding of the spectrum of these disorders.

DISORDERS OF CARBOHYDRATE ABSORPTION

These are described in Chapter 385.9.

Patients with **Fanconi-Bickel syndrome** present with tubular nephropathy, hypophosphatemic rickets, hepatomegaly, and nephromegaly due to glycogen accumulation in liver and small bowel; failure to thrive; and fasting hypoglycemia and postprandial hyperglycemia. The disorder is caused by homozygous pathogenic variants of GLUT2 *(SLC2A2),* the facilitative monosaccharide transporter at the basolateral membrane of enterocytes, hepatocytes, renal tubules, pancreatic islet cells, and cerebral neurons. Patients exhibit postprandial hyperglycemia secondary to low insulin secretion (impaired glucose-sensing mechanisms in β cells) and fasting hypoglycemia due to altered glucose transport out of the liver. The increased intracellular glucose level inhibits glycogen degradation leading to intracellular glycogen accumulation. Similarly, altered monosaccharide transport out of enterocytes may be responsible for the putative glycogen accumulation and result in the diarrhea and malabsorption observed in some patients. Therapy includes the substitution of electrolyte losses and vitamin D and supplying uncooked cornstarch to prevent hypoglycemia. Patients who present in the neonatal period need frequent small meals and galactose-free milk.

DISORDERS OF AMINO ACID AND PEPTIDE ABSORPTION

Protein digestion and absorption in the intestine is accomplished by a combination of proteases, peptidases, and transporters of peptides and amino acids. Amino acid transporters are essential for the absorption and transport of amino acids from luminal nutrients, through intracellular transfer and finally between cellular compartments. Due to their ontogenic origins, enterocytes and renal tubules share similar amino acid transporters. The highest intestinal transporter activity is found in the jejunum. The transporters causing Hartnup disease, cystinuria, iminoglycinuria, and dicarboxylic aminoaciduria are in the apical membrane, and those causing **lysinuric protein intolerance (LPI)** and blue diaper syndrome are anchored in the basolateral membrane of the intestinal epithelium.

Dibasic amino acids, including cystine, ornithine, lysine, and arginine, are taken up by the Na-independent heterodimeric transporter protein complex made up of SLC3A1 and SLC7A9. Cystinuria, a defect in this transporter, is the most common primary inherited aminoaciduria. This disorder is not associated with any GI or nutritional consequences because of compensation by an alternative transporter. However, hypersecretion of cystine in the urine leads to recurrent cystine stones, which account for up to 6–8% of all urinary tract stones in children. Ample hydration, urine alkalinization, and cystine-binding thiol drugs can increase the solubility of cystine. Cystinuria type A *(SLC3A1)*, or type 1 in the phenotypic classification, is inherited as an autosomal recessive trait, whereas cystinuria type B, classified phenotypically as type II and III, is due to pathogenic variants in SLC7A9. Parents of patients with type B cystinuria have increased cystine levels but do not form stones, which suggests that it is likely inherited in an autosomal dominant manner with incomplete penetrance. Cystinuria type I has been described in association with 2p21 deletion syndrome and hypotonia-cystinuria syndrome.

Lysinuric protein intolerance (LPI) is the second most common disorder of amino acid transport (see Chapter 105.14). It is caused by the y^+LAT-1 (SLC7A7) subunit of the cationic amino acid transporter present at the basolateral membrane of the intestinal and renal epithelium and causes a failure to deliver cytosolic dibasic cationic amino acids into the paracellular space. This defect is not compensated by the SLC3A1/SLC7A9 transporter at the apical membrane. The symptoms of LPI, which appear after weaning, include diarrhea, failure to thrive, hepatosplenomegaly, nephritis, respiratory insufficiency, alveolar proteinosis, pulmonary fibrosis, and osteoporosis. Abnormalities of the bone marrow with anemia and thrombocytopenia have also been described in a subgroup of LPI patients. The disorder is characterized by low plasma concentrations of the dibasic amino acids lysine, arginine, and ornithine, high concentrations of glutamine, alanine, glycine, serine, and proline, and a massive urinary excretion of lysine, as well as orotic acid, ornithine, and arginine to a lesser extent. Hyperammonemia episodes and coma along with emesis usually develop after fasting or with the ingestion of large amounts of protein, specifically alanine, likely due to a deficiency of intramitochondrial ornithine. Some patients show moderate intellectual disability. Cutaneous manifestations can include alopecia, perianal dermatitis, and sparse hair. Some patients learn to avoid protein-containing foods. Immune dysfunction is potentially attributable to nitric oxide overproduction secondary to arginine intracellular trapping and may be the underlying pathophysiologic route explaining many LPI complications such as hemophagocytic lymphohistiocytosis, autoimmune disorders, and an incompletely characterized immune deficiency. Treatment includes dietary protein restriction (<1.5 g/kg/day) and orally administered citrulline (100 mg/kg/day), which is well absorbed from the intestine and carnitine supplementation.

Hartnup disease is characterized by the malabsorption of all neutral amino acids (except proline), including the essential amino acid tryptophan. It is characterized by aminoaciduria, photosensitive pellagra-like rash, headaches, cerebellar ataxia, delayed intellectual development, and diarrhea. The clinical spectrum ranges from asymptomatic to severely affected with progressive neurodegeneration leading to death by adolescence. SLC6A19, which is the major luminal sodium-dependent neutral amino acid transporter of small intestine and renal tubules, has been identified as the defective protein. A similar phenotype is observed in defects in collectrin (CLTRN), and the requirement of angiotensin-converting enzyme 2 may explain the phenotypic heterogeneity of Hartnup disorder. Tryptophan is a precursor of nicotinamide adenine dinucleotide phosphate biosynthesis; therefore the disorder can be treated by nicotinamide in addition to a diet of 4 g protein/kg. The use of lipid-soluble esters of amino acids and tryptophan ethyl ester has also been reported.

Defects in specific, basolateral tryptophan transporter (SLC16A10) are the cause of **blue diaper syndrome** (indicanuria, Drummond syndrome). Intestinal bacteria convert the unabsorbed tryptophan to indican, which is responsible for the bluish discoloration of the urine after its hydrolysis and oxidation. Symptoms can include digestive disturbances such as vomiting, constipation, poor appetite, failure to thrive, hypercalcemia, nephrocalcinosis, fever, irritability, and ocular abnormalities.

The underlying defect of **iminoglycinuria** is the malabsorption of proline, hydroxyproline, and glycine as a consequence of the proton amino acid transporter SLC36A2 defect, with a possible participation

of modifier genes, one of which (SLC6A20) is present in the intestinal epithelium. This disorder is usually benign, but sporadic cases with encephalopathy, intellectual disability, deafness, blindness, kidney stones, hypertension, and gyrate atrophy have been described.

The neuronal glutamate transporter EAAT3 (SLC1A1) is affected in **dicarboxylic aminoaciduria**. This carrier is present in the small intestine, kidney, and brain and transports the anionic acids L-glutamate, L- and D-aspartate, and L-cysteine. There are single-case reports indicating that this disorder could be associated with hyperprolinemia and neurologic symptoms such as POLIP (polyneuropathy, ophthalmoplegia, leukoencephalopathy, intestinal pseudoobstruction) syndrome.

DISORDERS OF FAT TRANSPORT

These are described in Chapters 106.3 and 385.3.

DISORDERS OF VITAMIN ABSORPTION

Transporters and receptors of the intestinal epithelium have been described for water-soluble but not fat-soluble vitamins with the latter absorbed primarily into enterocytes by passive diffusion after the emulsification of fats by bile salts. Transfer proteins (retinol-binding protein [RBP4] and α-tocopherol transfer protein [TTP1]) have been involved in deficiency states of vitamins E (spinocerebellar ataxia) and A (ophthalmologic signs), respectively.

Vitamin B_{12} (cobalamin) is synthesized exclusively by microorganisms and is acquired mostly from meat and milk (see Chapter 503.2). Its absorption starts with the removal of cobalamin from dietary protein by gastric acidity and its binding to haptocorrin. In the duodenum, pancreatic proteases hydrolyze the cobalamin-haptocorrin complex, allowing the binding of cobalamin to intrinsic factor (IF), which originates from parietal cells from the stomach. The receptor of the cobalamin-IF complex (Cbl-IF) is located at the apical membrane of the ileal enterocytes and represents a heterodimer consisting of cubilin (CUBN) and amnionless (AMN). After endocytic uptake into endosomes, the Cbl-IF and its receptor binds to megalin and forms a cobalamin–transcobalamin (TC)-2 complex (after cleavage of IF) for further transcytosis. Vitamin B_{12} exits the lysosome via LMBD1 and ABCD4 and is released to the bloodstream most likely through the basolateral transporter multifunctional multidrug resistance protein 1 (MRP1). Biologically available circulating vitamin B_{12} is bound to TC, a nonglycosylated protein that carries 10–30% of the total vitamin B_{12}. TC-vitamin B_{12} complexes enter the cells via two members of the LDL receptor gene family, CD320 and renal Lrp2/megalin. As a cofactor for methionine synthase, cobalamin converts homocysteine to methionine. Cobalamin deficiency can be caused by inadequate intake of the vitamin (e.g., breastfeeding by mothers on a vegan diet) and primary or secondary achlorhydria including autoimmune gastritis, exocrine pancreatic insufficiency, bacterial overgrowth (see Chapter 385.4), ileal disease (Crohn disease, see Chapter 382.2), ileal (or gastric) resection, infections (fish tapeworm), and Whipple disease (see Chapter 388).

Clinical signs of congenital cobalamin malabsorption, which usually appear from a few months to more than 10 years, are pancytopenia including **megaloblastic anemia**, fatigue, failure to thrive, and neurologic symptoms, including developmental delay. Recurrent infections and bruising may be present. Laboratory evaluation indicates low serum cobalamin, hyperhomocysteinemia, methylmalonic acidemia, and mild proteinuria. The Schilling test is useful to differentiate between a lack of IF and the malabsorption of cobalamin. Several rare autosomal recessive disorders of congenital cobalamin deficiency affect absorption and transport of cobalamin (in addition to seven other inherited defects of cobalamin metabolism). These include pathogenic variants of the gastric IF *(GIF)* gene with absence of IF (but normal acid secretion and lack of autoantibodies against IF or parietal cells), variants of the *AMN* and *CUBN* gene subunits of the Cbl-IF receptor in ileum **(Imerslund-Grasbeck syndrome)**, and variants in the TC 2 cDNA. Two inborn defects were identified recently in the genes encoding LMBD1 and ABCD4 transporters and are responsible for the rare inborn defect in Cbl-IF, which results in the trapping of free vitamin B_{12} in lysosomes. These disorders require long-term parenteral cobalamin treatment: intramuscular injections of cobalamin. High-dose substitution with oral cyanocobalamin (1 mg biweekly) does not seem to be sufficient for all patients with congenital cobalamin deficiency. Intramuscular cobalamine injections of 1000 mcg/day for 7 days, then three times a week for 3 weeks, then once a month for 3 months, followed by a change to 1000 mcg daily oral cobalamine has been successful in some cases.

Folate is an essential vitamin required to synthesize methionine from homocysteine. It is found mainly in green leafy vegetables, legumes, and oranges. After its uptake by enterocytes, folate is converted to 5-methyltetrahydrofolate. Secondary folate deficiency is caused by insufficient folate intake, villous atrophy (e.g., celiac disease, inflammatory bowel disease), treatment with phenytoin and trimethoprim, among others (see Chapter 503.1). Several inherited disorders of folate metabolism and transport have been described.

Three mammalian folate transporter systems have been described in a variety of tissues: (1) the bidirectional reduced folate carrier 1 (RFC1, SLC19A1), (2) the glycosyl-phosphatidylinositol-anchored folate receptors (FOLR1, FOLR2, and FOLR4) responsible for folate-receptor mediated endocytosis, and (3) the human proton-coupled folate transporter (PCFT). Hereditary **folate malabsorption** is characterized by a defect of the PCFT of the brush border, leading to impaired absorption of folate in the upper small intestine as well as impaired transport of folate into the central nervous system. Symptoms of congenital folate malabsorption are diarrhea, failure to thrive, megaloblastic anemia presenting in the first few months of life, glossitis, infections *(Pneumocystis jirovecii)* with episodes of hypogammaglobulinemia, and neurologic abnormalities (seizures, intellectual impairment, and basal ganglia calcifications). Macrocytosis, with or without neutropenia, multilobulated polymorphonuclear cells, increased lactate dehydrogenase and bilirubin, increased saturation of transferrin, and decreased cholesterol can also be found. Low levels of folate are present in serum and cerebrospinal fluid. Plasma homocysteine concentrations as well as urine excretion of formiminoglutamic acid and orotic acid are elevated. Long-standing deficiency of folate (around 3-4 months) is best documented using red cell folate. Therapy involves large doses of oral (up to 150-400 mg/day of folic acid) or systemic (intrathecal) folate. Folinic acid has been used in intramuscular and/or oral form, more readily correcting the systemic and CSF folate levels. 150-400 mg of oral folinic acid daily has been used (starting dose 10-15 mg/kg daily). CSF folate levels should be followed, monitoring for clinical response of the systemic signs of disease. Sulfasalazine and methotrexate are potent inhibitors of PCFT. Therefore folate deficiency may develop during treatment with these drugs. Although the RFC1 is ubiquitously expressed, including the brush border membrane in the small intestine, involvement of RFC1 in intestinal folate uptake has not been confirmed.

The molecular basis of intestinal transport of other water-soluble vitamins such as vitamin C (Na^+-dependent vitamin C transporters 1 and 2), pyridoxine/vitamin B_6, and biotin/vitamin B_5 (Na^+-dependent multivitamin transporter) have been described; congenital defects of these transporter systems have not yet been found in humans. A **thiamine/vitamin B_1–responsive megaloblastic anemia** syndrome, which is associated with early-onset type 1 diabetes mellitus and sensorineural deafness, is caused by pathogenic variants of the thiamine transporter protein gene, THTR-1 (SLC19A2), present in the brush border.

DISORDERS OF ELECTROLYTE AND MINERAL ABSORPTION

Congenital chloride diarrhea (CCD) is a rare but relatively common group of congenital diarrheal disorders. It includes defects in *SLC26A3*, encoding a Na^+-independent Cl^-/HCO_3^- exchanger within the apical membrane of ileal and colonic epithelium, and *GUCY2C*, encoding a guanylate cyclase receptor in the intestine for the bacterial heat-stable enterotoxin. Defects in SLC26A3 have been found to have a prevalence in Finland of 1:20,000. Founder pathogenic variants have been described in Finnish, Polish, and Arab patients: V317del, I675-676ins, and G187X, respectively. The Cl^-/HCO_3^- exchanger absorbs chloride originating from gastric acid and the cystic fibrosis transmembrane conductance regulator and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.

Defects in GUCY2C have been identified, which leads to an autosomal dominant activation defect in guanylate cyclase C. This leads to

elevated levels of cyclic guanosine monophosphate (cGMP) and activation of the CFTR receptor. The mechanism is similar to the response to heat-stable enterotoxins from *Escherichia coli* and results in a chloride-losing diarrhea. Interestingly, a homozygous recessive inactivation defect has been described in a Bedouin cohort resulting in a meconium ileus phenotype due to the inactivation of CFTR.

Prenatally, CCD is characterized by maternal polyhydramnios, dilated fetal bowel loops, and preterm birth. Newborns with CCD present with severe life-threatening *secretory diarrhea* during the first few weeks of life. Volvulus has been reported in few patients with CCD. Laboratory findings are metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia (with high plasma renin and aldosterone activities). Fecal chloride concentrations are >90 mmol/L and exceed the sum of fecal sodium and potassium. Early diagnosis and aggressive lifelong enteral substitution of KCl in combination with NaCl (chloride doses of 6-8 mmol/kg/day for infants and 3-4 mmol/kg/day for older patients) prevent mortality and long-term complications (such as urinary infections, hyperuricemia with renal calcifications, renal insufficiency, and hypertension) and allow normal growth and development. Orally administered proton pump inhibitors, cholestyramine, and butyrate can reduce the severity of diarrhea. However, febrile diseases are likely to exacerbate symptoms as a consequence of severe dehydration and electrolyte imbalances. (See Chapter 71 for fluid and electrolyte management.) The diarrheal symptoms usually tend to regress with age, but the phenotype is highly variable. In familial cohorts carrying the same variant, individuals have demonstrated an increased incidence of inflammatory bowel disease as well as a phenotype of irritable bowel syndrome and motility issues.

The classic form of **congenital sodium diarrhea** (CSD) manifests with polyhydramnios, massive *secretory diarrhea*, severe metabolic acidosis, alkaline stools (fecal pH >7.5), and hyponatremia because of fecal losses of Na^+ (fecal Na^+ >70 mmol/L). Urinary secretion of sodium is low to normal. CSD is clinically and genetically heterogeneous. A syndromic form of CSD with superficial punctate keratitis, choanal or anal atresia, hypertelorism, and corneal erosions has been related to pathologic variants in *SPINT2,* which encodes a serine-protease inhibitor whose pathophysiologic action on intestinal Na^+ absorption is unclear. This form of CSD is also referred to as **congenital tufting enteropathy** (intestinal epithelial dysplasia) as it often shows clustered enterocytes that form "tufts" with branching crypts on histology (described in Chapter 385.3). Pathogenic variants in *SLC9A3,* the gene encoding the Na^+/H^+ antiporter 3 (NHE3), the major intestinal brush border Na^+/H^+ exchanger, were identified in nine patients with nonsyndromic CSD. IBD developed in two of nine patients with recessive SLC9A3 pathogenic variants, implicating NHE3 in the pathogenesis of IBD in a subset of patients.

The congenital form of **acrodermatitis enteropathica** manifests with severe deficiency of body zinc soon after birth in bottle-fed children or after weaning from breastfeeding (see Chapter 712). Clinical signs of this disorder are anorexia, diarrhea, failure to thrive, humoral and cell-mediated immunodeficiency (poor wound healing, recurrent infections), male hypogonadism, skin lesions (vesiculobullous dermatitis on the extremities and perirectal, perigenital, and perioral regions, and alopecia), and neurologic abnormalities (tremor, apathy, depression, irritability, nystagmus, photophobia, night blindness, and hypogeusia). The genetic defect of acrodermatitis enteropathica is caused by a pathogenic variant in the Zrt-Irt-like protein 4 (ZIP4, SLC39A4), normally expressed on the apical membrane, which enables the uptake of zinc into the cytosol of enterocytes. The zinc-dependent alkaline phosphatase and plasma zinc levels are low. Paneth cells in the crypt of the small intestinal mucosa show inclusion bodies. Acrodermatitis enteropathica requires long-term treatment with elemental zinc at 1-3 mg/kg/day. Maternal zinc deficiency impairs embryonic, fetal, and postnatal development. Chapter 72 described the *acquired* forms of zinc deficiency. Transient neonatal zinc deficiency is an autosomal dominant disorder with similar manifestations as acrodermatitis enteropathica. The disease is caused by pathogenic variants in ZnT2, the transporter responsible for supplying human milk with zinc.

Menkes disease and **occipital horn syndrome** are both caused by pathogenic variants in the gene encoding Cu^{2+} transporting adenosine triphosphatase (ATPase), α-polypeptide (ATP7A), which is also called Menkes or MNK protein. ATP7A is mainly expressed by enterocytes, placental cells, and the central nervous system, and is localized in the *trans*-Golgi network for copper transfer to enzymes in the secretory pathway or to endosomes to facilitate copper efflux. Copper values in liver and brain are low in contrast to an increase in mucosal cells, including enterocytes and fibroblasts. Plasma copper and ceruloplasmin levels decline postnatally. Clinical features of Menkes disease are progressive cerebral degeneration (convulsions), feeding difficulties, failure to thrive, hypothermia, apnea, infections (urinary tract), hypertelorism, hair abnormalities (kinky hair), hypopigmentation, bone changes, and cutis laxa. Patients with the classic form of Menkes disease usually die before the age of 3 years. A therapeutic trial with copper-histidinase should start before the age of 6 weeks. In contrast to Menkes disease, occipital horn syndrome usually manifests during adolescence with borderline intelligence, craniofacial abnormalities, skeletal dysplasia (short clavicles, pectus excavatum, genu valgum), connective tissue abnormalities, chronic diarrhea, orthostatic hypotension, obstructive uropathy, and osteoporosis. It should be differentiated from Ehlers-Danlos syndrome type V.

Active calcium absorption is mediated by the transient receptor potential channel 6 (TRPV6) at the brush border membrane, calbindin, and the Ca-ATPase, or the Na^+-Ca^{2+} exchanger for calcium efflux at the basolateral membrane within the proximal small bowel. A congenital defect of these transporters has not yet been described.

Intestinal absorption of dietary magnesium, which occurs via the transient receptor potential channel TRPM6 at the apical membrane, is impaired in familial **hypomagnesemia with secondary hypocalcemia**, which manifests with neonatal seizures and tetany.

Intestinal iron absorption consists of several complex regulated processes starting with the uptake of heme-containing iron by heme carrier protein 1 (HCP1) and Fe^{2+} (after luminal reduction of oxidized Fe^{3+}) by the divalent metal transporter 1 (DMT1) at the apical membrane, followed by the efflux of Fe^{2+} by ferroportin 1 (also called the iron-regulated transporter) at the basolateral membrane of duodenal enterocytes. Hepatic hormone hepcidin has a key role in iron homeostasis by interacting with ferroportin. When it binds to ferroportin, hepcidin induces phosphorylation of the iron exporter, causing its internalization and degradation. A decrease in the ferroportin protein level on the cell surface inhibits iron export from intracellular pools. Thus hepcidin controls plasma iron levels by reducing iron absorption in the gut, lowering iron release from hepatocytes, and preventing iron recycling by macrophages. Hepcidin deficiency causes iron overload in hereditary hemochromatosis and iron-loading anemias, whereas hepcidin excess causes or contributes to the development of iron-restricted anemia in inflammatory diseases, infections, some cancers, and chronic kidney disease. Pathogenic variants of the ferroportin 1 gene have been found in the autosomal dominant form of **hemochromatosis** type 4. Variants within the hemochromatosis (*HFE*) gene (Cys282 Tyr, His63Asn, Ser65Cys) of classic hemochromatosis reduce the endocytic uptake of diferric transferrin by the transferrin receptor-1 at the basolateral membrane of the intestinal epithelium. Hepcidin is the defective gene of juvenile hemochromatosis (type 2, subtype B). Elevated hepcidin results in hypoferremia and insufficient supply of iron for erythropoiesis, leading to different types of anemia. The underlying causes of hepcidin elevation in iron-restricted anemias are varied. An example of a genetic cause of hepcidin increase is the familial **iron-refractory iron deficiency anemia** (IRIDA), an autosomal recessive disorder caused by a pathogenic variant in matriptase-2 *(TMPRSS6),* a negative regulator of hepcidin expression. This anemia is characterized by very low plasma iron levels, unresponsiveness to oral iron therapy, and partial correction by parenteral iron. Pathologic variants in the DMT1 transporter *(SLC11A2)* are another cause of **IRIDA**. The development of severe microcytic, hypochromic anemia typifies these patients; however, surprisingly, some of them load iron in the liver.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 386

Intestinal Transplantation in Children with Intestinal Failure

Jorge D. Reyes and Danielle R. Wendel

The introduction of tacrolimus and the development of the abdominal multiorgan procurement techniques allowed the tailoring of various types of intestine grafts that can contain other intraabdominal organs, such as the liver, pancreas, and stomach. The understanding that the liver protects the intestine against rejection demonstrates the interaction between recipient and donor immunocytes (host-versus-graft and graft-versus-host), which under the cover of immunosuppression allows varying degrees of graft acceptance and eventual minimization of drug therapy. *Over the past several years the number of patients placed on the list for and those undergoing intestinal transplantation has decreased, which is a result of improvements in the care of patients with intestinal failure (IF) under a multidisciplinary intestinal care team management.* Advances in care include prevention and treatment of intestinal failure–associated liver disease (IFALD), advances in central venous catheter care, improved prevention of life-threatening central line–associated bloodstream infections, and corrective surgery enhancing absorptive surface and motility, which have led to increased survival and decreased morbidity.

INDICATIONS FOR INTESTINAL TRANSPLANT

IF describes a patient who has lost the ability to maintain nutritional support and adequate fluid requirements needed to sustain growth with their own intestine and is permanently dependent on parenteral nutrition (PN). The majority of these patients have short bowel syndrome as a result of a congenital deficiency or acquired condition (see Chapter 385.6). In others, the cause of IF is a functional disorder of motility or absorption (Table 386.1). Rarely do patients receive intestinal transplants for benign neoplasms, hepatic failure secondary to acute diffuse intestinal infarction, and failure of a first intestinal transplant. The complications of IF include loss of venous access, life-threatening infections, and IFALD.

Table 386.1 Causes of Intestinal Failure in Children Requiring Transplantation

SHORT BOWEL
• Volvulus
• Gastroschisis
• Necrotizing enterocolitis
• Intestinal atresia
• Trauma
INTESTINAL DYSMOTILITY
• Intestinal pseudoobstruction
• MMIHS
• Intestinal aganglionosis (Hirschsprung disease)
ENTEROCYTE DYSFUNCTION
• Microvillus inclusion disease
• Tufting enteropathy
• Other congenital enteropathies
TUMORS
• Invasive intraabdominal desmoid tumor
VASCULAR
• Acute diffuse intestinal infarction with hepatic failure

MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome.

Paucity of Venous Access

Administration of PN requires the insertion of a centrally placed venous catheter, there being only six readily accessible sites (bilateral internal jugular, subclavian, iliac veins). The loss of venous access generally occurs in the setting of recurrent catheter sepsis and thrombosis. Children who have lost three of four upper body central veins (right or left subclavian or internal jugular) or have an occlusion of a brachiocephalic vein should be considered for intestinal transplant evaluation due to the risk of losing the ability to provide PN.

Life-Threatening Infections

Life-threatening infections are usually catheter related, although their frequency is decreasing with improvements in central venous catheter care including antimicrobial locks. The absence of significant length of intestine is often associated with abnormal motility of the residual bowel (producing both delayed and/or rapid emptying), with varying degrees of bacterial overgrowth and translocation as a consequence of intestinal inflammation, loss of intestinal barrier function, and/or loss of gut immunity. This situation contributes to IFALD, multisystem organ failure, and metastatic infectious foci in lungs, kidneys, liver, bone, and the brain.

Liver Disease

The development of IFALD is the most serious complication of IF and may be a consequence of the toxic effects of PN on hepatocytes, a disruption of bile flow as a result of lack of enteral intake, alterations in bile acid metabolism, the frequent occurrence of bacterial overgrowth/translocation, and sepsis with endotoxin release into the portal circulation, all often in the setting of a premature liver. Soy-based intravenous lipids may contribute to liver disease; the incidence of liver disease has decreased with the use of fish oil–based products. IFALD varies in frequency depending on the patient's age and the etiology of the IF; it is most common in neonates with extreme short gut. Initially characterized by cholestasis and inflammation, later phases involve steatosis and fibrosis. Cholestasis in IFALD is defined as direct/conjugated bilirubin >2 mg/dL and more than 20% of total bilirubin after other etiologies have been excluded. The histology includes cholestasis, bile ductular reaction, portal inflammation, steatosis, periportal fibrosis, and liver macrophages. Development of IFALD, as evidenced by cholestasis, is one of the greatest predictors of mortality in children with short bowel syndrome.

TRANSPLANTATION OPERATION

Donor Selection

Intestinal grafts are usually procured from hemodynamically stable, ABO-identical brain-dead donors who have minimal clinical or laboratory evidence suggesting intraabdominal ischemia. Size matching varies according to age of the recipients, and present surgical techniques allow for significant reductions of the graft to achieve abdominal closure. Although the exact effect is still unknown, donor-specific antibodies (DSAs) have been linked to rejection and poor long-term outcomes in the recipient leading to increased use of pretransplant cross-matched results to improve organ allocation, especially in sensitized recipients. Exclusion criteria include a history of malignancy and intraabdominal evidence of infection; systemic viral or bacterial infections are not excluded. Donor preparation has been limited to the administration of systemic and enteral antibiotics. Prophylaxis for graft-versus-host disease with graft pretreatment using irradiation or a monoclonal antilymphocyte antibody has varied over time. Grafts have been preserved with the University of Wisconsin solution, as is the case with other types of abdominal organs.

Types of Intestinal Grafts

Intestinal allografts are used in various forms, either alone (as an **isolated intestine graft**) or as a composite graft, which can include the liver, duodenum, and pancreas (**liver-intestine graft**). When this composite graft includes the stomach, and the recipient operation requires the removal of all of the patient's gastrointestinal tract (as with

intestinal pseudoobstruction) and liver, then this replacement graft is known as a **multivisceral graft**.

The procurement of these various types of grafts focuses on the preservation of the arterial vessels of celiac and/or superior mesenteric arteries, as well as appropriate venous outflow, which would include the superior mesenteric vein or the hepatic veins in the composite grafts. The larger composite grafts inherently retain the celiac and superior mesenteric arteries; this includes multivisceral grafts, liver plus small bowel grafts, and *modified multivisceral grafts* in which the liver is excluded, but the entire gastrointestinal tract is replaced, including the stomach. The isolated intestine graft retains the superior mesenteric artery and vein. This graft can be accomplished with preservation of the vessels going to the pancreas, when that organ has been allocated to another recipient. The graft that is to be used in a particular recipient is dissected out in situ and then removed after cardiac arrest of the donor, with core cooling of the organs, using an infusion of preservation solution (Fig. 386.1).

Various modifications in these grafts have included the preservation of visceral ganglia at the base of the arteries, the inclusion of donor duodenum and pancreas for the liver and intestine graft, the inclusion of colon, the reduction of the liver graft (into left or right side) and variable reduction of the intestine graft, and living donor intestine (4-foot segment of ileum) graft.

The Recipient Operation

Because many children have had multiple previous abdominal operations, intestinal transplantation can be a formidable technical challenge; most children require replacement of the liver because of IFALD and often present with advanced liver failure. Transplantation of an isolated intestinal allograft involves exposure of the lower abdomen, infrarenal aorta, and inferior vena cava. Placement of vascular homografts using donor iliac artery and vein to these vessels allows arterialization and venous drainage of the intestinal graft. In patients who have retained their intestine and then undergo an enterectomy at the time of transplantation, use of the native superior mesenteric vessels is feasible.

Transplantation of a larger composite graft requires the removal and replacement of the native liver in the liver with intestine transplant, and complete abdominal exenteration in the multivisceral transplant. In a similar fashion, the infrarenal aorta is exposed for placement of an arterial conduit graft (donor thoracic aorta) for arterialization of the graft. The venous drainage is achieved to the retained hepatic veins, which are fashioned to a single conduit for anastomosis to the allograft liver.

The intestinal anastomosis to native proximal and distal bowel is performed, leaving an enterostomy of distal allograft ileum; this will be used for routine posttransplantation surveillance endoscopy and biopsy. This ostomy is closed 3-6 months after transplantation (Fig. 386.2).

POSTOPERATIVE MANAGEMENT

Immunosuppression

Successful immunosuppression for intestinal transplantation occurred with the introduction of tacrolimus in addition to corticosteroids. This required high levels of tacrolimus (in the nephrotoxic range), and although initial success rates were high, they were followed by rejection

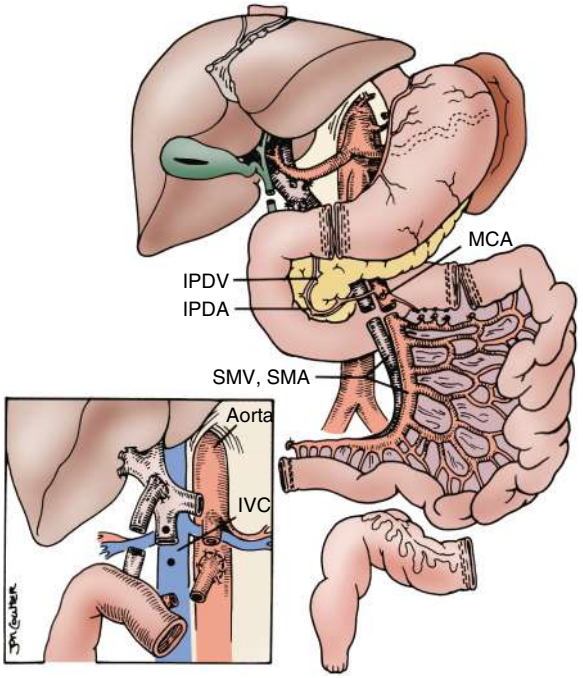

Fig. 386.1 Various abdominal organs can be dissected in situ, providing isolated or composite grafts to fit the individual patient's needs. Separation of intestine and pancreas is feasible, with preservation of the inferior pancreaticoduodenal artery *(IPDA)* and vein *(IPDV)*. The use of vascular grafts from the donor allow connections to the superior mesenteric pedicle (artery *[SMA]* and vein *[SMV]*) to aorta and inferior vena cava *(IVC)* or portal vein *(inset)*. MCA, Major coronary artery. *(From Abu-Elmagd K, Fung J, Bueno J, et al. Logistics and technique for procurement of intestinal, pancreatic and hepatic grafts from the same donor. Ann Surg. 2000;232:680–697.)*

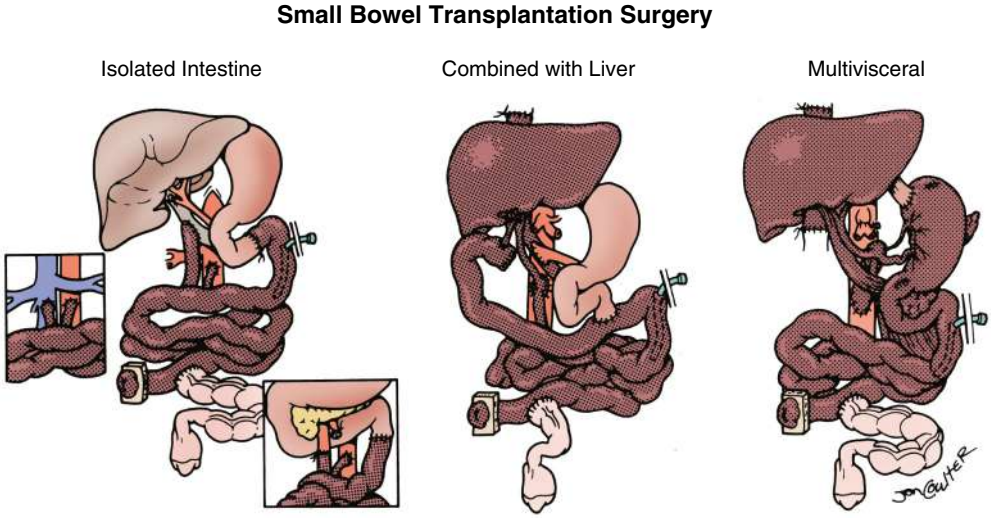

Fig. 386.2 Three basic intestinal transplant procedures (the graft is *shaded*). With the isolated intestine, the venous outflow may be to the recipient portal vein, inferior vena cava *(inset left)*, or superior mesenteric vein *(inset right)*. With the composite grafts, which include the liver, the arterialization is from the aorta with venous drainage out from the liver graft to the recipient inferior vena cava.

rates of >80%, infection, and late drug toxicities, resulting in a gradual loss of grafts and patients. The next generation of protocols incorporated the addition of other agents, such as azathioprine, cyclophosphamide, induction with an interleukin (IL)-2 antibody antagonist, mycophenolate mofetil, and rapamycin. This modification resulted in a decreased incidence in the severity of initial rejection; the inability to decrease immunosuppression later did not allow for stabilization of long-term survival. The introduction of induction therapy has resulted in improved transplant survival as a result of a significant decrease in the incidence of rejection, permitting the gradual decrease of immunosuppressive drug therapy, resulting in a decline in drug toxicity events and infections. The most common induction regimen used is T-cell–depleting agents followed by IL-2 receptor antagonists. A mainstay of maintenance immunosuppression is tacrolimus and prednisone dual therapy, although many centers add mycophenolate mofetil or rapamycin for triple-drug regimens when patients have had episodes of rejection. By 1 year the majority of patients are on tacrolimus monotherapy.

Allograft Assessment

There are no simple laboratory tools that allow assessment of the intestinal allograft. The gold standard for diagnosis of intestinal allograft rejection has been serial endoscopic surveillance and biopsies through the allograft ileostomy. Clinical signs and symptoms of rejection or infection of the allograft can overlap and mimic each other, producing either diarrhea or complete ileus with pseudoobstruction syndromes, abdominal pain, or gastrointestinal bleeding. Any changes in clinical status should warrant thorough evaluation for rejection with endoscopic biopsies and an evaluation for opportunistic infection, malabsorption, and other enteral infections.

The diagnosis of *acute rejection* is based on seeing destruction of crypt epithelial cells from apoptosis, in association with a mixed lymphocytic infiltrate. These histologic findings may or may not correlate with endoscopic evidence of injury, which varies from diffuse erythema and friability to ulcers and, in cases of severe rejection, exfoliation of the intestinal mucosa. *Chronic rejection* of the allograft can be diagnosed only through full-thickness sampling of the intestine, which shows the typical vasculopathy that can result in progressive ischemia of the allograft.

Rejection and Graft-Versus-Host Disease

Acute rejection rates for the intestinal allograft are significantly higher than with any other organ, in the range of 60–70%, and severe rejection requiring the use of antilymphocyte antibody preparations may be as high as 30%. Triple-drug regimens and the use of IL-2 antibody inhibitors have resulted in significant decreases in rejection rates; nonetheless, the amount of immunosuppression was incompatible with improvements in long-term patient and graft survival. Rejection rates of 40% are achievable with the use of antilymphocyte globulin. These protocols induce varying degrees of *prope tolerance (or almost tolerant)*, which can eventually allow for minimization of immunosuppression, thus reducing the risk of drug toxicity and infection. Vascular rejection has been an uncommon occurrence, and chronic rejection has been seen in approximately 10–15% of cases.

Many intestine transplant recipients are immunologically sensitized, increasing the risk of DSA formation. DSA can be pre-formed before transplant or develop de novo afterward. While the negative effects of DSA have been recognized in other types of solid organ transplant for years, the effects in intestinal transplants are less clear. Studies show increased episodes of both acute and chronic rejection as well as graft loss in recipients with positive DSA antibody mediated rejection.

Graft-versus-host disease is infrequent but potentially life-threatening; the mortality rate exceeds 80%, and most recipients die from infectious complications from bone marrow failure. The incidence seen in intestinal transplantation is 5–10% with increased risk associated with liver inclusive grafts. Although no standard treatment is available, early diagnosis, prevention of infection, and initiation of treatment with corticosteroids as soon as possible may improve outcomes.

Infections

Infectious complications are the most significant cause of morbidity and mortality after intestinal transplantation. The most common is infectious enteritis although there are also bacterial, fungal, and polymicrobial infections that occur as a result of a need for venous catheter placement in the immediate posttransplant period or during episodes of intestinal graft dysfunction. Infections as a consequence of immunosuppressive drug management are from cytomegalovirus (CMV; 22% incidence), Epstein-Barr virus (EBV; 21% incidence), and adenovirus enteritis (40% incidence). Despite improvements in monitoring and preventative measures, CMV remains the most common viral infection postintestinal transplantation. CMV may be acquired from blood transfusions, reactivation of endogenous viruses, or the donated allograft. The highest-risk recipients for CMV infection are those who are immunologically naïve and receive an allograft from a donor who is seropositive. The two CMV prevention strategies commonly employed are universal prophylaxis and preemptive therapy. Consensus guidelines recommend prophylaxis treatment for high-risk patients (donor+/recipient–). The preferred drugs for CMV prophylaxis are ganciclovir and oral valganciclovir.

Patients at the highest risk for EBV infection are those who are seronegative at the time of transplantation and those requiring a high-burden immunosuppressive therapy to maintain their graft. EBV disease varies from asymptomatic viremia to **posttransplant lymphoproliferative disorder (PTLD)**. The incidence of EBV-related PTLD is highest in patients receiving intestinal allografts compared to liver, heart, or kidney. Children have a higher incidence of PTLD compared to adults and are most likely to have EBV + PTLD. Early diagnosis and prevention of PTLD is essential, and the mainstay of therapy is to reduce immunosuppression, although some patients have required chemotherapy. The use of anti–B-cell monoclonal antibodies, such as the anti-CD20 antibody rituximab, in PTLD has been successful as noted in anecdotal reports. Successful management of these viral infections is achieved through early detection and preemptive therapy, for both CMV and EBV, before the development of a serious life-threatening infection. This approach has improved outcomes for CMV (see Chapters 223, 301, and 302).

Outcomes

Intestinal transplantation is the standard of care for children with IF who have significant complications of PN and can no longer tolerate such therapy. Graft survival at 1 and 5 years are ~68% and 50%, respectively. One-year graft survival was associated with first-time transplantation and liver-inclusive grafts, whereas poor overall graft survival was associated with retransplantation. Patient survival was associated with elective status of the procedure versus hospitalized status with sepsis continuing to be the most significant factor leading to patient death. Colon inclusion was associated with improved rates of enteral autonomy, which increased in general over the recent decades. Rejection remained the main factor associated with long-term graft loss with decreasing contributions from PTLD and technical complications. Combined adult and pediatric registry data show stable long-term graft survival of approximately 40%, although single centers have reported rates as high as 60–70%. Rehabilitation and quality-of-life studies have shown that more than 80% of survivors reach total independence from PN and have meaningful life activities. Consequently, there has been a shift in efforts to improve long-term outcomes and quality of life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 387

Acute Gastroenteritis in Children

E. Adrianne Hammershaimb and Karen L. Kotloff

The term *gastroenteritis* denotes inflammation of the gastrointestinal tract, most commonly the result of infections with bacterial, viral, or parasitic pathogens (Tables 387.1-387.3). Many of these infections are food-borne illnesses (Table 387.4). Several clinical syndromes are often described because they have different (albeit overlapping) etiologies, outcomes, and treatments. **Acute gastroenteritis** (AGE) captures the bulk of infectious cases of diarrhea. The most common manifestations are diarrhea and vomiting, which can also be associated with systemic features such as abdominal pain and fever. **Dysentery** refers to a syndrome characterized by frequent small stools containing visible blood, often accompanied by fever, tenesmus, and abdominal pain. This should be distinguished from bloody diarrhea (larger volume bloody stools with less systemic illness) because the etiologies may differ. **Prolonged** (lasting 7-13 days) and **persistent diarrhea** (lasting 14 days or longer) are important because of their impact on growth and nutrition.

BURDEN OF CHILDHOOD DIARRHEA

Although global mortality due to diarrheal diseases has declined substantially (39%) during the past 2 decades, it remains unacceptably high. In 2019 diarrheal disease caused an estimated 500,000, or 10% of all deaths in children under 5 years, making it the third leading cause of under-5 child mortality worldwide. Approximately 88% of those deaths occurred in sub-Saharan Africa and South Asia (71% and 17%, respectively). Over the same period, a smaller decline (10%) was observed in the incidence of diarrheal disease among children younger than 5 years. Almost 1 billion episodes occurred in 2019 worldwide, resulting in an estimated 45.5 million childhood disability-adjusted life years. The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of preventive rotavirus vaccination and improved case management of diarrhea, as well as improved nutrition of infants and children. These interventions have included widespread home- and hospital-based oral rehydration solution (ORS) therapy and improved nutritional management of children with diarrhea.

In addition to the risk of mortality, high rates of diarrhea can be associated with long-term adverse outcomes. Diarrheal illnesses, especially episodes among young children that are recurrent, prolonged, or persistent, can be associated with malnutrition, stunting, micronutrient deficiencies, and significant deficits in psychomotor and cognitive development.

PATHOGENS

Rotavirus is the most common cause of AGE among children throughout the world. Several other viruses occur less frequently. Norovirus and sapovirus are the two genera of *caliciviruses* that cause AGE. Norovirus genogroup II, genotype 4 (GII.4) has predominated globally since the mid-1990s. Among the more than 50 serotypes of adenovirus, 40 and 41 are most often associated with diarrhea. Astroviruses are identified less often (see Table 387.1). SARS-CoV-2 is also recognized as a cause of AGE in adults and in children, both as a manifestation of COVID-19 and as a symptom of multisystem inflammatory syndrome in children (MIS-C).

The major bacterial pathogens that cause AGE are nontyphoidal *Salmonella* (NTS), *Shigella, Campylobacter*, and *Yersinia* (see Table 387.2). Five pathotypes of *Escherichia coli* infect humans: Shiga toxin–producing (STEC), also known as enterohemorrhagic (EHEC), enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroaggregative (EAEC), and enteroinvasive (EIEC). Two serogroups of *Vibrio cholerae* (O1 and O139) produce epidemic cholera and cause nearly all sporadic cases. *Clostridioides difficile* (formerly *Clostridium difficile*) disease can be both nosocomial and community acquired in children. Bacterial pathogens that cause food-borne illness due to their ability to produce emetic and/or enterotoxins include *Bacillus cereus*, *Clostridium perfringens*, and *Staphylococcus aureus.* The significance of isolating *Aeromonas* and *Plesiomonas* in a diarrheal stool remains uncertain.

Giardia duodenalis, Cryptosporidium spp., *Cyclospora cayetanensis*, and *Entamoeba histolytica* are the most common parasites that cause diarrhea in the United States (see Table 387.3). At least 13 species of *Cryptosporidium* are associated with human disease, but *C. hominis* and, to a lesser extent, *C. parvum* are most common. The genus *Entamoeba* comprises six species that colonize humans, but only *E. histolytica* is considered a human pathogen. *G. duodenalis* (formerly *G. lamblia* and *G. intestinalis*) is a flagellate protozoan that infects the small intestine and biliary tract. Other protozoa that uncommonly cause AGE are *Cystoisospora belli* (formerly *Isospora belli*) and *Blastocystis hominis.*

EPIDEMIOLOGY IN THE UNITED STATES AND OTHER MIDDLE- AND HIGH-INCOME COUNTRIES

Risk Factors Related to Economic Development

Insufficient access to adequate hygiene, sanitation, and clean drinking water are the main factors leading to the heavy burden of AGE in developing countries. Although the severe consequences have become uncommon, infectious AGE remains ubiquitous in middle- and high-income countries. Economic development poses its own risks for transmission of enteric pathogens. The ability to mass produce and widely distribute food has led to large multistate outbreaks of AGE due to NTS, STEC, and other agents (see Table 387.4). Globalization has cultivated a taste for tropical fruits and vegetables, creating a mechanism for importation of novel pathogens. The increasing frequency of antimicrobial resistance among bacteria that cause AGE has been linked to the use of antibiotics as growth promotors for animals bred for food. Recreational swimming facilities and water treatment systems have provided a vehicle for massive outbreaks of *Cryptosporidium*, a chlorine-resistant organism. Venues serving catered food to large groups of people, such as hotels and cruise ships, are conducive to outbreaks, as are institutions where hygiene is compromised, such as daycare centers, prisons, and nursing homes. Hospitalization and modern medical therapy have created a niche for nosocomial *C. difficile* toxin infection. Childcare and school-based outbreaks are often due to norovirus and *Shigella* spp.

Endemic Diarrhea

In the United States, rotavirus was the most common cause of medically attended AGE among children younger than 5 years until the introduction of rotavirus vaccine for routine immunization of infants in 2006. Before 2006, annual epidemics swept across the country beginning in the southwest in November and reaching the northeast by May, affecting nearly every child by the age of 2 years. Since vaccine introduction, healthcare utilization for AGE has decreased markedly at a considerable cost savings. Norovirus is now the leading cause of AGE among children in the United States seeking healthcare, followed by sapovirus, adenoviruses 40 and 41, and astrovirus (see Table 387.1).

Laboratory-Based Surveillance for Food-Borne Pathogens

The most comprehensive resource for describing the burden of bacterial and protozoal diarrhea in the United States is the Foodborne Diseases Active Surveillance Network (FoodNet) maintained by the Centers for Disease Control and Prevention (CDC) (see Table 387.4). FoodNet performs active laboratory-based surveillance of nine bacterial and protozoal enteric pathogens commonly transmitted by food. Among children 0-19 years of age in 2019, NTS was most common, followed by *Campylobacter*, STEC, and *Shigella*. *Vibrio* and *Yersinia* were the least common. As of January 1, 2018, FoodNet has stopped conducting active surveillance for *Cryptosporidium*;

Table 387.1 Etiologies of Viral Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Caliciviruses (including noroviruses and sapoviruses)	12-48 hr	Nausea, vomiting, abdominal cramping, diarrhea, fever, myalgia, and some headache	1-3 days	Person-to-person (fecal-oral and aerosolized vomit), and food, water, and fomites contaminated with human feces	Very contagious (chlorine and heat resistant); produces large outbreaks in closed settings such as cruise ships, daycares, schools, and restaurants Shellfish	Multiplex PCR RT-qPCR of stool and vomit is the preferred method for outbreak investigation, available in public health laboratories Immunoassays for norovirus have poor sensitivity Norovirus genotyping (GI and GII) is performed by CDC
Rotavirus (groups A-C), astrovirus, and enteric adenovirus (serotypes 40 and 41)	2-4 days	Often begins with vomiting, followed by watery diarrhea, low-grade fever	3-8 days	Person-to-person (fecal-oral), fomites Aerosol transmission of rotavirus may be possible	Nearly all infants and children worldwide were infected by 2 yr of age before vaccine introduction	Multiplex PCR Immunoassays for rotavirus and enteric adenovirus
SARS-CoV-2	2-14 days	Acute COVID-19: Fever, chills, cough, shortness of breath, difficulty breathing, fatigue, myalgia, headache, anosmia, dysgeusia, sore throat, congestion, runny nose, nausea, vomiting, diarrhea is usually nonbloody but may be blood tinged MIS-C: fever, abdominal pain, vomiting, diarrhea, rash, conjunctivitis, dizziness or light-headedness	Acute COVID-19: May be self-limited, less than 2 wk Prolonged symptoms may last months (e.g., fatigue, anosmia, dysgeusia) MIS-C: unclear; often fatal if untreated	Respiratory aerosols and droplets; airborne precautions recommended	Unvaccinated immune status Local epidemiology and lack of transmission mitigating precautions	RT-PCR (may be included in a multiplex PCR) Antigen immunoassay Serology (may be useful for the diagnosis of MIS-C but not for acute COVID-19)

Note: Commercially available denotes that the diagnostic tests have been cleared by the U.S. Food and Drug Administration
RT, Real-time reverse transcriptase; PCR, polymerase chain reaction; CDC, Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children.
Adapted from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. *MMWR.* 2004;53(RR-4):1–33.

in 2015, *Cryptosporidium* was the fourth most commonly identified food-borne pathogen in U.S. children less than 19 years of age. Children younger than 5 years have the highest incidence of food-borne diarrheal disease, whereas the elderly have the highest frequency of hospitalization and death. Only 5% of these infections are associated with recognized outbreaks.

Toxin-mediated food-borne gastroenteritis may be infectious or noninfectious. Pathogens that cause toxin-mediated food-borne gastroenteritis include *S. aureus*, *B. cereus*, and *C. perfringens*. Ingestion of food contaminated with the preformed *S. aureus* heat-stable enterotoxin types A to E causes staphylococcal food poisoning. *B. cereus* produces two forms of gastrointestinal illness, one resembling staphylococcal food poisoning and caused by a preformed emetic toxin, and the other caused by a group of three enterotoxins formed in vivo. Ingested *C. perfringens* sporulates in the small intestine, releasing a heat-labile, single-polypeptide enterotoxin. Noninfectious agents may also cause food-borne gastrointestinal symptoms due to a direct toxic effect of the food (mushrooms), contamination (heavy metals), or fish or shellfish toxins (Table 387.5).

Diarrhea Outbreaks

The U.S. Foodborne Disease Outbreak Surveillance System quantifies enteric infections associated with food-borne outbreaks. In 2017, among all age-groups, norovirus was the most common agent (49%), followed by NTS (19%). Less common were *C. perfringens* (6%), *Campylobacter* (4%), STEC (3%), *S. aureus* (2%), and *B. cereus* (2%), followed much less often (each 1%) by *Clostridium botulinum, Shigella, Cryptosporidium, Yersinia, Listeria, Vibrio parahaemolyticus,* and *Shigella*. Outbreaks of enteric pathogens propagated by direct person-to-person contact are most often caused by norovirus and *Shigella* species; other pathogens include NTS, rotavirus, *Giardia*, *Cryptosporidium*, *C. difficile,* and *Campylobacter jejuni.*

Nosocomial Diarrhea

C. difficile is the most common cause of healthcare-associated infection in the United States. Severe disease occurs most often in those with predisposing conditions (e.g., recent antibiotics, gastric acid suppression, immunosuppression, gastrointestinal comorbidities). In contrast to adults, rates of colostomy and in-hospital mortality have not increased in children despite increasing rates of community and

Table 387.2 Etiologies of Bacterial Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Bacillus cereus (preformed emetic toxin)	1-6 hr	Sudden onset of severe nausea and vomiting; diarrhea may be present	24 hr	Soil and water	Improperly refrigerated cooked or fried rice, meats	Routine stool culture to look for overabundance of pathogen, does not detect toxins Reference laboratory used for outbreaks
B. cereus (enterotoxins formed in vivo)	8-16 hr	Abdominal cramps, watery diarrhea; nausea and vomiting may be present	1-2 days	Soil and water	Meats, stews, gravies, vanilla sauce	Routine stool culture to look for overab undance of pathogen, does not detect toxins Reference laboratory used for outbreaks
Campylobacter jejuni	1-5 days	Diarrhea, (10–20% of episodes are prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Wild and domestic animals and animal products	Raw and undercooked poultry, unpasteurized milk, untreated surface water	Stool culture on selective agar, microaerobic conditions, and incubation at 42°C Antigen detection by EIA Multiplex PCR
Clostridioides difficile toxin	Unknown Can appear weeks after antibiotic cessation	Mild to moderate watery diarrhea that can progress to severe, pseudomembranous colitis with systemic toxicity	Variable	Person-to-person (fecal-oral), mostly within healthcare facilities	Immunosuppression, intestinal disease or surgery, prolonged hospitalization, antibiotics	PCR,† immunoassay Multistep approach using EIA for GDH and toxins A and B ± NAAT
Clostridium perfringens toxin	8-16 hr	Watery diarrhea, nausea, abdominal cramps; fever is rare	1-2 days	Environment, human and animal intestines	Meats, poultry, gravy, dried or precooked foods with poor temperature control	None Reference laboratory used for outbreaks
Escherichia coli O157:H7 and other *Shiga* toxin–producing *E. coli* (STEC)	1-9 days (usually 3-4 days)	Watery diarrhea that becomes bloody in 1-4 days in ~40% of infections; in contrast to dysentery, bloody stools are large volume and fever/toxicity is minimal More common in children <4 yr old	4-7 days	Food and water contaminated with feces from ruminants; infected people and animals (fecal-oral); predominantly high-resource countries	Undercooked beef especially hamburger, unpasteurized milk and juice, raw fruits, and petting zoos, recreational swimming, daycare Antimotility agents and antibiotics increase risk of hemolytic uremic syndrome	Multiplex PCR to detect *E. coli* O157:H7 and non-O157:H7 *Shiga* toxin genes simultaneously with stool culture on sorbitol-MacConkey agar Immunoassay for O157:H7; presumptive *E. coli* O157:H7 isolates and all *Shiga* toxin-positive stool specimens that did not yield a presumptive *E. coli* O157:H7 isolate should be sent to a public health laboratory to identify non-O157:H7 STEC and for serotyping and whole genome sequencing
Enterotoxigenic *E. coli* (ETEC)	1-5 days	Watery diarrhea, abdominal cramps, some vomiting	3-7 days	Water or food contaminated with human feces	Infants and young children in LMIC and travelers	Multiplex PCR,† or reference laboratory
Salmonella, nontyphoidal	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Domestic poultry, cattle, reptiles, amphibians, birds	Ingestion of raw or undercooked food, improper food handling, travelers, immunosuppression, hemolytic anemia, achlorhydria, contact with infected animal	Multiplex PCR Routine stool culture

Continued

Table 387.2 Etiologies of Bacterial Gastroenteritis—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Shigella spp.	1-5 days (up to 10 days for *S. dysenteriae* type 1)	Abdominal cramps, fever, diarrhea Begins with watery stools that can be the only manifestation or proceed to dysentery	5-7 days	Infected people or fecally contaminated surfaces (fecal-oral)	Poor hygiene and sanitation, crowding, travelers, daycare, MSM, prisoners	Multiplex PCR Routine stool culture
Staphylococcus aureus (preformed enterotoxin)	1-6 hours	Sudden onset of severe nausea and vomiting Abdominal cramps Diarrhea and fever may be present	1-3 days	Birds, mammals, dairy, and environment	Unrefrigerated or improperly refrigerated meats, potato and egg salads, cream pastries	Routine stool culture to look for overabundance of pathogen, does not detect toxins Reference laboratory used for outbreaks
Vibrio cholerae O1 and O139	1-5 days	Watery diarrhea and vomiting, which can be profuse and lead to severe dehydration and death within hours	3-7 days	Food and water contaminated with human feces	Contaminated water, fish, shellfish, street-vended food from endemic or epidemic settings; blood group O, vitamin A deficiency	Stool culture (requires special TCBS media so laboratory must be notified) Rapid test is useful in epidemics but does not provide susceptibility or subtype so should not be used for routine diagnosis. FDA-approved multiplex PCR
Vibrio parahaemolyticus	2-48 hr	Watery diarrhea, abdominal cramps, nausea, vomiting Bacteremia and wound infections occur uncommonly, especially in high-risk patients, e.g., with liver disease and diabetes	2-5 days	Estuaries and marine environments; currently undergoing pandemic spread	Undercooked or raw seafood, such as fish, shellfish	Culture of stool, wound, or blood depending on suspected source Requires special TCBS media so laboratory must be notified Multiplex PCR
Vibrio vulnificus	1-7 days	Vomiting, diarrhea, abdominal pain Bacteremia and wound infections, particularly in patients with chronic liver disease (presents with septic shock and hemorrhagic bullous skin lesions)	2-8 days	Estuaries and marine environments	Undercooked or raw shellfish, especially oysters, other contaminated seafood, and open wounds exposed to seawater	Culture of stool, wound, or blood depending on suspected source Requires special TCBS media so laboratory must be notified Multiplex PCR
Yersinia enterocolitica and *Y. pseudotuberculosis*	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised; pseudoappendicitis occurs primarily in older children	5-7 days (sometimes >10 days) usually self-limiting	Swine products, occasionally person-to-person and animal-to-humans, water-borne, blood-borne (can multiply during refrigeration)	Undercooked pork, improper food handling, unpasteurized milk, tofu, contaminated water, transfusion from a bacteremic person, cirrhosis, chelation therapy	Stool culture or multiplex PCR Culture requires special media and incubation at 25°C. Not performed in many laboratories unless requested When clinically relevant, can isolate from vomit, blood, throat, lymph nodes, joint fluid, urine, and bile

†FDA-cleared multiplex PCR assays are available but cannot determine antimicrobial susceptibility to guide treatment or speciate the organism for outbreak investigation.

EIA, Enzyme immunoassays; PCR, polymerase chain reaction; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; LMIC, low- and middle-income countries; MSM, men who have sex with men; TCBS, thiosulfate-citrate-bile salts-sucrose agar; FDA, U.S. Food and Drug Administration.

Adapted from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. *MMWR*. 2004;53(RR-4):1–33.

Table 387.3 Etiologies of Parasitic Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Cryptosporidium	1-11 days	Diarrhea (usually watery), bloating, flatulence, cramps, malabsorption, weight loss, and fatigue may wax and wane Persons with AIDS or malnutrition have more severe disease	1-2 wk; may be remitting and relapsing over weeks to months	Person-to-person (fecal-oral), contaminated food and water (including municipal and recreational water contaminated with human feces)	Infants 6-18 mo of age living in endemic settings in LMIC, patients with AIDS, childcare settings, drinking unfiltered surface water, MSM, Ig deficiency	Immunoassays, PCR, and multiplex PCR are most sensitive Microscopy (direct fluorescent antibody staining is preferable to modified acid fast)
Cyclospora cayetanensis	1-11 days	Same as *Cryptosporidium*	Same as *Cryptosporidium*	Fresh produce (imported berries, lettuce)	Travelers, consumption of fresh produce imported from the tropics	Fecal microscopy, multiplex PCR May need to examine water or food
Entamoeba histolytica	2-4 wk	Gradual onset of cramps, watery diarrhea and often dysentery with cramps but rarely fever Can wax and wane with weight loss Dissemination to live and other organs can occur	Variable; may be protracted (several weeks to several months)	Fecal-oral transmission Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Persons living in or traveling to LMIC, institutionalized persons, MSM	Immunoassay or multiplex PCR are preferred Fecal microscopy of fresh stool for cysts and parasites on at least three samples can also be performed Serology for extraintestinal infections
Giardia duodenalis	1-4 wk	Diarrhea, stomach cramps, gas, weight loss; symptoms may wax and wane	2-4 wk	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Hikers drinking unfiltered surface water, persons living in or traveling to LMIC, MSM, IgA deficiency	Immunoassay or multiplex PCR preferred Fecal microscopy for ova and parasites can be performed; at least three samples recommended

LMIC, Low- and middle-income countries; PCR, polymerase chain reaction; MSM, men having sex with men.

hospital-acquired *C. difficile* infection, suggesting that *C. difficile* may be less pathogenic in children. Moreover, high rates of asymptomatic carriage among children younger than 2 years create diagnostic uncertainty, so children <1 year should never be routinely tested; testing and treatment in children 1-2 years of age should be reserved for those in whom noninfectious or other infectious causes have been ruled out, and children ≥2 years may be tested if they have prolonged or worsening diarrhea and relevant risk factors or exposures (see Table 387.2).

Zoonotic Transmission

Many diarrheal pathogens are acquired from animal reservoirs (see Tables 387.1-387.3). The ability of NTS to undergo transovarian passage in hens allows infection of intact grade A pasteurized eggs, a source of multiple large outbreaks. Although *Campylobacter* is prevalent in poultry, its lower outbreak potential has been attributed to its lack of transovarian spread in hens and stringent growth requirements, which limit its ability to replicate in foods. On the other hand, *Campylobacter* has an extensive reservoir in domestic and wild animals and remains a major cause of sporadic bacterial foodborne disease in industrialized countries, usually from consumption of contaminated chicken meat, beef, and milk. Its ubiquitous animal reservoir also has resulted in widespread contamination of surface waters, resulting in diarrhea among hikers and campers who drink from streams, ponds, and lakes in wilderness areas. The predilection for STEC to asymptomatically colonize the intestines of ruminant animals explains why unpasteurized dairy products, fruits harvested from fields where cattle graze, and undercooked hamburger are common vehicles. The major animal reservoir for *Yersinia* is pigs, so ingestion of raw or undercooked pork products is an important risk factor. Pets can be the source of NTS (asymptomatic young birds, amphibians, and reptiles), *Campylobacter*, and *Yersinia* (puppies and kittens that are usually ill with diarrhea).

Seasonality

Seasonality provides a clue to implicate specific pathogens, although patterns may differ in tropical and temperate climates. Rotavirus and norovirus peak in cool seasons, while enteric adenovirus infections occur throughout the year, with some increase in summer. *Salmonella*, *Shigella*, and *Campylobacter* favor warm weather, whereas the tendency for *Yersinia* to tolerate cold manifests as a winter seasonality, with higher prevalence in northern countries, and the ability to survive in contaminated blood products during refrigeration.

EPIDEMIOLOGY IN LOW- AND MIDDLE-INCOME COUNTRIES

Large epidemiologic studies conducted during the previous decade have advanced our understanding of the etiology of diarrheal disease among children in low-resource countries. The Global Enteric Multicenter

Table 387.4 Number of Laboratory-Diagnosed Bacterial and Parasitic Infections, Hospitalizations, Deaths, Outbreak-Associated Infections, and Crude Incidence by Pathogen — Foodborne Diseases Active Surveillance Network, 10 U.S. sites,* 2021†

	2021				
		NO. (%)			
PATHOGEN	NUMBER OF INFECTIONS§	HOSPITALIZATIONS¶	DEATHS**	OUTBREAK-ASSOCIATED INFECTIONS††	CRUDE INCIDENCE§§
Total	22,019	5,359 (24)	153 (0.7)	861 (4)	—
Campylobacter	8,974	1,822 (20)	33 (0.4)	51 (0.6)	17.8
Salmonella	7,148	1,974 (28)	52 (0.7)	597 (8)	14.2
STEC	2,542	600 (24)	10 (0.4)	79 (3)	5.0
Shigella	1,699	532 (31)	8 (0.5)	67 (4)	3.4
Yersinia	683	146 (21)	3 (0.4)	2 (0.3)	1.4
Vibrio	461	117 (25)	9 (2)	8 (2)	0.9
Listeria	148	140 (95)	37 (25)	9 (6)	0.3
Cyclospora	364	28 (8)	1 (0.3)	48 (13)	0.7

*Data were obtained from laboratories in Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, and selected counties in California, Colorado, and New York.† 2021 data are preliminary.§ Bacterial infections diagnosed by culture or CIDT. *Cyclospora* infections diagnosed by microcopy or polymerase chain reaction.¶ Admission to an inpatient unit or an observation stay of >24 hours within 7 days before or after specimen collection or determined to be related to the infection if beyond this time frame. Absolute change in percentage of infections resulting in hospitalization during 2021 compared with annual average for 2016–2018: *Campylobacter* (0.3), *Salmonella* (0.3), STEC (1), *Shigella* (8), *Yersinia* (−4), *Vibrio* (−5), *Listeria* (−2), *Cyclospora* (2), and overall (0.6). Unknown hospitalization status (10% of infections during 2021 and 4% during 2016–2018) was classified as not hospitalized.

**Attributed to infection when deaths occurred during hospitalization or within 7 days after specimen collection for nonhospitalized patients. Absolute change in percentage of infections resulting in death during 2021 compared with annual average for 2016–2018: *Campylobacter* (<0.1), *Salmonella* (0.3), STEC (<0.1), *Shigella* (0.4), *Yersinia* (−0.7), *Vibrio* (−0.2), *Listeria* (6), *Cyclospora* (0.1), and overall (0.2). Unknown death status (8% of infections during 2021 and 3% during 2016–2018) was not classified as a death.†† Generally defined as two or more cases of similar illness associated with a common exposure; some sites also stipulate that illnesses be from more than one household. Absolute change in percentage of outbreak-associated infections during 2021 compared with annual average for 2016–2018: *Campylobacter* (0.2), *Salmonella* (1), STEC (−1), *Shigella* (−1), *Yersinia* (0.2), *Vibrio* (−2), *Listeria* (1), *Cyclospora* (−10), and overall (<0.1). Unknown outbreak-association status (0.02% of infections during 2021 and 0% during 2016–2018) was classified as not outbreak-associated.§§ Cases per 100,000 population. Domestic incidences (cases with no or unknown travel) by pathogen during 2021: *Campylobacter* (17.0), *Salmonella* (13.1), STEC (4.6), *Shigella* (3.0), *Yersinia* (1.3), *Vibrio* (0.8), *Listeria* (0.3), and *Cyclospora* (0.6).

CIDT, Culture-independent diagnostic test; STEC, Shiga toxin–producing *E. coli*.

Modified from Collins JP, Shah HJ, Weller DL, et al. Preliminary incidence and trends of infections caused by pathogens transmitted commonly through food – foodborne diseases active surveillance network, 10 U.S. sites, 2016-2021. *MMWR*. 2022;71(4):1260–1263.

Study (GEMS) evaluated children younger than 5 years living in seven low-income countries in sub-Saharan Africa and South Asia and seeking healthcare for moderate to severe diarrhea (Fig. 387.1). Although a broad array of pathogens was identified, most episodes of moderate to severe diarrhea were attributed to four pathogens: rotavirus, *Cryptosporidium, Shigella*, and ETEC producing heat-stable toxin (ST) either alone or in combination with heat-labile toxin (LT), herein termed ST-ETEC and LT-ETEC, and, to a lesser extent, adenoviruses 40 and 41. On the other hand, several etiologic agents that are common causes of AGE in high-resource settings are notable for their low frequency in resource-limited settings: NTS, STEC, norovirus, and *C. difficile* toxin. The three agents associated with most deaths among children <5 years are rotavirus (29%), *Cryptosporidium* (12%), and *Shigella* (11%). The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) was a study of less severe, community-based diarrhea. Viral causes predominated (36.4% of the overall incidence), but *Shigella* had the single highest attributable incidence (26.1 attributable episodes per 100 child-years).

Host Risk Factors

Most pathogens show an age predilection. The incidence of rotavirus and NTS are highest in infancy. Endemic shigellosis peaks in 1- to 4-year olds, whereas *Campylobacter* and *Cryptosporidium* show a bimodal distribution with the greatest number of reported cases in infants and young children with a secondary peak in young adults. Pandemic *V. cholerae* and *Shigella. dysenteriae* type 1 produce high attack rates and mortality in all age-groups and often afflict displaced persons in emergency settings. Some agents (e.g., NTS, *Shigella, Campylobacter, Yersinia,* and *Cryptosporidium*) are more frequent and more severe when the host is immunocompromised or malnourished.

Additional risks factors for AGE include immunodeficiency, measles, malnutrition, and lack of exclusive or predominant breastfeeding. Malnutrition increases the risk of diarrhea and associated mortality, and moderate to severe stunting increases the odds of diarrhea-associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, South Asia, and Andean Latin America. The risks are especially high with malnutrition, particularly when associated with micronutrient deficiency. Vitamin A deficiency accounts for 157,000 deaths from diarrhea, measles, and malaria. Zinc deficiency is estimated to cause 116,000 deaths from diarrhea and pneumonia.

PATHOGENESIS OF INFECTIOUS GASTROENTERITIS

Intrinsic properties of the organism help to define the mode of transmission and incubation period (Table 387.6). Enteropathogens that are infectious in small inocula (*Shigella,* STEC, norovirus, rotavirus, *G. duodenalis, Cryptosporidium* spp., *C. difficile, E. histolytica*) are readily transmitted by person-to-person contact via the fecal-oral route. Pathogens with larger infectious doses, such as cholera, NTS, ETEC, and *Campylobacter*, generally require food or water vehicles (see Tables 387.1-387.3). Pathogens that produce preformed toxins (*S. aureus, B. cereus* emetic toxin) have shorter incubation periods (1-6 hours) compared with 8-16 hours for those that must elaborate enterotoxins in situ (e.g., *C. perfringens* and *B. cereus* enterotoxin). Incubation periods of 1-5 days are seen with pathogens that attach to the epithelium and elaborate enterotoxins (e.g., *V. cholerae*, ETEC) or cytotoxins (e.g., *S. dysenteriae* type 1 and STEC) or those that invade and disrupt the intestinal epithelium (*Shigella*, NTS, *Campylobacter*, and *Yersinia*). The requirement for protozoa to progress through a life cycle to trigger pathogenic processes results in a more extended incubation period. Other

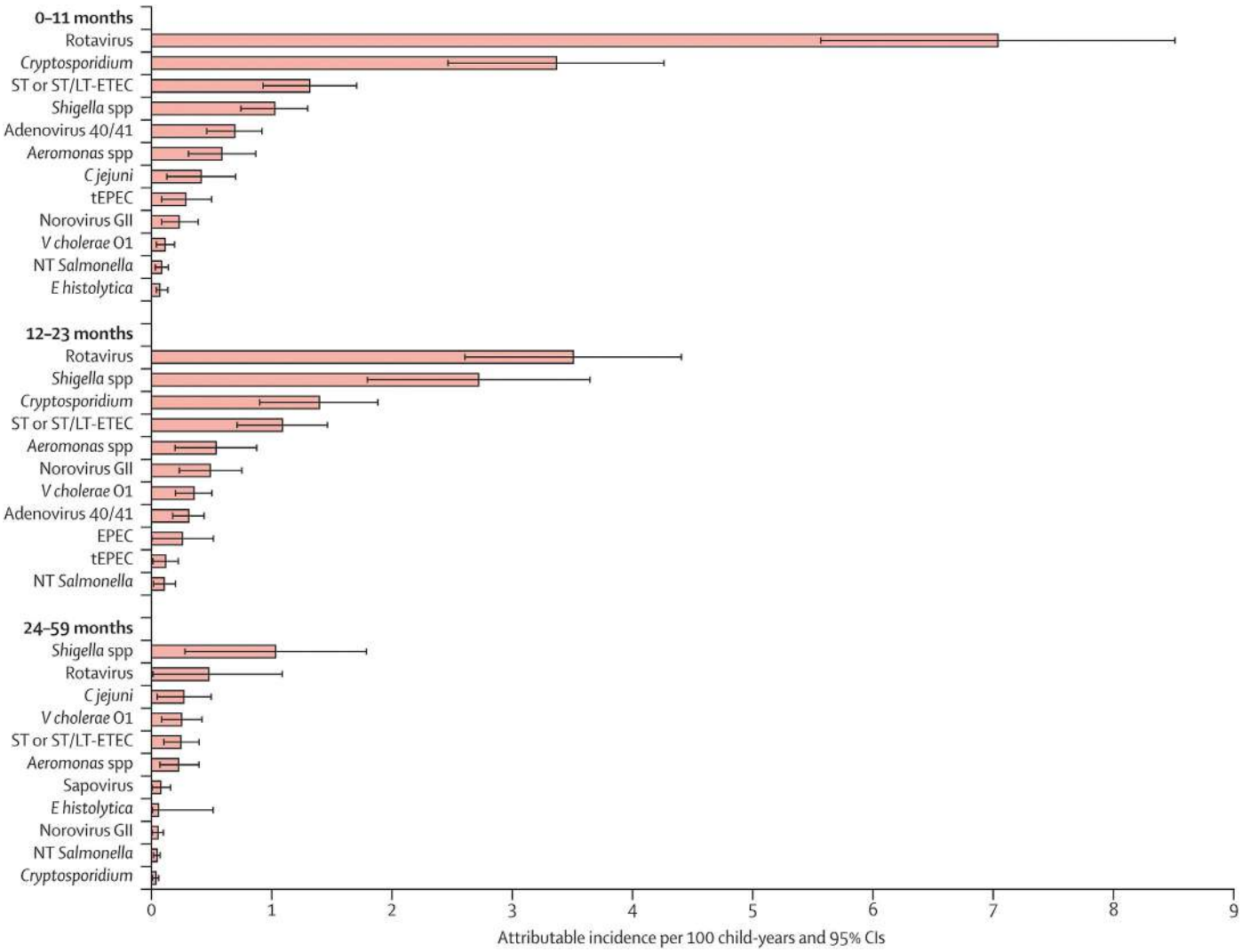

Fig. 387.1 Attributable incidence of pathogen-specific moderate to severe diarrhea per 100 child-years by age stratum, all sites combined. The bars show the incidence rates and the error bars show the 95% confidence intervals. ST/LT-ETEC, heat-stable toxin (ST) / heat labile toxin (LT)-enterotoxigenic *Escherichia coli*; tEPEC, traditional (t) enteropathogenic *Escherichia coli*. *(From Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study. Lancet. 2013;382:209–222. Fig. 4.)*

properties affecting transmissibility are bioavailability as conferred by a copious and/or prolonged fecal shedding, extended infectivity in the environment, and resistance to disinfection (all exhibited by norovirus and *Cryptosporidium*), or a large environmental or animal reservoir (e.g., *Campylobacter*). The ability to circumvent immune surveillance by frequent antigenic changes resulting from recombinational events (e.g., norovirus) or a large serotype diversity (e.g., *Shigella*) maintains a susceptible host population.

Viral AGE causes a cytolytic infection of the small intestinal villus tips resulting in decreased absorption of water, disaccharide malabsorption, inflammation, and cytokine activation. The rotavirus protein NSP4 acts as a viral enterotoxin that causes secretory diarrhea. In addition, rotavirus activates the enteric nervous system, causing decreased gastric emptying and increased intestinal mobility. There is a genetic susceptibility to both rotavirus and norovirus infection that is mediated by histo-blood group antigens on the epithelial cell surface and in mucus secretions (Fig. 387.2).

Pathogens primarily manifesting as secretory diarrhea attach to the surface of the epithelium and stimulate secretion of water and electrolytes by activating adenylate cyclase and raising intracellular cAMP (*V. cholerae* and LT-ETEC) and/or cGMP (ST-ETEC) (Figs. 387.3 and 387.4). The diarrheagenic phenotype of *C. difficile* is attributed to production of toxins A (an enterotoxin) and B (an enterotoxin and cytotoxin). The epidemic hypervirulent NAP1 *C. difficile* also makes binary toxin, which may enhance colonization and augment toxin production.

Shigella, NTS, *Campylobacter*, and *Yersinia* all possess an invasive phenotype and elicit diarrhea by a variety of mechanisms that generally involves elicitation of inflammatory cytokines with or without associated toxin production (Fig. 387.5). The pathogenesis of *Shigella*, the most common cause of bacillary dysentery, has been characterized in greatest detail. Following invasion, *Shigella* induces extensive destruction and inflammation of the intestinal epithelium, producing ulcers and microabscesses that manifest with diarrheal stools containing blood and pus. Production of enterotoxins contributes to secretory diarrhea, which can be seen early in shigellosis or as the sole manifestation. A single serotype of *Shigella*, *S. dysenteriae* type 1, elaborates the Shiga toxin, which increases the severity of illness and is responsible for the development of hemolytic uremic syndrome (HUS).

Cryptosporidia sporozoites released from ingested cysts penetrate intestinal epithelial cells and develop into trophozoites within the intracellular but extracytoplasmic environment. After undergoing asexual multiplication and sexual development, they are released in the colon as infectious oocysts capable of causing autoinfection. Host factors, in particular T-cell function, play a critical role in disease severity. *Cyclospora* cysts are not infectious in freshly passed stools but must sporulate in the environment for 1-2 weeks to become

Table 387.5 Food-Borne Noninfectious Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Antimony	5 min-8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine Can cause eosinophilia	Gastric lavage, BAL (dimercaprol)
Cadmium	5 min-8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr	GI: abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol Children more vulnerable
	3 hr	Neurologic: paresthesias, reversal of hot or cold, pain, weakness				
	2-5 days	Cardiovascular: bradycardia, hypotension, increase in T-wave abnormalities				
Copper	5 min-8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and the developing fetus are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, *Coprinus atramentaria*, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance	Self-limited	Wild mushrooms (cooking might not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care
Mushroom toxins, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood	Usually self-limited	Cured meats, any contaminated foods, spinach exposed to excessive nitrification	Analysis of the food, blood	Supportive care, methylene blue

Table 387.5 Food-Borne Noninfectious Illnesses—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, meiosis	Usually self-limited	Any contaminated food	Analysis of the food, blood	Atropine; 2-PAM (pralidoxime) is used when atropine is not able to control symptoms; rarely necessary in carbamate poisoning
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min-3 hr	Flushing, rash, burning sensation of skin, mouth and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning: 30 min-2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning: few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning: 24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				Elderly are especially sensitive to amnesic shellfish poisoning
Shellfish toxins (paralytic shellfish poisoning)	30 min-3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth and lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with NaF-containing insecticides and rodenticides	Testing of vomitus or gastric washings Analysis of the food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated food	Urine, hair	Supportive care
Tin	5 min-8 hr usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of the food	Supportive care

Continued

Table 387.5 Food-Borne Noninfectious Illnesses—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of the food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of the food, blood and feces, saliva or urine	Supportive care

BAL, Bronchoalveolar lavage; GI, gastrointestinal.
From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR.* 53(RR-4):1–33, 2004.

Table 387.6 Comparison of Three General Pathogenic Mechanisms of Enteric Infection

PARAMETER	TYPE OF INFECTION		
Mechanism	Noninflammatory (enterotoxin or adherence/superficial invasion)	Inflammatory, epithelial destruction (invasion, cytotoxin)	Penetrating
Location	Proximal small bowel	Colon	Distal small bowel
Illness	Watery diarrhea	Dysentery	Enteric fever
Stool examination	No fecal leukocytes Mild or no ↑ lactoferrin	Fecal polymorphonuclear leukocytes ↑↑ Lactoferrin	Fecal mononuclear leukocytes
Examples	*Vibrio cholerae* ETEC *Clostridium perfringens* *Bacillus cereus* *Staphylococcus aureus* Also*: *Giardia duodenalis* *Rotavirus* *Noroviruses* *Cryptosporidium* spp. EPEC, EAEC *Cyclospora cayetanensis*	*Shigella* EIEC STEC *Vibrio parahaemolyticus* *Clostridioides difficile* *Campylobacter jejuni* *Entamoeba histolytica*†	NTS *Yersinia enterocolitica* *Campylobacter fetus*

*Although not typically enterotoxic, these pathogens alter bowel physiology via adherence, superficial cell entry, cytokine induction, or toxins that inhibit cell function.
†Although amebic dysentery involves tissue inflammation, the leukocytes are characteristically pyknotic or absent, having been destroyed by the virulent amebae.
EAEC, Enteroaggregative *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli;* ETEC, enterotoxigenic *E. coli,* STEC, Shiga toxin–producing *E. coli;* NTS: nontyphoidal *Salmonella.*

infectious; they are usually transmitted in contaminated produce and water (see Table 387.3).

CLINICAL MANIFESTATION OF ACUTE GASTROENTERITIS

General Findings

Diarrhea is usually defined as the passage of three or more abnormally loose or liquid stools per day. Frequent passage of formed stools is not diarrhea, nor is the passing of loose, pasty stools by breastfed babies. Clinical clues as to the possible etiology of AGE are noted in Tables 387.1-387.3 and Table 387.7.

In the past, many guidelines divided patients into subgroups for mild (3–5%), moderate (6–9%), and severe (≥10%) dehydration; however, it is difficult to distinguish between mild and moderate dehydration based on clinical signs alone. Therefore current guidelines combine mild and moderate dehydration and simply use none, some, and severe dehydration. Commonly used guidelines include the World Health Organization (WHO) Integrated Management of Childhood Illness scale, the Clinical Dehydration Scale, the Modified Vesikari Score, and the Gorelick scale, but the accuracy and applicability of these scales varies by clinical setting and by the individual assigning the patients' scores. The signs that best predict dehydration are prolonged capillary refill time >2 seconds, abnormal skin turgor, hyperpnea (deep, rapid breathing suggesting acidosis), dry mucous membranes, absent tears, and general appearance (including activity level and thirst). As the number of signs increases, so does the likelihood of dehydration. Tachycardia, altered level of consciousness, and cold extremities with or without hypotension suggest severe dehydration.

Viral Diarrhea

Symptoms of rotavirus AGE usually begin with vomiting followed by frequent passage of watery, nonbloody stools associated with fever in about half the cases (see Table 387.1). The diarrhea lacks fecal leukocytes, but stools from 20% of cases contain mucus. Recovery with complete resolution of symptoms generally occurs within 7 days. Although disaccharide malabsorption is found in 10–20% of episodes, it is rarely clinically significant.

Other viral agents elicit similar symptoms and cannot be distinguished from rotavirus based on clinical findings. In an outbreak setting, the pattern of a brief incubation period (12-48 hours), short duration of illness, and clustering of cases is shared by caliciviruses and preformed bacterial toxin. However, unlike preformed toxins, caliciviruses cause secondary infections, which confirm the contagious nature of the outbreak. Diarrheal illnesses caused by enteric adenovirus infections tend to be more prolonged than rotavirus (7-10 days),

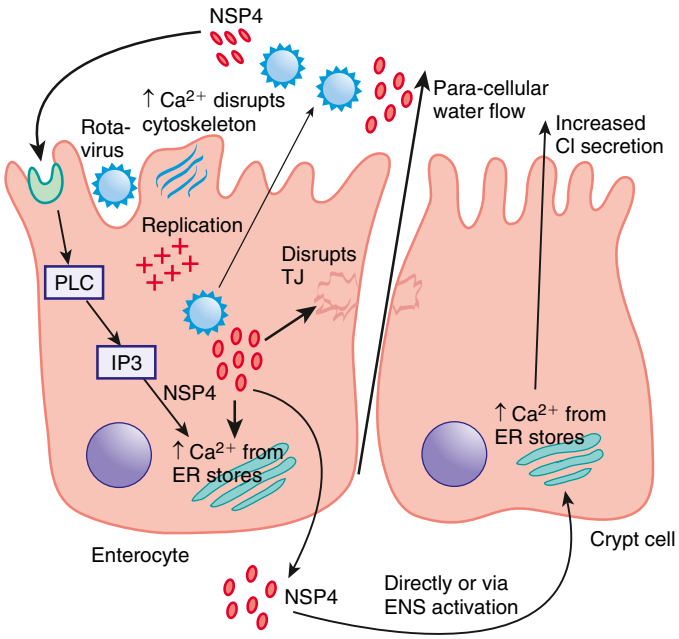

Fig. 387.2 Pathogenesis of rotavirus infection and diarrhea. ENS, Enteric nervous system; ER, endoplasmic reticulum; IP3, inositol trisphosphate; PLC, phospholipase C; TJ, tight junction. *(Adapted from Ramig RF. Pathogenesis of intestinal and systemic rotavirus infection. J Virol. 2004;78:10213–10220.)*

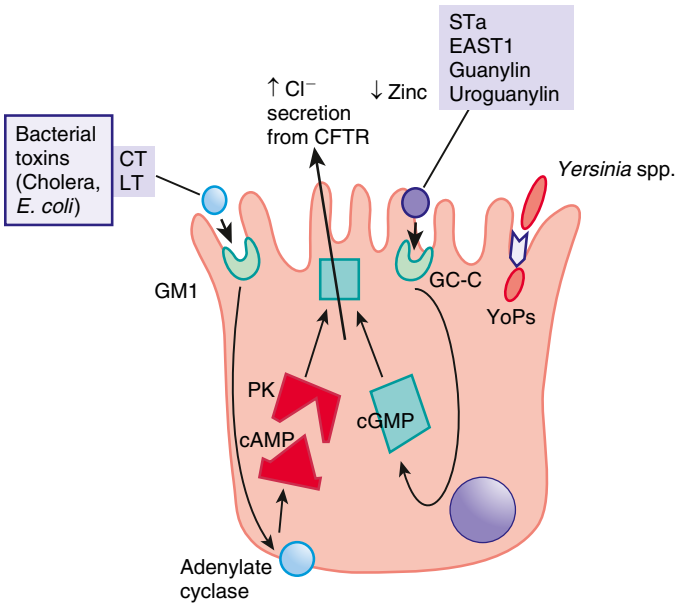

Fig. 387.3 Mechanism of secretory and penetrating diarrhea. cAMP, Cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator through which chloride is secreted; cGMP, cyclic guanosine monophosphate; YoPs, *Yersinia* outer proteins that alter host cell functions to promote disease; CT, cholera toxin; EAST1, enteroaggregative *E. coli* ST; GC-C, guanylate cyclase, the transmembrane receptor for STa and other toxins; GM1, a ganglioside containing one sialic acid residue that serves as the receptor for CT and LT; LT, heat labile toxin; PK, protein kinase; STa, heat stable toxin A. *(Modified from Thapar M, Sanderson IR. Diarrhoea in children: an interface between developing and developed countries. Lancet. 2004;363:641–653; and Montes M, DuPont HL. Enteritis, enterocolitis and infectious diarrhea syndromes. In Cohen J, Powderly WG, Opal SM, et al., eds. Infectious Diseases, 2nd ed. London: Mosby; 2004. pp. 31–52.)*

whereas astroviruses cause a shorter course (~5 days), usually without significant vomiting. The incubation period of SARS-CoV-2 varies depending on circulating variant and the host's vaccination status and immunocompetence with symptoms of acute COVID-19 developing 2-14 days after exposure and symptoms of MIS-C developing approximately ~4 weeks after exposure, with or without preceding known symptomatic COVID-19. Acute COVID-19 encompasses a spectrum of disease ranging from mild congestion and headache to acute respiratory failure, hypercoagulability, and multisystem organ failure, but it may be limited to AGE in some patients. Other gastrointestinal manifestations of acute COVID-19 include colitis, mesenteric adenitis, and pseudoappendicitis as a manifestation of mesenteric adenitis. Whereas fever is present in fewer than half of acute COVID-19 cases in children, it is a diagnostic criterion of MIS-C, in which abdominal pain and other gastrointestinal symptoms are a prominent feature, often accompanied by rash, conjunctivitis, and lymphadenopathy, and which may rapidly progress to cardiogenic shock if not identified and treated promptly.

Bacterial Diarrhea

Although there is considerable overlap, high fever >40°C, overt fecal blood, abdominal pain, no vomiting before diarrhea onset, and high stool frequency (>10 per day) are more common with bacterial pathogens (see Table 387.2). Although high fever and overt fecal blood are often absent in bacterial enteritis, when present, there is a high probability of a bacterial etiology. The classical bacterial agents, NTS, *Shigella, Campylobacter,* and *Yersinia,* present with one of five syndromes.

1. Acute diarrhea, the most common presentation, may be accompanied by fever and vomiting. Clinically silent bacteremia associated with uncomplicated NTS AGE can be seen among otherwise healthy children younger than 2 years living in industrialized countries.
2. Bloody diarrhea or frank dysentery is classically caused by *Shigella.* Watery diarrhea typically precedes dysentery and is often the sole clinical manifestation of mild infection. Progression to dysentery indicates colitis and may occur within hours to days. Patients with severe infection may pass more than 20 dysenteric stools in one day. Dysenteric illnesses due to *Campylobacter* have been confused with inflammatory bowel disease.
3. Invasive, nonfocal disease (enteric fever) is a febrile illness associated with bacteremia without localized infection. Diarrhea may be minimal or absent. Although classically the result of *S.* Typhi or Paratyphi A and B, enteric fever can result from systemic spread of the classical bacterial enteropathogens. Whereas enteric fever caused by *S.* Typhi or Paratyphi A and B primarily affect preschool and school-age children in endemic countries, other bacterial enteropathogens most often cause disease in infants (particularly <3 months), the immunocompromised, and children with malnutrition. Additional risk factors include hemolytic anemia and intravascular lesions for NTS, and iron overload, cirrhosis, and chelation therapy for *Yersinia* sepsis. The distinct clones of NTS that have arisen in sub-Saharan Africa described earlier often cause enteric-fever type illnesses in the absence of AGE. *Shigella* sepsis is rare and is seen most often in malnourished and immunocompromised hosts.
4. Localized extraintestinal invasive infections can result from either local invasion or bacteremic spread (see Table 387.7). Examples of local invasion include mesenteric adenitis, appendicitis, and rarely cholecystitis, mesenteric venous thrombosis, pancreatitis, and hepatic or splenic abscess. Bacteremic spread may result in pneumonia, osteomyelitis, meningitis (three conditions seen most commonly with NTS), abscesses, cellulitis, septic arthritis, and endocarditis. *Shigella* can cause noninvasive contiguous infections such as vaginitis and urinary tract infections.
5. Vertical transmission of *Shigella,* NTS, and *Campylobacter* can produce perinatal infection resulting in a spectrum of illness from isolated diarrhea or hematochezia to fulminant neonatal sepsis. One species of *Campylobacter, C. fetus,* is particularly virulent in pregnant women and can result in chorioamnionitis, abortion, and neonatal sepsis and meningitis.

Crampy abdominal pain and nonbloody diarrhea are the first symptoms of STEC infection, sometimes with vomiting. Within several days, diarrhea becomes bloody, and abdominal pain worsens. Bloody diarrhea lasts between 1 and 22 days (median 4 days). In contrast to

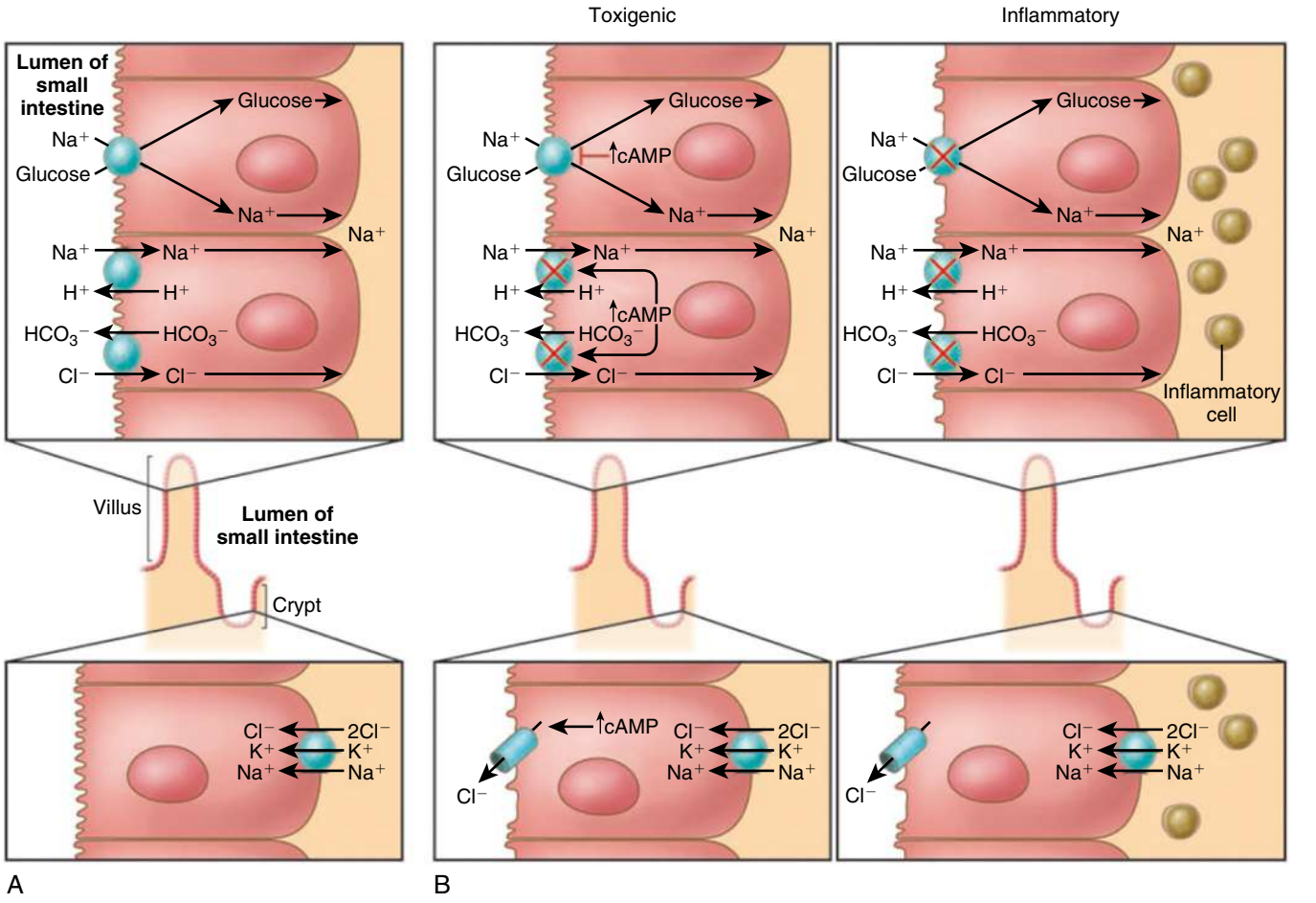

Fig. 387.4 Movement of Na^+ and Cl^- in the small intestine. **A,** Movement in normal subjects. Na^+ is absorbed by two different mechanisms in absorptive cells from villi: glucose-stimulated absorption and electroneutral absorption (which represents the coupling of Na^+/H^+ and Cl^-/HCO_3^- exchanges). **B,** Movement during diarrhea caused by a toxin and inflammation. *(From Petri WA, Miller M, Binder HJ, et al. Enteric infections, diarrhea and their impact on function and development. J Clin Invest. 2008;118:1277–1290.)*

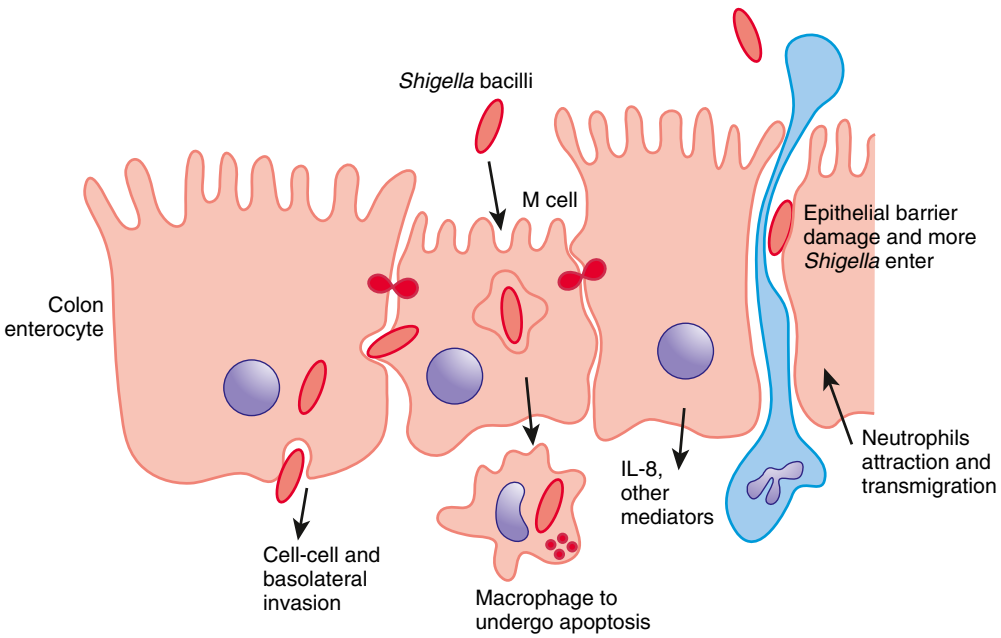

Fig. 387.5 Pathogenesis of *Shigella* infection and diarrhea. IL, Interleukin. *(Adapted from Opal SM, Keusch GT. Host responses to infection. In: Cohen J, Powderly WG, Opal SM, et al., eds. Infectious Diseases, 2nd ed. London: Mosby; 2004. pp. 31–52.)*

dysentery, the stools associated with STEC hemorrhagic colitis are large volume and rarely accompanied by high fever. ETEC causes a secretory watery diarrhea that affects infants and young children in developing countries and is the major causative agents of traveler's diarrhea, accounting for about half of all episodes in some studies. EPEC remains a leading cause of persistent diarrhea associated with malnutrition among infants from developing countries. EIEC, which is genetically, biochemically, and clinically nearly identical to *Shigella,* causes rare food-borne outbreaks in industrialized countries. EAEC has been associated with persistent diarrhea in immunocompromised persons and sporadic diarrhea in infants in countries with varying levels of economic development; however, some other studies have not found an association with disease.

C. difficile toxin is associated with several clinical syndromes. The most common is mild to moderate watery diarrhea, low-grade fever, and mild abdominal pain. Occasionally, the illness will progress to full-blown pseudomembranous colitis characterized by diarrhea, abdominal cramps, and fever. The colonic mucosa contains 2-5 mm raised, yellowish plaques. Fatal cases are associated with toxic megacolon, systemic toxicity, and multisystem organ failure, possibly related to systemic absorption of toxin. The illness associated with *S. aureus* and *B. cereus* emetic toxin is dominated by vomiting, whereas diarrhea is the major manifestation of *C. perfringens* and *B. cereus* enterotoxins.

Protozoal Diarrhea

Illnesses due to intestinal protozoa tend to be more prolonged, sometimes for 2 weeks or more, but are usually self-limited in the otherwise healthy host (see Table 387.3). In general, the duration and severity of *Cryptosporidium* diarrhea is strongly influenced by the immune and nutritional status of the host. A protozoal etiology should be suspected when there is a prolonged diarrheal illness characterized by episodes of sometimes explosive diarrhea with nausea, abdominal cramps, and abdominal bloating. The stools are usually watery but can be greasy and foul smelling due to concomitant malabsorption of fats, which is more likely to occur if the parasite load is high. Occasionally, diarrhea may alternate with constipation.

In addition to diarrhea, *E. histolytica* causes a range of other syndromes. Amebic dysentery is characterized by bloody or mucoid diarrhea, which may be profuse and lead to dehydration or electrolyte imbalances. Amebic granulomas (amebomas) may form in the colon, and extraintestinal disease most commonly manifests as liver abscesses but may also spread to the lungs, pericardium, genitourinary tract, skin, and, hematogenously, to the brain or other sites. Extraintestinal *Entamoeba* disease may occur with or without intestinal disease.

INTESTINAL AND EXTRAINTESTINAL COMPLICATIONS

The major complications of diarrhea from any cause are dehydration and electrolyte or acid-base derangements, which can be life-threatening (see Table 387.7). Avoiding delays in diagnosis and treatment and providing appropriate supportive care using either oral, enteral, or intravenous hydration can prevent or treat most of these conditions. Children who experience frequent episodes of acute diarrhea or prolonged or persistent episodes (seen especially in low-resource settings) are at risk for poor growth and nutrition and complications such as secondary infections and micronutrient deficiencies (iron, zinc, vitamin A). Ensuring continued nutritional support during diarrheal episodes is important because prolonged limitation of the diet may extend diarrheal symptoms. Reestablishing a normal diet generally restores villous anatomy and function with resolution of loose stools.

Viral AGE illnesses are usually self-limited and resolve after several days. Rarely, **intussusception** is triggered by lymphoid hyperplasia associated with viral AGE. Complications of bacterial AGE may be the result of local or systemic spread of the organism; in malnourished children and HIV-infected populations, associated **bacteremia** is well recognized. Toxic megacolon, intestinal perforation, and rectal prolapse can occur, particularly in association with *Shigella* in developing countries and *C. difficile*. The most dreaded complication of pediatric diarrhea in the United States is HUS, the leading cause of acquired renal failure in children, which develops in 5–10% of patients infected with STEC. It is usually diagnosed 2-14 days after the onset of diarrhea. HUS is unlikely to occur once diarrhea has remained resolved for 2 or 3 days with no evidence of hemolysis. Risk factors include age 6 months to 4 years, bloody diarrhea, fever, elevated leukocyte count, and treatment with antibiotics and antimotility agents. Patients may no longer excrete the organism at the time they develop HUS (see Chapter 560.5).

Pseudoappendicitis secondary to mesenteric adenitis is a notable complication of *Yersinia*, sometimes *Campylobacter* and COVID-19. Older children and adolescents are most often affected. It typically presents with fever and abdominal pain with tenderness localized to the right lower quadrant, with or without diarrhea, and can be confused with appendicitis. When available, ultrasound is the preferred method for diagnosing true appendicitis; abdominal CT or MRI may be helpful when ultrasound is not available.

Immune-mediated complications that are thought to result from immunologic cross reactivity between bacterial antigens and host tissues are more often seen in adults than children. These include reactive arthritis following infection with the classical bacterial enteropathogens and Guillain-Barré syndrome following *Campylobacter* infection.

Protozoan illnesses, when persistent, can lead to poor weight gain in the young and in immunocompromised individuals, weight loss, malnutrition, or vitamin deficiencies. Infection with *Entamoeba* can cause severe ulcerating colitis, colonic dilation, and perforation. The parasite may spread systemically, most commonly causing liver abscesses. In high-risk settings, it is critical to exclude *Entamoeba* infection and tuberculosis before initiating corticosteroids for presumed ulcerative colitis.

DIFFERENTIAL DIAGNOSIS

The physician should also consider noninfectious diseases that can present with bright red blood per rectum or hematochezia (Table 387.8). In an infant or young child without systemic symptoms, these may include anal fissures, intermittent intussusception, juvenile polyps, and Meckel diverticulum. Necrotizing enterocolitis can cause lower gastrointestinal bleeding in infants, especially premature neonates. Inflammatory bowel disease should be considered in older children. Examples of noninfectious causes of nonbloody diarrhea include congenital secretory diarrheas, endocrine disorders (hyperthyroidism), neoplasms, food intolerance, and medications (particularly antibiotics). Noninfectious causes of chronic or relapsing diarrhea include cystic fibrosis, celiac disease, milk protein, lactose, fructose, or sucrose intolerance and other food allergies, congenital or acquired disaccharidase deficiency, and functional gastrointestinal disorders. Significant abdominal pain should raise suspicion of other infectious processes in the abdomen such as appendicitis and pelvic inflammatory disease. Prominent vomiting with or without abdominal pain can be a manifestation of pyloric stenosis, intestinal obstruction, pancreatitis, appendicitis, and cholecystitis.

Clinical Evaluation of Diarrhea

In the initial evaluation of all patients with AGE, the physician should focus on the patient's hydration status and electrolyte balance, as well as evidence of sepsis or invasive bacterial infection, which could complicate bacterial AGE (Fig. 387.6). Once the patient is stabilized, the history and physical examination can focus on detecting risk factors and exposures, as well as the clinical features that may suggest specific etiologic agents.

Important elements of the medical history include the duration of diarrhea and a description of stools (frequency, amount, presence of blood or mucus), fever (duration, magnitude, pattern), vomiting (onset, amount, and frequency), and the amount and type of solid and liquid oral intake. Clinical signs of dehydration should be evaluated (Table 387.9): urine output (number of wet diapers per day and time since the last urination), whether eyes appear sunken, whether the child is active, whether the child drinks vigorously, and the date and value of the most recent weight measurement. A documented weight loss can be used to calculate the fluid deficit. The past medical history should identify comorbidities that might increase the risk or severity of AGE.

Table 387.7 Intestinal and Extraintestinal Complications of Enteric Infections

COMPLICATION	ASSOCIATED ENTERIC PATHOGEN(S)
INTESTINAL COMPLICATIONS	
Persistent diarrhea	All causes
Recurrent diarrhea (usually immunocompromised persons)	*Shigella* spp., NTS, *Campylobacter* spp., *Clostridioides difficile*, *Yersinia* spp., *Entamoeba histolytica*, *Cryptosporidium* spp.
Postinfectious irritable bowel syndrome	*Shigella* spp., NTS, *Campylobacter* spp., *C. difficile*
Protein-losing enteropathy	*Shigella* and *Salmonella* spp. rotavirus, CMV, *Giardiasis*, *Strongyloides stercoralis*, tuberculosis, HIV
Toxic megacolon	*Shigella* spp., NTS, *Campylobacter* spp., *C. difficile*, *Yersinia* spp., *E. histolytica*, STEC
Intestinal perforation	*Shigella* spp., NTS, *C. difficile*, *Yersinia* spp., *E. histolytica*, STEC
Rectal prolapse	*Shigella* spp., NTS, *Campylobacter* spp., *C. difficile*, *E. histolytica*, STEC
Pseudomembranous colitis	*Shigella* spp., NTS, *C. difficile*, *Yersinia* spp., STEC
Appendicitis	*Shigella* spp., NTS, *Yersinia* spp., *Schistosoma* spp., *Strongyloides stercoralis*, SARS-CoV-2
Intussusception	*Shigella* spp., NTS, *Campylobacter* spp., *Yersinia* spp., STEC
Chronic carriage	NTS
EXTRAINTESTINAL COMPLICATIONS	
Dehydration, metabolic abnormalities, malnutrition, micronutrient deficiency	All causes
Systemic invasion with bacteremia/parasitemia ± distant foci	*Shigella* spp., NTS, *Campylobacter* spp., *Yersinia* spp., *E. histolytica*
Local invasion Mesenteric adenitis Cholecystitis	 *Campylobacter* spp. (rarely), *Yersinia* spp., COVID-19 NTS, SARS-CoV-2
Local noninvasive spread Vulvovaginitis Urinary tract infection	 *Shigella* spp. *Shigella* spp., *Yersinia* spp.
Seizures, encephalopathy	*Shigella* spp., STEC
Leukemoid reaction, bandemia	*Shigella* spp., *Yersinia* spp.
Pharyngitis, adenopathy, rash	*Yersinia* spp., SARS-CoV-2*
Fetal/placental infection	*Campylobacter* fetus, *Shigella* spp.
POSTINFECTIOUS COMPLICATIONS	
Reactive arthritis	*Shigella* spp., NTS, *Campylobacter* spp., *C. difficile*, *Yersinia* spp.
Guillain-Barré syndrome	*Campylobacter* spp.
Hemolytic uremic syndrome	*Shigella dysenteriae* type 1, STEC
Glomerulonephritis, myocarditis, pericarditis	*Campylobacter* spp., *Yersinia* spp., SARS-CoV-2
Immunoglobulin A (IgA) nephropathy	*Campylobacter* spp.
Erythema nodosum	NTS, *Campylobacter* spp., *Yersinia* spp.
Hemolytic anemia	*Campylobacter* spp., *Yersinia* spp.

**Yersinia* spp. is associated with a scarlatiniform rash, cervical adenopathy, and exudative pharyngitis whereas SARS-CoV-2 is typically associated with a nonexudative pharyngitis and diffuse lymphadenopathy, and the rash of SARS-CoV-2 can be polymorphous.*

NTS, Nontyphoidal *Salmonella* spp.; CMV, cytomegalovirus; STEC, Shiga toxin–producing *E. coli*.

Certain physical signs are best assessed before approaching the child directly, so the child remains calm, including general appearance (activity, response to stimulation) and respiratory patterns. Skin turgor is assessed by pinching a small skinfold on the lateral abdominal wall at the level of the umbilicus. If the fold does not promptly return to normal after release, the recoil time is quantified as delayed slightly or ≥2 seconds. Excess subcutaneous tissue and hypernatremia may produce a false-negative test, and malnutrition can prolong the recoil time. To measure capillary refill time, the palmar surface of the child's distal fingertip is pressed until blanching occurs, with the child's arm at heart level. The time elapsed until restoration of normal color after release usually exceeds 2 seconds in the presence of dehydration. Mucous membrane moisture level, presence of tears, and extremity temperature should also be assessed.

Laboratory Diagnosis

Most cases of AGE do not require diagnostic laboratory testing. Stool specimens may be examined for mucus, blood, neutrophils, or fecal lactoferrin, a neutrophil product. The finding of more than five leukocytes per high-power field or a positive lactoferrin assay in an infant not breastfeeding suggests an infection with a classical bacterial enteropathogen; patients infected with STEC and *E. histolytica* usually have negative tests.

Table 387.8 Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis

SPECIFIC INFECTIOUS PROCESSES
Bacillary dysentery (*Shigella* spp.; invasive *Escherichia coli*)
Campylobacteriosis (*Campylobacter jejuni*)
Amebic dysentery (*Entamoeba histolytica*)
Bilharzial dysentery (*Schistosoma japonicum, S. mansoni*)
Vibriosis (*Vibrio cholera*)
Salmonellosis (nontyphoidal *Salmonella*)
Enteric fever (*Salmonella Typhi, Salmonella Paratyphi* A, B, and C)
Yersiniosis (*Yersinia enterocolitica*)
PROCTITIS
Gonococcal (*Neisseria gonorrhoeae*)
Herpetic (herpes simplex virus)
Chlamydial (*Chlamydia trachomatis*)
Syphilitic (*Treponema pallidum*)
OTHER SYNDROMES
Necrotizing enterocolitis of the newborn
Enteritis necroticans
Pseudomembranous enterocolitis (*Clostridioides difficile*)
Typhlitis
CHRONIC INFLAMMATORY PROCESSES
Enteropathogenic and enteroaggregative *Escherichia coli*
Gastrointestinal tuberculosis
Gastrointestinal mycosis
Parasitic enteritis
SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE
Idiopathic ulcerative colitis
Crohn disease
Radiation enteritis
Ischemic colitis
Allergic enteritis

Laboratory diagnosis of viral AGE may be helpful when an outbreak is suspected, cases are linked to a suspected outbreak, or when cohorting of patients is considered to limit the spread of infection. The preferred method of testing norovirus is real-time reverse-transcription quantitative polymerase chain reaction (RT-qPCR), available at most public health and virology laboratories. Commercial multiplex PCR tests are available in the United States for the diagnosis of bacterial, parasitic, and viral enteric pathogens, including rotavirus, enteric adenoviruses, astrovirus, norovirus, and sapovirus (see Table 387.1). Although SARS-CoV-2 has been identified in enteric specimens in research settings, the mainstay of clinical diagnosis remains upper respiratory sampling for either PCR or immunoassay.

Stool cultures for detection of bacterial agents are costly, so requests should be restricted to patients with clinical features predictive of bacterial AGE, have moderate or severe disease, are immunocompromised, in outbreaks with suspected HUS, or have a highly suggestive epidemiologic history. To optimize recovery of pathogens, stool specimens for culture need to be transported and plated quickly; if the latter is not quickly available, specimens might need to be transported in special transport media. If antibiotics will be administered and the child has not produced a stool sample, a rectal swab should be collected promptly so as not to delay initiation of antibiotics. After dipping the cotton tip into the medium that will be used for transport, it is gently inserted into the child's rectum and rotated 360 degrees. A properly collected rectal swab is stained or covered with fecal material. Standard stool culture methods performed in clinical microbiology laboratories recover *Shigella* and *Salmonella* species. If *Campylobacter*, *Yersinia*, or *Vibrio* species are suspected, the laboratory should be notified unless media are routinely used for their detection. All bloody stools should also be inoculated into media specific for detection of *E. coli* 0157:H7 or directly tested for the presence of Shiga-like toxin (or both). Except for *C. difficile*, nosocomial acquisition of a bacterial enteric pathogen is very unlikely. Nucleic acid amplification tests (NAAT) have replaced stool culture in some settings; reflex culture is necessary to identify

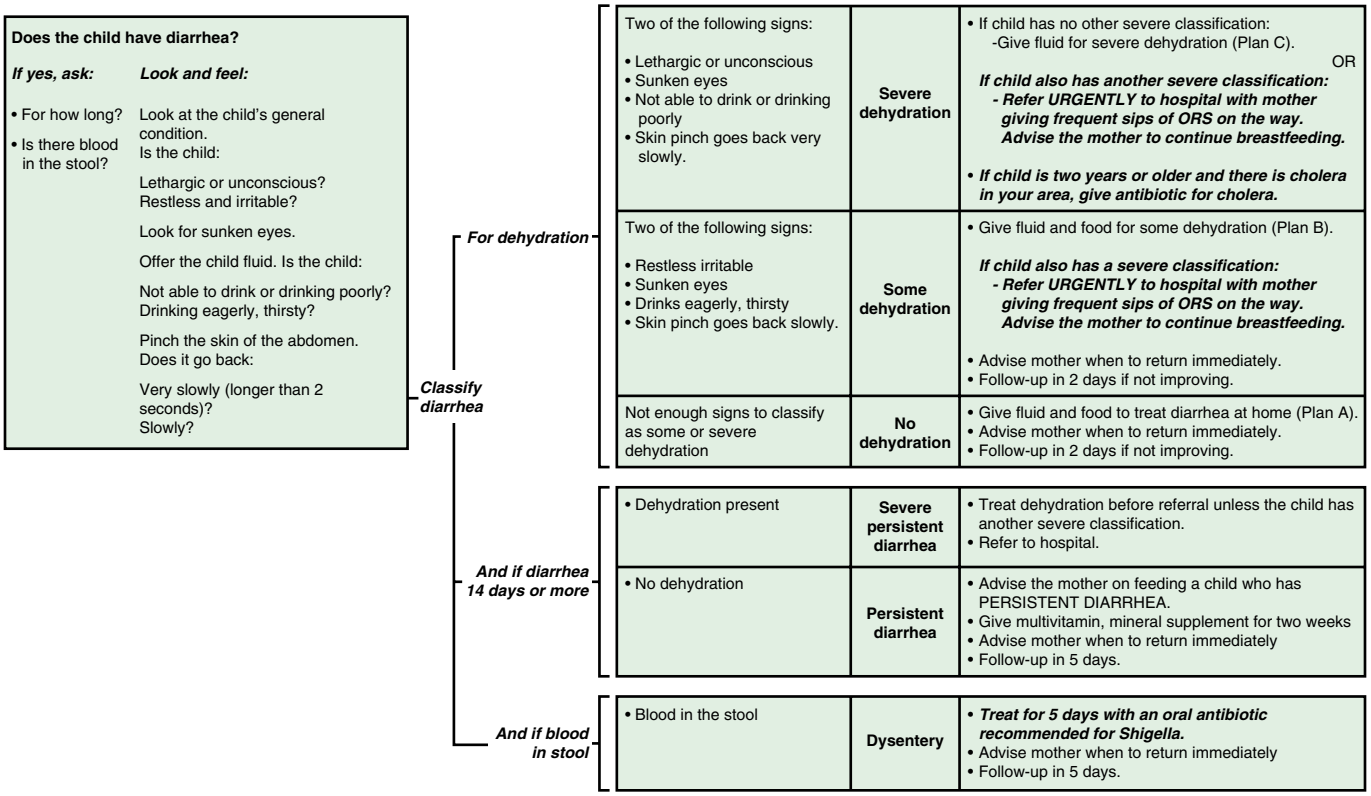

Fig. 387.6 Algorithm showing the Integrated Management of Childhood Illnesses (IMCI) protocol for the recognition and management of diarrhea in developing countries. ORS, Oral rehydration solution.

Table 387.9 Signs and Symptoms Associated with Dehydration

SYMPTOM	MINIMAL OR NO DEHYDRATION	SOME DEHYDRATION	SEVERE DEHYDRATION
Mental status[C,G4,W]	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, limp, unconscious/comatose
Thirst[W]	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate[G10]	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses[G10]	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing [G10]	Normal	Normal; fast	Deep, fast
Eyes[C,G10,W]	Normal	Slightly sunken	Deeply sunken
Tears[C,G4]	Present	Decreased	Absent
Mouth and tongue/mucous membranes[C,G4]	Moist	Dry, "sticky" or "tacky"	Parched
Skinfold[G10,W]	Instant recoil	Recoil in <2 sec (slow)	Recoil in >2 sec (very slow)
Capillary refill[G4]	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output[G10]	Normal to decreased	Decreased	Minimal

[C]Denotes inclusion in Clinical Dehydration Scale (CDS); CDS scores each category from 0 to 2 with an overall score of 0 = no dehydration (<3%), 1-4 = some dehydration (<6%).
[G4]Denotes inclusion in 4-point and 10-point Gorelick scales: ≥2 Clinical Signs ≥5% ΔBW; ≥3 Clinical Signs ≥10% ΔBW.
[G10]Denotes items included in 10-point Gorelick scale but not in the 4-point Gorelick scale: ≥3 Clinical Signs ≥5% ΔBW; ≥7 Clinical Signs ≥10% ΔBW. Gorelick Scale uses "no or minimal dehydration" and "moderate to severe dehydration."
[W]Denotes inclusion in the World Health Organization (WHO) scale.
BW, Body weight.

antimicrobial sensitivities. Hence, stool microbiologic assays are generally not indicated for patients in whom diarrhea develops more than 3 days after admission unless the patient is immunocompromised or to investigate a hospital outbreak (see Table 387.2).

For children older than 2 years who have recently received antibiotics or have other risk factors, evaluation for *C. difficile* infection may be appropriate. The cytotoxin assay detects toxin B, but testing for toxin A is also available in some laboratories; however, this test is laborious. Several tests are commercially available to detect toxin-producing *C. difficile* in stool, including enzyme immunoassays (EIA) for toxins A and B, cell culture cytotoxicity assay, PCR, and glutamate dehydrogenase (GDH) immunoassay. The sensitivities of cell culture, PCR, and GDH EIA are superior to that of toxin EIA. A multistep diagnostic approach combining toxin testing with NAAT and/or GDH EIA may improve the sensitivity, specificity, and positive predictive value of *C. difficile* testing. Testing for *C. difficile* toxin in children younger than 2 years is discouraged because the organism and its toxins are commonly detected in asymptomatic infants (see Table 387.2).

Evaluation for intestinal protozoa that cause diarrhea is usually indicated in patients who recently traveled to an endemic area, had contact with untreated water, and manifest suggestive symptoms. Previously, the most commonly used method was direct microscopy of stool for cysts and trophozoites. However, this approach is time-consuming and lacks sensitivity, in part because shedding can be intermittent. Analyzing three specimens from separate days is optimal, and fecal concentration techniques provide some benefit. The sensitivity and specificity of microscopy is substantially improved using immunofluorescence antibodies that are commercially available for visualization of *Cryptosporidium* and *Giardia* cysts. In addition, EIAs are available for *Cryptosporidium, Giardia,* and *Entamoeba* that are more sensitive and specific than direct microscopy and provide a useful diagnostic tool. (Not all commercial kits distinguish between pathogenic *E. histolytica* and nonpathogenic *E. dispar.*) Molecular methods (NAATs and multiplex PCR assays) have largely replaced microscopy and EIAs (see Table 387.3)

Several culture-independent rapid multiplex molecular panels for detection of viral, bacterial, and protozoal gastrointestinal pathogens directly from stool samples are approved by the U.S. Food and Drug Administration (FDA), including xTag GPP (14 pathogens), Verigene EP (9 pathogens), and the FilmArray GI Panel (22 pathogens). These methods offer several advantages over conventional diagnostics, including reduced sample volume requirements, broad coverage without the need to select specific tests, enhanced ability to detect co-infections, increased sensitivity, and rapid turnaround. However, the available tests do not provide strain specificity or susceptibility testing, so culture is still necessary to guide outbreak detection and treatment decisions.

Most episodes of diarrheal dehydration are isonatremic and do not warrant serum electrolyte measurements. Electrolyte measurements are most useful in children with severe dehydration, when intravenous fluids are administered, when there is a history of frequent watery stools, yet the skin pinch feels doughy without delayed recoil, which suggests hypernatremia, when the child is unable to drink due to anorexia or emesis, and when inappropriate or inadequate rehydration fluids have been administered at home. A suspicion for HUS prompts a complete blood count with review of the peripheral smear, serum electrolytes, and renal function tests. Patients with shigellosis can demonstrate bandemia or even a leukemoid reaction. Blood culture should be obtained if there is concern for systemic bacterial infection. This includes infants and children with fever and/or blood in the stool who are younger than 3 months, are immunocompromised, or have hemolytic anemia or other risk factors. If diarrhea persists with no cause identified, endoscopic evaluation may be indicated. Biopsy specimens help in diagnosing inflammatory bowel disease or identifying infecting agents that may mimic it. A sweat test is warranted if cystic fibrosis is suspected.

TREATMENT

The broad principles of management of AGE in children include rehydration and maintenance ORS plus replacement of continued losses in diarrheal stools and vomitus after rehydration, continued breastfeeding, and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is corrected. Zinc supplementation is recommended for children in developing countries.

Hydration

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kilogram and because they are dependent on others to meet these demands (Table 387.10). Dehydration must be evaluated rapidly and corrected in 4-6 hours according to the degree of dehydration and estimated daily requirements. When there is emesis, small volumes of ORS can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. The low-osmolality WHO ORS containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose/L, with total osmolarity of 245 mOsm/L, is now the global standard of care and more effective than home fluids. Soda beverages, fruit juices, and tea and other home fluids are not suitable for rehydration or maintenance therapy because they have inappropriately high glucose concentration and osmolalities and low sodium concentrations. Tables 387.9 and 387.10 outline a clinical evaluation plan and management strategy for children with moderate to severe diarrhea. Replacement for emesis or stool losses is noted in Table 387.10. Oral rehydration can also be given by a nasogastric tube if needed.

A small minority of children, including those with severe dehydration or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses. Signs of severe dehydration that might necessitate intravenous resuscitation include are shown in Table 387.9. Limitations to ORS include shock, decreased level of consciousness, ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and high stool output (>10 mL/kg/hr).

Enteral Feeding and Diet Selection

Continued breastfeeding and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is corrected aids in recovery from the episode. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), fresh fruits, lean meats, yogurt, and vegetables should be reintroduced while ORS is given to replace ongoing losses from emesis or stools and for maintenance. Fatty foods or foods high in simple sugars (juices, carbonated sodas) should be avoided. The usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2-3 g/kg/day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

If the normal diet includes infant formula, it should not be diluted, or changed to a lactose-free preparation unless lactose malabsorption is evident. With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose-containing diets. Withdrawal of milk and replacement with specialized lactose-free formulations are unnecessary. Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Rarely, when dietary intolerance precludes the administration of cow's milk–based formulations or whole milk, it may be necessary to administer specialized milk-free diets such as a comminuted or blenderized chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. In addition to rice-lentil formulations, the addition of green banana or pectin to the diet has also been shown to be effective in the treatment of persistent diarrhea. Figure 387.7 provides an algorithm for managing children with prolonged diarrhea in developing countries.

Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, the use of locally available age-appropriate foods should be promoted for the majority of acute diarrhea cases. Even among those children for whom lactose avoidance may be necessary, nutritionally complete diets comprised of locally available ingredients can be used at least as effectively

Table 387.10 Summary of Treatment Based on Degree of Dehydration

DEGREE OF DEHYDRATION	REHYDRATION THERAPY	REPLACEMENT OF LOSSES
Some dehydration	Infants and children: ORS, 75 mL/kg over 3-4 hr. Continue breastfeeding. After 4 hr, give food every 3-4 hr for children who normally receive solid foods.	*Infants and children:* <2 yr old: 50-100 mL ORS for each diarrheal stool or vomiting episode, up to ~500 mL/day ≥2 yr old: 100-200 mL ORS for each diarrheal stool or vomiting episode, up to ~1 L/day Replace losses as above as long as diarrhea or vomiting continues
Severe dehydration	Malnourished infants may benefit from smaller-volume, frequent boluses of 5-10 mL/kg body weight due to reduced capacity to increase cardiac output with larger volume resuscitation. Infants (<12 mo) and children (12 mo to 5 yr) without malnutrition: Give 20-30 mL/kg boluses of IV isotonic crystalloid solution (e.g., Ringer lactate or normal saline solution) over 30-60 min. Repeat boluses as necessary to restore adequate perfusion. Then give 70 mL/kg over 2.5-5 hr. (Note the slower infusion times are for infants.) If IV hydration is not possible, administer ORS 20 mL/kg/hr × 6 hours via nasogastric tube. Reassess the infant or child frequently and adjust infusion rate if needed. Give ORS as soon as the child can drink. Allow to feed (breast milk or solid food) as described for some dehydration. Adjust electrolytes and administer dextrose based on chemistry values.	*Infants and children:* <10 kg body weight (children <2 yr): 50-100 mL ORS for each diarrheal stool or vomiting episode >10 kg body weight (children ≥2 yr): 100-200 mL ORS for each diarrheal stool or vomiting episode *Adolescents and adults:* Ad libitum Replace losses as above as long as diarrhea or vomiting continue If unable to drink, either administer ORS through a nasogastric tube or give dextrose-containing IV fluids as appropriate based on chemistry values

Note: Low-osmolarity ORS can be given to all age-groups, with any cause of diarrhea. It is safe in the presence of hypernatremia, as well as hyponatremia (except when edema is present). Some commercially available formulations that can be used as ORS include Pedialyte Liters (Abbott Nutrition), CeraLyte (Cera Products), and Enfalac Lytren (Mead Johnson). Popular beverages that should not be used for rehydration include apple juice, Gatorade, and commercial soft drinks.

ORS, Oral rehydration solution; IV, intravenous.

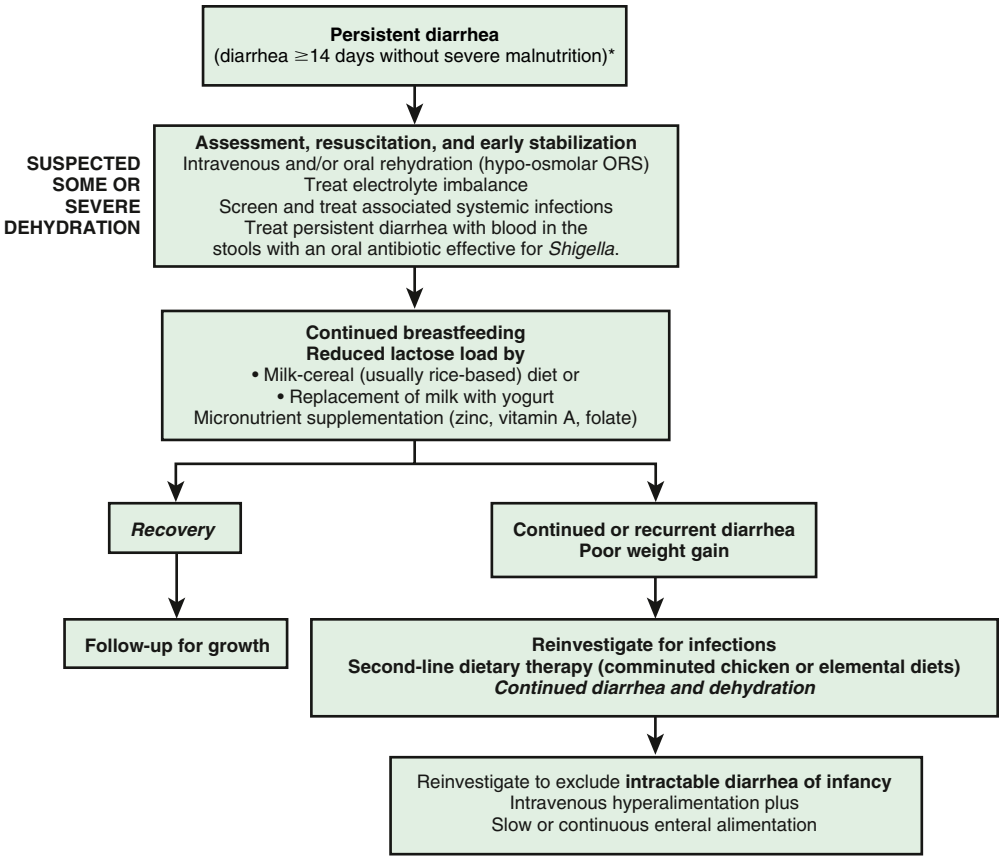

Fig. 387.7 Management algorithm for persistent diarrhea. ORS, Oral rehydration solution.

as commercial preparations or specialized ingredients. These same conclusions may also apply to the dietary management of children with persistent diarrhea, but the evidence remains limited.

Zinc Supplementation

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality by 46% and hospital admission by 23%. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 months of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/day is recommended by most guidelines, but 5 mg/day and 10 mg/day may be better tolerated and equally effective) in some form for 10-14 days during and continued after diarrhea. The role of zinc in well-nourished, zinc replete populations in developed countries is less certain.

Additional Therapies

The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings, although the evidence does not support a recommendation for their use in all settings. A variety of organisms *(Lactobacillus, Bifidobacterium)* have a good safety record; therapy has not been standardized, and the most effective (and safe) organism has not been identified. *Saccharomyces boulardii* is effective in antibiotic-associated and in *C. difficile* diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. Two large randomized placebo-controlled trials evaluating the efficacy of two *Lactobacillus*-based probiotic formulations failed to reduce a clinical severity score in Canadian infants and preschool children with AGE. *Lactobacillus rhamnosus* GG or a combination probiotic product containing *L. rhamnosus* R0011 and *L. helveticus* R0052 has shown variable efficacy; reduction is more evident in cases of childhood rotavirus diarrhea.

Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration, and is well established in emergency management of AGE in high-resource settings, reducing intravenous fluid requirements and hospitalization. Because persistent vomiting can limit oral rehydration therapy, a single sublingual dose of an oral dissolvable tablet of ondansetron (2 mg for children 8-15 kg, 4 mg for children 16-30 kg, and 8 mg for children >31 kg) may be given off-label. However, most children do not require specific antiemetic therapy; careful ORS is usually sufficient. Antimotility agents (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, antiemetic agents, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia).

Antibiotic Therapy

Judicious antibiotic therapy for suspected or proven bacterial infections can reduce the duration and severity of illness and prevent complications (Table 387.11). Several factors justify limited use. First, most episodes of AGE are self-limited among otherwise healthy children. Second, the increasing prevalence of antibiotic resistance has prompted restricted use of these drugs. Third, antibiotics may worsen outcomes, as some studies have shown that antibiotic therapy with STEC infection increases the risk of HUS and prolongs excretion of NTS without improving clinical outcomes. Therefore antibiotics are used primarily to treat severe infections, prevent complications in high-risk hosts, or to limit the spread of infection. Microbiologic (culture) confirmation of the etiology and susceptibility testing should be sought before treatment if possible.

Treatment of *C. difficile* infection warrants special consideration (see Table 387.11). Removal of the offending antibiotic, if possible, is the first step. Antibiotic therapy directed against *C. difficile* should be instituted if the symptoms are severe or persistent. In children, oral vancomycin and metronidazole for 7-14 days (first-line agents)

displayed equivalent efficacy in a prospective randomized trial; however, metronidazole may be preferred because of lower cost and concerns about inducing vancomycin-resistant enterococci. Twenty percent of patients treated for *C. difficile* diarrhea have a relapse. The first relapse should be treated with another course of antibiotics based on severity of illness. For multiply recurrent disease, tapering and/or pulsed regimen of oral vancomycin over a 4- to 6-week period has been proposed. Rifaximin is an alternative option in children ≥12 years to treat persistent or recurrent *C. difficile* colitis, and fecal microbiota transplant is being explored. Fidaxomicin is an alternate agent approved for patients >6 months of age. The phase 3, multicenter, randomized, single-blind SUNSHINE trial demonstrated equivalent clinical cure rates in pediatric patients receiving either oral vancomycin or fidaxomicin and increased rates of global cure in the fidaxomicin arm, but the study excluded patients with life-threatening and fulminant infection. In patients ≥18 years old, it is now preferred over vancomycin as the first-line therapy for the initial episode (whether severe or nonsevere) and recurrences. Bezlotoxumab, a monoclonal antibody against *C. difficile* toxins A and B, has been shown to reduce the recurrence rate and is recommended in addition to standard antibiotic therapy for adults experiencing a recurrence, but it has not been approved for use in children. Studies are underway to determine the safety, tolerability, pharmacokinetics, and efficacy of bezlotoxumab in children. In the absence of ongoing symptoms, a test of cure is not necessary. The role of probiotics in the prevention of *C. difficile*-associated diarrhea in children has not been established.

Antimicrobial therapy for parasitic infections is shown in Table 387.11. Antivirals such as remdesivir have not been studied for efficacy in the treatment of AGE related to SARS-CoV-2 infection.

PREVENTION

Promotion of Exclusive Breastfeeding and Vitamin A

Exclusive breastfeeding (administration of no other fluids or foods for the first 6 months of life) protects young infants from diarrheal disease through the promotion of passive immunity and through reduction in the intake of potentially contaminated food and water. In developing countries, exclusive breastfeeding for the first 6 months of life is widely

Table 387.11 Antimicrobial Therapy for Infectious Diarrhea

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Shigella spp.	In high-income countries, judicious treatment is recommended to curtail growing antibiotic resistance because most shigellosis is self-limited. Treatment should be reserved for severe disease (require hospitalization, have systemic disease or complications), immunocompromised, or to prevent or mitigate outbreaks in certain settings (e.g., childcare or food handling). Also consider treating patients with significant discomfort, intestinal comorbidities, institutional settings, or household exposure to high-risk individuals. WHO recommends empiric antibiotics for all children in developing countries with dysentery assuming that most cases are caused by *Shigella*.	First line: • Ciprofloxacin* 20 mg/kg/day PO bid × 3 days (max. 1.5 g/day); OR • Azithromycin†12 mg/kg once on first day, then 6 mg/kg once daily on days 2 through 4 (total course: 4 days); OR • Ceftriaxone 50-100 mg/kg/day IV or IM, qd × 3 days for severe illness requiring parenteral therapy. Second line: • Cefixime 8 mg/kg once daily for 3 days if susceptibility is known or likely based on local data; OR • Trimethoprim (TMP)-sulfamethoxazole (SMX): 4 mg/kg/day of TMP and 20 mg/kg/day SMX twice a day for 5 days (if susceptibility known or likely based on local data); OR • Ampicillin 100 mg PO, divided qid, max 2 g/day for 5 days if susceptibility known or likely based on local data (amoxicillin is not effective presumably due to rapid gut absorption)
ETEC	Watery diarrhea in a traveler returning from an endemic area that interferes with planned activities or is persistent (>14 days).	First line: • Azithromycin* 12 mg/kg once on first day, then 6 mg/kg once daily on days 2 and 3 (total course: 3 days) Second line: • Ciprofloxacin† 15 mg/kg/day PO bid × 3 days; OR • Children ≥12 yr: Rifaximin 600 mg/day (not per kilogram), divided tid × 3 days
STEC	Avoid antimicrobials and antimotility drugs.	
Salmonella, nontyphoidal	Antibiotics for uncomplicated gastroenteritis in normal hosts are ineffective, may prolong excretion, and are not recommended. Infection in infants younger than 3 mo and patients with immunocompromise, malignancy, chronic GI disease, severe colitis hemolytic anemia, or HIV infection Most strains are resistant to multiple antibiotics.	See treatment of *Shigella*. Patients without bacteremia can be treated orally for 5-7 days. Patients with bacteremia (proven or until blood culture results are available in a high-risk host) should be treated parenterally until blood cultures clear and then transitioned to PO to complete a total 7- to 10-day course. Focal or disseminated invasive infections (e.g., osteomyelitis, meningitis) and bacteremic patients with HIV/AIDS should be treated parenterally for 4-6 wk. Depending on susceptibilities, ampicillin, TMP-SMX, or fluoroquinolones may be used.
Yersinia spp.	Antibiotics are not usually required for diarrhea, which is usually self-limited and clinical benefits of antibiotics are not established. Neonates and immunocompromised patients and patients with bacteremia and/or focal invasive infections should be treated. Deferoxamine therapy should be withheld for severe infections or associated bacteremia.	For bacteremia or focal invasive infections, use parenteral third-generation cephalosporins. Can also consider TMP-SMX, aminoglycosides, fluoroquinolones, tetracycline or doxycycline, or chloramphenicol. Begin IV then switch to oral when clinically stable, for a total course of 2-6 wk.

Continued

Table 387.11 Antimicrobial Therapy for Infectious Diarrhea—cont'd

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Campylobacter spp.	Dysentery, moderate and severe gastroenteritis or at risk for severe disease (e.g., elderly, pregnant, or immunocompromised), and bacteremia or focal invasive infection. Treatment of gastroenteritis appears effective if given within 3 days of onset of illness.	**For gastroenteritis or dysentery:** • Erythromycin PO 40 mg/kg/day divided qid × 5 days • Azithromycin PO 10 mg/kg/day × 3 days **For bacteremia or focal invasive infection:** • Consider parenteral macrolides or carbapenems pending susceptibility results. Fluoroquinolone resistance is >50% in some areas of the world.
Clostridioides difficile	Colitis • Discontinue inciting antibiotics if possible. • Infectious disease consult suggested if disease is persistent or recurrent.	**First occurrence** *Mild-moderate:* • Metronidazole PO (or IV) 7.5 mg/kg/dose tid or qid × 10 days; max 500 mg per dose • If failure to respond in 5-7 days, consider switch to vancomycin PO 40 mg/kg/day divided qid × 10 days; max 125 mg/dose • For metronidazole-intolerant patients, start with vancomycin PO as above • For patients in whom oral therapy cannot reach the colon, add vancomycin PR 500 mg/100 mL normal saline q8h prn until improvement *Severe:* • Vancomycin PO as above *Severe and complicated:* • Vancomycin PO as above PLUS metronidazole IV 30 mg/kg/day divided qid, max 500 mg/dose • If complicated with ileus or toxic colitis and/or significant abdominal distension, give vancomycin PO PLUS metronidazole IV PLUS vancomycin PR as above × 10 days **First recurrence** *Mild-moderate:* • Same regimen as for first occurrence *Severe:* • Vancomycin PO as above **Subsequent recurrences:** • DO NOT use metronidazole due to risk of neurotoxicity with repeated or prolonged use • Vancomycin PO pulsed or prolonged taper (recommend consulting ID or GI for choice of regimen), OR • Vancomycin × 10 days followed by rifaximin 400 mg/dose tid × 14-20 days (N.B. that rifaximin is not approved in the United States for children <12 yr old), OR • Fidaxomicin × 10 days Children 6 mo to 5 yr: 16 mg/kg/dose (max 200 mg/dose) bid Children 6 yr and older: 200 mg/dose bid
Entamoeba histolytica	• Asymptomatic cyst excreters • Mild to moderate intestinal disease • Severe intestinal or extraintestinal disease (including liver abscess)	*Asymptomatic cyst excreters:* • Iodoquinol PO 30-40 mg/kg/day, (max 650 mg/dose) divided tid × 20 days; OR • Paromomycin PO 25-35 mg/kg/day divided tid × 7 days; OR • Diloxanide furoate 20 mg/kg/day (max 500 mg/dose), orally, divided tid × 10 days *Mild to moderate intestinal disease and severe intestinal or extraintestinal disease:* • Metronidazole PO 30-50 mg/kg/day divided tid × 7-10 days; OR • Children ≥3 yr: Tinidazole PO 50 mg/kg, single dose, max 2 g × 3 days, OR 5 days for severe disease FOLLOWED BY EITHER (to prevent relapse) Iodoquinol PO 30-40 mg/kg/day (max. 650 mg/dose) divided tid × 20 days; OR Paromomycin PO 25-35 mg/kg/day divided tid × 7 days
Giardia duodenalis	Persistent symptoms	• Tinidazole PO 50 mg/kg, single dose, max 2 g (for children ≥3 yr) • Nitazoxanide PO Age 1-3 yr: 100 mg bid × 3 days Age 4-11 yr: 200 mg bid × 3 days Age over 11 yr: 500 mg bid × 3 days • Metronidazole PO 15 mg/kg/day (max 250 mg/dose), divided tid × 5–7 days
Cryptosporidium spp.	Treat immunocompromised and HIV-infected hosts, although efficacy is equivocal. Treatment may not be needed in normal hosts.	*Immunocompetent children:* • Nitazoxanide, as for *Giardia* *Solid organ transplants:* • Nitazoxanide, as for *Giardia*, × 14 days or longer *HIV-infected children:* • Combined antiretroviral therapy is the primary treatment • Nitazoxanide, as for *Giardia* • Paromomycin

Table 387.11 Antimicrobial Therapy for Infectious Diarrhea—cont'd

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Cyclospora spp.	All symptomatic children	Age >2 mo: 8-10 mg/kg/day TMP and 40-50 mg/kg/day SMX PO divided bid × 7-10 days (HIV-infected children may need longer courses)
Cystoisospora spp.	Immunocompromised patients, symptoms that do not resolve after 5-7 days; treat prophylactically in HIV-infected patients with $CD4^+$ count <200 cells/mm^3	• Age >2 mo: 8-10 mg/kg/day TMP and 40-50 mg/kg/day SMX PO divided bid × 7-10 days; • Adults: 50-75 mg/day pyrimethamine PO, either qd or divided bid PLUS 10-25 mg/day leucovorin PO; OR • Ciprofloxacin 500 mg PO bid × 7 days
Blastocystis hominis	The significance of *B. hominis* as a cause of disease is controversial, so treatment should be reserved for those with suggestive symptoms and no other pathogen that could be the cause.	• Metronidazole PO 35-50 mg/kg/day divided tid × 10 days (max 500-750 mg/dose); OR • Age >2 mo: 8 mg/kg/day TMP and 40 mg/kg/day SMX PO divided BID × 7 days; OR • Nitazoxanide, as for *Giardia*, × 3 days; OR • Age ≥3 yr: 50 mg/kg (max 2 g) tinidazole PO once

*Azithromycin and fluoroquinolones should be avoided in patients taking the antimalarial artemether. These drugs can prolong the QT interval on electrocardiogram and trigger arrhythmias.

WHO, World Health Organization; PO, by mouth; prn, as needed; bid, two times a day; IV, intravenous; IM, intramuscular; qd, every day; ETEC, enterotoxigenic *E. coli*; qid, four times a day; STEC, Shiga toxin–producing *E. coli;* SGI, gastrointestinal; tid, three times a day; ID, infectious diseases; GI, gastrointestinal; N.B., *nota bene*.

regarded as one of the most effective interventions to reduce the risk of premature childhood mortality and has the potential to prevent 12% of all deaths of children younger than 5 years of age. Vitamin A supplementation reduces all-cause childhood mortality by 25% and diarrhea-specific mortality by 30%.

Rotavirus Immunization

Five live-attenuated oral **rotavirus** vaccines are available internationally and WHO prequalified: the three-dose pentavalent G1, G2, G3, G4, P[8] human-bovine vaccine (RotaTeq), the two-dose monovalent human G1P[8] vaccine (Rotarix), the three-dose monovalent human-bovine 116E G6P[11] vaccine (Rotavac), and two formulations of the three-dose pentavalent G1, G2, G3, G4, G9 human-bovine vaccine (Rotasiil and Rotasiil Thermo). The result has been substantial reductions in rotavirus-associated and all-cause hospitalizations for diarrheal disease in both vaccinated infants (direct protection) and unvaccinated individuals (indirect, or herd protection), as well as reductions in office visits for less severe rotavirus diarrhea. Reductions in all-cause diarrhea deaths have been demonstrated in some countries since the introduction of these vaccines.

Programmatic uptake is lagging in low-resource settings where most severe disease and death occurs; however, Gavi, the Vaccine Alliance, has supported introduction of rotavirus vaccine into approximately 45 countries. Even though vaccine efficacy against severe rotavirus AGE is lower (50–64%) in low-resource compared with high- resource countries; the number of severe rotavirus AGE prevented per vaccinated child is higher because of the substantially greater baseline rate of severe rotavirus gastroenteritis in developing countries. Vaccine (live virus)-associated rotavirus infection has been reported in children with severe combined immunodeficiency disease, but the vaccine has been shown to be safe in HIV-infected populations. Because of suboptimal efficacy, alternative vaccine formulations are being explored, including parenteral and neonatal vaccines.

Two licensed, efficacious two-dose oral inactivated cholera vaccines (Dukoral for children 2 years and older and Shanchol for children 1 year or older) are available in many countries but currently have no specific indication in endemic and epidemic settings where they could potentially reduce the burden of severe diarrhea and mortality in young children. For travelers, a single-dose live oral cholera vaccine (Vaxchora) is licensed for adults in the United States.

Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene

Much of the reduction in diarrhea prevalence in the developed world is the result of improvement in standards of hygiene, sanitation, and water supply. Strikingly, an estimated 88% of all diarrheal deaths worldwide can be attributed to unsafe water, inadequate sanitation, and poor hygiene. Handwashing with soap and safe excreta disposal can reduce the risk of diarrhea by 48% and 36%, respectively, whereas a 17% reduction is estimated as a result of improvements in water quality.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

387.1 Traveler's Diarrhea

E. Adrianne Hammershaimb and Karen L. Kotloff

Traveler's diarrhea is a common complication of visitors to developing countries and is caused by a variety of pathogens, in part depending on the season and the region visited. It is the most common (28%) travel-associated health problem in children. Traveler's diarrhea can manifest with watery diarrhea or as dysentery. Without treatment, 90% will have resolved within a week and 98% within a month of onset. Some individuals develop more severe or persistent diarrhea and become dehydrated or unwell and may experience complications such as bacteremia and intestinal perforation. Children younger than 2 years are at higher risk for traveler's diarrhea, as well as more severe disease. According to FoodNet, the pathogens identified most commonly in travelers in the United States were ETEC, *C. jejuni, Shigella* spp., and NTS. EAEC and *G. duodenalis* are also important.

TREATMENT

For infants and children, rehydration, as discussed in Chapter 387, is appropriate, followed by a standard diet. Adolescents and adults should increase their intake of electrolyte-rich fluids. Kaolin-pectin, anticholinergic agents, *Lactobacillus,* and bismuth salicylate are not effective therapies. Loperamide, an antimotility and antisecretory agent, reduces the number of stools in older children with watery diarrhea and improves outcomes when used in combination with antibiotics in traveler's diarrhea. However, loperamide should not be used in febrile or toxic patients with dysentery, in those with bloody diarrhea, and in children younger than 6 years.

The effectiveness of antibiotics depends on the pathogen and its susceptibility profile. In forming a treatment plan, the potential side effects should be weighed against the treatment need for a short-lasting and self-limiting disease such as traveler's diarrhea. Antibiotics are not recommended for mild diarrhea that is tolerable, is not distressing, and does not interfere with planned activities but may be considered for moderate diarrhea that is distressing and interferes with planned activities. Antibiotics are recommended for treatment of severe diarrhea that is incapacitating or completely prevents planned activities and

for treatment of dysentery. When empiric therapy is required abroad, azithromycin is suggested for young children, and fluoroquinolones are recommended for older children and adults and as second-line therapy for younger children, depending on local pathogens and susceptibility patterns. Short-duration (3 days) therapy is effective. Rifaximin is approved for use in children 12 years and older but should not be used to treat bloody diarrhea. Rifamycin is an alternative to rifaximin that may be used in patients 18 years and older. Fluoroquinolones, rifaximin, and rifamycin should be avoided in patients of all ages with dysenteric diarrhea. Travelers should be reminded that diarrhea can be a symptom of other severe diseases, such as malaria and MIS-C. Therefore if diarrhea persists or additional symptoms such as fever occur, travelers should seek medical advice. For up-to-date information on local pathogens and resistance patterns, see www.cdc.gov/travel.

If the patient has returned home with diarrhea, a microbiologic evaluation can be obtained before initiating antibiotic therapy. Prolonged diarrhea should prompt further investigation into possible parasitic infections or NTS. Prophylactic antibiotics for travelers are not recommended.

PREVENTION

In the pretravel visit, caregivers should be advised about diarrhea prevention, the signs, symptoms, and management of dehydration, and the use of ORS. ORS and age-appropriate antibiotics should be included in a routine health packet. Travelers should drink bottled or canned beverages or boiled water. They should avoid ice, salads, and fruit they did not peel themselves. Food should be eaten hot, if possible. Raw or poorly cooked seafood is a risk, as is eating in a restaurant rather than a private home. Swimming pools and other recreational water sites can also be contaminated.

Chemoprophylaxis is not routinely recommended for previously healthy children or adults. Nonetheless, travelers should bring azithromycin (younger than 16 years of age) or ciprofloxacin (older than 16 years of age) and begin antimicrobial therapy if diarrhea develops.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 388

Chronic Diarrhea

Anat Guz-Mark and Raanan Shamir

See also Chapters 382.3 and 385.

Chronic diarrhea is defined as stool volume of more than 10 g/kg/day in toddlers/infants and greater than 200 g/day in older children that lasts for 4 weeks or more. **Persistent** diarrhea begins acutely but lasts longer than 14 days. In practice this usually means having loose or watery stools more than 3 times a day, with a deviation from the previous regular stool pattern. *Awakening at night to pass stool, beyond the period of infancy, is often a sign of an organic cause of diarrhea.* The epidemiology has two distinct patterns. In *developing* countries, chronic diarrhea is, in many cases, the result of an intestinal infection that persists longer than expected. This syndrome is often defined as **protracted (persistent) diarrhea**, but there is no clear distinction between protracted (persistent) and chronic diarrhea. In countries with higher socioeconomic conditions, chronic diarrhea is less frequent, and the etiology often varies with age. The outcome of diarrhea depends on the cause and ranges from benign, self-limited conditions, such as toddler's diarrhea, to severe congenital diseases, such as microvillus inclusion disease, which may lead to progressive intestinal failure.

PATHOPHYSIOLOGY

The mechanisms of diarrhea are generally divided into **secretory** and **osmotic**, but often diarrhea is a *combination of both mechanisms*. In addition, *inflammation* and *motility disorders* may contribute to diarrhea. Secretory diarrhea is usually associated with large volume of watery stools and persists when oral feeding is withdrawn. Osmotic diarrhea is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea (Fig. 388.1). The cessation of diarrhea after a 24-hour fasting trial may define "diet-induced diarrhea," which is mainly osmotic in nature, whereas no or minimal change in stool volume and consistency despite fasting will suggest a secretory mechanism, also defined as "electrolyte-transport-related diarrhea."

Secretory diarrhea is characterized by active electrolyte and water fluxes toward the intestinal lumen, resulting from either the inhibition of neutral NaCl absorption in villous enterocytes or an increase in electrogenic chloride secretion in secretory crypt cells as a result of the opening of the cystic fibrosis transmembrane regulator (CFTR) chloride channel, or both. The result is more secretion from the crypts than absorption in the villi that persists during fasting. The other components of the enterocyte ion secretory machinery are (1) the Na-K 2Cl co-transporter for the electroneutral chloride entrance into the enterocyte; (2) the Na-K pump, which decreases the intracellular Na^+ concentration, determining the driving gradient for further Na^+ influx; and (3) the K^+ selective channel, that enables K^+, once it has entered the cell together with Na^+, to return to the extracellular fluid.

Electrogenic secretion is induced by an increase of intracellular concentration of cyclic adenosine monophosphate, cyclic guanosine monophosphate, or calcium in response to microbial enterotoxins, or to endogenous endocrine or nonendocrine molecules, including inflammatory cytokines. Another mechanism of secretory diarrhea is the inhibition of the electroneutral NaCl-coupled pathway that involves the Na^+/H^+ and the Cl^-/HCO_3^- exchangers. Defects in the genes of the Na^+/H^+ and the Cl^-/HCO_3^- exchangers are responsible for congenital sodium and congenital chloride diarrhea, respectively.

Osmotic diarrhea is caused by nonabsorbed nutrients in the intestinal lumen as a result of one or more of the following mechanisms: (1) intestinal damage (e.g., enteric infection); (2) reduced absorptive surface area (e.g., active celiac disease); (3) defective digestive enzyme or nutrient carrier (e.g., lactase deficiency); (4) decreased intestinal transit time (e.g., functional diarrhea); and (5) nutrient overload, exceeding the digestive capacity (e.g., overfeeding, sorbitol in fruit juice). Whatever the mechanism, the osmotic force generated by nonabsorbed solutes drives water into the intestinal lumen. A very common example of

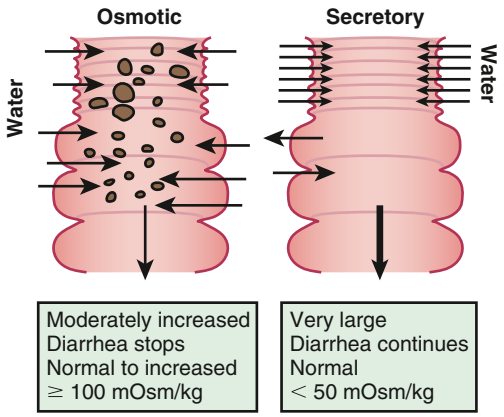

Fig. 388.1 Pathways of osmotic and secretory diarrhea. Osmotic diarrhea is caused by functional or structural damage of intestinal epithelium. Nonabsorbed osmotically active solutes drive water into the lumen. Stool osmolality and ion gap are generally increased. Diarrhea stops or improves dramatically in children when not eating. In secretory diarrhea, ions are actively pumped into the intestine by the action of exogenous and endogenous secretagogues. Usually there is no intestinal damage. Osmolality and ion gap are within normal levels. Large volumes of stools are lost independent of food ingestion.

osmotic diarrhea is lactose intolerance. Lactose, if not absorbed in the small intestine, reaches the colon, where it is fermented to short-chain organic acids, releasing hydrogen that is detected in the lactose breath test, and generating an osmotic overload.

In many children chronic diarrhea may be caused by the combination of multiple mechanisms.

ETIOLOGY

Table 388.1 summarizes the main etiologies of chronic diarrhea in infants and children.

Infectious

Enteric infections are by far the most frequent cause of persistent or chronic diarrhea, both in developing and industrialized countries; however, outcomes are often very different. In the former, comorbid conditions, such as HIV/AIDS, malaria, or tuberculosis, may result in malnutrition that impairs the child's immune response, thereby potentiating the likelihood of prolonging diarrhea or acquiring another enteric infection. Prolonged diarrhea in poor-resource countries may lead to undernutrition, which predisposes the child to additional episodes of diarrhea. Sequential infections with the same or different pathogens may also be responsible for chronic diarrhea. In *developing* countries, enteroadherent *Escherichia coli* and *Giardia lamblia* have been implicated in chronic diarrhea, whereas, in *developed* countries, chronic infectious diarrhea usually runs a more benign course and the etiology is often viral, with rotavirus and norovirus playing major roles (Table 388.2).

Chronic diarrhea in travelers to or expatriates from developing countries may depend on the country of origin. Nonetheless, common pathogens include *Giardia, E. coli, Shigella, Campylobacter, Salmonella,* and enteric viruses. Less common pathogens include amebiasis, *Strongyloides,* and tropical spruce.

Table 388.1 Main Etiologies of Chronic Diarrhea in Children Older and Younger than 2 Years of Age

ETIOLOGY	AGE <2 YR	AGE >2 YR
Infections	+++	+++
Postenteritis syndrome	+++	+++
Immune deficiency	++	Rare
Celiac disease	+++ (after gluten introduction)	+++
Food allergy	+++	+
Inflammatory bowel disease	+ (rare)	+++
Pancreatic insufficiency	++	++
Cholestasis and insufficient bile acids	++	++
Cystic fibrosis	++	+
Lactose intolerance	++ (mostly postinfectious)	+++
Intestinal lymphangiectasia	+	+
Motility disorders	++	Rare
Short bowel syndrome	+++	+
Toddler's and functional diarrhea	++	++
Excessive intake of fruit juices and fluids	++	++
Congenital diarrheal disorders, including structural enterocyte defects and enzymatic or transport malabsorption syndromes	++	Unlikely

Opportunistic microorganisms induce diarrhea exclusively, more severely, or for more prolonged periods, in specific populations, such as immunocompromised children. Specific agents cause chronic diarrhea or exacerbate diarrhea in many chronic diseases. *Clostridium difficile* or cytomegalovirus act as opportunistic agents in patients with malignant diseases as well as in patients with **inflammatory bowel disease (IBD).** *Cryptosporidium* may induce severe and protracted diarrhea in AIDS patients.

Small intestinal bacterial overgrowth (SIBO) results in chronic diarrhea by either a direct interaction between the microorganism and the enterocytes, or the consequence of deconjugation and dihydroxylation of bile salts and hydroxylation of fatty acids due to an increased proliferation of bacteria in the proximal intestine. *Risk factors for SIBO* in children include acid-suppressive therapies, alterations in gastrointestinal (GI) motility and anatomy, as well as poor sanitation conditions.

Postenteritis diarrhea syndrome (see Chapter 387) is a clinicopathologic condition in which small intestinal mucosal damage persists after acute gastroenteritis. Sensitization to food antigens, secondary disaccharidase deficiency, persistent infections, or reinfection with another enteric pathogen may be responsible for causing postenteritis diarrhea syndrome, which is thought to be related to dysregulation of the intestinal microbiota. Functional diarrhea, which may be related to the pathogenesis of irritable bowel syndrome, may be caused by complications of an acute gastroenteritis.

Inflammatory/Immunologic

Celiac disease (see Chapter 384) is a genetically determined immune-mediated intestinal disorder that affects about 1 in 100 individuals, depending on geographic origin. In the genetically susceptible host, gliadin, the major protein of gluten, reacts with the immune system to cause inflammation and villous atrophy. A reduction of intestinal absorptive surface is responsible for the diarrhea in celiac disease, which is reversible upon elimination of gluten from the diet.

Food allergy (mainly cow's milk protein allergy, see Chapter 192) may present during infancy with chronic diarrhea. An abnormal immune response to food proteins can cause a proctitis/colitis or an enteropathy, which may result in inflammatory or malabsorptive diarrhea. **Eosinophilic gastroenteropathy** is characterized by an eosinophilic infiltration of the intestinal wall and is strongly associated with atopy (see Chapter 383). However, although diarrhea in food allergy responds to withdrawal of the responsible food, this does not always occur in eosinophilic gastroenteropathy, in which immune-suppressive therapy may be needed.

IBDs, including Crohn disease, ulcerative colitis, and IBD-undetermined, cause chronic diarrhea that is often associated with abdominal pain, elevated inflammatory markers, and increased concentrations of fecal calprotectin or lactoferrin (see Chapter 382). The age of onset of IBD is broad, with rare cases described in the first few months

Table 388.2 Comparative List of Prevalent Agents and Conditions in Children with Persistent Infectious Diarrhea in Industrialized and Developing Countries

AGENT/DISEASE	
INDUSTRIALIZED COUNTRIES	**DEVELOPING COUNTRIES**
Clostridium difficile	Enteroaggregative *E. coli*
Enteroaggregative *Escherichia coli*	Atypical *E. coli*
Atypical *E. coli*	*Shigella* spp.
	Heat-stable/heat-labile enterotoxin-producing *E. coli*
Astrovirus	Rotavirus*
Norovirus	Cryptosporidium
Sapovirus	*Giardia lamblia*
Rotavirus*	Tropical sprue
Small intestinal bacterial overgrowth (SIBO)	
Postenteritis diarrhea syndrome	

*More frequent in industrialized than in developing countries as agent of chronic diarrhea.

of life, and the peak incidence in childhood occurs in adolescence. The severity of the symptoms is highly variable with a pattern characterized by long periods of well-being followed by exacerbations.

Autoimmune processes may target the intestinal epithelium, alone or in association with extraintestinal symptoms. **Autoimmune enteropathy** is associated with the production of antienterocyte and antigoblet cell antibodies, primarily immunoglobulin A, but also immunoglobulin G, directed against components of the enterocyte brush border or cytoplasm and by a cell-mediated autoimmune response with mucosal T-cell activation. An X-linked immune-dysregulation, polyendocrinopathy, and enteropathy (**IPEX syndrome**) is associated with variable gene mutations and phenotypes of chronic diarrhea (more on autoimmune enteropathy and IPEX syndrome is available in Chapter 382.3).

Immune deficiency can present as chronic diarrhea in children. In these cases (for example, severe combined immunodeficiency or AIDS) the child can be infected by an opportunistic pathogen, can exhibit a persistent diarrhea due to a pathogen usually causing an acute gastroenteritis, or be infected by multiple and recurrent different pathogens causing mucosal damage to the intestines. Other immunoregulatory defects, found in patients with agammaglobulinemia, isolated immunoglobulin A deficiency, and common variable immunodeficiency disorder, may result in mild persistent diarrhea.

Pancreatic Deficiency

Chronic diarrhea may be the manifestation of maldigestion caused by exocrine pancreatic disorders (see Chapters 397 and 399.2). In most patients with **cystic fibrosis**, exocrine pancreatic insufficiency results in steatorrhea and protein malabsorption. In **Shwachman-Diamond syndrome**, exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein-losing enteropathy. Specific isolated pancreatic enzyme defects, such as lipase deficiency, result in fat and/or protein malabsorption. Familial pancreatitis, associated with a pathogenic variant in the trypsinogen gene, may be associated with exocrine pancreatic insufficiency and chronic diarrhea. Pathogenic variants in *CFTR, CTRC, PRSS1, PRSS2, SPINK 1,* and *SPINK 5* are associated with hereditary pancreatitis.

Liver and Bile Acids Disorders

Liver disorders and **cholestasis** may lead to a reduction in the bile salts pool resulting in fat malabsorption causing chronic diarrhea in the form of steatorrhea. Bile acid loss may be associated with diseases affecting the terminal ileum, such as Crohn disease, or following ileal resection. In **primary bile acid malabsorption**, neonates and young infants present with chronic diarrhea and fat malabsorption caused by pathogenic variants of the ileal bile transporter gene. In addition to the fat malabsorption, the bile acid loss from the intestinal lumen is a form of secretory diarrhea by itself (called **cholerheic diarrhea or choleretic diarrhea**, which is usually associated with significant diaper dermatitis).

Carbohydrate Malabsorption

Rare genetic pathogenic variants (see Chapters 385.8 and 385.10) can cause carbohydrate malabsorption. More commonly, **lactose intolerance** is *secondary* to lactase deficiency caused by intestinal mucosal damage (usually as part of postenteritis syndrome, which is a self-limited process). Depending on ethnicity, a progressive, age-related, loss of lactase activity may begin around 7 years of age and affects approximately 80% of the non-White population, and acquired hypolactasia may be responsible for chronic diarrhea in older children receiving cow's milk (adult-type lactase deficiency).

Similarly, **fructose malabsorption** is common in Western countries with estimates as high as 40% of the population. These individuals cannot absorb fructose and often develop bloating, abdominal pain, diarrhea, and flatulence. Typically, they do not have liver disease. This is in contrast to **hereditary fructose intolerance**, a rare genetic disorder with incidence estimated to be 1 in 20,000-30,000. This disease is associated with pathogenic variants in the *ASDOB* gene that encodes for the aldolase B enzyme that is found primarily in the liver and is involved in the metabolism of fructose. Individuals with hereditary fructose intolerance may have nausea, abdominal pain/bloating, vomiting, diarrhea, and hypoglycemia. Continued ingestion of fructose results in *hepatomegaly* and eventually cirrhosis.

Protein-Losing Enteropathy

Chronic diarrhea can be the manifestation of obstructed intestinal lymphatic drainage, causing protein-losing enteropathy with steatorrhea, diarrhea, and lymphopenia. Early-onset protein-losing enteropathy and lymphangiectasia, together with complement activation, could be associated with congenital **CD55 deficiency**. Infantile-onset severe protein-losing enteropathy and altered lipid metabolism could be attributed to pathogenic variants in **DGAT1**.

Along with **intestinal lymphangiectasia**, many diseases that cause intestinal mucosal injury can also result in a secondary protein-losing enteropathy, characterized by low serum protein levels and elevated fecal α_1-antitrypsin (see Chapter 385.2).

Motility Disorders

Disorders of intestinal motility include abnormal development and function of the enteric nervous system, such as in **Hirschsprung disease** and **pediatric intestinal pseudoobstruction (PIPO),** previously termed **chronic intestinal pseudoobstruction.** PIPO encompasses both the neurogenic and the myogenic forms, and is sometimes associated with genitourinary manifestations. Other motility disorders may be secondary to extraintestinal disorders, such as in *hyperthyroidism* and *scleroderma*. Motility disorders are associated with either constipation or diarrhea, or both, with the former usually dominating the clinical picture.

Short Bowel Syndrome

Short bowel syndrome is the single most frequent etiology of intestinal failure in children (see Chapter 385.6). Many intestinal abnormalities such as stenosis, segmental atresia, gastroschisis, and malrotation may require surgical resection, but the most frequent primary cause of short bowel is *necrotizing enterocolitis*. Rarely, a child can be born with congenital short bowel. In these conditions, the residual intestine may be insufficient to carry on its digestive-absorptive functions, resulting in severe chronic diarrhea, malnutrition, and failure to thrive, requiring long-term treatment with parenteral nutrition.

Nonspecific Diarrhea, Including Toddler's Diarrhea

The most benign and common etiology of chronic diarrhea is nonspecific diarrhea that encompasses **functional diarrhea** (or **toddler's diarrhea**) in children younger than 4 years of age and **irritable bowel syndrome** in those, usually, 5 years of age and older. Toddler's diarrhea is defined by the daily painless recurrent passage of four or more large unformed stools, for 4 or more weeks, with onset in infancy or preschool years. Nighttime defecation is usually absent. The child appears unperturbed by the diarrhea, there is no evidence of failure to thrive, and the symptoms resolve spontaneously by school age.

Diarrhea may also be the result of an **excessive intake of fluids and nonabsorbable carbohydrates**. If the child's fluid intake was >150 mL/kg/24 hr, *fluid intake should be reduced not to exceed 90 mL/kg/24 hr* to decrease the stool frequency and volume. If the dietary history suggests that the child is ingesting significant amounts of fruit juice, especially apple juice, then *the consumption of juice should be decreased. Sorbitol, which is a nonabsorbable sugar, is found in apple, pear, and prune juices and often causes diarrhea in toddlers.* Moreover, apple and pear juices contain higher amounts of fructose than glucose, a feature postulated to cause diarrhea in toddlers. In older children, irritable bowel syndrome is often associated with abdominal pain and may be related to anxiety, depression, and other psychological disturbances (see Chapter 389). When the cause of the diarrhea remains undetermined and the clinical course is inconsistent with organic disorders, **factitious** disorder by proxy should be considered.

Congenital Diarrheal Disorders

The most severe etiology of chronic diarrhea includes a number of heterogeneous congenital conditions leading to syndromes often referred to as **intractable or protracted diarrhea**. The genetic and molecular basis of many causes of protracted diarrhea has been identified recently, and the classification of **congenital diarrheal disorders (CDDs)** has been proposed (Table 388.3), also referred to as congenital diarrheas and enteropathies (**CODEs**). These terms represent a group of rare but severe enteropathies, with a similar clinical presentation despite different pathogenesis and outcome. The diarrhea can be either secretory,

Table 388.3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DISEASE	GENE NAME	GENE LOCATION	TRANSMISSION AND INCIDENCE	MECHANISM
DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES				
GENES ENCODING BRUSH-BORDER ENZYMES				
Congenital lactase deficiency (LD)	*LCT*	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	*SI*	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucoamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
GENES ENCODING MEMBRANE CARRIERS				
Glucose-galactose malabsorption (GGM)	*SLC5A1*	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	*SLC2A2*	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	*SLC39A4*	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD)	*SLC26A3*	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	*SLC7A7*	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	*SLC10A2* *SLC51B*	13q33.1 15q22.31	AR	Secretory
Cystic fibrosis (CF)	*CFTR*	7q31.2	AR, 1 in 2,500	Osmotic
GENES ENCODING PANCREATIC ENZYMES				
Enterokinase deficiency (EKD)	*PRSS7*	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	*PRSS1* *PRSS2* *SPINK1* *CTRC* *CFTR*	7q34 7q34 5q32 1p36.21 7q31.2	AD, cases with compound pathogenic variants in different genes; SPINK1 pathogenic variants may also cause tropical pancreatitis	Osmotic, malabsorption
Congenital absence of pancreatic lipase (APL)	*PNLIP*	10q25.3	AR	Osmotic, malabsorption
GENES ENCODING PROTEINS OF LIPOPROTEIN METABOLISM				
Abetalipoproteinemia (ALP)	*MTP*	4q27	AR, about 100 cases described; higher frequency among Ashkenazi Jews	Osmotic
Hypobetalipoproteinemia (HLP)	*APOB* *ANGPTL3*	2p24.1 1p31.3	Autosomal codominant/AR	Osmotic
Chylomicron retention disease (CRD)	*SAR1B*	5q31.1	AR, about 40 cases described	Osmotic
GENES ENCODING OTHER TYPES OF PROTEINS				
Congenital sodium diarrhea (CSD)	*SPINT2* (only syndromic CSD) *SLC9A3*	19q13.2 5p15.33	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	*SBDS*	7q11	AR	Osmotic
Activating guanylate cyclase-C pathogenic variant	*GUCY2C*	12p12.3	AD	Secretory
GENES ENCODING FOR OTHER ENZYMES				
Defect in triglyceride synthesis	*DGAT1*	8q24.3	AR	Protein-losing enteropathy
DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION				
Microvillus inclusion disease (MVID)	*MYO5B* *STX3*	18q21.1 11q12.1	AR; rare	Secretory
Congenital tufting enteropathy (CTE)	*EPCAM*	2p21	AR; 1 in 50,000-100,000; higher among Arabs	Secretory
Trichohepatoenteric syndrome (THE)	*TTC37* *SKIV2L*	5q15 6p21.33	AR; 1 in 400,000	Secretory
Neonatal-onset chronic diarrhea-9 (DIAR9)	*WNT2B*	1p13.2	AR; few cases described	Osmotic

Continued

Table 388.3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance—cont'd

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES				
DISEASE	**GENE NAME**	**GENE LOCATION**	**TRANSMISSION AND INCIDENCE**	**MECHANISM**
DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION				
Congenital malabsorptive diarrhea (CMD), Enteric anendocrinosis	*NEUROG3*	10q22.1	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	*PCSK1*	5q15	AR	Osmotic
Intractable malabsorptive diarrhea of infancy (DIAR11)	*PERCC1*	16p13.3	AR; few cases described in Jewish Iraqi families	Presumed impaired function of enteroendocrine cells (EECs)
DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE				
Autoimmune polyglandular syndrome type 1 (APS1)	*AIRE*	21q22.3	AR; AD (1 family)	Inflammatory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	*FOXP3*	Xp11.23	X-linked (autosomal cases described), very rare	Inflammatory
IPEX-like syndrome	*CD25* *STAT5b* *STAT3* *STAT1(GOF)* *LRBA* *CTLA4*	Multiple	Not X-linked	Inflammatory
CD55 deficiency	*CD55*	1q32.2	AR, rare	Protein-losing enteropathy

AD, Autosomal dominant; AR, autosomal recessive; GOF, gain of function.

osmotic, or combined, depending on the specific defect. Often severe diarrhea presents at birth or shortly thereafter, but in milder forms diarrhea may go unrecognized for years. *CDDs can be classified in four groups*: defects of digestion, absorption, and transport of nutrients and electrolytes; defects of enterocyte differentiation and polarization; defects of enteroendocrine cell (EEC) differentiation; and defects of modulation of intestinal immune response.

Although CDDs are rare diseases, in most specific disorders the genetic defect and transmission are known. The incidence of genetic disorders associated with CDD can range from 1 in 2,500 for cystic fibrosis, 1 in 5,000 for sucrose-isomaltase deficiency, 1 in 60,000 for congenital lactase deficiency, to 1 in 400,000 for trichohepatoenteric syndrome. For most CDDs, such as IPEX syndrome or autoimmune polyglandular syndrome type 1, the clinical application of exome sequencing is likely to increase identification of more patients with these rare causes of chronic diarrhea. Selected CDDs are more frequent in ethnic groups where consanguineous marriages are common, or in some geographic areas because of founder effects. Congenital lactase deficiency is more common in Finland; lysinuric protein intolerance has a higher incidence either in Finland and in Japan because of founder effect, and a specific pathogenic variant is typically found in each of the two ethnic groups. A defect in the *DGAT1* gene was first identified using whole exome sequencing in an Ashkenazi Jewish family and associated with the early onset of vomiting and nonbloody diarrhea with protein-losing enteropathy. In few families of Jewish Iraqi origin with intractable diarrhea of infancy, a noncoding deletion was recently identified on chromosome 16p13, presumably leading to impairment in EEC function. For specific CDDs see Chapters 385.2 and 385.10.

Most cases of protracted diarrhea syndrome are not easily treated. The natural history of protracted diarrhea is related to the primary intestinal disease or the specific defect in nutrient absorption. Although some specific conditions may improve with nutritional therapy and dietary eliminations (for example, glucose-galactose malabsorption or congenital protein-losing enteropathy), most cases of CDDs result in chronic intestinal failure requiring long-term parenteral nutrition, with poorer prognosis, and are more likely to be candidates for intestinal transplantation (see Chapter 386). Some late-onset CDDs may be relatively mild and are recognized only later in life. Infantile-onset or neonatal IBDs are a distinct group of diseases, also occurring during infancy, characterized by more inflammatory and often bloody component in stools (see Chapter 382.3).

EVALUATION OF PATIENTS

Because of the wide spectrum of etiologies, the medical approach should be based on diagnostic algorithms that begin with assessment for infectious causes, and then consider the age of the child, growth, and clinical and epidemiologic factors. Early onset in the neonatal period is rare and may suggest a congenital or severe condition (see Chapter 382.3); however, infections and food allergy are more frequent in this age group, and together with GI malformations should be high on the differential diagnosis. In later infancy and up to 2 years of age, infections and allergies are the most common causes, while inflammatory diseases are more frequent in older children and adolescents. Celiac disease as well as functional nonspecific diarrhea should always be considered independently of age because of their relatively high frequency at all ages beyond early infancy.

Specific clues in the family and personal history may provide useful indications, suggesting a congenital, allergic, or inflammatory etiology. A history of *polyhydramnios* is consistent with congenital chloride/sodium diarrhea (where a typical sonographic finding of dilated fetal bowel loops is present), microvillus inclusion disease, cystic fibrosis, and other CDDs, as well as a family history of a chronic or intractable diarrhea in a relative presenting in the first month of life, and particularly *consanguinity*. An acute onset of diarrhea that runs a protracted course suggests postenteritis diarrhea, secondary lactase deficiency, SIBO, or the onset of nonspecific functional diarrhea. The association of diarrhea with specific foods may indicate a nutrient basis, such as intolerance to selected nutrients (fructose). Anthropometric evaluation is essential to understand if diarrhea has affected weight gain and growth, providing estimation of the severity of diarrhea. Normal weight and growth strongly support functional diarrhea that may respond to simple dietary management. It should be noted that a child with functional diarrhea may be inappropriately "treated" with a diluted hypocaloric diet in an effort to reduce the diarrhea, resulting in impaired growth.

Initial clinical examination should include the evaluation of general and nutritional status. Dehydration, marasmus, or kwashiorkor require prompt supportive interventions to stabilize the patient. Nutritional

evaluation should start with the evaluation of the weight and height curves, and anthropometric indices to determine the impact of diarrhea on growth. Weight is generally impaired before height, but with time, linear growth also becomes affected, and both parameters may be equally abnormal in the long term. **Assessment of nutritional status** includes a dietary history, physical examination, and biochemical testing including nutritional investigations. *Caloric intake* should be quantitatively determined, energy requirements determined, and the relationship between weight modifications and energy intake should be carefully considered. Assessment of body composition may be performed by measuring mid-arm circumference and triceps skinfold thickness or by bioelectrical impedance analysis, dual-emission x-ray absorptiometry scans, or air plethysmography. Biochemical markers including albumin, prealbumin, retinol binding protein, serum iron, and transferrin may assist in grading malnutrition, as the half-life of serum proteins may distinguish between short- and long-term malnutrition. Evaluation of micronutrient concentrations should always be considered. Zinc, magnesium, vitamin A, and folate deficiency are associated with chronic diarrhea and should be provided if needed.

In infants with chronic diarrhea, feeding history must be carefully obtained, providing clues for allergy or specific food intolerance, such as cow's milk protein allergy or sucrose-isomaltase deficiency. Associated symptoms and selected investigations provide important diagnostic clues. Signs of general inflammation such as fever, mucoid or bloody stools, and abdominal pain may suggest IBD. The presence of eczema or asthma is associated with an allergic disorder, whereas specific extraintestinal manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an autoimmune disease. Specific skin lesions may be suggestive of **acrodermatitis enteropathica,** which might respond to zinc supplementation. Typical facial abnormalities and woolly hair are associated with phenotypic diarrhea **(trichohepatoenteric syndrome)**.

INVESTIGATIONS

Microbiologic investigation should include a thorough list of intestinal bacterial, viral, and protozoan pathogens. Proximal intestinal bacterial overgrowth may be determined using the lactulose hydrogen breath test, but false-positive tests are common (see Chapter 385.8).

Initial investigations of a child with chronic diarrhea beyond the period of infancy should always include an assessment of intestinal inflammation using fecal markers as calprotectin or lactoferrin, and serology for celiac disease (see Chapter 384). The role of intestinal mucosal biopsy is determined by the noninvasive diagnostic evaluation in consultation with a pediatric gastroenterologist.

Noninvasive assessment of digestive-absorptive function and of intestinal inflammation plays a key role in the diagnostic workup (Table 388.4). Abnormalities in the digestive-absorptive function tests suggest small bowel involvement, whereas intestinal inflammation, as demonstrated by increased fecal calprotectin, supports colitis.

Determining the osmotic versus secretory nature of the diarrhea in neonates and infants with protracted diarrhea is especially important. The **stool osmolar gap**, sometimes called stool ion gap, is calculated as 290 mOsm/kg (or measured stool osmolality) minus [2 × (stool Na + stool K)]. If the osmolar gap is above 100 mOsm/kg, fecal osmolality is derived from ingested or nonabsorbed osmotically active solutes or nonmeasured ions. In contrast, a low gap (<50 mOsm/kg) is typically observed in secretory diarrhea. It is also important to measure Cl^- concentration in the stool to rule out **congenital chloride diarrhea**, which is characterized by low osmolar gap combined with high fecal Cl^- loss (>90 mmol/L).

Whereas most etiologies of chronic diarrhea can be exaggerated by feeding and have osmotic or mixed nature to the stool, secretory diarrhea necessitates investigation for congenital defects in enterocytes, defects in the intestinal immune response (IPEX and autoimmune enteropathy), and disorders of bile acid malabsorption. Because of the overlap between secretory and osmotic features of the diarrhea in many diseases, a classification based on the response to bowel rest was also introduced. Severe diarrhea that persists at bowel rest is characteristic of **congenital enteropathies** (**microvillus inclusion disease, tufting enteropathy**). Diarrhea that disappears at bowel rest can imply carbohydrate or fat malabsorptive syndromes, as well as defects in EECs. In most other etiologies the diarrhea can decrease significantly, but not disappear, in response to bowel rest, including some congenital diseases as well as acquired inflammatory and other enteropathies.

Histology is important in establishing mucosal involvement, noting changes in the epithelial cells and villus/crypt ration, presence of mucosal inflammation or in identifying specific intracellular inclusion bodies caused by pathogens, such as cytomegalovirus, or the presence of parasites. Electron microscopy is essential to detect subcellular structural abnormalities such as microvillus inclusion disease, though the latter can be diagnosed with specific staining of the basal membrane on regular biopsies. Immunohistochemistry allows the study of

Table 388.4 Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
α_1-Antitripsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5%-fold (older than 2 yr) increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 µg/g	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 µg/g (in children upto 4 yr of age) <50 µg/g (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5 per microscopic field	Colonic inflammation
Fecal lactoferrin	Absent	Inflammation
Nitric oxide in rectal dialysate	<5 µM of NO_2^-/NO_3^-	Rectal inflammation
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

mucosal immunity as well as of other cell types (smooth muscle cells and enteric neuronal cells).

Imaging may also have a role in the diagnostic approach. Abdominal ultrasound may help in detecting liver and pancreatic abnormalities or an increase in bowel wall thickness that suggests IBD. A preliminary plain abdominal x-ray is useful for detection of abdominal distention, suggestive of intestinal obstruction, or increased retention of colonic feces. Intramural or portal gas may be seen in necrotizing enterocolitis or intussusception. Structural abnormalities such as diverticula, malrotation, stenosis, blind loop, and congenital short bowel, as well as motility disorders, may be investigated through a barium meal and a small bowel follow-through. In older children, capsule endoscopy may be considered to further assess intestinal inflammation or bleeding, and capsule technology can be used to measure pressure, pH, and temperature through the GI tract, assessing motility. Bile malabsorption may be explored by the retention of the bile acid analog ^{75}Se-homocholic acid-taurine (^{75}SeHCAT) in the enterohepatic circulation.

Specific investigations should be carried out for specific diagnostic indications. Prick and patch test may support a diagnosis of food allergy. However, an elimination diet with withdrawal of the suspected harmful food from the diet and subsequent challenge is the most reliable strategy by which to establish a diagnosis.

Once infectious agents have been excluded and nutritional assessment performed, a stepwise approach to the child with chronic diarrhea may be applied. The main causes of chronic diarrhea should be investigated, based on the features of the diarrhea (watery, fatty, mucous, or bloody) and the specific nutrient(s) that is (are) affected. The use of whole exome sequencing or specific molecular analysis may be especially essential in children suspected of having CDD, and early genomic testing is recommended in these circumstances. A step-by-step diagnostic approach is important to minimize the unnecessary use of invasive procedures as well as the cost, while optimizing the yield of the diagnostic evaluation (Table 388.5).

TREATMENT

Chronic diarrhea associated with impaired nutritional status should always be considered a serious disease, and therapy should be started promptly. Treatment includes general supportive measures, nutritional rehabilitation, elimination diet, and medications. The latter include therapies for specific etiologies as well as interventions aimed at counteracting fluid secretion and/or promoting restoration of disrupted intestinal epithelium. Because death may be caused by dehydration or electrolyte abnormalities, replacement of fluid and electrolyte losses is the most important early intervention.

Nutritional rehabilitation is often essential and is based on clinical and biochemical assessment. In moderate to severe malnutrition, caloric intake should be carefully advanced to avoid the development of *refeeding syndrome* and may be progressively increased to 50% or more above the recommended dietary allowances to also allow catch-up growth. In children with steatorrhea, medium-chain triglycerides may be a major source of lipids. A lactose-free diet should be considered in children with chronic diarrhea. In these cases, lactose is generally replaced by maltodextrin or a combination of complex carbohydrates. A sucrose-free formula is indicated in sucrase-isomaltase deficiency. Semi-elemental or elemental diets have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhea, particularly in infancy and early childhood, and facilitating nutrient absorption. The sequence of elimination should usually begin from less to more restricted diets, that is, cow's milk protein hydrolysate to amino-acid–based formulas, depending on the child's condition. In severely compromised infants, it may be prudent to start with amino-acid–based feeding.

When oral nutrition is not feasible or fails, enteral or parenteral supplementation should be considered. **Enteral nutrition** may be provided via nasogastric or gastrostomy tube and is indicated in a child who is not able to be adequately fed orally. In extreme wasting and in cases of significant intestinal mucosal damage or dysfunction, enteral nutrition may not be tolerated, and **parenteral nutrition** is required.

Micronutrient and vitamin supplementation are part of nutritional rehabilitation, especially in malnourished children in developing countries. Zinc supplementation is important in both prevention and therapy of chronic diarrhea, since it promotes ion absorption, restores epithelial proliferation, and stimulates immune response. Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

Functional diarrhea in children may benefit from a diet based on the "4 F" principles (reduce fructose and fluids, increase fat and fiber). The use of probiotics (mostly Lactobacillus GG or *Saccharomyces boulardii*) in infectious and postinfectious diarrhea in children may be tried as adjunctive therapy with reduction in symptom duration, but there is insufficient evidence to recommend their routine use for chronic diarrhea.

Pharmacologic therapy includes, based on the etiology, antiinfectious drugs, immune suppression, and drugs that may inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected infectious diarrhea. Table 388.6 summarizes the antimicrobial treatment of infectious persistent diarrhea. Immune suppression

Table 388.5 Stepwise Diagnostic Approach to Children and Infants with Chronic Diarrhea

INITIAL EVALUATION	
Personal and family history: Prenatal sonography; feeding history; family history of protracted diarrhea; consanguinity	**Infectious workup:** Stool cultures; parasites; viruses
Physical examination: Signs of malnutrition; dysmorphism; skeletal abnormalities; organomegaly; dermatitis	**Allergic workup:** Elimination diet trial
⬇	
LABORATORY TESTS	
Stool analysis: Stool volume following fasting; stool electrolytes and ion gap; pH and reducing substances; steatocrit; fecal leukocytes and calprotectin; fecal elastase; α_1-antitrypsin	**Blood and serum analysis:** Serum electrolytes; lipid profile; albumin and prealbumin; amylase and lipase; inflammatory markers; ammonia; celiac serology
⬇	
IMAGING	
Abdominal ultrasound: Bowel wall thickening; liver and bile disorders	**X-ray, contrast studies, computed tomography, magnetic resonance imaging:** Congenital malformation; signs of motility disorders
⬇	
ENDOSCOPIES AND INTESTINAL HISTOLOGY	
Endoscopy and standard jejunal/colonic histology*; morphometry; PAS staining; intestinal immunohistochemistry; electron microscopy	
⬇	
GENETIC INVESTIGATION	
Specific molecular analysis	Whole exome sequencing
⬇	
OTHER SPECIAL INVESTIGATIONS	
Sweat test; specific carbohydrates breath tests; ^{75}SeHCAT measurement; antienterocyte antibodies; metabolic diseases workup; motility studies; neuroendocrine tumor markers	

*The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.

PAS, Periodic acid–Schiff; ^{75}SeHCAT, ^{75}Se-homocholic acid-taurine.

Table 388.6 Antimicrobial Treatment for Persistent Diarrhea

	DRUG	INDICATIONS	DOSAGE	DURATION
Antibiotics	Trimethoprim-sulfamethoxazole	*Salmonella* spp., *Shigella* spp.	6-12 mg/kg/day (of trimethoprim) in 2 divided doses daily per os	5-7 days
	Azithromycin	*Shigella* spp., *Campylobacter*	1 day: 12 mg/kg/day once daily per os 2-5 days: 6 mg/kg/day once daily per os * Alternative: 10 mg/kg/day once daily per os, for 3 days	5 days
	Ciprofloxacin	*Shigella* spp.	20-30 mg/kg/day in 2 divided doses, per os or IV	3 days
	Ceftriaxone	*Shigella* spp.	50-100 mg/kg/day once daily per IM or IV	2-5 days
	Metronidazole	*Giardia, Amebiasis, Blastocystis, Clostridium difficile*	15-35 mg/kg/day in 2-3 divided doses per os	7-10 days
	Paromomycin	*Amebiasis*	25-35 mg/kg/day in 3 divided doses per os	7 days
	Vancomycin	*C. difficile*	40 mg/kg/day in 4 divided doses per os	10 days
Antiparasitic	Nitazoxanide	*Amebiasis, Giardiasis, Blastocystis, Cryptosporidiosis*	100 mg every 12 hr for children ages 12-47 mo 200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr	3 days
	Albendazole	*Ascaris*, hookworm, and pinworm infection	400 mg	Once

*Depends on local susceptibility profile.
IM, Intramuscular; IV, intravenous; os, by mouth.

should be considered in selected conditions such as autoimmune enteropathy and IBD.

Treatment may be also directed at modifying specific pathophysiologic processes. Secretion of ions may be reduced by antisecretory agents, such as the enkephalinase inhibitor racecadotril. Some benefit from absorbents, such as diosmectite, has been described, with reduction of diarrhea duration in infectious diarrhea. In diarrhea caused by neuroendocrine tumors (NETs), microvillus inclusion disease and enterotoxin-induced severe diarrhea, a trial of somatostatin analog octreotide may be considered. Zinc promotes both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated.

When therapeutic attempts and other nutritional supportive measures have failed, the only option to treat children with intestinal failure, while maintaining adequate growth and development, may be long-term parenteral nutrition or eventually intestinal transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

388.1 Diarrhea from Neuroendocrine Tumors

Shimon Reif and Raanan Shamir

The incidence of NETs originating in the GI tract is increasing globally. Physicians' awareness, endoscopic screening, and increased sensitivity of diagnostic tools may at least in part explain this trend. Most of these tumors involve the gastro-entero-pancreatic tract. Neuroendocrine neoplasm cells possess features of both neural and epithelial cells. The commonly perceived notion of NETs is of slow-growing malignancies with a benign course. Although well-differentiated GI-NETs may exhibit indolent clinical behavior, studies indicate that they are frequently already metastatic at diagnosis, and in which case they are neuroendocrine carcinomas.

The majority of NETs (75–90%) are not associated with elevated hormone levels and do not cause a clinical syndrome such as diarrhea. Functional tumors are tumors that make excess hormone, leading to clinical syndromes. These include insulinoma, gastrinoma, vasoactive intestinal polypeptide (VIP) secreting tumors, glucagonoma, and somatostatinoma. A child with persisted watery secretary diarrhea should be evaluated for a functional NET.

The most common NET in children is **carcinoid,** which is generally a low-grade tumor, especially when it is small (<1 cm). It is equally distributed between the small and large intestine and can commonly be found in the appendix. Most carcinoids are found incidentally and are asymptomatic, especially those that are located in the appendix. Some NET patients (around 10%) will develop secretory diarrhea requiring symptom control to optimize quality of life and clinical outcomes. Such patients are defined as having carcinoid syndrome, characterized by excessive production of one or more peptides, which, when released into the circulation, exert their endocrine effects and can be measured by radioimmunologic methods (in the plasma or as their urinary metabolites). These peptides, therefore, also act as tumor markers. Compared to carcinoid, VIPomas are much less frequent. Because VIP is a more potent vasoactive peptide, it induces more profuse diarrhea, with up to 70% of patients having volumes greater than 3 L/day. Though rare as a cause of watery diarrhea, a NET should be considered in the differential diagnosis when diarrhea is unusually severe or takes a chronic course (resulting in electrolyte and fluid depletion). GI-NETs may be associated with flushing, palpitations, or bronchospasm. Family history may reveal multiple endocrine neoplasia (MEN) 1 or 2 syndromes (Table 388.7).

Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoloacetic acid (a metabolite of serotonin) and other specific biochemistry being guided by the suspected syndrome (see Table 388.7). Localization of any NET is best achieved using a multimodality approach. *Whole body* CT or MRI with somatostatin receptor PET screening may be required with gallium-68 DOTATOC (synthetic octreotate) PET.

Table 388.7 Diarrhea Caused by Neuroendocrine Tumors

TUMOR AND CELL TYPE	SITE	MARKERS	SIGNS OF HORMONE HYPERSECRETION	THERAPY
Carcinoid	Intestinal argentaffin cells, typically midgut, also foregut and hindgut, ectopic bronchial tree	**Serotonin (5-HT), urine 5-HIAA*** (diagnostic) Also produce substance P, neuropeptide K, somatostatin, VIP chromogranin A	Secretory diarrhea, crampy abdominal pain, flushing, wheezing (and cardiac valve damage if foregut site)	Resection Somatostatin analog, (palliative) Genetic MEN-1
Gastrinoma, Zollinger-Ellison syndrome	Pancreas, small bowel, liver, and spleen	**Gastrin**	Multiple peptic ulcers, secretory diarrhea	H_2-blockers, PPI, tumor resection, (gastrectomy) Genetic MEN-1
Mastocytoma	Cutaneous, intestine, liver, spleen	**Histamine, VIP**	Pruritus, flushing, apnea If VIP, diarrhea	H_1- and H_2-blockers, steroids, resection if solitary
Medullary carcinoma	Thyroid C-cells	**Calcitonin, VIP, prostaglandins**	Secretory diarrhea	Radical thyroidectomy ± lymphadenectomy (genetic MEN-2A/B, familial MTC)
Ganglioneuroma, pheochromocytoma, ganglioneuroblastoma, neuroblastoma	Chromaffin cells; abdominal > other sites; extraadrenal or adrenal	**Metanephrines** and **catecholamines, VIP** VMA, HMA in neuroblastoma	Hypertension, tachycardia, paroxysmal palpitations, sweating, anxiety, watery diarrhea†	Perioperative α-adrenergic (BP) and β-adrenergic blockade with volume support tumor resection Genetic MEN-2 (*RET* gene), VHL, NF-1, SDH
Somatostatinoma	Pancreas	**Somatostatin**	Secretory diarrhea, steatorrhea, cholelithiasis, diabetes	Resection Genetic MEN-1
VIPoma	Pancreas	**VIP, prostaglandins**	Secretory diarrhea, achlorhydria, hypokalemia	Somatostatin analogs, resection Genetic MEN-1

*Bold indicates major markers.
†Diarrhea has been reported only in adult patients with pheochromocytoma.
BP, Blood pressure; H_1, histamine receptor type 1; H_2, histamine receptor type 2; HMA, homovanillic acid; MEN-1, multiple endocrine neoplasia type 1; MTC, medullary thyroid carcinoma; NF-1, neurofibromatosis type 1; PPI, proton pump inhibitor; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease; VIP, vasoactive intestinal polypeptide; VMA, vanillylmandelic acid.

Therapeutic interventions to be considered include surgical, pharmacologic, and radioisotope therapy; choice of therapy is based on disease extent and location, tumor grade, pace of disease progression, symptoms, and comorbidities.

Tumor resection is the treatment of choice when the tumor is small and localized. The goals of resection are twofold: (1) management of the endocrine syndrome to control symptoms and (2) tumor control to improve survival. However, resection can precipitate life-threatening adrenergic crises. When arising in the appendix, carcinoid tumors less than 2 cm in size can be managed by simple appendectomy. When greater than 2 cm in size or arising from the base of the appendix, a right hemicolectomy is indicated. Fortunately, in pediatric patients, metastases are rare; when they occur, it is usually in the liver. Tumor histochemistry will confirm the NET type and classification. Pharmacologic treatment may include the use of long-acting somatostatin analogues as first-line therapy. This usually results in a pronounced improvement of symptoms including diarrhea. However, many patients become resistant to somatostatin. Diarrhea caused by pancreatic insufficiency, secondary to somatostatin analog use, is often oily and malodorous and should be treated with pancreatic enzyme replacement. Everolimus is an oral medication and a more specific target of rapamycin (mTOR) inhibitor, and has been reported as add-on treatment to octreotide, primarily in adult patients. The tyrosine kinase inhibitor sunitinib is another option. Data suggest a positive effect of ondansetron, a serotonin-3-receptor antagonist, on diarrhea. Peptide receptor radioisotope therapy also has been reported as a therapeutic modality.

Diarrhea and flushing associated with the carcinoid syndrome can be debilitating. Telotristat ethyl is an inhibitor of tryptophan hydroxylase that acts to reduce serotonin levels and has emerged as a promising agent for control of refractory carcinoid syndrome diarrhea.

The diagnosis of NET in children should prompt a genetic referral to exclude a familial syndrome.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 389

Disorders of Brain-Gut Interaction (Functional Gastrointestinal Disorders)

Asim Maqbool, Chris A. Liacouras, Jefferson N. Brownell, and Paul J. Ufberg

Disorders of brain-gut interaction (DBGI), formerly classified as functional gastrointestinal disorders (FGIDs), comprise a group of conditions that relate to the gastrointestinal (GI) tract and cannot be completely explained by other underlying etiologies such as GI, anatomic, physiologic, or biochemical abnormalities. Conversely, DBGI are defined as a group of disorders classified by GI symptoms related to any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, and/or central nervous system processing. DBGI are common worldwide in children of all ages and often pose diagnostic challenges, as there is no anatomic or laboratory-based testing that can be used to define them. The symptom-based criteria employed to classify DBGI have been developed and reevaluated through multiple iterations by expert consensus under the auspices of the Rome Foundation and are thus referred to, in their most recent form, as the Rome IV criteria. In this newest iteration, published in May 2016, the term *functional gastrointestinal disorders* has been retired due to its nonspecificity and potential for stigma in favor of the more specific DBGI. The criteria defining DBGI strive not to be entirely based on diagnoses of exclusion, but rather aim to be based on objective, unambiguous, and accurate criteria derived from the presentation as elicited during a medical history and clinical examination. They aim to provide a uniform, reliable, and reproducible framework to minimize unnecessary evaluations that are likely to have low diagnostic yield or relevance. It is important to recognize that DBGI may coexist or interact with other organic GI disorders, such as inflammatory bowel disease, celiac disease, or chronic pancreatitis; at the same time, DBGI themselves exist as related entities on a spectrum with considerable overlap. Ongoing research has implicated a complex interaction between gut microbiota and host immune responses, altered motility, visceral hypersensitivity, genetic factors, and the enteric nervous system in the pathophysiology of DBGI (Fig. 389.1). Furthermore, DBGI may be influenced by psychosocial stressors or a result of an otherwise benign episode of abdominal pain (Fig. 389.2). Early life physical or psychologic stressors may manifest later via DBGI. Maladaptive responses or lack of adequate coping skills may complicate the treatment of DBGI but may also allow for a valuable approach to management using behavioral therapies.

DBGI in children encompass two age-groups: infants/toddlers and children/adolescents. Rumination syndrome, functional constipation, and cyclical vomiting span both age-groups (Fig. 389.3).

DISORDERS OF BRAIN-GUT INTERACTION IN INFANTS AND TODDLERS

Infant regurgitation is the most common DBGI in the first year of life and describes effortless retrograde and involuntary passage of gastric contents from the stomach cephalad and is more commonly referred to as gastroesophageal reflux (Table 389.1). When refluxate reaches the oropharynx and is visible, it is labeled as regurgitation. This phenomenon is normal for healthy infants unless there are complications associated with the process, such as esophageal inflammation, dysphagia, feeding difficulties, inadequate oral intake to meet needs leading to failure to thrive, or the inability to protect the airway with risk for aspiration; in this setting gastroesophageal reflux *disease* is the correct designation (see Chapter 369). Unlike vomiting, regurgitation does not include the forceful expulsion of gastric contents. The peak incidence of infant regurgitation is 4 months of age, followed by a decline in frequency through 12 months of age.

Infant rumination is defined as a habitual regurgitation of gastric contents into the oropharynx to allow for mastication and swallowing (Table 389.2). It is thought to be a form of self-stimulation and may occur in the setting of emotional or sensory deprivation. The regurgitation of gastric contents is effortless, and the refluxate can be chewed and reswallowed instead of expelled from the oropharynx. Infant rumination occurs between 3 and 8 months of age and does not respond to measures used to manage regurgitation. This phenomenon does not occur during socialization/interaction with individuals, does not occur during sleep, and is not associated with distress. Empathy and nurturing lay the foundation for management.

Cyclic vomiting syndrome (CVS) is characterized by repeated episodes of stereotypical vomiting punctuated by periods of normal health in between. It has been reported in infants and children younger than 3 years of age and is most common between ages 2 and 7. The median age of presentation is 4 years (see Chapter 390).

Infant colic (see Chapter 23.1) is a normal developmental process associated with fussiness, irritability, and difficulty consoling the infant (Table 389.3). A trigger is not identifiable; the unexplained episodes of apparent discomfort are often quite stressful to the caregivers and identifying a cause may be their main concern. Infant colic typically occurs between 1 and 4 months of age, with episodes of crying occurring more often in the afternoon or evening. The behavior tends to peak after 4-6 weeks, followed by a gradual decline to resolution about 12 weeks after initial onset. The typical behavior usually leads to consultation with a pediatrician or a pediatric gastroenterologist out of suspicion for abdominal pain despite the absence of any correlating evidence. Associated behaviors, including facial grimace, abdominal distension, increasing gas, skin flushing, and drawing legs up to the abdomen are nondiagnostic but may be worrisome to the caregiver. Patients are often treated for gastroesophageal reflux, gas, or suspected allergy, leading to unnecessary dietary changes and medication use. Treatment includes multiple approaches based on caregiver vulnerabilities. Approaches may include reassuring the caregiver through demonstration that a held, rocked infant may be soothed, prospectively logging crying and other behaviors, and ensuring that caregiver exhaustion is addressed via support system. Probiotics have been investigated as a possible treatment; however, systematic reviews have not demonstrated any beneficial effect. Regardless of the primary approach, providing reassurance, education, and ensuring adequate coping skills and support for caregivers is key. Infant colic ultimately resolves on its own.

Functional diarrhea is often also referred to as *toddler's diarrhea* or *chronic nonspecific diarrhea of toddlerhood* and describes the daily painless passage of three or more large unformed stools for four or more weeks in a well-nourished child. The stools often contain visibly undigested food and mucus, which may be distressing to the caregiver. The onset is typically in infancy or preschool years and excludes steatorrhea and other malabsorptive etiologies (Table 389.4). Nutritional factors such as excessive total calorie intake, as well as excessive dietary intake of the sugar alcohol sorbitol and the carbohydrate fructose, coupled with a low-fat diet, have been implicated in this osmotic process. An evaluation of the diet for other possible etiologies as well as assessment for infections, inflammation, and medication use including antibiotics and laxatives is important. In addition, assessments of growth as well as ruling out fecal impaction and encopresis via digital rectal examination are important. Dietary changes such as reducing fruit juice and processed fructose intake are helpful in resolving symptoms. Care should be taken to not overly restrict the child's diet in an effort to avoid simple sugars. Fiber supplementation may be of some benefit, but evidence is lacking.

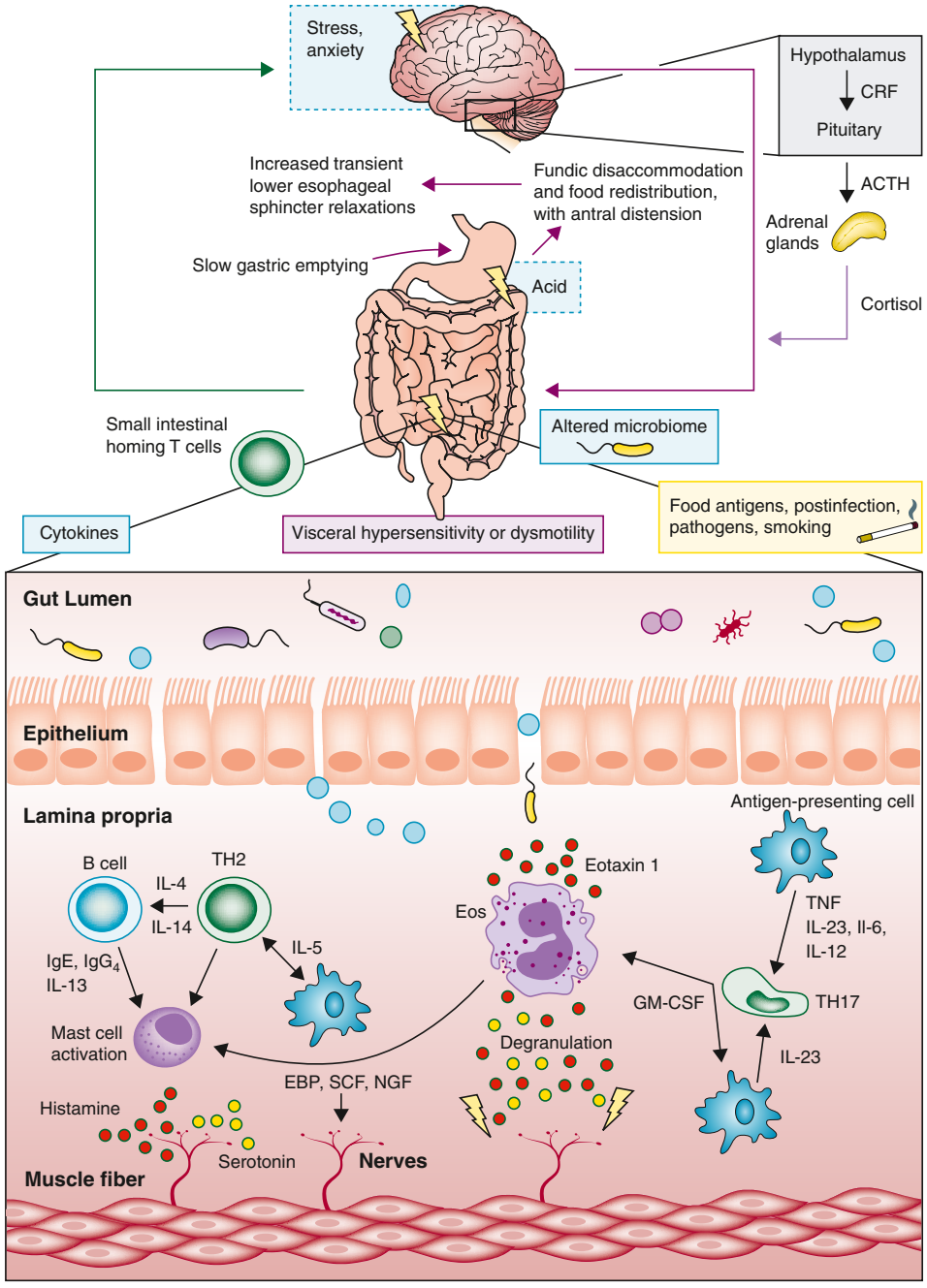

Fig. 389.1 Intestinal immune activation model of functional gastrointestinal disorders. It is hypothesized that, in a genetically primed host, environmental factors induce immune activation. Antigen presentation of luminal antigens, such as pathogens or food peptides, to T cells drives maturation of naive T cells to T-helper (TH) 2 cells. The release of associated cytokines (interleukin [IL]-4, IL-5, and IL-14) promotes the activation and recruitment of eosinophils (Eos), B cells, and mast cells. In addition to the traditional TH2 pathway, secretion of IL-23 from antigen-presenting cells, such as dendritic cells, B cells, and macrophages, promotes TH17 differentiation. The production of granulocyte-macrophage colony-stimulating factor (GM-CSF) from Th17 further drives Eos recruitment. Degranulation of mast cells and eosinophils results in the release of inflammatory mediators, which can damage the intestinal barrier and stimulate and damage enteric nerve fibers, which induces visceral hypersensitivity and motility disturbances resulting in gastrointestinal symptoms. α4β7 gut homing T cells are a marker of intestinal inflammation in both functional dyspepsia and irritable bowel syndrome, and correlate with delayed gastric emptying. Duodenal motor dysfunction might also impair duodenal acid clearance, inducing intestinogastric reflex responses that impair accommodation of the gastric fundus, and increase transient lower esophageal sphincter relaxations leading to gastroesophageal reflux. Signaling cascades, leading to further cytokine release, might result in extraintestinal symptoms, such as anxiety and fatigue. The site and extent of intestinal immune activation can define the phenotype (i.e., proximal intestinal involvement might give rise to functional heartburn, or functional dyspepsia, more distal involvement to irritable bowel syndrome, functional constipation, or functional diarrhea). CRF, Corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; Ig, immunoglobulin; TNF, tumor necrosis factor; EBP, enhancer binding protein; SCF, stem cell factor; NGF, nerve growth factor. *(From Black CJ, Drossman DA, Talley NJ, et al. Functional gastrointestinal disorders: advances in understanding and management. Lancet. 2020;396:16644–16674. Fig. 2.)*

Infant dyschezia describes apparent discomfort before defecation in an infant less than 9 months of age. Infants with dyschezia will strain before defecation for 10-20 minutes with associated screaming, crying, and possible red/purple facial discoloration. Typically, stools are passed several times daily and are not associated with other health problems or anatomic abnormalities. Dyschezia is the result of discoordinated abdominal and pelvic floor musculature contraction, raising the intraabdominal pressure. A good medical history and examination to rule out anatomic or neuromuscular abnormalities are key. Normal growth is to be expected. Reassurance provides the basis of management, and most caregivers will accept the explanation that the infant needs to learn the proper mechanics to stool, relaxing the pelvic floor while bearing down. Laxative, suppository, or digital manipulation is not required and may be counterproductive. Infant dyschezia typically resolves after 3-4 weeks of symptoms.

Functional constipation (see Chapter 378.3) is associated with chronic stool retention, often the result of deliberate withholding as the child voluntarily tries to avoid defecation due to fear or pain. To meet criteria for functional constipation, infants and children must have symptoms for 1 month, including at least two of five criteria listed in Table 389.5. There is often an episode of acute constipation that prompts further avoidance, creating a cycle of pain and withholding. In infancy, the onset is often at the time of diet changes with either the introduction of solid foods or the transition to cow's milk at 12 months of age. In toddlerhood, the initiation of toilet training often correlates with onset of constipation.

In addition to the clinical criteria, symptoms may include hematochezia due to an anal fissure. Though the blood coating the stool is often distressing to caregivers, the blood loss associated with constipation is typically not clinically significant. Physical examination may reveal a palpable abdominal mass, small amounts of fecal matter or a midline fissure on perianal exam, or a hard mass of stool in the rectal vault on digital rectal exam. It should be noted that if the history is typical for functional constipation, a digital rectal examination may not be necessary until treatment failure, if there is diagnostic uncertainty, or an anatomic malformation is suspected. Digital manipulation of the

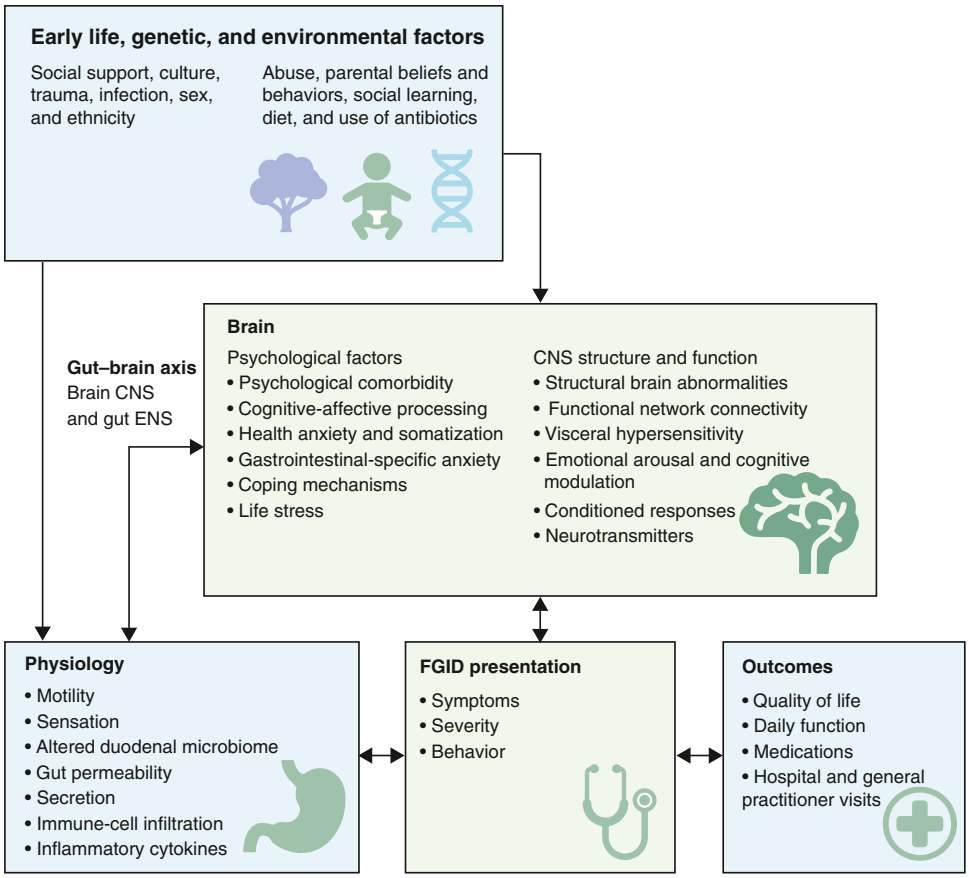

Fig. 389.2 Biopsychosocial model of functional gastrointestinal disorders (FGID). CNS, Central nervous system; ENS, enteric nervous system. *(From Black CJ, Drossman DA, Talley NJ, et al. Functional gastrointestinal disorders: advances in understanding and management. Lancet. 2020;396:16644–1674. Fig. 1, p 1667.)*

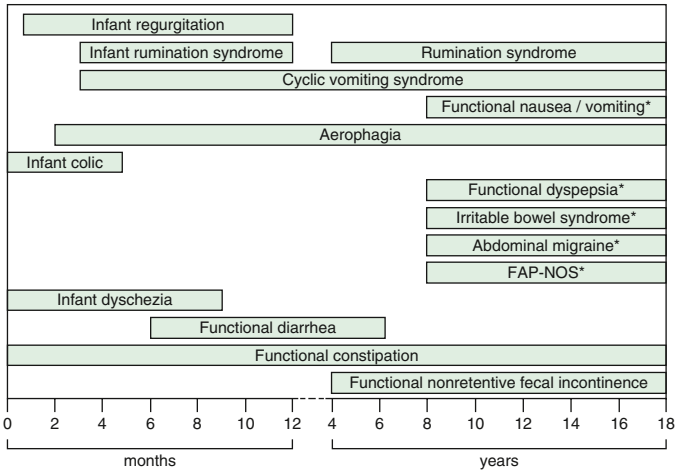

Fig. 389.3 Age distribution of functional gastrointestinal disorders in infants, toddlers, children, and adolescents. *History may not be reliable below this age. FAP-NOS, Functional abdominal pain-not otherwise specified. *(Modified from Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016;150:1443–1455.e2.)*

Table 389.1 Diagnostic Criteria for Infant Regurgitation

Must include both of the following in otherwise healthy infants 3 wk to 12 mo of age:

1. Regurgitation 2 or more times per day for 3 or more weeks
2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

Table 389.2 Diagnostic Criteria for Infant Rumination Syndrome

Must include all of the following for at least 2 mo:

1. Repetitive contractions of the abdominal muscles, diaphragm, and tongue
2. Effortless regurgitation of gastric contents, which are either expelled from the mouth or rechewed and reswallowed
3. Three or more of the following:
   a. Onset between 3 and 8 mo
   b. Does not respond to management for gastroesophageal reflux disease and regurgitation
   c. Unaccompanied by signs of distress
   d. Does not occur during sleep and when the infant is interacting with individuals in the environment

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

anal canal and rectum may further traumatize the child in whom painful defecation has prompted withholding behaviors.

The differential diagnosis for constipation is extensive. In infancy, care must be taken to exclude, via history or physical exam, etiologies including anatomic obstructions, Hirschsprung disease, spinal and neuromuscular abnormalities, and metabolic disorders. A defecation history extending to the first 24 hours of life is particularly important, as 90% of healthy infants and fewer than 10% of infants with Hirschsprung disease will pass their first bowel movement within the first 24 hours of life. Assessment for associated signs and symptoms and growth trends are important, as growth is often affected in the previously mentioned disorders. Red flags are noted in Table 389.6. Management involves naming and explaining the diagnosis, dietary and lifestyle changes, and early use of medications to soften stool with

Table 389.3 Diagnostic Criteria for Infant Colic

For clinical purposes, must include all of the following:

1. An infant who is <5 mo of age when the symptoms start and stop
2. Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
3. No evidence of infant failure to thrive, fever, or illness

"Fussing" refers to intermittent distressed vocalization and has been defined as "behavior that is not quite crying but not awake and content either." Infants often fluctuate between crying and fussing, so that the two symptoms are difficult to distinguish in practice

For clinical research purposes, a diagnosis of infant colic must meet the preceding diagnostic criteria and also include both of the following:

1. Caregiver reports infant has cried or fussed for 3 or more hours per day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician
2. Total 24-hr crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept, 24-hr behavior diary

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

Table 389.4 Diagnostic Criteria for Functional Diarrhea

Must include all of the following:

1. Daily painless, recurrent passage of four or more large, unformed stools
2. Symptoms last more than 4 wk
3. Onset between 6 and 60 mo of age
4. No failure to thrive if caloric intake is adequate

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

Table 389.5 Diagnostic Criteria for Functional Constipation

Must include 1 mo of at least two of the following in infants up to 4 yr of age:

1. Two or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum

In toilet-trained children, the following additional criteria may be used:

6. At least one episode per week of incontinence after the acquisition of toileting skills
7. History of large-diameter stools that may obstruct the toilet

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

daily osmotic laxatives preferred over stimulant laxatives. The primary goal is to achieve painless defection to facilitate resolution of the fear and withholding around defecation. Avoidance of toilet training until symptoms resolve and the child shows interest or willingness to proceed are generally advocated. Behavior modification including reassurance and positive incentive reward systems are useful.

DISORDERS OF BRAIN-GUT INTERACTION IN OLDER CHILDREN AND ADOLESCENTS

DBGI in children and adolescents are divided by symptoms into nausea and vomiting disorders, abdominal pain disorders, and defecation disorders. For individual diagnoses, the term *functional* is still used in some cases.

Table 389.6 Potential Alarm Features in Constipation

Passage of meconium >48 hours in a term newborn
Constipation starting in the first month of life
Family history of Hirschsprung disease
Ribbon stools
Blood in the stools in the absence of anal fissures
Failure to thrive
Bilious vomiting
Severe abdominal distension
Abnormal thyroid gland or newborn screen
Abnormal position of the anus
Absent anal or cremasteric reflex
Decreased lower extremity strength/tone/reflex
Sacral dimple
Tuft of hair on lower spine
Gluteal cleft deviation
Anal scars

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.e2. Table 3.

Nausea and Vomiting Disorders

Cyclic vomiting syndrome describes stereotypical, episodic attacks of vomiting with intervening periods of normal health and no vomiting symptoms (see Chapter 390). Per the Rome IV criteria, at least two episodes must occur in a 6-month period and not be attributable to another condition (Table 389.7). CVS can occur from infancy to adulthood, with 46% of patients having symptom onset at or before 3 years of age. In younger patients, extra care must be taken to rule out metabolic and anatomic disorders, as there is a higher likelihood of these disorders at younger ages. Chronic cannabis use in adolescents can be associated with repeated episodes of nausea and vomiting, termed the cannabinoid hyperemesis syndrome (see Chapter 157.3), and should be excluded in this age-group.

Functional nausea and functional vomiting may coexist or may occur independently of one another and describe isolated nausea or isolated vomiting (Table 389.8). Importantly, these conditions occur without coincident abdominal pain. The presentation may be accompanied by autonomic symptoms such as diaphoresis, pallor, tachycardia, and dizziness. The differential diagnosis includes anatomic, inflammatory, infectious, and motility etiologies. Anxiety and other behavioral conditions can be present with these DBGI and should be evaluated for and managed accordingly; children with functional nausea or functional vomiting should undergo psychologic evaluation. In children with psychologic comorbidities, cognitive-behavioral therapy or other psychologic interventions are appropriate. Cyproheptadine and transcutaneous gastric stimulation may be effective in the management of nausea.

Rumination syndrome in children and adolescents is defined similarly to the condition in infants, with the added notation that the effortless regurgitation of stomach contents may be associated with an unpleasant sensation or discomfort such as abdominal pressure or burning (Table 389.9). Repeated regurgitation and remastication or oral repulsion of the regurgitated gastric contents occurs soon after ingesting foodstuffs and does not occur during sleep. It is not preceded by active expulsion of gastric contents/retching and cannot be explained by any other medical condition. The diagnosis does not require prior failure of treatment for gastroesophageal reflux. A triggering event can often be identified before symptoms, which may occur following resolution of an infectious illness or with psychosocial stress. In adolescents, eating disorders may present similarly and must be ruled out. Other GI issues to be considered include anatomic, infectious, inflammatory, and motility disorders. An important distinction between rumination and other GI etiologies of vomiting includes effortless versus forceful regurgitation, and the time course, which is usually immediately following ingestion of foodstuffs. As with most

Table 389.7 Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include all of the following:

1. The occurrence of two or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-mo period
2. Episodes are stereotypical in each patient
3. Episodes are separated by weeks to months with return to baseline health between episodes
4. After appropriate medical evaluation, the symptoms cannot be attributed to another condition

Table 389.8 Diagnostic Criteria* for Functional Nausea and Functional Vomiting

FUNCTIONAL NAUSEA

Must include all of the following fulfilled for the last 2 mo:

1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals
2. Not consistently associated with vomiting
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition

FUNCTIONAL VOMITING

Must include all of the following:

1. On average, one or more episodes of vomiting per week
2. Absence of self-induced vomiting or criteria for an eating disorder or rumination
3. After appropriate evaluation, the vomiting cannot be fully explained by another medical condition

*Criteria fulfilled for at least 2 mo before diagnosis.
From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

Table 389.9 Diagnostic Criteria* for Rumination Syndrome in Children

Must include all of the following:

1. Repeated regurgitation and rechewing or expulsion of food that:
   a. Begins soon after ingestion of a meal
   b. Does not occur during sleep
2. Not preceded by retching
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out

*Criteria fulfilled for at least 2 mo before diagnosis.
From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

DBGI, a thorough understanding of the disorder and motivation to overcome it are key to treatment. Because rumination syndrome is essentially a learned habit, therapy focusing on managing the habit has proven effective. Deep breathing exercises to counteract the noxious stimulus are often employed to change the pressure differential and prevent regurgitation of gastric contents.

Aerophagia is often seen in neurocognitively impaired patients. It involves excessive air swallowing occurring throughout the day with progressive abdominal distention and with repetitive passage of gas via belching and/or flatus. Abdominal distension and flatus symptoms may be more severe in those children who cannot belch. Symptoms cannot be attributed to any other causes such as partial obstructions, small bowel bacterial overgrowth, GI dysmotility (pseudoobstruction), or to malabsorptive disorders. In children with age-appropriate cognition and neurologic status, chewing gum and gulping down liquids may be risk factors for aerophagia. Abdominal pain, nausea, and early satiety are possible associated GI symptoms; sleeping difficulty, headaches, and dizziness are also reported. Anxiety is a frequent comorbidity and may contribute to the behavior. Treatment is multidisciplinary and may include behavioral therapy, deep breathing, and potentially medications to relieve anxiety.

Table 389.10 Diagnostic Criteria* for Functional Dyspepsia

Must include one or more of the following bothersome symptoms at least 4 days/mo:

1. Postprandial fullness.
2. Early satiation.
3. Epigastric pain or burning not associated with defecation.
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Within functional dyspepsia, the following subtypes are now adopted:

1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching.
2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (1) burning quality of the pain but without a retrosternal component and (2) the pain is commonly induced or relieved by ingestion of a meal but may occur while fasting.

*Criteria fulfilled for at least 2 mo before diagnosis.
From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

Abdominal Pain Disorders

Functional dyspepsia (FD) describes postprandial fullness, early satiety, or epigastric pain or burning that is exclusive of defecation and not fully explainable by another or an underlying medical condition (Table 389.10). Subtypes of FD include *postprandial distress syndrome* (symptoms may preclude finishing a meal or be manifest by bloating, nausea, and excessive belching following a meal) as well as *epigastric pain syndrome* (epigastric pain/burning sufficient to preclude or disrupt normal activities, with pain not generalizable or localizable to other abdominal or chest regions, and not relieved by defecation or passage of flatus). Multiple pathophysiologic mechanisms have been proposed for FD; it is likely that each or multiple etiology contributes. An impaired gastric accommodation, visceral hypersensitivity, food allergy, delayed gastric emptying, and post-viral gastroparesis have all been implicated. The differential diagnosis includes GI etiologies of epigastric pain, including gastritis, esophagitis, and pancreatitis, among others. These etiologies can be guided by family, personal, and medical histories, exam, and by the nature of symptoms including abdominal pain and other alarm features (Tables 389.11 and 389.12). Initial treatment measures include a trial of dietary and lifestyle changes including avoiding spicy foods, caffeine, fatty foods, and nonsteroidal antiinflammatory drugs (NSAIDs). Gastric acid reduction therapy may be initiated. Assessment by a pediatric gastroenterologist and upper endoscopy are often performed. Treatment with cyproheptadine to improve gastric accommodation in patients with early satiety or attempts to treat visceral hypersensitivity in children with FD are reasonable, safe, and supported by available evidence. Low-dose tricyclic antidepressant therapy with amitriptyline may have efficacy in refractory cases. Early satiety may also respond to prokinetic medications such as erythromycin or metoclopramide. Percutaneous electrical stimulation of the stomach is a potential option for patients with FD refractory to standard therapy.

Irritable Bowel Syndrome (IBS) can be classified into the same four subtypes as adult IBS, depending on stool pattern: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with constipation and diarrhea, and unspecified IBS. Diagnosis of IBS requires abdominal pain on four or more days per month associated with defecation and/or a change in frequency of stool from baseline and/or a change in form/

Table 389.11 Alarm Symptoms Usually Needing Further Investigations in Children with Chronic Abdominal Pain

- Pain that wakes up the child from sleep
- Persistent right upper or right lower quadrant pain
- Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)
- Unexplained fever
- Genitourinary tract symptoms
- Dysphagia
- Odynophagia
- Chronic severe diarrhea or nocturnal diarrhea
- Gastrointestinal blood loss
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease

Table 389.12 Alarm Signs Usually Needing Further Investigations in Children with Chronic Abdominal Pain

- Localized tenderness in the right *upper* quadrant
- Localized tenderness in the right *lower* quadrant
- Localized fullness or mass
- Hepatomegaly
- Splenomegaly
- Jaundice
- Costovertebral angle tenderness
- Arthritis
- Spinal tenderness
- Perianal disease
- Abnormal or unexplained physical findings
- Hematochezia
- Anemia

appearance of stool (Table 389.13). Symptoms, including the predominant stool pattern, severity of pain, and functional impairment, reflect the degree of disordered brain-gut interaction. Visceral sensitivity may be attenuated or amplified by psychosocial stressors as well as mucosal proinflammatory cytokines related to infections or alterations in the gut microbiota.

As with other DBGI, the GI differential diagnosis includes anatomic, infectious, inflammatory, and motility disorders as well as conditions associated with malabsorption. Differentiation between those GI disorders and IBS is guided by the history, physical, and often biochemical markers of inflammation, particularly fecal calprotectin (see Tables 389.11 and 389.12). Management of symptoms may include dietary modification (under the guidance of a registered dietitian to prevent inadequate intake) to reduce or restrict foods that may provoke symptoms or cause gas (see section on fiber and the FODMAPS [fermentable oligo-di-monosaccharides and polyols] discussion Chapter 60). The use of probiotics has been effective in reducing symptoms in children with IBS, likely through production of short-chain fatty acids; drug therapy for IBS is noted in Table 389.14. In small trials, peppermint was effective in reducing pain in children with IBS. Cognitive-behavioral therapy is important to identify possible psychosocial stressors and to help identify coping mechanisms to maximize daily function and quality of life. Small studies have suggested that transcutaneous neurostimulation may also be efficacious.

Abdominal migraine shares some features with CVS. Stereotypical patterns and symptoms afflict the patient, are typically of acute onset, intense, lasting for at least an hour, either periumbilical or generalized in location, and usually are debilitating (Table 389.15). Episodes may also include associated anorexia, nausea, emesis, headaches, photophobia, and pallor. Episodes are separated by weeks to months, with at least two attacks occurring over a 6-month period. Between bouts, children return to baseline functioning and are symptom free.

Table 389.13 Diagnostic Criteria* for Irritable Bowel Syndrome

Must include all of the following:
1. Abdominal pain at least 4 days/mo associated with one or more of the following:
   a. Related to defecation
   b. A change in frequency of stool
   c. A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

*Criteria fulfilled for at least 2 mo before diagnosis.
From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

Table 389.14 Recommendations for Treatment of Irritable Bowel Syndrome

RECOMMENDATIONS FOR TREATMENT OF IRRITABLE BOWEL SYNDROME (IBS)
- Mild symptoms often respond to dietary changes.
- Antispasmodics can be used as needed for abdominal pain or postprandial symptoms.
- Antidepressants can improve abdominal pain and global symptoms. They may be considered for patients with moderate to severe symptoms.

IBS WITH CONSTIPATION (IBS-C)
- Fiber may relieve constipation in patients with mild symptoms.
- Polyethylene glycol can increase the frequency of bowel movements but may not improve overall symptoms or abdominal pain.
- Lubiprostone or linaclotide can be tried in patients whose symptoms have not responded to polyethylene glycol.

IBS WITH DIARRHEA (IBS-D)
- Taken as needed, loperamide can reduce postprandial urgency and stool frequency, but it does not improve global symptoms.
- Rifaximin and eluxadoline have been modestly more effective than placebo in relieving symptoms.

From Drugs for irritable bowel syndrome. *The Medical Letter*. 2016;58(1504):121–126.

Table 389.15 Diagnostic Criteria* for Abdominal Migraine

Must include all of the following occurring at least twice:
1. Paroxysmal episodes of intense, acute periumbilical, midline, or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
2. Episodes are separated by weeks to months
3. The pain is incapacitating and interferes with normal activities
4. Stereotypical pattern and symptoms in the individual patient
5. The pain is associated with two or more of the following:
   a. Anorexia
   b. Nausea
   c. Vomiting
   d. Headache
   e. Photophobia
   f. Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

*Criteria fulfilled for at least 6 mo before diagnosis.
From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

Triggers may vary, but common triggers include sleep hygiene disruption, fatigue, and travel, and are usually alleviated by sleep. The differential diagnosis includes anatomic obstructions or abnormalities predisposing to intermittent obstruction of the GI or urologic tract,

infectious or inflammatory conditions, hepatobiliary and pancreatic disorders, neurologic and metabolic conditions, and psychiatric disorders. Frequently, a family history of migraine headaches or abdominal migraines is present. Preventing exposure to known triggers once identified is important; further treatment depends on the frequency and severity of episodes as well as their impact on quality of life. Acute episodes may be treated similarly to migraine headaches with abortive medications such as triptans. Similar to CVS prophylaxis, cyproheptadine, amitriptyline, and propranolol may be effective. Oral pizotifen (antiserotonin, antihistamine) has been shown in small studies to be an effective prophylactic agent as well. Antimigraine therapies such as triptans may be effective in aborting bouts. A large number of children may have their symptom pattern evolve into migraine headaches as they progress toward adulthood.

Functional abdominal pain not otherwise specified (FAP-NOS) describes pain that occurs at least 4 times per month with either intermittent or continuous abdominal pain not associated with a particular activity or coincident to another physiologic event such as menses or eating and cannot be explained by any other underlying medical condition. These episodes occur in less than a 2-month span. In many ways, it is a DBGI of exclusion, as it does not meet criteria for either IBS, FD, or abdominal migraine. Psychosocial stressors may play a role, and behavioral approaches may be helpful to identify and manage stressors and other exacerbating factors. Pharmacologic data is limited, but small trials have suggested efficacy of amitriptyline and citalopram, though it should be noted that the latter is associated with suicidal ideation in adolescent patients.

DEFECATION DISORDERS

Functional constipation in children and adolescents describes decreased defecation frequency associated with volitional stool retention, similar to the classification in infants and toddlers. Large, hard, painful bowel movements are again a hallmark of the disorder, though patients in this age-group may also demonstrate fecal incontinence related to overflow of liquid stool beyond a large rectal stool ball as well as large-diameter stools that obstruct the toilet (Table 389.16). Onset in children peaks at the time of toilet training; in older children and adolescent, withholding may be triggered by a social stressor such as a major change in the school or home environment. Repeated distension of the rectum with large, hard stool over time may reduce the sensation to defecate and may lead to encopresis, the unintentional passage of liquid stool. Children experiencing encopresis often do not smell the stool that has passed, leading to embarrassment in social situations. Anorexia, abdominal distention, and pain are often coincident, though notably children do not meet criteria for IBS-C.

The diagnosis is based on medical history and physical examination. In addition to the clinical criteria, symptoms may include hematochezia due to an anal fissure. Though the blood coating the stool is often distressing to caregivers, the blood loss associated with constipation is typically not clinically significant. Physical examination may reveal a palpable abdominal mass, small amounts of fecal matter or a midline fissure on perianal exam, or a hard mass of stool in the rectal vault on digital rectal exam. It should be noted that if the history is typical for functional constipation, a digital rectal examination may not be necessary until treatment failure, diagnostic uncertainty, or an anatomic malformation is suspected. Digital manipulation of the anal canal and rectum may further traumatize the child or adolescent in whom painful defecation has prompted withholding behaviors. An abdominal x-ray is not required to make the diagnosis, and the stool burden observed rarely correlates with historical defecation pattern. The diameter of the rectum and any rectal stool on x-ray may be helpful to illustrate the degree of stool accumulation in the rectum.

Table 389.16 Diagnostic Criteria for Functional Constipation in Children with Chronic Abdominal Pain

Must include two or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:

1. Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
2. At least one episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that can obstruct the toilet

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

The differential diagnosis for constipation in children and adolescents is similar to infants and toddlers, though metabolic and anatomic abnormalities are much less likely to present in older children and adolescents. As in younger children, alarm symptoms should be assessed; in the absence of these symptoms, further testing is not indicated (see Table 389.6). Management includes disimpaction of the rectal stool ball followed by maintenance therapy with osmotic laxatives to soften stools for ease of passage, dietary changes to optimize fiber intake (a general rule is that daily fiber intake in grams can be approximated by adding age in years plus 5 to 10), and behavioral approaches similar to those employed for younger children (see Chapter 378.3).

Nonretentive fecal incontinence (NFI) describes the passage of stool in the absence of fecal retention that occurs in inappropriate settings for a specific society and culture, and that occurs without evidence of another or underlying medical condition in a child 4 years of age or older over at least a 1-month period. These patients otherwise have normal defecatory patterns and function, as well as normal colonic transit time, differentiating and distinguishing them from functional constipation. Another key difference is that children with NFI will have passage of their entire rectal contents as opposed to the smears or small amounts of stool in patients with functional constipation and encopresis. Psychologic comorbidities are frequent in children with NFI. A thorough medical history and physical examination including a comprehensive neurologic and digital rectal exam are required to fully appreciate what factors are involved in this condition. The diagnosis should be based on an otherwise normal defecation frequency, absence of an abdominal or rectal mass, a normal neurologic exam, and a normal transit marker study. Given the significant comorbidity of behavior and emotional axis issues, involvement of behavioral health professionals is essential to the evaluation and management of this condition. Therapy focuses on proactive regular toilet use. Unfortunately, biofeedback therapy, helpful in other disorders of defecation dynamics, has not proven beneficial in children with NFI.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 390

Cyclic Vomiting Syndrome

Asim Maqbool, Prasanna K. Kapavarapu, and Chris A. Liacouras

Cyclic vomiting syndrome (CVS) is an idiopathic disorder manifested as episodic vomiting, usually of sudden onset and high intensity/frequency (4/hr:12-15 episodes per day) of vomiting, with eventual resolution and return to a normal baseline between attacks (Fig. 390.1). Typical bouts last for 24-48 hours and usually respond promptly to hydration. To meet the criteria for CVS, identifiable organic disorders are excluded following an appropriate workup (Fig. 390.2). The guidelines for the frequency of episodes to fulfill the CVS criteria differ between societies. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) consensus statement in 2008 on CVS requires at least five vomiting episodes in any interval period or a minimum of three episodes in a 6-month period, whereas the 2016 Rome IV criteria on childhood functional gastrointestinal (GI) disorders requires at least two or more episodes in a 6-month period (Table 390.1).

The prevalence of CVS in children is estimated at ~2% in predominantly White populations, although it does occur in those of African or Asian descent, and Hispanic ethnicity. There is a slight female predominance. The median age of onset is 5 years, but it can begin in infancy and adolescence. Typically, there is a delay of 2.5 years in making the diagnosis despite multiple episodes and emergency room visits. The natural history of CVS is that most children outgrow it during preadolescence or adolescence, and of those, many will develop migraines. There are also later pediatric-onset (mean age 13 years) and adult-onset (mean age 32 years) subgroups indicating that in a minority it can begin or persist in adulthood.

One key clinical feature of CVS is its consistent and stereotypical pattern of vomiting within individuals. Typically, symptoms start at the same time, often during early morning hours, last the same duration, and demonstrate identical autonomic symptoms of pallor and listlessness, unrelenting nausea, abdominal pain, and in less than half, headaches and photophobia. About half of cases occur on a cycle as often as monthly; some cycle as infrequently as every 3-4 months. Other patients have unpredictable sporadic vomiting that may be associated with a specific trigger. Potential triggers include infectious illnesses, stress and especially excitement (holidays), sleep deprivation (sleepovers), dietary triggers (chocolate, monosodium glutamate), food allergy, onset of menses, and weather changes. Typically, the vomiting is intense, with greater than four bouts of emesis per hour at the peak, and can include gastric contents or frequent dry heaves. Although most attacks last 2 days, an episode can last anywhere from hours and rarely up to 10 days. CVS attacks are debilitating, often necessitating IV rehydration, and resulting in hospitalization. Seasonal variation apparently occurs in approximately a third of patients, with more attacks in winter and fewer during summer.

Subgroups of CVS include *migraine-related,* with either personal history of migraines or family history of migraines; *Sato variant,* driven by hyperresponsive hypothalamic-pituitary-adrenal axis

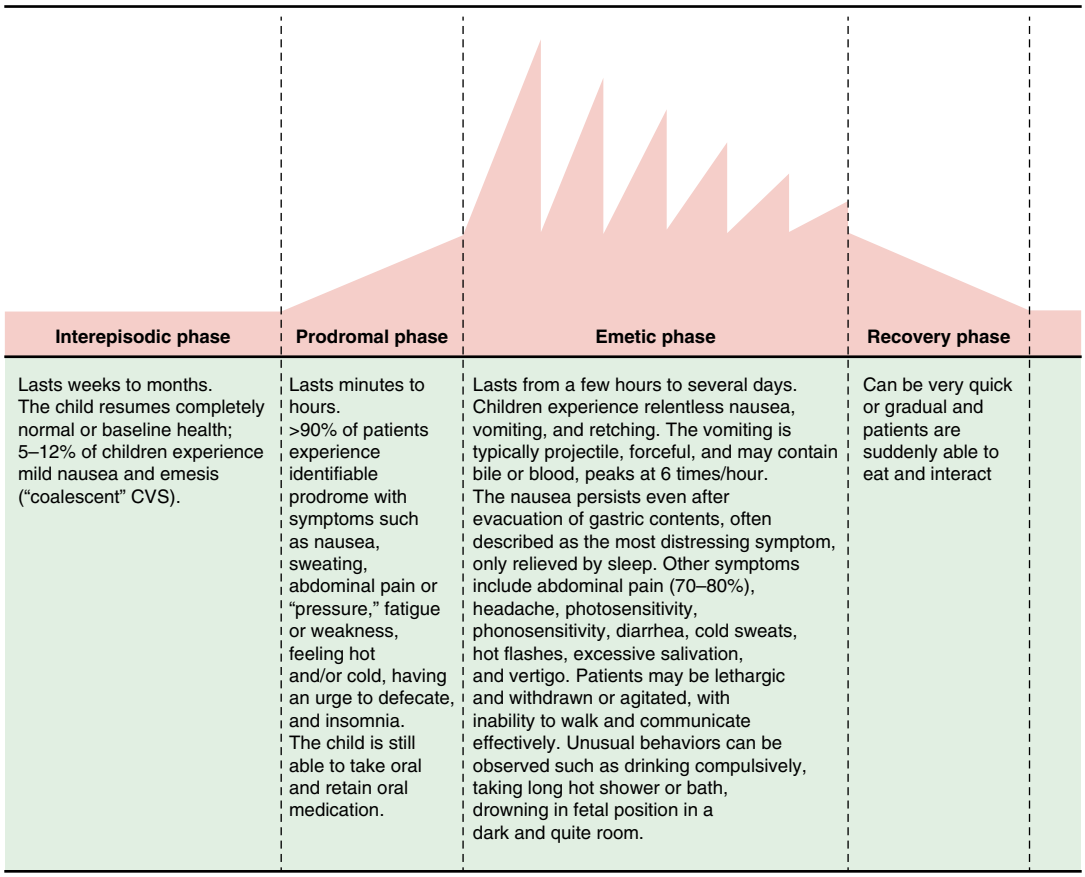

Fig. 390.1 Temporal pattern of cyclic vomiting syndrome. Schematic representation of the four phases. *(From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. Frontiers Neurol. 2020;11:Article 583425. Fig. 1.)*

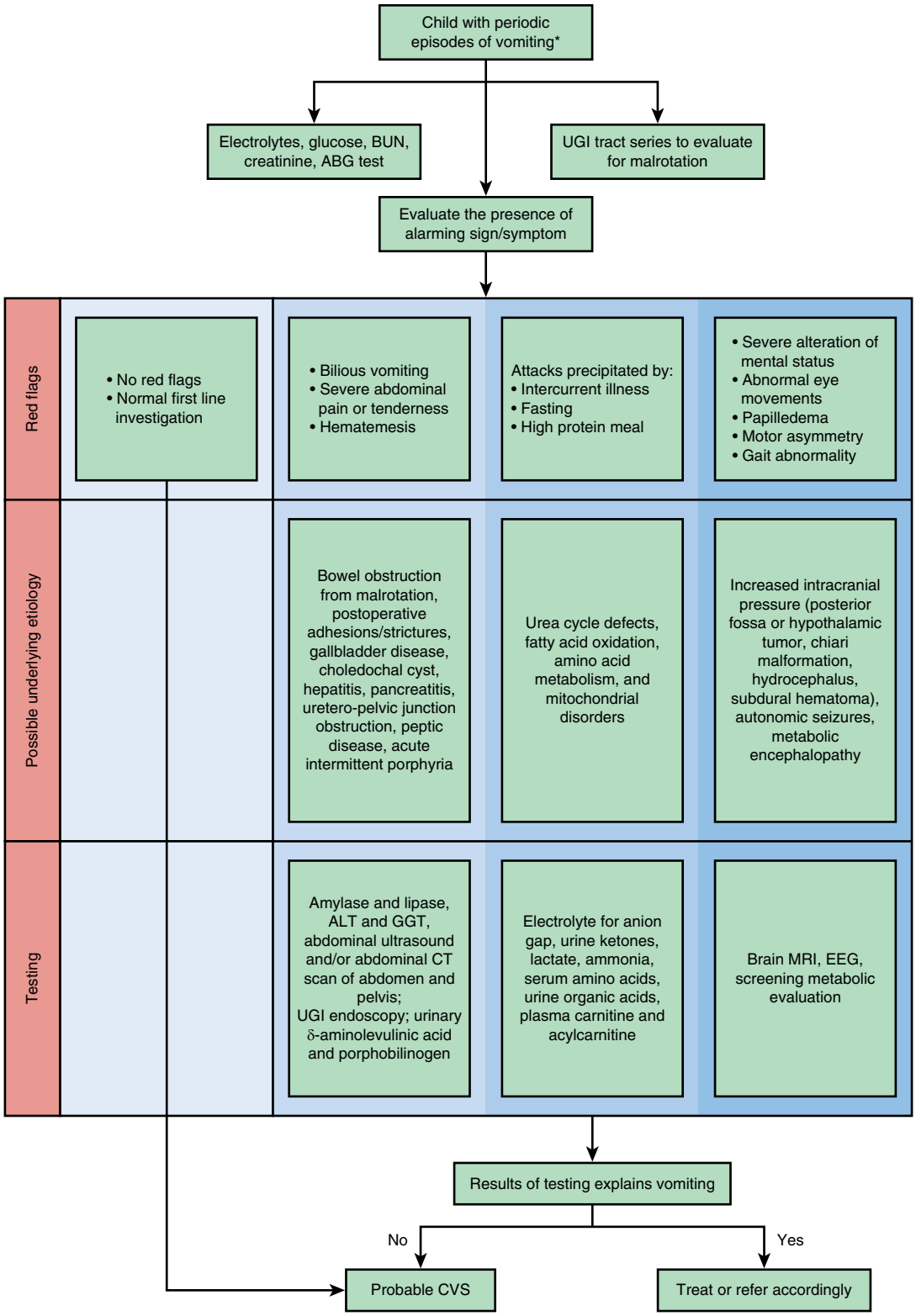

Fig. 390.2 Algorithm for the evaluation of children with cyclic vomiting pattern. *Fulfilling clinical criteria for CVS (see Table 390.1). ABG, Arterial-blood gas; ALT, alanine aminotransferase; CVS, cyclic vomiting syndrome; GGT, γ-glutamyl-transferase; UGI, upper gastrointestinal. *(From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. Frontiers Neurol. 2020;11:Article 583425. Fig. 2.)*

(elevated cortisol levels), hypertension, extreme lethargy, and presenting with more severe and prolonged CVS episodes; *catamenial* CVS, occurring in adolescent girls who are hormonally sensitive and presenting with CVS episodes either within a day, prior or post menstrual period; underlying *mitochondrial dysfunction,* associated with single nucleotide polymorphisms and evidence of improvement with mitochondrial supplements like coenzyme Q10; *and the coalescent form*, presenting with daily nausea between episodes of emesis (which becomes less frequent). CVS may also be more common in children with autism.

Table 390.1 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, International Classification of Headache Disorders 3, and Rome IV Diagnostic Criteria

NASPGHAN
1. At least five attacks in any interval or a minimum of three attacks during a 6-mo period 2. Episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days, occurring at least 1 wk apart 3. Stereotypical pattern and symptoms in the individual patient 4. Vomiting during attacks at least 4 times per hour for at least 1 hour 5. Return to baseline health between episodes 6. Not attributed to another disorder
ICHD-3
A. At least five attacks of intense nausea and vomiting fulfilling criteria B and C B. Stereotypical in the individual patient and recurring with predictable periodicity C. All of the following: 1. Nausea and vomiting occur ≥4 times per hour 2. Attacks last ≥1 hour and up to 10 days 3. Attacks occur ≥1 wk apart D. Complete freedom from symptoms between attacks E. Not attributable to another disorder
Note: History and physical exam do not show sign of gastrointestinal disease
PEDIATRIC ROME IV
1. Two or more periods of intense unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-mo period 2. Episodes are stereotypical in each patient 3. Episodes separated by weeks to months with return to baseline health between episodes 4. Symptoms not attributed to another medical condition
ADULT ROME IV
Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 wk)
1. ≥3 discrete episodes in the prior year and two episodes in past 6 mo, occurring ≥1 wk apart 2. Absence of vomiting between episodes, but other milder symptoms can be present between cycles
Supportive remarks
1. Personal or family history of migraine headaches
Criteria must be fulfilled for the last 6 mo with symptom onset at least 3 mo before diagnosis.

Note: All respective criteria must be met to meet consensus definitions for both NASPGHAN, ICHD-3, and Rome IV.
NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; ICHD-3, International Classification of Headache Disorders 3.
From Kovacic K, Li BUK. Cyclic vomiting syndrome: a narrative review and guide to management. *Headache*. 2021;61:231–243. Table 1.

Table 390.2 Diagnostic Tests for Ruling Out Conditions in the Differential Diagnosis with Cyclic Vomiting Syndrome

CONDITION	DIAGNOSTIC TESTING
GASTROINTESTINAL DISORDERS	
Peptic ulcer disease	Upper GI endoscopy
Gastroparesis	Scintigraphic gastric emptying study
Hepatitis	Abdominal ultrasound
Pancreatitis	Abdominal ultrasound
Cholecystitis	Abdominal ultrasound
Biliary tract anomalies	Hepatobiliary scintigraphy, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography
Malrotation with volvulus, postoperative adhesions/ strictures	Upper GI series with small bowel follow-through, abdominal CT scans, upper GI endoscopy
Chronic intestinal pseudoobstruction	Plain abdominal x-ray, upper GI series with small bowel follow-through, antroduodenal manometry
EXTRAINTESTINAL DISORDERS	
Central Nervous System	
Mass	Brain MRI, Brain CT
Hydrocephalus	Brain MRI, Brain CT
Subdural hematoma	Brain CT
Autonomic seizures	EEG
Renal Disorders	
Ureteropelvic junction obstruction	Abdominal ultrasound
Nephrolithiasis	Abdominal ultrasound, abdominal CT
Metabolic Disorders	Ammonia, organic acids, lactate, amino gap

From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. *Frontiers Neurol*. 2020;11:Article 583425. Table 3.

Multiple comorbid disorders can further comprise quality of life between episodes; these include anxiety, constipation-predominant irritable bowel syndrome, chronic fatigue or limited stamina, sleep disorders, postural orthostatic tachycardia syndrome, daily nausea, and complex regional pain syndrome. There is often a positive family history of migraines in children with CVS; attacks of both conditions share many clinical features. Although the pathophysiology is not fully known, there is suggestive evidence that an overresponsive hypothalamic-pituitary-adrenal axis (including corticotropin-releasing factor), autonomic nervous system dysregulation (sympathetic predominance), mitochondrial dysfunction (16519T and 3010A), and nuclear pathogenic variants *(RYR2)* may play contributory roles.

Patients with chronic vomiting should always be evaluated for potential etiologies other than CVS. The differential diagnosis includes GI anomalies (malrotation, duplication cysts, choledochal cysts, recurrent intussusceptions), CNS disorders (neoplasm, epilepsy, vestibular pathology), nephrolithiasis, cholelithiasis, hydronephrosis, metabolic-endocrine disorders (urea cycle, mitochondrial disorders, fatty acid metabolism, Addison disease, porphyria, hereditary angioedema, familial Mediterranean fever), chronic appendicitis, and inflammatory bowel disease (see Fig. 390.2; Tables 390.2 and 390.3). Laboratory evaluation is based on a careful history and physical examination and may include, if indicated, endoscopy, contrast upper GI radiography, brain MRI, and metabolic studies (lactate, organic acids, ammonia). Bilious emesis usually suggests a small bowel obstruction and is considered a red flag; however, children with CVS may have bile-stained emesis. A tender abdomen is also unusual for CVS and warrants further workup. Acute and chronic appendicitis can mimic CVS. Prior

Table 390.3 Relevant Causes of Vomiting in Metabolic Disorders

ASSOCIATED OR NOT WITH ENCEPHALOPATHY
Organic acidurias
Urea cycle disorders
Fatty acid oxidation disorders
MCT1 defect
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
Glutaric aciduria type I
ASSOCIATED WITH ACIDOSIS/KETOACIDOSIS
Organic acidurias
Mitochondrial diseases
ASSOCIATED WITH KETOSIS ONLY
Ketolysis defects
ASSOCIATED WITH SEVERE ABDOMINAL PAIN
Porphyrias (acute intermittent porphyria, coproporphyria)
ASSOCIATED WITH HEPATOPATHY
Organic acidurias
Urea cycle disorders
Galactosemia
Hereditary fructose intolerance
Tyrosinemia type I
Fatty acid oxidation disorders

From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. *Frontiers Neurol.* 2020;11:Article 583425, Table 5.

Table 390.4 Abortive and Rescue Pharmacotherapy

ANTI-MIGRAINE
Sumatriptan 20 mg intranasal at episode onset and may repeat once vs 25 mg PO once vs 3-6 mg SC once
SE: Chest and neck burning, coronary vasospasm, headache
Alternatives: *Rizatriptan, zolmitriptan, frovatriptan (longer half-life)*
ANTIEMETIC
Ondansetron 0.2-0.3 mg/kg per dose (≤12 mg) q4-6h IV/PO/rectal/topical
SE: Headache, drowsiness, dry mouth
Alternatives: *Granisetron*
Aprepitant 3-day regimen:
Weight <15 kg: 80 mg at start of episode on day 1, followed by 40 mg on days 2 and 3
Weight 15-20 kg: 80 mg on days 1, 2, and 3
Weight >20 kg: 125 mg on day 1 and 80 mg on days 2 and 3
Fosaprepitant 3-4 mg/kg (max. 150 mg) IV day one (aprepitant days 2-3)
SEDATIVE
Lorazepam 0.05-0.1 mg/kg per dose q6h IV/PO: useful adjunct to ondansetron
SE: Sedation, respiratory depression
Chlorpromazine 0.5-1 mg/kg per dose q6h IV/PO
SE: Drowsiness, hypotension, seizures, dystonic reaction
Diphenhydramine 1.25 mg/kg per dose q6h IV/PO: useful adjunct to chlorpromazine
SE: Hypotension, sedation, dizziness
ANALGESIC
Ketorolac 0.5-1 mg/kg per dose q6h IV/PO
SE: Gastrointestinal bleeding, dyspepsia

IV, Intravenous; PO, orally; SC, subcutaneously; SE, side effects.
Modified from Kovacic K, Li BUK. Cyclic vomiting syndrome: a narrative review and guide to management. *Headache.* 2021;61:231–243. Table 3.

abdominal surgery may increase risk for adhesion-related partial bowel obstructions.

Non-GI causes of frequent vomiting include renal, metabolic, endocrine, and neurologic disorders. Renal abnormalities to consider include acute or chronic ureteropelvic junction (UPJ) obstruction presenting with hydronephrosis (Dietl's crisis) and nephrolithiasis. The clinician must also consider metabolic disorders, especially in the infant or toddler less than 2 years of age. Fasting or high-protein meals that provoke emesis raise a red flag for metabolic disorders, such as disorders of fatty acid oxidation, organic acidemias, or partial ornithine transcarbamylase deficiency. Acute intermittent porphyria can present in the adolescent triggered by alcohol or medications. Endocrine disorders, including diabetic ketoacidosis, Addison disease, and pheochromocytoma, can mimic CVS episodes. Although an atypical presentation, CNS tumors can have episodic vomiting and papilledema; altered mental status and focal neurologic findings are red flags requiring neuroimaging. Pregnancy can present with CVS-like symptoms.

The management of acute CVS episodes includes early and aggressive hydration (especially with dextrose in normal saline), which may shorten episodes in addition to correcting fluid losses. Reducing extraneous sensory stimulation, similar to the management approach for migraines, may also be beneficial (Table 390.4). Regardless of intervention, episodes will eventually spontaneously resolve with return to a normal baseline. Triptans can be used as an *abortive medication* in patients with the *migraine-related* subgroup of CVS, a family history of migraines, at the onset of symptoms. Ondansetron may reduce nausea and emesis. Sedation may reduce severity or stop a CVS episode; drugs include antihistamines such as diphenhydramine and promethazine. Lorazepam or rectal diazepam can also be used. These measures are empiric; a lack of evidence base limits our understanding of efficacy. For rare but severe refractory cases, general anesthetics have been used. A dramatic change in presentation of attacks suggests a red flag such as acute hydronephrosis or small bowel obstruction from volvulus.

Prophylactic management begins with lifestyle measures (maintenance fluid intake, adequate calories, sleep hygiene, and exercise), including avoidance of known triggering foods (allergens, chocolate, aged cheese, monosodium glutamate; Table 390.5). Recommendations for prophylactic regimens include cyproheptadine in patients <5 years of age and amitriptyline in patients ≥5 years; propranolol serves as a secondary agent in both age-groups. When standard care fails, the addition of anticonvulsants such as topiramate has been implemented. For those with *catamenial CVS*, low-dose estrogen oral contraceptives or medroxyprogesterone acetate may prevent episodes. For those with *Sato variant*, CVS treatment with angiotensin-converting enzyme (ACE)-inhibitors or β blockers for acute hypertension may be helpful. Supplements such as coenzyme Q10, l-carnitine, and riboflavin have been reported to be useful adjuncts for those with underlying mitochondrial dysfunction. Treatment of *comorbid disorders*, especially anxiety (cognitive behavioral therapy, antianxiety agents) and postural orthostatic tachycardia syndrome (fluids, salt, fludrocortisone), may be needed for effective management of CVS. Newer drugs that are being explored in the management of CVS include mirtazapine and aprepitant. Mirtazapine is an antidepressant medication and is a potent antagonist of $5HT_2$ and $5HT_3$ receptors, with anti-migraine properties. It is of potential benefit in *migraine-related* CVS, starting at 7.5 mg at bed time, with a maximum dose of 15 mg; common side effects include drowsiness and increased appetite. Aprepitant is a neurokinin-1 receptor (NK_1R) antagonist used in postoperative and chemotherapy-related nausea and vomiting. In CVS, aprepitant is used for both prophylaxis and abortive purposes. In children, aprepitant has been shown to decrease the number of vomiting episodes per hour/frequency of episodes per year/number of hospitalizations per year and increase the interval period in between the episodes. Common reported side effects of aprepitant include headache, hiccups, neutropenia, and fatigue.

Table 390.5 Prophylactic Lifestyle Changes and Pharmacologic Options for Cyclic Vomiting Syndrome

LIFESTYLE MEASURES		
Reassurance and anticipatory guidance	• Episodes are not intentional • The natural history of CVS is that it will resolve with time	
Avoidance of triggers	• Identify dietary triggers ("vomit diary") and avoid precipitating factors • Triggering foods may include chocolate, cheese, monosodium glutamate • Fasting a common trigger • Excitement a potential trigger • Excessive activity/exhaustion • Avoid sleep deprivation and practice good sleep hygiene	
Managing triggers	• Provide supplemental energy as carbohydrates for fasting-induced episodes • Provision of snacks between meals, before sleep, and before exertion	
Migraine headache–type lifestyle interventions	• Aerobic exercise and avoidance of overexertion • Regular mealtime schedule—avoid skipping meals • Avoid/moderate caffeine intake	
PROPHYLACTIC PHARMACOLOGIC APPROACHES		
	AGE <5 YR	**AGE ≥5 YR**

	Antihistamines:
	• Cyproheptadine
	  • 0.25-0.5 mg/kg/day in two daily divided doses or as a single dose qhs
	  • Side effects of increased appetite, weight gain, and sedation
	• Pizotifen
	β blockers: (second choice)
	• Propranolol
	  • 0.25-1 mg/kg/day, most often 10 mg 2-3×/day.
	  • Side effects include lethargy and reduced exercise tolerance
	  • Contraindicated in asthma, diabetes, heart disease, depression
	  • Taper over 1-2 wk to discontinue
		Tricyclic antidepressants:
		• Amitriptyline
		  • Begin at 0.25-0.5 mg/kg qhs and increase weekly by 5-10 mg until achieve 1-1.5 mg/kg
		  • Monitor ECG for prolonged QTc interval at baseline before initiation and 10 days after peak dose achieved
		  • Side effects: constipation, sedation, arrhythmias, behavioral changes
		Alternatives: nortriptyline
		β blockers: (second choice):
		• Propranolol
		Other agents:
		Anticonvulsants:
		• Phenobarbital 2 mg/kg qhs
		• Side effects: sedation, cognitive impairment
		Alternatives:
		• Topiramate, valproic acid, gabapentin, levetiracetam

DIETARY SUPPLEMENTS		
	• L-Carnitine 50-100 mg/kg/day divided 2-3×/day, maximum dose of 2 g 2×/day • Coenzyme Q10 mg/kg/day divided 2-3×/day, maximum dose 100 mg 3×/day	

Medications listed in table are for off-label use.
CVS, Cyclic vomiting syndrome; qhs, every night at bedtime.
Modified from Li BU, Lefevre F, Chelimsky GG, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr.* 2008;47(3):379–393.

Cannabinoid hyperemesis syndrome (CHS) involves the endocannabinoid system (ECS), which plays a major role in nausea and vomiting. Cannabinoid receptors (CBRs) consist of cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R); the current hypothesis is that CBR agonists inhibit vomiting and CB1R antagonists initiate or potentiate vomiting. The current theory is that with chronic cannabis use, there is a paradoxical effect with downregulation of CB1R, which in turn potentiates vomiting in CHS. *CHS shares many features with CVS, including patterns of onset, frequency, and duration.* CHS, however, differs from CVS in that it is associated with prolonged cannabis use (>2 years), and relief of episodes occurs following sustained cessation (>6 months) of cannabis use. Another common feature across CHS is the observed association with pathologic bathing behavior, specifically, prolonged hot showers (see Chapter 157.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 391

Acute Appendicitis

José H. Salazar and John J. Aiken

Acute appendicitis remains the most common acute surgical condition in children and a major cause of childhood morbidity and healthcare costs, mostly associated with complicated/perforated appendicitis (PA). The peak incidence of acute appendicitis occurs in children in the second decade, and approximately 100,000 children are treated in children's hospitals for appendicitis each year. The broad spectrum of clinical presentation in acute appendicitis has been associated with significant practice variation in evaluation, diagnostic measures, and treatment of abdominal pain and suspected appendicitis. The traditional strategy of the liberal use of computed tomography (CT) to avoid misdiagnosis and early surgery to avoid progression to perforation has lacked validation in large reviews and resulted in high negative appendectomy rates and excessive radiation exposure. Perforation rates have remained ~40% and negative appendectomy rates as high as 10% in the past 2 decades. In current practice, most centers have adopted clinical practice guidelines (CPGs) combining history, physical examination findings, laboratory data, and appendicitis risk scoring systems to standardize care, improve diagnostic accuracy and outcomes, and direct cost-conscious resource use. Appendiceal ultrasound has emerged as a highly sensitive and specific imaging modality for diagnosis and led to a significant decrease in the use of CT and radiation exposure in the initial evaluation of children presenting with abdominal pain and possible suspected appendicitis. Although prompt appendectomy remains the standard treatment in acute appendicitis, advances in imaging techniques, improved antibiotic regimens, increased use of percutaneous drainage procedures by interventional radiologists, and emerging data on high success rates with initial antibiotic treatment alone have led to an increase in the initial nonoperative management of both simple and complicated (abscess, phlegmon) appendicitis. Laparoscopic appendectomy (LA, a minimally invasive technique) has emerged as the preferred surgical approach for both simple and PA, with an open surgical approach reserved as an alternative for selected cases or when attempted LA is technically difficult and/or deemed unsafe.

EPIDEMIOLOGY

The incidence of acute appendicitis increases with age, from a rate of 1-2 per 10,000 children from birth to 4 years of age, to a rate of 19-28 per 10,000 children younger than age 14 years annually. Children have a lifetime risk of 7–9%, and appendicitis is diagnosed in 1–8% of children presenting to the emergency department (ED) for evaluation of abdominal pain. Appendicitis is most common in older children, with peak incidence between the ages of 10 and 18 years; it is rare in children younger than 5 years of age (<5% of cases) and extremely rare (<1% of cases) in children younger than 3 years of age.

Infants with appendicitis are often misdiagnosed with sepsis, and because of the diagnostic delay, they present in advanced stages of the disease. Most infant cases are primary, but some may be associated with Hirschsprung disease, cystic fibrosis, inguinal hernia, prematurity, meconium plug syndrome, or complex multiorgan syndromes.

Mortality is low (<0.01%), but morbidity remains high, mostly in association with PA. Up to 40% of children have PA at presentation, and perforation rates approach 90% in young children (<3 years). Children with simple (nonperforated) appendicitis typically recover easily, with a low complication rate and rapid return to premorbid state and full activities. In contrast, PA is associated with substantial postoperative morbidity, including readmission rates estimated at 12.8%, postoperative intraabdominal abscess rates ~20%, surgical site infection (SSI) rate ~20%, prolonged length of stay (LOS), need for prolonged antibiotic exposure, increased postoperative use of CT, and significant delay in return to wellness and normal activities.

PATHOPHYSIOLOGY

The clinical entity of acute appendiceal inflammation followed by perforation, abscess formation, and peritonitis is most likely a disease of multiple etiologies, the final common pathway of which involves invasion of the appendiceal wall by bacteria. Genetic, environmental, and infectious etiologies (bacterial, viral, fungal, and parasitic) have all been implicated in acute appendicitis. One pathway to acute appendicitis begins with luminal obstruction; inspissated fecal material, lymphoid hyperplasia, ingested foreign body, parasites, and tumors have been described. Obstruction of the appendiceal lumen initiates a progressive cascade involving increasing intraluminal pressure, lymphatic and venous congestion and edema, impaired arterial perfusion, ischemia of the appendiceal wall, bacterial proliferation and invasion of the wall, and necrosis. This sequence correlates with the clinical disease progression from simple appendicitis to gangrenous appendicitis and, thereafter, appendiceal perforation.

Because the appendix has the highest concentration of gut-associated lymphoid tissue (GALT) in the intestine, some have hypothesized that the appendix may have an immune function similar to that of the thymus or bursa of Fabricius. Submucosal lymphoid follicles, which can obstruct the appendiceal lumen, are few at birth but multiply steadily during childhood, reaching a peak in number during the teen years, when acute appendicitis is most common.

Enteric infection likely plays a role in many cases of acute appendicitis in association with mucosal ulceration and invasion of the appendiceal wall by bacteria. Bacteria such as *Yersinia, Salmonella,* and *Shigella* spp. and viruses such as infectious mononucleosis, mumps, coxsackievirus B, and adenovirus are implicated. In addition, case reports demonstrate the occurrence of appendicitis from ingested foreign bodies, in association with carcinoid tumors of the appendix, *Ascaris* infestation, and rarely, after blunt abdominal trauma. Children with cystic fibrosis have an increased incidence of appendicitis; the cause is believed to be the abnormal thickened mucus. Appendicitis in neonates is rare and warrants diagnostic evaluation for cystic fibrosis and Hirschsprung disease.

Appendectomy decreases the risk of ulcerative colitis and increases the risk of recurrent *Clostridium difficile–associated colitis.* Appendicoliths and appendicitis are more common in developed countries with refined, low-fiber diets than in developing countries with a high-fiber diet; no causal relationship has been established between lack of dietary fiber and appendicitis. A family history is associated with a nearly threefold increased appendicitis risk, and genetic factors may account for 30% of appendicitis risk.

Clinical Features

Appendicitis in children has an immensely broad spectrum of clinical presentation; <50% of cases have the classic presentation. The signs and symptoms in acute appendicitis can vary depending on the timing of presentation, patient age, the abdominal/pelvic location of the appendix, and most importantly, individual variability in the evolution of the disease process. Children early in the disease process can appear well and demonstrate mild symptoms, minimal findings on physical examination, and normal laboratory studies, whereas those with perforation and advanced peritonitis can demonstrate severe illness with bowel obstruction, renal failure, and septic shock. Most patients with appendicitis demonstrate an insidious onset of illness characterized by generalized nonspecific malaise or anorexia in the first 12 hours, and a steady, escalating progression in severity of signs and symptoms over 2-3 days with increasing abdominal pain, vomiting, fever, and tachycardia; perforation is common beyond 48 hours of illness. Thus the opportunity for diagnosis before perforation in acute appendicitis in children is most often brief (48-72 hours), and a high percentage of patients are perforated at presentation.

Abdominal pain is consistently the *primary* symptom in acute appendicitis; beginning shortly (hours) after the onset of illness. There are no somatic pain fibers within the appendix; therefore early appendiceal inflammation results in pain that is vague, poorly localized, unrelated to activity or position, often colicky, and periumbilical in location as a result of visceral inflammation from a distended appendix. Progression

of the inflammatory process in the next 24 hours leads to involvement of the adjacent parietal peritoneal surfaces, resulting in somatic pain localized to the right lower quadrant (RLQ)—*thus the classic description of periumbilical mid-abdominal pain migrating to the RLQ. The position of the appendix is a critical factor affecting interpretation of presenting signs and symptoms and accurate diagnosis.* When the appendix is in a retrocecal or pelvic position, a slower progression of illness is typical and clinical presentation is likely to be delayed. Localized pain in the RLQ leads to spasm in the overlying abdominal wall muscles, and now the pain is predictably exacerbated by movement. The child often describes marked discomfort with the bumpy car ride to the hospital, moves cautiously, and has difficulty getting onto the examining room stretcher. Nausea and vomiting occur in more than half of the patients and typically *follow* the onset of abdominal pain by several hours. Anorexia is a classic and consistent finding in acute appendicitis, but occasionally affected patients are hungry. Diarrhea and urinary symptoms are also common, particularly in cases of PA when there is likely inflammation near the rectum and possible abscess in the pelvis. Painful voiding may not be from dysuria, but pressure transmitted to an inflamed peritoneum. As it progresses, appendicitis is often associated with adynamic ileus, leading to the complaint of constipation and possible misdiagnosis.

Because enteric infections can cause appendicitis, diarrhea may be a manifestation and gastroenteritis may be the assumed diagnosis. In contrast to gastroenteritis, the abdominal pain in early appendicitis is *constant* (not cramping or relieved by defecation), the emesis may become bile stained and persistent, and the clinical course worsens steadily rather than demonstrating a waxing and waning pattern often seen in viral gastroenteritis. Fever is common in appendicitis and typically low-grade unless perforation has occurred. Most patients demonstrate at least mild tachycardia, likely secondary to pain and dehydration. The temporal progression of symptoms from vague, mild pain, malaise, and anorexia to severe localized pain, fever, and vomiting typically occurs rapidly (24-48 hours) in the majority of cases. If the diagnosis is delayed beyond 48 hours, perforation is likely (>65%). When several days have elapsed in the progression of appendicitis, patients typically develop signs and symptoms evidencing advanced disease, including worsening and diffuse pain, abdominal distention, and bilious emesis suggestive of developing small bowel obstruction. The retrocecal appendix can demonstrate symptoms suggestive of septic arthritis of the hip or a psoas muscle abscess.

A primary focus in the management of appendicitis is the avoidance of sepsis and the infectious complications leading to increased morbidity, mostly seen with PA.

Bacteria can be cultured from the serosal surface of the appendix before microscopic or gross perforation and bacterial invasion of the mesenteric veins (pylephlebitis) can result (rarely) in thrombosis and possible liver abscess or portal hypertension. A period after perforation of lessened abdominal pain and acute symptoms has been described, presumably with the elimination of pressure within the appendix. If, after perforation, the omentum or adjacent intestine is able to wall off the fecal contamination, the evolution of illness is less predictable and delay in presentation is likely. If perforation leads to diffuse peritonitis, the child generally has escalating diffuse abdominal pain and rapid development of toxicity evidenced by dehydration and signs of sepsis, including hypotension, oliguria, acidosis, and high-grade fever. Young children have a poorly developed omentum and are often unable to control the spread of infection. Perforation and abscess formation with appendicitis can lead to intestinal fistula formation, scrotal cellulitis and abscess through a patent processus vaginalis (indirect inguinal hernia), or small bowel obstruction. The most likely diagnosis in children who present with signs and symptoms of mechanical small bowel obstruction who have not had prior abdominal surgery is complicated appendicitis.

Physical Examination

Although the hallmark of diagnosing acute appendicitis remains a careful and thorough history and physical examination, all clinicians know the arcane nature of acute appendicitis, the consistent or typical clinical features are not present in all patients, and the diagnosis can be a humbling experience even for the most experienced clinicians. A primary focus of the initial assessment is attention to the *temporal evolution* of the illness in relation to specific presenting signs and symptoms. In some patients, the diagnosis can be made on history and physical examination alone; in current practice the selective use of advanced imaging has improved diagnostic accuracy and resulted in significant progress in the lowering of negative appendectomy rates.

Physical examination begins with inspection of the child's demeanor and the appearance of the abdomen. Because appendicitis most often has an insidious onset, children rarely present <12 hours from the onset of illness. Children with early appendicitis (18-36 hours) typically appear mildly ill and move tentatively, hunched forward, and often with a slight limp favoring the right side. Supine, they often lie quietly on their right side with their knees pulled up to relax the abdominal muscles, and when asked to lie flat or sit up, they move cautiously and might use a hand to protect the RLQ. Early in appendicitis, the abdomen is typically flat; abdominal distention suggests more advanced disease characteristic of perforation or developing small bowel obstruction. Auscultation can reveal normal or hyperactive bowel sounds in early appendicitis, which are replaced by hypoactive bowel sounds as the disease progresses to perforation. *The judicious use of morphine analgesia to relieve abdominal pain does not change diagnostic accuracy or interfere with surgical decision-making, and patients should receive adequate pain control.* Localized abdominal tenderness is the single most reliable finding in the diagnosis of acute appendicitis. McBurney described the classic point of localized tenderness in acute appendicitis, which is the junction of the lateral and middle thirds of the line joining the right anterior-superior iliac spine and the umbilicus, but the tenderness can also localize to any of the aberrant locations of the appendix. Localized tenderness is a later and less consistent finding when the appendix is retrocecal in position (>50% of cases). In cases of an appendix localized entirely in the pelvis, tenderness on abdominal examination may be minimal. A gentle touch on the child's arm at the beginning of the examination with the reassurance that the abdominal examination will be similarly gentle can help to establish trust and increase the chance for a reliable and reproducible examination. The examination is best initiated in the left lower abdomen, so that the immediate part of the exam is not uncomfortable, and conducted in a counterclockwise direction, moving gently to the left upper abdomen, right upper abdomen, and, lastly, the right lower abdomen. This should alleviate anxiety, allow relaxation of the abdominal musculature, and enhance trust. The examiner makes several circles of the abdomen with sequentially more pressure. A soft, compressible, nontender abdominal wall is reassuring. In appendicitis, any abdominal wall movement, including coughing (Dunphy sign), may elicit pain. A consistent finding in acute appendicitis is guarding—rigidity of the overlying abdominal wall muscles in the RLQ. This rigidity may be voluntary, to protect the area of tenderness from the examiner's hand, or involuntary, if the inflammation has progressed to peritonitis causing spasm of the overlying muscle.

Abdominal tenderness may be vague or even absent early in the course of appendicitis and is often diffuse after rupture. Rebound tenderness and referred tenderness (Rovsing sign) are also consistent findings in acute appendicitis but are not always present. Rebound tenderness is elicited by deep palpation of the abdomen followed by the sudden release of the examining hand. This is often very painful to the child and has demonstrated poor correlation with peritonitis, so it should be avoided. Gentle finger percussion is a better test for peritoneal irritation. Similarly, digital rectal examination is uncomfortable and unlikely to contribute to the evaluation of appendicitis in most cases in children. Psoas and obturator internus signs are pain with passive stretch of these muscles. The psoas sign is elicited with active right thigh flexion or passive extension of the hip and is typically positive in cases of a retrocecal appendix. The obturator sign is demonstrated by adductor pain after internal rotation of the flexed thigh and typically positive in cases of a pelvic appendix. Physical examination may demonstrate a mass in the RLQ representing an inflammatory

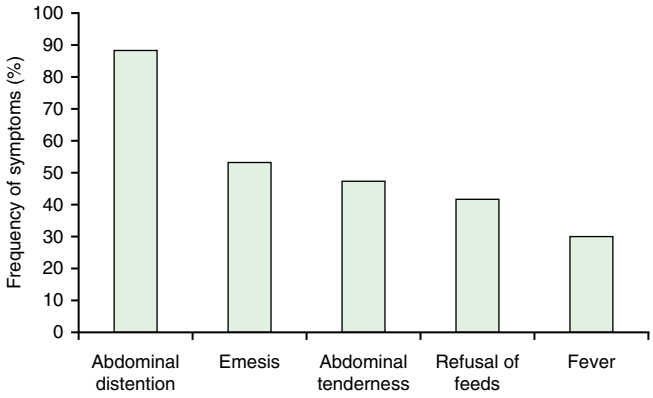

Fig. 391.1 Frequency of presenting symptoms in neonatal appendicitis. *(Data from Raveenthiran V. Neonatal appendicitis (Part 1): a review of 52 cases with abdominal manifestation. J Neonatal Surg. 2015;4:4.)*

Table 391.1 Pediatric Appendicitis Scores

FEATURE	SCORE
Fever >38°C (100.4°F)	1
Anorexia	1
Nausea/vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis >10,000 (10^9/L)	1
Polymorphonuclear neutrophilia >7,500 (10^9/L)	1
Total	10

From Acheson J, Banerjee J. Management of suspected appendicitis in children. *Arch Dis Child Educ Pract Ed.* 2010;95:9–13.

mass (phlegmon) around the appendix or a localized intraabdominal abscess (fluid collection).

Appendicitis in infants and toddlers does not follow the characteristic features observed in older children. Perforation is observed in most infants at presentation. The diagnosis is often delayed, and the initial impression is often sepsis (Fig. 391.1)

APPENDICITIS RISK SCORING SYSTEMS

Several risk scoring systems have become commonly used tools to promote standardization of the approach to the child with abdominal pain and suspected appendicitis. The clear aim is to maximize diagnostic accuracy in acute appendicitis and guide imaging evaluation and resource use. They all combine the predictive value of consistent symptoms, physical examination findings, and laboratory data yielding a numerical score. The systems most widely used are the Alvarado score and the Pediatric Appendicitis Score (PAS). The PAS combines elements of history (migration of pain, anorexia, nausea, vomiting) with physical examination findings (RLQ tenderness, rebound tenderness, fever) and laboratory data (white blood cell [WBC] >10,000, polymorphonuclear neutrophils >75%) to assign a risk score in the low, intermediate, or high-risk range for acute appendicitis (Table 391.1). Scores of ≤4 suggest a very low likelihood of appendicitis, whereas scores ≥8 are highly sensitive and specific for appendicitis. Intermediate scores, between 4 and 7 on the PAS, are considered inconclusive and typically trigger advanced imaging studies. Targeted (appendiceal) ultrasound has demonstrated high sensitivity and specificity (~90%) in the diagnosis of acute appendicitis in centers experienced with the technique and has become the initial imaging study of choice for suspected appendicitis. The notable benefits of ultrasound compared to CT scan include that it is well-tolerated, is noninvasive, and lacks ionizing radiation exposure. CT is reserved for cases of nonvisualization of the appendix on ultrasound or when the ultrasound findings are inconclusive.

The use of appendicitis risk scoring systems in conjunction with clinical judgment has demonstrated high sensitivity and specificity for acute appendicitis (80–90%), and their application has reduced practice variability, improved diagnostic accuracy, decreased preoperative radiation exposure, and enabled efficient resource use—all important elements of current quality improvement and safety initiatives. Their greatest value to date appears to be in predicting patients who have a low likelihood of the diagnosis of appendicitis (negative predictive value) and can avoid imaging studies, and particularly ionizing radiation exposure.

LABORATORY FINDINGS

A variety of laboratory tests have been used in the evaluation of children with suspected appendicitis. Individually, none are very sensitive or specific for appendicitis, but collectively they can affect the clinician's level of suspicion and decision-making to proceed with pediatric surgery consultation, discharge, or imaging studies.

A complete blood count with differential and urinalysis are obtained. The leukocyte count in early appendicitis may be normal and typically is only mildly elevated (11,000-16,000/mm^3) with a left shift as the illness progresses in the initial 24-48 hours. Whereas a normal WBC count never completely eliminates appendicitis, a count <8,000/mm^3 in a patient with a history of illness longer than 48 hours should be viewed as highly suspicious for an alternative diagnosis. The leukocyte count may be markedly elevated (>20,000/mm^3) in PA and rarely in nonperforated cases; a markedly elevated WBC count, other than in cases of advanced PA, should raise suspicion of an alternative diagnosis. Urinalysis often demonstrates a few white or red blood cells as a result of the proximity of the inflamed appendix to the ureter or bladder, but it should be free of bacteria. The urine is often concentrated and contains ketones from diminished oral intake and vomiting. Gross hematuria is uncommon, and in association with purpuric skin lesions and arthritis may indicate IgA vasculitis (Henoch-Schönlein purpura).

Electrolytes and liver chemistries are generally normal unless there has been a delay in diagnosis, leading to severe dehydration and/or sepsis. Amylase and liver enzymes are only helpful to exclude alternative diagnoses such as pancreatitis and cholecystitis and are not commonly obtained if appendicitis is the strongly suspected diagnosis. C-reactive protein (CRP) increases in proportion to the degree of appendiceal inflammation. It has not demonstrated high sensitivity or specificity in the diagnosis of appendicitis; some studies have demonstrated an association between disease severity (PA and abscess formation) and elevated CRP levels. In this context, CRP may have a role in identifying patients with complicated appendicitis, which may be managed initially nonoperatively with antibiotics and drainage of fluid collections.

IMAGING STUDIES

After a thorough initial evaluation, including history, physical examination, review of vital signs, and laboratory studies, if the diagnosis is uncertain, radiographic studies can substantially improve diagnostic accuracy.

Plain Radiographs

In the majority of cases, appendiceal ultrasound and CT scan have become the predominant studies in inconclusive cases of acute appendicitis. Plain abdominal radiographs may be helpful in rare select cases of abdominal pain/suspected appendicitis. Plain abdominal x-rays may demonstrate several findings suggestive of acute appendicitis, including sentinel loops of bowel and localized ileus, scoliosis from psoas muscle spasm, a colonic air-fluid level above the right iliac fossa (colon cutoff sign), a RLQ soft tissue mass, or a calcified appendicolith (5–10% of cases); they are normal in 50% of patients, have a low sensitivity, and are not generally recommended (Fig. 391.2). Plain films are most

helpful in evaluating complicated cases in which small bowel obstruction or free air is suspected.

Ultrasound

Ultrasound has emerged as the first-choice tool for children requiring an imaging study in the evaluation of suspected acute appendicitis. Ultrasound has demonstrated sensitivity and specificity approaching 90% in pediatric centers experienced with the technique and has substantial advantages, including low cost, ready availability, rapidity, and avoidance of sedation, contrast agents, and radiation exposure. Ultrasound can be particularly helpful in adolescent females, a group with a high negative appendectomy rate (normal appendix found at surgery), because of its ability to evaluate for ovarian pathology without ionizing radiation. Graded abdominal compression is used to displace the cecum and ascending colon and identify the appendix, which has a typical target appearance (Fig. 391.3). The ultrasound criteria for appendicitis include wall thickness >6 mm, luminal distention, lack of compressibility, a complex mass in the RLQ, or an appendicolith. The visualized appendix usually coincides with the site of localized pain and tenderness. In addition, ultrasound may identify PA on *initial evaluation;* initial management of PA has increasingly moved toward percutaneous drainage procedures, broad-spectrum antibiotics, and nonoperative treatment. An enlarged appendix (>6 mm), hyperemia, noncompressibility of the appendiceal wall, localized tenderness, and associated mesenteric fat stranding or fluid are all consistent with acute appendicitis. Findings that suggest advanced appendicitis on ultrasound include asymmetric wall thickening, abscess formation, associated free intraabdominal/pelvic fluid, surrounding tissue edema, and decreased local tenderness to compression. *The main limitation of ultrasound is an inability to visualize the appendix, which is reported in 25–60% of cases.* It has been postulated that a normal appendix must be visualized to exclude the diagnosis of appendicitis by ultrasound; however, one report concluded that in patients with a nonvisualized appendix on ultrasound imaging, no evidence of secondary inflammatory changes, and an absolute neutrophil count <8,000/mm^3, the likelihood of appendicitis was <3%. Certain conditions predictably decrease the sensitivity and reliability of ultrasound for appendicitis, including obesity, bowel distention, and uncontrolled pain.

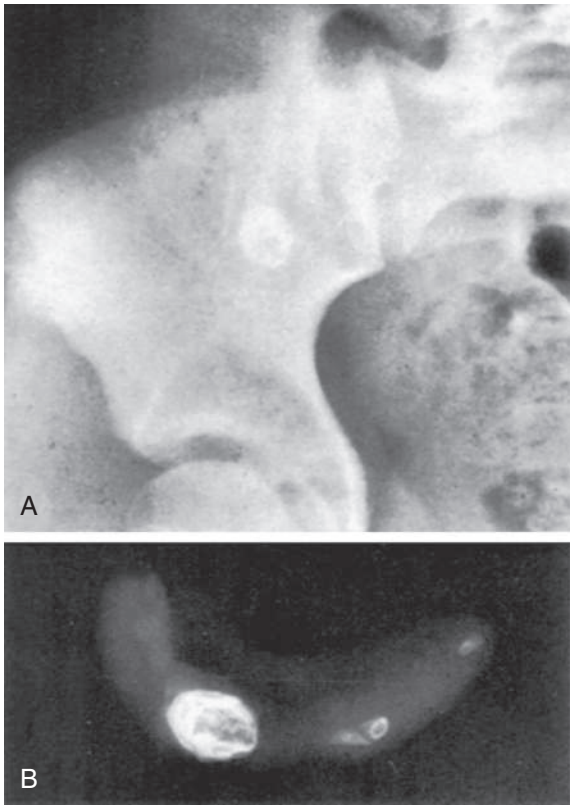

Fig. 391.2 Calcified appendicoliths are seen in a coned-down anteroposterior view of the right lower quadrant (**A**) and in the resected appendix of a 10-yr-old female with acute appendicitis (**B**). *(From Kuhn JP, Sloviso TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby; 2004:1682.)*

Computed Tomography

CT scan has been the gold-standard imaging study for evaluating children with suspected appendicitis and has a sensitivity of 97%, specificity 99%, positive predictive value 98%, and negative predictive value 98% (Figs. 391.4 and 391.5). The advantages of CT imaging include ready availability, rapid acquisition time, and lack of operator dependency. CT carries the significant negative effects of exposure of children to ionizing radiation and increased costs. The exam can be performed using intravenous and enteral (oral or rectal) contrast; however, the administration of enteral contrast has several drawbacks, including delay in diagnostic evaluation, increasing abdominal distention, risk of emesis and aspiration, and increasing radiation exposure without demonstrable improvement in accuracy of diagnosis. The use of oral contrast should be reserved for patients in whom alternative

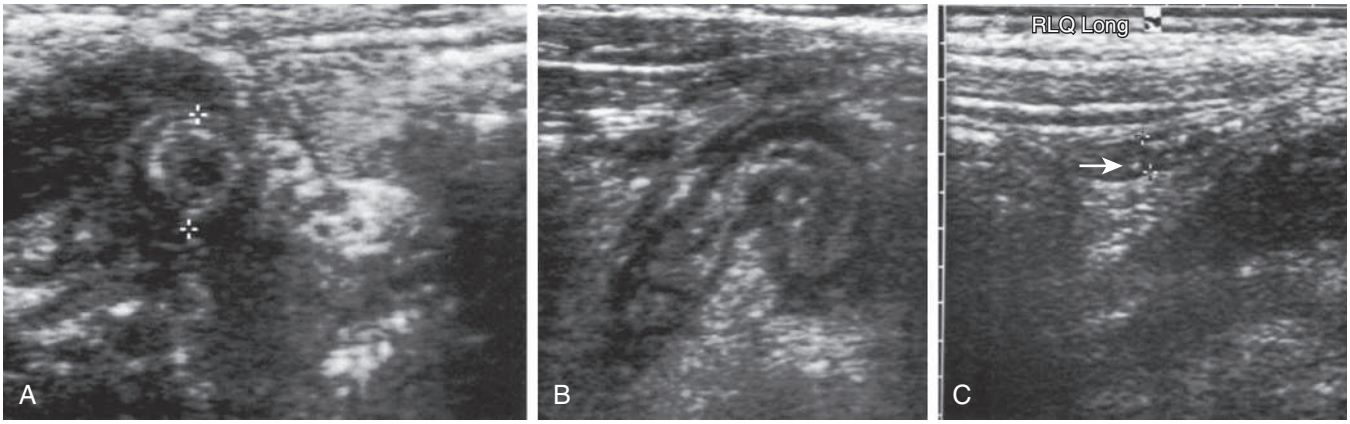

Fig. 391.3 Ultrasound examination of patients with appendicitis. **A,** Transverse ultrasound scan of the appendix demonstrates the characteristic "target sign." In this case, the innermost portion is sonolucent, compatible with fluid or pus. **B,** Longitudinal view of another patient demonstrates the alternating hyperechoic and hypoechoic layers with an outermost hypoechoic layer, suggesting periappendiceal fluid. **C,** Longitudinal ultrasound scan of the right lower quadrant demonstrates a dilated, noncompressible appendix. The bright echo within the appendix represents an appendicolith with acoustic shadowing *(arrow). (From Kuhn JP, Slovis TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby; 2004:1684.)*

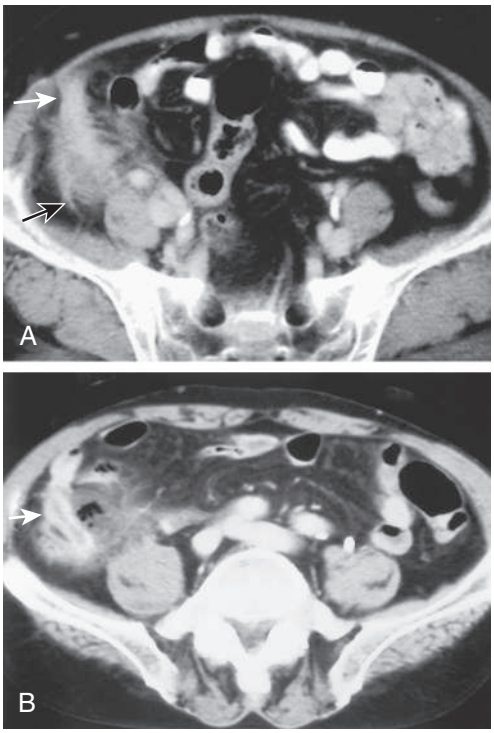

Fig. 391.4 A, Phlegmon *(black arrow)* is noted around the enlarged appendix *(white arrow)* in perforated appendicitis. B, Extraluminal air is shown adjacent to the wall-enhanced appendix *(arrow)* in perforated appendicitis. *(From Yeung KW, Chang MS, Hsiao CP. Evaluation of perforated and non-perforated appendicitis with CT. Clin Imaging. 2004;28:422–427, Figs. 1 and 3)*

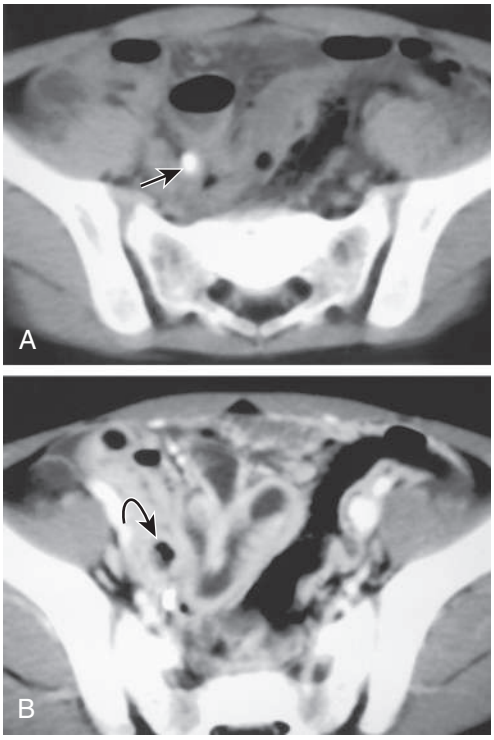

Fig. 391.5 A, Precontrast-enhanced CT reveals an appendicolith *(arrow)* in perforated appendicitis. B, Postcontrast-enhanced CT (1 cm below the level in A) reveals intraluminal air in the appendix *(curved arrow)* associated with ileal wall enhancement in perforated appendicitis. *(From Yeung KW, Chang MS, Hsiao CP. Evaluation of perforated and non-perforated appendicitis with CT. Clin Imaging. 2004;28:422–427, Fig. 5.)*

diagnoses are suspected, particularly Crohn disease. Because the finding of fat stranding in surrounding tissues is a key component of CT evaluation for appendicitis, CT is less reliable in thin children with minimal body fat.

The avoidance of enteral contrast, targeted CT imaging, and the use of pediatric-specific protocols can significantly lower radiation dosages without sacrificing diagnostic accuracy. The use of appendicitis risk scoring systems in conjunction with CPGs and increasing experience with appendiceal ultrasound have led to a decreased use of CT scans (<6.6% in most reports), without negatively affecting time to appendectomy or negative appendectomy rates.

Magnetic Resonance Imaging

MRI is at least equivalent to CT in diagnostic accuracy for appendicitis and does not involve ionizing radiation; however, its use in the evaluation of appendicitis is limited because it is less available, is associated with higher costs, and does not offer equivalent access for drainage of fluid collections. MRI may prove most useful in adolescent females when ultrasound imaging is equivocal. The use of MRI is becoming more common in institutions with high resources, and it has become a good alternative to CT in cases with equivocal ultrasound.

DIAGNOSIS AND TREATMENT

Acute appendicitis is believed to be a time-sensitive condition; thus any delay in diagnosis or treatment may lead to an increased risk of perforation and its attendant morbidity. The misdiagnosis of appendicitis is second only to meningitis as a cause of medical malpractice suits in pediatric emergency care. A careful history and physical examination remain primary in the initial assessment of a child presenting with abdominal symptoms. The classic history in acute appendicitis, although possibly not most common, is a 24-hour history of diffuse mid-abdominal pain that migrates and becomes localized to the RLQ. Patients should have a WBC count with differential analysis, as this is a component of most appendicitis risk scoring systems. A urinalysis is also typically obtained and a pregnancy test in appropriately selected patients. CPGs have become common practice in many centers for evaluation of patients with abdominal pain and suspected appendicitis to reduce practice variability and improve diagnostic accuracy and resource use. CPGs have been shown to have high positive and negative predictive values (~95%) and to decrease both LOS and costs without increasing morbidity or complications. These guidelines combine initial history, physical examination, and laboratory data with predictive risk scoring systems to cohort patients into low, intermediate, and high risk for the diagnosis of acute appendicitis. In general, low-risk patients can be discharged without imaging studies, high-risk patients would have pediatric surgical consultation, and the inconclusive or intermediate-risk group would most predictably benefit from a period of observation or proceeding with advanced imaging studies. If the initial assessment leads to a high level of suspicion for appendicitis, pediatric surgical consultation should be the next step, with the likelihood of an appendectomy without further studies. In patients with a low concern for appendicitis, the child may be discharged with family education regarding the natural history and progression of acute appendicitis and advice to return for repeat evaluation if the child is not improving on liquids and a bland diet in the next 24 hours. The group of patients with an intermediate-risk score would proceed with targeted ultrasound of the appendix if the center has experience with the technique. If the ultrasound study is unable to visualize the appendix, or the appendix is visualized but the findings are inconclusive, the next options would include admission for a period of observation and planned reassessment, CT imaging or MRI, or diagnostic laparoscopy.

The use of observation units, where the child may be observed with intravenous fluids, serial vital signs, and planned reexaminations, is another strategy. At the end of a period of observation, typically 12-24 hours, the clinician decides on discharge based on reassuring clinical status, proceeds to diagnostic laparoscopy and appendectomy, or proceeds with advanced imaging evaluation. The period of observation can occur at home provided the patient is physiologically well; a hospital-based observational unit has the advantage of being able to

provide intravenous fluids. An observation strategy seems most useful in patients who present with a brief history of illness (<12 hours) when advanced imaging studies predictably have lower sensitivity and specificity. If observed patients remain equivocal, advanced imaging should be more reliable further into the disease process.

DIFFERENTIAL DIAGNOSIS

The list of illnesses that can mimic acute appendicitis is extensive because many gastrointestinal, gynecologic, and inflammatory disorders can manifest with similar illness history, signs, and symptoms. Differential diagnosis, even limited to common conditions, includes gastroenteritis, mesenteric adenitis, Meckel diverticulitis, intussusception, inflammatory bowel disease, diabetes mellitus, sickle cell disease, streptococcal pharyngitis, lower lobe pneumonia, cholecystitis, pancreatitis, urinary tract infection (UTI), infectious enteritis, and, in females, ovarian torsion, ectopic pregnancy, ruptured/hemorrhagic ovarian cysts, and pelvic inflammatory disease (including tubo-ovarian abscess). *Epiploic appendagitis,* an inflammation of the fat-filled structures on the antimesenteric surface of the colon, may present with acute lower quadrant abdominal pain after torsion, thrombosis, and ischemic injury to the structure. Viral infections, bacterial infections, and parasitic infections can all closely mimic acute appendicitis. Intestinal tract lymphoma, tumors of the appendix (carcinoid in children), and ovarian tumors are rare but can also masquerade as acute appendicitis. Henoch-Schönlein purpura can initially present as severe abdominal pain. Urinary tract causes of abdominal pain include UTI, nephrolithiasis, and pyelonephritis. In patients with pyelonephritis, the fever and WBC count are likely much higher, symptoms of dysuria will be present, and the tenderness is located more in the flank or costovertebral angle. Rarely, appendicitis may recur in the stump of a previous appendectomy. *Children younger than 3 years of age and adolescent females have historically proven to be at particularly high risk for an incorrect diagnosis.*

Viral illnesses are common in children, often are associated with abdominal pain and vomiting, and thus mimic acute appendicitis. The classic patient with acute appendicitis describes abdominal pain as the preeminent symptom, and in general, symptoms of systemic illness such as headache, chills, and myalgias are infrequent in appendicitis and common when viral illness is the correct diagnosis.

Infection with SARS-CoV-2 (COVID-19) or associated with the development of multisystem inflammatory syndrome in children (MIS-C) has produced a pseudo-appendicitis picture with RLQ pain, mesenteric adenopathy, fat stranding, and phlegmon formation. Additional features of COVID-19 are usually, but not always, present (Fig. 391.6).

The diagnosis of appendicitis in adolescent females is especially challenging, and some series report negative appendectomy rates as high as 30–40%. Ovarian cysts are often acutely painful as a result of rupture, rapid enlargement, or hemorrhage. Rupture of an ovarian follicle associated with ovulation often causes midcycle lateralizing pain (mittelschmerz), but there is no progression of symptoms and systemic illness is absent. Ovarian tumors and torsion can also mimic acute appendicitis, although ovarian torsion is typically characterized by the acute onset of severe pain and is associated with more frequent and forceful nausea and vomiting than is typically seen in early appendicitis. In pelvic inflammatory disease, the pain is typically suprapubic, bilateral, and of longer duration. The need for accurate urgent diagnosis in females is influenced by concern that PA can predispose the patient to future ectopic pregnancy or tubal infertility, although data have not consistently demonstrated increased incidence of infertility after PA. For these reasons, adjunct diagnostic studies (ultrasound, CT, MRI, or diagnostic laparoscopy) should be used more liberally in females to keep negative appendectomy rates low.

Torsion of an undescended testis and epididymitis are common but should be discovered on physical exam. Meckel diverticulitis is an infrequent condition, but the clinical presentation closely mimics appendicitis. The diagnosis is rarely made before surgery. Primary spontaneous peritonitis (PSP) is classically seen in prepubertal females or patients with either nephrotic syndrome or cirrhosis and is frequently mistaken for appendicitis.

Atypical presentations of appendicitis are expected in association with other conditions such as pregnancy, Crohn disease, steroid treatment, and immunosuppressive therapy. Appendicitis in association with Crohn disease often has a protracted presentation with an atypical pattern of recurring but localized abdominal pain. It should be recognized that *missed* appendicitis is the most common cause of small bowel obstruction in children without a history of prior abdominal surgery.

ANTIBIOTICS

Antibiotics should be initiated promptly once the diagnosis of appendicitis is made or highly suspected. Antibiotics substantially lower the incidence of postoperative wound infections (SSIs) and intraabdominal abscesses—the source of the majority of the substantial morbidity and costs in PA. Many believe the time from onset of illness to the initiation of antibiotics has more impact on postoperative complication rates, LOS, and overall costs than time from diagnosis to surgery.

The antibiotic regimen should be directed against the typical bacterial flora found in the appendix, including anaerobic organisms (*Bacteroides, Clostridia,* and *Peptostreptococcus* spp.) and gram-negative aerobic bacteria (*Escherichia coli, Pseudomonas aeruginosa, Enterobacter,* and *Klebsiella* spp.). Many antibiotic combinations have demonstrated equivalent efficacy in controlled trials in terms of wound

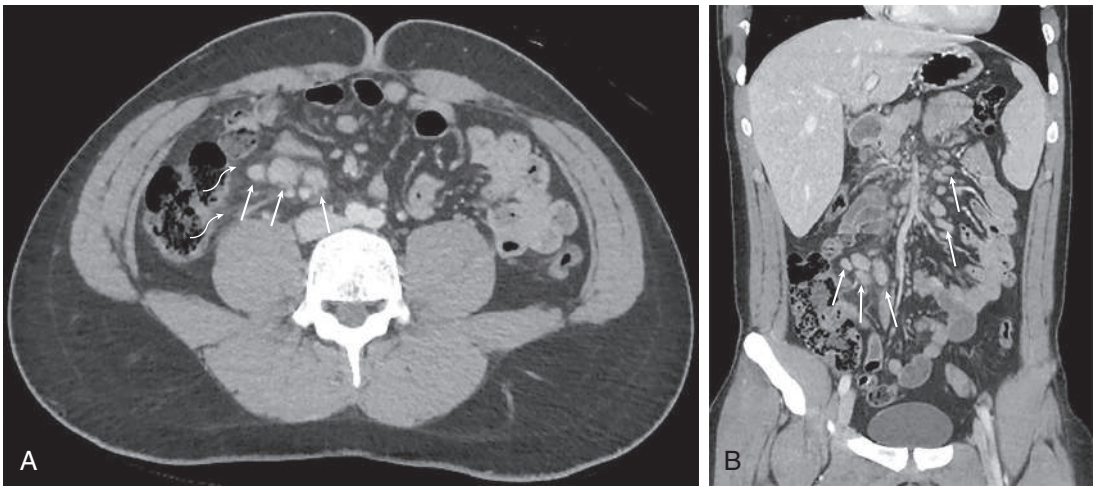

Fig. 391.6 Initial CT scan of a patient with COVID-19 presenting as mesenteric adenopathy. Axial image (**A**) and coronal reformat (**B**) of abdominopelvic CT with intravenous contrast agent in a 17-yr-old male demonstrate enlarged lymph nodes *(straight arrows)* and adjacent fat stranding *(curved arrows). (From Noda S, Ma J, Romberg EK, et al. Severe COVID-19 initially presenting as mesenteric adenopathy. Pediatr Radiol. 2021;51:140–143, Fig. 1.)*

infection rate, resolution of fever, LOS, and incidence of complications. Historically, a triple-antibiotic regimen consisting of ampicillin, gentamicin, and clindamycin was standard. Exhaustive studies of different antibiotic regimens have been performed, mostly aimed at lowering costs and frequency of dosing while maintaining efficacy. Both piperacillin/tazobactam and cefoxitin have demonstrated equivalent effectiveness and may decrease LOS and pharmaceutical costs compared to the triple-antibiotic regimen.

For simple (nonperforated) appendicitis, one preoperative dose of a single broad-spectrum agent (piperacillin/tazobactam) or equivalent is sufficient. In PA, the antibiotic is continued intravenously for 2-3 days postoperatively until the child is afebrile (≥24 hours), tolerating a general diet, and ready for discharge. Some centers prefer to add metronidazole in PA to augment coverage of anaerobes. The decision to discharge patients with PA managed with up-front appendectomy on a course of oral antibiotics (typically 3-5 days) remains controversial. The literature does not support improved outcomes with PA if antibiotics are extended beyond a 4- to 5-day course.

SURGICAL INTERVENTION

Once the diagnosis of appendicitis is confirmed or highly suspected, the standard treatment for acute appendicitis, both simple and complicated, in current practice is most often prompt appendectomy. LA (a minimally invasive technique) is the preferred surgical approach (65–70%) in both simple and PA, with open appendectomy markedly declining in the past decade. The laparoscopic approach has demonstrated slight improvement in clinical outcome measures (wound infection rate, intraabdominal abscess, analgesic requirements, wound cosmesis, and return to full activity); however, costs can be higher. The laparoscopic approach (diagnostic laparoscopy/LA) has particular advantages for obese patients, when alternative diagnoses are suspected, and in adolescent females to evaluate for ovarian pathology and alternative diagnoses while avoiding the ionizing radiation associated with CT imaging. The operation should proceed semi-electively within 12-24 hours of diagnosis. Children with appendicitis are typically at least mildly dehydrated and should receive supportive care before surgery, including fluid resuscitation to correct hypovolemia and electrolyte abnormalities, antipyretics to lower fever, and broad-spectrum antibiotics. These important fundamentals of care ensure safe anesthesia and optimize outcomes. In most cases, preoperative management can be accomplished during the period of diagnostic evaluation and prompt appendectomy can be performed. Pain management begins even before a definitive diagnosis is made, and consultation of a pain service, if available, is appropriate. Emergency surgery (middle of the night) *is rarely* indicated in acute appendicitis and should only be performed in the rare circumstance when physiologic resuscitation requires urgent control of advanced intraabdominal sepsis not amenable to percutaneous drainage by interventional radiology or when this is not available. No correlation has been demonstrated between timing of surgery and perforation rates or postoperative morbidity when the operation proceeds within 24 hours of diagnosis. When comparing emergent appendectomy (within 5 hours of admission) with urgent appendectomy (within 17 hours of admission), no differences in PA, operative time, readmission rate, postoperative complications, LOS, or hospital charges have been noted. In addition, occasionally unexpected pathology (appendiceal tumors, intestinal lymphoma, congenital renal anomalies, Crohn disease) is discovered at operation, and intraoperative consultation with other specialists and/or frozen section evaluation may be required. The laparoscopic approach, in conjunction with standardized, expedited postoperative recovery protocols, and improved (single drug) and shorter-duration antibiotic regimens have led to decreased LOS in both simple and complicated (perforated) appendicitis. The average LOS in most centers is approximately 24 hours for simple appendicitis and 4-5 days for perforated cases that recover without postoperative complications. In simple appendicitis, some centers have initiated same-day discharge.

PERFORATED APPENDICITIS

A major area of focus and challenge in the management of acute appendicitis is the group of patients with delayed presentation (>48 hours) of symptoms. Because acute appendicitis often has an insidious onset of generalized malaise, as many as 40–50% of patients have delayed presentation. This cohort of patients has a high incidence of PA at presentation (40–59%) and a 56% greater LOS stay than those presenting within ≤24 hours of the onset of symptoms. The risk for development of postoperative complications (SSI, intraabdominal abscess, small bowel obstruction) approaches 20–30% for children with PA versus an approximately 3% risk of complications in patients with simple appendicitis.

Management options for children presenting with PA include up-front appendectomy after a brief period of stabilization with intravenous fluids and antibiotics, antibiotics alone, and antibiotics in conjunction with percutaneous drainage of intraabdominal fluid collections/abscesses. The past decade has witnessed a substantial trend toward nonoperative management in children with delayed presentation and suspected PA to avoid the high complication rate in these patients and the potential technical challenges of operative treatment in the setting of marked intraabdominal inflammation/peritonitis. Based on patient status, findings on imaging studies, and availability of experienced interventional radiologists, initial nonoperative management of PA with percutaneous drainage of fluid collections, intravenous fluids, and broad-spectrum antibiotics has demonstrated success in >80% of patients. Antibiotics are initiated and typically continued intravenously for 1-2 days along with pain control. If the child demonstrates clinical recovery by resolution of fever and pain and can tolerate a general diet, the child is converted to oral antibiotics and discharged to complete an outpatient antibiotic course (typically 7-10 days of ciprofloxacin/metronidazole or amoxicillin/clavulanate). A patient who fails to demonstrate clinical recovery proceeds to prompt appendectomy. This nonoperative management, and particularly the transition to oral antibiotics, has contributed to a decreased LOS and costs in the management of PA. Patients who do not have up-front appendectomy will require a decision regarding interval appendectomy (IA) in 4-6 weeks, provided the child does not fail nonoperative management after discharge by recurrence of pain, fever, or vomiting.

NONOPERATIVE MANAGEMENT OF UNCOMPLICATED APPENDICITIS

Multiple studies in adults have demonstrated highly effective treatment of appendicitis with antibiotics alone. In addition, other conditions similar to appendicitis, such as diverticulitis, intraabdominal abscess in Crohn disease, and tubo-ovarian abscess, are primarily treated with antibiotics alone, with surgery reserved for failures of medical management. These outcomes have led many centers to evaluate initial nonoperative management of acute (simple) appendicitis in children, and currently several randomized controlled studies are ongoing. Advantages of the antibiotic-alone/nonoperative approach in acute appendicitis include avoidance of surgical complications and the risk of general anesthesia and an operative procedure that may not be necessary. Selection criteria for nonoperative management are designed to exclude signs and symptoms suggestive of PA and typically include duration of symptoms <48 hours, age >7 years, imaging confirmation of acute non-PA, appendiceal diameter <1.2 cm, *absence* of appendicolith, abscess, or phlegmon, and WBC >5,000 and <18,000 cells/μL. The clinical pathway for children enrolled consists of an initial 1-2 days of intravenous broad-spectrum antibiotics and pain control. If the child demonstrates clinical recovery by resolution of pain and fever and is tolerating a general diet, he or she is discharged to complete 7-10 days of oral antibiotics. If the child does not demonstrate clinical recovery, prompt appendectomy is performed. Early nonoperative trials found that predictors of failure of nonoperative management included pain >48 hours in duration, presence of an appendicolith, inflammatory mass or abscess on imaging, and elevated laboratory values (WBC >18,000, CRP >4 mg/dL). The largest prospective trial (nonrandomized, treatment assigned by parent selection) comparing surgery and medical management of appendicitis in the United States followed patients for 1 year. Out of the children who were initially treated medically, 37% underwent an appendectomy within 1 year. Multiple reports indicate a more rapid return to full activities; however, patients with nonoperative management had more subsequent ED visits, advanced

imaging studies, and hospitalizations compared with those managed operatively at the first visit. Controversies remain in the initial nonoperative management of PA.

RECURRENT APPENDICITIS

Prospective studies of the incidence of early recurrent appendicitis (within 1 year) describe a range between 10% and 30% in patients initially managed nonoperatively. The lifetime risk of recurrent appendicitis in children treated nonoperatively is unknown, but the few data that have been published beyond the 1-year follow-up suggest that the risk for recurrent appendicitis continues to increase past the first year. Currently under review is the need for delayed appendectomy (IA) in patients with complicated appendicitis initially managed nonoperatively. Although the trend in cases of PA at presentation is toward initial nonoperative management, the data remain uncertain, and there are no convincing data to recommend one approach in all patients.

INTERVAL APPENDECTOMY

In patients with PA initially treated nonoperatively, the decision to proceed with IA, typically in 4-6 weeks, is another area of management lacking consensus. Traditionally, most surgeons recommended IA to avoid recurrent appendicitis and to confirm the original diagnosis, citing reports that demonstrated an incidence of unexpected pathology in 30% of IA specimens. This has been questioned, with nonoperative management of simple appendicitis gaining acceptance and many debating the risk of recurrent appendicitis (5–20%), believing it to be lower. The lifetime risk of recurrent appendicitis is unknown. Decision-making for IA must be individualized to balance the risks of recurrent appendicitis with the risks of anesthesia and comorbid conditions such as obesity, congenital heart disease, chronic respiratory conditions, and others.

INCIDENTAL APPENDICOLITHS

The question of the incidental appendicolith is an intriguing one for pediatric practitioners. These are patients who do not have appendicitis but are found to have an appendicolith on imaging studies. An appendicolith is defined as a calcification within the appendiceal lumen. In adults, incidental appendicoliths identified by CT scans vary in incidence from <1% to as high as 10%. They have a characteristic dense and laminated appearance when compared to other lower abdominal calcifications, including phleboliths (venous calcifications) and, in females, ovarian calcifications, most commonly seen in ovarian tumors. They can be appreciated on plain film, ultrasound, and CT scan. When an appendicolith is noted in the evaluation of a child with abdominal pain and suspected appendicitis, the finding of the appendicolith confirms the diagnosis; surgical consultation and prompt appendectomy are indicated. Appendicoliths may be noted in the evaluation of patients who have no signs of appendicitis, such as imaging obtained after trauma or for nonspecific abdominal complaints in patients with a low likelihood of appendicitis. The concern in this setting is that the appendicolith may increase the eventual development of acute appendicitis. In addition, there is the concern that should appendicitis develop in association with an appendicolith, there may be a rapidly escalating course and early perforation. Some physicians believe that a persistent appendicolith may be associated with recurrent RLQ/iliac fossa pain.

Incidental appendicoliths may be transient and in most short-term follow-up studies have a low risk of subsequent acute appendicitis. In addition, the lifetime risk for the development of appendicitis in patients with an incidental appendicolith is approximately 5%, which is not different from the normal population. The risk of subsequent appendicitis may be higher in those presenting with abdominal pain or those younger than 19 years of age. Radiographically detected incidental appendicoliths are usually managed with observation, planned follow-up, and patient education for signs of acute appendicitis. After discussing the risks and benefits with the family and persistence of the appendicolith, an individualized approach is best between the physician and the family relative to elective appendectomy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 392

Surgical Conditions of the Anus and Rectum

392.1 Anorectal Malformations

Christina M. Shanti

To fully understand the spectrum of anorectal anomalies, it is necessary to consider the importance of the sphincter complex, a mass of muscle fibers surrounding the anorectum (Fig. 392.1). This complex is the combination of the puborectalis, levator ani, external and internal sphincters, and the superficial external sphincter muscles, all meeting at the rectum. Anorectal malformations are defined by the relationship of the rectum to this complex and include varying degrees of stenosis to complete atresia. The incidence is 1/3,000 live births. Significant long-term concerns focus on bowel control and urinary and sexual functions.

EMBRYOLOGY

The hindgut forms early as the part of the primitive gut tube that extends into the tail fold in the second week of gestation. At about day 13, it develops a ventral diverticulum, the allantois, or primitive bladder. The junction of the allantois and hindgut becomes the cloaca, into which the genital, urinary, and intestinal tubes empty. This is covered by a cloacal membrane. The urorectal septum descends to divide this common channel by forming lateral ridges, which grow in and fuse by the middle of the seventh week. Opening of the posterior portion of the membrane (the anal membrane) occurs in the eighth week. Failures in any part of these processes can lead to the clinical spectrum of anogenital anomalies.

Imperforate anus can be divided into low lesions, where the rectum has descended through the sphincter complex, and high lesions, where it has not. Most patients with imperforate anus have a fistula. There is a spectrum of malformation in males and females. In males, low lesions usually manifest with meconium staining somewhere on the perineum along the median raphe (Figs. 392.2A and 392.3). Low lesions in females also manifest as a spectrum from an anus that is only slightly anterior on the perineal body to a fourchette fistula that opens on the moist mucosa of the introitus distal to the hymen (Fig. 392.4A). A high imperforate anus in a male has no apparent cutaneous opening or fistula, but it usually has a fistula to the urinary tract, either the urethra or the bladder (Fig. 392.2B). Although there is occasionally a rectovaginal fistula, in females, high lesions are usually cloacal anomalies in which the rectum, vagina, and urethra all empty into a common channel or cloacal stem of varying length (see Fig. 392.4B).

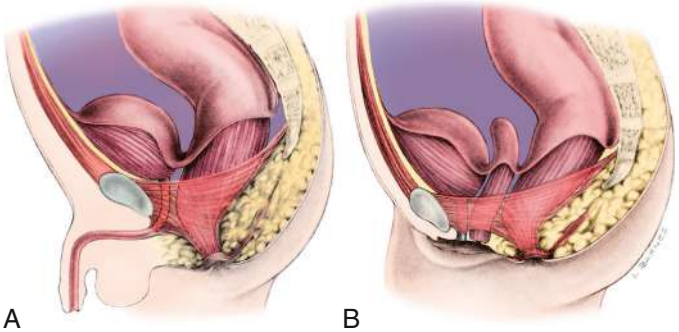

Fig. 392.1 Normal anorectal anatomy in relation to pelvic structures. A, Male. B, Female. *(From Peña A. Atlas of Surgical Management of Anorectal Malformations. New York: Springer-Verlag; 1989: 3.)*

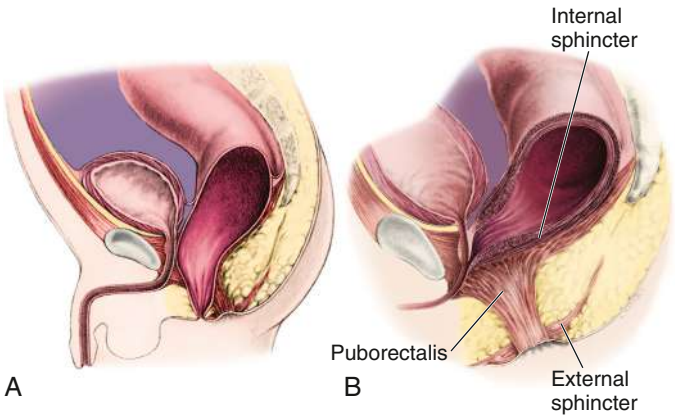

Fig. 392.2 Imperforate anus in males. A, Low lesions. B, High lesions. *(From Peña A. Atlas of Surgical Management of Anorectal Malformations. New York: Springer-Verlag; 1989:7, 26.)*



Fig. 392.3 This male infant has a rectoperineal fistula with a subepithelial tract filled with either mucus or meconium that extends into the scrotal raphe. *(From Rentea RM, Levitt MA. Anorectal atresia and cloacal malformations. In Holcomb III GW, Murphy JP, St. Peter SD, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020: Fig. 35.2, p. 578.)*

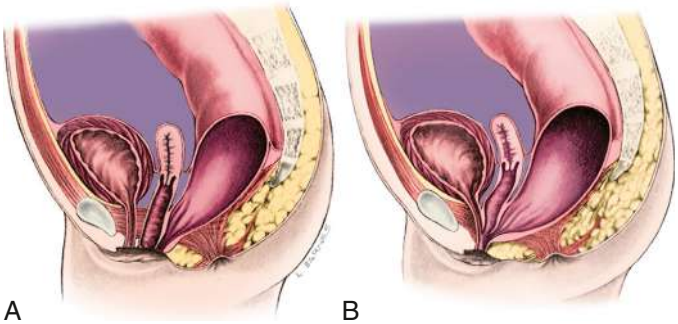

Fig. 392.4 Imperforate anus in females. A, Vestibular fistula. B, Cloaca. *(From Peña A. Atlas of Surgical Management of Anorectal Malformations. New York: Springer-Verlag; 1989: 50, 60.)*

The interesting category of males with imperforate anus and no fistula occurs mainly in children with trisomy 21. The most common lesions are the rectourethral bulbar fistula in males and the rectovestibular fistula in females; the second most common lesion in both sexes is the perianal fistula (Fig. 392.5).

ASSOCIATED ANOMALIES

Many anomalies are associated with anorectal malformations (Table 392.1). The most common are anomalies of the kidneys and urinary tract in conjunction with abnormalities of the sacrum. This complex is often referred to as *caudal regression syndrome*. Males with a rectovesical fistula and patients with a persistent cloaca have a 90% risk of urologic defects. Other common associated anomalies are cardiac anomalies and esophageal atresia with or without tracheoesophageal fistula. These can cluster in any combination in a patient. When combined, they are often accompanied by abnormalities of the radial aspect of the upper extremity and are termed the *VACTERL* (*v*ertebral, *a*nal, *c*ardiac, *t*racheal, *e*sophageal, *r*enal, *l*imb) *anomalad*.

Anorectal malformations, particularly anal stenosis and rectal atresia, can also present as the Currarino triad, which includes sacral agenesis, a presacral mass, and anorectal stenosis. These patients present with a funnel-appearing anus, have sacral bony defects on plain x-ray, and have a presacral mass (teratoma, meningocele, dermoid cyst, enteric cyst) on exam or imaging. It is an autosomal dominant disorder caused in most patients by a pathogenic variant in the *MNX1* gene.

A good correlation exists between the degree of sacral development and future function. Patients with an absent sacrum usually have permanent fecal and urinary incontinence. Spinal abnormalities and different degrees of dysraphism are often associated with these defects. Tethered cord occurs in approximately 25% of patients with anorectal malformations. Untethering of the cord can lead to improved urinary and rectal continence in some patients, although it seldom reverses established neurologic defects. The diagnosis of spinal defects can be screened for in the first 3 months of life by spinal ultrasound, although MRI is the imaging method of choice if a lesion is suspected. In older patients, MRI is needed.

MANIFESTATIONS AND DIAGNOSIS

Low Lesions

Examination of a newborn includes the inspection of the perineum. The absence of an anal orifice in the correct position leads to further evaluation. Mild forms of imperforate anus are often called *anal stenosis* or *anterior ectopic anus*. These are typically cases of an imperforate anus with a perineal fistula. The normal position of the anus on the perineum is approximately halfway (0.5 ratio) between the coccyx and the scrotum or introitus. Although symptoms, primarily constipation, have been attributed to anterior ectopic anus (ratio: <0.34 in females, <0.46 in males), many patients have no symptoms.

If no anus or fistula is visible, there may be a low lesion or *covered anus*. In these cases, there are well-formed buttocks and often a thickened raphe or *bucket handle*. After 24 hours, meconium bulging may be seen, creating a blue or black appearance. In these cases, an immediate perineal procedure can often be performed, followed by a dilation program.

In a male, the perineal (cutaneous) fistula can track anteriorly along the median raphe across the scrotum and even down the penile shaft (see Fig. 392.3). This is usually a thin track, with a normal rectum often just a few millimeters from the skin. Extraintestinal anomalies are seen in <10% of these patients.

In a female, a low lesion enters the vestibule or fourchette (the moist mucosa outside the hymen but within the introitus). In this case, the rectum has descended through the sphincter complex. Children with a low lesion can usually be treated initially with perineal manipulation and dilation. Visualizing these low fistulas is so important in the evaluation and treatment that one should avoid passing a nasogastric tube for the first 24 hours to allow the abdomen and bowel to distend, pushing meconium down into the distal rectum.

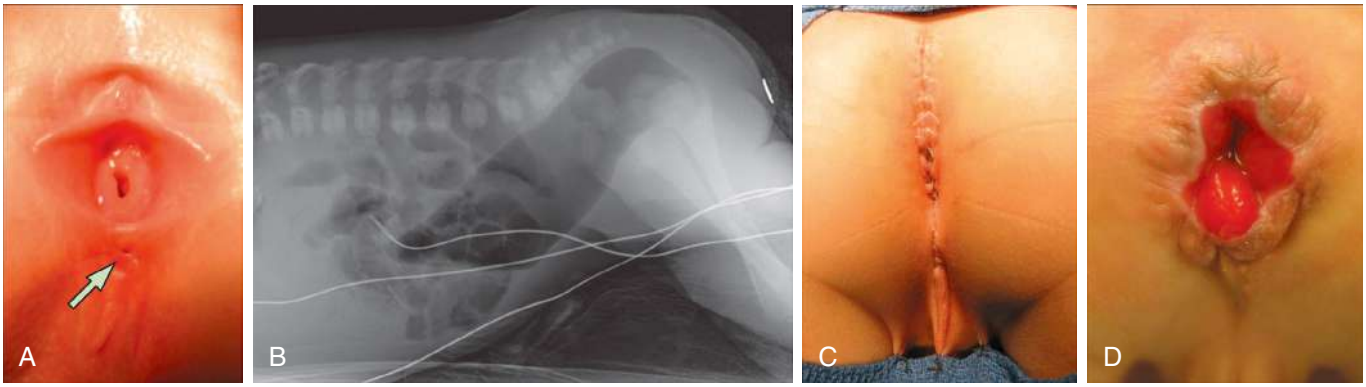

Fig. 392.5 Preoperative and postoperative images of anorectal malformations. **A,** Preoperative rectoperineal fistula. **B,** Radiograph with cross-table lateral film showing neonate in prone position and gas below the coccyx. **C,** Postoperative appearance after a posterior sagittal anorectoplasty. **D,** Postoperative large, patulous, and prolapsed anoplasty. *(From Bischoff A, Bealer J, Pená A. Controversies in anorectal malformations. Lancet Child/Adolesc. 2017;1:323–330.)*

Table 392.1 Associated Malformations

GENITOURINARY
Vesicoureteric reflux
Renal agenesis
Renal dysplasia
Ureteral duplication
Cryptorchidism
Hypospadias
Bicornuate uterus
Vaginal septa
VERTEBRAL
Spinal dysraphism
Tethered chord
Presacral masses
Meningocele
Lipoma
Dermoid
Teratoma
CARDIOVASCULAR
Tetralogy of Fallot
Ventricular septal defect
Transposition of the great vessels
Hypoplastic left-heart syndrome
GASTROINTESTINAL
Tracheoesophageal fistula
Duodenal atresia
Malrotation
Hirschsprung disease
CENTRAL NERVOUS SYSTEM
Spina bifida
Tethered cord

High Lesions

In a male with a high imperforate anus, the perineum appears flat. There may be air or meconium passed via the urethra when the fistula is high, entering the bulbar or prostatic urethra, or even the bladder. In *rectobulbar urethral fistulas* (the most common in males), the sphincter mechanism is satisfactory, the sacrum may be underdeveloped, and an anal dimple is present. In *rectoprostatic urethral fistulas,* the sacrum is poorly developed, the scrotum may be bifid, and the anal dimple is near the scrotum. In *rectovesicular fistulas,* the sphincter mechanism is poorly developed, and the sacrum is hypoplastic or absent. In males with trisomy 21, all the features of a high lesion may be present, but there is no fistula, the sacrum and sphincter mechanisms are usually well developed, and the prognosis is good.

In females with high imperforate anus, there may be the appearance of a rectovaginal fistula. A true rectovaginal fistula is rare. Most are either the fourchette fistulas described earlier or are forms of a cloacal anomaly.

Persistent Cloaca

In persistent cloaca, the embryologic stage persists in which the rectum, urethra, and vagina communicate in a common orifice, the cloaca. It is important to realize this anomaly, because the repair often requires repositioning the urethra and vagina as well as the rectum. Children of both sexes with a high lesion require a colostomy before repair.

Rectal Atresia

Rectal atresia is a rare defect occurring in only 1% of anorectal anomalies. It has the same characteristics in both sexes. The unique feature of this defect is that affected patients have a normal anal canal and a normal anus. The defect is often discovered while rectal temperature is being taken. An obstruction is present approximately 2 cm above the skin level. These patients need a protective colostomy. The functional prognosis is excellent because they have a normal sphincteric mechanism (and normal sensation), which resides in the anal canal.

APPROACH TO THE PATIENT

Evaluation includes identifying associated anomalies (see Table 392.1). Careful inspection of the perineum is important to determine the presence or absence of a fistula. If the fistula can be seen, it is a low lesion. The invertogram, or upside-down x-ray, is of little value, but a prone cross-table lateral plain x-ray at 24 hours of life (to allow time for bowel distention from swallowed air) with a radiopaque marker on the perineum can demonstrate a low lesion by showing the rectal gas bubble <1 cm from the perineal skin (see Fig. 392.5). A plain x-ray of the entire sacrum, including both iliac wings, is important to identify sacral anomalies and the adequacy of the sacrum. An abdominal-pelvic ultrasound and voiding cystourethrogram must be performed. The clinician should also pass a nasogastric tube to identify esophageal atresia and should obtain an echocardiogram. In males with a high lesion, the voiding cystourethrogram often identifies the rectourinary fistula. In females with a high lesion, more invasive evaluation, including vaginogram and endoscopy, is often necessary for careful detailing of the cloacal anomaly.

Good clinical evaluation and a urinalysis provide enough data in 80–90% of male patients to determine the need for a colostomy. Voluntary sphincteric muscles surround the most distal part of the bowel in cases of perineal and rectourethral fistulas, and the intraluminal bowel pressure must be sufficiently high to overcome the tone of those muscles before meconium can be seen in the urine or on the perineum. The presence of meconium in the urine and a flat bottom are considered indications for the creation of a colostomy. Clinical findings consistent with the diagnosis of a perineal fistula represent an indication

for an anoplasty without a protective colostomy. Ultrasound is valuable not only for the evaluation of the urinary tract, but it can also be used to investigate spinal anomalies in the newborn and to determine how close to the perineum the rectum has descended.

More than 90% of the time, the diagnosis in females can be established on perineal inspection. The presence of a single perineal orifice is a cloaca. A palpable pelvic mass (hydrocolpos) reinforces this diagnosis. A vestibular fistula is diagnosed by careful separation of the labia, exposing the vestibule. The rectal orifice is located immediately in front of the hymen within the female genitalia and in the vestibule. A perineal fistula is easy to diagnose. The rectal orifice is located somewhere between the female genitalia and the center of the sphincter and is surrounded by skin. Less than 10% of these patients fail to pass meconium through the genitalia or perineum after 24 hours of observation. Those patients can require a prone cross-table lateral film.

OPERATIVE REPAIR

Sometimes a perineal fistula, if it opens in a good position, can be treated by simple dilation. Hegar dilators are employed, starting with a No. 5 or 6 and letting the baby go home when the mother can use a No. 8. Twice-daily dilatations are done at home, increasing the size every few weeks until a No. 14 is achieved. By 1 year of age, the stool is usually well formed and further dilation is not necessary. By the time No. 14 is reached, the examiner can usually insert a little finger. If the anal ring is soft and pliable, dilation can be reduced in frequency or discontinued.

Occasionally, there is no visible fistula, but the rectum can be seen to be filled with meconium bulging on the perineum, or a covered anus is otherwise suspected. If confirmed by plain x-ray or ultrasound of the perineum that the rectum is <1 cm from the skin, the clinician can do a minor perineal procedure to perforate the skin and then proceed with dilation or do a simple perineal anoplasty.

When the fistula orifice is close to the introitus or scrotum, it is often appropriate to move it back surgically. This also requires postoperative dilation to prevent stricture formation. This procedure can be done any time from the newborn period to 1 year. It is preferable to wait until dilatations have been done for several weeks and the child is bigger. The anorectum is a little easier to dissect at this time. The posterior sagittal approach of Peña is used, making an incision around the fistula and then in the midline to the site of the posterior wall of the new location. The dissection is continued in the midline, using a muscle stimulator to be sure there is adequate muscle on both sides. The fistula must be dissected cephalad for several centimeters to allow posterior positioning without tension. If appropriate, some of the distal fistula is resected before the anastomosis to the perineal skin.

In children with a high lesion, a double-barrel colostomy is performed. This effectively separates the fecal stream from the urinary tract. It also allows the performance of an augmented pressure colostogram before repair to identify the exact position of the distal rectum and the fistula. The definitive repair or posterior sagittal anorectoplasty (PSARP) is performed at about 1 year of age. A midline incision is made, often splitting the coccyx and even the sacrum. Using a muscle stimulator, the surgeon stays strictly in the midline and divides the sphincter complex and identifies the rectum. The rectum is then opened in the midline, and the fistula is identified from within the rectum. This allows a division of the fistula without injury to the urinary tract. The rectum is then dissected proximally until enough length is gained to suture it to an appropriate perineal position. The muscles of the sphincter complex are then sutured around (and especially behind) the rectum.

Other operative approaches (such as an anterior approach) are used, but the most popular procedure is by laparoscopy. This operation allows division of the fistula under direct visualization and identification of the sphincter complex by transillumination of perineum. Other imaging techniques in the management of anorectal malformations include 3D endorectal ultrasound, intraoperative MRI, and colonoscopy-assisted PSARPs, which may help perform a technically better operation. None of these other procedures or innovations has demonstrated improved outcomes.

A similar procedure can be done for female high anomalies with variations to deal with separating the vagina and rectum from within the cloacal stem. When the stem is longer than 3 cm, this is an especially difficult and complex procedure.

Usually the colostomy can be closed 6 weeks or more after the PSARP. Two weeks after any anal procedure, twice-daily dilatations are performed by the family. By doing frequent dilatations, each one is not so painful and there is less tissue trauma, inflammation, and scarring.

OUTCOME

The ability to achieve rectal continence depends on both motor and sensory elements. There must be adequate muscle in the sphincter complex and proper positioning of the rectum within the complex. There must also be intact innervation of the complex and of sensory elements, as well as the presence of these sensory elements in the anorectum. Patients with low lesions are more likely to achieve true continence. They are also, however, more prone to constipation, which leads to overflow incontinence. It is very important that all these patients are followed closely and that the constipation and anal dilation are well managed until toilet training is successful. Tables 392.2 and 392.3 outline the results of continence and constipation in relation to the malformation encountered.

Children with high lesions, especially males with rectoprostatic urethral fistulas and females with cloacal anomalies, have a poorer chance of being continent, but they can usually achieve a socially acceptable defecation (without a colostomy) pattern with a bowel management

Table 392.2 Types of Anorectal Malformation by Sex

MALE (PERCENTAGE CHANCE OF BOWEL CONTROL*)
Rectoperineal fistula (100%)
Rectourethral bulbar fistula (85%)
Imperforate anus without fistula (90%)
Rectourethral prostatic fistula (65%)
Rectobladder neck fistula (15%)
FEMALE (PERCENTAGE CHANCE OF BOWEL CONTROL*)
Rectoperineal fistula (100%)
Rectovestibular fistula (95%)
Imperforate anus without fistula (90%)
Rectovaginal fistula (rare anomaly)†
Cloaca (70%)‡

*Provided patients have a normal sacrum, no tethered cord, and they receive a technically correct operation without complications.
†Rectovaginal anomalies are extremely unusual; usually their prognosis is like rectovestibular fistula.
‡Cloaca represents a spectrum; those with a common channel length <3 cm have the best functional prognosis.
From Bischoff A, Bealer J, Peña A. Controversies in anorectal malformations. *Lancet Child/Adolesc.* 2017;1:323–330.

Table 392.3 Constipation and Type of Anogenital Malformation

TYPE	PERCENTAGE
Vestibular fistula	61
Bulbar urethral fistula	64
Rectal atresia/stenosis	50
Imperforate with no fistula	55
Perineal fistula	57
Long cloaca	35
Prostatic fistula	45
Short cloaca	40
Bladder neck fistula	16

Modified from Levitt MA, Peña A. Outcomes from the correction of anorectal malformations. *Curr Opin Pediatr.* 2005;17:394–401.

program. Often, the bowel management program consists of a daily enema to keep the colon empty and the patient clean until the next enema. If this is successful, an *antegrade continence enema* (ACE) procedure, sometimes called the *Malone* or *Malone antegrade continence enema* (MACE) procedure, can improve the patient's quality of life. These procedures provide access to the right colon either by bringing the appendix out the umbilicus in a nonrefluxing fashion or by putting a plastic button in the right lower quadrant to access the cecum. The patient can then sit on the toilet and administer the enema through the ACE, thus flushing out the entire colon. Antegrade regimens can produce successful 24-hour cleanliness rates of up to 95%. Of special interest is the clinical finding that most patients improve their control with growth. Patients who wore diapers or pull-ups to primary school are often in regular underwear by high school. Some groups have taken advantage of this evidence of psychologic influences to initiate behavior modification early with good results.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

392.2 Anal Fissure

Christina M. Shanti

Anal fissure is a laceration of the anal mucocutaneous junction. It is an acquired lesion of unknown etiology. Although likely secondary to the forceful passage of a hard stool, it is mainly seen in infants younger than 1 year of age when the stool is frequently quite soft. Fissures may be the consequence and not the cause of constipation.

CLINICAL MANIFESTATIONS

A history of constipation is often described, with a recent painful bowel movement corresponding to the fissure formation after passing of hard stool. The patient then voluntarily retains stool to avoid another painful bowel movement, exacerbating the constipation, resulting in harder stools. Complaints of pain on defecation and bright red blood on the surface of the stool are often elicited.

The diagnosis is established by inspection of the perineal area. The infant's hips are held in acute flexion, the buttocks are separated to expand the folds of the perianal skin, and the fissure becomes evident as a minor laceration. Often a small skin appendage is noted peripheral to the lesion. This *skin tag* represents epithelialized granulomatous tissue formed in response to chronic inflammation. Findings on rectal examination can include hard stool in the ampulla and rectal spasm.

TREATMENT

The parents must be counseled as to the origin of the laceration and the mechanism of the cycle of constipation. The goal is to ensure that the patient has soft stools to avoid overstretching the anus. The healing process can take several weeks or even several months. A single episode of impaction with passing of hard stool can exacerbate the problem. Treatment requires that the primary cause of the constipation be identified (see Chapter 378.3). The use of dietary and behavioral modification and a stool softener is indicated. Parents should titrate the dose of the stool softener based on the patient's response to treatment. Stool softening is best done by increasing water intake or using an oral polyethylene glycolate such as MiraLAX or GlycoLax. Surgical intervention, including stretching of the anus, "internal" anal sphincterotomy, or excision of the fissure, is not indicated or supported by scientific evidence.

Chronic anal fissures in older patients are associated with constipation, prior rectal surgery, Crohn disease, and chronic diarrhea. They are managed initially like fissures in infants, with stool softeners with the addition of sitz baths. Topical 0.2% glyceryl trinitrate reduces anal spasm and heals fissures, but it is often associated with headaches. Calcium channel blockers, such as 2% diltiazem ointment and 0.5% nifedipine cream, are more effective and cause fewer headaches than glyceryl trinitrate. Injection of botulinum toxin from 12.5 to 25 units is also effective and probably chemically replicates the action of internal sphincterotomy, which is the most effective treatment in adults, although seldom used in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

392.3 Perianal Abscess and Fistula

Christina M. Shanti

Perianal abscesses usually manifest in *infancy* (~75% ≤1 year) and are of unknown etiology. Fistula appears to be secondary to the abscess rather than the cause. Links to congenitally abnormal crypts of Morgagni have been proposed, suggesting that deeper crypts (3-10 mm rather than the normal 1-2 mm) lead to trapped debris and cryptitis (Fig. 392.6).

Conditions associated with the risk of an anal fistula in *older children* include Crohn disease, tuberculosis, pilonidal disease, hidradenitis, HIV, trauma, foreign bodies, dermal cysts, sacrococcygeal teratoma, actinomycosis, lymphogranuloma venereum, and radiotherapy.

The most common organisms isolated from perianal abscesses are mixed aerobic *(Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus)* and anaerobic (*Bacteroides* spp., *Clostridium, Veillonella*) flora. A total of 10–15% yield pure growth of *E. coli, S. aureus,* or *Bacteroides fragilis.* There is a strong male predominance in those affected who are younger than 2 years of age, whereas the distribution is more equal in older patients, where the etiology shifts to associated conditions such as inflammatory bowel disease, leukemia, or immunocompromised states.

CLINICAL MANIFESTATIONS

In younger patients, symptoms are usually mild and can consist of low-grade fever, mild rectal pain, and an area of perianal cellulitis (Fig. 392.7). Often these spontaneously drain and resolve without treatment. In older patients with underlying predisposing conditions, the clinical course may be more serious. A compromised immune system can mask fever and allow rapid progression to toxicity and sepsis. Abscesses in these patients may be deeper in the ischiorectal fossa or even supralevator in contrast to those in younger patients, which are usually adjacent to the involved crypt.

Progression to fistula in patients with perianal abscesses occurs in 20–50% of cases and usually manifests with drainage from the perineal skin or multiple recurrences. Similar to abscess formation, fistulas have a strong male predominance. Histologic evaluation of fistula tracts typically reveals an epithelial lining of stratified squamous cells associated with chronic inflammation. It might also reveal an alternative etiology such as the granulomas of Crohn disease or even evidence of tuberculosis.

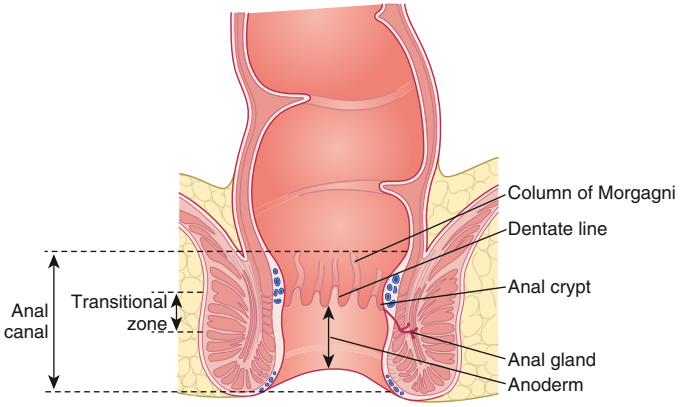

Fig. 392.6 Anatomy of the anal canal. *(Adapted from Brunicardi FC, Anderson DK, Billar TR, et al. Schwartz's Principles of Surgery, 8th ed. New York: McGraw-Hill; 2004.)*



Fig. 392.7 Perianal abscesses are often seen in male infants. The abscess typically presents as a fluctuant, tender mass in the perianal region. Incision and drainage is the initial management of these abscesses if conservative measures have failed. *(From Sullins VF, Jarboe M, Calkins CM. Acquired anorectal disorders. In: Holcomb III GW, Murphy JP, St. Peter SD, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020: Fig. 37.1, p. 613.)*

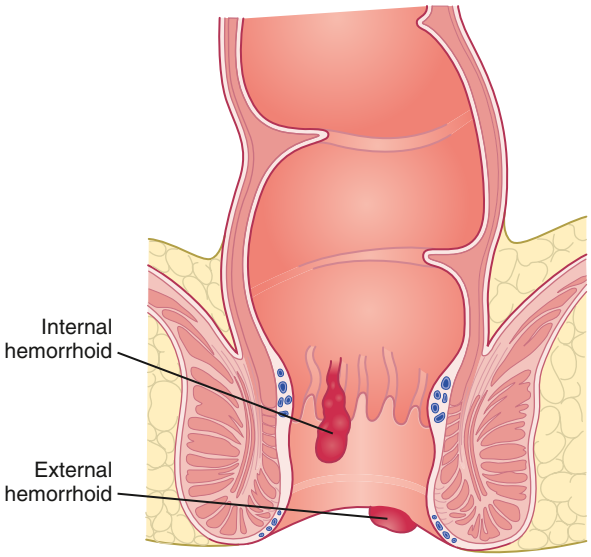

Fig. 392.8 Formation of hemorrhoids.

TREATMENT

Treatment is rarely indicated in infants with no predisposing disease because the condition is often self-limited. Even in cases of fistulization, conservative management (observation) is advocated because the fistula often disappears spontaneously. In one study, 87% of fistulas (in 97/112 infants) closed after a mean of 5 months of observation and conservative management (sitz baths). Antibiotics are not useful in these patients. When dictated by patient discomfort, abscesses may be incised and drained under local anesthesia. Fistulas requiring surgical intervention may be treated by fistulotomy (unroofing or opening), fistulectomy (excision of the tract leaving it open to heal secondarily), or placement of a seton (heavy suture threaded through the fistula, brought out the anus, and tied tightly to itself). In patients with inflammatory bowel disease, topical tacrolimus has been effective.

Older children with predisposing diseases might also do well with minimal intervention. If there is little discomfort and no fever or other sign of systemic illness, local hygiene and antibiotics may be best. The danger of surgical intervention in an immunocompromised patient is the creation of an even larger, nonhealing wound. There certainly are such patients with serious systemic symptoms who require more aggressive intervention along with treatment of the predisposing condition. Broad-spectrum antibiotic coverage must be administered, and wide excision and drainage are mandatory in cases involving sepsis and expanding cellulitis.

Fistulas in older patients are mainly associated with Crohn disease, a history of pull-through surgery for the treatment of Hirschsprung disease, or, in rare cases, tuberculosis. Those fistulas are often resistant to therapy and require treatment of the predisposing condition.

Complications of treatment include recurrence and, rarely, incontinence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

392.4 Hemorrhoids

Christina M. Shanti

Hemorrhoidal disease occurs in both children and adolescents, often related to a diet deficient in fiber and poor hydration. In younger children, the presence of hemorrhoids should also raise the suspicion of portal hypertension. A third of patients with hemorrhoids require treatment.

CLINICAL MANIFESTATIONS

Presentation depends on the location of the hemorrhoids. External hemorrhoids occur below the dentate line (Fig. 392.8; see Fig. 392.6) and are associated with extreme pain and itching, often because of acute thrombosis. Internal hemorrhoids are located above the dentate line and manifest primarily with bleeding, prolapse, and occasional incarceration.

TREATMENT

In most cases, conservative management with dietary modification, decreased straining, and avoidance of prolonged time spent sitting on the toilet results in resolution of the condition. Discomfort may be treated with topical analgesics or antiinflammatories such as Anusol (pramoxine) and Anusol-HC (hydrocortisone) and sitz baths. The natural course of thrombosed hemorrhoid involves increasing pain, which peaks at 48-72 hours, with gradual remission as the thrombus organizes and involutes over the next 1-2 weeks. In cases where the patient with external hemorrhoids presents with excruciating pain soon after the onset of symptoms, thrombectomy may be indicated. This is best accomplished with local infiltration of bupivacaine 0.25% with epinephrine 1:200,000, followed by incision of the vein or skin tag and extraction of the clot. This provides immediate relief; recurrence is rare, and further follow-up is unnecessary.

Internal hemorrhoids can become painful when prolapse leads to incarceration and necrosis. Pain usually resolves with reduction of hemorrhoidal tissue. Surgical treatment is reserved for patients failing conservative management. Techniques described in adults include excision, rubber banding, stapling, and excision using the LigaSure device. Complications are rare (<5%) and include recurrence, bleeding, infection, nonhealing wounds, and fistula formation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

392.5 Rectal Mucosal Prolapse

Christina M. Shanti

Rectal mucosal prolapse is the exteriorization of the rectal mucosa through the anus. In the unusual occurrence when all the layers of the rectal wall are included, it is called *procidentia* or *rectocele*. Most cases of rectal tissue protruding through the anus are prolapse and not polyps, hemorrhoids, intussusception, or other tissue.

Most cases of prolapse are idiopathic. The onset is often between 1 and 5 years of age. It usually occurs when the child begins standing and then resolves by approximately 3-5 years of age when the sacrum has taken its more adult shape and the anal lumen is oriented posteriorly. Thus the entire weight of the abdominal viscera is not pushing down on the rectum, as it is earlier in development.

Other predisposing factors include intestinal parasites (particularly in endemic areas), malnutrition, diarrhea, ulcerative colitis, pertussis, Ehlers-Danlos syndrome, meningocele (more often associated with procidentia owing to the lack of perineal muscle support), cystic fibrosis, and chronic constipation. Patients treated surgically for imperforate anus can also have varying degrees of rectal mucosal prolapse. This is particularly common in patients with poor sphincteric development. Rectal prolapse is also seen with higher incidence in patients with mental issues and behavior problems. These patients are particularly difficult to manage and are more likely to fail medical treatment.

CLINICAL MANIFESTATIONS

Rectal mucosal prolapse usually occurs during defecation, especially during toilet training. Reduction of the prolapse may be spontaneous or accomplished manually by the patient or parent. In severe cases, the prolapsed mucosa becomes congested and edematous, making it more difficult to reduce (Fig. 392.9). Rectal prolapse is usually painless or produces mild discomfort. If the rectum remains prolapsed after defecation, it can be traumatized by friction with undergarments, with resultant bleeding, wetness, and potentially ulceration. The appearance of the prolapse varies from bright red to dark red and resembles a beehive. It can be as long as 10-12 cm. See Chapter 393 for a distinction from a prolapsed polyp.

TREATMENT

Initial evaluation should include tests to rule out any predisposing conditions, especially cystic fibrosis and sacral root lesions. Reduction of protrusion is aided by pressure with warm compresses. An easy method of reduction is to cover the finger with a piece of toilet paper, introduce it into the lumen of the mass, and gently push it into the patient's rectum. The finger is then immediately withdrawn. The toilet paper adheres to the mucous membrane, permitting release of the finger. The paper, when softened, is later expelled.

Conservative treatment consists of careful manual reduction of the prolapse after defecation, attempts to avoid excessive pushing during bowel movements (with the patient's feet off the floor), use of laxatives and stool softeners to prevent constipation, avoidance of inflammatory conditions of the rectum, and treatment of intestinal parasitosis when present. If all this fails, surgical treatment may be indicated. Existing surgical options are associated with some morbidity, and therefore medical treatment should always be attempted first.

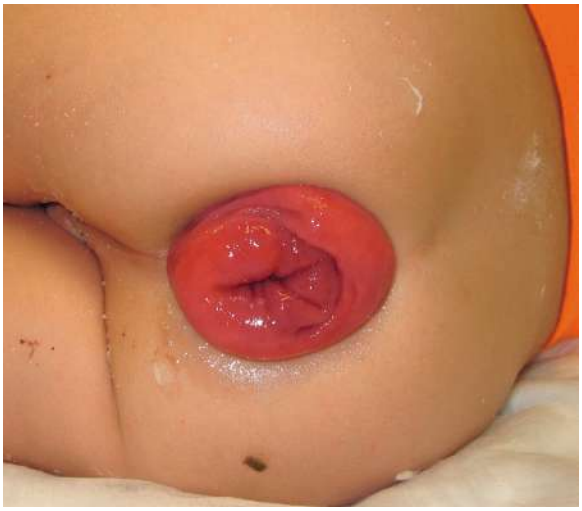

Fig. 392.9 This 2-year-old child developed persistent rectal prolapse. The prolapse occurred several times daily and was not responsive to medical management. The child underwent submucosal sclerotherapy with 5% morrhuate sodium and the prolapse resolved. *(From Sullins VF, Jarboe M, Calkins CM. Acquired anorectal disorders. In Holcomb III GW, Murphy JP, St. Peter SD, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020: Fig. 37.8, p. 616.)*

Sclerosing injections have been associated with complications such as neurogenic bladder. We have found linear cauterization effective and with few complications other than recurrence. In the operating room, the prolapse is re-created by traction on the mucosa. Linear burns are made through nearly the full thickness of the mucosa using electrocautery. One can usually make eight linear burns on the outside and four on the inside of the prolapsed mucosa. In the immediate postoperative period, prolapse can still occur, but in the next several weeks, the burned areas contract and keep the mucosa within the anal canal. The Delorme mucosal sleeve resection addresses mucosal prolapse via a transanal approach by incising, prolapsing, and amputating the redundant mucosa. The resulting mucosal defect is then approximated with absorbable suture.

For patients with procidentia or full-thickness prolapse or intussusception of the rectosigmoid (usually from myelodysplasia or other sacral root lesions), other, more invasive options exist. Those most commonly in use by pediatric surgeons today include a modification of the Thiersch procedure, which involves placing a subcutaneous suture to narrow the anal opening. Complications include obstruction, fecal impaction, and fistula formation. Laparoscopic rectopexy is effective and can be performed as an outpatient. The Altemeier perineal rectosigmoidectomy is a transanal, full-thickness resection of redundant bowel with a primary anastomosis to the anus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 393

Tumors of the Digestive Tract

Stacey G. Zahler, Mohammad Nasser Kabbany, and Karen F. Murray

Tumors of the digestive tract in children are also commonly syndromic tumors and tumors with known genetic association (Table 393.1). They usually manifest as painless rectal bleeding, but when large they can cause obstruction or serve as lead points for intussusception. Most intestinal polyps in children can be generally classified into two groups: hamartomatous (as seen in juvenile polyps and Peutz-Jeghers syndrome) or adenomatous (as seen in familial adenomatous polyposis syndrome).

HAMARTOMATOUS TUMORS

Hamartomas are benign tumors composed of tissues that are normally found in an organ but that are not organized normally. Juvenile, retention, or inflammatory polyps are hamartomatous polyps, which represent the most common intestinal tumors of childhood, occurring in 1–2% of children. Patients generally present in the first decade, most often at ages 2-5 years, and rarely at younger than 1 year. Polyps may be found anywhere in the gastrointestinal (GI) tract, most commonly in the rectosigmoid colon, with one third located proximal to splenic flexure; they are often solitary but may be multiple.

Histologically, juvenile polyps are composed of hamartomatous collections of mucus-filled glandular and stromal elements with inflammatory infiltrate, covered with a thin layer of epithelium (Fig. 393.1A). These polyps are often bulky, vascular, and prone to bleed as their growth exceeds their blood supply with resultant mucosal ulceration, or autoamputation with bleeding from a residual central artery.

Patients often present with painless rectal bleeding after defecation. Bleeding is generally scant and intermittent; rarely presenting findings can include iron-deficiency anemia and/or hypoalbuminemia. Extensive bleeding can occur but is generally self-limited, requiring supportive care until the bleeding stops spontaneously after autoamputation. Occasionally endoscopic polypectomy is required for control of bleeding. Abdominal pain or cramps are uncommon unless associated with intussusception. Patients can present with prolapse, with a dark, edematous, pedunculated mass protruding from the rectum. Mucus discharge and pruritus are associated with prolapse.

Patients presenting with rectal bleeding require a thorough workup; differential diagnosis includes anal fissure, other intestinal polyposis syndromes, Meckel's diverticulum, inflammatory bowel disease, intestinal infections, IgA vasculitis (Henoch-Schönlein purpura), angiodysplasia, or coagulopathy.

Diagnosis and therapy are best accomplished via **endoscopy**. Polyps may be visualized via ultrasound or cross-sectional imaging, but this provides no therapeutic advantage. Colonoscopy affords opportunity for biopsy, **polypectomy** by snare cautery, and visualization of synchronous lesions; up to 50% of children have one or more additional polyps, and approximately 20% may have more than five polyps. Retrieved polyps should be sent for histologic evaluation for definitive diagnosis.

Juvenile Polyposis Syndrome

Patients with juvenile polyposis syndrome (JPS) present with multiple juvenile polyps—usually five or more—but typically 50-200 are present within the GI tract. The incidence of JPS is between 1:10,000 and 1:160,000. Polyps are most likely isolated to the colon (98%) but may be distributed throughout the GI tract. There is often a family history (20–50%) with an autosomal dominant pattern of variable penetrance. Alterations in transforming growth factor-β pathways have been identified in some JPS patients and families; pathogenic variants in *SMAD4* or *BMPR1A* are found in 50–60% of patients with JPS. Genetic testing is available for both of these variants. Patients with the *SMAD4* pathogenic variant may have hereditary hemorrhagic telangiectasia and should be evaluated for brain and lung vascular malformations. A clinical diagnosis of JPS is established by the presence of one of the following: a lifetime total of five or more juvenile polyps in the colon, juvenile polyps outside the colon, or any number of juvenile polyps in a patient with a family history of JPS.

Histologically, these polyps are identical to solitary juvenile polyps; however, the risk of malignant transformation is greatly increased (10–50%). Malignancy occurs most commonly in the colorectal region, although gastric, upper GI, and pancreatic tumors have been described. The risk of malignancy is greater in patients with increased polyp burden and a positive family history. These patients should therefore undergo routine esophagogastroduodenoscopy and colonoscopy starting at 12-15 years of age. Age at which surveillance of the upper GI tract should begin varies between guidelines. It is not required during teenage years per current published pediatric guidelines unless symptomatic. Serial polypectomy or polyp biopsy should be undertaken if possible. If dysplasia or malignant degeneration is found, a total colectomy is indicated.

Juvenile polyposis of infancy is characterized by early polyp formation (in patients younger than 2 years of age) and may be associated with protein-losing enteropathy, hypoproteinemia, anemia, failure to thrive, and intussusception. Early **endoscopic or surgical intervention** may be needed.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder (incidence: ~1:120,000 total population) characterized by mucocutaneous pigmentation and extensive GI hamartomatous polyposis. Macular pigmented lesions may be dark brown to dark blue and are found primarily around the lips and oral mucosa, although these lesions may also be found on the hands, feet, or perineum (Fig. 393.2). Lesions can fade by puberty or adulthood, though buccal pigmentation can persist.

Polyps are primarily found in the small intestine (in order of prevalence: jejunum, ileum, duodenum) but may also infiltrate gastric or colonic regions. Histologically, polyps are defined by normal epithelium surrounding bundles of smooth muscle arranged in a branching or frondlike pattern called *arborization* (see Fig 393.1B). They may show "pseudo-invasion," which may be mistaken for malignancy. Symptoms arising from GI polyps in PJS are similar to those of other polyposis syndromes—namely bleeding and abdominal cramping from obstruction or recurrent intussusception. Patients have a 68% risk of intussusception during childhood and may require repeated laparotomies and intestinal resections.

The diagnosis of PJS is made clinically in patients with at least two histologically proven PJS polyps or any number of PJS polyps in patients with a known family history. Diagnosis also can be made in individuals with a family history of PJS with characteristic mucocutaneous hyperpigmentation. Genetic testing can reveal pathogenic variants in *LKB1/STK11* (19p13.3), a serine-threonine kinase that acts as a tumor suppressor gene. Up to 94% of patients with clinical characteristics of PJS have a pathogenic variant at this locus. Only 50% of patients with PJS have an affected family member, suggesting a high rate of de novo mutations

Patients with PJS have increased risk of GI and extraintestinal malignancies. Lifetime cancer risk has been reported to be in the range of 47–93%. Colorectal, breast, and reproductive tumors are most common. Even though risk of GI malignancy in childhood is quite low, GI surveillance for polyps should begin in childhood (by age 8 years of age or when symptoms occur) with upper and lower endoscopy. The small bowel may be evaluated radiographically, with magnetic resonance enterography, endoscopically with balloon or push enteroscopy, or with video capsule endoscopy. Polyps larger than 1.5 cm should be removed, although resection does not lower the cancer risk and is mainly to avoid complications. Patients with PJS should be monitored for signs of precocious puberty given their risk of having sex cord/

Table 393.1 General Features of the Inherited Colorectal Cancer Syndromes

SYNDROME	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCIATED LESIONS
HAMARTOMATOUS POLYPS						
Juvenile polyposis	Large and small intestine, gastric polyps	First decade	~10–50%	*SMAD4, BMPR1A* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Congenital abnormalities in 20% of the nonfamilial type, clubbing, AV malformations
Peutz-Jeghers syndrome	Small and large intestine	First decade	Increased	*LKB1/STK11* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots
Cowden syndrome	Colon	Second decade	13–18%	*PTEN* gene	Macrocephaly, breast/thyroid/endometrial cancers, developmental delay	
Bannayan-Riley-Ruvalcaba syndrome	Colon	Second decade	Increased	*PTEN* gene	Macrocephaly, speckled penis, thyroid/breast cancers, hemangiomas, lipomas	
ADENOMATOUS POLYPS						
Familial adenomatous polyposis (FAP)	Large intestine, often >100	16 yr (range: 8-34 yr)	100%	5q (*APC* gene), autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE, upper GI polyps, osteoma, hepatoblastoma, thyroid cancer
Attenuated familial adenomatous polyposis (AFAP)	Colon (fewer in number)	>18 yr	Increased	*APC* gene	Same as FAP	Fewer associated lesions
MYH-associated polyposis	Colon	>20 yr	High risk	*MYH* autosomal recessive	Same as FAP	May be confused with sporadic FAP or AFAP; few extraintestinal findings
Gardner syndrome	Large and small intestine	16 yr (range: 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid tumors, multiple osteomas, fibromas, epidermoid cysts
Hereditary nonpolyposis colon cancer (Lynch syndrome)	Large intestine	40 yr	30%	DNA mismatch repair genes *(MMR)* Autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, ureter, pancreas, stomach)

APC, adenomatous polyposis coli; AV, arteriovenous; CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal; PTEN, phosphatase and tensin homolog.

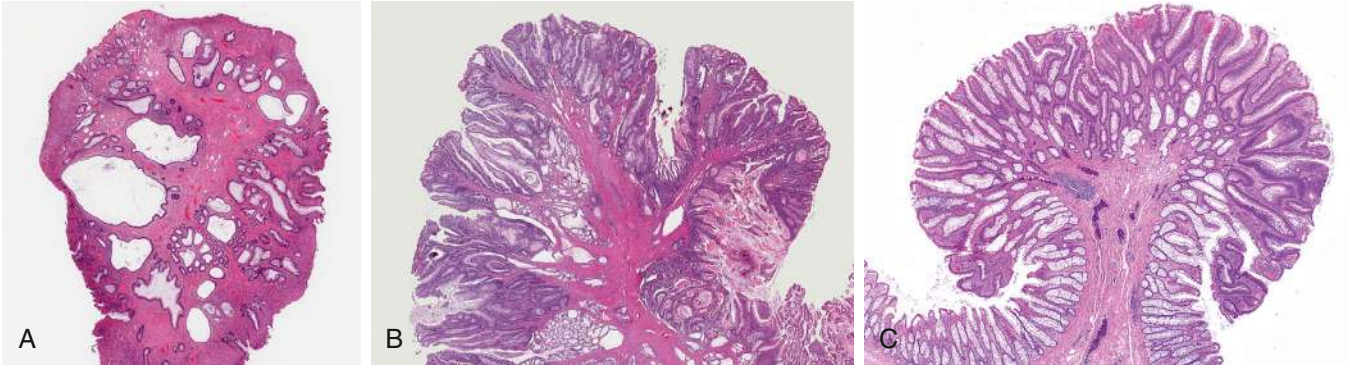

Fig. 393.1 Representative histologic sections of commonly found polyps in pediatric patients. **A**, Juvenile polyp. Cystically dilated and irregular colonic crypts within an inflamed, expanded stroma. **B**, Peutz-Jeghers polyp. Small bowel with large arborizing bundles of smooth muscle and otherwise normal epithelial component. **C**, Adenomatous polyp. Enlarged, hyperchromatic, and stratified nuclei confined to a tubular configuration. *(Images courtesy Dr. Thomas Plesec, Cleveland Clinic.)*



Fig. 393.2 Peutz-Jeghers syndrome. Characteristic bluish brown to black spots were first noted in early childhood on the lips of this boy who later developed hamartomatous gastrointestinal polyps. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 11.46, p. 312.)*

stromal tumors, particularly large-cell calcifying Sertoli cell tumors. Screening for breast, gynecologic, and testicular cancers should be routine after age 18 years.

Phosphatase and Tensin Homolog Hamartoma Tumor Syndromes

Pathogenic variants in the tumor suppressor gene *PTEN* are associated with several rare autosomal dominant syndromes, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus and Proteus-like syndrome. These patients present with multiple hamartomas in the skin (99%), brain, breast, thyroid, endometrium, and GI tract (60%). Other extraintestinal manifestations include macrocephaly, developmental delay, lipomas, and genital pigmentation. Patients have 9–18% lifetime risk of colorectal cancer. However, this risk is low in childhood. They also have increased risk of thyroid, breast, uterine, renal, and skin malignancies.

ADENOMATOUS TUMORS

Adenomatous Polyposis Coli-Associated Polyposis Syndromes

Familial adenomatous polyposis (FAP) is the most common genetic polyposis syndrome (incidence 1:5,000-1:17,000 persons) and is characterized by numerous adenomatous polyps throughout the colon and extraintestinal manifestations. FAP and related syndromes (attenuated FAP; Gardner and Turcot syndromes) are linked to pathogenic variants in the *APC* gene, a tumor suppressor mapped to 5q21, which is part of the WNT signaling pathway. *APC* regulates degradation of β-catenin, a protein with roles in regulation of the cytoskeleton, tissue architecture organization, cell migration and adherence, and numerous other functions. Intracellular accumulation of β-catenin may be responsible for colonic epithelial cell proliferation and adenoma formation. More than 400 pathogenic variants in the *APC* gene have been described, and up to 30% of patients present with no family history (sporadic variants). There is an association between disease phenotype and the location of the *APC* gene alteration. For example, a more severe colonic phenotype is associated with pathogenic variants between codons 1250 and 1464, specifically variants that include codon 1309.

Polyps generally develop late in the first or second decades of life (mean age of presentation is 16 years). At the time of diagnosis, five or more adenomatous polyps are present in the colon and rectum. By young adulthood, the number of polyps typically increases to hundreds or even thousands. Adenomatous polyps (or adenomas) are precancerous lesions within the surface epithelium of the intestine, displaying various degrees of dysplasia (see Fig. 393.1C). Without intervention, the risk of developing colon cancer is 100% by the fifth decade of life (average age of cancer diagnosis is 40 years). Other GI adenomas can develop, particularly in the stomach and duodenum (50–90%). The risk of periampullary or duodenal carcinoma is significantly elevated (4–12% lifetime risk) and represents, along with desmoid tumors, the most common cause of death after colorectal cancer. Extraintestinal malignancies occur at an increased rate in FAP, including hepatoblastoma in young patients (1.6% before age 5 years) and follicular or papillary thyroid cancer in adolescents.

Extraintestinal manifestations of FAP may be present from birth or develop in early childhood. Lesions include congenital hypertrophy of retinal pigment epithelium, desmoid tumors, epidermoid cysts, osteomas, fibromas, lipomas, and supernumerary, impacted, or missing teeth. Many of these nonmalignant soft tissue tumors appear before intestinal polyps develop. Expression of extraintestinal findings can depend on the location of the *APC* gene alteration.

Other syndromes associated with *APC* pathogenic variants include *Gardner syndrome,* classically characterized by multiple colorectal polyps, desmoid tumors, and soft tissue tumors, including fibromas, osteomas (typically mandibular), epidermoid cysts, and lipomas. Once thought to be a distinct clinical entity, Gardner syndrome shares many characteristics with FAP. Up to 20% of FAP patients present with the classic extraintestinal manifestations once associated with Gardner syndrome. Some (but not all) cases of *Turcot syndrome* are also related to *APC.* These patients present with colorectal polyposis and primary brain tumors (medulloblastoma). Attenuated FAP is characterized by a significantly increased risk of colorectal cancer but fewer polyps than classic FAP (average: 30 polyps). The average age of cancer diagnosis in this form of FAP is 50-55 years. Upper GI tumors and extraintestinal manifestations may be present but are less common.

The clinical presentation of FAP is variable. Polyps are generally sessile, of variable size, and initially asymptomatic. If symptoms develop, they can include rectal bleeding (possibly with secondary anemia), cramping, and diarrhea. The presence of symptoms at presentation does not correlate with malignant changes. Diagnosis should be suspected from family history, and ensuing colonoscopy is confirmatory. Histologic examination of biopsied polyps reveals adenomatous architecture (as opposed to inflammatory or hamartomatous polyps found in other polyposis syndromes) with varying degrees of dysplasia. Genetic testing for *APC* variants is clinically available, and index patients should be tested. If a pathogenic variant is identified, affected family members should be screened and appropriate genetic counseling should be provided. If the index patient does not demonstrate a defined variant, family members may undergo genetic testing, which might identify novel *APC* alterations. Children with identified *APC* mutations must undergo careful surveillance, with colonoscopy every 1-2 years starting early in the second decade of life or earlier if symptomatic. Once polyps are identified, colonoscopy should be performed annually. Patients should also have upper endoscopy in the third decade of life to monitor for gastric and especially duodenal lesions, earlier if symptomatic or if there is family history of aggressive duodenal adenoma burden or cancer.

Treatment of FAP requires **prophylactic proctocolectomy** to prevent inevitable colon cancer. Prophylactic colectomy should be planned in the late teens or early twenties, earlier if significant polyposis burden or malignancy is suspected. Ileoanal pull-through procedures restore bowel continuity, with acceptable functional outcomes. Surgical approaches include ileal pouch anal anastomosis (with J-pouch) versus ileorectal anastomosis; the type of surgery depends on rectal and colonic polyp burden and surgeon preference. It is very important to note that ongoing surveillance of the ileal pouch or rectal cuff is warranted after surgery. **Nonsteroidal antiinflammatory agents**, such as sulindac, and cyclooxygenase-2 inhibitors, such as celecoxib, might inhibit polyp progression. No guidelines have been established, however, and their efficacy in preventing malignant transformation of existing polyps is unknown.

Carcinoma

Primary carcinomas of the esophagus, stomach, or colon are extremely rare in children. Development of adenocarcinoma in adolescence or

early adulthood may be associated with a genetic predisposition or syndrome such as FAP, hereditary nonpolyposis colon carcinoma, PJS, radiation exposure, or inflammatory bowel disorders such as Crohn disease or ulcerative colitis.

Colorectal carcinoma (CRC), though rare (reported incidence of 1 case per 1,000,000 persons younger than 19 years of age), is the most common primary GI carcinoma in children. Patients with long-standing ulcerative colitis are at increased risk. Many cases are spontaneous (i.e., not associated with a genetic predisposition or syndrome); associated genetic syndromes occur in 3–5% of all CRC cases (see Table 393.1). Histologically, tumors tend to be poorly differentiated and pathologically aggressive. Patients may be asymptomatic, or they present with nonspecific signs and symptoms such as abdominal pain, constipation, and vomiting. Delay in diagnosis is common. Adolescents and young adults present with advanced-stage disease more often than in older patients; microscopic or gross metastases are often present at the time of diagnosis. **Surgical resection** is the primary treatment modality, although with delayed presentation and advanced-stage disease, complete resection may not be possible. Complete resection is necessary for cure, however. **Chemotherapy** is standard treatment for patients with more advanced, surgically unresectable disease, though its efficacy is variable. Targeted immunotherapy agents such as monoclonal antibodies against epidermal growth factor receptor or vascular endothelial growth factor receptor are gaining traction as useful systemic therapies. **Radiation therapy** has a limited role in patients with metastatic disease.

OTHER GASTROINTESTINAL TUMORS

Lymphoma

Lymphoma is the most common GI malignancy in the pediatric population. Approximately 30% of children with non-Hodgkin lymphoma present with abdominal tumors. Immunocompromised patients have an increased incidence of lymphoma. Predisposing conditions include HIV/AIDS, agammaglobulinemia, long-standing celiac disease, and bone marrow or solid-organ transplantation. Examples of non-Hodgkin lymphoma subtypes that commonly occur in the GI tract are Burkitt lymphoma and posttransplant lymphoproliferative disorder (PTLD). Lymphoma can occur anywhere in the GI tract, but it most commonly occurs in the distal small bowel and ileocecal region; for instance, Burkitt lymphoma is classically located at the terminal ileum. Presenting symptoms include crampy abdominal pain, vomiting, obstruction, bleeding, or palpable mass. Lymphoma should be considered in patients older than 3 years of age who present with intussusception. Treatment consists of a combination of **surgical resection** and **chemotherapy**, and the intensity of chemotherapy regimens depends on the extent of the tumor burden.

Nodular Lymphoid Hyperplasia

Lymphoid follicles in the lamina propria and submucosa of the gut normally aggregate in Peyer patches, most prominently in the distal ileum. These follicles can become hyperplastic, forming nodules that protrude into the lumen of the bowel during times of developmental lymphoid proliferation such as early childhood and adolescence. Some suggested etiologies are infectious (classically *Giardia*), allergic, or immunologic. Nodular lymphoid hyperplasia has been described in infants with enterocolitis secondary to dietary protein sensitivity. This phenomenon has also been described in patients with inflammatory bowel disease and Castleman disease. Patients may be asymptomatic or, especially in cases of immunodeficiency, may present with abdominal pain, rectal bleeding, diarrhea, or intussusception. Nodular lymphoid hyperplasia usually resolves spontaneously. The use of antiinflammatory medications or elimination diets is unlikely to change the clinical course, although in cases with severe pain or bleeding, **corticosteroids** may be effective.

Gastroenteric Neuroendocrine Tumors

Gastroenteric neuroendocrine tumors (NETs) arise from neuroendocrine cells found in the intestines (and in the pancreas; however, pancreatic NETs will not be discussed here). These tumors can be low, intermediate, or high-grade tumors, depending on the Ki-67 proliferative index on histopathology (i.e., how rapidly the cells proliferate). The World Health Organization (WHO) classification separates NETs from "neuroendocrine carcinomas." NETs can be functional or nonfunctional; some NETs overproduce and secrete hormones such as gastrin, serotonin, or ectopic hormones such as adrenocorticotropic hormone (ACTH). Several heritable tumor syndromes are associated with gastroenteric NETs, including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau (VHL) disease, tuberous sclerosis (TSC), or neurofibromatosis type 1 (NF1). Two of the most common NETs of the GI tract in children and adolescents are carcinoid tumors and gastrinomas.

Carcinoid Tumor

Carcinoid tumors are neuroendocrine tumors of enterochromaffin cells, which can occur throughout the GI tract, but in children they are typically found in the appendix. This is often an incidental diagnosis at the time of appendectomy. **Complete surgical resection** of small tumors (<1 cm) with clear surgical margins is curative. Appendiceal tumors >1.5 cm are at increased risk for nodal metastasis and thus mandate further bowel resection, typically a right hemicolectomy.

Carcinoid tumors outside the appendix (small intestine, rectum, stomach) are more likely to metastasize. Serum tumor markers may be helpful in monitoring for development of metastatic disease—chromogranin A is the most sensitive tumor marker for intestinal NETs. Carcinoid tumors of the midgut can metastasize to the liver and give rise to a constellation of symptoms called **carcinoid syndrome**. Serotonin, 5-hydroxytryptophan, or histamine may be secreted by the tumor, and elevated serum levels cause cramps, diarrhea, vasomotor disturbances (flushing), bronchoconstriction, and right heart failure. The diagnosis is confirmed by elevated urinary 5-hydroxyindoleacetic acid (5-HIAA). Symptomatic relief of carcinoid syndrome may be achieved with administration of **somatostatin analogs** (i.e., octreotide). Treatment of metastatic NETs is again **surgical resection**, and the extent of resection may be curative or palliative, depending on the goals of care and risk of surgical morbidity. Because NETs tend to be slow-growing, some patients may be closely monitored for periods without surgical intervention. **Chemotherapy** has been used, including medications such as temozolomide, 5-fluorouracil, and cisplatin. Clinical trials studying various targeted systemic therapies are ongoing. A mammalian target of rapamycin (mTOR) inhibitor, called **everolimus**, is FDA-approved for the treatment of nonfunctional NETs based on the results of several clinical trials.

Gastrinoma

A malignant NET that arises in the duodenum or the pancreas is called *gastrinoma,* and these tumors secrete gastrin, which causes gastric acid hypersecretion and Zollinger-Ellison syndrome. Clinical symptoms of gastrinoma include diarrhea (because of large amounts of acid secretion into the duodenum), abdominal pain, peptic ulcer disease, and bleeding. Strictures and perforation may develop with more severe disease. Unfortunately, about 75–80% of patients with gastrinoma present with metastases to the liver or lymph nodes at diagnosis, and approximately 12% can have bone metastases at diagnosis as well. Treatment of gastrinoma includes **proton pump inhibitors** and **surgical resection**.

Leiomyoma

Leiomyomas are rare benign tumors that can arise anywhere in the GI tract, although most often in the stomach, jejunum, or distal ileum. Age of presentation is variable, from the newborn period through adolescence. Patients may be asymptomatic or can present with an abdominal mass, obstruction, intussusception, volvulus, or pain and bleeding from central necrosis of the tumor. **Surgical resection** is the treatment of choice. Pathologically, these tumors may be difficult to distinguish from malignant leiomyosarcomas. Smooth muscle tumors occur with increased incidence in children with HIV or those requiring immunosuppression after transplantation.

Gastrointestinal Stromal Cell Tumors

Gastrointestinal stromal cell tumors (GISTs) are intestinal mesenchymal tumors that probably arise from interstitial cells of Cajal or their

precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The WHO recognized GIST in 1990 as a distinct neoplasm. Typically, GISTs arise in adults, after the third decade of life. Cases have also been reported in the pediatric population, generally in adolescents with a female predominance. A minority of pediatric cases were reported with Carney's triad (gastric gastrointestinal stromal tumor, pulmonary chondroma, and extraadrenal paraganglioma) or a history of neurofibromatosis. In children, tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Many patients (~45%) present with metastatic disease primarily to the lymph nodes, although metastases to the peritoneum or liver occur as well. Patients may be asymptomatic for years to decades or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of **surgical resection** of local disease. Recurrence rates are high, and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with pathogenic variants in the *KIT* oncogene. This alteration is less commonly found in pediatric GISTs (~15%). Adjuvant systemic therapy for *KIT*$^{+}$ lesions can be given, and typically **tyrosine kinase inhibitors (such as imatinib, sunitinib, or dasatinib)** are used. These medications are conveniently available as oral therapy. Patients with persistent, recurrent, or metastatic disease may benefit from treatment.

Vascular Tumors

Vascular malformations and hemangiomas are rare in children. The usual presentation is painless rectal bleeding, which may be chronic or acute, with massive or even fatal hemorrhage. There are usually no associated symptoms, although intussusception has been described. Half of patients have associated cutaneous hemangiomas or telangiectasia. These lesions may be associated with blue rubber bleb nevus syndrome, hereditary hemorrhagic telangiectasia, and other syndromes. About half of these lesions are in the colon and can be identified on colonoscopy. During acute bleeding episodes, bleeding can be localized via nuclear medicine bleeding scans, mesenteric angiography, or endoscopy. Colonic bleeding may be controlled by endoscopic means. Surgical intervention is required occasionally for isolated lesions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 394

Inguinal Hernias

José H. Salazar and John J. Aiken

Inguinal hernias are one of the most common conditions seen in pediatric practice, with an overall incidence of 0.8–4.5% in term infants and children and increasing to nearly 30% in premature and low birthweight (<1 kg) infants. Most inguinal hernias in infants and children are **congenital indirect** hernias (99%) because of a patent processus vaginalis (PV), an evagination of peritoneum in the inguinal area important in testicular descent. There is rarely any defect or deficiency in the abdominal wall musculature in congenital indirect inguinal hernia. Inguinal hernias are more common in males compared with females (8:1 ratio), but females have a higher incidence of bilateral inguinal hernias (~25%) compared with males (~12%). Two other types of inguinal hernia are seen rarely in children: **direct** (acquired) hernia (0.5–1.0%) and **femoral** hernia (<0.5%). Femoral hernias are substantially more common in females (2:1 ratio). Approximately 50% of inguinal hernias manifest clinically in the first year of life, most in the first 6 months. The incidence of incarceration in untreated hernias varies between 6% and 18% across ages. The risk of incarceration is greatest in infancy, with some reports of incarceration rates of 30–40% in the first year of life, mandating prompt identification and operative repair to minimize morbidity and complications related to incarceration and strangulation. Laparoscopic hernia (LH) repair has increasingly emerged in many pediatric centers as an effective alternative to traditional open hernia (OH) repair.

EMBRYOLOGY AND PATHOGENESIS

Indirect inguinal hernias in infants and children are congenital and result from an arrest of embryologic development—failure of obliteration of the PV rather than a weakness in the abdominal wall musculature. The pertinent developmental anatomy of indirect inguinal hernia relates to development of the gonads and descent of the testes through the inguinal canal and into the scrotum late in gestation. The testes descend from the urogenital ridge in the retroperitoneum to the area of the internal ring by about 28 weeks of gestation. The final descent of the testes into the scrotum occurs late in gestation, between weeks 28 and 36, guided by the PV and the gubernaculum. The PV, an outpouching of peritoneum in the inguinal region, is present in the developing fetus at 12 weeks of gestation. The PV develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testis accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal, and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 weeks to migrate from the external ring to its final position in the scrotum. The cordlike structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV also obliterates distally just above the testes, and the portion of the PV that envelops the testis becomes the tunica vaginalis. In females, the PV obliterates earlier, at approximately 7 months of gestation, and may explain why females demonstrate a much lower incidence of inguinal hernia. Proper closure of the PV effectively *seals off* the opening from the abdominal cavity into the inguinal region, containing the abdominal viscera within the abdominal cavity. Failure of the PV to close permits fluid or abdominal viscera to escape the abdominal cavity into the extraabdominal inguinal canal and accounts for a variety of inguinal-scrotal abnormalities commonly seen in infancy and childhood. Involution of the left-sided PV precedes that of the right, which is consistent with the increased incidence of indirect inguinal hernias on the right side (60%).

The ovaries descend into the pelvis from the urogenital ridge but do not exit from the abdominal cavity. The cranial portion of the gubernaculum in females differentiates into the ovarian ligament, and the inferior aspect of the gubernaculum becomes the round ligament, which passes through the internal ring and terminates in the labia majora. The PV in females is also known as the *canal of Nuck*.

Androgenic hormones produced by the fetal testis, adequate end-organ receptors, and mechanical factors such as increased intraabdominal pressure combine to regulate complete descent of the testis. The testes and spermatic cord structures (spermatic vessels and vas deferens) are located in the retroperitoneum but are affected by increases in intraabdominal pressure as a consequence of their intimate attachment to the descending PV. The genitofemoral nerve also has an important role: it innervates the cremaster muscle, which develops within the gubernaculum, and experimental division or injury to both nerves in the fetus prevents testicular descent. Failure of regression of smooth muscle (present to provide the force for testicular descent) has also been postulated to play a role in the development of indirect inguinal hernias. Several studies have investigated genes involved in the control of testicular descent for their role in closure of

precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The WHO recognized GIST in 1990 as a distinct neoplasm. Typically, GISTs arise in adults, after the third decade of life. Cases have also been reported in the pediatric population, generally in adolescents with a female predominance. A minority of pediatric cases were reported with Carney's triad (gastric gastrointestinal stromal tumor, pulmonary chondroma, and extraadrenal paraganglioma) or a history of neurofibromatosis. In children, tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Many patients (~45%) present with metastatic disease primarily to the lymph nodes, although metastases to the peritoneum or liver occur as well. Patients may be asymptomatic for years to decades or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of **surgical resection** of local disease. Recurrence rates are high, and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with pathogenic variants in the *KIT* oncogene. This alteration is less commonly found in pediatric GISTs (~15%). Adjuvant systemic therapy for *KIT*$^{+}$ lesions can be given, and typically **tyrosine kinase inhibitors (such as imatinib, sunitinib, or dasatinib)** are used. These medications are conveniently available as oral therapy. Patients with persistent, recurrent, or metastatic disease may benefit from treatment.

Vascular Tumors

Vascular malformations and hemangiomas are rare in children. The usual presentation is painless rectal bleeding, which may be chronic or acute, with massive or even fatal hemorrhage. There are usually no associated symptoms, although intussusception has been described. Half of patients have associated cutaneous hemangiomas or telangiectasia. These lesions may be associated with blue rubber bleb nevus syndrome, hereditary hemorrhagic telangiectasia, and other syndromes. About half of these lesions are in the colon and can be identified on colonoscopy. During acute bleeding episodes, bleeding can be localized via nuclear medicine bleeding scans, mesenteric angiography, or endoscopy. Colonic bleeding may be controlled by endoscopic means. Surgical intervention is required occasionally for isolated lesions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 394

Inguinal Hernias

José H. Salazar and John J. Aiken

Inguinal hernias are one of the most common conditions seen in pediatric practice, with an overall incidence of 0.8–4.5% in term infants and children and increasing to nearly 30% in premature and low birthweight (<1 kg) infants. Most inguinal hernias in infants and children are **congenital indirect** hernias (99%) because of a patent processus vaginalis (PV), an evagination of peritoneum in the inguinal area important in testicular descent. There is rarely any defect or deficiency in the abdominal wall musculature in congenital indirect inguinal hernia. Inguinal hernias are more common in males compared with females (8:1 ratio), but females have a higher incidence of bilateral inguinal hernias (~25%) compared with males (~12%). Two other types of inguinal hernia are seen rarely in children: **direct** (acquired) hernia (0.5–1.0%) and **femoral** hernia (<0.5%). Femoral hernias are substantially more common in females (2:1 ratio). Approximately 50% of inguinal hernias manifest clinically in the first year of life, most in the first 6 months. The incidence of incarceration in untreated hernias varies between 6% and 18% across ages. The risk of incarceration is greatest in infancy, with some reports of incarceration rates of 30–40% in the first year of life, mandating prompt identification and operative repair to minimize morbidity and complications related to incarceration and strangulation. Laparoscopic hernia (LH) repair has increasingly emerged in many pediatric centers as an effective alternative to traditional open hernia (OH) repair.

EMBRYOLOGY AND PATHOGENESIS

Indirect inguinal hernias in infants and children are congenital and result from an arrest of embryologic development—failure of obliteration of the PV rather than a weakness in the abdominal wall musculature. The pertinent developmental anatomy of indirect inguinal hernia relates to development of the gonads and descent of the testes through the inguinal canal and into the scrotum late in gestation. The testes descend from the urogenital ridge in the retroperitoneum to the area of the internal ring by about 28 weeks of gestation. The final descent of the testes into the scrotum occurs late in gestation, between weeks 28 and 36, guided by the PV and the gubernaculum. The PV, an outpouching of peritoneum in the inguinal region, is present in the developing fetus at 12 weeks of gestation. The PV develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testis accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal, and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 weeks to migrate from the external ring to its final position in the scrotum. The cordlike structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV also obliterates distally just above the testes, and the portion of the PV that envelops the testis becomes the tunica vaginalis. In females, the PV obliterates earlier, at approximately 7 months of gestation, and may explain why females demonstrate a much lower incidence of inguinal hernia. Proper closure of the PV effectively *seals off* the opening from the abdominal cavity into the inguinal region, containing the abdominal viscera within the abdominal cavity. Failure of the PV to close permits fluid or abdominal viscera to escape the abdominal cavity into the extraabdominal inguinal canal and accounts for a variety of inguinal-scrotal abnormalities commonly seen in infancy and childhood. Involution of the left-sided PV precedes that of the right, which is consistent with the increased incidence of indirect inguinal hernias on the right side (60%).

The ovaries descend into the pelvis from the urogenital ridge but do not exit from the abdominal cavity. The cranial portion of the gubernaculum in females differentiates into the ovarian ligament, and the inferior aspect of the gubernaculum becomes the round ligament, which passes through the internal ring and terminates in the labia majora. The PV in females is also known as the *canal of Nuck*.

Androgenic hormones produced by the fetal testis, adequate end-organ receptors, and mechanical factors such as increased intraabdominal pressure combine to regulate complete descent of the testis. The testes and spermatic cord structures (spermatic vessels and vas deferens) are located in the retroperitoneum but are affected by increases in intraabdominal pressure as a consequence of their intimate attachment to the descending PV. The genitofemoral nerve also has an important role: it innervates the cremaster muscle, which develops within the gubernaculum, and experimental division or injury to both nerves in the fetus prevents testicular descent. Failure of regression of smooth muscle (present to provide the force for testicular descent) has also been postulated to play a role in the development of indirect inguinal hernias. Several studies have investigated genes involved in the control of testicular descent for their role in closure of

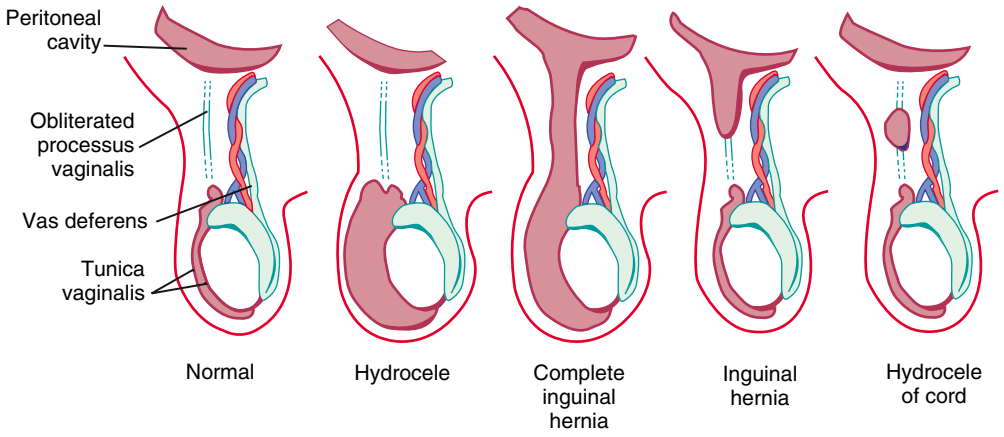

Fig. 394.1 Hernia and hydroceles. *(Modified from Scherer LR III, Grosfeld JL. Inguinal and umbilical anomalies. Pediatr Clin North Am. 1993;40:1121–1131.)*

the patent PV—for example, hepatocyte growth factor and calcitonin gene–related peptide. Unlike in adult hernias, there does not appear to be any deficiency in collagen synthesis associated with inguinal hernia in children (Fig. 394.1).

A **direct inguinal hernia** results from a weakness in the abdominal wall musculature in the inguinal region, specifically the transverse abdominis muscle, which forms the floor of the inguinal canal. A direct inguinal hernia originates **medial** to the deep inferior epigastric vessels and is external to the cremasteric fascia; the hernia sac protrudes directly through the posterior wall of the inguinal canal and does not protrude through the external ring. A **femoral hernia** originates medial to the femoral vein and descends inferior to the inguinal ligament along the femoral canal.

Incidence

The incidence of congenital indirect inguinal hernia in full-term newborn infants is estimated at 3.5–5.0%. The incidence of hernia in preterm and low birthweight infants is considerably higher, ranging from 9% to 11%, and approaches 30% in very low birthweight infants (<1,000 g) and preterm infants (<28 weeks of gestation). Inguinal hernia is much more common in males than in females, with a male-to-female ratio of approximately 8:1. Approximately 60% of inguinal hernias occur on the right side, 30% are on the left side, and 10% are bilateral. The incidence of bilateral hernias is higher in females (20–40%) and young children (<2 years). An increased incidence of congenital inguinal hernia has been documented in twins and in family members of patients with inguinal hernia. There is a history of another inguinal hernia in the family in 11.5% of patients. The sisters of affected females are at the highest risk, with a relative risk of 17.8. In general, the risk of brothers of a sibling is approximately 4-5, as is the risk of a sister of an affected brother. Both a multifactorial threshold model and autosomal dominance with incomplete penetrance and sex influence have been suggested as an explanation for this pattern of inheritance.

Inguinal hernia, scrotal hydrocele (communicating and noncommunicating), and hydrocele of the spermatic cord are conditions resulting from varying degrees of failure of closure of the PV. Closure of the PV is often incomplete at birth and continues postnatally; the rate of patency is inversely proportional to the age of the child. It has been estimated that the patency rate of the PV is as high as 80% at birth and decreases to ~40% during the first year of life and that ~20% of males have a persistent patency of the PV at 2 years of age. Patency of the PV after birth is an opening from the abdominal cavity into the inguinal region, and therefore a potential hernia, but not all patients will develop a clinical hernia. An inguinal hernia occurs clinically when intraabdominal contents escape the abdominal cavity and enter the inguinal region through the PV patency. Depending on the extent of patency of the PV, the hernia may be confined to the inguinal region or pass down into the scrotum. Complete failure of obliteration of the PV, mostly seen in infants, predisposes to a complete inguinal hernia characterized by a protrusion of abdominal contents into the inguinal canal and extending into the scrotum. Obliteration of the PV distally (around the testis) with patency proximally results in the classic indirect inguinal hernia with a bulge in the inguinal canal.

Table 394.1 Predisposing Factors for Hernias

Prematurity
Urogenital
• Cryptorchidism
• Exstrophy of the bladder or cloaca
• Ambiguous genitalia
• Hypospadias/epispadias
Increased peritoneal fluid
• Ascites
• Ventriculoperitoneal shunt
• Peritoneal dialysis catheter
Increased intraabdominal pressure
• Repair of abdominal wall defects
• Severe ascites (chylous)
• Meconium peritonitis
Chronic respiratory disease
• Cystic fibrosis
Connective tissue disorders
• Ehlers-Danlos syndrome
• Hunter-Hurler syndrome
• Marfan syndrome
• Mucopolysaccharidosis

A **hydrocele** occurs when only fluid enters the patent PV; the swelling may exist only in the scrotum (scrotal hydrocele), only along the spermatic cord in the inguinal region (hydrocele of the spermatic cord), or extend from the scrotum through the inguinal canal and even into the abdomen (abdominal-scrotal hydrocele). A hydrocele is termed a **communicating hydrocele** if it demonstrates fluctuation in size, often increasing in size after activity and, at other times, being smaller when the fluid decompresses into the peritoneal cavity often after lying recumbent. Occasionally, hydroceles develop in older children after trauma, inflammation, torsion of the appendix testes, or in association with tumors affecting the testis.

Although reasons for failure of closure of the PV are unknown, it is more common in cases of testicular nondescent (cryptorchidism) and prematurity. In addition, persistent patency of the PV is twice as common on the right side, presumably related to later descent of the right testis and interference with obliteration of the PV from the developing inferior vena cava and external iliac vein. Table 394.1 lists the risk factors identified as contributing to failure of closure of the PV and to the development of clinical inguinal hernia. The incidence of inguinal hernia in patients with cystic fibrosis is approximately 15%, believed to be related to an altered embryogenesis of the Wolffian duct structures, which

leads to an absent vas deferens and infertility in males with this condition. There is also an increased incidence of inguinal hernia in patients with **testicular feminization syndrome** and other disorders of sexual development. The rate of recurrence after repair of an inguinal hernia in patients with a connective tissue disorder approaches 50%, and often the diagnosis of connective tissue disorders in children results from investigation after development of a recurrent inguinal hernia.

Clinical Presentation and Diagnosis

An inguinal hernia typically appears as an intermittent, asymptomatic bulge or mass in the inguinal region or scrotum, most often noted on routine physical examination or by a parent; after bathing or urination are classic presentations. In females, the mass typically occurs in the upper portion of the labia majora. The bulge or mass is most visible at times of irritability or increased intraabdominal pressure (crying, straining, coughing). Most inguinal hernias present clinically in young children, approximately 50% in the first year, and most are asymptomatic or minimally symptomatic. The classic history from the parents is of intermittent groin, labial, or scrotal swelling that spontaneously reduces but that is gradually enlarging or is more persistent and is becoming more difficult to reduce. *Rarely an incarcerated hernia may present in an infant with emesis, dehydration, and abdominal distention suggestive of gastroenteritis or a bowel obstruction*. The **hallmark sign** of an inguinal hernia on physical examination is a smooth, firm mass that emerges through the external inguinal ring lateral to the pubic tubercle and enlarges with increased intraabdominal pressure. When the child relaxes, the hernia typically reduces spontaneously or can be reduced by gentle pressure, first posteriorly to free it from the external ring and then upward toward the peritoneal cavity. In males, the hernia sac contains intestines; female infants often have an ovary and fallopian tube in the hernia sac.

The diagnosis of inguinal hernia is clinical and generally is made by history and physical examination. Methods used to demonstrate the hernia on examination vary depending on the age of the child. A quiet infant can be made to strain the abdominal muscles by stretching the infant out supine on the bed with legs extended and arms held straight above the head. Most infants struggle to get free, thus increasing the intraabdominal pressure and pushing out the hernia. Older children can be asked to perform the Valsalva maneuver by blowing up a balloon or coughing. The older child should be examined while standing, and examination after voiding also can be helpful. With increased intraabdominal pressure, the protruding mass is obvious on inspection of the inguinal region or can be palpated by an examining finger invaginating the scrotum to palpate at the external ring. Another subtle and less definitive test is the *silk glove sign,* which describes the feeling of the layers of the hernia sac as they slide over the spermatic cord structures with rolling of the spermatic cord beneath the index finger at the pubic tubercle. In the absence of a bulge, the finding of increased thickness of the inguinal canal structures on palpation also suggests the diagnosis of an inguinal hernia. It is important on examination to note the position of the testes because retractile testes are common in infants and young males and can mimic an inguinal hernia with a bulge in the region of the external ring. Because in the female patient approximately 20–25% of inguinal hernias are **sliding** hernias (the contents of the hernia sac are adherent within the sac and therefore not reducible), a fallopian tube or ovary can be palpated in the inguinal canal as a firm, slightly mobile, nontender mass in the labia or inguinal canal. A **femoral** hernia appears as a protrusion on the medial aspect of the thigh, below the inguinal region, and does not enter the scrotum or labia.

Because most hernias in young children reduce spontaneously, the physical examination in the office can be equivocal. Infants and children with a strong history suggestive of inguinal hernia and an equivocal clinical examination may be offered ultrasound or referral to a pediatric surgeon. Diagnostic laparoscopy has been increasingly used to evaluate for suspected inguinal hernia; particularly in infants where the risk of incarceration and potential injury to the intestines or testis is high. In an older child with low risk of incarceration, the parents can be reassured and educated relative to the low risk of incarceration and morbidity. If an inguinal hernia is present, it will predictably become increasingly observed. A plan for a period of observation is thoughtful and safe, and the parents can be asked to take a digital image at home if the bulge is noted.

EVALUATION OF ACUTE INGUINAL-SCROTAL SWELLING

Commonly in pediatric practice, an inguinal-scrotal mass appears suddenly in an infant or child and is associated with pain and discomfort. The differential diagnosis includes incarcerated inguinal hernia, acute hydrocele, torsion of an undescended testis, infection (epididymitis/orchitis), and suppurative inguinal lymphadenitis. Differentiating between the incarcerated inguinal hernia and the acute hydrocele is probably the most difficult. The infant or child with an incarcerated inguinal hernia is likely to have associated findings suggesting intestinal obstruction, such as colicky abdominal pain, abdominal distention, vomiting, and cessation of stool, and may appear ill. Plain radiographs, if obtained, typically demonstrate distended intestines with multiple air-fluid levels. The infant with an acute hydrocele may have discomfort but is consolable and tolerates feedings without signs or symptoms suggesting intestinal obstruction.

On examination of the child with the acute scrotal hydrocele, the clinician may note that the mass is somewhat mobile. In addition, the inguinal region is flat and the mass confined to the scrotum. With the incarcerated hernia, there is a lack of mobility of the groin mass and marked swelling or a mass extending from the scrotal mass through the inguinal area and up to and including the internal ring. An experienced clinician can selectively use a bimanual examination to help differentiate groin abnormalities. The examiner palpates the internal ring per rectum, with the other hand placing gentle pressure on the inguinal region over the internal ring. In cases of an indirect inguinal hernia, intraabdominal viscera can be palpated extending through the internal ring.

Another method used in diagnostic evaluation is **transillumination** to ascertain if the mass contains only fluid (hydrocele) versus intestine (hernia); however, it must be noted that transillumination can be misleading because the thin wall of the infant's intestine can approximate that of the hydrocele wall, and both may transilluminate. This is also the reason aspiration to assess the contents of a groin mass is discouraged. **Ultrasonography** can help distinguish between a hernia, a hydrocele, and lymphadenopathy and is a simple and well-tolerated test. An expeditious diagnosis is important to avoid the potential complications of an incarcerated hernia, which can develop rapidly. Diagnostic laparoscopy is an effective and reliable tool in this setting by pediatric surgeons but requires general anesthesia.

The occurrence of suppurative adenopathy in the inguinal region can be confused with an incarcerated inguinal hernia. Examination of the watershed area of the inguinal lymph nodes might reveal a superficial infected or crusted skin lesion. In addition, the swelling associated with inguinal lymphadenopathy is typically located more inferior and lateral than the mass of an inguinal hernia, and there may be other associated enlarged nodes in the area. Torsion of an undescended testis can manifest as a painful erythematous mass in the groin. The absence of a gonad in the scrotum in the ipsilateral side should clinch this diagnosis. Infectious etiologies typically demonstrate swelling and tenderness of the testis, but often there is associated urinary symptoms and the swelling is confined to the scrotum and does not extend into the inguinal canal.

Incarcerated Hernia

Incarceration is a common consequence of untreated inguinal hernia in infants and presents as a *nonreducible* mass in the inguinal canal, scrotum, or labia. Contained structures can include the small bowel, appendix, omentum, colon, bladder, or, rarely, Meckel diverticulum. In females, the ovary, fallopian tube, or both are commonly incarcerated. Rarely, the uterus in infants can also be pulled into the hernia sac. A **strangulated hernia** is one that is tightly constricted in its passage through the inguinal canal, and as a result, the hernia contents have become ischemic or gangrenous. The incidence of incarceration of an inguinal hernia is between 6% and 18% throughout childhood

years, and two thirds of incarcerated hernias occur in the first year of life. The greatest risk is in infants younger than 6 months of age, with reported incidences of incarceration between 25% and 30%. Reports vary, but many believe a history of prematurity imparts an increased risk of incarceration in the first year of life.

Although incarceration may be tolerated in adults for years, most nonreducible inguinal hernias in children, unless treated, rapidly progress to *strangulation* with potential infarction of the hernia contents or intestinal obstruction. Initially, pressure on the herniated viscera leads to impaired lymphatic and venous drainage. This leads to swelling of the herniated viscera, which further increases the compression in the inguinal canal, ultimately resulting in total occlusion of the arterial supply to the trapped viscera. Progressive ischemic changes take place, culminating in gangrene and/or perforation of the herniated viscera. The testis is at risk of ischemia because of compression of the testicular blood vessels by the strangulated hernia. In females, herniation/incarceration of the ovary places it at risk of torsion with resultant ischemia.

The symptoms of an incarcerated hernia are irritability, feeding intolerance, and abdominal distention in the infant; pain presents in the older child. Within a few hours, the infant becomes inconsolable; lack of flatus or stool signals complete intestinal obstruction. A somewhat tense, nonfluctuant mass is present in the inguinal region and can extend down into the scrotum or labia. The mass is well defined, firm, and does not reduce. With the onset of ischemic changes, the pain intensifies, and the vomiting becomes bilious or feculent. Blood may be noted in the stools. The mass is typically markedly tender, and there is often edema and erythema of the overlying skin. The testes may be normal, demonstrate a reactive hydrocele, or may be swollen and hard on the affected side because of venous congestion resulting from compression of the spermatic veins and lymphatic channels at the inguinal ring by the tightly strangulated hernia mass. Abdominal radiographs demonstrate features of partial or complete intestinal obstruction, and gas within the incarcerated bowel segments may be seen below the inguinal ligament or within the scrotum.

Ambiguous Genitalia

Infants with disorders of sexual development commonly present with inguinal hernias, often containing a gonad, and require special consideration. In female infants with inguinal hernias, particularly if the presentation is bilateral inguinal masses, **testicular feminization syndrome** should be suspected (>50% of patients with testicular feminization have an inguinal hernia; see Chapter 628). Conversely, the true incidence of testicular feminization in all female infants with inguinal hernias is difficult to determine but is approximately 1%. In phenotypic females, if the diagnosis of testicular feminization is suspected preoperatively, the child should be screened with a buccal smear for Barr bodies and appropriate genetic evaluation before proceeding with the hernia repair. The diagnosis of testicular feminization is occasionally made at the time of operation by identifying an abnormal gonad (testis) within the hernia sac or absence of the uterus on laparoscopy or rectal exam. In the normal female infant, the uterus is easily palpated as a distinct midline structure beneath the symphysis pubis on rectal examination. Preoperative diagnosis of testicular feminization syndrome or other disorders of sexual development such as mixed gonadal dysgenesis and selected pseudohermaphrodites enables the family to receive genetic counseling, and gonadectomy can be accomplished at the time of the hernia repair if indicated.

Indications for Surgery

The presence of an inguinal hernia in the pediatric age-group constitutes the indication for operative repair. An inguinal hernia does not resolve spontaneously, and prompt repair eliminates the risk of incarceration and the associated potential complications, particularly in the first 6-12 months of life. The timing of operative repair depends on several factors, including age, general condition of the patient, and comorbid conditions. In full-term, healthy infants (younger than 1 year) with an inguinal hernia, repair should proceed promptly (within 2-3 weeks) after diagnosis because as many as 70% of incarcerated inguinal hernias requiring emergency operation occur in infants younger than 11 months. In addition, the incidence of complications associated with elective hernia repair (intestinal injury, testicular atrophy, recurrent hernia, wound infection) are low (~1%) but rise to as high as 18–20% when repair is performed emergently at the time of incarceration. The incidence of testicular atrophy after incarceration in infants younger than 3 months of age has been reported as high as 30%. Therefore an approach emphasizing prompt elective repair in infants is warranted; anesthetic risks must be considered when determining timing of elective surgery for inguinal hernia repair. The risk factors for apnea after general anesthesia include prematurity, multiple congenital anomalies, history of apnea and bradycardia, chronic lung disease, postconceptual age <60 weeks at the time of surgery, and anemia. Unfortunately, although this group of patients would be ideal for inguinal hernia repair under regional (spinal/caudal) anesthesia, inguinal hernia repair in this group is often remarkably technically challenging even for experienced pediatric surgeons, and success is elusive under regional techniques. The outcome advantage of a regional technique is lost if additional intravenous sedation is required. Institutional policies vary, but in general, full-term infants <50 weeks postconceptual age and preterm infants <55 weeks postconceptual age should be observed after repair for a minimum of 12 hours postoperatively and potentially overnight after general anesthesia for the development of apnea and bradycardia.

In children older than 1 year, the risk of incarceration is less, and the repair can be scheduled with less urgency. For the routine reducible hernia, the operation should be carried out electively shortly after diagnosis. Elective inguinal hernia repair in healthy children can be safely performed in an outpatient setting, with an expectation for full recovery within 48 hours. A regional caudal block or local inguinal nerve block using local anesthetic is useful to diminish perioperative pain and optimize recovery. Prophylactic antibiotics are not routinely used except for associated conditions, such as congenital heart disease or the presence of a ventriculoperitoneal shunt. *The operation should be performed at a facility with the ability to admit the patient to an inpatient unit as needed should concerns or complications arise.*

There is controversy as to the optimal timing of inguinal herniorrhaphy in preterm and low birthweight infants. In the past 2 decades, most pediatric surgeons have planned hernia repair shortly before discharge from the neonatal intensive care unit. This group has a high rate of incarceration but also a high risk of anesthesia-related postoperative complications with elective surgery, such as apnea, bradycardia, inability to extubate, hemodynamic instability (5–10%), and even cardiopulmonary arrest. In addition, this group has an increased rate of postoperative surgical-related complications such as wound infection (5–10%) and recurrent hernia (10%). At present, studies to develop evidence-based data for timing of inguinal hernia repair in premature infants are ongoing, but there is a lack of consensus, and patients should be individualized, with important consultation with both neonatology and pediatric anesthesia. The operation for inguinal hernia repair is most often performed under general anesthesia, but it can be performed under spinal/caudal anesthesia in selected high-risk infants in whom avoidance of intubation is preferable (e.g., because of chronic lung disease or bronchopulmonary dysplasia). In this setting, open repair (OH) is preferable to the laparoscopic approach, as it can be performed under local/regional techniques.

An incarcerated, irreducible hernia without evidence of strangulation in a clinically stable patient should initially be managed nonoperatively, unless there is evidence of bowel obstruction, peritonitis, or hemodynamic instability, because 70–95% of incarcerated inguinal hernias are successfully reduced. Manual reduction is performed using a surgical technique called *taxis,* first with traction caudad and posteriorly to free the mass from the external inguinal ring, and then upward to reduce the contents back into the peritoneal cavity. Reduction attempts usually require sedation (intravenous) and analgesics, and thus appropriate experience with monitoring and airway management are critical concerns. In addition, if reduction of the incarcerated hernia is successful, the infant may rapidly become somnolent and apneic, requiring important supportive measures by skilled personnel. Other techniques advocated to assist in the nonoperative reduction of an incarcerated inguinal hernia include elevation of the lower torso

and legs. Ice packs should be avoided in infants because of the risk of hypothermia but may be used for brief periods in the older child. If reduction is successful but difficult, the patient should be observed for several hours to ensure that feedings are tolerated and there is no concern that necrotic intestine was reduced; fortunately, this is an uncommon occurrence. Given the risk of early recurrent incarceration after a successful reduction, it is recommended that herniorrhaphy be performed after a brief period (1-4 days), by which time there is less edema, handling of the sac is easier, and the risk of complications is reduced.

If the inguinal hernia is unable to be reduced, or there is concern for an incomplete reduction, then operative reduction should be performed emergently. In addition, for any patient who presents with a prolonged history of incarceration of an inguinal hernia, signs of peritoneal irritation, or small bowel obstruction, surgery and operative reduction and repair of the hernia should be urgently performed. Initial management includes nasogastric intubation, intravenous fluids, and administration of broad-spectrum antibiotics. When fluid and electrolyte imbalance has been corrected and the child's condition is satisfactory, exploration is undertaken. In current practice, the laparoscopic approach may have advantages, as the abdominal cavity insufflation expands the internal ring, potentially aiding reduction of the incarcerated viscera and enabling visualization of the viscera for possible ischemic injury and/or perforation. The risk of postoperative complications such as testicular atrophy, bowel ischemia, wound infections, and recurrence of hernia is increased after emergency inguinal hernia repair: 4.5–33% compared with 1% in elective hernia repairs in healthy, full-term infants.

A common presentation in female patients is an irreducible ovary in the inguinal hernia in an otherwise asymptomatic patient. The inguinal mass is soft and nontender to gentle exam, and there is no swelling or edema; thus there are no findings suggesting strangulation. This represents a *sliding* hernia, with the fallopian tube and ovary fused to the wall of the hernia sac preventing reduction to the abdominal cavity. Overzealous attempts to reduce the hernia are unwarranted and potentially harmful to the tube and ovary. The risk that incarceration, most often resulting from torsion of the ovary in this setting, will lead to strangulation is not known. Most pediatric surgeons recommend elective repair of the hernia within 24-48 hours.

The appearance of necrotic ovaries and testes at the time of operation does not consistently provide evidence of irreversible damage or predict future functionality. Multiple studies report that even when ovaries appear persistently ischemic after relief of incarceration and detorsion, most ovaries, if preserved, will recover and demonstrate evidence of follicular development. Similarly, ischemic-appearing testes after relief of incarceration survive in as much as 50% of cases. Testicular atrophy occurs in 2.5–15% of incarcerated hernias. Given the potential for retained functionality, the current recommendation is to avoid testicular resection unless frank necrosis is present.

Open Inguinal Hernia Repair

The operation is performed through a small (2-3 cm) inguinal skin crease incision. The procedure involves opening of the inguinal canal; reduction of the contents of the hernia sac if present, careful separation of the hernia sac from the cremasteric muscle fibers, spermatic cord vessels, and vas deferens to avoid injury to these structures in the inguinal canal, division of the hernia sac, and high ligation of the hernia sac at the internal ring, thus preventing protrusion of abdominal contents into the inguinal canal. A communicating hydrocele is approached with the same technique, separation of the spermatic cord structures from the hernia sac, high ligation of the proximal portion of the hernia sac, and opening of the distal sac to relieve the hydrocele. In older children with a noncommunicating hydrocele, the approach may be through a scrotal incision with avoidance of manipulation of the spermatic cord vessels and vas deferens. Open inguinal hernia repair has a low rate of recurrence, vas deferens injury, and testicular atrophy (~1–2%).

In females, surgical repair is technically simpler because the hernia sac and round ligament can be ligated without concern for injury to the ovary and its blood supply, which generally remain within the abdomen. The hernia sac and round ligament are divided from their distal attachment in the labia majora, proximal dissection away from the cremasteric muscle fibers to the internal ring, and high ligation at the internal ring. In female infants, opening of the sac to visualize the ovary and fallopian tube may help avoid injury to these structures during suture ligation of the sac and also rule out testicular feminization syndrome. If the ovary and fallopian tube are within the sac and not reducible, the sac is suture ligated distal to these structures, and the internal ring is closed after reducing the sac and its contents to the abdominal cavity.

Laparoscopic Inguinal Hernia Repair

Laparoscopic repair (LH) is used by most pediatric surgeons. There are several techniques described, both transperitoneal and preperitoneal, depending on surgeon preference. The laparoscopic technique is fundamentally a high ligation of the indirect inguinal hernia sac (PV) at the internal ring to prevent protrusion of abdominal viscera into the inguinal canal. The laparoscopic technique affords confirmation of the diagnosis and inspection of the contralateral side for the presence of a hernia or a patent PV (potential hernia). Reported advantages of laparoscopic repair (LH) compared with open repair (OH) include better cosmesis, shorter length of stay (LOS), faster recovery, and greater ability to visualize and repair a contralateral hernia.

In LH, the inguinal canal is not explored, and the spermatic cord structures are not manipulated, which may portend reduced risk to the testicular blood supply or vas deferens, particularly in younger patients. Disadvantages of LH in infants and younger children are the increased risk associated with general anesthesia, the potential hemodynamic effects of abdominal insufflation (e.g., acidosis, compromised venous return), and technical challenges of the LH technique. Operative times have been similar for the OH and LH approaches; however, there is wide variability with the LH technique based on the experience of the surgeon and surgical team. Laparoscopic procedures in infants should always be performed expeditiously and with low insufflation pressure to avoid the risk of cardiorespiratory compromise and development of acidosis. Postoperative pain in both techniques is managed with oral acetaminophen for 24-48 hours; older children may require a brief period of postoperative NSAIDs or narcotics. In a prospective, randomized study, the laparoscopic approach was associated with decreased pain, parental perception of faster recovery, and parental perception of better wound cosmesis. At present, outcomes, recurrence rates, recovery metrics, complications, and family satisfaction appear similar for both approaches (OH and LH), and evidence is lacking to recommend one approach over the other.

Contralateral Inguinal Exploration

Most children (85%) present with a unilateral inguinal hernia. Controversy exists regarding when to proceed with contralateral groin exploration. The only purpose of contralateral exploration is to avoid the occurrence of a hernia on that side at a later date. The advantages of contralateral exploration include avoidance of parental anxiety and possibly a second anesthesia, the cost of additional surgery, and the risk of contralateral incarceration. The disadvantages of exploration include potential injury to the spermatic cord vessels, vas deferens, and testis and increased operative and anesthesia time.

Laparoscopy enables assessment of the contralateral side without risk of injury to the spermatic cord structures or testis. When performing OH repair, the laparoscope can be introduced through an umbilical incision or by passing a 30-degree or 70-degree oblique scope through the OH sac before ligation of the hernia sac on the involved side. If patency of the contralateral side is demonstrated, the surgeon can proceed with bilateral hernia repair, and if the contralateral side is properly obliterated, exploration and potential complications are avoided. When performing LH, visualization of the contralateral side is easily performed. The downside of this approach includes the risks associated with laparoscopy and that laparoscopy cannot differentiate between a patent PV and a true hernia (Figs. 394.2 and 394.3). In experienced hands, ultrasound has been proven to be a good alternative to surgical approaches to explore the contralateral groin. Infants and children

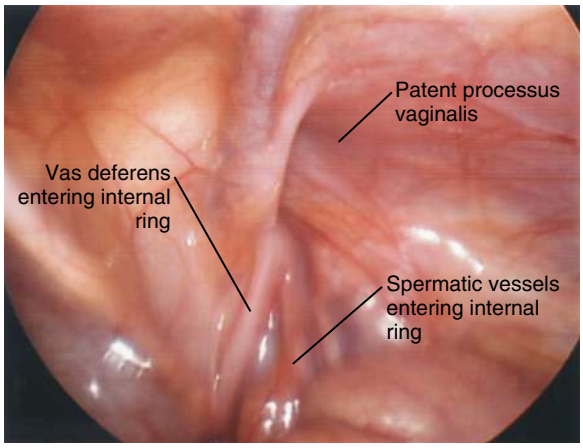

Fig. 394.2 Laparoscopic image of patent processus vaginalis on right side.

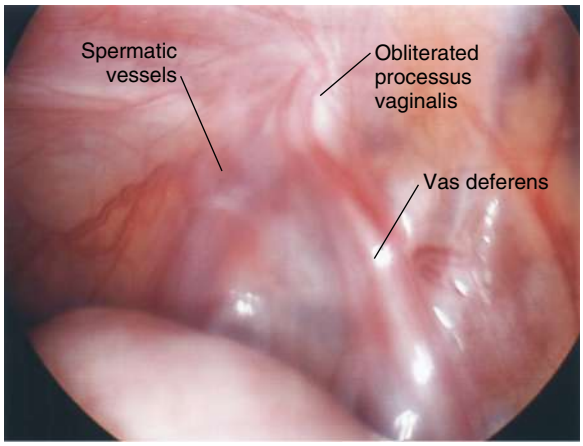

Fig. 394.3 Diagnostic laparoscopic image of obliterated processus vaginalis on left side.

with risk factors for development of an inguinal hernia or with medical conditions that increase the risk of general anesthesia should be approached with a low threshold for routine contralateral exploration.

DIRECT INGUINAL HERNIA

Direct inguinal hernias are rare in children, approximately 0.5–1%. Direct hernias appear as groin masses that extend toward the femoral vessels with exertion or straining. The etiology is from a muscular defect or weakness in the floor of the inguinal canal *medial* to the epigastric vessels. Thus direct inguinal hernias in children are generally considered an acquired problem. In one third of cases, the patient has a history of a prior indirect hernia repair on the side of the direct hernia, which suggests a possible missed direct hernia at the initial surgery or injury to the floor muscles of the inguinal canal at the time of the first herniorrhaphy. Patients with **connective tissue disorders** such as Ehlers-Danlos syndrome or Marfan syndrome and mucopolysaccharidosis such as Hunter-Hurler syndrome are at increased risk for the development of direct inguinal hernias either independently or after indirect inguinal hernia repair.

Operative repair of a direct inguinal hernia involves strengthening of the floor of the inguinal canal, and many standard techniques have been described, similar to repair techniques used in adults. The repair can be performed through a single limited incision, and therefore LH does not offer a significant advantage. Recurrence after repair, in contrast to that in adults, is extraordinarily rare. Because typically the area of muscular weakness is small and pediatric tissues have greater elasticity, primary repair is usually possible. Prosthetic material (mesh) for direct hernia repair or other approaches, such as preperitoneal repair, are rarely required in the pediatric age-group. The older child with a direct inguinal hernia and a connective tissue disorder may be the exception, and a laparoscopic approach and prosthetic material in such a case can be useful for repair.

FEMORAL HERNIA

Femoral hernias are rare in children (<1% of groin hernias in children). They are more common in females than in males (2:1 ratio). They are extremely rare in infancy and occur typically in older children, believed to most often be an acquired defect. Femoral hernias represent a protrusion through the femoral canal. The bulge of a femoral hernia is located below the inguinal ligament and typically projects on the medial aspect of the proximal thigh. Femoral hernias are more often missed clinically than direct hernias on physical examination or at the time of indirect hernia repair. Repair of a femoral hernia involves closure of the defect at the femoral canal, generally suturing the inguinal ligament to the pectineal ligament/fascia.

COMPLICATIONS

Complications after elective inguinal hernia repair are uncommon (~1.5%) but significantly higher in association with incarceration (~10%). The major risk of elective inguinal hernia repair in infants and children relates to the need for general anesthesia, and spinal/caudal anesthesia should be considered based on the experience of the surgeon and anesthesia team. Surgical complications can be related to technical factors (recurrence, iatrogenic cryptorchidism or *trapped testicle,* inadvertent injury to the vas deferens or spermatic vessels) or to the underlying process, such as bowel ischemia, gonadal infarction, and testicular atrophy after incarceration. Because LH repair generally does not involve inguinal exploration or manipulation of the testicular vessels or vas deferens, the risk of injury is potentially lower, but supportive data are unavailable at present.

Wound Infection

Wound infection occurs in <1% of elective inguinal hernia repairs in infants and children, but the incidence increases to 5–7% in association with incarceration and emergent repair. The patient typically develops fever and irritability 3-5 days after the surgery, and the wound demonstrates warmth, erythema, and fluctuance. Management consists of opening and draining the wound, a short course of antibiotics, and a daily wound dressing. The most common organisms are gram-positive (*Staphylococcus* and *Streptococcus* spp.), and consideration should be given to coverage of methicillin-resistant *Staphylococcus aureus.* The wound generally heals in 1-2 weeks with low morbidity and a good cosmetic result.

Recurrent Hernia

The recurrence rate of inguinal hernias after elective inguinal hernia repairs is generally reported as 0.5–1.0%, with rates as high as 2% for premature infants. The rate of recurrence after emergency repair of an incarcerated hernia is much higher, reported as 3–6% in most large series. The true incidence of recurrence is most certainly even higher, given the problem of accurate long-term follow-up. In the group of patients who develop recurrent inguinal hernia, the recurrence occurs in 50% within 1 year of the initial repair and in 75% by 2 years. Recurrence of an indirect hernia may be the result of a technical problem in the original procedure, such as failure to identify the sac properly, failure to perform high ligation of the sac at the level of the internal ring, or a tear in the sac that leaves a strip of peritoneum along the cord structures. Recurrence as a direct hernia can result from injury to the inguinal floor (transversalis fascia) during the original procedure or, more likely, failure to identify a direct hernia during the original exploration. Patients with *connective tissue disorders* (collagen deficiency) or

conditions that cause *increased intraabdominal pressure* (ventriculoperitoneal shunts, ascites, chronic lung disease, peritoneal dialysis) are at increased risk for recurrence.

Iatrogenic Cryptorchidism (Trapped Testicle)

Iatrogenic cryptorchidism describes malposition of the testis after inguinal hernia repair. This complication is usually related to disruption of the testicular attachment in the scrotum at the time of hernia repair or failure to recognize an undescended testis during the original procedure, allowing the testes to retract, typically to the region of the external ring. At the completion of inguinal hernia repair, the testis should be placed in a dependent intrascrotal position. If the testis will not remain in this position, proper fixation in the scrotum should be performed at the time of the hernia repair.

Incarceration

Incarceration of an inguinal hernia can result in injury to the intestines, the fallopian tube and ovary, or the ipsilateral testis. The incidence of incarceration of a congenital indirect inguinal hernia is reported as 6–18% throughout childhood and as high as 30% for infants younger than 6 months of age. Intestinal injury requiring bowel resection is uncommon, occurring in only 1–2% of incarcerated hernias. In cases of incarceration in which the hernia is reduced nonoperatively, the likelihood of intestinal injury is low; however, these patients should be observed closely for 6-12 hours after reduction of the hernia for signs and symptoms of intestinal obstruction, such as fever, vomiting, abdominal distention, or bloody stools. Laparoscopy affords the opportunity to inspect the reduced viscera for injury or necrosis in select cases.

The reported incidence of testicular infarction and subsequent testicular atrophy with incarceration is 4–12%, with higher rates among the irreducible cases requiring emergency operative reduction and repair. The testicular insult can be caused by compression of the gonadal vessels by the incarcerated hernia mass or as a result of damage incurred during operative repair. Young infants are at highest risk, with testicular infarction rates reported as high as 30% in infants younger than 2-3 months of age. These problems underscore the need for prompt reduction of incarcerated hernias and early repair once the diagnosis is known to avoid repeat episodes of incarceration.

Injury to the Vas Deferens and Male Fertility

Similar to the gonadal vessels, the vas deferens can be injured as a consequence of compression from an incarcerated hernia or during operative repair. This injury is almost certainly underreported because it is unlikely to be recognized until adulthood and, even then, possibly only if the injury is bilateral. Although the vulnerability of the vas deferens has been documented in many studies, no good data exist as to the actual incidence of this complication. One review reported an incidence of injury to the vas deferens of 1.6% based on pathology demonstrating segments of the vas deferens in the hernia sac specimen; this may be overstated, because others have shown that small glandular inclusions found in the hernia sac can represent müllerian duct remnants and are of no clinical importance. The relationship between male fertility and previous inguinal hernia repair is also unknown. There appears to be an association between infertile males with testicular atrophy and abnormal sperm count and a previous hernia repair. A relationship has also been reported between infertile males with spermatic autoagglutinating antibodies and previous inguinal hernia repair. The proposed etiology is that operative injury to the vas deferens during inguinal hernia repair might result in obstruction of the vas with diversion of spermatozoa to the testicular lymphatics, and this breach of the blood-testis barrier produces an antigenic challenge, resulting in formation of spermatic autoagglutinating antibodies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 5

Exocrine Pancreas

Chapter 395

Embryology, Anatomy, and Physiology of the Pancreas

Steven L. Werlin and Michael Wilschanski

INTRODUCTION

The human pancreas develops from the ventral and dorsal domains of the primitive duodenal endoderm beginning at about the fifth week of gestation (Fig. 395.1). The larger dorsal anlage, which develops into the tail, body, and part of the head of the pancreas, grows directly from the duodenum. The smaller ventral anlage develops as one or two buds from the primitive liver and eventually forms the major portion of the head of the pancreas. At about the 17th week of gestation, the dorsal and ventral anlagen fuse as the buds develop and the gut rotates. The ventral duct forms the proximal portion of the major pancreatic duct of Wirsung, which opens into the ampulla of Vater. The dorsal duct forms the distal portion of the duct of Wirsung and the accessory duct of Santorini, which empties independently in approximately 5% of people. Variations in fusion might account for pancreatic developmental anomalies. Pancreatic agenesis has been associated with a base pair deletion in the insulin promoter factor 1-*HOX* gene, *PDX1 (PAGEN1)*, *PTF1A (PAGEN 2)*, and *GATA 6 haploinsufficiency* genes. Other genes involved in pancreatic organogenesis include the *IHH*, *SHH* or sonic hedgehog gene, *SMAD2*, and *TGF-1β* genes.

The pancreas lies transversely in the upper abdomen between the duodenum and the spleen in the retroperitoneum (Fig. 395.2). The head, which rests on the vena cava and renal vein, is adherent to the C loop of the duodenum and surrounds the distal common bile duct. The tail of the pancreas reaches to the left splenic hilum and passes above the left kidney. The lesser sac separates the tail of the pancreas from the stomach.

By the 13th week of gestation, exocrine and endocrine cells can be identified. Primitive acini containing immature zymogen granules are found by the 16th week. Mature zymogen granules containing amylase, trypsinogen, chymotrypsinogen, and lipase are present at the 20th week. Centroacinar and duct cells, which are responsible for water, electrolyte, and bicarbonate secretion, are also found by the 20th week. The final three-dimensional structure of the pancreas consists of a complex series of branching ducts surrounded by grapelike clusters of epithelial cells. Cells containing glucagon are present at the 8th week. Islets of Langerhans appear between the 12th and 16th weeks.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

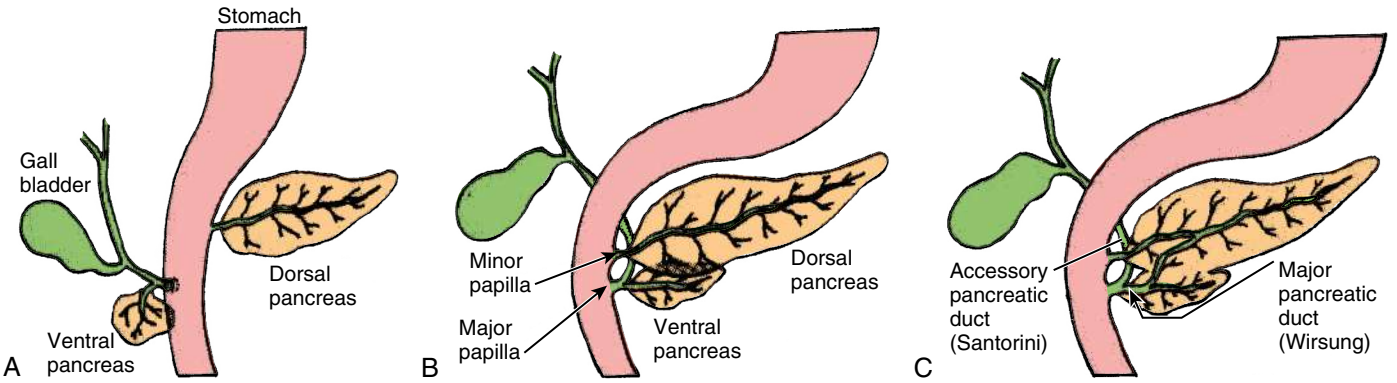

Fig. 395.1 Development of the exocrine pancreas. **A,** Gestational age 6 wk. **B,** Gestational age 7-8 wk. The ventral pancreas has rotated but has not yet fused with the dorsal pancreas. **C,** The ventral and dorsal pancreatic ductal systems have fused. *(From Werlin SL. The exocrine pancreas. In: Kelly VC, ed. Practice of Pediatrics, vol 3. Hagerstown, MD: Harper and Row, 1980: Fig. 16.1.)*

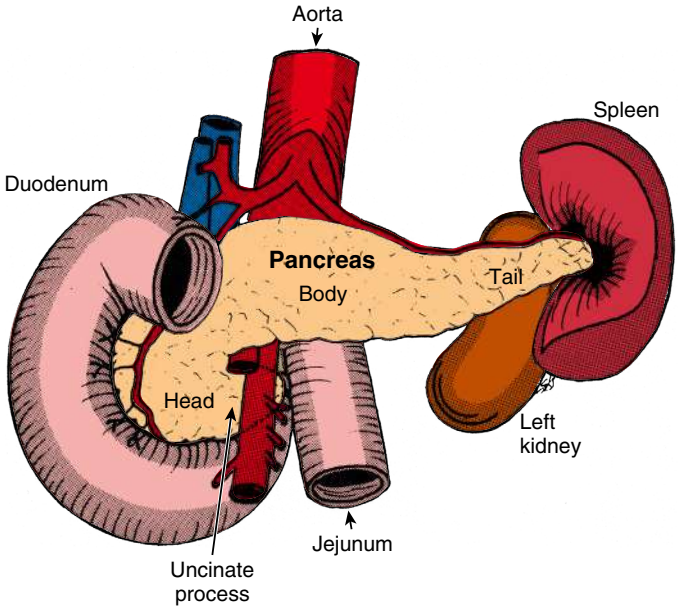

Fig. 395.2 Anterior view of the pancreas and relationship to neighboring structures. *(From Werlin SL. The exocrine pancreas. In: Kelly VC, ed. Practice of Pediatrics, vol 3. Hagerstown, MD: Harper and Row, 1980: Fig. 16.2.)*

395.1 Pancreatic Anatomic Abnormalities

Steven L. Werlin and Michael Wilschanski

Complete or partial **pancreatic agenesis** is a rare condition. Complete agenesis is associated with severe neonatal diabetes and usually death at an early age (see Chapter 629). Partial or dorsal pancreatic agenesis is often asymptomatic but may be associated with diabetes, congenital heart disease, polysplenia, and recurrent pancreatitis. Pancreatic agenesis is also associated with malabsorption.

An **annular pancreas** results from incomplete rotation of the left (ventral) pancreatic anlage, which may be a result of recessive pathogenic variants in the *IHH* or *SHH* genes. Patients usually present in infancy with symptoms of complete or partial bowel obstruction or in the fourth or fifth decade. There is often a history of maternal polyhydramnios. Other congenital anomalies, such as Down syndrome, tracheoesophageal fistula, intestinal atresia, imperforate anus, malrotation and cardiorenal abnormalities, and pancreatitis, may be associated with annular pancreas. Some children present with chronic vomiting, pancreatitis, or biliary colic. The treatment of choice is duodenojejunostomy. Division of the pancreatic ring is not attempted because a duodenal diaphragm or duodenal stenosis often accompanies annular pancreas.

Ectopic pancreatic rests in the stomach or small intestine occur in approximately 3% of the population. Most cases (70%) are found in the upper intestinal tract. Recognized on barium contrast studies by their typical umbilicated appearance, they are rarely of clinical importance. On endoscopy, they are irregular, yellow nodules 2-4 mm in diameter. A pancreatic rest may rarely be the lead point of an intussusception, produce hemorrhage, or cause bowel obstruction.

Pancreas divisum, which occurs in 5–15% of the population, is the most common pancreatic developmental anomaly. Because of the failure of the dorsal and ventral pancreatic anlagen to fuse, the tail, body, and part of the head of the pancreas drain through the small accessory duct of Santorini rather than the main duct of Wirsung. Some researchers believe that this anomaly may be associated with recurrent pancreatitis when there is relative obstruction of the outflow of the ventral pancreas. Diagnosis is made by endoscopic retrograde cholangiopancreatography or by magnetic resonance cholangiopancreatography. Pancreatitis in patients with pancreas divisum may be associated with pathogenic *CFTR* variants. Sphincterotomy is not recommended unless other anomalies are present or the patient has classic pancreatobiliary-type pain, recurrent pancreatitis, or chronic pancreatitis, and no other etiology is found.

Choledochal cysts are dilations of the biliary tract and usually cause biliary tract symptoms, such as jaundice, pain, and fever. On occasion, the presentation may be pancreatitis. The diagnosis is usually made with ultrasonography, CT or biliary scanning, or magnetic resonance cholangiopancreatography. Similarly, a choledochocele—an intraduodenal choledochal cyst—may manifest with pancreatitis. The diagnosis can be difficult and require magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasound.

A number of rare conditions, such as Ivemark (pathogenic variant in *GDF* gene) and Johanson-Blizzard (pathogenic variant in *UBR1* gene) syndromes, include pancreatic dysgenesis or dysfunction among their features. Many of these syndromes include renal and hepatic dysgenesis along with the pancreatic anomalies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

395.2 Pancreatic Physiology

Steven L. Werlin and Michael Wilschanski

The acinus is the functional unit of the exocrine pancreas. Acinar cells are arrayed in a semicircle around a lumen. Ducts that drain the acini are lined by centroacinar and ductular cells. This arrangement allows the secretions of the various cell types to mix.

The acinar cell synthesizes, stores, and secretes more than 20 enzymes, which are stored in zymogen granules, some in inactive forms. The relative concentration of the various enzymes in pancreatic juice is affected and perhaps controlled by the diet, probably by regulating the synthesis of specific messenger RNA. The main enzymes involved in digestion include *amylase*, which splits starch into maltose, isomaltose, and maltotriose; dextrins; and *trypsin* and *chymotrypsin*, endopeptidases secreted by the pancreas as inactive proenzymes. Trypsinogen is activated in the gut lumen by enterokinase, a brush-border enzyme. Trypsin can then activate trypsinogen, chymotrypsinogen, and procarboxypeptidase into their respective active forms. Pancreatic lipase requires *colipase*, a coenzyme also found in pancreatic fluid, for activity. Lipase liberates fatty acids from the 1 and 3 positions of triglycerides, leaving a monoglyceride.

The stimuli for exocrine pancreatic secretion are neural and hormonal. Acetylcholine mediates the cephalic phase; cholecystokinin (CCK) mediates the intestinal phase. CCK is released from the duodenal mucosa by luminal amino acids and fatty acids. Feedback regulation of pancreatic secretion is mediated by pancreatic proteases in the duodenum. Secretion of CCK is inhibited by the digestion of a trypsin-sensitive, CCK-releasing peptide released in the lumen of the small intestine or by a monitor peptide released in pancreatic fluid.

Centroacinar and duct cells secrete water and bicarbonate. Bicarbonate secretion is under feedback control and is regulated by duodenal intraluminal pH. The stimulus for bicarbonate production is secretin in concert with CCK. Secretin cells are abundant in the duodenum.

Although normal pancreatic function is required for digestion, maldigestion occurs only after considerable reduction in pancreatic function; lipase and colipase secretion must be decreased by 90–98% before fat maldigestion occurs.

Although amylase and lipase are present in the pancreas early in gestation, secretion of both amylase and lipase is low in infants. Adult levels of these enzymes are not reached in the duodenum until late in the first year of life. Digestion of the starch found in many infant formulas depends in part on the low levels of salivary amylase that reach the duodenum. This explains the diarrhea that may be seen in infants who are fed formulas high in glucose polymers or starch. Neonatal secretion of trypsinogen and chymotrypsinogen is at approximately 70% of the level found in the 1-year-old infant. The low levels of amylase and lipase in duodenal contents of infants may be partially compensated by salivary amylase and lingual lipase. This explains the relative starch and fat intolerance of premature infants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 396
Pancreatic Function Tests

Michael Wilschanski and Steven L. Werlin

Pancreatic function can be measured by direct and indirect methods. An indirect test, the measurement of *fecal elastase*, which is the standard screening test for pancreatic insufficiency, has a sensitivity and specificity >90%. When compared with a 72-hour fecal fat content in both pancreatic insufficient and sufficient patients, an elastase value of 100 μg/g stool has a 99% predictive value in ruling out pancreatic insufficiency based on an abnormal fecal fat finding. Falsely abnormal results can occur in many enteropathies and when the stool is very loose.

DIRECT TESTS

Classically, a triple-lumen tube was used to isolate the pancreatic secretions in the duodenum. Measurement of bicarbonate concentration and enzyme activity (*trypsin*, *chymotrypsin*, *lipase*, and *amylase*) is performed on the aspirated secretions. This test is cumbersome and infrequently used in children. Endoscopic collection of pancreatic secretions after stimulation with secretin and/or cholecystokinin is the commonly used direct test.

A 72-hour stool collection for quantitative analysis of fat content is the gold standard for the diagnosis of *malabsorption*. The collection can be performed at home, and the parent is asked to keep a careful dietary record, from which fat intake is calculated. A preweighed, sealable plastic container is used, which the parent keeps in the freezer. Freezing helps to preserve the specimen and reduce odor. Infants are dressed in disposable diapers with the plastic side facing the skin so that the complete sample can be transferred to the container. Normal fat absorption is >93% of intake. The presence of fat malabsorption does not differentiate between pancreatic dysfunction and enteropathies, such as celiac disease. Qualitative examination of the stool for microscopic fat globules can give false-positive and false-negative results.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 397
Disorders of the Exocrine Pancreas

Steven L. Werlin and Michael Wilschanski

DISORDERS ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Other than cystic fibrosis (CF), conditions that cause pancreatic insufficiency are very rare in children. They include Shwachman-Diamond syndrome (SDS), Johanson-Blizzard syndrome, Ivemark syndrome, Pearson syndrome, isolated enzyme deficiencies (see Chapter 385.8), enterokinase deficiency, chronic pancreatitis, protein-calorie malnutrition (see Chapters 64 and 385.7), and IMNEPD (infantile onset multisystem neurologic, endocrine, and pancreatic disease).

CYSTIC FIBROSIS

See Chapter 454.

By the end of the first year of life, 85–90% of children with CF have pancreatic insufficiency, which, if untreated, will lead to malnutrition. Treatment of the associated pancreatic insufficiency leads to improvement in absorption, better growth, and more normal stools. Pancreatic function can be monitored in children with CF with serial measurements of fecal elastase. Between 10–15% of children present with a *neonatal* intestinal obstruction called **meconium ileus**; in later life, a common intestinal complication is **distal intestinal obstruction syndrome,** which is unique to CF.

Ten percent of CF patients develop severe liver disease. Between 10–15% of CF patients are pancreatic sufficient, and their presentation tends to be later in life, including recurrent pancreatitis, male infertility, and chronic bronchiectasis. CF is part of the newborn screen in every state in the United States and in most countries in the Western world. Pathogenic gene variant specific therapy has caused great improvements in pulmonary function and weight gain, which is probably a direct effect on the gastrointestinal tract. The first drug to be released, Ivacaftor, reduced the number of episodes of pancreatitis in CF patients who were prone to recurrent pancreatitis; in younger patients, fecal elastase was significantly increased.

SHWACHMAN-DIAMOND SYNDROME

See Chapter 171.

SDS is an autosomal recessive syndrome (1/20,000 births) caused by a pathogenic variant of the Shwachman-Bodian-Diamond syndrome *(SBDS)* gene on chromosome 7, which causes ribosomal dysfunction in 90–95% of patients. Signs and symptoms of SDS include pancreatic insufficiency, neutrophil chemotaxis defects, metaphyseal dysostosis, failure to thrive, short stature, and neutropenia, which may be cyclic. Some patients with SDS have liver or kidney involvement, dental disease, or learning difficulty. SDS is a common cause of congenital neutropenia.

Patients typically present in infancy with poor growth and steatorrhea. More varied phenotypes have been described, including absence of pancreatic lipomatosis on imaging, normal fecal elastase levels, and normal skeletal survey. These children can be readily differentiated from those with CF by their normal sweat chloride levels, lack of pathogenic variants in the CF gene, characteristic metaphyseal lesions, and fatty pancreas characterized by a hypodense appearance on CT and MRI scans (Fig. 397.1).

Despite adequate pancreatic replacement therapy and correction of malabsorption, poor growth commonly continues. Pancreatic insufficiency is often transient, and steatorrhea frequently spontaneously improves with age. Recurrent pyogenic infections (otitis media, pneumonia, osteomyelitis, dermatitis, sepsis) are frequent and are a common cause of death. Thrombocytopenia is found in 70% of patients and anemia in 50%. Development of aplastic anemia or a *myelodysplastic syndrome* can occur, with transformation to *acute myeloid leukemia* in 24%. The pancreatic acini are replaced by fat with little fibrosis. Islet cells and ducts are normal. Bone marrow transplant is the treatment of choice in patients who develop acute myeloid leukemia.

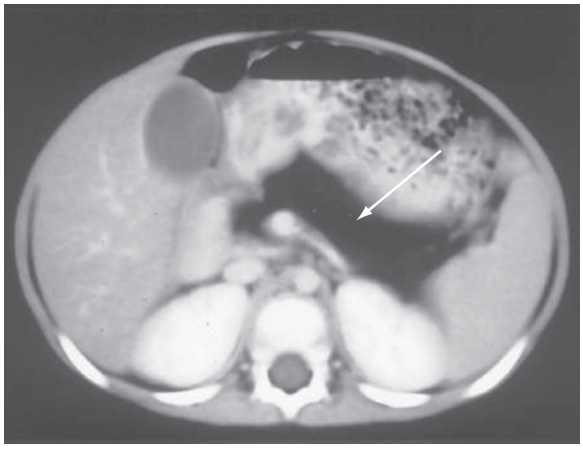

Fig. 397.1 CT appearance of the pancreas in a patient with Shwachman-Diamond syndrome. Note that the pancreas *(arrow)* retains a typical size and shape, but it is highly fatty and therefore appears as a very low-density structure. *(Courtesy Prof. Peter Durie, Hospital for Sick Children, Toronto, Ontario.)*

PEARSON SYNDROME

Pearson (marrow-pancreas) syndrome is caused by a contiguous mitochondrial gene depletion involving several mitochondrial genes affecting oxidative phosphorylation, which manifests in infants with severe macrocytic anemia and variable thrombocytopenia. The bone marrow demonstrates vacuoles in erythroid and myeloid precursors as well as ringed sideroblasts. In addition to its role in severe bone marrow failure, pancreatic insufficiency contributes to growth failure. Mitochondrial DNA mutations are transmitted through maternal inheritance to both sexes or are sporadic.

JOHANSON-BLIZZARD SYNDROME

The features of Johanson-Blizzard syndrome include exocrine pancreatic deficiency, aplasia or hypoplasia of the alae nasi, congenital deafness, hypothyroidism, developmental delay, short stature, ectodermal scalp defects, absence of permanent teeth, urogenital malformations, and imperforate anus. This syndrome is caused by a pathogenic variant in the *UBR1* gene found on chromosome 15.

ISOLATED ENZYME DEFICIENCIES

Isolated deficiencies of trypsinogen, enterokinase, lipase, and colipase have been reported. Although enterokinase is a brush-border enzyme, deficiency causes pancreatic insufficiency because enterokinase is required to activate trypsinogen to trypsin in the duodenum. Deficiencies of trypsinogen or enterokinase manifest with failure to thrive, hypoproteinemia, and edema. Isolated amylase deficiency is typically developmental and resolves by age 2-3 years.

OTHER SYNDROMES ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Pancreatic agenesis, congenital pancreatic hypoplasia, and congenital rubella are rare causes of pancreatic insufficiency. Pancreatic insufficiency has also been reported in celiac disease and inflammatory bowel disease. It may occur in duodenal atresia and stenosis and may also be seen in infants with familial or nonfamilial hyperinsulinemic hypoglycemia after a 95–100% pancreatectomy to control hypoglycemia. Pathogenic variants in at least six genes have been described. Pancreatic insufficiency, which may be found in children with celiac disease and undernutrition, recovers with nutritional rehabilitation.

Infantile onset multisystem neurology endocrine and pancreatic disease (IMNEPD) is a rare disease caused by pathogenic variants in the *PTRH2* gene. Neurologic features dominate the phenotype (microcephaly, intellectual disability, cerebellar atrophy, deafness, and neuropathy), but pancreatic insufficiency is seen in most patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 398

Treatment of Pancreatic Insufficiency

Michael Wilschanski and Steven L. Werlin

The most important treatment of pancreatic insufficiency (PI) is pancreatic enzyme replacement therapy (PERT). In modern enzyme capsules, the enzymes are enterically coated to protect the enzymes from degradation by gastric acid and from autodigestion in the small intestine. It is common for patients to change from one product to another using a 1:1 lipase ratio and then titrating for maximum efficacy (Table 398.1).

The North American CF Foundation has published dosing guidelines based on age and fat ingestion (Table 398.2). Because these products contain excess protease compared with lipase, the dosage is estimated from the lipase requirement. The final dosage of PERT for children is often established by trial and error. An adequate dose is one that is followed by resumption of normal growth and the return of stools to normal fat content, which, when desired, can be verified by a 72-hour fecal fat collection and normalization of stool consistency and color. Because there is no elastase in enzyme preparations, fecal elastase cannot be used to monitor appropriateness of PERT dosage. Enzyme replacement should be divided and given at the beginning of and during the meal. Enzymes should not be chewed, crushed, or dissolved in food, which would allow gastric acid to penetrate the enteric coating and destroy the enzymes. Enzymes must also be given with snacks that contain fat. Increasing enzyme supplements beyond the recommended dose does not improve absorption, might retard growth, and can cause fibrosing colonopathy (see later).

Table 398.1 FDA-Approved Pancreatic Enzyme Replacement Products for Exocrine Pancreatic Insufficiency*

DRUG	AVAILABLE STRENGTHS
IMMEDIATE-RELEASE	
Viokace (Allergan)‡,§,‖	10,440 or 20,880 units of lipase¶
DELAYED-RELEASE	
Creon (AbbVie)	3,000, 6,000, 12,000, 24,000, or 36,000 USP units of lipase¶,**
Pancreaze (Janssen)	2,600, 4,200, 10,500, 16,800, or 21,000 units of lipase¶,**
Pertzye (Digestive Care)	4,000, 8,000, 16,000, or 24,000 units of lipase¶,**
Zenpep (Allergan)	3,000, 5,000, 10,000, 15,000, 20,000, 25,000, or 40,000 units of lipase¶,**

*Pancrelipase products are not interchangeable. All of these products contain a combination of porcine-derived lipases, proteases, and amylases.
‡Viokace is only approved for use in adults.
§Should be used in combination with a proton pump inhibitor to maximize absorption in the duodenum.
‖FDA-approved only for treatment of adults with EPI because of chronic pancreatitis or pancreatectomy.
¶Should not be crushed or chewed.
**Capsules can be opened and contents sprinkled on soft acidic food (pH ≤ 4.5) such as applesauce.
From The Medical Letter. Pancreatic enzyme replacement products. Med Lett. 2017;59(1531):170.

Table 398.2 Pancreatic Enzyme Replacement Therapy: North American CF Foundation Consensus Statement

Infants (up to 12 mo)	2,000-4,000 U lipase/120 mL breast milk or formula
12 mo to 4 yr	1,000 U lipase/kg/meal initially, then titrate per response
Children >4 yr and adults	500 U lipase/kg/meal initially, up to maximum of 2,500 U lipase/kg/meal or 10,000 U lipase/kg/day or 4,000 U lipase/g fat ingested per day

PLUS: one half the standard meal dose to be given with snacks.

A major concern has been the ingestion of enzymes by infants. The importance of correct enzyme ingestion in infants and children is obvious, but there may be difficulty in feeding the infant microspheres, however small they may be. Enterically coated microspheres can be mixed with applesauce for oral use or crushed for use in tube feeding. Patients treated with this approach do achieve growth and weight gain. Pancreatic enzymes specifically prepared for infants and young children with smaller granules have been developed.

Treatment of exocrine PI by oral enzyme replacement usually corrects protein malabsorption, but steatorrhea is difficult to correct completely. Factors contributing to fat malabsorption include inadequate dosage, incorrect timing of doses in relation to food consumption or gastric emptying, lipase inactivation by gastric acid, and the observation that *chymotrypsin* in the enzyme preparation digests and thus inactivates *lipase*.

When adequate fat absorption is not achieved, gastric acid neutralization with an H_2-receptor antagonist or, more commonly, a proton pump inhibitor, decreases enzyme inactivation by gastric acid and thus improves delivery of lipase into the intestine. Enteric coating also protects lipase from acid inactivation.

Untoward effects secondary to PERT include allergic reactions and kidney stones. Fibrosing colonopathy, consisting of colonic fibrosis and strictures, can occur 7-12 months after severe overdose of PERT. This iatrogenic complication is now very uncommon.

Fat-soluble vitamin supplements are required by PI patients because of the ongoing mild to moderate fat malabsorption that occurs despite PERT.

Knowledge of novel mechanisms affecting absorption, such as intestinal microbiota, may, in the future, be therapeutic targets in the treatment of exocrine pancreatic insufficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 399

Pancreatitis

399.1 Acute Pancreatitis

Steven L. Werlin and Michael Wilschanski

Acute pancreatitis (AP) is the most common pancreatic disorder in children; 50 or more cases are usually seen in major pediatric centers per year. In children, blunt abdominal injuries, multisystem disease such as the hemolytic uremic syndrome and inflammatory bowel disease, biliary stones or microlithiasis (sludging), and drug toxicity are the most common etiologies. Although many drugs and toxins can induce AP in susceptible persons, in children, valproic acid, L-asparaginase, 6-mercaptopurine, and azathioprine are the most common causes of drug-induced pancreatitis. Alcohol should be considered in adolescents. Other cases follow organ transplantation or are caused by infections, metabolic disorders, or mutations in susceptibility genes. Only 10–20% of cases are idiopathic (Table 399.1).

After an initial insult, such as ductal disruption or obstruction, there is premature activation of trypsinogen to trypsin within the acinar cell. Trypsin then activates other pancreatic proenzymes, leading to autodigestion, further enzyme activation, and release of active proteases. Lysosomal hydrolases co-localize with pancreatic proenzymes within the acinar cell. Pancreastasis (similar in concept to cholestasis) with continued synthesis of enzymes occurs. Lecithin is activated by phospholipase A_2 into the toxic lysolecithin. Prophospholipase is unstable and can be activated by minute quantities of trypsin. After the insult, cytokines and other proinflammatory mediators are released.

The healthy pancreas is protected from autodigestion by pancreatic proteases that are synthesized as inactive proenzymes; digestive enzymes that are segregated into secretory granules at pH 6.2 by low calcium concentration, which minimizes trypsin activity; the presence of protease inhibitors both in the cytoplasm and zymogen granules; and enzymes that are secreted directly into the ducts.

Histopathologically, interstitial edema appears early. Later, as the episode of pancreatitis progresses, localized and confluent necrosis, blood vessel disruption leading to hemorrhage, and an inflammatory response in the peritoneum can develop.

The diagnosis of pancreatitis in children is made when two of three of the following are present: abdominal pain; serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal; and imaging findings characteristic of, or compatible with, AP.

CLINICAL MANIFESTATIONS

The severity of AP in children has been defined by a consensus committee.

Mild Acute Pancreatitis: AP that is not associated with organ failure, local or systemic complications, and usually resolves within the first week after presentation. This is the most common form of pediatric AP.

The patient with mild AP has moderate to severe abdominal pain, persistent vomiting, and possibly fever. The pain is epigastric or in either upper quadrant and steady, often resulting in the child's assuming an antalgic position with hips and knees flexed, sitting upright, or lying on the side. The child is uncomfortable, irritable, and appears acutely ill. The abdomen may be distended and tender, and a mass may be palpable. The pain can increase in intensity for 24-48 hours, during which time vomiting may increase and the patient can require hospitalization for fluid and electrolyte therapy and analgesia. There is no other organ failure, and imaging does not demonstrate peri- or pancreatic necrosis. The prognosis for complete recovery in the acute uncomplicated case after 4-7 days is excellent.

Moderately Severe Acute Pancreatitis: AP with either transient organ failure/dysfunction (lasting <48 hours) or development of local or systemic complications, such as exacerbation of previously diagnosed comorbid disease (such as lung or kidney disease). Imaging may reveal sterile (peri-) pancreatic necrosis. The prognosis for these patients is also excellent, but recovery may be prolonged.

Severe Acute Pancreatitis: AP with development of other organ dysfunction (lung, cardiac, renal) that persists longer than 48 hours. Persistent organ failure may be single or multiple. Severe AP is uncommon in children. In this life-threatening condition, the patient is acutely ill with severe nausea, vomiting, and abdominal pain. Shock, high fever, jaundice, ascites, hypocalcemia, and pleural effusions can occur. A bluish discoloration may be seen around the umbilicus (Cullen sign) or in the flanks (Grey Turner sign). The pancreas is necrotic and can be transformed into an inflammatory hemorrhagic mass. The mortality rate, which is approximately 20%, is related to the systemic inflammatory response syndrome with multiple organ dysfunction, shock, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, gastrointestinal bleeding, and systemic or intraabdominal infection. The percentage of necrosis seen on CT and failure of pancreatic tissue to enhance on CT (suggesting necrosis) predicts the severity of the disease.

DIAGNOSIS

AP is usually diagnosed by measurement of serum lipase and amylase activities. Serum lipase is considered the test of choice for AP because it is more specific than amylase for acute inflammatory pancreatic disease and should be determined when pancreatitis is suspected. The serum lipase rises by 4-8 hours, peaks at 24-48 hours, and remains elevated 8-14 days longer than serum amylase. Serum lipase greater than 7 times the upper limit of normal obtained within 24 hours of presentation may predict a severe course. Serum lipase can be elevated in nonpancreatic diseases. The serum amylase level is typically elevated for up to 4 days. A variety of other conditions can also cause hyperamylasemia without pancreatitis (Table 399.2). Elevation of salivary amylase can mislead the clinician to diagnose pancreatitis in a child with abdominal pain. The laboratory can separate amylase isoenzymes into pancreatic and salivary fractions. Initially serum amylase levels are normal in 10–15% of patients.

Other laboratory abnormalities that may be present in AP include hemoconcentration, coagulopathy, leukocytosis, hyperglycemia, glucosuria, hypocalcemia, elevated γ-glutamyl transpeptidase, and hyperbilirubinemia.

X-ray of the chest and abdomen might demonstrate nonspecific findings such as atelectasis, basilar infiltrates, elevation of the hemidiaphragm, left- (rarely right-) sided pleural effusions, pericardial effusion, and pulmonary edema. Abdominal x-rays might demonstrate a sentinel loop, dilation of the transverse colon (cutoff sign), ileus, pancreatic calcification (if recurrent), blurring of the left psoas margin, a pseudocyst, diffuse abdominal haziness (ascites), and peripancreatic extraluminal gas bubbles.

CT has a major role in the diagnosis and follow-up of children with pancreatitis. Findings can include pancreatic enlargement; a hypoechoic, sonolucent edematous pancreas; pancreatic masses; fluid collections; and abscesses (Fig. 399.1). Normal imaging studies at the time of diagnosis are not uncommon. In adults, CT findings are the basis of a widely accepted prognostic system (Table 399.3). Ultrasonography is more sensitive than CT for the diagnosis of biliary stones. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are essential in the investigation of recurrent pancreatitis, nonresolving pancreatitis, and disease associated with gallbladder pathology. Endoscopic ultrasonography also helps visualize the pancreaticobiliary system. Complications of AP are noted in Table 399.4.

Table 399.1 Etiology of Acute and Recurrent Pancreatitis in Children

DRUGS AND TOXINS
Acetaminophen overdose
Alcohol
Anabolic androgenic steroids
L-Asparaginase
Azathioprine
Cannabis
Carbamazepine
Cimetidine
Cisplatin
Corticosteroids
Cytosine arabinoside
Dapsone
Didanosine
Enalapril
Erythromycin
Estrogen
Furosemide
Glucagon-like peptide-1 agents
Interferon-α
Isoniazid
Lamivudine
Lisinopril
6-Mercaptopurine
Methyldopa
Mesalamine
Metronidazole
Organophosphate poisoning
Pentamidine
Procainamide
Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir
Rifampin
Sulfonamides: mesalamine, 5-aminosalicytates, sulfasalazine, trimethoprim-sulfamethoxazole
Sulindac
Tetracycline
Thiazides
Valproic acid
Venom (spider, scorpion, Gila monster lizard)
Vincristine
Volatile hydrocarbons

GENETIC
Cationic trypsinogen gene *(PRSS1)*
Carboxypeptidase A1 (*CPA1*)
Chymotrypsin C gene *(CTRC)*
Cystic fibrosis gene *(CFTR)*
Trypsin inhibitor gene *(SPINK1)*

INFECTIOUS
Ascariasis
COVID-19
Coxsackie B virus
Echovirus
Enterovirus
Epstein-Barr virus
Hepatitides A, B
Herpes viruses
Influenzae A, B
Leptospirosis
Malaria
Measles
Mumps
Mycoplasma
Rabies
Rubella
Reye syndrome: varicella, influenza B
Septic shock
Thyroid fever

OBSTRUCTIVE
Ampullary disease
Ascariasis
Biliary tract malformations
Choledochal cyst
Choledochocele
Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge)
Duplication cyst
Endoscopic retrograde cholangiopancreatography (ERCP) complication
Pancreas divisum
Pancreatic ductal abnormalities
Postoperative
Sphincter of Oddi dysfunction
Tumor

SYSTEMIC DISEASE
Autoimmune pancreatitis (IgG4-related systemic disease)
Brain tumor
Collagen vascular diseases
Congenital partial lipodystrophy
Crohn disease
Diabetes mellitus (ketoacidosis)
Head trauma
Henoch-Schönlein purpura
Hemochromatosis
Hemolytic uremic syndrome
Hyperlipidemia: types I, IV, V
Hyperparathyroidism/hypercalcemia
Kawasaki disease
Malnutrition
Organic acidemia
Peptic ulcer
Periarteritis nodosa
Renal failure
Scorpion venom
Systemic lupus erythematosus
Transplantation: bone marrow, heart, liver, kidney, pancreas
Vasculitis

TRAUMATIC
Blunt injury
Burns
Child abuse
Hypothermia
Surgical trauma
Total-body cast

TREATMENT

The aims of medical management are to relieve pain (often needing opioids) and restore metabolic homeostasis. Analgesia should be given in adequate doses. Fluid, electrolyte, and mineral balance should be restored and maintained. Intravenous fluids (lactated Ringer's solution) is often required to correct hypovolemia because of poor fluid intake and the fluid losses secondary to capillary leak from the systemic inflammatory response syndrome. Excessive fluids should be avoided; fluid therapy should be titrated to improve vital signs and renal function. Nasogastric suction is useful in patients who are vomiting. Early refeeding decreases the complication rate and length of stay. In patients with pancreatitis who are not vomiting, oral nutrition should not be stopped. Recovery is usually complete within 4-5 days.

Prophylactic antibiotics are not recommended in inflammatory pancreatitis or with sterile necrosis, but broad-spectrum antibiotics are used to treat *infected* areas of pancreatic necrosis. Elevated serum procalcitonin levels suggest infection. Gastric acid secretion is suppressed with proton pump inhibitors. Enteral alimentation by mouth, nasogastric tube, or nasojejunal tube (in severe cases or for those intolerant of oral or nasogastric feedings) within 2-3 days of onset reduces the length of hospitalization, complication rate, and survival in patients with severe AP. In children, surgical therapy of nontraumatic AP is rarely required but may include drainage of necrotic material or abscesses. Endotherapy for common bile duct stones, ductal strictures, and for drainage of fluid collections is the standard of care when indicated.

Table 399.2 Differential Diagnosis of Hyperamylasemia

PANCREATIC PATHOLOGY
Acute or chronic pancreatitis
Complications of pancreatitis (pseudocyst, ascites, abscess)
Factitious pancreatitis
SALIVARY GLAND PATHOLOGY
Parotitis (mumps, *Staphylococcus aureus*, cytomegalovirus, HIV, Epstein-Barr virus)
Sialadenitis (calculus, radiation)
Eating disorders (anorexia nervosa, bulimia)
INTRAABDOMINAL PATHOLOGY
Biliary tract disease (cholelithiasis)
Peptic ulcer perforation
Peritonitis
Intestinal obstruction
Appendicitis
SYSTEMIC DISEASES
Metabolic acidosis (diabetes mellitus, shock)
Renal insufficiency, transplantation
Burns
Pregnancy
Drugs (morphine)
Head injury
Cardiopulmonary bypass

PROGNOSIS

Children with mild AP do well and recover within 4-5 days. When pancreatitis is associated with trauma or systemic disease, the prognosis is typically related to the associated medical conditions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

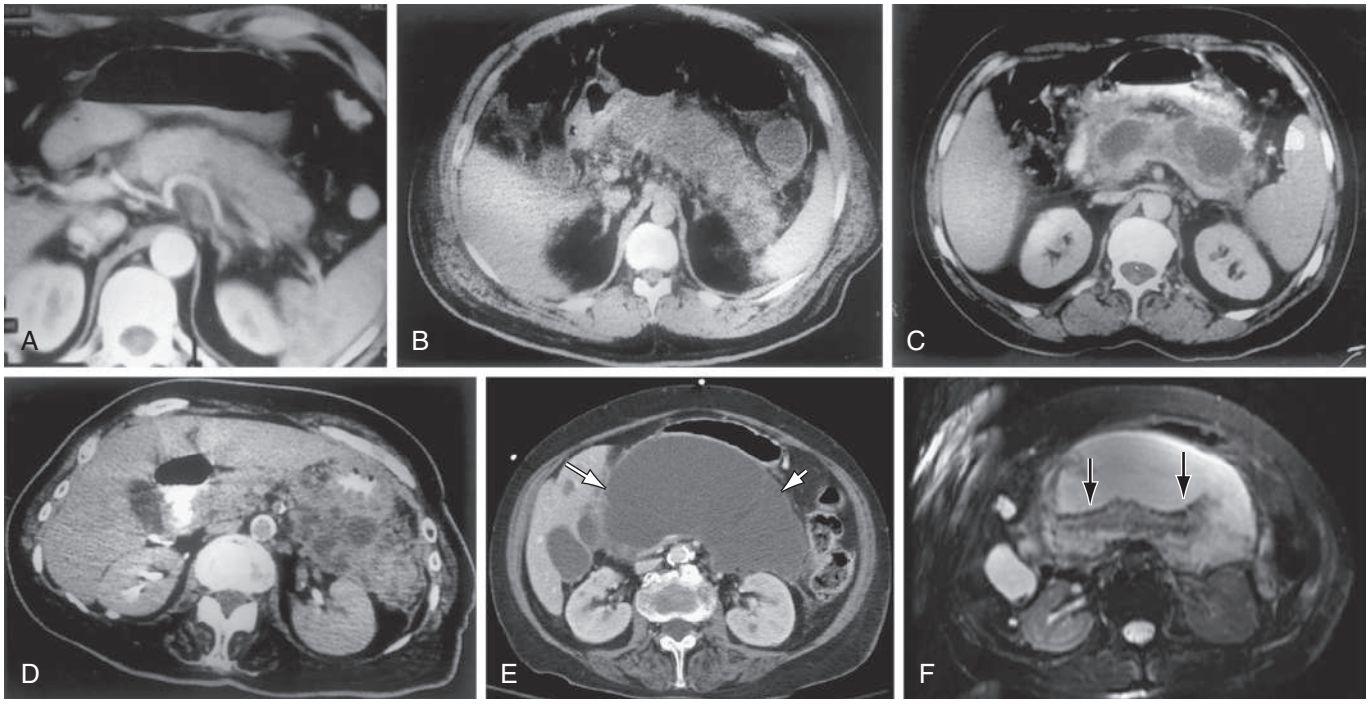

Fig. 399.1 CT and MRI appearance of pancreatitis. **A,** Mild acute pancreatitis. Arterial phase spiral CT. Diffuse enlargement of pancreas without fluid accumulation. **B,** Severe acute pancreatitis. Lack of enhancement of the pancreatic parenchyma because of the necrosis of the entire pancreatic gland. **C,** Pancreatic pseudocyst. A round fluid collection with thin capsule is seen within the lesser sac. **D,** Acute severe pancreatitis and peripancreatic abscess formation. Peripancreatic abscess formation is observed within the peripancreatic and the left anterior pararenal space. **E,** Pancreatic necrosis. A well-defined fluid attenuation collection in the pancreatic bed *(white arrows)* seen on contrast-enhanced CT imaging. **F,** The same collection is more complex appearing on the corresponding T2-weighted MR image. The internal debris and necrotic tissue are better appreciated because of the superior soft tissue contrast of MRI *(black arrows)*. *(**A-D** from Elmas N. The role of diagnostic radiology in pancreatitis. Eur J Radiol. 2001;38[2]:120–132. Figs. 1, 3b, 4a, and 5; E and F from Soakar A, Rabinowitz CB, Sahani DV. Cross-sectional imaging in acute pancreatitis. Radiol Clin North Am. 2007;45[3]:447–460. Fig. 14.)*

Table 399.3 Revised Definitions of Morphologic Features of Acute Pancreatitis

INTERSTITIAL EDEMATOUS PANCREATITIS
Acute inflammation of the pancreatic parenchyma and peripancreatic tissues but without recognizable tissue necrosis
CECT criteria
• Pancreatic parenchyma enhancement by intravenous contrast agent • No peripancreatic necrosis
NECROTIZING PANCREATITIS
Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
CECT criteria
• Lack of pancreatic parenchymal enhancement by intravenous contrast agent • Presence of findings of peripancreatic necrosis
ACUTE PANCREATITIS FLUID COLLECTION
Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. Applies only to areas of peripancreatic fluid seen within the first 4 wk after onset of interstitial edematous pancreatitis and without the features of a pseudocyst.
CECT criteria
• Occurs in the setting of interstitial edematous pancreatitis • Homogeneous collection with fluid density • Confined by normal peripancreatic fascial planes • No definable wall encapsulating the collection • Adjacent to pancreas (no intrapancreatic extension)
PANCREATIC PSEUDOCYST
An encapsulated collection of fluid with a well-defined inflammation wall, usually outside the pancreas, with little or no necrosis. Usually occurs more than 4 wk after onset of interstitial edematous pancreatitis.
CECT criteria
• Well circumscribed; usually round or oval • Homogeneous fluid density • No nonliquid component • Well-defined wall that is wholly encapsulated • Maturation usually needs >4 wk after onset of acute pancreatitis; occurs after interstitial edematous pancreatitis
ACUTE NECROTIC COLLECTION
A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can include the pancreatic parenchyma and/or the peripancreatic tissue.
CECT criteria
• Occurs only in the setting of acute necrotizing pancreatitis • Heterogeneous and nonliquid density of varying degrees in different locations (some seem homogeneous early in their course) • No definable wall encapsulating the collection • Intrapancreatic and/or extrapancreatic
WALLED-OFF NECROSIS
A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. Usually occurs >4 wk after onset of necrotizing pancreatitis.
CECT criteria
• Heterogeneous with liquid and nonliquid density, with varying locations (some can seem homogeneous) • Well-defined wall that is wholly encapsulated • Intrapancreatic and/or extrapancreatic • Maturation usually needs 4 wk after onset of acute necrotizing pancreatitis

CECT, Contrast-enhanced CT.
From PA Banks, TL Bollen, C Dervenis, et al. The Acute Pancreatitis Classification Working Group Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013;62:102–111.

Table 399.4 Complications of Acute Pancreatitis

LOCAL
Pseudocyst Sterile necrosis Infected necrosis Abscess GI bleeding • Pancreatitis-related • Splenic artery or splenic artery pseudoaneurysm rupture • Splenic vein rupture • Portal vein rupture • Splenic vein thrombosis leading to gastroesophageal variceal bleeding • Pseudocyst or abscess hemorrhage • Postnecrosectomy bleeding Nonpancreatitis-related • Mallory-Weiss tear • Alcoholic gastropathy • Stress-related mucosal gastropathy Splenic complications • Infarction • Rupture • Hematoma • Splenic vein thrombosis Fistulization to or obstruction of the small intestine or colon Hydronephrosis
SYSTEMIC
Respiratory failure Renal failure Shock Hyperglycemia Hypocalcemia Disseminated intravascular coagulation Fat necrosis (subcutaneous nodules) Retinopathy
PSYCHOSIS

From Tenner S, Steinberg WM. Acute pancreatitis. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease,* 10th ed. Philadelphia: Elsevier; 2016: Box 58.7, p. 991.

399.2 Acute Recurrent and Chronic Pancreatitis

Steven L. Werlin and Michael Wilschanski

Acute recurrent pancreatitis (ARP) is defined as ≥2 distinct episodes of AP with intervening return of enzymes to baseline. Chronic pancreatitis (CP) is defined as the presence of typical abdominal pain plus characteristic imaging findings including pancreatic calcifications, inflammation and fibrosis, or exocrine insufficiency plus imaging findings, or endocrine insufficiency plus imaging findings. Most children with CP describe a history of ARP and tend to be older at the time of diagnosis compared with children with ARP, suggesting that ARP and CP are a disease continuum. CP without prior AP or ARP may occur.

ARP and CP in children are often caused by pathogenic gene variants or congenital anomalies of the pancreatic or biliary ductal system (Tables 399.5 and 399.6). Variants in *PRSS1* (cationic trypsinogen), *SPINK1* (pancreatic trypsin inhibitor), in the cystic fibrosis gene *(CFTR)*, *CPA1*, and chymotrypsin C *(CTRC)* may all lead to CP (Fig. 399.2).

Cationic trypsinogen has a trypsin-sensitive cleavage site. Loss of this cleavage site in the abnormal protein permits uncontrolled activation of trypsinogen to trypsin, which leads to autodigestion of the pancreas. Pathogenic variants in *PRSS1* act in an autosomal dominant fashion with incomplete penetrance and variable expressivity. Symptoms often begin in the first decade but are usually mild at the onset.

Although spontaneous recovery from each attack occurs in 4-7 days, episodes become progressively more severe. Hereditary pancreatitis may be diagnosed by the presence of the disease in successive generations of a family. An evaluation during symptom-free intervals may be unrewarding until calcifications, pseudocysts, or pancreatic exocrine and endocrine insufficiency develop (Fig. 399.3; see Fig. 399.2). CP is a risk factor for the development of pancreatic cancer. Multiple variants of *PRSS1* associated with hereditary pancreatitis have been described.

Trypsin inhibitor acts as a fail-safe mechanism to prevent uncontrolled autoactivation of trypsin. Pathogenic variants in *SPINK1* have been associated with ARP or CP. In *SPINK1* variants, this fail-safe mechanism is lost; this gene may be a modifier gene and not the direct etiologic factor.

Pathogenic variants of *CFTR* that are associated with pancreatic sufficiency, or which do not typically produce pulmonary disease, can cause CP, possibly because of ductal obstruction. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than those with genotypes associated with moderate to severe phenotypes.

Pathogenic variants in the chymotrypsin C gene, which cause a loss of function, may also cause recurrent pancreatitis. Indications for genetic testing include recurrent episodes of AP, CP, a family history of pancreatitis, or unexplained pancreatitis in children. Pathogenic variants in carboxypeptidase A1 *(CPA1)* have been associated with early onset (<10 years) of CP.

Other conditions associated with chronic, relapsing pancreatitis are hyperlipidemia (types I, IV, and V), hyperparathyroidism, and ascariasis. Previously, most cases of recurrent pancreatitis in childhood were considered idiopathic; with the discovery of gene families associated with recurrent pancreatitis, this has changed. Congenital anomalies of the ductal systems, such as pancreas divisum, are also more common than previously recognized.

Table 399.5 Factors Contributing to the Etiology of Chronic Pancreatitis

	NO. (%)*
Chronic pancreatitis patients with history of ≥1 episode acute pancreatitis	73 (96)
Risk factors for pancreatitis	
Genetic	*51 (67)*
PRSS1	33 (43)
SPINK1	14 (19)
CFTR	11 (14)
CTRC	2 (3)
CPA1	~1%
Autoimmune	*3 (4)*
Obstructive	*25 (33)*
Pancreas divisum	15 (20)
Sphincter of Oddi dysfunction	1 (1)
Gallstones	3 (4)
Pancreatic duct malunion	2 (3)
Pancreatic duct obstruction	1 (1)
Other	*5 (7)*
Toxic/metabolic	8 (11)
Alcohol (determined by doctor)	1 (1)
Passive smoking (exposure)	3 (4)
Hyperlipidemia	1 (1)
Medication	1 (1)
Metabolic disease	1 (1)
None cited	8 (11)

PRSS1, serine protease 1; SPINK1, pancreatic trypsin inhibitor; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; CPA1, carboxypeptidase A1.
*The total exceeds 100% because some children have more than one factor.
Modified from Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr*. 2015;166:890–896. Table II.

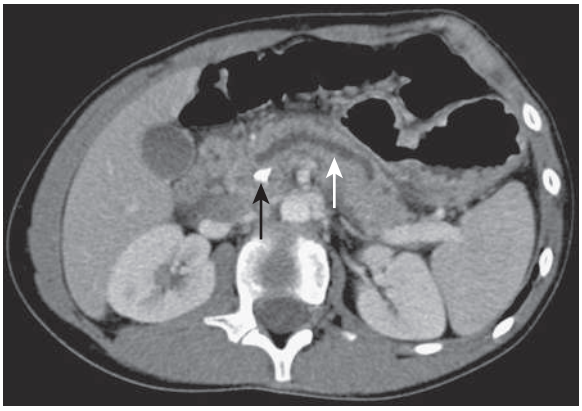

Fig. 399.2 Chronic pancreatitis. Computed tomogram showing calcification in the head of the pancreas *(black arrow)* and dilated pancreatic duct *(arrow)* in a 12-yr-old patient. *(Courtesy Dr. Janet Reid. From Wyllie R, Hyams JS, eds. Pediatric Gastrointestinal and Liver Disease, 3rd ed. Philadelphia: WB Saunders, 2006.)*

Table 399.6 Classification of Chronic Pancreatitis

CHRONIC CALCIFYING PANCREATITIS	CHRONIC OBSTRUCTIVE PANCREATITIS	STEROID-RESPONSIVE PANCREATITIS
Alcohol	Stricture	Autoimmune Pancreatitis
Smoking	Blunt trauma	Type 1
Genetic	Endoscopic stenting	Type 2 (IDCP)
Idiopathic	Acute pancreatitis	
Juvenile-onset	Anastomotic stricture	
Tropical	Tumor	
	Adenocarcinoma	
	IPMN	
	Serous cystadenoma Islet cell tumor	

IDCP, Idiopathic duct-centric pancreatitis; IPMN, intraductal papillary mucinous neoplasm.
From Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016;387:1957–1966. Fig 1.

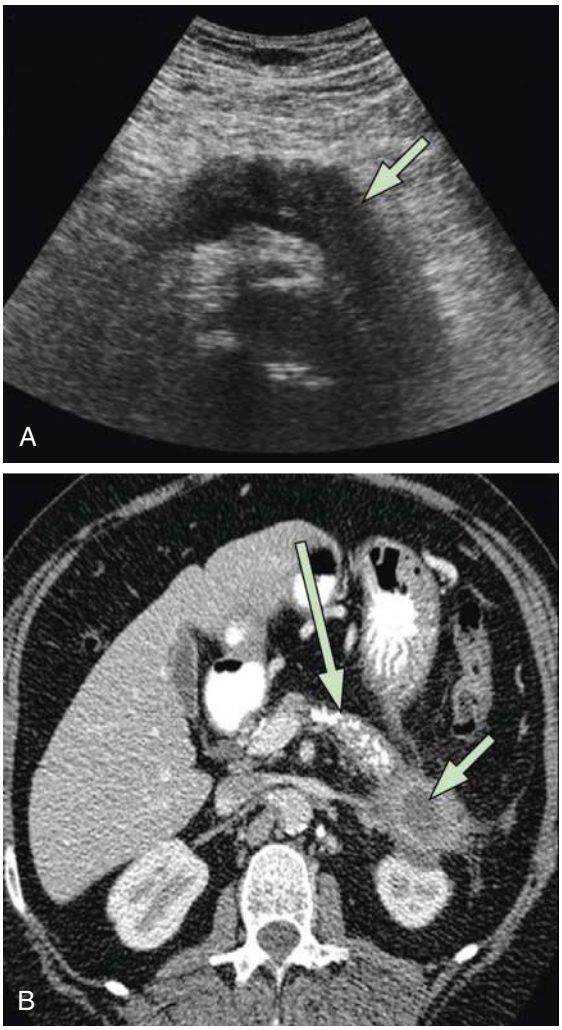

Fig. 399.3 Examples of ultrasound and multidetector images in patients with chronic pancreatitis. **A,** Transabdominal ultrasound scan showing a uniformly swollen, hypoechoic pancreas *(arrow)* typical of autoimmune pancreatitis. **B,** Multidetector CT showing pancreatic calculi in an atrophic pancreas *(long arrow)* and a pseudocyst at the tail of the pancreas *(short arrow). (From Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. Lancet. 2011;377:1184–1197. Fig. 5.)*

Autoimmune pancreatitis (AIP) typically manifests with jaundice, abdominal pain, and weight loss. The pancreas is typically enlarged and is hypodense on CT. The pathogenesis is unknown. **Type 1** is a systemic disease and is associated with high serum immunoglobulin G4 (IgG4). In addition to pancreatitis in type 1 disease, the patient may have retroperitoneal fibrosis, orbital inflammation, aortitis, sclerosing cholangitis, cutaneous vasculitis, pulmonary fibrosis, and sialadenitis. These extrapancreatic features may also be present in the absence of pancreatitis (Table 399.7). Tissue biopsy shows fibrosis, plasmacytosis, and positive staining for IgG4; serum IgG4 levels are not always elevated.

Type 2 is limited to diffuse or focal involvement of just the pancreas. IgG4 levels are normal. *Both types respond to steroids*. Children with AIP typically have type 2.

Table 399.7 Chronic Disorders Recognized to Be Part of IgG4-Related Disease

Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Fibrosing mediastinitis
Hypertrophic pachymeningitis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)
Küttner tumor (affecting the submandibular glands)
Mikulicz disease (affecting the salivary and lacrimal glands)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Retroperitoneal fibrosis (Ormond disease)
Riedel thyroiditis
Sclerosing mesenteritis
Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease

From Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet.* 2015;385:1460–1471. Panel 1.

Juvenile tropical pancreatitis is the most common form of CP in developing equatorial countries. The highest prevalence is in the Indian state of Kerala. Tropical pancreatitis occurs during late childhood or early adulthood, manifesting with abdominal pain and irreversible pancreatic insufficiency followed by diabetes mellitus within 10 years. The pancreatic ducts are obstructed with inspissated secretions, which later calcify. This condition is associated with pathogenic variants in *SPINK* in 50% of cases.

A thorough diagnostic evaluation of every child with more than one episode of pancreatitis is indicated. Serum lipid, calcium, and phosphorus levels are determined. Stools are evaluated for ascaris, and a sweat test is performed. Plain abdominal films are evaluated for the presence of pancreatic calcifications. Abdominal ultrasound or CT scanning is performed to detect the presence of a pseudocyst. The biliary tract is evaluated for the presence of stones. After genetic counseling, evaluation of *PRSS1*, *SPINK1*, *CFTR*, *CPA1*, and *CRTC* genotypes can be measured. Electrophysiologic tests such as nasal potential difference testing may be recommended when the diagnosis of cystic fibrosis (CF) is uncertain.

MRCP and ERCP are techniques that can be used to define the anatomy of the gland and are mandatory if surgery is considered. MRCP is the test of choice when endotherapy is not being considered and should be performed as part of the evaluation of any child with idiopathic, nonresolving, or recurrent pancreatitis and in patients with a pseudocyst before drainage. In these cases, a previously undiagnosed anatomic defect that may be amenable to endoscopic or surgical therapy may be detected. Endoscopic treatments include sphincterotomy, stone extraction, drainage of pseudocysts, and insertion of pancreatic or biliary endoprosthetic stents. These treatments allow the successful nonsurgical management of conditions previously requiring surgical intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 400

Pancreatic Fluid Collections

Michael Wilschanski and Steven L. Werlin

Pancreatic pseudocyst formation is an uncommon sequela to acute or chronic pancreatitis. A pancreatic pseudocyst is a circumscribed collection of fluid rich in pancreatic enzymes, blood, and necrotic tissue, typically located in the lesser sac of the abdomen. Pancreatic pseudocysts are usually complications of pancreatitis, although in children they frequently occur after abdominal trauma. They can enlarge or extend in almost any direction, thus producing a wide variety of symptoms (Fig. 400.1; see also Fig. 399.1C).

A pancreatic pseudocyst is suggested when an episode of pancreatitis fails to resolve or when a mass develops after an episode of pancreatitis. Clinical features usually include pain, nausea, and vomiting, but many patients are asymptomatic. The most common signs are a palpable mass in 50% of patients and jaundice in 10%. Other findings include ascites and pleural effusions (usually left-sided).

Pancreatic pseudocysts can be detected by transabdominal ultrasonography, CT scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). Because of its ease, availability, and reliability, ultrasonography is the first choice. Sequential ultrasonography studies have demonstrated that most small pseudocysts (<6 cm) resolve spontaneously. It is recommended that the patient with acute pancreatitis undergo an ultrasonographic evaluation 4 weeks after resolution of the acute episode for an evaluation of possible pseudocyst formation.

TREATMENT OF FLUID COLLECTIONS AND NECROSIS

Percutaneous and endoscopic drainage of pseudocysts have replaced open surgical drainage, except for complicated or recurrent pseudocysts. Whereas a pseudocyst must be allowed to mature for 4-6 weeks before surgical drainage is attempted, percutaneous or endoscopic drainage can be attempted earlier. In some cases, endoscopic creation of a cyst-gastrostomy is performed. When a surgical treatment is planned, an MRCP or ERCP is performed to define anatomic abnormalities and aid the surgeon in planning the approach. EUS is helpful when an endoscopic approach is chosen.

Necrotizing pancreatitis includes both pancreatic gland necrosis and peripancreatic fat necrosis. In the initial phases, the necrotic collection is a mix of semisolid and solid tissue. Over a period of 4 weeks or longer, the collection becomes more liquid and becomes encapsulated by a visible wall. At this point, the process is termed *walled-off pancreatic necrosis*. Sterile necrosis does not require therapy except in the rare case of a collection that obstructs a nearby viscus (e.g., duodenal, bile duct, or gastric obstruction).

The development of *infected* necrosis is the main indication for broad-spectrum antibiotic therapy. The development of fever, leukocytosis, an elevated procalcitonin level, and increasing abdominal pain suggests infection of the necrotic tissue. A CT scan may reveal evidence of air bubbles in the necrotic cavity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

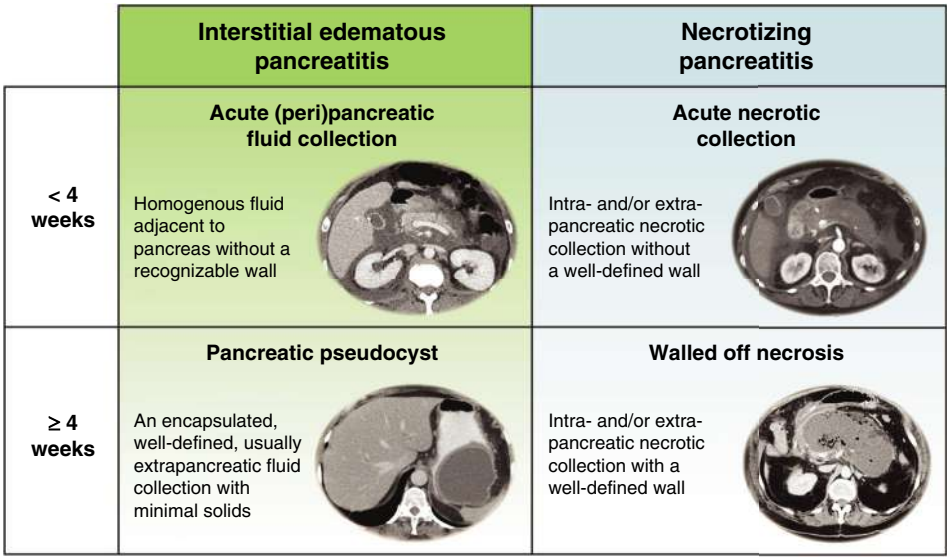

Fig. 400.1 Classification of acute pancreatitis and associated fluid collections. Based on international consensus according to the Acute Pancreatitis Classification Working Group (revised Atlanta criteria). *(From Trikudanathan, G, Wolbrink DRJ, van Santvoort HC, et al. Current concepts in severe acute and necrotizing pancreatitis: an evidence-based approach. Gastroenterol. 2019;156:1994–2007e3. Fig. 1.)*

Chapter 401

Pancreatic Tumors

Meghen B. Browning, Steven L. Werlin, and Michael Wilschanski

Pancreatic tumors can be of either endocrine or nonendocrine origin. Tumors of endocrine origin include gastrinomas and insulinomas, which are more typically seen in nonpancreatic sites. These occur in the autosomal dominantly inherited multiple endocrine neoplasia type 1 (MEN-1) and are often benign. Hypoglycemia accompanied by higher-than-expected insulin levels or refractory gastric ulcers (Zollinger-Ellison syndrome) indicate the possibility of a functional endocrine pancreatic tumor (see Chapter 381.1). The treatment of choice is surgical removal. If the primary tumor cannot be found, or if it has metastasized, cure might not be possible. Treatment with a high dose of a proton pump inhibitor to inhibit gastric acid secretion is then indicated. Insulinomas and persistent hyperinsulinemic hypoglycemia of infancy produce symptomatic hypoglycemia caused by pathogenic variants in a variety of genes, most commonly *GUUD1* and *KATP*. Massive subtotal or total pancreatectomy is the treatment of choice when medical treatment fails. These children might then develop pancreatic insufficiency and diabetes as a complication of surgery.

Nonfunctioning pancreatic endocrine tumors make up most of the remainder of the pancreatic endocrine tumors (PETs). Diagnosis is either incidental, because they tend to be asymptomatic, or made after the tumors are large enough to have mass effects. The nonfunctioning PETs, as well as the even-more-rare functioning PETs, are less likely to be histologically benign. Pancreatic tumors secreting a variety of hormones, including glucagon, somatostatin, parathyroid hormone, adrenocorticotropic hormone, and pancreatic polypeptide, have been described (Table 401.1). The treatment is surgical resection when possible.

The watery diarrhea–hypokalemia–acidosis syndrome is usually produced by the secretion of vasoactive intestinal peptide by a non–α-cell tumor (VIPoma). Vasoactive intestinal peptide levels are often, but not always, increased in the serum. Again, treatment is surgical removal of the tumor. When this is not possible, symptoms may be controlled by the use of octreotide acetate (cyclic somatostatin [Sandostatin]), a synthetic analog of somatostatin.

Pancreatoblastomas, pancreatic adenocarcinomas, and sarcomas of the pancreas are also rarely encountered. Pancreatoblastoma, a malignant embryonal tumor that secretes α-fetoprotein and can contain both endocrine and exocrine elements, is the most common pancreatic neoplasm in young children (<10 years of age). Genetic associations include familial adenomatous polyposis and Beckwith-Wiedemann syndromes. Presurgical chemotherapy should be considered for lesions not primarily resectable. Resection can be curative. The effectiveness of adjuvant chemotherapy is less clear. Sarcomas are very rarely primarily pancreatic but may include Ewing family tumors (Ewing sarcoma and primitive neuroectodermal tumor), rhabdomyosarcoma, or undifferentiated soft tissue sarcomas. They are treated with multimodality therapy, including chemotherapy and either resection or radiation. The pancreas can be a site of metastases for any of these entities. Histologically benign tumors, such as teratomas and vascular anomalies, may also rarely involve the pancreas.

Carcinoma of the exocrine pancreas, or ductal adenocarcinoma, is a major problem in adults, accounting for 2% of diagnoses and 5% of deaths from cancer. However, it is exceptionally rare in childhood. Pathogenic variants in the *PRSS1* and *MEN-1* genes lead to an increased incidence of pancreatic cancer in adult life but do not appear to account for pediatric cases. Acinar cell carcinoma is very rarely seen in children. The solid pseudopapillary tumor of the pancreas, also called *Frantz tumor*, is the most common pancreatic tumor in adolescents. It is a more indolent pancreatic carcinoma usually found in adolescent/young adult females. Typical presenting symptoms are abdominal pain, mass, or jaundice. The treatment of choice is total surgical removal. Prognosis is very good.

Pancreatic lesions in von Hippel-Lindau disease are usually benign and cystic. Cystadenomas, familial adenocarcinomas, and islet cell tumors are less common. Metastases have been reported, but effective adjuvant therapy has not been established.

Prognosis is good for completely resected endocrine tumors but very poor for sarcomas and carcinomas, except for rare subtypes. Children who survive partial or complete pancreatectomy may have decreased pancreatic exocrine and endocrine reserve.

Inflammatory myofibroblastic tumors (resembling IgG4-related lesions) may cause obstruction and be identified during evaluation for pain or jaundice. Pancreatic tumors and other entities, including intrapancreatic accessory spleens, may be found incidentally during imaging. Pancreatic imaging and biopsy when indicated confirm the diagnosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 401.1 Syndromes Associated with Pancreatic Neuroendocrine Tumors (pNETs)*

SYNDROME	INCIDENCE/10^6/YR	MALIGNANCY (%)	HORMONE
Insulinoma	1-2	<10	Insulin
Gastrinoma (ZES)	0.5-1.5	60–90	Gastrin
VIPoma (Verner-Morrison syndrome, WDHA, pancreatic cholera)	0.05-0.2	>60	VIP
Glucagonoma	0.01-0.1	50–80	Glucagon
Somatostatinoma	Rare	>70	Somatostatin
GRFoma	Unknown	>30	GH-RF
ACTHoma	Uncommon	>95%	ACTH
pNET secreting PTH-rP	Rare	84%	PTH-rP
Pancreatic carcinoid tumor	Rare (<1% of all carcinoids)	77%	Serotonin, tachykinins
pNET secreting renin	Rare	Unknown	Renin
pNET secreting erythropoietin	Rare	Unknown	Erythropoietin
pNET secreting luteinizing hormone	Rare	Unknown	Luteinizing hormone
pNET secreting cholecystokinin (CCKoma)	Rare	Unknown	CCK

*These syndromes may also be caused by a GI-NET (carcinoid).
GH-RF, Growth hormone–releasing factor; PP, pancreatic polypeptide; PTH-rP, parathyroid hormone–related protein; VIP, vasoactive intestinal polypeptide; WDHA, watery diarrhea, hypokalemia, achlorhydria; ZES, Zollinger-Ellison syndrome; ACTH, adrenocorticotropic hormone.
From Jensen RT, Norton JA, Oberg K. Neuroendocrine tumors. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 33.1.

Section 6

The Liver and Biliary System

Chapter 402

Morphogenesis of the Liver and Biliary System

Stacey S. Huppert and William F. Balistreri

During the early embryonic process of gastrulation, the three embryonic germ layers (endoderm, mesoderm, and ectoderm) are formed. The definitive endoderm is an epithelial sheet that occupies the ventral surface of the early embryo by approximately the second week of human gestation. The digestive and respiratory organs, as well as the thymus and thyroid, are all derived from the definitive endoderm.

Hepatogenesis can be divided into three distinct processes. First, through unknown mechanisms, the ventral foregut endoderm intrinsically acquires *competence* to receive signals arising from the cardiac mesoderm and the septum transversum mesenchyme (Fig. 402.1A). The thickened epithelium of the ventral foregut endoderm is visible morphologically just before the onset of hepatic-specific gene expression. "Pioneer" transcription factors, including the Forkhead Box A (FOXA) and GATA protein families, have the unique ability to engage closed and silent chromatin locally, converting it to an open and permissive chromatin state marking genes as competent. However, hepatic-specific genes will be expressed only if they are induced by additional transcription factors. There are no known hepatic-specific molecular markers associated with the morphologic initial ventral foregut endoderm thickening.

Signals originating from the mesoderm lead to *specification* of cells that have the potential to form the liver and activate hepatic-specific genes (see Fig. 402.1B). Fibroblast growth factor (FGF) from the cardiac mesoderm and bone morphogenetic protein (BMP) from septum transversum mesenchyme cells coordinately specify the hepatic—and suppress the pancreas—transcriptional programs in the cells of the ventral foregut endoderm.

The newly specified hepatic cells initially compose a columnar epithelium that transitions to a single-layer of pseudostratified epithelium attached to a laminin-containing basement membrane. The basement membrane is then broken down, and the hepatic cells delaminate from the ventral foregut endoderm and migrate in a rostral ventral direction into the septum transversum in the third to fourth week of human gestation to initiate liver *morphogenesis* (see Fig. 402.1C). After foregut closure, the hepatic cells proliferate and continue to migrate into the surrounding mesenchyme, interacting to form a bud that becomes vascularized. The rostral hepatic bud gives rise to the liver, including the intrahepatic bile ducts, and the caudal hepatic bud develops into the gallbladder and the extrahepatic common bile duct. The gallbladder anlage is visible around the seventh week of human gestation. Careful orchestration of signals between epithelial, mesenchymal, and endothelial cells are required to guide hepatogenesis (Table 402.1).

HEPATIC ARCHITECTURE

Within the ventral mesentery, proliferation of migrating cells forms anastomosing hepatic cords, with the network of primitive liver progenitors (i.e., hepatoblasts), sinusoids, and septal mesenchyme establishing the basic architectural pattern of the liver lobule (Fig. 402.2). The hepatic lobules are identifiable in the sixth week of human gestation. The bile canalicular structures, including microvilli and junctional complexes, are specialized intralobular network channels; these appear very early in gestation, and large canaliculi bounded by several hepatocytes are seen by the sixth to seventh week of human gestation.

The *caudal* part (pars cystica) of the hepatic diverticulum becomes the gallbladder, cystic duct, and common bile duct. The distal portions of the right and left hepatic ducts develop from the extrahepatic ducts, whereas the proximal portions develop from the first intrahepatic ductal plates. The extrahepatic bile ducts and the developing intrahepatic biliary tree maintain luminal continuity and patency from the beginning of organogenesis (see Fig. 402.2C).

Fetal hepatic blood flow is derived from the hepatic artery and from the portal and umbilical veins, which form the portal sinus. The portal venous inflow is directed mainly to the right lobe of the liver and umbilical flow primarily to the left. The ductus venosus shunts blood from the portal and umbilical veins to the hepatic vein, bypassing the

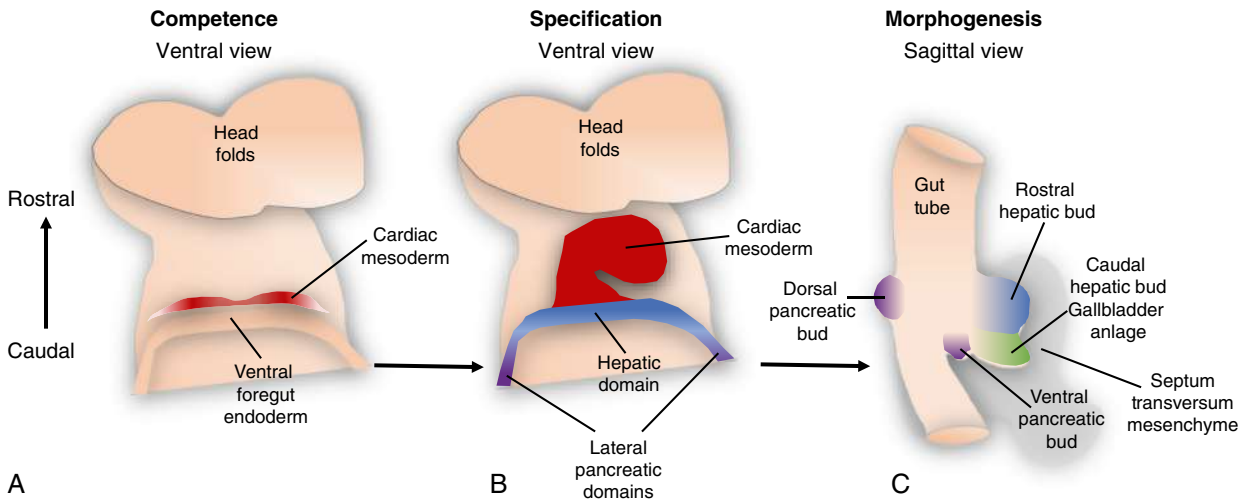

Fig. 402.1 Processes involved in early liver development. A, The ventral foregut endoderm acquires *competence* to receive signals arising from the cardiac mesoderm and septum transversum mesenchyme. B, Specific cells of the ventral foregut endoderm undergo *specification* and activation of liver-specific genes under the influence of mesodermal signals. C, Liver *morphogenesis* is initiated as the newly specified cells migrate into the septum transversum under the influence of signaling molecules and extracellular matrix released by septum transversum mesenchymal cells and of primitive endothelial cells.

Table 402.1 Selected Growth Factors, Receptors, Protein Kinases, and Transcription Factors Required for Normal Liver Development in Animal Models

INDUCTION OF HEPATIC FATE THROUGH CARDIAC MESODERM
• Fibroblast growth factors (FGFs) 1, 2, 8
• FGF receptors 1, 4
INDUCTION OF HEPATIC FATE THROUGH SEPTUM TRANSVERSUM
• Bone morphogenetic proteins 2, 4, 7
STIMULATION OF HEPATOBLAST GROWTH AND PROLIFERATION
• Hepatocyte growth factor (HGF)
• HGF receptor c-met
• "Pioneer" transcription factors Foxa1, Foxa2, FoxA3, and Gata4, Gata6
• Transcription factors Xbp1, Foxm1b, Hlx, Hex, Prox1, Tbx3
• Wnt signaling pathway, β-catenin
SPECIFICATION OF HEPATOCYTE LINEAGE
• HGF
• Transcription factors
• Hepatocyte nuclear factors (HNFs) 1α, 4α, 6, Cebpa
SPECIFICATION OF CHOLANGIOCYTE LINEAGE
• Jagged 1 (Notch ligand) and Notch receptors 1, 2
• Transforming growth factor-β and its downstream effectors Smad 2, Smad 3
• Hippo/Yap
• HNF6, HNF1β, Cebpb, Sox9, Sox4

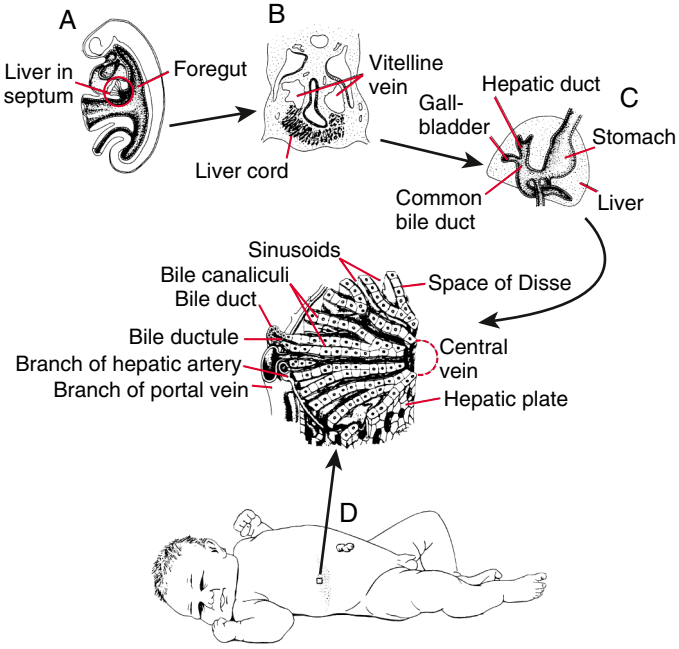

Fig. 402.2 Hepatic morphogenesis. **A,** Ventral outgrowth of hepatic diverticulum from foregut endoderm in the 3.5-wk embryo. **B,** Between the two vitelline veins, the enlarging hepatic diverticulum buds off epithelial (liver) cords that become the liver parenchyma, around which the endothelium of capillaries (sinusoids) align (4-wk embryo). **C,** Hemisection of embryo at 7.5 wk. **D,** Three-dimensional representation of the hepatic lobule as present in the newborn. *(From Andres JM, Mathis RK, Walker WA. Liver disease in infants. Part I: developmental hepatology and mechanisms of liver dysfunction. J Pediatr. 1977;90:686–697.)*

sinusoidal network. After birth, the ductus venosus becomes obliterated when oral feedings are initiated. The fetal oxygen saturation is lower in portal than in umbilical venous blood; accordingly, the right hepatic lobe has lower oxygenation and greater hematopoietic activity than the left hepatic lobe.

The transport and metabolic activities of the liver are facilitated by the structural arrangement of liver cell cords, which are formed by rows of hepatocytes, separated by sinusoids that converge toward the tributaries of the hepatic vein (the central vein) located in the center of the lobule (see Fig. 402.2D). This establishes the pathways and patterns of flow for substances to and from the liver. In addition to arterial input from the systemic circulation, the liver also receives venous input from the gastrointestinal tract via the portal system. The products of the hepatobiliary system are released by two different paths: through the hepatic vein and through the biliary system back into the intestine. Plasma proteins and other plasma components are secreted by the liver. Absorbed and circulating nutrients arrive through the portal vein or the hepatic artery and pass through the sinusoids and past the hepatocytes to the systemic circulation at the central vein. Biliary components are transported via the series of enlarging channels from the bile canaliculi through the bile ductule to the common bile duct. The intrahepatic bile duct system relies on its intricate three-dimensional structure to access all of the hepatocytes and effectively clear bile out of the liver.

Hepatocytes and cholangiocytes (i.e., bile duct epithelial cells) originate from the bipotential hepatoblast progenitor. Single-cell RNA sequencing data suggest that hepatoblasts enter the hepatocyte transcriptional program after hepatic specification from ventral foregut endodermal progenitors and transcriptionally move in unison toward the hepatocyte fate. The synchronicity suggests that the hepatocyte lineage specification is the default cell identity. Cholangiocyte differentiation is more nonsynchronous. Individual hepatoblasts upregulate the cholangiocyte transcriptional program coincident with repression of the hepatocyte transcriptional program. Cholangiocyte identity is initiated specifically in portal vein regions around the seventh to tenth week of human gestation, reinforcing that hepatoblasts are not pre-fated to the cholangiocyte transcriptional program but rather their location and signals arising from a niche influence their ultimate fate. Potential cholangiocytes form a temporary structure, termed the *intrahepatic ductal plate*, encircling the portal veins (Fig. 402.3A). Primitive ductal structures are asymmetrically composed of lumen-forming cells. The portal vein adjacent cells express early cholangiocyte markers, and parenchymal adjacent cells still express hepatoblast and hepatocyte markers. Remodeling of the ductal plate or tubulogenesis begins around the 11th to 15th week of human gestation starting at the larger hilar portal vein regions and moving toward the peripheral region of liver following the portal vein system. Newly committed cholangiocytes are incorporated into a *homogeneous intrahepatic bile duct network* encircling the portal vein (see Fig. 402.3B). The final rearrangement of the *hierarchical intrahepatic bile duct network* is thought to be associated with hepatocyte excretion of bilirubin into bile (see Fig. 402.3C). The intrahepatic bile duct architecture remains incomplete in the human liver periphery during the first years of life. If the unincorporated ductal plate or primitive ductal cells do not receive, or are unresponsive to, the proper signals, they may contribute to ductal plate malformation. This histopathologic lesion has been observed in liver biopsies of a variety of liver conditions, including congenital hepatic fibrosis, Caroli disease, biliary atresia, and autosomal dominant polycystic liver disease.

METABOLIC FUNCTIONS OF THE LIVER

The liver reaches a peak relative size of approximately 10% of the fetal weight at the ninth week of human gestation. Early in development, the liver is a primary site of hematopoiesis. In the seventh week of human gestation, hematopoietic cells outnumber functioning hepatocytes in the hepatic anlage. These early hepatocytes are smaller than at maturity (~20 μm vs 30-35 μm) and contain less glycogen. Near term, the hepatocyte mass expands to dominate the organ, as cell size and glycogen content increase. Hematopoiesis is virtually absent by the second postnatal month in full-term infants. As the density of hepatocytes increases with gestational age, the relative volume of the sinusoidal network decreases. The liver constitutes 5% of body weight at birth but only 2% in an adult.

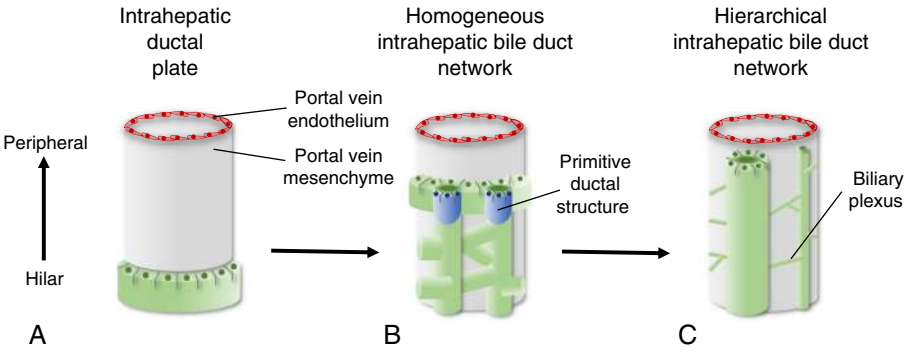

Fig. 402.3 Process of intrahepatic bile duct formation. **A,** Cholangiocytes are specified in the region adjacent to the portal vein system forming transient ductal plate. **B,** Ductal plates are quickly remodeled into luminal or primitive ductal structures surrounded by asymmetric gene expressing cells. These luminal structures form a dense homogeneous network that is communicating with the extrahepatic bile duct. **C,** Upon hepatocyte bile production, secretion, and canalicular membrane lengthening, the homogenous network begins to reorganize into a hierarchical network.

Several metabolic processes are immature in a healthy newborn infant, owing in part to the fetal patterns of activity of various enzymatic processes. Many fetal hepatic functions are carried out by the maternal liver, which provides nutrients and serves as a route of elimination of metabolic end products and toxins. Fetal liver metabolism is devoted primarily to the production of proteins required for growth. Toward term, primary functions become production and storage of essential nutrients, excretion of bile, and establishment of processes of elimination. Extrauterine adaptation requires de novo enzyme synthesis. Modulation of these processes depends on substrate and hormonal input via the placenta and on dietary and hormonal input in the postnatal period.

Carbohydrate Metabolism

The liver regulates serum glucose levels closely via several processes, including storage of excess carbohydrate as glycogen, a polymer of glucose readily hydrolyzed to glucose during fasting. To maintain serum glucose levels, hepatocytes produce free glucose by either glycogenolysis or gluconeogenesis. Immediately after birth, an infant is dependent on hepatic glycogenolysis. Gluconeogenic activity is present at a low level in the fetal liver and increases rapidly after birth. Fetal glycogen synthesis begins at about the ninth week of gestation, with glycogen stores most rapidly accumulated near term, when the liver contains 2-3 times the amount of glycogen of adult liver. Most of this stored glycogen is used in the immediate postnatal period. Re-accumulation is initiated at about the second week of postnatal life, and glycogen stores reach adult levels at approximately the third week in healthy full-term infants. In preterm infants, serum glucose levels fluctuate in part because efficient regulation of the synthesis, storage, and degradation of glycogen develops only near the end of full-term gestation. Dietary carbohydrates such as galactose are converted to glucose, but there is a substantial dependence on gluconeogenesis for glucose in early life, especially if glycogen stores are limited.

Protein Metabolism

During the rapid fetal growth phase, specific decarboxylases that are rate limiting in the biosynthesis of physiologically important polyamines have higher activities than in the mature liver. The rate of synthesis of albumin and secretory proteins in the developing liver parallels the quantitative changes in the endoplasmic reticulum. Synthesis of albumin appears at the seventh to eighth week in the human fetus and increases in inverse proportion to that of α-fetoprotein, which is the dominant fetal protein. By the third to fourth month of gestation, the fetal liver is able to produce fibrinogen, transferrin, and low-density lipoproteins. From this period on, fetal plasma contains each of the major protein classes at concentrations considerably below those achieved at maturity.

The postnatal patterns of protein synthesis vary with the class of protein. Lipoproteins of each class rise abruptly in the first week after birth to reach levels that vary little until puberty. Serum albumin concentrations are low in a neonate (~2.5 g/dL), reaching adult levels (~3.5 g/dL) after several months. Levels of ceruloplasmin and complement factors increase slowly to adult values in the first year. In contrast, transferrin levels at birth are similar to those of an adult, decline for 3-5 months, and rise thereafter to achieve their final concentrations. Low levels of activity of specific proteins have implications for the nutrition of an infant. A low level of cystathionine γ-lyase (cystathionase) activity impairs the *trans*-sulfuration pathway by which dietary methionine is converted to cysteine. Consequently, the latter must be supplied in the diet. Similar dietary requirements might exist for other sulfur-containing amino acids, such as taurine.

Lipid Metabolism

Fatty acid oxidation provides a major source of energy in early life, complementing glycogenolysis and gluconeogenesis. Newborn infants are relatively intolerant of prolonged fasting, owing in part to a restricted capacity for hepatic ketogenesis. Rapid maturation of the ability of the liver to oxidize fatty acid occurs in the first few days after birth. Milk provides the major source of calories in newborns; this high-fat, low-carbohydrate diet mandates active gluconeogenesis to maintain blood glucose levels. When the glucose supply is limited, ketone body production from endogenous fatty acids can provide energy for hepatic gluconeogenesis and an alternative fuel for brain metabolism. When carbohydrates are in excess, the liver produces triglycerides. Metabolic processes involving lipids and lipoproteins are predominantly hepatic; liver immaturity or disease affects lipid concentrations and lipoproteins.

Biotransformation

Newborn infants have a decreased capacity to metabolize and detoxify certain drugs, owing to underdevelopment of the hepatic microsomal component that is the site of the specific oxidative, reductive, hydrolytic, and conjugation reactions required for these biotransformations. The major components of the monooxygenase system, such as cytochrome P450, cytochrome-*c* reductase, and the reduced form of nicotinamide-adenine dinucleotide phosphate, are present in low concentrations in fetal microsomal preparations. In full-term infants, hepatic uridine diphosphate glucuronosyltransferase and enzymes involved in the oxidation of polycyclic aromatic hydrocarbons are expressed at very low levels.

Age-related differences in pharmacokinetics vary from compound to compound. The half-life of acetaminophen in a newborn is similar to that of an adult, whereas theophylline has a half-life of approximately 100 hours in a premature infant, as compared with 5-6 hours in an adult. These differences in metabolism, as well as factors such as binding to plasma proteins and renal clearance, determine appropriate drug dosage to maximize effectiveness and to avoid toxicity. Dramatic historical examples of the susceptibility of newborn infants to drug toxicity are the responses to chloramphenicol (the *gray baby* syndrome) or to benzoyl alcohol and its metabolic products, which involve ineffective glucuronide and glycine conjugation, respectively. The low concentrations of antioxidants (vitamin E, superoxide dismutase, glutathione peroxidase) in the fetal and early newborn liver lead to increased susceptibility to deleterious effects of oxygen toxicity and oxidant injury through lipid peroxidation.

Conjugation reactions, which convert drugs or metabolites into water-soluble forms that can be eliminated in bile, are also catalyzed by hepatic microsomal enzymes. Newborn infants have decreased activity of hepatic uridine diphosphate glucuronosyltransferase, which converts unconjugated bilirubin to the readily excreted glucuronide conjugate and is the rate-limiting enzyme in the excretion of bilirubin. There is rapid postnatal development of transferase activity irrespective of gestational age, which suggests that birth-related, rather than age-related, factors are of primary importance in the postnatal development of activity of this enzyme. Microsomal activity can be stimulated by administration of phenobarbital, rifampin, or other inducers of cytochrome P450. Alternatively, drugs such as cimetidine can inhibit microsomal P450 activity.

Hepatic Excretory Function

Hepatic excretory function and bile flow are closely related to hepatic *bile acid* excretion and enterohepatic recirculation. Bile secretion is first noted at the 12th week of human gestation. Bile acids, the major products of cholesterol degradation, are incorporated into mixed micelles with cholesterol and phospholipid. These micelles act as efficient vehicles for solubilization and intestinal absorption of lipophilic compounds, such as dietary fats and fat-soluble vitamins. Secretion of bile acids by the liver cells is the major determinant of bile flow in the mature animal. Accordingly, maturity of bile acid metabolic processes affects overall hepatic excretory function, including biliary excretion of endogenous and exogenous compounds.

In humans, the two primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in the liver. Before excretion, they are conjugated with glycine or taurine. In response to a meal, contraction of the gallbladder delivers bile acids (micelles) to the intestine to assist in fat digestion and absorption. After mediating fat digestion, the bile acids themselves are reabsorbed from the terminal ileum through specific active transport processes. They return to the liver via portal blood, are taken up by liver cells, and are re-excreted in bile. In an adult, this enterohepatic circulation involves 90–95% of the circulating bile acid pool. Bile acids that escape ileal reabsorption reach the colon, where the bacterial flora, through dihydroxylation and deconjugation, produce the secondary bile acids, deoxycholic and lithocholic acid. In an adult, the composition of bile reflects the excretion of the primary and also the secondary bile acids, which are reabsorbed from the distal intestinal tract.

Intraluminal concentrations of bile acids are low in newborn infants and increase rapidly after birth. The expansion of the bile acid pool is important because bile acids are required to stimulate bile flow and absorb lipids, a major component of the diet of a newborn. Nuclear receptors, such as farnesoid X receptor (FXR), control intrahepatic bile acid homeostasis through several mechanisms, including regulation of expression of the genes encoding two key proteins, cholesterol 7α-hydroxylase (CYP7A1) and bile salt export pump (BSEP). These proteins are important for bile acid synthesis and canalicular secretion, respectively. Neonatal expression of these nuclear receptors varies depending on the studied animal model.

Because of inefficient ileal reabsorption of bile acids and the low rate of hepatic clearance of bile acids from portal blood, serum concentrations of bile acids are commonly elevated in healthy newborns, often to levels that would suggest liver disease in older persons. Transient phases of *physiologic cholestasis* and *physiologic steatorrhea* can often be observed in low birthweight infants and in full-term infants after perinatal stress, such as hypoxia or infection, but are otherwise uncommon in healthy full-term newborns.

Many of the processes related to immaturity of the newborn in liver morphogenesis and function, as discussed earlier, are implicated in the increased susceptibility of infants to liver disease associated with parenteral nutrition. The reduced bile acid pool size, hepatic glutathione depletion, and deficient sulfation contribute to production of toxic lithocholic acid and thus to cholestasis, whereas deficiencies of essential amino acids, including taurine and cysteine, and excessive lipid infusion can lead to hepatic steatosis in these infants. Beyond the neonatal period, disturbances in bile acid metabolism may be responsible for diverse effects on hepatobiliary and intestinal function (Table 402.2).

Table 402.2 Causes of Impaired Bile Acid Metabolism and Enterohepatic Circulation

DEFECTIVE BILE ACID SYNTHESIS OR TRANSPORT
• Inborn errors of bile acid synthesis
• Progressive familial intrahepatic cholestasis
• Intrahepatic cholestasis (neonatal hepatitis)
• Acquired defects in bile acid synthesis secondary to severe liver disease
ABNORMALITIES OF BILE ACID DELIVERY TO THE BOWEL
• Celiac disease (sluggish gallbladder contraction)
• Extrahepatic bile duct obstruction (e.g., biliary atresia, gallstones)
ALTERED ENTEROHEPATIC CIRCULATION OF BILE ACIDS
• External bile fistula
• Cystic fibrosis
• Small bowel bacterial overgrowth syndrome (with bile acid precipitation, increased jejunal absorption, and "short-circuiting")
• Drug-induced entrapment of bile acids in intestinal lumen (e.g., cholestyramine)
BILE ACID MALABSORPTION
• Primary bile acid malabsorption (absent or inefficient ileal active transport)
• Secondary bile acid malabsorption
• Ileal disease or resection
DEFECTIVE UPTAKE OR ALTERED INTRACELLULAR METABOLISM
• Parenchymal disease
• Regurgitation from cells
• Portosystemic shunting
• Cholestasis

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 403

Manifestations of Liver Disease

James E. Squires and William F. Balistreri

PATHOLOGIC MANIFESTATIONS

Congenital and acquired alterations in hepatic structure and function (acute or chronic) can be manifest by varying patterns of reaction of the liver to cell injury. Hepatocyte injury can be caused by infection (viral, bacterial, parasitic), drugs or toxins, hypoxia, immunologic and structural disorders, or inborn errors of metabolism. The injury results in inflammatory cell infiltration and cell death (necrosis), which may be followed by a healing process of scar formation (fibrosis) and, potentially, nodule formation (regeneration). Cirrhosis is the result of any progressive fibrotic liver disease.

Cholestasis is an alternative or concomitant response to injury caused by extrahepatic or intrahepatic obstruction to bile flow. Substances that are normally excreted in bile, such as bile acids, conjugated bilirubin, cholesterol, and trace elements, accumulate in serum. Bile pigment accumulation in liver parenchyma can be seen in liver biopsy specimens. In *extrahepatic* obstruction, bile pigment may be visible in the intralobular bile ducts or throughout the parenchyma as bile lakes or infarcts. In *intrahepatic* cholestasis, an injury to hepatocytes or an alteration in hepatic physiology leads to a reduction in the rate of secretion of solute and water. Etiologies include alterations in enzymatic or canalicular transporter activity, permeability of the bile canalicular apparatus, organelles responsible for bile secretion, or ultrastructure of the cytoskeleton of the hepatocyte. The result may be clinically indistinguishable from obstructive cholestasis.

Cirrhosis, defined histologically by the presence of bands of fibrous tissue that link central and portal areas and form parenchymal nodules, is an end stage of any prolonged acute or chronic liver disease. Cirrhosis can be *macronodular,* with nodules of various sizes (up to 5 cm) separated by broad septa, or *micronodular,* with nodules of uniform size (<1 cm) separated by fine septa; mixed forms occur. The progressive scarring results in altered hepatic blood flow, with further impairment of liver cell function. Increased intrahepatic resistance to portal blood flow leads to portal hypertension.

The liver can be secondarily involved in neoplastic (metastatic) and nonneoplastic (storage diseases, fat infiltration) processes, as well as several systemic conditions and infectious processes. The liver can be affected by chronic passive congestion (congestive heart failure) or acute hypoxia, with hepatocellular damage.

CLINICAL MANIFESTATIONS

Hepatomegaly

Enlargement of the liver can be caused by several mechanisms (Table 403.1). Normal liver size estimations are based on age-related clinical indices, such as the degree of extension of the liver edge below the costal margin, the span of dullness to percussion, or the length of the vertical axis of the liver, as estimated from imaging techniques. In children, the normal liver edge can be felt up to 2 cm below the right costal margin. In a newborn infant, extension of the liver edge more than 3.5 cm below the costal margin in the right midclavicular line suggests hepatic enlargement. Measurement of liver span is carried out by percussing the upper margin of dullness and by palpating the lower edge in the right midclavicular line. This may be more reliable than an extension of the liver edge alone. The two measurements may correlate poorly.

The liver span increases linearly with body weight and age in both sexes, ranging from approximately 4.5-5.0 cm at 1 week of age to approximately 7-8 cm in males and 6.0-6.5 cm in females by 12 years of age. The lower edge of the right lobe of the liver extends downward (Riedel lobe) and can normally be palpated as a broad mass in some people. An enlarged left lobe of the liver is palpable in the epigastrium of some patients with cirrhosis. Downward displacement of the liver by the diaphragm (hyperinflation) or thoracic organs can create an erroneous impression of hepatomegaly.

Examination of the liver should note the consistency, contour, tenderness, and presence of any masses or bruits, as well as assessment of spleen size, along with documentation of the presence of ascites and any stigmata of chronic liver disease.

Ultrasound is useful in assessment of liver size and consistency, along with gallbladder size. Gallbladder length normally varies from 1.5 to 5.5 cm (average: 3 cm) in infants to 4 to 8 cm in adolescents; width ranges from 0.5 to 2.5 cm for all ages. Gallbladder distention may be seen in infants with sepsis. The gallbladder is often absent or abnormal in infants with biliary atresia.

Jaundice (Icterus)

Yellow discoloration of the sclera, skin, and mucous membranes is a sign of hyperbilirubinemia (see Chapter 137). Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2-3 mg/dL (34-51 μmol/L); the neonate might not appear jaundiced until the bilirubin level is >5 mg/dL (>85 μmol/L). Jaundice may be the earliest and only sign of hepatic dysfunction. Liver disease must be suspected in the infant who appears only mildly jaundiced but has dark urine or acholic (light-colored) stools. Immediate evaluation to establish the cause is required.

Measurement of the total serum bilirubin concentration allows quantitation of jaundice. Bilirubin occurs in plasma in four forms: *unconjugated* bilirubin tightly bound to albumin; *free* or *unbound bilirubin* (the form responsible for kernicterus, because it can cross cell membranes); *conjugated bilirubin* (the only fraction to appear in urine); and *δ fraction* (bilirubin covalently bound to albumin), which appears in serum when hepatic excretion of conjugated bilirubin is impaired in patients with hepatobiliary disease. The δ fraction permits conjugated bilirubin to persist in the circulation and delays resolution of jaundice. Although the terms *direct* and *indirect* bilirubin are used equivalently with *conjugated* and *unconjugated* bilirubin, this is not quantitatively correct, because the direct fraction includes both conjugated bilirubin and δ bilirubin.

Investigation of jaundice in an infant or older child must include determination of the accumulation of both unconjugated and conjugated bilirubin. Unconjugated hyperbilirubinemia might indicate increased production, hemolysis, reduced hepatic removal, or altered metabolism of bilirubin (Table 403.2). Conjugated hyperbilirubinemia reflects decreased excretion by damaged hepatic parenchymal cells or disease of the biliary tract, which may be a result of obstruction, sepsis, toxins, inflammation, and genetic or metabolic disease (Table 403.3).

Pruritus

Intense generalized itching can occur in patients with chronic liver disease, often in association with cholestasis (conjugated hyperbilirubinemia). Symptoms can be generalized or localized (commonly to palms and soles), are usually worse at night, are exacerbated with stress and heat, and are relieved by cool temperatures. Pruritus is unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic.

The pathogenesis of pruritus remains unknown; however, multiple suspected pruritogens have been reported, including bile acids, histamine, serotonin, progesterone metabolites, endogenous opioids, the potent neuronal activator lysophosphatidic acid (LPA), and the LPA-forming enzyme, autotaxin (ATX). Ultimately, a multifactorial process is suspected, as evidenced by the symptomatic relief of pruritus after administration of various therapeutic agents, including bile acid–binding agents (cholestyramine), choleretic agents (ursodeoxycholic acid), opiate antagonists (naltrexone), antihistamines, serotonin reuptake inhibitors (sertraline), antibiotics, and ileal bile acid transporter (IBAT) inhibitors. Plasmapheresis, molecular adsorbent recirculating system therapy, and surgical diversion of bile (partial and total biliary

Table 403.1 Causes of Hepatomegaly in Infants and Children

INFECTION AND INFLAMMATION	**STORAGE/METABOLIC DISEASE**
Viral hepatitis (hepatitis A, B, C, D, E; EBV; adenovirus, adeno-associated virus, echovirus, TORCH)	α_1-Antitrypsin deficiency
Autoimmune hepatitis	Wilson disease
Sepsis	Infants of diabetic mothers
Perinatal infections	Glycogen storage disease
Allograft rejection	Galactosemia
Graft-versus-host disease	Tyrosinemia
Systemic lupus erythematosus	Cystic fibrosis
Juvenile idiopathic arthritis	Gaucher disease
Primary sclerosing cholangitis	Niemann-Pick disease
Systemic granulomatous disorders with hepatic involvement	Gangliosidoses
Sarcoid	Hereditary fructose intolerance
Tuberculosis	Mitochondrial hepatic disorders including DNA depletion syndrome
Hepatic abscess (bacterial and parasitic)	Mucopolysaccharidoses
Parasitic infection	Amyloidosis
Visceral larva migrans	Hepatic porphyrias
Schistosomiasis	**EXPANSION OF EXTRACELLULAR MATRIX**
Leishmaniasis	Cirrhosis
Malaria	Fibrocystic disease (congenital hepatic fibrosis)
Liver flukes	**STEATOSIS**
Kupffer cell hyperplasia	Malnutrition
Macrophage activation syndrome	Nonalcoholic steatohepatitis (obesity)
Gestational alloimmune liver disease	Cystic fibrosis
BILIARY OBSTRUCTION	Parenteral nutrition
Biliary atresia	Diabetes mellitus
Choledochal cysts	Hereditary fructose intolerance
Stricture of common bile duct	Galactosemia
Primary sclerosing cholangitis	Wolman disease
INFILTRATION	Cholesterol ester storage disease
Extramedullary hematopoiesis	Mitochondrial hepatopathies
Erythroblastosis fetalis	β-Oxidation defects
Thalassemias	Medication toxicity (tetracycline, valproic acid)
Metastatic tumors	**HEPATIC MALIGNANCY/TUMOR**
Neuroblastoma	Primary or metastatic
Wilms tumor	**VASCULAR CONGESTION**
Leukemia	Congestive heart failure
Lymphoma	Budd-Chiari syndrome
Hemophagocytic lymphohistiocytosis (HLH)	Venoocclusive disease (VOD): radiation, high-dose chemotherapy, stem cell transplant, bush tea, pyrrolizidine alkaloids, familial VOD with immunodeficiency
Langerhans cell histiocytosis	**CYSTIC DISEASE**
	Fibrocystic disease
	Autosomal dominant polycystic kidney disease
	Congenital hepatic fibrosis
	Caroli syndrome
	Isolated polycystic liver disease

EBV, Epstein-Barr virus; TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus.
From Telega GW. Hepatomegaly. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Table 17.1, p. 307.

diversion) have been used in attempts to provide relief for medically refractory pruritus.

Spider Angiomas

Vascular spiders *(telangiectasias)*, characterized by central pulsating arterioles from which small, wiry venules radiate, may be seen in patients with chronic liver disease. These are usually most prominent in the superior vena cava distribution area (on the face and chest). Their size varies between 1 and 10 mm, and they exhibit central clearing with pressure. They presumably reflect altered estrogen metabolism in the presence of hepatic dysfunction.

Palmar Erythema

Blotchy erythema, most noticeable over the thenar and hypothenar eminences and on the tips of the fingers, is also noted in patients with chronic liver disease. Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes.

Xanthomas

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis, especially Alagille syndrome, can cause the deposition of lipid in the dermis and subcutaneous tissue. Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops.

Portal Hypertension

Portal hypertension occurs when there is increased portal resistance and/or increased portal flow. The portal system drains the splanchnic area (abdominal portion of the gastrointestinal tract, pancreas, and spleen) into the hepatic sinusoids. Normal portal pressure is between 1 and 5 mm Hg. Portal hypertension is defined as a portal pressure greater than or equal to 6 mm Hg. Clinically significant portal hypertension exists when pressure exceeds a threshold of 10-12 mm Hg. Portal hypertension is the main complication of cirrhosis and is directly responsible for two of the most common and potentially lethal complications: ascites and variceal hemorrhage.

Table 403.2 Differential Diagnosis of Unconjugated Hyperbilirubinemia

Physiologic Jaundice

Breastfeeding/Breast Milk Jaundice

Polycythemia

- Diabetic mother
- Fetal transfusion (maternal, twin)
- Intrauterine hypoxemia
- Delayed cord clamping
- Congenital adrenal hyperplasia
- Neonatal thyrotoxicosis

Hemolysis

Isoimmune
- Rh incompatibility
- ABO incompatibility
- Other (M, S, Kidd, Kell, Duffy)

Autoimmune
- Cold antibody
- Warm antibody

Erythrocyte membrane defects
- Hereditary spherocytosis
- Hereditary elliptocytosis
- Infantile pyknocytosis

Erythrocyte enzyme defects
- Glucose-6-phosphate dehydrogenase
- Pyruvate kinase
- Hexokinase
- Other

Hemoglobinopathy
- Thalassemia
- Sickle cell anemia

Sepsis
Hemangioma
Congenital erythropoietic porphyria
HUS
Familial TTP *(ADAM TS 13)*
Hemolysis from Wilson disease

Infection

Intestinal Obstruction

- Pyloric stenosis
- Intestinal atresia
- Hirschsprung disease
- Cystic fibrosis

Enclosed Hematoma (Cephalohematoma, Ecchymoses)

Congestive Heart Failure

Hypoxia

Acidosis

Hypothyroidism or Hypopituitarism

Drugs/Toxins

- Maternal oxytocin
- Vitamin K
- Antibiotics
- Phenol disinfectants
- Herbs

Familial Disorders of Bilirubin Metabolism

- Gilbert syndrome
- Crigler-Najjar syndrome types I and II
- Lucey-Driscoll syndrome

TTP, Thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome.
Modified from Telega GW. Jaundice. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Table 18.2, p. 326.

Ascites

Ascites is a consequence of increased hydrostatic and osmotic pressures within the hepatic and mesenteric capillaries resulting in transfer of fluid from the blood vessels to the lymphatics that overcomes the drainage capacity of the lymphatic system. Ascites can also be associated with nephrotic syndrome and other urinary tract abnormalities, metabolic diseases (such as lysosomal storage diseases), congenital or acquired heart disease, and hydrops fetalis. Factors favoring the intraabdominal accumulation of fluid include decreased plasma colloid (albumin) osmotic pressure, increased capillary hydrostatic pressure, increased ascitic colloid osmotic fluid pressure, and decreased ascitic fluid hydrostatic pressure. Abnormal renal sodium retention plays a central role.

Gastrointestinal Bleeding

Chronic liver disease may manifest as gastrointestinal hemorrhage. Bleeding may result from portal hypertensive gastropathy, gastric antral vascular ectasia, or varix rupture. Variceal hemorrhage is classically from an esophageal origin but may be caused by gastric, duodenal, peristomal, or rectal varices. Variceal hemorrhage results from increased pressure within the varix, which leads to changes in the diameter of the varix and increased wall tension. When the variceal wall strength is exceeded, physical rupture of the varix results. Given the high blood flow and pressure in the portosystemic collateral system, coupled with the lack of a natural mechanism to tamponade variceal bleeding, the rate of hemorrhage can be striking.

Encephalopathy

Hepatic encephalopathy can be manifest as any neurologic dysfunction, but it is most likely to present in subtle forms such as deterioration of school performance, sleep disturbances, depression, or emotional outbursts. It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances. The appearance of hepatic encephalopathy depends on the presence of portosystemic shunting, alterations in the blood-brain barrier, and the interactions of toxic metabolites with the central nervous system. Postulated causes include altered ammonia metabolism, synergistic neurotoxins, decreased cerebral oxygen metabolism and blood flow, or false neurotransmitters with plasma amino acid imbalance.

Endocrine Abnormalities

Endocrine abnormalities are more common in older adolescents and adults with hepatic disease than in children. They reflect alterations in hepatic synthetic, storage, and metabolic functions, including those concerned with hormonal metabolism in the liver. Proteins that bind hormones in plasma are synthesized in the liver, and steroid hormones are conjugated in the liver and excreted in the urine; failure of such functions can have clinical consequences. Endocrine abnormalities can also result from malnutrition or specific deficiencies.

Renal Dysfunction

Systemic disease or toxins can affect the liver and kidneys simultaneously, or parenchymal liver disease can produce secondary impairment of renal function. In hepatobiliary disorders, there may be renal alterations in sodium and water economy, impaired renal concentrating ability, and alterations in potassium metabolism. Ascites in patients with cirrhosis may be related to inappropriate retention of sodium by the kidneys and expansion of plasma volume, or it may be related to sodium retention mediated by diminished effective plasma volume.

Hepatorenal syndrome (HRS) is defined as functional renal failure in patients with end-stage liver disease. The pathophysiology of

Table 403.3 Mechanistic Classification of the Etiologies of Cholestasis

EXTRAHEPATIC DUCTS
Biliary atresia
Choledochal cyst
Spontaneous bile duct perforation
Choledocholithiasis, biliary sludge
Duct compression (may also be intrahepatic; e.g., hepatoblastoma, neuroblastoma, rhabdomyosarcoma, neonatal leukemia, systemic juvenile xanthogranuloma, Langerhans cell histiocytosis)
Bile duct stenosis, stricture
INTRAHEPATIC DUCT OBSTRUCTION/FORMATION
Alagille syndrome
"Nonsyndromic paucity of interlobular bile ducts" (e.g., Williams syndrome)
Cystic fibrosis
Ductal plate malformations: congenital hepatic fibrosis; ARPKD; Caroli disease; Ivemark, Jeune, Joubert, Bardet-Biedl syndromes
Sclerosing cholangitis
CANALICULAR MEMBRANE TRANSPORTERS
PFIC type 1, BRIC, Nielsen syndrome (familial Greenland cholestasis)
PFIC type 2 (bile salt export pump deficiency)
PFIC type 3 (MDR3 deficiency)
Tight junction protein 2 deficiency
Farnesoid X receptor variants
MYO5B deficiency
Neonatal Dubin-Johnson syndrome
Villin functional defect
Overload of excretory mechanism capacity: ABO blood group incompatibility with hemolysis
HEPATOCYTE TIGHT JUNCTIONS
Neonatal ichthyosis–sclerosing cholangitis syndrome–claudin-1 protein
Familial hypercholanemia caused by TJP2 (zonulin-2) deficiency
BILE ACID SYNTHESIS
First-degree: BASD
3-Oxo-Δ4-steroid 5β-reductase deficiency
3β-Hydroxy-Δ5-C27-steroid dehydrogenase/isomerase deficiency
Oxysterol 7α-hydroxylase deficiency
Familial hypercholanemia due to BAAT deficiency
Second-degree: organelle dysfunction
Smith-Lemli-Opitz syndrome (cholesterol formation)
Peroxisomal disorders: Zellweger, infantile Refsum, neonatal ALD
INFECTIOUS
Bacterial: sepsis (endotoxemia, e.g., UTI, gastroenteritis)
Listeria
Syphilis
TB
VIRAL
Herpes viruses: CMV, HSV, HHV-6, varicella
Parvovirus B19
Hepatitis A, B, C
Enterovirus: coxsackieviruses, echoviruses, "numbered" enteroviruses
Adenovirus
Adeno-associated virus
Rubella
HIV
Paramyxovirus
PROTOZOAL
Toxoplasmosis
TOXIC
Parenteral nutrition–associated liver disease
Fetal alcohol syndrome
Drugs: maternal amphetamines, anticonvulsants; infant antifungals
ENDOCRINE
Panhypopituitarism
Hypothyroidism, cortisol deficiency
McCune-Albright syndrome
Donohue syndrome (leprechaunism)
METABOLIC
α_1-Antitrypsin deficiency
Galactosemia
Fructosemia (hereditary fructose intolerance)
Glycogen storage disease type IV (Andersen disease)
Congenital disorders of glycosylation
Tyrosinemia type I
Niemann-Pick disease type C
Gaucher disease
Cerebrotendinous xanthomatosis
Farber disease
Wolman disease
β-Oxidation defects: short- and long-chain acyl-CoA dehydrogenase deficiencies
Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
Mucolipidosis II (I-cell disease)
Urea cycle defects
Citrin deficiency (formerly type II citrullinemia)
Mitochondrial respiratory chain disorders
Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE)
Wilson disease (>5 yr)
IMMUNE MEDIATED
Gestational alloimmune liver disease
Neonatal or acquired lupus erythematosus
Autoimmune hemolytic anemia with giant cell hepatitis
Hemophagocytic lymphohistiocytosis
Autoimmune hepatitis
OTHER
Hypoxic/ischemic/vascular
Shock/hypoperfusion/hypoxia
Budd-Chiari syndrome
Cardiac insufficiency (congenital heart disease, arrhythmia)
Multiple hemangiomata
Sinusoidal obstruction syndrome
ARC syndrome (arthrogryposis–renal tubular dysfunction–cholestasis; defective vacuolar protein sorting)
Chromosomal: trisomy 17, 18, 21
Congenital disorders of glycosylation
Hardikar syndrome
Lymphedema cholestasis syndrome (Aagenaes syndrome)
Kabuki syndrome
North American Indian childhood cirrhosis (*UTP4* variant)
Pseudo-TORCH (PTORCH-1) syndrome (*OCLN* variant)
"Idiopathic neonatal hepatitis"
COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)

ALD, Adrenoleukodystrophy; ARC, arthrogryposis-renal-cholestasis; ARPKD, autosomal recessive polycystic kidney disease; BAAT, bile acid coenzyme A: amino acid N-acyltransferase; BASD, bile acid synthetic defects; BRIC, benign recurrent intrahepatic cholestasis; CMV, cytomegalovirus; HHV-6, human herpesvirus type 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PFIC, progressive familial intrahepatic cholestasis; TORCH, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes infections; UTI, urinary tract infection.

Modified from Telega GW. Jaundice. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 18.3, p. 327.

hepatorenal syndrome is related to splanchnic vasodilation, mesenteric angiogenesis, and decreased effective blood volume with resulting decreased renal perfusion. The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms) with coexistent systemic vasodilation. The diagnosis is supported by the findings of oliguria (<1 mL/kg/day), a characteristic pattern of urine electrolyte abnormalities (urine sodium <10 mEq/L, fractional excretion of sodium of <1%, urine:plasma creatinine ratio <10, and normal urinary sediment), absence of hypovolemia, and exclusion of other kidney pathology. Both acute (HRS-AKI) and chronic (HRS-CKD) forms have been described. The best treatment of HRS is timely liver transplantation, with complete renal recovery expected.

Pulmonary Involvement

Hepatopulmonary syndrome (HPS) is characterized by the typical triad of hypoxemia, intrapulmonary vascular dilations, and liver disease. There is intrapulmonic right-to-left shunting of blood resulting from enlarged pulmonary vessels that prevents adequate exposure to oxygen-rich alveoli of red blood cells traveling through the center of the vessel. Shunting of vasodilatory mediators from the mesentery away from the liver is thought to contribute. HPS should be suspected and investigated in the child with chronic liver disease with a history of shortness of breath or exercise intolerance and clinical examination findings of cyanosis (particularly of the lips and fingers), digital clubbing, and oxygen saturations <96%, particularly in the upright position. Treatment is timely liver transplantation; resolution of pulmonary involvement usually follows.

Portopulmonary hypertension is a condition characterized by an increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension. It is defined by a pulmonary arterial pressure >25 mm Hg at rest and above 30 mm Hg with exercise, elevated pulmonary vascular resistance with pulmonary arterial occlusion pressure, or a left ventricular end diastolic pressure of <15 mm Hg. Although the pathophysiology is unclear, deficiency in endothelial prostacyclin synthase and increased circulating endothelin-1 have been implicated as a cause for the vasculopathy. Autopsy studies have demonstrated the coexistence of portal hypertension, microscopic pulmonary artery thromboembolism, endothelial and smooth muscle proliferation, and platelet aggregates contributing to portopulmonary hypertension development. Symptoms suggesting a diagnosis include exertional dyspnea, fatigue, syncope, palpitations, and chest pain. Pulmonary artery–directed therapy is the cornerstone of management, along with consideration of liver transplant.

Recurrent Cholangitis

Ascending infection of the biliary system is often seen in pediatric cholestatic disorders, most commonly because of gram-negative enteric organisms such as *Escherichia coli, Klebsiella, Pseudomonas,* and *Enterococcus.* Liver transplantation is the definitive treatment for recurrent cholangitis, especially when medical therapy is not effective.

Miscellaneous Manifestations of Liver Dysfunction

Nonspecific signs of acute and chronic liver disease include anorexia, which often affects patients with anicteric hepatitis and with cirrhosis associated with chronic cholestasis; abdominal pain or distention resulting from ascites, spontaneous peritonitis, or visceromegaly; malnutrition and growth failure; and bleeding, which may be a result of altered synthesis of coagulation factors (biliary obstruction with vitamin K deficiency or excessive hepatic damage) or to portal hypertension with hypersplenism. In the presence of hypersplenism, there can be decreased synthesis of specific clotting factors, production of qualitatively abnormal proteins, or alterations in platelet number and function. Altered drug metabolism can prolong the biologic half-life of commonly administered medications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

403.1 Evaluation of Patients with Possible Liver Dysfunction

James E. Squires and William F. Balistreri

Adequate evaluation of an infant, child, or adolescent with suspected liver disease begins with an appropriate and accurate history, a carefully performed physical examination, and skillful interpretation of signs and symptoms. Further evaluation is aided by judicious selection of diagnostic tests, followed using imaging modalities and/or a liver biopsy (Fig. 403.1). Most of the so-called liver "function" tests *do not* measure any specific hepatic function: a rise in serum aminotransferase levels reflects liver cell *injury,* an increase in immunoglobulin levels reflects an immunologic response to injury, or an elevation in serum bilirubin levels can reflect any of several disturbances of bilirubin metabolism (see Tables 403.2 and 403.3). Any single biochemical assay provides limited information, which must be placed in the context of the entire clinical picture. The most cost-efficient approach is to become familiar with the rationale, implications, and limitations of a selected group of tests so that specific questions can be answered. Young infants with cholestatic jaundice should be evaluated promptly to identify patients needing specific medical treatment or surgical intervention.

For a patient with suspected liver disease, evaluation addresses the following issues in sequence: Is liver disease present? If so, what is its nature? What is its severity? Is specific treatment available? How can we monitor the response to treatment? What is the prognosis? Importantly, more recent rapid genotype testing and gene chip technologies have transformed the field of diagnostics. These advances, paired with a greater understanding of the genetic basis for many pediatric liver diseases, are enabling more accurate and timely diagnoses while simultaneously eliminating the need for more invasive, costly, and time-intensive testing.

BIOCHEMICAL TESTS

Laboratory tests commonly used to screen for or to confirm a suspicion of liver disease include measurements of serum aminotransferase (Table 403.4), bilirubin (total and fractionated), alkaline phosphatase (AP), and gamma glutamyl-transpeptidase (GGT) levels, as well as determinations of prothrombin time (PT) or international normalized ratio (INR) and serum albumin level. These tests are complementary, provide an estimation of synthetic and excretory functions, and might suggest the nature of the disturbance (inflammation or cholestasis).

The severity of the liver disease may be reflected in clinical signs or biochemical alterations. Clinical signs include encephalopathy, variceal hemorrhage, worsening jaundice, apparent shrinkage of liver mass owing to massive necrosis, or onset of ascites. Biochemical alterations reflective of severity include hypoglycemia, acidosis, hyperammonemia, electrolyte imbalance, continued hyperbilirubinemia, marked hypoalbuminemia, or a prolonged PT or INR that is *unresponsive* to parenteral administration of vitamin K.

Acute liver cell injury (parenchymal disease) caused by viral hepatitis, drug- or toxin-induced liver disease, shock, hypoxemia, or metabolic disease is best suggested by a marked increase in serum aminotransferase levels. Cholestasis (obstructive disease) involves regurgitation of bile components into serum; the serum levels of total and conjugated bilirubin and serum bile acids are elevated. Elevations in serum AP, 5′ nucleotidase, and GGT levels are also sensitive indicators of obstruction or inflammation of the biliary tract. Fractionation of the total serum bilirubin level into conjugated and unconjugated bilirubin fractions helps to distinguish between elevations caused by processes such as hemolysis and those caused by hepatic dysfunction. A predominant elevation in the conjugated bilirubin level provides a relatively sensitive index of hepatocellular disease or hepatic excretory dysfunction.

Alanine aminotransferase (ALT, serum glutamate pyruvate transaminase) is *liver* specific, whereas aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase) is derived from other

differences in density of liver parenchyma, the average liver attenuation coefficient being reduced with fatty infiltration.

MRI is a useful alternative that limits radiation exposure. Magnetic resonance cholangiography can be of value in differentiating biliary tract lesions. MRI with Eovist (gadoxetate disodium) can assist in the detection and characterization of known or suspected focal liver lesions. In differentiating obstructive from nonobstructive cholestasis, CT scanning or MRI identifies the precise level of obstruction more often than ultrasound. Either CT scanning or ultrasound may be used to guide percutaneously placed fine needles for biopsies, aspiration of specific lesions, or cholangiography.

Elastography is a novel noninvasive method to assess for liver *stiffness,* a measure of the development of hepatic fibrosis in patients with liver disease. Both ultrasound and MR methods have been developed. These noninvasive techniques allow for monitoring fibrosis progression and development of cirrhosis, characterization of hepatic tumors, improved diagnostic capabilities in certain disease processes such as biliary atresia, and prognostic stratification of diseases such as nonalcoholic fatty liver disease and NASH.

Radionuclide scanning relies on selective uptake of a radiopharmaceutical agent. Commonly used agents include technetium-99m–labeled sulfur colloid, which undergoes phagocytosis by Kupffer cells; ^{99m}Tc-iminodiacetic acid agents, which are taken up by hepatocytes and excreted into bile in a fashion similar to bilirubin; and gallium-67, which is concentrated in inflammatory and neoplastic cells. The anatomic resolution possible with hepatic scintiscans is generally less than that obtained with CT scanning, MRI, or ultrasound.

The ^{99m}Tc-sulfur colloid scan can detect focal lesions (tumors, cysts, abscesses) >2-3 cm in diameter. This modality can help to evaluate patients with possible cirrhosis and with patchy hepatic uptake and a shift of colloid uptake from liver to bone marrow.

Cholangiography, direct visualization of the intrahepatic and extrahepatic biliary tree after injection of opaque material, may be required in some patients to evaluate the cause, location, or extent of biliary obstruction. Percutaneous transhepatic cholangiography with a fine needle is the technique of choice in infants and young children. The likelihood of opacifying the biliary tract is excellent in patients in whom CT scanning, MRI, or ultrasound demonstrates dilated ducts. Percutaneous transhepatic cholangiography has been used to outline the biliary ductal system.

Endoscopic retrograde cholangiopancreatography is an alternative method of examining the bile ducts in older children. The papilla of Vater is cannulated under direct vision through a fiberoptic endoscope, and contrast material is injected into the biliary and pancreatic ducts to outline the anatomy. The advantage of endoscopic retrograde cholangiopancreatography is that it allows therapeutic interventions of the extrahepatic biliary tree (stone extraction, stent placement).

Selective angiography of the celiac, superior mesenteric, or hepatic artery can be used to visualize the hepatic or portal circulation. Both arterial and venous circulatory systems of the liver can be examined. Angiography is often required to define the blood supply of tumors before surgery and is useful in the study of patients with known or presumed portal hypertension. The patency of the portal system, the extent of collateral circulation, and the caliber of vessels under consideration for a shunting procedure can be evaluated. MRI can provide similar information.

DIAGNOSTIC APPROACH TO INFANTS WITH JAUNDICE

Well-appearing infants can have cholestatic jaundice. Biliary atresia and neonatal hepatitis are the most common causes of cholestasis in early infancy. Biliary atresia portends a poor prognosis unless it is identified early. The best outcome for this disorder is with early surgical reconstruction (45-60 days of age). History, physical examination, and the detection of a conjugated hyperbilirubinemia via examination of total and direct bilirubin are the first steps in evaluating the jaundiced infant (see Fig. 403.1). Consultation with a pediatric gastroenterologist should be sought early in the course of the evaluation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 404
Cholestasis

Simon Lam and William F. Balistreri

404.1 Neonatal Cholestasis

Simon Lam and William F. Balistreri

Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring within the neonatal period. Cholestasis implies impediment to normal bile flow. In contrast to unconjugated hyperbilirubinemia, cholestasis (conjugated bilirubin elevation of any degree) in the neonate is *always pathologic,* and prompt differentiation of the cause is imperative.

Neonatal cholestasis occurs in approximately 1 in 2,500 live births. Although the clinical features for the diverse causes of neonatal cholestasis can be similar, the differential diagnosis remains broad, including infections, endocrine disorders, genetic/metabolic conditions, and various forms of mechanical obstruction. One approach is to evaluate the pathologies of the biliary system with an anatomic perspective, from the large extrahepatic bile ducts, to the smaller intrahepatic bile ducts, to the bile canaliculus, to the membrane transporters on the hepatocyte, and finally to the level of the hepatocyte (Fig. 404.1).

DISORDERS OF THE EXTRAHEPATIC BILE DUCTS

Biliary Atresia

Biliary atresia is an important cause of neonatal cholestasis and the leading indication for pediatric liver transplantations worldwide. The prevalence of biliary atresia varies from 1 in 3,000 in French Polynesia to 1 in 12,000-22,000 in North America and Europe. In most cases, infants with biliary atresia appear well but are jaundiced with a history of acholic stools (i.e., stools devoid of pigment appearing white or pale colored) (Fig. 404.2). **Biliary atresia splenic malformation (BASM)** syndrome affects 15% of patients with biliary atresia and is associated with other congenital abnormalities, including situs inversus (heterotaxia syndrome), congenital heart disease, intestinal malformation, primary ciliary dyskinesia, Kabuki syndrome, caudal regression syndrome, and polysplenia. The pathogenesis of biliary atresia is unknown. For nonsyndromic biliary atresia, it appears that bile duct destruction may be initiated in utero but is primarily a progressive postnatal event. Evidence for this includes elevated levels of conjugated/direct bilirubin in the first 1-3 days after birth. Leading hypotheses include (1) a complex interplay between genetic predisposition/susceptibility, (2) prenatal or postnatal biliary injury from viruses, toxins, or vascular insults, (3) increased susceptibility to ongoing biliary injury caused by a descending glycocalyx on the apical surface of the cholangiocytes or abnormal intracellular glutathione production, and (4) aberrant immune responses. Biliary atresia has been discordant among identical twins. The final common pathway is an *obliterative cholangiopathy,* leading to the destruction of the biliary tree, most commonly at the porta hepatis. Bile is therefore unable to flow through the atretic region of the *extrahepatic* bile ducts, causing increased pressure and reflux of biliary contents back into the *intrahepatic* biliary system resulting in hepatic injury, inflammation, and fibrosis (Fig. 404.3). Because bile is not excreted into the small bowel, fat/fat-soluble vitamin digestion is impaired, and stools are acholic. If left untreated, end-stage liver disease usually occurs by 2 years of life.

Typical abdominal ultrasound findings include nonvisualization of the gallbladder, a small-contracted gallbladder, and nonvisualization of the common bile duct. The triangular cord sign has also been reported as a specific ultrasound finding for biliary atresia, but may lack sensitivity. Notably, dilation of intrahepatic ducts is not a feature consistent with biliary atresia. Characteristic features on liver biopsy include bile duct proliferation, bile duct plugs, and portal stromal edema. Although abdominal ultrasonography and liver biopsies are helpful in the diagnostic workup for biliary atresia, an intraoperative cholangiogram remains the gold standard for diagnosis. After catheterization of the

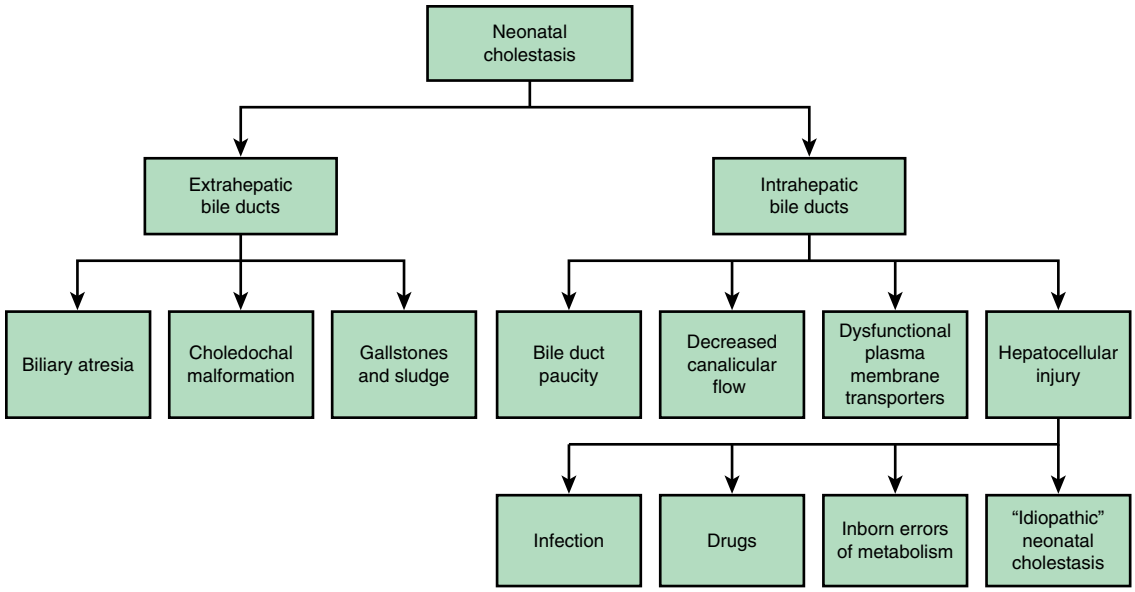

Fig. 404.1 Conceptual approach to neonatal cholestasis. There are areas of overlap: patients with biliary atresia will have some degree of intrahepatic/hepatocellular injury. Additional patients with "idiopathic" neonatal hepatitis may be determined in the future to be related to an enzyme or membrane transporter defect.

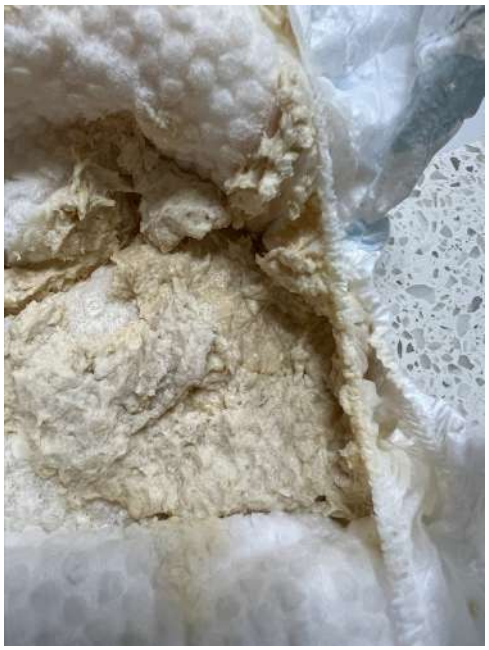

Fig. 404.2 Acholic stools from a 1-mo-old patient with biliary atresia. *(Courtesy Dr. S. Lam.)*

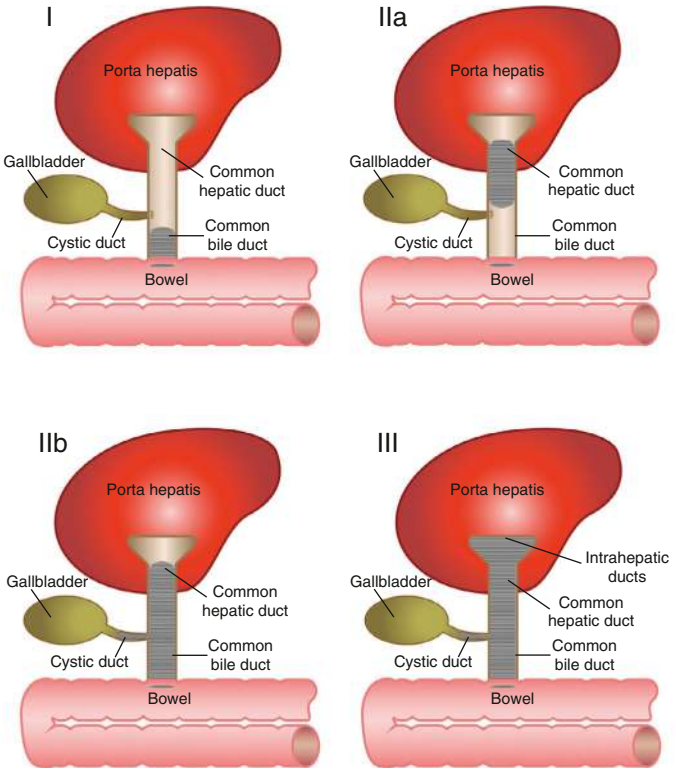

Fig. 404.3 Biliary atresia classified according to the area of involvement *(gray colored)*. Type I: Atresia of the distal bile duct with patent proximal extrahepatic bile duct. Type IIa: Atresia of the common hepatic duct. Type IIb: Atresia of the common hepatic duct, cystic duct, and common bile duct. Type III: Nonpatency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum. *(Modified from A-Kader HH, Feerick J, Rodriguez-Davalos M. After two centuries biliary atresia remains the darkest chapter in pediatric hepatology. Ann Pediatr Child Health. 2015;3:1044, Fig. 2.)*

gallbladder, a diagnosis of biliary atresia is made if contrast does not fill the intrahepatic biliary tree or drain into the small bowel. After the diagnosis is confirmed, the Kasai hepatoportoenterostomy (KPE) is typically performed. The atretic biliary remnant is removed and a Roux-en-Y jejunostomy is anastomosed to the biliary hilum to reestablish bile flow; this remains the accepted surgical intervention for patients with biliary atresia (Fig. 404.4). A prompt diagnosis of biliary atresia is key because the timing of surgical correction is strongly linked to the prognosis. Historically, KPE performed before 60 days

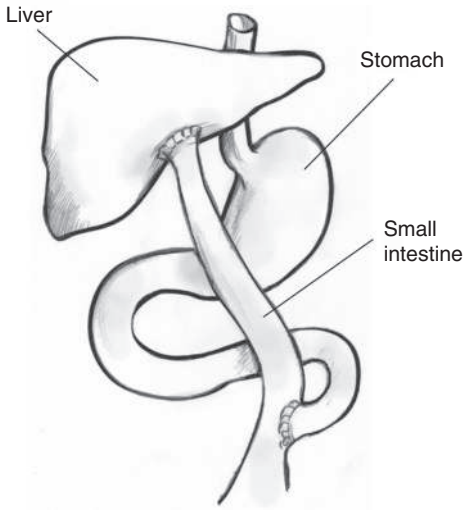

Fig. 404.4 Hepatoportoenterostomy (Kasai procedure). The atretic biliary remnant is removed and a Roux-en-Y jejunostomy is anastomosed to the biliary hilum to reestablish bile flow. *(Courtesy National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. https://www.niddk.nih.gov/news/media-library/18094.)*

of life was used as the benchmark surgical intervention. However, the earlier that the KPE is established, the better the outcome. A national study across all Canadian centers showed that when the KPE was performed at ≤30 days of age, survival with the native liver at 4 years of age was higher than when the surgery was performed between 31 and 90 days. Given the strong impact of early intervention with KPE, biliary atresia screening programs have been implemented in select countries. Clearly any infant with jaundice persisting beyond the first few weeks of life should have serum total and conjugated bilirubin levels assessed. In Taiwan, the national rate of KPE before 60 days of age increased from 60% to 74% after the implementation of a biliary atresia stool card screening program. Similarly, the proportion of patients with total bilirubin <2 mg/dL 3 months post-KPE, an important prognostic marker for survival with native liver, significantly increased from 37% to 60% after the implementation of the program. A two-stage screening protocol assessing conjugated bilirubin levels in the state of Texas also led to a significant decrease in the age at which patients with biliary atresia underwent the KPE. The first stage was performed before 60 hours of life; the second stage was performed at 2 weeks of age if an elevated conjugated bilirubin was detected in the first stage. Stage two conjugated bilirubin levels that were increasing or were greater than 1 mg/dL were considered positive and underwent further testing. A novel serum biomarker, matrix metalloproteinase 7 (MMP7), has been identified as a possible sensitive and specific marker for biliary atresia.

Choledochal Malformations

Choledochal malformations, formerly known as *choledochal cysts,* are rare congenital dilations of the biliary tree (Fig. 404.5). With a 4:1 female predominance, these malformations have also been reported to be more common in the Asian population, with an incidence of approximately 1 in 13,000 compared with 1 in 100,000-150,000 in Western populations. The underlying pathogenesis is unknown; however, the presence of an anomalous pancreaticobiliary ductal union present in approximately 90% of patients may contribute to the development of choledochal malformations. Leading hypotheses suggest that an anomalous pancreaticobiliary union leads to reflux of pancreatic contents into the common bile duct, causing chronic inflammation and biliary damage leading to cystic changes.

Approximately 80% of choledochal malformations are detected in infancy and early childhood. Although these lesions are often first discovered by ultrasonography, magnetic resonance cholangiopancreatography (MRCP) and, less commonly, an endoscopic retrograde cholangiopancreatography, may be needed to further characterize the malformation according to the Todani classification (see Fig. 405.5).

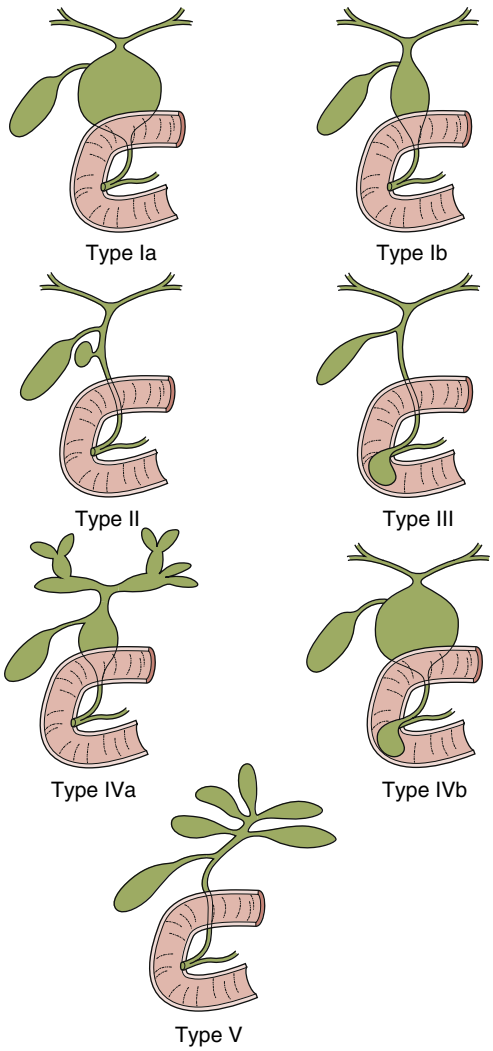

Fig. 404.5 These diagrams depict the five classifications for choledochal cyst according to Todani. *(From Todani T, Watanabe Y, Narusue M, et al. Congenital bile duct cysts: classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg. 1977;134:263–269.)*

In the neonatal period, choledochal malformations present with cholestasis and clay-colored stools; duodenal obstruction has also been reported. If untreated, long-term complications include cholangitis, pancreatitis, portal hypertension, and liver dysfunction. Importantly, biliary malignancies have also been associated with choledochal malformations, particularly with type I and IV malformations. Therefore although the approach differs based on subtype, surgical excision is the treatment of choice. The exceptions are type III cysts (choledochocele), which may be managed by endoscopic sphincterotomy. In those with extensive intrahepatic involvement (type IVa and V) not amenable to surgical resection, orthotropic liver transplantation may be required if symptomatic chronic liver disease develops.

Choledocholithiasis and Biliary Sludge

Choledocholithiasis in the neonatal age-group is rare. The incidence of biliary sludge or inspissated bile causing cholestasis has been reported to affect 1 in 175,000 births. Both choledocholithiasis and biliary sludge are often detected by abdominal ultrasound. In patients with choledocholithiasis, a stone is typically visualized, whereas biliary sludge is suspected when low-level echoes are seen without evidence of choledocholithiasis on abdominal ultrasound. Factors altering bile acid composition, such as hemolytic disease, or bile flow, such as fasting or use of parenteral nutrition, contribute to the formation of sludge and stones. Ceftriaxone, a third-generation cephalosporin, has been identified as a risk factor in neonates;

Table 404.1 Classic Criteria Based on Five Body Systems for a Diagnosis of Alagille Syndrome

SYSTEM/PROBLEM	DESCRIPTION
Liver/cholestasis	Usually presenting as jaundice with conjugated hyperbilirubinemia in the neonatal period, often with pale stools
Dysmorphic facies	Broad forehead; deep-set eyes, sometimes with upslanting palpebral fissures; prominent ears; straight nose with bulbous tip; and pointed chin giving the face a somewhat triangular appearance
Congenital heart disease	Most frequently peripheral pulmonary artery stenosis, but also pulmonary atresia, atrial septal defect, ventricular septal defect, and tetralogy of Fallot
Axial skeleton/vertebral anomalies	"Butterfly" vertebrae may be seen on an anteroposterior radiograph and occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Eye/posterior embryotoxon	Anterior chamber defects, most commonly posterior embryotoxon, which is prominence of the Schwalbe ring at the junction of the iris and cornea

From Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet.* 2012;20(3):251–257, Table 1.

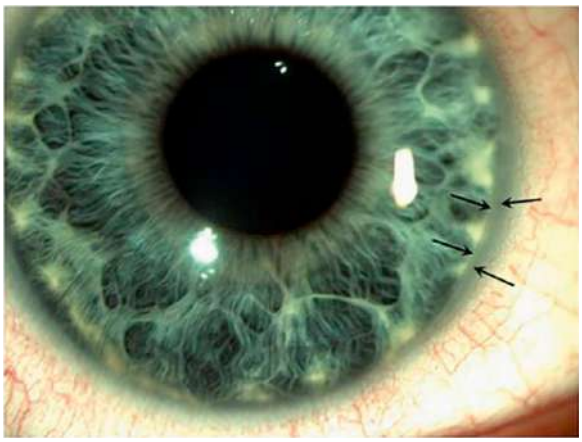

Fig. 404.6 Posterior embryotoxon. *(From Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012;20:251–257, Fig. 1.)*



Fig. 404.7 Butterfly vertebrae seen in the thoracic and upper lumbar regions. The child had undergone cardiac surgery, hence the presence of visible wires. *(From Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012;20:251–257, Fig. 2.)*

biliary sludge has been reported to occur in 30–46% of children after a mean of 9 days. It is thought that high drug concentrations in the biliary system may precipitate with calcium salts, causing sludge or gallstones.

Both choledocholithiasis and biliary sludge in the infant is usually managed conservatively because cholestasis usually resolves with spontaneous passage of the stone or sludge. Ursodeoxycholic acid has also been used to treat gallstones and sludge. However, its ability to significantly alter the natural history has not been demonstrated. Endoscopic or surgical interventions are rarely required, but may be reserved for those with severe disease.

INTRAHEPATIC DISORDERS

Alagille Syndrome

Alagille syndrome (ALGS) is a multisystem autosomal dominant disorder with hepatic, ophthalmologic (i.e., posterior embryotoxon), cardiac (i.e., peripheral pulmonary stenosis), skeletal (i.e., butterfly vertebrae), renal, and vascular involvement (i.e., moyamoya or aneurysms) (Table 404.1). Characteristic triangular facies, a prominent forehead, deep-set eyes, bulbous nose tip, and pointed chin may be noted. ALGS is caused by pathogenic variants in the *JAG1* gene in 98% of patients and the *NOTCH2* gene in the remaining 2%. Other genes associated with paucity of bile ducts, but not typical ALGS, include *KDM6A* and *HNF1β*. The estimated prevalence of ALGS is approximately 1 in 30,000 live births. A clinical diagnosis can also be made in the presence of cholestatic liver disease and associated eye (Fig. 404.6), heart, skeletal (Fig. 404.7), and facial features.

The majority of patients with ALGS are diagnosed within the first year of life, with many presenting with cholestasis and elevated liver enzymes. Cholestasis is thought to be a result of the paucity of intrahepatic bile ducts, a characteristic hepatic manifestation of AGLS, defined as an intrahepatic bile duct–to–hepatic artery ratio in the portal areas of <0.5; this is present in 75–100% of patients. However, bile duct paucity may not be present in the newborn period, and the liver biopsy may show inflammation and bile ductular proliferation. In addition, nonvisualization of the extrahepatic biliary tree because of intrahepatic disease may lead to a misdiagnosis of biliary atresia in some cases. Therefore expert review of histologic and radiographic studies is essential to making the correct diagnosis. The spectrum of bile duct paucity is noted in Figure 404.8.

In general, cholestasis in patients with ALGS typically worsens until 5-6 years of age and then stabilizes or improves in some children. Pruritus, a prominent and debilitating complication of this condition, can be noted within the first 6 months of life. Choleretics, rifampin, sertraline, and naltrexone have been traditionally used in attempts to reduce pruritus in patients with ALGS. Clinical approval of apical sodium-dependent bile acid transporter inhibitors (also known as *ileal bile acid cotransporters*) (such as maralixibat and odevixibat) offers an option for debilitating pruritus and reducing serum bile acid levels.

End-stage liver disease develops in approximately 18% of children, but cardiac and vascular complications are the leading causes of mortality. Therefore a multisystem approach is critical to ensure adequate care for a patient with ALGS.

CYSTIC FIBROSIS–ASSOCIATED LIVER DISEASE

Cystic fibrosis (CF) is caused by a pathogenic variant in the *CFTR* gene. The incidence of CF varies based on ethnicity, from 1 in 2,500 in Northern Europe to 1 in 350,000 in the Japanese population. In Europe and North America, newborn screening for CF is widely available. Sweat chloride measurements and genetic testing are required to confirm

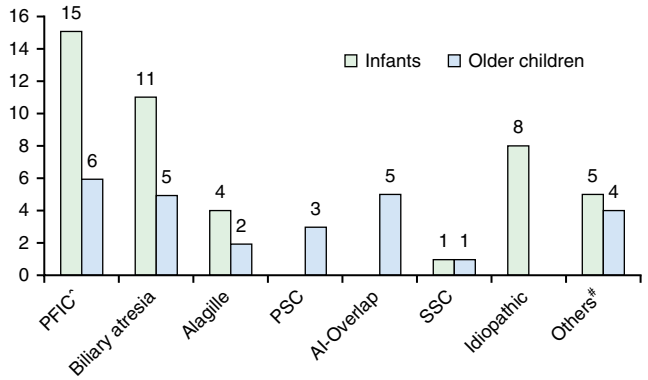

Fig. 404.8 Etiologic spectrum of ductal paucity. ^PFIC type 2 and type 3 were present in 14 and 1 infants and 3 and 3 older children, respectively. SSC was secondary to Langerhans cell histiocytosis in 2 children. #Other etiologies included in infants: cystic fibrosis (n = 1), giant cell hepatitis (n = 1), cytomegalovirus infection (n = 1), Caroli syndrome (n = 1), and Niemann-Pick type C (n = 1), whereas in older children: oxcarbazepine-induced vanishing bile duct syndrome (n = 1), congenital portosystemic shunt (n = 1), myeloproliferative disorder (n = 1), and hereditary fructose intolerance (n = 1). AI-Overlap, Autoimmune-overlap; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis. *(From Meena BL, Khanna R, Bihari C, et al. Bile duct paucity in childhood – spectrum, profile, and outcome. Eur J Pediatr. 2018;177:1261–1289.)*

the diagnosis. Cholestasis can be the first presenting symptom of CF-associated liver disease and has been reported to be present in approximately 6% of infants with CF. Infants with meconium ileus have been identified to be at increased risk for developing cholestasis in the neonatal period.

The cystic fibrosis transmembrane conductance regulator (CFTR), expressed on the apical surface of the biliary epithelial cells, functions to regulate chloride and bicarbonate secretion into the biliary canaliculus to provide adequate hydration for bile flow. When CFTR is nonfunctional or dysfunctional, the secretions become thick, leading to biliary obstruction. Postmortem examination of infants with CF revealed excessive mucus within the biliary tree.

Cholestasis in most infants with CF resolves by 9-10 months of age without significant sequelae. However, reports of clinically significant CF-associated liver disease causing liver failure and death have been reported in early childhood.

DISORDERS OF PLASMA MEMBRANE TRANSPORTERS

Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is the term used to denote a group of autosomal recessive disorders affecting bile acid transport (Table 404.2). Notably, all PFIC disorders typically present with low or normal GGT cholestasis except for PFIC3, which is associated with high GGT concentrations. Genetic testing is available to aid in the diagnosis of these disorders. **PFIC1** is caused by a pathogenic variant in *ATP8B1* encoding for a P-type ATPase (FIC1) highly expressed on the apical membrane of epithelial cells. Although its exact role is unknown, it likely functions as an aminophospholipid flippase to maintain homeostasis within the phospholipid bilayer by translocating phospholipids from the outer leaflet into the inner leaflet of the plasma membrane. Loss of ATP8B1 may result in an imbalance in the distribution of phospholipids, leading to instability of the canalicular membrane and decreased function of the transmembrane proteins, including the bile acid transporter (i.e., ABCB11). ATP8B1 is expressed on other epithelial cells, including the pancreas and small intestines. Therefore extrahepatic manifestations of *ATP8B1 (FIC1) deficiency* include diarrhea, pancreatic exocrine insufficiency, and sensorineural hearing loss. The liver histology was first described in Amish descendants with the surname Byler. Characteristic findings of "bland cholestasis" include preserved liver architecture with canalicular cholestasis and mild ductular proliferation. Inflammation is typically not a prominent feature with the absence of giant cells. On electron microscopy, the bile has a granular appearance and has been referred to as *Byler bile*. Progression to end-stage liver disease may occur. Significant diarrhea and hepatic steatosis have been reported in children after liver transplantation.

PFIC2 is caused by a pathogenic variant in *ABCB11* encoding the bile salt export pump (BSEP) located on the canalicular membrane of the hepatocyte. BSEP actively transports bile acids out of the hepatocyte into the canaliculus against a large concentration gradient. Pathogenic variants in *ABCB11 (BSEP deficiency)* lead to the inability to transport bile acids, resulting in cholestasis. In contrast to PFIC1, liver histology shows features of neonatal hepatitis with disruption of the liver architecture and giant cell transformation. Immunohistochemistry (IHC) may reveal the absence of the BSEP protein; however, the presence of staining does not exclude a dysfunctional protein. Medical therapies are generally supportive; there are currently no proven approaches to halt progression toward cirrhosis. Hepatocellular carcinoma is a recognized complication of this condition, with 10 patients diagnosed before 5 years of age in one report. Most children will eventually require liver transplantation. Notably, recurrence of BSEP deficiency has been reported in the liver allograft, likely the result of recipient antibody production against the BSEP protein in the transplanted liver.

PFIC3 is caused by a pathogenic variant in *ABCB4* encoding the class III multidrug resistance P-glycoprotein (MDR3) located on the canalicular membrane of the hepatocyte. MDR3 functions as an aminophospholipid floppase, transporting phosphatidylcholine (PC) from the inner leaflet to the outer leaflet (canalicular lumen) of the plasma membrane. With an abundance of PC in the canalicular lumen, mixed micelles containing PC, cholesterol, and excreted bile acids can be formed, thus protecting the biliary tree against the detergent properties of the bile acids. In the absence of available PC, biliary injury results from exposure to inadequately solubilized bile acids. Unlike other forms of PFIC, *MDR3 deficiency* is associated with elevated serum γ-glutamyl transferase (GGT) concentrations. Liver biopsies may show portal inflammation, fibrosis, and prominent ductal proliferation. Medical and surgical therapies are limited; however, ursodeoxycholic acid (UDCA), a hydrophilic bile acid, may have a role. In a single-center study, 77% of children with a clinical diagnosis of PFIC3 showed normalization or improvement in liver enzymes during treatment with UDCA. Furthermore, patients who responded to UDCA also showed resolution of hepatosplenomegaly and pruritus. Liver histology in four children also showed decreased fibrosis after 2 years of UDCA administration. However, response to UDCA has been linked to the type of pathogenic variant, with no response in children with a truncated protein from premature stop codons.

PFIC4 is caused by a pathogenic variant in *TJP2* encoding the tight junction protein 2, a cytosolic component for several classes of cell-cell junctions; TJP2 plays an important role in the localization of paracellular structures. When dysfunctional, the tight junctions between hepatocytes are impaired, predisposing to reflux of bile into the paracellular spaces and resulting in hepatocellular injury. Hepatocellular carcinoma has been reported. Extrahepatic manifestations include neurologic and respiratory involvement, thought to be related to the widespread distribution of the TJP2 protein. Histologic characteristics include nonspecific features with intracellular cholestasis and scant giant cells. There are no proven effective medical therapies, and liver transplantation has only been reported in a small number of patients.

PFIC5 is caused by a pathogenic variant in *NR1H4* encoding for the farnesoid X receptor (FXR), a master regulator of bile acid homeostasis. All patients described had severe liver dysfunction and coagulopathy not responsive to vitamin K beginning within the first several months of life. Progression to liver failure has been reported within the first 2 years of life with worsening coagulopathy, hypoglycemia, and hyperammonemia. Liver biopsy features include ductular reaction, diffuse giant cell transformation, intralobular cholestasis with variable degrees of inflammation, and fibrosis. None of the reported patients showed BSEP expression. Outcomes are universally poor, necessitating liver transplantation. Survival after liver transplantation has been reported to be satisfactory, but graft steatosis has been noted.

Table 404.2 Progressive Intrahepatic Familial Cholestasis Genetics and Transporter Defects and Associated γ-Glutamyl Transferase Levels

	LOCUS	GENE	DEFECT	GGT
PFIC-1 BRIC-1	18q21-22	*ATP8B1/FIC1*	ATP-dependent amino-phospholipid transport	Normal
PFIC-2 BRIC-2	2q24	*ABCB11/BSEP*	ATP-dependent bile acid transport	Normal
PFIC-3	7q21	*ABCB4/MDR3*	ATP-dependent translocation of phosphatidylcholine	High
PFIC-4		*TJP2*	Tight junction protein	Normal
PFIC-5		*NR1H4/FXR*	Nuclear bile acid receptor	Normal
PFIC-6		*MYO5B*	Myosin5b	Normal

BRIC, Benign recurrent intrahepatic cholestasis; GGT, γ-glutamyl transferase; PFIC, progressive familial intrahepatic cholestasis.
From Loomes KM, Emerick KM. Pediatric cholestatic liver disease. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease,* 6th ed. Philadelphia: Elsevier; 2021: Table 70.2, p. 771.

PFIC6 is caused by a pathogenic variant in *MYO5B* encoding for myosin 5B. *MYO5B deficiency* has also been linked to **microvillus inclusion disease**, in which some patients develop low GGT cholestasis. It is recognized that a form of low GGT cholestasis, resembling other PFIC disorders, can develop in the absence of intestinal disease in patients with MYO5B defects. Histologic features show giant cell hepatitis, fibrosis, and hepatocellular cholestasis. IHC reveals abnormal organization of both BSEP and MDR3 in the canaliculi and a granular and patchy pattern in the subcanalicular area. The prognosis for patients with PFIC6 appears to be better than with other forms of PFIC, with the median age of 5 years without progressive liver failure in the first case series reported. Cholestatic liver disease has developed in some patients who had undergone isolated intestinal transplant because of intestinal failure. This has prompted some to advocate for the consideration of a combined liver-intestine transplant in this patient population.

Endocrinopathies

Congenital hypothyroidism has long been associated with neonatal cholestasis. In a single-center study, 35% of patients with congenital hypothyroidism presented with cholestasis. Liver biopsies in these infants revealed intracellular bile pigment accumulation and variable giant cell formation. The pathogenesis remains unknown, but it is postulated that hormones, including thyroid hormone, regulate bile production and flow. Although screening for congenital hypothyroidism using thyroid-stimulating hormone (TSH) is common in many countries, central hypothyroidism resulting from pan-hypopituitarism (i.e., septo-optic dysplasia) may be missed because of a falsely low TSH. Prompt recognition and treatment are vital, as delayed treatment in congenital hypothyroidism may have severe neurodevelopmental consequences and lead to death in those with adrenal insufficiency. Fortunately, cholestasis usually resolves after appropriate hormone supplementation, and progression of liver disease is not expected.

HEPATOCYTE INJURY

Infections, drugs, metabolic disorders, and genetic conditions should also be considered as causes of cholestasis in an infant.

Infections

Bacterial, fungal, and viral infections may manifest as neonatal cholestasis. In a single-center study, urinary tract infections were found in 7.5% of asymptomatic, afebrile infants less than 8 weeks of age presenting with jaundice. Infections may result in hepatic injury through direct invasion from hepatotrophic microorganisms (i.e., cytomegalovirus [CMV]), or secondarily by exposure to endotoxins released from microbe membranes. In animal models, endotoxin has been shown to decrease bile flow. In sepsis, perfusion to the liver may also be impaired.

Congenital infections are unique to neonates and require particular attention. The so-called "TORCHeS" infections (*Toxoplasma gondii*, rubella, CMV, herpes simplex virus, and syphilis) are recognized causes of neonatal cholestasis. Although some affected infants are born with stigmata of a congenital infection, such as thrombocytopenic purpura in congenital rubella syndrome, others may present with neonatal cholestasis alone. Therefore is it important to assess for congenital infections in the cholestatic infant, as treatment and additional screening may be necessary upon diagnosis (i.e., hearing tests in congenital CMV infection).

Infusions, Drugs, and Medications

Although a multitude of drugs and medications can cause cholestasis, parenteral nutrition–associated liver disease (PNALD) is a common iatrogenic cause of cholestasis, particularly in the neonatal intensive care unit. Typically observed in infants requiring parenteral nutrition for more than 2 weeks, other risk factors for the development of PNALD include prematurity, low birthweight, nil per os (NPO), long duration of parenteral nutrition, imbalanced amino acid composition, bacteremia, and abdominal surgeries. The lipid emulsion used also has a significant impact on the development of PNALD. Specifically, soybean lipid emulsions contain ω-6 fatty acids and plant-based cholesterol products called phytosterols. ω-6 Fatty acids are thought to be proinflammatory, whereas phytosterols can impair bile flow caused by inefficient metabolism in the liver. In contrast, fish oil emulsions are rich in ω-3 fatty acids, which are antiinflammatory and do not contain phytosterols, thus protecting the liver against PNALD. The availability of SMOF—a soy, medium-chain triglyceride (MCT), olive oil, and fish oil emulsion—also offers the benefits of an ω-3 rich emulsion but also contains adequate essential fatty acids. Clinical trials have shown that SMOF was hepatoprotective in preterm infants, resulting in a lower incidence of PNALD with a lower peak bilirubin level and was associated with decreased hospital length of stay. UDCA may also provide some benefit to patients with PNALD; it was well tolerated without reported adverse events. Therefore the benefits of reducing liver enzymes must be weighed against the unknown efficacy of UDCA. Fortunately, as parenteral nutrition is weaned and enteral feeds are increased, PNALD resolves in most patients without long-term sequelae.

Alpha$_1$-Antitrypsin Deficiency

α_1-Antitrypsin (A1AT) deficiency is the most common form of inherited neonatal cholestasis, occurring in approximately 1 in 2,000-3,500 live births in North America. This autosomal recessive disorder is diagnosed by a low serum A1AT level, protein electrophoresis to identify pathologic phenotypes—most commonly ZZ—and molecular testing. Pathogenic variants in the *SERPINA1* gene may result in abnormal folding of the A1AT protein within the rough endoplasmic reticulum. The misfolded A1AT protein is unable to be secreted out of the hepatocyte, and intracellular accumulation leads to autophagy, mitochondrial injury, and progression to hepatocellular injury. It should be noted that A1AT is also an acute-phase reactant and may be falsely elevated during systemic inflammation; therefore a normal A1AT level in this clinical context may not exclude a diagnosis of A1AT deficiency.

A large Swedish study prospectively screened 200,000 newborns to identify those with A1AT deficiency; neonatal cholestasis occurred in ~11% of infants with the ZZ phenotype. A multicenter study of 350 patients with A1AT deficiency with a mean follow-up time of 2.5 years reported a slightly increased risk of developing portal hypertension in those with a history of neonatal cholestasis compared with those without, although there was no difference in the risk of liver transplantation or death.

Inborn Errors of Metabolism

Galactosemia is a rare inborn error of galactose metabolism cause by a deficiency in the galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), or UDP-galactose-4′-epimerase (GALE) enzyme. As such, galactose cannot be metabolized to glucose, leading to hypoglycemia and accumulation of toxic intermediate metabolites causing vomiting; feed intolerance; and hepatic, neurologic, ocular, and renal injury. An association between galactosemia and *Escherichia coli* sepsis has also been reported. Although rare, neonatal cholestasis may be the presenting symptom of an infant with galactosemia. Early diagnosis with enzyme and genetic testing and treatment with a strict galactose-free diet are essential to preserving neurologic function. Fortunately, many countries have adopted galactosemia as part of their newborn metabolic screen, which has aided in the early diagnosis and improved outcomes of these patients.

Type I tyrosinemia is an autosomal recessive disorder caused by a defect in the fumarylacetoacetate hydrolase (FAH) enzyme required for tyrosine metabolism. Accumulation of metabolites upstream of the FAH enzyme, including fumarylacetoacetate, succinylacetate, and succinylacetone, may precipitate hepatic and renal injury. Infants with tyrosinemia can be present with cholestasis, but usually also have evidence of hepatic dysfunction, including severe coagulopathy out of keeping with the degree of hepatocellular injury. High urine succinylacetone levels are highly suggestive of tyrosinemia type I. Treatment with nitisinone, a potent inhibitor of tyrosine degradation, and dietary therapy are the mainstays of therapy to prevent acute and chronic complications of tyrosinemia type I.

Hereditary fructose intolerance (HFI) is an autosomal recessive disorder caused by the deficiency of aldolase B enzyme. In the absence of aldolase B activity, large amounts of fructose-1-phosphate accumulate in the liver, leading to depletion of inorganic phosphate and adenosine triphosphate (ATP). As a result of depleted inorganic phosphate, new ATP cannot be generated, leading to hepatocyte necrosis and liver dysfunction. Although breast milk is fructose free, common infant formulas may contain fructose in various forms. Furthermore, sucrose, a disaccharide made up of glucose and fructose monosaccharides, is a common component of oral medications for infants. Therefore a careful review of unexpected fructose exposure should be undertaken in infants with liver dysfunction in which HFI is suspected. A diagnosis is confirmed by measuring enzyme activity or through molecular testing. Symptoms resolve with the institution of a strict fructose-free diet, and patients are expected to develop normally.

Lysosomal and peroxisomal disorders, including Niemann-Pick type A and C and Zellweger syndrome, respectively, are another group of conditions that may present with neonatal cholestasis. Typically, these conditions are multisystemic resulting in neurologic, cardiac, and hematologic manifestations depending on the disorder. Liver biopsies may show accumulation of storage materials within organelles on electron microscopy. The diagnosis is usually confirmed by genetic testing.

Mitochondrial hepatopathies result from deletion or depletion of mitochondrial genes including *POLG1, DGUOK,* and *MPV17* (Table 404.3). These conditions typically present with neonatal cholestasis and may evolve into neonatal acute liver failure characterized by lactic acidosis, coagulopathy, hypoglycemia, and hyperammonemia. An elevated lactate-to-pyruvate ratio >25 mol/mol is suggestive of a mitochondrial disorder. Liver biopsy may reveal microsteatosis and abnormal mitochondrial staining or abnormal architecture on electron microscopy. There is often multisystem involvement, including neurologic, cardiac, and musculoskeletal manifestations of mitochondrial dysfunction. Prognosis is poor with limited proven therapies.

Table 404.3 Phenotypic Classification of Primary Mitochondrial Hepatopathies

RC (electron transport) defects (OXPHOS)
- Neonatal liver failure
  - Complex I deficiency
  - Complex IV deficiency (*SCO1* variants)
  - Complex III deficiency (*BCS1L* variants)
  - Coenzyme Q deficiency
  - Multiple complex deficiencies (transfer and elongation factor variants)
  - mtDNA depletion syndrome (*DUGOK, MPV17, POLG, SUCLG1, C10orf2/Twinkle* variants)
- Later-onset liver dysfunction or failure
  - Alpers-Huttenlocher disease (*POLG* variants)
  - Pearson marrow pancreas syndrome (mtDNA deletion)
  - Mitochondrial neurogastrointestinal encephalopathy (*TYMP* variants)
  - NNH (*MPV17* variants)

Fatty acid oxidation defects
- Long-chain 3 hydroxyacyl-coenzyme A dehydrogenase
- Carnitine palmitoyltransferase I and II deficiencies
- Carnitine-acylcarnitinetranslocase deficiency

Urea cycle enzyme deficiencies

Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies

Phosphoenol pyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia

Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (*SLC25A13* variants)

NN, Navajo neurohepatopathy; OXPHOS, oxidative phosphorylation; RC, respiratory chain.

From Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes. *J Pediatr*. 2013;163(4):942–948, Table 1.

Bile Acid Synthesis Defects

Bile acid synthesis defects are a rare cause of neonatal cholestasis. Liver injury is postulated to result from the accumulation of hepatotoxic intermediate metabolites and absence of the normal trophic and choleretic effects of primary bile acids. Inborn errors of bile acid biosynthesis typically present with a form of low GGT cholestasis and low serum bile acid levels. Clinical presentation may vary from neonatal cholestasis to neonatal acute liver failure. Characteristic urine bile acid profiles may indicate specific enzyme defects. Supplementation with cholic acid may be helpful; however, patients who do not respond to bile acid replacement therapy may require liver transplantation.

Gestational Alloimmune Liver Disease

Gestational alloimmune liver disease (GALD) is a rapidly progressive disease characterized by iron deposition in the liver, heart, salivary glands, and endocrine organs without increased iron stores in the reticuloendothelial system. Infants present with liver dysfunction within the first few days of life. Familial cases and repeated miscarriages are commonly reported. The postulated pathophysiology involves maternal sensitization to fetal liver antigens. As a result, maternal antibodies against the fetal liver are transported across the placenta causing fetal liver injury in utero. Liver injury results in decreased hepatic hepcidin expression and thus dysregulated iron update into the developing fetus. Laboratory findings include hypoglycemia, hyperbilirubinemia, hypoalbuminemia, elevated ferritin, and coagulopathy. The diagnosis is usually confirmed by salivary biopsy or MRI demonstrating extrahepatic siderosis in the pancreas, myocardium, or thyroid follicles. Liver biopsies almost universally show cirrhosis, and positive staining for C5b-9 membrane attack complex has also been reported. The differential diagnosis is noted in Table 404.4. Treatment with exchange transfusion and intravenous immunoglobulin (IVIG) has been shown to

Table 404.4 Typical Laboratory Findings in Neonatal Liver Failure

	GALD	HLH	MITOCHONDRIAL	VIRAL	ISCHEMIC
Transaminase levels (IU/L)	Normal/mild increase (<100)	Moderate/significant increase (>1,000)	Moderate increase (100-500)	Significant increase (>1,000)	Significant increase (>1,000-6,000)
INR	Significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase
Ferritin level (ng/mL)	800-7,000	Significant increase (>20,000)	Variable	Significant increase (>20,000)	Variable depending on underlying cause of ischemia
Triglyceride levels	Normal	Increased	Normal	Normal	Normal
Hypoglycemia	Yes	Often	Yes	Often	Variable
Lactic acidosis	Normal	Normal	Increased	Normal	Often
α-Fetoprotein level (for age)	Increased	Normal	Normal/increased	Normal	Normal
Cholestasis	Progressive after birth	Moderate/significant	Moderate	None/mild at presentation	Mild/moderate

HLH, Hemophagocytic lymphohistiocytosis.
From Larson-Nath C, Vitola BE. Neonatal acute liver failure. *Clin Perinatol*. 2020;47:25–39: Table 2; with data from Sundaram et al. *J Pediatr*. 2011;159:813–818; Taylor et al. *Liver Transpl*. 2016;22(5):677–685; Bitar et al. *J Pediatr Gastroenterol Nutr*. 2017;64(1):70–75; Fellman et al. *Semin Fetal Neonatal Med*. 2011;16(4):222–228.

improve outcomes and reduce the need for liver transplantation. Given the high rate of recurrence of GALD in future pregnancies of affected mothers, maternal treatment with weekly IVIG beginning at 18 weeks gestational age should be considered and has been shown to decrease GALD in the developing fetus.

OTHER SYNDROMES ASSOCIATED WITH NEONATAL CHOLESTASIS

Neonatal Ichthyosis and Sclerosing Cholangitis

Neonatal ichthyosis and sclerosing cholangitis (NISCH) syndrome is a rare autosomal recessive condition caused by pathogenic variants in claudin-1 *(CLDN1)*, a membrane protein needed for the formation of tight junctions between cells. Infants may present with dry scaly skin, alopecia, and jaundice within the first few weeks of life. Defects in CLDN1 (similar to TJP2 deficiency) increase paracellular leakage and regurgitation of the toxic components of bile, leading to bile duct injury and cholestasis. Liver histology is variable, with most infants having evidence of hepatocellular cholestasis and bile duct plugs. Ductular proliferation, portal fibrosis, ductopenia, and characteristic findings of sclerosing cholangitis on cholangiogram have been described later in adolescence. Severity of liver disease is also variable ranging from transient neonatal cholestasis to progressive cirrhosis requiring liver transplantation.

Lymphedema-Cholestasis Syndrome (Aagenaes Syndrome)

Lymphedema-cholestasis syndrome is a rare cholestatic disorder manifest by cholestasis with pale stools by 1 week of life. On liver biopsy, multinucleated giant cell hepatitis was described in affected patients. The clinical course is variable, but jaundice reportedly resolves by 1-5 years of age. Intermittent episodes of cholestasis may recur but typically resolve in a period of months. Lower extremity lymphedema develops during the prepuberty period in all patients and can be disfiguring. Pathogenesis remains unknown, but a locus has been mapped to chromosome 15q and is thought to play a role in the abnormal development of lymphatic structures. The natural history of liver disease has been reported to be favorable, with cirrhosis developing in a small minority of patients.

Arthrogryposis, Renal Dysfunction, and Cholestasis

Arthrogryposis, renal dysfunction, and cholestasis (ARC) syndrome is a rare and autosomal recessive disorder caused by *VPS33B* or *VIPAR* pathogenic variants. Prominent clinical features include arthrogryposis, renal tubular acidosis, and a low GGT cholestasis. Additional features include agenesis of the corpus callosum, deafness, hypothyroidism, ichthyosis, recurrent infections, and congenital cardiac defects. With abnormal platelet count and function having also been described, life-threatening bleeding has been reported both spontaneously and after liver biopsy in affected patients. *VPS33B* or *VIPAR* plays a role in intracellular vesicular trafficking pathways, cell polarity, and membrane protein localization. As such, abnormal localization of canalicular membrane proteins, including BSEP and MDR3, have been reported in liver biopsies of patients with ARC syndrome and may contribute to the pathogenesis of cholestasis. Although the prognosis has been reported to be poor, successful liver transplantation for severe intractable pruritus and poor quality of life has been reported.

IDIOPATHIC NEONATAL HEPATITIS

Idiopathic neonatal hepatitis was a term used to describe infants with neonatal cholestasis for which a specific cause could not be determined. However, with the advent of molecular testing, the number of patients with "idiopathic neonatal hepatitis" is decreasing owing to the expanding knowledge of the molecular causes of cholestasis.

Management

Management of patients with neonatal cholestasis requires the clinician to identify the cause of cholestasis while ruling out conditions that require prompt intervention. Delayed diagnosis of sepsis, pan-hypopituitarism, or inborn errors of metabolism may have fatal consequences. Similarly, failure to promptly treat galactosemia or congenital hypothyroidism can have devastating neurologic sequelae. In patients with biliary atresia, the most common indication for pediatric liver transplant worldwide, early surgical intervention with KPE has been shown to improve survival with the native liver. Table 404.5 provides a framework for the initial investigation of a patient with neonatal cholestasis.

Table 404.5 Etiologies and Suggested Investigations for Patients with Neonatal Cholestasis

ETIOLOGY	RECOMMENDED INVESTIGATIONS
General investigations for all infants with cholestasis	CBC and differential, ALT, AST, total and conjugated bilirubin, GGT and ALP, INR, albumin, blood glucose Abdominal ultrasound with Doppler Review newborn metabolic screen Urinalysis
DISORDERS OF EXTRAHEPATIC BILE DUCTS	
Biliary atresia	MMP7, liver biopsy, intraoperative cholangiogram, examination of the biliary remnant
Choledochal malformation and choledocholithiasis/ microlithiasis	Abdominal US, MRCP
INTRAHEPATIC DISORDERS	
Alagille syndrome	Ophthalmologic examination, chest x-ray, echocardiogram, liver biopsy, and genetic testing for *JAG1* and *NOTCH2*
Cystic fibrosis	Sweat chloride, *CFTR* testing
Membrane transporter defects	
• PFIC1	*ATP8B1* genetic testing
• PFIC2	*ABCB11* genetic testing
• PFIC3	*MDR3* genetic testing
• PFIC4	*TJP2* genetic testing
• PFIC5	*NR1H4* (*FXR*) genetic testing
• PFIC6	*MYO5B* genetic testing
• ARC syndrome	*VPS33B* and *VIPAR* genetic testing
• NISCH syndrome	*CLDN1* genetic testing
Endocrinopathies	
• Hypothyroidism	TSH, free T_4
• Hypopituitarism	TSH, free T_4, cortisol and electrolytes, MRI brain
Hepatocyte injury	
• Infection	Complete blood count and differential, blood and urine cultures, urinalysis, "ToRCHeS" screen
• Total parental nutrition	History
Inborn errors of metabolism	
• Galactosemia	Galactose-1-phosphate uridyltransferase enzyme activity, genetic testing for *GALT*, *GALK*, or *GALE*
• Tyrosinemia	Urine succinylacetone, *FAH* genetic testing
• Hereditary fructose intolerance	Aldolase B (*ALDOB*) enzyme activity and genetic testing
Bile acid synthesis defect	Serum bile acids, urine bile acid profile, genetic testing
α_1-Antitrypsin deficiency	Blood α_1-antitrypsin concentrations, electrophoretic phenotyping, *SERPINA1* genetic testing
Lysosomal disorders	
• Neimann Pick A and C	Genetic testing for *SMPD1* for Neimann Pick A and *NPC1* or *NPC2* genes for Neimann Pick C
• Cholesterol esterase storage disease/Wolman	Liposomal acid lipase enzyme testing and *LIPA* genetic testing
• Mucopolysaccharidoses	Urine screen for glycosaminoglycans. Genetic testing for specific pathogenic variants associated with mucopolysaccharidoses
Peroxisomal biogenesis disorders	
• Zellweger syndrome • Infantile Refsum	Very long-chain fatty acid concentrations, genetic testing for PEX genes
Mitochondrial hepatopathy	Ammonia, lactate, pyruvate, creatinine kinase, echocardiogram, genetic testing for mitochondrial genes
Gestational alloimmune liver disease	MRI, buccal biopsy, serum ferritin, total iron-binding capacity ammonia

CBC, Complete blood count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; INR, international normalized ratio; MMP7, matrix metalloproteinase 7; US, ultrasound; MRCP, magnetic resonance cholangiopancreatography; JAG1, jagged-1; NOTCH2, notch receptor 2; CFTR, cystic fibrosis transmembrane conductance regulator; ATP8B1, ATPase phospholipid transporting 8B1; ABCB11, ATP-binding cassette subfamily B member 11; MDR3, class III multidrug resistance P-glycoproteins; TJP2, tight junction protein 2; NR1H4, nuclear receptor subfamily 1 group H member 4; MYO5B, myosin VB; VPS33B, vacuolar protein sorting-associated protein 33B; VIPAR, VPS33B interacting protein, apical-basolateral polarity regulator, Spe-39 homolog; CLDN1, claudin 1; TSH, thyroid-stimulating hormone; GALT, galactose-1-phosphate uridylyl transferase; GALK, galactokinase; GALE, UDP-galactose-4′-epimerase; FAH: fumarylacetoacetate hydrolase; SERPINA1, serpin family A member 1; SMPD1, sphingomyelin phosphodiesterase 1; NPC1, NPC intracellular cholesterol transporter 1; NPC2, NPC intracellular cholesterol transporter 2; LIPA, lysosomal acid lipase.

Table 404.6 Recommended Nutritional Support for Children with Cholestasis

ENERGY/NUTRIENT	REQUIREMENT
Energy	~130% of requirement for age
Fat	30–50% of total calories Start with MCT/LCT = 30%/70% of total fat calories
Protein	~130–150% of requirement for age
Carbohydrate	40–60% of total calories
Vitamin A	<10 kg: 5,000 IU/day >10 kg: 10,000 IU/day
Vitamin D	Cholecalciferol: 2,000-5,000 IU/day
Vitamin E	D-alpha-tocopheryl polyethylene glycol 1000 succinate: 15-25 IU/kg/day
Vitamin K	2-5 mg/day
Calcium	Meet DRI

Adapted from Mouzaki M, Bronsky J, Gupte G, et al. Nutrition support of children with chronic liver diseases: a joint position paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2019;69(4):498–511.

In infants with chronic cholestasis, growth failure and malnutrition are major concerns. Bile is an essential component of lipid digestion; therefore cholestasis leads to fat maldigestion and fat-soluble vitamin deficiencies (i.e., vitamin A, D, E, and K). Caloric support by an MCT-containing formula may be helpful, as MCT can be absorbed in a bile acid–independent manner. Supplementation with aqueous vitamin A, D, E, and K formations should be considered to avoid the complications of fat-soluble vitamin deficiencies. Table 404.6 has been adapted to provide initial guidance toward nutritional support in children with neonatal cholestasis. Regular monitoring of anthropometrics and fat-soluble vitamin levels is needed to ensure patients are provided with adequate nutrition for growth and development.

404.2 Cholestasis in the Older Child

Simon Lam and William F. Balistreri

Cholestasis with onset after the neonatal period is most often caused by acute viral hepatitis or exposure to hepatotoxic drugs. However, many of the conditions causing neonatal cholestasis can also cause chronic cholestasis in older patients (see Table 403.3). Consequently, older children and adolescents with conjugated hyperbilirubinemia should be evaluated for acute and chronic viral hepatitis, α_1-antitrypsin deficiency, Wilson disease, liver disease associated with inflammatory bowel disease, sclerosing cholangitis, autoimmune hepatitis, drug-induced liver injury, and the syndromes of intrahepatic cholestasis. Other causes include obstruction related to cholelithiasis, abdominal tumors, enlarged lymph nodes, or hepatic inflammation resulting from drug ingestion. Management of cholestasis in the older child is similar to that proposed for neonatal cholestasis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 405 Metabolic Diseases of the Liver

Julie Bonn and William F. Balistreri

INTRODUCTION

Metabolic liver diseases in children, although individually rare, altogether represent a significant cause of morbidity and mortality. This is because the liver has a central role in synthetic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace element, and vitamin metabolism. Therefore inborn errors of metabolism will result in metabolic abnormalities, specific enzyme deficiencies or defects, and disorders of protein transport that can have primary or secondary effects on the liver (Table 405.1). Liver disease can arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolized substrate accumulates proximal to a block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops, or when synthesis of an abnormal metabolite occurs. The spectrum of pathologic changes includes **hepatocyte injury**, with subsequent failure of other metabolic functions, often resulting in cirrhosis and/or liver cancer; abnormal **storage** of lipid, glycogen, or other products manifested as hepatomegaly, often with complications specific to deranged metabolism (hypoglycemia with glycogen storage disease); and absence of structural change despite profound **metabolic effects**, as seen in patients with urea cycle defects. Clinical manifestations of metabolic diseases of the liver mimic infections, intoxications, and hematologic and immunologic diseases (Table 405.2).

Many metabolic diseases are detected in expanded newborn metabolic screening programs (see Chapter 104). Clues are provided by family history of a similar illness or by the observation that the onset of symptoms is closely associated with a change in dietary habits; in patients with hereditary fructose intolerance, symptoms follow ingestion of fructose (sucrose). Clinical and laboratory evidence often guides the evaluation. Liver biopsy offers morphologic study and permits enzyme assays, as well as quantitative and qualitative assays of various other constituents (e.g., hepatic copper content in Wilson disease). Genetic/molecular diagnostic approaches are also available. Such studies require cooperation of experienced laboratories and careful attention to collection and handling of specimens. Treatment depends on the specific type of defect, and although relatively uncommon, altogether metabolic diseases of the liver account for up to 10% of the indications for liver transplantation in children, a number that may be underestimated given the acute nature of some of these conditions, precluding complete diagnostic investigation before transplantation.

405.1 Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)

Julie Bonn and William F. Balistreri

Bilirubin is the metabolic end product of heme. Before excretion into bile, it is first glucuronidated and made water-soluble by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT). UDPGT activity is deficient or altered in three genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, **unconjugated** hyperbilirubinemia. UGT1A1

Table 404.6 Recommended Nutritional Support for Children with Cholestasis

ENERGY/NUTRIENT	REQUIREMENT
Energy	~130% of requirement for age
Fat	30–50% of total calories Start with MCT/LCT = 30%/70% of total fat calories
Protein	~130–150% of requirement for age
Carbohydrate	40–60% of total calories
Vitamin A	<10 kg: 5,000 IU/day >10 kg: 10,000 IU/day
Vitamin D	Cholecalciferol: 2,000-5,000 IU/day
Vitamin E	D-alpha-tocopheryl polyethylene glycol 1000 succinate: 15-25 IU/kg/day
Vitamin K	2-5 mg/day
Calcium	Meet DRI

Adapted from Mouzaki M, Bronsky J, Gupte G, et al. Nutrition support of children with chronic liver diseases: a joint position paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2019;69(4):498–511.

In infants with chronic cholestasis, growth failure and malnutrition are major concerns. Bile is an essential component of lipid digestion; therefore cholestasis leads to fat maldigestion and fat-soluble vitamin deficiencies (i.e., vitamin A, D, E, and K). Caloric support by an MCT-containing formula may be helpful, as MCT can be absorbed in a bile acid–independent manner. Supplementation with aqueous vitamin A, D, E, and K formations should be considered to avoid the complications of fat-soluble vitamin deficiencies. Table 404.6 has been adapted to provide initial guidance toward nutritional support in children with neonatal cholestasis. Regular monitoring of anthropometrics and fat-soluble vitamin levels is needed to ensure patients are provided with adequate nutrition for growth and development.

404.2 Cholestasis in the Older Child

Simon Lam and William F. Balistreri

Cholestasis with onset after the neonatal period is most often caused by acute viral hepatitis or exposure to hepatotoxic drugs. However, many of the conditions causing neonatal cholestasis can also cause chronic cholestasis in older patients (see Table 403.3). Consequently, older children and adolescents with conjugated hyperbilirubinemia should be evaluated for acute and chronic viral hepatitis, α_1-antitrypsin deficiency, Wilson disease, liver disease associated with inflammatory bowel disease, sclerosing cholangitis, autoimmune hepatitis, drug-induced liver injury, and the syndromes of intrahepatic cholestasis. Other causes include obstruction related to cholelithiasis, abdominal tumors, enlarged lymph nodes, or hepatic inflammation resulting from drug ingestion. Management of cholestasis in the older child is similar to that proposed for neonatal cholestasis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 405 Metabolic Diseases of the Liver

Julie Bonn and William F. Balistreri

INTRODUCTION

Metabolic liver diseases in children, although individually rare, altogether represent a significant cause of morbidity and mortality. This is because the liver has a central role in synthetic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace element, and vitamin metabolism. Therefore inborn errors of metabolism will result in metabolic abnormalities, specific enzyme deficiencies or defects, and disorders of protein transport that can have primary or secondary effects on the liver (Table 405.1). Liver disease can arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolized substrate accumulates proximal to a block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops, or when synthesis of an abnormal metabolite occurs. The spectrum of pathologic changes includes **hepatocyte injury**, with subsequent failure of other metabolic functions, often resulting in cirrhosis and/or liver cancer; abnormal **storage** of lipid, glycogen, or other products manifested as hepatomegaly, often with complications specific to deranged metabolism (hypoglycemia with glycogen storage disease); and absence of structural change despite profound **metabolic effects**, as seen in patients with urea cycle defects. Clinical manifestations of metabolic diseases of the liver mimic infections, intoxications, and hematologic and immunologic diseases (Table 405.2).

Many metabolic diseases are detected in expanded newborn metabolic screening programs (see Chapter 104). Clues are provided by family history of a similar illness or by the observation that the onset of symptoms is closely associated with a change in dietary habits; in patients with hereditary fructose intolerance, symptoms follow ingestion of fructose (sucrose). Clinical and laboratory evidence often guides the evaluation. Liver biopsy offers morphologic study and permits enzyme assays, as well as quantitative and qualitative assays of various other constituents (e.g., hepatic copper content in Wilson disease). Genetic/molecular diagnostic approaches are also available. Such studies require cooperation of experienced laboratories and careful attention to collection and handling of specimens. Treatment depends on the specific type of defect, and although relatively uncommon, altogether metabolic diseases of the liver account for up to 10% of the indications for liver transplantation in children, a number that may be underestimated given the acute nature of some of these conditions, precluding complete diagnostic investigation before transplantation.

405.1 Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)

Julie Bonn and William F. Balistreri

Bilirubin is the metabolic end product of heme. Before excretion into bile, it is first glucuronidated and made water-soluble by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT). UDPGT activity is deficient or altered in three genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, **unconjugated** hyperbilirubinemia. UGT1A1

Table 405.1 Inborn Errors of Metabolism that Affect the Liver

COMMON DISORDERS OF CARBOHYDRATE METABOLISM
Disorders of galactose metabolism
• Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Disorders of fructose metabolism
• Hereditary fructose intolerance (aldolase deficiency)
• Fructose-1,6 diphosphatase deficiency
Glycogen storage diseases
• Type I
• Von Gierke Ia (glucose-6-phosphatase deficiency)
• Type Ib (glucose-6-phosphatase transport defect)
• Type III Cori/Forbes (glycogen debrancher deficiency)
• Type IV Andersen (glycogen branching enzyme deficiency)
• Type VI Hers (liver phosphorylase deficiency)
Congenital disorders of glycosylation (multiple subtypes)
DISORDERS OF AMINO ACID AND PROTEIN METABOLISM
Disorders of tyrosine metabolism
• Hereditary tyrosinemia type I (fumarylacetoacetate hydrolase deficiency)
• Tyrosinemia, type II (tyrosine aminotransferase deficiency)
Inherited urea cycle enzyme defects
• CPS deficiency (carbamoyl phosphate synthetase I deficiency)
• OTC deficiency (ornithine transcarbamoylase deficiency)
• Citrullinemia type I (argininosuccinate synthetase deficiency)
• Argininosuccinic aciduria (argininosuccinate deficiency)
• Argininemia (arginase deficiency)
• N-AGS deficiency (*N*-acetylglutamate synthetase deficiency)
Maple serum urine disease (multiple possible defects*)
DISORDERS OF LIPID METABOLISM
Wolman disease (lysosomal acid lipase deficiency)
Cholesteryl ester storage disease (lysosomal acid lipase deficiency)
Homozygous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)
Gaucher disease type I (β-glucocerebrosidase deficiency)
Niemann-Pick type C (NPC 1 and 2 variants)
DISORDERS OF BILE ACID METABOLISM
Defects in bile acid synthesis (several specific enzyme deficiencies)
Zellweger syndrome—cerebrohepatorenal (multiple pathogenic variants in peroxisome biogenesis genes)
DISORDERS OF METAL METABOLISM
Wilson disease (ATP7B pathogenic variants)
Hepatic copper overload
Indian childhood cirrhosis
Neonatal hemochromatosis
DISORDERS OF BILIRUBIN METABOLISM
Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase pathogenic variants)
• Type I
• Type II
Gilbert disease (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase polymorphism)
Dubin-Johnson syndrome (multiple drug-resistant protein 2 pathogenic variants)
Rotor syndrome
MISCELLANEOUS
α_1-Antitrypsin deficiency
Citrullinemia type II (citrin deficiency)
Cystic fibrosis (cystic fibrosis transmembrane conductance regulator pathogenic variants)
Erythropoietic protoporphyria (ferrochelatase deficiency)
Polycystic kidney disease
Mitochondrial hepatopathies (see Table 404.4 and Chapter 409)

*Maple syrup urine disease can be caused by mutations in branched-chain α-keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

is the primary UDPGT isoform needed for bilirubin glucuronidation. Complete absence of UGT1A1 activity causes CN type I, while CN type II is caused by decreased UGT1A1 activity to ~10% of normal.

Table 405.2 Clinical Manifestations that Suggest the Possibility of Metabolic Disease

Recurrent vomiting, failure to thrive, short stature
Dysmorphic features
Jaundice, hepatomegaly (± splenomegaly), fulminant hepatic failure, edema/anasarca
Hypoglycemia, organic acidemia, lactic acidemia, hyperammonemia, bleeding (coagulopathy)
Developmental delay, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy
Cardiac dysfunction/failure
Unusual odors
Rickets
Cataracts
Multiorgan involvement
Family history

Gilbert syndrome, the most common hereditary hyperbilirubinemia syndrome, occurs in 5–10% of the White population. Common polymorphisms resulting in a TA insertion in the promoter region of *UGT1A1* lead to decreased binding of the TATA binding protein and decrease normal gene activity by ~30%. Snapback primer genotyping can distinguish all *UGT1A1* promoter genotypes and can provide a definitive diagnosis. Unlike the CN syndromes, Gilbert syndrome usually occurs after puberty, is not associated with chronic liver disease, and no treatment is required. Disease manifestations include fluctuating mild elevations in total serum bilirubin concentration from 1 to 6 mg/dL with no evidence of liver injury or hemolysis. Fasting or dehydration may result in visible jaundice. Because UGT1A1 catalyzes water-soluble glucuronidation and detoxification of multiple substrates other than bilirubin (i.e., drugs, hormones, environmental toxins, and aromatic hydrocarbons), pathogenic variants in the *UGT1A1* gene are implicated in cancer risk and predispose to drug toxicity and episodic jaundice specifically in cancer chemotherapy.

CRIGLER-NAJJAR SYNDROME TYPE I (GLUCURONYL TRANSFERASE DEFICIENCY)

CN type I is a rare, autosomal recessive disease caused by homozygous or compound heterozygous pathogenic variants in the *UGT1A1* gene that result in a premature stop codon or frameshift pathogenic variant and complete absence of UGT1A1 activity. At least 59 pathogenic variants have been identified to date. Parents of affected children have partial defects in conjugation, as determined by hepatic-specific enzyme assay or by measurement of glucuronide formation, but have normal serum unconjugated bilirubin levels.

Clinical Manifestations

Severe unconjugated hyperbilirubinemia develops in homozygous affected infants in the first 3 days of life. Without treatment, serum unconjugated bilirubin concentrations reach 25-35 mg/dL in the first month, which can cause **kernicterus**. Stools are pale yellow. Persistent unconjugated hyperbilirubinemia at levels >20 mg/dL without hemolysis after the first week of life should suggest the syndrome.

Diagnosis

The diagnosis of CN type I is based on the early age of onset and the extreme level of bilirubin elevation in the absence of hemolysis. In affected infants, bile contains no bilirubin glucuronide and bilirubin concentration in bile is <10 mg/dL compared with normal concentrations of 50-100 mg/dL. The diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by percutaneous liver biopsy; open liver biopsy should be avoided because surgery and anesthesia can precipitate kernicterus. DNA diagnosis is also available and may be preferable. Identification of the heterozygous state in parents also strongly suggests the diagnosis. The differential diagnosis of unconjugated hyperbilirubinemia is discussed in Chapter 137.

Treatment

The serum unconjugated bilirubin concentration should be maintained at <20 mg/dL for the first few weeks of life, and even lower in low birthweight infants. This usually requires repeated exchange transfusions and phototherapy in the immediate neonatal period. Oral calcium phosphate supplementation renders phototherapy more effective, as it forms complexes with bilirubin in the gut. Phenobarbital therapy, through CYP450 enzyme induction, should be considered to determine responsiveness and differentiation between CN types I and II. In patients with type I, there is no response to phenobarbital treatment.

The risk of kernicterus persists into adult life, although the serum bilirubin levels required to produce brain injury beyond the neonatal period are considerably higher (usually >35 mg/dL). Therefore phototherapy is generally continued through the early years of life. In older infants and children, phototherapy is used mainly during sleep so as not to interfere with normal activities. Despite the administration of increasing intensities of light for longer periods, the serum bilirubin response to phototherapy decreases with age. Additional adjuvant therapy using agents that bind photobilirubin products such as cholestyramine or agar can also be used to interfere with the enterohepatic recirculation of bilirubin.

Prompt treatment of intercurrent infections, febrile episodes, and other types of illness might help prevent the later development of kernicterus, which can occur at bilirubin levels of 45-55 mg/dL. All reported patients with CN type I have eventually experienced severe kernicterus by young adulthood.

Orthotopic liver transplantation cures the disease and has been successful in a small number of patients. Isolated hepatocyte transplantation has been reported as bridge therapy to liver transplantation, with most, but not all, patients eventually requiring orthotopic transplantation. Other therapeutic modalities have included plasmapheresis and limitation of bilirubin production. The latter option, inhibiting bilirubin generation, is possible via inhibition of heme oxygenase using metalloporphyrin therapy. Finally, gene therapy using adeno-associated viral vectors has shown promise in a murine model and is in clinical trials in humans.

CRIGLER-NAJJAR SYNDROME TYPE II (PARTIAL GLUCURONYL TRANSFERASE DEFICIENCY)

CN type II is an autosomal recessive disease caused by homozygous missense pathogenic variants in *UGT1A1* resulting in reduced (partial) enzymatic activity. More than 45 pathogenic variants have been identified to date. Type II disease can be distinguished from type I by the marked decline in serum bilirubin level that occurs in type II disease after treatment with phenobarbital secondary to an inducible phenobarbital response element on the *UGT1A1* promoter.

Clinical Manifestations

When this disorder appears in the neonatal period, unconjugated hyperbilirubinemia usually occurs in the first 3 days of life; serum bilirubin concentrations can be in a range compatible with physiologic jaundice or can be at pathologic levels. The concentrations characteristically remain elevated into and after the third week of life, persisting in a range of 1.5-22 mg/dL; concentrations in the lower part of this range can create uncertainty about whether chronic hyperbilirubinemia is present. Development of kernicterus is unusual. Stool color is normal, and the infants are without clinical signs or symptoms of disease. There is no evidence of hemolysis. Liver enzymes, albumin, and prothrombin time/international normalized ratio (PT/INR) are typically normal.

Diagnosis

The concentration of bilirubin in the bile is nearly normal in patients with CN type II. Jaundiced infants and young children with type II respond readily to 5 mg/kg/day of oral phenobarbital, with a decrease in serum bilirubin concentration to 2-3 mg/dL in 7-10 days.

Treatment

Long-term reduction in serum bilirubin levels can be achieved with continued administration of phenobarbital at 5 mg/kg/day. Therapy must be lifelong. The cosmetic and psychosocial benefit should be weighed against the risks of an effective dose of the drug because there is a small long-term risk of kernicterus even in the absence of hemolytic disease. Orlistat, an irreversible inhibitor of intestinal lipase, increases fecal fat excretion and may decrease plasma unconjugated bilirubin concentrations (~10%) in patients with CN types I and II.

INHERITED CONJUGATED HYPERBILIRUBINEMIA

Conjugated hyperbilirubinemia can be caused by rare autosomal recessive conditions characterized by asymptomatic mild jaundice. In these conditions, the transfer of bilirubin and other organic anions from the hepatocyte into bile is defective. Chronic mild conjugated hyperbilirubinemia is usually detected during adolescence or early adulthood but can occur as early as 2 years of age. The results of other routine liver tests are normal. Jaundice can be exacerbated by infection, pregnancy, oral contraceptives, alcohol consumption, and surgery. There is usually no morbidity, and life expectancy is normal.

DUBIN-JOHNSON SYNDROME

Dubin-Johnson syndrome is an autosomal recessive inherited defect in hepatocyte secretion of bilirubin glucuronide. The defect in hepatic excretory function is not limited to conjugated bilirubin excretion but also involves several organic anions normally excreted from the liver cell into bile. Disease results from absent function of MRP2, encoded by the gene *ABCC2*, an adenosine triphosphate–dependent canalicular transporter. More than 10 different pathogenic variants, including compound heterozygous pathogenic variants in the *CMOAT* gene, have been identified and either affect localization of MRP2 with resultant increased degradation or impair MRP2 transporter activity in the canalicular membrane. Bile acid excretion and serum bile acid levels are normal. Total urinary coproporphyrin excretion is normal in quantity, but coproporphyrin I excretion increases to approximately 80% with a concomitant decrease in coproporphyrin III excretion. Normally, coproporphyrin III is >75% of the total. Cholangiography fails to visualize the biliary tract, and x-ray of the gallbladder is also abnormal. Liver histology demonstrates normal architecture, but hepatocytes contain black pigment similar to melanin. Liver function is normal, and the prognosis is excellent. The most commonly reported symptoms are abdominal pain and fatigue, jaundice, dark urine, and slight enlargement of the liver. Jaundice fluctuates in intensity and is aggravated by intercurrent disease. Rarely, Dubin-Johnson can present in the neonatal period with severe conjugated hyperbilirubinemia with serum bilirubin >20 mg/dL and hepatosplenomegaly. No treatment is indicated for disease that presents outside of the neonatal period.

Rotor Syndrome

Rotor syndrome is an autosomal recessive disease resulting from biallelic inactivating pathogenic variants in *SLCO1B1* and *SLCO1B3* that result in functional deficiencies of both OATP1B1 and OATP1B protein. Importantly, these pathogenic variants may confer significant drug toxicity risk. These patients present similarly to Dubin-Johnson syndrome, with asymptomatic mild and fluctuating conjugated hyperbilirubinemia, with total serum bilirubin levels between 2 and 5 mg/dL. Unlike Dubin-Johnson syndrome, total urinary coproporphyrin excretion is elevated with a relative increase in the amount of the coproporphyrin I isomer. If liver biopsy is performed, there is no abnormal pigmentation, in contrast to Dubin-Johnson. The gallbladder is normal by roentgenography. Rotor syndrome is benign, and no treatment is indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

405.2 Wilson Disease

Julie Bonn and William F. Balistreri

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder that can be associated with liver disease, degenerative changes in the brain, psychiatric symptoms, and Kayser-Fleischer (K-F) rings in the cornea (Fig. 405.1 and Table 405.3). The incidence is approximately 1/30,000 births worldwide. Specific treatment is available; however, this disease is progressive and potentially fatal if untreated. Prompt diagnostic evaluation for Wilson disease in all patients over age 5 presenting with any form of liver disease facilitates expeditious initiation of treatment of the disease, appropriate genetic counseling, and screening of first-degree relatives and also allows appropriate treatment of non-Wilsonian liver disease once copper toxicosis is ruled out.

PATHOGENESIS

The variant gene for Wilson disease is found on chromosome 13 (13q14.3) and encodes *ATP7B*, a copper transporting P-type adenosine triphosphatase (ATPase), which is mainly expressed in hepatocytes and is critical for biliary copper excretion and for copper incorporation into ceruloplasmin. Absence or malfunction of ATP7B results in decreased biliary copper excretion and diffuse accumulation of copper in the cytosol of hepatocytes. With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. Ionic copper inhibits pyruvate oxidase in the brain and ATPase in membranes, leading to decreased adenosine triphosphate-phosphocreatine and potassium content of tissue.

More than 500 pathogenic variants have been identified, of which >380 have a confirmed role in disease pathogenesis; genetic testing should be able to identify a pathologic variant. Most patients are compound heterozygotes. Pathogenic variants that abolish gene function are associated with an onset of disease symptoms as early as 3 years of age, when Wilson disease might not typically be considered in the differential diagnosis. Milder variants can be associated with neurologic symptoms or liver disease as late as 80 years of age. The most commonly occurring disease-causing *ATP7B* pathogenic variants result in a protein that binds copper but is unable to effectively traffic to the apical surface of hepatocytes to perform its copper-exporting function.

CLINICAL MANIFESTATIONS

Forms of Wilsonian hepatic disease include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding,

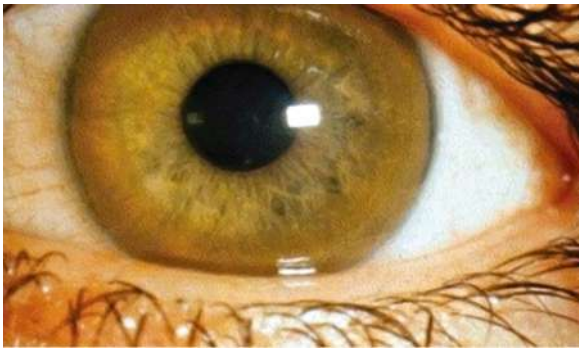

Fig. 405.1 Kayser-Fleischer ring. Brown discoloration at the outer margin of the cornea caused by deposition of copper in Descemet's membrane. Here it is clearly seen against the light green iris. Slit-lamp examination is required for secure detection. *(From Ala A, Walker AP, Ashkan K, et al. Wilson's disease. Lancet. 2007;369:397–408.)*

Table 405.3 The Most Common Clinical Manifestations of WD and Their Frequency of Disease Diagnosis

WD PRESENTATION AND FREQUENCY	SYMPTOMS
Hepatic (40–60%)	Asymptomatic elevation of liver enzymes (aminotransferases)
	Acute hepatitis (e.g., jaundice, abdominal pain)
	Acute liver failure (coagulopathy, jaundice, encephalopathy)
	Liver cirrhosis symptoms (compensated or decompensated) (fatigue, spider naevi, portal hypertension, splenomegaly, bleeding)
Neurologic (40–50%)	Involuntary movements (tremor, dystonia, ataxia, ballism, chorea, parkinsonian syndrome)
	Speech disturbances: dysarthria (extrapyramidal, dystonic, cerebellar, mixed, unclassified)
	Dysphagia
	Autonomic dysfunction (e.g., salivation, electrocardiographic abnormalities, orthostatic hypotension)
	Gait and balance disturbances
Psychiatric (10–25%)	Personality disorders (e.g., abnormal, antisocial behavior, irritability, disinhibition)
	Mood disorders (bipolar disorders, depression, suicidal attempts)
	Psychosis and other psychiatric alterations (rarely: e.g., psychosis, anorexia, sleep disturbances)
	Cognitive impairment
Ophthalmologic (K-F ring: 90–100% in neurologic patients, 40–50% in hepatic and 20–30% in presymptomatic); SC (1,2–25%)	Kayser–Fleischer ring (K-F ring); sunflower cataract (SC)
Other (lack of systematic multicenter data, mostly case reports, series reports, or single-center studies)	Renal (tubular dysfunction, nephrolithiasis and nephrocalcinosis, aminocyduria, hypercalciuria, hyperphosphaturia)
	Bone (osteoporosis, chondrocalcinosis, osteoarthritis, joints pain)
	Heart (cardiac arrhythmia, cardiomyopathy, myopathy)
	Skin (hyperpigmentation of lower legs, azure lunulae ("sky-blue moon") of the nails, anetoderma, xerosis, acanthosis nigricans, subcutaneous lipomas, dermatomyositis)
	Hematopoietic system (thrombocytopenia, hemolytic anemia, leukopenia)
	Gynecologic abnormalities (menstrual irregularity, delayed puberty, gynecomastia)
	Endocrinologic abnormalities (glucose intolerance, parathyroid insufficiency, disorders of growth)

From Litwin T, Dusek P, Szafranski T, et al. Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. *Therap Adv Psychopharmacol.* 2018;8(7):199–221, Table 1.

or other effects of hepatic dysfunction (delayed puberty, amenorrhea, coagulation defects) can be manifestations of Wilson disease.

Disease presentations are variable, with a tendency to familial patterns. Liver disease is the most common disease manifestation in children and can precede neurologic symptoms by as long as 10 years. Females are 3 times more likely than males to present with acute hepatic failure. When Wilson disease presents after age 20, *neurologic symptoms* are the most common manifestation.

Neurologic disorders can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, parkinsonism, choreiform movements, lack of motor coordination, deterioration in school performance, psychosis, or behavioral changes. K-F rings are absent in young patients with hepatic Wilson disease up to 50% of the time but are present in 95% of patients with neurologic symptoms. **Psychiatric manifestations** include depression, personality changes, anxiety, obsessive-compulsive behavior, or psychosis.

Coombs-negative **hemolytic anemia** may be an initial manifestation, possibly related to the release of large amounts of copper from damaged hepatocytes; this form of Wilson disease is usually fatal without liver transplantation. During hemolytic episodes, urinary copper excretion and serum free copper levels are markedly elevated. Manifestations of renal Fanconi syndrome and progressive renal failure with alterations in tubular transport of amino acids, glucose, and uric acid may be present. Unusual manifestations include arthritis, pancreatitis, nephrolithiasis, infertility or recurrent miscarriages, cardiomyopathy, and hypoparathyroidism.

PATHOLOGY

All grades of hepatic injury occur in patients with Wilson disease, with steatosis, hepatocellular ballooning and degeneration, glycogen granules, minimal inflammation, and enlarged Kupffer cells being most common. The earliest histologic feature of Wilson disease is mild steatosis, which may mimic nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Additionally, the lesion may be indistinguishable from that of autoimmune hepatitis. With progressive parenchymal damage, fibrosis and cirrhosis develop. Ultrastructural changes primarily involve the mitochondria and include increased density of the matrix material, inclusions of lipid and granular material, and increased intracristal space with dilation of the tips of the cristae.

DIAGNOSIS

Wilson disease should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychiatric illnesses, behavioral changes, Fanconi syndrome, or unexplained bone (osteoporosis, fractures) or muscle disease (myopathy, arthralgia). The clinical suspicion is confirmed by study of indices of copper metabolism.

Most patients with Wilson disease have decreased serum ceruloplasmin levels (<20 mg/dL). The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and therefore a reduced steady-state concentration of ceruloplasmin in the circulation. *Serum ceruloplasmin levels should be interpreted with caution.* Acute inflammatory states and elevated estrogen levels (pregnancy, hormone therapy, or use of oral contraception) can falsely increase ceruloplasmin levels. Additionally, serum ceruloplasmin may be low in autoimmune hepatitis, celiac disease, familial aceruloplasminemia, or carriers of ATP7B pathogenic variants (mild variants of Menkes disease: occipital horn syndrome) who do not show copper overload disease. The serum free copper level may be elevated in early Wilson disease (>1.6 μmol/L), and urinary copper excretion (normally <40 μg/day) is increased to >100 μg/day and often up to 1,000 μg or more per day. Typical urinary copper excretion in patients with untreated Wilson disease is >1.6 μmol/24 hr in adults and >0.64 μmol/24 hr in children. In equivocal cases, the response of urinary copper output to chelation may be of diagnostic help. Before a 24-hour urine collection patients are given two 500-mg oral doses of D-penicillamine 12 hours apart; affected patients excrete >1,600 μg/24 hr.

Demonstration of K-F rings, which might not be present in younger children, requires a slit-lamp examination by an ophthalmologist. After adequate treatment, K-F rings resolve. Liver biopsy can determine the extent and severity of liver disease and for measuring the hepatic copper content (normally <10 μg/g dry weight) but is only required if clinical signs and noninvasive tests do not allow a final diagnosis or if another liver disorder is suspected. Hepatic copper accumulation is the hallmark of Wilson disease, and measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis. Hepatic copper content >250 μg/g dry weight (>4 μmol/g dry weight) is the best biochemical evidence for Wilson disease, but lowering the threshold to 1.2 μmol/g dry weight improves sensitivity without significantly affecting specificity. Intermediate levels of hepatic copper may be present in asymptomatic carriers. In later stages of Wilson disease, hepatic copper content can be unreliable because cirrhosis leads to variable hepatic copper distribution and sampling error.

First-degree relatives of patients with Wilson disease should be screened for presymptomatic disease. This screening should include determination of the serum ceruloplasmin level and 24-hr urinary copper excretion. If these results are abnormal or equivocal, liver biopsy should be carried out to determine morphology and hepatic copper content. Genetic screening by either linkage analysis or direct DNA gene analysis is possible, especially if the mutation for the proband case is known or the patient is from an area where a specific gene variant is prevalent, such as in Central and Eastern Europe, where the *H1069Q* variant is present in 50–80% of patients.

TREATMENT

Once the diagnosis of Wilson disease is made, lifelong treatment should be initiated and is focused on limiting copper uptake and promoting copper excretion through dietary and pharmacologic measures. The normal diet contains 2-5 mg of copper per day. For patients with Wilson disease, the dietary intake of copper should be restricted to <1 mg/day. High copper content foods such as liver, shellfish, nuts, and chocolate should be avoided. If the copper content of the drinking water exceeds 0.1 mg/L, it may be necessary to demineralize the water.

The initial treatment in symptomatic patients is the administration of copper-chelating agents, which leads to rapid excretion of excess deposited copper. Chelation therapy is managed with oral administration of triethylene tetramine dihydrochloride (Trien, TETA, trientine) at a dose of 750-1500 mg/day in two or three divided doses, with 750 or 1000 mg used for maintenance therapy, for adults and 20 mg/kg/day rounded to the nearest 250 mg, given in two or three divided doses for children. D-penicillamine (β,β-dimethylcysteine) can be used as an alternative at a maximum of 1000-1500 mg/day in two to four divided doses before meals for adults and 20 mg/kg/day, rounded to the nearest 250 mg and given in two or three divided doses for pediatric patients. In response to chelation, urinary copper excretion increases, with marked improvement in hepatic and neurologic function and the disappearance of K-F rings.

Approximately 10–50% of patients initially treated with penicillamine for *neurologic* symptoms have a worsening of their condition. Toxic effects of penicillamine occur in 10–20% and consist of hypersensitivity reactions (i.e., Goodpasture syndrome, systemic lupus erythematosus, and polymyositis), interaction with collagen and elastin, deficiency of other elements such as zinc, and aplastic anemia and nephrosis. Because penicillamine is an antimetabolite of vitamin B_6, additional amounts of this vitamin are necessary. For these reasons, trientine is the preferred alternative and is considered first-line therapy for some patients. Trientine has few known side effects. Ammonium tetrathiomolybdate is another alternative chelating agent under investigation for patients with neurologic disease; initial results suggest that significantly fewer patients

experience neurologic deterioration with this drug compared to penicillamine. The initial dose is 120 mg/day (20 mg between meals 3 times daily and 20 mg with meals 3 times daily). Side effects include anemia, leukopenia, thrombocytopenia, and mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Because of its extensive decoppering effect, ammonium tetrathiomolybdate also has antiangiogenic effects.

Zinc has also been used as adjuvant therapy, maintenance therapy, or primary therapy in presymptomatic patients, owing to its unique ability to impair the gastrointestinal absorption of copper. Zinc acetate can be given to adults at a dose of 50 mg of elemental zinc 3 times a day, and 25 mg 3 times a day in children over age 5 years. Side effects are predominantly limited to gastric irritation but also include reduced leukocyte chemotaxis and elevations in serum lipase and/or amylase. Guidelines recommend that all symptomatic patients with Wilson disease receive a chelating agent (penicillamine or trientine). Patients should be counseled not to suddenly stop these medications, because sudden discontinuation of therapy can precipitate fulminant Wilson disease. Zinc may have a role as a first-line therapy in patients with neurologic disease, but exclusive monotherapy with zinc in symptomatic liver disease is controversial and not recommended. Antioxidants (vitamin E and curcumin) and pharmacologic chaperones (4-phenylbutyrate and curcumin) may have a role as adjunctive treatment, but more research is needed.

PROGNOSIS

Untreated patients with Wilson disease can die of hepatic, neurologic, renal, or hematologic complications. Medical therapy is rarely effective in those presenting with acute liver failure. The prognosis for patients receiving prompt and continuous penicillamine is variable and depends on the time of initiation of and the individual response to chelation. Liver transplantation should be considered for patients with acute liver failure or decompensated cirrhosis caused by Wilson disease. Liver transplantation for progressive neurologic disease remains controversial. Liver transplantation is curative, with a 5-year survival rate of 85–90%. In asymptomatic siblings of affected patients, early institution of chelation or zinc therapy can prevent disease manifestations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

405.3 Indian Childhood Cirrhosis

Julie Bonn and William F. Balistreri

Indian childhood cirrhosis (ICC) is a chronic liver disease of infants and young children unique to the Indian subcontinent, but variants of this syndrome have been described in other populations and have been named accordingly (Tyrolean or North American childhood cirrhosis). ICC-like disease has also been reported in the Middle East, West Africa, and Central America. Affected children present with jaundice, pruritus, lethargy, and hepatosplenomegaly with rapid progression to cirrhosis. Untreated severe ICC has a mortality of 40–50% within 4 weeks. Histologically, ICC is characterized by hepatocyte necrosis, Mallory bodies, intralobular fibrosis, inflammation, and excess hepatic copper deposition. Treatment is supportive, especially in the late stages of disease. Copper chelation with D-penicillamine has been beneficial in open-label preicteric cases of ICC; however, it is unclear whether these cases were simply less severely affected and would have spontaneously improved without treatment.

The etiology of ICC has remained elusive. It was once believed that excess copper ingestion in the setting of a genetic susceptibility to copper toxicosis was the most likely cause. Epidemiologic data demonstrate that the copper toxicity theory is unlikely. The increased hepatic copper content, usually >700 μg/g dry weight, seen in ICC is only seen in the late stages of disease and is accompanied by even higher levels of zinc, a non-hepatotoxic metal. Furthermore, the copper-contaminated utensils used to feed babies and implicated in excess copper ingestion are found in only 10–15% of all cases. The current hypothesis implicates the postnatal use of local hepatotoxic therapeutic remedies, although the exact causative agent is unknown. North American ICC is caused by pathogenic variants in the *UTP4* gene; it is seen in the Ojibway-Cree nation of Quebec.

Over the past few decades, as the awareness of the disease has increased, the incidence of ICC has decreased to the point of being virtually eliminated in some areas of India. However, established and atypical cases are probably being missed because of lack of histologic confirmation and lack of awareness of the protean manifestations and natural history of this disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

405.4 Neonatal Hemochromatosis

Julie Bonn and William F. Balistreri

See Chapter 404.

Neonatal hemochromatosis (NH) is a rare form of fulminant liver disease that manifests in the first few days of life. NH is associated with siderosis of extrahepatic tissues, similar to hereditary hemochromatosis, but is unrelated to the familial forms of hereditary hemochromatosis that occur in adulthood. **Gestational alloimmune liver disease (GALD)** has been identified as the cause of nearly all cases of NH, but they are not synonymous. GALD has a high rate of recurrence in families, with over 90% probability that subsequent infants will be affected. During gestation, the maternal immune system becomes sensitized to an unknown fetal hepatocyte cell surface antigen. Maternal immunoglobulin G (IgG) to this fetal antigen then crosses the placenta and induces hepatic injury via immune system activation. The defining feature of GALD is complement-mediated hepatocyte injury, the evidence for which comes from detection of the C5b-9 complex by immunohistochemistry on liver tissue of affected infants. Additional evidence of a gestational insult is given by the fact that affected infants may be born prematurely or with intrauterine growth restriction. Severely affected infants may also have renal hypoplasia and dysgenesis.

Excess non-transferrin-bound iron in GALD results from fetal liver injury that causes reduced synthesis of key iron regulatory and transport proteins. The pattern of extrahepatic siderosis appears to be determined by the normal capacity of various tissues to import non-transferrin-bound iron and not export cellular iron. It is thought that fetal liver injury is the primary event leading to the development of the NH phenotype, providing further evidence that this is not a primary iron overload disease.

GALD can be a rapidly fatal, progressive illness characterized by hepatomegaly, hypoglycemia, hypoprothrombinemia, hypoalbuminemia, hyperferritinemia, and hyperbilirubinemia (see Table 404.4). The coagulopathy is refractory to therapy with vitamin K. Liver biopsy demonstrates severe liver injury with acute and chronic inflammation, fibrosis, and cirrhosis; in some cases there are no surviving hepatocytes. The diagnosis is established in the neonate with severe liver injury and evidence of extrahepatic siderosis either by MRI indicating increased iron deposition in organs such as the pancreas or heart or by increased iron staining in oral submucosal gland biopsy. The differential diagnosis includes other causes of neonatal hepatic failure such as citrin deficiency, herpes simplex virus (HSV) hepatitis, and familial hemophagocytic lymphohistiocytosis (see Table 404.4).

The survival rate (50–80%) depends on the severity of the initial presentation and response to therapy. Intravenous immunoglobulin (IVIG) combined with double volume exchange transfusion has been shown to remove the injury-causing maternal IgG and

improve outcomes in infants with GALD. Liver transplantation should also be an early consideration. Recurrences of GALD in subsequent pregnancies may be modified with IVIG administered to the mother once weekly from the 18th week of gestation until delivery. The largest experience reports 48 women with previous infants with GALD who successfully delivered 52 babies after IVIG treatment. The majority of infants had biochemical evidence of liver disease with elevated serum α-fetoprotein and ferritin. All infants survived with medical therapy or no therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

405.5 Miscellaneous Metabolic Diseases of the Liver

Julie Bonn and William F. Balistreri

α_1-ANTITRYPSIN DEFICIENCY

α_1-Antitrypsin deficiency is an autosomal recessive disorder caused by a pathogenic variant in the *SERPINA1* gene. α_1-Antitrypsin, a protease inhibitor (Pi) synthesized by the liver, protects lung alveolar tissues from destruction by neutrophil elastase (see Chapter 442). α_1-Antitrypsin is present in more than 20 different codominant alleles, only a few of which are associated with defective Pis. The most common allele of the Pi system is M, and the normal phenotype is PiMM. The Z allele predisposes to clinical deficiency; patients with liver disease are usually PiZZ homozygotes and have serum α_1-antitrypsin levels <2 mg/mL (~10–20% of normal). The incidence of the PiZZ genotype in the White population is estimated at 1 in 2,000-4,000 live births. A small percentage of patients homozygous for deficiency of the major serum Pi α_1-antitrypsin develop neonatal cholestasis or later-onset childhood cirrhosis. Compound heterozygotes PiZ, PiSZ, and PiZI are not a cause of liver disease alone but can act as modifier genes, increasing the risk of progression in other liver diseases such as nonalcoholic fatty liver disease and hepatitis C. The null phenotype only causes lung disease and results from either stop codons in the coding exon of the *SERPINA1* gene or complete deletion of *SERPINA1* coding exons leading to the absence of α_1-antitrypsin protein.

Newly formed α_1-antitrypsin polypeptide normally enters the endoplasmic reticulum, where it undergoes enzymatic modification and folding before transport to the plasma membrane, where it is excreted as a 55-kDa glycoprotein. In affected patients with PiZZ, the rate at which the α_1-antitrypsin polypeptide folds is decreased, and this delay allows the formation of polymers that are retained in the endoplasmic reticulum. How the polymers cause liver damage is not completely elucidated, but research indicates that accumulation of abnormally folded protein leads to activation of stress and proinflammatory pathways in the endoplasmic reticulum and hepatocyte programmed cell death. In liver biopsies from patients, polymerized α_1-antitrypsin peptides can be seen by electron microscopy and histochemically as periodic acid–Schiff-positive diastase-resistant globules, primarily in periportal hepatocytes, but also in Kupffer cells and biliary epithelial cells. The pattern of neonatal liver injury can be highly variable, and liver biopsies might demonstrate hepatocellular necrosis, inflammatory cell infiltration, bile duct proliferation, periportal fibrosis, or cirrhosis.

The course of liver disease is highly variable in patients with α_1-antitrypsin deficiency. Prospective studies in Sweden have shown that only 10% of patients develop clinically significant liver disease by their fourth decade, indicating that other genetic traits or environmental factors likely influence the development of liver disease. Infants with liver disease are indistinguishable from other infants with "idiopathic" neonatal hepatitis, of whom they constitute approximately 5–10%. Jaundice, acholic stools, and hepatomegaly are present in the first week of life, but the jaundice usually clears by 2-4 months of age. Complete resolution, persistent liver disease, or the development of cirrhosis can follow. Older children can present with asymptomatic hepatomegaly or manifestations of chronic liver disease or cirrhosis with evidence of portal hypertension. Patients with cirrhosis due to α_1-antitrypsin deficiency are at high risk for developing hepatocellular carcinoma. Emphysema is not typically observed in children, but an increased risk for developing asthma is reported. Cigarette smoking promotes development of lung disease, so parents should be counseled on smoking cessation and exposure reduction as part of their anticipatory guidance, and older children and adolescents should be advised not to smoke or use electronic cigarettes and given cessation counseling if they do (see Chapter 157.2).

Treatment is supportive, although research is ongoing to develop therapies for α_1-antitrypsin deficiency–associated liver disease that stimulate intracellular degradation of the abnormally folded Z protein polymers. Liver transplantation is indicated for hepatocellular carcinoma or end-stage liver disease with portal hypertension, with survival rates of ~90%.

CITRIN DEFICIENCY

Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) presents in the first few months of life with manifestations that initially may be indistinguishable from other causes of neonatal cholestasis, especially biliary atresia. Patients may have jaundice, hepatomegaly, liver dysfunction with coagulopathy, fatty liver infiltration, and hyperammonemia with or without hypoglycemia. Presymptomatic patients may be identified from the newborn metabolic screen with hypergalactosemia, hypermethionemia, and hyperphenylalaninemia, but not all patients are identified by newborn screening.

Pathogenic variants in the *SLC25A13* gene cause NICCD with an autosomal recessive pattern of inheritance. SLC25A13 encodes citrin, a mitochondrial carrier protein (calcium binding aspartate-glutamate carrier) involved in the urea cycle, gluconeogenesis, and glycolysis. Pathogenic variants are more common in those of East Asian descent. Affected infants have hypergalactosemia, elevated bile acids, vitamin K–dependent coagulopathy, and elevated levels of citrulline and methionine. Treatment is supportive in the form of providing fat-soluble vitamin supplementation and dietary feeding with a low-galactose/-lactose formula enriched with medium-chain triglycerides. More severely affected patients can develop liver failure requiring liver transplantation in the first year of life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 406

Viral Hepatitis

Michael E. Rogers and William F. Balistreri

Viral hepatitis continues to be a major health problem in both developing and developed countries, but there has been significant progress in efforts to recognize and to treat infected subjects. This disorder is caused by at least five known pathogenic hepatotropic viruses: hepatitides A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) viruses (Table 406.1). Many other viruses (and diseases) can cause hepatitis, usually as a component of a multisystem disease. These include herpes simplex viruses (1, 2, 6a, 6b), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, HIV, rubella, measles, adenoviruses, adeno-associated virus, enteroviruses, parvovirus B19, arboviruses, and perhaps SARS-CoV-2 (Table 406.2).

The hepatotropic viruses are a heterogeneous group of infectious agents that cause similar acute clinical illness. In most pediatric patients, the acute phase causes no or mild clinical disease. Morbidity is related to rare cases of **acute liver failure (ALF)** in susceptible patients or to the development of a chronic disease state and attendant complications that several of these viruses (HBV, HCV, HDV) may cause.

ISSUES COMMON TO ALL FORMS OF VIRAL HEPATITIS

Differential Diagnosis

Although often asymptomatic or nonspecific, the clinical features that may raise the suspicion of viral hepatitis is clinical icterus, with yellow skin and/or mucous membranes. The liver is usually enlarged and tender to palpation and percussion. Splenomegaly and lymphadenopathy may be present. Clinical signs of bleeding, altered sensorium, or hyperreflexia should be carefully sought, because they mark the onset of encephalopathy and ALF.

The differential diagnosis varies with the age of presentation. In the newborn period, infection is a common cause of conjugated hyperbilirubinemia; the infectious cause is either a bacterial agent (e.g., *Escherichia coli*, *Listeria*, syphilis) or a nonhepatotropic virus (e.g., enteroviruses, cytomegalovirus, and herpes simplex virus, which may also cause a nonicteric severe hepatitis). Metabolic diseases (α_1-antitrypsin deficiency, cystic fibrosis, tyrosinemia), anatomic causes (biliary atresia, choledochal cysts), and inherited forms of intrahepatic cholestasis should always be excluded.

In later childhood, extrahepatic obstruction (gallstones, primary sclerosing cholangitis, pancreatic pathology), inflammatory conditions (autoimmune hepatitis, juvenile inflammatory arthritis, Kawasaki disease), immune dysregulation (hemophagocytic lymphohistiocytosis), infiltrative disorders (malignancies), toxins and medications, metabolic disorders (Wilson disease, cystic fibrosis), and infection (Epstein-Barr virus, varicella, malaria, leptospirosis, syphilis) should be ruled out.

Table 406.1 Features of the Hepatotropic Viruses

VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
Parenteral	Rare	Yes	Yes	Yes	No
Fecal-oral	Yes	No	No	No	Yes
Sexual	No	Yes	Rare	Yes	No
Perinatal	No	Yes	Uncommon (5–15%)	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

HAV, Hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.

Pathogenesis

The acute response of the liver to hepatotropic viruses involves a direct cytopathic and/or an immune-mediated injury. The entire liver is involved. Necrosis is usually most marked in the centrilobular areas. An acute mixed inflammatory infiltrate predominates in the portal areas but also affects the lobules. The lobular architecture remains intact, although balloon degeneration and necrosis of single cells or groups of parenchymal cells commonly occur. Fatty change is rare. Bile duct proliferation, but not bile duct damage, is common. Diffuse Kupffer cell hyperplasia is noticeable in the sinusoids. Neonates often respond to hepatic injury by forming *giant cells*. In fulminant hepatitis, parenchymal collapse occurs on the described background. With recovery, the liver morphology returns to normal within 3 months of the acute infection. If chronic hepatitis develops, the inflammatory infiltrate settles in the periportal areas and often leads to progressive scarring.

Common Biochemical Profiles in the Acute Infectious Phase

Acute liver injury caused by these viruses manifests in three main liver biochemical profiles. These serve as an important guide to diagnosis, supportive care, and monitoring in the acute phase of the infection for all viruses. As a reflection of *cytopathic injury* to the hepatocytes, there is a rise in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The magnitude of enzyme elevation does not correlate with the extent of hepatocellular necrosis and has little prognostic value. There is usually slow improvement over several weeks, but AST and ALT levels *lag* the serum bilirubin level, which tends to normalize first. Rapidly falling aminotransferase levels can predict a poor outcome, particularly if their decline occurs in conjunction with a rising bilirubin level and a prolonged international normalized ratio (INR) or prothrombin time (PT); this combination of findings usually indicates that massive hepatic injury has occurred.

Cholestasis, defined by elevated serum conjugated bilirubin levels, results from abnormal bile flow at the canalicular and cellular level because of hepatocyte damage and inflammatory mediators. Elevation of serum alkaline phosphatase, 5-nucleotidase, and γ-glutamyl transpeptidase levels marks cholestasis. Absence of cholestatic markers does not rule out progression to chronicity in HCV or HBV infections.

Altered synthetic function is the most important marker of liver injury. Synthetic dysfunction is reflected by abnormal protein synthesis (prolonged PT, high INR, low serum albumin levels), metabolic disturbances (hypoglycemia, lactic acidosis, hyperammonemia), poor clearance of medications dependent on liver function, and altered sensorium with increased deep tendon reflexes (hepatic encephalopathy). Monitoring of synthetic function should be the main focus in clinical follow-up to define the severity of the disease. In the acute phase, the degree of liver synthetic dysfunction guides treatment and helps to establish intervention criteria. *Abnormal liver synthetic function is a marker of liver failure and is an indication for prompt referral to a transplant center.* Serial assessment is necessary because liver dysfunction does not progress linearly.

HEPATITIS A

Hepatitis A virus is responsible for most forms of acute and benign hepatitis. Although fulminant hepatic failure caused by HAV can occur, it is rare (<1% of cases in the United States) and occurs more often in adults than in children and in hyperendemic communities.

Etiology

HAV is an RNA virus, a member of the picornavirus family. It is heat stable and has a limited host range—namely, the human and other primates.

Table 406.2 Causes and Differential Diagnosis of Hepatitis in Children

INFECTIOUS
Hepatotropic viruses
- HAV
- HBV
- HCV
- HEV
- HDV
- HFV
- HGV
- TT virus
- Non–hepatitis A-E viruses

SYSTEMIC INFECTION THAT MAY INCLUDE HEPATITIS
Adenovirus
Arbovirus
Coxsackievirus
Cytomegalovirus
Dengue virus
Enterovirus
Epstein-Barr virus
Herpes simplex viruses (1, 2, 6)
Human immunodeficiency virus
Lassa fever
Paramyxovirus (measles)
Parvovirus
Rubella
Varicella-zoster
Yellow fever
Unknown

NONVIRAL LIVER INFECTIONS
Abscess
Amebiasis
Bacterial sepsis
Brucellosis
Fitz-Hugh-Curtis syndrome
Histoplasmosis
Leptospirosis
Syphilis
Tuberculosis
Other

AUTOIMMUNE/INFLAMMATORY
Chronic autoimmune hepatitis
Other (e.g., systemic lupus erythematosus, juvenile idiopathic arthritis)
Celiac disease
Hemophagocytic lymphohistiocytosis

METABOLIC
α_1-Antitrypsin deficiency
Glycogen storage disease
Tyrosinemia
Wilson disease
Other

TOXIC
Iatrogenic/drug induced (e.g., acetaminophen)
Environmental (e.g., pesticides)
Mushroom poisoning
Hepatotoxic herbal agents (pyrrolizidine alkaloids, other toxins)

ANATOMIC
Choledochal cyst
Biliary atresia
Other

HEMODYNAMIC
Shock
Congestive heart failure
Budd-Chiari syndrome
Venoocclusive disease
Other

NONALCOHOLIC FATTY LIVER DISEASE
Idiopathic
- Sclerosing cholangitis
- Reye syndrome
- Other

Modified from Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 6th ed. Philadelphia: Elsevier; 2021: Box 75.1, p. 820.

Epidemiology

HAV infection occurs throughout the world but is most prevalent in developing countries. In the United States, 30–40% of the adult population has evidence of previous HAV infection. In 2018, more than 12,000 cases of HAV were reported in the United States to the Centers for Disease Control and Prevention (CDC). The overall incidence rate was 3.8 cases per 100,000 population, an increase from recent years (specifically in patients over the age of 20 years). However, as a result of aggressive implementation of childhood vaccination programs, the prevalence of symptomatic HAV cases worldwide has declined significantly. Nonetheless, outbreaks in developing countries and in daycare centers (where the spread of HAV from young, nonicteric, infected children can occur easily) as well as multiple foodborne and waterborne outbreaks have justified the implementation of intensified universal vaccination programs.

HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal-oral route. Perinatal transmission occurs rarely. HAV infection during pregnancy or at the time of delivery does not appear to result in increased complications of pregnancy or clinical disease in the newborn. In the United States, increased risk of infection is found in contacts with infected persons, childcare centers, and household contacts. Infection is also associated with contact with contaminated food or water and after travel to endemic areas. Common-source foodborne and waterborne outbreaks continue to occur, including several caused by contaminated shellfish, frozen berries, and raw vegetables; no known source is found in about half of the cases.

The mean incubation period for HAV is approximately 3 weeks. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 weeks after the onset of jaundice in older subjects. The duration of fecal viral excretion is prolonged in infants. The patient is therefore contagious before clinical symptoms are apparent and remains so until viral shedding ceases.

Clinical Manifestations

HAV is responsible for acute hepatitis only. Often, this is an *anicteric* illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is more likely to be symptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those who are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7-14 days (Fig. 406.1).

Other organ systems can be affected during acute HAV infection. Regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Tissue in the small intestine might show changes in villous structure, and ulceration of the gastrointestinal tract can occur, especially in fatal cases. Acute pancreatitis and myocarditis have been reported, though rarely, and nephritis, arthritis, leukocytoclastic vasculitis, and cryoglobulinemia can result from circulating immune complexes.

Diagnosis

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay or, rarely, by identifying viral particles in stool. An HAV viral polymerase chain reaction (PCR) assay is commercially available (Table 406.3). Anti-HAV is detectable when the symptoms are clinically apparent, and it remains positive for 4-6 months after the acute infection. A neutralizing anti-HAV (IgG) is usually detected within 8 weeks of symptom onset and is measured as part of a total anti-HAV in the serum. Anti-HAV (IgG) confers long-term protection. Rises in serum levels of ALT, AST, bilirubin, alkaline phosphatase, 5′-nucleotidase, and γ-glutamyl transpeptidase are almost universally found and do not help to differentiate the cause of hepatitis.

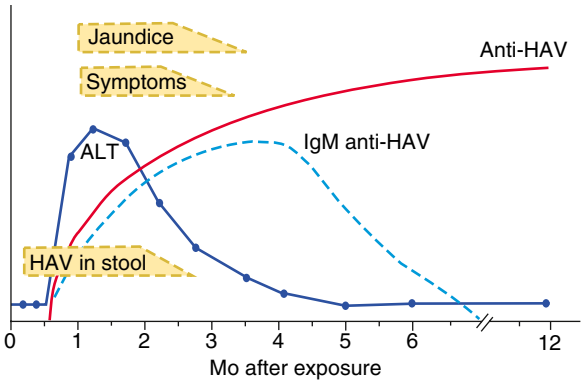

Fig. 406.1 The serologic course of acute hepatitis A. ALT, Alanine aminotransferase; HAV, hepatitis A virus; IgM, immunoglobulin class M. *(From Goldman L, Ausiello D, eds. Cecil Textbook of Medicine, 22nd ed. Philadelphia: WB Saunders; 2004:913.)*

Complications

Although most patients achieve full recovery, distinct complications can occur. *ALF* from HAV infection is an infrequent complication. Those at risk for this complication are elderly adults, but also immunocompromised patients or those with underlying liver disorders. The height of HAV viremia may be linked to the severity of hepatitis. In the United States, HAV represents <0.5% of pediatric-age ALF; HAV is responsible for up to 3% mortality in the adult population with ALF. In endemic areas of the world, HAV constitutes up to 40% of all cases of pediatric ALF. HAV can also progress to a *prolonged cholestatic syndrome* that waxes and wanes over several months. Pruritus and fat malabsorption are problematic and require symptomatic support with antipruritic medications and fat-soluble vitamin supplementation. This syndrome occurs in the absence of any liver synthetic dysfunction and resolves without sequelae.

Treatment

There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed and antipruritic agents and fat-soluble vitamins for the prolonged cholestatic form of disease. There is no benefit to the use of corticosteroid treatment during acute illness. Serial monitoring for signs of ALF is prudent and, if ALF is diagnosed, a prompt referral to a transplantation center can be lifesaving.

Prevention

Patients infected with HAV are contagious for 2 weeks before and approximately 7 days after the onset of jaundice and should be excluded from school, childcare, or work during this period. Careful handwashing is necessary, particularly after changing diapers and before preparing or serving food. In hospital settings, contact and standard precautions are recommended for 1 week after onset of symptoms.

Immunoglobulin

Indications for intramuscular administration of Ig include preexposure and postexposure prophylaxis (Table 406.4). Ig is recommended for *preexposure* prophylaxis for susceptible travelers to countries where HAV is endemic, and it provides effective protection for up to 2 months. *HAV vaccine* given any time before travel is preferred for *preexposure* prophylaxis in healthy persons, but *Ig* ensures an appropriate prophylaxis in children *younger than 6 months* old, patients allergic to a vaccine component, or those who elect not to receive the vaccine. If travel is planned in <2 weeks, older patients, immunocompromised

Table 406.3 Diagnostic Blood Tests: Serology and Viral Polymerase Chain Reaction

HAV	HBV	HCV	HDV	HEV
ACUTE/ACTIVE INFECTION				
Anti-HAV IgM (+)	Anti-HBc IgM (+)	Anti-HCV (+)	Anti-HDV IgM (+)	Anti-HEV IgM (+)
Blood PCR positive*	HBsAg (+) Anti-HBs (–) HBV DNA (+) (PCR)	HCV RNA (+) (PCR)	Blood PCR positive HBsAg (+) Anti-HBs (–)	Blood PCR positive*
PAST INFECTION (RECOVERED)				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc IgG (+)†	Anti-HCV (+) Blood PCR (–)	Anti-HDV IgG (+) Blood PCR (–)	Anti-HEV IgG (+) Blood PCR (–)
CHRONIC INFECTION				
N/A	Anti-HBc IgG (+) HBsAg (+) Anti-HBs (–) PCR (+) or (–)	Anti-HCV (+) Blood PCR (+)	Anti-HDV IgG (+) Blood PCR (–) HBsAg (+) Anti-HBs (–)	N/A
VACCINE RESPONSE				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc (–)	N/A	N/A	N/A

*Research tool.
†Still poses a risk for reactivation.
HAV, Hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.

Table 406.4 Indications and Updated Dosage Recommendations for GamaSTAN S/D Human Immune Globulin for Preexposure and Postexposure Prophylaxis Against Hepatitis A Infection

INDICATION	UPDATED DOSAGE RECOMMENDATION
Preexposure prophylaxis	
Up to 1 mo of travel	0.1 mL/kg
Up to 2 mo of travel	0.2 mL/kg
2 mo of travel or longer	0.2 mL/kg (repeat every 2 mo)
Postexposure prophylaxis	0.1 mL/kg

From Nelson NP. Updated dosing instruction for immune globulin (human) GamaSTAN S/D for hepatitis A virus prophylaxis. *MMWR*. 2017;66(36):959–960.

hosts, and those with chronic liver disease or other medical conditions should receive *both* Ig and the HAV vaccine.

Ig prophylaxis in *postexposure* situations should be used as soon as possible (it is not effective if administered more than 2 weeks after exposure). It is exclusively used alone for children younger than 12 months old or in whom vaccine is contraindicated (e.g., serious allergy to the vaccine). Ig in combination with HAV vaccine may be used in patients older than 40 years of age, with HAV vaccine preferred in healthy persons 12 months to 40 years old. An alternative approach is to immunize previously unvaccinated patients who are 12 months old or older with the age-appropriate vaccine dosage as soon as possible. Ig is not routinely recommended for sporadic nonhousehold exposure (e.g., protection of hospital personnel or schoolmates). The vaccine has several advantages over Ig, including long-term protection, availability, and ease of administration, with cost similar to, or less than, that of Ig.

Vaccine

The availability of at least three inactivated, highly immunogenic, and safe HAV vaccines has had a major impact on the prevention of HAV infection. These vaccines are approved for children older than 12 months. They are administered intramuscularly in a two-dose schedule, with the second dose given 6-12 months after the first dose. Seroconversion rates in children exceed 90% after an initial dose and approach 100% after the second dose; protective antibody titer persists for longer than 10 years in most patients. The immune response in immunocompromised persons, older patients, and those with chronic illnesses may be suboptimal; in those patients, combining the vaccine with Ig for preexposure and postexposure prophylaxis is indicated. HAV vaccine may be administered simultaneously with other vaccines. A combination HAV and HBV vaccine is approved in adults older than age 18. For healthy persons at least 12 months old, vaccine is preferable to Ig for preexposure and postexposure prophylaxis (see Table 406.3).

In the United States and some other countries, universal vaccination is recommended for all children older than 12 months. Nevertheless, studies show <50% of U.S. adolescents have received even a single dose of the vaccine and <30% have received the complete vaccine series. The vaccine is effective in curbing outbreaks of HAV because of rapid seroconversion and the long incubation period of the disease.

Prognosis

The prognosis for the patient with HAV is excellent, with no long-term sequelae. The only feared complication is ALF. Nevertheless, HAV infection remains a major cause of morbidity; it has a high socioeconomic impact during epidemics and in endemic areas.

HEPATITIS B

Etiology

HBV, a member of the Hepadnaviridae family, has a circular, partially double-stranded DNA genome composed of approximately 3,200 nucleotides. Four constitutive genes have been identified: the S (surface), C (core), X, and P (polymer) genes. The surface of the virus includes particles, designated as the hepatitis B surface antigen (HBsAg), which consist of 22-nm-diameter spherical particles and 22-nm-wide tubular particles with a variable length of up to 200 nm. The inner portion of the virion contains the hepatitis B core antigen (HBcAg), the nucleocapsid that encodes the viral DNA, and a nonstructural antigen called the hepatitis B e antigen (HBeAg), a nonparticulate soluble antigen derived from HBcAg by proteolytic self-cleavage. HBeAg serves as a marker of active viral replication and usually correlates with the HBV DNA levels. Replication of HBV occurs predominantly in the liver but also occurs in the lymphocytes, spleen, kidney, and pancreas.

Epidemiology

HBV has been detected worldwide, with an estimated 250 million persons chronically infected. The areas of highest prevalence of HBV infection are sub-Saharan Africa, China, parts of the Middle East, the Amazon basin, and the Pacific Islands. In the United States, the indigenous population in Alaska had the highest prevalence rate before the implementation of their universal vaccination programs. An estimated 1.25 million persons in the United States are chronic HBV carriers, with approximately 300,000 new cases of HBV occurring each year, the highest incidence being among adults 20-39 years of age. One in four chronic HBV carriers will develop serious sequelae in their lifetime. The number of new cases in children reported each year is thought to be low but is difficult to estimate because many infections in children are asymptomatic. In the United States, since the first vaccine for HBV was introduced, the overall incidence of HBV infection has been reduced by more than half. Since the implementation of universal vaccination programs in Taiwan and the United States, substantial progress has been made toward eliminating HBV infection in children in these countries. In fact, in Alaska, where HBV neared epidemic proportions, universal newborn vaccination with mass screening and immunization of susceptible Alaska indigenous peoples virtually eliminated symptomatic HBV and secondary hepatocellular carcinoma (HCC).

HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen. Efficient transmission occurs through blood exposure and sexual contact. Risk factors for HBV infection in children and adolescents include acquisition by intravenous drugs or blood products, contaminated needles used for acupuncture or tattoos, sexual contact, institutional care, and intimate contact with carriers. No risk factors are identified in approximately 40% of cases. HBV is not thought to be transmitted via indirect exposure, such as sharing toys. After infection, the incubation period ranges from 45 to 160 days, with a mean of approximately 120 days. In children, the most important risk factor for acquisition of HBV remains perinatal exposure to an HBsAg-positive mother. The risk of transmission is greatest if the mother is HBeAg-positive; up to 90% of these infants become chronically infected if untreated. Additional risk factors include high maternal HBV viral load (HBeAg/HBV DNA titers) and delivery of a prior infant who developed HBV despite appropriate prophylaxis. In most perinatal cases, serologic markers of infection and antigenemia appear 1-3 months after birth, suggesting that transmission occurred at the time of delivery. Virus contained in amniotic fluid or in maternal feces or blood may be the source. Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the HBV immunization, given within 12 hours of delivery, is highly effective in preventing infection and protects >95% of neonates born to HBsAg-positive mothers. Of the ~22,000 infants born each year to HBsAg-positive mothers in the United States, >98% receive immunoprophylaxis and are thus protected. Infants who fail to receive the complete vaccination series (e.g., homeless children, international adoptees, and children born outside the United States) have the highest incidence of developing chronic HBV. These and all infants born to HBsAg-positive mothers should have follow-up HBsAg and anti-HBs testing to determine appropriate follow-up. The mothers (HBeAg positive) of these infants who develop chronic HBV infection should receive antiviral therapy during the third trimester for subsequent pregnancies.

HBsAg is inconsistently recovered in human milk of infected mothers. Breastfeeding of nonimmunized infants by infected mothers does not seem to confer a greater risk of hepatitis than does formula feeding.

The risk of developing **chronic HBV infection**, defined as being positive for HBsAg for longer than 6 months, is inversely related to the age of acquisition. In the United States, although <10% of infections occur in children, these infections account for 20–30% of all chronic cases. This risk of chronic infection is 90% in children younger than 1 year; the risk is 30% for those 1-5 years of age and 2% for adults. Chronic HBV infection is associated with the development of chronic liver disease and HCC. The carcinoma risk is independent of the presence of cirrhosis and was the most prevalent cancer-related death in young adults in Asia, where HBV was endemic.

HBV has 10 genotypes (A-J). A is pandemic, B and C are prevalent in Asia, D is seen in Southern Europe, E in Africa, F in the United States, G in the United States and France, H in Central America, I in Southeast Asia, and J in Japan. Genetic variants have become resistant to some antiviral agents.

Pathogenesis

The acute response of the liver to HBV is similar to that of other viruses. Persistence of histologic changes in patients with hepatitis B indicates development of chronic liver disease. HBV, unlike the other hepatotropic viruses, is a predominantly noncytopathogenic virus that causes injury mostly by immune-mediated processes. The severity of hepatocyte injury reflects the degree of the immune response, with the most complete immune response associated with the greatest likelihood of viral clearance but also the most severe injury to hepatocytes. The first step in the process of acute hepatitis is infection of hepatocytes by HBV, resulting in expression of viral antigens on the cell surface. The most important of these viral antigens may be the nucleocapsid antigens—HBcAg and HBeAg. These antigens, in combination with class I major histocompatibility proteins, make the cell a target for cytotoxic T-cell lysis.

The mechanism for development of chronic hepatitis B is less well understood. To permit hepatocytes to continue to be infected, the core protein or major histocompatibility class I protein might not be recognized, the cytotoxic lymphocytes might not be activated, or some other, yet unknown mechanism might interfere with destruction of hepatocytes. This tolerance phenomenon predominates in the perinatally acquired cases, resulting in a high incidence of persistent HBV infection in children with no or little inflammation in the liver, normal liver enzymes, and markedly elevated HBV viral load. Although end-stage liver disease rarely develops in those patients, the inherent HCC risk is high, possibly related, in part, to uncontrolled viral replication cycles.

ALF has been seen in infants of chronic carrier mothers who have anti-HBe or are infected with a precore-variant strain. This fact led to the postulate that HBeAg exposure in utero in infants of chronic carriers likely induces tolerance to the virus once infection occurs postnatally. In the absence of this tolerance, the liver is massively attacked by T cells and the patient presents with ALF.

Immune-mediated mechanisms are also involved in the extrahepatic conditions that can be associated with HBV infections. Circulating immune complexes containing HBsAg can result in polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, polymyalgia rheumatica, leukocytoclastic vasculitis, and Guillain-Barré syndrome.

Clinical Manifestations

Many acute cases of HBV infection in children are asymptomatic, as evidenced by the high carriage rate of serum markers in persons who have no history of acute hepatitis (Table 406.5). The usual acute symptomatic episode is similar to that of HAV and HCV infections but may be more severe and is more likely to include involvement of the skin and joints (Fig. 406.2).

The first biochemical evidence of HBV infection is elevation of serum ALT levels, which begin to rise just before development of fatigue, anorexia, and malaise, at approximately 6-7 weeks after exposure. The illness is preceded, in a few children, by a serum sickness–like prodrome marked by arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Papular acrodermatitis, Gianotti-Crosti syndrome, can also occur. Other extrahepatic conditions associated with HBV infections in children include polyarteritis nodosa, glomerulonephritis, and aplastic anemia. Jaundice is present in approximately 25% of acutely infected patients and usually begins approximately 8 weeks after exposure and lasts approximately 4 weeks. In the usual course of resolving HBV infection, symptoms persist for 6-8 weeks. The percentage of children in whom clinical evidence of hepatitis develops is higher for HBV than for HAV, and the rate of ALF is also greater. Most patients do recover, but the chronic carrier state complicates up to 10% of cases acquired in adulthood. The rate of development of chronic infection depends largely on the mode and age of acquisition and occurs in up to 90% of perinatally infected cases. Cirrhosis and HCC are only seen with chronic infection. Chronic HBV infection has three identified phases: immune tolerant, immune active, and inactive. Most children fall in the immune-tolerant phase, against

Table 406.5 Typical Interpretation of Test Results for Hepatitis B Virus Infection

HBsAg	TOTAL ANTI-HBc	IgM ANTI-HBc	ANTI-HBs	HBV DNA	INTERPRETATION
–	–	–	–	–	Never infected
+	–	–	–	+ or –	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	–	+	Acute infection
–	+	+	+ or –	+ or –	Acute resolving infection
–	+	–	+	–	Recovered from past infection and immune
+	+	–	–	+	Chronic infection
–	+	–	–	+ or –	False-positive (i.e., susceptible), past infection, "low-level" chronic infection, or passive transfer of anti-HBc to infant born to HBsAg-positive mother
–	–	–	+	–	Immune if anti-HBs concentration is ≥10 mIU/mL after vaccine series completion; passive transfer after hepatitis B immune globulin administration

–, Negative; +, positive; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IgM, immunoglobulin class M.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1–29, Table 1.

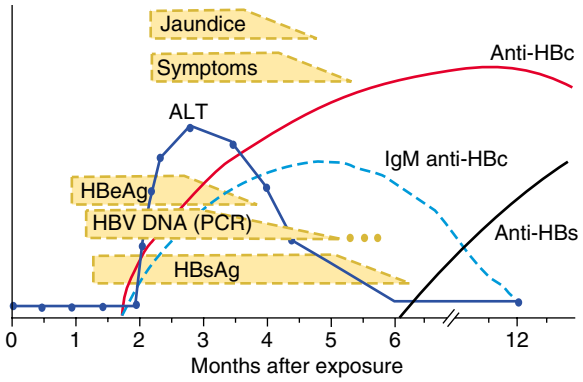

Fig. 406.2 The serologic course of acute hepatitis B. ALT, Alanine aminotransferase; HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IgM, immunoglobulin class M; PCR, polymerase chain reaction. *(From Goldman L, Ausiello D, eds. Cecil Textbook of Medicine, 22nd ed. Philadelphia: WB Saunders; 2004:914.)*

which no effective therapy has been developed. Most treatments target the immune active phase of the disease, characterized by active inflammation, elevated ALT/AST levels, and progressive fibrosis. Spontaneous HBeAg seroconversion, defined as the development of anti-HBe and loss of HBeAg, occurs in the immune-tolerant phase, albeit at low rates of 4–5% per year. It is more common in childhood-acquired HBV rather than in perinatally transmitted infections. Seroconversion can occur over many years, during which time significant damage to the liver may take place. There are no large studies that accurately assess the lifetime risks and morbidities of children with chronic HBV infection, making decisions regarding the rationale, efficacy, and timing of still less-than-ideal treatments difficult. Reactivation of chronic infection has been reported in immunosuppressed children treated with chemotherapy, biologic immunomodulators such as infliximab, or T-cell–depleting agents, leading to an increased risk of ALF or to rapidly progressing fibrotic liver disease (Table 406.6).

Diagnosis

The serologic profile of HBV infection is more complex than for HAV infection and differs depending on whether the disease is acute or chronic (Fig. 406.3, see Table 406.5). Several antigens and antibodies are used to confirm the diagnosis of acute HBV infection (see Table 406.3). Routine screening for HBV infection requires assay of multiple serologic markers (HBsAg, anti-HBc, anti-HBs). HBsAg is an early serologic marker of infection and is found in almost all infected persons; its rise closely coincides with the onset of symptoms. *Persistence of HBsAg beyond 6 months defines the chronic infection state.* During recovery from acute infection, because HBsAg levels fall before symptoms wane, IgM antibody to HBcAg (anti-HBc IgM) might be the only marker of acute infection. Anti-HBc IgM rises early after the infection and remains positive for many months before being replaced by anti-HBc IgG, which then persists for years. Anti-HBs marks serologic recovery and protection. Only anti-HBs is present in persons immunized with hepatitis B vaccine, whereas both anti-HBs and anti-HBc are detected in persons with resolved infection. HBeAg is present in active acute or chronic infection and is a marker of infectivity. The development of anti-HBe, termed *seroconversion,* marks improvement and is a goal of therapy in chronically infected patients. HBV DNA can be detected in the serum of acutely infected patients and chronic carriers. High DNA titers are seen in patients with HBeAg, and they typically fall once anti-HBe develops.

Complications

ALF with coagulopathy, encephalopathy, and cerebral edema occurs more commonly with HBV than the other hepatotropic viruses. The risk of ALF is further increased when there is coinfection or superinfection with HDV or in an immunosuppressed host. Mortality from ALF is >30%, and liver transplantation is the only effective intervention. Supportive care aimed at sustaining patients and early referral to a liver transplantation center can be lifesaving. As mentioned, HBV infection can also result in chronic hepatitis, which can lead to cirrhosis, end-stage liver disease complications, and HCC. Membranous glomerulonephritis with deposition of complement and HBeAg in glomerular capillaries is a rare complication of HBV infection.

Table 406.6 Causes of Hepatitis Flares in Patients with Chronic Hepatitis B

CAUSE OF FLARE	COMMENT
Spontaneous	Factors that precipitate viral replication are unclear
Immunosuppressive therapy	Flares are often observed during withdrawal of the agent; preemptive antiviral therapy is required
Antiviral therapy for HBV	
Interferon Nucleoside analog	Flares are often observed during the second to third month of therapy in 30% of patients; may herald virologic response
During treatment	Flares are no more common than with placebo
Drug-resistant HBV	Severe consequences can occur in patients with advanced liver disease
On withdrawal	Flares are caused by the rapid reemergence of wild-type HBV; severe consequences can occur in patients with advanced liver disease
HIV treatment	Flares can occur as a result of the direct toxicity of HAART or with immune reconstitution; HBV increases the risk of antiretroviral drug hepatotoxicity
Genotypic variation	
Precore and core promoter variants	Fluctuations in serum alanine aminotransferase levels are common with precore variants
Superinfection with other hepatitis viruses	May be associated with suppression of HBV replication

HAART, Highly active antiretroviral therapy; HBV, hepatitis B virus.
From Wells JT, Perillo R. Hepatitis B. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 79.1.

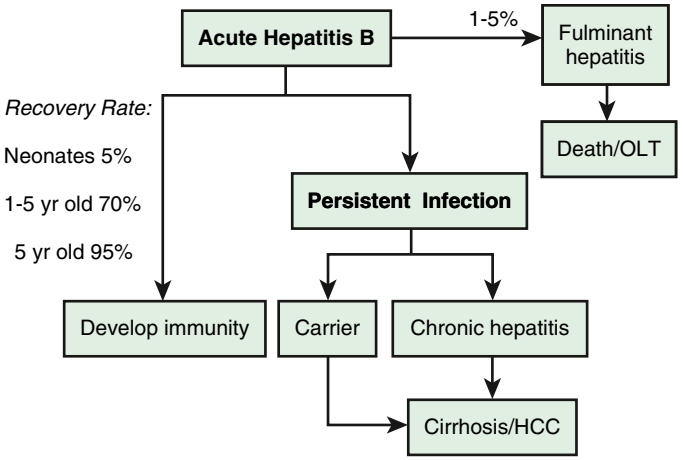

Fig. 406.3 Natural history of hepatitis B virus infection. HCC, Hepatocellular carcinoma; OLT, orthotopic liver transplant.

Treatment

Treatment of *acute* HBV infection is largely supportive. Close monitoring for liver failure and extrahepatic morbidities is key. Treatment of *chronic* HBV infection is in evolution; no drug currently achieves consistent, complete eradication of the virus. The natural history of chronic HBV infection in children is complex, and there is a lack of reliable long-term outcome data on which to base treatment recommendations. Treatment of chronic HBV infection in children should be individualized and done under the care of a pediatric hepatologist experienced in treating the disease.

The goal of treatment is to reduce viral replication, defined by having undetectable HBV DNA in the serum and development of anti-HBe, termed *seroconversion*. The development of anti-HBe transforms the disease into an inactive form, thereby decreasing infectivity, active liver injury and inflammation, fibrosis progression, and the risk of HCC. Treatment is only indicated for patients in the immune-active form of the disease, as evidenced by elevated ALT and/or AST, who have fibrosis on liver biopsy, putting the child at higher risk for cirrhosis during childhood.

Treatment Strategies

***Interferon-α2b* (IFN-α2b)** has immunomodulatory and antiviral effects. It has been used in children, with long-term viral response rates similar to the 25% rate reported in adults. IFN use is limited by its subcutaneous administration, treatment duration of 24 weeks, and side effects (flulike symptoms, marrow suppression, depression, retinal changes, autoimmune disorders). IFN is further contraindicated in decompensated cirrhosis. One advantage of IFN, compared with other treatments, is that viral resistance does not develop with its use.

Lamivudine is an oral synthetic nucleoside analog that inhibits the viral enzyme reverse transcriptase. In children older than 2 years of age, its use for 52 weeks resulted in HBeAg clearance in 34% of patients with an ALT >2 times normal; 88% remained in remission at 1 year. It has a good safety profile. Lamivudine must be used for ≥6 months after viral clearance, and the emergence of a variant viral strain (YMDD) poses a barrier to its long-term use. Combination therapy in children using IFN and lamivudine did not seem to improve the rates of response in most series.

Adefovir (a purine analog that inhibits viral replication) is approved for use in children older than 12 years of age, in whom a prospective 1-year study showed 23% seroconversion. No viral resistance was noted in that study but has been reported in adults.

Entecavir (a nucleoside analog that inhibits replication) is currently approved for use in children older than 2 years of age. Prospective data have shown a 21% seroconversion rate in adults with minimal resistance developing. Patients in whom resistance to lamivudine developed have an increased risk of developing resistance to entecavir.

Tenofovir (a nucleotide analog that inhibits viral replication) is also approved for use in children older than 12 years of age. Prospective data have shown a 21% seroconversion rate with a very low rate of developing resistance. Patients with lamivudine-resistant variants do not appear to have an increased rate of resistance. Concern exists over long-term use and bone mineral density.

Peginterferon-α_2 has the same mechanism of action as IFN but is given once weekly. This formulation has not been approved in the United States but is recommended for the treatment of chronic HBV in other countries. Patients most likely to respond to currently available drugs have low serum HBV DNA titers, are HBeAg-positive, have active hepatic inflammation (ALT greater than twice the upper limit of normal for at least 6 months), and have recently acquired disease.

Immune-tolerant patients—those with normal ALT and AST and who are HBeAg-positive with elevated viral load—are currently not considered for treatment, although the emergence of new treatment paradigms is promising for this large, yet hard-to-treat, subgroup of patients.

Prevention

The most effective prevention strategies have resulted from the screening of pregnant mothers and the use of HBIG and hepatitis B vaccine in infants (Tables 406.7 to 406.10). In HBsAg-positive and HBeAg-positive mothers, a 10% risk of chronic HBV infection exists compared with 1% in HBeAg-negative mothers. This knowledge offers screening strategies that may affect both mother and infant by using antiviral medications during the third trimester. Guidelines suggest that mothers with an HBV DNA viral load >200,000 IU/mL receive an antiviral such as telbivudine, lamivudine, or tenofovir during the third trimester, especially if they had a previous child who developed chronic HBV after receiving HBIG and the hepatitis B vaccine. This practice has proven safe, with normal growth and development in infants of treated mothers.

Table 406.7 Strategy to Eliminate Hepatitis B Virus Transmission in the United States*

- Screening of all pregnant women for HBsAg
  - HBV DNA testing for HBsAg-positive pregnant women, with suggestion of maternal antiviral therapy to reduce perinatal transmission when HBV DNA is >200,000 IU/mL
  - Prophylaxis (HepB vaccine and hepatitis B immunoglobulin) for infants born to HBsAg-positive† women
- Universal vaccination of all infants beginning at birth‡,§ as a safeguard for infants born to HBV-infected mothers not identified prenatally
- Routine vaccination of previously unvaccinated children age <19 yr
- Vaccination of adults at risk for HBV infection, including those requesting protection from HBV without acknowledgment of a specific risk factor

*Sources: Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: immunization of infants, children, and adolescents, *MMWR Recomm Rep*. 2005;54(No. RR-16):1–31; Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults, *MMWR Recomm Rep*. 2006;55(No. RR-16):1–33.

†Refer to Table 406.8 for prophylaxis recommendations for infants born to women with unknown HBsAg status.

‡Within 24 hr of birth for medically stable infants weighing ≥2,000 g.

§Refer to Table 406.8 for birth dose recommendations for infants weighing <2,000 g.

HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1–29, Box 2.

Household, sexual, and needle-sharing contacts of patients with chronic HBV infection should be identified and vaccinated if they are susceptible to HBV infection. Patients should be advised about the perinatal and intimate contact risk of transmission of HBV. HBV is not spread by breastfeeding, kissing, hugging, or sharing water or utensils. Children with HBV should not be excluded from school, play, childcare, or work, unless they are prone to biting. A support group might help children to cope better with their disease. Families should not feel obligated to disclose the diagnosis, as this information may lead to prejudice or mistreatment of the patient or the patient's family. All patients positive for HBsAg should be reported to the state or local health department.

HBIG is indicated only for specific *postexposure* circumstances and provides only temporary protection (3-6 months). It plays a pivotal role in preventing *perinatal* transmission when administered within 12 hours of birth.

Universal Vaccination

Two single-antigen vaccines (Recombivax HB and Engerix-B) are approved for children and are the only preparations approved for infant dosing under 6 weeks of life. Heplisav-B is approved only for people 18 years of age and older. Combination vaccines can be used for subsequent immunization dosing and enable integration of the HBV vaccine into the regular immunization schedule. The safety profile of the HBV vaccine is excellent. The most reported side effects are pain at the

Table 406.8 Hepatitis B Vaccine Schedules for Infants by Infant Birthweight and Maternal Hepatitis B Surface Antigen Status

BIRTHWEIGHT	MATERNAL HBsAg STATUS	SINGLE-ANTIGEN VACCINE		SINGLE-ANTIGEN + COMBINATION VACCINE†	
		DOSE	AGE	DOSE	AGE
≥2,000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG‡	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1-2 mo	2	2 mo
		3	6 mo§	3	4 mo
				4	6 mo§
	Unknown*	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		2	1-2 mo	2	2 mo
		3	6 mo§	3	4 mo
				4	6 mo§
	Negative	1	Birth (≤24 hr)	1	Birth (≤24 hr)
		2	1-2 mo	2	2 mo
		3	6-18 mo§	3	4 mo
				4	6 mo§
<2,000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2-3 mo	3	4 mo
		4	6 mo§	4	6 mo§
	Unknown	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2-3 mo	3	4 mo
		4	6 mo§	4	6 mo§
	Negative	1	Hospital discharge or age 1 mo	1	Hospital discharge or age 1 mo
		2	2 mo	2	2 mo
		3	6-18 mo§	3	4 mo
				4	6 mo§

*Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.
†Pediarix should not be administered before age 6 wk.
‡HBIG should be administered at a separate anatomic site from the vaccine.
§The final dose in the vaccine series should not be administered before age 24 wk (164 days).
HBIG, Hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.
From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1–29, Table 3.

Table 406.9 Recommended Doses of Hepatitis B Vaccine by Group and Vaccine Type

	SINGLE-ANTIGEN VACCINE				COMBINATION VACCINE			
	RECOMBIVAX		ENGERIX		PEDIARIX*		TWINRIX†	
Age-Group (yr)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)
Birth-10	5	0.5	10	0.5	10*	0.5	N/A	N/A
11-15	10‡	1	N/A	N/A	N/A	N/A	N/A	N/A
11-19	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	10	1	20	1	N/A	N/A	20†	1
HEMODIALYSIS PATIENTS AND OTHER IMMUNE-COMPROMISED PERSONS								
<20	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	40	1	40	2	N/A	N/A	N/A	N/A

*Pediarix is approved for use in persons age 6 wk through 6 yr (before the seventh birthday).
†Twinrix is approved for use in persons age ≥18 yr.
‡Adult formulation administered on a two-dose schedule.
N/A, Not applicable.
From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1–29, Table 2.

Table 406.10 Hepatitis B Vaccine Schedules for Children, Adolescents, and Adults

AGE GROUP	SCHEDULE* (INTERVAL REPRESENTS TIME IN MONTHS FROM FIRST DOSE)
Children (1-10 yr)	0, 1, and 6 mo 0, 1, 2, and 12 mo
Adolescents (11-19 yr)	0, 1, and 6 mo 0, 12, and 24 mo 0 and 4-6 mo† 0, 1, 2, and 12 mo 0, 7 days, 21-30 days, 12 mo‡
Adults (≥20 yr)	0, 1, and 6 mo 0, 1, 2, and 12 mo 0, 1, 2, and 6 mo§ 0, 7 days, 21-30 days, 12 mo‡

*Refer to package inserts for further information. For all ages, when the hepatitis B vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 8 wk. If only the third dose has been delayed, it should be administered as soon as possible. The final dose of the vaccine must be administered at least 8 wk after the second dose and should follow the first dose by at least 16 wk; the minimum interval between the first and second doses is 4 wk. Inadequate doses of hepatitis B vaccine or doses received after a shorter-than-recommended dosing interval should be readministered, using the correct dosage or schedule. Vaccine doses administered ≤4 days before the minimum interval or age are considered valid. Because of the unique accelerated schedule for Twinrix, the 4-day guideline does not apply to the first three doses of this vaccine when administered on a 0-day, 7-day, 21 to 30-day, and 12-mo schedule (new recommendation).

†A two-dose schedule of Recombivax adult formulation (10 μg) is licensed for adolescents age 11-15 yr. When scheduled to receive the second dose, adolescents age >15 yr should be switched to a three-dose series, with doses two and three consisting of the pediatric formulation administered on an appropriate schedule.

‡Twinrix is approved for use in persons age ≥18 yr and is available on an accelerated schedule with doses administered at 0, 7, 21-30 days, and 12 mo.

§A four-dose schedule of Engerix administered in two-1 mL doses (40 μg) on a 0-, 1-, 2-, and 6-mo schedule is recommended for adult hemodialysis patients.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1–29, Table 4.

injection site (up to 29% of cases) and fever (up to 6% of cases). Seropositivity is 90–95% with all vaccines, achieved after the second dose in most patients. The third dose serves as a booster and may have an effect on maintaining long-term immunity. For immunocompromised individuals, annual anti-HBs testing should be considered, with a fourth booster dose given when anti-HBs concentrations are <10 mIU/mL. Similar consideration may be given to children with cystic fibrosis, liver disease, or celiac disease if there is an ongoing risk for HBV exposure. In infants whose birthweight is <2,000 g born to HBsAg-positive mothers (or if their HBsAg status remains unknown), a fourth dose is recommended at 6 months of age (the birth dose does not count as part of the three-dose series) and these infants should be checked for anti-HBs and HBsAg after completing these shots. In this group of infants, if the anti-HBs level is <10 mIU/mL, they should repeat the three-dose series. Despite declines in the anti-HBs titer in time, most healthy vaccinated persons remain protected against HBV infection.

HBV vaccination recommendations are as noted in Tables 406.8 to 406.10.

Postvaccination testing for HBsAg and anti-HBs should be done at 9-18 months. If the result is positive for anti-HBs, the child is immune to HBV. If the result is positive for HBsAg only, the parent should be counseled and the child evaluated by a pediatric hepatologist. If the result is negative for both HBsAg and anti-HBs, a second complete hepatitis B vaccine series should be administered, followed by testing for anti-HBs to determine if subsequent doses are needed.

Administration of four doses of vaccine is permissible when combination vaccines are used after the birth dose; this does not affect vaccine response.

Postexposure Prophylaxis

Recommendations for postexposure prophylaxis for prevention of hepatitis B infection depend on the conditions under which the person is exposed to HBV (see Table 406.10). Vaccination should never be postponed if written records of the exposed person's immunization history are not available, but every effort should still be made to obtain those records.

Special Populations

Patients with cirrhosis may not respond as well to the HBV vaccine, and repeat anti-HBs titers should be performed. Adult studies suggest a higher dosage or shorter interval between dosages may increase immunization effectiveness. Patients with inflammatory bowel disease frequently have not been immunized or did not develop complete immunity to HBV, as demonstrated by inadequate anti-HBs levels. These patients may be at risk for fulminant HBV (reactivation) when immunosuppression is started as part of their treatment regimen, specifically with biologic agents such as infliximab.

Prognosis

In general, the outcome after acute HBV infection is favorable, despite a risk of ALF. The risk of developing chronic infection brings the risks of liver cirrhosis and HCC to the forefront. Perinatal transmission leading to chronicity is responsible for the high incidence of HCC in young adults in endemic areas. Importantly, HBV infection and its complications are effectively controlled and prevented with vaccination, and multiple clinical trials are ongoing in an effort to improve and guide treatment regimens.

HEPATITIS C

Etiology

HCV is a single-stranded RNA virus, classified as a separate genus within the Flaviviridae family, with marked genetic heterogeneity. It has at least six major genotypes and numerous subtypes and quasi-species, which permit the virus to escape host immune surveillance. Genotype variation might partially explain the differences in clinical course and response to treatment. Genotype 1 (a and b) is the most common genotype in the United States. The advent of direct-acting antiviral (DAA) therapy has brought a new and highly successful approach to the treatment and cure of hepatitis C.

Epidemiology

DAA therapy has made a major impact on decreasing the prevalence of HCV in the United States. However, HCV continues to be a major cause of chronic liver disease in adults and is associated with >10,000 deaths per year. Approximately 2.5 million people in the United States and 70 million people worldwide are estimated to be currently infected with HCV. The reported global estimated viremic prevalence in children with HCV (age 0-17 years) is hypothesized to be around 3.25 million children as of 2018. Appropriate identification and screening for infected individuals should be implemented.

Risk factors for HCV transmission in the United States included blood transfusion before 1992; with current blood donor screening practices, the risk of HCV transmission is approximately 0.001% per unit transfused. Illegal drug use with exposure to blood or blood products from HCV-infected persons accounts for the majority of adult cases in the United States. Sexual transmission, especially through multiple sexual partners, is the second most common cause of infection. Other risk factors include occupational exposure, but approximately 10% of new infections have no known transmission source. In children, perinatal transmission is the *most* prevalent mode of transmission (see Table 406.1). HCV infection rates in the United States in women of childbearing age and those who are pregnant have increased in parallel with the rising opioid epidemic. Based on the most recent census data, an estimated 29,000 women with HCV infection give birth each year in the United States, with the majority of their infants being infected with HCV. HIV coinfection and high viremia titers (HCV RNA-positive) in the mother can increase the transmission rate to 20%. The incubation period is 7-9 weeks (range: 2-24 weeks).

In 2020, the United States Preventive Services Task Force (USPSTF) and the CDC issued updated recommendations that encourage clinicians to screen all adults age 18-79 years for HCV infection. The USPSTF recommendations specifically suggest HCV screening for all pregnant women. This is important because the rate of HCV infection in pregnant women has continued to increase, with an associated increase in the number of infants exposed to HCV. The mode of delivery (vaginal vs cesarean section) does not typically affect risk of transmission. HCV RNA may be detected in breast milk and colostrum; however, breastfeeding does not appear to increase the rate of HCV transmission (with the exception of HIV coinfected mothers).

Pathogenesis

The pattern of acute hepatic injury is indistinguishable from that of other hepatotropic viruses. In chronic cases, lymphoid aggregates or follicles in portal tracts are found, either alone or as part of a general inflammatory infiltrate of the portal areas. HCV appears to cause injury primarily by cytopathic mechanisms, but immune-mediated injury can also occur. The cytopathic component appears to be mild because the acute illness is typically the least severe of all hepatotropic virus infections.

Clinical Manifestations

Acute HCV infection tends to be mild and insidious in onset (Fig. 406.4; see also Table 406.1). ALF rarely occurs. HCV is the most likely of all these viruses to cause chronic infection (Fig. 406.5). Of affected adults, <15% clear the virus; the rest develop chronic hepatitis. In pediatric studies, 20–40% of children achieved spontaneous sustained clearance of the virus within the first 5 years of life.

Chronic HCV infection is also clinically silent until a complication develops. Serum aminotransferase levels fluctuate and are sometimes normal, but histologic inflammation is universal. Progression of liver fibrosis is slow over several years, unless comorbid factors are present, which can accelerate fibrosis progression. Approximately 25% of infected patients ultimately progress to cirrhosis, liver failure, and, occasionally, primary HCC within 20-30 years of the acute infection. Although progression is rare within the pediatric age range, cirrhosis and HCC from HCV have been reported in children. The long-term morbidities constitute the rationale for diagnosis and treatment in children with HCV.

Chronic HCV infection can be associated with small vessel vasculitis and is a common cause of essential mixed cryoglobulinemia. Other extrahepatic manifestations predominantly seen in adults include cutaneous vasculitis, porphyria cutanea tarda, lichen planus, peripheral neuropathy, cerebritis, polyarthritis, membranoproliferative glomerulonephritis, and nephrotic syndrome. Antibodies to smooth muscle, antinuclear antibodies, and low thyroid hormone levels may also be present.

Diagnosis

In children older than 18 months of age, diagnostic criteria are the same as those established for adults. Clinically available assays for detection of HCV infection are based on detection of antibodies to HCV antigens (anti-HCV) or detection of viral RNA (see Table 406.3); neither can predict the severity of liver disease.

The most widely used serologic test is the third-generation enzyme immunoassay to detect anti-HCV. The predictive value of this assay is greatest in high-risk populations, but the false-positive rate can be as high as 50–60% in low-risk populations. False-negative results also occur because antibodies remain negative for as long as 1-3 months after clinical onset of illness. Anti-HCV is not a protective antibody and does not confer immunity; it is usually present simultaneously with the virus. The next step is to verify viral infection by detecting HCV RNA. This is accomplished via PCR testing. The diagnosis of chronic HCV infection is made based on the presence of detectable HCV RNA for more than 6 months. The *quantitative* PCR also aids in monitoring response to therapy.

For infants under 18 months of age, the diagnosis may be confounded by the passive transfer of maternal antibodies, which can last for 1 year or more postnatally. Thus anti-HCV testing is of limited value during the first year of life. Diagnosis in this age-group can be reliably established by HCV RNA positivity on two or more occasions after 2 months of age. Criteria for spontaneous clearance requires two negative HCV RNA tests spread at least 6 months apart, followed by negative anti-HCV testing after 18 months of age.

Screening for HCV should include all patients with the following risk factors: history of illegal drug use (even if only once), receiving clotting factors made before 1987 (when inactivation procedures were introduced) or blood products before 1992, hemodialysis, idiopathic liver disease, and children born to HCV-infected women (qualitative PCR in infancy and anti-HCV after 12-18 months of age). In children, it is also important to consider whether the mother has any of the risk factors noted earlier that would increase her possibility of developing HCV.

Determining HCV genotype is also important, particularly when therapy is considered, as certain DAA therapies may only target specific genotypes. Newer pangenotypic DAA agents, however, will hopefully lead to the practice of genotyping becoming moot in the near future (as discussed later).

Aminotransferase levels typically fluctuate during HCV infection and do not correlate with the degree of liver fibrosis. A liver biopsy was

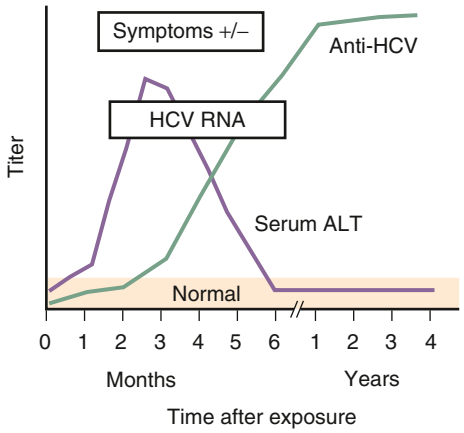

Fig. 406.4 Typical course of acute hepatitis C virus infection followed by recovery. Symptoms may or may not be present during acute infection. Anti-HCV, Antibody to HCV; ALT, alanine aminotransferase. *(Modified from the Centers for Disease Control and Prevention, www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/training.htm#one.)*

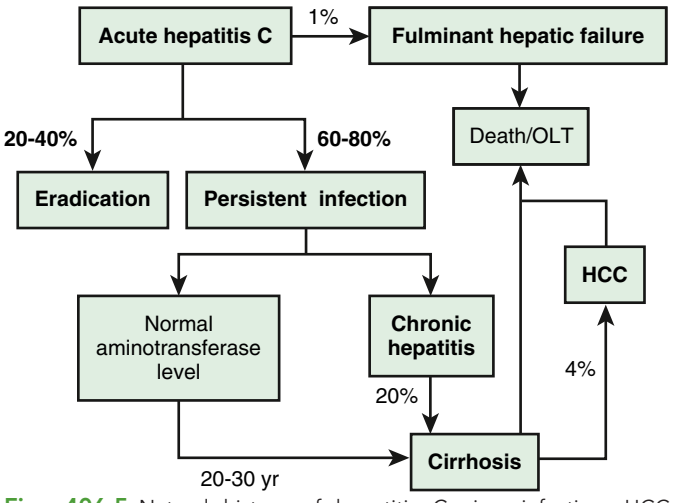

Fig. 406.5 Natural history of hepatitis C virus infection. HCC, Hepatocellular carcinoma; OLT, orthotopic liver transplant. *(From Hochman JA, Balistreri WF. Chronic viral hepatitis: always be current! Pediatr Rev. 2003;24[12]:399–410.)*

previously the only means to assess the presence and extent of hepatic fibrosis, outside of overt signs of chronic liver disease. Newer noninvasive modalities using ultrasound or magnetic resonance elastography, however, are now used to estimate the degree of fibrosis and decrease the need for biopsy. This technology, coupled with newer drug regimens, has eliminated the need for liver biopsy in many cases of HCV infection. A liver biopsy is now primarily indicated to rule out other causes of overt liver disease.

Complications

The risk of ALF caused by HCV is low, but the risk of chronic hepatitis is the highest of all the hepatitis viruses. In adults, risk factors for progression to hepatic fibrosis include older age, obesity, being male, and even moderate alcohol ingestion (two 1-oz. drinks per day). Progression to cirrhosis or HCC is a major cause of morbidity and one of the most common indications for liver transplantation in adults in the United States.

Treatment

The arrival of DAA therapies has led to a paradigm shift in the treatment and eradication of HCV in all populations. These DAAs are now available and have been shown to be as safe and effective in children (>3 years) and adolescents as in the adult populations. Pegylated-interferon (PEG-IFN) and ribavirin (RBV), the initial recommended combination for treatment of HCV in children and adolescents, are no longer recommended.

The goal of treatment is to achieve a sustained viral response (SVR), defined as the absence of viremia at a variable period after stopping the medications. SVR is associated with improved histology and decreased risk of morbidities. DAA therapies can achieve SVR after 8-12 weeks of treatment, as compared with the RBV and PEG-IFN combination, which required 48 weeks of treatment, close monitoring, and significant side effect profiles including pancytopenia. Furthermore, regimens of PEG-IFN have sustained efficacy of 50% in achieving SVR, whereas DAA regimens have been shown to be consistently more effective (SVR >95%) in children.

DAAs target three HCV proteins involved in the life cycle of this virus: (1) the nonstructural protein 3/4A (NS3/4A) protease inhibitors (PIs), which work by inhibiting HCV polyprotein processing; (2) NS5A inhibitors, which inhibit viral replication and assembly; and (3) NS5B polymerase inhibitors, which block HCV RNA replication. By combining two or more of these classes of drugs with different mechanisms attacking HCV, DAAs are able to achieve high SVR rates.

Several phase 2 clinical trials have been completed, revealing the safety and efficacy of DAA therapy in children as young as 3 years of age. For example, the first pediatric trial showed the safety and efficacy of the combination of ledipasvir (90 mg) and sofosbuvir (400 mg) for treatment of HCV genotype 1 over a 12-week period in children ages 12-17 years. This combination is Food and Drug Administration (FDA) approved for children as young as 3 years of age.

It is important to note that one of the main obstacles is determining an age when a young child is capable of daily compliance with the medications for the recommended 8- to 12-week period. The arrival of DAA therapies in the form of granules is a promising strategy for younger children who cannot swallow whole tablets. These granules can be sprinkled on a spoonful of nonacidic soft food (e.g., pudding or peanut butter). SVR has been achieved in 97% of patients as young as 3 years in phase 2 clinical trials using this formulation of delivery.

Treatment recommendations involve obtaining HCV PCR at baseline (before initiation of DAA therapy), at 12 weeks, and at 24 weeks post initiation of therapy. As long as there was no evidence of long-term damage (e.g., fibrosis, cirrhosis), then patients can have a repeat HCV PCR assessment at 1 year after completion of therapy to affirm SVR.

Newer Treatments

Pangenotypic agents, capable of being >92% effective at achieving SVR for all genotypes, have now been FDA approved for children ≥3 years. These include the agents sofosbuvir-velpatasvir, given at once-daily weight-based dosing for 12 weeks, and the combination of glecaprevir-pibrentasvir at three weight-based doses per day for 8 weeks. Thus the need to obtain expensive genotype testing may be unnecessary. With the rapid development of new medications and regimens, frequent review of up-to-date resources, such as www.hcvguidelines.org, will be vital to provide optimal care (Table 406.11).

Prevention

No vaccine is yet available to prevent HCV, although ongoing research suggests this will be possible in the future. Currently available Ig preparations are not beneficial, likely because preparations produced in the United States do not contain high titers of antibodies to HCV, because blood and plasma donors are screened for anti-HCV and excluded from the donor pool. Broad neutralizing antibodies to HCV were found to be protective and might pave the road for vaccine development.

Once HCV infection is identified, patients should be screened yearly with a liver ultrasound and serum α-fetoprotein for HCC and for any clinical evidence of liver disease. Vaccinating the affected patient against HAV and HBV will prevent superinfection with these viruses and the increased risk of developing severe liver failure. Beginning education to families on DAA therapies and initiating treatment at 3 years of age (or as soon as the child is developmentally ready to complete therapy) are also crucial to prevent the development of fibrosis. However, children with evidence of liver fibrosis should continue to be closely monitored even after eradication of their underlying HCV. Fortunately, adult studies are emerging that reveal mild reversal of fibrosis by DAA treatment. However, for patients with evidence of high-grade fibrosis or cirrhosis, they are still at high risk of developing HCC even after achieving SVR. More histologic data are needed to further support the hypothesis of improved liver scarring post DAA treatment. Children with evidence of fibrosis must be closely followed, given the continued risk of complications such as HCC and portal hypertension.

Prognosis

DAA therapies have revolutionized treatment for HCV and allow for resolution of the underlying hepatitis in young children and adolescents before development of irreversible chronic liver disease (fibrosis, cirrhosis, HCC). The World Health Organization (WHO) in 2016 set the ambitious goal of eliminating HCV by 2030, and these new DAA therapeutic agents have provided an important step toward achieving this goal.

HEPATITIS D

Etiology

HDV, the smallest known animal virus, is considered defective because it cannot produce infection without concurrent HBV infection. The 36-nm-diameter virus is incapable of making its own coat protein; its outer coat is composed of excess HBsAg from HBV. The inner core of the virus is single-stranded circular RNA that expresses the HDV antigen.

Epidemiology

HDV can cause an infection at the same time as the initial HBV infection (coinfection), or HDV can infect a person who is already infected with HBV (superinfection). Transmission usually occurs by intrafamilial or intimate contact in areas of high prevalence, which are primarily developing countries (see Table 406.1). In areas of low prevalence, such as the United States, the parenteral route is far more common. HDV infections are uncommon in children in the United States but must be considered when ALF occurs. The incubation period for HDV superinfection is approximately 2-8 weeks; with coinfection, the incubation period is similar to that of HBV infection.

Pathogenesis

Liver pathology in HDV-associated hepatitis has no distinguishing features except that damage is usually severe. In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. The most severe cases of HBV infection appear to result from coinfection of HBV and HDV.

Table 406.11 Completed Studies with Direct-Acting Antiviral Combinations in Children with Chronic Hepatitis C Virus Infection

THERAPY (DURATION)	HCV GENOTYPE	PARTICIPANT AGE IN YEARS (N)	YEAR	SVR12 (%)
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	1	12-17 (100)	2016	98
Sofosbuvir 400 mg + ribavirin (variable)	2 or 3	12-17 (52)	2017	98
Sofosbuvir 400 mg + ribavirin (variable)	1 or 3	5-18 (35)	2017	97
Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	1,4-6	12-17 (144)	2018	99
Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	1	6-11 (90)	2018	98
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	12-18 (40)	2018	100
Ledipasvir + sofosbuvir ± ribavirin (variable)		7-18 (22)	2018	91
Ledipasvir 22.5 mg + sofosbuvir 100 mg (12 wk)	4	0.5 (1)	2018	100
Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	4	6-12 (20)	2018	95
Ledipasvir + sofosbuvir (variable)	1 or 4	6-18 (9)	2019	100
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	11-17.5 (51)	2019	100
Ledipasvir 90 mg + sofosbuvir 400 mg (8 wk)	1	12-17 (14)	2019	100
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	13, 16 (2)	2019	100
Ledipasvir 180 mg + sofosbuvir 400 mg (12 wk)	not performed	12-18 (46)	2020	98
Ledipasvir 45 mg + sofosbuvir 200 mg (8 or 12 wk)	4	3-6 (22)	2020	100
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	9-12 (100)	2020	100
Sofosbuvir 400 mg + ribavirin (variable)	1 or 4	3-11 (54)	2020	98
Ledipasvir + sofosbuvir (variable)	1 or 4	3 to <6 (34)	2020	97
Glecaprevir 300 mg + pibrentasvir 120 mg (8-16 wk)	1-4	12-17 (47)	2020	100
Elbasvir + grazoprevir (12 wk)	1 or 4	3-17 (57)	2020	100
Sofosbuvir + velpatasvir (12 wk)	1-4, 6	3-17 (216)	2020	92
Ledipasvir 45 mg + sofosbuvir 200 mg (8 wk)	4	4-10 (30)	2020	100
Sofosbuvir + velpatasvir (12 wk)	1-6	3-17 (160)	2021	92
Glecaprevir + pibrentasvir (8 wk)	1-6	3-12 (81)	2021	96

Clinical Manifestations

The symptoms of hepatitis D are similar to, but usually more severe than, those of the other hepatotropic viruses. The clinical outcome for HDV infection depends on the mechanism of infection. In *coinfection,* acute hepatitis, which is much more severe than for HBV alone, is common, but the risk of developing chronic hepatitis is low. In *superinfection,* acute illness is rare and chronic hepatitis is common. The risk of ALF is highest with superinfection. Hepatitis D should be considered in any child who experiences ALF.

Diagnosis

HDV has not been isolated, and no circulating antigen has been identified. The diagnosis is made by detecting IgM antibody to HDV; the antibodies to HDV develop approximately 2-4 weeks after coinfection and approximately 10 weeks after a superinfection. A test for anti-HDV antibody is commercially available. PCR assays for viral RNA are available as research tools (see Table 406.2).

Treatment

The treatment is based on supportive measures once an infection is identified. There are no specific HDV-targeted treatments to date. The treatment is mostly based on controlling and treating HBV infection, without which HDV cannot induce hepatitis. Small research studies suggest that IFN is the preferred treatment regimen, but ongoing studies still seek the ideal management strategy, and the regimen should be personalized for each patient.

Prevention

There is no vaccine for hepatitis D. Because HDV replication cannot occur without hepatitis B coinfection, immunization against HBV also prevents HDV infection. Hepatitis B vaccines and HBIG are used for the same indications as for hepatitis B alone.

HEPATITIS E

Etiology

HEV has been cloned using molecular techniques. This RNA virus has a nonenveloped sphere shape with spikes and is similar in structure to the caliciviruses.

Epidemiology

Hepatitis E is the epidemic form of viral hepatitis. Transmission is fecal-oral (often waterborne) and is associated with shedding of 27- to 34-nm particles in the stool (see Table 406.1). The highest prevalence of HEV infection has been reported in the Indian subcontinent, the Middle East, Southeast Asia, and Mexico, especially in areas with poor sanitation. The prevalence, however, appears to be increasing in the United States and other developed countries and has been postulated to be the most common cause of acute hepatitis and jaundice in the world. The mean incubation period is approximately 40 days (range: 15-60 days).

Pathogenesis

HEV appears to act as a cytopathic virus. The pathologic findings are similar to those of the other hepatitis viruses.

Clinical Manifestations

The clinical illness associated with HEV infection is similar to that of HAV but is often more severe. As with HAV, chronic illness does not occur—the sole exception noted to date is chronic hepatitis E occurring in immunosuppressed patients (e.g., post-transplant). In addition to often causing a more severe episode than HAV, HEV tends to affect older patients, with a peak age between 15 and 34 years. HEV is a major pathogen in pregnant women, in whom it causes ALF with a high fatality incidence. HEV could also lead to decompensation of preexisting chronic liver disease.

Diagnosis

Recombinant DNA technology has resulted in the development of antibodies to HEV particles, and IgM and IgG assays are available to distinguish between acute and resolved infections (see Table 406.3). IgM antibody to viral antigen becomes positive after approximately 1 week of illness. Viral RNA can be detected in stool and serum by PCR.

Prevention

A recombinant hepatitis E vaccine is highly effective in adults. No evidence suggests that Ig is effective in preventing HEV infections. Ig pooled from patients in endemic areas might prove to be effective.

Acute Hepatitis of Unknown Etiology

In 2021 and 2022 multiple medical centers in over 35 countries reported cases of acute and often severe hepatitis. Clinical manifestations included jaundice, emesis, diarrhea, and hepatomegaly; fever was not always present. Liver enzyme (ALT, AST) and bilirubin levels were elevated in most; ~77% had hepatic failure requiring liver transplantation. Adenovirus (type 41) was detected by PCR in blood but not consistently in liver biopsy specimens (by immune histopathology, electron microscopy, or PCR). Adeno-associated virus 2 has been recovered in both plasma and liver tissue from most patients. A collaborative registry from 25 centers reported a median age of onset of 41 months (range <1-16 years) with ~27% requiring intensive care unit (ICU)–level care. In that cohort, only 22% had evidence of adenovirus infection. The WHO working case definition is noted in Table 406.12. Treatment is supportive, as indicated for other etiologies of acute hepatitis and hepatic failure. The use of corticosteroids is controversial (especially with adenoviremia); some centers have used cidofovir, an inhibitor of viral (adenovirus) DNA polymerases.

Until further clarification of the etiology, the initial evaluation must include the traditional viral, immune, and toxic etiologies of hepatitis and acute hepatic failure (see Table 406.2)

APPROACH TO ACUTE OR CHRONIC HEPATITIS

Identifying deterioration of the patient with acute hepatitis and the development of ALF is a major contribution of the primary care provider (Fig. 406.6). If ALF is identified, the clinician should immediately refer the patient to a transplantation center; this can be lifesaving.

Table 406.12 WHO Working Case Definitions of Severe Acute Hepatitis of Unknown Etiology

- **Confirmed case:** Not available at present
- **Probable case:** A person presenting with an acute hepatitis (nonhepatitis A-E[1]) with serum transaminase >500 IU/L (AST or ALT), who is 16 yr and younger, since October 1, 2021
- **Epidemiologically linked:** A person presenting with an acute hepatitis (nonhepatitis A-E[1]) of any age who is a close contact of a probable case, since October 1, 2021

[1]If hepatitis A-E serology results are pending but other criteria are met, these can be reported and will be classified as "pending classification." Cases with other explanations for their clinical presentation are discarded. Delta testing is not required, as it is only undertaken in persons who are HBsAg positive to establish presence of coinfection.

From World Health Organization: Disease Outbreak News. Acute hepatitis of unknown aetiology in children – Multi-country. Geneva: World Health Organization, July 12, 2022. Available at https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON400.

Once chronic infection is identified, close follow-up and referral to a pediatric hepatologist is recommended to enroll the patient in appropriate treatment trials. Treatment of chronic HBV in children should preferably be delivered within, or using data from, pediatric controlled trials, as indications, timing, regimen, and outcomes remain to be defined and cannot be extrapolated from adult data. New DAA therapies have changed the approach to treatment of HCV in children as young as 3 years of age. All patients with chronic viral hepatitis should avoid as much as possible further insult to the liver; HAV and HBV vaccines are recommended. Patients must avoid alcohol consumption and obesity, and they should exercise care when taking new medications, including nonprescription drugs and herbal medications.

International adoption and ease of travel continue to change the epidemiology of hepatitis viruses. In the United States, chronic HBV and HCV have a high prevalence among international adoptee patients; vigilance is required to establish early diagnosis in order to offer appropriate treatment and prophylactic measures to limit viral spread.

Chronic hepatitis can be a stigmatizing disease for children and their families. The pediatrician should offer, with proactive advocacy, appropriate support for them and needed education for their social circle. Scientific data and information about support groups are available for families on the websites for the American Liver Foundation (www.liverfoundation.org) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (www.naspghan.org) and through pediatric gastroenterology centers.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

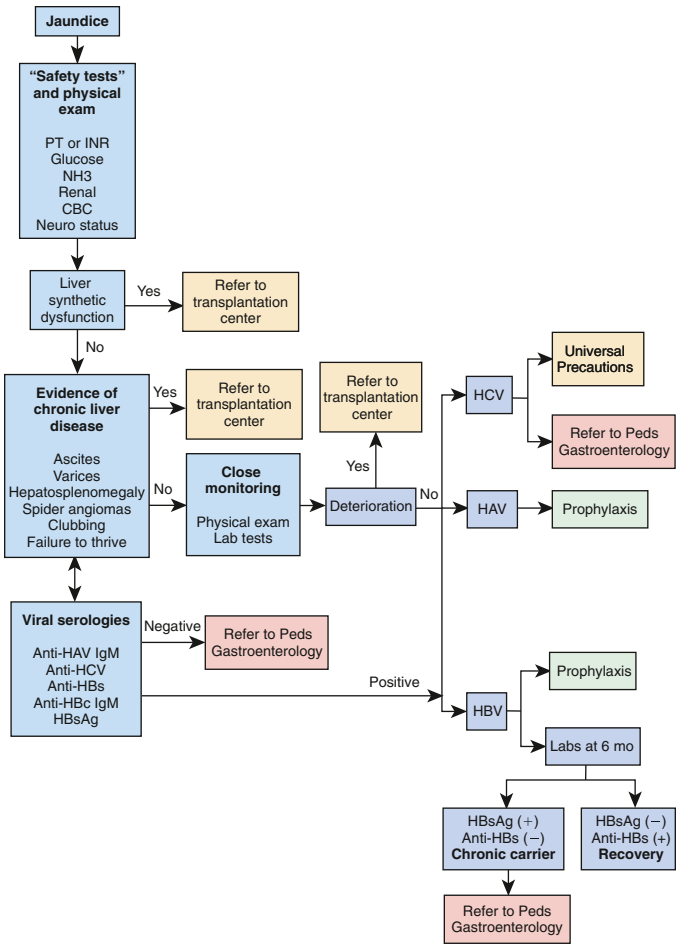

Fig. 406.6 Algorithm showing the clinical approach to viral hepatitis. CBC, Complete blood count with differential; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; INR, international normalization ratio; NH_3, ammonia; PT, prothrombin time.

Chapter 407

Liver Abscess

Hilary E. Miller-Handley and Joshua K. Schaffzin

Liver abscesses typically have one of two infectious etiologies: pyogenic, meaning involving bacteria, or parasitic, such as with amebiasis, ascariasis, or toxocariasis. Liver abscesses are typically difficult to detect because of their nonspecific presentation, and diagnosis requires a high index of suspicion. Radiographic diagnosis is often contributory, but further confirmation is often indicated to differentiate infectious abscess from hydatid cyst and noninfectious causes, such as malignancy (primary hepatic or metastasis). The differential diagnosis also includes traumatic injury (including procedural, such as a misplaced vascular catheter).

Pyogenic liver abscesses (PLA) are uncommon in children but have been reported in all ages. Bacteria can invade the liver through one of four sources: hematogenously through the hepatic artery (e.g., in the presence of bacteremia), through the biliary tract, through the portal vein (portal sepsis), and directly by contiguous infection. In neonates, a portal vein source can include the umbilical vein (e.g., in the presence of omphalitis or injury caused by an umbilical venous catheter). PLA of unknown source are classified as cryptogenic. Children with hepatobiliary malignancy, liver transplantation, primary immune deficiency disorders (i.e., chronic granulomatous disease [CGD] and hyper-IgE syndrome), and gastrointestinal pathology are at increased risk for a liver abscess. Diabetes mellitus is a risk factor associated with PLA in adults; however, it is not as clearly linked in children. PLA are also uncommon in adults, although the annual incidence is higher in Southeast Asia (estimated 17.6/100,000 population) than in the United States or Europe (estimated 2-5/100,000 population). They tend to occur more frequently in males and with older age.

Clinical signs and symptoms of PLA are nonspecific and can include fever, chills, malaise, fatigue, nausea, abdominal pain (with or without right upper quadrant tenderness), and hepatomegaly; jaundice is uncommon. The most common abnormal laboratory findings are elevated inflammatory markers and hypoalbuminemia. Hepatic function testing can be abnormally elevated, and leukocytosis is common. Radiologic confirmation is often obtained by ultrasound or CT (Fig. 407.1). Chest x-rays may show elevation of the right hemidiaphragm with a right pleural effusion. Solitary lesions of the right hepatic lobe are most common, although solitary abscesses can appear in any hepatic lobe or as multiple disseminated lesions (such as with disseminated candidiasis, bartonellosis, or, rarely, brucellosis).

Cultures of pyogenic liver abscesses are often polymicrobial. In children, *Staphylococcus aureus, Streptococcus* spp., enteric gram-negative organisms *(Escherichia coli, Klebsiella pneumoniae),* and anaerobic organisms are most common. In immunocompromised children, particularly those with CGD, *Serratia* spp. and *Aspergillus* spp. are also commonly identified. Among adults, *E. coli* and *K. pneumoniae* are the most common organisms, and aerobic gram-positive and anaerobic organisms are less common. Blood cultures are positive in about 25–35% of individuals with a PLA and may be helpful to determine a therapy plan.

Because of the wide range of causative organisms (i.e., aerobic gram-negative, *S. aureus*, and anaerobic organisms) empiric antimicrobial treatment needs to be broad. Potential empiric antimicrobial choices include piperacillin-tazobactam, ampicillin-sulbactam, or metronidazole with a third-generation cephalosporin. Depending on local prevalence and degree of suspicion, vancomycin may be added to cover methicillin-resistant *S. aureus*. Therapy should be modified based on culture susceptibilities. Treatment duration is not standardized and should be based on fever resolution, clinical and inflammatory marker improvement, and serial ultrasound monitoring. Many sources recommend completing 4-6 weeks of therapy, with the first 2 weeks administered parentally. Depending on the size and extent of the lesion(s), percutaneous or surgical drainage may be added to obtain samples for cultures and to shorten illness duration. Percutaneous options include single-pass needle or catheter aspiration, or insertion of a continuously draining catheter. In adults, unless there is evidence of rupture or spread, percutaneous drainage should be attempted first for large lesions (≥5-7 cm in diameter). Numerous case series of PLA in premature infants described complete resolution with antibiotic therapy alone, and some advocate for this as an initial approach in smaller lesions. Resolution can be monitored by trending inflammatory markers and/or serial imaging.

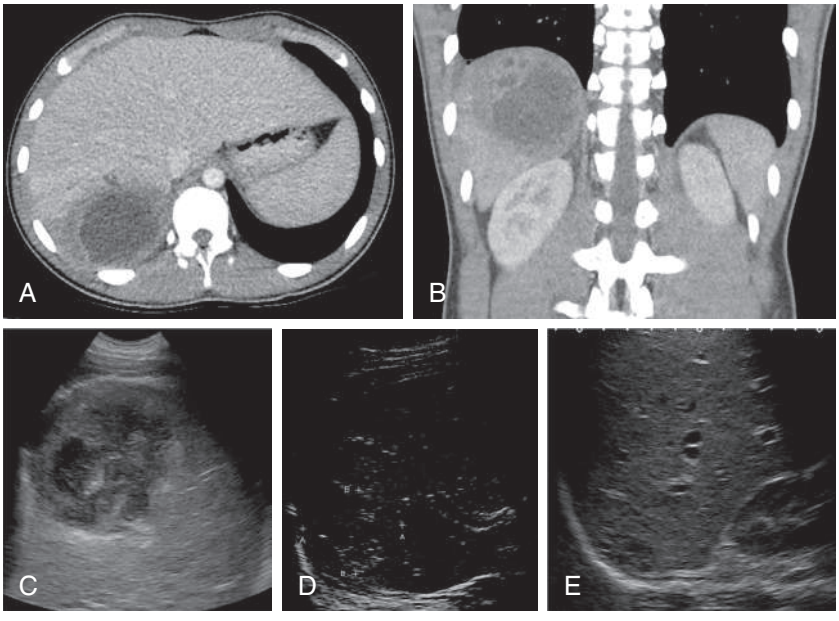

Fig. 407.1 CT (**A** and **B**) and ultrasound (**C**) images of a cryptogenic liver abscess in a 16-yr-old male without known risk factors. The lesion was drained percutaneously, and cultures grew multiple anaerobic organisms (*Fusobacterium nucleatum* and *Parvimonas micra*). He was successfully treated with 2 wk of parenteral followed by 4 wk of oral therapy and was followed with serial ultrasounds 5 days (**D**) and 34 days (**E**) after drainage. *(Courtesy Dr. Alexander Towbin, Cincinnati Children's Hospital, Cincinnati, Ohio.)*

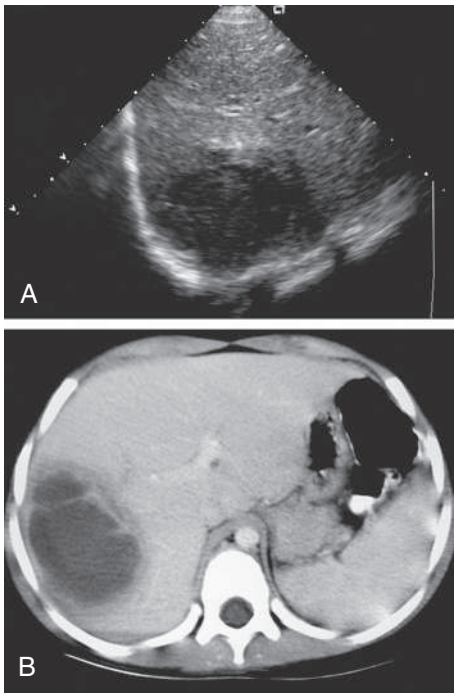

Fig. 407.2 Amebic abscess. **A,** Sonogram demonstrates a hypoechogenic mass in the right lobe of the liver with a more hypoechoic surrounding rim. **B,** CT scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. *(From Kuhn JP, Slovis TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby, 2004: p. 1473.)*

Amebic liver abscess (ALA) is the most common extraintestinal manifestation of *Entamoeba histolytica* infection. Although more common in endemic areas, cases can be diagnosed in the United States among travelers to, and immigrants from, endemic areas. Presentation can be delayed by months to years. ALA is more common among adults aged 18-55 years, and males predominate. Amoebic trophozoites invade colonic mucosa and reach the liver through the portal circulation. Patients may not have an associated colitis. Fever, right upper quadrant pain, anorexia, and weight loss are often present. Laboratory evaluation typically reveals a leukocytosis without eosinophilia and increased alkaline phosphatase. Ultrasonography or CT demonstrates the abscess (Fig. 407.2).

Diagnosis of ALA is often confirmed by serum ELISA. Serology is considered reliable in nonendemic areas but can be prone to false negatives early in the infection and cannot distinguish active infection from previous exposure. Testing for *E. histolytica* presence in stool is specific but not very sensitive, and patients with ALA may not have detectable organisms in their stool. Most sensitive and specific among stool assays is polymerase chain reaction (PCR), followed by stool antigen detection. Least reliable is microscopy because *E. histolytica* cannot easily be distinguished microscopically from its clinically benign relatives *Entamoeba dispar* and *Entamoeba moshkovskii*.

Before effective treatment, ALA-associated mortality was high; it has since decreased significantly. Treatment involves 7-10 days of a nitroimidazole (most commonly metronidazole) to kill trophozoites, followed by 7 days of a luminal agent (such as paromomycin) to kill colonic cysts. Patients with large abscesses (≥5-7 cm in diameter) may benefit from percutaneous aspiration in addition to medical therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 408

Liver Disease Associated with Systemic Disorders

Batul Kaj-Carbaidwala and William F. Balistreri

Liver involvement in systemic illnesses can be the result of the primary pathologic process, secondary to inflammatory or immune responses, or as a complication of therapy.

INFLAMMATORY BOWEL DISEASE

Hepatobiliary involvement in patients with inflammatory bowel disease (IBD, see Chapter 382) is relatively common; up to 30% of patients will have elevated liver enzymes, and 5% may develop chronic hepatobiliary diseases. Autoimmune diseases (primary sclerosing cholangitis [PSC], autoimmune hepatitis [AIH], PSC-AIH overlap syndrome, and immunoglobulin G4 [IgG4] sclerosing cholangitis) are commonly associated with IBD. Drug-induced liver injury has been associated with both induction and maintenance therapies (thiopurines, methotrexate, 5-ASA, biologics). IBD-related malnutrition can lead to hepatic steatosis and cholelithiasis. Poor intestinal health increases the risk of developing hepatic abscesses secondary to bacterial translocation and systemic infection. Hypercoagulability in IBD can predispose to infarction, Budd-Chiari, and portal venous thrombosis). Figure 408.1 shows a diagnostic approach in IBD patients with abnormal liver tests.

Primary sclerosing cholangitis (PSC) is the most common hepatobiliary disease associated with IBD, occurring in 2–8% of adult patients with ulcerative colitis and less often in Crohn disease. Up to 90% of patients with PSC have ulcerative colitis. In children with IBD, PSC typically occurs in the second decade of life, at a median age of 14 years. PSC is characterized by progressive inflammation and fibrosis of intra- and extrahepatic bile ducts, with eventual progression to cirrhosis and end-stage liver disease. Small- and large-duct disease differs in phenotype, with small-duct PSC reported to confer lower mortality and incidence of cholangiocarcinoma and longer transplant-free survival. Concomitant PSC-IBD is a distinct entity with multifactorial pathogenesis, including genetic predisposition, altered intestinal microbiome, and immune-mediated processes. Distinguishing features of PSC-IBD include pancolitis, rectal sparing and backwash ileitis in patients with UC-PSC and extensive colitis in Crohn-PSC. The clinical course is milder but with subclinical persistent intestinal inflammation. Presentation of PSC is typically asymptomatic with elevated liver enzymes (particularly serum alkaline phosphatase and gamma glutamyl transferase) and bilirubin. Ten percent to 15% of adults present with symptoms of anorexia, weight loss, pruritus, fatigue, right upper quadrant pain, and jaundice; intermittent acute cholangitis can also occur. Diagnosis is made with cholangiography demonstrating characteristic multifocal stricturing and dilation of the intra- and extrahepatic bile ducts (referred to as *beading*). Liver biopsy reveals periductal fibrosis and inflammation, fibroobliterative cholangitis, and portal fibrosis. Biopsy is not necessary for diagnosis but can be helpful when imaging findings are not clear (e.g., in small-duct disease) or when overlap syndrome is suspected. There are no approved pharmacologic therapies for PSC. Ursodeoxycholic acid (UDCA), corticosteroids, immunomodulators, and oral antibiotics (such as vancomycin) have been studied, without clear improvement in survival or long-term outcomes. UDCA is widely used in children with PSC; it may improve pruritus and lab parameters; however, it has not been shown to alter the clinical course. Endoscopic intervention (stents, dilatation) for dominant strictures is reserved for patients with symptoms or complications of biliary obstruction. Liver

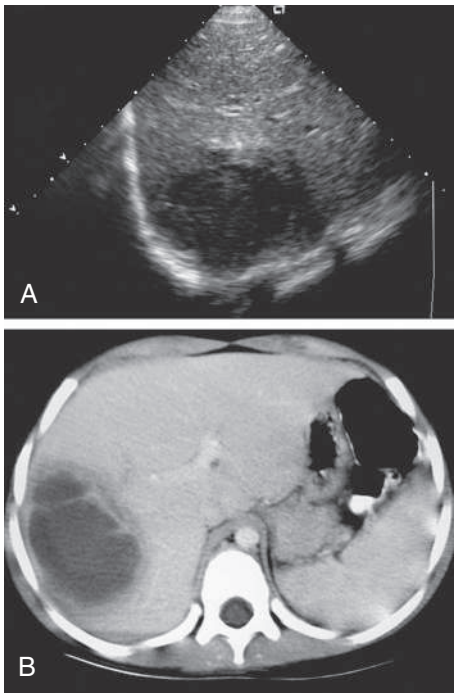

Fig. 407.2 Amebic abscess. **A,** Sonogram demonstrates a hypoechogenic mass in the right lobe of the liver with a more hypoechoic surrounding rim. **B,** CT scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. *(From Kuhn JP, Slovis TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby, 2004: p. 1473.)*

Amebic liver abscess (ALA) is the most common extraintestinal manifestation of *Entamoeba histolytica* infection. Although more common in endemic areas, cases can be diagnosed in the United States among travelers to, and immigrants from, endemic areas. Presentation can be delayed by months to years. ALA is more common among adults aged 18-55 years, and males predominate. Amoebic trophozoites invade colonic mucosa and reach the liver through the portal circulation. Patients may not have an associated colitis. Fever, right upper quadrant pain, anorexia, and weight loss are often present. Laboratory evaluation typically reveals a leukocytosis without eosinophilia and increased alkaline phosphatase. Ultrasonography or CT demonstrates the abscess (Fig. 407.2).

Diagnosis of ALA is often confirmed by serum ELISA. Serology is considered reliable in nonendemic areas but can be prone to false negatives early in the infection and cannot distinguish active infection from previous exposure. Testing for *E. histolytica* presence in stool is specific but not very sensitive, and patients with ALA may not have detectable organisms in their stool. Most sensitive and specific among stool assays is polymerase chain reaction (PCR), followed by stool antigen detection. Least reliable is microscopy because *E. histolytica* cannot easily be distinguished microscopically from its clinically benign relatives *Entamoeba dispar* and *Entamoeba moshkovskii*.

Before effective treatment, ALA-associated mortality was high; it has since decreased significantly. Treatment involves 7-10 days of a nitroimidazole (most commonly metronidazole) to kill trophozoites, followed by 7 days of a luminal agent (such as paromomycin) to kill colonic cysts. Patients with large abscesses (≥5-7 cm in diameter) may benefit from percutaneous aspiration in addition to medical therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 408

Liver Disease Associated with Systemic Disorders

Batul Kaj-Carbaidwala and William F. Balistreri

Liver involvement in systemic illnesses can be the result of the primary pathologic process, secondary to inflammatory or immune responses, or as a complication of therapy.

INFLAMMATORY BOWEL DISEASE

Hepatobiliary involvement in patients with inflammatory bowel disease (IBD, see Chapter 382) is relatively common; up to 30% of patients will have elevated liver enzymes, and 5% may develop chronic hepatobiliary diseases. Autoimmune diseases (primary sclerosing cholangitis [PSC], autoimmune hepatitis [AIH], PSC-AIH overlap syndrome, and immunoglobulin G4 [IgG4] sclerosing cholangitis) are commonly associated with IBD. Drug-induced liver injury has been associated with both induction and maintenance therapies (thiopurines, methotrexate, 5-ASA, biologics). IBD-related malnutrition can lead to hepatic steatosis and cholelithiasis. Poor intestinal health increases the risk of developing hepatic abscesses secondary to bacterial translocation and systemic infection. Hypercoagulability in IBD can predispose to infarction, Budd-Chiari, and portal venous thrombosis). Figure 408.1 shows a diagnostic approach in IBD patients with abnormal liver tests.

Primary sclerosing cholangitis (PSC) is the most common hepatobiliary disease associated with IBD, occurring in 2–8% of adult patients with ulcerative colitis and less often in Crohn disease. Up to 90% of patients with PSC have ulcerative colitis. In children with IBD, PSC typically occurs in the second decade of life, at a median age of 14 years. PSC is characterized by progressive inflammation and fibrosis of intra- and extrahepatic bile ducts, with eventual progression to cirrhosis and end-stage liver disease. Small- and large-duct disease differs in phenotype, with small-duct PSC reported to confer lower mortality and incidence of cholangiocarcinoma and longer transplant-free survival. Concomitant PSC-IBD is a distinct entity with multifactorial pathogenesis, including genetic predisposition, altered intestinal microbiome, and immune-mediated processes. Distinguishing features of PSC-IBD include pancolitis, rectal sparing and backwash ileitis in patients with UC-PSC and extensive colitis in Crohn-PSC. The clinical course is milder but with subclinical persistent intestinal inflammation. Presentation of PSC is typically asymptomatic with elevated liver enzymes (particularly serum alkaline phosphatase and gamma glutamyl transferase) and bilirubin. Ten percent to 15% of adults present with symptoms of anorexia, weight loss, pruritus, fatigue, right upper quadrant pain, and jaundice; intermittent acute cholangitis can also occur. Diagnosis is made with cholangiography demonstrating characteristic multifocal stricturing and dilation of the intra- and extrahepatic bile ducts (referred to as *beading*). Liver biopsy reveals periductal fibrosis and inflammation, fibroobliterative cholangitis, and portal fibrosis. Biopsy is not necessary for diagnosis but can be helpful when imaging findings are not clear (e.g., in small-duct disease) or when overlap syndrome is suspected. There are no approved pharmacologic therapies for PSC. Ursodeoxycholic acid (UDCA), corticosteroids, immunomodulators, and oral antibiotics (such as vancomycin) have been studied, without clear improvement in survival or long-term outcomes. UDCA is widely used in children with PSC; it may improve pruritus and lab parameters; however, it has not been shown to alter the clinical course. Endoscopic intervention (stents, dilatation) for dominant strictures is reserved for patients with symptoms or complications of biliary obstruction. Liver

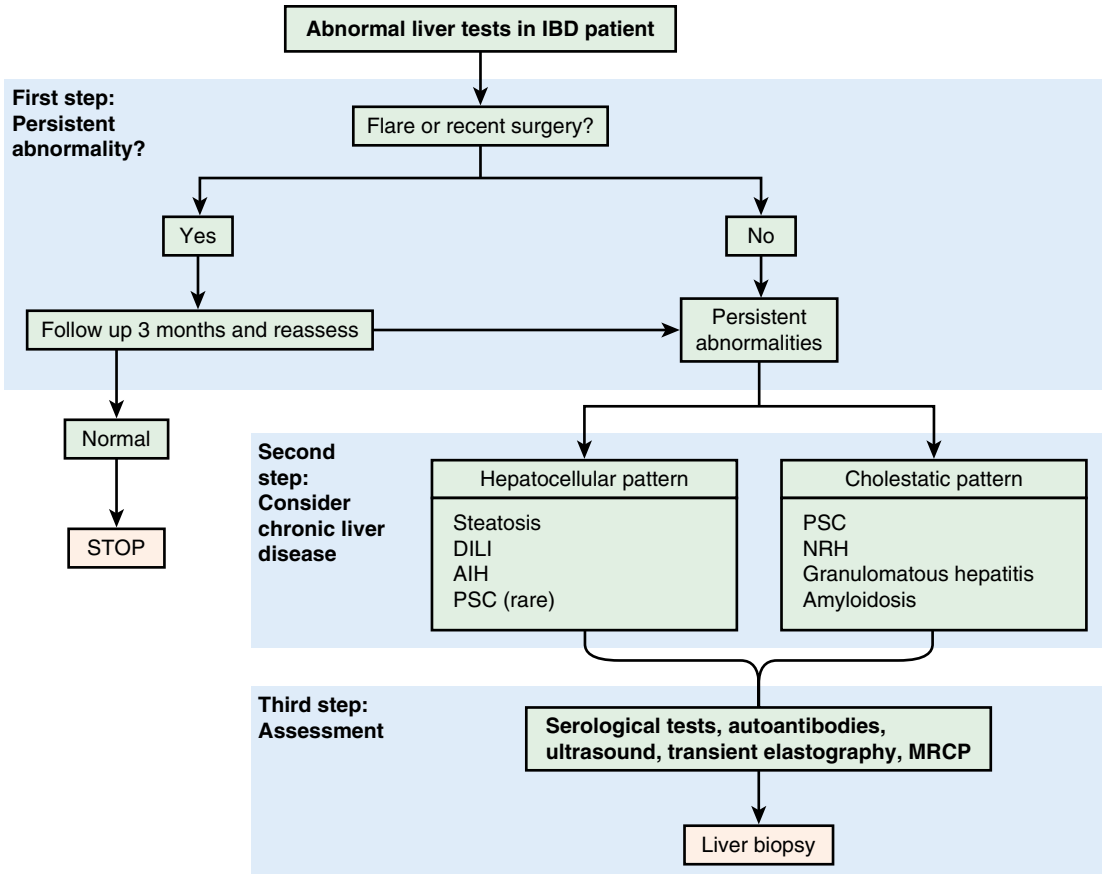

Fig. 408.1 Algorithm showing diagnostic approach to elevated liver enzymes in patients with IBD. AIH, Autoimmune hepatitis; DILI, drug induced liver injury; MRCP, magnetic resonance cholangiopancreatography; NRH, nodular regenerative hyperplasia; PSC, primary sclerosing cholangitis. *(From Restellini S, Chazouillères O, Frossard JL. Hepatic manifestations of inflammatory bowel diseases. Liver Int. 2017;37[4]:475–489. Fig 3)*

transplantation remains the only definitive treatment for PSC, with high 5-year survival rates but a relapse rate of ~20% in the allograft. Other management considerations include enteral supplementation to mitigate malnutrition related to chronic liver disease and antibiotic treatment of ascending cholangitis.

PSC is strongly associated with hepatobiliary malignancies (cholangiocarcinoma, hepatocellular carcinoma, gallbladder carcinoma) with a reported incidence varying between 9% and 14% in adults. Concomitant PSC-IBD also confers increased risk of colorectal carcinoma. There are no universal surveillance guidelines for children with PSC-IBD given the rarity of malignancy. In adults, ultrasound or MRCP with or without serum CA 19-9 assessment every 6-12 months are generally recommended.

PSC-autoimmune hepatitis overlap is a less common, unique phenotype with clinical and serologic features of AIH, as well as pruritus, cholestasis, histologic bile duct abnormalities, and/or abnormal cholangiography. Prevalence is estimated to be ~2% of children with IBD. Immunosuppressive medication (corticosteroids, azathioprine) is the mainstay of therapy for PSC-AIH overlap syndrome; however, long-term outcomes are not as favorable as in AIH alone. Long-term survival in children with overlap syndrome appears to be similar to those with PSC, with an overall median (50%) survival with native liver of 12.7 years.

CRITICAL ILLNESS

Mechanisms of liver injury in patients with sepsis/critical illness include hypoxic hepatitis because of ischemia and shock, cholestasis related to altered bile flow, drug-induced hepatocellular damage, and distinct pathologies, such as secondary sclerosing cholangitis. The management of critical illness–associated liver injury involves prompt recognition, early initiation of antimicrobials, and otherwise supportive care.

Bacterial sepsis should be excluded in any critically ill patient who develops cholestasis in the absence of markedly elevated serum aminotransferase or alkaline phosphatase (ALP) levels, even when other signs of infection are not evident. Gram-negative bacteremia is most common in these patients, in particular *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.* Lipopolysaccharides, bacterial endotoxins, and proinflammatory cytokines are thought to produce cholestatic liver injury either by impairing bile formation in hepatocytes or altering bile flow via disruption of canalicular transporters. Liver biopsy shows intrahepatic cholestasis with little or no hepatocyte necrosis. Kupffer cell hyperplasia and an increase in inflammatory cells are also common.

Secondary sclerosing cholangitis is a distinct entity in critical illness characterized by inflammation, fibrosis, and destruction of the bile ducts that can quickly progress to cirrhosis. It is thought to occur because of the vulnerability of biliary epithelium to hypoxia, leading to apoptosis or necrosis. Major risk factors include severe systemic hypotension, trauma, acute respiratory distress syndrome, and systemic inflammatory response syndrome.

CELIAC DISEASE

Celiac disease (see Chapter 384) is an autoimmune condition triggered by ingestion of gluten. Liver involvement in patients with celiac disease presents either as mild to moderate hepatitis with or without prolonged prothrombin time, or secondary to associated autoimmune disorders. In the former, histology demonstrates mild periportal and lobular inflammation. **Celiac hepatitis** refers to liver injury in patients with confirmed celiac disease in whom serum biochemistries and histology normalizes after establishment of a gluten-free diet. The exact mechanism remains unclear; it has been proposed that increased intestinal permeability may allow toxins, cytokines, and antigens to reach the liver and produce liver injury through release of proinflammatory

Table 408.1 Host- and Parenteral Nutrition–Related Factors in Development of Intestinal Failure–Associated Liver Disease

FACTORS IN THE DEVELOPMENT OF INTESTINAL FAILURE–ASSOCIATED LIVER DISEASE		
HOST	**TOTAL PARENTERAL NUTRITION**	
• Incompletely expressed enzyme activity • Inadequate bile salt uptake and excretion • Liver injury from endotoxins, inflammatory cytokines • Impaired biliary excretion • Prolonged parenteral nutrition (PN) exposure • SBBO, dilated bowel, mucosal atrophy → increased bacterial translocation → recurrent sepsis / direct endotoxin mediated liver injury • Impaired enterohepatic circulation • Decreased cholecystokinin release → biliary stasis • Extensive small bowel resection → more severe hepatic fibrosis	EXCESS MACRONUTRIENTS	• Glucose → Hyperinsulinism → Steatosis • Lipid minimization strategies may require additional dextrose calories
	AMINO ACID DEFICIENCY	• Decreased taurine conjugation of bile acids • Choline deficiency worsens steatosis
	LIPIDS	• Hepatotoxic phytosterols in soy-based lipids • Omega-6 LCPUFA is proinflammatory • Antioxidant imbalance
	MINERALS / TRACE ELEMENTS	• Mg, Cu, Al accumulate in cholestasis causing hepatocellular injury

SBBO, small bowel bacterial overgrowth; LCPUFA, long-chain polyunsaturated fatty acids; Mg, manganese; Cu, copper; Al, aluminum.

mediators. **Autoimmune liver diseases** (AIH, primary sclerosing cholangitis) have been associated with celiac disease; these are best treated with combination of gluten-free diet and immunosuppressive medications. Children with persistent, unexplained elevation of serum aminotransferase levels should be evaluated for celiac disease, given up to 9% reported incidence of celiac disease in this setting.

CARDIAC DISEASE

Cardio-hepatic interactions are complex and bidirectional; congestive heart failure (see Chapter 491), congenital cyanotic heart disease (see Chapters 475-480) and acute ischemic shock can all lead to liver injury. There exist distinct cardiac disorders associated with cirrhosis and end-stage liver disease. Various mechanisms are thought to contribute to liver injury in cardiac disease: (1) elevated central venous pressure transmitted to hepatic veins and ultimately hepatocytes results in centrilobular hepatocellular atrophy (congestive hepatopathy); and (2) decreased cardiac output leads to decreased hepatic arterial blood flow, causing centrilobular hepatocellular necrosis due to ischemia. Congenital cyanotic heart disease (hypoplastic left heart syndrome and coarctation of the aorta) are occasionally associated with hepatic necrosis or acute liver failure. Patients with hepatic manifestations of cardiac disease may present with lactic acidosis, elevated aminotransferase levels, cholestasis, prolonged prothrombin time, hyperammonemia, and hypoglycemia because of impaired hepatocellular metabolism. Jaundice, tender hepatomegaly, and, in some cases, ascites and splenomegaly can also occur.

Acute cardiogenic liver injury (shock liver or ischemic hepatitis) occurs after circulatory disturbances and can cause a dramatic rise in serum aminotransferase levels to >1,000 units/mL. These rapidly return to normal when perfusion and cardiac function improve, with delayed-onset hyperbilirubinemia that can persist for days to weeks.

Fontan-associated liver disease (FALD) is a distinct clinical entity that occurs in patients who have undergone surgical palliation for single ventricle heart disease. Chronically elevated systemic venous pressure after the Fontan procedure causes venous congestion and impaired hepatic blood flow. Patients almost invariably develop progressive hepatic fibrosis, which can lead to cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC). Annual risk of HCC in FALD-cirrhosis is reported as 1.5–5%; cases have been reported of HCC occurring in early adolescence.

The aim of therapy in all causes of cardiac-associated liver disease is to improve cardiac output, reduce systemic venous pressures, and correct hypoxemia. Even mild liver disease may increase mortality after cardiac surgery, with poorer outcomes in patients with progressive liver disease. Combined heart-liver transplant should be considered in Fontan patients with evidence of cirrhosis, especially if decompensated.

INTESTINAL FAILURE ASSOCIATED LIVER DISEASE

Intestinal failure–associated liver disease (IFALD; previously referred to as parenteral nutrition–associated liver disease) in children is characterized by progressive cholestasis, biliary cirrhosis, and steatohepatitis (see Chapters 385.6 and 386). Advanced IFALD is one of the most important factors contributing to mortality of children on long-term parenteral nutrition (PN) and is a major indication for intestinal and multivisceral transplantation. Host- and PN-related factors contribute to its development (Table 408.1). The pathogenesis of IFALD is multifactorial; sepsis, bacterial translocation, excess caloric intake, high amounts of protein, fat, or carbohydrate, nutrient deficiencies, and toxicities related to components such as manganese, aluminum, and copper can all contribute to hepatic injury. The type (soy-based), volume, and frequency of lipid administered are important risk factors. Prolonged enteral fasting compromises mucosal integrity and increases bacterial mucosal translocation. Fasting also decreases release of cholecystokinin, which leads to biliary stasis, cholestasis, and formation of biliary sludge and gallstones, which can exacerbate hepatic dysfunction. Sepsis, especially gram-negative bacteremia, can also exacerbate liver damage. Clinical manifestations range from mildly elevated serum aminotransferase levels to severe cholestatic liver injury, cirrhosis with portal hypertension and, rarely, hepatocellular carcinoma. Histologic findings include macrovesicular steatosis, canalicular cholestasis, and periportal inflammation.

In addition to cholestasis, biliary complications of intravenous (IV) nutrition include cholelithiasis and the development of biliary sludge, associated with thick, inspissated gallbladder contents. Hepatic steatosis or elevated serum aminotransferase levels can also occur in the absence of cholestasis, particularly in older children. This is generally mild and resolves after total PN (TPN) is discontinued. Serum bilirubin and bile acid levels remain within the normal range. Other causes of liver disease should also be considered, especially if evidence of hepatic dysfunction persists despite weaning from TPN and initiating enteral feeds. If serum ALP or aminotransferase levels remain elevated, liver biopsy may be necessary for accurate diagnosis.

Strategies in the management of IFALD aim to prevent or reverse the disease (Table 408.2). General goals include early initiation of enteral nutrition, minimization of fasting, and advancement of enteral feeds as tolerated. Improved TPN solutions that meet the specific needs of neonates can prevent deficiencies and toxicities. Introducing alternate sources of IV lipid, including fish oil and olive oil to provide more omega-3 fatty acids (and less of the harmful omega-6 fatty acids), have been beneficial. Ursodeoxycholic acid is widely used and may be beneficial in improving bile flow.

CYSTIC FIBROSIS

Cystic fibrosis (CF; see Chapter 454) is an autosomal recessive genetic disorder characterized by impaired chloride transport

Table 408.2 Evidence-Based IFALD Prevention and Treatment Strategies for Children on TPN

PREVENTION	EXAMPLES
Advancing enteral nutrition	Prokinetic and anti-diarrheal agents to improve enteral tolerance
	Medical induction of intestinal adaptation, i.e., glucagon-like peptide 2 (GLP-2) agonist
	Surgical lengthening procedures; serial transverse enteroplasty (STEP), Bianchi
Modifying lipid emulsions	**Lipid dose reduction
	*Use of combined lipid emulsion (soybean oil, medium chain triglyceride, olive oil, and fish oil)
Cycling TPN	Non-continuous TPN, with time off in a 24-hr period
Microbiome therapies	Addition of various pre- or probiotics
Prevention of central line infections	Antibiotic treatment to prevent bacterial translocation and small bowel bacterial overgrowth
	Use of ethanol locks
Prevention of cholestasis	***Oral choleretic agent: urso-deoxycholic acid
	**Trophic (small volume) feedings
TREATMENT	
Modifying lipid emulsions	Use of combined lipid emulsion (soybean oil, medium chain triglyceride, olive oil, and fish oil)
	**Use of fish oil emulsion
Organ transplantation	Consider isolated intestinal or liver-intestinal transplantation

*Possibly effective
**Probably effective
***Proven effective
Adapted from Lee WS, Chew KS, Ng RT, et al. Intestinal failure-associated liver disease (IFALD): insights into pathogenesis and advances in management. *Hepatol Int.* 2020;14(3):305–316.

across the apical membranes of epithelial cells in numerous organs. Up to 40% of patients with CF develop some form of hepatobiliary disease, usually in the first 2 decades of life. Hepatobiliary complications account for approximately 2.5% of overall mortality in patients with CF, with development of portal hypertension being a key prognostic factor.

Manifestations range from liver enzyme elevations to cirrhosis with portal hypertension. This can be related to recurrent infections, drug hepatotoxicity, steatosis (because of diabetes, chronic diarrhea, pancreatic insufficiency, malnutrition), cardiopulmonary disease–associated hepatic congestion, biliary disease (neonatal cholestasis, sclerosing cholangitis, micro-gallbladder, gallbladder dysfunction or pigmentary cholelithiasis) and the distinct clinical entity of cystic fibrosis-related liver disease (CLFD); the latter includes two main, sometimes concomitant, entities: primary focal biliary fibrosis and porto-sinusoidal vascular disease. The precise pathogenesis of CFLD remains incompletely understood but is likely multifactorial (Fig. 408.2). Genetic factors associated with increased risk of CFLD include the presence of two abnormal *CFTR* alleles without residual function or presence of *SERPINA1* Z allele. Clinical risk factors include older age, pancreatic insufficiency, male sex, and a history of meconium ileus.

Focal biliary fibrosis is the pathognomonic liver lesion in patients with CF, characterized by periductal inflammation, bile duct proliferation, and increased fibrosis within focal portal tracts. Most patients are asymptomatic. Liver stiffness measurements may aid in differentiating focal fibrosis from steatosis. Gradual progression to multi-lobular cirrhosis can occur and result in portal hypertension and end-stage liver disease in 1–8% of patients.

Porto-sinusoidal vascular disease occurs more frequently in adults than in children and presents as noncirrhotic portal hypertension. Features that may suggest this diagnosis include evidence of portal hypertension without hepatic parenchymal changes, marked splenomegaly, and development of porto-systemic shunts. A macronodular liver, likely related to regenerative nodular hyperplasia, is a common finding. Liver stiffness measures, however, are typically lower than with cirrhotic portal hypertension, which can aid in differentiation. Typical histologic features include obliterative portal venopathy, nodular regenerative hyperplasia, arterialization, periportal vessels, aberrant portal vessels, irregular portal tracts with centrilobular vein distribution, and sinusoidal dilatation.

Management of CFLD is primarily supportive and targeted at symptoms, including through optimization of nutrition and management of portal hypertensive complications. Treatment with oral UDCA (10-15 mg/kg/day) is widespread, but the survival benefit and effect on

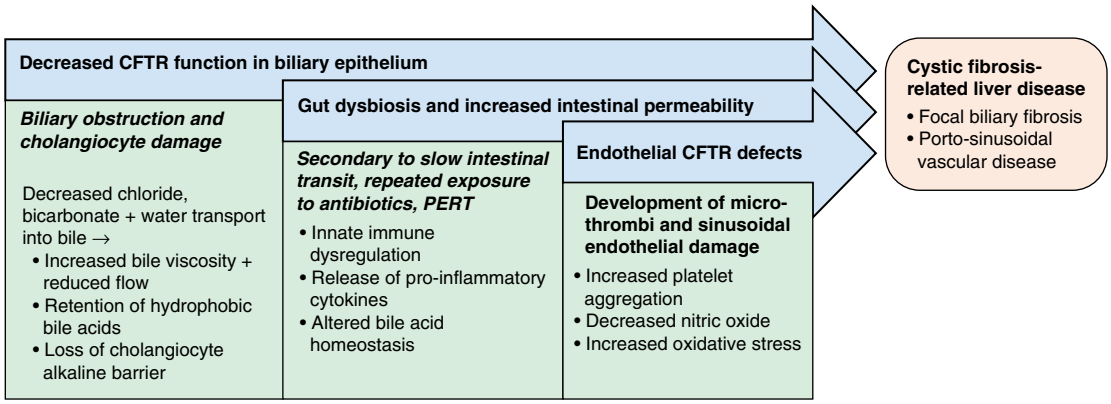

Fig. 408.2 Proposed mechanisms in the development of cystic fibrosis-related liver disease. PERT, Pancreatic enzyme replacement therapy. *(Data from Dana J, Debray D, Beaufrère A, et al. Cystic fibrosis-related liver disease: clinical presentations, diagnostic and monitoring approaches in the era of CFTR modulator therapies. J Hepatol. 2021;S0168-8278:02115–2.)*

clinical course remains controversial. Surgical porto-systemic shunts (distal splenorenal, portocaval) are useful in patients with refractory portal hypertensive complications. Liver transplantation may be offered in severe cases of parenchymal disease with acceptable long-term outcomes with combined liver-lung transplantation being offered at some centers. *CFTR* modulator therapies have shifted the paradigm of pulmonary and nutritional management in CF; however, their role in preventing or reversing CFLD remains unclear. All currently approved modulators may cause elevated liver enzymes; however, small studies have yielded promising results in improving CFLD.

BONE MARROW TRANSPLANTATION

Liver disease after hematopoietic stem cell transplantation (SCT, see Chapters 177-181) occurs in up to 90% of patients in the first 100 days. Etiologies are listed in Table 408.3. Graft-versus-host disease (GVHD), drug toxicity, and sepsis are the most common causes of liver dysfunction after allogeneic SCT. Diagnosis is often challenging because of the coexistence of multiple risk factors. Clinical course, symptoms and signs, liver biochemistries, and viral serology are helpful in making the correct diagnosis. Percutaneous liver biopsy may be necessary; histology can show extensive bile duct injury in GVHD, viral inclusions in cytomegalovirus disease, or the characteristic endothelial lesion in sinusoidal obstruction syndrome (SOS). Prompt and accurate diagnosis is key because treatment for GVHD with corticosteroids may worsen infectious hepatitis, and delayed treatment in SOS can lead to poorer outcomes. Management of liver disease post-HSCT is mainly supportive. Oral UDCA can decrease the incidence of severe liver disease in patients undergoing SCT and has been shown to reduce the incidence of SOS and transplant-related mortality in adults.

Graft-versus-host disease (see Chapter 179) results from donor immunocompetent cells triggering an inflammatory response in recipient organs. Acute GVHD comprises a triad of hepatitis, dermatitis, and enteritis, and usually occurs within 100 days of hematopoietic SCT (HSCT; typically at time of engraftment, 14-21 days after HSCT). Serum aminotransferase and bilirubin levels are markedly elevated. Chronic GVHD occurs later, with liver involvement (slowly progressive cholestasis) in up to 80%. Histologic features of GVHD include loss of intralobular bile ducts, endothelial injury of hepatic and portal venules, and hepatocellular necrosis. Treatment of GVHD varies depending on organ system involved (e.g., skin, intestine) and acute vs chronic presentation. Therapy comprises systemic corticosteroids, optimization of maintenance immunosuppression, and newer agents like ruxolitinib (JAK inhibitor), and it is recommended that management occur in collaboration with the hematopoietic stem cell transplant team. Oral UDCA has also been shown to be beneficial, particularly in chronic GVHD.

Sinusoidal obstruction syndrome (SOS; hepatic venoocclusive disease) usually develops in the first 21 days after SCT. The incidence ranges from 5–39% in pediatric patients, with reported mortality rates ranging from 0–47%. Risk factors for SOS are listed in Table 408.4. Pathogenesis is thought to be related to sinusoidal endothelial cell activation and hepatocyte damage from accumulation of toxic metabolites because of conditioning regimens. Patients typically present with jaundice, painful hepatomegaly, rapid weight gain, and ascites. Severe SOS has high morbidity and mortality, with multisystem organ failure. Diagnostic criteria for SOS include presence of hepatomegaly, right upper quadrant pain, ascites, weight gain >5% from baseline, and bilirubin >2 mg/dL before day 21 post HSCT. Exclusion of other causes of liver disease is also necessary. Liver biopsy is generally not needed for diagnosis, and indeed can be contraindicated because of the bleeding risk. However, the classic histologic features of sinusoidal dilatation, erythrocyte extravasation in space of Disse, collagen deposition in sinusoids and small hepatic veins and centrilobular necrosis, are diagnostic.

Treatment of SOS is with defibrotide, a mixture of oligonucleotides that has antithrombotic and thrombolytic properties. There is a survival benefit of defibrotide in both children and adults. Few significant adverse events are noted; bleeding and infection are the most common adverse effects seen in patients with severe SOS.

Table 408.3 Etiologies of Liver Disease After Hematopoietic Stem Cell Transplantation (HSCT)

Sepsis (viral, bacterial, fungal)
Toxicity (chemotherapy, PN, radiation)
Sinusoidal obstruction syndrome
Acute and chronic GVHD
Hemosiderosis / iron overload
Cholecystitis
Extrahepatic biliary obstruction

PN, Parenteral nutrition; GVHD, graft-versus-host disease.

Table 408.4 Risk Factors for the Development of Sinusoidal Obstruction Syndrome (SOS) After Hematopoietic Stem Cell Transplantation (HSCT)

PATIENT-RELATED FACTORS	HSCT-RELATED FACTORS
Younger age	Allogenic transplant
Hematologic malignancy	Bone marrow–derived stem cells
Disease relapse state	Fever during conditioning therapy
Preexisting liver disease	Second transplant
Previous liver radiation therapy	Myeloablative conditioning
Chronic viral hepatitis	Drug hepatotoxicity
Iron overload	

HEMOGLOBINOPATHIES

Hepatic dysfunction in patients with sickle cell anemia (see Chapter 511.1) or thalassemia (see Chapter 511.10) result from acute or chronic viral hepatitis, chronic iron overload, venous thrombosis, biliary obstruction (cholestasis, cholelithiasis), or acute hepatic crisis (sequestration, ischemic necrosis). Cholelithiasis and chronic iron overload (because of frequent blood transfusions) are common and treatable. Oral chelation therapy (commonly with deferasirox) in iron overload has been demonstrated to reverse or stabilize hepatic fibrosis in patients with thalassemia. Surgical and endoscopic management of gallstones may be necessary, especially in patients with choledocholithiasis.

Sickle Cell Disease

The pathogenesis of hepatobiliary manifestations in sickle cell disease (SCD) is shown in Figure 408.3. **Hepatic sickle cell crisis** or "sickle hepatopathy" occurs in ~10% of patients, when sickled cells obstruct small vessels and sinusoids. This leads to ischemia, inflammation, endothelial dysfunction, and, when flow is restored, reperfusion injury, manifest as intense RUQ pain and tenderness, fever, leukocytosis, and jaundice. Bilirubin levels may be markedly elevated; serum ALP levels may be only moderately elevated. Prompt diagnosis is key to allow early institution of therapy, although this can be challenging because of overlapping symptoms and signs with other hepatobiliary disorders detailed above. In general, hepatic sickle cell crisis is self-limited and symptoms resolve within 1-3 weeks. However, along the spectrum of sickle crises is the distinct entity of **sickle cell intrahepatic cholestasis** (SCIC), thought to be caused by the trapping of sickle cells in sinusoids causing localized hypoxia, hepatocyte ballooning and intra-canalicular cholestasis. This too manifests as hepatomegaly, abdominal pain, hyperbilirubinemia, and coagulopathy but can progress to acute liver failure, multiorgan dysfunction and death. Management of hepatic crises involves exclusion of biliary complications, supportive care, and exchange transfusion if there is evidence of liver synthetic dysfunction or (prolonged prothrombin time) or clinical concern for SCIC. Liver transplantation in SCD (in setting of cirrhosis, end-stage liver disease, and severe SCIC) remains controversial. Although there are some positive experiences reported in adults (with acceptable 5-year survival rates), there remain limited data in children and many clinical challenges. Preoperative optimization in tertiary centers involving

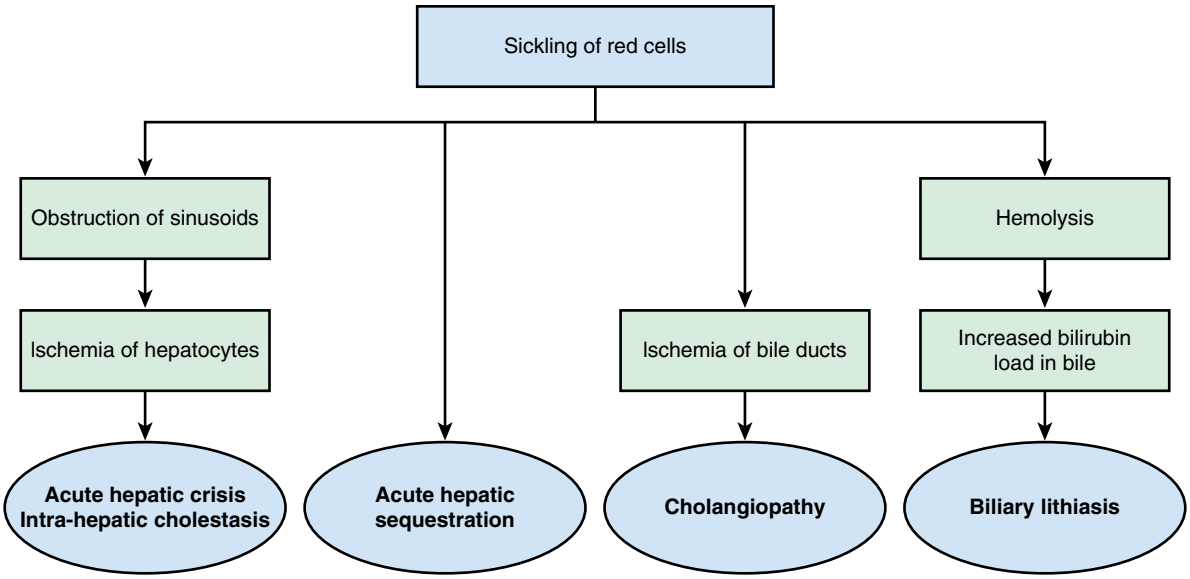

Fig. 408.3 Pathogenesis of liver disease in sickle cell disease. *(From Lacaille F, Allali S, de Montalembert M. The liver in sickle cell disease. J Pediatr Gastroenterol Nutr. 2021;72:5–10. Fig 1.)*

transplant hepatology and hematology teams is paramount, with attention to transfusion parameters, potential drug toxicity, nephroprotective measures, and intraoperative management to prevent acute crises. Of course, hepatic crises may recur in the allograft, with potential for allograft dysfunction and loss.

HISTIOCYTIC DISORDERS

Langerhans cell histiocytosis (LCH, see Chapter 556.1) is a rare disorder characterized by proliferation and accumulation of Langerhans cells (dendritic antigen-presenting histiocytes). It can affect single or multiple organs, with common sites being bone, skin, pituitary gland, spleen, lungs, and lymph nodes. In the liver, histiocytosis can cause hepatocellular dysfunction and/or a mass lesion. Liver involvement in LCH should be suspected in patients with hepatomegaly, ascites, and/or biochemical evidence of liver injury (elevated liver enzymes, bilirubin, or prothrombin time). Liver biopsy demonstrates Langerhans cell infiltrates (identified with positive immunohistochemical staining for CD1a and S100 antigen). Hepatic LCH carries a high mortality rate (30–50%, compared to <10% in patients without liver involvement). Three-year survival with liver involvement is >96% compared to 52% with liver involvement. In children, LCH is an important cause of secondary sclerosing cholangitis, which can lead to chronic liver disease and need for liver transplantation.

Treatment approaches in LCH vary by clinical severity; those with single-organ involvement and mild disease may be observed or offered immunomodulator monotherapy (oral 6 mercaptopurine, methotrexate, and others). Those with hepatic or multiorgan involvement may need to undergo systemic chemotherapy.

Hemophagocytic lymphohistiocytosis (HLH) (see Chapter 556.2) is a multiorgan, severe, and potentially fatal inflammatory process from excessive activation of lymphocytes and macrophages. Hepatobiliary manifestations include elevated aminotransferases (50–100%), cholestasis (50%), and hepatomegaly (90%). Acute liver failure may also occur. Liver biopsy shows portal inflammatory infiltrates, hemophagocytosis, and Kupffer cell hyperplasia but is not routinely obtained because of coagulopathy. The mainstay of treatment of HLH involves etoposide-based chemotherapy and bone marrow transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

408.1 Nonalcoholic Fatty Liver Disease

Sarah H. Orkin and William F. Balistreri

The term *nonalcoholic fatty liver disease* (NAFLD) spans a wide spectrum of histologic liver disease, from nonalcoholic fatty liver (NAFL; steatosis without inflammation) to nonalcoholic steatohepatitis (NASH; steatosis with lobular inflammation); the latter may then progress to fibrosis and end-stage liver disease (ESLD) requiring liver transplantation (Figs. 408.4 and 408.5). In fact, NASH currently is the fastest rising indication for liver transplantation in young adults. The burden of pediatric NAFLD is large; it is the most common cause of chronic liver disease in children and currently affects 1 in 10 youth in the general population, and 1 in 3 youth with obesity. Obesity has contributed to an increased prevalence of NAFLD in children; the severity of obesity is associated with more severe liver disease.

Known risk factors for pediatric NAFLD include male sex, Hispanic ethnicity, genetic predisposition (see Fig. 408.4), obesity, insulin resistance, obstructive sleep apnea, celiac disease, and psychotropic drug use (see Fig. 408.4). There is a lower prevalence of NAFLD in Black children. Autopsy data suggest that 10% of all children, and 38% of children with obesity age 2-19 years old have histologically confirmed NAFLD. Up to 25% of affected children may already have advanced fibrosis at the time of first liver biopsy. There are currently no available clinical, biochemical, or radiographic variables to help predict which children will have severe histologic disease on liver biopsy or who will be at risk of rapid progression. Recommendations in adults are to screen at-risk patients (see Fig. 408.4) with liver function tests as well as additional testing to exclude other diagnoses (chronic hepatitis). If there is evidence of liver disease, hepatic ultrasonography and noninvasive assessment of liver stiffness are indicated (see Fig. 408.5D,E).

Most patients with NAFLD are asymptomatic. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Clinical Practice Guideline recommend assessing the serum alanine aminotransferase (ALT) level as a screening tool for children starting between 9-11 years of age who are either obese (body mass index [BMI] ≥95th%) or overweight (BMI ≥ 85th% and <95th% with additional metabolic risk factors). In the United States, sex-specific cutoffs for serum ALT values have been determined to be 22 mg/dL in females and 26 mg/dL in males, and values persistently greater than

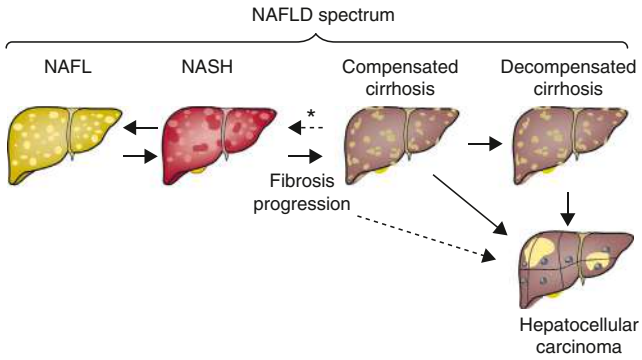

Factors associated with NAFLD and NASH progression

Comorbid illness	Genetic factors	Environmental factors
• Type 2 diabetes	• *PNPLA3*	• Fructose
• Insulin resistance	• *TM6SF2*	• Cholesterol
• Dyslipidemia	• *GCKR*	• Alcohol
• Obesity	• *MBOAT7*	• **Exercise**
• Hypertension	• ***HSD17B13***	• **Coffee**
• Hypopituitarism		

Fig. 408.4 Spectrum of NAFLD. Factors in black type have an established association with NAFLD and NASH progression (broadly classified into comorbid illness, genetic factors, and environmental factors). **Green type indicates a protective factor**. NAFL, Nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. *Fibrosis regression. *(From Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021; 397:2212–2222. Fig. 2.)*

two times the sex-specific upper limit of normal, in the absence of any other identified etiology for liver disease is generally regarded as presumed NAFLD. Most children presenting with obesity and elevated liver enzymes and presumed or confirmed NAFLD will have a negative workup for any alternative etiology for liver disease. Although imaging modalities such as ultrasonography or magnetic resonance imaging with proton-density fat fraction and magnetic resonance elastography (MRI-PDFF /MRE) can be used to evaluate the degree of steatosis and fibrosis by using liver stiffness on MRE as a surrogate for fibrosis, the gold standard for diagnosis of NAFLD is liver biopsy examination.

Histologically, NAFLD is diagnosed when steatosis involves >5% of hepatocytes (see Fig. 408.5). Other pertinent histologic characteristics include the presence and severity of lobular inflammation, cellular ballooning, and fibrosis (graded 0-4). The NASH Clinical Research Network has developed a validated tool for histologic assessment. Unlike adults, NASH in children manifest two distinct histologic types: **Type 1 NASH** resembles adult histologic findings with steatosis and balloon degeneration of hepatocytes and/or periportal fibrosis while **Type 2 NASH** includes steatosis and portal inflammation.

During evaluation other causes of steatosis should be kept in mind. **Lysosomal acid lipase deficiency (LAL-D)**, an autosomal recessive disorder due to pathogenic variants in *LIPA* gene, may result in hepatic steatosis. However, in contrast to NAFLD, patients with LAL-D usually demonstrate microvesicular or mixed micro- and macrovesicular steatosis, and not macrovesicular changes alone.

Children diagnosed with NAFLD should be screened for celiac disease plus comorbid conditions, including diabetes, hypertension,

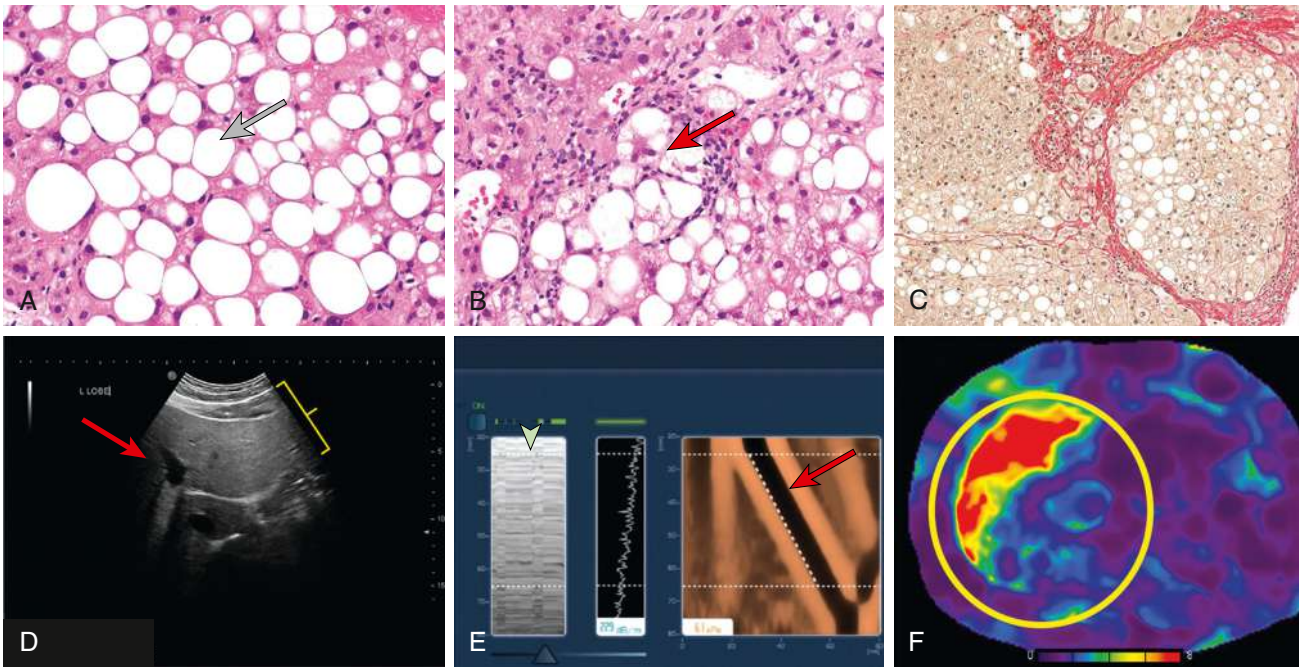

Fig. 408.5 Histologic and radiologic assessment of nonalcoholic fatty liver disease. **A**, Nonalcoholic fatty liver is characterized by macrovesicular steatosis with no or little necroinflammation. Large round nonstaining areas represent lipid droplets in hepatocytes *(arrow;* hematoxylin and eosin stain; magnification ×40). **B**, Apart from fat accumulation, nonalcoholic steatohepatitis (NASH) is characterized by the presence of lobular inflammation and hepatocyte ballooning. At the center of the image is a ballooned hepatocyte surrounded by inflammatory cells (*arrow*; hematoxylin and eosin stain; magnification ×40). **C**, As disease progresses, accumulating liver fibrosis will eventually result in cirrhosis. On the right of this image is a cirrhotic nodule surrounded by thick fibrous tissue. In some cases, steatosis and necroinflammation might reduce or disappear as the disease progresses to cirrhosis, a condition referred to as burned-out NASH (Sirius red; magnification ×10). **D**, Ultrasonography, the most common method to diagnose fatty liver, characterized by bright liver echotexture *(bracket)* and blurring of deeper structures *(arrow)*. **E**, Vibration-controlled transient elastography, a point-of-care measurement of liver stiffness for the estimation of fibrosis that can also estimate hepatic steatosis using the controlled attenuation parameter. The machine is equipped with an M-mode ultrasound for the localization of liver parenchyma *(arrowhead)*. The elastogram *(arrow)* represents the measurement of liver stiffness. A steeper slope indicates that the shear-wave velocity is higher, and the liver is stiffer. **F**, Magnetic resonance elastography of a patient with NASH cirrhosis, currently one of the most accurate noninvasive tests of liver fibrosis, with the color scheme reflecting stiffness in different parts of the liver. Red shows areas with greater stiffness *(circle)*. *(From Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397:2212–2222. Fig. 1.)*

Table 408.5 Potential Use of Off-Label Therapy for Nonalcoholic Steatohepatitis in Adults

	EFFECTS ON THE LIVER	QUALITY OF EVIDENCE	OTHER BENEFITS	KEY ADVERSE EVENTS	CONTRAINDICATIONS AND CAUTIONS
Pioglitazone	Improves hepatic steatosis and necroinflammation and can improve fibrosis	Several small* to moderate† phase 2 randomized controlled trials	Improves insulin sensitivity and diabetic control	Weight gain, fluid retention, bone loss, and might increase bladder cancer	Contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure; maximum dose 15 mg if used in combination with gemfibrozil or other strong CYP2C8 inhibitors
Vitamin E	Improves hepatic steatosis and necroinflammation; might prevent liver decompensation and mortality in patients with advanced liver fibrosis	Several small* to moderate† randomized controlled trials; data on clinical outcomes based on a retrospective cohort study with propensity score matching	Neutral metabolic effects	A meta-analysis suggests a small increase in overall mortality at high doses; might increase risk of bleeding, prostate cancer, heart failure, and hemorrhagic stroke	Caution in patients with high cardiovascular risk and those at high risk of bleeding
GLP-1 agonists‡	Improves hepatic steatosis and necroinflammation	Several small* to moderate† randomized controlled trials	Improves diabetic control, reduces major adverse cardiovascular events and weight	Nausea, vomiting, dyspepsia, diarrhea, and constipation	Discontinue GLP-1 agonists immediately in case of acute pancreatitis; might cause acute kidney injury rarely; semaglutide might increase diabetic retinopathy complications
SGLT2 inhibitors§	Improves hepatic steatosis, necroinflammation, and liver enzymes	Several small* randomized controlled trials with noninvasive tests; two small* uncontrolled paired liver biopsy studies	Improves diabetic control; modest weight reduction; might have renoprotective benefits; canagliflozin and empagliflozin reduce major adverse cardiovascular events	Genitourinary infection, acute kidney injury, and euglycemic diabetic ketoacidosis; might increase the risk of fractures and limb amputations	Contraindicated if estimated glomerular filtration rate is less than 45 mL/min per 1.73 m^2

*Small was defined as less than 50 participants in the active group.
†Moderate was defined as 50–100 participants in the active group.
‡For example, liraglutide and semaglutide.
§For example, canagliflozin, dapagliflozin, and empagliflozin.
From Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397:2212–2222.

dyslipidemia, and obstructive sleep apnea, and should be followed clinically at least annually. Counseling against use of alcohol should be provided, as well as minimization of other potentially hepatotoxic drugs, when medically feasible. Prior vaccination against hepatitis A and B should be verified.

There are no approved medical therapies for treatment of pediatric NAFLD. Thus the current management requires lifestyle modification, specifically diet and physical activity changes targeted at weight reduction. A key dietary change includes removal or reduction of sugar sweetened beverages because fructose can be taken up in an insulin-independent fashion and is a prime contributor to hepatic inflammation and steatosis.

Many studies have investigated therapeutic options for treatment of pediatric NAFLD. Vitamin E has been shown to improve balloon degeneration in a subset of children with NASH. Other potential therapeutic options being investigated include thiazolidinediones (pioglitazone), glucagon-like peptide 1 receptor agonists (GLP-1 agonists), and sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) as well as bariatric surgery for obesity (Table 408.5). Furthermore, emerging data on the role of the gut microbiome in the pathogenesis of NAFLD has positioned the gut flora as a suggested therapeutic target.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 409

Mitochondrial Hepatopathies

Sindhu Pandurangi and William F. Balistreri

A wide variety of mitochondrial disorders are associated with liver disease. Hepatocytes contain a high density of mitochondria because the liver, with its biosynthetic and detoxifying functions, is highly dependent on adenosine triphosphate. Defects in mitochondrial function can lead to impaired oxidative phosphorylation, increased generation of reactive oxygen species, impairment of other metabolic pathways, and activation of mechanisms of cellular death.

Mitochondrial disorders can be divided into primary, in which the mitochondrial defect is the primary cause of the disorder, and secondary, in which mitochondrial function is affected by exogenous injury or a genetic variant that affects nonmitochondrial proteins (see Chapter 107.4). Primary mitochondrial disorders can be caused by pathogenic variants affecting mitochondrial DNA (mtDNA) or by nuclear genes that encode mitochondrial proteins or cofactors (Table 409.1; see also Chapter 404). Specific patterns may be noted (Table 409.2). Secondary mitochondrial disorders include diseases with an uncertain etiology, such as Reye syndrome; disorders caused by endogenous or exogenous toxins, drugs, or metals; and other conditions in which mitochondrial oxidative injury may be involved in the pathogenesis of liver injury.

EPIDEMIOLOGY

Mitochondrial respiratory chain disorders of all types affect 1 in 20,000 children younger than 16 years of age; liver involvement has been reported in 10–20% of patients with respiratory chain defect. Primary mitochondrial disorders, including mtDNA depletion syndromes (MDSs), occur in 1 in 5,000 live births and are a known cause of acute liver failure in children <2 years of age.

More than 200 pathogenic variants, deletions, insertions, and rearrangements that involve mtDNA and nuclear DNA and encodes mitochondrial proteins are identified. Mitochondrial genetics are unique because mitochondria can replicate, transcribe, and translate their mitochondrial-derived DNA independently. A typical hepatocyte contains approximately 1,000 copies of mtDNA. Oxidative phosphorylation (the process of adenosine triphosphate production) occurs in the

Table 409.2 Hepatic Phenotypes of Mitochondrial Cytopathies

- Infantile liver failure
- Neonatal cholestasis
- Pearson syndrome
- Alpers disease
- Chronic liver disease
- Drug-induced mitochondrial toxicity

From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 5th ed. Philadelphia: Elsevier, 2016: Box 71.2, p. 876.

Table 409.1 Genotypic Classification of Primary Mitochondrial Hepatopathies and Organ Involvement

GENE	RESPIRATORY CHAIN COMPLEX	HEPATIC HISTOLOGY	OTHER ORGANS INVOLVED	CLINICAL FEATURES
Deletion	Multiple (Pearson)	Steatosis, fibrosis	Kidney, heart, CNS, muscle	Sideroblastic anemia, variable thrombocytopenia and neutropenia, persistent diarrhea
MPV17	I, III, IV	Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
DGUOK	I, III, IV	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17	I, III, IV	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1	I, III, IV	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1	I, III, IV	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle	I, III, IV	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L	III (GRACILE)		CNS ±, muscle ±, kidneys	Fanconi-type renal tubulopathy
SCO1	IV	Steatosis, fibrosis	Muscle	
TRMU	I, III, IV	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1	I, III, IV	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu	I, III, IV	Unknown	CNS	Severe lactic acidosis, rapidly fatal encephalopathy

CNS, Central nervous system; *GRACILE*, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; *PNS*, peripheral nervous system.
From Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes. *J Pediatr*. 2013;163:942–948. Table 2.

respiratory chain located in the inner mitochondrial membrane and is divided into five multienzyme complexes: reduced nicotinamide adenine dinucleotide coenzyme Q reductase (complex I), succinate–coenzyme Q reductase (complex II), reduced coenzyme Q–cytochrome-*c* reductase (complex III), cytochrome-*c* oxidase (complex IV), and adenosine triphosphate synthase (complex V). The respiratory chain peptide components are encoded by both nuclear and mtDNA genes; thus pathogenic variants in either genome can result in disorders of oxidative phosphorylation. Thirteen essential polypeptides are synthesized from the small 16.5-kilobase circular double-stranded mtDNA. mtDNA also encodes the 24 transfer RNAs required for intramitochondrial protein synthesis, whereas nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA, including DNA polymerase-γ (POLG), thymidine kinase 2, and deoxyguanosine kinase.

The expression of mitochondrial disorders is complex, and epidemiologic studies are hampered by technical difficulties in collecting and processing the tissue specimens needed to make accurate diagnoses, the variability in clinical presentation, and the fact that most disorders display maternal inheritance with variable penetrance (see Chapter 97). mtDNA undergoes pathogenic variant generation 10 times more often than nuclear DNA because of a lack of introns, protective histones, and an effective repair system in mitochondria. Mitochondrial genetics also displays a threshold effect in that the type and severity of pathogenic variants required for clinical expression varies among people and organ systems; this is explained by the concept of heteroplasmy, in which cells and tissues harbor both normal and pathologic variant mtDNA in various amounts because of random partitioning during cell division. Pathogenic variants, deletions, or duplications in either mitochondrial or nuclear genes can cause disease, and variants in nuclear genes that control mtDNA replication, transcription, and translation may lead to **MDS** or to a translational disorder.

CLINICAL MANIFESTATIONS

Defects in oxidative phosphorylation can affect any tissue to a variable degree, with the most energy-dependent organs being the most vulnerable. *One should consider the diagnosis of a mitochondrial disorder in a patient of any age who presents with progressive, multisystem involvement that cannot be explained by a specific diagnosis.* Certain mitochondrial disorders have characteristic gastrointestinal presentations, including vomiting, diarrhea, constipation, failure to thrive, and abdominal pain. Pearson marrow-pancreas syndrome manifests with sideroblastic anemia and exocrine pancreatic insufficiency, whereas mitochondrial neurogastrointestinal encephalomyopathy manifests with chronic intestinal pseudoobstruction and cachexia. Hepatic presentations range from chronic cholestasis, hepatomegaly, cirrhosis, and steatosis to fulminant hepatic failure and death. Patients with certain mitochondrial diseases may have normal or minimally elevated lactate levels even in the setting of a metabolic crisis. The lactate-to-pyruvate molar ratio (L:P) has been proposed as a screening test for mitochondrial disorders because it reflects the equilibrium between the product and substrate of the reaction catalyzed by lactase dehydrogenase. An L:P ≥ 25 has been considered to be highly suggestive of respiratory chain dysfunction; however, an elevated lactate or an elevated L:P can also represent secondary mitochondrial dysfunction occurring as a result of severe liver disease.

PRIMARY MITOCHONDRIAL HEPATOPATHIES

Neonatal Liver Failure

A common presentation of respiratory chain defects is severe liver failure manifested as jaundice, hypoglycemia, coagulopathy, renal dysfunction, and hyperammonemia, with onset within the first few weeks to months of life. **Cytochrome-*c* oxidase** (complex IV) is the most common deficiency in these infants, although complexes I and III and MDSs are also implicated (see Tables 409.1 and Chapter 404). The key biochemical features include a markedly elevated plasma lactate concentration, an elevated molar ratio of plasma lactate to pyruvate (L:P) (>25), and a raised ratio of β-hydroxybutyrate to acetoacetate (>4.0). Symptoms are nonspecific and include lethargy and vomiting. Most patients additionally have neurologic involvement that manifests as a weak suck, recurrent apnea, or myoclonic epilepsy. Liver biopsy shows predominantly microvesicular steatosis, cholestasis, bile duct proliferation, glycogen depletion, and iron overload. With standard therapy, the prognosis is poor, and most patients die from liver failure or infection in the first few months of life.

Alpers Syndrome (Alpers-Huttenlocher Syndrome or Alpers Hepatopathic Poliodystrophy)

Diagnostic criteria include refractory mixed-type seizures with a focal component; psychomotor regression that is episodic and triggered by intercurrent infections; and hepatopathy with or without acute liver failure. Alpers syndrome manifests from infancy up to 8 years of age with seizures, hypotonia, feeding difficulties, psychomotor regression, and ataxia. Patients develop hepatomegaly and jaundice and have a slower progression to liver failure than those with cytochrome-*c* oxidase deficiency. Elevated blood or cerebrospinal fluid lactate and pyruvate levels are supportive of the diagnosis, in addition to characteristic electroencephalographic findings (high-amplitude slow activity with polyspikes), asymmetric abnormal visual evoked responses, and low-density areas or atrophy in the occipital or temporal lobes on computed tomography scanning of the brain. In some patients, complex I deficiency has been found in liver or muscle mitochondria. The disease is inherited in an autosomal recessive fashion; pathogenic variants in the catalytic subunit of the nuclear gene mtDNA *POLG* have been identified in multiple families with Alpers syndrome, leading to the advent of molecular diagnosis for Alpers syndrome. Patients with *POLG* pathogenic variants are susceptible to *valproate-induced* liver dysfunction.

Mitochondrial DNA Depletion Syndrome

MDS is characterized by a tissue-specific reduction in mtDNA copy number, leading to deficiencies in complexes I, III, and IV. MDS manifests with phenotypic heterogeneity; multisystem and localized disease forms include myopathic, hepatocerebral, and liver-restricted presentations. Infants with the hepatocerebral form present in the neonatal period. The first symptoms are metabolic; these rapidly progress to hepatic failure with hypoglycemia and vomiting. This stage is followed by neurologic involvement affecting the central and peripheral systems. Laboratory studies are characterized by lactic acidosis, hypoglycemia, and markedly elevated α-fetoprotein in plasma. In some patients, iron overload has been found with elevated transferrin saturation, high ferritin levels, and iron accumulation in hepatocytes and Kupffer cells. Death usually occurs by 1 year of age. Spontaneous recovery has been reported in a patient with liver-restricted disease. Inheritance is autosomal recessive and pathogenic variants in the nuclear deoxyguanosine kinase gene *(DGUOK)* have been identified in many patients with hepatocerebral MDS. Thymidine kinase 2 has been implicated in the myopathic form; no known genetic defect has been identified in liver-restricted MDS. Multiple other nuclear genes including *POLG, MPV17,* Twinkle helicase gene, and *SUCLG1* have been implicated in hepatocerebral MDS. Greater than 100 affected individuals with *MPV17* MDS have been identified, most with early-onset hepatic and neurologic manifestations, although rare late-onset neuromyopathic phenotypes have also been identified.

Liver biopsies of patients with MDS show microvesicular steatosis, cholestasis, focal cytoplasmic biliary necrosis, and cytosiderosis in hepatocytes and sinusoidal cells. Ultrastructural changes are characteristic, with oncocytic transformation of mitochondria, which is characterized by mitochondria with sparse cristae, granular matrix, and dense or vesicular inclusions. If the native DNA-encoded complex II is normal and the activities of the other complexes are decreased, one should investigate mtDNA copy numbers for an MDS. Diagnosis is established by the demonstration of a low ratio of mtDNA (<10%) to nuclear DNA in affected tissues and/or genetic testing**.** Importantly, the sequence of the mitochondrial genome is normal.

Navajo Neurohepatopathy

Navajo neurohepatopathy (NNH) is an autosomal recessive sensorimotor neuropathy with progressive liver disease found only in Navajo

people of the southwestern United States. The incidence is 1 in 1,600 live births. Diagnostic criteria include sensory neuropathy, motor neuropathy, corneal anesthesia, and liver disease. Metabolic or infectious complications include failure to thrive, short stature, delayed puberty, or systemic infection. Affected individuals have evidence of central nervous system demyelination on radiographic imaging and peripheral nerves biopsies. An *MPV17* gene variant is implicated in the pathogenesis of NNH. Interestingly, this is the same gene implicated in MDS (see earlier), demonstrating that NNH may be a specific type of MDS found only in Navajos. NNH is divided into three phenotypic variations based on age of presentation and clinical findings.

Classic NNH appears in infancy with severe progressive neurologic deterioration manifesting clinically as weakness, hypotonia, loss of sensation with accompanying acral mutilation, corneal ulcerations, and poor growth. Liver disease, present in the majority of patients, is secondary and variable; it includes asymptomatic elevations of liver function tests, Reye syndrome–like episodes, and hepatocellular carcinoma or cirrhosis. γ-Glutamyl transpeptidase levels tend to be higher than in other forms of NNH. Liver biopsy might show chronic portal tract inflammation and cirrhosis but shows less cholestasis, hepatocyte ballooning, and giant cell transformation than in other forms of NNH.

Infantile NNH manifests between the ages of 1 and 6 months with jaundice and failure to thrive and progresses to liver failure and death by 2 years of age. Patients have hepatomegaly with moderate elevations in aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase. Liver biopsy demonstrates pseudoacinar formation, multinucleate giant cells, portal and lobular inflammation, canalicular cholestasis, and microvesicular steatosis. Progressive neurologic symptoms are not usually noticed at presentation but develop later.

Childhood NNH manifests from age 1-5 years with the acute onset of fulminant hepatic failure leading to death within months. Most patients also have evidence of neuropathy at presentation. Liver biopsies are similar to those in infantile NNH, except for significant hepatocyte ballooning and necrosis, bile duct proliferation, and cirrhosis, which are also seen.

There is no effective treatment for any of the forms of NNH, and neurologic symptoms often preclude liver transplantation. The identical *MPV17* pathogenic variant is seen in patients with both the infantile and classic forms of NNH, highlighting the clinical heterogeneity of NNH.

Pearson Syndrome

Pearson marrow-pancreas syndrome has a neonatal-onset with severe macrocytic anemia, variable neutropenia and thrombocytopenia, and ringed sideroblasts in the bone marrow. Diarrhea and fat malabsorption develop in early childhood secondary to extensive pancreatic fibrosis, acinar atrophy, and partial villous atrophy of the small intestine. The liver involvement includes hepatomegaly, steatosis, and cirrhosis. Liver failure and death have been reported before the age of 4 years. Other features of the syndrome include renal tubular disease, photosensitivity, diabetes mellitus, hydrops fetalis, and the late development of visual impairment, tremor, ataxia, proximal muscle weakness, external ophthalmoplegia, and a pigmentary retinopathy. Methylglutaconic aciduria is a useful diagnostic marker. Large deletions of mtDNA are reported in most patients, resulting in deficiency of complexes I and III. mtDNA deletions can be detected in patients' cultured fibroblasts as well as in peripheral blood lymphocytes.

Villous Atrophy Syndrome

Children with this disease present with severe anorexia, vomiting, chronic diarrhea, and villous atrophy in the first year of life. Hepatic involvement includes mild elevation of aminotransferase levels, hepatomegaly, and steatosis. Lactic acidosis is worsened with high-dextrose intravenous infusions or enteral nutrition. Diarrhea improves by 5 years of age in association with the normalization of intestinal biopsies. Subsequently, patients develop retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and proximal muscle weakness, with eventual death late in the first decade of life. The disease is attributed to a mtDNA rearrangement defect. A complex III deficiency was found in the muscle of affected patients.

GRACILE Syndrome

The acronym GRACILE summarizes the most important clinical features, namely fetal growth restriction (birthweight about −4 SD), aminoaciduria (caused by Fanconi-type tubulopathy), cholestasis (with steatosis and cirrhosis), iron overload, severe lactic acidosis, and early death. The syndrome is associated with pathogenic variants of the complex III assembly factor BCS1L. The liver histology shows microvesicular steatosis and cholestasis with abundant iron accumulation in hepatocytes and Kupffer cells. The liver iron content decreases slightly with age, concomitantly with increasing fibrosis and cirrhosis. Abnormal aminotransferase levels and coagulation are noted, but the cause of death seems to be related more to energy depletion than to liver failure. About half of these patients die within the first 2 weeks of life.

Pathogenic Variants in Nuclear Translation and Elongation Factor Genes

Pathogenic variants in nuclear translation factor genes *(TRMU)* of the respiratory chain enzyme complexes have been identified as the etiology of acute liver failure manifesting at ages 1 day to 6 months. The respiratory chain deficit was similar to that seen in MDS, where the activity of the native DNA-encoded complex II was normal whereas complexes I, III, and IV were decreased. The elongation factor EFG1 (gene *GFM1*) variant was associated with fetal growth restriction, lactic acidosis, and liver dysfunction that progresses into liver failure and death. The variant in the elongation factor EFTu manifests as severe lactic acidosis and lethal encephalopathy with mild hepatic involvement.

Secondary Mitochondrial Hepatopathies

Secondary mitochondrial hepatopathies are caused by exposure to a hepatotoxic metal, drug, toxin, or endogenous metabolite. In the past, the most common secondary mitochondrial hepatopathy was *Reye syndrome*, the prevalence of which peaked in the 1970s and had a mortality rate of >40%. Although mortality has not changed, the prevalence has decreased from >500 cases in 1980 to fewer than four cases annually since 1994. The decline in the reported incidence of Reye syndrome may be partially related to more accurate modern diagnosis of infectious, genetic, metabolic, or toxic disease, thus reducing the percentage of idiopathic or true cases of Reye syndrome. Reye syndrome is precipitated in a genetically susceptible person by the interaction of a viral infection (influenza, varicella) and salicylate and/or antiemetic use. Clinically it is characterized by a preceding viral illness that appears to be resolving and the acute onset of vomiting and encephalopathy (Table 409.3). Neurologic symptoms can rapidly progress to seizures, coma, and death. Liver dysfunction is invariably present when vomiting develops, with coagulopathy and elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and ammonia. Importantly, patients remain anicteric and serum bilirubin levels are normal. Liver biopsies show microvesicular steatosis without evidence of liver inflammation or necrosis. Death is usually secondary to increased intracranial pressure and cerebral herniation. Patients who survive

Table 409.3 Clinical Staging of Reye Syndrome and Reye-Like Diseases

Symptoms at the time of admission:

I. Usually quiet, **lethargic,** and sleepy, vomiting, laboratory evidence of liver dysfunction
II. Deep lethargy, **confusion,** delirium, combativeness, hyperventilation, hyperreflexia
III. Obtunded, **light coma** ± seizures, **decorticate** rigidity, intact pupillary light reaction
IV. Seizures, deepening coma, **decerebrate rigidity,** loss of oculocephalic reflexes, fixed pupils
V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebration** (intermittent); isoelectric electroencephalogram

Table 409.4 Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

- Metabolic disease
  - Organic aciduria
  - Disorders of oxidative phosphorylation
  - Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
  - Defects in fatty acid oxidation metabolism
  - Acyl–coenzyme A dehydrogenase deficiencies
  - Systemic carnitine deficiency
  - Hepatic carnitine palmitoyltransferase deficiency
  - 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency
  - Fructosemia
  - Infantile liver failure syndrome 1. Caused by leucyl-tRNA synthetase (LARS) gene variants
- Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
- Hemorrhagic shock with encephalopathy
- Drug or toxin ingestion (salicylate, valproate)

have full recovery of liver function but should be carefully screened for fatty-acid oxidation and fatty-acid transport defects (Table 409.4).

Acquired abnormalities of mitochondrial function can be caused by several drugs and toxins, including valproic acid, cyanide, amiodarone, chloramphenicol, iron, the emetic toxin of *Bacillus cereus,* and nucleoside analogs. Valproic acid is a branched fatty acid that can be metabolized into the mitochondrial toxin 4-envalproic acid. Children with underlying respiratory chain defects appear more sensitive to the toxic effects of this drug, and valproic acid is reported to precipitate liver failure in patients with **Alpers syndrome** and **cytochrome-*c* oxidase deficiency.** Nucleoside analogs directly inhibit mitochondrial respiratory chain complexes. The reverse transcriptase inhibitors zidovudine, didanosine, stavudine, and zalcitabine—used to treat patients infected with HIV—inhibit DNA POLG of mitochondria and can block elongation of mtDNA, leading to mtDNA depletion. Other conditions that can lead to mitochondrial oxidative stress include cholestasis, nonalcoholic steatohepatitis, α_1-antitrypsin deficiency, and Wilson disease.

DIAGNOSTIC EVALUATION

Screening tests include common biochemical tests (comprehensive metabolic profile, INR, α-fetoprotein, CPK, phosphorus, complete blood cell count, ammonia, lactate, pyruvate, serum ketone bodies: both quantitative 3-hydroxybutyrate and quantitative acetoacetate, total free fatty acids, serum acylcarnitine profile; serum-free and total carnitines, urine organic acids, and serum amino acids) (Table 409.5). These results will guide subsequent confirmatory testing to establish a molecular diagnosis. Genotyping, including single gene or panel screening for common mitochondrial disease, is used in clinical practice. Whole exome or genome sequencing is also helpful and is replacing single gene or gene panel testing. However, the identification of multiple gene variants of uncertain significance will require detailed clinical and biochemical confirmation for interpretation. Tissue (liver biopsy, skin fibroblast, and muscle biopsy) may be needed to make a specific biochemical diagnosis.

TREATMENT OF MITOCHONDRIAL HEPATOPATHIES

There is no effective therapy for most patients with mitochondrial hepatopathies; neurologic involvement often precludes orthotopic liver transplantation. Patients with mitochondrial disorders remain at risk for transplant-related worsening of their underlying metabolic disease, especially patients with *POLG*-related disease. Children who receive liver transplants for *DGUOK* MDS have decreased rates of survival post-transplant than those who are transplanted for other diseases. Liver transplantation for *MPV17*- related mtDNA depletion syndrome is associated with poor post-transplant outcomes because of multiorgan failure and sepsis. Several therapeutic drug combinations—including antioxidants, vitamins, cofactors, and electron acceptors—have been proposed, but no randomized controlled trials have been completed to evaluate them.

Treatment strategies are supportive and include the infusion of sodium bicarbonate for acute metabolic acidosis, transfusions for anemia and thrombocytopenia, and exogenous pancreatic enzymes for pancreatic insufficiency. It is important to discontinue or avoid medications that may exacerbate hepatopathy, including sodium valproate, tetracycline, and macrolide antibiotics, azathioprine, chloramphenicol, quinolones, and linezolid. Ringer lactate should be avoided because patients with liver dysfunction may not be able to metabolize lactate. Propofol should be avoided during anesthesia because of potential interference with mitochondrial function. In patients with lactic acidosis, lactate levels should be monitored during procedures. It is important to maintain anabolism using a balanced intake of fat and carbohydrates while avoiding unbalanced intakes (e.g., glucose only at a high intravenous rate) or fasting for >12 hours.

Table 409.5 Tiered Investigations in Suspected Mitochondrial Liver Disease

TIER 1
Pre-/postprandial plasma lactate, glucose, FFA, and 3-OH
Plasma carnitine, acylcarnitines
Plasma amino acids, creatine kinase, thymidine
Urinary organic acids, amino acids, tubular resorption phosphate, albumin/creatinine ratio CSF lactate/protein (if feasible)
Electrocardiography and echocardiography
Electroencephalography and visual-evoked potentials
Pathogenic variants in *POLG, DGUOK, MPV17,* and *TRMU*
TIER 2
Tissue analysis
Liver biopsy: (if feasible). Tissue for light microscopy, electron microscopy, and Oil Red O stain
Frozen tissue for respiratory chain enzyme activity analysis and mtDNA copy number
Muscle biopsy: Tissue for light microscopy, electron microscopy, Oil Red O stain, and histochemistry for respiratory chain complexes
Frozen tissue for respiratory chain enzyme activity analysis and mtDNA copy number
Skin biopsy: Set up for fibroblast culture
TIER 3
Cranial MRI/MRS
TIER 4
Extended molecular screening. This will be guided by the clinical phenotype, results of the tissue analysis, and local facilities.
Currently suggested genes should include *SUCLG1, BCS1L, SOC1, TFSM, TWINKLE, ACAD9, EARS2, GFM1, RRM2B, TK2,* and *SUCLA2.*

FFA, Free fatty acid; CSF, cerebrospinal fluid; MRS, magnetic resonance spectroscopy. From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 5th ed. Philadelphia: Elsevier, 2016: Box 71-3, p. 876.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 410

Autoimmune Hepatitis

Amy G. Feldman and Frederick J. Suchy

Autoimmune hepatitis (AIH) is an immune-mediated liver disease manifested by elevated serum aminotransaminase concentrations, liver-associated serum autoantibodies, and/or hypergammaglobulinemia. The serologic autoantibody profile defines two main types of autoimmune hepatitis: **AIH type 1**, with positivity for antinuclear antibodies (ANA) and/or anti–smooth muscle antibody (SMA) and **AIH type 2**, with positivity for anti–liver kidney microsomal type 1 antibody (anti-LKM-1). The targets of the inflammatory process can include hepatocytes and, to a lesser extent, bile duct epithelium. Autoimmune hepatitis typically refers to a primarily hepatocyte-specific process, whereas **autoimmune cholangiopathy** and **sclerosing cholangitis** predominately involve intrahepatic and extrahepatic bile duct injury. **Overlap** of the process involving both hepatocyte and bile duct–directed injury may be more common in children. Chronicity is determined either by duration of liver disease (typically >3-6 months), by evidence of chronic hepatic decompensation (hypoalbuminemia, thrombocytopenia) or physical stigmata of chronic liver disease (clubbing, spider telangiectasia, splenomegaly, ascites). The severity is variable; the affected child might have only biochemical evidence of liver dysfunction, might have stigmata of chronic liver disease, or can present in hepatic failure. De novo hepatitis can be seen in a subset of liver transplant recipients whose initial disease was not autoimmune.

ETIOLOGY

Autoimmune hepatitis arises in a genetically predisposed host after an unknown trigger leads to a T cell–mediated immune response targeting liver autoantigens. A dense portal mononuclear cell infiltrate invades the surrounding parenchyma and comprises T and B lymphocytes, macrophages, and plasma cells. The immunopathogenic mechanisms underlying autoimmune hepatitis are unsettled. Triggering factors can include molecular mimicry, infections, drugs, and the environment (toxins) in a genetically susceptible host. Several human leukocyte antigen class II molecules—particularly DR3, DR4, and DR7 isoforms—confer susceptibility to autoimmune hepatitis. Self-antigenic peptides are processed by populations of antigen-presenting cells and presented to CD4 and CD8 effector T cells. $CD4^+$ T lymphocytes recognizing a self-antigenic liver peptide orchestrate liver injury. Cell-mediated injury by cytokines released by $CD8^+$ cytotoxic T cells and/or antibody-mediated cytotoxicity can be operative. There is also evidence that regulatory T cells from patients with autoimmune hepatitis are impaired in their ability to control the proliferation of CD4 and CD8 effector cells. Cytochrome P450 2D6 is the main autoantigen in type 2 autoimmune hepatitis.

Antibody-coated hepatocytes may be lysed by complement or Fc-bearing natural killer lymphocytes. Heterozygous pathogenic variants in the autoimmune regulator gene *(AIRE),* which encodes a transcription factor controlling the negative selection of autoreactive thymocytes, can be found in some children with autoimmune hepatitis types 1 and 2. *AIRE* variants also cause **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy** (also called *autoimmune polyendocrinopathy syndrome*), in which autoimmune hepatitis occurs in approximately 20% of patients.

PATHOLOGY

The histologic features common to untreated cases include inflammatory infiltrates, consisting of lymphocytes and plasma cells that expand portal areas and often penetrate the lobule (interface hepatitis); moderate to severe piecemeal necrosis of hepatocytes extending outward from the limiting plate; variable necrosis, fibrosis, and zones of parenchymal collapse spanning neighboring portal triads or between a portal triad and central vein (bridging necrosis); and variable degrees of bile duct epithelial injury. Distortion of hepatic architecture can be severe; cirrhosis may be present in over a third of children at the time of diagnosis. Histologic features in acute liver failure may be obscured by massive necrosis and multilobular collapse. Other histologic features may suggest an alternative diagnosis; characteristic periodic acid–Schiff-positive, diastase-resistant granules are seen in α_1-antitrypsin deficiency, and macrovesicular and microvesicular steatosis is found in nonalcoholic steatohepatitis and often in Wilson disease. Bile duct injury can suggest an autoimmune cholangiopathy or an overlap syndrome. Ultrastructural analysis might suggest distinct types of storage disorders.

CLINICAL MANIFESTATIONS

The clinical features and course of autoimmune hepatitis are extremely variable. Signs and symptoms at the time of presentation comprise a wide spectrum of disease including a substantial number of asymptomatic patients and some who have an acute, even fulminant, onset. In 25–30% of patients with autoimmune hepatitis, particularly children, the illness mimics acute viral hepatitis. *In most, the onset is insidious*. Patients can be asymptomatic or have fatigue, malaise, behavioral changes, anorexia, and amenorrhea, sometimes for many months before jaundice or stigmata of chronic liver disease are recognized. **Extrahepatic manifestations** can include arthritis, vasculitis, nephritis, thyroiditis, Coombs-positive anemia, and rash (vitiligo, Sweet syndrome, pyoderma gangrenosum, erythema nodosum). Some patients' initial clinical features reflect cirrhosis (ascites, hypersplenism, bleeding esophageal varices, or hepatic encephalopathy). There may be mild to moderate jaundice in severe cases. Spider telangiectasias and palmar erythema may be present. The liver may be tender and slightly enlarged but might not be felt in patients with cirrhosis. The spleen is commonly enlarged. Edema and ascites may be present in advanced cases.

LABORATORY FINDINGS

The findings are related to the severity of presentation. In many asymptomatic cases, serum aminotransferase ranges between 100 and 300 IU/L, whereas levels in excess of 1,000 IU/L can be seen in young symptomatic patients. Serum bilirubin concentrations may be normal in mild cases but are commonly 2-10 mg/dL in more severe cases. Serum alkaline phosphatase and γ-glutamyl transpeptidase activities are normal to slightly increased but may be more significantly elevated in autoimmune cholangiopathy or in the setting of overlap with sclerosing cholangitis. Serum γ-globulin levels can show marked polyclonal elevations. Hypoalbuminemia is common. The prothrombin time or international normalized ratio (INR) is prolonged, most often as a result of vitamin K deficiency but also as a reflection of impaired hepatocellular function. A normochromic normocytic anemia, leukopenia, and thrombocytopenia are present and become more severe with the development of portal hypertension and hypersplenism.

Most patients with autoimmune hepatitis have hypergammaglobulinemia. Serum immunoglobulin G levels usually exceed 16 g/L. Characteristic patterns of serum autoantibodies define distinct subgroups of autoimmune hepatitis (Table 410.1). The most common pattern (type 1) is associated with the formation of non–organ-specific antibodies, such as antiactin (smooth muscle) and ANA. Approximately 50% of these patients are 10-20 years of age. High titers of a liver-kidney microsomal antibody are detected in another form (type 2) that usually affects children 2-14 years of age. A subgroup of primarily young females might demonstrate autoantibodies against a soluble liver antigen but not against nuclear or microsomal proteins. Antineutrophil cytoplasmic antibodies may

Table 410.1 Classification of Autoimmune Hepatitis

VARIABLE	TYPE 1 AUTOIMMUNE HEPATITIS	TYPE 2 AUTOIMMUNE HEPATITIS
Characteristic autoantibodies	Antinuclear antibody*	Antibody against liver-kidney microsome type 1*
	Smooth-muscle antibody*	
	Antiactin antibody	Antibody against liver cytosol type 1*
	Autoantibodies against soluble liver antigen and liver-pancreas antigen‡	Antibody against liver-kidney microsome type 3
	Atypical perinuclear antineutrophil cytoplasmic antibody	
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly early childhood
Sex of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range, variable	Generally severe
Histopathologic features at presentation	Broad range, mild disease to cirrhosis	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

*The conventional method of detection is immunofluorescence.
‡This antibody is detected by enzyme-linked immunosorbent assay.
§Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is seen only in patients with type 2 disease.
Modified from Krawitt EL. Autoimmune hepatitis. *N Engl J Med.* 2006;354:54–66.

be seen more commonly in autoimmune cholangiopathy. Autoantibodies are rare in healthy children, so that titers as low as 1:40 may be significant, although nonspecific elevation in autoantibodies can be observed in a variety of liver diseases. Up to 20% of patients with apparent autoimmune hepatitis might not have autoantibodies at presentation but have histologic features and clinical course consistent with the disorder. Other, less common autoantibodies include rheumatoid factor, antiparietal cell antibodies, atypical p-ANCA, antithyroid antibodies, and anti–liver cytosol type 1 antibody (anti-LC-1).

DIAGNOSIS

The diagnosis of autoimmune hepatitis is based on clinical, biochemical, immunologic, and histologic features and the exclusion of other known causes of liver disease. Diagnostic criteria with scoring systems have been developed for adults and modified slightly for children, although these scoring systems were developed as research rather than diagnostic tools and lack validation by prospective studies and lack accuracy in the setting of concurrent sclerosing cholangitis, nonalcoholic fatty liver disease, or fulminant liver failure. Autoimmune hepatitis should be considered in all children presenting with elevated liver function tests and/or signs of chronic liver disease, including children who are asymptomatic, in liver failure, or who have autoantibody-negative hepatitis. Important positive features include primary elevation in transaminases and not alkaline phosphatase (or GGT), elevated γ-globulin levels, the presence of autoantibodies (most commonly antinuclear, smooth muscle, or liver-kidney microsome), and characteristic histologic findings (Fig. 410.1). Other causes of acute hepatitis and chronic liver disease must be excluded including infection (Epstein-Barr virus [EBV], hepatitis A [Hep A], B, C, D), drug or toxin exposure, α_1-antitrypsin deficiency (see Chapter 405) and Wilson disease (see Chapter 405.2) (Table 410.2). To exclude these processes viral

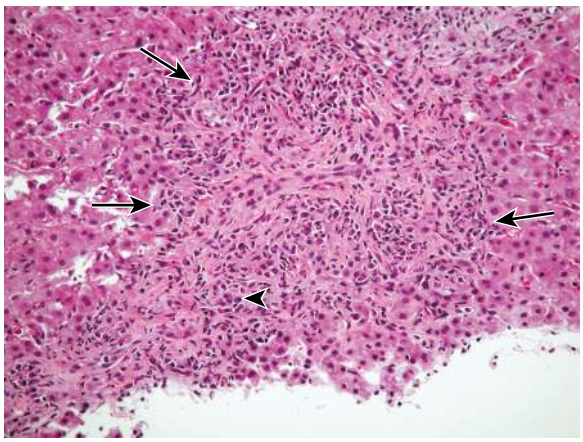

Fig. 410.1 Autoimmune hepatitis. Liver biopsy showing fibrous expansion of the portal tracts with moderate portal lymphocytic infiltrates rich in plasma cells *(arrowhead)*. There is extensive interface hepatitis *(arrows)*. Original magnification ×20. *(Courtesy Dr Margret Magid, Mount Sinai School of Medicine.)*

titers (Hep A IgM, Hep B surface Ag, Hep C Ab), α_1-antitrypsin level/phenotype and serum ceruloplasmin should be obtained. Magnetic resonance (MR) cholangiography may be very useful for screening for evidence of sclerosing cholangitis. An **overlap syndrome** with features of primary sclerosing cholangitis and autoimmune hepatitis is being increasingly recognized with wider application of MR cholangiography. Ultimately, liver biopsy is necessary to confirm compatible histologic features as well as to look for features of small duct primary sclerosing cholangitis.

Table 410.2 Disorders Producing Chronic Hepatitis

- Chronic viral hepatitis
  - Hepatitis B
  - Hepatitis C
  - Hepatitis D
- Autoimmune hepatitis
  - Anti–actin antibody-positive
  - Anti-nuclear antibody
  - Anti–liver-kidney microsomal antibody-positive
  - Anti–soluble liver antigen antibody-positive
  - Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
  - Overlap syndrome with sclerosing cholangitis and autoantibodies
  - Systemic lupus erythematosus
  - Celiac disease
- Drug-induced hepatitis
- Metabolic disorders associated with chronic liver disease
  - Wilson disease
  - Nonalcoholic steatohepatitis
  - α_1-Antitrypsin deficiency
  - Tyrosinemia
  - Niemann-Pick disease type 2
  - Glycogen storage disease type IV
  - Cystic fibrosis
  - Galactosemia
  - Bile acid biosynthetic abnormalities

TREATMENT

Prednisone, with or without azathioprine, improves the clinical, biochemical, and histologic features in most patients with autoimmune hepatitis and prolongs survival in most patients with severe disease. The goal is to suppress or eliminate hepatic inflammation with minimal side effects. Prednisone at an initial dose of 1-2 mg/kg/24 hr is continued until aminotransferase values return to normal. Budesonide (9 mg/daily) can be used instead of prednisone for children who do not have cirrhosis or severe acute autoimmune hepatitis. In some centers, azathioprine (1.5-2.0 mg/kg/24 hr, up to 100 mg/24 hr) is started at the same time as glucocorticoids, whereas other centers prefer to wait ~2 weeks before starting azathioprine to confirm steroid responsiveness and allow improvement in liver function. Measurement of thiopurine methyltransferase activity should be performed at some point in the beginning of therapy as patients with low activity (10% prevalence) or absent activity (prevalence 0.3%) are at risk for developing severe drug-induced myelotoxicity from accumulation of the unmetabolized drug. Once liver function tests normalize and biochemical remission is achieved the prednisone or budesonide dose should then be lowered (in 5-mg decrements for prednisone and 3-mg decrements for budesonide) over several months. Liver function tests should be monitored every 1-2 weeks while tapering steroids to ensure the child stays in biochemical remission. Once tapered off steroids, liver function tests should be monitored every 3-4 months to ensure the child stays in biochemical remission. Cyclosporine, tacrolimus, and mycophenolate mofetil can be trialed as *second-line agents* for cases refractory to standard therapy. Use of these agents should be reserved for practitioners with extensive experience in their administration because the agents have a more restricted therapeutic to toxic ratio.

If the child has sustained normal serum levels of aminotransferases, negative autoantibodies and normal IgG levels for at least 2 years after steroids have been withdrawn, a follow-up liver biopsy can be performed and if there is no evidence of ongoing inflammation, then gradual withdrawal of azathioprine can be attempted. However, there is a high rate of relapse after discontinuation of therapy and many children with autoimmune hepatitis require lifelong azathioprine.

Patients with primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome respond similarly to immunosuppressive therapy. Prednisone, azathioprine and ursodeoxycholic acid (UDCA) (10 mg/kg/dose BID) are recommended for children with overlap syndrome.

PROGNOSIS

The initial response to therapy in autoimmune hepatitis is generally prompt, with a >75% rate of remission. Transaminases and bilirubin fall to near-normal levels, often in the first 1-3 months. When present, abnormalities in serum albumin and prothrombin time respond over a longer period (3-9 months). In patients meeting the criteria for tapering and then withdrawal of treatment (25–40% of children), 50% are weaned from all medication. However, long-term biochemical remission has been possible in only 20% of children with type 1 autoimmune hepatitis and rarely in children with type 2 autoimmune hepatitis. Relapse usually responds to retreatment. Many children will not meet the criteria for an attempt at discontinuation of immunosuppression and should be maintained on the smallest dose of prednisone or azathioprine that minimizes biochemical activity of the disease. A careful balance of the risks of continued immunosuppression and ongoing hepatitis must be continually evaluated. This requires frequent screening for complications of medical therapy (monitoring of linear growth velocity, ophthalmologic examination, bone density measurement, blood pressure monitoring). Intermittent flares of hepatitis can occur and can necessitate recycling of prednisone therapy.

Some children have a relatively steroid-resistant form of hepatitis. More extensive evaluations of the etiology of their hepatitis should be undertaken, directed particularly at reassessing for the presence of either sclerosing cholangitis or Wilson disease. Nonadherence to medical therapy is one of the most common causes of "resistance" to medical therapy. Progression to cirrhosis can occur in autoimmune hepatitis despite a good response to drug therapy and prolongation of life. Corticosteroid therapy in fulminant autoimmune disease may be useful, although it should be administered with caution, given the predisposition of these patients to systemic bacterial and fungal infections.

Liver transplantation has been successful in patients with end-stage or fulminant liver disease associated with autoimmune hepatitis (see Chapter 416). Disease recurs after transplantation in approximately 30% of patients and is associated with increased concentrations of serum autoantibodies and interface hepatitis on liver biopsy. Patients generally respond well to an increase in immunosuppression, particularly to the addition of azathioprine.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 411

Drug- and Toxin-Induced Liver Injury

Frederick J. Suchy and Amy G. Feldman

The liver is the main site of drug metabolism and is particularly susceptible to structural and functional injury after the ingestion, parenteral administration, or inhalation of chemical agents, drugs, plant derivatives (home remedies), herbal or nutritional supplements, or environmental toxins. The possibility of drug use or toxin exposure at home or in the parents' workplace should be explored for every child with liver dysfunction. Host factors related to hepatotoxicity include age, genetic predisposition, nutritional status, concomitant medications, and underlying diseases. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure (Table 411.1). Liver injury may be the only clinical feature of an adverse drug reaction or may be accompanied by systemic manifestations and damage to other organs. In hospitalized patients, clinical and laboratory findings may be confused with the underlying illness. After acetaminophen, antimicrobials, supplements, and central nervous system agents are the most commonly implicated drug classes causing liver injury in children.

There is growing concern about environmental hepatotoxins that are insidious in their effects. Many environmental toxins—including the plasticizers, biphenyl A, and the phthalates—are ligands for nuclear receptors that transcriptionally activate the promoters of many genes involved in xenobiotic and lipid metabolism and may contribute to obesity and **nonalcoholic fatty liver disease**. Some herbal, weight loss, and body building supplements have been associated with hepatic injury or even liver failure (Table 411.2) related to their intrinsic toxicity or because of contamination with fungal toxins, pesticides, or heavy metals.

Hepatic metabolism of drugs and toxins is mediated by a sequence of enzymatic reactions that in large part transform hydrophobic, less-soluble molecules into more nontoxic, hydrophilic compounds that can be readily excreted in urine or bile (see Chapter 94). Relative liver size, liver blood flow, and extent of protein binding also influence drug metabolism. Phase 1 of the process involves enzymatic activation of the substrate to reactive intermediates containing a carboxyl, phenol, epoxide, or hydroxyl group. Mixed-function monooxygenase, cytochrome-*c* reductase, various hydrolases, and the cytochrome P450 (CYP) system are involved in this process. Nonspecific induction of these enzymatic pathways, which can occur during intercurrent viral infection, with starvation, and with the administration of certain drugs such as anticonvulsants, can alter drug metabolism and increase the potential for hepatotoxicity. A single agent can be metabolized by more than one biochemical reaction. The reactive intermediates that are potentially damaging to the cell are enzymatically conjugated in phase 2 reactions with glucuronic acid, sulfate, acetate, glycine, or glutathione. Some drugs may be directly metabolized by these conjugating reactions without first undergoing phase 1 activation. Phase 3 is the energy-dependent excretion of drug metabolites and their conjugates by an array of membrane transporters in the liver and kidney such as the multidrug resistant protein 1.

Pathways for **biotransformation** are expressed early in the fetus and infant, but many phase 1 and phase 2 enzymes are immature, particularly in the first year of life. CYP3A4 is the primary hepatic CYP expressed postnatally and metabolizes more than 75 commonly used therapeutic drugs and several environmental pollutants and procarcinogens. Hepatic CYP3A4 activity is poorly expressed in the fetus but increases after birth to reach 30% of adult values by 1 month and 50% of adult values between 6 and 12 months of age. CYP3A4 can be induced by a number of drugs, including phenytoin, phenobarbital, and rifampin. Enhanced production of toxic metabolites can overwhelm the capacity of phase 2 reactions. Conversely, numerous inhibitors of CYP3A4 from several different drug classes, such as erythromycin and cimetidine, can lead to toxic accumulations of CYP3A4 substrates. By contrast, although CYP2D6 is also developmentally regulated (maturation by 10 years of age), its activity depends more on genetic polymorphisms than on sensitivity to inducers and inhibitors because more than 70 allelic variants of CYP2D6 significantly influence the metabolism of many drugs. Uridine diphosphate glucuronosyltransferase 1A6, a phase 2 enzyme that glucuronidates acetaminophen, is also absent in the human fetus, increases slightly in the neonate, but does not reach adult levels until sometime after 10 years of age. Mechanisms for the uptake and excretion of organic ions can also be deficient early in life. Impaired drug metabolism via phase 1 and phase 2 reactions present in the first few months of life is followed by a period of enhanced metabolism of many drugs in children through 10 years of age compared with adults.

Genetic polymorphisms in genes encoding enzymes and transporters mediating phases 1, 2, and 3 reactions can also be associated with impaired drug metabolism and an increased risk of hepatotoxicity. Some cases of **idiosyncratic hepatotoxicity** can occur as a result of aberrations (polymorphisms) in phase 1 drug metabolism, producing intermediates of unusual hepatotoxic potential combined with developmental, acquired, or relative inefficiency of phase 2 conjugating reactions. Genome-wide association studies have identified HLA associations in certain cases of **drug- and toxin-induced liver injury (DILI)**. Children may be less susceptible than adults to hepatotoxic reactions; liver injury after the use of the anesthetic halothane is rare in children, and acetaminophen toxicity is less common in infants than in adolescents, whereas most cases of fatal hepatotoxicity associated with sodium valproate use have been reported in children. Excessive or prolonged therapeutic administration of acetaminophen combined with reductions in caloric or protein intake can produce hepatotoxicity in children. In this setting, acetaminophen metabolism may be impaired by reduced synthesis of sulfated and glucuronated metabolites and reduced stores of glutathione. Immaturity of hepatic drug metabolic pathways can prevent degradation of a toxic agent; under other circumstances, the same immaturity might limit the formation of toxic metabolites. Severe sodium valproate hepatotoxicity is often associated with an underlying inherited mitochondrial disorder **(Alpers syndrome).**

Chemical hepatotoxicity can be predictable or idiosyncratic. Predictable hepatotoxicity implies a high incidence of hepatic injury in exposed persons depending on dose. It is understandable that only a few drugs in clinical use fall into this category. These agents might damage the hepatocyte directly through alteration of membrane lipids (peroxidation) or through denaturation of proteins; such agents include carbon tetrachloride and trichloroethylene. Indirect injury can occur through interference with metabolic pathways essential for cell integrity or through distortion of cellular constituents by covalent binding of a reactive metabolite; examples include the liver injury produced by acetaminophen or by antimetabolites such as methotrexate or 6-mercaptopurine.

Idiosyncratic hepatotoxicity is unpredictable and accounts for the majority of adverse reactions. Higher doses of drugs metabolized in the liver pose a greater risk for hepatotoxicity. Idiosyncratic drug reactions in certain patients can reflect aberrant pathways for drug metabolism, possibly related to genetic polymorphisms, with production of toxic intermediates (isoniazid and sodium valproate can cause liver damage through this mechanism). Duration of drug use before liver injury varies (weeks to ≥1 year) and the response to reexposure may be delayed.

An idiosyncratic reaction can also be immunologically mediated as a result of prior sensitization **(hypersensitivity)**; extrahepatic manifestations of hypersensitivity can include fever, rash, arthralgia, and eosinophilia. Duration of exposure before reaction is generally 1-4 weeks, with prompt recurrence of injury on reexposure. Studies indicate that arene oxides, generated through oxidative (CYP) metabolism of aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine),

Table 411.1 Most Common or Well-Described Drug-Induced Liver Injury Agents and the Patterns of Their Liver Injury

	LATENCY*	TYPICAL PATTERN OF INJURY/IDENTIFYING FEATURES
ANTIBIOTICS		
Amoxicillin/clavulanate	Short to moderate	Cholestatic injury but can be hepatocellular; drug-induced liver injury onset is frequently detected after drug cessation
Isoniazid	Moderate to long	Acute hepatocellular injury similar to acute viral hepatitis
Trimethoprim/sulfamethoxazole	Short to moderate	Cholestatic injury but can be hepatocellular; often with immunoallergic features (e.g., fever, rash, and eosinophilia)
Fluoroquinolones	Short	Variable—hepatocellular, cholestatic, or mixed in relatively similar proportions
Macrolides	Short	Hepatocellular but can be cholestatic
Nitrofurantoin		Hepatocellular
Acute form (rare)	Short	Typically hepatocellular; often resembles idiopathic autoimmune hepatitis
Chronic form	Moderate to long (months-years)	Hepatocellular
Minocycline	Moderate to long	Hepatocellular and often resembles autoimmune hepatitis
ANTIEPILEPTICS		
Phenytoin	Short to moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (e.g., fever, rash, and eosinophilia) (anticonvulsant hypersensitivity syndrome)
Carbamazepine	Moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Lamotrigine	Moderate	Hepatocellular often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Valproate		
Hyperammonemia	Moderate to long	Elevated blood ammonia and encephalopathy
Hepatocellular	Moderate to long	Hepatocellular
Reye-like syndrome	Moderate	Hepatocellular, acidosis; microvesicular steatosis on biopsy
ANALGESICS		
Nonsteroidal antiinflammatory agents	Moderate to long	Hepatocellular injury
Diclofenac		Hepatocellular injury with autoimmune features
IMMUNE MODULATORS		
Interferon-beta	Moderate to long	Hepatocellular
Interferon-alpha	Moderate	Hepatocellular, autoimmune hepatitis–like
Anti-TNF agents	Moderate to long	Hepatocellular. Can have autoimmune hepatitis features
Azathioprine	Moderate to long	Cholestatic or hepatocellular but can present with portal hypertension (veno-occlusive disease and nodular regenerative hyperplasia)
IMMUNE-CHECKPOINT INHIBITORS		
Ipilimumab (CTLA-4 inhibitor) Nivolumab, pembrolizumab, and cemiplimab (PD-1 inhibitors) Atezolizumab, avelumab, and durvalumab (PDL-1 inhibitors)	Under 12 wk	Initially mixed pattern but evolves primarily into hepatocellular pattern, without significant autoantibodies
MISCELLANEOUS		
Methotrexate (oral)	Long	Fatty liver, fibrosis
Allopurinol	Short to moderate	Hepatocellular or mixed. Often with immune-allergic features. Granulomas often present on biopsy
Amiodarone (oral)	Moderate to long	Hepatocellular, mixed, or cholestatic. Macrovesicular steatosis and steatohepatitis on biopsy
Androgen-containing steroids	Moderate to long	Cholestatic. Can present with peliosis hepatis, nodular regenerative hyperplasia, or hepatocellular carcinoma
Inhaled anesthetics	Short	Hepatocellular. May have immune-allergic features ± fever
Sulfasalazine	Short to moderate	Mixed, hepatocellular, or cholestatic. Often with immunoallergic features
Proton pump inhibitors	Short	Hepatocellular; very rare

*Short = 3-30 days; moderate = 30-90 days; long >90 days.
CTLA-4, Cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death receptor-1; PDL-1, programmed cell death receptor-ligand 1; TNF, tumor necrosis factor.
From Chalasani NP, Maddur H, Russo MW, et al. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol.* 2021;116(5):878–898. Table 6.

Table 411.2 Hepatotoxic Herbal Remedies, Dietary Supplements, and Weight Loss Products

REMEDY	POPULAR USES	SOURCE	HEPATOTOXIC COMPONENT	TYPE OF LIVER INJURY
Ayurvedic herbal medicine	Multiple	Multiple	Uncertain (may contain heavy metal contaminants)	Hepatitis
Barakol	Anxiolytic	*Cassia siamea*	Uncertain	Reversible hepatitis or cholestasis
Black cohosh	Menopausal symptoms	*Cimicifuga racemosa*	Uncertain	Hepatitis (causality uncertain)
"Bush tea"	Fever	*Senecio, Heliotropium, Crotalaria* spp.	Pyrrolizidine alkaloids	SOS
Cascara	Laxative	*Cascara sagrada*	Anthracene glycoside	Cholestatic hepatitis
Chaparral leaf (greasewood, creosote bush)	"Liver tonic," burn salve, weight loss	*Larrea tridentata*	Nordihydroguaiaretic acid	Acute and chronic hepatitis, FHF
Chaso/onshido	Weight loss	—	*N*-nitro-fenfluramine	Acute hepatitis, FHF
Chinese medicines (traditional)				
Jin bu huan	Sleep aid, analgesic	*Lycopodium serratum*	Levo-tetrahydropalmatine	Acute or chronic hepatitis or cholestasis, steatosis
Ma huang	Weight loss	*Ephedra* spp.	Ephedrine	Severe hepatitis, FHF
Shou-wu-pian	Antiaging, neuroprotection, laxative	*Polygonum multiflorum* Thunb. (fleeceflower root)	Anthraquinone	Acute hepatitis or cholestasis
Syo-saiko-to	Multiple	*Scutellaria* root	Diterpenoids	Hepatocellular necrosis, cholestasis, steatosis, granulomas
Comfrey	Herbal tea	*Symphytum* spp.	Pyrrolizidine alkaloid	Acute SOS, cirrhosis
Germander	Weight loss, fever	*Teucrium chamaedrys, T. capitatum, T. polium*	Diterpenoids, epoxides	Acute and chronic hepatitis, FHF, autoimmune injury
Greater celandine	Gallstones, IBS	*Chelidonium majus*	Isoquinoline alkaloids	Cholestatic hepatitis, fibrosis
Green tea leaf extract	Multiple	*Camellia sinensis*	Catechins	Hepatitis (causality questioned)
Herbalife	Nutritional supplement, weight loss	—	Various; ephedra	Severe hepatitis, FHF
Hydroxycut	Weight loss	*Camellia sinensis*, among other constituents	Uncertain	Acute hepatitis, FHF
Impila	Multiple	*Callilepis laureola*	Potassium atractylate	Hepatic necrosis
Kava	Anxiolytic	*Piper methysticum*	Kava lactone, pipermethystine	Acute hepatitis, cholestasis, FHF
Kombucha	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis
Limbrel (Flavocoxid)	Osteoarthritis	Plant bioflavonoids	Baicalin, epicatechin	Acute mixed hepatocellular-cholestatic injury
Lipokinetix	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis, jaundice, FHF
Mistletoe	Asthma, infertility	*Viscus album*	Uncertain	Hepatitis (in combination with skullcap)
Oil of cloves	Dental pain	Various foods, oils	Eugenol	Zonal necrosis
Pennyroyal (squawmint oil)	Abortifacient	*Hedeoma pulegioides, Mentha pulegium*	Pulegone, monoterpenes	Severe hepatocellular necrosis
Prostata	Prostatism	Multiple	Uncertain	Chronic cholestasis
Sassafras	Herbal tea	*Sassafras albidum*	Safrole	HCC (in animals)
Senna	Laxative	*Cassia angustifolia*	Sennoside alkaloids; anthrone	Acute hepatitis
Skullcap	Anxiolytic	*Scutellaria*	Diterpenoids	Hepatitis
Valerian	Sedative	*Valeriana officinalis*	Uncertain	Elevated liver enzymes

FHF, Fulminant hepatic failure; HCC, hepatocellular carcinoma; SOS, sinusoidal obstruction syndrome.
From Lewis JH. Liver disease caused by anesthetics, chemicals, toxins, and herbal preparations. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 89.6.

can initiate the pathogenesis of some hypersensitivity reactions. Arene oxides, formed in vivo, can bind to cellular macromolecules, thus perturbing cell function and possibly initiating immunologic mechanisms of liver injury.

The pathogenesis of hepatoxicity is most likely multifactorial, particularly the role played by the host immune system. Activation of liver nonparenchymal Kupffer cells and infiltration by neutrophils perpetuate toxic injury by many drugs by release of reactive oxygen and nitrogen species as well as cytokines. Stellate cells can also be activated, potentially leading to hepatic fibrosis and cirrhosis.

The pathologic spectrum of drug-induced liver disease is extremely wide, is rarely specific, and can mimic other liver diseases (Table 411.3; see also Table 411.1). Predictable hepatotoxins, such as acetaminophen, produce centrilobular necrosis of hepatocytes. **Steatosis** is an important feature of tetracycline (microvesicular) and ethanol (macrovesicular) toxicities. A cholestatic hepatitis can be observed, with injury caused by erythromycin estolate and chlorpromazine. **Cholestasis** without inflammation may be a toxic effect of estrogens and anabolic steroids. Use of oral contraceptives and androgens has also been associated with benign and malignant liver tumors. Some idiosyncratic drug reactions can produce mixed patterns of injury, with diffuse cholestasis and cell necrosis. Chronic hepatitis has been associated with the use of methyldopa and nitrofurantoin.

Clinical manifestations can be mild and nonspecific, such as fever and malaise. Fever, rash, and arthralgia may be prominent in cases of hypersensitivity. In ill hospitalized patients, the signs and symptoms of hepatic drug toxicity may be difficult to separate from the underlying illness. The differential diagnosis should include acute and chronic viral hepatitis, biliary tract disease, septicemia, ischemic and hypoxic liver injury, malignant infiltration, and inherited metabolic liver disease.

Table 411.3 Patterns of Hepatic Drug Injury

DISEASE	DRUG
Centrilobular necrosis	Acetaminophen Carbon tetrachloride Cocaine Ecstasy Iron Halothane
Microvesicular steatosis	Valproic acid Tetracycline Toluene Methotrexate
Acute hepatitis	Isoniazid Anti–tumor necrosis factor agents Valproic acid
General hypersensitivity	Sulfonamides Phenytoin Minocycline
Fibrosis	Methotrexate
Cholestasis	Chlorpromazine Aniline Erythromycin Paraquat Estrogens Sertraline
Sinusoidal obstruction syndrome (venoocclusive disease)	Irradiation plus busulfan Arsenic Cyclophosphamide
Portal and hepatic vein thrombosis	Estrogens Androgens
Biliary sludge	Ceftriaxone
Hepatic adenoma or hepatocellular carcinoma	Oral contraceptives Anabolic steroids

The laboratory features of drug- or toxin-related liver disease are extremely variable. Hepatocyte damage can lead to elevations of serum aminotransferase activities and serum bilirubin levels and to impaired synthetic function as evidenced by decreased serum coagulation factors and albumin. Hyperammonemia can occur with liver failure or with selective inhibition of the urea cycle (sodium valproate). Toxicologic screening of blood and urine specimens can aid in detecting drug or toxin exposure. Percutaneous liver biopsy may be necessary to distinguish drug injury from complications of an underlying disorder or from intercurrent infection. Vanishing bile duct syndrome can be seen in a small portion of patients with idiosyncratic DILI.

Slight elevation of serum aminotransferase activities (generally <2-3 times normal) can occur during therapy with drugs, particularly anticonvulsants, capable of inducing microsomal pathways for drug metabolism. Liver biopsy reveals proliferation of smooth endoplasmic reticulum but no significant liver injury. Liver test abnormalities often resolve with continued drug therapy.

TREATMENT

Treatment of drug- or toxin-related liver injury is mainly supportive. Contact with the offending agent should be avoided. Corticosteroids might have a role in immune-mediated disease. Treatment with *n*-acetylcysteine, by stimulating glutathione synthesis, is effective in preventing or attenuating hepatotoxicity when administered within 16 hours after an acute overdose of acetaminophen and appears to improve survival in patients with severe liver injury even up to 36 hours after ingestion. Intravenous L-carnitine may be of value in treating valproic acid–induced hepatotoxicity. Orthotopic liver transplantation may be required for treatment of drug- or toxin-induced hepatic failure.

PROGNOSIS

The prognosis of DILI depends on its type and severity. Injury is usually completely reversible when the hepatotoxic factor is withdrawn. The mortality of submassive hepatic necrosis with fulminant liver failure can, however, exceed 50%. Hyperbilirubinemia, coagulopathy, and elevated serum creatinine are associated with an increased risk of death or need for liver transplantation. With continued use of certain drugs, such as methotrexate, effects of hepatoxicity can proceed insidiously to cirrhosis, even with normal or near normal liver tests. Neoplasia can follow long-term androgen therapy. Rechallenge with a drug suspected of having caused previous liver injury is rarely justified and can result in fatal hepatic necrosis.

PREVENTION

The prevention of drug-induced liver injury remains a challenge. Monitoring of liver biochemical tests may be useful in some cases, but it can prove difficult to sustain for agents used for many years. Children who take medications with potential for hepatotoxicity, such as some anticonvulsants and antineoplastic drugs, require frequent monitoring for evidence of liver injury. Such testing may be particularly important in patients with preexisting liver disease. For drugs with hepatotoxic potential, even if episodes are infrequent in children, such as with the use of isoniazid, patients should be advised to immediately stop the medication with onset of nausea, vomiting, abdominal pain, and fatigue until liver damage is excluded. Obvious symptoms of liver disease, such as jaundice and dark urine, can lag behind severe hepatocellular injury. Monitoring for toxic metabolites and genotyping can be effective in preventing severe toxicity with the use of azathioprine. Advances in pharmacogenomics, such as the use of gene chips to detect variants in some of the CYP enzymes, hold promise of a personalized approach to prevent hepatotoxicity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 412

Acute Hepatic Failure

Frederick J. Suchy and Amy G. Feldman

Acute liver failure is a clinical syndrome associated with significant morbidity and mortality resulting from massive necrosis of hepatocytes or from severe functional impairment of hepatocytes. The synthetic, excretory, and detoxifying functions of the liver are all severely impaired. In adults, hepatic **encephalopathy** has been an essential diagnostic feature. However, in pediatrics, this narrow definition may be problematic because early hepatic encephalopathy can be difficult to detect in infants and children, and some children in acute liver failure may not develop encephalopathy (Table 412.1). The accepted definition in children includes biochemical evidence of acute liver injury (usually <8 weeks duration); no evidence of chronic liver disease; and hepatic-based coagulopathy defined as a prothrombin time (PT) >15 seconds or international normalized ratio (INR) >1.5 not corrected by vitamin K in the *presence* of clinical hepatic encephalopathy, or a PT >20 seconds or INR >2 *regardless* of the presence of clinical hepatic encephalopathy.

Liver failure in the perinatal period can be associated with prenatal liver injury and even cirrhosis. Examples include **gestational alloimmune liver disease** (GALD), tyrosinemia, familial **hemophagocytic lymphohistiocytosis** (HLH), and some cases of congenital viral (herpes simplex virus [HSV]) infection. Liver disease may be noticed at birth or after several days of apparent well-being. Fulminant **Wilson disease** and fulminant **autoimmune hepatitis** also occurs in older children who were previously asymptomatic but, by definition, have preexisting liver disease (Table 412.2). Other forms of acute-on-chronic liver failure can occur when a patient with an underlying liver disease such as biliary atresia develops hepatic decompensation after viral or **drug-induced hepatic injury**. In some cases of liver failure, particularly in the idiopathic form of acute hepatic failure, the onset of encephalopathy occurs later, from 8 to 28 weeks after the onset of jaundice.

ETIOLOGY

Infection

Acute hepatic failure can be a complication of **viral hepatitis** (A, B, D, and, rarely, E), Epstein-Barr virus (EBV), HSV, adenovirus, adeno-associated virus, enterovirus, influenza A, cytomegalovirus, parvovirus B19, human herpesvirus (HHV)-6, varicella zoster infection, parechovirus, coronavirus-2 (SARS-CoV-2) and other respiratory illnesses (see Table 412.2; see also Chapter 406). An unusually high rate of fulminant hepatic failure occurs in young people who have combined infections with the hepatitis B virus (HBV) and hepatitis D. Pathogenic gene variants in the precore and/or promoter region of HBV DNA are associated with fulminant and severe hepatitis. HBV is also responsible for some cases of fulminant liver failure in the absence of serologic markers of HBV infection but with HBV DNA found in the liver. Hepatitis E virus is an uncommon cause of fulminant hepatic failure in the United States but can occur in pregnant women, in whom mortality rates rise dramatically to up to 25%. Patients with chronic hepatitis C are at risk if they have superinfection with hepatitis A virus.

Autoimmune Hepatitis

Acute hepatic failure is caused by **autoimmune hepatitis** in approximately 5–28% of cases (see Chapter 410). Patients have a positive autoimmune marker (e.g., antinuclear antibody, anti–smooth muscle antibody, liver-kidney microsomal antibody, or soluble liver antigen) and possibly an elevated serum immunoglobulin G level. If a biopsy can be performed, liver histology often demonstrates interface hepatitis and a plasma cell infiltrate.

Metabolic Diseases

Metabolic disorders account for 28–36% of cases of pediatric acute liver failure and include galactosemia, tyrosinemia, hereditary fructose intolerance, Niemann-Pick type C, mitochondrial hepatopathies (in particular, mitochondrial DNA depletion disorders), urea cycle defects, defects in β-oxidation of fatty acids, and disorders of bile acid synthesis in infants and young children and **Wilson disease** and acute fatty liver of pregnancy in older children (see Table 412.2; see also Chapters 405.1 and 405.5). Family history of consanguinity, recurrent pregnancy loss, stillbirths, or death of children before the age of 1 and/or patient history of diarrhea, vomiting, failure to thrive, or developmental delay should alert one to the possibility of metabolic disease. Patients with Wilson disease who present in acute

Table 412.1 Hepatic Encephalopathy in Pediatric Acute Liver Failure

STAGE		CLINICAL	REFLEXES	NEUROLOGIC SIGNS	EEG CHANGES
0		None	Normal	None	Normal
I	Infant/child	Inconsolable, crying, inattention to task, parents describe child as "not acting like self"	Normal or hyperreflexia	Difficult or impossible to assess	Normal or diffuse slowing to theta rhythm, triphasic waves
	Adolescent/young adult	Confused, mood changes, altered sleep habits, forgetful	Normal	Tremor, apraxia, impaired handwriting	
II	Infant/child	Inconsolable, crying, inattention to task, parents describe child as "not acting like self"	Normal or hyperreflexia	Difficult or impossible to assess	Abnormal, generalized slowing, triphasic waves
	Adolescent/young adult	Drowsy, inappropriate behavior, decreased inhibitions	Hyperreflexia	Dysarthria, ataxia	
III	Infant/child	Somnolence, stupor, combativeness	Hyperreflexia	Difficult or impossible to assess	Abnormal, generalized slowing, triphasic waves
	Adolescent/young adult	Stuporous, obeys simple commands	Hyperreflexia, (+) Babinski	Rigidity	
IV	Infant/child	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate	Abnormal, very slow, delta activity
	Adolescent/young adult	Comatose, arouses with painful stimuli (IVa) or no response	Absent	Decerebrate or decorticate	

EEG, Electroencephalography.
Modified from Squires RH Jr. Acute liver failure in children. *Semin Liver Dis*. 2008;28(2):157–166. Table 1.

Table 412.2 Etiologies of Acute Liver Failure

DRUG-INDUCED LIVER INJURY
Acetaminophen
Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsone, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir, ketoconazole
Antiepileptics: valproic acid, phenytoin, carbamazepine
Antituberculosis drugs: isoniazid, rifampin-isoniazid, pyrazinamide
Antihypertensives: methyldopa, hydralazine, labetalol, nicotinic acid (slow release)
NSAIDs: diclofenac, ibuprofen, indomethacin, naproxen
Herbs and supplements: ma huang, kava kava, Herbalife, green tea extract, ginseng, black cohosh, anabolic steroids
Anesthetics: halothane
Miscellaneous: propylthiouracil, amitriptyline, statins, amiodarone, methotrexate
VIRAL HEPATITIS
Hepatitis A, B (±D), C, and E
Adenovirus, adeno-associated virus, CMV, EBV, herpes virus, parvovirus, varicella zoster virus
PREGNANCY-RELATED LIVER DISEASE
Acute fatty liver of pregnancy
HELLP syndrome
Preeclampsia-associated liver disease
Acute hepatic rupture
ISCHEMIC HEPATITIS
Systemic hypotension
Budd-Chiari syndrome
Hepatic artery thrombosis
Congestive hepatopathy
REVERSIBLE ETIOLOGIES
Autoimmune hepatitis
Leptospirosis, hepatic amoebiasis, malaria, rickettsial disease
GENETIC
Wilson disease
Galactosemia
Urea cycle defects
Hereditary fructose intolerance
Hemochromatosis
Mitochondrial disorders
α_1-Antitrypsin deficiency
Tyrosinemia
Pathogenic variants in *NBAS, DLD, CPT1A, FAH, LARS1, MPV17, NPC1, POLG, SUCLG1, TWINK, DGUOK, RINT1, SCYL1, ITCH*
MISCELLANEOUS
Malignancy
Mushroom poisoning
Heat injury
Reye syndrome
Hemophagocytic lymphohistiocytosis
Gestational alloimmune liver disease
Idiopathic

NSAID, Nonsteroidal antiinflammatory drug; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HELLP, hemolysis, elevated liver enzymes, low platelet count.
Modified from Montrief T, Koyfman A, Long B. Acute liver failure: a review for emergency physicians. *Am J Emerg Med.* 2019;37:329–337. Table 3.

liver failure often have high bilirubin levels, low alkaline phosphatase levels, low uric acid levels, aspartate aminotransferase levels that are higher than alanine aminotransferase levels, and a Coombs-negative hemolytic anemia.

Neoplasm

Acute liver failure can occur with malignancies, including leukemia, lymphoma, and **familial HLH**. Acute liver failure is a common feature of HLH caused by several gene defects, infections by mostly viruses of the herpes group, and a variety of other conditions, including organ transplantation and malignancies. Impaired function of natural killer cells and cytotoxic T-lymphocyte cells with uncontrolled hemophagocytosis and cytokine overproduction is characteristic for genetic and acquired forms of HLH. Patients with HLH present with a combination of fever, splenomegaly, cytopenias, high triglyceride levels, very high ferritin levels, low natural killer cell activity, and high soluble CD25 levels; they may also have hemophagocytosis on bone marrow or liver biopsy (see Chapter 556).

Gestational Alloimmune Liver Disease

GALD is the most common cause of acute liver failure in the neonate (see Chapter 405.4). In this alloimmune process, maternal immunoglobulin (Ig) G antibodies bind to fetal liver antigens and activate the terminal complement cascade, resulting in hepatocyte injury and death. Infants with GALD present at birth or within the first few days of life with low/normal aminotransferases that are out of proportion to their degree of liver failure. They may have significant hypoglycemia, jaundice, coagulopathy, and hypoalbuminemia. Alpha fetoprotein levels are typically high, as are serum ferritin levels. Extrahepatic iron deposition can be observed on MRI or buccal biopsy.

Drug-Induced Liver Injury

Various hepatotoxic drugs and chemicals can also cause drug-induced liver injury and acute hepatic failure (see Table 412.2; see also Chapter 411). Predictable liver injury can occur after exposure to carbon tetrachloride or *Amanita phalloides* mushrooms or after acetaminophen overdose. Acetaminophen is the most common identifiable etiology of acute hepatic failure in children and adolescents in the United States and England. In addition to the acute intentional ingestion of a massive dose, a therapeutic misadventure leading to severe liver injury can also occur in ill children given doses of acetaminophen exceeding weight-based recommendations for many days. Such patients can have reduced stores of glutathione after a prolonged illness and a period of poor nutrition. Idiosyncratic damage can follow the use of drugs such as halothane, isoniazid, ecstasy, or sodium valproate. Herbal and weight loss supplements are additional causes of hepatic failure (see Chapter 411). The website Liver Tox (https://www.ncbi.nlm.nih.gov/books/NBK547852/) is available to provide up-to-date information about liver injury attributable to medications, herbals, and dietary supplements.

Vascular

Ischemia and hypoxia resulting from hepatic vascular occlusion, severe heart failure, cyanotic congenital heart disease, or circulatory shock can produce liver failure. Venoocclusive disease (VOD) is a clinical process characterized by weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia resulting from hepatic sinusoidal obstruction, most commonly after hematopoietic stem cell transplant. Liver failure is uncommon with VOD but can occur.

Idiopathic Acute Liver Failure

Idiopathic acute liver failure accounts for 40–50% of acute hepatic failure cases in children. The disease occurs sporadically and usually without the risk factors for common causes of viral hepatitis. It is likely that the etiology of these cases is heterogeneous, including unidentified or variant viruses, excessive immune activation, and undiagnosed genetic or metabolic disorders. There is increasing recognition of some children presenting with indeterminate acute hepatitis or acute liver failure who have evidence of immune activation, including markedly elevated soluble interleukin 2 receptor (sIL-2R) levels but never fulfilling diagnostic criteria for HLH.

Other

There is a growing category of autosomal recessive disorders including pathogenic variants in the neuroblastoma amplified sequence gene *NBAS*, *LARS*, *SCYL1*, and *RINT1* that can result in recurrent episodes of pediatric acute liver failure, sometimes associated with concurrent fevers (see Table 412.2). Patients with *NBAS* variants may also have short stature, skeletal abnormalities, intellectual disability, ophthalmic and facial abnormalities, cardiac abnormalities, and low serum

immunoglobulins. Patients with *SCYL1* variants may have low gamma-glutamyl transpeptidase (GGT), cholestasis, and a variable neurologic phenotype. Patients with *RINT1* variants may have persistently abnormal liver function tests (LFTs) between acute liver failure episodes. Most patients recovered with restoration of normal liver function after control of fever and maintenance of energy balance with the infusion of intravenous glucose.

PATHOLOGY

Liver biopsy usually reveals patchy or confluent massive necrosis of hepatocytes. Multilobular or bridging necrosis can be associated with collapse of the reticulin framework of the liver. There may be little or no regeneration of hepatocytes. A zonal pattern of necrosis may be observed with certain insults. Centrilobular damage is associated with acetaminophen hepatotoxicity or with circulatory shock. Evidence of severe hepatocyte dysfunction rather than cell necrosis is occasionally the predominant histologic finding (microvesicular fatty infiltrate of hepatocytes is observed in Reye syndrome, β-oxidation defects, and tetracycline toxicity).

PATHOGENESIS

It is unknown why only approximately 1–2% of patients with viral hepatitis experience liver failure. Massive destruction of hepatocytes might represent both a direct cytotoxic effect of the virus and an immune response to the viral antigens. Of patients with HBV-induced liver failure, 30–50% become negative for serum hepatitis B surface antigen within a few days of presentation and often have no detectable HBV antigen or HBV DNA in serum. These findings suggest a hyperimmune response to the virus that underlies the massive liver necrosis. Formation of hepatotoxic metabolites that bind covalently to macromolecular cell constituents is involved in the liver injury produced by drugs such as acetaminophen and isoniazid; acute hepatic failure can follow depletion of intracellular substrates involved in detoxification, particularly glutathione. Whatever the initial cause of hepatocyte injury, various factors can contribute to the pathogenesis of liver failure, including impaired hepatocyte regeneration, altered parenchymal perfusion, endotoxemia, and decreased hepatic reticuloendothelial function.

CLINICAL MANIFESTATIONS

Acute hepatic failure can be the presenting feature of liver disease, or it can complicate previously known liver disease **(acute-on-chronic liver failure)**. Progressive jaundice, fetor hepaticus, fever, anorexia, vomiting, and abdominal pain are common. A rapid decrease in liver size without clinical improvement is an ominous sign. A hemorrhagic diathesis and ascites can develop. In addition, acute liver failure is a multisystem disorder (Fig. 412.1).

Patients should be closely observed for hepatic encephalopathy, which is initially characterized by minor disturbances of consciousness or motor function. Irritability, poor feeding, and a change in sleep rhythm may be the only findings in infants; asterixis may be demonstrable in older children. Patients are often somnolent, confused, or combative on arousal and can eventually become responsive only to painful stimuli. Patients can rapidly progress to deeper stages of coma in which extensor responses and decerebrate and decorticate posturing appear. Respirations are usually increased early, but respiratory failure can occur in stage IV coma (see Table 412.1). The pathogenesis of hepatic encephalopathy is likely related to increased serum levels of ammonia, false neurotransmitters, amines, increased γ-aminobutyric acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like compounds. Decreased hepatic clearance of these substances can produce marked central nervous system dysfunction. The mechanisms responsible for cerebral edema and intracranial hypertension in acute liver failure suggest both cytotoxic and vasogenic injury (Fig. 412.2). There is increasing evidence for an inflammatory response (synthesis and release of inflammatory factors from activated microglia and endothelial cells), which acts in synergy with hyperammonemia to cause severe astrocyte swelling/brain edema.

LABORATORY FINDINGS

Serum direct and indirect bilirubin levels and serum aminotransferase activities may be markedly elevated. Serum aminotransferase activities do not correlate well with the severity of the illness and can decrease as a patient deteriorates. The blood ammonia concentration is usually increased, but hepatic coma can occur in patients with a normal blood ammonia level. PT and the INR are prolonged and do not improve after parenteral administration of vitamin K. Hypoglycemia can occur,

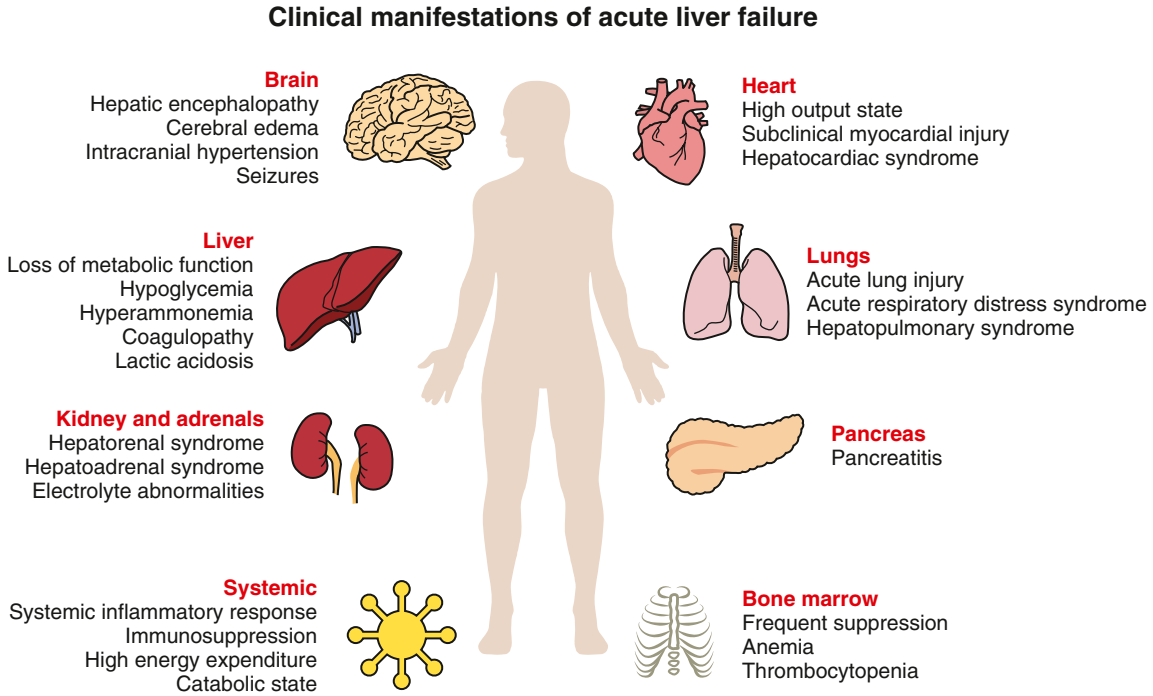

Fig. 412.1 Clinical manifestations of acute liver. *(From Montrief T, Koyfman A, Long B. Acute liver failure: a review for emergency physicians. Am J Emerg Med. 2019;37:329–337. Fig.1.)*

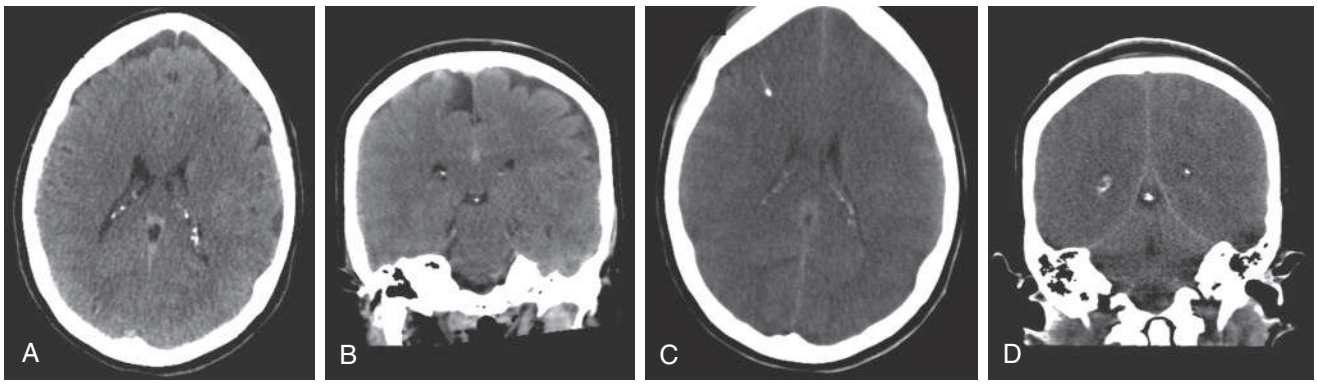

Fig. 412.2 CT of the head in a patient with acute liver failure (ALF) who developed cerebral edema. **A,** Axial scan before the development of cerebral edema. **B,** Coronal scan before the development of cerebral edema. **C,** Axial scan after the development of cerebral edema. **D,** Coronal scan after development of cerebral edema. All in a dying patient with brainstem herniation because of acetaminophen-induced ALF. **C** and **D** show the loss of gray–white demarcation and effacement of sulci. *(From Stravitz RT, Lee WM. Acute liver failure. Lancet. 2019;394:869–880. Fig. 3.)*

Table 412.3 Investigations in Acute Liver Failure

SERUM CHEMISTRIES Basic metabolic panel: sodium, potassium, bicarbonate, calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine Amylase, lipase Serum lactate	**VIRAL HEPATITIS SEROLOGIES** Anti-HAV IgM Hep B surface Ag, anti-hep B core Ab IgM Hep D Ab, hep D RNA Anti-HCV, ±hepatitis C RNA PCR ±Anti-HEV IgM Anti-VZV IgM Anti-HSV IgM
HEPATIC PANEL AST, ALT, albumin, total bilirubin, alkaline phosphatase	**AUTOIMMUNE MARKERS** Antinuclear antibody Anti–smooth muscle antibody Serum IgG levels
ARTERIAL BLOOD Blood gas Serum ammonia	**URINE** Pregnancy test Urinalysis and urine culture Toxicology
TOXICOLOGIC Blood alcohol level Acetaminophen level Urine toxicology screen Serum salicylate level	**MISCELLANEOUS** Serum ceruloplasmin Blood cultures Electrocardiogram Exome sequencing Mitochondrial DNA Specific gene panels
HEMATOLOGIC Complete blood count Blood type and screen Coagulation studies: PT/INR, fibrinogen, PTT, TEG, D-dimer	**IMAGING** CT brain scan without contrast Abdominal US Chest x-ray Echocardiogram Transcranial Doppler

PT, Prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; TEG, thromboelastography.
Modified from Montrief T, Koyfman A, Long B. Acute liver failure: a review for emergency physicians. *Am J Emerg Med.* 2019;37:329–337. Table 4.

Table 412.4 Potential Disease-Directed Therapies in Pediatric Acute Liver Failure

	THERAPY
Acetominophen toxicity	*N*-acetylcysteine
Drug-induced liver injury	Cessation of offending agent; consider steroids
Neonatal acute liver failure secondary to gestational alloimmune disease	Exchange transfusion and immunoglobulin
Autoimmune liver disease	Steroids
Vascular etiologies (e.g., Budd-Chiari syndrome and sinusoidal obstruction syndrome)	Anticoagulation and hepatic decompression (usually with a transhepatic portosystemic shunt)
Wilson disease	Copper chelation
Herpes simplex virus	Acyclovir
Adenovirus	Cidofovir
Hepatitis A	No specific treatment
Hepatitis B	Lamivudine, entecavir, tenofovir
Hepatitis E	Ribavirin, α-interferon
Galactosemia	Lactose-free diet
Hereditary fructose intolerance	Fructose-free, sucrose-free, and sorbitol-free diet
Tyrosinemia	2-(2-nitro-4-trifluoromethylbenzoyl)-1,3- cyclohexanedione in addition to a diet restricted in tyrosine and phenylalanine
Urea cycle defects	Protein restriction, ammonia scavengers; renal replacement therapy might be required

Modified from Deep A, Alexander EC, Bulut Y, et al. Advances in medical management of acute liver failure in children: promoting native liver survival. *Lancet Child Adolesc.* 2022;6:725–737.

particularly in infants. Hypokalemia, hyponatremia, metabolic acidosis, or respiratory alkalosis can also develop. Laboratory studies are important to monitor the course of liver failure, to detect complications, and to better define the etiology (Table 412.3).

TREATMENT

Specific therapies for identifiable causes of acute liver failure include *N*-acetylcysteine (acetaminophen), acyclovir (HSV), penicillin (*Amanita* mushrooms), nucleos(t)ide analogs such as entecavir (HBV), and prednisone (autoimmune hepatitis) (Table 412.4). Immunosuppression with corticosteroids should also be considered in children with the indeterminate form of fulminant hepatic failure with immune activation to avoid progression to liver transplantation or death. However, controlled trials have shown a worse outcome in patients treated with corticosteroids in patients without an immune basis for liver injury. Treatment of GALD involves intravenous immunoglobulin (IVIG)

(1 g/kg) followed by a combination of double-volume exchange transfusion to remove existing reactive antibody and a second dose of IVIG (1 g/kg) to block antibody-induced complement activation.

Management of other types of acute hepatic failure is supportive. No therapy is known to reverse hepatocyte injury or to promote hepatic regeneration (Fig. 412.3). Continuous kidney replacement therapy and extracorporeal liver support have been used as potential bridging therapies pending native liver recovery or liver transplantation.

An infant or child with acute hepatic failure should be cared for in an institution able to perform a liver transplantation if necessary and managed in an intensive care unit (ICU) with continuous monitoring of vital functions. Endotracheal intubation may be required to prevent aspiration, to reduce cerebral edema by hyperventilation, and to facilitate pulmonary toilet. Mechanical ventilation and supplemental oxygen are often necessary in advanced coma. Sedatives should be avoided unless needed in the intubated patient because these agents can aggravate or precipitate encephalopathy. Opiates may be better tolerated than benzodiazepines. Prophylactic use of proton pump inhibitors should be considered because of the high risk of gastrointestinal bleeding.

Hypovolemia should be avoided and treated with cautious infusions of *isotonic* fluids and blood products. Renal dysfunction can result from dehydration, acute kidney injury, or functional renal failure **(hepatorenal syndrome)**. Electrolyte and glucose solutions should be administered intravenously to maintain urine output, to correct or prevent hypoglycemia, and to maintain normal serum potassium concentrations. In a cardiovascularly stable patient, fluids should be kept around 90% of maintenance. Hyponatremia is common and should be avoided; it is usually dilutional and not a result of sodium depletion. Parenteral supplementation with calcium, phosphorus, and magnesium may be required. Hypophosphatemia, probably a reflection of liver regeneration, and early phosphorus administration are associated with a better prognosis in acute liver failure, whereas hyperphosphatemia predicts a failure of spontaneous recovery. Coagulopathy should be treated with parenteral administration of vitamin K. Fresh-frozen plasma, cryoprecipitate, platelets, activated factor VII, or prothrombin complex concentrates can be used to treat clinically significant bleeding or can be given if an invasive procedure such as placement of a central line or an intracranial monitor needs to be performed. Plasmapheresis can permit temporary correction of the bleeding diathesis without resulting in volume overload. Continuous hemofiltration is useful for managing fluid overload, acute renal failure, and hyperammonemia.

Patients should be monitored closely for infection, including sepsis, pneumonia, peritonitis, and urinary tract infections. At least 50% of patients experience serious infection. Gram-positive organisms *(Staphylococcus aureus, Staphylococcus epidermidis)* are the most common pathogens, but gram-negative and fungal infections are also observed.

Gastrointestinal hemorrhage, infection, constipation, sedatives, electrolyte imbalance, and hypovolemia can precipitate encephalopathy and should be identified and corrected. Protein intake should be restricted to 1 g/kg, depending on the degree of encephalopathy. If encephalopathy or hyperammonemia develops, lactulose or rifaximin can be administered. *N*-acetylcysteine is not effective in improving the outcome of patients with acute liver failure not associated with acetaminophen.

Cerebral edema is an extremely serious complication of hepatic encephalopathy that responds poorly to measures such as corticosteroid

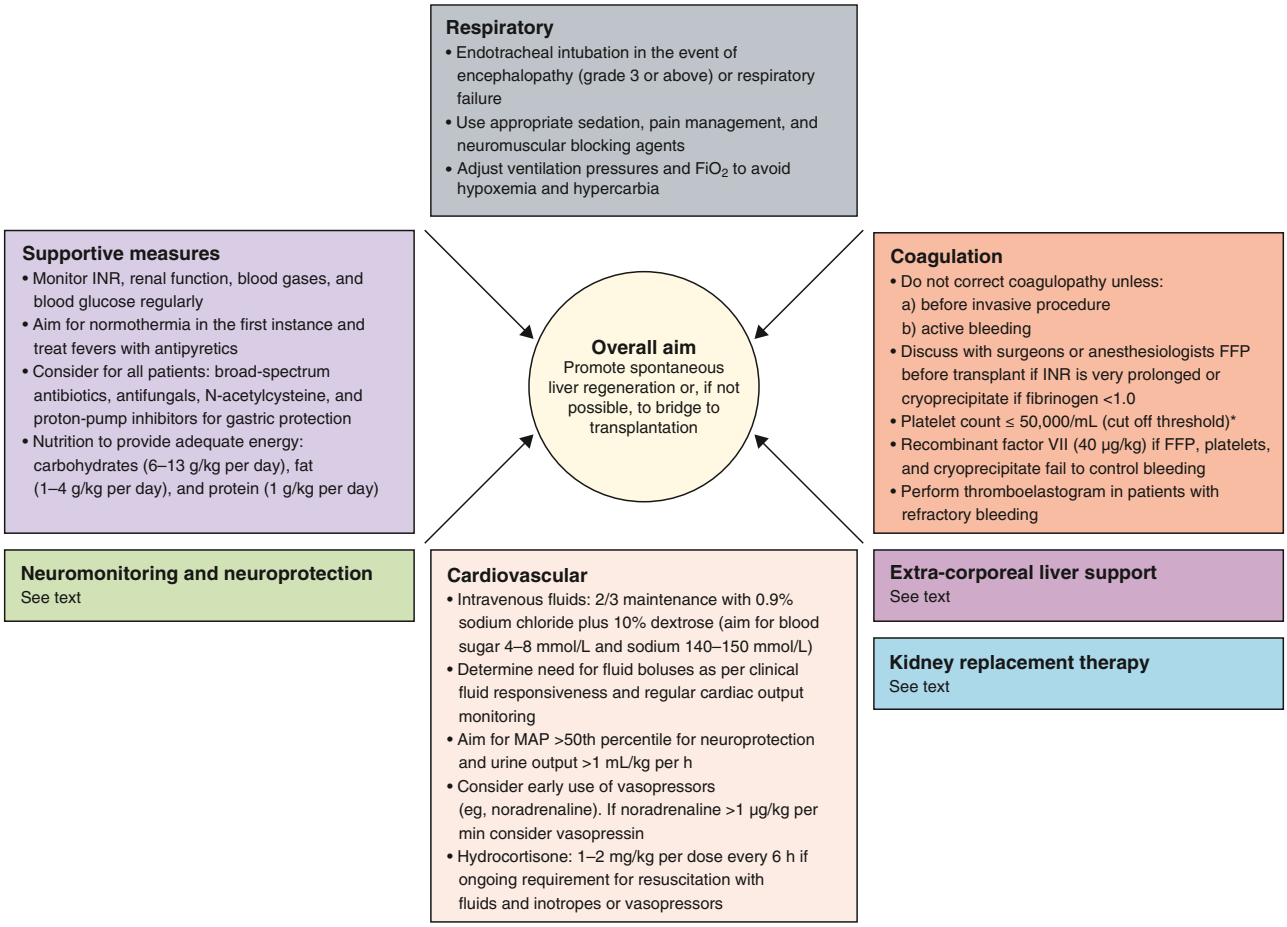

Fig. 412.3 Nontransplant management for pediatric acute liver failure. FFP, Fresh-frozen plasma; FiO_2, fractional concentration of oxygen in inspired air; INR, international normalized ratio; MAP, mean arterial pressures. *Platelet counts of ≤50,000 is controversial. *(Modified from Deep A, Alexander EC, Bulut Y, et al. Non-transplant management for paediatric acute liver failure. Advances in medical management of acute liver failure in children: promoting native liver survival. Lancet Child Adolesc. 2022;6:725–737. Fig. 2.)*

administration and osmotic diuresis. Monitoring intracranial pressure can be useful in preventing severe cerebral edema, maintaining cerebral perfusion pressure, and establishing the suitability of a patient for liver transplantation.

Temporary liver support continues to be evaluated as a bridge for the patient with liver failure to liver transplantation or regeneration. Nonbiologic systems, essentially a form of liver dialysis with an albumin-containing dialysate, and biologic liver support devices that involve perfusion of the patient's blood through a cartridge containing liver cell lines or porcine hepatocytes can remove some toxins, improve serum biochemical abnormalities, and, in some cases, improve neurologic function, but there has been little evidence of improved survival, and few children have been treated.

Orthotopic liver transplantation can be lifesaving in patients who reach advanced stages (III, IV) of hepatic coma. Various predictive tests suggest a poor prognosis and need for liver transplantation (Table 412.5). Reduced-size allografts and living donor transplantation have been important advances in the treatment of infants with hepatic failure. Partial auxiliary orthotopic or heterotopic liver transplantation is successful in a small number of children, and, in some cases, it has allowed regeneration of the native liver and eventual withdrawal of immunosuppression. Orthotopic liver transplantation should not be done in patients with liver failure and neuromuscular dysfunction secondary to a mitochondrial disorder because progressive neurologic deterioration is likely to continue after transplantation.

PROGNOSIS

Children with acute hepatic failure fare better than adults. Improved survival can be attributed to careful intensive care and if necessary, liver transplantation. In the largest prospective study from the Pediatric Acute Liver Failure Study Group, 709 children were assessed at 21 days: 50.3% of patients survived with supportive care alone, 36.2% survived after liver transplantation, and 13.4% died. Prognosis varies considerably with the cause of liver failure and stage of hepatic encephalopathy. Survival rates with supportive care may be as high as 90% in acetaminophen overdose and with fulminant hepatitis A. By contrast, spontaneous recovery can be expected in only approximately 40% of patients with liver failure caused by the idiopathic (indeterminate) form of acute liver failure or an acute onset of Wilson disease. Prognosis is also poor for spontaneous recovery in patients with mitochondrial deficits, hemophagocytic syndromes, herpes simplex disease, and idiosyncratic drug reactions. In patients who progress to stage IV coma (see Table 412.1), the prognosis is extremely poor. Brain stem herniation is the most common cause of death. Major complications such as sepsis, severe hemorrhage, or renal failure increase the mortality. The prognosis is particularly poor in patients with liver necrosis and multiorgan failure. Age <1 year, stage IV encephalopathy, an INR >4, PT >90 seconds, low factor V levels, and the need for dialysis before transplantation are associated with increased mortality. Pre-transplantation serum bilirubin concentration or the height of hepatic enzymes is *not* predictive of posttransplantation survival. A plasma ammonia concentration >200 μmol/L is associated with a fivefold increased risk of death. Children with acute hepatic failure are more likely to die while on the waiting list compared with children with other liver transplant–requiring diagnoses. Because of the severity of their illness, the 6-month post–liver transplantation survival of approximately 75% for acute liver failure is significantly lower than the 90% achieved in children with chronic liver disease. Patients who recover from fulminant hepatic failure with only supportive care do not usually develop cirrhosis or chronic liver disease. Aplastic anemia occurs in approximately 10% of children with the idiopathic form of fulminant hepatic failure and is often fatal without bone marrow transplantation. Long-term survivors demonstrate average IQ and visual spatial ability but greater than expected impairments in motor skills, attention, executive function, and health-related quality of life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 412.5 Tests and Indices for Predicting Mortality and Need for Liver Transplantation in Patients with Acute Liver Failure

	CAUSE OF ACUTE LIVER FAILURE	THRESHOLD FOR POOR PROGNOSIS OR NEED FOR LIVER TRANSPLANTATION
King's College Criteria	Acetominophen	Arterial pH <7.30 or all of the following: prothrombin time >100 s (international normalized ratio >6.5), creatinine >3.4 mg/dL, and grade 3 or 4 encephalopathy
King's College Criteria	Non-acetominophen	Prothrombin time >100 s (international normalized ratio >6.5) or any three of the following: non-A, non-B viral hepatitis, or drug or halothane cause; jaundice to encephalopathy >7 days; age between 10 and 40 years; prothrombin time >50 s; bilirubin >17.4 mg/dL
Factor V (Clichy criteria)	Viral	Age <30 years with clotting factor V <20% or any age with clotting factor V <30% and grade 3 or 4 encephalopathy
Liver biopsy	Mixed causes	Hepatocyte necrosis >70%
Arterial phosphate	Acetominophen	>1.2 mmol/L
Serum lactate	Acetominophen	>3.5 mmol/L
APACHE II score	Acetominophen	Score >15
MELD score	Acetominophen	Score >33
BiLE score	Mixed causes	Score >6.9
Volumetric CT	Non-acetominophen	Liver volume <1000 cm^3
ALFSG Prognostic Index*	Mixed causes	Continuous

*The ALFSG Prognostic Index, in contrast to the other indices listed, is designed to predict transplant-free survival rather than death or need for liver transplantation.
MELD, Model for end-stage liver disease; BiLE, bilirubin, lactate, and etiology score; ALFSG, Acute Liver Failure Study Group.
From Stravitz RT, Lee WM. Acute liver failure. *Lancet*. 2019;394:869–880. Table 2.

Chapter 413

Cystic Diseases of the Biliary Tract and Liver

Frederick J. Suchy and Amy G. Feldman

Cystic lesions of liver may be initially recognized during infancy and childhood. Hepatic fibrosis can also occur as part of an associated developmental defect (Table 413.1). Cystic *renal* disease is usually associated and often determines the clinical presentation and prognosis. Virtually all proteins encoded by genes mutated in combined cystic diseases of the liver and kidney are at least partially localized to primary cilia in renal tubular cells and cholangiocytes.

A solitary, congenital **liver cyst** (nonparasitic) can occur in childhood and has been identified in some cases on prenatal ultrasound. Abdominal distention and pain may be present, and a poorly defined right-upper-quadrant mass may be palpable. These benign lesions are best left undisturbed unless they compress adjacent structures or a complication occurs, such as hemorrhage into the cyst. Operative management is generally reserved for symptomatic patients and enlarging cysts.

Table 413.1 Syndromes Associated with Congenital Hepatic Fibrosis

DISORDER	ASSOCIATED FEATURES
Autosomal recessive polycystic kidney disease	Ductal plate malformation, Caroli syndrome
Autosomal dominant polycystic kidney disease	Ductal plate malformation, Caroli syndrome
Autosomal dominant polycystic liver disease	Rarely, congestive heart failure
Jeune syndrome	Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia, Caroli syndrome
Joubert syndrome	Central nervous system defects, cardiac malformations
COACH syndrome	Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, hepatic fibrosis
Meckel-Gruber syndrome	Cystic renal dysplasia, abnormal bile duct development with fibrosis, posterior encephalocele, polydactyly
Carbohydrate-deficient glycoprotein syndrome type 1b	Phosphomannose isomerase 1 deficiency chronic diarrhea, protein-losing enteropathy
Ivemark syndrome type 2	Autosomal-recessive renal-hepatic-pancreatic dysplasia
Nephronophthisis type 3	Tapetoretinal degeneration
Bardet-Biedl syndrome	Retinal degeneration, obesity, limb deformities, hypogonadism
Oral-facial-digital syndrome type 1	Oral clefts, hamartomas or cysts of the tongue, digital anomalies pancreatic cysts
Miscellaneous syndromes	Intestinal lymphangiectasia, enterocolitis, cystic short rib (Beemer-Langer) syndrome, osteochondrodysplasia

Adapted from Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children,* 3rd ed. New York: Cambridge University Press; 2014: p. 713.

CHOLEDOCHAL MALFORMATIONS

Choledochal malformations (previously known as **choledochal cysts**) are congenital dilatations of the common bile duct that can cause progressive biliary obstruction and biliary cirrhosis. Cylindrical (fusiform) and spherical (saccular) dilatations of the extrahepatic ducts are the most common types (see Table 413.1). Choledochal malformations are classified according to the Todani method (see Fig. 404.5). **Type I** choledochal malformations, the most common variant, involve a saccular or fusiform dilation of the common bile duct. **Type II** malformations are congenital diverticula protruding from the common bile duct. **Type III** malformations, or choledochoceles, involve a herniation of the intraduodenal segment of the common bile duct into the duodenum. **Type IVa** malformations, or **Caroli disease**, involve multiple intrahepatic and extrahepatic cysts. **Type IVb** malformations involve only the extrahepatic duct. Solitary liver cysts **(type V)** are very rare.

The pathogenesis of choledochal malformations remains uncertain. Some reports suggest that junction of the common bile duct and the pancreatic duct before their entry into the sphincter of Oddi might allow reflux of pancreatic enzymes into the common bile duct, causing inflammation, localized weakness, and dilation of the duct. It has also been proposed that a distal congenital stenotic segment of the biliary tree leads to increased intraluminal pressure and proximal biliary dilation.

Approximately 75% of cases appear during childhood. The infant typically presents with cholestatic jaundice; severe liver dysfunction including ascites and coagulopathy can rapidly evolve if biliary obstruction is not relieved. An abdominal mass is rarely palpable. In an older child, the classic triad of abdominal pain, jaundice, and mass occurs in <33% of patients.

Features of acute cholangitis (fever, right-upper-quadrant tenderness, jaundice, and leukocytosis) may be present. The diagnosis is made by ultrasonography; choledochal malformations have been identified prenatally using this technique. Magnetic resonance cholangiography is useful in the preoperative assessment of choledochal malformations anatomy.

Because of bile stasis and inflammation, choledochal malformations have the potential to develop into cholangiocarcinoma; therefore the treatment of choice is primary excision of the abnormal biliary segment and a Roux-en-Y choledochojejunostomy. The postoperative course can be complicated by recurrent cholangitis or stricture at the anastomotic site. Long-term follow-up is necessary to ensure that no malignancy develops.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) manifests predominantly in childhood (see Chapter 563.2). Bilateral enlargement of the kidneys is caused by a generalized dilation of the collecting tubules. The disorder is invariably associated with **congenital hepatic fibrosis** and various degrees of biliary ductal ectasia, discussed in detail later. Approximately 40% of patients have nonobstructive intrahepatic ductal dilatation **(Caroli disease)**.

The polycystic kidney and hepatic disease 1 *(PKHD1)* gene, altered in ARPKD, encodes a protein that is called fibrocystin, which is localized to cilia on the apical domain of renal collecting cells and cholangiocytes. The primary defect in ARPKD may be ciliary dysfunction related to the abnormality in this protein. Fibrocystin appears to have a role in the regulation of cellular adhesion, repulsion, and proliferation and/or the regulation and maintenance of renal collecting tubules and bile ducts, but its exact role in normal and cystic epithelia remains unknown.

Kidney and liver disease are independent and variable in severity; they are not readily explainable by the type of *PKHD1* pathogenic variants. Approximately 750 *PKHD1* pathogenic variants have been identified, of which approximately half are missense changes. Phenotypic variability among affected siblings suggests the importance of modifier genes as well as possibly environmental influences.

In ARPKD, the cysts arise as ectatic expansions of the collecting tubules and bile ducts, which remain in continuity with their structures of origin. ARPKD normally presents in early life, often shortly after birth, and is generally more severe than autosomal dominant polycystic kidney disease (ADPKD). Fetal ultrasound may visualize large echogenic kidneys, also described as bright, with low or absent amniotic fluid (oligohydramnios). However, in many instances, the features of ARPKD are not visualized on sonography until the third trimester or after birth.

Patients with ARPKD can die in the perinatal period from renal failure or lung dysgenesis. The kidneys in these patients are usually markedly enlarged and dysfunctional. Respiratory failure can result from compression of the chest by grossly enlarged kidneys, from fluid retention, or from concomitant pulmonary hypoplasia. The clinical pathologic findings within a family tend to breed true, although there has been some variability in the severity of the disease and the time for presentation within the same family. In patients surviving infancy because of a milder renal phenotype, liver disease may be a prominent part of the disorder. The liver disease in ARPKD is related to congenital malformation of the liver with varying degrees of periportal fibrosis, bile ductular hyperplasia, ectasia, and dysgenesis. Initial symptoms are liver related in approximately 26% of patients. This can manifest clinically as variable cystic dilation of the intrahepatic biliary tree with congenital hepatic fibrosis. Congenital hepatic fibrosis and Caroli disease likely result from an abnormality in remodeling of the embryonic ductal plate of the liver. **Ductal plate malformation** refers to the persistence of excess embryonic bile duct structures in the portal tracts. The synthetic function of the liver remained largely intact even in patients with advanced portal hypertension. ARPKD patients with recurrent cholangitis or complications of portal hypertension may require combined liver-kidney transplant.

Cystic Dilation of the Intrahepatic Bile Ducts (Caroli Disease/Caroli Syndrome)

In Caroli disease, there is isolated ectasia or nonobstructing segmental dilatation of the larger intrahepatic ducts. Caroli syndrome is the more common variant, in which malformations of small bile ducts are associated with congenital hepatic fibrosis. Congenital saccular dilation can affect several segments of the intrahepatic bile ducts; the dilated ducts are lined by cuboidal epithelium and are in continuity with the main duct system, which is usually normal. Choledochal malformations have also been associated with Caroli disease. Bile duct dilation leads to stagnation of bile and formation of biliary sludge and intraductal lithiasis. There is a marked predisposition to ascending cholangitis, which may be exacerbated by calculus formation within the abnormal bile ducts.

Affected patients usually experience symptoms of acute cholangitis as children or young adults. Fever, abdominal pain, mild jaundice, and pruritus occur, and a slightly enlarged, tender liver is palpable. Elevated alkaline phosphatase activity, direct-reacting bilirubin levels, and leukocytosis may be observed during episodes of acute infection. In patients with Caroli disease, clinical features may be the result of a combination of recurring episodes of cholangitis, reflecting the intrahepatic ductal abnormalities and portal hypertensive bleeding resulting from hepatic fibrosis. Ultrasonography shows the dilated intrahepatic ducts, but definitive diagnosis and extent of disease must be determined by percutaneous transhepatic, endoscopic, or magnetic resonance cholangiography.

Cholangitis and sepsis should be treated with appropriate antibiotics. Calculi can require surgery. Partial hepatectomy may be curative in rare cases in which cystic disease is confined to a single lobe. The prognosis is otherwise guarded, largely because of difficulties in controlling cholangitis and biliary lithiasis and because of a significant risk for developing cholangiocarcinoma.

Congenital Hepatic Fibrosis

Congenital hepatic fibrosis is usually associated with ARPKD and is characterized pathologically by diffuse periportal and perilobular fibrosis in broad bands that contain distorted bile duct–like structures and that often compress or incorporate central or sublobular veins (see Table 413.1). Irregularly shaped islands of liver parenchyma contain normal-appearing hepatocytes. Caroli disease and choledochal malformations may be associated. Most patients have renal disease, mostly ARPKD and rarely nephronophthisis. Congenital hepatic fibrosis also occurs as part of the **COACH syndrome** (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis). Congenital hepatic fibrosis has been described in children with a congenital disorder of glycosylation caused by mutations in the gene encoding phosphomannose isomerase (see Chapter 107.7).

Several different forms of congenital hepatic fibrosis have been defined clinically: portal hypertensive (most common) cholangitic, mixed, and latent. The disorder usually has its onset in childhood, with hepatosplenomegaly or with bleeding secondary to portal hypertension. In a recent study, splenomegaly, as a marker for portal hypertension, developed early in life and was present in 60% of children younger than 5 years of age.

Cholangitis can occur in these patients because they have abnormal biliary tracts even without Caroli disease. Hepatocellular function is usually well preserved. Serum aminotransferase activities and bilirubin levels are usually normal in the absence of cholangitis and choledocholithiasis; serum alkaline phosphatase activity may be slightly elevated. The serum albumin level and prothrombin time are normal. Liver biopsy is rarely required for diagnosis, particularly in patients with obvious renal disease.

Treatment of this disorder should focus on control of bleeding from esophageal varices and aggressive antibiotic treatment of cholangitis. Infrequent mild bleeding episodes may be managed by endoscopic sclerotherapy or band ligation of the varices. After more severe hemorrhage, portacaval anastomosis can relieve portal hypertension. The prognosis may be greatly improved by a shunting procedure, but survival in some patients may be limited by renal failure.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD (see Chapter 563.3), the most commonly inherited cystic kidney disease, affects 1 in 1,000 live births. It is characterized by progressive renal cyst development and cyst enlargement and an array of extrarenal manifestations. There is a high degree of intrafamilial and interfamilial variability in the clinical expression of the disease. The prevalence of hepatic cysts in children with ADPKD is <5%, with no reports of severe cases. However, hepatic cysts increase in number and size with age with prevalence in patients ages 15-24 years on MRI close to 60%.

ADPKD is caused by pathogenic variants in one of two genes, *PKD1* or *PKD2*, which account for 85–90% and 10–15% of cases, respectively. The proteins encoded by these genes, polycystin-1 and polycystin-2, are expressed in renal tubule cells and in cholangiocytes. Polycystin-1 functions as a mechanosensor in cilia, detecting the movement of fluid through tubules and transmitting the signal through polycystin-2, which acts as a calcium channel.

Dilated noncommunicating cysts are most commonly observed. Other hepatic lesions are rarely associated with ADPKD, including the **ductal plate malformation, congenital hepatic fibrosis**, and **biliary microhamartomas** (the von Meyenburg complexes). Approximately 50% of patients with renal failure have demonstrable hepatic cysts that are derived from the biliary tract but not in continuity with it. The hepatic cysts increase with age. In one study, the prevalence of hepatic cysts was 58% in patients 15-24 years old. Hepatic cystogenesis appears to be influenced by estrogens. Although the frequency of cysts is similar in males and females, the development of large hepatic cysts is mainly a complication in females. Hepatic cysts are often asymptomatic but can cause pain and are occasionally complicated by hemorrhage, infection, jaundice from bile duct compression, portal hypertension with variceal bleeding, or hepatic venous outflow obstruction from mechanical compression of hepatic veins, resulting in tender hepatomegaly and exudative ascites. Cholangiocarcinoma can occur. Subarachnoid hemorrhage can result from the associated cerebral arterial aneurysms.

Selected patients with severe symptomatic polycystic liver disease and favorable anatomy benefit from liver resection or fenestration. Combined liver-kidney transplantation may be required. There is considerable evidence for a role of cyclic adenosine monophosphate in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. Several clinical trials in adults have shown that somatostatin analogs can blunt hepatic cyst expansion by blocking secretin-induced cyclic adenosine monophosphate generation and fluid secretion by cholangiocytes. Surgical or pharmacologic therapies for hepatic cysts are not likely to be required in childhood.

AUTOSOMAL DOMINANT POLYCYSTIC LIVER DISEASE

Autosomal dominant polycystic *liver* disease is a distinct clinical and genetic identity in which multiple cysts develop and are unassociated with cystic kidney disease. Liver cysts arise from but are not in continuity with the biliary tract. Females are more commonly affected than males, and the cysts often enlarge during pregnancy. Cysts are rarely identified in children. Cyst complications are related to effects of local compression, infection, hemorrhage, or rupture. The genes associated with autosomal dominant polycystic liver disease are *PRKCSH* and *SEC63*, which encode hepatocystin and Sec63, respectively. Hepatocystin is a protein kinase C substrate adK-H, which is involved in the proper folding and maturation of glycoproteins. It has been localized to the endoplasmic reticulum. *SEC63* encodes the protein SEC63P, which is a component of the protein translocation machinery in the endoplasmic reticulum.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 414

Diseases of the Gallbladder

Frederick J. Suchy and Amy G. Feldman

The incidence of gallbladder disease, particularly cholelithiasis and biliary dyskinesia, has been increasing in children and has been associated with a rise in the number of cholecystectomies.

ANOMALIES

The gallbladder is congenitally absent in approximately 0.1% of the population. Hypoplasia or absence of the gallbladder can be associated with extrahepatic biliary atresia or cystic fibrosis. Duplication of the gallbladder occurs rarely. Gallbladder ectopia may occur with a transverse, intrahepatic, left-sided, or retroplaced location. Multiseptate gallbladder, characterized by the presence of multiple septa dividing the gallbladder lumen, is another rare congenital anomaly of the gallbladder.

ACUTE HYDROPS

Table 414.1 lists the conditions associated with hydrops of the gallbladder.

Acute noncalculous, noninflammatory distention of the gallbladder can occur in infants and children. It is defined by the absence of calculi, bacterial infection, or congenital anomalies of the biliary system. The disorder may complicate acute infections and Kawasaki disease, but the cause is often not identified. Hydrops of the gallbladder may also develop in patients receiving long-term parenteral nutrition, presumably because of gallbladder stasis during the period of enteral fasting. Hydrops is distinguished from acalculous cholecystitis by the absence of a significant inflammatory process and is a generally benign prognosis.

Table 414.1 Conditions Associated with Hydrops of the Gallbladder

Cholelithiasis
Cholecystitis
Kawasaki disease
Streptococcal pharyngitis
Staphylococcal infection
Leptospirosis
Ascariasis
Threadworm
Sickle cell crisis
Typhoid fever
Thalassemia
Total parenteral nutrition
Prolonged fasting
Viral hepatitis
Sepsis
IgA vasculitis (Henoch-Schönlein purpura)
Mesenteric adenitis
Necrotizing enterocolitis

Affected patients usually have right upper quadrant pain with a palpable mass. Fever, vomiting, and jaundice may be present and are usually associated with a systemic illness such as streptococcal infection. Ultrasonography shows a markedly distended echo-free gallbladder, without dilation of the biliary tree. Acute hydrops is usually treated conservatively with a focus on supportive care and managing the intercurrent illness; cholecystostomy and drainage are rarely needed. Spontaneous resolution and return of normal gallbladder function usually occur over a period of several weeks. If a laparotomy is required, a large edematous gallbladder is found to contain white, yellow, or green bile. Obstruction of the cystic duct by mesenteric adenopathy is occasionally observed. Cholecystectomy is required if the gallbladder is gangrenous. Pathologic examination of the gallbladder wall shows edema and mild inflammation. Cultures of bile are usually sterile.

CHOLECYSTITIS AND CHOLELITHIASIS

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), gram-negative organisms—particularly *Salmonella* and *Leptospira interrogans*—and a number of viral infections (hepatitis A, Epstein-Barr [EB] virus, and cytomegalovirus). Parasitic infestation with *Ascaris* or *Giardia lamblia* may be found. Acalculous cholecystitis may be associated with abdominal trauma or burn injury or with a severe systemic illness such as leukemia, end-stage liver disease, and systemic vasculitis.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Patients may recover with treatment of systemic and biliary infection. Because the gallbladder can become gangrenous, daily ultrasonography is useful in monitoring gallbladder distention and wall thickness. Cholecystectomy is required in patients who fail to improve with conservative management. Cholecystostomy drainage is an alternative approach in a critically ill patient.

Cholelithiasis is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders (Table 414.2). Gallstones are rarely detected by ultrasonography in the fetus but generally remain asymptomatic and resolve spontaneously during the first year of life. In an ultrasonographic survey of

Selected patients with severe symptomatic polycystic liver disease and favorable anatomy benefit from liver resection or fenestration. Combined liver-kidney transplantation may be required. There is considerable evidence for a role of cyclic adenosine monophosphate in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. Several clinical trials in adults have shown that somatostatin analogs can blunt hepatic cyst expansion by blocking secretin-induced cyclic adenosine monophosphate generation and fluid secretion by cholangiocytes. Surgical or pharmacologic therapies for hepatic cysts are not likely to be required in childhood.

AUTOSOMAL DOMINANT POLYCYSTIC LIVER DISEASE

Autosomal dominant polycystic *liver* disease is a distinct clinical and genetic identity in which multiple cysts develop and are unassociated with cystic kidney disease. Liver cysts arise from but are not in continuity with the biliary tract. Females are more commonly affected than males, and the cysts often enlarge during pregnancy. Cysts are rarely identified in children. Cyst complications are related to effects of local compression, infection, hemorrhage, or rupture. The genes associated with autosomal dominant polycystic liver disease are *PRKCSH* and *SEC63*, which encode hepatocystin and Sec63, respectively. Hepatocystin is a protein kinase C substrate adK-H, which is involved in the proper folding and maturation of glycoproteins. It has been localized to the endoplasmic reticulum. *SEC63* encodes the protein SEC63P, which is a component of the protein translocation machinery in the endoplasmic reticulum.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 414

Diseases of the Gallbladder

Frederick J. Suchy and Amy G. Feldman

The incidence of gallbladder disease, particularly cholelithiasis and biliary dyskinesia, has been increasing in children and has been associated with a rise in the number of cholecystectomies.

ANOMALIES

The gallbladder is congenitally absent in approximately 0.1% of the population. Hypoplasia or absence of the gallbladder can be associated with extrahepatic biliary atresia or cystic fibrosis. Duplication of the gallbladder occurs rarely. Gallbladder ectopia may occur with a transverse, intrahepatic, left-sided, or retroplaced location. Multiseptate gallbladder, characterized by the presence of multiple septa dividing the gallbladder lumen, is another rare congenital anomaly of the gallbladder.

ACUTE HYDROPS

Table 414.1 lists the conditions associated with hydrops of the gallbladder.

Acute noncalculous, noninflammatory distention of the gallbladder can occur in infants and children. It is defined by the absence of calculi, bacterial infection, or congenital anomalies of the biliary system. The disorder may complicate acute infections and Kawasaki disease, but the cause is often not identified. Hydrops of the gallbladder may also develop in patients receiving long-term parenteral nutrition, presumably because of gallbladder stasis during the period of enteral fasting. Hydrops is distinguished from acalculous cholecystitis by the absence of a significant inflammatory process and is a generally benign prognosis.

Table 414.1 Conditions Associated with Hydrops of the Gallbladder

Cholelithiasis
Cholecystitis
Kawasaki disease
Streptococcal pharyngitis
Staphylococcal infection
Leptospirosis
Ascariasis
Threadworm
Sickle cell crisis
Typhoid fever
Thalassemia
Total parenteral nutrition
Prolonged fasting
Viral hepatitis
Sepsis
IgA vasculitis (Henoch-Schönlein purpura)
Mesenteric adenitis
Necrotizing enterocolitis

Affected patients usually have right upper quadrant pain with a palpable mass. Fever, vomiting, and jaundice may be present and are usually associated with a systemic illness such as streptococcal infection. Ultrasonography shows a markedly distended echo-free gallbladder, without dilation of the biliary tree. Acute hydrops is usually treated conservatively with a focus on supportive care and managing the intercurrent illness; cholecystostomy and drainage are rarely needed. Spontaneous resolution and return of normal gallbladder function usually occur over a period of several weeks. If a laparotomy is required, a large edematous gallbladder is found to contain white, yellow, or green bile. Obstruction of the cystic duct by mesenteric adenopathy is occasionally observed. Cholecystectomy is required if the gallbladder is gangrenous. Pathologic examination of the gallbladder wall shows edema and mild inflammation. Cultures of bile are usually sterile.

CHOLECYSTITIS AND CHOLELITHIASIS

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), gram-negative organisms—particularly *Salmonella* and *Leptospira interrogans*—and a number of viral infections (hepatitis A, Epstein-Barr [EB] virus, and cytomegalovirus). Parasitic infestation with *Ascaris* or *Giardia lamblia* may be found. Acalculous cholecystitis may be associated with abdominal trauma or burn injury or with a severe systemic illness such as leukemia, end-stage liver disease, and systemic vasculitis.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Patients may recover with treatment of systemic and biliary infection. Because the gallbladder can become gangrenous, daily ultrasonography is useful in monitoring gallbladder distention and wall thickness. Cholecystectomy is required in patients who fail to improve with conservative management. Cholecystostomy drainage is an alternative approach in a critically ill patient.

Cholelithiasis is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders (Table 414.2). Gallstones are rarely detected by ultrasonography in the fetus but generally remain asymptomatic and resolve spontaneously during the first year of life. In an ultrasonographic survey of

Table 414.2 Conditions Associated with Cholelithiasis

Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, others)
Ileal resection or disease
Cystic fibrosis
Cirrhosis
Cholestasis
Crohn disease
Obesity
Insulin resistance
Prolonged parenteral nutrition
Prematurity with complicated medical or surgical course
Prolonged fasting or rapid weight reduction
Treatment of childhood cancer
Abdominal surgery
Pregnancy
Sepsis
Genetic *(ABCB4, ABCG5/G8)* progressive familial intrahepatic cholestasis
Gilbert disease
Cephalosporins

1570 children (ages 6-19 years) the overall prevalence of gallstone disease was 0.13% (0.27% in female subjects). Older reports consistently found that >70% of gallstones were the pigment type, 15–20% were cholesterol stones, and the remainder were composed of a mixture of cholesterol, organic matrix, and calcium bilirubinate. Black pigment gallstones, composed mostly of calcium bilirubinate and glycoprotein matrix, are a frequent complication of chronic hemolytic anemias. However, because of obesity, cholesterol gallstones now predominate in children, while the number of patients with hemolytic anemia-associated gallstones have remained stable.

Brown pigment stones form mostly in infants as a result of biliary tract infection. Unconjugated bilirubin is the predominant component, formed by the high β-glucuronidase activity of infected bile. Cholesterol gallstones are composed purely of cholesterol or contain >50% cholesterol along with a mucin glycoprotein matrix and calcium bilirubinate. Calcium carbonate stones have also been described in children.

Patients with hemolytic disease (including sickle cell anemia, the thalassemias, and red blood cell enzymopathies) and Wilson disease are at increased risk for black pigment cholelithiasis. In sickle cell disease, pigment gallstones can develop before age 4 years and have been reported in 17–33% of patients 2-18 years of age. Genetic variation in the promoter of uridine diphosphate-glucuronosyltransferase 1A1 (the [TA]7/[TA]7 and [TA]7/[TA]8 genotypes) underlies Gilbert syndrome, a relatively common, chronic form of unconjugated hyperbilirubinemia, and is a risk factor for pigment gallstone formation in sickle cell disease.

Cirrhosis and chronic cholestasis also increase the risk for pigment gallstones. Sick premature infants may also have gallstones; their treatment is often complicated by such factors as bowel resection, necrotizing enterocolitis, prolonged parenteral nutrition without enteral feeding, cholestasis, frequent blood transfusions, and use of diuretics. Cholelithiasis in premature infants is often asymptomatic and may resolve spontaneously. Brown pigment stones are found in infants with obstructive jaundice and infected intra- and extrahepatic bile ducts. These stones are usually radiolucent, owing to a lower content of calcium phosphate and carbonate and a higher amount of cholesterol than in black pigment stones. MDR3 deficiency caused by *ABCB4* pathologic gene variant is a cholestatic syndrome related to impaired biliary phospholipid excretion. It is associated with symptomatic and recurring cholelithiasis. Patients may show intrahepatic lithiasis, sludge, or microlithiasis along the biliary tree.

Obesity has assumed an increasingly important role as a risk factor for cholesterol cholelithiasis in children, particularly in adolescent females. Cholesterol gallstones are also found in children with disturbances of the enterohepatic circulation of bile acids, including patients with ileal disease and bile acid malabsorption, such as those with ileal resection, ileal Crohn disease, and cystic fibrosis. Pigment stones can also occur in these patients.

Cholesterol gallstone formation results from an excess of cholesterol in relation to the cholesterol-carrying capacity of micelles in bile. Supersaturation of bile with cholesterol, leading to crystal and stone formation, could result from decreased bile acid or from an increased cholesterol concentration in bile. Other initiating factors that may be important in stone formation include gallbladder stasis or the presence in bile of abnormal mucoproteins or bile pigments that may serve as a nidus for cholesterol crystallization.

Prolonged use of high-dose ceftriaxone, a third-generation cephalosporin, has been associated with the formation of calcium-ceftriaxone salt precipitates *(biliary pseudolithiasis)* in the gallbladder. Biliary sludge or cholelithiasis can be detected in >40% of children who are treated with ceftriaxone for at least 10 days. In rare cases, children become jaundiced and develop abdominal pain; precipitates usually resolve spontaneously within several months after discontinuation of the drug.

Acute or chronic cholecystitis is often associated with gallstones. The acute form may be precipitated by impaction of a stone in the cystic duct. Proliferation of bacteria within the obstructed gallbladder lumen can contribute to the process and lead to biliary sepsis. Chronic calculous cholecystitis is more common. It can develop insidiously or follow several attacks of acute cholecystitis. The gallbladder epithelium commonly becomes ulcerated and scarred.

More than 50% of patients with gallstones have symptoms, and 18% present with a complication as the first indication of cholelithiasis, such as pancreatitis, choledocholithiasis or acute calculous cholecystitis. The most important clinical feature of cholelithiasis is recurrent abdominal pain, which is often colicky and localized to the right upper quadrant. An older child may have intolerance for fatty foods. Acute cholecystitis is characterized by fever, pain in the right upper quadrant, and often a palpable mass. Jaundice occurs more commonly in children than adults. Pain may radiate to an area just below the right scapula. A plain x-ray of the abdomen may reveal opaque calculi, but radiolucent (cholesterol) stones are not visualized. Accordingly, ultrasonography is the method of choice for gallstone detection. Hepatobiliary scintigraphy is a valuable adjunct in that failure to visualize the gallbladder provides evidence of cholecystitis. Laboratory evaluation may reveal elevated aminotransferase levels, leukocytosis, and mild hyperbilirubinemia. Marked elevations of the direct bilirubin, alkaline phosphatase, or gamma-glutamyl transpeptidase (GGT) levels should prompt evaluation for choledocholithiasis.

Patients with cholecystitis and persistent fever or concern for obstruction should be hospitalized and started on antibiotics. Cholecystectomy is curative. Laparoscopic cholecystectomy is routinely performed in symptomatic infants and children with cholelithiasis. Common bile duct stones are unusual in children, occurring in 2–6% of cases with cholelithiasis, often in association with obstructive jaundice and pancreatitis. Rarely a common bile duct stone may appear after a successful cholecystectomy. Operative cholangiography should be done at the time of surgery, however, to detect unsuspected common duct calculi. Endoscopic retrograde cholangiography with extraction of common duct stones is an option before laparoscopic cholecystectomy in older children and adolescents.

Asymptomatic patients with cholelithiasis pose a more difficult management problem. Studies in adults indicate a lag time of more than a decade between initial formation of a gallstone and development of symptoms. Spontaneous resolution of cholelithiasis has been reported in infants and children. However, if surgery is deferred for any patient, parents should be counseled about signs and symptoms consistent with cholecystitis or obstruction of the common bile duct by a gallstone. In patients with chronic hemolysis or ileal disease, cholecystectomy can be carried out at the same time as another surgical procedure. Because laparoscopic surgery can safely be performed in children with sickle cell disease, elective cholecystectomy is being

done more frequently at the time of gallstone diagnosis before symptoms or complications develop. In cases associated with liver disease, severe obesity, or cystic fibrosis, the surgical risk of cholecystectomy may be substantial so that the risks and benefits of the operation need to be carefully considered.

BILIARY DYSKINESIA

Biliary dyskinesia is a motility disorder of the biliary tract that may cause biliary colic in children, often in association with nausea and fatty food intolerance, but symptoms may overlap with functional abdominal pain. There are no gallstones on imaging. Sphincter of Oddi dysfunction may be a variant that can present with chronic abdominal pain and recurrent pancreatitis. The diagnosis is based on a cholecystokinin–di-isopropyl iminodiacetic acid scan or an ultrasound done with a fatty meal demonstrating a gallbladder ejection fraction of <35%. Reproduction of pain on cholecystokinin administration may also be seen, as well as the absence of gallbladder filling on an otherwise normal ultrasound examination. Although laparoscopic cholecystectomy is performed for many patients with this disorder, short-term and long-term symptomatic improvement is highly variable.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 415

Portal Hypertension and Varices

Amy G. Feldman and Frederick J. Suchy

Portal hypertension, defined as an elevation of portal pressure >10-12 mm Hg or a hepatic venous pressure gradient >4 mm Hg, is a major cause of morbidity and mortality in children with liver disease. Portal hypertension occurs when there is increased portal resistance or increased blood flow through the portal system. When portal hypertension occurs, children can develop varices, splenomegaly, ascites, and gastrointestinal bleeding.

ETIOLOGY

Portal hypertension can result from obstruction to portal blood flow anywhere along the course of the portal venous system (prehepatic, intrahepatic, or posthepatic). Table 415.1 outlines the various disorders associated with portal hypertension.

Portal vein thrombosis is the most common cause of extrahepatic portal hypertension. The obstruction can occur at any level of the portal vein. In neonates, portal vein thrombosis can occur from umbilical infection (omphalitis) with or without a history of catheterization of the umbilical vein, dehydration, and/or sepsis. Rare developmental anomalies producing extrahepatic portal hypertension include agenesis, atresia, stenosis, or a web of the portal vein. In older children, portal vein thrombosis can occur with intraabdominal infection (appendicitis, peritonitis, pancreatitis), inflammatory bowel disease, celiac disease, primary sclerosing cholangitis, or biliary infection. Portal vein thrombosis is also associated with hypercoagulable states, such as deficiencies of factor V Leiden, protein C, or protein S. The portal vein can be replaced by a fibrous remnant or contain an organized thrombus. At least half of reported cases have no defined cause. Uncommonly, presinusoidal hypertension can be caused by increased flow through the portal system as a result of a congenital or acquired arteriovenous fistula.

Table 415.1 Causes of Portal Hypertension

EXTRAHEPATIC PORTAL HYPERTENSION
Portal vein agenesis, atresia, stenosis
Portal vein thrombosis or cavernous transformation
Splenic vein thrombosis
Increased portal flow
Arteriovenous fistula
INTRAHEPATIC PORTAL HYPERTENSION
Hepatocellular disease
Acute and chronic viral hepatitis
Cirrhosis
Congenital hepatic fibrosis
Wilson disease
α_1-Antitrypsin deficiency
Glycogen storage disease type IV
Hepatotoxicity
Methotrexate
Parenteral nutrition
Biliary tract disease
Biliary atresia
Cystic fibrosis
Choledochal cyst
Sclerosing cholangitis
Intrahepatic bile duct paucity
Idiopathic portal hypertension
Postsinusoidal obstruction
Budd-Chiari syndrome
Venoocclusive disease



Fig. 415.1 Coronal CT image of the abdomen in a patient with cirrhosis. The liver is shrunken *(green cross)*, shows nodularity *(white arrowhead)*, and is surrounded by ascites *(green arrowheads)*. The spleen is enlarged *(star)*. Gastro-esophageal varices are seen *(white arrow)*. There is a splenorenal shunt between a tributary of the splenic vein *(green arrow)* and the left renal vein *(red arrow)*. The left renal vein is seen entering the inferior vena cava *(green curved arrow)*. *(From Ginés P, Krag A, Abraldes JG, et al. Liver cirrhosis. Lancet. 2021;398:1359–1374. Fig. 1.)*

The intrahepatic causes of portal hypertension are numerous. The most common cause of portal hypertension in children is **cirrhosis** (Fig. 415.1). The numerous causes of cirrhosis include recognized disorders such as biliary atresia, autoimmune hepatitis, chronic viral

hepatitis, and metabolic liver disease such as α_1-antitrypsin deficiency, Wilson disease, glycogen storage disease type IV, hereditary fructose intolerance, and cystic fibrosis.

Portal infiltration with malignant cells or granulomas can also contribute. An idiopathic form of portal hypertension characterized by splenomegaly, hypersplenism, and portal hypertension without occlusion of portal or splenic veins and with no obvious disease in the liver has been described. In some patients, noncirrhotic portal fibrosis has been observed.

Postsinusoidal causes of portal hypertension are also observed in childhood. **Budd-Chiari syndrome** occurs with obstruction to hepatic veins anywhere between the efferent hepatic veins and the entry of the inferior vena cava into the right atrium. In most cases, no specific cause can be found, but thrombosis can occur from inherited and acquired hypercoagulable states (antithrombin III deficiency, protein C or S deficiency, factor V Leiden or prothrombin gene variants, paroxysmal nocturnal hemoglobinemia, antiphospholipid syndrome, pregnancy, oral contraceptives) and can complicate hepatic or metastatic neoplasms, collagen vascular disease, infection, and trauma. Additional causes of the Budd-Chiari syndrome include Behçet syndrome, inflammatory bowel disease, celiac disease, sarcoidosis, pancreatitis, aspergillosis, dacarbazine therapy, autoinflammatory-recurrent fever syndromes, and inferior vena cava webs.

Sinusoidal obstruction syndrome (venoocclusive disease) is the most common cause of hepatic vein obstruction in children. In this disorder, occlusion of the centrilobular venules or sublobular hepatic veins occurs. The disorder most frequently occurs in bone marrow transplant recipients after total body irradiation with or without cytotoxic drug therapy, but it can also be seen in patients on azathioprine, mercaptopurine, thioguanine, and those taking herbal remedies that contain pyrrolizidine alkaloids.

PATHOPHYSIOLOGY

The primary hemodynamic abnormality in portal hypertension is increased resistance to portal blood flow. This is the case whether the resistance to portal flow has an intrahepatic cause such as cirrhosis or is because of portal vein obstruction. Portosystemic shunting should decompress the portal system and thus significantly lower portal pressures. However, despite the development of significant collaterals deviating portal blood into systemic veins, portal hypertension is maintained by an overall increase in portal venous flow and thus maintenance of portal hypertension. A hyperdynamic circulation is achieved by tachycardia, an increase in cardiac output, decreased systemic vascular resistance, and increased splanchnic dilation. Overall, the increase in portal flow likely contributes to an increase in variceal transmural pressure. The increase in portal blood flow is related to the contribution of hepatic and collateral flow; the actual portal blood flow reaching the liver is reduced. It is also likely that hepatocellular dysfunction and portosystemic shunting lead to the generation of various humoral factors that cause vasodilation and an increase in plasma volume.

Many complications of portal hypertension can be accounted for by the development of a remarkable collateral circulation. Collateral vessels can form prominently in areas in which absorptive epithelium joins stratified epithelium, particularly in the esophagus or anorectal region. The superficial submucosal collaterals, especially those in the esophagus and stomach, and, to a lesser extent, those in the duodenum, colon, or rectum, are prone to rupture and bleeding under increased pressure. In portal hypertension, the vascularity of the stomach is also abnormal and demonstrates prominent submucosal arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins. The resulting lesion, a vascular ectasia, has been called *congestive gastropathy* and contributes to a significant risk of bleeding from the stomach.

CLINICAL MANIFESTATIONS

Bleeding is the most common presentation of portal hypertension in children. In large series of children with portal hypertension, two thirds presented with hematemesis or melena, most commonly from rupture of an esophageal varix (see Fig. 415.1). Less commonly, patients bleed from portal gastropathy, gastric antral ectasia, or stomal, intestinal, or anorectal varices. The risk of a first bleed in children with cirrhosis is 22% but rises to 38% in children with known varices over a 5-year period. In children with biliary atresia, 15–25% have bleeding on long-term follow-up. The age of first bleed is dependent on the underlying etiology of portal hypertension. Hemorrhage, particularly in children with portal vein obstruction, can be precipitated by a minor febrile, intercurrent illness. The mechanism is often unclear; aspirin or other nonsteroidal antiinflammatory drugs may be a contributing factor by damaging the integrity of a congested gastric mucosa or interfering with platelet function. Coughing during a respiratory illness can also increase intravariceal pressure.

Splenomegaly is the second most common finding in children with portal hypertension and may be initially recognized on routine physical examination (see Fig. 415.1). Because more than half of patients with portal vein obstruction do not experience bleeding until after 6 years of age, underlying liver disease should be considered in any child with splenomegaly, especially if there is concurrent cytopenia. Most children with splenomegaly are asymptomatic.

Ascites is the presenting sign of portal hypertension in 7–21% of children. Ascites can develop at any time with cirrhosis or if there is new onset portal vein obstruction. Children with portal hypertension can also suffer from growth impairment, minimal hepatic encephalopathy, and impaired quality of life. Some develop **portal hypertensive biliopathy**, where portal vein obstruction occurs as a result of external compression of the bile ducts by cavernous transformation of the portal vein.

Children with portal hypertension may also develop pulmonary complications, including **hepatopulmonary syndrome** (HPS) and **portopulmonary hypertension** (PP-HTN). HPS is defined as an arterial oxygenation defect induced by intrapulmonary microvascular dilation, resulting from release of a number of endogenous vasoactive molecules, including endothelin-1 and nitric oxide into the venous circulation. HPS develops in ≥10% of patients with portal hypertension. Patients with HPS may present with dyspnea, cyanosis, clubbing, and spider nevi. PP-HTN is defined by a pulmonary arterial pressure greater than 25 mm Hg at rest or a left-ventricular end-diastolic pressure of less than 15 mm Hg. Patients with PP-HTN most commonly present with exertional dyspnea. Histologically, these patients have pulmonary arteriopathy with laminar intimal fibrosis.

DIAGNOSIS

In patients with established chronic liver disease or in those in whom portal vein obstruction is suspected, an experienced ultrasonographer should be able to demonstrate the patency of the portal vein, and Doppler flow ultrasonography can demonstrate the direction of flow within the portal system. The pattern of flow correlates with the severity of cirrhosis and encephalopathy. Reversal of portal vein blood flow (hepatofugal flow) is more likely to be associated with variceal bleeding. Ultrasonography is also effective in detecting the presence of esophageal varices. Another important feature of extrahepatic portal vein obstruction is cavernous transformation of the portal vein, in which an extensive complex of small collateral vessels forms in the paracholedochal and epicholedochal venous system to bypass the obstruction. Other imaging techniques also contribute to further definition of the portal vein anatomy but are required less often; contrast-enhanced CT and magnetic resonance angiography provide information similar to ultrasonography. Selective arteriography of the celiac axis, superior mesenteric artery, and splenic vein may be useful in precise mapping of the extrahepatic vascular anatomy. This is not required to establish a diagnosis but can prove valuable in planning surgical decompression of portal hypertension. The platelet count, spleen length measured by ultrasonography, and serum albumin are the best noninvasive predictors of portal hypertension in children.

In a patient with hypoxia (HPS), intrapulmonary microvascular dilation is demonstrated with contrast-enhanced bubble echocardiography that shows delayed appearance in the left heart of microbubbles from a saline bolus injected into a peripheral vein.

Endoscopy is the most reliable method for detecting esophageal varices and for identifying the source of gastrointestinal bleeding. Although bleeding from esophageal or gastric varices is most common in children with portal hypertension, up to one third of patients, particularly those with cirrhosis, have bleeding from some other source, such as portal hypertensive gastropathy or gastric or duodenal ulcerations. There is a strong correlation between variceal size as assessed endoscopically and the probability of hemorrhage. Red spots apparent over varices at the time of endoscopy are a strong predictor of imminent hemorrhage.

TREATMENT

The therapy of portal hypertension can be divided into emergency treatment of potentially life-threatening hemorrhage and prophylaxis directed at prevention of initial or subsequent bleeding.

Treatment of patients with acute variceal hemorrhage must focus on stabilization of the patient. Fluid resuscitation should be administered, initially in the form of crystalloid infusion, followed by the replacement of red blood cells. Care should be taken to avoid over transfusing children with portal hypertension-induced bleeding because this can result in overfilling the intravascular space and increasing portal pressure. A reasonable goal hemoglobin level after variceal bleed is between 7 and 9 g/dL. Correction of coagulopathy by administration of vitamin K and/or infusion of platelets or fresh-frozen plasma may be required. A nasogastric tube should be placed to document the presence of blood within the stomach and to monitor for ongoing bleeding. An H_2-receptor blocker or proton pump inhibitor should be given intravenously to reduce the risk of bleeding from gastric erosions. Intravenous antibiotics should be considered because there is high risk of infectious complications during variceal bleeding.

Pharmacologic therapy to decrease portal pressure should be initiated in patients with continued bleeding. Vasopressin or one of its analogs is commonly used and is thought to act by increasing splanchnic vascular tone and thus decreasing portal blood flow. Vasopressin is administered initially with a bolus of 0.33 units/kg over 20 min, followed by a continued infusion of the same dose on an hourly basis or a continuous infusion of 0.2 units/1.73 m^2/min. The drug has a half-life of approximately 30 minutes. Its use may be limited by the side effects of vasoconstriction, which can impair cardiac function and perfusion to the heart, bowel, and kidneys and can also, as a result, exacerbate fluid retention. More commonly, the somatostatin analog, octreotide, is used because it decreases splanchnic blood flow with few side effects. Octreotide is initially administered with a bolus of 1 μg/kg followed by a continuous intravenous infusion of 1.0-5.0 μg/kg/hr. A total of 15% of children with a portal hypertensive bleed will have persistent hemorrhage despite initiation of some form of splanchnic vasoconstriction.

After an episode of variceal hemorrhage or in patients in whom bleeding cannot be controlled with pharmacologic therapy, endoscopy with variceal band ligation or variceal sclerotherapy should be performed. Endoscopic band ligation is preferred because it has been shown in adults to be more effective and has fewer side effects. For smaller children in whom the banding device cannot be used, sclerosants can be injected either intra- or paravariceal until bleeding has stopped. Sclerotherapy treatments may be associated with bleeding, bacteremia, esophageal ulceration, and stricture formation. After band ligation or sclerosis, repeat endoscopy should be performed until varices are obliterated.

In patients who continue to bleed despite pharmacologic and endoscopic methods to control hemorrhage, a Sengstaken-Blakemore tube may be emergently placed to stop hemorrhage by mechanically compressing esophageal and gastric varices. The device is rarely used now, but it may be the only option to control life-threatening hemorrhage until a more definite procedure can be performed. It carries a significant rate of complications and a high rate of bleeding when the device is removed, and it poses a particularly high risk for pulmonary aspiration. The tube is not well tolerated in children without significant sedation and intubation.

Various surgical procedures have been devised to divert portal blood flow and to decrease portal pressure. A portacaval shunt diverts nearly all of the portal blood flow into the subhepatic inferior right vena cava. Although portal pressure is significantly reduced, because of the significant diversion of blood from the liver, patients with parenchymal liver disease have a marked risk for hepatic encephalopathy. Even mild hepatic encephalopathy can impair cognitive function, including school performance. More selective shunting procedures, such as mesocaval or distal splenorenal shunt (see Fig. 415.1), can effectively decompress the portal system while allowing a greater amount of portal blood flow to the liver. The small size of the vessels makes these operations technically challenging in infants and small children, and there is a significant risk of failure as a result of shunt thrombosis. A shunt may be a good option for a child with relatively well-preserved liver function, as sometimes occurs in patients with biliary atresia, congenital hepatic fibrosis, or cystic fibrosis. For children with an extrahepatic portal vein thrombosis, a Meso-Rex shunt (superior mesenteric vein to left portal vein bypass) may successfully restore physiologic portal blood flow and inflow of hepatotrophic factors. In one large single-center experience, 84% of children with idiopathic extrahepatic portal vein thrombosis were successfully treated with a Meso-Rex shunt. Growth and cognitive function improve after this procedure.

A transjugular intrahepatic portosystemic shunt (TIPS), in which a stent is placed by an interventional radiologist between the right hepatic vein and the right or left branch of the portal vein, can aid in the management of portal hypertension in children, especially in those needing temporary relief before liver transplantation. The transjugular intrahepatic portosystemic shunt procedure can precipitate hepatic encephalopathy and is prone to thrombosis.

Orthotopic liver transplantation represents a much better therapy for portal hypertension resulting from intrahepatic disease and cirrhosis. A prior portosystemic shunting operation does not preclude a successful liver transplantation but makes the operation technically more difficult.

Long-term treatment with nonspecific β blockers, such as propranolol, has been used extensively in adults with portal hypertension. These agents might act by lowering cardiac output and inducing splanchnic vasoconstriction. Evidence in adult patients shows that β blockers can reduce the incidence of variceal hemorrhage and improve long-term survival. A therapeutic effect is thought to result when the pulse rate is reduced by ≥25%. There is limited published experience with the use of this therapy in children.

PROGNOSIS

Portal hypertension secondary to intrahepatic disease has a poor prognosis. Portal hypertension is usually progressive in these patients and is often associated with deteriorating liver function. Efforts should be directed toward prompt treatment of acute bleeding and prevention of recurrent hemorrhage with available methods. Patients with progressive liver disease and significant esophageal varices ultimately require orthotopic liver transplantation. Liver transplantation is the only effective therapy for HPS and should also be considered for patients with portal hypertension secondary to hepatic vein obstruction or resulting from severe venoocclusive disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 416

Liver Transplantation

Jorge D. Reyes and Evelyn K. Hsu

Survival rates for pediatric liver transplantation are >90% in the United States, in large part thanks to refinements made in the critical care management of children with liver failure and advances in perioperative care and immunosuppression management. Protocols for immune suppression withdrawal in the setting of allograft tolerance have introduced the possibility of transplantation for children without the need for long-term immunosuppression. In the United States, a national allocation system matches donor organs with waitlist candidates (the Organ Procurement and Transplantation Network and the United Network for Organ Sharing [UNOS]); this organization has been given the responsibility of allocating scarce organs to the neediest patients and has undergone continuous revisions with this goal in mind—the most significant in 2002, with the adoption of the Pediatric End-Stage Liver Disease (PELD) and Medical End-Stage Liver Disease (MELD; for adolescents) illness severity scoring system.

INDICATIONS

The diseases for which liver transplantation is indicated can be categorized into the following groups:

- *Obstructive biliary tract disease:* biliary atresia, sclerosing cholangitis, and traumatic or postsurgical injury
- *Metabolic disorders with liver parenchymal disease:* α_1-antitrypsin deficiency, tyrosinemia type I, glycogen storage disease type IV, Wilson disease, gestational alloimmune liver disease (GALD, previously known as *neonatal hemochromatosis*), and cystic fibrosis
- *Metabolic disorders without liver parenchymal disease:* Crigler-Najjar type I, familial hypercholesterolemia, primary oxalosis (with kidney), organic acidemia, and urea cycle defects
- *Acute hepatitis:* fulminant hepatic failure, viral, toxin, or drug-induced
- *Chronic hepatitis with cirrhosis:* hepatitis B or C, autoimmune
- *Intrahepatic cholestasis:* idiopathic neonatal hepatitis, Alagille syndrome, progressive familial intrahepatic cholestasis, and bile acid synthetic disorders
- *Primary liver tumors:* benign tumors (hamartomas, hemangioendothelioma), unresectable hepatoblastoma, and hepatocellular carcinoma
- *Miscellaneous:* cryptogenic cirrhosis, congenital hepatic fibrosis, Caroli disease, polycystic kidney and liver disease, and cirrhosis induced by total parenteral nutrition
- *Emerging indications:* graft-versus-host disease (a complication of bone marrow transplantation), hemophilia, and portosystemic shunts

Biliary atresia is the most common indication for liver transplantation in children, accounting for about half of all pediatric liver transplants performed in the United States, followed by metabolic liver disease and inborn errors of metabolism, autoimmune and familial cholestatic disorders, and acute hepatic necrosis. Biliary atresia may present in two clinical patterns: an acquired form for which there may be nonrandom clustering of potential etiologies (80% of cases) and a syndromic/embryonic form that includes other anomalies, such as polysplenia preduodenal portal vein, intestinal malrotation, situs anomalies, and absence of the retrohepatic vena cava. Hepatoportoenterostomy benefits survival if performed within the first 60 days of life; however, some patients with successful drainage later develop cirrhosis with portal hypertension (variceal bleeding and ascites). Children with biliary atresia (or any other obstructive biliary disorder) who do not achieve successful drainage will experience continued decline and end-stage liver disease, usually requiring liver transplantation within the first year of life.

Inborn errors of metabolism result from a single enzyme deficiency that results in alteration of synthesis, breakdown, transport, or function of carbohydrate, fat, or protein. These disorders can be grouped into those diseases that cause liver parenchymal disease and eventual cirrhosis with end-stage liver disease, as well as liver cancer (i.e., α_1-antitrypsin deficiency, Wilson disease, cystic fibrosis, progressive familial intrahepatic cholestasis), and those inborn errors that manifest principally by their hepatic enzyme deficiency with no hepatocellular injury; complications occur in "satellite" systems such as the brain (hyperammonemic conditions), the kidney (hyperoxaluria type 1), or heart (familial hypercholesterolemia). Some metabolic disorders place patients at risk for decompensation throughout their entire lives, and others manifest principally after adolescence. Liver transplantation is a form of enzyme replacement; the value and risk: benefit of doing so in the absence of cirrhosis has prompted the pursuit of gene therapy and hepatocyte transplantation as possible alternatives, but the therapeutic benefit of these modalities of treatment is as yet equivocal.

Although a proportion of children with **acute hepatic failure** will survive without transplant, it accounts for approximately 10% of pediatric liver transplantation and requires the most intense concentration of multimodal management/support yet devised. This diagnosis lacks clear etiology in the majority of cases, and posttransplantation survival varies but is worse than the general population, likely because of multifactorial issues related to comorbidities and listing/transplantation graft option availability.

Primary hepatic malignancies in children are rare (<2% of all pediatric malignancies) and account for about 7% of pediatric transplants. Hepatoblastoma accounts for the majority of cases (75% of primary liver tumors in childhood) and usually presents in an advanced stage; adjuvant chemotherapy and total hepatectomy with transplantation provide cure and long-term survival for the majority of these children. Survival of >85% has been reported by the International Society of Pediatric Oncology and several American centers.

The impact of chronic liver disease and its impact on growth, development, and quality of life of children can be devastating. Liver transplantation is a valid therapy and cure. The allocation of deceased donor livers in the United States follows guidelines based on the severity of liver disease as reflected in the PELD/MELD scoring system implemented in 2002, which is calculated from the measurable values of bilirubin, albumin, or creatinine (depending on age) and international normalization ratio. The PELD scoring system was initially modeled from a cohort of 884 children on the pediatric liver transplant wait list and is intended to predict death, decompensation, or transplantation within 3 months. Since 2002, the number of liver transplants performed in children in the United States has remained relatively stable, whereas the number of liver transplants performed in adults has steadily increased by approximately 10% per year. A change (2020) to the allocation algorithm that prioritized local adults over critically ill children nationally has in the short term led to increased rates of transplantation in adolescent patients. This and other issues highlight the importance of advocacy on behalf of children in this growing field.

Contraindications to liver transplantation include uncontrolled infection of extrahepatic origin, extrahepatic malignancies, and severely disabling and uncorrectable disease in other organ systems, principally the brain, heart, and lungs. Although combined liver and heart or lung transplantation has been performed in adults and children, such cases require special consideration and centers dedicated to the complexities of posttransplantation management.

TECHNICAL INNOVATIONS

There are no limitations on age or weight for liver transplantation. To enhance the availability of liver grafts to children and optimize the timing of transplantation, techniques allowing the use of reduced-size or segmental grafts (a right or left lobe of liver, or the left lateral segment of the left lobe) were developed; this allows a liver from a larger donor to be implanted into a child, overcoming the barrier of size mismatch. In the same era, techniques were developed for the use of segments from living donors (usually the left lateral segment for small pediatric recipients), and then split-liver grafts from deceased donors where the

left lateral segment is transplanted into a child and the remaining segments of right lobe and medial segment of left lobe are transplanted into an adult, allowing increased utilization of deceased donor grafts without affecting adult waitlist mortality. Reduction of a liver graft is performed ex vivo (i.e., outside of the body); split-liver procurement surgery can be performed either ex vivo or in situ (in the hemodynamically stable brain-dead donor). Donors suitable for aforementioned graft variants should ideally be young (younger than 45 years of age), healthy, and nonobese; however, variations are guided by the severity of illness and urgency for transplantation of the recipient. Not all centers have the degree of surgical expertise required to perform these more complex surgeries; thus options may be limited for children at centers that accept only size-matched organs. This has implications for their waitlist survival.

The implantation of a liver (either whole organ or segment) involves removal of the native liver and encompasses four anastomoses: the suprahepatic vena cava, the portal vein, the hepatic artery, and the bile duct. Modifications of the procedure generally involve retaining (or not) of the retrohepatic vena cava, the performance (or not) of a temporary portocaval shunt to decompress the splanchnic venous system during the anhepatic phase, and the use of vascular homografts of donor iliac vein or artery to replace the native inflow (guided by the presence of recipient anomalies or thrombosis of native vessels). The donor bile duct may be connected to a loop of recipient intestine (Roux-en-Y limb) or the native bile duct. UNOS reported outcomes analyzing graft types, and outcomes have shown improved graft survival in children younger than 3 years of age for live donor grafts when compared with deceased donor whole, split, and reduced grafts. After the first year, however, patient and allograft survivals were similar, independent of graft type.

IMMUNOSUPPRESSION

The long-term goal of effective clinical immunosuppression after solid-organ transplantation is to inhibit antigen-induced T-lymphocyte activation and cytokine production and to interrupt alloimmune–major histocompatibility complex recognition. To prevent weakening the host response to infection, this goal should be achieved while preserving host immunocompetence. A major emphasis is on the prevention of acute and chronic rejection and preserving the ability to reverse refractory acute rejection. These efforts have been successful; the challenge for the future of pediatric liver transplantation is achieving long-term survival and improved quality of life. This inherently involves strategies to minimize the long-term toxicity of immunosuppressive drug therapy, which can include renal failure, cardiovascular complications, and infections. Strategies of drug minimization, steroid-free therapy, and complete withdrawal of drugs have been accomplished in select patients and under careful medical supervision.

Immediately peri- or posttransplantation induction immunosuppressive therapy can involve antilymphocyte antibody induction with depleting antibodies (monoclonal or polyclonal), such as antithymocyte globulin antibody or the use of a chimeric mouse–human antibody that blocks the interleukin-2 receptor of the T cell, thus preventing activation and replication of antigen-selected T cells. Corticosteroids act through the suppression of antibody production and cytokine synthesis (interleukin-2, and interferon-γ), decreasing proliferation of T cells (helper, suppressor, and cytotoxic), B cells, and neutrophils. Maintenance immunosuppression is achieved by using calcineurin phosphatase inhibitor (cyclosporine or tacrolimus); these drugs interfere with the production and release of interleukin-2, a critical factor in the cytotoxic T-cell response. Calcineurin phosphatase inhibitors are most effectively directed toward inhibiting T-cell–mediated acute cellular rejection. Tacrolimus is the mainstay of most immunosuppressive regimens, and its ability to progress or initiate maintenance immunosuppression in the absence of corticosteroids is of particular benefit in children. Adjuvant immunosuppression, such as azathioprine or mycophenolate mofetil, which inhibits the synthesis of purine nucleosides and subsequently the proliferation of T and B lymphocytes as well as antibody formation, may be added to enhance the antirejection profile, allow for decrease in the calcineurin dosage, or manage chronic rejection. Rapamycin, a macrolide that binds its molecular target of mammalian target of rapamycin receptor, decreases interleukin-2 production and, in turn, T- and B-cell activation and proliferation.

COMPLICATIONS

Posttransplantation complications can be related to the pretransplantation condition of the recipient and the donor match and type, immunologic responses to the graft and the need for enhanced immunosuppressive drug therapy, and toxicity effects of these drugs or infections from over-immunosuppression. Post-transplant complications can occur at varying specific frequencies over a fairly well-defined time course (early, late, remote).

The most anticipated early complications involve those inherent to the transplantation operation: primary nonfunction of the graft, hepatic artery thrombosis, portal/hepatic venous strictures or occlusions, and biliary strictures. Primary nonfunction of the graft is rare in pediatric recipients given the selection criteria of potential donors. Hepatic artery thrombosis is the most frequent and early vascular complication; it occurs in 5–10% of recipients and can have devastating consequences on the graft (acute necrosis and gangrene, biliary leaks/stricture/bilomas) and may require urgent retransplantation. Portal vein or hepatic vein strictures/occlusions are rare and generally occur later posttransplantation. Biliary strictures are the most frequent surgical complication (10–30%) after liver transplantation and should be included in the differential diagnosis of any posttransplantation liver allograft dysfunction. Management of these complications varies and may include interventional radiologic procedures, reoperation, or retransplantation. Advancements in interventional radiology technique have allowed for a less invasive and equally efficacious approach to resolving these complications.

Rejection usually occurs after the first 2 weeks after transplantation, with the highest incidence (30–60%) within the first 90 days. Diagnosis of rejection is suspected based on abnormal liver function studies; rarely are there systemic signs such as fever, abdominal pain, new-onset ascites, or hydrothorax. Diagnosing rejection requires biopsy confirmation; treatment algorithms include high doses of corticosteroids and antilymphocyte antibodies. Chronic rejection is less frequent (5–10%) and is characterized by progressive damage and loss of bile ductules with consequent cholestasis; treatment involves long-term enhancement of maintenance immunosuppression with corticosteroids and other agents.

The need to treat rejection can place the patient at a higher risk of drug toxicity or infection. The most common transplantation-related infections are cytomegalovirus and Epstein-Barr virus infections, for which there are well-developed algorithms of prophylaxis and screening. Epstein-Barr virus–induced **posttransplant lymphoproliferative disease** (PTLD) represents a unique complication of over-immunosuppression and infection occurring in approximately 10% of patients. It is managed primarily by withdrawal of immunosuppression and antiviral therapy; some patients require chemotherapy.

OUTCOMES

UNOS data reveal a 1-year patient and graft survival for biliary atresia of 95% and 87%, respectively. Examination of 461 5-year survivors of pediatric liver transplantation in a North American registry found a first graft survival of 88%, with 12% requiring a second graft and 2% requiring a third transplant. The same investigators published a study of 167 10-year survivors and found that only 30% of the group had an "ideal outcome" of normal liver-associated enzymes, no retransplant, and no evidence of PTLD, chronic rejection, hypertension, or renal disease. Longer-term survival is inherently dependent on adequacy of long-term immunosuppression management, adherence to care protocols, and prevention of infection/toxicities/chronic rejection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 7
Peritoneum

Chapter 417
Peritoneal Malformations

Jamie F. Merves and Chris A. Liacouras

Numerous anomalies can occur during peritoneal development. Many are rarely of clinical importance, but peritoneal bands and cysts can result in manifestations such as abdominal pain and obstruction. Additionally, peritoneal encapsulation can occur because of an accessory peritoneal sac. Absence or duplication of the omentum occurs rarely.

Congenital peritoneal bands represent anatomically unabsorbed portions of omentum and mesentery and most commonly occur in the regions of the duodenum, duodenojejunal flexure, ileocecal junction, and ascending colon. Although usually benign, they may be responsible for symptoms ranging from nonspecific chronic abdominal pain to intestinal obstruction, malrotation, volvulus, and internal herniation with potential for resulting associated necrosis. Evaluation includes abdominal radiography, fluoroscopy, and, less commonly, CT and angiography. Even when discovered incidentally, surgical management generally remains the standard of care to prevent complications.

Omental cysts arise from obstructed or ectopic lymphatic channels within the omentum. They may be congenital or can result from trauma. They are usually asymptomatic, but abdominal pain or partial small bowel obstruction can result from compression or torsion of the small bowel from traction on the omentum. **Mesenteric cysts** are also rare and may coexist with omental cysts. They most commonly arise from the small bowel mesentery but can also occur in the large bowel mesentery or retroperitoneum. They too arise from lymphatic anomalies, and the cysts can be single or multiple and are often large. Presentation varies but most frequently involves abdominal pain, distention, and appreciation of an abdominal mass and/or suspected ascites on examination. Gastrointestinal symptoms may also include nausea, emesis, constipation, or loose stools. Mesenteric cysts are mostly benign lesions but may act as lead points for torsion and intussusception and can develop hemorrhage, infection, and, rarely, malignant transformation. Cysts are usually well defined and identified on imaging via ultrasound or CT scan. Treatment is typically simple excision, which can be performed laparoscopically in most cases, with excellent results and generally good prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 418
Ascites

Jessica W. Wen and Chris A. Liacouras

Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Multiple causes of ascites have been described in different age-groups (Tables 418.1-418.3). In children, hepatic and renal disease are the most common causes, but ascites can also be caused by cardiac disease, trauma, infection, or neoplasia.

Table 418.1 Causes of Fetal Ascites

Gastrointestinal disorders
Meconium peritonitis
Intestinal malrotation
Small intestinal or colonic atresia
Intussusception
Volvulus
Hepatobiliary disorders
Gestational alloimmune liver disease
Cystic fibrosis
Biliary atresia
Portal venous malformations
Infection
Parvovirus
Syphilis
Cytomegalovirus
Toxoplasmosis
Acute maternal hepatitis
Genitourinary disorders
Hydronephrosis
Polycystic kidney disease
Urinary obstruction
Ovarian cyst
Persistent cloaca
Chylous ascites
Lymphangiectasia
Lymphatic malformations
Cardiac disorders
Arrhythmia
Heart failure
Chromosomal abnormalities
Trisomy
Turner syndrome
Neoplasm
Neuroblastoma
Leukemia
Hematologic
Hemolytic anemias
Metabolic disease
Niemann-Pick type C
Congenital disorders of glycosylation
Lysosomal storage diseases
Other
Maternal/fetal injury
Congenital lupus erythematosus
Idiopathic

Modified from Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr.* 2011;52(5):503–513. Table 1.

The clinical hallmark of ascites is abdominal distention. Early satiety and dyspnea can occur with a moderate amount of ascites. Considerable intraperitoneal fluid can accumulate before ascites is detectable by the classic physical signs: bulging flanks, dullness to percussion, shifting dullness, a fluid wave, and the *puddle sign* (percussion of a supine person's abdomen over the umbilicus becomes dull as the patient is moved to a prone position and ascitic fluid puddles in dependent regions). Umbilical herniation can be associated with tense ascites. Ultrasound examination is useful for detecting small amounts of ascites.

Abdominal paracentesis can provide symptomatic relief and may be diagnostic of the cause of the ascites. Determining the serum-ascites albumin gradient can help determine the cause of ascites. A gradient greater than 1.1 g/dL (high-gradient ascites) is consistent with ascites caused by portal hypertension, whereas a gradient <1.1 g/dL (low-gradient ascites) indicates ascites of non-portal-hypertensive etiology.

The course, prognosis, and treatment of ascites depend entirely on the cause. For most patients, treatment consists of dietary sodium restriction and diuretic therapy with spironolactone, with the addition of furosemide in more severe cases. Supplemental albumin can also aid in ascitic fluid mobilization. Refractory cases may require large volume paracentesis or transjugular intrahepatic portosystemic shunting. Patients with any type of ascites are at increased risk for spontaneous bacterial peritonitis.

Section 7
Peritoneum

Chapter 417
Peritoneal Malformations

Jamie F. Merves and Chris A. Liacouras

Numerous anomalies can occur during peritoneal development. Many are rarely of clinical importance, but peritoneal bands and cysts can result in manifestations such as abdominal pain and obstruction. Additionally, peritoneal encapsulation can occur because of an accessory peritoneal sac. Absence or duplication of the omentum occurs rarely.

Congenital peritoneal bands represent anatomically unabsorbed portions of omentum and mesentery and most commonly occur in the regions of the duodenum, duodenojejunal flexure, ileocecal junction, and ascending colon. Although usually benign, they may be responsible for symptoms ranging from nonspecific chronic abdominal pain to intestinal obstruction, malrotation, volvulus, and internal herniation with potential for resulting associated necrosis. Evaluation includes abdominal radiography, fluoroscopy, and, less commonly, CT and angiography. Even when discovered incidentally, surgical management generally remains the standard of care to prevent complications.

Omental cysts arise from obstructed or ectopic lymphatic channels within the omentum. They may be congenital or can result from trauma. They are usually asymptomatic, but abdominal pain or partial small bowel obstruction can result from compression or torsion of the small bowel from traction on the omentum. **Mesenteric cysts** are also rare and may coexist with omental cysts. They most commonly arise from the small bowel mesentery but can also occur in the large bowel mesentery or retroperitoneum. They too arise from lymphatic anomalies, and the cysts can be single or multiple and are often large. Presentation varies but most frequently involves abdominal pain, distention, and appreciation of an abdominal mass and/or suspected ascites on examination. Gastrointestinal symptoms may also include nausea, emesis, constipation, or loose stools. Mesenteric cysts are mostly benign lesions but may act as lead points for torsion and intussusception and can develop hemorrhage, infection, and, rarely, malignant transformation. Cysts are usually well defined and identified on imaging via ultrasound or CT scan. Treatment is typically simple excision, which can be performed laparoscopically in most cases, with excellent results and generally good prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 418
Ascites

Jessica W. Wen and Chris A. Liacouras

Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Multiple causes of ascites have been described in different age-groups (Tables 418.1-418.3). In children, hepatic and renal disease are the most common causes, but ascites can also be caused by cardiac disease, trauma, infection, or neoplasia.

Table 418.1 Causes of Fetal Ascites

Gastrointestinal disorders
Meconium peritonitis
Intestinal malrotation
Small intestinal or colonic atresia
Intussusception
Volvulus
Hepatobiliary disorders
Gestational alloimmune liver disease
Cystic fibrosis
Biliary atresia
Portal venous malformations
Infection
Parvovirus
Syphilis
Cytomegalovirus
Toxoplasmosis
Acute maternal hepatitis
Genitourinary disorders
Hydronephrosis
Polycystic kidney disease
Urinary obstruction
Ovarian cyst
Persistent cloaca
Chylous ascites
Lymphangiectasia
Lymphatic malformations
Cardiac disorders
Arrhythmia
Heart failure
Chromosomal abnormalities
Trisomy
Turner syndrome
Neoplasm
Neuroblastoma
Leukemia
Hematologic
Hemolytic anemias
Metabolic disease
Niemann-Pick type C
Congenital disorders of glycosylation
Lysosomal storage diseases
Other
Maternal/fetal injury
Congenital lupus erythematosus
Idiopathic

Modified from Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr.* 2011;52(5):503–513. Table 1.

The clinical hallmark of ascites is abdominal distention. Early satiety and dyspnea can occur with a moderate amount of ascites. Considerable intraperitoneal fluid can accumulate before ascites is detectable by the classic physical signs: bulging flanks, dullness to percussion, shifting dullness, a fluid wave, and the *puddle sign* (percussion of a supine person's abdomen over the umbilicus becomes dull as the patient is moved to a prone position and ascitic fluid puddles in dependent regions). Umbilical herniation can be associated with tense ascites. Ultrasound examination is useful for detecting small amounts of ascites.

Abdominal paracentesis can provide symptomatic relief and may be diagnostic of the cause of the ascites. Determining the serum-ascites albumin gradient can help determine the cause of ascites. A gradient greater than 1.1 g/dL (high-gradient ascites) is consistent with ascites caused by portal hypertension, whereas a gradient <1.1 g/dL (low-gradient ascites) indicates ascites of non-portal-hypertensive etiology.

The course, prognosis, and treatment of ascites depend entirely on the cause. For most patients, treatment consists of dietary sodium restriction and diuretic therapy with spironolactone, with the addition of furosemide in more severe cases. Supplemental albumin can also aid in ascitic fluid mobilization. Refractory cases may require large volume paracentesis or transjugular intrahepatic portosystemic shunting. Patients with any type of ascites are at increased risk for spontaneous bacterial peritonitis.

Table 418.2 Causes of Neonatal Ascites

- **Hepatobiliary disorders**
  - Cirrhosis
  - α_1-Antitrypsin deficiency
  - Congenital hepatic fibrosis
  - Viral hepatitis
  - Budd-Chiari syndrome
  - Gestational alloimmune liver disease
  - Biliary atresia
  - Bile duct perforation
  - Portal venous malformation
  - Ruptured mesenchymal hamartoma
- **Gastrointestinal disorders**
  - Intestinal malrotation
  - Intestinal perforation
  - Acute appendicitis
  - Intestinal atresia
  - Pancreatitis
- **Chylous ascites**
  - Intestinal lymphangiectasia
  - Lymphatic duct obstruction
  - Lymphatic duct trauma
- **Parenteral nutrition extravasation**
- **Metabolic disease** (see Table 418.1)
- **Genitourinary disorders**
  - Obstructive uropathy
  - Posterior urethral valves
  - Ureterocele
  - Lower ureteral stenosis
  - Ureteral atresia
  - Imperforate hymen
  - Bladder rupture
  - Bladder injury from umbilical artery catheterization
  - Nephrotic syndrome
  - Ruptured corpus luteum cyst
- **Cardiac**
  - Arrhythmia
  - Heart failure
- **Other**
  - Cutis marmorata telangiectatica congenita
  - Intravenous vitamin E
  - Pseudo-ascites
  - Small bowel duplication
  - Abdominal trauma
  - Idiopathic

From Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr.* 2011;52(5):503–513. Table 2.

418.1 Chylous Ascites

Jessica W. Wen and Chris A. Liacouras

Chylous ascites refers to peritoneal fluid that contains lymphatic drainage with a characteristic milky appearance that is rich in triglycerides. Chylous ascites can result from congenital anomaly, injury, or obstruction of the intraabdominal portion of the thoracic duct. Although uncommon, it can occur at any age. In the pediatric population, the most common cause is lymphatic malformation (lymphangiectasia). Other causes include surgical injury to the lymphatics, trauma, cirrhosis, peritoneal bands, generalized lymphangiomatosis, chronic inflammatory processes of the bowel, and mycobacterial infection. Malignancy is a common cause in the adult population but uncommon in pediatrics. Congenital anomalies of the lymphatic system can be associated with Turner, Noonan, yellow nail, and Klippel-Trenaunay-Weber syndromes. Other etiologies include nephrotic syndrome, familial visceral myopathy, sarcoidosis, intestinal malrotation and volvulus, pancreatitis, constrictive pericarditis, and Behçet disease. Postsurgical chylous ascites has been associated with a variety of abdominal surgical procedures, including Nissen fundoplication, appendectomy, liver and kidney transplant, and others. It can occur early, within a week post operation, or weeks to months later due to adhesions and extrinsic compression of lymphatic vessels.

The most common presentation is painless abdominal distention, and it may be accompanied by poor weight gain and loose stools. Peripheral edema is common. Massive chylous ascites can result in scrotal edema, inguinal and umbilical herniation, and respiratory difficulties.

Diagnosis of chylous ascites depends on the demonstration of milky ascitic fluid obtained via paracentesis after a fat-containing feeding. Ascites fluid analysis reveals high protein content, elevated triglycerides, and lymphocytosis. If the patient has had nothing by mouth, the fluid may appear serous. Hypoalbuminemia, hypogammaglobulinemia, and lymphopenia are common in these patients. MR lymphangiography will identify lymphatic malformations.

Table 418.3 Causes of Ascites in Infants and Children

- **Hepatobiliary disorders**
  - Cirrhosis
  - Congenital hepatic fibrosis
  - Acute hepatitis
  - Budd-Chiari syndrome
  - Bile duct perforation
  - Liver transplantation
- **Gastrointestinal disorders**
  - Acute appendicitis
  - Intestinal atresia
  - Pancreatitis
  - Pyloric duplication
- **Serositis**
  - Crohn disease
  - Eosinophilic enteropathy
  - IgA vasculitis (Henoch-Schönlein purpura)
- **Chylous ascites**
  - Intestinal lymphangiectasia
  - Lymphatic duct obstruction
  - Lymphatic duct trauma
- **Parenteral nutrition extravasation**
- **Infectious**
  - Tuberculosis
  - Abscess
  - Schistosomiasis
- **Neoplasm**
  - Lymphoma
  - Wilms tumor
  - Clear cell renal sarcoma
  - Glioma
  - Germ cell tumor
  - Ovarian tumor
  - Mesothelioma
  - Neuroblastoma
- **Metabolic disease**
- **Genitourinary disorders**
  - Nephrotic syndrome
  - Peritoneal dialysis
- **Cardiac**
  - Heart failure
- **Pseudo-ascites**
  - Celiac disease
  - Cystic mesothelioma
  - Omental cyst
  - Ovarian cyst
- **Other**
  - Systemic lupus erythematosus
  - Ventriculoperitoneal shunt
  - Vitamin A toxicity
  - Chronic granulomatous disease
  - Nonaccidental trauma
  - Protein losing enteropathy
  - Idiopathic

Modified from Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr.* 2011;52(5):503–513. Table 3.

Treatment includes a high-protein, low-fat diet supplemented with medium-chain triglycerides that are absorbed directly into the portal circulation and decrease lymph production. Parenteral alimentation may be necessary if nutrition remains impaired on oral feedings; this may also significantly decrease lymph flow and facilitate sealing at the point of lymph leakage. Octreotide, a somatostatin analog, has been used subcutaneously in chylous ascites. The mechanism is not clearly understood; however, it decreases intestinal blood flow, leading to decreased portal pressure, and it also inhibits lymphatic secretion through somatostatin receptors in the intestinal wall. Paracentesis should be repeated only if abdominal distention causes respiratory distress. Lymphangiography with adjunctive embolization may be very successful in treating chylous ascites with identified site of leakage or a malformation. Laparotomy may be indicated if conservative management has been unsuccessful for potential surgical ligation of lymphatics.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 419
Peritonitis

Jessica W. Wen and Chris A. Liacouras

Inflammation of the peritoneal lining of the abdominal cavity can result from infectious, autoimmune, neoplastic, and chemical processes. Infectious peritonitis is usually defined as primary (spontaneous) or secondary. In primary peritonitis, the source of infection originates outside the abdomen and seeds the peritoneal cavity via hematogenous, lymphatic, or transmural spread. Secondary peritonitis arises from the abdominal cavity itself through extension from or rupture of an intraabdominal viscus or an abscess within an organ. Tertiary peritonitis refers to recurrent diffuse or localized disease and is associated with poorer outcomes than secondary peritonitis.

Clinically, patients have abdominal pain, abdominal tenderness, and rigidity on exam. Peritonitis can result from rupture of a hollow viscus, such as the appendix or a Meckel diverticulum; disruption of the peritoneum from trauma or peritoneal dialysis catheter; chemical peritonitis from other bodily fluid, including bile and urine; and infection. Meconium peritonitis is described in Chapter 135. Peritonitis is considered a surgical emergency and requires exploration and lavage of the abdomen, except in spontaneous bacterial peritonitis.

419.1 Acute Primary Peritonitis

Jessica W. Wen and Chris A. Liacouras

ETIOLOGY AND EPIDEMIOLOGY

Primary peritonitis usually refers to bacterial infection of the peritoneal cavity without a demonstrable intraabdominal source. Most cases occur in children with ascites resulting from cirrhosis or nephrotic syndrome. Infection can result from translocation of gut bacteria as well as immune dysfunction. Rarely, primary peritonitis occurs in previously healthy children. Pneumococci (most common), group A streptococci, enterococci, staphylococci, and gram-negative enteric bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae*, are most commonly found. *Mycobacterium tuberculosis*, *Neisseria meningitidis*, and *Mycobacterium bovis* are rare causes. A small percentage are polymicrobial or culture negative.

CLINICAL MANIFESTATIONS

Onset may be insidious or rapid and is characterized by fever, abdominal pain, and a toxic appearance. Vomiting and diarrhea may be present. Hypotension and tachycardia are common, along with shallow, rapid respirations because of discomfort associated with breathing. Abdominal palpation might demonstrate rebound tenderness and rigidity. Bowel sounds are hypoactive or absent. However, signs and symptoms may be subtle at times, and increased vigilance is needed in cirrhotic patients who have ascites and present with unexplained leukocytosis, azotemia, or metabolic acidosis.

DIAGNOSIS AND TREATMENT

Peripheral leukocytosis with a marked predominance of polymorphonuclear cells is common, although the white blood cell (WBC) count can be affected by preexisting hypersplenism in patients with cirrhosis. Patients with nephrotic syndrome generally have proteinuria, and low serum albumin in these patients is associated with an increased risk of peritonitis. X-ray examination of the abdomen reveals dilation of the large and small intestines, with increased separation of loops secondary to bowel wall thickening. Distinguishing primary peritonitis from appendicitis may be difficult in patients without a history of nephrotic syndrome or cirrhosis; accordingly, the diagnosis of primary peritonitis is made by CT scan, laparoscopy, or laparotomy. In a child with known renal or hepatic disease and ascites, the presence of peritoneal signs should prompt diagnostic paracentesis. Infected fluid usually reveals a WBC count of ≥250 cells/mm^3, with >50% polymorphonuclear cells.

Primary peritonitis is usually *monomicrobial*. The presence of mixed bacterial flora on ascitic fluid examination or free air on abdominal roentgenogram in children with presumed peritonitis mandates further evaluation to localize a perforation as a likely *intraabdominal* source of the infection. Inoculation of ascitic fluid obtained at paracentesis directly into blood culture bottles increases the yield of positive cultures. Parenteral antibiotic therapy with broad-spectrum coverage, such as cefotaxime, should be started promptly, with subsequent changes dependent on sensitivity testing (vancomycin for resistant pneumococci). Patients with risk factor for multidrug resistant organisms such as nosocomial infection, recent exposure to antibiotics, or with sepsis or septic shock should receive broad-spectrum coverage with piperacillin/tazobactam with consideration for addition of vancomycin if prior infection or positive surveillance swab for methicillin-resistant *Staphylococcus aureus*. Therapy should be continued for 5-10 days.

Culture-negative neutrocytic ascites is a variant of primary peritonitis with an ascitic fluid WBC count of >500 cells/mm^3, a negative culture, no intraabdominal source of infection, and no prior treatment with antibiotics. It should be treated in a similar way to primary peritonitis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

419.2 Acute Secondary Peritonitis

Jessica W. Wen and Chris A. Liacouras

Acute secondary peritonitis most often results from entry of enteric bacteria into the peritoneal cavity through a necrotic defect in the wall of the intestines or other viscus as a result of obstruction or infarction or after rupture of an intraabdominal visceral abscess. It most commonly follows perforation of the appendix. Other causes include incarcerated hernias, rupture of a Meckel diverticulum, midgut volvulus, intussusception, hemolytic uremic syndrome, peptic ulceration, inflammatory bowel disease, necrotizing cholecystitis, necrotizing enterocolitis, typhlitis, and traumatic perforation.

Peritonitis in the neonatal period most often occurs as a complication of necrotizing enterocolitis but may be associated with meconium ileus or spontaneous (or indomethacin-induced) rupture of the stomach or intestines. In postpubertal females, bacteria from the genital tract *(Neisseria gonorrhoeae, Chlamydia trachomatis)* can gain access to the peritoneal cavity via the fallopian tubes, causing secondary peritonitis. The presence of a foreign body, such as a ventriculoperitoneal catheter or peritoneal dialysis catheter, can predispose to peritonitis, with skin microorganisms, such as *Staphylococcus epidermidis, S. aureus,* and *Candida albicans*, contaminating the shunt. Secondary peritonitis results from direct toxic effects of bacteria as well as local and systemic release of inflammatory mediators in response to organisms and their products (lipopolysaccharide endotoxin). The development of sepsis depends on various host and disease factors, as well as the promptness of antimicrobial and surgical intervention.

CLINICAL MANIFESTATIONS

Similar to primary peritonitis, characteristic symptoms include fever, diffuse abdominal pain, nausea, and vomiting. Physical findings of peritoneal inflammation include rebound tenderness, abdominal wall rigidity, a paucity of body motion (lying still), and decreased or absent bowel sounds from paralytic ileus. Massive exudation of fluid into the peritoneal cavity, along with the systemic release of vasodilative substances, can lead to the rapid development of shock. A toxic appearance, irritability, and restlessness are common. Basilar atelectasis, as well as intrapulmonary shunting, can develop, with progression to acute respiratory distress syndrome.

Laboratory studies reveal a peripheral WBC count >12,000 cells/mm^3, with a marked predominance of polymorphonuclear forms. X-rays of the abdomen can reveal free air in the peritoneal cavity, evidence of ileus or obstruction, peritoneal fluid, and obliteration of the psoas shadow. Other peritoneal fluid findings suggestive of secondary peritonitis include elevated total protein (>1 g/dL), and low glucose (<50 mg/dL).

TREATMENT

Aggressive fluid resuscitation and support of cardiovascular function should begin immediately. Stabilization of the patient before surgical intervention is mandatory. Antibiotic therapy must provide coverage for organisms that predominate at the site of presumed origin of the infection. Initial empiric antibiotics for spontaneous bacterial peritonitis has included cefotaxime or ceftriaxone. In contrast to primary peritonitis, secondary peritonitis is typically *polymicrobial*. For perforation of the lower gastrointestinal tract, a regimen of ampicillin, gentamicin, and clindamycin or metronidazole will adequately address infection by *E. coli*, *Klebsiella*, and *Bacteroides* spp. and enterococci. Alternative therapy could include piperacillin/tazobactam or a carbapenem. Surgery to repair a perforated viscus should proceed after the patient is stabilized and antibiotic therapy is initiated. Intraoperative peritoneal fluid cultures will indicate whether a change in the antibiotic regimen is warranted. Empirical treatment for peritoneal dialysis catheter–related peritonitis may include intraperitoneal vancomycin or a first-generation cephalosporin (such as cefazolin) for gram-positive organism coverage, and third- or fourth-generation cephalosporin (such as cefepime or ceftazidime), aminoglycoside, carbapenem or aztreonam (for patients allergic to cephalosporins) for gram-negative organism coverage. Serious infection from peritoneal dialysis catheters can generally be prevented with good catheter hygiene and prompt removal and replacement with signs of progressive infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

419.3 Acute Secondary Localized Peritonitis (Peritoneal Abscess)

Jessica W. Wen and Chris A. Liacouras

ETIOLOGY

Intraabdominal abscesses occur less commonly in children and infants than in adults, but they can develop in visceral intraabdominal organs (hepatic, splenic, renal, pancreatic, tubo-ovarian abscesses) or in the interintestinal, periappendiceal, subdiaphragmatic, subhepatic, pelvic, or retroperitoneal spaces. Most commonly, periappendiceal and pelvic abscesses arise from a perforation of the appendix. Transmural inflammation with fistula formation can result in intraabdominal abscess formation in children with inflammatory bowel disease.

CLINICAL MANIFESTATIONS

Prolonged fever, anorexia, vomiting, and lassitude suggest the development of an intraabdominal abscess. The peripheral WBC count is elevated, as is the erythrocyte sedimentation rate. With an appendiceal abscess, there is localized tenderness and a palpable mass in the right lower quadrant. A pelvic abscess is suggested by abdominal distention, rectal tenesmus with or without the passage of small-volume mucous stools, and bladder irritability. Rectal examination might reveal a tender mass anteriorly. Subphrenic gas collection, basal atelectasis, elevated hemidiaphragm, and pleural effusion may be present with a subdiaphragmatic abscess. Psoas abscess can develop from extension of infection from a retroperitoneal appendicitis, Crohn disease, or perirenal or intrarenal abscess. Abdominal findings may be minimal, and presentation can include a limp, hip pain, and fever. Ultrasound examination, CT scanning, and MRI may be used to localize intraabdominal abscesses; MRI gives the best resolution of disease involvement.

TREATMENT

An abscess should be drained, and appropriate antibiotic therapy provided. Drainage can be performed under radiologic control (ultrasonogram or CT guidance) and an indwelling drainage catheter left in place, or surgically depending on location of abscess. Initial broad-spectrum antibiotic coverage such as a combination of ampicillin, gentamicin, and clindamycin or ciprofloxacin and metronidazole should be started and can be modified, depending on the results of sensitivity testing. The treatment of appendiceal rupture complicated by abscess formation may be problematic because intestinal phlegmon formation can make surgical resection more difficult. Intensive antibiotic therapy for 4-6 weeks followed by an interval appendectomy is often the treatment course followed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 420
Epigastric Hernia

John J. Aiken

Epigastric hernias in children are ventral hernias in the midline of the abdominal wall between the xiphoid process of the sternum and the umbilicus. Epigastric hernias are more likely to be congenital than acquired. The defect typically contains only preperitoneal fat without a peritoneal sac or abdominal viscera. Because most epigastric hernias are small and asymptomatic, the true incidence is unknown, but the reported incidence in childhood varies from <1% to as high as 5%. The etiology of epigastric hernia is unknown. The two main hypotheses are the vascular lacunae hypothesis and the tendinous fiber decussation hypothesis; the former proposes that the protrusion is through small spaces created where the vascular lacunae penetrate the linea alba, and the latter proposes that epigastric hernia occurs exclusively at sites where affected patients do not have triple lines of decussation. In addition, undiagnosed collagen disorders, increased intraabdominal pressure, and, in older patients, previous midline incision may play a role in the development of epigastric hernia. Epigastric hernias may be single or multiple and are 2-3 times more common in males than females. Through the small midline defect there is often herniation of preperitoneal fat into the superficial abdominal wall, although as the defect becomes progressively larger, the rare possibility exists of herniation of intraabdominal contents. Epigastric (incisional) hernias can occur in a previous incision site or be associated with ventricular-peritoneal shunts.

CLINICAL PRESENTATION

Epigastric hernias typically appear in young children as a visible or palpable mass in the midline, between the umbilicus and the xiphoid process of the sternum, noted by the parents or primary care practitioner. The mass is almost always small (<1 cm), asymptomatic, and typically reported as always present, but most apparent at times of irritability or straining. Occasionally the mass is intermittent, and the child relates pain localized to the site. Physical examination demonstrates a firm mass, directly in the midline, anywhere between the umbilicus and the xiphoid process. The mass may be intermittent if the fat reduces with relaxation of the abdominal muscles. Epigastric hernias typically contain only preperitoneal fat, and most are not reducible because of the small size of the fascial defect. Rarely, a fascial defect is noted without a palpable mass. Herniation of intestines or abdominal viscera in an epigastric hernia would be exceptionally rare if the defect enlarges over time. The mass may be tender to examination, but strangulation of the hernia contents is uncommon. Physical examination is almost always diagnostic, and imaging studies are generally unnecessary. If the diagnosis is unclear, imaging may be useful. Ultrasound typically shows a small mass that is isoechoic to the adjacent subcutaneous fat and possibly connection through a small fascial defect with the preperitoneal fat. MRI imaging might be helpful in diagnosis but is not routinely used.

The natural history of epigastric hernia is for gradual enlargement over time as intermittently more preperitoneal fat is extruded through the defect at times of straining or increased intraabdominal pressure. Left untreated, the defect can enlarge and allow herniation of intraabdominal viscera within a peritoneal sac, mostly seen in adults. Epigastric hernias do not resolve spontaneously, and therefore operative repair is the recommended treatment. The site should be carefully marked preoperatively because the mass and defect can be difficult to localize in a relaxed abdominal wall after induction of anesthesia. A limited transverse incision is made over the mass, and dissection is performed to delineate the edges of the fascial defect. If herniated fat is present, it is dissected free of the subcutaneous tissues and can be reduced or ligated and excised. The defect is closed using absorbable suture. The skin is closed with an absorbable subcuticular suture. Postoperative complications are rare, and the recurrence rate is low.

420.1 Incisional Hernia

John J. Aiken

Hernia formation in the site of a previous laparotomy is uncommon in childhood. Incisional hernias can also occur at the incision sites for the laparoscopic ports used in minimally invasive surgery. Factors associated with an increased risk of incisional hernia include increased intraabdominal pressure, wound infection, and midline incision. The laparoscopic port sites pose a technical challenge to visualize the fascia in a small incision. Transverse abdominal incisions are favored because of their increased strength and blood supply, which reduces the likelihood of wound infection and incisional hernia. Although most incisional hernias require repair, operation should be deferred until the child is in optimal medical condition. Some incisional hernias resolve, especially those occurring in infants. Some recommend elastic bandaging to discourage enlargement of the hernia and to promote spontaneous healing. Initial management should be conservative, with repair deferred until around 1 year of age. Incarceration is very uncommon in incisional hernias but is an indication for prompt repair. Newborns with abdominal wall defects represent the largest group of children with incisional hernias.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

The Respiratory System

PART XVII

Section 1

Development and Function

Chapter 421

Diagnostic Approach to Respiratory Disease

Daniel J. Lesser, Julie Ryu, Kelan G. Tantisira, and Gabriel G. Haddad

HISTORY

The history of the illness begins with a narrative provided by the parent/caretaker with input from the patient when possible. It should include questions about respiratory symptoms (dyspnea, cough, pain, wheezing, snoring, apnea, cyanosis, exercise intolerance), as well as their chronicity, timing during day or night, and associations with environmental exposures and activities including exercise or food intake. The respiratory system interacts with a number of other systems, and questions related to cardiac, gastrointestinal, central nervous, hematologic, and immune systems may be relevant. Questions related to gastrointestinal reflux, congenital abnormalities (airway anomalies, ciliary dyskinesia), or immune status may be important in a patient with repeated pneumonia. The family history is essential and should include inquiries about siblings and other close relatives with similar symptoms or any chronic disease with respiratory components.

PHYSICAL EXAMINATION

Respiratory dysfunction usually produces detectable alterations in the pattern of breathing. Values for normal respiratory rates are presented in Table 79.1 and depend on many factors—most importantly, age. Repeated respiratory rate measurements are necessary because respiratory rates, especially in the young, are exquisitely sensitive to extraneous stimuli. Sleeping respiratory rates are more reproducible in infants than those obtained during feeding or activity. These rates vary among infants but average 40-50 breaths/min in the first few weeks of life and usually <60 breaths/min in the first few days of life.

Respiratory control abnormalities can cause the child to breathe at a low rate or periodically. Mechanical abnormalities produce compensatory changes that are generally directed at altering minute ventilation to maintain alveolar ventilation. Decreases in lung compliance require increases in muscular force and breathing rate, leading to variable increases in chest wall retractions and nasal flaring. The respiratory excursions of children with restrictive disease are shallow. An expiratory grunt is common as the child attempts to raise the **functional residual capacity (FRC)** by closing the glottis at the end of expiration. The FRC is the amount of air left in the lungs after tidal expiration. Children with obstructive disease might take slower, deeper breaths. When the obstruction is **extrathoracic** (from the nose to the mid-trachea), inspiration is more prolonged than expiration, and an inspiratory stridor (a predominant inspiratory monophonic noise) can usually be heard (Fig. 421.1). When the obstruction is **intrathoracic**, expiration is more prolonged than inspiration, and the patient often has to make use of accessory expiratory muscles. Intrathoracic obstruction results in air trapping and therefore a larger residual volume along with a possible increase in FRC (Fig. 421.2).

Lung percussion has limited value in small infants because it cannot discriminate between noises originating from tissues that are close to each other. In adolescents and adults, percussion is usually dull in restrictive lung disease (pleural effusion, pneumonia, atelectasis), but it is tympanitic in obstructive disease (asthma, pneumothorax).

Auscultation confirms the presence of inspiratory or expiratory prolongation and provides information about the symmetry and quality of air movement. In addition, it often detects abnormal or adventitious sounds such as **stridor**; **crackles** or **rales**, high-pitched, interrupted sounds found during inspiration and, more rarely, during early expiration, which denote opening of previously closed air spaces; or **wheezes**, musical, continuous sounds usually caused by the development of turbulent flow in narrow airways (Table 421.1). **Digital clubbing** is a sign of chronic hypoxia and chronic lung disease (Fig. 421.3) but may be a result of nonpulmonary etiologies (Table 421.2).

BLOOD GAS ANALYSIS

The main function of the respiratory system is to remove carbon dioxide from and add oxygen to the systemic venous blood brought to the lung. The composition of the inspired gas, ventilation, perfusion, diffusion, and tissue metabolism has a significant influence on the arterial blood gases.

The total pressure of the atmosphere at sea level is 760 torr. With increasing altitude, the atmospheric pressure decreases. The total atmospheric pressure is equal to the sum of partial pressures exerted by each of its component gases. Alveolar air is 100% humidified, so in alveolar gas calculations, the inspired gas is also presumed to be 100% humidified. At a temperature of 37°C (98.6°F) and 100% humidity, water vapor exerts a pressure of 47 torr, regardless of altitude. In a natural setting, the atmosphere consists of 20.93% oxygen. **Partial pressure of oxygen in inspired gas (P_{IO_2})** at sea level is therefore (760 − 47) × 20.93% = 149 torr. When breathing 40% oxygen at sea level, P_{IO_2} is (760 − 47) × 40% = 285 torr. At higher altitudes, breathing different concentrations of oxygen, P_{IO_2} is less than at sea level, depending on the prevalent atmospheric pressures. In Denver (altitude of 5,000 feet and barometric pressure of 632 torr), P_{IO_2} in room air is (632 − 47) × 20.93% = 122 torr, and in 40% oxygen, it is (632 − 47) × 40% = 234 torr.

Minute volume is a product of V_T and respiratory rate. Part of the V_T occupies the conducting airways (anatomic dead space), which does not contribute to gas exchange in the alveoli. **Alveolar ventilation** is the volume of atmospheric air entering the alveoli and is calculated as (V_T − dead space) × respiratory rate. Alveolar ventilation is inversely proportional to arterial P_{CO_2} (P_{ACO_2}). When alveolar ventilation is halved, P_{ACO_2} is doubled. Conversely, doubling of alveolar ventilation decreases P_{ACO_2} by 50%. **Alveolar P_{O_2} (P_{AO_2})** is calculated by the **alveolar air equation** as follows, where R is the respiratory quotient. For practical purposes, P_{ACO_2} is substituted by **arterial P_{CO_2}** (P_{ACO_2}), and R is assumed to be 0.8. According to the alveolar air equation, for a given P_{IO_2}, a rise in P_{ACO_2} of 10 torr results in a decrease in P_{AO_2} by 10 ÷ 0.8, or 10 × 1.25, or 12.5 torr. Thus proportionately inverse changes in P_{AO_2} occur to the extent of 1.25 times the changes in P_{ACO_2} (or P_{ACO_2}).

After the alveolar gas composition is determined by the inspired gas conditions and the process of ventilation, gas exchange occurs by the process of diffusion and equilibration of alveolar gas with pulmonary capillary blood. Diffusion depends on the alveolar capillary barrier and the amount of available time for equilibration. In health, the

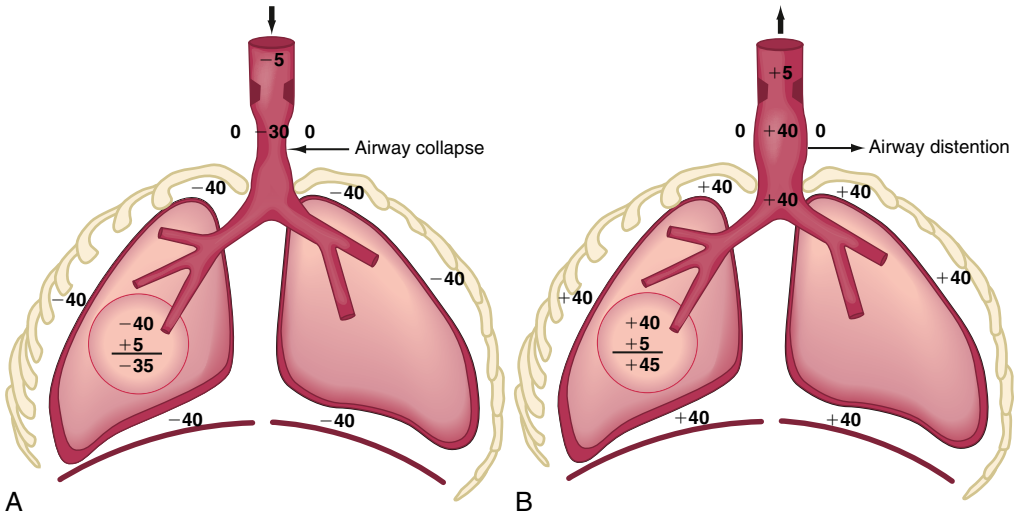

Fig. 421.1 A, In extrathoracic airway obstruction, the increased negative pressure during inspiration is transmitted up to the site of obstruction. This results in collapse of the extrathoracic airway below the site of obstruction, making the obstruction worse during inspiration. Note that the pressures are compared with the atmospheric pressure, which is traditionally represented as 0 cm. Terminal airway pressure is calculated as intrapleural pressure plus lung recoil pressure. Lung recoil pressure is arbitrarily chosen as 5 cm for the sake of simplicity. B, During expiration, the positive pressure below the site of obstruction results in distention of the extrathoracic airway and amelioration of symptoms. *(Courtesy Dr. Ashok Sarnaik.)*

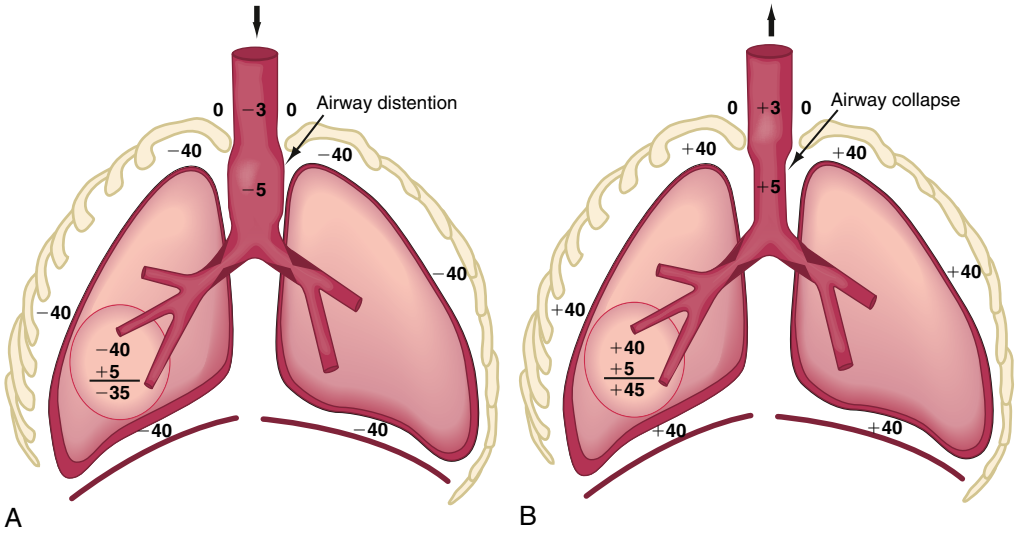

Fig. 421.2 A and B, In intrapulmonary airway obstruction, an even wider segment of intrathoracic airway is subjected to pressure changes compared with those observed in intrathoracic-extrapulmonary airway obstruction. Such lesions are associated with marked increase in airway obstruction during expiration. *(Courtesy Dr. Ashok Sarnaik.)*

Table 421.1 Respiratory Sounds

BASIC SOUNDS	MECHANISMS	ORIGIN	ACOUSTICS	RELEVANCE
Lung	Turbulent flow, vortices, other	Central (expiration), lobar to segmental airways (inspiration)	Low-pass filtered noise (<100 to >1,000 Hz)	Regional ventilation, airway caliber
Tracheal	Turbulent flow, flow impinging on airway walls	Pharynx, larynx, trachea, large airways	Noise with resonances (<100 to >3,000 Hz)	Upper airway configuration
ADVENTITIOUS SOUNDS				
Wheezes	Airway wall flutter, vortex shedding, other	Central and lower airways	Sinusoidal (<100 to >1,000 Hz, duration typically >80 msec)	Airway obstruction, flow limitation
Rhonchi	Rupture of fluid films, airway wall vibration	Larger airways	Series of rapidly dampened sinusoids (typically <300 Hz and duration <100 msec)	Secretions, abnormal airway collapsibility
Crackles	Airway wall stress-relaxation	Central and lower airways	Rapidly dampened wave deflections (duration typically <20 msec)	Distal airway and alveolar closure, secretions

Modified from Pasterkamp H, Kraman SS, Wodicka GR. Respiratory sounds. Advances beyond the stethoscope. *Am J Respir Crit Care Med.* 1997;156(3):974–987.

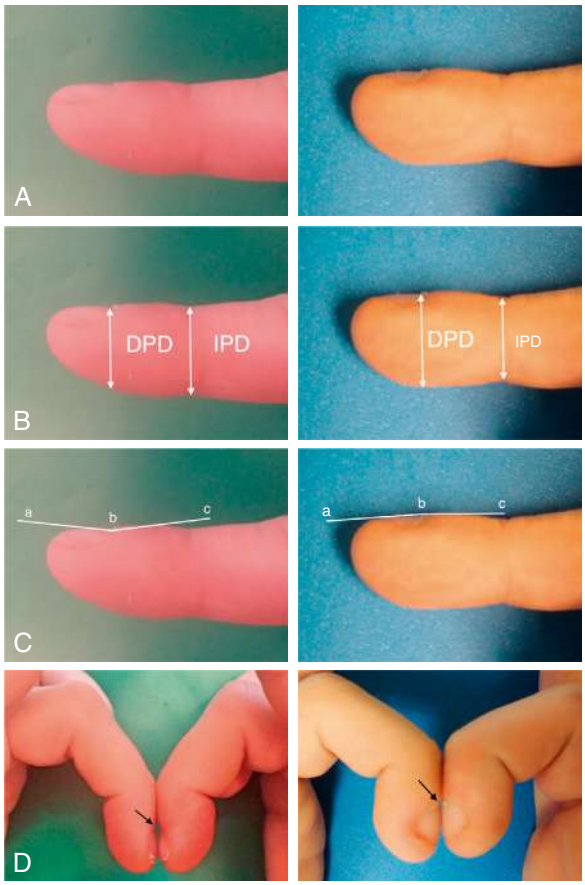

Fig. 421.3 A, Normal and clubbed finger viewed in profile. B, The normal finger demonstrates a distal phalangeal finger depth *(DPD)*/interphalangeal finger depth *(IPD)* ratio <1. The clubbed finger demonstrates a DPD/IPD ratio >1. C, The normal finger on the left demonstrates a normal profile *(abc)* with an angle less than 180 degrees. The clubbed finger demonstrates a profile angle >180 degrees. D, Schamroth sign is demonstrated in the clubbed finger with the loss of the diamond-shaped window in between finger beds *(arrow)* that is demonstrated in the normal finger. *(From Wilmott RW, Deterding RR, Li A, et al, eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 1.14, p. 20.)*

Table 421.2 Nonpulmonary Diseases Associated with Clubbing

CARDIAC
Cyanotic congenital heart disease
Bacterial endocarditis
Chronic heart failure
HEMATOLOGIC
Thalassemia
Congenital methemoglobinemia (rare)
GASTROINTESTINAL
Crohn disease
Ulcerative colitis
Celiac disease
Chronic dysentery, sprue
Polyposis coli
Severe gastrointestinal hemorrhage
Small bowel lymphoma
Liver cirrhosis (including α1-antitrypsin deficiency)
Chronic active hepatitis
OTHER
Thyroid deficiency (thyroid acropachy)
Thyrotoxicosis
Chronic pyelonephritis (rare)
Toxic (e.g., arsenic, mercury, beryllium)
Lymphomatoid granulomatosis
Fabry disease
Raynaud disease, scleroderma
Hodgkin disease
Familial
UNILATERAL CLUBBING
Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)
Subluxation of shoulder
Median nerve injury
Local trauma

From Pasterkamp H. The history and physical examination. In: Wilmott RW, Boat TF, Bush A, et al., eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*, 8th ed. Philadelphia: Elsevier; 2012.

equilibration of alveolar gas and pulmonary capillary blood is complete for both oxygen and carbon dioxide. In diseases in which the alveolar capillary barrier is abnormally increased (alveolar interstitial diseases) and/or when the time available for equilibration is decreased (increased blood flow velocity), diffusion is incomplete. Because of its greater solubility in liquid medium, carbon dioxide is 20 times more diffusible than oxygen. Therefore diseases with diffusion defects are characterized by marked **alveolar-arterial oxygen ($A\text{-}aO_2$)** gradients and hypoxemia. Significant elevation of CO_2 does not occur as a result of a diffusion defect unless there is coexistent hypoventilation.

Venous blood brought to the lungs is "arterialized" after diffusion is complete. After complete arterialization, the pulmonary capillary blood should have the same P_{O_2} and P_{CO_2} as in the alveoli. The arterial blood gas composition is different from that in the alveoli, even in normal conditions, because there is a certain amount of dead space ventilation and venous admixture in a normal lung. Dead space ventilation results in a higher Pa_{CO_2} than PA_{CO_2}, whereas venous admixture or right-to-left shunting results in a lower Pa_{O_2} compared with the alveolar gas composition (Fig. 421.4). Pa_{O_2} is a reflection of the amount of oxygen dissolved in blood, which is a relatively minor component of total blood oxygen content. For every 100 torr P_{O_2}, there is 0.3 mL of dissolved O_2 in 100 mL of blood. The total blood oxygen content is composed of the dissolved oxygen and the oxygen bound to hemoglobin (Hb). Each gram of Hb carries 1.34 mL of O_2 when 100% saturated with oxygen. Thus 15 g of Hb carry 20.1 mL of oxygen. **Arterial oxygen content (Ca_{O_2})**, expressed as mL O_2/dL blood, can be calculated as $(Pa_{O_2} \times 0.003) + (Hb \times 1.34 \times S_{O_2})$, where Hb is grams of Hb per deciliter of blood and S_{O_2} is the percentage of oxyhemoglobin saturation. The relationship of P_{O_2} and the amount of oxygen carried by the Hb is the basis of the O_2-Hb dissociation curve (Fig. 421.5). The P_{O_2} at which Hb is 50% saturated is referred to as P_{50}. At a normal pH, Hb is 94% saturated at P_{O_2} of 70, and little further gain in saturation is accomplished at a higher P_{O_2}. At P_{O_2} <50, there is a steep decline in saturation and therefore the oxygen content.

Oxygen delivery to tissues is a product of oxygen content and cardiac output. When Hb is near 100% saturated, blood contains approximately 20 mL of oxygen per 100 mL or 200 mL/L. In a healthy adult, cardiac output is approximately 5 L/min, oxygen delivery 1,000 mL/min, and oxygen consumption 250 mL/min. Mixed venous blood returning to the heart has a P_{O_2} of 40 torr and is 75% saturated with oxygen. Blood oxygen content, cardiac output, and oxygen consumption are important determinants of mixed venous oxygen saturation. Given a steady-state blood oxygen content and oxygen consumption, the mixed venous saturation is an important indicator of cardiac output. A declining mixed venous saturation in such a state indicates decreasing cardiac output.

Clinical observations and interpretation of blood gas values are critical in localizing the site of the lesion and estimating its severity (Table 421.3). In airway obstruction above the carina (subglottic stenosis, vascular ring), blood gases reflect overall alveolar hypoventilation. This is manifested by an elevated PA_{CO_2} and a proportionate decrease in Pa_{O_2} as determined by the alveolar air equation. A rise in Pa_{CO_2} of 20 torr decreases Pa_{O_2} by 20 × 1.25 or 25 torr. In the absence of

significant parenchymal disease and intrapulmonary shunting, such lesions respond very well to supplemental oxygen in reversing hypoxemia. Similar blood gas values, demonstrating alveolar hypoventilation and response to supplemental oxygen, are observed in patients with a depressed respiratory center and ineffective neuromuscular function, resulting in respiratory insufficiency. Such patients can be easily distinguished from those with airway obstruction by their poor respiratory effort.

In intrapulmonary airway obstruction (asthma, bronchiolitis), blood gases reflect ventilation-perfusion imbalance and venous admixture. In these diseases, the obstruction is not uniform throughout the lungs, resulting in areas that are hyperventilated and others that are hypoventilated. Pulmonary capillary blood coming from hyperventilated areas has a higher P_{O_2} and lower P_{CO_2}, whereas that coming from hypoventilated regions has a lower P_{O_2} and higher P_{CO_2}. A lower blood P_{CO_2} can compensate for the higher P_{CO_2} because the Hb-CO_2 dissociation curve is relatively linear. In mild disease, the hyperventilated areas predominate, resulting in hypocarbia. An elevated Pa_{O_2} in hyperventilated areas cannot compensate for the decreased Pa_{O_2} in hypoventilated areas because of the shape of the O_2-Hb dissociation curve. This results in venous admixture, arterial desaturation, and decreased Pa_{O_2} (see Fig. 421.4). With increasing disease severity, more areas become hypoventilated, resulting in normalization of Pa_{CO_2} with a further decrease in Pa_{O_2}. A normal or slightly elevated Pa_{CO_2} in asthma should be viewed with concern as a potential indicator of impending respiratory failure. In severe intrapulmonary airway obstruction, hypoventilated areas predominate, leading to hypercarbia, respiratory acidosis, and hypoxemia. The degree to which supplemental oxygenation raises Pa_{O_2} depends on the severity of the illness and the degree of venous admixture.

In alveolar and interstitial diseases, blood gas values reflect both intrapulmonary right-to-left shunting and a diffusion barrier. Hypoxemia is a hallmark of such conditions occurring early in the disease process. Pa_{CO_2} is either normal or decreased. An increase in Pa_{CO_2} is observed only later in the course, as muscle fatigue and exhaustion result in hypoventilation. Response to supplemental oxygen is relatively poor with shunting and diffusion disorders compared with other lesions.

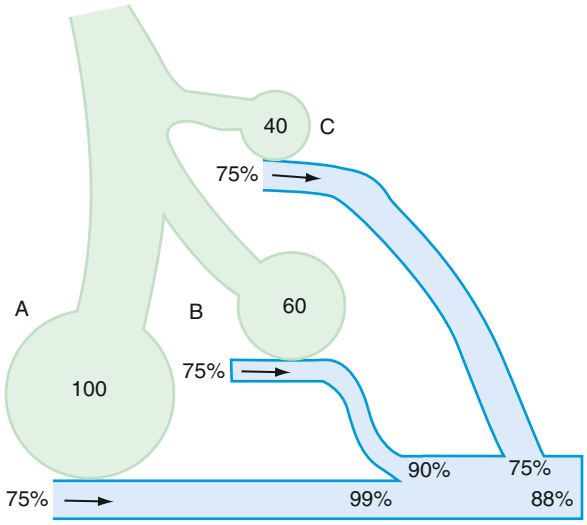

Fig. 421.4 Diagram demonstrating the effects of decreased ventilation-perfusion ratios on arterial oxygenation in the lungs. Three alveolar-capillary units are illustrated. Unit *A* has normal ventilation and an alveolar P_{O_2} of 100 mm Hg (shown by the number in the middle of the space). The blood that circulates through this unit raises its oxygen saturation from 75% (the saturation of mixed venous blood) to 99%. Unit *B* has a lower ventilation-perfusion ratio and a lower alveolar P_{O_2} of 60 mm Hg. The blood that circulates through this unit reaches a saturation of only 90%. Finally, unit *C* is not ventilated at all. Its alveolar P_{O_2} is equivalent to that of the venous blood, which travels through the unit unaltered. The oxygen saturation of the arterial blood reflects the weighted contributions of these three units. If it is assumed that each unit has the same blood flow, the arterial blood would have a saturation of only 88%. Ventilation-perfusion mismatch is the most common mechanism of arterial hypoxemia in lung disease. Supplemental oxygen increases the arterial P_{O_2} by raising the alveolar P_{O_2} in lung units that, like *B*, have a ventilation-perfusion ratio >0.

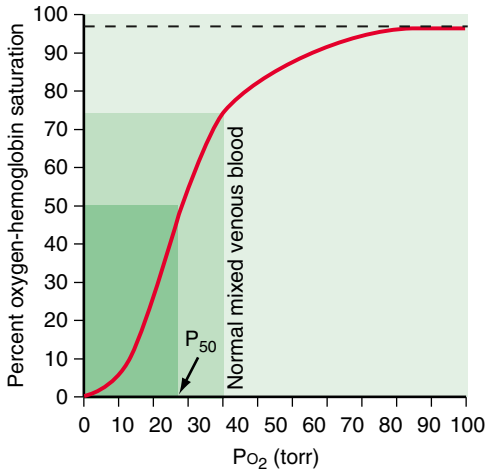

Fig. 421.5 Oxygen-hemoglobin dissociation curve. P_{50} of adult blood is around 27 torr. Under basal conditions, mixed venous blood has a P_{O_2} of 40 torr and oxygen-hemoglobin saturation of 75%. In arterial blood, these values are 100 torr and 97.5%, respectively. Note that there is a steep decline in oxygen-hemoglobin saturation at Pa_{O_2} <50 torr, but relatively little increase in saturation is gained at P_{O_2} >70 torr. *(Courtesy Dr. Ashok Sarnaik.)*

Table 421.3 Interpretation of Arterial Blood Gas Values

LESION	EFFECT	TYPICAL ABG
Central (above the carina) airway obstruction *or* Depressed respiratory center *or* Ineffective neuromuscular function	Uniform alveolar hypoventilation	Early increase in P_{CO_2}. Proportionate decrease in P_{O_2} depending on alveolar air equation Response to supplemental oxygen: excellent
Intrapulmonary airway obstruction	Venous admixture mismatch	*Mild*: ↓ P_{CO_2}, ↓ P_{O_2} *Moderate*: "normal" P_{CO_2}, ↓↓ P_{O_2} *Severe*: ↑↑ P_{CO_2}, ↓↓↓ P_{O_2} Response to supplemental oxygen: good
Alveolar-interstitial pathology	Diffusion defect R → L shunt	Early decrease in P_{O_2} depending on severity Normal or low P_{CO_2}, ↑ P_{CO_2} if fatigue develops Response to supplemental oxygen: fair to poor

ABG, Arterial blood gas.
Courtesy Dr. Ashok Sarnaik.

Most clinical entities present with mixed lesions. A child with a vascular ring might also have an area of atelectasis; the arterial blood gas reflects both processes. The blood gas values reflect the more dominant lesion.

An arterial blood gas analysis is probably the single most useful rapid test of pulmonary function. Although this analysis does not specify the cause of the condition or the specific nature of the disease process, it can give an overall assessment of the functional state of the respiratory system and clues about the pathogenesis of the disease. Because the detection of cyanosis is influenced by skin color, perfusion, and blood Hb concentration, the clinical detection by inspection is an unreliable sign of hypoxemia. Arterial hypertension, tachycardia, and diaphoresis are late, and not exclusive, signs of hypoventilation.

Blood gas exchange is evaluated most accurately by the direct measurement of arterial pressure of oxygen (Po_2), pressure of carbon dioxide (Pco_2), and pH. The blood specimen is best collected anaerobically in a heparinized syringe containing only enough heparin solution to displace the air from the syringe. The syringe should be sealed, placed in ice, and analyzed immediately. Although these measurements have no substitute in many conditions, they require arterial puncture and have been replaced to a great extent by less invasive monitoring, such as capillary samples and/or oxygen saturation.

The age and clinical condition of the patient need to be taken into account when interpreting blood gas tensions. With the exception of neonates, values of arterial Po_2 <85 mm Hg are usually abnormal for a child breathing room air at sea level. Calculation of the alveolar-arterial oxygen gradient is useful in the analysis of arterial oxygenation, particularly when the patient is not breathing room air or in the presence of hypercarbia. Values of arterial Pco_2 >45 mm Hg usually indicate hypoventilation or a severe ventilation-perfusion mismatch, unless they reflect respiratory compensation for metabolic alkalosis (see Chapter 73).

In general practice **pulse oximetry** is used to monitor a patient's peripheral arterial saturation (SpO_2). This noninvasive method uses spectrophotometry to assess oxygenated and deoxygenated hemoglobin ratios to determine the SpO_2. Values are most accurate with arterial saturations above 90%; with saturations <90%, the accuracy is reduced. *Pulse oximetry often produces falsely high SpO_2 values in Black and dark-skinned patients, creating a risk for missed (occult) hypoxia, which may lead to underuse of oxygen therapy for Black patients.*

TRANSILLUMINATION OF THE CHEST

In infants up to at least 6 months of age, a pneumothorax (see Chapter 132) can often be diagnosed by transilluminating the chest wall using a fiberoptic light probe. Free air in the pleural space often results in an unusually large halo of light in the skin surrounding the probe. Comparison with the contralateral chest is often helpful in interpreting findings. This test is unreliable in older patients and in those with subcutaneous emphysema or atelectasis.

RADIOGRAPHIC TECHNIQUES

Chest X-Rays

A posteroanterior and a lateral view (upright and in full inspiration) should be obtained, except in situations in which the child is medically unstable (Fig. 421.6). Portable images, although useful in the latter situation, can give a somewhat distorted image. Expiratory images can be misinterpreted, although a comparison of expiratory and inspiratory images may be useful in evaluating a child with a suspected foreign body (localized failure of the lung to empty reflects bronchial obstruction: see Chapter 435). Although images taken in a recumbent position are difficult to interpret when there is fluid within the pleural space or a cavity, if pleural fluid is suspected (see Chapter 451), decubitus images are indicated.

Upper Airway Film

A lateral view of the neck can yield invaluable information about upper airway obstruction (see Chapter 433) and particularly about the condition of the retropharyngeal, supraglottic, and subglottic spaces (which should also be viewed in an anteroposterior projection) (Fig. 421.7).

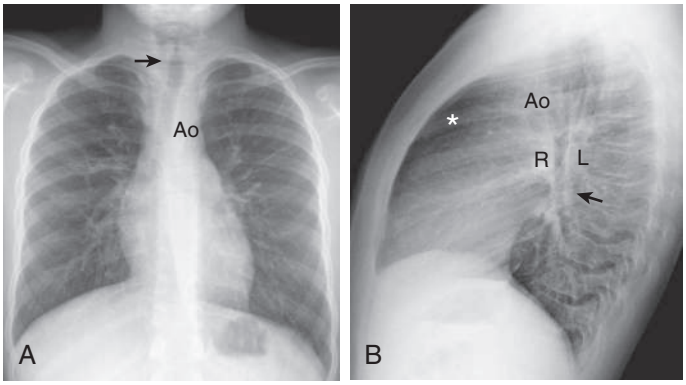

Fig. 421.6 Normal appearance of the trachea and lungs on chest radiography. **A,** On the frontal view, there is normal shouldering of the subglottic trachea *(arrow)*. The trachea courses inferiorly with a fairly uniform diameter to the level of the carina apart from a mild, smooth indentation at the level of the aortic arch *(Ao)*. The lungs are symmetrically inflated, with normal arborization of the vasculature. The hemidiaphragms are domed, not flattened. The normal heart size is less than 50% of the transverse dimension of the chest. **B,** On the lateral view, the trachea is of uniform diameter to the level of the aortic arch, with the exception of a mild, smooth impression from the aortic arch anteriorly (Ao). The hemidiaphragms are domed. The heart occupies less than 50% of the anteroposterior dimension of the chest and should not fill the retrosternal clear space *(asterisk)*. The bronchus intermedius *(arrow)* courses posterior to the right pulmonary artery *(R)*, and the arch of the left pulmonary artery *(L)* projects posterior to the carina. *(From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 2.11.)*

Knowing the phase of respiration during which the film was taken is often essential for accurate interpretation. Magnified airway images are often helpful in delineating the upper airways. Patients with suggested obstruction should not be unattended in the radiology department.

Sinus and Nasal Images

The general utility of radiologic examination of the sinuses is uncertain because a large number of images have positive findings (low sensitivity and specificity). Imaging studies are not necessary to confirm the diagnosis of sinusitis in children younger than age 6 years. CT scans are indicated if surgery is required, in cases of complications caused by sinus infection, in immunodeficient patients, in those with cystic fibrosis, and for recurrent infections unresponsive to medical management.

Chest Ultrasound

Chest ultrasound, which has no radiation and is more available in low-resource settings, has been shown to have more sensitivity and similar specificity in diagnosing community-acquired pneumonia compared to chest x-ray. Chest ultrasound can also detect pleural effusions and differentiate atelectasis from pneumonia.

Chest Computed Tomography

Chest CT often provides images of higher quality and sensitivity compared with radiography. Chest CT identifies early abnormalities such as air trapping, mucus plugging, or bronchiectasis in young children with cystic fibrosis before pathologic changes are detectable by either plain chest radiographs or pulmonary function testing. However, several caveats must be noted. Conventional chest CT involves higher radiation doses than plain images (see Chapter 758). The time required to perform chest CT examinations and the complications of respiratory and body motion mandate the use of sedation for this procedure in many infants and young children. However, improvements in imaging protocols and techniques have drastically reduced required radiation doses and imaging time. Chest CT is particularly useful in evaluating pulmonary nodules, pleural lesions, solid or cystic parenchymal lesions, pulmonary embolism, bronchiectasis, interstitial lung disease, and air trapping. The use of intravenous contrast material during CT

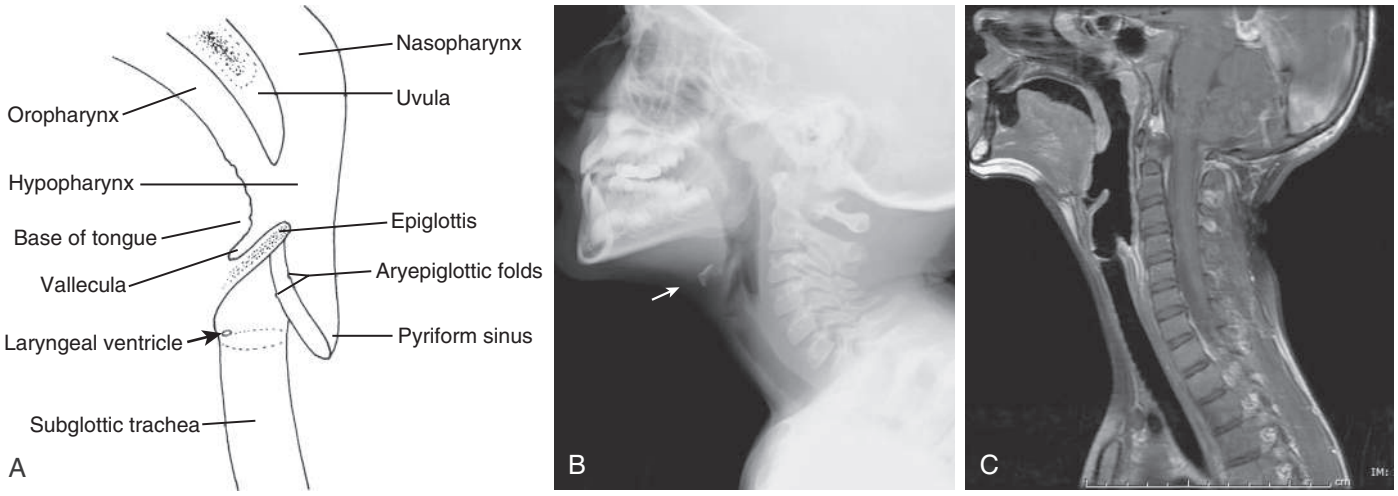

Fig. 421.7 A, Diagram depicting the normal anatomy of the upper airway. B, Corresponding lateral radiograph of the neck soft tissues. C, Sagittal T1-weighted magnetic resonance image. The hyoid bone "points to" the epiglottis on the radiograph *(arrow). (From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 2.5.)*

imaging enhances vascular structures, distinguishing vessels from other soft tissue densities.

Magnetic Resonance Imaging

Although CT is often considered the gold standard for chest imaging, advances in MRI techniques have broadened the indications for pediatric chest MRI. Pediatric chest MRI has shown utility in imaging several disease processes. In cases of pneumonia, chest MRI can be used to demonstrate pulmonary consolidation in addition to complications such as abscess, necrosis, and effusions with or without loculation. Congenital malformations can also be visualized using chest MRI. Bronchogenic cysts, congenital pulmonary airway malformation, sequestration, and pulmonary aplasia or agenesis can be well characterized using MR techniques. Furthermore, MRI can be applied to imaging congenital large airway disorders such as airway malacia and external airway compression caused by vascular rings and slings. Last, dynamic techniques using cine MR imaging provide four-dimensional imaging as airway structure changes throughout the breathing cycle. Cine MRI assesses both lower airway caliber in children with trachea or bronchomalacia and upper airway anatomy to diagnose a site of obstruction in children with obstructive sleep apnea. Aside from imaging time, MR may in some cases be inferior to CT for imaging of bronchiectasis without airway wall thickening, focal air trapping, signs of interstitial lung disease, and small pulmonary nodules. MR protocols currently vary across centers, and collaboration with radiologists experienced in specialized chest imaging will result in high-quality imaging with minimization of ionizing radiation while weighing the need for sedation.

Fluoroscopy

Fluoroscopy can be used to assess diaphragm function in cases of suspected paralysis and to differentiate from eventration. Occasionally, the modality is used to evaluate airway dynamics with the benefit of visualization during awake and spontaneous breathing. The use of ionizing radiation with this modality should be taken into consideration, especially if repeated studies in the same patient are undertaken. Procedures such as needle aspiration or biopsy of a peripheral lesion may be accomplished with the aid of fluoroscopy, CT, or ultrasonography.

Barium Swallow

A barium swallow study, performed with fluoroscopy and spot images, is indicated in the evaluation of patients with recurrent pneumonia, persistent cough of undetermined cause, stridor, or persistent wheezing. The technique can be modified by using barium of different textures and thicknesses, ranging from thin liquid to solids, to evaluate swallowing mechanics and test for laryngeal penetration or pulmonary aspiration. Imaging of the esophageal phase is important and can be used to detect the presence of esophageal dysfunction, vascular rings (see Chapter 434), and tracheoesophageal fistulas (see Chapter 365). A contrast esophagram has been used in evaluating newborns with suggested esophageal atresia, but this procedure entails a high risk of pulmonary aspiration and is not usually recommended for this indication. Barium swallows have lower utility in evaluating gastroesophageal reflux (see Chapter 369).

Pulmonary Arteriography and Aortograms

Pulmonary arteriography has been used to allow detailed evaluation of the pulmonary vasculature. This imaging technique has also been helpful in assessing pulmonary blood flow and in diagnosing congenital anomalies, such as lobar agenesis, unilateral hyperlucent lung, vascular rings, and arteriovenous malformations. Thoracic aortograms demonstrate the aortic arch, its major vessels, and the systemic (bronchial) pulmonary circulation. They are useful in evaluating vascular rings and suspected pulmonary sequestration.

Ventilation-Perfusion Relation and Radionuclide Lung Scans

Gravitational force pulls the lung away from the nondependent part of the parietal pleura. Consequently, alveoli and airways in the nondependent parts (the upper lobes in upright position) of the lung are subjected to greater negative intrapleural pressure during tidal respiration and are kept relatively more inflated compared with the dependent alveoli and airways (the lower lobes in upright position). The nondependent alveoli are less compliant because they are already more inflated. Ventilation therefore occurs preferentially in the dependent portions of the lung that are more amenable to expansion during tidal inspiration. Although perfusion is also greater in the dependent portions of the lung because of greater pulmonary arterial hydrostatic pressure from gravity, the increase in perfusion is greater than the increase in ventilation in the dependent portions of the lung. Thus the ratios favor ventilation in the nondependent portions and perfusion in the dependent portions. Because the airways in the dependent portion of the lung are narrower, they close earlier during expiration. The lung volume at which the dependent airways start to close is referred to as the **closing capacity**. In normal children, the FRC is greater than the closing capacity. During tidal respiration, airways remain patent both in the dependent and the nondependent portions of the lung. In newborns, the closing capacity is greater than the FRC, resulting in perfusion of poorly ventilated alveoli during tidal respiration. Therefore normal neonates have a lower Pao_2 compared with older children.

The relationship is adversely affected in a variety of pathophysiologic states. Air movement in areas that are poorly perfused is referred to as **dead space ventilation**. Examples of dead space ventilation include

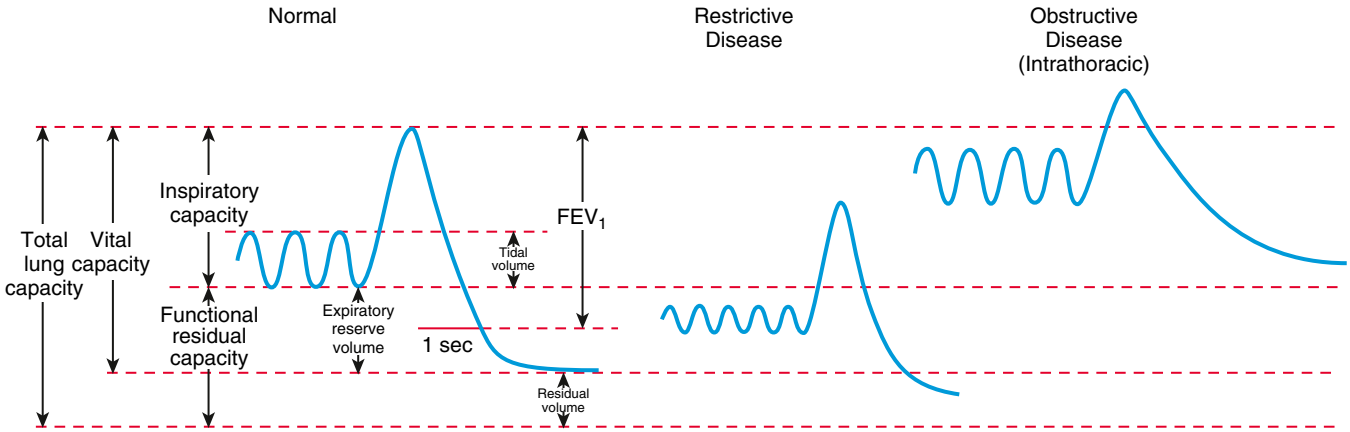

Fig. 421.8 Spirogram showing lung volumes and capacities. Forced expiratory volume 1 *(FEV_1)* is the maximum volume exhaled in 1 second after maximum inspiration. Restrictive diseases are usually associated with decreased lung volumes and capacities. Intrathoracic airway obstruction is associated with air trapping and abnormally high functional residual capacity and residual volume. FEV_1 and vital capacity are decreased in both restrictive and obstructive diseases. The ratio of FEV_1 to vital capacity is normal in restrictive disease but decreased in obstructive disease.

pulmonary thromboembolism and hypovolemia. Perfusion of poorly ventilated alveoli is referred to as **intrapulmonary right-to-left shunting** or **venous admixture**. Examples include pneumonia, asthma, and hyaline membrane disease. In intrapulmonary airway obstruction, the closing capacity is abnormally increased and can exceed the FRC. In such situations, perfusion of poorly ventilated alveoli during tidal respiration results in venous admixture.

The usual scan uses intravenous injection of material (macroaggregated human serum albumin labeled with ^{99m}Tc) that will be trapped in the pulmonary capillary bed. The distribution of radioactivity, proportional to pulmonary capillary blood flow, is useful in evaluating pulmonary embolism, as well as congenital cardiovascular and pulmonary defects. Acute changes in the distribution of pulmonary perfusion can reflect alterations of pulmonary ventilation.

The distribution of pulmonary ventilation can also be determined by scanning after the patient inhales a radioactive gas such as xenon-133. After the intravenous injection of xenon-133 dissolved in saline, pulmonary perfusion and ventilation can be evaluated by continuous recording of the rate of appearance and disappearance of the xenon over the lung. Appearance of xenon early after injection is a measure of perfusion, and the rate of washout during breathing is a measure of ventilation in the pediatric population. The most important indication for this test is the demonstration of defects in the pulmonary arterial distribution that can occur with congenital malformations or pulmonary embolism. **Spiral reconstruction CT** with contrast medium enhancement is helpful in evaluating pulmonary thrombi and emboli. Abnormalities in regional ventilation are also easily demonstrable in congenital lobar emphysema, cystic fibrosis, and asthma.

PULMONARY FUNCTION TESTING

Traditionally, lung volumes are measured with a spirogram (Fig. 421.8). **Tidal volume (V_T)** is the amount of air moved in and out of the lungs during each breath; at rest, V_T is normally 6-7 mL/kg body weight. **Inspiratory capacity** is the amount of air inspired by maximum inspiratory effort after tidal expiration. **Expiratory reserve volume** is the amount of air exhaled by maximum expiratory effort after tidal expiration. The volume of gas remaining in the lungs after maximum expiration is **residual volume**. **Vital capacity (VC)** is defined as the amount of air moved in and out of the lungs through maximum inspiration and expiration. VC, inspiratory capacity, and expiratory reserve volume are decreased in lung pathology but are also effort dependent. **Total lung capacity (TLC)** is the volume of gas occupying the lungs after maximum inhalation.

The **flow-volume relationship** offers a valuable means at the bedside or in an office setting to detect abnormal pulmonary mechanics and response to therapy with relatively inexpensive and easy-to-use devices. After maximum inhalation, the patient forcefully exhales through a mouthpiece into the device until residual volume is reached, followed by maximum inhalation (Fig. 421.9). Flow is plotted against volume. **Maximum forced expiratory flow (FEF_{max})** is generated in the early part of exhalation, and it is a commonly used indicator of airway obstruction in asthma and other obstructive lesions. Provided maximum pressure is generated consistently during exhalation, a decrease in flow is a reflection of increased airway resistance

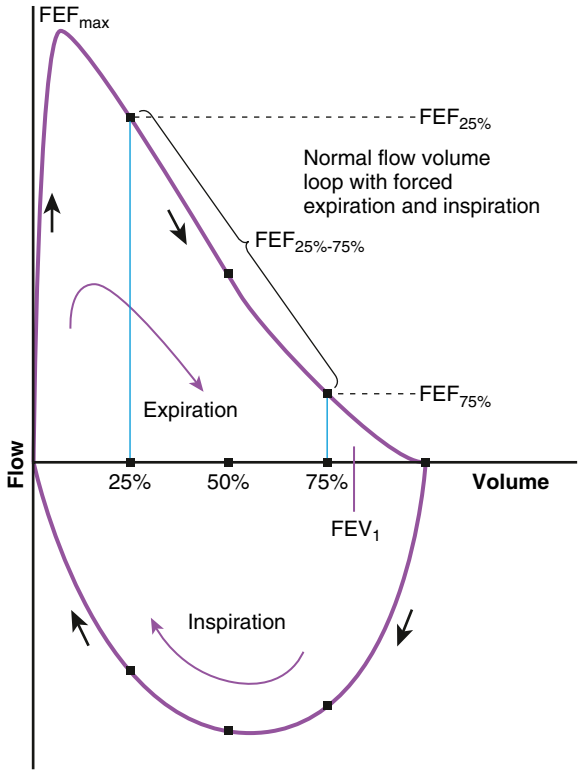

Fig. 421.9 Flow-volume loop in a normal person performed after maximal inspiration followed by forced complete expiration and forced complete inhalation. Maximum forced expiratory flow *(FEF_{max})* represents maximum flow during expiration. This is attained soon after initiation of the expiration. Fall in expiratory flow is gradual until it reaches zero after exhalation is complete. $FEF_{25–75\%}$ represents mean flow from 25% ($FEF_{25\%}$) to 75% ($FEF_{75\%}$) of exhaled forced expiratory volume *(FEV)*, also termed *forced vital capacity* (FVC). FEV_1 is the amount of volume after 1 second of forced exhalation. Normally FEV_1 is around 80% of FVC. *(Courtesy Dr. Ashok Sarnaik.)*

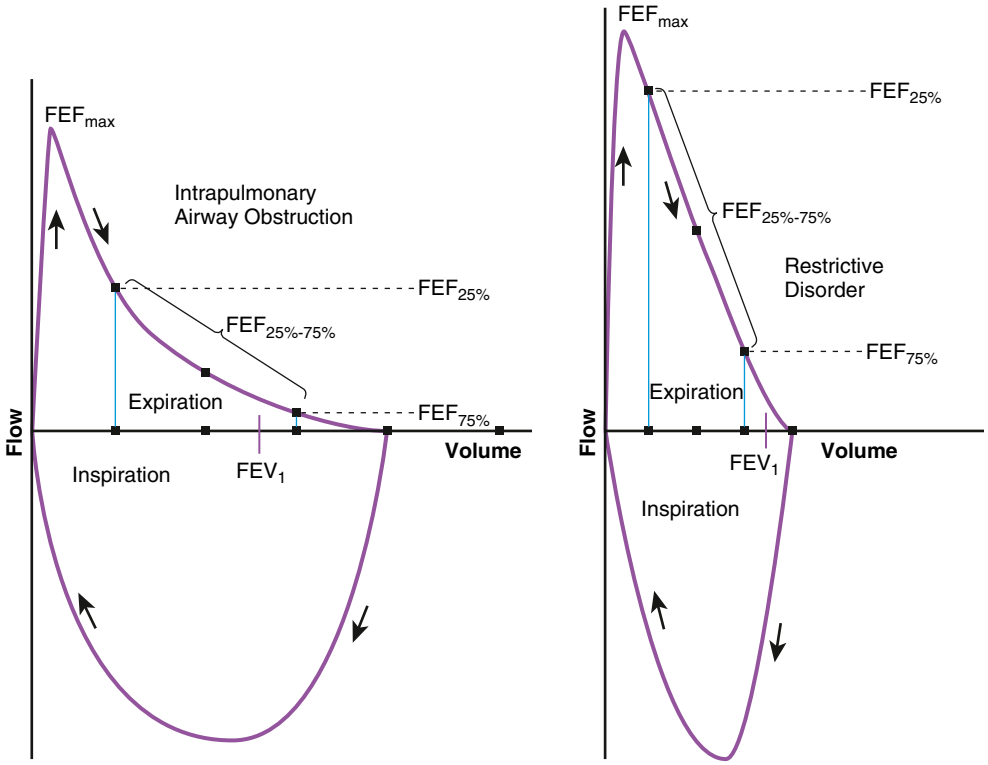

Fig. 421.10 Flow-volume loops in intrapulmonary airway obstruction and restrictive disorders. Note that in intrapulmonary airway obstruction, there is a decrease in maximum forced expiratory flow *(FEF$_{max}$)*, FEF$_{25–75\%}$, and forced expiratory volume 1/forced vital capacity *(FEV$_1$/FVC%)*. The middle part of the expiratory loop appears concave. In restrictive disorders, the flow-volume loop assumes a more vertically oblong shape with reduction in FVC but not the FEV$_1$/FVC%. Expiratory and inspiratory flow rates are relatively unaffected. *(Courtesy Dr. Ashok Sarnaik.)*

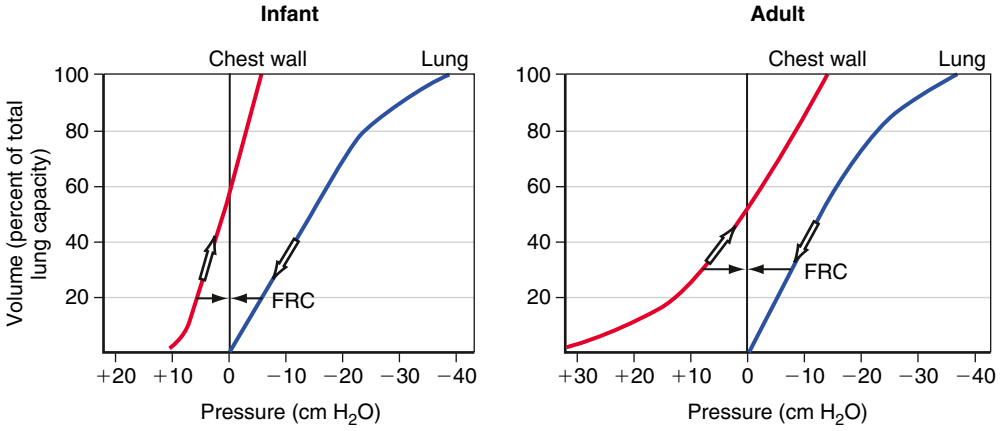

Fig. 421.11 Schematic of interaction between chest wall and lung recoil in infants compared with adults. The elastic recoil of a relatively more compliant chest wall is balanced by the lung recoil at a lower-volume functional residual capacity *(FRC)* in infants compared with adults. *(Courtesy Dr. Ashok Sarnaik.)*

(R$_{AW}$). The total volume exhaled during this maneuver is **forced vital capacity (FVC)**. **Volume exhaled in 1 second** is referred to as **forced expiratory volume 1 (FEV$_1$)**. FEV$_1$/FVC is expressed as a percentage of FVC. FEF$_{25–75\%}$ is the mean flow between 25% and 75% of FVC, and is considered relatively effort independent. Individual values and shapes of flow-volume curves show characteristic changes in obstructive and restrictive respiratory disorders (Fig. 421.10). In intrapulmonary airway obstruction such as asthma or cystic fibrosis, there is a reduction of FEF$_{max}$, FEF$_{25–75\%}$, FVC, and FEV$_1$/FVC. Also, there is a characteristic concavity in the middle part of the expiratory curve. In restrictive lung disease such as interstitial pneumonia (see Chapter 448.5) and kyphoscoliosis (see Chapter 467.5), FVC is decreased with relative preservation of airflow and FEV$_1$/FVC. The flow-volume curve assumes a vertically oblong shape compared with normal. Changes in shape of the flow-volume loop and individual values depend on the type of disease and the extent of severity. Serial determinations provide valuable information regarding disease evolution and response to therapy.

FRC has important pathophysiologic implications. Chest wall compliance is a major determinant of FRC. Because the chest wall and the lungs recoil in opposite directions at rest, FRC is reached at the point where the outward elastic recoil of the thoracic cage counterbalances the inward lung recoil. This balance is attained at a lower lung volume in a young infant's ribs because they are oriented much more horizontally and the diaphragm is flatter and less domed. Consequently, the infant is unable to duplicate the efficiency of upward and outward movement of obliquely oriented ribs or the downward displacement of a domed diaphragm in an adult to expand the thoracic capacity. This creates an extremely high thoracic compliance compared with older children and adults (Fig. 421.11). The measured FRC in infants is higher than expected because infant respiratory muscles maintain the thoracic cage in an inspiratory position at all times. In addition, young infants experience some amount of air trapping during expiration.

Alveolar gas composition changes during inspiration and expiration. **Alveolar P_{O_2} (PA_{O_2})** increases and **alveolar P_{CO_2} (PA_{CO_2})** decreases during inspiration as fresh atmospheric gas enters the lungs. During exhalation, PA_{O_2} decreases and PA_{CO_2} increases as pulmonary capillary blood continues to remove oxygen from and add CO_2 into the alveoli (Fig. 421.12). FRC acts as a buffer, minimizing the changes in PA_{O_2} and PA_{CO_2} during inspiration and expiration. FRC represents the

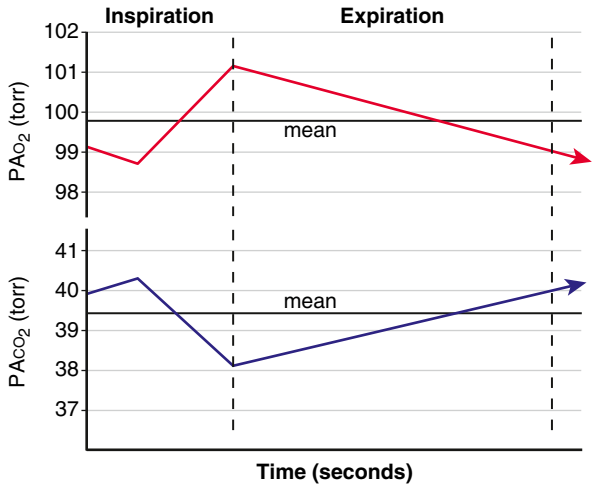

Fig. 421.12 Alveolar P_{O_2} rises and P_{CO_2} falls during inspiration as fresh atmospheric gas is brought into the lungs. During expiration, the opposite changes occur as pulmonary capillary blood continues to remove O_2 and add CO_2 from the alveoli without atmospheric enrichment. Note that during the early part of inspiration, alveolar P_{O_2} continues to fall and P_{CO_2} continues to rise because of inspiration of the dead space that is occupied by the previously exhaled gas. *(Courtesy Dr. Ashok Sarnaik; modified from Comroe JH. Physiology of Respiration, 2nd ed. Chicago: Year Book Medical Publishers; 1974:12.)*

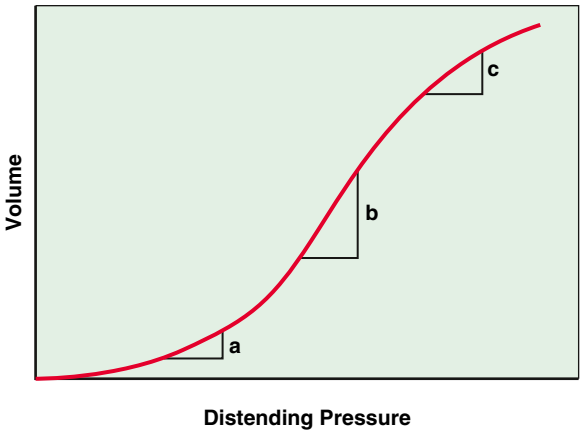

Fig. 421.13 Lung compliance is significantly influenced by the functional residual capacity (FRC). The same change in pressure is associated with less change in volume when FRC is abnormally decreased *(a)* or abnormally increased *(c)* compared with the normal state *(b)*. *(Courtesy Dr. Ashok Sarnaik.)*

environment available for pulmonary capillary blood for gas exchange at all times.

A decrease in FRC is often encountered in alveolar interstitial diseases and thoracic deformities. The major pathophysiologic consequence of decreased FRC is **hypoxemia**. Reduced FRC results in a sharp decline in PA_{O_2} during exhalation because a limited volume is available for gas exchange. P_{O_2} of pulmonary capillary blood therefore falls excessively during exhalation, leading to a decline in **arterial P_{O_2} (PA_{O_2})**. Any increase in PA_{O_2} (and therefore Pa_{O_2}) during inspiration cannot compensate for the decreased Pa_{O_2} during expiration. The explanation for this lies in the shape of the O_2-Hb dissociation curve, which is sigmoid shaped (see Fig. 421.5). Because most of the oxygen in blood is combined with Hb, it is the percentage of **oxyhemoglobin (S_{O_2})** that gets averaged rather than the P_{O_2}. Although an increase in arterial P_{O_2} cannot increase O_2-Hb saturation >100%, there is a steep desaturation of Hb below a P_{O_2} of 50 torr; thus decreased S_{O_2} during exhalation as a result of low FRC leads to overall arterial desaturation and hypoxemia. The adverse pathophysiologic consequences of decreased FRC are ameliorated by applying **positive end-expiratory pressure (PEEP)** and increasing the inspiratory time during mechanical ventilation.

The lung pressure-volume relationship is markedly influenced by FRC (Fig. 421.13). Pulmonary compliance is decreased at abnormally low or high FRC.

FRC is abnormally increased in intrathoracic airway obstruction, which results in incomplete exhalation, and is abnormally decreased in alveolar-interstitial diseases. At excessively low or high FRC, tidal respiration requires higher inflation pressures compared to normal FRC. Abnormalities of FRC result in increased work of breathing with spontaneous respiration and increased barotrauma in mechanical ventilation.

The measurement of respiratory function in infants and young children can be difficult because of the lack of cooperation. Attempts have been made to overcome this limitation by creating standard tests that do not require the patient's active participation. Respiratory function tests still provide only a partial insight into the mechanisms of respiratory disease at early ages.

Whether restrictive or obstructive, most forms of respiratory disease cause alterations in lung volume and its subdivisions. Restrictive diseases typically decrease **TLC**. TLC includes residual volume, which is not accessible to direct determinations. It must therefore be measured indirectly by gas dilution methods or, preferably, by **plethysmography**. Restrictive disease also decreases **VC**. Obstructive diseases produce gas trapping and thus increase residual volume and FRC, particularly when these measurements are considered with respect to TLC.

Lung Clearance Index (LCI) is a test that uses multiple-breath washouts to demonstrate airway physiology. The test involves the gradual replacement of a tracer gas such as nitrogen, which is normally in the lungs or within biologically inert gas, with 100% oxygen. This gradual washout of the tracer gas requires no complex respiratory maneuvers but has some technical challenges. The variability of LCI in healthy children and adolescents is low, and LCI has been shown to discriminate against healthy individuals and patients with chronic conditions such as cystic fibrosis or asthma. LCI reports gas mixing efficiency, which is an index of lung function, with the diseased lung taking a longer time to wash out the tracer gas than a healthy lung. LCI has been shown to be able to detect lung disease before FEV_1 and therefore may be a tool for early detection of lung pathology.

Airway obstruction is most commonly evaluated from determinations of gas flow in the course of a forced expiratory maneuver. The **peak expiratory flow** is reduced in advanced obstructive disease. The wide availability of simple devices that perform this measurement at the bedside makes it useful for assessing children who have airway obstruction. Evaluation of peak flows requires a voluntary effort, and peak flows may not be altered when the obstruction is moderate or mild. Other gas flow measurements require that the child inhale to TLC and then exhale as far and as fast as possible for several seconds. Cooperation and good muscle strength are therefore necessary for the measurements to be reproducible. FEV_1 correlates well with the severity of obstructive diseases. The **maximal midexpiratory flow rate**, the average flow during the middle 50% of the forced VC, is a more reliable indicator of mild airway obstruction. Its sensitivity to changes in residual volume and VC, however, limits its use in children with more severe disease. The construction of flow-volume relationships during the forced VC maneuvers overcomes some of these limitations by expressing the expiratory flows as a function of lung volume.

A **spirometer** is used to measure VC and its subdivisions and expiratory (or inspiratory) flow rates (see Fig. 421.8). A simple manometer can measure the maximal inspiratory and expiratory force a subject generates, normally at least 30 cm H_2O. This is useful in evaluating the neuromuscular component of ventilation. Expected normal values for VC, FRC, TLC, and residual volume are obtained from prediction equations based on body height.

Flow rates measured by spirometry usually include the FEV_1 and the **maximal midexpiratory flow rate**. More information results from a maximal expiratory flow-volume curve, in which expiratory flow rate

is plotted against expired lung volume (expressed in terms of either VC or TLC). Flow rates at lung volumes less than approximately 75% VC are relatively independent of effort. Expiratory flow rates at low lung volumes (<50% VC) are influenced much more by small airways than flow rates at high lung volumes (FEV_1). The flow rate at 25% VC is a useful index of small airway function. Low flow rates at high lung volumes associated with normal flow at low lung volumes suggest upper airway obstruction.

Airway resistance (R_{AW}) is measured in a plethysmograph, or alternatively, the reciprocal of R_{AW}, **airway conductance**, may be used. Because R_{AW} measurements vary with the lung volume at which they are taken, it is convenient to use **specific airway resistance**, SR_{AW} ($SR_{AW} = R_{AW}$/lung volume), which is nearly constant in subjects older than age 6 years (normally <7 sec/cm H_2O).

Impulse oscillometry (IOS) is a tool that can be used in minimally cooperative patients such as young children. This technology uses properties of sound waves at different frequencies during normal tidal breathing to estimate resistance in airflow. This tool can differentiate small from large airway obstruction and measures bronchodilatory response. Although the tool is fairly easy to use, normative values are few, which limits the use across patients, but it may be a good tool to track airway resistance across time in conditions such as asthma.

The **diffusing capacity for carbon monoxide** is related to oxygen diffusion and is measured by rebreathing from a container with a known initial concentration of carbon monoxide or by using a single-breath technique. Decreases in diffusing capacity for carbon monoxide reflect decreases in effective alveolar capillary surface area or decreases in diffusibility of the gas across the alveolar-capillary membrane. Primary diffusion abnormalities are unusual in children; therefore this test is most commonly employed in children with rheumatologic or autoimmune diseases and in children exposed to toxic drugs to the lungs (e.g., oncology patients) or chest wall radiation. Regional gas exchange can be conveniently estimated with the perfusion-ventilation xenon scan. Determining arterial blood gas levels also discloses the effectiveness of alveolar gas exchange.

Pulmonary function testing, although rarely resulting in a diagnosis, is helpful in defining the type of process (obstruction, restriction) and the degree of functional impairment, in following the course and treatment of disease, and in estimating the prognosis. It is also useful in preoperative evaluation and in confirming functional impairment in patients with subjective complaints but a normal physical examination. In most patients with obstructive disease, a repeat test after administering a bronchodilator is warranted.

Most tests require some cooperation and understanding by the patient. Interpretation is greatly facilitated if the test conditions and the patient's behavior during the test are known. Infants and young children who cannot or will not cooperate with test procedures can be studied in a limited number of ways, which often require sedation. Flow rates and pressures during tidal breathing, with or without transient interruption of the flow, may be useful to assess some aspects of R_{AW} or obstruction and to measure compliance of the lungs and thorax. Expiratory flow rates can be studied in sedated infants with passive compression of the chest and abdomen using a rapidly inflatable jacket. Gas dilution or plethysmographic methods can also be used in sedated infants to measure FRC and R_{AW}.

The measurement of **fractional exhaled nitric oxide** (FENO) is used as a surrogate measure for eosinophilic inflammation of the lower airways. It can be used as a part of a diagnostic evaluation for asthma, a tool for predicting or assessing an individual's response to antiinflammatory therapy, and in monitoring adherence to treatment. A number of commercially available devices are available for measurement of FENO. Some degree of cooperation is required, but FENO has been measured in preschool-age children. Normal cutoff values vary by age and device. FENO has been used to distinguish asthma (particularly allergic asthma) from other wheezing phenotypes. FENO achieves moderate diagnostic performance for the detection of asthma in children, with sensitivity, specificity, and diagnostic odds ratios of 0.79, 0.81, and 16.52, respectively. Children managed using FENO may have fewer asthma exacerbations. A decrease of FENO by 20% is considered indicative of a positive response to antiinflammatory therapy. Some studies using FENO have contradictory results, and it is likely that FENO may be more useful in some asthma phenotypes than in others.

The measurement of **nasal nitric oxide** (nNO) is accomplished by collecting exhaled gas from a nostril during glottic closure and correlates to nasal mucosal inflammation. There is great interest in the use of nNO to diagnose **primary ciliary dyskinesia** (PCD, see Chapter 425), because of challenges diagnosing PCD with currently available techniques. A cutoff value of less than or equal to 77 nL/min showed excellent sensitivity and specificity using a standardized technique at multiple centers. Equipment for measurement of nNO is not yet FDA-approved in the United States.

MICROBIOLOGY: EXAMINATION OF LUNG SECRETIONS

The specific diagnosis of infection in the lower respiratory tract depends on the proper handling of an adequate specimen obtained in an appropriate fashion. Nasopharyngeal or throat cultures are often used but might not correlate with cultures obtained by more direct techniques from the lower airways. Sputum specimens are preferred and are often obtained from patients who do not expectorate by deep throat swab immediately after coughing or by saline nebulization. Specimens can also be obtained directly from the tracheobronchial tree by nasotracheal aspiration (usually heavily contaminated), by transtracheal aspiration through the cricothyroid membrane (useful in adults and adolescents but hazardous in children), and in infants and children by a sterile catheter inserted into the trachea either during direct laryngoscopy or through a freshly inserted endotracheal tube. A specimen can also be obtained at bronchoscopy.

A specimen obtained by direct expectoration is usually assumed to be of tracheobronchial origin, but often, especially in children, it is not from this source. The presence of alveolar macrophages (large mononuclear cells) is the hallmark of tracheobronchial secretions. Nasopharyngeal and tracheobronchial secretions can contain ciliated epithelial cells, which are more commonly found in sputum. Nasopharyngeal and oral secretions often contain large numbers of squamous epithelial cells. Sputum can contain both ciliated and squamous epithelial cells.

During sleep, mucociliary transport continually brings tracheobronchial secretions to the pharynx, where they are swallowed. An early-morning fasting gastric aspirate often contains material from the tracheobronchial tract that is suitable for culture for acid-fast bacilli.

The absence of polymorphonuclear leukocytes in a Wright-stained smear of sputum or **bronchoalveolar lavage** (BAL) fluid containing adequate numbers of macrophages may be significant evidence against a bacterial infectious process in the lower respiratory tract, assuming that the patient has normal neutrophil counts and function. Eosinophils suggest allergic disease. Iron stains can reveal hemosiderin granules within macrophages, suggesting pulmonary hemosiderosis. Specimens should also be examined by Gram stain. Bacteria within or near macrophages and neutrophils can be significant. Viral pneumonia may be accompanied by intranuclear or cytoplasmic inclusion bodies visible on Wright-stained smears, and fungal forms may be identifiable on Gram or silver stains.

With advances in the area of genomics and the speed with which it is possible to identify microbes, microbiologic analysis has been expanded. Specific bacteria in the lungs of children with cystic fibrosis (see Chapter 454) are linked to morbidity and mortality. There is a correlation between patient age and morbidity and mortality (as expected), but important microbes also are correlated either negatively or positively with early or late pathogenic processes. *Haemophilus influenzae* (see Chapter 240) is negatively correlated, and *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (see Chapter 251.3) have a strong positive correlation with patient age in cystic fibrosis. The microbiota diversity is much broader in those who are healthier individuals or those who are younger patients with cystic fibrosis than the older and sicker population.

In addition, the microbiomes in the respiratory tract of smokers and nonsmokers differ substantially. In all patients, most of the bacteria found in the lungs are also present in the oral cavity, but some bacteria,

such as *Haemophilus* and enterobacteria, are much more represented in the lungs than in the mouth. Principal differences in microbiome composition between smokers and nonsmokers are found in the mouth. For example, *Neisseria* levels are much lower in smokers as compared with nonsmokers. Overall, the microbiome diversity in smokers was also reduced compared with nonsmokers.

THE MICROBIOME

Whereas some studies have looked at the microbiome in the lungs and others in the gut, there is evidence to believe that there is a gut-lung axis regarding the microbiome. For example, the airway epithelium regulates local immunity (IgA antibodies, defensins) and can stimulate a Th2 airway response. Other cytokines are also involved such as transforming growth factor beta (TGFB). Bacteriophages are also important in the airways because these may protect the airways from certain bacteria. Importantly, the gut microbiome, influenced by many factors such as diet, environment, mode of childbirth, socioeconomic status, and antibiotic use, affects in a major way the development of immunity in the growing infant and child. Similarly, the lungs are not sterile, and bacteria exist in the lungs of children. It is possible therefore that the microbiome in one site affects the response to the microbiome in another through either immunity or predisposition to inflammation.

The Amish and Hutterite populations are genetically identical, but they have very different asthma prevalence, with the Hutterite having 4-6 times more asthma than the Amish population. One study showed that the Amish household had ~7 times more dust endotoxin. Extracts from the Amish dust inhibited airway hyper-responsiveness, but this did not happen from the Hutterite samples. Although this does not separate between the lung and gut, it suggests that the hygiene hypothesis is important and that microbes and immunity are tied together in the genesis of asthma, especially in children, and in the formative stages of immunity and allergic diseases.

Ciliary Structure and Function

Cilia are cellular organelles that project from respiratory epithelial surfaces into the lumen. They are microscopic hairlike structures, are motile, and beat in a coordinated fashion from distal to proximal airways to clear mucus, fluid, and inhaled particles. They generally beat at a fast pace, on the order of 10-20 Hz.

Their structure is typical, consisting of nine peripheral doublet microtubules arranged in a circular fashion, with two single microtubules centrally located. As such, this structure is called an *axoneme*. Each microtubule has an inner and an outer dynein arm, with radial spokes connecting each peripheral pair with the central microtubules.

Each epithelial cell lining the respiratory tract has around 200 such cilia. The cilia on the surface beat synchronously not only over the surface of one such cell but across many cells. How cells communicate to induce the rhythmic beating function of cilia across a sheet of cells is not well understood.

Hundreds of proteins make up each cilium in the respiratory tract, and many pathogenic variants have been described. Such variants render these cilia dysfunctional, leading to a respiratory disease, PCD. Often the structure is also abnormal, but cilia can be dysfunctional without an apparent EM abnormal structure (Fig. 421.14).

Cardiopulmonary Exercise Testing

Exercise testing (see Chapter 472.5) is a direct approach for measuring respiratory gas exchange and assessing causes of exercise limitations. Measurements of heart and respiratory rate, minute ventilation, oxygen consumption, carbon dioxide production, and arterial blood gases during incremental exercise loads often provide invaluable information about the physiologic source of the symptom. Exercise is a strong provocateur of bronchospasm in susceptible patients, so exercise testing can be useful in the diagnosis of asthma as the cause of difficulty breathing with exertion. Several diseases or physiologic states distinct from asthma may mimic symptoms of exercise-induced bronchoconstriction. In addition to cardiac disease and decreased fitness, exercise-induced laryngeal obstruction (EILO) leads to significant limitations. In selected cases, performance of laryngoscopy during cardiopulmonary exercise testing lends essential diagnostic information. Application of cardiopulmonary testing for assessment of aerobic fitness and disease limitations provides invaluable diagnostic information to aid clinicians investigating exercise intolerance.

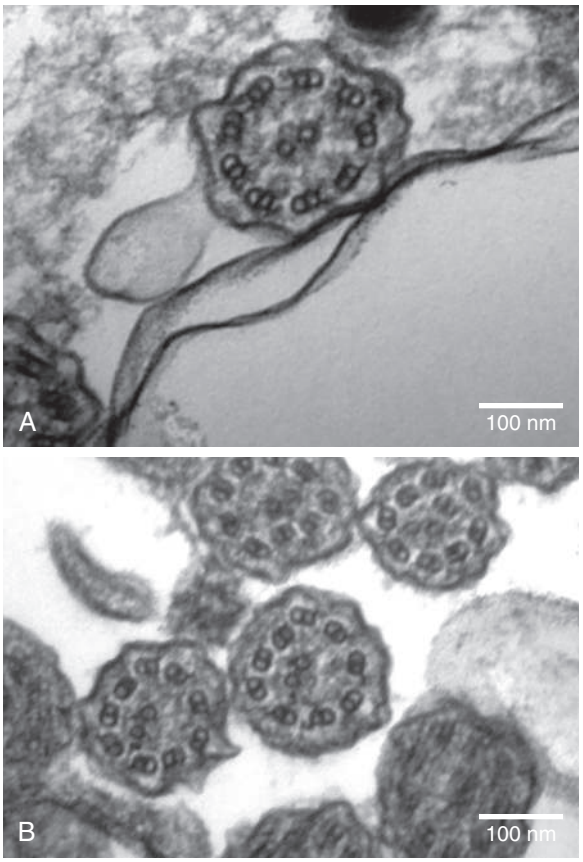

Fig. 421.14 A, Cross-section of a normal EM cilium structure. Note the typical axoneme structure, consisting of the nine peripheral doublet microtubules arranged in a circular fashion, with two single microtubules centrally located. Each microtubule has an inner and an outer dynein arm. B, Abnormal axoneme, as there are a number of doublets missing the dynein arms, which are clear in A, with normal cilium. Note also the disorganized location of the nine peripheral microtubules in some of the cilia. *(Courtesy Dr. Denise Malicki, UCSD/Rady Children's Hospital.)*

Sleep Studies

See Chapter 31.

AIRWAY VISUALIZATION AND LUNG SPECIMEN–BASED DIAGNOSTIC TESTS

Laryngoscopy

The evaluation of stridor, problems with vocalization, and other upper airway abnormalities usually requires direct inspection. Although indirect (mirror) laryngoscopy may be reasonable in older children and adults, it is rarely feasible in infants and small children. Direct laryngoscopy may be performed with either a rigid or a flexible instrument. The safe use of the rigid scope for examining the upper airway requires topical anesthesia and either sedation or general anesthesia, whereas the flexible laryngoscope can often be used in the office setting with or without sedation. Further advantages to the flexible scope include the ability to assess the airway without the distortion that may be introduced by the use of the rigid scope and the ability to assess airway dynamics more accurately. Because there is a relatively high incidence of concomitant lesions in the upper and lower airways, it is often prudent to examine the airways above and below the glottis, even when the primary indication is in the upper airway (stridor).

Bronchoscopy and Bronchoalveolar Lavage

Bronchoscopy is the inspection of the airways. Flexible bronchoscopy is commonly used in pediatrics to visualize the airways. There are several sizes of scopes that enable visualization of the proximal and distal airways. Many fiberoptic bronchoscopes also have a channel that allows for the collection of fluids, or in larger scopes allows for the insertion of tools such as forceps, baskets, or brushes. The smallest scope is a 2.2-mm-outer-diameter bronchoscope that does not have a channel; therefore only visualization of the airways is possible. The smallest bronchoscope with a channel is a 2.8-mm-outer-diameter scope, which has a 1.2-mm working channel. This scope is commonly used in pediatrics and is predominately used to visualize the airways and to collect a lavage sample. In larger "adult" scopes (4.9-5.5 mm outer diameter and 2.0 mm working channel), small instruments such as forceps can be inserted. Therapeutic bronchoscopes require an even larger channel (2.8 mm working channel, which requires a larger outer diameter of 6.0-6.3 mm), so they are not used often in the pediatric population. A smaller scope (4.1 mm outer diameter) with a larger working channel (2.0 mm) has become available and may make interventional pediatric bronchoscopy more common in the future. For urgent or emergent therapeutic interventions, such as foreign body aspiration or large volume hemoptysis, surgical rigid bronchoscopy remains the preferred approach, as it provides the largest working channel and permits simultaneous ventilation during the procedure.

Visualization of the airway has improved through advances in optics and insertable tools. **Narrow-band imaging** and **autofluorescence** imaging bronchoscopes are two types of bronchoscopes that can aid in the detection of airway lesions. These scopes appear no different than the conventional bronchoscope but use different bandwidths of lights to highlight mucosal and submucosal vasculature. These bronchoscopes allow the operator to see airway mucosal lesions that would be difficult to see or not be seen under normal white light. The autofluorescence imaging bronchoscope uses the fluorophores, such as tryptophan, collagen, elastin, and porphyrins, within the airway tissue to emit fluorescence when irradiated with a light source. Changes in concentrations of the fluorophores in bronchial mucosa would appear as an irregular lesion when viewed with an autofluorescence imaging bronchoscope. The narrow-band imaging bronchoscope also uses light absorption characteristics of Hb to enhance images of blood vessels. This bronchoscope uses blue wavelengths in the range of 390-445 nm to visualize the mucosal layer capillaries and green wavelengths at 530 and 550 nm to detect deeper submucosal thick blood vessels. Both types of bronchoscopes allow the operator to detect findings that would not be seen under normal white light. These scopes are being used more often in adults, where lesions are biopsied to detect premalignant and malignant lesions, although use has been described to better delineate characteristics of a subglottic cyst in a 3-month-old infant. These scopes are noninvasive and would be well tolerated in children, but are currently only available in larger "adult" sizes.

The most common diagnostic tool used in conjunction with fiberoptic bronchoscopy is **bronchoalveolar lavage (BAL)**. BAL is a method used to obtain a representative specimen of fluid and secretions from the lower respiratory tract, which is useful for the cytologic and microbiologic diagnosis of lung diseases, especially in those who are unable to expectorate sputum. BAL is performed after the general inspection of the airways and before tissue sampling with a brush or biopsy forceps. It is accomplished by gently wedging the scope into a lobar, segmental, or subsegmental bronchus and sequentially instilling and withdrawing sterile nonbacteriostatic saline in a volume sufficient to ensure that some of the aspirated fluid contains material that originated from the alveolar space. Nonbronchoscopic BAL can be performed in intubated patients by instilling and withdrawing saline through a catheter passed though the artificial airway and blindly wedged into a distal airway, although nonbronchoscopic BAL is less accurate and therefore has less reliable results. In either case, the presence of alveolar macrophages documents that an alveolar sample has been obtained. Because the methods used to perform BAL involve passage of the equipment through the upper airway, there is a risk of contamination of the specimen by upper airway secretions. Careful cytologic examination and quantitative microbiologic cultures are important for correct interpretation of the data. BAL can often obviate the need for more invasive procedures such as open lung biopsy, especially in immunocompromised patients.

Indications for diagnostic bronchoscopy and BAL include recurrent or persistent pneumonia or atelectasis, unexplained or localized and persistent wheeze, the suspected presence of a foreign body, hemoptysis, suspected congenital anomalies, mass lesions, interstitial disease, and pneumonia in the immunocompromised host. Indications for therapeutic bronchoscopy and BAL include bronchial obstruction by mass lesions, foreign bodies or mucus plugs, and general bronchial toilet and bronchopulmonary lavage. The patient undergoing bronchoscopy ventilates around the flexible scope, whereas with the rigid scope, ventilation is accomplished through the scope. Rigid bronchoscopy is preferentially indicated for extracting foreign bodies and removing tissue masses. It is also indicated in patients with massive hemoptysis. In other cases, the flexible scope has multiple advantages: it can be passed through endotracheal or tracheostomy tubes, can be introduced into bronchi that come off the airway at acute angles, and can be safely and effectively inserted with topical anesthesia and conscious sedation.

Transbronchial and endobronchial biopsies. Transbronchial biopsies are performed by passing forceps (1.2 mm pediatric or 2.0 mm adult) through the distal visualized airways to sample small airways and alveolar tissues. Transbronchial biopsy (TBB) in children is standard practice to monitor the lung allograft after transplantation, either as a surveillance or clinically indicated procedure. For the nontransplant patient, transbronchial biopsies can be used to facilitate the diagnosis of diffuse lung disease (such as interstitial pneumonitis, bronchiolitis obliterans, lymphoma, eosinophilic pneumonia, sarcoidosis, or hypersensitivity pneumonia) or large focal processes (such as infections or unresolving pneumonia). Transbronchial biopsies do produce smaller samples than video-assisted thoracoscopic surgery (VATS) or open lung biopsies, but with a lower attendant risk; the risk of pneumothorax has been estimated to be 2–8%. Endobronchial biopsies can be performed in children, but there are relatively few clinical situations where they are broadly applied.

The **endobronchial ultrasound (EBUS)**, is a scope that allows ultrasound images to be captured from the tip of the scope and also contains a working channel to collect a needle biopsy. This technology is particularly useful in the evaluation of mediastinal lymph nodes. This scope may be useful in the diagnosis of other conditions such as sarcoidosis, tuberculosis, and the staging of lung cancers. EBUS has been investigated in older pediatric patients as an alternative to CT-guided transthoracic fine needle aspiration for the evaluation of mediastinal lymph nodes and can be safely performed in children age 9+ years. A meta-analysis of 153 pediatric patients revealed a pooled sampling adequacy and combined diagnostic yield of EBUS of 98% (95% confidence interval [CI], 92–100%) and 61% (95% CI, 43–77%), respectively, and was generally safely tolerated.

Bronchial thermoplasty (BT) is a technology that can be used to treat patients with severe asthma. This technique uses the working channel of a fiberoptic bronchoscope to deliver targeted thermal energy to the airways to ablate the airway smooth muscle (ASM). The ablation of ASM may reduce the ability to bronchoconstrict. It may also affect the ASM's role in immunomodulation, ultimately altering the pathophysiology of asthma. BT requires a minimum of a 2.0-mm working channel, which limits this technology to bronchoscopes of at least an outer diameter of 4.1 mm. BT is performed over three bronchoscopy sessions to ablate different sections of the lung: right lower lobe, left lower lobe, and bilateral upper lobes. The right middle lobe is usually not ablated because of the potential risk of stenosis. The treatments are divided into three separate procedures to allow for shorter procedure times (30-60 minutes per session) and decrease the risk of widespread irritation. Patients are also given oral steroids for 3 days before the procedure to decrease airway inflammation associated with the ablation procedure. Although BT is gaining momentum in the treatment of severe asthma in the adult population, the long-term ramifications of ASM ablation in a child are still unknown. In adult studies that investigated BT as a therapeutic tool for asthma, small studies

demonstrated an improvement in clinical symptoms, and in a smaller cohort of patients (12 patients), no significant structural abnormalities were seen on chest radiographs 5 years after the procedure.

Complications: Regardless of the instrument used, the procedure performed, or the resulting indications, the most common complications are related to sedation. The relatively more common complications related to the bronchoscopy itself include transient hypoxemia, laryngospasm, bronchospasm, and cardiac arrhythmias. Iatrogenic infection, bleeding, pneumothorax, and pneumomediastinum are rare but reported complications of bronchoscopy or BAL, with increased complications when concomitant biopsies are taken. Bronchoscopy in the setting of possible pulmonary abscess or hemoptysis must be undertaken with advance preparations for definitive airway control, mindful of the possibility that pus or blood might flood the airway. Subglottic edema is a more common complication of rigid bronchoscopy than of flexible procedures, in which the scopes are smaller and less likely to traumatize the mucosa. Post-bronchoscopy croup is treated with oxygen, mist, vasoconstrictor aerosols, and corticosteroids as necessary.

Thoracoscopy

The pleural cavity can be examined through a thoracoscope, which is similar to a rigid bronchoscope. The thoracoscope is inserted through an intercostal space and the lung is partially deflated, allowing the operator to view the surface of the lung, the pleural surface of the mediastinum and the diaphragm, and the parietal pleura. Multiple thoracoscopic instruments can be inserted, allowing endoscopic biopsy of the lung or pleura, resection of blebs, abrasion of the pleura, and ligation of vascular rings.

Thoracentesis

For diagnostic or therapeutic purposes, fluid can be removed from the pleural space by needle. In general, as much fluid as possible should be withdrawn, and an upright chest roentgenogram should be obtained after the procedure. Complications of thoracentesis include infection, pneumothorax, and bleeding. Thoracentesis on the right may be complicated by puncture or laceration of the capsule of the liver and, on the left, by puncture or laceration of the capsule of the spleen. Specimens obtained should always be cultured, examined microscopically for evidence of bacterial infection, and evaluated for total protein and total differential cell counts. Lactic acid dehydrogenase, glucose, cholesterol, triglyceride (chylous), and amylase determinations may also be useful. If malignancy is suspected, cytologic examination is imperative.

Transudates result from mechanical factors influencing the rate of formation or reabsorption of pleural fluid and generally require no further diagnostic evaluation. Exudates result from inflammation or other disease of the pleural surface and underlying lung, so they require a more complete diagnostic evaluation. In general, transudates have a total protein of <3 g/dL or a ratio of pleural protein to serum protein <0.5, a total leukocyte count of less than 2,000/mm^3 with a predominance of mononuclear cells, and low lactate dehydrogenase levels. Exudates have high protein levels and a predominance of polymorphonuclear cells (although malignant or tuberculous effusions can have a higher percentage of mononuclear cells). Complicated exudates often require continuous chest tube drainage and have a pH <7.2. Tuberculous effusions can have low glucose and high cholesterol content.

Lung Biopsy

Lung biopsy may be the only way to establish a diagnosis, especially in protracted, noninfectious disease. In infants and small children, thoracoscopic or open surgical biopsies are the procedures of choice, and in expert hands there is low morbidity. Biopsy through the 3.5-mm-diameter pediatric bronchoscopes limits the sample size and diagnostic abilities. In addition to ensuring that an adequate specimen is obtained, the surgeon can inspect the lung surface and choose the site of biopsy. In older children, transbronchial biopsies can be performed using flexible forceps through a bronchoscope, an endotracheal tube, a rigid bronchoscope, or an endotracheal tube, usually with fluoroscopic guidance. This technique is most appropriately used when the disease is diffuse, as in the case of *Pneumocystis* pneumonia, or after rejection of a transplanted lung. The diagnostic limitations related to the small size of the biopsy specimens can be mitigated by the ability to obtain several samples. The risk of pneumothorax related to bronchoscopy is increased when transbronchial biopsies are part of the procedure; however, the ability to obtain biopsy specimens in a procedure performed with topical anesthesia and conscious sedation is advantageous.

Genetic Testing

Genetic testing enables precise diagnosis of an expanding array of respiratory diseases. In addition to diagnosis, genetic testing can contribute to discussions of disease severity and prognosis, aids counseling surrounding family planning, and serves as a cornerstone for development and application of novel therapeutics. Applications range from identification of known diseases in a child with nonspecific symptoms to early identification in an otherwise asymptomatic individual. Whole genome sequencing can be applied to rapidly diagnose children presenting with rare diseases or new phenotypes of known disorders.

Acute respiratory distress in the neonatal period rarely occurs secondary to several known genetic disorders. Genetic testing can be considered for *full-term* infants with unexplained severe respiratory disease or premature infants with lung disease *out of proportion* to what would be expected for gestational age. Genetic pulmonary disorders causing neonatal respiratory distress include surfactant dysfunction from pathogenic variants in *ABCA3, SFTPB,* or *SFTPC* genes; brain-lung-thyroid syndrome due to variants in *NKX2-1;* pulmonary alveolar proteinosis associated with abnormalities in the granulocyte macrophage colony-stimulating factor (GM-CSF) receptor; and primary disorders of lung development, such as alveolar capillary dysplasia, caused by pathogenic variants in *FOXF1*.

Although disorders associated with obstructive lung disease, abnormal mucus clearance, and bronchiectasis may present at any age, newborn screening for cystic fibrosis can often facilitate genetic diagnosis in infancy with subsequent early interventions to prevent or slow the onset of lung disease. Although cystic fibrosis is a monogenic disorder, pathogenic variants in many different genes cause PCD. Presently, the spectrum of genetic variants leading to PCD has not yet been fully identified, and the disease should still be suspected even if a genetic panel is negative. As clinical genetic panels and understanding of variants of unknown significance expand, it is expected that diagnosis of PCD will streamline.

Several systemic diseases associated with diffuse lung disease can be diagnosed genetically, including Birt-Hogg-Dube, Ehlers-Danlos, Marfan, hereditary hemorrhagic telangiectasia, and Hermansky-Pudlak syndrome. Children presenting with unexplained alveolar hypoventilation suspected of congenital central hypoventilation syndrome should undergo *PHOX2B* pathogenic variant specific testing, the gold standard for diagnosis. The previous disorders are only a partial list of the many known childhood diseases associated with a genetic and respiratory component. When there is high suspicion for a genetic condition but gene panels or single-gene analysis are normal, practitioners can pursue whole exome/genome sequencing. Whole exome/genome sequencing can also be applied as first-line genetic testing in critically ill patients in need of rapid diagnosis. Genetic counseling is paramount when pursuing genetic testing, especially in the pediatric population. The spectrum of diseases able to be diagnosed using genetic testing will continue to grow and is expected to not only encompass the rare disorders discussed earlier but also the more common respiratory disorders seen in childhood.

ACKNOWLEDGMENT

The editors are grateful to Dr. Ashok Sarnaik, much of whose work on the "Blood Gas Analysis" and "Pulmonary Function Testing" sections from previous editions of this chapter is retained here.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 422

Chronic or Recurrent Respiratory Symptoms

Anne G. Griffiths

Respiratory tract symptoms, including cough, dyspnea, wheeze, and stridor, may persist for long periods in a number of children; other children have persistent or recurring lung infiltrates with or without symptoms. Determining the cause of these chronic findings can be difficult because symptoms can be caused by a close succession of unrelated acute respiratory tract infections or by a single pathophysiologic process. Specific and easily performed diagnostic tests do not exist for many acute and chronic respiratory conditions. Pressure from the affected child's family for a quick remedy because of concern over symptoms related to breathing may complicate diagnostic and therapeutic efforts.

A systematic approach to the diagnosis and treatment of these children consists of assessing whether the symptoms are the manifestation of a minor problem or a life-threatening process; determining the likely underlying pathogenic mechanism; selecting the simplest effective therapy for the underlying process, which often is only symptomatic therapy; and then carefully evaluating its effect. Failure of this approach to identify the process responsible or to effect improvement signals the need for more extensive and perhaps invasive diagnostic efforts, including bronchoscopy.

JUDGING THE SERIOUSNESS OF CHRONIC RESPIRATORY COMPLAINTS

Clinical manifestations suggesting that respiratory tract illness may be life-threatening or associated with the potential for chronic disability are listed in Table 422.1. If none of these findings is detected, the chronic respiratory process is less likely to be serious. Active, well-nourished, and appropriately growing infants who present with intermittent noisy breathing but no other physical or laboratory abnormalities require only symptomatic treatment and parental reassurance. Benign-appearing but persistent symptoms are occasionally the harbinger of a serious lower respiratory tract problem. By contrast, occasionally children (e.g., with infection-related asthma) have recurrent life-threatening episodes but few or no symptoms in the intervals. Repeated examinations over an extended period, both when the child appears healthy and when the child is symptomatic, may be helpful in sorting out the severity and chronicity of lung disease.

RECURRENT OR PERSISTENT COUGH

Cough is a reflex response of the lower respiratory tract to stimulation of irritant or cough receptors in the airways' mucosa. The most common cause of recurrent or persistent cough in children is airway reactivity (asthma). Because cough receptors also reside in the pharynx, paranasal sinuses, stomach, and external auditory canal, the source of a persistent cough may need to be sought beyond the lungs. Specific lower respiratory stimuli include excessive secretions, aspirated foreign material, inhaled dust particles or noxious gases, cold or dry air, and an inflammatory response to infectious agents or allergic processes. Table 422.2 lists some of the conditions responsible for chronic cough. Table 422.3 presents characteristics of cough that can aid in distinguishing a cough's origin. Additional useful information can include a history of atopic conditions (asthma, eczema, urticaria, allergic rhinitis), a seasonal or environmental variation in frequency or intensity of cough, and a strong family history of atopic conditions, all suggesting an allergic cause; symptoms of malabsorption or a family history indicating cystic fibrosis; symptoms related to feeding, suggesting aspiration or gastroesophageal reflux; a choking episode, suggesting foreign body aspiration; headache or facial edema associated with sinusitis; and a smoking or vaping history in older children and adolescents or the presence of a smoker in the home (Table 422.4).

The physical examination can provide further information pertaining to the cause of chronic cough. Posterior pharyngeal drainage combined with a nighttime cough suggests chronic upper airway disease such as sinusitis. An overinflated chest suggests chronic airway obstruction, as in asthma or cystic fibrosis. An expiratory wheeze, with or without diminished intensity of breath sounds, strongly suggests asthma or asthmatic bronchitis, but may also be consistent with a diagnosis of cystic fibrosis, bronchomalacia, vascular ring, aspiration of foreign material, or pulmonary hemosiderosis. Careful auscultation during forced expiration may reveal expiratory wheezes that are otherwise undetectable and that are the only indication of underlying reactive airways. Coarse crackles suggest bronchiectasis, including cystic fibrosis, but can also occur with an acute or subacute exacerbation of asthma. Clubbing of the digits is often seen in most patients with bronchiectasis but in only a few other respiratory conditions with chronic cough (see Table 422.2). Tracheal deviation suggests foreign body aspiration, pleural effusion, a mediastinal mass or an enlarged lymph node.

Allowing sufficient examination time to detect a spontaneous cough is important. If a spontaneous cough does not occur, asking the child to take a maximal breath and forcefully exhale repeatedly usually induces a cough reflex. Most children can cough on request by 4-5 years of age. Children who cough as often as several times a minute with regularity are likely to have a habit (tic) cough (see Chapter 37). If the cough is loose, every effort should be made to obtain sputum; many older children can comply. It is sometimes possible to pick up sputum with a throat swab quickly inserted into the lower pharynx while the child coughs with the tongue protruding. Clear mucoid sputum is most often associated with an allergic reaction or asthmatic bronchitis. Cloudy (purulent) sputum suggests a respiratory tract infection but can also reflect increased cellularity (eosinophilia) from an asthmatic process. Very purulent sputum is characteristic of bronchiectasis (see Chapter 452). Malodorous expectorations suggest anaerobic infection of the lungs. In cystic fibrosis (see Chapter 454), the sputum, even when purulent, is rarely foul smelling.

Laboratory tests can help in the evaluation of a chronic cough. Sputum quality assessment includes a low number of squamous epithelial cells, found only in the upper airway, and a higher number of leukocytes. However, laboratories use different values, and in the case of cystic fibrosis, pathogens found are associated with lower respiratory infection even in the absence of satisfactory quality by various criteria. Sputum eosinophilia suggests asthma, asthmatic bronchitis, or hypersensitivity reactions of the lung (see Chapter 448), but a polymorphonuclear cell response suggests infection; if sputum is unavailable, the presence of eosinophilia in nasal secretions also suggests atopic disease. If most of the cells in sputum are macrophages, postinfectious hypersensitivity of cough receptors should be suspected. Sputum macrophages can be stained for hemosiderin content, which is diagnostic of pulmonary hemosiderosis (see Chapter 457), or for lipid content, which in large amounts suggests, but is not specific for, repeated aspiration. Rarely, children may expectorate partial casts of the airway, which can be characterized by investigating causes of plastic bronchitis. However, in young children, bronchoalveolar lavage may be needed for optimal ascertainment of alveolar macrophages. Children whose coughs persists for more than 6 weeks should be tested for cystic fibrosis regardless of their race or ethnicity (see Chapter 454). Sputum culture is helpful in evaluation of cystic fibrosis, but less so for other conditions because throat flora can contaminate the sample.

Hematologic assessment can reveal a microcytic anemia that is the result of pulmonary hemosiderosis (see Chapter 457) or hemoptysis, or eosinophilia that accompanies asthma and other hypersensitivity reactions of the lung. Infiltrates on the chest radiograph suggest cystic fibrosis, bronchiectasis, foreign body, hypersensitivity pneumonitis, tuberculosis, or other infection. When asthma-equivalent cough is suggested, a trial of bronchodilator therapy may be diagnostic. If the cough does not respond to initial therapeutic efforts, more specific diagnostic procedures may be warranted, including an immunologic or allergic evaluation, chest and paranasal sinus imaging, esophagograms,

Table 422.1 Indicators of Serious Chronic Lower Respiratory Tract Disease in Children

Persistent fever
Ongoing limitation of activity
Failure to grow
Failure to gain weight appropriately
Clubbing of the digits
Persistent tachypnea and labored ventilation
Shortness of breath and exercise intolerance
Chronic purulent sputum
Persistent hyperinflation
Substantial and sustained hypoxemia
Refractory infiltrates on chest x-ray
Persistent pulmonary function abnormalities
Hemoptysis
Family history of heritable lung disease
Cyanosis and hypercarbia
Unusual (opportunistic) or recurrent nonpulmonary infections

Table 422.2 Differential Diagnosis of Recurrent and Persistent Cough in Children

RECURRENT COUGH
Asthma
Drainage from upper airways
Aspiration
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients
Symptomatic Chiari malformation
Idiopathic pulmonary hemosiderosis
Hypersensitivity (allergic) pneumonitis
PERSISTENT COUGH
Hypersensitivity of cough receptors after infection
Reactive airway disease (asthma)
Chronic sinusitis
Chronic rhinitis (allergic or nonallergic)
Bronchitis or tracheitis caused by infection or smoke exposure
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency
Tic cough
Foreign body aspiration
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft, or tracheoesophageal fistula
Gastroesophageal reflux, with or without aspiration
Pertussis
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst)
Tracheomalacia, bronchomalacia
Endobronchial or endotracheal tumors
Endobronchial tuberculosis
Hypersensitivity pneumonitis
Fungal infections
Inhaled irritants, including tobacco smoke
Irritation of external auditory canal
Angiotensin-converting enzyme inhibitors

Table 422.3 Characteristics of Cough and Other Clinical Features and Possible Causes

SYMPTOMS AND SIGNS	POSSIBLE UNDERLYING ETIOLOGY*
Auscultatory findings (wheeze, crepitations/crackles, differential breath sounds)	Asthma, bronchitis, pneumonia, congenital lung disease, foreign body aspiration, airway abnormality
Cough characteristics (e.g., cough with choking, cough quality, cough starting from birth)	Congenital airway or lung abnormalities
Cardiac abnormalities (including murmurs)	Any cardiac illness
Chest pain	Asthma, functional, pleuritis
Chest wall deformity	Any chronic lung disease, neuromuscular disorders
Daily moist or productive cough	Chronic bronchitis, suppurative lung disease
Digital clubbing	Suppurative lung disease, arteriovenous shunt
Dyspnea (exertional or at rest)	Compromised lung function of any chronic lung or cardiac disease
Failure to thrive	Compromised lung function, immunodeficiency, cystic fibrosis
Feeding difficulties (including choking and vomiting)	Compromised lung function, aspiration, anatomic disorders
Hemoptysis	Bronchitis, foreign body aspiration, suctioning trauma, pulmonary hemorrhage
Immune deficiency	Atypical and typical recurrent respiratory or nonrespiratory infections
Medications or drugs	Angiotensin-converting enzyme inhibitors, puffers, illicit drug use
Neurodevelopmental abnormality	Aspiration
Recurrent pneumonia	Immunodeficiency, congenital lung problem, airway abnormality
Symptoms of upper respiratory tract infection	Can coexist or be a trigger for an underlying problem

*This is not an exhaustive list; only the more common respiratory diseases are mentioned.

Modified from Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation. Thoracic Society of Australia and New Zealand. *Med J Aust.* 2006;184(8):398–403, Table 2.

tests for gastroesophageal reflux (see Chapter 369), and special microbiologic studies including rapid viral testing. Evaluation of ciliary morphology, nasal endoscopy, laryngoscopy, and bronchoscopy may also be indicated.

Tic cough or somatic cough disorder (psychogenic cough or habit cough) must be considered in any child with a cough that has lasted for weeks or months, that has been refractory to treatment, and that disappears with sleep or with distraction. Typically, the cough is abrupt and loud and has a harsh, honking, or barking quality. A disassociation between the intensity of the cough and the child's affect is typically striking. This cough may be absent if the physician listens outside the examination room, but it will reliably appear immediately on direct attention to the child and the symptom. It typically begins with an upper respiratory infection but then lingers. The child misses many days of school because the cough disrupts the classroom. This disorder accounts for many unnecessary medical procedures and courses of medication. It is treatable with assurance that a pathologic lung condition is absent and that the child should resume full activity, including school. This assurance, together with speech therapy techniques that allow the child to reduce musculoskeletal tension in the neck and chest and that increase the child's awareness of the initial sensations that trigger cough, has been highly successful. Self-hypnosis is another successful therapy, often effective with one session. The designation "tic cough" or "somatic cough disorder" is preferable to "habit cough" or "psychogenic cough" because it carries no stigma and because most of

Table 422.4 Clinical Clues About Cough

CHARACTERISTIC	THINK OF
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, *Chlamydia* spp., *Mycoplasma* spp.
Followed by "whoop"	Pertussis
All day, never during sleep	Tic cough
Barking, brassy	Croup, tic cough, tracheomalacia, tracheitis, epiglottitis
Hoarseness	Laryngeal involvement (croup, recurrent laryngeal nerve involvement), papillomatosis
Abrupt onset	Foreign body, pulmonary embolism
During or following exercise	Reactive airway disease
Accompanies eating, drinking	Aspiration, gastroesophageal reflux, tracheoesophageal fistula
Throat clearing	Postnasal drip, vocal tic
Productive (sputum)	Infection, cystic fibrosis, bronchiectasis
Night cough	Sinusitis, reactive airway disease, gastroesophageal reflux
Seasonal	Allergic rhinitis, reactive airway disease
Immunosuppressed patient	Bacterial pneumonia, *Pneumocystis jiroveci, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* cytomegalovirus, fungi
Dyspnea	Hypoxia, hypercarbia
Animal exposure	*Chlamydia psittaci* (birds), *Yersinia pestis* (rodents), *Francisella tularensis* (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)
Geographic	Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)
Workdays with clearing on days off	Occupational exposure

From Kliegman RM, Greenbaum LA, Lyle PS. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: WB Saunders; 2004:19.

these children do not have significant emotional problems. When the cough disappears, it does not reemerge as another symptom. Nonetheless, other symptoms such as irritable bowel syndrome may be present in the patient or family.

FREQUENTLY RECURRING OR PERSISTENT STRIDOR

Stridor, a harsh, medium-pitched, inspiratory sound associated with obstruction of the laryngeal area or the extrathoracic trachea, is often accompanied by a croupy cough and hoarse voice. Stridor is most commonly observed in children with croup (see Chapter 433); foreign bodies and trauma can also cause acute stridor. A few children, however, acquire recurrent stridor or have persistent stridor from the first days or weeks of life (Table 422.5). Most congenital anomalies of large airways that produce stridor become symptomatic soon after birth. Increase of stridor when a child is supine suggests **airway malacia**, such as laryngomalacia or tracheomalacia. It is important to note that when evaluating for a specific anatomic cause of abnormal breath sounds, it is not uncommon to identify additional congenital anomalies of the airway. An accompanying history of hoarseness or aphonia suggests involvement of the vocal cords. Associated dysphagia may also suggest a vascular ring. In a child with intermittent stridor (with wheezing) that accompanies physical activity and is not responsive to asthma therapies, **paradoxical vocal cord dysfunction** may be considered. Paradoxical vocal cord dysfunction may be highly supported by history and confirmed by laryngoscopy during an exercise challenge test if symptoms are successfully elicited. Speech therapy and behavior modification may be therapeutic.

Table 422.5 Causes of Recurrent or Persistent Stridor in Children

RECURRENT
Allergic (spasmodic) croup
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways
Laryngomalacia
PERSISTENT
Laryngeal obstruction
Laryngomalacia
Papillomas, hemangiomas, other tumors
Cysts and laryngoceles
Laryngeal webs
Bilateral abductor paralysis of the cords
Foreign body
Tracheobronchial disease
Tracheomalacia
Subglottic tracheal webs
Endobronchial, endotracheal tumors
Subglottic tracheal stenosis, congenital or acquired
Extrinsic masses
Mediastinal masses
Vascular ring
Lobar emphysema
Bronchogenic cysts
Thyroid enlargement
Esophageal foreign body
Tracheoesophageal fistula
OTHER
Gastroesophageal reflux
Macroglossia, Pierre Robin syndrome
Cri-du-chat syndrome
Paradoxical vocal cord dysfunction
Hypocalcemia
Vocal cord paralysis
Chiari crisis
Severe neonatal episodic laryngospasm caused by *SCN4A* pathogenic variant

Physical examination for recurrent or persistent stridor is usually unrewarding, although changes in its severity and intensity resulting from changes of body position should be assessed. Anteroposterior and lateral radiographs, contrast esophagography, fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI) are potentially useful diagnostic tools. In most cases, direct observation by laryngoscopy is necessary for definitive diagnosis. Undistorted views of the larynx are best obtained with fiberoptic laryngoscopy.

RECURRENT OR PERSISTENT WHEEZE

See also Chapter 439.

Parents often complain that their child wheezes, when, in fact, they are reporting respiratory sounds that are audible without a stethoscope, produce palpable resonance throughout the chest, and occur most prominently in inspiration. Some of these children have stridor, although many have audible sounds when the supraglottic airway is incompletely cleared of feedings or secretions.

True wheezing is a relatively common and particularly troublesome manifestation of obstructive *lower* respiratory tract disease in children. The site of obstruction may be anywhere from the intrathoracic trachea to the small bronchi or large bronchioles, but the sound is generated by turbulence in larger airways that collapse with forced expiration (see Chapter 421). Children younger than 2-3 years are especially prone to wheezing, because bronchospasm, mucosal edema, and accumulation of excessive secretions have a relatively greater obstructive effect on their smaller airways. In addition, the compliant airways in young children collapse more readily with active expiration. Isolated episodes of acute wheezing, such as can occur with bronchiolitis, are not uncommon, but wheezing that recurs or persists for more than 4 weeks suggests other diagnoses. Most recurrent or persistent wheezing in children is the result of airway reactivity. Nonspecific environmental factors such as cigarette smoke may be important contributors.

Frequently recurring or persistent wheezing starting at or soon after birth suggests a variety of other diagnoses, including congenital structural abnormalities involving the lower respiratory tract or tracheobronchomalacia (see Chapter 434). Wheezing that attends cystic fibrosis is most common in the first year of life. Sudden onset of severe wheezing in a previously healthy child should suggest foreign body aspiration.

Either wheezing or coughing when associated with tachypnea and hypoxemia may be suggestive of **interstitial lung disease** (see Chapter 448.5). However, many patients with interstitial lung disease demonstrate no symptoms other than rapid breathing on initial physical examination. Although chest roentgenograms may be normal in interstitial lung disease, diffuse abnormalities on chest x-ray may support further evaluation in patients suspected to have interstitial lung disease with characteristic findings described on high-resolution CT scan and lung biopsy.

Repeated examination may be required to verify a history of wheezing in a child with episodic symptoms and should be directed toward assessing air movement, ventilatory adequacy, and evidence of chronic lung disease, such as fixed overinflation of the chest, growth failure, and digital clubbing. Patients should be assessed for oropharyngeal dysphagia in cases of suspected recurrent aspiration. Clubbing suggests chronic lung infection and is rarely prominent in uncomplicated asthma. Tracheal deviation from foreign body aspiration should be sought. It is essential to rule out wheezing secondary to congestive heart failure. Allergic rhinitis, urticaria, eczema, or evidence of ichthyosis vulgaris suggests asthma or asthmatic bronchitis. The nose should be examined for polyps, which can exist with allergic conditions or cystic fibrosis.

Sputum eosinophilia and elevated serum immunoglobulin E levels suggest allergic reactions. A forced expiratory volume in 1 second increase of 15% in response to bronchodilators confirms reactive airways. Specific microbiologic studies, special imaging studies of the airways and cardiovascular structures, diagnostic studies for cystic fibrosis, and bronchoscopy should be considered if the response is unsatisfactory.

RECURRENT AND PERSISTENT LUNG INFILTRATES

Radiographic lung infiltrates resulting from acute pneumonia usually resolve within 1-3 weeks, but a substantial number of children, particularly infants, fail to completely clear infiltrates within a 4-week period. These children may be febrile or afebrile and may display a wide range of respiratory symptoms and signs. Persistent or recurring infiltrates present a diagnostic challenge (Table 422.6).

Table 422.6 Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period

- Aspiration
  - Pharyngeal incompetence (e.g., cleft palate)
  - Laryngotracheoesophageal cleft
  - Tracheoesophageal fistula
  - Gastroesophageal reflux
  - Lipid aspiration
  - Neurologic dysphagia
  - Developmental dysphagia
- Congenital anomalies
  - Lung cysts (congenital pulmonary airway malformation)
  - Bronchopulmonary sequestration
  - Congenital lobar emphysema
  - Bronchogenic cysts
  - Bronchial stenosis or aberrant bronchus
  - Vascular ring
  - Congenital heart disease with large left-to-right shunt
  - Pulmonary lymphangiectasia
- Genetic conditions
  - Cystic fibrosis
  - Primary ciliary dyskinesia
  - Sickle cell disease (acute chest syndrome)
- Immunodeficiency, phagocytic deficiency
  - Humoral, cellular, combined immunodeficiency states
  - Chronic granulomatous disease and related phagocytic defects
  - Hyper–immunoglobulin E syndromes
  - Complement deficiency states
- Immunologic and autoimmune diseases
  - Asthma
  - Allergic bronchopulmonary aspergillosis
  - Hypersensitivity pneumonitis
  - Pulmonary hemosiderosis
  - Collagen-vascular diseases
- Granulomatosis with polyangiitis
- Infection, congenital
  - Cytomegalovirus
  - Rubella
  - Syphilis
- Infection, acquired
  - Cytomegalovirus
  - Tuberculosis
  - HIV
  - Other viruses
- *Chlamydia*
- *Mycoplasma, Ureaplasma*
  - Pertussis
  - Fungal organisms
- *Pneumocystis jiroveci*
  - Visceral larva migrans
  - Inadequately treated bacterial infection
- Interstitial pneumonitis and fibrosis
  - Usual interstitial pneumonitis
  - Lymphocytic interstitial pneumonia (AIDS)
  - Nonspecific interstitial pneumonia (NSIP)
  - Genetic disorders of surfactant synthesis, secretion
  - Desquamative interstitial pneumonia
  - Cryptogenic organizing pneumonia
  - Acute interstitial pneumonia (Hamman-Rich syndrome)
  - Alveolar proteinosis
  - Drug-induced, radiation-induced inflammation and fibrosis
- Neoplasms and neoplastic-like conditions
  - Primary or metastatic pulmonary tumors
  - Leukemia
  - Histiocytosis
  - Eosinophilic pneumonias
- Other etiologies
  - Bronchiectasis (congenital, postinfectious)
  - Sarcoidosis

Symptoms associated with chronic lung infiltrates in the first several weeks of life (but not related to neonatal respiratory distress syndrome) suggest infection acquired in utero or during descent through the birth canal. Early appearance of chronic infiltrates can also be associated with cystic fibrosis or congenital anomalies that result in aspiration or airway obstruction. A history of recurrent infiltrates such as in **middle lobe syndrome** (see Chapter 444), wheezing, and cough may reflect asthma, even in the first year of life.

A controversial association has been posed regarding recurrent lung infiltrates in pulmonary hemosiderosis related to cow's milk hypersensitivity or unknown causes appearing in the first year of life. Children with a history of bronchopulmonary dysplasia often have episodes of respiratory distress attended by wheezing and new lung infiltrates. **Recurrent pneumonia** in a child with frequent otitis media, nasopharyngitis, adenitis, or dermatologic manifestations suggests an immunodeficiency state, complement deficiency, or phagocytic defect (see Chapters 164, 167, and 172). Primary ciliary dyskinesia is also of consideration in patients with frequent otitis media and suppurative sinopulmonary disease, with or without accompanying heterotaxy or history of neonatal respiratory distress (see Chapter 455). Pulmonary sequestration may be suspected in patients with recurrent findings on radiograph that occur in the same location, both during illness and when well (see Chapter 444). Traction bronchiectasis may also be suggested on radiography with persistent findings in a given region of the film after a history of respiratory infection. Particular attention must be directed to the possibility that the infiltrates represent lymphocytic interstitial pneumonitis or opportunistic infection associated with HIV infection or immunocompromise (see Chapter 322). A history of paroxysmal coughing in an infant suggests pertussis syndrome or cystic fibrosis. Persistent infiltrates in a toddler, especially with loss of volume, may suggest foreign body aspiration.

Overinflation and infiltrates suggest cystic fibrosis or chronic asthma. A silent chest with infiltrates should arouse suspicion of alveolar proteinosis (see Chapter 456), *Pneumocystis jiroveci* infection (see Chapter 290), genetic disorders of surfactant synthesis and secretion causing interstitial pneumonitis, or tumors. Growth should be carefully assessed to determine whether the lung process has had systemic effects, indicating substantial severity and chronicity, as in cystic fibrosis or alveolar proteinosis. Cataracts, retinopathy, or microcephaly suggest in utero infection. Chronic rhinorrhea can be associated with atopic disease, cow's milk intolerance, cystic fibrosis, primary ciliary dyskinesia, or congenital syphilis. The absence of tonsils and cervical lymph nodes suggests an immunodeficiency state.

Diagnostic studies should be performed selectively, based on information obtained from history and physical examination and on a thorough understanding of the conditions listed in Table 422.6. Cytologic evaluation of sputum, if available, may be helpful. Chest CT often provides more precise anatomic detail concerning the infiltrate or further characterizes a region of anatomic abnormality. Bronchoscopy is indicated for detecting foreign bodies, congenital or acquired anomalies of the tracheobronchial tract, and obstruction by endobronchial or extrinsic masses (see Chapters 434-438). Bronchoscopy provides access to secretions that can be studied cytologically and microbiologically. Alveolar lavage fluid is diagnostic for alveolar proteinosis and persistent pulmonary hemosiderosis and can suggest aspiration syndromes. Ciliary biopsy may be obtained from the inferior epithelial surface of nasal turbinates or from the lower airway during bronchoscopy. If all appropriate studies have been completed and the condition remains undiagnosed, lung biopsy might yield a definitive diagnosis, such as in interstitial lung disease or fungal disease.

Optimal medical or surgical treatment of chronic lung infiltrates often depends on a specific diagnosis, but chronic conditions may be self-limiting (severe and prolonged viral infections in infants); in these cases, symptomatic therapy can maintain adequate lung function until spontaneous improvement occurs. Helpful measures include airway clearance therapy for excessive secretions, antibiotics for bacterial infections, supplementary oxygen for hypoxemia, and maintenance of adequate nutrition. Because the lung of a young child has remarkable recuperative potential, normal lung function may ultimately be achieved with treatment despite the severity of pulmonary insult occurring in infancy or early childhood.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

422.1 Extrapulmonary Diseases with Pulmonary Manifestations

John Palla and Susanna A. McColley

Respiratory symptoms commonly originate from extrapulmonary processes. The respiratory system adapts to metabolic demands and is exquisitely responsive to cortical input; therefore **tachypnea** is common in the presence of metabolic stress such as fever, and dyspnea may be related to anxiety. **Cough** most commonly arises from upper or lower respiratory tract disorders, but it can originate from the central nervous system, as with cough tic or somatic cough, and it can be a prominent symptom in children with gastroesophageal reflux disease. **Chest pain** does not commonly arise from pulmonary processes in otherwise healthy (no history of asthma) children but more often has a neuromuscular, musculoskeletal, or inflammatory etiology. **Cyanosis** can be caused by cardiac and/or hematologic disorders. **Dyspnea** and **exercise intolerance** can have a number of extrapulmonary causes. These extrapulmonary disorders may be suspected on the basis of the history and physical examination, or they may be considered in children in whom diagnostic studies have atypical findings or who show poor response to usual therapy. Table 422.7 lists more common extrapulmonary causes of such symptoms.

EVALUATION

In the evaluation of a child or adolescent with respiratory symptoms, it is important to obtain a detailed medical history, family history, and review of systems to evaluate the possibility of extrapulmonary origin. A comprehensive physical examination is also essential to identify signs of extrapulmonary disease.

Disorders of other organ systems, and many systemic diseases, can have significant respiratory system involvement. Although it is most common to encounter these complications in patients with known diagnoses, respiratory system disease is sometimes the sole or most prominent symptom at the time of presentation. Acute aspiration during feeding can be the presentation of neuromuscular disease in an infant who initially appears to have normal muscle tone and development. Pulmonary complications can be life-threatening, particularly in immunocompromised patients. The onset of respiratory findings may be insidious; for example, pulmonary vascular involvement in patients with systemic vasculitis may appear as an abnormality in diffusing capacity of the lung for carbon monoxide before the onset of symptoms. Table 422.8 lists disorders that commonly have respiratory complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 422.7 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Musculoskeletal	Inflammation (overuse, postviral, idiopathic), injury	Reproducible pain with palpation
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
Chest pain	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain
Cyanosis	Congenital heart disease	Right-to-left shunt	Neonatal onset, lack of response to oxygen
	Methemoglobinemia	Increased levels of methemoglobin interfere with delivery of oxygen to tissues	Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose	Variable, but often metabolic acidosis	Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry
	Anxiety, panic disorder	Increased respiratory drive and increased perception of respiratory efforts	Occurs during stressful situation, other symptoms of anxiety and/or depression
Exercise intolerance	Anemia	Inadequate oxygen delivery to tissues	Pallor, tachycardia, history of bleeding, prolonged or heavy menstrual periods, history of inadequate diet
Exercise intolerance	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding leads to suspicion of pulmonary origin	History and physical findings suggest nasal source; normal chest examination and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source; normal chest examination and chest radiography
Wheezing, cough, dyspnea	Congenital or acquired cardiac disease	Pulmonary overcirculation (atrioseptal defect, ventriculoseptal defect, patent ductus arteriosus), left ventricular dysfunction	Murmur Refractory to bronchodilators Radiographic changes (prominent pulmonary vasculature, pulmonary edema)
Wheezing, cough	Gastroesophageal reflux disease	Laryngeal and bronchial response to stomach contents	Emesis, pain, heartburn
		Vagally mediated bronchoconstriction	Refractory to bronchodilators

Table 422.8 Disorders with Frequent Respiratory Tract Complications

UNDERLYING DISORDER(S)	RESPIRATORY COMPLICATIONS	DIAGNOSTIC TESTS
Autoimmune disorders	Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper and lower airway disease (granulomatosis with polyangiitis)	Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT
Central nervous system disease (static or progressive)	Aspiration of oral or gastric contents, impaired airway clearance	Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy
Immunodeficiency	Infection, bronchiectasis, impaired mucociliary clearance	Chest radiography, fiberoptic bronchoscopy, chest CT
Liver disease	Pleural effusion, hepatopulmonary syndrome	Chest radiography, assessment of platypnea-orthodeoxia
Malignancy and its therapies	Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft versus host disease (bone marrow transplant), fibrosis	Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy
Neuromuscular disease	Hypoventilation, atelectasis, pneumonia, restrictive lung disease, impaired airway clearance	Spirometry, lung volume determination, respiratory muscle force measurements
Obesity	Restrictive lung disease, obstructive sleep apnea syndrome, asthma	Spirometry, lung volume determination, nocturnal polysomnography

Chapter 423

Sudden Infant Death Syndrome

Fern R. Hauck, Rebecca F. Carlin, Rachel Y. Moon, and Carl E. Hunt

Sudden infant death syndrome (SIDS) is defined as the sudden, unexpected death of an infant that remains unexplained after a thorough postmortem examination, which includes a complete autopsy, investigation of the scene of death, review of the medical history, and appropriate laboratory testing. An autopsy is essential to identify possible natural explanations for sudden unexpected death such as congenital anomalies or infection and to diagnose nonaccidental trauma. The autopsy typically cannot distinguish between SIDS and intentional suffocation, but the scene investigation and medical history may be of help if inconsistencies are evident. **Sudden unexpected infant death (SUID)** is a term that generally encompasses all SUIDs that occur during sleep, including SIDS (ICD-10 R95), accidental suffocation and strangulation in bed (ICD-10 W75), and ill-defined deaths, also known as *undetermined* (ICD-10 R99).

EPIDEMIOLOGY

SIDS, accidental suffocation and strangulation in bed, and ill-defined deaths are among the most common causes of overall infant mortality. SIDS is one of the leading causes of postneonatal (28 days to 1 year of age) mortality. The annual rate of SIDS in the United States was stable at 1.3-1.4 per 1,000 live births (approximately 7,000 infants per year) before 1992, when it was recommended that infants sleep nonprone as a way to reduce the risk for SIDS. Since then, particularly after initiation of the national Back to Sleep (now called *Safe to Sleep*) campaign in 1994, the rate of SIDS progressively declined and then leveled off in 2001 at 0.55 per 1,000 live births (2,234 infants). There has been a slower rate of decline since that time; in 2020 the rate was 0.38 per 1,000 live births (~1,200 infants). The initial decline in the number of SIDS deaths in the United States and other countries has been largely attributed to increasing use of the supine position for sleep. In 1992, 82% of sampled infants in the United States were placed prone for sleep. Although several other countries have decreased prone sleeping prevalence to ≤2%, in the United States in 2016, only 78% of infants were usually being placed supine for sleep. Among Black infants, these rates were even lower, at 62%.

There is increasing evidence that infant deaths previously classified as SIDS are now being classified by medical examiners and coroners as the result of other causes, notably **accidental suffocation and strangulation in bed** (ICD 10 W75) and **ill-defined deaths** (ICD 10 R99). Between 1994 and 2018, there was a sevenfold increase in the rate of accidental suffocation and strangulation in bed, from 0.03 to 0.22 deaths per 1,000 live births. There was also a 57% increase in the rate of ill-defined deaths between 1995 and 2018, from 0.21 to 0.33 deaths per 1,000 live births. These sudden and unexpected infant deaths are primarily associated with unsafe sleeping environments, including side and prone positioning, sharing a sleep surface with others, and soft bedding in the sleep environment. Based on these trends and the commonality of many of the sleep environment risk factors that are associated with both SIDS and other sleep-related SUID, risk-reduction measures that will be described later are applicable to all sleep-related SUID.

PATHOLOGY

There are no autopsy findings *pathognomonic* for SIDS, and no findings are required for the diagnosis, but some findings are commonly seen on postmortem examination (Table 423.1). Petechial hemorrhages are found in 68–95% of infants who died of SIDS and are more extensive than in explained causes of infant mortality. Pulmonary edema is often present and may be substantial. The reasons for these findings are unknown.

SIDS infants have several identifiable changes in the lungs and other organs (see Table 423.1). Nearly 65% of these infants have structural evidence of preexisting, chronic, low-grade asphyxia, and other studies have identified biochemical markers of asphyxia. Infants who died of SIDS have higher levels of vascular endothelial growth factor (VEGF) in the cerebrospinal fluid (CSF). These increases may be related to VEGF polymorphisms (see "Genetic Risk Factors" and Table 423.3) or might indicate recent hypoxemic events because VEGF is upregulated by hypoxia.

Numerous studies have shown brain abnormalities that may cause or contribute to an impaired autonomic response to an exogenous stressor, including in the hippocampus and brainstem, the latter being the major area responsible for respiratory and autonomic regulation (see Table 423.1). The primary affected sites of chemoreception and respiratory drive include peripheral chemoreceptors (e.g., carotid body) and multiple central chemoreceptors, including the retrotrapezoid nucleus, serotonergic raphe nuclei, locus coeruleus, orexinergic neurons, solitary tract nucleus, and the dorsal motor nucleus of the vagus.

The ventral medulla has been a particular focus for studies in infants who died of SIDS (see Table 423.1). It is an integrative area for vital autonomic functions, including breathing, arousal, and chemosensory function. Some SIDS infants have hypoplasia of the arcuate nucleus and up to 60% have histopathologic evidence of less extensive bilateral or unilateral hypoplasia. Consistent with the apparent overlap between putative mechanisms for SIDS and for unexpected late fetal deaths, approximately 30% of sudden intrauterine unexplained deaths also have hypoplasia of the arcuate nucleus. Imaging mass spectroscopy of postmortem medullary tissue has identified abnormal expression of multiple peptides, especially in the raphe, hypoglossal, and pyramidal nuclei that include components for developmental neuronal/glial/axonal growth, cell metabolism, cytoarchitecture, and apoptosis. These findings suggest that SIDS infants have abnormal neurologic development

Table 423.1 Common Postmortem and Research Pathologic Abnormalities Observed in Sudden Infant Death Syndrome Infants

COMMON OBSERVATIONS
Petechial hemorrhages, lungs, and pleura
Pulmonary edema
RESEARCH FINDINGS
Evidence of preexisting chronic low-grade asphyxia
Increased cerebrospinal levels of vascular endothelial growth factor (VEGF)
• Secondary to preexisting asphyxia
• VEGF polymorphisms
NEUROPATHOLOGY RESEARCH FINDINGS
Abnormalities leading to impaired autonomic responses
Peripheral and central chemoreceptor abnormalities
Ventral medullary abnormalities
• Hypoplastic arcuate nucleus
• Abnormalities in serotonin (5-HT) neurons
• Decreases in 5-HT_{1A} and 5-HT_{2A} receptor immunoreactivity
• Extensive serotonergic brainstem abnormalities

contributing to pathogenesis, with the impairments suggesting delayed neurologic maturation.

Neurotransmitter studies of the arcuate nucleus have also identified several receptor abnormalities relevant to state-dependent autonomic control overall and to ventilatory and arousal responsiveness in particular. These deficits include significant decreases in binding to kainate, muscarinic cholinergic, and serotonin (5-HT) receptors. Studies of the ventral medulla have identified morphologic and biochemical deficits in 5-HT neurons and decreased γ-aminobutyric acid receptor A receptor binding in the medullary serotonergic system. Immunohistochemical analyses reveal an increased number of 5-HT neurons and an increase in the fraction of 5-HT neurons showing an immature morphology, suggesting a failure or delay in the maturation of these neurons (see Table 423.1). High neuronal levels of interleukin (IL)-1β are present in the arcuate and dorsal vagal nuclei in infants with SIDS compared with controls, perhaps contributing to molecular interactions affecting cardiorespiratory and arousal responses.

The neuropathologic data provide compelling evidence for altered 5-HT homeostasis creating an underlying vulnerability contributing to SIDS. 5-HT is an important neurotransmitter, and the 5-HT neurons in the medulla project extensively to neurons in the brainstem and spinal cord that influence respiratory drive, arousal, cardiovascular control, circadian regulation and non–rapid eye movement (NREM) sleep, thermoregulation, and upper airway reflexes. Decreases in 5-HT_{1A} and 5-HT_{2A} receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla. There are extensive serotonergic brainstem abnormalities in infants with SIDS, including increased 5-HT neuronal count, a lower density of 5-HT_{1A} receptor-binding sites in regions of the medulla involved in homeostatic function, and a lower ratio of 5-HT transporter (5-HTT) binding density to 5-HT neuronal count in the medulla (see Table 423.1). Male infants with SIDS have lower receptor-binding density than do female infants with SIDS. Overall, these 5-HT–related studies suggest that the synthesis and availability of 5-HT are decreased within 5-HT pathways, and medullary tissue levels of 5-HT and its primary biosynthetic enzyme (tryptophan hydroxylase) are lower in infants with SIDS compared with age-matched controls. Although a subset of infants with SIDS has serotonergic abnormalities in serotonin neurons in the medullary reticular formation, the neuropathologic abnormalities in SIDS involve more than just a serotonergic deficiency in specific medullary nuclei and appear to involve failure of the network of neurochemical transmitters in various subcortical locations. For example, there is a complex relationship between serotonergic neurotransmission in the medulla and acetylcholine and nicotinic receptors.

ENVIRONMENTAL RISK FACTORS

Major risk factors for SIDS and SUID are outlined in Table 423.2 and include both nonmodifiable and modifiable risk factors.

The persistent ethnic disparities seen in SIDS and SUID rates likely reflect broader societal inequities. Low socioeconomic status (SES), unemployment, housing instability, and other factors that create barriers to optimal health outcomes are highly correlated with race/ethnicity in the United States and are also associated with both higher risk of SIDS and increased prevalence of known risk factors for these deaths (see the next section). Although these factors are consistently associated with higher risk, SIDS affects infants from all social strata. In the United States, Black, American Indian, and Alaska Native infants are 2-3 times more likely than White infants to die of SIDS, whereas Asian, Pacific Islander, and Hispanic infants have the lowest incidence. Greater efforts are needed to address this persistent disparity and to ensure that SIDS risk-reduction education reaches all parents and other care providers, including other family members and personnel at daycare centers.

Table 423.2 Risk Factors Associated with Sudden Infant Death Syndrome

MATERNAL AND ANTENATAL RISK FACTORS
Elevated second-trimester serum α-fetoprotein
Smoking
Alcohol use
Drug use (cocaine, heroin)
Nutritional deficiency
Inadequate prenatal care
Low socioeconomic status
Younger age
Lower education
Single marital status
Shorter interpregnancy interval
Intrauterine hypoxia
Fetal growth restriction
INFANT RISK FACTORS
Age (peak 1-4 mo)
Male gender
Ethnicity (Black, American Indian, Alaska Native)
Growth failure
No breastfeeding
No pacifier (dummy)
Preterm birth
Prone and side sleep position
Recent febrile illness (mild infections)
Inadequate immunizations
Smoking exposure (prenatal and postnatal)
Unsafe sleep environment, including soft sleeping surface, soft bedding
Bed sharing with parent(s) or other children
Sleeping in a room separate from parent(s)
Thermal stress, overheating
Colder season, no central heating

Nonmodifiable Environmental Risk Factors

Infants are at greatest risk of SIDS at 1-4 months of age, with most deaths having occurred by 6 months. This characteristic age has decreased in some countries as the SIDS incidence has declined, with deaths occurring at earlier ages and with a flattening of the peak age incidence. Similarly, the commonly observed winter seasonal predominance of SIDS has declined or disappeared in some countries as prone prevalence has decreased, supporting prior findings of an interaction between sleep position and factors more common in colder months (overheating as a consequence of elevated interior temperatures or bundling with blankets and heavy clothing, or infection). Male infants are 30–50% more likely to be affected by SIDS than are female infants.

Modifiable Environmental Risk Factors

Pregnancy-Related Factors

An increased SIDS risk is associated with numerous obstetric factors, suggesting that the in utero environment of future SIDS infants is suboptimal. SIDS infants are more commonly of higher birth order, independent of maternal age, and of gestations after shorter interpregnancy intervals. Parents of SIDS infants generally receive less prenatal care and initiate care later in pregnancy, and this likely reflects difficulties in accessing care. In addition, low birthweight, preterm birth, and slower intrauterine and postnatal growth rates are risk factors.

Cigarette Smoking

There is a major association between **intrauterine exposure to cigarette smoking** and risk for SIDS. The incidence of SIDS was 2-3 times greater among infants of mothers who smoked in

studies conducted before SIDS risk-reduction campaigns and 4 times higher in studies after implementation of SIDS risk-reduction campaigns. The risk of death is progressively greater as daily cigarette use increases. The effects of smoking by the infant's father and other household members are more difficult to interpret because they are highly correlated with maternal smoking. There appears to be a small independent effect of paternal smoking, but data on other household members have been inconsistent. The effect of prenatal smoking on SIDS risk is not believed to be caused by lower birthweight, which is often found among infants of smoking mothers, but more likely because of alterations in autonomic function, cardiovascular reflexes, or arousal making the infants more vulnerable to a sleep-related death.

It is difficult to assess the independent effect of infant exposure to **environmental tobacco smoke** because parental smoking behaviors during and after pregnancy are also highly correlated. However, a twofold increased risk of SIDS is found for infants exposed only to postnatal maternal environmental tobacco smoke. There is a dose-response for the number of household smokers, number of people smoking in the same room as the infant, and the number of cigarettes smoked. These data suggest that keeping the infant free of environmental tobacco smoke can further reduce an infant's risk of SIDS.

Drug and Alcohol Use

Most studies link maternal **prenatal drug use**, especially opiates, with an increased risk of SIDS, ranging from a 2- to 15-fold increased risk. Studies looking at the association between maternal **alcohol use** prenatally or postnatally and SIDS have conflicting results. In one study, periconceptional alcohol use and binge drinking in the first trimester were associated with a sixfold and an eightfold increased risk of SIDS, respectively. Similarly, a study from Western Australia found that a report of maternal alcohol use during pregnancy was associated with an almost sevenfold increased risk of SIDS. A Danish cohort study found that mothers admitted to the hospital for an alcohol- or drug-related disorder at any time before or after the birth of their infants had a 3-times higher risk of their infant dying from SIDS, and a Dutch study reported that maternal alcohol consumption in the 24 hours before the infant died carried an eightfold increased risk of SIDS. Siblings of infants with fetal alcohol syndrome have a 10-fold increased risk of SIDS compared with controls. Although there are conflicting reports of illicit drug use and SIDS overall, prenatal drug use, especially opiates, is associated with an increased risk of SIDS, ranging from 2- to 15-fold. Data on cannabis use and SIDS are extremely limited, with only one study from New Zealand reporting results for postpartum maternal use. This study found that nighttime cannabis use was associated with a twofold increased risk of SIDS, whereas daytime use was not associated with increased risk.

Infant Sleep Environment

Sleeping prone has consistently been shown to increase the risk of SIDS. As rates of prone positioning have decreased in the general population, the odds ratios for SIDS in infants still sleeping prone have increased. *The highest risk of SIDS occurs in infants who are usually placed nonprone but are placed prone for last sleep ("unaccustomed prone") or found prone ("secondary prone").* The "unaccustomed prone" position may be more likely to occur in daycare or other settings outside the home and highlights the need for all infant caretakers to be educated about appropriate sleep positioning.

Side-Sleeping: A Significant Risk Factor. The initial SIDS risk-reduction campaign recommendations considered side-sleeping to be nearly equivalent to the supine position in reducing the risk of SIDS. Subsequent studies documented that side-sleeping infants were twice as likely to die of SIDS as infants sleeping supine. This increased risk may be related to the relative instability of the position. Infants who are placed on their side and roll to prone are at exceptional risk, with one study finding they are almost 9 times more likely to die of SIDS than those placed supine. Although the majority of SIDS occurrences are still associated with infants being found prone, a higher proportion of SIDS is now attributed to being placed on the side for sleeping than for being placed prone. The current recommendations call for supine position for sleeping for all infants except those few with specific medical conditions for which recommending a different position may be justified, such as those with anatomic or functional upper airway compromise when supine.

Many parents and healthcare providers were initially concerned that supine sleeping would be associated with an increase in adverse consequences, such as difficulty sleeping, vomiting, or aspiration. However, evidence suggests that the risk of regurgitation and choking is highest for prone-sleeping infants. Some newborn nursery staff still tend to favor side positioning, which models inappropriate infant care practice to parents. Infants sleeping on their backs do not have more episodes of cyanosis or apnea, and reports of apparent life-threatening events actually decreased in Scandinavia after increased use of the supine position. These results provide reassurance for parents and healthcare providers and should contribute to universal acceptance of supine as the safest and optimal sleep position for infants.

Soft Sleep Surfaces and Soft or Loose Bedding. Infants should sleep on firm, flat, noninclined surfaces without soft or loose bedding. Soft sleep surfaces and soft or loose bedding, including comforters, pillows of any kind, bumper pads, stuffed animals, mattress toppers, pillow-top mattresses, sheepskins, polystyrene bean pillows, and old or soft mattresses, are associated with increased risk of SIDS. Infant sleep positioners, including pillows and wedges, which are often marketed to hold infants on their side or at an angle to help with reflux, are also not recommended. Based on available research, swaddling infants, or wrapping them in a blanket, is not recommended as a strategy to reduce SIDS. Infants who roll to the prone position while swaddled are at particularly high risk of SIDS. Wearable blankets are an acceptable alternative. Weighted blankets, weighted sleepers, weighted swaddles, or other weighted objects should not be placed on or near the sleeping infant.

Overheating. Overheating, based on indicators such as higher room temperature, a history of fever, sweating, and excessive clothing or bedding, has been associated with increased risk of SIDS. Some studies have identified an interaction between overheating and prone sleeping, with overheating increasing the risk of SIDS only when infants are sleeping prone. Higher external environmental temperatures have not been associated with increased SIDS incidence in the United States.

Bed Sharing. Several studies have implicated bed sharing as a risk factor for SIDS. Bed sharing is particularly hazardous when other children are in the same bed; when the parent is sleeping with an infant on a couch, sofa, or other soft or confining sleeping surface; when the mother is a smoker; and when the bed sharer has used alcohol or arousal-altering drugs or medications. Infants younger than 4 months of age are at increased risk even when mothers are nonsmokers. A meta-analysis of 19 studies found that low-risk infants (i.e., those who were breastfed and never exposed to cigarette smoke in utero or after birth) still had a fivefold increased risk of SIDS until the age of 3 months if bed sharing. Risk is also increased with longer duration of bed sharing during the night, whereas returning the infant to the infant's own crib has not been associated with increased risk. It is recommended that infants who are brought into the parents' bed for feeding or comforting be returned to their crib or bassinet when the parent is ready to sleep. Room sharing *without* bed sharing is associated with lower SIDS rates and is therefore recommended.

Commercial Devices Marketed to Reduce the Risk of SIDS. A large number of commercial devices have been marketed that claim to reduce the risk of SIDS or other sleep-related infant deaths, including in-bed sleepers, but there is no evidence that any of these devices reduce the risk of these deaths. A 2021 Consumer Product Safety Commission

ruling states that any infant sleep product must meet existing federal safety standards for cribs, bassinets, play yards, and bedside sleepers.

Infant Feeding Care Practices and Exposures

Breastfeeding Is Associated with a Lower Risk of Sudden Infant Death Syndrome. A meta-analysis found that breastfeeding was associated with a 45% reduction in SIDS after adjusting for confounding variables and that this protective effect increased for exclusive breastfeeding compared with partial breastfeeding. A subsequent meta-analysis found that breastfeeding for under 2 months was not associated with a reduced risk of SIDS, but any breastfeeding for 2 months or more and exclusive breastfeeding for 2-6 months was associated with an approximate halving of risk. Nursing pillows are a risk factor for infant suffocation and should be avoided.

Pacifier use is associated with a lower risk of SIDS in the majority of studies. Although it is not known if this is a direct effect of the pacifier itself or from associated infant or parental behaviors, use of the pacifier is protective even if it is dislodged during sleep. Concerns have been expressed about recommending pacifiers as a means of reducing the risk of SIDS for fear of adverse consequences, particularly interference with breastfeeding. However, well-designed clinical trials have found no association between pacifiers and breastfeeding duration.

Upper respiratory tract infections have generally not been found to be an independent risk factor for SIDS, but these and other minor infections may still have a role in the causal pathway of SIDS when other risk factors are present. Risk for SIDS has been found to be increased after illness among prone sleepers, those who were heavily wrapped, and those whose heads were covered during sleep.

No adverse association between **immunizations** and SIDS has been found. Indeed, SIDS infants are less likely to be immunized than control infants, and in immunized infants who die of SIDS, no temporal relationship between vaccine administration and death has been identified. In a meta-analysis of case-control studies that adjusted for potentially confounding factors, the risk of SIDS for infants immunized with diphtheria, tetanus, and pertussis was half that for nonimmunized infants.

GENETIC RISK FACTORS

There are some genetic differences identified in infants who died of SIDS compared with healthy infants and to infants dying from other causes (see Table 423.3). Pathogenic gene variants occurring at higher incidence in SIDS infants compared with controls include multiple cardiac ion channelopathy genes that are proarrhythmic, autonomic nervous system development genes, proinflammatory genes related to infection and immunity, and several serotonin (5-HT) genes. In ~15% of patients with SIDS, postmortem gene sequencing reveals a specific monogenic pathogenic variant (see Table 423.4; Fig. 423.1). Some of these genes are more plausible than others in predisposing *infants* to sudden unexpected death.

Multiple studies have established the importance of a pathway to SIDS that involves cardiac sodium or potassium channel dysfunction resulting in either **long QT syndrome (LQTS)** or other proarrhythmic conditions (see Table 423.4 and Fig. 423.1). LQTS is a known cause of sudden death in children and adults as the result of a prolonged cardiac action potential causing either increased depolarization or decreased repolarization current. The first evidence supporting a causal role for LQTS in SIDS was a large Italian study in which a corrected QT interval >440 msec on an electrocardiogram (ECG) performed on days 3-4 of life was associated with an odds ratio of 41 for SIDS. Several case reports have subsequently provided proof of the concept that cardiac channelopathy polymorphisms are associated with SIDS. LQTS is associated with polymorphisms related mainly to gain-of-function variants primarily in the sodium channel gene *(SCN5A)* that encodes critical channel pore-forming α subunits or essential channel-interacting proteins. LQTS also is associated with mainly loss-of-function variants in potassium channel genes. **Short QT syndrome (SQTS)** is another cause of life-threatening arrhythmia or sudden death, often during rest or sleep. Gain-of-function variants in genes including *KCNH2* and *KCNQ1* have been causally linked to SQTS, and some of these deaths have occurred in infants, suggesting that SQTS may also be causally linked to SIDS (see Table 423.4).

Table 423.3 Genetic Risk Factors for Sudden Infant Death Syndrome (SIDS): Observed Polymorphisms

Multiple cardiac ion channelopathy genes
Autonomic developmental genes
Proinflammatory genes affecting infection and immunity
• Increased proinflammatory function
• Decreased antiinflammatory function
Genes affecting both serotonergic and adrenergic neurons

Table 423.4 Identified and Possible Monogenic Associations with SIDS

ARRHYTHMIAS/CHANNELOPATHIES
LQTS* *(SCN5A, ANK2, CALM2)*
SQTS *(KCNH2, KCNQ1)*
Brugada syndrome* *(SCN5A, TRPM4, SCN3B, GPD1L, SCN10A)*
Catecholaminergic polymorphic ventricular tachycardia* *(RYR2)*
EPILEPSY SYNDROMES
Genes associated with sudden unexpected death in epilepsy *(SCN1A, DEPDC5)*
Nondystrophic myotonia *(SCN4A)*
Dravet syndrome *(SCN1A)*
METABOLIC DISORDERS
Pyruvate dehydrogenase deficiency
Medium-chain acyl-dehydrogenase deficiency
Systemic primary carnitine deficiency
Carnitine palmitoyltransferase deficiency
Glutaric acidemia type II
Maple syrup urine disease
Congenital disorders of glycosylation
Glycogen storage disease
CARDIAC/CARDIOMYOPATHIES*
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy *(RYR2)*
Catecholaminergic ventricular tachycardia *(RYR2, CASQ2, CALM2)*
Left ventricular noncompaction
Marfan syndrome
Mitral valve prolapse
Ehlers-Danlos syndrome

*For many phenotypic disorders, most, but not all, genes have been identified
LQTS, Long QT syndrome; SQTS, short QT syndrome.

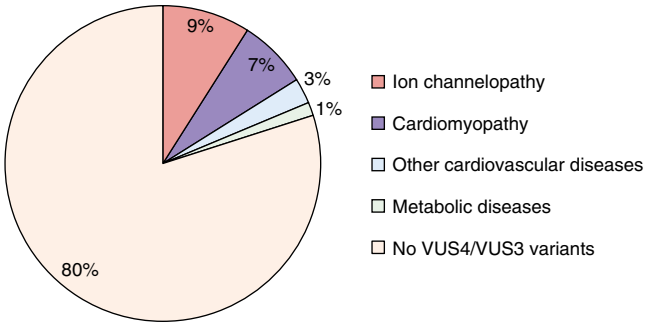

Fig. 423.1 Percentage of SIDS infants with likely causative variants in genes associated with cardiomyopathies, ion channelopathies, other cardiovascular diseases, and metabolic diseases. VUS, variant of unknown significance. *(From Neubauer J, Lecca MR, Russo G, et al. Postmortem whole-exome analysis in a large sudden infant death syndrome cohort with a focus on cardiovascular and metabolic genetic diseases. Eur J Hum Genetics. 2017;25:404–409, Fig. 1.)*

Other cardiac ion–related channelopathy pathogenic gene variants that are also proarrhythmic include Brugada syndrome *(BrS1, BrS2)* and catecholaminergic polymorphic ventricular tachycardia *(CPVT1)* (see Table 423.4). Collectively, these pathogenic variants in cardiac ion channels provide a lethal proarrhythmic substrate in some infants and may account for 5–10% or more of SIDS cases. In one study, using targeted massively parallel sequencing, 15.7–18.6% of Dutch SIDS cases were considered to be explained genetically by cardiac arrhythmias.

Impaired central respiratory regulation is an important biologic abnormality in SIDS, and genetic polymorphisms have been identified in SIDS infants that affect both serotonergic and adrenergic neurons. Monoamine oxidase A (MAOA) metabolizes both of these neurotransmitters, and a recent study has observed a high association between SIDS and low-expressing MAOA alleles in males, perhaps contributing to the higher incidence of SIDS in males. Many genes are involved in the control of 5-HT synthesis, storage, membrane uptake, and metabolism. Polymorphisms in the promoter region of the 5-HTT protein gene occur with greater frequency in SIDS than in control infants. The long "L" allele increases effectiveness of the promoter and reduces extracellular 5-HT concentrations at nerve endings compared with the short "S" allele. The L/L genotype has been associated with increased 5-HT transporters in some studies of neuroimaging and postmortem binding, but more recent studies have not found any relationship between SIDS and the long (L) allele or the LL genotype.

An association has also been observed between SIDS and a 5-HTT intron 2 polymorphism, which differentially regulates *5-HTT* expression. There were positive associations between SIDS and the intron 2 genotype distributions in Black infants who died of SIDS compared with Black controls. The human *FEV* gene is specifically expressed in central 5-HT neurons in the brain, with a predicted role in specification and maintenance of the serotoninergic neuronal phenotype. An insertion pathogenic variant has been identified in intron 2 of the *FEV* gene, and the distribution of this variant differs significantly in SIDS compared with control infants.

Molecular genetic studies in infants who died of SIDS have also identified pathogenic genetic variants pertinent to early embryologic development of the autonomic nervous system. Protein-changing pathogenic variants related to the *PHOX2a, RET, ECE1, TLX3,* and *EN1* genes have been identified, particularly in Black infants who died of SIDS. Eight polymorphisms in the *PHOX2B* gene occurred significantly more frequently in SIDS compared with control infants. Abnormalities in both the structure and expression of the *PHOX2B* gene, which is involved in neuronal maturation, have also been reported in significantly more SIDS infants than in controls. One study has reported an association between SIDS and a distinct tyrosine hydroxylase gene *(THO1)* allele, which regulates gene expression and catecholamine production.

Multiple studies have observed altered expression of genes involved in the inflammatory process and immune system regulation. Differences in SIDS infants compared with controls have been reported for two complement *C4* genes. Some SIDS infants have loss-of-function polymorphisms in the gene promoter region for IL-10, another antiinflammatory cytokine. IL-10 polymorphisms associated with decreased IL-10 levels could contribute to SIDS by delaying initiation of protective antibody production or reducing capacity to inhibit inflammatory cytokine production. However, other studies have not found differences in IL-10 genes in SIDS infants compared with age-matched controls.

An association has been reported between single-nucleotide polymorphisms in the proinflammatory gene encoding IL-8 and SIDS infants found prone compared with SIDS infants found in other sleep positions. IL-1 is another proinflammatory gene, and a higher prevalence of the IL-1 receptor antagonist, which would predispose to higher risk for infection, has been reported in infants who died of SIDS. Significant associations with SIDS are also reported for polymorphisms in VEGF, IL-6, and tumor necrosis factor-α (TNF-α). These three cytokines are proinflammatory, and these gain-of-function polymorphisms would result in increased inflammatory response to infectious or inflammatory stimuli and hence contribute to an adverse imbalance between proinflammatory and antiinflammatory cytokines. As apparent proof of principle, elevated levels of IL-6 and VEGF have been reported from CSF in SIDS infants. There were no group differences in the IL6-174G/C polymorphism in a Norwegian SIDS study, but the aggregate evidence nevertheless suggested an activated immune system in SIDS and implicated genes involved in the immune system. Almost all SIDS infants in one study had positive histories for prone sleeping and fever before death and positive HLA-DR expression in laryngeal mucosa, and high HLA-DR expression was associated with high levels of IL-6 in CSF.

GENE-ENVIRONMENT INTERACTIONS

Interactions between genetic and environmental risk factors determine the actual risk for SIDS in individual infants (see Fig. 423.2; Table 423.5). Equally important, there is a dynamic interaction between genetic or intrinsic vulnerability and the *sleep environment* (see Fig. 423.3). There appears to be an interaction between prone sleep position and impaired ventilatory and arousal responsiveness. Facedown or nearly facedown sleeping does occasionally occur in prone-sleeping infants, but normal healthy infants arouse before such episodes become life-threatening. However, infants with insufficient arousal responsiveness to hypoxia may be at risk for sudden death from resulting episodes of airway obstruction and asphyxia. There may also be links between modifiable risk factors (such as soft bedding, prone sleep position, and thermal stress) and genetic risk factors, such as ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Cardiorespiratory control deficits could be related to

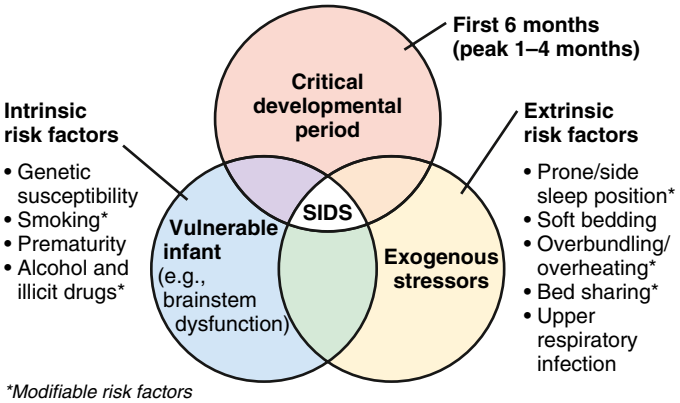

Fig. 423.2 Schematic of the triple-risk model for sudden infant death syndrome (SIDS) showing the critical interactions between intrinsic risk factors (including genetic risk factors) resulting in a vulnerable infant, a critical developmental period or age, and exogenous stressors or extrinsic risk factors. *(Modified from Filiano JJ, Kinney HC. A perspective on the neuropathologic findings in victims of the sudden infant death syndrome: the triple risk model. Biol Neonate. 1994;65:194–197.)*

Table 423.5 Interactions Between Genetic and Environmental Risk Factors that Determine the Actual Risk for SIDS in Individual Infants

GENETIC RISK FACTOR	ENVIRONMENTAL RISK FACTOR
Intrinsic vulnerability Impaired ventilatory and arousal responses	Sleep environment Nonsupine sleep position Soft bedding
Cardiac ion channelopathy	Sleep-related hypoxemia or hypercarbia leading to acidosis
Diminished immune responses to infections	Respiratory or other benign infections
Diminished brainstem autonomic control	Cigarette smoke exposure

5-HTT polymorphisms, for example, or to polymorphisms in genes pertinent to autonomic nervous system development. Affected infants could be at increased risk for sleep-related hypoxemia and hence more susceptible to adverse effects associated with unsafe sleep position or sleep environment. Infants at increased risk for sleep-related hypoxemia could also be at greater risk for fatal arrhythmias in the presence of a cardiac ion channelopathy polymorphism.

In >50% of SIDS victims, recent febrile illnesses, often related to upper respiratory infection, have been documented (see Table 423.2). Benign infections might increase the risk for SIDS if interacting with genetically determined proinflammatory or impaired immune responses. Deficient inflammatory responsiveness can also occur as a result of mast cell degranulation, which has been reported in SIDS infants. This is consistent with an anaphylactic reaction to a bacterial toxin, and some family members of SIDS infants also have mast cell activation and degranulation, suggesting that increased susceptibility to an anaphylactic reaction is another genetic factor influencing fatal outcomes to otherwise minor infections. Interactions between upper respiratory infections or other minor illnesses and factors such as prone sleeping might also play a role in the pathogenesis of SIDS.

The increased risk of SIDS associated with fetal and postnatal exposure to cigarette smoke may be related at least in part to genetic or epigenetic factors, including those affecting brainstem autonomic control. Infant studies document decreased ventilatory and arousal responsiveness to hypoxia after fetal nicotine exposure, and impaired autoresuscitation after apnea has been associated with postnatal nicotine exposure. Decreased brainstem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms occurs in rats exposed to cigarette smoke prenatally, another potential cause of impaired hypoxic responsiveness. Tobacco smoke exposure also increases susceptibility to viral and bacterial infections and increases bacterial binding after passive coating of mucosal surfaces with smoke components, implicating interactions between smoking, cardiorespiratory control, and immune status. Flavin-monooxygenase 3 *(FMO3)* is one of the enzymes that metabolizes nicotine, and a polymorphism has been identified that occurs more frequently in SIDS infants compared with controls and more frequently in infants whose mothers reported heavy smoking. This polymorphism would result in increased nicotine levels and hence is a potential genetic risk factor for SIDS in infants exposed to cigarette smoke.

In infants with a cardiac ion channelopathy, risk for a fatal arrhythmia during sleep may be significantly enhanced by predisposing perturbations that increase electrical instability. These perturbations could include REM sleep with bursts of vagal and sympathetic activation, minor respiratory infections, or any other cause of sleep-related hypoxemia or hypercarbia, especially if resulting in acidosis. The prone sleeping position is associated with increased sympathetic activity.

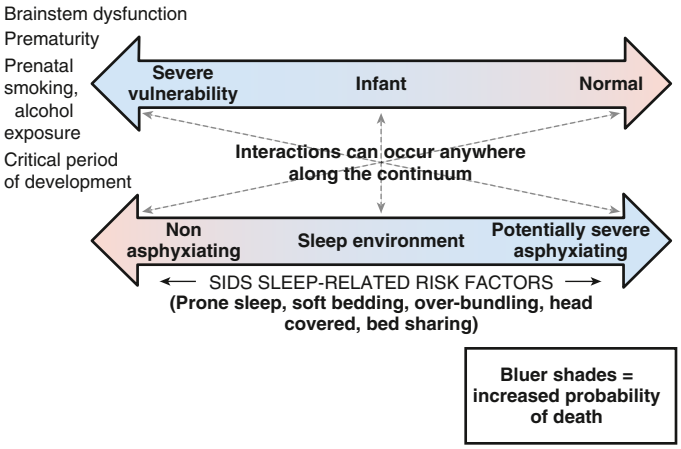

Fig. 423.3 Dynamic interactions between intrinsic vulnerability to sudden infant death syndrome (SIDS) and degree of risk in the sleep environment, ranging from nonasphyxiating (completely safe) to potentially severe asphyxiating (highly unsafe). Intrinsic vulnerability could be related to genetic risk factors, fetal or early infant exposures, or other factors. *(Modified from Hunt CE, Darnall RA, McEntire BL, Hyma BA. Assigning cause for sudden unexpected infant death. Forensic Sci Med Pathol. 2015;11:283–288.)*

INFANT GROUPS AT INCREASED RISK FOR SUDDEN INFANT DEATH SYNDROME

Subsequent Siblings of an Infant Who Died of Sudden Infant Death Syndrome

The next-born siblings of first-born infants dying of any noninfectious natural cause are at significantly increased risk for infant death from the same cause, including SIDS. The relative risk is 9.1 for the same cause of recurrent death versus 1.6 for a different cause of death. The relative risk for recurrent SIDS (range: 5.4-5.8) is similar to the relative risk for non-SIDS causes of recurrent death (range: 4.6-12.5). The risk for recurrent infant mortality from the same cause as in the index sibling thus appears to be increased to a similar degree in subsequent siblings for both explained causes and for SIDS. This increased risk for recurrent SIDS in families is consistent with genetic risk factors interacting with environmental risk factors (see Table 423.5 and Figs. 423.2 and 423.3). *Recurrent SIDS in a family should also alert the clinician to consider other causes of sudden and unexpected death, such as metabolic diseases, cardiac channelopathies, or nonaccidental causes.*

Preterm Birth

Despite reductions of more than 50% in SIDS and SUID among infants born preterm since initiation of the Back to Sleep (Safe to Sleep) campaign in the United States in 1994, the risk of death remains significantly higher for these infants than for those born full term. The risk increases as gestational age decreases. Compared with infants born at 37-42 weeks, the odds ratio for SIDS is greatest for infants born at 24-28 weeks of gestation (2.57, 95% confidence interval 2.08, 3.17). Even at 33-36 weeks gestational age at birth, the risk of SIDS remains significantly increased compared with infants born at term. The peak chronological age for SIDS is later in infants born preterm, with chronological age at death inversely proportional to gestational age at birth.

Although infants born preterm are at increased risk for apnea, apnea of prematurity per se *does not* seem to be related to the increased SIDS risk. Premature infants' increased risk is instead likely related in part to immaturity of brainstem responses; physiologic studies have found impaired cortical arousals, lower baroreflex sensitivity, and impaired autonomic control. Sociodemographic and environmental risk are also important. Infants born preterm have more sociodemographic risk factors overall than infants born at term. In addition, infants born preterm are more likely to be placed prone at home; this may be in part because these infants are often placed prone while mechanically ventilated in the neonatal intensive care unit (NICU), and safe sleep practices are often not well-modeled during the remainder of the NICU admission. The association between prone position and SIDS in preterm and low birthweight infants is equal to or greater than this association in infants born full term.

Physiologic Studies

Physiologic studies have been performed in healthy infants in early infancy, a few of whom later died of SIDS. Physiologic studies have also been performed on infant groups who were believed to be at increased risk for SIDS, especially those with brief resolved unexplained events (**BRUEs**; see Chapter 424) and subsequent siblings of infants who died of SIDS. In the aggregate, these studies have indicated brainstem abnormalities in the neuroregulation of cardiorespiratory control or other autonomic functions and are consistent with the autopsy findings and genetic studies in infants who died of SIDS. In addition to physiologic abnormalities in chemoreceptor sensitivity, other observed physiologic abnormalities have been found in respiratory pattern, control of heart and respiratory rate or variability, and arousal responsiveness to asphyxial situations. A deficit in arousal responsiveness may be a necessary prerequisite for death to occur but may be insufficient to cause death in the absence of other genetic or environmental risk factors.

Autoresuscitation (gasping) is a critical component of the arousal response to asphyxia, and a failure of autoresuscitation in infants may be the final and most devastating physiologic failure. In one study, most normal full-term infants younger than 9 postnatal weeks of age aroused in response to mild hypoxia, whereas only 10–15% of infants older than 9 weeks of age aroused. These data suggest that ability to arouse to mild to moderate hypoxic stimuli may be at a nadir at the age range of greatest risk for SIDS.

The ability to shorten the QT interval as heart rate increases appears to be impaired in some infants who died of SIDS, suggesting that such infants may be predisposed to ventricular arrhythmia. Although this is consistent with the observations of cardiac ion channel gene polymorphisms in some infants who subsequently die of SIDS, there are no antemortem QT interval data for these infants that confirm the importance of this finding. Infants who were studied physiologically and then died of SIDS a few weeks later had higher heart rates and lower heart rate variability in all sleep-wake states and diminished heart rate variability during wakefulness. These infants also had longer QT intervals than control infants during both REM and NREM sleep, especially in the late hours of the night when SIDS most likely occurs. However, the QT interval exceeded 440 msec in only one of these infants who subsequently died.

It has been postulated that the decreased heart rate variability and increased heart rate observed in infants who later died of SIDS may in part be related to decreased vagal tone, perhaps from vagal neuropathy or brainstem damage in areas responsible for parasympathetic cardiac control. The power spectrum analysis of heart rate variability is one way to assess sympathetic and parasympathetic cardiac control. In a comparison of heart rate power spectra before and after obstructive apneas in clinically asymptomatic infants, infants later dying of SIDS did not have the decreases in low-frequency to high-frequency power ratios observed in infants who survived. Some infants may thus have different autonomic responsiveness to obstructive apnea, perhaps indicating impaired autonomic nervous system control associated with higher vulnerability to external or endogenous stresses, and hence reduced electrical stability of the heart; this may create a vulnerability for SIDS.

Home cardiorespiratory monitors with memory capability have recorded the terminal events in some infants who died of SIDS. However, these recordings did not include pulse oximetry and could not identify obstructed breaths because of reliance on transthoracic impedance for breath detection. In most instances, there was sudden and rapid progression of severe bradycardia that was either unassociated with central apnea or appeared to occur too soon to be explained by the central apnea. These observations are consistent with an abnormality in autonomic control of heart rate variability or with obstructed breaths resulting in bradycardia or hypoxemia and associated with impaired autoresuscitation or arousal.

CLINICAL STRATEGIES

Home Monitoring

SIDS cannot be *prevented* in individual infants because it is not possible to identify prospectively infants who will go on to have SIDS, and no effective intervention has been established even if infants at risk could be prospectively identified. Studies of cardiorespiratory pattern or other autonomic abnormalities do not have sufficient sensitivity and specificity to be clinically useful as screening tests. Although there are a growing number of consumer products marketed to monitor infants during sleep, there is no evidence that home electronic surveillance using existing technology reduces the risk of SIDS. Although a prolonged QT interval in an infant may be treated if diagnosed, neither the role of routine postnatal electrocardiographic screening, the cost-effectiveness of diagnosis and treatment, nor the safety of treatment in infants has been established. Parental electrocardiographic screening is not helpful, in part because spontaneous pathogenic variants are common.

Reducing the Risk of SIDS and SUID

Reducing risk behaviors and increasing protective behaviors among infant caregivers to achieve further reductions and eventual elimination of SIDS and SUID is a critical goal. Plateaus in placing infants supine for sleep and persistent high rates of soft bedding use and surface sharing in the United States are cause for concern and require renewed educational efforts. Recent studies indicate soft or loose bedding is present in the sleep environment of greater than 50% of infants in the United States. A 2015 Centers for Disease Control and Prevention (CDC) survey of parents in 14 states and New York City found that 52.7% of White non-Hispanic, 76.5% of Black non-Hispanic, 66.7% of Hispanic, 76.8% of Asian or Pacific Islander, and 83.9% of American Indian or Alaska Native parents reported surface sharing with their infants. The American Academy of Pediatrics (AAP) guidelines for reducing infant deaths in the sleep environment were updated in 2022 and are aimed at reducing the risk of all sudden and unexpected sleep-related infant deaths. The guidelines are appropriate for most infants, but physicians and other healthcare providers might, on occasion, need to consider alternative approaches. The major components of the AAP guidelines are:

- Full-term and premature infants should be placed for sleep in the supine position. There are no adverse health outcomes from supine sleeping. Side-sleeping is not recommended.
- Infants should be put to sleep on a noninclined, firm mattress. Waterbeds, sofas, soft mattresses, or other soft surfaces should not be used. In addition, car seats, strollers, swings, and other sitting devices should not be used for sleeping. Sleeping in such sitting devices can increase the risk of gastroesophageal reflux and upper airway obstruction from head or neck flexion. Sleeping on an inclined surface can also increase the risk of head or neck flexion and makes it easier for infants to roll into an unsafe side or prone position.
- Feeding of human milk is recommended. Unless it is contraindicated or the parent is unable to do so, it is recommended that infants be fed with human milk (i.e., not offered any formula or other nonhuman milk-based supplements) exclusively for ~6 months, with continuation of human milk feeding for 1 year or longer as mutually desired by parent and infant.
- It is recommended that infants sleep in the same room as their parents but in their own crib or bassinet that conforms to the safety standards of the Consumer Product Safety Commission. Placing the crib or bassinet near the parents' bed facilitates feeding and contact. If parents bring the infant into the adult bed for feeding or comforting, the infant should be returned to a separate sleep surface when the parents are ready for sleep. Couches and armchairs are associated with an extremely high increased risk of SIDS, accidental suffocation, and entrapment and should never be used for infant sleep.
- There should be no soft materials and loose bedding in the infant's sleep environment (over, under, or near the infant). These include pillows, including nursing pillows, comforters, quilts, sheepskins, bumper pads, positioners, and stuffed toys. Sleep clothing, such as a wearable blanket, can be used in place of blankets. Weighted blankets, weighted sleepers, weighted swaddles, or other weighted objects should not be placed on or near the sleeping infant.
- Offering a pacifier at bedtime and naptime is recommended. The pacifier should be used when placing the infant down for sleep and need not be reinserted once it falls out. For breastfed infants, delay introduction of the pacifier until breastfeeding is firmly established. This is defined as having sufficient milk supply, con-

sistent, comfortable, and effective latch for milk transfer, and appropriate infant weight gain as defined by established normative growth curves. The time required to establish breastfeeding is variable.

- Parents should not smoke during pregnancy or after birth, and infants should not be exposed to secondhand smoke.
- Parents should avoid alcohol, marijuana, opioids, and illicit drug use during pregnancy and after birth.
- Avoid overheating and overbundling. The infant should be lightly clothed for sleep and the thermostat set at a comfortable temperature. The use of hats or other infant head coverings indoors is not recommended.
- Pregnant persons should obtain regular prenatal care, following guidelines for prenatal visits.
- Infants should be immunized in accordance with recommendations of the AAP and the CDC. There is no evidence that immunizations increase the risk of SIDS. Indeed, recent evidence suggests that immunizations may have a protective effect against SIDS.
- Avoid the use of commercial devices that are inconsistent with safe sleep recommendations. Devices advertised to maintain sleep position, "protect" a bed-sharing infant, or reduce the risk of rebreathing are not recommended because there is no evidence to support their safety or efficacy.
- Home cardiorespiratory and/or O_2 saturation monitoring may be of value for selected infants who have extreme instability, but there is no evidence that monitoring decreases the incidence of SIDS, and it is therefore not recommended for this purpose.
- Infants should have some time in the prone position (tummy time) while awake and observed. Alternating the placement of the infant's head and orientation in the crib can also minimize the risk of head flattening from supine sleeping (positional plagiocephaly).
- Swaddling cannot be recommended as a strategy to reduce SIDS, as there is insufficient evidence. If infants are placed in a swaddle, it should be using a light blanket that is snug around the shoulders but looser around the hips to avoid hip dysplasia. Swaddled infants should always be placed supine, and once infants can roll to the prone or side position, all swaddling should be discontinued.
- Healthcare professionals, staff in newborn nurseries and NICUs, and childcare providers should adopt the SIDS reduction recommendations beginning at birth, or as soon as clinically able, to model safe sleep for caregivers.
- Media and manufacturers should follow safe sleep guidelines in their messaging, advertising, and social media.
- The national Safe to Sleep campaign should be continued with additional emphasis placed on strategies to increase breastfeeding while decreasing bed sharing and tobacco smoke exposure. The campaign should continue to have a special focus on the groups with higher rates of SIDS, including educational strategies tailored to individual racial-ethnic groups. Secondary care providers need to be targeted to receive these educational messages, including daycare providers, grandparents, foster parents, and babysitters. Efforts should also be made to introduce sleep recommendations before pregnancy and ideally in early education settings and school curricula to educate older siblings and teenage and adult babysitters and establish these practices as normative behavior. Research and surveillance should be continued on the risk factors, causes, and pathophysiologic mechanisms of SIDS and other sleep-related SUID, with the ultimate goal of preventing these deaths entirely. Federal and private funding agencies need to remain committed to this research.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

423.1 Sudden Unexpected Postnatal Collapse/Sudden Unexpected Early Neonatal Death

Sarah Vepraskas

Sudden unexplained postnatal collapse (SUPC) is a rare but potentially fatal event that occurs when a spontaneously breathing, previously healthy newborn suddenly becomes limp, pale, or cyanotic, bradycardic, unresponsive, apneic, and/or has cardiac and/or respiratory failure and requires cardiopulmonary resuscitation. SUPC results in death in about half of the infants and significant impairment in many survivors.

There is not a consensual definition for SUPC in the medical literature, although there is increasing awareness of SUPC as a clinical entity, with over 400 cases described. The most common definition of SUPC used is by the British Association of Perinatal Medicine and includes any term or near-term (defined as >35 weeks' gestation) infant who meets the following criteria: (1) is well at birth (normal 5-minute Apgar and deemed well enough for routine care),(2) collapses unexpectedly in a state of cardiorespiratory extremis such that resuscitation with intermittent positive-pressure ventilation is required, (3) collapses within the first 7 days of life, and (4) either dies, goes on to require intensive care, or develops encephalopathy. A majority of reported events occur within 2 hours after birth, often at the time of the first breastfeeding attempt. Other potential medical conditions that place infants at higher risk, such as prematurity (<35 weeks' gestation), perinatal asphyxia, sepsis, or congenital malformations, should be excluded before a diagnosis of SUPC is made.

Population-based studies estimate the incidence of SUPC to be 2.6-38 cases per 100,000 live births. The incidence varies widely because of the lack of both a definition consensus and standardized reporting system as well as differing inclusion and exclusion criteria. Furthermore, a consensus for coding SUPC has not been established, which likely also contributes to it being underreported.

The published estimations of SUPC are lower than what occur in the hospital and reflect only the critical events. When a defined time for the SUPC event is described, approximately one third of reported events occur during the first 2 hours, another one third between 2 and 24 hours, and another one third between 1 and 7 days after birth.

PATHOGENESIS

In most SUPC cases an underlying condition is never identified, although the literature suggests there is a variety of etiologies. Many of the events may be related to suffocation or entrapment, but it seems to have a complex pathophysiology that is poorly understood. One hypothesis is that the transition from fetal to extrauterine life could make the newborn more vulnerable during the first hour of life. During birth there is an initial surge of adenosine and prostaglandins, followed by a postnatal surge of catecholamines. A healthy newborn baby is aroused and awake after birth and starts continuous breathing movements. Shortly after birth, there is a rapid decrease in the inhibitory neuromodulator adenosine as the partial pressure of oxygen in the arterial blood rapidly increases and contributes to the increased activity in the newborn infant compared with the fetus. After the hormone surges, there is a period of diminished responsiveness to external stimuli and increased vagal tone; it is possible that autonomic instability could make infants vulnerable during this transitioning period.

It is also possible that impaired cardiorespiratory control resulting from hypoxic ischemic injury occurring days *before* birth could contribute to fatal cases of SUPC. Mild gliosis in brainstem areas involved in cardiorespiratory control was found at autopsy of seven infants with

SUPC. However, there are insufficient data to support an association between in utero hypoxic events and SUPC. Monogenic etiologies have not been explored to the same degree reported for SIDS in infants ≥2 months (see Table 423.4).

RISK FACTORS

Many reported SUPC cases occur while the infant is in the prone position, during skin-to-skin contact (SSC) with their mothers. SSC is traditionally defined as beginning at birth and lasting continually until the end of the first breastfeeding.

Additional risk factors for SUPC include the first breastfeeding attempt, cosleeping, a mother in the episiotomy position, a primiparous mother, and parents left alone with baby during the first hour after birth.

SSC and rooming-in have become common practice for healthy newborns and align with the Baby-Friendly Hospital Initiative (BFHI), a global program launched by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to encourage and recognize hospitals and birthing centers that promote the optimal level of care for infant feeding and mother/baby bonding. The BFHI recognizes and awards birthing facilities that successfully implement the "Ten Steps to Successful Breastfeeding," with step 4 being to initiate breastfeeding within 1 hour of birth and step 7 recommending the practice of rooming-in. The AAP clinical report on safe sleep and SSC in the newborn period both reviews the evidence supporting SSC and rooming-in during the newborn period and addresses the safety concerns and provides suggestions to improve safety after delivery. The literature supporting SSC also emphasizes the importance that mother and baby should not be left unattended during this early period.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of SUPC should be made only after other pathologic causes are excluded. One study consisting of 45 cases of unexpected collapse in newborns found that one third of infants had an underlying pathologic or clinical condition, such as sepsis, ductal-dependent congenital heart disease, congenital diaphragmatic hernia, intracranial hemorrhage, or a metabolic disorder. Additional etiologies to consider include airway obstruction, pneumonia, respiratory distress syndrome, hypoglycemia, vascular thrombosis or embolism, and pulmonary hypertension of the newborn. The differential diagnosis of SUPC is broad, and many conditions overlap with the differential diagnoses for BRUE (see Chapter 424), SUID, and SIDS.

For those infants who survive the event, testing to screen for an underlying pathology should be performed and tailored to the specific details of each case. A thorough history and physical exam should be performed before initiating the diagnostic workup to assist one in focusing the evaluation. Laboratory tests to consider include electrolytes; metabolic evaluation including glucose, ammonia, and lactate; an infectious evaluation including blood cultures, urinalysis, and urine cultures; and CSF analysis with CSF culture. Chest radiography, neuroimaging, echocardiogram, electrocardiogram, and comprehensive metabolic screening (included as part of the newborn screen in most states) could also be useful diagnostic tools. Postmortem examination in the case of death from presumed SUPC should be performed because underlying etiology of the event may be discovered during autopsy. In the event that no identifiable etiology is discovered, next-generation gene testing for at-risk pathogenic variants should be performed (see Table 423.4).

OUTCOME

Approximately half of SUPC cases are thought to result in death, and there is remaining disability in most reported cases. A review of 17 and 45 SUPC cases in Germany and the United Kingdom showed a mortality rate of 42% and 27%, respectively. In the German study, almost two thirds of the surviving cases had neurologic deficits, and in the United Kingdom study, one third of infants either died or had residual neurologic deficits. Rates of death and neurologic abnormalities reported in the two aforementioned studies are comparable with other available case reports.

TREATMENT

Although there is no definitive treatment for infants who have suffered from SUPC, therapeutic hypothermia (TH) has been studied as a plausible therapy because 75% of newborns with no known cause for collapse develop a typical postasphyxia encephalopathy, evoking hypoxic-ischemic encephalopathy (HIE) (see Chapter 122.4). Given the low incidence, diversity of etiologies, uncertain pathophysiology, and underreporting, it would be difficult to perform an outcomes trial using TH for infants with SUPC. Case reports on outcomes using TH for SUPC infants report variable short-term outcomes; long-term data are lacking. In a sample of 22 infants who suffered SUPC and were treated in Portuguese hypothermia centers, a significant proportion had poor outcomes. In contrast, another case report of four patients with HIE and TH treatment after SUPC described three children as developmentally normal at 24-month follow-up and one child as having mild cerebral palsy.

PREVENTION

The known risk factors for SUPC can be used to aid in preventive efforts. Specifically, safety during SSC and rooming-in should be emphasized. Initiatives developed to standardize the procedure for immediate postnatal SSC have not proven to reduce the risk of SUPC. Frequent assessments of newborns should be performed, including observation of breathing, activity, color, tone, and position, to ensure they are in a position to avoid obstructive breathing or events leading to SUPC. It has also been suggested that continuous monitoring by trained staff members be done during SSC. However, that may be obtrusive to mother-infant bonding. Some have suggested continuous pulse oximetry during this period, but there is no evidence to support this practice, and this overmonitoring could lead to unnecessary parental concern. Because many cases of SUPC occur within the first few hours of life, the delivery unit should be staffed to permit frequent newborn assessments while preserving the developing mother-child bond.

Many of the same safety concerns that occur during SSC immediately after birth continue to be a concern during rooming-in if the mother is not given guidance on the safe rooming-in practices. Cosleeping should not be permitted on the postpartum unit. Mothers and families need to be informed of the risks of cosleeping. Staffing ratios should be determined to meet the needs of both mother and infant to allow for frequent assessments, rapid response time to call lights, and time for maternal education.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 424

Brief Resolved Unexplained Events and Other Acute Events in Infants

Amy M. DeLaroche and Joel S. Tieder

Infants may experience acute, self-resolving changes in their breathing, tone, mental status, and skin color. Usually these events are normal manifestations of developmental immaturity. Nonetheless, caregivers may worry that the acute event could have been life-threatening or is a sign of an undiagnosed medical problem and seek medical attention. In most cases, after a comprehensive history and physical examination, a clinician will determine the event to have been a benign or normal process, such as gastroesophageal reflux (GER) or periodic breathing of the newborn. At times, however, the event defies a simple explanation and drives uncertainty about risk from a serious underlying cause or a future event. This situation poses a diagnostic and management challenge for both the family and the clinician.

Historically, these events were feared as precursors to sudden infant death syndrome (SIDS) and were referred to as *near-miss SIDS, aborted crib deaths,* or *apparent life-threatening events (ALTEs).* These terms have been replaced because we now know that these events are not associated with SIDS and are rarely life-threatening. These terms were additionally problematic because they relied on the subjective interpretation of the caregiver, included a nonspecific constellation of symptoms, and did not distinguish well-appearing patients from those with symptoms.

Most of these acute events in infants are best described as brief resolved unexplained events (BRUEs). A BRUE is a diagnosis of exclusion and should be used only when the event is transient and remains unexplained after an appropriate medical evaluation.

DEFINITION

A BRUE (pronounced *brew*) is an event that occurs in an infant younger than 1 year that is described by the observer as a *sudden, brief,* and *resolved* episode that involved at least one of the following:

- Cyanosis or pallor
- Absent, decreased, or irregular breathing
- Marked change in tone, either hypertonia or hypotonia
- Altered level of responsiveness

The diagnosis of BRUE applies only to infants who were asymptomatic before the event and during the initial medical evaluation and when no explanation for the event is found through appropriate history and physical examination (Fig. 424.1).

Infants who experience a BRUE are categorized as either lower or higher risk for a subsequent event or a serious underlying disorder based on patient factors, characterization of the event, additional historical factors, and the physical examination.

A lower-risk infant is defined as:

- Age >60 days
- Gestational age ≥32 weeks and postconceptional age ≥45 weeks
- Occurrence of only 1 BRUE (no prior BRUE ever and not occurring in a cluster)
- Duration of event <1 minute
- No cardiopulmonary resuscitation (CPR) by trained medical provider required
- No concerning historical features
- No concerning physical examination finding

EPIDEMIOLOGY

The exact incidence of BRUEs is unknown, but BRUEs may account for up to 0.02% of pediatric emergency department visits. In a multicenter study of hospitals, 87% of patients met higher-risk criteria and 63% were hospitalized. Since the American Academy of Pediatrics published the Clinical Practice Guideline and introduced the term *BRUE,* hospitalizations have been decreasing, especially for lower-risk infants.

BRUEs are not precursors to SIDS. The incidence of mortality after a BRUE from an underlying cause is extremely low, as only 1 patient in a cohort of 2,036 patients died during a readmission after being evaluated for a BRUE. Overall, the risk of death among patients with a BRUE is estimated to approximate the baseline risk of death among infants in the first year of life.

For patients presenting with a BRUE, numerous risks must still be considered. First is the risk of an underlying diagnosis that could lead to serious morbidity or mortality if not diagnosed in a timely fashion. This is estimated to be 4% for patients presenting to the emergency department with a BRUE and includes a wide variety of illnesses, such as cardiac arrhythmias, infections, and brain injury. In one study of infants with a serious underlying diagnosis identified after evaluation for a BRUE, seizures were the most commonly identified diagnosis followed by airway abnormalities, abusive head trauma, bacterial or viral infections, and intussusception. Less common etiologies were arrhythmias, central apnea, and ingestions. These diagnoses may become evident in the emergency department, the inpatient service, outpatient follow-up, or on readmission to the hospital.

In contrast, it is more common for a benign explanation to be identified, with choking, reflux, breath-holding spells, acrocyanosis, colic, viral infections, dysphagia, and overfeeding noted in over half of patients diagnosed with a less serious explanation for the event (Table 424.1). Second is the risk of a recurrent event, which occurred in 2.7% of patients during their emergency department visit for a BRUE and in 18.2% of patients hospitalized for a BRUE. These events can be stressful for caregivers, particularly when the cause is unknown. Third is the risk that the caregivers become unnecessarily concerned about their healthy child. Clinicians should be aware of the challenges caregivers face when perceiving a threat of losing their child, there is medical uncertainty, or when their child is hospitalized. Recurrent events that occur during a period of observation can lead to better characterization and explanation of the event and, in some cases, may reassure caregivers. Fourth are the risks associated with medical care, such as nosocomial infections and inaccurate testing.

INITIAL HISTORY

An appropriate history and physical examination are key to evaluating an infant who has experienced an acute event (Table 424.2). Attention should be given to characterizing the event and interpreting the subjective experience of the caregiver to provide an objective description. The following questions can guide this process:

What was the infant doing before, during, and after the event? An event occurring during or after feeding will likely have a different explanation than one occurring during sleep or after crying. The sequence of events can also be diagnostic. A **breath-holding spell** begins with crying, followed by a period of apnea, perioral cyanosis, change of consciousness, and return to baseline.

Did the infant change color? It is often normal for infants to have blue discoloration **(perioral cyanosis or acrocyanosis)** around the lips or hands because of circulatory immaturity. Turning red or purple is also common when infants cry or become upset. The clinician's goal is to distinguish less concerning color change from **central cyanosis**, which is blue discoloration of the face, trunk, gums, or tongue that can indicate hypoxemia.

Did the infant experience central or obstructive apnea, or just choking or gagging? It is normal for infants to exhibit respiratory pauses of up to 20 seconds while awake and asleep. These can reflect **periodic breathing of the newborn** or normal REM sleep. Much more concerning are periods of no air movement that last longer than 20 seconds. **Obstructive apnea** results in paradoxical movement of the diaphragm and upper airway. In infants, this is most commonly caused by upper

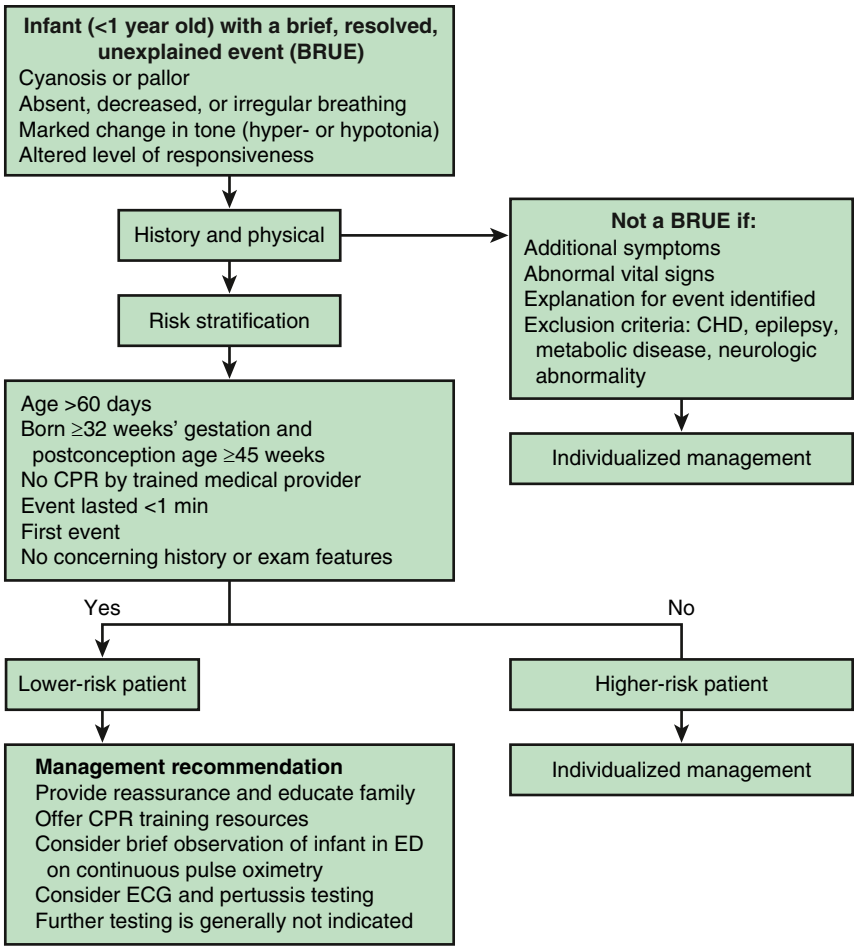

Fig. 424.1 Algorithm for diagnosis, risk stratification, and management of a brief resolved unexplained event (BRUE). CHD, Congenital heart disease; ECG, electrocardiogram; ED, emergency department. *From The Harriet Lane House Staff at The Charlotte R. Bloomberg Children's Center of The Johns Hopkins Hospital. The Harriet Lane Handbook. 23rd ed. Philadelphia: Elsevier, 2024. Fig 25.11; with data from Tieder JS, Bonkowsky JL, Etzel RA, et al. Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants [published correction appears in Pediatrics. 2016 Aug;138(2):]. Pediatrics. 2016;137(5):e20160590.*

and lower respiratory tract infections (e.g., bronchiolitis) and may precede the recognition of symptoms typically seen in viral respiratory infections. Infants also commonly gag or choke briefly during or shortly after feeds or with GER or vomiting. The resulting reflexive pause in respiration to protect the airway is sometimes referred to as **laryngospasm**. **Central apnea** is always concerning and occurs when the brainstem does not properly control the respiratory muscles. This may be seen in brain trauma from **nonaccidental trauma** and in rare disorders such as **congenital central hypoventilation syndrome**.

Was there a concerning change in muscle tone? Seizures in infants are concerning and difficult to diagnose, and they rarely present as typical seizure activity. They can present as staring spells, periods of episodic increased or decreased tone, or **infantile spasms**. It is normal for infants to have rapid jerking movements because of neurologic immaturity and infant reflexes (e.g., Moro, startle, and fencing reflex), and sometimes these can appear similar to seizures. One of the most serious and time-sensitive causes of seizures or central apnea is undiagnosed brain trauma from nonaccidental trauma, which may result in no other symptoms or physical examination findings upon presentation.

Was there an altered level of responsiveness? Episodic changes in consciousness and mental status can be difficult to assess in infants because of neurologic immaturity and variability in sleep-wake cycles. However, abrupt changes where the infant appears to lose consciousness after episodes of apnea or color change can be concerning for hypoxemia, hypoglycemia, or seizures.

Did the event self-resolve, or was an intervention required? Infants with choking from GER, vomit, or feeding difficulties generally improve spontaneously or with help clearing the airway. A serious underlying cause is more likely if CPR was indicated and then provided, though this may be difficult to assess if no medically trained individuals witnessed the event.

Additional History

A careful, detailed history can lead to an explanation; the key elements are summarized in Tables 424.1 and 424.2. A clinician should inquire about other symptoms (e.g., fever, upper respiratory infection [URI] symptoms, spitting up). A history of breathing problems, prenatal or perinatal concerns, prematurity, and growth and developmental problems is important. Premature infants, particularly those still under 43 weeks corrected gestational age, are at higher risk for underlying causes, such as apnea of prematurity. A careful feeding history can detect oropharyngeal dysphagia or GER-related problems (i.e., laryngospasm).

A targeted family history can reveal risk for sudden death, cardiac arrhythmias, and metabolic, genetic, and neurologic disease. A social history, particularly by someone trained to detect nonaccidental trauma, can reveal recent trauma, prior child welfare involvement, substance abuse, poisoning or misuse of medications, and environmental exposures (e.g., secondhand tobacco smoke and mold). It is important to understand who observed the event, who normally takes care of the infant, and if there are any discrepancies in the explanation of the event.

Consider infectious exposures. Infants exposed to underimmunized family members are at risk for pertussis. Respiratory syncytial virus (RSV) and other respiratory viruses, as well as pertussis, can present with apnea before the onset of URI symptoms.

Physical Examination

A careful physical examination may reveal a causative or underlying diagnosis. Abnormal growth and head circumference may reflect feeding, developmental, and neurologic problems. Abnormal vital signs and pulse oximetry can suggest infectious, cardiac, and neurologic abnormalities. A careful skin and mouth examination can reveal subtle signs. For example, child abuse should be suspected in infants with bruises, petechiae, or a torn frenulum. Signs of airway abnormalities,

Table 424.1 Symptom-Based Approach to BRUEs: Other Conditions that Might Be Confused with a BRUE

DIAGNOSTIC CATEGORIES	EXPLANATORY CAUSES TO CONSIDER	SUGGESTIVE HISTORICAL FINDINGS	SUGGESTIVE PHYSICAL EXAMINATION FINDINGS	TESTING TO CONSIDER
Gastrointestinal	GER Intussusception Volvulus Oropharyngeal dysphagia	Coughing, vomiting, choking, gasping temporally related to feeds or regurgitation of gastric contents Feeding difficulties Recent preceding feed Irritability after feeds Milk in mouth/nose Bilious emesis Pulling legs to chest Bloody/mucousy stool Lethargy after event	Gastric contents in the nose and mouth Choking, gagging, or oxygen desaturation temporally related to feeding or regurgitation of gastric contents	Upper GI to assess for anatomic anomalies Clinical swallow evaluation Abdominal ultrasound pH probe
Infectious	Upper and lower respiratory tract infection (RSV, pertussis, pneumonia) Bacteremia Meningitis Urinary tract infection	Preceding URI symptoms Multiple events on the day of presentation Sick exposures Foul-smelling urine	Fever/hypothermia Lethargy Ill appearance Coryza Cough Wheeze Tachypnea	NP swab for RSV, pertussis Chest radiograph CBC and blood culture Cerebrospinal fluid analysis and culture Urinalysis and culture
Neurologic	Seizures Breath-holding spells Congenital central hypoventilation syndrome Neuromuscular disorders Congenital malformations of the brain and brainstem Malignancy Intracranial hemorrhage	Multiple events Loss of consciousness Change in tone Abnormal muscular movements Eye deviation Preceding triggers	Papilledema Abnormal muscular movements Hypertonicity or flaccidity Abnormal reflexes Microcephaly or macrocephaly Dysmorphic features Signs of trauma or poisoning (see "Child maltreatment" below)	EEG Neuroimaging
Respiratory/ ENT	Apnea of prematurity Apnea of infancy Periodic breathing Airway anomaly Aspiration Foreign body Obstructive sleep apnea	Prematurity Foreign body Aspiration Noisy breathing	Wheezing Stridor Crackles Rhonchi Tachypnea	Chest radiograph Neck radiograph Laryngoscopy Bronchoscopy Esophagoscopy Polysomnography
Child maltreatment	Nonaccidental head trauma Smothering Poisoning Factitious syndrome imposed on another (formerly Munchausen syndrome by proxy)	Multiple events Unexplained vomiting or irritability Recurrent BRUEs Historical discrepancies Family history of unexplained death, SIDS, or BRUEs Single witness of event Delay in seeking care	Bruising (especially in a nonmobile child) Ear trauma, hemotympanum Acute abdomen Painful extremities Oral bleeding/trauma Frenulum tears Unexplained irritability Retinal hemorrhages Depressed mental status	Skeletal survey CT/MRI of the head Dilated funduscopic examination if head imaging concerning for trauma Toxicology screen Social work evaluation
Cardiac	Dysrhythmia (prolonged QT syndrome, Wolff-Parkinson-White syndrome) Cardiomyopathy Congenital heart disease Myocarditis	Feeding difficulties Growth difficulties Diaphoresis Prematurity	Abnormal heart rate/rhythm Murmur Decreased femoral pulses	Four-extremity blood pressure Preductal and postductal oxygen saturation measurements ECG Echocardiogram Serum electrolytes, calcium, magnesium
Metabolic/ genetic	Hypoglycemia Inborn errors of metabolism Electrolyte abnormalities Genetic syndromes including those with craniofacial malformations	Severe initial event Multiple events Event associated with period of stress or fasting Developmental delay Associated anomalies Growth difficulties Severe/frequent illnesses Family history of BRUE, consanguinity, seizure disorder, or SIDS	Dysmorphic features Microcephaly Hepatomegaly	Serum electrolytes; glucose, calcium, and magnesium levels Lactate Ammonia Pyruvate Urine organic and serum amino acids Newborn screen

BRUE, Brief resolved unexplained event; ECG, electrocardiogram; EEG, electroencephalogram; ENT, ear, nose, and throat; GER, gastroesophageal reflux; GI, gastrointestinal; NP, nasopharyngeal; RSV, respiratory syncytial virus; SIDS, sudden infant death syndrome; URI, upper respiratory infection.

From Kliegman RK, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*. Philadelphia: Elsevier; 2018: Table 5.3.

Table 424.2 Important Historical Features of a BRUE

PREEVENT	
Condition of child	Awake vs asleep
Location of child	Prone vs supine, flat or upright, in crib/car seat, with pillows, blankets
Activity	Feeding, crying, sleeping
EVENT	
Respiratory effort	None, shallow, gasping, increased Duration of respiratory pauses
Color	Pallor, red, cyanotic Peripheral, whole body, circumoral, lighting of room
Tone/movement	Rigid, tonic-clonic, decreased, floppy Focal vs diffuse Ability to suppress movements
Level of consciousness	Alert, interactive, sleepy, nonresponsive
Duration	Time until normal breathing, normal tone, normal behavior Detailed history of caregiver actions during event to aid in defining time course
Associated symptoms	Vomiting, sputum production, blood in mouth/nose, eye rolling
POSTEVENT	
Condition	Back to baseline, sleepy, postictal, crying If altered after event, duration of time until back to baseline
INTERVENTIONS	
What was performed	Gentle stimulation, blowing in face, mouth-to-mouth, cardiopulmonary resuscitation
Who performed intervention	Medical professional vs caregiver
Response to intervention	Resolution of event vs self-resolving
Duration of intervention	How long was intervention performed
MEDICAL HISTORY	
History of present illness	Preceding illnesses, fever, rash, irritability, sick contacts
Medical history	Prematurity, prenatal exposures, gestational age, birth trauma Noisy breathing since birth Any medical problems, prior medical conditions, prior hospitalizations Developmental delay Medications
Feeding history	Gagging, coughing with feeds, poor weight gain
Family history	Neurologic problems Cardiac arrhythmias Sudden death, childhood deaths, BRUEs Neonatal problems Consanguinity
Social history	Home situation Caregivers Smoke exposure Medications in the home

BRUE, Brief resolved unexplained event.
From Kliegman RK, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis.* Philadelphia: Elsevier; 2018: Table 5.4.

such as inspiratory or expiratory stridor or stertor, can lead to a diagnosis of respiratory infections, vascular rings, hemangioma, laryngomalacia, tracheomalacia, or facial dysmorphism.

Testing

In the past, it was common for clinicians to routinely test infants presenting with such events using complete blood counts (CBCs), appropriate cultures, and GER testing. However, it is known that these tests are unlikely to reveal a cause and even more likely to lead to a false-positive result. False positives can, in turn, contribute to missed diagnoses, additional unnecessary testing, patient harm, greater parental concern, and increased costs.

In lower-risk infants, routine laboratory testing and diagnostic imaging (CBC, bacterial cultures, blood gas and glucose, metabolic panels, urinalysis, GER testing, chest radiograph, neuroimaging, electroencephalogram [EEG], sleep study) is *not* recommended. *The few situations where testing may be considered in the lower-risk population include:*

- *Pertussis* testing in underimmunized or exposed individuals.
- ECG may reveal a prolonged QtC syndrome if there is a concerning family history, but routine testing is not indicated.
- Rapid viral testing can help diagnose subclinical viral causes, but these tests can be positive from recent past infections that may not be the cause of the concerning event.
- A brief period of continuous pulse oximetry and serial observations to detect hypoxemia and apnea.

In higher-risk infants, routine screening tests may not be needed. Testing should be done because of concerns from the history and physical or to further characterize repeat BRUEs.

- Continuous pulse oximetry or cardiorespiratory monitoring under a period of observation may help characterize repeat events.
- A swallow evaluation by a trained feeding expert might reveal oropharyngeal dysphagia in premature or young infants.
- Head imaging with CT or MRI is indicated when there is suspicion of nonaccidental trauma because of bruising in nonambulatory infants, concerning bruising patterns, history of unexplained death in a sibling, or inconsistent history of the event.
- Neurology consult or EEG or head imaging may lead to a diagnosis of epilepsy if there is a concern for seizure. However, it is reasonable to perform this consultation and testing as an outpatient in well-appearing infants.
- Otolaryngology consultation to detect anatomic disorders of the airway (e.g., laryngomalacia, tracheomalacia, and tracheoesophageal fistula).
- Pulmonary/sleep medicine consultation to detect disordered breathing (e.g., central apnea and obstructive sleep apnea).

Management

Although the value of hospital admission is debatable, lower-risk infants are much less likely to benefit from admission compared to higher-risk infants. Nationally, there is a trend away from routine admission for all BRUE patients, particularly those meeting lower-risk BRUE criteria. For all BRUEs, it is uncommon for a hospital admission to lead to a diagnosis of a serious underlying disorder. Sometimes, however, a longer period of observation than is practical in a clinic or emergency department can help characterize repeat events, should they recur, and reduce the uncertainty of a recurrent event for caregivers. Additional benefits of hospitalization include serial assessments of feeding, breathing, sleep, and social patterns. *The decision for hospital admission should incorporate the needs and preferences of the family and patient and the ability to follow up closely with a primary care physician.* In weighing the risks and benefits of this decision, it is important to recognize that hospitalization can unnecessarily increase stress for the family and patient through false alarms and iatrogenic complications. CPR education should be considered for all families. Home apnea monitoring should not be done. Close outpatient follow-up with a primary care physician is important, as almost half of serious underlying diagnoses are not identified during the first visit for a BRUE.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

Disorders of the Respiratory Tract

Chapter 425

Congenital Disorders of the Nose

Joseph Haddad Jr.

NORMAL NEWBORN NOSE

In contrast to children and adults, who *preferentially* breathe through their nose unless nasal obstruction interferes, most newborn infants are *obligate* nasal breathers. Significant nasal obstruction presenting at birth, such as choanal atresia, may be a life-threatening situation for the infant unless an alternative to the nasal airway is established. Acquired nasal congestion with obstruction is common in the first year of life and can affect the quality of breathing during sleep; it may be associated with a narrow nasal airway, viral or bacterial infection, enlarged adenoids, or maternal estrogenic stimuli similar to rhinitis of pregnancy. The internal nasal airway doubles in size in the first 6 months of life, leading to resolution of symptoms in many infants. Supportive care with a bulb syringe and saline nose drops, topical nasal decongestants, and antibiotics, when indicated, improve symptoms in affected infants.

PHYSIOLOGY

The nose is responsible for the initial warming and humidification of inspired air and olfaction. In the anterior nasal cavity, turbulent airflow and coarse hairs enhance the deposition of large particulate matter; the remaining nasal airways filter out particles as small as 6 μm in diameter. In the turbinate region, the airflow becomes laminar and the airstream is narrowed and directed superiorly, enhancing particle deposition, warming, and humidification. Nasal passages contribute as much as 50% of the total resistance of normal breathing. Nasal flaring, a sign of respiratory distress, reduces the resistance to inspiratory airflow through the nose and can improve ventilation (see Chapter 421).

Although the nasal mucosa is more vascular (especially in the turbinate region) than in the lower airways, the surface epithelium is similar, with ciliated cells, goblet cells, submucosal glands, and a covering blanket of mucus. The nasal secretions contain lysozyme and secretory immunoglobulin A (IgA), both of which have antimicrobial activity, and IgG, IgE, albumin, histamine, bacteria, lactoferrin, and cellular debris, as well as mucous glycoproteins, which provide viscoelastic properties. Aided by the ciliated cells, mucus flows toward the nasopharynx, where the airstream widens, the epithelium becomes squamous, and secretions are wiped away by swallowing. Replacement of the mucous layers occurs about every 10-20 minutes. Estimates of daily mucus production vary from 0.1 to 0.3 mg/kg/24 hr, with most of the mucus being produced by the submucosal glands.

CONGENITAL DISORDERS

Congenital *structural nasal malformations* are uncommon compared with acquired abnormalities. The nasal bones can be congenitally absent so that the bridge of the nose fails to develop, resulting in *nasal hypoplasia.* Congenital absence of the nose *(arrhinia),* complete or partial duplication, or a single centrally placed nostril can occur in isolation but is usually part of a malformation syndrome. Rarely, *supernumerary teeth* are found in the nose, or teeth grow into it from the maxilla.

Nasal bones can be sufficiently malformed to produce severe narrowing of the nasal passages. Often, such narrowing is associated with a high and narrow hard palate. Children with these defects can have significant obstruction to airflow during infections of the upper airways and are more susceptible to the development of chronic or recurrent hypoventilation (see Chapter 31). Rarely, the alae nasi are sufficiently thin and poorly supported, resulting in inspiratory obstruction, or there may be congenital nasolacrimal duct obstruction with cystic extension into the nasopharynx, causing respiratory distress.

CHOANAL ATRESIA

This is the most common congenital anomaly of the nose and has a frequency of approximately 1 in 7,000 live births. It consists of a unilateral or bilateral bony (90%) or membranous (10%) septum between the nose and the pharynx; most cases are a combination of bony and membranous atresia. The pathogenesis is unknown, but theories include persistence of the buccopharyngeal membranes or failure of the oronasal membrane to rupture. The unilateral defect is more common, and the female:male ratio is approximately 2:1. Approximately 50–70% of affected infants have other congenital anomalies (CHARGE syndrome [see later], Treacher-Collins, Kallmann syndrome, VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, and renal defects] association, Pfeiffer syndrome), with the anomalies occurring more often in bilateral cases.

CHARGE syndrome (*c*oloboma, *h*eart disease, *a*tresia or stenosis of the choanae, *r*etarded growth and development or central nervous system [CNS] anomalies or both, *g*enital anomalies or hypogonadism or both, and *e*ar [external, middle, inner ear] anomalies or deafness or both) is one of the more common anomalies associated with choanal atresia—approximately 10–20% of patients with choanal atresia have it. The CNS involvement (~90%) includes reduced function of cranial nerves I, V, VII, VIII, IX, and X, as well as vision and hearing deficits. Most (~90%) patients with CHARGE syndrome have autosomal dominant de novo pathogenic variants in the *CHD7* gene, which is involved in chromatin organization. Immunologic deficiencies may be noted that overlap with the 22q11.2 deletion syndrome.

Clinical Manifestations

Newborn infants have a variable ability to breathe through their mouths, so nasal obstruction does not produce the same symptoms in every infant. When the obstruction is unilateral, the infant may be asymptomatic for a prolonged period, often until the first respiratory infection, when unilateral nasal discharge or persistent nasal obstruction can suggest the diagnosis. Infants with bilateral choanal atresia who have difficulty with mouth breathing make vigorous attempts to inspire, often suck in their lips, and develop cyanosis. Distressed children then cry (which relieves the cyanosis) and become calmer, with normal skin color, only to repeat the cycle after closing their mouths. Those who can breathe through their mouths at once have trouble when sucking and swallowing, becoming cyanotic when they attempt to feed.

Diagnosis

The diagnosis is established by the inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx. The atretic plate may be seen directly with fiberoptic rhinoscopy. The anatomy is best evaluated by using high-resolution CT (Fig. 425.1).

Treatment

Initial treatment consists of prompt placement of an oral airway, maintaining the mouth in an open position, or intubation. A standard oral airway (such as that used in anesthesia) can be used, or a feeding nipple can be fashioned with large holes at the tip to facilitate air passage. Once an oral airway is established, the infant can be fed by gavage until breathing and eating without the assisted airway is possible. In

bilateral cases, intubation or, less often, tracheotomy may be indicated. If the child is free of other serious medical problems, operative intervention is considered in the neonate; transnasal repair is the treatment of choice, with the introduction of small magnifying endoscopes and smaller surgical instruments and drills. Stents are usually left in place for weeks after the repair to prevent closure or stenosis, although a large meta-analysis demonstrated that there is no benefit to stenting. Another option is a transpalatal repair, and this is done when a transnasal endoscope cannot be placed through the nose because of thick bony atresia or stenosis. Tracheotomy should be considered in cases of bilateral atresia in which the child has other potentially life-threatening problems and in whom early surgical repair of the choanal atresia may not be appropriate or feasible. Operative correction of unilateral obstruction may be deferred for several years. In both unilateral and bilateral cases, restenosis necessitating dilation or reoperation, or both, is common. Mitomycin C has been used to help prevent the development of granulation tissue and stenosis, although its efficacy is questionable.

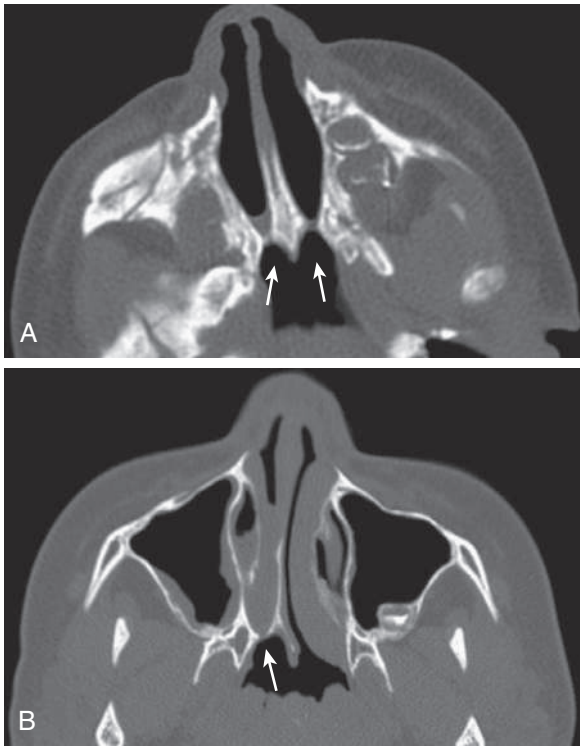

Fig. 425.1 Choanal atresia. **A,** Axial CT image in a 1-day-old neonate with severe respiratory distress shows bilateral bony choanal atresia with retained fluid in the right nasal cavity, medial bowing of the lateral nasal wall, and a thickened vomer *(arrows)*. **B,** Axial CT image in a 12-yr-old child with chronic nasal obstruction and purulent rhinorrhea shows unilateral *(right)* bony atresia with fluid in the nasal cavity *(arrow)*. *(From Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 12th ed. Philadelphia: Saunders; 2013: Fig. 8.13.)*

CONGENITAL DEFECTS OF THE NASAL SEPTUM

Perforation of the septum is most commonly acquired after birth secondary to infection, such as syphilis or tuberculosis, or trauma; rarely, it is developmental. Continuous positive airway pressure cannulas are a cause of iatrogenic perforation. Trauma from delivery is the most common cause of septal deviation noted at birth. When recognized early, it can be corrected with immediate realignment using blunt probes, cotton applicators, and topical anesthesia. Formal surgical correction, when required, is usually postponed to avoid disturbance of midface growth.

Mild septal deviations are common and usually asymptomatic; abnormal formation of the septum is uncommon unless other malformations are present, such as cleft lip or palate.

Congenital isolated absence of a membranous nasal septum has also been reported.

PYRIFORM APERTURE STENOSIS

Infants with this bony abnormality of the anterior nasal aperture present at birth or shortly thereafter with severe nasal obstruction leading to noisy breathing and respiratory distress that worsen with feeding and improve with crying. It can occur in isolation or in association with other malformations including holoprosencephaly, hypopituitarism, and cardiac and urogenital malformations. Diagnosis is made by CT of the nose (Fig. 425.2) with a pyriform aperture width less than ~11 mm. Medical management (nasal decongestants, humidification, nasopharyngeal airway insertion, management of reflux) is typically attempted for about 2 weeks; if the child still cannot feed or breathe without difficulty, then surgical repair by means of an anterior, sublabial approach may be needed. A drill is used to enlarge the stenotic anterior bone apertures.

CONGENITAL MIDLINE NASAL MASSES

Dermoids, gliomas, and *encephaloceles* (in descending order of frequency) occur intranasally or extranasally and can have intracranial connections or extend intracranially with communication to the subarachnoid space. The theory for the embryologic development of congenital midline nasal masses is faulty retraction of the dural diverticulum. Dermoids and epidermoids are the most common

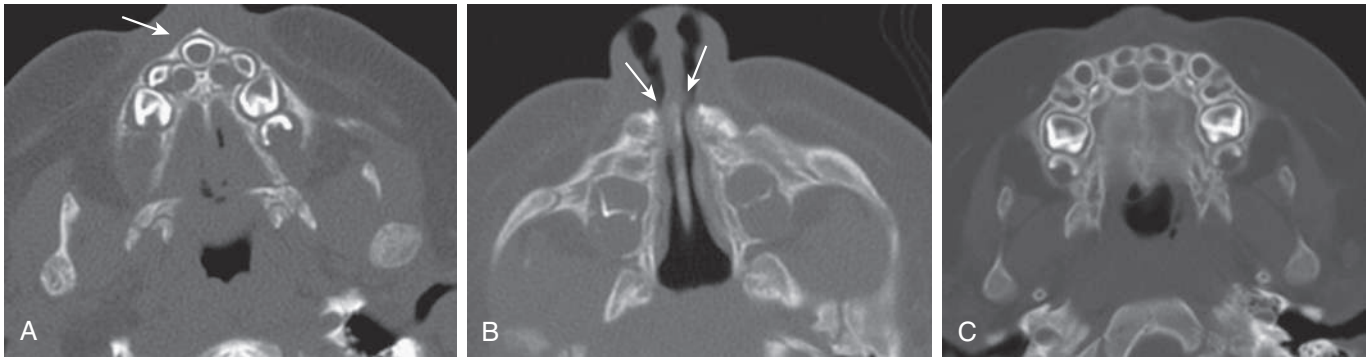

Fig. 425.2 Congenital nasal pyriform aperture stenosis in a 1½-mo-old infant with episodes of respiratory distress during breastfeeding. **A,** Axial CT image shows a triangular hard palate and solitary central maxillary mega-incisor *(arrow)*. **B,** An axial CT image shows narrowing of the anterior and inferior nasal passages *(arrows)*. **C,** Normal infant maxilla for comparison. *(From Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 12th ed. Philadelphia: Saunders; 2013: Fig. 8.14.)*



Fig. 425.3 Nasal dermoid manifesting as a midline sinus *opening. (From Elluru RG. Congenital and acquired malformations of the nose and nasopharynx. In: Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 5.5, p. 67.)*

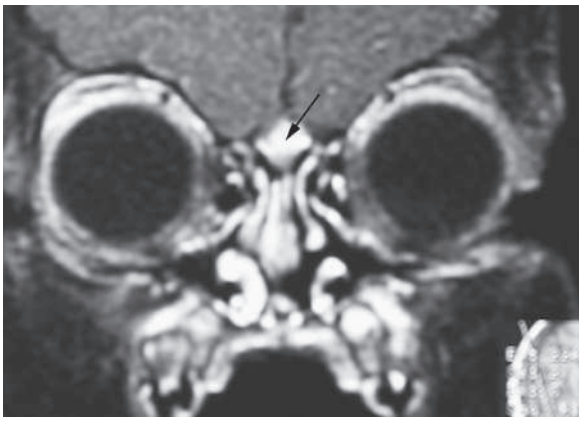

Fig. 425.4 Coronal CT scan of nasal dermoid with intracranial extension *(arrow). (From Manning SC, Bloom DC, Perkins JA, et al. Diagnostic and surgical challenges in the pediatric skull base. Otolaryngol Clin North Am. 2005;38:773–794, Fig. 2.)*

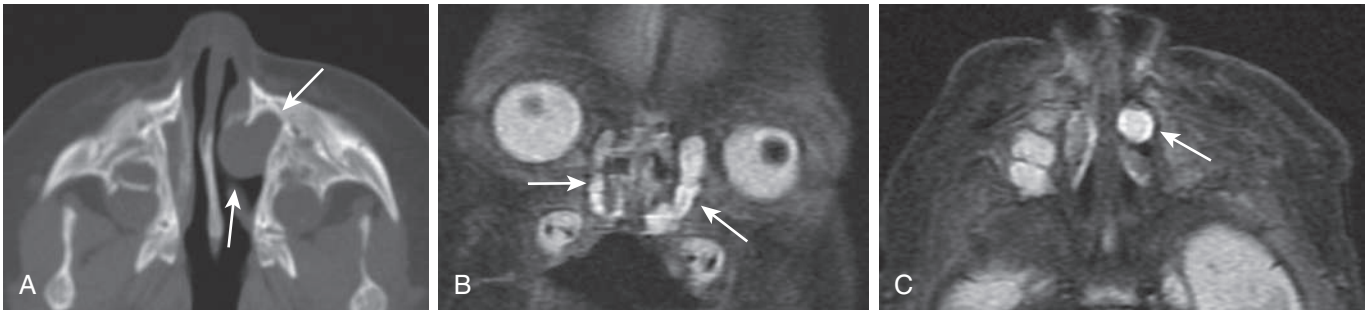

Fig. 425.5 Congenital nasolacrimal duct mucoceles in a 1-day-old neonate. **A,** Axial CT image shows a left nasal round soft tissue mass with enlargement of the ipsilateral nasolacrimal duct and canal *(arrows).* **B** and **C,** Coronal and axial fast spin echo inversion recovery MR images show bilateral cystic enlargement of the nasolacrimal sacs and ducts *(arrows). (From Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 12th ed. Philadelphia: Saunders; 2013: Fig. 8.15, p. 78.)*

type of congenital midline nasal mass and have been reported to represent up to 61% of lesions. Nasal dermoids are firm, noncompressible, and painless and often have a dimple or pit on the nasal dorsum (sometimes with hair being present) (Fig. 425.3). They can predispose to intracranial infections if an intracranial fistula or sinus is present, although recurrent infection of the dermoid itself is more common; given the risk for serious infection, surgical excision is always indicated for nasal dermoids. Gliomas or heterotopic brain tissue are firm, whereas encephaloceles are soft and enlarge with crying or the Valsalva maneuver. Diagnosis is based on physical examination findings and results from imaging studies. CT provides the best bony detail, but magnetic resonance imaging (MRI) is also helpful because of its superior ability to define intracranial extension (Fig. 425.4). Surgical excision of these masses is generally required, with the extent and surgical approach based on the type and size of the mass.

Encephaloceles may be *sincipital* (nasofrontal, nasoethmoidal, naso-orbital) or *basal* (transethmoidal, sphenoethmoidal, transsphenoidal, spheno-orbital); presentations include a glabellar or nasal mass, nasal obstruction, hypertelorism, and orbital/visual changes.

Other nasal masses include *hemangiomas, congenital nasolacrimal duct obstruction* (which can occur as an intranasal mass) (Fig. 425.5), nasal polyps, and tumors such as rhabdomyosarcoma (see Chapter 549). Nasal polyps are rarely present at birth, but the other masses often present at birth or in early infancy (see Chapter 427).

Poor development of the paranasal sinuses and a narrow nasal airway are associated with recurrent or chronic upper airway infection in Down syndrome (see Chapter 57).

DIAGNOSIS AND TREATMENT

In children with congenital nasal disorders, supportive care of the airway is given until the diagnosis is established. Diagnosis is made through a combination of flexible scoping and imaging studies, primarily CT scan. In the case of surgically correctable congenital problems such as choanal atresia, surgery is performed after the child is deemed healthy and free of life-threatening problems such as congenital heart disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 426

Acquired Disorders of the Nose

Joseph Haddad Jr. and Sonam N. Dodhia

Tumors, septal perforations, and other acquired abnormalities of the nose and paranasal sinuses can manifest with epistaxis. Midface trauma with a nasal or facial fracture may also be accompanied by epistaxis. Trauma to the nose can cause a *septal hematoma;* if treatment is delayed, this can lead to necrosis of septal cartilage and a resultant *saddle nose deformity.* Other abnormalities that can cause a change in the shape of the nose and paranasal bones, with obstruction but few other symptoms, include *fibroosseous lesions* (ossifying fibroma, fibrous dysplasia, cementifying fibroma) and *mucoceles of the paranasal sinuses.* These conditions may be suspected on physical examination and confirmed by CT scan and biopsy. Although these are considered benign lesions, they can all greatly change the anatomy of surrounding bony structures and often require surgical intervention for management.

426.1 Nasal Foreign Bodies

Joseph Haddad Jr. and Sonam N. Dodhia

ETIOLOGY

Foreign bodies (food, beads, crayons, small toys, erasers, paper wads, buttons, batteries, beans, stones, pieces of sponge or capsule sponge toys, and other small objects) are often placed in the nose by young or developmentally delayed children and constitute ≤1% of pediatric emergency department visits. Nasal foreign bodies can go unrecognized for long periods because they initially produce few symptoms and are difficult to visualize. First symptoms include unilateral obstruction, sneezing, relatively mild discomfort, and, rarely, pain. Presenting clinical symptoms include history of insertion of foreign bodies (86%), mucopurulent nasal discharge (24%), foul nasal odor (9%), epistaxis (6%), nasal obstruction (3%), and mouth breathing (2%). Irrigation results in mucosal swelling because some foreign bodies are hygroscopic and increase in size as water is absorbed; signs of local obstruction and discomfort can increase with time. The patient might also present with a generalized body odor known as *bromhidrosis.*

DIAGNOSIS

Unilateral nasal discharge and obstruction should suggest the presence of a foreign body, which can often be seen on examination with a nasal speculum or wide otoscope placed in the nose. Purulent secretions may have to be cleared so that the foreign object can be visualized; a headlight, suction, and topical decongestants are often needed. The object is usually situated anteriorly, but unskilled attempts at removal can force the object deeper into the nose. A long-standing foreign body can become embedded in granulation tissue or mucosa and appear as a nasal mass. A lateral skull radiograph assists in diagnosis if the foreign body is metallic or radiopaque or if foreign body is suspected but physical exam with sinus endoscopy or anterior rhinoscopy is negative.

TREATMENT

An initial examination of the nose is made to determine if a foreign body is present and whether it needs to be removed emergently. Planning is then made for office or operating room extrication of the foreign body. Prompt removal minimizes the danger of aspiration and local tissue necrosis, and this can usually be performed with the aid of topical anesthesia, with forceps or nasal suction. Common noninvasive techniques include simple nose blowing and the "mother's kiss" technique. The "mother's kiss" approach has been successful in acute situations where a person occludes the unaffected nostril and then, with a complete seal over the child's mouth, attempts to dislodge the foreign body by blowing into the mouth. A similar approach uses an Ambu bag over the mouth with the unaffected nostril occluded. Other noninvasive options include blowing air into a drinking straw in a child's mouth and applying high-flow oxygen (10-15 L/min) to the unaffected nostril. Alternatively, a Katz catheter (made specifically for the removal of foreign bodies from the nose and ear) can be inserted above and distal to the object, inflated, and drawn back with gentle traction. If there is marked swelling, bleeding, or tissue overgrowth, general anesthesia may be needed to remove the object. Infection usually clears promptly after the removal of the object, and generally no further therapy is necessary. Magnets can be used to extract metal foreign bodies, 2% lidocaine can be used to kill live insects before removal, and irrigation should be avoided with vegetable matter or sponges because of the risk of foreign body swelling. Age (>5) and disk-shaped foreign body are predictors for operating room removal of foreign body.

COMPLICATIONS

Serious complications include posterior dislodgement and aspiration, trauma caused by the object itself or removal attempts, infection, and choanal stenosis. Infection is common and gives rise to a purulent, malodorous, or bloody discharge. Local tissue damage from long-standing foreign body or alkaline injury from a disk battery can lead to local tissue loss and cartilage destruction. A synechia or scar band can then form, causing nasal obstruction. Loss of septal mucosa and cartilage can cause a septal perforation or saddle nose. Disk batteries are especially dangerous when placed in the nose; they leach base, which causes pain and local tissue destruction in a matter of hours. Magnets also carry a risk of septal perforation and necrosis.

Tetanus is a rare complication of long-standing nasal foreign bodies in nonimmunized children (see Chapter 257). Toxic shock syndrome is also rare and most commonly occurs from nasal surgical packing (see Chapter 227.2); oral antibiotics should be administered when nasal surgical packing is placed.

PREVENTION

Tempting objects, such as round, shiny beads, should be used only under adult supervision. Disk batteries should be stored away from the reach of small children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

426.2 Epistaxis

Joseph Haddad Jr. and Sonam N. Dodhia

Although rare in infancy, nosebleeds are common in children between the ages of 3 and 8, then decline in incidence after puberty. They are also more common during winter months. Diagnosis and treatment depend on the location and cause of the bleeding.

ANATOMY

The most common site of bleeding is the Kiesselbach plexus, an area in the anterior septum where vessels from both the internal carotid (anterior and posterior ethmoid arteries) and external carotid (sphenopalatine and terminal branches of the internal maxillary arteries) converge. The thin mucosa in this area and the anterior location make it prone to exposure to dry air and trauma.

ETIOLOGY

Epistaxis can be classified as primary (idiopathic; majority of cases) or secondary based on cause, and this has implications for diagnosis and management. Common causes of secondary nosebleeds from the anterior septum include digital trauma, foreign bodies, dry air, and inflammation, including upper respiratory tract

infections, sinusitis, and allergic rhinitis (Table 426.1). There is often a family history of childhood epistaxis. Nasal steroid sprays are commonly used in children, and their chronic use may be associated with nasal mucosal bleeding. Young infants with significant gastroesophageal reflux into the nose rarely present with epistaxis secondary to mucosal inflammation. Susceptibility is increased during respiratory infections and in the winter when dry air irritates the nasal mucosa, resulting in formation of fissures and crusting. Severe bleeding may be encountered with congenital vascular abnormalities, such as *hereditary hemorrhagic telangiectasia (HHT)* (see Chapter 481.3), varicosities, hemangiomas, and in children with thrombocytopenia, deficiency of clotting factors, particularly von Willebrand disease (see Chapter 526), hypertension, renal failure, or venous congestion. Screening for HHT is recommended for patients with obvious nasal/oral telangiectasias and those with a personal or familial history of recurrent nosebleeds. Recurrent epistaxis despite cauterization is associated with mild coagulation disorders. The family history may be positive for abnormal bleeding (epistaxis or other sites); specific testing for von Willebrand disease is indicated because the prothrombin time or partial thromboplastin time may be normal despite having a bleeding disorder. Nasal polyps or other intranasal growths may be associated with epistaxis. Recurrent, and often severe, unilateral nosebleeds may be the initial presenting symptom in **juvenile nasal angiofibroma**, which occurs in adolescent males.

CLINICAL MANIFESTATIONS

Epistaxis usually occurs without warning, with blood flowing slowly but freely from one nostril or occasionally from both. In children with nasal lesions, bleeding might follow physical exercise. When bleeding occurs at night, the blood may be swallowed and become apparent only when the child vomits or passes blood in the stools. Posterior epistaxis can manifest as anterior nasal bleeding, or, if bleeding is copious, the patient might vomit blood as the initial symptom.

Table 426.1 Possible Causes of Epistaxis

Epistaxis digitorum (nose picking)
Rhinitis (allergic or viral)
Chronic sinusitis
Foreign bodies
Intranasal neoplasm or polyps
Irritants (e.g., cigarette smoke)
Septal deviation
Septal perforation
Trauma, including child abuse
Vascular malformation or telangiectasia (hereditary hemorrhage telangiectasia)
Hemophilia
von Willebrand disease
Platelet dysfunction
Thrombocytopenia
Hypertension
Leukemia
Liver disease (e.g., cirrhosis)
Medications (e.g., aspirin, anticoagulants, nonsteroidal antiinflammatory drugs, topical corticosteroids)
Cocaine use

From Kucik CJ, Clenney T. Management of epistaxis. *Am Fam Physician*. 2005;71(2):305–311.

TREATMENT

Most nosebleeds stop spontaneously in a few minutes. The nares (lower third of the nose) should be compressed for 5 minutes, and the child kept as quiet as possible, in an upright position with the head tilted forward to avoid blood trickling back into the throat. Cold compresses applied to the nose can also help. If these measures do not stop the bleeding, local application of a solution of oxymetazoline (Afrin) or phenylephrine (Neo-Synephrine) (0.25–1%) may be useful. If bleeding persists, an anterior nasal pack may need to be inserted; if bleeding originates in the posterior nasal cavity, combined anterior and posterior packing is necessary. After bleeding is under control, and if a bleeding site is identified, its obliteration by cautery with silver nitrate may prevent further difficulties. Because the septal cartilage derives its nutrition from the overlying mucoperichondrium, only one side of the septum should be cauterized at a time to reduce the chance of a septal perforation. During the winter, or in a dry environment, a room humidifier, saline drops, and petrolatum (Vaseline) applied to the septum can help to prevent epistaxis. Ointments prevent infection, increase moisture, decrease bleeding, and are commonly used in clinical practice. Patients with severe epistaxis despite conservative medical measures should be considered for surgical ligation techniques or embolization. In patients with severe or repeated epistaxis, blood transfusions may be necessary. Otolaryngologic evaluation is indicated for these children and for those with bilateral bleeding or with hemorrhage that does not arise from the Kiesselbach plexus. For those with recurrent epistaxis, there may be short-term benefits to using bipolar electrocautery over silver nitrate chemical cautery, although treatments were equivocal after 2 years. Secondary epistaxis should be managed by identification of the cause, application of appropriate nasal therapy, and correct systemic medical management. Hematologic evaluation (for coagulopathy and anemia), along with nasal endoscopy and diagnostic imaging, may be needed to make a definitive diagnosis in cases of severe recurrent epistaxis. Replacement of deficient clotting factors may be required for patients who have an underlying hematologic disorder (see Chapter 525). Profuse unilateral epistaxis associated with a nasal mass in an adolescent boy near puberty might signal a **juvenile nasopharyngeal angiofibroma**. This unusual tumor has also been reported in a 2-year-old and in 30- to 40-year-olds, but the incidence peaks in adolescent and preadolescent boys. CT with contrast medium enhancement and magnetic resonance imaging (MRI) are part of the initial evaluation; arteriography, embolization, and extensive surgery may be needed.

Surgical intervention may also be needed for bleeding from the internal maxillary artery or other vessels that can cause bleeding in the posterior nasal cavity.

PREVENTION

The discouragement of nose picking and attention to proper humidification of the bedroom during dry winter months help to prevent many nosebleeds. Prompt attention to nasal infections and allergies is beneficial to nasal hygiene. Prompt cessation of nasal steroid sprays prevents ongoing bleeding.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 427

Nasal Polyps

Joseph Haddad Jr.

Nasal polyps are benign pedunculated tumors formed from edematous, usually chronically inflamed nasal mucosa. They commonly arise from the ethmoidal sinus and occur in the middle meatus. Occasionally they appear within the maxillary antrum and can extend to the nasopharynx (antrochoanal polyp).

It is estimated that between 1% and 4% of the population will develop nasal polyps at some point; the incidence of nasal polyps increases with age. Antrochoanal polyps represent only 4–6% of all nasal polyps in the general population but account for approximately one third of polyps in the pediatric population. Large or multiple polyps can completely obstruct the nasal passage. The polyps originating from the ethmoidal sinus are usually smaller and multiple as compared with the large and usually single antrochoanal polyp.

Cystic fibrosis (CF; see Chapter 454) is the most common childhood cause of nasal polyposis, and up to 50% of CF patients experience obstructing nasal polyposis, which is rare in non-CF children. Therefore CF should be suspected in any child younger than 12 years old with nasal polyps, even in the absence of typical respiratory and digestive symptoms. Nasal polyposis is also associated with chronic sinusitis (see Chapter 429) and allergic rhinitis. Large population studies have noted a significant familial risk in having chronic rhinosinusitis with polyposis. In the *Samter triad,* nasal polyps are associated with aspirin sensitivity and asthma; this condition is rare in children.

CLINICAL MANIFESTATIONS

Obstruction of nasal passages is prominent, with associated hyponasal speech and mouth breathing. Profuse unilateral mucoid or mucopurulent rhinorrhea may also be present. An examination of the nasal passages shows glistening, gray, grapelike masses squeezed between the nasal turbinates and the septum.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Examination of the external nose and rhinoscopy should be performed. Ethmoidal polyps can be readily distinguished from the well-vascularized turbinate tissue, which is pink or red; antrochoanal polyps may have a fleshier appearance (Fig. 427.1). Antrochoanal polyps may prolapse into the nasopharynx; flexible nasopharyngoscopy can assist in making this diagnosis. Prolonged presence of ethmoidal polyps in a child can widen the bridge of the nose and erode adjacent osseous structures. Tumors of the nose cause more local destruction and distortion of the anatomy. CT scan of the midface is key to diagnosis and planning for surgical treatment (Fig. 427.2).

TREATMENT

Local or systemic decongestants are not usually effective in shrinking the polyps, although they may provide symptomatic relief from the associated mucosal edema. Intranasal steroid sprays, and sometimes systemic steroids, can provide some shrinkage of nasal polyps with symptomatic relief and have proved useful in children with CF and adults with nasal polyps. Topical nasal steroid therapy, fluticasone, mometasone, and budesonide appear to result in nasal symptom improvement but were found to have no effect on those with CF. Dupilumab inhibits interleukin (IL)-4 and IL-13, proinflammatory cytokines involved in polyp formation, and is approved in patients ≥18 years of age for the treatment of chronic rhinosinusitis with nasal polyps.

Polyps should be removed surgically if complete obstruction, uncontrolled rhinorrhea, or deformity of the nose appears. If the underlying pathogenic mechanism cannot be eliminated (such as CF), the polyps may soon return. Functional endoscopic sinus surgery provides more complete polyp removal and treatment of other associated nasal disease; in some cases, this has reduced the need for frequent surgeries. Nasal steroid sprays should also be started preventively, once postsurgical healing occurs.

Antrochoanal polyps do not respond to medical measures and must be removed surgically, typically via endoscopic sinus surgery, or, alternatively, with a mini-Caldwell procedure. Because these types of polyps are not associated with any underlying disease process, the recurrence rate is much less than for other types of polyps.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

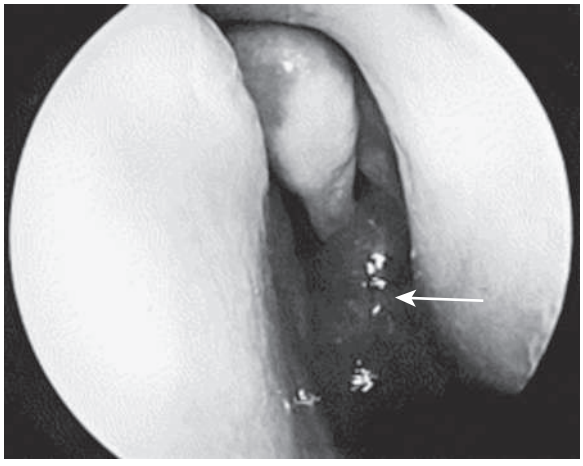

Fig. 427.1 Antrochoanal polyp viewed endoscopically *(arrow). (From Basak S, Karaman CZ, Akdilli A, et al. Surgical approaches to antrochoanal polyps in children. Int J Pediatr Otorhinolaryngol. 1998;46:197–205.)*

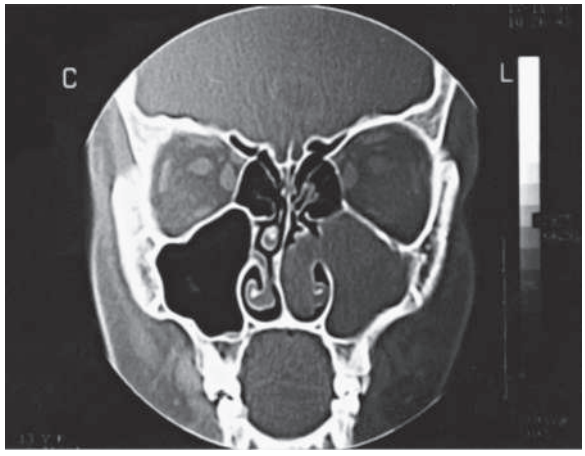

Fig. 427.2 A typical CT image of an isolated antrochoanal polyp on the left side. *(From Basak S, Karaman CZ, Akdilli A, et al. Surgical approaches to antrochoanal polyps in children. Int J Pediatr Otorhinolaryngol. 1998;46:197–205.)*

Chapter 428

The Common Cold

Katherine M. Richardson and Jennifer E. Schuster

The common cold is an acute viral infection of the upper respiratory tract in which the symptoms of rhinorrhea and nasal obstruction are prominent. Systemic symptoms and signs such as headache, myalgia, and fever are absent or mild. The common cold is frequently referred to as *infectious rhinitis* but may also include self-limited involvement of the sinus mucosa and is more correctly termed *rhinosinusitis*.

ETIOLOGY

The most common pathogens associated with the common cold are the more than 200 types of human rhinoviruses (see Chapter 310), but the syndrome can be caused by many different virus families (Table 428.1). Human rhinoviruses (HRVs) are associated with more than 50% of colds in adults and children. In young children, other viral etiologies of the common cold include respiratory syncytial virus (RSV; see Chapter 307), human metapneumovirus (MPV; see Chapter 308), parainfluenza viruses (PIVs; see Chapter 306), seasonal coronaviruses (see Chapter 311), and adenoviruses (see Chapter 309). Common cold symptoms may also be caused by influenza viruses and nonpolio enteroviruses. Many viruses that cause rhinitis are also associated with other symptoms and signs such as cough, wheezing, and fever.

EPIDEMIOLOGY

Colds occur year-round, but the incidence is greatest from the early fall until the late spring, reflecting the seasonal prevalence of the viral pathogens associated with cold symptoms. In the Northern Hemisphere, the highest incidence of HRV infection occurs in the early fall (August-October) and in the late spring (April-May); however, HRVs are typically detected year-round. Historically, the seasonal incidence for PIV usually peaks in the summer, fall, and late spring and is highest between December and April for RSV, influenza viruses, MPV, and coronaviruses. Adenoviruses are detected at a low prevalence throughout the cold season, and enteroviruses may also be detected during summer months or throughout the year.

Young children have an average of six to eight colds per year, but 10–15% of children have at least 12 infections per year. The incidence of illness decreases with increasing age, with two to three illnesses per year by adulthood. The incidence of infection is primarily a function of exposure to the virus. Children in out-of-home daycare centers during the first year of life have 50% more colds than children cared for only at home. The difference in the incidence of illness between these groups of children decreases as the length of time spent in daycare increases, and in fact many children in daycare have asymptomatic viral infections. However, the incidence of illness remains higher in the daycare group through at least the first 3 years of life. When they begin primary school, children who attended daycare have less frequent colds than those who did not. Mannose-binding lectin deficiency with impaired innate immunity may be associated with an increased incidence of colds in children.

PATHOGENESIS

Viruses that cause the common cold are spread by three mechanisms: direct hand contact (self-inoculation of one's own nasal mucosa or conjunctivae after touching a contaminated person or object), inhalation of small-particle aerosols that are airborne from coughing, or deposition of large-particle aerosols that are expelled during a sneeze and land on nasal or conjunctival mucosa. Although the different common cold pathogens could be spread by any of these mechanisms, some routes of transmission appear to be more efficient than others for particular viruses. Studies of HRV and RSV indicate that direct contact is an efficient mechanism of transmission of these viruses, although transmission by large-particle aerosols can also occur. By contrast, influenza viruses and coronaviruses appear to be most efficiently spread by small-particle aerosols.

The respiratory viruses have evolved different mechanisms to avoid host defenses. Infections with HRV and adenoviruses result in the development of serotype-specific protective immunity. Repeated infections with these pathogens occur because there are a large number of distinct serotypes of each virus. Influenza viruses change the antigens presented on the surface of the virus because of genetic drift and thus behave as though there were multiple viral serotypes. The interaction of coronaviruses (see Chapter 311) with host immunity is not well defined, but it appears that multiple distinct strains of coronaviruses are capable of inducing at least short-term protective immunity, with possibility for some cross protection between different coronaviruses. There are four types of PIV, two antigenic subgroups of RSV, and four genotypes of MPV. In addition to antigenic diversity, many of these viruses are able to reinfect the upper airway because mucosal immunoglobulin A (IgA) induced by previous infection is short lived, and the brief incubation period of these viruses allows the establishment of infection before immune memory is able to respond. Although reinfection is not completely prevented by the adaptive host response to these viruses, the severity of illness is moderated by preexisting immunity.

Table 428.1 Pathogens* Associated with the Common Cold

ASSOCIATION	PATHOGEN	RELATIVE FREQUENCY**	OTHER COMMON SYMPTOMS AND SIGNS
Agents primarily associated with the common cold	Rhinoviruses	Frequent	Wheezing/bronchiolitis
	Coronaviruses, including SARS-CoV-2 variants	Frequent	
Agents primarily associated with other clinical syndromes that also cause common cold symptoms	Respiratory syncytial virus	Occasional	Bronchiolitis in children <2 yr of age
	Human metapneumovirus	Occasional	Pneumonia and bronchiolitis
	Bocavirus	Occasional	Uncertain role
	Influenza viruses	Uncommon	Influenza-like illness, pneumonia, croup
	Parainfluenza viruses	Uncommon	Croup, bronchiolitis
	Adenoviruses	Uncommon	Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema)
	Enteroviruses Coxsackievirus A Other nonpolio enteroviruses	Uncommon	Herpangina (fever and ulcerated papules on posterior oropharynx) Aseptic meningitis

*It is not unusual to have one or more respiratory pathogens.
**Relative frequency of colds caused by the agent.

Viral infection of the nasal epithelium can be associated with destruction of the epithelial lining, as with influenza viruses and adenoviruses, or there can be no apparent histologic damage, as with HRV, coronaviruses, and RSV. Regardless of the histopathologic findings, infection of the nasal epithelium is associated with an acute inflammatory response characterized by release of a variety of inflammatory cytokines, such as interleukin-8, that attract polymorphonuclear cells into the nasal submucosa and epithelium and infiltration of the mucosa by inflammatory cells. This acute inflammatory response appears to be partially or largely responsible for many of the symptoms associated with the common cold, rather than direct damage to the respiratory tract by the virus. Viral shedding of most respiratory viruses peaks 3-5 days after inoculation, often coinciding with symptom onset; low levels of viral shedding may persist for up to 3 weeks in the otherwise recovering healthy host. Inflammation can obstruct the sinus ostia or eustachian tube, predisposing to bacterial sinusitis or otitis media, respectively.

CLINICAL MANIFESTATIONS

Symptoms of the common cold vary by age and virus. In infants, fever and nasal discharge may predominate. Fever is uncommon in older children and adults. The onset of common cold symptoms typically occurs 1-3 days after viral infection. The first symptom noted is often sore or scratchy throat, followed closely by nasal obstruction and rhinorrhea. The sore throat usually resolves quickly, and, by the second and third day of illness, nasal symptoms predominate. Cough is associated with two thirds of colds in children and usually begins after the onset of nasal symptoms. Cough may persist for an additional 1-2 weeks after resolution of other symptoms. Influenza viruses, RSV, MPV, and adenoviruses are more likely than HRV or coronaviruses to be associated with fever and other constitutional symptoms, and HRV is more commonly associated with wheezing, particularly in older children. Other symptoms of a cold may include headache, hoarseness, irritability, difficulty sleeping, or decreased appetite. Vomiting and diarrhea are uncommon. The usual cold persists for approximately 1 week, although 10% last for 2 weeks.

The physical findings of the common cold are limited to the upper respiratory tract. Increased nasal secretion is usually obvious; a change in the color or consistency of the secretions is common during the course of the illness and does not indicate sinusitis or bacterial superinfection, but may indicate accumulation of polymorphonuclear cells. Examination of the nasal cavity might reveal swollen, erythematous nasal turbinates, although this finding is nonspecific and of limited diagnostic value. Abnormal middle ear pressure is common during a cold. Anterior cervical lymphadenopathy or conjunctival injection may also be noted on exam.

DIAGNOSIS

The most important task of the physician caring for a patient with a cold is to exclude other conditions that are potentially more serious or treatable. The differential diagnosis of the common cold includes noninfectious disorders and other upper respiratory tract infections (Table 428.2).

Table 428.2 Conditions that Can Mimic the Common Cold

CONDITION	DIFFERENTIATING FEATURES
Allergic rhinitis	Prominent itching and sneezing, nasal eosinophils; Hansel stain can aid diagnosis
Vasomotor rhinitis	May be triggered by irritants, weather changes, spicy foods, etc.
Rhinitis medicamentosa	History of nasal decongestant use
Foreign body	Unilateral, foul-smelling secretions
	Bloody nasal secretions
Sinusitis	Presence of fever, headache or facial pain, or periorbital edema or persistence of rhinorrhea or cough for longer than 10-14 days
Streptococcosis	Mucopurulent nasal discharge that excoriates the nares, no cough
Pertussis	Onset of persistent or severe paroxysmal cough
Congenital syphilis	Persistent rhinorrhea with onset in the first 3 mo of life

LABORATORY FINDINGS

Routine laboratory studies are not helpful for the diagnosis and management of the common cold. A nasal smear for eosinophils (Hansel stain) may be useful if allergic rhinitis is suspected (see Chapter 184). A predominance of polymorphonuclear cells in the nasal secretions is characteristic of uncomplicated colds and *does not* indicate bacterial superinfection. Self-limited radiographic abnormalities of the paranasal sinuses are common during an uncomplicated cold; imaging is not indicated for most children with simple rhinitis.

The viral pathogens associated with the common cold can be detected by polymerase chain reaction (PCR), culture, antigen detection, or serologic methods. These studies are generally not indicated in patients with colds, because a specific etiologic diagnosis is useful only when treatment with an antiviral agent is contemplated, such as for influenza viruses. Bacterial cultures, PCR, or antigen detection are useful only when group A streptococcus (see Chapter 229) or *Bordetella pertussis* (see Chapter 243) is suspected. The isolation of bacterial pathogens from nasopharyngeal specimens is not an indication of bacterial nasal infection and is not a specific predictor of the etiologic agent in sinusitis.

TREATMENT

The management of the common cold consists primarily of supportive care and anticipatory guidance.

Antiviral Treatment

Specific antiviral therapy is not available for HRV infections. The neuraminidase inhibitors oseltamivir, zanamivir, and peramivir, as well as polymerase acidic endonuclease inhibitor baloxavir marboxil, have a modest effect on the duration of symptoms associated with influenza viral infections in children. The difficulty of distinguishing influenza from other common cold pathogens and the necessity that therapy be started early in the illness (within 48 hours of onset of symptoms) to be beneficial are practical limitations to the use of these agents for mild upper respiratory tract infections. Antibacterial therapy is of no benefit in the treatment of the common cold and should be avoided to minimize possible adverse effects and the development of antibiotic resistance.

Supportive Care and Symptomatic Treatment

Supportive interventions are frequently recommended by providers. Maintaining adequate oral hydration may help to prevent dehydration and to thin secretions and soothe respiratory mucosa. The common home remedy of ingesting warm fluids may soothe mucosa, increase nasal mucus flow, or loosen respiratory secretions. Topical nasal saline may temporarily remove secretions, and saline nasal irrigation may reduce symptoms. Cool, humidified air has not been well studied but may loosen nasal secretions; however, cool-mist humidifiers and vaporizers must be cleaned after each use. The World Health Organization suggests that neither steam nor cool-mist therapy be used in treatment of a cold.

The use of oral nonprescription therapies (often containing antihistamines, antitussives, and decongestants) for cold symptoms in children is controversial. Although some of these medications are effective in adults, no study demonstrates a significant effect

in children, and there may be serious side effects. Young children cannot participate in the assessment of symptom severity, so studies of these treatments in children have generally been based on observations by parents or other observers, a method that is likely to be insensitive for detection of treatment effects. Because of the lack of direct evidence for effectiveness and the potential for unwanted side effects, it is recommended that nonprescription cough and cold products not be used for infants and children younger than 4 years of age. A decision whether to use these medications in older children must consider the likelihood of clinical benefit compared with the potential adverse effects of these drugs. The prominent or most bothersome symptoms of colds vary in the course of the illness. If symptomatic treatments are used, it is reasonable to target therapy to specific bothersome symptoms, and care should be taken to ensure that caregivers understand the intended effect and can determine the proper dosage of the medications. It is also important to instruct caregivers to read labels carefully in case multiple medications are present in one formula to avoid overdose.

Zinc, given as oral lozenges to previously healthy patients, reduces the duration but not the severity of symptoms of a common cold if begun within 24 hours of symptoms. The function of the HRV 3C protease, an essential enzyme for HRV replication, is inhibited by zinc, but there has been no evidence of an antiviral effect of zinc in vivo. The effect of zinc on symptoms has been inconsistent, with some studies reporting dramatic treatment effects (in adults), whereas other studies find no benefit. Side effects are common and include decreased taste, bad taste, and nausea.

Fever

Fever is not usually associated with an uncomplicated common cold, and antipyretic treatment is generally not indicated**.** Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease discomfort from cold-related headache or myalgias.

Nasal Obstruction

Either topical or oral adrenergic agents may be used as nasal decongestants in older children and adults. Effective topical adrenergic agents such as xylometazoline, oxymetazoline, or phenylephrine are available as either intranasal drops or nasal sprays. Reduced-strength formulations of these medications are available for use in younger children, although they are not recommended for use in children younger than 6 years old. Systemic absorption of the imidazolines (oxymetazoline, xylometazoline) has very rarely been associated with bradycardia, hypotension, and coma. Prolonged use of the topical adrenergic agents should be avoided to prevent the development of **rhinitis medicamentosa**, an apparent rebound effect that causes the sensation of nasal obstruction when the drug is discontinued. The oral adrenergic agents are less effective than the topical preparations and are occasionally associated with systemic effects such as central nervous system stimulation, hypertension, and palpitations. Pseudoephedrine may be more effective than phenylephrine as an oral agent to treat nasal congestion—its benefit seems to be greatest in the first day of treatment; after this it does not show much benefit over placebo. Aromatic vapors (such as menthol) for external rub may improve the perception of nasal patency but do not affect spirometry.

Saline nose drops (wash, irrigation) can improve nasal symptoms and may be used in all age-groups.

Rhinorrhea

The first-generation antihistamines may reduce rhinorrhea by 25–30%. The effect of the antihistamines on rhinorrhea appears to be related to the anticholinergic rather than the antihistaminic properties of these drugs, and therefore the second-generation or nonsedating antihistamines have no effect on common cold symptoms. The major adverse effects associated with the use of the antihistamines are sedation or paradoxical hyperactivity. Overdose may be associated with respiratory depression or hallucinations. Rhinorrhea may also be treated with ipratropium bromide, a topical anticholinergic agent. This drug produces an effect comparable to the antihistamines but is not associated with sedation. The most common side effects of ipratropium are nasal irritation and bleeding.

Sore Throat

The sore throat associated with colds is generally not severe, but treatment with mild analgesics is occasionally indicated, particularly if there is associated myalgia or headache. The use of acetaminophen during HRV infection is associated with suppression of neutralizing antibody responses, but this observation has no apparent clinical significance. Aspirin *should not* be given to children with respiratory infections because of the risk of Reye syndrome in children with influenza (see Chapter 305). NSAIDs are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of an effect on respiratory symptoms.

Cough

Cough suppression is generally not necessary in patients with colds. Cough in some patients appears to be from upper respiratory tract irritation associated with postnasal drip. Cough in these patients is most prominent during the time of greatest nasal symptoms, and treatment with a first-generation antihistamine may be helpful. Cough lozenges or hard candy may be temporarily effective and are unlikely to be harmful in children for whom they do not pose risk of aspiration (older than age 6 years). **Honey** has a modest effect on relieving nocturnal cough and is unlikely to be harmful in children older than 1 year of age. Honey should be avoided in children younger than 1 year of age because of the risk for botulism (see Chapter 237).

In some patients, cough may be a result of **virus-induced reactive airways disease**. These patients can have cough that persists for days to weeks after the acute illness and might benefit from bronchodilator or other therapy. Dextromethorphan hydrobromide has no effect on cough from colds and has potential enhanced toxicity. Expectorants such as guaifenesin are not effective antitussive agents.

Ineffective Treatments

Vitamin C, guaifenesin, and inhalation of warm, humidified air are no more effective than placebo for the treatment of cold symptoms.

Echinacea is a popular herbal treatment for the common cold. Although echinacea extracts have biologic effects, echinacea is not effective as a common cold treatment. The lack of standardization of commercial products containing echinacea also presents a formidable obstacle to the rational evaluation or use of this therapy.

There is no evidence that the common cold or persistent acute purulent rhinitis of less than 10 days in duration benefits from antibiotics. In fact, there is evidence that antibiotics cause significant adverse effects when given for acute purulent rhinitis.

COMPLICATIONS

The most common complication of a cold is **acute otitis media** (AOM; see Chapter 680), which may be indicated by new-onset fever and earache after the first few days of cold symptoms. AOM is reported in 5–30% of children who have a cold, with the higher incidence occurring in young infants and in children cared for in a group daycare setting. Symptomatic treatment of the common cold symptoms has no effect on the subsequent development of AOM, which can be viral or bacterial.

Sinusitis is another complication of the common cold (see Chapter 429). Self-limited sinus inflammation is a part of the pathophysiology of the common cold, but 0.5–2% of viral upper respiratory tract infections in adults and 5–9% in children are complicated by acute bacterial sinusitis. The differentiation of common cold symptoms from bacterial sinusitis may be difficult. The diagnosis of bacterial sinusitis should be considered if rhinorrhea or daytime cough persists without improvement for at least 10-14 days; if acute symptoms worsen over time; or if acute signs of more severe sinus involvement

such as fever, facial pain, or facial swelling develop. There is no evidence that symptomatic treatment of the common cold alters the frequency of development of bacterial sinusitis. Bacterial pneumonia is an uncommon complication of the common cold; however, both RSV and HRV have been implicated in pneumonia, especially in developing and emerging countries.

Exacerbation of **asthma** is a potentially serious complication of colds. The majority of asthma exacerbations in children are associated with common cold viruses. There is no evidence that treatment of common cold symptoms prevents this complication; however, studies are underway in patients with underlying asthma to determine effectiveness of preventive or acute treatment at the onset of upper respiratory tract infection symptoms.

PREVENTION

Chemoprophylaxis or immunoprophylaxis is generally not available for the common cold. Immunization or chemoprophylaxis against influenza can prevent colds caused by this pathogen, but influenza is responsible for only a small proportion of all colds. Palivizumab is recommended to prevent severe RSV lower respiratory infection in high-risk infants but does not prevent upper respiratory infections from this virus. Vitamin C, garlic, or echinacea do not prevent the common cold. Zinc sulfate taken for a minimum of 5 months may reduce the rate of cold development. However, because of duration of use and adverse effects of bad taste and nausea, this is not a recommended prevention modality in children.

Hand-to-hand transmission of HRV followed by self-inoculation may be prevented by frequent handwashing and avoiding touching one's mouth, nose, and eyes. Some studies report the use of alcohol-based hand sanitizers and virucidal hand treatments were associated with decreased transmission. In the experimental setting, virucidal disinfectants or virucidal-impregnated tissues also reduce transmission of cold viruses; under natural conditions none of these interventions prevents common colds.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 429

Sinusitis

Diane E. Pappas and Sarah R. Boggs

Sinusitis is a common illness of childhood and adolescence. There are two common etiologies of acute sinusitis—viral and bacterial—with significant acute and chronic morbidity as well as the potential for serious complications. Fungal sinusitis is rare in immunocompetent patients but can also occur. The common cold produces a viral, self-limited *rhinosinusitis* (see Chapter 428). Approximately 6–7% of viral upper respiratory tract infections in children and adolescents are complicated by acute symptomatic bacterial sinusitis. Some children with underlying predisposing conditions (cystic fibrosis, primary ciliary dyskinesia, immunoglobulin deficiencies) have chronic sinus disease that may or may not be infectious.

Typically, the ethmoidal and maxillary sinuses are present at birth, but only the ethmoidal sinuses are pneumatized. The maxillary sinuses are not pneumatized until 4 years of age. The sphenoidal sinuses are present by 5 years of age, whereas the frontal sinuses begin development at age 7-8 years and are not completely developed until adolescence. The ostia draining the sinuses are narrow (1-3 mm) and drain into the ostiomeatal complex in the middle meatus. The paranasal sinuses are normally sterile and maintained by the mucociliary clearance system.

The bacterial pathogens causing **acute bacterial sinusitis** in children and adolescents include *Streptococcus pneumoniae* (~30%; see Chapter 228), nontypeable *Haemophilus influenzae* (~50%; see Chapter 240), and *Moraxella catarrhalis* (~10%; see Chapter 242). Approximately 50% of *H. influenzae* and 100% of *M. catarrhalis* are β-lactamase positive. As a result of routine use of pneumococcal conjugate vaccine (PCV) 13 in children, nontypeable *H. influenzae* is the most common cause of acute bacterial sinusitis in children; *S. pneumoniae* resistance has also decreased. Similarly, as a result of routine use of the *H. influenzae* type b vaccination in children, almost all *H. influenzae* infections are nontypeable *H. influenzae*. Approximately 25% of *S. pneumoniae* may be penicillin resistant. *Staphylococcus aureus,* other streptococci, and anaerobes are uncommon causes of *acute* bacterial sinusitis in children. Although *S. aureus* (see Chapter 227.1) is an uncommon pathogen for acute sinusitis in children, the increasing prevalence of methicillin-resistant *S. aureus* is a significant concern. *H. influenzae*, α- and β-hemolytic streptococci, *M. catarrhalis, S. pneumoniae,* and coagulase-negative staphylococci are commonly recovered from children with *chronic* sinus disease. *Fusobacterium necrophorum* and *Streptococcus anginosus* are emerging pathogens causing sinusitis with high potential for intracranial extension.

EPIDEMIOLOGY

Acute bacterial sinusitis can occur at any age, though it is more common in older children and adolescents as the sinus cavities become pneumatized. Predisposing conditions may include viral upper respiratory tract infections (associated with out-of-home daycare or a school-age sibling), allergic rhinitis, and tobacco smoke exposure. Children with immune deficiencies, particularly of antibody production (immunoglobulin [Ig]G, IgG subclasses, IgA; see Chapter 166), cystic fibrosis (see Chapter 454), ciliary dysfunction (see Chapter 455), abnormalities of phagocyte function, gastroesophageal reflux, anatomic defects (cleft palate), nasal polyps, cocaine abuse, and nasal foreign bodies (including nasogastric tubes), can develop chronic or recurrent sinus disease. Immunosuppression for bone marrow transplantation or malignancy with profound neutropenia and lymphopenia predisposes to severe fungal *(Aspergillus, Mucor)* sinusitis, often with intracranial extension. Patients with nasotracheal intubation or nasogastric tubes may have obstruction of the sinus ostia and develop sinusitis with the multiple-drug-resistant organisms of the intensive care unit.

Acute sinusitis is defined by a duration of <30 days, subacute by a duration of 1-3 months, and chronic by a duration of longer than 3 months.

PATHOGENESIS

Acute bacterial sinusitis typically follows a viral upper respiratory tract infection (including COVID-19 infection). Initially, the viral infection produces a viral rhinosinusitis; magnetic resonance imaging (MRI) evaluation of the paranasal sinuses demonstrates abnormalities (mucosal thickening, edema, inflammation) of the paranasal sinuses in 68% of healthy children in the normal course of the common cold. Nose blowing has been demonstrated to generate sufficient force to propel nasal secretions into the sinus cavities. Bacteria from the nasopharynx that enter the sinuses are normally cleared readily, but during viral rhinosinusitis, inflammation and edema can block sinus drainage and impair mucociliary clearance of bacteria. The growth conditions are favorable, and high titers of bacteria are produced.

CLINICAL MANIFESTATIONS

Children and adolescents with sinusitis can present with nonspecific complaints, including nasal congestion, purulent nasal discharge

Table 429.1 Symptoms of Acute Bacterial Sinusitis

MAJOR SYMPTOMS	MINOR SYMPTOMS
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure alone or exacerbated by bending forward	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

Modified from Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID*. 2012;54:e72–e112, Table 2.

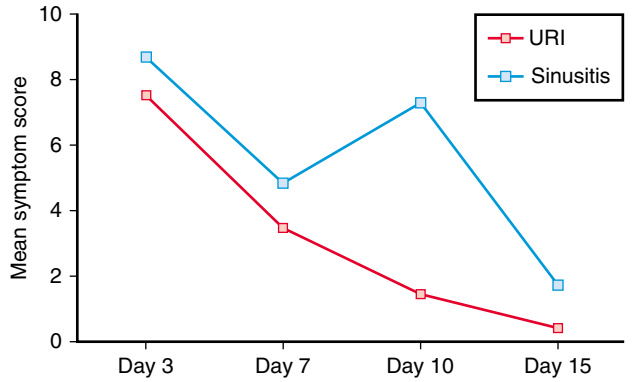

Fig. 429.1 Sinusitis vs URI biphasic symptoms. Mean symptom score by day of illness. *(Modified from DeMuri GP, Eickhoff JC, Gern JC, Wald ER. Clinical and virological characteristics of acute sinusitis in children. Clin Infect Dis. 2019;69:1764–1770, Fig. 1.)*

(unilateral or bilateral), fever, and cough. Less common symptoms include bad breath (halitosis), a decreased sense of smell (hyposmia), and periorbital edema (Table 429.1). Complaints of headache and facial pain are rare in children. Additional symptoms include maxillary tooth discomfort and facial pain or pressure exacerbated by bending forward. Physical examination might reveal erythema and swelling of the nasal mucosa with purulent nasal discharge. Sinus tenderness may be detectable in adolescents and adults.

DIAGNOSIS

The clinical diagnosis of *acute* bacterial sinusitis is based on history, which unfortunately overlaps significantly with that of the common cold. In order to differentiate between the two, current pediatric guidelines define acute bacterial sinusitis as either (1) persistent symptoms of upper respiratory tract infection (rhinitis, common cold), including nasal discharge and/or daytime cough for longer than 10 days without improvement, (2) sudden worsening or new symptoms, known as two-phase illness, or "double sickening," including nasal discharge, daytime cough, or fever after initial improvement (Fig. 429.1), or (3) severe onset with temperature of at least 39°C (102°F) and purulent nasal discharge for 3-4 consecutive days. Bacteria are recovered from maxillary sinus aspirates in 70% of children with such persistent or severe symptoms. Children with *chronic* sinusitis have a history of persistent respiratory symptoms, including cough, nasal discharge, or nasal congestion, lasting longer than 90 days.

Sinus aspirate culture is the only accurate method of diagnosis but is not practical for routine use for immunocompetent patients. It may be a necessary procedure for immunosuppressed patients with suspected fungal sinusitis. In adults, *rigid nasal endoscopy* is a less invasive method for obtaining culture material from the sinus but detects a great excess of positive cultures compared with aspirates. Findings on radiographic studies (sinus plain films, computed tomography [CT] scans), including opacification, mucosal thickening, or presence of an air-fluid level, are not diagnostic and are not recommended in otherwise healthy children. Such findings can confirm the presence of sinus inflammation but cannot be used to differentiate among viral, bacterial, or allergic causes of inflammation.

Given the nonspecific clinical picture, differential diagnostic considerations include viral upper respiratory tract infection (including COVID-19), allergic rhinitis, nonallergic rhinitis, and nasal foreign body. Viral upper respiratory tract infections are characterized by clear and usually nonpurulent nasal discharge, cough, and initial fever; symptoms do not usually persist beyond 10-14 days, although a few children (10%) have persistent symptoms even at 14 days. In a study using nasal sampling, new viruses were present in 29% of sinusitis episodes in children, suggesting sequential upper respiratory infections (URIs) as the cause of persistent symptoms in many cases. Allergic rhinitis can be seasonal; evaluation of nasal secretions should reveal significant eosinophilia.

TREATMENT

It is unclear whether antimicrobial treatment of clinically diagnosed acute bacterial sinusitis offers any substantial benefit. Two randomly controlled trials in children with acute bacterial sinusitis showed improvement after antibiotic therapy, whereas a third found that antimicrobial therapy did not affect resolution of symptoms, duration of symptoms, or days missed from school. A similar study in adults demonstrated improved symptoms at day 7 but not day 10 of treatment. Approximately 50% of children with acute bacterial sinusitis recover without antimicrobial treatment. Centers for Disease Control and Prevention (CDC) guidelines offer that either (1) antibiotic treatment is initiated at the time of diagnosis or (2) the clinician/family may choose continued observation for an additional 3 days, with the caveat that antibiotic therapy will be initiated if symptoms worsen or do not improve. Continued observation is generally not recommended for children with persistent symptoms treated with antibiotics in the preceding 30 days or those with underlying conditions.

Due to the high prevalence of antibiotic-resistant *S. pneumoniae* in some communities, amoxicillin-clavulanate is recommended by some authorities as the preferred initial therapy for acute bacterial sinusitis; high-dose amoxicillin alone may also be considered. In a large cohort of pediatric and adolescent patients from a nationwide healthcare utilization database, both antibiotics were equally effective (equivalent treatment failure rates), but those who received amoxicillin-clavulanate had a higher rate of adverse events. Alternative treatments for the penicillin-allergic patient include cefpodoxime, cefdinir, or levofloxacin. *Azithromycin and trimethoprim-sulfamethoxazole are no longer indicated because of a high prevalence of antibiotic resistance.* Ceftriaxone (50 mg/kg, IV or IM) may be given to children who are vomiting or who are at risk for poor compliance; it should be followed by a course of oral antibiotics. For those with worsening symptoms or failure to improve after 3 days of antibiotic therapy, antibiotic therapy may be changed or the child may be referred to an otolaryngologist for further evaluation (maxillary sinus aspiration for culture and susceptibility testing may be necessary) (Table 429.3). The appropriate duration of therapy for sinusitis has yet to be determined; individualization of therapy is a reasonable approach, with treatment recommended in children for a minimum of 10 days or 7 days after resolution of symptoms. Frontal sinusitis can rapidly progress to serious intracranial complications and may necessitate initiation of parenteral ampicillin-sulbactam, ceftriaxone, or levofloxacin until substantial clinical improvement is achieved (Figs. 429.2 and 429.3). Treatment is then completed with oral antibiotic therapy.

The use of decongestants, antihistamines, mucolytics, and intranasal corticosteroids has not been adequately studied in children and is not recommended for the treatment of acute uncomplicated bacterial sinusitis. Likewise, saline nasal washes or nasal sprays can help liquefy secretions and act as a mild vasoconstrictor, but the effects have not been systematically evaluated in children.

Table 429.2 Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children

INDICATION	TREATMENT
Initial empirical therapy for mild to moderate disease*	Amoxicillin-clavulanate (45 mg amoxicillin/kg/day PO divided bid, max 4 g amoxicillin/day) × 10 days*
Initial therapy for acute worsening ("double sickening") of symptoms OR severe disease†	Amoxicillin-clavulanate (90 mg amoxicillin/kg/day PO divided bid, max 4 g amoxicillin/day) × 10 days
β-Lactam allergy	
Type I hypersensitivity	Levofloxacin (10-20 mg/kg/day PO divided every 12-24 hr, max 500 mg/day) × 10 days
Non–type I hypersensitivity	Cefpodoxime‡ (10 mg/kg/day PO divided bid) × 10 days
Severe infection requiring hospitalization	Ampicillin/sulbactam (200-400 mg ampicillin/kg/day IV divided every 6 hr, max 8g ampicillin/day) Ceftriaxone (50 mg/kg/day IV divided every 12 hr, max 4 g/day) Levofloxacin (10-20 mg/kg/day IV divided every 12-24 hr, max 500 mg/day)

*Amoxicillin 90 mg/kg/day, divided bid, max 4g/day, can also be considered.
†Acute worsening ("double sickening") OR severe disease: worsening nasal discharge, daytime cough, or fever starting after a period of initial improvement OR severe onset with temperature of at least 39°C (102°F) and purulent nasal discharge for 3-4 consecutive days.
‡Cefdinir (14 mg/kg/day in one or two divided doses, max 600 mg/day) is an alternative that is more palatable in liquid form than cefpodoxime but has less coverage of bacterial sinusitis pathogens.

Table 429.3 Indications for Referral to a Specialist

- Severe infection (high persistent fever with temperature >39°C [>102°F], orbital edema, severe headache, visual disturbance, altered mental status, meningeal signs)
- Recalcitrant infection with failure to respond to extended courses of antimicrobial therapy
- Immunocompromised host
- Multiple medical problems that might compromise response to treatment (e.g., hepatic or renal impairment, hypersensitivity to antimicrobial agents, organ transplant)
- Unusual or resistant pathogens
- Fungal sinusitis or granulomatous disease
- Nosocomial infection
- Anatomic defects causing obstruction and requiring surgical intervention
- Multiple recurrent episodes of acute bacterial rhinosinusitis (three to four episodes per year) suggesting chronic sinusitis
- Chronic rhinosinusitis (with or without polyps or asthma) with recurrent acute bacterial rhinosinusitis exacerbations
- Evaluation of immunotherapy for allergic rhinitis

From Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID*. 2021;54:e72–e112, Table 14.

COMPLICATIONS

Because of the close proximity of the paranasal sinuses to the brain and eyes, serious orbital and/or **intracranial complications** can result from acute bacterial sinusitis and progress rapidly. Organisms causing orbital and/or intracranial complications of bacterial sinusitis in children include members of the *Streptococcus anginosus* group, *S. aureus, S. pneumoniae,* methicillin-resistant *S. aureus* (MRSA), and methicillin-sensitive *S. aureus* (MSSA); ~30% of infections were polymicrobial.

Orbital complications, including periorbital cellulitis and more often orbital cellulitis (see Chapter 674), are most often secondary to acute bacterial ethmoiditis. *Periorbital* cellulitis produces erythema and swelling of the tissues surrounding the globe, whereas *orbital* cellulitis involves the intraorbital structures and produces proptosis, chemosis, decreased visual acuity, double vision and impaired extraocular movements, and eye pain (Fig. 429.4). In addition to IV antibiotics, orbital cellulitis may require surgical drainage of the ethmoid sinuses or orbit.

Intracranial complications can include epidural abscess, meningitis, cavernous sinus thrombosis, subdural empyema, and brain abscess (see Chapter 644). Children with altered mental status, nuchal rigidity, severe headache, focal neurologic findings, or signs of increased intracranial pressure (headache, vomiting) require immediate CT scan with contrast of the brain, orbits, and sinuses to evaluate for the presence of intracranial complications of acute bacterial sinusitis. Diagnosis of intracranial complications may be challenging, as many patients present with nonspecific symptoms present for the preceding 7-10 days (most commonly headache, fever, congestion, nausea, and vomiting); typically, patients will have been seen by a healthcare provider one or more times before diagnosis. About 50% of patients will present with an abnormal neurologic exam, although only ~30% of patients will present with neurologic symptoms (altered mental status, seizures).

Treatment with broad-spectrum IV antibiotics (usually cefotaxime or ceftriaxone combined with vancomycin and metronidazole) should be initiated immediately, pending culture and susceptibility results. Abscesses can require surgical drainage; endoscopic sinus surgery (ESS) without powered instruments and proper personal protective equipment (PPE) are recommended to minimize risks of aerosolization. Other complications include osteomyelitis of the frontal bone **(Pott puffy tumor)**, which is characterized by edema and swelling of the forehead (see Fig. 429.2), and **mucoceles**, which are chronic inflammatory lesions commonly located in the frontal sinuses that can expand, causing displacement of the eye with resultant diplopia. Surgical drainage is usually required.

PREVENTION

Prevention is best accomplished by frequent handwashing and avoiding persons with colds. This was confirmed most recently in New Zealand: when strict nonpharmaceutical infection control measures were implemented during the COVID-19 pandemic, infections caused by common cold viruses (influenza, respiratory syncytial virus [RSV], human metapneumovirus, enterovirus, adenovirus, parainfluenza virus, and rhinovirus) were greatly reduced. Once restrictions were eased, only rhinovirus infections quickly increased, whereas the prevalence of other respiratory viral infections remained reduced. This may be because of the fact that most rhinovirus infections are transmitted in the home where public restrictions are not in place. Commercially available alcohol-based hand sanitizers have been shown in vitro to be effective against COVID-19 and the common cold viruses.

Because acute bacterial sinusitis can be a complication of influenza infection, prevention of influenza infection by yearly influenza vaccine will prevent some cases of complicating sinusitis. Chemoprophylaxis against influenza with oseltamivir or zanamivir may be useful for prevention of influenza-associated sinusitis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

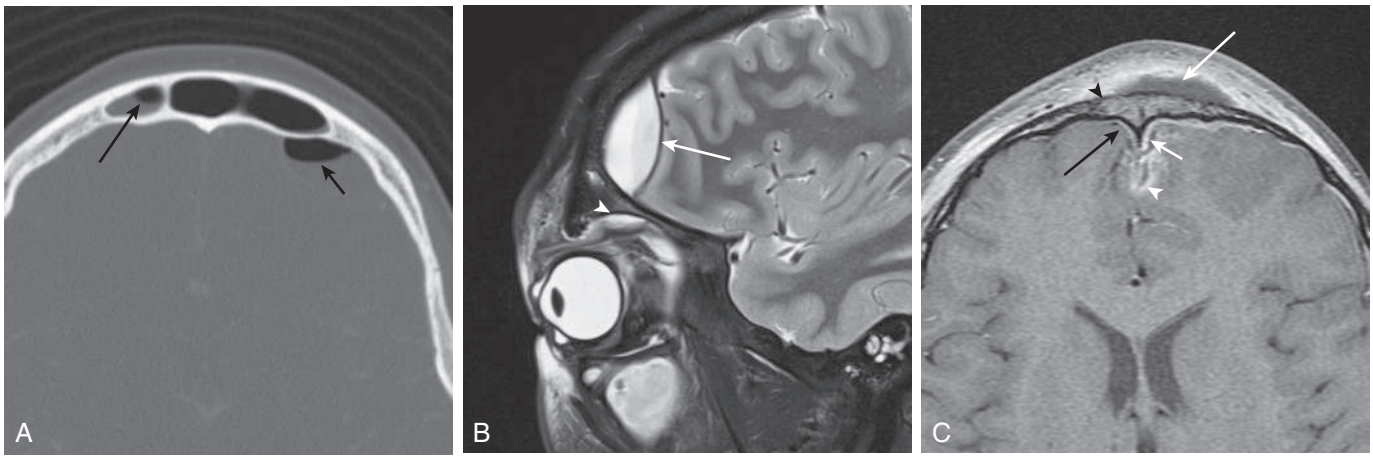

Fig. 429.2 Acute complicated sinusitis. **A,** Frontal sinusitis and epidural abscess. Axial computed tomography image shows a frontal sinus air-fluid level *(long arrow)*. There is also an intracranial air-fluid level associated with an epidural abscess *(short arrow)*. **B,** Frontal sinusitis, epidural abscess, and orbital abscess. Sagittal fat-suppressed (FS) T2-weighted magnetic resonance (MR) image demonstrates a biconvex epidural abscess *(arrow)* containing a sediment level. There is also a small superior extraconal subperiosteal abscess *(arrowhead)*. Periorbital STS is present, and there are secretions within the maxillary antrum. **C,** Pott puffy tumor, frontal osteomyelitis, and subdural empyema. Axial gadolinium-enhanced FS T1-weighted MR image shows frontal scalp swelling ventral to an elliptical low signal intensity, peripherally enhancing, frontal subperiosteal abscess *(long white arrow)*. There is enhancement of the subjacent frontal bone, consistent with osteomyelitis *(black arrowhead)*. There is also dural enhancement *(black arrow)* and a small left frontal interhemispheric subdural empyema *(short white arrow)* with subtle enhancement of the adjacent frontal leptomeninges and cortex caused by meningitis and cerebritis *(white arrowhead)*. *(From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 10.40.)*



Fig. 429.3 Axial plane contrast-enhanced CT scan of an 11-yr-old obtunded female with a subfrontal lobe abscess secondary to frontal sinusitis. The CT scan demonstrates an eliptiform ring-enhancing fluid-filled cavity adjacent to the frontal lobe with contralateral shift of the midline. *(From Parikh SR, Brown SM. Image-guided frontal sinus surgery in children. Operative Tech Otolaryngol Head Neck Surg. 2004;15:37–41.)*

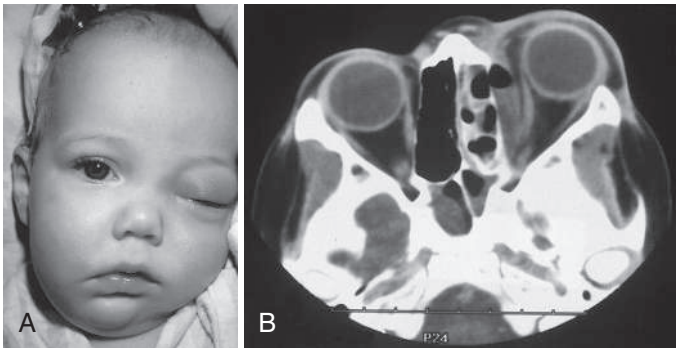

Fig. 429.4 Orbital complications of acute sinusitis. **A,** An 11-mo-old infant with a swollen left eye and limited ocular movement. **B,** Axial CT shows opacification of sinuses and an inflammatory mass with an air-fluid level displacing the medial rectus laterally. *(From Cooper ML, Slovis T. The sinuses. In Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 43-7, p. 573.)*

Chapter 430

Acute Pharyngitis

Joseph Gigante

Pharyngitis refers to inflammation of the pharynx, including erythema, edema, exudates, or an enanthem (ulcers, vesicles). Pharyngeal inflammation can be related to environmental exposures, such as tobacco smoke, air pollutants, and allergens; from contact with caustic substances, hot food, and liquids; and from infectious agents. The pharynx and mouth can be involved in various inflammatory conditions such as periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, Kawasaki disease, multisystem inflammatory syndrome in children (MIS-C), inflammatory bowel disease (IBD), Stevens-Johnson syndrome, and systemic lupus erythematous (SLE). Noninfectious etiologies are typically evident from history and physical exam, but it can be more challenging to distinguish from among the numerous infectious causes of acute pharyngitis.

Acute infections of the upper respiratory tract account for a substantial number of visits to pediatricians, and many feature sore throat as a symptom or evidence of pharyngitis on physical examination. The usual clinical task is to distinguish important, potentially serious, and treatable causes of acute pharyngitis from those that are self-limited and require no specific treatment or follow-up. Specifically, identifying patients who have **group A streptococcus** (GAS; *Streptococcus pyogenes*; see Chapter 229) pharyngitis and treating them with antibiotics forms the core of the management paradigm.

INFECTIOUS ETIOLOGIES

Viruses

In North America and most industrialized countries, GAS is the most important bacterial cause of acute pharyngitis, but viruses predominate as acute infectious causes of pharyngitis. Viral upper respiratory tract infections are typically spread by contact with oral or respiratory secretions and occur most commonly in fall, winter, and spring—that is, the respiratory season. Important viruses that cause pharyngitis include influenza, parainfluenza, adenoviruses, coronaviruses, enteroviruses, rhinoviruses, respiratory syncytial virus (RSV), cytomegalovirus, Epstein-Barr virus (EBV), herpes simplex virus (HSV), and human metapneumovirus (HMPV) (Table 430.1). Most viral pharyngitis, except mononucleosis, is mild. Common nonspecific symptoms such as rhinorrhea and cough develop gradually before they become prominent. However, specific findings are sometimes helpful in identifying the infectious viral agent (Table 430.2). Sore throat is also seen in COVID-19 infection and MIS-C; it is rare to be the only symptom and is part of the multisystem involvement in both disorders.

Table 430.1 Infectious Agents that Cause Pharyngitis

VIRUSES	BACTERIA
Adenovirus	*Streptococcus pyogenes* (group A streptococcus)
Coronavirus including COVID-19	*Arcanobacterium haemolyticum*
Cytomegalovirus	*Fusobacterium necrophorum*
Epstein-Barr virus	*Corynebacterium diphtheriae*
Enteroviruses	*Neisseria gonorrhoeae*
Herpes simplex virus (1 and 2)	Group C streptococci
Human immunodeficiency virus	Group G streptococci
Human metapneumovirus	*Francisella tularensis*
Influenza viruses (A and B)	*Yersinia pestis*
Measles virus	*Chlamydophila pneumoniae*
Parainfluenza viruses	*Chlamydia trachomatis*
Respiratory syncytial virus	*Mycoplasma pneumoniae*
Rhinoviruses	Mixed anaerobes (Vincent angina)

Gingivostomatitis and ulcerating vesicles throughout the anterior pharynx and on the lips and perioral skin are seen in primary oral HSV infection. High fever and difficulty taking oral fluids are common. This infection can last for 14 days.

Discrete **papulovesicular** lesions or **ulcerations** in the posterior oropharynx, severe throat pain, and fever are characteristic of **herpangina**, caused by various enteroviruses. In **hand-foot-mouth disease**, there are vesicles or ulcers throughout the oropharynx, on the palms and soles, and sometimes on the trunk and extremities. Coxsackie A16 is the most common agent, but enterovirus 71 and Coxsackie A6 can also cause this syndrome. Enteroviral infections are most common in the summer.

Various adenoviruses cause pharyngitis. When there is concurrent **conjunctivitis**, the syndrome is called *pharyngoconjunctival fever*. The pharyngitis tends to resolve within 7 days, but conjunctivitis may persist for up to 14 days. Pharyngoconjunctival fever can be epidemic or sporadic; outbreaks have been associated with exposure in swimming pools.

Intense, diffuse pharyngeal erythema and Koplik spots, the pathognomonic enanthem, occur in advance of the characteristic rash of measles. Splenomegaly, lymphadenopathy, or hepatomegaly may be the clue to EBV infectious mononucleosis in an adolescent with exudative tonsillitis. Primary infection with HIV can manifest as **acute retroviral syndrome**, with nonexudative pharyngitis, fever, arthralgia, myalgia, adenopathy, and often a maculopapular rash.

Bacteria Other than Group A Streptococcus

In addition to GAS, bacteria that cause pharyngitis include group C and group G streptococcus, *Arcanobacterium haemolyticum, Francisella tularensis, Neisseria gonorrhoeae, Mycoplasma pneumoniae, Chlamydophila (formerly Chlamydia) pneumoniae, Chlamydia trachomatis, Fusobacterium necrophorum,* and *Corynebacterium diphtheriae. Haemophilus influenzae* and *Streptococcus pneumoniae* may be cultured from the throats of children with pharyngitis, but their role in causing pharyngitis has not been established.

Group C and group G streptococcus and *A. haemolyticum* pharyngitis have been diagnosed most commonly in adolescents and adults.

Table 430.2 Epidemiologic and Clinical Features Suggestive of Group A Streptococcal and Viral Pharyngitis

FEATURE, BY SUSPECTED ETIOLOGIC AGENT
Group A Streptococcal
• Sudden onset of sore throat • Age 5-15 yr • Fever • Headache • Nausea, vomiting, abdominal pain • Tonsillopharyngeal inflammation • Patchy tonsillopharyngeal exudates • Palatal petechiae • Anterior cervical adenitis (tender nodes) • Winter and early spring presentation • History of exposure to strep pharyngitis • Scarlatiniform rash • No cough or coryza
Viral
• Conjunctivitis • Coryza • Cough • Diarrhea • Hoarseness • Discrete ulcerative stomatitis • Viral exanthema • As part of the spectrum of COVID-19 and MIS-C

From Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2012;55(10):e86–e102, Table 4.

They resemble group A β-hemolytic streptococcus (GABHS) pharyngitis. A scarlet fever–like rash may be present with *A. haemolyticum* infections.

F. necrophorum is an important etiology of pharyngitis in older adolescents and adults (15-30 years old). Prevalence in studies has varied from 10% to 48% of patients with non-GABHS pharyngitis, but large surveillance studies have not been performed. *F. necrophorum* was detected by polymerase chain reaction (PCR) in 20.5% of patients with pharyngitis in a study based in a university health clinic and in 9.4% of an asymptomatic convenience sample; some patients had more than one bacterial species detected by PCR. Pharyngitis patients with *F. necrophorum* had signs and symptoms similar to GAS pharyngitis: ~30% had fever, ~30% had tonsillar exudates, ~65% had anterior cervical adenopathy, and most did not have cough. This organism is difficult to culture from the throat, and diagnostic testing with PCR is not generally available. *F. necrophorum* pharyngitis is associated with the development of **Lemierre syndrome** (see Chapter 432): internal jugular vein septic thrombophlebitis. Approximately 80% of cases of Lemierre syndrome are caused by this bacterium. Patients present initially with fever, sore throat, exudative pharyngitis, and/or peritonsillar abscess. The symptoms may persist, neck pain and swelling develop, and the patient appears toxic. Septic shock may ensue, along with metastatic complications from septic emboli that can involve the lungs, bones and joints, central nervous system, abdominal organs, and soft tissues. The case fatality rate is 4–9%.

Gonococcal pharyngeal infections are usually asymptomatic but can cause acute ulcerative or exudative pharyngitis with fever and cervical lymphadenitis. Young children with proven gonococcal disease should be evaluated for sexual abuse.

Diphtheria is extremely rare in most developed countries because of extensive immunization with diphtheria toxoid. However, it remains endemic in many areas of the world, including the former Soviet bloc countries, Africa, Asia, the Middle East, and Latin America. It can be considered in patients with recent travel to or from these areas and in unimmunized patients. Key physical findings are bull neck (extreme neck swelling) and a gray pharyngeal pseudomembrane that can cause respiratory obstruction.

Ingestion of water, milk, or undercooked meat contaminated by *F. tularensis* can lead to oropharyngeal tularemia. Severe throat pain, tonsillitis, cervical adenitis, oral ulcerations, and a pseudomembrane (as in diphtheria) may be present. *M. pneumoniae* and *C. pneumoniae* cause pharyngitis, but other upper and lower respiratory infections are more important and more readily recognized. Development of a severe or persistent cough subsequent to pharyngitis may be the clue to infection with one of these organisms.

Group A Streptococcus

Streptococcal pharyngitis is relatively uncommon before 2-3 years of age, is quite common among children 5-15 years old, and declines in frequency in late adolescence and adulthood. Illness occurs throughout the year but is most prevalent in winter and spring. It is readily spread among siblings and schoolmates. GAS causes 15–30% of pharyngitis in school-age children.

Colonization of the pharynx by GAS can result in either asymptomatic carriage or acute infection. After an incubation period of 2-5 days, pharyngeal infection with GAS classically presents as rapid onset of significant sore throat and fever (see Table 430.2). The pharynx is red, and the tonsils are enlarged and often covered with a white, grayish, or yellow exudate that may be blood-tinged. There may be petechiae or doughnut lesions on the soft palate and posterior pharynx, and the uvula may be red and swollen. The surface of the tongue can resemble a strawberry when the papillae are inflamed and prominent (strawberry tongue). Initially, the tongue is often coated white, and with the swollen papillae, it is called a *white strawberry tongue*. When the white coating is gone after a few days, the tongue is often quite red and is called a *red strawberry tongue*. Enlarged and tender anterior cervical lymph nodes are frequently present. Headache, abdominal pain, and vomiting are frequently associated with the infection, but in the absence of clinical pharyngitis, gastrointestinal signs and symptoms should not be attributed to GAS. Ear pain is a frequent complaint, but the tympanic membranes are usually normal. Diarrhea, cough, coryza, ulcerations, croup/laryngitis/hoarseness, and conjunctivitis *are not* associated with GAS pharyngitis and increase the likelihood of a viral etiology (see Table 430.2).

Patients infected with GAS that produce streptococcal pyrogenic exotoxin A, B, or C may demonstrate the fine, red, papular (sandpaper) rash of **scarlet fever**. It begins on the face and then becomes generalized. The cheeks are red, and the area around the mouth is less intensely red (more pale), giving the appearance of circumoral pallor. The rash blanches with pressure, and it may be more intense in skin creases, especially in the antecubital fossae, axillae, and inguinal creases (Pastia lines or sign). Pastia lines are sometimes petechial or slightly hemorrhagic. Capillary fragility can cause petechiae distal to a tourniquet or constriction from clothing, a positive tourniquet test or Rumpel-Leeds phenomenon. Erythema fades in a few days, and when the rash resolves, it typically peels like a mild sunburn. Sometimes there is sheetlike desquamation around the free margins of the fingernails. Streptococcal pyrogenic exotoxin A, encoded by the gene *spe A,* is the exotoxin most commonly associated with scarlet fever.

The M protein is an important GAS virulence factor that facilitates resistance to phagocytosis. The M protein is encoded by the *emm* gene and determines the M type (or *emm* type). Molecular methods have identified more than 240 *emm* genes (*emm* types, M types). The M protein is immunogenic and protects against reinfection with the homologous M type; an individual can experience multiple episodes of GAS pharyngitis in a lifetime because natural immunity is M type–specific and does not prevent infection with a new M type. Numerous GAS M types can circulate in a community simultaneously, and they enter and leave communities unpredictably and for unknown reasons.

DIAGNOSIS

The clinical presentations of streptococcal and viral pharyngitis often overlap. In particular, the pharyngitis of mononucleosis can be difficult to distinguish from GAS pharyngitis. Physicians relying solely on clinical judgment often overestimate the likelihood of a streptococcal etiology. Various clinical scoring systems have been described to assist in identifying patients who are likely to have GAS pharyngitis. Criteria developed for adults by Centor and modified for children by McIsaac give one point for each of the following criteria: history of temperature >38°C (100.4°F), absence of cough, tender anterior cervical adenopathy, tonsillar swelling or exudates, and age 3-14 years. It subtracts a point for age ≥45 years. At best, a McIsaac score ≥4 is associated with a positive laboratory test for GAS in less than 70% of children with pharyngitis (Table 430.3), so it, too, overestimates the likelihood of GAS. *Consequently, laboratory testing is essential for an accurate diagnosis.* Clinical findings and/or scoring systems can best be used to assist the clinician in identifying patients in need of testing. Evaluating patients indiscriminately can lead to overdiagnosis and overtreatment. Streptococcal antibody tests are not useful in assessing patients with acute pharyngitis.

Throat culture, rapid antigen-detection tests (RADTs), or PCR tests are the diagnostic tests for GAS most available in routine clinical care. Throat culture plated on blood agar remains the gold standard for diagnosing streptococcal pharyngitis. There are both false-negative cultures as a consequence of sampling errors or prior antibiotic treatment and false-positive cultures as a consequence of misidentification of other bacteria as GAS. Streptococcal RADTs detect the group A carbohydrate of GAS. They are used by the vast majority of office-based pediatricians. All RADTs have very high specificity, generally ≥95%, so when a RADT is positive, it is assumed to be accurate and throat culture is unnecessary. Because RADTs are generally much less sensitive than culture, confirming a negative rapid test with a throat culture is recommended. RADTs and throat culture exhibit spectrum bias: they are more sensitive when the pretest probability of GAS is high (signs and symptoms are typical of GAS infection, higher McIsaac scores) and less sensitive when the pretest probability is low. Avoidance of testing when patients have signs and symptoms more suggestive of a viral infection is recommended by expert guidelines.

Table 430.3 Positive Predictive Value of McIsaac Score in Children in Clinical Studies*

SCORE	McISAAC, 2004 (n = 454) (%)	EDMONSON, 2005 (n = 1184) (%)	TANZ, 2009 (n = 1848) (%)	FINE, 2012 (n = 64,789) (%)
0	–	–	7	17
1	–	0.5	19	23
2	20.5	8.9	20	34
3	27.5	42.4	29	50
≥4	67.8	48.2	49	68
GAS prevalence	34	38	30	37

*One point is given for each of the following criteria: history of temperature >38°C (100.4°F), absence of cough, tender anterior cervical adenopathy, tonsillar swelling or exudates, and age 3-14 yr.
Note that the Centor score lacks only the age criterion. Positive predictive value refers to the proportion of patients with documented GAS by rapid antigen-detection test and/or throat culture.

Many laboratories have replaced throat culture with one of the highly sensitive and specific **GAS molecular tests**. A variety of methods are available to amplify the DNA of a specific GAS gene from a throat swab in less than 1 hour. In studies both sensitivity and specificity are reported to be ≥98% when compared with standard throat culture. PCR usually matches the molecular test when used to adjudicate discrepancies between the culture and molecular test results. Some of these nucleic acid amplification tests are approved by the FDA for use in physician office laboratories and can be used as the initial test for GAS or as a confirmatory test when the RADT is negative. Unlike throat culture and RADTs, molecular tests may not exhibit spectrum bias—that is, although test sensitivity is extremely high, it is independent of the pretest probability that GAS is the cause of illness (using signs and symptoms, McIsaac score), thus increasing the potential to identify a chronic GAS carrier who actually has an intercurrent illness not caused by GAS (discussed later). However, the ability of these stand-alone tests to deliver a definitive result in less than 1 hour makes them attractive (there is one test that takes 15 minutes)—the potential to swab symptomatic children, have them wait or send them home, and electronically prescribe an antibiotic when the test is positive can speed initiation of therapy and subsequent return to school and activities. Concerns about molecular tests include the following: (1) they are so sensitive they may cause unnecessary treatment of more patients who are carriers than would ordinarily occur with RADT and/or culture; (2) unless rigorous technique is followed, they may be prone to contamination with exogenous GAS DNA from other swabs, a particular concern in physician offices when performed by staff who are not trained laboratory technologists; and (3) they are much more expensive than throat culture.

Testing for bacteria other than GAS is performed infrequently and should be reserved for patients with persistent symptoms and symptoms suggestive of a specific non-GAS bacterial pharyngitis—for example, when there is concern for gonococcal infection or sexual abuse. Special culture media and a prolonged incubation are required to detect *A. haemolyticum.* A complete blood cell count showing many atypical lymphocytes and a positive mononucleosis slide agglutination test can help confirm a clinical suspicion of EBV infectious mononucleosis. Viral cultures are often unavailable and are generally too expensive and slow to be clinically useful. PCR is more rapid, and multiplex PCR (respiratory viral panel) testing for respiratory pathogens can identify a variety of viral and bacterial agents within a few hours. This may be useful in determining the isolation needs of hospitalized patients, assisting in patient prognosis, and epidemiology, but in the absence of specific treatment for most viral infections, such testing is usually not necessary or useful. In fact, interpreting such tests can be difficult unless the patient has signs or symptoms characteristic of a specific pathogen.

TREATMENT

Specific therapy is unavailable for most viral pharyngitis. However, nonspecific, symptomatic therapy can be an important part of the overall treatment plan. An oral antipyretic/analgesic agent (acetaminophen or ibuprofen) can relieve fever and sore throat pain. Anesthetic sprays and lozenges (often containing benzocaine, phenol, or menthol) can provide local relief in children who are developmentally appropriate to use them. Systemic corticosteroids are sometimes used in children who have evidence of upper airway compromise caused by mononucleosis. Although corticosteroids are used commonly in adults with pharyngitis, large-scale studies capable of providing safety and efficacy data are lacking in children. *Corticosteroids cannot be recommended for treatment of most cases of pediatric pharyngitis.*

Antibiotic therapy of bacterial pharyngitis depends on the organism identified. On the basis of in vitro susceptibility data, oral penicillin is often suggested for patients with group C streptococcal isolates, and oral erythromycin is recommended for patients with *A. haemolyticum,* but the clinical benefit of such treatment is uncertain.

Most untreated episodes of GAS pharyngitis resolve uneventfully within a few days, but early antibiotic therapy hastens clinical recovery by 12-24 hours and also reduces suppurative complications of GAS pharyngitis such as peritonsillar abscess and cervical adenitis. *The primary benefit and intent of antibiotic treatment is the prevention of acute rheumatic fever (ARF)*; it is highly effective when started within 10 days of onset of illness. Antibiotic therapy does not prevent acute poststreptococcal glomerulonephritis (APSGN). Antibiotic treatment should not be delayed for children with symptomatic pharyngitis and a positive test for GAS. Presumptive antibiotic treatment can be started when there is a clinical diagnosis of scarlet fever, a symptomatic child has a household contact with documented streptococcal pharyngitis, or there is a history of ARF in the patient or a family member, but a diagnostic test should be performed to confirm the presence of GAS, and antibiotics should be discontinued if GAS is not identified.

A variety of antimicrobial agents are effective for GAS pharyngitis (Table 430.4). Group A streptococci are universally susceptible to penicillin and all other β-lactam antibiotics. Penicillin is inexpensive, has a narrow spectrum of activity, and has few adverse effects. Amoxicillin is often preferred for children because of its taste, availability as chewable tablets and liquid, and the convenience of once-daily dosing. The duration of oral penicillin and amoxicillin therapy is 10 days. A single intramuscular dose of benzathine penicillin or a benzathine–procaine penicillin G combination is effective and ensures compliance. Follow-up testing for GAS is unnecessary after completion of therapy and is not recommended unless symptoms recur.

Patients allergic to the penicillins can be treated with a 10-day course of a narrow-spectrum, first-generation cephalosporin (cephalexin or cefadroxil) if the previous reaction to penicillin was not an immediate, type I hypersensitivity reaction. Frequently, penicillin-allergic patients are treated for 10 days with erythromycin, clarithromycin, or clindamycin, or for 5 days with azithromycin.

The increased use of macrolides and related antibiotics for a variety of infections, especially the azalide azithromycin, is associated with increased rates of resistance to these drugs among GAS in many

Table 430.4 Recommended Treatment for Acute Streptococcal Pharyngitis

MOST PATIENTS				
	WEIGHT <27 KG	**WEIGHT ≥27 KG**	**ROUTE**	**DURATION**
Amoxicillin	50 mg/kg once daily (maximum 1,000 mg)		Oral	10 days
Penicillin V	250 mg bid	500 mg bid	Oral	10 days
Benzathine penicillin G	600,000 units	1.2 million units	IM	Once
Benzathine penicillin G + procaine penicillin G	900,000 units + 300,000 units	900,000 units + 300,000 units	IM	Once
PENICILLIN-ALLERGIC PATIENTS				
	ORAL DOSE	**FREQUENCY**	**DURATION**	
Cephalosporins*	Varies with agent chosen		10 days	
Erythromycins				
Ethylsuccinate	40 mg/kg/day up to 1,000 mg/day	bid	10 days	
Estolate	20-40 mg/kg/day up to 1,000 mg/day	bid	10 days	
Clarithromycin	15 mg/kg/day up to 500 mg/day	bid	10 days	
Azithromycin†	12 mg/kg day 1; 6 mg/kg days 2-5	qd	5 days	
Clindamycin	20 mg/kg/day up to 1.8 g/day	tid	10 days	

*First-generation cephalosporins are preferred; dosage and frequency vary among agents. Do not use in patients with a history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.
†Maximum dose is 500 mg the first day and 250 mg subsequent days.

countries. Approximately 5% of GAS in the United States and more than 10% in Canada are macrolide-resistant (macrolide resistance includes azalide resistance), but there is considerable local variation in both countries. Rates are much higher in many European and Asian countries. Some macrolide-resistant GAS isolates are also resistant to clindamycin. Although not a major hindrance for treatment of pharyngitis, clindamycin resistance may be important in management of invasive GAS infections. The use of macrolides and related antibiotics should be restricted to patients who cannot safely receive a β-lactam drug for GAS pharyngitis. Tetracyclines, fluoroquinolones, or sulfonamides should *not* be used to treat GAS pharyngitis.

CHRONIC GROUP A STREPTOCOCCUS CARRIERS

Streptococcal carriers are patients who continue to harbor GAS in the pharynx despite appropriate antibiotic therapy or when they are well. They have little or no evidence of an inflammatory response to the organism. The pathogenesis of chronic carriage is not known; it is assuredly not related to penicillin resistance or nonadherence to therapy, and there is little direct evidence to support the concept of co-pathogenicity (presence of β-lactamase–producing organisms in the pharynx). Carriage generally poses little risk to patients and their contacts, but it can confound testing in subsequent episodes of sore throat. A child who is chronically colonized with GAS (streptococcal carrier) can have a positive test for GAS if it is obtained when the child is evaluated for pharyngitis that is actually caused by a viral infection. Patients with repeated test-positive pharyngitis create anxiety among their families and physicians. It is usually unnecessary to attempt to eliminate chronic carriage. Instead, evaluation and treatment of clinical pharyngitis should be undertaken without regard for chronic carriage, using clinical criteria to determine the need for testing, treating test-positive patients in routine fashion, and avoiding antibiotics in patients who have negative tests. This approach often requires considerable effort to reassure the patient and family that chronic carriage is not a significant health risk. Expert opinion suggests that eradication might be attempted in select circumstances: a community outbreak of ARF or APSGN; personal or family history of ARF; an outbreak of GAS pharyngitis in a closed or semiclosed community, nursing home, or healthcare facility; repeated episodes of symptomatic GAS pharyngitis in a family with ping pong spread among family members despite adequate therapy; when tonsillectomy is being considered because of chronic carriage or recurrent streptococcal pharyngitis; and extreme, unmanageable anxiety related to GAS carriage ("streptophobia") among family members. Clindamycin given by mouth for 10 days is effective therapy (20 mg/kg/day divided in three doses; adult dose 150-450 mg tid). Amoxicillin-clavulanate (40 mg amoxicillin/kg/day up to 2,000 mg amoxicillin/day divided tid for 10 days) and 4 days of oral rifampin (20 mg/kg/day up to 600 mg divided in two doses) plus either intramuscular benzathine penicillin given once or oral penicillin given for 10 days have also been used (rifampin is started on the first day of penicillin therapy).

RECURRENT PHARYNGITIS

True recurrent GAS pharyngitis can occur for several reasons: reinfection with the same M type if type-specific antibody has not developed, poor compliance with oral antibiotic therapy, macrolide resistance if a macrolide was used for treatment, and infection with a new M type. Unfortunately, determining the GAS M type in an acute infection is not available to the clinician. Treatment with intramuscular benzathine penicillin eliminates nonadherence to therapy. Apparent recurrences can represent pharyngitis of another cause in the presence of streptococcal carriage. Chronic GAS carriage is particularly likely if the illnesses are mild and otherwise atypical for GAS pharyngitis.

Tonsillectomy may lower the incidence of pharyngitis for 1-2 years among children with frequent episodes of documented pharyngitis (≥7 episodes in the previous year or ≥5 in each of the preceding 2 years, or ≥3 in each of the previous 3 years). However, the frequency of pharyngitis (GAS and non-GAS) generally declines over time without tonsillectomy. By 2 years posttonsillectomy, the incidence of pharyngitis in severely affected children is similar among those who have tonsillectomy and those who do not. Few children are so severely affected, and the limited clinical benefit of tonsillectomy for most must be balanced against the risks of anesthesia and surgery. *Undocumented history of recurrent pharyngitis is an inadequate basis for recommending tonsillectomy.*

Recurrent GAS pharyngitis is rarely, if ever, a sign of an immune disorder. However, recurrent pharyngitis can be part of a recurrent fever or autoinflammatory syndrome such as PFAPA syndrome. Prolonged

pharyngitis (>1 week) can occur in infectious mononucleosis and Lemierre syndrome, but it also suggests the possibility of another disorder such as neutropenia, a recurrent fever syndrome, or an autoimmune disease such as SLE or IBD. In such instances, pharyngitis would be one of a number of clinical findings that together should suggest the underlying diagnosis.

COMPLICATIONS AND PROGNOSIS

Viral respiratory tract infections can predispose to bacterial middle ear infections and bacterial sinusitis. The complications of GAS pharyngitis include local suppurative complications, such as parapharyngeal abscess, and subsequent nonsuppurative illnesses, such as ARF, APSGN, poststreptococcal reactive arthritis, and possibly pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS, sometimes referred to as *CANS* [childhood acute neuropsychiatric symptoms] or *PANS* [pediatric acute-onset neuropsychiatric syndrome], recognizing that many infections other than GAS may predispose to these syndromes).

PREVENTION

Vaccines intended to prevent infection with various viruses (e.g., RSV) and GAS are being developed. A recombinant multivalent GAS M-type vaccine uses the terminal portions of various M proteins to take advantage of their immunogenicity. Other GAS vaccines are based on more conserved epitopes in order to avoid the necessity of matching the vaccine with the M types prevalent in a community or target population. None of the investigational GAS vaccines are near licensing for use. A recent comprehensive study of the immune response to childhood GAS pharyngeal acquisition raises questions about how to best design effective vaccines. This is complicated by the variety of clinical scenarios and clinical syndromes associated with GAS and the need to determine the intended clinical benefit(s) of vaccination. Antimicrobial prophylaxis with daily oral penicillin prevents recurrent GAS infections but is recommended only to prevent recurrences of ARF.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 431

Tonsils and Adenoids

Karen B. Zur

The *Waldeyer ring* (the lymphoid tissue surrounding the opening of the oral and nasal cavities into the pharynx) comprises the palatine tonsils, the pharyngeal tonsil or adenoid, lymphoid tissue surrounding the eustachian tube orifice in the lateral walls of the nasopharynx, the lingual tonsil at the base of the tongue, and scattered lymphoid tissue throughout the remainder of the pharynx, particularly behind the posterior pharyngeal pillars and along the posterior pharyngeal wall. The *palatine tonsil* consists of lymphoid tissue located between the palatoglossal fold (anterior tonsillar pillar) and the palatopharyngeal fold (posterior tonsillar pillar). This lymphoid tissue is separated from the surrounding pharyngeal musculature by a thick fibrous capsule. The *adenoid* is a single aggregation of lymphoid tissue that occupies the space between the nasal septum and the posterior pharyngeal wall. A thin fibrous capsule separates it from the underlying structures; the adenoid does not contain the complex crypts that are found in the palatine tonsils, but rather more simple crypts. Lymphoid tissue at the base of the tongue forms the *lingual tonsil* that also contains simple tonsillar crypts.

NORMAL FUNCTION

Located at the opening of the pharynx to the external environment, the tonsils and adenoid are well situated to provide primary defense against foreign matter. The immunologic role of the tonsils and adenoids is to induce secretory immunity and to regulate the production of the secretory immunoglobulins. Deep crevices within tonsillar tissue form tonsillar crypts that are lined with squamous epithelium and host a concentration of lymphocytes at their bases. The lymphoid tissue of the Waldeyer ring is most immunologically active between 4 and 10 years of age, with a decrease after puberty. Adenotonsillar hypertrophy is greatest between ages 3 and 6 years; in most children tonsils begin to involute after age 8 years. No major immunologic deficiency has been demonstrated after removal of either or both of the tonsils and adenoid.

PATHOLOGY

Acute Infection

Most episodes of acute pharyngotonsillitis are caused by viruses (see Chapter 430). Group A β-hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx (see Chapter 229).

Chronic Infection

The tonsils and adenoids can be chronically infected by multiple microbes, which can include a high incidence of β-lactamase–producing organisms. Both aerobic species, such as streptococci and *Haemophilus influenzae,* and anaerobic species, such as *Peptostreptococcus, Prevotella,* and *Fusobacterium,* contribute. The tonsillar crypts can accumulate desquamated epithelial cells, lymphocytes, bacteria, and other debris, causing cryptic tonsillitis. With time, these cryptic plugs can calcify into tonsillar concretions or tonsilloliths. Biofilms appear to play a role in chronic inflammation of the tonsils.

Upper Airway Obstruction

Enlargement of the tonsils and/or adenoids is a major cause of upper airway obstruction in children. Airway obstruction in children is typically manifested in sleep-disordered breathing, including obstructive sleep apnea, obstructive sleep hypopnea, and upper airway resistance syndrome (see Chapter 31). Sleep-disordered breathing secondary to adenotonsillar hypertrophy is a cause of growth failure. Solid dysphagia can also be seen in this group of patients, with symptoms such as prolonged chewing, pocketing of solids in the mouth, choking or gagging when swallowing solids, and weight loss.

Tonsillar Neoplasm

Rapid enlargement of one tonsil is highly suggestive of a tonsillar malignancy, typically lymphoma, in children.

CLINICAL MANIFESTATIONS

Acute Infection

Symptoms of GABHS infection include odynophagia, dry throat, malaise, fever and chills, dysphagia, referred otalgia, headache, muscular aches, and enlarged cervical nodes. Signs include dry tongue, erythematous enlarged tonsils, tonsillar or pharyngeal exudate, palatine petechiae, and enlargement and tenderness of the jugulodigastric lymph nodes (Fig. 431.1; see Chapter 229).

Chronic Infection

Children with chronic or cryptic tonsillitis often present with halitosis, chronic sore throats, foreign-body sensation, or a history of expelling foul-tasting and foul-smelling cheesy lumps. Examination reveals tonsils of a range of sizes, often containing copious debris within the crypts. The offending organism is not usually GABHS.

Airway Obstruction

The diagnosis of airway obstruction (see Chapter 31) can frequently be made by history and physical examination. Daytime symptoms of airway obstruction secondary to adenotonsillar hypertrophy include chronic mouth breathing, nasal obstruction, hyponasal speech, hyposmia,

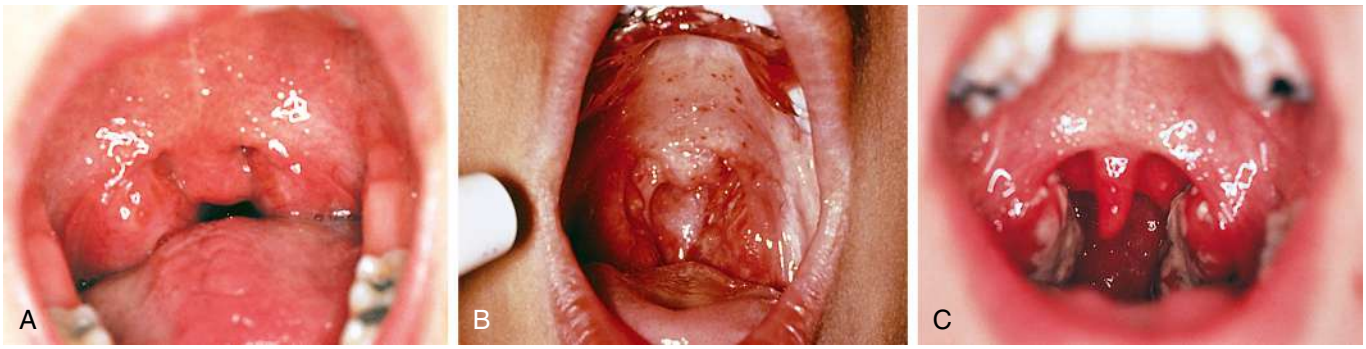

Fig. 431.1 Pharyngotonsillitis. This common condition has a number of causative pathogens and a wide spectrum of severity. **A,** The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens. **B,** This intense erythema, seen in association with acute tonsillar enlargement and palatal petechiae, is highly suggestive of group A β-streptococcal infection, though other pathogens can produce these findings. **C,** This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection. *(B courtesy Michael Sherlock, MD, Lutherville, MD. From Yellon RF, McBride TP, Davis HW. Otolaryngology. In Zitelli BJ, Davis HW, eds. Atlas of Pediatric Physical Diagnosis, 4th ed. Philadelphia: Mosby; 2002:852.)*

decreased appetite, poor school performance, hyperactivity, and, rarely, symptoms of right-sided heart failure. Nighttime symptoms consist of loud snoring, choking, gasping, frank apnea, restless sleep, abnormal sleep positions, sleep walking, night terrors, diaphoresis, enuresis, and sleep talking. Large tonsils are typically seen on examination, although the absolute size might not indicate the degree of obstruction. The size of the adenoid tissue can be demonstrated on a lateral neck radiograph or with flexible endoscopy. Other signs that can contribute to airway obstruction include the presence of a craniofacial syndrome or hypotonia.

These daytime and nocturnal comorbidities should be explored in patients with enlarged tonsils and/or adenoids. Sleep studies (polysomnograms, PSG) are not routinely recommended unless significant co-morbidities exist.

Tonsillar Neoplasm

The rapid unilateral enlargement of a tonsil, especially if accompanied by systemic signs of night sweats, fever, weight loss, and lymphadenopathy, is highly suggestive of a tonsillar malignancy. The diagnosis of a tonsillar malignancy should also be entertained if the tonsil appears grossly abnormal. Among 54,901 patients undergoing tonsillectomy, 54 malignancies were identified (0.087% prevalence); all but 6 malignancies had been suspected based on suspicious anatomic features preoperatively.

TREATMENT

Medical Management

The treatment of acute pharyngotonsillitis is discussed in Chapter 430 and antibiotic treatment of GABHS in Chapters 229 and 430. Because copathogens such as staphylococci or anaerobes can produce β-lactamase that can inactivate penicillin, the use of cephalosporins or clindamycin may be more efficacious in the treatment of *chronic* throat infections. A tonsillolith or debris may be expressed manually with either a cotton-tipped applicator, gargling after meals, or the use of a water jet.

Tonsillectomy

The American Academy of Otolaryngology (AAO)–Head and Neck Surgery *Taskforce on Clinical Practice Guidelines: Tonsillectomy in Children* most recently issued evidence-based guidelines in 2019 (Table 431.1, Fig. 431.2).

Tonsillectomy alone is most often performed for recurrent or chronic pharyngotonsillitis, and in young children is often accompanied by an adenoidectomy (see next section). Tonsillectomy has been shown to be effective in reducing the number of infections and the symptoms of chronic tonsillitis such as halitosis, persistent or recurrent sore throats, and recurrent cervical adenitis in severely affected patients. In resistant cases of cryptic tonsillitis, tonsillectomy may be curative. The 2019 guidelines recommend watchful waiting for recurrent throat infections if there have been <7 episodes in the past year, <5 episodes/yr in the past 2 years, or <3 episodes/yr in the past 3 years (see Table 431.1 and Fig. 431.2).

Table 431.1 Paradise Criteria for Tonsillectomy

CRITERION	DEFINITION
Minimum frequency of sore throat episodes	At least seven episodes in the previous year **OR** at least five episodes in each of the previous 2 years **OR** at least three episodes in each of the previous 3 years
Clinical features	Sore throat *plus* at least one of the following features qualifies as a counting episode: • Temperature of greater than 38.3°C (101°F) ***OR*** • Cervical adenopathy (tender lymph nodes or lymph node size >2 cm) ***OR*** • Tonsillar exudate ***OR*** • Culture positive for group A β-hemolytic streptococcus
Treatment	Antibiotics had been administered in the conventional dosage for proven or suspected streptococcal episodes
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record ***OR*** If the episodes are *not fully documented* in the patient record, subsequent observation by a physician of two episodes of throat infection with patterns of frequency and clinical features consistent with the initial history*

*Allows for tonsillectomy recommendation in patients who meet all but the documentation criterion. A 12-mo observation period is usually recommended before consideration of tonsillectomy because of the tendency to improve with time.
Adapted from Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children (update). *Otolaryngol Head Neck Surg.* 2019;160(1S):S1–S42, Table 5.

Rarely in children, tonsillectomy is indicated for biopsy of a unilaterally enlarged tonsil to exclude a neoplasm or to treat recurrent hemorrhage from superficial tonsillar blood vessels.

Tonsillectomy has not been shown to offer clinical benefit over conservative treatment in children with mild infectious symptoms 2 years after surgery unless other factors or comorbidities exist. However, the 2019 Clinical Practice Guidelines did recommend assessing for additional modifying factors that may favor the need for a tonsillectomy,

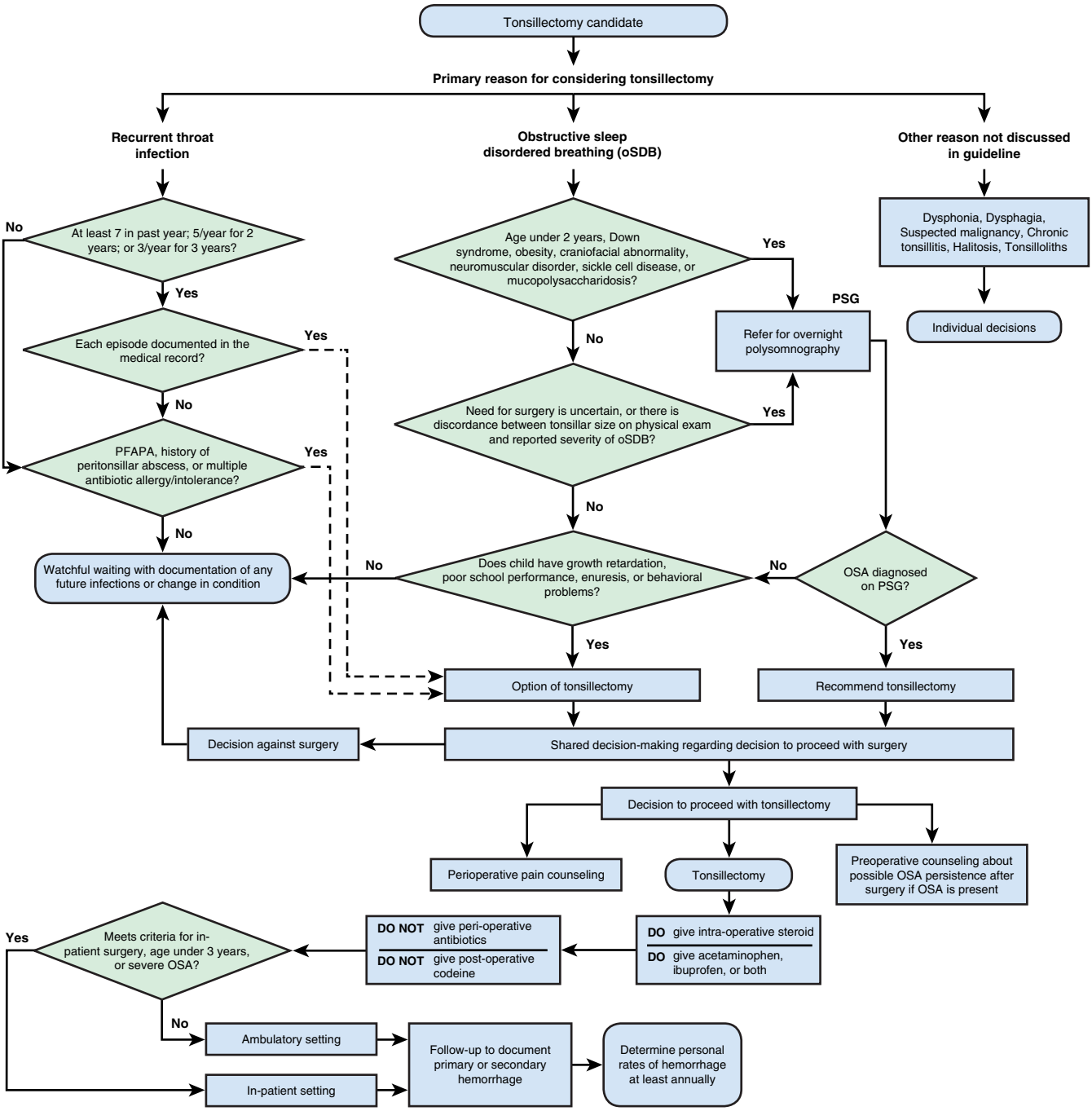

Fig. 431.2 Tonsillectomy in children: clinical practice algorithm. OSA, Obstructive sleep apnea; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; PSG, polysomnography. *(Modified from Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children, update. Otolaryngol Head Neck Surg. 2019;160:S1–S42, Fig. 2.)*

including intolerance or allergies to antibiotics, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis), or a history of more than one peritonsillar abscess (PTA).

Adenoidectomy

Adenoidectomy alone may be indicated for the treatment of chronic nasal infection (chronic adenoiditis), chronic sinus infections that have failed medical management, and recurrent bouts of acute otitis media, including those in children with tympanostomy tubes who suffer from recurrent otorrhea. Adenoidectomy may be helpful in children with chronic or recurrent otitis media with effusion. Adenoidectomy alone may be curative in the management of patients with nasal obstruction, chronic mouth breathing, and loud snoring suggesting sleep-disordered breathing. Adenoidectomy may also be indicated for children in whom upper airway obstruction is suspected of causing craniofacial or occlusive developmental abnormalities.

Tonsillectomy and Adenoidectomy

The criteria for a tonsillectomy and adenoidectomy (T&A) for recurrent infections are the same as those for tonsillectomy alone. The other major indication for performing both procedures together is upper airway obstruction secondary to adenotonsillar hypertrophy that results in sleep-disordered breathing, failure to thrive, craniofacial or occlusive developmental abnormalities, speech abnormalities, or, rarely, cor pulmonale. A high proportion of children with failure to thrive in the context of adenotonsillar hypertrophy resulting in sleep-disordered

Table 431.2 Role of PSG in Assessing High-Risk Populations Before Tonsillectomy for oSDB

ROLE OF PSG	RATIONALE
Avoid unnecessary or ineffective surgery in children with primarily nonobstructive events	Identify primarily nonobstructive events or central apnea that may not have been suspected before the study and may not benefit from surgery
Confirm the presence of obstructive events that would benefit from surgery	The increased morbidity of surgery in high-risk children requires diagnostic certainty before proceeding
Define the severity of oSDB to assist in preoperative planning	Children with severe OSA may require preoperative cardiac assessment, pulmonary consultation, anesthesia evaluation, or postoperative inpatient monitoring in an intensive care setting
Provide a baseline PSG for comparison after surgery	Persistent OSA despite surgery is more common in high-risk patients than in otherwise healthy children
Document the baseline severity of oSDB	High-risk patients are more prone to complications of surgery or anesthesia

OSA, Obstructive sleep apnea; oSDB, obstructive sleep-disordered breathing; PSG, polysomnography.
From Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children (update). *Otolaryngol Head Neck Surg.* 2019;160(IS):S1–S42, Table 6.

breathing experience significant growth acceleration after a T&A. Most children do not require a sleep study before surgery; however, in a high-risk population, polysomnography may help in the decision for or against surgery (Table 431.2). High risk factors include age under 2 years, Down syndrome, obesity, craniofacial abnormality, neuromuscular disorder, sickle cell disease, and mucopolysaccharidosis.

COMPLICATIONS

Poststreptococcal Glomerulonephritis and Acute Rheumatic Fever

The two major complications of untreated GABHS infection are poststreptococcal glomerulonephritis and acute rheumatic fever (see Chapters 559.4 and 229).

Peritonsillar Infection

Peritonsillar infection can occur as either cellulitis or a frank abscess in the region superior and lateral to the tonsillar capsule (see Chapter 432). These infections usually occur in children with a history of recurrent tonsillar infection and are polymicrobial, including both aerobes and anaerobes. Unilateral throat pain, referred otalgia, drooling, and trismus are presenting symptoms. The affected tonsil is displaced down and medially with swelling of the anterior tonsillar pillar and palate. The diagnosis of an abscess can be confirmed by CT or by needle aspiration, the contents of which should be sent for culture.

Retropharyngeal Space Infection

Infections in the retropharyngeal space develop in the lymph nodes that drain the oropharynx, nose, and nasopharynx (see Chapter 432).

Parapharyngeal Space Infection

Tonsillar infection can extend into the parapharyngeal space, causing symptoms of fever, neck pain and stiffness, and signs of swelling of the lateral pharyngeal wall and neck on the affected side. The diagnosis is confirmed by contrast medium–enhanced CT, and treatment includes intravenous antibiotics and external incision and drainage if an abscess is demonstrated on CT (see Chapter 432). Septic thrombophlebitis of the jugular vein, **Lemierre syndrome**, manifests with fever, toxicity, neck pain and stiffness, and respiratory distress caused by multiple septic pulmonary emboli and is a complication of a parapharyngeal space or odontogenic infection from *Fusobacterium necrophorum*. Concurrent Epstein-Barr virus mononucleosis (see Chapter 301) can be a predisposing event before the sudden onset of fever, chills, and respiratory distress in an adolescent patient. Treatment includes high-dose intravenous antibiotics (ampicillin-sulbactam, clindamycin, penicillin, or ciprofloxacin) and anticoagulation.

Table 431.3 Risks of Tonsillectomy or Adenoidectomy or Both

Cost
Risk of anesthetic events
- Malignant hyperthermia
- Cardiac arrhythmia
- Vocal cord trauma
- Aspiration with resulting bronchopulmonary obstruction or infection
- Postoperative nausea and vomiting (PONV)

Risk of miscellaneous surgical or postoperative complications
- Pain
- Dysphagia
- Hemorrhage
- Airway obstruction from edema of tongue, palate, or nasopharynx, or retropharyngeal hematoma
- Prolonged muscular paralysis
- Dehydration
- Palatopharyngeal insufficiency
- Facial edema
- Trauma: dental, larynx, vessels, pharyngeal wall, soft palate
- Laryngospasm
- Mediastinitis
- Cardiac arrest

Modified from Bluestone CD, ed. *Pediatric Otolaryngology*, 4th ed. Philadelphia: WB Saunders; 2003:1213.

Recurrent or Chronic Pharyngotonsillitis

See Chapter 430.

CHRONIC AIRWAY OBSTRUCTION

Although rare, children with chronic airway obstruction from enlarged tonsils and adenoids can present with cor pulmonale.

The effects of chronic airway obstruction and mouth breathing on facial growth remain a subject of controversy. Studies of chronic mouth breathing, both in humans and animals, have shown changes in facial development, including prolongation of the total anterior facial height and a tendency toward a retrognathic mandible, the so-called *adenoid facies*. Adenotonsillectomy can reverse some of these abnormalities. Other studies have disputed these findings.

Tonsillectomy and Adenoidectomy

The risks and potential benefits of surgery must be considered (Table 431.3). The mortality is low (~0.007%); most often associated with other complex medical conditions. Dehydration caused by odynophagia (painful swallowing) is not uncommon in the first postoperative week. The child is encouraged to drink liquids; however, early resumption of a solid diet is also recommended to help with the pain and return of oral function.

Postoperative pain needs to be managed, and opioid-free tonsillectomies are now recommended. Clinicians are encouraged to counsel the caregivers about the importance of hydration and managing postoperative pain with nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen and to reinforce this information on the day of surgery. The child is encouraged to hydrate, chew, and rest. Codeine is associated with excessive sedation and fatalities and *is not* recommended.

Bleeding can occur in the immediate postoperative period or be delayed after separation of the eschar. The risk of bleeding is variable among institutions, ranging in the literature from 0.1 to 7.5% and averaging around 4.2% in the first 10 days after surgery. Although recurrent bleeding is unlikely, a bleeding diathesis should be ruled out if it occurs.

The updated Clinical Guidelines for Tonsillectomy include a recommendation for a single intravenous dose of intraoperative dexamethasone (0.5 mg/kg), which decreases postoperative nausea and vomiting and reduces swelling. There is no evidence that use of dexamethasone in postoperative tonsillectomy patients results in an increased risk of postoperative bleeding, and it could be used as a supplement to the pain management regimen.

Routine use of antibiotics in the postoperative period is ineffective, and thus the AAO Clinical Practice Guidelines advise against its use.

Swelling of the tongue and uvula can lead to acute airway obstruction and globus sensation in the first few hours after surgery. Children with underlying hypotonia (trisomy 21) or craniofacial anomalies are at greater risk for suffering this complication.

Rare complications include anesthesia-related issues (malignant hyperthermia, arrhythmias, intubation trauma, aspiration), velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, torticollis, and, very rarely, death from uncontrolled bleeds.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 432

Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/ Abscess

Diane E. Pappas and Sarah R. Boggs

The *retropharyngeal* and the *lateral pharyngeal lymph nodes* that drain the mucosal surfaces of the upper airway and digestive tracts are located in the neck within the *retropharyngeal space* (located between the pharynx and the cervical vertebrae and extending down into the superior mediastinum) and the *lateral pharyngeal space* (bounded by the pharynx medially, the carotid sheath posteriorly, and the muscles of the styloid process laterally). The lymph nodes in these deep neck spaces communicate with each other, allowing bacteria from either cellulitis or node abscess to spread to other nodes. Infection of the nodes usually occurs as a result of extension from a localized infection of the oropharynx. A **retropharyngeal abscess** can also result from penetrating trauma to the oropharynx, dental infection, and vertebral osteomyelitis. Once infected, the nodes may progress through three stages: *cellulitis, phlegmon,* and *abscess.* Infection in the retropharyngeal and lateral pharyngeal spaces can result in airway compromise or posterior mediastinitis, making timely diagnosis important.

RETROPHARYNGEAL AND LATERAL PHARYNGEAL ABSCESS

Retropharyngeal abscess occurs most commonly in children younger than 3-4 years of age; as the retropharyngeal nodes involute after 5 years of age, infection in older children and adults is much less common. In the United States, abscess formation occurs most commonly in winter and early spring. Males are affected more often than females, and approximately two thirds of patients have a history of recent ear, nose, or throat infection.

Clinical manifestations of retropharyngeal abscess are nonspecific and include fever, irritability, decreased oral intake, and drooling. Neck stiffness, torticollis, and refusal to move the neck may also be present. The verbal child might complain of sore throat and neck pain. Other signs can include muffled voice, stridor, respiratory distress, or even obstructive sleep apnea. Physical examination can reveal bulging of the posterior pharyngeal wall, although this is present in <50% of infants with retropharyngeal abscess. Cervical lymphadenopathy may also be present. Lateral pharyngeal abscess commonly presents as fever, dysphagia, and a prominent bulge of the lateral pharyngeal wall, sometimes with medial displacement of the tonsil. The differential diagnosis includes acute epiglottitis and foreign body aspiration. In the young child with limited neck mobility, meningitis must also be considered. Other possibilities include lymphoma, hematoma, and vertebral osteomyelitis.

Incision and drainage and culture of an abscessed node provides the definitive diagnosis, but CT can be useful in identifying the presence of a retropharyngeal, lateral pharyngeal, or parapharyngeal abscess (Figs. 432.1 and 432.2). Deep neck infections can be accurately identified and localized with CT scans, but CT accurately identifies abscess formation in only 63% of patients. Soft tissue neck films taken during inspiration with the neck extended might show increased width or an air-fluid level in the retropharyngeal space. CT with contrast medium enhancement can reveal central lucency, ring enhancement, or scalloping of the walls of a lymph node. Scalloping of the lymph node wall is thought to be a late finding and predicts abscess formation.

Retropharyngeal and lateral pharyngeal infections are most often polymicrobial; the usual pathogens include group A streptococcus (see Chapter 229), oropharyngeal anaerobic bacteria (see Chapter 259), and *Staphylococcus aureus* (see Chapter 227.1). In children younger than age 2 years, there has been an increase in the incidence of retropharyngeal abscess, particularly with *S. aureus,* including methicillin-resistant strains. Other pathogens can include *Haemophilus influenzae, Klebsiella,* and *Mycobacterium avium-intracellulare.* When a retropharyngeal abscess is associated with cervical osteomyelitis, it may be secondary to retropharyngeal extension to the vertebral body (often polymicrobial) or a primary osteomyelitis with extension to the retropharyngeal space. In endemic areas and among patients at risk for tuberculosis, Pott disease should be considered (Fig. 432.3).

Treatment options include intravenous antibiotics with or without surgical drainage. Empiric antibiotic coverage should be guided by local susceptibility patterns for *S. aureus.* Initial therapy should include either ampicillin-sulbactam (50 mg ampicillin/kg every 6 hours, max 2000 mg ampicillin/dose) or clindamycin (15 mg/kg every 8 hours, max 600 mg/dose). For patients who are ill-appearing at presentation or who do not improve after 24-48 hours of antibiotic therapy, consideration should be given to the addition of either vancomycin or linezolid for coverage of methicillin-resistant *S. aureus* (MRSA). When narrowing antibiotic selection based on culture results, it is important to remember that these infections are typically polymicrobial and some pathogens, particularly oral anaerobes, may not be easily cultured.

Studies show that >50% of children with retropharyngeal or lateral pharyngeal abscess as identified by CT can be successfully treated without surgical drainage; the older the child, the more likely it is that antimicrobial treatment alone will be successful. Drainage is necessary in the patient with respiratory distress or failure to improve with intravenous antibiotic treatment. The typical treatment course is intravenous antibiotic therapy for several days until the patient has begun to improve, followed by a course of oral antibiotics for an additional 14 days. Amoxicillin-clavulanate (90 mg amoxicillin/kg/day, divided every 12 hours, max 2000 mg amoxicillin/dose) or clindamycin (13 mg/kg every 8 hours, max 450 mg/dose) are recommended oral regimens. Complications of retropharyngeal or lateral pharyngeal abscess include significant upper airway obstruction, rupture leading to

Bleeding can occur in the immediate postoperative period or be delayed after separation of the eschar. The risk of bleeding is variable among institutions, ranging in the literature from 0.1 to 7.5% and averaging around 4.2% in the first 10 days after surgery. Although recurrent bleeding is unlikely, a bleeding diathesis should be ruled out if it occurs.

The updated Clinical Guidelines for Tonsillectomy include a recommendation for a single intravenous dose of intraoperative dexamethasone (0.5 mg/kg), which decreases postoperative nausea and vomiting and reduces swelling. There is no evidence that use of dexamethasone in postoperative tonsillectomy patients results in an increased risk of postoperative bleeding, and it could be used as a supplement to the pain management regimen.

Routine use of antibiotics in the postoperative period is ineffective, and thus the AAO Clinical Practice Guidelines advise against its use.

Swelling of the tongue and uvula can lead to acute airway obstruction and globus sensation in the first few hours after surgery. Children with underlying hypotonia (trisomy 21) or craniofacial anomalies are at greater risk for suffering this complication.

Rare complications include anesthesia-related issues (malignant hyperthermia, arrhythmias, intubation trauma, aspiration), velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, torticollis, and, very rarely, death from uncontrolled bleeds.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 432

Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/ Abscess

Diane E. Pappas and Sarah R. Boggs

The *retropharyngeal* and the *lateral pharyngeal lymph nodes* that drain the mucosal surfaces of the upper airway and digestive tracts are located in the neck within the *retropharyngeal space* (located between the pharynx and the cervical vertebrae and extending down into the superior mediastinum) and the *lateral pharyngeal space* (bounded by the pharynx medially, the carotid sheath posteriorly, and the muscles of the styloid process laterally). The lymph nodes in these deep neck spaces communicate with each other, allowing bacteria from either cellulitis or node abscess to spread to other nodes. Infection of the nodes usually occurs as a result of extension from a localized infection of the oropharynx. A **retropharyngeal abscess** can also result from penetrating trauma to the oropharynx, dental infection, and vertebral osteomyelitis. Once infected, the nodes may progress through three stages: *cellulitis, phlegmon,* and *abscess.* Infection in the retropharyngeal and lateral pharyngeal spaces can result in airway compromise or posterior mediastinitis, making timely diagnosis important.

RETROPHARYNGEAL AND LATERAL PHARYNGEAL ABSCESS

Retropharyngeal abscess occurs most commonly in children younger than 3-4 years of age; as the retropharyngeal nodes involute after 5 years of age, infection in older children and adults is much less common. In the United States, abscess formation occurs most commonly in winter and early spring. Males are affected more often than females, and approximately two thirds of patients have a history of recent ear, nose, or throat infection.

Clinical manifestations of retropharyngeal abscess are nonspecific and include fever, irritability, decreased oral intake, and drooling. Neck stiffness, torticollis, and refusal to move the neck may also be present. The verbal child might complain of sore throat and neck pain. Other signs can include muffled voice, stridor, respiratory distress, or even obstructive sleep apnea. Physical examination can reveal bulging of the posterior pharyngeal wall, although this is present in <50% of infants with retropharyngeal abscess. Cervical lymphadenopathy may also be present. Lateral pharyngeal abscess commonly presents as fever, dysphagia, and a prominent bulge of the lateral pharyngeal wall, sometimes with medial displacement of the tonsil. The differential diagnosis includes acute epiglottitis and foreign body aspiration. In the young child with limited neck mobility, meningitis must also be considered. Other possibilities include lymphoma, hematoma, and vertebral osteomyelitis.

Incision and drainage and culture of an abscessed node provides the definitive diagnosis, but CT can be useful in identifying the presence of a retropharyngeal, lateral pharyngeal, or parapharyngeal abscess (Figs. 432.1 and 432.2). Deep neck infections can be accurately identified and localized with CT scans, but CT accurately identifies abscess formation in only 63% of patients. Soft tissue neck films taken during inspiration with the neck extended might show increased width or an air-fluid level in the retropharyngeal space. CT with contrast medium enhancement can reveal central lucency, ring enhancement, or scalloping of the walls of a lymph node. Scalloping of the lymph node wall is thought to be a late finding and predicts abscess formation.

Retropharyngeal and lateral pharyngeal infections are most often polymicrobial; the usual pathogens include group A streptococcus (see Chapter 229), oropharyngeal anaerobic bacteria (see Chapter 259), and *Staphylococcus aureus* (see Chapter 227.1). In children younger than age 2 years, there has been an increase in the incidence of retropharyngeal abscess, particularly with *S. aureus,* including methicillin-resistant strains. Other pathogens can include *Haemophilus influenzae, Klebsiella,* and *Mycobacterium avium-intracellulare.* When a retropharyngeal abscess is associated with cervical osteomyelitis, it may be secondary to retropharyngeal extension to the vertebral body (often polymicrobial) or a primary osteomyelitis with extension to the retropharyngeal space. In endemic areas and among patients at risk for tuberculosis, Pott disease should be considered (Fig. 432.3).

Treatment options include intravenous antibiotics with or without surgical drainage. Empiric antibiotic coverage should be guided by local susceptibility patterns for *S. aureus.* Initial therapy should include either ampicillin-sulbactam (50 mg ampicillin/kg every 6 hours, max 2000 mg ampicillin/dose) or clindamycin (15 mg/kg every 8 hours, max 600 mg/dose). For patients who are ill-appearing at presentation or who do not improve after 24-48 hours of antibiotic therapy, consideration should be given to the addition of either vancomycin or linezolid for coverage of methicillin-resistant *S. aureus* (MRSA). When narrowing antibiotic selection based on culture results, it is important to remember that these infections are typically polymicrobial and some pathogens, particularly oral anaerobes, may not be easily cultured.

Studies show that >50% of children with retropharyngeal or lateral pharyngeal abscess as identified by CT can be successfully treated without surgical drainage; the older the child, the more likely it is that antimicrobial treatment alone will be successful. Drainage is necessary in the patient with respiratory distress or failure to improve with intravenous antibiotic treatment. The typical treatment course is intravenous antibiotic therapy for several days until the patient has begun to improve, followed by a course of oral antibiotics for an additional 14 days. Amoxicillin-clavulanate (90 mg amoxicillin/kg/day, divided every 12 hours, max 2000 mg amoxicillin/dose) or clindamycin (13 mg/kg every 8 hours, max 450 mg/dose) are recommended oral regimens. Complications of retropharyngeal or lateral pharyngeal abscess include significant upper airway obstruction, rupture leading to

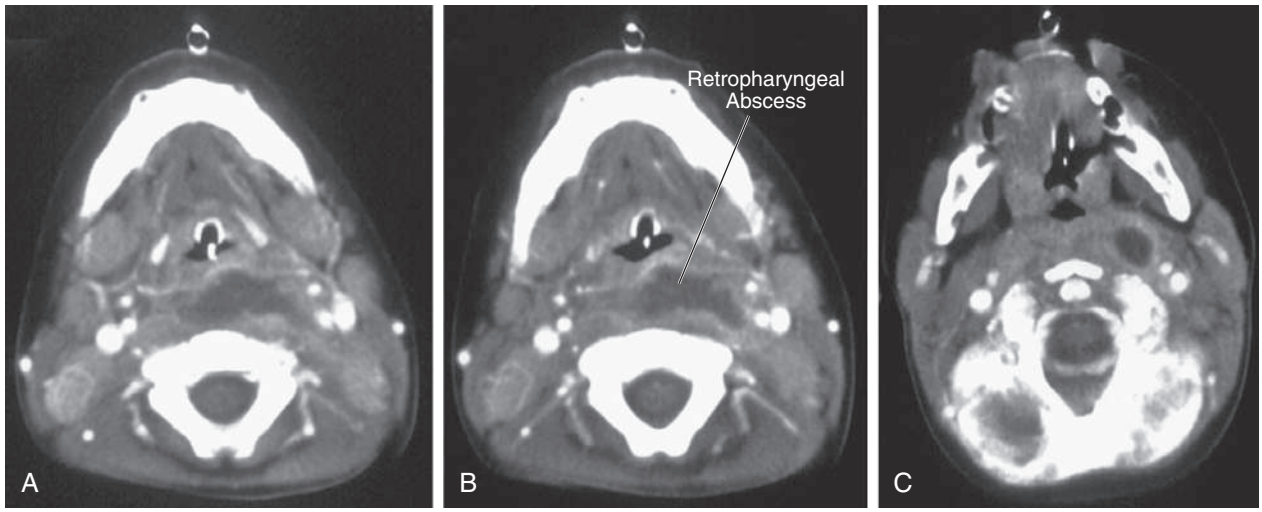

Fig. 432.1 CT of retropharyngeal abscess. **A,** CT image at level of epiglottis. **B,** Sequential CT slice exhibiting ring-enhancing lesion. **C,** Further sequential CT slice demonstrating inferior extent of lesion. *(From Philpott CM, Selvadurai D, Banerjee AR. Paediatric retropharyngeal abscess. J Laryngol Otol. 2004;118:925.)*

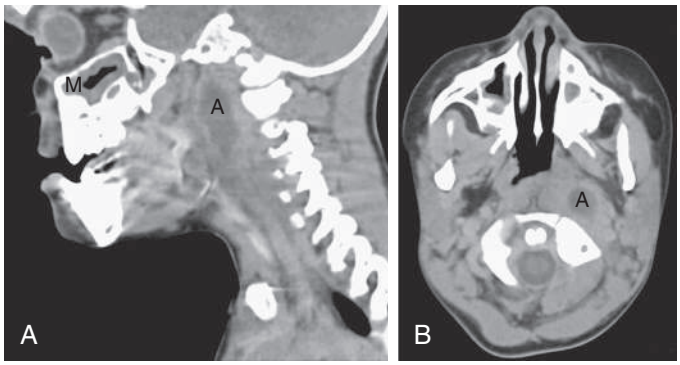

Fig. 432.2 CT of parapharyngeal abscess in a 3-yr-old child. **A,** Sagittal section demonstrating parapharyngeal abscess *(A)* and mucosal swelling *(M)* in the maxillary sinus. **B,** Coronal section of parapharyngeal abscess *(A)*.

aspiration pneumonia, and extension to the mediastinum with resultant mediastinitis. Thrombophlebitis of the internal jugular vein and erosion of the carotid artery sheath can also occur.

An uncommon but characteristic infection of the parapharyngeal space is **Lemierre disease**, in which infection from the oropharynx extends to cause septic thrombophlebitis of the internal jugular vein and embolic abscesses in the lungs (Fig. 432.4). The causative pathogen is *Fusobacterium necrophorum,* an anaerobic bacterial constituent of the oropharyngeal flora. The typical presentation is that of a previously healthy adolescent or young adult with a history of recent pharyngitis who becomes acutely ill with fever and septic pulmonary emboli producing hypoxia, tachypnea, and respiratory distress. Other upper respiratory infections (parotitis, otitis media, mastoiditis, sinusitis, and dental infections) are much less likely to precipitate Lemierre disease. There is a known association with recent Epstein-Barr infection.

Chest x-ray or CT demonstrates multiple cavitary nodules, often bilateral and often accompanied by pleural effusion. Blood culture may be positive. Treatment involves prolonged intravenous antibiotic therapy with either piperacillin-tazobactam, imipenem or meropenem, or ceftriaxone *plus* metronidazole; vancomycin should be added in areas with a high prevalence of MRSA. Surgical drainage of extrapulmonary metastatic abscesses may occasionally be necessary (see Chapters 430 and 431).

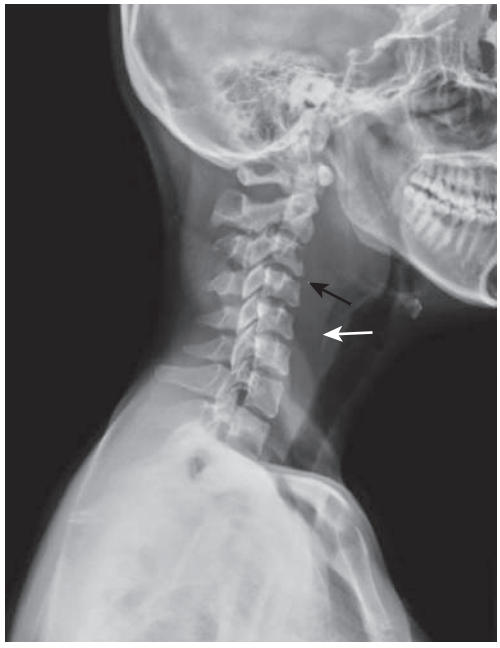

Fig. 432.3 Pott disease. Cervical spine radiography, lateral view, showed prevertebral soft tissue anterior to the C1-C7 level *(white arrow),* focal destruction of the C3 vertebra *(black arrow),* and straightening of the cervical spine. *(Modified from Hsu HE, Chen CY. Tuberculous retropharyngeal abscess with Pott disease and tuberculous abscess of the chest wall – a case report. Medicine. 2019;98:e16280, Fig. 1A.)*

PERITONSILLAR CELLULITIS AND/OR ABSCESS

Peritonsillar cellulitis and/or abscess, which is relatively common compared to the deep neck infections, is caused by bacterial invasion through the capsule of the tonsil, leading to cellulitis and/or abscess formation in the surrounding tissues. The typical patient with a peritonsillar abscess is an adolescent with a recent history of acute pharyngotonsillitis. Clinical manifestations include sore throat, fever, trismus, muffled or garbled voice, and dysphagia. Physical examination reveals an asymmetric tonsillar bulge with displacement of the uvula. An asymmetric tonsillar bulge is diagnostic, but it may be poorly visualized because of trismus. CT is helpful for revealing the abscess, but small studies in adults and children have demonstrated that ultrasound may be used to differentiate



Fig. 432.4 CT of Lemierre disease. **A**, CT demonstrating the nodular appearance of pulmonary infiltrates *(arrow)*. **B**, CT of the neck demonstrating thrombosis of the right internal jugular vein *(arrow)*. *(From Plymyer MR, Zoccola DC, Tallarita G. An 18 year old man presenting with sepsis following a recent pharyngeal infection. Arch Pathol Lab Med. 2004;128:813. Copyright 2004. College of American Pathologists.)*

peritonsillar abscess from peritonsillar cellulitis and avoids radiation exposure, as well as the need for sedation that CT often necessitates in children. Group A streptococci and mixed oropharyngeal anaerobes are the most common pathogens, with more than four bacterial isolates per abscess typically recovered by needle aspiration.

A study in Britain evaluating the impact of outpatient management recommendations (increased outpatient or short-stay management, drainage under local anesthetic, prompt discharge) found that admissions were reduced by over 50% and aspiration under local anesthetic increased with no change in readmission or mortality rates. Similarly, a U.S. study found that initial outpatient management is associated with greater use of antibiotics alone and less frequent use of incision and drainage; the recurrence rate was the same regardless of inpatient or outpatient management. These studies suggest that initial outpatient management of peritonsillar abscess in pediatric patients should be considered, especially for older patients who have mild to moderate symptoms; inpatient therapy is indicated for younger patients and those presenting with more severe illness, including trismus and odynophagia. Either amoxicillin-clavulanate or clindamycin would be an acceptable oral regimen.

Inpatient therapy is indicated for younger patients and for those presenting with more severe illness, including significant trismus and odynophagia. If outpatient management with antibiotics alone is unsuccessful or if inpatient management is indicated initially, treatment consists of surgical drainage or needle aspiration along with intravenous antibiotic therapy. As with retropharyngeal abscesses, empiric antibiotic therapy should include either ampicillin-sulbactam or clindamycin, with the addition of vancomycin in patients who are not improving or in areas with high rates of MRSA.

Surgical drainage may be accomplished through needle aspiration, incision and drainage, or tonsillectomy. Needle aspiration can involve aspiration of the superior, middle, and inferior aspects of the tonsil to locate the abscess. Intraoral ultrasound can be used to diagnose and guide needle aspiration of a peritonsillar abscess. General anesthesia may be required for the uncooperative patient. Approximately 95% of peritonsillar abscesses resolve after needle aspiration and antibiotic therapy. A small percentage of these patients require a repeat needle aspiration. The 5% with infections that fail to resolve after needle aspiration require incision and drainage. Tonsillectomy should be considered if there is failure to improve within 24 hours of antibiotic therapy and needle aspiration, history of recurrent peritonsillar abscess or recurrent tonsillitis, or complications from peritonsillar abscess. The feared, albeit rare, complication is rupture of the abscess, with resultant aspiration pneumonitis. There is a 10% recurrence risk for peritonsillar abscess.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 433

Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

Kristine Knuti Rodrigues and Genie E. Roosevelt

Airway resistance is inversely proportional to the fourth power of the radius (see Chapter 421). Because the lumen of an infant's or child's airway is narrow, minor reductions in cross-sectional area resulting from mucosal edema or other inflammatory processes cause an exponential increase in airway resistance and a significant increase in the work of breathing. The larynx is composed of four major cartilages (epiglottic, arytenoid, thyroid, and cricoid cartilages, ordered from superior to inferior) and the soft tissues that surround them. The cricoid cartilage encircles the airway just below the vocal cords and defines the narrowest portion of the upper airway in children younger than 10 years of age.

Inflammation involving the vocal cords and structures inferior to the cords is called **laryngitis**, **laryngotracheitis**, or **laryngotracheobronchitis**, and inflammation of the structures superior to the cords (i.e., arytenoids, aryepiglottic folds ["false cords"], epiglottis) is called **supraglottitis**. The term **croup** refers to a heterogeneous group of mainly acute and infectious processes that are characterized by a barklike or metallic/brassy cough and may be associated with hoarseness, inspiratory stridor, and respiratory distress. **Stridor** is a harsh, high-pitched respiratory sound that is usually inspiratory but can be biphasic and is produced by turbulent airflow; it is not a diagnosis, but a sign of upper airway obstruction (see Chapter 421). Croup typically affects the larynx, trachea, and bronchi. When the involvement of the larynx is sufficient to produce symptoms, these symptoms dominate the clinical picture more so than the tracheal and bronchial signs. A distinction has been made between spasmodic or recurrent croup and laryngotracheobronchitis. Some clinicians believe that spasmodic croup might have an allergic component and improves rapidly without treatment, whereas laryngotracheobronchitis is always associated with a viral infection of the respiratory tract. Others believe that the signs and symptoms are similar enough to consider them within the spectrum of a single disease because studies have documented viral etiologies in both acute and recurrent croup.

433.1 Infectious Upper Airway Obstruction

Kristine Knuti Rodrigues and Genie E. Roosevelt

With the exceptions of diphtheria (see Chapter 233), bacterial tracheitis, and epiglottitis, most other acute infections of the upper airway are caused by viruses. The parainfluenza viruses (types 1, 2, and 3; see Chapter 306) account for approximately 75% of cases; other viruses associated with croup include influenza A and B, adenovirus, respiratory syncytial virus, COVID-19, and measles. Influenza A is associated with severe laryngotracheobronchitis. *Mycoplasma pneumoniae* has rarely been isolated from children with croup and causes mild disease (see Chapter 269). Most patients with croup are between the ages of 3 months and 5 years, with the peak in the second year of life. The incidence of croup is higher in males. It occurs most commonly in the late fall and winter but can occur throughout the year. Approximately 15% of patients have a strong family history of croup. Recurrences are frequent from 3 to 6 years of age and decrease with growth of the airway. Recurrent croup is defined as two or more crouplike episodes. Patients with recurrent croup have a higher incidence of asthma, allergies, and gastroesophageal reflux; less than 9% of patients with recurrent croup demonstrate clinically significant findings on bronchoscopy (e.g., subglottic stenosis, reflux changes, bronchomalacia/tracheomalacia).

In the past, *Haemophilus influenzae* type b was the most commonly identified etiology of **acute epiglottitis**. Since the widespread use of the *H. influenzae* type b vaccine, invasive disease caused by *H. influenzae* type b in pediatric patients has been reduced by 99% (see Chapter 240). Therefore other agents, such as *Streptococcus pyogenes, Streptococcus pneumoniae,* nontypable *H. influenzae,* and *Staphylococcus aureus,* represent a larger portion of pediatric cases of epiglottitis in vaccinated children. In the prevaccine era, the typical patient with epiglottitis caused by *H. influenzae* type b was 2-4 years of age, although cases were seen in the first year of life and in patients as old as 7 years of age. Currently, the most common presentation of epiglottitis is an adult with a sore throat, although cases still do occur in underimmunized children or with other less common bacteria; vaccine failures have rarely been reported.

CLINICAL MANIFESTATIONS

Croup (Laryngotracheobronchitis)

Viruses typically cause croup, the most common form of acute upper respiratory obstruction. The term *laryngotracheobronchitis* refers to viral infection of the glottic and subglottic regions. Some clinicians use the term *laryngotracheitis* for the most common and most typical form of croup and reserve the term *laryngotracheobronchitis* for the more severe form that is considered an extension of laryngotracheitis associated with bacterial superinfection that occurs 5-7 days into the clinical course.

Most patients have an upper respiratory tract infection with some combination of rhinorrhea, pharyngitis, mild cough, and low-grade fever for 1-3 days before the signs and symptoms of upper airway obstruction become apparent. The child then develops the characteristic barking cough, hoarseness, and inspiratory stridor. The low-grade fever can persist, although temperatures may occasionally reach 39–40°C (102.2–104°F); some children are afebrile. Symptoms are characteristically worse at night and often recur with decreasing intensity for several days and resolve completely within a week. Agitation and crying greatly aggravate the symptoms and signs. The child may prefer to sit up in bed or be held upright. Other family members might have mild respiratory illnesses with laryngitis. Most young patients with croup progress only as far as stridor and slight dyspnea before they start to recover.

Physical examination can reveal a hoarse voice, coryza, normal to moderately inflamed pharynx, and a slightly increased respiratory rate. Patients vary substantially in their degrees of respiratory distress. Rarely, the upper airway obstruction progresses and is accompanied by an increasing respiratory rate; nasal flaring; suprasternal, infrasternal, and intercostal retractions; and continuous stridor. Croup is a disease of the upper airway, and alveolar gas exchange is usually normal.

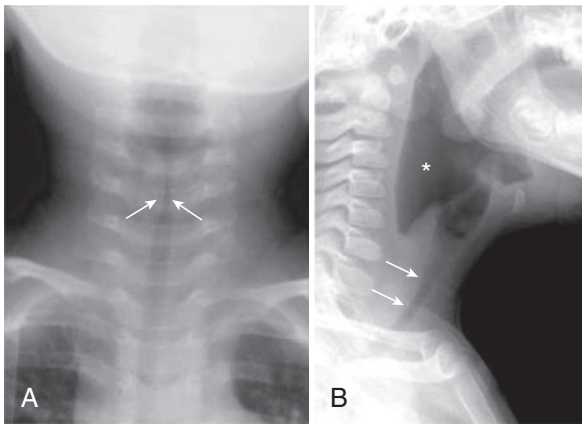

Fig. 433.1 Croup. **A,** Frontal soft tissue neck radiograph demonstrates a "steeple" appearance of the subglottic trachea *(arrows).* **B,** Lateral soft tissue neck radiograph in another patient shows a dilated hypopharynx *(asterisk),* along with haziness and narrowing of the subglottic region *(arrows). (From Laya BF, Lee EY. Upper airway disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 51.8, p. 481.)*

Hypoxia and low oxygen saturation are seen only when complete airway obstruction is imminent. *The child who is hypoxic, cyanotic, pale, or obtunded needs immediate airway management.* Occasionally, the pattern of severe laryngotracheobronchitis is difficult to differentiate from epiglottitis, despite the usually more acute onset and rapid course of the latter.

Croup is a clinical diagnosis and does not require a radiograph of the neck. Radiographs of the neck can show the typical subglottic narrowing, or steeple sign, of croup on the posteroanterior view (Fig. 433.1). However, the steeple sign may be absent in patients with croup, may be present in patients without croup as a normal variant, and may rarely be present in patients with epiglottitis. The radiographs do not correlate well with disease severity. Radiographs should be considered only after airway stabilization in children who have an atypical presentation or clinical course. Radiographs may be helpful in distinguishing between severe laryngotracheobronchitis and epiglottitis, but airway management should always take priority.

Acute Epiglottitis (Supraglottitis)

This now rare, but still dramatic and potentially lethal, condition is characterized by an acute rapidly progressive and potentially fulminating course of high fever, sore throat, dyspnea, and rapidly progressing respiratory obstruction. The degree of respiratory distress at presentation is variable. The initial lack of respiratory distress can deceive the unwary clinician; respiratory distress can also be the first manifestation. Often, the otherwise healthy child suddenly develops a sore throat and fever. Within a matter of hours, the patient appears toxic, swallowing is difficult, and breathing is labored. Drooling is usually present, and the neck is hyperextended in an attempt to maintain the airway. The child may assume the tripod position, sitting upright and leaning forward with the chin up and mouth open while bracing on the arms. A brief period of air hunger with restlessness may be followed by rapidly increasing cyanosis and coma. Stridor is a late finding and suggests near-complete airway obstruction. Complete obstruction of the airway and death can ensue unless adequate treatment is provided. *The barking cough typical of croup is rare.* Usually, no other family members are ill with acute respiratory symptoms.

The diagnosis requires visualization under controlled circumstances of a large, cherry red, swollen epiglottis by laryngoscopy. Occasionally, the other supraglottic structures, especially the aryepiglottic folds, are more involved than the epiglottis itself. In a patient in whom the

diagnosis is certain or probable based on clinical grounds, laryngoscopy should be performed expeditiously in a controlled environment such as an operating room or intensive care unit. Anxiety-provoking interventions such as phlebotomy, intravenous line placement, placing the child supine, or direct inspection of the oral cavity should be avoided until the airway is secure. If epiglottitis is thought to be possible but not certain in a patient with acute upper airway obstruction, the patient may first undergo lateral radiographs of the upper airway. Classic radiographs of a child who has epiglottitis show the thumb sign (Fig. 433.2). Proper positioning of the patient for the lateral neck radiograph is crucial to avoid some of the pitfalls associated with interpretation of the film. Adequate hyperextension of the head and neck is necessary. In addition, the epiglottis can appear to be round if the lateral neck is taken at an oblique angle. If the concern for epiglottitis still exists after the radiographs, direct visualization should be performed. A physician skilled in airway management and use of intubation equipment should accompany patients with suspected epiglottitis at all times. An older cooperative child might voluntarily open the mouth wide enough for a direct view of the inflamed epiglottis.

Establishing an airway by endotracheal or nasotracheal intubation or, less often, by tracheostomy is indicated in patients with epiglottitis, regardless of the degree of apparent respiratory distress, because as many as 6% of children with epiglottitis without an artificial airway die compared with <1% of those with an artificial airway. No clinical features have been recognized that predict mortality. Pulmonary edema can be associated with acute airway obstruction. The duration of intubation depends on the clinical course of the patient and the duration of epiglottic swelling, as determined by frequent examination using direct laryngoscopy or flexible fiberoptic laryngoscopy. In general, children with acute epiglottitis are intubated for 2-3 days, because the response to antibiotics is usually rapid. Most patients have concomitant bacteremia; occasionally, other infections are present, such as pneumonia, cervical adenopathy, or otitis media. Meningitis, arthritis, and other invasive infections with *H. influenzae* type b are rarely found in conjunction with epiglottitis (but bacteremia is present).

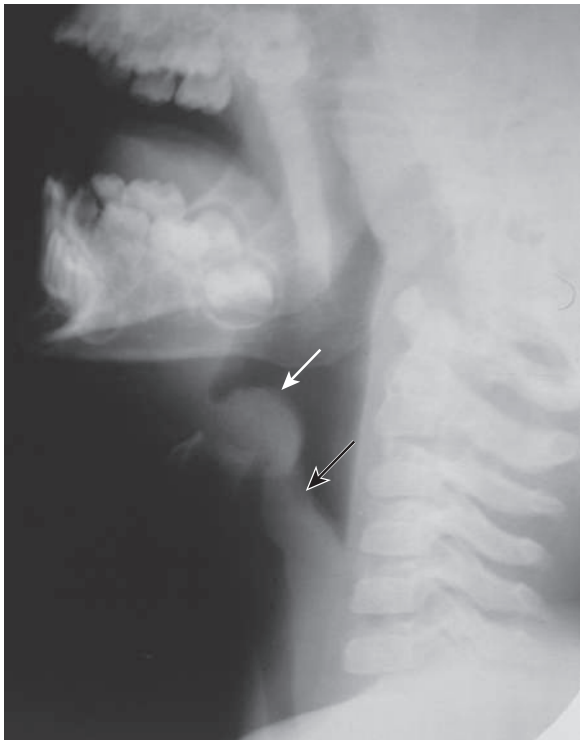

Fig. 433.2 Epiglottitis in a 5-yr-old male with respiratory distress and drooling. A lateral soft tissue neck radiograph shows a markedly thickened epiglottis *(white arrow)*, which is referred to as the "thumb" sign. The aryepiglottic folds *(black arrow)* also are thickened. *(From Laya BF, Lee EY. Upper airway disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 51.2, p. 477.)*

Acute Infectious Laryngitis

Laryngitis is a common illness. Viruses cause most cases; diphtheria is an exception but is extremely rare in highly developed, industrialized countries (see Chapter 233). The onset is usually characterized by an upper respiratory tract infection during which sore throat, cough, and hoarseness appear. The illness is generally mild; respiratory distress is unusual except in the young infant. Hoarseness and loss of voice may be out of proportion to systemic signs and symptoms. The physical examination is usually not remarkable except for evidence of pharyngeal inflammation. Inflammatory edema of the vocal cords and subglottic tissue may be demonstrated laryngoscopically. The principal site of obstruction is usually the subglottic area.

Spasmodic Croup

Spasmodic croup occurs most often in children 1-3 years of age and is clinically similar to acute laryngotracheobronchitis, except that the history of a viral prodrome and fever in the patient and family are often absent. The cause is viral in some cases, but allergic and other factors may also contribute.

Occurring most commonly in the evening or nighttime, spasmodic croup begins with a sudden onset that may be preceded by mild to moderate coryza and hoarseness. The child awakens with a characteristic barking, metallic/brassy cough, noisy inspiration, and respiratory distress and appears anxious and frightened. The patient is usually afebrile. The severity of the symptoms generally diminishes within several hours, and the following day, the patient often appears well except for slight hoarseness and cough. Similar, but usually less severe, attacks without extreme respiratory distress can occur for another night or two. Such episodes often recur several times. Spasmodic croup might represent more of an allergic reaction to viral antigens than direct infection, although the pathogenesis is unknown.

DIFFERENTIAL DIAGNOSIS

These four syndromes must be differentiated from one another and from a variety of other entities that can present as upper airway obstruction. **Bacterial tracheitis** is the most important differential diagnostic consideration and has a high risk of airway obstruction. Diphtheritic croup is extremely rare in North America and Europe, although a major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990 from the lack of routine immunization. Early symptoms of **diphtheria** include malaise, sore throat, anorexia, and low-grade fever. Within 2-3 days, pharyngeal examination reveals the typical gray-white membrane, which can vary in size from covering a small patch on the tonsils to covering most of the soft palate. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. The course is usually insidious, but respiratory obstruction can occur suddenly. **Measles** croup almost always coincides with the full manifestations of systemic disease, and the course may be fulminant (see Chapter 293).

Sudden onset of respiratory obstruction can be caused by aspiration of a **foreign body** (see Chapter 435). The child is usually 6 months to 3 years of age. Choking and coughing occur suddenly, usually without prodromal signs of infection, although children with a viral infection can also aspirate a foreign body. A **retropharyngeal** or **peritonsillar abscess** can mimic respiratory obstruction (see Chapter 432). CT scans of the upper airway are helpful in evaluating for possible retropharyngeal abscess. A peritonsillar abscess is a clinical diagnosis. Other possible causes of upper airway obstruction include extrinsic compression of the airway (laryngeal web, vascular ring) and intraluminal obstruction from masses (laryngeal papilloma, subglottic hemangioma); these tend to have chronic or recurrent symptoms.

Upper airway obstruction is occasionally associated with **angioedema** of the subglottic areas as part of anaphylaxis and generalized allergic reactions, edema after endotracheal intubation for either general anesthesia or respiratory failure, hypocalcemic tetany, infectious mononucleosis, trauma, and tumors or malformations of the larynx. A

crouplike cough may be an early sign of asthma. Vocal cord dysfunction can also occur. Epiglottitis, with the characteristic manifestations of drooling or dysphagia and stridor, can also result from the accidental ingestion of very hot liquid.

COMPLICATIONS

Complications occur in approximately 15% of patients with viral croup. The most common is extension of the infectious process to involve other regions of the respiratory tract, such as the middle ear, the terminal bronchioles, or the pulmonary parenchyma. Bacterial tracheitis may be a complication of viral croup rather than a distinct disease. If associated with toxin-producing *S. aureus* or *S. pyogenes,* toxic shock syndrome can develop. **Bacterial tracheitis** may have a biphasic illness, with the second phase after a crouplike illness associated with high fever, toxicity, and airway obstruction. Alternatively, the onset of tracheitis occurs without a second phase and appears as a continuation of the initial crouplike illness, but with higher fever and worsening respiratory distress rather than the usual recovery after 2-3 days of viral croup. Pneumonia, cervical lymphadenitis, otitis media, or, rarely, meningitis or septic arthritis can occur during the course of epiglottitis. Pneumomediastinum and pneumothorax are the most common complications of tracheotomy.

TREATMENT

The mainstay of treatment for children with **croup** is airway management and treatment of hypoxemia. Treatment of the respiratory distress should take priority over any testing. Most children with either acute spasmodic croup or infectious croup can be managed safely at home. Despite the observation that cold night air is beneficial, a Cochrane review has found no evidence supporting the use of cool mist in the emergency department for the treatment of croup.

Nebulized racemic epinephrine is the established treatment for moderate and severe croup. The mechanism of action is believed to be constriction of the precapillary arterioles through the β-adrenergic receptors, causing fluid resorption from the interstitial space and a decrease in the laryngeal mucosal edema. Traditionally, racemic epinephrine, a 1:1 mixture of the D- and L-isomers of epinephrine, has been administered. A dose of 0.25-0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline can be used as often as every 20 minutes. Racemic epinephrine was initially chosen over the more active and more readily available L-epinephrine to minimize anticipated cardiovascular side effects such as tachycardia and hypertension. Current evidence does not favor racemic epinephrine over L-epinephrine (5 mL of 1:1,000 solution) in terms of efficacy or safety.

The indications for the administration of nebulized epinephrine include moderate to severe stridor at rest, the possible need for intubation, respiratory distress, and/or hypoxemia. The duration of activity of racemic epinephrine is <2 hours. Consequently, observation is mandated. The symptoms of croup might reappear, but racemic epinephrine does not cause rebound worsening of the obstruction. Patients can be safely discharged home after a 2- to 3-hour period of observation provided they have no stridor at rest; have received steroids; and have normal air entry, normal pulse oximetry, and normal level of consciousness. Nebulized epinephrine should still be used cautiously in patients with tachycardia, heart conditions such as tetralogy of Fallot, and ventricular outlet obstruction because of possible side effects.

The effectiveness of oral corticosteroids in viral croup is well established. Corticosteroids decrease the edema in the laryngeal mucosa through their antiinflammatory action. Oral steroids are beneficial, even in mild croup, as measured by improved symptoms at 2 hours, reduced return visits, reduced hospitalization, shorter duration of hospitalization, and reduced need for subsequent interventions such as epinephrine administration. Most studies that demonstrated the efficacy of oral dexamethasone used a single dose of 0.6 mg/kg to a maximum dose of 16 mg; a dose as low as 0.15 mg/kg may be just as effective. More randomized controlled trials are needed to further evaluate the effectiveness of lower dose dexamethasone compared to 0.6 mg/kg. Prednisolone at a dose of 1 mg/kg has also been found to be noninferior to standard and low-dose dosing of dexamethasone. Intramuscular dexamethasone and nebulized budesonide have an equivalent clinical effect; oral dosing of dexamethasone is as effective as intramuscular administration. The only adverse effect in the treatment of croup with corticosteroids is the development of *Candida albicans* laryngotracheitis in a patient who received dexamethasone 1 mg/kg/24 hr for 8 days. Corticosteroids should not be administered to children with varicella or tuberculosis (unless the patient is receiving appropriate antituberculosis therapy) because they worsen the clinical course.

Antibiotics are not indicated in croup. Nonprescription cough and cold medications should not be used in children younger than 6 years of age. A helium-oxygen mixture (heliox) may be considered in the treatment of children with severe croup for whom intubation is being considered, although the evidence is inconclusive. Children with croup should be hospitalized for any of the following: progressive stridor, severe stridor at rest, respiratory distress, hypoxemia, cyanosis, depressed mental status, poor oral intake, persistent moderate croup symptoms (stridor and/or retractions at rest without agitation) after 4 hours after one dose of nebulized epinephrine and systemic glucocorticoids requiring more than one dose of nebulized epinephrine, or the need for reliable observation.

Epiglottitis is a medical emergency and warrants immediate treatment with an artificial airway placed under controlled conditions, either in an operating room or intensive care unit. All patients should receive oxygen en route unless the mask causes excessive agitation. Racemic epinephrine and corticosteroids are ineffective. Cultures of blood, epiglottic surface, and, in selected cases, cerebrospinal fluid should be collected after the airway is stabilized. Ceftriaxone (dose 100 mg/kg/24 hr in one or two divided doses) plus vancomycin (dose 15 mg/kg/24 hr every 8 hours) should be given parenterally, pending culture and susceptibility reports, because 10–40% of *H. influenzae* type b cases are resistant to ampicillin. After insertion of the artificial airway, the patient should improve immediately, and respiratory distress and cyanosis should disappear. Epiglottitis resolves after a few days of antibiotics, and the patient may be extubated; antibiotics should be continued for at least 10 days. Chemoprophylaxis is not routinely recommended for household, childcare, or nursery contacts of patients with invasive *H. influenzae* type b infections, but careful observation is mandatory, with prompt medical evaluation when exposed children develop a febrile illness. **Indications for rifampin prophylaxis** (20 mg/kg orally once a day for 4 days; maximum dose: 600 mg) for all household members include if a child within the home is younger than 4 years of age and incompletely immunized, is younger than 12 months of age and has not completed the primary vaccination series, or is immunocompromised.

Acute laryngeal swelling on an **allergic basis** responds to epinephrine (1 mg/mL concentration, previously referred to as 1:1,000 dilution, in dosage of 0.01 mL/kg to a maximum of 0.5 mL/dose) administered intramuscularly or racemic epinephrine (dose of 0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline) (see Chapter 190). Corticosteroids may be considered, although there is little evidence of benefit (1-2 mg/kg/24 hr of prednisone for 1-2 days). However, patients who require hospitalization or have a history of asthma may benefit from corticosteroids. After recovery, the patient and parents should be discharged with a preloaded syringe of epinephrine to be used in emergencies. Reactive mucosal swelling, severe stridor, and respiratory distress unresponsive to mist therapy may follow endotracheal intubation for general anesthesia in children. Racemic epinephrine and corticosteroids are helpful.

Endotracheal/Nasotracheal Intubation and Tracheotomy

With the introduction of routine intubation or, less often, tracheotomy for epiglottitis, the mortality rate for epiglottis has decreased to almost zero. These procedures should always be performed in an operating room or intensive care unit if time permits; prior intubation and general anesthesia greatly facilitate performing a tracheotomy without complications. The use of an endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended to facilitate intubation and reduce long-term sequelae. The choice of procedure should be based on the local expertise and experience with the procedure and postoperative care.

Intubation or, less often, tracheotomy is required for most patients with bacterial tracheitis and all young patients with epiglottitis. It is rarely required for patients with laryngotracheobronchitis, spasmodic croup, or laryngitis. Severe forms of laryngotracheobronchitis that require intubation in a high proportion of patients have been reported during severe measles and influenza A virus epidemics. Assessing the need for these procedures requires experience and judgment because they should not be delayed until cyanosis and extreme restlessness have developed (see Chapter 86). An endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended.

The endotracheal tube or tracheostomy must remain in place until edema and spasm have subsided and the patient is able to handle secretions satisfactorily. It should be removed as soon as possible, usually within a few days. Adequate resolution of epiglottic inflammation that has been accurately confirmed by fiberoptic laryngoscopy, permitting much more rapid extubation, often occurs within 24 hours. Racemic epinephrine and dexamethasone (0.5 mg/kg/dose 6-12 hr before extubation with a maximum dose of 16 mg) may be useful in the treatment of upper airway edema seen postintubation.

PROGNOSIS

In general, the length of hospitalization and the mortality rate for cases of acute infectious upper airway obstruction increase as the infection extends to involve a greater portion of the respiratory tract, except in epiglottitis, in which the localized infection itself can prove to be fatal. Most deaths from croup are caused by a laryngeal obstruction or by the complications of tracheotomy. Rarely, fatal out-of-hospital arrests caused by viral laryngotracheobronchitis have been reported, particularly in infants and in patients whose course has been complicated by bacterial tracheitis. Untreated epiglottitis has a mortality rate of 6% in some series, but if the diagnosis is made and appropriate treatment is initiated before the patient is moribund, the prognosis is excellent. The outcome of acute laryngotracheobronchitis, laryngitis, and spasmodic croup is also excellent.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

433.2 Bacterial Tracheitis

Kristine Knuti Rodrigues and Genie E. Roosevelt

Bacterial tracheitis is an acute bacterial infection of the upper airway that is potentially life-threatening. *S. aureus* (see Chapter 227.1) is the most commonly isolated pathogen, with isolated reports of methicillin-resistant *S. aureus*, *S. pneumoniae, S. pyogenes, Moraxella catarrhalis,* and nontypable *H. influenzae*; anaerobic organisms have also been implicated. The mean age is between 5 and 7 years. There is a slight male predominance. Bacterial tracheitis often follows a viral respiratory infection (especially laryngotracheitis or influenza virus infection), so it may be considered a bacterial complication of a viral disease, rather than a primary bacterial illness. This life-threatening entity is more common than epiglottitis in vaccinated populations.

CLINICAL MANIFESTATIONS

Typically, the child has a metallic/brassy cough, apparently as part of a viral laryngotracheobronchitis. High fever and toxicity with respiratory distress can occur immediately or after a few days of apparent improvement. The patient can lie flat, does not drool, and does not have the dysphagia associated with epiglottitis. The usual treatment for croup (racemic epinephrine) is ineffective. Intubation or tracheostomy may be necessary, but only 50–60% of patients require intubation for management, with younger patients more likely to need intubation. The major pathologic feature appears to be mucosal swelling at the level of the cricoid cartilage, complicated by copious, thick, purulent secretions, sometimes causing pseudomembranes. Suctioning these secretions, although occasionally affording temporary relief, usually does not sufficiently obviate the need for an artificial airway.

DIAGNOSIS

The diagnosis is based on evidence of bacterial upper airway disease, which includes high fever, purulent airway secretions, and an absence of the classic findings of epiglottitis. X-rays are not needed but can show the classic findings (Fig. 433.3); purulent material is noted below the cords during endotracheal intubation (Fig. 433.4).

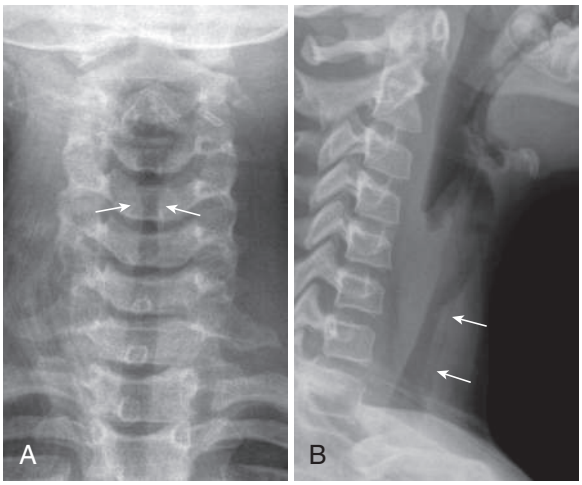

Fig. 433.3 Bacterial tracheitis in a 9-yr-old female with a high fever, cough, and stridor. **A,** Frontal soft tissue neck radiograph shows subglottic tracheal narrowing *(arrows).* **B,** Lateral soft tissue neck radiograph shows irregular linear membranous debris within the trachea *(arrows). (From Laya BF, Lee EY. Upper airway disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 51.9, p. 481.)*

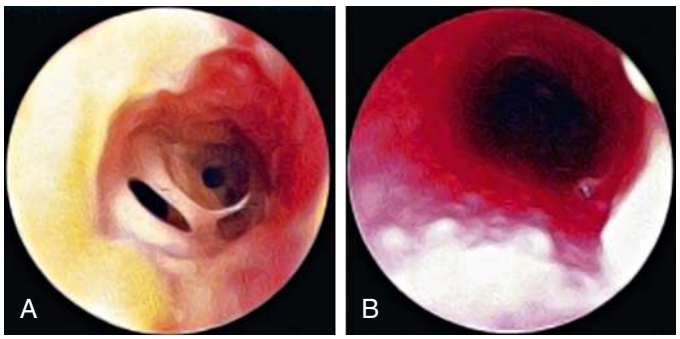

Fig. 433.4 Thick tracheal membranes seen on rigid bronchoscopy. The supraglottis was normal. **A,** Thick adherent membranous secretions. **B,** The distal tracheobronchial tree is unremarkable. In contrast to croup, tenacious secretions are seen throughout the trachea, and in contrast to bronchitis, the bronchi are not affected. *(From Salamone FN, Bobbitt DB, Myer CM, et al. Bacterial tracheitis reexamined: is there a less severe manifestation? Otolaryngol Head Neck Surg. 2004;131:871–876.Copyright 2004 American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc.)*

TREATMENT

Appropriate antimicrobial therapy, which usually includes antistaphylococcal agents, should be instituted in any patient whose course suggests bacterial tracheitis. Empiric therapy recommendations for bacterial tracheitis include vancomycin or clindamycin and a third- or fourth-generation cephalosporin (e.g., ceftriaxone or cefepime). When bacterial tracheitis is diagnosed by direct laryngoscopy or is highly suspected on clinical grounds, an artificial airway should be strongly considered. Supplemental oxygen is usually necessary.

COMPLICATIONS

Chest radiographs often show patchy infiltrates and may show focal densities. Subglottic narrowing and a rough and ragged tracheal air column can often be demonstrated radiographically. If airway management is not optimal, cardiorespiratory arrest can occur. Toxic shock syndrome has been associated with staphylococcal and group A streptococcal tracheitis (see Chapter 227.2).

PROGNOSIS

The prognosis for most patients is excellent. Patients usually become afebrile within 2-3 days of the institution of appropriate antimicrobial therapy, but prolonged hospitalization may be necessary. In recent years, there appears to be a trend toward a less morbid condition. With a decrease in mucosal edema and purulent secretions, extubation can be accomplished safely, and the patient should be observed carefully while antibiotics and oxygen therapy are continued.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 434

Congenital Anomalies of the Larynx, Trachea, and Bronchi

Michael Gorelik and James W. Schroeder Jr.

The larynx functions as a breathing passage, a valve to protect the lungs during swallowing, and the primary organ of communication. Symptoms related to congenital anomalies of the larynx include airway obstruction, noisy breathing, difficulty feeding, and abnormalities of phonation (see Chapter 421). Obstructive congenital lesions of the upper airway create turbulent airflow according to the laws of fluid dynamics. Turbulent airflow across a narrowed segment of the respiratory tract produces distinctive sounds that are diagnostically useful. The location of the obstruction produces characteristic changes in the sound of inspiration and/or expiration. Intrathoracic lesions typically cause expiratory wheezing and/or stridor, often masquerading as asthma or other pulmonary processes. The expiratory wheezing contrasts to the inspiratory stridor caused by the extrathoracic lesions of congenital laryngeal anomalies, specifically laryngomalacia and bilateral vocal cord paralysis. Stertor describes the low-pitched inspiratory snoring sound typically produced by soft tissue from nasal or nasopharyngeal obstruction.

The timing of noisy breathing in relation to the sleep–wake cycle is important. Obstruction of the pharyngeal airway (by enlarged tonsils, adenoids, pharyngeal soft tissue, tongue, or syndromes with midface hypoplasia) typically produces worse obstruction during sleep than during waking. Obstruction that is worse when awake is typically laryngeal, tracheal, or bronchial and is exacerbated by exertion. The location of the obstruction dictates the respiratory phase, tone, and nature of the sound, and these qualities direct the differential diagnosis.

With airway obstruction, the degree of the obstructing lesion and the resulting work of breathing determine the necessity for diagnostic procedures and surgical intervention. Obstructive symptoms vary from mild to severe stertor or stridor with episodes of apnea, cyanosis, suprasternal (tracheal tugging) and subcostal retractions, dyspnea, and tachypnea. Significant congenital anomalies of the trachea and bronchi can create serious respiratory difficulties from the first minute of life and may sometimes be diagnosed in the prenatal period. If a severe obstruction is suspected prenatally, an airway birth plan should be developed by a high-risk maternal–fetal medicine expert, a neonatologist, and a pediatric airway surgeon. *Congenital high airway obstruction syndrome,* or *CHAOS,* can lead to immediate postnatal distress (see Chapters 117 and 118). Chronic obstruction can cause failure to thrive and chronic hypoxemia and may have long-term effects on growth and development.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.1 Laryngomalacia

Michael Gorelik and James W. Schroeder Jr.

Laryngomalacia accounts for 45–75% of congenital laryngeal anomalies in children with stridor. Stridor is inspiratory and can vary from high- to low-pitched. It can be present at rest and exacerbated by any exertion: crying, agitation, or feeding. The stridor is caused, in part, by decreased laryngeal tone leading to supraglottic collapse during inspiration, which creates a narrow airway and turbulent airflow. Symptoms usually appear within the first 2 weeks and increase in severity for up to 6 months, although gradual improvement can begin at any time. Many infants who do not require surgical intervention often have spontaneous resolution of stridor around 7-9 months of age, and the majority will have complete resolution of stridor by 18 months of age. Gastroesophageal reflux disease, laryngopharyngeal reflux disease, and neurologic disease with associated muscle hypotonia can influence the severity of the disease and thereby the clinical course.

DIAGNOSIS

The diagnosis is made primarily based on clinical symptoms and is confirmed by outpatient, awake flexible laryngoscopy (Fig. 434.1). When the work of breathing is moderate to severe, airway films and chest radiographs are indicated. Laryngomalacia can contribute to feeding difficulties and dysphagia in some children because of decreased laryngeal sensation and poor suck-swallow-breath coordination. When the inspiratory stridor sounds wet or is associated with a cough or when there is a history of repeat upper respiratory illness or pneumonia, dysphagia should be considered. When dysphagia is suspected, a contrast swallow study and/or a fiberoptic endoscopic evaluation of swallowing (FEES) may be considered. Because 15–60% of infants with laryngomalacia have synchronous airway anomalies, complete bronchoscopy is undertaken for patients with moderate to severe obstruction.

TREATMENT

Expectant observation is suitable for most infants because most symptoms resolve spontaneously as the child and airway grow. Laryngopharyngeal reflux is managed with antireflux medications, such as histamine H_2-receptor antagonists or proton pump inhibitors (PPIs).

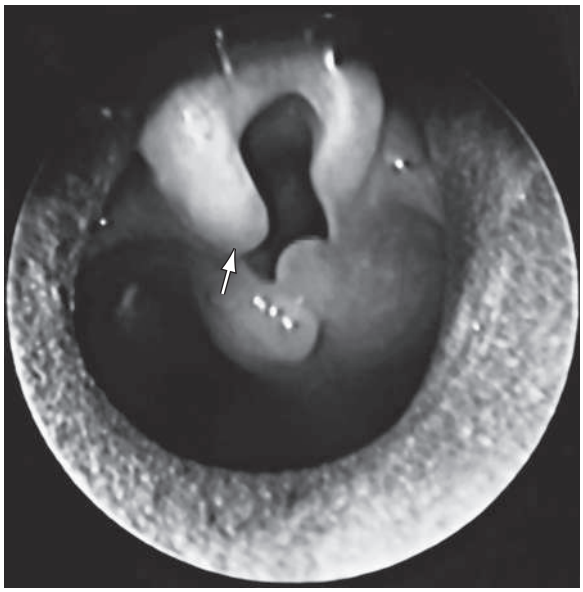

Fig. 434.1 Endoscopic example of laryngomalacia. On inspiration, the epiglottic folds collapse into the airway. The lateral tips of the epiglottis are also collapsing inward *(arrow)*. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008.)*

The risk-to-benefit ratio should be assessed in each patient because these medications, particularly PPIs, have been associated with iron-deficiency anemia and increased incidence of pneumonia, gastroenteritis, and *Clostridium difficile* infections, among others. In 15–20% of patients with laryngomalacia, symptoms are severe enough to cause progressive respiratory distress, cyanosis, failure to thrive, or cor pulmonale. In these patients, surgical intervention via supraglottoplasty is considered. Supraglottoplasty is 90% successful in relieving upper airway obstruction caused by laryngomalacia. Some comorbidities, such as cardiac disease, neurologic disease, pulmonary disorders, or craniofacial anomalies, may be poor prognostic indicators that would suggest earlier intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.2 Congenital Subglottic Stenosis

Michael Gorelik and James W. Schroeder Jr.

Congenital subglottic stenosis is the second most common cause of stridor. The subglottis is the narrowest part of the upper airway in a child and is located in the space extending from the undersurface of the true vocal folds to the inferior margin of the cricoid cartilage. Subglottic stenosis is a narrowing of the subglottic larynx and in a term newborn is defined as a cricoid diameter of less than 3.5 mm resulting from malformation of the cricoid cartilage. Subglottic stenosis manifests in the infant with respiratory distress and biphasic or primarily inspiratory stridor. It may be congenital or acquired. Symptoms may present spontaneously with a higher degree of stenosis but manifest after a respiratory tract infection because of edema and thickened secretions of a narrow and already compromised airway leading to recurrent or persistent crouplike symptoms.

Biphasic or primarily inspiratory stridor is the typical presenting symptom for congenital subglottic stenosis. In a child with recurrent bronchiolitis or croup, a diagnosis of congenital subglottic stenosis should be considered. The stenosis can be caused by an abnormally shaped elliptical cricoid cartilage; by a first tracheal ring that becomes trapped underneath the cricoid cartilage; or by soft tissue thickening caused by ductal cysts, submucosal gland hyperplasia, or fibrosis. Acquired subglottic stenosis refers to stenosis caused by extrinsic factors, most commonly resulting from prolonged intubation, and is discussed in further detail in Chapter 436.

DIAGNOSIS

The diagnosis made by airway radiographs is confirmed by direct laryngoscopy and bronchoscopy. During diagnostic laryngoscopy, the subglottic larynx is visualized directly and sized objectively using endotracheal tubes (Fig. 434.2). The percentage of stenosis is determined by comparing the size of the patients' larynx to a standard of laryngeal dimensions based on age. Stenosis >50% is usually symptomatic and often requires treatment. As with all cases of upper airway obstruction, tracheostomy is avoided when possible. Subglottic stenosis is typically measured using the Myer-Cotton system, with grade I through grade IV subglottic stenosis indicating the severity of narrowing. Other factors to consider aside from the degree of narrowing are whether the stenotic segment is soft or firm, which can determine the appropriate type of surgical intervention. Dilation and endoscopic laser surgery can be attempted in grade I and II, although they may not be effective because most congenital stenoses are cartilaginous. Anterior cricoid split, anterior-posterior cricoid split, tracheostomy, or laryngotracheal reconstruction with cartilage graft augmentation are surgical options typically reserved for grade III and IV subglottic stenosis. The differential diagnosis includes other anatomic anomalies, as well as a subglottic hemangiomas or respiratory papillomatosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.3 Vocal Cord Paralysis

Michael Gorelik and James W. Schroeder Jr.

Vocal cord paralysis is the third most common congenital laryngeal anomaly that produces stridor in infants and children. Congenital central nervous system lesions such as Chiari malformation, myelomeningocele, and hydrocephalus or birth trauma may be associated with bilateral paralysis. Additionally, congenital anomalies of the heart or great vessels can be associated with vocal cord paralysis. Bilateral vocal cord paralysis produces airway obstruction at the level of the glottis and is manifested by respiratory distress and high-pitched inspiratory stridor, aphonatory or dysphonic sound, or inspiratory weak cry. More than 50% of cases of vocal cord paralysis in children are bilateral.

Unilateral vocal cord paralysis is most often iatrogenic, as a result of surgical treatment for aerodigestive (tracheoesophageal fistula) and cardiovascular (patent ductus arteriosus repair) anomalies and thyroid or parathyroid surgery, although it may also be idiopathic. Unilateral paralysis can lead to aspiration, coughing, and choking. Often the cry is weak and breathy, whereas stridor and other symptoms of airway obstruction are less common. Vocal cord paralysis in older children may be the result of a Chiari malformation or tumors compressing the vagus or recurrent laryngeal nerve. Vocal cord paralysis/palsies have also been reported in patients with Guillain-Barré syndrome (GBS) and its Miller Fisher variant either as an isolated finding or associated with other features of GBS. Other neurologic disorders producing vocal cord paralysis include stroke, multiple sclerosis, and other polyneuropathies. The prognosis for spontaneous recovery is better for unilateral, acquired, and right-sided paralysis.

DIAGNOSIS

The diagnosis of vocal cord paralysis is made by awake flexible laryngoscopy. The examination will demonstrate an inability or weakness to abduct the involved vocal cord. A thorough investigation for the underlying primary cause is indicated. Because of the association with other congenital lesions, evaluation includes neurology and cardiology consultations, imaging of the course of the recurrent laryngeal nerve, and diagnostic endoscopy of the larynx, trachea, and bronchi. During endoscopy, it is critical to palpate the cricoarytenoid joint to rule out joint fixation, which can be

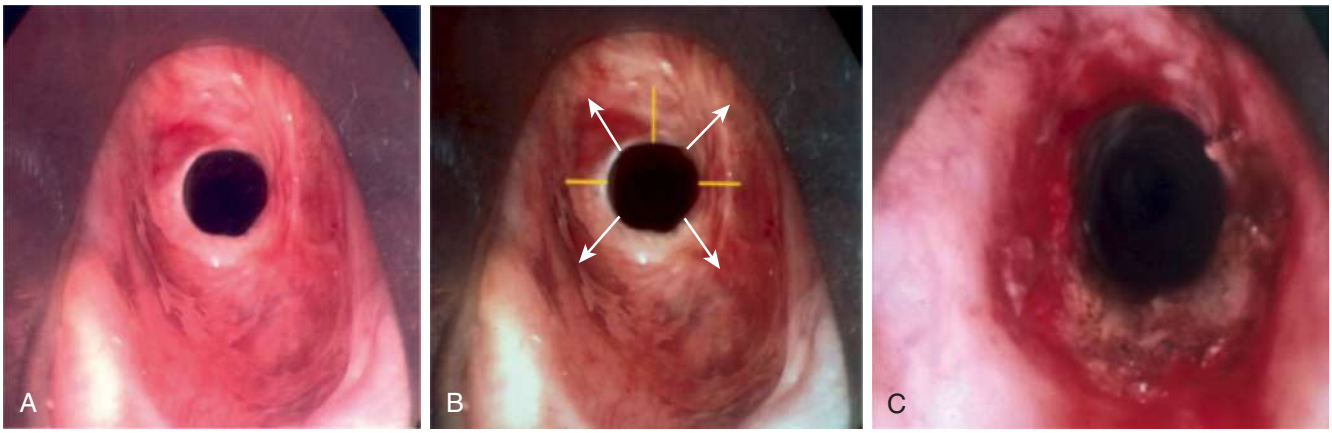

Fig. 434.2 Endoscopic repair of subglottic stenosis with radial cuts at 12, 3, and 9 o'clock positions using a laryngeal sickle knife or laser. **A,** Preoperative view. **B,** Diagram of planned incisions. **C,** After cuts and balloon dilation. *(From Lawlor CM, Rahbar R, Choi SS. Glottic and subglottic stenosis and related voice disorders. In: Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 28.8, p. 409.)*

mistaken for bilateral vocal fold paralysis. Intraoperative laryngeal electromyography (EMG) is the most specific and sensitive test to determine the presence of vocal cord paralysis.

TREATMENT

Treatment is based on the severity of the symptoms. Idiopathic vocal cord paralysis in infants usually resolves spontaneously within 6-12 months. If it is not resolved by 2-3 years of age, function typically does not recover. Patients with unilateral vocal cord paralysis often do not require intervention secondary to spontaneous recovery or compensation for the contralateral vocal cord. If there is persistent dysphonia or aspiration, surgical options include vocal fold injection, surgical medialization, or reinnervation using the ansa cervicalis, which has been successful in regaining unilateral vocal cord function. Postoperative voice therapy is helpful to achieve optimum results.

Bilateral paralysis may require temporary tracheotomy in 50% of patients. Airway augmentation procedures in bilateral vocal cord paralysis typically focus on widening the posterior glottis, such as an endoscopically placed or open posterior glottis cartilage graft, arytenoidectomy, or arytenoid lateralization, sometimes in conjunction with cordotomy. These procedures are generally successful in reducing the obstruction; however, they may result in dysphagia and aspiration.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.4 Congenital Laryngeal Webs and Atresia

Michael Gorelik and James W. Schroeder Jr.

Congenital laryngeal webs account for about 5% of congenital laryngeal anomalies. They are typically located in the anterior glottis with subglottic extension and associated subglottic stenosis. During early embryogenesis, laryngeal webs form if the laryngotracheal lumen fails to fully recannulate. The clinical presentation ranges from asymptomatic, to dysphonia, to severe airway compromise secondary to the degree of obstruction caused by the web. Laryngeal webs are categorized from type I to type IV, which is the most severe.

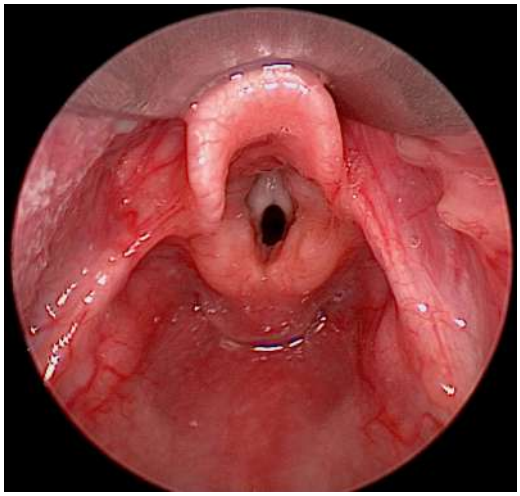

Fig. 434.3 Anterior glottic web, endoscopic view. *(Courtesy Dr. Jeff Rastatter, Division of Pediatric Otolaryngology, Lurie Children's Hospital, Chicago, IL.)*

Laryngeal atresia occurs as a complete glottic web due to failure of laryngeal and tracheal recanalization and may be associated with tracheal agenesis and tracheoesophageal fistula. Laryngeal atresia may be detected in the prenatal period, and preparations should be made for establishment of definitive airway, either before or at birth. Other times, congenital laryngeal atresia is a cause of respiratory distress in the newborn and is diagnosed only upon initial direct laryngoscopy.

Diagnosis is made by direct laryngoscopy (Fig. 434.3). Thick webs may be suspected in lateral radiographs of the airway. Chromosomal and congenital cardiovascular anomalies, as well as chromosome 22q11 deletion, are common in patients with laryngeal webs. Treatment may require only incision or dilation for thin webs. Thick webs can require laryngofissure and temporary stenting. Webs with associated subglottic stenosis are likely to require cartilage augmentation of the cricoid cartilage (laryngotracheal reconstruction). Voice outcomes are variable after surgical management.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

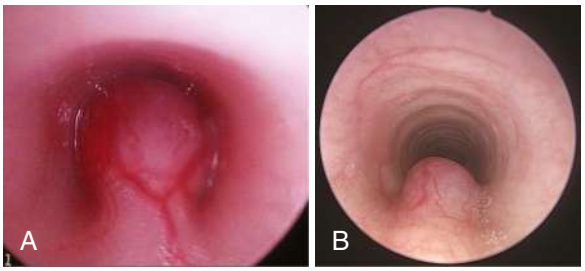

Fig. 434.4 A and B, Case of tracheal hemangioma prepropranolol and postpropranolol therapy (pictures 2 weeks apart). *(From Bush A, Abel R, Chitty L, et al. Congenital lung disease. In: Wilmott RW, Deterding RR, Li A, et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 18.18, p. 308.)*

434.5 Congenital Subglottic Hemangioma

Michael Gorelik and James W. Schroeder Jr.

See also Chapter 438.3.

Subglottic infantile hemangiomas are benign vascular malformations and a rare cause of early infancy respiratory distress. They present more commonly in females than in males, with symptoms of a barky cough and inspiratory or biphasic stridor in the absence of dysphonia. Symptoms typically present within the first 1-6 months of life. The most common presenting symptom is biphasic stridor, somewhat more prominent during inspiration. This is exacerbated by crying and acute viral illnesses. A barking cough, hoarseness, and symptoms of recurrent or persistent croup are typical and can mask the diagnosis. Roughly 50% of those with a subglottic hemangioma will have a cutaneous hemangioma, but only 1% of children who have cutaneous hemangiomas will have a subglottic hemangioma (see Chapter 691). However, a facial hemangioma in the beard distribution (preauricular area, lips, chin, and neck) is associated with a much higher incidence of subglottic hemangiomas and, when present, should prompt further investigation. Chest and neck radiographs can show the characteristic asymmetric narrowing of the subglottic larynx. CT and MRI can also assist with the diagnosis. Airway vascular lesions may also be associated with **PHACES syndrome**, characterized by posterior fossa malformations, hemangioma, arterial lesions of the head and neck, cardiac anomalies, eye anomalies, and sternal cleft (see Chapter 691). More than 50% of children with PHACES syndrome have an airway vascular lesion. Treatment options range from conservative monitoring, medical management, steroid injection, laser treatment, and open surgical resection to tracheotomy and airway reconstruction. Propranolol has become a mainstay in initial therapy of subglottic hemangioma; however, it is estimated that up to 50% of patients with subglottic hemangioma may not have a long-term response to propranolol, indicating a need for close airway monitoring in these patients (Fig. 434.4). Treatment is further discussed in Chapter 438.3.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.6 Laryngoceles and Saccular Cysts

Michael Gorelik and James W. Schroeder Jr.

Saccular cysts and laryngoceles are uncommon etiologies of pediatric airway obstruction. A laryngocele is an abnormal air-filled dilation of the laryngeal saccule that arises vertically between the false vocal cord, the base of the epiglottis, and the inner surface of the thyroid cartilage. As there is open communication with the laryngeal lumen when it intermittently fills with air, this can lead to hoarseness and dyspnea. Laryngoceles may be confined to the larynx or extend into the neck and are described as internal, external, or both. A saccular cyst (congenital cyst of the larynx) is distinguished from the laryngocele in that its lumen is isolated from the interior of the larynx and it contains mucus, not air. Saccular cysts can be located in the anterior and lateral portions of the glottis and supraglottis. In infants and children, laryngoceles cause hoarseness and dyspnea that may increase with crying. Saccular cysts may cause respiratory distress and stridor at birth and may require early airway intervention. Infection of saccular cysts can lead to rapid expansion and acute airway compromise. Intubation can be challenging because the supraglottic and laryngeal anatomy may be distorted. In addition, complete airway obstruction may occur on induction with neuromuscular blockade because of decreased laryngeal tone. A saccular cyst may be visible on radiography, but the diagnosis is made by laryngoscopy (Fig. 434.5). Needle aspiration of the cyst confirms the diagnosis but rarely provides a cure. Surgical excision is the therapy of choice for management of saccular cysts and laryngoceles. Approaches include endoscopic CO_2 laser excision, endoscopic extended ventriculotomy (marsupialization or unroofing), or, traditionally, external excision.



Fig. 434.5 Endoscopic photograph of a saccular cyst. *(From Ahmad SM, Soliman AMS. Congenital anomalies of the larynx. Otolaryngol Clin North Am. 2007;40:177–191, Fig. 3.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.7 Posterior Laryngeal Cleft and Laryngotracheoesophageal Cleft

Michael Gorelik and James W. Schroeder Jr.

The posterior laryngeal cleft is the result of a deficiency in the midline of the posterior larynx caused by a failure of fusion of the posterior cricoid lamina. This results in an abnormal communication between the posterior larynx and esophagus leading to aspiration. Posterior laryngeal clefts are categorized into four types depending how far inferiorly the cleft extends. A **type I cleft** extends to, but not beyond, the vocal cords. A **type II cleft** extends beyond the vocal cords to, but not through, the cricoid cartilage. A **type III cleft** extends through the cricoid cartilage into the cervical trachea. A

type IV cleft extends into the thoracic trachea. Laryngeal clefts can occur in families and are likely to be associated with tracheal agenesis, tracheoesophageal fistula, and multiple congenital anomalies, including Opitz-Frias syndrome, Townes-Brock syndrome, chromosome 1q43 deletion, trisomy 21, and Pallister-Hall syndrome.

Type I clefts may cause mild symptoms, but at least 60% of these will cause no symptoms and will not require surgical repair. Type I and, more commonly, type II clefts can present with feeding problems, recurrent aspiration, pneumonias, or respiratory complaints. Infants with type III and IV clefts will present more commonly in the newborn period with significant aspiration and respiratory distress.

Diagnostic workup includes an esophagogram, which is undertaken to evaluate the presence of aspiration or laryngeal penetration of ingested contrast material. A FEES exam may be undertaken by an otolaryngologist with the assistance of a speech-language and pathology team to observe patterns of liquid spillage during swallow and may identify a cleft. However, the gold standard of diagnosis remains operative laryngoscopy and bronchoscopy with palpation of the posterior larynx. This assists in determining the length of the cleft and guides treatment options.

Treatment is based on the cleft type and the symptoms; in general, a type I cleft may be managed endoscopically, whereas higher grades may require an open procedure. Stabilization of the airway is the first priority. Gastroesophageal reflux must be controlled, and a careful assessment for other congenital anomalies is undertaken before repair. Several endoscopic and open cervical and transthoracic surgical repairs have been described.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.8 Vascular and Cardiac Anomalies

Michael Gorelik and James W. Schroeder Jr.

Aberrant cardiopulmonary vascular anatomy may directly affect the trachea and bronchi, resulting in respiratory and feeding problems (Fig. 434.6). The aberrant innominate artery is the most common cause of secondary tracheomalacia (see Chapter 481). It may be asymptomatic and discovered incidentally, or it may cause severe symptoms. Expiratory wheezing and cough occur and, rarely, reflex apnea or "dying spells." Surgical intervention is rarely necessary. Infants are most commonly treated expectantly because the problem is often self-limited.

The term *vascular ring* is used to describe vascular anomalies that result from abnormal development of the aortic arch complex. Vascular rings are categorized as complete or incomplete. Double aortic arch is the most common type of complete vascular ring, followed by right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum. These account for more than 95% of complete rings. The double aortic arch encircles and compresses both the trachea and esophagus. With few exceptions, these patients are symptomatic by 3 months of age. Respiratory symptoms predominate, but dysphagia may be present. The diagnosis is established by barium esophagogram that shows a posterior indentation of the esophagus by the vascular ring (see Fig. 434.6). CT or MRI with angiography provides the cardiothoracic surgeon the information needed. Surgical treatment for symptomatic patients entails division of the vascular ring.

Other vascular anomalies include the pulmonary artery sling, which also requires surgical correction. The most common open (incomplete) vascular ring is the left aortic arch with aberrant right subclavian artery. It is usually asymptomatic, although dysphagia lusoria has been described. This is characterized as dysphagia caused by an aberrant subclavian artery coursing behind the esophagus, leading to esophageal compression and difficulty with bolus transit.

Congenital cardiac defects are likely to compress the left main bronchus or lower trachea. Any condition that produces significant pulmonary hypertension increases the size of the pulmonary arteries, which in turn causes compression of the left main bronchus. Surgical correction of the underlying pathology to relieve pulmonary hypertension relieves the airway compression.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.9 Tracheal Stenoses, Webs, and Atresia

Michael Gorelik and James W. Schroeder Jr.

Long-segment congenital tracheal stenosis with *complete* tracheal rings typically presents within the first year of life, usually after a crisis has been precipitated by an acute respiratory illness. The diagnosis may be suggested by plain radiographs. CT with contrast delineates associated intrathoracic anomalies such as the pulmonary artery sling (in ~30%) or other cardiac anomalies (in about 25%), which can occur in one third of patients to one fourth of patients, respectively. Bronchoscopy is the best method to define the degree and extent of the stenosis and the associated abnormal bronchial branching pattern. Care must be taken to avoid traumatic passage of a telescope or bronchoscope through a stenotic or edematous segment, as even minor mucosal trauma may precipitate complete airway obstruction. Treatment of clinically significant stenosis involves tracheal resection of short-segment stenosis, slide tracheoplasty for long-segment stenosis, or tracheal rings. Total autologous tracheal replacement is another option. Congenital soft tissue stenosis and thin webs are rare. Dilation may be all that is required.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.10 Foregut Cysts

Michael Gorelik and James W. Schroeder Jr.

The embryologic foregut gives rise to the pharynx, lower respiratory tract, esophagus, stomach, duodenum, and hepatobiliary tract. Foregut duplication cysts arise if heterotopic rests of foregut-derived epithelium persist anywhere along this tract. Foregut duplications account for approximately one third of all duplications. The bronchogenic cyst, intramural esophageal cyst (esophageal duplication), and enteric cyst can all produce symptoms of respiratory obstruction and dysphagia. The diagnosis is suspected when chest radiographs or CT scan delineates the mass and, in the case of enteric cyst, the associated vertebral anomaly. The treatment of all foregut cysts is surgical excision.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

434.11 Tracheomalacia and Bronchomalacia

See Chapter 437.

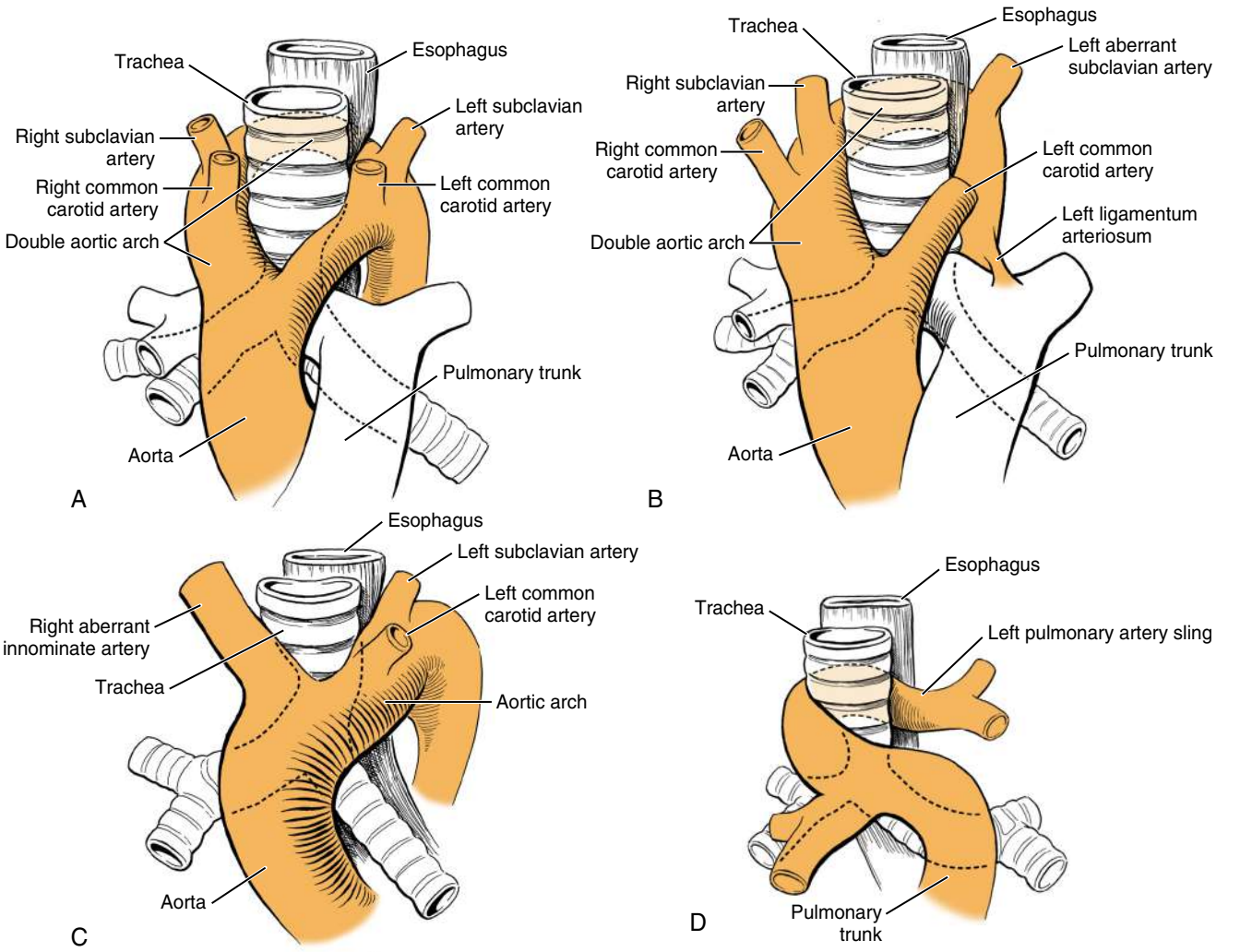

Fig. 434.6 Vascular rings. **A,** Double aortic arch. **B,** Right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum. **C,** Aberrant innominate artery. **D,** Left pulmonary artery sling. *(From Green GF, Ohye RG. Diagnosis and management of tracheal anomalies and tracheal stenosis. In: Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 30.6, p. 445.)*

Chapter 435

Foreign Bodies in the Airway

Michael Gorelik and James W. Schroeder Jr.

Choking is a leading cause of morbidity and mortality among children, especially those younger than 4 years of age. From 2001 to 2009, an average of 12,435 children ages 0-14 years in the United States were treated in emergency departments for choking on food without fatality. The majority of children found to have foreign body aspiration are older infants and toddlers (Fig. 435.1), with males being 1.7 times more likely than females to aspirate a foreign body. Roughly 80% of airway foreign body aspirations occur in children younger than 3 years old, with a peak in incidence between ages 1 and 2. Food items ranging from nuts, seeds, popcorn, and food particles to hardware and pieces of toys account for 59.5–81% of all cases. Nonfood and inorganic objects such as coins, paper clips, pen caps, or small toys are more commonly aspirated by older children. Globular, compressible, or round objects such as hot dogs, grapes, nuts, balloons, marshmallows, meats, and candies are particularly hazardous because of their ability to completely occlude the airway.

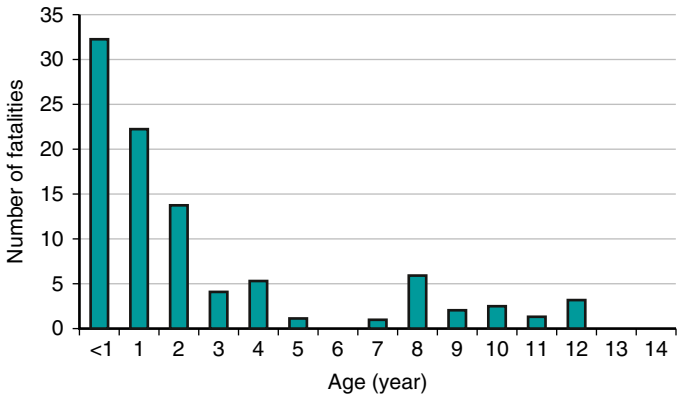

Fig. 435.1 Number of fatalities versus victim age, all fatality types. *(From Milkovich SM, Altkorn R, Chen X, et al. Development of the small parts cylinder: lessons learned. Laryngoscope. 2008;118[11]:2082–2086.)*

Younger children are at a higher risk for foreign body aspiration largely secondary to their developmental vulnerabilities and immature swallow function. Infants and toddlers often use their mouths to explore their surroundings, and children are more likely to be distracted, playing, or ambulatory while eating. Infants have the ability to suck and swallow and are equipped with basic involuntary reflexes (gag, cough, and glottis closure) that help to protect against aspiration during swallowing. Dentition develops at approximately 6 months of age with the eruption of the incisors, whereas molars do not erupt until approximately 1.5 years of age. Mature mastication takes longer to develop.

Despite these various protective mechanisms, a child's airway is more vulnerable to obstruction than an adult's airway. Young children are more likely to experience significant obstruction by small foreign bodies because of the smaller diameter of the pediatric airway. Mucus and secretions may form a seal around the foreign body, making it more difficult to dislodge by forced exhalation. In addition, the force of air generated by an infant's or young child's cough is less effective in dislodging an airway obstruction. For these reasons, it is recommended that children younger than 5 years of age avoid foods like hard candy or chewing gum and that raw fruits and vegetables be cut into small pieces. Additionally, children with developmental delays or neurologic and muscular disorders are at higher risk for foreign body aspiration.

CLINICAL MANIFESTATIONS

Foreign bodies of the airway have variable presentations and complications, depending on the characteristics, duration, and location of the foreign body. The clinical manifestations range from an asymptomatic state to severe respiratory distress. A high index of suspicion is often required, as delayed presentation is common, with more than 50% of cases presenting after 24 hours of the suspected aspiration event. The most serious complication of foreign body aspiration is complete obstruction of the airway, which may be recognized in the conscious child as sudden respiratory distress followed by an inability to speak or cough.

There are typically three stages of symptoms that result from aspiration of an object into the airway:

1. **Initial event:** Paroxysms of coughing, choking, gagging, and possible airway obstruction occur immediately after aspiration of the foreign body. This may be accompanied by tachypnea and stridor. The child is sometimes able to expel the foreign body during this stage.
2. **Asymptomatic interval:** The foreign body becomes lodged, reflexes fatigue, and the immediate irritating symptoms subside. The lack of symptoms can be particularly misleading to the provider when a child presents in this stage and accounts for a large percentage of delayed diagnoses and overlooked foreign bodies. Some patients with delayed presentation may eventually develop dyspnea, wheezing, or chronic cough.
3. **Complications:** Obstruction, erosion, or infection develops, which again directs attention to the presence of a foreign body. In this third stage, complications include fever, cough, hemoptysis, pneumonia, and atelectasis. Acute or chronic complications have been reported in almost 15% of cases of foreign bodies of the airway.

DIAGNOSIS

The clinical history is the most important factor in determining the need for operative bronchoscopy. A positive history must never be ignored, but a negative history can be misleading. Because nuts and seeds are the most common bronchial foreign bodies, the physician should specifically question the child's parents about these items, though it is important to keep in mind that aspiration events can be unwitnessed. Choking or coughing episodes accompanied by new-onset wheezing and asymmetric breath sounds are highly suggestive of a foreign body in the airway, and bronchoscopy should be carried out promptly. A comprehensive physical exam is also essential, including examination of the nose, oral cavity, pharynx, neck, and lungs. Several reliable physical exam findings for airway foreign bodies include cough, decreased lung sounds, and wheezing. In addition to history and physical examination, radiology studies have an important role in diagnosing foreign bodies in the airway. Plain films are typically recommended first, although many foreign bodies are radiolucent (80–96%), and therefore providers often must rely on secondary findings (such as air trapping, asymmetric hyperinflation, obstructive emphysema, atelectasis, mediastinal shift, and consolidation) to indicate suspicion of a foreign body. Expiratory or lateral decubitus films can assist in revealing these suggestive secondary findings. The indication for computed tomography of the chest is currently being explored because of its high sensitivity and specificity, its ability to detect radiolucent objects, and its potential to eliminate the need for anesthesia and a procedure. However, with the known risks of radiation and the time-sensitive need for intervention, advanced imaging is rarely obtained. However, even in the absence of radiologic evidence on plain films, when the history and physical examination are suggestive of aspiration, bronchoscopy should be pursued.

TREATMENT

The treatment of choice for airway foreign bodies is prompt endoscopic removal with rigid instruments by a specialist (otolaryngologist or pulmonologist). Bronchoscopy is deferred only until providers have obtained preoperative studies and the patient has been prepared by adequate hydration and emptying of the stomach, though this can depend on the acuity of the clinical scenario. Airway foreign bodies are usually removed the same day the diagnosis is first considered. As with any treatment modality, providers must give careful consideration to the risks and benefits of the bronchoscopy procedure when the diagnosis is unclear. Potential complications of rigid bronchoscopy include bronchospasm, desaturation, bleeding, and airway edema; need for intubation; repeat procedures; and the inherent risks of anesthesia. Many surgeons maintain a lower threshold for intervention with the appropriate clinical history given the high risk of complications for a missed foreign body. Beyond the understanding of diagnosis and management of airway foreign bodies, there is a strong need and push for awareness, education, and prevention among caregivers, healthcare providers, and manufacturers of food and toys.

435.1 Laryngeal Foreign Bodies

Michael Gorelik and James W. Schroeder Jr.

Although laryngeal foreign bodies are less common (2–12% of cases) than bronchial or tracheal foreign bodies, they are particularly dangerous because of the risk of complete laryngeal obstruction, which can lead to asphyxiation unless it is promptly relieved with the Heimlich maneuver (see Chapter 79 and Figs. 79.6 and 79.7). As with airway foreign bodies in other locations, the presenting symptoms of laryngeal foreign bodies are determined by the size, shape, nature, and degree of obstruction. Objects that conform to the larynx can lead to complete obstruction, whereas with smaller objects the presentation can range from dysphonia, aphonia, stridor, cough, dyspnea, cyanosis, hemoptysis, and crouplike symptoms.

Clinical history is critical to establish an early diagnosis, and prompt intervention is critical.

435.2 Tracheal Foreign Bodies

Michael Gorelik and James W. Schroeder Jr.

Tracheal foreign bodies account for 3–12% of airway foreign body cases. Children who have tracheal foreign bodies can present with dysphonia, dysphagia, dry cough, or biphasic stridor. Posteroanterior and lateral soft tissue neck radiographs (airway films) are abnormal in 92% of children, whereas chest radiographs are abnormal in only 58% of these cases.

435.3 Bronchial Foreign Bodies

Michael Gorelik and James W. Schroeder Jr.

The majority of airway foreign bodies lodge in a bronchus (80–90% of cases) with a propensity to the right side. Occasionally, fragments of a foreign body may produce bilateral involvement or shifting infiltrates if they move from lobe to lobe. Some children with bronchial foreign bodies present asymptomatically, whereas others have asymmetric breath sounds, cough, and wheezing. Posteroanterior and lateral chest radiographs (including the abdomen) are standard in the diagnostic evaluation of infants and children suspected of having aspirated a foreign object. An expiratory posteroanterior chest film is most helpful. During expiration, the bronchial foreign body obstructs the exit of air from the obstructed lung, producing obstructive emphysema and air trapping. The persistent inflation of the obstructed lung causes a shift of the mediastinum toward the opposite side (Fig. 435.2). Air trapping is an immediate complication, whereas atelectasis is a late finding. Lateral decubitus chest films or fluoroscopy can provide the same information as expiratory films but are often unnecessary. Low-dose CT is considered by some a standard imaging study if previous conventional imaging is nondiagnostic. Clinical history and physical examination, not radiographs, ultimately determine the indication for bronchoscopy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

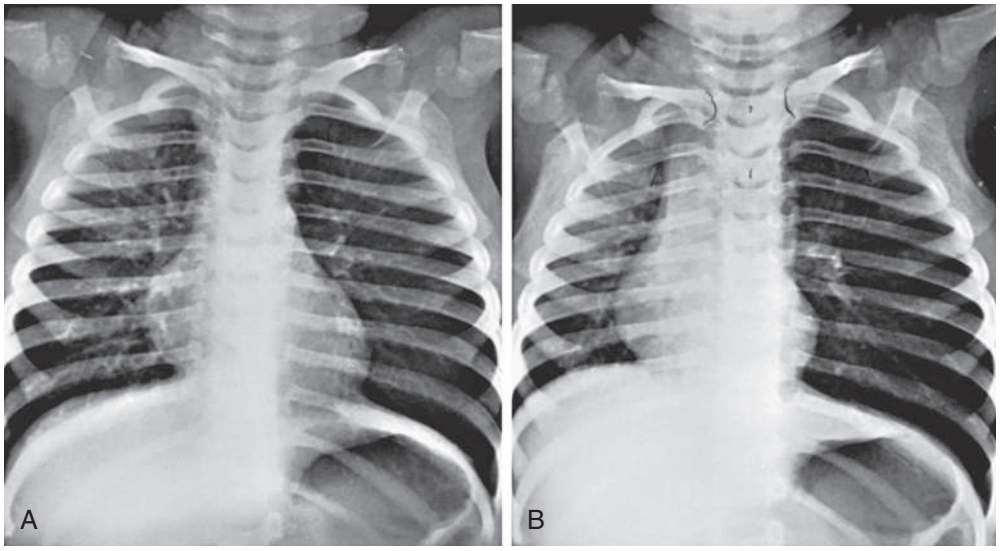

Fig. 435.2 A, Normal inspiratory chest radiograph in a toddler with a peanut fragment in the left main bronchus. B, Expiratory radiograph of the same child showing the classic obstructive emphysema (air trapping) on the involved (left) side. Air leaves the normal right side, allowing the lung to deflate. The medium shifts toward the unobstructed side.

Chapter 436

Laryngotracheal Stenosis and Subglottic Stenosis

Taher S. Valika and James W. Schroeder Jr.

Laryngotracheal stenosis is the second most common cause of stridor in neonates and is the most common cause of airway obstruction requiring tracheostomy in infants. The glottis (vocal cords) and the upper trachea are compromised in most cases of laryngeal stenosis, particularly those that develop after endotracheal intubation. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. **Subglottic stenosis** is considered congenital when there is no other apparent cause such as a history of laryngeal trauma or intubation. Approximately 90% of cases manifest in the first year of life. Management relies on optimizing the airway, while ensuring the patient continues to grow. Knowledge of preventive measures is imperative to all healthcare members.

436.1 Congenital Subglottic Stenosis

See Chapter 434.2.

436.2 Acquired Laryngotracheal Stenosis

Taher S. Valika and James W. Schroeder Jr.

Ninety percent of acquired stenoses are a result of endotracheal intubation. The narrowest portion of the pediatric larynx is the subglottic region because of the narrow cricoid cartilage. When the pressure of the endotracheal tube against the cricoid mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage (Fig. 436.1). Granulation tissue forms around the ulcerations. These changes and edema throughout the larynx usually resolve spontaneously after extubation. Chronic edema and fibrous stenosis develop in only a small percentage of cases.

A number of factors predispose to the development of laryngeal stenosis. Laryngopharyngeal reflux of acid and pepsin from the stomach is known to exacerbate endotracheal tube trauma. More damage is caused in areas left unprotected, owing to loss of mucosa. Congenital subglottic stenosis narrows the larynx, which makes the patient more likely to develop acquired subglottic stenosis because significant injury is more likely to occur with use of an endotracheal tube of age-appropriate size. *Other risk factors for the development of acquired subglottic stenosis include sepsis, malnutrition, chronic inflammatory disorders, and immunosuppression.* An oversized endotracheal tube is the most common factor contributing to laryngeal injury. A tube that allows a small air leak at the end of the inspiratory cycle minimizes potential trauma. Other extrinsic factors—traumatic intubation, multiple reintubations, movement of the endotracheal tube, and duration of intubation—can contribute to varying degrees in individual patients.

CLINICAL MANIFESTATIONS

Symptoms of acquired and congenital stenosis are similar. Spasmodic croup, the sudden onset of severe croup in the early morning hours, is usually caused by laryngopharyngeal reflux with transient laryngospasm and subsequent laryngeal edema. These frightening episodes resolve rapidly, often before the family and child reach the emergency department. Other presentations can also involve neonates who fail extubation, despite multiple attempts, and children with permanent dyspnea, stridor, or dysphonia.



Fig. 436.1 Bronchoscopy in a 2-mo-old infant showing mucosal erosion and cartilage exposure in the subglottic region. The child was intubated with an age-appropriate tube but with an excess of air in the cuff. *(Courtesy Dr. Taher S. Valika, Division of Pediatric Otolaryngology, Ann & Robert H. Lurie Children's Hospital of Chicago.)*

DIAGNOSIS

The diagnosis can be made by posteroanterior and lateral airway radiographs. The gold standard to confirm the diagnosis is via direct laryngoscopy and bronchoscopy in the operating room. High-resolution CT imaging and ultrasonography are of limited value. This is similar to the workup associated with congenital subglottic stenosis.

TREATMENT

The severity, location, and type (cartilaginous or soft tissue) of the stenosis determine the treatment. Mild cases can be managed without operative intervention because the airway will improve as the child grows. Moderate soft tissue stenosis is treated by endoscopy using gentle dilations or CO_2 laser. Severe laryngotracheal stenosis is likely to require laryngotracheal reconstructive (expansion) surgery or resection of the narrowed portion of the laryngeal and tracheal airway (cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

Fundamental knowledge of the airway can help reduce the incidence of stenoses. The use of age-appropriate tubes and cuffless tubes, treatment of gastroesophageal reflux, and reducing the duration of mechanical ventilation have led to an overall decrease in laryngotracheal stenoses in the past decade.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 437
Bronchomalacia and Tracheomalacia

Jonathan D. Finder

Tracheomalacia and bronchomalacia refer to *chondromalacia* of a central airway, leading to insufficient cartilage to maintain airway patency throughout the respiratory cycle. These are common causes of persistent wheezing in infancy. Tracheomalacia and bronchomalacia can be either primary or secondary (Table 437.1). Primary tracheomalacia and bronchomalacia are often seen in premature infants, although most affected patients are born at term. Secondary tracheomalacia and bronchomalacia refer to the situation in which the central airway is compressed by an adjacent structure (e.g., vascular ring; see Fig. 434.6) or is deficient in cartilage because of tracheoesophageal fistula (see Chapter 365). Bronchomalacia is common after lung transplantation, assumed to be secondary to the loss of bronchial artery supply leading to ischemia of the bronchial cartilage. This form of bronchomalacia may take months to

Table 437.1 Classification of Tracheomalacia

PRIMARY TRACHEOMALACIA
Congenital absence of tracheal-supporting cartilages
SECONDARY TRACHEOMALACIA
Esophageal atresia, tracheoesophageal fistula
Vascular rings (double aortic arch)
Tracheal compression from an aberrant innominate artery
Tracheal compression from mediastinal masses
Abnormally soft tracheal cartilages associated with connective tissue disorders
Prolonged mechanical ventilation, chronic lung disease

From McNamara VM, Crabbe DC. Tracheomalacia. *Paediatr Respir Rev.* 2004;5:147–154.

436.2 Acquired Laryngotracheal Stenosis

Taher S. Valika and James W. Schroeder Jr.

Ninety percent of acquired stenoses are a result of endotracheal intubation. The narrowest portion of the pediatric larynx is the subglottic region because of the narrow cricoid cartilage. When the pressure of the endotracheal tube against the cricoid mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage (Fig. 436.1). Granulation tissue forms around the ulcerations. These changes and edema throughout the larynx usually resolve spontaneously after extubation. Chronic edema and fibrous stenosis develop in only a small percentage of cases.

A number of factors predispose to the development of laryngeal stenosis. Laryngopharyngeal reflux of acid and pepsin from the stomach is known to exacerbate endotracheal tube trauma. More damage is caused in areas left unprotected, owing to loss of mucosa. Congenital subglottic stenosis narrows the larynx, which makes the patient more likely to develop acquired subglottic stenosis because significant injury is more likely to occur with use of an endotracheal tube of age-appropriate size. *Other risk factors for the development of acquired subglottic stenosis include sepsis, malnutrition, chronic inflammatory disorders, and immunosuppression.* An oversized endotracheal tube is the most common factor contributing to laryngeal injury. A tube that allows a small air leak at the end of the inspiratory cycle minimizes potential trauma. Other extrinsic factors—traumatic intubation, multiple reintubations, movement of the endotracheal tube, and duration of intubation—can contribute to varying degrees in individual patients.

CLINICAL MANIFESTATIONS

Symptoms of acquired and congenital stenosis are similar. Spasmodic croup, the sudden onset of severe croup in the early morning hours, is usually caused by laryngopharyngeal reflux with transient laryngospasm and subsequent laryngeal edema. These frightening episodes resolve rapidly, often before the family and child reach the emergency department. Other presentations can also involve neonates who fail extubation, despite multiple attempts, and children with permanent dyspnea, stridor, or dysphonia.



Fig. 436.1 Bronchoscopy in a 2-mo-old infant showing mucosal erosion and cartilage exposure in the subglottic region. The child was intubated with an age-appropriate tube but with an excess of air in the cuff. *(Courtesy Dr. Taher S. Valika, Division of Pediatric Otolaryngology, Ann & Robert H. Lurie Children's Hospital of Chicago.)*

DIAGNOSIS

The diagnosis can be made by posteroanterior and lateral airway radiographs. The gold standard to confirm the diagnosis is via direct laryngoscopy and bronchoscopy in the operating room. High-resolution CT imaging and ultrasonography are of limited value. This is similar to the workup associated with congenital subglottic stenosis.

TREATMENT

The severity, location, and type (cartilaginous or soft tissue) of the stenosis determine the treatment. Mild cases can be managed without operative intervention because the airway will improve as the child grows. Moderate soft tissue stenosis is treated by endoscopy using gentle dilations or CO_2 laser. Severe laryngotracheal stenosis is likely to require laryngotracheal reconstructive (expansion) surgery or resection of the narrowed portion of the laryngeal and tracheal airway (cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

Fundamental knowledge of the airway can help reduce the incidence of stenoses. The use of age-appropriate tubes and cuffless tubes, treatment of gastroesophageal reflux, and reducing the duration of mechanical ventilation have led to an overall decrease in laryngotracheal stenoses in the past decade.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 437
Bronchomalacia and Tracheomalacia

Jonathan D. Finder

Tracheomalacia and bronchomalacia refer to *chondromalacia* of a central airway, leading to insufficient cartilage to maintain airway patency throughout the respiratory cycle. These are common causes of persistent wheezing in infancy. Tracheomalacia and bronchomalacia can be either primary or secondary (Table 437.1). Primary tracheomalacia and bronchomalacia are often seen in premature infants, although most affected patients are born at term. Secondary tracheomalacia and bronchomalacia refer to the situation in which the central airway is compressed by an adjacent structure (e.g., vascular ring; see Fig. 434.6) or is deficient in cartilage because of tracheoesophageal fistula (see Chapter 365). Bronchomalacia is common after lung transplantation, assumed to be secondary to the loss of bronchial artery supply leading to ischemia of the bronchial cartilage. This form of bronchomalacia may take months to

Table 437.1 Classification of Tracheomalacia

PRIMARY TRACHEOMALACIA
Congenital absence of tracheal-supporting cartilages
SECONDARY TRACHEOMALACIA
Esophageal atresia, tracheoesophageal fistula
Vascular rings (double aortic arch)
Tracheal compression from an aberrant innominate artery
Tracheal compression from mediastinal masses
Abnormally soft tracheal cartilages associated with connective tissue disorders
Prolonged mechanical ventilation, chronic lung disease

From McNamara VM, Crabbe DC. Tracheomalacia. *Paediatr Respir Rev.* 2004;5:147–154.

present after transplantation. Laryngomalacia can accompany primary bronchomalacia or tracheomalacia. Involvement of the entire central airway (laryngotracheobronchomalacia) is also seen.

CLINICAL MANIFESTATIONS

Primary tracheomalacia and bronchomalacia are principally disorders of infants, with a male:female ratio of 2:1. The dominant finding—low-pitched, monophonic wheezing heard predominantly during expiration—is most prominent over the central airways. Parents often describe persistent respiratory congestion even in the absence of a viral respiratory infection. When the lesion involves only one main bronchus (more commonly the left), the wheezing is louder on that side and there may be unilateral palpable fremitus. In cases of tracheomalacia, the wheeze is loudest over the trachea. Hyperinflation and/or subcostal retractions do not occur unless the patient has concurrent dysphagia with chronic aspiration, viral bronchiolitis, asthma, or other causes of peripheral airway obstruction. In the absence of asthma, patients with tracheomalacia and bronchomalacia are not helped by administration of a bronchodilator. Acquired tracheomalacia and bronchomalacia are seen in association with vascular compression (vascular rings, slings, and innominate artery compression) or in association with the loss of bronchial artery supply in lung transplantation. Persistent tracheomalacia is the rule after correction of tracheoesophageal fistula. Other causes of acquired tracheomalacia and bronchomalacia (especially left-sided) include cardiomegaly. The importance of the physical exam cannot be understated; one study found that pediatric pulmonologists made a correct assessment of malacia based on symptoms, history, and lung function before bronchoscopy in ~70% of cases. The cough in tracheomalacia and bronchomalacia can lead to collapse of the airway, which can lead to difficulty in airway clearance. The cough in tracheomalacia and bronchomalacia often has a barking, croupy quality. This can be managed in older patients with handheld positive expiratory pressure devices. Persistent cough in older children with tracheomalacia can cause irritation of the airway mucosa from the physical trauma and induce some degree of habitual cough.

DIAGNOSIS

Definitive diagnoses of tracheomalacia and bronchomalacia are established by flexible or rigid bronchoscopy (Fig. 437.1). The lesion is difficult to detect on plain radiographs. Although fluoroscopy can demonstrate dynamic collapse and avoid the need for invasive diagnostic techniques, it is poorly sensitive. Pulmonary function testing can show a pattern of decreased peak flow and flattening of the flow-volume loop. Other important diagnostic modalities include MRI and CT scanning. Dynamic airway assessment using three-dimensional CT reconstruction at end-inspiration and end-expiration can be diagnostic and avoid the need for invasive evaluation. MRI with angiography is especially useful when there is a possibility of vascular ring and should be performed when a right aortic arch is seen on plain film radiography.

TREATMENT

Postural drainage can help with clearance of secretions. β-Adrenergic agents *should be avoided* in the absence of asthma because they can exacerbate loss of airway patency due to decreased airway tone. Nebulized ipratropium bromide may be useful. Endobronchial stents have been used in severely affected patients but have a high incidence of complications, ranging from airway obstruction caused by granulation tissue to erosion into adjacent vascular structures. Continuous positive airway pressure via tracheostomy may be indicated for severe cases. A surgical approach (aortopexy and bronchopexy) is rarely required and only for patients who have life-threatening apnea, cyanosis, and bradycardia (cyanotic spells) from airway obstruction and/or who demonstrated vascular compression. Reports of creation and use of three-dimensional (3D) printed, bioresorbable external tracheobronchial stents in pediatric patients with life-threatening tracheobronchomalacia have shown great promise.

PROGNOSIS

Primary bronchomalacia and tracheomalacia have excellent prognoses because airflow improves as the child and the airways grow. Patients with primary airway malacia usually take longer to recover from common respiratory infections. Wheezing at rest usually resolves by age 3 years. Prolonged bacterial bronchitis has been reported as a complication of bronchomalacia. The prognosis in secondary and acquired forms varies with cause. Patients with concurrent asthma need considerable supportive treatment and careful monitoring of respiratory status.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

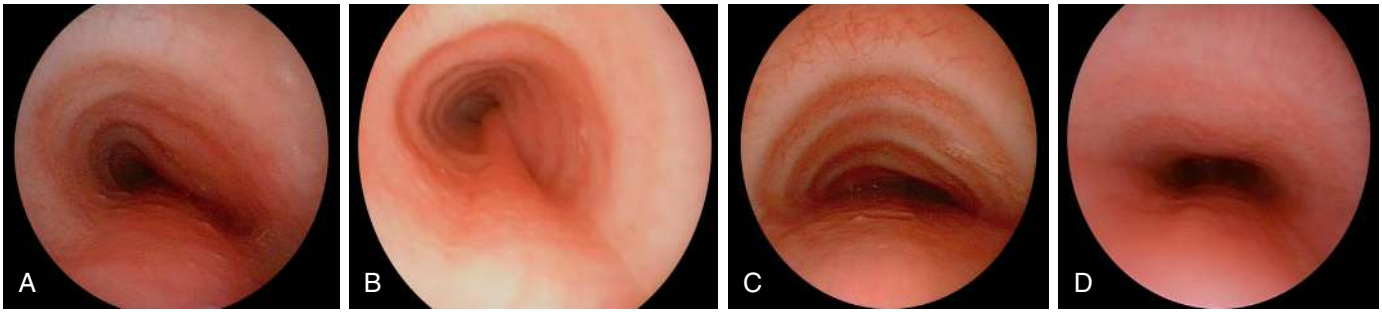

Fig. 437.1 Four examples of tracheomalacia appearances. **A,** Comma-shaped trachea caused by innominate artery compression requiring aortopexy. **B,** Bunched-up trachealis muscle and compressed trachea caused by a double aortic arch. **C,** Flattened trachea and increased trachealis diameter with a tracheoesophageal fistula in the posterior wall. **D,** Ovoid-shaped trachea from external compression by the innominate artery. *(From Deacon JWF, Widger J, Soma MA. Paediatric tracheomalacia—a review of clinical features and comparison of diagnostic imaging techniques. Int J Pediatr Otorhinolaryngol. 2017;98:75–81.)*

Chapter 438

Neoplasms of the Larynx, Trachea, and Bronchi

Saied Ghadersohi, Lauren D. Holinger, and James W. Schroeder Jr.

438.1 Vocal Nodules

Saied Ghadersohi and James W. Schroeder Jr.

Vocal nodules, which are not true neoplasms, are the most common cause of chronic hoarseness in children. Chronic vocal abuse or misuse (i.e., frequent yelling and screaming) produces localized vascular congestion, edema, hyalinization, and epithelial thickening in the bilateral vocal cords. This grossly appears as nodules that disrupt the normal vibration of the cords during phonation. Vocal abuse is the main factor, and the voice is worse in the evenings. The differential diagnosis can include unilateral lesions such as vocal cord cysts and polyps; however, these usually have an acute inciting event and are rarer in children.

Diagnosis is typically via laryngoscopy and stroboscopy to assess the characteristics of the bilateral nodules. Occasionally biopsy is needed in atypical-behaving/-appearing lesions. Treatment is primarily nonsurgical, with voice therapy used in children >4 years of age who can participate in therapy and clinical monitoring with behavioral therapy in younger children or those with developmental delay. In addition, laryngopharyngeal reflux commonly exacerbates vocal abuse–induced irritation of the cord; therefore antireflux therapy can also be implemented (see Chapter 369). Surgical excision of vocal cord nodules in children is controversial and is rarely indicated but may be necessary if the child is unable to communicate adequately, becomes aphonic, or requires tension and straining to make an utterance.

438.2 Recurrent Respiratory Papillomatosis

Saied Ghadersohi and James W. Schroeder Jr.

Papillomas are the most common respiratory tract neoplasms in children, occurring in 4.3 in 100,000. They are simply warts—benign tumors—caused by the human papillomavirus (HPV), most commonly types 6 and 11 (see Chapter 313). Seventy-five percent of recurrent respiratory papilloma (RRP) cases occur in children younger than age 5 years, but the diagnosis may be made at any age. In general, neonatal-onset disease is a poor prognostic factor with higher mortality and need for tracheostomy. Sixty-seven percent of children with RRP are born to mothers who had condylomas during pregnancy or parturition. The mode of HPV transmission is still not clear but is thought to be through exposure to HPV when traversing the birth canal of an infected mother. Other identified risk factors include first born, >10 hours of labor, and a young mother. However, HPV exposure is fairly common and RRP remains rare; additionally, in mothers with vaginal condylomata, only 1 in 231-400 vaginal births go on to develop respiratory papillomatosis. Therefore other risk factors contribute to transmission, and cesarean-section delivery for prevention cannot be recommended. However, preventive measures can include the prospective widespread use of the quadrivalent HPV vaccine to help eliminate maternal and paternal HPV reservoirs and possibly decrease cases of RRP caused by HPV-6 and -11.

CLINICAL MANIFESTATIONS

The clinical course involves remissions and exacerbations of recurrent papilloma, most commonly on the larynx (usually the vocal cords), causing progressively worsening hoarseness, sleep-disordered breathing, exertional dyspnea, stridor, and, if left untreated, eventually severe airway obstruction (Fig. 438.1). Although it is a benign disease, lesions can spread throughout the aerodigestive tract in 31% of patients, most commonly the oral cavity, trachea, and bronchi. Rarely these lesions can undergo malignant conversion (1.6%); however, some patients may have spontaneous remission. Patients may be initially diagnosed with asthma, croup, vocal nodules, or allergies.



Fig. 438.1 Laryngoscopic view of respiratory papillomas causing near-complete obstruction at glottic level. *(From Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118:1236–1245.)*

DIAGNOSIS AND TREATMENT

Diagnosis of RRP is via laryngoscopy and bronchoscopy. Biopsy should be obtained at the initial surgical intervention and regular intervals to rule out malignancy and to subtype the HPV, as it can affect prognosis. Treatment of RRP is endoscopic surgical removal with three goals. First, debulking/complete removal of the lesions; second, preservation of normal structures; and finally, prevention of scar formation in the affected areas. Most surgeons in North America prefer the microdebrider, although microsurgery, CO_2, and KTP laser techniques have been described. Despite these techniques, some form of adjunct therapy may be needed in up to 20% of cases. The most widely accepted indications for adjunct therapy are a need for more than four surgical procedures per year, rapid regrowth of papillomata with airway compromise, or distal multisite spread of disease. Adjunct therapies can be inhaled or administered intralesionally or systemically and include antiviral modalities (interferon, ribavirin, acyclovir, cidofovir), antiangiogenic agents such as bevacizumab (Avastin), photodynamic therapy, dietary supplement (indole-3-carbinol), nonsteroidal antiinflammatory drugs (COX-2 inhibitors, Celebrex), retinoids, and mumps vaccination.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

438.3 Congenital Subglottic Hemangioma

Saied Ghadersohi and James W. Schroeder Jr.

See also Chapter 434.5.

Typically, congenital subglottic hemangiomas are symptomatic within the first 2 months of life, with almost all occurring before 6 months of age. Much like the cutaneous infantile hemangiomas, these lesions have two phases: a **proliferative phase** with rapid growth in the first 6 months of life and then they stabilize by 1 year and a slow **involution phase** typically by age 3. Patients present with usually inspiratory but sometimes biphasic stridor. The infant can have a barking cough and temporarily respond to steroids, similar to persistent croup. Fifty percent of congenital subglottic hemangiomas are associated

with facial lesions, but the converse is not true. Radiographs classically delineate an asymmetric subglottic narrowing. The diagnosis is made by direct laryngoscopy.

DIAGNOSIS AND TREATMENT

The diagnosis of subglottic hemangioma is based on history and laryngoscopic exam. MRI imaging with contrast can also be obtained to confirm the diagnosis of a vascular lesion. If the lesion does not respond to medical therapy, then biopsy (with GLUT1 staining; positive suggests hemangioma) may be indicated to rule out other vascular tumors. Subglottic hemangiomas are treated similarly to cutaneous hemangiomas (see Chapter 691). Propranolol is the first-line treatment of cutaneous and subglottic infantile hemangiomas. Typically, treatment is with 1-3 mg/kg/day of propranolol for 4-12 months (see Chapter 691). Prescreening patients with cardiology workup (i.e., electrocardiogram) is advised. Side effects include hypotension, bradycardia, bronchospasm, and hypoglycemia, which can be avoided by giving the medication with a feed.

There remains a role for systemic steroids, racemic epinephrine, and helium/oxygen treatment in the acute management of the airway and in lesions that are slow or nonresponsive to propranolol treatment (i.e., large hemangiomas with critical airway narrowing).

Surgical management is offered in severe cases or those not responsive to medical therapy. Interventions can range from intralesional steroid injection to avoid systemic steroid side effects, CO_2, or KTP laser endoscopic excision or open surgical excision, and ultimately as a last resort tracheostomy can establish a safe airway, allowing time for the lesion to involute per its natural course.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

438.4 Vascular Malformations

Saied Ghadersohi and James W. Schroeder Jr.

Based on the International Society for the Study of Vascular Anomalies classification system, these lesions can be classified into vascular malformations and vascular tumors. The most common vascular tumors are infantile/subglottic hemangiomas. Vascular malformations are not true neoplastic lesions. They have a normal rate of endothelial turnover and various channel abnormalities. They are subcategorized based on high or low flow and by their predominant type (capillary, venous, arterial, lymphatic, or a combination thereof). Overall, vascular malformations are uncommon, and they rarely occur in the larynx and airway. When they do occur, they are often an extension from elsewhere in the head and neck. It should be noted that these lesions can expand with a viral upper respiratory infection or hemorrhage into the lesion. They can be diagnosed with direct visualization during laryngoscopy or bronchoscopy or seen on CT/MRI imaging. Treatment usually entails a tailored multidisciplinary team approach with early surgery, laser resection, or sclerotherapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

438.5 Other Laryngeal Neoplasms

James W. Schroeder Jr. and Lauren D. Holinger

Neurofibromatosis (see Chapter 636.1) rarely involves the larynx. When children are affected, limited local resection is undertaken to maintain an airway and optimize the voice. Complete surgical extirpation is virtually impossible without debilitating resection of vital laryngeal structures. Most surgeons select the option of less aggressive symptomatic surgery because of the poorly circumscribed and infiltrative nature of these fibromas. **Rhabdomyosarcoma** (see Chapter 549) and other malignant tumors of the larynx are rare. Symptoms of hoarseness and progressive airway obstruction prompt initial evaluation by flexible laryngoscopy in the office.

438.6 Tracheal Neoplasms

Saied Ghadersohi, James W. Schroeder Jr., and Lauren D. Holinger

Tracheal tumors are extremely rare and include malignant and benign neoplasms; they may initially be misdiagnosed as asthma. The two most common benign tumors are inflammatory pseudotumor and hamartoma. The **inflammatory pseudotumor** is probably a reaction to a previous bronchial infection or traumatic insult. Growth is slow, and the tumor may be locally invasive. Hamartomas are tumors of primary tissue elements that are abnormal in proportion and arrangement.

Tracheal neoplasms manifest with stridor, wheezing, cough, or pneumonia and are rarely diagnosed until 75% of the lumen has been obstructed (Fig. 438.2). Chest radiographs or airway films can identify the obstruction. Pulmonary function studies demonstrate an abnormal flow-volume loop. A mild response to bronchodilator therapy may be misleading. Treatment is based on the histopathology.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

438.7 Bronchial Tumors

Saied Ghadersohi and James W. Schroeder Jr.

Bronchial tumors are rare. In one series, carcinoid tumors were the most common, followed by mucoepidermoid and inflammatory pseudotumors. These patients can present with persistent pneumonia despite adequate treatment. The diagnosis is confirmed at bronchoscopy and biopsy; treatment depends on the histopathology.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

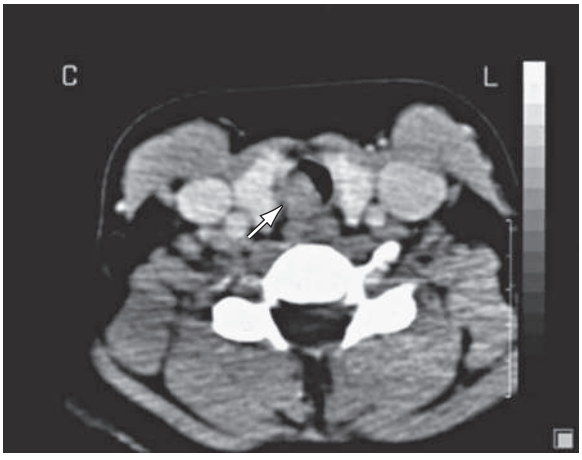

Fig. 438.2 CT scan of the trachea with a circumscribed intraluminal tracheal mass *(arrow)* in the tracheal wall. *(From Venizelos I, Papathomas T, Anagnostou E, et al. Pediatric inflammatory myofibroblastic tumor of the trachea: a case report and review of the literature. Pediatr Pulmonol. 2008;43:831–835.)*

Chapter 439
Wheezing, Bronchiolitis, and Bronchitis

439.1 Wheezing in Infants: Bronchiolitis

Samantha A. House and Shawn L. Ralston

Wheezing, the production of a musical continuous sound that originates in narrowed airways, is heard on expiration as a result of airway obstruction. Infants are more likely to wheeze than are older children as a result of differing lung mechanics. Obstruction of airflow is affected by both airway size and compliance of the infant lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the fourth power. In children younger than 5 years, small-caliber peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing, such as that caused by inflammation related to viral infection, is then more likely to result in wheezing.

Infant chest wall compliance is also quite high; thus the inward pressure produced in normal expiration subjects the intrathoracic airways to collapse. Differences in tracheal cartilage and airway smooth muscle tone increase the collapsibility of the infant airways in comparison with older children. These mechanisms combine to make the infant more susceptible to airway obstruction, increased resistance, and subsequent wheezing. The mechanical portion of the infant propensity to wheeze resolves with normal growth and muscular development.

Although wheezing in infants most frequently results from inflammation due to acute viral infections, there are many potential causes of wheezing (Table 439.1).

Acute Bronchiolitis

Acute bronchiolitis is a diagnostic term used to describe the clinical picture produced by multiple different viral lower respiratory tract infections in infants and very young children. The respiratory findings observed in bronchiolitis include tachypnea, wheezing, crackles, and rhonchi, which result from inflammation of the small airways (Fig. 439.1). Despite its commonality, a universal set of diagnostic criteria for bronchiolitis does not exist, with significant disagreement about the upper age limit for appropriate use of the diagnosis. Some clinicians restrict the term to children younger than 1 year, and others extend it to the age of 2 years or beyond.

The pathophysiology of acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucus, and cellular debris (see Fig. 439.1). Resistance in the small air passages is increased during both inspiration and exhalation, but because the radius of an airway is smaller during expiration, the resultant respiratory obstruction leads to expiratory wheezing, air trapping, and lung hyperinflation. If obstruction becomes complete, trapped distal air will be resorbed and the child will develop atelectasis. Hypoxemia may result from ventilation-perfusion mismatch. Hypercapnia may develop with severe obstructive disease.

Respiratory syncytial virus (RSV) is responsible for more than 50% of cases of bronchiolitis. Other causal agents include human metapneumovirus, rhinovirus, parainfluenza, influenza, coronavirus, bocavirus, and adenovirus, among others. Viral *co-infection* can occur; the impact of co-infection on severity and clinical manifestations of bronchiolitis remains unclear. Respiratory viruses can be identified in more than one third of asymptomatic patients younger than the age of 1 year, calling into question the specificity of nucleic acid amplification tests for active infection with some viruses. Although bacterial pneumonia is sometimes confused clinically with bronchiolitis, viral bronchiolitis is only rarely followed by bacterial superinfection.

Over 100,000 young children are typically hospitalized annually in the United States with the diagnosis of bronchiolitis, making it the most common diagnosis resulting in hospitalization for children younger than 1 year of age in the United States over the past several decades. Hospitalization rates have been relatively stable in pre–COVID-19 pandemic years despite introduction and routine use of RSV immunoprophylaxis in selected high-risk populations. Nonetheless, variants of COVID-19 have been associated with a bronchiolitis-like syndrome. In addition, a robust RSV surge was observed in the late-pandemic period. Co-infection with COVID-19 has been observed,

Table 439.1 Differential Diagnosis and Etiologies of Wheezing in Infancy

INFECTION
Viral
Respiratory syncytial virus
Human metapneumovirus
Parainfluenza
Adenovirus
Influenza
Rhinovirus
Bocavirus
Coronavirus, including COVID-19 variants
Enterovirus
Other
Chlamydia trachomatis
Tuberculosis
Histoplasmosis
Papillomatosis
ASTHMA
ANATOMIC ABNORMALITIES
Central Airway Abnormalities
Malacia of the larynx, trachea, and/or bronchi
Laryngeal or tracheal web
Tracheoesophageal fistula (specifically H-type fistula)
Laryngeal cleft (resulting in aspiration)
Extrinsic Airway Anomalies Resulting in Airway Compression
Vascular ring or sling
Mediastinal lymphadenopathy from infection or tumor
Mediastinal mass or tumor
Esophageal foreign body
Intrinsic Airway Anomalies
Airway hemangioma or other tumor
Congenital pulmonary airway malformation (cystic adenomatoid malformation)
Bronchial or lung cyst
Congenital lobar emphysema
Aberrant tracheal bronchus
Sequestration
Congenital heart disease with left-to-right shunt (increased pulmonary edema)
Foreign body
Immunodeficiency States
Immunoglobulin A deficiency
B-cell deficiencies
AIDS
Bronchiectasis
MUCOCILIARY CLEARANCE DISORDERS
Cystic fibrosis
Primary ciliary dyskinesia
Bronchiectasis
ASPIRATION SYNDROMES
Gastroesophageal reflux disease
Pharyngeal/swallow dysfunction
OTHER
Bronchopulmonary dysplasia
Eosinophilic granulomatosis with polyangiitis
Interstitial lung disease, including bronchiolitis obliterans
Heart failure
Anaphylaxis
Inhalation injury—burns

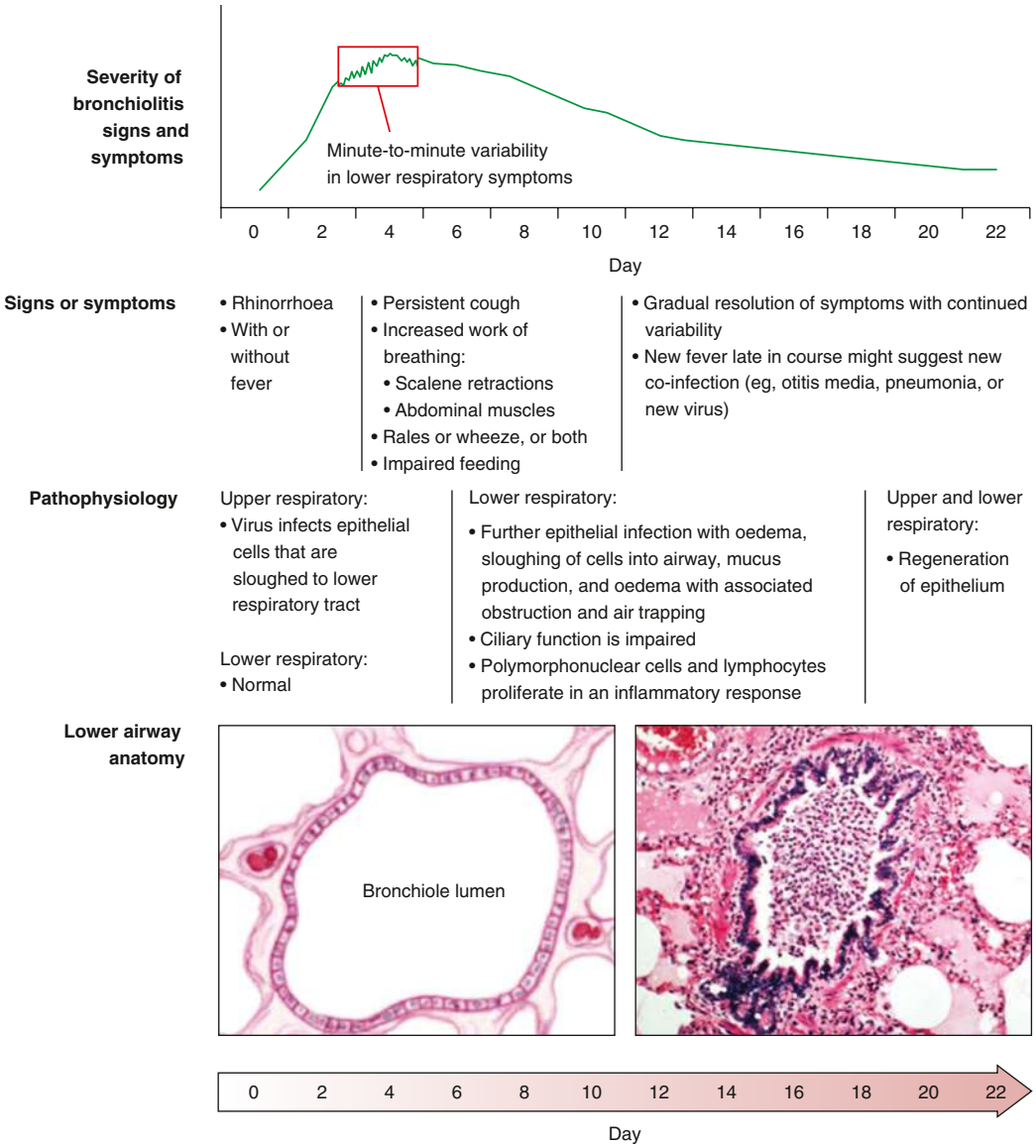

Fig. 439.1 Typical clinical course and pathophysiology of viral bronchiolitis. *(From Florin TA, Plint PC, Zorc JJ. Viral bronchiolitis. Lancet. 2017;389:211–224, Fig. 1.)*

but its implications on disease presentation and severity are not well characterized.

Bronchiolitis is more common in males, those exposed to secondhand tobacco smoke, those who have not been breastfed, and those living in crowded conditions. The risk is also higher for infants with mothers who smoked during pregnancy. Older family members, including older siblings, are a common source of infection; they might experience only minor upper respiratory symptoms (colds) given that bronchiolar edema may be less clinically apparent as airway size increases.

Asthma (see Chapter 185) is another important cause of wheezing, and the possibility of this diagnosis complicates the treatment of young children with bronchiolitis, although diagnosing asthma in the very young can be difficult. In prospective, longitudinal population cohort studies of infants, up to half of the cohort experienced a wheezing illness before school age, although when followed into adulthood only about 5–8% of patients prove to have asthma. In the largest U.S. cohort, three patterns of infant wheezing were proposed: transient early wheezing, comprising about 20% of the cohort, characterized by lower lung function at birth that improves with growth, resulting in resolution of wheezing by age 3; persistent wheezing, comprising about 14% of the cohort, characterized by declining lung function and wheezing before and after age 3; and late-onset wheezing, comprising 15% of the cohort, characterized by relatively stable lung function and wheezing that does not begin until after age 3. The remaining 50% of the population did not suffer a wheezing illness. Following the cohort into adulthood revealed continued declines in the rates of persistent symptoms. Similar patterns are also seen in birth cohort studies in other countries.

Multiple studies attempting to predict which infants suffering from early wheezing illnesses will go on to have asthma in later life have failed to achieve discriminant validity. Interestingly, in both U.S. and UK prospective cohorts, wheezing with an onset *after* the first 18-36 months of life is one of the strongest predictors of eventual asthma in both cohorts. Other proposed risk factors for persistent wheezing include parental history of asthma and allergies, maternal smoking, persistent rhinitis (apart from acute upper respiratory tract infections), allergen sensitization, eczema, and peripheral eosinophilia, although no single factor is strongly discriminative. There is no evidence that early administration of systemic or inhaled corticosteroids to high-risk populations can prevent the development of asthma.

Table 439.2 Pertinent Medical History in the Wheezing Infant

Did the onset of symptoms begin at birth or thereafter?
Is the infant a noisy breather, and when is it most prominent?
Is the noisy breathing present on inspiration, expiration, or both?
Is there a history of cough apart from wheezing?
Was there an earlier lower respiratory tract infection?
Is there a history of recurrent upper or lower respiratory tract infections?
Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress?
Is there a history of eczema?
Does the infant cough after crying or cough at night?
How is the infant growing and developing?
Is there associated failure to thrive?
Is there a history of electrolyte abnormalities?
Are there signs of intestinal malabsorption, including frequent, greasy, or oily stools?
Is there a maternal history of genital herpes simplex virus infection?
What was the gestational age at delivery?
Was the patient intubated as a neonate?
Does the infant bottle-feed in the bed or the crib, especially in a propped position?
Are there any feeding difficulties, including choking, gagging, arching, or vomiting with feeds?
Is there any new food exposure?
Is there a toddler in the home or lapse in supervision in which foreign body aspiration could have occurred?
Is there a change in caregivers or a chance of nonaccidental trauma?

Clinical Manifestations

The initial history of a wheezing infant should explore the onset, duration, and associated factors (Table 439.2), as well as *birth history* (weeks of gestation, neonatal complications including history of intubation or oxygen requirement, maternal complications) and prenatal smoke exposure. Past medical history, including any comorbid conditions, should be assessed. *Family history* of cystic fibrosis, immunodeficiencies, asthma in a first-degree relative, or any other recurrent respiratory conditions in children should be obtained. *Social history* should include any tobacco or other smoke exposure, daycare exposure, number of siblings, pets, and concerns regarding the home environment (e.g., dust mites, construction dust, heating and cooling techniques, mold, cockroaches). The patient's growth chart should be reviewed for signs of failure to thrive.

Acute bronchiolitis is usually preceded by exposure (daycare, preschool, siblings) to contacts with a minor respiratory illness within the previous week (see Fig. 439.1). The infant first develops signs of upper respiratory tract infection with sneezing and clear rhinorrhea. This may be accompanied by diminished appetite and fever. Gradually, respiratory distress ensues, with paroxysmal cough, dyspnea, and irritability. The infant is often tachypneic, which can interfere with feeding. Though rare, apnea may occur in very young infants and may precede lower respiratory signs early in the disease. Infants at a postconceptual age of <44 weeks are at highest risk for *apneic* events, with premature birth providing an additional risk factor.

On physical examination, evaluation of the patient's vital signs with special attention to the respiratory rate and oxygen saturation is an important initial step. The exam is often dominated by wheezing and crackles. Expiratory time may be prolonged. Work of breathing may be markedly increased, with nasal flaring and retractions. *Complete obstruction to airflow can eliminate the turbulence that causes wheezing; thus the lack of audible wheezing is not reassuring if the infant shows other signs of respiratory distress.* Poorly audible breath sounds suggest severe disease with nearly complete bronchiolar obstruction.

Diagnostic Evaluation

Evaluation of wheezing in infancy and early childhood depends on suspected etiology. The diagnosis of **acute bronchiolitis** is clinical and should be considered in an infant presenting with a first episode of wheezing after a period of upper respiratory symptoms. Chest radiography is not routinely indicated in children with suspected bronchiolitis. Areas of atelectasis associated with bronchiolitis are often observed on chest radiographs and may be difficult to distinguish from bacterial pneumonia; as a result, obtaining chest radiography in a patient whose clinical course and exam are consistent with bronchiolitis may lead to unnecessary antibiotic use. Laboratory testing is also not routinely indicated; the white blood cell and differential counts are usually normal and are not predictive of bacterial superinfection. Viral testing (polymerase chain reaction or rapid immunofluorescence) is not routinely recommended in the diagnosis of bronchiolitis but may be helpful if such testing prevents more invasive evaluations or treatments. Concurrent serious bacterial infection (sepsis, pneumonia, meningitis) is unlikely, although confirmation of viral bronchiolitis may obviate the need for a sepsis evaluation in the young febrile infant. Otitis media may complicate bronchiolitis.

For young children with wheezing in whom the presentation does not clinically fit with the diagnosis of bronchiolitis, including those without other signs of viral infection, with very severe presentation, or with a complicated clinical course, further workup should be considered and should be dictated by individual clinical context. Children with recurrent or refractory episodes of wheezing in infancy, particularly if associated with failure to thrive, may require evaluation for chronic disorders such as cystic fibrosis or immunodeficiency.

Treatment

The treatment of children with viral bronchiolitis is supportive management. Those who are experiencing hypoxia, respiratory distress (inability to feed, extreme tachypnea, or significantly increased work of breathing), or apnea should be hospitalized. Risk factors for severe disease include younger age, preterm birth, or underlying comorbidity. Hypoxemic children should receive supplemental oxygen. There is a developing consensus surrounding target oxygen saturations; national guidelines in the United States propose a threshold of 90%. Oxygen can be administered via a number of delivery devices, and some children with severe disease may require positive pressure ventilation. High-flow nasal oxygen cannula (HFNC) use has become common, though studies to date have failed to demonstrate a consistent benefit on clinical outcomes. Despite an apparent stabilization with HFNC, such therapy has not consistently shortened the length of hospital stay or duration of oxygen therapy. Continuous pulse oximetry monitoring can be discontinued once patients are no longer requiring supplemental oxygen and are clinically improving.

Some children may also require support with supplemental hydration. Fluid can be administered intravenously or enterally via nasogastric tube, with some preference given to the latter because of an association between better outcomes with continued provision of enteral nutrition. If intravenous fluids are administered, care should be taken to use isotonic fluids because of the risk of hyponatremia. Frequent suctioning of nasal and oral secretions often provides relief of distress and improves work of breathing and ability to feed, although this should be limited to the nares or oropharynx because deep tracheal suctioning does not provide additional benefit and may cause harm. Chest physiotherapy has been extensively evaluated and provides *no benefit* to children with bronchiolitis.

Pharmacologic agents have largely proven *ineffective* in the management of bronchiolitis. Multiple systematic reviews and meta-analyses have failed to demonstrate any impact on clinical outcomes with use of albuterol or corticosteroids in bronchiolitis; neither are currently recommended for management. Response to bronchodilators is unlikely and unpredictable in children younger than 1 year. The use of inhaled or oral steroids in very young children with wheezing has not been shown to affect the disease trajectory or prevent the progression of childhood wheezing or development of asthma. There is debate over the use of

inhaled hypertonic saline in children with bronchiolitis, although most studies and meta-analyses fail to demonstrate any major benefit. Racemic epinephrine has not been found to improve the length of stay or clinical outcomes among inpatients with bronchiolitis, although there is some evidence to suggest that it may reduce the risk of hospitalization when used in the outpatient setting. Ribavirin, the only currently available antiviral medication targeting RSV, is also *not* currently recommended because of minimal impact on disease outcomes and because it is costly, difficult to administer, and associated with important toxicities.

PROGNOSIS

Infants with acute bronchiolitis are generally considered to be at highest risk for further respiratory compromise in the first 72 hours after onset of cough and dyspnea. The case fatality rate is <1% in developed countries, with death attributable to respiratory arrest and/or failure or severe dehydration and electrolyte disturbances. *A majority of deaths caused by bronchiolitis occur in children with complex medical conditions or comorbidities such as bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency.* The median duration of symptoms in ambulatory patients is approximately 14 days; 10% may be symptomatic for 3 weeks. Severe lower respiratory tract infection at an early age has been identified as a possible risk factor for the development of asthma, although most children with early childhood wheezing will not go on to suffer from asthma. It is unclear whether viral infections causing bronchiolitis incite an immune response that manifests as asthma later in life or whether those infants have an inherent predilection for asthma that is first manifested as viral bronchiolitis.

PREVENTION (See also Chapter 307)

Meticulous hand hygiene is the best measure to prevent transmission of the viruses responsible for bronchiolitis. Nirsevimab, a one dose long-acting monoclonal antibody, is approved for prevention of RSV infection in newborns and infants. Nirsevimab is indicated for infants < 8 months of age born during or entering their first RSV season (in the continental US this may be October to March, although there may be regional differences), including those previously recommended to receive palivizumab (which is not given). Nirsevimab dose in the first RSV season is 50 mg if < 5 kg and 100 mg in infants ≥ 5 kg. In addition, older infants (8-19 months) who are at increased risk of severe RSV infection entering their second RSV season should also receive nirsevimab. These older infants include those with:

- Chronic lung disease of prematurity that requires chronic steroid or diuretic therapy or supplemental oxygen
- Severe immunocompromising conditions
- Cystic fibrosis with severe lung disease or poor weight gain
- American Indian and Alaska Native

The single dose of nirsevimab in the second RSV season is 200 mg given as two 100 mg injections in different sites. Nirsevimab may be coadministered with other routine childhood immunizations. Because of the availability of nirsevimab, immunization of high-risk populations with palivizumab is no longer recommended even if they received palivizumab in the previous RSV season.

In addition to immunization after birth, there is an FDA-approved maternal vaccine to prevent neonatal and infant RSV infections. The one dose vaccine (bivalent RSV prefusion F protein) is approved for use in women between 32-36 weeks' gestation. Nirsevimab is the only recommended approach to RSV prevention by the ACIP (CDC) and the AAP.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

439.2 Bronchitis

Samantha A. House and Shawn L. Ralston

Nonspecific bronchial inflammation is termed *bronchitis* and can occur in multiple childhood conditions. Acute bronchitis is a clinical syndrome, usually viral in origin, with cough as a prominent feature. *Acute tracheobronchitis* is a term used when the trachea is prominently involved, such as with pertussis, parainfluenza, or diphtheria.

ACUTE BRONCHITIS

Acute bronchitis often follows a viral upper respiratory tract infection. It is more common in the winter when respiratory viral syndromes predominate. The tracheobronchial epithelium is invaded by the infectious agent, leading to activation of inflammatory cells and release of cytokines. Constitutional symptoms, including fever and malaise, follow. The tracheobronchial epithelium can become damaged or hypersensitized, leading to a protracted cough lasting 1-3 weeks.

The child first presents with nonspecific upper respiratory infectious symptoms, such as rhinitis. Three to four days later, a frequent, hacking cough develops, which may or may not be productive. After several days, the sputum can become purulent, indicating leukocyte migration but not necessarily bacterial infection. Many children swallow their sputum, which can produce emesis. Chest pain may be a prominent complaint in older children and is exacerbated by coughing. The mucus gradually thins, usually within 5-10 days, and then the cough gradually abates. The entire episode usually lasts about 2 weeks and seldom longer than 3 weeks.

Findings on physical examination vary with the age of the patient and stage of the disease. Early findings include no or low-grade fever and upper respiratory signs such as nasopharyngitis, conjunctivitis, and rhinitis. Auscultation of the chest may be unremarkable at this early phase. As the syndrome progresses and cough worsens, breath sounds become coarse, with coarse and fine crackles and scattered wheezing possible. Chest radiographs may be normal or may demonstrate increased bronchial markings.

The principal objective of the clinician is to exclude bacterial illnesses requiring antibiotic treatment, such as pneumonia, pertussis, or bacterial tracheitis. Obtaining sputum can be difficult in young children, and isolation of bacteria may not always indicate infection; thus sputum cultures are not generally recommended outside of specific diseases such as cystic fibrosis. Absence of vital sign abnormalities (tachycardia, tachypnea, fever) and a normal physical examination of the chest reduce the likelihood of pneumonia.

Differential Diagnosis

Persistent or recurrent symptoms should lead the clinician to consider entities other than acute bronchitis. Many entities manifest with cough as a prominent symptom (Table 439.3).

Table 439.3 Disorders with Cough as a Prominent Finding

CATEGORY	DIAGNOSES
Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Primary ciliary dyskinesia Other chronic lung diseases
Other chronic disease or congenital disorders	Laryngeal cleft Swallowing disorders Gastroesophageal reflux Airway compression (such as a vascular ring or hemangioma) Congenital heart disease
Infectious or immune disorders	Immunodeficiency Eosinophilic lung disease Tuberculosis Allergy Sinusitis Tonsillitis or adenoiditis *Chlamydia, Ureaplasma* (infants) *Bordetella pertussis* *Mycoplasma pneumoniae*
Acquired	Foreign body aspiration, tracheal or esophageal

Treatment

There is no specific therapy for acute bronchitis. The disease is typically a response to a viral infection and is self-limited. Antibiotics, although often prescribed, do not hasten improvement. Frequent shifts in position can facilitate pulmonary drainage in infants. Older children are sometimes more comfortable with humidity, but this does not shorten the disease course. Cough suppressants are contraindicated in the youngest children, and although they may relieve symptoms, they can also increase the risk of superinfection and therefore should be used judiciously. Antihistamines and expectorants are not indicated. Nonprescription cough and cold medicines should not be used in children younger than 4 years of age, and their use is cautioned in children age 4-11 years.

CHRONIC BRONCHITIS

Chronic bronchitis is well recognized in adults, formally defined as 3 months or longer of productive cough each year for 2 or more years. The disease can develop insidiously, with episodes of acute obstruction alternating with quiescent periods. Some predisposing conditions can lead to progression of airflow obstruction or chronic obstructive pulmonary disease, with smoking as the major factor (up to 80% of patients have a smoking history). Other conditions include air pollution, occupational exposures, and repeated infections.

The applicability of this definition to children is unclear. The existence of chronic bronchitis as a distinct entity in children is controversial. Like adults, children with chronic inflammatory diseases or those with toxic exposures can develop damaged pulmonary epithelium. Thus chronic or recurring cough in children should lead the clinician to search for underlying pulmonary or systemic disorders (see Table 439.3). One proposed entity that shares characteristics with asthma and other forms of suppurative lung disease is persistent or protracted bacterial bronchitis. Protracted bacterial bronchitis is defined as three or more of the following criteria: (1) continuous wet or productive cough >4 weeks, (2) no signs or symptoms to suggest other causes, and (3) cough resolves with appropriate course of oral antibiotics.

CIGARETTE SMOKING AND AIR POLLUTION

Exposure to environmental irritants, such as tobacco smoke and air pollution, can incite or aggravate cough. There is a well-established association between tobacco exposure and pulmonary disease, including bronchitis and wheezing. This can occur through cigarette smoking or by exposure to secondhand smoke. Marijuana smoke, electronic cigarettes, and other inhalants are irritants sometimes overlooked when eliciting a history.

A number of pollutants compromise lung development and likely precipitate lung disease, including particulate matter, ozone, acid vapor, and nitrogen dioxide. Proximity to motor vehicle traffic is an important source of these pollutants. Because these substances coexist in the atmosphere, the relative contribution of any one to pulmonary symptoms is difficult to discern.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 440

Plastic Bronchitis

Brett J. Bordini

Plastic bronchitis is a rare condition characterized by recurrent episodes of airway obstruction secondary to the formation of large proteinaceous branching casts that take on the shape of and obstruct the tracheobronchial tree. It is not a single disease entity, but rather represents a state of altered respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or cardiac disease, although plastic bronchitis may also arise in lymphatic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease (Table 440.1). In comparison with the smaller bronchial and bronchiolar casts seen with mucus plugging, the lesions of plastic bronchitis are more extensive, with casts that can outline large segments of the airway to the level of the terminal bronchioles (Fig. 440.1). These casts may be spontaneously expectorated or may require bronchoscopic removal for relief of potentially fatal airway obstruction. Cast composition varies, although it typically consists of either a fibrin-predominant or mucin-predominant laminated matrix with or without inflammatory cell infiltration. Plastic bronchitis may be classified according to an associated disease, the cast histology, or a combination.

Table 440.1 Conditions Associated with Plastic Bronchitis

PROVEN CONDITIONS
Congenital heart disease with Fontan physiology
Pulmonary lymphatic anomalies
Influenza A pulmonary infection
Adenovirus infection
Mycoplasma pneumoniae infection
POSSIBLE CONDITIONS
Toxic inhalation
Sickle cell acute chest syndrome
Hypersecretory and near-fatal asthma (eosinophilic casts)
Noonan syndrome
UNLIKELY AND UNPROVEN CONDITIONS
Bacterial pneumonia
Bronchiectasis
Cystic fibrosis
Chronic obstructive pulmonary disease
Nephrotic syndrome

Modified from Rubin BK. Plastic bronchitis. *Clin Chest Med.* 2016;37:405–408, Box 1.



Fig. 440.1 Tracheobronchial casts after bronchoscopic extraction. Casts show branched architecture corresponding to the bronchial tree. *(From Corrin B, Nicholson AG. Pathology of the Lungs, 3rd ed. London: Churchill Livingstone; 2011: Fig. 3.20.)*

EPIDEMIOLOGY

Plastic bronchitis is rare, with an estimated prevalence of 6.8 cases per 100,000 pediatric patients. Prevalence varies according to the underlying associated disease with rates as high as 14% in patients who have undergone staged palliation of complex congenital heart disease and much lower rates in patients with asthma and atopic disease. A slight male predominance exists for cast formation in the setting of structural heart disease, whereas cast formation in the setting of asthma and atopic disease demonstrates a female predominance. Children with single-ventricle Fontan physiology are at high risk for developing plastic bronchitis.

PATHOGENESIS

The mechanism of cast formation is unclear, although it is believed to vary based on the underlying disease association and cast type. One

classification system differentiates type 1 inflammatory casts, composed primarily of fibrin with neutrophilic or, more often, eosinophilic infiltration, and type 2 acellular casts, composed primarily of mucin with little to no cellular infiltration. Type 1 casts tend to be associated with inflammatory and infectious disorders of the lung, whereas type 2 casts tend to be associated with surgically palliated structural heart disease, particularly single-ventricle lesions. However, these distinctions are not absolute; patients with structural heart disease can have fibrin-predominant casts, and patients with asthma or atopic disease can have mucin-predominant casts, with both mucin casts and fibrin casts demonstrating various degrees of cellular infiltration.

Cast formation in the setting of structural heart disease may result from alterations in pulmonary blood flow or lymphatic drainage, particularly after staged surgical palliation. Under these circumstances, increased central venous pressure is believed to compromise the integrity of the bronchial mucosa, impeding lymphatic flow and resulting in the development of collateral lymphatic vessels and potentially of lymphoalveolar fistulae that may exude proteinaceous material into the airway lumen.

CLINICAL MANIFESTATIONS

Patients with plastic bronchitis may present with cough, dyspnea, wheeze, or pleuritic chest pain. Depending on the degree of airway obstruction, patients may be hypoxemic or in severe respiratory distress. The expectoration of large, branched casts that are often tan in color and rubbery in consistency is pathognomonic for plastic bronchitis. Lung examination may reveal diminished breath sounds or wheezing in the affected area. Rarely, auscultation may reveal a sound similar to a flag flapping in the wind *(bruit de drapeau)*, believed to be related to the free end of a cast striking the bronchial wall during inspiration or expiration. Further examination may provide clues to underlying comorbidities.

DIAGNOSIS

The expectoration or endoscopic discovery of large tracheobronchial casts is pathognomonic for plastic bronchitis. History should be directed at assessing for conditions known to have an associated risk of tracheobronchial cast formation, such as uncorrected or surgically palliated complex congenital heart disease (Fontan physiology); a history of atopic disease or asthma; lymphatic disorders such as Noonan syndrome, Turner syndrome, lymphangiectasia, and yellow nail syndrome; sickle cell disease; and infectious exposures, particularly to tuberculosis, adenovirus, influenza, or atypical mycobacteria. Other predisposing conditions include cystic fibrosis, allergic bronchopulmonary aspergillosis, bronchiectasis, toxic inhalants, and granulomatous lung diseases.

Physical examination may provide indications of an underlying diagnosis. Digital clubbing of the fingers or toes may suggest long-standing hypoxemia associated with cardiac or pulmonary disease. Cardiac examination may provide information suggesting the presence of unrecognized structural heart disease.

Chest radiography may demonstrate collapse of the involved areas of the lung or areas of bronchiectasis distal to sites of long-standing obstruction.

There should be a high index of suspicion for plastic bronchitis in patients with known comorbidities who present with sudden respiratory decompensation. In the absence of cast expectoration, direct visualization of casts via bronchoscopy is required for diagnosis and is potentially therapeutic in relieving airway obstruction. Cast histology should be defined to allow for specific therapies directed at alleviating residual obstruction or preventing recurrence. In particular, the predominant component of the cast's laminated matrix—either fibrin or mucin—should be defined, and signs of inflammation or infiltration, such as the presence of neutrophils, eosinophils, or Charcot-Leyden crystals, should be documented.

TREATMENT

Treatment is directed at correcting the underlying condition associated with the development of plastic bronchitis, at relieving acute airway obstruction secondary to the presence of casts, and at preventing the development of further casts. Rigid or flexible bronchoscopy is typically required for cast removal, and if the predominant content of the cast is known, therapy with either fibrinolytics such as tissue plasminogen activator or mucolytics such as *N*-acetylcysteine or deoxyribonuclease may be considered as an adjunct to direct removal. Aerosolized heparin or mucolytics have also been used for treatment or prevention of recurrence, with varying success.

In the setting of inflammatory airway disease, additional preventive measures include inhaled or systemic corticosteroids, low-dose azithromycin, and leukotriene inhibitors to minimize airway inflammation. Bronchodilators have not been shown to prevent cast formation or aid in their removal, though may be used in the setting of concomitant bronchospasm.

In patients with surgically palliated complex congenital heart disease, measures aimed at decreasing central venous pressure, such as sildenafil or Fontan conduit fenestration, have had varied success. Lymphangiography may be undertaken to identify aberrant lymphatic vessels contributing to plastic bronchitis in the setting of congenital heart disease or lymphangitic disorders. MRI-guided selective lymphatic embolization of these channels has led to resolution of plastic bronchitis while preserving central lymphatic flow. Thoracic duct ligation has been helpful in patients in whom selective embolization has failed. Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been used to treat lymphatic malformations, with varying success. Octreotide and low-fat diets have demonstrated modest success in adult patients. Cardiac transplantation typically results in resolution of plastic bronchitis in the setting of repaired complex congenital heart disease.

COMPLICATIONS AND PROGNOSIS

Prognosis is related primarily to the underlying condition associated with the development of plastic bronchitis. Patients whose plastic bronchitis is related to surgically palliated complex congenital heart disease are at high risk for plastic bronchitis–related mortality. Mortality can be high if casts obstruct significant portions of the airway, regardless of underlying etiology. Mortality estimates vary from 6% to 50% in the setting of asthma or atopic disease and from 14% to 50% in the setting of complex congenital heart disease, with central airway obstruction leading to death in the majority of patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 441

Emphysema and Overinflation

Steven R. Boas and Vicki K. Masson

Pulmonary emphysema consists of distention of air spaces with irreversible disruption of the alveolar septa. It can involve part or all of a lung. **Overinflation** is distention with or without alveolar rupture and is often reversible. **Compensatory overinflation** can be acute or chronic and occurs in normally functioning pulmonary tissue when, for any reason, a sizable portion of the lung is removed or becomes partially or completely airless, which can occur with pneumonia, atelectasis, empyema, and pneumothorax. **Obstructive overinflation** results from partial obstruction of a bronchus or bronchiole, when it becomes more difficult for air to leave the alveoli than to enter. Air gradually accumulates distal to the obstruction, the so-called *bypass, ball-valve,* or *check-valve* type of obstruction.

LOCALIZED OBSTRUCTIVE OVERINFLATION

When a ball-valve type of obstruction partially occludes the main stem bronchus, the entire lung becomes overinflated; individual lobes are affected when the obstruction is in lobar bronchi. Segments or subsegments are affected when their individual bronchi are blocked. When most or all of a lobe is involved, the percussion note is hyperresonant over the area and the breath sounds are decreased in intensity. The distended lung can extend across the mediastinum into the opposite hemithorax. Under fluoroscopic scrutiny during exhalation, the overinflated area does not decrease and the heart and the mediastinum shift to the opposite side because the unobstructed lung empties normally.

Unilateral Hyperlucent Lung

The differential diagnosis for this resultant **unilateral hyperlucent lung** is quite broad and can involve the lung parenchyma, airways, pulmonary vasculature, chest wall (see Chapter 467), and mediastinum. Localized obstructions that can be responsible for overinflation include airway foreign bodies and the inflammatory reaction to them (see Chapter 435), abnormally thick mucus (cystic fibrosis, see Chapter 454), endobronchial tuberculosis or tuberculosis of the tracheobronchial lymph nodes (see Chapter 261), and endobronchial or mediastinal tumors.

Patients with unilateral hyperlucent lung can present with clinical manifestations of pneumonia, but in some patients the condition is discovered only when a chest radiograph is obtained for an unrelated reason. A few patients have hemoptysis. Physical findings can include hyperresonance and a small lung with the mediastinum shifted toward the more abnormal lung.

Swyer-James or Macleod Syndrome

The condition is thought to result from an insult to the lower respiratory tract after, most commonly, adenovirus (see Chapter 309) or respiratory syncytial virus (see Chapter 307), *Mycoplasma pneumoniae* (see Chapter 269), or measles (see Chapter 293). The infection can cause pulmonary vascular hypoplasia with resultant hypoperfusion, leading to unilateral hyperlucent lung (underdevelopment). Clinically, children with this condition often have chronic cough, recurrent pneumonia, hemoptysis, and wheezing, although some are asymptomatic. Some patients show a classic mediastinal shift away from the lesion with exhalation. CT scanning or bronchography can often demonstrate bronchiectasis. Thoracoscopic evaluation may be useful. The triad of unilateral hyperlucent lung, diffusely decreased ventilation, and matching decreased perfusion of the affected lung supports the diagnosis. In some patients, previous chest radiographs have been normal or have shown only an acute pneumonia, suggesting that a hyperlucent lung is an acquired lesion. For those with recurrent infection or severe lung destruction, treatment may include immunization with influenza and pneumococcal vaccines, as well as surgical resection. However, without treatment, some individuals may become less symptomatic with time.

Congenital Lobar Emphysema (Congenital Large Hyperlucent Lobe)

Congenital lobar emphysema (CLE) can result in severe respiratory distress in early infancy and can be caused by localized obstruction. Familial occurrence has been reported. In 50% of cases, a cause of CLE can be identified (Table 441.1). Congenital deficiency of the bronchial cartilage, external compression by aberrant vessels, bronchial stenosis, redundant bronchial mucosal flaps, and kinking of the bronchus caused by herniation into the mediastinum have been described as leading to bronchial obstruction and subsequent CLE and commonly affect the left upper lobe. Extrapulmonary lesions are noted in Table 441.2.

Clinical manifestations usually become apparent in the neonatal period but are delayed for as long as 5-6 years in 5% of patients. Many cases are diagnosed by antenatal ultrasonography. Infants with prenatally diagnosed cases are not always symptomatic at birth. In some patients, CLE remains undiagnosed until school age or beyond. Clinical signs range from mild tachypnea and wheeze to severe dyspnea with cyanosis. CLE can affect one or more lobes; it affects the upper and middle lobes, and the left upper lobe is the most common site. The affected lobe is essentially nonfunctional because of the overdistention, and atelectasis of the ipsilateral normal lung can ensue. With further distention, the mediastinum is shifted to the contralateral side, with impaired function seen as well

Table 441.1 Etiology of Congenital Lobar Emphysema

1. Idiopathic (50%)
2. Bronchial cartilage absence, hypoplasia, or dysplasia (25%)
3. Parenchymal diseases
   - Polyalveolar lobe
   - Pulmonary alveolar glycogenosis
4. Internal bronchial obstruction
   - Bronchial stenosis
   - Bronchomalacia
   - Meconium aspiration
   - Hypertrophic mucosa membranes
   - Mold mucous plaques
   - Foreign body aspiration
   - Bronchial polyp
5. External bronchial obstruction
   - Pulmonary artery sling anomaly
   - Pulmonary rotation anomaly
   - Bronchogenic cyst
   - Lymphadenopathy
   - Mediastinal mass
   - Duplication of esophagus

From Demir OF, Hangul M, Kose M. Congenital lobar emphysema: diagnosis and treatment options. *J Chronic Obstr Pulm Dis.* 2019;14:921–928, Table 1. Originally published by and used with permission from Dove Medical Press Ltd.

Table 441.2 Concomitant Malformations Accompanying Congenital Lobar Emphysema

Cardiac malformations 14–20%	Patent ductus arteriosus Atrial septal defect Ventricular septal defect Tetralogy of Fallot Pulmonary stenosis Pulmonary valve atresia Aortic coarctation Pulmonary hypertension Left aortic arch Right descending aorta Left ligamentum arteriosum Double superior vena cava
Renal anomalies	Aplastic kidney Horseshoe kidney
Musculoskeletal anomalies	Pectus excavatum Hiatal hernia Diaphragmatic hernia
Gastrointestinal tract	Omphalocele Pyloric stenosis
Others	Cleft palate Chondroectodermal dysplasia Chondrodystrophy Cystinosis Bronchial atresia Tracheal bronchus
Syndromes	Williams-Beuren syndrome Miller-Dieker syndrome Niemann-Pick disease Fanconi aplastic anemia

From Demir OF, Hangul M, Kose M. Congenital lobar emphysema: diagnosis and treatment options. *J Chronic Obstr Pulm Dis.* 2019;14:921–928, Table 2. Originally published by and used with permission from Dove Medical Press Ltd.

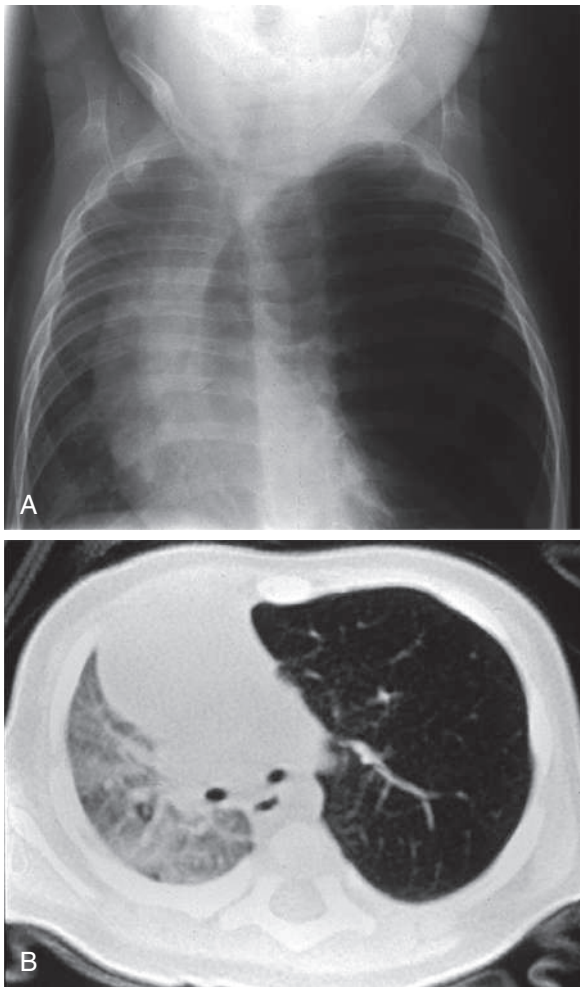

Fig. 441.1 Chest x-ray (A) and CT scan (B) of a congenital large hyperlucent lobe (congenital lobar emphysema). *(From Bush A, Abel R, Chitty L, et al. Congenital lung disease. In: Wilmott RW, Deterding RR, Li A, et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 18.32.)*

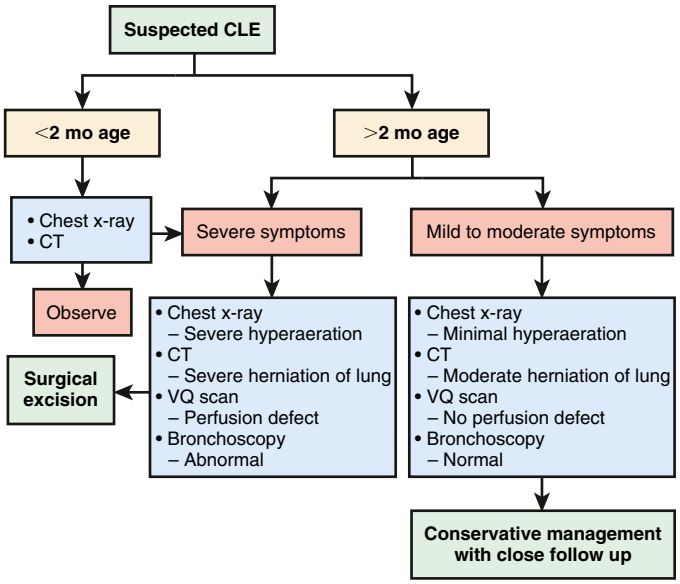

Fig. 441.2 Algorithm for evaluation and treatment of congenital lobar emphysema (CLE). *(Adapted from Karnak I, Senocak ME, Ciftci AO, et al. Congenital lobar emphysema: diagnostic and therapeutic considerations. J Pediatr Surg. 1999;34:1347–1351, Fig. 4.)*

(Fig. 441.1). A radiolucent lobe and a mediastinal shift are often revealed by radiographic examination. A CT scan can demonstrate the aberrant anatomy of the lesion, and MRI or MR angiography can demonstrate any vascular lesions that might be causing extraluminal compression. Nuclear imaging studies are useful to demonstrate perfusion defects in the affected lobe. Figure 441.2 outlines the evaluation of an infant presenting with suspected CLE. The differential diagnosis includes pneumonia with or without an effusion, pneumothorax, and cystic adenomatoid malformation.

Treatment by immediate surgery and excision of the lobe may be lifesaving when cyanosis and severe respiratory distress are present, but some patients respond to medical treatment. Selective intubation of the unaffected lung may be of value. Some children with apparent CLE have reversible overinflation, without the classic alveolar septal rupture implied in the term *emphysema.* Bronchoscopy can reveal an endobronchial lesion.

Pulmonary Vascular Abnormalities

Unilateral hyperlucency may result from **unilateral pulmonary agenesis** (see Chapter 444) that typically presents in the neonatal period. Volume loss of the affected lung results in a mediastinal shift with hyperinflation of the contralateral lung. An **anomalous origin of the left pulmonary artery** (see Chapter 481), also known as a *pulmonary artery sling,* can impinge the right main stem bronchus with resultant right-sided hyperinflation or atelectasis producing hyperlucency on either the ipsilateral or contralateral side. **Pulmonary venolobar syndrome** (see Chapter 475), also known as **scimitar syndrome**, can also result in a hyperlucent contralateral lung dependent on the extent of hypoplasia of the right lung.

GENERALIZED OBSTRUCTIVE OVERINFLATION

Acute generalized overinflation of the lung results from widespread involvement of the bronchioles and is usually reversible. It occurs more commonly in infants than in children and may be secondary to a number of clinical conditions, including asthma, cystic fibrosis, acute bronchiolitis, interstitial pneumonitis, atypical forms of acute laryngotracheobronchitis, aspiration of zinc stearate powder, chronic passive congestion secondary to a congenital cardiac lesion, and miliary tuberculosis.

Pathology

In chronic overinflation, many of the alveoli are ruptured and communicate with one another, producing distended saccules. Air can also enter the interstitial tissue (i.e., interstitial emphysema), resulting in pneumothorax and pneumomediastinum (see Chapters 461 and 462).

Clinical Manifestations

Generalized obstructive overinflation is characterized by dyspnea, with difficulty in exhaling. The lungs become increasingly overdistended, and the chest remains expanded during exhalation. An increased respiratory rate and decreased respiratory excursion result from the overdistention of the alveoli and their inability to be emptied normally through the narrowed bronchioles. Air hunger is responsible for forced respiratory movements. Overaction of the accessory muscles of respiration results in retractions at the suprasternal notch, the supraclavicular spaces, the lower margin of the thorax, and the intercostal spaces. Unlike the flattened chest during inspiration and exhalation in cases of laryngeal obstruction, minimal reduction in the size of the overdistended chest during exhalation is observed. The percussion note is hyperresonant. On auscultation, the inspiratory phase is usually less prominent than the expiratory phase, which is prolonged and roughened. Fine or medium crackles may be heard. Cyanosis is more common in the severe cases.



Fig. 441.3 Increased transradiancy in the right lower zone. A large emphysematous bulla occupies the lower half of the right lung, and the apical changes are in keeping with previous tuberculosis. *(From Padley SPG, Hansell DM. Imaging techniques. In: Albert RK, Spiro SG, Jett JR, eds. Clinical Respiratory Medicine, 3rd ed. Philadelphia: Mosby; 2008: Fig. 1.48.)*

Diagnosis

Radiographic and fluoroscopic examinations of the chest assist in establishing the diagnosis. Both leaves of the diaphragm are low and flattened, the ribs are farther apart than usual, and the lung fields are less dense. The movement of the diaphragm during exhalation is decreased, and the excursion of the low, flattened diaphragm in severe cases is barely discernible. The anteroposterior diameter of the chest is increased, and the sternum may be bowed outward.

Bullous Emphysema

Bullous emphysematous blebs or cysts (pneumatoceles) result from overdistention and rupture of alveoli during birth or shortly thereafter, or they may be sequelae of pneumonia and other infections. They have been observed in tuberculosis lesions during specific antibacterial therapy and in end-stage cystic fibrosis lung disease. Bullous emphysema can also result from inhalational marijuana use. These emphysematous areas presumably result from rupture of distended alveoli, forming a single or multiloculated cavity. The cysts can become large and might contain some fluid; an air-fluid level may be demonstrated on the radiograph (Fig. 441.3). The cysts should be differentiated from pulmonary abscesses. In most cases, treatment is not required, as the cysts disappear spontaneously within a few months, although they can persist for a year or more. Aspiration or surgery is not indicated except in cases of severe respiratory and cardiac compromise.

Subcutaneous Emphysema

Subcutaneous emphysema results from any process that allows free air to enter into the subcutaneous tissue (Fig. 441.4). The most common causes include pneumothorax or pneumomediastinum (see Chapters 461 and 462). In addition, it can be a complication of fracture of the orbit, which permits free air to escape from the nasal sinuses. In the neck and thorax, subcutaneous emphysema can follow tracheotomy, deep ulceration in the pharyngeal region, esophageal wounds, or any perforating lesion of the larynx or trachea. It is occasionally a complication of thoracentesis, asthma, or abdominal surgery. Rarely, air is formed in the subcutaneous tissues by gas-producing bacteria.

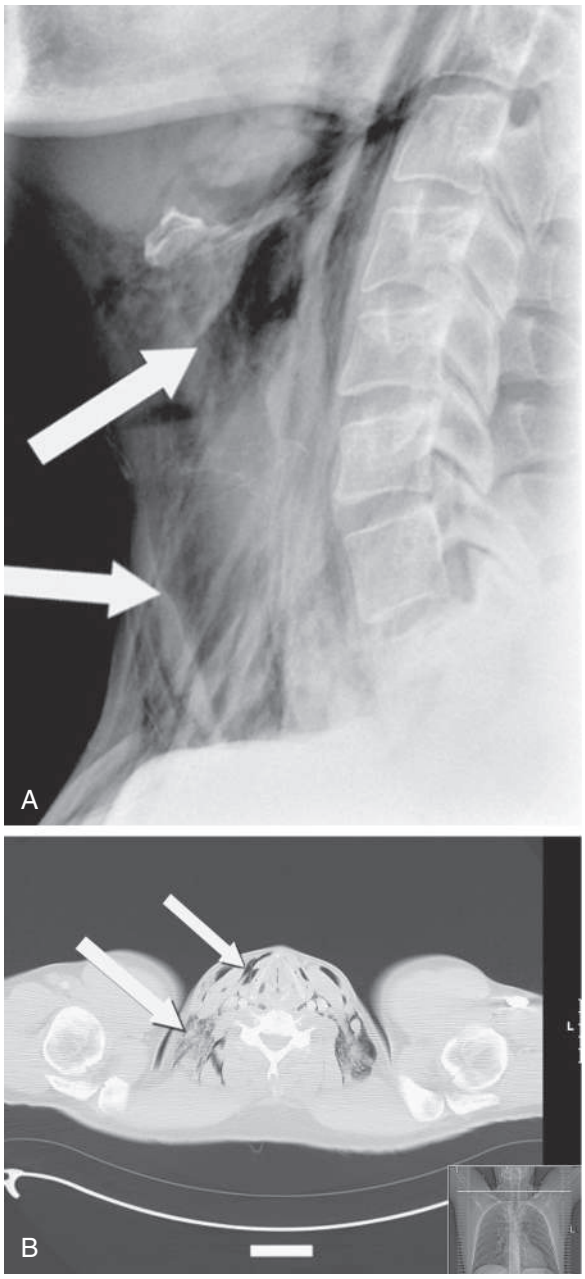

Fig. 441.4 A, Lateral x-ray of neck showing subcutaneous emphysema. B, Axial section CT neck/thorax showing subcutaneous emphysema and pneumomediastinum. *(From Zakaria R, Khwaja H. Subcutaneous emphysema in a case of infective sinusitis: a case report. J Med Case Rep. 2010;4:235, Figs. 1 and 2.)*

Tenderness over the site of emphysema and a crepitant quality on palpation of the skin are classic manifestations. Subcutaneous emphysema is usually a self-limited process and requires no specific treatment. Minimization of activities that can increase airway pressure (cough, performance of high-pressure pulmonary function testing maneuvers) is recommended. Resolution occurs by resorption of subcutaneous air after elimination of its source. Rarely, dangerous compression of the trachea by air in the surrounding soft tissue requires surgical intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 442

α_1-Antitrypsin Deficiency and Emphysema

Vicki K. Masson and Steven R. Boas

Homozygous deficiency of α_1-antitrypsin (α_1-AT) rarely produces lung disease in children, but it is an important cause of early-onset severe panacinar pulmonary emphysema in adults in the third and fourth decades of life and a significant cause of liver disease in children (see Chapter 405.5). It is associated with panniculitis and antineutrophil cytoplasmic antibody (cANCA)–associated vasculitis in adults with the PI MZ phenotype.

PATHOGENESIS

The type and concentration of α_1-AT are inherited as a series of codominant alleles on chromosomal segment 14q31-32.3. (See Chapter 405.5 for a discussion of genotypes and liver disease.) The autosomal recessive deficiency affects 1 in 1,600-5,000 people, but it remains underdiagnosed. Worldwide there are an estimated 116,000,000 carriers and 1,100,000 subjects with severe α_1-AT deficiency. The normal α_1-AT PiM protein is secreted by the liver into the circulation at a rate of approximately 34 mg/kg/day; it is also produced by lung epithelial cells and monocytes. Pathogenic variant proteins are not produced (null) or are misfolded (PiZ and others); they can polymerize in the endoplasmic reticulum or be degraded, with subsequent low serum levels. Early adult-onset emphysema associated with α_1-AT deficiency occurs most commonly with PiZZ (pathogenic variant in *SERPINA1* gene), although Pi (null) (null) and, to a lesser extent, other pathogenic Pi types such as SZ have been associated with emphysema.

α_1-AT and other serum antiproteases help to inactivate proteolytic enzymes released from dead bacteria or leukocytes in the lung. Deficiency of these antiproteases leads to an accumulation of proteolytic enzymes in the lung, resulting in destruction of pulmonary tissue with subsequent development of emphysema. Polymerized pathogenic proteins in the lungs may also be proinflammatory, and there is evidence of increased oxidative stress. The concentration of proteases (elastase) in an individual's leukocytes may also be an important factor in determining the severity of clinical pulmonary disease with a given level of α_1-AT.

CLINICAL MANIFESTATIONS

Most patients who have the PiZZ defect have little or no detectable pulmonary disease during childhood. A few have early onset of chronic pulmonary symptoms, including dyspnea, wheezing, and cough, and panacinar emphysema has been documented by lung biopsy; it is probable that these findings occur secondarily to infection, which caused inflammation with consequent early disease. Smoking increases the risk of emphysema in patients with mutant Pi types. A newborn screen to identify children with the PiZZ phenotype provides useful guidance in support of smoking cessation for close contacts and reduces adolescent smoking rates.

Physical examination in *childhood* is usually normal. Affected children rarely have growth failure, an increased anteroposterior diameter of the chest with a hyperresonant percussion note, crackles to indicate active infection, or clubbing. Severe emphysema can depress the diaphragm, making the liver and spleen more easily palpable.

LABORATORY FINDINGS

Serum immunoassay measures low levels of α_1-AT; normal serum levels are ~80-220 mg/dL. Serum electrophoresis reveals the phenotype, and genotype is determined by polymerase chain reaction; whole gene sequencing is possible. In the rare patient with lung disease in adolescence, chest radiograph reveals overinflation with depressed diaphragms. Chest CT can show more hyperexpansion in the lower lung zones, with occasional bronchiectasis; CT densitometry can be a sensitive method to follow changes in lung disease. Lung function testing is usually normal in children, but it can show airflow obstruction and increased lung volumes, particularly in adolescents who smoke.

TREATMENT

Therapy for α_1-AT deficiency is intravenous replacement **(augmentation)** with enzyme derived from pooled human plasma. A level of 80 mg/dL is protective for emphysema. This target level for augmentation therapy is usually achieved with initial doses of 60 mg/kg IV weekly and results in the appearance of the transfused antiprotease in pulmonary lavage fluid. The Food and Drug Administration has approved the use of purified blood-derived human enzyme for ZZ and null-null patients. Replacement therapy is indicated for those with moderately severe obstructive lung disease (forced expiratory volume in 1 second is 30–65% of predicted) or those with mild lung disease experiencing a rapid decline in lung function. Augmentation therapy is not indicated for persons with the PiMZ type who have pulmonary disease, because their disease is not from enzyme deficiency. Recombinant sources of α_1-AT are under development, but current products are rapidly cleared from the circulation when given intravenously; they may be useful for inhalation therapy. Inhalation of the plasma-derived product is under evaluation. Lung transplantation has been performed for end-stage disease. Multiple strategies for gene therapy are under development.

SUPPORTIVE THERAPY

Standard supportive therapy for chronic lung disease includes aggressive treatment of pulmonary infection, routine use of pneumococcal and influenza vaccines, bronchodilators, and advice about the serious risks of smoking and smoke exposure. Such treatment is also indicated for asymptomatic family members found to have PiZZ or null-null phenotypes but not those with the PiMZ type. The clinical significance of the PiSZ type is unclear, but nonspecific treatment is reasonable. All persons with low levels of serum antiprotease should be warned that the development of emphysema is partially mediated by environmental factors and that cigarette smoking is particularly deleterious. Although early identification of affected persons could help to prevent development of obstructive lung disease, population screening programs are being considered but are currently suspended.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 443

Other Distal Airway Diseases

443.1 Bronchiolitis Obliterans

Catherine Kier and Steven R. Boas

Bronchiolitis obliterans (BO) is a histopathologic diagnosis characterized by chronic obstructive lung disease of the bronchioles and smaller airways resulting from an insult to the lower respiratory tract leading to inflammation and fibrosis of the small airways. In the nontransplant patient, BO most commonly occurs in the pediatric population after respiratory infections, particularly adenovirus (see Chapter 309), but also *Mycoplasma pneumoniae* (see Chapter 269), measles (see Chapter 293), *Legionella pneumophila* (see Chapter 254), influenza (see Chapter 305), and pertussis (see Chapter 243); other causes include inflammatory diseases (juvenile idiopathic arthritis, systemic lupus erythematosus [see Chapter 199], scleroderma [see Chapter 201], Stevens-Johnson syndrome [see Chapter 193]) and inhalation of toxic fumes or particulate exposure (NO_2, incinerator fly ash, NH_3, diacetyl flavorings from microwave popcorn, papaverine, fiberglass) (Table 443.1). Postinfectious BO (PIBO) may be more common in the Southern Hemisphere. BO is also commonly seen in post lung or bone marrow transplant recipients.

Bronchiolitis obliterans syndrome (BOS) is a clinical diagnosis related to graft deterioration after transplantation, defined as a progressive decline in lung function based on forced expiratory volume in 1 second (FEV_1). The airway obstruction is generally irreversible. BOS is considered once other causes of airway obstruction are excluded. It is recognized as a long-term complication of both lung and bone marrow transplantation, with more than one third of survivors of lung transplantation developing this disorder. Risk factors for the development of BOS include the presence of cytomegalovirus (CMV) pneumonitis, *Aspergillus* colonization, primary graft dysfunction, gastroesophageal reflux, and community-acquired respiratory viruses, as well as prolonged transplantation ischemic time.

PATHOGENESIS

After the initial insult, inflammation affecting terminal bronchioles, respiratory bronchioles, and alveolar ducts can result in the obliteration of the airway lumen (Fig. 443.1). Epithelial damage resulting in abnormal repair is characteristic of BO. Complete or partial obstruction of the airway lumen can result in air trapping or atelectasis. Parenchymal involvement is not seen. **Bronchiolitis obliterans organizing pneumonia (BOOP)**, or what is now termed **cryptogenic organizing pneumonia (COP)**, is a histopathologic diagnosis. Although it is similar to many of the histologic features of BO, COP is also characterized by extension of the inflammatory process from distal alveolar ducts into alveoli with proliferation of fibroblasts (parenchymal involvement).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Cough, fever, cyanosis, dyspnea, chest pain, and respiratory distress followed by initial or no improvement with antibiotics may be the early signs of BO. In this phase, BO is easily confused with pneumonia, bronchitis, or bronchiolitis. Progression of the disease can ensue, with increasing dyspnea, chronic cough, sputum production, and wheezing. Physical examination findings are usually nonspecific and can include wheezing, hypoxemia, and crackles. Chest radiographs may be relatively normal compared with the extent of physical findings but can demonstrate hyperlucency and patchy infiltrates. Occasionally, Swyer-James syndrome (unilateral hyperlucent lung; see Chapter 441) develops. Pulmonary function tests demonstrate variable findings but typically show signs of airway obstruction with a variable degree of bronchodilator response, although more commonly irreversible. Exercise testing shows reduced exercise capacity and impaired oxygen consumption. Ventilation-perfusion scans reveal a typical moth-eaten appearance of multiple matched defects in ventilation and perfusion. High-resolution chest CT often demonstrates patchy areas or a mosaic pattern of hyperlucency, air trapping, and bronchiectasis (Fig. 443.2). Table 443.2 provides an overview of CT findings of BO and related disorders. Physical and radiologic signs can wax and wane over weeks or months. Open lung biopsy or transbronchial biopsy remains the best means of establishing the diagnosis of BO or COP.

TREATMENT

Treatment is a combination of optimal supportive care and anti-inflammatory therapy to impair lymphocyte proliferation. For PIBO, it is recommended that bronchoscopy with bronchoalveolar lavage be performed to rule out persistent viral, bacterial, or fungal pathogens before initiation of systemic antiinflammatory treatment. Corticosteroids should be given early, pulse steroid therapy with methylprednisolone is preferred, and a prolonged course of oral steroids should be avoided to minimize severe side effects and complications or mortality from infections. Immunomodulatory agents, such as sirolimus, tacrolimus, aerosolized cyclosporine, hydroxychloroquine, and macrolide antibiotics, have been used in post–lung transplantation recipients with BO with variable success. Supportive measures with oxygen, antibiotics for secondary infections, and bronchodilators are adjunct therapies. The role of gastroesophageal reflux and its association with BO has been raised, with treatment suggested whenever the diagnosis is made. Azithromycin may be effective in patients with BOS. A combination of fluticasone, azithromycin, montelukast, and pulse steroid may halt pulmonary progression of BOS. Potential future treatment options include using mesenchymal stem/stromal cells (MSCs) for immunomodulatory and possibly profibrotic effects and extracorporeal photopheresis (ECP) and total lymphoid irradiation (TLI) for BOS, but additional trials and studies are needed. Patients with asymptomatic or nonprogressive COP can be observed.

PROGNOSIS

Some patients with BO experience rapid deterioration in their condition and die within weeks of the initial symptoms; most nontransplant patients survive with chronic disability. BO tends to be severe once progression ensues. In contrast to BO, a better prognosis exists for patients with COP, with complete recovery seen in many patients, although outcome depends on the underlying systemic disease. COP can relapse, especially if treatment duration is <1 year; COP is amenable to repeat courses of oral corticosteroids. Unlike the more common idiopathic COP, progressive COP characterized by acute respiratory distress syndrome is rare but is aggressive in its clinical course, leading to death.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

443.2 Follicular Bronchitis

Catherine Kier and Steven R. Boas

Follicular bronchitis and pediatric lymphocytic interstitial pneumonia are lymphoproliferative lung disorders characterized by the presence of lymphoid follicles alongside the airways (bronchi or bronchioles) and

Table 443.1 Etiology of Bronchiolitis Obliterans

POSTINFECTION
Adenovirus types 3, 7, and 21
Influenza
Parainfluenza
Measles
Respiratory syncytial virus
Varicella
Mycoplasma pneumoniae
POSTTRANSPLANTATION
Chronic rejection of lung or heart/lung transplantation
Graft versus host disease associated with bone marrow transplantation
CONNECTIVE TISSUE DISEASE/INFLAMMATORY
Juvenile idiopathic arthritis
Sjögren syndrome
Scleroderma
Systemic lupus erythematosus
Castleman disease
Inflammatory bowel disease
TOXIC FUME INHALATION
NO_2
NH_3
Diacetyl flavorings (microwave popcorn)
Sulfur mustards
Fly ash (incinerator)
Fiberglass
CHRONIC HYPERSENSITIVITY PNEUMONITIS
Avian antigens
Mold
ASPIRATION
Stomach contents: gastroesophageal reflux
Foreign bodies
DRUGS
Penicillamine
Cocaine
STEVENS-JOHNSON SYNDROME
Idiopathic
Drug induced
Infection related

From Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr.* 2008;20:272–278.

infiltration of the walls of bronchi and bronchioles. The disease presents early and is associated with immune dysregulation. Autoantibodies have been found in some children, and in a few patients, disease-causing pathogenic variants have been found in *COPA*. Most children present with symptoms in the first 2 years of life, but with a lag time of diagnosis to about 4 years. Cough, moderate respiratory distress, fever, and fine crackles are common clinical findings. Fine crackles generally persist over time, and recurrence of symptoms is common. Chest radiographs may be relatively benign initially (air trapping, peribronchial thickening) but evolve into the typical interstitial pattern. Chest CT can show hilar lymphadenopathy, pulmonary nodules, ground-glass opacity, focal consolidation, and bronchiectasis but can also appear normal (see Table 443.2). Definitive diagnosis is made by open lung biopsy (Fig. 443.3). Treatment is limited—systemic steroids, intravenous pulse or oral, showed high response rates. Prognosis is related to early diagnosis and treatment, which are critical to improve the outcome. Some patients have significant progression of pulmonary disease, and others develop only mild obstructive airway disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

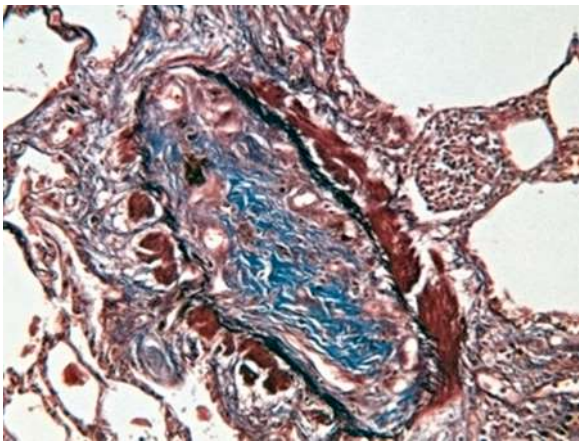

Fig. 443.1 Complete obliteration of airway lumen with fibromyxoid tissue in lung transplant recipient with bronchiolitis obliterans. *(From Kurland G, Michelson P. Bronchiolitis obliterans in children. Pediatr Pulmonol. 2005;39:193–208.)*



Fig. 443.2 High-resolution CT scan of the chest of a child with bronchiolitis obliterans demonstrating mosaic perfusion and vascular attenuation. Air-trapping is demonstrated by lack of increase in attention or decrease in lung volume in dependent lung. *(Image courtesy Alan Brody, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.)*

443.3 Pulmonary Alveolar Microlithiasis

Catherine Kier and Steven R. Boas

Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by the formation of lamellar concretions of calcium phosphate, or "microliths," within the alveoli, creating a classic pattern on the radiograph (Fig. 443.4).

EPIDEMIOLOGY AND ETIOLOGY

Although the mean age at the time of diagnosis is in the mid-30s, the onset of the disease can occur in childhood and in newborns. PAM is inherited in an autosomal recessive disorder and is caused by a pathogenic variant in the type II sodium phosphate cotransporter NPT2b *(SCL34A2)*. To date, there are 27 identified pathogenic variants. This gene is expressed in high levels in the lungs,

Table 443.2 High-Resolution CT Patterns in a Child with Interstitial Lung Disease

	STUDIES (N)	GROUND-GLASS OPACITY	THICK SEPTA	NODULES	MOSAIC PATTERN	HONEYCOMBING
Bronchiolitis obliterans	4	—	—	—	X	—
Nonspecific interstitial pneumonitis	6	X	—	—	—	X
Desquamative interstitial pneumonitis	4	X	—	—	—	X
Follicular bronchitis or neuroendocrine cell hyperplasia of infancy	4	X	—	—	X	—
Lymphocytic interstitial pneumonitis	4	—	—	X	—	—
Lymphangiomatosis	2	—	X	—	—	—
Lymphangiectasia	2	—	X	—	—	—
Pulmonary alveolar proteinosis	2	X	X	—	—	—

From Long FR. Interstitial lung disease. In: Slovis T, ed. *Caffey's Pediatric Diagnostic Imaging,* 11th ed. Philadelphia: Mosby; 2008: Table 74.1; original data from Lynch DA, Hay T, Newell JD Jr, et al. Pediatric diffuse lung disease: diagnosis and classification using high-resolution CT. *AJR Am J Roentgenol.* 1999;173:713–718; and Copley SJ, Coren M, Nicholson AG, et al. Diagnostic accuracy of thin-section CT and chest radiography of pediatric interstitial lung disease. *AJR Am J Roentgenol.* 2000;174:549–554.



Fig 443.3 Follicular bronchiolitis in a 3-year-old child with mosaic attenuation and cylindrical bronchiectasis. CT findings suggested bronchiolitis obliterans, but a biopsy documented the presence of follicular bronchiolitis. *(From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 73.71.)*

predominantly on the surface of alveolar type II cells. Although the precise role of this protein is unknown, it is speculated that it helps to remove phosphate generated from surfactant metabolism in the alveolar space, as well as functioning as a phosphate regulator in other organs.

In some families, progression of disease is rapid. An equal male and female incidence is noted. Although PAM is found throughout the world, there is a high incidence in Turkey and a lesser incidence in Italy and Japan.

CLINICAL MANIFESTATIONS

In early stages of the disease, patients are usually asymptomatic. When symptomatic, patients with PAM usually complain of dyspnea on exertion, nonproductive cough, and fever. Physical examination of the lungs can reveal fine inspiratory crackles and diminished breath sounds. Clubbing occurs, although this is usually a more advanced sign. Discordance between the clinical and radiographic manifestations is common. Many children are often asymptomatic on initial presentation and present with symptoms during adulthood. Complications of pneumothorax, pleural adhesions and calcifications, pleural fibrosis, apical bullae, and extrapulmonary sites of microliths have been reported (kidneys, prostate, gallbladder, sympathetic chain, and testes). Progression to respiratory failure may occur.

DIAGNOSIS

Chest radiography typically reveals bilateral infiltrates with a fine micronodular appearance or sandstorm appearance with greater density in the lower and middle lung fields (see Fig. 443.4). CT of the chest shows diffuse micronodular calcified densities, with thickening of the microliths along the septa and around distal bronchioles, especially in the inferior and posterior regions (see Table 443.2). Diffuse uptake of technetium-99 methylene diphosphonate by nuclear scan has been reported. Bronchoalveolar lavage (BAL) may be helpful. Open lung and transbronchial lung biopsy reveal 0.1- to 0.3-mm laminated calcific concretions within the alveoli. Although the alveoli are often normal initially, progression to pulmonary fibrosis with advancing disease usually ensues. Sputum expectoration might reveal small microliths, although this finding is not diagnostic for PAM and is not typically seen in children. Detection of calcium deposits in BAL fluid on bronchoscopy supports the diagnosis. Pulmonary function testing reveals restrictive lung disease with impaired diffusing capacity as the disease progresses, whereas exercise testing demonstrates arterial oxygen desaturation.

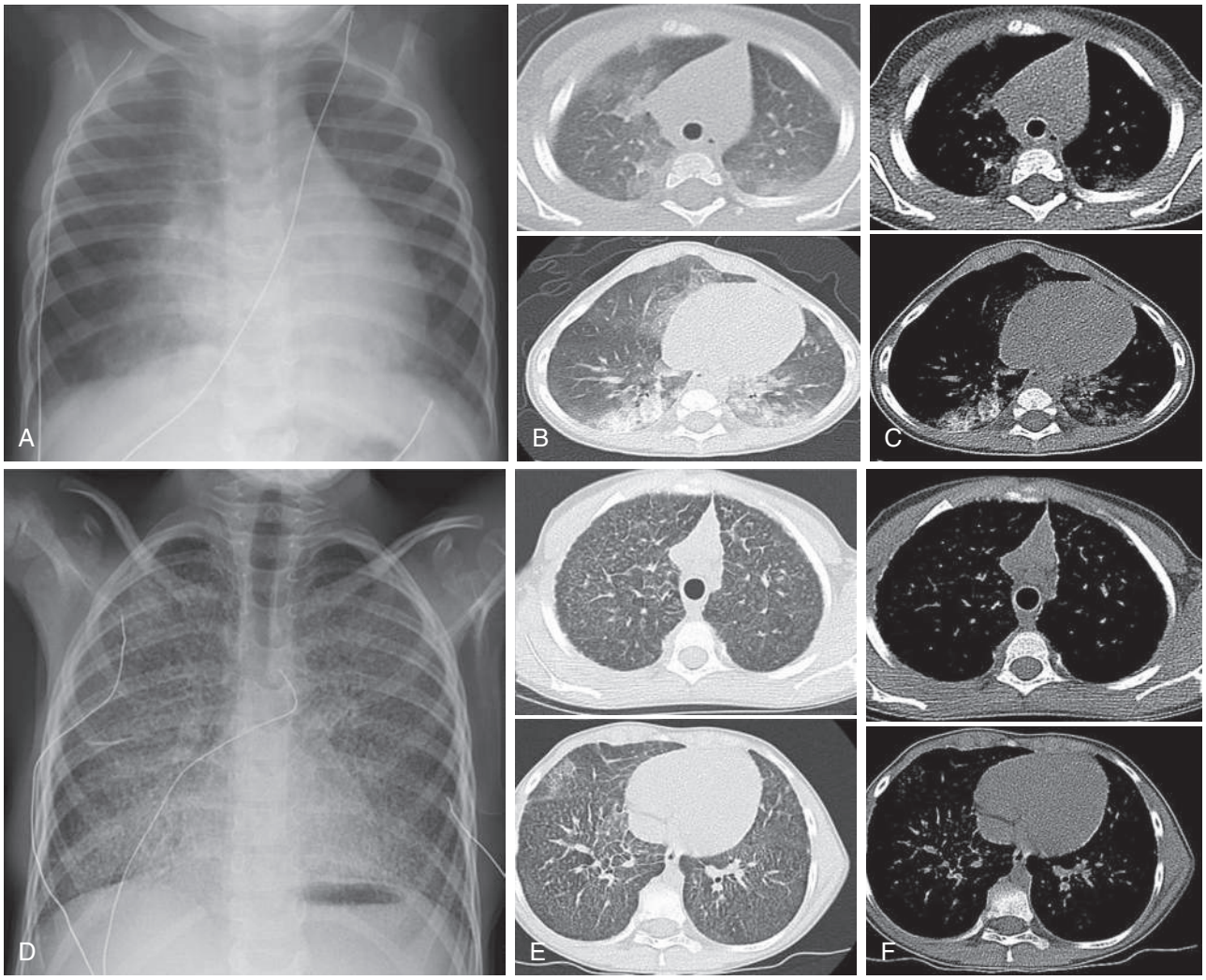

Fig. 443.4 Pulmonary alveolar microlithiasis. Chest radiograph and high-resolution CT performed at the age of 1 year and 8 years. **A,** Chest radiograph shows bilateral alveolo-interstitial opacities with middle lobe consolidation. Chest CT imaging shows diffuse but patchy ground-glass opacities, alveolar consolidations in the middle and lower lobes, and calcifications in the lower lobes, at parenchymal (**B**) and mediastinal (**C**) windows. **D,** Chest radiograph shows diffuse, even predominant in the lower and middle lobes, dense reticulonodular opacities. Chest CT imaging shows patchy ground-glass opacities, homogenous miliary consolidations with micronodular calcifications and subpleural and interlobular reticulations, parenchymal retractions, and architectural distortion suggestive of fibrosis onset mostly in the upper lobes, at parenchymal (**E**) and mediastinal (**F**) windows. *(From Sigur E, Roditis L, Labouret G, et al. Pulmonary alveolar microlithiasis in children less than 5 years of age. J Pediatr. 2020;217:158–164.e1, Fig. 1.)*

The diagnosis can usually be established radiographically. However, lung tissue biopsy, BAL, and detection of a pathogenic variant in the *SCL34A2* gene can also be used to help confirm the diagnosis. The differential diagnosis includes sarcoidosis, miliary tuberculosis, hemosiderosis, healed disseminated histoplasmosis, pulmonary calcinosis, and metastatic pulmonary calcifications.

TREATMENT

No specific treatment is effective, although some clinicians have used glucocorticosteroids, etidronate disodium, and bronchopulmonary lavage with limited success. Lung transplantation has been performed for this condition without recurrence in the transplanted lung.

PROGNOSIS

Progressive cardiopulmonary disease can ensue, leading to cor pulmonale, superimposed infections, and subsequent death in mid-adulthood. Because of the familial nature of this disease, counseling and chest radiographs of family members are indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 444

Congenital Disorders of the Lung

444.1 Pulmonary Agenesis and Aplasia

Joshua A. Blatter and Jonathan D. Finder

Pulmonary agenesis differs from hypoplasia in that agenesis entails the complete absence of a lung. Agenesis differs from aplasia by the absence of a bronchial stump or carina that is seen in aplasia. Bilateral pulmonary agenesis is incompatible with life, manifesting as severe respiratory distress and failure. Pulmonary agenesis is thought to be an autosomal recessive trait, with an estimated incidence of 1 in 10,000-15,000 births.

CLINICAL MANIFESTATIONS AND PROGNOSIS

Unilateral agenesis or hypoplasia can have few symptoms and nonspecific findings, resulting in only 33% of the cases being diagnosed while the patient is living. Symptoms tend to be associated with central airway complications of compression, stenosis, and/or tracheobronchomalacia. In patients in whom the right lung is absent, the aorta can compress the trachea and lead to symptoms of central airway compression. Right lung agenesis has a higher morbidity and mortality than left lung agenesis. Pulmonary agenesis is often seen in association with other congenital anomalies such as the **VACTERL sequence** (*v*ertebral anomalies, *a*nal atresia, *c*ongenital heart disease, *t*racheoesophageal fistula, *r*enal anomalies, and *l*imb anomalies), ipsilateral facial and skeletal malformations, and central nervous system and cardiac malformations. Compensatory growth of the remaining lung allows improved gas exchange, but the mediastinal shift can lead to scoliosis and airway compression. Scoliosis can result from unequal thoracic growth.

DIAGNOSIS AND TREATMENT

Chest radiographic findings of unilateral lung or lobar collapse with a shift of mediastinal structures toward the affected side can prompt referral for suspected foreign body aspiration, mucus plug occlusion, or other bronchial mass lesions. The diagnosis requires a high index of suspicion to avoid the unnecessary risks of bronchoscopy, including potential perforation of the rudimentary bronchus. CT of the chest is diagnostic, although the diagnosis may be suggested by chronic changes in the contralateral aspect of the chest wall and lung expansion on chest radiographs. Because pulmonary agenesis can be associated with a wide variety of congenital lesions, whole body MRI can be useful to determine whether other systems (e.g., cardiac, gastrointestinal) are affected. Conservative treatment is usually recommended, although surgery has offered benefit in selected cases. Referral for management of scoliosis may be necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

444.2 Pulmonary Hypoplasia

Joshua A. Blatter and Jonathan D. Finder

Pulmonary hypoplasia involves a decrease in both the number of alveoli and the number of airway generations. The hypoplasia may be bilateral in the setting of bilateral lung constraint, as in oligohydramnios or thoracic dystrophy. Pulmonary hypoplasia is usually secondary to other intrauterine disorders that produce an impairment of normal lung development (see Chapter 124). Conditions such as deformities of the thoracic spine and rib cage (thoracic dystrophy), pleural effusions with fetal hydrops, congenital pulmonary airway malformation, and congenital diaphragmatic hernia physically constrain the developing lung. Any condition that produces oligohydramnios (fetal renal insufficiency or prolonged premature rupture of membranes) can also lead to diminished lung growth. In these conditions, airway and arterial branching are inhibited, thereby limiting the capillary surface area. Large unilateral lesions, such as congenital diaphragmatic hernia or pulmonary airway malformation, can displace the mediastinum and thereby produce a contralateral hypoplasia, although usually not as severe as that seen on the ipsilateral side. **Fetal akinesia deformation syndrome** is also associated with pulmonary hypoplasia, in part because of decreased fetal breathing movements.

CLINICAL MANIFESTATIONS

Pulmonary hypoplasia is usually recognized in the newborn period, owing to either the respiratory insufficiency or the presentation of persistent pulmonary hypertension (see Chapter 130). Later presentation (tachypnea) with stress or respiratory viral infection can be seen in infants with mild pulmonary hypoplasia.

DIAGNOSIS AND TREATMENT

A variety of imaging techniques, including MRI and ultrasound, with estimation of oligohydramnios, can be helpful to identify hypoplasia but not to predict pulmonary function. Mechanical ventilation and oxygen may be required to support gas exchange. Specific therapy to control associated pulmonary hypertension, such as inhaled nitric oxide, may be useful. In cases of severe hypoplasia, the limited capacity of the lung for gas exchange may be inadequate to sustain life. Extracorporeal membrane oxygenation can provide gas exchange for a critical period of time and permit survival. Rib-expanding devices (vertically expansible prosthetic titanium ribs and magnetic expansion control rods) can improve the survival of patients with thoracic dystrophies (see Chapter 741).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

444.3 Congenital Pulmonary Airway Malformation (Congenital Cystic Adenomatoid Malformation)

Joshua A. Blatter and Jonathan D. Finder

Congenital pulmonary airway malformation **(CPAM)**, formerly known as *cystic adenomatoid malformation,* consists of hamartomatous or dysplastic lung tissue mixed with more normal lung, usually confined to one lobe. This congenital pulmonary disorder occurs in approximately 1-4 in 100,000 births. Prenatal ultrasonographic findings are classified as **macrocystic** (single or multiple cysts >5 mm) or **microcystic** (echogenic cysts <5 mm). Five histologic and location patterns have been described (Fig. 444.1). **Type 0** (acinar dysplasia) is least common (<2%) and consists of microcystic disease throughout the lungs. The prognosis is poorest for this type, and infants die at birth. **Type 1** (60–70%) is macrocystic and consists of a single or several large (>2 cm in diameter) cysts lined with ciliated pseudostratified epithelium; the lesion is localized involving only a part of one lobe. One third of cases have mucus-secreting cells. Presentation is in utero or in the newborn period. Cartilage is rarely seen in the wall of the cyst. This type has a good prognosis for survival. **Type 2** (15–20%) is microcystic and consists of multiple small cysts with histology similar to that of the type 1 lesion. Type 2 is associated with other serious congenital anomalies (renal, cardiac, diaphragmatic hernia, esophageal atresia, skeletal) and carries a poor prognosis. **Type 3** (5–10%) is seen mostly in males; the lesion is a mixture of microcysts and solid tissue with bronchiole-like structures lined with cuboidal ciliated epithelium and separated by areas of nonciliated cuboidal epithelium. The prognosis for this type, like type 0, is poor. **Type 4** (~10%) is commonly macrocystic and lacks mucus cells. It is associated with malignancy (type 1

pleuropulmonary blastoma) and can present either in childhood or in asymptomatic adults.

ETIOLOGY

The lesion probably results from an embryologic injury before the 35th day of gestation, with maldevelopment of terminal bronchiolar structures. Histologic examination reveals little normal lung and many glandular elements. Cysts are common; cartilage is rare. The presence of cartilage might indicate a somewhat later embryologic insult, perhaps extending into the 10th to 24th week. Although growth factor interactions and signaling mechanisms have been implicated in altered lung-branching morphogenesis, the exact roles in the maldevelopment seen here remain obscure.

DIAGNOSIS

Cystic airway malformations can be diagnosed in utero by ultrasonography (Fig. 444.2). To better define and differentiate the lesion from other congenital lung malformations, fetal MRI is indicated (Fig. 444.3). Fetal cystic lung abnormalities can include CPAM (40%), pulmonary sequestration (14%) (see Chapter 444.4), or both (26%); the median age at diagnosis is usually 21 weeks of gestation. In one series, only 7% had severe signs of fetal distress, including hydrops, pleural effusion, polyhydramnios, ascites, or severe facial edema; 96% of the fetuses were born alive, two of whom died in the neonatal period. CPAM volume ratio (CVR)—CPAM volume divided by head circumference—can be used to predict the risk of fetal hydrops. A CVR >1.6 is a high-risk factor for developing hydrops. Lesions causing fetal hydrops have a poor prognosis. Large lesions, by compressing adjacent lung, can produce pulmonary hypoplasia in nonaffected lobes (see Chapter 444.2). Even lesions that appear large in early gestation can regress considerably or decrease in relative size and be associated with good pulmonary function in childhood. MRI allows accurate diagnosis and sizing of the lesion and is indicated even in asymptomatic neonates.

CLINICAL MANIFESTATIONS

Patients can present in the newborn period or early infancy with respiratory distress, recurrent respiratory infection, and pneumothorax. The lesion may be confused with a diaphragmatic hernia (see Chapter 131). Neonatal presentations include respiratory distress, cyanosis, tachypnea, or a pneumothorax; hydrops is the most severe presentation. Patients with smaller lesions are usually asymptomatic until mid-childhood, when episodes of recurrent or persistent pulmonary infection or chest pain occur. Breath sounds may be diminished, with mediastinal shift away from the lesion on physical examination. Chest radiographs reveal a cystic mass, sometimes with mediastinal shift (Fig. 444.4). Occasionally, an air-fluid level suggests a lung abscess (see Chapter 453).

TREATMENT

Antenatal intervention in severely affected infants is controversial but can include excision of the affected lobe for microcystic lesions, aspiration of macrocystic lesions, and, rarely, open fetal surgery. Maternal therapy with intravenous betamethasone may inhibit CPAM growth and reverse hydrops. If hydrops persists, a thoracoamniotic shunt may

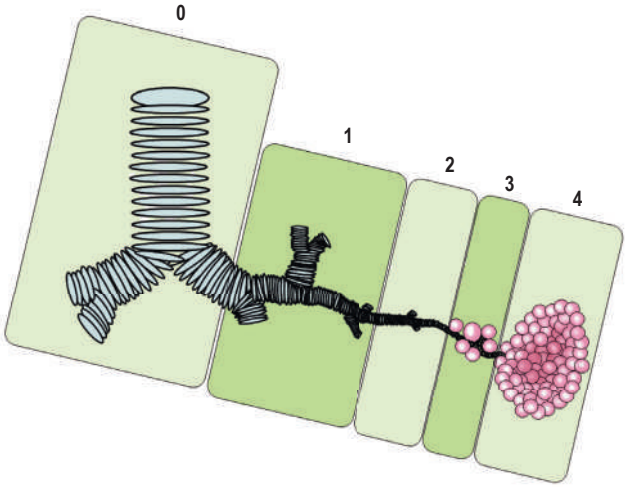

Fig. 444.1 Types of congenital pulmonary airway malformations. Type 0, tracheobronchial; type 1, bronchial; type 2, bronchiolar; type 3, alveolar duct; type 4, distal acinar. *(Adapted from Stocker JT. Cystic lung disease in infants and children. Fetal Pediatr Pathol. 2009;28:155–184.)*

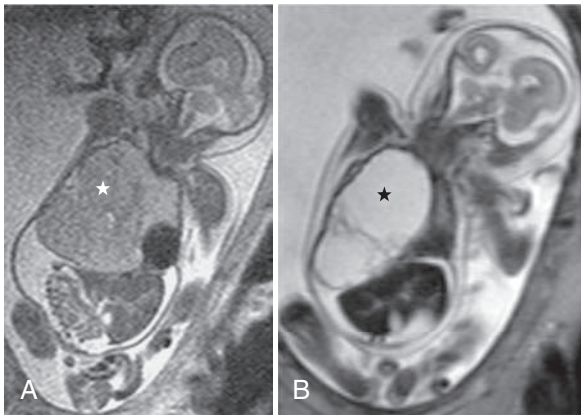

Fig. 444.3 These two fetal MRIs depict a practical prenatal classification for congenital pulmonary airway malformations. **A,** Microcystic lesion presenting as a solid hyperintense mass *(star)*. **B,** Macrocystic lesion containing a large cyst >5.0 mm in diameter *(star)*. *(From Laje P, Flake AW. Congenital bronchopulmonary malformations. In: Holcomb III GW, Murphy JP, St. Peter SD, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020: Fig. 22.3, p. 350.)*

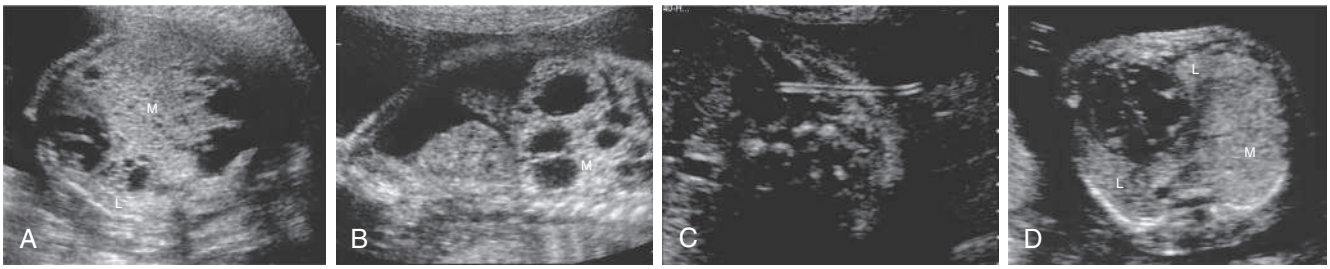

Fig. 444.2 Congenital pulmonary airway malformation (CPAM). **A,** Massive right CPAM mass *(M)* with pronounced mediastinal shift is seen. Note the small size of the compressed left lung *(L)*. **B,** Hydrops fetalis was present; ascites can be seen. **C,** A shunt was placed in the largest cavity. **D,** Resolution of the hydrops was seen within 1 week. Cross section through the thorax shows expansion of the ipsilateral and contralateral lungs, repositioning of the heart, and reduction of the mass. *(From Obican SG, Odibo A. Invasive fetal therapy. In: Lockwood CJ, Copel JA, Dugoff L, et al., eds. Creasy & Resnik's Maternal-Fetal Medicine, 9th ed. Philadelphia: Elsevier; 2023: Fig 34-11, p. 633.)*

be indicated. In the postnatal period, surgery is indicated for symptomatic patients. Although surgery may be delayed for asymptomatic infants because postnatal resolution has been reported, true resolution appears to be quite rare in that abnormalities usually remain detectable on CT or MRI. Sarcomatous and carcinomatous degeneration have been described in patients with CPAM, so surgical resection by 1 year of age is typically recommended to limit malignant potential. If surgery is not performed, the child should have imaging at least yearly to track progression of the lesion. The mortality rate is <10%. Another indication for surgery is to rule out **pleuropulmonary blastoma (PPB)**, a malignancy that can appear radiographically similar to type 1 CPAM or appear concurrently in a type 4 CPAM (mixed lesion). PPB is associated with germline or somatic pathogenic variants in *DICER1*. PPB usually has a systemic feeding vessel and is not connected to the bronchial tree. However, it is often difficult to distinguish a PPB from a CPAM without surgery. In addition to the risk of malignancy, "asymptomatic" patients may have chronic inflammation with subtle systemic manifestations, which parents report resolves after the lesion is resected.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

444.4 Pulmonary Sequestration

Joshua A. Blatter and Jonathan D. Finder

Pulmonary sequestration is a congenital anomaly of lung development that can be intrapulmonary or extrapulmonary, according to the location within the visceral pleura. The majority of sequestrations are intrapulmonary.

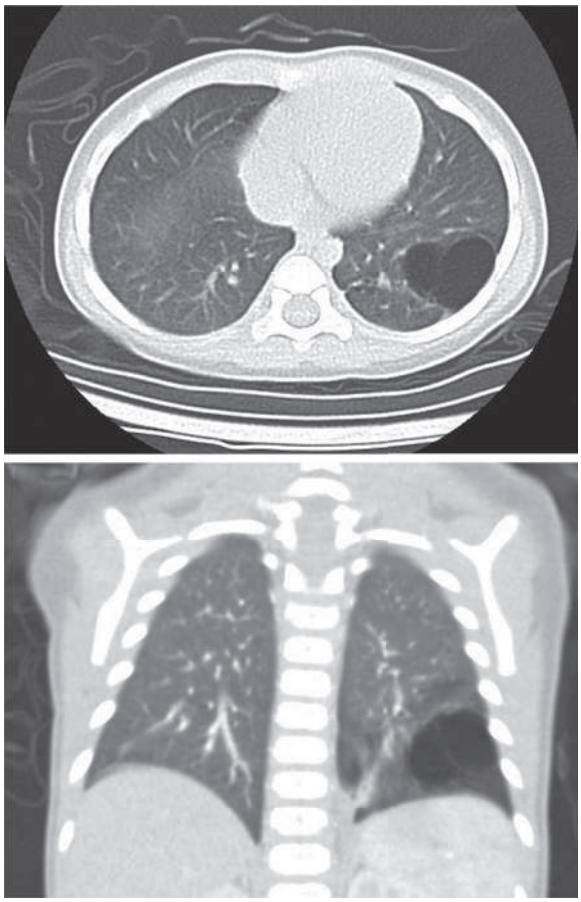

Fig. 444.4 CT scans of CPAM in the left lower lobe of the lung. *(From Wong KKY, Flake AW, Tibboel D, et al. Congenital pulmonary airway malformation: advances and controversies. Lancet Child Adolesc. 2018;2:290–296, Fig. 1.)*

PATHOPHYSIOLOGY

The lung tissue in a sequestration does not connect to a bronchus and receives its arterial supply from the systemic arteries (commonly off the aorta) and returns its venous blood to the right side of the heart through the inferior vena cava **(extralobar)** or pulmonary veins **(intralobar)**. The sequestration functions as a space-occupying lesion within the chest; it does not participate in gas exchange and does not lead to a left-to-right shunt or alveolar dead space. Communication with the airway can occur as the result of rupture of infected material into an adjacent airway. Collateral ventilation within intrapulmonary lesions via pores of Kohn can occur. Pulmonary sequestrations can arise through the same pathoembryologic mechanism as a remnant of a diverticular outgrowth of the esophagus. Some propose that intrapulmonary sequestration is an acquired lesion primarily caused by infection and inflammation; inflammation leads to cystic changes and hypertrophy of a feeding systemic artery. This is consistent with the rarity of this lesion in an autopsy series of newborns. Gastric or pancreatic tissue may be found within the sequestration. Cysts also may be present. Other associated congenital anomalies, including CPAM (see Chapter 444.3), diaphragmatic hernia (see Chapter 131), and esophageal cysts, are not uncommon. Some believe that intrapulmonary sequestration is often a manifestation of CPAM and have questioned the existence of intrapulmonary sequestration as a separate entity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Recurrent pneumonia in the same lung location is suggestive of a sequestration. Physical findings in patients with sequestration include an area of dullness to percussion and decreased breath sounds over the lesion. During infection, crackles may also be present. A continuous or purely systolic murmur may be heard over the back. If findings on routine chest radiographs are consistent with the diagnosis, further delineation is indicated before surgical intervention (Fig. 444.5). CT with contrast can demonstrate both the extent of the lesion and its vascular supply. MR angiography is also useful. Ultrasonography can help to rule out a diaphragmatic hernia and demonstrate the systemic artery. Surgical removal is recommended. Identifying the blood supply before surgery avoids inadvertently severing its systemic artery. Coil embolization (transumbilical in neonates; arterial in older patients) has been successful in treating patients with sequestration.

Intrapulmonary sequestration is generally found in a lower lobe and does not have its own pleura. Patients usually present with infection. In older patients, hemoptysis is common. A chest radiograph during a period when there is no active infection reveals a mass lesion; an air-fluid level may be present. During infection, the margins of the lesion may be blurred. There is no difference in the incidence of this lesion in each lung.

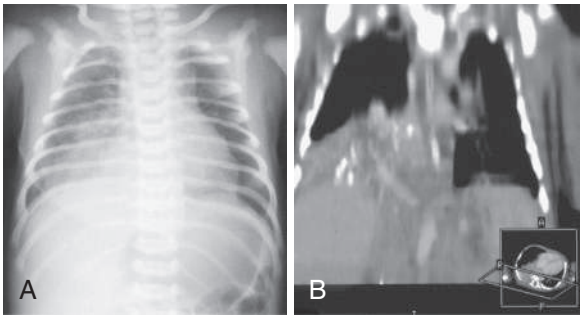

Fig. 444.5 A, Plain chest x-ray showing changes in the region of the right lower/middle lobe of the lung. B, CT showing parenchymal changes in the right lower lobe of the lung in keeping with a sequestration. *(From Corbett HJ, Humphrey GME. Pulmonary sequestration. Paediatr Respir Rev. 2004;5:59–68.)*

Extrapulmonary sequestration is much more common in boys and almost always involves the left lung. This lesion is enveloped by a pleural covering and is associated with diaphragmatic hernia and other abnormalities such as colonic duplication, vertebral abnormalities, and pulmonary hypoplasia. Many of these patients are asymptomatic when the mass is discovered by routine chest radiography. Other patients present with respiratory symptoms or heart failure. Subdiaphragmatic extrapulmonary sequestration can manifest as an abdominal mass on prenatal ultrasonography. The advent of prenatal ultrasonography has also enabled evidence that fetal pulmonary sequestrations can spontaneously regress.

TREATMENT

Treatment of intrapulmonary sequestration is surgical removal of the lesion, a procedure that usually requires excision of the entire involved lobe. Segmental resection occasionally suffices. Surgical resection of the involved area is often recommended for extrapulmonary sequestration as well, but observation can be considered for asymptomatic patients with small lesions. Coil embolization of the feeding artery has also been successful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

444.5 Bronchogenic Cysts

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Bronchogenic cysts arise from abnormal budding of the tracheal diverticulum of the foregut before the 16th week of gestation and are originally lined with ciliated epithelium. They are more commonly found on the right and near a midline structure (trachea, esophagus, carina), but peripheral lower lobe and perihilar intrapulmonary cysts are not infrequent. Diagnosis may be precipitated by enlargement of the cyst, which causes symptoms by pressure on an adjacent airway. When the diagnosis is delayed until an infection occurs, the ciliated epithelium may be lost, and accurate pathologic diagnosis is then impossible. Cysts are rarely demonstrable at birth. Later, some cysts become symptomatic by becoming infected or by enlarging and compromising the function of an adjacent airway.

CLINICAL MANIFESTATIONS AND TREATMENT

Fever, chest pain, and productive cough are the most common presenting symptoms. Dysphagia may be present; some bronchogenic cysts are asymptomatic. A chest radiograph reveals the cyst, which can contain an air-fluid level (Fig. 444.6). CT scan or MRI is obtained in most cases to better demonstrate the anatomy and extent of the lesion before surgical resection. Treatment of symptomatic cysts is surgical excision after appropriate antibiotic management. Asymptomatic cysts are generally excised in view of the high rate of infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

444.6 Congenital Pulmonary Lymphangiectasia

Joshua A. Blatter and Jonathan D. Finder

Congenital pulmonary lymphangiectasia is characterized by greatly dilated lymphatic ducts throughout the lung. It can occur in three pathologic circumstances: **pulmonary venous obstruction** that produces an elevated transvascular pressure and engorges the pulmonary lymphatics and **generalized lymphangiectasia**, as a generalized disease of several organ systems, including lymphedema, lungs, and the intestines either associated with other syndromes (Noonan, Hennekam, yellow nail, trisomy 21) or nonsyndromic. Gorham-Stout disease (vanishing bone disease) presents with pulmonary and abdominal chylous effusions, destructive bone cysts, and multiple lymphangiomas; **primary lymphangiectasia** limited to the lung is the third type, which is a manifestation of an abnormality in lymphatic development.

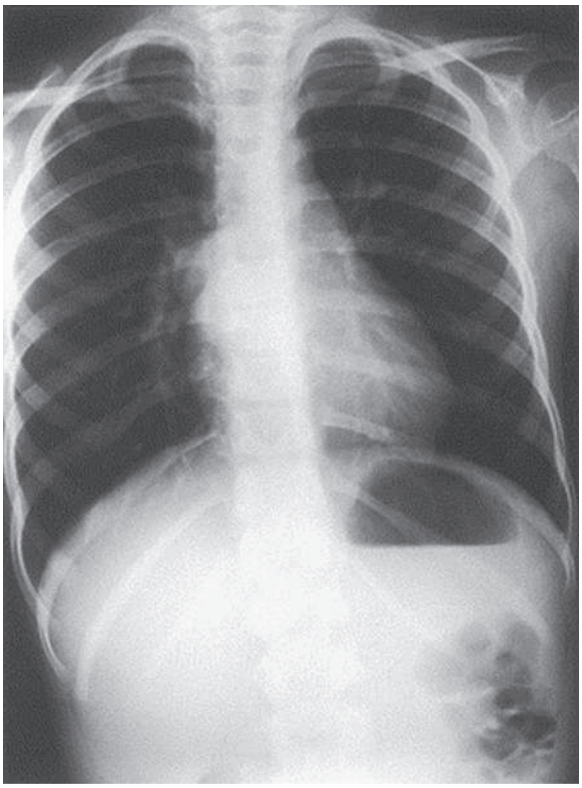

Fig. 444.6 Chest x-ray showing an ovoid, well-defined soft tissue density causing splaying of the carina because of a bronchogenic cyst. *(From Williams HJ, Johnson KJ. Imaging of congenital cystic lung lesions. Paediatr Respir Rev. 2002;3:120–127.)*

CLINICAL MANIFESTATIONS AND TREATMENT

Children with pulmonary venous obstruction or severe pulmonary lymphangiectasia present with dyspnea and cyanosis in the newborn period. Hydrops fetalis may be diagnosed antenatally. Chest radiographs reveal diffuse, dense, reticular densities with prominence of Kerley B lines. Pleural effusions are common; thoracentesis will reveal **chylothorax** in this setting. If the lung is not completely involved, the spared areas appear hyperlucent. Respiration is compromised because of impaired diffusion and decreased pulmonary compliance. The diagnosis can be suggested by CT scan and/or cardiac catheterization; definitive diagnosis requires lymphangiography, lymphoscintigraphy, or lung biopsy (either thoracoscopic or open) (Fig. 444.7).

Treatment is supportive and includes administration of oxygen, mechanical ventilation, nutritional support (including gastrostomy placement and use of feedings containing medium-chain triglycerides), and careful fluid management with diuretics. Octreotide, the somatostatin analog, can reduce chylous effusion in some patients. Primary pulmonary lymphangiectasia in the neonate can produce severe pulmonary dysfunction that can require long-term mechanical ventilation; long-term survival and resolution of respiratory insufficiency are possible even in severe cases, especially if the chylous effusions can be managed. Occasionally, the pulmonary venous obstruction is secondary to left-sided cardiac lesions; relief of the latter can produce improvement in pulmonary dysfunction. Sildenafil may reduce pulmonary venous resistance and decrease lymphatic congestion. Sirolimus, which suppresses lymphangiogenesis, may also be beneficial. Lymphangiographic-directed lymphatic injection with ethiodized oil may be another therapeutic option. Generalized lymphangiectasia produces milder pulmonary dysfunction, and survival to mid-childhood and beyond is not unusual.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

444.7 Lung Hernia

Joshua A. Blatter and Jonathan D. Finder

A lung hernia is a protrusion of the lung beyond its normal thoracic boundaries. Approximately 20% are congenital, with the remainder being noted after chest trauma or thoracic surgery or in patients with pulmonary diseases such as cystic fibrosis (see Chapter 454) or asthma (see Chapter 185), which cause frequent cough and generate high intrathoracic pressure. A congenital weakness of the suprapleural membrane (Sibson fascia) or musculature of the neck can play a role in the appearance of a lung hernia. More than half of congenital lung hernias and almost all acquired hernias are cervical. Congenital cervical hernias usually occur anteriorly through a gap between the scalenus anterior and sternocleidomastoid muscles. Cervical herniation is usually prevented by the trapezius muscle (posteriorly, at the thoracic inlet) and by the three scalene muscles (laterally).

CLINICAL MANIFESTATIONS AND TREATMENT

The presenting sign of a cervical hernia (Sibson hernia) is usually a neck mass noticed while straining or coughing. Some lesions are asymptomatic and detected only when a chest film is taken for another reason. Findings on physical examination are normal except during Valsalva maneuver, when a soft bulge may be noticed in the neck. In most cases, no treatment is necessary, although these hernias can cause problems during attempts to place a central venous catheter through the jugular or subclavian veins. They can resolve spontaneously.

Paravertebral or parasternal hernias are usually associated with rib anomalies. Intercostal hernias usually occur parasternally, where the external intercostal muscle is absent. Posteriorly, despite the seemingly inadequate internal intercostal muscle, the paraspinal muscles usually prevent herniation. Straining, coughing, or playing a musical instrument can have a role in causing intercostal hernias, but in most cases, there is probably a preexisting defect in the thoracic wall.

Surgical treatment for lung hernia is occasionally justified for cosmetic reasons. In patients with severe chronic pulmonary disease and chronic cough and for whom cough suppression is contraindicated, permanent correction might not be achieved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

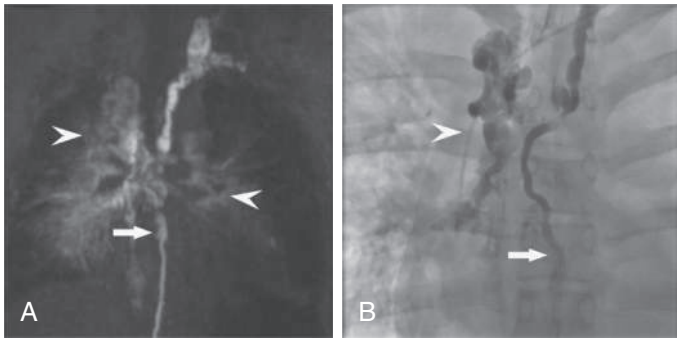

Fig. 444.7 **A,** Dynamic contrast MR lymphangiogram (DCMRL) in a patient with pulmonary lymphangiectasia demonstrating dilated thoracic duct (TD) *(arrow)* and abnormal pulmonary lymphatic perfusion in the lung hilum *(arrowheads).* **B,** Corresponding fluoroscopy image of the TD of the same patient after injection of contrast material through the microcatheter positioned in the proximal part of the TD, which confirms the dilation of the TD *(arrow)* and retrograde flow of the contrast in the mediastinal lymphatic ducts *(arrowhead). (From Itkin M, McCormack FX. Nonmalignant adult thoracic lymphatic disorders. Clin Chest Med. 2016;37:409–420, Fig. 7.)*

444.8 Other Congenital Malformations of the Lung

Joshua A. Blatter and Jonathan D. Finder

CONGENITAL LOBAR EMPHYSEMA AND PULMONARY CYSTS

See Chapter 441.

PULMONARY ARTERIOVENOUS MALFORMATION

See Chapters 481 and 493.

BRONCHOBILIARY FISTULA

A bronchobiliary fistula consists of a fistulous connection between the right middle lobe bronchus and the left hepatic ductal system (Fig. 444.8). Although diagnosis can be delayed until adulthood, this rare anomaly typically manifests with life-threatening bronchopulmonary infections in early infancy. Females are more commonly affected. Definitive diagnosis requires endoscopy or exploratory surgery. Treatment includes surgical excision of the entire intrathoracic portion of the fistula. If the hepatic portion of the fistula does not communicate with the biliary system or duodenum, the involved segment might also have to be resected. Bronchobiliary communications also occur as acquired lesions resulting from hepatic disease complicated by infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

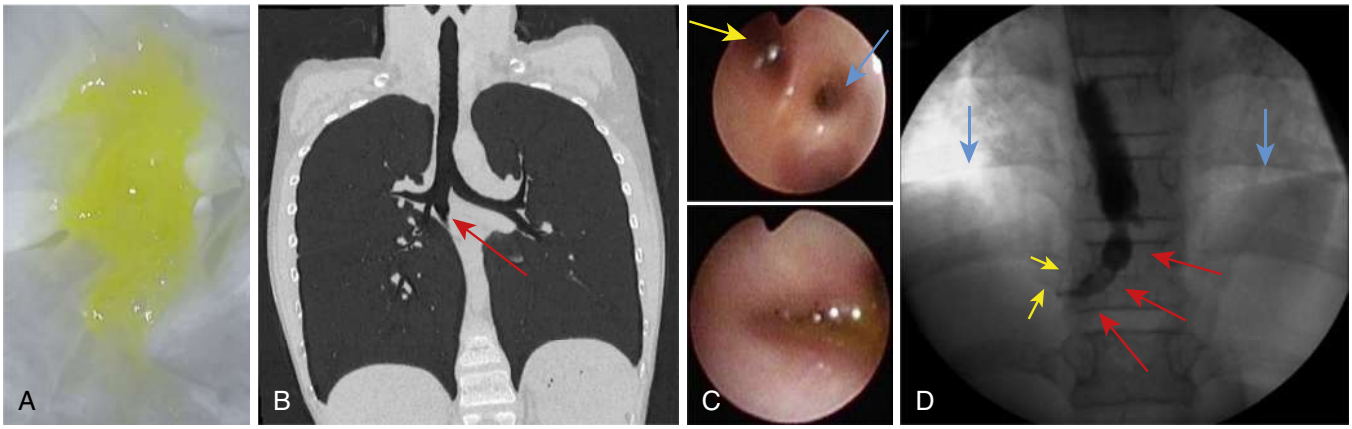

Fig. 444.8 Bronchobiliary fistula. **A,** Unusually bright yellow, serous sputum was observed. The sputum differed in appearance from the yellow sputum containing leukocytes associated with infections. **B,** CT scan revealed an abnormal bronchial bifurcation originating in the right main bronchus and extending downward *(arrow).* **C (Top),** Bronchoscopic images of the right second carina revealed an anomalous orifice *(yellow arrow)* in the medial side of the right intermediate bronchus *(blue arrow).* **(Bottom),** Close-up photo of the abnormal orifice with yellow, serous secretion. **D,** Fistulography with a balloon catheter revealed contrast material slowly proceeding through the intraabdominal region *(red arrows)* to the intrahepatic region *(yellow arrows)* below the diaphragm *(blue arrow). (From Shimizu A, Otani Y, Ishitate M. Congenital bronchobiliary fistula with bright yellow serous sputum. J Pediatr. 2020;243:235–236, Fig. 1.)*

Chapter 445

Pulmonary Edema

Brandon T. Woods

Pulmonary edema is an abnormal fluid collection in the interstitium and air spaces of the lung resulting in oxygen desaturation, decreased lung compliance, and respiratory distress. The condition is common in the acutely ill child.

PATHOPHYSIOLOGY

Although pulmonary edema is traditionally separated into two categories according to cause (*cardiogenic* and *noncardiogenic*), the end result of both processes is a net fluid accumulation within the interstitial and alveolar spaces. Noncardiogenic pulmonary edema in its most severe state is also known as *acute respiratory distress syndrome* (see Chapters 86 and 421).

The *hydrostatic pressure* and colloid *osmotic (oncotic) pressure* on either side of a pulmonary vascular wall, along with vascular permeability, are the forces and physical factors that determine fluid movement through the vessel wall. Baseline conditions lead to a net filtration of fluid from the intravascular space into the interstitium. This extra interstitial fluid is usually rapidly reabsorbed by pulmonary lymphatics. Conditions that lead to altered vascular permeability, increased pulmonary vascular pressure, and decreased intravascular oncotic pressure increase the net flow of fluid out of the vessel (Table 445.1). Once the capacity of the lymphatics for fluid removal is exceeded, water accumulates in the lung.

To understand the sequence of lung water accumulation, it is helpful to consider its distribution among four distinct compartments, as follows:

- *Vascular compartment:* This compartment consists of all blood vessels that participate in fluid exchange with the interstitium. The vascular compartment is separated from the interstitium by capillary endothelial cells. Several endogenous inflammatory mediators, as well as exogenous toxins, are implicated in the pathogenesis of pulmonary capillary endothelial damage, leading to the leakiness seen in several systemic processes.
- *Interstitial compartment:* The importance of this space lies in its interposition between the alveolar and vascular compartments. As fluid leaves the vascular compartment, it collects in the interstitium before overflowing into the air spaces of the alveolar compartment.
- *Alveolar compartment:* This compartment is lined with type 1 and type 2 epithelial cells. These epithelial cells have a role in active fluid transport from the alveolar space, and they act as a barrier to exclude fluid from the alveolar space. The potential fluid volume of the alveolar compartment is many times greater than that of the interstitial space, perhaps providing another reason that alveolar edema clears more slowly than interstitial edema.
- *Pulmonary lymphatic compartment:* There is an extensive network of pulmonary lymphatics. Excess fluid present in the alveolar and interstitial compartments is drained via the lymphatic system. When the capacity for drainage of the lymphatics is surpassed, fluid accumulation occurs.

ETIOLOGY

The specific clinical findings vary according to the underlying mechanism (see Table 445.1).

Transudation of fluid as a result of increased pulmonary vascular pressure *(capillary hydrostatic pressure)* occurs in several cardiac processes. A significant left-to-right shunting lesion, such as a septal defect, leads to a pressure and volume load on the pulmonary vasculature. The resultant pulmonary edema is one of the hallmarks of congestive heart failure. Left ventricular failure, mitral valve disease, and pulmonary venous obstructive lesions cause increased backpressure in the pulmonary vasculature. This results in an increase in pulmonary capillary pressure.

Table 445.1 Etiology of Pulmonary Edema

INCREASED PULMONARY CAPILLARY PRESSURE
Cardiogenic, such as left ventricular failure
Noncardiogenic, as in pulmonary venoocclusive disease, pulmonary venous fibrosis, mediastinal tumors
INCREASED CAPILLARY PERMEABILITY
Bacterial and viral pneumonia
Acute respiratory distress syndrome
Immune reconstitution inflammatory syndrome (IRIS)
Cytokine release syndrome (CRS): CAR-T therapy
Inhaled toxic agents
Circulating toxins
Vasoactive substances such as histamine, leukotrienes, and thromboxanes
Diffuse capillary leak syndrome, as in sepsis, SIRS
Immunologic reactions, such as transfusion reactions
Smoke inhalation
Aspiration pneumonia/pneumonitis
Drowning and near drowning
Radiation pneumonia
Uremia
LYMPHATIC INSUFFICIENCY
Congenital and acquired
DECREASED ONCOTIC PRESSURE
Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition
INCREASED NEGATIVE INTERSTITIAL PRESSURE
Upper airway obstructive lesions, such as croup and epiglottitis
Reexpansion pulmonary edema
MIXED OR UNKNOWN CAUSES
Neurogenic pulmonary edema
High-altitude pulmonary edema
Eclampsia
Pancreatitis
Pulmonary embolism
Heroin (narcotic) pulmonary edema

SIRS, systemic inflammatory response syndrome.
Modified from Robin E, Carroll C, Zelis R. Pulmonary edema. *N Engl J Med.* 1973;288:239, 292; and Desphande J, Wetzel R, Rogers M. In: Rogers M, ed. *Textbook of Pediatric Intensive Care*, 3rd ed. Baltimore: Williams & Wilkins; 1996:432–442.

Increased capillary permeability is usually secondary to endothelial damage. Such damage can occur secondary to direct injury to the alveolar epithelium or indirectly through systemic processes that deliver circulating inflammatory mediators or toxins to the lung. Inflammatory mediators (tumor necrosis factor, leukotrienes, thromboxanes) and vasoactive agents (nitric oxide, histamine) formed during pulmonary and systemic processes potentiate the altered capillary permeability that occurs in many disease processes, with sepsis being a common cause.

Fluid homeostasis in the lung largely depends on drainage via the lymphatics. Experimentally, pulmonary edema occurs with obstruction of the lymphatic system. Increased lymph flow and dilation of lymphatic vessels occur in chronic edematous states.

A decrease in intravascular oncotic pressure leads to pulmonary edema by altering the forces promoting fluid reentry into the vascular space. This occurs in dilutional disorders, such as fluid overload with hypotonic solutions, and in protein-losing states, such as nephrotic syndrome and malnutrition.

The **excessive negative interstitial pressure** seen in upper airway diseases, such as croup and laryngospasm, may promote pulmonary edema. Aside from the physical forces present in these diseases, other mechanisms may also be involved. Theories implicate an increase in CO_2 tension, decreased O_2 tension, and extreme increases in cardiac afterload, leading to transient cardiac insufficiency.

The mechanism causing **neurogenic pulmonary edema** is not clear. A massive sympathetic discharge secondary to a cerebral injury may produce increased pulmonary and systemic vasoconstriction, resulting in a shift of blood to the pulmonary vasculature, an increase in capillary pressure, and edema formation. Inflammatory mechanisms may also play a role by increasing capillary permeability.

The mechanism responsible for **high-altitude pulmonary edema** is unclear, but it may also be related to sympathetic outflow, increased pulmonary vascular pressures, and hypoxia-induced increases in capillary permeability (see Chapter 87).

Active ion transport followed by passive osmotic water movement is important in clearing the alveolar space of fluid. There are some experimental data that β-agonists and growth factors increase alveolar fluid removal. Interindividual genetic differences in the rates of these transport processes may be important in determining which individuals are susceptible to altitude-related pulmonary edema. Although the existence of these mechanisms suggests that therapeutic interventions may be developed to promote resolution of pulmonary edema, no such therapies currently exist.

CLINICAL MANIFESTATIONS

The clinical features depend on the mechanism of edema formation. In general, interstitial edema and alveolar edema prevent the inflation of alveoli, leading to atelectasis and decreased surfactant production. This results in diminished pulmonary compliance and tidal volume. The patient must increase respiratory effort and/or the respiratory rate so as to maintain minute ventilation. The earliest clinical signs of pulmonary edema include increased work of breathing, tachypnea, and dyspnea. As fluid accumulates in the alveolar space, auscultation reveals fine crackles and wheezing, especially in dependent lung fields. In cardiogenic pulmonary edema, a gallop may be present as well as peripheral edema and jugular venous distention.

Chest radiographs can provide useful ancillary data, although findings of initial radiographs may be normal. Early radiographic signs that represent accumulation of interstitial edema include peribronchial and perivascular cuffing. Diffuse streakiness reflects interlobular edema and distended pulmonary lymphatics. Diffuse, patchy densities, the so-called *butterfly pattern,* represent bilateral interstitial or alveolar infiltrates and are a late sign. Cardiomegaly is often seen with cardiogenic causes of pulmonary edema. Heart size is usually normal in noncardiogenic pulmonary edema (Table 445.2). Chest tomography demonstrates edema accumulation in the dependent areas of the lung. As a result, changing the patient's position can alter regional differences in lung compliance, functional residual capacity, and alveolar ventilation.

Measurement of brain natriuretic peptide, often elevated in heart disease, can help to differentiate cardiac from pulmonary causes of pulmonary edema. A brain natriuretic peptide level >500 pg/mL suggests heart disease; a level <100 pg/mL suggests lung disease.

TREATMENT

The treatment of a patient with noncardiogenic pulmonary edema is largely supportive, with the primary goal being to ensure adequate

Table 445.2 Distinguishing Cardiogenic and Noncardiogenic Pulmonary Edema

	HISTORY	EXAMINATION	LABORATORY TESTS	IMAGING

CARDIOGENIC	• Heart disease
	• Renal disease
	• Uncontrolled HTN
	• Edema
	• Orthopnea
	• Recent administration of IV fluids or blood products
		• Heart failure examination findings:
		  • Distended neck veins
		  • S3 heart sound
		  • Dependent edema
		  • Elevated blood pressure
		• Cool extremities
			• ↑ BNP >1200 pg/mL
			• ↑ Creatinine (in setting of volume overload)
			• ↑ Troponin
				• CXR:
				  • CMG pleural effusions
				  • Kerley B lines*
				  • Bedside USG: homogenous B lines and sliding pleura in at least two lung regions
				• TEE:
				  • ↓ LVEF
				  • Diastolic filling defect
				  • Severe mitral or aortic valvular disease
				  • Pericardial effusion with tamponade
				  • VSD

NONCARDIOGENIC	• Sepsis
	• Aspiration event
	• Trauma (long bone fractures)
	• Burn injury
	• Pancreatitis
	• Multiple transfusions
		• Signs of active infection
		• Extensive burn injury
		• Evidence of trauma (absence of heart failure examination findings)
			• ↑ WBC
			• BNP <200 pg/mL
				• CXR:
				  • Diffuse central and peripheral infiltrates
				  • Normal heart size
				  • No or minimal pleural effusions
				• Bedside USG: Presence of nonhomogeneous B lines, limited pleural sliding, and other patterns such as subpleural consolidations in at least two to three lung regions
				• TEE:
				  • Normal LV and valvular function
				  • No evidence of volume overload

*Thin 1–2 cm hyperechoic lines indicating thickened interlobular septae in the lung apices or bases.
BNR, brain natriuretic peptide.
Modified from Pannu SR, Christman JW, Crouser ED: Pulmonary edema. In Vincent JL, Moore FA, Bellomo R, Marini JJ (eds). *Textbook of Critical Care,* 8th ed. Philadelphia: Elsevier, 2024. Table 11.1.

ventilation and oxygenation. Additional therapy is directed toward the underlying cause. Patients should receive supplemental oxygen to increase alveolar oxygen tension and pulmonary vasodilation. Patients with pulmonary edema of cardiogenic causes should be managed with diuretics, inotropic agents, and systemic vasodilators to reduce left ventricular afterload. Diuretics are also valuable in the treatment of pulmonary edema associated with total body fluid overload (sepsis, renal insufficiency). Morphine is often helpful as a vasodilator and a mild sedative.

Positive airway pressure improves gas exchange in patients with pulmonary edema. In tracheally intubated patients, positive end-expiratory pressure can be used to optimize pulmonary mechanics. Noninvasive forms of ventilation, such as mask or nasal prong continuous positive airway pressure, are also effective. The mechanism by which positive airway pressure improves pulmonary edema is not entirely clear but is not associated with decreasing lung water. Rather, continuous positive airway pressure prevents complete closure of alveoli at the low lung volumes present at the end of expiration. It may also recruit already collapsed alveolar units. This leads to increased functional residual capacity and improved pulmonary compliance, improved surfactant function, and decreased pulmonary vascular resistance. The net effect is to decrease the work of breathing, improve oxygenation, and decrease cardiac afterload.

When mechanical ventilation becomes necessary, especially in noncardiogenic pulmonary edema, care must be taken to minimize the risk of development of complications from volutrauma or barotrauma, including pneumothorax, pneumomediastinum, and primary alveolar damage (see Chapter 86.1). Lung protective strategies include setting low tidal volumes, relatively high positive end-expiratory pressure, and allowing for permissive hypercapnia.

High-altitude pulmonary edema should be managed with altitude descent and supplemental oxygen. Portable continuous positive airway pressure or a portable hyperbaric chamber is also helpful. Nifedipine (10 mg initially and then 20-30 mg by slow release every 12-24 hours) in adults is also helpful. If there is a history of high-altitude pulmonary edema, nifedipine and β-adrenergic agonists (inhaled) may prevent recurrence (see Chapter 87).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 446

Acute Aspiration

Anastassios C. Koumbourlis

ASPIRATION SYNDROMES

Aspiration of material that is foreign to the lower airway produces a varied clinical spectrum ranging from an asymptomatic condition to acute life-threatening events. Except for cases of self-harm, episodes of acute aspiration are almost always unintentional. Whether the aspiration will lead to the development of symptoms and how severe these will be depends on the amount and nature of the aspirated material.

This chapter focuses on aspiration of **biologic liquids** (e.g., gastric contents) and chemical substances such as hydrocarbons or oils. Other chapters discuss the mechanical obstruction of large- or intermediate-size airways from solid foreign bodies (see Chapter 435), drowning (see Chapter 88), and chronic or recurrent (micro)aspiration (see Chapter 447).

GASTRIC CONTENTS

Aspiration of gastric contents may occur in the context of vomiting in persons who are not able to protect their airways. This can be the result of either a chronic neurologic impairment or temporary suppression of the normal protective reflexes. Such circumstances include drowning, seizures, trauma (especially head injury), and cardiopulmonary resuscitation. The most common nonacute condition that may predispose to aspiration is anesthesia that suppresses the protective airway reflexes (e.g., cough, glottic closure) not only during the procedure but even for hours afterward. Fortunately, because of the strict guidelines of fasting before receiving anesthesia, the actual incidence of aspiration during anesthesia is extremely low (<0.4%). It should be noted that in-office sedation/anesthesia for dental procedures also has the potential to cause suppression of the protective airway reflexes. Other conditions that may lead to vomiting and aspiration are alcohol intoxication and use of illicit drugs such as opiates, both of which can cause severe suppression of the level of consciousness.

The consequences of aspiration of gastric contents vary, depending primarily on the pH and volume of the aspirate and on the amount of particulate material it contains. Increased clinical severity is noted with aspirated volumes greater than 0.8 mL/kg and/or pH <2.5, but significant injury may also occur by fluids with alkaline pH such as bile or even with human breast milk.

Acute aspiration may cause **chemical pneumonitis** that may progress to **acute respiratory distress syndrome (ARDS)** consisting of hypoxemia, hemorrhagic pneumonitis, atelectasis, intravascular fluid shifts, and pulmonary edema. These processes occur rapidly (within minutes to 1-2 hours). There is also a marked increase in lung parenchymal neutrophil infiltrations, mucosal sloughing, and alveolar consolidation that often correlates with increasing infiltrates on chest radiographs. These changes tend to occur later (24-72 hours) and are more prolonged after aspiration of particulate material. Aspiration of gastric contents does not cause infection per se, but it predisposes to infection because of impairment of the airway epithelial defenses. If the patient demonstrates clinical worsening, especially with fever and leukocytosis, secondary bacterial pneumonia should be suspected.

HYDROCARBON ASPIRATION

Hydrocarbons are organic compounds that consist entirely of hydrogen and carbon. They are found in abundance in nature in fossil fuels (crude oil, coal, natural gas) and in plants (and some animals). Hydrocarbons are used in numerous common household or industrial products, thus increasing the possibility of accidental (and/or intentional) exposure. The major types of hydrocarbons and their common uses can be found in Table 446.1.

There are thousands of unintentional exposures to hydrocarbons each year, with the vast majority occurring in children under the age of 5, who drink out of curiosity from poorly secured and unlabeled containers. During adolescence, many exposures are intentional for recreational purposes (e.g., glue sniffing). Among adults a common accidental exposure occurs while attempting to siphon gasoline or among performers such as "fire eaters." Aspiration of hydrocarbons can occur while drinking the substance or often in the context of vomiting that follows an ingestion. Hydrocarbons have a noxious, unpleasant taste, and they are highly irritating to mucous membranes, thus preventing ingestion and aspiration of large volumes. One exception is the **mineral seal oil** that has a sweet taste that can lead to the ingestion of fairly large amounts.

The toxicity of the hydrocarbons depends on the specific properties of the compound and the amount that was aspirated. The major properties are:

- **Viscosity:** that is the resistance to flow through an orifice. Low viscosity allows *deeper penetration* into the tracheobronchial tree, and it is the property that primarily determines the aspiration potential for hydrocarbons.
- **Surface tension:** that refers to the cohesiveness of molecules along a liquid surface. Low surface tension allows compounds to *spread over a larger area.*

ventilation and oxygenation. Additional therapy is directed toward the underlying cause. Patients should receive supplemental oxygen to increase alveolar oxygen tension and pulmonary vasodilation. Patients with pulmonary edema of cardiogenic causes should be managed with diuretics, inotropic agents, and systemic vasodilators to reduce left ventricular afterload. Diuretics are also valuable in the treatment of pulmonary edema associated with total body fluid overload (sepsis, renal insufficiency). Morphine is often helpful as a vasodilator and a mild sedative.

Positive airway pressure improves gas exchange in patients with pulmonary edema. In tracheally intubated patients, positive end-expiratory pressure can be used to optimize pulmonary mechanics. Noninvasive forms of ventilation, such as mask or nasal prong continuous positive airway pressure, are also effective. The mechanism by which positive airway pressure improves pulmonary edema is not entirely clear but is not associated with decreasing lung water. Rather, continuous positive airway pressure prevents complete closure of alveoli at the low lung volumes present at the end of expiration. It may also recruit already collapsed alveolar units. This leads to increased functional residual capacity and improved pulmonary compliance, improved surfactant function, and decreased pulmonary vascular resistance. The net effect is to decrease the work of breathing, improve oxygenation, and decrease cardiac afterload.

When mechanical ventilation becomes necessary, especially in noncardiogenic pulmonary edema, care must be taken to minimize the risk of development of complications from volutrauma or barotrauma, including pneumothorax, pneumomediastinum, and primary alveolar damage (see Chapter 86.1). Lung protective strategies include setting low tidal volumes, relatively high positive end-expiratory pressure, and allowing for permissive hypercapnia.

High-altitude pulmonary edema should be managed with altitude descent and supplemental oxygen. Portable continuous positive airway pressure or a portable hyperbaric chamber is also helpful. Nifedipine (10 mg initially and then 20-30 mg by slow release every 12-24 hours) in adults is also helpful. If there is a history of high-altitude pulmonary edema, nifedipine and β-adrenergic agonists (inhaled) may prevent recurrence (see Chapter 87).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 446

Acute Aspiration

Anastassios C. Koumbourlis

ASPIRATION SYNDROMES

Aspiration of material that is foreign to the lower airway produces a varied clinical spectrum ranging from an asymptomatic condition to acute life-threatening events. Except for cases of self-harm, episodes of acute aspiration are almost always unintentional. Whether the aspiration will lead to the development of symptoms and how severe these will be depends on the amount and nature of the aspirated material.

This chapter focuses on aspiration of **biologic liquids** (e.g., gastric contents) and chemical substances such as hydrocarbons or oils. Other chapters discuss the mechanical obstruction of large- or intermediate-size airways from solid foreign bodies (see Chapter 435), drowning (see Chapter 88), and chronic or recurrent (micro)aspiration (see Chapter 447).

GASTRIC CONTENTS

Aspiration of gastric contents may occur in the context of vomiting in persons who are not able to protect their airways. This can be the result of either a chronic neurologic impairment or temporary suppression of the normal protective reflexes. Such circumstances include drowning, seizures, trauma (especially head injury), and cardiopulmonary resuscitation. The most common nonacute condition that may predispose to aspiration is anesthesia that suppresses the protective airway reflexes (e.g., cough, glottic closure) not only during the procedure but even for hours afterward. Fortunately, because of the strict guidelines of fasting before receiving anesthesia, the actual incidence of aspiration during anesthesia is extremely low (<0.4%). It should be noted that in-office sedation/anesthesia for dental procedures also has the potential to cause suppression of the protective airway reflexes. Other conditions that may lead to vomiting and aspiration are alcohol intoxication and use of illicit drugs such as opiates, both of which can cause severe suppression of the level of consciousness.

The consequences of aspiration of gastric contents vary, depending primarily on the pH and volume of the aspirate and on the amount of particulate material it contains. Increased clinical severity is noted with aspirated volumes greater than 0.8 mL/kg and/or pH <2.5, but significant injury may also occur by fluids with alkaline pH such as bile or even with human breast milk.

Acute aspiration may cause **chemical pneumonitis** that may progress to **acute respiratory distress syndrome (ARDS)** consisting of hypoxemia, hemorrhagic pneumonitis, atelectasis, intravascular fluid shifts, and pulmonary edema. These processes occur rapidly (within minutes to 1-2 hours). There is also a marked increase in lung parenchymal neutrophil infiltrations, mucosal sloughing, and alveolar consolidation that often correlates with increasing infiltrates on chest radiographs. These changes tend to occur later (24-72 hours) and are more prolonged after aspiration of particulate material. Aspiration of gastric contents does not cause infection per se, but it predisposes to infection because of impairment of the airway epithelial defenses. If the patient demonstrates clinical worsening, especially with fever and leukocytosis, secondary bacterial pneumonia should be suspected.

HYDROCARBON ASPIRATION

Hydrocarbons are organic compounds that consist entirely of hydrogen and carbon. They are found in abundance in nature in fossil fuels (crude oil, coal, natural gas) and in plants (and some animals). Hydrocarbons are used in numerous common household or industrial products, thus increasing the possibility of accidental (and/or intentional) exposure. The major types of hydrocarbons and their common uses can be found in Table 446.1.

There are thousands of unintentional exposures to hydrocarbons each year, with the vast majority occurring in children under the age of 5, who drink out of curiosity from poorly secured and unlabeled containers. During adolescence, many exposures are intentional for recreational purposes (e.g., glue sniffing). Among adults a common accidental exposure occurs while attempting to siphon gasoline or among performers such as "fire eaters." Aspiration of hydrocarbons can occur while drinking the substance or often in the context of vomiting that follows an ingestion. Hydrocarbons have a noxious, unpleasant taste, and they are highly irritating to mucous membranes, thus preventing ingestion and aspiration of large volumes. One exception is the **mineral seal oil** that has a sweet taste that can lead to the ingestion of fairly large amounts.

The toxicity of the hydrocarbons depends on the specific properties of the compound and the amount that was aspirated. The major properties are:

- **Viscosity:** that is the resistance to flow through an orifice. Low viscosity allows *deeper penetration* into the tracheobronchial tree, and it is the property that primarily determines the aspiration potential for hydrocarbons.
- **Surface tension:** that refers to the cohesiveness of molecules along a liquid surface. Low surface tension allows compounds to *spread over a larger area.*

Table 446.1 Classes and Uses of Common Hydrocarbons (HC)

CLASS AND CHEMICAL COMPOSITION	SOURCES AND EXAMPLES	USES
Aliphatic HC: Straight-chain compounds	**Source**: crude oil **Examples:** propane, kerosene, mineral seal oil	Furniture polishes, lamp oil, and lighter fluid
Aromatic HC: Cyclic compounds containing a benzene ring	**Source**: fossil fuels **Examples**: benzene, toluene, xylene	Solvents, glues, nail polishes, paints, and paint removers
Halogenated HC: compounds in which at least one hydrogen atom is replaced by a halogen (chlorine, bromine, fluorine)	**Source**: synthetic **Examples:** chloroform, bromopropane, carbon tetrachloride, methylene chloride, tetrachloroethylene	Solvents for dry cleaning, solvents for degreasing of metals, adhesives, refrigeration (Freon); insecticides
Terpene HC: cyclic hydrocarbons that consist of 5-carbon building blocks (isoprene)	**Source**: mostly plants **Examples**: turpentine, pine oil	Paint thinners (turpentine) and cleaning products (pine oil)

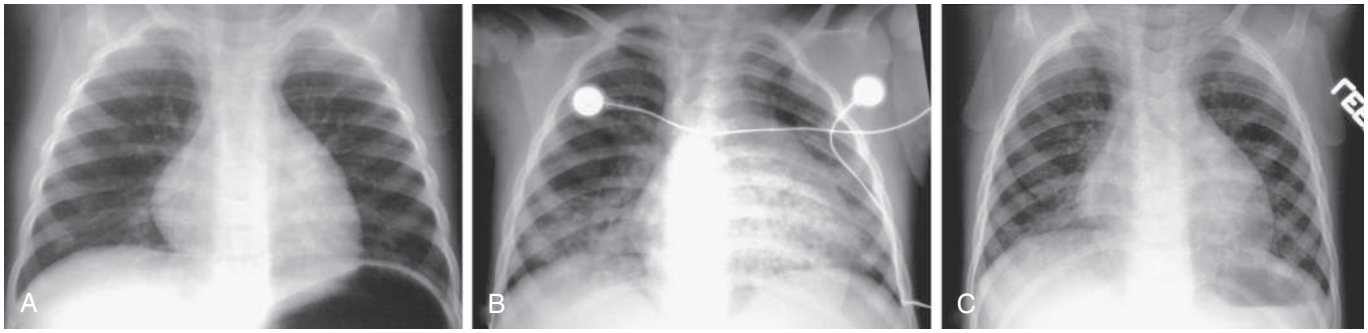

Fig. 446.1 Chest radiographs of a 17-mo-old toddler with hydrocarbon ingestion. **A,** Three hours after ingestion, the lungs are clear. **B,** At 24 hours, there are bibasilar coalescing nodular opacities. **C,** Three days later there is much clearing. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008:1287.)*

- **Volatility:** that is the *ability to vaporize*. High volatility increases the risk of pulmonary absorption and central nervous system (CNS) depression.

Hydrocarbons with lower surface tensions (gasoline, turpentine, naphthalene) have more potential for aspiration toxicity than heavier mineral or fuel oils. Ingestion of >30 mL of hydrocarbon, the approximate volume of an adult swallow, is associated with an increased risk of severe pneumonitis.

Most patients with hydrocarbon aspiration tend to remain asymptomatic. When symptomatic, patients have cough, choking, gagging, and vomiting. These usually appear within the first 30 minutes after the aspiration, but they may appear as late as 24 hours. Radiographic findings may present within hours and consist of interstitial or alveolar infiltrates in the perihilar regions and/or in the lower lobes (Fig. 446.1). Additional symptoms develop gradually and may include fever and increased work of breathing. Breath sounds may be decreased (or even absent) with wheezing and/or crackles (especially in the lower lobes). Symptomatic patients (especially those with radiographic abnormalities) require hospitalization for prolonged observation and treatment. Most patients require only supportive therapy (e.g., supplemental oxygen and hydration), and they get discharged within 2-3 days. A small number of patients (~5%) may develop ARDS with severe hypoxemia. Because hydrocarbons evaporate, they displace the alveolar gas, thus exacerbating the hypoxemia that is caused by the development of pulmonary edema and atelectasis that characterize ARDS. Necrotizing pneumonia with pneumatoceles, lipoid pneumonia, and hemorrhagic pulmonary edema are typical manifestations of severe cases, and they are often complicated by bacterial superinfection and sepsis, pleural effusions, and air leaks. Fatalities may occur, but most patients are expected to recover. Pneumatoceles can resolve over the course of months.

ASPIRATION OF OTHER SUBSTANCES

Any substance that is not supposed to be found in the airways can cause clinically significant disease. Other substances that can cause significant lung injury when aspirated or inhaled include baby powder (talc), chlorine, shellac, beryllium, and mercury vapors. Repeated exposure to low concentrations of these agents can lead to chronic lung disease, such as interstitial pneumonitis and granuloma formation. Corticosteroids may help reduce fibrosis development and improve pulmonary function, although the evidence for this benefit is limited.

One substance that deserves special mentioning is cinnamon, which achieved "notoriety" during the past decade because of the popularity among teenagers and young adults of the so-called "cinnamon-challenge" in which a person attempts to swallow dry cinnamon. Cinnamon is a caustic substance that causes the person to cough violently while it elicits a severe gag that is apparently the "amusing" part of the challenge for the spectators. Despite the gag, the possibility of aspiration is relatively high. Cinnamon causes significant airway inflammation and a potential hypersensitivity reaction that in rare cases may lead to respiratory distress and failure.

PRINCIPLES OF MANAGEMENT

Suctioning of the aspirated material can be effective only if it is performed during or immediately after the aspiration occurs (e.g., vomiting occurring in a patient who is seizing). Once aspiration occurs, the aspirated fluid will be drawn (or pushed) quickly into the distal airways with every spontaneous or positive pressure breath. Thus gastric emptying is generally contraindicated because the vomiting increases the possibility of aspiration. An exception to this rule is the ingestion of a large volume (>30 mL) of certain hydrocarbons with inherent systemic toxicity, especially if the patient exhibits signs of altered mental status. Such compounds include **c**amphor, **h**alogenated carbons, **a**romatic hydrocarbons, and those containing metals and **p**esticides (mnemonic: CHAMP). *Gastric emptying should be performed after a cuffed endotracheal tube has been inserted for protection from aspiration.* However, because intubating a patient with a full stomach is a high-risk procedure by itself, it should be performed by a specialist with experience in rapid sequence intubation to prevent vomiting and further aspiration.

Bronchoscopy should be considered if there is suspicion of aspiration of significant particulate material that could be potentially removed (see Chapter 435).

Patients in whom large-volume or toxic aspiration is suspected should be observed for several hours (e.g., 6-8 hours) for signs of respiratory distress and/or hypoxemia. A chest radiograph is warranted. A "negative" chest radiograph taken shortly after the event does not rule out the presence, nor does it predict the severity of aspiration, because the radiographic findings usually lag behind the clinical symptoms (see Fig. 447.1).

If the chest radiograph findings and oxygen saturation are normal and the patient remains asymptomatic after several hours of observation, no other treatment is necessary. The caregivers should be instructed to bring the child back to the hospital if respiratory symptoms or fever develop.

Supplemental oxygen is indicated to treat hypoxemia and/or to decrease the work of breathing. High-flow nasal cannula or noninvasive ventilation such as continuous positive airway pressure or bilevel positive airway pressure should be instituted for patients who develop increased work of breathing, progressive hypoxemia, and/or progressive hypercapnia. If these measures fail to control the symptoms, endotracheal intubation and mechanical ventilation are indicated. In rare cases of refractory respiratory failure, extracorporeal membrane oxygenation may become necessary. Exogenous surfactant has been used with success in some reported cases.

There is no specific pharmacologic therapy for aspiration. Bronchodilators may be tried to prevent and/or reverse the bronchospasm triggered by the aspirate (especially if the patient has a history of airway hyperreactivity/asthma). Use of inhaled and especially of systemic corticosteroids may be reasonable considering that severe aspiration triggers a massive inflammatory response, but their actual benefit is rather inconclusive. Animal studies suggest that to be effective corticosteroids should be given nearly simultaneously with the aspiration event. Prophylactic *antibiotics are not generally indicated* because aspiration causes a "chemical" and not an infectious pneumonitis. However, the possibility of a secondary infection is high because of organisms (usually anaerobes) from the oropharynx that enter the lower airways with the aspirate and/or organisms that may already colonize the lower airways (e.g., in patients with artificial airways and/or underlying conditions such as bronchiectasis). Thus the decision to start antibiotics prophylactically should be based on the patient's respiratory status, immune status, and colonization status (if known). Empiric antibiotic therapy is usually targeted against anaerobic organisms. In hospitalized or chronically ill patients (especially those with an artificial airway), coverage of *Pseudomonas, Staphylococcus aureus,* and enteric gram-negative organisms should also be considered. If empiric antibiotics are given, they can be discontinued if the condition improves rapidly and the cultures are negative.

PREVENTION

The best prevention of unintentional aspiration is to keep toxic substances out of reach from young children in containers that are clearly labeled and with safety caps. Prevention of aspiration should always be the goal when airway manipulation is necessary for intubation or other invasive procedures. Feeding with enteral tubes passed beyond the pylorus, elevating the head of the bed 30-45 degrees in mechanically ventilated patients, and oral decontamination reduce the incidence of aspiration complications in the intensive care unit. Acid neutralization is not routinely recommended, but it may be considered if the airway epithelium is damaged and thus unable to neutralize the acid. Minimizing use of sedation, monitoring for gastric residuals, and gastric acid suppression may all help prevent aspiration. *Any patient with altered consciousness, especially one who is receiving nasogastric or gastrostomy tube feedings, is at high risk for aspiration.*

PROGNOSIS

Most patients without any underlying conditions usually recover in 2-3 weeks with minimal or no chronic residual clinical symptoms, abnormal radiographic, or lung function changes. Prolonged lung damage may occur, including scarring, bronchiolitis obliterans, and bronchiectasis. The mortality is relatively low (approximately 5%) and occurs primarily among patients with severe acute or chronic comorbidities. In adults the mortality is much higher (exceeding 20%), but it is difficult to separate the contribution of the aspiration from the effect of the underlying conditions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 447

Chronic Recurrent Aspiration

Anastassios C. Koumbourlis

The air that enters the lungs with every breath travels through the same narrow spaces that solid foods and liquids use to enter the esophagus. That aspiration does not occur routinely is the result of several mechanisms that protect the lower airways. The swallowing mechanism is a complex process that starts early in fetal life but fully matures months after birth; its goal is to receive, process, and transfer the food bolus from the mouth to the esophagus while preventing food particles and/or fluids from entering the trachea. When fully developed, the swallow consists of four phases. The first two (oral preparatory and oral) are voluntary and involve the preparation of the food bolus and its transfer to the back of the throat, whereas the last two (pharyngeal and esophageal) are involuntary. Under normal circumstances, by the time the food bolus reaches the pharynx, the respiration transiently stops, the vocal cords close at the midline, the arytenoid cartilages come close to each other, and the epiglottis flexes toward the posterior wall covering the larynx. This allows the food bolus to slide around the epiglottis into the pyriform sinuses and then into the esophagus where peristalsis and gravity help it move to the stomach. If these four phases are not synchronized (e.g., drinking too fast), aspiration may occur. Oropharyngeal incoordination is reportedly the most common underlying problem (with prevalence as high as 48%) associated with recurrent pneumonia in hospitalized children. A wide variety of conditions may impair one or more of the phases of the normal swallow (Table 447.1). Various maxillofacial and oropharyngeal anatomic abnormalities such as micrognathia, macroglossia, and cleft palate affect primarily the first two phases of swallowing, whereas neurologic conditions (affecting the central or the peripheral nervous system and the motor neuron junction) and primary muscle conditions affect the last two. In addition to the mechanisms for airway protection that are part of the normal swallow, there are several reflexes that can prevent aspiration. These include:

1. **The pharyngeal reflex**: Commonly referred to as the "gag" reflex, it can be elicited by touching the posterior pharyngeal wall, the soft palate, the tonsils, and/or the larynx. The gag reflex causes bilateral acute contraction of the pharyngeal muscles and elevation of the soft palate that prevent the bolus from advancing to the glottis. Damage to the glossopharyngeal and/or vagal nerves affects the reflex unilaterally or bilaterally.
2. **The laryngeal spasm**: When the glottis and/or subglottis get irritated, they produce acute contraction of the laryngeal muscles that close the vocal cords. This mechanism is very important when liquid and/or particles reach the larynx from below (gastroesophageal reflux [GER] or regurgitation) without involving the normal swallowing mechanism. Despite its protective role, laryngospasm may have negative consequences, especially in infants, who have normally low breathing reserves and can develop hypoxemia and hypercapnia within seconds. In addition, if during laryngospasm the infant attempts to exhale, the

Table 447.1 Conditions Associated with Chronic Aspiration

DIRECT	IMPAIRED SWALLOWING MECHANISM	PREDISPOSING FACTORS
Anatomic causes • Tracheoesophageal fistula • Bronchoesophageal fistula • Laryngotracheal cleft	Anatomic causes • Cleft lip/cleft palate* • Micrognathia • Macroglossia • Scarring (e.g., burns) • Trauma • Facial rigidity (scleroderma, dermatomyositis)	Anatomic causes • Choanal stenosis • Laryngomalacia • Esophageal stricture • Esophageal foreign body • External compression of the esophagus (e.g., vascular ring, mass)
Functional causes • Vocal cord paralysis in abduction • Central nervous system disorders suppressing the airway-protective reflexes (severe encephalopathy, coma)	Functional causes • Muscle weakness (neuromuscular disorders) • Bulbar dysfunction (motor neuron disorders) • Nonspecific hypotonia (e.g., trisomy 21)	Functional causes • Gastroesophageal reflux • Esophageal achalasia • Immature swallowing (e.g., prematurity) • Severe tachypnea

*Preoperative and postoperative.

Hering-Breuer reflex may cause apnea (this may be a cause of the GER-related apnea often seen among premature infants).

3. **The cough reflex**: The presence of material in the glottis and subglottis will normally elicit a cough to expel the "foreign substance." Thus coughing while eating or drinking is an indication of impaired swallowing and of possible aspiration. However, the absence of cough while eating or drinking does not rule out aspiration because several groups of patients (e.g., premature infants or patients with neuromuscular disorders) may not be able to cough, resulting into the so-called "silent aspiration."

When anatomic abnormalities connect the respiratory and gastrointestinal tracts, the airway protective mechanisms are completely bypassed, and chronic aspiration ensues. Such abnormalities can be found at the level of the larynx (e.g., laryngotracheoesophageal cleft) or at the proximal tracheobronchial tree (e.g., tracheoesophageal and/or bronchoesophageal fistula).

CLINICAL PRESENTATION

Repeated aspiration of even small quantities of gastric, nasal, or oral contents can lead to chronic airway inflammation presenting as recurrent bronchitis, bronchiolitis, and/or pneumonitis. The symptoms vary, but they usually include chronic unexplained cough (especially during or after feeding), gagging, and wheezing. Noisy ("gurgly") breathing caused by accumulation of secretions in the hypopharynx is both a predisposing and a predictive factor of aspiration. Infants (especially those born prematurely) may present with apneic episodes associated with laryngospasm. This can happen while drinking, as a result of oropharyngeal incoordination, or in between feedings due to episodes of GER that reaches the laryngeal area eliciting the laryngeal spasm. Fever is not usually a symptom of aspiration, but it may develop at any point because the chronic airway inflammation caused by the aspiration predisposes to secondary infections.

Pathologic Sequelae

Chronic aspiration can lead to irreversible lung damage in the form of bronchiectasis, granulomatous inflammation, fibrosis, and bronchiolitis obliterans. Recurrent episodes of lipoid pneumonia have been reported after use of oil-based home/folk remedies popular in several parts of the world that are given orally or nasally to children with impaired swallow.

Predisposing Factors

Many of the anatomic and functional abnormalities listed in Table 447.1 predispose the affected patients to aspiration, although technically they do not cause aspiration by themselves. These include but are not limited to the following:

- **Gastroesophageal reflux** (see Chapter 369): GER is a physiologic mechanism that is present from birth and throughout life. When severe, it predisposes to aspiration by bringing gastric contents near the larynx. However, aspiration will not occur unless the protective airway reflexes are defective. In general, GER is less frequently associated with recurrent pneumonia than is dysphagia. Gastroesophageal reflux disease (GERD; see Chapter 369) can cause pharyngeal and laryngeal edema and vocal cord nodules that may interfere with the swallowing mechanism and lead to aspiration. GERD has been associated with chronic microaspiration and bronchiolitis obliterans in lung transplant recipients.
- **Anatomic and functional abnormalities** such as cleft lip/palate, micrognathia, macroglossia, and laryngomalacia can interfere with the mechanism of bolus formation.
- **Nonspecific hypotonia**, seen in conditions such as trisomy 21 and in otherwise healthy infants (especially those born prematurely), may cause oropharyngeal discoordination and lead to recurrent microaspiration.
- **Increased work of breathing**, due to conditions that cause significant nasal obstruction and/or significant tachypnea place otherwise healthy infants at risk for aspiration because they may attempt to breathe and drink at the same time. Thus when a child with an acute respiratory illness who is being fed enterally deteriorates unexpectedly, the possibility of aspiration should be considered.

DIAGNOSIS

A history of unexplained recurrent/persistent respiratory symptoms such as cough and wheezing should always raise suspicions of chronic aspiration. It is then important to determine whether the aspiration occurs from above because of swallowing impairment or from below because of GER. The circumstances around and the timing of the symptoms may offer clues about the exact mechanism. Observation of a feeding is an essential part of the examination when a diagnosis of recurrent aspiration is being considered. Particular attention should be given to nasopharyngeal reflux and difficulty with sucking or swallowing. Symptoms such as choking, cough, stridor, or wheezing occurring during feedings are much more likely the result of impaired swallow. Coughing during or immediately after swallowing points toward anatomic abnormalities (e.g., laryngeal cleft or tracheoesophageal fistula). Symptoms occurring in between feedings, especially in a child with frequent spitting up, vomiting, arching, or complaining of epigastric discomfort, are more likely to be associated with GER.

Voice changes such hoarseness or muffled cry suggest GERD, whereas noisy (wet) breathing suggests pooling of secretions in the hypopharynx. The oral cavity should be inspected for gross abnormalities and

Table 447.2 Diagnostic Modalities for the Detection of Chronic Aspiration

DIAGNOSTIC MODALITY	ADVANTAGES	DISADVANTAGES
Chest radiograph	• Easy to obtain and inexpensive • Low radiation exposure	• Findings are not pathognomonic • Does not distinguish between aspiration from above or from below
Computed tomography of the chest	• Provides details that may be missed in plain chest x-ray (CXR)	• Findings are not pathognomonic • Does not distinguish between aspiration from above or from below • More expensive • Considerably higher radiation exposure
Esophagogram	• Provides information on the anatomy and function of the esophagus (e.g., stricture, hiatal hernia, foreign body, achalasia, decreased motility) • Detects gastroesophageal reflux (GER) • Detects tracheoesophageal fistula and external compression (vascular ring)	• Considerable radiation exposure • Short viewing time • May miss a small H-type tracheoesophageal fistula if the patient is in the supine position
Videofluoroscopic swallowing study (VFSS)	• Gold standard for the detection of aspiration even in patients without obvious respiratory symptoms	• Considerable radiation exposure • Requires the presence of a trained speech pathologist • May lead to aspiration of barium that cannot be cleared by the lung
Milk scintiscan	• More "physiologic" • Provides significantly longer viewing time • High specificity • No radiation exposure	• Low sensitivity • Does not provide any anatomic details
Salivagram	• High sensitivity (similar to VFSS) • No radiation exposure	• Infants may spit out the radionucleotide before it is mixed with the saliva and swallowed • Does not provide information about GER
Fiberoptic endoscopic evaluation of swallowing (FEES)	• Provides direct observation of the swallowing mechanism • Can be performed at the bedside or in the office	• Moderately invasive • Young patients may "fight" the insertion of the laryngoscope in their nose
"Dye" studies	• Simple, easy to perform even at home	• Requires the presence of an artificial airway • Possible toxicity from repeated use
Quantification of lipid-laden macrophages in the bronchoalveolar lavage (BAL) fluid	• High sensitivity	• Requires the performance of a bronchoscopy and BAL • Low specificity • Does not distinguish whether the lipids are the result of aspiration or release from cell damage/death

stimulated to assess the gag reflex. Drooling or excessive accumulation of secretions in the mouth suggests dysphagia. Sudden development of crackles or wheezes, especially in the dependent lung segments after feeding, is highly suggestive of aspiration.

The laboratory diagnosis of recurrent microaspiration is challenging because of the lack of pathognomonic tests. Several diagnostic modalities are currently used for the diagnosis of aspiration (Table 447.2) that can be grouped in the following:

- **Radiographs and computed tomography of the chest**: Aspiration may produce the "typical" segmental or lobar infiltrates in the dependent areas of the lung. However, their presence is not pathognomonic, and their absence does not rule out the diagnosis. Thus any abnormal radiographic finding (e.g., diffuse infiltrates, lobar infiltrates, bronchial wall thickening, and bronchiectasis) that cannot be explained by any other process should raise the possibility of chronic aspiration, especially if the patient has any of the aforementioned predisposing factors (Fig. 447.1).
- **Contrast studies**: Various tests, such as esophagogram, modified barium swallow (MBS), and videofluoroscopic swallowing study (VFSS), are currently considered the "gold standard" for the diagnosis of chronic aspiration. The patient swallows the contrast material (usually barium) under direct fluoroscopic visualization, which provides information on the swallow itself, on the presence of penetration and/or aspiration, and on the anatomy and function of the esophagus.
- **Nuclear scans**: These tests (milk scintigram and salivagram) are based on the oral administration of radionucleotides. Their detection in the lungs is proof of aspiration. A major benefit is that they do not expose the patient to radiation. However, the milk scan has very low sensitivity; the salivagram has much better sensitivity but it does not provide any information on the anatomy or function of the esophagus.
- **Endoscopic studies**: The fiberoptic endoscopic evaluation of swallowing (FEES) allows direct observation of the swallow and documents the aspiration in real time without radiation exposure. However, the child's reaction to placement of the endoscope may alter the assessment of function, depending on the level of comfort and cooperation.

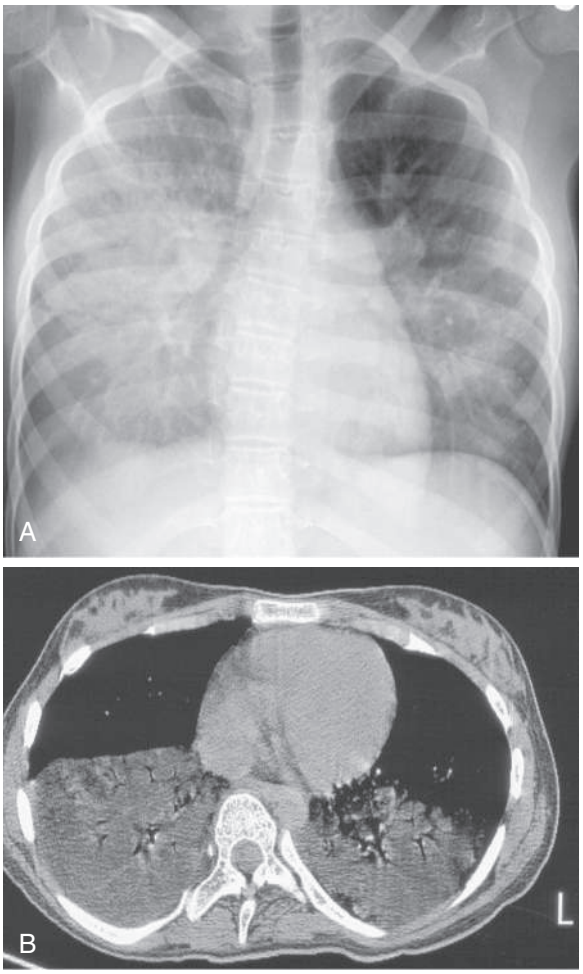

Fig. 447.1 A, Chest radiograph of a developmentally delayed 15-yr-old with chronic aspiration of oral formula. Note posterior (dependent areas) distribution with sparing of heart borders. B, Chest CT scan of same patient. Note lung consolidation in dependent regions is of similar density to subcutaneous fat.

- **Dye studies**: These can be useful tests for patients with artificial airways. A small amount of food coloring (such as methylene blue) is placed in the patient's mouth or into the stomach. If it appears in the tracheobronchial secretions in a few minutes, it confirms aspiration.
- **Analysis of bronchoalveolar lavage (BAL) fluid**: The quantification of lipid-laden alveolar macrophages is a sensitive test for aspiration in children. Its major limitation is that it cannot distinguish between exogenous and endogenous origin of the lipids. The BAF fluid can be also examined for various food substances, including lactose, glucose, food fibers, and milk antigens, as well as pepsin. The specificity and sensitivity of these tests have not been well studied.

MANAGEMENT

There is no specific treatment for aspiration. The focus of its management is the prevention or at least the minimization of the resulting morbidity. The recommended interventions depend largely on the severity of the aspiration and on the nature and prognosis of the underlying condition.

Mild morbidity (e.g., oropharyngeal incoordination due to prematurity):

- **Modifications of the food intake** based on the results of the MBS (e.g., thickening of the liquids, pureed food).
- **Modification of the feeding techniques** (e.g., positioning of the infant in a semierect position, use of special nipples, limiting the amount of food).

These approaches can be used in dysphagia caused by immaturity of the swallowing mechanism (such as that observed in prematurely born and even in term infants) and in impaired swallowing caused by factors that can improve spontaneously (e.g., GER, laryngomalacia) or be corrected surgically (e.g., cleft lip/palate).

Moderate morbidity (e.g., difficulty sucking and swallowing because of chronic lung disease, neuromuscular disorders; presence of tracheostomy):

- **Nasogastric tube feedings**: they can be used temporarily during periods of transient dysphagia. They are minimally invasive but they have several drawbacks such as easy dislodgement and exacerbation of GER (because the lower esophageal sphincter remains open). They can also cause aspiration if placed incorrectly by inexperienced caregivers.
- **Gastrostomy**: should be strongly considered for patients who are not expected to develop or recover the ability to eat by mouth within a relatively short period.
- **Postpyloric feedings**: providing the nutrition into the duodenum or the jejunum is safer because it minimizes (but does not eliminate) GER. Postpyloric feedings can be given either by nasoduodenal or nasojejunal tube or by gastrojejunal (G-J) tube (the latter can be easily threaded through the existing gastrostomy). G-J tubes are recommended for patients with neuromuscular disorders who tend to have significant problems with gastric and intestinal motility.

Severe morbidity:

- **Surgical repair**: Abnormalities such as tracheoesophageal fistula and laryngeal cleft require surgical repair as soon as the infant is stable enough to undergo the operation.
- **Nissen fundoplication** should be reserved for patients whose recurrent aspiration is primarily the result of GER not responding to medical treatment and conservative management. Fundoplication minimizes, but does not eliminate, GER. If tight, it can cause severe retching in patients without muscle weakness.

Management of Oropharyngeal Secretions

The management of nasopharyngeal and oropharyngeal secretions poses a big problem in patients with impaired swallow because the secretions tend to pool in the hypopharynx from where they can easily be aspirated. Saliva can cause inflammation in the tracheobronchial mucosa and introduces organisms from the oropharynx into the lower airways, where they can become pathogenic. The currently available treatments and interventions include the following:

- **Anticholinergic agents**: Medications such as glycopyrrolate and scopolamine are widely used but are of limited effectiveness. When they are given via the gastrostomy tube, they may cause significant dryness in the lower airway, promoting mucus plugging. Nebulization of the intravenous preparation of glycopyrrolate can be effective, but this is not an officially approved use, and the preparation cannot be bought in retail pharmacies.
- **Botox (botulinum toxin type A) injection**: Botox injections in the salivary glands provide a transient decrease in the amount of secretions. To be effective, they need to be repeated every few months under anesthesia.
- **Salivary gland ligation**: This is currently the more definitive intervention for the management of oropharyngeal secretions. Once done, it is irreversible, and therefore it is reserved for very severe cases that are refractory to any other intervention.
- **Tracheostomy**: The role of tracheostomy in the management of chronic aspiration and/or in the management of excessive oropharyngeal secretions is rather controversial. Tracheostomy per se does not prevent aspiration (unless a cuffed tube is used). It actually impairs the swallowing mechanism, and because it is a "foreign body" inside the trachea, it tends to stimulate the production

of more secretions than usual. In addition, it bypasses the natural defenses of the upper airways while it exposes the lower airways directly to the environment, thus increasing the possibility of infection. Its major advantage is that it provides easy access for the suctioning of the lower airways. Most importantly, it provides a secure airway from which positive pressure can be applied, avoiding the risks of emergency endotracheal intubations. It should be considered for patients at high risk for recurrent severe respiratory failure.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 448

Immune and Inflammatory Lung Disease

448.1 Hypersensitivity Pneumonia

Michelle L. Hernandez and Stephanie D. Davis

Hypersensitivity pneumonia (HP), aptly called *extrinsic allergic alveolitis* because the inciting agent is almost uniformly inhaled from the environment, is a complex immunologic-mediated syndrome of the pulmonary alveoli and interstitium. There are numerous specific disease names based on the origin of the inhaled offending antigen to describe HP. Prompt recognition of the signs and symptoms allows for complete reversal of the disease without long-term adverse consequences if the source of the exposure is recognized and abated. Failure to recognize the disease early may lead to chronic irreversible lung changes with persistent symptoms in the patient.

ETIOLOGY

The most common sources of offending agents that cause HP include agricultural aerosols, inhaled protein antigens from animals, antigens from microorganisms of bacteria, fungi, or protozoan origin, and chemicals of low and high molecular weight (Table 448.1). Many of these inciting agents are associated with *occupational diseases,* which occur in locations where children do not regularly work. However, these same diseases can occur in children because of exposures to many similar antigen sources in nonoccupational environments, or in occupational environments with teenage workers. In addition to HP, the same antigens (i.e., antigens from animal proteins and contaminated metal working fluids or other inhaled antigens) may lead to allergic asthma or chronic bronchitis.

More than 300 antigens have been associated with HP. In children, the primary sources have been the result of exposure to **pet birds** (or feathers in bedding and pillows) such as parakeets, canaries, cockatiels, or cockatoos. Aerosol spread of bird droppings can also occur through the vent of a clothes dryer or through heating vents from a garage where the birds were housed. Humidifiers and hot tubs are notorious for contamination with **thermophilic organisms** (bacteria and mold) as well as *Mycobacterium avium* complex. Buildings with inadequate ventilation and insufficient air turnover present an increased risk of mold exposure from prior flooding or damp condensation. Despite exposures to the same antigen sources, members of the same family may exhibit different presentations of allergic disease. For instance, some family members may have symptoms of asthma or rhinitis, whereas another may have HP.

PATHOGENESIS

The pathogenesis of HP is complex and appears to have a genetic component. Recurrent exposures to environmental agents associated with HP (see Table 448.1) trigger an inflammatory response promoting the development of immune complexes. These immune complexes activate the complement pathway, ultimately resulting in the accumulation of neutrophils in the airway that release enzymes such as neutrophil elastase that damage surrounding lung tissue. Activated macrophages in the lung promote recruitment of lymphocytes into the tissues. Pathology shows alveolitis with a mixed cellular infiltration composed of lymphocytes, macrophage, plasma cells, and neutrophils. Continued exposure to the offending antigen results in the formation of loose, noncaseating granulomas located near the respiratory or terminal bronchioles. Some patients with chronic exposure develop progressive pulmonary fibrosis similar to patients with interstitial pulmonary fibrosis (IPF). Although the mechanisms are not entirely clear, this is thought to occur secondary to recruitment and activation of fibroblasts and uncontrolled production of extracellular matrix cytokines, including transforming growth factor beta (TGF-ß). It is critical when a biopsy is being performed (transbronchial or surgical) that the pathologist knows that HP is being considered because there are other **interstitial lung diseases** that produce similar granulomas with subtle location differences depending on their disease origin. Genetic predisposition also appears to be important, primarily in genes involved with antigen processing and presentation (such as major histocompatibility complex [MHC] I and II), lung homeostasis and wound repair, and telomere-related gene mutations.

Clinical Manifestations and Classification

The prevalence of HP is higher among older individuals but can affect children and young adults. It is estimated that HP accounts for 50% of all childhood idiopathic lung diseases (ILDs). HP had been traditionally classified as acute, subacute, or chronic. However, because of the great variability and overlap in the presentation and course of HP, the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax (ATS/JRS/ALAT) guidelines recategorized HP into two phenotypes based on the predominant presence or absence of fibrosis on imaging or histopathologic examination: (1) **nonfibrotic phenotype** and (2) **fibrotic phenotype**.

Regardless of fibrotic or nonfibrotic phenotype, common symptoms include cough and dyspnea after exposure. The time to symptom presentation after exposure can vary from hours to years and may be recurrent in nature. Acute symptoms can be confused with bacterial or viral disease leading to treatment with antibiotics. For example, as early as 4-8 hours after exposure, patients can present with the abrupt onset of cough, chest tightness, dyspnea, fever, chills, body aches, and fatigue (Table 448.2). Rarely, findings of wheezing are present on the initial examination. Rather, tachypnea with fine crackles may be heard by auscultation in the lung bases and presence of mid-inspiratory squeaks. The duration of symptoms has not been definitively associated with the fibrotic or nonfibrotic phenotype.

The long-term prognosis of HP is quite variable, with some patients developing progressive shortness of breath, cough (productive), weight loss, malaise, loss of appetite, hypoxia, and clubbing of the fingers. Those who have been diagnosed with nonfibrotic HP and are able to avoid exposure to the responsible agent may achieve stabilization or full recovery. In contrast, fibrotic HP is associated with reduced survival secondary to respiratory failure, especially among those with a usual interstitial pneumonia (UIP)–like pattern.

Diagnosis

A diagnosis of HP is certain when the known exposure with the associated immune response to the offending antigen is identified, the medical history and physical examination findings are abnormal on examination, and the pattern of the high-resolution computed tomography (HRCT) of the chest and bronchoalveolar lavage (BAL) findings

Table 448.1 Antigen Sources Associated with Specific Causes of Hypersensitivity Pneumonitis

HYPERSENSITIVITY PNEUMONITIS	ANTIGEN SOURCE
Bagassosis (mold on pressed sugar cane)	*Thermoactinomyces sacchari* *Thermoactinomyces vulgaris*
Bat lung (bat droppings)	Bat serum protein
Bible printer's lung	Moldy typesetting water
Bird fancier's lung (parakeets, budgerigars, pigeons, parrots, cockatiels, geese)	Droppings, feathers, serum proteins
Byssinosis ("brown lung") (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)	Cotton mill dust (carding and spinning areas of cotton, flax, and soft hemp)
Canary fancier's lung	Serum proteins
Cheese washer's lung (moldy cheese)	*Penicillium casei* *Aspergillus clavatus*
Chemical hypersensitivity pneumonitis	Diphenylmethane diisocyanate (MDI) Toluene diisocyanate (TDI)
Coffee worker's lung	Coffee bean dust
Composter's lung	*T. vulgaris* *Aspergillus* species
Contaminated basement (sewage) pneumonitis	*Cephalosporium*
Coptic lung (mummy handler's lung)	Cloth wrappings of mummies
Detergent worker's lung (washing powder lung)	*Bacillus subtilis* enzymes
Dry rot lung	*Merulius lacrymans*
Duck fever	Feathers, serum proteins
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)
Esparto dust (mold in plaster dust)	*Aspergillus fumigatus* Thermophilic actinomycetes
Feather duvet lung (feather bed, pillow, duvet)	Avian proteins on feathers
Fish meal worker's lung	Fish meal
Furrier's lung (sewing furs; animal fur dust)	Animal pelts
Grain measurer's lung	Cereal grain *(Sporobolomyces)* Grain dust (mixture of dust, silica, fungi, insects, and mites)
Hot tub lung (mists; mold on ceiling and around tub)	*Cladosporium* spp. *Mycobacterium avium* complex
Humidifier fever	*Thermoactinomyces (T. vulgaris, T. sacchari, T. candidus)* *Klebsiella oxytoca* *Naegleria gruberi* *Acanthamoeba polyphaga* *Acanthamoeba castellani*
Laboratory worker's lung (rats, gerbils)	Urine, serum, pelts, proteins
Lifeguard lung	Aerosolized endotoxin from pool-water sprays and fountains
Lycoperdonosis (*Lycoperdon* puffballs)	Puffball spores
Machine operator's lung	*Pseudomonas fluorescens* Aerosolized metal working fluid
Malt worker's disease (moldy barley)	*Aspergillus fumigatus, Aspergillus clavatus*
Maple bark disease (moldy maple bark)	*Cryptostroma corticale*
Miller's lung (dust-contaminated grain)	*Sitophilus granarius* (i.e., wheat weevil)
Moldy hay, grain, silage (farmer's lung)	Thermophilic actinomycetes Fungi (e.g., *Aspergillus umbrosus*)
Mollusk shell hypersensitivity pneumonitis	Sea snail shell
Mushroom worker's lung	Mushroom spores Thermophilic actinomycetes
Paprika slicer's lung (moldy paprika pods)	*Mucor stolonifer*
Pauli reagent alveolitis	Sodium diazobenzene sulfate
Pearl oyster shell pneumonitis	Oyster shells
Pituitary snuff taker's disease	Dried, powdered cattle or pig pituitary proteins
Potato riddler's lung (moldy hay around potatoes)	Thermophilic actinomycetes *T. vulgaris* *Faenia rectivirgula* *Aspergillus spp.*
Poultry worker's lung (feather plucker's disease)	Serum proteins (chicken products)
Pyrethrum (pesticide)	Pyrethrum
Sauna taker's lung	*Aureobasidium* spp., other sources
Sequoiosis (moldy wood dust)	*Graphium* *Pullularia* *Trichoderma spp.* *Aureobasidium pullulans*
Suberosis (moldy cork dust)	*Thermoactinomyces viridis* *Penicillium glabrum* *Aspergillus conidia*
Summer-type pneumonitis	*Trichosporon cutaneum*
Tea grower's lung	Tea plants
Thatched-roof lung (huts in New Guinea)	*Saccharomonospora viridis* (dead grasses and leaves)
Tobacco grower's lung	*Aspergillus* spp. *Scopulariopsis brevicaulis*
Turkey handling disease	Serum proteins (turkey products)
Unventilated shower	*Epicoccum nigrum*
Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)	Aflatoxin-producing fungus, *Fusarium* spp.
Velvet worker's lung	Unknown (? nylon velvet fiber, tannic acid, potato starch)
Vineyard sprayer's lung	Copper sulfate (Bordeaux mixture)
Wine maker's lung (mold on grapes)	*Botrytis cinerea*
Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)	*Alternaria* spp. *Bacillus subtilis*
Wood pulp worker's disease (oak and maple trees)	*Penicillium* spp.
Wood trimmer's disease (contaminated wood trimmings)	*Rhizopus* spp., *Mucor* spp.

Table 448.2 Clinical History Leading to a Diagnosis of Hypersensitivity Pneumonitis

Recurrent pneumonia
Pneumonia after repeat exposures (week, season, situation)
Cough, fever, and chest symptoms after making a job change or home change
Cough, fever, wheezing after return to school or only at school
Pet exposure (especially birds that shed dust such as pigeons, canaries, cockatiels, cockatoos)
Bird contaminant exposure (e.g., pigeon infestation)
Farm exposure to birds and hay
History of water damage
Use of hot tub, sauna, swimming pool
Other family members or workers with similar recurrent symptoms
Improvement after temporary environment change (e.g., vacation)

are consistent with HP (Table 448.3). These findings must prompt the clinician to identify the exposure in order to secure the diagnosis and eliminate the offending antigen. Without therapy, the progressive inflammatory response leads to air trapping, honeycombing, emphysema, and mild fibrosis in the chronic state. Diagnostic components are reviewed next.

LABORATORY

Most of the abnormal laboratory findings in HP are not specific and represent evidence of activated inflammatory markers or lung injury. For example, nonspecific elevation of immune globulins or the erythrocyte sedimentation rate and C-reactive protein may be found. Circulating immune complexes may be detected. Lactate dehydrogenase may be elevated in the presence of lung inflammation and normalizes with response to therapy.

Serum IgG precipitins to the offending agent are frequently positive and have a poor positive predictive value for disease. For example, among asymptomatic pigeon breeders, precipitating antibodies are nearly universal. False negatives can also be seen as a result of fluctuating serum antibody levels over time and a lack of standardized commercial antigens and reagents available for laboratory testing. It is critical that laboratories familiar with the performance of these tests be used. Those laboratories often recognize the value of processing antigens for precipitation from the environmental source directly as the test substrate with patient serum. Skin testing for immunoglobulin E (IgE)-mediated disease is not warranted unless there is evidence of mixed lung pathology such as asthma and interstitial lung opacities.

Radiology

Chest radiograph almost always precedes the use of HRCT of the chest in children because of the need for sedation and concerns regarding the risk of being exposed to an increased radiation dose from HRCT. The plain radiograph may demonstrate a ground-glass appearance, interstitial prominence, with a predominant location in the upper and middle lung fields. It is common for a chest radiograph to be considered normal by a radiologist early in the disease. Late in the disease, interstitial fibrosis may become prominent in the presence of increasing dyspnea, hypoxemia on room air, and even clubbing of the fingers. Mediastinum widening from lymphadenopathy is not usually present; when present, the lymph nodes are prominent along the airway near the carina, suggesting that the antigen source is inhaled, and this represents the response of the immune system.

HRCT of the chest is important in distinguishing nonfibrotic from fibrotic HP and may reduce the need for a lung biopsy. HRCT of the chest in **nonfibrotic HP** demonstrates (1) at least one abnormality revealing evidence of parenchymal infiltration (such as ground-glass opacities or mosaic attenuation) and (2) at least one abnormality revealing evidence of small airway disease (such as ill-defined, centrilobular nodules or air trapping), both distributed in a diffuse pattern. **Fibrotic HP** is characterized by (1) a lung fibrosis (irregular linear opacities/coarse reticulation; traction bronchiectasis and honeycombing) located in a random or mid-lung zone and (2) at least one abnormality that is consistent with small airway disease.

Table 448.3 Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

1. Identified exposure to offending antigen(s) by:
- Medical history of exposure to suspected antigen in the patient's living environment
- Investigations of the environment confirm the presence of an inciting antigen
- Identification of specific immune responses (immunoglobulin G serum precipitin antibodies against the identified antigen) are suggestive of the potential etiology but are insufficient in isolation to confirm a diagnosis
- Abnormal response to an inhalation challenge testing to the offending antigen via reexposure to the environment or inhalation challenge to the suspected antigen

2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
- Respiratory and often constitutional signs and symptoms
  - Cough
  - Breathlessness
  - Crackles on auscultation of the chest
  - Weight loss
  - Episodic fever
  - Wheezing
  - Fatigue

NOTE: These findings are especially suggestive of hypersensitivity pneumonitis when they appear or worsen several hours after antigen exposure.

- High-resolution chest CT findings typical of HP:
  - Nonfibrotic HP pattern:
    - At least one HRCT abnormality indicative of parenchymal infiltration (such as ground-glass opacities or mosaic attenuation) in a diffuse distribution
    - At least one HRCT abnormality indicative of small airway disease (such as ill-defined, centrilobular nodules or air trapping) in a diffuse distribution
  - Fibrotic HP pattern:
    - Lung fibrosis (irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing) in a random or mid-lung zone predominant location
    - At least one abnormality that is indicative of small airway disease

3. Bronchoalveolar lavage with lymphocytosis (>20%, often >50%):
- Usually with low CD4:CD8 ratio (i.e., CD8 is higher than normal)

4. Histopathology showing compatible changes with nonfibrotic or fibrotic hypersensitivity pneumonitis and the absence of features in any biopsy site to suggest an alternative diagnosis
- Nonfibrotic HP (purely inflammatory):
  - Cellular interstitial pneumonia
  - Chronic cellular bronchiolitis with a lymphocytic peribronchial infiltration
  - Poorly formed nonnecrotizing granulomas located near respiratory or terminal bronchioles
- Fibrotic HP (mixed inflammatory plus fibrotic or purely fibrotic):
  - Chronic fibrosing interstitial pneumonia
  - Airway-centered fibrosis
  - Poorly formed nonnecrotizing granulomas

Data from Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of hypersensitivity pneumonitis in adults. An official ATS/JRS/ALAT clinical practice guideline [published correction appears in *Am J Respir Crit Care Med.* 2021 Jan 1;203(1):150–151] [published correction appears in *Am J Respir Crit Care Med.* 2022 Aug 15;206(4):518]. *Am J Respir Crit Care Med.* 2020;202(3):e36–e69.

Bronchoalveolar Lavage

BAL is one of the most sensitive tests in supporting the diagnosis of HP. Lymphocytosis frequently exceeding 50% of the recovered cells is seen in the BAL fluid and should alert the clinician to the possibility of HP. Sarcoid, IPF, cryptogenic organizing pneumonia, berylliosis, granite workers lung disease, amiodarone pneumonia, lymphoma, and Langerhans cell histiocytosis may demonstrate lymphocytosis on BAL. All BAL specimens should have *flow cytometry* measurements of T-cell markers (CD3, CD4, and CD8 at a minimum). The predominant phenotype of the lymphocytosis is $CD3^+/CD8^+/CD56^+/CD57^+/CD10^-$. In the normal circulation, lymphocytes with CD4 markers predominate at a ratio of approximately 2:1 compared with CD8 lymphocytes. *In HP, this ratio becomes approximately equal to or less than 1 (CD4:CD8 ≤1) with either an increase in CD8 lymphocytes or a decline in CD4 lymphocytes.* Although this ratio helps the clinician in making a diagnosis of HP, this BAL finding is not 100% diagnostic for HP. Cryptogenic organizing pneumonia, a rare disease in children, also may present with BAL, where the CD4:CD8 is ≤1, and may be confused initially with HP. This is in sharp contrast to other lymphocytic granulomatous diseases, like sarcoidosis, where the CD4:CD8 is ≥2.

Lung Biopsy

Lung biopsy is necessary to confirm a diagnosis of HP when critical elements are not present, including antigen exposure, a medical history classic for HP, characteristic physical exam findings, chest HRCT findings, and $CD8^+$ lymphocytes in the BAL. Open lung biopsy is often the route of choice in young children because of the difficulty in safely obtaining satisfactory amounts of tissue by transbronchial biopsy. Lack of positive serum precipitins to an offending antigen and lack of an exposure history are common reasons for obtaining lung biopsies. It is crucial to inform the pathologist about the suspicion of HP so that the findings can be interpreted appropriately.

Histopathologic examination of **nonfibrotic HP (purely inflammatory)** demonstrates three primary features: (1) cellular interstitial pneumonia, (2) chronic cellular bronchiolitis with a lymphocytic peribronchial infiltration, and (3) nonnecrotizing granulomas near respiratory or terminal bronchioles. **Fibrotic HP (mixed inflammatory plus fibrotic or purely fibrotic)** is histologically characterized by (1) chronic fibrosing interstitial pneumonia, (2) airway-centered fibrosis, and (3) poorly formed nonnecrotizing granulomas. Furthermore, there is an absence of features in any biopsy site to suggest an alternative diagnosis.

Of note, poorly formed noncaseating granulomas and multinucleated giant cells are seen in HP. This is in sharp contrast to the well-formed granulomas seen in sarcoidosis.

Antigen Challenge by Inhalation

Inhalation challenge can support the diagnosis of HP by demonstrating a causal relationship between environmental exposure and symptoms. Inhalation challenge can be performed by two methods: (1) reexposure to the environment where the suspected antigen is present and (2) a direct inhalation challenge at the hospital to material collected from the suspected source of the antigen. As the second method has resulted in severe exacerbation of disease in some individuals, performing this challenge is discouraged.

Two abnormal response patterns may be seen. Most commonly, where there is **HP without asthma**, symptoms occur 8-12 hours after direct challenge in the hospital or after reexposure to the source of the antigen. The challenges replicate some or all of the symptoms observed in the acute syndrome with fever, dyspnea, fatigue, and crackles on lung auscultation. Blood drawn before challenge and then repeated during these symptoms often demonstrates an increased neutrophil count compared to baseline. Pulmonary function tests demonstrate a fall in forced vital capacity (FVC) and often a concurrent fall in the forced expiratory volume at 1 second (FEV_1), with a stable or increasing ratio of FEV_1:FVC reflecting a restrictive defect. Hypoxemia may accompany this decline in pulmonary function along with a fall in the diffusion capacity of carbon monoxide (DLCO). To see the complete effect, exercise during this period may show a considerable fall in oxygenation despite normal arterial blood gas oxygen tension and normal pulse oximetry at rest. This finding denotes the onset of worsening restrictive lung disease.

Where there is **HP with concomitant allergic asthma**, these patients may experience a biphasic response to the inhalation challenge. These patients may develop an early reduction in FEV_1, followed by a second drop in FEV_1 and FVC 4-6 hours later. The patient may also have accompanying fever and leukocytosis.

TREATMENT

The control of environmental exposure to the offending antigen is key to curing HP and remains the ideal method of treatment and prevention of recurrence. The clinical and pathologic manifestations of nonfibrotic (purely inflammatory) HP are reversible with removal of the offending antigen. Counseling parents and children about the risk of exposure to birds and feathered bedding or other environmental antigens, biologic aerosols, or agricultural dusts that are known to induce HP is important. Certainly, the source of the antigen and type of antigen appear to affect the response to treatment and long-term prognosis. Older individuals who contract farmer's lung are likely to recover with minimal permanent residual effect, whereas individuals with bird fancier's lungs from antigens produced by pigeons have a worse prognosis, especially if fibrosis is detected on lung biopsy. The pediatrician should advise—in the strongest terms—removal of the antigen source from the affected child's environment. This may be an extraordinary challenge given various children's living circumstances and lack of independent control of the environment in which they live.

In addition, pediatricians should be familiar with recommendations about the maintenance of heating, ventilation, and air conditioning systems, in addition to humidifiers and vaporizers. Daily drainage, cleansing of residue, and routine cleaning with hydrogen peroxide or bleach help rid humidifiers and vaporizers of harmful pathogens such as thermophiles that cause HP.

Removal of the antigen alone is sufficient to normalize lung function in most patients, but symptoms and pulmonary functions return to normal faster with the use of glucocorticoids. Among those with nonfibrotic HP, glucocorticoids at a dose of 0.5 mg/kg/day of prednisone or equivalent (up to a maximum dose of 30 mg prednisone daily) will reduce the immune inflammatory response in the lungs. Comparative trials in adults demonstrate that the use of 4 weeks of therapy is as effective as 12 weeks of therapy. Because of the rapid reversal of symptoms, successful abatement of the environment is sometimes compromised when the family sees improvement before the antigen source removal.

As with nonfibrotic HP, removal of the offending antigen is also recommended for fibrotic HP. However, there is a paucity of clinical trial data outlining the best immunomodulatory strategies for fibrotic HP. Among those patients with fibrotic HP with inflammatory features present, a trial of glucocorticoids may be pursued at a dose of 0.5 mg/kg per day (up to 30 mg per day) for 4-8 weeks, followed by tapering for 3 months. For patients who have not responded to both antigen removal and corticosteroid treatment, azathioprine and mycophenolate mofetil have been used, but their efficacy has not been tested in clinical trials. Case reports have also reported the use of rituximab for HP treatment because of its ability to reduce immune cell complexes. Results have reported mixed clinical efficacy. Antifibrotic drugs that are used for IPF such as nintedanib or pirfenidone are being tested in clinical trials.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

448.2 Occupational and Environmental Lung Disease

Michelle L. Hernandez and Stephanie D. Davis

Although occupational and environmental lung diseases include **occupational asthma**, **irritant-induced asthma**, HP, hard metal inhalation lung disease, berylliosis, and air pollution, this chapter focuses on occupational asthma and irritant-induced asthma. Berylliosis has a propensity to form granulomas (see Chapter 448.3). Although some diseases will be seen with regularity, the important role that a workplace, school, daycare, neighbors' housing, multiple family housing, and indoor and outdoor environments may have in the causation of signs and symptoms in the patient is often not considered by the clinician.

Occupational asthma *differs* from work-exacerbated asthma. Individuals with occupational asthma develop asthma after exposure to immunologic or nonimmunologic stimuli found in the workplace, whereas those with work-exacerbated asthma already have asthma that worsens in the workplace because of a myriad of exposures.

The vast array of exposures that may cause disease of the lungs is daunting, such as the inhalation of baking flour or household cleaning fluids causing asthma, microwave popcorn that uses diacetyl flavoring resulting in bronchiolitis obliterans, and exposure to thermophilic organisms or mold resulting in HP. The acute eosinophilic pneumonias associated with the new onset of smoking and chemical inhalation of 1,1,1-trichloroethane (Scotchgard) require a high index of suspicion and unique lines of questioning. The same antigen encountered in a work, school, home, or outdoor environment may result in different disease presentations among patients because of host factors, dose exposure, and genetic susceptibility. One of the most prominent examples is an investigation of workers who inhaled metal working fluid. Despite similar exposures, some developed HP, others developed asthma, and some displayed no symptoms at all. Immunologic evaluation in some exposures has shown similar immune responses in different individuals, but a wide range of disease provocation. When high molecular weight proteins cause asthma, symptoms of rhinoconjunctivitis frequently precede the onset of pulmonary symptoms. The medical history in occupational and environmental lung diseases has used an expanded construct with a simple acronym, **WHACOS** (Table 448.4).

CLASSIFICATION AND PATHOGENESIS

Occupational and environmental lung diseases include numerous syndromes of human lung disease such as **occupational asthma**, **irritant-induced asthma**, reactive upper airway disease syndrome, HP (see Chapter 448.1), air pollution–induced disease, hard metal inhalation lung disease, berylliosis, occupation-induced lung cancer (e.g., mesothelioma from asbestosis), and chronic obstructive pulmonary disease. Most of these diseases are not problematic for children, but adolescents may be at risk to develop lung disease through exposure through part-or full-time work or by single exposures, as seen in some types of irritant-induced asthma.

Table 448.4 A Construct (WHACOS) that Has Been Used in Medical Interviewing of Patients, Coworkers, and Family Members when Environmental or Occupational Lung Disease Is Being Considered

W	***W**hat* do you do?
H	***H**ow* do you do what you do?
A	Are symptoms ***A**cute* or are they *Chronic*?
C	Do any ***C**oworkers*, family, classmates, or friends have the same symptoms?
O	Do you have any hobbies, travel, or animal/pet exposures ***O**utside* of school or work?
S	Are you ***S**atisfied* with work or school?

Occupational and Environmental Asthma

It is important to remember that in patients with occupational- or environmental-induced disease, the onset of symptoms has a lag time between exposure and symptoms. In **occupational asthma**, there may be an immediate response within 30 minutes to 2 hours of exposure, demonstrated as a decline in pulmonary function, specifically the FEV_1. Usually, lung function returns to normal spontaneously unless persistent exposure occurs. Some patients demonstrate no immediate reduction in lung function, but rather experience a delayed response of 4-6 hours after the exposure. Treating physicians can take advantage of this physiology by using spirometry before and after work or school or using peak flow measurements hourly during exposure and after leaving the exposure. Because workers and school children have prolonged periods of exposure followed by a number of days without exposure, the use of pulmonary function plus nonspecific bronchial responsiveness (e.g., methacholine) testing is helpful. For example, pulmonary function tests before starting work or school on a Monday of a typical week may be normal. By Friday of this typical work or school week, the baseline pulmonary function indices may have fallen, and nonspecific bronchial responsiveness may have become more sensitive to a lower concentration of histamine, methacholine, or mannitol. By Monday, the tests may have returned to normal or near normal with no change other than reduced exposure.

High molecular weight causes of occupational and environmental asthma can be characterized as allergens, which are normally proteins and enzymes, inhaled from multiple sources (Table 448.5). These include various animals, shellfish, fish, enzymes (e.g., *Bacillus subtilis* in laundry detergent), and flour or cereals. Occupational and environmental asthma is also caused by a number of low molecular weight agents, including reactive chemicals, transition metals, and wood dusts (Table 448.6). These **low molecular weight agents** are sufficient to induce an immune response, but often *not by an IgE-mediated mechanism.* These low molecular weight chemicals appear to act as haptens that bind directly to human proteins, causing an immune response in the human host.

The pathogenesis of asthma in patients exposed to **high molecular weight** antigens follows the experience of nonoccupational asthma in patients where atopy, sex, genetics, concentration of antigen, duration of exposure, and other individual factors all contribute to the development of disease. Most individuals require a concentration and duration of exposure sufficient to cause IgE antibody sensitization to the offending allergen with development of bronchial hyperresponsiveness and airway inflammatory disease upon reexposure. If the allergen exposure is sufficient, these proteins can drive the immune response to a T-lymphocyte type 2 phenotype (Th2), even in patients without prior atopic disposition. This occurred in the case of latex allergy, where many nonatopic individuals and patients exposed to allergen in their personal healthcare environment developed occupational allergy to multiple proteins from natural rubber latex. Atopic individuals are at the highest risk of developing latex allergy. A longitudinal study demonstrated that powdered latex gloves with high allergen content were the reason for the epidemic of latex allergy and occupational asthma. Unfortunately, despite primary removal of the offending sensitizing agent, symptoms caused by asthma and bronchial hyperresponsiveness continue in roughly 70% of individuals.

Diagnosis of Occupational Asthma

Occupational asthma should be assessed with a full history, physical examination and objective confirmation of an asthma diagnosis using spirometry, and nonspecific bronchial responsiveness. The negative predictive value of methacholine challenge while the patient is still in the workplace is high (98%): a negative methacholine challenge makes the diagnosis of occupational asthma very unlikely in a patient who is continuously exposed to the suspected causative agent. In addition to comparing measures of nonspecific bronchial responsiveness while on and off work, induced sputum and fractional exhaled nitric oxide (FeNO) can increase the diagnostic sensitivity to 94% through identifying the presence of eosinophilic inflammation. Specific IgE testing

Table 448.5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

OCCUPATION OR ENVIRONMENT	SOURCE
ANIMAL-DERIVED ANTIGENS	
Agricultural worker	Cow dander
Bakery	Lactalbumin
Butcher	Cow bone dust, pig, goat dander
Cook	Raw beef
Dairy industry	Lactoserum, lactalbumin
Egg producer	Egg protein
Farmer	Deer dander, mink urine
Frog catcher	Frog
Hairdresser	Sericin
Ivory worker	Ivory dust
Laboratory technician	Bovine serum albumin, laboratory animal, monkey dander
Nacre buttons	Nacre dust
Pharmacist	Endocrine glands
Pork producer	Pig gut (vapor from soaking water)
Poultry worker	Chicken
Tanner	Casein (cow's milk)
Various	Bat guano
Veterinarian	Goat dander
Zookeeper	Birds
CRUSTACEANS, SEAFOOD, FISH	
Canning factory	Octopus
Diet product	Shark cartilage
Fish food factory	Gammarus shrimp
Fish processor	Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes
Fisherman	Red soft coral, cuttlefish
Jewelry polisher	Cuttlefish bone
Laboratory grinder	Marine sponge
Oyster farm	Hoya (oyster farm prawn or sea-squirt)
Restaurant seafood handler	Scallop and shrimp
Scallop plant processor	King scallop and queen scallop
Technician	Shrimp meal *(Artemia salina)*
ARTHROPODS	
Agronomist	Bruchus lentis
Bottling	Ground bug
Chicken breeder	Herring worm *(Anisakis simplex)*
Engineer at electric power plant	Caddis flies *(Phryganeidae)*
Entomologist	Lesser mealworm (*Alphitobius diaperinus* Panzer), moth, butterfly
Farmer	Grain pests (*Eurygaster* and *Pyrale*)
Fish bait handler	Insect larvae *(Galleria mellonella)*, mealworm larvae *(Tenebrio molitor)*, green bottle fly larvae *(Lucila caesar)*, daphnia, fish-feed Echinodorus larva *(Echinodorus plasmosus)*, Chiromids midge *(Chironomus thummi thummi)*
Fish processing	Herring worm *(Anisakis simplex)*
Flight crew	Screw worm fly *(Cochliomyia hominivorax)*
Honey processors	Honeybee
Laboratory worker	Cricket, fruit fly, grasshopper *(Locusta migratoria)*, locust
Mechanic in a rye plant	Confused flour beetle *(Tribolium confusum)*
Museum curator	Beetles (Coleoptera)
Seed house	Mexican bean weevil *(Zabrotes subfasciatus)*
Sericulture	Silkworm, larva of silkworm
Sewage plant worker	Sewer fly *(Psychoda alternata)*
Technician	Arthropods *(Chrysoperla carnea, Leptinotarsa decemlineata, Ostrinia nubilalis,* and *Ephestia kuehniella)*, sheep blowfly *(Lucilia cuprina)*
Wool worker	*Dermestidae* spp.
ACARIANS	
Apple grower	Fruit tree red spider mite *(Panonychus ulmi)*
Citrus farmer	Citrus red mite *(Panonychus citri)*
Farmer	Barn mite, two-spotted spider mite *(Tetranychus urticae)*, grain mite
Flour handler	Mites and parasites
Grain-store worker	Grain mite
Horticulturist	*Amblyseius cucumeris*
Poultry worker	Fowl mite
Vine grower	McDaniel spider mite *(Tetranychus mcdanieli)*
MOLDS	
Agriculture	*Plasmopara viticola*
Baker	*Alternaria, Aspergillus* (unspecified)
Beet sugar worker	*Aspergillus* (unspecified)
Coal miner	*Rhizopus nigricans*
Coffee maker	*Chrysonilia sitophila*
Laborer	*Sooty molds (Ascomycetes,* deuteromycetes)
Logging worker	*Chrysonilia sitophila*
Plywood factory worker	*Neurospora*
Sausage processing	*Penicillium nalgiovense*
Sawmill worker	*Trichoderma koningii*
Stucco worker	*Mucor* spp. (contaminating esparto fibers)
Technician	*Dictyostelium* discoideum (mold), *Aspergillus niger*
MUSHROOMS	
Agriculture	*Agaricus bisporus* (white mushroom)
Baker	Baker's yeast *(Saccharomyces cerevisiae), Boletus edulis*
Greenhouse worker	Sweet pea *(Lathyrus odoratus)*
Hotel manager	*Boletus edulis*
Mushroom producer	*Pleurotus cornucopiae*

Table 448.5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma—cont'd

OCCUPATION OR ENVIRONMENT	SOURCE
Mushroom soup processor	Mushroom unspecified
Office worker	Boletus edulis
Seller	*Pleurotus ostreatus* (spores of white spongy rot)
ALGAE	
Pharmacist	Chlorella
Thalassotherapist	Algae (species unspecified)
FLOURS	
Animal fodder	Marigold flour *(Tagetes erecta)*
Baker	Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour *(Lathyrus sativus)*
Food processing	White Lupin flour *(Lupinus albus)*
POLLENS	
Florist	Cyclamen, rose
Gardener	Canary island date palm *(Phoenix canariensis)*, bell of Ireland *(Moluccella laevis)*, bell pepper, chrysanthemum, eggplant *(Solanum melongena)*, *Brassica oleracea* (cauliflower and broccoli)
Laboratory worker	Sunflower (*Helianthus* spp.), thale cress *(Arabidopsis thaliana)*
Olive farmers	White mustard *(Sinapis alba)*
Processing worker	*Helianthus annuus*
PLANTS	
Brewery chemist	Hops
Brush-makers	Tampico fiber in agave leaves
Butcher	Aromatic herb
Chemist	Linseed oilcake, *Voacanga africana* seed dust
Cosmetics	Dusts from seeds of sacha inchi *(Plukenetia volubilis)*, chamomile (unspecified)
Decorator	Cacoon seed (Entage gigas)
Floral worker	Decorative flower, safflower *(Carthamus tinctorius)* and yarrow *(Achillea millefolium)*, spathe flower, statice *(Limonium tataricum)*, baby's breath *(Gypsophila paniculata)*, ivy *(Hedera helix)*, flower (various), sea lavender *(Limonium sinuatum)*
Food industry	Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot *(Daucus carota L.)*, green bean *(Phaseolus multiflorus)*, lima bean *(Phaseolus lunatus)*, onion, potato, Swiss chard *(Beta vulgaris L.)*, courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (*Allium cepa*, red onion), rice, saffron *(Crocus sativus)*, spices, grain dust
Gardener	Copperleaf *(Acalypha wilkesiana)*, grass juice, weeping fig *(Ficus benjamina)*, umbrella tree (*Schefflera* spp.), amaryllis (*Hippeastrum* spp.), Madagascar jasmine sap *(Stephanotis floribunda)*, vetch *(Vicia sativa)*
Hairdresser	Henna (unspecified)
Herbal tea processor	Herbal tea, sarsaparilla root, sanyak *(Dioscorea batatas)*, Korean ginseng *(Panax ginseng)*, tea plant dust *(Camellia sinensis)*, chamomile (unspecified)
Herbalist	Licorice roots (*Glycyrrhiza* spp.), wonji *(Polygala tenuifolia)*, herb material
Horticulture	Freesia (Freesia hybrida), paprika *(Capsicum annuum)*, Brazil ginseng *(Pfaffia paniculata)*
Laborer	Citrus food handling (*dl*-limonene, *l*-citronellol, and dichlorophen)
Oil industry	Castor bean, olive oil cake
Pharmaceutical	Rose hip, passion flower *(Passiflora alata)*, cascara sagrada *(Rhamnus purshiana)*
Powder	Lycopodium powder
Sewer	Kapok
Sheller	Almond shell dust
Stucco handler	Esparto (*Stipa tenacissima* and *Lygeum spartum*)
Tobacco manufacturer	Tobacco leaf
PLANT-DERIVED NATURAL PRODUCTS	
Baker	Gluten, soybean lecithin
Candy maker	Pectin
Glove manufacturer	Latex
Health professional	Latex
Rose extraction	Rose oil
BIOLOGIC ENZYMES	
Baker	Fungal amylase, fungal amyloglucosidase and hemicellulase
Cheese producer	Various enzymes in rennet production (proteases, pepsine, chymosins)
Detergent industry	Esterase, *Bacillus subtilis*
Factory worker	*Bacillus subtilis*
Fruit processor	Pectinase and glucanase
Hospital personnel	Empynase (pronase B)
Laboratory worker	Xylanase, phytase from *Aspergillus niger*
Pharmaceutical	Bromelin, flaviastase, lactase, pancreatin, papain, pepsin, serratia peptidase, and lysozyme chloride; egg lysozyme, trypsin
Plastic	Trypsin
VEGETABLE GUMS	
Carpet manufacturing	Guar
Dental hygienist	*Gutta-percha*
Gum importer	Tragacanth
Hairdresser	Karaya
Printer	Acacia

Table 448.6 Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma

CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE
Diisocyanates	
• Diphenylmethane • Hexamethylene • Naphthalene • Toluene	• Polyurethane • Roofing materials • Insulations • Paint
Anhydrides	Manufacturers or users
• Trimellitic • Phthalic	• Paint • Plastics • Epoxy resins
Dyes	Personal or business use of dyes
• Anthraquinone • Carmine • Henna • Persulfate	• Hair dye • Fur dye • Fabric dye
Glue or resin	Plastic
• Methacrylate • Acrylates • Epoxy	• Manufacturers • Healthcare professionals • Orthopedic specialists
Metals	Metal work
• Chromic acid • Potassium dichromate • Nickel sulfate • Vanadium • Platinum salts	• Plating • Welding
Drugs	Exposure to drugs in environment
• β-Lactams • Opioids • Other	• Pharmaceutical workers • Farmers • Healthcare workers
Chemicals	Exposure in the healthcare field
• Formaldehyde • Glutaraldehyde • Ethylene oxide	• Laboratory work • Healthcare professionals
Wood dust	Workers/hobbyists
• Western red cedar (plicatic acid) • Exotic woods • Maple • Oak	• Sawmill • Carpentry • Woodworking

(via percutaneous skin testing or serum IgE) to the causative agent is often impractical given the lack of commercial extracts to the over 300 known causative agents for occupational asthma (see Table 448.5).

Treatment of Occupational Asthma

The management of occupational asthma is centered on exposure reduction and optimized pharmacotherapy with inhaled corticosteroids (ICS) following the National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA) guidelines (reviewed in Chapter 185). Ideally, patients would be completely removed from the exposure for the best outcomes. However, in cases where this is not feasible, respiratory protection devices and work accommodations to reduce the exposure should be pursued under the guidance of an occupational hygienist. Because of a lack of commercially available extracts for the causative agent, allergen-specific immunotherapy has limited applicability for the treatment of occupational asthma for patients who cannot avoid the exposure. For these reasons, omalizumab therapy has been successfully used in small case series to attenuate the IgE response, resulting in reduced exacerbations and systemic and/or inhaled corticosteroid requirements.

Irritant-Induced Asthma and Reactive Airways Disease Syndrome

Irritant-induced asthma is also a form of work-related asthma and has both **acute and subacute** phenotypes. As opposed to occupational asthma, irritant-induced asthma results from **nonimmunologic** provocation of bronchial hyperresponsiveness with airflow obstruction.

The most well-characterized presentation of **acute irritant-induced asthma** is **reactive airways dysfunction syndrome (RADS)**, where patients present with acute respiratory symptoms within minutes or hours after a single inhalation of an *elevated concentration* of irritant aerosol, gas, or smoke. Many of these exposures are accidental in nature. The clinical manifestations and pathophysiology of RADS have been studied through experimental design or epidemiology studies involving exposure to chlorine gas, acetic acid, dimethylaminoethanol, chlorofluorocarbons, epichlorohydrin, and diisocyanates. Patients with RADS typically can pinpoint the exact time of onset of symptoms and the exact number of hours post exposure. The symptoms are so severe that nearly 80% of subjects in one study presented to an emergency department for care. The lower airway symptoms of cough, dyspnea, chest tightness, and wheezing are prominent features in RADS, with cough being most prevalent. Because of the toxic nature of the inhaled chemical, it is predictable that an upper airway syndrome of throat and nose burning will often accompany the lower airway symptoms. This part of the complex has been referred to as **respiratory upper airway dysfunction syndrome**.

Predisposing factors for the development of RADS are not well characterized. Cigarette smoking may increase the risk of developing RADS when exposure through inhalation of irritant chemicals occurs. In addition to host factors, the type of chemical appears to be important. Higher concentrations of chemicals, the type of chemical (vapor or wet aerosols), and bleaching agents are the most offending agents to cause RADS. Dry particle aerosols are less likely to cause RADS. Analysis of the World Trade Center firefighters indicates that the presence of bronchial hyperresponsiveness before this catastrophe did not increase the risk for an individual to develop RADS.

The pathogenesis of RADS follows a typical pattern, driven by the initial injury to the airway epithelium. Initial histology demonstrates rapid mucosal denudation accompanied by a submucosal fibrinous, hemorrhagic exudate. Subepithelial edema subsequently occurs with epithelial layer regeneration, basal and parabasal cells increase, and eventually areas of fibrosis form. The desquamation, fibrosis, basement membrane thickening, and basal cell regeneration are more characteristic of RADS than occupational asthma. This may explain the limited response to bronchodilator therapy in this syndrome compared to asthma.

In contrast to the acute onset of symptoms after exposure seen with RADS, individuals with **subacute irritant-induced asthma** present with a more insidious onset of symptoms. Because of the recurrent nature of the low concentration of the chemical exposure, patients may initially not be able to identify the underlying trigger. **Subacute irritant-induced asthma** has been described through epidemiologic studies and characterized by (1) the insidious onset of symptoms occurring after *multiple high exposures to irritants* (such as what occurred among some rescue workers at the World Trade Center) or (2) single or multiple exposures to irritant chemicals in *low concentrations*. Similar to allergic rhinitis, patients may describe nasal congestion, rhinorrhea, sneezing, postnasal drip, ocular irritation, and conjunctival injection. Pulmonary symptoms include those typically seen with asthma exacerbations.

Table 448.7 Criteria for Reactive Airways Disease (Dysfunction) Syndrome

- Documented absence of preceding respiratory symptoms
- Onset after single specific high-level exposure incident
- Exposure to very high concentration of gas, smoke, fumes, or vapors with *irritant* properties
- Onset of symptoms within 24 hours after exposure with persistence for ≥3 months
- Symptoms similar to asthma with cough, wheeze, and dyspnea
- Presence of airflow obstruction on pulmonary function ± nonspecific bronchial (methacholine) hyper-responsiveness
- Other pulmonary disease excluded

Data from Varney VA, Evans J, Bansal. Successful treatment of reactive airways dysfunction syndrome by high-dose vitamin D. *J Asthma Allergy*. 2011;4:87–91.

Diagnosis of Irritant-Induced Asthma

Initial evaluation of the patient with acute (RADS) or subacute irritant-induced asthma usually includes the medical history, physical examination, and pulse oximetry. Because of the acute nature of RADS, a chest radiograph is obtained in order to rule out other acute causes of dyspnea, including pneumonia or pulmonary edema. In patients with both acute and subacute irritant-induced asthma, the chest radiograph is frequently normal or may reveal hyperinflation. Ideally, if the patient is not in significant distress, complete pulmonary function testing with spirometry, assessment of bronchodilator reversibility, and nonspecific bronchial provocation with methacholine are helpful in the initial evaluation.

Table 448.7 lists the criteria for a diagnosis of **RADS**. Asthma-like symptoms and airway hyperresponsiveness occur and often persist for prolonged periods. Unlike typical asthma, *RADS is often not reversible after administration of a bronchodilator*. This is probably a consequence of the direct injury to the epithelium and subsequent submucosal fibrosis.

Treatment of RADS and Irritant-Induced Asthma

Treatment of acute (RADS) and subacute irritant-induced asthma focuses on prevention of exposure. Because the exposure in RADS is often associated with a single known exposure, this task is readily accomplished. The low, persistent exposures associated with subacute irritant-induced asthma are more challenging to identify and remove.

Implementing treatment guidelines for asthma is recommended when intervention is required beyond antigen removal. Managing an acute presentation of RADS is exactly the same as managing an acute asthma exacerbation. Short-acting β-agonist treatment may not be effective; a trial of inhaled ipratropium may add benefit in the short term. For moderate to severe symptoms and FEV_1 values that are less than 70% of predicted, administration of systemic glucocorticoids (2 mg/kg prednisone equivalent, up to 60 mg daily) can be beneficial based on some clinical case studies and animal studies. Unlike the typical 5-day courses of systemic glucocorticoids for asthma exacerbations, many patients remain symptomatic beyond 5 days as a result of the extent of the airway epithelial injury. Steroid treatment may be prolonged up to 10-15 days after the onset of symptoms; a slow taper of corticosteroids may be implemented after the 10-15 days. High-dose ICS therapy with or without long-acting β-agonists may be added while the systemic steroids are being tapered. The initial high-dose ICS regimens are based on the NAEPP and the GINA guidelines. For patients whose initial symptoms are not as severe and/or spirometry demonstrates milder airway obstruction (FEV_1 greater than or equal to 70% of predicted), high-dose ICS therapy alone can be started without requiring systemic corticosteroid treatment. Once patients' asthma symptoms are improved, ICS doses can be tapered by increments of 25–50% over a period of up to 6 months in some case series based on patient symptoms. However, prolonged ICS treatment beyond 6 months has also been noted.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

448.3 Granulomatous Lung Disease

Timothy J. Vece, Eveline Y. Wu, and Stephanie D. Davis

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (GPA), formerly *Wegener granulomatosis,* is a disease that involves both the lower and upper respiratory tracts with granulomatous inflammation of small- to medium-sized vessels (see Chapter 210). Pulmonary disease is frequently associated with glomerulonephritis. The simultaneous presence of pulmonary and renal disease should immediately raise the suspicion for GPA, microscopic polyangiitis, or anti–glomerular basement membrane (anti-GBM) disease (see Chapter 448.5).

Epidemiology

The prevalence of GPA during childhood is rare, but epidemiologic data suggest an increase in cases in the last 2 decades. The median age at diagnosis is 10-14 years, and there is a female predominance of 3-4:1. Improved clinical recognition, disease classification, and tests, such as antineutrophil cytoplasmic antibodies (ANCAs), have helped in the diagnosis of this rare disorder.

Etiology and Pathogenesis

In GPA, the development of both upper and lower airway disease with granulomas implies that exposure to antigens in the airways of an endogenous or exogenous source is involved with aberrant innate and adaptive immune responses. Neutrophils are a key effector cell. There is also a predominantly T-lymphocyte type 1 response with overexpression of interferon-γ (IFN-γ) and tumor necrosis factor (TNF). In vitro studies demonstrate a skewed T-lymphocyte type 17 response by blood $CD4^+$ T cells in GPA, suggesting there is an immune regulatory defect that leads to excessive production of T-lymphocyte type 1 and type 17 cytokines (interleukin [IL]-17, TNF, and IFN-γ). Such an inflammatory response may be sufficient to induce and sustain granuloma formation.

ANCAs are autoantibodies reactive against proteins in the cytoplasmic granules of neutrophils and monocytes and are found in 90% of patients with GPA. The most common ANCAs in GPA have a cytoplasmic fluorescence pattern (c-ANCA) and usually indicate antibodies against proteinase-3 (PR3-ANCA). Perinuclear fluorescence (p-ANCA) usually indicate antibodies directed toward myeloperoxidase (MPO-ANCA), which are less common in GPA. Approximately 5–10% of children develop the clinical phenotype of GPA in the absence of detectable ANCA.

Clinical Manifestations

Children with GPA present with respiratory complaints accompanied by fever, loss of energy, and vague joint symptoms. Some may present with severe nasal disease manifested as ulceration, septal perforation, pain, sinusitis, and/or epistaxis. The septal perforation may lead to deformation of the nasal bridge from erosion of the underlying cartilage, but this is more common in adults. Sinusitis may be present, and pulmonary disease occurs in the majority of patients. Symptoms range from cough, hemoptysis (seen in less than 50% of pediatric patients), dyspnea, and chest discomfort to asymptomatic infiltrates on chest radiography. Occasionally, patients with GPA will present with hemoptysis or recurrent fleeting infiltrates from *pulmonary hemorrhage*. The pathology is confusing because granulomatous disease may be difficult to demonstrate, and *pulmonary capillaritis,* the other main component seen on histology, can be seen in other disorders, including anti-GBM disease, microscopic polyangiitis, idiopathic pulmonary capillaritis, and IgA vasculitis (Henoch-Schönlein purpura). Distinguishing GPA from other pulmonary-renal syndromes is easiest when there are classical symptoms of upper airway disease (nasal/sinus), lower airway disease with necrosis and granulomas on lung biopsy along with vasculitis, and renal disease consistent with glomerulonephritis.

As many as 20% of patients with GPA will present with subglottic or endobronchial stenosis from scarring and inflammatory changes.

Although it may be the presenting symptom, it often occurs in conjunction with other disease manifestations. Dyspnea and voice changes are common complaints from patients.

Skin, ocular (uveitis), and joint symptoms are common in GPA and have been found to accompany the lung and renal disease up to 50% of the time. Biopsy of the skin may show nonspecific leukocytoclastic vasculitis, venulitis, or capillaritis.

Laboratory and Pathology

PR3-ANCA are found in 70–90% of children with GPA, and in the correct clinical situation are sufficient for the diagnosis of ANCA-associated vasculitis, although it may be difficult to differentiate GPA from MPA. In unusual or uncertain cases, tissue diagnosis is required. In lung tissue, the usual pathology demonstrates multiple parenchymal nodules that may be located in either the bronchial, vascular, or interstitial tissues (Fig. 448.1). The granulomatous inflammation is often found in areas of necrosis and/or vasculitis.

Renal biopsy rarely demonstrates granulomas or vasculitis. Rather, kidney tissues may show focal, segmental, or necrotizing glomerulonephritis without deposits of immune complexes. Kidney biopsy is preferred when a histopathologic diagnosis is required, as kidney biopsy has a lower morbidity and mortality than lung biopsy. When the tissues fail to demonstrate classical findings, a variety of diseases (e.g., tuberculosis, sarcoid, microscopic polyangiitis, malignancy, and other autoimmune disorders) must be considered in the evaluation.

Radiology

Chest imaging findings are quite variable in GPA. Chest radiography may reveal multiple infiltrates, nodules, cavitary lesions, or ILD. Fleeting infiltrates may be seen when recurrent hemorrhage is a clinical manifestation. HRCT of the chest often demonstrates more extensive lung disease and the cavitation associated with the necrotizing nature of the disease (Fig. 448.2).

Treatment

Rapidly progressive, debilitating disease may occur if there is a failure to diagnose GPA. One early series of patients reported that death occurred in 90% of patients within 2 years of diagnosis. Glucocorticoid therapy alone resulted in relapses and inadequate control of disease in many subjects.

Therapy is divided into *induction* and *maintenance* phases. Systemic corticosteroids, while ineffective as monotherapy, are a mainstay of therapy in conjunction with other immune-suppressive agents. Prednisone can be given orally. Alternatively, intravenous methylprednisolone may be used at a dosage of 10-30 mg/kg (max 1 g) administered weekly or for 3 consecutive days monthly. Combination therapy traditionally includes cyclophosphamide given either orally at 2 mg/kg/day or intravenous dosing at 15 mg/kg monthly. Rituximab, an anti-CD20 antibody, is as effective as cyclophosphamide in inducing remission of GPA. Rituximab dosing is either 350 mg/m^2 given weekly for the first 4 weeks or 750 mg/m^2 given on initiation of therapy and 2 weeks after initiation. A second dose of 500 mg/m^2 is often given 6 months after the first course of rituximab. Induction therapy should be continued for 3-6 months.

Continued therapy is required past the initial induction phase to maintain remission. Because of the toxicity of cyclophosphamide, other immune-suppressive agents are preferred. Methotrexate and azathioprine have been shown to be noninferior to cyclophosphamide in maintaining remission, whereas mycophenolate mofetil has higher relapse rates than azathioprine. Rituximab is also used for maintenance remission and is associated with lower risk of major relapse compared with azathioprine, particularly for patients with GPA and PR3-ANCA. Systemic steroid dosages should be progressively weaned at the beginning of the maintenance phase of therapy to a dosage of 5-10 mg/day. Maintenance therapy should be continued for an additional 1.5-2 years.

Adjuvant therapy with plasma exchange may be considered when life-threatening GPA disease presents. This is advocated on the premise that ANCAs are inducing disease and will be removed from the circulation with this intervention; its use has been favorably evaluated in GPA-induced renal disease. Adjuvant plasma exchange has been studied mainly in patients with severe renal vasculitis, but there are also reports of success in severe pulmonary hemorrhage. The results

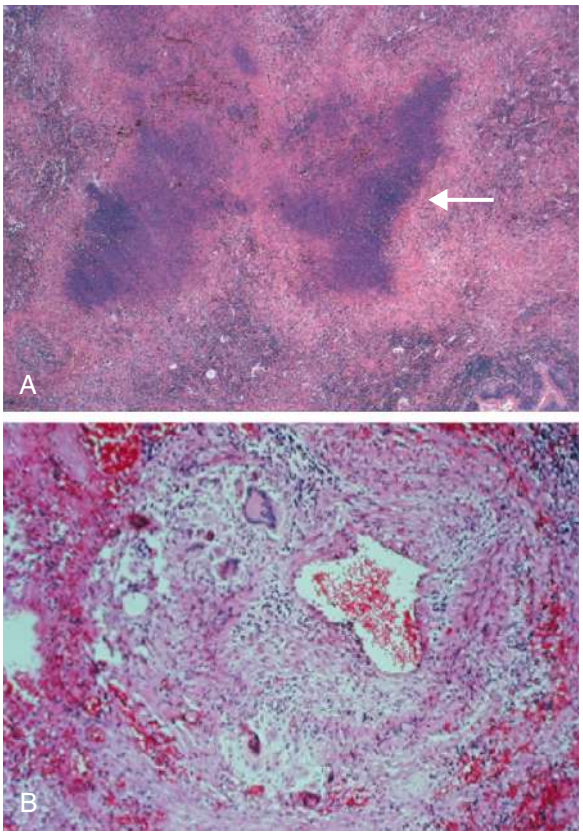

Fig. 448.1 **A,** Low-power view of granulomatous inflammation and geographic necrosis *(arrow)* in a lung biopsy from a patient with GPA. **B,** Granulomatous vasculitis involving a small pulmonary artery in the lung of a patient with GPA. The vessel wall is markedly thickened with an inflammatory infiltrate that includes multinucleated giant cells. *(From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 62.1B and C.)*



Fig. 448.2 Chest CT scan of a patient with granulomatosis with polyangiitis shows typical nodular lung infiltrate with cavitation. *(From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 62.1A.)*

of a meta-analysis of patients with renal vasculitis in nine trials suggest that adjuvant plasma exchange may be associated with improved renal outcome. Other adjuvant therapy includes high-dose intravenous immunoglobulin (IVIG) in recalcitrant disease, which acts to cross-link IgG and likely decrease circulating ANCA antibodies.

Recurrent disease remains a major problem, with relapse rates of up to 50% reported in most studies. ANCA levels do not always correlate with disease activity or severity. Patients with isolated disease of the sinuses and nose may not require such toxic therapy. Therapy with topical corticosteroid and antibiotics for infection appear to be warranted. If unsuccessful, steroids with methotrexate appear to be an effective therapy.

The development of subglottic stenosis requires specific treatment. Use of cyclophosphamide with oral corticosteroid may only partially treat the airway disease or not treat the airway disease at all. Local injection of a prolonged-acting corticosteroid may reduce the inflammation and prevent further scarring. If this complication is found at presentation, simultaneous airway intervention with induction of corticosteroid and cyclophosphamide is warranted and encouraged.

SARCOIDOSIS

Sarcoidosis is an idiopathic multisystem inflammatory disease with a characteristic histology of *noncaseating granulomas* (see Chapter 209). It has been postulated that sarcoidosis represents an exaggerated immune response to a yet-to-be-identified agent from the environment that is likely inhaled in a susceptible host. Sarcoidosis remains a diagnosis of exclusion from other diseases, with granuloma formation noted on histology, such as chronic granulomatous disease (CGD), granulomatous lymphocytic interstitial lung disease (GLILD) associated with common variable immune deficiency (CVID), HP associated with some drugs and inhalation agents, GPA, typical and atypical *Mycobacterium, Pneumocystis jiroveci,* and malignancy.

Epidemiology and Pathogenesis

The Black population is disproportionately affected by sarcoidosis; however, it can present in any group. Because an asymptomatic sarcoid-like distribution of noncaseating granulomas may be found at autopsy, the contribution of the granulomas to the disease is not clear. In countries that perform chest radiograph screening, up to 50% of people diagnosed with sarcoidosis are asymptomatic. The mortality and severity of sarcoidosis are poorer among Black patients; this is likely multifactorial, with racism and healthcare inequities playing a significant role. Sarcoidosis is more endemic in the Southeastern and South Central United States. There have been clusters of disease in families, and genetic testing suggests that the MHC linkage on the short arm of chromosome 6 is most likely to be observed.

Unrecognized infection or inhalation of an immune response–inducing antigen continues to be at the forefront of consideration as a cause of the disease. Clusters of sarcoidosis in small populations, variable prevalence by geography and race, the transfer of disease by organ transplant, and the reproducible noncaseating granuloma formation only noted in patients with sarcoidosis in the skin when homogenized lymph node tissue from patients with sarcoid is injected intradermally (Kveim-Siltzbach test) have supported this hypothesis.

Clinical Manifestations

Sarcoidosis is rarely found in young children. Skin rash, uveitis, and arthritis are seen most often in younger children without pulmonary symptoms. In older children, the presentation is similar to adults, with multisystem disease being the most common. In Northern Europe, erythema nodosum with the ocular involvement of iridocyclitis is seen most frequently. Despite the lack of symptoms, chest radiography may be abnormal in approximately 90% of children. The pulmonary disease can be less progressive compared with adults, and patients can recover spontaneously without corticosteroids. Rarely, pulmonary disease may progress to fibrosis. Ocular disease is more likely to be progressive and warrant intervention, as the inflammatory response may lead to blindness from complications of iritis.

Patients may present with malaise, fever, and weight loss. Those with lung disease are more likely to be asymptomatic as the presentation. When symptomatic, patients demonstrate shortness of breath, cough, and dyspnea. Younger children are more likely to manifest the disease as iridocyclitis, skin rash, and arthritis. Black children appear to have more frequent lymph node involvement, nonspecific elevations of gamma globulin, erythema nodosum, and hypercalcemia.

Physical exam may reveal only an elevated respiratory rate without crackles or rales by auscultation. Pleural involvement has been seen but is uncommon. When present, a lymphocytic predominant exudate may be observed in the pleural fluid. Unusual but reported findings include cases of pneumothorax, hemothorax, and chylothorax. One specific syndrome, **Lofgren syndrome**, with hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgias, is almost exclusively seen in females. This syndrome has a strong association with HLA-DQB1*0201 and polymorphisms in the C-C chemokine receptor 2 (CCR2); these genetic markers are a predictor of a good outcome.

Although almost 90% of patients with sarcoidosis demonstrate parenchymal or mediastinal disease on chest radiography, there are many who have minimal to no symptoms. Approximately 40% of adults with stage 1 disease have endobronchial involvement found at bronchoscopy. The higher the staging level of the disease, the more likely patients are to have airway involvement.

Diagnostic Laboratory Testing

The most common but nonspecific findings are hypergammaglobulinemia, elevated acute-phase reactants, hypercalciuria, hypercalcemia, elevated alkaline phosphatase when liver disease is present, and, occasionally, anemia of chronic disease. Serum angiotensin-converting enzyme may be elevated in 75% of patients with untreated sarcoidosis. False-positive tests occur from other diseases, so it is not considered a diagnostic test but may be used for monitoring disease activity.

Pulmonary function tests can be performed accurately in most children older than the age of 4 years. There are no specific diagnostic findings of spirometry, lung volumes, or diffusion capacity in sarcoidosis. Restrictive lung disease has been reported, but obstruction may be present because of an airway granuloma or lymph node compression. A decline in diffusion capacity when alveolitis is present in hypersensitivity pneumonitis could help diagnostically when attempting to differentiate sarcoidosis from HP before biopsy.

BAL is of great help when differentiating other diseases from sarcoidosis. BAL in sarcoidosis shows a marked predominance of $CD4^+$ T cells. *A lymphocyte percentage >16% on BAL, a CD4:CD8 ratio >4:1, and noncaseating granulomas on bronchial biopsy in the presence of abnormal angiotensin-converting enzyme levels are nearly completely diagnostic for sarcoidosis.* In addition, T cells are activated on BAL in sarcoidosis. BAL in HP shows a significant change in the balance of $CD4^+$ to $CD8^+$ T cells, with the two cell types being nearly equal compared with the normal mild predominance of $CD4^+$ T cells in the circulation. A ratio of CD4:CD8 of <1 predicts 100% of patients with BAL lymphocytosis to *not* have sarcoidosis. Neutrophil counts >2% and/or eosinophil counts >1% exclude the diagnosis of sarcoidosis.

The analysis of D-dimers in BAL fluid from subjects with sarcoidosis demonstrates an elevation in 80% of patients compared with no detectable D-dimers in unaffected controls.

Histopathology

The characteristic feature of sarcoidosis is the noncaseating granuloma formation in the lung (Fig. 448.3). These granulomas are found in the bronchial walls, alveolar septa, and vascular walls of pulmonary arteries and veins. The formation of noncaseating granulomas is likely preceded by alveolitis involving the interstitium more than the alveolar spaces. There is an accumulation of inflammatory cells, including monocytes, macrophages, and lymphocytes, that accompanies the granulomas. Multinucleated giant cells are frequently found among the epithelioid cells within the granuloma follicle. These may show cytoplasmic inclusions (e.g., asteroid bodies and Schaumann bodies) and some birefringent crystalline particles made of calcium oxalate and other calcium salts. These are most often identified in the upper lobes of the lungs, which may lead to confusion with diseases such as HP, eosinophilic granuloma, collagen vascular disease, pneumoconiosis, and infectious disease such as tuberculosis or histoplasmosis.

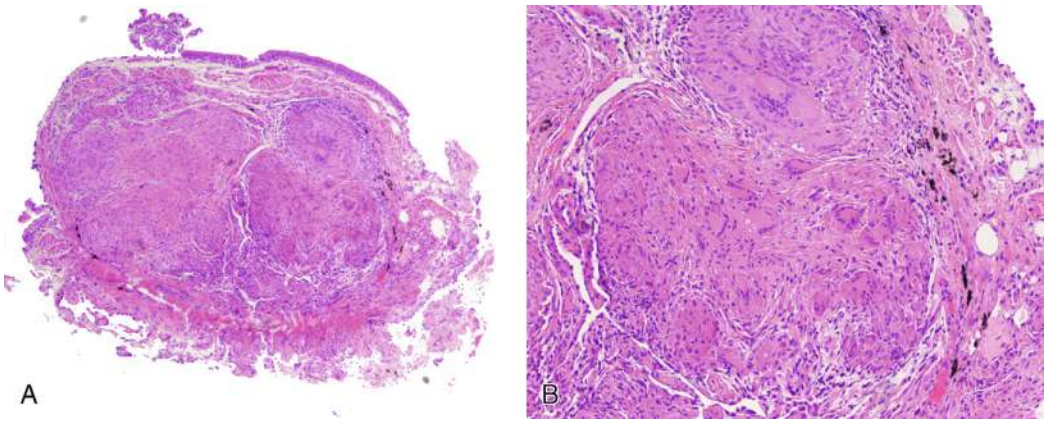

Fig. 448.3 Transbronchial biopsy specimen showing a sarcoid granuloma. **A,** The granulomas are located below the bronchiolar epithelial layer that appears at the top of the frame. **B,** A higher-power view of the same biopsy specimen. The epithelioid granuloma is tightly packed and contains multiple multinucleated giant cells. There is no caseous necrosis. Special stains for acid-fast bacilli and fungi were negative. *(From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 62.6.)*

Radiology

Pulmonary imaging in sarcoidosis has included plain chest radiography, HRCT of the chest, positron emission tomography using fluorine-18-fluorodeoxyglucose, or radiotracer using gallium-67. The staging of sarcoidosis is performed using plain radiography and is outlined as follows:

- Stage I—Bilateral hilar lymphadenopathy accompanied by right paratracheal lymphadenopathy.
- Stage II—Bilateral hilar lymphadenopathy accompanied by reticular opacities. If symptomatic, patients have cough and dyspnea. Occasional fever and fatigue accompany the respiratory symptoms.
- Stage III—Reticular opacities are found predominantly in the upper lobes with regression of hilar lymphadenopathy.
- Stage IV—Reticular opacities start to coalesce and lead to volume loss in the lung fields and traction bronchiectasis from conglomeration of the inflamed tissues. Extensive calcium deposits may be seen at this stage.

HRCT of the chest may be helpful in further staging of the disease and in revealing abnormalities not appreciated on chest radiography. Findings in patients with sarcoidosis by HRCT of the chest include hilar lymphadenopathy, paratracheal nodules, middle to upper lung parenchymal ground-glass appearance, bronchial wall thickening, bronchiectasis, cystic changes, and fibrosis. The ground-glass appearance suggests that alveolitis, as seen in hypersensitivity pneumonitis, may be present. Biopsy has usually shown granuloma formation as the predominant histologic finding.

Treatment

Because pulmonary sarcoidosis spontaneously resolves without therapy in almost 75% of patients, clear guidelines for treatment focused on minimizing therapeutic side effects is imperative. Glucocorticosteroids (GCSs) have long been the mainstay of therapy in sarcoidosis and are often used because of extrapulmonary disease. When pulmonary disease is progressive, GCS therapy is aimed at the prevention of fibrosis, honeycombing, and irreversible lung disease. Assuring that disseminated infections, heart failure, thromboembolism, or pulmonary hypertension are not present is important. In addition to HRCT of the chest, performance of pulmonary function tests, electrocardiogram, and echocardiogram should be considered before starting GCS therapy.

GCS therapy is often not started in the asymptomatic patient with stage I or II disease. This scrutiny of the benefit of therapy was highlighted when a prospective evaluation of GCS therapy for pulmonary disease found that nearly 50% of patients receiving GCSs had active or relapsing disease 2 years later. In contrast, 90% of patients who did not receive GCSs had spontaneous remission of disease, with the other 10% needing intervention 2 years later. Absolute indications include progressive stage III disease with symptoms of shortness of breath, cough, or other chest symptoms such as pain. Progressive restriction shown on pulmonary function testing is an indication for therapy. Specific pulmonary function changes where lung capacity declines a total of 10% or greater, FVC declines 15% or more, or diffusion capacity degradation is noted to be ≥20% are all indications for GCS intervention.

Initially, patients are treated with oral prednisone depending on the severity of symptoms. Stability is usually achieved within 6-8 weeks, after which slow, progressive tapering of GCS may occur every 4-8 weeks. Many favor the use of alternate-day steroids to reduce the side effects of GCSs, but little data exist to show efficacy.

For patients who do not tolerate GCSs or develop progressive disease, alternative immunosuppressive agents may add benefit to the regimen. Progressive disease also is a reminder for the clinician to reassess the diagnosis of sarcoidosis and review the possibility that beryllium or an infection may be the underlying reason for the progressive disease.

BERYLLIOSIS

Chronic berylliosis disease (CBD), a rare disease, is caused almost exclusively by environmental, and specifically occupational, exposure to beryllium. Examples of these high-risk industries include beryllium and beryllium alloy production, nuclear weapon development, the dental industry, and aircraft/automotive manufacturing. CBD is similar in appearance and pathogenesis to sarcoidosis; however, patients have had a previous exposure to beryllium. Although uncommon in pediatrics, CBD is important to consider in adolescents who work in high-risk industries.

Diagnosis

The most important step in the diagnosis of CBD is establishing a beryllium exposure by performing a thorough history. Special attention should be given to the patient's work history, and in younger children, the work history of the parents, as there are reports of secondary exposure to beryllium causing CBD in at-risk patients. Symptom history is nonspecific, with the most common being dry cough, shortness of breath particularly on exertion, and weight loss. Workplace screening for beryllium sensitization is now implemented in high-risk professions. Given this, the majority of patients are often asymptomatic at the time of diagnosis. The physical exam is also nonspecific in CBD, with most patients having a normal examination; however, crackles and digital clubbing may develop as the disease progresses.

Laboratory testing is a critical step in establishing a diagnosis. Beryllium sensitization is established by performing a beryllium lymphocyte proliferation test (BeLPT). This test is performed by isolating mononuclear cells from patients (either through blood or bronchoalveolar lavage fluid [BALF]) and culturing these cells in different concentrations of beryllium salts. Results are reported as a ratio of stimulated lymphocytes in the beryllium culture versus a control. A BeLPT is considered positive if two or more of the six stimulation indices exceed normal. A diagnosis of beryllium sensitization is confirmed by two positive blood BeLPT tests or one positive BALF BeLPT test. BeLPT screening is performed for employees in high-risk occupations.

Radiography is often obtained but may be nonspecific. Chest x-rays are often not sensitive enough to diagnose CBD. Computed tomography (CT) of the chest reveals a pattern similar to sarcoidosis, with nodules following a bronchovascular distribution. Hilar lymphadenopathy is less common in CBD compared to sarcoidosis. In later stages of the disease, evidence of fibrosis may be seen on the CT scan of the chest.

Pulmonary function testing (PFT) is also commonly performed in the evaluation of CBD. As a result of increased screening with BeLPT, most patients with CBD are now diagnosed before PFT abnormalities become apparent. If PFT abnormalities are noted, these changes are variable, demonstrating an obstructive, restrictive, or mixed pattern. Diffusion capacity for carbon monoxide is often low, especially in advanced disease. Finally, exercise stress testing is also abnormal in advanced CBD.

Bronchoscopy and BAL are important in the evaluation of CBD. BALF often reveals lymphocyte counts above 20%. Furthermore, BeLPT can be performed on BALF, which can confirm beryllium sensitivity. In conjunction with a positive BeLPT and a history of beryllium exposure, lung biopsy is needed to establish a definitive diagnosis of CBD. Biopsy can be obtained either through transbronchial biopsies or surgical lung biopsy. Unlike most pediatric ILDs, transbronchial biopsies are acceptable because of the bronchovascular distribution of CBD. Biopsies reveal noncaseating granulomas with a core of epithelial histiocytes surrounded by a rim of $CD4^+$ lymphocytes. Although lung biopsy is essential for diagnosis, a presumptive diagnosis of CBD can be made with a combination of a history of symptoms consistent with CBD, beryllium exposure, beryllium sensitization, PFT abnormalities, radiography changes, and BALF abnormalities.

Treatment

Treatment is not well studied in CBD. Most physicians do not treat asymptomatic patients with normal lung function indices. If lung function declines, first-line therapy is often systemic corticosteroids. Although some patients can stop corticosteroids over time, many will continue to progress without systemic treatment. In patients with persistent disease despite corticosteroids or in those patients who require ongoing treatment and would benefit from steroid-sparing therapy, other medications have been used such as azathioprine, methotrexate, mycophenolate, infliximab, or cyclophosphamide.

GRANULOMATOUS LUNG DISEASE IN PRIMARY IMMUNE DEFICIENCY

Primary immune deficiency (PID) often presents with recurrent or persistent pulmonary symptoms. Patients may experience recurrent infections, pneumonia, bronchiectasis, and ILD with or without fibrosis. Immune dysregulation occurs in many of the PIDs and may manifest with development of granulomatous lung disease and an autoimmune response. Most effort is focused on identifying the infectious pathogens in the PID that may be leading to the pulmonary symptoms; however, immune dysregulation may be the primary problem. This requires counterintuitive therapies with suppression of the immune system concurrently with immune deficiency therapy such as IVIG. The two most prominent PIDs associated with granulomatous lung disease are **chronic granulomatous disease** (see Chapter 170) and **common variable immune deficiency** (see Chapter 166.2).

The classic organism causing granuloma formation in the lung is *Mycobacterium tuberculosis*. Nontuberculous mycobacterial infections also can cause granulomas in the presence of a specific PID. These infections have been seen in patients with defective IL-12, IL-23, and IFN-γ signaling or when there are autoantibodies to IFN-γ. Defective regulation of nuclear factor-kappa B (nuclear factor-kappa B essential modifier defects) have also been reported in patients with nontuberculous mycobacteria. The clinician must be certain that this low-virulence organism is not causing disease before therapy for immune dysregulation is considered. Another PID associated with granulomatous disease involves defects in the INF-γ pathway. These disorders are grouped under the name **Mendelian susceptibility to mycobacterial disease**.

Pathogenesis

In CGD, there are defects in the phagocytic nicotinamide adenine dinucleotide phosphate oxidase system. These defects lead to impairment in the respiratory burst capacity to generate reactive oxygen species (see Chapter 170).

Patients with CVID have abnormalities in B lymphocytes and hypogammaglobulinemia. Pulmonary manifestations of CVID include organizing pneumonia, ILD, mucosa-associated lymphoid tissue lymphoma, and noncaseating granulomas in **granulomatous and lymphocytic interstitial lung disease (GLILD)** (see Chapter 166.2). Elevated levels of TNF from polymorphisms have been implicated as a possible mechanism. GLILD is becoming recognized more frequently in CVID and other immune disorders. It is defined by the presence of a granulomatous and a lymphocytic proliferative pattern in the lung. Granulomas may be found in other organs, including the bone marrow, spleen, gastrointestinal tract, skin, and liver in GLILD.

The etiology of GLILD is unknown. In a case cohort study, a majority of subjects with pathology diagnostic of GLILD were found to have human herpesvirus-8 infection of the lung. These findings in this subgroup of patients with GLILD may point to a mechanism underlying the development of pulmonary granulomas.

GLILD is sometimes misdiagnosed as sarcoidosis initially because both involve pulmonary granuloma, often accompanied by hilar and/or mediastinal lymphadenopathy. Sarcoidosis has several features that distinguish it from GLILD, such as normal or elevated serum immunoglobulin levels and frequent spontaneous remissions.

Clinical Manifestations of Granulomatous Lung Disease in Primary Immune Deficiency

Chronic respiratory disease as a result of recurrent infections is common in CGD. This is accompanied by clubbing in some patients and additional organ manifestations in the skin, liver, and genitourinary and gastrointestinal tracts. Granulomas are especially problematic in the gastrointestinal and genitourinary tracts. The inhalation of fungal spores and hyphae has led to acute pneumonia in CGD with rapid progression to respiratory failure, with hypoxemia, dyspnea, and fever. This entity, characterized as *mulch pneumonia,* appears to be best treated with antifungal medications and corticosteroids. Patients with GLILD present with progressive exercise intolerance and hypoxemia.

Radiography

Hilar and/or mediastinal lymphadenopathy occur with granulomatous lung involvement. These may manifest as parenchymal nodules and/or ground-glass abnormalities and can be seen commonly in CVID and CGD. Differentiating infectious causes of pulmonary infiltration in PID is often difficult on chest radiography; HRCT of the chest is often mandatory in the initial evaluation of the patients with CVID as a result of nonspecific findings on chest radiograph.

Laboratory and Pulmonary Function Testing

A definitive diagnosis of GLILD is made by lung biopsy with granulomatous disease. Transbronchial biopsy in children is often insufficient, and lung biopsy by video-assisted thoracoscopy or open biopsy is preferred. Unless the patient's underlying immune deficiency is unknown, other laboratory testing (except testing for infectious organisms) does not contribute significantly to the diagnosis of GLILD. When the child is old enough, complete PFT with spirometry, lung volumes, and diffusion capacity should be obtained at baseline and then followed serially to assess therapeutic response or progression of disease.

Therapy

The presence of GLILD in CVID can be associated with significant morbidity and possibly death. Without therapy, progressive pulmonary fibrosis and respiratory failure may occur in GLILD. The parenchymal disease may not always be controlled or relieved by glucocorticoid treatment. Other treatments include TNF antagonists, cyclosporine, or a combination therapy with rituximab and azathioprine. Response to therapy is monitored clinically and by interval HRCT of the chest and PFT, including spirometry, lung volumes, and diffusing capacity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

448.4 Eosinophilic Lung Disease

Timothy J. Vece and Stephanie D. Davis

The eosinophilic lung diseases are a group of heterogeneous pulmonary disorders with a predominant diffuse infiltration of eosinophils in the alveolar spaces or interstitial pulmonary spaces. Collectively, the disorders are often referred to as *pulmonary infiltrates with eosinophilia* and include acute eosinophilic pneumonia, chronic eosinophilic pneumonia, simple eosinophilic pneumonia (also known as *Loeffler eosinophilic pneumonia*), and eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss). The lung architecture is well preserved throughout the inflammatory response, often with complete reversal of the inflammation without long-term sequelae in the majority of cases. The peripheral white blood cell count often (but not always) reveals elevated eosinophils, and BALF shows an elevation in eosinophils. Prompt recognition of these diseases allows for lifesaving interventions in idiopathic **acute eosinophilic pneumonia (AEP) syndrome** or resolution of persistent symptoms in patients with chronic disease.

ETIOLOGY

Eosinophilic lung diseases are often classified under two subheadings: idiopathic disease and known causation (Tables 448.8-448.10). They are frequently further subdivided into acute and chronic or infectious and noninfectious. The division of acute or chronic is arbitrary based on the length of symptoms present but is relevant to the clinician in determining the etiology of the symptoms (Table 448.11). Loeffler eosinophilic pneumonia, induced by *Ascaris lumbricoides, Strongyloides,* and other ascarids, produces transient symptoms that self-resolve and is classified as neither acute nor chronic.

PATHOLOGY AND PATHOGENESIS

Eosinophilic lung disease, regardless of the stage of disease or etiology, shows mixed cellular infiltration of the alveoli and interstitial spaces with a predominance of eosinophils when open lung biopsy is performed. This may be accompanied by a fibrinous exudate with intact lung architecture. Other findings include eosinophilic microabscesses, a nonnecrotizing nongranulomatous vasculitis, and occasional multinucleated giant cells, again without granuloma formation. BAL is the diagnostic procedure of choice, especially with the acute types of eosinophilic pneumonia, where peripheral eosinophilia is often absent; the differential cell count on the BAL is ≥20% eosinophils and is often more than 40%. This highly sensitive and specific test has allowed clinicians to forego lung biopsy.

Eosinophils are filled with numerous toxic granules. Evidence of eosinophil degranulation may be found by electron microscopy, biopsy, urine excretion, and BALF. Most commonly, eosinophil-derived neurotoxin, leukotriene E_4, and other granule proteins, such as major basic protein, Charcot Leyden crystals, or proinflammatory cytokines, are identified and support the evidence that eosinophils are not only present but contributing to the disease process.

CLINICAL MANIFESTATIONS

Specific eosinophilic lung diseases present with a variable clinical picture; however, there are some common findings across many of the eosinophilic diseases. Dyspnea is the most common and prevalent symptom in patients with acute or chronic eosinophilic pneumonia and is accompanied by cough in the majority of patients (90%). Rhinitis and sinusitis symptoms are of lower prevalence with wide variability in children with eosinophilic pulmonary disease. **Acute eosinophilic pneumonia** often presents with respiratory failure and the requirement for mechanical ventilation at high levels of positive end expiratory pressure and high concentrations of oxygen, whereas chronic eosinophilic pneumonia has a more indolent presentation (see Table 448.11). Although malignancy (e.g., eosinophilic leukemia) and organizing pneumonia may present with a need for mechanical ventilation, this is uncommon. A history of asthma is common in the chronic eosinophilic pneumonias and in **allergic bronchopulmonary aspergillosis (ABPA)**; it often precedes the diagnosis of these two conditions.

Table 448.8 Key Elements in the Medical History, Laboratory Findings, and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease

MEDICAL HISTORY AND EXAMINATION
- Drug exposure (especially antibiotics, NSAIDs, antiepileptics, antileukotriene modifiers in EGPA)
- Environmental inhalation exposures to dust or inhaled chemicals
- New onset of smoking cigarettes
- Travel or immigration status from areas endemic with various parasites or coccidioidomycosis
- Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)
- ABPA concurrent in 7–15% of patients with cystic fibrosis
- Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm
- Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)

DIAGNOSTIC IMAGING AND TESTING
- Radiography helpful in AEP, CEP, and ABPA
  - Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung
- Simple chest radiography findings
  - Nonlobar infiltrate
  - Classic description as mirror image of pulmonary edema with peripheral infiltrates
  - Bilateral pleural effusion in AEP
  - Central bronchiectasis in ABPA
- High-resolution computed tomography of the chest
  - Middle and upper lobe nonlobar infiltrates with areas of ground-glass appearance
  - Mucus plugging in ABPA
  - Central bronchiectasis in ABPA (confused with cystic fibrosis)
- Blood eosinophil count
  - Elevated in many eosinophilic lung diseases
  - Magnitude of eosinophil blood count does not distinguish different pulmonary diseases
  - Not elevated in AEP
  - May occasionally not be elevated in CEP or after use of corticosteroids
- Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA
- Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely
- P-ANCA (MPO ANCA) is positive in 40–70% of EGPA (CSS)
- BAL eosinophil percentage
  - ≥25% eosinophils diagnostic in AEP
  - ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia
  - Eosinophil percentages below these criteria may require lung biopsy
  - <25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis

ABPA, Allergic bronchopulmonary aspergillosis; AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia; CSS, Churg-Strauss syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; IAEP, idiopathic acute eosinophilic pneumonia; MPO ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; NSAID, nonsteroidal antiinflammatory drug; P-ANCA, perinuclear antineutrophil cytoplasmic antibody.

Other symptoms of fever, myalgia, fatigue, weight loss, poor appetite, and night sweats may accompany the acute or chronic eosinophilic pneumonias. When abnormalities of the liver are detected, or if arthralgia, skin changes, pericardial effusion, or peripheral neuropathy accompany the disease presentation, a diagnosis of **eosinophilic granulomatosis with polyangiitis (EGPA)** (formerly known as *Churg-Strauss syndrome*) or **hypereosinophilic syndrome (HES)** should be aggressively investigated.

Chest Imaging

The chest radiograph is one of the most helpful tests for evaluating the child with dyspnea. The characteristic feature of fluffy alveolar

Table 448.9 Classification of the Eosinophilic Pneumonias in Clinical Practice

Eosinophilic Pneumonias of Unknown Cause
Solitary idiopathic eosinophilic pneumonias
Idiopathic chronic eosinophilic pneumonia
Idiopathic acute eosinophilic pneumonia
Eosinophilic pneumonia in systemic syndromes
Eosinophilic granulomatosis with polyangiitis
Idiopathic hypereosinophilic syndromes (lymphocytic or myeloproliferative variant)
Eosinophilic Pneumonias of Known Cause
Allergic bronchopulmonary aspergillosis and related syndromes (including bronchocentric granulomatosis)
Eosinophilic pneumonias of parasitic origin
Eosinophilic pneumonias of other infectious causes
Drug-induced eosinophilic pneumonias
Eosinophilic Airways Diseases
Idiopathic hypereosinophilic constrictive bronchitis
Other Pulmonary Syndromes with Possible (Usually Mild) Eosinophilia
Organizing pneumonia, asthma, idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, malignancies, and so forth

From Cottin V. Eosinophilic lung diseases. *Clin Chest Med.* 2016;37:535–556, Box 1, p. 536.

Table 448.10 Drugs Commonly Causing Eosinophilic Pneumonia

Antiinflammatory drugs and related drugs: acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, and tolfenamic acid
Antibiotics: ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, and trimethoprim-sulfamethoxazole
Other drugs: captopril, carbamazepine, and GM-CSF
A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at www.pneumotox.com.

From Cottin V, Cordier JF. Eosinophilic lung diseases. *Immunol Allergy Clin North Am.* 2012;32(4):557–586, Box 6, p. 575.

Table 448.11 Diagnostic Criteria for Idiopathic Chronic Eosinophilic Pneumonia and for Idiopathic Acute Eosinophilic Pneumonia

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA
1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance.
2. Eosinophilia at bronchoalveolar lavage differential cell count ≥40% (or peripheral blood eosinophils ≥1,000/mm^3).
3. Respiratory symptoms present for at least 2-4 wk.
4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia).
IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA
1. Acute onset with febrile respiratory manifestations (≤1 mo, and especially ≤7 days duration before medical examination).
2. Bilateral diffuse infiltrates on imaging.
3. Pa_{O_2} on room air ≤60 mm Hg (8 kPa), or Pa_{O_2}/F_{IO_2} ≤300 mm Hg (40 kPa), or oxygen saturation on room air <90%.
4. Lung eosinophilia, with ≥25% eosinophils at BAL differential cell count (or eosinophilic pneumonia at lung biopsy when done).
5. Absence of determined cause of acute eosinophilic pneumonia (including infection or exposure to drugs known to induce pulmonary eosinophilia). Recent onset of tobacco smoking or exposure to inhaled dusts may be present.

BAL, Bronchoalveolar lavage.
From Cottin V. Eosinophilic lung diseases. *Clin Chest Med.* 2016;37:535–556, Box 2, p. 538.

infiltrates in the peripheral lung field is classic (Fig. 448.4). The images may be easily recognizable by astute clinicians who have identified the etiology of the disease without elevated blood eosinophil counts or BAL.

HRCT of the chest is the best advanced imaging modality for eosinophilic lung disease. Spontaneous migration of lung opacities is commonly seen in the chronic pneumonias. Most often HRCT of the chest shows simultaneous evidence of bilateral alveolar infiltrates with both confluent consolidations and ground-glass appearance. The most prominent areas of abnormality are visualized in the upper lobes and subpleural regions. Specific diseases have unique findings, such as *proximal bronchiectasis* in **ABPA** and pleural effusion in acute eosinophilic pneumonia. HRCT of the chest is most sensitive in identifying the correct etiology of the disease when chest radiographic findings are nonspecific.

LOEFFLER SYNDROME

The **transient pulmonary infiltrates with eosinophilia syndrome** that is most often seen in children (formerly known as Loeffler syndrome) is characterized by migrating pulmonary infiltrates with peripheral blood eosinophilia. This syndrome is caused by helminthic infections. *A. lumbricoides* or roundworm is the most common parasite causing this disease in the United States. When a fertilized egg is ingested from contaminated food from areas with poor sanitation, it becomes a larval worm that can penetrate the duodenum of the small intestine and migrate in the circulation to the liver, heart, and lungs. In the pulmonary venous circulation, the larvae can break through the interstitial space to the alveoli. The juvenile larva may subsequently migrate to the trachea, where they are expectorated and swallowed. Other nematodes cannot mature in the intestinal tract, so their disease is limited to a single passage into the lungs.

Visceral larva migrans from multiple nematodes may cause eosinophilic lung disease. The most common etiologies are the dog roundworm, *Toxocara canis,* but *Toxocara cati, Strongyloides stercoralis, Baylisascaris procyonis,* and *Lagochilascaris minor* can all produce visceral larva migrans. Outside the United States, the common lung fluke, *Paragonimus westermani,* may cause a similar pulmonary disease in older children and adolescents. Western Africa, Central and South America, and East Asia are regions where paragonimiasis may be found, especially in those who eat raw crabs or crawfish. Many other parasites may have a transient pulmonary syndrome, but their manifestations are most commonly in other organs.

The pulmonary syndrome is classic with cough, dyspnea, migratory peripheral pulmonary infiltrates, and blood eosinophilia that is self-limited. Young children most often have a history of pica and eating dirt that is contaminated with the eggs. Because the larva can migrate to other organs and multiply in the intestinal and biliary tract, symptoms of abdominal pain, vomiting, rarely obstruction, cholecystitis, and pancreatitis may be found. Diagnosis is frequently made by examination of the stool, where the eggs may be detected microscopically. Treatment is aimed at the intestinal disease and not the pulmonary disease per se. It is possible that anthelminthic treatment of other organ disease during the pulmonary phase will increase the inflammatory response in the lung, leading to the need for treatment with corticosteroids.

ACUTE EOSINOPHILIC PNEUMONIA

A unique and dramatic presentation of the eosinophilic pneumonias is **AEP** (see Table 448.11). AEP mimics infectious pneumonia or acute respiratory distress syndrome with its rapid onset and marked hypoxemia. This disease most frequently occurs in the teenage and young adult populations. Essentially all patients present within 7 days of symptom onset with dyspnea, fever, and cough, and more than 50% have chest pain. Myalgia and abdominal pain also frequently accompany this disease. Rarely, patients have presented up to 4-5 weeks after the onset of symptoms. Physical exam demonstrates tachypnea, tachycardia, and crackles in the lung fields. Many patients rapidly deteriorate and require mechanical ventilation.

There is an *absence* of circulating eosinophilia, which contrasts with the dramatic number of eosinophils seen in the BAL representing at

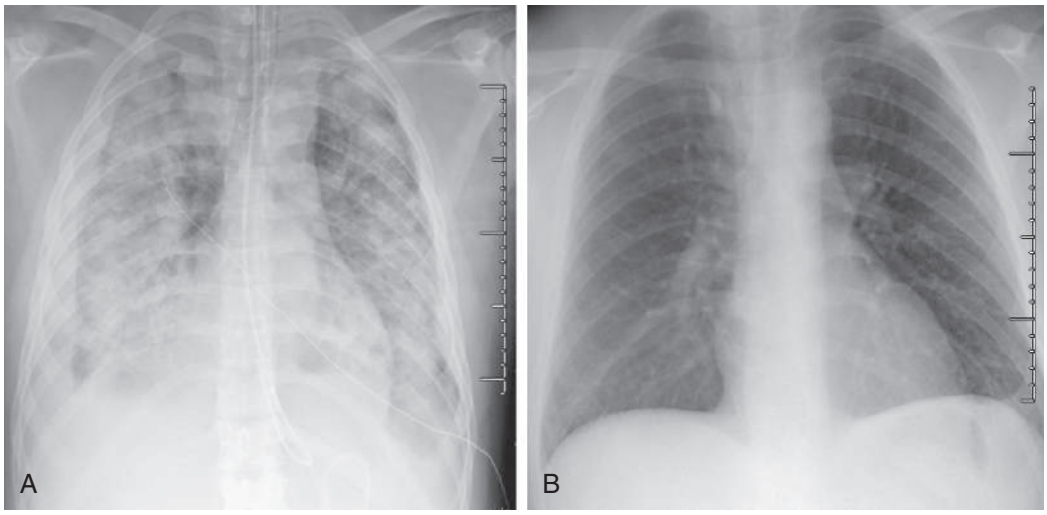

Fig. 448.4 A, Acute eosinophilic pneumonia demonstrating the mirror image pulmonary edema with a right pleural effusion on admission. B, Complete clearing upon discharge from the hospital after corticosteroid usage.

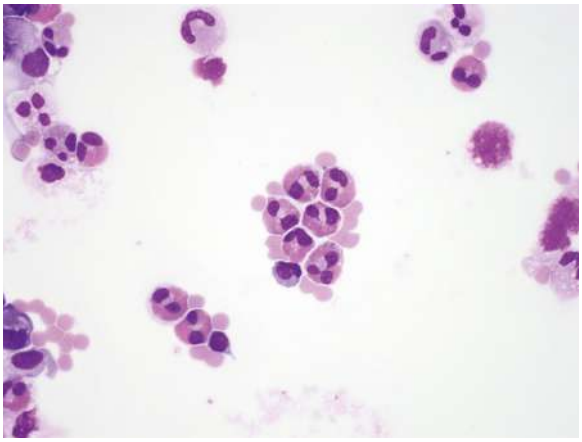

Fig. 448.5 Light microscopy of eosinophils in bronchoalveolar lavage fluid.

least 20% of the inflammatory cells (often 40–55%) (Fig. 448.5). This feature helps distinguish it from the chronic pulmonary disease of eosinophilic origin.

Although this disease has been labeled as idiopathic, there have been identifiable exposures (e.g., 1,1,1-trichloroethane or Scotchgard). Numerous reports link the onset of smoking tobacco, change in smoking frequency, reinitiation of smoking in young male adolescents or adults, and even massive secondary smoke exposure as critical associations with the onset of AEP. World Trade Center dust is associated with development of AEP. A single smoke challenge study is associated with recurrence. Some medications are also linked to the onset of AEP. The most complete and current resource for medications linked to pulmonary disease is "The Drug-Induced Respiratory Disease Website" (http://www.pneumotox.com). When AEP is identified in a patient, the pediatrician should educate the patient and family about the link to smoking exposure and the risk of AEP upon reexposure.

In addition to smoke exposure, AEP has been reported after smoking cocaine; typically, within hours to days after use. Whether this is a unique eosinophilic response to cocaine that represents one manifestation of *crack lung* or is a separate disease is unknown. Crack lung refers to diffuse alveolitis with pulmonary hemorrhage from an unknown mechanism that occurs within 48 hours of cocaine smoke inhalation.

Lung function has not been measured frequently in the disease because the patients have proceeded rapidly to the intensive care unit (ICU) for mechanical ventilation. When measured, a restrictive pattern of lung disease and reduced diffusion capacity are the usual findings. Arterial blood gases will also show a significant increase in the alveolar-arterial gradient.

The criteria for diagnosis include the acute onset of disease, bilateral pulmonary infiltrates, reduced oxygen saturation or Pao_2 ≤60 mm Hg, BAL of ≥25% eosinophils, and absence of a determined cause of eosinophilia (see Table 448.11). The recent onset of tobacco exposure, dust, or chemical inhalation are supporting factors in confirming a diagnosis.

Treatment has uniformly been the use of a corticosteroid (e.g., methylprednisolone 1-2 mg/kg/day) either intravenously or orally. A minimum or maximum treatment time has not been determined. Rare fatalities have been reported. Complete recovery has been seen in days, with resolution of pleural effusions within 4 weeks of treatment. Most important, relapse and persistent symptoms are rare, which sharply contrasts with the idiopathic chronic eosinophilic pneumonias. Follow-up testing of pulmonary function is usually normal, which supports the contention that lung parenchyma heals without evidence of compromise or fibrosis.

CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia is another idiopathic pulmonary condition without a known exposure to toxin, dust, or chemical inhalation. Eosinophils infiltrate the lung parenchyma resulting in dyspnea, cough, fever, and weight loss. It is primarily a problem for adults, with a female predominance (2:1 female:male) and usually in patients who are nonsmokers. Chest examination reveals tachypnea, crackles, and wheezing; a diagnosis of asthma is a common finding. The classic finding on chest x-ray of the *radiographic negative of pulmonary edema* is found in these patients: central clear lung fields but fluffy, patchy peripheral infiltrates; however, this is not seen in all cases.

When compared to AEP, the onset of disease is indolent and subtle, but the accompanying fever and weight loss may lead the clinician toward a concern for an underlying malignancy before the chest radiograph and laboratory investigation. *Peripheral* blood eosinophilia is commonly as high as 5,000/mm^3 or greater, accompanied by BAL eosinophilia >40% on the differential count (see Table 448.11). The peripheral eosinophilia sharply contrasts with the lack of eosinophils seen in the blood in AEP. HRCT scan of the chest contrasts with the AEP, with pleural effusion as a rare finding, as well as rare cavitation.

In contrast to AEP, PFT shows a mixed obstructive and restrictive pattern, especially given that asthma often occurs concurrently with this disease.

Inflammatory markers associated with migration and activation of eosinophils are predictably found in BAL and the urine. These include the T-lymphocyte type 2 cytokines of IL-4, IL-5, IL-6, IL-10, IL-13, and IL-18. However, T-lymphocyte type 1 cytokines of IL-2 and IL-12 are also present with many of the potent eosinophilic chemoattractants such as CCL5 (RANTES [regulated upon activation, normal T-cell expressed and secreted]) and CCL11 (eotaxin-1).

Toxic granule proteins of major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein are frequently present. Unfortunately, these important molecules help confirm the eosinophilic nature of the disease, but their presence adds no additional sensitivity or specificity over the presence of eosinophils on BAL.

Treatment is similar to most eosinophilic lung syndromes, where corticosteroids (oral) are the mainstay of treatment. The minimum dose of steroid needed to induce remission is not known, but most clinicians recommend prednisone (or equivalent) at 0.5 mg/kg/day for 2 weeks. The dose is reduced to half (0.025 mg/kg/day) for an additional 2 weeks if symptoms have abated. The remaining dose of steroid may need to be weaned over 6 months. Alternatively, IV methylprednisolone is used, starting with 10-30 mg/kg/dose (maximum 1 g) given either 3 consecutive days per month or 1 day per week. Symptoms and pulmonary infiltrates rapidly disappear after initiation of this treatment but frequently recur with tapering of the steroid. Asthma that occurs concurrently in patients with chronic eosinophilic pneumonia represents a phenotype of the disease that appears to have lower relapse risk, yet up to 50% of all identified patients with chronic eosinophilic pneumonia relapse during or after corticosteroid taper.

Many believe that this disease is a precursor to the development of EGPA (formerly Churg-Strauss syndrome). The utility of ICS in chronic eosinophilic pneumonia is unknown but is warranted for the persistent asthma phenotype of the disease. A subset of patients develops permanent lower airway obstruction without reversibility, which requires patients with this disease to have close follow-up and monitoring of pulmonary function tests.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME)

EGPA syndrome is a systemic disease involving multiple organs but most prominently the lung. Patients present with difficult-to-control asthma, allergic rhinitis, and peripheral eosinophilia (>10% or >1,500 cells/μL) in the blood. Evidence of vasculitis must be present in at least two organs. The polyangiitis appears later in the disease process, with asthma being the precursor symptom in more than 90% of the cases reported. EGPA affects multiple organs, including the skin, heart, gastrointestinal tract, kidneys, and central nervous system (Table 448.12). Rhinitis and upper airway disease are present in 75% of the patients but are not specific. Symptoms of fever, weight loss, fatigue, arthralgia, and myalgia may be seen in approximately two thirds of patients. Cardiac and renal involvement is insidious in onset, and screening should occur for these manifestations. The multiple organ involvement results in the morbidity and mortality of this disease. The typical progression of the disease is in three phases: rhinitis and asthma first, tissue eosinophilia second, and, finally, systemic vasculitis of small and medium vessels.

The pathogenesis of EGPA is still unknown but several factors are suspected to contribute to the development of the disease. The possible link between leukotriene-receptor antagonists (zafirlukast, montelukast, or pranlukast) is controversial but still considered possible. It is suspected that use of this class of adjunctive medications in severe asthma allows for the reduction in the use of corticosteroids leading to the full-blown (unmasking) manifestation of EGPA. Many refrain from use of leukotriene-receptor antagonists when EGPA syndrome has been diagnosed.

Clinical and laboratory findings pinpoint the diagnosis with high specificity (99.7%) and sensitivity (85%) when at least four of six criteria developed by the American College of Rheumatology are met (asthma, eosinophilia >10%, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy findings of extravascular eosinophil infiltrates). In contrast to GPA, the rhinitis is not destructive, and nasal septal perforation does not occur in EGPA.

Radiography of the chest or HRCT of the chest demonstrates migratory, peripheral predominant opacities, ground-glass appearance, nodules, bronchiectasis, and bronchial wall thickening. Pleural effusion should raise suspicion for the presence of heart failure from cardiomyopathy.

Laboratory findings include striking eosinophilia, with values generally between 5,000 and 20,000/mm^3 at the time of diagnosis. These counts often parallel vasculitis activity. The BAL shows striking eosinophilia with differential counts often >60%. Biopsies of other organ systems reflect the activity of eosinophils and are not specific for the EGPA diagnosis.

ANCAs may be present in EGPA syndrome. The perinuclear-ANCA targeting myeloperoxidase is specifically found in EGPA in approximately 40% of the patients; the absence of myeloperoxidase-ANCA does not exclude the diagnosis. Those patients with eosinophilic pneumonia, fever, and cardiac involvement are less likely to have myeloperoxidase-ANCA detected. Those with peripheral neuropathy, renal glomerular disease, and skin purpura usually have detectable myeloperoxidase-ANCAs (see Table 448.12).

Pulmonary function tests show an obstructive pattern caused by the asthma component. The pulmonary obstruction is responsive to oral corticosteroid use, but often mild obstruction persists.

Treatment of EGPA with systemic oral corticosteroids remains the mainstay of therapy at a starting dose of 0.5 to 1 mg/kg/day. This therapy is often required for up to 12 months or longer, with a steady taper in dosage over that time. EGPA resistant to corticosteroids has responded to cyclophosphamide, IFN-α, cyclosporine, IVIG, and plasmapheresis. The use of anti–IL-5 (mepolizumab) has been encouraging and may be used as a steroid-sparing agent in the future.

Table 448.12 Eosinophilic Granulomatosis with Polyangiitis

	VASCULITIC PHENOTYPE	EOSINOPHILIC TISSULAR DISEASE PHENOTYPE
Respective frequency	~40%	~60%
ANCA	Present (mostly perinuclear-ANCA with anti-MPO specificity)	Absent
Predominant manifestations	Glomerular renal disease Peripheral neuropathy Purpura Biopsy-proven vasculitis	Cardiac involvement (eosinophilic myocarditis) Eosinophilic pneumonia Fever

ANCA, Antineutrophil cytoplasmic antibody; MPO, myeloperoxidase.

Data from Sablé-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med.* 2005;143:632–638; and Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum.* 2005;52:2926–2935.

From Cottin V, Cordier JF. Eosinophilic lung diseases. *Immunol Allergy Clin North Am.* 2012;32(4):557–586, Table 2, p. 569.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA is a complex hypersensitivity reaction that occurs in the lungs and bronchi in response to exposure and colonization of *Aspergillus* species (usually *Aspergillus fumigatus*; see Chapter 283). This disease occurs in patients with preexisting asthma and up to 15% of patients with cystic fibrosis (see Chapter 454). The quantity of *Aspergillus* exposure does not correlate with the severity of disease.

The clinical pattern of disease (Table 448.13) is remarkably similar with a presentation of difficult-to-treat asthma. The patient suffers from periods of acute obstructive lung disease with bronchial mucous plugs, elevated total IgE antibody, elevated specific IgE and IgG anti-*Aspergillus* antibodies, skin prick test reactions to *Aspergillus* species, precipitating antibodies to *Aspergillus* species, and proximal bronchiectasis. Other clinical manifestations include dyspnea, cough, shortness of breath, and peripheral eosinophilia, along with pulmonary eosinophilia seen on BAL with infiltration of the parenchyma. The use of systemic corticosteroids may lower the total IgE antibody levels such that a diagnosis may be in question when the initial tests are conducted.

ABPA should be considered in patients with cystic fibrosis when clinical deterioration occurs without evidence of an identifiable cause. Symptoms heralding such deterioration include increasing cough, wheezing, loss of exercise tolerance, worsening exercise-induced asthma, reduction of pulmonary function, or increased sputum production without another discernible reason. Clinical findings of elevated total IgE antibody, anti-*Aspergillus* IgE antibodies, precipitating antibodies to *A. fumigatus,* and/or new abnormalities on chest radiography that fail to clear with antibiotics should alert the clinician to the possibility of ABPA.

Table 448.13 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS–CENTRAL BRONCHIECTASIS
• Medical history of asthma*
• Immediate skin prick test reaction to *Aspergillus* antigens*
• Precipitating (IgG) serum antibodies to *Aspergillus fumigatus**
• Total IgE concentration >500 IU/mL (>1,000 ng/mL)*
• Central bronchiectasis on chest CT*
• Peripheral blood eosinophilia >500/mm^3
• Lung infiltrates on chest x-ray or chest HRCT
• Elevated specific serum IgE and IgG to *A. fumigatus*
ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS SEROPOSITIVE†
• Medical history of asthma†
• Immediate skin prick test reaction to *A. fumigatus* antigens†
• Precipitating (IgG) serum antibodies to *A. fumigatus*†
• Total IgE concentration >417 IU/mL (>1,000 ng/mL)†

*The criteria required for a diagnosis of ABPA with central bronchiectasis.
†The first four criteria are required for a diagnosis of seropositive ABPA.
ABPA, Allergic bronchopulmonary aspergillosis; CSD, corticosteroid dependent; HRCT, high-resolution computed tomography.

When evaluating a child with asthma symptoms, the clinician must distinguish asthma from ABPA. If the diagnosis is suspected, skin prick test for evidence of IgE-specific antibody directed against *A. fumigatus* is essential. Intradermal skin testing, when the skin prick test is negative, although not routinely performed because of poor specificity, may be conducted. The absence of a positive skin prick test and intradermal test to *A. fumigatus* excludes the diagnosis of ABPA. The prevalence of ABPA in patients with an existing diagnosis of asthma and an abnormal immediate skin prick test response to *A. fumigatus* has been evaluated. Between 2% and 32% of patients with asthma with concurrent skin prick test–positive reactions to *Aspergillus* have evidence of ABPA.

Patients with cystic fibrosis who are less than 6 years of age rarely develop ABPA. When the total IgE antibody in patients with cystic fibrosis exceeds 500 IU/mL (1,200 ng/mL), a strong clinical suspicion of ABPA is necessary.

ABPA pathology has characteristic findings of mucoid bronchi impaction, eosinophilic pneumonia, and granulomas. Histologic features characteristic of asthma are also present. Septated hyphae are often found in the mucus-impacted bronchial tree. However, the fungi are not invasive in this unique disease. *Aspergillus* may be cultured from sputum in more than 60% of patients. Interestingly, hyphae may not be detected on microscopy.

Staging of the disease (Table 448.14) represents distinct phases; however, progression does not necessary occur in sequence from stage 1 to stage 5. Staging of ABPA is important for treatment considerations. In many hypersensitivity diseases where IgE antibody contributes to the pathogenesis (e.g., asthma), total IgE is often used to screen for an atopic state but is not a test that helps the clinician with serial measures. In sharp contrast, the measurement of IgE during acute exacerbations, remission, and recurrent ABPA disease is helpful in identifying the activity of disease and may herald the recurrence. During stage 1 disease, the level of IgE antibody is often very high. During stage 2 remission, a fall in the levels may be as much as 35% or more. Recurrence of activity may result in a marked rise of total IgE with a doubling of the baseline level seen during remission. During the use of glucocorticoid therapy, monthly or bimonthly levels of IgE are followed serially to assist the clinician in tapering therapy. Because exacerbations of ABPA are not accompanied by changes in symptoms in approximately 25% of the recurrences, serial IgE accompanied by chest radiography is helpful to the clinician to guide therapy.

Radiography

Plain chest x-ray shows evidence of infiltrates, especially in the upper lobes and the classic findings of bronchiectasis (Fig. 448.6). HRCT of the chest demonstrates central bronchiectasis (Fig. 448.7) and mucus impaction of the airways (finger-in-glove appearance). HRCT may add value for the patient with a positive skin prick test and normal chest radiograph to detect characteristic abnormalities of ABPA.

Treatment

The mainstay of therapy for ABPA has been systemic glucocorticoids with adjunct therapy including antifungal medications and anti-IgE therapy with omalizumab. Exacerbations in stages 1 and 3

Table 448.14 Staging of Allergic Bronchopulmonary Aspergillosis

Stage 1	Acute	Upper and middle lobe infiltration	High IgE
Stage 2	Remission	No infiltrate off steroids >6 mo	Normal to high IgE
Stage 3	Exacerbation	Upper and middle lobe infiltration	High IgE
Stage 4	CSD asthma	Minimal infiltrate	Normal to high IgE
Stage 5	End stage	Fibrosis and/or bullae	Normal

CSD, Corticosteroid dependent.

may be treated for 14 days with 0.5-1 mg/kg of glucocorticoids followed by every-other-day usage and tapering over 3 months or as long as 6 months. Stage 2 remission phase and stage 5 where fibrosis has occurred do not require glucocorticoid therapy. Stage 4 denotes a state where glucocorticoid weaning has not been successful and continued long-term therapy is required.

Antifungal therapy with a 16-week course of itraconazole improves the response rate during exacerbations, allowing the reduction of glucocorticoid dosage by 50% and resulting in a reduction of total serum IgE of 25% or more. The proposed mechanisms of action have been to either reduce the antigen load driving the immune response or possibly raising the corticosteroid serum levels by slowing the metabolism of the steroid. This latter mechanism would be true for prednisone, which is methylated in the liver, but not for methylprednisolone, which does not require methylation.

The adult dosage recommendation for itraconazole is 200 mg 3 times per day for 3 days followed by 200 mg twice daily for the remainder of the 16 weeks. Children should receive 5 mg/kg/day in a single dose. If the proper calculated dose exceeds 200 mg, then the total dose should be divided equally and given twice daily. Serum levels of itraconazole are necessary to ensure proper drug absorption when in capsule form.

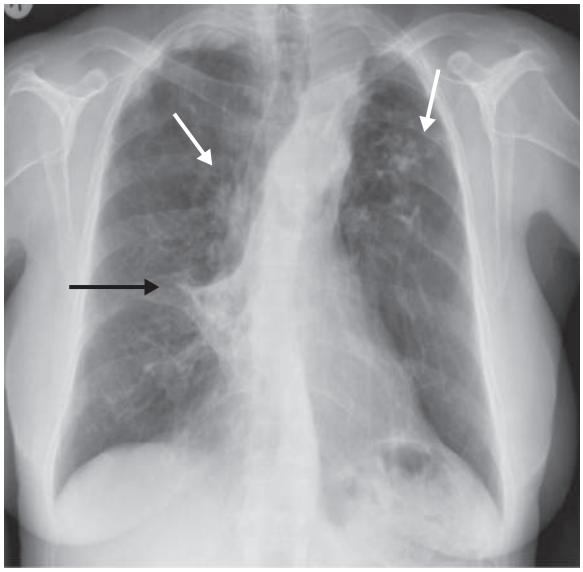

Fig. 448.6 Transitory opacities *(white arrows)* and lobar collapse *(black arrow)* in patient with allergic bronchopulmonary aspergillosis. *(From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE. Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 61.2.)*

The liquid form is more readily absorbed and has achieved substantially higher levels. The use of proton pump inhibitors and histamine 2 antagonists may reduce absorption of itraconazole. Voriconazole has been used as a substitute antifungal medication. Proper dosing has been established for invasive *Aspergillus* disease but not for ABPA. Hepatotoxicity may occur with these drugs so liver function must be monitored.

Omalizumab, an anti-IgE humanized monoclonal antibody, has been used in a case series of patients with cystic fibrosis and ABPA and in a small cohort of adults without cystic fibrosis but with ABPA. Both case series demonstrated significant reductions in asthma exacerbations, ABPA exacerbations, and glucocorticoid usage. The dose prescribed has been 300-375 mg every 2 weeks by subcutaneous injection.

HYPEREOSINOPHILIC SYNDROME

See Chapter 169.

HES is a descriptive name of a group of disorders that are characterized by the persistent overproduction of eosinophils accompanied by eosinophil infiltration in multiple organs with end-organ damage from mediator release. The term *HES* should only be used when there is eosinophilia with end-organ damage from the eosinophils and not from another cause. The discovery of underlying genetic, biochemical, or neoplastic reasons for HES has led to the classification of primary, secondary, and idiopathic HES (Table 448.15). Specific

Table 448.15 Hypereosinophilic Syndrome Variants

Myeloproliferative	Nonclonal Clonal–F1P1L1/PDGFRA-positive chronic eosinophilic leukemia
Lymphocytic	Nonclonal T cells Clonal T-cell expansion with T-cell activation
Overlap	Organ restricted
Familial	Family history of eosinophilia without known cause
Associated	Eosinophilia in chronic disease like inflammatory bowel disease or EGPA (Churg-Strauss syndrome)
Undefined	Asymptomatic Cyclic angioedema with eosinophilia (Gleich syndrome) Symptomatic without myeloproliferation or lymphocytic form

EGPA, Eosinophilic granulomatosis with polyangiitis; PDGFRA, platelet-derived growth factor receptor-α.

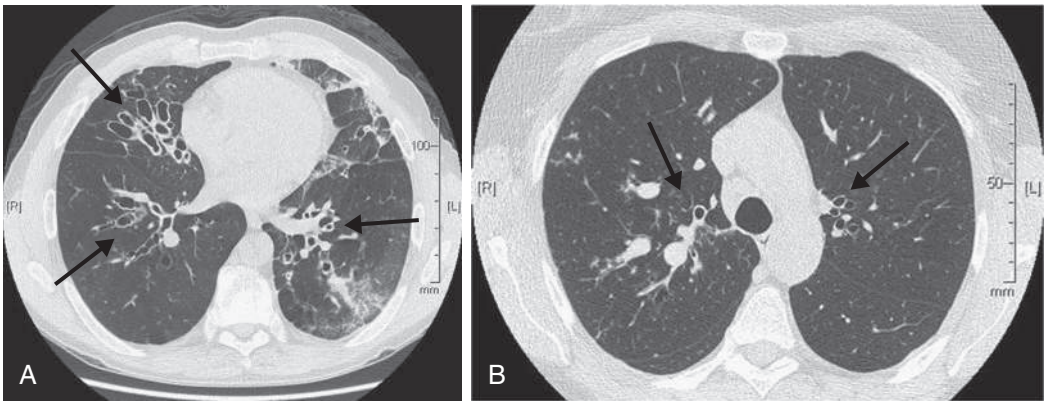

Fig. 448.7 A, Central bronchiectasis in patient with ABPA *(arrows)*. B, Central bronchiectasis in the upper lobes *(arrows)*. *(From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE. Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 61.3.)*

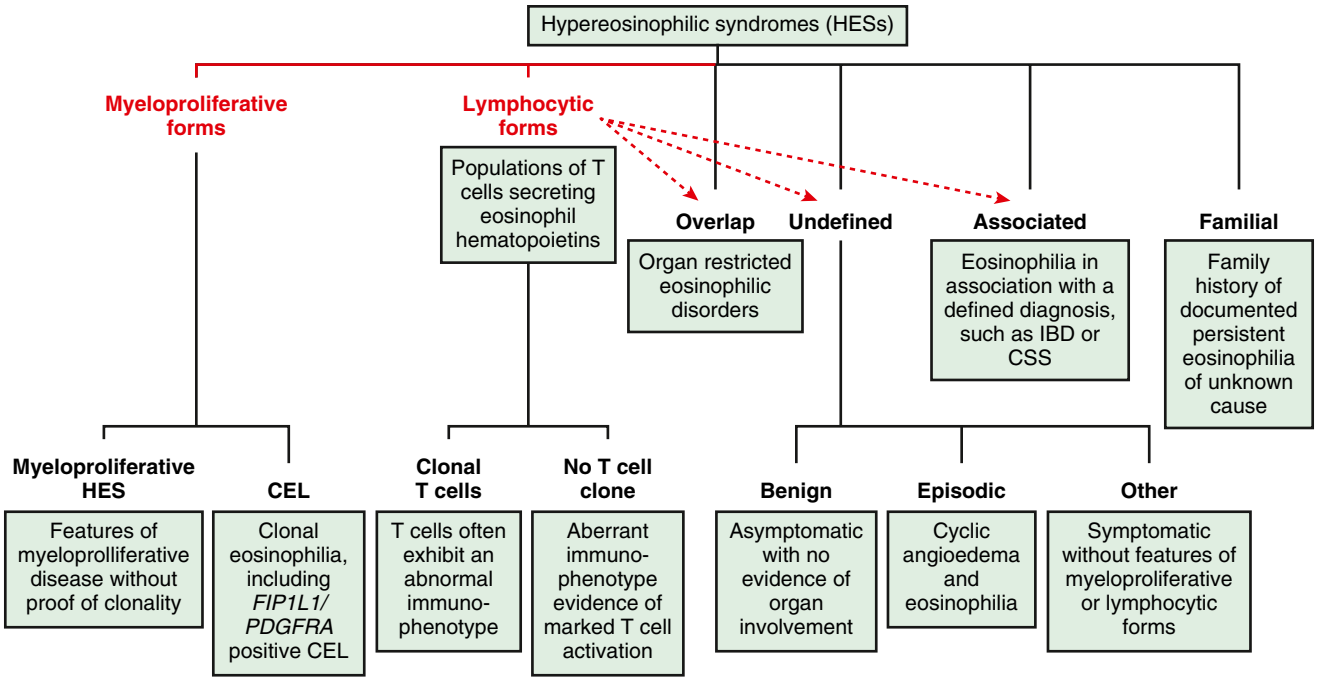

Fig. 448.8 A revised classification of hypereosinophilic syndrome (HES). Changes from the previous classification are indicated in *red type*. *Dashed arrows* identify HES forms in some patients who have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. *(From Simon H, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol. 2010;126:45–49, Fig. 1.)*

syndromes such as EGPA have eosinophilia, but the contribution of eosinophils to the organ damage is incompletely understood.

Some variants of HES have pathogenic variants in tyrosine kinase receptor platelet-derived growth factor receptor-α (*PDGFRA)*; males are almost exclusively affected. *PDGFRA* can also form a fusion gene with *FIP1L1* in some patients with HES. Patients with *PDGFRA-PIP1L1* are more likely to be responsive to imatinib, a tyrosine kinase inhibitor. Otherwise, HES appears to be distributed equally among females and males.

Hypereosinophilia is defined as an absolute eosinophil number in the blood that exceeds 1.5×10^9 eosinophils on two separate occasions separated by at least 1 month and/or a tissue diagnosis of hypereosinophilia. Tissues are abnormal when more than 20% of nucleated cells in the bone marrow are of eosinophil origin, a pathologist determines the presence of eosinophilia, or the presence of extensive eosinophilic granule proteins are determined on biopsy to be deposited in large quantities. These disorders can be subclassified into primary (neoplastic), secondary (reactive), and idiopathic (Fig. 448.8).

Clinical manifestations of HES include organ involvement of the heart (5%), gastrointestinal tract (14%), skin (37%), and respiratory system (25–63%). HES is complicated by thrombosis and/or neurologic disease in many patients, although the exact prevalence of this problem is incompletely categorized. Peripheral neuropathy, encephalopathy, transverse sinus thrombosis, or cerebral emboli are the most common neurologic complications. The exact mechanism of the manifestations is unclear, especially in major artery thrombosis such as the femoral artery.

The most frequent pulmonary symptoms include cough and dyspnea. Many patients have obstructive lung disease with clinical wheezing. Evidence of pulmonary fibrosis and pulmonary emboli are seen with regularity. Because biopsy shows eosinophilic infiltrates similar to other pulmonary eosinophilic diseases of the lung, it is the constellation of other organ involvement or thromboembolic phenomena that leads the clinician to a high index of suspicion for HES.

Laboratory evaluation should include evaluation of liver enzymes, kidney function tests, creatine kinase, and troponin. The extent of cardiac involvement should be evaluated by electrocardiogram and echocardiogram. Some unique biomarkers may be tested when evaluating the myeloproliferative and T-lymphocyte HES diagnoses. Vitamin B_{12} and serum tryptase may be elevated, especially the latter, when the myeloproliferative disease is accompanied by mastocytosis. These two biomarkers are most frequently elevated when the *FIP1L1-PDGFRA* fusion pathogenic variant is present.

Because of the extensive pulmonary disease that is seen in HES, pulmonary function tests (spirometry, lung volumes) should be performed at diagnosis. Dead space ventilation may be significantly elevated in patients with pulmonary emboli. Pulse oximetry may be helpful in the evaluation as well.

Chest radiography and CT of the chest are helpful in the evaluation. Spiral chest CT should also be performed when pulmonary emboli are being considered. In one series of patients, nearly half of the patients with HES had evidence of pulmonary abnormalities, including ground-glass–appearing infiltrates, pulmonary emboli, mediastinal lymphadenopathy, and/or pleural effusion.

Treatment of HES depends on the type of variant (myeloproliferative, lymphocytic forms, undefined, associated with systemic diseases such as EGPA, or familial). Rarely, some patients present with marked eosinophilia, where the total count exceeds 100,000 cells/μL, and vascular insufficiency symptoms. Prednisone is indicated to acutely reduce the eosinophil count after diagnostic tests are performed and when safe. If the patient is unstable, the glucocorticoid should be administered to prevent progression of symptoms. Other acute therapies aimed at reduction of eosinophil counts include vincristine, imatinib mesylate, or even leukapheresis. Imatinib is especially used in patients found to have the *FIP1L1-PDGFRA* fusion variant.

When eosinophil counts are not as dramatically elevated, therapy begins with glucocorticoids at 1 mg/kg for patients who do not have the *FIP1L1-PDGFRA* variant. Patients with this variant are resistant

to glucocorticoids, and initial treatment should begin with imatinib, a tyrosine kinase inhibitor. In cases where genetic testing for *FIP1L1-PDGFRA* is not readily available, surrogate markers for the presence of this variant are vitamin B_{12} levels >2,000 pg/mL or serum tryptase >11.5 ng/mL. These findings denote the presence of resistant disease that should initially be treated with imatinib. The goal of therapy is to reduce and maintain eosinophil counts below 1.5×10^9 at the lowest dose of prednisone possible to reduce or avoid corticosteroid-related side effects. If corticosteroid doses cannot be lowered below 10 mg/day, then imatinib can be added as combination therapy in order to spare the dose of steroid. Caution must be used in the presence of cardiac disease, as introduction of imatinib has precipitated left ventricular failure.

Additional or alternative adjunct therapies that have shown promise include hydroxyurea, IFN-α, anti–IL-5 monoclonal antibody therapy, and a monoclonal antibody directed against CD52. Failure of these modalities may signal a need for hematopoietic stem cell transplantation. This therapy has been successful in some patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

448.5 Interstitial Lung Disease

Timothy J. Vece and Stephanie D. Davis

Interstitial lung disease in children (chILD) is caused by a large group of rare, heterogeneous, familial, or sporadic diseases that involve the pulmonary parenchyma and cause significant impairment of gas exchange (Tables 448.16-448.18). Although there are some shared diseases, childhood ILD is often different from ILD in adults, especially notable for the absence of IPF in children. Furthermore, certain ILDs only occur in children (e.g., neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis). Despite wide variations in cause, these disorders are classified together because of the similar clinical, physiologic, radiographic, and pathologic processes involving disruption of the alveolar interstitium and/or airways. Prevalence estimates vary widely with a range of 0.13-16.2 cases/100,000 children. This large range in prevalence is likely a result of the lack of standardization of the diseases that are included in the definition of ILD in children. The pathophysiology is more complex than that of adult disease because pulmonary injury occurs during the process of lung growth and differentiation. In ILD, the initial injury causes damage to the alveolar epithelium and capillary endothelium. Genetic causes of ILD are becoming increasingly important, especially the disorders of surfactant metabolism (DSM) and immune dysregulatory disorders.

CLASSIFICATION AND PATHOLOGY

Through the work of the children's ILD research network in the United States and the children's ILD-European Union group, consensus on a classification scheme has been reached. The classification is broken down based on histologic pattern and by age, with 2 years of age serving as a cutoff. The classification scheme was first applied to biopsies from children less than 2 years of age and was later extended to children greater than 2 years of age (see Tables 448.16 and 448.17). Growth disorders such as alveolar simplification, unique diseases of infancy such as neuroendocrine cell hyperplasia of infancy **(NEHI)**, and disorders of surfactant metabolism **(DSM)** are common in children less than 2 years of age. In contrast, disorders of the immunocompromised host, such as ILD related to immune deficiency, and disorders of systemic diseases such as the collagen vascular disorders, are much more common in older children.

Neuroendocrine Cell Hyperplasia of Infancy

See Chapter 448.6.

Table 448.16 The Pediatric Interstitial Lung Diseases in Children Under 2 Years of Age

AGE-RELATED INTERSTITIAL LUNG DISEASES IN INFANCY AND EARLY CHILDHOOD
Diffuse developmental disorders
Acinar dysplasia
Congenital alveolar dysplasia
Alveolar capillary dysplasia with misalignment of pulmonary veins (some caused by *FOXF1* pathogenic variants)
Growth abnormalities reflecting deficient alveolarization
Pulmonary hypoplasia
Chronic neonatal lung disease
Chromosomal disorders
Congenital heart disease
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenosis (infantile cellular interstitial pneumonia)
Surfactant dysfunction disorders (pulmonary alveolar proteinosis)
Surfactant protein B variant
Surfactant protein C variant
ABCA3 variant
Granulocyte-macrophage colony-stimulating factor receptor *(CSF2RA)* variant
NKX2.1 (transcription factor for SP-B, SPC, ABCA3)
INTERSTITIAL LUNG DISEASE DISORDERS WITH KNOWN CAUSES
Infectious/postinfectious processes
Adenovirus viruses
Influenza viruses
Chlamydia pneumoniae
Mycoplasma pneumoniae
Environmental agents
Hypersensitivity pneumonitis
Toxic inhalation
Aspiration syndromes
PULMONARY DISEASES ASSOCIATED WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCY
Opportunistic infections
Granulomatous lymphocytic interstitial lung disease associated with common variable immunodeficiency syndrome
Lymphoid intestinal pneumonia (HIV infection)
Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection
IDIOPATHIC INTERSTITIAL LUNG DISEASES
Desquamative interstitial pneumonitis
Lymphocytic interstitial pneumonitis and related disorders
Nonspecific interstitial pneumonitis (cellular/fibrotic)
Eosinophilic pneumonia
Bronchiolitis obliterans syndrome
Pulmonary hemosiderosis and acute idiopathic pulmonary hemorrhage of infancy
Pulmonary vascular disorders
Pulmonary lymphatic disorders
Pulmonary microlithiasis
SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS
Anti-GBM disease
Granulomatosis with polyangiitis
Microscopic polyangiitis
Idiopathic pulmonary capillaritis
Gaucher disease and other storage diseases
Malignant infiltrates
Hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Sarcoidosis
Systemic sclerosis
Polymyositis/dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Lymphangioleiomyomatosis
Pulmonary hemangiomatosis
Neurocutaneous syndromes
Hermansky-Pudlak syndrome

Modified from Deutsch GH, Young LR, Deterding RR, et al. Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med.* 2007;176:1120–1128.

Table 448.17 The Pediatric Interstitial Lung Diseases in Children over 2 Years of Age

DISORDERS OF THE IMMUNOCOMPETENT HOST
Disorders of Infancy
Growth abnormalities
NEHI
Disorders of surfactant metabolism
Systemic Disease
Immune-mediated disorders
• Connective tissue disease related lung disease
• Pulmonary hemorrhage syndromes
Storage diseases
Sarcoidosis
DISORDERS OF THE IMMUNOCOMPROMISED HOST
Opportunistic infections
Related to treatment
• Chemotherapy
• Radiation
Drug hypersensitivity
Related to transplantation
• Rejection
• GVHD
• PTLD
Lymphoid Infiltrates

GVHD, Graft-versus-host disease; NEHI, neuroendocrine cell hyperplasia of infancy; PTLD, posttransplant lymphoproliferative disease.
Modified from Fan LL, Dishop MK, Galambos C, et al. Diffuse lung disease in biopsied children 2 to 18 years of age. Application of the chILD Classification Scheme. *Ann Am Thorac Soc.* 2015;12(10):1498–1505.

Disorders of Surfactant Metabolism

One of the more important groups of disorders in childhood ILD is the **DSM** (Table 448.19). These disorders likely account for previously unknown cases of neonatal respiratory distress in full-term infants. Surfactant protein B deficiency, caused by pathogenic variants in the surfactant protein B gene, leads to severe neonatal respiratory distress. Chest CT imaging often reveals a pattern of diffuse ground-glass opacities with septal thickening. Histopathology reveals alveolar proteinosis with interstitial widening, and electron microscopy shows disorganized lamellar bodies. Most children die within the first 2 months of life without a lung transplant. Surfactant protein C deficiency can cause disease in older infants, children, or adults. Chest CT imaging reveals diffuse ground-glass opacities with septal thickening early in the disease or significant fibrosis and honeycombing with cyst formation in more advanced disease. Histopathologic findings vary with age, with alveolar proteinosis and interstitial widening seen in young children, and fibrosis seen in older children and adults. Electron microscopy reveals normal lamellar bodies. *ABCA3* variants cause variable lung disease in children, with some having severe disease similar to surfactant protein B deficiency, whereas others have less severe disease similar to surfactant protein C. Chest CT imaging most often reveals diffuse ground-glass opacities with septal thickening early in the disease (Fig. 448.9). Histopathology depends on the age of the child; however, electron microscopy shows characteristic changes in the lamellar bodies with an eccentric electron dense body without the characteristic concentric circles, the so-called *fried egg appearance*. **DSM** caused by pathogenic variants in the gene *NKX2.1* has also been described. *NKX2.1* encodes for thyroid transcription factor 1 (TTF-1), which is a major regulator of surfactant protein transcription. Pathogenic variants in *NKX2.1* cause variable disease in the lungs, brain, and thyroid **(brain-lung-thyroid syndrome)** (see Table 448.19). Lung disease is variable and can present similar to surfactant protein B deficiency, similar to surfactant protein C deficiency, or as recurrent pulmonary infections. Finally, variants in the α and β subunits of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor leads to alterations in surfactant catabolism. Alveolar macrophages are critical for surfactant recycling and are unable to perform this function effectively in patients with these variants. The inability to recycle surfactant leads to subsequent accumulation of proteinaceous material and pulmonary alveolar proteinosis.

Interstitial Lung Disease Due to Systemic Disease

ILD due to systemic disease is more common in older children with diffuse lung disease. The most common lung disease seen on biopsy is nonspecific interstitial pneumonia; however, other patterns are seen depending on the underlying disorder. For example, lymphocytic interstitial pneumonia may be seen in Sjögren syndrome or cryptogenic organizing pneumonia in dermatomyositis. Findings on chest CT scans depend on the underlying ILD, with nonspecific interstitial pneumonia revealing areas of ground-glass opacities and septal thickening in the early cellular phase of the disease (Fig. 448.10) and progressing to diffuse fibrosis with traction bronchiectasis and peripheral cysts in the later fibrotic stage of the disease. The exact mechanism for disease is unknown but likely is caused by autoantibodies to respiratory tissue.

Pulmonary vasculitis, either caused by granulomatosis with polyangiitis, microscopic polyangiitis, idiopathic pulmonary capillaritis, or anti-GBM syndrome (formerly Goodpasture disease), is another common manifestation of systemic diseases. The disease is likely the result of autoantibody stimulation of lymphocytes with resultant inflammation of pulmonary endothelium causing interstitial changes and pulmonary hemorrhage. Histopathology reveals diffuse alveolar hemorrhage, interstitial widening, and with the exception of anti-GBM disease, neutrophilic inflammation of the pulmonary vasculature.

Genetic causes of immune dysregulation may also be responsible for ILD in children. Pathogenic variants in both *STAT3b* and *LRBA* have been shown to cause lymphocytic interstitial pneumonia and lymphoproliferative disease. Pathogenic variants in coatomer-associated protein-alpha *(COPA)*, a protein involved in endoplasmic reticulum to Golgi transport, cause familial pulmonary hemorrhage and/or ILD.

Persistent pulmonary symptoms can occur after respiratory infections caused by adenoviruses, influenza viruses, *Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*. The resultant pulmonary disease is called **bronchiolitis obliterans** and is characterized by obstructive lung disease and obliteration or constriction of the bronchioles on lung biopsy. There is a characteristic appearance on HRCT of the chest with mosaicism, vascular attenuation, and central bronchiectasis, which if present, can obviate the need for lung biopsy (Fig. 448.11). Aspiration is a frequent cause of chronic lung disease in childhood and can mimic ILD. Children with developmental delay or neuromuscular weakness are at an increased risk for aspiration of food, saliva, or foreign matter secondary to swallowing dysfunction and/or gastroesophageal reflux (GER). An undiagnosed tracheoesophageal fistula can also result in pulmonary complications related to aspiration of gastric contents leading to interstitial pneumonia.

Children experiencing an exaggerated immunologic response to organic dust, molds, or bird antigens may demonstrate hypersensitivity pneumonitis. Children with malignancies may have ILD related to the primary malignancy, an opportunistic infection, or related to chemotherapy or radiation treatment.

CLINICAL MANIFESTATIONS

A detailed history is needed to assess the severity of symptoms and the possibility of an underlying systemic disease in a patient with suspected ILD. One should also ask about any family history of lung disease. Identification of precipitating factors, such as exposure to

Table 448.18 Pathogenic Variants Associated with Children's Interstitial and Diffuse Lung Disease

DISORDER (GENE)	INHERITANCE	CLINICAL PRESENTATION	TREATMENT APPROACH
ABCA3 deficiency *(ABCA3)*	Autosomal recessive	Loss of functional protein causes severe respiratory failure in newborn babies or gradual development of respiratory symptoms in older children and adults	Reported responses to immune suppression with hydroxychloroquine; azithromycin; lung transplantation considered
COPA syndrome *(COPA)*	Autosomal dominant	Autoimmune interstitial lung, joint, and kidney disease arising in the first 2 decades of life	Janus kinase inhibitors; lung transplantation considered
Pulmonary alveolar proteinosis (colony stimulating factor 2 receptor α *[CSF2RA]*)	X-linked	Primary PAP; dyspnea and cough in early childhood	Whole lung lavage
Pulmonary alveolar proteinosis (colony-stimulating factor 2 receptor β *[CSF2RB]*)	Autosomal recessive	Primary PAP; dyspnea and cough in early childhood	Whole lung lavage
Filamin A syndrome *(FLNA)*	X-linked recessive	Dyspnea in infancy	Symptomatic; lung transplantation considered
Alveolar capillary dysplasia with misalignment of the pulmonary veins *(FOXF1)*	Autosomal dominant (usually with paternal imprinting)	Acute respiratory distress within first few hr of birth; without transplant few survive to 1 yr	Lung transplantation considered
Immunodeficiency 21: profound deficiency with pulmonary alveolar proteinosis *(GATA2)*	PAP form is autosomal dominant	Profound B-cell loss with normal T-cell numbers leads to opportunistic infection and PAP	Hematopoietic stem cell transplantation
Interstitial lung and liver disease (*MARS*[methionyl-tRNA synthetase])	Autosomal recessive	Failure to thrive, hypotonia, intermittent lactic acidosis, severe cirrhosis, respiratory failure (PAP), and interstitial lung disease in infancy or early childhood	Symptomatic; whole lung lavage considered
Brain-lung-thyroid syndrome *(NKX2-1)*	Autosomal dominant	Infant respiratory distress and recurrent pulmonary infection with associated hypothyroidism and neurologic impairment	Symptomatic; lung transplantation considered
Lung disease, immunodeficiency, and chromosome breakage syndrome *(NSMCE3)*	Autosomal recessive	Failure to thrive in infancy with immunodeficiency and viral-induced fatal lung disease	Hematopoietic stem cell transplantation
Infantile-onset pulmonary alveolar proteinosis *(OAS1)*	Autosomal dominant	Onset of dyspnea and respiratory distress often associated with a viral infection; hypogammaglobulinemia and splenomegaly	Hematopoietic stem cell transplantation
Surfactant protein B deficiency *(SFTPB)*	Autosomal recessive	Acute neonatal fatal respiratory distress; some reports of dyspnea in older children	Symptomatic; lung transplantation considered
Surfactant protein C mutation *(SFTPC)*	Autosomal dominant	Acute neonatal respiratory distress, but also presents in older children and adults	Consider corticosteroids and hydroxychloroquine; lung transplantation considered in severe or progressive cases
Lysinuric protein intolerance *(SLC7A7)*	Autosomal recessive	Short stature, hepatosplenomegaly; recurrent infection; early childhood respiratory failure in some (PAP); pulmonary fibrosis in a third in later life	Poor response to GMCSF; low-protein diet and citrulline supplementation
Acinar dysplasia *(TBX4)*	Autosomal dominant	Acute fatal neonatal respiratory insufficiency; patellar aplasia or hypoplasia syndrome; pulmonary arterial hypertension	Lung transplantation considered
STING associated vasculopathy with onset in infancy *(TMEM173)*	Autosomal dominant	Infant-onset systemic inflammation with skin lesions, vasculopathy, and pulmonary fibrosis	Janus kinase inhibitors

PAP, Pulmonary alveolar proteinosis; GMCSF, granulocyte-macrophage colony-stimulating factor.
From Cunningham S, Jaffe A, Young LR. Children's interstitial and diffuse lung disease. *Lancet Child Adolesc.* 2019;3:568–577.

Table 448.19 Clinical Features, Age, and Onset of Surfactant Protein Dysfunction Syndromes (SPDS)

SPDS	CLINICAL FEATURES	AGE AND ONSET
SFTPB	*Neonatal* • Respiratory distress	Neonate, acute
ABCA3	*Neonatal* • Respiratory distress *Infancy* • Cough • Tachypnoea, hypoxemia • Failure to thrive *Childhood* • Wheeze, crackles • Exercise intolerance • Dyspnea • Retractions, crackles, digital clubbing • Low body weight	Neonate, acute Infancy and childhood, subacute Late childhood and adulthood, chronic
SFTPC	*Neonatal* • Respiratory distress *Childhood* • Cough • Tachypnea, hypoxemia	Neonate, acute (infrequent) Infancy and childhood, subacute Late childhood and adulthood, chronic
NKX2.1	*Respiratory* • Neonatal respiratory distress • Recurrent infections • Chronic interstitial lung disease *Neurologic* • Chorea • Ataxia • Developmental delay • Hypotonia • Hypothyroidism	Any age Acute or chronic
GMCSFR	*Infancy* Respiratory distress Cough	*Infancy* Chronic
Anti-GMCSF antibodies	Respiratory Cough Exercise intolerance Hypoxemia	*Teenage years* Chronic

ABCA3, ATP binding cassette number A3.
From Gupta A, Zheng SL. Genetic disorders of surfactant protein dysfunction: when to consider and how to investigate. *Arch Dis Child.* 2017;102:84–90, Table 2, p. 86.

molds or birds and a severe lower respiratory infection, is important in establishing the diagnosis and instituting potential avoidance measures. Patients may develop hypoxia and hypercarbia. Tachypnea, crackles on auscultation, retractions, and digital clubbing may be noted on physical examination in children with ILD. However, chest physical examination findings can be normal. Failure to thrive, likely because of increased work of breathing leading to high caloric needs, is also common in ILD. Wheeze and fever are less common but have been noted in childhood ILD, especially in bronchiolitis obliterans. Cyanosis accompanied by a prominent P_2 heart sound is indicative of severe disease with the development of secondary pulmonary hypertension. Anemia or hemoptysis suggests a pulmonary vascular disease or pulmonary hemosiderosis. Rashes or joint complaints are consistent with an underlying connective tissue disease.

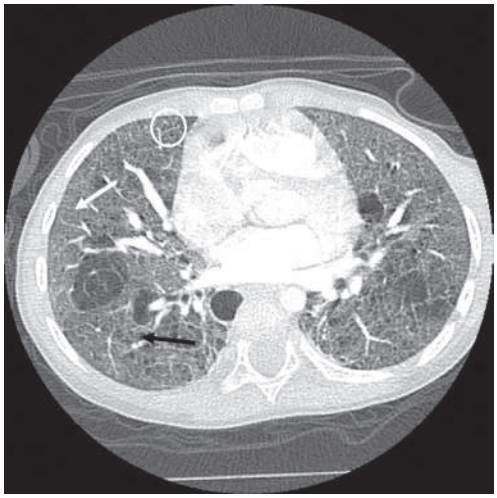

Fig. 448.9 Chest CT from a 2-year-old with a disorder of surfactant metabolism from pathogenic variants in *ABCA3*. Note the ground-glass opacities *(white arrow)*, septal thickening *(circle)*, and early cyst formation *(black arrow)*. *(Courtesy R. Paul Guillerman, MD.)*

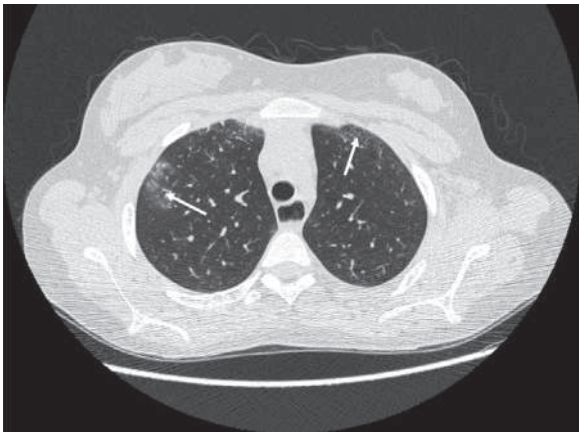

Fig. 448.10 Chest CT from an 11-yr-old patient with systemic sclerosis and cellular nonspecific interstitial pneumonia. Note the areas of ground-glass opacities in the periphery *(arrows)*. *(Courtesy R. Paul Guillerman, MD.)*

DIAGNOSIS

Radiography

Chest radiographic abnormalities can be classified as interstitial, reticular, nodular, reticulonodular, or honeycombed. The chest radiographic appearance may also be normal despite significant clinical impairment and may correlate poorly with the extent of disease. HRCT of the chest better defines the extent and distribution of disease and can provide specific information for selection of a biopsy site. Chest CT imaging may reveal air trapping, ground-glass patterns, mosaic patterns of attenuation, hyperinflation, bronchiectasis, cysts, and/or nodular opacities. Serial HRCT scans have been beneficial in monitoring disease progression and severity.

Pulmonary Function Tests

Pulmonary function tests are important in defining the degree of respiratory dysfunction and in following the response to treatment. In ILD, pulmonary function abnormalities demonstrate a restrictive ventilatory deficit with decreased lung volumes and reduced

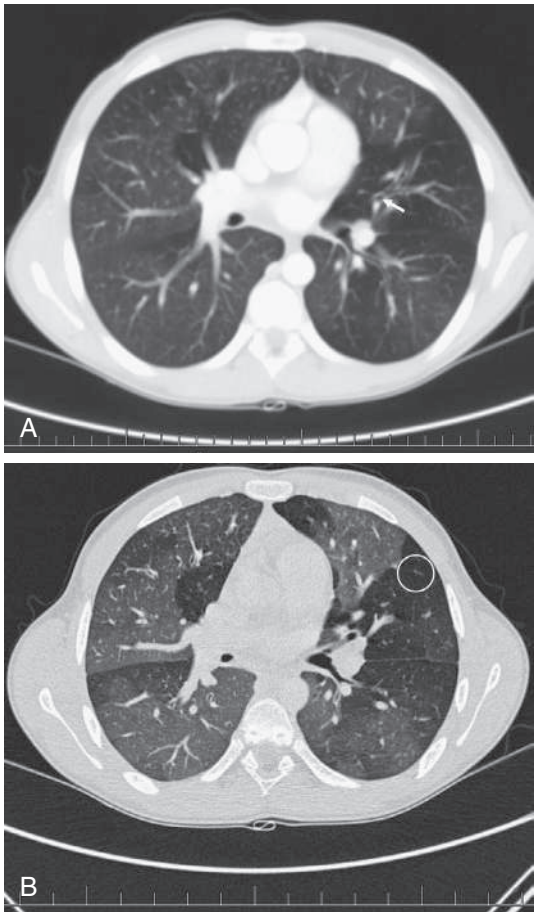

Fig. 448.11 Chest CT from an 11-yr-old patient with bronchiolitis obliterans after Stevens-Johnson syndrome. **A,** Volumetric scan at full inspiration shows central bronchiectasis *(arrow)* and mosaic attenuation. **B,** High-resolution image taken in exhalation better highlights the mosaic attenuation and vascular attenuation *(circle)*.

lung compliance. However, obstructive impairment may be seen in some forms of ILD such as bronchiolitis obliterans. The functional residual capacity is often reduced but is usually less affected than vital capacity and total lung capacity (TLC). The residual volume (RV) is usually maintained; therefore ratios of functional residual capacity:total lung capacity and RV:TLC are increased. Diffusion capacity of the lung is often reduced. Exercise testing may detect pulmonary dysfunction, even in the early stage of ILD, with a decline in oxygen saturation.

Bronchoalveolar Lavage

BAL may provide helpful information regarding secondary infection, bleeding, and aspiration and allows cytology and molecular analyses. Evaluation of cell counts, differential, and lymphocyte markers may be helpful in determining the presence of hypersensitivity pneumonitis or sarcoid. Although BAL does not usually determine the exact diagnosis, it can be diagnostic for disorders such as pulmonary alveolar proteinosis.

Lung Biopsy

Lung biopsy for histopathology by conventional thoracotomy or video-assisted thoracoscopy *is sometimes the final step and is often necessary for a diagnosis*. Biopsy yields a diagnosis in greater than 80% of patients. Because of the low diagnostic yield, transbronchial biopsies are not recommended for the evaluation of ILD in children. Evaluation for possible systemic disease may also be necessary.

Molecular Diagnosis

For those genetic-based disorders, gene panels or whole exome sequencing may yield a rapid diagnosis (see Table 448.18).

TREATMENT

Supportive care of patients with ILD is essential and includes supplemental oxygen for hypoxia and adequate nutrition for growth failure. Antimicrobial treatment may be necessary for secondary infections. Some children may receive symptomatic relief from the use of bronchodilators. Antiinflammatory treatment with corticosteroids remains the initial treatment of choice for many forms of childhood ILD. Controlled trials in children are lacking, however, and the clinical responses reported in case studies are variable. The usual dose of prednisone is 1-2 mg/kg/24 hr or 10-30 mg/kg of IV methylprednisolone given either weekly or for 3 consecutive days per month. Treatment length varies but is often initially given for 3-6 months with tapering of dosage dictated by clinical response. Alternative but not adequately evaluated agents include hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and IVIG. Investigational approaches involve specific agents directed against the action of cytokines, growth factors, or oxidants. In severe, progressive, or end-stage ILD, lung transplantation is an option, and outcomes are similar to other end-stage lung diseases in children. Appropriate treatment for underlying systemic disease or aspiration syndrome is indicated. Preventive measures include avoidance of all inhalation irritants, such as tobacco smoke and, when appropriate, molds and bird antigens. Supervised pulmonary rehabilitation programs may be helpful.

For those disorders with fibrotic ILD, antifibrotic therapy may be another option. The greatest experience with antifibrotic therapy has been in adults with IPF. Other indications for antifibrotic therapy include fibrosing ILD, autoimmune ILD, hypersensitivity pneumonitis, and nonspecific ILD. Nintedanib and pirfenidone have been approved for patients ≥18 years; both have demonstrated efficacy in slowing the decline in pulmonary function.

Genetic Counseling

A high incidence of ILD in some families suggests a genetic predisposition to either development of the disease or severity of the disorder. Genetic counseling may be beneficial if a positive familial history is obtained.

PROGNOSIS

The overall mortality of ILD is variable and depends on the specific diagnosis. Some children recover spontaneously without treatment, but other children steadily progress to death. Pulmonary hypertension and severe fibrosis are considered poor prognostic indicators.

ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE (ANTI-GBM DISEASE)

Anti-GBM disease, formerly known as Goodpasture disease, is the prototypical immunologic-mediated ILD (see Chapter 560.4). Because of the concurrent presentation of renal (glomerulonephritis) and pulmonary (alveolar hemorrhage) disease, the differential diagnosis focuses on distinguishing anti-GBM disease from vasculitis, infection, and other syndromes such as GPA, microscopic polyangiitis, Henoch-Schönlein purpura, and idiopathic pulmonary hemorrhage syndromes.

Pathophysiology

Immunology Factors

The development of anti-GBM antibodies against antigens that are present on the basement membranes of the glomerulus and alveolar directly correlates with the development of pulmonary and renal

disease. Removal of such antibodies by plasmapheresis results in improvement of the disease process in some patients but not in all.

Genetic Factors

Genetics appears to contribute strongly to the development of this disease, with the presence of MHC class II alleles DR15, DR4, DRB1*1501, DRB1*04, and DRB1*03 predisposing to disease. The disease is triggered by environmental factors in those with a genetic predisposition. There may be other genetic factors as well, and our understanding of the genetics involved in anti-GBM disease is evolving.

Environmental Factors

Exposure to cigarette smoke appears to be a strong factor in the development anti-GBM disease. Whether smoking alters the ultrastructure of the basement membrane or exogenous particles or noxious substances in smoke alter the type IV collagen is unknown. Smokers are more likely to develop pulmonary hemorrhage than nonsmokers who have anti-GBM disease. Other injuries to the alveoli from infection, hydrocarbon inhalation, or cocaine inhalation have been reported as associated events before the development of anti-GBM disease.

Clinical Manifestations

The majority of patients present with many days or weeks of cough, dyspnea, and fatigue, and up to 60% present with hemoptysis. Young children tend to swallow small amounts of blood from hemoptysis and may present with vomiting blood. Occasionally, the hemoptysis is large and resultant anemia is a consequence of large quantities of blood loss. Younger patients tend to present with both the pulmonary and renal syndrome concurrently. Adults are less likely to develop pulmonary disease.

Laboratory

Serologic detection of anti-GBM antibodies is positive in more than 90% of patients with anti-GBM disease. A complete blood count may show anemia that is normocytic and normochromic, as seen in chronic inflammatory disease. Urinalysis may reveal hematuria and proteinuria, and blood tests demonstrate renal compromise with elevated blood urea nitrogen and creatinine. Studies for ANCAs should also be performed and are positive in approximately 25–30% of patients concurrently with anti-GBM antibodies. The ANCA that is often positive is anti–myeloperoxidase ANCA.

Chest Radiography

Chest radiography in anti-GBM disease will often show widely scattered patches of pulmonary infiltrates. If these infiltrates are in the periphery of the lung, they may be difficult to distinguish from the eosinophilic lung diseases. Interstitial patterns of thickening may be found as well. HRCT of the chest reveals a diffuse ground-glass pattern or opacities.

Pulmonary Function Testing

Spirometry may be suggestive of a restrictive defect with reduction in FVC and FEV_1. DLCO is a valuable test when pulmonary hemorrhage is a strong consideration. The intent of this test is to measure the ability of the lung to transfer inhaled gas to the red blood cell in the pulmonary capillary bed. This test takes advantage of hemoglobin's high affinity to bind carbon monoxide. Current data suggest that DLCO directly correlates with the volume of blood in the pulmonary capillary bed. In pulmonary hemorrhage syndromes, blood in the alveoli plus the blood in the capillary bed increase the DLCO significantly and should alert the clinician to the possibility of pulmonary hemorrhage.

Bronchoscopy and Bronchoalveolar Lavage

Defining pulmonary hemorrhage can often be best assessed through bronchoscopy with BAL. The visual presence of blood during bronchoscopy will be obvious. Infections must be ruled out in many cases. The cytology from the BAL may reveal hemosiderin-laden macrophages through Prussian blue staining. These macrophages would have engulfed and broken down the red blood cells, leaving iron in these cells.

Tissue Histopathology

The most common tissue obtained for diagnosis is a kidney biopsy. Kidney biopsies most commonly reveal crescentic glomerulonephritis with positive anti-GBM. Staining for IgG and complement is found by immunofluorescence along the basement membrane in a linear pattern. This antibody deposition pattern led to the investigation of endogenous antigens in the basement membrane. Although less likely to be performed in anti-GBM disease, lung biopsy in patients with active disease reveals capillaritis from neutrophils, hemosiderin-laden macrophages, type II pneumocyte hyperplasia, and interstitial thickening at the level of the alveolus.

Treatment

More than half of patients with anti-GBM disease who forego treatment die within 2 years from either respiratory failure, renal failure, or both. After a diagnosis is made, therapy with corticosteroids coupled with oral cyclophosphamide is initiated. The addition of daily plasmapheresis may accelerate improvement. Alternative therapies are rituximab or mycophenolate. Anti-GBM antibodies are monitored during treatment. Survival is affected by the need for ongoing dialysis. Kidney transplant is an option for those with significant renal impairment. Patients who do not require persistent dialysis have a survival rate at 1 year of 80% or more.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

448.6 Neuroendocrine Cell Hyperplasia of Infancy

W. Adam Gower

NEHI is an idiopathic form of diffuse lung disease that typically presents during the first year of life with persistent tachypnea, retractions, hypoxemia, crackles, and failure to thrive. Initial descriptions of NEHI used the term *persistent tachypnea of infancy*; some authors now use this to refer to both NEHI and pulmonary interstitial glycogenosis. Characteristic findings are seen on chest imaging studies and lung histopathology. Pulmonary function studies typically demonstrate an obstructive pattern with air trapping. *There are no effective specific therapies for NEHI, and the usual approach is supportive care.* The natural course is typically one of gradual improvement of symptoms, although exacerbations may occur throughout childhood, and potentially into adulthood. The long-term consequences of this disorder are not well-delineated.

EPIDEMIOLOGY

The prevalence of NEHI is not known, but it is generally considered to be a rare lung disease. Some studies have noted a slight male predominance. Otherwise, no other clear maternal or patient-level risk factors have been identified. Cases of NEHI have been reported in the literature from North and South America, Europe, Asia, and Australia.

PATHOPHYSIOLOGY

The primary clue to the pathophysiology of NEHI is increased numbers of neuroendocrine cells (NECs) in the airways of affected children. NECs are normally found in the airways, where they exist as both as individual cells and innervated clusters known as *neuroendocrine bodies* (NEBs), and secrete factors such as gastrin releasing peptide (GRP) and serotonin (5-HT). They are thought to be involved in local oxygen sensing and may transmit signals to other cells. Increases in NECs are seen in several respiratory disorders

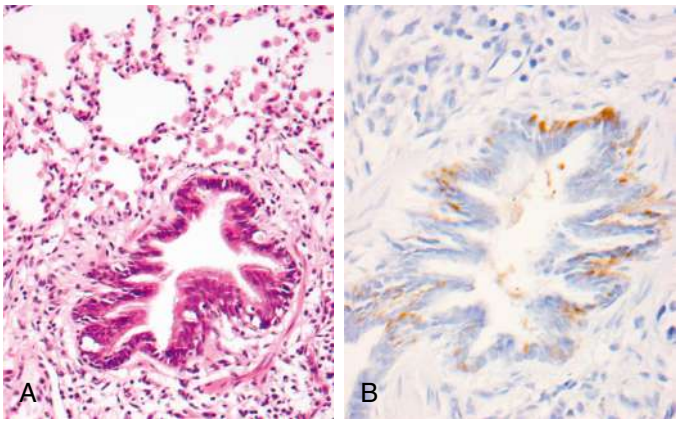

Fig. 448.12 Neuroendocrine cell hyperplasia of infancy. **A,** A small airway showing only minimal chronic inflammation on routine staining. **B,** Staining for bombesin shows increased numbers of neuroendocrine cells within the surface epithelium. *(From Corrin B, Nicholson AG. Pathology of the Lungs, 3rd ed. Philadelphia: Churchill Livingstone; 2011: Fig. 2.19.)*

of childhood, usually with other additional findings, where they are thought to be reactive to other primary pathology. It is unclear whether their presence in increased numbers in NEHI causes the clinical picture or is the result of abnormal pulmonary physiology secondary to some other primary factor. Increased numbers of NECs seem to be associated with increased small airway obstruction in those with NEHI.

Although most cases appear to be sporadic, familial NEHI has been described, suggesting a possible inherited mechanism and/or shared environmental factors between affected siblings. The association of NEHI with heterozygosity for a variant in the gene *Nkx2.1* has been described in one kindred. Variants in this gene are also known to cause a wide spectrum of disorders, including more severe forms of diffuse lung disease (see Chapter 448.5).

CLINICAL PRESENTATION

The symptoms of NEHI characteristically appear during infancy, although the diagnosis may be delayed until after the first year of life. The typical presentation includes persistent tachypnea, hypoxemia, retractions, and poor weight gain in an otherwise healthy infant. The exam reveals crackles or clear lung sounds, and cough, wheezing, and digital clubbing are not typical.

DIAGNOSIS

The diagnosis of NEHI requires that other more common causes of the presenting symptoms be ruled out. Strong consideration should be given to consultation with a pediatric pulmonologist when possible. Although children with NEHI may have comorbid GER and/or swallowing dysfunction, this is thought to be secondary to tachypnea and increased work of breathing rather than the cause of respiratory symptoms. Plain chest films may show hyperinflation. When biopsy material from the lung is stained with immunohistochemical reagents highlighting bombesin, increased numbers of positive-staining cells are noted in the airways. In general, biopsies from children with NEHI are remarkably void of fibrosis, inflammation, or signs of injury (Fig. 448.12).

Although the pattern of NEC hyperplasia seen in histopathology has classically been the gold standard for diagnosis of NEHI, HRCT of the chest has a high specificity, such that biopsy may be avoided in most cases. The classic pattern seen on chest CT is ground-glass opacities

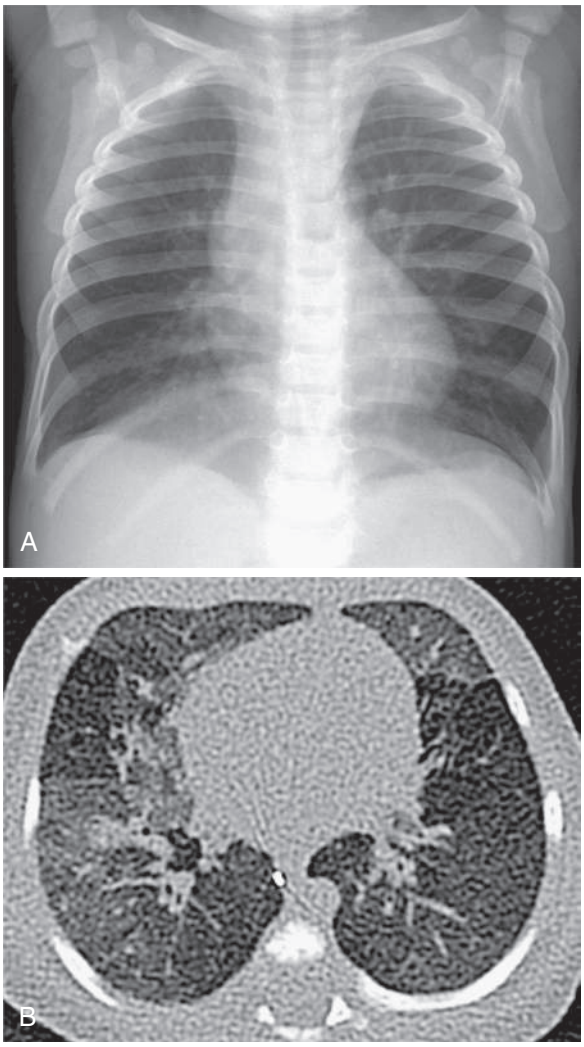

Fig. 448.13 **A,** Neuroendocrine cell hyperplasia of infancy in a 15-mo-old. Chest radiograph demonstrates pulmonary hyperinflation and parahilar opacities resembling reactive airways disease or bronchiolitis. **B,** Neuroendocrine cell hyperplasia of infancy. Axial expiratory CT image shows characteristic geographic ground-glass opacities involving the paramediastinal right middle lobe and lingula and the right lower lobe. *(From Zucker EJ, Lee EY. Diffuse lung disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Figs. 56.7 and 56.8, p. 541.)*

in the lingula, right middle lobe, and perihilar regions, with air trapping on expiratory images. The lungs otherwise appear normal (Fig. 448.13). If a patient with clinically diagnosed NEHI has a more severe clinical course than expected, biopsy may be helpful to rule out other pathology.

The diagnosis of NEHI is supported by an obstructive pattern that does not reverse with bronchodilators, on either infant pulmonary function testing (iPFT) or standard spirometry. Static lung volumes may show air trapping with increased RV relative to the TLC. BAL findings are notable for lack of inflammatory markers, as compared to other pulmonary diseases of infancy.

Genetic testing may be useful to rule out disorders of surfactant metabolism and other causes of infant diffuse lung disease. Targeted testing for variants in *Nkx2.1* can be considered, but as this association has been found in only one kindred thus far, the diagnostic value of such testing is limited.

NATURAL COURSE AND TREATMENT

Because the symptoms of NEHI typically improve and eventually largely resolve over the first few years of life, the standard approach to treatment of NEHI is supportive. The time frame for clinical improvement in NEHI is variable. Symptoms with rest may improve, whereas those on exertion or with sleep persist. Affected children may require supplemental oxygen to maintain normal saturations, sometimes only with sleep or illnesses, but often at all times. Clinicians should have a low threshold to evaluate for sleep-related breathing disorders, and these should be treated accordingly. Inhaled or systemic corticosteroids are generally not thought to be helpful in treating the primary manifestations of NEHI.

Because they may expend more energy to breathe, children with NEHI may have difficulty gaining weight and often require supplemental nutrition. This may be delivered by gastrostomy tube. Management of GER and/or dysfunctional swallowing, when present, may be helpful. Mild abnormalities of the immune system may be seen in some patients with NEHI and, when present, may be addressed with specific therapy such as prophylactic antibiotics and/or immunoglobulin replacement.

When clinical symptoms improve, the need for supplemental oxygen and/or nutritional support typically decreases, and patients may be weaned as tolerated. Children with NEHI whose symptoms have improved may experience exacerbations later in childhood. These episodes may be associated with increased air trapping.

Although the symptoms of NEHI typically resolve during childhood, limited data suggest that some may persist into the adult years. This may manifest as exercise intolerance or an asthma-like picture. Obstruction with air trapping may be seen on PFT, and persistent abnormalities may be identified on chest imaging. No cases of respiratory failure, need for lung transplantation, or death caused by NEHI have been reported.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

448.7 Fibrotic Lung Disease

Deborah R. Liptzin, Jason P. Weinman, and Robin R. Deterding

Pulmonary fibrosis is scarring in the lung parenchyma (as opposed to bronchiectasis, which is scarring of the airways). Idiopathic pulmonary fibrosis is a common form of fibrotic lung disease in adults. This presents with usual interstitial pneumonia (a pathologic finding with patchy interstitial fibrosis, fibroblastic foci, and honeycomb change) (see Chapter 448.5). Additional adult fibrotic lung diseases include sarcoidosis, silicosis, coal worker's pneumoconiosis, and hypersensitivity pneumonitis (e.g., farmer's lung). In children, fibrotic lung disease is rare, and *idiopathic* pulmonary fibrosis has not been described. The differential diagnosis of *fibrotic* lung disease includes surfactant dysfunction pathogenic variants (see Chapter 444); immunocompromised patients with opportunistic infections, radiation-induced fibrosis, or status-post hematopoietic stem cell transplantation; patients with systemic disease processes that can lead to pulmonary fibrosis (systemic vasculitis, collagen vascular disease, juvenile idiopathic arthritis, storage diseases, Langerhans cell histiocytosis, sarcoidosis, systemic lupus erythematosus, systemic sclerosis, and nonspecific interstitial pneumonia); and pleuropulmonary fibroelastosis. Airway fibrosis can be seen in bronchiolitis obliterans (see Chapter 443.1) and aspiration (see Chapter 446) (Tables 448.20-448.22).

CLINICAL PRESENTATION

Pulmonary fibrosis classically presents with nonspecific respiratory symptoms such as cough, crackles, wheezes, prolonged expiratory phase, exercise intolerance, and hypoxemia, especially at nighttime.

Table 448.20 Diseases Associated with Pulmonary Fibrosis

- Idiopathic pulmonary fibrosis/nonspecific interstitial pneumonia
- Familial pulmonary fibrosis/familial interstitial pneumonia
- Hypersensitivity pneumonitis (many agents)
- Cryptogenic organizing pneumonia
- Adverse reaction to therapy (drugs, radiation)
- Pleuroparenchymal fibroelastosis
- Hermansky-Pudlak syndrome
- Sarcoidosis
- Eosinophilic pneumonia (primary or parasitic)
- Langerhans cell histiocytosis
- Dyskeratosis congenita
- Tuberous sclerosis
- Neurofibromatosis
- Erdheim-Chester disease
- Gaucher disease
- Niemann-Pick disease
- Familial hypocalciuric hypercalcemia
- Lysinuric protein intolerance
- IgG4-mediated immune disorder
- Myelodysplastic syndrome
- Progressive systemic sclerosis
- Other connective tissue diseases (SLE, dermatomyositis)
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

Symptom onset can be insidious or rapid. In children, oxygen desaturation with activity may be the earliest sign of fibrotic lung disease, and cough, crackles, and wheezes may be later findings. Children with surfactant dysfunction pathogenic variants can present with respiratory failure in the neonatal period.

EVALUATION

Pulmonary function tests typically show restriction and reduced diffusion capacity. Air trapping can also be seen. Patients may desaturate with exercise challenges such as 6-minute walks, and this may be the first indication of disease in children.

There are a variety of findings on CT scan that suggest pulmonary fibrosis, and these findings can evolve over time. In surfactant dysfunction variants, ground-glass opacities are prominent early on with subsequent evolution to more typical findings of fibrosis such as reticular abnormalities, honeycombing, architectural distortion, and/or traction bronchiectasis. Typical findings in pediatric nonspecific interstitial pneumonia include subpleural sparing, ground-glass opacities, cystic change, reticular abnormalities, and bronchiectasis (Fig. 448.14). Novel measures of quantifying fibrosis have been described in the literature, and CT findings consistent with fibrosis are being used as criteria for study enrollment. Of note, CT findings and pulmonary function tests can be discrepant with stable pulmonary function tests over time, whereas the CT scan can evolve over the same period.

In certain disease processes such as surfactant deficiency (positive genetic testing) or genetic disorders of surfactant metabolism, biopsy is not necessary for diagnosis of fibrosis. Cryobiopsy is becoming popular in the adult pulmonary landscape but is in its infancy in the pediatric pulmonary field. In the absence of a definitive diagnosis, a thoracoscopic wedge biopsy is necessary for diagnosis and to guide treatment. Transbronchial biopsies in pediatrics are of limited utility because the small instruments typically obtain inadequate tissue specimens; transbronchial biopsies in pediatrics are limited to monitoring post–lung transplantation and for diagnosis of sarcoidosis. Pathologic findings in pulmonary fibrosis are variable, depending on the duration and etiology of disease (see Table 448.21), but typically include a component of interstitial inflammation, interstitial expansion by dense collagen, and lobular

Table 448.21 Pediatric Fibrotic Lung Diseases

DISEASES	CT FINDINGS	PATHOLOGY FINDINGS	ADDITIONAL EVALUATION	TREATMENT
Surfactant dysfunction	**Early:** Diffuse ground-glass opacities, septal thickening (crazy paving) **Chronic:** Decreased ground-glass opacities with reticulation and cystic lucencies	Variable: fibrosis, honeycomb cysts at end stage, NSIP, CPI, few globules of pulmonary alveolar proteinosis, foamy macrophages and cholesterol clefts (endogenous lipoid pneumonia)	Genetic testing	Supportive care (nutrition, respiratory support, vaccinations), antifibrotic therapy *plus* hydroxychloroquine, azithromycin, high-dose intravenous steroids; genetic counseling
Aspiration	**Acute:** Consolidation and centrilobular (tree in bud) nodules with a dependent distribution **Chronic:** bronchiectasis, architectural distortion	Airway-centered lesions/ bronchiolitis, food particles with or without granulomas, foamy macrophages (endogenous lipoid pneumonia), organizing pneumonia	Video fluoroscopic or fiberoptic endoscopic swallow evaluation	Stop aspiration through thickening feeds, gastric feeds, cleft repair
Radiation fibrosis	Architectural distortion, volume loss, traction bronchiectasis; often with geometric distribution related to radiation field	Pleural, septal, and paraseptal fibrosis; reactive atypia of alveolar epithelium and endothelium		Steroids may help
Bronchopulmonary dysplasia	Hyperlucent regions, cystic lucencies, architectural distortion (linear and subpleural triangular opacities)	Alveolar simplification and enlargement; patchy hyperinflation; interstitial fibrosis, with or without interlobular septal fibrosis	Consider evaluation for pulmonary hypertension and/or aspiration	Consider inhaled corticosteroids, inhaled steroids, diuretics
Nonspecific interstitial pneumonia (NSIP)	Basilar predominant findings of ground-glass opacities (often with subpleural sparing), reticulation, architectural distortion, and traction bronchiectasis	Interstitial lymphocytic inflammation and fibrosis with homogenous distribution		Consider steroids
Hypersensitivity pneumonitis (chronic)	Patchy and often parahilar reticulation, ground-glass opacities, centrilobular nodules; honeycombing (rare)	Airway-centered small noncaseating granulomas, multinucleated giant cells, lymphocytic bronchiolitis and peribronchiolitis, airway fibrosis, organizing pneumonia	Lymphocytosis in bronchoalveolar lavage, precipitins to specific antigen	Remove trigger, intravenous steroids
Autoimmune connective tissue disorders (collagen vascular disease)	See NSIP; honeycombing (rare)	NSIP; lymphoid hyperplasia; fibrosis and cystic change; pleuritis and pleural fibrosis (variable); chronic vasculopathy (variable); airway fibrosis (variable)	Serologic studies	Disease-specific immune modulation
Drug reactions	Peripheral predominant consolidation or ground glass opacities; reverse halo sign; see NSIP; honeycombing (rare)	Variable: organizing pneumonia, NSIP, UIP, DAD, pulmonary hemorrhage, eosinophilic pneumonia		Drug avoidance
Infection	**Acute:** Consolidation and centrilobular (tree in bud) nodules; appearance and distribution vary with type of infection **Chronic:** May progress to IPF/UIP with honeycombing	**Acute:** Neutrophilic alveolitis (bacterial) or lymphocytic bronchiolitis (viral) **Chronic:** Variable airway fibrosis (constrictive/obliterative bronchiolitis) and interstitial fibrosis		Antimicrobials
Immunodeficiency	Bronchiectasis, consolidation, centrilobular nodules	Follicular bronchiolitis or diffuse lymphoid hyperplasia; NSIP; LIP; GLILD	Immunologic and genetic testing	Treat underlying immunodeficiency
Usual interstitial pneumonia (UIP)	Honeycombing, reticulation, traction bronchiectasis, ground-glass opacities (less prominent than NSIP)	Fibroblast foci; interstitial, septal, and pleural fibrosis with heterogenous distribution; minimal to absent inflammation	Genetic testing	

Table 448.22 Genes Associated with Familial* or Idiopathic Pulmonary Fibrosis

GENE	GENE FUNCTION
IL1RN	Inhibitor of proinflammatory effect of IL-1α and IL-1β
IL8	Proinflammatory cytokine
FAM13A	Signal transduction
TLR3	Pathogen recognition and activation of innate immunity
TERT	Enzyme in telomerase complex maintaining telomere length
HLA-DRB1	Major histocompatibility complex—immune system
DSP	Tightly links adjacent cells
OBFC1	Stimulates the activity of DNA polymerase-α-primase
MUC5B	Influence on rheological properties of airway mucus, mucociliary transport, and airway defense
MUC2	Mucin production
TOLLIP	Regulator of innate immune responses mediated by toll-like receptor and the transforming growth factor β signaling pathway
ATP11A	Phospholipid translocation
MDGA2	Cell-cell interaction
MAPT	Promotes microtubule assembly and stability
SPPL2C	Protein cleavage
DPP9	Cell-cell adhesion
TGFB1	Set of peptides that controls proliferation, differentiation, and other functions in many cell types
SFTPC†	Component of surfactant fluid
SFTPA2†	To modulate innate and adaptive immunity
ABCA3†	Transport of lipids across plasma membrane
TERC†	Template in telomerase complex
DKC1†	Stabilization of the template in telomerase complex
TINF2†	Telomere maintenance
RTELI†	DNA helicase
PARN†	mRNA stability

*Also called familial interstitial pneumonia.
†Rarer variant.
Adapted from Kaur A, Mathai SK, Schwartz DA. Genetics in idiopathic pulmonary fibrosis pathogenesis, prognosis, and treatment. *Frontiers Med.* 2017;4:154, Tables 1 and 2.

remodeling (parenchymal architectural distortion and honeycomb cysts). Interlobular septal fibrosis, pleural fibrosis, and chronic pulmonary arteriopathy are common associated findings. Dense



Fig. 448.14 Chest CT demonstrates typical CT findings in a pediatric patient with nonspecific interstitial pneumonia, including basilar-predominant ground-glass opacities *(blue arrows)*, reticulation *(yellow arrows)*, mild cystic change *(green arrows)*, and bronchiectasis *(orange arrow)*.

globules of pulmonary alveolar proteinosis material in infancy may indicate a genetic disorder of surfactant metabolism. Reactive lymphoid follicles suggest an immunologic process, such as autoimmune disease or immunodeficiency. Organizing pneumonia (polypoid aggregates of fibroblasts, *Masson bodies*) is a common feature in hypersensitivity pneumonitis and autoimmune diseases. The usual interstitial pneumonia pattern signaled by fibroblast foci arising within a background of dense interstitial fibrosis is almost never seen in children. Connective tissue stains, such as Masson trichrome, elastic Verhoff von Giesen, and Movat pentachrome, aid in determining the severity and distribution of collagen deposition.

TREATMENT

Treatment varies based on disease process (see Tables 448.20-448.22). Because of the nature of rare disease, treatment regimens are largely based on expert opinion, as controlled clinical trials are challenging to perform. *Antifibrotic agents approved in adults with fibrotic lung disease include pirfenidone and nintedanib, and weight-based dosing of nintedanib has been shown to have an acceptable safety profile in children.*

Monitoring may include evaluation of pulmonary function (spirometry, lung volumes, and diffusion capacity); functional evaluation of exercise (6-minute walk); and screening for comorbidities such as pulmonary hypertension, aspiration, poor weight gain, and sleep-associated breathing disorders. Respiratory support varies depending on each patient's needs, from no support to oxygen via nasal cannula and with ventilation (noninvasive or invasive); treatments may occur only with exercise and/or sleep or may be all the time. Comorbidities such as pulmonary hypertension or aspiration should be treated appropriately. Genetic counseling and recurrence risk should be provided with genetic forms of fibrotic lung disease. Patients should be counseled about preventing further lung damage from infection (up-to-date on vaccines, including pneumococcus, influenza, SARS-CoV-2, and respiratory syncytial virus) or particulate matter (air pollution, wildfires, wood-burning stoves, and environmental exposure to tobacco or marijuana).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 449

Community-Acquired Pneumonia

Matthew S. Kelly and Thomas J. Sandora

Pneumonia, defined as inflammation of the lung parenchyma, is the leading infectious cause of death globally among children younger than 5 years, accounting for an estimated 880,000 deaths in 2015 (Fig. 449.1). Pneumonia mortality is closely linked to poverty; more than 99% of child pneumonia deaths are in low- and middle-income countries, with the highest pneumonia mortality rate occurring in Africa and South Asia.

In the United States, mortality from pneumonia in children declined by 97% between 1939 and 1996. This decline can largely be attributed to the development of antibiotics and vaccines and the expansion of medical insurance coverage for children. Effective vaccines against measles (see Chapter 293) and pertussis (see Chapter 243) contributed to the decline in child pneumonia mortality during the 20th century. *Haemophilus influenzae* type b (see Chapter 240) was also an important cause of bacterial pneumonia in young children but became uncommon after licensure of a conjugate vaccine in 1987. The introduction of pneumococcal conjugate vaccines (PCVs) (see Chapter 228) has been an important contributor to the further reductions in pneumonia mortality achieved over the past 2 decades. Epidemics (influenza, severe acute respiratory system coronavirus, Middle East respiratory syndrome, respiratory syncytial virus [RSV]) and pandemics (COVID-19) contribute to the incidence, morbidity, and mortality in pediatric patients with pneumonia. In addition, unexpected global increases in group A streptococcus (GAS) infections have contributed to both morbidity and mortality in children with pneumonia.

ETIOLOGY

Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration (of food or gastric acid, foreign bodies, hydrocarbons, and lipoid substances), hypersensitivity reactions, and drug- or radiation-induced pneumonitis (see Chapter 448). The cause of pneumonia in an individual patient is often difficult to determine because direct sampling of lung tissue is invasive and rarely performed. Bacterial cultures of sputum or upper respiratory tract samples typically do not accurately reflect the cause of lower respiratory tract infection in children. *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial pathogen in children 3 weeks to 5 years of age, whereas *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are the most frequent bacterial pathogens in children 5 years and older. In addition to pneumococcus, other bacterial causes of pneumonia in previously healthy children in the United States include GAS (*Streptococcus pyogenes*; see Chapter 229) and *Staphylococcus aureus* (see Chapter 227.1) (Tables 449.1-449.3). *S. pneumoniae* or *S. aureus* pneumonia often complicates an illness caused by influenza viruses.

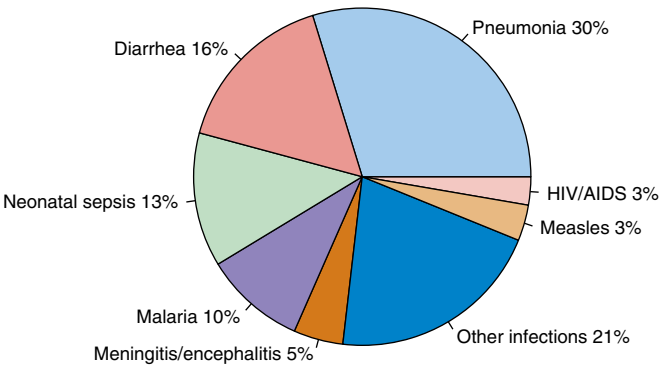

Fig. 449.1 Pneumonia is the leading infectious killer of children worldwide, as shown by this illustration of global distribution of cause-specific infectious mortality among children younger than age 5 yr in 2017. Pneumonia causes nearly one third of all under-5 deaths from infection. *(From World Health Organization Global Health Observatory Data Repository, 2017 estimates.)*

S. pneumoniae, H. influenzae, GAS, and *S. aureus* are the major causes of hospitalization and death from bacterial pneumonia among children in developing countries, although in children with HIV infection, *Mycobacterium tuberculosis* (see Chapter 261), nontuberculous mycobacteria (see Chapter 263), *Salmonella* (see Chapter 244), *Escherichia coli* (see Chapter 246), *Pneumocystis jirovecii* (see Chapter 290), and cytomegalovirus (see Chapter 302) should also be considered. The incidence of pneumonia caused by *H. influenzae* or *S. pneumoniae* has been significantly reduced in areas where routine immunization has been implemented.

Viral pathogens are the most common causes of lower respiratory tract infections in infants and children older than 1 month but younger than 5 years of age (see Table 449.2). Viruses can be detected in 40–80% of children with pneumonia using molecular diagnostic methods (e.g., polymerase chain reaction [PCR]), with more than one respiratory virus identified in up to 20% of cases. Of the respiratory viruses, RSV (see Chapter 307) and rhinoviruses (see Chapter 310) are the most commonly identified pathogens, especially in children younger than 2 years of age. However, the role of rhinoviruses in severe lower respiratory tract infection remains unclear, as these viruses are frequently detected with co-infecting pathogens and among asymptomatic children. Other common viruses causing pneumonia include influenza viruses (see Chapter 305), human metapneumovirus (see Chapter 308), parainfluenza viruses (see Chapter 306), adenoviruses (see Chapter 309), enteroviruses (see Chapter 297), and coronaviruses (see Chapter 311), including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19; see Chapter 449.1).

Lower respiratory tract viral infections are much more common in the fall and winter in both the Northern and Southern Hemispheres in relation to the seasonal epidemics of respiratory viruses that occur each year. The typical pattern of these epidemics usually begins in the fall, when parainfluenza virus infections appear and most often manifest as croup. Later in winter, RSV, human metapneumovirus, and influenza viruses cause widespread infection, including upper respiratory tract infections, bronchiolitis, and pneumonia. RSV is particularly severe among infants and young children, whereas influenza viruses cause disease and excess hospitalization in all age groups. Knowledge of the prevailing viruses circulating in the community may lead to a presumptive initial diagnosis for children with acute respiratory illnesses.

Immunization status is relevant because children fully immunized against *H. influenzae* type b and *S. pneumoniae* are less likely to have pneumonia caused by these pathogens. Children who are immunocompromised or who have certain medical comorbidities may be at risk for specific pathogens, such as *Pseudomonas* spp. in patients with cystic fibrosis (see Chapter 454).

PATHOGENESIS

The lower respiratory tract possesses a number of defense mechanisms against infection, including mucociliary clearance, macrophages and secretory immunoglobulin A, and clearing of the airways by coughing. Previously, it was believed that the lower respiratory tract was—in the absence of infection—kept sterile by these mechanisms, supported primarily by culture-based studies. However, recent use of culture-independent techniques, including high-throughput sequencing methods, suggests that the lower respiratory tract contains diverse microbial communities. These data have challenged the traditional model of pneumonia pathogenesis that maintained that pneumonia was the result of invasion of the sterile lower respiratory tract by a single pathogen. More recent conceptual models postulate that pneumonia results from disruption of a complex lower respiratory ecosystem that is the

Table 449.1 Causes of Infectious Pneumonia

BACTERIAL	
Common	
Streptococcus pneumoniae	Consolidation, empyema
Group B streptococcus	Neonates
Group A streptococcus	Empyema
Staphylococcus aureus	Pneumatoceles, empyema; infants; nosocomial pneumonia
*Mycoplasma pneumoniae**	Adolescents; summer to fall epidemics
*Chlamydophila pneumonie**	Adolescents
Chlamydia trachomatis	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
Uncommon	
Haemophilus influenzae type b	Unimmunized
Moraxella catarrhalis	
Neisseria meningitidis	
Francisella tularensis	Animal, tick, fly contact; bioterrorism
Nocardia species	Immunocompromised patients
*Chlamydophila psittaci**	Bird contact (especially parakeets)
Yersinia pestis (plague)	Rat contact; bioterrorism
Legionella species*	Exposure to contaminated water; nosocomial
*Coxiella burnetii** (Q fever)	Animal (goat, sheep, cattle) exposure
VIRAL	
Common	
Respiratory syncytial virus	Bronchiolitis
Parainfluenza types 1-4	Croup
Influenza A, B	High fever; winter months
Adenovirus	Can be severe; often occurs between January and April
Human metapneumovirus	Similar to respiratory syncytial virus
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2):COVID-19	Global pandemic
Uncommon	
Rhinovirus	Rhinorrhea
Enterovirus D68, others	Neonates
VIRAL	
Uncommon	
Herpes simplex	Neonates, immunocompromised persons
Cytomegalovirus	Infants; immunocompromised persons (particularly HIV-infected infants)
Measles	Rash, coryza, conjunctivitis
Varicella	Unimmunized; immunocompromised persons
Hantavirus	Southwestern United States, rodents
Coronaviruses (SARS-CoV-1, Middle East respiratory syndrome [MERS])	Asia, Arabian Peninsula
FUNGAL	
Histoplasma capsulatum	Ohio/Mississippi River valley; bird, bat contact
Blastomyces dermatitidis	Ohio/Mississippi River valley, upper Midwest states
Coccidioides immitis	Southwestern United States, Great Lakes states
Cryptococcus neoformans and *C. gattii*	Bird contact; immunocompromised; Northwestern United States (*C. gattii*)
Aspergillus species	Immunocompromised persons; nodular lung infection
Mucormycosis	Immunocompromised persons
Pneumocystis jirovecii	Immunocompromised persons (particularly HIV-infected infants); steroids
RICKETTSIAL	
Rickettsia rickettsiae	Tick bite
MYCOBACTERIAL	
Mycobacterium tuberculosis	Travel to endemic region; exposure to high-risk persons
Mycobacterium avium complex	Immunocompromised (particularly HIV-infected) persons
Other nontuberculous mycobacteria	Immunocompromised persons; cystic fibrosis
PARASITIC	
Various parasites (e.g., *Ascaris*, *Strongyloides* species)	Eosinophilic pneumonia

*Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, and poor response to β-lactam antibiotics.
Adapted from Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004: p. 29.

Table 449.2 Pneumonia Etiologies Grouped by Age of the Patient

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli,* other gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,* nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus), enterovirus D68, *S. pneumoniae, H. influenzae* (type b,* nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus), enterovirus D68, *S. pneumoniae, H. influenzae* (type b,* nontypeable), *Mycoplasma pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypeable), influenza viruses, adenovirus, COVID-19, other respiratory viruses, *Legionella pneumophila*

**H. influenzae* type b is uncommon with routine immunization.
Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al., eds. *Nelson Essentials of Pediatrics,* 5th ed. Philadelphia: Elsevier; 2006: p. 507.

site of dynamic interactions between potential pneumonia pathogens, resident microbial communities, and host immune defenses.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, which results in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes such patients particularly susceptible to severe infection. Atelectasis, interstitial edema, and hypoxemia from ventilation-perfusion

Table 449.3 Pneumonia: Etiology Suggested by Exposure History

EXPOSURE HISTORY	INFECTIOUS AGENT
Exposure to concurrent illness in school dormitory or household setting	*Neisseria meningitidis, Mycoplasma pneumoniae*
Exposure to persons with known or suspected COVID-19	SARS-CoV-2
ENVIRONMENTAL EXPOSURES	
Exposure to contaminated aerosols (e.g., air coolers, hospital water supply)	Legionnaires' disease
Exposure to goat hair, raw wool, animal hides	Anthrax
Ingestion of unpasteurized milk	Brucellosis
Exposure to bat droppings (caving) or dust from soil enriched with bird droppings	Histoplasmosis
Exposure to water contaminated with animal urine	Leptospirosis
Exposure to rodent droppings, urine, saliva	Hantavirus
Potential bioterrorism exposure	Anthrax, plague, tularemia
ZOONOTIC EXPOSURES	
Employment as abattoir work or veterinarian	Brucellosis
Exposure to cattle, goats, pigs	Anthrax, brucellosis
Exposure to ground squirrels, chipmunks, rabbits, prairie dogs, rats in Africa or southwestern United States	Plague
Hunting or exposure to rabbits, foxes, squirrels	Tularemia
Bites from flies or ticks	Tularemia
Exposure to birds (parrots, budgerigars, cockatoos, pigeons, turkeys)	Psittacosis
Exposure to infected dogs and cats	*Pasteurella multocida*, Q fever *(Coxiella burnetii)*
Exposure to infected goats, cattle, sheep, domestic animals, and their secretions (milk, amniotic fluid, placenta, feces)	Q fever *(C. burnetii)*
TRAVEL EXPOSURES	
Residence in or travel to San Joaquin Valley, southern California, southwestern Texas, southern Arizona, New Mexico	Coccidioidomycosis
Residence in or travel to Mississippi or Ohio river valleys, Great Lakes States, Caribbean, Central America, or Africa	Histoplasmosis, blastomycosis
Residence in or travel to southern China	Avian influenza
Residence in or travel to Arabian Peninsula	MERS-CoV
Residence in or travel to Southeast Asia	Paragonimiasis, melioidosis
Residence in or travel to West Indies, Australia, or Guam	Melioidosis

MERS-CoV, Middle East respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
From Ellison RT III, Donowitz GR. Acute pneumonia. In: Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 69.3, p. 828.

mismatch often accompany airway obstruction. Viral infection of the respiratory tract can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions, and disrupting the microbial communities that reside in the respiratory tract.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the upper respiratory tract and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue in the setting of bacteremia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. *M. pneumoniae* (see Chapter 269) attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. When the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as is seen in viral pneumonia. *S. pneumoniae* produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of the lung, often resulting in the characteristic lobar consolidation. Lower respiratory tract infection caused by GAS typically results in more diffuse lung involvement with interstitial pneumonia. The pathology includes necrosis of tracheobronchial mucosa; formation of large amounts of exudate, edema, and local hemorrhage, with extension into the interalveolar septa; and involvement of lymphatic vessels with frequent pleural involvement. *S. aureus* pneumonia manifests as confluent bronchopneumonia, which is often bilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, and, at times, bronchopulmonary fistulas.

Recurrent pneumonia is defined *as two or more* episodes in a single year *or three or more* episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 449.4).

CLINICAL MANIFESTATIONS

Pneumonia is frequently preceded by several days of symptoms of an upper respiratory tract infection, typically rhinitis and cough. In viral pneumonia, fever is usually present but temperatures are generally lower than in bacterial pneumonia. Tachypnea is the most consistent clinical manifestation of pneumonia. Increased work of breathing manifested by intercostal, subcostal, and suprasternal retractions; nasal flaring; and use of accessory muscles is also common. Severe infection may be accompanied by cyanosis and lethargy, especially in infants. Auscultation of the chest may reveal crackles and wheezing, but it is often difficult to localize the source of these adventitious sounds in young children with hyperresonant chests. It is often not possible to distinguish viral pneumonia clinically from disease caused by *Mycoplasma* and other bacterial pathogens.

Bacterial pneumonia in adults and older children typically begins suddenly with high fever, cough, and chest pain. Other symptoms that may be seen include drowsiness with intermittent periods of restlessness; rapid respirations; anxiety; and, occasionally, delirium. In many children, splinting on the affected side to minimize pleuritic pain and improve ventilation is noted; such children may lie on one side with the knees drawn up to the chest. Lower lobe pneumonia may cause abdominal pain (but no tenderness), or the pain may be referred to the ipsilateral shoulder.

Physical findings depend on the stage of pneumonia. Early in the course of illness, diminished breath sounds, scattered crackles, and rhonchi are commonly heard over the affected lung field. With the development of increasing consolidation or complications of pneumonia such as pleural effusion or empyema, dullness on percussion is noted and breath sounds may be diminished. A lag in respiratory excursion often occurs on the affected side. Abdominal distention may be prominent because of gastric dilation from swallowed air or ileus. The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.

Table 449.4 Differential Diagnosis of Recurrent Pneumonia

HEREDITARY DISORDERS
Cystic fibrosis
Sickle cell disease
DISORDERS OF IMMUNITY
HIV/AIDS
Bruton agammaglobulinemia
Selective immunoglobulin G subclass deficiencies
Common variable immunodeficiency syndrome
Severe combined immunodeficiency syndrome
Chronic granulomatous disease
Hyperimmunoglobulin E syndromes
Leukocyte adhesion defect
DISORDERS OF CILIA
Primary ciliary dyskinesia
Kartagener syndrome
ANATOMIC DISORDERS
Pulmonary sequestration
Lobar emphysema
Congenital pulmonary airway malformation
Gastroesophageal reflux
Foreign body
Tracheoesophageal fistula (H type)
Bronchiectasis
Aspiration (oropharyngeal incoordination)
Aberrant bronchus

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al., eds. *Nelson Essentials of Pediatrics*, 5th ed. Philadelphia: Elsevier; 2006: p. 507.

Symptoms described in adults with pneumococcal pneumonia may be noted in older children but are rarely observed in infants and young children, in whom the clinical pattern is considerably more variable. In infants, there may be a prodrome of upper respiratory tract infection and poor feeding, leading to the abrupt onset of fever, restlessness, apprehension, and respiratory distress. These infants typically appear ill, with respiratory distress manifested as grunting; nasal flaring; retractions of the supraclavicular, intercostal, and subcostal areas; tachypnea; tachycardia; air hunger; and often cyanosis. Auscultation may be misleading, particularly in young infants, with meager findings disproportionate to the degree of tachypnea. Some infants with bacterial pneumonia may have associated gastrointestinal disturbances characterized by vomiting, anorexia, diarrhea, and abdominal distention secondary to a paralytic ileus. Rapid progression of symptoms is characteristic in the most severe cases of bacterial pneumonia. Cyanosis often predicts multilobular involvement. Risk factors for severe pneumonia include temperature >38.5°C, tachypnea, retractions, nasal flaring, grunting, capillary refill >2 seconds, cyanosis, tachycardia, and poor feeding.

DIAGNOSIS

In 2011, the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) published clinical practice guidelines for community-acquired pneumonia in children older than 3 months of age. These evidence-based guidelines provide recommendations for diagnostic testing and treatment of previously healthy children with pneumonia in both outpatient and inpatient settings. With the advent of advanced technologies and changing epidemiologic pathogens, these guidelines have required modifications.

An infiltrate on chest radiograph (posteroanterior and lateral views) supports the diagnosis of pneumonia; images may also identify a complication such as a pleural effusion or empyema. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 449.2). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 449.3). The radiographic appearance alone does not accurately identify

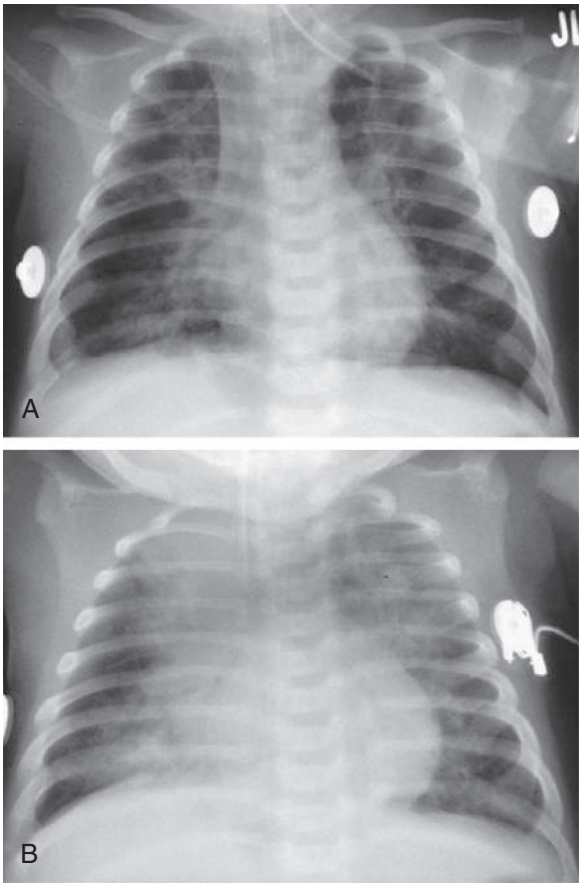

Fig. 449.2 A, Radiographic findings characteristic of respiratory syncytial virus pneumonia in a 6-mo-old infant with rapid respirations and fever. Anteroposterior radiograph of the chest shows hyperexpansion of the lungs with bilateral fine air space disease and streaks of density, indicating the presence of both pneumonia and atelectasis. An endotracheal tube is in place. B, One day later, the anteroposterior radiograph of the chest shows increased bilateral pneumonia.

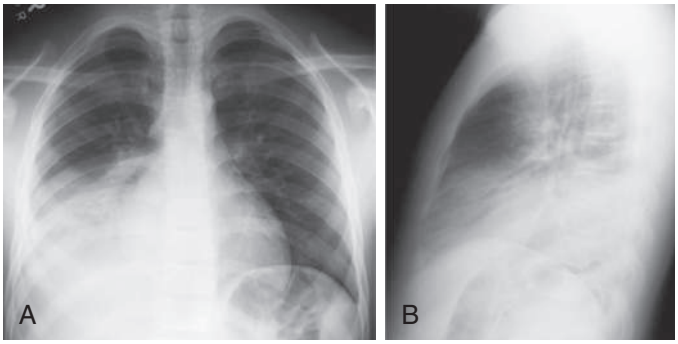

Fig. 449.3 Radiographic findings characteristic of pneumococcal pneumonia in a 14-yr-old male with cough and fever. Posteroanterior (A) and lateral (B) chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.

pneumonia etiology, and other clinical features of the illness must be considered. Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia. Moreover, current PIDS-IDSA guidelines do not recommend that a chest radiograph be performed for children with suspected pneumonia (tachypnea, cough, fever, localized crackles, or decreased breath sounds) who are well enough to be managed as outpatients because imaging in this context only rarely changes management.

Point-of-care use of portable or handheld ultrasonography is highly sensitive and specific in diagnosing pneumonia in children by

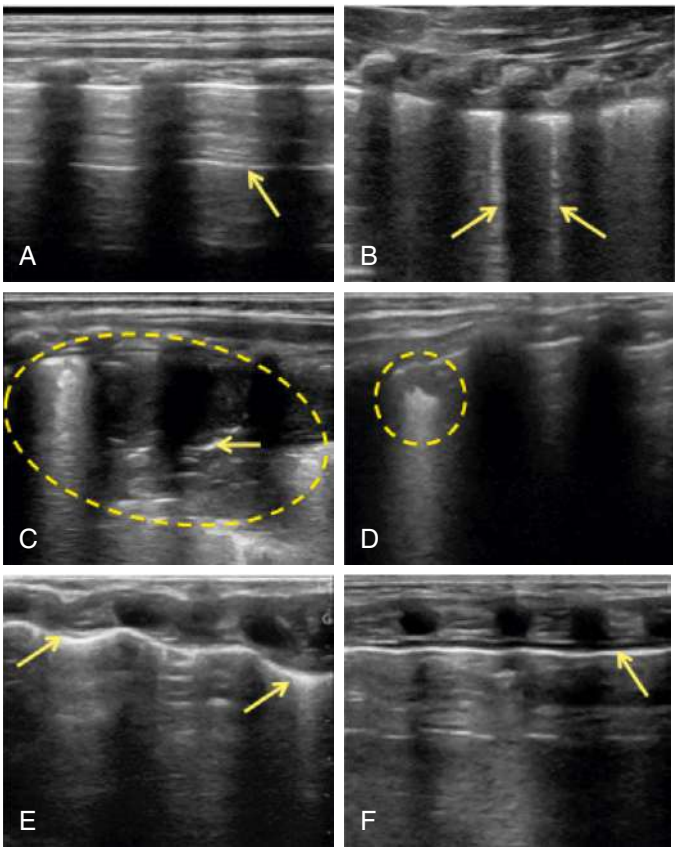

Fig. 449.4 Lung ultrasound patterns. **A,** Negative lung ultrasound pattern with A-line *(arrow)* and no other findings. Positive lung ultrasound patterns with **(B)** B-lines *(arrows)*; **(C)** large consolidation (>1 cm) with tissue-like echo-texture *(circle)* and ultrasonographic bronchograms *(arrow)*; **(D)** small consolidation (<1 cm; *circle*); **(E)** pleural line abnormality with thickening and irregularity *(arrows)*; and **(F)** pleural effusion *(arrow). (From Varshney T, Mok E, Shapiro AJ, et al. Point-of-care lung ultrasound in young children with respiratory tract infections and wheeze. Emerg Med J. 2016;33:603–610, Fig. 1.)*

determining lung consolidations and air bronchograms or effusions (Fig. 449.4). However, the reliability of this imaging modality for pneumonia diagnosis is highly user-dependent, which has limited its widespread use.

The peripheral white blood cell (WBC) count can be useful in differentiating viral from bacterial pneumonia. In viral pneumonia, the WBC count can be normal or elevated but is usually not higher than 20,000/mm^3, with a lymphocyte predominance. Bacterial pneumonia is often associated with an elevated WBC count, in the range of 15,000-40,000/mm^3, and a predominance of polymorphonuclear leukocytes. A large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are also suggestive of a bacterial etiology. Atypical pneumonia caused by *C. pneumoniae* or *M. pneumoniae* is difficult to distinguish from pneumococcal pneumonia on the basis of radiographic and laboratory findings; although pneumococcal pneumonia is associated with a higher WBC count, erythrocyte sedimentation rate, procalcitonin, and C-reactive protein level, there is considerable overlap.

The definitive diagnosis of a viral infection rests on the detection of the viral genome or antigen in respiratory tract secretions. Reliable PCR assays are widely available for the rapid detection of many respiratory viruses, including RSV, parainfluenza, influenza, human metapneumovirus, adenovirus, enterovirus, rhinovirus, and SARS-CoV-2. Serologic techniques can also be used to diagnose a recent respiratory viral infection but generally require testing of acute and convalescent serum samples for a rise in antibodies to a specific virus. This diagnostic technique is laborious, slow, and not generally clinically useful because the infection usually has resolved by the time it is confirmed serologically. Serologic testing may be valuable as an epidemiologic tool to define the incidence and prevalence of various respiratory viral pathogens.

Table 449.5 Factors Suggesting Need for Hospitalization of Children with Pneumonia

Age <6 mo
Immunocompromised state
Toxic appearance
Moderate to severe respiratory distress (retractions, nasal flaring, grunting)
Cyanosis/hypoxemia (oxygen saturation <90% breathing room air, sea level)
Shock (tachycardia, hypotension, prolonged capillary refill time)
Complicated pneumonia*
Sickle cell anemia with acute chest syndrome
Vomiting or inability to tolerate oral fluids or medications
Severe dehydration
No response to appropriate oral antibiotic therapy
Social factors (e.g., inability of caregivers to administer medications at home or follow up appropriately)
High-risk pathogen

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, or sepsis.
Adapted from Baltimore RS. Pneumonia. In: Jenson HB, Baltimore RS, eds. *Pediatric Infectious Diseases: Principles and Practice.* Philadelphia: WB Saunders; 2002: p. 801.

The definitive diagnosis of a typical bacterial infection requires isolation of an organism from the blood, pleural fluid, or lung. Culture of sputum is of little value in the diagnosis of pneumonia in young children, and percutaneous lung aspiration is invasive and not routinely performed. Blood culture is positive in only 10% of children with pneumococcal pneumonia (bacteremia is more common in GAS and *H. influenzae* pneumonias) and is not recommended for nontoxic-appearing children treated as outpatients. Blood cultures are recommended for children who fail to improve or have clinical deterioration, have complicated pneumonia (Table 449.5), or require hospitalization. Pertussis infection can be diagnosed by PCR or culture of a nasopharyngeal specimen; although culture is considered the gold standard for pertussis diagnosis, it is less sensitive than the available PCR assays. Acute infection caused by *M. pneumoniae* can be diagnosed on the basis of a PCR test result from a respiratory specimen or seroconversion in an immunoglobulin G assay. Cold agglutinins at titers >1:64 are also found in the blood of roughly half of patients with *M. pneumoniae* infections; however, cold agglutinins are nonspecific because other pathogens such as influenza viruses may also cause increases. Serologic evidence, such as antistreptolysin O and anti-DNase B titers, may also be useful in the diagnosis of GAS pneumonia.

Noninvasive diagnostic tests *may* help differentiate children with bacterial versus viral causes of pneumonia. Various biomarkers, including C-reactive protein, procalcitonin, and ESR, have been evaluated for their ability to differentiate these pneumonia etiologies. For many of these biomarkers, values differ in children with bacterial compared with viral causes of pneumonia (except adenovirus and influenza), but the reliability of these tests is not sufficiently high to justify routine clinical use. Cell-free next-generation sequencing of plasma or blood has been helpful in identifying pathogens in patients suspected of having bacterial pneumonia; identified pathogens include *S. pneumoniae, S. aureus,* and *Fusobacterium nucleatum* (blood cultures were negative in most of these patients). In addition, culture and PCR analysis of pleural fluid may also yield an organism.

TREATMENT

Treatment of suspected bacterial pneumonia is based on the presumptive cause and the age and clinical appearance of the child. For mildly ill children who do not require hospitalization, amoxicillin is recommended. With the emergence of penicillin-resistant pneumococci, high doses of amoxicillin (90 mg/kg/day orally divided twice daily) should be prescribed unless local data indicate a low prevalence of resistance.

Therapeutic alternatives include cefuroxime and amoxicillin/clavulanate. For school-age children and adolescents or when infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic is an appropriate choice for outpatient management. Azithromycin is generally preferred, but clarithromycin or doxycycline (for children 8 years or older) are alternatives. For adolescents, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) may also be considered as an alternative if there are contraindications to other agents.

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on local epidemiology, the immunization status of the child, and the clinical manifestations at the time of presentation. In areas without substantial high-level penicillin resistance among *S. pneumoniae,* children who are fully immunized against *H. influenzae* type b and *S. pneumoniae* and are not severely ill should receive ampicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime may be used. If infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic should be included in the treatment regimen. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin. For children with respiratory failure in the setting of influenza–methicillin-resistant *S. aureus* (MRSA) co-infection, data from a multicenter study support combination therapy with vancomycin and a second antibiotic with MRSA activity (e.g., clindamycin).

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for preschool-age patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. However, up to 30% of patients with known viral infection, particularly influenza viruses, may have coexisting bacterial pathogens. Therefore if the decision is made to withhold antibiotic therapy on the basis of presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection, and antibiotic therapy should be initiated.

Table 449.5 notes the indications for admission to a hospital. Hospitalized children should receive supportive care and may require intravenous fluids; respiratory support, including supplemental oxygen, continuous positive airway pressure (CPAP), or mechanical ventilation; or vasoactive medications for hypotension or sepsis physiology.

The optimal duration of antibiotic treatment for pneumonia has not been well-established in controlled studies. However, antibiotics should generally be continued until the patient has been afebrile for 72 hours. Several studies suggest that shorter courses (5-7 days) may also be effective, particularly for children managed on an outpatient basis. Available data do not support prolonged courses of treatment for uncomplicated pneumonia. Some studies suggest that a reduction of previously elevated serum procalcitonin levels to an absolute level (0.1-0.25 μg/L) may help determine when to stop treatment.

Despite substantial gains over the past 15 years, less than two thirds of children with symptoms of pneumonia are taken to an appropriate caregiver in low- and middle-income countries, and fewer than half receive antibiotics. The World Health Organization and other international groups have developed systems to train mothers and local healthcare providers in the recognition and appropriate antibiotic treatment of pneumonia. In addition to antibiotics, oral zinc (10 mg/day for <12 months, 20 mg/day for ≥12 months given for 7 days) may reduce mortality among children in low- and middle-income countries with clinically defined severe pneumonia. Bubble CPAP improves mortality from pneumonia with hypoxemia compared with standard oxygen therapy in settings without access to ventilator-derived CPAP or mechanical ventilation.

PROGNOSIS

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), within 48-72 hours of initiation of antibiotics. Radiographic evidence of improvement lags substantially behind clinical improvement. A number of possibilities must be considered when a patient does not improve with appropriate antibiotic therapy: (1) complications, such as pleural effusion or empyema (see Table 449.5); (2) bacterial resistance; (3) nonbacterial etiologies such as viruses or fungi and aspiration of foreign bodies or food; (4) bronchial obstruction from endobronchial lesions, foreign body, or mucous plugs; (5) preexisting diseases such as immunodeficiencies, ciliary dyskinesia, cystic fibrosis, pulmonary sequestration, or congenital pulmonary airway malformation; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, and granulomatosis with polyangiitis, formerly called *Wegener granulomatosis*). A chest radiograph is the first step in determining the reason for a lack of response to initial treatment. Bronchoalveolar lavage may be indicated in children with respiratory failure. High-resolution CT scans may better identify complications or an anatomic reason for a poor response to therapy.

Mortality from community-acquired pneumonia in developed countries is rare, and most children with pneumonia do not experience long-term pulmonary sequelae. Some data suggest that up to 45% of children have symptoms of asthma 5 years after hospitalization for pneumonia; this finding may reflect either undiagnosed asthma at the time of presentation or a propensity for development of asthma after pneumonia.

COMPLICATIONS

Complications of pneumonia (see Table 449.5) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, and pericarditis) or bacteremia and hematologic spread (Figs. 449.5-449.7). Meningitis, endocarditis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H. influenzae* type b infection.

S. aureus, S. pneumoniae, and *S. pyogenes* (GAS) are the most common causes of parapneumonic effusions and empyema. Nonetheless many effusions that complicate bacterial pneumonia are sterile. Analysis of pleural fluid parameters, including pH, glucose, protein, and lactate dehydrogenase, can differentiate transudative from exudative effusions (Table 449.6). However, current PIDS-IDSA guidelines do not recommend that these tests be performed because this distinction rarely changes management. Pleural fluid should be sent for Gram stain and bacterial culture, as this may identify the bacterial cause of pneumonia. Molecular methods, including bacterial species–specific PCR



Fig. 449.5 Chest radiograph of large right-sided pleural effusion complicating community-acquired pneumonia. *(From de Benedictis FM, Kerem E, Chang AB, et al. Complicated pneumonia in children. Lancet. 2010;396:786–798, Fig. 1, p. 789.)*

assays, detect pathogens and can often determine the bacterial etiology of the effusion if the culture is negative, particularly if the pleural fluid sample was obtained after initiation of antibiotics. A pleural fluid WBC count with differential may be helpful if there is suspicion for pulmonary tuberculosis or a noninfectious etiology for the pleural effusion, such as malignancy.

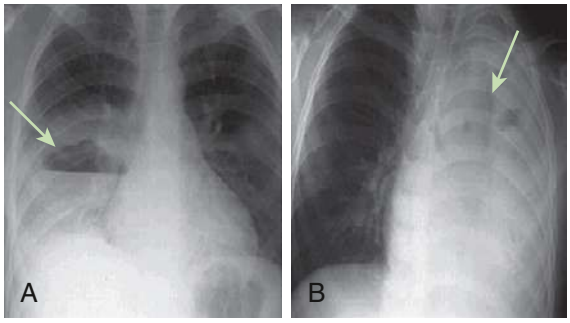

Fig. 449.6 Chest radiographs of lung abscess and necrotizing pneumonia. **A,** Lung abscess. A single thick walled, irregular cavity containing an air-fluid level can be seen *(arrow)*. **B,** Necrotizing pneumonia. A completely opacified left hemithorax with multiple necrotic areas can be seen *(arrow)*. *(From de Benedictis FM, Kerem E, Chang AB, et al. Complicated pneumonia in children. Lancet. 2010;396:786–798, Fig. 2, p. 789.)*

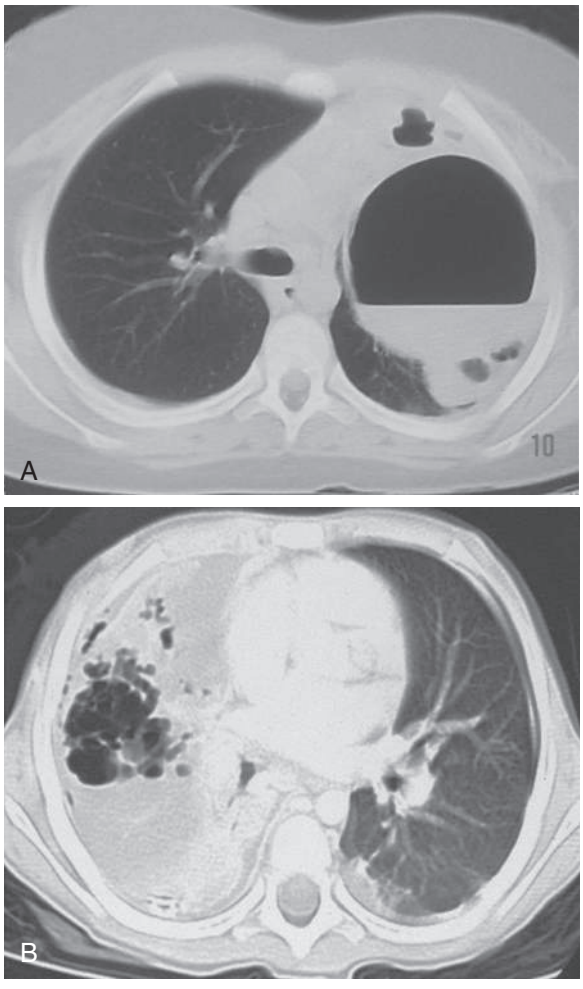

Fig. 449.7 Chest CT in complicated community-acquired pneumonia. **A,** Lung abscess. A large cavity containing an air-fluid level can be seen. **B,** Necrotizing pneumonia with cavitation. *(From de Benedictis FM, Kerem E, Chang AB, et al. Complicated pneumonia in children. Lancet. 2010;396:786–798, Fig. 4, p. 790.)*

Small (<1 cm on lateral decubitus radiograph), free-flowing parapneumonic effusions often do not require drainage but respond to appropriate antibiotic therapy. Larger effusions should typically be drained, particularly if the effusion is purulent or associated with respiratory distress. Chest ultrasound, or alternatively CT, may be helpful in determining whether loculations are present. The mainstays of therapy include antibiotic therapy and drainage by tube thoracostomy with the instillation of fibrinolytic agents (tissue plasminogen activator). Video-assisted thoracoscopy is a less often employed alternative that enables debridement or lysis of adhesions and drainage of loculated areas of pus. Early diagnosis and intervention, particularly with fibrinolysis or, less often, video-assisted thoracoscopy, may obviate the need for thoracotomy and open debridement.

PREVENTION

The introduction of PCVs resulted in a substantial reduction in the incidence of pneumonia hospitalizations among children. The annual rate of all-cause pneumonia hospitalization among children younger than 2 years of age in the United States was 12.5 per 1,000 children during the period from 1997 to 1999. In 2000, seven-valent pneumococcal conjugate vaccine (PCV7) was licensed and recommended. In 2006, the pneumonia hospitalization rate in this age-group was 8.1 per 1,000 children, a 35% decrease from the prevaccine rate. In 2010, 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States; data indicate that introduction of this vaccine resulted in a 16–27% further reduction in pneumonia hospitalizations among children relative to the post-PCV7 era.

Influenza vaccine may also prevent pneumonia hospitalizations among children and should be administered to all children >6 months of age. For infants <6 months of age, household contacts and other primary caregivers should receive the influenza vaccine. Maintaining high rates of vaccination for *H. influenzae* type b, pertussis, and measles remains important for the prevention of pneumonia from these causes. Several RSV vaccines are currently under development; introduction of an effective vaccine against RSV would be anticipated to substantially reduce pneumonia incidence among children, particularly young infants. Several vaccines that are highly effective in preventing COVID-19 have received Emergency Use Authorization by the U.S. Food and Drug Administration for use in children 6 months of age or older (see Chapter 449.1); such vaccines are often updated to cover emergence of new variants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

449.1 COVID-19

Matthew S. Kelly and Thomas J. Sandora

See also Chapter 311.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), has created a global pandemic. As of July 2023, SARS-CoV-2 caused more than 767 million cases and 6.9 million deaths worldwide. SARS-CoV-2 is spread primarily through person-to-person respiratory transmission; viral particles in respiratory secretions that are released when an infected individual coughs, sneezes, or talks can infect another person when inhaled or through contact with mucous membranes. Direct person-to-person contact and fomites are believed to play minor roles in SARS-CoV-2 transmission. The incubation period for the virus can be up to 14 days after exposure, with most cases occurring within 4-5 days. Public health measures such as face masks, physical distancing, stay-at-home orders, and restrictions on public gatherings are highly effective in interrupting SARS-CoV-2 transmission (see Chapter 214). Several vaccines have been developed that are effective in preventing SARS-CoV-2 infection and severe COVID-19. SARS-CoV-2 has undergone substantial genetic evolution since it was first identified; several viral variants have emerged that are associated with different clinical symptoms along with increased transmissibility and reduced vaccine effectiveness.

Table 449.6 Features Differentiating Exudative from Transudative Pleural Effusion

FEATURE	TRANSUDATE	EXUDATE
Appearance	Serous	Cloudy
Leukocyte count	<10,000/mm^3	>50,000/mm^3
pH	>7.2	<7.2
Protein	<3.0 g/dL	>3.0 g/dL
Ratio of pleural fluid protein to serum	<0.5	>0.5
LDH	<200 IU/L	>200 IU/L
Ratio of pleural fluid LDH to serum	<0.6	>0.6
Glucose	≥60 mg/dL	<60 mg/dL

LDH, Lactate dehydrogenase.
From Septimus EJ. Pleural effusion and empyema. In: Bennett JE, Blaser MJ, Dolin R, et al. eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 70-1, p. 851.

Some data suggest that children and adolescents may be less susceptible to SARS-CoV-2 infection than adults. In a meta-analysis that included data from 18 contact-tracing studies, children and adolescents less than 20 years of age had a 44% lower odds of being an infected contact compared to adults 20 years of age or older. However, widespread transmission of SARS-CoV-2 has occurred among children in schools and other congregate childcare settings, typically when face masks and other mitigation measures have not been in place.

CLINICAL MANIFESTATIONS

In children, COVID-19 is generally a mild illness, characterized most frequently by low-grade fever (30–50%) and cough (30–50%). Other commonly reported symptoms include nasal congestion or rhinorrhea, myalgias, and pharyngitis. Older children and adolescents often report headache, loss of smell (anosmia), or loss of taste (dysgeusia). Gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting occur less frequently but may be the presenting complaints in some children. Skin findings occur infrequently with SARS-CoV-2 infection, although maculopapular rash, urticarial lesions, and reddish-purple nodules on the toes (sometimes referred to as "COVID toes") have been described. Tachypnea and signs of increased work of breathing should raise suspicion for pneumonia, the most common serious clinical manifestation of COVID-19. Severe neurologic symptoms such as seizures and encephalopathy have been reported among children hospitalized for severe COVID-19. *There are no signs or symptoms that can reliably distinguish COVID-19 from other illnesses caused by respiratory viruses or bacteria.* Up to 20–30% of children and adolescents with COVID-19 have asymptomatic infections; these individuals can still effectively transmit the virus to others.

Children and adolescents with SARS-CoV-2 infection are at a lower risk of severe COVID-19 than adults. Despite accounting for 10–20% of SARS-CoV-2 infections in the United States as of August 2021, children and adolescents represented less than 3% of hospitalizations and less than 0.5% of deaths from COVID-19. Children with underlying medical conditions are at higher risk of developing severe COVID-19. Data on risks associated with specific conditions in children are currently lacking, but the Centers for Disease Control and Prevention suggests that children with obesity, medical complexity, neurodevelopmental disorders, congenital heart disease, asthma or chronic lung disease, diabetes, or sickle cell disease may be at higher risk of progression to severe illness (Table 449.7). Children are also at higher risk of **multisystem inflammatory syndrome in children** (MIS-C; see Chapter 207), a postinfectious inflammatory condition that typically occurs in the 4-6 weeks after SARS-CoV-2 infection.

DIAGNOSIS

The IDSA recommends that children who have symptoms compatible with COVID-19, or asymptomatic individuals with known or suspected exposure to an individual diagnosed with COVID-19, be tested for SARS-CoV-2 using a nucleic acid amplification test (NAAT). In symptomatic individuals with a low clinical suspicion of COVID-19, a single NAAT test is considered sufficient, and testing should not be repeated if the result is negative. If the clinical suspicion for COVID-19 is considered intermediate or high but the initial test is negative, a repeat test should be performed 24-48 hours after initial testing. When available, standard laboratory-based NAATs or rapid reverse transcriptase (RT)-PCR tests are recommended over rapid isothermal NAATs because of higher sensitivity (98% for both standard laboratory-based NAATs and rapid RT-PCR vs 81% for rapid isothermal NAATs), despite comparable specificity. Rapid antigen tests are widely available and have high specificity but low to modest sensitivity compared with NAAT. Antigen test sensitivity is highly dependent on viral load, and therefore is influenced by the presence of symptoms and the timing of the test. For these reasons, IDSA does not recommend antigen tests as the preferred testing strategy, but rather maintains that antigen testing can identify some individuals infected with SARS-CoV-2 when molecular testing is not available.

A variety of specimen types can be tested for the presence of SARS-CoV-2, including nasopharyngeal (NP) swab, NP wash/aspirate, nasal wash/aspirate, oropharyngeal (OP) swab, nasal mid-turbinate (MT) swab, anterior nares (AN) swab, or saliva. Assay performance is highly dependent on collection procedure. IDSA recommends collecting an NP swab, MT swab, AN swab, saliva, or a combined AN/OP swab rather than an OP swab alone for symptomatic individuals suspected of having COVID-19. For hospitalized patients with suspected pneumonia and clinical suspicion for COVID-19, IDSA suggests a strategy of initially obtaining an upper respiratory specimen (e.g., NP swab) rather than a lower respiratory sample. However, if the initial specimen is negative and suspicion for disease remains high, a lower respiratory specimen (e.g., sputum, bronchoalveolar lavage fluid, or tracheal aspirate) should be collected rather than repeating the test from an upper respiratory sample.

Common laboratory abnormalities among children hospitalized for severe COVID-19 include lymphopenia, elevated aminotransaminases, and elevated markers of inflammation (e.g., C-reactive protein). Although imaging findings are neither sensitive nor specific for COVID-19, the most common abnormalities on chest radiography in children are perihilar bronchial wall thickening and/or air space consolidation. CT scans may show ground-glass opacities (mainly in the lower lobes) and/or air space consolidation. Chest radiography should be used as the first imaging modality to assess for pneumonia in symptomatic children, whereas CT should be reserved for assessing

Table 449.7 Framework for Assessing the Risk of Progression to Severe COVID-19 Based on Patient Conditions and COVID-19 Vaccination Status

CONDITIONS	RISK LEVEL BY VACCINATION STATUS[a]		
	UNVACCINATED	PRIMARY SERIES	UP TO DATE
STRONG OR CONSISTENT ASSOCIATION WITH PROGRESSION TO SEVERE COVID-19			
• Moderately or severely immunocompromised	High	High	High
• Obesity (BMI ≥95th percentile for age), especially severe obesity (BMI ≥120% of 95th percentile for age)[b] • Medical complexity with dependence on respiratory technology[c] • Severe neurologic, genetic, metabolic, or other disability that results in impaired airway clearance or limitations in self-care or activities of daily living • Severe asthma or other severe chronic lung disease requiring ≥2 inhaled or ≥1 systemic medications daily • Severe congenital or acquired cardiac disease • Multiple moderate to severe chronic diseases	High	Intermediate	Intermediate
MODERATE OR INCONSISTENT ASSOCIATION WITH PROGRESSION TO SEVERE COVID-19			
• Age <1 yr • Prematurity in children age ≤2 yr • Sickle cell disease • Diabetes mellitus (poorly controlled) • Nonsevere cardiac, neurologic, or metabolic disease[d]	Intermediate	Intermediate	Intermediate
WEAK OR UNKNOWN ASSOCIATION WITH PROGRESSION TO SEVERE COVID-19			
• Mild asthma • Overweight • Diabetes mellitus (well controlled)	Low	Low	Low

[a]**Unvaccinated** = individuals who are not eligible for COVID-19 vaccination or are <2 wk from the final dose of the primary series. **Vaccinated with primary series** = individuals who completed the primary series of two or three doses (the current CDC term is *fully vaccinated*) and are >2 wk after the final dose of the primary series but have not received a booster if they are eligible for a booster. **Vaccinated and up to date** = individuals who received the recommended primary series and booster doses.
[b]The degree of risk conferred by obesity in younger children is less clear than it is in older adolescents.
[c]This includes patients with a tracheostomy and those who require NIV.
[d]The data for this group are particularly limited.
BMI, Body mass index; CDC, Centers for Disease Control and Prevention; NIV, noninvasive ventilation; the Panel, the COVID-19 Treatment Guidelines Panel
From NIH COVID-19 Treatment Guidelines (Table 3b). https://www.covid19treatmentguidelines.nih.gov/tables/assessing-risk/

for complications, particularly in children with coexisting medical conditions.

TREATMENT

For ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease (e.g., obesity or overweight, immunosuppression, medical-related technologic dependence, or a chronic medical condition such as kidney disease, diabetes, cardiovascular disease, sickle cell disease, or neurodevelopmental disorders), current treatment options include nirmatrelvir/ritonavir (≥12 years of age) or a 3-day course of remdesivir. Nirmatrelvir is an inhibitor of the main protease of SARS-CoV-2; coadministration with ritonavir results in higher concentrations and a longer half-life. Remdesivir is an antiviral agent that works by interfering with viral RNA transcription (see Table 449.8). As of July 2023, no monoclonal antibodies have been authorized for COVID-19 treatment or prophylaxis because of reduced susceptibility of circulating Omicron subvariants to these products.

For hospitalized children with severe illness (SpO_2 ≤94% on room air, including patients on supplemental oxygen) or critical illness (mechanical ventilation or extracorporeal membrane oxygenation [ECMO]), dexamethasone treatment is recommended (Table 449.8). Inflammatory injury from the host immune response is thought to play a role in patients with severe or critical illness.

The IDSA recommends remdesivir for hospitalized patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, but suggests against routine administration to patients on mechanical ventilation and/or ECMO. A panel of pediatric infectious diseases physicians and pharmacists recommended that remdesivir could be considered on a case-by-case basis for children with severe or critical COVID-19. Children receiving remdesivir should have daily measurements of creatinine and transaminases.

Tocilizumab is a monoclonal anti–interleukin (IL)-6-receptor blocking antibody. The IDSA suggests tocilizumab in addition to standard of care for hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic

inflammation. Baricitinib is a selective Janus kinase 1 and 2 inhibitor that has been studied as a substitute for dexamethasone in patients who cannot receive corticosteroids because of a contraindication (see Table 449.8).

PREVENTION

Vaccination is the most effective intervention to prevent COVID-19 infection and is highly protective against severe illness, hospitalization, and death. COVID-19 vaccination is available for use in children ≥6 months of age. Vaccine modifications are necessary when new variants emerge.

Because the emergence of viral variants with the potential to escape vaccine-induced immunity remains a threat, nonpharmaceutical interventions to mitigate transmission of SARS-CoV-2 still play an important role in the public health response. Face mask use, eye protection, and physical distancing have all been demonstrated to reduce the risk of infection. A cross-sectional study conducted in the United States found an increase in reported mask-wearing was associated with an increased odds of transmission control. A modeling study by the Centers for Disease Control and Prevention demonstrated that high vaccination coverage and compliance with nonpharmaceutical interventions are essential to control COVID-19.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 449.8 Therapeutic Management of Hospitalized Children with COVID-19

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized for COVID-19	For children age ≥12 yr admitted for COVID-19, use prophylactic anticoagulation unless contraindicated.
Does Not Require Supplemental Oxygen	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19,[a] consider using remdesivir[b] for children age 12-17 yr. There is insufficient evidence for using remdesivir in children age 28 days to <12 yr. For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression, see footnote *a*.
Requires Conventional Oxygen	Use one of the following options: • Remdesivir[b] • Dexamethasone plus remdesivir[b] for children with increasing oxygen needs, particularly adolescents
Requires Oxygen Through High-Flow Device or NIV[d]	Use one of the following options: • Dexamethasone • Dexamethasone plus remdesivir[b] For children who do not have rapid (e.g., within 24 hr) improvement in oxygenation after initiation of dexamethasone, baricitinib[e] or tocilizumab can be considered for children aged 12-17 yr (BIII) and for children age 2-11 yr, respectively.
Requires MV or ECMO[f]	Dexamethasone[f] For children who do not have rapid (e.g., within 24 hr) improvement in oxygenation after initiation of dexamethasone, baricitinib[e] or tocilizumab may be considered for children age 12-17 yr and for children age 2-11 yr, respectively.

[a] For example, for children who are severely immunocompromised regardless of COVID-19 vaccination status and those who are unvaccinated and have additional risk factors for progression.
[b] The clinical benefit of remdesivir is greatest if it is initiated within 10 days of symptom onset. Remdesivir should be given for 5 days or until hospital discharge, whichever comes first.
[c] Conventional oxygen refers to oxygen supplementation that is not high-flow oxygen, NIV, MV, or ECMO.
[d] Patients who are receiving NIV or MV at baseline and require a substantial increase in baseline support should be treated per the recommendations for patients requiring new NIV or MV.
[e] Tofacitinib is an alternative if baricitinib is not available.
[f] For children who started receiving remdesivir before admission to the ICU, remdesivir should be continued to complete the treatment course.
ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; NIV, noninvasive ventilation.
From NIH COVID-19 Treatment Guidelines (Table 3c). https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/hospitalized-children-therapeutic-management/

Chapter 450

E-Cigarette or Vaping Product Use–Associated Lung Injury (EVALI)

Lynn A. D'Andrea and Louella B. Amos

Beginning in 2019, there was a nationwide outbreak of patients who presented with acute lung injury believed to be related to vaping, designated as *E-cigarette or vaping product use–associated lung injury* (EVALI).

EPIDEMIOLOGY

As of January 2020, there were >2,500 hospitalized EVALI patients reported by all 50 states (approximately two thirds of patients were male). The median patient age was 21 years (range 13-85 years). The Centers for Disease Control and Prevention (CDC) stopped collecting data on EVALI cases in early 2020 because of the COVID-19 pandemic; although the number of cases may have decreased, EVALI must be considered in patients with features associated with the condition (Fig. 450.1).

Among hospitalized patients with information on substances used, ~90% reported using any tetrahydrocannabinol (THC)-containing product and ~70% reported using any nicotine-containing product; 40–60% reported both THC and nicotine use. The THC products were often flavored, prefilled THC cartridges obtained from black market sources.

PATHOPHYSIOLOGY

Carrier solvents or humectants such as propylene glycol and glycerin, as well as nicotine vapor itself, can cause airway inflammation

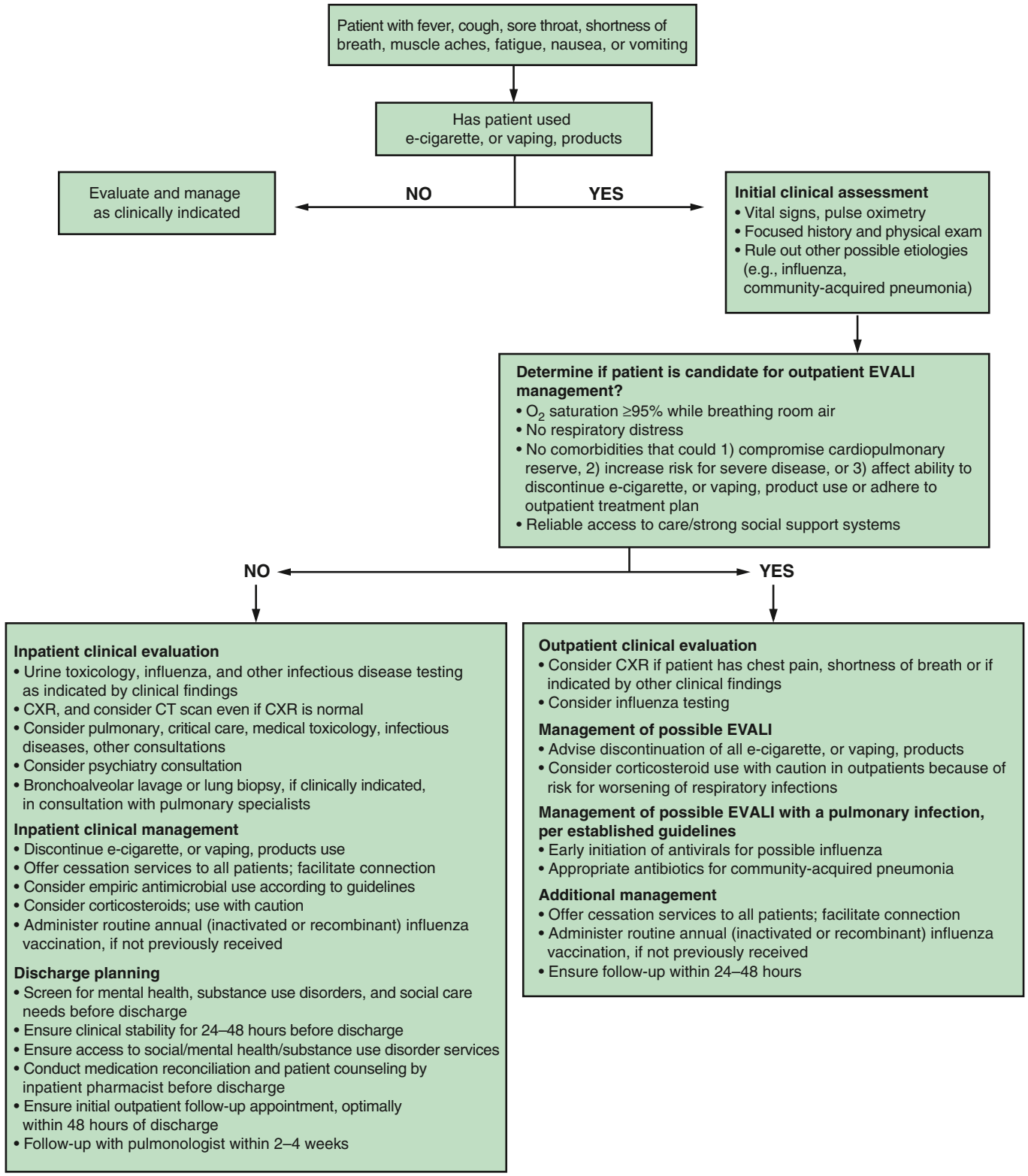

Fig. 450.1 Updated algorithm for management of patients with suspected e-cigarette, or vaping, product use–associated lung injury (EVALI), December 2019. CT, Computed tomography; CXR, chest x-ray.* Influenza vaccination recommendations: https://www.cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm?s_cid=rr6803a1_w. *(From Evans ME, Twentyman E, Click ES, et al. Update: interim guidance for health care professionals evaluating and caring for patients with suspected E-cigarette, or vaping, product use-associated lung injury and for reducing the risk of rehospitalization and death following hospital discharge – United States, December 2019. MMWR. 2020;68:1189-1194, Fig. p. 1191.)*

that can induce airway remodeling and disrupt alveolar macrophage function. Flavoring additives generate by-products that directly injure airway epithelium. Vitamin E acetate that was used as a diluent in the THC-containing products disrupts alveolar macrophage function and surfactant homeostasis. EVALI is best considered an airway-centered chemical pneumonitis rather than an exogenous lipoid pneumonia. Thermal injury can also be a factor in acute lung injury.

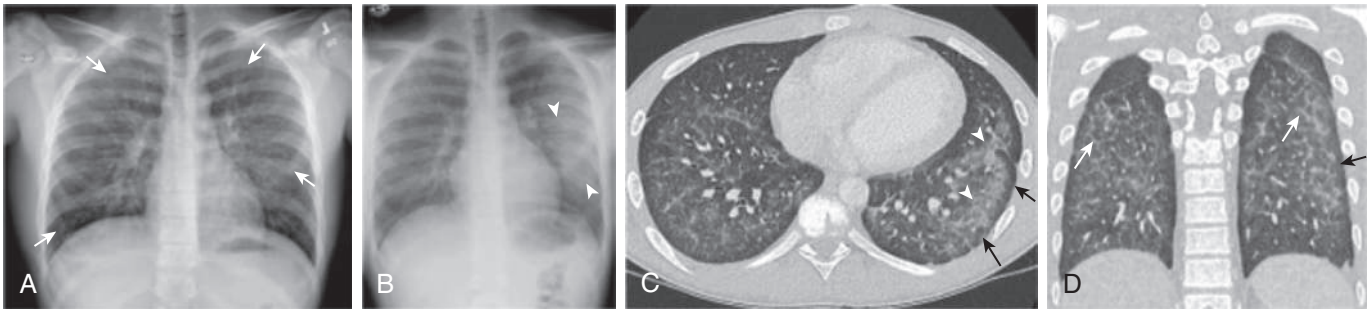

Fig. 450.2 E-cigarette, or vaping, product use–associated lung injury in a 16-yr-old male who presented with chest pain, shortness of breath, and cough for 1 month. **A,** Posteroanterior (PA) radiograph of the chest demonstrates faint nodular opacities in both lungs *(arrows)* with diffusely increased interstitial markings. **B,** PA radiograph of the chest obtained 2 days later demonstrates progression of the nodular opacities into confluent opacities in the left mid-lung *(arrowheads).* Axial **(C)** and coronal **(D)** chest CT images in lung windows (slice thickness 0.63 mm, kVp 100, mAs 61-106) obtained 4 days after the initial chest radiograph demonstrate centrilobular ground-glass nodules in both lungs and confluent ground-glass opacities in the left lower lobe *(arrowheads)* with subpleural sparing *(black arrows)* and interstitial septal thickening *(white arrows). (From Thakrar PD, Boyd KP, Swanson CP, et al. E-cigarette, or vaping, product use-associated lung injury in adolescents: a review of imaging features. Pediatr Radiol. 2020;50:338–344, Fig. 1, p. 340.)*

CLINICAL MANIFESTATIONS

Acutely, patients often present with a combination of respiratory distress, gastrointestinal (GI), and constitutional symptoms. Respiratory symptoms include shortness of breath, cough, hemoptysis, and chest or pleuritic pain. On physical examination, patients have tachypnea with hypoxemia and tachycardia. GI symptoms include nausea, vomiting, diarrhea, and abdominal pain.

Subacute constitutional and GI symptoms can occur day to weeks before the acute presentation. Constitutional symptoms include weight loss, fatigue, fever, myalgias, and chills.

DIAGNOSIS

There is no specific test for lung injury associated with EVALI; rather, evaluation should primarily focus on excluding infectious causes. It is important to evaluate for other possible causes (rheumatologic, neoplastic, cardiac) as appropriate (see Fig. 450.1).

Imaging

Chest radiographic evaluation is key in the diagnosis of EVALI, although findings are generally nonspecific (Fig. 450.2). Chest CT imaging is most consistent with acute lung injury from toxic inhalation, with centrilobular ground-glass opacities with subpleural sparing. The most common radiologic findings reported on chest x-ray are bilateral infiltrates, and ground-glass opacities predominantly at the bases. The most common radiologic findings reported on chest CT are bilateral infiltrates, bilateral ground-glass opacities, and subpleural sparing, followed by small pleural effusions and centrilobular nodularity. Pneumothorax and pneumomediastinum are less common.

Laboratory

Laboratory evaluation is suggestive of inflammation with neutrophilic leukocytosis, elevated C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Elevated transaminases (AST/ALT) and lactate dehydrogenase (LDH) have been reported in some patients. Urine drug screening is useful to confirm the presence of THC or nicotine.

Other Testing

Pulmonary Function Testing

The acute effects of EVALI on lung function are variable. In a case series of adolescents hospitalized with EVALI, predischarge testing demonstrated that >50% had an abnormality on spirometry, with a restrictive pattern occurring twice as often as obstruction; ~60% of patients had a decreased diffusion capacity, and ~50% had an abnormal 6-minute walk test. Patients continued to have abnormal testing at follow-up, including abnormal spirometry (both obstructive and restrictive patterns), decreased diffusion capacity, and rarely, 6-minute walk test. One follow-up study also identified abnormal 6-minute walk tests as a marker of lung injury and submaximal exercise capacity. However, another follow-up study showed ~85% of previously hospitalized pediatric patients had normal spirometry.

Bronchoscopy

Bronchoscopy with bronchoalveolar lavage is used to evaluate for possible infectious processes. Gross pathologic abnormalities can include mucosal hypervascularity, diffuse mucosal erythema, punctate mucosal hemorrhage, and frank airway bleeding consistent with a pulmonary hemorrhage. Cytopathologic findings commonly include lipid-laden macrophages on oil-red-O staining and elevated neutrophil counts more than 10% of total cell differential. Hemosiderin-laden macrophages are absent. Bacterial cultures are negative.

Caution is required when performing bronchoscopy with lavage, as it may worsen the patient's respiratory status. Many patients develop significant airway reactivity (bronchospasm) that requires intraprocedure management.

TREATMENT

Treatment focuses on supportive care. Supplemental oxygen may be required to maintain oxygen saturations in an appropriate range. Bronchodilators should be considered if there is an element of bronchospasm. Some patients have been treated with systemic corticosteroids with good improvement of their symptoms, but this should be considered on a case-by-case basis (see Fig. 450.1). Antibiotics should *only* be used for secondary infection.

Less often, patients have required more invasive respiratory support, including high-flow nasal cannula, mechanical ventilation, and rarely, extracorporeal membrane oxygenation (ECMO). There are rare case reports of patients requiring lung transplantation.

Follow-up should include recommendations regarding vaping cessation; some patients will require assistance with nicotine replacement therapy (see Chapter 157.2). Many adolescents require support from a mental health provider (see Fig. 450.1).

Advocacy and Prevention

In December 2019, the federal government passed legislation raising the age for purchasing tobacco products, including e-cigarettes, from 18 to 21 years. The FDA set the deadline for e-cigarette manufacturers to submit their marketing applications or risk having their products taken off the market. As of September 2021, the FDA ordered over 90% of e-cigarette products off the market; however, many products appealing to youth, including disposable flavored e-cigarettes, remain available, and the black market continues to thrive.

The initial EVALI outbreak primarily affected young adults, was driven by the use of THC-containing products from black market sources, and was strongly linked to vitamin E acetate. However, 15–20% of reported EVALI cases describe the exclusive use of nicotine-containing products. It is recommended that the term *EVALI* refer to all e-cigarette-related lung injuries, including other chronic respiratory symptoms of vaping (e.g., chronic wheeze, recurrent bronchitis, asthma exacerbations, emphysema).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 451

Pleurisy, Pleural Effusions, and Empyema

Aarthi P. Vemana and Suraiya K. Haider

Pleurisy is the inflammation of the pleura; it may be accompanied by an effusion. The most common cause of pleural effusion in children is bacterial pneumonia (see Chapter 449); other common causes include heart failure (see Chapter 491), rheumatologic and immune causes, and metastatic or intrathoracic malignancy. A variety of other diseases account for the remaining cases, including tuberculosis (see Chapter 261), lupus erythematosus (see Chapter 199), aspiration pneumonitis (see Chapter 446), uremia, pancreatitis, subdiaphragmatic abscess, and rheumatoid arthritis.

Inflammatory processes in the pleura are usually divided into three types: dry pleurisy, serofibrinous or serosanguineous, and purulent pleurisy or empyema.

451.1 Dry Pleurisy

Aarthi P. Vemana and Suraiya K. Haider

Dry pleurisy, formerly called *plastic pleurisy,* may be associated with acute bacterial or viral pulmonary infections or may develop during the course of an acute upper respiratory tract illness. The condition is also associated with tuberculosis and autoimmune and systemic inflammatory diseases such as systemic lupus erythematosus.

PATHOLOGY AND PATHOGENESIS

The process is usually limited to the visceral pleura, with small amounts of yellow serous fluid and adhesions between the pleural surfaces. In tuberculosis, pleurisy can be caused by a severe delayed-type hypersensitivity reaction to *Mycobacterium tuberculosis*; the adhesions develop rapidly, and the pleura are often thickened. Occasionally, fibrin deposition and adhesions are severe enough to produce a fibrothorax that markedly inhibits the excursions of the lung.

CLINICAL MANIFESTATIONS

The primary disease often overshadows signs and symptoms of pleurisy. Pain, the principal symptom, is exaggerated by deep breathing, coughing, and straining. Occasionally, pleural pain is described as a dull ache, which is less likely to vary with breathing. The pain is often localized over the chest wall and is referred to the shoulder or the back. Pain with breathing is responsible for grunting and guarding of respirations, and the child often lies on the affected side in an attempt to decrease respiratory excursions. Early in the illness, a leathery, rough, inspiratory, and expiratory friction rub may be audible, but it usually disappears rapidly. If the layer of exudate is thick, increased dullness to percussion and decreased breath sounds may be heard. Pleurisy may be asymptomatic. Chronic pleurisy is occasionally encountered with conditions such as atelectasis, pulmonary abscess, connective tissue diseases, and tuberculosis.

LABORATORY FINDINGS

Dry pleurisy may be detected on radiographs as a diffuse haziness at the pleural surface or a dense, sharply demarcated shadow (Figs. 451.1 and 451.2). The latter finding may be indistinguishable from small amounts of pleural exudate. Chest radiographic findings may be normal, but ultrasonography or CT findings will be positive.

DIFFERENTIAL DIAGNOSIS

Pleurisy pain must be distinguished from other diseases, such as epidemic pleurodynia, trauma to the rib cage (rib fracture), lesions of the dorsal root ganglia, tumors of the spinal cord, herpes zoster, gallbladder disease, and trichinosis. Even if evidence of pleural fluid is not found on physical or radiographic examination, a CT- or ultrasound-guided pleural tap in suspected cases often results in the recovery of a small amount of exudate, which, when cultured, may reveal the underlying bacterial cause in patients with an acute pneumonia. Patients with pleurisy and pneumonia should always be screened for tuberculosis.

TREATMENT

Therapy should be aimed at the underlying disease. When pneumonia is present, neither immobilization of the chest with adhesive plaster nor therapy with drugs capable of suppressing the cough reflex is indicated. If pneumonia is not present or is under good therapeutic control, strapping of the chest to restrict expansion may afford relief from pain. Analgesia with nonsteroidal antiinflammatory agents may be helpful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

451.2 Serofibrinous or Serosanguineous Pleurisy with Pleural Effusion

Aarthi P. Vemana and Suraiya K. Haider

Serofibrinous pleurisy is defined by a fibrinous exudate on the pleural surface and an exudative effusion of serous fluid into the pleural cavity. In general, it is associated with infections of the lung or with inflammatory conditions of the abdomen or mediastinum; occasionally, it is found with connective tissue diseases such as lupus erythematosus, periarteritis, and rheumatoid arthritis, and it may be seen with primary or metastatic neoplasms of the lung, pleura, or mediastinum. Tumors are commonly associated with a hemorrhagic fluid. Infectious etiologies include *Streptococcus pneumonia, Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA), group A streptococcus, and viral infections, including COVID-19 (although pleural disease is seen in approximately 10%).

PATHOGENESIS

Pleural fluid originates from the capillaries of the parietal pleura and is absorbed from the pleural space via pleural stomas and the lymphatics of the parietal pleura. The rate of fluid formation is dictated by the Starling law, by which fluid movement is determined by the balance of hydrostatic and osmotic pressures in the pleural space and pulmonary capillary bed and the permeability of the pleural membrane. Normally, approximately 10 mL of fluid is present in the pleural space, but if formation exceeds clearance, fluid accumulates. Pleural inflammation increases the permeability of the plural surface, with increased proteinaceous fluid formation; there may also be some obstruction to lymphatic absorption.

CLINICAL MANIFESTATIONS

Because serofibrinous pleurisy is often preceded by the dry type, early signs and symptoms may be those of dry pleurisy. As fluid accumulates, pleuritic pain may disappear. The patient may become asymptomatic if the effusion remains small, or there may be only signs and symptoms of the underlying disease. Large fluid collections can produce cough, dyspnea, retractions, tachypnea, orthopnea, or cyanosis. In children with bacterial pneumonia, pleural effusion should be suspected when symptoms do not improve after 48 hours of appropriate therapy.

Physical findings depend on the amount of effusion. Dullness to flatness may be found on percussion. Breath sounds are decreased or absent, and there is a diminution in tactile fremitus, a shift of the mediastinum away from the affected side, and, occasionally, fullness of the intercostal spaces. If the fluid is not loculated, these signs may shift with changes in position. If extensive pneumonia is present, crackles and

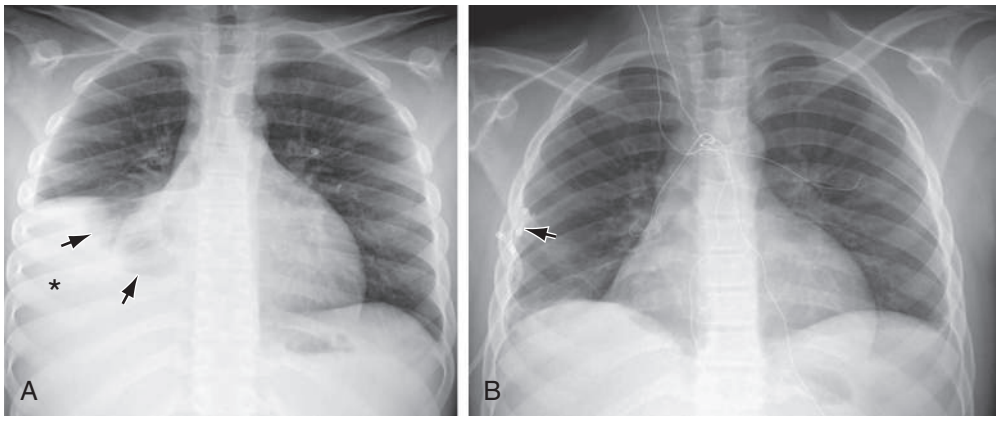

Fig. 451.1 A, Right pleural effusion *(asterisk)* caused by lupus erythematosus in a 12-yr-old child. Note compressed middle and lower lobes of the right lung *(arrows)*. B, The effusion was evacuated, and the right lung was completely reexpanded after insertion of the pigtail chest tube *(arrow)*.

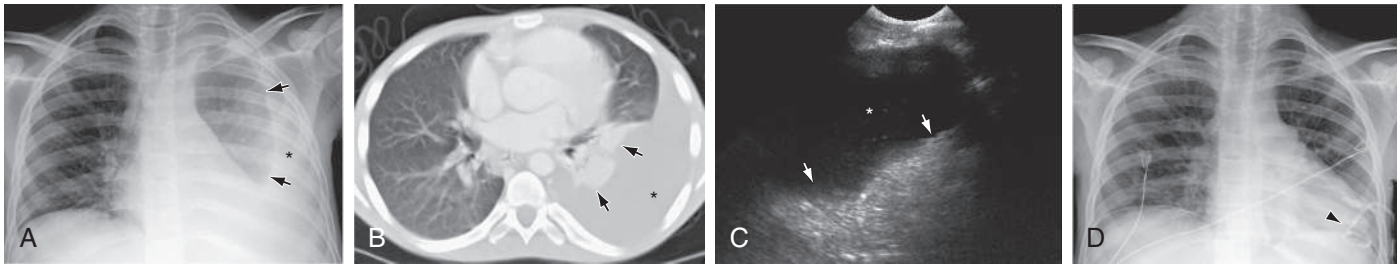

Fig. 451.2 Left pleural effusion in a teenager with AIDS and *Mycobacterium avium-intracellulare* infection. The pleural effusion *(asterisk)* is clearly seen on the chest radiograph (A), CT scan (B), and ultrasonogram (C) of the left chest. *Arrows* point to the compressed and atelectatic left lung. D, A pigtail chest tube *(arrowhead)* was inserted, resulting in reexpansion of the left lung.

rhonchi may also be audible. Friction rubs are usually detected only during the early or late plastic stage. In infants, physical signs are less definite, and bronchial breathing may be heard instead of decreased breath sounds.

LABORATORY FINDINGS

Radiographic examination shows a homogeneous density obscuring the normal markings of the underlying lung, obliterating the costophrenic or cardiophrenic angles. Radiographs should be performed with the patient both supine and upright to demonstrate a shift of the effusion with a change in position; the decubitus position may be helpful. Especially with large effusions, ultrasonography can identify the presence of septations, the lack of free movement of the fluid with gravity, and guide placement of a chest tube or site of thoracentesis loculated. Examination of the fluid is essential to differentiate **exudates** from **transudates** and to determine the type of exudate (see Table 449.6). Depending on the clinical scenario, pleural fluid is sent for culture for bacterial, fungal, and mycobacterial cultures; microbial analysis (quantitative polymerase chain reaction [qPCR], rapid antigen testing, and immunochromatography); Gram staining; and chemical evaluation of content, including protein, lactic dehydrogenase and glucose, amylase, specific gravity, total cell count and differential, cytologic examination for malignancy, and pH. Complete blood count and serum chemistry analysis should be obtained; hypoalbuminemia is often present. **Exudates** usually have at least one of the following features: protein level >3.0 g/dL, with pleural fluid:serum protein ratio >0.5; pleural fluid lactic dehydrogenase values >200 IU/L; or fluid:serum lactic dehydrogenase ratio >0.6. Although systemic acidosis reduces the usefulness of pleural fluid pH measurements, pH <7.20 suggests an exudate. Glucose is usually <60 mg/dL in malignancy, rheumatoid disease, and tuberculosis; the finding of many small lymphocytes and a pH <7.20 suggest tuberculosis. The fluid of serofibrinous pleurisy is clear or slightly cloudy and contains relatively few leukocytes and, occasionally, some erythrocytes. Gram staining may occasionally show bacteria; however, acid-fast staining rarely demonstrates tubercle bacilli. Cytologic examination may reveal malignant cells, if present.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Unless the patient has a classic-appearing lobar pneumonia and the effusion is small, thoracentesis should be performed when pleural fluid is present or is suggested. Thoracentesis can differentiate serofibrinous pleurisy, empyema, hydrothorax, hemothorax, and chylothorax. Exudates are usually associated with an infectious process. In hydrothorax, the fluid has a specific gravity <1.015, and evaluation reveals only a few mesothelial cells rather than leukocytes. Chylothorax and hemothorax usually have fluid with a distinctive appearance, but differentiating serofibrinous from purulent pleurisy is impossible without microscopic examination of the fluid. Serofibrinous fluid may rapidly become purulent.

COMPLICATIONS

Unless the fluid becomes purulent, it usually disappears relatively rapidly, particularly with appropriate treatment of bacterial pneumonia. It persists somewhat longer if a result of tuberculosis or a connective tissue disease and may recur or remain for a long time if caused by a neoplasm. When the effusion is absorbed, adhesions often develop between the two layers of the pleura, but usually little or no functional impairment results. Pleural thickening may develop and is occasionally mistaken for small quantities of fluid or for persistent pulmonary infiltrates. Pleural thickening may persist for months, but the process usually disappears, leaving no residua.

TREATMENT

Treatment of the underlying pneumonia with antibiotics should be continued. If the effusion is less than 10 mm in size on a chest x-ray, there is no need for drainage. Drainage of large effusions can shorten the course of treatment and provide symptomatic relief. When a diagnostic thoracentesis is performed, as much fluid as possible should be removed for therapeutic purposes. Rapid removal of ≥1 L of pleural fluid may be associated with the development of **reexpansion pulmonary edema**. If sufficient fluid reaccumulates to cause tachypnea, chest tube drainage should be performed. In older children, tube thoracostomy is considered necessary if the pleural fluid pH is <7.20

or the pleural fluid glucose level is <50 mg/dL. If the fluid is thick, loculated, or clearly purulent, chest tube drainage with fibrinolytic therapy or, less often, video-assisted thoracoscopic surgery (VATS) is indicated. Patients with pleural effusions may need analgesia, particularly after thoracentesis or insertion of a chest tube. Those with acute pneumonia may need supplemental oxygen in addition to specific antibiotic treatment. Monitoring with serial chest x-ray should be considered in children who have had complications or needed fibrinolytic treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

451.3 Empyema

Aarthi P. Vemana and Suraiya K. Haider

Empyema is an accumulation of pus in the pleural space. It is most often associated with pneumonia (see Chapter 449) caused by gram-positive organisms such as *S. pneumoniae* (see Chapter 228), group A streptococcus, and *S. aureus* (see Chapter 227.1). The relative incidence of *Haemophilus influenzae* (see Chapter 240) empyema has decreased since the introduction of the *H. influenzae* type b vaccination. Gram-negative organisms, tuberculosis, fungi, viruses, and malignancy are less common causes. The disease can also be produced by rupture of a lung abscess into the pleural space, contamination introduced from trauma or thoracic surgery, or, rarely, mediastinitis or the extension of intraabdominal abscesses.

EPIDEMIOLOGY

Empyema is most frequently encountered in infants and preschool children. Although rates of bacterial pneumonia have decreased, the incidence of parapneumonic effusions has increased. This may be related to a shift toward more virulent organisms after the introduction of the 13-valent pneumococcal conjugate vaccine, with a trend toward serotypes not covered by the vaccine. Empyema occurs in 5–10% of children with bacterial pneumonia and in up to 86% of children with necrotizing pneumonia.

PATHOLOGY

Empyema has three stages: exudative, fibrinopurulent, and organizational. During the exudative stage, fibrinous exudate forms on the pleural surfaces. In the fibrinopurulent stage, fibrinous septa form, causing loculation of the fluid and thickening of the parietal pleura. If the pus is not drained, it may dissect through the pleura into lung parenchyma, producing bronchopleural fistulas and pyopneumothorax, or into the abdominal cavity. Rarely, the pus dissects through the chest wall (i.e., empyema necessitatis). During the organizational stage, there is fibroblast proliferation; pockets of loculated pus may develop into thick-walled abscess cavities, or the lung may collapse and become surrounded by a thick, inelastic envelope (peel).

CLINICAL MANIFESTATIONS

The initial signs and symptoms are primarily those of bacterial pneumonia. Children treated with antibiotic agents may have an interval of a few days between the clinical pneumonia phase and the evidence of empyema. Most patients are febrile, develop increased work of breathing or respiratory distress, and often appear more ill. Physical findings are identical to those described for serofibrinous pleurisy, and the two conditions are differentiated only by thoracentesis, which should always be performed when empyema is suspected.

LABORATORY FINDINGS

Radiographically, all pleural effusions appear similar, but the absence of a shift of the fluid with a change of position indicates a loculated empyema (Figs. 451.3-451.5 and see Fig. 449.5). Ultrasonography, CT, and, less frequently, magnetic resonance imaging can all be used to further define the size of the effusion, identify septations, and assess loculations. The maximal amount of fluid obtainable should be withdrawn by thoracentesis and studied (see Chapter 451.2). The effusion is an empyema if bacteria are present on Gram staining, the pH is <7.20, and there are >100,000 neutrophils/μL (see Chapter 449). Cultures of the fluid must always be performed to help identify the causal organism. Using standard culture methods, the organism can be identified in up to 60% of cases. The yield improves significantly with concomitant use of nucleic acid amplification techniques. Blood cultures may be positive and have a higher yield than cultures of the pleural fluid. Laboratory analysis shows leukocytosis and elevated erythrocyte sedimentation rate and elevated C-reactive protein.

COMPLICATIONS

With staphylococcal infections, bronchopleural fistulas and pyopneumothorax commonly develop. Other local complications include purulent pericarditis, pulmonary abscesses, peritonitis from extension through the diaphragm, and osteomyelitis of the ribs. Septic complications such as meningitis, arthritis, and osteomyelitis may also occur. Septicemia is often encountered in *H. influenzae* and pneumococcal infections. The effusion may organize into a thick "peel," which may restrict lung expansion and may be associated with persistent fever and temporary scoliosis.

TREATMENT

The aim of empyema treatment is to sterilize pleural fluid and restore normal lung function. Treatment includes systemic antibiotics, thoracentesis, chest tube drainage, and use of a fibrinolytic agent; VATS and open decortication are used if there is poor resolution with the preceding therapies (see Chapter 461).

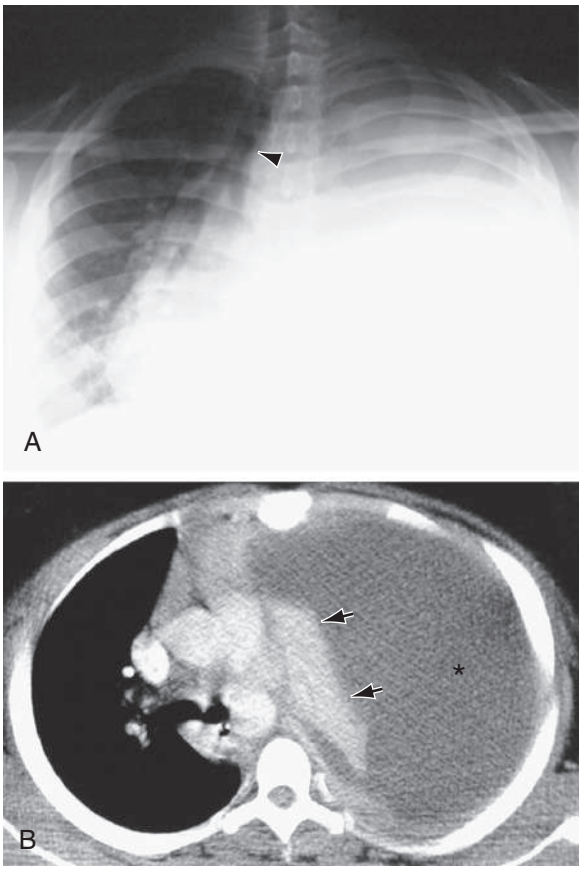

Fig. 451.3 Empyema and pneumonia in a teenager. **A,** Chest radiograph shows opacification of the left thorax. Note shift of mediastinum and trachea *(arrowhead)* to the right. **B,** Thoracic CT scan shows massive left pleural effusion *(asterisk)*. Note the compression and atelectasis of the left lung *(arrows)* and shift of the mediastinum to the right.

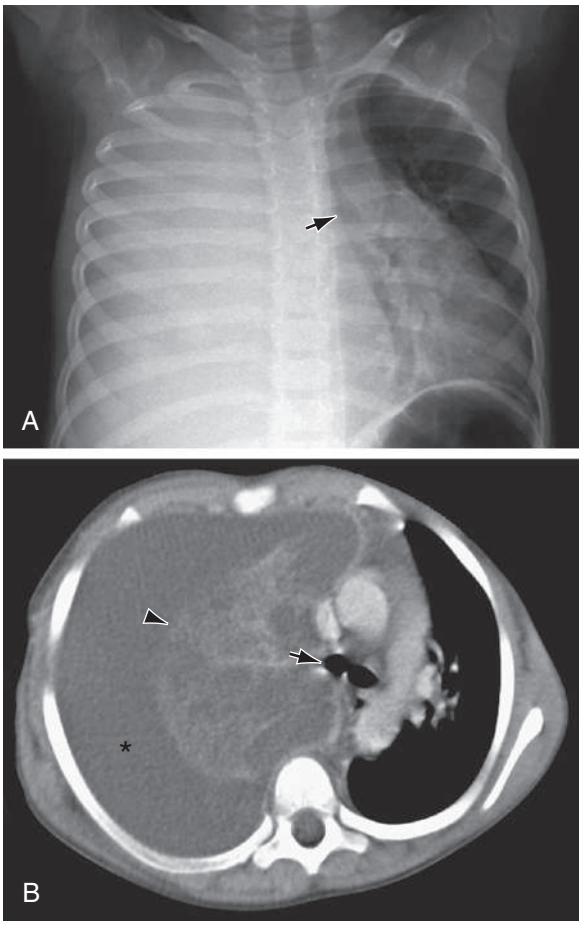

Fig. 451.4 Pneumonia and parapneumonic effusion in a 4-yr-old child. **A,** Chest radiograph shows complete opacification of the right thorax as a result of a large pleural effusion. Note the shift of the mediastinum and trachea *(arrow)* to the left. **B,** Thoracic CT scan shows a large right pleural effusion *(asterisk)* surrounding and compressing the consolidated right lung *(arrowhead)*. Note the shift of the mediastinum and tracheal carina *(arrow)* to the left.

If empyema is diagnosed early, antibiotic treatment plus thoracentesis achieves a complete cure. The selection of antibiotic should be based on the in vitro sensitivities of the responsible organism. See Chapters 227, 228, and 240 for treatment of infections by *Staphylococcus, S. pneumoniae*, and *H. influenzae*, respectively. Treatment with systemic antibiotics is usually needed for 2-4 weeks, with the duration being guided by individual clinical response to treatment. Instillation of antibiotics into the pleural cavity does not improve results.

After empyema has been confirmed, interventions include closed chest tube drainage with fibrinolytics, decortication with VATS (video-assisted thoracoscopic surgery), and, less often, open thoracotomy. Multiple aspirations of the pleural cavity should not be attempted. Closed-chest tube drainage is controlled by an underwater seal or continuous suction; sometimes more than one tube is required to drain loculated areas. Closed drainage is usually continued for 5-7 days. Chest tubes that are no longer draining are removed.

Instillation of fibrinolytic agents into the pleural cavity via the chest tube often promotes drainage, decreases the length of time a chest tube is in place, decreases fever, lessens the need for surgical intervention, and shortens hospitalization. The optimal fibrinolytic drug and dosages have not been determined. Streptokinase 15,000 units/kg in 50 mL of 0.9% saline, urokinase 40,000 units in 40 mL saline, and tissue plasminogen activator (tPA) 4 mg in 20-40 mL of saline have been used in the pediatric population. Although the combination of fibrinolytic therapy with dornase alfa (DNAse) improves outcomes in adults with empyema, it has not been shown to consistently improve outcomes in pediatric patients with empyema. There is a risk of anaphylaxis with streptokinase, and all three drugs can be associated with hemorrhage and other complications.

If pneumatoceles form, no attempt should be made to treat them surgically or by aspiration, unless they reach sufficient size to cause respiratory compromise or become secondarily infected. Pneumatoceles usually resolve spontaneously with time. Extensive fibrinous changes may take place over the surface of the lungs owing to empyema, but they eventually resolve. The long-term clinical prognosis for adequately treated empyema is excellent, and follow-up pulmonary function studies suggest that residual restrictive disease is uncommon, with or without surgical intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

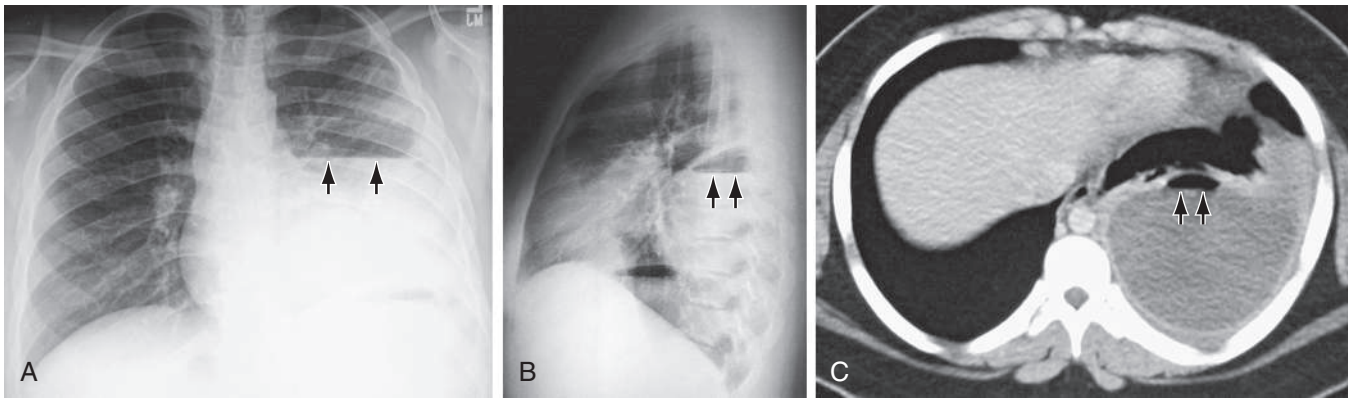

Fig. 451.5 Loculated hydropneumothorax. Frontal **(A)** and lateral **(B)** chest radiographs show loculated hydropneumothorax that complicated pneumonia in a 14-yr-old child. *Arrows* point to the horizontal air-fluid level at the interface between the intrapleural effusion and air. **C,** Thoracic CT scan helps to localize the loculated hydropneumothorax, with its air-fluid level *(arrows)*.

Chapter 452

Bronchiectasis

Oren J. Lakser

Bronchiectasis is characterized by irreversible abnormal dilation and anatomic distortion of the bronchial tree and represents the common end stage of many nonspecific and unrelated antecedent events. Its incidence has been decreasing overall in industrialized countries, but it persists as a problem in lower- and middle-income countries and among some ethnic groups in industrialized nations (particularly in aboriginal children). Females are afflicted more frequently than males.

PATHOPHYSIOLOGY AND PATHOGENESIS

In industrialized nations, cystic fibrosis (see Chapter 454) is the most common cause of clinically significant bronchiectasis. Other conditions associated with bronchiectasis include primary ciliary dyskinesia (see Chapter 455), postinfectious conditions, especially pertussis, measles, and tuberculosis, immune deficiency syndromes (especially humoral immunity), foreign body aspiration, and aspiration of gastric contents (Table 452.1). Bronchiectasis has also been associated with severe asthma in children. It can also be congenital, as in **Williams-Campbell syndrome**, in which there is an absence of annular bronchial cartilage, and **Marnier-Kuhn syndrome** (congenital tracheobronchomegaly), in which there is a connective tissue disorder. Other disease entities associated with bronchiectasis are **yellow nail syndrome** (pleural effusion, lymphedema, discolored nails) and **right middle lobe syndrome**. Right middle lobe syndrome is mostly associated with other generalized causes of bronchiectasis, including asthma, cystic fibrosis, primary ciliary dyskinesia, severe pneumonia, aspiration pneumonia, foreign bodies, and immune-deficient states.

Three basic mechanisms are involved in the pathogenesis of bronchiectasis. **Obstruction** can occur because of tumor, foreign body, impacted mucus because of poor mucociliary clearance, external compression, bronchial webs, and atresia. **Infections** caused by *Bordetella pertussis,* measles, rubella, togavirus, respiratory syncytial virus, adenovirus, and *Mycobacterium tuberculosis* induce chronic inflammation, progressive bronchial wall damage, and dilation. More recently, nontypeable *Haemophilus influenzae* seems to be a common cause of infection in adults and children with bronchiectasis. *Streptococcus pneumoniae* and *Moraxella catarrhalis* are more common in children with bronchiectasis than in adult patients. **Chronic inflammation** similarly contributes to the mechanism by which obstruction leads to bronchiectasis. Both inadequate and exaggerated/dysregulated immune responses may play a role in the development of bronchiectasis. Activation of toll-like receptors results in the activation of nuclear factor κB and the release of proinflammatory cytokines interleukin (IL)-1β, IL-8, and tumor necrosis factor-α. IL-8 is a chemoattractant for neutrophils, which are the main inflammatory cell involved in the pathogenesis of bronchiectasis. Once activated, neutrophils produce neutrophil elastase and matrix metalloproteinase (MMP)-8 and MMP-9. IL-6, IL-8, and tumor necrosis factor-α are elevated in the airways of patients with bronchiectasis. Eosinophils are also elevated in the airways of indigenous children with bronchiectasis, which promotes neutrophil recruitment, goblet cell hyperplasia, and airway destruction. There is an increase in proinflammatory cytotoxic T lymphocytes in the peripheral blood of children with bronchiectasis. The mechanism by which bronchiectasis occurs in congenital forms is likely related to abnormal cartilage formation. The common thread in the pathogenesis of bronchiectasis consists of difficulty clearing secretions and recurrent infections with a "vicious cycle" of infection and inflammation resulting in airway injury and remodeling. This cycle results in a spectrum of pediatric suppurative lung disorders: protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD), and bronchiectasis. CSLD patients suffer from symptoms of bronchiectasis without its radiographic features. In early stages, bronchiectasis consists primarily of bronchiolar wall thickening and destruction of elastin resulting in bronchial dilatation. In later stages, the bronchial walls develop cartilage destruction with associated pulmonary artery/arteriole vascular remodeling, resulting in pulmonary hypertension.

Bronchiectasis can manifest in any combination of three pathologic forms, best defined by high-resolution CT (HRCT) scan (Fig. 452.1). In **cylindrical** bronchiectasis, the bronchial outlines are regular, but there is diffuse dilation of the bronchial unit. The bronchial lumen ends abruptly because of mucous plugging. In **varicose** bronchiectasis, the degree of dilation is greater, and local constrictions cause an irregularity of outline resembling that of varicose veins. There may also be small sacculations. In **saccular** (cystic) bronchiectasis, bronchial dilation progresses and results in ballooning of bronchi that end in fluid- or mucus-filled sacs. This is the most severe form of bronchiectasis. The following definitions have been proposed: **prebronchiectasis** (chronic or recurrent endobronchial infection with nonspecific HRCT changes; may be reversible), **HRCT bronchiectasis** (clinical symptoms with HRCT evidence of bronchial dilation; may persist, progress, or improve and resolve), and **established bronchiectasis** (like the previous but with no resolution within 2 years). Early diagnosis and aggressive therapy are important to prevent the development of established bronchiectasis.

CLINICAL MANIFESTATIONS

The most common complaints in patients with bronchiectasis are chronic wet cough and/or production of copious purulent sputum. Younger children may swallow the sputum. In particular, wet or productive cough failing to respond to 4 weeks of oral antibiotics is predictive of the presence of chest CT–defined bronchiectasis. Hemoptysis is seen with some frequency. Fever can occur with infectious exacerbations. Anorexia and poor weight gain may occur as time passes. Physical examination typically reveals crackles localized to the affected area, but wheezing and digital clubbing may also occur. In severe cases, dyspnea and hypoxemia can occur. Pulmonary function studies may demonstrate an obstructive, restrictive, or mixed pattern. Typically, impaired diffusion capacity is a late finding.

Table 452.1 Conditions That Predispose to Bronchiectasis in Children

PROXIMAL AIRWAY NARROWING
Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)
Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)`
Airway stenosis and malacia (tracheal, bronchial)
AIRWAY INJURY
Bronchiolitis obliterans (e.g., postviral, after lung transplantation)
Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia, tuberculosis, *B. pertussis*)
ALTERED PULMONARY HOST DEFENSES
Cystic fibrosis
Primary ciliary dyskinesia
Impaired cough (e.g., neuromuscular weakness conditions)
ALTERED IMMUNE STATES
Primary abnormalities (e.g., agammaglobulinemia, hypogammaglobulinemia, common variable immune deficiency, hyper IgE, hyper IgM, neutrophil dysfunction, gain-of-function *STAT1* variants)
Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)
OTHER
Systemic pseudohypoaldosteronism
Epithelial sodium channel variants *(SCNN1A, SCNN1B)*
Allergic bronchopulmonary aspergillosis
Plastic bronchitis
Right middle lobe syndrome

From Redding GJ. Bronchiectasis in children. *Pediatr Clin North Am.* 2009;56:157–171, Box 1.

DIAGNOSIS

Conditions that can be associated with bronchiectasis should be ruled out by appropriate investigations (e.g., sweat test, immunologic workup). Chest radiographs of patients with bronchiectasis tend to be nonspecific. Typical findings can include increase in size and loss of definition of bronchovascular markings, crowding of bronchi, and loss of lung volume. In more severe forms, cystic spaces, occasionally with air-fluid levels and honeycombing, may occur. Compensatory overinflation of the unaffected lung may be seen. Thin-section HRCT scanning and multidetector CT scanning are the gold standards because they have excellent sensitivity and specificity. CT provides further information on disease location, presence of mediastinal lesions, and the extent of segmental involvement. The main features of bronchiectasis in CT scans include (1) increased bronchoarterial ratio and *signet-ring* appearance; (2) bronchial wall thickening; (3) mucous plugging; (4) lack of bronchial tapering to the lung periphery—"tramlines"; (5) bronchial structures in the lung periphery; and (6) air trapping (mosaic perfusion), most obvious on expiration. The lower lobes (left > right) are more commonly affected. Early in the course, tree-in-bud appearance can also be seen. These CT findings are used to define the bronchiectasis as *cylindrical* ("tram lines," "signet ring appearance"), *varicose* (bronchi with "beaded contour"), *cystic* (cysts in "strings and clusters"), or mixed forms (Fig. 452.2).

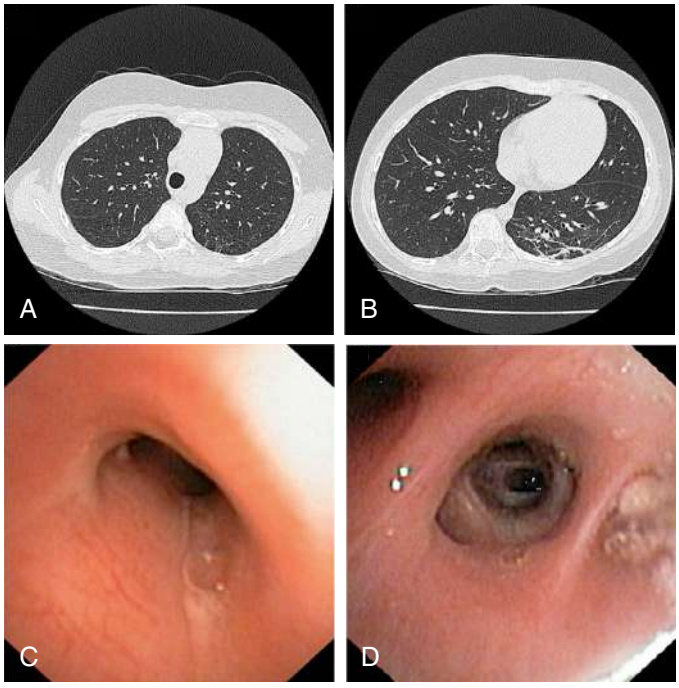

Fig. 452.1 High-resolution chest CT scans (**A** and **B**) and bronchoscopy images (**C** and **D**) in a child with bronchiectasis. (**C** and **D**) Bronchoscopy findings. Images from a chest high-resolution computed tomography (cHRCT) scan (**A** and **B**) in a 10-yr-old girl who presented with a chronic wet cough. The child was treated with a 2-wk course of IV antibiotics (after failing oral antibiotic treatment). The scan was reported as having no evidence of bronchiectasis by pediatric radiologists. At bronchoscopy thick mucus was seen in the trachea (**C**) and the right lower lobe (**D**). The case highlights the need to consider the diagnosis of bronchiectasis on the basis of history, examination findings, and using the pediatric cutoff (bronchoarterial ratio >0.8) for defining bronchiectasis on the cHRCT scan. *(From Goyal V, Grimwood K, Marchant J, et al. Pediatric bronchiectasis: no longer an orphan disease. Pediatr Pulmonol. 2016;51:450–469.)*

TREATMENT

The initial therapy for patients with bronchiectasis is medical and aims at decreasing airway obstruction and controlling infection. Airway clearance techniques (e.g., gravity-assisted drainage, active cycle of breathing, positive expiratory pressure [PEP], acapella, high-frequency chest wall oscillation), antibiotics, and bronchodilators are essential. Two to four weeks of parenteral antibiotics (in hospital or at home) is often necessary to manage more severe acute exacerbations adequately. Exacerbations can be defined as the presence of one major criteria (wet cough enduring longer than 72 hours, increased cough frequency over 72 hours) *plus* one laboratory criteria (C-reactive protein >3 mg/L, serum IL-6 >2 ng/L, serum amyloid A >5 mg/L, elevated neutrophil percentage), two major criteria, or one major criterion *plus* two minor criteria (change in sputum color, breathlessness, chest pain, crackles/crepitations, wheeze). The presence of dyspnea (increased work of breathing) and/or hypoxemia should be considered a severe exacerbation, irrespective of duration.

Antibiotic choice is dictated by the identification and sensitivity of organisms found on deep throat, sputum (induced or spontaneous), or bronchoalveolar lavage fluid cultures. The most common organisms found in children with bronchiectasis include *H. influenzae* non–type b, *S. pneumoniae*, *M. catarrhalis*, *Mycoplasma pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus aureus*. Viruses (most commonly human rhinovirus) are often found in children with bronchiectasis suffering from an exacerbation. A 14-day course of amoxicillin/clavulanic acid (22.5 mg/kg/dose twice daily) has been particularly successful at treating most pulmonary exacerbations. Azithromycin (5 mg/kg/day) is a reasonable alternative in those with penicillin allergy. For those experiencing frequent exacerbations of more than three per year, long-term prophylactic macrolide antibiotics (which also have immunomodulatory and antiinflammatory properties) or nebulized antibiotics (e.g., tobramycin, colistin, aztreonam, ciprofloxacin) may be beneficial (reduced exacerbations and hospitalizations, improved lung function) but may also increase antibiotic

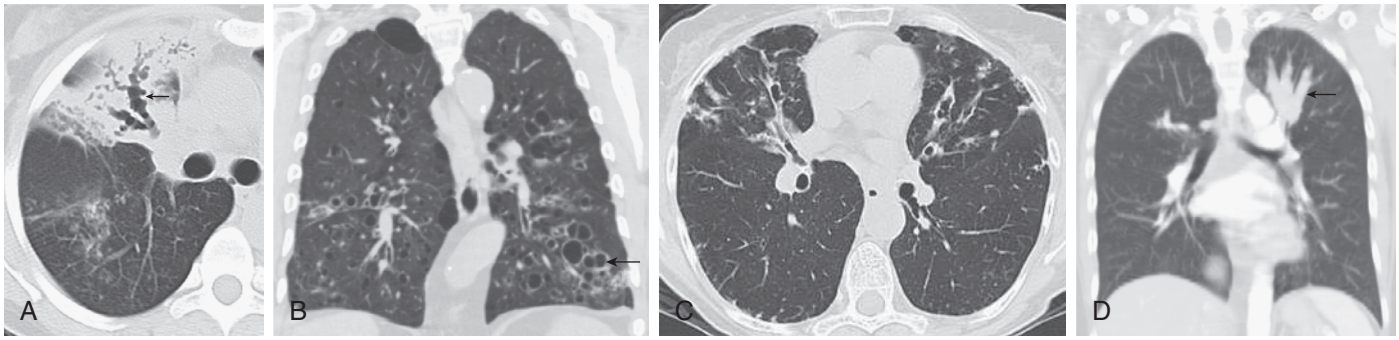

Fig. 452.2 Bronchiectasis. **A,** Axial CT image demonstrates a beaded appearance of dilated bronchi *(arrow)* in the right upper lobe, consistent with varicoid bronchiectasis. **B,** Coronal reformation CT image shows multiple foci of cystic bronchiectasis, with a few air-fluid levels *(arrow)*. Also note paraseptal emphysema, most marked at the right apex. **C,** Bronchiectatic form of chronic atypical mycobacterial infection. Axial CT scan shows extensive bronchiectasis, bronchial wall thickening, and centrilobular nodules, most severe in the middle lobe and lingula. **D,** Allergic bronchopulmonary aspergillosis. Coronal reformation CT image demonstrates impacted bronchi in the left upper lobe *(arrow)* producing a "gloved finger" appearance. *(From Boiselle PM. Airway. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Figs 40-30, 32-34.)*

resistance. Airway hydration (inhaled hypertonic saline or mannitol) also improves quality of life in adults with bronchiectasis, but there are few studies in children. Any underlying disorder (immunodeficiency, aspiration) that may be contributing must be addressed. When localized bronchiectasis becomes more severe or resistant to medical management, segmental or lobar resection may be warranted and may improve growth and reduce the need for intravenous antibiotics. Lung transplantation can also be performed in patients with bronchiectasis. There is no strong evidence to support the routine use of inhaled corticosteroids, although some studies demonstrate improved quality of life and reduced exacerbations in patients with bronchiectasis treated with inhaled corticosteroids. Preventive strategies, including immunization against typical respiratory pathogens (influenza, pneumococci), are generally recommended.

Development of novel treatments is ongoing and centered around targeting three components of the vicious cycle of bronchiectasis: bacterial infection (vitamin D supplementation, exogenous granulocyte-macrophage stimulating factor, phosphodiesterase 4 inhibitors, statins), neutrophilic inflammation (e.g., neutrophil elastase inhibitors, cathepsin C inhibitors, CXCR2 receptor antagonists), and mucociliary clearance (epithelial sodium channel inhibitors).

PROGNOSIS

Children with bronchiectasis often suffer from recurrent pulmonary illnesses, resulting in missed school days, stunted growth, osteopenia, and osteoporosis. The prognosis for patients with bronchiectasis has improved considerably in the past few decades. In some children and adolescents, their bronchiectasis is reversible and/or preventable. Factors important for reversibility and/or prevention of bronchiectasis include early identification and treatment of inhaled foreign bodies, preventing early and severe pneumonia, preventing recurrent protracted bacterial bronchitis, treating primary immunodeficiency disorders causing bronchiectasis, promoting breastfeeding and immunization, and avoiding tobacco smoke and other pollutants.

Thus earlier recognition or prevention of predisposing conditions, specialist multidisciplinary management, more powerful and broad-spectrum antibiotics, and improved surgical outcomes will further improve the prognosis for children with bronchiectasis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 453

Pulmonary Abscess

Oren J. Lakser

Lung infection that destroys the lung parenchyma, resulting in cavitations and central necrosis, can result in localized areas composed of thick-walled purulent material called *lung abscesses. Primary* lung abscesses occur in previously healthy patients with no underlying medical disorders and are usually solitary. *Secondary* lung abscesses occur in patients with underlying or predisposing conditions and may be multiple. Lung abscesses are much less common in children (estimated at 0.7 per 100,000 admissions per year) and result in less morbidity than in adults.

PATHOLOGY AND PATHOGENESIS

Multiple conditions predispose children to the development of pulmonary abscesses, including aspiration, pneumonia, cystic fibrosis (see Chapter 454), gastroesophageal reflux (see Chapter 369), tracheoesophageal fistula (see Chapter 365.1), immunodeficiencies, postoperative complications of tonsillectomy and adenoidectomy, seizures, a variety of neurologic diseases, and other conditions associated with impaired mucociliary defense. Lung abscesses have been associated with e-cigarette or vaping product use–associated lung injury (EVALI; see Chapter 450). In children, aspiration of infected materials or a foreign body is the predominant source of the organisms causing abscesses. Initially, pneumonitis impairs drainage of fluid or the aspirated material. Inflammatory vascular obstruction occurs, leading to tissue necrosis, liquefaction, and abscess formation. Abscess can also occur as a result of pneumonia and hematogenous seeding from another site.

If the aspiration event occurred while the child was recumbent, the right and left upper lobes and apical segment of the right lower lobes are the dependent areas most likely to be affected. In a child who was upright, the posterior segments of the upper lobes were dependent and therefore are most likely to be affected. Primary abscesses are found most often on the right side, whereas secondary lung abscesses, particularly in immunocompromised patients, have a predilection for the left side.

Both anaerobic and aerobic organisms can cause lung abscesses. Common anaerobic bacteria that can cause a pulmonary abscess include *Bacteroides* spp., *Fusobacterium* spp., and *Peptostreptococcus* spp. Abscesses can be caused by aerobic organisms such as *Streptococcus angiosus*, group A streptococcus, *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and very rarely, *Mycoplasma pneumoniae.* Aerobic and anaerobic cultures should be part of the workup for all patients with lung abscess. Occasionally, concomitant viral-bacterial infection can be detected. Fungi can also cause lung abscesses, particularly in immunocompromised patients.

CLINICAL MANIFESTATIONS

The most common symptoms of pulmonary abscess in the pediatric population are fever, cough, and emesis. Other common symptoms include tachypnea, dyspnea, chest pain, sputum production, weight loss, and hemoptysis. Physical examination typically reveals tachypnea, dyspnea, retractions with accessory muscle use, decreased breath sounds, and dullness to percussion in the affected area. Crackles and, occasionally, a prolonged expiratory phase may be heard on lung examination.

DIAGNOSIS

Diagnosis is most commonly made on the basis of chest radiography. Classically, the chest radiograph shows a parenchymal inflammation with a cavity containing an air-fluid level (Fig. 453.1). A chest CT scan can provide better anatomic definition of an abscess, including location and size (Fig. 453.2). Ultrasound can also help provide rapid diagnosis and procedural guidance.

An abscess is usually a thick-walled lesion with a low-density center progressing to an air-fluid level. Abscesses should be distinguished from **pneumatoceles**, which often complicate severe bacterial pneumonias and are characterized by thin- and smooth-walled, localized air collections with or without air-fluid level (Fig. 453.3). Pneumatoceles often resolve spontaneously with the treatment of the specific cause of the pneumonia. The differential diagnosis of a cavitary lung lesion is noted in Table 453.1.

The determination of the etiologic bacteria in a lung abscess can be helpful in guiding antibiotic choice. Although Gram stain of sputum can provide an early clue as to the class of bacteria involved, sputum cultures typically yield mixed bacteria and therefore are not always reliable. Attempts to avoid contamination from oral flora include direct lung puncture, percutaneous (aided by CT guidance) or transtracheal aspiration, and bronchoalveolar lavage specimens obtained bronchoscopically. Bronchoscopic aspiration should be avoided, as it can be complicated by massive intrabronchial aspiration, and great care should therefore be taken during the procedure. To avoid invasive procedures in previously normal hosts, empiric therapy can be initiated in the absence of culturable material.

TREATMENT

Conservative management is recommended for pulmonary abscess. Most experts advocate a 2- to 3-week course of parenteral antibiotics

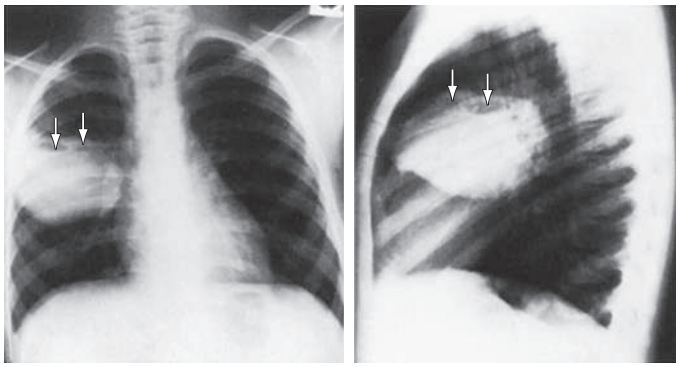

Fig. 453.1 Multiloculated lung abscess *(arrows). (From Brook I. Lung abscess and pulmonary infections due to anaerobic bacteria. In Chernick V, Boat TF, Wilmott RW, et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 7th ed. Philadelphia: WB Saunders; 2006:482.)*

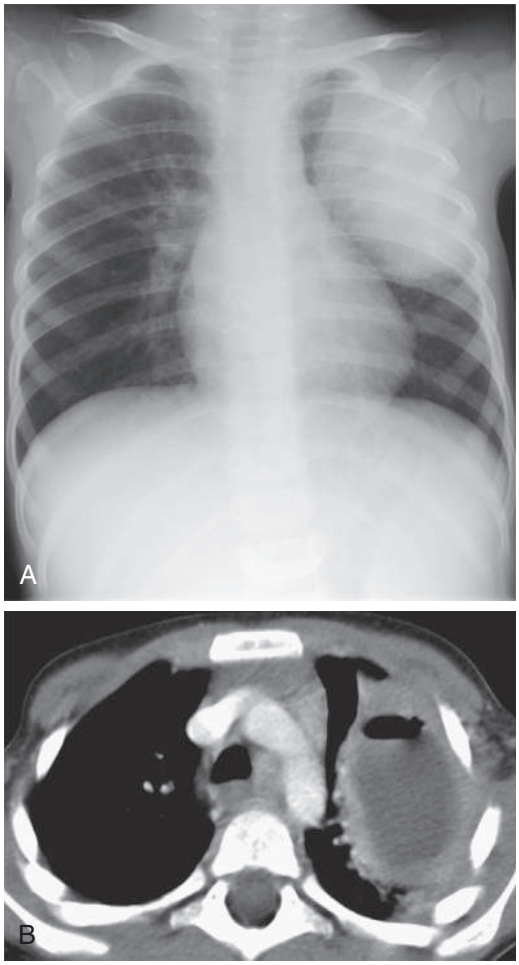

Fig. 453.2 Pulmonary abscess in a 2-yr-old male with persistent cough. **A,** Chest radiograph shows large oval mass in the left upper lobe. **B,** CT scan demonstrates an abscess with a thick enhancing wall that contains both air and fluid. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008, Fig. 78-3, p. 1297.)*

for uncomplicated cases, followed by a course of oral antibiotics to complete a total of 3-4 weeks. Antibiotic choice should be guided by results of Gram stain and culture but initially should include agents with aerobic and anaerobic coverage. Treatment regimens should include a penicillinase-resistant agent active against *S. aureus* and anaerobic coverage, typically with clindamycin or ampicillin-sulbactam. If gram-negative

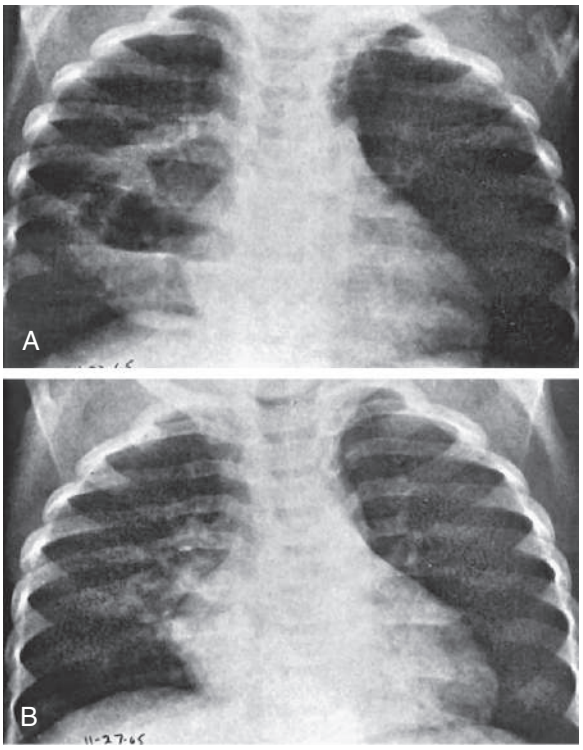

Fig. 453.3 Appearance over a period of 5 days of a large, multiloculated pneumatocele in a segment of alveolar consolidation. **A,** There is a large cavity with two air-fluid levels in a segment of alveolar pneumonia in the right upper lobe. **B,** Five days later, the cavity and most of the pneumonic consolidation have disappeared. *(From Silverman FN, Kuhn JP. Essentials of Caffey's Pediatric X-ray Diagnosis. Chicago: Year Book; 1990:303.)*

bacteria are suspected or isolated, piperacillin-tazobactam or a carbapenem should be added. With improvement, oral antibiotics (clindamycin or amoxicillin-clavulanate) can be used to finish the 4 weeks of total therapy. Early CT-guided percutaneous aspiration or drainage has been advocated by some; it may hasten the recovery and shorten the course of parenteral antibiotic therapy. Nonetheless, antibiotic therapy is successful in ~85% of patients with uncomplicated lung abscesses.

For severely ill patients, patients with larger abscess, or those whose status fails to improve after 7-10 days of appropriate antimicrobial therapy, surgical intervention should be considered. Minimally invasive percutaneous aspiration techniques, often with CT guidance, are the initial and, often, only intervention required. Thoracoscopic drainage has also been successfully used with minimal complications. In rare, complicated cases, thoracotomy (e.g., video-assisted thoracoscopic surgery [VATS] with or without bronchoscopic occlusion) with surgical drainage or lobectomy and/or decortication may be necessary. Abscess drainage is reportedly required in ~20% of cases of pulmonary abscess in children.

PROGNOSIS

Overall, the prognosis for children with primary pulmonary abscesses is excellent. The presence of aerobic organisms may be a negative prognostic indicator, particularly in those with secondary lung abscesses. Most children become asymptomatic within 7-10 days, although the fever can persist for as long as 3 weeks. Radiologic abnormalities usually resolve in 1-3 months but can persist for years (e.g., B-line artifacts on lung ultrasound). Long-term sequalae can also include air trapping/hyperinflation on lung function testing. With treatment, mortality is typically less than 5%.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 453.1 Differential Diagnosis of a Cavitary Lesion on Chest Radiograph

INFECTIOUS CAUSES
Bacteria
Oral anaerobes
Less commonly: *Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa,* enteric gram-negative rods, *Pasteurella multocida, Burkholderia cepacia, Burkholderia pseudomallei, Haemophilus influenzae* types b and c, *Legionella,* group A streptococcus, *Streptococcus pneumoniae, Streptococcus anginosus, Nocardia, Rhodococcus equi, Actinomyces, Clostridium, Capnocytophaga*
Septic Pulmonary Embolism
Originating in septic phlebitis, including Lemierre syndrome and vegetations from tricuspid endocarditis
Mycobacteria
Tuberculosis and nontuberculous pathogens
Fungi
Endemic mycoses (*Histoplasma, Coccidioides,* blastomycosis), *Cryptococcus, Aspergillus,* Zygomycetes
Parasites
Paragonimus westermani, Entamoeba histolytica, Echinococcus
NONINFECTIOUS CAUSES
Neoplasm
Primary lung cancer, metastatic carcinoma (particularly squamous cell)
Pulmonary infarction caused by bland embolus
Vasculitis
Wegener granulomatosis, rheumatoid lung nodule
Airway Disease
Bullae, blebs, or cystic bronchiectasis
Developmental cause
Pulmonary sequestration
Other
Sarcoidosis, achalasia, or transdiaphragmatic bowel herniation giving appearance of cavity with air-fluid level

Modified from Lorber B. Bacterial lung abscess. In: Bennett JE, Dolin R, Blaser M, eds. *Principles and Practice of Infectious Diseases,* 8th ed. Philadelphia: Elsevier; 2014:855–859.

Table 454.1 Complications of Cystic Fibrosis

RESPIRATORY
Bronchiectasis, bronchitis, bronchiolitis, pneumonia
Atelectasis
Hemoptysis
Pneumothorax
Nasal polyps
Sinusitis
Reactive airway disease
Mucoid impaction of the bronchi
Allergic bronchopulmonary aspergillosis
Cor pulmonale
Respiratory failure
GASTROINTESTINAL
Meconium ileus, meconium plug (neonate)
Meconium peritonitis (neonate)
Distal intestinal obstruction syndrome (non-neonatal obstruction)
Rectal prolapse
Intussusception
Volvulus
Fibrosing colonopathy (strictures)
Appendicitis
Intestinal atresia
Pancreatitis (recurrent)
Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)
Neonatal obstructive jaundice
Hepatic steatosis
Gastroesophageal reflux
Cholelithiasis
Inguinal hernia
Growth failure (malabsorption)
Vitamin deficiency states (vitamins A, K, E, D)
Insulin deficiency, symptomatic hyperglycemia, diabetes
Malignancy (rare)
OTHER
Infertility (female)
Congenital absence of vas deferens, azoospermia
Delayed puberty
Edema: hypoproteinemia
Dehydration: heat exhaustion
Hyperchloremic metabolic alkalosis: dehydration
Hypertrophic osteoarthropathy: arthritis
Urinary calculi
Clubbing
Amyloidosis
Diabetes mellitus
Aquagenic palmoplantar keratoderma (skin wrinkling)

Adapted from Silverman FN, Kuhn JP. *Essentials of Caffey's Pediatric X-ray Diagnosis.* Chicago: Year Book; 1990:649.

Chapter 454

Cystic Fibrosis

Marie E. Egan, Michael S. Schechter, and Judith A. Voynow

Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is the most common life-limiting recessive genetic trait among Whites. Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the primary defect, leads to a wide and variable array of presenting manifestations and complications.

CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children. It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis, and nonautoimmune insulin-dependent hyperglycemia. Because CF may manifest as failure to thrive and hepatic dysfunction, including cirrhosis, this disorder enters into the differential diagnosis of many pediatric conditions (Table 454.1).

GENETICS

CF occurs most frequently in White populations of Northern Europe, North America, and Australia/New Zealand. The prevalence in these populations varies but approximates 1 in 3,500 live births (compared with 1 in 9,200 individuals of Hispanic descent and 1 in 15,000 African Americans). Although less frequent in African, Hispanic, Middle Eastern, South Asian, and Eastern Asian populations, the disorder does exist in these populations as well (Fig. 454.1).

CF is inherited as an autosomal recessive trait. The *CF* gene codes for the CFTR protein, which is 1,480 amino acids. CFTR is expressed largely in epithelial cells of airways, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system, but is expressed in other cell types at lower levels. CFTR is a member of

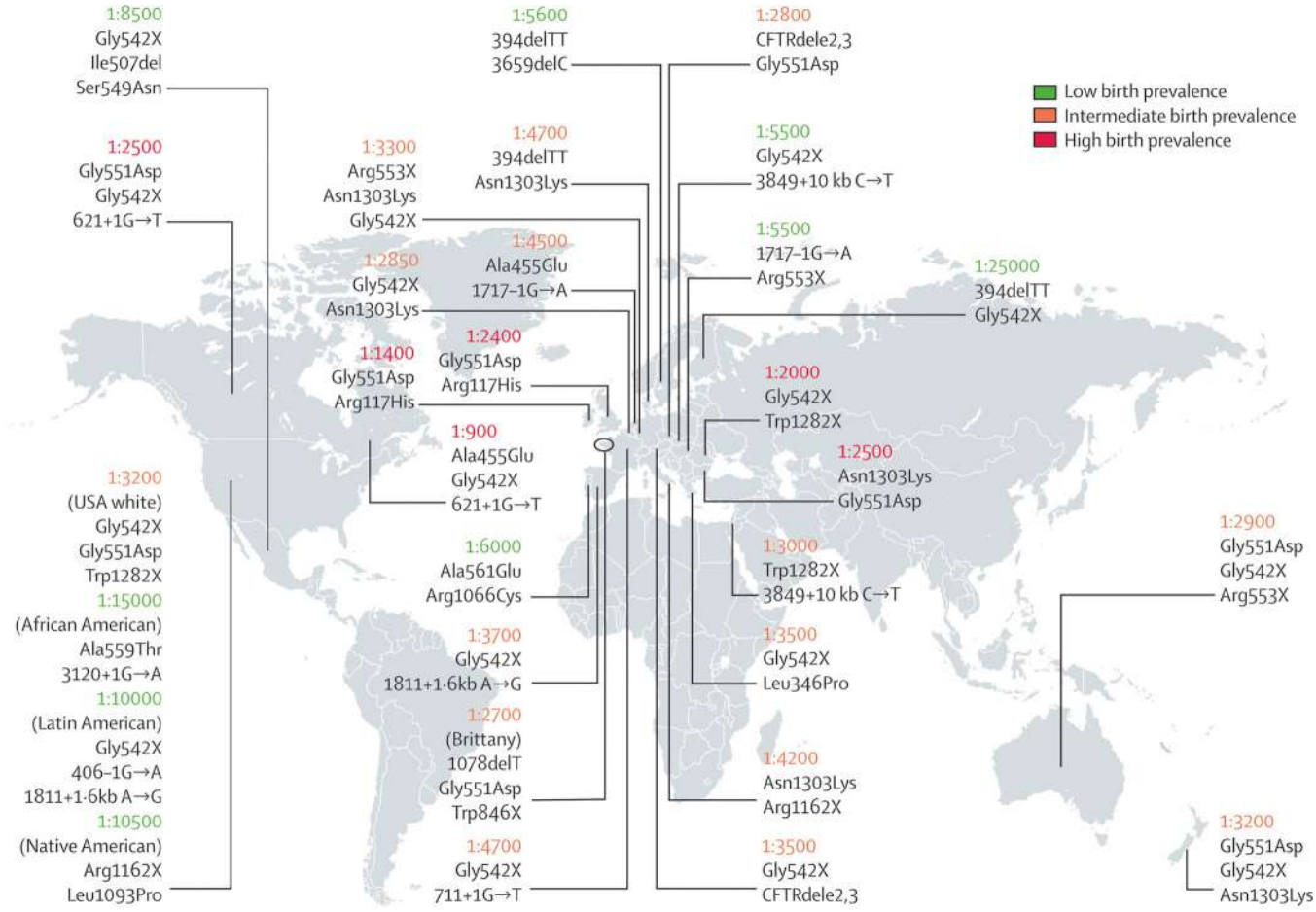

Fig. 454.1 Approximate cystic fibrosis birth prevalence and common pathogenic variants for selected countries. Birth prevalence is reported as the number of live births per case of cystic fibrosis. Common/important pathogenic variants in each region are listed below the prevalence figures. The birth prevalence can vary greatly among ethnic groups in a country. *(From O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373:1891–1902.)*

the adenosine triphosphate (ATP)–binding cassette superfamily of proteins. It functions as an anion channel and is essential for proper chloride and bicarbonate transport across epithelia. More than 1,900 *CFTR* polymorphisms have been described, many of which are not clearly of clinical significance. Those that are associated with clinical manifestations may be grouped into six main classes based on how they affect protein structure and function (Fig. 454.2). Class I-III pathogenic variants are generally considered to be *severe* pathogenic variants in that they lead to a complete or nearly complete absence of CFTR function, whereas class IV-VI pathogenic variants are associated with some residual functional protein. The most prevalent pathogenic variant of *CFTR* is the deletion of a single phenylalanine residue at amino acid 508 (F508del). This pathogenic variant is responsible for the high incidence of CF in northern European populations and is considerably less frequent in other populations, such as those of southern Europe and Israel. Nearly 50% of individuals with CF in the United States Cystic Fibrosis Foundation (CFF) Patient Registry are homozygous for F508del, and approximately 87% carry at least one F508del gene. The remaining patients have an extensive array of pathogenic variants, none of which has a prevalence of more than several percentage points, except in certain populations; for example, the W1282X pathogenic variant occurs in 60% of Ashkenazi Jews with CF. Through the use of probes for 40 of the most common pathogenic variants, the genotype of 80–90% of Americans with CF can be ascertained. Genotyping using a discrete panel of pathogenic variant probes is quick and less costly than more comprehensive sequencing and is the approach typically used in state newborn screening (NBS) programs. In remaining patients, sequencing the entire *CFTR* gene and looking for deletions and duplications are necessary to establish the genotype.

The relationship between CFTR genotype and clinical phenotype is highly complex. The CFTR pathogenic variant class is strongly associated with pancreatic dysfunction and will usually predict this manifestation in any given patient. Respiratory complications and lung function decline are also correlated with pathogenic variant class severity but with greater variation because of the influence of non-CFTR modifier gene polymorphisms and environmental influences on the manifestations of lung disease in any one individual. Studies have identified specific non-CFTR modifier genes of importance; genome-wide association studies identified a polymorphism on chromosome 11 in the intergenic region between EHF (an epithelial transcription factor) and APIP (an inhibitor of apoptosis) that is associated with lung disease severity and may influence the expression of *EHF* and *APIP,* as well as other genes in the region, including *PDHX, CD44,* and *ELF5*. A region on chromosome 20 may also be found to relate to lung disease severity. This region encompasses several genes *(MC3R, CASS4, AURKA)* that may play a role in lung host defense involving neutrophil function, apoptosis, and phagocytosis. Genome-wide association studies analysis also identified genetic regions that predispose to risk for liver disease, CF-related diabetes, and meconium ileus.

The high frequency of *CFTR* pathogenic variants has been ascribed to resistance to the morbidity and mortality associated with infectious dysenteries through the ages. Cultured CF intestinal epithelial cells homozygous for the F508del pathogenic variant are unresponsive to the secretory effects of cholera toxin. CFTR heterozygous mice experience less mortality when treated with cholera toxin than their unaffected wild-type littermates.

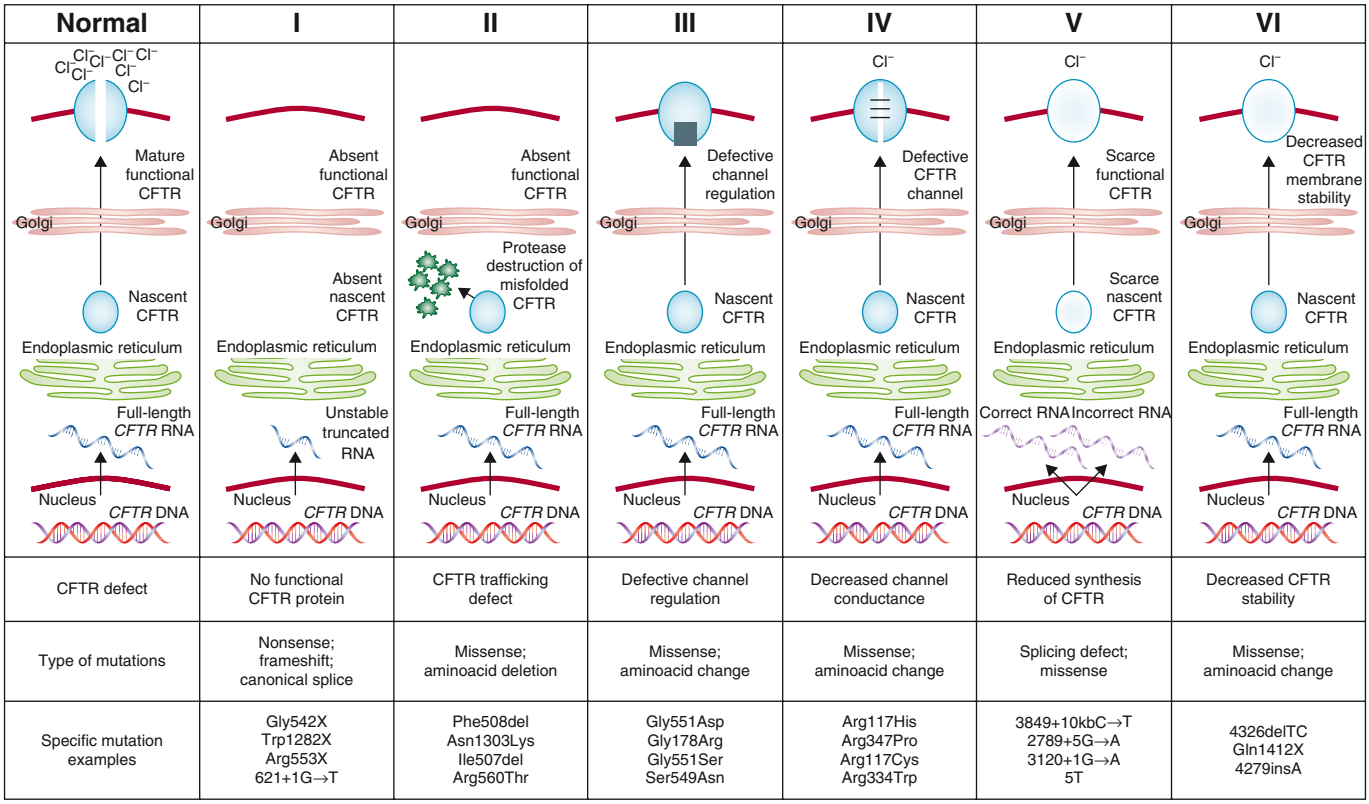

Fig. 454.2 Classes of cystic fibrosis transmembrane conductance regulator *(CFTR)* pathogenic variants. Pathogenic variants in the *CFTR* gene can be divided into six classes. Class I pathogenic variants result in no protein production. Class II pathogenic variants (including the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmic reticulum and subsequent degradation in the proteasome. Class III pathogenic variants affect channel regulation, impairing channel opening (e.g., Gly551Asp). Class IV pathogenic variants show reduced conduction—that is, decreased flow of ions (e.g., Arg117His). Class V pathogenic variants cause substantial reduction in mRNA or protein, or both. Class VI pathogenic variants cause substantial plasma membrane instability and include Phe508del when rescued by most correctors (rPhe508del). *(From Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. Lancet Respir Med. 2013;1:158–163.)*

PATHOGENESIS

A number of long-standing observations of CF are of fundamental pathophysiologic importance; they include failure to clear mucous secretions, a paucity of water in mucous secretions, an elevated salt content of sweat and other serous secretions, and chronic infection limited to the respiratory tract. In addition, there is a greater negative potential difference across the respiratory epithelia of patients with CF than across the respiratory epithelia of control subjects. Aberrant electrical properties are also demonstrated for CF sweat gland duct and rectal epithelia. The membranes of CF epithelial cells are unable to secrete chloride or bicarbonate in response to cyclic adenosine monophosphate–mediated signals, and at least in the respiratory epithelial cells, excessive amounts of sodium are absorbed through these membranes. These defects can be traced to a dysfunction of CFTR. CFTR function is highly regulated and energy dependent; it requires both cyclic adenosine monophosphate–stimulated protein kinase A phosphorylation of the regulatory domain and ATP binding and hydrolysis at the nucleotide binding domains. CFTR also interacts with other ion channels, signal transduction proteins, and the cytoskeleton (Fig. 454.3 and see Fig. 454.2).

Many hypotheses have been postulated to explain how CFTR dysfunction results in the clinical phenotype (Fig. 454.4). It is likely that no one hypothesis explains the full spectrum of disease. One model is that airway hydration homeostasis requires both CFTR and $P2Y_2$-regulated calcium-activated chloride secretion. When extracellular ATP is depleted, such as after viral infections, calcium-activated chloride secretion is not activated, and the failure of CFTR chloride secretion results in dehydrated airway secretions, increased concentration of mucin solids, and more viscoelastic mucus that is not cleared by normal mucociliary transport. Another mechanism that is supported by both primary human airway studies and investigations in the CF pig is that variant CFTR causes failure of HCO_3^- secretion and a more acidic airway surface liquid, which increases mucous viscoelasticity, resulting in poor mucociliary clearance. Mucous secretions are tethered to submucosal gland ducts and are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles. Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system. CFTR dysfunction in airway smooth muscle has been implicated in tracheal and airway abnormalities in humans and in animal models of the disease (pig and mice). These data suggest that CFTR expression in this nonepithelial tissue contributes to airway constriction.

It is plausible that similar pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens), leading to desiccation of proteinaceous secretions and obstruction. Because the function of sweat gland duct cells is to absorb rather than secrete chloride, salt is not retrieved from the isotonic primary sweat as it is transported to the skin surface; chloride and sodium levels are consequently elevated.

Chronic infection in CF is limited to the airways. One explanation for infection is a sequence of events starting with failure to clear inhaled bacteria promptly and then proceeding to persistent infection and an inflammatory response in airway walls. Another explanation for early infection is the failure of innate immune proteins to kill bacteria in an abnormally acidic airway milieu. In addition, it has been proposed that abnormal CFTR creates a proinflammatory state or amplifies the inflammatory response to initial infections (viral or bacterial). Some investigators have identified primary differences in CF-affected immune cells (including macrophage, neutrophils, lymphocytes, and

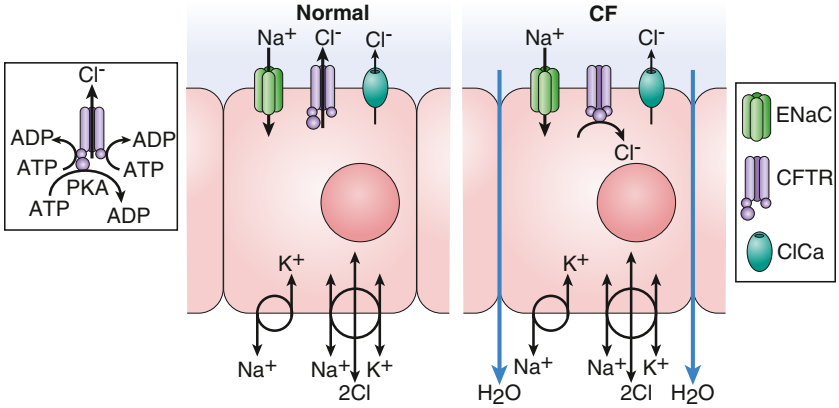

Fig. 454.3 Schematic diagram depicting cystic fibrosis *(CF)* epithelial channel defects, characterized by impaired chloride secretion, massive sodium absorption, and movement of water through the epithelium, leading to a dehydrated airway surface. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; CFTR, cystic fibrosis transmembrane conductance regulator; ClCa, alternative chloride channel; ENaC, epithelium sodium channel; PKA, protein kinase A. *(From Michelson P, Faro A, Ferkol T. Pulmonary disease in cystic fibrosis. In Wilmott RW, Deterding RR, Li A et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 51.1, p. 778.)*

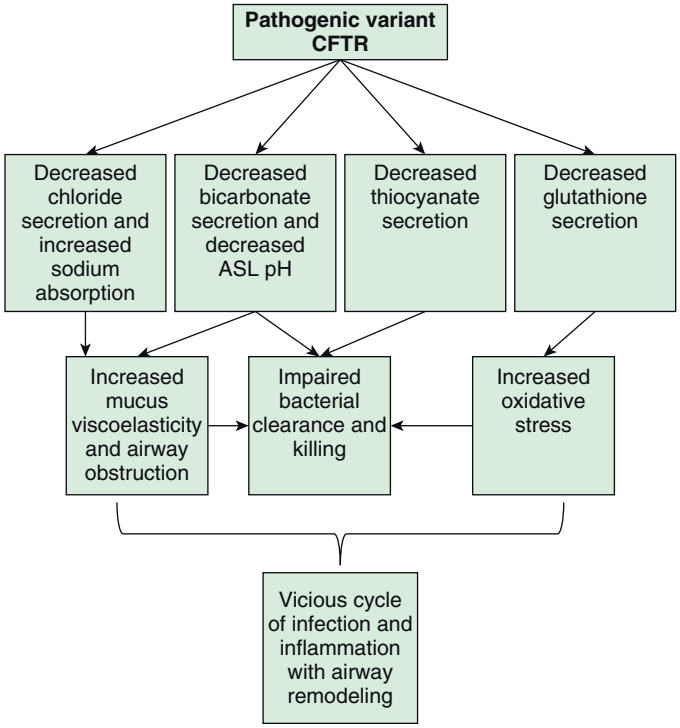

Fig. 454.4 Schema of variant cystic fibrosis transmembrane conductance regulator *(CFTR)* mechanisms of chronic airway disease. CFTR conducts several anions, including chloride, bicarbonate, thiocyanate, and glutathione. The loss of CFTR function affects critical airway epithelial functions: (1) It increases the risk for dehydration of airway surface liquid *(ASL)* with loss of chloride efflux and associated increased sodium channel activity. (2) The loss of secreted bicarbonate and/or acidic pH of the ASL increases mucous viscoelasticity resulting in failure of mucociliary transport. (3) Acidic pH in the ASL impairs normal innate immune clearance of bacteria. (4) Loss of thiocyanate impairs lactoperoxidase bacterial killing. (5) Loss of glutathione secretion depletes the antioxidant capacity of the airway resulting in increased inflammation, increased mucous secretion, and increased mucous viscoelasticity. These factors lead to a vicious cycle of infection and inflammation that is progressive.

dendritic cells) and have suggested that these alterations contribute to this proinflammatory state and to a dysregulated immune response. It appears that inflammatory events occur first in small airways, perhaps because it is more difficult to clear altered secretions and microorganisms from these regions. The agents of airway injury include neutrophil products, such as oxidative radicals and proteases, and immune reaction products. These inflammatory products further aggravate airway obstruction by increasing mucin secretion and altering mucin structure to promote both intramolecular and intermolecular interactions. Excessive inflammatory cell polymers in CF sputum, including DNA, filamentous actin, and glycosaminoglycans, further contribute to abnormal mucous viscoelastic properties and airway obstruction. Chronic bronchiolitis and bronchitis are the initial lung manifestations (see Chapter 439), but after months to years, structural changes in airway walls produce bronchiolectasis and **bronchiectasis**. With advanced lung disease, infection may extend to peribronchial lung parenchyma.

A central feature of lung disease in patients with CF is the high prevalence of airway infection with *Staphylococcus aureus* (see Chapter 227.1), *Pseudomonas aeruginosa* (see Chapter 251.1), and *Burkholderia cepacia* complex (see Chapter 251.2), organisms that rarely infect the lungs of other individuals. It has been postulated that the CF airway epithelial cells or surface liquids may provide a favorable environment for harboring these organisms. CF airway epithelium may be compromised in its innate defenses against these organisms, through either acquired or genetic alterations. Antimicrobial activity is diminished in CF secretions; this diminution may be related to hyperacidic surface liquids or other effects on innate immunity. Another puzzle is the propensity for *P. aeruginosa* to undergo mucoid transformation in the CF airways. The complex polysaccharide produced by these organisms generates a biofilm that provides a hypoxic environment and thereby protects *Pseudomonas* against antimicrobial agents.

Altered lipid homeostasis has been implicated as a predisposing factor for respiratory tract infection and inflammation. Concentrations of lipoxins—molecules that suppress neutrophilic inflammation—are suppressed in CF airways. There is an imbalance of lipids with increased arachidonic acid and decreased docosahexaenoic acid, which promotes inflammation. There is also an imbalance of ceramide in the CF airway that is proinflammatory. Supporting the idea that altered lipid uptake affects infection and inflammation is the observation that the 10–15% of individuals with CF who retain substantial exocrine pancreatic function have delayed acquisition of *P. aeruginosa* and slower deterioration of lung function. However, it appears that nutritional factors are contributory only because preservation of pancreatic function does not preclude development of typical lung disease.

The variation in progression of lung disease seen in patients with CF is also influenced by social and physical environment factors, whose impact matches that of the CFTR genotype. Exposure to environmental tobacco smoke and outdoor air pollutants and early acquisition of respiratory virus infections, as well as pathogenic organisms like *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), have been implicated as causes of worsening disease. Sex/gender disparities also seem to exist, with females having a poorer prognosis. Although studies have suggested that estrogen may influence disease exacerbations, the gap seems to be narrowing.

Although most CF care is delivered at specialty centers and is broadly influenced by current clinical guidelines, there is enough variability in treatment approaches to cause large variation in respiratory and

nutritional outcomes across the care networks in both North America and Europe. Social determinants of health are associated with significant disparities in outcome; socioeconomic status has been shown to be a strong predictor of mortality, as well as both nutritional status and lung function on both sides of the Atlantic. The specific mechanism of effect is unclear, but evidence suggests a role for socioeconomic status–related differences in health behaviors and disease self-management practices, stress and mental health issues, and environmental tobacco smoke exposure. Differential access to specialty care and medications are also known to affect clinical outcomes.

PATHOLOGY

The earliest pathologic lesion in the lung is that of bronchiolitis (mucous plugging and an inflammatory response in the walls of the small airways); with time, mucous accumulation and inflammation extend to the larger airways *(bronchitis)* (see Chapter 439.2). Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection. Organisms appear to be confined to the endobronchial space; invasive bacterial infection is not characteristic. With long-standing disease, evidence of airway destruction such as **bronchiolar obliteration**, **bronchiolectasis**, and **bronchiectasis** (see Chapter 452) becomes prominent. Imaging modalities demonstrate both increased airway wall thickness and luminal cross-sectional area relatively early in lung disease evaluation. Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent with advanced lung disease, with the upper lobes being most commonly involved. These enlarged air spaces may rupture and cause pneumothorax. Interstitial disease is not a prominent feature, although areas of fibrosis appear eventually. Bronchial arteries are enlarged and tortuous, contributing to a propensity for hemoptysis in bronchiectatic airways. Small pulmonary arteries eventually display medial hypertrophy, which would be expected in secondary pulmonary hypertension.

The **paranasal sinuses** are uniformly filled with secretions containing inflammatory products, and the epithelial lining displays hyperplastic and hypertrophied secretory elements (see Chapter 429). Polypoid lesions within the sinuses and erosion of bone have been reported. The nasal mucosa may form large or multiple **polyps**, usually from a base surrounding the ostia of the maxillary and ethmoidal sinuses.

The **pancreas** is usually small, occasionally cystic, and often difficult to find at postmortem examination. The extent of involvement varies at birth. In infants, the acini and ducts are often distended and filled with eosinophilic material. In 85–90% of patients, the lesion progresses to complete or almost complete disruption of acini and replacement with fibrous tissue and fat. Infrequently, foci of calcification may be seen on radiographs of the abdomen. The islets of Langerhans contain normal-appearing β cells, although they may begin to show architectural disruption by fibrous tissue in the second decade of life.

The **intestinal tract** shows only minimal changes. Esophageal and duodenal glands are often distended with mucous secretions. Concretions may form in the appendiceal lumen or cecum. Crypts of the appendix and rectum may be dilated and filled with secretions.

Focal biliary cirrhosis secondary to blockage of intrahepatic bile ducts is uncommon in early life, although it is responsible for occasional cases of prolonged neonatal jaundice. This lesion becomes much more prevalent and extensive with age and is found in 70% of patients at postmortem examination. This process can proceed to symptomatic multilobular biliary cirrhosis that has a distinctive pattern of large, irregular parenchymal nodules and interspersed bands of fibrous tissue. Approximately 30–70% of patients have fatty infiltration of the liver, in some cases despite adequate nutrition. At autopsy, hepatic congestion secondary to cor pulmonale can be observed. The gallbladder may be hypoplastic and filled with mucoid material and often contains stones. The epithelial lining often displays extensive mucous metaplasia. Atresia of the cystic duct and stenosis of the distal common bile duct have been observed.

Glands of the uterine cervix are distended with mucus, copious amounts of which collect in the cervical canal. In >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic, resulting in male infertility.

CLINICAL MANIFESTATIONS

Since the universal adoption of CF NBS, along with the evolution of aggressive and proactive treatment approaches, the clinical face of CF is quite different from what it was in earlier decades. Diagnosis is typically accomplished before 1 month of age, before any obvious clinical symptoms or signs, and treatment is targeted at immediately correcting nutritional deficiencies and delaying the respiratory complications of the disease. The interaction of pathogenic variant heterogeneity and environmental factors leads to highly variable involvement of the lungs, pancreas, and other organs. A summary of the time course of potential development of clinical manifestations is shown in Figure 454.5.

Respiratory Tract

Infants diagnosed by CF NBS are generally asymptomatic from a respiratory standpoint. Nonetheless, the majority are infected with *S. aureus*, *Haemophilus influenza*, or even *P. aeruginosa* within the first month of life, and chest CT scans show characteristic heterogeneous air trapping in ~65% of infants by their first birthday, and bronchiectasis is found in more than

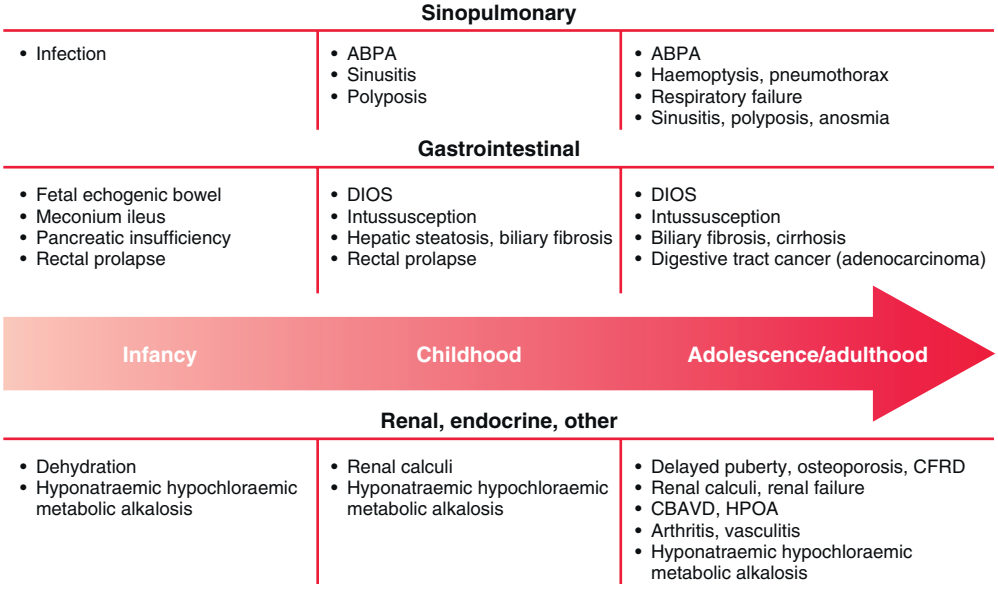

Fig. 454.5 Approximate age of onset of clinical manifestations of cystic fibrosis. ABPA, Allergic bronchopulmonary aspergillosis; CBAVD, congenital bilateral absence of the vas deferens; *CFRD,* cystic fibrosis–related diabetes mellitus; DIOS, distal intestinal obstruction syndrome; HPOA, hypertrophic pulmonary osteoarthritis. *(From O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373:1891–1902.)*

10% of 1-year-olds and ~60% of 5-year-olds. The earliest symptom is usually a cough that may begin with a viral respiratory tract infection but then persists unless treated with antibiotics. With treatment, the generally realized goal is for patients to remain asymptomatic throughout childhood, except for the periodic development of cough, chest congestion, sputum production, and/or wheezing that define a *pulmonary exacerbation*.

The rate of progression of lung disease is the chief determinant of morbidity and mortality. As lung disease slowly progresses, chronic cough, sputum production, exercise intolerance, shortness of breath, and inability to maintain weight are noted. Common pulmonary complications include atelectasis, hemoptysis, and pneumothorax; these usually appear in late adolescence or beyond. Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished; this has become increasingly uncommon in childhood. Infection with certain strains of *B. cepacia* and other multidrug-resistant organisms such as non-tuberculous mycobacteria may be associated with particularly rapid pulmonary deterioration.

Children with CF are unlikely to exhibit any abnormal findings on physical exam except during pulmonary exacerbations. Eventual physical findings include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing. Expiratory wheezes may be heard, a manifestation of airway inflammation and edema that may or may not be associated with bronchodilator responsiveness. Cyanosis is a late sign. Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent. Nasal obstruction, rhinorrhea, and anosmia are common, caused by inflamed, swollen mucous membranes or, in some cases, nasal polyposis. Nasal polyps are most troublesome between 5 and 20 years of age and often require repeated surgeries to control.

Intestinal Tract

In 15–20% of newborn infants with CF, the ileum is completely obstructed by meconium **(meconium ileus)**. The frequency is greater among siblings born subsequent to a child with meconium ileus, and concordance is particularly striking in monozygotic twins, reflecting a genetic contribution from one or more unknown modifying genes. Abdominal distention, emesis, and failure to pass meconium appear in the first 24-48 hours of life (see Chapter 135) and often require surgical intervention. Abdominal radiographs (Fig. 454.6) show dilated loops of bowel with air-fluid levels and, frequently, a collection of granular, "ground-glass" material in the lower central abdomen. Rarely, **meconium peritonitis** results from intrauterine rupture of the bowel wall and can be detected radiographically as the presence of peritoneal or scrotal calcifications. These infants may need bowel resection, leading to significant nutritional challenges caused by short bowel syndrome superimposed upon pancreatic insufficiency.

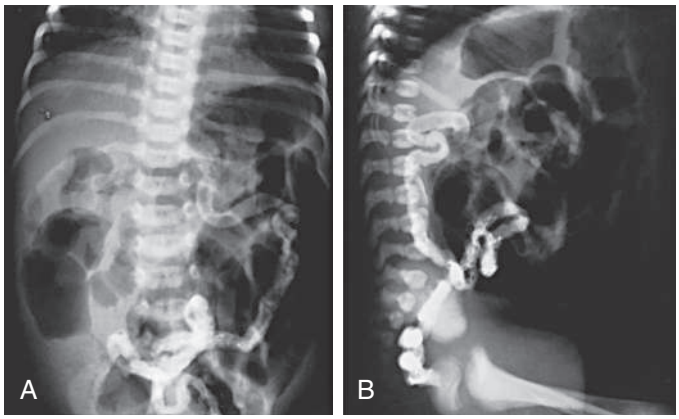

Fig. 454.6 A and B, Contrast enema study in a newborn infant with abdominal distention and failure to pass meconium. Notice the small diameter of the sigmoid and ascending colon and dilated, air-filled loops of small intestine. Several air-fluid levels in the small bowel are visible on the upright lateral view.

Constipation and ileal obstruction with fecal material **(distal intestinal obstruction syndrome [DIOS])** occur in older children, causing cramping abdominal pain, abdominal distention, and obstruction that can be treated with medical approaches to bowel evacuation—typically oral hyperosmotic polyethylene glycol preparations, and occasionally, in more severe cases, hyperosmotic contrast enemas.

More than 85% of children with CF have *exocrine* pancreatic insufficiency, causing protein and fat malabsorption. Symptoms, if untreated, include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large. Weight gain can be challenging, but attainment of normal growth and development is an expectation of treatment. A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are classic and rarely seen physical signs. Excessive flatus may be a problem even in well-nourished children. Supplementation with fat-soluble vitamin preparations has made deficiencies of vitamins A, E, and K unusual, but vitamin D deficiency continues to be prevalent, and although rickets is rare, osteoporosis is common, especially in older patients and those with more severe lung disease. Class IV-VI pathogenic variants are associated with pancreatic *sufficiency,* but patients with these pathogenic variants are prone to recurrent pancreatitis when they reach adolescence.

Historically a relatively common event, **rectal prolapse** occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.

Biliary Tract

Infants may occasionally present with **neonatal jaundice** suggestive of biliary obstruction. Evidence of later liver dysfunction is most often detected in the first 15 years of life and can be found in up to 30% of individuals. **Biliary cirrhosis** develops in about 5–7% of patients. Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism. Biliary colic secondary to cholelithiasis may occur in the second decade or later. Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.

Cystic Fibrosis–Related Diabetes and Pancreatitis

Endocrine pancreatic insufficiency tends to develop in the second decade and beyond and is more common in patients with a family history of type 2 diabetes mellitus. It most commonly begins with postprandial hyperglycemia and may or may not be accompanied by weight loss or flattening weight gain. Fasting hyperglycemia and elevated hemoglobin A_{1c} are later manifestations. Ketoacidosis usually does not occur because insulin deficiency is relative and not absolute, but eye, kidney, and other vascular complications have been noted in patients living ≥10 years after the onset of hyperglycemia. Recurrent acute pancreatitis occurs occasionally in adolescents and adults who have residual function CFTR pathogenic variants with exocrine pancreatic sufficiency.

Genitourinary Tract

Virtually all males are **azoospermic** because of failure of development of wolffian duct structures, but sexual function is generally unimpaired. The female fertility rate is diminished, especially in women who have poor nutrition or advanced lung disease. Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with advanced lung disease and may lead to glucose intolerance that persists after the pregnancy is over. Urinary incontinence associated with cough occurs in 18–47% of female children and adolescents.

Sweat Glands

Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather. These children may present with **hypochloremic alkalosis**. Hyponatremia is a risk particularly in warm climates. Frequently, parents notice salt *frosting* of the skin or a salty taste when they kiss the child. A few genotypes are associated with relatively normal sweat chloride values.

DIAGNOSIS AND ASSESSMENT

CF is diagnosed when an individual has both a clinical presentation of the disease (such as elevated immunoreactive trypsinogen in the newborn period or signs and symptoms discussed earlier in older patients) and evidence of CFTR dysfunction (physiologic assays and/or the presence of disease-causing CFTR genetic variants) (Table 454.2). This simple formulation is complicated by the existence of CFTR genetic variants that are associated with little or no compromise of CFTR function and are therefore of no or varying clinical consequence, leading to a number of patients who fall into "gray" areas.

DIAGNOSIS OF CF VIA NEWBORN SCREENING

All CF NBS algorithms begin in the first days of life with the measurement of serum immunoreactive trypsinogen (IRT), a pancreatic proenzyme that is elevated in almost all infants with CF. Because IRT levels can fluctuate day by day and season by season, most states set a cutoff level based on an average of IRT levels (e.g., ≥95% percentile). Depending on the state, three different CF NBS algorithms are used:

1. IRT/DNA: This is the most commonly used algorithm. A CFTR gene pathogenic variant screening panel (whose composition varies by state) is applied to the original blood spot. Because not all pathogenic variants are included in the screening panel, the finding of just one CFTR pathogenic variant represents a positive screen. Some states (California, New York) perform gene sequencing from the dried blood spot in response to finding one CFTR gene pathogenic variant.
2. IRT/IRT: The IRT is repeated 2-4 weeks later. In infants without CF, the second IRT is usually normal, whereas in infants with CF, it is persistently elevated, representing a positive screen. This approach has been shown to have lower sensitivity than IRT/DNA.
3. IRT/IRT/DNA: Lower cutoffs are used for IRT than in the states with IRT/IRT algorithms, and in infants with persistently elevated IRT, pathogenic variant screening is performed, and the finding of at least one pathogenic variant represents a positive screen.

A positive CF NBS test only identifies infants with a high likelihood of having CF, but it is not diagnostic for CF. Any infant with a positive CF NBS test should have a sweat chloride test (SCT) performed to confirm the diagnosis of CF. In states using the IRT-IRT algorithm, about 20% of those who have a positive CF NBS are subsequently diagnosed with CF by SCT. In states using the IRT-DNA algorithm, only about 10% of infants who are found to have just one CF-causing pathogenic variant from the screening panel are found to have CF (depending on the pathogenic variant screening panel and ethnic background of the child). Even in cases where two CF-causing pathogenic variants have been identified, sweat testing is indicated to rule out laboratory error or misidentification of newborn blood spots.

Table 454.2 Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
A history of CF in a sibling
or
A positive newborn screening test
plus
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
Two elevated sweat chloride concentrations obtained on separate days
or
Identification of two CF pathogenic variants
or
An abnormal nasal potential difference measurement

DIAGNOSIS OF CYSTIC FIBROSIS OUTSIDE OF NEWBORN SCREENING

Although most cases of CF are diagnosed through NBS, there is still a need to consider the diagnosis in the occasional older patient. This is because NBS is not performed everywhere, and even for individuals who were screened, there is the possibility of a false negative. Most older patients whose diagnosis was missed early in life will have unusual class IV, V, or VI pathogenic variants and therefore *normal* pancreatic function. A CF diagnosis in individuals outside of NBS relies on (1) clinical evidence, such as a chronic productive cough resulting from either bronchitis or chronic sinusitis, nasal polyps, allergic bronchopulmonary aspergillosis or unexplained bronchiectasis, congenital bilateral absence of the vas deferens (CBAVD) (in males) or recurrent pancreatitis, and (2) evidence of CFTR dysfunction (such as CFTR molecular genetic analysis, SCT, or other CFTR physiologic tests).

Sweat Testing

The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to the diagnosis of CF. The procedure requires meticulous attention to detail, and its accuracy can only be assumed when performed at CF Foundation–accredited care centers. An electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands because the measurement is validated under conditions of maximal sweat production. Sweat testing is accurate at any postnatal age, but adequate sweat rates are harder to attain in infants less than 36 weeks gestational age and/or less than 2 kg in weight. Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.

More than 60 mmol/L of chloride in sweat is diagnostic of CF when one or more criteria are present. In individuals with a positive NBS, a sweat chloride level less than 30 mmol/L indicates that CF is unlikely. Borderline (or intermediate) values of 30-59 mmol/L have been reported in patients of all ages who have CF with atypical involvement and require further testing. Table 454.3 lists the conditions associated with false-negative and false-positive sweat test results.

Table 454.3 Conditions Associated with False-Positive and False-Negative Sweat Test Results

WITH FALSE-POSITIVE RESULTS
Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy
WITH FALSE-NEGATIVE RESULTS
Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator pathogenic variants with preserved sweat duct function

DNA Testing

Several commercial laboratories provide screening panels that test for the most common CFTR pathogenic variants. The American College of Medical Genetics recommends at least 23; other panels screen for >100 pathogenic variants. The sensitivity of these panels depends on the race/ethnicity of the population tested, but is always well under 100%, so it is important to view them as screening, but not definitive, diagnostic tests. Whole CFTR gene sequencing with additional attention to deletions and duplications is available but is expensive and only helpful in very select situations.

Other Physiologic Measures of CFTR Function

The finding of increased potential differences across nasal epithelium **(nasal potential difference)**, that is the increased voltage response to topical amiloride application, followed by the absence of a voltage response to a β-adrenergic agonist, has been used to confirm the diagnosis of CF in patients with equivocal or frankly normal sweat chloride values. Intestinal current measurements may also provide additional helpful information, particularly in children who are unable to cooperate with nasal potential difference testing. These procedures are primarily used in research applications and have never undergone extensive validation as a clinical tool.

OTHER LABORATORY TESTING OF IMPORTANCE IN DIAGNOSIS AND MANAGEMENT

Pancreatic Function

The diagnosis of pancreatic insufficiency can be made by the quantification of *elastase-1 activity* in a fresh stool sample by an enzyme-linked immunosorbent assay specific for human elastase. The quantification of fat malabsorption with a 72-hour stool collection is rarely performed in the clinical setting. CF-related diabetes affects approximately 20% of adolescents and 40–50% of adults, and clinical guidelines recommend yearly oral glucose tolerance testing (OGTT) after age 10. OGTT may sometimes be clinically indicated at an earlier age. Spot testing of blood and urine glucose levels and glycosylated hemoglobin levels are not sufficiently sensitive.

Radiology

Hyperinflation of lungs occurs early and is often accompanied by nonspecific peribronchial thickening (Fig. 454.7). Bronchial thickening and plugging and ring shadows suggesting bronchiectasis usually appear first in the upper lobes. Nodular densities, patchy atelectasis, and confluent infiltrate follow. Hilar lymph nodes may be prominent. With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow cardiac shadow are noted.

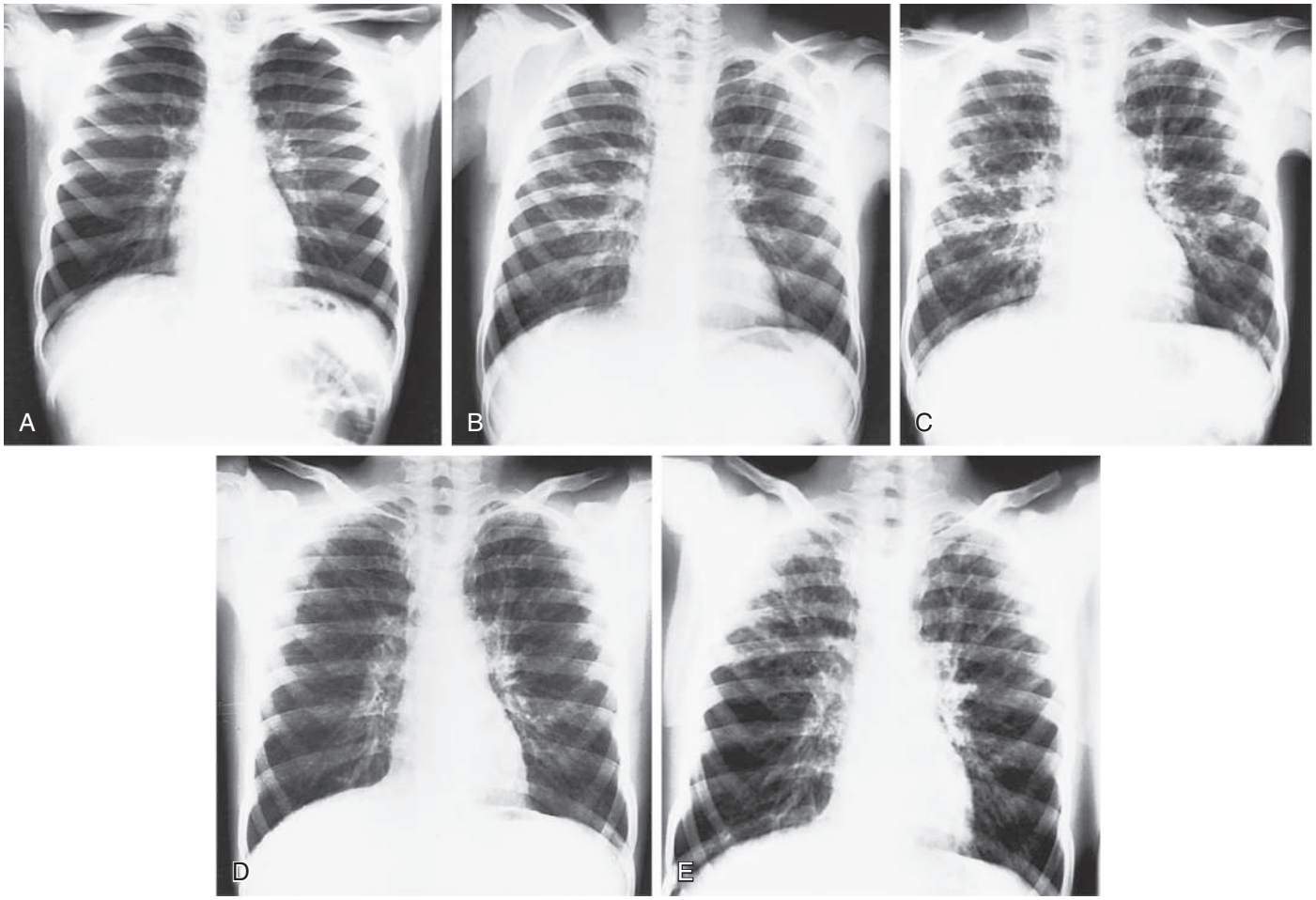

Fig. 454.7 Serial radiographs in a child show the changing appearance of cystic fibrosis over 6 yr. **A,** At 9 yr, frontal radiograph shows minimal peribronchial thickening and hyperaerated lungs indistinguishable from asthma. **B,** Nineteen mo later, the radiographic picture has worsened considerably. Extensive peribronchial thickening is now noted. Mucoid impaction of the bronchus is seen in the left upper lobe, and hilar shadows have become abnormally prominent. **C,** Ten mo later, further deterioration is obvious. Widespread typical changes of cystic fibrosis (CF) are noted throughout both lungs. **D,** Follow-up studies show considerable improvement, which suggested that some of the changes evident on (C) were from superimposed infection. **E,** One yr later, note the progressive changes of CF—most severe in the upper lobes bilaterally. *(From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 73-54.)*

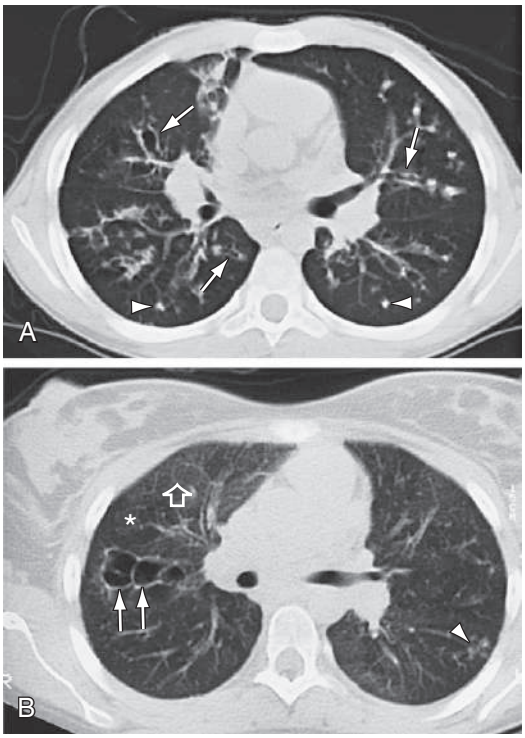

Fig. 454.8 CT scans of the chest in cystic fibrosis. **A,** A 12-yr-old male with moderate lung disease. Airway and parenchymal changes are present throughout both lungs. Multiple areas of bronchiectasis *(arrows)* and mucous plugging *(arrowheads)* can be seen. **B,** A 19-yr-old female has mostly normal lung with one area of saccular bronchiectasis in the right upper lobe *(arrows)* and a focal area of peripheral mucous plugging in the left lower lobe *(arrowhead).* Lung density is heterogeneous with areas of normal lung *(open arrow)* and areas of low attenuation reflecting segmental and subsegmental air trapping *(asterisk).*

Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease. Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually. CT of the chest can detect heterogeneous hyperinflation and localized thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and bronchiectasis (Fig. 454.8). CT abnormalities are commonly seen as early as the first year of life and even in asymptomatic children with normal lung function.

Radiographs of paranasal sinuses reveal panopacification and, often, failure of frontal sinus development. CT provides better resolution of sinus changes if this information is required clinically.

Fetal ultrasonography may show pancreatic changes indicative of CF and suggest ileal obstruction with meconium early in the second trimester, but this finding is not predictive of meconium ileus at birth.

Pulmonary Function

Infant pulmonary function testing is done routinely for clinical evaluation at a few CF centers, but given its complexity and the need for sedation, for the most part it is reserved for research protocols. Lung clearance index (LCI), measured by multiple breath washout, can be done in infants and young children and is a sensitive measure of ventilation inhomogeneity caused by small airways disease. Currently it is primarily used for research, but given its ease and applicability, it may be adopted as a standard monitoring tool in the future as CF care centers become more accustomed to its use.

Standard pulmonary function studies are usually obtained starting at about 4 years of age and are routinely done by age 6. **Forced expiratory volume in 1 second** (FEV_1) is the measurement that has been shown to correlate most closely with mortality and shows a gradual decline averaging 2–3% per year throughout childhood. Although a small number of children may already show evidence of airway obstruction

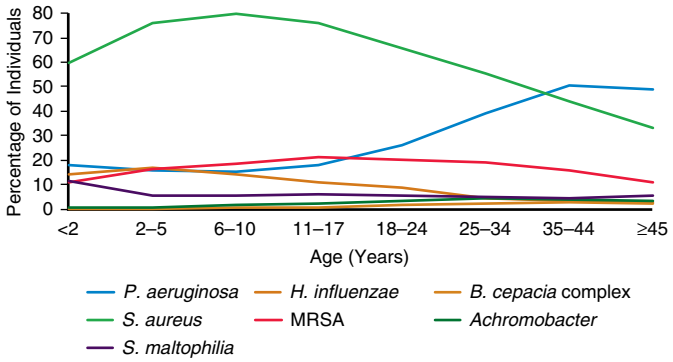

Fig. 454.9 Prevalence of respiratory microorganisms by age cohort, 2021. *(From the Cystic Fibrosis Patient Registry 2021. Annual Data Report. p. 30. © 2022 Cystic Fibrosis Foundation. Bethesda, Maryland. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf)*

by age 6, trends over the past several decades, as reported by the CFF patient registry, show a steady improvement in average FEV_1 of the CF population. The proportion of people with CF age 18 years who are in the normal/mild lung disease category (FEV_1 ≥70% predicted) has increased from 33.8% in 1989 to 78.3% in 2019. The proportion in the severe lung disease category (FEV_1 <40% predicted) has decreased from 24.0% in 1988 to 2.6% in 2019. Residual volume and functional residual capacity are increased early in the course of lung disease and are the cause of decreasing forced vital capacity (FVC) measurement. Restrictive changes, characterized by declining total lung capacity and vital capacity, correlate with extensive lung injury and fibrosis and are a late finding. Testing at each clinic visit is recommended to evaluate the course of the pulmonary involvement and allow for early intervention when clinically significant decrements are documented—an acute drop in FEV_1 is probably the most sensitive indicator of a pulmonary exacerbation that should be treated with systemic antibiotics.

Microbiologic Studies

H. influenza and *S. aureus* are the most common organisms recovered in young children (Fig. 454.9). *Pseudomonas* may be acquired early and is an organism of key significance. *P. aeruginosa* appears to have a special propensity for the CF airway and over time characteristically develops a biofilm associated with a mucoid appearance in the microbiology lab and which correlates with more rapid progression of lung disease. Once *P. aeruginosa* develops a mucoid phenotype, it is extremely difficult to eradicate from the airway. A wide range of other organisms are frequently recovered, particularly in advanced lung disease; they include a variety of gram-negative rods, including the *B. cepacia* complex, which may be associated with a fulminant downhill course **(cepacia syndrome)**; *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans;* assorted fungi, especially *Aspergillus fumigatus,* which is most important because of the relatively common development of **allergic bronchopulmonary aspergillosis**; and nontuberculous mycobacterial species, especially *Mycobacterium avium* complex and *Mycobacterium abscessus*. Airway cultures are obtained regularly, most typically using oropharyngeal swabs in young children, and then sputum (which may be induced) in older children capable of expectoration. Oropharyngeal swabs typically give a good indication of the lower airway flora, but fiberoptic bronchoscopy may be used to gather lower respiratory tract secretions of infants and young children who do not expectorate if there is a concern for false-negative cultures, especially regarding the presence of *P. aeruginosa*.

The CF airway microbiome consists of a large number of additional organisms, especially anaerobes that are identified through antigen detection but not culture methods. The significance of this finding and its therapeutic implications remain somewhat unclear, but it has long been appreciated that response to antibiotic treatment of pulmonary exacerbations is not always predictable based on culture and sensitivity of airway cultures.

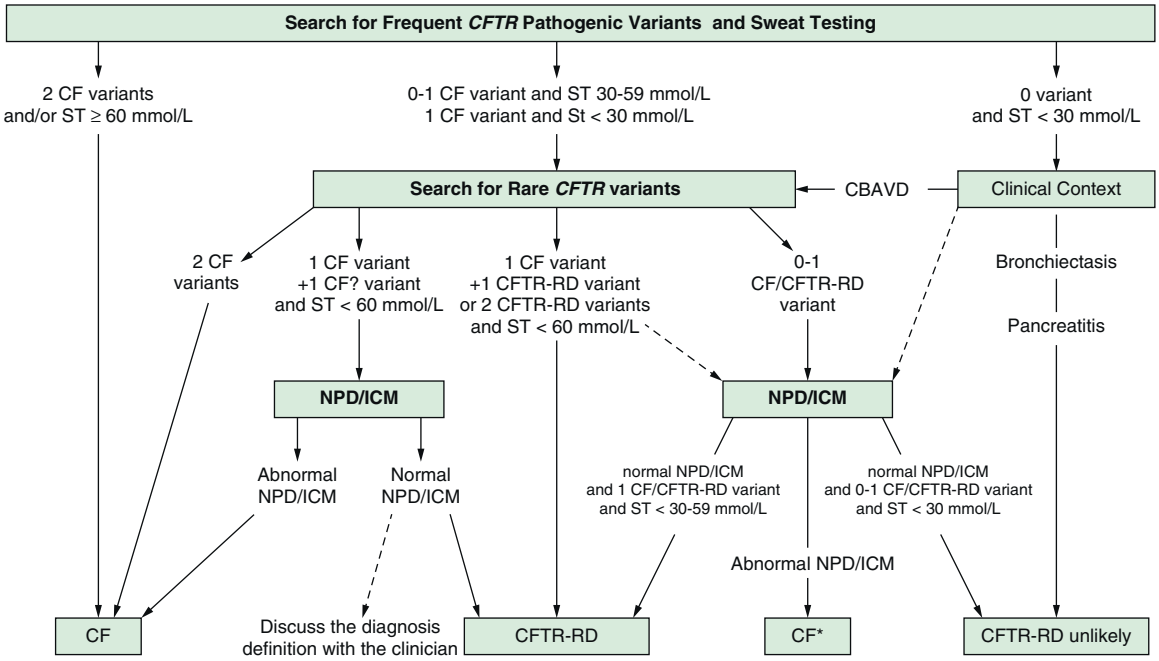

Fig. 454.10 2015 European Cystic Fibrosis Society recommended algorithm for diagnosis of CFTR-RD. Global diagnostic algorithm for CF and CFTR-RD. A global flowchart of genetic and functional diagnostic testing in CF and CFTR-RD is presented. CBAVD, Congenital bilateral absence of the vas deferens; CF, cystic fibrosis; CF? pathogenic variant, pathogenic variant of unproven or uncertain clinical significance; CF*, diagnosis of CF or consider this diagnosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTR-RD, CFTR-related disorders; ICM, intestinal current measurement; NPD, nasal potential difference; ST, sweat test (repeated; false positive should be excluded/sought in a specialized center). *(From Bombieri C, Claustres M, De Boeck K, et al. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros. 2011;10[Suppl 2]:S86–102, Fig 1.)*

MANIFESTATIONS OF REDUCED CFTR FUNCTION THAT DO NOT MEET CRITERIA FOR CF

CFTR-Related Metabolic Syndrome

There is a subset of infants with a positive newborn screen for CF who have inconclusive diagnostic testing. The term for this condition, used in the United States, is *CFTR-related metabolic syndrome* (CRMS); in Europe, the analogous term is *CF screen positive, inconclusive diagnosis* (CFSPID). Data from the CF Foundation National Patient Registry show that approximately one infant is diagnosed with CRMS for every five cases of CF. An infant is determined to have CRMS if they are asymptomatic with a positive CF NBS test and either (1) sweat test <30 mmol/L and two *CFTR* pathogenic variants, at least one of which has unclear phenotypic consequences, or (2) sweat test 30-59 mmol/L and zero or one CF-causing CFTR pathogenic variant.

CRMS should be *distinguished* from CFTR-related disorder (CFTR-RD), described later, in that CRMS is a diagnosis that arises only from CF NBS in otherwise asymptomatic individuals.

Data on long-term outcomes of infants with CRMS are limited because universal CF NBS is relatively new and CRMS has only recently been recognized. The majority of CRMS infants appear to have normal growth and do not develop any pulmonary manifestations of CF, although it is not unusual for them to grow *P. aeruginosa* from their airways in the absence of any other clinical manifestations. However, a small percentage (~5–10%) will develop signs and symptoms of CF, including measures of CFTR dysfunction such as a clinically elevated sweat chloride or abnormalities in other CFTR functional assays. This is a diagnosis that it is important for the general pediatrician to be aware of, because these children are often lost to follow-up by CF care centers.

CFTR-Related Disorder

The diagnosis of CFTR-RD has been defined as a monosymptomatic clinical entity associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF. Common manifestations include CBAVD, recurrent pancreatitis, chronic sinusitis, nasal polyposis, or bronchiectasis. This is more typically diagnosed in adults but sometimes might appear in late adolescence. An approach to the evaluation of patients with CFTR-RD is seen in Figure 454.10.

TREATMENT

General Approach to Care

Initial efforts after diagnosis should be intensive and should include baseline assessment, initiation of treatment to prevent pulmonary involvement in young infants or reverse it in those diagnosed later, nutritional maintenance or remediation, and education of the patient and parents. Follow-up evaluations are scheduled every 1-3 months, depending on the age at diagnosis, because many aspects of the condition require careful monitoring. An interval history and physical examination should be obtained at each visit. A sputum sample or, if that is not available, a lower pharyngeal swab taken during or after a forced cough is obtained for culture and antibiotic susceptibility studies. Because irreversible loss of pulmonary function from low-grade infection can occur gradually and without acute symptoms, emphasis is placed on a thorough pulmonary history and physical exam and routine pulmonary function testing. Table 454.4 lists symptoms and signs that suggest the need for more intensive antibiotic and physical therapy (PT). Protection against exposure to MRSA, *P. aeruginosa, B. cepacian,* and other resistant gram-negative organisms is essential, including contact isolation procedures and careful attention to cleaning of inhalation therapy equipment. A nurse, physical therapist, respiratory therapist, social worker, and dietitian, as members of the multidisciplinary care team, should evaluate children regularly and contribute to the development of a comprehensive daily care plan. Considerable education and programs to empower families and older children to take responsibility for care are likely to result in the best adherence to daily care programs. Screening patients and caregivers for anxiety and depression annually is expected to identify issues that can interfere with adherence to daily care. Standardization of practice, on the part of both caregivers and families, as well as close monitoring and early intervention for new or increasing symptoms, appears to result in the best long-term outcomes.

Because secretions of CF patients are not adequately hydrated, attention in early childhood to oral hydration, especially during warm weather or with acute gastroenteritis, may minimize complications associated with impaired mucous clearance. Intravenous therapy for dehydration should be initiated early.

Table 454.4 Symptoms and Signs Associated with Exacerbation of Pulmonary Infection in Patients with Cystic Fibrosis

SYMPTOMS
Increased frequency and duration of cough
Increased sputum production
Change in appearance of sputum
Increased shortness of breath
Decreased exercise tolerance
Decreased appetite
Feeling of increased congestion in the chest
SIGNS
Increased respiratory rate
Use of accessory muscles for breathing
Intercostal retractions
Change in results of auscultatory examination of chest
Decline in measures of pulmonary function consistent with the presence of obstructive airway disease
Fever and leukocytosis
Weight loss
New infiltrate on chest radiograph

From Ramsey B. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med.* 1996;335:179.

The goal of therapy is to maintain a stable condition for prolonged periods. This can be accomplished for most patients by interval evaluation and adjustments of the home treatment program. Some children have episodic acute or low-grade chronic lung infection that progresses. For these patients, intensive inhalation and airway clearance and intravenous antibiotics are indicated. Improvement is most reliably accomplished in a hospital setting; selected patients have demonstrated successful outcomes while completing these treatments at home. Intravenous antibiotics may be required infrequently or as often as every 2-3 months. The goal of treatment is to return patients to their previous pulmonary and functional status.

The basic daily care program varies according to the age of the child, the degree of pulmonary involvement, other system involvement, and the time available for therapy. The major components of this care are pulmonary and nutritional therapies. Because therapy is medication intensive, iatrogenic problems frequently arise. Monitoring for complications is also an important part of management.

Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapies

CFTR modulator therapies are small molecules taken orally that correct the processing and function of the variant CFTR protein in multiple organs and reduce or correct manifestations of disease. They have been developed to target specific classes of pathogenic variants (see Fig. 454.2). Ivacaftor is a small-molecule potentiator of the CFTR pathogenic variant G551D (present in ~5% of patients). Ivacaftor activates the CFTR-G551D variant protein, a class III CFTR pathogenic variant that results in protein localized to the plasma membrane but loss of chloride channel function (Table 454.5; Fig. 454.11). Ivacaftor therapy results in improvement in FEV_1 by an average of 10.6%, decreases the frequency of pulmonary exacerbations by

Table 454.5 Cystic Fibrosis Transmembrane Regulator Modulators for Cystic Fibrosis

DRUG	FDA-APPROVED INDICATION	FORMULATIONS	USUAL DOSAGE
Ivacaftor	4 mo with a responsive pathogenic variant*	25, 50, 75 mg granule packets† 150 mg tablets	<6 yr: weight-based dosing‡; ≥6 yr: 150 mg q12h
Lumacaftor/ivacaftor	≥2 yr, F508del-homozygous	100/125, 200/125 mg tabs; 100/125, 150/188 mg granule packets†	6-11 yr: 200/250 mg q12h ≥12 yr: 400/250 mg q12h§
Tezacaftor/ivacaftor	≥6 yr, F508del-homozygous or F508del-heterozygous with another responsive pathogenic variant‖	Tablets: tezacaftor once per day and ivacaftor twice per day q12h	6-11 yr, <30 kg; AM: 50 mg tezacaftor + 75 mg ivacaftor PM: 75 mg ivacaftor 6-11 yr, ≥30 kg and 12 yr: AM: 100 mg tezacaftor + 150 mg tab ivacaftor PM: 150 mg tab ivacaftor
Elexacaftor/tezacaftor/ivacaftor	≥6 yr, one copy of F508del	Tablets: 2 triple-combination tablets (orange) in AM and one ivacaftor tablet (blue) in PM	6-11 yr, <30 kg; AM: elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg (2 combination tablets) PM: ivacaftor 75 mg 6-11 yr, ≥30 kg and 12 yr: AM: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (2 combination tablets) PM: ivacaftor 150 mg
	2 yr - <6 yr, one copy of F508del	ELX 80 or 100 mg TEZ 40 or 50 mg IVA 60 or 75 mg	<14 kg: AM: ELX 80 / TEZ 40 AM and PM: IVA 60 ≥14 kg: AM: ELX 100 / TEZ 50 AM and PM: IVA 75

*Approved pathogenic variants: G551D, S549N, G1244E, G178R, S1251N, G551S, G1349D, S1255P, R117H, E56K, K1060T, P67L, E193K, A1067T, R74W, L206W, G1069R, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, R117C, A455E, S977F, F1074L, F1052V, D115H; 3849 þ 10 kb C>T, 2789 þ5G>A, 3273-26A>G, 711þ3A>G, E831X.
†The granules should be mixed with 5 mL of room-temperature or cold soft food or liquid and consumed within 1 hr.
‡In patients 4 mo to 6 yr old, the recommended dosage is 25 mg every 12 hr for weight 5 kg to <7 kg, 50 mg every 12 hr for those weighing <14 kg, and 75 mg every 12 hr for those weighing ≥14 kg.
§In patients 2-5 yr old, the recommended dosage is 100/125 mg every 12 hr for those weighing <14 kg and 150/188 mg every 12 hr for those weighing ≥14 kg.
‖F508del heterozygotes with the following pathogenic variants: E56K, K1060T, P67L, E193K, A1067T, R74W, L206W, D110E, D110H, R347H, D579G, R1070Q, D1270N, R352Q, S945L, R1070W, R117C, A455E, S977F, F1074L, F1052V, D1152H, 3849þ10kb C>T, 2789 þ5G>A, 3273-26A>G, 711þ3A>G.
Modified from The Medical Letter on Drugs and Therapeutics: Tezacaftor/Ivacaftor (Symdeko) for cystic fibrosis. *Med Lett.* 2018;60(1558):174–176, Table 3.

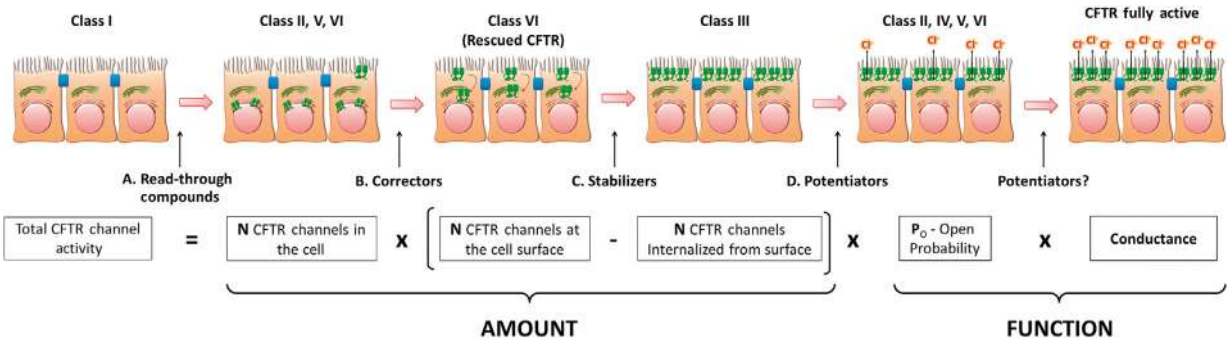

Fig. 454.11 Cystic fibrosis transmembrane conductance regulator *(CFTR)* pharmacologic modulators have different modes of action. **A,** Read-through compounds, which include aminoglycoside antibiotics (e.g., gentamicin, tobramycin), act by suppressing premature termination codons (PTCs), thus permitting translation to continue to the normal termination of the transcript and thus increasing the total amount of complete CFTR being produced in the cell. **B,** Correctors (e.g., VX-809, also known as lumacaftor; VX-661) potentially promote folding of variant CFTR protein, allowing it to escape ER degradation and reach the cell surface, thus increasing the number of channels present at the plasma membrane. **C,** Stabilizers include compounds (e.g., hepatocyte growth factor) that enhance CFTR retention/anchoring at the cell surface, thus also contributing to increase the number of channels present at the cell surface. **D,** Potentiators (e.g., VX-770, also known as ivacaftor) activate CFTR, that is, increase the open probability *(P_o)* of the channel by regulating its gating and possibly also the conductance. *(From Bell SC, De Boeck K, Amaral MD. New pharmacological approaches for cystic fibrosis: promises, progress, pitfalls. Pharmacol Therapeu. 2015;145:19–34, Fig. 4.)*

55%, decreases sweat chloride by an average of 48 mEq/L, and increases weight gain by an average of 2.7 kg. Ivacaftor is approved for patients older than 2 years of age with class III and class IV pathogenic variants.

The combination of ivacaftor with lumacaftor, a corrector that stabilizes misfolded F508del and enables trafficking of the variant molecule to the apical cell membrane where it is potentiated by ivacaftor, is available for patients older than 6 years of age who are homozygous for the F508del pathogenic variant (see Fig. 454.11). This medication is associated with smaller increments in pulmonary and nutritional outcomes but is an important proof-of-concept treatment.

Tezacaftor and ivacaftor is another combination indicated for patients ≥6 years with one or two Phe508del alleles. This combination improves predicted FEV_1 and overall well-being (see Table 454.5). VX-445 combined with tezacaftor-ivacaftor adds another CFTR correction agent; the triple combination improves predicted FEV_1 and reduces sweat chloride levels.

Elexacaftor/tezacaftor/ivacaftor, a triple combination therapy for patients ≥6 years with at least one copy of Phe508del alleles was approved in 2019 (see Table 454.5). This therapy is a highly effective modulator, and 90% of patients with CF are eligible to use this treatment. In a phase 3 randomized, double-blind trial for patients homozygous for Phe508del comparing elexacaftor/tezacaftor/ivacaftor to tezacaftor/ivacaftor alone, patients on triple therapy had a significant increase in FEV_1 percent predicted of 10% and a dramatic decrease in sweat chloride levels by 45 mM compared with double therapy at 4 weeks. In a phase 3 randomized, double-blind, placebo-controlled clinical trial for patients with one copy of Phe508del, triple therapy was associated with a decrease in sweat chloride by 41.8 mmol/L and a marked increase in FEV_1 percent predicted of 14% at 24 weeks. The success of these highly effective CFTR modulator therapies, ivacaftor for class III pathogenic variants and elexacaftor/tezacaftor/ivacaftor for Phe508del, has been life-changing. Ivacaftor and the triple combination therapy are being evaluated for therapeutic efficacy in younger children and infants with CF.

However, at least 10% of patients with CF have pathogenic variants that are not responsive to these highly effective modulator therapies. Patients with class I pathogenic variants caused by premature termination codons and failure to translate CFTR protein will require new approaches to therapy to acquire normal CFTR protein and function. Gene therapy, gene editing, and antisense oligonucleotide therapeutic approaches are currently being developed.

Pulmonary Therapy

The object of pulmonary therapy is to clear secretions from airways and to control infection. When a child is not doing well, every potentially useful aspect of therapy should be reconsidered.

Inhalation Therapy

Human recombinant Dnase (2.5 mg) enzymatically dissolves extracellular DNA released by neutrophils, a major contributor to the characteristically sticky and viscous CF airway secretions. Recombinant human Dnase is usually given as a single daily aerosol dose; it improves pulmonary function, decreases the number of pulmonary exacerbations, and promotes a sense of well-being. Benefit for those with mild, moderate, and severe lung disease has been documented. Improvement is sustained for 12 months or longer with continuous therapy.

Nebulized hypertonic saline, acting as a hyperosmolar agent, is believed to draw water into the airway and rehydrate mucus and the periciliary fluid layer, resulting in improved mucociliary clearance. Seven percent hypertonic saline nebulized 2-4 times daily increases mucous clearance and reduces pulmonary exacerbation, with only a slight short-term improvement in pulmonary function.

Airway Clearance Therapy

Airway clearance treatment begins in infancy with chest percussion (with or without postural drainage) and derives its rationale from the idea that cough clears mucus from large airways, but chest vibrations are required to shear secretions from the airway wall and move secretions from small airways, where expiratory flow rates are low. **Chest PT** can be particularly useful for patients with CF because they accumulate secretions in small airways first, even before the onset of symptoms. Cessation of chest PT in children with mild to moderate airflow limitation results in deterioration of lung function within 3 weeks, and prompt improvement of function occurs when therapy is resumed, but it is less clear which available modality is best. Airway clearance therapy is recommended 2-4 times a day, depending on the severity of lung dysfunction, and usually increased during acute exacerbations. Cough, huffing, or forced expirations are encouraged intermittently throughout the session. Vest-type mechanical percussors *(high-frequency chest wall oscillation)* are commonly used past infancy because of their convenience, as are a variety of oscillatory positive expiratory pressure devices (such as Acapella and Aerobika) and other controlled breathing techniques (e.g., *autogenic drainage*). Routine aerobic exercise appears to slow the rate of decline of pulmonary function, and benefit has also been documented with weight training. No one airway clearance technique can be shown to be superior to any other, so all modes should be considered in the development of an airway clearance prescription. Adherence to daily therapy is important but rarely achieved; therefore airway clearance technique plans are individualized for each patient.

Antibiotic Therapy

Antibiotics are the mainstay of therapy designed to control progression of lung infection. The goal is to reduce the intensity of endobronchial infection and to delay progressive lung damage. The usual guidelines

Table 454.6 Antimicrobial Agents for Cystic Fibrosis Lung Infection

ROUTE	ORGANISMS	AGENTS	DOSAGE (mg/kg/24 hr)	NO. DOSES/24 hr
Oral	*Staphylococcus aureus*	Dicloxacillin	25-50	4
		Linezolid	20	2
		Cephalexin	50	4
		Clindamycin	10-30	3-4
		Amoxicillin-clavulanate	25-45	2-3
	Haemophilus influenzae	Amoxicillin	50-100	2-3
	Pseudomonas aeruginosa	Ciprofloxacin	20-30	2-3
	Burkholderia cepacia	Trimethoprim-sulfamethoxazole	8-10*	2-4
	Empirical	Azithromycin	10, day 1; 5, days 2-5	1
		Erythromycin	30-50	3-4
Intravenous	*S. aureus*	Nafcillin	100-200	4-6
		Vancomycin	40	3-4
	P. aeruginosa	Tobramycin	8-12	1
		Amikacin	15-30	2-3
		Ticarcillin	400	4
		Piperacillin	300-400	4
		Ticarcillin-clavulanate	400†	4
		Piperacillin-tazobactam	240-400‡	3
		Meropenem	60-120	3
		Imipenem-cilastatin	45-100	3-4
		Ceftazidime	150	3
		Aztreonam	150-200	4
	B. cepacia	Chloramphenicol	50-100	4
		Meropenem	60-120	3
Aerosol		Tobramycin (inhaled)	300§	2
		Aztreonam (inhaled)	75	3

*Quantity of trimethoprim.
†Quantity of ticarcillin.
‡Quantity of piperacillin.
§In mg per dose.

for acute chest infections, such as fever, tachypnea, or chest pain, are often absent. Consequently, all aspects of the patient's history and examination, including anorexia, weight loss, and diminished activity, must be used to guide the frequency and duration of therapy. Antibiotic treatment varies from intermittent short courses of one antibiotic to nearly continuous treatment with one or more antibiotics. Dosages for some antibiotics are often 2-3 times the amount recommended for minor infections because patients with CF have proportionately more lean body mass and higher clearance rates for many antibiotics than other individuals. In addition, it is difficult to achieve effective drug levels of many antimicrobials in respiratory tract secretions.

Oral Antibiotic Therapy

Indications for oral antibiotic therapy in a patient with CF include the presence of respiratory tract symptoms, physical signs, or changes in pulmonary function testing or chest x-ray. Treatment is guided by identification of pathogenic organisms in respiratory tract cultures and in vitro sensitivity testing. Common organisms, including *S. aureus (MRSA or methicillin-susceptible S. aureus [MSSA]),* nontypeable *H. influenzae, P. aeruginosa, B. cepacian,* and other gram-negative rods, are encountered with increasing frequency. The usual course of therapy is 2 weeks, and maximal doses are recommended. Table 454.6 lists useful oral antibiotics. The quinolones are the only broadly effective oral antibiotics for *Pseudomonas* infection, but resistance against these agents may emerge. Macrolides may reduce the virulence properties of *P. aeruginosa,* such as biofilm production, and contribute antiinflammatory effects. Long-term therapy with azithromycin 3 times a week improves lung function in patients with chronic *P. aeruginosa* infection.

Aerosolized Antibiotic Therapy

Aerosolized antibiotics are often used as part of daily therapy when the airways are infected with *P. aeruginosa*. Aerosolized tobramycin inhalation solution or powder, or aztreonam inhalation solution used as a suppressive therapy (on 1 month, off 1 month), may reduce symptoms, improve pulmonary function, and decrease the occurrence of pulmonary exacerbations. Although these therapies are sometimes used in acute pulmonary exacerbations, the evidence to support this application is limited.

Another important indication for aerosolized antibiotic therapy is to eradicate *P. aeruginosa* in the airways after initial detection. Early infection may be cleared for months to several years in this way, although eventual reinfection is common. Other antibiotics have been used via

inhalation, including liposomal amikacin and levofloxacin for *P. aeruginosa,* and there was no inferiority of efficacy compared with inhaled tobramycin.

Intravenous Antibiotic Therapy

For the patient who has not responded to oral antibiotics and intensive home measures with return of signs, symptoms, and FEV_1 to baseline, intravenous antibiotic therapy is indicated. This therapy is usually initiated in the hospital but is sometimes completed on an ambulatory basis if the likelihood of complete adherence to the therapeutic regimen is good. The ideal duration of treatment is unknown; although many patients show improvement within 7 days, many CF physicians believe that it is usually advisable to extend the period of treatment to at least 14 days. Permanent intravenous access can be provided for long-term or frequent courses of therapy in the hospital or at home. Thrombophilia screening should be considered before the use of totally implantable intravenous devices or for recurring problems with venous catheters.

Table 454.6 lists commonly used intravenous antibiotics. In general, treatment of *Pseudomonas* infection is thought to require two-drug therapy. A third agent may be given for optimal coverage of *S. aureus* or other organisms. Aminoglycosides are usually effective when given every 24 hours to minimize toxicity and optimize convenience. Some CF physicians use peak and trough levels to guide dosing, but most clinical pharmacists recommend measuring levels at other times, commonly 2 and 12 hours, to use pharmacokinetic calculations to guide dosing. Changes in therapy should be guided by lack of improvement more than by culture results; sensitivities do not always predict response to therapy, and this may be because of the presence of other organisms that are not detected by culture methods. If patients do not show improvement, complications such as right heart failure; asthma; or infection with viruses, *A. fumigatus* (especially allergic bronchopulmonary aspergillosis, ABPA) (see Chapter 283), nontuberculous mycobacteria (see Chapter 263), or other unusual organisms should be considered. *B. cepacia* complex and *Acinetobacter* are gram-negative rods that may be particularly refractory to antimicrobial therapy. Infection control in both the outpatient and inpatient medical setting is critically important to prevent nosocomial spread of resistant bacterial organisms between patients.

Bronchodilator Therapy

Reversible airway obstruction occurs in many children with CF, sometimes in conjunction with frank asthma or allergic bronchopulmonary aspergillosis. Reversible obstruction is conventionally defined as improvement of ≥12% in FEV_1 or FVC after inhalation of a bronchodilator. In many patients with CF, these may improve by only 5–10% (physiologic response), but subjects may report subjective benefit.

Antiinflammatory Agents

Corticosteroids are useful for the treatment of allergic bronchopulmonary aspergillosis and severe asthma occasionally encountered in children with CF. Prolonged systemic corticosteroid treatment of CF lung disease reduces the decline in lung function modestly but causes predictably prohibitive side effects. Inhaled corticosteroids have theoretical appeal, but there are contradictory and weak data regarding efficacy unless the patient has clinically diagnosable asthma. Ibuprofen, given chronically in high doses adjusted to achieve a peak serum concentration of 50-100 μg/mL, is associated with a slowing of disease progression, particularly in younger patients with mild lung disease. However, there are concerns regarding side effects of nonsteroidal antiinflammatory drugs, so this therapy has not gained broad acceptance. Macrolide antibiotics have an antiinflammatory effect, and 3 days/week of azithromycin has been shown to reduce the likelihood of the development of pulmonary exacerbations, especially in patients with chronic *Pseudomonas* airway infection, so this is a commonly used therapy.

Other Therapies

Attempts to clear recalcitrant atelectasis and airway plugging with bronchopulmonary lavage and direct instillation of various medications are sometimes used in exceptional cases; there is no evidence for sustained benefit from repeated procedures. Expectorants such as iodides and guaifenesin do not effectively assist with the removal of secretions from the respiratory tract. Inspiratory muscle training can enhance maximum oxygen consumption during exercise along with FEV_1.

TREATMENT OF PULMONARY COMPLICATIONS

Atelectasis

Lobar atelectasis occurs relatively infrequently; it may be asymptomatic and noted only at the time of a routine chest radiograph. Aggressive intravenous therapy with antibiotics and increased chest PT directed at the affected lobe may be effective. If there is no improvement in 5-7 days, bronchoscopic examination of the airways may be indicated. If the atelectasis does not resolve, continued intensive home therapy is indicated because atelectasis may resolve during a period of weeks or months.

Hemoptysis

Endobronchial bleeding usually reflects airway wall erosion into hypertrophied bronchial vessels secondary to infection. Although more common in patients with advanced disease, it is sometimes seen in adolescents with relatively mild lung disease. Blood streaking of sputum is particularly common. Small-volume hemoptysis (<20 mL) is usually viewed as a need for intensified antimicrobial therapy and chest PT. **Massive hemoptysis**, defined as total blood loss of ≥250 mL in a 24-hr period, is rare in the first decade and occurs in <1% of adolescents, but it requires close monitoring and the capability to replace blood losses rapidly. Bronchoscopy rarely reveals the site of bleeding. Bronchial artery embolization can be useful to control persistent, significant hemoptysis.

Pneumothorax

Pneumothorax (see Chapter 461) is encountered uncommonly in children and teenagers with CF, although it may lead to significant compromise in lung function and occasionally may be life-threatening. The episode may be asymptomatic but is often attended by chest and shoulder pain, shortness of breath, or hemoptysis. A small air collection that does not grow can be observed closely. Chest tube placement with or without pleurodesis is often the initial therapy. Intravenous antibiotics are also begun on admission. Video-assisted thoracoscopic surgery (VATS) with plication of blebs, apical pleural stripping, and basal pleural abrasion should be considered if the air leak persists. Surgical intervention is usually well tolerated even in cases of advanced lung disease. The thoracotomy tube is removed as soon as possible. Previous pneumothorax with or without pleurodesis is not a contraindication to subsequent lung transplantation.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis occurs in 5–10% of patients with CF and may manifest as wheezing, increased cough, shortness of breath, and marked hyperinflation or, most commonly, a decrease in FEV_1 that does not respond to antibiotic therapy (see Chapter 283). In some patients, a chest radiograph shows new focal infiltrates. A highly elevated total serum immunoglobulin E (IgE) level (>1,000) is usually the initial indication of the diagnosis. The presence of rust-colored sputum, the recovery of *Aspergillus* organisms from the sputum, a positive skin test for *A. fumigatus,* the demonstration of specific IgE and IgG antibodies against *A. fumigatus,* or the presence of eosinophils in a fresh sputum sample supports the diagnosis. Treatment is directed at controlling the inflammatory reaction with oral corticosteroids. Oral antifungals are usually reserved for patients who relapse after initial steroid treatment. For refractory cases, omalizumab, humanized monoclonal anti-IgE, has been effective.

Nontuberculous Mycobacteria Infection

See Chapter 263.

Injured airways with poor clearance may be colonized by *M. avium*-complex but also *M. abscessus, Mycobacterium chelonae,* and *Mycobacterium kansasii.* Distinguishing endobronchial colonization (frequent) from invasive infection (infrequent) is challenging. Persistent fevers and new infiltrates or cystic lesions coupled with the finding of acid-fast organisms on sputum smear suggest infection. Infection with these organisms, or at least its recognition, has become increasingly

common. Treatment is prolonged and requires multiple antimicrobial agents. Symptoms may improve, but the nontuberculous mycobacteria are not usually cleared from the lungs.

Sleep-Disordered Breathing

Particularly with advanced pulmonary disease and during chest exacerbations, individuals with CF may experience more sleep arousals, less time in rapid eye movement sleep, nocturnal hypoxemia, hypercapnia, and associated neurobehavioral impairment. Nocturnal hypoxemia may hasten the onset of pulmonary hypertension and right-sided heart failure. Efficacy of specific interventions for this complication of CF has not been systematically assessed. Prompt treatment of airway symptoms and nocturnal oxygen supplementation or bilevel positive airway pressure support should be considered in selected cases, especially in patients with advanced lung disease.

Acute Respiratory Failure

Acute respiratory failure (see Chapter 86) rarely occurs in patients with mild to moderate lung disease and is usually the result of a severe viral or other infectious illness. Because patients with this complication can regain their previous status, intensive therapy is indicated. In addition to aerosol, postural drainage, and intravenous antibiotic treatment, oxygen is required to raise the arterial Pao_2. An increasing Pco_2 may require ventilatory assistance. Endotracheal or bronchoscopic suction may be necessary to clear airway inspissated secretions and can be repeated daily. Right-sided heart failure should be treated vigorously. High-dose steroids have been anecdotally reported to be of benefit in this setting. Recovery is often slow. Intensive intravenous antibiotic therapy and postural drainage should be continued for 1-2 weeks after the patient has regained baseline status.

Chronic Respiratory Failure

Patients with CF acquire chronic respiratory failure after prolonged deterioration of lung function. Although this complication can occur at any age, it is seen most frequently in adult patients. Because a long-standing Pao_2 <50 mm Hg promotes the development of right-sided heart failure, patients usually benefit from low-flow oxygen to raise arterial Po_2 to ≥55 mm Hg. Increasing hypercapnia may prevent the use of optimal fraction of inspired oxygen. Most patients improve somewhat with intensive antibiotic and pulmonary therapy measures and can be discharged from the hospital. Low-flow oxygen therapy is needed at home, especially with sleep. Noninvasive ventilatory support can improve gas exchange and has been documented to enhance quality of life. Ventilatory support may be particularly useful for patients awaiting lung transplantation. These patients usually display pulmonary hypertension and cor pulmonale, and this complication should be treated. Caution should be exercised to avoid ventilation-suppressing metabolic alkalosis that results from CF-related chloride depletion and, in many cases, from diuretic-induced bicarbonate retention. Chronic pain (headache, chest pain, abdominal pain, and limb pain) is frequent at the end of life and responds to judicious use of analgesics, including opioids. Dyspnea has been ameliorated with nebulized fentanyl.

Pulmonary Hypertension and Cor Pulmonale

Individuals with long-standing, advanced pulmonary disease, especially those with severe hypoxemia (Pao_2 <50 mm Hg), often acquire pulmonary hypertension and chronic right-sided heart failure. Evidence for concomitant left ventricular dysfunction is often found. The arterial Po_2 should be maintained at >50 mm Hg, if possible, and hypercarbia corrected with noninvasive ventilation or intubation if necessary. Intensive pulmonary therapy, including intravenous antibiotics, is most important. Adjunctive therapy with salt restriction, diuretics, and pulmonary vasodilators may be indicated. The prognosis for heart failure is poor, but a number of patients survive for ≥5 years after the appearance of heart failure. Heart-lung transplantation may be an option.

Lung Transplantation

Lung transplantation is an option for end-stage lung disease (see Chapter 492). Criteria for referral continue to be a subject of investigation and ideally include estimates of longevity with and without transplant based on lung function and exercise tolerance data. Survival and quality of life after lung transplantation are better in patients with CF than other chronic lung diseases, probably because of the relatively younger age of recipients with CF, but the current estimated 5-year survival is about 50%, somewhat reduced compared with that of other solid organ transplants. Because of bronchiolitis obliterans (see Chapter 443.1) and other transplant-related complications, transplanted lungs cannot be expected to function for the lifetime of a recipient, and repeat transplantation is increasingly common. The demand for donor lungs exceeds the supply, and waiting lists and duration of waits continue to be a problem. Importantly, since the initiation of treatment with elexacaftor/tezacaftor/ivacaftor, some patients with chronic lung disease have significantly improved so that they no longer require listing for lung transplantation.

Nutritional Therapy

Up to 90% of patients with CF have loss of exocrine pancreatic function leading to inadequate digestion and absorption of fats and proteins. They require dietary adjustment and augmentation, pancreatic enzyme replacement, and supplementary vitamins. In general, children with CF need to exceed the usual required daily caloric intake to grow. Daily supplements of the fat-soluble vitamins are required.

Diet

Historically, at the time of diagnosis, many infants presented with nutritional deficits; this situation has changed because of newborn screening, but even at 2-4 weeks, it is not uncommon to see that weight gain has begun to fall off the standard curve.

Most children with CF have a higher-than-normal caloric need because of malabsorption despite the use of pancreatic enzyme supplementation. Encouragement to eat high-calorie foods is important and often begins with more concentrated, high-calorie formulas in the first year. Even so, most mothers can breastfeed successfully. It is vitally important to promote adequate weight gain in the early years, both because of a clear relationship to later lung function and because early deficiencies make later catch-up growth more difficult. Not infrequently, feeding problems can negatively affect parent–child interactions at meal time, and behavioral interventions can improve caloric intake. The liberal use of appetite stimulants, especially cyproheptadine, in early childhood makes the struggle a bit easier. Poorly controlled lung disease increases metabolism and decreases appetite and needs to be considered when efforts to improve weight gain are unsuccessful.

Maintenance of good weight gain and body mass index in the first year of life leads to better long-term preservation of lung function, but there is a strong correlation between body mass index and FEV_1 that persists through all ages in people with CF. Better nutrition also leads to improved quality of life and psychologic well-being and provides better reserves when weight loss occurs in association with intermittent acute pulmonary exacerbations.

Malabsorption is an important contributor to nutritional deficiencies, and it is important to ensure that pancreatic enzyme dosing is adequate and consistently being taken correctly with all meals and feedings. Appetite stimulants when cyproheptadine is not successful may include megestrol, oxandrolone, dronabinol, antidepressants such as mirtazapine, and even growth hormone. CF-related diabetes needs to be ruled out.

When all these therapies fail, weight stabilization or gain can be achieved with nocturnal feeding via nasogastric tube or gastrostomy tube. These are most commonly resorted to in infants and adolescents, the two age-groups that have the most difficulty with weight gain because of high-normal demands.

Pancreatic Enzyme Replacement

Pancreatic exocrine replacement therapy given with ingested food reduces, but does not fully correct, stool fat and nitrogen losses. Current products are enteric-coated, pH-sensitive enzyme microspheres that come in capsules and are given to children before they can swallow by opening the capsule and mixing the beads in small amounts of acidic foods such as applesauce. Strengths ranging from 3 to 40,000 IU of lipase/capsule are available. Administration of excessive doses has been linked to fibrosing colonopathy and **colonic strictures**, so

recommendations are for enzyme dosing to stay below 2,500 lipase units/kg/meal in most circumstances. Snacks should also be covered. Some enzyme replacement therapies provide bicarbonate in addition to the enzymes, which may be helpful for a subset of patients to correct acid pH in the duodenum, which is caused by a lack of exocrine pancreatic secretions; neutralization of duodenal pH permits optimal activation of enteric-coated pancreatic exocrine replacement therapy granules. Some individuals prefer proton pump inhibitor therapy to achieve the same effect.

Vitamin and Mineral Supplements

Because pancreatic insufficiency results in malabsorption of fat-soluble vitamins (A, D, E, K), vitamin supplementation is recommended. Several vitamin preparations containing all four vitamins for patients with CF are available. They should be taken daily. Despite this supplementation, vitamin D deficiency is common and should be treated with doses of cholecalciferol (vitamin D3) rather than ergocalciferol (vitamin D2). The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, be treated with an initial dose of 400-500 IU vitamin D3 per day, from 12 months to 10 years of age, an initial dose of 800 to 1000 IU of vitamin D3 per day, and from 10 years of age and older, an initial dose of 800 to 2000 IU of vitamin D3 per day. Higher doses are recommended for those who are vitamin D deficient. Salt supplementation is also needed during infancy and is started at the time of diagnosis. There may be additional vitamin and micronutrient needs if a child with CF required an intestinal resection as a newborn as a result of meconium ileus.

TREATMENT OF INTESTINAL COMPLICATIONS

Meconium Ileus

When meconium ileus (see Chapter 135) is suspected, contrast enemas with reflux of contrast material into the ileum not only confirm the diagnosis but may also result in the passage of meconium and clearing of the obstruction. Children in whom this procedure fails require operative intervention. Children who have had meconium ileus are at greater risk for nutritional deficiency and are more likely to develop problems with DIOS when older. Infants with meconium ileus should be assumed to have CF unless proven otherwise.

Distal Intestinal Obstruction Syndrome and Other Causes of Abdominal Symptoms

Despite appropriate pancreatic enzyme replacement, a number of patients accumulate fecal material in the terminal portion of the ileum and in the cecum, which may result in partial or complete obstruction. For intermittent symptoms, pancreatic enzyme replacement should be continued or even increased, and stool hydrators such as polyethylene glycol should be given. If this fails or symptoms are more severe, large-volume bowel lavage with a balanced salt solution containing polyethylene glycol may be taken by mouth or by nasogastric tube. When there is complete obstruction, a contrast enema, accompanied by large amounts of intravenous fluids, can be therapeutic.

Rectal Prolapse

See Chapter 392.5.

Although uncommon, rectal prolapse occurs most often in infants with CF and less frequently in older children with the disease. It was much more frequently seen in the past among undiagnosed young children with steatorrhea, malnutrition, and repetitive cough. The prolapsed rectum can usually be replaced manually by continuous gentle pressure with the patient in the knee-chest position. To prevent an immediate recurrence, the buttocks can be temporally taped closed. Adequate pancreatic enzymes, stool softener, and control of pulmonary infection result in improvement. On very rare occasions, a patient may continue to have rectal prolapse and may require referral to a pediatric surgeon.

Hepatobiliary Disease

A wide range of hepatobiliary complications are observed in CF, including asymptomatic elevations in liver function tests, biliary cirrhosis, and portal hypertension. Often liver function abnormalities (elevations in aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT]) associated with biliary cirrhosis are treated with ursodeoxycholic acid, leading to a reduction in these values. However, the evidence to support ursodeoxycholic acid's effectiveness in preventing the progression of CF-related liver disease has not been clearly documented. Portal hypertension with esophageal varices, hypersplenism, or ascites occurs in ≤8% of children with CF (see Chapter 415).

Obstructive jaundice in newborns with CF needs no specific therapy once the etiology has been established. End-stage liver disease is an indication for liver transplantation in children with CF (see Chapter 416).

Pancreatitis

Recurrent pancreatitis is seen primarily in patients with pancreatic sufficiency, and it can lead to the development of pancreatic insufficiency. Patients can be treated with pancreatic enzyme therapy and a low-fat diet (in well-nourished patients) to rest the pancreas. Further treatment of this disorder is discussed in Chapter 399.

Cystic Fibrosis–Related Hyperglycemia and Diabetes

Onset of hyperglycemia occurs most frequently *after* the first decade. Approximately 20% of young adults are treated for hyperglycemia, although the incidence of CF-related diabetes may be up to 50% in adults with CF. Ketoacidosis is rarely encountered. The pathogenesis includes both impaired insulin secretion and insulin resistance. Routine screening consisting of an annual 2-hour OGTT is recommended in children older than 10 years of age, although some cases may begin earlier. Although glucose intolerance with blood sugars that remain less than 200 are not treated unless nutrition is compromised or lung function seems affected, recent data suggest the prediabetic state is associated with clinical decline, so close monitoring is warranted. The development of significant hyperglycemia favors acquisition of *P. aeruginosa* and *B. cepacia* in the airways and may adversely affect pulmonary function. Thus careful control of blood glucose level is an important goal. When treatment is indicated, insulin should be instituted, as it is the only therapy shown to improve the nutritional and metabolic outcomes in CFRD. In addition to insulin therapy, patients are often encouraged to exercise, which has been shown to reduce postprandial glycemic excursions. Medical nutritional therapy for CFRD differs from that recommended in type 1 diabetes and type 2 diabetes, as patients are encouraged to continue the nutritional therapy needed to manage CF, that is a higher-caloric diet that is high in fat and salt and not carbohydrate restricted. Strict carbohydrate counting with adjustments in insulin dosing is essential for good glycemic control. Patients with CFRD are at risk for microvascular complications, including retinopathy, nephropathy, and neuropathy, providing an additional rationale for good control of blood glucose levels. These long-term vascular complications of diabetes are more commonly observed in adults with CFRD, as they occur more commonly after a decade of the disease.

Bone and Joint Complications

Hypertrophic osteoarthropathy causes elevation of the periosteum over the distal portions of long bones and bone pain, overlying edema, and joint effusions. Acetaminophen or ibuprofen may provide relief. Control of lung infection usually reduces symptoms. Intermittent arthropathy unrelated to other rheumatologic disorders occurs occasionally, has no recognized pathogenesis, and usually responds to nonsteroidal antiinflammatory agents. Back pain or rib fractures from vigorous coughing may require pain management to permit adequate airway clearance. These and other fractures may stem from diminished bone mineralization, the result of reduced vitamin D absorption, corticosteroid therapy, diminished weight-bearing exercises, and perhaps other factors. There may be a bone phenotype in CF that is unrelated to therapies or nutritional status and may be related to CFTR dysfunction.

OTHER COMPLICATIONS

Nasal Polyps

Nasal polyps (see Chapter 427) occur in 15–20% of patients with CF and are most prevalent in the second decade of life. Local corticosteroids and nasal decongestants occasionally provide some relief. When the polyps completely obstruct the nasal airway, rhinorrhea becomes constant, or widening of the nasal bridge is noticed, surgical removal of the polyps is

indicated; polyps may recur promptly or after a symptom-free interval of months to years. Polyps inexplicably stop developing in many adults.

Rhinosinusitis

Opacification of paranasal sinuses is universal in CF and is not an indication for intervention. Acute or chronic sinus-related symptoms are treated initially with antimicrobials, with or without maxillary sinus aspiration for culture. Functional endoscopic sinus surgery has anecdotally provided benefit.

Salt Depletion

Salt losses from sweat in patients with CF can be high, especially in warm arid climates. Children should have free access to salt, especially when thirsty in hot weather. Salt supplements are often prescribed to newborns and to children who live in hot weather climates. Hypochloremic alkalosis should be suspected in any patient who feels unwell in hot weather or who has had symptoms of gastroenteritis, and prompt fluid and electrolyte therapy should be instituted as needed.

Anxiety and Depression

The stress and emotional impact of caring for CF is significant. Studies have found high rates of depression and anxiety in both patients and their parent caregivers, 2-3 times that of the general population. Positive screening for depression in particular is associated with decreased lung function, lower body mass index, worse adherence, worse health-related quality of life, more frequent hospitalizations, and increased mortality. Annual screening for anxiety and depression, with psychologic and/or pharmacologic interventions and follow-up, is therefore indicated.

Surgery

Patients with good or excellent pulmonary status can tolerate general anesthesia without any intensive pulmonary measures before the procedure but should be adherent to their usual prescribed airway clearance therapy. Those with moderate or severe pulmonary infection usually do better with a 1- to 2-week course of intensive antibiotic treatment and increased airway clearance before surgery. If this approach is impossible, prompt intravenous antibiotic therapy is indicated once it is recognized that major surgery is required. General anesthesia may provide an opportunity to perform bronchoscopy to evaluate the airway and obtain good cultures, and this should be considered in any child with CF who will undergo surgery for any indication.

After major surgery, cough should be encouraged, and airway clearance treatments should be reinstituted as soon as possible, usually within 24 hours.

PROGNOSIS

CF remains a life-limiting disorder, although survival has dramatically improved (Figs. 454.12 and 454.13). With exceptions, most children remain relatively healthy into adolescence or adulthood. The slow progression of lung disease eventually does reach disabling proportions. Life table data indicate a median cumulative survival of more than 40 years, and the expectation is younger children with the disease have a life expectancy far in excess of this estimate. Outcomes are variable and related to CFTR pathogenic variant class, modifier genes, biologic and chemical exposures, disease management, and socioeconomic status. With the advent of highly effective CFTR modulator therapies, the landscape is expected to change even more dramatically. Not only will quality of life and longevity further improve, but investigations have begun into how the burden of care may be lessened by a decrease in the current dependence on onerous daily airway clearance therapies and the need for recurrent hospitalizations for pulmonary exacerbations.

Children with CF should not be restricted in their activities. A high percentage eventually attend and graduate from college. Most adults with CF find satisfactory employment, and an increasing number marry. Transitioning care from pediatric to adult care centers by 21 years of age is an important objective and requires a thoughtful, supportive approach involving both the pediatric and internal medicine specialists.

With increasing life span for patients with CF, a new set of psychosocial considerations has emerged, including the impact of anxiety and depression, dependence-independence issues, self-care, peer relationships, sexuality, reproduction, substance abuse, educational and vocational planning, medical care costs and other financial burdens, and anxiety concerning health and prognosis. Many of these issues are best addressed in an anticipatory fashion, before the onset of psychosocial dysfunction. With appropriate medical and psychosocial support, children and adolescents with CF generally cope well. Achievement of an independent and productive adulthood is a realistic goal for many.

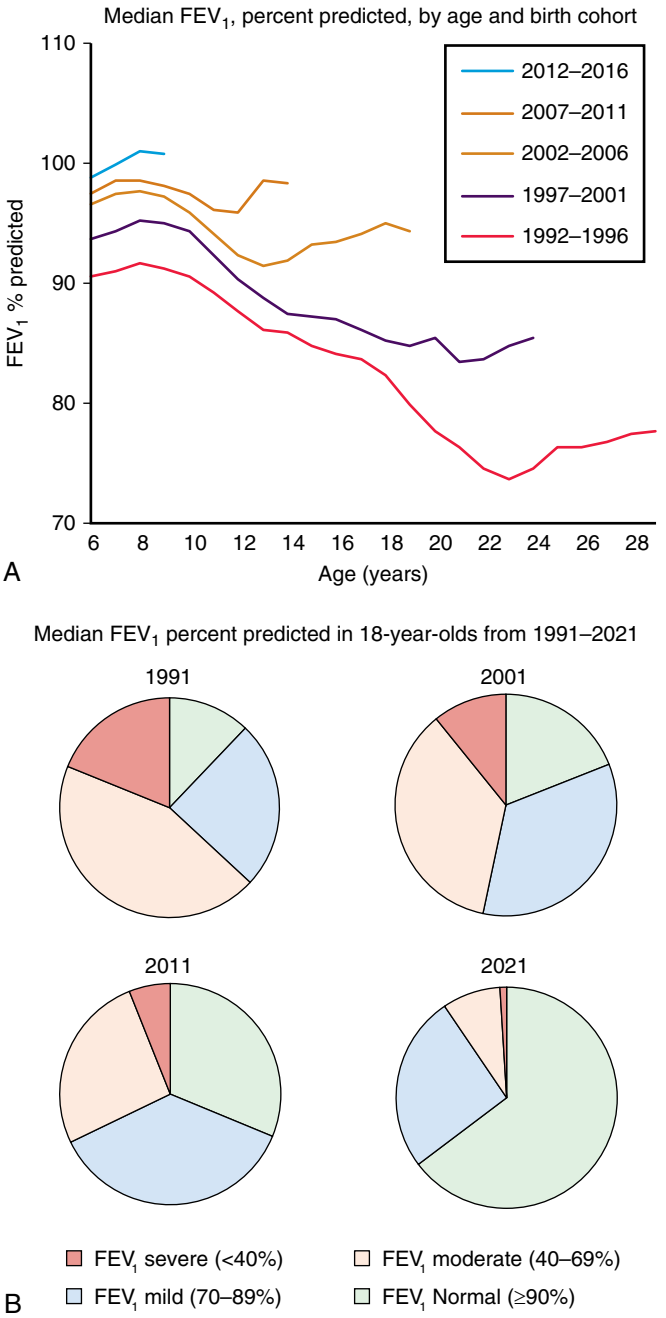

Fig. 454.12 Median FEV_1, percent predicted, by age and birth cohort (A), and in 18-yr-olds from 1991 to 2021 (B). *(From the Cystic Fibrosis Patient Registry 2021. Annual Data Report. pp. 42–43. © 2022 Cystic Fibrosis Foundation. Bethesda, Maryland.* https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf*)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

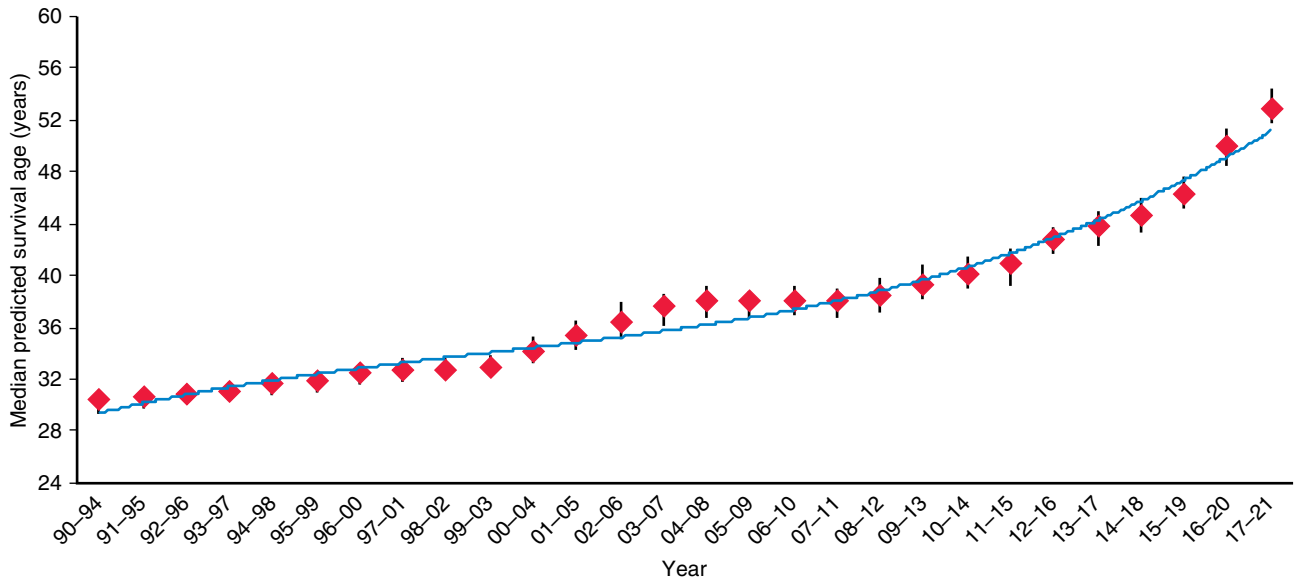

Fig. 454.13 Median predicted survival age, 1990–2021 in 5-yr increments. Created using the currently recommended method for calculating median predicted survival. For more information about the methodology, please see the Technical Supplement available at cff.org. *(From the Cystic Fibrosis Patient Registry 2021. Annual Data Report. p. 70. © 2022 Cystic Fibrosis Foundation. Bethesda, Maryland.* https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf*)*

Chapter 455

Primary Ciliary Dyskinesia (Immotile Cilia Syndrome, Kartagener Syndrome)

Thomas W. Ferkol Jr.

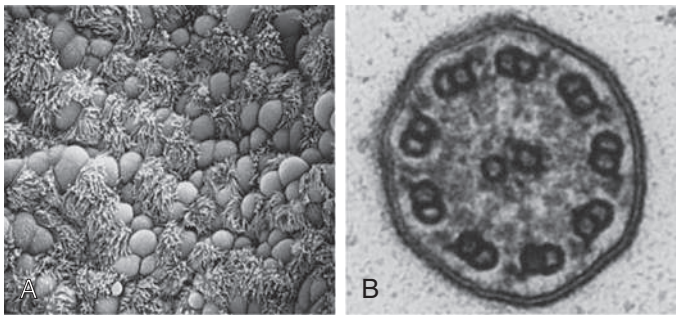

Fig. 455.1 Electron photomicrographs showing an airway epithelium grown in primary culture showing ciliated and nonciliated cells (**A**) and a normal motor cilium (**B**).

See also Chapter 101.3.

Primary ciliary dyskinesia (PCD) is an inherited disorder characterized by ciliary dysfunction leading to chronic sinopulmonary disease, persistent middle ear effusions, laterality defects, and infertility. The reported prevalence in the general population varies, ranging between 1 in 2,200 and 40,000 live births, but in children with repeated respiratory infections, it has been estimated to be as high as 5%.

NORMAL CILIARY ULTRASTRUCTURE AND FUNCTION

Three types of cilia exist in humans: motile cilia, primary (sensory) cilia, and nodal cilia. The respiratory epithelium in the nasopharynx, middle ear, paranasal sinuses, and larger airways are lined by a ciliated, pseudostratified columnar epithelium that is essential for mucociliary clearance. A mature ciliated epithelial cell has approximately 200 uniform **motile cilia**, hairlike organelles that move fluids, mucus, and inhaled particulates vectorially from conducting airways (Fig. 455.1). Motile cilia are anatomically and functionally oriented in the same direction, moving with intracellular and intercellular synchrony. Anchored by a basal body to the apical cytoplasm and extending from the apical cell surface into the airway lumen, each cilium is a complex, specialized structure, composed of hundreds of proteins. A cilium contains a central fibrillar structure, or axoneme, that consists of helical protofilaments made of alpha- and beta-tubulin monomers. A circular array of peripheral microtubular doublets are arranged around a central pair, leading to the characteristic "9+2" arrangement seen on cross-sectional views on transmission electron microscopy (see Fig. 455.1). Distinct inner and outer dynein arms are attached to the A microtubule. Each dynein arm is a multimer, containing multiple adenosine triphosphatases, called *dyneins,* that serve as motors of the cilium and promote microtubule sliding, which is converted into bending. The inner dynein arm influences the bend shape of the cilium, whereas the outer dynein arm controls beat force and frequency. The inner dynein arm and radial spokes are also parts of the dynein regulatory complex, a key regulator of motor activity. Nexin links connecting adjacent outer microtubular doublets limit the degree of sliding between microtubules. All these structures lead to synchronized ciliary beating, resulting in a ciliary stroke and coordinated beating at a frequency constant throughout the airway, ranging between 8 and 14 hertz, but this can be negatively affected by several factors, such as anesthetics and dehydration. Alternatively, beat frequency may be accelerated by exposure to irritants or bioactive molecules, including β-adrenergic agents, acetylcholine, and serotonin. Cilia beat frequency can be increased through the activity of nitric oxide synthases that are localized in the apical cytoplasm. The coordinated wavelike pattern of ciliary motion has

important functions in fluid and cell movement, and any disturbance in the precise, orchestrated movement of the cilia can lead to disease.

Primary (sensory) cilia are solitary, immotile organelles present during interphase on most cell types. These cilia lack a central microtubule doublet and dynein arms, thus creating a "9+0" arrangement (Fig. 455.2). Once considered nonfunctional vestigial remnants, primary cilia are important signaling organelles that sense the extracellular environment. They are mechanoreceptors, chemosensors, and osmosensors and, in specialized cases, detect changes in light, temperature, and gravity. Primary cilia defects (ciliopathies) are linked to wide-ranging pediatric conditions, such as various polycystic kidney diseases, nephronophthisis, Bardet-Biedl syndrome, Meckel-Gruber syndrome, Joubert syndrome, Alström syndrome, Ellis-van Creveld syndrome, and Jeune thoracic dystrophy (see Chapter 101.3).

The third type of cilia exists only during a brief period of embryonic development. **Nodal cilia** have a "9+0" microtubule arrangement similar to that of primary cilia, but they exhibit a whirling, rotational movement (see Fig. 455.2), resulting in leftward flow of extracellular fluid that establishes body sidedness. Nodal cilia defects result in body orientation abnormalities, such as **situs inversus totalis**, **situs ambiguus**, and **heterotaxy** associated with congenital heart disease, asplenia, and polysplenia (see Chapter 480.11).

GENETICS OF PRIMARY CILIARY DYSKINESIA

PCD is a genetically heterogeneous disorder, usually inherited by an autosomal recessive pattern, but autosomal dominant and X-linked inheritance are known. Pathogenic variants in any of the hundreds of proteins that are involved in ciliary assembly, structure, or function could theoretically cause disease. Indeed, 50 different genes have been linked to PCD (Fig. 455.3), including those that encode proteins integral to the outer dynein arm, dynein regulatory complex, radial spoke, and central apparatus proteins. Pathogenic variants in genes coding several cytoplasmic proteins not part of the cilia axoneme have also been identified, leading to defective protein transport and cilia assembly. Over 70% of all people with PCD tested have pathogenic variants in one of these genes. In addition, motile ciliopathies *distinct* from classical PCD have been described. Children with biallelic variants in *CCNO* and *MCIDAS,* two proteins required for centriole production, have oligocilia and clinical features similar to PCD.

Insights into the genetic bases of motile ciliopathies have also yielded greater understanding of genotype-phenotype relationships in PCD. For instance, cross-sectional and longitudinal studies showed that children with the inner dynein arm–microtubular disorganization defect, primarily the result of biallelic pathogenic variants in *CCDC39* or *CCDC40,* had more severe lung disease. In contrast, people with pathogenic variants in *RSPH1* appear to have milder respiratory phenotypes.

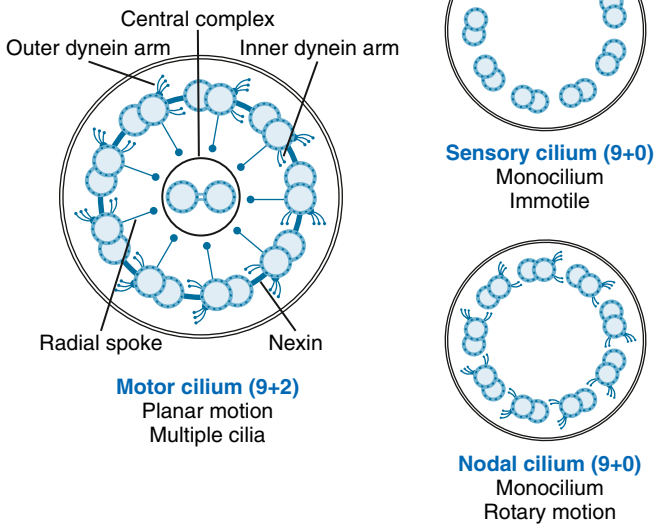

Fig. 455.2 Schemata showing the three general classes of normal cilia: motile cilia (motile "9+2"), nodal cilia (motile "9+0"), and primary cilia (nonmotile "9+0"), which demonstrate the complex structure and arrangement of the ciliary axoneme.

CLINICAL MANIFESTATIONS OF PRIMARY CILIARY DYSKINESIA

PCD has several characteristic clinical features (Table 455.1). **Neonatal respiratory distress** (NRD) is a common feature, and most affected term newborns develop increased work of breathing, tachypnea, and upper and middle lobe atelectasis on chest radiographs. The association of respiratory distress in *term neonates* with PCD has been underappreciated. Often diagnosed with transient tachypnea of the newborn or pneumonia, PCD infants frequently require supplemental oxygen flow for days to weeks.

Chronic, year-round productive (wet) cough that begins before 6 months of age is another characteristic feature of PCD. Bacterial cultures of sputum or lavage fluid frequently yield nontypeable *Haemophilus influenzae* (see Chapter 240), *Staphylococcus aureus* (see Chapter 227.1), *Streptococcus pneumoniae* (see Chapter 228), and *Pseudomonas aeruginosa* (see Chapter 251.1). Persistent airway infection and inflammation lead to **bronchiectasis**, even in preschool children (see Chapter 452). Children with PCD also have a higher prevalence of pectus excavatum and scoliosis.

Roughly 80% of patients with PCD have **chronic rhinosinusitis**, manifested by daily nasal congestion and copious, watery nasal

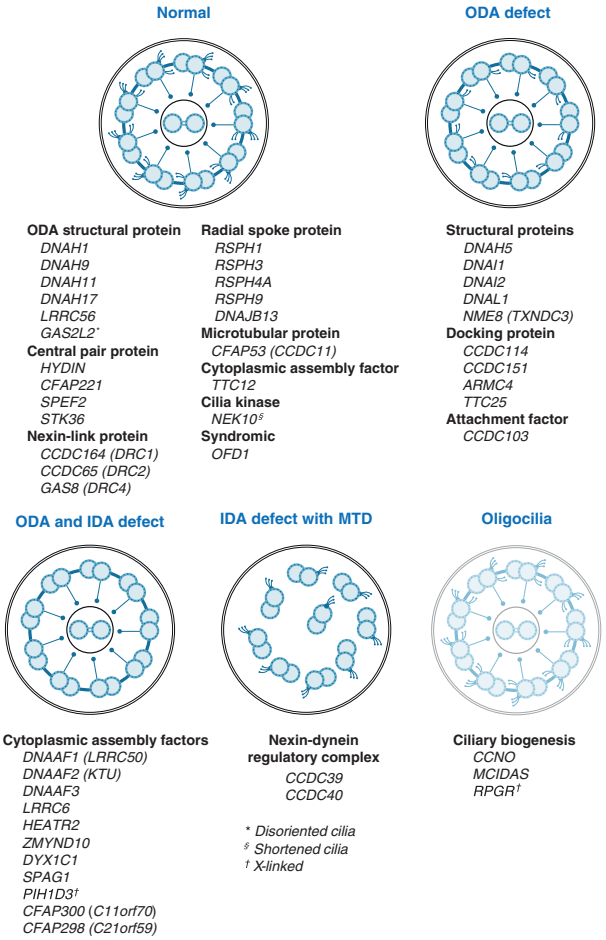

Fig. 455.3 Classification of genes associated with primary ciliary dyskinesia based on ultrastructural findings. IDA, Inner dynein arm; MTD, microtubular disorganization; ODA, outer dynein arm.

Table 455.1 Clinical Features of Primary Ciliary Dyskinesia

LOWER RESPIRATORY
Unexplained respiratory distress in term neonate
Daily productive (wet) cough since early infancy
Chronic bronchitis
Bronchiectasis
UPPER RESPIRATORY
Chronic otitis media and persistent middle ear effusions
Conductive hearing loss
Sensorineural hearing loss
Daily nonseasonal rhinosinusitis since early infancy
Chronic rhinosinusitis
Nasal polyposis
CARDIAC
Situs inversus totalis
Heterotaxy
Congenital cardiac defects
GENITOURINARY
Male subfertility
Female subfertility
MUSCULOSKELETAL
Pectus excavatum
Scoliosis
CENTRAL NERVOUS SYSTEM
Retinitis pigmentosa
Hydrocephalus (rare)

Table 455.2 Consensus-Based Primary Ciliary Dyskinesia (PCD) Diagnostic Criteria by Age

NEWBORNS (0-1 MO OF AGE)
Situs inversus totalis and unexplained neonatal respiratory distress (NRD) at term birth, plus at least one of the following: • Diagnostic ciliary ultrastructure on electron micrographs • Two pathogenic variants in PCD-associated gene
CHILDREN (1 MO TO 5 YR)
Two or more major PCD clinical criteria (NRD,* daily wet cough, persistent nasal congestion, laterality defect), plus at least one of the following (nasal nitric oxide not included in this age-group because it is not yet sufficiently tested): • Diagnostic ciliary ultrastructure on electron micrographs • Two pathogenic variants in one PCD-associated gene • Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy on multiple occasions
CHILDREN (5-18 YR OF AGE) AND ADULTS
Two or more PCD clinical criteria (NRD,* daily productive cough or bronchiectasis, persistent nasal congestion, laterality defect), plus at least one of the following: • Nasal nitric oxide during plateau <77 nL/min on two occasions, >2 mo apart (with CF excluded) • Diagnostic ciliary ultrastructure on electron micrographs • Two pathogenic variants in one PCD-associated gene • Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy on multiple occasions

*In term neonates.

discharge that begins early in infancy and persists into childhood. Inadequate innate mucous clearance leads to chronic sinusitis (see Chapter 429) and nasal polyposis. Middle ear disease occurs in many children with PCD, with varying degrees of **chronic otitis media with effusion**. Both conductive and sensorineural hearing loss occur at increased frequency in people with PCD, though the former is more common. Middle ear findings may be most helpful in distinguishing PCD from cystic fibrosis (CF) (see Chapter 454) or other causes of chronic lung disease.

Left-right laterality defects (e.g., *situs inversus totalis*) are found in ~50% of all children with PCD. Without functional nodal cilia in the embryonic period, thoracoabdominal orientation is random. Approximately 25% of children who have situs inversus totalis have PCD. Thus situs inversus totalis alone does not establish the diagnosis. Other laterality defects, such as **heterotaxy**, are also associated with PCD and may coexist with congenital cardiac defects, asplenia, or polysplenia. PCD should be strongly considered in term infants who have unexplained NRD and situs anomalies.

Most males with PCD have dysmotile spermatozoa because flagellar and ciliary ultrastructure is similar. Male infertility or subfertility is typical but not always found in this disease. Subfertility has also been reported in affected women, possibly related to ciliary dysfunction in the fallopian tubes.

A few case reports have associated neonatal hydrocephalus with PCD. The ependyma of the brain ventricles are lined by ciliated epithelium and are important for cerebrospinal fluid flow through the ventricles and aqueduct of Sylvius. The finding of enlarged brain ventricles on sonograms, when linked with situs inversus totalis, has been proposed as a prenatal diagnostic marker for PCD.

Several conditions have overlapping features of motile and primary ciliopathies. X-linked retinitis pigmentosa has been associated with recurrent respiratory infections in families with *RPGR* gene pathogenic variants. Intraflagellar transport proteins are essential for photoreceptor assembly and, when mutated, lead to apoptosis of the retinal pigment epithelium (see Chapter 670).

DIAGNOSIS OF PRIMARY CILIARY DYSKINESIA

The diagnosis of PCD has been challenging. A high index of suspicion is necessary, but pediatricians should only perform testing in children who have clinical manifestations consistent with the disease. PCD has four criteria-defined features that should be used to screen at-risk children: unexplained NRD in full-term infants, left-right laterality defects, persistent rhinitis that begins before 6 months of age, and daily wet or productive cough that also starts before 6 months of age (Table 455.2). Even though chronic otitis media is common in PCD, many unaffected infants and toddlers also have chronic middle ear involvement, which makes this feature less useful in distinguishing children with PCD from others.

Imaging studies show extensive involvement of the paranasal sinuses. Chest radiographs frequently demonstrate bilateral lung overinflation, peribronchial infiltrates, and lobar atelectasis. Computed x-ray tomography of the chest often reveals bronchiectasis, often involving the anatomic right middle lobe or lingula, even in young children. Situs inversus totalis in a child who has chronic respiratory tract symptoms is highly suggestive of PCD, but this configuration occurs in only 50% of people with the condition. Pulmonary function tests may be normal early but demonstrate obstructive airway disease as the disease progresses. Typical findings include decreased forced expiratory volume in 1 second (FEV_1), reduced expiratory flow rates, and increased residual volume. Bronchodilator responsiveness is variable. Longitudinal analyses of children with PCD show wide variation in intrathoracic airway obstruction.

No single test will diagnose every person with PCD. Historically, transmission electron microscopy has been the gold standard to assess structural defects within the cilium. These ultrastructural defects are found in cilia throughout the upper and lower airways and oviduct and in sperm flagella. Curettage from the nasal epithelium or endobronchial brushing can provide an adequate specimen for review. Identification of a specific, previously established defect in the ciliary structure with concurrent phenotypic features is sufficient to make the diagnosis. There are several characteristic ciliary abnormalities: outer dynein arm defects, combined inner and outer dynein arm defects, and inner

dynein arm defects with microtubular disorganization (see Fig. 455.3). Inner dynein arm defects alone are largely artifactual. It is important to note that ultrastructural examination of cilia as a diagnostic test for PCD has limitations. First, the absence of axonemal defects does not exclude PCD; nearly 30% of affected individuals have normal ciliary ultrastructure. Other children with symptoms consistent with PCD have been found to have ciliary aplasia or few motile cilia on the epithelial surface (see Fig. 455.3)

Careful interpretation of the ultrastructural findings is necessary because ciliary defects can be acquired. Nonspecific changes (e.g., compound cilia or blebs) may be seen in relation to exposure to environmental pollutants or infection. Frequently, the diagnosis of PCD can be delayed or missed because of inadequate tissue collection or sample processing or misinterpretation of ciliary defects. Some investigators have advocated culturing of airway epithelial cells and allowing the secondary changes to resolve. Alternatively, immunofluorescent staining for axonemal protein markers may overcome some limitations of transmission electron microscopy.

Another useful approach has exploited the observation that nasal nitric oxide concentrations are reduced in subjects with PCD. Because nasal nitric oxide measurements are relatively easy to perform and noninvasive, this method is a valuable screen for PCD. When compared to other diagnostic tools, nasal nitric oxide can be sensitive and specific for PCD in cooperative older children and adults. Unfortunately, few studies in children under 5 years have been reported, and the accuracy of nasal nitric oxide measurements in infants has not been established. It is important to note that children who have pathogenic variants in some PCD-associated genes can have nondiagnostic nasal nitric oxide concentrations. Conversely, people with CF (see Chapter 454) or primary immunodeficiencies (see Chapter 165), conditions that have clinical features that overlap with PCD, can have reduced nasal nitric oxide levels. Thus reduced nasal nitric oxide concentrations alone are never sufficient to make the diagnosis of PCD.

Qualitative tests to assess ciliary function have been used to screen for PCD. Ciliary beat frequency measurements using standard light microscopy have been used as a screen, but this approach can be misleading and should never be used as a diagnostic tool. High-resolution, high-speed digital imaging of ciliary motion in multiple planes permits comprehensive analysis of cilia beating, which has shown that certain beat patterns are associated with specific ultrastructural defects. This technique is available only at specialized centers, primarily in Europe, and requires sophisticated software and expertise.

PCD is highly heterogenic owing to the large number of proteins involved in cilia assembly, structure, and function. Advances in gene sequencing techniques have led to the identification of a growing number of disease-associated genes. Genetic testing has become increasingly available and is considered a first-line test for PCD, incorporated into published diagnostic algorithms. Nevertheless, current, commercially available testing for pathogenic variants in at least 30 genes will only identify approximately 70% of affected children (see Fig. 455.3).

TREATMENT

No therapies have been shown to correct ciliary dysfunction in PCD. Many of the treatments applied to children with the condition are similar to those used in other chronic suppurative lung diseases characterized by impaired airway clearance and bronchiectasis, such as CF (see Chapter 454), but few have been adequately studied to demonstrate efficacy in PCD.

Strategies to enhance mucociliary clearance are central to PCD therapy, and routine airway clearance techniques using postural drainage, percussion vests, positive expiratory pressure devices, or other techniques should be instituted daily. Because ciliary function is impaired, cough becomes a critical mechanism for mucous clearance and should not be suppressed. Exercise can enhance airway clearance in people with PCD and should be encouraged. Inhaled hypertonic saline and mucolytic agents are often used in CF care, but only small case series or single-site clinical trials showed any improvement in people with PCD after treatment. Thrice-weekly azithromycin as an antiinflammatory agent is reported to reduce the frequency of pulmonary exacerbations but has no effect on lung function or quality-of-life measures.

When children with PCD develop increasing respiratory symptoms consistent with infection, antimicrobial therapy should be instituted based on respiratory culture results and bacterial sensitivities. Maintenance therapy with inhaled or oral antibiotics can be used cautiously in patients with PCD who have bronchiectasis or frequent respiratory exacerbations. Immunizations against pertussis, influenza, and pneumococci are cornerstones of care. Additional preventive measures include avoidance of cigarette or marijuana smoke, electronic cigarette aerosols, and other airway irritants.

Rarely, surgical resection of bronchiectatic lung has been performed on people with PCD, typically in cases of localized disease with severe hemoptysis or intractable infections. It is unclear whether surgical interventions provide reduction in symptoms or survival benefit.

Progression to end-stage lung disease and respiratory failure has been reported in people with PCD. Adults have undergone successful heart-lung, double-lung, or living-donor lobar lung transplantation. Situs inversus totalis complicates the procedure because of anatomic considerations. Otherwise, survival is similar to that for other transplant recipients.

Treatment of chronic otitis media and middle ear effusions in people with PCD is controversial. Myringotomy tubes are frequently placed in affected children, and some studies reported enhanced hearing in children with chronic conductive hearing loss after the procedure. However, others did not find improvement in hearing acuity. Intractable mucoid otorrhea, tympanosclerosis, and permanent membrane perforation are known complications of myringotomy tubes in people with PCD, leading some to recommend against surgical management. Although hearing tends to improve with time, children and adolescents with PCD should be routinely screened and hearing aids used when necessary.

Chronic rhinitis and sinusitis are frequent clinical manifestations of PCD. No treatments have been shown to be effective, although patients are often treated with nasal washes, paranasal sinus lavage, and systemic antibiotics when they are symptomatic. As with any overuse of antimicrobial agents, the development of resistant organisms is a concern. When nasal symptoms are severe or refractory to medical management, endoscopic sinus surgery can be used to promote drainage or local delivery of medications, but the benefit may be short lived.

PROGNOSIS

Although signs and symptoms related to upper respiratory involvement predominate early in PCD, clinical manifestations of lower respiratory tract disease tend to increase with age and become the leading cause of morbidity and mortality in patients with PCD. It is believed that progression and extent of lung disease can be slowed with early diagnosis and therapy. Routine surveillance studies recommended the following for the care of children with PCD: (1) regular spirometry to monitor pulmonary function, (2) chest imaging, and (3) sputum or oropharyngeal cultures to assess respiratory flora.

Children with PCD usually have a slower decline in pulmonary function than those with CF, and its prognosis and long-term survival are better. Many can have a normal or near-normal life span, whereas others experience progressive bronchiectasis and respiratory deterioration at a younger age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 456

Diffuse Lung Diseases in Childhood

See also Chapter 448.

456.1 Inherited Disorders of Surfactant Metabolism

Jennifer A. Wambach, Lawrence M. Nogee, Aaron Hamvas, and F. Sessions Cole III

Pulmonary surfactant is a mixture of phospholipids and proteins synthesized, packaged, and secreted by alveolar type II pneumocytes (AEC2s) that line the distal air spaces. This mixture forms a monolayer at the air-liquid interface that lowers surface tension at end expiration of the respiratory cycle, preventing atelectasis and ventilation-perfusion mismatch. Four surfactant-associated proteins have been characterized: surfactant proteins A and D (SP-A, SP-D) participate in host defense in the lung, whereas surfactant proteins B and C (SP-B, SP-C) contribute to the surface tension–lowering activity of pulmonary surfactant. The adenosine triphosphate–binding cassette protein member A3, ABCA3, is a transporter located on the limiting membrane of lamellar bodies, the intracellular storage organelle for surfactant within AEC2s, and has an essential role in surfactant phospholipid metabolism. The proper expression of the surfactant proteins and ABCA3 is dependent on a number of transcription factors, particularly thyroid transcription factor 1 (TTF-1). Two genes for SP-A *(SFTPA1, SFTPA2)* and one gene for SP-D *(SFTPD)* are located on human chromosome 10, whereas single genes encode SP-B *(SFTPB)*, SP-C *(SFTPC)*, TTF-1 *(NKX2-1)*, and ABCA3 *(ABCA3)*, which are located on human chromosomes 2, 8, 14, and 16, respectively. Inherited disorders of SP-B, SP-C, ABCA3, and TTF-1 have been recognized in humans and are collectively termed **surfactant dysfunction disorders** (Table 456.1). Variants in *SFTPD* have not been associated with disease, and pathogenic variants in the genes encoding SP-A have only been found in adults with idiopathic pulmonary fibrosis or lung cancer.

PATHOLOGY

These disorders share a unique constellation of features, including AEC2 hyperplasia, alveolar macrophage accumulation, interstitial thickening and inflammation, and alveolar proteinosis. A number of different descriptive terms have historically been applied to these disorders, including ones borrowed from adult forms of interstitial lung disease (**desquamative interstitial pneumonia**, nonspecific interstitial pneumonia) and a disorder unique to infancy **(chronic pneumonitis of infancy)**. These diagnoses in infants and children are strongly indicative of surfactant dysfunction disorders but do not distinguish which gene is responsible. Because the prognosis and inheritance patterns differ depending on the gene involved, genetic testing should be offered when one of these conditions is reported in the lung biopsy or autopsy of an infant or child. Other disorders, including genetic causes of **pulmonary alveolar proteinosis** (see Chapter 456.2), and disorders of immune dysregulation can be associated with similar pathologies.

DEFICIENCY OF SURFACTANT PROTEIN B (SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 1; SMDP1; OMIM #265120)

Clinical Manifestations

Infants with an inherited deficiency of SP-B present in the *immediate* neonatal period with respiratory failure. This autosomal recessive disorder is clinically and radiographically similar to the respiratory distress syndrome (RDS) of premature infants (see Chapter 126) but typically affects full-term infants. The initial degree of respiratory distress is variable, but the disease is progressive and is refractory to

Table 456.1 Comparison of Surfactant Dysfunction Disorders

	SP-B DEFICIENCY	SP-C DISEASE	ABCA3 DEFICIENCY	TTF-1 DISORDERS
Gene name	*SFTPB*	*SFTPC*	*ABCA3*	*NKX2-1*
Age of onset	Birth	Birth to adulthood	Birth to childhood; rarely adult	Birth to childhood
Inheritance	Recessive	Dominant/sporadic	Recessive	Sporadic/dominant
Mechanism	Loss of function	Gain in toxic function or dominant negative	Loss of function	Loss of function Gain in function
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
DIAGNOSIS				
Biochemical (tracheal aspirate)	Absence of SP-B and presence of incompletely processed proSP-C	None	None	None
Genetic (DNA)	Sequence *SFTPB*	Sequence *SFTPC*	Sequence *ABCA3*; copy number variant detection	Sequence *NKX2-1*; copy number variant detection
Ultrastructural (lung biopsy–electron microscopy)	Disorganized lamellar bodies	Not specific; may have dense aggregates	Small dense lamellar bodies with eccentrically placed dense cores	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation if progressing	Lung transplantation or compassionate care for infants with biallelic null variants; lung transplantation for other variants if progressing	Supportive care; treat coexisting conditions (hypothyroidism)

SP, Surfactant protein.

mechanical ventilation, surfactant replacement therapy, and glucocorticoid administration. Almost all affected infants have died without lung transplantation, but prolonged survival is possible in cases of partial deficiency of SP-B. Humans heterozygous for loss-of-function variants in *SFTPB* are clinically healthy as adults but may be at increased risk for obstructive lung disease if they also have a history of smoking.

Genetics

Multiple loss-of-function variants in *SFTPB* have been identified. The most common is a net two base-pair insertion in codon 133 (originally termed *121ins2,* currently termed *c.397delCinsGAA, p.Pro133Glufs*95*) that results in a frameshift, an unstable SP-B messenger RNA (mRNA) transcript, and absence of SP-B protein production. This pathogenic variant has accounted for 60–70% of the alleles found to date in infants identified with SP-B deficiency and is present in approximately 0.07% of European-descent individuals in large-scale sequencing projects. Most other pathogenic variants have been family-specific. A large deletion encompassing two exons of *SFTPB* has also been reported.

Diagnosis

A rapid, definitive diagnosis can be established with sequence analysis of *SFTPB,* which is available through clinical laboratories (Genetic Testing Registry, https://www.ncbi.nlm.nih.gov/gtr). Sequencing of *SFTPB* is usually performed as part of a multigene panel using next-generation sequencing (NGS) methods that includes genes for other surfactant dysfunction disorders and can be designed to detect deletions or duplications of one or more exons (copy number variants). For families in which *SFTPB* variants were previously identified, antenatal diagnosis can be established by preimplantation genetic diagnosis (PGD) or molecular assays of DNA from chorionic villous biopsy or amniocytes, which permit advanced planning of a therapeutic regimen. Other laboratory tests remain investigational, including analysis of tracheal aspirate (effluent) for the presence or absence of SP-B protein and for incompletely processed precursor proSP-C peptides that have been identified in SP-B–deficient human infants. Immunostaining of lung biopsy tissue for the surfactant proteins can also support the diagnosis, although immunohistochemical assays for SP-B and SP-C are also generally available only on a research basis. Staining for SP-B is usually absent, but robust extracellular staining for proSP-C because of incompletely processed proSP-C peptides is observed and is diagnostic for SP-B deficiency. Such studies require a lung biopsy in a critically ill infant but may be performed on lung blocks acquired at the time of autopsy, allowing for retrospective diagnosis. With electron microscopy, a lack of tubular myelin, disorganized lamellar bodies, and an accumulation of abnormal-appearing multivesicular bodies suggest abnormal lipid packaging and secretion.

SURFACTANT PROTEIN C–ASSOCIATED INTERSTITIAL LUNG DISEASE (SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 2; SMDP2; OMIM #610913)

SP-C is a very low molecular weight, extremely hydrophobic protein that, along with SP-B, enhances the surface tension–lowering properties of surfactant phospholipids. The mature SP-C protein (35 amino acids) is derived from proteolytic processing of a larger precursor protein (proSP-C).

Clinical Manifestations

The clinical presentation of patients with *SFTPC* pathogenic variants is quite variable. Some patients present at birth with symptoms, signs, and radiographic findings typical of RDS. Others present later in life, *ranging from early infancy until well into adulthood,* with gradual onset of respiratory insufficiency, hypoxemia, failure to thrive, and chest radiograph findings of **interstitial lung disease**, or as **pulmonary fibrosis** in the fifth or sixth decade of life. The age and severity of disease vary even within families with the same *SFTPC* variant. The natural history is also quite variable, with some patients improving either spontaneously or as the result of therapy or prolonged mechanical ventilation, some with persistent respiratory insufficiency, and some progressing to the point of requiring lung transplantation. This variability in presentation, severity, and course of the disease does not appear to correlate with the specific *SFTPC* variant and also hinders accurate assessment of prognosis.

Genetics

Multiple pathogenic variants in *SFTPC* have been identified in association with acute and chronic lung disease in patients ranging in age from newborn to adult. A pathogenic variant on only *one SFTPC* allele is sufficient to cause disease. Approximately half of these variants arise spontaneously, resulting in sporadic disease, but the remainder are inherited as a *dominant trait*. *SFTPC* pathogenic variants have been identified in diverse racial and ethnic groups. A threonine substitution for isoleucine in codon 73 (termed *p.I73T* or *p.Ile73Thr*) has accounted for 25–35% of the cases identified to date but is rare (not identified in gnomAD in ~140,000 individuals). Pathogenic variants in *SFTPC* are thought to cause disease because of a toxic gain in function resulting from the production of misfolded or abnormal proSP-C that accumulates within the AEC2 and causes cellular injury or alters the normal intracellular routing of proSP-C. Lung tissue from individuals with pathogenic variants in *SFTPC* demonstrates accumulation of pro-SPC. Many pathogenic *SFTPC* variants are located in the carboxy-terminal domain of pro-SP-C, which has a similar homology to other members of the *BRICHOS* family of membrane proteins, the abnormal aggregation of which have been implicated in the pathophysiology of familial dementia and some cancers. Pathogenic variants within the BRICHOS domain (amino acid residues 90-197) of *SFTPC* result in aggregation of misfolded protein in the endoplasmic reticulum, activation of the unfolded protein response, inflammation, and subsequent fibrosis. Non-BRICHOS domain pathogenic variants result in mistrafficking of pro-SPC to the plasma membrane and endosomes rather than the lamellar bodies, a late block in macroautophagy, inflammation, and subsequent fibrosis. The different underlying pathogenic mechanisms of *SFTPC* variants do not appear to correlate with the clinical presentation and may necessitate different therapeutic approaches.

Diagnosis

Sequencing of *SFTPC,* the only definitive diagnostic test, is available usually as part of an NGS multiple-gene panel in clinical laboratories. Because most *SFTPC* pathogenic variants are missense variants, distinguishing true disease-causing variants from rare yet benign sequence variants may be difficult. Immunostaining of lung tissue may demonstrate proSP-C aggregates but is available only on a research basis.

DISEASE CAUSED BY PATHOGENIC VARIANTS IN *ABCA3* (SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 3; SMDP3; OMIM #610921)

Clinical Manifestations

Lung disease caused by pathogenic variants in *ABCA3* generally presents as either a severe, lethal form that manifests in the *immediate newborn period,* clinically similar to SP-B deficiency, or a chronic form that appears most typically in the first year of life with **interstitial lung disease** similar to SP-C–associated interstitial lung disease. Infants who are homozygous or compound heterozygous for null variants, that is, the variant is predicted to result in the absence of protein expression (i.e., nonsense or frameshift variants), typically present with lethal neonatal respiratory failure, whereas infants with missense, in-frame insertion/deletions or splicing variants have more variable age of onset and outcomes. Heterozygosity for an *ABCA3* variant may contribute to the risk for RDS in late preterm and term infants, who, in contrast to ABCA3-deficient infants with variants on both alleles, may eventually completely recover from their initial lung disease.

Genetics

Recessive variants in *ABCA3* were first described among infants who presented with lethal RDS in the newborn period, but now have been identified in older infants and children with **interstitial lung disease**. There is considerable allelic heterogeneity: more than 400 variants

scattered throughout the gene have been identified, most of which are family-specific. The presence of null variants on both alleles that are predicted to preclude any ABCA3 production has been associated with early-onset disease and a uniformly fatal prognosis without lung transplant. A missense variant that results in a valine substitution for glutamine in codon 292 (p.Glu292Val or p.E292V) in association with a second *ABCA3* variant has been found in children with severe neonatal respiratory failure and in older children with interstitial lung disease and is present in approximately 0.7% of European-descent individuals. *ABCA3* variants have been identified in diverse racial and ethnic groups. The precise frequency of disease is unknown; large-scale sequencing projects indicate that the overall carrier rate for *ABCA3* variants may be as high as 1 in 50 to 1 in 70 individuals. However, many *ABCA3* variants are private, have not been previously identified in affected individuals, and functional data are only available for a limited number of disease-associated variants, thereby limiting these estimates. Two mechanistic classes of *ABCA3* variants have been identified: those that disrupt intracellular trafficking of ABCA3 to the lamellar bodies with retention of the variant protein in the endoplasmic reticulum and those that traffic normally but impair adenosine triphosphate (ATP)–mediated phospholipid transport into the lamellar bodies. ABCA3 deficiency may contribute to a substantial proportion of *unexplained fatal lung disease* in term infants and of *interstitial lung disease* in older children.

Diagnosis

Sequence analysis of *ABCA3* is available in clinical laboratories, usually as part of an NGS multiple-gene panel, and is the most definitive approach for diagnosis. Considerable variation in *ABCA3* necessitates careful interpretation regarding the functionality of an individual variant and its contribution to the clinical presentation. Additionally, *sequence analysis is not 100% sensitive,* as functionally significant variants may exist in untranslated regions that are not generally analyzed. As large deletions spanning one or more exons have been identified, it is important that the gene panel be able to detect such variants. In situations when the sequence analysis results are inconclusive, lung biopsy with electron microscopy to examine lamellar body morphology may be a useful adjunct to the diagnostic approach. Small lamellar bodies that contain electron-dense inclusions may be observed in association with *ABCA3* pathogenic variants. These findings support the hypothesis that ABCA3 function is necessary for lamellar body biogenesis. There are no biochemical markers to establish the diagnosis.

DISEASE CAUSED BY PATHOGENIC VARIANTS IN *NKX2-1* (THYROID TRANSCRIPTION FACTOR 1, CHOREOATHETOSIS, HYPOTHYROIDISM, AND NEONATAL RESPIRATORY DISTRESS, OMIM #600635)

Clinical Manifestations

A large deletion of the region of chromosome 14 (14q13.3) encompassing the *NKX2-1* locus was first recognized in an infant with *hypothyroidism* and *neonatal RDS*. Multiple large deletions involving the *NKX2-1* locus and contiguous genes as well as missense, frameshift, nonsense, and small insertion or deletion variants scattered throughout the gene have been reported in individuals with hypothyroidism, lung disease, and neurologic symptoms, including benign familial chorea. Manifestation of dysfunction in all three organ systems has been referred to as **brain-thyroid-lung syndrome**, but disease may manifest in only one or two organ systems. The lung disease can range from severe and eventually *lethal neonatal respiratory distress* to *chronic lung disease in childhood and adulthood*. Recurrent pulmonary infections have been reported, likely caused by reduced expression of the pulmonary collectins, SP-A and SP-D, but could also result from decreased expression of other *NKX2-1* transcriptionally regulated proteins. No clear genotype-phenotype correlations have emerged, but children harboring complete gene deletions have generally had more severe and earlier-onset disease. This observation could also be related to the deletion of other adjacent genes. Although limited data are available, the pulmonary phenotype may depend on the expression of which *NKX2-1* target genes are most affected. Children with decreased SP-B or ABCA3 expression may present with acute neonatal respiratory failure, whereas those with decreased SP-C or pulmonary collectin expression are more likely to have chronic lung disease.

Genetics

The *NKX2-1* gene is small, spanning less than 3,000 bases, with only three exons. TTF-1 is expressed not only in the lung but also in the thyroid gland and in the central nervous system. In the lung it is important for the expression of a wide variety of proteins, including the surfactant proteins, ABCA3, club cell secretory protein, and many others. Two transcripts that differ depending on whether the transcriptional start site is in the first or second exon have been recognized, although the shorter transcript is the predominant transcript in the lung. Most *NKX2-1* pathogenic variants are thought to result in a loss of function, with the mechanism of disease thus being haploinsufficiency, but discordant effects on different target genes have been reported. Loss-of-function variants in *NKX2-1* are rare in large sequencing projects, but the prevalence of disease is unknown. Pathogenic variants in diverse ethnic groups have been recognized. Most reported variants and deletions have occurred de novo, resulting in sporadic disease, but familial disease transmitted in a dominant manner has been recognized.

Diagnosis

Sequence analysis of the *NKX2-1* gene is available through clinical laboratories, usually as part of an NGS multiple-gene panel, and is the preferred method for diagnosis. Because large deletions comprise a significant fraction of reported variant alleles, specific methods to assess for deletions should also be performed, such as a chromosomal microarray or gene-targeted deletion/duplication analysis. A pathogenic variant on one allele is sufficient to cause disease. Although isolated pulmonary disease has been recognized, the majority of reported affected individuals have manifestations in two or more other organ systems. Thus the presence of **hypothyroidism** or neurologic abnormality in a proband or a family history of chorea should prompt consideration of the diagnosis. The most specific neurologic finding is **chorea**, but hypotonia, developmental delay, ataxia, and dysarthria have been reported. In very young, nonambulatory infants the neurologic symptoms may not be evident, or muscle weakness or hypotonia may be attributed to the severity of lung disease or a result of the hypothyroidism. Affected individuals may not be overtly hypothyroid but have compensated hypothyroidism with borderline low thyroxine (T_4) and high thyroid-stimulating hormone levels. The lung pathology associated with *NKX2-1* pathogenic variants may be typical of that of other surfactant dysfunction disorders, but because *NKX2-1* is important for lung development, growth abnormalities and arrested pulmonary development also may be seen. Immunostaining studies of surfactant protein expression have yielded variable results, with decreased expression of one or more surfactant-related proteins observed in some patients. No characteristic electron microscopy findings have been identified.

TREATMENT OF SURFACTANT DYSFUNCTION DISORDERS

Virtually all patients with SP-B deficiency die within the first year of life. Conventional neonatal intensive care interventions can maintain extrapulmonary organ function for a limited time (weeks to several months). Replacement therapy with commercially available surfactants is ineffective. Lung transplantation has been successful, but the pretransplantation, transplantation, and posttransplantation medical and surgical care is highly specialized and available only at pediatric pulmonary transplantation centers. Prompt recognition is critical if patients are to be considered for lung transplantation. Palliative care consultation is helpful.

No specific treatment is available for patients with lung disease caused by pathogenic variants in *SFTPC* or *ABCA3*. Therapeutic approaches used for interstitial lung diseases, such as the use of corticosteroids, quinolones, and macrolide antibiotics, have been reported but not systematically evaluated (Fig. 456.1). Infants with severe and progressive respiratory failure attributable to ABCA3 deficiency may be candidates

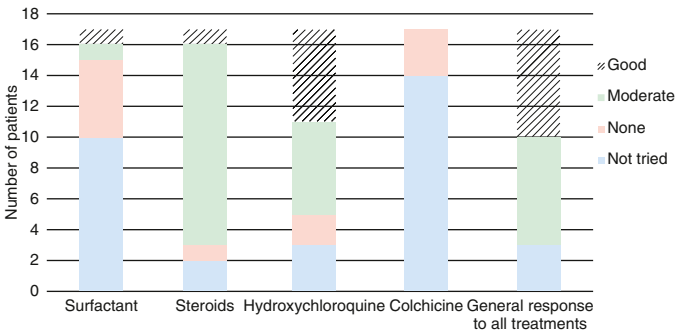

Fig. 456.1 Response to therapies for 17 patients with *SFTPC* variants. *(Data from Kröner C, Reu S, Teusch V, et al. Genotype alone does not predict the clinical course of SFTPC deficiency in paediatric patients. Eur Respir J. 2015;46:197–206.)*

for lung transplantation. The variable natural history of patients with *SFTPC* variants and older children with ABCA3 deficiency makes predictions of prognosis difficult. Lung transplantation is reserved for patients with progressive and refractory respiratory failure who would otherwise qualify for transplantation irrespective of their diagnosis.

Treatment for patients with *NKX2-1* variants is largely supportive. Hypothyroidism, if present, should be treated with thyroid hormone replacement. Corticosteroids and other agents used for other types of surfactant dysfunction have not been formally evaluated. Some individuals have progressive lung disease and have undergone lung transplantation. The variable progression of disease and presence of extrapulmonary disease may make evaluation and selection of subjects for transplantation particularly difficult.

Parents of children with surfactant dysfunction disorders should be offered genetic counseling to inform recurrence risk for future pregnancies, to present antenatal diagnostic options and offer delivery at a center with neonatal intensive care, and to facilitate discussions regarding whether testing should be offered to other family members who may not be symptomatic.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

456.2 Pulmonary Alveolar Proteinosis

Jennifer A. Wambach, Lawrence M. Nogee, F. Sessions Cole III, and Aaron Hamvas

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the intraalveolar and terminal airway accumulation of surfactant leading to progressive hypoxemic respiratory failure. PAP can result from abnormalities in surfactant production or surfactant clearance. Histopathologic examination shows distal air spaces are filled with a granular, eosinophilic material that stains positively with periodic acid–Schiff reagent and is diastase resistant. This material contains large amounts of surfactant proteins and lipids, and the primary mechanism for its accumulation is impaired catabolism by alveolar macrophages. PAP is classified as either *primary* due to disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling or *secondary* due to several different diseases that reduce alveolar macrophage number or function (Table 456.2). A fulminant, usually lethal, form of PAP manifesting shortly after birth has been termed **congenital alveolar proteinosis**, but because this condition is caused by disrupted surfactant metabolism or surfactant dysfunction within alveolar type II cells, the disease is included under inherited disorders of surfactant metabolism (see Chapter 456.1).

ETIOLOGY AND PATHOPHYSIOLOGY

Primary Alveolar Proteinosis

Disordered signaling of GM-CSF leading to impaired alveolar macrophage maturation is the major underlying cause of primary PAP in children and adults. Most cases of primary PAP in older children and adults are mediated by *neutralizing autoantibodies* directed against GM-CSF, which can be detected in serum and bronchoalveolar lavage (BAL) fluid. These autoantibodies block binding of GM-CSF to its receptor, thereby inhibiting alveolar macrophage maturation and function and surfactant clearance. Variants in the genes encoding both the α and β subunits of the GM-CSF receptor *(CSF2RA, CSFR2B)* in children with PAP account for a genetic basis for some cases of primary PAP in childhood.

Secondary Alveolar Proteinosis

Alveolar proteinosis has also been reported in children, including young infants, with **lysinuric protein intolerance**, a rare autosomal recessive disorder caused by pathogenic variants in the cationic amino acid transporter SLC7A7 (see Chapter 105.14). These children generally present with vomiting, hyperammonemia, and failure to thrive, although their pulmonary disease may prove fatal. A case of *recurrence* of the disease after lung transplantation supports a primary role for alveolar macrophage dysfunction in the pathogenesis of PAP associated with lysinuric protein intolerance. PAP is also a prominent feature in patients with biallelic variants in the gene encoding methionyl tRNA synthetase *(MARS)*, who have a multiorgan phenotype that also includes liver disease as a prominent feature and is prevalent among individuals on Reunion Island. The mechanism for PAP in patients with *MARS* variants is unknown. Heterozygous variants in the gene encoding the transcription factor GATA2 have also been associated with a phenotype that includes PAP, as well as immune deficiencies, myelodysplasia, and lymphatic abnormalities. The mechanism for PAP in patients with such variants likely is related to the role of GATA2 in alveolar macrophage development. Heterozygous gain-in-function variants in the *OAS1* gene have been identified in infants and children with a phenotype that includes PAP, hypogammaglobulinemia, and immune dysfunction. *OASl* gene products are important in the innate immune response to viral infection, and gene activation leads to inhibition of protein synthesis and apoptosis, with apoptosis of alveolar macrophages likely resulting in PAP. PAP may also be associated with some subtypes of Niemann-Pick disease (see Chapter 106.4).

Secondary alveolar proteinosis also may occur in association with *infection,* particularly in immunocompromised individuals. However, because the same pathologic process occurs in severely immunodeficient mice raised in a pathogen-free environment, it is not clear whether this phenotype results from a secondary infection or the underlying immunodeficiency. Environmental exposures to dust, silica, and chemicals and chemotherapeutic agents; hematologic disorders (myelodysplastic syndrome); and nonhematologic malignancies have also been associated with the development of secondary alveolar proteinosis.

CLINICAL MANIFESTATIONS

Infants and children with PAP present with dyspnea, fatigue, cough, weight loss, chest pain, or hemoptysis. In the later stages, cyanosis and digital clubbing may be seen. Pulmonary function changes include decreased diffusing capacity of carbon monoxide, lung volumes with a restrictive abnormality, and arterial blood gas values indicating marked hypoxemia and/or chronic respiratory acidosis. Alveolar proteinosis in infants and children is rare, and males are affected three times as often as females.

DIAGNOSIS

Histopathologic examination of lung biopsy specimens currently remains the gold standard for diagnosis of PAP in children, although this is likely to change as molecular tests become available. Immunohistochemical staining reveals abundant quantities of alveolar and intracellular surfactant proteins A, B, and D. Latex agglutination tests for the presence of anti–GM-CSF antibodies in BAL fluid or blood are highly sensitive and specific for the autoimmune forms of alveolar proteinosis. Elevations of GM-CSF in peripheral blood suggest a GM-CSF receptor defect, and molecular analysis of these genes should be pursued. The examination of sputum or BAL fluid for surfactant components has been used for diagnosis in adults, but these methods have not been validated in children. Examination of peripheral blood and/or bone marrow for clonogenic stimulation of monocyte-macrophage

Table 456.2 Comparison of Pulmonary Alveolar Proteinosis Syndromes

	AUTO-IMMUNE	GM-CSF RECEPTOR DEFICIENCY	LYSINURIC PROTEIN INTOLERANCE	*MARS* DEFICIENCY	*GATA2* DEFICIENCY	*OAS1*-ASSOCIATED POLYMORPHIC AUTOINFLAMMATORY IMMUNO-DEFICIENCY
Gene(s)		*CSFR2A, CSFR2B*	*SLC7A7*	*MARS*	*GATA2*	*OAS1*
Age of onset	Adult > child	Childhood to adult	Childhood	Childhood to adult	Childhood to adult	Infancy
Inheritance	NA	Recessive	Recessive	Recessive	Sporadic/dominant	Sporadic/dominant
Mechanism	Neutralizing antibodies to GM-CSF	Loss of function	Loss of function	Loss of function	Loss of function; haploinsufficiency	Gain in function
Other manifestations			Emesis; failure to thrive	Liver disease; hypothyroidism	Immune deficiency; myelodysplasia	Systemic inflammation, including fever, dermatitis, diarrhea, leukocytosis, splenomegaly
DIAGNOSIS						
Biochemical	Detection of serum GM-CSF autoantibody	Elevated serum GM-CSF levels	Increased cationic amino acids in urine, especially lysine	None	None	Hypogammaglobulinemia
Genetic (*DNA*)	NA	Sequence CSFR2A, CSFR2B	Sequence *SLC7A7*	Sequence *MARS*	Sequence *GATA2*	Sequence *OAS1*
Treatment	Whole lung lavage; inhaled GM-CSF	Whole lung lavage; hematopoietic stem cell transplantation	Whole lung lavage, dietary protein restriction, administration of citrulline and nitrogen scavenging drugs	Whole lung lavage	Whole lung lavage; hematopoietic stem cell transplantation	Whole lung lavage, intravenous immunoglobulin (IVIG), hematopoietic stem cell transplantation

GM-CSF, Granulocyte-macrophage colony-stimulating factor.

precursors, GM-CSF receptor and ligand expression, and GM-CSF binding and signaling studies are available through research protocols.

TREATMENT

The natural history of primary PAP is highly variable, making prognostic and therapeutic decisions difficult. Total lung lavage has been associated with prolonged remission of PAP in adults and remains a therapeutic option for patients with childhood PAP (Fig. 456.2). Younger infants with PAP may be more likely to have genetic mechanisms underlying their disease, and the role of repeated BAL in children has not been well studied, nor is it likely to be effective. It may provide a temporizing measure in some circumstances and may benefit patients with autoimmune or secondary PAP. Subcutaneous or inhaled administration of recombinant GM-CSF may improve pulmonary function in some adults with later-onset PAP. The role of exogenous GM-CSF treatment in children has not been well studied, although successful treatment with inhaled recombinant GM-CSF (molgramostim) has been reported in adults with autoimmune-mediated PAP. Because children with GM-CSF receptor defects generally have high serum levels of GM-CSF, exogenous GM-CSF seems unlikely to be effective in most such cases. Depending on the nature of the variant(s) responsible for the deficiency, some responsiveness of the receptor may be retained such that a response to exogenous GM-CSF is possible. Because the primary defect for PAP resides in the alveolar macrophage, which is a bone marrow–derived cell, lung transplantation would not be expected to correct primary PAP.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

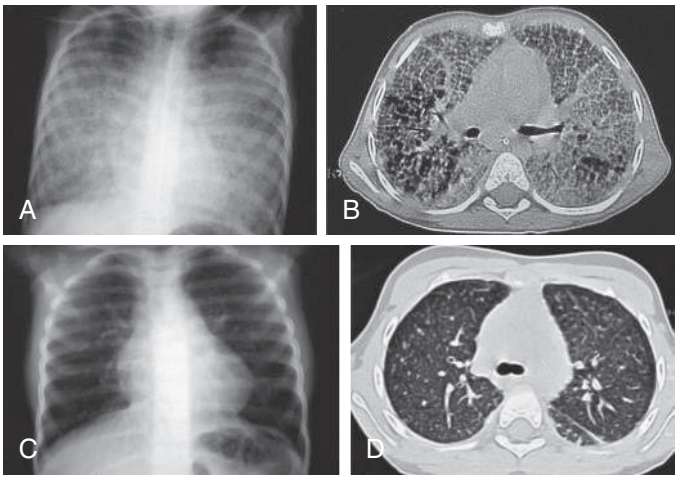

Fig. 456.2 **A** and **B**, Severe pulmonary alveolar proteinosis in a 5-year-old child before therapeutic lung lavage. **A**, Chest radiograph shows diffuse alveolar and interstitial infiltrates. **B**, CT scan demonstrates major air space opacities and crazy-paving pattern. **C** and **D**, Same patient after 12 therapeutic lung lavages. **C**, Chest radiograph demonstrates improvement of alveolointerstitial infiltrates. **D**, CT scan shows regression of the air space opacities with a residual micronodular pattern. *(From De Blic J. Pulmonary alveolar proteinosis in children. Paediatr Respir Rev. 2004;5:316–322.)*

Chapter 457

Pulmonary Hemosiderosis

Mary A. Nevin

Pulmonary hemorrhage may be characterized as focal or diffuse based on the location(s) of bleeding (see Chapter 458.2). The diagnosis of pulmonary hemosiderosis refers to the subset of patients with **diffuse alveolar hemorrhage (DAH)**. Bleeding in DAH occurs as a result of injury to the microvasculature of the lung and may be slow and insidious because of the low-pressure pulmonary circulation. Pulmonary hemosiderosis has classically been characterized by the triad of iron-deficiency anemia, hemoptysis, and radiographic evidence of alveolar infiltration. However, many of those affected, particularly young patients, are likely to present atypically, and a high index of suspicion for this condition must be maintained. Pulmonary hemosiderosis can exist in isolation, but more commonly occurs in association with an underlying condition. Defining a precise etiology for hemorrhage may be elusive. A diagnosis of **idiopathic pulmonary hemosiderosis (IPH)** is made when DAH occurs in isolation and an exhaustive evaluation for an underlying pathologic etiology is found to be unrevealing or nondiagnostic.

ETIOLOGY

The pathogenesis of pulmonary hemosiderosis is diverse, but DAH may be classified based on histopathologic examination. Three histopathologic patterns have been described: pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage. Of these, pulmonary capillaritis is most frequently encountered and appears to carry a negative prognosis in those affected with DAH.

The histopathologic finding of **pulmonary capillaritis** is characterized by neutrophilic inflammation of the alveolar interstitium, endothelial edema, and fibrinoid necrosis. DAH with pulmonary capillaritis is frequently associated with an underlying systemic vasculitic process or collagen vascular disease.

Disorders associated with pulmonary capillaritis include systemic lupus erythematosus (SLE; see Chapter 199), drug-induced capillaritis, anti–glomerular basement membrane (GBM) antibody syndrome (Goodpasture syndrome), IgA vasculitis (Henoch-Schönlein purpura) (see Chapter 210), and antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, including granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiitis (MPA; see Chapter 210), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Additional etiologies of pulmonary capillaritis include primary antiphospholipid antibody syndrome, rheumatoid arthritis, hypocomplementemic urticarial vasculitis, and acute lung transplant rejection. DAH in individuals with ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) is frequently associated with pathologic evidence of pulmonary capillaritis. In patients with Goodpasture syndrome, antiphospholipid syndrome, and SLE, DAH has been reported with pathologic evidence of capillaritis, but bland hemorrhage has also been described. Isolated pulmonary capillaritis may also be seen in the absence of ANCA positivity.

Drugs, including propylthiouracil, aspirin, hydralazine, and tumor necrosis factor alpha (TNF-α) antagonists, have been implicated as an etiology for pulmonary capillaritis and DAH. Finally, alveolar hemorrhage with capillaritis has been increasingly described as a complication of hematopoietic cell transplantation

Pulmonary hemosiderosis with the histopathologic finding of **bland hemorrhage** is found when there is an absence of alveolar capillary inflammation or endothelial and cellular disruption. Both anti-GBM disease and SLE may be associated with bland hemorrhage, although the finding of capillaritis is more typical. Other causes of bland hemorrhage include cardiac or cardiopulmonary derangements (pulmonary hypertension, mitral stenosis, mitral regurgitation, arteriovenous malformation), disseminated intravascular coagulation (DIC), coagulopathies, and anticoagulant therapy. Bland hemorrhage is also described in IPH.

Diffuse alveolar damage (DAD) is characterized by diffuse alveolar and interstitial edema with hyaline membrane formation. It is the pathognomonic finding in acute respiratory distress syndrome (ARDS) and is seen with a variety of infections, including opportunistic pathogens in immunocompromised individuals. Drug toxicity (sirolimus, nitrofurantoin, amphetamines, vaping), radiation therapy, and pulmonary embolus and infarction are other described etiologies for DAD with pulmonary hemorrhage. Table 457.1 provides a summary and classification of the diagnoses that may manifest with recurrent or chronic pulmonary hemorrhage.

EPIDEMIOLOGY

Disorders that present as DAH are highly variable in their severity and in their associated symptomatology and identifiable

Table 457.1 Diffuse Alveolar Hemorrhage Syndromes

DISORDERS WITH PULMONARY CAPILLARITIS
Granulomatosis with polyangiitis (Wegener granulomatosis)
Microscopic polyangiitis
Systemic lupus erythematosus (SLE)
Systemic sclerosis
Polymyositis
Anti-GBM antibody syndrome (Goodpasture)
Antiphospholipid antibody syndrome
IgA vasculitis (Henoch-Schönlein purpura)
Hypocomplementemic urticarial vasculitis
Rheumatoid arthritis
Immunoglobulin A nephropathy
Behçet syndrome
Cryoglobulinemia
Endocarditis
Drug-induced capillaritis (retinoic acid, propylthiouracil, etanercept, infliximab, hydralazine)
Idiopathic pulmonary-renal syndrome
Acute lung transplant rejection
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Hematopoietic cell transplantation
DISORDERS WITH BLAND HEMORRHAGE
Anti-GBM antibody syndrome (Goodpasture)
Systemic lupus erythematosus (SLE)
Idiopathic pulmonary hemosiderosis
Heiner syndrome
Acute idiopathic pulmonary hemorrhage of infancy
Thrombocytopenia syndromes (ITP, TTP)
Hemolytic uremic syndrome
Mitral stenosis
Celiac disease (Lane-Hamilton syndrome)
Nonaccidental trauma
Drugs (anticoagulation, toxins)
DISORDERS WITH DIFFUSE ALVEOLAR DAMAGE
Systemic lupus erythematosus (SLE)
Polymyositis
Immunodeficiency and opportunistic infection
Pulmonary infarction
Radiation therapy
Acute respiratory distress syndrome (ARDS)
Pulmonary hypertension
Pulmonary edema
Drugs (amphetamines, propylthiouracil, penicillamine, vaping)

Modified from Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. *Curr Opin Pediatr.* 2007;19:314–320.

abnormalities in laboratory testing; the diagnosis may be significantly delayed, making frequency estimates unreliable. Similarly, the prevalence of IPH is largely unknown. Of children and young adults diagnosed with IPH in the past, it has been postulated that the etiology of the hemorrhage might have been discovered if they had been studied with the newer and more advanced diagnostics available today; specific serologic testing has vastly improved our ability to appreciate immune-mediated disease. Estimates of prevalence obtained from Swedish and Japanese retrospective case analyses vary from 0.24 to 1.23 cases per million. Children and adolescents have traditionally accounted for 30% of cases. The ratio of affected males:females is 1:1 in the childhood diagnosis group, and males are only slightly more affected in the group diagnosed as young adults. In pediatric and adolescents undergoing allogeneic hematopoietic cell transplantation, pulmonary hemorrhage has been described in 2% of the population.

PATHOLOGY

DAH has been associated with diffuse inflammation, cytokine activation, and autoimmune responses. Elevations of both ferritin and interleukin (IL)-6 have been described as key factors in the exaggerated inflammatory response seen in pulmonary hemorrhage. In pulmonary capillaritis, key histologic features include (1) fibrin thrombi, which occlude capillaries, (2) fibrin clots adherent to interalveolar septae, (3) fibrinoid necrosis of capillary walls, and (4) interstitial erythrocytes and hemosiderin. Illustrative but nonspecific pathologic findings, such as vascular smooth muscle hypertrophy (pulmonary hypertension) or thrombosis (vascular thrombosis with infarction), may be found in those disorders that cause DAH without pulmonary capillaritis. The finding of blood in the airways or alveoli is representative of a recent hemorrhage. With repeated episodes of pulmonary hemorrhage, lung tissue appears brown secondary to this presence of hemosiderin. The presence of persistent blood in three bronchoalveolar lavage (BAL) specimens from the same lobe is highly suggestive of the diagnosis. **Hemosiderin-laden macrophages *(HLMs)*** are seen with recovering, recurrent, or chronic pulmonary hemorrhage and are identifiable both in BSL fluid and in pathologic specimens of lung tissue. Approximately 48 hours is necessary for the alveolar macrophages to convert iron from erythrocytes into hemosiderin. In a murine model, HLMs appear 3 days after a single episode of pulmonary hemorrhage and peak at 7-10 days. HLMs may be detectable for weeks to months after a hemorrhagic event. Other nonspecific pathologic findings include thickening of alveolar septa, goblet cell hyperplasia, and hypertrophy of type II pneumocytes. Fibrosis may be seen with chronic disease.

PATHOPHYSIOLOGY

Diffuse Alveolar Hemorrhage Associated with Pulmonary Capillaritis

Granulomatosis with polyangiitis is a recognized etiology for DAH in children (see Chapter 448.3). This disease is classically characterized by necrotizing granuloma formation (with or without cavitation) of the upper and lower respiratory tract and by a necrotizing glomerulonephritis and small vessel vasculitis. In children, presentations attributable to the upper airway, including subglottic stenosis, may suggest the diagnosis. The presence of ANCAs may be helpful in diagnosis and management, but the clinician must be aware that other ANCA-positive vasculitides, such as MPA and **eosinophilic granulomatosis with polyangiitis**, may share this nonspecific laboratory finding. In small vessel vasculitides, ANCAs cause an inflammatory reaction that results in injury to the microvasculature. Antiproteinase-3 antibodies (cANCAs) are classically associated with granulomatosis with polyangiitis, whereas antimyeloperoxidase antibodies (pANCAs) are typically found in patients with MPA.

Patients with **MPA** (previously the microscopic variant of polyarteritis nodosa) demonstrate a systemic necrotizing vasculitis with a predilection for small vessels (venules, arterioles, capillaries) but without necrotizing granuloma formation. This diagnosis is precluded by the finding of immune complex deposition in order to differentiate MPA from other diseases (Henoch-Schönlein purpura, cryoglobulinemic vasculitis) that are associated with immune complex–mediated small vessel vasculitis.

Anti-GBM antibody syndrome (Goodpasture disease) is an immune complex–mediated disease in which anti-GBM antibody binds to the basement membrane of both the alveolus and the glomerulus. GBM antibodies attach to type IV collagen contained in the vascular endothelium. At the alveolar level, immunoglobulin (Ig) G, IgM, and complement are deposited at alveolar septa. Electron microscopy shows disruption of basement membranes and vascular integrity, which allows blood to escape into alveolar spaces.

Although alveolar hemorrhage is a relatively uncommon complication in SLE, its occurrence is often severe and potentially life-threatening; mortality rates exceed 50% in some cohorts, and early recognition is crucial to allow timely implementation of immunomodulatory therapies.

In **IgA vasculitis (Henoch-Schönlein purpura),** pulmonary hemorrhage is a rare but recognized complication. Pathologic findings have included transmural neutrophilic infiltration of small vessels, alveolar septal inflammation, and intraalveolar hemorrhage. Vasculitis is the proposed mechanism for hemorrhage.

Pulmonary renal syndromes are defined as those where pulmonary and renal disease manifestations are predominant. These include the aforementioned granulomatosis with polyangiitis, anti-GBM antibody syndrome, SLE, and MPA. As Henoch-Schönlein purpura may also have renal involvement, it has been suggested for inclusion as a pulmonary renal syndrome.

Pulmonary Hemorrhage in Infancy

An infant's neonatal course may be complicated by pulmonary hemorrhage. The most common diagnoses in infants with DAH are congenital heart disease (including pulmonary hypertension) and prematurity. Additional diagnostic considerations in an infant with pulmonary hemorrhage include congenital or acquired lung disease (congenital diaphragmatic hernia, sepsis), congenital or acquired coagulopathies (extracorporeal membrane oxygenation [ECMO], liver failure), and infection. Pulmonary hemorrhage in infants may be unrecognized if the volume of blood is insufficient to reach the proximal airways. Even with more significant blood loss, the tussive force of an infant may be insufficient to produce hemoptysis. Because the radiographic findings in pulmonary hemorrhage may be appreciated instead as a worsening picture of respiratory distress syndrome, edema, or infection, a high index of suspicion is required.

Acute Idiopathic Pulmonary Hemorrhage of Infancy

In 1994 and 1997, case reports suggested clusters of infantile pulmonary hemorrhage in association with environmental exposure to *Stachybotrys chartarum*. A review by the Centers for Disease Control and Prevention did not support an association between exposure to the mold and infantile pulmonary hemorrhage. Acute idiopathic pulmonary hemorrhage of infancy (AIPHI) has been defined as pulmonary hemorrhage in a previously healthy infant who is less than 1 year of age and born at a gestational age of greater than 32 weeks. Three criteria must simultaneously be met; these include (1) the sudden onset of bleeding or "frank" evidence of blood in the airway; (2) severe presentation leading to respiratory distress or failure and resulting in hospitalization in intensive care with intubation and mechanical ventilation; and (3) diffuse bilateral pulmonary infiltrates found on chest radiographs or computerized tomographic imaging. AIPHI is believed to be a rare diagnosis, and an exhaustive search for an identifiable etiology of pulmonary hemorrhage is advocated.

Pulmonary hemosiderosis in association with non-IgE–mediated cow's milk hypersensitivity is characterized by variable and

reversible (with elimination of cow's milk protein) symptoms of milk intolerance in infants and young children. Symptoms can include grossly bloody or occult heme-positive stools, vomiting, failure to thrive, gastroesophageal reflux, upper airway congestion, and iron-deficiency anemia. Association with pulmonary hemorrhage has remained controversial, but multiple case series have provided support for the anecdotal association.

A number of case reports and case series have suggested an association between **celiac disease** (see Chapter 384) and DAH. In these reports, a resolution of intestinal and pulmonary symptoms along with resolution of radiographic disease has been seen after the adoption of a gluten-free diet. Consideration of testing for celiac disease in those patients with pulmonary hemorrhage and suggestive gastrointestinal symptomatology may be warranted.

DAH has been described in association with numerous other conditions. These are typically noninflammatory in nature and may be diversely attributable to cardiac, vascular, lymphatic, or hematologic etiologies. DAH has also rarely been attributed to nonaccidental trauma.

The diagnosis of IPH is a diagnosis of exclusion and is only made when there is evidence of chronic or recurrent DAH and when exhaustive evaluations for primary or secondary etiologies have negative results. Renal and systemic involvement should be absent, and a biopsy specimen should not reveal any evidence of granulomatous disease, vasculitis, infection, infarction, immune complex deposition, or malignancy. Some patients initially diagnosed with IPH will later be found to have Goodpasture syndrome, SLE, or MPA; therefore some cases of IPH may represent unrecognized immune-mediated disorders.

CLINICAL MANIFESTATIONS

The clinical presentation of pulmonary hemosiderosis is highly variable. In most symptomatic cases, DAH is heralded by symptoms of hemoptysis and dyspnea with associated hypoxemia and the finding of alveolar infiltration on chest radiograph. The diagnosis may be problematic, as young children often lack the ability to effectively expectorate and may not present with hemoptysis. Because the presence of blood in the lung is a trigger for airway irritation and inflammation, the patient may present after an episode of hemorrhage with wheezing, cough, dyspnea, and ventilatory derangements, reflecting bronchospasm, edema, mucus plugging, and inflammation; this presentation may result in an incorrect diagnosis of asthma or bronchiolitis. A lack of pulmonary symptoms does not preclude the diagnosis of DAH, and children may present only with chronic fatigue or pallor. In particular, young infants and children with DAH may come to attention with entirely nonspecific and nonpulmonary symptomatology such as failure to thrive or jaundice.

Primary or reported symptoms may reflect an underlying and associated disease process or comorbid condition. Presentations can vary widely from a relative lack of symptoms to shock or sudden death. Bleeding may occasionally be recognized from the presence of alveolar infiltrates on a chest radiograph alone. It should be noted, however, that the absence of an infiltrate does not rule out an ongoing hemorrhagic process.

On physical examination, the patient may be pale with tachycardia and tachypnea. During an acute exacerbation, children are frequently febrile. Examination of the chest may reveal retractions and differential or decreased aeration, with crackles or wheezes. The patient may present in shock with respiratory failure from massive hemoptysis.

LABORATORY FINDINGS AND DIAGNOSIS

Bronchoscopic evaluation is an important tool in the diagnosis of pulmonary hemosiderosis. The yield is highest if performed within the first 48-72 hours after an acute hemorrhage. Cultures should be sent for bacterial, viral, fungal, and mycobacterial pathogens. In addition, the evaluation of BAL fluid with silver stain for pneumocystis is advocated. When the pulmonologist recovers persistent or worsening blood with repeated BAL of the same lung segment, the diagnosis of DAH is supported. The presence of greater than 20% HLMs in BAL fluid is considered diagnostic. In the absence of bronchoscopy, sputum or pulmonary secretions should be analyzed for significant evidence of blood or HLMs and may provide supportive evidence in a patient who is able to adequately expectorate secretions from the lower airway. Gastric secretions may also reveal HLMs.

Pulmonary hemorrhage is classically associated with a microcytic, hypochromic anemia. Reduced serum iron levels, a decreased or normal total iron-binding capacity, and normal to increased ferritin levels may be found with chronic disease. The reticulocyte count is frequently elevated. Patients with pulmonary capillaritis have lower hematocrits and higher erythrocyte sedimentation rates. The anemia of IPH can mimic a hemolytic anemia. Elevations of plasma bilirubin are caused by absorption and breakdown of hemoglobin in the alveoli. Any or all of these hematologic manifestations may be absent in the presence of recent hemorrhage.

White blood cell count and differential should be evaluated for evidence of infection and eosinophilia. A peripheral smear and direct Coombs test may suggest a vasculitic process. A stool specimen positive for occult blood may suggest associated gastrointestinal disease but can also reflect swallowed blood. Renal and liver functions should be reviewed. A urinalysis should be obtained to assess for evidence of a pulmonary-renal syndrome. A coagulation profile, quantitative immunoglobulins (including IgE), and complement studies are recommended. Testing for von Willebrand disease is also indicated.

Testing for ANCA (cANCA, pANCA), antinuclear antibody, anti–double-stranded DNA, rheumatoid factor, antiphospholipid antibody (APL), myeloperoxidase, lupus anticoagulant, anticardiolipin antibody, and anti-GBM antibody evaluates for a number of immune-mediated and vasculitic processes that may be associated with pulmonary capillaritis.

Chest x-rays may reveal evidence of acute or chronic disease. Hyperaeration is frequently seen, especially during an acute hemorrhage. Infiltrates are typically symmetric and may spare the apices of the lung. Atelectasis may be appreciated. With chronic disease, fibrosis, lymphadenopathy, and nodularity may be seen. High-resolution CT imaging may reveal diffuse ground-glass opacification and alveolar opacification. With large bleeds, a fluid collection may be appreciated.

The presence of a cardiac murmur, cardiomegaly on x-ray, or a clinical suspicion of congenital or acquired heart disease suggests the need for a complete cardiac evaluation, including electrocardiogram and echocardiogram.

Pulmonary function tests generally reveal obstructive lung disease in the acute period. With more chronic disease, fibrosis and restrictive disease tend to predominate. Oxygen saturation levels may be decreased. Lung volumes may reveal air trapping acutely and decreases in total lung capacity chronically. The diffusing capacity of carbon monoxide may be low or normal in the chronic phase but is likely to be elevated in the setting of an acute hemorrhage, because carbon monoxide binds to the hemoglobin in extravasated red blood cells.

Lung biopsy is warranted when DAH occurs without discernible etiology, extrapulmonary disease, serologic evidence of vasculitis, or circulating GBM antibodies. When surgically obtained, pulmonary tissue should be evaluated for evidence of immune complex deposition, inflammatory change in the pulmonary vascular bed, and granulomatous disease. Transbronchial biopsy is not generally recommended, as the lung involvement in DAH is frequently nonhomogeneous and "patchy" in character.

Many have supported a diagnosis of IPH without lung biopsy if the patient has a typical presentation with diffuse infiltration on

radiography, anemia, HLMs in BAL, sputum or gastric aspirate, absence of systemic disease, and negative serology for immune-mediated disease. However, a number of patients meeting these criteria have been proven to have pulmonary capillaritis on review of pathologic lung tissue specimens. Therefore a lung biopsy may be recommended in an effort to guide therapy or determine prognosis in an individual with DAH of unknown etiology.

TREATMENT

Supportive therapy, including volume resuscitation, ventilatory support, supplemental oxygen, and transfusion of blood products, may be warranted in the patient presenting acutely with pulmonary hemorrhage. In the presence of ARDS, high oxygen concentrations and high positive end-expiratory pressure (PEEP) may be required. Surgical or medical therapy should be directed at any treatable underlying condition. High-dose systemic corticosteroids are frequently used as first-line treatment and are expected to be of particular benefit in the setting of immune-mediated disease. Steroids inhibit the acute inflammatory response (neutrophil influx, cytokine storm) associated with hemorrhage and may decrease progression toward fibrotic disease. High-dose steroids may contribute to morbidity and mortality in patients who have an infectious etiology for their hemorrhage and in those who are immunocompromised. A thorough evaluation for immunocompetence and pan-cultures for infectious organisms are therefore strongly advocated.

Medication dosing may vary with regard to primary diagnosis, age, comorbidities, and other factors. Clinical-pharmacologic correlation is advocated. Low- to moderate-dose treatment regimens may be provided in the form of methylprednisolone 2-4 mg/kg/day divided every 6-12 hours or in the form of prednisone 0.5-1 mg/kg daily and decreased to every other day after resolution of acute symptoms. High-dose corticosteroid therapy generally uses 10-30 mg/kg/day of IV methylprednisolone for 3-5 days and is followed by a tapering dose over 4-6 weeks. Successful treatment is also associated with the use of pulse steroid therapy; methylprednisolone may be given at a dose of 10-30 mg/kg (maximum 1 g) infused over 1 hour for 3-5 consecutive days and repeated weekly or monthly. Early treatment with corticosteroids appears to decrease episodes of hemorrhage, but high doses of steroids carry the risk of renal disease, immunosuppression, and potentially fatal infections.

A variety of steroid-sparing and alternative immunosuppressive agents, including cyclophosphamide, Cytoxan, azathioprine, hydroxychloroquine, methotrexate, 6-mercaptopurine, and IVIG, have all been used successfully as adjunctive therapy in patients with severe, chronic, unremitting, or recurrent hemorrhage.

Plasmapheresis is a recognized adjunctive therapy for DAH with pulmonary capillaritis in ANCA-associated vasculitis, SLE, and anti-GBM antibody disease. Pheresis is generally performed daily or every other day for 14 days. In each plasma exchange, the total volume of plasma is replaced with fresh-frozen plasma (FFP) or albumin. In recent analyses, the long-term efficacy of plasmapheresis as compared with corticosteroid therapy has been questioned. At this time, treatment guidelines suggest the use of plasmapheresis in patients with ANCA-associated vasculitis who are critically ill with hypoxemic respiratory failure.

Rituximab has evolved as an additional adjunctive therapeutic option. It is a monoclonal antibody that targets CD-20 and has been found to be an effective option for individuals with connective tissue and autoimmune disorders.

Any coagulopathic disorders should be corrected in an effort to achieve hemostasis. Cryoprecipitates, FFP, and platelets may be transfused depending on the identified deficiency. Vitamin K may also be supplemented.

Prothrombotic factors, including antifibrinolytics such as tranexamic acid (TXA), thrombin, and factor VIIa, have been used in the treatment of DAH. TXA acts by preventing the conversion of plasminogen into plasmin and hinders fibrinolysis. Inhalational TXA has been associated with favorable treatment outcomes in children with DAH. TXA has been described as being less efficacious in those with hematologic malignancies and those individuals with massive or recurrent bleeding. Further study is indicated to define associated risk and populations expected to benefit most consistently from this therapy.

Recombinant factor VIIa (FVIIa) may be used in an effort to achieve hemostasis in those with massive hemorrhage. A therapeutic response to low doses of FVIIa has been reported with direct intrapulmonary instillation, but the use of this agent is still anecdotal outside of hemophilia. Factor VIIa appears to decrease the requirement for transfusions and to be an effective adjunctive therapy for critically ill children with massive hemorrhage. The efficacy of FVIIa in neonates and infants less than 1 year of age is yet to be established.

In the most critically ill children, additional life-sustaining interventions may be required; ECMO combined with immunosuppression was reported to be successful in allowing recovery from a severe hemorrhage with hypoxemic respiratory failure in the setting of pANCA-positive MPA. In neonatal and infantile pulmonary hemorrhage, clinical improvement in blood gas and ventilatory requirements have been described with intrapulmonary administration of exogenous surfactant.

The potential adverse effects of these pharmacologic and therapeutic interventions should be recognized, and treated patients must be closely monitored for drug-related complications. Cushing syndrome, systemic hypertension, diabetes, and immunodeficiency are well-recognized complications of chronic steroid therapy. Thrombocytopenia in association with low-dose cyclophosphamide has also been reported. Chronically immunosuppressed patients are at risk for opportunistic infection; *Legionella* pneumonia infection has been described in a survivor of IPH.

In chronic disease, progression to debilitating pulmonary fibrosis has been described. Lung transplantation has been performed in patients with IPH refractory to immunosuppressive therapy. In one reported case study, IPH recurred in the transplanted lung.

PROGNOSIS

The outcome of patients suffering from DAH is multideterminant; underlying disease process, recurrence patterns, severity of hemorrhage, and delays in presentation are recognized prognostic factors. Some conditions respond well to immunosuppressive therapies, and remissions of disease are well documented. Other syndromes, especially those associated with pulmonary capillaritis, carry a poorer prognosis. In IPH, mortality is generally attributable to massive hemorrhage or, alternatively, to progressive fibrosis, respiratory insufficiency, and right-sided heart failure.

The long-term prognosis in patients with IPH varies among studies. Initial case study reviews suggested an average survival after symptom onset of only 2.5 years. Subsequent reviews have demonstrated vastly improved 5-year (86%) and 8-year (93%) survival in association with the use of immunosuppressive therapies. In IPH, the presence of hypoxia at clinical presentation and a positive antinuclear antibody have been demonstrated to be risk factors for recurrence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 458

Pulmonary Embolism, Infarction, and Hemorrhage

458.1 Pulmonary Embolus and Infarction

Mary A. Nevin

Venous thromboembolism (VTE) is a term that describes both deep venous thrombosis (DVT) and pulmonary embolism (PE). PE is defined as obstruction of a pulmonary artery, typically as a result of thrombus formation. Although VTE remains relatively rare in occurrence, these events have become recognized as increasingly prevalent clinical problems and are associated with significant morbidity and mortality in the pediatric population. An increased incidence of VTE has been described in infants, children, and adolescents; this has been attributed to multiple factors, including increased survival from previously fatal critical and chronic illnesses, the increased use of central venous catheters, and improved diagnostic tools. Pulmonary emboli are more likely to be silent or to present atypically in infants and children as compared to adults, and a delay in diagnosis is commonly encountered. A diagnosis of PE may only be discovered on postmortem examination. In a retrospective study of PE found at the time of autopsy, the investigators discovered antemortem consideration of the diagnosis in only 15% of cases. Although children are more likely than their adult counterparts to have one or more predisposing factors favoring VTE (Table 458.1), a PE is often the first presenting symptom, and a high index of suspicion is needed to allow timely and accurate recognition as well as optimal management of PE in children.

ETIOLOGY

In the adult population, PE and VTE may be idiopathic in ~30% of patients. Children with DVT and PE are much more likely to have one or more identifiable conditions or circumstances placing them at risk. At least one identifiable risk factor for PE and VTE has been found in ≥80% of affected children. Most children have multiple and coexisting risk factors. In the pediatric population, the most common risk factors for VTE include the presence of an indwelling central venous catheter, congenital heart disease or vascular anomalies, trauma, immobility, recent surgery, malignancy, congenital and acquired thrombophilia, obesity and pregnancy, or hormonal drug therapies, including oral contraceptives. Individuals with nephrotic syndrome, inflammatory bowel disease, systemic lupus erythematosus, and sickle cell disease are also recognized as being at increased risk for thromboembolic disease. Both SARS-CoV-2/COVID-19 infection and the COVID-19–associated multisystem inflammatory syndrome in children (MIS-C) have been associated with a hypercoagulable state and increased risk for VTE, particularly in children and young adults who are critically ill with respiratory complications.

Although an embolus can also consist of air, septic material, amniotic fluid, or neoplastic tissue, emboli most commonly originate from thrombus formation. The most common risk factor for VTE in children is the presence of a central venous catheter (CVC); these indwelling lines are used for long-term administration of chemotherapy, antibiotics, and parental nutrition. The presence of a catheter in a vessel lumen, as well as instilled medications, can induce endothelial damage and favor thrombus formation. The use of a CVC is associated with ~90% of recognized VTE in neonates and ~30–60% of VTE in children. Septic emboli are rare in children but have been seen in osteomyelitis, endocarditis, Lemierre syndrome, and individuals with cellulitis.

Children with malignancy are recognized as being at high risk for VTE. Thromboembolic disease has been described in 7–16% of those with soft tissue sarcoma and in 5.2% of individuals with acute lymphocytic leukemia (ALL). A child with malignancy may have numerous risk factors that relate to both the primary disease process and therapeutic interventions. Infection related to chronic immunosuppression, indwelling catheters, and the hypercoagulable state of malignancy itself are additional factors that favor VTE. Chemotherapeutic agents such as L-asparaginase have been implicated as conferring risk for VTE. In addition, steroids may contribute to the risk of VTE by increasing factor VIII. In a retrospective cohort of patients with VTE, pediatric malignancy was the chronic medical condition most strongly associated with recurrent VTE.

In the neonatal period, VTE is frequently associated with the presence of an indwelling CVC. Comorbid medical conditions often confer additional risk for thromboembolic disease in the neonate; the most common associated diagnoses are congenital heart disease and sepsis. Another known contributor is the relative immaturity of newborn infant coagulation; plasma concentrations of vitamin K–dependent coagulation factors (II, VII, IX, X); factors XII, XI, and pre-kallikrein and high molecular weight kininogen are physiologically lower in neonates and children (see Chapter 524). Infants with congenitally acquired homozygous deficiencies of antithrombin, protein C, and protein S may also present with thromboembolic disease in the neonatal period. Testing for these acquired thrombophilias is frequently problematic in this age-group, as physiologic levels of protein S and antithrombin are not seen until 6 months of age, and mature levels of protein C may not occur until a child reaches adolescence. Furthermore, coagulant proteins may be artificially low in the setting of acute VTE (see Chapter 527).

Pulmonary air embolism is a defined entity in the newborn or young infant and is attributed to the conventional ventilation of critically ill (and generally premature) infants with severe pulmonary disease. Usually, the pulmonary air embolism is preceded by an air-leak syndrome. Infants may become symptomatic and critically compromised by as little as 0.4 mL/kg of intravascular air; these physiologic derangements are thought to be secondary to the effects of nitrogen.

Thrombophilia may be inherited or acquired and may manifest in neonates and in older infants, children, and adolescents. **Inherited thrombophilias** include deficiencies of antithrombin, protein C, and protein S, as well as pathogenic variants of factor V Leiden (FVL) and prothrombin G20210 pathogenic variant (see Chapter 527). The most frequent inherited thrombophilia is the FVL pathogenic variant. It is more common in people of European descent and relatively uncommon in those of African and Asian heritage. Acquired thrombophilic conditions include the presence of lupus anticoagulant (may be present without the diagnosis of systemic lupus erythematosus), anticardiolipin antibody, and anti–β_2-glycoprotein 1 antibody. Methylenetetrahydrofolate reductase (MTHFR) pathogenic variants associated with high levels of plasma homocysteine have also been hypothesized to be a risk factor for VTE, but the prognostic significance is unclear, and an isolated MTHFR pathogenic variant is not an absolute indication for VTE prophylaxis. Diagnostic testing for thrombophilic disorders is unlikely to be beneficial in the acute management of VTE but may be indicated to determine risk of recurrent VTE in both the index case and their relatives. Avoidance of prothrombotic risk factors such as oral contraceptive agents may also be recommended in those individuals with an inherited thrombophilia.

Sickle cell disease is associated with an increased risk for PE and pulmonary infarction. The primary risk factor for VTE in sickle cell disease is the presence of an indwelling CVC. Other risk factors for thrombosis include infection, splenectomy, and immobility.

The incidence of VTE in female adolescents 12-18 years of age is ~3 per 10,000. In patients with known exposure to estrogen-containing long-acting reversible contraception (LARC), more than 96% also had one or more comorbidities. Over 50% of those with VTE had four or more comorbidities. The most common comorbid conditions were obesity and tobacco use. Although estrogen is a known procoagulant, VTE in female adolescents does not appear attributable *solely* to estrogen-containing LARC, and additional risk factors should be sought in affected individuals.

EPIDEMIOLOGY

A wide range of incidence of PE has been described in both hospitalized (8.6-57 per 100,000) children and in the general population (0.14-0.9 per 100,000). There is a suggestion that the incidence of PE has increased over time. The etiology for these increases in pediatric thromboembolism is

Table 458.1 Risk Factors for Pulmonary Embolism

ENVIRONMENTAL
Long-haul air travel (>4 hr)
Obesity
Cigarette smoking
Hypertension
Immobility
WOMEN'S HEALTH
Oral contraceptives, including progesterone-only and, especially, third-generation pills
Pregnancy or puerperium
Hormone replacement therapy
Septic abortion
MEDICAL ILLNESS
Personal or family history of prior pulmonary embolism or deep venous thrombosis
Cancer
L-Asparaginase therapy
Heart failure
Chronic obstructive pulmonary disease
Diabetes mellitus
Inflammatory bowel disease
Antipsychotic drug use
Long-term indwelling central venous catheter
Permanent pacemaker
Internal cardiac defibrillator
Stroke with limb paresis
Spinal cord injury
Nursing home confinement or current or repeated hospital admission
SURGICAL
Trauma, including fractures
Orthopedic surgery
General surgery
Neurosurgery, especially craniotomy for brain tumor
Vascular anomalies
May-Turner syndrome
THROMBOPHILIA
Factor V Leiden mutation
Prothrombin gene (20210G A) pathogenic variant
Hyperhomocysteinemia (including pathogenic variant in methylenetetrahydrofolate reductase)
Antiphospholipid antibody syndrome
Deficiency of antithrombin III, protein C, or protein S
High concentrations of factor VIII or XI
Increased lipoprotein (a)
Heparin-induced thrombocytopenia
Paroxysmal nocturnal hemoglobinuria
Nephrotic syndrome
NONTHROMBOTIC
Air
Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)
Amniotic fluid
Bone fragments, bone marrow
Fat
Tumors (Wilms tumor)

Modified from Goldhaber SZ. Pulmonary embolism. *Lancet.* 2004;363:1295–1305.

regarded as multifactorial, with increased survival from chronic and critical illnesses, increased frequency of indwelling CVCs, increased clinical suspicion, and more precise imaging and diagnostic techniques being cited as contributing factors. The 2-year mortality rate from PE in two studies was ~8.5%, with the highest mortality rates occurring in infants. In other analyses, inpatient VTE has been estimated to increase the risk of mortality by two to six times. Massive PE has historically been associated with death in up to 30% of cases. Currently, the mortality from PE in children approximates the rates of mortality from VTE. In survivors of VTE, chronic complications, increased healthcare use, and increased healthcare costs are recognized.

The incidence of pediatric VTE is recognized as having a bimodal distribution, with peaks occurring in infants less than 1 year of age and in adolescence. Males are statistically more likely to have VTE, except for the 13- to 18-year-old age-group, where females are affected more frequently.

Pediatric deaths from isolated pulmonary emboli are rare. The source of the emboli may be lower or upper extremity veins as well as the pelvis and right heart. In adults, the most common location for DVT is the lower leg. However, one pediatric VTE/PE registry found ~65% of DVTs occurring in the upper extremity.

PATHOPHYSIOLOGY

Favorable conditions for thrombus formation include injury to the vessel endothelium, hemostasis, and hypercoagulability. In the case of PE, a thrombus is dislodged from a vein, travels through the right atrium, and lodges within the pulmonary arteries. VTE is most common in segmental pulmonary arteries (52%), with central arteries being obstructed less frequently (6%). In children, emboli that obstruct <50% of the pulmonary circulation are generally clinically silent unless there is significant coexistent cardiopulmonary disease. When greater than 50% of the pulmonary circulation is obstructed, right ventricular afterload is increased, with resultant right ventricular dilation and increases in right ventricular and pulmonary arterial pressures. In severe cases, a reduction of cardiac output and hypotension may result from concomitant decreases in left ventricular filling. In rare instances of death from massive pulmonary embolus, marked increases in pulmonary vascular resistance and heart failure are usually present.

Arterial hypoxemia results from unequal ventilation and perfusion; the occlusion of the involved vessel prevents perfusion of distal alveolar units, thereby creating an increase in dead space and hypoxia with an elevated alveolar-arterial oxygen tension difference (see Chapter 421). The vascular supply to lung tissue is abundant, and pulmonary infarction is unusual with PE but may result from distal arterial occlusion and alveolar hemorrhage.

CLINICAL MANIFESTATIONS

The presentation of VTE is highly variable and more likely to present atypically or silently in the pediatric age-group. A high index of suspicion is therefore necessary. The symptoms reported most in association with PE include chest pain, hypoxia (cyanosis), dyspnea, tachycardia, tachypnea, and syncope. A tenderness, swelling, or palpable cord may be palpated at the location of a DVT. Hemoptysis may also be a presenting symptom. Pleuritic chest pain is the most common presenting symptom in adolescents (84%). Massive PE may manifest as cardiopulmonary (hypotension) failure. Confirmatory testing should follow a clinical suspicion for PE.

In older adolescents and adults, clinical prediction rules have been published and are based on risk factors, clinical signs, and symptoms (Table 458.2). The Pulmonary Embolism Rule Out Criteria (PERC) and Wells criteria are clinical prediction rules that are commonly used in adults but lack reliability in the pediatric population. The Wells score has a sensitivity of 72–86% and a specificity of 60% when applied to children. The PERC tool has a higher sensitivity but a specificity of only 24% in children. When the PERC tool is applied in the pediatric setting, a high false-positive rate is seen, with over 75% of patients without PE having a positive PERC result. In a population at high risk from exposure to ionizing radiation, more discerning tools have been sought for this age-group.

In children and adolescents less than 22 years of age, the risk of PE is low (1.3%) in children who were not receiving estrogen therapy or in those who did not present with tachycardia or hypoxia (SpO_2 <95%); the prediction model reported a sensitivity of 89% and a specificity of 56%. Another clinical prediction model for the diagnosis of PE in adolescents and young adults identified five risk factors, including immobilization, hypercoagulability, exposure to estrogen-containing drugs, indwelling CVC, and a prior history of PE and/or DVT; the probability of PE as demonstrated by computed tomography pulmonary angiography (CTPA) with the presence of any three or more risk factors was 89%, and the probability of PE was extremely low (0.5%) when none of these risk factors were identified. These data and prediction tools may allow risk stratification and optimal use of diagnostic testing, including CTPA, but require prospective analysis and clinical validation.

Table 458.2 Scores to Assess the Clinical Probability of Venous Thromboembolism

WELLS SCORE FOR DEEP VEIN THROMBOSIS	POINTS
Active cancer	+1
Paralysis, paresis, or recent plaster cast on lower extremities	+1
Recent immobilization >3 days or major surgery within past 4 wk	+1
Localized tenderness of deep venous system	+1
Swelling of entire leg	+1
Calf swelling >3 cm compared with asymptomatic side	+1
Unilateral pitting edema	+1
Collateral superficial veins	+1
Previously documented deep vein thrombosis	+1
Alternative diagnosis at least as likely as deep vein thrombosis	−2
Clinical pretest probability	
Unlikely	Total score ≤2 (prevalence 4%)
Likely	Total score >2 (prevalence 27%)
WELLS SCORE FOR PULMONARY EMBOLISM	
Original	
Alternative diagnosis less likely than pulmonary embolism	+3
Clinical signs and symptoms of deep vein thrombosis	+3
Heart rate >100 beats per min	+1.5
Previous deep vein thrombosis or pulmonary embolism	+1.5
Immobilization or surgery within the past 4 wk	+1.5
Active cancer	+1
Hemoptysis	+1
Clinical Pretest Probability	
Low	Total score ≤1 (prevalence 4%)
Intermediate	Total score 2-6 (prevalence 21%)
High	Total score >6 (prevalence 67%)
Unlikely	Total score ≤4 (prevalence 8%)
Likely	Total score >4 (prevalence 41%)
Simplified	
Alternative diagnosis less likely than pulmonary embolism	+1
Clinical signs and symptoms of deep vein thrombosis	+1
Heart rate >100 beats per min	+1
Previous deep vein thrombosis or pulmonary embolism	+1
Immobilization or surgery within the past 4 wk	+1
Active cancer	+1
Hemoptysis	+1
Clinical Pretest Probability	
Unlikely	Total score ≤1 (prevalence 11%)
Likely	Total score >1 (prevalence 36%)
REVISED GENEVA SCORE FOR PULMONARY EMBOLISM	
Original	
Heart rate ≥95 beats per min	+5
Heart rate 75-94 beats per min	+3
Pain on lower-limb deep venous palpation and unilateral edema	+4
Unilateral lower-limb pain	+3

Table 458.2 Scores to Assess the Clinical Probability of Venous Thromboembolism—cont'd

REVISED GENEVA SCORE FOR PULMONARY EMBOLISM	
Previous deep vein thrombosis or pulmonary embolism	+3
Active cancer	+2
Hemoptysis	+2
Surgery or fracture within the past 4 wk	+2
Age >65 yr	+1
Clinical Pretest Probability	
Low	Total score <4 (prevalence 9%)
Intermediate	Total score 4-10 (prevalence 28%)
High	Total score >10 (prevalence 72%)
Simplified	
Heart rate ≥95 beats per min	+2
Heart rate 75-94 beats per min	+1
Pain on lower-limb deep venous palpation and unilateral edema	+1
Unilateral lower-limb pain	+1
Previous deep vein thrombosis or pulmonary embolism	+1
Active cancer	+1
Hemoptysis	+1
Surgery or fracture within the past 4 wk	+1
Age >65 yr	+1
Clinical Pretest Probability	
Unlikely	Total score ≤2 (prevalence 13%)
Likely	Total score >2 (prevalence 42%)
YEARS CRITERIA FOR PULMONARY EMBOLISM	
Clinical signs of deep vein thrombosis	+1
Hemoptysis	+1
Pulmonary embolism is the most likely diagnosis	+1
Clinical Pretest Probability	
Low	Total score 0 (prevalence 3%)
High	Total score ≥1 (prevalence 23%)
PULMONARY EMBOLISM RULE-OUT CRITERIA	
Age <50 yr	—
Heart rate <100 beats per min	—
Pulse oximetry reading on room air >94%	—
No unilateral leg swelling	—
No hemoptysis	—
No recent trauma or surgery	—
No history of venous thromboembolism	—
No oral hormone use	—

Pulmonary embolism can be considered excluded in patients with all Pulmonary Embolism Rule-Out Criteria and a low clinical pretest probability, assessed by gestalt, or in clinical settings with a low (<5%) prevalence of pulmonary embolism. If any criterion applies, pulmonary embolism cannot be ruled out in these patients. Prevalence estimates correspond to emergency department settings. Vital signs should be age adjusted.

Modified from Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. *Lancet*. 2021;398:64–77.

LABORATORY FINDINGS AND DIAGNOSIS

Blood gas analysis is expected to reveal hypoxemia with an abnormal A-a gradient. Lower-than-normal $Paco_2$ levels may also be seen secondary to hyperventilation, a finding that may persist even when oxygenation is optimized. Abnormalities of oxygenation and ventilation are likely to be less significant in the pediatric population, in the setting of less underlying cardiopulmonary disease and greater reserve. The results of an electrocardiogram and chest radiograph are expected to be nonspecific. ECG findings may include ST-T segment changes, tachycardia, right axis deviation, and right bundle branch block. Chest radiographs are frequently abnormal (88%); the most common finding is cardiomegaly (27%) and pleural

effusion (23%). These studies lack sensitivity and specificity in the diagnosis of PE.

A review of results of a complete blood count and coagulation profile is warranted. Prothrombotic diseases should be highly suspected based on medical or family history; additional laboratory evaluations include fibrinogen assays, protein C, protein S, and antithrombin III studies and analysis for FVL pathogenic variant, along with evaluation for lupus anticoagulant and anticardiolipin antibodies.

Echocardiograms may be used to assess ventricular size and function. An echocardiogram is indicated if there is any suspicion of intracardiac thrombi or endocarditis.

Noninvasive venous ultrasound testing with Doppler flow can be used to confirm DVT in the lower extremities; in pediatrics, the utility of ultrasonography is limited, as it may not detect thrombi in the upper extremities or pelvis (Fig. 458.1A).

In children, D-dimer levels demonstrate reasonable sensitivity but poor specificity for venous thrombosis because D-dimer levels are also increased in infectious, inflammatory, and neoplastic disorders, all of which are also risk factors for PE. Other studies have suggested that D-dimer may be a sensitive tool for PE in adolescents when a level of >750 mg/mL is seen; these data have not been found to be applicable to younger children or neonates.

In the evaluation of a suspected PE, a ventilation–perfusion ($\dot{V}$–$\dot{Q}$) radionuclide scan is a safe diagnostic study associated with exposure to low levels of ionizing radiation. With a definitive or high-probability scan, the likelihood of PE is 85%. With low-probability results, there is still a 20% chance of PE. In addition, children may have difficulty cooperating with the ventilation portion of the $\dot{V}$–$\dot{Q}$ scan.

Although conventional pulmonary angiography had been considered the gold standard for detection of PE, the invasive nature of this study, the high exposure to radiation, and the risk of complications have limited its use. *Computed tomography/multidetector CT with pulmonary angiography has become the diagnostic study of choice for PE* (see Fig. 458.1B). The criteria for PE include two or more consecutive images revealing a complete or partial filling defect of a pulmonary artery. CT studies detect emboli in lobar and segmental vessels with acceptable sensitivities. Poorer sensitivities may be encountered in the evaluation of the subsegmental pulmonary vasculature. Dual-energy scanning provides additional functional and anatomic information without additional radiation exposure. In most institutions, dose reduction techniques can be employed to limit a child's radiation exposure.

Magnetic resonance angiography (MRA) is also considered a viable diagnostic option for patients with VTE. High-resolution 3D contrast-enhanced MRA and time-resolved MRA are sensitive and specific for PE. The lack of ionizing radiation is attractive, but longer imaging times and the need for general anesthesia in most children may limit its use.

TREATMENT

In the acute management of VTE, careful monitoring and support of cardiopulmonary stresses are crucial. Once the affected individual has been stabilized, the primary approach to treatment of VTE is with anticoagulation. Appropriate and timely treatment with anticoagulation may prevent thrombus extension and recurrence. It is also indicated to prevent embolization.

Evaluations for prothrombotic disease must precede anticoagulation. Acute-phase anticoagulation therapy may be provided with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). UFH binds reversibly to antithrombin III and potentiates its ability to inhibit thrombin and coagulation factor Xa. LMWH has become the drug of choice for both short-term and longer-term anticoagulation in children; enoxaparin is the LMWH most used in the pediatric population. It acts similarly to inhibit factor Xa but can be administered subcutaneously, and the need for serum monitoring is decreased. The risk of heparin-induced thrombocytopenia is also decreased with LMWH as compared to UFH. UFH may still be chosen in patients who have an elevated risk of bleeding, as UFH has a shorter half-life than LMWH. UFH is also used preferentially in patients with compromised renal function.

In monitoring of drug levels, laboratories must be aware of the drug chosen in order to use the appropriate assay. For UFH, the therapeutic range is 0.3-0.7 anti-Xa activity units/mL. In LMWH, the therapeutic range is 0.50-1.0 units/mL. When the anti-Xa assay is not available, the activated partial thromboplastin time may be used, with a goal of 60-85 seconds, or approximately 1.5-2 times the upper limit of age-appropriate normal values. The recommended duration of heparinization during acute treatment is 5-10 days; this length of therapy has been extrapolated from adult data. Long-term therapy with heparin should be avoided whenever possible. Side effects include heparin-induced thrombocytopenia, bleeding, and osteoporosis.

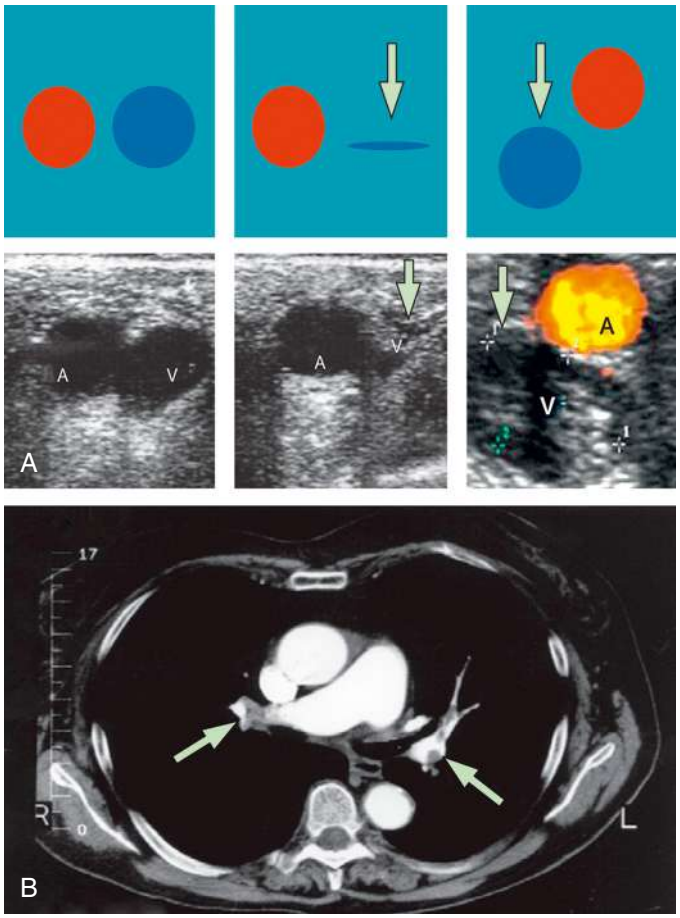

Fig. 458.1 A, Compression ultrasound. *Top images,* from left to right, representation of vein and artery without and with *(arrow)* gentle compression with the echocardiographic probe. *Bottom images*, corresponding echocardiographic findings. The third image from the left shows a thrombus in the vein (vein not compressible by the probe). B, CT angiography showing several emboli *(arrows)* in the main right pulmonary artery and in left lobar and segmental arteries. A, Artery; V, vein. *(From Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379:1835–1844, Fig. 2, p. 1838.)*

THERAPEUTIC OPTIONS

Extension of anticoagulation therapy occurs in the subacute phase and may use LMWH, LMWH analogues, or warfarin. Warfarin is a vitamin K antagonist that may be used in children and adolescents; use is generally initiated after establishing effective anticoagulation with heparin because severe congenital deficiencies of protein C may be associated with warfarin skin necrosis. When the international normalized ratio (INR) is measured between 1.0 and 1.3, the starting dose for warfarin in children is recommended as 0.2 mg/kg administered orally once daily. Titration of dosing may be needed to achieve a therapeutic INR of 2 to 3. Dosing requirements may vary, and clinical pharmacologic correlation is required. The INR is generally monitored 5 days after initiating therapy or a similar period after dose changes and weekly thereafter until stable. The INR should be obtained with any evidence of abnormal bleeding and should be discontinued at least 5 days before invasive procedures. The use of an anticoagulation team and/or established treatment algorithms is recommended in order to optimize patient safety.

With the first occurrence of VTE, anticoagulation is recommended for 3-6 months in the setting of an identifiable, reversible, and resolved risk factor (e.g., postoperative state). Longer treatment is indicated in patients with idiopathic VTE (6-12 months) and in those with chronic clinical risk factors (12 months to lifelong). In the setting of a congenital thrombophilic condition, the duration of therapy is often indefinite. Inhibitors of factor Xa (e.g., enoxaparin) may become an alternative therapy for both acute PE and long-term treatment (Table 458.3).

In adults with DVT or PE, subsequent therapy with apixaban, dabigatran, edoxaban, or rivaroxaban (direct oral anticoagulants [DOACs]) is recommended over vitamin K antagonists. Some pediatric centers have adapted this therapy, particularly for adolescent patients. The recommended duration of such therapy for uncomplicated patients is 3 months.

Thrombolytic agents such as recombinant tissue plasminogen activator by peripheral vein may be used in combination with anticoagulants in the early stages of treatment; their use is most likely to be considered in children with hemodynamically significant PE (hypotension, echocardiogram evidence of right ventricular dysfunction) or other severe potential clinical sequelae of VTE. Combined therapy may reduce the incidences of progressive thromboembolism, PE, and postthrombotic syndrome. The mortality rate appears to be unaffected by additional therapies; nonetheless, the additional theoretical risk of hemorrhage limits the use of combination therapy in all but the most compromised patients. The use of thrombolytic agents in patients with active bleeding, recent cerebrovascular accidents, or trauma is contraindicated.

Catheter-assisted thrombus removal (thrombectomy) should be limited to those with large emboli that result in persistent hemodynamic compromise refractory to standard therapy. Catheter-assisted thrombus removal (less often, surgical embolectomy) is indicated in patients with hypotension who are a high bleeding risk or have failed systemic thrombolysis or are in life-threatening shock before systemic thrombolysis can be effective (within hours of thrombolysis). Surgical embolectomy is indicated with embolic Wilms tumor.

In adults with acute proximal DVT of the leg, inferior vena cava filters are used *only* if there is a contraindication to anticoagulation therapy.

PROGNOSIS

Mortality in pediatric patients with PE is likely to be attributable to an underlying disease process rather than to the embolus itself. Short-term complications include major hemorrhage (either because of the thrombosis or secondary to anticoagulation). Chronic complications include recurrence and pulmonary hypertension with the risk of cor pulmonale. Conditions associated with a poorer prognosis include malignancy, infection, and cardiac disease. The mortality rate in children from PE is 2.2%. An exhaustive evaluation for underlying pathology is advocated in an effort to prevent recurrence and progressive disease. Postthrombotic syndrome is a recognized complication of pediatric thrombotic disease. Venous valvular damage can be initiated by the presence of DVT and may result in persistent venous hypertension with ambulation and valvular reflux. Symptoms include edema, pain, increases in pigmentation, and ulcerations. Affected pediatric patients may suffer lifelong disability.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 458.3 Anticoagulant Therapies for Deep Vein Thrombosis and Pulmonary Embolism

	ROUTE	RENAL CLEARANCE (%)	HALF-LIFE	INITIAL TREATMENT DOSING	MAINTENANCE TREATMENT DOSING	EXTENDED TREATMENT DOSING
Unfractionated heparin (UFH)	Intravenous	~30	~1.5 hr	Maintain aPTT 1.5 times upper limit of normal		
Low molecular weight heparin (LMWH)	Subcutaneous	~80	3-4 hr	Weight-based dosing	Weight-based dosing*	
Fondaparinux	Subcutaneous	100	17-21 hr	Weight-based dosing	Weight-based dosing	
Vitamin K antagonists	Oral	Negligible	Acenocoumarol 8-11 hr; warfarin 36 hr; phenprocoumon 160 hr	Target at INR at 2.0-3.0 and give parallel heparin treatment for at least 5 days	Maintain INR at 2.0-3.0	Maintain INR at 2.0-3.0
Dabigatran	Oral	~80†	14-17 hr	Requires at least 5 days heparin lead-in	150 mg twice a day	150 mg twice a day
Rivaroxaban	Oral	~33‡	7-11 hr	15 mg twice a day for 3 wk	20 mg once a day	20 mg once a day
Apixaban	Oral	~25‡	8-12 hr	10 mg twice a day for 1 wk	5 mg twice a day	2.5 mg twice a day
Edoxaban	Oral	~35‡	6-11 hr	Requires at least 5 days heparin lead-in	60 mg once a day§	60 mg once a day§
Aspirin	Oral	~10	15 min			80-100 mg once a day

*Treatment with low molecular weight heparin is recommended for patients with active cancer and pregnant women.
†Dabigatran is contraindicated in patients with a creatinine clearance below 30 mL/min.
‡Apixaban, edoxaban, and rivaroxaban are contraindicated in patients with a creatinine clearance below 15 mL/min.
§The recommended edoxaban dose is 30 mg once a day for patients with a creatinine clearance of 30-50 mL/min, a body weight less than or equal to 60 kg, or for those on certain strong P-glycoprotein inhibitors.
Medication dosing may vary with regard to primary diagnosis, age, comorbidities, and other factors. Clinical-pharmacologic correlation is advocated.
aPTT, Activated partial thromboplastin time; INR, international normalized ratio.
From Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388:3060–3069, Table 2.

458.2 Pulmonary Hemorrhage and Hemoptysis

Mary A. Nevin

Hemoptysis may be defined as the expectoration of blood from the lower respiratory tract. Infants and small children lack the tussive force to expectorate blood, and if blood from the lower airway is expectorated, it is frequently swallowed. Pulmonary hemorrhage in children and adolescents is uncommon but represents a serious and potentially fatal occurrence in children.

ETIOLOGY

Table 458.4 and Table 457.1 in Chapter 457 present conditions that can manifest as pulmonary hemorrhage or hemoptysis in children. The most common etiologies for pulmonary hemorrhage in the neonate and infant are congenital heart disease, premature lung disease, and coagulopathy (congenital or acquired with liver failure or anticoagulant medications). Infection and foreign body aspiration are the most common etiologies for hemoptysis in children. The chronic presence of a foreign body can lead to localized airway inflammation and hemorrhage. Secondary infection may also be present if the foreign body has been in the airway for days to weeks. Bleeding is more likely to occur in association with a chronically retained foreign body of vegetable origin.

Hemorrhage may be related to chronic airway inflammation and infection with bronchiectasis in the setting of cystic fibrosis (CF). Non-CF bronchiectasis may also be seen in children with chronic aspiration disorders, immunodeficiency syndromes, primary ciliary dyskinesia with or without Kartagener syndrome, HIV, and other infections. Hemoptysis attributable to inflammation and erosion of bronchial and bronchiolar airways may therefore occur in these clinical settings as well. Pulmonary hemorrhage caused by infection is also seen in patients with cavitary disease in association with tuberculosis. Hemoptysis may also occasionally reflect the intense inflammation of an acute pulmonary infection such as bronchitis or bronchopneumonia.

Bleeding is frequently encountered in patients with tracheostomies and is often attributable to suction trauma or friable granulation tissue. In these situations, bleeding tends to be limited and responsive to modifications of the care regimen. Rarely, bleeding from a tracheostomy may be brisk and bright red. In this case, otolaryngology should evaluate for the presence of a tracheo-innominate artery fistula.

Cardiopulmonary disease is associated with hemoptysis in children and adolescents. Associated conditions include mitral stenosis, pulmonary edema in the setting of congestive heart failure, high-altitude pulmonary edema (HAPE), pulmonary venous obstructive disease, and pulmonary hypertension. Although early corrective surgical intervention has been associated with improved hemodynamics, collateral circulations may contribute to bleeding.

Traumatic injury to the airway and pulmonary contusion may result from motor vehicle crashes or other direct-force injuries. Children who have been victims of nonaccidental trauma or deliberate suffocation can also be found to have blood in the mouth or airway (see Chapter 17). Factitious hemoptysis may rarely be encountered in the setting of self-inflicted trauma to the oral mucosa by biting or in the setting of factitious disorder by proxy (formerly Munchausen by proxy; see Chapter 17.2).

Rare causes for hemoptysis include tumors and vascular anomalies such as arteriovenous malformations (AVMs) (Fig. 458.2). Congenital vascular malformations in the lung may be seen in the setting of **hereditary hemorrhagic telangiectasia (HHT)**. Symptoms and signs of pulmonary AVM include dyspnea, hemoptysis, poor exercise tolerance, digital clubbing, and cyanosis. A high index of suspicion is needed, as more than half of children with pulmonary AVM may be asymptomatic. AVMs in individuals with HHT may be associated with severe complications, including massive hemoptysis, hemothorax, and stroke. In individuals with HHT, pulmonary AVMs are prevalent (60%) and can occur at any age. Any tumors or lesions must be cautiously investigated when encountered with a flexible fiberoptic bronchoscope, as bleeding may be massive and difficult to control.

Bronchial **Dieulafoy disease** has been recognized as a rare etiology for pulmonary hemorrhage. The classic bronchoscopic appearance is a small, submucosal bronchial lesion with a white cap. Massive hemorrhage may ensue. If nonsurgical bronchial artery embolization is not able to achieve hemostasis, surgical resection of the affected lung segment or lobe may be considered.

Table 458.4 Etiology of Pulmonary Hemorrhage (Hemoptysis)

FOCAL HEMORRHAGE
Bronchitis and bronchiectasis (especially cystic fibrosis related)
Infection (acute or chronic), pneumonia, abscess
Tuberculosis
Trauma
Pulmonary arteriovenous malformation (with or without hereditary hemorrhagic telangiectasia)
Foreign body (chronic)
Neoplasm, including hemangioma and metastatic disease
Pulmonary embolus with or without infarction
Bronchogenic cysts
DIFFUSE HEMORRHAGE
Idiopathic of infancy
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, and congestive heart failure)
Prematurity
Cow's milk hyperreactivity (Heiner syndrome)
Goodpasture syndrome
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)
IgA vasculitis (Henoch-Schönlein purpura) and other vasculitic disorders
Granulomatous disease (granulomatosis with polyangiitis)
Celiac disease
Coagulopathy (congenital or acquired)
Malignancy
Immunodeficiency
Exogenous toxins, especially inhaled
Hyperammonemia
Pulmonary hypertension
Pulmonary alveolar proteinosis
Idiopathic pulmonary hemosiderosis
Tuberous sclerosis
Lymphangiomyomatosis or lymphangioleiomyomatosis
Physical injury or abuse
Catamenial
Vaping

See also Table 457.1.

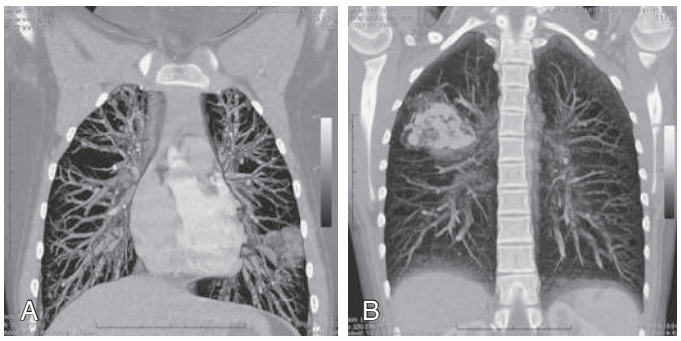

Fig. 458.2 **A**, Volume-rendering reconstruction of the contrast-enhanced spiral CT showing a large arteriovenous fistula in the left upper lobe (lingula). **B**, Volume-rendering reconstruction of the contrast-enhanced spiral CT showing an arteriovenous fistula in the right upper lobe. *(From Grzela K, Krenke K, Kulus M. Pulmonary arteriovenous malformations: clinical and radiological presentation. J Pediatr. 2011;158:856, Figs. 1 and 2.)*

Syndromes associated with vasculitic, autoimmune, and idiopathic disorders may be associated with diffuse alveolar hemorrhage (see Chapter 457).

EPIDEMIOLOGY

The frequency with which pulmonary hemorrhage occurs in the pediatric population is difficult to define. The difficulties in timely diagnosis are primarily related to the variability in disease presentation. As such, the incidence of pulmonary hemorrhage may be significantly underestimated. Chronic bronchiectasis as seen in CF (see Chapter 454) or ciliary dyskinesia (see Chapter 455) can cause hemoptysis, but usually occurs in children older than 10 years of age.

PATHOPHYSIOLOGY

The vascular supply of the lung has two components. The pulmonary artery provides blood to the bronchi to the level of the terminal bronchioles and to the alveolar capillary bed. The pulmonary circulation is characterized by low pressure and high volume. Conversely, the bronchial circulation originates from the aorta or intercostal arteries. The pressure in the bronchial artery circulation is systemic. This circulation provides blood the conducting airways. Hemoptysis may occur from either the pulmonary or bronchial circulation. Bleeding from the pulmonary circulation is expected to be insidious; slow bleeding in the lower airways typically manifests with anemia, fatigue, and dyspnea, and hemoptysis may be absent. Syndromes associated with diffuse alveolar hemorrhage are discussed in Chapter 457. Bleeding from the bronchial circulation may be massive and associated with rapid exsanguination. Blood that comes from the lung is frequently difficult to differentiate from blood that originates at the nasopharynx, mouth, or gastrointestinal (GI) tract. The blood that originates from the airway is classically bright red or rust colored. Alveolar blood may have a frothy appearance. Blood originating from the GI tract is typically brownish in color. The pH of pulmonary blood is alkaline, whereas blood from the GI tract is expected to be acidic.

In patients with CF, chronic endobronchial infection, inflammation, mucus plugging, and thickening of the airway surface layer predispose to growth and dilation of the bronchial arteries. Blood in the airway is highly irritative and initiates an influx of neutrophils and inflammatory mediators that serve to exacerbate the already vibrant inflammatory response. As such, pulmonary hemorrhage may be recurrent in late-stage CF. Massive and life-threatening hemorrhage may occur. With repeated or chronic hemorrhage, pulmonary fibrosis can become a prominent pathologic finding.

CLINICAL MANIFESTATIONS

The presenting symptoms and signs of pulmonary hemorrhage are highly variable in the pediatric population. Older children and young adults experiencing focal hemorrhage may be able to localize the bleeding by a sensation of "warmth" or "bubbling" in the chest. This can occasionally aid the clinician in locating the area involved. Rapid and large-volume blood loss manifests as hypoxemic and hypercarbic respiratory failure and hypovolemic shock. Chronic, insidious blood loss may manifest as anemia, fatigue, dyspnea, or poor exercise tolerance. Severely anemic individuals may present with syncope. Radiographic infiltrates may be seen in a focal or diffuse distribution on chest radiograph. The presence of a cavitary lesion or radiopaque foreign body suggests tubercular or fungal infection and foreign body aspiration, respectively.

LABORATORY FINDINGS AND DIAGNOSIS

A patient with suspected hemorrhage should have a laboratory evaluation with complete blood count and coagulation studies. The complete blood count result may demonstrate a microcytic, hypochromic anemia but may be normal in acute blood loss. The diagnosis of pulmonary hemorrhage is best confirmed by bronchoscopy with direct visualization of bleeding and/or a bronchoalveolar lavage specimen that confirms the presence of **hemosiderin-laden macrophages** on Prussian blue staining. Within 48-72 hours of an episode of bleeding, alveolar macrophages convert the iron from erythrocytes into hemosiderin. It may take weeks to clear these hemosiderin-laden macrophages completely from the alveolar spaces, thereby allowing differentiation between acute and chronic hemorrhage.

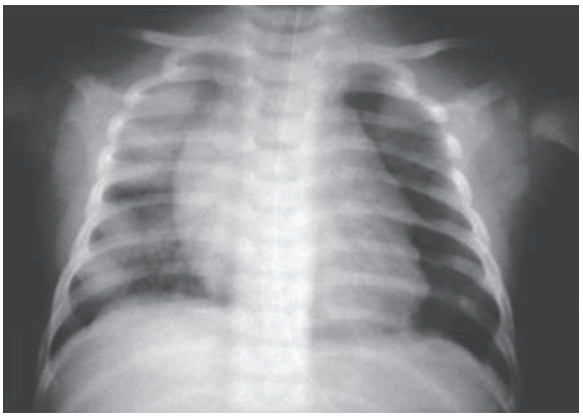

Fig. 458.3 Radiographic appearance of acute idiopathic pulmonary hemorrhage in infancy. *(From Brown CM, Redd SC, Damon SA, Centers for Disease Control and Prevention. Acute idiopathic pulmonary hemorrhage among infants: recommendations from the Working Group for Investigation and Surveillance. MMWR Recomm Rep. 2004;53:1–12.)*

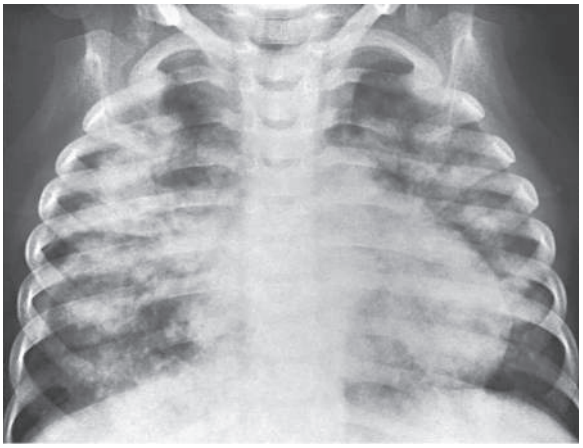

Fig. 458.4 Diffuse pulmonary hemorrhage that was thought to be the result of idiopathic pulmonary hemosiderosis in a 3-yr-old child. Frontal radiograph reveals bilateral air space consolidation that is patchy. Tracheal washing contained large numbers of macrophages filled with hemosiderin. Ten days later, most of the consolidative changes in the lungs had cleared. The patient's anemia was successfully treated with blood transfusion. *(Courtesy Bertram Girdany, MD, Pittsburgh, PA; from Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008.)*

Chest radiographs may demonstrate fluffy bilateral densities, as seen in acute idiopathic pulmonary hemorrhage of infancy (Fig. 458.3) or the patchy consolidation seen in idiopathic pulmonary hemosiderosis (Fig. 458.4). Alveolar infiltrates seen on chest radiograph may be regarded as a representation of recent bleeding, but their absence does not rule out the occurrence of pulmonary hemorrhage. Infiltrates, when present, are often symmetric and diffuse and may be preferentially located in the perihilar regions and lower lobes. The costophrenic angles and lung apices are frequently spared. CT may be indicated to assess for underlying disease processes.

Lung biopsy is rarely necessary unless bleeding is chronic or an etiology cannot be determined with other methods. Pulmonary function testing, including a determination of gas exchange, is important to assess the severity of the ventilatory defect. In older children, spirometry may demonstrate evidence of predominantly obstructive disease in the acute

period. Restrictive disease secondary to fibrosis is typically seen with more chronic disease. Diffusion capacity of carbon monoxide measurements are typically elevated in the setting of pulmonary hemorrhage because of the strong affinity of the intraalveolar hemoglobin for carbon monoxide.

TREATMENT

In mild to moderate hemoptysis (>5 mL blood), potential irritants to the lung (hypertonic saline, DNase, chest physiotherapy, and inhaled antibiotics) are typically held. In patients with CF, vitamin K may be given empirically, given a predilection toward vitamin K deficiency with comorbid pancreatic insufficiency.

In the setting of massive hemorrhage (>240 mL), emergent circulatory and ventilatory support is provided and a requirement for volume resuscitation and transfusion of blood products should be anticipated. If respiratory failure ensues, mechanical ventilatory support with high positive end-expiratory pressure (PEEP) may tamponade a bleeding vessel and improve oxygenation. If bleeding is unilateral, selective ventilation of the unaffected lung may be recommended. Rigid bronchoscopy may be used for localization of bleeding and for removal of debris, but active bleeding may be exacerbated by airway manipulation. In patients with CF who are unstable with massive hemorrhage, proceeding directly to bronchial artery embolization (BAE) has been advocated. Improved outcomes of BAE have been seen when the bleeding vessel is identified by multidetector CT imaging. Cessation of bleeding is achieved in approximately 80% of patients, but bleeding may be recurrent, and more than one BAE may be required. Rare complications include inadvertent embolization of spinal and mesenteric arteries, leading to paralysis and ischemic bowel, respectively. If embolization fails, total or partial lobectomy may be required.

Antifibrinolytic therapy with tranexamic acid (TXA) has been used to control bleeding in patients with hemophilia and in patients with CF, as well as in other conditions (bronchiectasis, tuberculosis, allergic bronchopulmonary aspergillosis). This medication may be administered by inhaled, oral, or parenteral routes. Inhaled TXA may be as effective as intravenous dosing; the inhaled route has fewer systemic effects. The use of this medication is currently off label.

Depending on institutional capabilities, extracorporeal membrane oxygenation (ECMO) and emergent listing for lung transplantation may also be considered for patients with end-stage disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 459

Atelectasis

Ranna A. Rozenfeld

Atelectasis is the incomplete expansion or complete collapse of air-bearing tissue, resulting from obstruction of air intake into the alveolar sacs. Segmental, lobar, or whole lung collapse is associated with the absorption of air contained in the alveoli, which are no longer ventilated.

PATHOPHYSIOLOGY

The causes of atelectasis can be divided into five groups (Table 459.1). Respiratory syncytial virus (see Chapter 307) and other viral infections, including influenza viruses in young children, can cause multiple areas of atelectasis. Mucous plugs are a common predisposing factor to atelectasis. Massive collapse of one or both lungs is most often a postoperative complication but occasionally results from other causes, such as trauma, asthma, pneumonia, tension pneumothorax (see Chapter 461), aspiration of foreign material (see Chapters 435 and 446), paralysis, or after extubation. Massive atelectasis is usually produced by a combination of factors, including immobilization or decreased use of the diaphragm and the respiratory muscles, obstruction of the bronchial tree, and abolition of the cough reflex.

Table 459.1 Anatomic Causes of Atelectasis

CAUSE	CLINICAL EXAMPLES
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the ingress of air	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

CLINICAL MANIFESTATIONS

Symptoms vary with the cause and extent of the atelectasis. A small area is likely to be asymptomatic. When a large area of previously normal lung becomes atelectatic, especially when it does so suddenly, dyspnea accompanied by rapid shallow respiration, tachycardia, cough, and often cyanosis occurs. If the obstruction is removed, the symptoms disappear rapidly. Although it was once believed that atelectasis alone can cause fever, studies have shown no association between atelectasis and fever. Physical findings include limitation of chest excursion, decreased breath sound intensity, and coarse crackles. Breath sounds are decreased or absent over extensive atelectatic areas.

Massive atelectasis usually presents with dyspnea, cyanosis, and tachycardia. An affected child is extremely anxious and, if old enough, complains of chest pain. The chest appears flat on the affected side, where decreased respiratory excursion, dullness to percussion, and feeble or absent breath sounds are also noted. Postoperative atelectasis usually manifests within 24 hours of operation but may not occur for several days.

Acute lobar collapse is a frequent occurrence in patients receiving intensive care. If undetected, it can lead to impaired gas exchange, secondary infection, and subsequent pulmonary fibrosis. Initially, hypoxemia may result from ventilation-perfusion mismatch. In contrast to atelectasis in adult patients, in whom the lower lobes and, in particular, the left lower lobe is most often involved, 90% of cases in children involve the upper lobes and 63% involve the right upper lobe. There is also a high incidence of upper lobe atelectasis and, especially, right upper lobe collapse in patients with atelectasis being treated in neonatal intensive care units. This high incidence may be a result of the movement of the endotracheal tube into the right mainstem bronchus, where it obstructs or causes inflammation of the bronchus to the right upper lobe.

DIAGNOSIS

The diagnosis of atelectasis can usually be established by chest radiograph. Typical findings include volume loss and displacement of fissures. Atypical presentations include atelectasis manifesting as a masslike opacity and atelectasis in an unusual location. Lobar atelectasis may be associated with pneumothorax. Several studies have shown

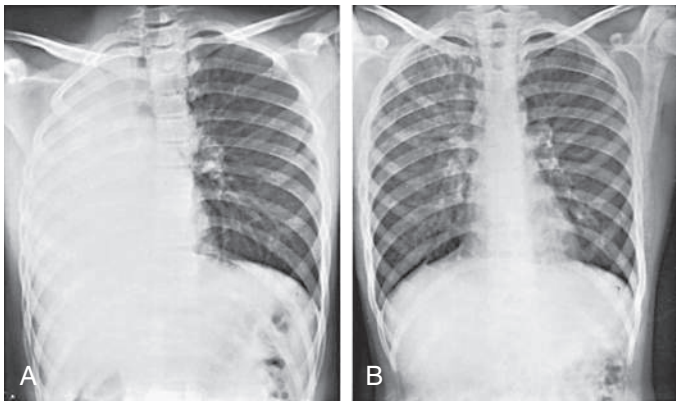

Fig. 459.1 A, Massive atelectasis of the right lung. The patient has asthma. The heart and other mediastinal structures shift to the right during the atelectatic phase. B, Comparison study after reaeration subsequent to bronchoscopic removal of a mucous plug from the right mainstem bronchus.

lung ultrasound to be a viable alternative to chest radiograph when diagnosing atelectasis, especially in patients with neuromuscular disease, to avoid radiation exposure.

In children with asthma, chest radiography demonstrates an abnormality rate of 44%, compared with a thorax high-resolution CT scan abnormality rate of 75%. Children with asthma and atelectasis have an increased incidence of right middle lobe syndrome, acute asthma exacerbations, pneumonia, and upper airway infections.

In foreign-body aspiration, atelectasis is one of the most common radiographic findings. The site of atelectasis usually indicates the site of the foreign body (see Chapter 426.1). Atelectasis is more common when diagnosis of foreign-body aspiration is delayed for greater than 2 weeks. Bronchoscopic examination reveals a collapsed main bronchus when the obstruction is at the tracheobronchial junction and may also disclose the nature of the obstruction.

Massive atelectasis is typically diagnosed on chest radiograph. Typical findings include elevation of the diaphragm, narrowing of the intercostal spaces, and displacement of the mediastinal structures and heart toward the affected side (Fig. 459.1).

TREATMENT

Treatment depends on the cause of the collapse (Table 459.2). If effusion or pneumothorax is responsible, the external compression must first be removed. Often vigorous efforts at cough, deep breathing, and percussion will facilitate expansion. Aspiration with sterile tracheal catheters may facilitate removal of mucous plugs. Continuous positive airway pressure may improve atelectasis.

Bronchoscopic examination is immediately indicated if atelectasis is the result of a foreign body or any other bronchial obstruction that can be relieved. For bilateral atelectasis, bronchoscopic aspiration should also be performed immediately. It is also indicated when an isolated area of atelectasis persists for several weeks. If no anatomic basis for atelectasis is found and no material can be obtained by suctioning, the introduction of a small amount of saline followed by suctioning allows recovery of bronchial secretions for culture and, possibly, for cytologic examination. Frequent changes in the child's position, deep breathing, and chest physiotherapy may be beneficial. Intrapulmonary percussive ventilation is a chest physiotherapy technique that is safe and effective. Oxygen therapy is indicated when there is dyspnea or desaturation. Intermittent positive pressure breathing and incentive spirometry are recommended when atelectasis does not improve after chest physiotherapy.

In some conditions, such as asthma, bronchodilator and corticosteroid treatment may accelerate atelectasis clearance. Recombinant human deoxyribonuclease, which is approved only for the treatment of cystic fibrosis, has been used off-label for patients without cystic fibrosis who have persistent atelectasis. This product reduces the viscosity of purulent bronchial debris. In patients with acute severe asthma, diffuse airway plugging with thick viscous secretions frequently occurs, with the resulting atelectasis often refractory to conventional therapy. Recombinant human deoxyribonuclease is used in the nebulized form for nonintubated patients with acute asthma and intratracheally for atelectasis in intubated asthmatics, with resolution of atelectasis unresponsive to conventional asthma therapies. Recombinant human deoxyribonuclease is also used in ventilated infants and children with atelectasis not caused by asthma.

Table 459.2 Treatment for Atelectasis

CAUSE OF ATELECTASIS	TREATMENT
Pleural effusion or pneumothorax	Relieve compression
Mucous plug	Tracheal or bronchoscopic aspiration Continuous positive airway pressure
Foreign body	Bronchoscopic examination
Asthma	Bronchodilator and corticosteroid treatment Recombinant human deoxyribonuclease (off-label use) Hypertonic saline with or without bronchodilator
Neuromuscular diseases	Intermittent positive pressure breathing Mechanical insufflator-exsufflator Noninvasive bilevel positive pressure ventilation
Cystic fibrosis	Airway clearance therapies Hypertonic saline with or without bronchodilator Recombinant human deoxyribonuclease

Hypertonic saline solution increases mucociliary clearance in patients with asthma, bronchiectasis, and cystic fibrosis and infants with acute bronchiolitis. It is delivered via nebulization either via face mask or endotracheal tube. It can be delivered alone or in combination with a bronchodilator. This therapy is being used in the outpatient and inpatient setting and in both the neonatal intensive care unit and the pediatric intensive care unit to help facilitate airway clearance, though studies of its use in bronchiolitis have had mixed results (see Chapter 439.1). Lobar atelectasis in cystic fibrosis is discussed in Chapter 454.

Atelectasis can occur in patients with neuromuscular diseases. These patients tend to have an ineffective cough and difficulty expelling respiratory tract secretions, which lead to pneumonia and atelectasis. Several devices and treatments are available to assist these patients, including intermittent positive-pressure breathing, a mechanical insufflator-exsufflator, and noninvasive bilevel positive-pressure ventilation via nasal mask or full-face mask. Patients with neuromuscular disease who have undergone surgery are at substantial risk for postoperative atelectasis and subsequent pneumonia. Migrating atelectasis in the newborn infant, a rare and unique presentation, may be secondary to neuromuscular disease.

There is an association between the development of lobar collapse and the requirement for mechanical ventilation. Although lobar collapse is rarely a cause of long-term morbidity, its occurrence may necessitate the prolongation of mechanical ventilation or reintubation. In ventilated patients, positive-end expiratory pressure or continuous positive airway pressure is generally indicated.

Airway clearance therapies used for adults are often recommended and/or used in pediatric populations. However, given the differences in respiratory physiology and anatomy between children and adults, practices applicable to one may or may not apply to the other. Atelectasis caused by cystic fibrosis is the only pediatric entity that clearly benefits from airway clearance therapy, although atelectasis caused by neuromuscular disease, cerebral palsy, or mechanical ventilation probably benefits from such therapy. Thus far, no specific airway clearance therapy has been demonstrated to be superior.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 460

Pulmonary Tumors

John Palla and Susanna A. McColley

See also Chapter 438.

Primary tumors of the lung are rare in children and adolescents (Table 460.1). An accurate estimate of frequency is currently not possible because the literature is composed of case reports and case series. A high incidence of "inflammatory pseudotumors" further clouds the statistics. Bronchial adenomas (including bronchial carcinoid, adenoid cystic carcinoma, and mucoepidermoid carcinomas) are the most common primary malignant tumors; bronchial carcinoid tumors represent ~80%. Pediatric carcinoid tumors are predominantly low-grade malignancies, but children with these tumors should be evaluated and monitored by a pediatric oncologist. Carcinoid syndrome from a bronchial carcinoid tumor is rare in children. Metastatic lesions are the most common forms of pulmonary malignancy in children; primary processes include Wilms tumor, osteogenic sarcoma, germ cell tumors, and hepatoblastoma (see Part XX, Cancer and Benign Tumors). Adenocarcinoma and undifferentiated histology are the most common pathologic findings in primary lung cancer; pulmonary blastoma is rarer and frequently occurs in the setting of a primary cystic lesion or is associated with a congenital pulmonary airway malformation (see Chapter 444.3). Lymphoma is the most common cause of mediastinal mass in children; other mediastinal tumors include thymoma, thyroid cancer, and teratoma. Neuroblastoma may present as a posterior mediastinal mass.

Table 460.1 Pulmonary Tumors in Children

MALIGNANT
Bronchial adenomas (40–60%)
Carcinoid
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Pleuropulmonary blastoma (15%)
Bronchogenic carcinoma (10–15%)
Adenocarcinoma
Small-cell carcinoma
Bronchoalveolar carcinoma
Squamous-cell carcinoma
Undifferentiated carcinoma
Fetal-lung adenocarcinoma
Pulmonary mesothelioma
Sarcomas (20–25%)
Rhabdomyosarcoma
Synovial sarcoma
Hemangiopericytoma (solitary fibrous tumor)
Leiomyosarcoma
Angiosarcoma
Bronchopulmonary fibrosarcoma
BENIGN
Hamartomas
Hemangiomas
Lymphangioma
Leiomyomas
Myofibroblastic tumors
Inflammatory myofibroblastic tumor
Myofibromatosis
Congenital peribronchial myofibroblastic tumor
Neurogenic tumors
Mature teratoma

From Goldberg JM, Pappo AS, Bishop M. Rare tumors of childhood. In Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier; 2015: Table 65.4, p. 2130.

CLINICAL MANIFESTATIONS AND EVALUATION

There is often a delay in the diagnosis of pediatric pulmonary tumors given their rarity and nonspecific presenting symptoms. Pulmonary tumors may manifest as fever, hemoptysis, wheezing, cough, pleural effusion, chest pain, dyspnea, recurrent or persistent pneumonia, and/or atelectasis. Localized wheezing, and wheezing unresponsive to bronchodilators, can occur with bronchial tumors. Tumors may be suspected from plain chest radiographs; however, CT or MRI imaging of the chest is necessary for precise anatomic definition (Table 460.2; Figs. 460.1 and 460.2). Depending on the

Table 460.2 Imaging Characteristics of Primary Malignant Lung Tumors

NEOPLASM	IMAGING CHARACTERISTICS
Inflammatory myofibroblastic tumor (IMT)	Solitary (95%) or multiple (5%) Usually sharply circumscribed, lobulated mass Typically located in the peripheral portion of the lungs Soft tissue mass with either homogeneous or heterogeneous attenuation may have both solid and cystic and calcific components
Carcinoid or salivary gland tumor	Centrally located lesion: intraluminal soft tissue mass with distal atelectasis or obstructive pneumonitis Peripherally located lesion: oval or lobulated intraluminal or exophytic mass and occasionally calcify
Bronchogenic carcinoma	Central mass lesion with bronchial obstruction or, less commonly, small peripheral lesion
Pleuropulmonary blastoma	Cystic or mixed cystic and solid lesion adjacent to pleura; can be very large, with mediastinal displacement
Epithelioid hemangioendothelioma	Multiple well- or ill-defined nodular opacities up to 3 cm in diameter; very rare in childhood

From Chu WCW, Epelman M, Lee EY. Neoplasia. In Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Table 55.3, p. 531.

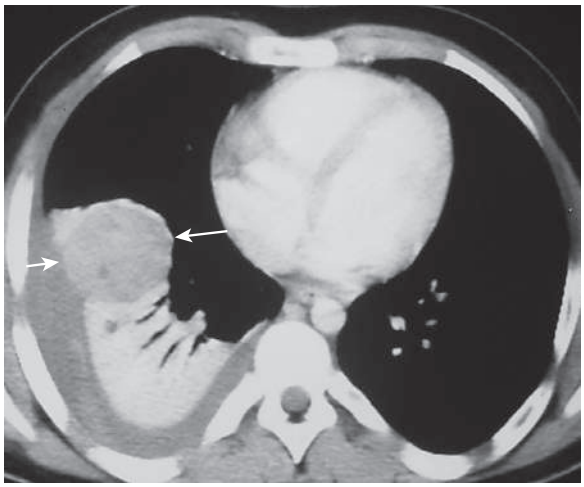

Fig. 460.1 Inflammatory myofibroblastic tumor. An afebrile 13-yr-old male who presented with increasing dyspnea and right-sided pleuritic chest pain. Axial contrast-enhanced CT of the chest shows a rounded heterogeneously enhancing lesion *(arrows)* located adjacent to an area of atelectatic lung. Pleural fluid at the same level demonstrates increased attenuation consistent with a hemothorax. *(Modified from Chu WCW, Epelman M, Lee EY. Neoplasia. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 55.8A, p. 531.)*

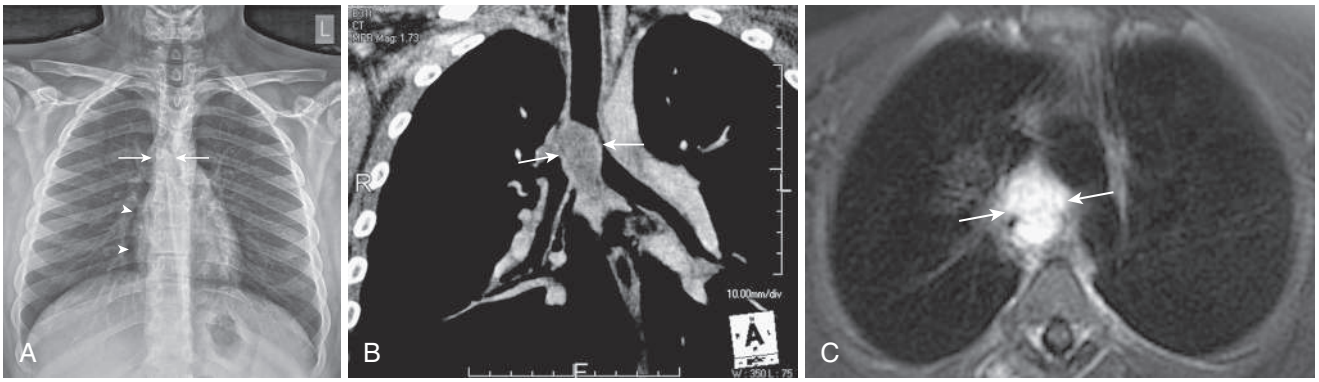

Fig. 460.2 Adenoid cystic carcinoma. A 14-yr-old male with a progressively worsening chronic cough and respiratory difficulty for 1 yr who presented with hoarseness and crepitus over the neck. **A,** Chest radiograph shows pneumomediastinum *(arrowheads)* and an apparent soft tissue density projecting over the carina *(arrows).* **B,** Coronal contrast-enhanced CT image shows a lobulated soft tissue mass *(arrows)* centered near the carina, which results in the narrowing of the adjacent airway. **C,** Axial contrast-enhanced T1-weighted MRI demonstrates avid enhancement of the mass *(arrows). (From Chu WCW, Epelman M, Lee EY. Neoplasia. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019. Fig. 55.11: p. 532.)*

tumor size and location, pulmonary function tests may be normal or may show an obstructive, restrictive, or mixed pattern; there is no responsiveness to bronchodilators. Bronchial tumors are occasionally diagnosed during fiberoptic bronchoscopy performed for persistent or recurrent pulmonary infiltrates or hemoptysis (see Chapter 438).

Patients with symptoms or with radiographic or other laboratory findings suggesting pulmonary malignancy should be evaluated carefully for a tumor at another site before surgical excision is carried out. Isolated primary lesions and isolated metastatic lesions discovered long after the primary tumor has been removed are best treated by excision. The prognosis varies and depends on the type of tumor involved; outcomes for inflammatory pseudotumors and primary pulmonary carcinoid tumors treated with resection are good.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 461
Pneumothorax

Suraiya K. Haider and Aarthi P. Vemana

Pneumothorax is the accumulation of extrapulmonary air within the chest, most commonly from leakage of air from within the lung. Air leaks can occur spontaneously and be classified as primary or secondary, or occur due to trauma or an iatrogenic cause (Table 461.1). Pneumothorax in the neonatal period is also discussed in Chapter 132.

ETIOLOGY AND EPIDEMIOLOGY

A **primary spontaneous pneumothorax** occurs without trauma or obvious underlying lung disease. Spontaneous pneumothorax with or without exertion occurs occasionally in teenagers and young adults, most frequently in males who are tall and thin and thought to have subpleural blebs. Smoking cigarettes, marijuana, crack cocaine, e-cigarette vaping, and ecstasy/MDMA (methylenedioxymethamphetamine) have been associated with developing a pneumothorax.

A pneumothorax arising as a complication of an underlying lung disorder but without trauma is a **secondary spontaneous pneumothorax.** Familial cases of spontaneous pneumothorax occur and have been associated with pathogenic variants in the folliculin gene *(FCLN).* Over 150 unique *FCLN* variants have been associated with the **Birt-Hogg-Dube syndrome** (skin fibrofolliculomas, multiple basal lung cysts, renal malignancies) or in patients with familial or recurrent spontaneous pneumothoraces. Individuals with other inherited disorders, such as α_1-antitrypsin (see Chapter 442) and homocystinuria, are also predisposed to pneumothorax. Patients with collagen synthesis defects such as vascular Ehlers-Danlos syndrome (see Chapter 700) and Marfan syndrome (see Chapter 743) are at increased risk for the development of pneumothorax.

Pneumothorax can occur in pneumonia, usually with empyema; it can also be secondary to a pulmonary abscess, gangrene, infarct, rupture of a cyst or an emphysematous bleb (in asthma), or foreign bodies in the lung. In infants with staphylococcal pneumonia, the incidence of pneumothorax is relatively high. It can be found in children hospitalized with asthma exacerbations and usually resolves without treatment. Pneumothorax is a serious complication of cystic fibrosis (see Chapter 454). Pneumothorax also occurs in patients with lymphoma or other malignancies and in graft-versus-host disease with bronchiolitis obliterans. Catamenial pneumothorax, an unusual condition that is related to menses, is associated with diaphragmatic defects and pleural blebs.

External chest or abdominal blunt or penetrating trauma can tear a bronchus or abdominal viscus, with leakage of air into the pleural space. Iatrogenic pneumothorax can complicate transthoracic needle aspiration, tracheotomy, subclavian line placement, thoracentesis, or transbronchial biopsy. It may occur during mechanical or noninvasive ventilation, high-flow nasal cannula therapy, acupuncture, and other diagnostic or therapeutic procedures.

Pneumothorax can be associated with a serous effusion (hydropneumothorax), a purulent effusion (pyopneumothorax), or blood (hemopneumothorax). Bilateral pneumothorax is rare after the neonatal period but has been reported after lung transplantation and with *Mycoplasma pneumoniae* infection and tuberculosis.

Table 461.1 Causes of Pneumothorax in Children

SPONTANEOUS

Primary Idiopathic (no underlying lung disease)

Spontaneous rupture of subpleural blebs

Drug use (smoking cigarettes, marijuana, crack cocaine, use of e-cigarettes)

Valsalva maneuver

Secondary (underlying lung disease)

Congenital lung disease
- Congenital pulmonary airway malformation
- Bronchogenic cysts
- Pulmonary hypoplasia
- Birt-Hogg-Dube syndrome

Conditions associated with increased intrathoracic pressure
- Asthma
- Bronchiolitis
- Cystic fibrosis
- Airway foreign body

Infection
- Tuberculosis
- *Pneumocystis jirovecii*
- Echinococcosis
- Pneumatocele
- Lung abscess
- Bronchopleural fistula
- COVID-19 infection

Lung disease
- Langerhans cell histiocytosis
- Tuberous sclerosis
- Marfan syndrome
- Vascular Ehlers-Danlos syndrome
- Pulmonary fibrosis
- Sarcoidosis
- Rheumatoid arthritis, scleroderma, ankylosing spondylitis
- Metastatic neoplasm—usually osteosarcoma (rare)
- Pulmonary blastoma
- Catamenial

TRAUMATIC

Noniatrogenic

Penetrating trauma

Blunt trauma

Iatrogenic

Thoracotomy

Thoracoscopy, thoracentesis

Tracheostomy

Tube or needle puncture

Mechanical ventilation

High-flow therapy (moved from noniatrogenic)

Adapted from Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. *Eur Respir Rev.* 2010;19(117):217–219, 2010. Tables 1 & 2, p. 218.

PATHOGENESIS

The tendency of the lung to collapse, or elastic recoil, is balanced in the normal resting state by the inherent tendency of the chest wall to expand outward, creating negative pressure in the intrapleural space. When air enters the pleural space, the lung collapses. Hypoxemia occurs because of alveolar hypoventilation, ventilation-perfusion mismatch, and intrapulmonary shunt. In simple pneumothorax, intrapleural pressure is atmospheric, and the lung collapses up to 30%. In **tension pneumothorax**, a continuing leak causes increasing positive pressure in the pleural space, with further compression of the lung, shift of mediastinal structures toward the contralateral side, and decreases in venous return and cardiac output causing hemodynamic instability.

CLINICAL MANIFESTATIONS

The onset of pneumothorax is usually abrupt, and the severity of symptoms depends on the extent of the lung collapse and the amount of preexisting lung disease. Pneumothorax may cause dyspnea, chest pain, and cyanosis. When it occurs in infancy, symptoms and physical signs may be difficult to recognize. Moderate pneumothorax may cause little displacement of the intrathoracic organs and few or no symptoms. The severity of pain usually does not directly reflect the extent of the collapse.

Usually, there is respiratory distress, with retractions; markedly decreased breath sounds; and a tympanitic percussion note over the involved hemithorax. The larynx, trachea, and heart may be shifted toward the unaffected side. When fluid is present, there is usually a sharply limited area of tympany above a level of flatness to percussion. The presence of bronchial breath sounds or, when fluid is present in the pleural cavity, of gurgling sounds synchronous with respirations suggests an open fistula connecting with air-containing tissues.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of pneumothorax is usually established by radiographic examination (Figs. 461.1-461.6). The amount of air outside the lung varies with time. A radiograph that is taken early shows less lung collapse than one that was taken later if the leak continues. Expiratory views accentuate the contrast between lung markings and the clear area of the pneumothorax (see Fig. 461.1). Variations exist in the measurement techniques defining the size of a pneumothorax. A large pneumothorax is measured by The American College of Chest Physicians as ≥3 cm from the lung apex to the thoracic cupola, and by the British Thoracic Society as ≥2 cm from the lung margin to the chest wall at the level of the hilum (Table 461.2).

It may be difficult to determine whether a pneumothorax is under tension. Tension pneumothorax is present when there is a shift of mediastinal structures away from the side of the air leak. A shift may be absent in situations in which the other hemithorax resists the shift, such as in the case of bilateral pneumothorax. On occasion, the diagnosis of tension pneumothorax is made only based on evidence of circulatory compromise or on hearing a "hiss" of rapid exit of air under tension with the insertion of the thoracostomy tube. When the lungs are both stiff, such as in cystic fibrosis or respiratory distress syndrome, the unaffected lung may not collapse easily, and shift may not occur (see Fig. 461.3).

Pneumothorax must be differentiated from localized or generalized emphysema, an extensive emphysematous bleb, large pulmonary cavities or other cystic formations, diaphragmatic hernia, compensatory overexpansion with contralateral atelectasis, and gaseous distention of the stomach. In most cases, chest radiography or CT differentiates among these possibilities. In addition, CT may identify underlying pathology such as blebs (Fig. 461.7). Further evaluation to determine if a diaphragmatic hernia is present should include a barium swallow with a small amount of barium to demonstrate that it is not free air but is a portion of the gastrointestinal tract that is in the thoracic cavity (see Chapter 131). Ultrasound can also be used to establish the diagnosis.

TREATMENT

Therapy varies with the extent of the collapse and the nature and severity of the underlying disease. A small or even moderate-sized pneumothorax in an otherwise normal child may resolve without specific treatment, usually within 1 week. A small pneumothorax-complicating asthma may also resolve spontaneously. Administering 100% oxygen may hasten resolution, but patients with chronic hypoxemia should be monitored closely during the administration of supplemental oxygen. Pleural pain deserves analgesic treatment.

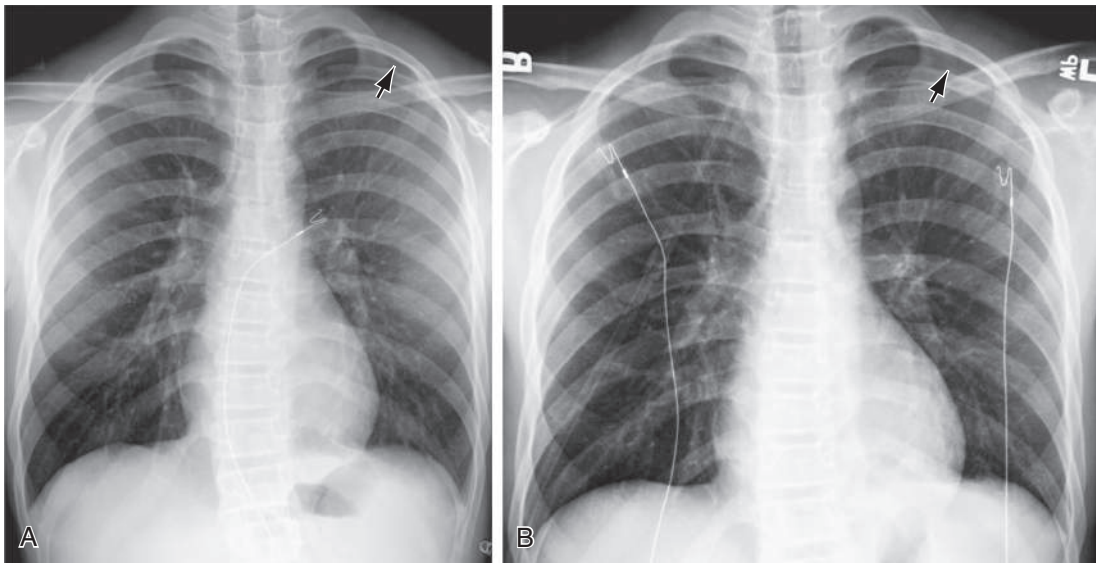

Fig. 461.1 Utility of an expiratory film in detection of a small pneumothorax. **A,** Teenager with stab wound and subtle radiolucency in the left apical region *(arrow)* on inspiratory chest radiograph. The margin of the visceral pleura is very faintly visible. **B,** On an expiratory film, the pneumothorax *(arrow)* is more obvious as the right lung has deflated and become more opaque, providing better contrast with the air in the pleural space.

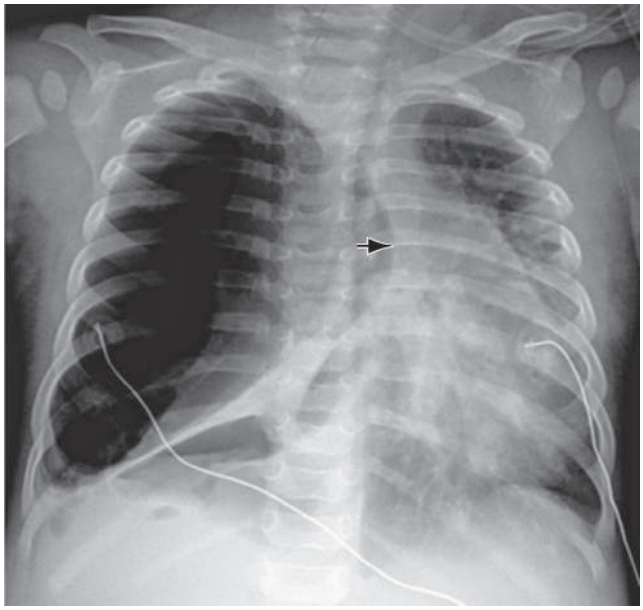

Fig. 461.2 Right pneumothorax, with lung collapse of a compliant lung. Shift of the mediastinum to the left *(arrow)* indicates that this is a tension pneumothorax.

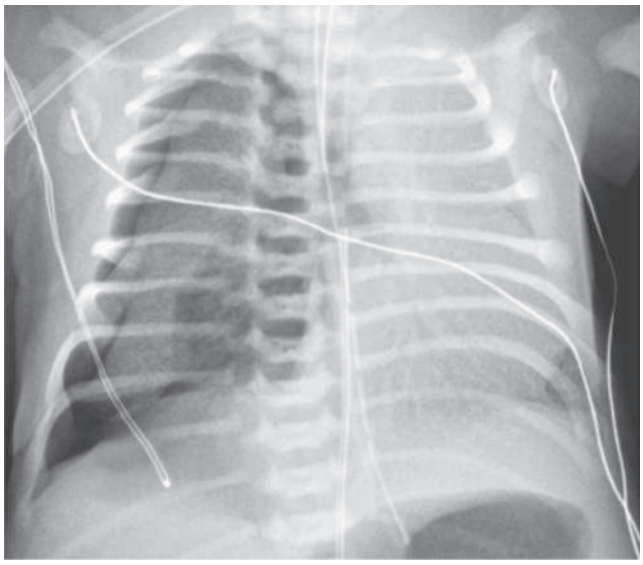

Fig. 461.3 Right pneumothorax, with only limited collapse of a poorly compliant lung.

Needle aspiration into the second intercostal space in the midclavicular line may be required on an emergency basis for tension pneumothorax and is as effective as tube thoracostomy in the emergency room management of primary spontaneous pneumothorax. If the pneumothorax is recurrent, secondary, or under tension, or there is more than a small collapse, catheter drainage or other invasive measures may be necessary. Pneumothorax in patients with cystic fibrosis or Marfan syndrome frequently recurs, and definitive treatment may be justified with the first episode. Similarly, if pneumothorax-complicating malignancy does not improve rapidly with observation, chemical pleurodesis or surgical thoracotomy is often necessary. In cases with severe air leaks or bronchopleural fistula, occlusion with an endobronchial balloon has been successful.

Closed thoracotomy (simple insertion of a chest tube) and drainage of the trapped air through a catheter, the external opening of which is kept in a dependent position under water, is adequate to reexpand the lung in most patients; pigtail catheters are frequently used. Consideration can be given to a sclerosing procedure to induce the formation of

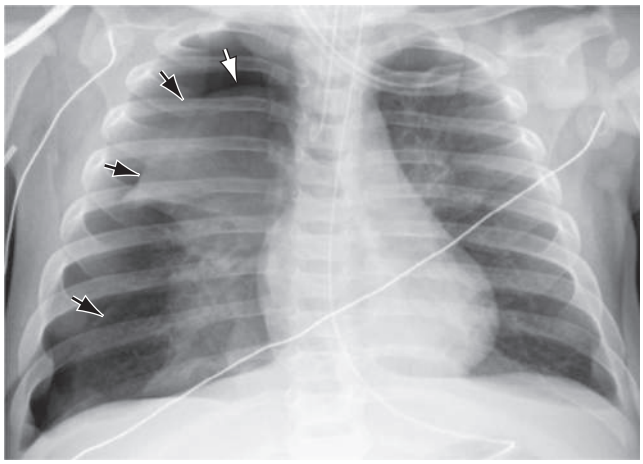

Fig. 461.4 Pneumothorax, with collapse of right lung *(arrows)*, caused by barotrauma in a 7-mo-old child who was intubated for respiratory failure.

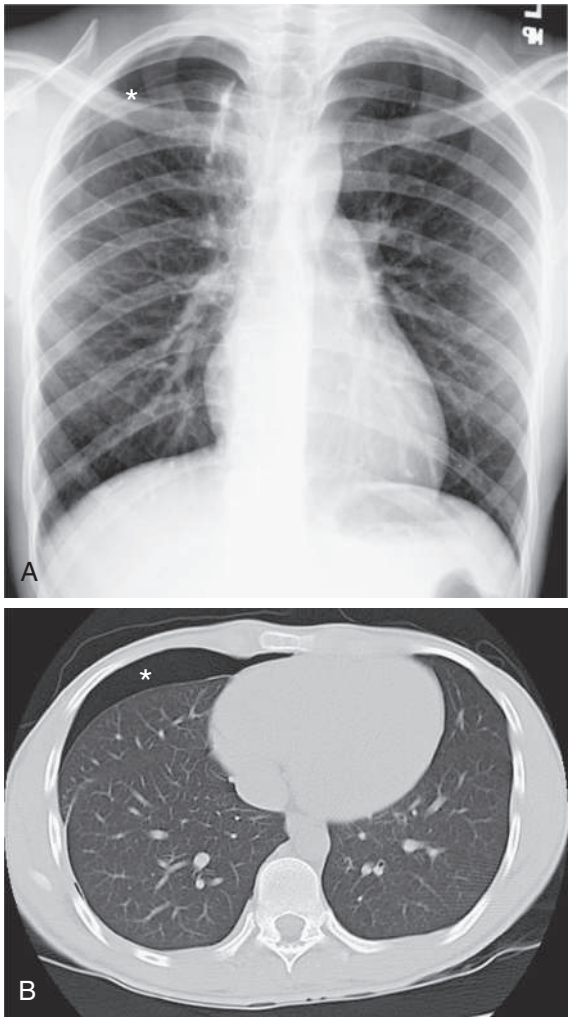

Fig. 461.5 Teenager in whom a spontaneous right pneumothorax developed because of a bleb. Patient had a persistent air leak despite recent surgical resection of the causative apical bleb. Chest radiograph (**A**) and CT scan (**B**) clearly show the persistent pneumothorax *(asterisk)*.

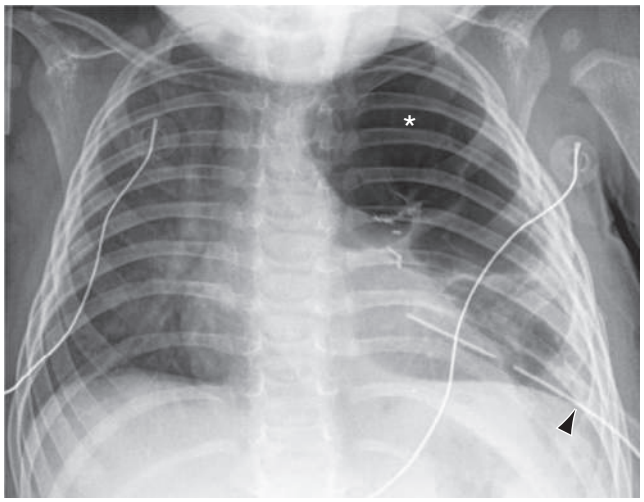

Fig. 461.6 Bronchopleural fistula following surgical resection of the left upper lobe as a result of congenital lobar emphysema. Chest radiograph shows localized pneumothorax *(asterisk)* that persisted despite prior insertion of a large-bore chest tube *(arrowhead)*.

strong adhesions between the lung and chest wall with the introduction of doxycycline or iodopovidone into the pleural space (chemical pleurodesis).

Open thoracotomy through a limited incision, with plication of blebs, closure of the fistula, stripping of the pleura (usually in the apical lung, where the surgeon has direct vision), and basilar pleural abrasion is also an effective treatment for *recurrent* pneumothorax. Stripping and abrading the pleura leaves raw, inflamed surfaces that heal with sealing adhesions. Video-assisted thoracoscopic surgery (VATS) is a preferred therapy for blebectomy, pleural stripping, pleural brushing, and instillation of sclerosing agents, with less morbidity than occurs with traditional open thoracotomy. In cases with a persistent air leak following thoracic surgery, an autologous blood patch pleurodesis may also be considered.

There is a risk of recurrence after surgical treatment in the pediatric population, although this is often not related to surgical failure but rather associated with the formation of new or undetected bullae. Clear benefit for treatment of asymptomatic blebs/bullae in the contralateral lung has not been established in the pediatric population.

Pleural adhesions help prevent recurrent pneumothorax, but they also make subsequent thoracic surgery difficult. When lung transplantation may be a future consideration (e.g., in cystic fibrosis), steps should be taken to avoid, if at all possible, chemical or mechanical pleurodesis. It should also be kept in mind that the longer a chest tube is in place, the greater the chance of pulmonary deterioration, particularly in a patient with cystic fibrosis in whom strong coughing, deep breathing, and postural drainage are important. These are all difficult to accomplish with a chest tube in place.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 461.2 Summary of the Main Features of the BTS, Belgian, and ACCP Guidelines for Spontaneous Pneumothorax Management

	BTS	BELGIAN	ACCP
Definition of large pneumothorax	>2 cm between lung margin and chest wall (at level of the hilum)	≥20% using light index and/or complete dehiscence from lateral chest wall	≥3 cm apex-to-cupola distance
First line small PSP management	Observation if asymptomatic; aspiration if symptomatic	Observation if asymptomatic; aspiration if symptomatic	Observation for 3-6 hr and outpatient follow-up Aspirate or ICC if pneumothorax enlarges Presence of symptoms >24 hr does not alter treatment
First line large PSP management	Observation if asymptomatic; aspiration if symptomatic	Aspiration	Insertion of ICC
First line small SSP management	Admission and insertion of ICC; aspiration can be considered as an alternative	Admission and observation; aspiration if symptomatic	Admission and observation; insertion of ICC if symptomatic
First line large SSP management	Admission and insertion of ICC	Admission and insertion of ICC	Admission and insertion of ICC

BTS, British Thoracic Society; ACCP, American College of Chest Physicians; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax; ICC, intercostal chest catheter.
From Lieu N, Ngo P, Chennapragada SM, et al. Update in management of paediatric primary spontaneous pneumothorax. *Paediat Respir Rev.* 2022;41:73–79. Table 1.

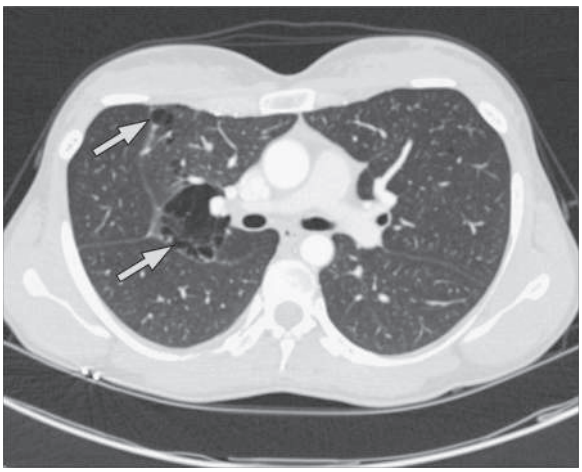

Fig. 461.7 High-resolution CT thorax showing multiple basal cysts. *(From Hopkins TG, Maher ER, Reid E, et al. Recurrent pneumothorax. Lancet. 2011;377:1624. Fig. 1.)*

Chapter 462

Pneumomediastinum

Aarthi P. Vemana and Suraiya K. Haider

Air or gas in the mediastinum is called *pneumomediastinum* and is typically caused by alveolar rupture, which can be due to either a spontaneous or traumatic cause. A spontaneous pneumomediastinum can either be primary without an underlying etiology or can occur secondary to an underlying cause. *Primary* pneumomediastinum can be due to increases in intrathoracic pressure as is seen with a Valsalva maneuver, vomiting, Boerhaave syndrome (esophageal perforation), weightlifting, inhalation of recreational drugs, use of e-cigarettes, recreational use of MDMA, and choking events. Causes of *secondary* pneumomediastinum include lower respiratory tract infections including COVID-19, asthma exacerbations, mechanical ventilation, anorexia nervosa, normal menses, and diabetes mellitus with ketoacidosis. Traumatic causes of pneumomediastinum include both iatrogenic (dental extractions, adenotonsillectomy, high flow nasal cannula therapy, esophageal perforation, inhalation of helium gas, and flexible bronchoscopy) and noniatrogenic (inhaled foreign body and penetrating chest trauma).

PATHOGENESIS

According to the **Macklin effect**, after an intrapulmonary alveolar rupture, air dissects along the pressure gradient through the perivascular sheaths and other soft tissue planes toward the hilum and enters the mediastinum.

CLINICAL MANIFESTATIONS

Dyspnea and transient stabbing chest pain that may radiate to the neck are the principal features of pneumomediastinum. Other symptoms may be present and may include globus pharyngeus, abdominal pain, cough, chest tightness, facial swelling, choking, tachypnea, fever, stridor, and sore throat. Pneumomediastinum is difficult to detect by physical examination alone. Subcutaneous emphysema is present in the majority of patients. When present, **Hamman sign** (a mediastinal "crunch") is nearly pathognomonic for pneumomediastinum. Cardiac dullness to percussion may be decreased, but if the chest is chronically overinflated, it is unlikely that the clinician can be sure of this finding.

LABORATORY FINDINGS

Chest radiography reveals mediastinal air, with a more distinct cardiac border than normal (Figs. 462.1 and 462.2). A "spinnaker sail sign" or "angel wing sign" occurs when air deviates the thymus upward and outward, which is seen more often in pediatric patients. On the lateral projection, the posterior mediastinal structures are clearly defined, there may be a lucent ring ("ring sign") around the right pulmonary artery, and retrosternal air can usually be seen. Vertical streaks of air in the mediastinum and subcutaneous air are often observed (see Fig. 462.1). If a pneumomediastinum is clinically suspected but is not visualized on a chest x-ray, a chest CT can be performed to confirm the diagnosis and identify tracheal injury, if present.

TREATMENT

Treatment is directed primarily at the underlying obstructive pulmonary disease or other precipitating condition. Children who have had pneumomediastinum should be screened for asthma. Analgesics are occasionally needed for chest pain. Children can be observed in the emergency room and discharged if stable. They should be cautioned to avoid heavy lifting and the Valsalva maneuver. Hospital admission with supplemental oxygen administration is more common for patients with secondary pneumomediastinum. In severe cases, consideration should be given to

the use of more invasive interventions, including tracheotomy, surgical repair, and skin incisions over the neck and anterior chest wall. The use of prophylactic antibiotics to prevent deep neck space infections and mediastinitis has not been shown to provide additional benefit.

COMPLICATIONS

Pneumomediastinum is rarely a major problem in older children because the mediastinum can be depressurized by escape of air into the neck or abdomen. In the newborn, however, the rate at which air can leave the mediastinum is limited, and pneumomediastinum can lead to dangerous cardiovascular compromise or pneumothorax (see Chapters 132 and 461).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

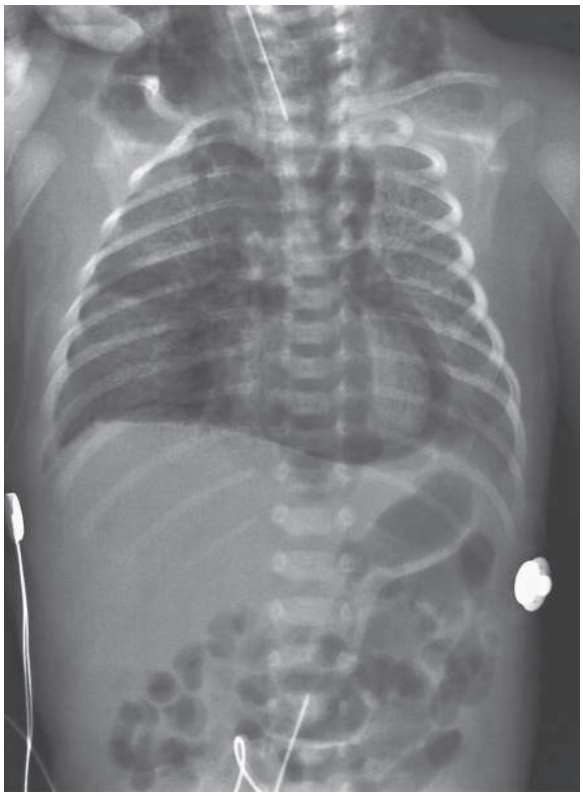

Fig. 462.1 Large pneumomediastinum surrounding the heart and dissecting into the neck. *(From Clark DA. Atlas of Neonatology, 7th ed. Philadelphia: WB Saunders; 2000.)*

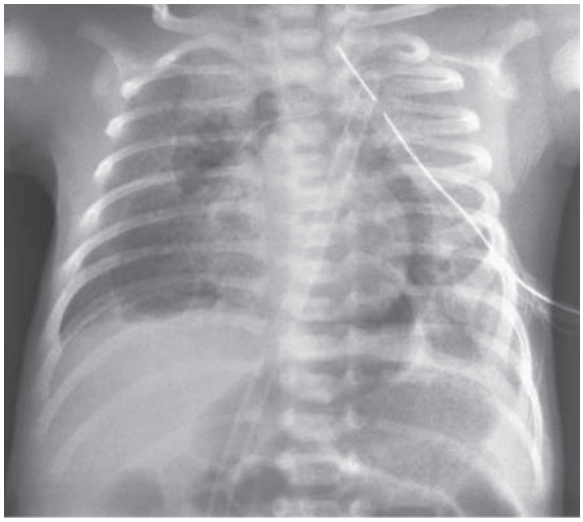

Fig. 462.2 Sail sign—thymic elevation. *(From Clark DA. Atlas of Neonatology, 7th ed. Philadelphia: WB Saunders; 2000: p. 94.)*

Chapter 463
Hydrothorax

Aarthi P. Vemana and Suraiya K. Haider

Hydrothorax is a transudative pleural effusion; typically, it is caused by abnormal pressure gradients in the lung. Hydrothorax is most often associated with cardiac, renal, or hepatic disease. It can also be a manifestation of severe nutritional edema and hypoalbuminemia. Rarely, it results from superior vena cava obstruction by neoplasms, enlarged lymph nodes, pulmonary embolism, or adhesions. It may occur from a ventriculoperitoneal (VP) shunt, central venous catheter, peritoneal dialysis, or after corrective spinal fusion for treatment of adolescent idiopathic scoliosis.

CLINICAL MANIFESTATIONS

Hydrothorax is usually bilateral, but in cardiac or hepatic disease it can be limited to the right side or greater on the right than on the left side. The physical signs are the same as those described for serofibrinous pleurisy (see Chapter 451.2), but in hydrothorax there is more rapid shifting of the level of dullness with changes of position. Depending on the etiology, it can be associated with an accumulation of fluid in other parts of the body.

LABORATORY FINDINGS

The fluid is **transudative**, noninflammatory, has few cells, and has a lower specific gravity (<1.015) than that of a serofibrinous exudate (see Chapters 449 and 451). The ratio of pleural fluid to serum total protein is <0.5, the ratio of pleural fluid to serum lactic dehydrogenase is <0.6, and the pleural fluid lactic dehydrogenase value is less than 66% of the upper limit of the normal serum lactic dehydrogenase range. In a patient with a VP shunt, B-transferrin assays and radionuclide tracer shunt series may be helpful for diagnosis. Peritoneal scintigraphy may be considered to evaluate for a peritoneal-pleural leak. In hepatic hydrothorax, the pleural fluid resembles spontaneous bacterial peritonitis, with positive bacterial cultures and polymorphonuclear leukocyte counts >250 cell/mm^3.

TREATMENT

Therapy is directed at the underlying disorder. If a transudative fluid is clinically suspected, aspiration may not be needed unless pressure symptoms are noted or there are atypical symptoms, such as fever, pleuritic pain, or asymmetric effusions. Aspirated fluid may be diagnostic using PCR for bacteria and cytology and flow cytometry for malignancies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com Bibliography.

Chapter 464
Hemothorax

Suraiya K. Haider and Aarthi P. Vemana

Hemothorax, an accumulation of blood in the pleural cavity, is rare in children. Bleeding into the chest cavity most commonly occurs after chest trauma, either blunt or penetrating. It can be the result of iatrogenic trauma, including surgical procedures and venous line insertion. Hemothorax can also result from erosion of a blood vessel in association with inflammatory processes, such as tuberculosis

and empyema. It may complicate a variety of congenital anomalies, including sequestration, patent ductus arteriosus, and pulmonary arteriovenous malformation (see Fig. 458.2 in Chapter 458), or occur in association with vascular Ehlers-Danlos syndrome. It is also an occasional manifestation of intrathoracic neoplasms, costal exostoses, blood dyscrasias, bleeding diatheses, thrombolytic therapy, thoracic endometriosis, or rarely COVID-19 infections. Rupture of an aneurysm is unlikely during childhood. Hemothorax may occur spontaneously but is rare in children. A pleural hemorrhage associated with a pneumothorax is a *hemopneumothorax;* it is usually the result of a ruptured bulla with lung volume loss causing a torn pleural adhesion.

CLINICAL MANIFESTATIONS

In addition to the symptoms and signs of pleural effusion (see Chapter 451.2), hemothorax is associated with hemodynamic compromise related to the amount and rapidity of bleeding, with ventilatory collapse. Spontaneous hemothorax presents with sudden onset of chest or back pain or dyspnea and can progress rapidly to hemorrhagic shock.

DIAGNOSIS

The diagnosis of a hemothorax is initially suspected from radiographs, ultrasounds, or CT scans but can be made definitively with thoracentesis (Fig. 464.1). In every case, an effort must be made to determine and treat the cause.

TREATMENT

Therapy includes supplemental oxygen, fluid resuscitation (including possible blood transfusion), and tube thoracostomy. Video-assisted thoracoscopic surgery (VATS) can be considered in most patients with stable vital signs to visualize the source of bleeding, remove blood clots, resect bullae or blebs, and to perform pleurodesis. An open thoracotomy may be indicated if there is uncontrolled bleeding or in a hemodynamically compromised patient. Inadequate removal of blood in extensive hemothorax leading to a retained hemothorax can increase the risk for development of pneumonia, empyema, or substantial restrictive disease secondary to organization of fibrin. Fibrinolytic therapy or a decortication may then be necessary. Embolization is the treatment of choice for an arteriovenous malformation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

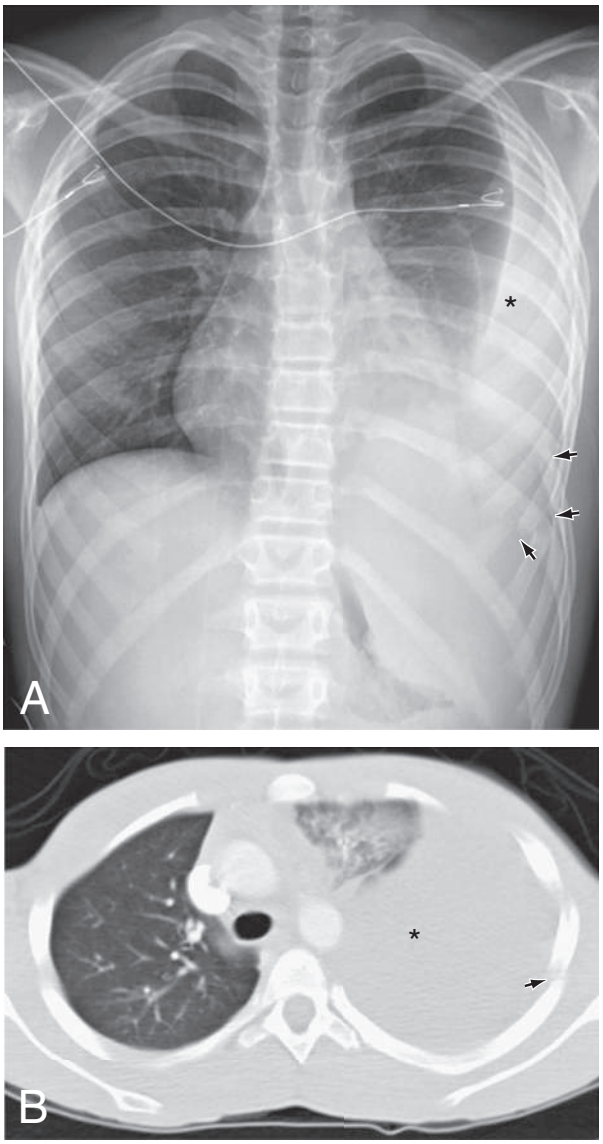

Fig. 464.1 Chest radiograph (A) and CT scan (B) of hemothorax *(asterisk)* and associated rib fractures *(arrows)* in a teenager involved in a motor vehicle accident.

Chapter 465
Chylothorax

Suraiya K. Haider and Aarthi P. Vemana

Chylothorax is a pleural collection of fluid formed by the escape of chyle from the thoracic duct or lymphatics into the thoracic cavity. Chylothorax in children occurs most frequently because of thoracic duct injury as a complication of cardiothoracic surgery (post Fontan surgery) (Fig. 465.1). Other cases are associated with chest injury (Fig. 465.2), extracorporeal membrane oxygenation, or primary or metastatic intrathoracic malignancy, particularly lymphoma. In newborns, rapidly increased venous pressure during delivery may lead to thoracic duct rupture. Chylothorax has also been associated with Down syndrome, Noonan syndrome, Turner syndrome, and congenital myotonic dystrophy. Genetic pathogenic variants involving the VEGFC/VEGFR3, PI3K/AKT/mTOR, and RAS/MAPK pathways can impact lymphangiogenesis leading to lymphatic malformations. Refractory chylothorax in the fetus has been associated with a missense variant in integrin $\alpha_9\beta_1$ gene. Persistent or recurrent chylothorax has been described in association with pathogenic variants in the *PIEZO1* gene. Less common causes include lymphangiomatosis (Fig. 465.3), restrictive pulmonary diseases, thrombosis of the duct, superior vena cava, or subclavian vein; tuberculosis or histoplasmosis, Gorham-Stout disease, and congenital anomalies of the lymphatic system (Fig. 465.4). Chylothorax can occur in trauma and child abuse (see Chapter 16). It is important to establish the etiology because treatment varies with the cause. In some patients, no specific cause is identified.

CLINICAL MANIFESTATIONS

The signs and symptoms of chylothorax are the same as those from pleural effusion of similar size, including cough, chest discomfort, and dyspnea. Chyle is not irritating, so pleuritic pain is uncommon. Onset is often gradual. However, after trauma to the thoracic duct, chyle may accumulate in the posterior mediastinum for days and then rupture into the pleural space with sudden onset of dyspnea, hypotension, and hypoxemia. Approximately 50% of newborns with chylothorax present with respiratory distress in the first day of life. Chylothorax is rarely bilateral and usually occurs on the right side.

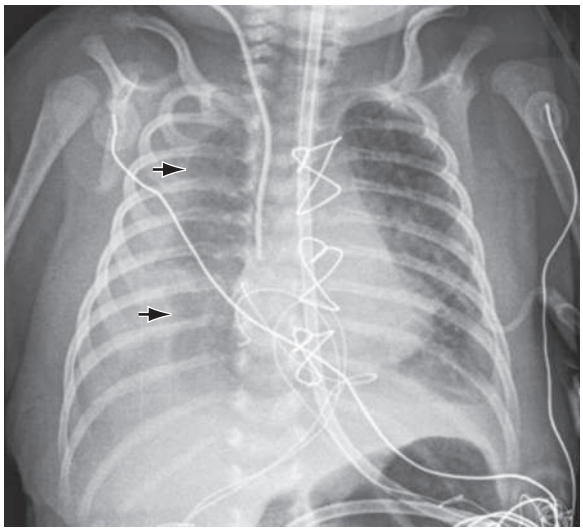

Fig. 465.1 Chylothorax *(arrows)* following cardiac surgery in a 2-wk-old infant.

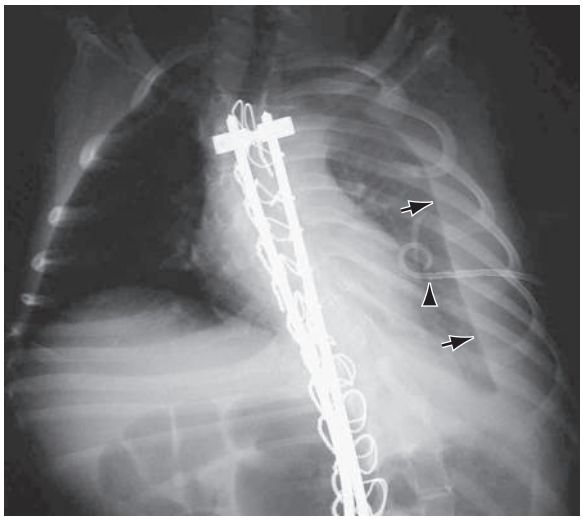

Fig. 465.2 Left chylothorax *(arrows)* following spinal fusion with Harrington rods. It is postulated that the thoracic duct was injured during spine surgery. The pigtail chest tube *(arrowhead)* needed to be retracted to better drain the effusion.

LABORATORY FINDINGS AND IMAGING

Chest radiographs can help to delineate the location of an effusion; CT scans show normal pleural thickness and may demonstrate a mediastinal mass such as a lymphoma, as the etiology of the chylothorax. Thoracentesis demonstrates a chylous effusion, a milky fluid containing triglycerides, protein, lymphocytes, and other constituents of chyle; fluid may be yellow or bloody. In newborn infants or those who are not ingesting food, the fluid may be clear. A pseudochylous milky fluid may be present in chronic serous effusion, in which fatty material arises from degenerative changes in the fluid and not from lymph. In chylothorax, the fluid triglyceride level is >110 mg/dL, the pleural fluid:serum triglyceride ratio is >1.0, and pleural fluid:serum cholesterol ratio is <1.0; lipoprotein analysis reveals chylomicrons. Fluid immunoglobulin levels are elevated. The cells are primarily (>80%) lymphocytes and often exceed 1,000 cells per mm^3. After diagnosing chylothorax, a lymphangiogram can localize the site of the leak, and lymphoscintigraphy may

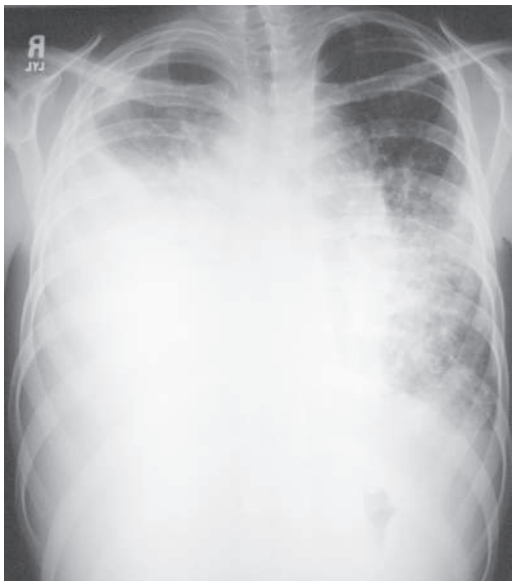

Fig. 465.3 Large right chylous effusion opacifying much of the right thorax in a teenager with pulmonary lymphangiomatosis and hemangiomatosis. Note the associated interstitial lung disease.

demonstrate abnormalities of the lymphatic trunks and peripheral lymphatics. MR lymphangiography also allows for visualization of the peripheral and segments of the central lymphatics. Dynamic contrast-enhanced magnetic resonance lymphangiography can provide real-time evaluation of the central lymphatic flow with good spatial resolution to guide management options.

TREATMENT

Treatment involves symptomatic support and decreasing or stopping chyle accumulation. Management is divided into two categories: nonsurgical and surgical. Nutritional management strategies include a combination of nil-per-os (NPO) and total parenteral nutrition, or enteral feeds using either a low-fat or medium-chain triglyceride diet or defatted human milk (also known as skimmed human milk). Thoracentesis is repeated as needed to relieve pressure symptoms; tube thoracostomy is often performed. Somatostatin and octreotide have been used to manage chylothorax. Various octreotide dosages have been described, including 1–4 μg/kg/hr intravenously and 10 μg/kg/day subcutaneously. Retrospective analyses have shown beneficial effects with the use of steroids, in particular, hydrocortisone, methylprednisolone, and dexamethasone combined with somatostatin or octreotide. Use of propranolol or sirolimus in severe or refractory cases may be effective. Further studies are required to confirm the optimal dosage for steroids, propranolol, and sirolimus. Other therapeutic approaches include pressure control ventilation with positive end-expiratory pressure and inhalation of nitric oxide. If medical management is unsuccessful, surgical options should be considered and can include a pleuroperitoneal shunt, thoracic duct ligation, and pleurodesis with the use of a sclerosing agents such as fibrin glue or povidone-iodine. Treatment is similar for traumatic chylothorax. Chemical pleurodesis or irradiation is used in malignant chylothorax. OK432 (picibanil) has been used to treat fetal and newborn chylothorax. Etilefrine, a sympathomimetic agent with both α- and β-adrenergic activity, has been successfully used in a few patients. Constriction of the thoracic duct by this drug may reduce pleural chyle accumulation. Percutaneous thoracic duct embolization or treatment of other lymphatic vessels is a successful interventional radiology strategy. Surgery should be considered earlier in neonates with massive chylothorax and chyle output of >50 mL/kg/day despite maximum medical therapy for 3 days.

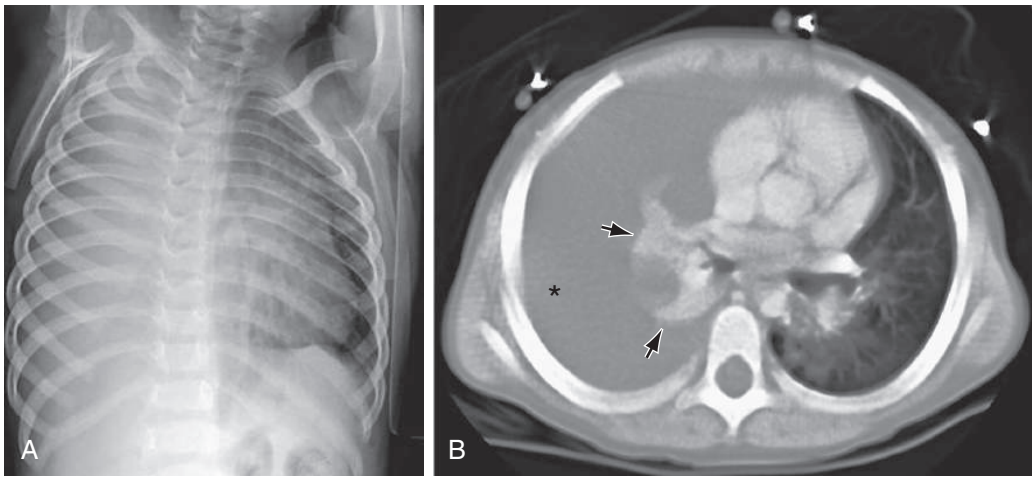

Fig. 465.4 Spontaneous chylothorax in a 4 yr old with a duplication of chromosome 6. **A,** Chest radiograph shows opacification of the right thorax. **B,** CT scan shows the chylous pleural effusion *(asterisk)* compressing the atelectatic right lung *(arrows)*.

COMPLICATIONS

If repeated thoracenteses are required due to the rapid reaccumulation of chyle, malnutrition may occur with significant loss of calories, protein, and electrolytes. Immunodeficiencies, including hypogammaglobulinemia and abnormal cell-mediated immune responses, have been associated with repeated and chronic thoracenteses for chylothorax. The loss of T lymphocytes is associated with increased risk of infection in neonates; otherwise, infection is uncommon, but patients should not receive live virus vaccines. Lack of resolution of chylothorax can lead to malnutrition, infection, and death.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 466

Bronchopulmonary Dysplasia

Sharon A. McGrath-Morrow and J. Michael Collaco

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of infancy and childhood that occurs primarily in preterm infants born at less than 32 weeks' gestation. BPD is characterized by alveolar hypoplasia, often with concomitant small airway dysfunction and impaired pulmonary vascular growth. Contributing factors to the development of BPD may include early gestational age, low birthweight, lung barotrauma, exposure to hyperoxia, lung inflammation, and pre- and postnatal infections, as well as potential modifier genes and epigenetic factors. The currently accepted definition for diagnosis includes an oxygen requirement for 28 days postnatally, and the disorder is graded as mild, moderate, or severe based on supplemental oxygen and ventilation requirements at specific time points (Table 466.1). For initial inpatient presentation and management, see Chapter 127.

CLINICAL MANIFESTATIONS

Physical findings of the pulmonary exam vary with the severity of the disease and with respiratory illnesses. Although some patients may appear to be comfortably breathing when well, they can experience significant deterioration when ill or with periods of stress due to decreased pulmonary reserve secondary to alveolar hypoplasia and small airway disease. Children with BPD may exhibit tachypnea, head bobbing, and retractions when ill or at baseline depending on the severity of the disease. Although breath sounds may be clear, many patients have baseline wheeze or coarse crackles. A persistent, fixed wheeze or stridor suggests subglottic stenosis (see Chapter 436) or large airway malacia. Fine crackles may be present in patients prone to fluid overload. Chest radiographs may demonstrate air trapping, focal atelectasis, interstitial changes, and/or peribronchial thickening.

The most severely affected patients may require respiratory support to achieve adequate gas exchange. Supplemental oxygen may be required to maintain acceptable oxygen saturations and often is needed to minimize the work of breathing. Chronic respiratory insufficiency may be evidenced as elevation of serum bicarbonate, elevated carbon dioxide on blood gas analysis, hypoxemia, or polycythemia; the most severe cases may require tracheostomy and ventilation to achieve long-term respiratory stability. Patients must be monitored for the development of pulmonary hypertension, especially if they require supplemental oxygen and have chronic respiratory insufficiency.

Aspiration from dysphagia and/or gastroesophageal reflux (GERD) (see Chapter 369) can compromise pulmonary status. The risk of aspiration may increase during periods of illness due to worsening tachypnea and air trapping. Other comorbidities resulting from premature birth that complicate the management of BPD include fixed and functional upper airway obstruction, CNS injuries leading to abnormal control of breathing, abnormal airway tone, increased aspiration risk, gastrointestinal dysmotility, systemic hypertension, and poor growth. Of note, infants with significant lung disease can exhibit growth failure from the elevated energy expenditure essential to maintaining the increased metabolic demands of respiration and/or ongoing hypoxia.

A *pulmonary exacerbation* in a child with BPD is typically triggered during viral respiratory infections. Other frequent risk factors for pulmonary exacerbations may include weather changes, exposure to cigarette smoke, exposure to emissions from vaping devices, attending daycare, and aspiration. During an exacerbation, the infant may exhibit increased work of breathing, crackles, and wheezing, with tachypnea and retractions becoming more prominent. Underlying pulmonary hypertension may worsen with pulmonary exacerbations as well.

Table 466.1 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria

GESTATIONAL AGE	<32 WEEKS	≥32 WEEKS
Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 days but <56 days' postnatal age or discharge to home, whichever comes first
TREATMENT WITH >21% OXYGEN FOR AT LEAST 28 DAYS PLUS		
Mild BPD	Breathing room air by 36 weeks' PMA or discharge, whichever comes first	Breathing room air by 56 days' postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 weeks' PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days' postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks' PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days' postnatal age or discharge, whichever comes first

BPD, Bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.
Adapted from Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163:1723.

TREATMENT

Treatment is directed toward decreasing the work of breathing and normalizing gas exchange to allow for optimal growth and neurodevelopment. After initial hospital discharge, infants and children with BPD are at high risk for rehospitalization. Up to 50% of infants with BPD are readmitted for acute respiratory illnesses within the first 2 years of life. These children also may require multiple daily medications, supplemental oxygen, and/or chronic ventilation.

Adherence to prescribed daily medication regimens may decrease the risk of acute care use and chronic respiratory symptoms; however, there are no standard guidelines for the management of BPD concerning post-NICU care. Although commonly used, there are limited data regarding the efficacy of diuretics in the outpatient setting.

With regard to respiratory support, targeted oxygen saturations should be ≥92% outside of the NICU to ensure adequate growth and neurocognitive development. Pulse-oximetry and polysomnography may be helpful for titration purposes. Before initial hospital discharge, infants and children who require chronic ventilatory support have been shown to benefit from standardized protocols to determine medical readiness, assess familial proficiency in respiratory care, and establish adequate support in an outpatient setting. After discharge, these patients will require close follow-up from pulmonologists and otolaryngologists to manage ventilator titration and weaning and tracheostomy care and decannulation, respectively. As infants and children with tracheostomies are at high risk for adverse events, including death, an awake and alert trained caregiver is recommended at all times.

Pulmonary function testing in children with a history of BPD has consistently demonstrated obstructive small airway disease. Small airway disease in this population may be partially responsive to bronchodilators but may also have a fixed obstructive component. Inhaled corticosteroids and β-agonists may be effective in treating symptoms, such as wheezing or chronic cough.

Adequate caloric intake is important to ensure catch-up lung growth. Some children may require fortified breast milk or formula to achieve adequate growth. Patients at risk for aspiration and those with inadequate oral intake may require tube feeding to meet nutritional goals. Placement of a gastrostomy tube should be considered before discharging home. Aspiration secondary to dysphagia and/or gastroesophageal reflux should be considered in patients with recurrent respiratory symptoms or pneumonia without obvious infectious etiologies. Because of their tenuous respiratory status, some infants and children with BPD may not be able to tolerate even minimal amounts of aspiration from gastroesophageal reflux. There are limited data regarding risks and benefits of antireflux medications in infants with BPD, such as histamine-2 blockers, proton pump inhibitors, and motility agents. Medications that reduce gastric acidity may increase the risk of pneumonia in some children. Consideration for either Nissen fundoplication or gastrojejunostomy tubes may be required in cases of failure of antireflux medical therapy.

Up to 15–25% of infants with severe BPD will be diagnosed with pulmonary hypertension, which may be secondary to decreased pulmonary vascular growth and/or a reactive vascular bed. Other risk factors for developing pulmonary hypertension may include extreme prematurity and decreased intrauterine growth; recurrent aspiration, hypoxia, and hypercarbia may worsen severity. Pulmonary hypertension in infants is associated with increased morbidity and mortality compared to infants without pulmonary hypertension. Although definitive diagnosis of pulmonary hypertension requires cardiac catheterization, in practice transthoracic echocardiography provides a low-risk screening tool. Screening should also attempt to identify potential structural causes of pulmonary hypertension, such as pulmonary vein stenosis. Serum biomarkers, such as brain natriuretic protein, may be useful in tracking response to therapy. Abrupt worsening of pulmonary hypertension *(pulmonary hypertensive crises)* can occur in the context of illnesses and with anesthesia. Crises can occur even in stable children with a history of pulmonary hypertension who become acutely ill. Although pulmonary hypertension that is associated with BPD can improve with adequate lung growth, therapies such as sildenafil and other antipulmonary hypertensive agents have been used in management.

Prevention of respiratory viral illness is vitally important; frequent handwashing by caregivers (especially before they handle the baby) and avoidance of contact with children and adults with current respiratory symptoms are essential. Respiratory syncytial virus (see Chapter 307) immunoprophylaxis should be considered based on the severity of lung disease and the patient's gestational age and current age. Another environmental factor that can worsen respiratory symptoms is exposure to secondhand tobacco smoke (see Chapter 759.1).

PROGNOSIS

The prognosis for infants with BPD is generally good, although the presence of BPD may result in a longer initial hospitalization compared with preterm infants without BPD. Most infants are weaned off of oxygen during the first year of life, and those requiring home mechanical ventilation are often weaned from this support during toddlerhood. Many children exhibit an asthma-like phenotype during early childhood, characterized by episodes of wheezing or coughing triggered by upper respiratory tract infections, exertion, allergens, etc. For some of these children, symptoms improve by school age; others may continue to have asthma-like exacerbations with viral illnesses and exercise throughout childhood that may persist into adulthood. Even asymptomatic patients with a history of BPD can continue to demonstrate small airway flow limitations by spirometry. Lastly, obstructive sleep apnea may also be more common in infants, children, and young adults with a history of BPD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 467

Skeletal Diseases Influencing Pulmonary Function

Steven R. Boas and Catherine Kier

Pulmonary function is influenced by the structure of the chest wall (see Chapter 421). Chest wall abnormalities can lead to restrictive or obstructive pulmonary disease, impaired respiratory muscle strength, and decreased ventilatory performance in response to physical stress. The congenital chest wall deformities include *pectus excavatum, pectus carinatum, sternal clefts, Poland syndrome*, and skeletal and *cartilage dysplasias*. Vertebral anomalies such as kyphoscoliosis can alter pulmonary function in children and adolescents.

467.1 Pectus Excavatum (Funnel Chest)

Steven R. Boas and Catherine Kier

ETIOLOGY

Pectus excavatum—midline narrowing of the thoracic cavity—is usually an isolated skeletal abnormality. The cause is unknown. Pectus excavatum can occur in isolation, or it may be associated with a connective tissue disorder—Marfan (see Chapter 743) or Ehlers-Danlos syndrome (see Chapter 700). It may be acquired secondarily to chronic lung disease, neuromuscular disease, or trauma.

EPIDEMIOLOGY

Pectus excavatum occurs in 1 in 400 births with a 9:1 male preponderance and accounts for >90% of congenital chest wall anomalies. There is a positive family history in ~30% of cases.

CLINICAL MANIFESTATIONS

The deformity is present at or shortly after birth in one third of cases but is usually not associated with any symptoms at that time. In time, fatigue, chest pain, palpitations, recurrent respiratory infections, wheezing, stridor, and cough may be present. Decreased exercise tolerance is one of the most common symptoms. Because of the cosmetic nature of this deformity, children may experience significant psychologic stress. Physical examination may reveal sternal depression, protracted shoulders, kyphoscoliosis, dorsal lordosis, inferior rib flares, rib cage rigidity, forward head tilt, scapular winging, and loss of vertebral contours (Fig. 467.1). Patients may exhibit paroxysmal sternal motion and a shift of point of maximal impulse to the left. Innocent systolic murmurs may be heard.

LABORATORY FINDINGS

Lateral chest radiograms demonstrate sternal depression. The Haller index on chest CT (maximal internal transverse diameter of the chest divided by the minimal anteroposterior diameter at the same level) in comparison with age- and gender-appropriate normative values have been used historically to help determine the extent of the anatomic abnormality. However, the correlation of the Haller index with the physiologic compromise or associated systems appears suboptimal. The use of 3D chest optical imaging or "surface scan" is gaining popularity in the evaluation. An electrocardiogram may show a right-axis deviation or Wolff-Parkinson-White syndrome (see Chapter 485); an echocardiogram may demonstrate mitral valve prolapse (see Chapter 477.3) and ventricular compression. Results of static pulmonary function tests may be normal but commonly show an obstructive defect in the lower airways and, less commonly, a restrictive defect as the result of abnormal chest wall mechanics. Exercise testing may demonstrate either normal tolerance or limitations from underlying cardiopulmonary dysfunction that are associated with the severity of the defect. Pulmonary limitations, such as ventilatory limitations and associated flow volume loop abnormalities, are commonly seen in younger children and adolescents, whereas additional cardiac limitations secondary to stroke volume impairments are more commonly seen in older adolescents and young adults.

TREATMENT

Treatment is based on the severity of the deformity and the extent of physiologic compromise as defined by physical examination and physiologic assessment of cardiopulmonary function (lung function and exercise tolerance assessment). Therapeutic options include careful observation, the use of physical therapy to address musculoskeletal compromise, corrective surgery, cosmetic surgery, and noninvasive thoracoscopic techniques. For patients with significant physiologic compromise, surgical correction may improve the cosmetic deformity and may help minimize progression or even improve the cardiopulmonary compromise. The two main surgical interventions are the Ravitch and Nuss procedures. The Nuss procedure is a minimally invasive thoracoscopic repair that has been associated with good cosmetic and functional outcomes.

The extent of the anatomic defect, including the degree of asymmetry, may help determine the appropriate surgical approach. Although surgical repair may result in improved exercise tolerance for some individuals, usually observed at submaximal exercise intensities, many patients do not show improvement in either respiratory or cardiac function. Normalization of lung perfusion scans and maximal voluntary ventilation have also been observed after surgery. Use of a magnetic brace with gradual remodeling (Magnetic Mini Mover procedure) of the pectus deformity is under clinical investigation, with some promising results seen for prepubertal children. Surgically placed silicone implants for cosmetic appearance have also been used with high patient satisfaction. For selected patients, the use of a more noninvasive approach (i.e., cup suction) has been gaining popularity. Regardless of the treatment approach, addressing secondary musculoskeletal findings is commonly employed before and after any intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

467.2 Pectus Carinatum and Sternal Clefts

Steven R. Boas and Catherine Kier

PECTUS CARINATUM

Pectus carinatum is a sternal deformity accounting for 5–15% of congenital chest wall anomalies. Anterior displacements of the mid and lower sternum and adjacent costal cartilages are the most common types. They are most commonly associated with protrusion of the upper sternum; depression of the lower sternum occurs in only 15% of patients. Asymmetry of the sternum is common, and localized depression of the lower anterolateral chest is also often observed. Males are affected four times more often than females. There is a high familial occurrence and a common association of mild to moderate scoliosis. Mitral valve disease and coarctation of the aorta are associated with this anomaly. Three types of anatomic deformity occur (upper, lower, and lateral pectus carinatum), with corresponding physiologic changes and treatment algorithms.

CLINICAL MANIFESTATIONS

In early childhood, symptoms appear minimal. School-age children and adolescents commonly complain of dyspnea with mild exertion, decreased endurance with exercise, and exercise-induced wheezing. The incidence of increased respiratory infections and use of asthma



Fig. 467.1 Pectus excavatum in a 15-yr-old male. Note the presence of protracted shoulders, inferior rib flares, and sternal depression.

medication is higher than in nonaffected individuals. On physical examination, a marked increase in the anteroposterior chest diameter is seen, with a resultant reduction in chest excursion and expansion (Fig. 467.2). Spirometry has demonstrated both restrictive and obstructive patterns, although the majority of individuals have normal values. Increases in residual volume are often present and result in tachypnea and diaphragmatic respirations. Exercise testing shows variable results. Chest radiographs show an increased anteroposterior diameter of the chest wall, emphysematous-appearing lungs, and a narrow cardiac shadow. The pectus severity score (width of chest divided by distance between sternum and spine; analogous to the Haller index) is reduced.

TREATMENT

For symptomatic patients with pectus carinatum, minimally invasive surgical correction procedures may result in an improvement of the clinical symptoms. Many surgeons prefer to use **bracing techniques** as a first-line treatment, especially for younger patients. Although surgery is performed for some individuals who are symptomatic, it is often performed for cosmetic and psychologic reasons.

STERNAL CLEFTS

Sternal clefts are rare congenital malformations that result from the failure of the fusion of the sternum during the eighth week of gestation. No familial predisposition has been described. Sternal clefts occur in less than 1% of all chest wall deformities. Sternal clefts are classified as partial or complete. Partial sternal clefts are more common and may involve the superior sternum in association with other lesions, such as vascular dysplasias and supraumbilical raphe, or the inferior sternal clefts, which are often associated with other midline defects (pentalogy of Cantrell). Complete sternal clefts with complete failure of sternal fusion are rare. These disorders may also occur in isolation. The paradoxic movement of thoracic organs with respiration may alter pulmonary mechanics. Rarely, respiratory infections and even significant compromise result. Surgery is required early in life before fixation and immobility occur.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

467.3 Asphyxiating Thoracic Dystrophy (Thoracic-Pelvic-Phalangeal Dystrophy)

Steven R. Boas and Catherine Kier

A multisystem autosomal recessive disorder, asphyxiating thoracic dystrophy results in a constricted and narrow rib cage. Also known as *Jeune syndrome*, the disorder is associated with characteristic skeletal abnormalities as well as variable involvement of other systems, including renal, hepatic, neurologic, pancreatic, and retinal abnormalities (see Chapter 741).

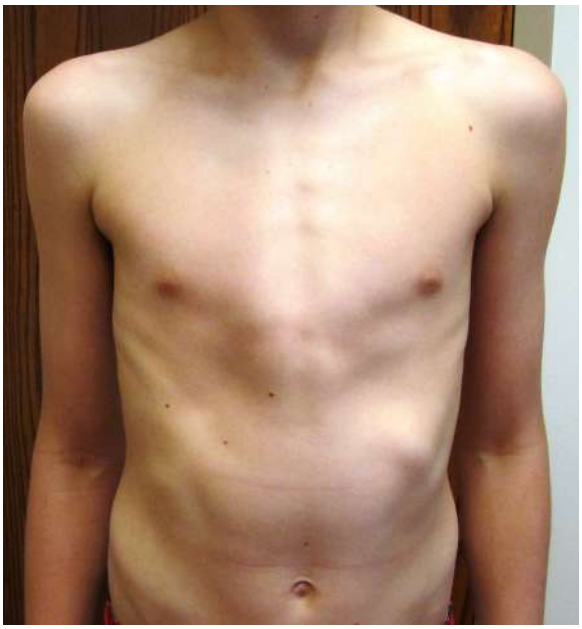

Fig. 467.2 Pectus carinatum in a 13-yr-old male. Note the central sternal prominence.

CLINICAL MANIFESTATIONS

Most patients with this disorder die shortly after birth from respiratory failure, although less-aggressive forms have been reported in older children. For those who survive the neonatal period, progressive respiratory failure often ensues, owing to impaired lung growth, recurrent pneumonia, and atelectasis originating from the rigid chest wall.

DIAGNOSIS

Physical examination reveals a narrowed thorax that, at birth, is much smaller than the head circumference. The ribs are horizontal, and the child has short extremities. Chest radiographs demonstrate a bell-shaped chest cage with short, horizontal, flaring ribs, and high clavicles.

TREATMENT

No specific treatment exists, although thoracoplasty to enlarge the chest wall and long-term mechanical ventilation have been tried. Rib-expanding (vertical expandable prosthetic titanium rib [VEPTR]) procedures have resulted in improved survival (Fig. 467.3).

PROGNOSIS

For some children with asphyxiating thoracic dystrophy, improvement in the bony abnormalities occurs with age. However, children younger than age 1 year often succumb to respiratory infection and failure. Progressive renal disease often occurs in older children. Use of vaccines for influenza and other respiratory pathogens is warranted, as is the aggressive use of antibiotics for respiratory infections.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

467.4 Achondroplasia

Steven R. Boas and Catherine Kier

Achondroplasia is the most common condition characterized by disproportionate short stature (see Chapter 737). This condition is inherited as an autosomal dominant disorder that results in disordered growth. Much has been learned about this disorder, including its genetic origins (95% of cases are caused by pathogenic variants in the gene coding for fibroblast growth factor receptor type 3) and how to minimize its serious complications.

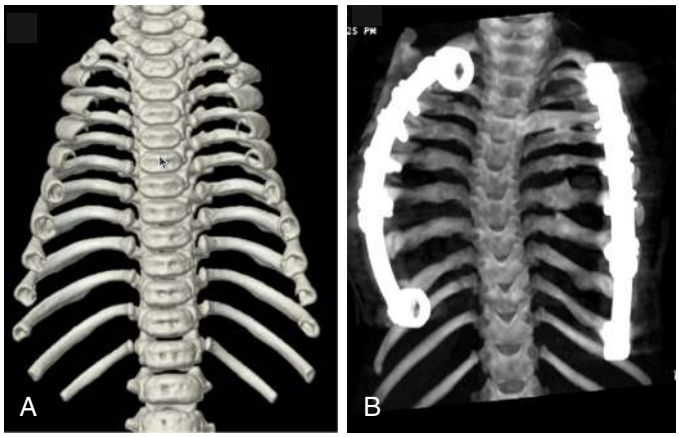

Fig. 467.3 A, Seven-mo-old with Jeune syndrome preoperatively. B, 18 mo after VEPTR insertion. *(From Mayer OH. Chest wall hypoplasia—principles and treatment. Pediatr Respir Rev. 2015;16:30–34, Fig. 3.)*

CLINICAL MANIFESTATIONS

Restrictive pulmonary disease, affecting <5% of children with achondroplasia who are younger than 3 years, is more likely at high elevation. Recurrent infections, cor pulmonale, and dyspnea are commonly associated. There is an increased risk of obstructive sleep apnea or hypopneas. Hypoxemia during sleep is a common feature. Risk of airway malacia is greater than the general population. Onset of restrictive lung disease can begin at a very young age. On examination, the breathing pattern is rapid and shallow, with associated abdominal breathing. The anteroposterior diameter of the thorax is reduced. Special growth curves for chest circumference of patients with achondroplasia from birth to 7 years are available. Three distinct phenotypes exist: phenotypic group 1 patients possess relative adenotonsillar hypertrophy, group 2 patients have muscular upper airway obstruction and progressive hydrocephalus, and group 3 patients have upper airway obstruction without hydrocephalus. Kyphoscoliosis may develop during infancy.

DIAGNOSIS

Pulmonary function tests reveal a reduced vital capacity that is more pronounced in males. The lungs are small but functionally normal. Sleep studies are recommended because of the high prevalence of sleep-disordered breathing. Chest radiographs demonstrate the decreased anteroposterior diameter along with anterior cupping of the ribs. The degree of foramen magnum involvement correlates with the extent of respiratory dysfunction.

TREATMENT

Treatment of sleep apnea, if present, is supportive (see Chapter 31). Physiotherapy and bracing may minimize the complications of both kyphosis and severe lordosis. Aggressive treatment of respiratory infections and scoliosis is warranted.

PROGNOSIS

The life span is normal for most children with this condition, except for the phenotypic groups with hydrocephalus or with severe cervical or lumbar spinal compression.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

467.5 Kyphoscoliosis: Adolescent Idiopathic Scoliosis and Congenital Scoliosis

Steven R. Boas and Catherine Kier

Adolescent idiopathic scoliosis (AIS) is characterized by lateral bending of the spine (see Chapter 720). It commonly affects children during their teen years and during periods of rapid growth. The cause is unknown. Congenital scoliosis is uncommon, affecting females more than males, and is apparent in the first year of life (see Chapter 720.2).

CLINICAL MANIFESTATIONS

The pulmonary manifestations of scoliosis may include chest wall restriction, leading to a reduction in total lung capacity, abnormal gas exchange, airway obstruction, and hypoinflation with associated atelectasis. The angle of scoliosis deformity has been correlated with the degree of lung impairment only for patients with thoracic curves. Vital capacity, forced expiratory volume in 1 sec (FEV_1), work capacity, oxygen consumption, diffusion capacity, chest wall compliance, and partial pressure of arterial oxygen decrease as the severity of thoracic curve increases. These findings can be seen in even mild to moderate AIS (Cobb angle <30 degrees) but generally do not occur in other, nonthoracic curves. Respiratory compromise is often more severe in children younger than 5 years of age with large scoliotic curves. Reduction in peripheral muscle function is associated with AIS through either intrinsic mechanisms or deconditioning. Severe impairment can lead to cor pulmonale or respiratory failure and can occur before 20 years old. Children with severe scoliosis (Cobb's angle >70 degrees), especially males, may have abnormalities of breathing during sleep, and the resultant periods of hypoxemia may contribute to the eventual development of pulmonary hypertension.

DIAGNOSIS

Physical examination and an upright, posteroanterior radiograph with subsequent measurement of the angle of curvature (Cobb technique) remain the gold standard for the assessment of scoliosis. Curves >10 degrees define the presence of scoliosis. Lung volume, respiratory muscle strength, and exercise capacity determination are essential in assessing the degree of respiratory compromise associated with scoliosis.

TREATMENT

Depending on the extent of the curve and the degree of skeletal maturation, treatment options include reassurance, observation, physical therapy, bracing, and surgery (spinal fusion). Influenza vaccine should be administered, given the extent of pulmonary compromise that may coexist. Because vital capacity is a strong predictor for the development of respiratory failure in untreated AIS, surgical goals are to diminish the scoliotic curve, maintain the correction, and prevent deterioration in pulmonary function. Abnormalities of vital capacity and total lung capacity, exercise intolerance, and the rate of change of these variables over time should be taken into consideration for the timing of surgical correction. Preoperative assessment of lung function (i.e., lung volumes, oxygen consumption, muscle strength, ventilation/perfusion) may assist in predicting postsurgical pulmonary difficulties. Many patients undergoing surgical correction may be managed postoperatively without mechanical ventilation. Even patients with mild scoliosis may have pulmonary compromise immediately after spinal fusion, secondary to pain, and a body cast that may restrict breathing and interfere with coughing. Children with a preoperative FEV_1 <40% predicted are at risk for requiring prolonged postoperative mechanical ventilation. Rib-expanding procedures have been successful in severe cases of congenital scoliosis. Choice of surgical approach may also impact lung function postoperatively.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

467.6 Congenital Rib Anomalies

Steven R. Boas and Catherine Kier

Isolated defects of the highest and lowest ribs have minimal clinical pulmonary consequences. Missing midthoracic ribs are associated with the absence of the pectoralis muscle (Poland syndrome), and lung function can become compromised. Associated kyphoscoliosis and hemivertebrae may accompany this defect. If the rib defect is small,

no significant sequelae ensue. When the second to fifth ribs are absent anteriorly, lung herniation and significant abnormal respiration ensue. The lung is soft and nontender and may be easily reducible on examination. Complicating sequelae include severe lung restriction (secondary to scoliosis), cor pulmonale, and congestive heart failure. Symptoms are often minimal but can cause dyspnea. Respiratory distress is rare in infancy.

DIAGNOSIS

Chest radiographs demonstrate the deformation and absence of ribs with secondary scoliosis. Most rib abnormalities are discovered as incidental findings on a chest film.

TREATMENT

If symptoms are severe enough to cause clinical compromise or significant lung herniation, then homologous rib grafting can be performed. Rib-expanding procedures are also of great value. A modified Nuss procedure has been used to correct associated chest wall anomalies with rib abnormalities. Adolescent girls with congenital rib anomalies may require cosmetic breast surgery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 468

Chronic Respiratory Insufficiency

468.1 Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Denise M. Goodman and Steven O. Lestrud

Care has improved for the growing population of children with chronic respiratory failure requiring invasive (ventilation through a tracheostomy) and noninvasive (mask ventilation) ventilation, including those with predisposing conditions such as acute respiratory failure, prematurity, and neuromuscular disease. Although it is difficult to determine the prevalence of chronic ventilation, estimates range from approximately 4-6/100,000 children, or 3,000-4,000 children nationally who receive home ventilation. There may be roughly three times more children receiving mask ventilation than invasive mechanical ventilation. The conditions leading to the need for home ventilation are diverse. About 65% of children have a primary neurologic indication, including neuromuscular weakness or abnormal ventilatory control, and ~30% have chronic lung disease (Table 468.1).

Patients with primarily pulmonary indications have a greater likelihood of ultimately being weaned from the need for ventilation than do those with neuromuscular or central nervous system disease. Mortality for patients requiring chronic ventilation is ~12–34%, depending on underlying disease. The lower mortality range is for children with neonatal lung disease, with the higher value for children with complex congenital heart disease. Approximately 12–40% of children are eventually weaned from ventilation and decannulated, reflecting the underlying cause for which ventilation is required. This can usually be accomplished within the first 5 years of life. Nonetheless, the care of these children can be challenging. One study reported that up to 40% of chronically ventilated children are readmitted within the first year of discharge, usually within the first 3 months. Children requiring long-term mechanical ventilation (LMV) benefit from comprehensive care coordination incorporating generalists, specialists, home nursing, therapies, and a durable medical equipment (DME) resource.

Table 468.1 Indications for Long-Term Mechanical Ventilation

PULMONARY/ALVEOLAR
Bronchopulmonary dysplasia (BPD)
Severe acquired lung disease, such as after pediatric acute respiratory distress syndrome (PARDS)
Pulmonary fibrosis syndromes
AIRWAY
Severe tracheomalacia
Severe bronchomalacia
Obstructive sleep apnea (OSA)
Storage diseases
CHEST
Kyphoscoliosis
Skeletal dysplasias
Obesity
NEUROMUSCULAR
Spinal muscular atrophy
Spinal cord injury
Diaphragmatic dysfunction
Mitochondrial diseases
CENTRAL NERVOUS SYSTEM (CNS)
Congenital central hypoventilation syndrome (CCHS)
Rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysfunction (ROHHAD)
Severe ischemic brain injury
Myelomeningocele with Arnold-Chiari type II malformation
Acquired hypoventilation syndromes

MODALITIES FOR RESPIRATORY SUPPORT

The goals of home mechanical ventilation are to maintain adequate oxygenation and ventilation, minimizing metabolic demands of chronic respiratory failure to ensure adequate somatic growth and optimal developmental gains.

Invasive Positive Pressure Ventilation

The term *invasive* designates ventilation through a tracheostomy. Some devices are suitable for both noninvasive positive pressure ventilation (NPPV) and invasive ventilation, whereas other devices are suitable for only one approach. The ideal home ventilator is lightweight, portable, and quiet. All home ventilators differ from hospital-based ventilators in that air movement is affected either by a piston or turbine that is electrically controlled. This contrasts with hospital ventilators, which are often gas-driven. A home ventilator should be able to provide continuous flow and have a wide range of settings (particularly for pressure, volume, pressure support, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and troubleshoot.

Although families and care teams may at first resist placement, a **tracheostomy** has several advantages. It provides a secure and stable airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions and deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable cuff. Tracheostomy tubes with and without cuff inflation should be sized to control the

air leak around the tube and promote adequate gas exchange, yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube. The child's caregivers need to learn stoma care, elective and emergent tracheostomy changes, proper securing of the tube, suctioning of secretions, and recognition of emergencies such as tube obstruction or decannulation.

Optimal Ventilator Support

Factors such as underlying neuromuscular disease; medications such as sedatives, analgesics, steroids, and muscle relaxants; and prolonged immobility, as well as use of mechanical ventilation, may decondition the respiratory muscles and the diaphragm, resulting in muscle weakness. Consequently, it is important to avoid 24 hour a day patient synchrony with ventilation and titrate the amount of ventilator support to prevent fatigue yet facilitate spontaneous breathing. While assessing ventilator needs, frequent evaluation of gas exchange is needed and can usually be done noninvasively. Ventilator settings should be stable for a given period, dictated by the severity of pulmonary disease, before discharge home.

OTHER MANAGEMENT CONSIDERATIONS

Airway Clearance

One of the most important considerations is maintenance of airway patency. Adequate removal of secretions may minimize intercurrent pulmonary infections. In turn, infections may cause a transient increase in secretions, requiring an escalation of clearance strategies. If the child has an adequate cough, then periodic suctioning may be all that is needed. Some children, however, need additional help mobilizing and clearing secretions. This becomes particularly important in children with neuromuscular disease, for whom regularly scheduled clearance therapies are an imperative. **Vest therapy** (high-frequency chest wall oscillation) uses an inflatable vest that encircles the chest. Air inflates and deflates the vest with phasic pulses against the chest wall, loosening secretions. This device still requires a preserved and strong enough cough to expel secretions. The **cough assist** device provides more active airway clearance, delivering a forceful positive pressure adjunct during inspiration and active negative pressure during expiration. Thus the cough is more effective because of the rapid pressure changes. The cough assist can be used with an artificial airway or mask. Controls will set the inspiratory and expiratory pressures and periods.

Inhalation Medications

Clearance of secretions may be promoted with delivery of hypertonic (3% saline) nebulizations. These are often timed to cough-assist sessions to maximize the clearance benefits of both. Children requiring ventilation also commonly need bronchodilators.

Mucolytics and Anticholinergics

Some patients may need additional interventions as a result of excess secretions. Anticholinergic drugs, principally glycopyrrolate, are often effective, but must be dosed carefully to avoid thickening secretions excessively, which can lead to inspissated secretions and life-threatening plugging of the airway. Oral secretions are sometimes amenable to localized injection of botulinum toxin or select surgical ligation of salivary ducts. It is also wise to ensure that the patient is adequately hydrated, as dehydration may produce thick tenacious secretions. At times a mucolytic may be used. Hypertonic saline is the most common mucolytic, but a number of other agents have been tried, such as dornase alfa and *N*-acetylcysteine.

Monitoring

A patient who is ventilated in the home must be electronically and/or physically monitored at all times. Infants and young children, children who are cognitively impaired, and children who are completely tracheostomy dependent for airway patency because of suprastomal obstruction must be under direct observation of the caregivers at all times. Caregivers should also closely monitor children whose pulmonary status is fragile or fluctuant. Continuous monitoring of O_2 saturation and heart rate is recommended during sleep and either continuous or intermittent monitoring during the daytime, depending on patient stability. Patients with congenital central hypoventilation syndrome (CCHS) or pulmonary hypertension are particularly vulnerable to episodes of hypoxemia and/or hypercarbia, and those with pulmonary hypertension are particularly susceptible to rapid drops in O_2 saturation.

Supplemental Oxygen

Supplemental oxygen may be delivered from a tank or concentrator. Whether on room air or oxygen at baseline, even mild intercurrent infections may lead to an increase in oxygen requirement. In these situations, the child should be evaluated in person rather than over the phone to ensure that a more serious illness is not developing.

Physical, Occupational, and Speech Therapy

The technology needed to support physical well-being should not overshadow the inherent needs common to all children—to play, grow, develop, and interact. Ongoing physical therapy, occupational therapy, and speech therapy can help a child reach full potential, and many achieve complete catch-up development. Early intervention programs and access to play groups are important factors to attaining cognitive and social milestones. When typical development is not attainable, therapies can improve mobilization and muscle strength. Core trunk and abdominal strength is particularly important for pulmonary rehabilitation and essential for successful weaning off ventilation. Other important skills include oromotor skills for feeding and communication. Evaluation of swallow is a key component of therapy for children with chronic respiratory failure. Sign language is frequently used for communication because of delayed speech or hearing loss. Audiology specialists should be involved in the assessment of hearing because there is a higher incidence of hearing loss in patients undergoing long-term ventilation.

PREPARING FOR DISCHARGE

A number of threads need to come together for a safe and effective discharge, including medical stability, family education, financial support (insurance or a state waiver program), availability of a DME company, and, when appropriate, home private-duty nursing. A poor outcome may occur with any of the many medical or process factors or family factors, including not only education but also home readiness and psychosocial supports. A standardized discharge process can ensure that all details are addressed, minimizing length of stay and improving safety. An awake and attentive trained caregiver should be in the home of a child with invasive ventilation at all times; this expectation may differ for those receiving NPPV depending on clinical circumstance. For those receiving invasive ventilation, the caregiver may be a nurse, but nursing resources are often scarce, so many programs require two trained family caregivers. The training given to the family includes tracheostomy stoma care, suctioning, equipment expertise, administration of medications, and facility with other devices, such as gastrostomy tubes. In addition, the family is instructed in emergency preparedness, including what to do for acute changes in clinical status, desaturation, or airway obstruction or decannulation. Cardiopulmonary resuscitation training is essential. Parents also need to be able to travel portably with the child and equipment. A standardized emergency bag containing critical tracheostomy and ventilator supplies should accompany the child at all times. Other preparations center around home readiness, including accessibility (number of stairs, if any), members of the household, assuring no smoking in the home, and notification of utility companies such as the electric or heating company to ensure the home is serviced quickly in the event of power interruption. The family must also have a functioning telephone to ensure adequate accessibility and communication between the family and care team. For those going home with invasive mechanical ventilation, both a primary and backup ventilator may be needed, as well as batteries, a self-inflating bag and mask, suctioning equipment, supplemental oxygen, and appropriate monitoring, including a pulse oximeter. The use of high-fidelity

simulation as a means to rehearse skills is increasing. Family training often culminates in an autonomous 24-hour stay *in the hospital* during which time one caregiver must continuously remain awake, and all cares, including ventilator checks, suctioning, tracheostomy tube changes, medications, and the like, are provided by the family.

CARE BY THE GENERAL PEDIATRICIAN

See Chapter 468.4.

Nutrition

Ventilated patients may have nutritional needs that are equal to, greater than, or lesser than those of comparably aged well children. Growth should be tracked at each well child and subspecialty visit. Excessive growth is as harmful as inadequate growth, and excess calories may lead to increased carbon dioxide (CO_2) production. Anthropometry or measured energy expenditure may be needed to assure a more precise prescription of nutritional support. Many children with tracheostomies have oral aversion and/or dyscoordination of swallowing, with resultant risk for aspiration. In these children a gastrostomy tube may ensure adequate nutrition in the interim, while ongoing speech therapy promotes oral feeding.

Infections

Tracheitis (see Chapter 433.2), bronchiolitis (see Chapter 439), and pneumonia (see Chapter 449) are common in patients with chronic respiratory failure. Infections may be caused by community-acquired viruses (adenovirus, influenza, respiratory syncytial virus, parainfluenza, rhinovirus) or community- or hospital-acquired bacteria. Common pathogens are gram-negative, highly antimicrobial-resistant pathogens that may cause further deterioration in pulmonary function. Bacterial infection is most likely in the presence of fever, deteriorating lung function (hypoxia, hypercarbia, tachypnea, and retractions), leukocytosis, and mucopurulent sputum. The presence of leukocytes and organisms on Gram stain of tracheal aspirate, along with the visualization of new infiltrates on radiographs, may be consistent with bacterial infection.

Infection must be distinguished from tracheal *colonization* of bacteria, which is asymptomatic and associated with normal amounts of clear tracheal secretions. Colonization may also be distinguished from infection in that colonization usually has few, if any, white blood cells on Gram stain of tracheal secretions. If infection is suspected, it must be treated with antibiotics, based on the culture and sensitivities of organisms recovered from the tracheal aspirate. At times an inhaled antibiotic such as tobramycin might avert progression of infection. Antibiotics should be used judiciously to prevent further colonization with drug-resistant organisms. However, some patients who have recurrent infections may benefit from prophylaxis with inhaled antibiotics. Clinical decisions will be based on the child's appearance, any increased need for ventilation or supplemental oxygen, and consultation with the subspecialist. A final caveat is that if a respiratory viral panel is desired, this must be obtained from nasal secretions similar to a well child; tracheal aspirate does not provide an appropriate specimen.

CARE BY THE SUBSPECIALTY TEAM

Weaning Off of the Ventilator

Typically, the ventilator settings are reduced, minimizing ventilator parameters to achieve physiologic respiratory rates and 6-8 mL/kg tidal volumes. Subsequent maneuvers will evaluate the patient free breathing, initially with simple observed transition times of 5-10 minutes, extending time off as clinically indicated. This can be done in the outpatient setting during visits with the pulmonologist or other subspecialist responsible for ventilator management. Additional factors that reflect tolerance of increased work of breathing, including weight gain, energy levels, general behavior, and sleep patterns, are also monitored carefully. When the child has completely weaned off ventilator support while awake and is only on the ventilator approximately 6 hours nightly during sleep, a polysomnogram study performed off the ventilator may be considered before complete liberation from the mechanical ventilation device. Successful liberation from mechanical ventilation, if it occurs, often takes place between the ages of 2 and 5 years. One thought is that with ambulation and development of core strength, respiratory reserve improves, facilitating weaning. Even so, residual lung disease is common. Children with a history of bronchopulmonary dysplasia (BPD) and previous ventilator dependence often have significant airway obstruction on pulmonary function testing.

PSYCHOSOCIAL CONSIDERATIONS

Caring for a child on long-term ventilatory support in the home is a complex, physically demanding, emotionally taxing, and expensive process for the family. It changes the family routines, priorities, and overall lifestyle and may adversely affect relationships both within the family and with extended family and friends. Practical considerations include loss of spontaneity in family outings, sleep disturbance, extra expenses, having strangers in the house providing care, and adhering to medical regimens and follow-up visits. Intangible stresses are also prominent, including disruption in the usual parent–child caregiving roles and stresses between parent partners and with other children. The loss of normality, sense of isolation, and concerns regarding what is best for the child are additional sources of distress. All of these stresses are exacerbated by challenges in securing reliable home private-duty nurse resources; this issue may delay hospital discharge and complicate postdischarge care, at times even leading to readmission because of lack of adequate support. For children with a life-limiting condition, there is the additional need to periodically revisit the child's current medical state, sense of well-being, and trajectory of illness, as critical decisions will eventually arise regarding end-of-life care. The general pediatrician can often be a familiar and comfortable safe place to explore these issues, as parents may be conflicted in wanting to be a "good" parent while feeling guilty about their own needs and vulnerabilities. Finally, families may find transportation to frequent outpatient visits difficult; telemedicine may offer an alternative for select situations.

ADULT TRANSITION

There are a growing number of children surviving into adulthood who require chronic ventilation. There are little empiric data regarding this transition, including identifying patients for whom transition is appropriate, implementing a standardized transition process, partnering with adult pulmonologists, or replicating in an adult environment the care coordination provided by the pediatric care team. The pulmonary team ideally initiates ongoing discussions regarding self-care responsibilities and transitioning of medical care to adult providers with the adolescent and his or her parents when the patient reaches the early teens. Discussion about self-care should take into consideration realistic expectations about the adolescent's physical and cognitive capabilities. The actual transition of care occurs for most young adults at age 18-21 years and includes referral to an internist and an adult pulmonologist. Transition of medical care also includes transition from pediatric to adult support services for funding sources and nursing care. Ideally, an outpatient visit that includes current and future adult medical providers together is completed to facilitate communication and formally transition care.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

468.2 Congenital Central Hypoventilation Syndrome

Amy Zhou, Susan M. Slattery, Casey M. Rand, and Debra E. Weese-Mayer

CCHS is a clinically complex *neurocristopathy* that includes a variable severity of respiratory and autonomic dysregulation, as well as Hirschsprung disease and neural crest tumors in a subset of patients. In the **classic** CCHS presentation, symptoms of alveolar hypoventilation manifest in the newborn period and during sleep only—with

Table 468.2 Clinical Manifestations of CCHS

ORGAN SYSTEM	CLINICAL MANIFESTATIONS
Ophthalmologic	Decreased/absent pupillary light response Anisocoria Strabismus Lack of convergent gaze Marcus Gunn jaw winking
Respiratory	Alveolar hypoventilation Absent perception of dyspnea
Cardiovascular	Bradycardia Prolonged sinus pauses (>3 seconds) Transient asystole Decreased heart rate variability Low normal daytime blood pressure Orthostatic hypotension Nondipping blood pressure circadian pattern Decreased BP response to exercise Syncope
Gastrointestinal	Hirschsprung disease (20%) Constipation Esophageal dysmotility
Endocrine	Hyperinsulinism Hypoglycemia Hyperglycemia
Neurologic	Decreased anxiety Decreased pain perception Seizures Neurocognitive deficits
Skin	Sporadic profuse sweating
Tumors	Neuroblastoma Ganglioneuroma Ganglioneuroblastoma
Others	Decreased baseline body temperature Poor heat tolerance

CCHS, Congenital central hypoventilation syndrome; BP, blood pressure; GI, gastrointestinal.

From Bishara J, Keens TG, Perez IA. The genetics of congenital central hypoventilation syndrome: clinical implications. *App Clin Genetics*. 2018;11:135–144, Table 1. Originally published by and used with permission from Dove Medical Press Ltd.

diminished tidal volume and a typically monotonous respiratory rate leading to cyanosis and hypercarbia. In more **severe** cases of CCHS, the hypoventilation manifests during wakefulness and sleep. In the **later-onset** cases of CCHS **(LO-CCHS)**, onset of overt symptoms is delayed until 1 month of age or older (often into childhood and adulthood). Hypoventilation is typically during sleep only and usually milder in LO-CCHS. CCHS and LO-CCHS are further characterized by partial to complete failure of peripheral and central chemoreceptors to properly respond to hypercarbia and hypoxemia during wakefulness and sleep, coupled with physiologic and/or anatomic autonomic nervous system (ANS) dysregulation (ANSD). Physiologic dysregulation may include all organ systems affected by the ANS, specifically the respiratory, cardiac, sudomotor, vasomotor, ophthalmologic, neurologic, and enteric systems (Table 468.2). The anatomic or structural ANSD includes Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma).

GENETICS

The *PHOX2B* gene is the disease-defining gene for CCHS. *PHOX2B* encodes a highly conserved homeodomain transcription factor, is essential to the embryologic development of the ANS from the neural crest, and is expressed in key regions and systems that explain much of the CCHS phenotype. Individuals with CCHS are *heterozygous* for either a **polyalanine repeat expansion pathogenic variant (PARPV)** in exon 3 of the *PHOX2B* gene (normal number of alanines is 20 with normal genotype 20/20), such that individuals with CCHS have 24-33 alanines on the affected allele (genotype range is 20/24-20/33), or a **nonpolyalanine repeat expansion pathogenic variant (NPARPV)** resulting from a missense, nonsense, frameshift, stop codon, in-frame indels (in-frame insertions, deletions, or duplications), full exon/gene deletions, or splice-site pathologic genetic variant. Approximately 90–92% of cases of CCHS have PARPVs and the remaining 8–10% of cases have NPARPVs (Table 468.3).

Stepwise clinical *PHOX2B* testing for probands with the CCHS phenotype is advised. **Step 1**: *PHOX2B* screening test (fragment analysis), then if negative; **Step 2**: *PHOX2B* sequencing test, then if negative; **Step 3**: *PHOX2B* multiplex ligation-dependent probe amplification (MLPA) test to minimize the risk of false-negative findings, minimize the expense and need for more than one blood sample, and expedite confirmation of the diagnosis.

Genetic counseling is essential for family planning and for delivery room preparation in anticipation of a CCHS birth and ensuring adequate ventilation for the mother during pregnancy. *PHOX2B* testing is also advised for both parents of a child with CCHS to anticipate the risk of recurrence in subsequent pregnancies (if mosaic) and to determine if a parent has yet-undiagnosed LO-CCHS. Fragment analysis *PHOX2B* testing (also known as the *screening test*) will best identify low-level somatic mosaicism. Prenatal testing for a *PHOX2B* variant is clinically available (www.genetests.org) for families with a known *PHOX2B* gene variant.

Ventilator Dependence and Control of Breathing

Patients with CCHS have deficient CO_2 sensitivity during wakefulness *and* sleep such that they do not respond with a normal increase in ventilation in either state, nor do they arouse in response to hypercarbia and/or hypoxemia during sleep. During wakefulness, a subset of patients may respond sufficiently to avoid significant hypercarbia, but most individuals with CCHS have hypoventilation that is severe enough that hypercarbia is apparent in the resting *awake* state. Children with CCHS also have altered sensitivity to hypoxia while awake and asleep. A key feature of CCHS is the *lack* of respiratory distress or sense of asphyxia with physiologic compromise (hypercarbia and/or hypoxemia). This lack of responsiveness to hypercarbia and/or hypoxemia, which can result in respiratory failure, does not consistently improve with advancing age. A subset of older children with CCHS may show an increase in ventilation (specifically an increase in respiratory rate rather than an increase in tidal volume) when they are exercised at various work rates. This response is possibly secondary to neural reflexes from rhythmic limb movements, although an increase in minute ventilation is often insufficient to avoid physiologic compromise.

The greater the number of extra alanines, the more likely the need for continuous ventilatory support, at least among the most common *PHOX2B* PARPV genotypes (20/25, 20/26, 20/27). Although *PHOX2B* genotype seems to anticipate the severity of hypoventilation, it does not correlate with exogenous ventilatory challenge responses. Infants and young children as a group have reasonable ventilatory response slopes while awake, but this advantage seems to vanish by school age.

Hirschsprung Disease (see Chapter 378.4)

Overall, 20% of children with CCHS also have Hirschsprung disease (HSCR), known as *Haddad syndrome,* and any infant or child with CCHS who presents with constipation should undergo rectal biopsy to screen for the absence of ganglion cells. The frequency of Hirschsprung disease seems to increase with the longer polyalanine repeat tracts (genotypes 20/27-20/33) and in those with NPARPVs. Even in cases without frank HSCR disease, individuals with CCHS may display symptoms of gastrointestinal abnormalities such as severe constipation and abnormal esophageal motility, suggesting ganglion cell dysfunction.

Table 468.3 Congenital Central Hypoventilation Syndrome–Related Symptoms by PARPV vs NPARPV and PARPV Genotype

FEATURE		GENOTYPE				
		PARPV GENOTYPE			NPARPVS	
		20/24[1], 20/25	20/26	20/27	NPARPV IN GENERAL	38BP DELETION
Respiratory (hypoventilation)		Asleep only	Awake with exertion and eating and asleep	Awake and asleep	Awake and asleep	Awake and asleep
Cardiac arrhythmia: Abrupt sinus pauses ≥3 seconds warranting cardiac pacemaker		Variable: None with childhood onset; a subset will have prolonged sinus pauses in adulthood	19%	>80%	None with childhood onset to date	
Hirschsprung disease		<0.1%	20–30%	30%	80–90%	95–100% severe long segment disease (i.e., entire colon and some small intestine)
Severe constipation			~50+%	~50+%		
Esophageal dysmotility/dysphagia			First year of life	First year of life		
Neural crest tumors	Neuroblastoma	0%	0%	See footnote 2	50%	
	Ganglioneuroblastoma	0%	0%	0%	<5%	
	Ganglioneuroma	0%	0%	0%	<5%	
ANSD: Pupillary response to light		Normal response	Midsize pupils with attenuated response to light	Small pupils at rest; nearly absent response to light	Large pupils at rest; negligible response to light	

ANSD, Autonomic nervous system dysregulation; NPARPV, nonpolyalanine repeat expansion pathogenic variant (i.e., missense, nonsense, frameshift, stop codon, splice site); PARPV, polyalanine repeat expansion pathogenic variant.

1. Genotype 20/24 would be considered a susceptibility allele (needs another factor to manifest) or a low- or variable-penetrance allele with features that can be triggered by pharmacologic agents (a pharmaco-genetic phenomenon) or a gene × environment interaction (without main effects).

2. Generally 0%; however, an infant with the 20/33 genotype had metastatic neuroblastoma (12).

From Weese-Mayer DE, Rand CM, Khaytin I, et al. Congenital central hypoventilation syndrome. Updated 2021 Jan 28. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from https://www.ncbi.nlm.nih.gov/books/NBK1427/. Table 2, pp. 7–8.

Tumors of Neural Crest Origin (see Chapter 547)

Tumors of neural crest origin are more frequent in patients with NPARPVs (50%) than in those with PARPVs (1%). These extracranial tumors are more often neuroblastomas in individuals with NPARPVs, but ganglioneuromas and ganglioneuroblastomas occur in a small subset of patients.

Cardiac Asystoles

Transient, abrupt, and prolonged sinus pauses have been identified in patients with CCHS, necessitating implantation of cardiac pacemakers when the pauses are ≥3 seconds. Among patients with the most common *PHOX2B* genotypes, 19% of those with the 20/26 genotype and 83% of those with the 20/27 genotype have cardiac pauses of 3 seconds or longer. The risk for sinus pauses among children with NPARPVs is unknown at present.

Heart rate variability is characteristically decreased in CCHS, likely because of reduced cardiac baroreflex sensitivity and blunted sympathetic response. One report demonstrated a genotype-phenotype relationship for heart rate variability during exogenous ventilatory response testing, prompting assessment of risk for sinus pauses. Introduction of 72-hour Holter recordings every 12 months, at a minimum, has allowed for early identification of these abrupt sinus pauses, permitting timely cardiac pacemaker implantation.

Autonomic Nervous System Dysregulation

A higher number of polyalanine repeats on the affected allele among patients with a PARPV is associated with an increased number of physiologic symptoms of ANSD. In addition, there is a spectrum of physiologic ANSD symptoms, including decreased heart rate variability, esophageal/gastric/colonic dysmotility, decreased pupillary response to light, reduced basal body temperature, altered distribution and amount of diaphoresis, altered vasomotor tone, and altered pain and anxiety perception.

Characteristic Facial Morphology

Characteristic facial features have been described for children with CCHS. Using facial photogrammetry, five features were used to correctly predict 86% of CCHS cases and 82% of controls in a matched case control study. A typical CCHS face is characterized by an upper and midface that is short relative to its width, resulting in a characteristic broad, flat, boxlike appearance (Fig. 468.1). The lateral one third of the upper lip vermillion border is overturned so it is flesh-colored instead of pink. Results also suggest that male CCHS patients are more strongly affected than females.

Neuropathology

Brain imaging studies and functional MRI (fMRI) responses have identified structural anomalies in CCHS cases that may contribute to the observed respiratory and autonomic phenotypes. These findings may be primarily the result of *PHOX2B* variant–induced failure of neurogenesis in the human embryo, but a significant contribution from postnatal hypoxic, hypercarbic, or perfusion damage cannot be excluded. The neuroanatomic defects in CCHS are likely the result of focal *PHOX2B* (mis)expression coupled with sequelae of recurrent hypoxemia/hypercarbia in the subset of suboptimally managed patients. The following regions pertinent to respiratory control in the pons and medulla of the brainstem show *PHOX2B* expression: locus coeruleus, dorsal respiratory group, nucleus ambiguus, and parafacial respiratory group, among other areas. Physiologic evidence suggests that the respiratory failure in these children is mostly based on defects in central mechanisms, but peripheral mechanisms (mainly carotid bodies) may also be important.

CLINICAL MANIFESTATIONS

Patients with CCHS usually present with symptoms in the first few hours after birth. Most children are the products of uneventful pregnancies and are term infants with appropriate weight for gestational age. Variable Apgar scores have been reported. The affected infants do not show signs of respiratory distress, but their shallow respirations and respiratory pauses (apnea) usually evolve to respiratory failure with apparent cyanosis in the first days of life. In neonates with CCHS, $Paco_2$ accumulates during sleep to very high levels, sometimes >90 mm Hg, and may decline to normal levels after the infants awaken. This problem becomes most apparent when multiple attempts at extubation fail in an intubated neonate who appears well with ventilatory support but develops respiratory failure without respiratory distress after removal of the support. However, more *severely* affected infants with CCHS hypoventilate awake and asleep; thus the previously described difference in $Paco_2$ between states may not be apparent. Often, the respiratory rate is higher in rapid eye movement (REM) sleep than in non-REM sleep in individuals with CCHS, and in general, respiratory rates are higher in infants and children with CCHS than similarly aged peers with intact control of breathing.



Fig. 468.1 Characteristic CCHS facies. Photographs of representative CCHS. These two children with CCHS both have the representative facies. The female with CCHS (A) has a *PHOX2B* genotype of 20/25, and the male with CCHS (B) has a 20/27 genotype. Note the decreases in sloping of the forehead, upper face height, upper facial inclination, nasolabial angle, upper and lower lip heights, and the inferior inflection of the lateral vermillion border of the upper lip. *(Modified from Todd ES, Weinberg SM, Berry-Kravis EM, et al. Facial phenotype in children and young adults with PHOX2B-determined congenital central hypoventilation syndrome: quantitative pattern of dysmorphology. Pediatr Res. 2006;59:39–45, Fig. 2A and 2C.)*

LO-CCHS should be suspected in infants, children, and adults who have unexplained centrally mediated hypoventilation and/or seizures or cyanosis, especially subsequent to the use of anesthetic agents and/or sedation, acute respiratory illness or recurrent severe respiratory illness with difficulty weaning from ventilator support (and failed extubations), and potentially obstructive sleep apnea (OSA) unresponsive to traditional intervention. These individuals may have other evidence of chronic hypoventilation, including pulmonary hypertension, polycythemia, elevated bicarbonate concentration, difficulty concentrating, and mild unexplained neurocognitive impairment. A heightened level of suspicion has led to increasing numbers of older children and adults diagnosed with LO-CCHS receiving proper treatment. This later presentation reflects the variable penetrance of a subset of *PHOX2B* variants and the potential role of an exogenous cofactor in unmasking the hypoventilation phenotype.

In addition to treatment for the alveolar hypoventilation, children with CCHS require comprehensive physiologic evaluation during sleep and wakefulness, including age-appropriate activities of daily living such as eating, as their hypoxemia and hypercarbia from insufficient artificial ventilation may go unnoticed. It is necessary to provide coordinated care to optimally manage associated multisystem abnormalities such as Hirschsprung disease, tumors of neural crest origin, and symptoms of physiologic ANSD, including cardiac asystole, among other findings (details provided in American Thoracic Society [ATS] 2010 Statement on CCHS) (Table 468.4).

DIFFERENTIAL DIAGNOSIS

Testing should be performed to rule out primary neuromuscular, lung, and cardiac disease as well as an identifiable brainstem lesion that could account for the symptoms characteristic of CCHS (Table 468.5). The availability of clinical *PHOX2B* genetic testing allows for early and definitive diagnosis of CCHS (see Table 468.3). Because individual subfeatures of CCHS mimic many treatable and/or genetic diseases, the following disorders should also be considered: altered airway or intrathoracic anatomy (diagnosis made with bronchoscopy and chest CT), diaphragm dysfunction (diagnosis made with diaphragm fluoroscopy), a structural hindbrain or brainstem abnormality (diagnosis made with MRI of the brain and brainstem), Möbius syndrome (diagnosis made with MRI of the brain and brainstem and neurologic examination), and specific metabolic diseases, such as Leigh syndrome, pyruvate dehydrogenase deficiency, and discrete carnitine deficiency. However, profound hypercarbia without respiratory distress during sleep will quickly lead the clinician to consider the diagnosis of CCHS or LO-CCHS.

MANAGEMENT

Supported Ventilation: Diaphragm Pacing

Depending on the severity of the hypoventilation, the individual with CCHS can have various options for artificial ventilation: positive pressure ventilation (noninvasive via mask or invasive via tracheostomy) or negative pressure ventilation (pneumosuit, chest cuirass, or diaphragm pacing). Chronic mechanical ventilation is addressed in Chapters 468.1 and 468.4. Diaphragm pacing offers another mode of supported ventilation, involving bilateral thoracoscopic implantation of electrodes beneath the phrenic nerves, with connecting wires to subcutaneously implanted receivers. The external transmitter, which is much smaller and lighter in weight than a ventilator, sends a signal to flat, donut-shaped antennae that are placed on the skin over the subcutaneously implanted receivers. A signal travels from the external transmitter to the phrenic nerve to stimulate contraction of the diaphragm. A tracheostomy is typically required, because the pacers induce a negative pressure on inspiration as a result of the contraction of the diaphragm being unopposed by pharyngeal dilatation, resulting

Table 468.4 Recommended Evaluations in Patients with CCHS

	EVALUATION	FREQUENCY	*PHOX2B* GENOTYPE
Pulmonary	Comprehensive physiologic testing during sleep and wakefulness, including continuous pulse oximetry, cardiorespiratory monitoring, capnography, and polysomnography	<3 yr of age: every 6 mo ≥3 yr: annually	All *PHOX2B* PARM and NPARM
Cardiovascular	Ambulatory cardiac monitoring (≥72 hr), blood pressure, and echocardiogram	Annually	All *PHOX2B* PARM and NPARM
Gastrointestinal	Barium enema or anorectal manometry; confirmation by rectal biopsy	At initial diagnosis and subsequently if symptoms appear	20/26-20/33 PARM and NPARM
Neurodevelopmental	Comprehensive neurocognitive tests	<3 yr of age: every 6 mo ≥3 yr: annually	All *PHOX2B* PARM and NPARM
Oncologic	Chest radiograph, abdominal ultrasound, and urine catecholamines (homovanillic acid and vanillylmandelic acid)	0-6 yr of age: every 3 mo 6-10 yr of age: every 6 mo >10 yr of age: per oncologist recommendation	20/28-20/33 PARM and NPARM
Ophthalmologic	Comprehensive ocular testing by an ophthalmologist	Annually	All *PHOX2B* PARM and NPARM

NPARM, Nonpolyalanine repeat expansion mutation; PARM, polyalanine repeat expansion mutation; PHOX2B, paired-like homeobox 2B.
Data from the 2010 American Thoracic Society Statement on CCHS *Am J Respir Crit Care Med.* 2010;181:626–644.
From Kasi AS, Li H, Harford KL, et al. Congenital central hypoventilation syndrome: optimizing care with a multidisciplinary approach. *J Multidisp Healthcare.* 2022;15:455–469, Table 1. Originally published by and used with permission from Dove Medical Press Ltd.

Table 468.5 Differential Diagnoses of Congenital Central Hypoventilation Syndrome

METABOLIC
Mitochondrial defects (e.g., Leigh disease)
Pyruvate dehydrogenase deficiency
Hypothyroidism
NEUROLOGIC
Structural central nervous system abnormalities (e.g., Arnold Chiari malformation, Möbius syndrome)
Vascular injury (e.g., central nervous system [CNS] hemorrhage, infarct)
Trauma
Tumor
PULMONARY
Primary lung disease
Respiratory muscle weakness (e.g., diaphragm paralysis, congenital myopathy, myasthenia gravis)
GENETIC
Prader-Willi syndrome
Familial dysautonomia and other neuropathies
OTHER
Sedative drugs
Rapid-onset obesity, hypothalamic dysregulation hypoventilation, autonomic dysregulation (ROHHAD)

Modified from Healy F, Marcus CL. Congenital central hypoventilation syndrome in children. *Pediatr Respir Rev.* 2011;12:253–263, Table 1.

in airway obstruction with paced breaths. Individuals with CCHS who are ventilator-dependent for 24 hours a day are ideal candidates for diaphragm pacing to provide increased ambulatory freedom (without the ventilator tether) while they are awake; however, they still require mechanical ventilator support while they are asleep. This balance between awake pacing and asleep mechanical ventilation allows for a rest from phrenic nerve stimulation at night. In addition, a growing but still limited number of children and adults who require artificial ventilatory support only during sleep are now using diaphragm pacing. This is likely because of the introduction of thoracoscopic diaphragm pacer implantation and shortened postoperative recovery time. However, in the absence of a tracheostomy, diaphragm pacing during sleep may cause airway obstruction at varied levels of the airway, depending on the specific patient. The potential for these obstructions needs to be carefully considered before diaphragm pacer implantation, and certainly before tracheal decannulation.

Monitoring in the Home

Home monitoring for individuals with CCHS and LO-CCHS is *distinctly different* from and more conservative than that for other children requiring long-term ventilation, because CCHS individuals lack innate ventilatory and arousal responses to hypoxemia and hypercarbia. In the event of physiologic compromise, other non-CCHS children will show clinical signs of respiratory distress. By contrast, for children and adults with CCHS and LO-CCHS, the only means of determining adequate ventilation and oxygenation is with objective measures from a pulse oximeter, end-tidal CO_2 monitor, and close supervision of these values by a highly trained registered nurse (RN) in the home and at school. While awake, patients with CCHS themselves are unable to sense or adequately respond to a respiratory challenge that may occur with ensuing respiratory illness, increased exertion, or even the simple activity of eating. At a minimum, it is essential that individuals with CCHS have continuous monitoring with pulse oximetry and end-tidal CO_2 with RN supervision during all sleep time, but ideally 24 hours a day. These recommendations apply to all CCHS and LO-CCHS patients regardless of the nature of their artificial ventilatory support, but especially those with diaphragm pacers, as only the most recent transmitter has mechanical dysfunction alarms intrinsic to the diaphragm pacer device.

Noninvasive Ventilatory Support Equipment

Supplemental oxygen with positive pressure support can be administered by nasal cannula, pillows, nasal mask, or full-face mask via an actual ventilator, but this is suitable only for highly cooperative children with milder hypoventilation during sleep only. Long-term use of mask ventilation in infants and young children may result in

midface dysplasia or pressure wounds. Mask ventilation does not offer the stable airway provided by a tracheostomy with mechanical ventilation, especially in the rapidly developing infant and young child.

Positive Pressure Ventilators

Ideally, a ventilator intended for home use is lightweight and small, quiet so it does not interfere with activities of daily living or sleep, is able to entrain room air, preferably has continuous flow, and has a wide range of settings (particularly for pressure support, pressure, volume, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and troubleshoot. Children who are chronically ventilated via positive pressure ventilation will require surgical placement of a tracheostomy tube. The tracheostomy tube provides stable access to the airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions or deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable tight-to-the-shaft cuff. Tracheostomy tubes with and without cuff inflation should be sized to control the air leak around the tube and promote adequate gas exchange yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube.

Optimizing Neurocognitive Performance

Impaired oxygen delivery to the brain, whether acute or chronic, can have detrimental effects on neurocognitive development. The ATS statement on CCHS recommends positive pressure ventilation via tracheostomy in the first several years of life to ensure optimal oxygenation and ventilation. The method of choice for respiratory support in later years will depend on a variety of factors, including severity of disease, patient age, level of patient and family cooperation, and availability and quality of home healthcare, among other factors. The level of oxygen stability obtained with each modality varies. Thus the method of respiratory assistance, especially in infancy and early childhood, is likely to play a factor in neurocognitive outcome.

Past literature has indicated reduced neurocognitive performance in school-age children with CCHS, with mean full scale intellectual quotient (IQ) values one standard deviation below the normal IQ of 100. Even in preschool years, children with CCHS and the 20/26 and 20/27 *PHOX2B* genotypes demonstrate reduced neurocognitive performance compared to children with the 20/25 genotype. In these cases, *PHOX2B* genotype is clearly associated with both mental and motor outcomes. An association is also found between IQ and CCHS-related features such as severe cyanotic breath holding spells, sinus pauses, seizures, and severity of hypoventilation. One study reported a negative correlation between neurocognitive performance scores and length of polyalanine expansion, suggesting that both the specific gene variant and ventilatory method may influence neurocognitive outcome. Findings from a neurocognition study in preschool-age children suggest the potential for excellent neurocognitive outcome in some patients with CCHS. Neurodevelopmental monitoring would be most beneficial beginning in early infancy and followed closely with advancing age.

Efforts are underway to evaluate and characterize the CCHS phenotype longitudinally through the International CCHS Registry (https://clinicaltrials.gov/show/NCT03088020) (Northwestern University). Delineating markers of disease progression and understanding the clinical manifestations of CCHS with advancing age will provide more accurate guidelines to healthcare providers, allowing physicians, families, and patients to better anticipate healthcare needs of affected individuals and for use as biomarkers for future pharmacologic intervention studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

468.3 Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Sarah F. Barclay, Ilya Khaytin, Amy Zhou, Casey M. Rand, and Debra E. Weese-Mayer

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare, poorly understood disorder with childhood onset, the first sign of which is sudden, rapid, and extreme weight gain in a previously healthy child. The acronym describes the presenting symptoms and the typical order in which they will manifest or unfold, as the condition evolves over months to years. Despite its rarity, *ROHHAD must be considered whenever rapid-onset obesity is observed in a child, because in the absence of appropriate treatment, a high mortality rate is associated with the severe central hypoventilation that will invariably develop.*

The diagnosis is initially considered after the observation of rapid-onset obesity (15-20 lb gain) after age 1.5 years, accompanied by at least one additional sign of hypothalamic dysfunction (HD). *Central hypoventilation may not be present at the time of rapid weight gain but will develop over time, and artificial ventilatory support will be required at least during sleep, if not 24 hours a day.* Signs of autonomic nervous system dysregulation typically occur after the weight gain, HD, and hypoventilation have been identified. Additionally, approximately 40% of ROHHAD patients will have or develop a tumor of neural crest origin, typically ganglioneuroma or ganglioneuroblastoma (a small number of neuroblastomas have been identified).

ROHHAD is distinct from LO-CCHS (see Chapter 468.2). ROHHAD is primarily distinguished from LO-CCHS by the presence of obesity and other signs of HD and by the absence of a CCHS-related pathogenic *PHOX2B* variant.

CLINICAL MANIFESTATIONS

Children with ROHHAD initially appear healthy, with an unremarkable medical history. The *initial* symptoms present between ages 18 months and 7 years. Typically, the first symptom observed is **rapid-onset obesity**, with weight gain of 15-30 lb in 6-12 months. The growth charts from a representative child followed longitudinally illustrate the characteristic accelerated increase in weight and body mass index (BMI) (Fig. 468.2). This is considered one sign of HD in these patients.

The second common sign of HD, seen in most ROHHAD patients, is **disordered water balance**, including hypernatremia and hyponatremia and both adipsia and polydipsia. **Growth hormone (GH) deficiency** is also observed in most patients. In some, this manifests clinically as slowed growth rate and short stature, whereas in others a failed GH stimulation test is the only manifestation. **Hyperprolactinemia** is observed near universally in patients with ROHHAD. Other symptoms of HD, occurring in >25–50% of ROHHAD patients, include **poor thermoregulation**, **central hypothyroidism**, **central adrenal insufficiency**, and **delayed or precocious puberty**. The number of hypothalamic abnormalities that will be observed and the sequential order in which they will appear are variable, and some symptoms may not manifest for months to 1-2 years after the initial diagnosis. However, all ROHHAD patients will present with at least one of these signs of HD beyond the rapid-onset weight gain.

Sleep-disordered breathing (SDB) is one of the key symptoms of ROHHAD, often manifesting as one of the most severe features of the phenotype, with the greatest potential for severe morbidity and death. More than half of ROHHAD patients have initial **obstructive sleep apnea (OSA)**; although SDB is known to be associated with obesity and OSA is often seen in obese individuals, over time, when the ROHHAD phenotype unfolds, SDB will evolve beyond what could potentially be explained as obesity related. All ROHHAD patients will eventually develop **central alveolar hypoventilation**, requiring artificial ventilation as life support, even when the upper airway obstruction is relieved as an intervention for OSA. About half of ROHHAD patients will require artificial ventilation only during sleep, whereas half will require

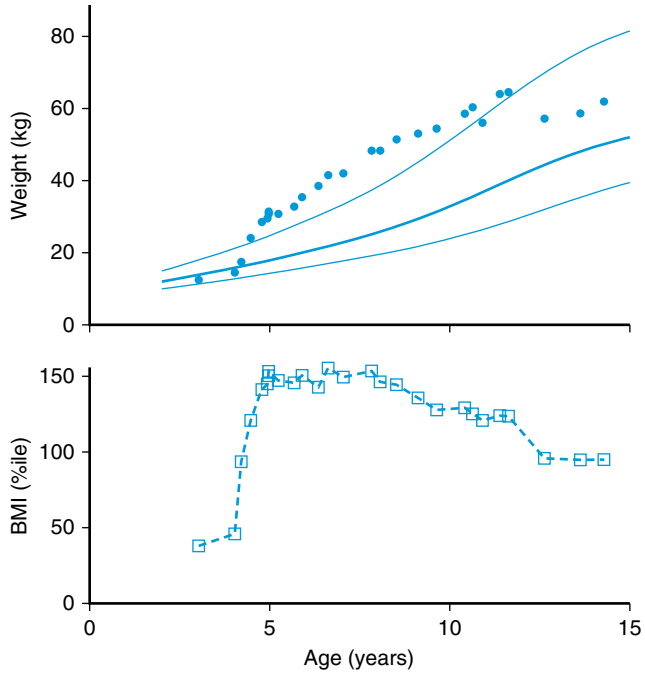

Fig. 468.2 Growth curves of weight and body mass index *(BMI)* from an individual child with ROHHAD. Weight and BMI percentiles for a child with ROHHAD from the time of diagnosis until age 14.3 yr, demonstrating the rapid onset of obesity. Weight and BMI percentiles were calculated using published CDC growth charts and methods. *Solid lines* in weight graph represent 3rd, 50th, and 97th percentiles. *Dots* and *open squares* are individual measurements for the child.

continuous artificial ventilation (during sleep and wakefulness). Up to 50% of children with ROHHAD will have a cardiorespiratory arrest before their hypoventilation is identified and treated. Unfortunately, many ROHHAD patients die from cardiorespiratory arrest because of unrecognized or inadequately managed hypoventilation. Thus if a ROHHAD diagnosis is suspected, it is crucial that a comprehensive respiratory physiology evaluation be performed, including overnight polysomnography and awake physiologic recording in activities of daily living and followed serially long after the hypoventilation is identified and intervention provided.

All ROHHAD patients have symptoms of **autonomic nervous system (ANS) dysregulation (ANSD)**; the specific symptoms and the order and timing of their appearance will vary among patients. The most common manifestations of ANSD in ROHHAD are ophthalmologic, including **pupillary dysfunction**, **strabismus**, and **alacrima**. Many ROHHAD patients will have **gastrointestinal dysmotility**, presenting as either chronic constipation or, less commonly, chronic diarrhea. Other signs of ANSD include **altered sweating**, **decreased body temperature**, **decreased sensitivity to pain**, and **cold hands and feet** indicating altered vasomotor tone. **Bradycardia** is observed in some ROHHAD patients, typically related to **extreme hypothermia**.

Neural crest tumors are observed in ~40% of ROHHAD patients, most frequently ganglioneuromas and ganglioneuroblastomas of the chest or abdomen; rarely a neuroblastoma has been reported. These tumors can occur at any age, so proactive imaging evaluation throughout childhood and adolescence to identify the tumors is essential.

Patients do not always have behavioral or psychologic disorders if artificial ventilation is optimized. For those who do, however, the disorders can be quite severe, including anxiety, depression, rage, lethargy, irritability, aggressiveness, psychosis, and obsessive-compulsive disorder. Developmental disorders described include neurocognitive delay, developmental regression, attention-deficit/hyperactivity disorder, and pervasive developmental disorder. These disorders are most likely accentuated by poorly managed hypoventilation because the majority of ROHHAD patients have no behavioral issues and a normal IQ.

Seizures have been reported in some ROHHAD patients, likely caused by episodes of hypoxemia, when hypoventilation either has not yet been diagnosed or has been inadequately managed.

DIAGNOSIS

The diagnostic criteria for ROHHAD include rapid-onset obesity after 1.5 years of age; central hypoventilation beginning after age 1.5 years; ≥1 of the following signs of HD: disordered water balance, hyperprolactinemia, failed GH stimulation test, central hypothyroidism, corticotropin deficiency, and altered onset of puberty; and features of autonomic dysregulation. Additionally, it must be *confirmed* that no CCHS-related *PHOX2B* pathogenic variant is present to rule out a diagnosis of CCHS or LO-CCHS.

Because no single diagnostic test is currently available for ROHHAD, the diagnosis must be based on observation of the clinical presentation and therefore requires expert consultation in multiple pediatric subspecialties, including respiratory physiology, endocrinology, autonomic medicine, cardiology, oncology, nutrition, critical care, sleep, and psychiatry, with orchestration by the child's pediatrician. When a child with rapid-onset obesity is seen by a general pediatrician or family physician, the steep trajectory of weight gain should signal prompt consideration of a ROHHAD diagnosis, with immediate referral to a center with expertise in this unique constellation of symptoms. Early recognition is critical for a positive outcome in children with ROHHAD. *If alveolar hypoventilation is not identified and aggressively managed, cardiorespiratory arrest can occur and has proved fatal in many cases.*

A **characteristic set of facial features** has been described for CCHS, which, using facial photogrammetry, is able to identify 86% of genetically confirmed CCHS cases (see Chapter 468.2). Although such formal evaluation of ROHHAD facies has not been completed, a preliminary report indicates that ROHHAD patients have similar facial mapping characteristics to CCHS patients, especially the characteristic **"lip trait,"** in which the lateral one third of the upper vermillion border is flesh-colored instead of pink (Fig. 468.3). This is distinct from the general lip changes observed with increasing BMI in a study of adolescent females, which include fuller-looking lips and downturned corners of the mouth.

Initial evaluations should include overnight polysomnography to identify OSA or central hypoventilation, awake comprehensive physiologic recording in age-appropriate activities of daily living, cardiac evaluation to assess for cor pulmonale and rhythm disturbance, endocrine function evaluation, screening for neural crest tumors (chest radiograph, abdominopelvic ultrasound, or meta-iodobenzylguanidine [MIBG] scan), and a behavioral and psychological evaluation, especially if any behavioral, psychologic, or developmental disorders are seen or suspected. Brain imaging should be performed to rule out intracranial lesions that may account for the observed hypothalamic-pituitary abnormalities (using the hypothalamic-pituitary protocol). If the criteria are met and a ROHHAD diagnosis is made, successful management requires ongoing teamwork among the various subspecialists, with a pediatrician team leader to orchestrate all testing, the family, and the child to provide optimized integrated care for the child.

MANAGEMENT

There is currently no cure for ROHHAD. Rather, treatment consists of early identification, meticulous monitoring, and anticipatory along with symptomatic management of the various phenotypic features as they develop ("unfold"). Comprehensive initial evaluations should determine the nature and severity of hypoventilation, HD, and ANSD, and appropriate interventions should be implemented in a time-sensitive manner. Obesity in ROHHAD is very difficult to control, but in consultation with a nutritionist and endocrinologist, the trajectory of advancing weight gain can be diminished with moderate exercise and calorie restriction, leading to improved BMI with advancing age. Specific signs of HD and ANSD should be evaluated by a pediatric endocrinologist and expert in pediatric autonomic medicine, respectively, and treated as necessary longitudinally as the phenotype



Fig. 468.3 Characteristic CCHS "lip trait" shown in a child with ROHHAD. Shown here is the mouth of a child with ROHHAD at age 4 (A) and 11 (B) years. The lateral one third of the upper vermillion border is flesh-colored instead of pink. This is not a characteristic feature of obese faces in general (the upper lip is neural crest in origin).

"unfolds" and "refolds." Such treatments or management strategies may include hormone replacement; regimented fluid intake; ophthalmologic assessment and treatment; longitudinal monitoring of peripheral, core, and ambient temperature; and management of constipation with stool softeners. Disordered water balance to prevent dehydration should be addressed, as well as regulation of heart rate, because bradycardia is seen in some patients (usually with decreased core temperature), though cardiac pacemakers are rarely indicated.

Neural crest tumors should be assessed and resected by a pediatric surgeon together with a pediatric oncologist, because the sheer size of these benign tumors creates serious compromise to surrounding tissues. If no tumor is identified initially, screening should continue every 6 months until adulthood, because a malignant neuroblastoma has been identified in an adolescent ROHHAD patient.

Most critical is the management of hypoventilation. Initial intervention for OSA will likely involve surgical relief of the upper airway obstruction. This will usually unveil central hypoventilation, and initiation of supported ventilation will be required. If no central hypoventilation is identified, the patient should continue to be vigilantly monitored by a respiratory physiologist because all ROHHAD patients will eventually develop central hypoventilation requiring artificial ventilation during sleep at a minimum. Individuals with ROHHAD have attenuated to absent physiologic responsiveness to hypoxemia/hypercarbia, and they lack behavioral awareness of hypoxemia/hypercarbia. Optimal oxygenation and ventilation can then be maintained using a mechanical ventilator with mask initially then, if necessary, by tracheostomy to secure the airway and optimize ventilation. This should be accompanied by highly trained home nursing and continuous monitoring with oximetry and capnography during sleep, with spot checks during wakefulness. The goal should be to maintain hemoglobin saturation values of ≥95% and end-tidal CO_2 values of 35-45 mm Hg, with vigilant evaluation for awake hypoventilation necessitating artificial ventilation up to 24 hours a day as necessary.

Given that the ROHHAD phenotype evolves with advancing age, ongoing care requires regularly scheduled evaluation of all the systems involved to identify and treat further symptoms as they appear. Comprehensive evaluation should ideally occur at a Center of Excellence for ROHHAD and should include respiratory physiology assessment both asleep and awake (in varied levels of age-appropriate exertion, concentrational tasks, quiet play, and eating), screening of chest and abdomen for neural crest tumors in the adrenals or along the sympathetic chain, evaluation of the hypothalamic-pituitary axis with hormonal replacement as necessary, age-appropriate noninvasive evaluation of ANS dysregulation, comprehensive cardiac evaluation for sequelae of recurrent hypoxemia and/or bradycardia, and neurocognitive testing. These evaluations should initially occur at 2- to 3-month intervals, but this schedule may be altered with advancing age, depending on each patient's clinical condition.

With proper and meticulous management, the ROHHAD phenotype has been observed to "refold," with the possibility of achieving weight control, eventually recovering spontaneous awake breathing, and improvement of other autonomic measures. Without proper management, oxygen deprivation can lead to irreversible deterioration in patients. However, with prompt diagnosis and aggressive management, including careful attention to the child's airway, breathing, and circulation, complications can be minimized and the prognosis can be quite favorable, although long-term outcome remains the focus of an international registry (https://clinicaltrials.gov/show/NCT03135730).

Paraneoplastic/Autoimmune Hypothesis

Paraneoplastic syndromes are rare disorders caused by a neoplasm triggering an altered immune response that aberrantly attacks and destroys neurons, leading to the nervous system symptoms. An autoimmune or paraneoplastic basis for ROHHAD has been suggested based on neural crest tumors occurring in 40% of ROHHAD patients and reports of encephalitis seen on autopsy. The evidence so far is conflicting, with some reports supporting the autoimmune hypothesis, whereas others do not. Further, the onset of ROHHAD symptoms often precedes identification of a neural crest tumor in ROHHAD patients, and in many cases, neural crest tumors have not been discovered with MRI or even an autopsy. Of note, with excision of the identified neural crest tumor there has not been consistent "recovery" from ROHHAD. Rather, the ROHHAD phenotype continues to "unfold."

DIFFERENTIAL DIAGNOSIS

Congenital central hypoventilation syndrome is a rare pediatric disorder of the ANS and respiratory control. CCHS is caused by pathogenic variants in the *PHOX2B* gene, which plays an important role in the differentiation and development of the ANS from neural crest progenitor cells (see Chapter 468.2). The hallmark feature of CCHS is life-threatening hypoventilation while sleeping (and, in some cases, also while awake). CCHS patients require artificial ventilatory life support, typically by tracheostomy and mechanical ventilator. Unlike ROHHAD, however, CCHS usually presents in the newborn period, although later-onset CCHS has been diagnosed after 1 month of age, in later childhood, in adolescence, and even in adulthood. CCHS also presents with other symptoms of ANS dysregulation, including altered heart rate regulation, vasomotor tone, and temperature regulation, ophthalmologic manifestations, and reduced gastrointestinal motility. However, CCHS patients *are not* obese and only rarely have isolated measures of HD. When hypoventilation is observed, a simple blood test can confirm a CCHS diagnosis by looking for pathogenic *PHOX2B* variants.

Prader-Willi syndrome (PWS) shares childhood obesity as one of the most prominent features with ROHHAD. PWS is caused by chromosomal abnormalities at chromosome 15q11-q13, specifically by a lack of the paternal contribution at this region (from genomic deletion, uniparental disomy, or imprinting error), whereas methylation differences, loss of heterozygosity, and pathogenic variants in this region

have been ruled out in a ROHHAD cohort. Infants with PWS present with neonatal hypotonia and failure to thrive (malnutrition). Later, children with PWS develop extreme hyperphagia and obesity. Other major symptoms of PWS include intellectual impairment, maladaptive behaviors, short stature caused by GH insufficiency, hypogonadism, and SDB. In addition, many PWS patients show signs of ANS dysregulation, including altered temperature perception and regulation, strabismus, and high pain threshold.

ROHHAD should also be distinguished from other **obesity-related genetic disorders**. Smith-Magenis syndrome, Carpenter syndrome, and 16p11.2 deletion syndrome present with obesity. However, all of them are additionally marked by early developmental delay, unlike ROHHAD, which has normal neurodevelopment in the absence of cardiorespiratory arrest. Therefore testing for genetic causes of obesity should be undertaken in obese children whose phenotype does not appear to match that of ROHHAD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

468.4 Long-Term Ventilation and Technology Support: Indications, Principles, Decision-Making, Pragmatics, and Home Provision

Robert J. Graham

INDICATIONS, GOALS, AND DECISION-MAKING

The decision to implement LMV has many challenges from a diversity of underlying pathophysiology, uncertain disease trajectories, the development of new condition-specific therapies, personal experiences, and values held by providers, patients, parents, and the broader community, variability in resources, and lack of standards. Although optimizing gas exchange (i.e., oxygenation and CO_2 removal), mitigating the impact of intercurrent respiratory infections, and supporting neuromuscular-skeletal limitations, growth, and development remain among the primary objectives, LMV represents a tool for the comprehensive care of children with complex needs.

LMV has a role within the broad spectrum of palliative care. It is used proactively to attenuate cumulative morbidities (respiratory and cardiac) associated with progressive neuromuscular conditions, such as Duchenne muscular dystrophy. LMV is also used reactively when acute illness (e.g., acute respiratory distress syndrome or an acute flaccid myelitis) does not resolve. In infants with premature lung disease or complex airway anomalies, LMV may be implemented as a temporary measure, as these conditions may improve with maturity or surgical interventions. LMV can also represent a bridge to lung transplant for those with intrinsic pulmonary or pulmonary vascular disease. More commonly, LMV has become a destination therapy to optimize symptom management and prolong life in complex conditions. Etiologies of the chronic respiratory failure include but are not limited to congenital anomalies (e.g., complex cardiac conditions, central nervous system disorders, interruptions in aerodigestive morphogenesis, and skeletal dysplasias), acquired central neurologic injuries from perinatal, infectious, traumatic, and hypoxic-ischemic events, metabolic disorders, or progressive neuromuscular conditions. Progress in other areas of medicine, such as gene-targeted therapy in spinal muscular atrophy and myotubular myopathy, may alter the LMV decision-making landscape as families foresee the prospect of improvement.

NONINVASIVE AND TRANSTRACHEAL SUPPORTS

The essential modalities for LMV include negative pressure, noninvasive positive pressure ventilation (NIPPV with either continuous or biphasic support provided through an occlusive mask interface), or transtracheal positive pressure. Considerations for a given child or young adult should include but are not limited to anatomic factors, physiologic goals, long-term care goals, comfort, tolerability/compliance, and safety (mobility/portability, monitoring, device availability and backup, training capacity).

Negative pressure devices, such as the cuirass ventilator, do not require any interface with the face or trachea and are more *natural* from a mechanical perspective. The need for oxygen supplementation is not addressed directly through such a device. *NIPPV* can address dynamic upper airway obstruction and can augment respiratory mechanics and gas exchange. This modality may, however, have limitations if upper airway obstruction is severe or fixed or the need for oxygen supplementation is high. Masks, prongs, and pillows of varying sizes are available for nasal, oral, combination, and full interface, including those for infants. A mouthpiece interface has also been demonstrated to be effective and feasible. The choice of continuous positive airway pressure (CPAP) versus biphasic positive airway pressure (BiPAP) is dependent on the underlying pathophysiology. Conceptually, CPAP can overcome a dynamic upper airway obstruction and allow for spontaneous ventilation, while BiPAP is more versatile in compensating for upper airway obstruction and supporting lung recruitment and gas exchange. CPAP is limited to management of mild OSA. In addition, BiPAP may allow for home escalation for the management of intercurrent illness with oversight of the medical team. Although NIPPV can be maintained 24 hours a day, efficacy of ventilation, difficult airway considerations (i.e., whether the child can anatomically be intubated), developmental needs, implications for midface hypoplasia, and secretion clearance are among factors that affect the decision to pursue tracheostomy placement and invasive LMV.

Transtracheal LMV provides the most secure and effective respiratory support. Fixed and dynamic upper airway obstruction is bypassed with tracheostomy tube placement. Secretions are more readily cleared from the lower airway. Positive pressure and oxygen delivery via a tracheostomy tube more consistently address primary impairments in gas exchange (within limits) as well as mechanical disadvantages from neuromuscular insufficiency and restrictive disease. When possible, placement of a tracheostomy tube in a child should be coordinated at an institution with pediatric expertise, including in long-term tracheostomy care, because the short-term morbidities and, potentially, mortality are not insignificant.

Individuals using NIPPV are at risk for pressure ulcerations on the face and on the scalp. Proper fit of the interface must be assured because a tighter fit is not necessarily commensurate with better support. Alternating masks on a regular basis may alleviate pressure on a given site. Additional nonadhesive dressings can also be used to facilitate the mask seal and minimize skin breakdown. For those with a tracheostomy tube in place, care of tracheostomy ties and regular assessment of the stoma are required. Moisture-wicking dressings can attenuate risk of maceration, but their use should be balanced against the value of exposure to air for drying. Stomal assessment should include evaluation for granulation, fissures, and traction created by additional torque from ventilator tubing, which should be maintained midline and without weight displacement on the tracheostomy tube itself. Any areas of integument interruption are potential niduses for infection and of great concern for immunocompromised hosts.

AUGMENTED SECRETION CLEARANCE

See Chapter 468.1.

AERODIGESTIVE AND COMMUNICATION CONSIDERATIONS

Assessment of swallowing and speaking capacity should be part of an assessment for LMV and may help guide the modality. Implementation of noninvasive or transtracheal supports will not further impair either of these functions. Rather, the underlying condition is the primary determinant. This consideration is most notable in children or young adults with neurologic injury or neuromuscular conditions. Decision-making around placement of a transabdominal gastric or gastrojejunal enteral feeding tube, if not already in place, should coincide with decisions around LMV. Nasogastric tubes, it should be appreciated, may impair the NIPPV mask seal and cause laryngeal irritation in the long term. Antireflux surgery (i.e., fundoplication) should also be discussed

at this time as providers consider ongoing implications of esophageal reflux, aerophagia, and challenges maintaining jejunostomy tubes.

Use of NIPPV must be approached cautiously in those with impaired swallowing, as positive pressure will increase the risk of macroaspiration and microaspiration. Individuals using NIPPV can eat and drink while on support with risk versus benefit determination and assessment of impact on quality of life. Aerophagia on NIPPV is also problematic, regardless of bulbar function and swallowing capacity; abdominal distention is uncomfortable, contributes to satiety and vomiting risk, and further impairs respiratory mechanics with decreased functional residual capacity and increased inspiratory workload. If a gastrostomy is present, active evacuation of swallowed air and use of passive *venting* tubes can be helpful.

Children with swallowing capacity can continue to eat and drink by mouth with a tracheostomy tube in place on LMV. The presence of a cuffed tracheostomy tube does not prevent aspiration if swallowing is impaired. Speaking may be facilitated by LMV, as settings can be increased or a speaking valve used to increased airflow across the vocal cords. Regardless, multidisciplinary care with a speech-language pathologist, feeding specialist, and augmented communication services can be helpful for many children and their families using LMV. Conditioned aversions to oral stimulation can be challenging for infants, but developmental gains should not be impeded by LMV.

GAS EXCHANGE AND VENTILATOR STRATEGIES

Pressure- or volume-regulated modes, spontaneous or controlled settings, and mixed modes are all feasible for NIPPV and transtracheal supports with new devices. The appropriate support should coincide with oxygenation and ventilation goals on a case-by-case basis. Consideration, however, should be given to the site of care and contingencies for presentation to acute cure during intercurrent illness or emergency. Providers should assess limitations in oxygen supplementation outside of the hospital; measured or estimated delivered fractional inspired oxygen (FIO_2) will inform families and providers of capacity when adding oxygen in liters/minute flow to the ventilator circuit; dilution can have a dramatic effect, and achieving FIO_2 >0.60 may be difficult when oxygen is added to a home ventilator circuit. Safety allowances should also account for the duration of portable oxygen provision, which is based upon liter flow and tank/reservoir volume.

Monitoring of CO_2 in the homecare setting is not usual, although portable end-tidal CO_2 devices are available. Conditions such as CCHS warrant vigilance, and parameters for implementation, or titration, of mechanical ventilation should be discussed with families. Recognition that significant and indolent hypercapnia can precede hypoxia is necessary, and long-term effects on cerebral and pulmonary vasculature should be considered. In the absence of direct CO_2 monitoring, periodic measurement of serum bicarbonate may be helpful to assess for renal compensation for altered CO_2 clearance; however, interpretation may be altered in the presence of diuretic therapy, metabolic disease, or ketogenic diets.

CARDIOPULMONARY INTERACTIONS

Closely linked to the gas-exchange goals are considerations for cardiopulmonary interactions. Although there are subtle implications for systemic venous return of any form of positive pressure ventilation, LMV can be used to decrease transmural myocardial load and to optimize right ventricular afterload through lung recruitment and pulmonary vascular reactivity. The prolonged survival of young males with Duchenne muscular dystrophy is in part the result of consistent respiratory support to optimize lung health and to attenuate myocardial dysfunction. Primary or secondary pulmonary hypertension, whether overt or indolent, requires consideration of oxygenation and ventilation goals. Echocardiograms are not required for all children or young adults with LMV, but this modality may be helpful to guide management in cohorts with congenital heart lesions, cardiomyopathies, severe obstructive pulmonary disease, significant central dysregulation, and on a case-by-case basis.

When considering gas-exchange goals and cardiopulmonary interactions, providers must also consider daytime and nocturnal differences. Neuromuscular-derived hypoventilation is more prominent at night, as is upper airway obstructive disease; the latter is more important for those using noninvasive LMV. Daytime support provision must account for increased oxygen consumption and demand based on variable activity and stressors, including environmental temperature. Providers and families must factor in mobility, behavioral tolerance, and quality of life.

CHEST WALL/THORACIC CONFIGURATION

Positive pressure through LMV in early childhood for children with neuromuscular conditions and/or restrictive lung disease is also used to improve thoracic compliance and configuration. Lung inflation can be used to attenuate the impact of thoracic asphyxiation as well as progressive parasol chest deformation in diaphragm-dependent conditions, such spinal muscular atrophy. This use has implications for atelectasis and secretion inspissation, associated pulmonary vasoconstriction, and cumulative restrictive or asymmetric pulmonary mechanics.

NUTRITION AND WEIGHT GAIN

See Chapter 468.1.

DEVELOPMENTAL CONSIDERATIONS

Decisions regarding the LMV modality, noninvasive or transtracheal, requires consideration of development as well. Beyond safety factors, tolerance of interventions, availability of appropriate-sized interfaces, and portability, there remains substantial subjectivity with respect to perspective on the implication for social interactions (i.e., devices covering the face versus a device in the neck). Although there are no published series, long-term or near-continuous NIV also has implications for midface hypoplasia and potentially compounds upper airway obstructive symptoms, as is evident by images of *BiPAP faces*. Swallowing and speech capacity primarily reflect the child's underlying condition and conditioned aversions rather than the LMV itself.

PROJECTED INTERVENTIONS AND NEEDS

The trajectory and management of the underlying disease, as well as symptom management, are the primary drivers in determining the need and duration of LMV. Stakeholders should also consider future interventions, specifically surgical procedures. LMV, noninvasive or transtracheal, can be used to optimize perioperative standing and facilitate recovery and provision of opiate-based analgesia that could alter respiratory drive. The maintenance of a tracheostomy tube in anticipation of sequential surgeries (e.g., spinal instrumentation, craniofacial and airway reconstruction, or serial cardiac interventions) may be required for practical reasons but also minimizes the need for repeated intubation.

PREPARING FOR THE LIVED EXPERIENCE OF LMV AND OTHER TECHNOLOGY SUPPORTS

Emotional challenges are associated with the integration of technology supports into "routine" care and assuming an altered role as a parent and care provider. Addressing practical needs, however, can help attenuate some of the anxiety and allow families to focus on, or revisit, the global goals of care, quality of life, and the role of technology. The family will need to consider each of the following implications.

Financial (e.g., insurance, subsidies, alternative funding, and parental employment): Independent of personal resources, the majority of families with children requiring technology assistance report some degree of financial burden. These costs arise from the direct outlay for equipment and medications, lost work time or need to discontinue/change vocations, home adaptations, and other indirect costs. Accessing a financial counselor or case manager may help identify and navigate through local, state/regional, and government/federal resources. Additional considerations should also be paid to personal trusts, wills, and estate planning, as all of these have implications for long-term benefits and financial supports for the individual with special healthcare needs.

Equipment and supplies: Ideally, the equipment intended for use at home will be tested before discharge to home. Testing ensures proper function and any tolerance. Electrical compatibility with the home

service should be confirmed. Delivery of backup devices (e.g., tracheostomy tubes, including a smaller size for contingency planning; batteries for ventilators; and portable oxygen tanks as a supplement to electric oxygen concentrators) and emergency supplies (e.g., self-inflating respiratory bags, epinephrine for those who have allergy histories, or prophylactic antiepileptic medication for those prone to breakthrough seizures) should be confirmed. Medication supplies and refills should be sufficient to allow for the scheduling of follow-up visits. Providers responsible for recertification or reordering should be identified.

Training: Standards for training and demonstration of competency vary among institutions and across providers. Families and their medical teams should come to an agreement on minimum safety preparation and the number of responsible parties available to assist in the home. Hospital-based training around ventilator use and troubleshooting, central-line care, tracheostomy tube exchanges and suctioning, wound care, and other interventions could include basic life support classes and one-on-one sessions with nurses, respiratory therapists, or other staff, with hands-on or mannequin simulation. Assumption of full care by families while in the hospital can be informative for all stakeholders and reassuring to families; supported replication of the demands of homecare before discharge is ideal.

Augmented staff: Home nursing, hospice, personal care assistants, extended family, and friends represent additional resources for the child and their family. Allowances vary based on the child's age, independence, medical condition, technology dependence, goals of care, and other factors. These individuals may require additional training, but augmenting numbers of proficient homecare providers is crucial for safety and consistency of care. When considering homecare provision, families should consider the type of personnel and how additional supports would allow the child to attend school, the parent to work or maintain the household, continue care when the parent is sick or incapacitated, or assist with other children. The challenges of establishing, training, and maintaining a home staff require time and tolerance, recognizing that the child's safety is the priority.

Monitoring: Conceptually, monitoring is used to detect early physiologic changes, determine adequacy of LMV, and minimize cumulative morbidities or risk of mortality. Continuous direct observation is not practical, or often desirable, in the community setting. Recommendations for monitoring children and young adults on LMV vary based on underlying vulnerability, care setting, activity (e.g., home, long-term care facility, school, or in transport via car), and adjuvant supports (e.g., home nursing or personal care assistant). Pulse oximetry can be used intermittently or on a continuous basis, with oxygen and heart rate parameters determined on a case-by-case basis. Typically, capnography is not available except in cases of central hypoventilation syndromes but can complement oximetry. Internal ventilator alarm settings for both NIPPV and transtracheal ventilators are used to monitor high- and low-pressure parameters and minute ventilation. Stakeholders must acknowledge, however, that internal alarms may be insufficient in the setting of a large mask or peritracheal leak or in the event of a device malfunction.

The child's individual risks and the environmental circumstances drive the balance of extrinsic monitoring (e.g., pulse oximetry and heart rate) and intrinsic device alarms. There are also pragmatic considerations of signal-to-noise when determining monitoring parameters; recurrent false alarms will desensitize providers and may disturb a child's sleep; conversely, wide alarm parameters circumvent early warning systems with significant consequences. Alarm fatigue, as experienced by hospital-based providers, should be discussed, as it can be of great consequence where the resources are not as robust. Simple audio and video monitors (i.e., video cameras) can be used to augment surveillance and may help families in their activities of daily living.

Adaptations to the homecare setting: Modifications to the home may be required to ease care and optimize safety. Ramps for wheelchair access will permit ingress and egress. Lift systems can minimize physical burden and injury risk to providers. Doorways can be expanded to permit access to multiple rooms. Alternative bath and toileting accommodations may be needed. Electrical system upgrades with grounding and increased amperage are often required for equipment demand and safety.

Transportation: Discharge planning for a child or young adult with technology dependence should include transportation to school, community programs, routine family activities, and scheduled or urgent medical services. Proximity (rural or urban), the child's mobility, weather, and the need for monitoring en route are other considerations. Adaptive car seats or car beds can be purchased. Personal vehicles may need expensive modifications, including lifts and power inverters. Allowances may also be required for one person to drive while another (i.e., nurse, parent, or care assistant) tends to the child. If traveling long distances, perhaps on vacation, advanced planning might include identification of hospitals along the route and reciprocal equipment companies to assist with unexpected supply needs.

Air transportation: If a family anticipates travel by plane, contingencies should be made for oxygen support at altitude, recognizing that most commercial airlines pressurize their cabins to the equivalent of 7,000-8,000 feet. Portable oxygen sources may have less liter flow capacity than stationary or home devices; there is also a need to differentiate continuous versus on-demand flow options. Space and limited supplies inflight should be considerations. Power wheelchairs are prone to damage when placed in cargo holds, and ground crews likely require explicit instructions. Providers may need to write letters for airport security and airlines for excess baggage, electronic equipment, medication, and fluid allowance. Families can also consider sending additional supplies to the final destination in advance.

Environmental stressors: Extreme temperatures, heat or cold, variability in humidity, and other environmental variables can greatly affect the well-being of a child with underlying cardiorespiratory insufficiency or other special healthcare needs. Home adaptations to permit climate control for the child's room may be required. Families may consider prewarming, or cooling, vehicles for routine excursions, and limitations on day-to-day activities are warranted at times. Augmented hydration needs should be reviewed with medical providers, along with routine sunscreen and preventive measures.

Preparation for transition to the homecare setting may include a period of quiescence, depending on the circumstances and family preferences. Establishing a period of stability, when there has been no need to alter supports, may minimize unplanned readmissions.

Community Resources

The transition from the acute care or rehabilitation facility to homecare setting is often much anticipated and welcomed. This step can also be frightening and overwhelming, whether it represents the first time home or a return after an acute illness or planned surgery. Hospital-based providers can partner with families to alleviate some anxiety and to avoid potential pitfalls through proactive engagement. Hand-off to outpatient and community stakeholders can include the following:

The community medical practice: Updates on problem lists, projected follow-up, medication and equipment needs, routine health maintenance and preventive measures (e.g., immunizations), special considerations for nutrition, identification of specialty providers and follow-up schedules, and case-specific risks.

First responders: Confirmation that the family has the capacity to call emergency services, outreach to police and ambulance services to outline baseline needs, special condition-specific interventions or precautions, identification of equipment that may need to be taken with the child in the event of an emergency, determination of emergency destination (i.e., local hospital or referral center), and clarification of resuscitation status and life-sustaining therapies.

Therapy programs: Physical, occupational, speech-language/feeding, and other therapists benefit from hospital-based assessments and outlines of expectations, restrictions, and uncertainties.

Educational programs/schools/day habilitation: Integration into community services requires evaluation of developmental needs and potential adaptive settings, equipment, services, staffing, and transportation for all ages.

Power and water: Alerting local housing, social, power, and water authorities to medical necessities can facilitate prioritization of service

restoration during natural disasters or other interruptions and identify programs to defray incurred costs with increased technology-driven electrical usage (e.g., home ventilators, oxygen concentrators, and climate control).

Families may find additional resources through faith-based institutions, nonprofit and advocacy groups (e.g., Kiwanis, Shriners, Boy Scouts), and condition-specific entities, such as the Muscular Dystrophy Association. Outreach to other families with similar circumstances can also be helpful with the caveat that their recommendations reflect their own goals and lived experience with special healthcare needs.

Subacute Care

Local resources for medical services should be identified in advance. This begins with the primary care and first responders but extends to local and regional hospitals. It is important to determine the range of services available and to identify specific providers who would familiarize themselves with a given case. The child with technology dependence will experience intercurrent illnesses or unexpected accidents that require evaluation, but may not always necessitate transport to tertiary care or referral centers. Individual care plans can be developed in conjunction with the family and local providers and may include thresholds for transfer.

Families should also consider bringing home equipment and supplies when presenting to urgent and acute care settings. Devices such as pediatric NIPPV masks and cough-assist machines or compounded medications may not be available at every facility. Short-term evaluations may become protracted, and lack of routine care provision may compound the immediate issues.

Emergency and Acute Care

Providers and families should acknowledge that children with special healthcare needs (CSHCN) and LMV are at risk for repeated hospitalization. Progression of underlying illnesses (e.g., heart failure), planned surgical interventions (e.g., spinal instrumentation, bronchoscopy surveillance, tendon releases), or superimposed acute illnesses (e.g., pneumonia, gastroenteritis, appendicitis, recurrent seizures) may necessitate readmission. Those children who are technology dependent have a higher likelihood of requiring critical care services because of the nature of their needs and their vulnerability. Preventable equipment-related issues may be obviated through the planning described previously. Once hospitalized, CSHCN are at greater risk of medical error and incur more interventions when compared with otherwise healthy children. Parents should be encouraged to develop a medical passport and reference list of providers to facilitate communication and consistency of care. Referencing established care guidelines and, again, developing individualized care plans may be helpful.

Quality of Life

CSHCN of increasing complexity and technology dependence are thriving in the homecare setting as a result of advances in medical care, shared decision-making, community services, and most notably, extensive, vigilant, and proactive care efforts by their families. Adaptations allow for participation in all aspects of family, school, and community activities. Although individual trajectory and subsequent needs may be difficult to predict, all stakeholders should acknowledge the impact of chronic care on the family unit and health-related quality of life. The evolution of a medical home for this cohort of children will require provisions for family mental health, sibling supports, respite, and other measures to optimize outcomes.

TRANSITIONING FROM ACUTE CARE TO REHABILITATION OR COMMUNITY SETTING

Disposition of children and young adults with LMV will vary based on their relative stability, local support services, and goals of care. A proactive, flexible, comprehensive care model is required to assure safe and effective provision. The impacts of care needs on the child and family are inextricably linked.

ROUTINE HEALTH MAINTENANCE

Airway Evaluation

There is no standard for regular airway assessment for children with LMV, specifically those with transtracheal support, but annual evaluation should represent the minimum. Office-based transtracheal tube endoscopy can facilitate assessment of tube upsizing for linear growth, presence of granulation tissue, airway inflammation, and general mucosal integrity. Formal diagnostic laryngoscopy and bronchoscopy under general anesthesia are required to assess for suprastomal and laryngeal-level pathology along with the rare acquired tracheaesophageal fistulae. Independent of routine evaluation, recurrent or unexpected tracheal bleeding may warrant evaluation for a tracheavascular fistula via CT angiogram and bronchoscopy.

Bacterial Colonization

Chronic respiratory failure lends itself to airway bacterial colonization because of alterations in secretion clearance, aerodigestive interactions, the presence of artificial airways with the development of biofilms, and other factors. Hydrophilic and gram-negative bacteria (e.g., *Pseudomonas, Serratia,* and *Stenotrophomonas*) are common. There is no standard of care for determining pathogenicity versus colonization. Use of systemic or inhaled antibacterial agents to decrease colonization load, frequency of tracheostomy tube exchanges to reduce biofilm accumulation, utility of viral screening, and threshold for treatment of an acute lower airway process or tracheitis is provider and case dependent. Providers should appreciate that recurrent empiric antibacterial treatment may select for resistant bacterial strains and has implications for enteric bacterial colonization.

Dental Care

Routine daily and office-based dental care should follow standard recommendations for all children. Extrapolation from the acute care setting and general population would suggest that oropharyngeal care and minimization of bacterial overgrowth would affect the risk of superimposed respiratory illness in LMV and long-term cardiovascular outcomes, respectively. Special consideration with respect to aspiration risk, developmental tolerance, and prophylaxis and procedural sedation for intervention may require engagement of specialty providers.

Immunizations

No immunizations are specifically indicated for individuals receiving LMV. Routine provision is recommended, including seasonal vaccinations for viral pathogens. Expansion of exposure precautions, as experienced during the COVID-19 pandemic, also remain essential.

Radiography, Laboratory, Polysomnography, and Pulmonary Function Testing

There are no recommendations for routine chest radiography, standard or cross-sectional, in the context of LMV. The cumulative radiation exposure would need to be considered. Gas exchange adequacy can often be assessed noninvasively. Venous, capillary, or arterial puncture for determining resting and long-term oxygenation and ventilation status may be of limited utility and validity, as intercurrent illness, technique with tourniquet, and associated agitation will alter results. Condition-specific (e.g., muscular dystrophy) recommendations for polysomnography, spirometry, or pulmonary function testing have been established and may be extrapolated with some validity. Regular assessment may also be helpful when gauging disease trajectory, LMV titration, safety parameters, and weaning potential.

LONG-TERM MECHANICAL VENTILATION WEANING AND TRACHEAL DECANNULATION

Reassessment of the role of LMV should be part of routine and family-centered care. Determination should include but is not limited to the factors described earlier with open discussion of goals of care, developmental appropriateness, physiologic and anatomic consideration, growth implications, new treatments, and contingencies. As there are currently no definitive conditioning regimens or LMV

weaning strategies, providers can determine the value of time off versus decreased level of supports as well as pragmatic considerations for the child and family. Continuity of care, however, holds implicit value. Monitoring provision may need to be increased during weaning.

If tracheal decannulation is required, a formal diagnostic laryngoscopy and bronchoscopy should be considered to rule out granulation (suprastomal and infrastomal) and dynamic airway collapse that may prohibit immediate tracheostomy tube removal. If positive pressure or oxygen supplementation will still be required after decannulation, determination of the child's tolerance of noninvasive ventilation or other interventions (e.g., cough assist) should be determined in advance. Desensitization may be required.

Ultimately, LMV has an increasing role in the support of children and young adults with chronic respiratory failure. Decision-making about any technology supports can be challenging from an emotional, practical, and ethical perspective. As families and other stakeholders explore options, the goal at these consequential junctures should be to align expectations, hopes, and potential lived experiences. Everyone should acknowledge the uncertainties and the potential to withhold, withdraw, and regularly reassess, even in the community setting. As this population of CSHCN and technology dependence ages, transition from pediatric to adult services should also be anticipated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

The Cardiovascular System

PART XVIII

Section 1

Developmental Biology of the Cardiovascular System

Chapter 469

Cardiac Development

Daniel Bernstein and William R. Goodyer

INTRODUCTION

Cardiac defects have traditionally been grouped by common morphologic patterns: for example, **abnormalities of the outflow tracts** (conotruncal lesions such as tetralogy of Fallot and truncus arteriosus) and **abnormalities of atrioventricular septation** (primum atrial septal defect, atrioventricular septal defect). These morphologic categories may be revised or eventually supplanted by new categories as our understanding of the genetic and molecular basis of congenital heart disease progresses.

469.1 Early Cardiac Morphogenesis

Daniel Bernstein and William R. Goodyer

In the early presomite embryo, the first identifiable cardiac progenitor cell clusters migrate from the primitive streak and are arranged in the anterior lateral plate mesoderm on both sides of the embryo's central axis in a horseshoe pattern, also known as the *cardiac crescent*. These cell clusters are marked by their expression of the basic helix-loop-helix (bHLH) transcription factor mesoderm posterior 1 (MESP1) and subsequently form paired cardiac tubes by 18 days of gestation. This *cardiac progenitor zone* is shaped by a balanced gradient of positive and negative signals arising from the tissues surrounding the cardiac mesodermal cells, with signals from the surrounding ventral/lateral tissues promoting cardiogenesis through signaling molecules such as bone morphogenetic protein (BMP), sonic hedgehog (SHH), and fibroblast growth factor 8 (FGF8) and signals from dorsal/medial structures such as members of the canonical Wnt/β-catenin pathway inhibiting cardiogenesis. Cardiogenic signals activate the genetic expression of cardiac-specific transcription factors (e.g., *TBX, GATA, NKX2.5*) to activate developmental cardiac gene expression The paired tubes fuse in the midline on the ventral surface of the embryo to form the primitive *heart tube* by 22 days. This straight heart tube is composed of an outer myocardial layer, an inner endocardium, and a middle layer of extracellular matrix (ECM) known as the *cardiac jelly*. There are two distinct cell lineages: the **first heart field** (regulated mainly by *NKX2.5*) provides precursor cells for the left ventricle and parts of the atria; the **second heart field** (regulated mainly by *ISL1*) provides precursors for the right ventricle, outflow tracts, and caudal aspects of the atria. Premyocardial cells, including epicardial cells and cells derived from the neural crest, continue their migration into the region of the heart tube. Regulation of this early phase of cardiac morphogenesis is controlled in part by the interaction of specific signaling molecules or ligands, usually expressed by one cell type, with specific receptors, usually expressed by another cell type. Positional information is conveyed to the developing cardiac mesoderm by factors such as *retinoids* (isoforms of vitamin A), which bind to specific nuclear receptors and regulate gene transcription. Migration of epithelial cells into the developing heart tube is directed by ECM proteins (e.g., fibronectin) that interact with cell surface receptors (the *integrins*). The clinical importance of these signaling pathways is revealed by the spectrum of **cardiac teratogenic effects** caused by the retinoid-like drug isotretinoin.

As early as 20-22 days, before cardiac looping, the embryonic heart begins to contract and exhibit phases of the cardiac cycle that are surprisingly similar to those in the mature heart. Morphologists initially identified segments of the heart tube that were believed to correspond to structures in the mature heart (Fig. 469.1). The *sinus venosus* (systemic venous system and part of right atrium), *primitive atrium* (right and left atria), *primitive ventricle* (left ventricle), and *bulbus cordis* that can be broken down into three sections (the proximal one third, right ventricle; mid-third, conus cordis to outflow tracts; and distal third, truncus arteriosus to aorta and pulmonary artery). However, this model is oversimplified. Only the **trabecular** (most heavily muscularized) portions of the left ventricular myocardium are present in the early cardiac tube; the cells that will become the inlet portion of the left ventricle migrate into the cardiac tube at a later stage (after looping is initiated). Even later to appear are the primordial cells that give rise to the great arteries (truncus arteriosus), including cells derived from the neural crest, which are not present until after cardiac looping is complete. Chamber-specific transcription factors participate in the differentiation of atria from ventricles and in the right and left ventricles. The bHLH transcription factor gene *(HAND2)* is expressed in the developing right ventricle. Disruption of this gene or of other transcriptional factors such as *MEF2c* in mice leads to hypoplasia of the right ventricle. Other genetic markers of the second heart field (early right ventricle) cells include *IRX4, TBX20, ISL1, TNNT2, MLC2v,* and *TBX1*. The transcription factor *HAND1* is expressed in the developing left ventricle and conotruncus and is also critical to their development. Other genetic markers of the first heart field (early left ventricle) cells include *TBX5, NKX2.5, TNNT2, MLC2v,* and *HCN4*.

One mechanism of how regulation of developmentally coordinated groups of genes is achieved is through the expression of small, noncoding RNAs known as **microRNAs**, each of which regulates the expression of multiple target genes. Another is through modifications in **chromatin**, the DNA scaffolding that acts as a controller of gene expression. Chromatin remodeling mediated by genes or enzymes such as *BRG1, CHD7,* histone demethylases, and methyltransferases is associated with cardiac developmental defects, including septal defects, dilated cardiomyopathy, and double-outlet right ventricle.

469.2 Cardiac Looping

Daniel Bernstein and William R. Goodyer

At approximately 22-24 days, the heart tube begins to bend ventrally and toward the right (see Fig. 469.1). The heart is the first organ to escape from the bilateral symmetry of the early embryo. An asymmetric signaling program that also affects the position of the lungs, liver, spleen, and gastrointestinal tract determines the direction of cardiac looping. During gastrulation, before organ formation begins, asymmetric expression of *SHH* and nodal (a member of the transforming growth factor beta [TGF-β] family) are directed in the lateral

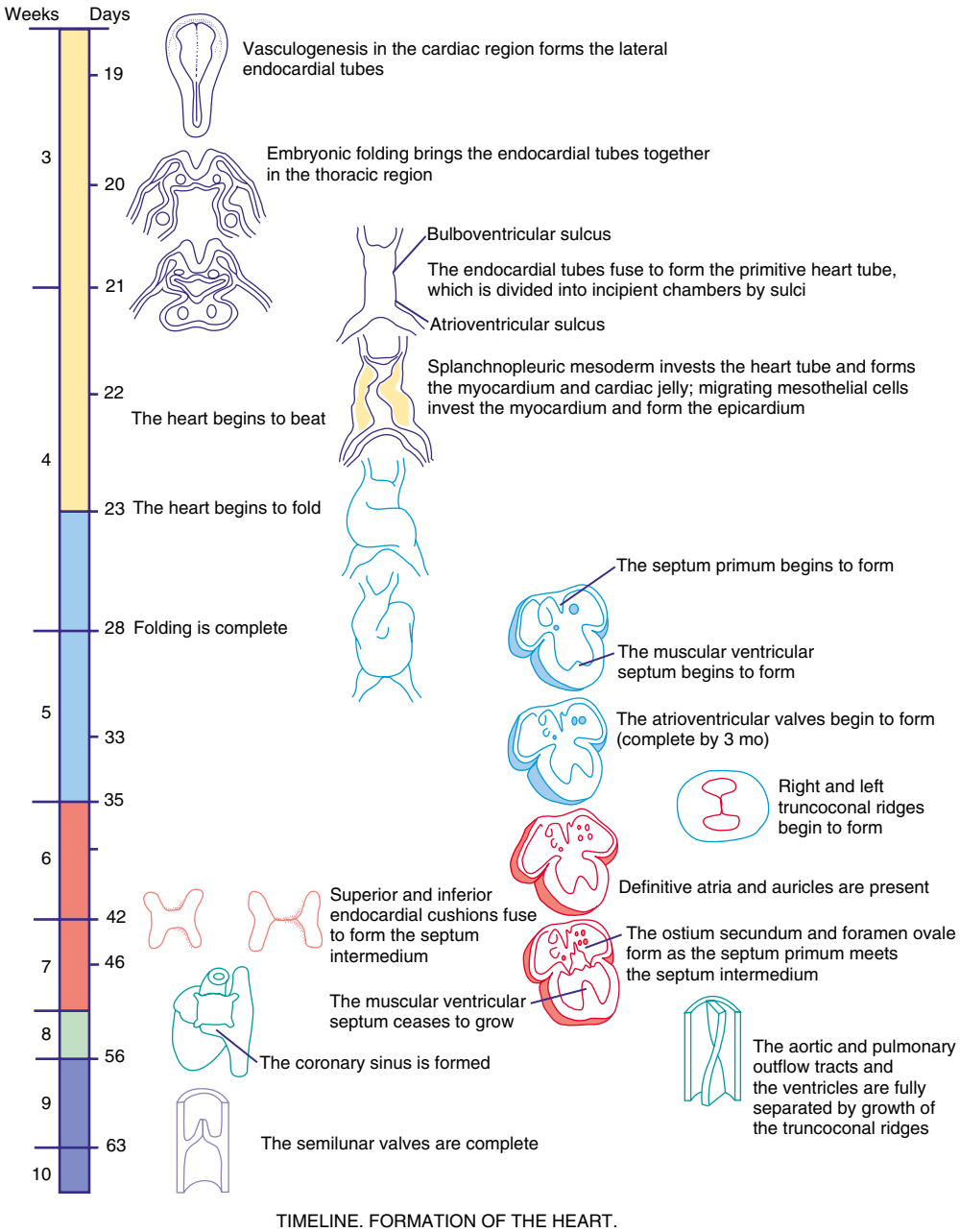

Fig. 469.1 Timeline of cardiac morphogenesis. *(From Larsen WJ. Essentials of Human Embryology. New York: Churchill Livingstone; 1998.)*

mesoderm. These directionality signals set up a concentration gradient between the right and left sides of the embryo in the expression of critical signaling molecules. This asymmetric signaling is then amplified and propagated through the transcription factor gene (*PITX2*), which is expressed on the left side of the early heart tube, *LEFTY1* and *left-right Dynein* (*LRD*). Interestingly, mice in which *LRD* has been inactivated display random left-right (L-R) orientation of the heart and abdominal viscera, with 50% of their hearts looping to the right and 50% looping to the left. Other potential mechanisms of cardiac looping include differential growth rates for myocytes on the convex versus the concave surface of the curve, differential rates of programmed cell death (apoptosis), and mechanical forces generated within myocardial cells at the inner and outer edges of the bending heart tube through their actin cytoskeleton.

Looping brings the future left ventricle leftward and in continuity with the sinus venosus (future left and right atria), whereas the future right ventricle is shifted rightward and in continuity with the truncus arteriosus (future aorta and pulmonary artery). This pattern of development explains the relatively common occurrence of the cardiac anomalies **double-outlet right ventricle** and **double-inlet left ventricle** and the extreme rarity of double-outlet left ventricle and double-inlet right ventricle (see Chapter 479.5). When cardiac looping is abnormal **(situs inversus**, **heterotaxia)**, the incidence of serious cardiac malformations is high, and there are usually associated abnormalities in the L-R patterning of the lungs and abdominal viscera, including absence of the spleen **(asplenia)** or multiple small spleens **(polysplenia)**.

469.3 Cardiac Septation

Daniel Bernstein and William R. Goodyer

When looping is complete, the external appearance of the heart is like that of a mature heart; internally, the structure resembles a single continuous tube, although it now has several bulges resulting in the appearance of primitive chambers. The common atrium (comprising both right and left atria) is connected to the primitive ventricle (future

left ventricle) via the atrioventricular canal. The primitive ventricle is connected to the *bulbus cordis* (future right ventricle) via the *bulboventricular foramen*. The distal portion of the bulbus cordis is connected to the *truncus arteriosus* via an outlet segment (the *conus*).

The heart tube now consists of several layers of myocardium and a single layer of endocardium separated by cardiac jelly (acellular ECM secreted by the myocardium). Septation of the heart begins at approximately day 26 with the ingrowth of large tissue masses, the *endocardial cushions,* at both the atrioventricular and conotruncal junctions (see Fig. 469.1). These cushions consist of protrusions of ECM (cardiac jelly), which, in addition to their role in development, also serve a physiologic function as primitive heart valves. Endocardial cells dedifferentiate and migrate into the cardiac jelly in the region of the endocardial cushions, eventually becoming mesenchymal cells (endothelial-mesenchymal transformation) that will form part of the atrioventricular valves. The endocardium, secondary heart field, and neural crest all contribute to the formation of the valve leaflets. Besides direct contribution to valve tissue, these progenitor cells also interact with each other and with other cells in the heart to orchestrate cardiac valve development.

Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions. Most of the atrioventricular valve tissue is derived from the ventricular myocardium in a process involving undermining of the ventricular walls. Because this process occurs asymmetrically, the tricuspid valve annulus sits closer to the apex of the heart than the mitral valve annulus. Physical separation of these two valves produces the atrioventricular septum, the absence of which is the primary common defect in patients with **atrioventricular canal defects** (see Chapter 475.5). If the process of undermining is incomplete, the right atrioventricular valve may not separate normally from the ventricular myocardium, a possible cause of **Ebstein anomaly** (see Chapter 479.7).

Septation of the atria begins at around 30 days with growth of the septum primum downward toward the endocardial cushions (see Fig. 469.1). The orifice that remains is the ostium primum. The endocardial cushions then fuse and, together with the completed septum primum, divide the atrioventricular canal into right and left segments. A second opening appears in the posterior portion of the septum primum, the ostium secundum, and it allows a portion of the fetal venous return to the right atrium to pass across to the left atrium. Finally, the septum secundum grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ridge of the ostium secundum forms the *foramen ovale,* through which fetal blood passes from the inferior vena cava to the left atrium (see Chapter 470).

Septation of the ventricles begins at about embryonic day 25 with protrusions of endocardium in both the inlet (primitive ventricle) and outlet (bulbus cordis) segments of the heart. The inlet protrusions fuse into the bulboventricular septum and extend posteriorly toward the inferior endocardial cushion, where they give rise to the inlet and trabecular portions of the interventricular septum. **Ventricular septal defects** can occur in any portion of the developing interventricular septum (see Chapter 475.6). The outlet or conotruncal septum develops from ridges of cardiac jelly, similar to the atrioventricular cushions. These ridges fuse to form a spiral septum that brings the future pulmonary artery into communication with the anterior and rightward right ventricle and the future aorta into communication with the posterior and leftward left ventricle. Differences in cell growth of the outlet septum lead to lengthening of the segment of smooth muscle beneath the pulmonary valve (conus), a process that separates the tricuspid and pulmonary valves. In contrast, disappearance of the segment beneath the aortic valve leads to fibrous continuity of the mitral and aortic valves. Within the lumen of distal outflow tract, local tissue swellings *(truncal cushions)* arise and are later populated by mesenchymal cells originating from the neural crest, participating in the formation of the semilunar (pulmonary and aortic) valves. Defects in these processes are responsible for **conotruncal** and **aortic arch defects** (truncus arteriosus, tetralogy of Fallot, pulmonary atresia, double-outlet right ventricle, interrupted aortic arch), a group of cardiac anomalies often associated with deletions of the **DiGeorge** critical region of **chromosome 22q11** (see Chapters 472 and 473). The transcription factor gene *(TBX1)* has been implicated as a candidate gene, which may be responsible for DiGeorge syndrome. Several genes have been implicated in valve formation, including *PTPN11,* which encodes the tyrosine phosphatase SHP-2, and when present in a mutated form, is one of the genes responsible for **Noonan syndrome**, associated with pulmonary valve stenosis, and *NOTCH1,* a regulator of cell differentiation associated with aortic valve disease.

469.4 Aortic Arch Development

Daniel Bernstein and William R. Goodyer

The aortic arch, head and neck vessels, proximal pulmonary arteries, and ductus arteriosus develop from the aortic sac, arterial arches, and dorsal aortae. When the straight heart tube develops, the distal outflow portion bifurcates into the right and left first aortic arches, which join the paired dorsal aortae (Fig. 469.2). The dorsal aortae will fuse to form the descending aorta. The proximal aorta from the aortic valve to the left carotid artery arises from the aortic sac. The first and second arches largely regress by about 22 days, with the first aortic arch giving rise to the maxillary artery and the second to the stapedial and hyoid arteries. The third arches participate in the formation of the innominate artery and the common and internal carotid arteries. The right fourth arch gives rise to the innominate and right subclavian arteries, and the left fourth arch participates in formation of the segment of the aortic arch between the left carotid artery and the ductus arteriosus. The fifth arch does not persist as a major structure in the mature circulation. The sixth arches join the more distal pulmonary arteries, with the right sixth arch giving rise to a portion of the proximal right pulmonary artery and the left sixth arch to the proximal left pulmonary artery and to the ductus arteriosus. The aortic arch between the ductus arteriosus and left subclavian artery is derived from the left-sided dorsal aorta, whereas the aortic arch distal to the left subclavian artery is derived from the fused right and left dorsal aortae. Abnormalities in development of the paired aortic arches are responsible for **right aortic arch**, **double aortic arch**, and **vascular rings** (see Chapter 481.1).

469.5 Cardiac Differentiation

Daniel Bernstein and William R. Goodyer

The process by which the totipotential cells of the early embryo become committed to specific cell lineages is termed *differentiation*. Precardiac mesodermal cells differentiate into mature cardiac muscle cells with an appropriate complement of cardiac-specific contractile elements, regulatory proteins, receptors, and ion channels. Expression of the contractile protein myosin occurs at an early stage of cardiac development, even before fusion of the bilateral heart primordia. Differentiation in these early mesodermal cells is regulated by signals from the anterior endoderm, a process known as *induction*. Several putative early signaling molecules include fibroblast growth factor, activin, and insulin. Signaling molecules interact with receptors on the cell surface; these receptors activate second messengers, which in turn activate specific nuclear transcription factor genes (*GATA-4, MEF2, NKX, bHLH,* and retinoic acid receptor family) that induce the expression of specific gene products to regulate cardiac differentiation. Some of the primary disorders of cardiac muscle, the **cardiomyopathies**, may be related to defects in some of these signaling molecules (see Chapter 488).

Developmental processes are chamber specific. Early in development, ventricular myocytes express both ventricular and atrial isoforms of several proteins, such as atrial natriuretic peptide (ANP) and myosin light chain (MLC). Mature ventricular myocytes do not express ANP and express only a ventricular-specific MLC 2v isoform, whereas mature atrial myocytes express ANP and an atrial-specific MLC 2a isoform. Heart failure (see Chapter 491), volume overload (see Chapters 475 and 477), and pressure overload hypertrophy (see Chapter 476)

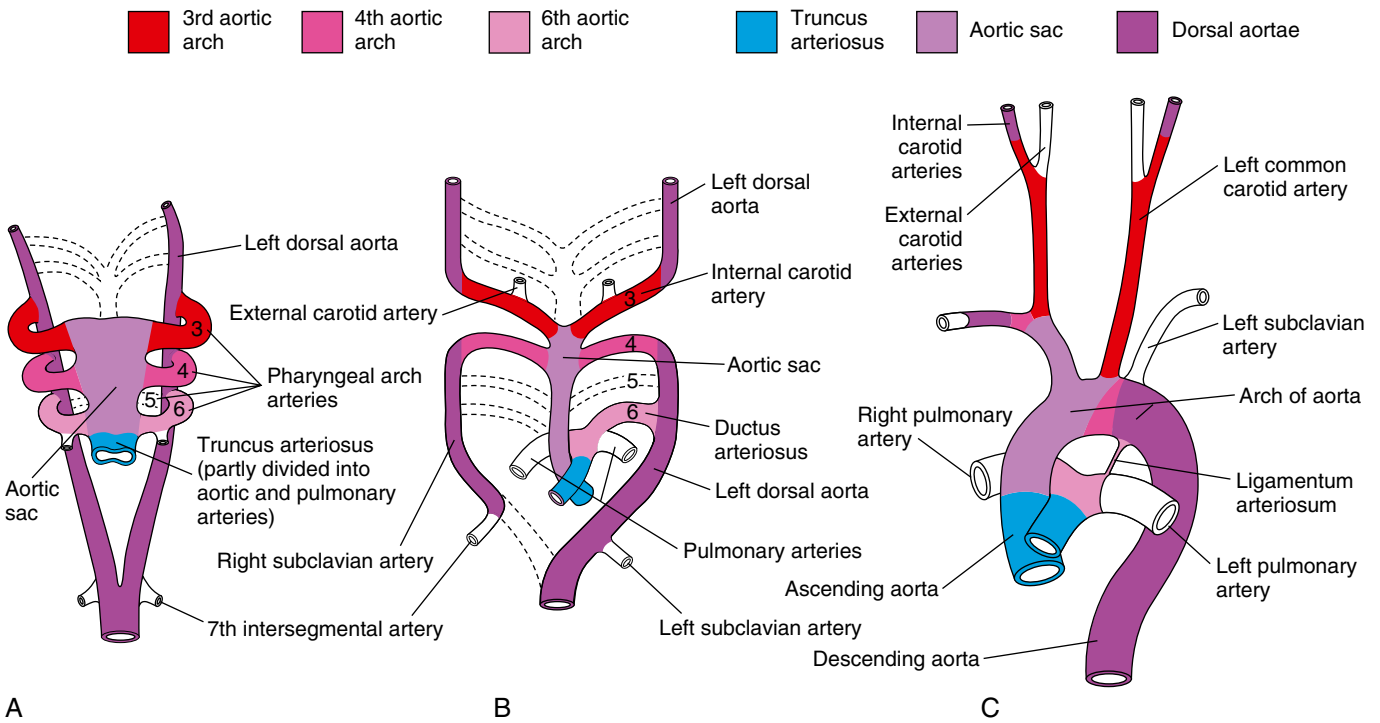

Fig. 469.2 Schematic drawings illustrating the changes that result during transformation of the truncus arteriosus, aortic sac, aortic arches, and dorsal aortae into the adult arterial pattern. The vessels that are *not* shaded or colored are not derived from these structures. **A,** Aortic arches at 6 weeks; by this stage, the first two pairs of aortic arches have largely disappeared. **B,** Aortic arches at 7 weeks; the parts of the dorsal aortae and aortic arches that normally disappear are indicated by *broken lines*. **C,** Arterial vessels of 6-mo-old infant. *(From Moore KL, Persaud TVN, Torchia M. The Developing Human. Philadelphia: Elsevier; 2007.)*

are associated with a recapitulation of fetal cell phenotypes in which mature myocytes re-express fetal proteins. Because different isoforms have different contractile behavior (fast vs slow activation, high vs low adenosine triphosphatase activity), expression of different isoforms may have important functional consequences.

469.6 Developmental Changes in Cardiac Function

Daniel Bernstein and William R. Goodyer

During development, the composition of the myocardium undergoes profound changes that result in an increase in the number and size of myocytes. During prenatal life, this process involves myocyte division **(hyperplasia)**, whereas after the first few postnatal weeks, subsequent cardiac growth occurs mostly by an increase in myocyte size **(hypertrophy)**. The myocytes themselves change shape from round to cylindrical, the proportion of myofibrils (which contain the contractile apparatus) increases, and the myofibrils become more regular in their orientation.

The *plasma membrane* (known as the *sarcolemma* in myocytes) is the location of the ion channels and transmembrane receptors that regulate the exchange of chemical information from the cell surface to the cell interior. Ion fluxes through these channels control the processes of depolarization and repolarization. Developmental changes have been described for the sodium-potassium pump, the sodium-hydrogen exchanger, and voltage-dependent calcium channels. As the myocyte matures, extensions of the sarcolemma develop toward the interior of the cell (the T-tubule system), which dramatically increases its surface area and enhances rapid activation of the myocyte. Regulation of the membrane's α- and β-adrenergic receptors with development enhances the ability of the sympathetic nervous system to control cardiac function as the heart matures.

The *sarcoplasmic reticulum* (SR), a series of tubules surrounding the myofibrils, is the principal mediator of the intracellular calcium concentration. Calcium release to the myofibrils for initiation of contraction is mediated by the ryanodine receptor (RYR), and calcium reuptake for initiation of relaxation is mediated by the sarcoplasmic reticulum calcium ATPase (SERCA). This SR calcium transport system is less well developed in immature hearts, which thus depend more on transport of calcium from outside the cell for contraction. In a mature heart, the majority of the calcium required for contraction comes from within the cardiomyocyte via the SR. This developmental phenomenon may explain the sensitivity of the infant heart to sarcolemmal calcium channel blockers such as verapamil, which can result in a marked depression in contractility (see Chapter 484).

The major contractile proteins (myosin, actin, tropomyosin, and troponin) are organized into the functional unit of cardiac contraction, the *sarcomere*. Each has several isoforms that are expressed differentially by location (atrium vs ventricle) and by developmental stage (embryo, fetus, newborn, adult).

Changes in myocardial structure and myocyte biochemistry result in easily quantifiable differences in cardiac function with development. Fetal cardiac function is less responsive to changes in preload (filling volume). Thus the most effective means of increasing cardiac output in the fetus is through increasing the heart rate. After birth and with further maturation, preload and afterload play an increasing role in regulating cardiac function. The rate of cardiac relaxation is also developmentally regulated. The decreased ability of the immature SR calcium pump (SERCA) to remove calcium from the contractile apparatus is manifested as a decreased ability of the fetal heart to enhance relaxation in response to sympathetic stimulation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 470

The Fetal to Neonatal Circulatory Transition

Daniel Bernstein

470.1 The Fetal Circulation

Daniel Bernstein

The transition from the fetal to the postnatal circulation represents one of the most dramatic circulatory adaptations at any time of life. In the fetal circulation, the right and left ventricles exist in a parallel circuit, as opposed to the series circuit of the newborn or adult (Fig. 470.1A). In the fetus, the placenta provides for gas and metabolite exchange. Because the lungs do not provide gas exchange, blood is diverted away from the pulmonary circulation, which is vasoconstricted. Three cardiovascular structures unique to the fetus are important for maintaining this parallel circulation: the *ductus venosus, foramen ovale,* and *ductus arteriosus.*

The placenta is not as efficient an oxygen-exchange organ as the lungs, so that umbilical venous partial pressure of oxygen (Po_2), the highest O_2 level provided to the fetus, is only 30-35 mm Hg. Approximately 50% of the umbilical venous blood enters the hepatic circulation, whereas the rest bypasses the liver and joins the inferior vena cava (IVC) via the ductus venosus, where it partially mixes with poorly oxygenated IVC blood derived from the lower part of the fetal body. This combined lower body plus umbilical venous blood flow (Po_2 of 26-28 mm Hg) enters the right atrium and is preferentially directed by a flap of tissue at the right atrium–IVC junction, the eustachian valve, across the foramen ovale to the left atrium (see Fig. 470.1B). This is the major source of left ventricular (LV) blood flow in the fetus, because pulmonary venous return from the vasoconstricted lungs is minimal. LV blood is then ejected into the ascending aorta, where it supplies predominantly the fetal upper body and brain.

Fetal superior vena cava (SVC) blood, which is considerably less oxygenated (Po_2 of 12-14 mm Hg) than IVC blood, enters the right atrium and preferentially flows across the tricuspid valve, rather than the foramen ovale, into the right ventricle. From the right ventricle, this blood is ejected into the pulmonary artery. Because the pulmonary arterial circulation is vasoconstricted, only approximately 5% of right ventricular (RV) outflow enters the lungs. The major portion of this blood bypasses the lungs and flows right to left through the ductus arteriosus into the descending aorta to perfuse the lower part of the fetal body, including providing flow to the placenta via the two umbilical arteries. Thus the upper part of the fetal body (including the coronary and cerebral arteries and those to the upper extremities) is perfused exclusively from the left ventricle with blood that has a slightly higher Po_2 than the blood perfusing the lower part of the fetal body, which is derived mostly from the right ventricle. Only a small volume of blood from the ascending aorta (10% of fetal cardiac output) flows all the way around the aortic arch (aortic isthmus) to the descending aorta.

The **total fetal cardiac output**—the combined output of both the left and right ventricles—is approximately 450 mL/kg/min. Approximately 65% of descending aortic blood flow returns to the placenta; the remaining 35% perfuses the fetal organs and tissues. In the human fetus, RV output is approximately 1.3 times LV flow. Thus during fetal life the right ventricle is not only pumping against the higher systemic blood pressure but also performing slightly greater volume work than the left ventricle. This results in the RV wall being as thick (hypertrophied) as the LV wall during fetal and immediate neonatal life, explaining the unique features of the neonatal electrocardiogram (showing what would be read as *right ventricular hypertrophy* in an adult).

Blood flow is believed to be an important determinant of growth of fetal cardiac chambers, valves, and blood vessels. Thus in the presence of a narrowing (stenosis) of an upstream structure such as the mitral valve, flow downstream into the left ventricle is limited and LV growth may be compromised, which may be one of the mechanisms of **hypoplastic left heart syndrome** (HLHS; see Chapter 480.10). Similarly, stenosis of a downstream structure such as the aortic valve can also disrupt flow into the LV and contribute to HLHS. Fetal cardiac interventional treatments, currently experimental, are aimed at opening stenotic aortic valves in mid-gestation fetuses and allowing more normal LV growth. However, the outcome of these procedures does not enhance LV growth in all patients, suggesting that in the majority of cases of HLHS there is a different mechanism, suspected to be a defect in the LV cardiomyocytes themselves (i.e., a cell-autonomous defect).

470.2 The Transitional Circulation

Daniel Bernstein

At birth, mechanical expansion of the lungs and an increase in arterial Po_2 result in a rapid decrease in pulmonary vascular resistance (PVR). Concomitantly, removal of the low-resistance placental circulation leads to an increase in systemic vascular resistance (SVR). The output from the right ventricle now flows entirely into the pulmonary circulation, and because PVR becomes lower than SVR, the shunt through the ductus arteriosus reverses and becomes left to right. Over several days the high arterial Po_2 constricts and eventually closes the ductus arteriosus, which eventually becomes the ligamentum arteriosum. The increased volume of pulmonary blood flow returning to the left atrium from the lungs increases left atrial volume and pressure sufficiently to close the flap of the foramen ovale functionally, although the foramen may remain patent on probing with a catheter for several years. A patent foramen ovale can be a source of embolic stroke in later life.

Removal of the placenta from the circulation also results in closure of the ductus venosus. The left ventricle is now coupled to the high-resistance systemic circulation, and its wall thickness and mass begin to increase. In contrast, the right ventricle is now coupled to the low-resistance pulmonary circulation, and its wall thickness and mass decrease. The left ventricle, which in the fetus pumped blood only to the upper part of the body and brain, must now deliver the entire systemic cardiac output (approximately 350 mL/kg/min), an almost 200% increase in output. This marked increase in LV performance is achieved through a combination of hormonal and metabolic signals, including an increase in the level of circulating catecholamines and in the density of myocardial β-adrenergic receptors, through which catecholamines have their effect.

When superimposed on these dramatic physiologic changes, congenital structural cardiac defects often impede this smooth transition and greatly increase the burden on the newborn myocardium. Importantly, because the ductus arteriosus and foramen ovale do not close completely at birth, they can provide a lifesaving pathway for blood to bypass a congenital defect (the patent ductus arteriosus in tetralogy of Fallot, pulmonary atresia, coarctation of aorta or HLHS; the foramen ovale in transposition of the great vessels). Alternatively, persistent fetal pathways can present an additional stress to the circulation (patent ductus arteriosus in the premature infant). Therapeutic agents can be used to either maintain these fetal pathways open (e.g., *prostaglandin E_1*) or hasten their closure (e.g., *indomethacin*). This pharmacology explains why indomethacin and similar drugs are contraindicated or used with extreme caution during the third trimester.

470.3 The Neonatal Circulation

Daniel Bernstein

At birth, the fetal circulation must immediately adapt to extrauterine life as gas exchange is transferred from the placenta to the lungs (see

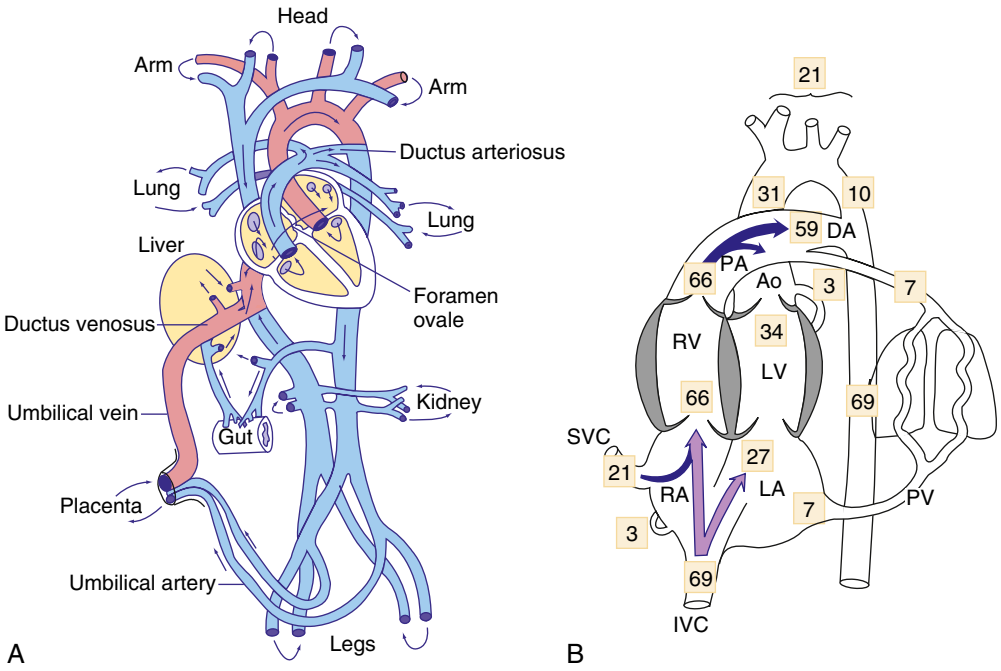

Fig. 470.1 A, The human circulation before birth (partly after Dawes). *Red* indicates more highly oxygenated blood, and *arrows* indicate the direction of flow. More highly oxygenated blood from the placenta passes through the foramen ovale from the right to the left atrium, thus bypassing the lungs. B, Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels. Figures are those obtained from studies of late-gestation fetal lambs. Ao, Aorta; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. *(From Rudolph AM. Congenital Diseases of the Heart. Chicago: Year Book; 1974.)*

Chapter 124). Some of these changes are virtually instantaneous with the first breath, whereas others develop over hours or weeks. With the onset of breathing and lung ventilation, pulmonary vascular resistance is greatly decreased because of both active (i.e., Po_2-metabolic-related) and passive (i.e., mechanical stretch-related) pulmonary vasodilation. In a normal neonate, closure of the ductus arteriosus and the fall in PVR decreases pulmonary arterial and RV pressures. The largest decline in PVR from the high fetal levels to the lower "adult" levels in the human infant usually occurs within 2-3 days, but may be prolonged for ≥7 days after birth. However, over the next several weeks of life, PVR continues to decrease further, now secondary to physical remodeling of the pulmonary vasculature, including thinning of vascular smooth muscle and recruitment of new vessels. This decrease in PVR significantly influences the timing of the clinical appearance of many congenital heart lesions dependent on the relative levels of SVR and PVR. For example, the left-to-right shunt through a large ventricular septal defect (VSD) may be minimal in the first week after birth, when PVR is still high. As PVR decreases in the next 1-2 weeks, the volume of the left-to-right shunt through the VSD increases and eventually leads to the signs and symptoms of heart failure.

There are several significant differences between the neonatal circulation and that of older infants: (1) right-to-left or left-to-right shunting may persist across the patent foramen ovale; (2) in the presence of cardiopulmonary disease, continued patency of the ductus arteriosus may allow left-to-right, right-to-left, or bidirectional shunting; (3) the neonatal pulmonary vasculature constricts more vigorously in response to hypoxemia, hypercapnia, and acidosis; (4) the wall thickness and muscle mass of the neonatal left and right ventricles are almost equal; and (5) newborn infants at rest have a relatively high oxygen consumption, associated with a relatively high cardiac output. The newborn cardiac output, indexed to body weight (200 mL/kg/min), falls in the first 2 months of life to approximately 150 mL/kg/min and then more gradually to the normal adult cardiac output of 75 mL/kg/min. Although fetal hemoglobin is beneficial to delivery of oxygen in the low-Po_2 fetal circulation, the high percentage of fetal hemoglobin present in the newborn may actually interfere with delivery of oxygen to tissues in the high-systemic Po_2 neonatal circulation, and therefore adult hemoglobin production begins immediately (see Chapter 124).

The foramen ovale is usually functionally closed by the third month of life, although it is possible to pass a catheter through the overlapping flaps in a large percentage of children and in 15–25% of adults. Functional closure of the ductus arteriosus is usually complete by 10-15 hours of postnatal age in a normal neonate, although the ductus may remain patent much longer in the presence of congenital heart disease, especially when associated with cyanosis. In premature newborn infants, a systolic murmur with late accentuation or a continuous murmur may be audible beneath the left clavicle, and in the context of respiratory distress syndrome, the presence of a patent ductus arteriosus should be suspected (see Chapter 126.1).

The normal ductus arteriosus differs morphologically from the adjoining aorta and pulmonary artery in that the ductus has a significant amount of circularly arranged smooth muscle in its medial layer. During fetal life, patency of the ductus arteriosus appears to be maintained by the combined relaxant effects of low oxygen tension and endogenously produced prostaglandins, specifically prostaglandin E_2. In a full-term neonate, oxygen is the most important factor controlling ductal closure. When the Po_2 of the blood passing through the ductus reaches about 50 mm Hg, the ductal wall begins to constrict. The effects of oxygen on ductal smooth muscle may be direct or mediated by its effects on prostaglandin synthesis. Gestational age also appears to play an important role; the ductus of a premature infant is less responsive to oxygen, even though its musculature is well developed.

470.4 Persistent Pulmonary Hypertension of the Neonate (Persistence of Fetal Circulatory Pathways)

See Chapter 130.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

Evaluation of the Cardiovascular System and the Child with a Heart Murmur

Chapter 471

History and Physical Examination in Cardiac Evaluation

Daniel Bernstein

One of the most common reasons for cardiac evaluation in young children is the heart murmur; **innocent or functional murmurs (Still murmurs)** may be heard in up to 30% of patients at some time during childhood. Functional murmurs are usually accentuated by fever and first noticed during a visit for an intercurrent illness. Thus the general pediatrician must be able to distinguish those murmurs that are functional from those that are potentially pathologic and refer patients with pathologic-sounding murmurs or murmurs of uncertain nature for evaluation by a pediatric cardiologist.

Patients may require further laboratory evaluation (e.g., electrocardiogram and echocardiogram), or the family may be reassured that no significant problem exists. Although the ready availability of echocardiography may entice the clinician to skip a good history and physical exam, an initial evaluation by a skilled cardiologist is preferred for several reasons: (1) a cardiac examination allows the cardiologist to guide the echocardiographic evaluation toward confirming or eliminating specific diagnoses, thereby increasing its accuracy; (2) because most childhood murmurs are innocent, evaluation by a pediatric cardiologist can eliminate unnecessary and expensive laboratory tests; and (3) the cardiologist's knowledge and experience are important in reassuring the patient's family and preventing unnecessary, and all too common, restrictions on healthy physical activity. An experienced pediatric cardiologist can differentiate an innocent murmur from serious congenital heart disease by history and physical examination alone with high sensitivity and specificity.

HISTORY

The evaluation begins with a comprehensive cardiac history because a diagnosis of a functional murmur can only be made in the absence of any concerning symptoms, signs, or family history. A comprehensive cardiac history starts with details of the perinatal period, including the presence of cyanosis, respiratory distress, or prematurity. **Maternal complications** such as gestational diabetes, teratogenic medications, infections, systemic lupus erythematosus, or substance misuse can be associated with cardiac problems. If cardiac symptoms began during infancy, the timing of the initial symptoms should be noted to provide important clues about the specific cardiac condition.

Many of the symptoms of **heart failure** in infants and children are age specific. In infants, feeding difficulties are common. Inquiry should be made about the frequency of feeding and either the volume of each feeding or the time spent on each breast. An infant with heart failure often takes less volume per feeding and becomes dyspneic or diaphoretic while nursing. After falling asleep exhausted, the baby, inadequately fed, will awaken for the next feeding after a brief time. This cycle continues around the clock and must be carefully differentiated from colic or other feeding disorders. Additional symptoms and signs include those of respiratory distress: rapid breathing, nasal flaring, cyanosis, and chest retractions. In older children, heart failure may be manifested as exercise intolerance, difficulty keeping up with peers during sports or the need for a nap after coming home from school, poor growth, or chronic abdominal complaints. Eliciting a history of fatigue in an older child requires questions about age-specific activities, including stair climbing, walking, bicycle riding, physical education class, and competitive sports; information should be obtained regarding more severe manifestations such as orthopnea and nocturnal dyspnea.

Parents often overlook their baby's **cyanosis** at rest; it may be mistaken for a normal individual variation in color. Cyanosis during crying or exercise, however, is more often noted as abnormal by observant parents. Many infants and toddlers turn "blue around the lips" when crying vigorously or during breath-holding spells; this condition must be carefully differentiated from **cyanotic heart disease** by inquiring about inciting factors, the length of episodes, and whether the tongue and mucous membranes also appear cyanotic. Newborns often have cyanosis of their extremities **(acrocyanosis)** when undressed and cold; this response to cold must be carefully differentiated from true cyanosis, where the mucous membranes are also blue.

Chest pain is an unusual manifestation of cardiac disease in pediatric patients, although it is a frequent cause for referral to a pediatric cardiologist, especially in adolescents. Nonetheless, a careful history, physical examination, and, if indicated, laboratory or imaging tests will assist in identifying the cause of chest pain (Table 471.1). For patients with some forms of repaired congenital heart disease (CHD), for example, those with surgery on the aortic root or those with a history of Kawasaki disease (see Chapter 493.1), chest pain should be evaluated carefully for a coronary etiology.

Cardiac disease may be a manifestation of a known congenital malformation syndrome with typical physical findings (Table 471.2) or a manifestation of a generalized disorder affecting the heart and other organ systems (Table 471.3). **Extracardiac malformations** may be noted in 20–45% of infants with CHD. Between 5% and 10% of patients have a known chromosomal abnormality. Specific gene or whole exome sequencing can enhance the diagnostic approach to CHD (Fig. 471.1).

A careful family history may also reveal early (at age <50 years) coronary artery disease or stroke (suggestive of familial hypercholesterolemia or thrombophilia), sudden death (suggestive of cardiomyopathy or familial arrhythmic disorder), generalized muscle disease (suggestive of one of the muscular dystrophies, dermatomyositis, or familial or metabolic cardiomyopathy), or first-degree relatives with CHD.

GENERAL PHYSICAL EXAMINATION

In the evaluation of a child with a heart murmur, a general physical examination is always performed, with specific attention directed toward the presence of cyanosis, abnormalities in growth, chest wall abnormalities, and any evidence of respiratory distress. Although the murmur may be the most prominent part of the overall examination, any murmur must be placed in context of other physical findings. Associated findings such as quality of the pulses, presence of a ventricular heave or thrill, or splitting of the second heart sound provide important clues to a specific cardiac diagnosis.

Accurate measurement of height and weight and plotting on a standard growth chart are important because both cardiac failure and chronic cyanosis can result in failure to thrive. Growth failure is manifested predominantly by poor weight gain; if length and especially head circumference is also affected, additional congenital malformations or metabolic disorders should be suspected.

Mild cyanosis may be too subtle for early detection, and clubbing of the fingers and toes is not usually manifested until late in the first year of life, even in the presence of severe arterial oxygen desaturation. Cyanosis is best observed over the nail beds, lips, tongue, and mucous membranes. Delayed recognition of cyanosis in infants with darker skin color

Table 471.1 Differential Diagnosis of Chest Pain in Pediatric Patients

MUSCULOSKELETAL (COMMON)
Trauma (accidental, abuse)
Exercise, overuse injury (strain, bursitis)
Costochondritis
Tietze syndrome
Herpes zoster (cutaneous or without rash)
Pleurodynia
Fibrositis
Slipping rib
Rib fracture
Precordial catch
Sickle cell anemia vasoocclusive crisis
Osteomyelitis (rare)
Primary or metastatic tumor (rare)
Fibromyalgia
Nerve entrapment, radiculopathy
PULMONARY (COMMON)
Pneumonia
Pleurisy
Pleurodynia
Asthma
Chronic cough
Pneumothorax
Infarction (sickle cell anemia)
Foreign body
Embolism (rare)
Pulmonary hypertension (rare)
Tumor (rare)
Bronchiectasis
GASTROINTESTINAL (LESS COMMON)
Esophagitis (gastroesophageal reflux, infectious, pill)
Esophageal foreign body
Esophageal spasm
Cholecystitis
Subdiaphragmatic abscess
Perihepatitis (Fitz-Hugh-Curtis syndrome)
Peptic ulcer disease
Pancreatitis
Splenic rupture
CARDIAC (LESS COMMON)
Pericarditis
Postpericardiotomy syndrome
Endocarditis
Myocarditis
Cardiomyopathy
Mitral valve prolapse
Aortic or subaortic stenosis
Arrhythmias (supraventricular, ventricular, tachycardias)
Marfan syndrome (dissecting aortic aneurysm)
Kawasaki disease
Cocaine, sympathomimetic ingestion
Ischemia (familial hypercholesterolemia, anomalous coronary artery, post-repair of congenital heart disease involving reimplantation of the coronary arteries [e.g., d-transposition of the great arteries])
Takotsubo cardiomyopathy (primary or secondary)
IDIOPATHIC (COMMON)
Anxiety, hyperventilation
Panic disorder
OTHER (LESS COMMON)
Spinal cord or nerve root compression
Breast-related pathologic condition (mastalgia)
Castleman disease (lymph node neoplasm)

can lead to delayed treatment and poorer outcomes. Careful observation of the color of the tongue, mucous membranes, and nail beds, where cyanosis is most noticeable, is critical in recognizing cyanosis in these patients. Confirmation with pulse oximetry is easily performed.

Differential cyanosis, manifested as blue lower extremities and pink upper extremities (usually the right arm), is seen with right-to-left shunting across a ductus arteriosus in the presence of coarctation or an interrupted aortic arch. Circumoral cyanosis or blueness around the forehead may be the result of prominent venous plexuses in these areas, rather than decreased arterial oxygen saturation. The extremities of infants often turn blue when the infant is unwrapped and cold (acrocyanosis), and this condition can be distinguished from central cyanosis by examination of the tongue and mucous membranes.

Heart failure in infants and children usually results in some degree of hepatomegaly and occasionally splenomegaly. The sites of **peripheral edema** are age dependent. In infants, edema is usually seen around the eyes and over the flanks, especially on initially waking. Older children and teenagers manifest both periorbital edema and pedal edema. An initial complaint in these older patients may be that their clothes are now too tight.

The **heart rate** of newborn infants is rapid and subject to wide fluctuations (Table 471.4). The average rate ranges from 120 to 140 beats/min and may increase to 170+ beats/min during crying and activity or drop to 70-90 beats/min during sleep. As the child grows older, the average pulse rate decreases and may be as low as 40 beats/min at rest in very athletic adolescents. Persistent **tachycardia** (>200 beats/min in neonates, 150 beats/min in infants, or 120 beats/min in older children), bradycardia, or an irregular heartbeat other than sinus arrhythmia requires investigation to exclude pathologic arrhythmias (see Chapter 484). **Sinus arrhythmia** can usually be distinguished by the rhythmic nature of the heart rate variations, occurring in concert with the respiratory cycle, with a P wave before every QRS complex, and a normal p-wave axis.

Careful evaluation of the character of the **pulses** is an important early step in the physical diagnosis of CHD. A wide pulse pressure with bounding pulses may suggest an aortic runoff lesion such as patent ductus arteriosus (PDA), aortic insufficiency, an arteriovenous communication, or increased cardiac output secondary to anemia, anxiety, or conditions associated with increased catecholamine or thyroid hormone secretion. The presence of diminished pulses in all extremities is associated with pericardial tamponade, left ventricular outflow obstruction, or cardiomyopathy. The radial and femoral pulses should always be palpated simultaneously. Normally, the femoral pulse should be appreciated immediately before the radial pulse. In infants with coarctation of the aorta, the femoral pulses may be decreased. However, in older children with coarctation of the aorta, blood flow to the descending aorta may channel through collateral vessels and results in the femoral pulse being palpable but delayed until after the radial pulse **(radial-femoral delay)**.

Blood pressure (BP) should be measured in either leg and in the right arm to be certain that coarctation of the aorta is not overlooked. Palpation of the femoral or dorsalis pedis pulse, or both, is not reliable alone to exclude coarctation because collaterals may have developed. Most commonly, BP is measured using an automated oscillatory device, but it is often necessary for the physician to manually recheck BP by auscultation. In older children, a cuff that covers approximately two thirds of the upper part of the arm or leg should be used for BP measurement. A cuff that is too small results in falsely high readings, whereas a cuff that is too large records slightly decreased BP. Pediatric clinical facilities should be equipped with 3-, 5-, 7-, 12-, and 18-cm cuffs to accommodate the large spectrum of pediatric patient sizes. When auscultating blood pressure directly, the first Korotkoff sounds indicate systolic pressure. As cuff pressure is slowly decreased, the sounds usually become muffled before they disappear. Diastolic pressure may be recorded when the sounds become muffled (preferred) or when they disappear altogether; the former is usually slightly higher and the latter slightly lower than true diastolic pressure. For lower-extremity BP determination, the stethoscope is placed over the popliteal artery. Typically, the BP recorded in the legs with the cuff technique is approximately 10 mm Hg higher than that in the arms. In infants, BP can be determined by auscultation or palpation.

BP varies with the age of the child and is closely correlated to height and weight. Significant increases occur during adolescence, and many temporary variations take place before the more stable levels of adult life are attained. Exercise, excitement, coughing, crying, and struggling may raise the systolic BP of infants and children as much as 40-50 mm Hg greater than their usual levels. Variability in BP in children of

Table 471.2 Congenital Malformation Syndromes Associated with Congenital Heart Disease

SYNDROME	FEATURES
CHROMOSOMAL DISORDERS	
Trisomy 21 (Down syndrome)	Endocardial cushion defect, VSD, ASD
Trisomy 21p (cat-eye syndrome)	Miscellaneous, total anomalous pulmonary venous return
Trisomy 18	VSD, ASD, PDA, TOF, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 13	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 9	Miscellaneous, VSD
XXXXY	PDA, ASD
Penta X	PDA, VSD
Triploidy	VSD, ASD, PDA
XO (Turner syndrome)	Bicuspid aortic valve, coarctation of aorta
Fragile X	Mitral valve prolapse, aortic root dilatation
Duplication 3q2	Miscellaneous
Deletion 4p	VSD, PDA, aortic stenosis
Deletion 9p	Miscellaneous
Deletion 5p (cri du chat syndrome)	VSD, PDA, ASD, TOF
Deletion 10q	VSD, TOF, conotruncal lesions*
Deletion 13q	VSD
Deletion 18q	VSD
Deletion 1p36	ASD, VSD, PDA, TOF, cardiomyopathy
Deletion/duplication 1q21.1	ASD, VSD, PS
Deletion 17q11 (William syndrome)	Supravalvar AS, branch PS
Deletion 11q 24-25 (Jacobsen syndrome)	VSD, left sided lesions
SYNDROME COMPLEXES	
CHARGE association (*c*oloboma, *h*eart, *a*tresia choanae, *r*etardation, *g*enital, and *e*ar anomalies)	VSD, ASD, PDA, TOF, endocardial cushion defect
DiGeorge sequence, CATCH 22 (*c*ardiac defects, *a*bnormal facies, *t*hymic aplasia, *c*left palate, *h*ypocalcemia, and deletion 22q11)	Aortic arch anomalies, conotruncal anomalies
Alagille syndrome (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, PS, TOF
VATER association (vertebral, *a*nal, *t*racheo*e*sophageal, *r*adial, and *r*enal anomalies)	VSD, TOF, ASD, PDA
FAVS (*f*acio*a*uriculo*v*ertebral *s*pectrum)	TOF, VSD
CHILD (congenital *h*emidysplasia with *i*chthyosiform erythroderma, *l*imb *d*efects)	Miscellaneous
Mulibrey nanism (muscle, liver, brain, eye)	Pericardial thickening, constrictive pericarditis
Asplenia syndrome	Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve
Polysplenia syndrome	Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve
PHACE syndrome (*p*osterior brain fossa anomalies, facial *h*emangiomas, *a*rterial anomalies, *c*ardiac anomalies and aortic coarctation, *e*ye anomalies)	VSD, PDA, coarctation of aorta, arterial aneurysms
TERATOGENIC AGENTS	
Congenital rubella	PDA, peripheral pulmonic stenosis
Fetal hydantoin syndrome	VSD, ASD, coarctation of aorta, PDA
Fetal alcohol syndrome	ASD, VSD

Continued

Table 471.2 Congenital Malformation Syndromes Associated with Congenital Heart Disease—cont'd

SYNDROME	FEATURES
Fetal valproate effects	Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of aorta
Retinoic acid embryopathy	Conotruncal anomalies
OTHERS	
Apert syndrome	VSD
Autosomal dominant polycystic kidney disease	Mitral valve prolapse
Carpenter syndrome	PDA
Conradi syndrome	VSD, PDA
Crouzon disease	PDA, coarctation of aorta
Cutis laxa	Pulmonary hypertension, pulmonic stenosis
De Lange syndrome	VSD
Ellis–van Creveld syndrome	Single atrium, VSD
Holt-Oram syndrome	ASD, VSD, first-degree heart block
Infant of diabetic mother	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Kartagener syndrome	Dextrocardia
Meckel-Gruber syndrome	ASD, VSD
Noonan syndrome	Pulmonic stenosis, ASD, cardiomyopathy
Pallister-Hall syndrome	Endocardial cushion defect
Primary ciliary dyskinesia	Heterotaxia disorders
Rubinstein-Taybi syndrome	VSD
Scimitar syndrome	Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava
Smith-Lemli-Opitz syndrome	VSD, PDA
TAR syndrome (thrombocytopenia and absent radius)	ASD, TOF
Treacher Collins syndrome	VSD, ASD, PDA

*Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.
ASD, Atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

approximately the same age and body build should be expected, and at least three serial measurements on different dates should be obtained when confirming the diagnosis of hypertension (Figs. 471.2 and 471.3).

Although of little use in infants, in cooperative older children, inspection of the **jugular venous pulse** wave provides information about central venous and right atrial pressure. The neck veins should be inspected with the patient sitting at a 90-degree angle. The external jugular vein should not be visible above the clavicles unless central venous pressure is elevated. Increased venous pressure transmitted to the internal jugular vein may appear as venous pulsations without visible distention; such pulsation is not seen in normal children reclining at an angle of 45 degrees. Because the great veins are in direct communication with the right atrium, changes in pressure and the volume of this chamber are also transmitted to the veins. The one exception occurs in superior vena cava obstruction, in which venous pulsatility is lost.

CARDIAC EXAMINATION

The heart should be examined in a systematic manner, starting with inspection and palpation. Any abnormalities on inspection and/or palpation strongly suggest a pathologic rather than a functional etiology of any heart murmur. A **precordial bulge** to the left of the sternum with or without increased precordial activity suggests cardiac enlargement, especially in younger children where the chest wall is still relatively flexible; such bulges can often best be appreciated by having the child lay supine with the examiner looking up from the child's feet. A **substernal heave** indicates the presence of right ventricular hypertrophy or enlargement, whereas an **apical heave** is noted with left ventricular hypertrophy or enlargement. An overall **hyperdynamic precordium** suggests a volume load such as that found with a large left-to-right shunt, although it may be normal in a thin patient. An overly silent precordium with a barely detectable apical impulse suggests a large pericardial effusion or severe cardiomyopathy but may be normal in an obese patient.

The relationship of the **apical impulse** to the midclavicular line is also helpful in the estimation of cardiac size: the apical impulse shifts laterally and inferiorly with enlargement of the left ventricle. Right-sided apical impulses signify dextrocardia, tension pneumothorax, or left-sided thoracic space-occupying lesions (e.g., diaphragmatic hernia).

Thrills are the palpable equivalent of murmurs and correlate with the area of maximal auscultatory intensity of the murmur. It is important to palpate the suprasternal notch and neck for aortic bruits, which may indicate the presence of aortic stenosis. Right lower sternal border and apical systolic thrills are characteristic of ventricular septal defect (VSD) and mitral insufficiency, respectively. Diastolic thrills are occasionally palpable in the presence of atrioventricular valve stenosis. The timing and localization of thrills should be carefully noted. Although the presence of a thrill is usually linked to a murmur of grade IV or greater, after a patient has had cardiac surgery, the presence of scar within the chest may eliminate the ability to feel a thrill even with a very loud murmur.

Table 471.3 Cardiac Manifestations of Systemic Diseases

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
INFLAMMATORY DISORDERS	
Sepsis	Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension
COVID-19	Myocarditis, multisystem inflammatory syndrome in children (MIS-C)
Juvenile idiopathic arthritis	Pericarditis, rarely myocarditis
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary atherosclerosis (with steroids), congenital heart block
Scleroderma	Pulmonary hypertension, myocardial fibrosis, cardiomyopathy
Dermatomyositis	Cardiomyopathy, arrhythmias, heart block
Kawasaki disease	Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency
Sarcoidosis	Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias
Lyme disease	Arrhythmias, myocarditis
Löffler hypereosinophilic syndrome	Endomyocardial disease
INBORN ERRORS OF METABOLISM	
Refsum disease	Arrhythmia, sudden death
Hunter or Hurler syndrome	Valvular insufficiency, heart failure, hypertension
Fabry disease	Mitral insufficiency, coronary artery disease with myocardial infarction
Glycogen storage disease IIa (Pompe disease)	Short P-R interval, cardiomegaly, heart failure, arrhythmias
Carnitine deficiency	Heart failure, cardiomyopathy
Gaucher disease	Pericarditis
Homocystinuria	Coronary thrombosis
Alkaptonuria	Atherosclerosis, valvular disease
Morquio-Ullrich syndrome	Aortic incompetence
Scheie syndrome	Aortic incompetence
CONNECTIVE TISSUE DISORDERS	
Arterial calcification of infancy	Calcinosis of coronary arteries, aorta, heart failure, hypertension
Marfan syndrome	Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse
Congenital contractural arachnodactyly	Mitral insufficiency or prolapse
Ehlers-Danlos syndrome	Mitral valve prolapse, dilatated aortic root
Osteogenesis imperfecta	Aortic incompetence
Pseudoxanthoma elasticum	Peripheral arterial disease
NEUROMUSCULAR DISORDERS	
Friedreich ataxia	Cardiomyopathy
Duchenne dystrophy	Cardiomyopathy, heart failure
Tuberous sclerosis	Cardiac rhabdomyoma
Familial deafness	Occasionally arrhythmia, sudden death
Neurofibromatosis	Pulmonic stenosis, pheochromocytoma, coarctation of aorta
Riley-Day syndrome	Episodic hypertension, postural hypotension
Von Hippel-Lindau disease	Hemangiomas, pheochromocytomas
ENDOCRINE-METABOLIC DISORDERS	
Graves disease	Tachycardia, arrhythmias, heart failure
Hypothyroidism	Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrocardiogram
Pheochromocytoma	Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy
Carcinoid	Right-sided endocardial fibrosis

Continued

Table 471.3 Cardiac Manifestations of Systemic Diseases—cont'd

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
HEMATOLOGIC DISORDERS	
Sickle cell anemia	High-output heart failure, cardiomyopathy, pulmonary hypertension
Thalassemia major	High-output heart failure, hemochromatosis
Hemochromatosis (first or second degree)	Cardiomyopathy
OTHERS	
Appetite suppressants (fenfluramine and dexfenfluramine)	Cardiac valvulopathy, pulmonary hypertension
Cockayne syndrome	Atherosclerosis
Jervell and Lange-Nielsen syndrome	Prolonged Q-T interval, sudden death
Kearns-Sayre syndrome	Heart block
LEOPARD syndrome (lentiginosis)	Pulmonic stenosis, prolonged Q-T interval
Progeria	Accelerated atherosclerosis
Osler-Weber-Rendu disease	Arteriovenous fistula (lung, liver, mucous membrane)
Romano-Ward syndrome	Prolonged Q-T interval, sudden death
Weill-Marchesani syndrome	Patent ductus arteriosus
Werner syndrome	Vascular sclerosis, cardiomyopathy

LEOPARD, Multiple *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth, *s*ensorineural *d*eafness.

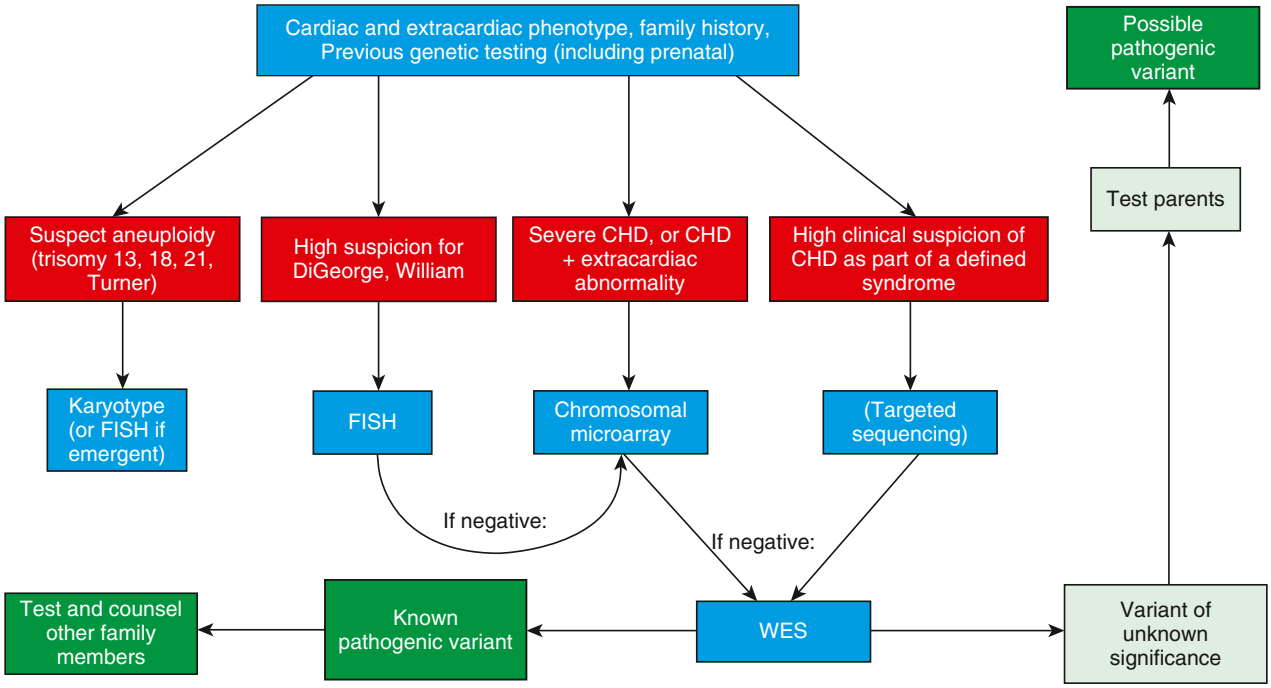

Fig. 471.1 Genetics screening algorithm for congenital heart disease (CHD) patients. FISH, Fluorescence in situ hybridization; WES, whole exome sequencing. *(From Simmons MA, Brueckner M. The genetics of congenital heart disease . . . understanding and improving long-term outcomes in congenital heart disease: a review for the general cardiologist and primary care physician. Curr Opin Pediatr. 2017;29:520–528, Fig 2.)*

Auscultation is an art that improves with practice. The diaphragm of the stethoscope is placed firmly on the chest for high-pitched sounds; a lightly placed bell is optimal for low-pitched sounds. The physician should initially move the stethoscope across the chest, concentrating on the characteristics of the heart sounds; their variation with respiration; and the presence of clicks, rubs, or gallops. Repeat the process, concentrating on murmurs, their maximum location, and their radiation. In some CHDs, such as atrial septal defect (ASD), the murmur is nonspecific and sounds identical to many functional murmurs; it is the abnormality of the second heart sound that points to a pathologic condition. The patient should ideally be supine, lying quietly, and breathing normally. The **first heart sound** (S_1) is best heard at the apex, whereas the **second heart sound** (S_2) should be evaluated at the upper left and right sternal borders. S_1 is caused by closure of the atrioventricular valves (mitral and tricuspid) and can be either single or split. S_2 is caused by closure of the semilunar valves (aortic and pulmonary) (Fig. 471.4). During inspiration, the decrease in intrathoracic pressure results in increased filling of the right side of the heart, which leads to

Table 471.4 Pulse Rates at Rest

AGE	LOWER LIMITS OF NORMAL (beats/min)		AVERAGE (beats/min)		UPPER LIMITS OF NORMAL (beats/min)	
Newborn	70		125		190	
1-11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	75		100		115	
8 yr	70		90		110	
10 yr	70		90		110	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90

an increased right ventricular ejection time and thus delayed closure of the pulmonary valve; inspiration decreases pulmonary venous return, decreasing filling of the left ventricle and moving closure of the aortic valve earlier. Consequently, **splitting of the second heart sound** widens during inspiration and narrows during expiration.

S_2 can appear to be single during expiration, because we can only hear two sounds if they are separated by 20-30 msec. The presence of a normally split S_2 is strong evidence against the diagnosis of ASD, defects associated with pulmonary arterial hypertension, severe pulmonary valve stenosis, aortic and pulmonary atresia, and truncus arteriosus. Wide S_2 splitting is noted in ASD, pulmonary stenosis (where the pulmonary second sound is soft), Ebstein anomaly, total anomalous pulmonary venous return, and right bundle branch block. An accentuated pulmonic component of S_2 with narrow splitting is a sign of pulmonary hypertension. A single S_2 occurs in pulmonary or aortic atresia or severe stenosis, truncus arteriosus, and, often, transposition of the great arteries.

A **third heart sound** (S_3) is best heard with the bell at the apex in mid-diastole, during passive ventricular filling. An S_3 can be pathologic but may be normal in children, often accentuated in patients with fever and tachycardia. A **fourth heart sound** (S_4), occurring in conjunction with atrial systole and the final stages of ventricular filling, may be heard just before the S_1 in late diastole. An S_4 is always pathologic and an indication of decreased ventricular compliance, as occurs in patients with ventricular dysfunction (e.g., in dilated cardiomyopathy). An S_3 may merge with an S_4, a finding known as a **summation gallop**.

Ejection clicks, which are heard in early systole, are usually caused by a mildly to moderately stenotic aortic or pulmonary valve or to a dilated ascending aorta or pulmonary artery. They are heard so close to S_1 that they may be mistaken for a split S_1. However, ejection clicks are heard at the upper left or right sternal borders, whereas a split S_1 is heard at the lower left sternal border or apex. **Aortic** ejection clicks are best heard at the left middle to right upper sternal border and are constant in intensity. They occur in conditions where the aortic valve (mild to moderate aortic stenosis) is stenotic or the aorta is dilated (e.g., tetralogy of Fallot, truncus arteriosus). **Pulmonary** ejection clicks are associated with mild to moderate pulmonary stenosis and are best heard at the left middle to upper sternal border and vary with respiration, often disappearing with inspiration. A good place to hear ejection clicks is right over the sternum, since bone conducts high-frequency sound much better than the muscle of the intercostal spaces. A midsystolic click heard at the apex, often preceding a late systolic murmur, suggests mitral valve prolapse.

Murmurs should be described according to their intensity, pitch, timing (systolic or diastolic), variation in intensity, time to peak intensity, location of maximal intensity, and radiation to other areas. Auscultation for murmurs should be carried out starting at the upper right sternal border then moving slowly across the upper precordium, down the left and right sternal borders, and out to the apex and to the left axilla. Auscultation should also always be performed in the right axilla and over both sides of the back, as many CHD murmurs radiate to these locations. Systolic murmurs are classified as ejection, holosystolic or pansystolic, or late systolic according to the timing of the murmur in relation to S_1 and S_2. The intensity of systolic murmurs is graded from I to VI: **I**, barely audible; **II**, medium intensity; **III**, loud but no thrill; **IV**, loud with a thrill; **V**, very loud but still requiring positioning of the stethoscope at least partly on the chest; and **VI**, so loud that the murmur can be heard with the stethoscope off the chest. In patients who have undergone prior heart surgery, a murmur of grade IV or greater may be heard in the absence of a thrill because of scar tissue, which does not transmit vibrations well, within the chest.

Systolic ejection murmurs start a short time after a well-heard S_1, increase in intensity, peak, and then decrease in intensity; they usually end before S_2. In patients with severe pulmonary stenosis, however, the murmur may extend beyond the first component of S_2, thus obscuring it. **Pansystolic or holosystolic murmurs** begin simultaneously with S_1 and continue throughout systole, on occasion becoming gradually decrescendo. It is important to remember that after closure of the atrioventricular valves (S_1), a brief period occurs during which ventricular pressure increases but the semilunar valves remain closed (isovolumic contraction; see Fig. 471.4). Thus holosystolic murmurs (heard during both isovolumic contraction and the ejection phases of systole) cannot be caused by flow across the semilunar valves because these valves are closed during isovolumic contraction! Holosystolic murmurs must therefore be related to blood exiting the contracting ventricle via either an abnormal opening (VSD) or atrioventricular (mitral or tricuspid) valve insufficiency. Systolic ejection murmurs usually imply increased flow or stenosis across one of the ventricular outflow tracts (aortic or pulmonic). In infants with rapid heart rates, it is often difficult to distinguish between ejection and pansystolic murmurs. If a clear and distinct S_1 can be appreciated, the murmur is most likely ejection in nature.

A **continuous murmur** is a murmur that continues from systole into diastole and indicates continuous flow, such as in the presence of a PDA or other aortopulmonary communication. This murmur should be differentiated from a **to-and-fro murmur**, where the systolic component of the murmur ends at or before S_2 and the diastolic murmur begins after S_2 with semilunar valve closure (aortic stenosis and insufficiency; pulmonary stenosis and insufficiency). A **late systolic murmur** begins well beyond S_1 and continues until the end of systole and is usually heard after a midsystolic click in patients with mitral valve prolapse and insufficiency.

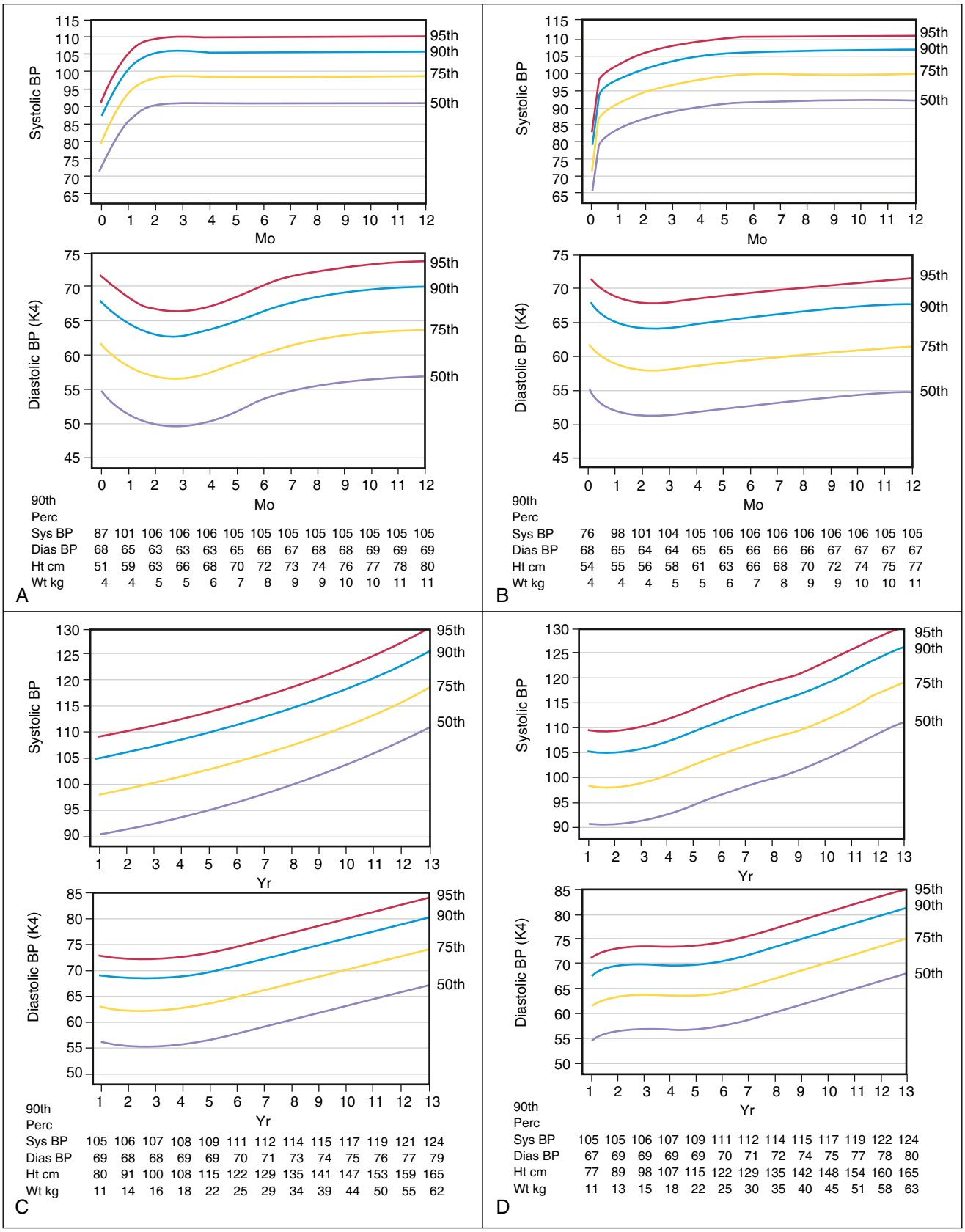

Fig. 471.2 Age-specific percentiles of blood pressure (BP) measurements: birth to 13 yr. **A,** Males from birth to 12 mo of age. **B,** Females from birth to 12 mo of age. **C,** Males 1-13 yr of age. **D,** Females 1-13 yr of age. Korotkoff phase IV (K4) used for diastolic BP. Dias, Diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987. National Heart, Lung, and Blood Institute, Bethesda, MD. Pediatrics. 1987;79:1–25. Copyright 1987 by the American Academy of Pediatrics.)*

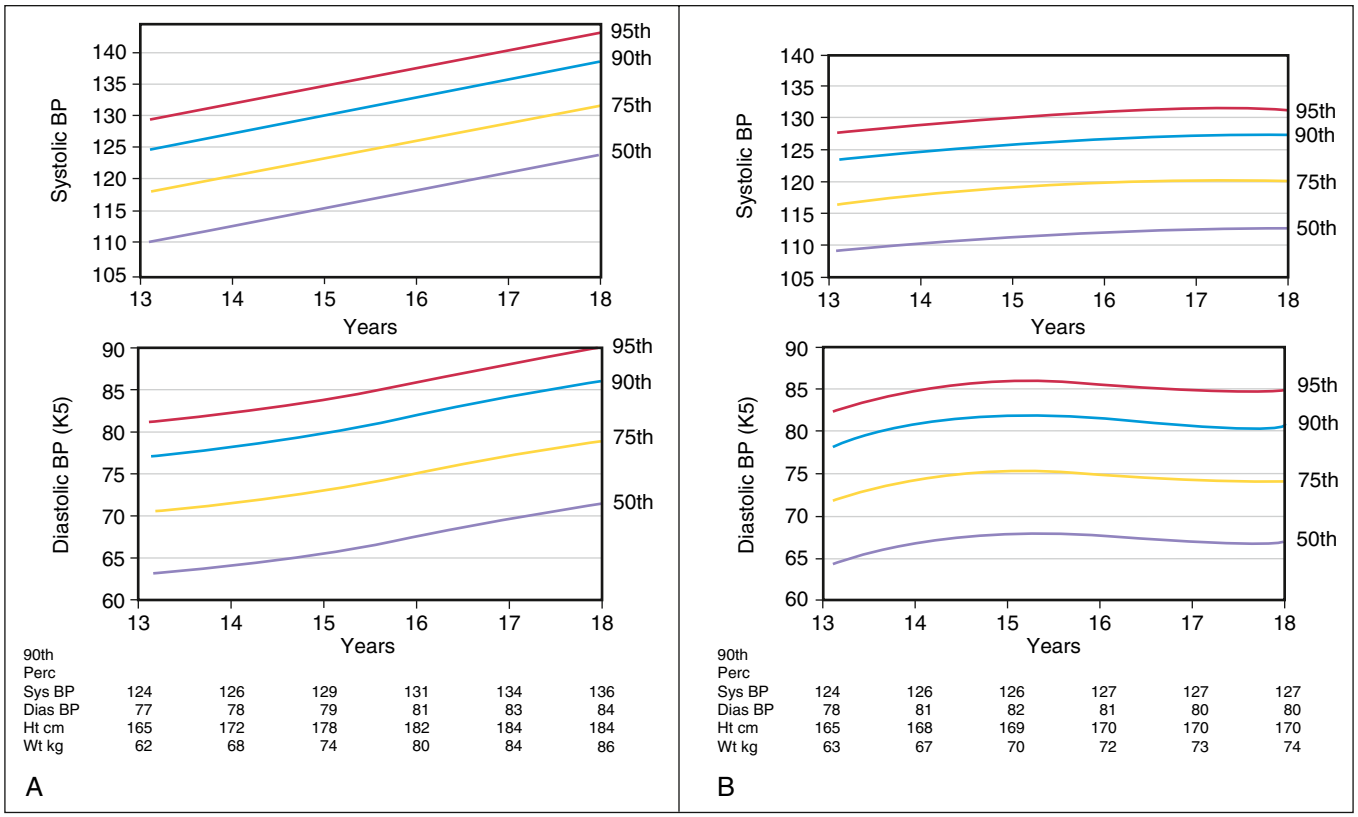

Fig. 471.3 Age-specific percentiles of blood pressure (BP) measurements: age 13-18 yr. **A**, Males 13-18 yr of age. **B**, Females 13-18 yr of age. Korotkoff phase V (K5) used for diastolic BP. Dias, Diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987, National Heart, Lung, and Blood Institute, Bethesda, MD. Pediatrics. 1987;79:1–25. Copyright 1987 by the American Academy of Pediatrics.)*

Several types of **diastolic murmurs** (graded I-IV) can be identified. A **decrescendo diastolic murmur** is a blowing murmur usually along the left sternal border that begins with S_2 and diminishes toward mid-diastole. When louder and high-pitched, this murmur is usually associated with aortic valve insufficiency or pulmonary insufficiency related to pulmonary hypertension. When softer and low-pitched, this murmur is usually associated with pulmonary valve insufficiency in the absence of pulmonary hypertension. A to-and-fro murmur is typically noted after surgical repair of the pulmonary outflow tract in patients with tetralogy of Fallot. A **rumbling mid-diastolic murmur** at the left mid and lower sternal border may be caused by increased blood flow across the tricuspid valve, such as occurs with ASD or, much less often, because of actual stenosis of this valve. When this murmur is heard at the apex, it is caused by increased flow across the mitral valve, such as occurs with large left-to-right shunts at the ventricular level (VSDs), at the great vessel level (PDA, aortopulmonary shunts), or with increased flow because of mitral insufficiency. When an apical diastolic rumbling murmur is longer and is accentuated at the end of diastole (presystolic), it usually indicates anatomic mitral valve stenosis.

The absence of a precordial murmur does not rule out significant congenital or acquired heart disease. Congenital heart defects, some of which are ductal dependent, may not demonstrate a murmur if the ductus arteriosus closes. These lesions include pulmonary or tricuspid valve atresia and transposition of the great arteries. Murmurs may seem insignificant in patients with ASDs, anomalous pulmonary venous return, some forms of atrioventricular septal defects, coarctation of the aorta, or anomalous origin of a coronary artery. Careful attention to other components of the physical examination (growth failure, cyanosis, peripheral pulses, precordial impulse, heart sounds) increases the index of suspicion of congenital heart defects in these patients. In contrast, loud murmurs may be present in the absence of structural heart disease, for example, in patients with a large noncardiac arteriovenous malformation, mitral regurgitation caused by left ventricular dilation associated with myocarditis or cardiomyopathy, and severe anemia.

Many murmurs are not associated with significant hemodynamic abnormalities. These murmurs are referred to as *functional, normal, insignificant,* or *innocent*. During routine random auscultation, >30% of children may have an innocent murmur at some time in their lives; this percentage increases when auscultation is done under nonbasal circumstances (high cardiac output because of fever, infection, or anxiety). The most common **innocent murmur** is a medium-loud, medium-pitched, vibratory or "musical," relatively short *systolic ejection murmur,* which is heard best along the left sternal border and has no significant radiation to the apex, base, or back. It is heard most frequently in children between 3 and 7 years of age. The intensity of the murmur often changes with respiration and position and may be attenuated or even disappear in the sitting or prone position. Innocent *pulmonic* murmurs are also common in children and adolescents and originate from normal turbulence during ejection into the pulmonary artery. These are higher pitched, brief, early systolic murmurs of grades I-II in intensity and are best heard in the second left parasternal space with the patient in the supine position. Features suggestive of heart disease include murmurs that are holosystolic, grade III or higher, harsh, located at the left upper sternal border, and associated with an early or midsystolic click or an abnormal S_2.

A **venous hum** is another example of a common innocent murmur heard during childhood. Venous hums are produced by turbulence of blood in the jugular venous system; they have no pathologic significance and may be heard in the neck or anterior portion of the upper part of the chest. Appreciated as a soft humming sound heard in both systole and diastole, it can be exaggerated or made to disappear by

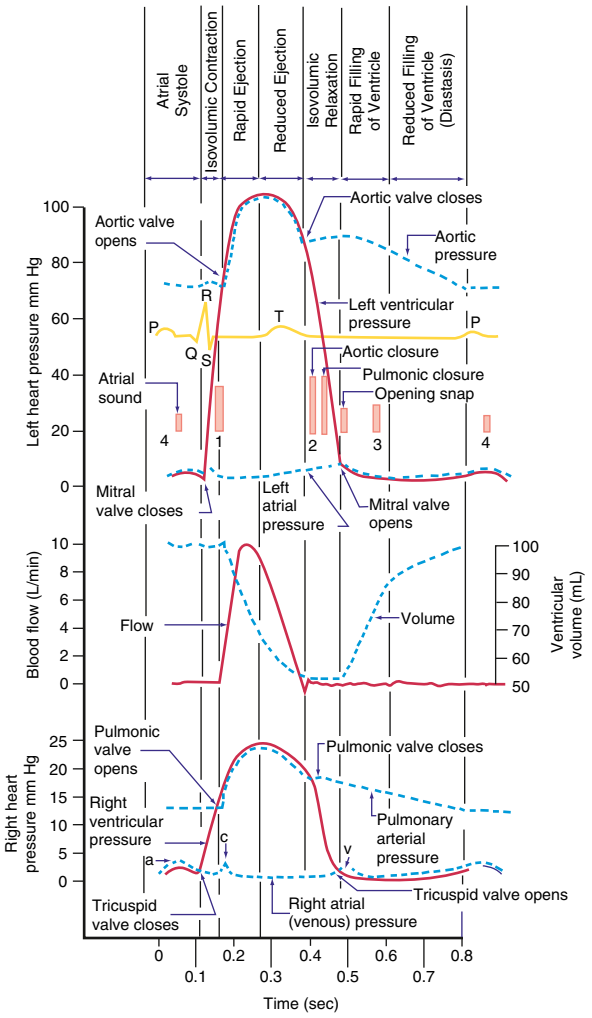

Fig. 471.4 Idealized diagram of the temporal events of a cardiac cycle (the Wiggers diagram).

varying the position of the head, or it can be decreased by lightly compressing the jugular venous system in the neck. These simple maneuvers are sufficient to differentiate a venous hum from the murmurs produced by organic cardiovascular disease, particularly a PDA.

The lack of significance of an innocent murmur should be discussed with the child's parents. It is important to offer complete reassurance because lingering doubts about the importance of a cardiac murmur may have profound effects on child-rearing practices, most often in the form of overprotectiveness. An underlying fear that a cardiac abnormality is present may negatively affect a child's self-image and development. The physician should explain that an innocent murmur is simply a "noise" and does not indicate the presence of a cardiac defect. When asked, "Will it go away?" the best response is to state that because the murmur has no clinical significance, it does not matter whether it "goes away." Parents should be warned that the intensity of the murmur might increase during febrile illnesses, a time when, typically, another physician may examine the child (e.g., in the emergency department). With growth, however, innocent murmurs are less well heard and often disappear completely. If there is a suspicion of structural heart disease, additional studies are indicated to rule out a congenital heart defect. However, "routine" electrocardiographic, chest radiographic, and echocardiographic examinations should be avoided in well children with a clearly innocent murmur.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 472

Laboratory Cardiac Evaluation

Daniel Bernstein

472.1 Radiologic Cardiac Assessment

Daniel Bernstein

Despite the widespread easy access to advanced imaging techniques, such as echocardiography, computed tomography (CT) scan, and magnetic resonance imaging (MRI), the chest x-ray film remains a highly valuable diagnostic tool and is often the first imaging study performed in a child suspected of having a cardiac defect. It can provide important information about cardiac size and shape, pulmonary blood flow (vascularity), pulmonary edema, and associated lung and thoracic anomalies that may be associated with congenital syndromes (e.g., skeletal dysplasias, extra or deficient number of ribs, abnormal vertebrae, diaphragmatic hernia, previous cardiac surgery). Combined with a careful physical examination, the chest radiograph can help the clinician to establish a diagnosis of congenital heart disease (CHD), as opposed to pulmonary disease, and to narrow the differential diagnosis to specific categories of CHD (e.g., left-to-right shunt lesions vs obstructive lesions).

The most frequently used measurement of cardiac size is the maximal width of the cardiac shadow in a posteroanterior (PA) chest film taken mid-inspiration. A vertical line is drawn down the middle of the sternal shadow, and perpendicular lines are drawn from the sternal line to the extreme right and left borders of the heart; the sum of the lengths of these lines is the **maximal cardiac width**. The **maximal chest width** is obtained by drawing a horizontal line between the right and left inner borders of the rib cage at the level of the top of the right diaphragm. When the maximal cardiac width is more than half the maximal chest width (cardiothoracic ratio >50%), the heart is usually enlarged. Cardiac size should be evaluated only when the film is taken during inspiration with the patient in an upright position, which can be difficult to achieve in younger patients. A diagnosis of "cardiac enlargement" on expiratory or prone films is a common cause of unnecessary referrals and laboratory studies.

The **cardiothoracic ratio** is a less useful index of cardiac enlargement in infants than in older children because the horizontal position of the heart may increase the ratio to about 60% in the absence of true enlargement. Furthermore, the thymus may overlap not only the base of the heart but also virtually the entire mediastinum, thus obscuring the true cardiac silhouette.

A *lateral* chest radiograph may be helpful in infants and in older children with pectus excavatum or other conditions that result in a narrow anteroposterior (AP) chest dimension. The heart may appear small in the lateral view and suggest that the apparent enlargement in the PA projection was caused by either the thymus (anterior mediastinum only) or flattening of the cardiac chambers as a result of a structural chest abnormality.

In the PA view, the left border of the cardiac shadow consists of three convex shadows produced, from above downward, by the aortic knob, the main and left pulmonary arteries, and the left ventricle (Fig. 472.1). In cases of moderate to marked left atrial enlargement, the atrium may be visualized between the pulmonary artery and the left ventricle. The right ventricular outflow tract (RVOT) does not contribute to the shadows formed by the left border of the heart. The aortic knob is not as easily seen in infants and children as in adults. The side of the aortic arch (left or right) can often be inferred as being opposite the side of the midline from which the air-filled trachea is visualized. This observation is important because a right-sided aortic arch is often present in

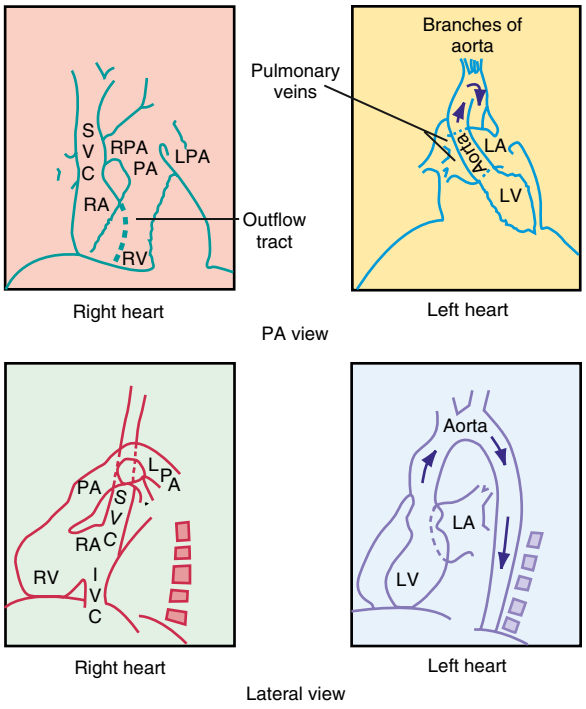

Fig. 472.1 Idealized diagrams showing normal position of the cardiac chambers and great blood vessels. IVC, Inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. *(Adapted and redrawn from Dotter CT, Steinberg I. Angiocardiographic interpretation. Radiology. 1949;153:513.)*

cyanotic CHD, particularly in tetralogy of Fallot. Three structures contribute to the right border of the cardiac silhouette. In the view from above, they are the superior vena cava, the ascending aorta, and the right atrium.

Enlargement of cardiac chambers (i.e., increased chamber volume) or major arteries and veins results in prominence of the areas in which these structures are normally outlined on the chest radiograph. In contrast, the electrocardiogram is a more sensitive and accurate index of **ventricular hypertrophy**, which is a thickening of the ventricular wall and may or may not be associated with dilation of the affected cardiac chamber.

The chest radiograph is also an important tool for assessing the degree of pulmonary vascularity. **Pulmonary overcirculation** is usually associated with left-to-right shunt lesions, whereas **pulmonary undercirculation** is associated with obstruction of the RVOT in cyanotic lesions. The esophagus is closely related to the great vessels, and a barium esophagogram can help delineate these structures in the initial evaluation of suspected vascular rings, although this has largely been supplanted by CT.

Echocardiographic examination best defines the morphologic features of intracardiac chambers, cardiac valves, and intracardiac shunts. CT is used as an adjunct to echocardiogram to evaluate extracardiac vascular morphology. MRI is used most often to provide a more quantitative assessment of inflammation as well as ventricular volumes, cardiac function, and shunt and regurgitant fractions than is possible with echocardiogram.

472.2 Electrocardiography

Daniel Bernstein

DEVELOPMENTAL CHANGES

The marked changes that occur in cardiac physiology and chamber dominance during the perinatal transition (see Chapter 470) are reflected in the evolution of the electrocardiogram (ECG) during the neonatal period. Because vascular resistance in the pulmonary and systemic circulations is nearly equal in a term fetus, the intrauterine work of the heart results in an equal mass of both the right and left ventricles. After birth, systemic vascular resistance (SVR) rises when the placental circulation is eliminated, and pulmonary vascular resistance (PVR) falls when the lungs expand. These changes are reflected in the ECG over the first few weeks of life as the right ventricular (RV) wall begins to thin.

The ECG demonstrates these anatomic and hemodynamic features principally by changes in QRS and T-wave morphologic features. Typically, pediatric ECGs include several additional leads rarely used in adults, such as V_3R and V_4R, which are mirror images of leads V_3 and V_4 and are important in the evaluation of **right ventricular hypertrophy** (RVH). On occasion, lead V_1 is inappropriately positioned too far leftward to reflect RV forces accurately. This problem is present particularly in premature infants, in whom the electrocardiographic electrode gel may produce contact among all the precordial leads. An additional lead used in children is V_7, located more laterally than V_6 and useful for assessing left-sided forces.

During the first postnatal days of life, right axis deviation, large R waves, and upright T waves in the right precordial leads (V_3R or V_4R and V_1) are the norm (Fig. 472.2). As PVR decreases in the first few days after birth, the right precordial T waves become negative. In the great majority of cases, this change occurs within the first 48 hours of postnatal life. Upright T waves that persist in leads V_3R, V_4R, or V_1 beyond 1 week of life are an abnormal finding indicating RVH or RV strain, even in the absence of QRS voltage criteria. The T wave in V_1 should never be positive before 6 years of age; however, it may remain negative into adolescence or early adulthood. This finding represents one of the most important yet subtle differences between pediatric and adult ECGs and is a common source of error when adult cardiologists interpret pediatric ECGs.

In a newborn the mean **QRS frontal-plane axis** normally lies in the range of +110 to +180 degrees, reflecting the codominance of the fetal right and left ventricles. The right-sided chest leads reveal a larger positive **(R)** than negative **(S)** wave and may do so for months because the right ventricle remains relatively thick throughout early infancy. Left-sided leads (V_5 and V_6) also reflect right-sided dominance in the early neonatal period, when the R:S ratio in these leads may be <1. A dominant R wave in V_5 and V_6, reflecting left ventricular (LV) forces, quickly becomes evident within the first few days of life (Fig. 472.3). As the child matures, the QRS axis gradually shifts leftward and the RV forces slowly regress. Leads V_1, V_3R, and V_4R display a prominent R wave until 6 months to 8 years of age. Most children have an R:S ratio >1 in lead V_4R until age 4 years. The T waves are inverted in leads V_4R, V_1, V_2, and V_3 during infancy and may remain so into the middle of the second decade of life and beyond. The processes of RV thinning and LV growth are best reflected in the QRS-T pattern over the right precordial leads. The diagnosis of RVH or left ventricular hypertrophy (LVH) in a pediatric patient can be made only with an understanding of the normal developmental physiology of these chambers at various ages until adulthood is reached. As the left ventricle becomes dominant, the ECG evolves to the characteristic pattern of older children (Fig. 472.4) and adults (Fig. 472.5).

Ventricular hypertrophy usually results in increased voltage in the R and S waves in the chest leads. The height of these deflections is governed by the proximity of the specific electrode to the surface of the heart; by the sequence of electrical activation through the ventricles, which can result in variable degrees of cancellation of right vs left forces; and by hypertrophy of the myocardium.

The diagnosis of **pathologic RVH** is difficult in the first week of postnatal life because physiologic RVH is a normal finding. Serial tracings are often necessary to determine whether marked right axis deviation and potentially abnormal right precordial forces or T waves, or both, will persist beyond the neonatal period (Fig. 472.6). In contrast, an adult ECG pattern (see Fig. 472.5) seen in a neonate suggests LVH. The exception is a premature infant, who may display a more "mature" ECG than a full-term infant (Fig. 472.7) as a result of lower PVR secondary

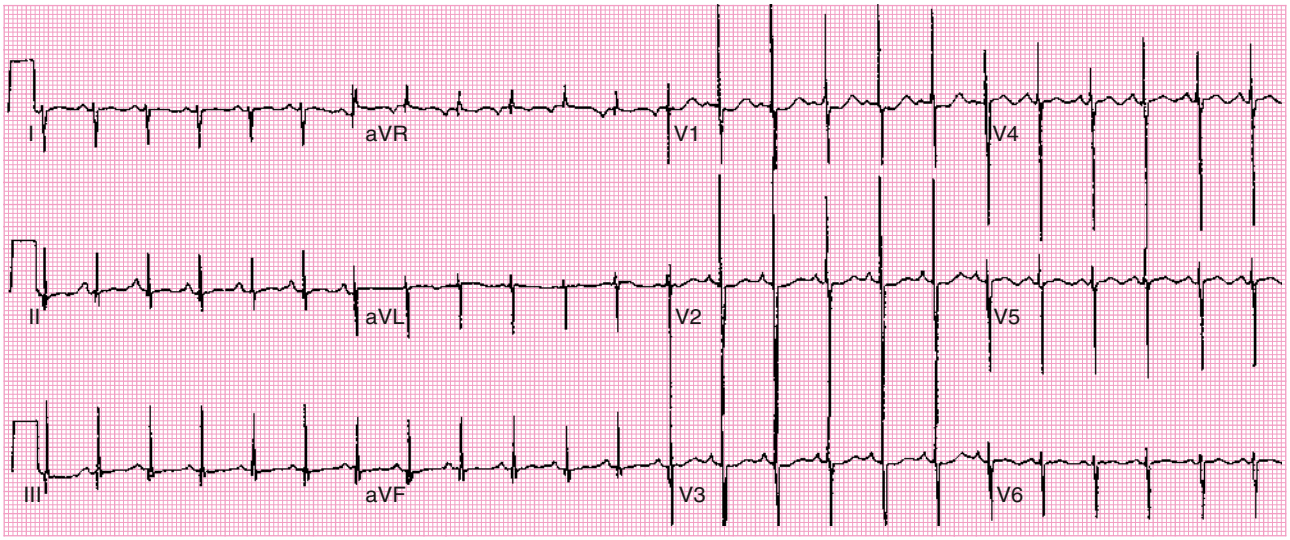

Fig. 472.2 Normal ECG from a 5-day-old, term-gestation infant. The frontal plane QRS axis is 150 degrees. There is prominent voltage in the precordial leads and a suggestion of right ventricular preponderance but not right ventricular hypertrophy. The QRS duration is 60 ms. *(From Gering LE, Knilans TK, Surawicz B, et al. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.2, p. 651).*

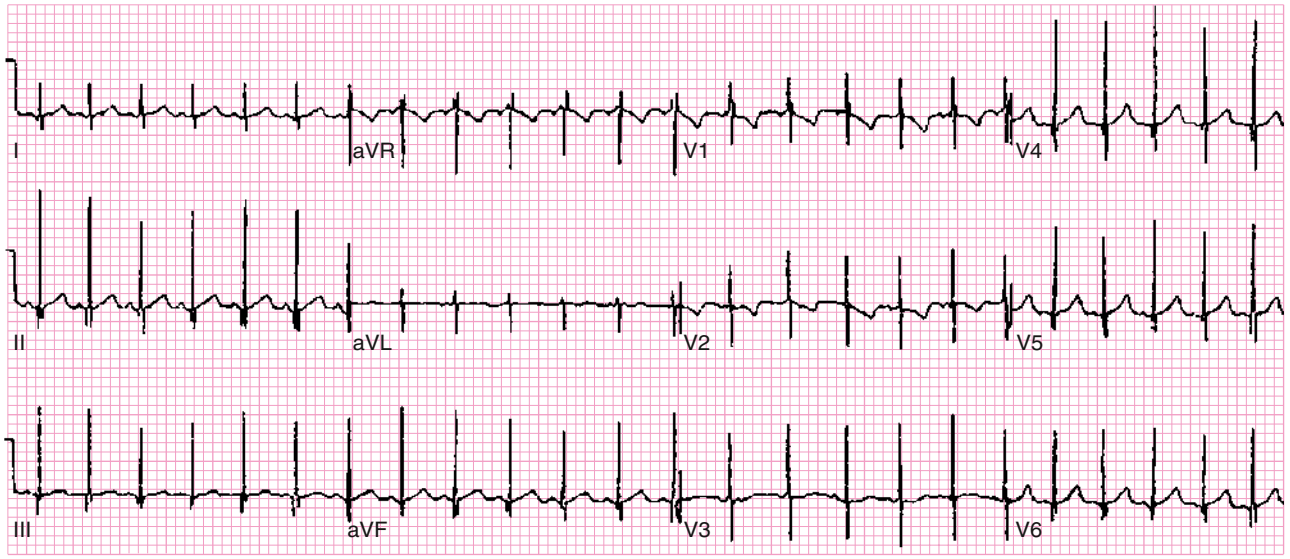

Fig. 472.3 Normal ECG from a healthy 8-mo-old infant. The frontal plane QRS axis is 60 degrees. There is less evidence of right ventricular preponderance than in the newborn tracing, with a smaller R wave in lead V_1 and smaller S wave in lead V_6. *(From Gering LE, Knilans TK, Surawicz B, et al. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.3, p. 652).*

to underdevelopment of the medial muscular layer of the pulmonary arterioles. Some premature infants display a pattern of generalized low voltage across the precordium.

The ECG should always be evaluated systematically to avoid overlooking a minor but important abnormality. One approach is to begin with an assessment of rate and rhythm, followed by a calculation of the mean frontal-plane QRS axis, measurements of segment intervals, assessment of voltages, and lastly assessment of ST and T-wave abnormalities.

RATE AND RHYTHM

A brief rhythm strip should be examined to assess whether a P wave always precedes each QRS complex. Using the full 12-lead ECG, the P-wave axis should then be estimated as an indication of whether the rhythm is originating from the **sinus node**. If the atria are situated normally in the chest, the P-wave axis should be oriented downward and to the left (i.e., should be upright in leads I and aVF and inverted in lead aVR). With atrial inversion **(situs inversus)**, the P wave may be inverted in lead I. Inverted P waves in leads II and aVF are seen in low atrial, nodal, or junctional rhythms. The absence of P waves indicates a rhythm originating more distally in the conduction system. In this case, the morphologic features of the QRS complexes are important in differentiating a **junctional** (usually a narrow QRS complex) from a **ventricular** (usually a wide QRS complex) rhythm.

P WAVES

Tall (>2.5 mm), narrow, and spiked P waves are indicative of **right atrial enlargement** and are seen in pulmonary stenosis, Ebstein anomaly of the tricuspid valve, tricuspid atresia, and sometimes cor pulmonale. These abnormal waves are most obvious in leads II, V_3R,

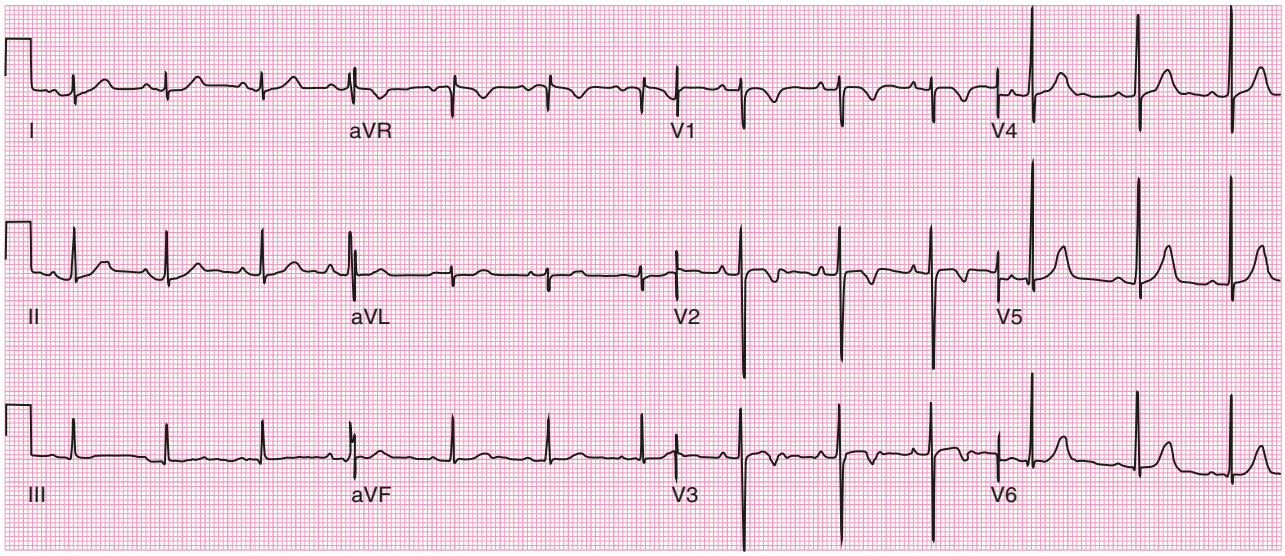

Fig. 472.4 Normal ECG from a healthy 3-yr-old child. The frontal plane QRS axis is 60 degrees. The R/S ratio in lead V_1 is less than 1, and there is no appreciable S wave in lead V_6. The R wave in lead V_6 is more prominent than that of the infant, suggesting more left ventricular preponderance but not left ventricular hypertrophy. *(From Gering LE, Knilans TK, Surawicz B, et al. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.4, p. 652).*

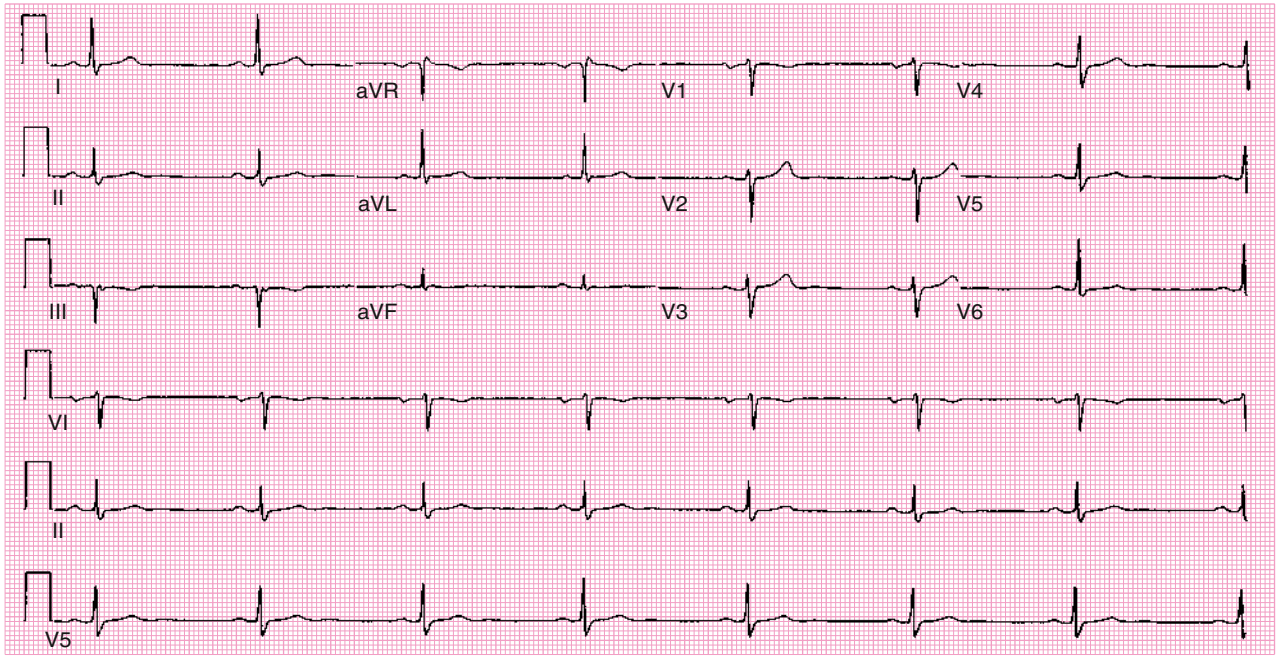

Fig. 472.5 Electrocardiogram of a normal 17-yr-old, a member of the school's track team. At this age the ECG should be similar to that in a normal adult: the dominant wave in V_1 should be the S wave and there is a normal R-wave progression, growing taller across the precordium from right to left. The heart rate is slow at 43 bpm (sinus bradycardia), which can be typical of a performance athlete. Note that all precordial lead T waves are positive, except for V_1. This R-wave progression pattern in a young infant, where there should be right ventricular dominance, would indicate the presence of left ventricular hypertrophy.

and V_1 (Fig. 472.8A). Similar waves are sometimes seen in thyrotoxicosis. **Broad P waves**, commonly **bifid** and sometimes **biphasic**, are indicative of **left atrial enlargement** (Fig. 472.8B). They are seen in some patients with large left-to-right shunts (ventricular septal defect [VSD], patent ductus arteriosus) and with severe mitral stenosis or mitral regurgitation. Left atrial enlargement, however, is one of the most common false-positive readings generated by computerized ECG machines. Flat P waves may be encountered in patients with hyperkalemia.

QRS COMPLEX

Right Ventricular Hypertrophy

For the most accurate assessment of ventricular hypertrophy, pediatric ECGs should include the right precordial leads V_3R and V_4R. The diagnosis of RVH depends on demonstration of the following changes (see Fig. 472.6): (1) a qR pattern in the RV surface leads; (2) a positive T wave in leads V_3R-V_4R and V_1-V_3 between ages 6 days and 6 years; (3) a monophasic R wave in V_3R, V_4R, or V_1; (4) an rsR′ pattern in the right precordial leads with the second R wave

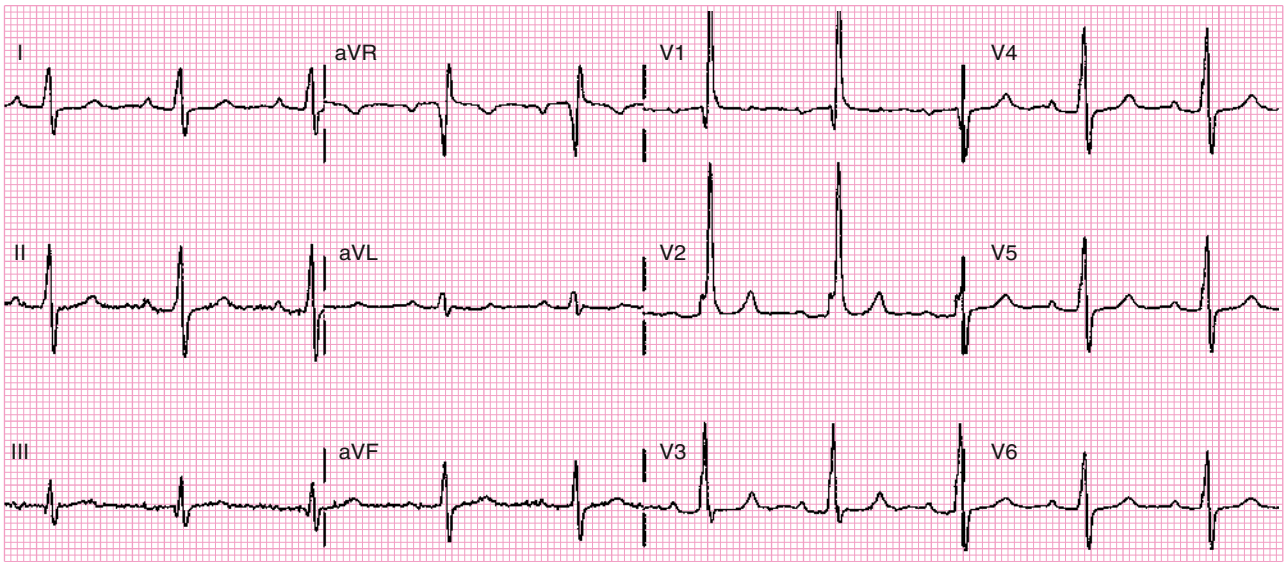

Fig. 472.6 Electrocardiogram of an infant with right ventricular hypertrophy (tetralogy of Fallot). Note the tall R waves in the right precordial leads (V_1-V_2) and deep S waves in V_6. The R-wave progression (taller in the right precordial leads vs the left) is counter to the normal pattern.

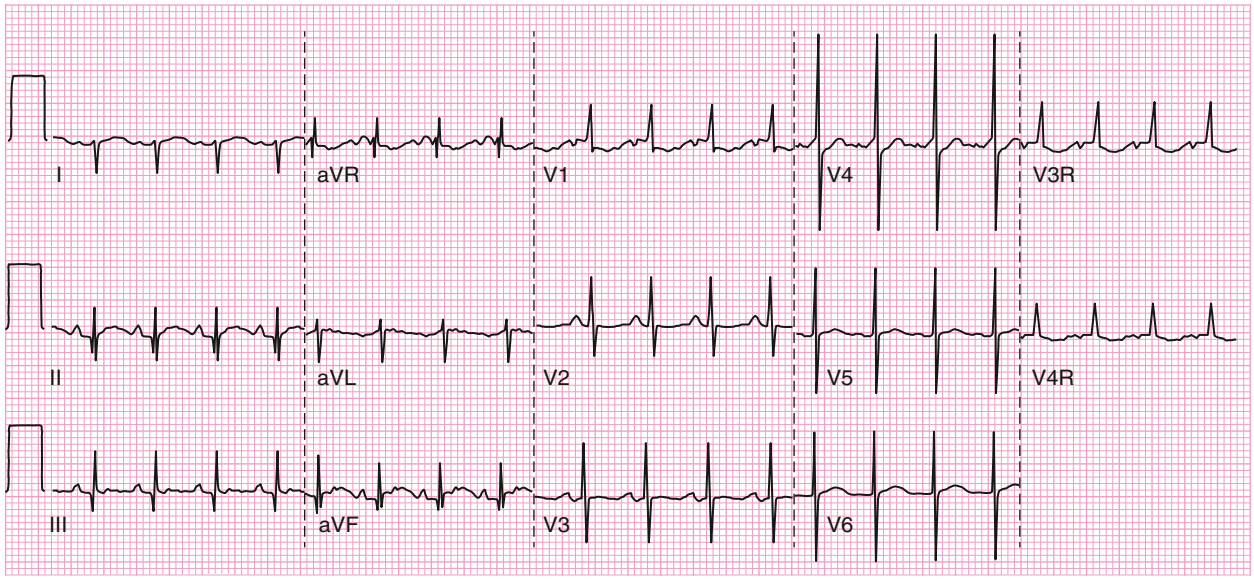

Fig. 472.7 Normal ECG from an 8-day-old, 28-wk-gestation premature infant. The frontal plane QRS axis is 150 degrees, there is a monophasic R wave in lead V_1, and the R/S ratio is less than 1 in lead V_6. This illustrates relative right ventricular preponderance without right ventricular hypertrophy. The QRS duration is less than 40 ms. *(From Gering LE, Knilans TK, Surawicz B, Tavel ME. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.1, p. 650).*

taller than the first; (5) age-corrected increased voltage of the R wave in leads V_3R-V_4R or the S wave in leads V_6-V_7, or both; (6) marked right axis deviation (>120 degrees in patients beyond the newborn period); and (7) complete reversal of the normal adult precordial RS pattern. At least two of these changes should be present to support a diagnosis of RVH.

Abnormal ventricular loading can be characterized as either pressure overload (as a result of RVOT obstruction, as in pulmonic stenosis) or volume overload (as a result of a left-to-right shunt as in atrial septal defect [ASD], semilunar valve regurgitation, or dilated cardiomyopathy). These two types of abnormal loads result in distinct electrocardiographic patterns. The **pressure overload pattern** is characterized by tall, pure R waves in the right precordial leads. In older children, the T waves in these leads are initially upright and later become inverted. In infants and children <6 years, the T waves in V_3R-V_4R and V_1 are abnormally upright. The **volume overload pattern** (typically seen in patients with ASD) is characterized by an rsR′ pattern (Fig. 472.9) and a slightly increased QRS duration (which is known as a *minor right ventricular conduction delay* rather than a true bundle branch block). Patients with mild to moderate pulmonary stenosis may also exhibit an rsR′ pattern in the right precordial leads.

Left Ventricular Hypertrophy

The following features indicate the presence of LVH (Fig. 472.10): (1) increased voltage (for age) of the S wave in V_3R and V_1 or the R wave in V_6-V_7, or both. In older children and adults, the criteria for LVH **(Sokolow index)** is a combination of S wave in V_1 or V_2 plus R wave in V_5 or V_6 ≥35 mm and (2) a deep Q wave in the left precordial leads. Remember that an infant with an ECG that would be considered "normal" for an older child may in fact have LVH; therefore reference to

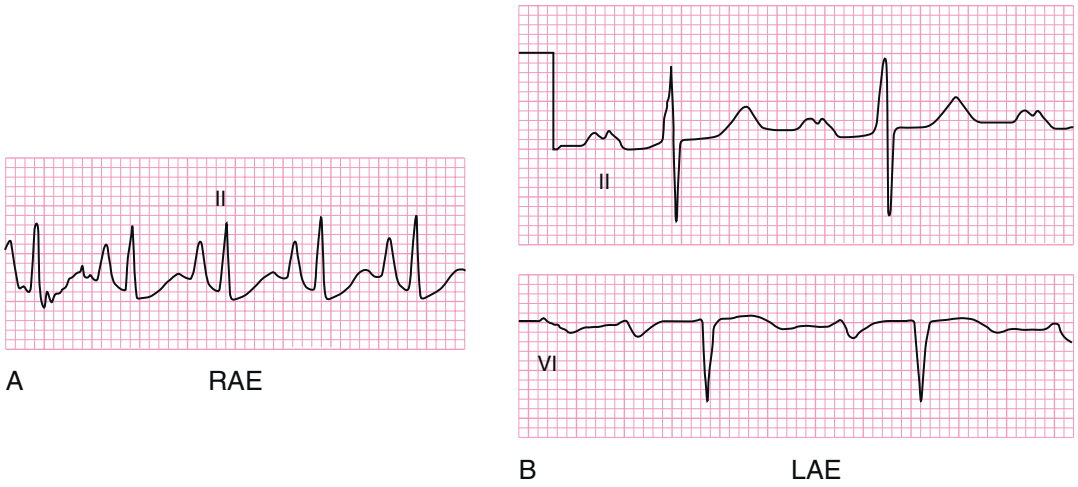

Fig. 472.8 Atrial enlargement. **A,** Peaked narrow P waves in lead II characteristic of right atrial enlargement (RAE). **B,** Wide, bifid, M-shaped P waves in lead II and biphasic p waves in lead V_1 typical of left atrial enlargement (LAE).

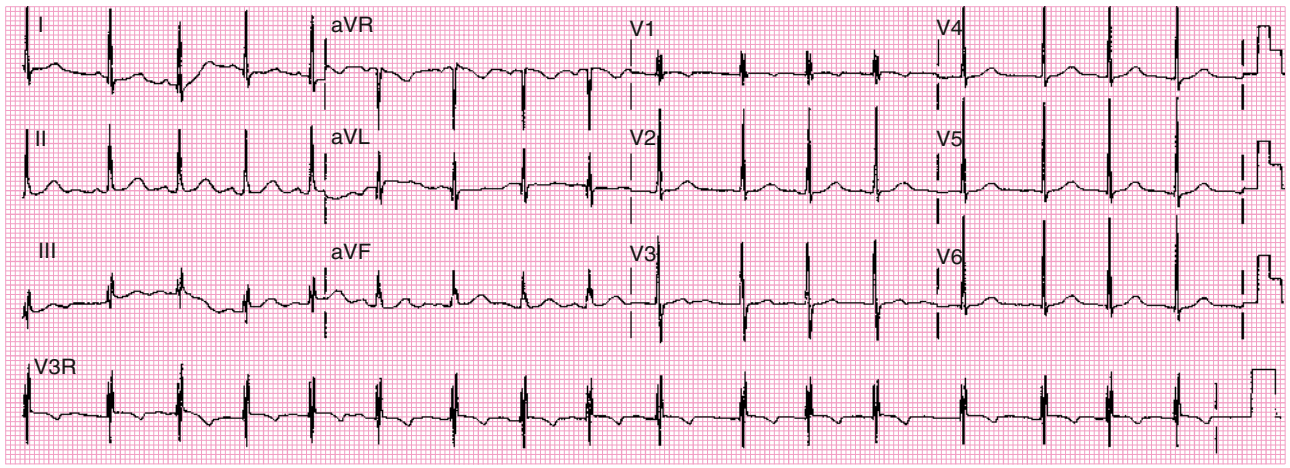

Fig. 472.9 Electrocardiogram showing a minor right ventricular conduction delay characterized by an RsR′ pattern in V_1. Note that the QRS duration is not prolonged (60 msec) as it would be if this were a right bundle branch block (RBBB).

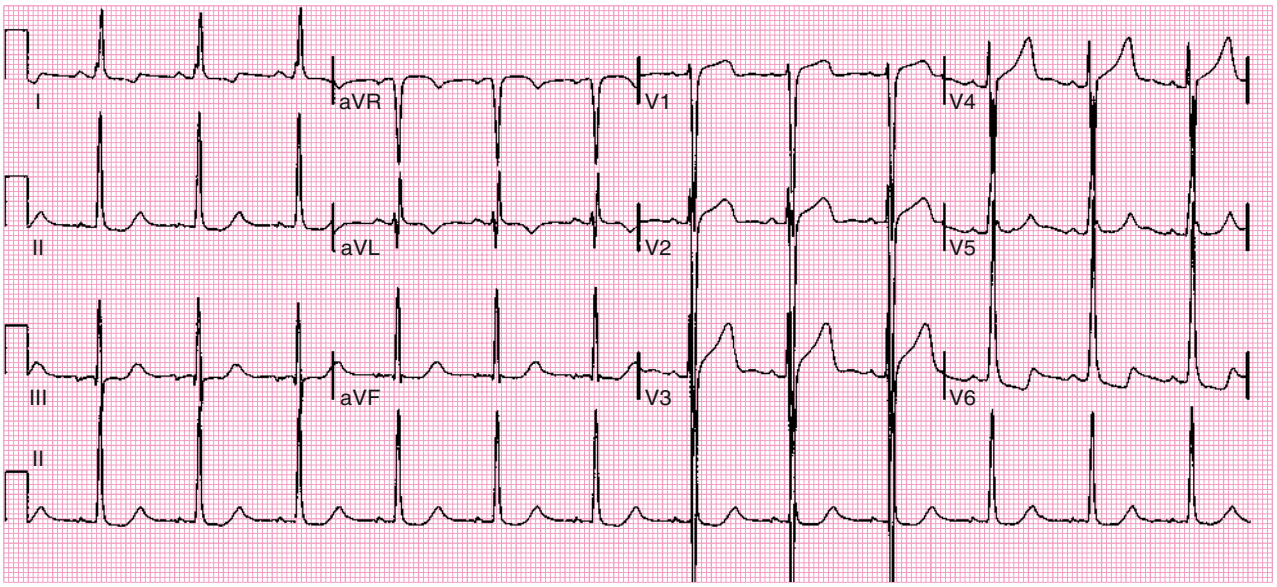

Fig. 472.10 Electrocardiogram showing left ventricular hypertrophy (LVH) in a 12-yr-old child with aortic stenosis. Note the deep S waves in V_1-V_3 and tall R in V_5-V_6. In addition, T-wave inversion is present in lead V_6, a sign of left ventricular strain.

standard voltages for age is always important. Further evidence for LVH includes depression of the ST segments and inversion of the T waves in the left precordial leads (V_5, V_6, and V_7), known as a **left ventricular strain** pattern—these findings suggest the presence of more severe hypertrophy.

Bundle Branch Block

A complete **right bundle branch block** (RBBB; prolonged QRS complex, which is usually upright with an rSR′ in lead V_1; wide S wave in lead V_6) may be congenital or may be acquired after surgery for CHD, especially when a right ventriculotomy has been performed, as in repair of the tetralogy of Fallot. **Left bundle branch block** (LBBB; prolonged QRS complex, which is usually upright with an rSR′ in lead V_6; wide S wave in lead V_1) is less common in children; this pattern is often seen in adults with cardiomyopathy, but much less in children with cardiomyopathy. LBBB may be seen after surgery on the aortic or mitral valve caused by surgical injury to one of the left-sided conduction bundles. Alternatively, a bundle branch block pattern may be indicative of a bypass tract associated with one of the preexcitation syndromes (see Chapter 484).

P-R AND Q-T INTERVALS

The duration of the P-R interval shortens with increasing heart rate; assessment of this interval should be based on age- and rate-corrected nomograms. A long P-R interval is diagnostic of a **first-degree heart block**, the cause of which may be congenital, postoperative (after open heart surgery), inflammatory (myocarditis, pericarditis, Lyme disease, rheumatic fever), or pharmacologic (digitalis, calcium channel blockers).

The duration of the Q-T interval varies with the cardiac rate; a corrected Q-T interval (Q-Tc) can be calculated by dividing the measured Q-T interval by the square root of the preceding R-R interval. A normal Q-Tc should be <0.45. It is often lengthened with hypokalemia and hypocalcemia; in the former, a U wave may be noted at the end of the T wave (Fig. 472.11). A significant number of medications can also lengthen the Q-T interval, so a careful history of medication exposure is important in evaluating a patient with a borderline or long QT interval. A congenitally prolonged Q-T interval may also be seen in children with one of the long QT syndromes (Fig. 472.12). These patients are at high risk for ventricular arrhythmias, including a dangerous form of ventricular tachycardia known as **torsades de pointes**, and sudden death (see Chapter 484.5).

ST SEGMENT AND T-WAVE ABNORMALITIES

Coronary ischemia, leading to typical ST and T-wave abnormalities seen in adults, is rare in children. A slight elevation of the ST segment is often seen in normal teenagers, especially males, and is attributed to **early repolarization** of the heart (Fig. 472.13). It can sometimes be difficult to distinguish between ischemic ST segment changes and benign early repolarization; however, the following characteristics suggest early repolarization: (1) ST elevation limited to the lateral leads (V_5-V_6), (2) a characteristic notch at the J point (junction between the end of the QRS and the beginning of the ST segment), and (3) a concave rather than convex ST segment. Lack of any concerning symptoms is also critical. Early repolarization often resolves with exercise-induced tachycardia. In pericarditis, irritation of the epicardium may cause elevation of the ST segment, followed by abnormal T-wave inversion as healing progresses.

Depression of the ST segment may also occur in coronary ischemia or in any condition that produces myocardial injury, including severe anemia, carbon monoxide poisoning, glycogen storage disease of the heart, myocardial tumors, and mucopolysaccharidoses. An aberrant origin of the left coronary artery from the pulmonary artery may lead to changes indistinguishable from those of acute myocardial infarction in adults. ECG findings of ischemia may be seen in patients with Kawasaki disease who have developed coronary artery aneurysms (see Chapters 208 and 493.1). Similar changes may occur in patients with other rare abnormalities of the coronary arteries and in those with cardiomyopathy, even in the presence of normal coronary arteries. These patterns are often misread in young infants because of the unfamiliarity of pediatricians with this "infarct" pattern, and thus a high index of suspicion must be maintained in infants with dilated cardiomyopathy or with symptoms compatible with coronary ischemia (e.g., inconsolable crying).



Fig. 472.12 Prolonged Q-T interval in a patient with long QT syndrome.

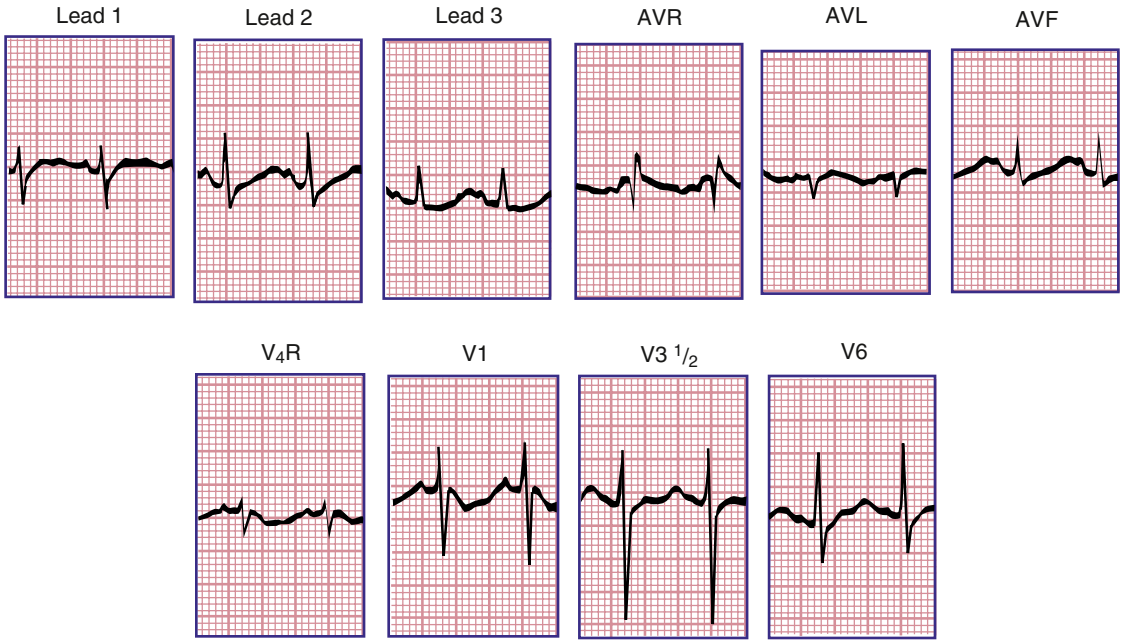

Fig. 472.11 Electrocardiogram in hypokalemia. Serum potassium, 2.7 mEq/L; serum calcium, 4.8 mEq/L at the time of the tracing. Note the widened TU wave and depression of the ST segment in V_4R, V_1, and V_6.

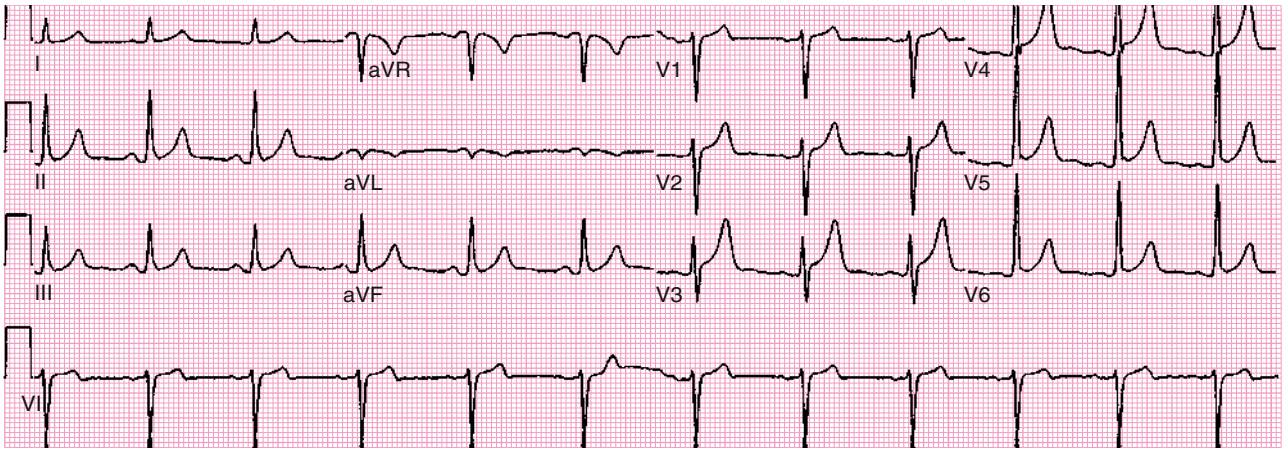

Fig. 472.13 Early repolarization seen in the mid-precordial to lateral leads (V_2-V_5) in a teenage boy. These minor ST segment elevations, with typical concave slope and combined with a high J point, suggest this is a benign variant and not true ischemia.

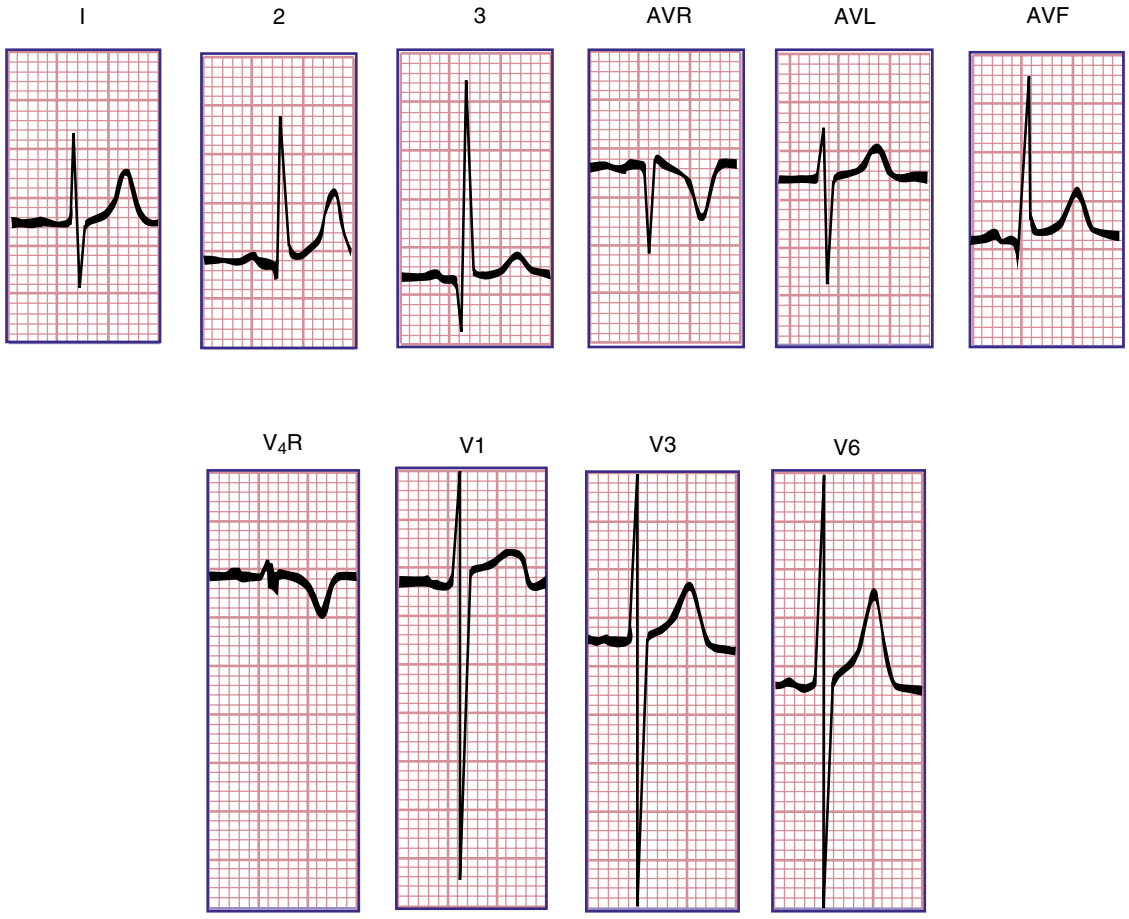

Fig. 472.14 Electrocardiogram in hyperkalemia. Serum potassium, 6.5 mEq/L. Note the tall, tent-shaped T waves, especially in leads 1, 2, and V_6.

T-wave inversion may occur in myocarditis and pericarditis, or it may be a sign of either RVH or LVH and ventricular strain. Hypothyroidism may produce flat or inverted T waves in association with generalized low voltage. In hyperkalemia, the T waves are usually of high voltage and are tent shaped (Fig. 472.14), although tall T waves can be an early sign of myocardial infarction.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

472.3 Hematologic Data in Cardiovascular Evaluation

Daniel Bernstein

In acyanotic infants with large left-to-right shunts, the onset of heart failure often coincides with the nadir of the normal physiologic anemia of infancy. Increasing the hematocrit in these patients to >40% may decrease shunt volume and result in an improvement in symptoms; however, this form of treatment is generally reserved for infants who are not otherwise surgical candidates (extremely premature infants or others in whom surgery is delayed for other reasons). In these select infants, regular evaluation of the hematocrit and booster transfusions when appropriate may be helpful in improving growth.

Polycythemia is frequently noted in chronically *cyanotic* patients with right-to-left shunts. Patients with severe polycythemia, rarely seen in this age of early surgical repair, are in a delicate balance between the risks of intravascular thrombosis and a bleeding diathesis. The preparation of cyanotic, polycythemic patients for elective noncardiac surgery, such as dental extraction, includes evaluation and treatment of abnormal coagulation.

Because of the high viscosity of polycythemic blood (hematocrit >65%), patients with unrepaired cyanotic CHD are at risk for the development of **vascular thromboses**, especially of cerebral veins. Dehydration increases the risk of thrombosis, and thus adequate fluid intake must be maintained during hot weather or intercurrent gastrointestinal illnesses. Diuretics should be used with caution in these patients and may need to be decreased if fluid intake is a concern. Polycythemic infants with concomitant **iron deficiency** are at even greater risk for cerebrovascular accidents, thought to be the result of the decreased deformability of microcytic red blood cells. Iron therapy may reduce this risk, but surgical repair of the cardiac anomaly is the best therapy.

Severely cyanotic patients who are inoperable should have periodic determinations of hemoglobin and hematocrit. Increasing polycythemia is often associated with headache, fatigue, dyspnea, or a combination of these conditions. Partial exchange transfusion may be required to treat symptomatic (most often headache or chest pain) individuals whose hematocrit has risen to the 65–70% level. This procedure is not without risk, especially in patients with an extreme elevation in pulmonary vascular resistance. Because these patients do not tolerate wide fluctuations in circulating blood volume, blood should be replaced with fresh-frozen plasma or albumin.

472.4 Echocardiography

Daniel Bernstein

Transthoracic echocardiography (TTE) has replaced cardiac catheterization for the *diagnosis* of most forms of CHD. The echocardiographic examination can be used to evaluate cardiac structures in congenital heart lesions using two-dimensional (2D) and three-dimensional (3D) imaging, estimate intracardiac pressures and gradients across stenotic valves and vessels using **echo-Doppler** and color flow Doppler, quantitate cardiac contractile function (both systolic and diastolic), determine the direction of flow across a defect, examine the integrity of the coronary arteries, and detect the presence of vegetations from endocarditis, pericardial fluid, cardiac tumors, and chamber thrombi.

Echocardiography may also be used to assist in the performance of interventional procedures, including pericardiocentesis, balloon atrial septostomy (see Chapter 480.2), ASD or VSD closure, transcatheter valve implantation, and endocardial biopsy. **Transesophageal echocardiography** (TEE) is used routinely to monitor ventricular function in patients during surgical procedures and can provide an immediate assessment of the results of surgical repair of congenital heart lesions. A complete TTE examination usually entails a combination of M-mode and 2D and 3D imaging, as well as pulsed, continuous, and color Doppler flow studies. Doppler tissue imaging provides a more quantitative assessment of ventricular systolic and diastolic function.

M-MODE ECHOCARDIOGRAPHY

M-mode echocardiography displays a one-dimensional slice of cardiac structure varying over time (Fig. 472.15). It is used mostly for the measurement of cardiac dimensions (wall thickness and chamber size) and cardiac function (fractional shortening, wall thickening). M-mode echocardiography is also useful for assessing the motion of intracardiac structures: the opening and closing of valves and movement of free walls and septa (Fig. 472.16). The most frequently used index of cardiac function in children is **percent fractional shortening** (%FS), which contrasts to adults, where **ejection fraction** is the most common functional measurement. %FS is calculated as (LVED − LVES)/LVED, where LVED is left ventricular dimension at end diastole and LVES is left ventricular dimension at end systole. Normal fractional shortening is approximately 28–42%. Other M-mode indices of cardiac function include the mean velocity of fiber shortening (mean V_{CF}), systolic time intervals (LVPEP = LV preejection period, LVET = LV ejection time), and isovolemic contraction time. M-mode assessments of cardiac function are more susceptible to errors because of differences in wall motion between different segments of the heart (more frequently seen in adults with ischemic heart disease, but which can be seen in

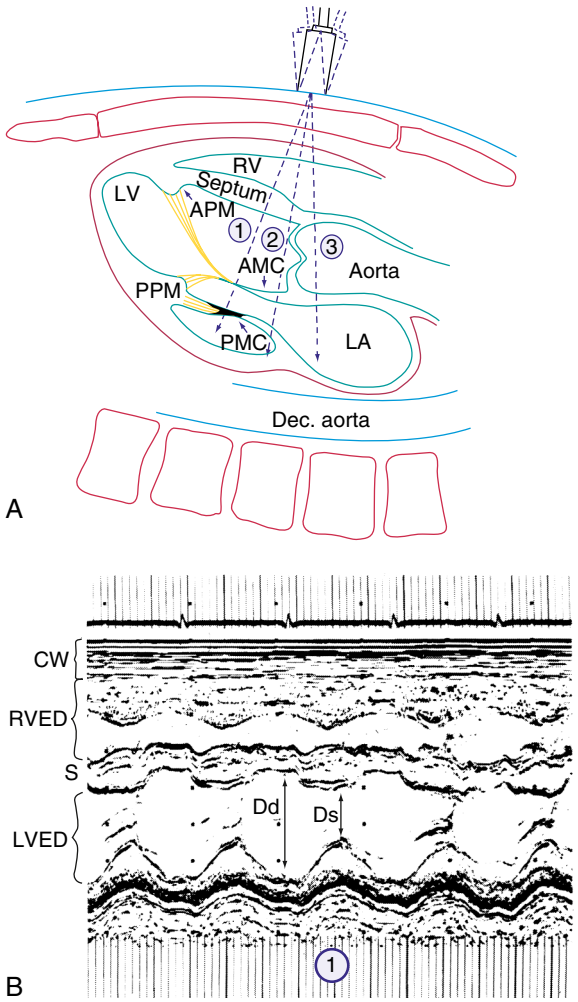

Fig. 472.15 M-mode echocardiogram. A, Diagram of a sagittal section of a heart showing the structures traversed by the echo beam as it is moved superiorly to positions (1), (2), and (3). B, Echocardiogram from transducer position (1); this view is the best one for measuring cardiac dimensions and fractional shortening. Fractional shortening is calculated as (LVED − LVES)/LVED. AMC, Anterior mitral cusp; APM, anterior papillary muscle; Dec. aorta, descending aorta; LA, left atrium; LV, left ventricle; PMC, posterior mitral cusp; PPM, posterior papillary muscle; RV, right ventricle. CW, Chest wall; Ds, LV dimension in systole; LVED, LV dimension at end diastole (Dd); RVED, RV dimension at end diastole.

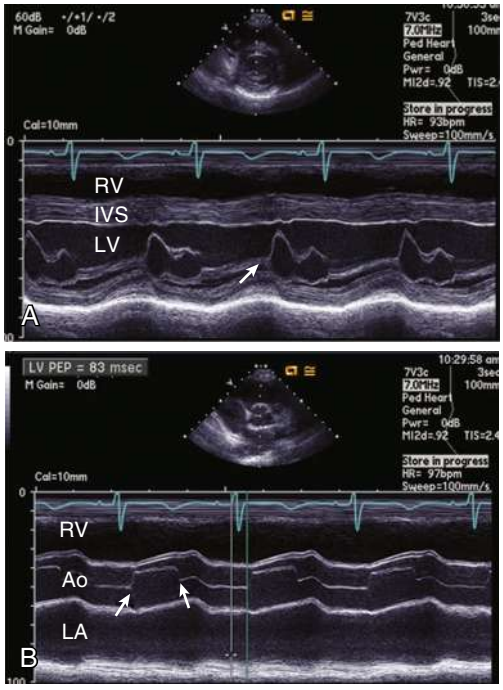

Fig. 472.16 M-mode echocardiograms. The small figure at the top of each panel shows the 2D parasternal short-axis echocardiogram image from which the M-modes are derived. The cursor can be seen midway through the image, indicating the one-dimensional line through which the M-mode is being sampled. **A,** M-mode echocardiogram of a normal mitral valve. *Arrow* shows the opening of the anterior leaflet in early diastole (see ECG tracing earlier for reference). **B,** M-mode echocardiogram of a normal aortic valve. The opening and closing of the aortic leaflets in systole are outlined by the two *arrows*. Ao, Aorta; IVS, interventricular septum; LV, left ventricle; RV, right ventricle.

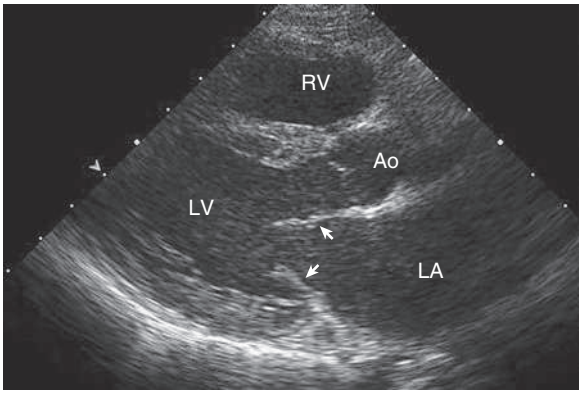

Fig. 472.17 Normal parasternal long-axis echocardiographic window. The transducer is angulated slightly posteriorly, imaging the left-sided cardiac structures. If the transducer were to be angulated more anteriorly, the right ventricular structures would be imaged. The mitral valve leaflets can be seen in the partially open position in early diastole *(arrows)*. The closed aortic valve leaflets can be seen just below the label Ao (aorta). LA, Left atrium; LV, left ventricle; RV, right ventricle.

children with congenital and acquired heart disease, especially after surgical repair).

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional echocardiography provides a real-time image of cardiac structures. The contracting heart is imaged using several standard views, including parasternal long axis (Fig. 472.17), parasternal short axis (Fig. 472.18), apical four-chamber (Fig. 472.19), subcostal (Fig. 472.20), and suprasternal (Fig. 472.21), each of which emphasizes specific structures. Two-dimensional echocardiography

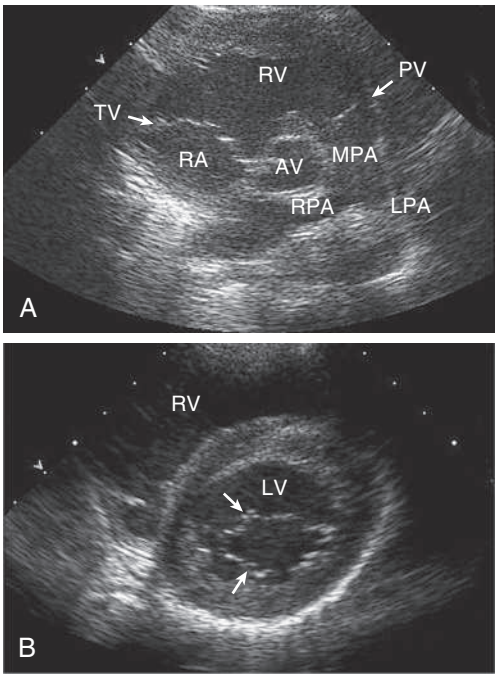

Fig. 472.18 Normal parasternal short-axis echocardiographic windows. **A,** With the transducer angled superiorly and rightward, the aortic valve (AV) is imaged, surrounded by both inflow and outflow portions of the right ventricle (RV). **B,** With the transducer angled inferiorly and leftward, the left ventricular chamber is imaged along with a cross-sectional view of the mitral valve *(arrows)*. LPA, Left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; TV, tricuspid valve. LV, left ventricle; RV, right ventricle.

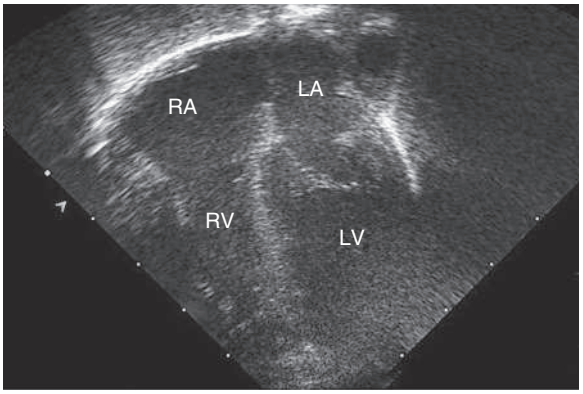

Fig. 472.19 Normal apical four-chamber echocardiographic window showing all four cardiac chambers and both atrioventricular valves opened in diastole. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

has replaced cardiac angiography for the preoperative diagnosis and follow-up of the vast majority of congenital heart lesions. However, when information from the cardiac examination or other studies is not consistent with the echocardiogram, or in very complex defects, cardiac catheterization remains an important tool to confirm the anatomic diagnosis and evaluate the degree of physiologic derangement. MRI is an extremely valuable adjunct to provide a better quantification of ventricular size and function. Cardiac CT is another modality that is valuable to assess cardiac and adjacent vascular structures.

DOPPLER ECHOCARDIOGRAPHY

Doppler echocardiography displays blood flow based on the change in frequency imparted to sound waves by the movement of

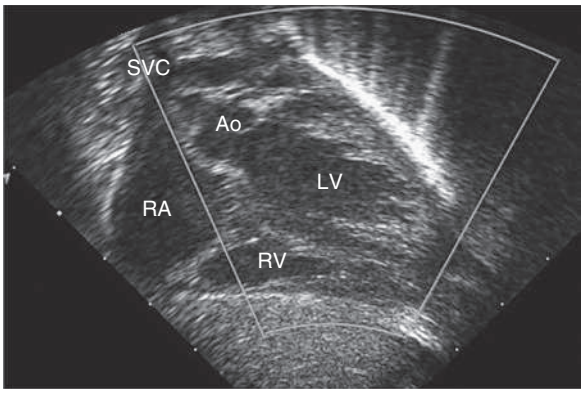

Fig. 472.20 Normal subcostal echocardiographic window showing the left ventricular outflow tract. The right-sided structures are not fully imaged in this view. Ao, Ascending aorta; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

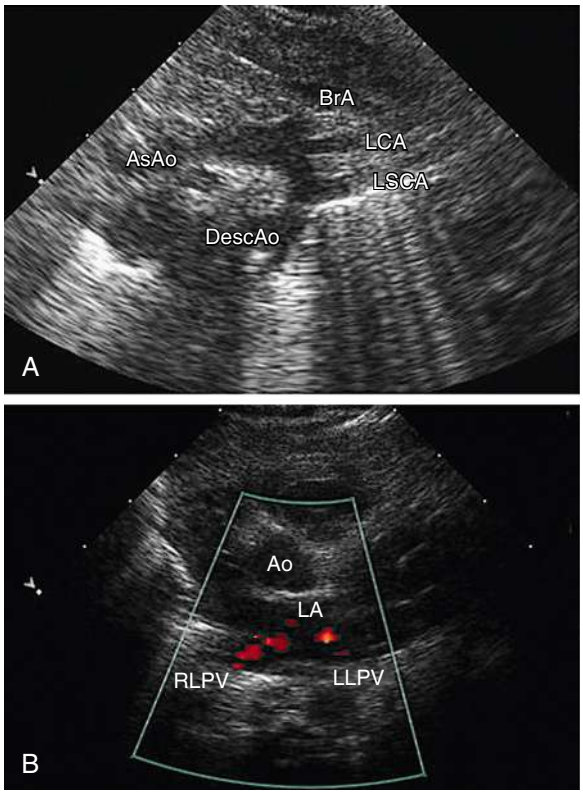

Fig. 472.21 **A,** Normal suprasternal echocardiographic window showing the aortic arch and its major branches. **B,** Normal high parasternal window showing color Doppler imaging of normal pulmonary venous return to the left atrium (LA) of both right (RLPV) and left (LLPV) lower pulmonary veins. AsAo, Ascending aorta; BrA, brachiocephalic artery; DescAo, descending aorta; LCA, left carotid artery; LSCA, left subclavian artery.

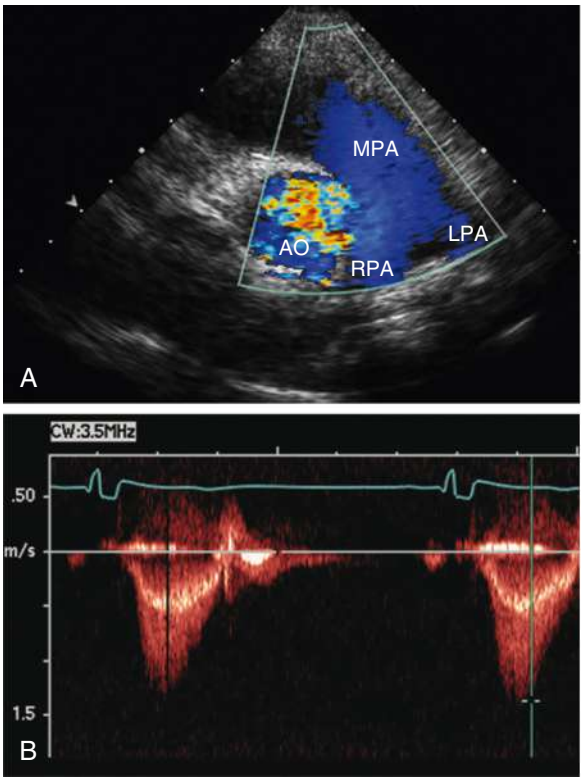

Fig. 472.22 Color and pulsed Doppler evaluation of pulmonary arterial flow. **A,** Color Doppler evaluation of a parasternal short-axis view showing normal flow through the pulmonary valve to the main and branch pulmonary arteries. The color of the Doppler flow is *blue,* indicating that the flow is moving away from the transducer (which is located at the top of the figure, at the apex of the *triangular* ultrasound window). Note that the color assigned to the Doppler signal does not indicate the oxygen saturation of the blood. **B,** Pulsed-wave Doppler flow pattern through the pulmonary valve showing a low velocity of flow (<1.5 m/sec), indicating the absence of a pressure gradient across the valve. The envelope of the flow signal is below the line, indicating that the flow is moving away from the transducer. AO, Aorta; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

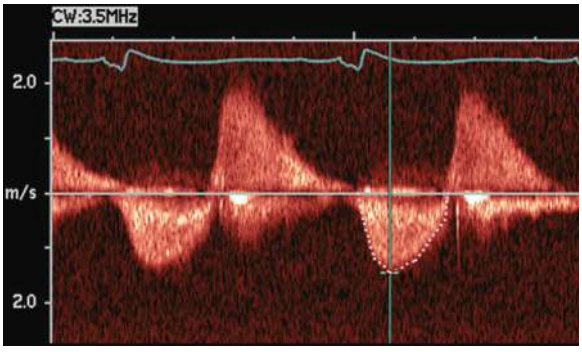

Fig. 472.23 Doppler evaluation of a patient who had previously undergone repair of tetralogy of Fallot and who has mild pulmonary stenosis and moderate pulmonary regurgitation. The tracing shows the to-and-fro flow across the pulmonary valve, with the signal below the line representing forward flow in systole (see ECG tracing for reference) and the signal above the line representing regurgitation during diastole.

erythrocytes. The speed and direction of blood flow in the line of the echo beam change the transducer's reference frequency. This frequency change can be translated into volumetric flow (L/min) data for estimating systemic or pulmonary blood flow and into pressure (mm Hg) data for estimating gradients across valves or across septal defects or vascular communications such as shunts. Color Doppler permits highly accurate assessment of the presence and direction of intracardiac shunts and allows identification of small or multiple left-to-right or right-to-left shunts (Fig. 472.22). The severity of valvular insufficiency can be evaluated qualitatively with both pulsed and color Doppler (Fig. 472.23). Alterations in venous Doppler flow patterns can be used to detect abnormalities of systemic and pulmonary veins, and alterations of atrioventricular valve Doppler flow patterns can be used to assess ventricular

diastolic functional abnormalities, particularly the **E/A ratio**, the ratio of peak velocity flow in diastole (i.e., the ratio of the early diastole E wave to the peak velocity flow in late diastole caused by atrial contraction).

M-mode, 2D, and Doppler echocardiographic methods of assessing LV systolic and diastolic function (e.g., end-systolic wall stress, dobutamine stress echocardiography, Doppler tissue imaging) have proved useful in the serial assessment of patients at risk for the development of both systolic and diastolic ventricular dysfunction and ventricular dyssynchrony (where the coordination of left and right ventricular contraction is abnormal). Such patients include those with cardiomyopathies, those receiving anthracycline drugs for cancer chemotherapy, those at risk for iron overload, and those being monitored for rejection or coronary artery disease after heart transplantation.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Real-time 3D echocardiographic reconstruction is most valuable for the detailed assessment of cardiac morphology (Fig. 472.24). Details of valve structure, the size and location of septal defects, abnormalities of the ventricular myocardium, and details of the great vessels, which may not be as readily apparent using 2D imaging, can often be appreciated on 3D echocardiography. Reconstruction of the view that the surgeon will encounter in the operating room makes this technique a valuable adjunct for preoperative imaging.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TEE is a sensitive imaging technique that produces a clearer view of smaller lesions such as vegetations in endocarditis, especially in larger patients. It is useful in visualizing posteriorly located structures such as the atria, aortic root, and atrioventricular valves. TEE is useful as an intraoperative technique for monitoring cardiac function during both cardiac and noncardiac surgery and for screening for residual cardiac defects after the patient is initially weaned from cardiopulmonary bypass but before being disconnected from the bypass circuit. This technique has been especially helpful in evaluating the degree of residual regurgitation or stenosis after valve repairs and in searching for small muscular VSDs that may have been missed during the closure of larger defects. It is always preferable to make the diagnosis of **excessive valve regurgitation** while the patient is still in the operating room, so that the repair can be revised or the valve replaced, rather than after surgery, when the patient is already in the postoperative care unit. However, hemodynamic measurements made while the chest is open and the patient is still under anesthesia may be different from those made under more normal conditions, as when the patient is ready to be discharged from the hospital.

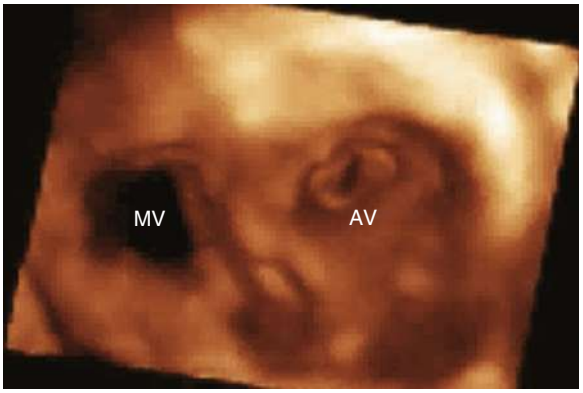

Fig. 472.24 Three-dimensional echocardiogram showing a short-axis view of the left ventricle. AV, Aortic valve; MV, mitral valve. *(Courtesy Dr. Norman Silverman, Stanford University, Stanford, CA.)*

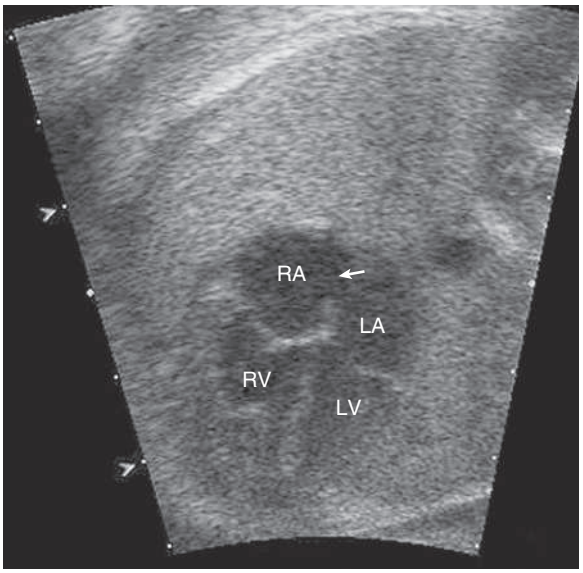

Fig. 472.25 Normal four-chamber view echocardiogram on a fetus at 20 wk of gestation. The foramen ovale *(arrow)* can be seen between the right and left atria. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

FETAL ECHOCARDIOGRAPHY

Fetal echocardiography can be used to evaluate cardiac structures and function or disturbances in cardiac rhythm (Fig. 472.25). Obstetricians may detect a possible heart defect when screening during routine obstetric ultrasonography (e.g., cardiac four-chamber view) or may refer the patient because of unexplained hydrops fetalis, a family history of CHD, or a maternal condition associated with fetal cardiac pathology, such as gestational diabetes, drug use, or infection. Fetal echocardiography can diagnose most significant congenital heart lesions as early as 17-19 weeks of gestation; accuracy at this early stage is limited, however, and families should understand that these studies cannot totally eliminate the possibility of CHD. Serial fetal echocardiograms have also demonstrated the importance of flow disturbance in the pathogenesis of CHD; such studies can show the intrauterine progression of a moderate lesion, such as aortic stenosis, into a more severe lesion, such as **hypoplastic left heart syndrome** (HLHS). M-mode echocardiography can diagnose rhythm disturbances in the fetus and can determine the success of antiarrhythmic therapy administered to the mother. A screening fetal echocardiogram is recommended for women with a previous child or first-degree relative with CHD, for those who are at higher risk of having a child with cardiac disease (e.g., insulin-dependent diabetes, women exposed to teratogenic drugs during early pregnancy), and in any fetus in whom a chromosomal abnormality is suspected or confirmed.

Early detection provides the opportunity to counsel and educate the parents about the severity of the cardiac lesion and potential therapeutic or palliative care options. Referral to a high-risk perinatal service is then performed for further ultrasound screening for associated anomalies of other organs and potential amniocentesis or sequencing of cell-free DNA in maternal blood for karyotyping. For fetuses with ductal dependent lesions, delivery can be planned at a tertiary care center, enhancing safety by avoiding the requirement for postnatal transport of an unstable infant. For fetuses with complex CHD at high risk for complications immediately at birth (e.g., HLHS with intact atrial septum), delivery can be arranged with an operating room and surgeon standing by. In utero treatment of CHD is an experimental procedure, with the most common procedure being aortic balloon valvuloplasty for HLHS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

472.5 Exercise Testing

Daniel Bernstein

The normal cardiorespiratory system adapts to the extensive demands of exercise with a several-fold increase in oxygen consumption and cardiac output. Because of the large reserve capacity for exercise, significant abnormalities in cardiovascular performance may be present without symptoms at rest or during ordinary activities. When patients are evaluated in a resting state, significant abnormalities in cardiac function may not be appreciated, or if detected, their implications for quality of life may not be recognized. Permission for children with cardiovascular disease to participate in various forms of physical activity is frequently based on totally subjective criteria. As the importance of aerobic exercise is increasingly recognized, even for children with complex congenital heart lesions, exercise testing can provide a quantitative evaluation of the child's ability to participate safely in both competitive and noncompetitive sports. Exercise testing can also play an important role in evaluating symptoms and quantitating the severity of cardiac abnormalities. In children with coronary artery abnormalities (e.g., Kawasaki disease or COVID-19 with coronary aneurysms), exercise testing can detect ischemia that might otherwise be overlooked.

In older children, exercise studies are generally performed on a graded treadmill apparatus with timed intervals of increasing grade and speed. In younger children, exercise studies are often performed on a bicycle ergometer. Many laboratories have the capacity to measure both cardiac and pulmonary function noninvasively during exercise. This allows measurement of both resting and maximal oxygen consumption (Vo_{2max}) and the point at which anaerobic threshold is reached, which are important indicators of cardiovascular fitness.

As a child grows, the capacity for muscle work is enhanced with increased body size and skeletal muscle mass. All indices of cardiopulmonary function do not increase in a uniform manner. A major response to exercise is an increase in cardiac output, principally achieved through an increase in heart rate, but stroke volume (SV), systemic venous return, and pulse pressure are also increased. SVR is greatly decreased as the blood vessels in working muscle dilate in response to increasing metabolic demands. As the child becomes older and larger, the response of the heart rate to exercise remains prominent, but cardiac output increases because of growing cardiac volume capacity and thus SV. Responses to dynamic exercise are not dependent solely on age. For any given body surface area, boys have a larger SV than size-matched girls. This increase is also mediated by posture. Augmentation of SV with upright, dynamic exercise is facilitated by the pumping action of working muscles, which overcomes the static effect of gravity and increases systemic venous return.

Dynamic exercise testing defines not only endurance and exercise capacity but also the effect of such exercise on myocardial blood flow and cardiac rhythm. Significant ST segment depression or elevation reflects abnormalities in myocardial perfusion, such as might occur during exercise in children with extremely hypertrophied left ventricles. The **exercise ECG** is considered abnormal if the ST segment depression is >2 mm and extends for at least 0.06 seconds after the J point (onset of the ST segment) in conjunction with a horizontal-, upward-, or downward-sloping ST segment. A decrease in blood pressure before maximal exercise is reached is regarded as a risk indicator in patients with hypertrophic cardiomyopathy. Provocation of rhythm disturbances during an exercise study is an important method of evaluating select patients with known or suspected rhythm disorders. The effect of pharmacologic management can also be tested in this manner.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

472.6 Cardiac Imaging Studies

Daniel Bernstein

Magnetic resonance imaging (MRI) and **magnetic resonance angiography (MRA)** are extremely helpful in the diagnosis and management of patients with CHD and inflammatory lesions (Table 472.1). These techniques produce tomographic images of the heart in any projection (Fig. 472.26 and Fig. 472.27), with excellent contrast resolution of fat, myocardium, and lung, as well as moving blood from blood vessel walls. MRI is useful in evaluating areas that are less well visualized by echocardiography, such as distal branch pulmonary artery anatomy and anomalies in systemic and pulmonary venous return.

MRA allows the acquisition of images in several tomographic planes. Within each plane, images are obtained at different phases of the cardiac cycle. Thus when displayed in a dynamic "cine" format, changes in wall thickening, chamber volume, and valve function can be displayed and analyzed. Blood flow velocity and blood flow volume can be calculated. MRA is an excellent technique for following patients serially after repair of complex CHD, such as tetralogy of Fallot. In these patients, MRA can be used to assess RV volume and mass and to quantify the amount of regurgitation through either the pulmonary or tricuspid valve. Other MRI techniques, such as myocardial delayed enhancement and tissue T1 weighting, can be used to quantify areas of myocardial scar in patients with cardiomyopathy or in patients after CHD repair, especially tetralogy of Fallot. **Magnetic resonance spectroscopy**, predominantly a research tool at present, provides a means of demonstrating relative concentrations of high-energy metabolites (adenosine triphosphate, adenosine diphosphate, inorganic phosphate, and phosphocreatine) within regions of the working myocardium.

Computer processing of MRA images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels, a technique known as *fly-through imaging.* These images allow the cardiologist to image the interiors of various cardiovascular structures (Fig. 472.28). These techniques are especially helpful in imaging complex peripheral arterial stenoses.

CT scanning can be used to perform rapid, respiration-gated cardiac imaging in children with resolutions down to 0.5 mm. Three-dimensional reconstruction of CT images is especially useful in evaluating branch pulmonary arteries, anomalies in systemic and pulmonary venous return, and great vessel anomalies such as coarctation of the aorta (Fig. 472.29).

Radionuclide angiography may be used to detect and quantify shunts and to analyze the distribution of blood flow to each lung. This technique is particularly useful in quantifying the volume of blood flow distribution between the two lungs in patients with abnormalities of the pulmonary vascular tree or to quantify the success of balloon angioplasty and intravascular stenting procedures. Gated blood pool scanning can be used to calculate hemodynamic measurements, quantify valvular regurgitation, and detect regional wall motion abnormalities. Thallium imaging can be performed to evaluate cardiac muscle perfusion. These methods can be used at the bedside of seriously ill children and can be performed serially, with minimal discomfort and low radiation exposure.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

472.7 Diagnostic and Interventional Cardiac Catheterization

Daniel Bernstein

The catheterization laboratory, once the site for initial diagnosis of CHD, has become the center of high-technology interventional procedures, allowing for the nonsurgical repair or palliation of heart defects that once required open heart surgery. Some centers have developed

Table 472.1 Cardiac MRI Assessment of Myocardial Inflammation

CAUSE	SPECIFIC CAUSE OF MECHANISM	KEY MRI FINDING
Infection	Infectious agents can induce cardiac injury by directly infecting cardiomyocytes or through cellular or humoral immune activation Viral: Enteroviruses, coronaviruses, adenoviruses, parvovirus B19, Herpesviridae 6, CMV, EBV, HIV, influenza; SARS-CoV-2 can infect cardiomyocytes by binding to the ACE2 receptor, although immune dysregulation is likely a more prominent mechanism of myocardial injury Bacterial: *Borrelia burgdorferi* (Lyme disease), *Treponema pallidum,* group A streptococcus (likely postinfectious) Protozoal: *Trypanosoma cruzi* (Chagas disease), *Toxoplasma gondii* Parasitic: *Echinococcus granulosus, Trichinella spiralis*	**Viral myocarditis:** Linear subepicardial or midwall LGE, commonly involving the basal inferolateral wall, basal anterior septum, mid-inferolateral wall, and basal to mid-inferior wall, with corresponding T2 hyperintensity or high T2 **Chagas disease:** LGE present in up to 70% of patients, most commonly at the left ventricular apex, apical inferior and lateral wall, and basal to mid-inferolateral wall; LGE is usually midwall or subepicardial and, less commonly, subendocardial or transmural with apical aneurysms **Bacterial and parasitic myocarditis:** Limited data on MRI findings with no specific pattern **COVID-19:** Findings may be similar to non-COVID viral myocarditis, although some studies have indicated a higher prevalence of diffuse myocardial edema, with global elevation of T1 and T2 mapping values
Postvaccination	mRNA COVID-19 vaccines: Proposed mechanisms include immune activation and dysregulation and molecular mimicry between viral spike protein and an unknown cardiac protein	**mRNA COVID-19 vaccination:** There are currently limited MRI data, mostly from case series to date; MRI findings appear to be typical for viral myocarditis, although the severity and extent of MRI abnormalities reported have been relatively mild; axillary lymphadenopathy ipsilateral to the vaccination site may be present and may be a useful clue, particularly if a history of recent vaccine administration is not provided
Systemic disease	Several systemic diseases are associated with myocardial inflammation: Vasculitides: EGPA, Kawasaki disease Connective tissue disorders: Systemic sclerosis, SLE, rheumatoid arthritis, dermatomyositis Granulomatous disease: Sarcoidosis	**EGPA:** MRI findings include patchy midwall and subepicardial LGE with corresponding T2 hyperintensity and subendocardial apical LGE with or without apical thrombus; concomitant pulmonary opacities might be present **SLE:** Patchy or linear midwall and subepicardial LGE in one third of patients; elevated T1 and T2 value decrease after antiinflammatory treatment; higher prevalence of pericardial and pleural effusion and thickening than in other causes of myocarditis **Sarcoidosis**: Patchy and nodular LGE with associated high T2, most common at the basal septum and basal inferolateral segment; associated findings include mediastinal and hilar lymphadenopathy and pulmonary opacities
Drug related	Hypersensitivity reactions: Penicillin, cephalosporins, benzodiazepines, tricyclic antidepressants Toxic reactions: Anthracyclines, amphetamines, cyclophosphamide Immune activation or dysregulation: ICI-related myocarditis	**ICI-related myocarditis**: Diffusely elevated T1 and T2 values in 78% and 43% of patients, respectively; in one study, only 48% of patients met both T1 and T2 modified Lake Louise criteria; LGE present in 48% of patients, most commonly subepicardial or midmyocardial, and predominating in the basal and mid-inferior and inferolateral segments
Other	Hypereosinophilic syndrome, cocaine, postradiation injury, thyrotoxicosis, giant cell myocarditis	**Hypereosinophilic syndrome:** Similar MRI findings to EGPA, with higher prevalence of subendocardial LGE **Giant cell myocarditis:** MRI appearance is similar to cardiac sarcoidosis, although LGE tends to be more extensive and right ventricular involvement more common

ACE2, Angiotensin-converting enzyme 2; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EGPA, eosinophilic granulomatosis with polyangiitis; ICI, immune checkpoint inhibitor; LGE, late gadolinium enhancement; SLE, systemic lupus erythematosus.
From Sanchez Tijmes F, Thavendiranathan P, Udell JA, et al. Cardiac MRI assessment of nonischemic myocardial inflammation: state of the art review and update on myocarditis associated with COVID-19 vaccination. *Radiol Cardiothorac Imaging.* 2021;3(6):e210252, Table 1.

hybrid catheterization laboratories, combining standard fluoroscopic imaging with an operating suite, allowing combined approaches to treat complex congenital heart lesions.

DIAGNOSTIC CARDIAC CATHETERIZATION

Diagnostic catheterization is still performed (1) to assist in the initial diagnosis of some complex congenital heart lesions (e.g., tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries, pulmonary atresia with intact ventricular septum and coronary sinusoids, HLHS with mitral stenosis); (2) in cases in which other imaging studies are equivocal; (3) in patients for whom hemodynamic assessment is critical (to determine the size of a left-to-right shunt in borderline cases or to determine the presence or absence of pulmonary vascular disease in an older patient with a left-to-right shunt); (4) between stages of repair of complex CHD (e.g., hypoplastic left or right heart syndromes); (5) for long-term surveillance of patients with complex CHD (e.g., after Fontan palliation for single ventricles); (6) for myocardial biopsy in the diagnosis of cardiomyopathy or in screening for cardiac rejection after cardiac transplantation; and (7) for electrophysiologic study in the evaluation of cardiac arrhythmias (see Chapter 484).

Cardiac catheterization should be performed with the patient in as close to a basal state as possible. Conscious sedation or low-level anesthesia is routine. If a deeper level of general anesthesia is required, careful choice of an anesthetic agent is warranted to avoid depression of cardiovascular function and subsequent distortion of the calculations of cardiac output, PVR and SVR, and shunt ratios.

Cardiac catheterization in critically ill infants with CHD should be performed in a center where a pediatric cardiovascular surgical team is available in the event that an operation is required immediately afterward. The complication rate of cardiac catheterization is greatest in critically ill infants; they must be studied in a thermally neutral

environment and monitored closely for hypothermia, hypoglycemia, acidosis, or excessive blood loss.

Catheterization may be limited to the right-sided cardiac structures, the left-sided structures, or both the right and left sides of the heart. The catheter is passed into the heart under fluoroscopic guidance through a percutaneous entry point in a femoral or jugular vein. In infants and in a number of older children, the left side of the heart can be accessed by passing the catheter across a patent foramen ovale to the left atrium and left ventricle. If the foramen is closed, the left side of the heart can be catheterized by passing the catheter retrograde via a percutaneous entry site in the femoral artery or, if necessary, via a transatrial septal puncture. The catheter can also be manipulated through abnormal intracardiac defects (ASD, VSD). Blood samples are obtained for measuring oxygen saturation in each cardiac chamber or blood vessel, allowing the calculation of shunt volumes. Pressures are measured for gradients across septal defects or valves and for calculating valve areas. Radiopaque contrast is injected to delineate cardiac and vascular structures. A catheter with a thermosensor tip (Swan-Ganz catheter) can be used to measure cardiac output by thermodilution. Specialized catheters can be used to measure more sophisticated indices of cardiac function; those with pressure-transducer tips can measure the first derivative of LV pressure (dP/dt). Conductance catheters can be used to generate pressure-volume loops, from which indices of both contractility (end-systolic elastance) and relaxation can be

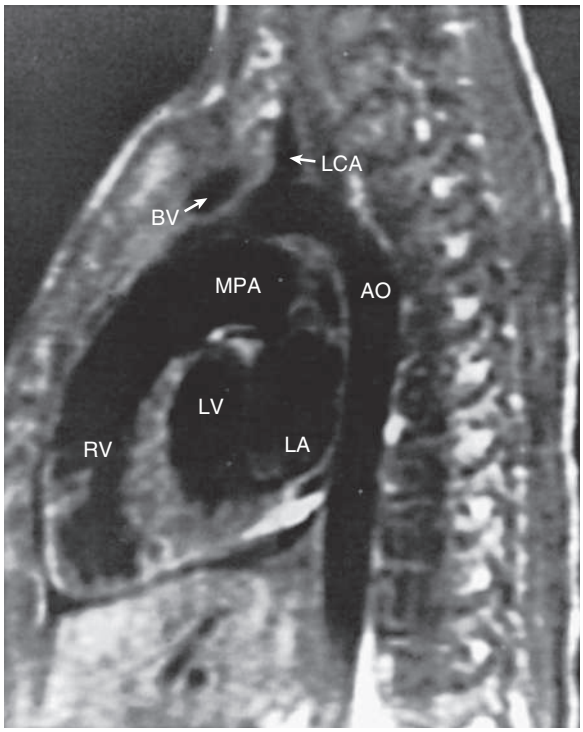

Fig. 472.26 Normal sagittal MRI. AO, Aorta; BV, brachiocephalic vein; LA, left atrium; LCA, left coronary artery; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle. *(From Bisset GS III. Cardiac and great vessel anatomy. In: El-Khoury GY, Bergman RA, Montgomery WJ, eds. Sectional Anatomy by MRI/CT. New York: Churchill Livingstone; 1990.)*

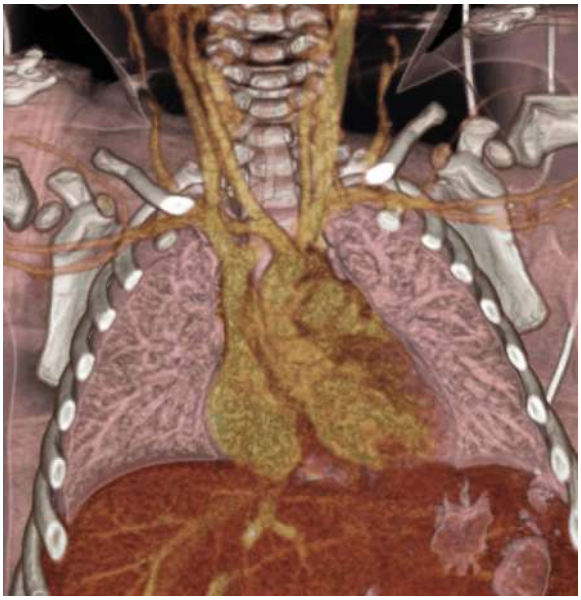

Fig. 472.28 Fly-through CT imaging in a patient with an aberrant right subclavian artery. Compression of the trachea by the aberrant artery can be visualized.

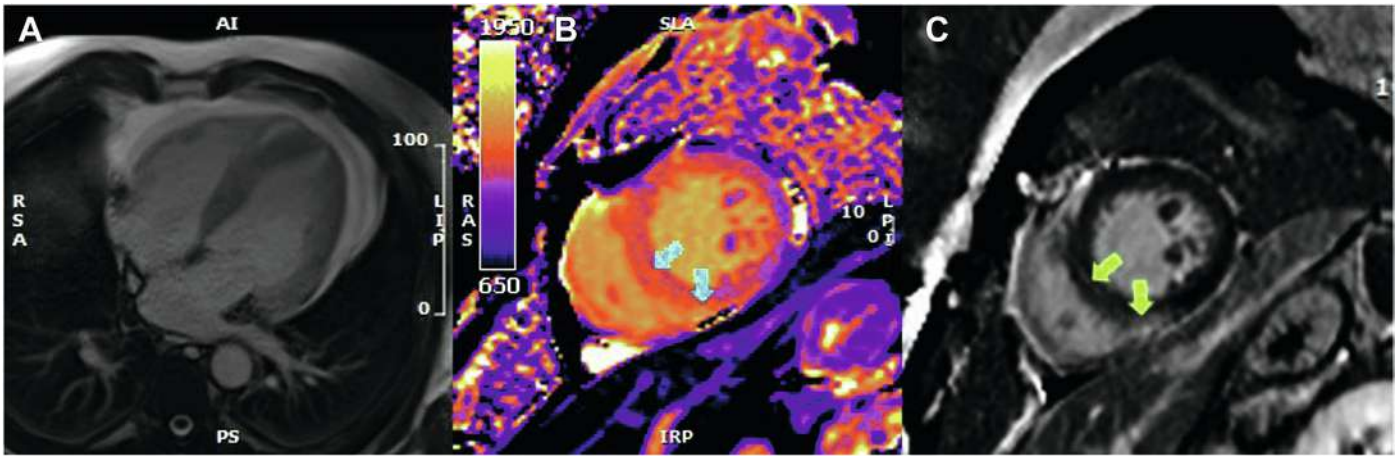

Fig 472.27 Cardiac magnetic resonance imaging (CMRI) findings in a patient with mRNA vaccine-associated myocarditis. Patient presented to hospital 2 days after the second COVID-19 mRNA vaccine with chest pain. Troponin T was elevated at 105 ng/L (normal < 15 ng/L). **A,** CMRI demonstrated normal left ventricular function. **B,** T1 mapping suggested myocardial edema in the inferoseptum and inferior segments (arrows) with corresponding nonischemic scar on late gadolinium enhancement imaging (**C,** *arrows*). *(From Crosier R, Kafil TS, Paterson DI. Imaging for Cardiovascular Complications of COVID-19: Cardiac Manifestations in Context. Can J Cardiol. 2023;39:779–792. Fig. 7.)*

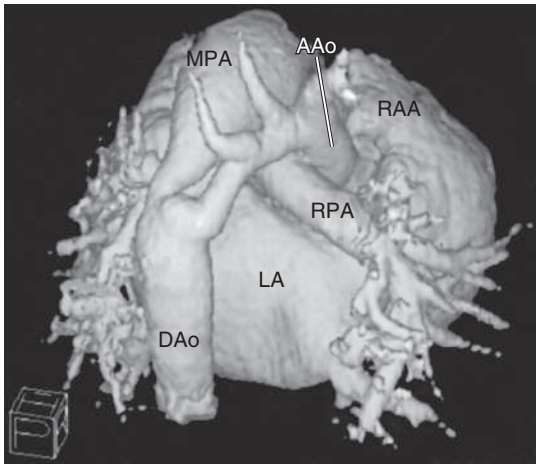

Fig. 472.29 Three-dimensional reconstruction of CT images from a neonate with severe coarctation of the aorta. The patent ductus arteriosus can be seen toward the left leading from the main pulmonary artery to the descending aorta. The tortuous and narrow coarctated segment is just to the right of the ductus. The transverse aorta is hypoplastic as well. AAo, Ascending aorta; DAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RAA, right atrial appendage; RPA, right pulmonary artery. *(Courtesy Dr. Paul Pitlick, Stanford University, Stanford, CA.)*

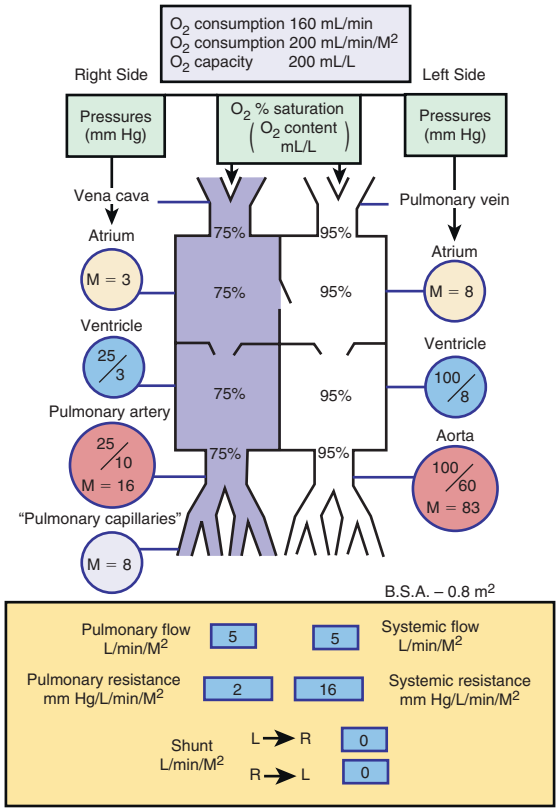

Fig. 472.30 Diagram of normal circulatory dynamics with pressure readings, oxygen content, and percent saturation. B.S.A., body surface area. *(Modified from Nadas AS, Fyler DC. Pediatric Cardiology, 3rd ed. Philadelphia: Saunders; 1972.)*

derived, although these are almost exclusively used in research studies. Complete hemodynamics can be calculated, including cardiac output, intracardiac left-to-right and right-to-left shunts, and SVR and PVR. Figure 472.30 depicts normal circulatory dynamics.

THERMODILUTION MEASUREMENT OF CARDIAC OUTPUT

The thermodilution method for measuring cardiac output is performed with a flow-directed, thermistor-tipped Swan-Ganz catheter. A known change in the heat content of the blood is induced at one point in the circulation (usually the right atrium or inferior vena cava) by injecting room-temperature saline, and the resultant change in temperature is detected at a point downstream (usually the pulmonary artery). This method is used to measure cardiac output in the catheterization laboratory in patients without shunts. Monitoring cardiac output by the thermodilution method can occasionally be useful in managing critically ill infants and children in an intensive care setting after cardiac surgery or in the presence of shock. In this case, a triple-lumen catheter is used for both cardiac output determination and measurement of pulmonary artery and pulmonary capillary wedge pressures.

ANGIOCARDIOGRAPHY

The major blood vessels and individual cardiac chambers may be visualized by selective injection of contrast material into specific chambers or great vessels. **Fluoroscopy** is used to visualize the catheter as it passes through the various heart chambers. After the cardiac catheter is properly placed in the chamber to be studied, contrast medium is injected with a power injector and cineangiograms are exposed. Modern catheterization labs use digital imaging technology, allowing for a significant reduction in radiation exposure. **Biplane cineangiocardiography** allows detailed evaluation of specific cardiac chambers and blood vessels in two planes simultaneously with the injection of a single bolus of contrast material. Various angled views (e.g., left anterior oblique, cranial angulation) are used to display specific anatomic features optimally in individual lesions.

Rapid injection of contrast medium under pressure into the circulation is not without risk, and each injection should be carefully planned. Contrast agents consist of hypertonic solutions, with some containing organic iodides, which can cause complications, including nausea, a generalized burning sensation, central nervous system symptoms, renal insufficiency, and allergic reactions. For patients with known renal insufficiency who require angiography, there are protocols to protect the kidneys involving prehydration and medications. Hypertonicity of the contrast medium may result in transient myocardial depression and a drop in blood pressure, followed soon afterward by tachycardia, an increase in cardiac output, and a shift of interstitial fluid into the circulation. This shift can transiently increase the symptoms of heart failure in critically ill patients.

INTERVENTIONAL CARDIAC CATHETERIZATION

Catheter treatment is the standard of practice for most cases of isolated pulmonary or aortic valve stenosis and for recoarctation of the aorta. A special catheter with a sausage-shaped balloon at the distal end is passed through the obstructed valve. Rapid filling of the balloon with a mixture of contrast material and saline solution results in tearing of the stenotic valve tissue, usually at the site of inappropriately fused raphe. Valvular pulmonary stenosis can be treated successfully by **balloon angioplasty**; in most patients, angioplasty has replaced surgical repair as the initial procedure of choice. The clinical results of this procedure are similar to those obtained by open heart surgery, but without the need for sternotomy or prolonged hospitalization. **Balloon valvuloplasty** for aortic stenosis has also yielded excellent results, although, as with surgery, aortic stenosis often recurs as the child grows, and multiple procedures may thus be required. One complication of both valvuloplasty and surgery is the creation of **valvular insufficiency**. This complication has more serious implications when it occurs on the aortic vs the pulmonary side of the circulation because regurgitation is less well tolerated at systemic arterial pressures.

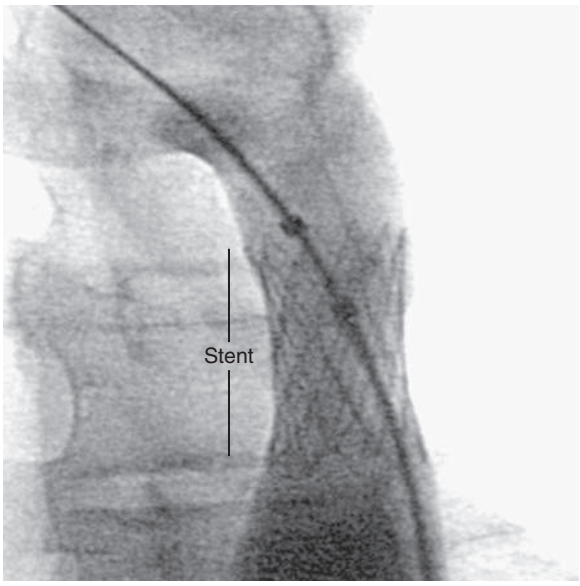

Fig. 472.31 Descending aortic angiogram showing intravascular stent placed in the descending aorta for treatment of recurrent coarctation of the aorta.

Balloon angioplasty is the procedure of choice for patients with restenosis of **coarctation of the aorta** after earlier surgery. It remains controversial whether angioplasty is the best procedure for native (unoperated) coarctation of the aorta in the infant because of greater recurrence risk and reports of late aneurysm formation, and most centers still refer primary coarctation in infants and young children for surgical repair. However, in older patients with previously undiagnosed coarctation, especially those with decreased LV function, primary angioplasty with stent placement may be considered. Other applications of the balloon angioplasty technique include amelioration of mitral stenosis, dilation of surgical conduits (e.g., RV-PA conduits), relief of branch pulmonary artery (PA) narrowing, dilation of systemic or pulmonary venous obstructions, and the pioneering balloon atrial septostomy **(Rashkind procedure)** for transposition of the great arteries (see Chapter 480.2).

Interventional catheterization techniques are being adapted for use in the fetus with lesions such as aortic stenosis to prevent their progression to more complex lesions such as HLHS. In these procedures, after administration of appropriate anesthesia, a needle is passed through the maternal abdominal wall, the uterine wall, and the fetal chest wall and directly into the fetal left ventricle (see Fig. 480.13). A coronary angioplasty balloon catheter is passed through the needle and across the stenotic aortic valve, which is then dilated. With the restoration of normal LV blood flow, it is hoped that normal LV growth potential is restored. Midterm results with this technique in a growing number of patients continue to show mixed results, with good ventricular growth leading to a two-ventricle circulation in approximately 25% of highly preselected patients.

In patients with branch pulmonary artery stenoses, **intravascular stents** are delivered over a balloon catheter and expanded within the vessel lumen (Fig. 472.31). Once placed, the stents can often be dilated to successively greater sizes as the patient grows, although their use in younger infants and children is limited by the extent they can be further expanded.

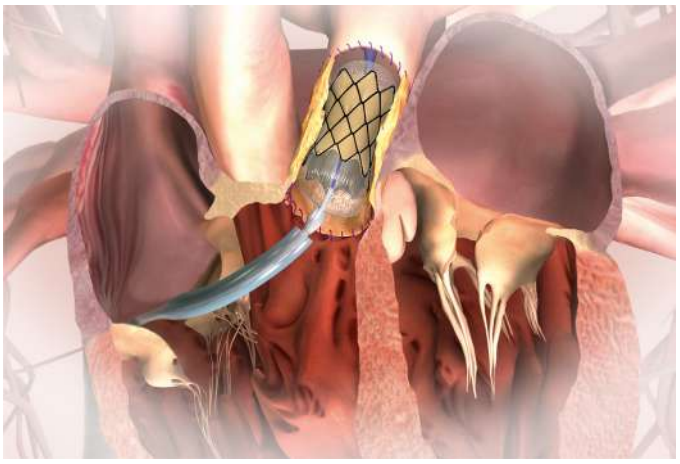

Fig. 472.32 Illustration of implantation of a Melody stent-valve delivered to the pulmonary position by a catheter inserted into the right femoral vein. *(Copyright Medtronic 2017, used with permission.)*

Closure of a small patent ductus arteriosus (PDA) is routinely achieved with catheter-delivered **coils** (see Fig. 475.11), whereas a larger PDA can be closed with a variety of sandwich-type devices. Closure of anomalous vascular connections (coronary fistulas, venovenous collaterals in cyanotic heart lesions) can also be achieved using coils. Secundum ASDs are now routinely closed with a double disk occluder (e.g., **Amplatzer**) device (see Fig. 475.3). Versions of these devices are currently in clinical trials for closure of surgically difficult-to-reach muscular VSDs and for the more common perimembranous VSD. Catheter-delivered devices may also be used as an adjunct to complex surgical repairs (e.g., dilation or stenting of branch pulmonary artery or pulmonary vein stenosis). High-risk patients undergoing the Fontan operation (see Fig. 479.9) often have a small fenestration created between the right and left sides of the circulation to serve as a "pop-off valve" for high right-sided pressure in the early surgical period. Patients with these "fenestrated Fontans" are usually candidates for subsequent closure of the fenestration with a catheter-delivered device.

One of the greatest advances in interventional catheterization over the past decade has been **transcatheter valve implantation**. Typically, a porcine valve is sewn into an expandable stent (commercially available), which is then collapsed around a balloon catheter. The device is positioned across a stenotic or insufficient pulmonary or aortic valve and the balloon inflated, expanding both the stent and the tissue valve. The balloon catheter is then removed, leaving the new valve in place, well anchored by the stent to the walls of the main pulmonary artery or aorta. At this time, the most common application in children is replacement of the **pulmonary valve** (Melody or Harmony Valve) in patients who have had prior surgery for tetralogy of Fallot (usually because of residual pulmonary insufficiency) (Fig. 472.32). In older adults, the most common application is replacement of a stenotic aortic valve (transcatheter aortic valve replacement or TAVR). Stent valves have even been placed in the tricuspid position in children with tricuspid insufficiency. For older patients with mitral and tricuspid valve insufficiency, a clip device (Mitraclip) can be delivered by catheter to create a double-orifice valve, reducing the amount of insufficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

Congenital Heart Disease

Chapter 473

Epidemiology and Genetic Basis of Congenital Heart Disease

Daniel Bernstein

Congenital heart disease (CHD) occurs in approximately 0.6–1.3% of live births. The incidence is higher in stillborns (3–4%), spontaneous abortuses (10–25%), and premature infants (approximately 2%, excluding patent ductus arteriosus [PDA]). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valve (present in 1–2% of adults). Congenital cardiac defects have a wide spectrum of severity in infants: approximately 2-3 in 1,000 newborn infants will be symptomatic with heart disease in the first year of life. The diagnosis is established by 1 week of age in 40–50% of patients with CHD and by 1 month of age in 50–60%. Approximately 13% of infants with CHD have associated extracardiac malformations. With advances in both corrective and palliative surgery, 90% of children with CHD survive to adulthood, and in the United States, there are more adults living with CHD than there are children with CHD. Despite these advances, CHD remains the leading cause of death in children with congenital malformations. When patients with repaired or palliated CHD reach older adulthood, the risk of morbidity and mortality begins to increase (see Chapter 483.1). Table 473.1 summarizes the relative frequency of the most common congenital cardiac lesions.

Most congenital defects are well tolerated in the fetus because of the parallel nature of the fetal circulation. Even the most severe cardiac defects, such as **hypoplastic left heart syndrome (HLHS)**, can usually be well compensated for by the fetal circulation. In HLHS the entire fetal cardiac output is ejected by the right ventricle via the ductus arteriosus into both the descending and ascending aortae (the latter filling in a retrograde fashion), so that fetal organ blood flow is minimally perturbed. Because the placenta provides for gas exchange and the normal fetal circulation has mixing between more highly and more poorly oxygenated blood at the foramen ovale and ductus arteriosus, fetal organ oxygen delivery is also not dramatically affected. It is only after birth, when the fetal pathways begin to close and the umbilical cord is cut, that the full hemodynamic impact of an anatomic abnormality becomes apparent. One notable exception is the case of severe regurgitant lesions, most frequently of the tricuspid valve. In these lesions, such as **Ebstein anomaly** of the tricuspid valve or severe right ventricular outflow obstruction (see Chapter 479.7), the parallel fetal circulation cannot compensate for the severe volume or pressure load imposed on the right side of the heart. In utero heart failure, often with fetal pleural and pericardial effusions, and generalized ascites **(nonimmune hydrops fetalis)** may occur.

Although the most significant transitions in the circulation occur in the immediate perinatal period, the circulation continues to undergo changes after birth, and these later changes may also have a hemodynamic impact on cardiac lesions and their apparent incidence. When pulmonary vascular resistance (PVR) falls in the first several weeks of life, left-to-right shunting through intracardiac defects increases and symptoms and signs become more apparent. Thus in patients with a **ventricular septal defect (VSD)**, heart failure is often first noticed between 1 and 3 months of age (see Chapter 475.6) and not in the immediate newborn period. The severity of various defects can also change dramatically with growth; some VSDs may become smaller and even close as the child ages. Alternatively, stenosis of the aortic or pulmonary valve, which may be only moderate in the newborn period, may become worse if valve orifice growth does not keep pace with patient growth (see Chapter 476.5). The physician should always be alert for associated noncardiac congenital malformations, which can adversely affect the patient's prognosis (Tables 473.2 and 473.3). Developmental delay of various degrees is also a concern in many patients with CHD and may have its origins in alterations in fetal blood flow patterns caused by the heart defect, postnatal hypoxemia, and the effects of cardiopulmonary bypass during open heart surgery.

ETIOLOGY

The cause of most congenital heart defects is still unknown. Many cases of CHD are multifactorial and may result from a combination of **genetic** predisposition and an as-yet-to-be-determined **environmental** stimulus. Overall, variants in approximately 400 genes have been identified as potentially causative of CHD. Despite these advances, half of cases still lack a known genetic cause. A small percentage of congenital heart lesions are related to known chromosomal abnormalities, in particular, trisomies 21, 13, and 18 and Turner syndrome; heart disease is found in >90% of patients with trisomy 18, 50% of patients with trisomy 21, and 40% of those with Turner syndrome (see Table 473.3). Ethnic factors may have a role in CHD; certain types of VSDs (supracristal) are more common in Asian children. There are also male:female differences for many common forms of CHD. The risk of CHD increases if a first-degree relative (parent or sibling) is affected, again emphasizing the role of genetics, even if the individual genes have not yet been identified.

A growing list of congenital heart lesions has been associated with specific chromosomal abnormalities, and several have even been linked to specific gene defects (see Table 473.3 and Table 473.4). **Fluorescence**

Table 473.1 Relative Frequency of Major Congenital Heart Lesions*

LESION	% OF ALL LESIONS
Ventricular septal defect	35–30
Atrial septal defect (secundum)	6–8
Patent ductus arteriosus	6–8
Coarctation of aorta	5–7
Tetralogy of Fallot	5–7
Pulmonary valve stenosis	5–7
Aortic valve stenosis	4–7
D-Transposition of great arteries	3–5
Hypoplastic left ventricle	1–3
Hypoplastic right ventricle	1–3
Truncus arteriosus	1–2
Total anomalous pulmonary venous return	1–2
Tricuspid atresia	1–2
Single ventricle	1–2
Double-outlet right ventricle	1–2
Others	5–10

*Excluding patent ductus arteriosus in preterm neonates, bicuspid aortic valve, physiologic peripheral pulmonic stenosis, and mitral valve prolapse.

Table 473.2 Genes and Loci Associated with Congenital Heart Disease

SYNDROME	GENE(S)	LOCI	CARDIAC DISEASE	CONGENITAL HD (%)	OTHER CLINICAL FINDINGS
Alagille	*JAG 1* *NOTCH2*	20p12.2 1p12-p11	PPS, TOF, PA	>90	Bile duct paucity, posterior embryotoxon, butterfly vertebrae, renal defects
CFC	*BRAF* *KRAS* *MAP2K1* *MAP2K2*	7q34 12p12.1 15q22.31 19p13.3	PVS, ASD, HCM	75	Curly hair, sparse eyebrows, feeding problems, developmental delay, intellectual disability
Cantu	*ABCC9*	12p12.1	PDA, BAV, HCM, CoA, PE, AS	75	Hypertrichosis at birth, macrocephaly, narrow thorax, coarse facies, macroglossia, broad hands, advanced bone age
Char	*TFAP2B*	6p12.3	PDA, VSD	58	Wide-set eyes, down-slanting palpebral fissures, thick lips, hand anomalies
CHARGE	*CHD7*	8q12	TOF, PDA, DORV, AVSD, VSD	75–85	Coloboma, choanal atresia, genital hypoplasia, ear anomalies, hearing loss, developmental delay, poor growth, intellectual disability
Costello	*HRAS*	11p15.5	PVS, ASD, VSD, HCM, arrhythmias	44–52	Short stature, feeding problems, broad facies, bitemporal narrowing, redundant skin, intellectual disability
22q11.2DS	*TBX1*	22q11.2 deletion	Conotruncal defects, VSD, IAA, ASD, VR	74–85	Cleft palate, bifid uvula, velopharyngeal insufficiency, microcephaly, hypocalcemia, immune deficit, psychiatric disorder, learning disability
Ellis-van Creveld	*EVC* *EVC2*	4p16.2 4p16.2	Common atrium	60	Skeletal dysplasia, short limbs, polydactyly, short ribs, dysplastic nails, respiratory insufficiency
Holt-Oram	*TBX5*	12q24.1	VSD, ASD, AVSD, conduction defects	50	Absent, hypoplastic, or triphalangeal thumbs; phocomelia; defects of radius; limb defects more prominent on left
Kabuki	*KMT2D* *KDM6A*	12q13 Xp11.3	CoA, BAV, VSD, TOF, TGA, HLHS	50	Growth deficiency, wide palpebral fissures, large protuberant ears, fetal finger pads, intellectual disability, clinodactyly
Noonan	*PTPN11* *SOS1* *RAF1* *KRAS* *NRAS* *RIT1* *SHOC2* *SOS2* *BRAF*	12q24.13 2p22.1 3p25.2 12p12.1 1p13.2 1q22 10q25.2 14q21.3 7q34	Dysplastic PVS, ASD, TOF, AVSD, HCM, VSD, PDA	75	Short stature, hypertelorism, down-slanting palpebral fissures, ptosis, low posterior hairline, pectus deformity, bleeding disorder, chylothorax, cryptorchidism
VACTERL association	Unknown		VSD, ASD, HLHS, PDA, TGA, TOF, TA	53–80	Vertebral anomalies, anal atresia, tracheoesophageal fistula, renal anomalies, radial dysplasia, thumb hypoplasia, single umbilical artery
Williams-Beuren	7q11.23 deletion (*ELN*)	7q11.23	SVAS, PAS, VSD, ASD	80	Unusual facies, thick lips, strabismus, stellate iris pattern, intellectual disability
Carpenter	*RAB23*	6p11.2	VSD, ASD, PDA, PS, TOF, TGA	50	Craniosynostosis, brachydactyly, syndactyly, polydactyly, obesity

Table 473.2 Genes and Loci Associated with Congenital Heart Disease—cont'd

SYNDROME	GENE(S)	LOCI	CARDIAC DISEASE	CONGENITAL HD (%)	OTHER CLINICAL FINDINGS
Coffin-Siris	*ARID1B* *SMARCB1* *ARID1A* *SMARCB1* *SMARCA4* *SMARCE1*	6q25 22q11 1p36.1 22q11.23 19p13.2 17q21.2	ASD, AVSD, VSD, MR, PDA, PS, DEX, AS	20–44	Developmental delay, coarse facies, hypoplastic distal phalanges, short stature, intellectual disability
Cornelia de Lange	*NIPBL* *SMC1L1* *SMC3*	5p13 Xp11.22 10q25	PVS, VSD, ASD, PDA	33	Microbrachycephaly, synophrys, arching eyebrows, growth retardation, intellectual disability, micromelia
Goldenhar	Unknown		VSD, PDA, TOF, CoA, conotruncal defects	32	Hemifacial microsomia, epibulbar dermoids, microtia, hemivertebrae
Mowat-Wilson	*ZEB2*	2q22.3	VSD, CoA, ASD, PDA, PAS	54	Short stature, microcephaly, Hirschsprung disease, intellectual disability, seizures
Rubinstein-Taybi	*CBP* *EP300*	16p13.3 22q13.2	PDA, VSD, ASD, HLHS, BAV	33	Microcephaly, growth retardation, down-slanting palpebral fissures, low-set malformed ears, prominent or beaked nose, intellectual disability, broad thumbs and toes
Smith-Lemli-Opitz	*DHCR7*	11q12-13	AVSD, HLHS, ASD, PDA, VSD	50	Microcephaly, ptosis, genital anomalies, renal anomalies, broad nasal tip with anteverted nostrils, intellectual disability, syndactyly
Adams-Oliver	*ARHGAP31* *DOCK6* *RBPJ* *EOGT* *NOTCH1* *DLL4*	3q13 19p13.2 4p15.2 3p14.1 9q34.3 15q15.1	ASD, VSD, CoA, HLHS, DORV	20	Aplasia cutis congenita, terminal transverse defects of hands, fingers, toes, feet
Baller-Gerold	*RECQL4*	8q24.3	VSD, TOF, subaortic disease	25	Craniosynostosis, micrognathia, small mouth, radial aplasia/hypoplasia, imperforate anus, renal anomalies
Beckwith-Wiedemann	*CDKNIC*	11p15.4	VSD, HLHS, PS	6.5	Macrosomia, macroglossia, omphalocele, risk of malignancy
Coffin-Lowry	*RSK2*	Xp22.2	LVNC, MVP, AVA	5–14	Growth deficiency, coarse facies, everted lower lip, hypodontia, intellectual disability
Duane-radial ray (Okihiro)	*SALL4*	20q13.2	ASD, PVS, VSD	<10	Unilateral or bilateral Duane anomaly, hypoplasia of thumbs, hypoplastic radius and ulna, renal malformations, ear anomalies
Fragile X	*FMR1*	Xq27.3	MVP, aortic dilation	<10	Macrocephaly, intellectual disability, hand flapping, speech abnormality, autism spectrum disorder, macroorchidism, seizures, prominent forehead, large ears
Nance-Horan	*NHS*	Xp22.13	TOF, VSD, PDA	<10	Congenital cataracts, strabismus, peg-shaped supernumerary teeth, other dental anomalies, prominent ears, brachymetacarpalia

Continued

Table 473.2 Genes and Loci Associated with Congenital Heart Disease—cont'd

SYNDROME	GENE(S)	LOCI	CARDIAC DISEASE	CONGENITAL HD (%)	OTHER CLINICAL FINDINGS
Peter's Plus	*B3GALTL*	13q12.3	ASD, VSD, PVS, BPV, subvalvular AS	<30	Short limb growth deficiency, intellectual disability, autism spectrum disorder, prominent forehead, cupid's bow upper lip, cleft lip ± cleft palate, Peter's anomaly, cataracts, hydronephrosis
Roberts	*ESC02*	8p21.1	ASD, AS	<20	Growth deficiency of prenatal onset, cleft lip ± cleft palate, hypertelorism, sparse hair, hypomelia with variable limb reduction defects, cryptorchidism
Robinow	*RDR2 (AR)* *WNT5A (AD)*	9q22	RVOTO	29 AD 13 AR	Macrocephaly, frontal bossing, prominent eyes, small upturned nose, short forearms, hemivertebrae, hypoplastic phalanges of hands and toes, hypoplastic genitalia
Saethre-Chotzen	*TWIST*	7p21p22	VSD	<10	Craniosynostosis, brachycephaly, high flat forehead, hypertelorism, ptosis, partial cutaneous syndactyly, broad great toes, strabismus
Short rib polydactyly type I	*DYNC2H1*	11q22.3	TGA, DORV, DOLV, AVSD, HRH	<25	Short stature, postaxial polydactyly of hands or feet, short horizontal ribs, small iliac bones, polycystic kidneys, early death from respiratory insufficiency
Simpson-Golabi-Behmel	*GPC3*	Xq26.2	TGA, VSD, PVS, CoA, AS, PDA, BAV, CM	26	Macrosomia, coarse face, macroglossia, hepatosplenomegaly, nephromegaly, variable cognitive disability
Sotos	*NSD1*	5q35.3	ASD, PDA, VSD	21	Excessive size, large hands and feet, prominent forehead, hypotonia, variable intellectual disability, scoliosis, advanced bone age
Townes-Brocks	*SALL1*	16p12.1	ASD, TOF, VSD, TA, PA, PDA	14–25	Auricular anomalies, preauricular tags, hearing loss, thumb hypoplasia/polydactyly, imperforate anus, renal agenesis, multicystic kidney, microphthalmia

22q11.2DS, 22q11.2 deletion syndrome; AD, autosomal dominant; AR, autosomal recessive; AS, aortic stenosis; ASD, atrial septal defect; AVA, aortic valve anomaly; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; BPV, bicuspid pulmonary valve; CFC, cardiofaciocutaneous; CHARGE, coloboma, heart defects, choanal atresia, retarded growth and development, genital anomalies, and ear anomalies; CM, cardiomyopathy; CoA, coarctation of the aorta; DEX, dextrocardia; DOLV, double-outlet left ventricle; DORV, double-outlet right ventricle; HCM, hypertrophic cardiomyopathy; HD, heart disease; HLHS, hypoplastic left heart; HRH, hypoplastic right heart; IAA, interruption of aortic arch; LVNC, left ventricular noncompaction; MR, mitral regurgitation; MVP, mitral valve prolapse; PA, pulmonary atresia; PAS, pulmonary artery stenosis; PDA, patent ductus arteriosus; PE, pericardial effusion; PPS, peripheral pulmonary stenosis; PS, pulmonary stenosis; PVS, pulmonary stenosis; RVOTO, right ventricular outflow tract obstruction; SVAS, supravalvular aortic stenosis; TA, truncus arteriosus; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VACTERL, association of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal and limb anomalies; VR, vascular ring; VSD, ventricular septal defect.

From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Table 5.

in situ hybridization (FISH) analysis allows rapid screening of suspected cases if a specific chromosomal abnormality is suspected. Chromosome microarray tools, including **array comparative genome hybridization** and **single nucleotide polymorphism (SNP) arrays**, have identified copy number variations (microdeletions or microduplications) or SNPs in many patients with CHD and suspicion of a congenital anomaly syndrome. These variants are submicroscopic and thus not visible on routine chromosome analysis. Comparative genome hybridization has in many cases replaced routine karyotyping in the clinical workup of newborns with CHD. Overall, 25% of cases of CHD can be associated with a gene alteration using these methodologies. Whole exome and whole genome sequencing are available for clinical genetic evaluations. The advantage of whole genome sequencing is that it allows the assessment of noncoding DNA sequences, which could participate in the regulation of gene expression of cardiac developmental gene pathways (Table 473.5).

A well-characterized genetic cause of CHD is the deletion of a large region (1.5-3 Mb) of chromosome 22q11.2, known as the **DiGeorge**

Table 473.3 Chromosomal Aneuploidies and Copy Number Variants Associated with Congenital Heart Disease

CHROMOSOME CHANGE	MAIN FEATURES	PERCENT WITH CONGENITAL HD	HEART ANOMALY
I. ANEUPLOIDES (IDENTIFIABLE BY ROUTINE KARYOTYPE)			
Trisomy 8 mosaicism	Widely spaced eyes, broad nasal bridge, small jaw, high arched palate, cryptorchidism, renal anomalies, skeletal/vertebral anomalies	25	VSD, PDA, CoA, PVS, TAPVR, TrA
Trisomy 9/mosaicism	Prenatal and postnatal growth restriction, microcephaly, deep-set eyes, low-set ears, severe intellectual disability	65	PDA, LSVC, VSD, TOF/PA, DORV
Trisomy 13 (Patau syndrome)	Cleft lip and palate, scalp defects, hypotelorism, microphthalmia or anophthalmia, colobomata of irides, holoprosencephaly, microcephaly, deafness, severe intellectual disability, rib abnormalities, polydactyly, omphalocele, renal abnormalities, hypospadias, cryptorchidism, uterine abnormalities	57–80	ASD, VSD, PDA, HLHS, laterality defects, atrial isomerism
Trisomy 18 (Edwards syndrome)	IUGR, polyhydramnios, micrognathia, short sternum, hypertonia, rocker-bottom feet, overlapping fingers and toes, TEF, CDH, omphalocele, renal anomalies, biliary atresia, severe intellectual disability	80–90	ASD, VSD, PDA, TOF, DORV, TGA, CoA, BAV, BPV, polyvalvular nodular dysplasia
Trisomy 21 (Down syndrome)	Hypotonia, hyperextensibility, epicanthal folds, up-slanting palpebral fissures, single palmar transverse crease, clinodactyly of fifth finger, brachydactyly, variable intellectual disability, premature aging	40–50	AVSD, VSD, ASD, (TOF, TGA less common)
Monosomy X (Turner syndrome, 45,X)	Lymphedema of hands and feet, widely spaced hypoplastic nipples, webbed neck, primary amenorrhea, short stature, normal intelligence, or mild learning disability	23–35	CoA, BAV, AS, HLHS, aortic dissection
II. CHROMOSOME ABNORMALITIES (IDENTIFIABLE ON KARYOTYPE AND CHROMOSOMAL MICROARRAY)			
3p25 deletion	Prenatal and postnatal growth deficiency, polydactyly, microcephaly, intellectual disability, renal anomalies	33	VSD, AVSD, tricuspid atresia
Deletion 4p16.3 (Wolf-Hirschhorn syndrome)	Microcephaly, widely spaced eyes, broad nasal bridge (Greek helmet appearance), downturned mouth, micrognathia, preauricular skin tags, severe intellectual disability, seizures, poor growth	50–65	ASD, VSD, PDA, LSVC, aortic atresia, dextrocardia, TOF, tricuspid atresia
Deletion 4q	Growth restriction, intellectual disability, cleft palate, broad nasal bridge, micrognathia, abnormal ears, genitourinary defects	50	VSD, PDA, AS, ASD, TOF, CoA
Deletion 5p (cri-du-chat)	Catlike cry, prenatal and postnatal growth restriction, round face, widely spaced eyes, epicanthal folds, single palmar transverse crease, severe intellectual disability	30–60	VSD, ASD, PDA
Deletion 9p syndrome	Craniosynostosis, trigonocephaly, up-slanting palpebral fissures, abnormal ear pinnae, scoliosis, micropenis, cryptorchidism, intellectual disability	35–50	VSD, PDA, PVS
Deletion 10p	Frontal bossing, short down-slanting palpebral fissures, small low-set ears, micrognathia, cleft palate, short neck, urinary/genital and upper-limb anomalies	42	BAV, ASD, VSD, PDA, PVS, CoA
Duplication 10q24-qter	Prenatal growth restriction, intellectual disability, camptodactyly, renal anomalies, cryptorchidism	50	AVSD, VSD
III. COPY NUMBER VARIANTS (IDENTIFIABLE BY CHROMOSOMAL MICROARRY)			
1p36 deletion	Growth deficiency, intellectual disability, microcephaly, deep-set eyes, low-set ears, hearing loss, hypotonia, seizures, CNS defects, genital anomalies	70	PDA, VSD, ASD, BAV, Ebstein anomaly, noncompaction cardiomyopathy

Continued

Table 473.3 Chromosomal Aneuploidies and Copy Number Variants Associated with Congenital Heart Disease—cont'd

CHROMOSOME CHANGE	MAIN FEATURES	PERCENT WITH CONGENITAL HD	HEART ANOMALY
1q21.1 deletion	Short stature, microcephaly, colobomas, microphthalmia, hearing loss, seizures, mild intellectual disability, autism spectrum disorder, skeletal malformations	N/A	PDA, VSD, ASD, TrA, TOF
1q21.1 duplication	Large head size, hemivertebrae, variable intellectual disability, variable autistic features, hypospadias, clubfoot	N/A	TOF, TGA, PVS
1q41q42 microdeletion	Growth restriction, intellectual disability, microcephaly, diaphragmatic hernia, seizures, short limbs	40	BAV, ASD, VSD, TGA
1q43q44 microdeletion	Prenatal and postnatal poor growth, intellectual disability, limited speech, microcephaly, deep-set eyes, microcephaly, large low-set ears, cleft palate, agenesis of corpus callosum	N/A	VSD, CoA, HLHS
2q31.1 microdeletion	Prenatal and postnatal poor growth, large ventricles, microcephaly, narrow forehead, down-slanting palpebral fissures, cleft palate/cleft lip, limb defects, hypoplastic genitalia	25	VSD, ASD, PDA
2q37 microdeletion	Short stature, obesity, intellectual disability, sparse hair, arched eyebrows, epicanthal folds, thin upper lip, small hands and feet, clinodactyly	30	VSD, ASD, CoA, hypoplastic aortic arch
Deletion 7q11.23 (Williams-Beuren syndrome)	Infantile hypercalcemia, skeletal and renal anomalies, cognitive deficits, "social" personality, elfin facies	53–85	Supravalvar AS and PS, PPS
8p23.1 deletion	Microcephaly, poor growth, deep-set eyes, malformed ears, small chin, genital anomalies in males, intellectual disability	50–75	AVSD, PVS, VSD, TOF
9q34.3 Subtelomeric deletion (Kleefstra syndrome)	Short stature, obesity, intellectual disability, microcephaly, behavior abnormalities, brain anomalies, hypertelorism, arched eyebrows, midface hypoplasia	31–44	ASD, VSD, TOF, pulmonary arterial stenosis
Deletion 11q (Jacobsen syndrome)	Growth restriction, developmental delay, thrombocytopenia, platelet dysfunction, widely spaced eyes, strabismus, broad nasal bridge, thin upper lip, prominent forehead, intellectual disability	56	HLHS, AS, VSD, CoA, Shone complex
15q24 microdeletion	Prenatal and postnatal growth restriction, intellectual disability, abnormal corpus callosum, microcephaly, high forehead, down-slanting palpebral fissures, tapered eyebrows, abnormal ear pinnae, hearing loss, hypospadias, scoliosis, coloboma, strabismus	40	PDA, pulmonary arterial stenosis, PVS
16p11.2p12.2 microdeletion	Hypotonia, intellectual disability, long narrow face, deep-set eyes, low-set malformed ears	33	TOF, BAV, pulmonary atresia
17q21 microdeletion	Abnormal hair pigmentation, up-slanting palpebral fissures, epicanthal folds, bulbous nasal tip, strabismus, ptosis, long slender fingers, hip dislocation, renal anomalies, spine deformities, cryptorchidism, global developmental delay	27	PVS, ASD, VSD, BAV
Deletion 20p12 (Alagille syndrome)	Bile duct paucity, cholestasis, skeletal or ocular anomalies, broad forehead, widely spaced eyes, underdeveloped mandible	85–94	Peripheral PA hypoplasia, TOF, PVS (left-sided heart lesions and septal defects less common)
22q11.2DS (DiGeorge, velocardiofacial, and conotruncal anomaly face syndrome)	Hypertelorism, micrognathia, low-set posteriorly rotated ears, thymic and parathyroid hypoplasia, hypocalcemia, feeding/speech/learning/behavioral disorders, immunodeficiency, palate/skeletal/renal anomalies, learning disability	75	IAA-B, TrA, isolated aortic arch anomalies, TOF, conoventricular VSD

Table 473.3 Chromosomal Aneuploidies and Copy Number Variants Associated with Congenital Heart Disease—cont'd

CHROMOSOME CHANGE	MAIN FEATURES	PERCENT WITH CONGENITAL HD	HEART ANOMALY
22q11.2 duplication	Very variable phenotype, some with velopharyngeal insufficiency, cleft palate, hearing loss, minor facial anomalies, mild learning disability to normal learning ability, hypotonia, scoliosis, frequent infections	15	TOF, HLHS, VSD, PVS, TrA
22q13 microdeletion (Phelan-McDermid syndrome)	Normal growth, intellectual disability, dolichocephaly, dysplastic ears, pointed chin, large fleshy hands, hypotonia	>25	PDA, VSD, ASD, TAPVR

22q11.2DS, 22q11.2 deletion syndrome; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; BPV, bicuspid pulmonary valve; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; HD, heart disease; HLHS, hypoplastic left heart syndrome; IAA-B, interrupted aortic arch type B; IUGR, intrauterine growth retardation; LSVC, persistent left superior vena cava; N/A, not available; PA, pulmonary artery; PDA, patent ductus arteriosus; PPS, peripheral pulmonary stenosis; PS, pulmonary stenosis; PVS, pulmonic valve stenosis; TAPVR, total anomalous pulmonary venous return; TEF, tracheoesophageal fistula; TGA, D-transposition of the great arteries; TOF, tetralogy of Fallot; TOF/PA, tetralogy of Fallot with pulmonary atresia; TrA, truncus arteriosus; VSD, ventricular septal defect.
From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Appendix Table.

Table 473.4 Disease Genes for Nonsyndromic Congenital Cardiovascular Disease

GENE	CARDIOVASCULAR MALFORMATION	NONSYNDROMIC (NS) OR SYNDROMIC (S)
TRANSCRIPTION FACTORS		
CITED2	ASD, VSD	NS
GATA4	ASD, VSD, AVSD, PVS, TOF	NS
GATA6	PTA, TOF	NS
MED13L	TGA	NS
NR2F2	AVSD, AS, CoA, VSD, HLHS, TOF	NS
NKX2-5	ASD, atrioventricular conduction delay, TOF, HLHS	NS
NKX2.6	PTA	NS
TBX20	ASD, VSD, MS, DCM	NS
ZFPM2/FOG2	TOF, DORV	NS
CELL SIGNALING AND ADHESION PROTEINS		
ACVR1/ALK2	AVSD	NS
CRELD1	ASD, AVSD	NS
GJA1	HLHS, VSD, PA	S (oculodentodigital dysplasia) and NS
JAG1	TOF, PVS, PAS	S (Alagille syndrome) and NS
NOTCH1	BAV, AS, HLHS, TOF, PVS	S (Adams-Oliver syndrome) and NS
PDGFRA	TAPVR	NS
SMAD6	BAV, CoA, AS	NS
TAB2	BAV, AS, TOF	NS
STRUCTURAL PROTEINS		
ACTC1	ASD, HCM, DCM, LVNC	NS
DCHS1	MVP	NS
ELN	SVAS	S (Williams-Beuren syndrome) and NS
MYH6	ASD, HCM, DCM	NS
MYH7	Ebstein anomaly, LVNC, HCM, DCM	NS
MYH11	PDA, TAA	NS

AS, Aortic valve stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; CoA, coarctation of aorta; DCM, dilated cardiomyopathy; DORV, double-outlet right ventricle; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; LVNC, left ventricular noncompaction cardiomyopathy; MS, mitral valve stenosis; MVP, mitral valve prolapse; NS, nonsyndromic; PA, pulmonary atresia; PAS, pulmonary artery stenosis; PDA, patent ductus arteriosus; PTA, persistent truncus arteriosus; PVS, pulmonary vein stenosis; S, syndromic; SVAS, supravalvar aortic stenosis; TAA, thoracic aortic aneurysm; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.
From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Table 8.

Table 473.5 Clinical Genetic Tests

	GENOMIC VS TARGETED	ANEUPLOIDIES AND CHROMOSOMAL REARRANGEMENTS	COPY NUMBER VARIATION	SNPs AND INDELs	EXAMPLE OF CLINICAL USE
Karyotype	Genomic	+++	+	–	Confirmation of trisomy 21
Array CGH	Genomic	++	+++	–	Multiple congenital anomalies without obvious syndromic association
FISH	Targeted	+	+	–	Suspected 22q11.2 deletion syndrome
Gene panel testing	Targeted	–	+	+++	Suspected monogenic disease with a small differential diagnosis
Exome sequencing	Genomic	–	–	+++	Broad genetic differential diagnosis without obvious syndromic association, or previous negative panel testing
Genome sequencing	Genomic	+	+	+++	Broad genetic differential diagnosis without obvious syndromic association, or previous negative panel testing and need for rapid turnaround time

Sensitivity of tests for the types of genetic variation are indicated as not detected (–), low (+), medium (++), or high (+++). Array CGH indicates comparative genomic hybridization using arrays; FISH, fluorescence in situ hybridization; INDEL, insertion or deletion; and SNP, single nucleotide polymorphism.
From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Table 1.

critical region. At least 30 genes have been mapped to the deleted region; *Tbx1,* a transcription factor involved in early outflow tract development, is one gene that has been implicated as a possible cause of DiGeorge syndrome. The estimated prevalence of 22q11.2 deletions is 1 in 4,000 live births; these occur in 2% of all patients with CHD. Cardiac lesions associated with 22q11.2 deletions are most often seen in association with either DiGeorge syndrome or **Shprintzen (velocardiofacial) syndrome**. The acronym **CATCH 22** has been used to summarize the major components of these syndromes: **C**ardiac defects, **A**bnormal facies, **T**hymic aplasia, **C**left palate, and **H**ypocalcemia. The specific cardiac anomalies are **conotruncal** defects (tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, subarterial VSD) and **branchial arch** defects (coarctation of the aorta, interrupted aortic arch, right aortic arch). Congenital airway anomalies such as tracheomalacia and bronchomalacia are sometimes present. In addition to extracardiac defects, studies in adults with repaired tetralogy of Fallot have linked the presence of a 22q11.2 microdeletion to increased all-cause mortality. Although the risk of recurrence is extremely low in the absence of a parental 22q11.2 deletion, the risk rises to 50% if one parent carries the deletion. More than 90% of patients with the clinical features of DiGeorge syndrome have a deletion at 22q11.2. A second genetic locus on the short arm of chromosome 10 (10p13p14) has also been identified, the deletion of which shares some, but not all, phenotypic characteristics with the 22q11.2 deletion; patients with del(10p) have an increased incidence of sensorineural hearing loss.

Other structural heart lesions associated with specific chromosomal abnormalities include **familial secundum atrial septal defect** (ASD) associated with **heart block** (the transcription factor Nkx2.5 on chromosome 5q35), familial ASD without heart block (the transcription factor GATA4), **Alagille syndrome** (Jagged1 on chromosome 20p12), and **Williams syndrome** (elastin on chromosome 7q11). Of interest, patients with VSDs and atrioventricular septal defects have been found to have multiple Nkx2.5 pathogenic variants in cells isolated from diseased heart tissues, but not from normal heart tissues or from circulating lymphocytes, indicating a potential role for *somatic* rather than germline changes leading to mosaicism in the pathogenesis of congenital heart defects. Tables 473.2 to 473.4 are a compilation of known genetic causes of CHD.

The most progress in identifying the genetic origin of cardiovascular disease has been made in the genetic **cardiomyopathies**, and in particular, **hypertrophic cardiomyopathy** (HCM). Over 1,000 different pathogenic variants in over a dozen genes have been implicated, most of which encode proteins of the cardiac sarcomere, either the contractile thick filament (myosin) or associated regulatory subunits (e.g., troponin or myosin binding protein C), although variants in metabolic/mitochondrial genes are also common in those presenting with HCM in infancy and early childhood. Variants of the cardiac β-**myosin heavy-chain gene *MYH7*** and the **myosin-binding protein C** gene are the most common (Table 473.6), with additional common variants including cardiac troponin T and I, α-tropomyosin, regulatory and essential myosin light chains, titin, and α-myosin heavy chain. Some patients (~15%) may carry variants in more than one sarcomeric gene. Routine clinical laboratory tests are available for most of these genes, so that patients with clinical findings of HCM or children of parents who have been diagnosed with HCM should be tested. However, not all genes causing HCM have been identified, so a negative test does not eliminate a genetic cause.

Progress has also been made in identifying the genetic basis of **dilated cardiomyopathy**, which is familial in 20–30% of cases. Autosomal dominant inheritance is most often encountered, and similar to HCM, multiple genes have been identified (see Table 473.3). X-linked inheritance accounts for 5–10% of cases of familial dilated cardiomyopathy. Pathogenic variants in the dystrophin gene are the most common in this group, causing **Duchenne or Becker muscular dystrophy**. Variants in the gene encoding tafazzin are associated with **Barth syndrome** and for some cases of isolated noncompaction of the left ventricle (LVNC). Autosomal recessive inheritance is associated with a variant in cardiac troponin I. Mitochondrial myopathies may be caused by alterations of enzymes of the electron transport chain encoded by nuclear DNA or enzymes of fatty acid oxidation encoded by mitochondrial DNA. Table 473.6 is a compilation of the most common genetic causes of cardiomyopathy.

The genetic basis of **heritable arrhythmias**, most notably the **long QT syndromes**, has been linked to pathogenic variants of genes coding for subunits of cardiac potassium and sodium channels (Table 473.7). Other heritable arrhythmias include **arrhythmogenic right ventricular dysplasia**, familial atrial fibrillation, familial complete heart block, and **Brugada syndrome**. Table 473.7 is a compilation of the most common genetic causes of arrhythmias.

Of all cases of CHD, 2–4% are associated with known environmental or adverse maternal conditions and teratogenic influences, including

Table 473.6 Genetics of Hypertrophic Cardiomyopathies

CARDIOMYOPATHY	CHROMOSOMAL LOCATION	GENE
Hypertrophic cardiomyopathy	14q1	β-Myosin heavy chain
	15q2	α-Tropomyosin
	1q31	Troponin T
	19p13.2-19q13.2	Troponin I
	11p13-q13	Myosin-binding protein C
	12q23	Cardiac slow myosin regulatory light chain
	13p21	Ventricular slow myosin essential light chain
	2q31	Titin
	3p25	Caveolin-3
	Mitochondrial DNA	tRNA-glycine
	Mitochondrial DNA	tRNA-isoleucine
Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	7q36.1	AMP-activated protein kinase
OTHER GENETIC DISEASES CAUSING CARDIAC HYPERTROPHY		
Familial amyloid disease	18q12.1	Transthyretin (TTR)
Noonan syndrome	12q24.1, 2p22.1, 3p25, 12p12.1	Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homolog 1 (SOS1), RAF1 protooncogene, GTPase KRAS
Fabry disease	Xq22	α-Galactoside A (GLA)
Danon disease	Xq24	Lysosomal-associated membrane protein 2 (LAMP2)
Hereditary hemochromatosis	6p21.3	Hereditary hemochromatosis protein (HFE)
Pompe disease	17q25	Acid α-glucosidase (GAA)
Dilated cardiomyopathy		
X-linked	Xp21	Dystrophin
	Xp28	Tafazzin
Autosomal recessive	19p13.2-19q13.2	Troponin I

Autosomal dominant: Genes encoding multiple proteins have been identified, including cardiac actin; desmin; δ-sarcoglycan; β-myosin heavy chain; cardiac troponin C and T; α-tropomyosin; titin; metavinculin; myosin-binding protein C; muscle LIM protein; α-actinin-2; phospholamban; Cypher/LIM binding domain 3; α-myosin heavy chain; SUR2A (regulatory subunit of K_{ATP} channel); and lamin A/C.

Isolated noncompaction of the left ventricle: Autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include those for α-dystrobrevin, Cypher/ZASP, lamin A/C, tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).

Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al. A clinical approach to inherited hypertrophy: the use of family history in diagnosis, risk assessment, and management. *Circ Cardiovasc Genet.* 2013;6:118–131.

maternal diabetes mellitus, maternal phenylketonuria, or systemic lupus erythematosus; congenital rubella syndrome; and maternal ingestion of drugs (lithium, ethanol, warfarin, thalidomide, antimetabolites, vitamin A derivatives, anticonvulsant agents). Associated noncardiac malformations noted in identifiable syndromes may be seen in as many as 25% of patients with CHD.

Gender differences in the occurrence of specific cardiac lesions have been identified. Transposition of the great arteries and left-sided obstructive lesions are slightly more common in males (65%), whereas ASD, VSD, PDA, and pulmonic stenosis are more common in females. No ethnic differences in the occurrence of congenital heart lesions as a whole have been noted, although there are some exceptions: supracristal VSD in children of Asian background and transposition of the great arteries, which has a higher occurrence in White infants.

GENETIC COUNSELING

Parents who have a child with CHD require counseling regarding the probability of a cardiac malformation occurring in subsequent children (Table 473.8 and see Chapter 98.1). Except for syndromes caused by a pathogenic variant of a single gene, many forms of CHD, but not all, are still relegated to a multifactorial inheritance pattern, which should result in a low risk of recurrence. When more genetic etiologies are identified, these risks are constantly updated; therefore consultation with a cardiac geneticist or genetic counselor is important.

The degree of severity may vary, as may the presence of associated defects. Careful echocardiographic screening of first-degree relatives will often uncover mild forms of CHD that were clinically silent. For example, the incidence of bicuspid aortic valve is more than double (5% vs 2% in the general population) in the relatives of children with left ventricular outflow obstruction (aortic stenosis, coarctation of the aorta, HLHS). Consultation with a knowledgeable genetic counselor is the most reliable way of providing the family with up-to-date information regarding the risk of recurrence.

Fetal echocardiography improves the rate of detection of congenital heart lesions in at-risk patients (see Chapter 472.4). This type of ultrasound is much more comprehensive than the screening ultrasound performed by an obstetrician and is usually performed and interpreted by a pediatric cardiologist specializing in fetal echocardiography. The resolution and accuracy of fetal echocardiography are excellent but are not perfect; families should be counseled that a normal fetal echocardiogram does not guarantee the absence of CHD. Congenital heart lesions may evolve in the course of the pregnancy; moderate aortic

Table 473.7 Genetics of Arrhythmias

ARRHYTHMIA	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED
Complete heart block	19q13	Not known
Long QT syndrome		
LQT1 (autosomal dominant)	11p15.5	*KVLQT1* (K^+ channel)
LQT2 (autosomal dominant)	7q35	*HERG* (K^+ channel)
LQT3 (autosomal dominant)	3p21	*SCN5A* (Na^+ channel)
LQT4 (autosomal dominant)	4q25-27	Not known
LQT5 (autosomal dominant)	21q22-q22	*KCNE1* (K^+ channel)
LQT6	21q22.1	*KCNE2* (K^+ channel)
LQT7	17q23	KCNJ2 (K^+ channel)
LQT8	12p13.3	CACNAIC (L type Ca^{2+} channel)
LQT9	3p25	CAV-3 (caveolin-3, Na^+ current)
LQT10	11q23	SCN4B (Na^+ channel)
LQT11	7q21	AKAP9 (A-kinase anchoring protein)
LQT12	20q11.21	SNTA1 (A1-synthrophin)
LQT13	11q24.3	KCNJ5 (K^+ channel)
Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)	11p15.5 21q22.1	*KVLQT1* (K^+ channel), KCNE1 (K^+ channel)
Arrhythmogenic right ventricular dysplasia (ARVD): 11 genes are now associated with ARVD (*ARVD1* through *ARVD11*) usually with autosomal dominant inheritance, but with variable penetrance. These genes include *TGFβ_3* (transforming growth factor β), *RYR2* (ryanodine receptor), *LAMR1* (laminin receptor-1), *PTPLA* (protein tyrosine phosphatase), *DSP* (desmoplakin), *PKP2* (plakophilin-2), *DSG2* (desmoglein), and *DSC2* (desmocollin).		
Familial atrial fibrillation (autosomal dominant)	10q22-q24, 6q14-16	Not known
	11p15.5	*KVLQT1* (K^+ channel)
	11p15.5	*KCNQ1* (K^+ channel)
	21q22	*KCNE2* (K^+ channel)
	17q23.1-q24.2	*KCNJ2* (K^+ channel)
	7q35-q36	*KCNH2* (K^+ channel)
Brugada syndrome (right bundle branch block, ST segment elevation, unexpected sudden death)	3p21-p24	*SCN5A* (Na^+ channel), rarely CACNA1C, HCN4, TRPM4
	3p22-p24	*GPD1L* (glycerol-3-phosphate dehydrogenase)
Catecholaminergic polymorphic ventricular tachycardia	1q43	*RYR2* (autosomal dominant)
	1p13.1	*CASQ2* (autosomal recessive)

stenosis with a normal-sized left ventricle at 18 weeks of gestation may progress to aortic atresia with a hypoplastic left ventricle by 34 weeks because of decreased flow through the atria, ventricle, and aorta in the latter half of gestation. This progression has prompted initial clinical trials of interventional treatment, such as fetal aortic balloon valvuloplasty, for the prevention of HLHS (see Chapter 472.7). In addition to diagnosing CHD in utero and subsequent parental counseling, the benefit of fetal ultrasound is that it allows for careful planning of perinatal care, especially in cases where immediate intervention in the neonatal period is warranted.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 473.8 Recurrence Risks for Isolated (Nonsyndromic) Congenital Heart Disease

DEFECT	FATHER AFFECTED (%)	MOTHER AFFECTED (%)	ONE SIBLING AFFECTED (%)	TWO SIBLINGS AFFECTED (%)
ASD	1.5–3.5	4–6	2.5–3	8
AVSD	1–4.5	11.5–14	3–4	10
VSD	2–3.5	6–10	3	10
AS	3–4	8–18	2	6
PVS	2–3.5	4–6.5	2	6
TOF	1.5	2–2.5	2.5–3	8
CoA	2–3	4–6.5	2	6
PDA	2–2.5	3.5–4	3	10
HLHS	21†		2–9*	6
TGA	2†		1.5	5
L-TGA	3–5†		5–6	NR
EA	NR	6	1	3
TrA	NR	NR	1	3
TA	NR	NR	1	3
PA	NR	NR	1	3

*Eight percent recurrence risk for HLHS; up to 22% recurrence risk for any congenital HD.
†Recurrence when one parent is affected, irrespective of sex; used in the absence of sex-stratified risks.
AS, Aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; EA, Ebstein anomaly; HLHS, hypoplastic left heart syndrome; L-TGA, congenitally corrected transposition of the great arteries; NR, not reported/insufficient data; PA, pulmonary atresia; PDA, patent ductus arteriosus; PVS, pulmonary valve stenosis; TA, tricuspid atresia; TGA, D-transposition of the great arteries; TOF, tetralogy of Fallot; TrA, truncus arteriosus; VSD, ventricular septal defect.
From Cowan JR, Ware SM. Genetics and genetic testing in congenital heart disease. *Clin Perinatol*. 2015;42(2): 373–393, Table 5.

Chapter 474

Evaluation and Screening of the Infant or Child with Congenital Heart Disease

Daniel Bernstein

The initial evaluation for suspected congenital heart disease (CHD) involves a systematic approach with two major components (Fig. 474.1). First, congenital cardiac defects can be divided into two major groups based on the presence or absence of **cyanosis**, which can be determined by physical examination aided by pulse oximetry. Second, these groups can usually be further subdivided based on whether the chest radiograph shows evidence of increased, normal, or decreased pulmonary vascular markings. Next, the electrocardiogram (ECG) can be used to determine whether right, left, or biventricular **hypertrophy** exists. The character of the heart sounds and the presence and character of any murmurs further narrow the differential diagnosis. The final diagnosis is then confirmed by echocardiography, cardiac computed tomography (CT) or magnetic resonance imaging (MRI), and/or cardiac catheterization. In a cyanotic or otherwise sick newborn, echocardiographic exam, if available, should not be delayed while awaiting these other modalities.

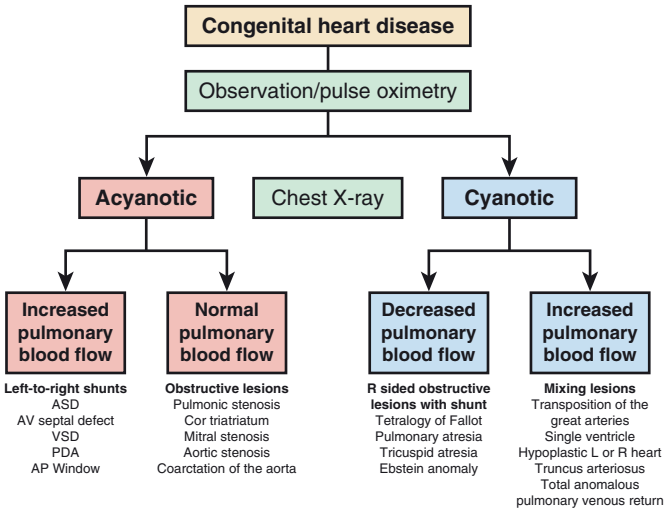

Fig. 474.1 A general algorithmic approach to the initial diagnosis of congenital heart disease, based on observation/pulse oximetry and chest x-ray, to separate patients into four major physiologic subgroups of congenital heart disease. This schematic is a broad, but useful, diagnostic overview; only the most common forms of congenital heart disease are included. A patient's initial presentation may sometimes straddle two of these physiologic groups and can evolve between them over the first week or two of life. For example, in a patient with a VSD, the pulmonary blood flow will be relatively normal in the newborn period and only increase as the pulmonary vascular resistance begins to drop. Similarly, a patient with a mixing lesion may not show pulmonary overcirculation at birth. ASD, Atrial septal defect; AV, atrioventricular; VSD, ventricular septal defect; PDA, patent ductus arteriosus, AP, aortopulmonary; L, left; R, right

Routine **pulse oximetry screening** is recommended for all newborns to detect unsuspected critical cyanotic CHD; lesions include hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, truncus arteriosus, neonatal coarctation of the aorta, and aortic arch hypoplasia/atresia. Many of these lesions are ductal dependent, and if the ductus arteriosus closes, severe cardiac decompensation will ensue. In addition, pulse oximetry may detect respiratory disorders and primary pulmonary hypertension. Screening is performed between 24 and 48 hours of life and before discharge in asymptomatic newborns. The neonate passes if the oxygen saturation is 95% or greater in the right hand or either foot AND the difference is 3% or less between the right hand and foot. The screen is failed if the saturation is less than 90% in either the right hand or foot. If it is between 90% and 94% OR there is more than a 3% difference between the right arm and foot, the screen should be repeated once in 1 hour. If the saturation is 90–94% OR there is a 3% difference after the third screen, urgent **echocardiography** is indicated. In addition, a careful reexamination of the pulses and blood pressure in the upper and lower extremity and cardiac auscultation are indicated in children with an initial positive screen.

ACYANOTIC CONGENITAL HEART LESIONS

Acyanotic congenital heart lesions can be classified according to the predominant physiologic load that they place on the heart. Although many congenital heart lesions induce more than one physiologic disturbance, it is helpful to focus on the primary load abnormality for purposes of classification. The most common lesions are those that produce a **volume load**, and the most common of these are the left-to-right shunt lesions. Atrioventricular (AV) valve regurgitation and dilated cardiomyopathies are other causes of increased volume load. The second major class of lesions causes an increase in **pressure load**, most often secondary to ventricular outflow obstruction (pulmonic or aortic valve stenosis) or narrowing of a great vessel (branch pulmonary artery stenosis or coarctation of the aorta). The chest radiograph and ECG are useful tools for differentiating between these major classes of volume- and pressure-overload lesions while awaiting confirmation with echocardiography.

Lesions Resulting in Increased Volume Load

The most common lesions resulting in increased volume load are those that cause **left-to-right shunting** (see Chapter 475): atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defects (previously known as *AV canal* or *endocardial cushion defects*), and patent ductus arteriosus. The pathophysiologic common denominator in this group is the presence of a **communication** between the systemic and pulmonary sides of the circulation, which results in **shunting** of fully oxygenated blood back into the lungs for a second passage. This shunt can be quantitated by calculating the ratio of pulmonary-to-systemic blood flow (Qp:Qs). Thus a 3:1 shunt implies three times the normal pulmonary blood flow, which is a moderately large shunt likely to cause symptoms of heart failure.

The direction and magnitude of the shunt across such a communication depend on the size of the defect, the relative pulmonary and systemic pressures and vascular resistances, and the compliances of the two chambers connected by the defect. These factors are dynamic and may change dramatically with age; intracardiac defects may grow smaller with time; pulmonary vascular resistance (PVR), which is high in the immediate newborn period, decreases to normal adult levels by several weeks of life; and chronic exposure of the pulmonary circulation to high pressure and blood flow results in a gradual increase in PVR (**Eisenmenger physiology**; see Chapter 482.2). Thus a lesion such as a large VSD may be associated with little shunting and few symptoms during the initial first 2 weeks of life. When PVR declines over the next 2-4 weeks, the volume of the left-to-right shunt increases, and symptoms begin to appear.

The increased volume of blood in the lungs decreases pulmonary compliance and increases the work of breathing. Fluid leaks into the interstitial space and alveoli and causes pulmonary edema. The infant develops the symptoms we refer to as **heart failure**, such as tachypnea, tachycardia, sweating, chest retractions, nasal flaring, and wheezing. For children with large left-to-right shunts, however, the term *heart failure* is a misnomer; total left ventricular output is not decreased but is several times greater than normal, although much of this output is ineffective because it returns through the defect back to the lungs. To maintain this high level of left ventricular output, heart rate and stroke volume are increased, in part mediated by the Frank-Starling relation as the increased ventricular volume stretches the cardiac sarcomeres and in part mediated by an increase in sympathetic nervous system activity. The increase in catecholamine release, combined with the increased work of breathing, results in an elevation in total body oxygen consumption (caused by increased β-receptor stimulation), often beyond the oxygen transport ability of the circulation. Sympathetic activation leads to peripheral vasoconstriction (caused by increased α-receptor stimulation) and to the additional symptoms of sweating and irritability, and the imbalance between oxygen supply and demand leads to failure to thrive. Remodeling of the heart occurs, with predominantly chamber dilation caused by the increased volume load and a lesser degree of hypertrophy. If left untreated, the PVR eventually begins to rise, and by several years of age, the shunt volume will decrease and symptoms will appear to improve. If still uncorrected, the shunt will eventually reverse to right-to-left as the PVR rises (see Chapter 482.2). At this point, the patient may be inoperative if the pulmonary vascular resistance is elevated and fixed (unresponsive to vasodilators), and heart-lung transplant may be the only surgical option.

Additional lesions that impose a volume load on the heart include the **regurgitant lesions** (see Chapter 477) and the **dilated cardiomyopathies** (see Chapter 488.1). Regurgitation through the AV valves is most frequently encountered in patients with partial or complete AV septal defects (AV canal or endocardial cushion defects). In these lesions, the combination of a left-to-right shunt with AV valve regurgitation increases the volume load on the heart and often leads to earlier and more severe symptoms than for isolated septal defects. Regurgitation through the tricuspid valve is seen in **Ebstein anomaly** (see Chapter 479.7). Regurgitation involving one of the semilunar (aortic or pulmonary) valves also results in a volume load but is often also associated with some degree of stenosis, leading to a combined pressure and volume load. Aortic regurgitation may be encountered in patients with a VSD directly under the aortic valve **(supracristal VSD)**, leading to two sources of volume load on the left ventricle.

In contrast to left-to-right shunts, in which intrinsic cardiac muscle contractile function is generally either normal or increased, heart muscle function can be decreased in the cardiomyopathies. **Cardiomyopathies** may affect systolic contractility (dilated cardiomyopathy) or diastolic relaxation (restrictive cardiomyopathy) or both. Decreased cardiac function results in increased atrial and ventricular filling pressure, and pulmonary edema occurs secondary to increased capillary pressure. Poor cardiac output leads to decreased end-organ blood flow, sympathetic activation, and the symptoms of poor perfusion and decreased urine output. The major causes of cardiomyopathy in infants and children include viral myocarditis,

metabolic disorders, and pathogenic gene variants in sarcomeric and other cardiac structural, functional, and energy production genes (see Chapter 488).

Lesions Resulting in Increased Pressure Load

The pathophysiologic common denominator of lesions resulting in increased pressure load is an obstruction to normal blood flow. The most frequent are **obstructions to ventricular outflow**: valvular pulmonic stenosis, valvular aortic stenosis, and coarctation of the aorta (see Chapter 476). Less common are **obstructions to ventricular inflow**: tricuspid or mitral stenosis, cor triatriatum, and obstruction of the pulmonary veins. Ventricular outflow obstruction can occur at the valve, below the valve (double-chambered right ventricle, subaortic membrane), or above the valve (branch pulmonary stenosis or supravalvular aortic stenosis). Unless the obstruction is severe, cardiac output will be maintained and the clinical symptoms of heart failure will be either subtle or absent. The heart compensates for the increased afterload by increasing wall thickness (hypertrophy), but in later stages the affected chamber develops fibrosis and will begin to dilate and can progress to ventricular failure.

The clinical picture is different when obstruction to outflow is severe, which is usually encountered in the immediate newborn period. The infant may become critically ill within several hours of birth. Severe pulmonic stenosis in the newborn period **(critical pulmonic stenosis)** results in signs of right-sided heart failure (hepatomegaly, peripheral edema) and cyanosis from right-to-left shunting across the foramen ovale. Severe aortic stenosis in the newborn period **(critical aortic stenosis)** is characterized by signs of left-sided heart failure (pulmonary edema, poor perfusion), often combined with signs of right-sided failure (hepatomegaly, peripheral edema), and may progress rapidly to total circulatory collapse. In older children, severe untreated pulmonic stenosis leads to symptoms of right-sided heart failure, but usually not to cyanosis unless a pathway persists for right-to-left shunting (e.g., patency of the foramen ovale).

Coarctation of the aorta in older children and adolescents is usually manifested as upper body hypertension and diminished pulses in the lower extremities. In the immediate newborn period, presentation of coarctation can range from decreased pulses in the lower extremities to total circulatory collapse, depending on the severity of the narrowing. The clinical presentation of coarctation may be delayed because of the normally patent ductus arteriosus in the first few days of life. In these patients, even as the ductus begins to close, the open aortic end of the ductus serves as a conduit for blood flow to partially bypass the obstruction; in more severe coarctations, blood leaving the right ventricle traverses the ductus to directly supply the descending aorta (as it did in the fetus). These infants then become symptomatic, often dramatically, when the ductus finally closes, usually within the first few weeks of life. Differential cyanosis (normal saturation in the right arm and low saturation in the foot) is a hallmark sign of this condition, and if picked up on oximetry screen before hospital discharge can be lifesaving.

CYANOTIC CONGENITAL HEART LESIONS

The cyanotic group of congenital heart lesions can also be further divided according to pathophysiology. In one major subdivision, pulmonary blood flow is *decreased,* usually from an **obstruction to right ventricular outflow** (tetralogy of Fallot, tetralogy with pulmonary atresia, or pulmonary atresia with an intact septum) or to an **obstruction to right ventricular inflow** (tricuspid atresia). In the second major subdivision, pulmonary blood flow is *increased* and oxygenated and deoxygenated blood are *mixing* (transposition of the great arteries, single ventricle, truncus arteriosus, total anomalous pulmonary venous return [TAPVR] without obstruction). In the case of TAPVR with obstruction, pulmonary flow is decreased but because there is no exit from the pulmonary veins, the lungs appear to be markedly congested. The chest radiograph is a valuable tool for initial differentiation between these two categories.

Cyanotic Lesions with Decreased Pulmonary Blood Flow

For cyanosis to occur, these lesions must include both an obstruction to pulmonary blood flow (at the tricuspid valve or pulmonary valve level) *and* a pathway by which systemic venous blood can shunt from right to left and enter the systemic circulation (via a patent foramen ovale, ASD, or VSD). Common lesions in this group include tricuspid atresia, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, pulmonary atresia with intact septum (with atrial-level shunting), and various forms of single ventricle with pulmonary stenosis or atresia (see Chapter 457). In these lesions, the degree of cyanosis depends on the degree of obstruction to pulmonary blood flow. If the obstruction is mild, cyanosis may be absent at rest. However, these patients may have hypercyanotic (tet) spells during conditions of stress. In contrast, if the obstruction is severe, pulmonary blood flow may be totally dependent on patency of the ductus arteriosus. When the ductus closes in the first few days of life, the neonate experiences profound hypoxemia.

Cyanotic Lesions with Increased Pulmonary Blood Flow

This group of lesions is not associated with obstruction to pulmonary blood flow. Cyanosis is caused by either abnormal ventricular-arterial connections or total mixing of systemic venous (deoxygenated) and pulmonary venous (oxygenated) blood within the heart (see Chapter 480). **Transposition of the great arteries** (or **vessels**) is the most common of the former group of lesions. In this condition the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. Systemic venous blood returning to the right atrium is pumped directly back to the body, and oxygenated blood returning from the lungs to the left atrium is pumped back into the lungs. The **persistence of fetal pathways** (foramen ovale and ductus arteriosus) allows for some degree of mixing in the immediate newborn period, keeping the systemic saturation from falling until the ductus begins to close; these infants can then become extremely cyanotic quite precipitously.

Total mixing lesions include cardiac defects with a common atrium or ventricle, TAPVR, and truncus arteriosus (see Chapter 480). In this group, deoxygenated systemic venous blood and oxygenated pulmonary venous blood mix completely at some location in the heart, and as a result, the oxygen saturation is equal in the pulmonary artery and aorta. If pulmonary blood flow is not obstructed, these infants have a combination of cyanosis and pulmonary overcirculation leading to heart failure. In contrast, if pulmonary stenosis is present, these infants may have cyanosis alone, similar to patients with tetralogy of Fallot.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 475

Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions

475.1 Atrial Septal Defect

Daniel Bernstein

Atrial septal defects **(ASDs)** can occur in any portion of the atrial septum—**secundum**, **primum**, or **sinus venosus**—depending on which embryonic septal structure has failed to develop normally (Fig. 475.1) (see Chapter 469). Less often, the atrial septum may be almost absent, with the creation of a functional single atrium. Isolated secundum ASDs account for approximately 7% of all congenital heart defects. The majority of cases of ASD are sporadic; autosomal dominant inheritance does occur as part of **Holt-Oram syndrome** (hypoplastic or absent thumbs, radii, triphalangism, phocomelia, first-degree heart block, ASD) or in families with both secundum ASD and heart block (see Table 473.2).

An isolated valve-incompetent **patent foramen ovale (PFO)** is a common echocardiographic finding during infancy. It is usually of no hemodynamic significance and is not considered an ASD; a PFO may play an important role if other structural heart defects are present. If another cardiac anomaly is causing increased right atrial pressure (pulmonary stenosis or atresia, tricuspid valve abnormalities, right ventricular dysfunction), venous blood may shunt across the PFO into the left atrium with resultant cyanosis. Because of the anatomic structure of the PFO, left-to-right shunting is unusual outside the immediate newborn period. In the presence of a large volume load or a hypertensive left atrium (e.g., secondary to mitral stenosis), the foramen ovale may be sufficiently dilated to result in a significant atrial left-to-right shunt. A valve-competent but probe-patent (able to be pushed opened with a catheter) PFO may be present in 15–30% of adults. An isolated PFO does not require surgical treatment, although it is a risk for paradoxical (right-to-left) systemic embolization. In adults who have had a thromboembolic stroke, echocardiographic screening for a PFO is routinely performed, and device closure of the PFO is a common treatment option.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

475.2 Ostium Secundum Defect

Daniel Bernstein

An ostium secundum defect in the region of the fossa ovalis is the most common form of ASD and is associated with structurally normal atrioventricular (AV) valves (see Fig. 475.1). **Mitral valve prolapse** has been described in association with this defect but is rarely an important clinical consideration. Secundum ASDs may be single or multiple (fenestrated atrial septum), and openings ≥2 cm in diameter are common in symptomatic older children. Large defects may extend inferiorly toward the inferior vena cava (IVC) and ostium of the coronary sinus, superiorly toward the superior vena cava (SVC), or posteriorly. Females outnumber males 3:1 in incidence. **Partial anomalous pulmonary venous return** (PAPVR), usually of the right upper pulmonary vein, may be an associated lesion.

PATHOPHYSIOLOGY

The degree of left-to-right shunting depends on the size of the defect, the relative compliance of the right and left ventricles, and the relative vascular resistance in the pulmonary and systemic circulations. In large defects, a considerable shunt of oxygenated blood flows from the left to the right atrium (Fig. 475.2). This blood is added to the usual venous return to the right atrium and is pumped by the right ventricle to the lungs. With large defects, the ratio of pulmonary-to-systemic blood flow (Qp:Qs) is usually between 2:1 and 4:1. The paucity of symptoms in infants with ASDs is related to the structure of the right ventricle in early life, when its muscular wall is still thick and less compliant, thus limiting the left-to-right shunt. As the infant becomes older and pulmonary vascular resistance (PVR) drops, the right ventricular (RV) wall becomes thinner, and the left-to-right shunt across the ASD increases. The increased blood flow through the right side of the heart results in enlargement of the right atrium and ventricle and dilation of the pulmonary artery. The left atrium may also be enlarged as the increased pulmonary blood flow returns to the left atrium, but the left ventricle and aorta are normal in size. Despite the large pulmonary blood flow, pulmonary arterial pressure is usually initially normal

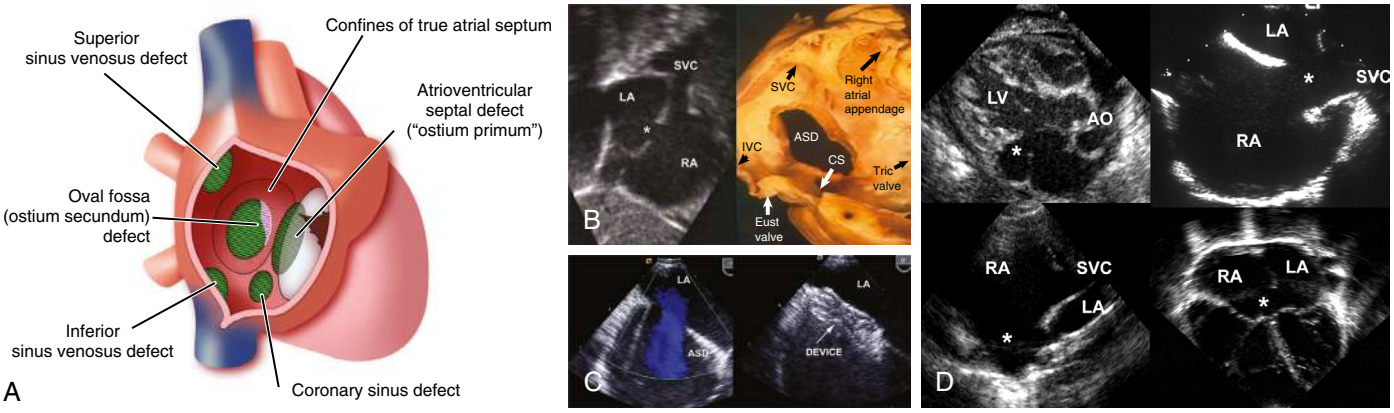

Fig. 475.1 Atrial septal defects (ASDs). **A,** Schematic diagram outlining the different types of interatrial shunting that can be encountered. Note that only the central defect is suitable for device closure. **B,** *Left,* Subcostal right anterior oblique view of a secundum ASD *(asterisk)* that is suitable for device closure. *Right,* Specimen as seen in a similar view, outlining the landmarks of the defect. **C,** *Left,* Transesophageal echocardiogram with color flow before device closure. *Right,* Taken after release of an Amplatzer device. **D,** Montage of echocardiographic interatrial communications that are not secundum ASDs *(asterisks)* and therefore not suitable for device closure. *Top left,* Coronary sinus defect caused by unroofing; *top right,* superior sinus venosus defect; *bottom left,* inferior sinus venosus defect; *bottom right,* ASD in the setting of an atrioventricular septal defect. AO, Aorta; CS, coronary sinus; Eust, eustachian; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; SVC, superior vena cava; Tric, tricuspid. *(From Webb GD, Smallhorn JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019, Fig 75.17, p. 1536.)*

because of the absence of a high-pressure communication between the pulmonary and systemic circulations. PVR remains low throughout childhood, although it may begin to increase in adulthood and may eventually result in reversal of the shunt and clinical cyanosis **(Eisenmenger syndrome)**.

CLINICAL MANIFESTATIONS

A child with an ostium secundum ASD is often asymptomatic; the lesion is often discovered during routine physical examination. Even an extremely large secundum ASD rarely produces clinically evident heart failure in childhood. However, on closer evaluation, younger children may show subtle signs of failure to thrive, and older children may have varying degrees of exercise intolerance. Often, the degree of limitation may go unnoticed by the family until after repair, when the child's growth or activity level greatly increases.

The physical findings of an ASD are usually characteristic but fairly subtle and require careful examination of the heart, paying special attention to the heart sounds. Examination of the chest may reveal a mild left precordial bulge. An RV systolic lift may be palpable at the left sternal border. Sometimes a pulmonic ejection click can be heard. In most patients with an ASD, the characteristic finding is that the second heart sound (S_2) is **widely split and fixed** in its splitting during all phases of respiration. Normally, the duration of RV ejection varies with respiration, with inspiration increasing RV volume and delaying closure of the pulmonary valve, widening the S_2 split. With an ASD, RV diastolic volume is constantly increased because of the shunt, and ejection time is prolonged throughout all phases of respiration. A systolic ejection murmur is heard; it is usually no greater than a grade 3/6, medium pitched, without harsh qualities, seldom accompanied by a thrill, and best heard at the left middle and upper sternal border. It is produced by the increased flow across the RV outflow tract into the pulmonary artery. Because the atria are at low pressure, flow across the ASD itself does not cause an audible murmur. A short, rumbling mid-diastolic murmur produced by the increased volume of blood flow across the tricuspid valve (see Fig. 475.2) is often audible at the lower-left sternal border. This finding, which may be subtle and is heard best with the bell of the stethoscope, usually indicates a Qp:Qs ratio of at least 2:1.

DIAGNOSIS

The chest radiograph shows varying degrees of enlargement of the right ventricle and atrium, depending on the size of the shunt. The pulmonary artery is enlarged, and pulmonary vascularity is increased. These signs vary and may not be conspicuous in mild cases. Cardiac enlargement is often best appreciated on the lateral chest radiograph because the right ventricle protrudes anteriorly as its volume increases. The **electrocardiogram** (ECG) shows RV volume overload: the QRS axis may be normal or exhibit right axis deviation, and a minor RV conduction delay (rsR′ pattern in the right precordial leads) may be present (Fig. 475.3). **Right ventricular hypertrophy** would be unusual

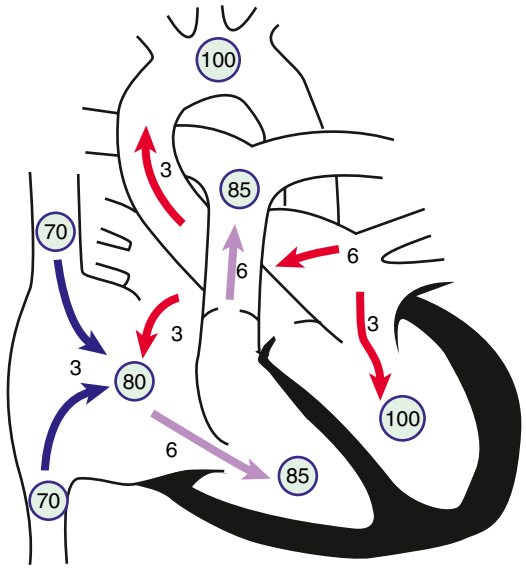

Fig. 475.2 Physiology of atrial septal defect (ASD). *Circled numbers* represent oxygen saturation (S_{O_2}) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and mixes with an additional 3 L of fully saturated blood shunting left to right across the ASD; the result is an increase in S_{O_2} in the right atrium. Six liters of blood flow through the tricuspid valve and cause a mid-diastolic flow rumble. S_{O_2} may be slightly higher in the right ventricle because of incomplete mixing at the atrial level. The full 6 L flow across the right ventricular outflow tract and cause a systolic ejection flow murmur. Six liters return to the left atrium, with 3 L shunting left to right across the defect and 3 L crossing the mitral valve to be ejected by the left ventricle into the ascending aorta (normal cardiac output).

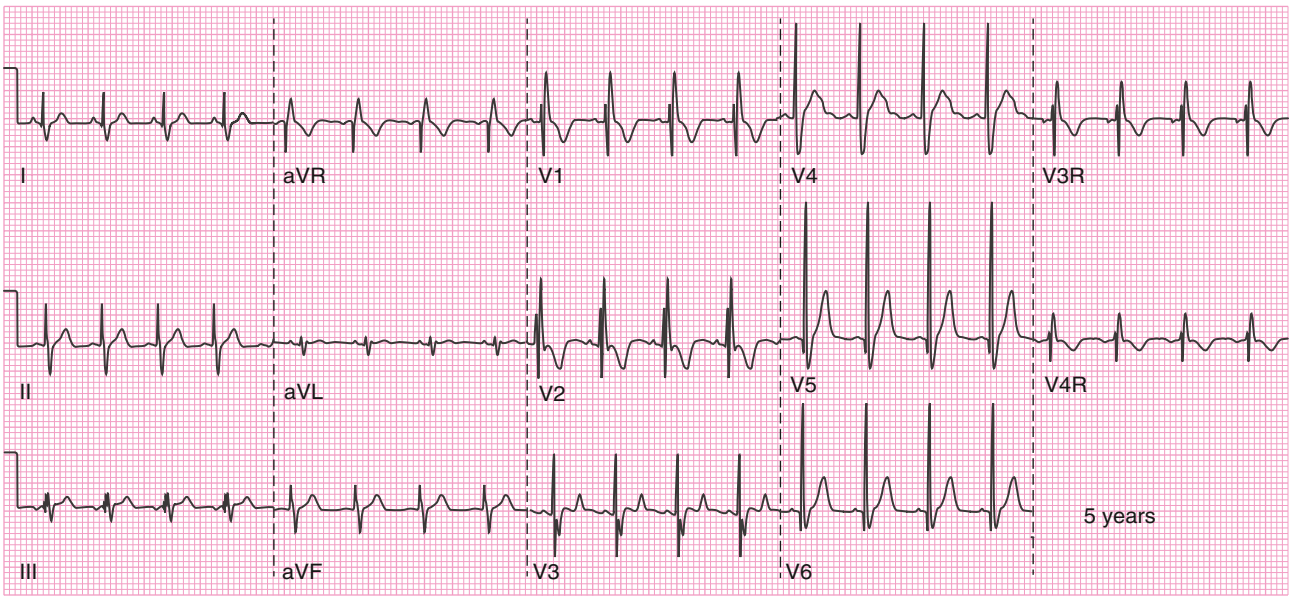

Fig. 475.3 Electrocardiogram in a child with an atrial septal defect showing rSR′ pattern (minor RV conduction delay) pattern in the right precordial leads.

in the absence of pulmonary hypertension or other lesions (e.g., valvar pulmonic stenosis).

The **echocardiogram** shows findings characteristic of RV volume overload, including an increased RV end-diastolic dimension and flattening and abnormal motion of the ventricular septum (see Fig. 475.1). A normal septum moves posteriorly during systole and anteriorly during diastole (synchronous with the left ventricular contractions). With RV overload and normal PVR, septal motion is either flattened or reversed—that is, anterior movement in systole. The location and size of the ASD are readily appreciated by two-dimensional (2D) scanning, with a characteristic brightening of the echo image seen at the edge of the defect caused by the increased reflectivity of ultrasound at the tissue-blood interface (T-artifact). The shunt is confirmed by pulsed and color flow Doppler. The normal entry of all pulmonary veins into the left atrium should be confirmed given the potential for anomalous return of the right upper pulmonary vein.

Patients with the classic features of a hemodynamically significant ASD on physical examination and chest radiography in whom echocardiographic identification of an isolated secundum ASD is made need not undergo diagnostic catheterization before repair, with the exception of an older patient, in whom PVR may be a concern. If pulmonary vascular disease is suspected, cardiac catheterization confirms the presence of the defect and allows measurement of the shunt ratio and pulmonary pressure and resistance.

If catheterization is performed, usually at the time of device closure, the oxygen content of blood from the right atrium will be much higher than that from the SVC (see Fig. 475.2). This feature is not specifically diagnostic because it may occur with PAPVR to the right atrium, with a **ventricular septal defect** (VSD) in the presence of tricuspid insufficiency, with AV septal defects associated with left ventricular–to–right atrial shunts, and with aorta–to–right atrial communications (ruptured sinus of Valsalva aneurysm). Pressure in the right side of the heart is usually normal, but small to moderate pressure gradients (<25 mm Hg) may be measured across the RV outflow tract because of functional pulmonary stenosis related to excessive blood flow. If the pressure gradient across the pulmonary valve is greater, pathologic pulmonary stenosis is likely present. In children and adolescents, PVR is almost always normal. The shunt is variable and depends on the size of the defect, but it may be of considerable volume. **Cineangiography**, performed with the catheter through the defect and in the right upper pulmonary vein, demonstrates the defect and confirms the location of the right upper pulmonary venous drainage (normal or aberrant into the SVC). **Pulmonary angiography** demonstrates the defect on the *levophase* (return of contrast to left side of the heart after passing through the lungs).

COMPLICATIONS

Secundum ASDs are usually isolated, although they may be associated with PAPVR, pulmonary valvular stenosis, VSD, pulmonary artery branch stenosis, and persistent left SVC, as well as mitral valve prolapse and insufficiency. Secundum ASDs are associated with autosomal dominant **Holt-Oram syndrome**. The gene responsible for this syndrome, situated in the region 12q21-q22 of chromosome 12, is *TBX5,* a member of the T-box transcriptional family. A **familial form of secundum ASD** associated *with* AV conduction delay has been linked to pathogenic variants in another transcription factor, Nkx2.5. Patients with **familial ASD** *without* heart block may carry a variant in the transcription factor GATA4, located on chromosome 8p22-23 (see Table 473.2).

TREATMENT

Transcatheter device or surgical closure is advised for all symptomatic patients and for asymptomatic patients with a Qp:Qs ratio of at least 2:1 and those with RV enlargement. The timing for elective closure is usually after the first year of life and before entry into school. Closure carried out at open heart surgery is associated with a mortality rate of <1%. Repair is preferred during early childhood because surgical mortality and morbidity are significantly greater in adulthood; the long-term risk of arrhythmia caused by chronic atrial dilation is also greater after ASD repair in adults. For most patients, *the procedure of choice is percutaneous catheter device closure using an atrial septal occlusion device,* implanted transvenously in the cardiac catheterization laboratory (Fig. 475.4). The results are excellent, and patients are usually discharged from the hospital the following day. The incidence of serious complications (e.g., device erosion) is very low and can be decreased by identifying high-risk patients, such as those with a deficient rim of septum in the area where the device would be anchored. Echocardiography can usually determine whether a patient is a good candidate for device closure. In patients with small secundum ASDs and minimal left-to-right shunts without RV enlargement, the consensus is that closure is usually not required. Infants with small to moderate-sized ASDs can be watched closely, because these defects will often grow smaller in the first year of life. It is unclear whether the persistence of a small ASD into adulthood increases the risk for stroke enough to warrant prophylactic closure of these defects in all patients, including those with no history of stroke.

PROGNOSIS

Small to moderate-sized ASDs detected in term infants may grow smaller or close spontaneously. Secundum ASDs are well tolerated during childhood, and significant symptoms do not usually appear until the third decade or later. Pulmonary hypertension, atrial dysrhythmias, tricuspid or mitral insufficiency, and heart failure are late manifestations; these symptoms may initially appear

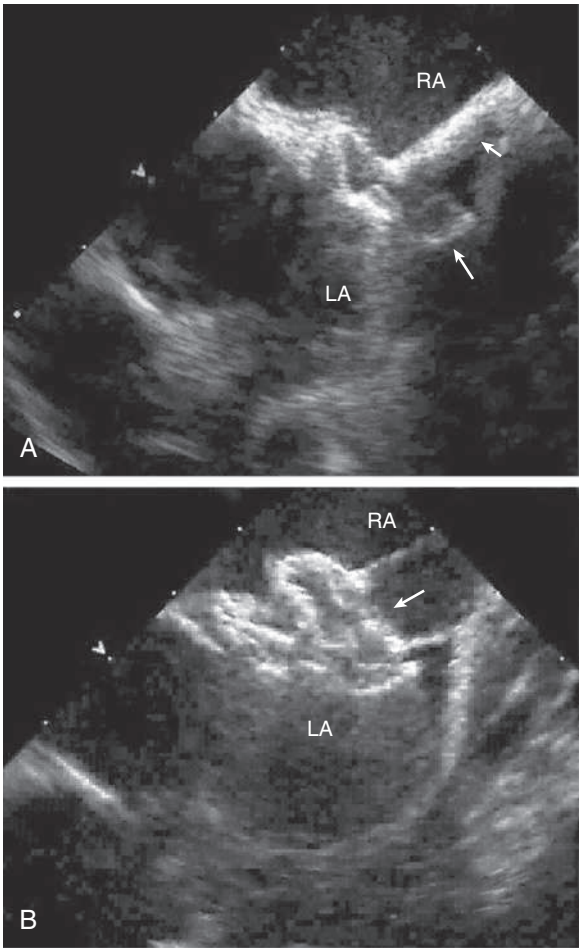

Fig. 475.4 Intravascular ultrasound imaging of transcatheter occlusion of an atrial septal defect (ASD). **A,** Catheter *(small arrow)* has been advanced across the ASD, and the left-sided disk of the device *(large arrow)* has been extruded from the sheath into the left atrium (LA). **B,** The right atrial disk *(arrow)* has now been extruded into the right atrium (RA). The two halves of the device are then locked together and the catheter detached from the occluder device and removed.

during the increased volume load of pregnancy. Infective endocarditis is extremely rare, and antibiotic prophylaxis for isolated secundum ASDs is not recommended.

The results after surgical or device closure in children with moderate-sized to large shunts are excellent. Symptoms, if present, disappear rapidly, and growth is frequently enhanced. Heart size decreases to normal, and the ECG shows decreased RV volume load. Late right-sided heart failure and arrhythmias are less common in patients who have had early repair, becoming more common in patients who undergo surgery after 20 years of age. Although early and midterm results with device closure are excellent, the long-term effects are not yet known. Reports of resolution of migraine headaches with aura in patients after device closure of an ASD or PFO suggest a possible thromboembolic etiology; however, whether to close such defects is still unclear.

475.3 Sinus Venosus Atrial Septal Defect

Daniel Bernstein

A sinus venosus ASD is situated in the upper part of the atrial septum in close relation to the entry of the superior vena cava (see Fig. 475.1). Often, one or more pulmonary veins (usually from the right lung) drain anomalously into the SVC. The SVC sometimes straddles the defect; in this case, some systemic venous blood enters the left atrium, but only rarely does it cause clinically evident cyanosis. The hemodynamic disturbance, clinical picture, ECG, and radiograph are similar to those seen in secundum ASD. The **diagnosis** can usually be made by echocardiography. If questions remain after echocardiogram regarding pulmonary venous drainage, cardiac CT or MRI is usually diagnostic. Cardiac catheterization is rarely required, except in adult patients in whom PVR assessment may be important. **Anatomic correction** generally requires surgical insertion of a patch to close the defect while incorporating the entry of any anomalous pulmonary veins into the left atrium. If the anomalous vein drains high in the SVC, the vein can be left intact and the ASD closed to incorporate the SVC mouth into the left atrium. The SVC proximal to the venous entrance is then detached and anastomosed directly to the right atrial appendage (Warden procedure). This procedure avoids direct suturing of the pulmonary vein, with less chance of future stenosis. Surgical results are generally excellent. Rarely, sinus venosus defects involve the IVC.

475.4 Partial Anomalous Pulmonary Venous Return

Daniel Bernstein

One or several pulmonary veins may return anomalously to the SVC or IVC, right atrium, or coronary sinus and produce a left-to-right shunt of oxygenated blood. *Partial* anomalous pulmonary venous return (PAPVR) usually involves some or all of the veins from only one lung, typically the right. When an associated ASD is present, it is generally of the sinus venosus type but can be secundum (see Chapters 475.2 and 475.3). When an ASD is detected by echocardiography, one must always search for associated PAPVR. The history, physical signs, and electrocardiographic and radiologic findings are indistinguishable from those of an isolated ostium secundum ASD. Occasionally, an anomalous vein draining into the IVC is visible on chest radiography as a crescentic shadow of vascular density along the right border of the cardiac silhouette **(scimitar syndrome)**; in these patients an ASD is not usually present, but **pulmonary sequestration** or **lung hypoplasia** and anomalous arterial supply to that lobe are common findings. **Total anomalous pulmonary venous return** (TAPVR) is a cyanotic lesion and is discussed in Chapter 480.7. Echocardiography generally confirms the diagnosis. MRI and CT are also useful if there is a question regarding pulmonary venous drainage or in cases of scimitar syndrome. If cardiac catheterization is performed, the presence of anomalous pulmonary veins is demonstrated by selective pulmonary arteriography, and anomalous pulmonary arterial supply to the right lung is demonstrated by descending aortography.

The prognosis for PAPVR is excellent, similar to that for ostium secundum ASDs. When a significant left-to-right shunt is present, surgical repair is performed. The associated ASD should be closed in such a way that pulmonary venous return is directed to the left atrium. A single anomalous pulmonary vein without an atrial communication may be difficult to redirect to the left atrium; if the shunt is small and the right ventricle is not enlarged, it may be left unoperated.

475.5 Atrioventricular Septal Defects (Ostium Primum and Atrioventricular Canal or Endocardial Cushion Defects)

Daniel Bernstein

The abnormalities encompassed by atrioventricular (AV) septal defects are grouped together because they represent a spectrum of a basic embryologic abnormality, a **deficiency of the AV septum**. In the normal heart, the tricuspid valve sits slightly lower (more toward the cardiac apex) than does the mitral valve, and thus a small portion of septum (the AV septum) separates the left ventricle from the right atrium. This septum is deficient in all forms of AV septal defect. When the AV septum is absent and there is also an **ostium primum** defect, the main communication is situated in the lower portion of the atrial septum and overlies the mitral and tricuspid valves. In most cases a **cleft in the anterior leaflet of the mitral valve** is also noted. The tricuspid valve is usually functionally normal, although some anatomic abnormality of the septal leaflet is present. The ventricular septum is intact.

An **AV septal defect**, formerly known as an *AV canal defect* or *endocardial cushion defect,* consists of a defect of the AV septum and contiguous atrial and ventricular septal defects with a common AV valve. The severity of the AV valve abnormality varies considerably. In a **complete AV septal defect**, a single AV valve is common to both ventricles and consists of an anterior and a posterior bridging leaflet related to the ventricular septum, with a lateral leaflet in each ventricle. The anterior bridging leaflet can be divided into right- and left-sided components or may be single and free floating over the ventricular septum. Complete AV septal defect is one of the most common forms of congenital heart disease in children with **Down syndrome**.

Transitional varieties of these defects also occur and include ostium primum defects with clefts in the anterior mitral and septal tricuspid valve leaflets and small VSDs and, less commonly, ostium primum defects with normal AV valves. In some patients the atrial septum is intact but a VSD is seen in the inlet septum, similar to that found in the complete form of AV septal defect. Sometimes, AV septal defects are associated with varying degrees of hypoplasia of one of the ventricles, known as either **left-dominant** or **right-dominant AV septal defect**. If the affected ventricular chamber is too small to establish a two-ventricle circulation, surgical palliation, aiming for an eventual Fontan procedure, is performed (see Chapters 479.4 and 480.10).

PATHOPHYSIOLOGY

In ostium primum defects, the basic abnormality is the combination of a left-to-right shunt across the atrial defect and mitral (or occasionally tricuspid) insufficiency. The shunt is usually moderate to large, the degree of mitral insufficiency is generally mild to moderate, and pulmonary artery pressure (PAP) is typically normal or only mildly increased. The physiology of this lesion is therefore similar to that of an ostium secundum ASD.

In complete AV septal defects, left-to-right shunting occurs at both the atrial and the ventricular level (Fig. 475.5). Additional shunting may occur directly from the left ventricle to the right atrium (known as a *Gerbode shunt*) because of absence of the AV septum. Pulmonary

hypertension and an early tendency to increase PVR are common. AV valvular insufficiency, which may be moderate to severe, further increases the volume load on one or both ventricles. If the defect is large enough, some right-to-left shunting may also occur at the atrial and ventricular levels and lead to mild arterial desaturation. With time, progressive pulmonary vascular disease increases the right-to-left shunt so that clinical cyanosis develops (**Eisenmenger physiology**; see Chapter 482.2). The risk for development of pulmonary vascular disease is greater in patients with Down syndrome, and therefore surgical correction is usually considered early in these patients, within the first 3-6 months of life.

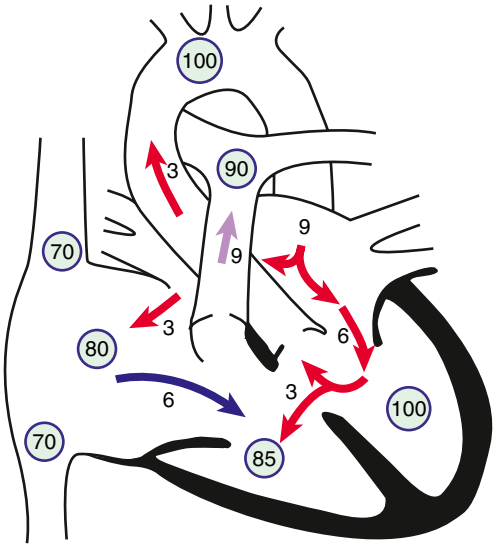

Fig. 475.5 Physiology of atrioventricular (AV) septal defect. *Circled numbers* represent oxygen saturation (S_{O_2}) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 3:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and mixes with 3 L of fully saturated blood shunting left to right across the atrial septal defect; the result is an increase in S_{O_2} in the right atrium. Six liters of blood flow through the right side of the common AV valve, joined by an additional 3 L of saturated blood shunting left to right at the ventricular level, further increasing S_{O_2} in the right ventricle. The full 9 L flow across the right ventricular outflow tract into the lungs. Nine liters return to the left atrium, with 3 L shunting left to right across the defect and 6 L crossing the left side of the common AV valve and causing a mid-diastolic flow rumble. Three liters of this volume shunt left to right across the ventricular septal defect, and 3 L are ejected into the ascending aorta (normal cardiac output).

CLINICAL MANIFESTATIONS

Many children with an isolated ostium primum defect are asymptomatic, and the anomaly is discovered during a general physical examination. In patients with moderate shunts and mild mitral insufficiency, the physical signs are similar to those of the secundum ASD, but with an additional apical holosystolic murmur caused by mitral insufficiency.

A history of exercise intolerance, easy fatigability, and recurrent pneumonia may be obtained, especially in infants with large left-to-right shunts and severe mitral insufficiency. In these patients, cardiac enlargement is moderate or marked and the precordium is hyperdynamic. Auscultatory signs produced by the left-to-right shunt include a normal or accentuated first heart sound (S_1); wide, fixed splitting of S_2; a pulmonary systolic ejection murmur sometimes preceded by a click; and a low-pitched, mid-diastolic rumbling murmur at the lower-left sternal edge or apex, or both, as a result of increased flow through the AV valves. **Mitral insufficiency** may be manifested by a harsh (occasionally very high-pitched) **apical holosystolic murmur** that radiates to the left axilla.

With *complete* AV septal defects, heart failure and intercurrent pulmonary infection usually appear in infancy. The liver is enlarged, and the infant often develops respiratory symptoms, feeding intolerance, and failure to thrive. Cardiac enlargement is moderate to marked, and a systolic thrill is frequently palpable at the lower-left sternal border. A precordial bulge and lift may be present as well. S_1 is normal or accentuated. S_2 is fixed and widely split if the pulmonary flow is massive. A low-pitched, mid-diastolic rumbling murmur is audible at the lower-left sternal border, indicative of increased blood flow across the right side of the common AV valve, and a pulmonary systolic ejection murmur is produced by the large pulmonary flow. The harsh apical holosystolic murmur of mitral insufficiency may also be present.

DIAGNOSIS

Chest radiographs of children with complete AV septal defects often show moderate to severe cardiac enlargement caused by the prominence of both ventricles and atria. The pulmonary artery is large, and pulmonary vascularity is increased.

The ECG in patients with a complete AV septal defect is *distinctive* and usually diagnostic. Principal abnormalities include (1) superior and rightward orientation of the mean frontal QRS axis (−90 to −180 degrees) represented by the QRS being negative in both lead I and lead aVF, (2) counterclockwise inscription of the superiorly oriented QRS vector loop (manifested by a Q wave in leads I and aVL), (3) signs of biventricular hypertrophy or isolated RV hypertrophy, (4) RV conduction delay (rSR′ pattern in leads V_3R and V_1), (5) normal or tall P waves, and (6) occasional prolongation of the P-R interval (Fig. 475.6).

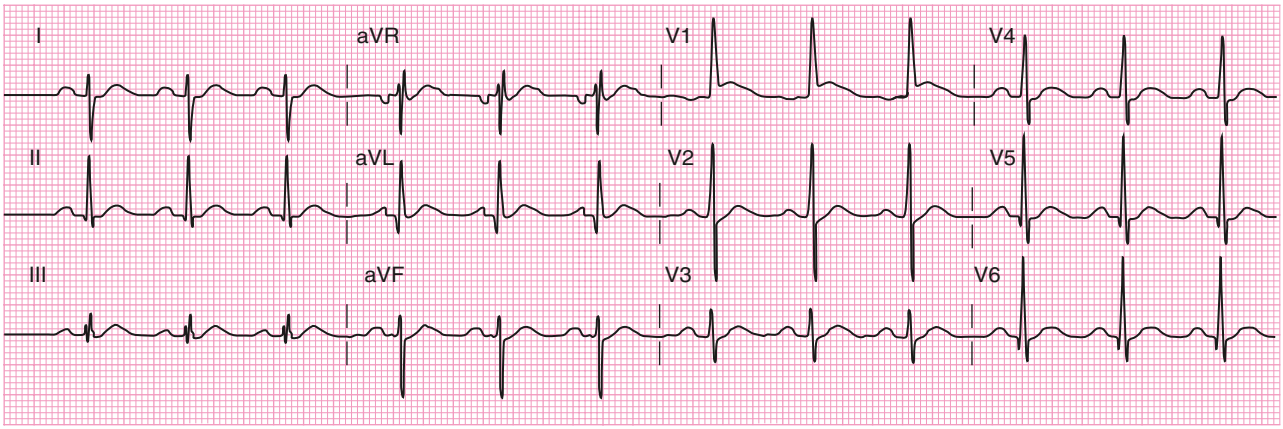

Fig. 475.6 Electrocardiogram from an infant with atrioventricular septal defect. Note that the QRS complexes are negative in both leads I and roughly equipotential in lead III, so the QRS axis is −150 degrees. There is also right ventricular hypertrophy (RVH) and a minor right ventricular conduction delay with an RSR′ pattern in aVR.

The echocardiogram is diagnostic and shows signs of RV enlargement (Fig. 475.7). There is encroachment of the mitral valve into the left ventricular outflow tract (LVOT); the abnormally low position of the AV valves results in a "gooseneck" deformity of the LVOT. In normal hearts the tricuspid valve inserts slightly more toward the apex than does the mitral valve. In AV septal defects, both valves insert at the same level because of absence of the AV septum. In complete AV septal defects, the inlet portion of the ventricular septum is also deficient, and the common AV valve is readily appreciated. Pulsed and color flow Doppler echocardiography will demonstrate left-to-right shunting at the atrial, ventricular, or left ventricular–to–right atrial levels and can be used to semiquantitate the degree of AV valve insufficiency. Echocardiography is useful for determining the insertion points of the chordae of the common AV valve, the relative size of the two ventricles, and evaluating the presence of associated lesions such as patent ductus arteriosus (PDA) or coarctation of the aorta.

Cardiac catheterization and angiocardiography are rarely required to confirm the diagnosis unless pulmonary vascular disease is suspected, as when the diagnosis has been delayed beyond early infancy, especially in patients with Down syndrome in whom the development of pulmonary vascular disease may be more rapid. Catheterization demonstrates the magnitude of the left-to-right shunt, the degree of PVR elevation, and the severity of insufficiency of the common AV valve. By oximetry, the shunt is usually demonstrable at both the atrial and the ventricular level. Arterial oxygen saturation is normal or only mildly reduced unless pulmonary vascular disease is present. Children with ostium primum defects generally have normal or only moderately elevated PAP. Conversely, complete AV septal defects are associated with RV and pulmonary arterial hypertension and, in older patients, increased PVR (see Chapter 482.2).

Selective left ventriculography will demonstrate deformity of the common AV valve and distortion of the LVOT caused by the abnormally apical position of this valve (gooseneck deformity). The abnormal anterior leaflet of the mitral valve is serrated, and insufficiency is noted. Direct shunting of blood from the left ventricle to the right atrium may also be demonstrated.

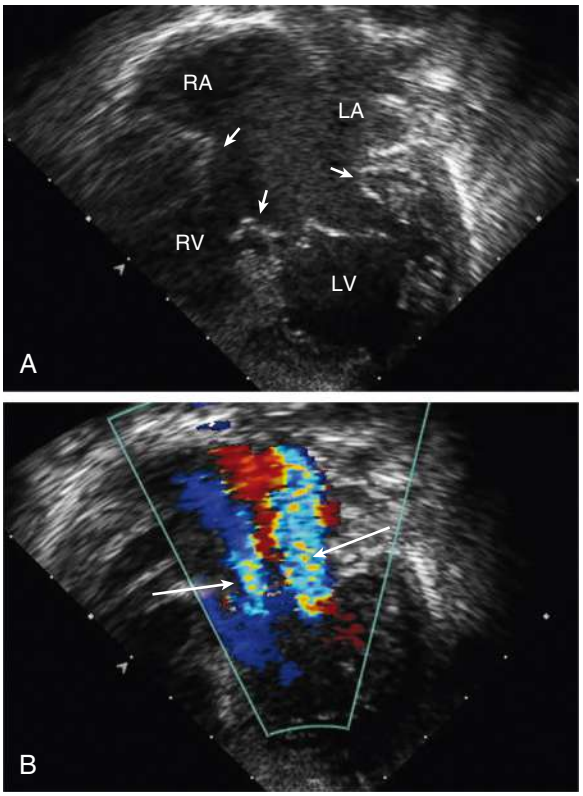

Fig. 475.7 Echocardiograms of atrioventricular (AV) septal defect. **A,** Subcostal four-chamber view demonstrating the common AV valve *(arrows)* spanning the atrial and ventricular septal defects. **B,** Doppler imaging shows two jets of regurgitation through the left side of the common AV valve *(arrows)*. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TREATMENT

Ostium primum defects are approached surgically from an incision in the right atrium. The cleft in the mitral valve is located through the atrial defect and is repaired by direct suture. The defect in the atrial septum is usually closed by insertion of a patch prosthesis. The surgical mortality rate for ostium primum defects is very low.

Surgical treatment of complete AV septal defects is more complex, although highly successful. The postoperative course may be prolonged in infants with severe cardiac failure and in those with pulmonary hypertension. Because of the risk of **pulmonary vascular disease** developing as early as 6-12 months of age, surgical intervention must be performed during infancy. Full correction of these defects can be readily accomplished. Palliation with *pulmonary arterial banding* is uncommon now and reserved for the small subset of patients who have other associated lesions that make early corrective surgery too risky. However, banding may not be effective in patients with a large amount of AV valve regurgitation, as the higher pressure will only increase the regurgitation. The atrial and ventricular defects are patched, using either one or two separate patches, and the AV valves are reconstructed. Uncommon complications include surgically induced heart block requiring placement of a permanent pacemaker and excessive LVOT narrowing requiring surgical revision. More common long-term complications include residual tricuspid or mitral regurgitation, because full repair of very abnormal valves is often not possible. This requires long-term surveillance because these patients may require replacement with a prosthetic valve later in life.

PROGNOSIS

The prognosis for unrepaired complete AV septal defects depends on the magnitude of the left-to-right shunt, degree of PVR elevation, and severity of AV valve insufficiency. Before the advent of early corrective surgery, death from cardiac failure during infancy was common, and patients who survived without surgery usually developed pulmonary vascular disease. Most unoperated patients with ostium primum defects and minimal AV valve involvement are asymptomatic or have only minor, nonprogressive symptoms until they reach the third or fourth decade of life, similar to the course of patients with secundum ASDs. Today, long-term results after surgical repair are excellent. Late postoperative **complications** include atrial arrhythmias and heart block, progressive narrowing of the LVOT requiring surgical revision, and eventual worsening of AV valve regurgitation (usually on the left side) requiring reoperation or replacement with a prosthetic valve.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

475.6 Ventricular Septal Defect

Daniel Bernstein

Ventricular septal defect is the most common cardiac malformation and accounts for 25% of cases of congenital heart disease. Defects may occur in any portion of the ventricular septum, but the most common are of the **membranous** type (Fig. 475.8). These defects are in a posteroinferior position, anterior to the septal leaflet of the tricuspid valve. VSDs between the crista supraventricularis and the papillary muscle of the conus may be associated with pulmonary stenosis and other manifestations of tetralogy of Fallot (see Chapter 479.1). VSDs superior to the crista supraventricularis **(supracristal)** are less common; these are found just beneath the pulmonary valve and may impinge on an aortic sinus and cause aortic insufficiency (see Chapter 475.7). Supracristal

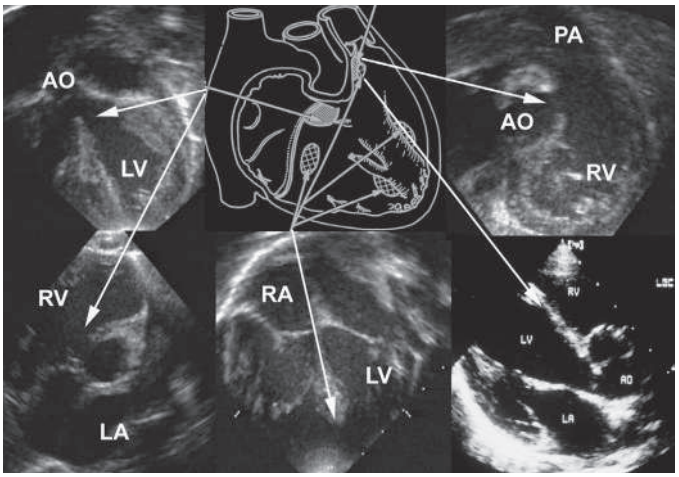

Fig. 475.8 Different types of ventricular septal defects (VSDs). The **central diagram** outlines the location of the various types of defects as seen from the right ventricle. **Two left images** show a perimembranous VSD as seen in the five-chamber and short-axis views. Note the defect is roofed by the aorta and is next to the tricuspid valve. **Bottom middle** echocardiogram shows a muscular apical defect. **Top right image** is a right anterior oblique view in a doubly committed VSD. **Bottom right image** is a short axis view showing an outlet VSD with prolapse of the right coronary cusp. AO, Aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. *(From Webb GD, Smallhorn JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019, Fig 75.21, p. 1514.)*

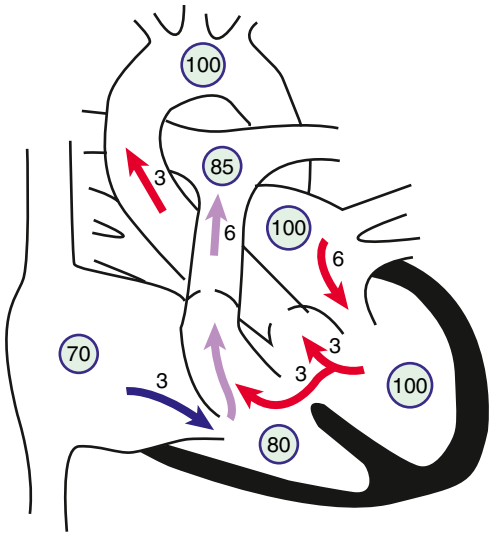

Fig. 475.9 Physiology of a moderate-to-large ventricular septal defect. *Circled numbers* represent oxygen saturation (So_2) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and flows across the tricuspid valve. An additional 3 L of blood shunt left to right across the VSD, resulting in increased So_2 in the right ventricle. Six liters of blood are ejected into the lungs (2:1 shunt). Pulmonary arterial saturation may be further increased because of incomplete mixing at the right ventricular level. Six liters return to the left atrium, cross the mitral valve, and cause a mid-diastolic flow rumble. Three liters of this volume shunt left to right across the VSD, and 3 L are ejected into the ascending aorta (normal cardiac output).

VSDs are more common in patients of Asian descent. VSDs in the midportion or apical region of the ventricular septum are muscular in type and may be single or multiple ("Swiss cheese" septum).

PATHOPHYSIOLOGY

The physical size of the VSD is a major determinant of the size of the left-to-right shunt. When the defect is large, the level of pulmonary vascular resistance (PVR) in relation to systemic vascular resistance (SVR) is the major determinant of the shunt's magnitude, since the large defect will essentially equalize pressure between the two ventricles. When a small communication is present (usually <5 mm), the VSD is deemed to be pressure **restrictive**, meaning that right ventricular (RV) pressure is normal or only slightly elevated. The higher pressure in the left ventricle drives the shunt left to right, and the size of the defect limits the magnitude of the shunt. In larger, **nonrestrictive** VSDs (usually >10 mm), RV and left ventricular (LV) pressures are equalized. In these defects the direction of shunting and the shunt magnitude are determined by the PVR/SVR ratio (Fig. 475.9).

After birth in patients with a large VSD, PVR may remain elevated, delaying the normal postnatal decrease, and thus the size of the left-to-right shunt may initially be limited. Because of normal involution of the media of small pulmonary arterioles, PVR begins to fall in the first few weeks after birth, and the size of the left-to-right shunt then increases. Eventually, a large left-to-right shunt develops, and clinical symptoms become apparent. In most cases during early infancy, PVR is only slightly elevated, and the major contribution to pulmonary hypertension is the large communication allowing exposure of the pulmonary circulation to systemic pressure and the large pulmonary blood flow. With continued exposure of the pulmonary vascular bed to high systolic pressure and high flow, pulmonary vascular obstructive disease eventually develops. When the PVR/SVR ratio approaches 1:1, the shunt becomes bidirectional, signs of heart failure abate, and the patient begins to show signs of cyanosis (**Eisenmenger physiology**; see Chapter 482.2), intermittent at first, but then more constant. In rare infants with a large VSD, more often in those with Down syndrome, PVR never decreases after birth, and symptoms may remain minimal until Eisenmenger physiology becomes evident.

The magnitude of intracardiac shunts is usually described by the Qp:Qs ratio. If the left-to-right shunt is small (Qp:Qs <1.5:1), the cardiac chambers are not appreciably enlarged, and the pulmonary vascular bed is probably normal. If the shunt is large (Qp:Qs >2:1), left atrial and LV volume overload occurs, and RV and pulmonary arterial hypertension may be present if the defect is large. The main pulmonary artery, left atrium, and left ventricle are enlarged.

CLINICAL MANIFESTATIONS

The clinical findings of patients with a VSD vary according to the size of the defect and pulmonary blood flow and pressure. Small VSDs with trivial left-to-right shunts and normal pulmonary artery pressure (PAP) are common. These patients are asymptomatic, and the cardiac lesion is usually found during routine physical examination. Characteristically, a loud, harsh, or blowing holosystolic murmur is present and heard best over the lower-left sternal border, and it is frequently accompanied by a thrill. In a few cases the murmur ends before the second heart sound (S_2), presumably because of closure of the defect during late systole. A short, loud, harsh systolic murmur localized to the apex in a neonate is often a sign of a tiny VSD in the apical muscular septum. These tiny defects most often close during infancy. In premature infants the murmur of a VSD may be heard early because PVR decreases more rapidly.

Large VSDs with excessive pulmonary blood flow and pulmonary hypertension are responsible for signs of congestive heart failure: dyspnea, feeding difficulties, poor growth, profuse perspiration, and recurrent pulmonary infections in early infancy. Cyanosis is usually absent, but duskiness is sometimes noted during infections or crying. Prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. It is less likely to be prominent in the newborn period before PVR drops. The

pulmonic component of S_2 may be increased as a result of pulmonary hypertension. The presence of a mid-diastolic, low-pitched rumble at the apex is caused by increased blood flow across the mitral valve and usually indicates a Qp:Qs ratio ≥2:1. This murmur is best appreciated with the bell of the stethoscope.

DIAGNOSIS

In patients with small VSDs, the chest radiograph is usually normal, although minimal cardiomegaly and a borderline increase in pulmonary vasculature may be observed. The ECG is generally normal but may suggest LV hypertrophy. The presence of RV hypertrophy on ECG is worrisome and a warning that the defect is not small and that the patient has pulmonary hypertension or an associated lesion such as pulmonic stenosis. In large VSDs the chest radiograph shows gross cardiomegaly with prominence of both ventricles, the left atrium, and the pulmonary artery (Fig. 475.10). Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The ECG shows biventricular hypertrophy; the P waves may be notched (indicative of left atrial [LA] enlargement).

The 2D echocardiogram shows the position and size of the VSD (see Fig. 475.8). In small defects, especially those of the muscular septum, the defect itself may be difficult to image and is visualized only by color Doppler examination. In defects of the **membranous septum**, a thin membrane (called a **ventricular septal aneurysm** but consisting of abnormal tricuspid valve tissue) can partially cover the defect and limit the volume of the left-to-right shunt. Echocardiography is also useful for estimating shunt size by examining the degree of volume overload of the left atrium and left ventricle; in the absence of associated lesions, the extent of their increased dimensions is a good reflection of the size of the left-to-right shunt. Pulsed Doppler examination shows whether the VSD is pressure restrictive by calculating the pressure gradient across the defect. Such calculation allows an estimation of RV pressure and helps determine whether the patient is at risk for the development of early pulmonary vascular disease. The echocardiogram can also be useful to determine the presence of aortic valve insufficiency or aortic leaflet prolapse, which can be associated especially with supracristal VSDs.

The hemodynamics of a VSD can also be demonstrated by cardiac catheterization, although catheterization currently is performed only when laboratory data do not fit well with the clinical findings or when pulmonary vascular disease is suspected. Oximetry demonstrates increased oxygen content in the right ventricle; because some defects eject blood almost directly into the pulmonary artery (streaming), the full magnitude of the oxygen saturation increase may only be apparent when pulmonary arterial blood is sampled. Small, restrictive VSDs are associated with normal right-sided heart pressures and PVR. Large, nonrestrictive VSDs are associated with equal or near-equal pulmonary and systemic systolic pressure and variable elevations in PVR. Pulmonary blood flow may be 2-4 times systemic blood flow. In patients with such "hyperdynamic pulmonary hypertension," PAP is at systemic level, but PVR is only minimally elevated because of the high pulmonary blood flow (resistance is equal to the mean pressure divided by flow). However, if left untreated until Eisenmenger syndrome is present, systolic and diastolic PAP will be elevated and the degree of left-to-right shunting minimal. In these cases, desaturation of blood in the left ventricle is usually encountered. The size, location, and number of ventricular defects can be demonstrated by left ventriculography. Contrast medium passes across the defect(s) to opacify the right ventricle and pulmonary artery. Administration of 100% oxygen with and without nitric oxide can be used to determine whether PVR, if elevated, is still reactive and therefore more likely to decrease after surgical repair.

TREATMENT

The natural course of a VSD depends to a large degree on the size of the defect. A significant number (30–50%) of small defects close spontaneously, most frequently during the first 2 years of life. Small *muscular* VSDs are more likely to close (up to 80%) than *membranous* VSDs (up to 35%). Most defects that close do so before age 4 years, although spontaneous closure has been reported in adults. VSDs that close often have ventricular septal aneurysm (accessory tricuspid valve) tissue covering them that limits the magnitude of the shunt. Most children with small restrictive defects remain asymptomatic, without evidence of an increase in heart size, PAP, or PVR; a long-term risk is infective endocarditis. Some long-term studies of adults with unoperated small VSDs show an increased incidence of arrhythmia, subaortic stenosis, and exercise intolerance. It is recommended that an isolated, small, hemodynamically insignificant VSD is not an indication for surgery. However, with the declining risk of open heart surgery, whether all VSDs should be closed electively in mid-childhood is still debated.

It is less common for moderate or large VSDs to close spontaneously, although even defects large enough to result in heart failure may become smaller, and up to 8% may close completely. More frequently, infants with large defects have repeated episodes of respiratory infection and heart failure despite optimal medical management. Heart failure may be manifested in many of these infants primarily as failure to thrive. Pulmonary hypertension occurs as a result of high pulmonary blood flow. These patients are at risk for pulmonary vascular disease if the defect is not repaired during early infancy.

Patients with VSD are also at risk for the development of **aortic valve regurgitation**, the greatest risk occurring in patients with a supracristal VSD (see Chapter 475.7), where the position of the defect undermines support for the right coronary or noncoronary leaflet of the aortic valve. A small number of patients with VSD develop **acquired infundibular pulmonary stenosis**, which then protects the pulmonary circulation from the short-term effects of pulmonary overcirculation and the long-term effects of pulmonary vascular disease. In these patients the clinical picture changes from that of a VSD with a large left-to-right shunt to a VSD with pulmonary stenosis. The shunt may diminish in

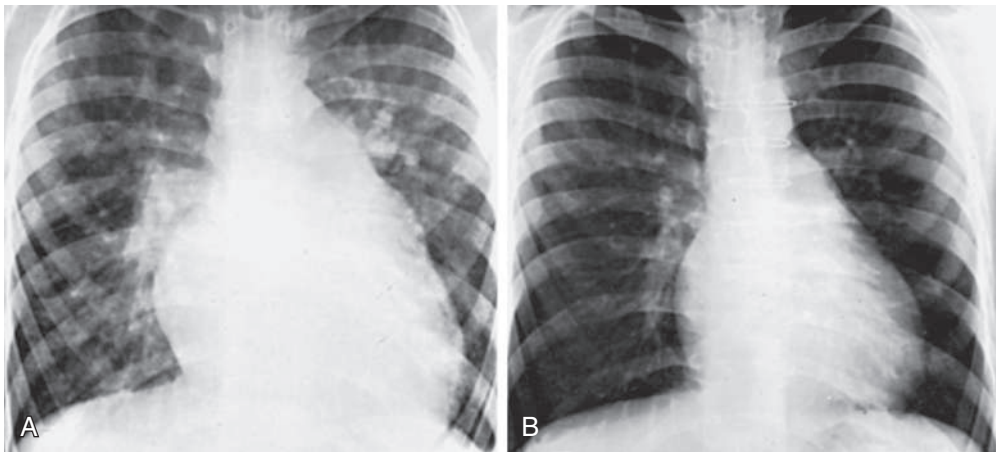

Fig. 475.10 A, Preoperative radiograph in a patient with a ventricular septal defect with a large left-to-right shunt and pulmonary hypertension. Significant cardiomegaly, prominence of the pulmonary arterial trunk, and pulmonary overcirculation are evident. B, Three years after surgical closure of the defect, heart size is greatly decreased and the pulmonary vasculature is normal.

size, become balanced, or even become a net right-to-left shunt. These patients must be carefully distinguished from those in whom an Eisenmenger physiology develops (see Chapter 482.2).

In patients with small VSDs, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life, with no restrictions on physical activity. Surgical repair is not recommended; however, routine follow-up with the cardiologist is important. As protection against infective endocarditis, the integrity of primary and permanent teeth should be carefully maintained; with the latest revision of the American Heart Association (AHA) guidelines, antibiotic prophylaxis is no longer recommended for dental visits or surgical procedures (see Chapter 486). These patients can be monitored by a combination of clinical examination and noninvasive laboratory tests until the VSD has closed spontaneously. Echocardiography is used to estimate PAP, screen for the development of LVOT pathology (subaortic membrane or aortic regurgitation), and confirm spontaneous closure.

In infants with a large VSD and heart failure, management is directed at reducing symptoms and optimizing the patient's fluid status so that they are in optimal condition for surgical repair. In infants in the first year of life, if early treatment is successful, the size of the defect may sometimes diminish in size with clinical improvement. Selected patients in this group can be observed closely with echocardiographic monitoring. The clinician must be alert not to confuse clinical improvement caused by a decrease in defect size with clinical changes caused by the development of Eisenmenger physiology. Because surgical closure can be carried out at low risk in most infants, medical management should not be pursued in symptomatic infants after an initial unsuccessful trial. Because pulmonary vascular disease can usually be prevented when surgery is performed within the first year of life, even infants with well-controlled heart failure should not have surgery delayed inordinately unless there is echocardiographic evidence that the defect is becoming pressure restrictive.

Indications for surgical closure of a VSD include patients at any age with large defects in whom clinical symptoms and failure to thrive cannot be controlled medically or in whom the defect is not decreasing in size; infants between 6 and 12 months of age with moderate to large defects associated with pulmonary hypertension, even if the symptoms are controlled by medication; and patients older than 24 months with a Qp:Qs ratio greater than 2:1. Patients with a supracristal VSD of any size are usually referred for surgery because of their higher risk for developing aortic valve regurgitation (see Chapter 475.7). Severe pulmonary vascular disease nonresponsive to pulmonary vasodilators is a contraindication to closure of a VSD.

Transcatheter closure has been used successfully in treating larger muscular VSDs, which may be difficult to access by surgery. Perimembranous and intracristal VSD catheter closure is more complex because of the proximity of the defect to the tricuspid valve and conduction system; devices have been designed more specifically to address these issues and are currently being investigated. Preliminary data suggest that, for carefully selected patients (usually children beyond infancy), the results appear to be comparable to surgical repair. Hybrid methods employing a sternotomy with device placement through the anterior wall of the right ventricle under transesophageal echocardiographic and fluoroscopic visualization have also been performed in difficult-to-approach defects.

PROGNOSIS

The results of primary surgical repair are excellent, and complications leading to long-term problems (residual ventricular shunts requiring reoperation or device closure and heart block requiring a pacemaker) are rare. Surgical risks are somewhat higher for defects in the muscular septum, particularly apical defects and multiple (Swiss cheese–type) VSDs. Some of these patients may require pulmonary arterial banding if symptomatic, with subsequent debanding and repair of multiple VSDs at an older age.

After surgical closure of the left-to-right shunt, the hyperdynamic heart becomes quiet, cardiac size decreases toward normal (see Fig. 475.10), thrills and murmurs are absent, and pulmonary artery hypertension regresses. The patient's clinical status greatly improves. Most infants begin to thrive, often quite rapidly after hospital discharge, and cardiac medications are no longer required. Catch-up growth occurs in most patients within the next year. In some patients, after successful surgery, systolic ejection murmurs of low intensity persist for months. The long-term prognosis after surgery is excellent. Patients with a small VSD and those who have undergone surgical closure without residua are considered to be at standard risk for health and life insurance.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

475.7 Supracristal Ventricular Septal Defect with Aortic Insufficiency

Daniel Bernstein

A supracristal VSD can be complicated by **prolapse of the aortic valve** into the defect and aortic insufficiency, which may eventually develop in 50–90% of these patients. Although supracristal VSD accounts for approximately 5% of all patients with VSD, the incidence is higher in Asian children and in males. The VSD, which may be small or moderate in size, is located anterior to and directly below the pulmonary valve in the outlet septum, superior to the muscular ridge known as the *crista supraventricularis,* which separates the trabecular body of the right ventricle from the smooth outflow portion. The right or, less often, the noncoronary aortic cusp prolapses into the defect and may partially or even completely occlude it. Such occlusion may limit the amount of left-to-right shunting and give the false impression that the defect is not large. Aortic insufficiency is most often not recognized until after 5 years of age, or even later. Although most common with supracristal VSDs, aortic insufficiency is occasionally associated with VSDs located in the membranous septum.

Early heart failure secondary to a large left-to-right shunt rarely occurs, but without surgery, moderate to severe aortic insufficiency and left ventricular failure may eventually ensue. The murmur of a supracristal VSD is usually heard at the mid- to upper-left sternal border, as opposed to the lower-left sternal border, and it is sometimes confused with that of pulmonic stenosis. A decrescendo diastolic murmur will be appreciated at the upper-right or mid-left sternal borders if there is aortic insufficiency. More advanced degrees of aortic insufficiency will be associated with a wide pulse pressure and a hyperdynamic precordium. These clinical findings must be distinguished from PDA or other defects associated with aortic runoff.

The clinical manifestations vary widely, from trivial aortic regurgitation and small left-to-right shunts in asymptomatic children to florid aortic insufficiency and massive cardiomegaly in symptomatic adolescents. Closure of all supracristal ventricular VSDs is usually recommended to prevent the development of aortic regurgitation, even in an asymptomatic child. Patients who already have significant aortic insufficiency require surgical intervention to prevent irreversible left ventricular dysfunction. Surgical options depend on the degree of damage to the valve, and for mild insufficiency, may include simple closure of the defect to bolster the valve apparatus without touching the valve itself, valvuloplasty for more significant degrees of involvement, and replacement with a prosthesis or homograft or aortopulmonary translocation (Ross procedure) for severe involvement.

475.8 Patent Ductus Arteriosus

Daniel Bernstein

During fetal life, most of the pulmonary arterial blood is shunted right to left through the ductus arteriosus into the aorta (see Chapter 470). Functional closure of the ductus normally occurs soon after birth, usually within the first week of life, but if the ductus remains patent when

PVR falls, aortic blood then is shunted left to right into the pulmonary artery. The aortic end of the ductus is just distal to the origin of the left subclavian artery, and the ductus enters the pulmonary artery at its bifurcation. Female patients with patent ductus arteriosus (PDA) outnumber males 2:1. PDA is also associated with maternal rubella infection during early pregnancy, an uncommon occurrence in the vaccination era. PDA is a common problem in premature infants because the smooth muscle in the wall of the preterm ductus is less responsive to high Po_2 and therefore less likely to constrict after birth. In these infants the shunt through a PDA can cause severe hemodynamic derangements and several major sequelae (see Chapter 131.3).

When a term infant is found to have a PDA, the wall of the ductus is deficient in both the mucoid endothelial layer and the muscular media, whereas in the premature infant, the PDA usually has a normal structure. Thus a PDA persisting beyond the first few weeks of life in a term infant rarely closes spontaneously or with pharmacologic intervention, whereas if early pharmacologic or surgical intervention is not required in a premature infant, spontaneous closure occurs in most instances. A PDA is seen in 10% of patients with other congenital heart lesions and often plays a critical role in providing a source of pulmonary blood flow when the right ventricular outflow tract is stenotic or atretic (see Chapter 479) or in providing systemic blood flow in the presence of aortic coarctation or interruption (see Chapters 476.6-476.8) or in hypoplastic left heart syndrome.

A PDA is a common finding (~90%) in patients with **smooth muscle dysfunction syndrome (SMDS)** caused by a heterozygous pathogenic variant in *ACTA2*. Additional features include congenital mydriasis, pulmonary hypertension, aortic and other arterial aneurysms, moyamoya-like cerebrovascular disease, and intestinal hypoperistalsis.

PATHOPHYSIOLOGY

Because of the higher aortic pressure postnatally, blood shunts left to right through the ductus, from the aorta to the pulmonary artery. The extent of the shunt depends on the size of the ductus and on the PVR/SVR ratio. If the PDA is small, pressures within the pulmonary artery, the right ventricle, and the right atrium are normal. If the PDA is large, PAP may be elevated to systemic levels during both systole and diastole. Thus patients with a large PDA are at high risk for the development of pulmonary vascular disease if left unoperated.

CLINICAL MANIFESTATIONS

A small PDA is usually asymptomatic and is usually diagnosed by the presence of a heart murmur. A large PDA will result in heart failure similar to that encountered in infants with a large VSD. Stunting of physical growth may be a major manifestation in infants with large shunts. A small PDA is associated with normal peripheral pulses, and a large PDA results in bounding peripheral arterial pulses and a *wide pulse pressure,* caused by runoff of blood into the pulmonary artery during diastole. Although normal in size when the ductus is small, the heart is moderately or grossly enlarged in cases with a large communication; in these patients the apical impulse is prominent and, with cardiac enlargement, is heaving. A **thrill**, maximal in the second left interspace, is often present and may radiate toward the left clavicle, down the left sternal border, or toward the apex. It is usually systolic but may also be palpated throughout the cardiac cycle. The classic continuous murmur is described as "machinery-like" in quality. It begins soon after onset of S_1, reaches maximal intensity at the end of systole, and wanes in late diastole. It may be localized to the second left intercostal space or radiate down the left sternal border or to beneath the left clavicle. When PVR is increased, the diastolic component of the murmur may be less prominent or absent. In patients with a large left-to-right shunt, a low-pitched mitral mid-diastolic murmur may be audible at the apex as a result of the increased volume of blood flow across the mitral valve.

DIAGNOSIS

If the left-to-right shunt is small, the ECG is normal; if the ductus is large, LV or biventricular hypertrophy is present. The diagnosis of an isolated, uncomplicated PDA is untenable when RV hypertrophy is present on the ECG.

Radiographic studies in patients with a large PDA show a prominent pulmonary artery with increased pulmonary vascular markings. Cardiac size depends on the degree of left-to-right shunting; it may be normal or moderately to greatly enlarged. The chambers involved are the left atrium and left ventricle. The aortic knob may be normal or prominent.

On echocardiogram the cardiac chambers will be normal in size if the ductus is small. With large shunts, LA and LV dimensions are increased. The ductus can easily be visualized directly and its size estimated. Color and pulsed Doppler examinations demonstrate systolic or diastolic (or both) retrograde turbulent flow in the pulmonary artery and aortic retrograde flow in diastole in the presence of a large shunt (Fig. 475.11).

The clinical signs and echocardiographic findings are sufficiently distinctive to allow an accurate diagnosis by noninvasive methods in most patients. In rare patients with atypical findings, cardiac catheterization may be indicated for confirmation of diagnosis. Cardiac catheterization will demonstrate either normal or increased pressure in the right ventricle and pulmonary artery, depending on the size of the ductus. The presence of oxygenated blood shunting into the pulmonary artery confirms the left-to-right shunt. The catheter may pass from the pulmonary artery through the ductus into the descending aorta. Injection of contrast medium into the ascending aorta shows opacification of the pulmonary artery from the aorta and identifies the ductus.

Other conditions can produce systolic and diastolic murmurs in the pulmonic area in an acyanotic patient (see Chapter 471). An **aortico-pulmonary window defect** may rarely be clinically indistinguishable from a patent ductus, although in most cases the murmur is only systolic and is loudest at the right rather than the left upper sternal border

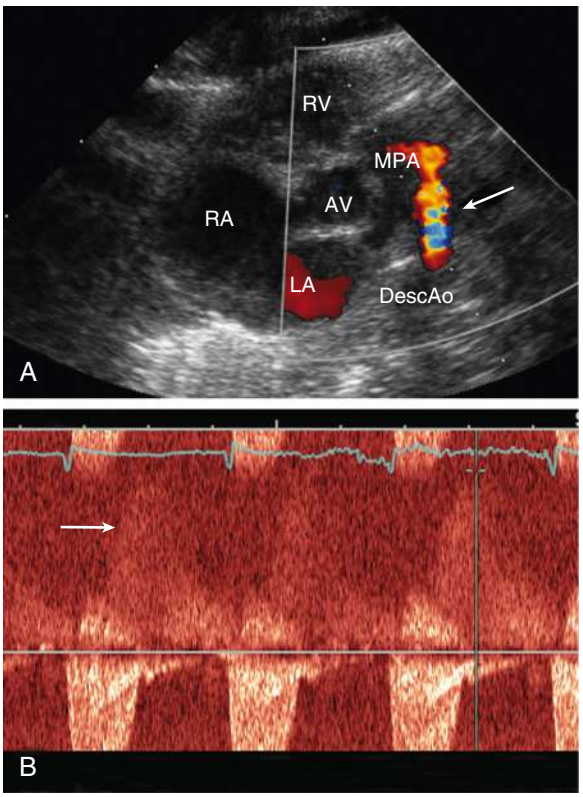

Fig. 475.11 Echocardiogram in a newborn with a small to moderate-size patent ductus arteriosus. **A,** Color Doppler evaluation in a parasternal short-axis view shows flow *(arrow)* from the aorta into the main pulmonary artery. **B,** Doppler evaluation demonstrates retrograde diastolic flow into the pulmonary artery. AV, Aortic valve; DescAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.

(see Chapter 475.9). A sinus of Valsalva aneurysm that has ruptured into the right side of the heart or pulmonary artery, a coronary AV fistula, and an aberrant left coronary artery with massive collaterals from the right coronary display dynamics similar to that of a PDA with a continuous murmur and a wide pulse pressure. Truncus arteriosus with torrential pulmonary flow also can present with aortic runoff physiology. A peripheral AV fistula also results in a wide pulse pressure, but the distinctive precordial murmur of a PDA is not present. VSD with aortic insufficiency, repaired tetralogy of Fallot, and combined aortic and mitral insufficiency (usually from rheumatic fever) may be confused with a PDA, but the murmurs should be differentiated by their to-and-fro rather than continuous nature. In a to-and-fro murmur there is a quiet segment between the systolic and diastolic components, whereas in a continuous murmur there is flow disturbance throughout the cardiac cycle (even if the murmur is louder during systole than diastole). The combination of a large VSD and a PDA result in findings more like those of an isolated VSD. Echocardiography should be able to eliminate these other diagnostic possibilities.

PROGNOSIS AND COMPLICATIONS

Spontaneous closure of the ductus after infancy is extremely rare. Patients with a small PDA may live a normal span with few or no cardiac symptoms, but late manifestations may occur. In patients with a large PDA, cardiac failure most often occurs in early infancy but may occur later in life, even with a moderate-sized communication.

Infective endarteritis may be seen at any age. Pulmonary or systemic emboli may occur. Rare complications include aneurysmal dilation of the pulmonary artery or the ductus, calcification of the ductus, noninfective thrombosis of the ductus with embolization, and paradoxical emboli. Pulmonary hypertension (Eisenmenger syndrome) usually develops in patients with a large PDA who do not undergo ductal closure (see Chapter 482.2).

TREATMENT

Irrespective of age, patients with a PDA require either catheter or surgical closure. In patients with a small PDA, the rationale for closure is prevention of bacterial endarteritis or other late complications. In patients with a moderate to large PDA, closure is accomplished to treat heart failure and prevent the development of pulmonary vascular disease. Once the diagnosis of a moderate to large PDA is made, treatment should not be unduly postponed after adequate medical therapy for cardiac failure has been instituted.

Transcatheter PDA closure is routinely performed in the cardiac catheterization laboratory (Fig. 475.12). Small PDAs are generally closed with intravascular coils. Moderate to large PDAs may be closed with an umbrella-like or pluglike device or with a catheter-introduced sac into which several coils are released. Surgical closure of a PDA can be accomplished by a standard left thoracotomy or using thoracoscopic minimally invasive techniques. The case fatality rate with interventional or surgical treatment is considerably less than 1%; thus closure of the ductus is indicated even in asymptomatic patients. Pulmonary hypertension is not a contraindication to surgery at any age if it can be demonstrated at cardiac catheterization that the shunt flow is still predominantly left to right and that severe pulmonary vascular disease is not present. After closure, symptoms of cardiac failure rapidly disappear. Infants who had failed to thrive usually have immediate improvement in physical development. The pulse and blood pressure return to normal, and the machinery-like murmur disappears. A functional systolic murmur over the pulmonary area may persist; it may represent turbulence in a persistently dilated pulmonary artery. The radiographic signs of cardiac enlargement and pulmonary overcirculation disappear over several months, and the ECG becomes normal.

PATENT DUCTUS ARTERIOSUS IN LOW BIRTHWEIGHT INFANTS

See Chapter 126.1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

475.9 Aortopulmonary Window Defect

Daniel Bernstein

An aortopulmonary window defect consists of a communication between the ascending aorta and the main pulmonary artery. The presence of pulmonary and aortic valves and an intact ventricular septum distinguishes this anomaly from **truncus arteriosus** (see Chapter 480.8). An aortopulmonary window is an associated lesion in patients with **smooth muscle dysfunction syndrome** (see Chapter 475.8). Symptoms of heart failure appear during early infancy; occasionally, minimal cyanosis is present. The defect is usually large, and the cardiac murmur is usually systolic with an apical mid-diastolic rumble as a result of the increased blood flow across the mitral valve. In the rare instance when the communication is smaller and pulmonary hypertension is absent, the findings on examination can mimic those of a PDA (wide pulse pressure and a continuous murmur at the upper sternal borders). The ECG shows either LV or biventricular hypertrophy. Radiographic studies demonstrate cardiac enlargement and prominence of the pulmonary artery and intrapulmonary

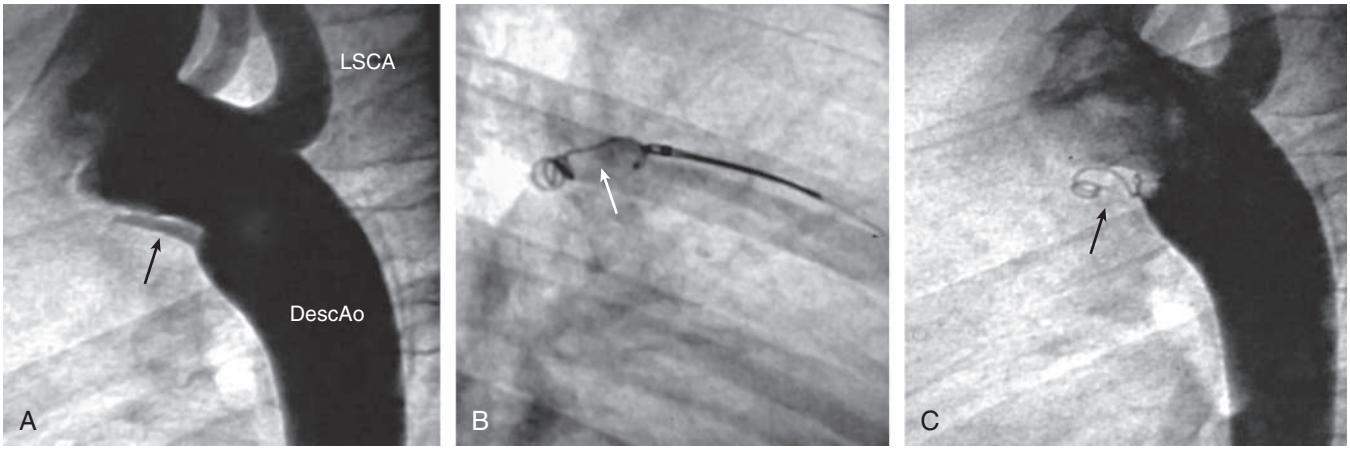

Fig. 475.12 Transcatheter closure of a small patent ductus arteriosus using a coil. **A,** Angiogram of transverse and descending aorta shows small PDA *(arrow).* **B,** Coil *(arrow)* has been extruded from the sheath and is being positioned in the ductal lumen. **C,** Angiogram demonstrating total occlusion of PDA by coil *(arrow).* DescAo, Descending aorta; LSCA, left subclavian artery.

vasculature. The echocardiogram shows enlarged left-sided heart chambers; the window defect can best be delineated with color flow Doppler. CT or MR angiography can also be used to visualize the defect (see Fig. 472.26).

Cardiac catheterization, usually performed in older children to evaluate pulmonary vascular resistance, reveals a left-to-right shunt at the level of the pulmonary artery, as well as hyperkinetic pulmonary hypertension, because the defect is almost always large. Selective aortography with injection of contrast medium into the ascending aorta demonstrates the lesion, and manipulation of the catheter from the main pulmonary artery directly to the ascending aorta is also diagnostic.

An aortopulmonary window defect is surgically corrected during infancy. If surgery is not carried out in infancy, survivors carry the risk of progressive pulmonary vascular obstructive disease, similar to that of other patients who have large intracardiac or great vessel communications.

475.10 Coronary Artery Fistula

Daniel Bernstein

A congenital fistula may exist between a coronary artery and an atrium, ventricle (especially the right), or pulmonary artery. Sometimes, multiple fistulas exist. Regardless of the recipient chamber, the clinical signs are similar to those of PDA, although the machinery-like murmur may be more diffuse. If the flow is substantial, the involved coronary artery may be dilated or aneurysmal. The anatomic abnormality is usually demonstrable by color flow Doppler echocardiography and, during catheterization, by contrast injection into the ascending aorta. Small fistulas may be hemodynamically insignificant and may even close spontaneously. If the shunt is large, treatment consists of either transcatheter coil embolization or, for lesions not amenable to catheter intervention, surgical closure of the fistula.

475.11 Ruptured Sinus of Valsalva Aneurysm

Daniel Bernstein

When one of the sinuses of Valsalva of the aorta is weakened by congenital or acquired disease, an aneurysm may form and eventually rupture, usually into the right atrium or ventricle. This condition is rare in childhood. The onset is usually sudden. The diagnosis should be suspected in a patient in whom symptoms of acute heart failure develop in association with a new, loud, to-and-fro murmur. Color Doppler echocardiography and cardiac catheterization demonstrate the left-to-right shunt at the atrial or ventricular level. Urgent surgical repair is generally required. This condition is often associated with infective endocarditis of the aortic valve.

Chapter 476
Acyanotic Congenital Heart Disease: Obstructive Lesions

476.1 Pulmonary Valve Stenosis with Intact Ventricular Septum

Daniel Bernstein

Of the various forms of right ventricular (RV) outflow obstruction with an intact ventricular septum, the most common is isolated **valvular pulmonary stenosis**, which accounts for 7–10% of all congenital heart defects. The valve cusps are deformed to various degrees and, as a result, the valve opens incompletely during systole. The valve may be bicuspid or tricuspid and the leaflets partially fused together with an eccentric outlet. This fusion may be so severe that only a pinhole central opening remains. If the valve is not severely thickened, it produces a domelike obstruction to RV outflow during systole. Isolated infundibular or subvalvular stenosis, supravalvular pulmonary stenosis, and branch pulmonary artery stenosis are also encountered. In cases where pulmonary valve stenosis is associated with a **ventricular septal defect** (VSD) but without anterior deviation of the infundibular septum and overriding aorta, this condition is better classified as pulmonary stenosis with VSD rather than as **tetralogy of Fallot** (see Chapter 479.1). Pulmonary stenosis and an **atrial septal defect** (ASD) are also occasionally seen as associated defects.

The clinical and laboratory findings reflect the dominant lesion, but it is important to rule out any associated anomalies. Pulmonary stenosis as a result of valve dysplasia is the most common cardiac abnormality in **Noonan syndrome** (see Chapter 101.1) and is associated, in approximately 50% of cases, with a pathogenic variant in *PTPN11,* encoding the protein tyrosine phosphatase SHP-2 on chromosome 12. *SOS1* gene variants cause an additional 10–15%, and *RAF1* and *RIT1* genes each account for about 5% of cases. These genes are components of the RAS/MAPK cell signaling pathway, important for cell division; however, the mechanism by which these gene changes cause pulmonic stenosis is unknown. Pulmonary stenosis can also be a component of **LEOPARD syndrome** (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness syndrome), often associated with hypertrophic cardiomyopathy. Pathogenic variants in *PTPN11, RAF1, BRAF,* and *MAP2K1* have been implicated in LEOPARD syndrome. Pulmonary stenosis, of the valve or more commonly of the branch pulmonary arteries, is a common finding in patients with arteriohepatic dysplasia, also known as **Alagille syndrome** (see Chapter 404); pathogenic variants have been found in *JAGGED1* or *NOTCH2,* components of the Notch signaling pathway.

PATHOPHYSIOLOGY

The obstruction to outflow from the right ventricle to the pulmonary artery results in increased RV systolic pressure and wall stress, which lead to hypertrophy of the right ventricle (Fig. 476.1). The severity of these abnormalities depends on the size of the restricted valve opening. In severe cases, RV pressure may be higher than systemic arterial systolic pressure, whereas with milder obstruction, RV pressure is only mildly or moderately elevated. Pulmonary artery pressure (PAP, distal to the obstruction) is either normal or decreased. Arterial oxygen saturation will be normal even in cases of severe stenosis, unless an intracardiac communication such as a VSD or ASD is allowing blood to shunt from right to left. However, when severe pulmonic stenosis occurs in a neonate, decreased RV compliance often leads to cyanosis as a result of right-to-left shunting through a **patent foramen ovale** (PFO), a condition termed **critical pulmonic stenosis**.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Patients with mild or moderate stenosis usually have no symptoms. Growth and development are most often normal. If the stenosis is severe, signs of RV failure such as hepatomegaly, peripheral edema, and exercise intolerance may be present. In a neonate or young infant with critical pulmonic stenosis, signs of RV failure may be more prominent; cyanosis is often present because of right-to-left shunting at the foramen ovale.

With **mild pulmonary stenosis**, central venous pressure is normal. The heart is not enlarged, the apical impulse is normal, and the RV impulse is not palpable. A sharp pulmonic ejection click (caused by doming of the valve) is heard immediately after the first heart sound (S_1) at the left upper sternal border and over the sternum, more prominently during expiration. The second heart sound (S_2) is split, with a pulmonary component of normal intensity that may be slightly

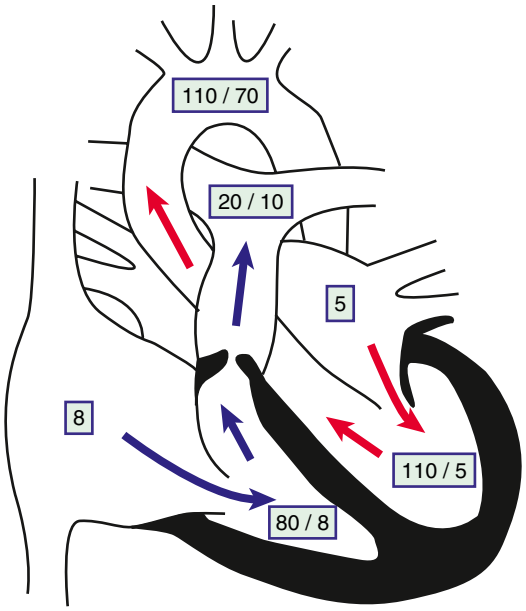

Fig. 476.1 Physiology of valvular pulmonary stenosis. *Boxed numbers* represent pressure in mm Hg. Because of the absence of right-to-left or left-to-right shunting, blood flow through all cardiac chambers is normal at 3 L/min/m^2. The pulmonary-to-systemic blood flow ratio (Qp:Qs) is 1:1. Right atrial pressure is increased slightly as a result of decreased right ventricular compliance. The right ventricle is hypertrophied, and systolic and diastolic pressures are increased. The pressure gradient across the thickened pulmonary valve is 60 mm Hg. The main pulmonary artery pressure is slightly low, and poststenotic dilation is present. Left-sided heart pressure is normal. Unless right-to-left shunting is occurring through a foramen ovale, the patient's systemic oxygen saturation will be normal.



Fig. 476.2 Radiograph of patient with valvular pulmonary stenosis and normal aortic root. The heart size is within normal limits, but poststenotic dilation of the pulmonary artery is present.

delayed. A relatively short, low- or medium-pitched systolic ejection murmur is maximally audible over the pulmonic area at the upper left sternal border and radiates minimally to the lung fields bilaterally. The electrocardiogram (ECG) is either normal or shows mild **right ventricular hypertrophy** (RVH) (e.g., slightly increased voltages in the right precordial leads); inversion of the T waves in the right precordial leads may be the only finding. Note that the T wave in lead V_1 should normally be inverted after the first week of life until at least 6-8 years of age. Therefore a positive T wave in V_1 in a young child is a sign of RVH even in the absence of voltage criteria. The only abnormality demonstrable radiographically is usually poststenotic dilation of the pulmonary artery. Two-dimensional (2D) echocardiography shows RVH and a slightly thickened pulmonic valve, which domes in systole. Doppler studies demonstrate a right ventricle–to–pulmonary artery (RV-PA) pressure gradient of ≤30 mm Hg.

In **moderate pulmonic stenosis**, central venous pressure may be slightly elevated; in older children, a prominent *a* wave may be noted in the jugular pulse. An RV lift may be palpable at the lower-left sternal border. S_2 is split, with a delayed and soft pulmonic component. As valve motion becomes more limited with more severe degrees of stenosis, both the pulmonic ejection click and the pulmonic S_2 may become inaudible. With increasing degrees of stenosis, the systolic ejection murmur becomes louder and harsher (higher frequency), the peak of the murmur is prolonged later into systole, and the murmur radiates more prominently to both lung fields, heard best over the back.

The ECG reveals RVH, sometimes with a prominent spiked P wave. Radiographically, the heart can vary from normal size to mildly enlarged with uptilting of the apex because of the prominence of the right ventricle; pulmonary vascularity is usually normal or slightly decreased. The echocardiogram shows a thickened pulmonic valve with restricted systolic motion. Doppler examination demonstrates an RV-PA pressure gradient of 30-60 mm Hg. Mild tricuspid regurgitation may be present and allows for Doppler confirmation of RV systolic pressure.

In **severe pulmonary stenosis**, mild to moderate cyanosis may be noted in patients with an interatrial communication (ASD or PFO). In the absence of any intracardiac shunt, cyanosis is absent. Hepatic enlargement and peripheral edema, if present, are an indication of RV failure. Elevation of central venous pressure is common and is identified as a large presystolic jugular *a* wave. The heart is moderately or greatly enlarged, and a conspicuous parasternal RV lift is present and frequently extends to the left midclavicular line. The pulmonic component of S_2 is usually inaudible. A loud, long, and harsh systolic ejection murmur, usually accompanied by a thrill, is maximally audible in the pulmonic area and may radiate over the entire precordium, to both lung fields, and to the back. The peak of the murmur occurs later in systole as valve opening becomes more restricted. The murmur frequently encompasses the aortic component of S_2 but is not preceded by an ejection click.

The ECG shows marked RVH, frequently accompanied by a tall, spiked P wave. Radiographic studies confirm the presence of cardiac enlargement with prominence of the right ventricle and right atrium. Prominence of the main pulmonary artery (MPA) segment may be seen as a sign of poststenotic dilation (Fig. 476.2). Intrapulmonary vascularity is decreased. The 2D echocardiogram shows severe deformity of the pulmonary valve and RVH (Fig. 476.3). In the late stages of the disease, systolic dysfunction of the right ventricle may be seen, and in these cases the ventricle becomes dilated, with prominent tricuspid regurgitation. Doppler studies demonstrate a high gradient (>60 mm Hg) across the pulmonary valve. The classic findings of severe pulmonary stenosis in older children are rarely seen today because of early intervention. In the newborn period, signs of critical pulmonic stenosis are accompanied by cyanosis.

Cardiac catheterization is not generally required for diagnostic purposes but is undertaken to perform a therapeutic **balloon valvuloplasty** procedure. Catheterization demonstrates an abrupt pressure gradient across the pulmonary valve. PAP is either normal or low. The severity of the stenosis is graded based on the ratio of RV systolic pressure to systemic systolic pressure or the RV-PA pressure gradient: 10-30 mm Hg in mild cases, 30-60 mm Hg in moderate cases, and >60 mm Hg or with RV pressure greater than systemic pressure in severe cases. If cardiac output is low or a significant right-to-left shunt exists across the atrial septum, the pressure gradient may underestimate the degree of valve stenosis. Selective right ventriculography demonstrates the

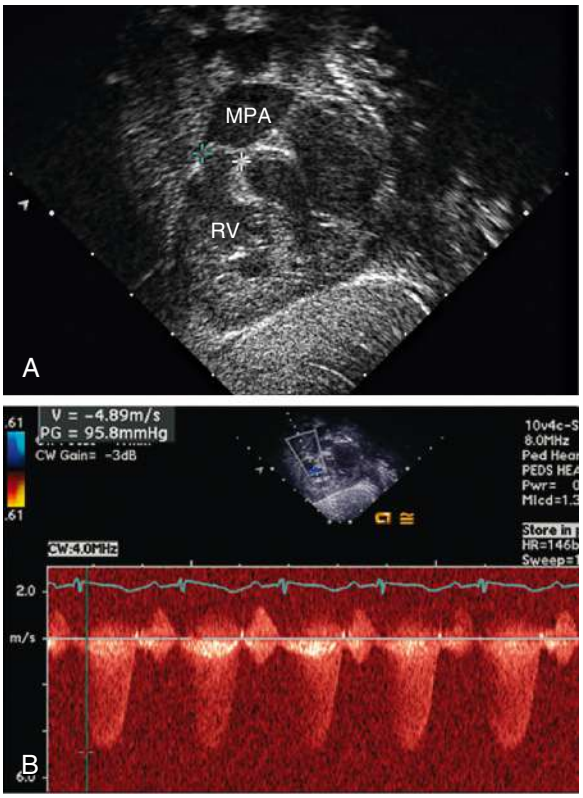

Fig. 476.3 Echocardiogram demonstrating valvar pulmonic stenosis. A, Subcostal view showing thickened pulmonary valve leaflets *(between crosshatches)*. B, Doppler study indicating a 95 mm Hg peak pressure gradient across the stenotic valve. MPA, Main pulmonary artery; RV, right ventricle.

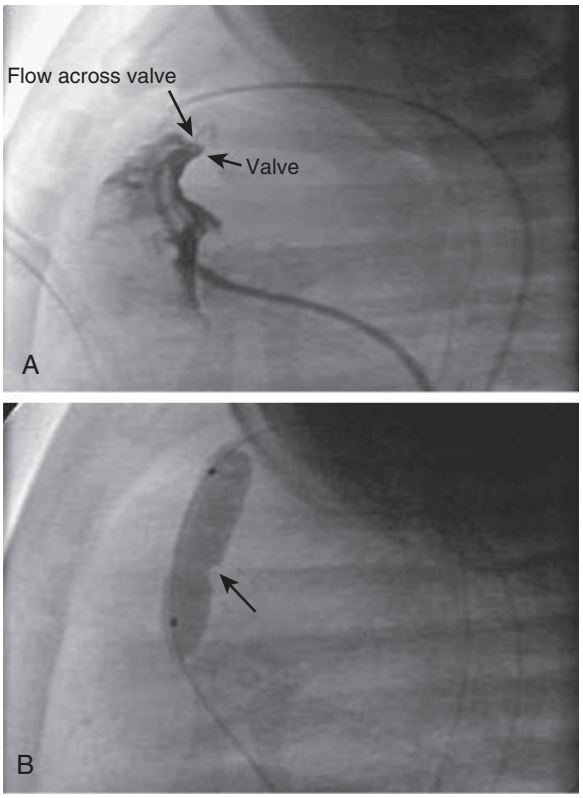

Fig. 476.4 Valvar pulmonary stenosis and balloon valvuloplasty. A, Right ventricular angiogram showing severely stenotic pulmonary valve with narrow jet of blood flowing across. B, Inflation of the balloon catheter showing the indentation *(arrow)* made on the balloon from the stenotic valve. *(Photos courtesy Dr. Jeffrey Feinstein, Stanford University, Stanford, CA.)*

thickened, poorly mobile valve. In mild to moderate stenosis, doming of the valve in systole is readily seen. Flow of contrast medium through the stenotic valve in ventricular systole produces a narrow jet of dye that fills the dilated MPA. Subvalvular hypertrophy may be present and may intensify the obstruction.

TREATMENT

Patients with moderate or severe isolated pulmonary stenosis require relief of the obstruction. Balloon valvuloplasty is the initial treatment of choice for the majority of patients (Fig. 476.4). Patients with severely thickened pulmonic valves, especially common in those with **Noonan syndrome**, may require surgical intervention. In a neonate with critical pulmonic stenosis and cyanosis, urgent treatment by either balloon valvuloplasty or surgical valvotomy is warranted.

Excellent results are obtained in most patients. The gradient across the pulmonary valve is greatly reduced or abolished. In the early period after balloon valvuloplasty, a small to moderate residual gradient may remain because of muscular infundibular narrowing; it usually resolves with time. A short, early decrescendo diastolic murmur may be heard at the midsternal to upper left sternal border as a result of pulmonary valvular insufficiency. The degree of insufficiency is usually not clinically significant, although it can occasionally worsen over time as the child grows. No difference in patient status after valvuloplasty or surgery has been noted at late follow-up; recurrence is unusual after successful treatment except in those patients with extremely dysplastic valves. In the small minority of patients where the degree of **pulmonary regurgitation** is more severe, RV dilation may ensue, and these patients require careful follow-up and may require surgical intervention (repair or valve replacement) or placement of a transcatheter stent-valve (e.g., Melody or Harmony valve).

PROGNOSIS AND COMPLICATIONS

Heart failure occurs only in severe cases and most often during the first month of life. The development of cyanosis from a right-to-left shunt across a foramen ovale is almost exclusively seen in the neonatal period when the stenosis is severe. Infective endocarditis is a risk but is not common in childhood.

Children with mild stenosis can lead a normal life, but their progress should be evaluated at regular intervals. Patients who have small gradients rarely show progression and do not need intervention, but a significant gradient is more likely to develop in children with moderate stenosis as they grow older. Worsening of obstruction over time may also be caused by the development of secondary subvalvular muscular hypertrophy. In untreated severe stenosis, the course may abruptly worsen with the development of RV dysfunction and cardiac failure. Infants with critical pulmonic stenosis require urgent catheter balloon valvuloplasty or surgical valvotomy. Development of RV failure many years after pulmonary balloon valvuloplasty is uncommon. Nonetheless, patients should be followed serially for worsening pulmonary insufficiency and RV dilation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

476.2 Infundibular Pulmonary Stenosis and Double-Chamber Right Ventricle

Daniel Bernstein

Infundibular pulmonary stenosis is caused by muscular or fibrous obstruction in the outflow tract of the right ventricle. The site of obstruction may be close to the pulmonary valve or well below it; an

infundibular chamber may be present between the right ventricular cavity and the pulmonary valve. In many cases, a VSD may have been present initially and later closed spontaneously. When the pulmonary valve is also stenotic, the combined defect is primarily classified as valvular stenosis with secondary infundibular hypertrophy. The hemodynamics and clinical manifestations of patients with isolated infundibular pulmonary stenosis are similar, for the most part, to those described for isolated valvular pulmonary stenosis (see Chapter 476.1).

A common variation in RV outflow obstruction below the pulmonary valve is that of a **double-chambered right ventricle**. In this condition, a muscular band is present in the mid-RV region; the band divides the chamber into two parts and creates obstruction between the inlet and outlet portions. An associated VSD is often noted, and these may close spontaneously. Obstruction is not usually seen early in life but may progress rapidly in a similar manner to the progressive infundibular obstruction observed with tetralogy of Fallot (see Chapter 479.1).

The diagnosis of isolated RV infundibular stenosis or double-chambered right ventricle is usually made by echocardiography. The ventricular septum must be evaluated carefully to determine whether an associated VSD is present. When the obstruction is moderate to severe, surgery is indicated. After surgery, the pressure gradient is abolished or greatly reduced, and the long-term outlook is excellent.

476.3 Pulmonary Stenosis in Combination with an Intracardiac Shunt

Daniel Bernstein

Valvular or infundibular pulmonary stenosis, or both, may be associated with either an ASD or a VSD. In these patients the clinical features depend on the degree of pulmonary stenosis, which determines whether the net shunt is from left to right or from right to left. Neonates with severe pulmonary stenosis (termed **critical pulmonary stenosis**) usually have right-to-left shunting through the foramen ovale (see Chapter 476.1).

The presence of a large left-to-right shunt at the atrial or ventricular level is evidence that the pulmonary stenosis is mild. These patients have symptoms similar to those of patients with an isolated ASD or VSD. With increasing age, worsening of the RV outflow obstruction may limit the shunt and result in a gradual improvement in symptoms. Eventually, particularly in patients with pulmonary stenosis and VSD, a further increase in obstruction may lead to right-to-left shunting and cyanosis. When a patient with a VSD has evidence of decreasing heart failure and increased RV forces on the ECG, one must differentiate between the development of increasing pulmonary stenosis vs the onset of pulmonary vascular disease (**Eisenmenger syndrome**; see Chapter 482.2).

These anomalies are readily repaired surgically. Defects in the atrial or ventricular septum are closed, and the pulmonary stenosis is relieved by resection of infundibular muscle or pulmonary valvotomy, or both, as indicated. Patients with a predominant right-to-left shunt can have symptoms similar to those of patients with tetralogy of Fallot (see Chapter 479.1).

476.4 Peripheral Pulmonary Stenosis

Daniel Bernstein

Single or multiple constrictions may occur anywhere along the major branches of the pulmonary arteries and may range from mild to severe and from localized to extensive. Frequently, these defects are associated with other types of congenital heart disease, including valvular pulmonic stenosis, tetralogy of Fallot, patent ductus arteriosus (PDA), VSD, ASD, and supravalvular aortic stenosis. A familial tendency has been recognized in some patients with peripheral pulmonic stenosis. Peripheral pulmonary stenosis is a common cardiac sequelae of congenital rubella syndrome. The combination of supravalvular aortic stenosis with pulmonary arterial branch stenosis, idiopathic hypercalcemia of infancy, elfin facies, and intellectual disability is known as **Williams syndrome**, a condition associated with hemizygous microdeletion of ~25-27 genes (Williams-Beuren syndrome critical region: WBSCR1), including *ELN, LIMK1, GTF21,* and *GTF21RD1* in region 7q11.23 on chromosome 7. Peripheral pulmonary stenosis is also associated with **Alagille syndrome**, which may be associated with a pathogenic variant in the *JAGGED1* or *NOTCH2* genes.

A mild constriction has little effect on the pulmonary circulation. With multiple severe constrictions, pressure is increased in the right ventricle and in the pulmonary artery proximal to the site of obstruction. When the anomaly is isolated, the diagnosis is suspected by the presence of murmurs in widespread locations over the chest, either anteriorly or posteriorly. These murmurs are usually systolic ejection in quality but may be continuous. Most often, the physical signs are dominated by the associated anomaly, such as valvar pulmonary stenosis or tetralogy of Fallot (see Chapter 479.1).

In the immediate newborn period, a mild and transient form of peripheral pulmonic stenosis may be present. Physical findings are generally limited to a soft systolic ejection murmur, which can be heard over either or both lung fields. It is the absence of other physical findings of valvular pulmonic stenosis (RV lift, soft pulmonic S_2, systolic ejection click, murmur loudest at upper left sternal border) that supports this diagnosis. This murmur usually disappears by age 1-2 months.

If the stenosis is severe, the ECG shows evidence of RVH and right atrial hypertrophy, and the chest radiograph shows cardiomegaly and prominence of the MPA. The pulmonary vasculature is usually normal; in some cases, small intrapulmonary vascular shadows are seen that represent areas of poststenotic dilation. Echocardiography is limited in its ability to visualize the distal branch pulmonary arteries. Doppler examination demonstrates the acceleration of blood flow through the stenoses and, if tricuspid regurgitation is present, allows an estimation of RV systolic pressure. MRI and CT are extremely helpful in delineating distal obstructions. If moderate to severe disease is suspected, the diagnosis is usually confirmed by cardiac catheterization.

Severe obstruction of the MPA and its primary branches can be relieved during corrective surgery for associated lesions such as the tetralogy of Fallot or valvular pulmonary stenosis. If peripheral pulmonic stenosis is isolated, it may be treated by catheter balloon dilation, sometimes with placement of an intravascular stent (see Fig. 472.31).

476.5 Aortic Stenosis

Daniel Bernstein

Congenital aortic stenosis accounts for approximately 5% of cardiac malformations recognized in childhood and is more frequent in males (3:1). A bicuspid aortic valve (BAV) is one of the most common congenital heart lesions overall, identified in 1–2% of adults. If isolated, it is not even counted in the overall incidence (0.8% of live births) of congenital heart disease. There is a high incidence of family clustering, with multiple individuals affected with BAV or other left-sided heart lesions. BAV may be encountered in conjunction with other left-sided heart lesions (coarctation of the aorta, aortopathy, mitral stenosis, **Shone complex**, and hypoplastic left heart syndrome) or in conjunction with syndromes such as Loeys-Dietz, Down, Turner, and velocardiofacial (DiGeorge). Several genes have been implicated in BAV, including *NOTCH1, GATA4, GATA5,* and *SMAD6.*

In the most common form, **valvular aortic stenosis**, the leaflets are thickened and the commissures are fused to varying degrees. Left ventricular (LV) systolic pressure is increased as a result of the obstruction to outflow. The LV wall hypertrophies in compensation; as its compliance decreases, end-diastolic pressure increases as well, impairing ventricular filling in the more severe cases.



Fig. 476.5 Williams syndrome. *(From Jones KL, Smith DW. The Williams elfin facies syndrome: a new perspective. J Pediatr. 1975;86:718.)*

Subvalvular (subaortic) stenosis with a discrete fibromuscular shelf (subaortic membrane) below the aortic valve is also an important form of left ventricular outflow tract (LVOT) obstruction. This lesion is frequently associated with other forms of congenital heart disease such as mitral stenosis and coarctation of the aorta **(Shone complex)** and may progress in severity with age, sometimes rapidly. Subvalvular aortic stenosis may also become apparent after successful surgery for other congenital heart defects (coarctation of the aorta, PDA, VSD), may develop in association with mild lesions that have not been surgically repaired, or may occur as an isolated abnormality. Subvalvular aortic stenosis may also be caused by a markedly hypertrophied ventricular septum in association with hypertrophic cardiomyopathy (see Chapter 488.2).

Supravalvular aortic stenosis, the least common type, may be sporadic, familial, or associated with **Williams syndrome**, which includes developmental delay (IQ range: 41-80), elfin facies (full face, broad forehead, flattened bridge of the nose, long upper lip, and rounded cheeks) (Fig. 476.5), and idiopathic hypercalcemia of infancy. Additional features include loquacious personality, hypersensitivity to sound, spasticity, hypoplastic nails, dental anomalies (partial anodontia, microdontia enamel hypoplasia), joint hypermobility, nephrocalcinosis, hypothyroidism, and poor weight gain. Narrowing of the coronary artery ostia can occur in patients with supravalvar aortic stenosis and should be carefully evaluated. Stenosis of other arteries, particularly the branch pulmonary arteries, may also be present. Williams syndrome is caused by hemizygous microdeletion of ~25 genes in the WBSCR1 at 7q11.23 on chromosome 7 (see Chapter 476.2).

CLINICAL MANIFESTATIONS

Symptoms in patients with aortic stenosis depend on the severity of the obstruction. Severe aortic stenosis that occurs in early infancy is termed **critical aortic stenosis** and is associated with LV failure and signs of low cardiac output. Heart failure, cardiomegaly, and pulmonary edema are severe, the pulses are weak in all extremities, and the skin may be pale or grayish. Urine output may be diminished. If cardiac output is significantly decreased, the intensity of the murmur at the right upper sternal border may be minimal. The endocardial surface may be fibrotic and stiff (endocardial fibroelastosis) in the most severe cases.

Outside of the newborn period, most infants and children with less severe forms of aortic stenosis remain asymptomatic and display normal growth and development. The murmur is usually discovered during routine physical examination. Rarely, fatigue, chest pain, dizziness, or syncope with exercise may develop in an older child with previously undiagnosed severe obstruction to LV outflow. Sudden death has been reported with aortic stenosis but usually occurs in patients with severe LVOT obstruction in whom the diagnosis and surgical relief have been delayed.

The physical findings are dependent on the degree of obstruction to LV outflow. In mild stenosis, the pulses, heart size, and apical impulse are all normal. With increasing degrees of severity, the pulses become diminished in intensity and the heart may be enlarged, with an LV apical thrust. Mild to moderate valvular aortic stenosis is usually associated with an early systolic ejection click, best heard at the left sternal border and over the sternum. Unlike the click in pulmonic stenosis, its intensity does not vary with respiration. Clicks are unusual in more severe aortic stenosis or in discrete subaortic stenosis. If the stenosis is severe, S_1 may be diminished because of decreased compliance of the thickened left ventricle. Normal splitting of S_2 is present in mild to moderate obstruction. In patients with severe obstruction, the intensity of the aortic component of S_2 is diminished, and S_2 may be split paradoxically (becoming wider in expiration). A fourth heart sound (S_4) may be audible as a result of decreased LV compliance.

The intensity, pitch, and duration of the systolic ejection murmur are other indications of severity. The louder, harsher (higher pitch), and longer the murmur, the greater the degree of obstruction. The murmur will also peak later in systole with increase severity. The typical murmur is audible maximally at the right upper sternal border and radiates to the neck and the left midsternal border. It is usually accompanied by a thrill in the suprasternal notch and, in older patients, over the carotids. In patients with subvalvular aortic stenosis, the murmur may be maximal along the left sternal border or even at the apex. A soft, decrescendo diastolic murmur is present in patients who also have aortic insufficiency, not uncommon with a bicuspid aortic valve or in patients who have had surgery or balloon valvuloplasty. Occasionally, an apical short mid-diastolic rumbling murmur is audible; this murmur should raise suspicion of associated mitral valve stenosis. Careful attention to both upper- and lower-extremity peripheral pulses is essential. Patients with mild aortic stenosis will have normal pulses; as the severity increases, the pulses will become more diminished. Discrepancy between upper- and lower-extremity pulses or a delay in femoral pulses (radio-femoral delay) suggests associated coarctation of the aorta. Discrepancy between the right and left arm pulses in the presence of normal femoral pulses is a sign of possible supravalvar aortic stenosis.

LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis can usually be made on the basis of the physical examination, and the severity of obstruction confirmed by laboratory tests. If the pressure gradient across the aortic valve is mild, the ECG is likely to be normal. The ECG may occasionally be normal even with mild to moderate obstruction, but evidence of left ventricular hypertrophy (LVH) and LV strain (inverted T waves in left precordial leads) is generally present if moderate to severe stenosis is long-standing. The chest radiograph frequently shows a prominent ascending aorta. Heart size is typically normal or slightly increased. Valvular calcification is noted only in older children and adults. Echocardiography identifies both the site and the severity of the obstruction. Two-dimensional imaging shows LVH and the thickened and abnormally moving aortic valve (Fig. 476.6). The echocardiogram will also demonstrate the number of valve leaflets and their morphology, which leaflets are fused, and the presence of a subaortic membrane or supravalvar stenosis. Associated anomalies of the mitral valve or aortic arch (coarctation of the aorta) or a VSD or PDA are present in up to 20% of cases. In the absence of LV failure, the shortening fraction of the left ventricle may be increased because the ventricle is hypercontractile. In infants with critical aortic

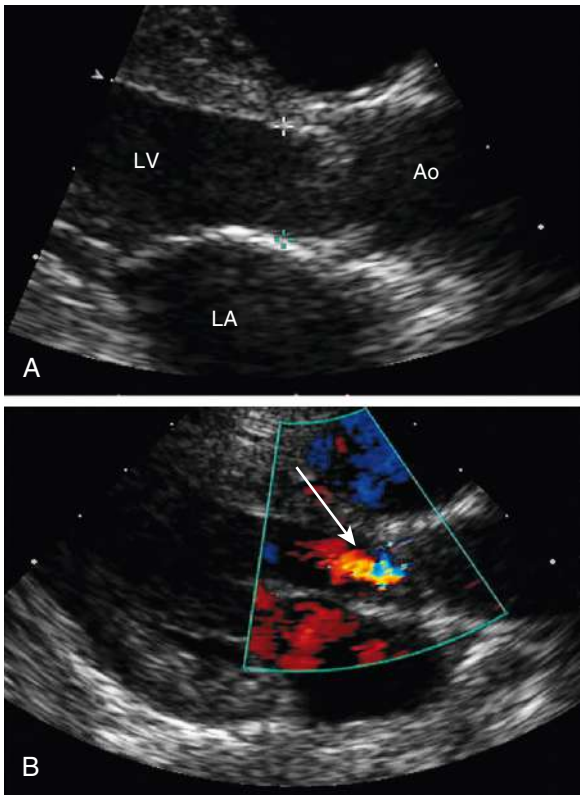

Fig. 476.6 Echocardiogram showing valvar aortic stenosis with regurgitation. **A,** In this parasternal long-axis view, the stenotic aortic valve can be seen doming in systole. The *crosshatch* marks delineate the aortic annulus. **B,** Doppler study shows the presence of aortic regurgitation *(arrow)*. Ao, Aorta; LA, left atrium; LV, left ventricle.

stenosis, the LV shortening fraction is often decreased and may be quite poor. The endocardium may appear bright, indicative of the development of endocardial fibrous scarring, known as **endocardial fibroelastosis**. Doppler studies show the specific site of obstruction and determine the peak and mean systolic LVOT gradients. When severe aortic obstruction is associated with LV dysfunction, the Doppler-derived valve gradient may greatly underestimate the severity of the obstruction because of the low cardiac output across the valve.

Cardiac catheterization is usually not required for diagnostic purposes, but it is usually performed in conjunction with aortic balloon valvuloplasty. Left heart catheterization demonstrates the magnitude of the pressure gradient from the left ventricle to the aorta. The aortic pressure curve is abnormal if the obstruction is severe. In patients with severe obstruction and decreased LV compliance, left atrial pressure is increased and pulmonary hypertension may be present. When a critically ill infant with LVOT obstruction undergoes cardiac catheterization, LV function is often greatly decreased. As with the echocardiogram, the gradient measured across the stenotic aortic valve may underestimate the degree of obstruction because of low cardiac output. Measurement of cardiac output by thermodilution and calculation of the aortic valve area may be helpful.

TREATMENT

Balloon valvuloplasty is indicated for children with moderate to severe valvular aortic stenosis to prevent progressive LV dysfunction and the risk of syncope and sudden death. Valvuloplasty should be advised when the catheter-derived peak-to-peak systolic gradient between the left ventricle and aorta exceeds 60-70 mm Hg at rest, assuming normal cardiac output, or for lesser gradients when symptoms or electrocardiographic changes are present. For more rapidly progressive subaortic obstructive lesions, a gradient of 40-50 mm Hg or the presence of aortic insufficiency is considered an indication for surgery. Balloon valvuloplasty is the procedure of choice even in the neonatal period. Surgical treatment is usually reserved for extremely dysplastic aortic valves that are not amenable to balloon therapy or in patients who also have subvalvar or *supravalvar* aortic stenosis.

Discrete subaortic stenosis can be surgically resected without damage to the aortic valve, the anterior leaflet of the mitral valve, or the conduction system. This type of obstruction is not usually amenable to catheter treatment. Relief of supravalvular stenosis is also achieved surgically, and the results are excellent if the area of obstruction is discrete and not associated with a hypoplastic aorta. In association with supravalvular aortic stenosis, one or both coronary arteries may be stenotic at their origins because of a thick supraaortic fibrous ridge. For patients who have aortic stenosis in association with severe tunnel-like subaortic obstruction, the LVOT can be enlarged by "borrowing" space anteriorly from the right ventricular outflow tract (RVOT) (the **Konno procedure**).

Regardless of whether surgical or catheter treatment has been carried out, aortic insufficiency or calcification with restenosis is likely to occur years or even decades later and eventually require reoperation and often aortic valve replacement. Thus these patients require regular follow-up with a cardiologist. When recurrence develops, it may not be associated with early symptoms. Signs of recurrent stenosis include electrocardiographic signs of LVH, an increase in the Doppler echocardiographic gradient, deterioration in echocardiographic indices of LV function, and recurrence of signs or symptoms during graded treadmill exercise. Evidence of significant aortic regurgitation includes symptoms of heart failure, cardiac enlargement on radiograph, and LV dilation on echocardiogram. The choice of reparative procedure depends on the relative degree of stenosis and regurgitation.

When **aortic valve replacement** is necessary, the choice of procedure often depends on the age of the patient. Homograft valves tend to calcify more rapidly in younger children, but they do not require chronic anticoagulation. Mechanical prosthetic valves are much longer lasting but require anticoagulation, which can be difficult to manage in young children, and they are not available in sizes appropriate for the youngest patients. In adolescent females who are nearing childbearing age, consideration of the teratogenic effects of anticoagulants may warrant the use of a homograft valve. None of these options is perfect for a younger child who requires valve replacement because neither homograft nor mechanical valves grow with the patient. An alternative operation is **aortopulmonary translocation (Ross procedure)**; it involves removing the patient's own pulmonary valve and using it to replace the abnormal aortic valve. A homograft is then placed in the pulmonary position. The potential advantage of this procedure is the possibility for growth of the translocated living "neoaortic" valve and the increased longevity of the homograft valve when placed in the lower-pressure pulmonary circulation. The long-term success of this operation, especially in young children, is still being investigated.

Transcatheter aortic valve replacement (or implantation) (TAVR) uses porcine or bovine (Melody or Sapien) valve tissue sewn into a self-expanding frame. These devices can be implanted in the cardiac catheterization laboratory using a femoral or carotid approach, or transapically through the chest wall, or in a hybrid procedure after a surgical thoracotomy. Initially used mainly in adults who were too ill to be candidates for standard surgical replacement, TAVR is gaining acceptance for carefully selected children who are not good surgical candidates. Short-term outcomes are equivalent to surgical valve replacement. Long-term complications include possible valve regurgitation or perivalvular leaks.

PROGNOSIS

Neonates with critical aortic stenosis may have severe heart failure and deteriorate rapidly to a low-output shock state. Emergency surgery or balloon valvuloplasty is lifesaving, but the mortality risk is not trivial. Neonates who die of critical aortic stenosis frequently have significant LV endocardial fibroelastosis. Those who survive may develop signs of LV diastolic dysfunction (restrictive cardiomyopathy) and eventually require cardiac transplantation (see Chapter 492).

In older infants and children with mild to moderate aortic stenosis, the prognosis is reasonably good, although disease progression over

5-10 years is common. Patients with aortic valve gradients <40-50 mm Hg are considered to have *mild* disease; those with gradients of 40-70 mm Hg have *moderate* disease. These patients usually respond well to treatment (either surgery or valvuloplasty), although reoperations on the aortic valve are often required later in childhood or in adult life, and many patients eventually require valve replacement. In unoperated patients with severe obstruction, sudden death is a significant risk and often occurs during or immediately after exercise. Subaortic stenosis secondary to hypertrophic cardiomyopathy is one of the causes of sudden cardiac death in adolescents and young adults.

Patients with moderate to severe degrees of aortic stenosis should not participate in active competitive sports. In those with milder disease, sports participation is less severely restricted. The status of each patient should be reviewed at least annually and intervention advised if progression of signs or symptoms occurs. Prophylaxis against infective endocarditis is no longer recommended unless a prosthetic or transcatheter (TAVR) valve has been inserted.

Older children and adults with isolated bicuspid aortic valve are at increased risk for developing dilation of their ascending aorta, even in the absence of significant stenosis. This risk increases with age, and the rate of increase is greatest in those with the largest aortic roots. In children, this dilation is usually mild and remains stable over many years of observation, but in young adults and older patients, the aorta can dilate substantially and progressively. Whether these patients have some undiagnosed form of connective tissue disorder remains to be determined (this form of dilation is similar to that seen in Marfan syndrome). Patients with Turner syndrome and bicuspid aortic valve also have an increased risk of aortic dilation. Although dissection and rupture are described complications of severe aortic root dilation in adults, there are not yet sufficient data to determine these risks in children, and careful monitoring with echocardiogram, CT, or MRI is warranted.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

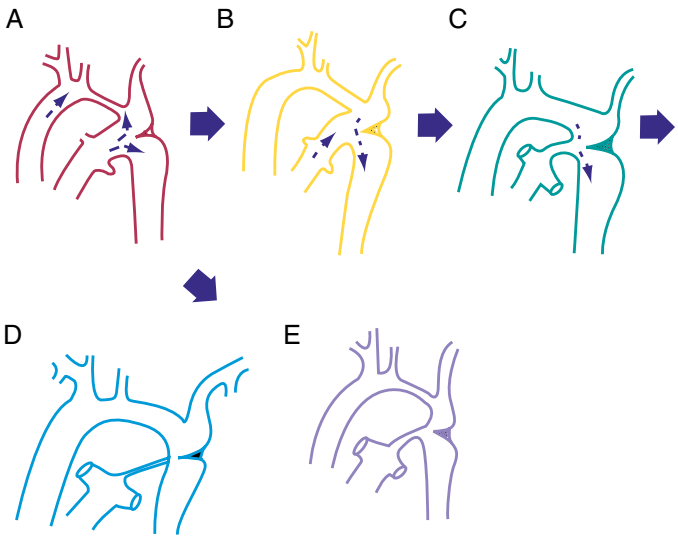

Fig. 476.7 Metamorphosis of coarctation. **A,** Fetal prototype with no flow obstruction. **B,** Late gestation. The aortic ventricle increases its output and dilates the hypoplastic segment. Antegrade aortic flow bypasses the shelf via the ductal orifice. **C,** Neonate. Ductal constriction initiates the obstruction by removing the bypass and increasing antegrade arch flow. **D,** Mature juxtaductal stenosis. The bypass is completely obliterated, and intimal hypoplasia on the edge of the shelf is aggravating the stenosis. Collaterals develop. **E,** Persistence of the infantile-type fetal prototype. An intracardiac left-sided heart obstruction precludes an increase in antegrade aortic flow before or after birth. Both isthmus hypoplasia and a contraductal shelf are present. Lower-body flow often depends on the patency of the ductus. *(From Gersony WM. Coarctation of the aorta. In: Adams FH, Emmanouilides GC, Riemenshneider T, eds. Moss Heart Disease in Infants, Children, and Adolescents, 4th ed. Baltimore: Williams & Wilkins; 1989.)*

476.6 Coarctation of the Aorta

Daniel Bernstein

Constrictions of the aorta of varying degrees may occur at any point from the transverse arch to the iliac bifurcation, but 98% occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus **(juxtaductal coarctation)**. The anomaly is responsible for 5–8% of congenital heart disease and occurs twice as often in males as in females. Coarctation of the aorta is associated with a bicuspid aortic valve in >70% of patients; mitral valve abnormalities (a supravalvular mitral ring or parachute mitral valve) and subaortic stenosis are other associated lesions. When this group of left-sided obstructive lesions occurs together, they are referred to as **Shone complex**. Coarctation of the aorta is found in up to 20% of patients with **Turner syndrome** (see Chapters 99.4 and 626.1); ~5–12% of females with coarctation have Turner syndrome.

PATHOPHYSIOLOGY

Coarctation of the aorta can occur as a discrete juxtaductal obstruction or as tubular hypoplasia of the transverse aorta starting at one of the head or neck vessels and extending to the ductal area (previously referred to as *preductal* or *infantile-type coarctation;* Fig. 476.7). Often, both components are present. It is postulated that coarctation may be initiated in fetal life by the presence of a cardiac abnormality that results in decreased blood flow anterograde through the aortic valve (e.g., bicuspid aortic valve, VSD). Alternatively, it has been theorized that coarctation may be caused by abnormal extension of contractile ductal tissue into the aortic wall.

In patients with discrete juxtaductal coarctation, ascending aortic blood flows through the narrowed segment to reach the descending aorta, although LV hypertension and hypertrophy result. In the first few days of life, the PDA may serve to widen the juxtaductal area of the aorta and provide temporary relief from the obstruction. Net left-to-right ductal shunting occurs in these acyanotic infants. With more severe juxtaductal coarctation or in the presence of transverse arch hypoplasia, RV blood is ejected through the ductus to supply the descending aorta. Perfusion of the lower part of the body is then dependent on RV output. In this situation the femoral pulses are palpable, and differential blood pressures may not be helpful in making the diagnosis. However, the ductal right-to-left shunting is manifested as differential cyanosis, with the upper extremities being well oxygenated and the lower extremities cyanotic. This is one of the main reasons for performing upper- and lower-limb oxygen saturation screening in the newborn because subtle differences in saturation may not be discernable visually. Such infants may have severe pulmonary hypertension and high pulmonary vascular resistance. Signs of heart failure are prominent. Occasionally, severely hypoplastic segments of the aortic isthmus may become completely atretic and result in an interrupted aortic arch, with the left subclavian artery arising either proximal or distal to the interruption.

Blood pressure (BP) is elevated in the vessels that arise proximal to the coarctation; BP and pulse pressure are lower below the constriction. The hypertension is not caused by the mechanical obstruction alone, but also involves neurohumoral mechanisms. Unless surgically corrected in infancy, coarctation of the aorta usually results in the development of an extensive collateral circulation, chiefly from branches of the subclavian, superior intercostal, and internal mammary arteries, to create channels for arterial blood to bypass the area of coarctation. The vessels contributing to the collateral circulation may become greatly enlarged and tortuous by early adulthood.

CLINICAL MANIFESTATIONS

Coarctation of the aorta recognized after infancy may not be associated with significant symptoms, although these may be revealed on closer questioning. Some children or adolescents complain about weakness or pain/claudication (or both) in the legs after exercise, but in many cases, even patients with severe coarctation are asymptomatic. Older

children are frequently brought to the cardiologist's attention when they are found to be hypertensive on routine physical examination.

The classic sign of coarctation of the aorta is a disparity in pulsation and BP in the arms and legs. The femoral, popliteal, posterior tibial, and dorsalis pedis pulses are weak (or absent in up to 40% of patients), in contrast to bounding pulses palpated in the arms and carotid vessels. However, in patients with large numbers of collaterals, the pulse and BP may not be much diminished in the lower extremities; in these cases, diagnosis depends on palpation of the radial and femoral pulses simultaneously for the presence of a **radial-femoral delay**. Normally, the femoral pulse occurs slightly before the radial pulse. A radial-femoral delay occurs when blood flow to the descending aorta is dependent on collaterals, in which case the femoral pulse is felt after the radial pulse. In normal persons *(except neonates),* systolic BP in the legs obtained by the cuff method is usually 10-20 mm Hg higher than that in the arms. In coarctation of the aorta, BP in the legs is lower than that in the arms; frequently, it is difficult to obtain. This differential in BPs is common in patients with coarctation who are older than 1 year, approximately 90% of whom have systolic hypertension in an upper extremity >95th percentile for age. It is important to determine the BP in each arm; a BP higher in the right than the left arm suggests involvement of the left subclavian artery in the area of coarctation. Occasionally, the right subclavian may arise anomalously from below the area of coarctation and result in a left arm BP that is higher than the right. With exercise, a more prominent rise in upper arm BP occurs, and the upper- to lower-extremity pressure gradient will increase.

The precordial impulse and heart sounds are usually normal; the presence of a systolic ejection click or thrill in the suprasternal notch suggests a bicuspid aortic valve (present in 70% of cases). A short systolic murmur is often heard along the left sternal border at the third and fourth intercostal spaces. The murmur is well transmitted to the left infrascapular area and occasionally to the neck. With a bicuspid aortic valve, the typical murmur of aortic stenosis can be heard at the upper right and mid-left sternal borders. Occasionally, more significant degrees of obstruction are noted across the aortic valve. The presence of a low-pitched mid-diastolic murmur at the apex suggests mitral valve stenosis. In older patients with well-developed collateral blood flow, systolic or continuous murmurs may be heard over the left and right sides of the chest laterally and posteriorly. In these patients, a palpable thrill can sometimes be appreciated in the intercostal spaces on the back.

Neonates or infants with more severe coarctation, usually including some degree of transverse arch hypoplasia, initially have signs of lower-body hypoperfusion, acidosis, and severe heart failure. These signs may be delayed days or weeks until after closure of the ductus arteriosus. If detected before ductal closure, patients may exhibit **differential cyanosis**, best demonstrated by simultaneous oximetry of the upper and lower extremities. On physical examination the heart is large, and a systolic murmur is heard along the left sternal border.

Diagnosis

Findings on chest x-ray examination depend on the age of the patient and on the effects of hypertension and the collateral circulation. Cardiac enlargement and pulmonary congestion are noted in infants with severe coarctation. In patients with less severe forms of coarctation, the findings may not be that striking until after the first decade, when the heart tends to be mildly or moderately enlarged because of LV prominence. The enlarged left subclavian artery typically produces a prominent shadow in the left superior mediastinum. **Notching of the inferior border of the ribs** from pressure erosion by enlarged collateral vessels is common by late childhood. In most patients the descending aorta has an area of poststenotic dilation.

The ECG is usually normal in young children with milder degrees of coarctation but demonstrates LV hypertrophy in older patients. Neonates and young infants display right or biventricular hypertrophy. The segment of coarctation can generally be visualized by 2D echocardiography (Fig. 476.8); associated anomalies of the mitral and aortic valve can also be demonstrated. The descending aorta is hypopulsatile, and color Doppler demonstrates the specific site of the obstruction. Pulsed and continuous wave Doppler studies determine the pressure gradient directly at the area of coarctation; in the presence of a PDA, however, the severity of the narrowing may be underestimated. CT and MRI

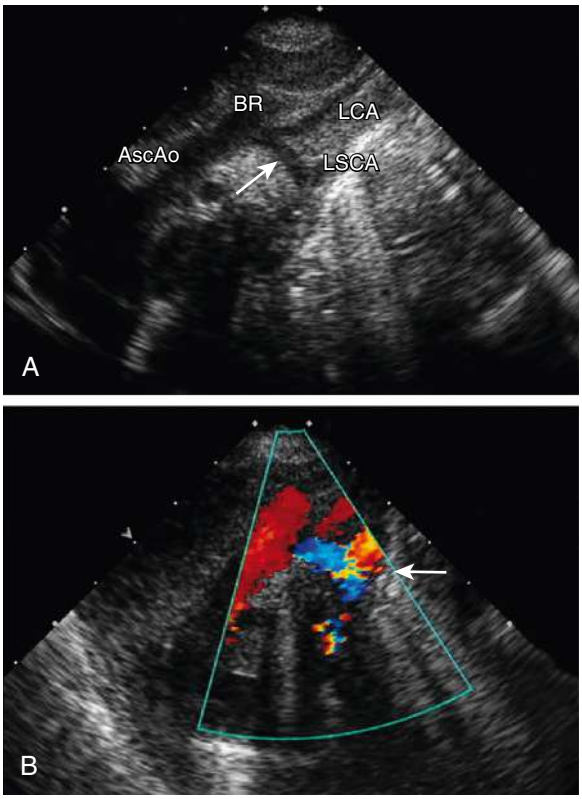

Fig. 476.8 Echocardiogram demonstrating coarctation of the aorta with hypoplastic transverse arch. **A,** Suprasternal notch 2D echocardiogram showing marked narrowing beginning just distal to the brachiocephalic artery. **B,** Color Doppler demonstrates turbulent flow in the juxtaductal area *(arrow).* AscAo, Ascending aorta; BR, brachiocephalic artery; LCA, left carotid artery; LSCA, left subclavian artery.

are valuable noninvasive tools for evaluation of coarctation when the echocardiogram is equivocal (Fig. 476.9). Cardiac catheterization with selective left ventriculography and aortography is useful in occasional patients with additional anomalies and as a means of visualizing collateral blood flow. In cases that are well defined by echocardiography, CT, or MRI, diagnostic catheterization is not usually required before surgery.

TREATMENT

In **neonates** with severe coarctation of the aorta, closure of the ductus often results in hypoperfusion, acidosis, and rapid deterioration. These patients should be given an infusion of prostaglandin E_1 to reopen the ductus and reestablish adequate lower-extremity blood flow. Once a diagnosis has been confirmed and the patient stabilized, surgical repair should be performed. **Older infants** with heart failure but good perfusion should be managed with anticongestive measures to improve their clinical status in preparation for surgical intervention. There is usually no reason to delay surgical repair waiting for patient growth; successful repairs have been performed even in small premature infants.

Older children with significant coarctation of the aorta should be treated relatively soon after diagnosis. Delay is unwarranted, especially after the second decade of life, when there may be decreased LV function and degenerative changes in the aortic wall. For patients with significant left ventricular dysfunction, relief of the obstruction can improve function as afterload on the ventricle is dramatically decreased; however, if fibrosis has occurred, patients can have residual left ventricular dysfunction. If cardiac function is normal, satisfactory repair and long-term outcome are possible well into mid-adult life.

Surgery remains the treatment of choice for isolated juxtaductal coarctation of the aorta in neonates, infants, and young children at most centers; several surgical techniques are used. The area of coarctation can be excised and a primary reanastomosis performed. Most often, the transverse aorta is opened and an "extended end-to-end" anastomosis performed to increase the effective cross-sectional area of the repair. The subclavian

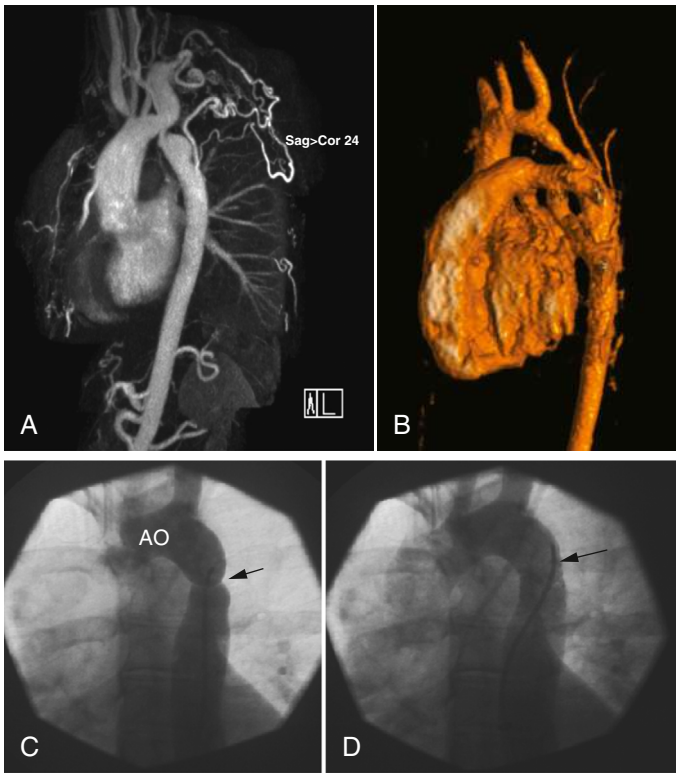

Fig. 476.9 Coarctation of the aorta. A, CT angiogram of coarctation. B, 3D reconstruction. Angiograms of the coarctation before (C) and after (D) stenting *(arrows)*. AO, Aorta. *(Adapted from Webb GD, Smallhorn JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 75.41, p. 1561.)*

flap procedure, which involves division of the left subclavian artery and its incorporation into the wall of the repaired coarctation, has fallen out of favor because of a higher degree of residual stenosis. Some centers favor a patch aortoplasty, in which the area of coarctation is enlarged with a roof of prosthetic material. The use of **primary angioplasty** for native coarctation has been effective in older children and adults. In infants ≥3 months of age, balloon angioplasty has been as effective as surgery but is associated with higher rates of recoarctation requiring intervention (repeat angioplasty or surgery) and aortic aneurysm formation. Surgery is the treatment of choice for the symptomatic neonate. Angioplasty is the treatment of choice for recoarctation. **Primary stent placement** in the catheterization laboratory is considered in older children, where the stent can be expanded if needed to keep up with patient growth and for young adults (see Fig. 476.9). For patients who present with severe LV dysfunction, where surgical intervention may be associated with increased risk, catheter-based treatments are often considered.

After surgery, a striking increase in the amplitude of the pulse in the lower extremities is noted. In the immediate postoperative course, *rebound hypertension* can occur and requires medical management. This exaggerated acute hypertension gradually subsides, and in most patients, antihypertensive medications can be discontinued. Residual murmurs are common and may result from associated cardiac anomalies, a residual flow disturbance across the repaired area, or collateral blood flow. Rare operative problems include spinal cord injury from aortic cross-clamping (if collaterals are poorly developed), chylothorax, diaphragm injury, and laryngeal nerve injury. If a left subclavian flap approach is used, the radial pulse and BP in the left arm are diminished or absent.

POSTCOARCTECTOMY SYNDROME

Postoperative **mesenteric arteritis** may be associated with acute hypertension and abdominal pain in the immediate postoperative period. The pain varies in severity and may occur in conjunction with anorexia, nausea, vomiting, leukocytosis, intestinal hemorrhage, bowel necrosis, and small bowel obstruction. Relief is usually obtained with antihypertensive drugs (e.g., nitroprusside, esmolol, captopril) and intestinal decompression; surgical exploration is rarely required for bowel obstruction or infarction.

PROGNOSIS

Although restenosis in older patients after coarctectomy is rare, a significant number of infants operated on before 1 year of age require revision later in childhood. All patients should be monitored carefully for the development of recoarctation and for aortic aneurysm at the anastomotic site. Should recoarctation occur, **balloon angioplasty** is the procedure of choice. In these patients, scar tissue from a previous surgery may make reoperation more difficult, yet it makes balloon angioplasty safer because of the lower incidence of aneurysm formation. Relief of obstruction with this technique is usually excellent. **Intravascular stents** are typically used, especially in adolescents and young adults, with generally excellent results.

Repair of coarctation in the second decade of life or beyond may be associated with a higher incidence of premature cardiovascular disease, even in the absence of residual cardiac abnormalities. Early onset of **adult-type chronic hypertension** may occur, even in patients with adequately resected coarctation.

Abnormalities of the aortic valve are present in a majority of patients. Bicuspid aortic valves are common but do not generally produce clinical signs unless the stenosis is significant. The association of a PDA with coarctation of the aorta is also common. VSDs and ASDs may be suspected by signs of a left-to-right shunt; they are exacerbated by the increased resistance to flow through the left side of the heart. Mitral valve abnormalities are also occasionally seen, as is subvalvular aortic stenosis.

Severe neurologic damage or even death may rarely occur from associated cerebrovascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, rupture of other vessels with defective elastic and medial tissue, or rupture of normal vessels; these events are secondary to hypertension. Children with **PHACE syndrome** (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies syndrome) may have strokes (see Table 691.5). Abnormalities of the subclavian arteries may include involvement of the left subclavian artery in the area of coarctation, stenosis of the orifice of the left subclavian artery, and anomalous origin of the right subclavian artery.

Untreated, the great majority of older patients with coarctation of the aorta would succumb between ages 20 and 40 years; some live well into middle life without serious disability. The common serious complications are related to systemic hypertension, which may result in premature coronary artery disease, heart failure, hypertensive encephalopathy, or intracranial hemorrhage. Heart failure may be worsened by associated anomalies. Infective endocarditis or endarteritis is a significant complication in these adult patients. Aneurysms of the descending aorta or the enlarged collateral vessels may develop.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

476.7 Coarctation with Ventricular Septal Defect

Daniel Bernstein

In most cases, coarctation is the major anomaly causing the severe symptoms, and resection of the coarcted segment results in striking improvement. Repair of both the VSD and coarctation is usually performed at the same operation through a midline sternotomy using cardiopulmonary bypass.

476.8 Coarctation with Other Cardiac Anomalies and Interrupted Aortic Arch

Daniel Bernstein

Coarctation often occurs in infancy in association with other major cardiovascular anomalies, including hypoplastic left heart, severe mitral or aortic valve disease, transposition of the great arteries, and variations of

double-outlet or single-ventricle. The clinical manifestations depend on the effects of the associated malformations and on the coarctation itself.

Coarctation of the aorta associated with severe **mitral** and **aortic valve disease** may have to be treated within the context of hypoplastic left heart syndrome (see Chapter 480.10), even if the LV chamber is not severely hypoplastic. Such patients usually have a long segment of narrow, transverse aortic arch in addition to an isolated coarctation at the site of the ductus arteriosus. Coarctation of the aorta with **transposition of the great arteries** or **single ventricle** may be repaired alone or in combination with other corrective or palliative measures.

Complete interruption of the aortic arch is the most severe form of coarctation and is usually associated with other intracardiac pathology. Interruption may occur at any level, although it is most often seen between the left subclavian artery and the insertion of the ductus arteriosus **(type A)**, followed in frequency by those between the left subclavian and left carotid arteries **(type B)**, or between the left carotid and brachiocephalic arteries **(type C)**. In newborns with an interrupted aortic arch, the ductus arteriosus provides the sole source of blood flow to the descending aorta, and differential oxygen saturations between the right arm (normal saturation) and the legs (decreased saturation) is noted. When the ductus begins to close, severe congestive heart failure, lower-extremity hypoperfusion, and anuria usually develop, progressing to shock. Patients with an interrupted aortic arch can be supported with prostaglandin E_1 to keep the ductus open before surgical repair. As one of the **conotruncal malformations**, an interrupted aortic arch, especially type B, can be associated with **DiGeorge syndrome** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization demonstrates deletion of a segment of chromosome 22q11, known as the **DiGeorge critical region**.

476.9 Congenital Mitral Stenosis

Daniel Bernstein

Congenital mitral stenosis is a rare anomaly that can be either isolated or associated with other defects, the most common being subvalvar and valvar aortic stenosis and coarctation of the aorta **(Shone complex)**. The mitral valve may be funnel shaped, with thickened leaflets and chordae tendineae that are shortened and deformed. Other mitral valve anomalies associated with stenosis include **parachute** mitral valve, caused by a single papillary muscle, and **double-orifice** mitral valve.

If the stenosis is moderate to severe, symptoms usually appear within the first 2 years of life. These infants have failure to thrive and various degrees of dyspnea and pallor. In some patients, wheezing may be a dominant symptom, and a misdiagnosis of bronchiolitis or reactive airway disease may have been made. Heart enlargement because of dilation and hypertrophy of the right ventricle and left atrium is common. Most patients have rumbling apical diastolic murmurs, but because the pressure gradients in diastole are not very high, the auscultatory findings may be relatively obscure. S_2 is split with a loud P_2 if pulmonary hypertension is present. An opening snap of the mitral valve may be present. The ECG reveals RVH and may show bifid or spiked P waves indicative of left atrial enlargement. Radiographs usually show left atrial and RV enlargement and pulmonary congestion in a perihilar or venous pattern. The echocardiogram is diagnostic and shows thickened mitral valve leaflets, a significant reduction of the mitral valve orifice, abnormal papillary muscle structure (or a single papillary muscle), and an enlarged left atrium with a normal or small left ventricle. A **double-orifice mitral valve** is one variant that can usually be seen on echocardiogram. Doppler studies demonstrate a mean pressure gradient across the mitral orifice during diastole. Associated anomalies such as aortic stenosis and coarctation can be evaluated. Cardiac catheterization is often performed to confirm the transmitral pressure gradient before surgery. An increase in RV, pulmonary artery, and pulmonary capillary wedge pressure can be noted. Angiocardiography shows delayed emptying of the left atrium and the small mitral orifice.

The results of surgical treatment depend on the anatomy of the valve, but if the mitral orifice is significantly hypoplastic, reduction of the gradient may be difficult. In some patients, a mitral valve prosthesis is required, and if the valve orifice is too small, the prosthesis may be placed in the supramitral position. However, whatever prosthesis is used, it must be replaced serially as the child grows. These patients must be anticoagulated, usually with warfarin, and although manageable in older children, complications of excessive and insufficient anticoagulation are more common in infancy. Transcatheter balloon valvuloplasty has been used as a palliative procedure with mixed results, except in the situation of rheumatic mitral stenosis. Recent experience using the percutaneous Melody stent-valve in selected patients in the mitral position is encouraging.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

476.10 Pulmonary Venous Hypertension

Daniel Bernstein

A variety of lesions may give rise to chronic pulmonary venous hypertension, which, when extreme, may result in pulmonary arterial hypertension and right-sided heart failure. These lesions include congenital **mitral stenosis**, **mitral insufficiency**, **total anomalous pulmonary venous return with obstruction**, **left atrial myxomas**, **cor triatriatum**, individual **pulmonary vein stenosis**, and **supravalvular mitral rings**. Early symptoms can be confused with chronic pulmonary disease such as asthma because of a lack of specific cardiac findings on physical examination. Subtle signs of pulmonary hypertension may be present. The ECG shows RVH with spiked P waves. Radiographic studies demonstrate prominence of the pulmonary veins in the hilar region and enlargement of the right ventricle and atrium and the main pulmonary artery; the left atrium is normal in size or only slightly enlarged.

The echocardiogram may demonstrate left atrial myxoma, cor triatriatum, stenosis of one or more pulmonary veins, or a mitral valve abnormality (e.g., supravalvar mitral ring). Cardiac catheterization excludes the presence of a shunt and demonstrates pulmonary hypertension with elevated pulmonary arterial wedge pressure. Left atrial pressure is normal if the lesion is at the level of the pulmonary veins, but it is elevated if the lesion is at the level of the mitral valve. Selective pulmonary arteriography usually delineates the anatomic lesion. Cor triatriatum, left atrial myxoma, and supravalvular mitral rings can all be successfully managed surgically.

The differential diagnosis includes **pulmonary venoocclusive disease**, an idiopathic process that produces obstructive lesions in one or more pulmonary veins. The cause is uncertain, and disease that begins in one vein can spread to others. Although it is usually encountered in patients after repair of obstructed total anomalous pulmonary venous return (see Chapter 480.7), it can occur sporadically or in families in the absence of congenital heart disease. Pathogenic variants in *BMPR2* may be seen in the familial or sporadic cases. The patient initially presents with symptoms similar to left-sided heart failure on the basis of congested lungs with apparent pulmonary edema. Dyspnea, fatigue, and pleural effusions are common. Left atrial pressure is normal, but pulmonary arterial wedge pressure is usually elevated. A normal wedge pressure may be encountered if collaterals have formed, or the wedge recording is performed in an uninvolved segment. Angiographically, the pulmonary veins return normally to the left atrium, but one or more pulmonary veins are narrowed, either focally or diffusely. Sporadic or familial cases present with a primary pulmonary hypertension phenotype, with dyspnea and cyanosis. However, treatment with a primary pulmonary hypertension regimen will precipitate pulmonary edema.

Studies using lung biopsy have demonstrated pulmonary venous and, occasionally, arterial involvement. Pulmonary veins and venules demonstrate fibrous narrowing or occlusion, and pulmonary artery thrombi may be present. Attempts at surgical repair, balloon dilation, and transcatheter stenting have not significantly improved the generally poor prognosis of these patients. Use of antiproliferative agents with imatinib with or without bevacizumab has demonstrated success in preliminary studies. Combined heart-lung transplantation is often the only alternative therapeutic option (see Chapter 492.2).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 477

Acyanotic Congenital Heart Disease: Regurgitant Lesions

477.1 Pulmonary Valvular Insufficiency and Congenital Absence of the Pulmonary Valve

Daniel Bernstein

Pulmonary valvular insufficiency most often accompanies other cardiovascular diseases (surgical repair of pulmonary valve stenosis) or may be secondary to severe **pulmonary hypertension**. Some degree of incompetence of the valve is an expected result after surgery for right ventricular outflow tract (RVOT) obstruction, including pulmonary valvotomy in patients with **valvular pulmonic stenosis** or valvotomy with infundibular resection in patients with **tetralogy of Fallot**. Isolated congenital insufficiency of the pulmonary valve is rare, and these patients are usually asymptomatic because the insufficiency is generally mild.

The prominent physical sign is a decrescendo diastolic murmur at the upper and mid-left sternal border, which has a lower pitch than the murmur of aortic insufficiency because of the lower pressure involved. Radiographs of the chest show prominence of the main pulmonary artery and, if the insufficiency is severe, right ventricular (RV) enlargement. The electrocardiogram (ECG) is normal or shows an rSR′ pattern in the right precordial leads (V_1, V_2) and minimal or no RV hypertrophy. Pulsed and color Doppler studies demonstrate retrograde flow from the pulmonary artery into the right ventricle during diastole. Echocardiography can give qualitative measures of RV volume; cardiac magnetic resonance angiography (MRA) is the best method for quantifying RV volume, the regurgitant fraction, and RV systolic function (ejection fraction). Mild pulmonary valvular insufficiency is generally well tolerated and does not require surgical treatment. When pulmonary insufficiency is moderate to severe and the right ventricle becomes significantly dilated and/or if tricuspid insufficiency has begun to develop, re-repair, replacement with a homograft valve, or transcatheter stent-valve placement may become necessary to preserve RV function.

Congenital absence of the pulmonary valve is usually associated with a ventricular septal defect (VSD), often in the context of tetralogy of Fallot (see Chapter 479.1). In many of these neonates, the pulmonary arteries become widely dilated and compress the bronchi, resulting in recurrent episodes of wheezing, pulmonary collapse, and pneumonitis. The presence and degree of cyanosis are variable. Florid pulmonary valvular incompetence may not be well tolerated, and death may occur from a combination of bronchial compression, hypoxemia, and heart failure. Correction involves plication of the massively dilated pulmonary arteries, closure of the VSD, and placement of a homograft across the RVOT.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

477.2 Congenital Mitral Insufficiency

Daniel Bernstein

Congenital mitral insufficiency is rare as an isolated lesion and is more often associated with other anomalies. It is most frequently encountered in combination with an **atrioventricular septal defect**, either an ostium primum defect or a complete atrioventricular septal defect (see Chapter 475.5) where the insufficient jet is through a cleft in the mitral valve. Mitral insufficiency is also seen in patients with dilated cardiomyopathy (see Chapter 488.1) when the left ventricular (LV) function deteriorates, the chamber dilates, and the valve ring is stretched. In adults, mitral insufficiency can be the result of ischemic injury to a papillary muscle; this is uncommon in children. Mitral insufficiency may also be encountered in conjunction with coarctation of the aorta, VSD, corrected transposition of the great vessels, anomalous origin of the left coronary artery from the pulmonary artery, or Marfan syndrome. In the absence of other congenital heart disease, endocarditis or rheumatic fever should be suspected in a patient with isolated mitral insufficiency.

In mitral insufficiency caused by a congenitally malformed valve, the mitral valve annulus may be dilated, the chordae tendineae short and may insert anomalously, and the valve leaflets are deformed. When mitral insufficiency is severe enough to cause clinical symptoms, the left atrium enlarges as a result of the regurgitant flow, and the left ventricle becomes dilated and mildly hypertrophied. Pulmonary venous pressure is increased, and the increased pressure can ultimately result in pulmonary hypertension and RV hypertrophy and dilation. Mild lesions produce no symptoms; the only abnormal sign is an apical holosystolic murmur of mitral regurgitation. In contrast, moderate to severe regurgitation results in symptoms that can appear at any age, including poor growth, frequent respiratory infections, fatigue on exertion, and episodes of pulmonary edema or congestive heart failure. Often, a diagnosis of reactive airways disease will have been made because of the similarity in pulmonary symptoms, including wheezing, which may be a dominant finding in infants and young children. The presence of a murmur helps distinguish these two etiologies.

The typical murmur of mitral insufficiency is a moderately high-pitched, apical blowing, holosystolic murmur. The murmur radiates from the apex toward the mid-left sternal border. If the insufficiency is moderate to severe, it is usually associated with a low-pitched, apical mid-diastolic rumbling murmur indicative of increased diastolic flow across the mitral valve (physiologic mitral stenosis). The pulmonic component of the second heart sound will be accentuated if there is pulmonary hypertension. The ECG usually shows bifid P waves consistent with left atrial enlargement, signs of LV hypertrophy, and sometimes signs of RV hypertrophy. Radiographic examination shows enlargement of the left atrium, which at times can be massive. The left ventricle is also enlarged and pulmonary vascularity prominent, especially in the perihilar areas. The echocardiogram demonstrates the enlarged left atrium and left ventricle and defines the structure of the valve, the presence or absence of a cleft, and the chordal apparatus. 3D echocardiography is especially useful for this imaging. Color Doppler demonstrates the extent of the insufficiency, and pulsed Doppler of the pulmonary veins detects retrograde flow when mitral insufficiency is severe. Cardiac catheterization shows elevated left atrial pressure and left ventricular end-diastolic pressure. Pulmonary artery hypertension of varying severity may be present. Selective left ventriculography demonstrates the severity of mitral regurgitation.

Surgical **mitral valvuloplasty** can result in striking improvement in symptoms and heart size, but in some patients, installation of a prosthetic mechanical mitral valve may be necessary. Before surgery, associated anomalies must be identified, as they will need to be addressed at the time of valve repair. If the valve requires replacement, several alternatives are available, including mechanical (used mainly for older children) and bioprosthetic, as well as the use of the Melody stent-valve. These can be inserted during a **hybrid procedure** (surgery and catheterization). A cardiac catheter laboratory–inserted device (MitraClip), used mostly in adults, has been used in a few selected pediatric patients to cinch together the anterior and posterior mitral valve leaflets, reducing insufficiency by creating a double-orifice mitral valve.

477.3 Mitral Valve Prolapse

Daniel Bernstein

Mitral valve prolapse (MVP) results from an abnormal mitral valve mechanism that causes billowing of one or both mitral leaflets, especially the posterior cusp, into the left atrium toward the end of ventricular systole. The abnormality is predominantly congenital but may not be recognized until adolescence or adulthood. Primary mitral valve prolapse is common, is present in 2–3% of the population, is more common in females, and may be sporadic or inherited as an autosomal dominant trait (less often X-linked) with variable expression. Pathogenic variants in *DCHS1, LMCD1, TNS1,* and *DZIP1* are possible genes associated with nonsyndromic MVP. It is a common finding in patients with Marfan syndrome, Loeys-Dietz syndrome, mitral-aortic-skeleton-skin (MASS) phenotype, familial myxomatous valvular degeneration, fragile X syndrome, mucopolysaccharidoses, Stickler syndrome, straight back syndrome, pectus excavatum, scoliosis, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum and can also be associated with hyperthyroidism. Fibromyxomatous degeneration of the valve leaflets causes them to be thickened and elongated.

The abnormal signs are auscultatory, although occasional patients may have chest pain and/or palpitations. The apical murmur is late systolic and may be preceded by a click, but these signs may vary in the same patient, and at times, only the click is audible. Sudden standing, or the strain phase of the Valsalva maneuver, decreases LV volume, so the click moves closer to S_1 and the murmur becomes longer. Squatting (or the release phase of the Valsalva maneuver) increases LV volume, so that the click moves away from S_1 and the murmur is shortened. Arrhythmias may occur, primarily unifocal or multifocal premature ventricular contractions. In young adults, MVP has been associated with sudden cardiac death secondary to ventricular arrhythmias.

The ECG is usually normal but may show biphasic T waves, especially in leads II, III, aVF, and V_6; the T-wave abnormalities may vary at different times in the same patient. The chest radiograph is normal. The echocardiogram shows a characteristic posterior movement of the posterior mitral leaflet during mid- or late ventricular systole or demonstrates pansystolic prolapse of both the anterior and posterior mitral leaflets. These echocardiographic findings must be interpreted cautiously because the appearance of minimal mitral prolapse may be a normal variant. Prolapse is more precisely defined by single or bileaflet prolapse of >2 mm beyond the long-axis annular plane of the valve with or without leaflet thickening. Prolapse with valve thickening >5 mm is "classic"; a lesser degree is "nonclassic." Two-dimensional echocardiography shows that both the free edge and the body of the mitral leaflets move posteriorly in systole toward the left atrium. Doppler is then used to assess the presence and severity of mitral regurgitation.

This lesion is not progressive in childhood, and specific therapy is not indicated. Antibiotic prophylaxis is not recommended during surgery and dental procedures (see Chapter 486). This recommendation is controversial because certain features (regurgitation, thickened redundant leaflets) may increase the risk of endocarditis.

Adults (males more often than females) with MVP are at increased risk for cardiovascular complications (sudden death, arrhythmia, cerebrovascular accident, progressive valve dilation, heart failure, and endocarditis) if they have thickened (>5 mm) and redundant mitral valve leaflets. Risk factors for morbidity also include poor LV function, moderate to severe mitral regurgitation, and left atrial enlargement. MVP with severe valve regurgitation, or heart failure, or significant arrhythmias may require initial valve repair or replacement. Beta-blocking agents have been used for patients with palpitations and some arrhythmias. Most patients are asymptomatic and require no treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

477.4 Tricuspid Regurgitation

Daniel Bernstein

Isolated congenital tricuspid regurgitation is most often associated with **Ebstein anomaly of the tricuspid valve** (see Chapter 479.7). Ebstein anomaly may occur either without cyanosis or with varying degrees of cyanosis, depending on the severity of the tricuspid regurgitation and the presence of an atrial-level communication (patent foramen ovale or atrial septal defect). Older children tend to have the acyanotic form or only develop cyanosis with exercise, whereas if detected in the newborn period, Ebstein anomaly is usually associated with severe cyanosis.

In pediatric patients, tricuspid regurgitation is most often associated with congenital heart disease and/or RV dysfunction. When the right ventricle becomes dilated because of volume overload (e.g., pulmonary insufficiency) or intrinsic myocardial disease (dilated cardiomyopathy), the tricuspid annulus also enlarges, with separation of the leaflets and resultant valve insufficiency. This form of regurgitation may improve if the cause of the RV dilation is corrected, or it may require surgical plication of the valve annulus. Tricuspid regurgitation can also be encountered in patients with congenitally corrected transposition of the great arteries (see Chapter 479) and in patients with hypoplastic left heart syndrome after surgical palliation; in both of these situations the RV is pumping at systemic pressure. Isolated tricuspid regurgitation is also encountered in newborns with perinatal asphyxia. The cause may be related to an increased susceptibility of the papillary muscles to ischemic damage and subsequent transient papillary muscle dysfunction. Lastly, tricuspid regurgitation is seen in up to 30% of children after heart transplantation, which can be a risk factor for graft dysfunction, but is also seen as a result of valve injury caused by endomyocardial biopsy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 478

Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate with Cyanosis and Respiratory Distress

Daniel Bernstein

See also Chapter 124.

A severely ill neonate with cardiorespiratory distress and cyanosis is a diagnostic challenge. The clinician must perform a rapid evaluation to determine whether congenital heart disease (CHD) is a cause so that potentially lifesaving measures can be instituted. The differential diagnosis of neonatal cyanosis is presented in Table 121.2.

477.3 Mitral Valve Prolapse

Daniel Bernstein

Mitral valve prolapse (MVP) results from an abnormal mitral valve mechanism that causes billowing of one or both mitral leaflets, especially the posterior cusp, into the left atrium toward the end of ventricular systole. The abnormality is predominantly congenital but may not be recognized until adolescence or adulthood. Primary mitral valve prolapse is common, is present in 2–3% of the population, is more common in females, and may be sporadic or inherited as an autosomal dominant trait (less often X-linked) with variable expression. Pathogenic variants in *DCHS1, LMCD1, TNS1,* and *DZIP1* are possible genes associated with nonsyndromic MVP. It is a common finding in patients with Marfan syndrome, Loeys-Dietz syndrome, mitral-aortic-skeleton-skin (MASS) phenotype, familial myxomatous valvular degeneration, fragile X syndrome, mucopolysaccharidoses, Stickler syndrome, straight back syndrome, pectus excavatum, scoliosis, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum and can also be associated with hyperthyroidism. Fibromyxomatous degeneration of the valve leaflets causes them to be thickened and elongated.

The abnormal signs are auscultatory, although occasional patients may have chest pain and/or palpitations. The apical murmur is late systolic and may be preceded by a click, but these signs may vary in the same patient, and at times, only the click is audible. Sudden standing, or the strain phase of the Valsalva maneuver, decreases LV volume, so the click moves closer to S_1 and the murmur becomes longer. Squatting (or the release phase of the Valsalva maneuver) increases LV volume, so that the click moves away from S_1 and the murmur is shortened. Arrhythmias may occur, primarily unifocal or multifocal premature ventricular contractions. In young adults, MVP has been associated with sudden cardiac death secondary to ventricular arrhythmias.

The ECG is usually normal but may show biphasic T waves, especially in leads II, III, aVF, and V_6; the T-wave abnormalities may vary at different times in the same patient. The chest radiograph is normal. The echocardiogram shows a characteristic posterior movement of the posterior mitral leaflet during mid- or late ventricular systole or demonstrates pansystolic prolapse of both the anterior and posterior mitral leaflets. These echocardiographic findings must be interpreted cautiously because the appearance of minimal mitral prolapse may be a normal variant. Prolapse is more precisely defined by single or bileaflet prolapse of >2 mm beyond the long-axis annular plane of the valve with or without leaflet thickening. Prolapse with valve thickening >5 mm is "classic"; a lesser degree is "nonclassic." Two-dimensional echocardiography shows that both the free edge and the body of the mitral leaflets move posteriorly in systole toward the left atrium. Doppler is then used to assess the presence and severity of mitral regurgitation.

This lesion is not progressive in childhood, and specific therapy is not indicated. Antibiotic prophylaxis is not recommended during surgery and dental procedures (see Chapter 486). This recommendation is controversial because certain features (regurgitation, thickened redundant leaflets) may increase the risk of endocarditis.

Adults (males more often than females) with MVP are at increased risk for cardiovascular complications (sudden death, arrhythmia, cerebrovascular accident, progressive valve dilation, heart failure, and endocarditis) if they have thickened (>5 mm) and redundant mitral valve leaflets. Risk factors for morbidity also include poor LV function, moderate to severe mitral regurgitation, and left atrial enlargement. MVP with severe valve regurgitation, or heart failure, or significant arrhythmias may require initial valve repair or replacement. Beta-blocking agents have been used for patients with palpitations and some arrhythmias. Most patients are asymptomatic and require no treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

477.4 Tricuspid Regurgitation

Daniel Bernstein

Isolated congenital tricuspid regurgitation is most often associated with **Ebstein anomaly of the tricuspid valve** (see Chapter 479.7). Ebstein anomaly may occur either without cyanosis or with varying degrees of cyanosis, depending on the severity of the tricuspid regurgitation and the presence of an atrial-level communication (patent foramen ovale or atrial septal defect). Older children tend to have the acyanotic form or only develop cyanosis with exercise, whereas if detected in the newborn period, Ebstein anomaly is usually associated with severe cyanosis.

In pediatric patients, tricuspid regurgitation is most often associated with congenital heart disease and/or RV dysfunction. When the right ventricle becomes dilated because of volume overload (e.g., pulmonary insufficiency) or intrinsic myocardial disease (dilated cardiomyopathy), the tricuspid annulus also enlarges, with separation of the leaflets and resultant valve insufficiency. This form of regurgitation may improve if the cause of the RV dilation is corrected, or it may require surgical plication of the valve annulus. Tricuspid regurgitation can also be encountered in patients with congenitally corrected transposition of the great arteries (see Chapter 479) and in patients with hypoplastic left heart syndrome after surgical palliation; in both of these situations the RV is pumping at systemic pressure. Isolated tricuspid regurgitation is also encountered in newborns with perinatal asphyxia. The cause may be related to an increased susceptibility of the papillary muscles to ischemic damage and subsequent transient papillary muscle dysfunction. Lastly, tricuspid regurgitation is seen in up to 30% of children after heart transplantation, which can be a risk factor for graft dysfunction, but is also seen as a result of valve injury caused by endomyocardial biopsy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 478

Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate with Cyanosis and Respiratory Distress

Daniel Bernstein

See also Chapter 124.

A severely ill neonate with cardiorespiratory distress and cyanosis is a diagnostic challenge. The clinician must perform a rapid evaluation to determine whether congenital heart disease (CHD) is a cause so that potentially lifesaving measures can be instituted. The differential diagnosis of neonatal cyanosis is presented in Table 121.2.

CARDIAC DISEASE LEADING TO CYANOSIS

CHD produces cyanosis when obstruction to right ventricular inflow or outflow causes intracardiac right-to-left shunting or when complex anatomic defects cause an admixture of pulmonary (deoxygenated) and systemic (oxygenated) venous return somewhere in the heart. Cyanosis from pulmonary edema may also develop in patients with heart failure caused by left-to-right shunts, although the degree of desaturation is usually less severe. In general, right ventricular outflow obstruction without an intracardiac shunt (e.g., isolated valvar pulmonary stenosis) does not cause cyanosis; however, in the newborn period, cyanosis may be caused by right-to-left shunting across the foramen ovale in the presence of elevated right-sided filling pressures. **Persistent pulmonary hypertension of the newborn (PPHN)** is another cause of right-to-left shunting at the atrial level in the newborn period (see Chapter 130).

DIFFERENTIAL DIAGNOSIS

The **hyperoxia test** is one method of distinguishing cyanotic CHD from pulmonary disease. This test is based on the premise that neonates with cyanotic CHD usually are unable to significantly raise their arterial blood partial pressure of oxygen (Pao_2) during administration of 100% oxygen, whereas in infants with pulmonary disease, high levels of intraalveolar Po_2 will overcome at least some of the ventilation-perfusion abnormalities and reverse the hypoxia. This test is performed using a hood rather than nasal cannula or face mask to guarantee delivery of almost 100% oxygen to the patient. False-positive tests can occur if this is not done correctly. In a healthy newborn, the Pao_2 should rise above 300 mm Hg; if between 150 and 300 mm Hg, noncardiac etiologies (pulmonary disease, central nervous system disorders, methemoglobinemia) are most likely. This is not 100% confirmative, however, because some patients with cyanotic CHD may be able to increase their Pao_2 to >150 mm Hg because of favorable intracardiac streaming patterns. In infants with cyanosis from a central nervous system disorder, the Pao_2 usually normalizes completely during artificial ventilation. If the Pao_2 is between 100 and 150 mmHg, then cyanotic congenital heart lesions, increased pulmonary blood flow (mixing lesions, see Chapter 480), or PPHN are more likely. If the Pao_2 is less than 100 mm Hg, then CHD with decreased pulmonary blood flow (see Chapter 479) is more likely. Another clue to etiology is that hypoxia in many heart lesions is relatively constant, whereas in respiratory disorders and in PPHN, Pao_2 often varies with time or changes in ventilator management. For example, hyperventilation may improve the hypoxia in neonates with PPHN but only occasionally in those with cyanotic CHD.

Although a significant heart murmur usually suggests a cardiac basis for the cyanosis, several of the more severe cardiac defects (e.g., transposition of the great vessels) may not initially be associated with a murmur. The chest radiograph may be helpful in the differentiation of pulmonary and cardiac disease; in the latter, it also indicates whether pulmonary blood flow is increased, normal, or decreased (Fig. 478.1) as well as shows alterations in cardiac size.

Two-dimensional echocardiography with Doppler is the definitive noninvasive test to determine the presence of CHD. With today's high-quality echocardiography, cardiac catheterization is less often used for diagnostic purposes and is usually performed to examine structures that are less well visualized by echocardiography, such as distal branch pulmonary arteries and aortopulmonary collateral arteries in patients with tetralogy of Fallot with pulmonary atresia (see Chapter 479.2) or coronary arteries and right ventricular sinusoids in patients with pulmonary atresia and intact ventricular septum (see Chapter 479.3). If echocardiography is not immediately available to confirm a diagnosis of cyanotic CHD, the clinician caring for a newborn with possible cyanotic CHD should not hesitate to start a prostaglandin infusion (for a possible ductal-dependent lesion). Because of the risk of hypoventilation associated with prostaglandins, a practitioner skilled in neonatal endotracheal intubation must be available.

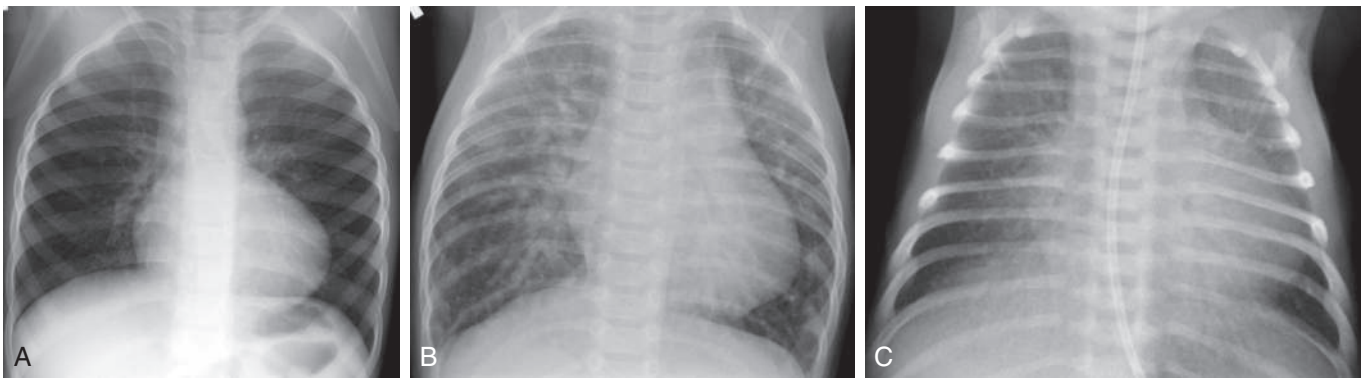

Fig. 478.1 Physiology of congenital heart disease delineated by chest radiography. **A,** Mild cardiomegaly with an upturned cardiac apex, a concave main pulmonary artery segment, and symmetric, severely diminished pulmonary blood flow in a 4-yr-old child with tetralogy of Fallot/pulmonary atresia. **B,** Moderate cardiomegaly and symmetric, increased pulmonary blood flow in a 3-mo-old infant with a large atrial septal defect and ventricular septal defect. **C,** Moderate cardiomegaly with interstitial edema in an 8-day-old newborn with critical aortic stenosis. *(From Frost JL, Krishnamurthy R, Sena L. Cardiac imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology—The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 3.9, p. 68.)*

Chapter 479

Cyanotic Congenital Heart Disease: Lesions Associated with Decreased Pulmonary Blood Flow

479.1 Tetralogy of Fallot

Daniel Bernstein

Tetralogy of Fallot is one of the **conotruncal** family of heart lesions in which the primary defect is an anterior deviation of the *infundibular septum* (the muscular septum that separates the aortic and pulmonary outflows during division of the truncus arteriosus). The consequences of this deviation are the four components that Fallot initially described: (1) obstruction to right ventricular (RV) outflow (pulmonary stenosis); (2) a malalignment type of ventricular septal defect (VSD); (3) dextroposition of the aorta so that it overrides the ventricular septum; and (4) right ventricular hypertrophy (RVH; Fig. 479.1). Obstruction to pulmonary artery blood flow is usually at both the RV infundibulum (subpulmonic area) and the pulmonary valve. The main pulmonary artery (MPA) may also be small, and various degrees of branch pulmonary artery stenosis may be present. Complete obstruction of RV outflow (tetralogy with pulmonary atresia) is classified as an *extreme* form of tetralogy of Fallot (see Chapter 479.2) and may be associated with various degrees of hypoplasia of the branch pulmonary arteries. The degree of pulmonary outflow obstruction and whether the ductus arteriosus is open or closed determine the degree of the patient's cyanosis and the age at first presentation.

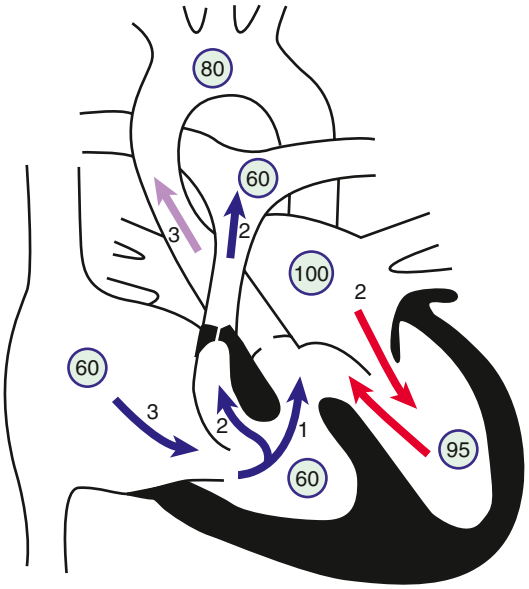

Fig. 479.1 Physiology of tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). Atrial (mixed venous) oxygen saturation is decreased because of the systemic hypoxemia. A volume of 3 L/min/m^2 of desaturated blood enters the right atrium and traverses the tricuspid valve. Two liters flow through the right ventricular outflow tract into the lungs, whereas 1 L shunts right to left through the ventricular septal defect (VSD) into the ascending aorta. Thus pulmonary blood flow is two-thirds normal (Qp:Qs [pulmonary-to-systemic blood flow ratio] of 0.7:1). Blood returning to the left atrium is fully saturated. Only 2 L of blood flow across the mitral valve. Oxygen saturation in the left ventricle may be slightly decreased because of right-to-left shunting across the VSD. Two liters of saturated left ventricular blood mixing with 1 L of desaturated right ventricular blood are ejected into the ascending aorta. Aortic saturation is decreased, and cardiac output is normal.

PATHOPHYSIOLOGY

The pulmonary valve annulus may range from being nearly normal in size to being severely hypoplastic. The valve itself is often bicuspid or unicuspid and, occasionally, is the only site of stenosis. More often, the subpulmonic or infundibular muscle, known as the *crista supraventricularis,* is hypertrophic, which contributes to the subvalvar stenosis and results in an infundibular chamber of variable size and contour. When the right ventricular outflow tract (RVOT) is completely obstructed **(pulmonary atresia)**, the anatomy of the branch pulmonary arteries is extremely variable. An MPA segment may be in continuity with RV outflow, separated by a fibrous but imperforate pulmonary valve; the MPA may be moderately or severely hypoplastic but still supply part or all of the pulmonary bed; or the entire main pulmonary artery segment may be absent. Occasionally, the branch pulmonary arteries may be discontinuous. In these extreme cases, pulmonary blood flow may be supplied by a **patent ductus arteriosus** (PDA) or by multiple **major aortopulmonary collateral arteries (MAPCAs)** arising from the ascending and/or descending aorta or aortic branches and supplying various lung segments.

The VSD is usually nonrestrictive and large, is located just below the aortic valve, and is related to the posterior and right aortic cusps. Rarely, the VSD may be in the inlet portion of the ventricular septum (tetralogy with atrioventricular septal defect). The normal fibrous continuity of the mitral and aortic valves is usually maintained, and if not (because of the presence of a subaortic muscular conus), the defect is classified as a **double-outlet right ventricle** (DORV) instead of tetralogy of Fallot (see Chapter 479.5). The aortic arch is right sided in 20% of cases, and the aortic root is usually large and overrides the VSD to varying degrees. When the aorta overrides the VSD by >50% (in which case it may also be a subaortic conus), this defect is also classified as a form of DORV; however, the circulatory dynamics and the method of repair for these types of DORV are the same as for tetralogy of Fallot.

Systemic venous return to the right atrium and right ventricle is normal. When the right ventricle contracts in the presence of marked pulmonary stenosis, blood is shunted into the overriding aorta or across the VSD into the aorta. Persistent arterial desaturation and cyanosis result, with the degree of desaturation dependent on the severity of the pulmonary obstruction. Pulmonary blood flow, when severely restricted by the obstruction to RV outflow, is often supplemented by a PDA during the immediate newborn period. Peak systolic and diastolic pressures in each ventricle are similar and at the systemic level. A large pressure gradient occurs across the obstructed RVOT, and pulmonary artery pressure is either normal or lower than normal. The degree of RV outflow obstruction determines the timing of the onset of symptoms and the severity of cyanosis. When obstruction to RV outflow is mild to moderate and a balanced shunt is present across the VSD, the patient may not be visibly cyanotic (**acyanotic** or "pink" tetralogy of Fallot). When obstruction is severe, cyanosis will be present from birth and worsen dramatically when the ductus arteriosus begins to close.

CLINICAL MANIFESTATIONS

Infants with mild degrees of RV outflow obstruction may initially even have symptoms of heart failure caused by a ventricular-level left-to-right shunt. In these patients, cyanosis is not present at birth, but with increasing hypertrophy of the RV infundibulum as the patient grows, cyanosis occurs later in the first few months of life. In contrast, in infants with more severe degrees of RV outflow obstruction, neonatal cyanosis is noted immediately. In these infants, pulmonary blood flow

may be partially or almost totally dependent on flow through the ductus arteriosus. When the ductus begins to close in the first few hours or days of life, severe cyanosis and circulatory collapse may occur. All degrees of variation exist between these two clinical extremes. Older children with long-standing cyanosis who have not undergone surgery may have dusky blue skin, mucous membranes, and nailbeds (the latter two are key to diagnosing cyanosis in children with darker skin color). Patients may have gray sclerae with engorged blood vessels and (usually after 2 years of age) clubbing of the fingers and toes. Chapter 483 describes the extracardiac manifestations of long-standing cyanotic congenital heart disease.

In older children with unrepaired tetralogy, dyspnea occurs on minimal exertion. They may play actively for a short time and then sit or lie down or walk a block or so before stopping to rest. Characteristically, children assume a **squatting** position for the relief of dyspnea caused by physical effort; squatting increases venous return to the right side of the heart and also increases systemic vascular resistance, both serving to increase flow through the obstructed RV outflow. The child is usually able to resume physical activity after a few minutes of squatting.

Paroxysmal hypercyanotic attacks (hypoxic, "blue," or "tet" spells) may develop during the first year of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respirations ensue, and syncope may follow. The spells occur most frequently in the morning on initially awakening or after episodes of vigorous crying. Temporary disappearance or a decrease in intensity of the typical systolic ejection murmur occurs as flow across the RVOT diminishes during the spell. Tet spells may last from a few minutes to a few hours. Short episodes are followed by generalized weakness and sleep. Severe spells may progress to unconsciousness and occasionally to convulsions, stroke, and death. The onset of these spells is usually spontaneous and unpredictable. They are associated with reduction of an already compromised pulmonary blood flow, which, when prolonged, results in severe systemic hypoxia and metabolic acidosis. Infants who are only mildly cyanotic at rest may be more prone to the development of hypoxic spells because they have not acquired the homeostatic mechanisms that would allow them to better tolerate rapid lowering of arterial oxyhemoglobin saturation (Sao_2), such as polycythemia.

Depending on the frequency and severity of hypercyanotic attacks, one or more of the following procedures should be instituted in sequence: (1) placement of the infant on the abdomen in the knee-chest position while making certain that the infant's clothing is not constrictive; (2) administration of oxygen (although increasing inspired oxygen will not reverse cyanosis caused by intracardiac shunting); (3) injection of morphine subcutaneously or intranasal fentanyl or intranasal midazolam; (4) administer propranolol or esmolol; and (5) begin a phenylephrine intravenous infusion. Calming and holding the infant in a knee-chest position may abort progression of an early spell. Premature attempts to obtain blood samples may cause further agitation and may be counterproductive; transcutaneous oxygen saturation monitoring is helpful in these cases but is limited in not measuring the degree of acidosis if the spell is prolonged.

Because metabolic acidosis develops when arterial oxygen tension (Pao_2) is <40 mm Hg, rapid correction (within several minutes) with intravenous (IV) administration of sodium bicarbonate is necessary if the spell is unusually severe and the child shows a lack of response to the foregoing therapy. Recovery from the spell is usually rapid once the pH has returned to normal. Repeated blood pH measurements may be necessary because rapid recurrence of acidosis may ensue. For spells that are resistant to this therapy, intubation and anesthetic sedation are often sufficient to break the spell. Drugs that increase systemic vascular resistance, such as IV phenylephrine, can improve RV outflow, decrease the right-to-left shunt, and improve symptoms. β-Adrenergic blockade by the IV administration of propranolol (0.15-0.25 mg/kg/dose given slowly; can be repeated once in 15 minutes) has also been used. Spells are quite rare because most infants with tetralogy of Fallot undergo reparative surgery in early infancy.

Growth and development may be delayed in patients with severe untreated tetralogy of Fallot, particularly when their Sao_2 is chronically <70%. Puberty may also be delayed in patients who have not undergone surgery.

The peripheral pulses are usually normal, as are central venous and arterial pressures. In older infants and children, the left anterior hemithorax may bulge anteriorly because of long-standing RVH. A substernal RV impulse can usually be detected. A systolic thrill may be felt along the left sternal border in the third and fourth parasternal spaces. The systolic murmur is usually loud and harsh; it may be transmitted widely, especially to the lungs, but is most intense at the mid- and upper-left sternal border. The murmur is generally ejection in quality at the upper-left sternal border, but it may sound more holosystolic toward the lower-left sternal border. It may be preceded by a click at the upper sternal border or over the sternum. The murmur is caused by turbulence through the RVOT. It tends to become louder, longer, and harsher as the severity of pulmonary stenosis increases from mild to moderate; however, it can become less prominent with severe obstruction, especially during a hypercyanotic spell, because of shunting of blood away from the RV outflow through the overriding aortic valve. Either the second heart sound (S_2) is single or the pulmonic component is soft because of the decreased excursion of the stenotic valve. Infrequently, a continuous murmur may be audible, especially if prominent MAPCAs are present.

DIAGNOSIS

The typical radiologic configuration as seen in the anteroposterior (AP) view consists of a narrow base, concavity of the left heart border in the area usually occupied by the pulmonary artery, and normal overall heart size. The hypertrophied right ventricle causes the rounded apical shadow to be uptilted so that it is situated higher above the diaphragm than normal and pointing horizontally to the left chest wall. The cardiac silhouette has been likened to that of a *boot* ("coeur en sabot") (Fig. 479.2). The hilar areas and lung fields are relatively clear because of diminished pulmonary blood flow or the small size of the pulmonary arteries, or both. The aorta is usually large, and in approximately 20% of patients it arches to the right, which results in an indentation of the leftward-positioned air-filled tracheobronchial shadow in the AP view.

The electrocardiogram (ECG) demonstrates right-axis deviation and evidence of RVH; because prominent right-sided forces are normal in the newborn period, the ECG may be technically normal at this time. A dominant R wave appears in the right precordial chest leads (V_1, V_2) or an RSR′ pattern. In some cases, the only sign of RVH may initially



Fig. 479.2 Chest radiograph of 8-yr-old child with tetralogy of Fallot. Note the normal heart size, some elevation of the cardiac apex, concavity in the region of the main pulmonary artery, right-sided aortic arch, and diminished pulmonary vascularity.

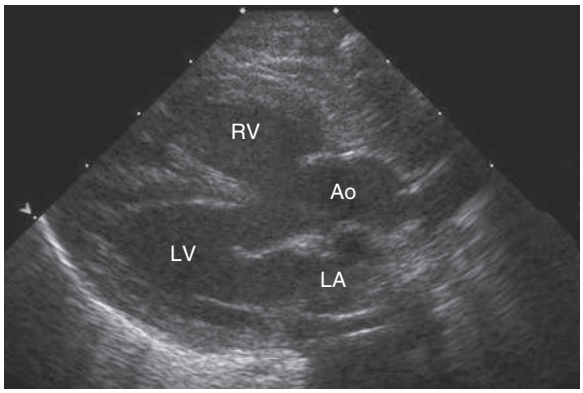

Fig. 479.3 Echocardiogram of patient with tetralogy of Fallot. This parasternal long-axis 2D view demonstrates anterior displacement of the outflow ventricular septum that resulted in stenosis of the subpulmonic right ventricular outflow tract, overriding of the aorta, and an associated ventricular septal defect. Ao, Overriding aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

be a positive T wave in leads V_3R and V_1. The P wave may be tall and peaked, suggesting right atrial enlargement (see Fig. 472.6).

Two-dimensional (2D) echocardiography with Doppler establishes the diagnosis (Fig. 479.3) and provides information about the extent of aortic override of the septum, the location and degree of the RVOT obstruction, the size of the pulmonary valve annulus and main and proximal branch pulmonary arteries, and the side of the aortic arch. The echocardiogram is also useful in determining whether a PDA is supplying a portion of the pulmonary blood flow. In a patient with tetralogy of Fallot without pulmonary atresia, echocardiography usually obviates the need for catheterization before surgical repair. However, in patients with pulmonary atresia, catheterization and CT angiography are usually necessary to image the size and source of blood supply (native pulmonary arteries or MAPCAs) to each lung vascular segment.

Cardiac catheterization demonstrates a systolic pressure in the right ventricle equal to the systemic pressure because the right ventricle is connected directly to the overriding aorta. If the pulmonary artery is entered, the pressure is greatly decreased, although crossing the RVOT, especially in severe cases, may precipitate a tet spell. Pulmonary artery pressure is usually lower than normal, in the range of 5-10 mm Hg. The Sao_2 level depends on the magnitude of the right-to-left shunt; in "pink tets," the systemic So_2 may be normal, whereas in a moderately cyanotic patient at rest, it is usually 75–85%.

Selective right ventriculography will demonstrate all the anatomic features. Contrast medium outlines the heavily trabeculated right ventricle. The infundibular stenosis varies in length, width, contour, and distensibility (Fig. 479.4). The pulmonary valve is usually thickened, and the annulus may be small. In patients with tetralogy and pulmonary atresia, echocardiography alone is not adequate to assess the anatomy of the true pulmonary arteries and collateral MAPCAs. Cardiac CT is extremely helpful, and cardiac catheterization with injection into each arterial collateral is usually indicated. Complete and accurate information regarding the size and peripheral distribution of the main pulmonary arteries and any collateral vessels (MAPCAs) is important when evaluating these children for complex reparative surgery.

Aortography or coronary arteriography outlines the course of the coronary arteries. In 5–10% of patients with the tetralogy of Fallot, coronary artery abnormalities may be present, most often an aberrant coronary artery crossing over the RVOT; care must be taken not to cut this artery during surgical repair. Verification of normal coronary arteries is important when considering surgery in young infants, who may need a patch across the pulmonary valve annulus. Echocardiography can usually delineate the coronary artery anatomy; angiography is reserved for cases in which questions remain.

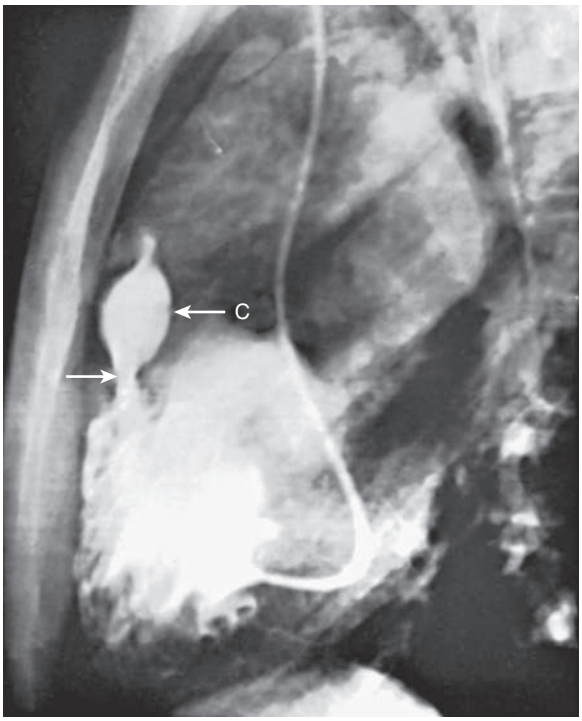

Fig. 479.4 Lateral view of selective right ventriculogram in patient with tetralogy of Fallot. The *left arrow* points to an infundibular stenosis that is below the infundibular chamber (C). The narrowed pulmonary valve orifice is seen at the distal end of the infundibular chamber.

COMPLICATIONS

Before the advent of corrective surgery, patients with tetralogy of Fallot were susceptible to several serious complications. For this reason, most children undergo complete repair (or in rare situations palliation) in the first few months of life; consequently, these complications are now rare. **Cerebral thromboses**, usually occurring in the cerebral veins or dural sinuses and occasionally in the cerebral arteries, are sequelae of extreme polycythemia and dehydration. Thromboses occur most often in patients younger than 2 years. These patients may have iron-deficiency anemia, frequently with hemoglobin and hematocrit levels in the normal range (but too low for cyanotic heart disease). Therapy consists of adequate hydration and supportive measures. Phlebotomy and volume replacement with albumin or saline are indicated in extremely polycythemic patients who are symptomatic.

Brain abscess is less common than cerebrovascular events and extremely rare today. Patients with a brain abscess are usually older than 2 years. The onset of the illness is often insidious and consists of low-grade fever or a gradual change in behavior, or both. Some patients have an acute onset of symptoms that may develop after a recent history of headache, nausea, and vomiting. Seizures may occur; localized neurologic signs depend on the site and size of the abscess and the presence of increased intracranial pressure. Head CT or MRI confirms the diagnosis. Antibiotic therapy may help keep the infection localized, but surgical drainage of the abscess is usually necessary (see Chapter 644).

Bacterial endocarditis may occur in the RV infundibulum or on the pulmonic, aortic, or rarely, tricuspid valve. Endocarditis may complicate palliative shunts or, in patients with corrective surgery, any residual pulmonic stenosis or VSD. Heart failure is not a usual feature in patients with tetralogy of Fallot, with the exception of some young infants with "pink" or acyanotic tetralogy of Fallot. When the degree of pulmonary obstruction worsens with age, the symptoms of heart failure resolve, and eventually the patient experiences cyanosis, usually by 4-6 months of age. These patients are at increased risk for hypercyanotic spells at this time.

ASSOCIATED ANOMALIES

A PDA may be present, and defects in the atrial septum are occasionally seen. A right aortic arch occurs in approximately 20% of patients, and other anomalies of the pulmonary arteries and aortic arch may also be seen. Persistence of a left superior vena cava draining into the coronary sinus is common but not a concern. Multiple VSDs are occasionally present and should be diagnosed before corrective surgery. Coronary artery anomalies are present in 5–10% and can complicate surgical repair. Tetralogy of Fallot may also occur with an atrioventricular septal defect, often associated with Down syndrome.

Congenital absence of the pulmonary valve produces a distinct syndrome that is usually marked by signs of upper airway obstruction (see Chapter 477.1). Cyanosis may be absent, mild, or moderate; the heart is large and hyperdynamic; and a loud to-and-fro murmur is present. Marked aneurysmal dilation of the main and branch pulmonary arteries results in compression of the bronchi and then produces stridulous or wheezing respirations and recurrent pneumonia. If the airway obstruction is severe, reconstruction of the trachea at the time of corrective cardiac surgery may be required to alleviate the symptoms.

Absence of a branch pulmonary artery, most often the left, should be suspected if the radiographic appearance of the pulmonary vasculature differs between the right and left sides; absence of a pulmonary artery is often associated with hypoplasia of the affected lung. It is important to recognize the absence of a pulmonary artery because occlusion of the remaining pulmonary artery during surgery seriously compromises the already reduced pulmonary blood flow.

As one of the conotruncal malformations, tetralogy of Fallot can be associated with **DiGeorge syndrome** or **velocardiofacial syndrome**, also known by the acronym **CATCH 22** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization (FISH) demonstrates deletions of a large segment of **chromosome 22q11.2** known as the **DiGeorge critical region**. Deletion or pathogenic variants in *Tbx1* have been implicated as a possible cause of DiGeorge syndrome, although several other genes have been identified as possible candidates or as modifier genes (see Chapter 473).

TREATMENT

Treatment of tetralogy of Fallot depends on the severity of the RVOT obstruction. Infants with severe tetralogy require urgent medical treatment and surgical intervention in the neonatal period. Therapy is aimed at providing an immediate increase in pulmonary blood flow to prevent the sequelae of severe hypoxia. Prolonged, severe hypoxia may lead to shock, respiratory failure, and intractable acidosis and will significantly reduce the chance of survival, even when surgically amenable lesions are present. It is critical that normal body temperature be maintained during the transfer because cold increases oxygen consumption, which places additional stress on a cyanotic infant, whose oxygen delivery is already limited. Blood glucose levels should be monitored because hypoglycemia is more likely to develop in infants with cyanotic heart disease.

Neonates with marked RVOT obstruction may deteriorate rapidly because as the ductus arteriosus begins to close, pulmonary blood flow is further compromised. The IV administration of **prostaglandin E_1** (PGE_1; 0.05-0.1 μg/kg/min), a potent and specific relaxant of ductal smooth muscle, causes dilation of the ductus arteriosus and usually provides adequate pulmonary blood flow until a surgical procedure can be performed. This agent should be administered intravenously as soon as cyanotic CHD is clinically suspected and continued through the preoperative period and during cardiac catheterization. Because prostaglandin can cause apnea, an individual skilled in neonatal intubation should be readily available.

Infants with less severe RVOT obstruction who are stable and awaiting surgical intervention require careful observation. Acyanotic patients can progress fairly quickly to having cyanotic episodes. Prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes. In the past, oral propranolol (0.5-2 mg/kg every 6 hours) was used to decrease the frequency and severity of hypercyanotic spells, but with the excellent surgical results available today, surgical treatment is indicated, usually before spells begin.

Infants with symptoms and severe cyanosis in the first month of life usually have marked obstruction of the RVOT. Two options are available in these infants. The first option is **corrective open heart surgery** performed in early infancy (or even in the newborn period in critically ill infants). This approach has widespread acceptance with excellent short- and long-term results and has supplanted palliative shunts (see later) for most cases. Early total repair carries the theoretical advantage that early physiologic correction allows for improved growth of the branch pulmonary arteries. In infants with less severe cyanosis who can be maintained with good growth and absence of hypercyanotic spells, primary repair is performed electively in the first few months.

Corrective surgical therapy consists of relief of the RVOT obstruction by resecting obstructive muscle bundles and by patch closure of the VSD. If the pulmonary valve is stenotic, as it usually is, a valvotomy is performed. If the pulmonary valve annulus is too small or the valve is extremely thickened, a valvectomy may be performed, the pulmonary valve annulus split open, and a transannular patch placed across the pulmonary valve ring. The advantage of a patch that is not circumferential is that it preserves part of the normal valve annulus and leaflets, allowing for future growth. A right ventriculotomy was once the standard approach; a transatrial-transpulmonary approach is routinely performed to reduce the long-term risks of a large right ventriculotomy. In the past, surgeons placed large transannular patches with the goal of eliminating any possibility of residual pulmonary stenosis, even if these resulted in wide-open pulmonary insufficiency. Currently, surgeons use smaller patches and are more accepting of small RVOT gradients if the degree of valve insufficiency can be minimized. In tetralogy patients, pulmonary valve insufficiency is one of the main reasons for reoperation long-term.

The second option, rarely used today, is a palliative systemic-to-pulmonary artery shunt **(Blalock-Taussig or B-T shunt)** performed to augment pulmonary artery blood flow. The B-T shunt augmented pulmonary blood flow, decreasing hypoxia, improving linear growth, and augmenting growth of the branch pulmonary arteries. Initially performed via direct anastomosis of the subclavian artery to the pulmonary artery, today, the modified B-T shunt consists of a Gore-Tex conduit anastomosed side to side from the subclavian artery to the homolateral branch of the pulmonary artery (Fig. 479.5). Sometimes the shunt is brought directly from the ascending aorta to the MPA; in this case it is called a *central shunt*. Postoperative complications after a B-T shunt include chylothorax, diaphragmatic paralysis, and Horner syndrome. Rarely, postoperative pulmonary overcirculation leading to symptoms of cardiac failure may be caused by too large a shunt. Long-term problems associated with the original B-T shunt (absent radial pulse and arm length discrepancy) are rarely seen with the current procedure.

B-T shunts are usually reserved for patients with comorbidities, such as other major congenital anomalies or prematurity, that would make full repair a higher-risk option. Many surgeons still recommend full repair in these situations, being preferable to the combined risks of a staged procedure, and successful complete repairs have been done even in small premature infants.

PROGNOSIS

After successful total correction, patients are generally asymptomatic and are able to lead unrestricted lives. Uncommon immediate postoperative problems include RV failure, transient heart block, residual VSD with left-to-right shunting, and (rarely) myocardial infarction from interruption of an aberrant coronary artery. The long-term effects of isolated, surgically induced pulmonary valvular insufficiency or of insufficiency and mild stenosis (as is more typical with modern-era smaller transannular patches) are still being defined as more patients with repaired tetralogy of Fallot reach adulthood, but pulmonary insufficiency is generally well tolerated through childhood and early adolescence. Many patients after tetralogy repair, and all those with transannular patch repairs, have a to-and-fro murmur at the left sternal border, usually indicative of mild outflow obstruction and mild

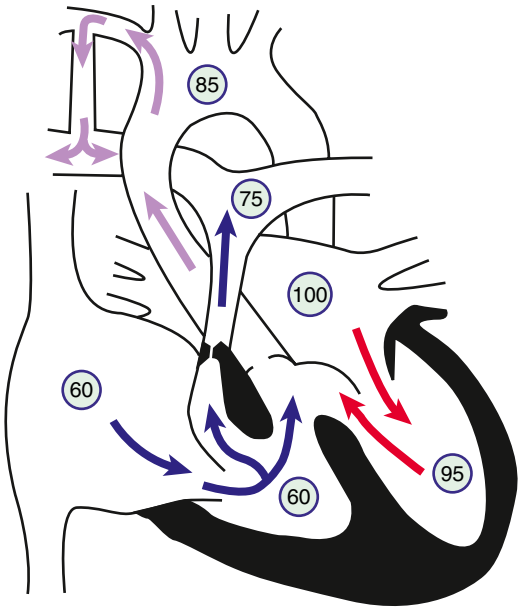

Fig. 479.5 Physiology of Blalock-Taussig shunt in patient with tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The intracardiac shunting pattern is as described for Figure 479.1. Blood shunting left to right across the shunt from the right subclavian artery to the right pulmonary artery increases total pulmonary blood flow and results in a higher oxygen saturation than would exist without the shunt.

to moderate pulmonary insufficiency. Patients with more marked or long-standing pulmonary valve insufficiency may also have moderate to more severe degrees of RV enlargement and may develop tricuspid regurgitation as the tricuspid valve annulus dilates. These patients will develop a holosystolic murmur at the lower-left and -right sternal borders. Patients with a moderate to severe residual gradient (stenosis) across the RVOT usually require balloon angioplasty or catheter placement of a stent or reoperation, but milder degrees of residual obstruction usually do not require reintervention.

Follow-up of patients 5-20 years after surgery indicates generally excellent outcomes, with minimal symptoms and good exercise tolerance. Despite being asymptomatic, many patients may have lower-than-normal exercise capacity and maximal heart rate on formal cardiopulmonary exercise testing. These abnormal findings are more common in patients who underwent placement of a transannular outflow tract patch and may be less frequent when surgery is performed at an early age. When these children move into adolescence and adulthood, some (more often those with transannular patches) will develop RV dilation as a result of long-term pulmonary regurgitation. Careful surveillance for excessive RV dilation and early signs of RV dysfunction is critical. After reaching adulthood, lifelong follow-up by a specialist in adult congenital heart disease (CHD) is important. Serial echocardiography and the more quantitative magnetic resonance angiography (MRI/MRA) are valuable tools for assessing the degree of RV dilation, identifying the presence of early stages of RV dysfunction, and quantifying the regurgitant fraction. A significant portion of patients with tetralogy of Fallot have been found to have some degree of fibrosis within the right ventricle by MRI. Valve repair or replacement is indicated for those patients with increasing RV dilation and if tricuspid regurgitation is more than mild. For patients requiring valve replacement, nonsurgical (transcatheter) options are available. Several stent-valves can be delivered in the cardiac catheterization laboratory, and these have been used successfully in patients with repaired tetralogy of Fallot. The initial versions of these devices (the Melody valve) were designed to be used predominantly in patients who have previously had a homograft or other artificial conduit placed between the RV and pulmonary arteries; often stent-valves (the Harmony valve) have been designed to be inserted into the native RVOT.

Conduction disturbances can occur after surgery. The atrioventricular node and the bundle of His and its divisions are close to the VSD and may be injured during surgery; however, permanent complete heart block after tetralogy repair is rare. When present, it should be treated by placement of a permanently implanted pacemaker. Even transient complete heart block in the immediate postoperative period is rare; it may be associated with an increased incidence of late-onset complete heart block and sudden death. In contrast, right bundle branch block is extremely common on the postoperative ECG. The duration of the QRS interval has been shown to predict both the presence of residual hemodynamic derangement and the long-term risk of arrhythmia (mainly ventricular tachycardia) and sudden death. Biventricular pacing (in which a pacemaker is used to resynchronize the activation of the right and left ventricles) has been shown to improve hemodynamics in patients with RV dysfunction and long ventricular conduction delays on ECG.

Many children have **premature ventricular beats** after repair of the tetralogy of Fallot. These beats, if isolated and infrequent, may be benign but are of particular concern in patients with residual hemodynamic abnormalities. Approximately 10% of patients with repaired tetralogy are at risk of life-threatening ventricular arrhythmias, and 30% are at risk of atrial arrhythmias as they reach adulthood. Long-duration electrocardiographic monitoring studies, such as Holter (24-48 hours) or ZioPatch (1-2 weeks), should be performed on a regular basis to ensure that occult episodes of ventricular tachycardia are not occurring. Exercise studies may be useful in provoking cardiac arrhythmias that are not apparent at rest. In the presence of complex ventricular arrhythmias or severe residual hemodynamic abnormalities, prophylactic antiarrhythmic drug therapy or an implantable defibrillator is warranted. Surgical or transcatheter intervention is indicated if significant residual RVOT obstruction or severe pulmonary insufficiency is present because arrhythmia risk may improve after hemodynamics are restored to a more normal level.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

479.2 Tetralogy of Fallot with Pulmonary Atresia

Daniel Bernstein

Tetralogy of Fallot with pulmonary atresia is the most extreme form of the tetralogy of Fallot. The pulmonary valve is atretic (absent), and the pulmonary trunk may be hypoplastic or atretic as well. The entire RV output is ejected into the aorta. Pulmonary blood flow is then dependent on multiple **major aortopulmonary collateral arteries (MAPCAs)** arising from the ascending and/or descending aorta or aortic branches and supplying various lung segments or, rarely, on a PDA. The ultimate prognosis depends on the presence or absence of true branch pulmonary arteries and, if present, the degree of development. This is best assessed by a combination of CT and cardiac catheterization. If repair is approached early in life and performed at a center with expertise in this highly complex surgery, the mid-term outcomes are good. However, if the pulmonary arteries are severely hypoplastic and surgical intervention fails to establish low pulmonary vascular pressures, lung or heart-lung transplantation may be the only therapy (see Chapter 492.2). Tetralogy of Fallot with pulmonary atresia is also associated with the 22q11.2 deletion and DiGeorge syndrome. The association of severe **tracheomalacia** or **bronchomalacia** with these severe forms of tetralogy/pulmonary atresia may complicate postoperative recovery.

CLINICAL MANIFESTATIONS

Patients with tetralogy of Fallot/pulmonary atresia have findings similar to those in patients with severe tetralogy of Fallot. Cyanosis usually appears within the first few hours or days after birth; however, the prominent systolic murmur associated with tetralogy is usually absent. The first heart sound (S_1) may be followed by an ejection click caused

by the enlarged aortic root, S_2 is single and loud, and continuous murmurs of collateral flow may be heard over the entire precordium and over the back. Most patients are moderately cyanotic and are initially stabilized with a PGE_1 infusion pending cardiac catheterization and/or CT scan to further delineate the anatomy. Patients with several large MAPCAs may be less cyanotic and, once the diagnosis is confirmed, can be taken off prostaglandin while awaiting palliative surgical intervention. Some patients may even develop symptoms of heart failure caused by increased pulmonary blood flow via these collateral vessels.

DIAGNOSIS

The chest radiograph demonstrates a varying heart size, depending on the amount of pulmonary blood flow, a concavity at the position of the pulmonary arterial segment, and often the reticular pattern of bronchial collateral flow. The ECG shows RVH. The echocardiogram identifies aortic override, a thick RV wall, and atresia of the pulmonary valve. Pulsed and color Doppler echocardiographic studies show an absence of forward flow across the pulmonary valve, with pulmonary blood flow being supplied by MAPCAs, which can usually be seen using color Doppler arising from the descending aorta. At cardiac catheterization, right ventriculography reveals a large aorta, opacified immediately by passage of contrast medium through the VSD but with no dye entering the lungs through the RVOT. It is important in planning surgical repair to delineate carefully the often diminutive native pulmonary arteries, if present, to determine whether they are continuous or discontinuous and whether they arborize to all lung segments. The location and arborization of all MAPCAs and the presence of any localized stenosis, which become more common as the patient grows older, are determined by selective contrast injection into each vessel from its origin in the aorta. CT angiography is extremely valuable in mapping the extent of MAPCA arborization.

TREATMENT

The surgical procedure of choice depends on whether the MPA segment is present and, if so, on the size and branching pattern of the branch pulmonary arteries. If these arteries are well developed, a one-stage surgical repair with a homograft conduit inserted between the right ventricle and pulmonary arteries and closure of the VSD is usually feasible. If the pulmonary arteries are hypoplastic, extensive reconstruction may be required. This may involve several staged surgical procedures. If the native pulmonary artery is present but small, a connection made between the aorta and the hypoplastic native pulmonary artery **(aortopulmonary window)** can be performed in the newborn period to induce growth of the native pulmonary arteries. At 3-4 months of age, the multiple MAPCAs are gathered together **(unifocalization procedure)** and eventually incorporated into the final repair along with the native pulmonary arteries. This series of operations may be accomplished through successive right and left lateral thoracotomies or through a single midline sternotomy if the anatomy is favorable.

To be a candidate for full repair, the pulmonary arteries must be of adequate size to accept the full volume of RV output. Complete repair includes closure of the VSD and placement of a homograft conduit from the right ventricle to the pulmonary artery. At the time of reparative surgery, previous shunts are taken down. Because of patient growth and homograft narrowing caused by proliferation of intimal tissue and calcification, replacement of the homograft conduit replacement is usually required in later life, and multiple replacements may be needed. Some of these patients are candidates for placement of a transcatheter stent-valve in the pulmonary position. Patients with obstruction of the very distal branches of the pulmonary arteries may undergo repeat surgical procedures or transcatheter balloon dilation and stenting of the multibranch pulmonary arterial stenosis. Careful follow-up is warranted for these patients, with a combination of echocardiogram, catheterization, and CT or MRI, to ensure maximal chance of growth of all pulmonary artery segments. Serial radionuclide lung perfusion scans can be used to assess pulmonary perfusion to each lung segment and the percentage of flow to the right vs the left lung.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

479.3 Pulmonary Atresia with Intact Ventricular Septum

Daniel Bernstein

Pulmonary atresia with an intact ventricular septum presents in the newborn period with severe cyanosis. The pulmonary valve leaflets are completely fused to form a membrane, and the RVOT is atretic. Because no VSD is present, no egress of blood from the right ventricle can occur. Any blood that enters the right ventricle will regurgitate back across the tricuspid valve into the right atrium. Right atrial pressure increases, and blood shunts via the foramen ovale into the left atrium, where it mixes with pulmonary venous blood and enters the left ventricle (Fig. 479.6). The combined left and right ventricular output is pumped solely by the left ventricle into the aorta. In a newborn with pulmonary atresia, the only source of pulmonary blood flow occurs via a PDA. The right ventricle and tricuspid valve are usually hypoplastic, although the degree of hypoplasia varies considerably. Patients who have a small RV cavity also tend to be those with the smallest tricuspid valve annulus, which limits RV inflow. Patients with pulmonary atresia and intact ventricular septum may have **coronary sinusoidal channels** within the RV wall that communicate directly with the coronary arterial circulation. The high RV pressure results in desaturated blood flowing retrograde through these channels into the coronary arteries. Sometimes there are also stenoses of the coronary arteries proximal to where the sinusoids enter, so that distal coronary artery flow is dependent on flow from the right ventricle (known as *right ventricle–dependent coronary circulation*). The prognosis in patients with these sinusoids and proximal stenosis of the coronary arteries is more guarded than in those patients without sinusoids or with sinusoids but no coronary stenoses. Rarely, the proximal coronary artery may be totally absent.

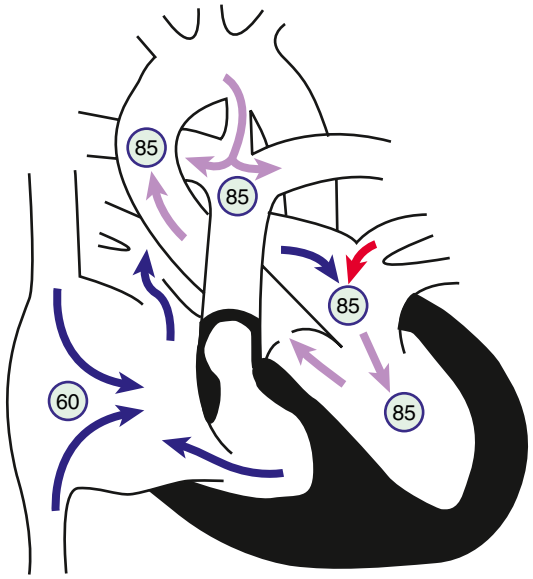

Fig. 479.6 Physiology of pulmonary atresia with intact ventricular septum. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. A small amount of the blood entering the right atrium may cross the tricuspid valve, which is often stenotic as well. The right ventricular cavity is hypertrophied and may be hypoplastic. No outlet from the right ventricle exists because of the atretic pulmonary valve; thus any blood entering the right ventricle returns to the right atrium via tricuspid regurgitation. Most of the desaturated blood shunts right to left via the foramen ovale into the left atrium, where it mixes with fully saturated blood returning from the lungs. The only source of pulmonary blood flow is via the patent ductus arteriosus. Aortic and pulmonary arterial oxygen saturation will be identical (definition of a total mixing lesion).

CLINICAL MANIFESTATIONS

When the ductus arteriosus closes in the first hours or days of life, infants with pulmonary atresia and an intact ventricular septum become markedly cyanotic because their only source of pulmonary blood flow is removed. Untreated, most patients die within the first week of life. Physical examination reveals severe cyanosis and respiratory distress. S_2, representing only aortic closure, is single and loud. Often, no murmurs are audible; sometimes a systolic or continuous murmur can be heard secondary to ductal blood flow. A harsh holosystolic murmur may be heard at the lower left and right sternal borders if there is significant tricuspid regurgitation.

DIAGNOSIS

The ECG shows a frontal QRS axis between 0 and +90 degrees, the amount of leftward shift reflecting the degree of RV hypoplasia. Tall, spiked P waves indicate right atrial enlargement. QRS voltages are consistent with left ventricular dominance or hypertrophy; RV forces are usually decreased in proportion to the decreased size of the RV cavity. Because the normal newborn ECG shows increased right-sided forces, if a normal "adult" ECG R-wave progression is seen, it suggests RV hypoplasia of some degree. Most patients with small right ventricles have decreased RV forces, but occasionally, patients with larger, thickened RV cavities may have evidence of RVH. The chest radiograph shows decreased pulmonary vascularity, the degree depending on the size of the branch pulmonary arteries and the patency of the ductus. Unlike in patients with pulmonary atresia and tetralogy of Fallot, the presence of MAPCAs is rare.

The 2D echocardiogram is useful in estimating RV dimensions and the size of the tricuspid valve annulus, which have been shown to be of prognostic value. Echocardiography can often suggest the presence of sinusoidal channels but cannot be used to evaluate coronary stenoses. Thus cardiac catheterization is necessary for complete evaluation. Pressure measurements reveal right atrial and RV hypertension. Ventriculography demonstrates the size of the RV cavity, the atretic RVOT, the degree of tricuspid regurgitation, and the presence or absence of intramyocardial sinusoids filling the coronary vessels. Aortography shows filling of the pulmonary arteries by the PDA and is helpful in determining the size and branching patterns of the pulmonary arterial bed. An aortogram or, if necessary, selective coronary angiography is performed to evaluate for the presence of proximal coronary artery stenosis (RV-dependent coronary circulation) or proximal coronary artery atresia.

TREATMENT

Infusion of PGE_1 (0.05-0.1 μg/kg/min) is usually effective in keeping the ductus arteriosus open before intervention, thus reducing hypoxemia and acidemia before surgery. The choice of surgical procedure depends on whether there is an RV-dependent coronary circulation and on the size of the RV cavity. In patients with only mild to moderate RV hypoplasia without sinusoids, or in patients with sinusoids but no evidence of coronary stenoses, a surgical pulmonary valvotomy is carried out to relieve outflow obstruction. Often, the RVOT is widened with a patch. To provide adequate pulmonary blood flow, an aortopulmonary (Blalock-Taussig) shunt may also be performed during the same procedure. An alternative approach uses interventional catheterization, in which the imperforate pulmonary valve is first punctured either with a wire or a radiofrequency ablation catheter, followed by a balloon valvuloplasty. If this course is taken, it may take days to weeks before the RV muscle regresses enough for the patient to be weaned from prostaglandin, and many of these patients will still require surgical intervention.

The aim of surgery or interventional catheterization is to encourage growth of the RV chamber by allowing some forward flow through the pulmonary valve while using the shunt to ensure adequate pulmonary blood flow. Later, if the tricuspid valve annulus and RV chamber grow to adequate size, the shunt is taken down and any remaining atrial-level shunt can be closed. If the RV chamber remains too small for use as a pulmonary ventricle, the patient is treated as having a single-ventricle circulation, with a **Glenn procedure** followed by a modified **Fontan procedure** (see Chapter 479.4), allowing blood to bypass the hypoplastic right ventricle by flowing to the pulmonary arteries directly from the venae cavae. When coronary artery stenoses are present and retrograde coronary perfusion occurs from the right ventricle through myocardial sinusoids, the prognosis is more guarded because of a higher risk of arrhythmias, coronary ischemia, and sudden death. It is important for these patients not to try to open the RVOT, because dropping the RV pressure rapidly will reduce coronary perfusion, leading to ischemia. These patients are usually treated with an aortopulmonary shunt, followed by the Glenn and Fontan procedure. Although at higher risk than those without coronary stenoses, recent reports show good success with this approach; however, long-term complications are higher than in other groups of single-ventricle patients. A small number of these infants (e.g., those with atresia of a proximal coronary artery) are best referred for heart transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

479.4 Tricuspid Atresia

Daniel Bernstein

In tricuspid atresia, there is no outlet from the right atrium to the right ventricle; the entire systemic venous return leaves the right atrium and enters the left side of the heart through the foramen ovale or, most often, an atrial septal defect (ASD) (Fig. 479.7). The physiology of the circulation and the clinical presentation will depend on the presence and type of other congenital heart defects, most notably on whether the great arteries are normally related or are transposed (aorta arising from the right ventricle, pulmonary artery from the left ventricle). In patients with normally related great arteries, left ventricular (LV)

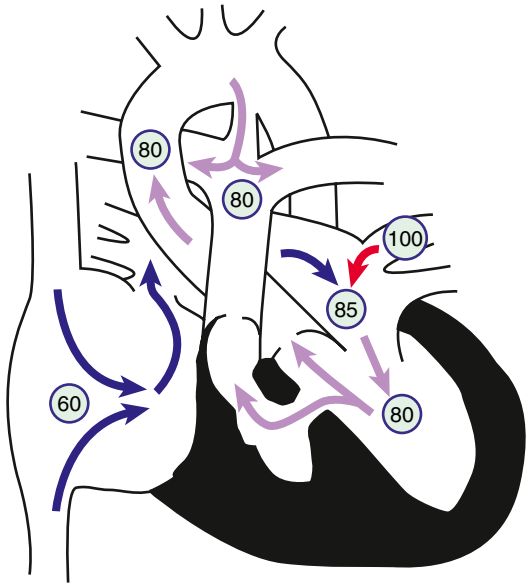

Fig. 479.7 Physiology of tricuspid atresia with normally related great vessels. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. The tricuspid valve is nonpatent, and the right ventricle may manifest varying degrees of hypoplasia. The only outlet from the right atrium involves shunting right to left across an atrial septal defect or patent foramen ovale to the left atrium. There, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected either through the aorta or via a ventricular septal defect (VSD) into the right ventricle. In this example, some pulmonary blood flow is derived from the right ventricle and the rest from a patent ductus arteriosus (PDA). In patients with tricuspid atresia, the PDA may close or the VSD may grow smaller and result in a marked decrease in systemic oxygen saturation.

blood supplies the systemic circulation through the aorta. Blood also flows into the right ventricle through a VSD (if the ventricular septum is intact, the right ventricle will be completely hypoplastic and pulmonary atresia will also be present [see Chapter 479.3]). *Pulmonary blood flow (and thus the degree of cyanosis) depends on the size of the VSD and the presence and severity of any associated pulmonic stenosis.* Pulmonary blood flow may be augmented by or be totally dependent on a PDA. The inflow portion of the right ventricle is always missing, but the outflow portion can be of variable size. The clinical presentation of patients with tricuspid atresia and *normally related great arteries* will depend on the degree of obstruction to pulmonary blood flow. Patients with a smaller VSD or moderate degrees of pulmonary stenosis are recognized in the early days or weeks of life by decreased pulmonary blood flow and cyanosis, especially after the PDA begins to close. Alternatively, in those with a large VSD and minimal or no RVOT obstruction, pulmonary blood flow may be normal or increased; these patients have only mild cyanosis and can present with signs of pulmonary overcirculation and heart failure.

In patients with tricuspid atresia and **transposition of the great arteries (TGA)**, LV blood flows directly into the pulmonary artery, whereas systemic blood must traverse the VSD and right ventricle to reach the aorta. In these patients, pulmonary blood flow is usually massively increased, and heart failure develops early. If the VSD is restrictive, systemic blood flow may be compromised and the patient may present with signs of decreased perfusion. **Coarctation of the aorta** is often noted in this setting.

CLINICAL MANIFESTATIONS

Some degree of cyanosis is usually evident at birth, with the extent depending on the degree of limitation to pulmonary blood flow. Unique to tricuspid atresia, an increased LV impulse may be noted, in contrast to most other causes of cyanotic heart disease, in which an increased RV impulse is usually present. Most patients have holosystolic murmurs audible along the left sternal border; S_2 is usually single. Pulses in the lower extremities may be weak or absent in the presence of transposition and with coarctation of the aorta. Patients with tricuspid atresia are at risk for spontaneous narrowing or even closure of the VSD, which can occasionally occur rapidly and lead to a marked increase in cyanosis.

DIAGNOSIS

Radiologic studies show either pulmonary undercirculation (most often in patients with normally related great arteries) or overcirculation (most often in patients with transposed great arteries). Left-axis deviation and LV hypertrophy are generally noted on the ECG (except in patients with TGA), and these unique features are a hallmark of tricuspid atresia, distinguishing it from most other cyanotic heart lesions, which are associated with right-axis deviation and RV hypertrophy. In the right precordial leads, the normally prominent R wave is replaced by an rS complex. The left precordial leads show a qR complex, followed by a normal, flat, biphasic, or inverted T wave. RV_6 is normal or tall, and SV_1 is generally deep. The P waves are usually biphasic, with the initial component tall and spiked in lead II. 2D echocardiography reveals the presence of a fibromuscular membrane in place of a tricuspid valve, a variably small right ventricle, variably sized VSD, and a slightly to moderately enlarged left ventricle (Fig. 479.8). The relationship of the great vessels (normal or transposed) can be determined. The degree of obstruction at the level of the VSD or at the RVOT can be determined by Doppler examination. Blood flow through a patent ductus can be evaluated by color flow and pulsed Doppler.

Cardiac catheterization, indicated usually only if questions remain after echocardiography, shows normal or slightly elevated right atrial pressure with a prominent *a* wave. If the right ventricle is entered through the VSD, the pressure may be lower than on the left if the VSD is restrictive in size. Right atrial angiography shows immediate opacification of the left atrium from the right atrium, followed by left ventricular filling and visualization of the aorta. Absence of direct flow to the right ventricle results in an angiographic filling defect between the right atrium and the left ventricle.

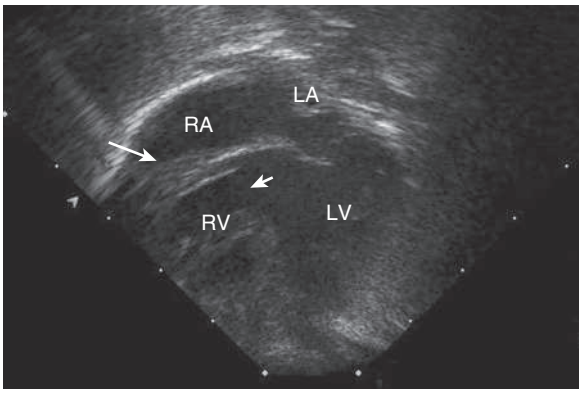

Fig. 479.8 Echocardiogram demonstrating tricuspid atresia. The floor of the right atrium consists of a fibromuscular membrane *(longer arrow)* instead of the normal tricuspid valve apparatus. The large secundum atrial septal defect can be seen between the right and left atria. The *short arrow* shows the ventricular septal defect. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TREATMENT

Management of patients with tricuspid atresia depends on the adequacy of pulmonary blood flow. Moderately or severely cyanotic neonates (most often those with normally related great arteries) should be maintained on an IV infusion of PGE_1 (0.05-0.1 μg/kg/min) until a surgical aortopulmonary shunt procedure can be performed to increase pulmonary blood flow. The Blalock-Taussig procedure (see Chapter 479.1) or a variation is the preferred anastomosis. Rare patients with restrictive atrial-level communications also benefit from a Rashkind balloon atrial septostomy (see Chapter 480.2) or surgical septectomy.

Infants with increased pulmonary blood flow because of an unobstructed pulmonary outflow tract (more often patients with TGA) may require early surgery or pulmonary arterial banding (especially for patients in the first 1-2 months of life) to decrease the symptoms of heart failure and protect the pulmonary bed from the development of pulmonary vascular disease. Infants with just adequate pulmonary blood flow who are well balanced between cyanosis and pulmonary overcirculation can be watched closely for the development of increasing cyanosis, which may occur as the VSD begins to get smaller or the pulmonary outflow becomes narrower and is an indication for surgery.

The next stage of palliation for patients with tricuspid atresia involves the creation of an anastomosis between the superior vena cava and the pulmonary arteries (**bidirectional Glenn shunt**; Fig. 479.9A). This procedure is performed at usually between 2 and 6 months of age. The Glenn shunt provides a stable source of pulmonary blood flow as well as reducing the volume load on the left ventricle.

The **modified Fontan operation** is the preferred approach for longer-term palliation. It is usually performed between 2 and 3 years of age, after the patient is ambulatory. Initially, this procedure was performed by anastomosing the right atrium or atrial appendage directly to the pulmonary artery. The procedure used most often now is a modification of the Fontan procedure, known as a **cavopulmonary isolation procedure**, which involves anastomosing the inferior vena cava directly to the pulmonary arteries using a homograft or Gore-Tex tube running outside the heart (external-conduit Fontan; Fig. 479.9C). An older version of this procedure uses an internal baffle that runs along the lateral wall of the right atrium (lateral-tunnel Fontan; see Fig. 479.9B). In a completed Fontan repair, desaturated blood flows from both venae cavae directly into the pulmonary arteries. Oxygenated blood returns to the left atrium, enters the left ventricle, and is ejected into the systemic circulation. The volume load is completely removed from the left ventricle, and the right-to-left shunt is abolished. Because of the reliance on passive filling of the pulmonary circulation, the Fontan procedure is contraindicated in patients with elevated pulmonary vascular resistance, in those with pulmonary artery hypoplasia, and in patients with LV dysfunction. The patient also must not have significant mitral insufficiency. Patients who are not in normal sinus rhythm

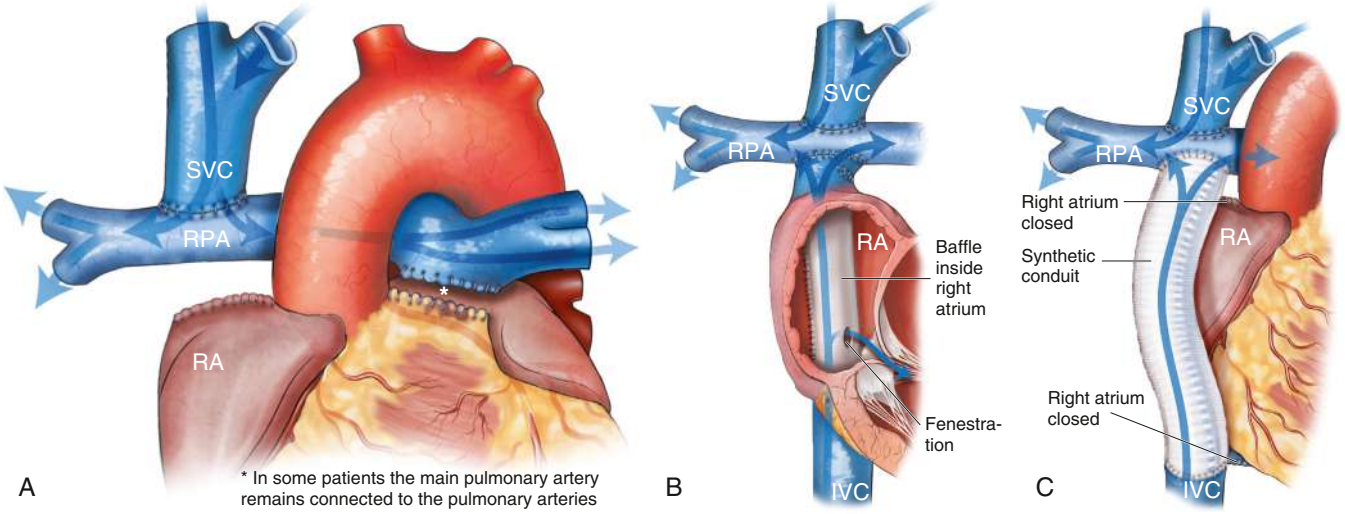

Fig. 479.9 Staged surgical approach to palliation of the patient with a single-ventricle circulation. **A,** Bidirectional Glenn shunt. The superior vena cava (SVC) is divided and detached from the right atrium (RA) and anastomosed end-to-side to the pulmonary artery, which has also been divided and detached from the right ventricle. **B,** Lateral tunnel Fontan. Inferior vena caval flow is directed upward through a synthetic or pericardial baffle sutured to the RA wall. The lower portion of the SVC (previously divided during the Glenn shunt) is now sutured directly to the right pulmonary artery. Thus blood flows from the upper body via the SVC directly into the lungs via the previous Glenn shunt and from the lower body via the baffle, through the RA but not emptying into the RA, directly into the lungs. The only remaining blood flow entering into the RA is from the coronary sinus, which represents the small amount of venous return coming directly from the left ventricle. The RA is thus excluded from the Fontan circuit. **C,** Extracardiac Fontan. The inferior vena cava (IVC) is detached from the RA, and an extracardiac synthetic conduit or homograft is used to direct that flow, outside the heart, to the inferior aspect of the right pulmonary artery (RPA). Both Fontan approaches achieve the same endpoint in isolating the venous circulation (blue blood) from the arterial circulation (red blood). The external conduit Fontan procedure is more common today because of concerns about atrial arrhythmias and/or blood clots related to the baffle in the RA. Many surgeons orient the connection from the IVC more centrally on the pulmonary arteries than shown in (**C**) to avoid a "collision" of flow from the upper and lower bodies, which in flow dynamic modeling studies has been shown to reduce the efficiency of the Fontan circulation, especially during exercise. *(Adapted from Burchill LJ, Wald RM, Mertens L. Single ventricles: echocardiographic assessment after the Fontan operation. In Otto CM, ed. The Practice of Clinical Echocardiography, 5th ed. Philadelphia: Elsevier; 2017, Figs. 49-6, 8, and 9.)*

are at increased risk, and if a pacemaker is required in these patients, dual-chamber pacing is the preferred approach.

Postoperative problems after the Fontan procedure are most often related to the increase in central venous pressure that occurs when the vena cavae are connected directly to the pulmonary arteries. Normal central venous pressure is 0-5 mm Hg, whereas after the Fontan operation, central venous pressure can rise to 10-15 mm Hg, and occasionally even more. In the immediate postoperative period, this elevation of systemic venous pressure can lead to fluid retention and pleural or pericardial effusions. The occurrence of these effusions has been markedly reduced with the cavopulmonary isolation procedure now in use, although prolonged chest tube drainage can still occur, but eventually resolves. Some centers use a fenestration at the time of the Fontan, consisting of a small communication between the inferior vena cava and the pulmonary artery conduit and the left atrium. This serves as a "pop-off" during early postoperative recovery and may hasten hospital discharge. The fenestration will result in some amount of right-to-left shunting and is therefore usually closed with a catheter closure device after the immediate postoperative period.

Late complications of the Fontan procedure include stenosis of the superior or inferior vena cava anastomosis, vena cava or pulmonary artery thromboembolism, protein-losing enteropathy, plastic bronchitis, renal dysfunction, immune deficiency, supraventricular arrhythmias (atrial flutter, paroxysmal atrial tachycardia), and hepatic injury, referred to as **Fontan-associated liver disease (FALD)**, as a result of persistently elevated central venous pressures. Rarely liver disease may predispose to the development of hepatocellular carcinoma. As more patients survive into young and middle adult years, the occurrence of these complications increases, and these patients require careful follow-up in a center skilled at caring for **adults with congenital heart disease (ACHDs)**. Oral budesonide or sildenafil has been used with varying success to treat protein-losing enteropathy associated with the Fontan procedure. MRI lymphangiography followed by thoracic duct ligation, decompression, or embolization is used to treat plastic bronchitis and other complications of a Fontan procedure. LV dysfunction may be a late occurrence, usually not until adolescence or young adulthood. Heart transplantation is a successful treatment option for pediatric patients with "failed" Fontan circuits but is a somewhat riskier procedure when performed in older adults. Patients with combined heart failure and liver dysfunction have been treated with combined heart-liver transplantation with good result.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

479.5 Double-Outlet Right Ventricle

Daniel Bernstein

Double-outlet right ventricle **(DORV)** is characterized when both the aorta and pulmonary artery arise from the right ventricle. The only outlet from the left ventricle occurs through a VSD emptying into the right ventricle, although some degree of override of the septum may place either the aorta or pulmonary artery partially over the left ventricle. Normally, the aortic and mitral valves are in fibrous continuity; in DORV the aortic and mitral valves are separated by a smooth muscular **conus**, like that seen under the normal pulmonary valve. In DORV the great arteries may be *normally related,* with the aorta closer to (or slightly overriding) the VSD, or the great arteries may be *malposed,* with the pulmonary artery closer to (or slightly overriding) the VSD. The degree to which the great artery closest to the VSD may override the defect is variable but must be at least 50% committed to the right ventricle to be termed DORV. When the VSD is subaortic, the defect may be viewed as part of a continuum with the **tetralogy of Fallot**, and the physiology, history, physical examination, ECG, and radiography depend on the degree of pulmonary stenosis, like the situation in tetralogy of Fallot (see Chapter 479.1). If the VSD is subpulmonic, there may be subvalvar, valvar, or supravalvar aortic stenosis, and

coarctation is a possibility as well. This is known as the **Taussig-Bing malformation**. The clinical presentation of these patients will depend on the degree of aortic obstruction, but because the pulmonary artery is usually wide open, the presentation will usually include some degree of pulmonary overcirculation and heart failure. If the aortic obstruction is severe or there is a coarctation, poor pulses, hypoperfusion, and cardiovascular collapse are possible presenting signs, especially when the PDA begins to close.

The 2D echocardiogram demonstrates both great vessels arising from the right ventricle and mitral-aortic valve discontinuity. The relationships between the aorta and pulmonary artery to the VSD can be delineated, and the presence of either pulmonary obstruction or aortic obstruction can be evaluated. The aortic arch is imaged to evaluate for coarctation. Cardiac catheterization is not necessarily required if the echocardiogram is straightforward. Angiography will show that the aortic and pulmonary valves lie in the same horizontal plane and that both arise predominantly or exclusively from the right ventricle.

Surgical correction depends on the relationship of the great vessels to the VSD. If the VSD is *subaortic,* the repair will be like that used for tetralogy of Fallot with patch closure of the VSD so that the left ventricle ejects blood into the aorta. In cases where the aorta is more distant from the left ventricle, repair may consist of creating an intraventricular tunnel so that the left ventricle ejects blood through the VSD, into the tunnel, and into the aorta. The pulmonary obstruction is relieved either with an outflow patch or with a right ventricle–to–pulmonary artery homograft conduit **(Rastelli operation)**. If the VSD is *subpulmonic,* the great vessels can be switched (see Chapter 479.6) and the Rastelli operation performed. However, if there is substantial aortic obstruction or if one of the ventricles is hypoplastic, a Norwood-style single-ventricle repair may be necessary (see Chapter 480.10). In selected small infants, palliation with an aortopulmonary shunt can provide symptomatic improvement and allow for adequate growth before corrective surgery is performed.

479.6 Transposition of the Great Arteries with Ventricular Septal Defect and Pulmonary Stenosis

Daniel Bernstein

The combination of TGA with VSD and pulmonary stenosis may mimic tetralogy of Fallot in its clinical features (see Chapter 479.1). However, because of the transposed great vessels, the site of obstruction is in the left as opposed to the right ventricle. The obstruction can be either valvular or subvalvular; the latter type may be *dynamic,* related to the interventricular septum or atrioventricular valve tissue, or *acquired,* as in patients with transposition and VSD after pulmonary arterial banding.

The age at which clinical manifestations initially appear varies from soon after birth to later infancy, depending on the degree of pulmonic stenosis. Clinical findings include cyanosis, decreased exercise tolerance, and poor physical development, like those described for tetralogy of Fallot; the heart is usually more enlarged. The pulmonary vasculature as seen on radiograph depends on the degree of pulmonary obstruction. The ECG usually shows right-axis deviation, right and left ventricular hypertrophy, and sometimes tall, spiked P waves. Echocardiography confirms the diagnosis and is useful in sequential evaluation of the degree and progression of the LV outflow tract obstruction. Cardiac catheterization, if necessary, shows that pulmonary arterial pressure is low and that oxygen saturation in the pulmonary artery exceeds that in the aorta, since pulmonary blood flow is coming directly from the left ventricle. Selective right and left ventriculography demonstrates the origin of the aorta from the right ventricle, the origin of the pulmonary artery from the left ventricle, the VSD, and the site and severity of the pulmonary stenosis.

An infusion of PGE_1 (0.05-0.1 μg/kg/min) should be started in neonates who present with cyanosis. When necessary, **balloon atrial septostomy** is performed to improve atrial-level mixing and to decompress the left atrium (see Chapter 480.2). Cyanotic infants may be palliated with an aortopulmonary shunt (see Chapter 479.1), followed by a Rastelli operation when older, as the preferred corrective procedure. The Rastelli procedure achieves physiologic and anatomic correction by (1) closure of the VSD using an intraventricular tunnel so that LV blood flow is directed to the aorta and (2) connection of the right ventricle to the distal pulmonary artery by an extracardiac homograft conduit (Fig. 479.10). These conduits will eventually become stenotic with patient growth and require replacement. Patients with milder degrees of pulmonary stenosis amenable to simple valvotomy may be able to undergo complete correction with an **arterial switch procedure** (see Chapter 480.2) and closure of the VSD. Surgical correction by the **Mustard or Senning operation** (see Chapter 480.2) with simultaneous closure of the VSD and relief of LV outflow obstruction may be an alternative when the position of the VSD is not suitable for a Rastelli operation; however, this procedure leaves the right ventricle as the systemic pumping chamber and has fallen out of favor.

479.7 Ebstein Anomaly of the Tricuspid Valve

Daniel Bernstein

Ebstein anomaly consists of downward displacement of an abnormal tricuspid valve into the right ventricle. The defect arises from failure of the normal process by which the tricuspid valve is separated from the RV myocardium (see Chapter 469). The anterior cusp of the valve retains some attachment to the valve ring, but the other leaflets are adherent to the wall of the right ventricle. The right ventricle is thus divided into two parts by the abnormal tricuspid valve: the first, a thin-walled "atrialized" portion, is continuous with the cavity of the right atrium; the second, often smaller, portion consists of normal ventricular myocardium. The right atrium is enlarged as a result of tricuspid valve regurgitation, although the degree is extremely variable. In more severe forms of Ebstein anomaly, the effective output from the right side of the heart is decreased because of a combination of the poorly functioning small right ventricle, tricuspid valve regurgitation, and RVOT obstruction produced by the large, sail-like, anterior tricuspid valve leaflet. The severity of tricuspid valve displacement has been grouped into four degrees (A through D), known as the *Carpentier classification.* In newborns, RV function may be so compromised that it is unable to generate enough force to open the pulmonary valve in systole, thus producing "functional" pulmonary atresia. Some infants have true anatomic pulmonary atresia. The increased volume of right atrial blood shunts through the foramen ovale (or through an associated ASD) to the left atrium and produces cyanosis (Fig. 479.11).

CLINICAL MANIFESTATIONS

The severity of symptoms and the degree of cyanosis are highly variable and depend on the extent of displacement of the tricuspid valve and the severity of RVOT obstruction. In many patients with milder forms of tricuspid valve displacement, symptoms are mild and may be delayed until the teenage years or young adult life; the patient may initially have fatigue, exercise intolerance, or palpitations as a result of cardiac dysrhythmias. The atrial right-to-left shunt is responsible for cyanosis, which may only be evident during exercise and, if long-standing, polycythemia. Jugular venous pulsations, an index of central venous pressure, may be normal or increased in those with tricuspid insufficiency. On palpation, the precordium is quiet. A holosystolic murmur caused by tricuspid regurgitation is audible over most of the anterior left side of the chest. A gallop rhythm is common and often associated with multiple clicks at the lower-left sternal border. A scratchy diastolic murmur may also be heard at the left sternal border. This murmur may mimic a pericardial friction rub.

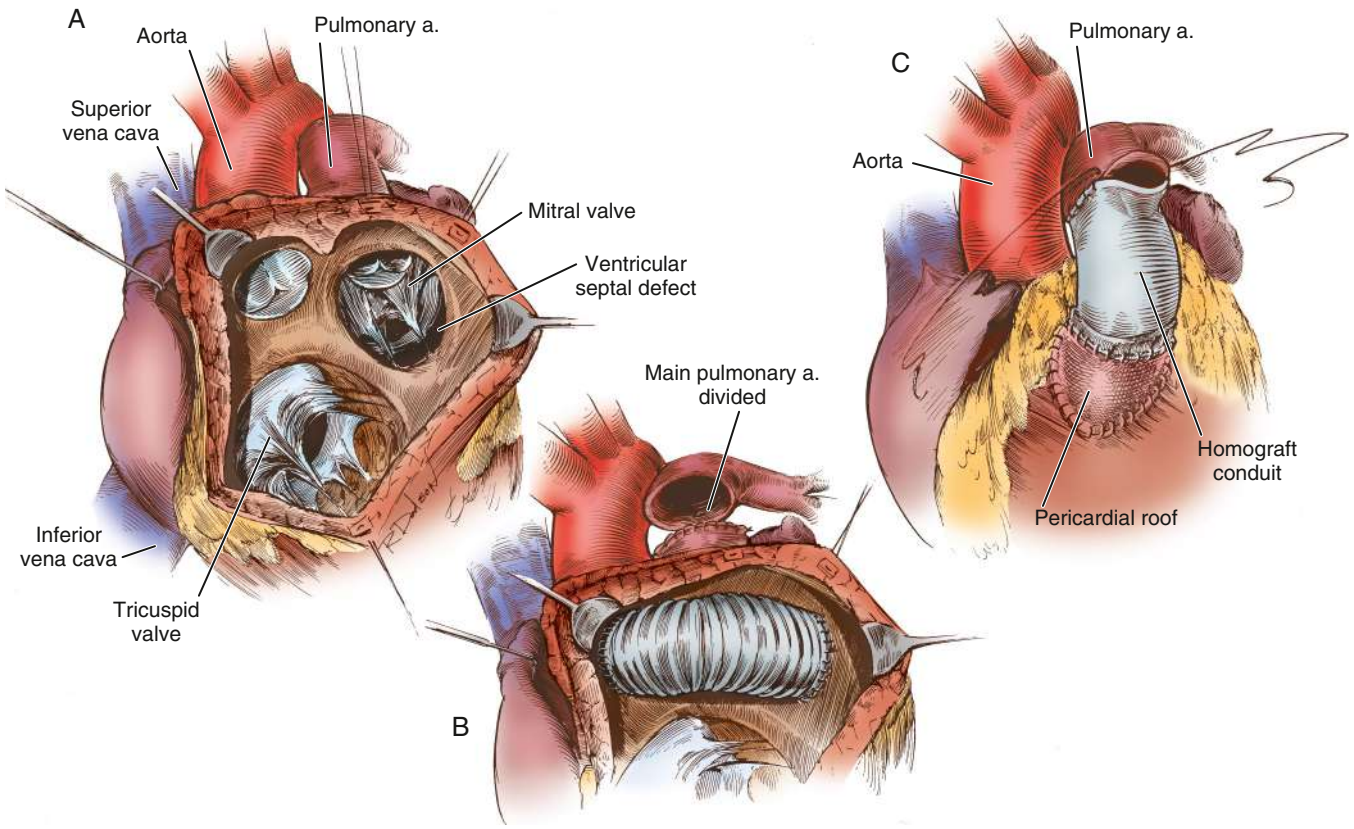

Fig. 479.10 A, Taussig-Bing type of double-outlet right ventricle with subpulmonary stenosis necessitating repair by the Rastelli technique. B, The main pulmonary artery is divided and oversewn proximally. The pulmonary valve lies within the baffle pathway. C, Completion of the Rastelli repair with a right ventricle–pulmonary artery allograft conduit. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al. Single-ventricle tricuspid atresia. In: Castañeda AR, Jonas RA. Mayer JE Jr, Hanley FL, eds. Cardiac Surgery of the Neonate and Infant. Philadelphia: Saunders; 1994.)*

Newborns with severe forms of Ebstein anomaly have marked cyanosis, massive cardiomegaly, and long holosystolic murmurs. Death may result from cardiac failure, hypoxemia, and pulmonary hypoplasia, the result of severe long-standing intrauterine right atrial enlargement. Spontaneous improvement may occur in some neonates as pulmonary vascular resistance falls and improves the ability of the right ventricle to provide pulmonary blood flow. The majority are dependent on a PDA, and thus on a prostaglandin infusion, for pulmonary blood flow. Fetuses diagnosed with Ebstein anomaly on fetal ultrasound can be particularly challenging. Severe leakage of the tricuspid valve is one of the few congenital heart lesions that cannot be bypassed by the parallel fetal circulation (see Chapter 470), and thus cardiac enlargement and fetal heart failure may supervene. When the heart enlarges, particularly the right atrium, compression of the lungs can result and the fetus is at risk for development of pulmonary hypoplasia.

DIAGNOSIS

The ECG usually shows a right bundle branch block without increased right precordial voltage, normal or tall and broad P waves, and a normal or prolonged P-R interval. **Wolff-Parkinson-White syndrome** may be present, and these patients may have episodes of supraventricular tachycardia (see Chapter 484). On radiographic examination, heart size varies from slightly enlarged to massive, box-shaped cardiomegaly caused by enlargement of the right atrium. *In newborns with severe Ebstein anomaly, the heart may be so enlarged as to totally obscure the pulmonary fields* (Fig. 479.12). Echocardiography is diagnostic and shows the degree of displacement of the tricuspid valve leaflets, a dilated right atrium, and any RVOT obstruction (Fig. 479.13). Pulsed and color Doppler examination demonstrates the degree of tricuspid regurgitation. In severe cases the pulmonary valve may appear immobile, and pulmonary blood flow may come solely from the ductus arteriosus. It may be difficult to distinguish true from functional pulmonary valve atresia. Cardiac catheterization, which is not usually necessary, confirms the presence of a large right atrium, an abnormal tricuspid valve, and any right-to-left shunt at the atrial level. The risk of arrhythmia is significant during catheterization and angiographic studies.

TREATMENT

Neonates with milder degrees of cyanosis can sometimes be managed medically, waiting to see how they do once their pulmonary vascular resistance decreases over the first few weeks of life. Those with moderate to severe hypoxia are initially treated with prostaglandins, mechanical ventilation and inhaled nitric oxide in an attempt to enhance pulmonary blood flow by reducing pulmonary vascular resistance. Surgical options for these patients include an aortopulmonary (Blalock-Taussig) shunt, tricuspid valve replacement (most often with a bioprosthetic valve), or surgical repair of the tricuspid valve (cone procedure). In the critically ill neonate, closure of the valve (creating tricuspid atresia physiology) with an aortopulmonary shunt (Starnes procedure), with eventual single-ventricle repair using the Fontan palliation (see Chapter 479.4) is

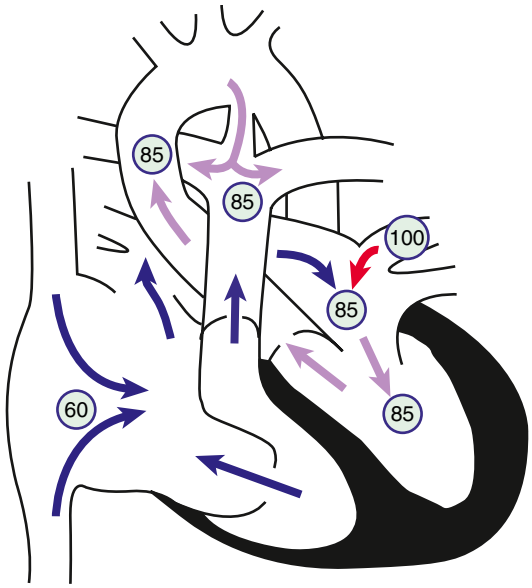

Fig. 479.11 Physiology of Ebstein anomaly of the tricuspid valve. *Circled numbers* represent oxygen saturation values. Inferior displacement of the tricuspid valve leaflets into the right ventricle has resulted in a thin-walled, low-pressure "atrialized" segment of right ventricle. The tricuspid valve is grossly insufficient. Right atrial blood flow is shunted right to left across an atrial septal defect or patent foramen ovale into the left atrium. Some blood may cross the right ventricular outflow tract and enter the pulmonary artery; however, in severe cases, the right ventricle may generate insufficient force to open the pulmonary valve, and "functional pulmonary atresia" results. In the left atrium, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected via the aorta. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). Severe cyanosis will develop in neonates with a severe Ebstein anomaly when the PDA closes.

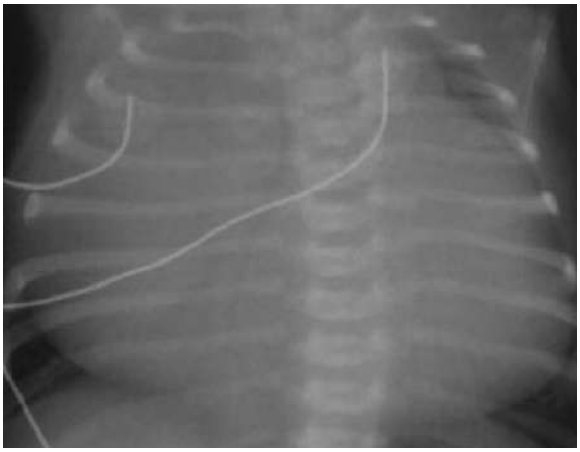

Fig. 479.12 Massive cardiomegaly in a newborn infant with severe Ebstein anomaly. The heart is so enlarged (in part because of a massive right atrium) that lung hypoplasia is a major concern.

an option. Many infants with Ebstein anomaly who have undergone valve repair will also have a bidirectional Glenn shunt performed to reduce the volume load on the right ventricle and reduce the amount of tricuspid regurgitation (see Chapter 479.4). In older children with mild or moderate disease, control of supraventricular dysrhythmias (medications or radiofrequency ablation), if present,

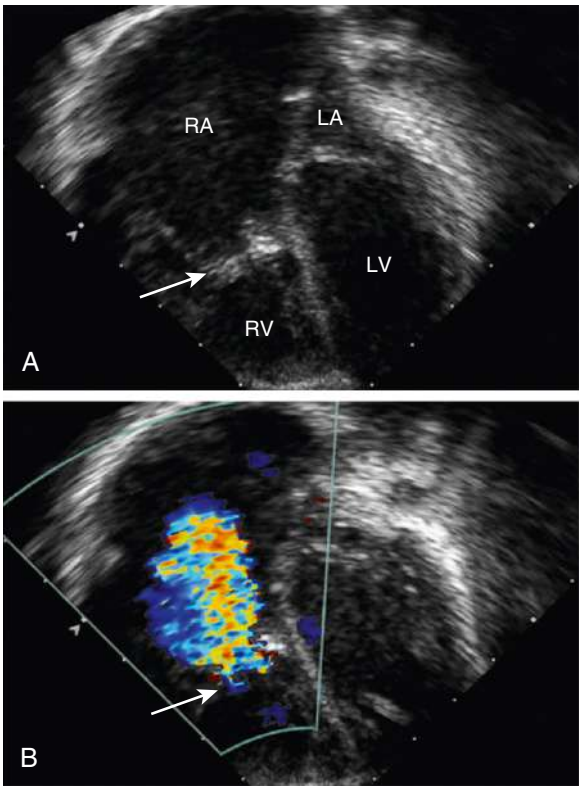

Fig. 479.13 Echocardiographic demonstration of Ebstein anomaly of the tricuspid valve. **A,** Subcostal, four-chamber, 2D view showing severe displacement of the tricuspid valve leaflets *(arrow)* inferiorly into the right ventricle. The location of the tricuspid valve annulus is outlined by the arrow. The portion of the right ventricle between the valve annulus and the valve leaflets is the "atrialized" component. **B,** Color Doppler examination showing severe regurgitation of the dysplastic tricuspid valve. Note that the regurgitant turbulent flow *(arrow)* begins halfway into the right ventricular chamber, at the location of the displaced valve leaflets. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

is of primary importance; surgical treatment may not be necessary until adolescence or young adulthood. Older patients with severe tricuspid regurgitation can undergo repair or replacement of the abnormal tricuspid valve along with closure of the ASD. In some patients, a bidirectional Glenn shunt is also performed, with the superior vena cava anastomosed to the pulmonary arteries. This procedure reduces the volume of blood that the dysfunctional right side of the heart has to pump, thus creating a "one-and-one-half ventricle repair."

PROGNOSIS AND COMPLICATIONS

The prognosis in Ebstein anomaly is extremely variable and depends on the severity of the defect. The prognosis is more guarded for neonates or infants with cyanosis. Patients with milder degrees of Ebstein anomaly usually survive well into adult life. An associated form of left ventricular cardiomyopathy, **isolated left ventricular noncompaction (LVNC)**, is seen in up to 18% of patients with Ebstein anomaly, and the severity of the LV dysfunction directly affects the prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 480

Cyanotic Congenital Heart Disease: Lesions Associated with Increased Pulmonary Blood Flow

480.1 d-Transposition of the Great Arteries

Daniel Bernstein

d-Transposition of the great arteries or vessels (d-TGA or d-TGV) accounts for approximately 5% of all congenital heart disease. In this anomaly, the systemic veins return, as normal, to the right atrium and the pulmonary veins return to the left atrium. The connections between the atria and ventricles are also normal (i.e., **atrioventricular concordance**). The aorta arises from the right ventricle and the pulmonary artery from the left ventricle (Fig. 480.1). In normally related great vessels (i.e., in the normal heart) the aorta is posterior and to the right of the pulmonary artery. Whereas in d-TGA the aorta is anterior and to the right of the pulmonary artery (the *d* indicates a dextropositioned aorta, *transposition* indicates that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle). Desaturated blood returning from the body to the right side of the heart goes inappropriately out via the aorta and back to the body again, whereas oxygenated pulmonary venous blood returning to the left side of the heart is returned directly to the lungs. Thus the systemic and pulmonary circulations exist as two parallel circuits. Survival in the immediate newborn period is provided by the foramen ovale and the ductus arteriosus, which permit some mixture of oxygenated and deoxygenated blood. Approximately 50% of patients with d-TGA also have a ventricular septal defect (VSD), which usually provides for better mixing. The clinical findings and hemodynamics vary in relation to the presence or absence of associated defects (e.g., VSD or pulmonary stenosis). d-TGA is more common in infants of diabetic mothers and in males (a ratio of 3:1). When accompanied by other cardiac defects such as pulmonic stenosis or right aortic arch, d-TGA can be associated with deletion of chromosome 22q11.2 (**DiGeorge syndrome**; see Chapter 473).

480.2 d-Transposition of the Great Arteries with Intact Ventricular Septum

Daniel Bernstein

d-TGA with an intact ventricular septum is also referred to as **simple TGA** or **isolated TGA**. Before birth, oxygenation in the upper and lower body fetal circulation is only slightly abnormal, given that oxygenated blood enters the heart from the placenta, umbilical vein, and inferior vena cava. After birth, once the ductus arteriosus begins to close, the minimal mixing of systemic and pulmonary blood by the patent foramen ovale is usually insufficient and severe hypoxemia ensues, generally within the first few days of life.

CLINICAL MANIFESTATIONS

Cyanosis and tachypnea are most often recognized within the first hours or days of postnatal life. Untreated, most of these infants would not survive the neonatal period. Hypoxemia is usually moderate to severe, depending on the degree of atrial-level shunting and whether the ductus is partially open or totally closed. This condition is a medical emergency, and only early diagnosis and appropriate intervention can avert the development of prolonged severe hypoxemia and acidosis, which lead to death. Physical findings, other than cyanosis, may be remarkably nonspecific. The precordial impulse may be normal, or a parasternal heave may be present. The second heart sound (S_2) is usually single and loud, although it may be split. Murmurs may be absent, or a soft systolic ejection murmur may be noted at the mid-left sternal border.

DIAGNOSIS

The electrocardiogram (ECG) is usually normal, showing the expected neonatal right-sided dominant pattern. Chest radiographs may show mild cardiomegaly and a narrow mediastinum (the classic "egg-shaped heart"). In the early newborn period, the pulmonary blood flow is generally normal. As pulmonary vascular resistance (PVR) drops during the first several weeks of postnatal life, evidence of increased pulmonary blood flow becomes apparent. Arterial blood partial pressure of oxygen (Pao_2) is low and does not rise appreciably after the patient breathes 100% oxygen (hyperoxia test), although this test may not be totally reliable. Echocardiography is diagnostic and confirms the transposed ventricular-arterial connections (Fig. 480.2). The size of the interatrial communication and the ductus arteriosus can be visualized and the degree of mixing assessed by pulsed and color Doppler examination. The presence of any associated lesion, such as left ventricular outflow tract obstruction or a VSD, can also be assessed. The origins of the coronary arteries can be imaged, although echocardiography is not as accurate as catheterization for

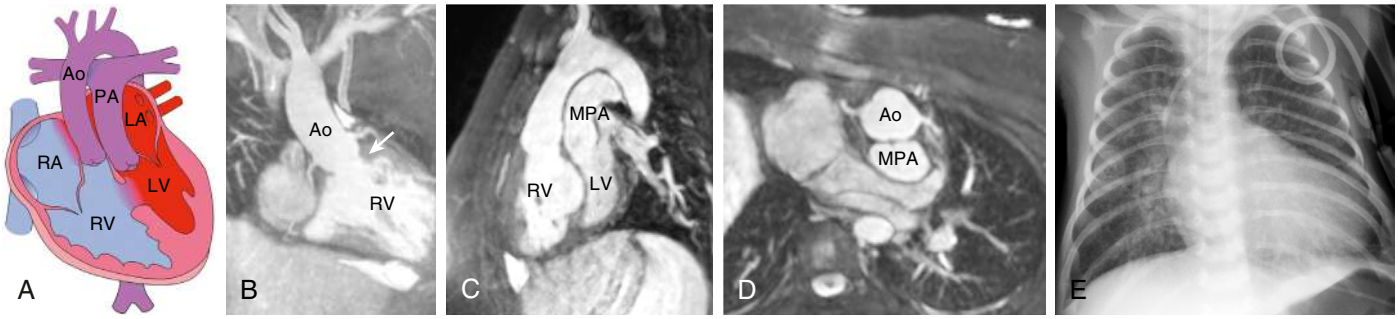

Fig. 480.1 d-Looped transposition of the great arteries (TGA). **A,** Diagram of d-TGA, with the main pulmonary artery (MPA) arising from the left ventricle (LV) and the aorta (Ao) arising from the right ventricle (RV). The degree of cyanosis is variable and depends on the presence of intracardiac shunts such as an atrial septal defect or a ventricular septal defect (VSD) to get oxygenated blood into the systemic circulation. LA, Left atrium; PA, pulmonary artery; RA, right atrium. **B** and **C,** Oblique reformatted images from a 3D steady-state free-precession sequence show (**B**) the Ao arising from the anterior RV with a subaortic conus *(arrow),* and (**C**) the MPA arising from the posterior LV. **D,** The Ao and MPA have a parallel "back-to-front" arrangement. **E,** This parallel back-to-front arrangement contributes to the narrow mediastinum and "egg on a string" appearance seen on chest radiography. This patient has a large VSD with increased pulmonary blood flow. *(From Frost JL, Krishnamurthy R, Sena L. Cardiac imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017, Fig 3-20, p. 75.)*

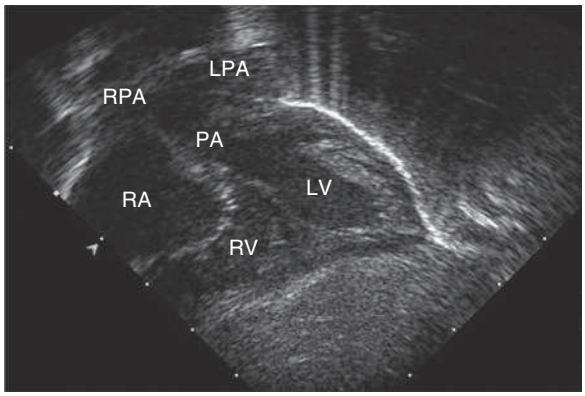

Fig. 480.2 Subcostal four-chamber 2D echocardiographic demonstration of d-transposition of the great arteries. The pulmonary artery (PA) can be seen arising directly from the left ventricle (LV). The immediate bifurcation of this great vessel into the branch pulmonary arteries differentiates it from the aorta, which branches more distally from the heart. LPA, Left pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

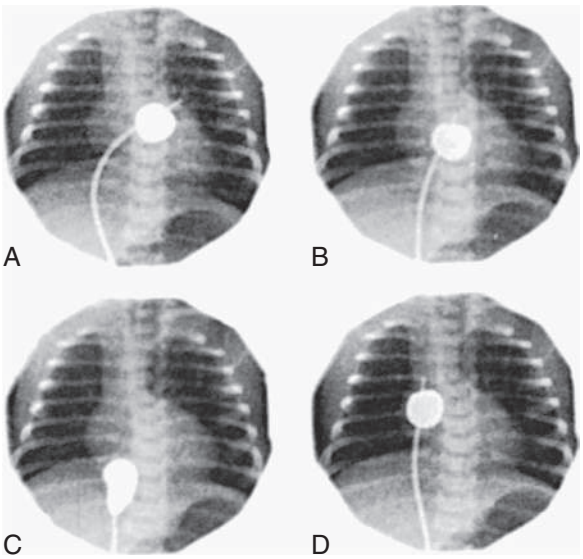

Fig. 480.3 Rashkind balloon atrial septostomy. Four frames from a continuous cineangiogram show the creation of an atrial septal defect in a hypoxemic newborn infant with transposition of the great arteries and an intact ventricular septum. **A**, Balloon inflated in the left atrium. **B**, The catheter is jerked suddenly so that the balloon ruptures the foramen ovale. **C**, Balloon in the inferior vena cava. **D**, Catheter advanced to the right atrium to deflate the balloon. The time from **A** to **C** is <1 sec.

this purpose. Cardiac catheterization may be performed in patients for whom noninvasive imaging is diagnostically inconclusive, where an unusual coronary artery anomaly is suspected, or in patients who require emergency **balloon atrial septostomy (i.e., the Rashkind procedure)**. Catheterization will show right ventricular pressure to be at a systemic level because this ventricle is supporting the systemic circulation. The blood in the left ventricle (LV) and pulmonary artery has a higher oxygen saturation than that in the aorta. Depending on the age at catheterization, LV and pulmonary artery pressure can vary from a systemic level to <50% of systemic-level pressure. Right ventriculography demonstrates the anterior and rightward aorta originating from the right ventricle (RV), as well as the intact ventricular septum. Left ventriculography shows that the pulmonary artery arises exclusively from the LV.

Anomalous coronary arteries are noted in 10–15% of patients and can be defined by an aortic root injection or by selective coronary arteriography.

TREATMENT

When transposition is suspected, an infusion of prostaglandin E_1 (PGE_1, 0.05-0.1 μg/kg/min) should be initiated immediately to maintain patency of the ductus arteriosus and improve oxygenation. Because of the risk of apnea associated with prostaglandin infusion, an individual skilled in neonatal endotracheal intubation should be available. Hypothermia intensifies the metabolic acidosis resulting from hypoxemia, and thus the patient should be kept warm. Prompt correction of acidosis and hypoglycemia is essential.

Infants who remain severely hypoxic or acidotic despite prostaglandin infusion should undergo **Rashkind balloon atrial septostomy** (Fig. 480.3). A Rashkind atrial septostomy is also usually performed in patients in whom any significant delay in surgery is expected. If surgery is planned during the first 2 weeks of life and the patient is stable, catheterization and atrial septostomy may often be avoided.

A successful Rashkind atrial septostomy should result in a rise in Pao_2 to 35-50 mm Hg and elimination of any pressure gradient across the atrial septum. Some patients with TGA and VSD (see Chapter 480.3) may require balloon atrial septostomy because of poor mixing, even though the VSD is large. Others may benefit from decompression of the left atrium to alleviate the symptoms of increased pulmonary blood flow and left-sided heart failure.

The **arterial switch (Jatene) procedure** is the surgical treatment of choice for neonates with d-TGA and an intact ventricular septum and is usually performed within the first 2 weeks of life. The reason for this time frame is that as PVR declines after birth, pressure in the LV (connected to the pulmonary vascular bed) also declines. This pressure drop results in a decrease in LV mass over the first few weeks of life. If the arterial switch operation is attempted after LV pressure (and mass) has declined too far, the LV will be unable to generate adequate pressure to pump blood to the high-pressure systemic circulation. The arterial switch operation involves dividing the aorta and pulmonary artery just above the sinuses and reanastomosing them in their correct anatomic positions. The coronary arteries are removed from the old aortic root along with a button of aortic wall and reimplanted in the old pulmonary root (now called the **neoaorta**). By using a button of great vessel tissue, the surgeon avoids having to suture directly onto the coronary artery (Fig. 480.4); this is the major innovation that has allowed the arterial switch to replace previous atrial switch operations for d-TGA. Rarely, a two-stage arterial switch procedure, with initial placement of a pulmonary artery band, may be used in patients presenting late who already have had a reduction in LV muscle mass and pressure. The arterial switch procedure has a survival rate of >95% for uncomplicated d-TGA. It restores the normal physiologic relationships of systemic and pulmonary arterial blood flow and eliminates the long-term complications of the previously used atrial switch procedure.

Previous operations for d-TGA consisted of some form of **atrial switch procedure** (**Mustard** or **Senning** operation). These procedures produced excellent early survival (85–90%) but had significant long-term morbidities. Atrial switch procedures reverse blood flow at the atrial level by creating an interatrial baffle that directs systemic venous blood returning from the venae cavae to the left atrium, where it will enter the LV, the pulmonary artery, and the lungs. The same baffle also permits oxygenated pulmonary venous blood to cross over to the right atrium, RV, and aorta. Atrial switch procedures involve significant atrial surgery and have been associated with the late development of atrial conduction disturbances, sick sinus syndrome with bradyarrhythmia and tachyarrhythmia, atrial flutter, sudden death, superior or inferior vena cava syndrome, edema, ascites, and protein-losing enteropathy. The atrial switch procedure also leaves the RV as the systemic pumping chamber, and this "systemic" RV often begins to fail in young adulthood. Atrial switch operations are currently reserved for patients whose anatomy is such that they are not candidates for the arterial switch procedure.

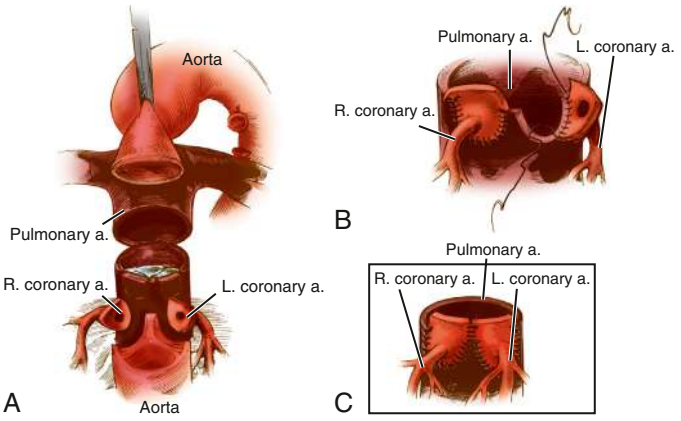

Fig. 480.4 Method for translocating the coronary arteries in the arterial switch (Jatene) procedure. **A,** The aorta (anterior) and the pulmonary artery (posterior) have been transected to allow visualization of the left and right coronary arteries. The coronaries have been excised from their respective sinuses, including a large flap (button) of arterial wall. Equivalent segments of the wall of the pulmonary artery (which will become the neoaorta) are also removed. **B,** The aortocoronary buttons are sutured into the proximal portion of the neoaorta. With this technique all sutures are placed in the button of aortic wall rather than directly on the coronary arteries. **C,** Completed anastomosis of the left and right coronary arteries to the neoaorta. *(Adapted from Castañeda AR, Jonas RA, Mayer JE Jr, et al. Cardiac Surgery of the Neonate and Infant. Philadelphia: Saunders; 1994.)*

480.3 Transposition of the Great Arteries with Ventricular Septal Defect

Daniel Bernstein

If the VSD associated with d-TGA is small, the clinical manifestations, laboratory findings, and treatment are similar to those described previously for transposition with an intact ventricular septum. A harsh systolic murmur is audible at the lower left sternal border, resulting from flow through the defect. Many of these small defects eventually close spontaneously and may not need to be addressed at the time of surgery.

When the VSD is large and not restrictive to ventricular ejection, significant mixing of oxygenated and deoxygenated blood usually occurs and clinical manifestations of cardiac failure are seen. The degree of cyanosis may be subtle and sometimes may not be recognized until an oxygen saturation measurement is performed. The murmur is holosystolic and generally indistinguishable from that produced by a large VSD in patients with normally related great arteries. The heart is usually significantly enlarged.

Cardiomegaly, a narrow mediastinal waist, and increased pulmonary vascularity are demonstrated on the chest radiograph. The ECG findings can be variable. It can show prominent P waves and isolated RV hypertrophy or biventricular hypertrophy. Occasionally, dominance of the LV is present. Usually, the QRS axis is to the right, but it can be normal or even to the left. The diagnosis is confirmed by echocardiography, and the extent of pulmonary blood flow can also be estimated by the degree of enlargement of the left atrium and ventricle. In equivocal cases, the diagnosis can be confirmed by cardiac catheterization. Right and left ventriculography indicate the presence of arterial transposition and demonstrate the site and size of the VSD. Systolic pressure is equal in the two ventricles, the aorta, and the pulmonary artery. Left atrial pressure may be much higher than right atrial pressure, a finding indicative of a restrictive communication at the atrial level. At the time of cardiac catheterization, Rashkind balloon atrial septostomy may be performed to decompress the left atrium, even when adequate mixing is occurring at the ventricular level.

Surgical treatment is advised soon after diagnosis because heart failure and failure to thrive are difficult to manage and pulmonary vascular disease can develop unusually rapidly in these patients. Preoperative management with diuretics and other anticongestive therapies (including elective intubation and positive pressure ventilation) stabilize the patient before surgery.

Patients with d-TGA and a VSD without pulmonic stenosis can be treated with an arterial switch procedure combined with VSD closure. In these patients, the arterial switch operation can be safely performed after the first 2 weeks of life because the VSD results in equal pressure in both ventricles and prevents regression of LV muscle mass. At major centers, however, there is no reason to delay repair, as results are excellent when the surgery is performed in the neonatal period.

480.4 l-Transposition of the Great Arteries (Corrected Transposition)

Daniel Bernstein

In l-transposition of the great arteries (l-TGA), both the atrioventricular and the ventriculoarterial relationships are discordant: the right atrium is connected to an LV and the left atrium to an RV, which is also known as **ventricular inversion**. The great arteries are also transposed, with the aorta arising from the RV and the pulmonary artery from the LV. In contrast to d-TGA, the aorta arises to the left of the pulmonary artery (thus the designation *l* for levo-transposition). The aorta may be anterior to the pulmonary artery, although often they are nearly side by side.

The physiology of l-TGA is quite different from that of d-TGA. Desaturated systemic venous blood returns via the vena cavae to a normal right atrium, from which it passes through a bicuspid atrioventricular (mitral) valve into a right-sided ventricle that has the architecture and smooth wall morphologic features of the normal LV (Fig. 480.5). Because transposition is also present, however, the desaturated blood ejected from this LV enters the transposed pulmonary artery and flows into the lungs, as it would in the normal circulation. Oxygenated pulmonary venous blood returns to a normal left atrium, passes through a tricuspid atrioventricular valve into a left-sided ventricle, which has the trabeculated morphologic features of a normal RV, and is then ejected into the transposed aorta. The double inversion of the atrioventricular and ventriculoarterial relationships result in desaturated right atrial blood appropriately flowing to the lungs and oxygenated pulmonary venous blood appropriately flowing to the aorta. The circulation is thus physiologically "corrected." Without other defects, the hemodynamics would be almost normal. In most patients, however, associated anomalies coexist: VSD, Ebstein-like abnormalities of the left-sided atrioventricular (tricuspid) valve, pulmonary valvular or subvalvular stenosis (or both), and atrioventricular conduction disturbances (complete heart block, accessory pathways such as Wolff-Parkinson-White syndrome).

CLINICAL MANIFESTATIONS

Symptoms and signs are widely variable and are usually determined by the associated lesions. If there is a VSD and pulmonary outflow is unobstructed, the clinical signs are similar to those of an isolated VSD. If l-TGA is associated with pulmonary stenosis and a VSD, the clinical signs are more similar to those of tetralogy of Fallot.

DIAGNOSIS

The chest radiograph may suggest the abnormal position of the great arteries; the ascending aorta occupies the upper left border of the cardiac silhouette and has a straight profile. The ECG, in addition to any atrioventricular conduction disturbances, may show abnormal P waves; absent Q waves in V_6; abnormal Q waves in leads III, aVR, aVF, and V_1; and upright T waves across the precordium. The echocardiogram is diagnostic. The characteristic echocardiographic features of the RV (moderator band, coarser trabeculations, tricuspid valve that sits more inferiorly compared with the bicuspid mitral valve, and a smooth muscular conus or infundibulum separating the atrioventricular valve

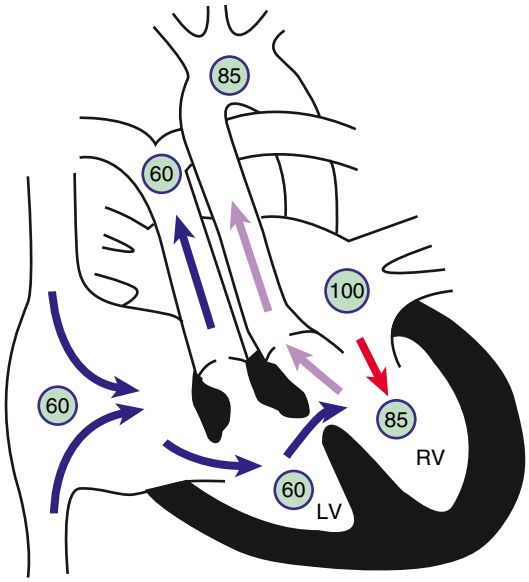

Fig. 480.5 Physiology of l-transposition or corrected transposition of the great arteries (l-TGA) with a ventricular septal defect and pulmonic stenosis (VSD + PS). *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Blood from the right atrium flows through the mitral valve into the "inverted" left ventricle (LV). The left ventricle is, however, attached to the transposed pulmonary artery. Therefore despite the anomalies, desaturated blood still winds up in the pulmonary circulation. Saturated blood returns to the left atrium, traverses the tricuspid valve into the "inverted" right ventricle (RV), and is pumped into the transposed aorta. This circulation would be totally "corrected" were it not for the frequent association of other congenital anomalies, in this case, VSD + PS. Because of the stenotic pulmonary valve, some left ventricular blood flow crosses the VSD and into the right ventricle and the ascending aorta, and systemic desaturation results.

from the semilunar valve) allow the echocardiographer to determine the presence of **atrioventricular discordance** (right atrium connected to LV; left atrium to RV) and ventriculoarterial discordance (RV connected to aorta; LV to pulmonary artery).

Surgical treatment of the associated anomalies, most often the VSD, is complicated by the position of the bundle of His, which can be injured at surgery and result in heart block. Identification of the usual course of the bundle in corrected transposition (running superior to the defect) has been accomplished by mapping the conduction system so that the surgeon can avoid the bundle of His during repair. Even without surgical injury, patients with l-TGA are at risk for developing heart block as they grow older.

Because simple surgical correction leaves the RV as the systemic pumping chamber, and thus vulnerable to late ventricular failure, surgeons have become more aggressive about trying operations that use the LV as the systemic pumping chamber. This is accomplished by performing an atrial switch operation (see Chapter 480.3) to reroute the systemic and pulmonary venous returns in combination with an arterial switch operation to reroute the ventricular outflows **(double switch procedure)**. The long-term benefit of this approach in preserving systemic ventricular function is still under investigation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

480.5 Double-Outlet Right Ventricle Without Pulmonary Stenosis

Daniel Bernstein

In double-outlet RV without pulmonary stenosis, both the aorta and the pulmonary artery arise from the RV (see Chapter 479.5). The only outlet from the LV is through a VSD. In the absence of obstruction to pulmonary blood flow, clinical manifestations are similar to those of an uncomplicated VSD with a large left-to-right shunt, although mild systemic desaturation may result from mixing of oxygenated and deoxygenated blood in the RV. The ECG usually shows biventricular hypertrophy. Echocardiography is diagnostic and shows the right ventricular origin of both great arteries, their anteroposterior relationship, and the relationship of the VSD to each of the great arteries. Surgical correction is dependent on these relationships. If the VSD is subaortic, it is accomplished by creation of an intracardiac tunnel. Blood is then ejected from the LV via the VSD into the aorta. If the VSD is subpulmonic, an arterial switch may be performed in combination with an intracardiac tunnel. If pulmonary blood flow is excessive enough to cause congestive heart failure, pulmonary arterial banding may be required in infancy, followed by surgical correction when the child is bigger. When associated pulmonary stenosis is present, cyanosis is more marked, pulmonary blood flow is decreased, and clinical presentation may be similar to that of tetralogy of Fallot.

480.6 Double-Outlet Right Ventricle with Malposition of the Great Arteries (Taussig-Bing Anomaly)

Daniel Bernstein

In double-outlet RV with malposed great arteries, the VSD is usually directly subpulmonic and the aorta distant from the LV. Sometimes both the pulmonary and the aortic valve may be located close to the VSD (**doubly committed** VSD) and sometimes neither is (**doubly uncommitted** VSD). The term *malposition* is used instead of *transposition* because both great arteries arise from the RV. Aortic obstructive lesions are common, including valvular and subvalvular aortic stenosis, coarctation of the aorta, and interruption of the aortic arch. Because pulmonary blood flow is unobstructed, patients experience cardiac failure early in infancy and are at risk for the development of pulmonary vascular disease and cyanosis. If aortic obstructive lesions are a component, patients can present with poor systemic output and cardiovascular collapse, particularly after the ductus arteriosus begins to close. Cardiomegaly is usual, and a parasternal systolic ejection murmur is audible, sometimes preceded by an ejection click and loud closure of the pulmonary valve. The ECG shows right axis deviation and right, left, or biventricular hypertrophy. The chest radiograph shows cardiomegaly and prominence of the pulmonary vasculature. The anatomic features of the anomaly and associated abnormalities are usually demonstrated by echocardiography, augmented if necessary by either cardiac catheterization, MRI, or CT. Palliation may be achieved by corrective surgery or pulmonary arterial banding in early infancy and surgical correction at a later age, which may be accomplished by an arterial switch procedure (see Chapter 480.2) combined with an intracardiac baffle or some modification of the Rastelli procedure (see Chapter 479.5).

480.7 Total Anomalous Pulmonary Venous Return

Daniel Bernstein

Abnormal development of the pulmonary veins may result in either partial or complete anomalous drainage into the systemic venous circulation. Partial anomalous pulmonary venous return (PAPVR) is usually an acyanotic lesion (see Chapter 475.4). Total anomalous pulmonary venous return (TAPVR) is associated with total mixing of systemic venous and pulmonary venous blood flow within the heart and thus produces cyanosis.

In TAPVR, there is no direct pulmonary venous connection into the left atrium (Fig. 480.6). The pulmonary veins may drain **above** the diaphragm: into the right atrium directly, into the coronary sinus, or into the superior vena cava by a "vertical vein"; or they may drain **below** the

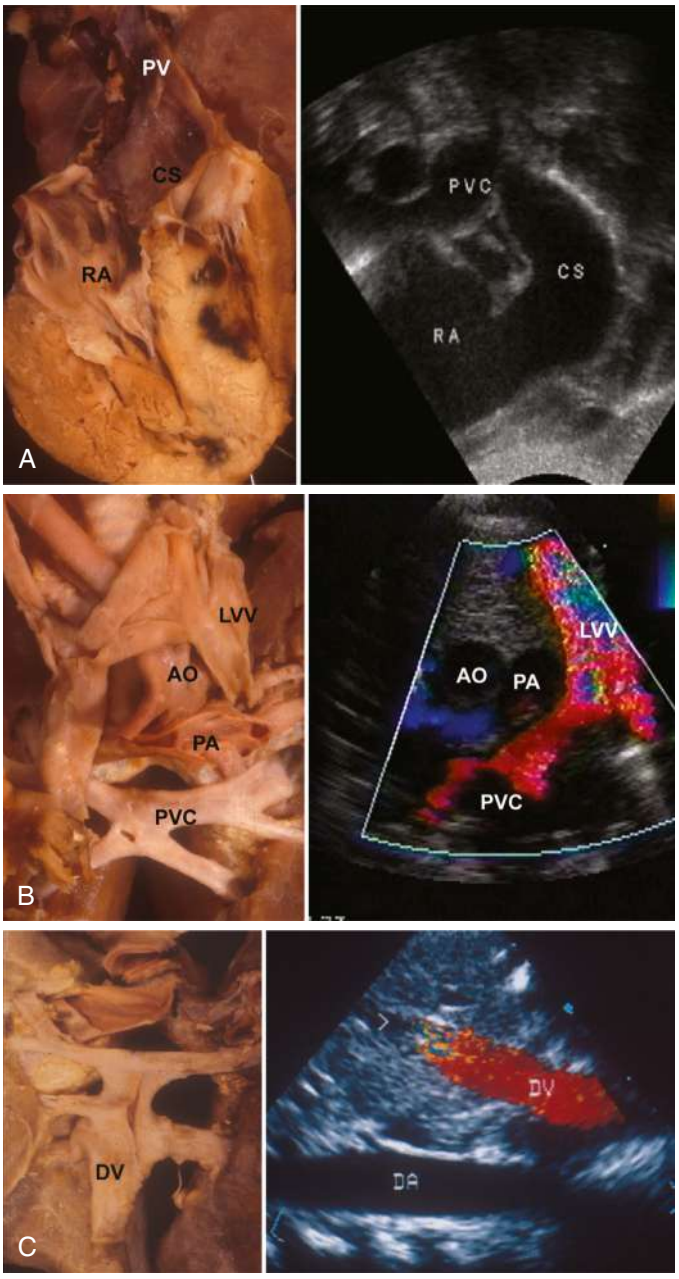

Fig. 480.6 A, Subcostal view demonstrating total anomalous pulmonary drainage to the coronary sinus. Note the dilated coronary sinus in both images. The echocardiogram also demonstrates an associated confluence that connects to the coronary sinus. B, Suprasternal view demonstrating total anomalous pulmonary venous drainage to a left vertical vein. Note the direction of flow in the vertical vein that differentiates it from a left superior vena cava. C, Total anomalous pulmonary venous drainage below the diaphragm. The specimen shows the pulmonary veins as they enter the confluence, whereas the echocardiogram demonstrates the descending veins as they enter the liver. Note that the direction of flow is away from the heart. AO, Aorta; CS, coronary sinus; DA, descending aorta; DV, descending vein; LVV, left vertical vein; PA, pulmonary artery; PV, pulmonary vein; PVC, pulmonary venous confluence; RA, right atrium. *(From Webb GD, Smallhorn, JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 75-32, p. 1553.)*

diaphragm and join into a "descending vein" that enters the inferior vena cava or one of its major tributaries, often through the ductus venosus. This latter form of anomalous venous drainage is most often associated with *obstruction* to venous flow, usually as the ductus venosus closes soon after birth, although **supracardiac** anomalous veins may also become obstructed. Occasionally, the drainage may be **mixed**, with some veins draining above and others below the diaphragm.

Table 480.1 Total Anomalous Pulmonary Venous Return

SITE OF CONNECTION (% OF CASES)	% WITH SIGNIFICANT OBSTRUCTION
Supracardiac (50)	
Left superior vena cava (40)	40
Right superior vena cava (10)	75
Cardiac (25)	
Coronary sinus (20)	10
Right atrium (5)	5
Infracardiac (20)	95–100
Mixed (5)	

All forms of TAPVR involve mixing of oxygenated and deoxygenated blood before or at the level of the right atrium **(total mixing lesion)**. This mixed right atrial blood either passes into the RV and pulmonary artery or passes through an atrial septal defect (ASD) or patent foramen ovale into the left atrium, which will be the only source of oxygenated systemic blood flow. The right atrium and ventricle and the pulmonary artery are generally enlarged, whereas the left atrium and ventricle may be normal or small. The clinical manifestations of TAPVR depend on the presence or absence of *obstruction* of the venous channels (Table 480.1). If pulmonary venous return is obstructed, severe pulmonary congestion and pulmonary hypertension develop; rapid deterioration occurs without surgical intervention. *Obstructed TAPVR is a pediatric cardiac surgical emergency because prostaglandin therapy is usually not effective.*

CLINICAL MANIFESTATIONS

Two major clinical patterns of TAPVR are seen, depending on the presence or absence of obstruction. Those neonates with severe obstruction to pulmonary venous return, most prevalent in the **infracardiac** group (see Table 480.1), present with severe cyanosis and respiratory distress. Murmurs may not be present. These infants are severely ill and fail to respond to mechanical ventilation. Rapid diagnosis and surgical correction are necessary for survival. In contrast, those with mild or no obstruction to pulmonary venous return are usually characterized by the development of heart failure as the PVR falls, with mild to moderate degrees of desaturation. Systolic murmurs may be audible along the left sternal border, and a gallop rhythm may be present. Some infants may have mild obstruction in the neonatal period and develop worsening obstruction as time passes.

DIAGNOSIS

The ECG demonstrates RV hypertrophy (usually a qR pattern in V_3R and V_1, and P waves are frequently tall and spiked). In neonates with marked pulmonary venous obstruction, the chest radiograph demonstrates a very dramatic perihilar pattern of pulmonary edema and a small heart (Fig. 480.7A). This appearance can sometimes be confused with primary pulmonary disease, and the differential diagnosis includes persistent pulmonary hypertension of the newborn, respiratory distress syndrome, pneumonia, pulmonary lymphangiectasia, and other heart defects (hypoplastic left heart syndrome). In older children, if the anomalous pulmonary veins enter the innominate vein and persistent left superior vena cava (see Fig. 480.7B), a large supracardiac shadow can be seen, which together with the normal cardiac shadow forms a *snowman* appearance. In most cases without obstruction, the heart is enlarged, the pulmonary artery and RV are prominent, and pulmonary vascularity is increased.

The echocardiogram demonstrates a large RV and usually identifies the pattern of abnormal pulmonary venous connections

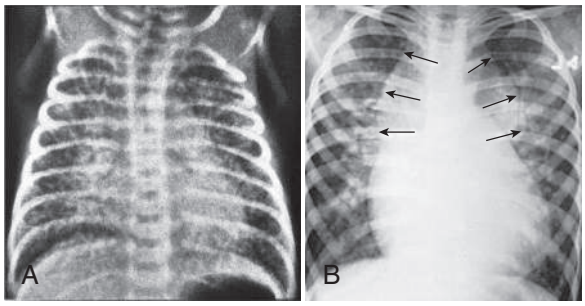

Fig. 480.7 Chest radiographs of total anomalous pulmonary venous return (TAPVR). **A,** A newborn with TAPVR to a descending vein (below the diaphragm) with obstruction, showing marked pulmonary venous congestion and normal heart size. **B,** TAPVR to the left superior vena cava (preoperative image). *Arrows* point to the supracardiac shadow, which produces the "snowman" or figure 8 configuration. Cardiomegaly and increased pulmonary vascularity are evident.

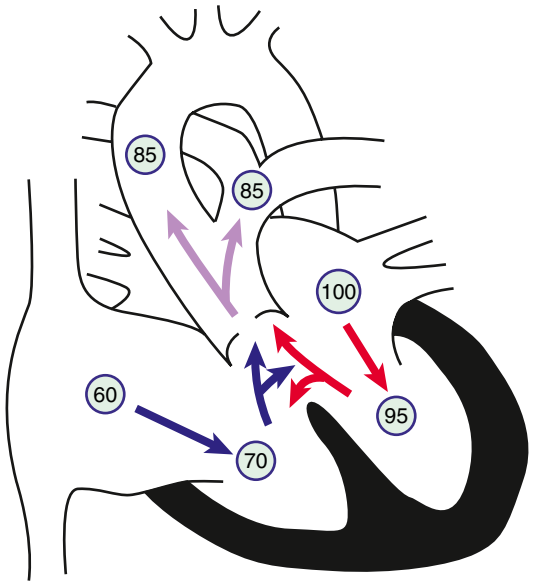

Fig. 480.8 Physiology of truncus arteriosus. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the truncus. Saturated blood returning from the left atrium enters the left ventricle and is also ejected into the truncus. The common aortopulmonary trunk gives rise to the ascending aorta and to the main or branch pulmonary arteries. Oxygen saturation in the aorta and pulmonary arteries is usually the same (definition of a total mixing lesion). As pulmonary vascular resistance decreases in the first few weeks of life, pulmonary blood flow increases dramatically, and mild cyanosis and congestive heart failure result.

(see Fig. 480.6). The demonstration of any vein with Doppler flow away from the heart is pathognomonic of TAPVR because normal venous flow is usually toward the heart. Shunting occurs from right to left at the atrial level. The size of the left atrium and LV can be measured and the presence of any associated cardiac defects determined.

Echocardiography should be adequate to demonstrate TAPVR in most cases; however, if there is question about the drainage of one or more pulmonary veins, cardiac catheterization, MRI, or CTA is performed. Catheterization shows that the oxygen saturation of blood in both atria, both ventricles, and the aorta is similar, indicative of a **total mixing lesion**. An increase in systemic venous saturation occurs at the site of entry of the abnormal pulmonary venous channel, either above or below the diaphragm. In older patients without pulmonary venous obstruction, pulmonary arterial and RV pressure may be only moderately elevated, but in infants with pulmonary venous obstruction, pulmonary hypertension is usual. Selective pulmonary arteriography shows the anatomy of the pulmonary veins and their point of entry into the systemic venous circulation.

Fetal diagnosis of TAPVR is feasible in many, but not all, cases, with the main ultrasonographic signs being ventricular disproportion, increased area behind the left atrium, and the finding of a vertical vein. Color Doppler is key to making this diagnosis. Prenatal diagnosis can be helpful in planning for urgent surgical treatment after birth.

TREATMENT

Surgical correction of TAPVR is performed during early infancy, with emergent repair performed for those patients with venous obstruction. If surgery cannot be performed urgently, extracorporeal membrane oxygenation (ECMO) may be required to maintain oxygenation. Surgically, the pulmonary venous confluence is anastomosed directly to the left atrium, the ASD is closed, and any connection to the systemic venous circuit is interrupted. Early results are generally good, even for critically ill neonates. The postoperative period may be complicated by pulmonary artery hypertensive crises. In some patients, especially those in whom the diagnosis is delayed or the obstruction is severe, recurrent stenosis and development of pulmonary venoocclusive disease may occur. Attempts have been made to treat recurrent stenosis with surgery, balloon angioplasty, stents, and antiproliferative chemotherapy. The long-term prognosis in patients with recurrent obstruction is poor. In those with aggressive venoocclusive disease, **heart-lung transplantation** may be the only option (see Chapter 492.2).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

480.8 Truncus Arteriosus

Daniel Bernstein

In truncus arteriosus, a single arterial trunk (truncus arteriosus) arises from the heart and supplies the systemic, pulmonary, and coronary circulations. A VSD is always present, with the truncus overriding the defect and receiving blood from both the RV and the LV (Fig. 480.8). The number of truncal valve cusps varies from two to as many as six, and the valve may be stenotic, regurgitant, or both. The pulmonary arteries can arise together from the posterior left side of the persistent truncus arteriosus and then divide into left and right pulmonary arteries **(type I)**. In types II and III truncus arteriosus, no main pulmonary artery is present, and the right and left pulmonary arteries arise from separate orifices on the posterior **(type II)** or lateral **(type III)** aspects of the truncus arteriosus. *Type IV truncus* is a term no longer used because, in this case, there is no identifiable connection between the heart and pulmonary arteries, and pulmonary blood flow is derived from **major aortopulmonary collateral arteries (MAPCAs)** arising from the transverse or descending aorta; this is essentially a form of pulmonary atresia (see Chapter 479.2).

Both ventricles are at systemic pressure, and both eject blood into the truncus. When PVR is relatively high immediately after birth, pulmonary blood flow may be normal; as PVR drops in the first few weeks of life, blood flow to the lungs is greatly increased and heart failure ensues. Truncus arteriosus is a **total mixing lesion** with complete admixture of pulmonary and systemic venous return. Because of the large volume of pulmonary blood flow, clinical cyanosis is usually mild. If the lesion is left untreated, PVR eventually increases, pulmonary blood flow decreases, and cyanosis becomes more prominent (**Eisenmenger physiology**; see Chapter 482.2).

CLINICAL MANIFESTATIONS

The clinical signs of truncus arteriosus vary with age and depend on the level of PVR. In the immediate newborn period, signs of heart failure are usually absent; a murmur and minimal cyanosis may be the only initial findings. If unrepaired, during the next 1-2 months of life,

pulmonary blood flow begins to become torrential and the clinical picture is dominated by heart failure, with still mild cyanosis. Runoff of blood from the truncus to the pulmonary circulation may result in a wide pulse pressure and bounding pulses. These findings will be further exaggerated if truncal valve insufficiency is present. The heart is usually enlarged, and the precordium is hyperdynamic. S_2 is loud and single. A systolic ejection murmur, sometimes accompanied by a thrill, is generally audible along the left sternal border. The murmur is frequently preceded by an early systolic ejection click caused by the abnormal truncal valve. In the presence of truncal valve insufficiency, a medium- to high-pitched early diastolic decrescendo murmur is heard at the mid-left sternal border. An apical mid-diastolic rumbling murmur caused by increased flow through the mitral valve is often audible with the bell of the stethoscope, especially as heart failure develops. Truncus arteriosus is a conotruncal malformation and may be associated with **DiGeorge syndrome**, linked to a deletion of a large region of **chromosome 22q11** (see Chapter 473).

DIAGNOSIS

The ECG shows right, left, or combined ventricular hypertrophy. The chest radiograph also shows considerable variation. Cardiac enlargement will develop over the first several weeks of life and is a result of the prominence of both ventricles. The truncus may produce a prominent shadow that follows the normal course of the ascending aorta and aortic knob; the aortic arch is right sided in 50% of patients. Sometimes a high bulge left of the aortic knob is produced by the main or left pulmonary artery. Pulmonary vascularity is increased after the first few weeks of life. Echocardiography is diagnostic and demonstrates the large truncal artery overriding the VSD and the pattern of origin of the branch pulmonary arteries (Fig. 480.9). Associated anomalies such as an interrupted aortic arch may be noted. Pulsed and color Doppler studies are used to evaluate truncal valve regurgitation. If required, cardiac catheterization shows a left-to-right shunt at the ventricular level, with right-to-left shunting into the truncus. Systolic pressure in both ventricles and the truncus is similar. Angiography reveals the large truncus arteriosus and better defines the origin of the pulmonary arteries.

TREATMENT

Most centers perform routine neonatal repair shortly after diagnosis. If surgery is delayed and PVR falls over the first several weeks of life, heart failure symptoms will worsen. Anticongestive medications can be used to better prepare these patients for surgery; however, delay of surgery much beyond this time period may increase the likelihood of developing pulmonary vascular disease. At surgery, the VSD is closed, the pulmonary arteries are separated from the truncus, and continuity is established between the RV and the pulmonary arteries with a homograft conduit. Immediate surgical results are excellent, but these conduits will develop either regurgitation or stenosis over time and must be replaced, often several times, as the child grows. If regurgitation is the primary problem, patients can now be treated with a transcatheter stent-valve (see Chapter 479.1)

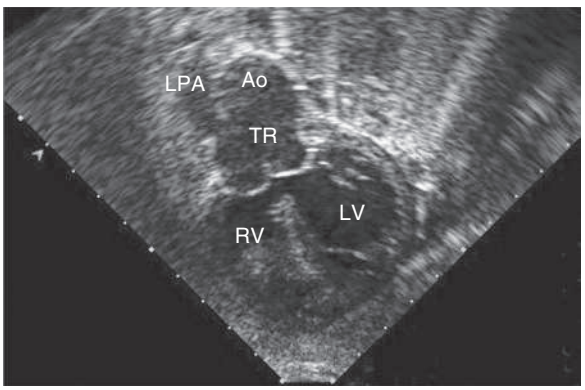

Fig. 480.9 Subcostal 2D echocardiographic demonstration of truncus arteriosus. The large truncal valve can be seen overriding the ventricular septal defect. In this case, only the left pulmonary artery (LPA) arises from the truncus (TR). The pulmonary arteries are discontinuous, and the right pulmonary artery arises from the descending aorta via the ductus arteriosus (not shown). Ao, Aorta; LV, left ventricle; RV, right ventricle.

PROGNOSIS AND COMPLICATIONS

Surgical results have been excellent, and many patients with repaired truncus are now entering mid-adulthood, with several centers reporting 30- and 40-year-old survivors. The need to replace the RV-to-pulmonary artery conduit as the child grows means that these patients will need to undergo multiple operations by the time they reach adulthood. The development of transcatheter stent-valves may reduce this in the future (see Chapter 472). When truncus arteriosus is associated with DiGeorge syndrome, the associated endocrine, immunologic, craniofacial, and airway abnormalities may complicate recovery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

480.9 Single Ventricle (Double-Inlet Ventricle, Univentricular Heart)

Daniel Bernstein

With a single ventricle, both atria empty through a common atrioventricular valve or through two separate valves into a single ventricular chamber, with total mixing of systemic and pulmonary venous return. This chamber may have left, right, or indeterminate (both right and left) ventricular morphologic characteristics. The aorta and pulmonary artery both arise from this single chamber, although one of the great vessels may originate from a rudimentary outflow chamber. The aorta may be posterior, anterior (malposition), or side-by-side with the pulmonary artery and either to the right or to the left. Pulmonary stenosis or atresia is common.

CLINICAL MANIFESTATIONS

The clinical picture is variable and depends on the associated intracardiac anomalies. If pulmonary outflow is obstructed, the findings are usually similar to those of tetralogy of Fallot: marked cyanosis without heart failure. If pulmonary outflow is unobstructed, the findings are similar to those of transposition with VSD: minimal cyanosis with increasing heart failure.

In patients with **pulmonary stenosis**, cyanosis is present in early infancy. Cardiomegaly is mild or moderate, a left parasternal lift is palpable, and a systolic thrill is common. The systolic ejection murmur is usually loud; an ejection click may be audible, and S_2 is single and loud. In patients with **unobstructed pulmonary flow**, as PVR drops, torrential pulmonary blood flow develops, and these patients present with tachypnea, dyspnea, failure to thrive, and recurrent pulmonary infections. Cyanosis is only mild or moderate. Cardiomegaly is generally marked, and a left parasternal lift is palpable. A systolic ejection murmur is present but is not usually loud or harsh, and S_2 is loud and closely split. A third heart sound (S_3) is common and may be followed by a short mid-diastolic rumbling murmur caused by increased flow through the atrioventricular valves. The eventual development of pulmonary vascular disease reduces pulmonary blood flow so that the cyanosis increases and signs of cardiac failure appear to improve (**Eisenmenger physiology**; see Chapter 482.2).

DIAGNOSIS

ECG findings are nonspecific. P waves are normal, spiked, or bifid. The precordial lead pattern suggests right ventricular hypertrophy, combined ventricular hypertrophy, or sometimes left ventricular dominance. The initial QRS forces are usually to the left and anterior. Radiographic examination confirms the degree of cardiomegaly. If present, a rudimentary outflow chamber may produce a bulge on the upper left border of the cardiac silhouette in the posteroanterior projection. In the absence of pulmonary stenosis, pulmonary vasculature is

increased, whereas in the presence of pulmonary stenosis, pulmonary vasculature is diminished. Echocardiography will confirm the absence or near-absence of the ventricular septum and can usually determine whether the single ventricle has right, left, or mixed morphologic features. The presence of a rudimentary outflow chamber under one of the great vessels can be identified, and pulsed Doppler can be used to determine whether flow through this communication (known as a **bulboventricular foramen**) is obstructed.

If cardiac catheterization is performed, the pressure in the single ventricular chamber is at systemic level; however, a gradient may be demonstrated across the entrance to the rudimentary outflow chamber. Pressure measurements and angiography demonstrate whether pulmonary stenosis is present.

TREATMENT

If pulmonary stenosis is severe, a **Blalock-Taussig aortopulmonary shunt** is performed to provide a reliable source of pulmonary blood flow (see Chapter 479.1). If pulmonary blood flow is unrestricted, pulmonary arterial banding is used to control heart failure and prevent progressive pulmonary vascular disease. The **bidirectional Glenn shunt** is usually performed at 2-4 months of age, followed by a **modified Fontan operation** (cavopulmonary isolation procedure; see Chapter 479.4) at 2-3 years. If subaortic stenosis is present because of a restrictive connection to a rudimentary outflow chamber (*restrictive* bulboventricular foramen), surgical relief can be provided by anastomosing the proximal pulmonary artery to the side of the ascending aorta **(Damus-Stansel-Kaye operation)**.

PROGNOSIS AND COMPLICATIONS

Unoperated, some patients succumb during infancy from heart failure. Others may survive to adolescence and early adult life but finally succumb to the effects of chronic hypoxemia or, in the absence of pulmonary stenosis, to the effects of pulmonary vascular disease. Patients with moderate pulmonary stenosis have the best prognosis because pulmonary blood flow, though restricted, is still adequate. Surgical palliation, eventually leading to Fontan-type circulatory physiology (see Chapter 479.4), has very good short- and intermediate-term results.

480.10 Hypoplastic Left Heart Syndrome

Daniel Bernstein

The term *hypoplastic left heart syndrome* (HLHS) is used to describe a related group of anomalies that include various degrees of underdevelopment of the left side of the heart: stenosis or atresia of the aortic and mitral valves and hypoplasia of the left ventricular cavity and ascending aorta. HLHS categories are based on anatomic characteristics: (1) mitral and aortic atresia (MA-AA), (2) mitral stenosis with aortic atresia (MS-AA), and (3) mitral and aortic stenosis (MS-AS). The LV may be only moderately hypoplastic, very small and nonfunctional, or totally atretic. The LV cavity may be slitlike, miniaturized, or small and thick walled with endocardial fibroelastosis. In patients with MS-AA, there may be anomalous connections between the ventricle and the coronary arteries, which some reports associate with an increased postoperative risk.

The etiology of HLHS may be the result of poor left-sided fetal blood flow (no flow–no grow hypothesis). Alternatively, there may be intrinsic defects of myogenic and endocardial programming affecting differentiation, proliferation, maturation, and apoptosis. Although no single gene is associated with all patients, multiple genes *(GJA1, NKX2-5, SAP130, PCDHA, Notch 1, MY46)* and pathways (transforming growth factor beta [TGF-β], Wnt) have been implicated.

In the immediate neonatal period, the RV maintains both the pulmonary circulation and the systemic circulation via the ductus arteriosus (Fig. 480.10). Pulmonary venous blood passes through an ASD (which may or may not be restrictive) or dilated foramen ovale from the left to the right side of the heart, where it mixes with systemic venous blood (total mixing lesion). Minimal (mitral stenosis subtypes)

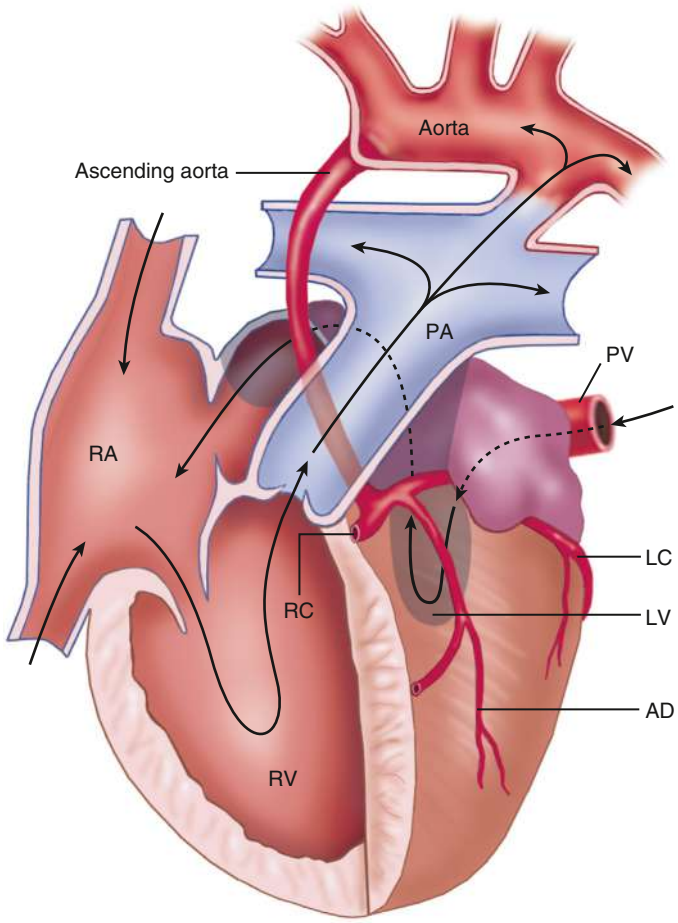

Fig. 458.10 Hypoplastic left heart with aortic hypoplasia, aortic valve atresia, and a hypoplastic mitral valve and left ventricle. AD, Anterior descending; LC, left circumflex; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RC, right coronary artery; RV, right ventricle. *(From Webb GD, Smallhorn, JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 75-28, p. 1548. Adapted from historical illustrations in Neufeld HN, Adams P Jr, Edwards JE, et al. Diagnosis of aortic atresia by retrograde aortography. Circulation. 1962;25:278; and Edwards JE, Dry TJ, Parker RL, et al. An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield: Charles C. Thomas; 1954.)*

or no (mitral atresia subtype) blood enters the hypoplastic LV. All the RV blood is ejected into the main pulmonary artery, where it then supplies both the descending and the ascending aorta (retrograde flow) via the ductus arteriosus. The major hemodynamic abnormalities are inadequate maintenance of the systemic circulation and, depending on the size of the atrial-level communication, either pulmonary venous hypertension (restrictive foramen ovale) or pulmonary overcirculation (moderate or large ASD).

CLINICAL MANIFESTATIONS

Although cyanosis may not always be obvious in the first 48 hours of life, a grayish-blue skin color is soon apparent and denotes a mix of cyanosis and poor perfusion. The condition is diagnosed in most infants in the first few hours or days of life. Once the ductus arteriosus begins to close, signs of poor systemic perfusion and shock predominate. All the peripheral pulses may be weak or absent. A palpable RV parasternal lift may be present along with a nondescript systolic murmur.

This lesion may be isolated or associated in 5–15% of patients with known genetic syndromes, such as Turner syndrome; trisomy 13, 18, or 21; Jacobsen syndrome (11q deletion); Holt-Oram syndrome; and Rubinstein-Taybi syndrome. In these circumstances, noncardiac

manifestations of the syndrome may be evident and influence the clinical outcomes. Occasionally, HLHS is familial and inherited as an autosomal recessive or dominant trait; there are also families with constellations of different severities of left-sided obstructive lesions, ranging from bicuspid aortic valve, to coarctation of the aorta, to Shone complex, to HLHS.

DIAGNOSIS

On chest radiograph, the heart is variable in size in the first days of life, but cardiomegaly develops rapidly and is associated with increased pulmonary vascularity. The initial ECG may show only the normal neonatal pattern of RV dominance, but later, P waves become prominent and RV hypertrophy is usual with reduced LV forces. The echocardiogram is diagnostic and demonstrates hypoplasia or atresia of the mitral valve and aortic root, a variably small left atrium and LV, and a large right atrium and RV (Fig. 480.11). The size of the atrial communication, by which pulmonary venous blood leaves the left atrium, is assessed by pulsed and color flow Doppler studies. The small ascending aorta and transverse aortic arch are identified; a discrete coarctation of the aorta in the juxtaductal area may be present, although in the presence of a large ductus, it may be difficult to identify. Doppler echocardiography demonstrates whether the mitral and aortic valves are severely stenotic or totally atretic. The presence of left ventricular–to–coronary sinusoidal connections can be identified. The diagnosis of HLHS can usually be made without the need for cardiac catheterization. If catheterization is necessary, the hypoplastic ascending aorta is demonstrated by angiography.

TREATMENT

Surgical therapy for HLHS is associated with improved survival rates, reported as high as 90–95% for the first-stage palliation in experienced centers. The first-stage repair is designed to construct a reliable source of systemic blood flow arising from the single RV using a combination of aortic and pulmonary arterial tissue and to limit pulmonary blood flow to avoid heart failure and prevent the development of pulmonary vascular disease. The surgical procedure typically used is the **Norwood procedure** (Fig. 480.12) or the **Sano procedure**. Primary heart transplantation, previously advocated by a few centers, is much less common because of the substantially improved survival rates with standard surgery and the limited supply of donor organs in this age-group.

Preoperative medical management includes maintaining ductus arteriosus patency with PGE_1 (0.05-0.1 μg/kg/min) to support systemic blood flow, avoiding excess pulmonary blood flow, and maintaining adequate flow from the left to the right atrium. Correction of acidosis and hypoglycemia and prevention of hypothermia are also key components. Excessive pulmonary blood flow, which worsens as the PVR begins to fall, can lead to both respiratory distress and systemic hypoperfusion. This can be prevented through managing ventilator settings to keep the P_{CO_2} in the 45-50 mm Hg range and avoiding supplemental oxygen (which acts as a pulmonary vasodilator) if the system arterial O_2 saturation is in the 70-80 mm Hg range. If the atrial septum is restrictive, a Rashkind balloon atrial septostomy, septal balloon dilation, or rarely, a blade septostomy of the atrial septum may be indicated.

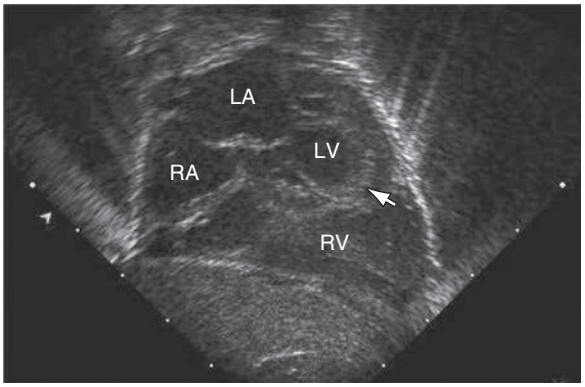

Fig. 480.11 Subcostal 2D echocardiographic diagnosis of hypoplastic left heart syndrome. The small left ventricular chamber can be seen, the apex of which *(arrowhead)* does not form the apex of the heart. The atrial septum can be seen bowing from the left to the right, indicating that the communication between the two atria is pressure restrictive. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

The Norwood or Sano procedure is usually performed in three stages. **Stage I** (see Fig. 480.12), usually performed in the first week of life, includes an atrial septectomy and transection and ligation of the distal main pulmonary artery; the proximal pulmonary artery is then connected to the transversely opened hypoplastic aortic arch to form a "neoaorta," extending through the coarcted segment of the juxtaductal aortic arch. In the Norwood operation, a synthetic aortopulmonary (Blalock-Taussig) shunt connects the aorta to the main pulmonary artery to provide controlled pulmonary blood flow. In the Sano modification, an RV–to–pulmonary artery conduit is used instead of an aortopulmonary shunt to provide pulmonary blood flow, temporarily creating a double-outlet RV. The operative risk for these first-stage procedures has improved dramatically in the past 2 decades, and the best reported results demonstrate a 90–95% survival rate. After the first stage, the patient's oxygen saturation usually ranges from 75% to 85% because of the continued admixture of oxygenated and deoxygenated blood in the right atrium. In the past, there was a high interstage mortality rate in infants discharged from the hospital between stages I and II. This has largely been prevented by performing careful interstage surveillance in home monitoring programs run by pediatric cardiac centers.

Stage II consists of a Glenn shunt anastomosis to connect the superior vena cava to the pulmonary arteries (see Chapter 480.4) at 2-6 months of age. **Stage III**, usually performed at 2-3 years, consists of a modified Fontan procedure (cavopulmonary isolation) to connect the inferior vena cava to the pulmonary arteries via either an intraatrial or external baffle. After stage III, all systemic venous return enters the pulmonary circulation directly. Pulmonary venous flow enters the left atrium and is directed across the atrial septum to the tricuspid valve and subsequently to the right (now the systemic) ventricle. Blood leaves the RV via the neoaorta, which supplies the systemic circulation. The old aortic root now attached to the neoaorta provides coronary blood flow. The risks associated with stages II and III are less than those of stage I; interstage mortality (usually between stages I and II) has been dramatically reduced with the use of home monitoring programs and interstage close follow-up. The short- and long-term benefits of using the Norwood vs the Sano procedure remain to be demonstrated.

An alternative therapeutic approach, initially developed for high-risk standard surgical candidates, is to perform a **hybrid procedure** for the first stage. This involves performing a Rashkind balloon atrial septostomy, cardiac catheter laboratory placement of a stent in the ductus arteriosus, and open chest surgical placement of bilateral pulmonary artery bands. After the hybrid procedure, patients can be weaned off prostaglandin and discharged from the hospital. However, after a hybrid procedure, patients need to undergo a more extensive second-stage procedure involving construction of a neoaorta and removal of the pulmonary artery bands.

Another alternative therapy is **cardiac transplantation**, either in the immediate neonatal period, thereby obviating stage I of the Norwood procedure, or after a successful stage I Norwood procedure is performed as a bridge to transplantation. After transplantation, patients usually have normal cardiac function and no symptoms of heart failure; however, these patients have the chronic risk of organ rejection and lifelong immunosuppressive therapy (see Chapter 492.1). The combination of donor shortage and improved results with standard surgical and hybrid procedures has caused most centers to stop recommending transplantation except when associated lesions make the Norwood operation an exceptionally high-risk procedure (e.g., significant coronary artery anomalies) or for patients who develop poor ventricular function at some time after the standard surgical approach.

PROGNOSIS AND COMPLICATIONS

Untreated patients most often succumb during the first few months of life, usually during the first or second week. Up to 30% of infants with HLHS

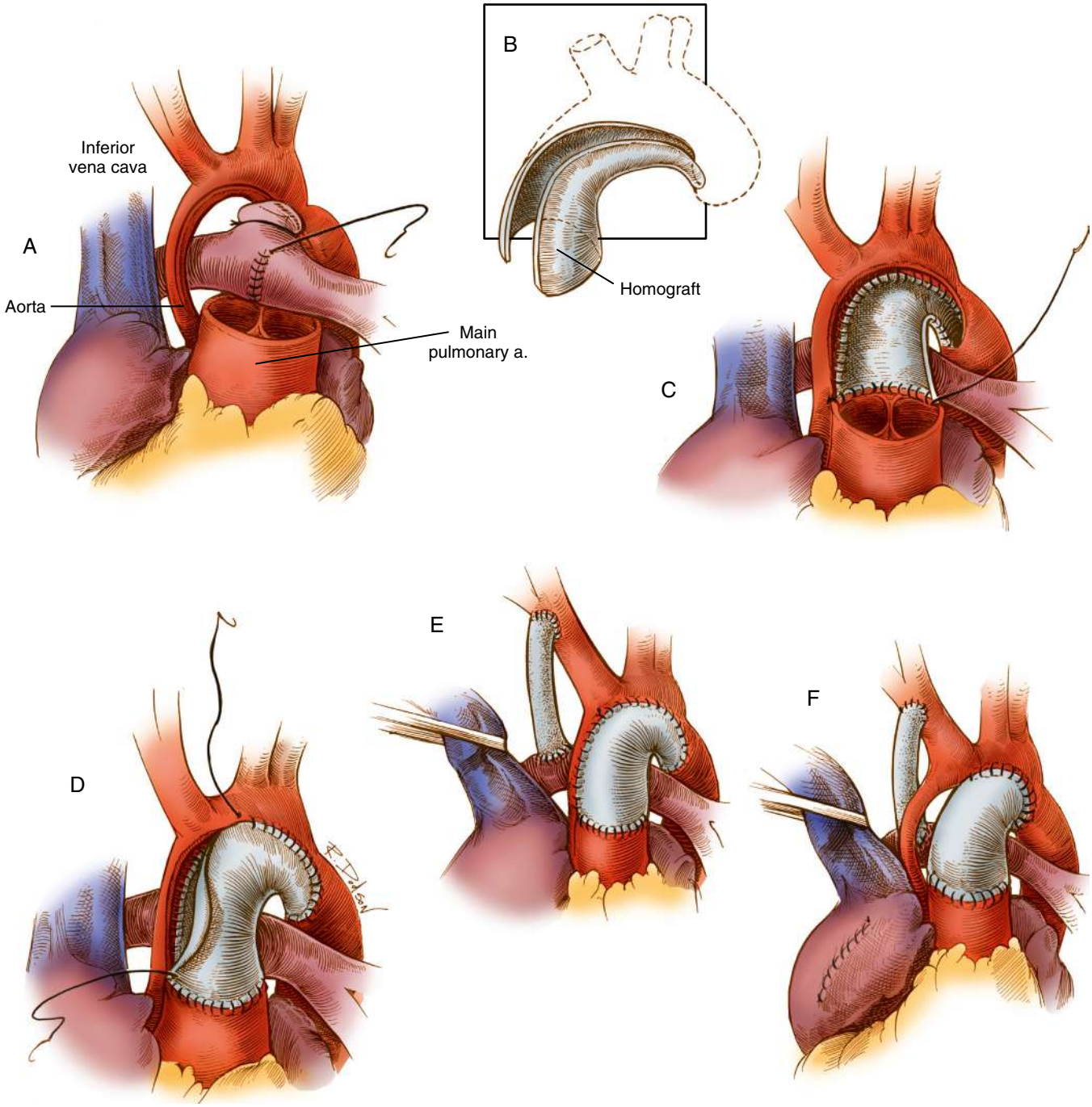

Fig. 480.12 Norwood procedure, one of the two current techniques for first-stage palliation of hypoplastic left heart syndrome. **A,** Incisions used for the procedure incorporate a cuff of arterial wall allograft. The distal divided main pulmonary artery may be closed by direct suture or with a patch. **B,** Dimensions of the cuff of the arterial wall allograft. **C,** The arterial wall allograft is used to supplement the anastomosis between the proximal divided main pulmonary artery and the ascending aorta, aortic arch, and proximal descending aorta. **D** and **E,** The procedure is completed by an atrial septectomy and a 3.5-mm modified right Blalock shunt. **F,** When the ascending aorta is particularly small, an alternative procedure involves placement of a complete tube of arterial allograft. The tiny ascending aorta may be left in situ, as indicated, or implanted into the side of the neoaorta. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al. Single-ventricle tricuspid atresia. In: Cardiac Surgery of the Neonate and Infant. Philadelphia: Saunders; 1994.)*

have evidence of either a major or a minor central nervous system abnormality. Other dysmorphic features may be found in up to 40% of patients. Thus careful preoperative evaluation (genetic, neurologic, ophthalmologic) should be performed in patients being considered for surgical therapy.

Intermediate-term follow-up after completion of all three stages of the Norwood procedure demonstrates generally good exercise capacity and long-term complications equivalent to other patients who have had the Fontan palliation (see Chapter 479.4). Some studies show that patients with HLHS have a higher risk of neurodevelopmental problems than those with other complex congenital heart lesions. Whether the poor neurodevelopmental outcome is the result of genetically associated central nervous system malformations, alteration of prenatal circulation dynamics or prenatal central nervous system injury, complications of bypass surgery, or poor preoperative and/or postoperative perfusion is unknown. Whether a specific HLHS subtype, specifically MS-AA with ventricular-coronary connections, is associated with increased postoperative mortality is still unclear, as studies have shown contradictory results.

PREVENTION

Serial fetal echocardiographic studies demonstrate that in some fetuses, HLHS may be a progressive in utero lesion, beginning with simple valvar aortic stenosis in mid-gestation. The decreased flow through the stenotic aortic valve reduces flow through the LV during development, resulting in gradual ventricular chamber hypoplasia. The potential for preventing this hypoplasia has been demonstrated by performing in utero aortic balloon valvuloplasty in mid-gestation fetuses (Fig. 480.13). Early results are encouraging, although even if the aortic valve is successfully opened, adequate ventricular growth occurs in only ~50% of patients. At present, this procedure is regarded as experimental.

Because of the high mortality of HLHS with an intact or restrictive atrial septum, in utero attempts to improve atrial mixing with either fetal atrial septoplasty or atrial stent placement are undergoing clinical investigation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

480.11 Abnormal Positions of the Heart and the Heterotaxy Syndromes (Asplenia, Polysplenia)

Daniel Bernstein

Classification and diagnosis of abnormal cardiac position are best performed through a *segmental* approach, with the position of the viscera and atria defined first, then the ventricles, followed by the great vessels (Fig. 480.14). Determination of **visceroatrial situs** can be made by radiographic demonstration of the position of the abdominal organs and the tracheal bifurcation for recognition of the right and left bronchi and by echocardiography. The atrial situs is usually similar to the situs of the viscera and lungs. In **situs solitus** the viscera are in their normal positions (stomach and spleen on the left, liver on the right), the three-lobed right lung is on the right, and the two-lobed left lung on the left; the right atrium is on the right, and the left atrium is on the left. When the abdominal organs and lung lobation are reversed, an arrangement known as **situs inversus** occurs: the left atrium is on the right and the right atrium on the left. If the visceroatrial situs cannot be readily determined, a condition known as **situs indeterminus** or **heterotaxia** exists. The two major heterotaxy syndromes are **asplenia syndrome** (right isomerism or bilateral right-sidedness), which is associated with a centrally located liver, absent spleen, and two morphologic right lungs (Figs. 480.15 and 480.16), and **polysplenia syndrome** (left isomerism or bilateral left-sidedness), which is associated with multiple small spleens, absence of the intrahepatic portion of the inferior vena cava, and two morphologic left lungs (Figs. 480.17 and 480.18). The heterotaxia syndromes are usually associated with severe congenital heart lesions: ASD, VSD, atrioventricular septal defect, hypoplasia of one of the ventricles, pulmonary stenosis or atresia, and anomalous systemic venous or pulmonary venous return (Table 480.2).

Human heterotaxia syndromes may be related to disorders in both motile and primary cilia function and in utero left-right axis development. Genes involved in heterotaxy syndromes, including *NODAL* (known asymmetric gene), and those influenced by *NODAL* such as the TGF-β superfamily *(LEFTY2)* and *Pitx2,* have been implicated in the

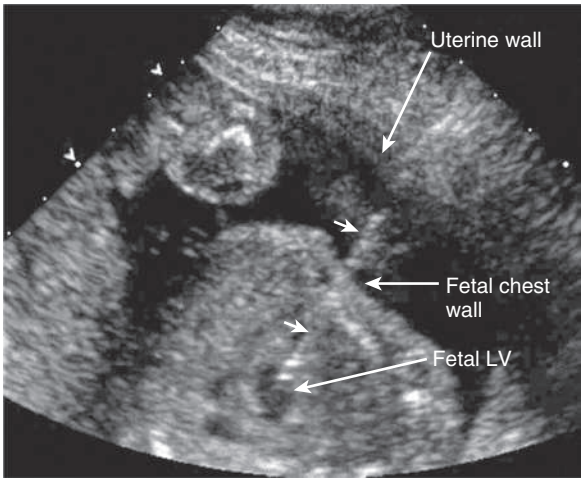

Fig. 480.13 Fetal treatment of critical aortic stenosis to prevent development of hypoplastic left heart syndrome. Fetal ultrasound showing insertion of a needle *(arrowheads)* via the maternal abdominal wall, through the uterus and the fetal chest wall, and into the fetal left ventricle (LV). A balloon catheter is next inserted via the needle into the left ventricular chamber and across the stenotic aortic valve. The balloon is inflated to dilate the valve, and the catheter and needle are removed. *(Courtesy Dr. Stanton Perry, Stanford University, Stanford, CA.)*

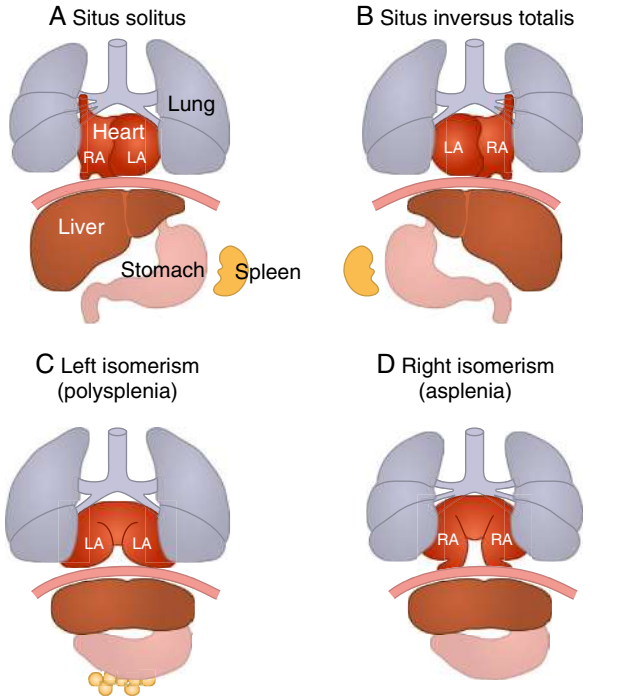

Fig. 480.14 Variations in thoracoabdominal situs in congenital heart disease. **A,** *Situs solitus:* On the right side there is a three-lobed lung, a right atrium (with superior and inferior vena cava entering), and the liver; on the left side there is a two-lobed lung, a left atrium (with pulmonary veins entering), the stomach, and the spleen. **B,** *Situs inversus totalis:* All the structures are mirror-image reversed: On the right side there is a two-lobed lung, a left atrium, the stomach, and the spleen; on the left side there is a three-lobed lung, a right atrium, and the liver. **C,** *Left isomerism (polysplenia):* There are two left sides: On the right side there is a two-lobed lung and a structure that resembles the left atrium; on the left side there is also a two-lobed lung and a structure that resembles the left atrium; there is usually a midline liver and stomach and multiple small spleens. **D,** *Right isomerism (asplenia):* There are two right sides: On the right side there is a three-lobed lung and a structure that resembles the right atrium; on the left side there is also a three-lobed lung and a structure that resembles the right atrium; there is usually a midline liver and stomach and an absent spleen. *(Adapted from Fliegauf M, Benzing T, Omran H. When cilia go bad: cilia defects and ciliopathies. Nat Rev Mol Cell Biol. 2007;8:880–893, Fig. 2.)*

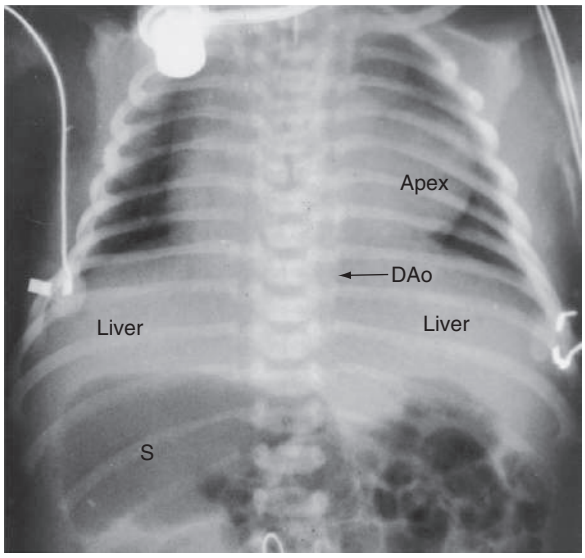

Fig. 480.15 X-ray from asplenic male neonate with right isomerism. The liver is transverse, the stomach (S) is on the right, and the heart is midline, but the base to apex axis points to the left. DAo, Descending aorta. *(Modified from Perloff JK, Marelli AJ. Perloff's Clinical Recognition of Congenital Heart Disease, 6th ed. Philadelphia: Saunders; 2012: Fig. 3-31, p. 32.)*

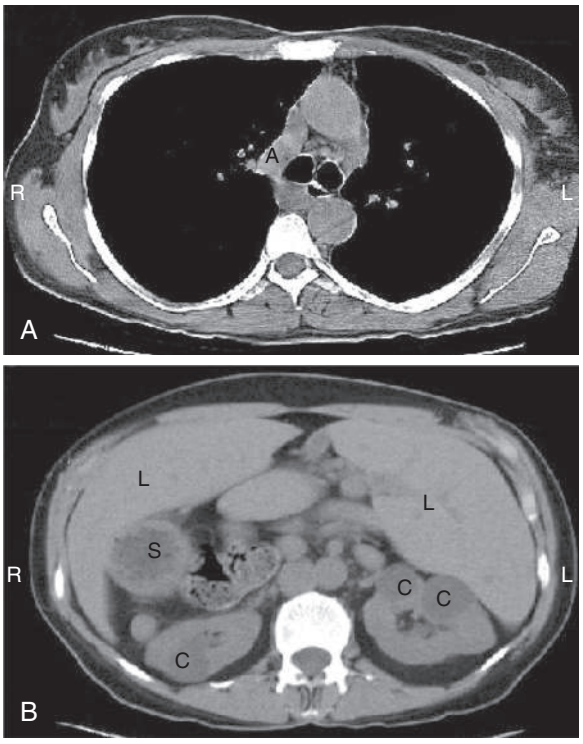

Fig. 480.16 Right isomerism with asplenia. Noncontrast-enhanced CT scan of a female with primary ciliary dyskinesia demonstrates features of right isomerism with asplenia. **A,** Large azygous vein arch is noted, which compensates for the inferior vena cava interruption. **B,** CT scan through the upper abdomen demonstrates midline liver (L), dextrogastria (s), and absent spleen. Bilateral renal cysts (C) are also noted. *(From Chmura K, Chan ED, Noone PG, Zariwala M, Winn RA, Knowles MR, Iseman MD, Gardner EM. A middle-aged woman with recurrent respiratory infections. Respiration. 2005;72(4):427–430.)*

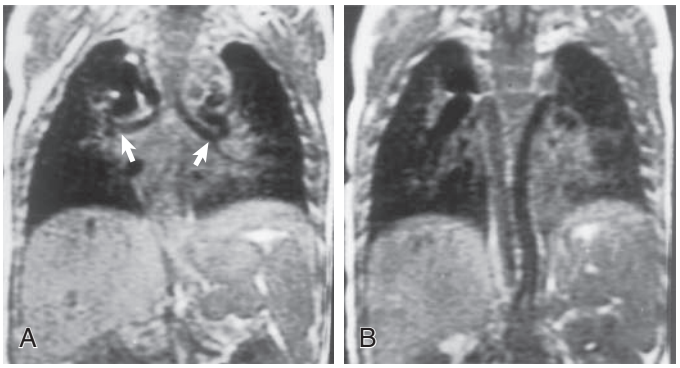

Fig. 480.17 **A,** Coronal T1-weighted MRI of a patient with heterotaxy syndrome (polysplenia) demonstrates a bilateral hyparterial bronchial branching pattern *(arrows)* and left upper quadrant spleens. **B,** More posterior coronal T1-weighted MRI shows left azygos-hemiazygos continuation to the left superior vena cava and right thoracic aorta. *(From Applegate KE, Goske MJ, Pierce G, Murphy D. Situs revisited: imaging of the heterotaxy syndrome. Radiographics. 1999;19:837–852, Fig. 4.)*

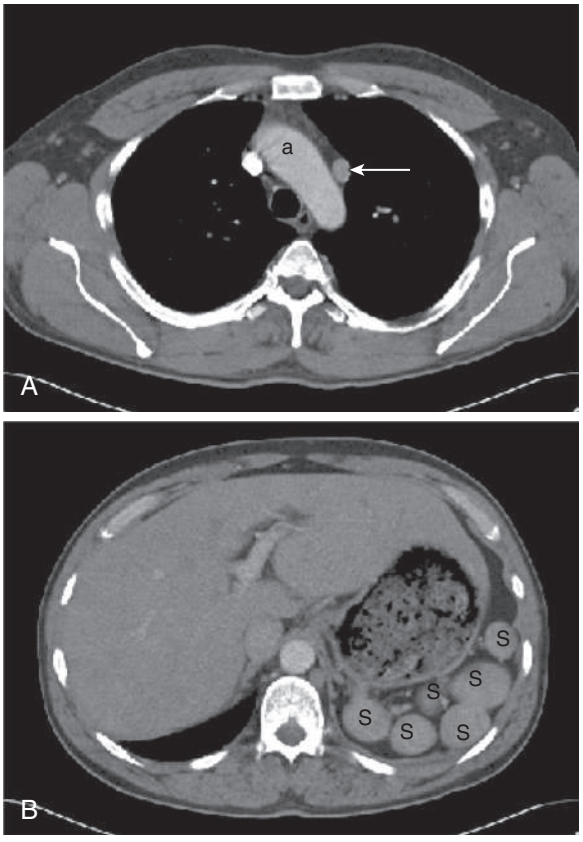

Fig. 480.18 Left isomerism with polysplenia. Contrast-enhanced computed tomography scan of a male with primary ciliary dyskinesia demonstrates features of left isomerism with polysplenia. **A,** Note bilateral superior vena cavae at the level of the aortic arch (a). The right superior vena cava is enhanced after intravenous contrast material administration through a right antecubital vein. Left-sided superior vena cava indicated by *arrow*. **B,** Upper abdomen image demonstrates left upper quadrant splenules (S). *(From Kennedy MP, Omran H, Leigh MW, et al. Congenital heart disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. Circulation. 2007;11:2814–2821, Fig. 3.)*

Table 480.2 Comparison of Cardiosplenic Heterotaxy Syndromes

FEATURE	ASPLENIA (RIGHT ISOMERISM)	POLYSPLENIA (LEFT ISOMERISM)
Spleen	Absent	Multiple
Sidedness (isomerism)	Bilateral right	Bilateral left
Lungs	Bilateral trilobar with eparterial bronchi	Bilateral bilobar with hyparterial bronchi
Sex	Male (65%)	Female ≥ male
Right-sided stomach	Yes	Less common
Symmetric liver	Yes	Yes
Partial intestinal rotation or malrotation	Yes	Yes
Risk for midgut volvulus	Yes	Yes
Dextrocardia (%)	30–40	30–40
Pulmonary blood flow	Decreased (usually)	Increased (usually)
Severe cyanosis	Yes	No
Transposition of great arteries (%)	60–75	15
Total anomalous pulmonary venous return (%)	70–80	Rare
Common atrioventricular valve (%)	80–90	20–40
Single ventricle (%)	40–50	10–15
Absent inferior vena cava with azygos continuation	No	Characteristic
Bilateral superior venae cavae	Yes	Yes
Other common defects	PA, PS, right-sided aortic arch	Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle
Risk of pneumococcal sepsis	Yes	Yes
Howell-Jolly and Heinz bodies, pitted erythrocytes	Yes	No
Risk of nosocomial infection	Yes	Yes
Absent gallbladder; biliary atresia	No	Yes

PA, Pulmonary atresia; PS, pulmonary stenosis.

development of heterotaxia syndromes (Fig. 480.19 and Table 480.3). Diagnostic gene panels are available to identify a possible genetic basis.

The next segment is localization of the **ventricles**, which depends on the direction of development of the embryonic cardiac loop. Initial protrusion of the loop to the right **(d-loop**) carries the future RV anteriorly and to the right, whereas the LV remains posterior and on the left (the normal relationship). With situs solitus, a d-loop yields normal atrioventricular connections (right atrium connecting to RV, left atrium to LV). Protrusion of the loop to the left **(l-loop)** carries the future RV to the left and the LV to the right. In this case, in the presence of situs solitus, the right atrium connects with the LV and the left atrium with the RV **(ventricular inversion)**.

The final segment is that of the **great vessels**. With each type of cardiac loop, the ventricular-arterial relationships may be regarded as either normal (RV to pulmonary artery, LV to aorta); transposed (RV to aorta, LV to pulmonary artery); or in the event of a double-outlet ventricle, either normally related or **malposed**. A further classification can be based on the position of the aorta (normally to the right and posterior) relative to the pulmonary artery. In transposition, the aorta is usually anterior and either to the right of the pulmonary artery **(d-transposition)** or to the left **(l-transposition)**.

These segmental relationships can usually be determined by echocardiographic studies demonstrating both atrioventricular and ventriculoarterial relationships. The clinical manifestations of these syndromes of abnormal cardiac position are determined primarily by their associated cardiovascular anomalies.

Dextrocardia occurs when the heart is in the right side of the chest. **Levocardia** (the normal situation) is present when the heart is in the left side of the chest. Dextrocardia without associated situs inversus or levocardia in the presence of situs inversus is most often complicated by other severe cardiac malformations. Surveys of older children and adults indicate that dextrocardia with situs inversus and normally related great arteries ("mirror-image" dextrocardia) is often associated with a functionally normal heart, although congenital heart disease of a less severe nature is common.

Anatomic or functional abnormalities of the lungs, diaphragm, and thoracic cage may result in displacement of the heart to the right **(dextroposition)**. In this case, however, the cardiac apex is pointed

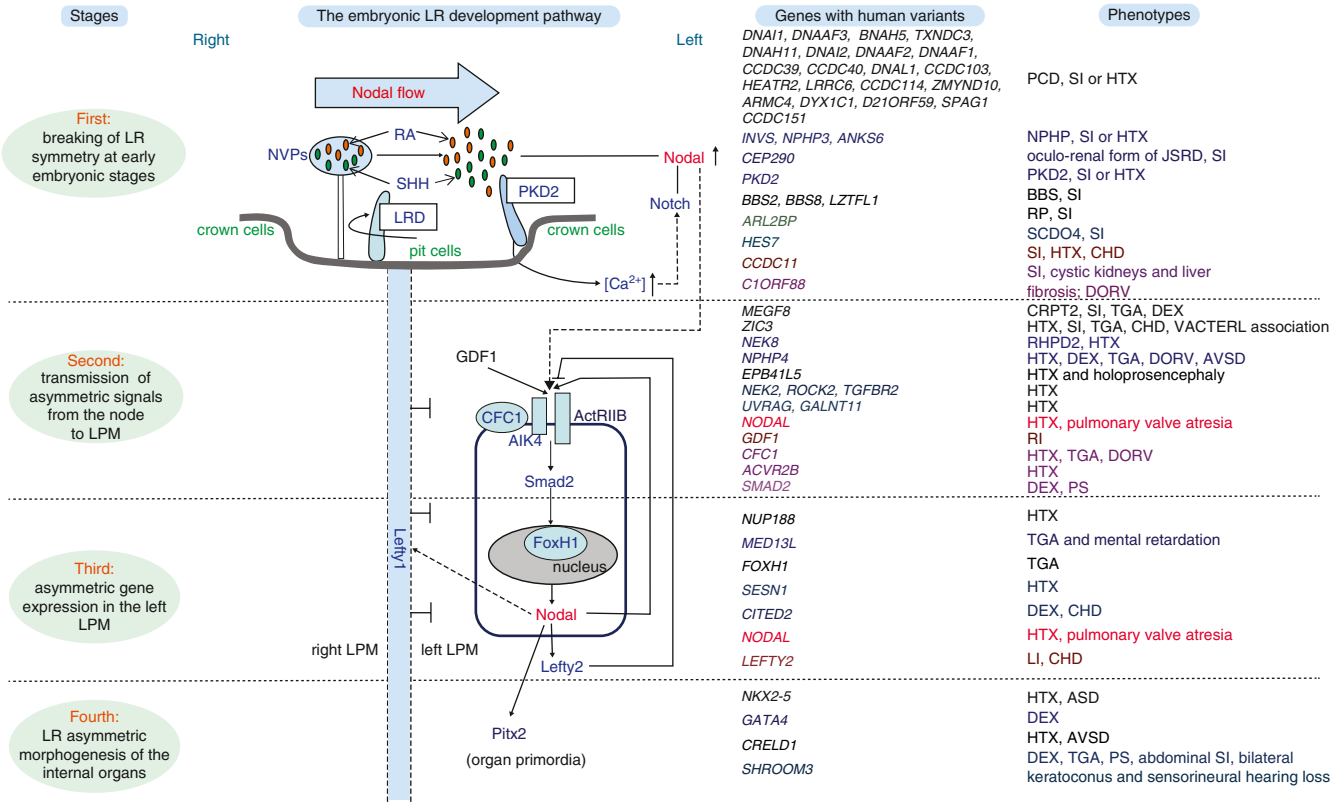

Fig. 480.19 Pathway of left-right (LR) development in the mouse embryo, list of genes associated with human LR asymmetry disorders, and corresponding phenotypes in humans. LRD-containing monocilia generate leftward nodal flow, and polycystin 2–containing cilia sense nodal flow and initiate an asymmetric calcium signal, which induces nodal expression around the node. Nodal signaling is involved in asymmetric morphogenesis by inducing expression of the nodal-responsive genes *(NODAL, LEFTY2,* and *PITX2)* in the left lateral plate mesoderm (LPM) and expression of *LEFTY1* at the midline. Pathogenic variants of genes associated with ciliopathies and nodal signal transduction pathway have been identified in human LR asymmetry disorders. *Full arrows* indicate a direct positive effect on gene expression, *dotted arrows* indicate an indirect effect, and *lines* indicate inhibition. ASD, Atrial septal defect; AVSD, atrioventricular septal defects; BBS, Bardet-Biedl syndrome; CHD, congenital heart disease; CRPT2, Carpenter syndrome 2; DEX, dextrocardia; DORV, double-outlet right ventricle; HTX, heterotaxy; JSRD, Joubert syndrome–related disorders; LI, left isomerism; NPHP, nephronophthisis; NVPs, nodal vesicular parcels; PCD, primary ciliary dyskinesia; PKD2, polycystic kidney disease 2; PS, pulmonary stenosis; RA, retinoic acid; RHPD2, renal-hepatic-pancreatic dysplasia 2; RI, right isomerism; RP, retinitis pigmentosa; SCDO4, spondylocostal dysostosis 4; SHH, sonic hedgehog; SI, situs inversus; TGA, transposition of the great arteries. *(From Deng H, Xia H, Deng S. Genetic basis of human left-right asymmetry disorders. Expert Rev Mol Med. 2014;16:e19, Fig 1.)*

Table 480.3 Ciliopathies with Heterotaxy Defects

CILIOPATHY	FEATURES	GENE(S)	CARDIAC DEFECTS
Primary ciliary dyskinesia	Bronchiectasis, sinusitis, otitis media, infertility, situs defects	*AK7, ARMC4, C21orf59, CCDC103, CCDC114, CCDC151, CCDC39, CCDC40, CCDC65, CCNO, DNAAF1, DNAAF2, DNAAF3, DNAAF5, DNAH11, DNAH5, DNAH6, DNAI2, DNAL1, DNAJB13, DRC1, DYX1C1, GAS8, HEATR2, HYDIN, LRRC6, MCIDAS, NME8, PIH1D3, RPGR, TXNDC3, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1, TTC25, ZMYND10*	Dextrocardia; heterotaxy spectrum heart defects in ~12%; heterotaxy not thought to occur with genes associated with central pair or radial spoke
Meckel-Gruber syndrome	Renal cysts, CNS anomalies (encephalocele), polydactyly, hepatic fibrosis, congenital heart defects	*MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, NPHP3, TCTN2, B9D1, B9D2, TMEM231, KIF14, TMEM107*	Situs inversus; heterotaxy; HLHS
Joubert and related syndromes	Hypoplasia of the cerebellar vermis (molar tooth sign), dysregulated breathing pattern, retinal dystrophy, renal anomalies	*AH1, C5ORF42, CC2D2A, CSPP1, TMEM216, NPHP1, CEP290, TMEM67, RPGRIP1L, INPP5E, TCTN2, MKS1, CEP104, CEP120, CEP41, KIAA0556, PDE6D, PIBF1, TCTN1, TCTN3, ARL13B, CEP41, KIAA0586, TMEM237, TMEM231, TMEM138, KIAA0753, TMEM107, KIF7, OFD1, C2CD3, IFT172, ARL13B, ZNF423, TTC21B, PDE60, POC18, B9D2, B9D1*	Laterality defects; heart defects, including septal defects, aortic valve anomalies, coarctation; in some cases, associated with features of OFD

Table 480.3 Ciliopathies with Heterotaxy Defects—cont'd

CILIOPATHY	FEATURES	GENE(S)	CARDIAC DEFECTS
Short rib thoracic dysplasias, including Jeune chondrodysplasia, Saldino-Mainzer	Skeletal dysplasia; thoracic deformities; polydactyly; renal cysts; retinitis pigmentosa	*IFT80, DYNC2H1, TTC21B, WDR19, NEK1, WDR35, WDR60, IFT140, IFT172, WDR34, CEP120, KIAA0586, DYNC2LI1, IFT52, TCTEX1D2*	Rare; septal defects, laterality defects
Carpenter syndrome	Acrocephaly; polysyndactyly, hypogenitalism, obesity, congenital heart defects	*RAB23, MEGF8, RAB23*	PDA, PS, VSD, situs inversus, heterotaxy

HLHS, Hypoplastic left heart syndrome; OFD, oral-facial-digital; PDA, patent ductus arteriosus; PS, pulmonary stenosis; and VSD, ventricular septal defect.
Modified from Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation*. 2018;138(21):e653–e711, Table 6.

normally to the left, as opposed to dextrocardia, where the cardiac apex is pointed to the right or anteriorly. This anatomic position is less often associated with congenital heart lesions, although hypoplasia of a lung may be accompanied by anomalous pulmonary venous return from that lung (**scimitar syndrome**; see Chapter 475.4).

The ECG is difficult to interpret in the presence of lesions with discordant atrial, ventricular, and great vessel anatomy. Diagnosis usually requires detailed echocardiographic and sometimes MRI, CT, or cardiac catheterization studies. The **prognosis** and **treatment** of patients with one of the cardiac positional anomalies are determined by the underlying defects and are covered in their respective chapters. Asplenia increases the risk of serious infections, such as bacterial (usually pneumococcal) sepsis, and thus requires daily antibiotic prophylaxis. Patients with polysplenia frequently have poor splenic function and also require prophylaxis against bacterial sepsis. Patients with heterotaxia are also at increased risk of intestinal malrotation and volvulus and of ciliary dyskinesia and associated pulmonary complications (see Chapters 101.3 and 455).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 481

Other Congenital Heart and Vascular Malformations

481.1 Anomalies of the Aortic Arch

Daniel Bernstein

RIGHT AORTIC ARCH

In this abnormality, the aorta curves to the right and, if it descends on the right side of the vertebral column, is usually associated with other cardiac malformations. It is found in 20% of cases of tetralogy of Fallot and is also common in truncus arteriosus. A right aortic arch without other cardiac anomalies is not associated with symptoms. It can often be visualized on the chest radiograph. The trachea is deviated slightly to the left of the midline rather than to the right, as in the presence of a normal left arch. On a barium esophagogram, MRI, or CT scan, the esophagus is indented on its right border at the level of the aortic arch.

VASCULAR RINGS

Congenital abnormalities of the aortic arch and its major branches result in the formation of vascular rings around the trachea and esophagus with varying degrees of compression (Table 481.1). The origin of these lesions can best be appreciated by reviewing the embryology of the aortic arch (see Fig. 469.1). The most common anomalies include (1) double aortic arch (Fig. 481.1A), (2) right aortic arch with a left ligamentum arteriosum, (3) anomalous innominate artery arising farther to the left on the arch than usual, (4) anomalous left carotid artery arising farther to the right than usual and passing anterior to the trachea, (5) anomalous right subclavian artery, and (6) anomalous left pulmonary artery **(vascular sling)**. In the latter anomaly, the abnormal vessel arises from an elongated main pulmonary artery or from the right pulmonary artery. It courses between and compresses the trachea and the esophagus. Associated congenital heart disease may be present in 5–50% of patients, depending on the vascular anomaly.

Clinical Manifestations

If the vascular ring produces compression of the trachea and/or esophagus, symptoms are frequently present during infancy. Chronic wheezing is exacerbated by crying, feeding, and flexion of the neck. Extension of the neck tends to relieve the noisy respiration. Choking on solid food and vomiting may also be symptoms. Affected infants may have a brassy cough, pneumonia, or rarely, sudden death from aspiration.

Diagnosis

Standard radiographic examination is not usually helpful. In the past, performing a barium esophagogram was the standard method of diagnosis (Fig. 481.2), which has been replaced by echocardiography in combination with either MRI or CT (Fig. 481.3). Cardiac catheterization is reserved for cases with associated anomalies or in rare cases where these other modalities are not diagnostic. Bronchoscopy is helpful in more severe cases to determine the extent of airway narrowing and whether additional surgery is required on the airway.

Treatment

Surgery is advised for symptomatic patients who have evidence of tracheal compression. The anterior vessel is usually divided in patients with a double aortic arch (see Fig. 481.1B). Compression produced by a right aortic arch and left ligamentum arteriosum is relieved by division of the latter. Anomalous innominate or carotid arteries cannot be divided; attaching the adventitia of these vessels to the sternum usually relieves the tracheal compression. An anomalous left pulmonary artery is corrected by division at its origin and reanastomosis to the main pulmonary artery after it has been brought in front of the trachea. Severe tracheomalacia, if present, may require reconstruction of the trachea as well.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 481.1 Vascular Rings

LESION	SYMPTOMS	PLAIN FILM	BARIUM SWALLOW	BRONCHOSCOPY	MRI ECHO	TREATMENT
DOUBLE ARCH 	Stridor Respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile	Diagnostic	Ligate and divide smaller arch (usually left)
RIGHT ARCH AND LIGAMENTUM/DUCTUS 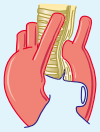	Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—r. pulsatile	Diagnostic	Ligate ligamentum or ductus
ANOMALOUS INNOMINATE 	Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compression	Unnecessary	Conservative apnea, then suspend
ABERRANT RIGHT SUBCLAVIAN 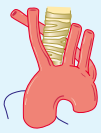	Occasional swallowing dysfunction	Normal	AP—oblique defect upward to right Lat.—small defect on right posterior wall	Usually normal	Diagnostic	Ligate artery
PULMONARY SLING 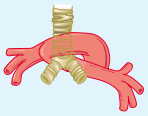	Expiratory stridor Respiratory distress	AP—low l. hilum, r. emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus	Diagnostic	Detach and reanastomose to main pulmonary artery in front of trachea

AP, Anteroposterior; L and l., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.
From Kliegman RM, Greenbaum LA, Lye PS. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004:88.

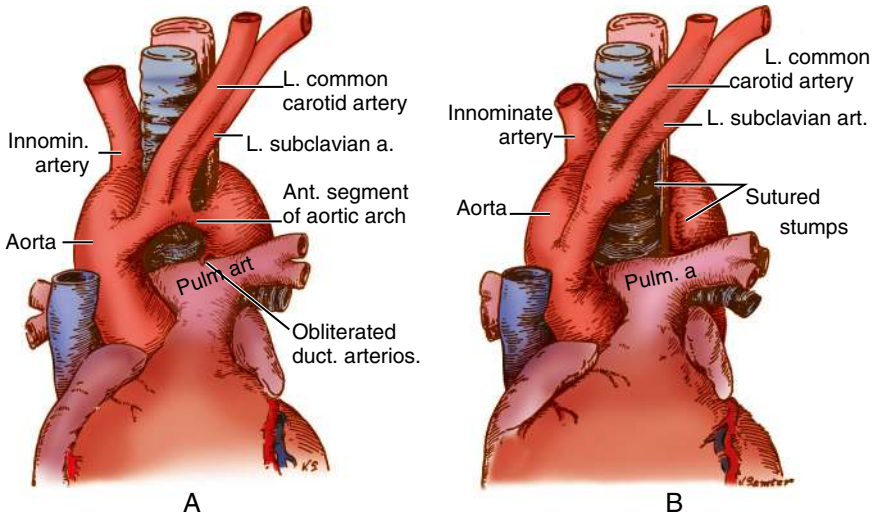

Fig. 481.1 Double aortic arch. **A,** Small anterior segment of the double aortic arch (most common type). **B,** Operative procedure for release of the vascular ring. L., Left; a. and art., artery; ant., anterior; innom., innominate; duct. arterios., ductus arteriosus; pulm., pulmonary.

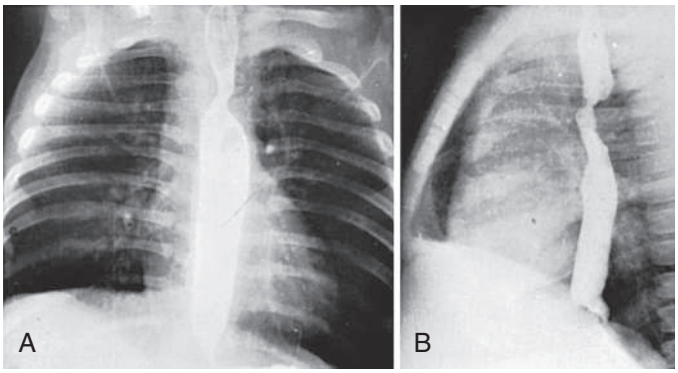

Fig. 481.2 Double aortic arch in an infant age 5 mo. **A,** Anteroposterior view. The barium-filled esophagus is constricted on both sides. **B,** Lateral view. The esophagus is displaced forward. The anterior arch was the smaller and was divided at surgery.

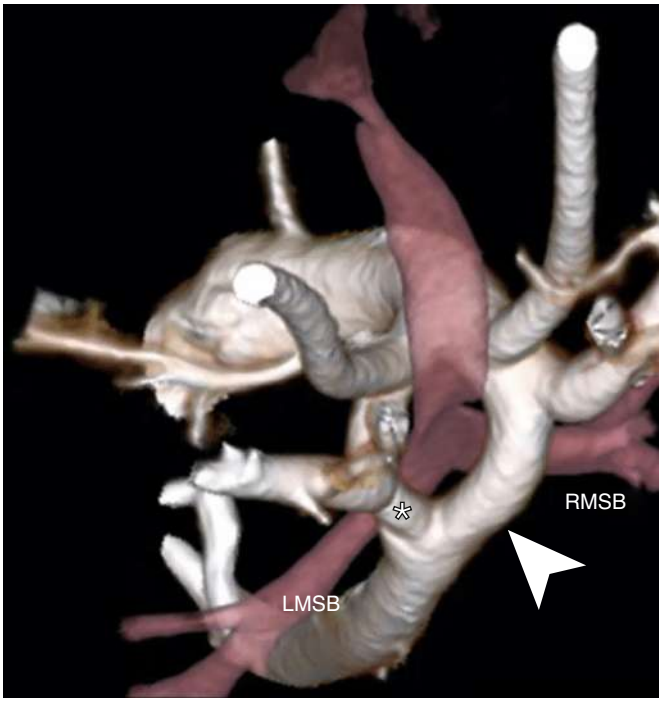

Fig. 481.3 Double aortic arch in a 12-year-old. Superior (bird's eye view) three-dimensional volume-rendered CT image shows the larger dominant arch *(arrowhead)* on the right side, coursing over the right mainstem bronchus *(RMSB).* There is mild indentation of the trachea. The smaller left arch *(asterisk)* courses over the left mainstem bronchus *(LMSB). (From Madueme PC: Computed tomography and magnetic resonance imaging of vascular rings and other things: a pictorial review. Pediatr Radiol 2022;52:1839–1848.(Fig. 2, p. 1840.)*

481.2 Anomalous Origin of the Coronary Arteries

Daniel Bernstein

Table 481.2 provides a classification system for coronary artery anomalies. Although many of these are isolated, congenital anomalies of the coronary arteries may also be seen in patients with congenital heart disease (tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries, single ventricle, tricuspid atresia, truncus arteriosus, quadricuspid or bicuspid aortic valves, double-outlet ventricle). In addition, acquired lesions of the coronary arteries associated with existing congenital heart disease may develop because of alterations in blood flow or postoperative stenoses, especially in patients whose surgery involves the aortic root.

Table 481.2 Congenital Anomalies of Coronary Arteries Unassociated with Congenital Heart Disease

ANOMALOUS AORTIC ORIGIN
• Eccentric ostium within an aortic sinus
• Ectopic ostium above an aortic sinus
• Conus artery from the right aortic sinus
• Circumflex coronary artery from the right aortic sinus or from the right coronary artery
• Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)
• Atresia of the left main coronary artery
• Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery
• Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery
• Origin of a single coronary artery from the right or left aortic sinus
• Anomalous origin from a noncardiac systemic artery
ANOMALOUS AORTIC ORIGIN WITH ANOMALOUS PROXIMAL COURSE
• Acute proximal angulation
• Ectopic right coronary artery passing between aorta and pulmonary trunk
◦ Ectopic left main coronary artery
◦ Between aorta and pulmonary trunk
◦ Anterior to the pulmonary trunk
◦ Posterior to the aorta
• Within the ventricular septum (intramyocardial)
• Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk
ANOMALOUS ORIGIN OF A CORONARY ARTERY FROM THE PULMONARY TRUNK
• Left main coronary artery
• Left anterior descending coronary artery
• Right coronary artery
• Both right and left coronary arteries
• Circumflex coronary artery
• Accessory coronary artery

From Perloff JK, Marelli J. *Perloff's Clinical Recognition of Congenital Heart Disease,* 6th ed. Philadelphia: Saunders; 2012: Table 32-3, p. 532.

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY

In anomalous origin of the left coronary artery from the pulmonary artery **(ALCAPA)**, the blood supply to the left ventricular (LV) myocardium is severely compromised. Soon after birth, as pulmonary artery pressure falls, perfusion pressure to the left coronary artery (LCA) becomes inadequate; myocardial ischemia, infarction, and fibrosis result. In some cases, interarterial collateral anastomoses develop between the right coronary artery (RCA) and LCA. Blood flow in the LCA is then reversed, and it empties into the pulmonary artery, a condition known as *myocardial steal syndrome.* The LV becomes dilated, and its performance is decreased. Mitral insufficiency is a frequent complication secondary to a dilated valve ring or infarction of a papillary muscle. Localized aneurysms may also develop in the LV free wall. Rare patients have adequate myocardial blood flow during childhood and, later in life, a continuous murmur and a small left-to-right shunt via the dilated coronary system (aorta to RCA to LCA to pulmonary artery).

Clinical Manifestations

Evidence of heart failure becomes apparent within the first few months of life and may be exacerbated by respiratory infection. Recurrent attacks of discomfort, restlessness, irritability, sweating, dyspnea, and pallor occur and represent an infantile version of **angina pectoris**. Diagnosis is often made only after a chest x-ray is obtained looking for other sources of irritability and rapid breathing. Cardiac enlargement ranges from moderate to massive. A gallop rhythm is common.

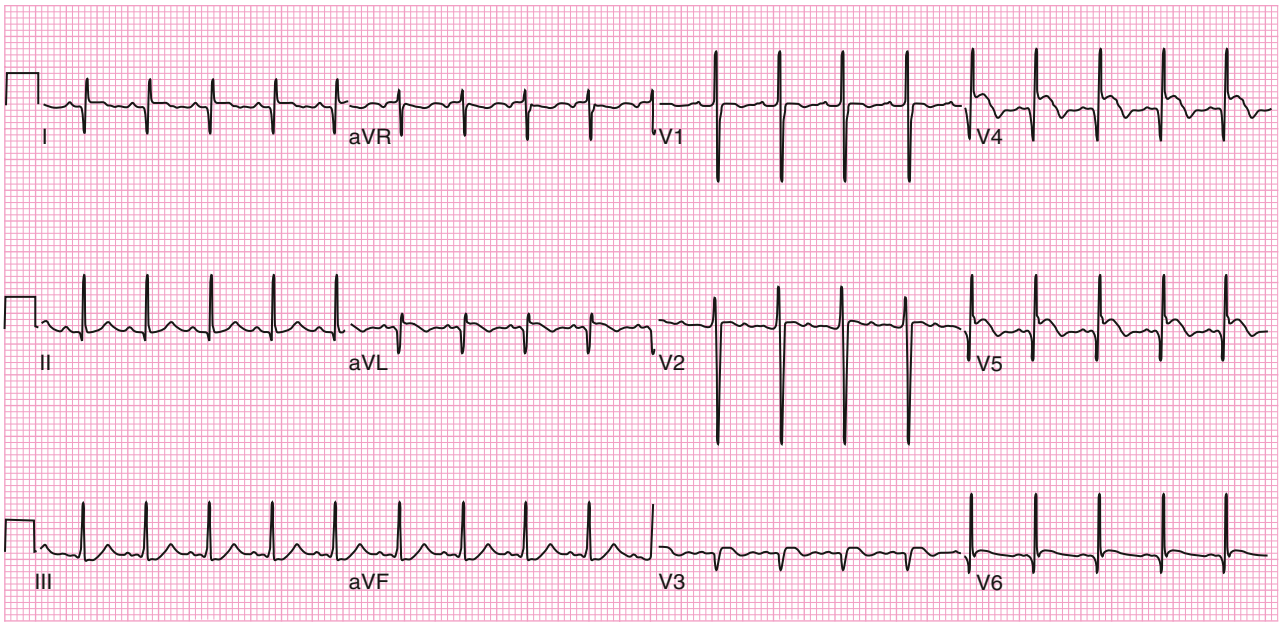

Fig. 481.4 Electrocardiogram of a 2-mo-old with anomalous origin of the left coronary artery from the pulmonary artery. Myocardial infarction is evidenced by abnormal Q waves in leads I and aVL and in the anterolateral precordial leads (V_3, V_4, V_5, V_6). There is also ST elevation in leads V_4 and V_5, a sign of ongoing ischemia. Another sign of ALCAPA is the diminution or loss of R waves in the midprecordial leads (V_2, V_3).

Murmurs may be of the nonspecific ejection type or may be holosystolic because of mitral insufficiency. Older patients with abundant intercoronary anastomoses may have continuous murmurs and less LV dysfunction. However, during older childhood and adolescence, they may experience angina during exercise. Rare patients with an anomalous RCA may also have such clinical findings, especially if the RCA supplies the inferoposterior portion of the LV (right dominant system).

Diagnosis

Radiographic examination confirms cardiomegaly. The electrocardiogram (ECG) can resemble the pattern described in anterolateral wall myocardial infarction in adults, although this pattern can vary over the first weeks of life. A QR pattern followed by flattened or inverted T waves is typically seen in leads I and aVL (Fig. 481.4). The anterolateral precordial leads (V_3-V_6) may show deep Q waves or elevated ST segments and inverted T waves (the more typical adult findings of a lateral myocardial infarction) or may be relatively normal. Decreased or absent R waves may be seen over the mid-precordial leads (V_3, V_4). Given the subtlety of these ECG findings and that an infarct pattern is not usually expected in infants, a high index of suspicion should be maintained for patients with the symptoms described earlier. Two-dimensional (2D) echocardiography with color Doppler usually confirms the diagnosis; however, in rare cases, echocardiography may not be definitive in diagnosing this condition. On 2D imaging alone, the LCA may appear as though it is arising from the aorta. Color Doppler ultrasound has improved the accuracy of diagnosis of this lesion, demonstrating the presence of retrograde flow in the LCA. If needed, CT or MRI can confirm the origin of the coronary arteries. Cardiac catheterization is also diagnostic; aortography shows immediate opacification of the RCA only. In patients who have developed collaterals, this vessel is large and tortuous. After filling of the intercoronary anastomoses, the LCA is opacified, and contrast can be seen to enter the pulmonary artery. Pulmonary arteriography should opacify the origin of the anomalous LCA. Selective left ventriculography usually demonstrates a dilated LV that empties poorly and mitral regurgitation.

Treatment and Prognosis

Untreated, death often occurs from heart failure within the first 6 months of life. Those who survive without surgery generally have abundant intercoronary collateral anastomoses. Medical management includes standard therapy for heart failure (diuretics, angiotensin-converting enzyme inhibitors, and β blockers).

Surgical treatment consists of detaching the anomalous coronary artery from the pulmonary artery and anastomosing it to the aorta to establish normal myocardial perfusion. In patients who have already sustained a significant myocardial infarction, cardiac transplantation may be the only option (see Chapter 492.1).

ANOMALOUS ORIGIN OF THE RIGHT CORONARY ARTERY FROM THE PULMONARY ARTERY

Anomalous origin of the RCA from the pulmonary artery is not usually manifested in infancy or early childhood. The LCA is enlarged, whereas the RCA is thin walled and mildly enlarged. In early infancy, perfusion of the RCA is from the pulmonary artery, whereas later, perfusion is from collaterals of the left coronary vessels. Angina and sudden death can occur in adolescence or adulthood. When recognized, this anomaly should be repaired by reanastomosis of the RCA to the aorta.

ANOMALOUS AORTIC ORIGIN OF A CORONARY ARTERY

In anomalous aortic origin of a coronary artery (AAOCA), one or both coronary arteries arise from their nonusual sinus (e.g., LCA from the right sinus of Valsalva) or high on the aorta, above the sinotubular junction. There are multiple anatomic variations, with different physiologic consequences, and therefore with different risks of coronary ischemia, arrhythmia, and potentially sudden death. Fortunately, most variants of AAOCA are benign, and the challenge for clinicians is to recognize which variants place their patient at a greater risk of a life-threatening event.

The aberrant artery may be a left, right, or major branch coronary artery. The site of origin may be the wrong sinus of Valsalva (anomalous origin of a coronary artery from the opposite sinus, **ACAOS**) or a proximal coronary artery. The ostium may be hypoplastic, slitlike, or of normal caliber. The aberrant vessel may pass anteriorly, posteriorly, or between the aorta and right ventricular outflow tract (RVOT); it may take an intramural course, tunneling in the conal or interventricular septal tissue. Obstruction resulting from hypoplasia of the ostia, tunneling between the aorta and RVOT or interventricular septum, and acute angulation produce myocardial ischemia and infarction. Although unobstructed vessels usually produce no

Table 481.3 Classification of Coronary Anomalies Based on Ischemia

ISCHEMIA	CLASSIFICATION
Absence of ischemia	Most anomalies (split RCA, ectopic RCA from right cusp; ectopic RCA from left cusp)
Episodic ischemia	Anomalous origin of a coronary artery from the opposite sinus (ACAOS); coronary artery fistulas; myocardial bridge
Typical ischemia	Anomalous left coronary artery from the pulmonary artery (ALCAPA); coronary ostial atresia or severe stenosis

RCA, Right coronary artery.
From Mehran R, Dangas GD. Coronary angiography and intravascular imaging. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease,* 11th ed. Philadelphia: Elsevier; 2019: Fig. 20.8, p. 385.

symptoms (Table 481.3), patients with coronary obstruction may initially present with an acute coronary event, either acute myocardial infarction, ventricular arrhythmias, angina pectoris, or syncope; sudden death may occur, especially in young athletes.

Diagnostic modalities include ECG, 2D echocardiography, CT or MRI, radionuclide perfusion scan, and cardiac catheterization with selective coronary angiography. Exercise stress testing can play an important role in assessing risk (e.g., in patients who present only with chest pain), but is usually contraindicated in those who present with a sudden cardiac arrest, documented ischemia, or ventricular arrhythmia.

Treatment is indicated for obstructed vessels, for patients with symptoms, and for those who present with a sudden cardiac event and consists of reanastomosis of the aberrant vessel to the correct aortic sinus. The management of asymptomatic patients with ectopic coronary origin without obstruction remains controversial, as the ability to predict risk is still incompletely understood. Management decisions should be based on the specific anatomy, results of laboratory investigations, and shared decision-making with patients and their families after careful explanation of risks and benefits. Surgery is not without complications and should be performed at centers experienced in AAOCA surgery.

The risk appears to be highest with anomalous LCA from the right sinus of Valsalva with interarterial course (see Table 481.3); however, there are patients with anomalous RCA who are also at risk.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

481.3 Pulmonary Arteriovenous Fistula

Daniel Bernstein

Fistulous vascular communications in the lungs may be large and localized or multiple, scattered, and small. The most common form of this unusual condition is **Osler-Weber-Rendu syndrome** (hereditary hemorrhagic telangiectasia type I), which is also associated with angiomas of the nasal and buccal mucous membranes, gastrointestinal (GI) tract, or liver. Pathogenic variants in the endoglin gene, a cell surface component of the transforming growth factor (TGF)-β receptor complex, cause this syndrome. The usual communication is between the pulmonary artery and pulmonary vein; direct communication between the pulmonary artery and left atrium is extremely rare. Desaturated blood in the pulmonary artery is shunted through the fistula into the pulmonary vein, thus bypassing the lungs, and then enters the left side of the heart, *resulting in systemic arterial desaturation and sometimes clinically detectable cyanosis.* The shunt across the fistula is at low pressure and resistance, so pulmonary artery pressure is normal; cardiomegaly and heart failure are not present.

The clinical manifestations depend on the magnitude of the shunt. Large fistulas are associated with dyspnea, cyanosis, clubbing, a continuous murmur, and polycythemia. Hemoptysis is rare, but when it occurs, it may be massive. Features of Osler-Weber-Rendu syndrome are seen in approximately 50% of patients (or other family members) and include recurrent epistaxis and GI tract bleeding. Transitory dizziness, diplopia, aphasia, motor weakness, or convulsions may result from cerebral thrombosis, abscess, or paradoxical emboli. Soft systolic or continuous murmurs may be audible over the site of the fistula. The ECG is normal. Chest radiographs may show opacities produced by large fistulas; multiple small fistulas may be visualized by fluoroscopy (as abnormal pulsations), MRI, or CT. Selective pulmonary arteriography demonstrates the site, extent, and distribution of the fistulas.

Treatment consisting of excision of solitary or localized lesions by lobectomy or wedge resection results in complete disappearance of symptoms. In most patients, fistulas are so widespread that surgery is not possible. Any direct communication between the pulmonary artery and the left atrium can be obliterated.

Patients who have undergone a **Glenn cavopulmonary anastomosis** for cyanotic congenital heart disease (see Chapter 479.4) are also at risk for the development of pulmonary **arteriovenous malformations** (AVMs). In these patients the AVMs are usually multiple, and the risk increases over time after the Glenn procedure. Pulmonary AVMs rarely occur after full palliation by completion of the **Fontan operation**. This finding suggests that the pulmonary circulation requires an as-yet-undetermined hepatic factor to suppress the development of AVMs. The hallmark of the development of pulmonary AVMs is a gradual decrease in the patient's oxygen saturation, which is usually lower than normal to begin with. The diagnosis can often be made with contrast echocardiography; cardiac catheterization is the definitive test. Completion of the Fontan circuit, so that inferior vena cava blood flow (containing hepatic venous drainage) is routed through the lungs, usually results in improvement or resolution of the malformations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

481.4 Ectopia Cordis

Daniel Bernstein

In the most common thoracic form of ectopia cordis, the sternum is split and the heart protrudes outside the chest. In other forms, the heart protrudes through the diaphragm into the abdominal cavity or may be situated in the neck. Associated intracardiac anomalies are seen in 40% (tetralogy of Fallot, conotruncal lesions). **Pentalogy of Cantrell** consists of ectopia cordis, midline supraumbilical abdominal defect, deficiency of the anterior diaphragm, defect of the lower sternum, and an intracardiac defect (ventricular septal defect, tetralogy of Fallot, or diverticulum of the left ventricle). Death may occur early in life, usually from infection, cardiac failure, or hypoxemia. Surgical therapy for neonates without overwhelmingly severe cardiac anomalies consists of covering the heart with skin without compromising venous return or ventricular ejection. Repair or palliation of associated defects is also necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

481.5 Diverticulum of the Left Ventricle

Daniel Bernstein

Left ventricular diverticulum is a rare anomaly in which the diverticulum protrudes into the epigastrium. The lesion may be isolated or associated with complex cardiovascular anomalies. A pulsating mass is usually visible and palpable in the epigastrium. Systolic or systolic-diastolic murmurs produced by blood flow into and out of the diverticulum may be audible over the lower part of the sternum and the mass. The ECG shows a pattern of complete or incomplete left bundle branch block. The chest radiograph may or may not show the mass. Associated abnormalities include defects of the sternum, abdominal wall, diaphragm, and pericardium (see earlier). Surgical treatment of the diverticulum and associated cardiac defects can be performed in selected cases. Occasionally, a diverticulum may be small and not associated with clinical signs or symptoms. These small diverticula are diagnosed at echocardiographic examination for other indications.

Chapter 482
Pulmonary Hypertension

482.1 Primary Pulmonary Hypertension

Daniel Bernstein and Rachel K. Hopper

Pulmonary hypertension (PH) refers to an elevated pressure in the pulmonary arteries and is associated with significant morbidity and mortality in children. The etiologies of PH are varied, but all lead to similar symptoms and can ultimately result in right-sided heart failure (Tables 482.1 and 482.2). PH is often characterized by progressive vascular disease of the pulmonary arteries (pulmonary arterial hypertension [PAH], previously called *primary PH*). PH occurs at any age, although in pediatric patients the mean age at diagnosis is 7-10 years. In patients with idiopathic or familial PAH, females outnumber males 1.7:1; in other patients, both genders are represented equally. Pathogenic variants in the *BMPR2* gene, a member of the transforming growth factor (TGF)-β receptor family, on chromosome 2q33 have been identified in 70% of patients with **familial pulmonary arterial hypertension** and in 10–20% with idiopathic sporadic PAH (see Table 482.2). Other potential disease-causing genes include *ALK1* and *ENG* (both associated with hereditary hemorrhagic telangiectasia) and *SMAD9, CAV1, KCNK3,* and *SOX17* (associated with congenital heart disease and PAH). *TBX4* is associated with developmental lung disease and PAH. Viral infection, such as with the vasculotropic human herpesvirus 8, has been suggested as a trigger factor in some patients.

PAH is associated with precapillary obstruction of the pulmonary vascular bed as a result of hyperplasia of the muscular and elastic tissues and a thickened intima of the small pulmonary arteries and arterioles (Fig. 482.1). Secondary remodeling may be found in the larger pulmonary arteries as well. **Pulmonary venoocclusive disease**, mixed precapillary and postcapillary vascular disease, may account for some cases of PAH. Before a diagnosis of PAH can be made, other causes of elevated pulmonary artery pressure must be eliminated; these include chronic pulmonary parenchymal disease, persistent obstruction of the upper airway, congenital cardiac malformations, left-sided heart disease, recurrent pulmonary emboli, developmental lung disease, liver disease, autoimmune disease, and moyamoya disease (see Table 482.1). PAH accounts for nearly half of all pediatric PH (45%), with PAH associated with congenital heart disease being the most common in pediatric patients, followed by idiopathic or familial disease. PH associated with chronic lung disease is growing to encompass a larger portion of new cases, nearly half of all pediatric PH (49%). Bronchopulmonary dysplasia related to prematurity and other developmental lung diseases are increasingly recognized as contributing to PH in children (see Table 482.2).

PH places an afterload burden on the right ventricle, which results in right ventricular hypertrophy (RVH). Dilation of the pulmonary artery is present, and pulmonary valve insufficiency may occur. In the later stages of the disease, the right ventricle dilates, tricuspid insufficiency develops as the tricuspid valve leaflets are pulled apart, and cardiac output is decreased. Arrhythmias, syncope, and sudden death are known complications.

CLINICAL MANIFESTATIONS

The predominant symptoms include exercise intolerance (dyspnea) and fatigability; occasionally, precordial chest pain, dizziness, or headaches are noted. Syncope may be noted in approximately 30% of pediatric patients. Patients often undergo an incorrect evaluation and are treated for asthma or seizures before a proper diagnosis is made. Peripheral cyanosis may be present, especially during exercise or in patients with a patent foramen ovale or other intracardiac communication through which blood can shunt from right to left. In the late stages of disease, patients may have cold extremities and a gray appearance associated with low cardiac output. Arterial oxygen-hemoglobin saturation is usually normal unless there is an associated intracardiac shunt. If right-sided heart failure has supervened, jugular venous pressure is elevated, and hepatomegaly and edema are present. Jugular venous *a* waves are present, and in those with functional tricuspid insufficiency, a conspicuous jugular *cv* wave and systolic hepatic pulsations are manifested. The heart is moderately enlarged, and a right ventricular heave can be noted. The first heart sound is often followed by an ejection click emanating from the dilated pulmonary artery. The second heart sound (S_2) is narrowly split, with a loud pulmonic component that is sometimes booming in quality; it is frequently palpable at the upper left sternal border. A presystolic (S_4) gallop rhythm may be audible at the lower left sternal border. The systolic murmur is soft and short and is sometimes followed by a blowing decrescendo diastolic murmur caused by pulmonary insufficiency. In later stages, a holosystolic murmur of tricuspid insufficiency is appreciated at the lower left sternal border.

DIAGNOSIS

Chest radiographs reveal a prominent pulmonary artery and right ventricle (Fig. 482.2). The pulmonary vascularity in the hilar areas may be prominent, in contrast to the peripheral lung fields in which pulmonary markings are decreased. The electrocardiogram (ECG) shows RVH, often with spiked P waves. Echocardiography is used to screen for any congenital cardiac malformations and assess right ventricular size and function. Doppler evaluation of the tricuspid valve, if insufficiency is present, will allow estimation of the right ventricular (and thus pulmonary arterial) systolic pressure.

At cardiac catheterization, the presence of left-sided obstructive lesions (pulmonary venous stenosis, mitral stenosis, restrictive cardiomyopathy) that result in pulmonary venous hypertension can be evaluated (see Chapters 476.9, 480.7, and 488.3). Elevated pulmonary artery pressures with a normal pulmonary capillary wedge pressure and high vascular resistance is diagnostic of PAH. If the wedge pressure is elevated and left ventricular end-diastolic pressure (LVEDP) is normal, obstruction at the level of the pulmonary veins, left atrium, or mitral valve should be suspected. If LVEDP is also elevated, the diagnosis of restrictive cardiomyopathy should be entertained. The risks associated with cardiac catheterization are increased in severely ill patients with PAH and should occur at centers with expertise in pediatric PH.

PROGNOSIS AND TREATMENT

Many forms of PAH are progressive, and no cure is currently available. Figure 482.3 provides a general treatment approach to PH. Current medical therapies are pulmonary vasodilatory agents, which relieve symptoms, improve quality of life, and delay clinical worsening; however, they do not stop the progression of the disease. Some success has been reported with oral **calcium channel blockers (CCBs)** such as nifedipine in children who demonstrate pulmonary vasoreactivity when these agents are administered during catheterization. Continuous intravenous infusion of the arachidonic acid metabolite **prostacyclin** (epoprostenol) provides relief as long as the infusion is continued and has been shown to improve survival in children with PAH. **Treprostinil**, a prostacyclin analog with a longer half-life, has also been shown to be effective. Nebulized and oral forms of prostacyclin, as well as other oral pulmonary vasodilators, such as endothelin receptor antagonists and phosphodiesterase type 5 inhibitors, have been used with success in adults and in a small number of clinical studies in children (Table 482.3). In patients with PH secondary to left-sided heart disease or lung disease, pulmonary vasodilators should only be considered after optimization of the underlying condition and in consultation with a PH expert.

Anticoagulation may be of value in patients with previous pulmonary thromboemboli; some of these patients may respond to balloon angioplasty of narrowed pulmonary artery segments. Riociguat, a soluble guanylate cyclase stimulator, with vasorelaxation, antiproliferation, and antifibrotic properties, has proved effective in adults with chronic thromboembolic or idiopathic PH. Diuretics are often used to manage right heart failure. Despite many advances, definitive therapy is still lung transplantation (see Chapter 492.2). Palliative interventions may

Table 482.1 Classification of Pulmonary Hypertension (PH)*

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug- and toxin-induced PAH
   - 1.4 PAH associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Schistosomiasis
   - 1.5 PAH long-term responders to calcium channel blockers
   - 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   - 1.7 Persistent PH of the newborn syndrome
2. Pulmonary hypertension due to left heart disease
   - 2.1 PH due to heart failure with preserved LVEF
   - 2.2 PH due to heart failure with reduced LVEF
   - 2.3 Valvular heart disease
   - 2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH
3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Obstructive lung disease
   - 3.2 Restrictive lung disease
   - 3.3 Other lung disease with mixed restrictive/obstructive pattern
   - 3.4 Hypoxia without lung disease
   - 3.5 Developmental lung disorders
4. PH due to pulmonary artery obstructions
   - 4.1 Chronic thromboembolic pulmonary hypertension
   - 4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   - 5.1 Hematologic disorders
   - 5.2 Systemic and metabolic disorders
   - 5.3 Others
   - 5.4 Complex congenital heart disease.

*Modified as compared with the Nice 2013 classification.
HIV, Human immunodeficiency virus; PVOD, pulmonary venoocclusive disease; PCH, pulmonary capillary hemangiomatosis, LVEF, left ventricular ejection fraction.
From Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913.

Table 482.2 Developmental and Genetic Lung Diseases Associated with Pulmonary Hypertension

Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Down syndrome
Noonan syndrome
Alveolar capillary dysplasia (ACD) with "misalignment of veins" *(FOXF1)*
Cobalamin C deficiency
Lung hypoplasia, acinar dysplasia
Surfactant protein abnormalities
Surfactant protein B deficiency
Surfactant protein C deficiency
ATP-binding cassette A3 variants
Thyroid transcription factor 1 (TTF1)/*Nkx2.1* homeobox pathogenic variants
T-box transcription factor 4 *(TBX4)*
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia
Other pathogenic variants (*BMPR2, ACVRL1, EIF2AK4, CAV1, ENG, KCNK3, SMAD9, SOX17*)

Adapted with data from Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J.* 2019;53(1):1801916; and Ivy DD, Abman SH, Barst RJ et al. Pediatric pulmonary hypertension. *J Amer Coll Cardiol.* 2013;62(25):Suppl D, D118–D126, 2013.

include atrial septostomy or a surgical Potts shunt to create a right-to-left shunt as a pop-off to allow decompression of the right ventricle (see Fig. 482.3). In patients with severe PH and low cardiac output, the terminal event is often sudden and related to a lethal arrhythmia. Patients with PH diagnosed in infancy, especially those in premature infants with chronic lung disease, have a high risk of early mortality, but PH generally improves over time if lung growth and protection from infection and injury are achieved. Infants with PH caused by pulmonary vein stenosis often have rapid progression and high mortality.

482.2 Pulmonary Vascular Disease (Eisenmenger Syndrome)

Daniel Bernstein and Rachel K. Hopper

The term *Eisenmenger syndrome* refers to patients with an intracardiac defect or aortopulmonary connection through which blood is shunted

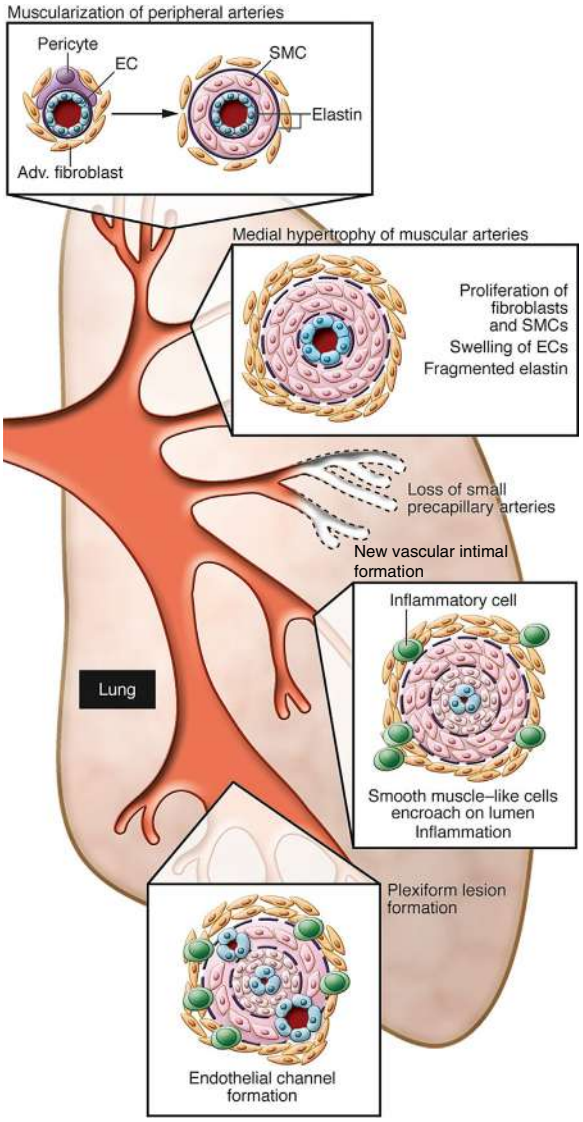

Fig. 482.1 Vascular abnormalities associated with pulmonary arterial hypertension: abnormal muscularization of distal and medial precapillary arteries, loss of precapillary arteries, thickening of large pulmonary arterioles, and new vascular intimal formation that is occlusive in vessels <500-100 μM and in plexiform lesions therein. Adv. adventitial; EC, endothelial cell; SMC, smooth muscle cell. *(From Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest. 2012;122:4306–4313, Fig 1.)*

partially or totally from right to left as a result of the development of pulmonary vascular disease. This physiologic abnormality can occur with unrepaired ventricular or atrioventricular septal defects, patent ductus arteriosus, aortopulmonary window, or any other communication between the aorta and pulmonary artery and in many forms of complex congenital heart disease with unrestricted pulmonary blood flow. Pulmonary vascular disease with an isolated atrial septal defect can occur, but this is less common and usually does not occur until late in adulthood.

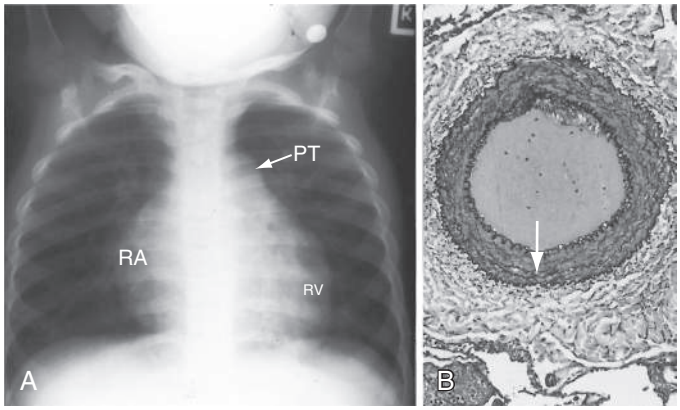

Fig. 482.2 A, Radiograph from a 3-yr-old child with pulmonary arterial hypertension. Pulmonary vascularity is reduced. The pulmonary trunk (PT), right atrium (RA), and right ventricle (RV) are considerably enlarged. B, Histology of an intrapulmonary artery at necropsy shows medial hypertrophy *(arrow). (From Perloff JK, Marelli AJ. Perloff's Clinical Recognition of Congenital Heart Disease, 6th ed. Philadelphia: Saunders; 2012: Fig. 14-17, p. 207.)*

In Eisenmenger syndrome, pulmonary vascular resistance (PVR) after birth either remains high or, after having decreased during early infancy, rises thereafter because of chronic increased shear stress on pulmonary arterioles. Factors playing a role in the rapidity of development of pulmonary vascular disease include increased pulmonary artery pressure, increased pulmonary blood flow, and the presence of hypoxia or hypercapnia. Early in the course of disease, PH is the result of markedly increased pulmonary blood flow (*hyperkinetic* PH). This form of PH decreases with the administration of pulmonary vasodilators such as nitric oxide, or oxygen, or both. With the development of Eisenmenger syndrome, PH is the result of pulmonary vascular disease (obstructive pathologic changes in the pulmonary vessels). This form of PH is usually only minimally responsive to pulmonary vasodilators or oxygen or may be totally unresponsive.

PATHOLOGY AND PATHOPHYSIOLOGY

The pathologic changes of Eisenmenger syndrome occur in the small pulmonary arterioles and muscular arteries (<300 μm) and are graded on the basis of histologic characteristics **(Heath-Edwards classification)**:

- **Grade I** change involves medial hypertrophy alone.
- **Grade II** consists of medial hypertrophy and intimal hyperplasia.
- **Grade III** involves near-obliteration of the vessel lumen.
- **Grade IV** includes arterial dilation.
- **Grades V and VI** include plexiform lesions, angiomatoid formation, and fibrinoid necrosis.

Grades IV-VI indicate irreversible pulmonary vascular obstructive disease. Eisenmenger physiology is usually defined by an absolute elevation in pulmonary arterial resistance to >12 Wood units (resistance units indexed to body surface area) or by a ratio of pulmonary-to-systemic vascular resistance of ≥1.0.

Pulmonary vascular disease occurs more rapidly in patients with trisomy 21 who have left-to-right shunts. It also complicates the natural history of patients with elevated pulmonary venous pressure secondary to mitral stenosis or left ventricular dysfunction,

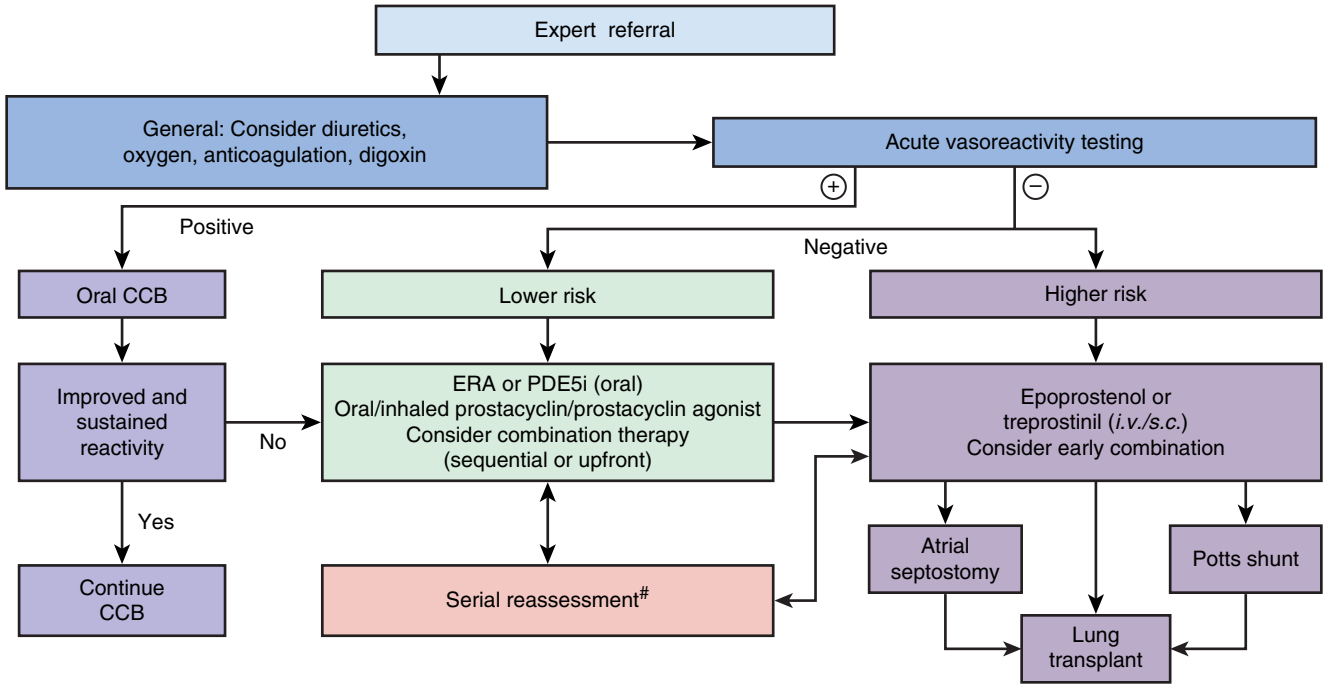

Fig. 482.3 6th World Symposium on Pulmonary Hypertension Consensus pediatric idiopathic/familial PAH treatment algorithm. Use of all agents is considered off-label in children aside from sildenafil in Europe and bosentan in age >3 yr in the United States. CCB, Calcium channel blocker; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; IV, intravenous; PDE-5i, phosphodiesterase-5 inhibitor; SC, subcutaneous; PO, by mouth; #, deterioration or not meeting treatment goals. *(From Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53[1]:1801916.)*

Table 482.3 Summary of Drugs Used to Treat Pulmonary Hypertension*

DRUG AND MECHANISM OF ACTION	DOSES USED IN PEDIATRIC STUDIES	COMMON SIDE EFFECTS
Epoprostenol (prostacyclin [PGI_2], a potent vasodilator; also inhibits platelet aggregation)	1-2 ng/kg/min initially Increase based on clinical course and tolerance to 5-80 ng/kg/min Some patients may require even higher doses Must be given by continuous infusion that is not interrupted	Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain, foot and bone pain
Iloprost (synthetic analog of PGI_2)	2.5-5.0 μg 6-9 times daily (limited data in children) via inhalation	Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)
Treprostinil (synthetic analog of PGI_2)	1-2 ng/kg/min initially Target dose ranges from 20-80 ng/kg/min Given either IV or SC via continuous infusion Longer half-life than epoprostenol *Inhaled:* 6-54 mcg (1-9 patient activated breaths) every 6 hr *Oral:* initially 0.125 mg 3 times daily Target dose ranges from 1 to 10 mg 3 times daily	Flushing, headache, diarrhea, hypotension, jaw pain Pain at infusion site when given SC Inhaled form can exacerbate reactive airway symptoms Increased gastrointestinal side effects with oral formulation
Selexipag (prostacyclin IP receptor agonist)	50-1600 mcg PO twice daily; limited data in children	Headache, pain in jaw, joints or limbs, myalgias, nausea, vomiting, diarrhea, flushing
Ambrisentan (selective endothelin EtA receptor antagonist)	Target dose ranges from 1.25 to 10 mg daily; use ½ dose for first mo	Flushing, headache, hypotension, fluid retention/edema, nasopharyngitis/congestion, vomiting; teratogenicity risk
Bosentan (nonselective endothelin receptor EtA and EtB antagonist)	Starting dose: 0.3-1 mg/kg/dose twice daily PO for first mo For patients <10 kg: max. 2 mg/kg/dose twice daily; 10-20 kg: max. 2 mg/kg/dose twice daily (32 mg tablets); 20-40 kg: 62.5 mg/dose twice daily; >40 kg: 125 mg/dose twice daily	Flushing, headache, hypotension, nasopharyngitis/congestion, fluid retention, edema, vomiting, anemia, elevated transaminases (monthly LFTs required); teratogenicity risk. Caution in concomitant use of CYP3A4 inducers and inhibitors
Macitentan (nonselective endothelin receptor EtA and EtB antagonist)	5-10 mg daily PO; limited data in children	Flushing, headache, fluid retention/edema, anemia, nasopharyngitis/congestion; teratogenicity risk.
Sildenafil (phosphodiesterase type 5 inhibitor)	0.5-1 mg/kg/dose given 3-4 times daily PO For 10-20 kg, use 10 mg 3 times daily; >20 kg, 20 mg 3 times daily Initial dosing should be ½ final target dose to evaluate for hypotension	Flushing, headache, dyspepsia, diarrhea, hypotension, priapism, visual disturbance (blue coloration), tinnitus
Tadalafil (phosphodiesterase type 5 inhibitor)	1 mg/kg/dose given daily PO Maximum adult dose 40 mg daily Initial dosing should be ½ final target dose to evaluate for hypotension	Similar to sildenafil
Riociguat (soluble guanylate cyclase stimulator)	Limited pediatric data Starting adult dose 1 mg tid, can increase to maximum 2.5 mg tid	Hypotension, headache, dizziness, dyspepsia Use with PDE5 inhibitors contraindicated
Calcium channel blockers (amlodipine, diltiazem, nifedipine)	Previously widely used, now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization	Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated LFTs

*Modified as compared with the Nice 2013 classification.
Note: These medications should only be administered under the direction of a specialist in pulmonary hypertension.
cGMP, Cyclic guanosine monophosphate; IV, Intravenously; LFT, liver function test; SC, subcutaneously.

especially in those with restrictive cardiomyopathy (see Chapter 488.3). Pulmonary vascular disease can also occur in any patient with transmission of systemic pressure to the pulmonary circulation via a shunt at the interventricular or great vessel level and in patients chronically exposed to low partial pressure of oxygen (because of high altitude). Patients with cyanotic congenital heart lesions associated with unrestricted pulmonary blood flow are at particularly high risk.

CLINICAL MANIFESTATIONS

Symptoms do not usually develop until the second or third decade of life, although a more fulminant course may occur. Intracardiac or extracardiac communications that would normally shunt from left to right are converted to right-to-left shunting as PVR exceeds systemic vascular resistance. Cyanosis becomes apparent, and dyspnea, fatigue, and a tendency toward dysrhythmias begin to occur. In the late stages of the disease, heart failure, chest pain, headaches,

syncope, and hemoptysis may be seen. Physical examination reveals a right ventricular heave and a narrowly split S_2 with a loud pulmonic component. Palpable pulmonary artery pulsation may be present at the left upper sternal border. A holosystolic murmur of tricuspid regurgitation may be audible along the left sternal border. An early decrescendo diastolic murmur of pulmonary insufficiency may also be heard along the left sternal border. The degree of cyanosis depends on the stage of the disease. Clubbing of the distal digits may be seen in late disease as a result of chronic hypoxia.

DIAGNOSIS

On chest radiograph, the heart varies in size from normal to greatly enlarged; the latter usually occurs late in the course of the disease. The main pulmonary artery is generally prominent, similar to other causes of PAH (see Fig. 482.2A). The pulmonary vessels are enlarged in the hilar areas and taper rapidly in caliber in the peripheral branches. The right ventricle and atrium are prominent. The ECG shows marked RVH. The P wave may be tall and spiked. Cyanotic patients have various degrees of polycythemia that depend on the severity and duration of hypoxemia.

The echocardiogram shows a thick-walled right ventricle and demonstrates the underlying congenital heart lesion. 2D echocardiography assists in eliminating from consideration lesions such as obstructed pulmonary veins, supramitral membrane, mitral stenosis, and restrictive cardiomyopathy. Doppler studies demonstrate the direction of the intracardiac shunt and the presence of a typical hypertension waveform in the main pulmonary artery. Tricuspid and pulmonary regurgitation can be used in the Doppler examination to estimate pulmonary artery systolic and diastolic pressures.

Cardiac catheterization usually shows a bidirectional shunt at the site of the defect. Systolic pressure is generally equal in the systemic and pulmonary circulations. Pulmonary capillary wedge pressure is normal unless a left-sided heart obstructive lesion or left ventricular failure is the cause of the PAH. Arterial oxygen-hemoglobin saturation is decreased depending on the magnitude of the right-to-left shunt. The response to vasodilator therapy (oxygen, prostacyclin, nitric oxide) may identify patients with less severe disease. Selective pulmonary artery injections may be necessary if pulmonary venous obstruction is suspected because of high wedge pressure and low LVEDP.

TREATMENT

The best management for patients who are at risk for the development of late pulmonary vascular disease is prevention by early surgical elimination of large intracardiac or great vessel communications during infancy. Some patients may be missed because they have not shown early clinical manifestations. Rarely, PVR never decreases at birth in these infants, and therefore they never acquire enough left-to-right shunting to become clinically apparent. Such delayed recognition is a particular risk in patients with congenital heart disease who live at high altitude. It is also a risk in infants with trisomy 21, who have a propensity for earlier development of pulmonary vascular disease. Because of the high incidence of congenital heart disease associated with trisomy 21, routine echocardiography is recommended at the time of initial diagnosis, even in the absence of other clinical findings.

Medical treatment of Eisenmenger syndrome is primarily symptomatic. Many patients benefit substantially from either oral **(CCBs, endothelin antagonist**, **phosphodiesterase inhibitors)** or chronic continuous intravenous **(prostacyclin)** therapy. Combined heart-lung or bilateral lung transplantation is the only surgical option for many of these patients (see Chapter 492.2). Heart-lung transplantation may be the option if there is associated complex congenital heart disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 483

General Principles of Treatment of Congenital Heart Disease

Daniel Bernstein

Most patients who have minor congenital heart lesions do not require treatment. The parents and child should be made aware that a normal life is expected and that no restriction of the child's activities is necessary. Overprotective parents may use the presence of a minor congenital heart lesion or even a functional heart murmur as a means to exert excessive control over their child's activities. Although fears may not be expressed overtly, the child may become anxious regarding early death or debilitation, especially when an adult member of the family acquires unrelated symptomatic heart disease. The family may have an unexpressed fear of sudden death, and the rarity of this manifestation should be emphasized in discussions directed at improving their understanding of the child's congenital heart defect. General health maintenance, including a well-balanced "heart-healthy" diet, aerobic exercise, and avoidance of smoking, should be encouraged.

Even patients with moderate to severe congenital heart disease (CHD) need not be restricted from all physical activity, although many will tend to limit their own activities. Physical education should be modified appropriately to the child's capacity to participate; the extent of such modification can be guided by formal exercise testing in an appropriately equipped pediatric exercise laboratory. Although competitive sports for some patients may need to be discouraged, decisions are made on an individual basis. The influence of coach and peer pressure should be considered when recommending competitive vs noncompetitive athletics. Many cardiologists will also prohibit certain high-impact activities ("collision sports") such as tackle football or contact martial arts in patients who have had prior open heart surgery.

Routine immunizations should be given, with the inclusion of influenza vaccine during the appropriate season. Vaccination against the SARS-CoV-2 virus has been recommended for children with heart disease who are eligible based on age. Prophylaxis against respiratory syncytial virus (RSV) is recommended during RSV season in young infants with unrepaired CHD and significant hemodynamic abnormalities or in those with cardiomyopathy and heart failure. Careful consideration of the timing of administration of live-virus vaccination is required in patients who are potential candidates for heart or heart-lung transplantation, and these patients cannot receive live-virus vaccines after they have received their transplant.

Bacterial infections should be treated vigorously. **Prophylaxis against bacterial endocarditis** should be carried out during dental procedures for appropriate patients (see Chapter 486).

Cyanotic patients need to be monitored for noncardiac manifestations of oxygen deficiency (Table 483.1); however, it is rare today for a patient to remain significantly cyanotic beyond the first few years of life, although mild degrees of cyanosis may be seen in patients with a single ventricle (e.g., hypoplastic left heart) who have a fenestration in their Fontan conduits allowing right-to-left shunting. These patients should be carefully observed for excessive **polycythemia**. Cyanotic patients should avoid situations where dehydration may occur, which leads to increased viscosity and increases the risk of stroke. Diuretics may need to be decreased or temporarily discontinued during episodes of acute gastroenteritis or during excessively hot weather. High altitudes and sudden changes in the thermal environment should also be avoided. Treatment of iron deficiency is important in cyanotic patients, who

Table 483.1 Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

PROBLEM	ETIOLOGY	THERAPY
Polycythemia	Persistent hypoxia	Phlebotomy if symptomatic
Relative anemia	Nutritional deficiency	Iron replacement
CNS abscess	Right-to-left shunting	Antibiotics, drainage
CNS thromboembolic stroke	Right-to-left shunting or polycythemia	Anticoagulation, phlebotomy
Low-grade DIC, thrombocytopenia	Polycythemia	None for DIC unless bleeding, then phlebotomy
Hemoptysis	Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion	Embolization
Plastic bronchitis	Fontan procedure	Bronchoscopy, vascular coiling, lymphatic ablation
Gum disease	Polycythemia, gingivitis, bleeding	Dental hygiene
Gout	Polycythemia, diuretic agent	Allopurinol
Arthritis, clubbing	Hypoxic osteoarthropathy	None
Pregnancy complications: miscarriage, fetal growth retardation, prematurity increase, maternal illness	Poor placental perfusion, poor ability to increase cardiac output	Pregnancy prevention counseling, high-risk obstetric management
Infections	Associated asplenia, DiGeorge syndrome, endocarditis	Antibiotics
	Fatal RSV pneumonia with pulmonary hypertension	RSV monoclonal antibodies* (prevention)
Failure to thrive	Increased oxygen consumption, decreased nutrient intake	Treat heart failure; correct defect early; increase caloric intake
Protein-losing enteropathy	s/p Fontan; high right-sided pressures	Oral budesonide or sildenafil
Chylothorax	Injury to thoracic duct	Medium-chain triglyceride diet Octreotide Surgical ligation of thoracic duct
Neurodevelopmental disabilities	Chronic hypoxia, cardiac surgery, genetic	Early school-based evaluation and intervention
Psychosocial adjustment	Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations	Counseling

*Palivizumab, nirsevimab.
CNS, Central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; s/p, status post (after).

may have a low mean corpuscular hemoglobin concentration despite polycythemia. The risk of stroke for these patients can be reduced if the red blood cells are not microcytic. Phlebotomy with partial exchange transfusion is carried out only in symptomatic patients with severe polycythemia (usually those with hematocrit >65%).

Patients with moderate to severe forms of CHD or a history of rhythm disturbance should be carefully monitored during anesthesia for even routine surgical or dental procedures. Consultation with an anesthesiologist experienced in the care of children with CHD is recommended even if the surgical procedure is not cardiac related.

Females with unrepaired severe CHD should be counseled on the risks associated with childbearing and on the use of contraceptives and other methods to prevent pregnancy (see Chapter 483.1). Females with mild to moderate CHD and many who have had corrective surgery can have normal pregnancies, although those with residual hemodynamic derangements or with systemic right ventricles (RVs) should be followed by a high-risk perinatologist and a cardiologist with expertise in caring for adults with CHD. Pregnancy may be highly dangerous to both mother and fetus for patients with palliated (rather than repaired) complex CHD, chronic cyanosis, or pulmonary arterial hypertension; for patients with a Fontan circulation, the miscarriage rate has been reported as ranging from 27% to 50% and the rate of prematurity at 69%. Risks to the mother include heart failure, thromboembolism, and arrhythmia. Several risk stratification schemes have been developed for pregnant women with CHD, including the Cardiac Disease in Pregnancy **(CARPREG)** score, the Zwangerschap bij Aangeboren HARtAfwijkingen **(ZAHARA)** score, and the World Health Organization (WHO) classification. Based on the WHO system, patients for whom pregnancy is associated with increased risk of mortality or morbidity include those with a systemic RV (e.g., corrected transposition with good function), Fontan circulation, repaired coarctation of the aorta bicuspid aortic valve with enlarged aortic root of 45-50 mm, **Marfan syndrome** with enlarged aortic root of 40-45 mm, atrioventricular septal defects, moderate mitral stenosis, severe aortic stenosis, and mechanical valve replacement. Patients for whom pregnancy is considered contraindicated include those with pulmonary arterial hypertension, Ehlers-Danlos syndrome, severe recoarctation of the aorta, Fontan circulation with any complications, severe aortic or mitral stenosis, severe aortic dilation, and systemic ventricular dysfunction with ejection fraction <30%.

POSTOPERATIVE MANAGEMENT

After successful open heart surgery, the severity of the congenital heart defect, the age and condition (nutritional status) of the patient before surgery, the events in the operating room (OR), and the quality of the postoperative care influence the patient's course. **Intraoperative** factors that influence survival and that should be noted when a patient returns from the OR include the duration of **cardiopulmonary bypass** (CPB), duration of **aortic cross-clamping** (time the heart is not being perfused), and duration of **profound hypothermia** (used in some newborns; time the entire body is not being perfused). Surgical techniques to provide ongoing perfusion to the upper body and brain even during surgery on the aortic arch (e.g., in hypoplastic left heart syndrome [HLHS]) have eliminated the use of profound hypothermia in many centers.

Immediate postoperative care should be provided in an intensive care unit (ICU) staffed by a team of physicians, nurses, and technicians experienced with the unique problems encountered after open heart surgery in childhood. In most major centers, this occurs in a dedicated pediatric cardiovascular ICU. Preparation for postoperative monitoring begins in the OR, where the anesthesiologist or surgeon places an arterial catheter to allow direct arterial pressure measurements and arterial sampling for blood gas determination. A central venous catheter is also placed for measuring central venous pressure and for infusions of cardioactive medications. In more complex cases, right or left atrial or pulmonary artery catheters may be inserted directly into these cardiac structures and used for pressure monitoring purposes. Temporary pacing wires are placed on the atrium or ventricle, or both, in case temporary postoperative heart block occurs. Transcutaneous oximetry provides for continuous monitoring of arterial oxygen saturation. Near-infrared spectroscopy is used to monitor cerebral and other end-organ perfusion in the perioperative period.

Functional failure of one organ system may cause profound physiologic and biochemical changes in another. Respiratory insufficiency, for example, leads to hypoxia, hypercapnia, and acidosis, which in turn compromise cardiac, vascular, and renal function. The latter problems cannot be managed successfully until adequate ventilation is reestablished. Thus it is essential that the primary source of each postoperative problem be identified and treated.

Respiratory failure is a serious postoperative complication encountered after open heart surgery. CPB performed in the presence of pulmonary congestion results in decreased lung compliance, copious tracheal and bronchial secretions, atelectasis, and increased breathing effort. Because fatigue and subsequently hypoventilation and acidosis may rapidly ensue, mechanical positive pressure endotracheal ventilation is usually continued after open heart surgery for a minimum of several hours in relatively stable patients and for up to 2-3 days or longer in severely ill patients, especially infants. Protocols for early extubation have been successfully used in older children with uncomplicated intraoperative courses. Patients with certain congenital heart lesions, particularly those with **DiGeorge syndrome**, may also have airway abnormalities (micrognathia, tracheomalacia, bronchomalacia) that can make both ventilation and extubation more difficult.

The electrocardiogram (ECG) should be monitored continuously during the postoperative period. A change in heart rate, even without arrhythmia, may be the first indication of a serious complication such as hemorrhage, hypothermia, hypoventilation, or heart failure. **Cardiac rhythm disorders** must be diagnosed quickly because a prolonged untreated arrhythmia may add a severe hemodynamic burden to the heart in the critical early postoperative period (see Chapter 484). Injury to the heart's conduction system during surgery can result in postoperative complete heart block. This complication is usually temporary and is treated with surgically placed pacing wires that can later be removed. Occasionally, complete heart block is permanent. If heart block persists beyond 10-14 days postoperatively, insertion of a permanent pacemaker is required. Tachyarrhythmias are a common problem in postoperative patients. Junctional ectopic tachycardia (JET) can be a particularly troublesome rhythm to manage, although it usually responds to antiarrhythmic medications such as intravenous amiodarone.

Heart failure with poor cardiac output after cardiac surgery may be secondary to respiratory failure, serious arrhythmias, myocardial injury, blood loss, hypovolemia, a significant residual hemodynamic abnormality, or any combination of these factors. Treatment specific to the cause should be instituted. Catecholamines, phosphodiesterase inhibitors, nitroprusside and other afterload-reducing agents, and diuretics are the cardioactive agents most often used in patients with myocardial dysfunction in the early postoperative period (see Chapter 491). Postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide (iNO). In the rare patients who are unresponsive to standard pharmacologic treatment, various ventricular assist devices are available, depending on the patient's size. If pulmonary function is adequate, a **left ventricular assist device (LVAD)** may be used. If pulmonary function is inadequate, **biventricular assist devices (BVAD)** or **extracorporeal membrane oxygenation (ECMO)** may be used. These extraordinary measures are helpful in maintaining the circulation until cardiac function improves, usually within 2-5 days. They have also been used as a bridge to transplantation in patients with severe nonremitting postoperative cardiac failure.

Acidosis secondary to low cardiac output, renal failure, or hypovolemia must be prevented or, if present, promptly corrected. Serial monitoring of arterial blood gases (ABGs) and lactate concentrations is performed. A low arterial pH may be a sign of decreased perfusion, and acidosis can worsen cardiac function and may be the forerunner of arrhythmias or cardiac arrest.

Renal function may be compromised by congestive heart failure and further impaired by prolonged CPB. Blood and fluid replacement, cardiac inotropic agents, and vasodilators will usually reestablish normal urine flow in patients with hypovolemia or cardiac failure. Renal failure secondary to tubular injury contributes to postoperative fluid overload and may require temporary peritoneal or hemodialysis or hemofiltration. With attention paid to renal injury during the perioperative period, the incidence and severity of chronic renal failure can be reduced.

Neurologic abnormalities can develop after CPB, especially in the neonatal period. Seizures may occur when the patient awakens from sedation and can usually be controlled with anticonvulsant medications. In the absence of other neurologic signs, self-limited isolated seizures in the immediate postoperative period usually carry a good long-term prognosis. Thromboembolism and stroke are rarer but serious complications of open heart surgery. In the long term, both subtle and more substantial learning disabilities may develop. Patients who have undergone surgery entailing CPB, especially in the newborn period, should be watched carefully during their early school years for signs of mild to moderate learning disabilities or attention deficit disorders, which are often amenable to early remedial intervention. The risk is higher in patients who have undergone repair using hypothermic total circulatory arrest than in those where systemic blood flow is maintained using CPB. With the increased recognition of the genetic link between CHD and moderate or greater neurodevelopmental delay, many of these cases may have multifactorial etiologies.

Postpericardiotomy syndrome may occur toward the end of the first postoperative week or may sometimes be delayed until weeks or months after surgery (Table 483.2). This febrile illness is characterized by fever, decreased appetite, listlessness, nausea, and vomiting. Chest pain is not always present, so a high index of suspicion should be maintained in any recently postoperative patient. Echocardiography is diagnostic. In most instances, postpericardiotomy syndrome is self-limited; when pericardial fluid accumulates rapidly, the potential danger of cardiac tamponade should be recognized (see Chapter 489).

Table 483.2 Postpericardiotomy Syndrome (PPS) Findings

FINDING	PERCENTAGE
SYMPTOMS	
Pleuritic or pericarditic chest pain	>50
Intermittent, low-grade fever	~50
CLINICAL FINDINGS	
Pericardial friction rub	20–30
Elevated C-reactive protein (CRP)	80–90
Elevated erythrocyte sedimentation rate (ESR)	80–90
Leukocytosis	80–90
Electrocardiogram (ECG): low voltage of the QRS, T-wave inversion, ST elevation or depression	~50
IMAGING	
Chest x-ray: pleural effusion	>90
Heart echocardiography: pericardial effusion	~90
Mild (<10 mm)	~75*
Moderate (10-20 mm)	~10*
Large (>20 mm)	~5
Pleuropericardial involvement	>80

*Of all PPS patients

From Lehto J, Kiviniemi T. Postpericardiotomy syndrome after cardiac surgery. *Ann Med.* 2020;52(6):243–264, Table 1.

Rarely, arrhythmias may also occur. Symptomatic patients usually respond to salicylates, indomethacin, or colchicine and bed rest. Occasionally, corticosteroid therapy or pericardiocentesis is required. Late recurrences are rare and can lead to chronic pericarditis.

Hemolysis of mechanical origin is seen, although rarely, after repair of certain cardiac defects, for example, atrioventricular septal defects (AVSDs), or after the insertion of a mechanical prosthetic valve. It is caused by unusual turbulence of blood at increased pressure. Reoperation may be necessary in rare patients with severe and progressive hemolysis who require frequent blood transfusions, but in most cases the problem slowly regresses.

Infection is another potentially serious postoperative problem. Patients usually receive a broad-spectrum antibiotic for the initial postoperative period. Potential sites of infection include the lungs (generally related to postoperative atelectasis), the subcutaneous tissues at the incision site, the sternum, and the urinary tract (especially after an indwelling catheter has been in place). Sepsis with infective endocarditis is an infrequent complication and can be difficult to manage, especially if prosthetic material was placed at surgery (see Chapter 486). Patients who undergo CPB during a viral infection, even if mild, can develop severe complications; therefore many anesthesiologists will postpone elective surgery if a child presents with a viral infection, either upper respiratory or gastrointestinal.

INTERSTAGE MANAGEMENT

One group of infants at particularly high risk for both morbidity and mortality are those who have completed their first-stage **Norwood** or **Sano** palliation for HLHS and are awaiting the next stage **(Glenn shunt)** of their three-stage palliation. Mortality in this group of infants had been reported as high as 10–15%, motivating the National Pediatric Cardiology Quality Improvement Collaborative **(NPC-QIC)** to develop an **interstage home monitoring program** that has been successful in reducing interstage mortality by 44%.

LONG-TERM MANAGEMENT

Patients who have undergone surgery for CHD can be divided into three major categories: lesions for which total repair has been achieved; lesions for which both anatomic and physiologic corrections have been achieved; and lesions for which only palliation, although potentially long term, has been achieved. There is some disagreement among cardiologists as to exactly in which category a particular congenital heart lesion might fall, and to some degree every case should be considered individually. Many argue that only for isolated patent ductus arteriosus (PDA) is total repair really achieved, with no requirement for long-term follow-up. Patients who are able to undergo anatomic and physiologic correction include many of the left-to-right shunt lesions (atrial and ventricular septal defects) and milder forms of obstructive lesions (e.g., valvar pulmonic stenosis, some forms of valvar aortic stenosis, coarctation of aorta) and some forms of cyanotic heart disease (e.g., uncomplicated tetralogy of Fallot, simple transposition of great arteries). These patients usually have achieved total or near-total physiologic correction of their lesion; however, they are still at some risk of long-term sequelae, including late heart failure or arrhythmia, or recurrence of a significant physiologic abnormality (e.g., recoarctation of aorta, worsening mitral regurgitation in patients with AVSDs, long-standing pulmonary regurgitation in patients with tetralogy of Fallot repaired with transannular patch). These patients require regular follow-up with a pediatric cardiologist (and, when old enough, with an **adult congenital heart disease specialist**; see Chapter 483.1); however, their long-term prognosis is generally very good, although some will require repeat surgeries or catheter-based interventions. Patients with more complex lesions, such as those with single-ventricle physiology (e.g., hypoplastic left or right heart syndrome), are at much higher risk of long-term sequelae and require even closer follow-up. These patients, particularly those who have undergone the Fontan procedure, are at risk long-term for arrhythmia, thrombosis, protein-losing enteropathy, plastic bronchitis, hepatic dysfunction (Fontan-associated liver disease or FALD), renal dysfunction, and heart failure. Some may eventually require heart, heart-liver, or heart-kidney transplantation.

Physical limitations in patients with CHD are variable, ranging from minimal to none in patients with physiologic correction to mild to moderate in patients with palliative procedures. The extent to which a patient should be allowed to participate in athletics, both recreational and competitive, can best be determined by the cardiologist, often with formal cardiopulmonary exercise testing (see Chapter 472.5).

Long-term morbidities affecting neurologic function and behavior are influenced by many factors, including the effects of any genetic alterations on the developing central nervous system (CNS). There may be a greater role for prenatal CNS abnormalities (anatomic, genetic, or secondary lesions caused by alterations in fetal cerebral blood flow or oxygenation); these include microcephaly, cerebral atrophy, and altered cerebral biochemistry. Chronic hypoxemia and failure to thrive may also influence the developing brain, and there is evidence that the type of intervention required (CPB, hypothermic total circulatory arrest, catheter-based therapy) plays a substantial role. Data from the **Pediatric Cardiac Genomics Consortium** have shown that there is also a genetic component to these learning disabilities. Performing exome sequencing on patients and their parents (trios), de novo gene variants were found in 2% of patients with CHD but in 20% of patients with CHD and neurodevelopmental delay. The identity of these gene variants and their mechanism of action is under study. In general, in the absence of a significant genetic syndrome or major perioperative complication, most children function at a fairly high level after repair of congenital heart defects and are able to attend regular school. Group mean scores on standard cognitive tests are no different from the general population; however, some areas appear to be more at risk than others, including certain aspects of motor function, speech, visual-motor tracking, and phonologic awareness. Awareness of these potential issues is critical to obtaining prompt remedial assistance if a child is found to be struggling in school.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

483.1 Congenital Heart Disease in Adults

Salil Ginde and Michael G. Earing

Approximately 90% of children with CHD survive to adulthood. More adults than children are living with CHD in the United States, with a 5% increase every year. In the past decade, 35% of hospitalizations for CHD were patients older than 18 years (mean age: 55 years).

LONG-TERM MEDICAL CONSIDERATIONS

Approximately 25% of adults with CHD have a mild form that has allowed them to survive into adulthood without surgical or interventional cardiac catheterization. The most common lesions in this category include mild aortic valve stenosis (usually in the setting of a bicuspid aortic valve), small restrictive ventricular septal defects (VSDs), mild pulmonary valve stenosis, and mitral valve prolapse (Table 483.3). These patients need less frequent follow-up to assess for progression of disease and to identify associated complications. Many adults with CHD living in the United States are patients who have had previous intervention (Table 483.4). Although most children who undergo surgical intervention will survive to adulthood, with few exceptions, *total correction is not the rule.* The few exceptions include PDA, VSDs, and atrial septal defects (ASDs); this is true only if they are closed early, before the development of irreversible pulmonary vascular changes, and if no residual lesions exist.

It has become apparent that even the simplest congenital heart lesions can be associated with long-term complications, including both cardiac and noncardiac problems (Tables 483.5 and 483.6 and Fig. 483.1). *Cardiac* complications include arrhythmias and conduction defects, ventricular dysfunction, residual shunts, valvular lesions (regurgitation and stenosis), hypertension, and aneurysms. *Noncardiac* sequelae **(comorbidities)** include pulmonary, renal, and hepatic dysfunction that is caused either directly or indirectly by the underlying CHD. Abnormal pulmonary function most often presents as restrictive lung physiology and likely results

Table 483.3 Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization

Mild pulmonary valve stenosis
Bicuspid aortic valve
Small to moderate-sized atrial septal defect
Small ventricular septal defect
Small patent ductus arteriosus
Mitral valve prolapse
Partial atrioventricular canal (ostium primum atrial septal defect and cleft mitral valve)
Marfan syndrome
Ebstein anomaly
Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)

Table 483.4 Most Common Congenital Heart Defects in Patients Surviving to Adulthood After Surgery or Interventional Catheterization

Aortic valve disease after balloon valvuloplasty or surgical valvotomy
Pulmonary valve stenosis after balloon valvuloplasty or surgical valvotomy
Tetralogy of Fallot
Ventricular septal defect
Complete atrioventricular canal defect
Transposition of the great arteries
Coarctation of the aorta
Complex single ventricles after the modified Fontan procedure

Table 483.5 Risks in Adults Who Have Congenital Heart Disease

RHYTHM DISORDERS
Supraventricular tachycardia (including atrial fibrillation)
Right bundle branch block
Heart block
Ventricular tachycardia
Sudden death
COARCTATION OF AORTA
Essential hypertension
Recoarctation
Aneurysm formation
RESIDUAL LESIONS (SHUNTS)
Ventral septal defect
Atrial septal defect
Patent ductus arteriosus
ACQUIRED LESIONS
Subacute bacterial endocarditis
Subvalvular stenosis
Supravalvular stenosis
Valvular insufficiency
Valvular restenosis
Eisenmenger complex
PREGNANCY RISK
See Figs. 483.2 and 483.3

Table 483.6 Adolescent Transition Issues Requiring Coordination of Patient Care Between the Cardiologist and Primary Care Physician

Antibiotic prophylaxis for endocarditis
Medications and drug interactions
Anticoagulation with prosthetic valves
Exercise and sports participation
Educational and vocational planning
Contraception and pregnancy
Drug, alcohol, and tobacco use
Noncardiac surgical planning
Anesthetic issues
New symptoms or acute illnesses
Comorbid conditions
Travel

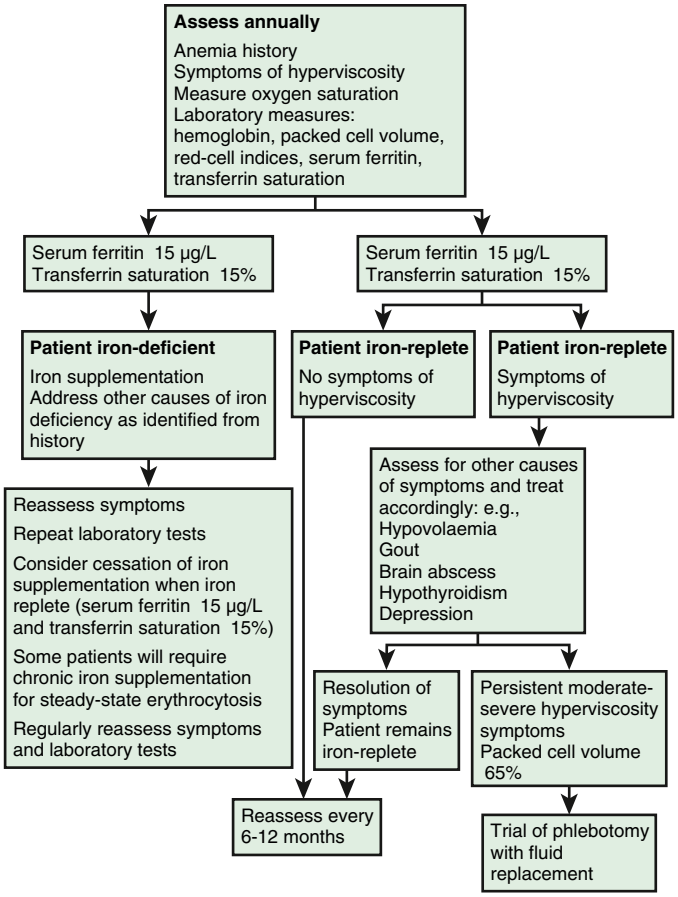

Fig. 483.1 Algorithm detailing crucial issues to address at transition to adulthood in patients with cyanotic congenital heart disease. *(From Spence MS, Balaratnam MS, Gatzoulis MA. Clinical update: cyanotic adult congenital heart disease. Lancet. 2007;370:1531.)*

from prior sternotomy or thoracotomy, scoliosis, diaphragmatic dysfunction, or parenchymal lung disease. Reduced pulmonary function contributes to reduced exercise tolerance and is a risk factor for mortality in adults with CHD. Renal dysfunction may result from chronic cyanosis, multiple surgeries requiring CPB, or from other comorbid conditions, such as hypertension and diabetes mellitus. Hepatic injury from chronic liver congestion in patients with elevated central venous pressures, particularly patients palliated with the Fontan procedure, can result in hepatic fibrosis, cirrhosis, hepatic dysfunction, and rarely, hepatocellular carcinoma. Adults with CHD are at risk for developmental abnormalities such as intellectual impairment, somatic abnormalities such as facial dysmorphism (cleft palate/lip), CNS abnormalities such as seizure disorders from previous thromboembolic events or cerebrovascular accidents, and impairments of hearing or vision loss. Psychosocial problems involving employment, life and health insurance, participation in sports, sexual activity, and contraception are common. Mental health issues, such as anxiety and depression, are common in adults with CHD and are often underrecognized and significantly affect quality of life. As a result of these long-term complications, the majority of adults with CHD need lifelong follow-up, ideally in an integrated, collaborative, and multidisciplinary program. When adults with CHD are hospitalized, it is usually for heart failure or an arrhythmia; others may require catheterization or another cardiac surgical procedure.

SPECIFIC LESIONS

Left-to-Right Shunts

In general, the long-term outcomes of adults with a history of shunt lesions that underwent repair early in life are good with near-normal life expectancy and relatively low risk for cardiac complications. However, if the initial lesion has a shunt that is large and nonrestrictive (allowing transmission of near-systemic pressure to the pulmonary arteries) and is unrepaired, irreversible pulmonary vascular changes can occur, resulting in pulmonary hypertension at systemic levels with reversed or bidirectional shunting at the level of the defect (**Eisenmenger syndrome**; see Chapter 482.2).

Atrial Septal Defects

See Chapter 475.1.

Although most individuals with an ASD are diagnosed during childhood after a murmur is noted, a minority of patients present with symptoms for the first time as adults. Most patients are asymptomatic during the first and second decades of life. In the third decade, an increasing number of patients then develop exercise intolerance, palpitations from atrial arrhythmias, and cardiac enlargement. If untreated, survival into adulthood is the rule; life expectancy is reduced, however, and there is significant long-term morbidity. After age 40 the mortality rate increases by 6% per year, and >20% of patients will have developed atrial fibrillation (AF). By age 60 the number of patients with AF increases to >60%.

Late Outcome After Closure of Atrial Septal Defect

Most patients who have undergone early ASD closure will have excellent long-term survival with low morbidity if repair is undertaken before age 25 years. Older age at repair is associated with decreased late survival with an associated increased risk for the development of atrial arrhythmias, thromboembolic events, and pulmonary hypertension. Long-term late complications and survival after transcatheter device closure remain unknown; early and intermediate results are excellent, with a high rate of ASD closure and few major complications.

Ventricular Septal Defects

See Chapter 475.6.

Although isolated VSDs are among the most common forms of CHD, the diagnosis of a VSD in an adult is rare. The primary reason is that most patients with a hemodynamically significant VSD will have undergone repair in childhood or will have died earlier in life. As result, the spectrum of isolated VSD in adults is limited to (1) those with small restrictive defects, (2) those with Eisenmenger syndrome, and (3) those who had their defects closed in childhood.

For patients with **small restrictive VSD**, long-term survival is excellent, with estimated 25-year survival of 96%. In addition, the long-term morbidity for patients with a restrictive VSD also appears to be low. Their clinical course is not completely benign. Reported long-term complications include endocarditis, progressive aortic regurgitation secondary to prolapse of the aortic valve into the defect (highest risk is with supracristal type but also can occur in setting of perimembranous defect), and the development of both right and left outflow tract obstruction from a double-chamber RV or a subaortic membrane. For patients who develop **Eisenmenger syndrome**, survival into the third decade is common. With increasing age, the long-term complications of right-sided heart failure, paradoxical emboli, and polycythemia usually result in progressive decline in survival, with death at an average age of 37 years.

Adults with **previous VSD closure**, without pulmonary hypertension or residual defects, live a normal life expectancy. Because patients with small VSDs are asymptomatic, these patients should be managed conservatively. Given the long-term risks, they do need intermittent follow-up for life to monitor for the development of late complications. The exception to this rule is patients with small supracristal or perimembranous VSD with associated prolapse of the aortic cusp into the defect resulting in progressive aortic regurgitation. These patients should be considered for surgical repair at diagnosis to prevent progressive aortic valve damage.

Complete Atrioventricular Canal

See Chapter 475.5.

The natural history for patients with complete AVSD is characterized by the early development of pulmonary vascular disease, leading to irreversible damage often by age 1 year (especially in children with Down syndrome). Thus patients who present in adulthood can be categorized into two groups: those with Eisenmenger syndrome and those who had their defects closed in childhood.

Overall, for those patients who underwent early repair before the development of pulmonary vascular disease, the long-term prognosis is good. The most common long-term complication is **left atrioventricular valve regurgitation**, with approximately 5–10% of patients requiring surgical revision for left atrioventricular valve repair or replacement during follow-up. The second most common long-term complication for this patient group is **subaortic stenosis**, occurring in up to 5% of patients after repair. Other long-term complications include residual atrial- or ventricular-level shunts, complete heart block, atrial and ventricular arrhythmias, and endocarditis.

For patients who have developed Eisenmenger syndrome, all are symptomatic with exertional dyspnea, fatigue, palpitations, edema, and syncope. Survival is similar to other forms of Eisenmenger syndrome, with a mean age at death of 37 years. Strong predictors for death include syncope, age at presentation of symptoms, poor functional class, low oxygen saturation (<85%), elevated serum creatinine and uric acid concentrations, and Down syndrome.

Patients who underwent previous repair and develop significant left atrioventricular valve regurgitation causing symptoms, atrial arrhythmias, or deterioration in ventricular function should undergo elective valve repair or replacement. Those previously repaired patients who develop significant subaortic stenosis (defined as a peak cardiac catheterization or echo gradient of >50 mm Hg) should undergo surgical repair.

Patent Ductus Arteriosus

See Chapter 475.8.

A PDA is usually an isolated lesion in the adult patient. The size of the defect is the primary determinant of clinical course in the adult patient. These clinical courses can be grouped into five main categories: silent PDAs; small, hemodynamically insignificant PDAs; moderate-size PDAs; large PDAs; and previously repaired PDAs.

A **silent** PDA is a tiny defect that cannot be heard by auscultation and is only detected by other means such as echocardiography. Life expectancy is always normal in this population, and the risk for endocarditis is extremely low.

Patients with a **small** PDA have an audible long-ejection or continuous murmur heard best at the left upper sternal border that radiates to the back. In addition, they have normal peripheral pulses. Because there is negligible left-to-right shunting these patients have normal left atrial and left ventricle (LV) size and normal pulmonary artery pressure by echocardiography and chest x-ray film. These patients, like those with silent PDAs, are asymptomatic and live a normal life expectancy. They have a higher risk for endocarditis.

Patients with **moderate-size** PDAs may present during adulthood. These patients often will have wide, bounding peripheral pulses and an audible continuous murmur. These patients all have significant volume overload and develop some degree of left atrial and LV enlargement and some degree of pulmonary hypertension. These patients are symptomatic with dyspnea, palpitations, and heart failure.

Patients with **large** PDAs typically present with signs of severe pulmonary hypertension and Eisenmenger syndrome. By adulthood, the continuous murmur is typically absent and there is differential cyanosis (lower-extremity saturations lower than the right arm saturation). These patients have a similar prognosis as other patients with Eisenmenger syndrome.

Patients who underwent **repair** of a PDA before the development of pulmonary hypertension have a normal life expectancy without restrictions.

All patients with *clinical evidence* of a PDA are at increased risk for endocarditis. As result, all PDAs except for small silent PDAs and those patients with severe irreversible pulmonary hypertension should be considered for closure. Catheter device closure is the preferred method in most centers today. Surgical closure is reserved for patients with PDA too large for device closure or when the anatomy is distorted, as in the setting of a large ductal aneurysm.

Cyanotic Heart Disease

See Chapters 478, 479, and 480.

Unlike the acyanotic forms of CHD, the majority of patients with cyanotic CHD will have had at least one and often several previous interventions before adulthood. The most frequent defects seen in the outpatient adult CHD setting are tetralogy of Fallot, complete transposition of the great arteries (TGA, also known as *d-transposition*), pulmonary valve stenosis, and various forms of functional single ventricles. Other defects include total anomalous pulmonary venous return, truncus arteriosus, and double-outlet RV.

Tetralogy of Fallot

See Chapter 479.1.

In the developed world, the unoperated adult patient with tetralogy of Fallot is a rarity because the majority of patients will have undergone palliation or, more often, repair in childhood. Only 11% of unoperated patients are alive by age 20 and only 3% by age 40.

Late survival after repair of tetralogy of Fallot is excellent. Repair is typically performed at 3-12 months of age and consists of patch closure of the VSD and relief of the pulmonary outflow tract obstruction by patch augmentation of the right ventricular outflow tract, pulmonary valve annulus, or both. Survival rates at age 32 and 35 years have been reported to be 86% and 85%, respectively, compared with 95% in age- and sex-matched controls. Most patients live an unrestricted life. Many patients do develop late symptoms that include exertional dyspnea, palpitations, syncope, and sudden cardiac death. Late complications include endocarditis, aortic regurgitation with or without aortic root dilation (typically caused by damage to the aortic valve during VSD closure or secondary to an intrinsic aortic root abnormality), left ventricular dysfunction (secondary to inadequate myocardial protection during previous repair or chronic LV volume overload caused by long-standing palliative arterial shunts), residual pulmonary valve obstruction, residual pulmonary valve regurgitation, RV dysfunction (as a result of pulmonary regurgitation or pulmonary stenosis), atrial arrhythmias (typically atrial flutter), ventricular arrhythmias, and heart block.

Reintervention is necessary in approximately 10% of patients after reparative surgery at 20-year follow-up. With longer follow-up, the incidence of reintervention continues to increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary valve regurgitation. Pulmonary valve replacement, either surgical or transcatheter, is indicated when severe pulmonary valve regurgitation is associated with RV or LV systolic dysfunction, severe RV dilation, and/or progressive reduction in objective exercise tolerance. Although pulmonary valve replacement is associated with improved functional status, it has not been shown to improve mortality or risk for ventricular arrhythmias and sudden cardiac death in adults with tetralogy of Fallot. Implantable cardioverter defibrillators may be considered in patients with a history of recurrent ventricular arrhythmias or other risk factors such as ventricular dysfunction.

Transposition of the Great Arteries

See Chapter 480.1.

The natural history of patients with unrepaired TGA is so poor that very few patients survive past childhood without intervention. The first definitive operations for TGA was the **atrial switch** procedure, where the systemic and pulmonary venous returns are rerouted in the atrium by constructing baffles. The systemic venous return from the superior and inferior venae cavae is directed through the mitral valve and into the left ventricle (connected to the pulmonary artery). The pulmonary venous return is then directed through the tricuspid valve into the RV (connected to the aorta). The procedure results in physiologic correction and can be performed with low mortality but leave the left as the pulmonary ventricle and the right as the systemic ventricle. Long-term follow-up studies after the *atrial switch* procedure show a small but ongoing attrition rate with numerous other intermediate- and long-term complications. Two specific problems are most concerning: loss of sinus rhythm with development of atrial arrhythmias, occurring in 50% of TGA patients by age 25, and development of systemic ventricular dysfunction, occurring in 50% by age 35. Other long-term complications include endocarditis, baffle leaks, baffle obstruction, tricuspid valve regurgitation, and sinus node dysfunction requiring pacemaker placement.

The **arterial switch** operation is the procedure of choice to treat TGA. The great arteries are transected and reanastomosed to the correct ventricle (LV to aorta, RV to pulmonary artery) with coronary artery transfer. Operative survival after the arterial switch procedure in the current surgical era is very good, with a surgical mortality rate of 2–5%. Long-term data on survival and complications are not available, but intermediate results are promising. Reported intermediate complications include endocarditis, pulmonary outflow tract obstruction (at the supravalvular level or at the takeoff of the peripheral pulmonary arteries), aortic valve regurgitation, and coronary artery compromise (ranging from minor stenosis to complete occlusion).

The **Rastelli operation** represents a third type of repair for TGA, typically when there is associated VSD and pulmonary outflow tract obstruction. This operation involves the creation of an intracardiac baffle that closes the VSD in a way that directs flow from the LV to the aorta. The pulmonary valve is oversewn, and a valved conduit placed between the RV and pulmonary artery. Operative mortality is low, but patients require multiple reoperations for replacement of the pulmonary conduit during long-term follow-up. Other complications include complete heart block and left ventricular outflow tract obstruction.

Because of the high incidence of observed and potential medical problems, all patients who have had atrial, arterial, or Rastelli repair of TGA should have lifelong follow-up by a cardiologist at a center specializing in adult CHD.

Pulmonary Valve Stenosis

See Chapter 476.1.

Most patients with pulmonary valve stenosis are asymptomatic and present with a cardiac murmur. Survival into adult life and the need for intervention, however, are directly correlated to the degree of obstruction. Patients with **trivial** stenosis (defined as a peak gradient <25 mm Hg) followed for 25 years remain asymptomatic and have no significant progression of obstruction over time. For those patients with **moderate** pulmonary valve stenosis (defined as a peak gradient of 25-49 mm Hg), there is an approximately 20% chance of requiring intervention by age 25. For those patients with severe stenosis (defined as a peak gradient >50 mm Hg), the majority ultimately require an intervention, either surgery or balloon valvuloplasty, by age 25.

After surgical valvotomy for isolated pulmonary stenosis, long-term survival is excellent. With longer follow-up, the incidence of late complications and the need for reintervention do increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary regurgitation. Other long-term complications include recurrent atrial arrhythmias, endocarditis, and residual right ventricular outflow tract obstruction.

Patients with **moderate to severe** pulmonary stenosis (defined as a peak gradient >50 mm Hg) should be considered for intervention even in the absence of symptoms. Percutaneous balloon valvuloplasty has been the accepted treatment for patients of all ages. Previously, surgical valvotomy had been the gold standard. Surgical valvotomy is reserved for patients who are unlikely to have successful results from balloon valvuloplasty, such as those with an extremely dysplastic or calcified valve.

Left-Sided Obstructive Lesions

Coarctation of the Aorta

See Chapter 476.6.

The clinical presentation of coarctation of the aorta depends on the severity of obstruction and the associated anomalies. Unrepaired coarctation typically presents with symptoms before adulthood. These symptoms include headaches related to hypertension, leg fatigue or cramps, exercise intolerance, and systemic hypertension (may be asymptomatic). Those untreated patients surviving to adulthood thus typically have only mild coarctation of the aorta. In the era before surgery, without treatment, the mean age of death was 32 years. Causes of death included left ventricular failure, intracranial hemorrhage, endocarditis, aortic rupture/dissection, and premature coronary artery disease (CAD).

After surgical repair, long-term survival is good but is directly correlated with the age at repair, with those repaired after age 14 years having a lower 20-year survival than those who were repaired earlier: 91% vs 79%. With longer follow-up, the incidence of long-term complications

continues to rise. The most common long-term complication is persistent or new systemic hypertension at rest or during exercise. Other long-term complications include aneurysms of the ascending or descending aorta, recoarctation at the site of previous repair, CAD, aortic stenosis or regurgitation (in the setting of an associated bicuspid aortic valve), rupture of an intracranial aneurysm, and endocarditis.

Patients with significant native or residual coarctation of the aorta (symptomatic patients with a peak gradient across the coarctation >20 mm Hg) should be considered for intervention, either surgery or catheter intervention with balloon angioplasty, with or without stent placement. Surgical repair in the adult patient is technically difficult and is associated with high morbidity. Catheter-based intervention is the preferred method in most experienced adult CHD centers.

Aortic Valve Stenosis

See Chapter 476.5.

The natural history of aortic valve stenosis in adults is quite variable but is characterized by progressive stenosis over time. By age 45 years, approximately 50% of bicuspid aortic valves will have some degree of stenosis.

Most patients with aortic valve stenosis are asymptomatic and are diagnosed after a murmur is detected. The severity of obstruction at diagnosis correlates with the pattern of progression. Symptoms are rare until patients have severe aortic valve stenosis (mean gradient by echocardiography >40 mm Hg). Symptoms include chest pain, exertional dyspnea, near-syncope, and syncope. When any of these symptoms is present, the risk of sudden cardiac death is quite high, so surgical intervention is mandated. For patients requiring surgical valvotomy to relieve the stenosis before adulthood, the majority of patients do well. However, at 25-year follow-up, up to 40% of patients will have required a second operation for residual stenosis or regurgitation.

Patients with symptoms and severe aortic valve stenosis should be considered for intervention. Treatment involves manipulating the valve to reduce stenosis. This can be accomplished by balloon dilation of the valve, open surgical valvotomy, or valve replacement. In absence of significant aortic regurgitation, most centers favor balloon dilation or surgical valvotomy for children and young adults who have pliable valves with fusion of commissures. In older adults, aortic valve replacement is the treatment of choice. Typically, surgery is performed for aortic valve replacement in younger adults with congenital aortic valve stenosis; however, transcatheter aortic valve replacement is increasingly commonly performed in older adults who may be higher-risk surgical candidates.

Endocarditis Prophylaxis

See Chapter 486.

Only patients with cardiac conditions associated with the highest risk for adverse outcomes should continue antibiotic prophylaxis before surgery: previous endocarditis, prosthetic valves (biological and mechanical), unrepaired cyanotic CHD, including palliative shunts and conduits, completely repaired congenital heart defects with prosthetic material or device, surgically placed or by catheter intervention during the first 6 months after the procedure, and repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization). Except for the conditions just listed, antibiotic prophylaxis is no longer recommended for other forms of CHD.

PREGNANCY AND CONGENITAL HEART DISEASE

CHD is the most common form of heart disease encountered during pregnancy in developed countries. Heart disease does not preclude a successful pregnancy but increases the risk to both the mother and the baby. During pregnancy, substantial hemodynamic changes occur. The hemodynamic changes in pregnancy result in a steady increase in cardiac output during pregnancy until the 32nd week of gestation, at which time the cardiac output reaches a plateau at 30–50% above the prepregnancy level. At delivery, with uterine contractions, an additional 300-500 mL of blood enters the circulation. This, in conjunction with increased blood pressure and heart rate during labor, increases the cardiac output at delivery to 80% of the prepregnancy level.

Despite these hemodynamic changes, the outcome of pregnancy is favorable in most women with CHD, provided that functional class and systemic ventricular function are good. The WHO modified categorization of risk stratification is shown in Figures 483.2 and 483.3. Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, regardless of functional class. Other contraindications to pregnancy include severe obstructive left-sided lesions (coarctation of the aorta, aortic valve stenosis, mitral valve stenosis, hypertrophic cardiomyopathy), Marfan syndrome with coexisting dilated ascending aorta (defined as >4 cm), persistent cyanosis, and systemic ventricular dysfunction (ejection fraction of ≤40%). The need for full anticoagulation during pregnancy, although not a contraindication, poses an increased risk to both mother and fetus. The relative risks and benefits of the different anticoagulant approaches need to be discussed fully with the mother.

Pregnancy counseling should begin early in adolescence and should be part of the routine cardiac follow-up visit. Counseling should include a discussion about the risk of CHD in the offspring. In the general population, the incidence of CHD is 1%. In the offspring of a mother with CHD, the risk increases to 5–6%. Often the cardiac lesion in the offspring is not the same as that in the mother, except in the case of a syndrome with autosomal dominant inheritance (i.e., Marfan syndrome, hypertrophic cardiomyopathy). Risk stratification should include the specific CHD lesion but also needs to consider the maternal functional class. Although the specific CHD lesion is important, multiple studies demonstrate that the maternal functional class before pregnancy is highly predictive of both maternal and fetal outcomes, with those in the best functional class having the best outcomes. A cardiopulmonary exercise test performed before conception can predict maternal and neonatal outcomes in pregnant women with CHD. A blunted heart rate response to exercise is associated with a higher risk for adverse maternal and neonatal events. It is recommended that women with CHD at higher risk for pregnancy-related complications based on anatomy, functional status, and exercise testing be managed collaboratively during pregnancy by adult CHD cardiologists, obstetricians, and anesthesiologists with specialized experience in adults with CHD.

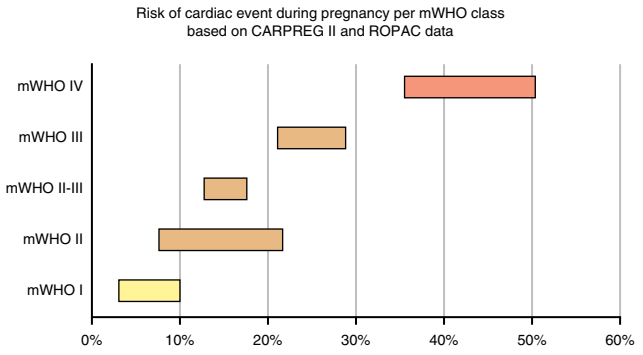

	Predictors of cardiac event during pregnancy	OR in study cohort	Event rate in study cohort
CARPREG II	Prior cardiac event or arrhythmia	5.9	33%
	NYHA III or IV or cyanosis	4.9	46%
	Mechanical valve	4.2	38%
	Ventricular dysfunction	2.3	30%
	High risk left-sided valve disease/left ventricular outflow tract obstruction	2.1	22%
	Pulmonary hypertension	3.3	32%
	Coronary artery disease	3.0	29%
	High risk aortopathy	2.7	18%
	No prior cardiac intervention	1.6	18%
	Late pregnancy assessment	1.6	20%
ZAHARA	Cardiac medication, other than anticoagulation	4.2	26%
	Atrioventricular valve regurgitation	2.0–2.3	17%
ROPAC	Atrial fibrillation at pre-pregnancy visit	5.1	52%
	Signs of heart failure at pre-pregnancy visit	3.3–4.2	63%

Fig. 483.2 Risk tools modified WHO (mWHO), CARdiac disease in PREGnancy (CARPREG), Zwangerschap bij Aangeboren HARtAfwijking (ZAHARA), Registry of Pregnancy and Cardiac disease (ROPAC). ORs and rates are derived from cohorts consisting of approximately 60% of patients with congenital heart disease (63% in CARPREG II and 58% in ROPAC). OR, Odds ratio. *(From van Hagen IM, Roos-Hesselink JW. Pregnancy in congenital heart disease: risk prediction and counselling. Heart. 2020;106:1853–1861, Fig. 1.)*

CONTRACEPTION

A critical part of caring for adults with CHD is to provide (or make available) advice on contraception. Unfortunately, data are limited on the safety of various contraceptive techniques in adult CHD patients. The estrogen-containing oral contraceptives (OCs) can be used in many adult CHD patients but are not recommended in adult CHD patients at risk for thromboembolism, such as those with cyanosis, prior Fontan procedure, AF, or pulmonary artery hypertension. In addition, OCs may disrupt anticoagulation control. Although slightly less effective than OCs containing combined estrogen/progesterone, medroxyprogesterone, the progesterone-only pills, and levonorgestrel are good options for most adult CHD patients. Medroxyprogesterone and levonorgestrel, however, can cause fluid retention and thus need to be used with caution in patients with heart failure. These medications are also associated with depression and often breakthrough bleeding. Tubal ligation, although the most secure method of contraception, can be a high-risk procedure in patients with complex CHD or those with pulmonary hypertension. Hysteroscopic sterilization (Essure) may be reasonable for high-risk patients. In the past, intrauterine devices (IUDs) were seldom used in cardiac patients because of the associated risk of bacteremia, pelvic inflammatory disease, and endocarditis. IUDs such as Mirena appear to be safe and effective and are rapidly becoming one of the most common forms of contraception in the adult CHD population.

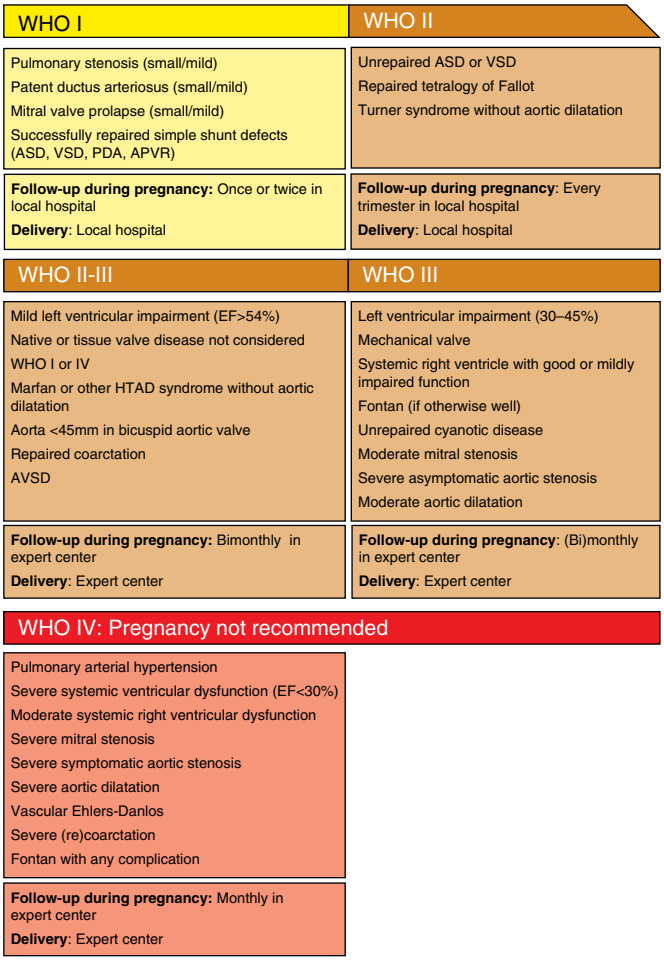

Fig. 483.3 Advised counseling for pregnancy in congenital heart disease. APVR, Anomalous pulmonary venous return; ASD, atrial septal defect; AVSD, atrioventricular septal defect; EF, ejection fraction; ESC, European Society of Cardiology; HTAD, hereditary thoracic aorta disease; PDA, persistent ductus arteriosus; VSD, ventricular septal defect; WHO, World Health Organization. *(From van Hagen IM, Roos-Hesselink JW. Pregnancy in congenital heart disease: risk prediction and counselling. Heart. 2020;106:1853–1861, Fig. 2.)*

ADOLESCENT TRANSITION

It is well recognized that as part of the process of obtaining independence, adolescents or young adults must develop a forward-looking, independent approach to their medical care. For children with heart disease, the transition process must begin during early adolescence and should be encouraged by both the primary care provider and the pediatric cardiologist, who must identify an appropriate adult CHD program to which transition and transfer will be made at an appropriate time (see Table 483.6).

A successful transition program includes the following elements:

- Development of a written transition plan that should begin by age 14 years
- Because adolescents and young adults are frequently unaware of the details of their cardiac diagnosis and history, a complete, concise, portable medical record, including all pertinent aspects of cardiac care, should be shared with adolescents and their family and prepared for transmittal to the eventual adult care destination.
- The primary care provider and cardiologist must address unique adolescent medical issues as they affect the cardiovascular system. In addition to medical problems, education, vocational planning, psychosocial issues, and access to medical care should be discussed with adolescents and their families.

Young adults tend to avoid medical care because of lack of education, denial, or difficulty with access to the medical care system. Thus a critical goal of the adolescent transition process is to identify an appropriate site for ongoing medical care and ensure maintenance of the medical record and continuity of care for the young adult. The site of care for a young adult with CHD may be a pediatric program or facility or a specialized center or program for the adult with CHD. The critical issues are the continuity of care, the preparation of the patient, and the patient's participation in the process.

HEART FAILURE AND TRANSPLANT

Heart failure is increasingly prevalent in adults with CHD and is associated with increased morbidity and mortality. Causes for heart failure in this population include unrepaired or residual valve dysfunction, shunts, arrhythmias, venous obstruction, and systolic and/or diastolic ventricular dysfunction. Data on medical and device therapy to treat heart failure in adults with CHD are limited because of the relatively small study populations and heterogenous heart defects. Concomitant failure of noncardiac organs, such as lung, kidney, and liver failure, is common in adult CHD patients with heart failure and further complicates the management. Currently, management of symptomatic CHD patients with systolic ventricular dysfunction is primarily extrapolated from data in adults with heart failure in the setting of acquired heart disease and includes:

- Medical therapy that includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, aldosterone antagonists, and diuretics
- Electrical device therapies such as implantable cardioverter defibrillators to reduce the risk for sudden cardiac death and permanent pacemaker placement for cardiac resynchronization therapy to improve symptoms of heart failure
- Mechanical circulatory support, such as ventricular assist devices, for patients with severe, refractory heart failure symptoms
- Referral to adult CHD heart failure/transplant specialist and center

Proper timing for heart transplantation in adults with CHD is unclear and may vary for individual lesions. Patients with single ventricle anatomy and complex anatomy often have lower priority with the current transplant allocation system, and therefore often have longer wait times before receiving a heart transplant. Early posttransplant mortality is higher in adults with CHD compared with adults with acquired heart disease because of increased perioperative mortality. However, once beyond the perioperative period, patients with ACHD do as well as or better than those with acquired heart disease, with expected 10-year survival equivalent to or better than that of adults without CHD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Cardiac Arrhythmias

Chapter 484

Disturbances of Rate and Rhythm of the Heart

Aarti S. Dalal and George F. Van Hare

The term *arrhythmia* refers to a disturbance in heart rate or rhythm. Such disturbances can lead to heart rates that are abnormally fast, slow, or irregular. They may be transient or incessant; congenital or acquired; or caused by infection, a toxin, or drugs. They may be associated with particular forms of congenital heart disease (CHD), may be a complication after surgical repair of CHD, may be a result of genetic causes, or may be the result of a maternal connective tissue disease. Arrhythmias, either slow or fast, may lead to acutely decreased cardiac output. If incessant, they may lead to a cardiomyopathy. Initially stable and organized arrhythmias can degenerate into a more dangerous arrhythmia such as ventricular fibrillation. Arrhythmias may lead to syncope or to sudden death (see Chapter 485). When a patient has an arrhythmia, it is important to determine whether the rhythm is likely to lead to symptoms or to deteriorate into a life-threatening condition. Rhythm abnormalities such as single premature atrial and ventricular beats are common, and in children without heart disease, usually pose no risk to the patient.

A number of **pharmacologic agents** are available for treating arrhythmias; many have not been studied extensively in children. Insufficient data are available regarding pharmacokinetics, pharmacodynamics, and efficacy in the pediatric population, and therefore the selection of an appropriate agent is based on the judgement and experience of the clinician. Fortunately, most rhythm disturbances in children can be reliably controlled with a single agent (Table 484.1). **Transcatheter ablation** is acceptable therapy not only for life-threatening or drug-resistant arrhythmias but also for the cure of arrhythmias. For patients with bradycardia, **implantable pacemakers** are small enough for use in all ages, even in premature infants. Implantable cardioverter-defibrillators are available for use in high-risk patients with malignant ventricular arrhythmias and an increased risk of sudden death.

484.1 Principles of Antiarrhythmic Therapy

Aarti S. Dalal and George F. Van Hare

Many antiarrhythmic agents are available for rhythm control. The majority are not approved by the U.S. Food and Drug Administration (FDA) for use in children; their use is therefore considered "off-label." Pediatric cardiologists have experience with these drugs, with well-recognized standards for dosing.

With the availability of potentially curative ablation procedures, medical therapy has become less important. Intolerable drug side effects, as well as the potential for an arrhythmia induced by an antiarrhythmic drug, can seriously limit medical therapy and will lead the physician and family toward a potentially curative ablation procedure.

Antiarrhythmic drugs are frequently categorized using the **Vaughan-Williams classification**. This system comprises four classes: **class I** includes agents that primarily block the sodium channel, **class II** drugs are the β blockers, **class III** includes agents that prolong repolarization by blocking potassium channels, and **class IV** drugs are the calcium channel blockers. Class I is further divided by the strength of the sodium channel blockade (see Table 484.1).

484.2 Sinus Arrhythmias and Extrasystoles

Aarti S. Dalal and George F. Van Hare

Phasic sinus arrhythmia represents a normal physiologic variation in impulse discharges from the sinus node related to respirations. The heart rate slows during expiration and accelerates during inspiration. Occasionally, if the sinus rate becomes slow enough, an **escape beat** arises from the atrioventricular (AV) junction region (Fig. 484.1). Normal phasic sinus arrhythmia is caused by the activity of the parasympathetic nervous system and can be quite prominent in healthy children. It may mimic frequent premature contractions, but the relationship to the phases of respiration can be appreciated with careful auscultation. Drugs that increase vagal tone, such as digoxin, may exaggerate sinus arrhythmia; it is usually abolished by exercise. Other irregularities in sinus rhythm, especially bradycardia associated with periodic apnea, are common in premature infants.

Sinus bradycardia is a result of slow discharge of impulses from the sinus node, the heart's "natural pacemaker." A sinus rate <90 beats/min in neonates and <60 beats/min in older children is considered sinus bradycardia. Sinus bradycardia is commonly seen in highly conditioned athletes. In healthy individuals without symptoms, it has no clinical significance. Sinus bradycardia may occur in systemic disease (hypothyroidism, anorexia nervosa), and it resolves when the disorder is under control. It may also be seen in association with conditions in which there is high vagal tone, such as gastrointestinal obstruction or intracranial processes. Low birthweight infants display great variation in sinus rate. Sinus bradycardia is common in these infants, in conjunction with apnea, and may be associated with junctional escape beats; premature atrial contractions are also frequent. These rhythm changes, especially bradycardia, appear more often during sleep and are not associated with symptoms. Usually, no therapy is necessary.

A **wandering atrial pacemaker** is defined as an intermittent shift in the pacemaker of the heart from the sinus node to another part of the atrium. It is not uncommon in childhood and usually represents a normal variant. It may also be seen in association with sinus bradycardia in which the shift in atrial focus is an escape phenomenon.

Extrasystoles are produced by the premature discharge of an ectopic focus that may be situated in the atrium, the AV junction, or the ventricle. Usually, isolated extrasystoles are of no clinical or prognostic significance. Under certain circumstances, however, premature beats may be caused by organic heart disease (inflammation, ischemia, fibrosis) or drug toxicity.

Atrial extrasystoles, also known as **premature atrial contractions** or **complexes (PACs)**, are common in childhood, usually in the absence of cardiac disease. Depending on the degree of prematurity of the beat (coupling interval) and the preceding R-R interval (cycle length), PACs may result in a normal, a prolonged (aberrancy), or an absent (blocked PAC) QRS complex. Blocked PACs occur when the premature impulse cannot conduct to the ventricle because of refractoriness of the AV node or distal conducting system (Fig. 484.2). Atrial extrasystoles must be distinguished from premature ventricular contractions. Careful scrutiny of the electrocardiogram (ECG) for a premature P wave preceding the QRS will show either a premature P wave superimposed on and deforming the preceding T wave or a P wave that is premature and has a different contour from that of the other sinus P waves. PACs usually reset the sinus node pacemaker, leading to an incomplete compensatory pause, but this feature is not always present and so is not regarded as a completely reliable means of differentiating atrial from ventricular premature complexes in children.

Ventricular extrasystoles, also known as **premature ventricular contractions** or **complexes (PVCs)**, may arise in any region of either ventricle. PVCs are characterized by premature, widened, bizarre QRS complexes that are not preceded by a premature P wave (Fig. 484.3). When all premature beats have identical contours, they are classified

Table 484.1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS IA: INHIBITS NA^+ FAST CHANNEL, PROLONGS REPOLARIZATION					
Quinidine	SVT, atrial fibrillation, atrial flutter, VT; in atrial flutter, an AV node–blocking drug (digoxin, verapamil, propranolol) must be given first to prevent 1:1 conduction	Oral: 30-60 mg/kg/24 hr divided q6h (sulfate) or q8h (gluconate) 200 mg q6 (1-1.5 g/day divided q6), sulfate; 324 mg q8-12h (1.5 g/day divided q8-12h), gluconate Max dose: 2.4 g/24 hr	Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole, syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis	Enhances digoxin, may increase PTT when given with warfarin	2-6 µg/mL
Procainamide	SVT, atrial fibrillation, atrial flutter, VT	Oral: 15-50 mg/kg/day divided q3-6h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-60 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr	PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis, proarrhythmia	Toxicity increased by amiodarone and cimetidine	4-8 µg/mL With NAPA <40 µg/mL
Disopyramide	SVT, atrial fibrillation, atrial flutter	Oral (immediate release): <1 yr: 10-30 mg/kg/day divided q6h 1-4 yr: 10-20 mg/kg/day divided q6h >4-12 yr: 10-15 mg/kg/day divided q6h >12- ≤18 yr: 6-15 mg/kg/day divided q6h Max dose: 1.6 g/day Adults: <50 kg: 100 mg q6h; >50kg:150 mg q6h Long-acting dosing is 200-300 q12h	Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia		2-7 µg/mL
CLASS IB: INHIBITS NA^+ FAST CHANNEL, SHORTENS REPOLARIZATION					
Lidocaine	VT, VF	IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg) Adult infusion rate: 1-4 mg/min	CNS effects, confusion, convulsions, high-grade AV block, asystole, coma, paresthesias, respiratory failure	Propranolol, cimetidine, increases toxicity	1.5-5.0 µg/mL
Mexiletine	VT	Oral: 6-15 mg/kg/24 hr divided q8h Max dose: 15 mg/kg/day or 1.2 g/day. Adults: 150-300 mg q8-12h (max 1.2 g/day)	GI upset, skin rash, neurologic	Cimetidine	0.5-2 mcg/mL
Phenytoin	Digitalis intoxication	Oral: 4-8 mg/kg/24 hr divided q12h Max dose: 300-600 mg/day IV: 10-15 mg/kg over 1 hr load	Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity	10-20 µg/mL
CLASS IC: INHIBITS NA^+ CHANNEL					
Flecainide	SVT, atrial tachycardia, VT	BSA dosing: 50-200 mg/m^2/day divided q8-12h Weight based: 3-6 mg/kg/day divided q8h Max dosing: 8 mg/kg/day Max adult dosing: 400 mg/day	Blurred vision, nausea, decrease in contractility, proarrhythmia	Amiodarone increases toxicity	0.2-1 µg/mL

Table 484.1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class—cont'd

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
Propafenone	SVT, atrial tachycardia, atrial fibrillation, VT	Oral: 150-300 mg/m^2/24 hr divided q8h	Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia	Increases digoxin levels	0.2-1 μg/mL
CLASS II: β BLOCKERS					
Propranolol	SVT, long QT	Oral: 1-4 mg/kg/24 hr divided q6h Max dose 60 mg/24 hr IV: 0.01-0.15 mg/kg/dose SLOW over 5-10 min Max dose: 1-3 mg/dose	Bradycardia, loss of concentration, school performance problems, bronchospasm, hypoglycemia, hypotension, heart block, CHF	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function	
Atenolol	SVT	Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h	Bradycardia, loss of concentration, school performance problems	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function	
Nadolol	SVT, long QT	Oral: 1-2 mg/kg/24 hr given once daily	Bradycardia, loss of concentration, school performance problems, bronchospasm, hypoglycemia, hypotension, heart block, CHF	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function	
CLASS III: PROLONGS REPOLARIZATION					
Amiodarone	SVT, JET, VT	Oral: 10-15 mg/kg/day IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 5-20 mg/kg/day continuous infusion Max daily dose: 2.2 g/day	Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis	Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin	1-2.5 mg/L
CLASS IV AND MISCELLANEOUS MEDICATIONS					
Digoxin	SVT (not WPW), atrial flutter, atrial fibrillation	Oral/load instructions: Premature: 20 μg/kg Newborn: 30 μg/kg >6 mo: 40 μg/kg Give 1/2 total dose followed by 1/4 q8-12h × 2 doses Maintenance: 10 μg/kg/24 hr divide q12h Max dose: 0.5 mg IV: 3/4 PO dose Max dose: 0.5 mg	PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval	Quinidine Amiodarone, verapamil, increase digoxin levels	1-2 mg/mL
Verapamil	SVT (not WPW)	Oral: 2-8 mg/kg/day divided q8h Max dose: 480 mg/day IV: 0.1-0.3 mg/kg/dose Max dose: 5-10 mg/dose	Bradycardia, asystole, high-degree AV block, PR prolongation, hypotension, CHF	Use with β blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity	
Adenosine	SVT	IV: 50-300 μg/kg by need rapid IV push Begin with 50 μg/kg and increase by 50-100 μg/kg/dose Max dose: 18 mg	Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole		

AV, Atrioventricular; CHF, congestive heart failure; CNS, central nervous systems; GI, gastrointestinal; IV, intravenous; JET, junctional ectopic tachycardia; NAPA, *N*-acetyl procainamide; PAC, premature atrial contraction; PTT, partial thromboplastin time; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus–like illness; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

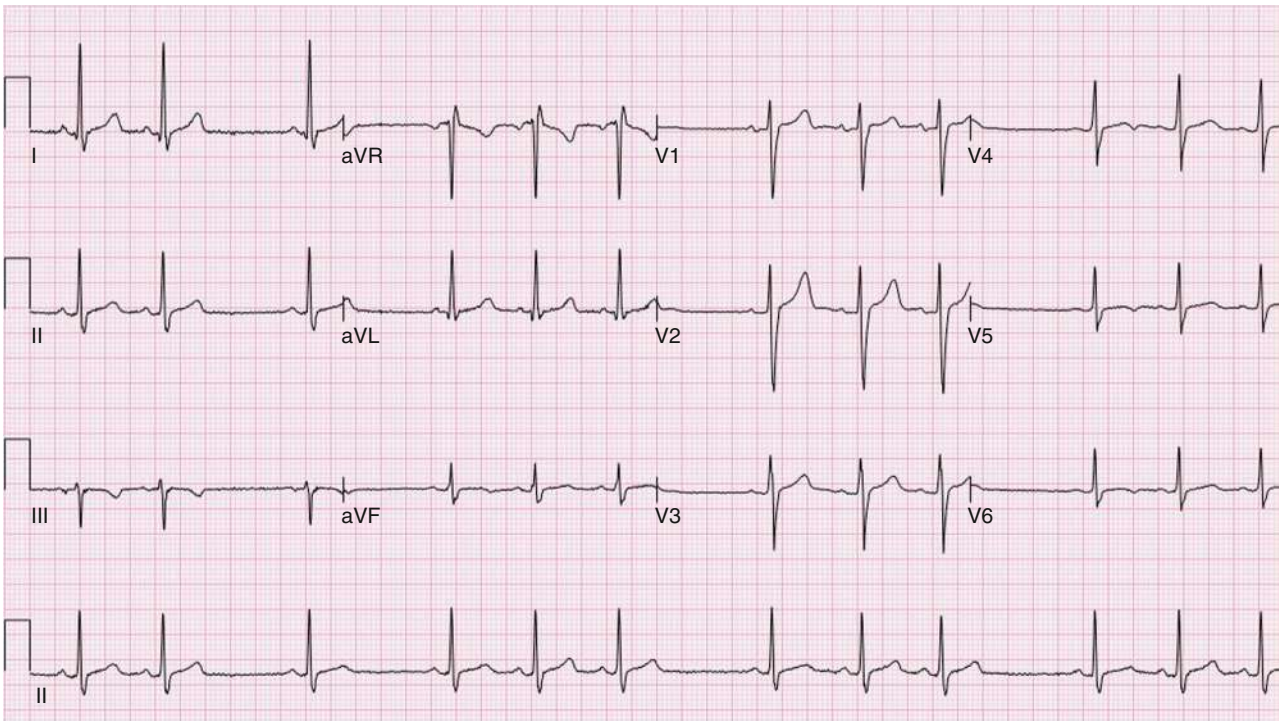

Fig. 484.1 Phasic sinus arrhythmia. Note the variation in P-P interval with no significant change in P-wave morphology or PR interval. This rhythm is normal.

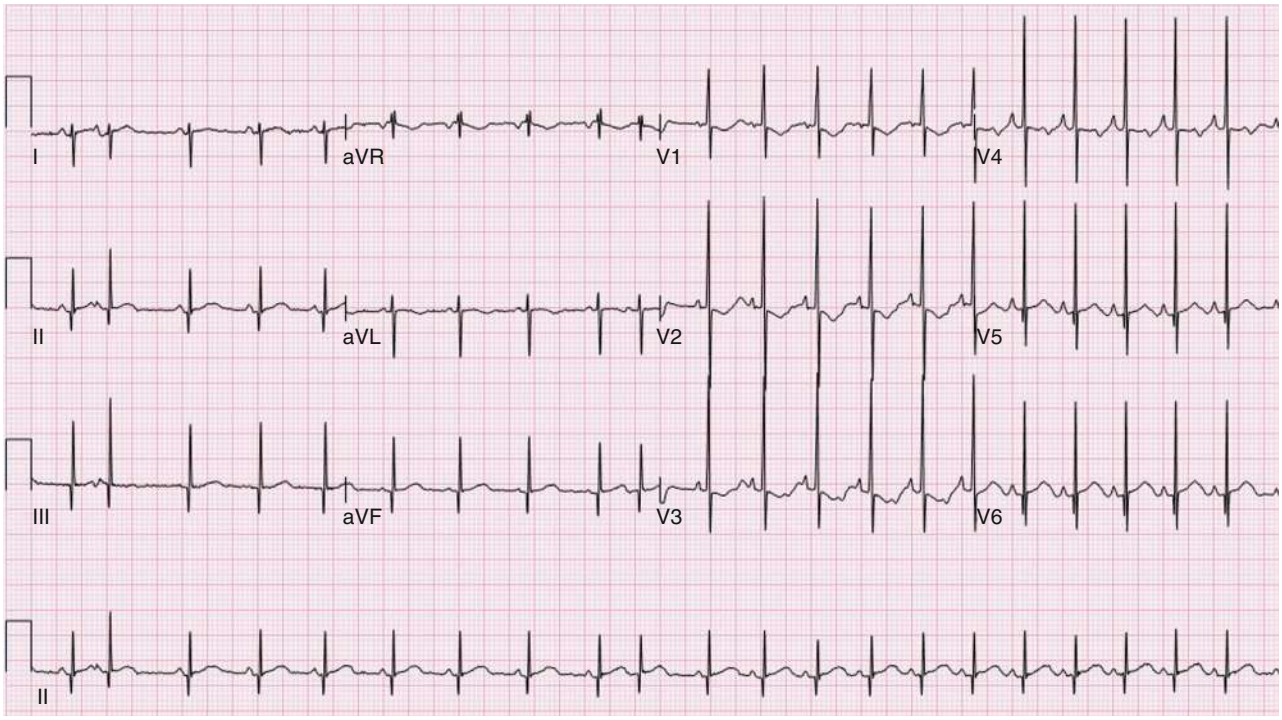

Fig. 484.2 Premature atrial contraction (PAC). The second and tenth beats are premature, and deformation of the previous T wave identifies the presence of a premature atrial contraction.

as *uniform or monomorphic,* suggesting origin from a common site. When PVCs vary in contour, they are designated as *multiform or polymorphic,* suggesting origin from more than one ventricular site. Ventricular extrasystoles are often, but not always, followed by a full compensatory pause because of a lack of resetting of the sinus node. The presence of **fusion beats**, that is, complexes with morphologic features that are intermediate between those of normal sinus beats and those of PVCs, proves the ventricular origin of the premature beat. Extrasystoles produce a smaller stroke and pulse volume than normal and, if quite premature, may not be audible with a stethoscope or palpable at the radial pulse. When frequent, extrasystoles may assume a definite rhythm, for example, alternating with normal beats **(bigeminy)** or occurring after two normal beats **(trigeminy)**. Most patients are unaware of single PVCs, although some may be aware of a "skipped beat" over the precordium. This sensation is caused by the increased stroke volume of the normal beat after a compensatory pause. Anxiety,

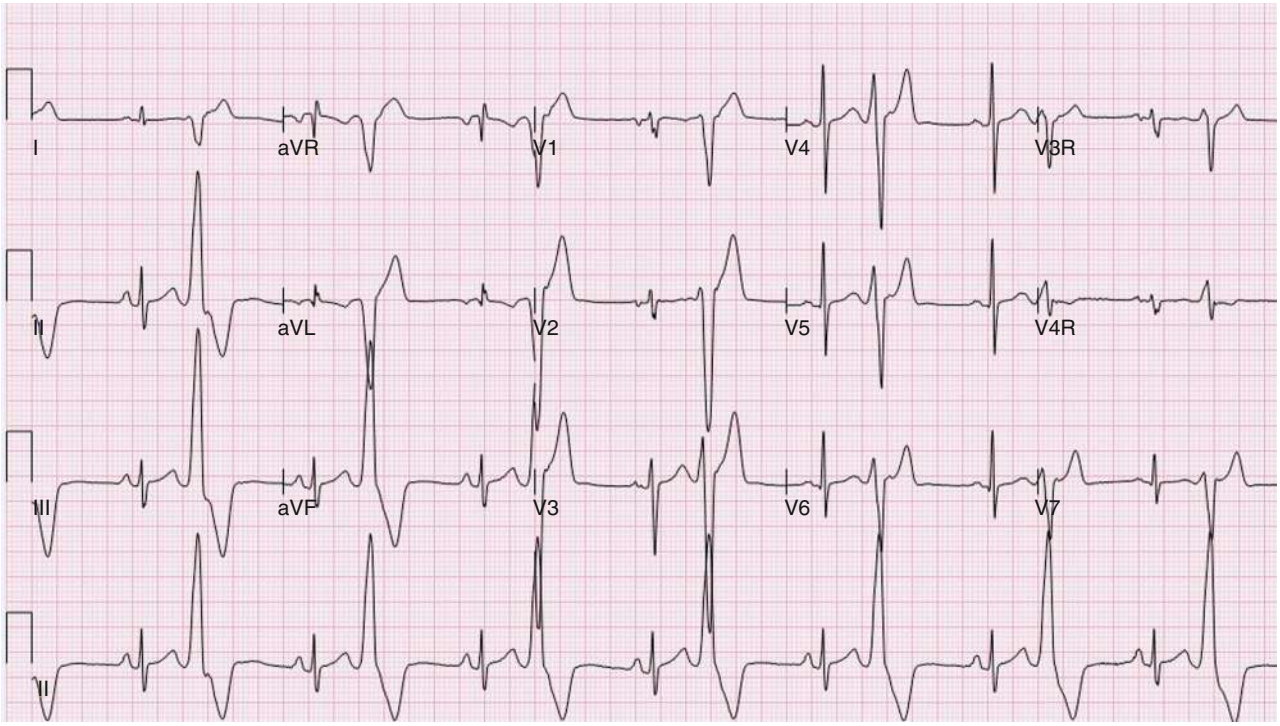

Fig. 484.3 Premature ventricular contractions in a bigeminal rhythm. Note that the premature beat is wide and has a completely different morphology from that of the sinus beat. The premature beat is not preceded by a discernible premature P wave or any appreciable deformation of the preceding T wave.

a febrile illness, or ingestion of various drugs or stimulants may make PVCs more frequent.

It is important to distinguish PVCs that are benign from those that are likely to lead to more severe arrhythmias. The former usually disappear (or are "suppressed) at higher sinus rates, as seen during exercise. If they persist or become more frequent during exercise, the arrhythmia may have greater significance. The following criteria are indications for further investigation of PVCs that could require **suppressive therapy**: (1) ≥2 PVCs in a row; (2) multiform PVCs; (3) increased ventricular ectopic activity with exercise; (4) R-on-T phenomenon (premature ventricular depolarization occurs on the T wave of the preceding beat); (5) extreme frequency of beats (e.g., >20% of total beats on Holter monitoring); and (6) most importantly, the presence of underlying heart disease, a history of heart surgery, or both. The best therapy for benign PVCs is reassurance that the arrhythmia is not life threatening, although highly symptomatic individuals may benefit from suppressive therapy.

Malignant PVCs are usually secondary to another medical problem (electrolyte imbalance, hypoxia, drug toxicity, cardiac injury, or a channelopathy). Successful treatment includes correction of the underlying abnormality if possible. An intravenous **lidocaine** bolus and drip is the first line of therapy, with more effective drugs such as **amiodarone** reserved for refractory cases or for patients with underlying ventricular dysfunction or hemodynamic compromise.

484.3 Supraventricular Tachycardia

Aarti S. Dalal and George F. Van Hare

Supraventricular tachycardia (SVT) is a general term that includes essentially all forms of paroxysmal or incessant tachycardia except ventricular tachycardia. The category of SVT can be divided into three major subcategories: reentrant tachycardias using an accessory pathway, reentrant tachycardias without an accessory pathway, and ectopic or automatic tachycardias. **Atrioventricular reciprocating tachycardia (AVRT)** involves an accessory pathway and is the most common mechanism of SVT in infants. **Atrioventricular node reentry tachycardia (AVNRT)** is rare in infancy but increases during childhood and into adolescence. **Atrial flutter** is rarely seen in children with normal hearts, whereas intraatrial reentry tachycardia (also known as *atrial flutter*) is sometimes seen in patients after cardiac surgery. Atrial and junctional ectopic tachycardias are more often associated with abnormal hearts (cardiomyopathy) and the immediate postoperative period after surgery for CHD.

CLINICAL MANIFESTATIONS

Reentrant SVT is characterized by an abrupt onset and termination; it may occur when the patient is at rest or exercising, and in infants it may be precipitated by an acute infection. Attacks may last only a few seconds or may persist for hours. The heart rate usually exceeds 180 beats/min in older children and adolescents and 220 bpm in infants and younger children. Rates of SVT are often as high as 300 beats/min in newborns and infants. The only complaint may be awareness of the rapid heart rate.

Many older children tolerate these episodes extremely well, and it is unlikely that short paroxysms are a danger to life. If heart rate is exceptionally rapid or the episode is prolonged, precordial discomfort and heart failure may occur. In children, SVT may be exacerbated by exposure to caffeine, nonprescription decongestants, or bronchodilators.

In young patients, the diagnosis may be more obscure because of their inability to communicate their symptoms. The heart rate during infancy is normally higher than in older children and increases greatly with crying. Occasionally, infants with SVT initially present with heart failure because the tachycardia may go unrecognized for a long time, **leading to tachycardia-induced cardiomyopathy**. The heart rate during SVT episodes is frequently in the range of 240-300 beats/min. If the episode lasts 6-24 hours or more, heart failure may be recognized, and the infant may present with poor feeding; an ashen color; and will be restless and irritable, with tachypnea, poor pulses, and hepatomegaly. When tachycardia occurs in the fetus, it can cause **hydrops fetalis**, the in utero manifestation of heart failure.

In neonates, SVT is usually manifested as a narrow QRS complex (<0.08 second). The P wave is visible on a standard ECG in only 50–60%

of neonates with SVT, but it is detectable with a transesophageal lead in most patients. *Differentiation from sinus tachycardia* may be difficult but is important because sinus tachycardia requires treatment of the underlying problem (e.g., sepsis, hypovolemia) rather than antiarrhythmic medication. If the rate is >230 beats/min with an abnormal P-wave axis (a normal P wave is positive in leads I and aVF), sinus tachycardia is *not* likely. The heart rate in SVT also tends to be *relatively fixed,* whereas in sinus tachycardia the heart rate *varies* with changes in parasympathetic and sympathetic tone. AVRT uses a bypass tract that may be able to conduct bidirectionally **(Wolff-Parkinson-White [WPW] syndrome)** or may be retrograde only **(concealed accessory pathway)**. Patients with WPW syndrome have a small but real risk of sudden death. If the accessory pathway rapidly conducts in antegrade fashion, the patient is at risk for atrial fibrillation begetting ventricular fibrillation. Risk stratification, including 24-hour Holter monitoring and exercise study, may help differentiate patients at higher risk for sudden death from WPW. However, it is important to note that intermittent preexcitation may not decrease a patient's risk profile. Syncope is an ominous symptom in WPW, and any patient with syncope and WPW syndrome should have an **electrophysiology study** (EPS) and consideration for catheter ablation.

The typical electrocardiographic features of WPW syndrome are seen when the patient is not having tachycardia. These features include a short P-R interval and slow upstroke of a widened QRS (delta wave) (Fig. 484.4). This may not be evident in every lead on an ECG. Although most often presenting in patients with a normal heart, WPW syndrome may also be associated with **Ebstein anomaly** of the tricuspid valve, congenitally corrected transposition of the great

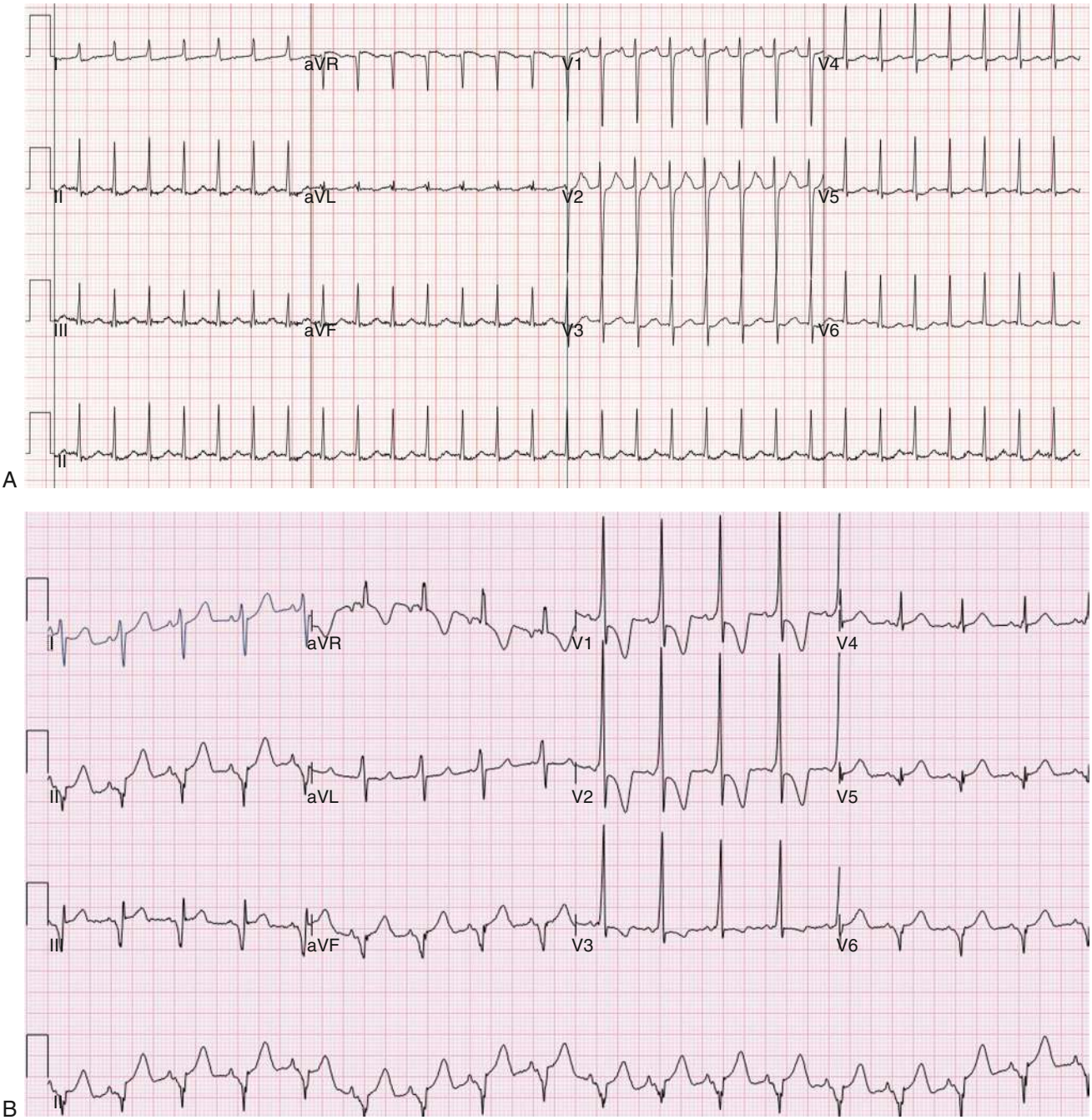

Fig. 484.4 A, Supraventricular tachycardia in a child with Wolff-Parkinson-White (WPW) syndrome. Note the normal QRS complexes during the tachycardia, as well as clear retrograde P waves seen on the upstroke of the T waves. B, Later, the typical features of WPW syndrome are apparent (short P-R interval, wide QRS with slurred upstroke known as a *delta wave*).

arteries, or certain forms of hypertrophic cardiomyopathy. WPW may also be associated with hypokalemic periodic paralysis, Danon disease, tuberous sclerosis, and rarely with pathogenic variants in *PRKAG2*.

The critical anatomic structure is an accessory pathway consisting of an electrically active myocardial fiber connecting atrium to ventricle on either the right or the left side of the AV ring (Fig. 484.5). During sinus rhythm, the impulse is carried over both the AV node and the accessory pathway; it produces some degree of fusion of the two depolarization fronts that results in an abnormal QRS complex. During AVRT, an impulse is carried in *antegrade* fashion through the AV node **(orthodromic tachycardia)**, which results in a normal QRS complex, and in *retrograde* fashion through the accessory pathway to the atrium, thereby perpetuating the tachycardia. In these cases, only after cessation of the tachycardia is the typical ECG features of WPW syndrome recognized (see Fig. 484.4). When rapid antegrade conduction occurs through the accessory pathway during tachycardia and the retrograde reentry pathway to the atrium is by the AV node **(antidromic tachycardia)**, the QRS complexes are wide and the potential for more serious arrhythmias (ventricular fibrillation) is greater, especially if atrial fibrillation occurs.

AVNRT involves the use of two functional pathways within the AV node: the *slow* and *fast* AV node pathways. This arrhythmia is more often seen in adolescence and young adulthood. It is one of the few forms of SVT that is occasionally associated with syncope. This arrhythmia is often seen in association with exercise.

TREATMENT

In infants, **vagal stimulation** can be induced by transiently placing an ice bag over the entire face to abort the attack for 15-30 seconds (this can be repeated if needed). Older children may be taught **vagal maneuvers** such as the Valsalva maneuver, straining, breath holding, or standing on their head. *Ocular pressure must never be performed, and carotid sinus massage is rarely effective*. When these measures fail, several pharmacologic alternatives are available (see Table 484.1). In stable patients, **adenosine** by rapid intravenous push is the treatment of choice (0.1 mg/kg, up to 6 mg) because of its rapid onset of action and minimal effects on cardiac contractility. The dose may need to be increased (0.2 mg/kg, up to 12 mg) if no effect on the tachycardia is seen. Because of the potential for adenosine to initiate atrial fibrillation, it should never be administered without a means for direct current **(DC) cardioversion** near at hand. Calcium channel blockers such as **verapamil** have also been used in the initial treatment of SVT in older children. Verapamil may reduce cardiac output and produce hypotension and cardiac arrest in infants younger than 1 year and therefore is contraindicated in this age-group. In urgent situations when symptoms of severe heart failure have already occurred, *synchronized* DC cardioversion (0.5-2 J/kg) is recommended as the initial management (see Chapter 79). Pace termination using esophageal pacing catheter is also an option.

Once the patient has been converted to sinus rhythm, a longer-acting agent is selected for maintenance therapy. In patients without an antegrade accessory pathway (non-WPW), the β-**adrenergic blockers** are the mainstay of drug therapy. **Digoxin** has been used for decades and may be effective in infants, but less so in older children. In children with WPW, digoxin or calcium channel blockers may *increase* the rate of antegrade conduction of impulses through the bypass tract, with the possibility of ventricular fibrillation, and are therefore contraindicated. These patients are usually managed with β blockers. In patients with resistant tachycardias, flecainide, propafenone, sotalol, and amiodarone are all acceptable next-line agents. Most antiarrhythmic agents have the potential of causing new dangerous arrhythmias (**proarrhythmia**) and decreasing heart function. Flecainide and propafenone should be limited to use in patients with hearts having otherwise normal cardiac function.

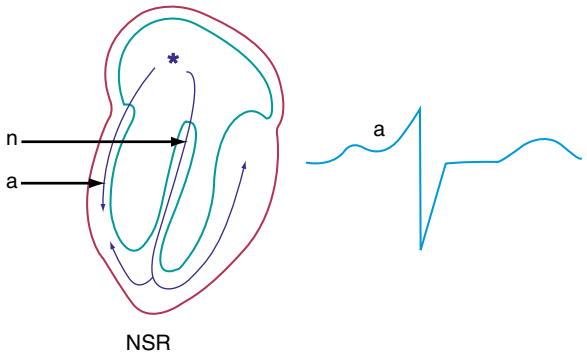

Fig. 484.5 Schematic representation of the heart with a right-sided accessory pathway (WPW syndrome). The *asterisk* indicates initiation of the sinus beat. The *arrows* indicate the direction and spread of excitation. The electrocardiographic complex shown represents a fusion beat that combines activation over the normal *(n)* and accessory *(a)* pathways. The latter inscribes the delta wave. NSR, Normal sinus rhythm.

If cardiac failure occurs because of prolonged tachycardia in an infant with a normal heart, cardiac function usually returns to normal after sinus rhythm is reinstituted, although it may take days to weeks. Infants with SVT diagnosed within the first 3-4 months of life have a lower incidence of recurrence than those initially diagnosed at a later age. These patients have up to an 80% chance of resolution by the first year of life, although approximately 30% will have recurrences later in childhood; if medical therapy is required, it can be tapered by 12-18 months and the patient watched for signs of recurrence. Parents should be taught to measure the heart rate in their infants, so that prolonged asymptomatic episodes of SVT may be detected before heart failure occurs.

The use of **24-hour electrocardiographic (Holter) monitoring** assists in following the course of therapy and detecting brief runs of asymptomatic tachycardia, particularly in younger children and infants. Direct-to-consumer heart monitoring devices ("wearables") are beginning to replace traditional monitors as newer technology allows for miniaturization and improved accuracy of at-home monitoring devices. These devices have helped identify asymptomatic tachycardia in infants and young children. Some centers use **transesophageal pacing** to evaluate the effects of therapy in infants. More detailed electrophysiology studies performed in the cardiac catheterization laboratory are often indicated in patients with refractory SVT who are candidates for catheter ablation. During an EPS, multiple electrode catheters are placed transvenously in different locations in the heart. Pacing is performed to evaluate the conduction characteristics of the accessory pathway and to initiate the tachyarrhythmia, and mapping is performed to locate the accessory pathway. **Catheter ablation** of an accessory pathway is frequently used in children and teenagers and in patients who require multiple agents or find drug side effects intolerable or for whom arrhythmia control is poor. Ablation may be performed either by **radiofrequency ablation**, which creates tissue heating, or **cryoablation**, in which tissue is frozen (Fig. 484.6). The overall initial success rate for catheter ablation in experienced pediatric laboratories ranges from 90% to 98%, depending on the location of the accessory pathway. Surgical ablation of bypass tracts is rarely done and proposed only in carefully selected patients.

The management of SVT caused by AVNRT is almost identical to that for AVRT. Children with AVNRT are not at increased risk of sudden death because they do not have a manifest accessory pathway. In practice, their episodes are more likely to be brought on by exercise or other forms of stress, and the heart rates can be quite fast, leading to chest pain, dizziness, and occasionally syncope. If chronic antiarrhythmic medication is desired, β blockers are the drugs of choice; acutely, AVNRT responds to adenosine. Less is known about the natural history, but patients with AVNRT are seen quite frequently in adulthood, so spontaneous resolution seems unlikely. Patients are quite amenable to catheter ablation, either using radiofrequency energy or cryoablation, with high success rates and low complication rates.

Atrial ectopic tachycardia is an uncommon tachycardia in childhood. It is characterized by a variable rate (seldom >200 beats/min), identifiable P waves with an abnormal axis, and either a sustained or incessant nonsustained tachycardia (Fig. 484.7). This form of atrial tachycardia has a single automatic focus. Identification of this mechanism is aided by monitoring the ECG while initiating vagal or pharmacologic therapy. Unlike reentrant tachycardias, which "break" suddenly, automatic tachycardias such as atrial tachycardia tend to

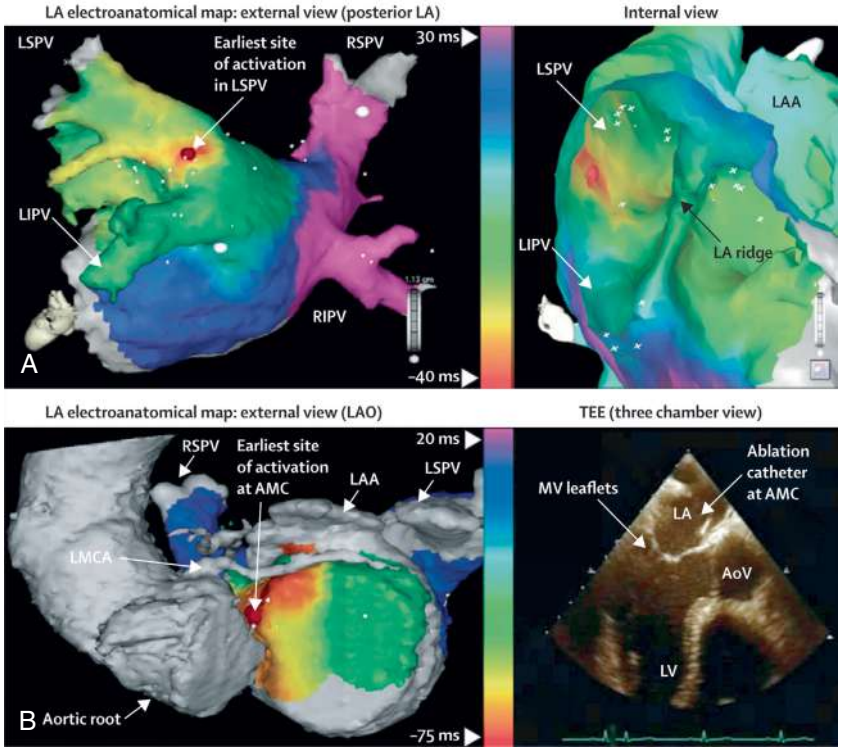

Fig. 484.6 Three-dimensional electroanatomic map of focal atrial tachycardias. Focal site of early activation *(red)* is shown, with radial propagation away from that central site. The activation map was superimposed onto the patient's cardiac CT scan, taken the day before the procedure and imported into the mapping system. This patient had two separate atrial foci. **A**, Tachycardia #1: Earliest site of activation, mapped to the posterior aspect of the LSPV ostium. Posterior external view *(left side)* and endoluminal or internal view looking posterior to anterior from within the left atrium into the mouth of the LSPV *(right side)* are shown. **B**, Tachycardia #2: Earliest site mapped to the aortomitral continuity. The anatomic relation between the mitral annulus and the aortic root can be clearly appreciated *(left side)*. The location of the ablation catheter at the site of earliest atrial activation during atrial tachycardia is shown on the TEE image *(right side)*. AMC, Aortomitral continuity; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; LAO, left anterior oblique; LIPV, left inferior pulmonary vein; LMCA, left main coronary artery; LSPV, left superior pulmonary vein; LV, left ventricle; MV, mitral valve; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; TEE, transesophageal echocardiogram. *(From Lee G, Sanders P, Kalman JM. Catheter ablation of atrial arrhythmias: state of the art. Lancet. 2012;380:1509–1518, Fig 3.)*

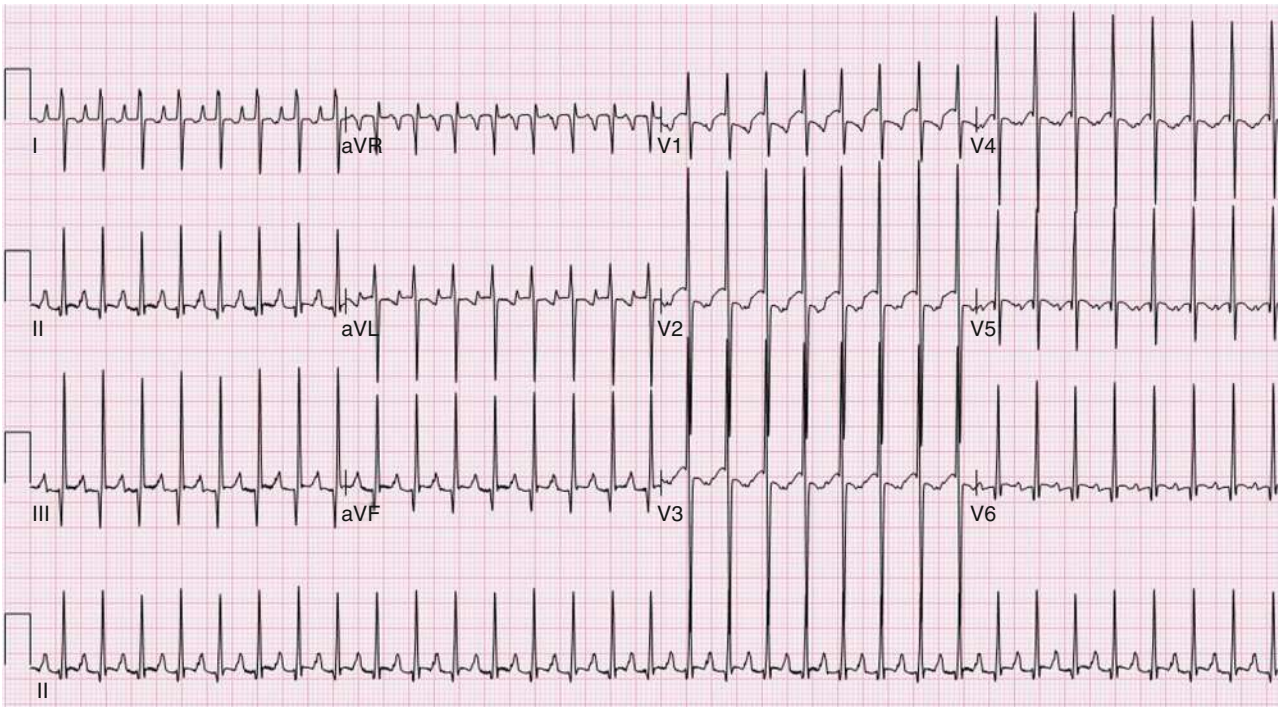

Fig. 484.7 Atrial ectopic tachycardia. Note the abnormal P waves and relative prolongation of the PR interval.

"warm up" and "cool down" (i.e., rates tend to gradually increase and decrease). Atrial ectopic tachycardias are usually more difficult to control pharmacologically than the more common reentrant tachycardias. If pharmacologic therapy with a single agent is unsuccessful, catheter ablation is suggested and has a high success rate, usually >90%. Long-term treatment or ablation may not be necessary in some cases, as atrial ectopic tachycardia may resolve spontaneously in some patients.

Chaotic or multifocal atrial tachycardia is defined as atrial tachycardia with ≥3 ectopic P-wave morphologies, frequent blocked P waves, and varying P-R intervals of conducted beats. This arrhythmia occurs most often in infants younger than 1 year of age, usually without concomitant cardiac disease, although some evidence suggests an association with viral myocarditis or pulmonary disease. The goal of drug treatment is rate control, or slowing of the ventricular rate, because conversion to sinus rhythm may not be possible. Multiple agents are often required. When this arrhythmia occurs in infancy, it usually terminates spontaneously by 3 years of age.

Accelerated junctional ectopic tachycardia (JET) is an automatic (non-reentry) arrhythmia in which the junctional rate exceeds that of the sinus node and AV dissociation may result. This arrhythmia is most often recognized in the early postoperative period after cardiac surgery and may be extremely difficult to control. Reduction of the infusion rate of exogenous catecholamines and mitigating causes of endogenous catecholamines such as fever and pain are important adjuncts to management. Intravenous amiodarone and procainamide are effective in the treatment of postoperative JET. Congenital JET may be seen in the absence of surgery. It is often incessant, can be difficult to treat, and can lead to a dilated cardiomyopathy. Patients who require chronic therapy may respond to amiodarone or sotalol. Congenital JET can be cured by catheter ablation, but long-term AV block requiring a pacemaker is an occasional important complication.

Atrial flutter, also known as *intraatrial reentrant tachycardia,* is an atrial tachycardia characterized by atrial activity at a rate of 250-300 beats/min in children and adolescents and 400-600 beats/min in neonates. The mechanism of common atrial flutter consists of a reentrant rhythm originating in the right atrium circling the tricuspid valve annulus. Because the AV node cannot transmit such rapid impulses, some degree of **AV block** is virtually always present, and the ventricles respond to every second to fourth atrial beat (Fig. 484.8). Occasionally, the response is variable, and the rhythm appears irregular.

In older children, atrial flutter usually occurs in the setting of CHD; neonates with atrial flutter frequently have normal hearts. Atrial flutter may occur during acute infectious illnesses but is most often seen in patients with large stretched atria, such as those associated with long-standing mitral or tricuspid insufficiency, tricuspid atresia, Ebstein anomaly, or rheumatic mitral stenosis. Atrial flutter can also occur after any palliative or corrective cardiac surgery involving an atriotomy. Uncontrolled atrial flutter may precipitate heart failure. Vagal maneuvers or adenosine may produce a temporary slowing of the heart rate as a result of increased AV block, allowing a diagnosis to be made. The diagnosis is confirmed by ECG, which demonstrates the rapid and regular atrial saw-toothed flutter waves. *Atrial flutter usually converts immediately to sinus rhythm by synchronized DC cardioversion, which is most often the treatment of choice.* If pacing wires or atrial pacemaker leads are present, pace termination with atrial overdriving pacing may be a treatment option. In infants, an esophageal pacing lead can also be used, but care must be taken to avoid inadvertent ventricular pacing. Patients with chronic atrial flutter in the setting of CHD may be at increased risk for thromboembolism and stroke and should thus undergo anticoagulation before elective cardioversion. β Blockers or calcium channel blockers may be used to slow the ventricular response in atrial flutter by prolonging the AV node refractory period. Other agents may be used to maintain sinus rhythm, including **class I agents** such as procainamide or propafenone or **class III** agents such as amiodarone and sotalol. **Catheter ablation** has been used in patients with normal hearts and those with CHD with moderate success. After cardioversion, neonates with normal hearts may be followed off antiarrhythmic therapy or may be treated with digoxin, propranolol, or sotalol for 6-12 months, after which the medication can usually be discontinued, because neonatal atrial flutter generally does not recur.

Atrial fibrillation is uncommon in children and is rare in infants. The atrial excitation is chaotic and more rapid (400-700 beats/min) and produces an *irregularly irregular* ventricular response and pulse (Fig. 484.9). This rhythm disorder is often associated with atrial

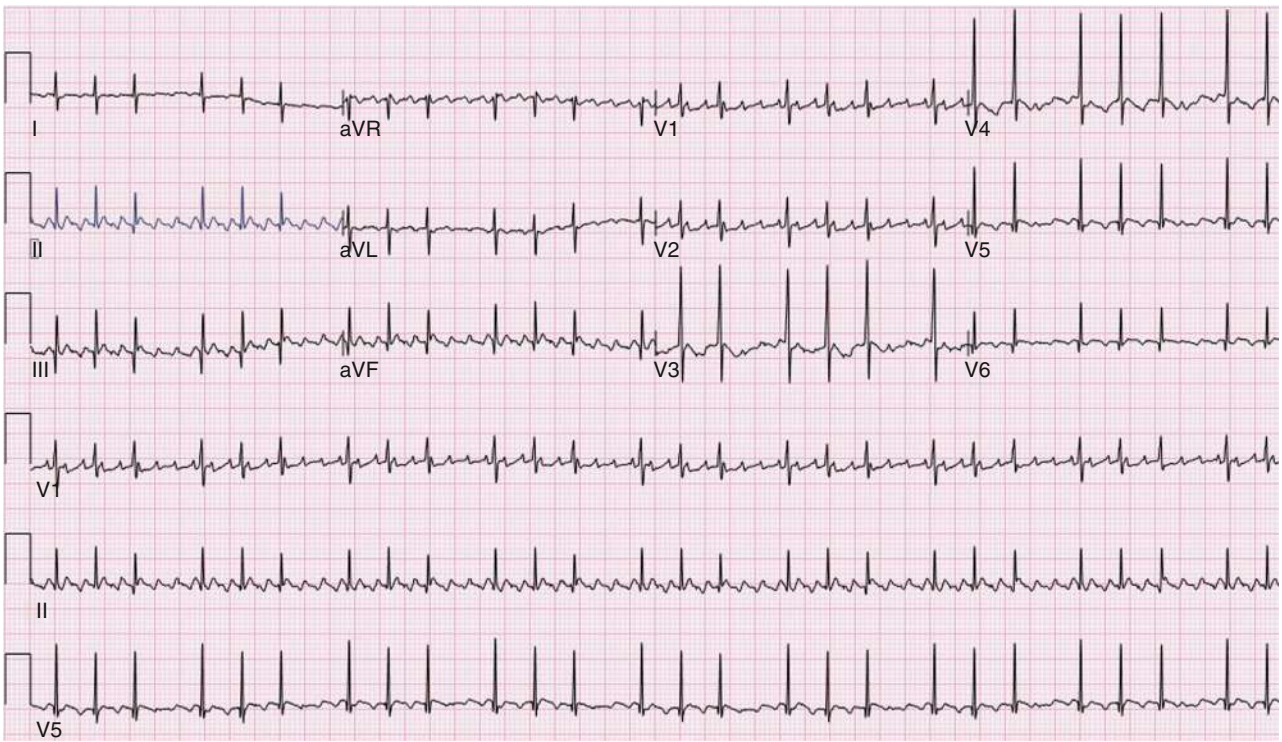

Fig. 484.8 Neonatal atrial flutter. Note that there is variable AV conduction and the flutter waves have a cycle length of 160 msec, corresponding to an atrial rate of 375 bpm.

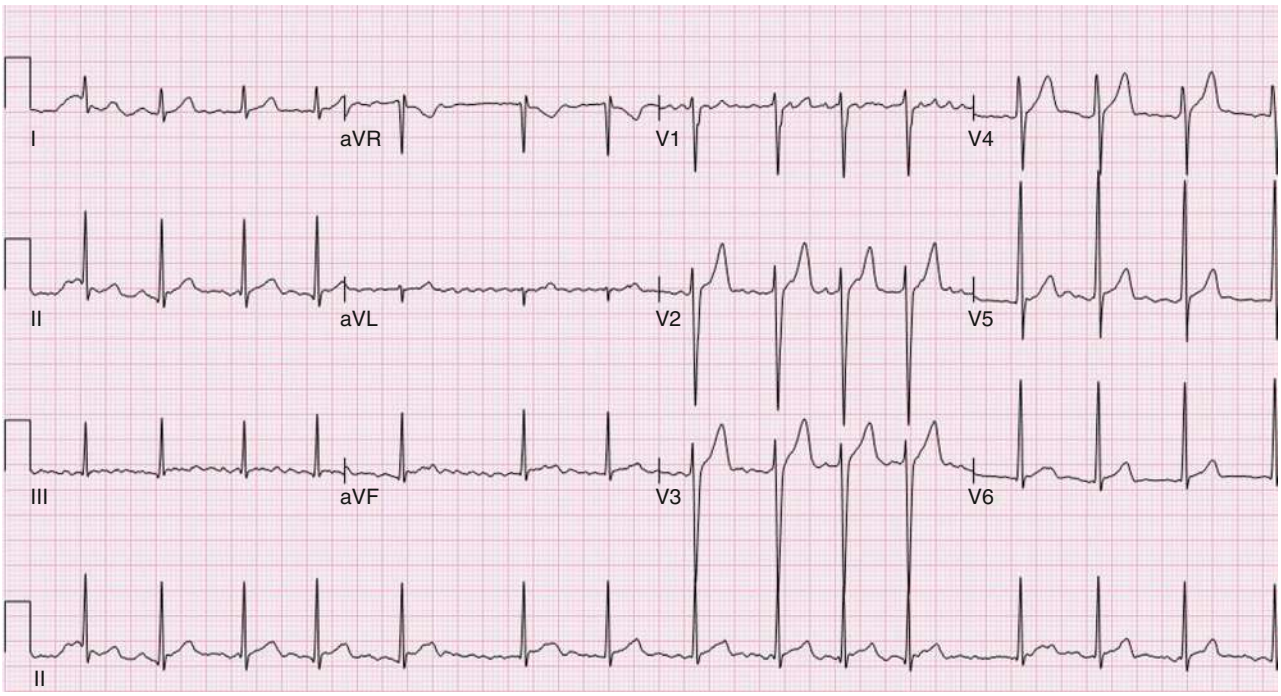

Fig. 484.9 Atrial fibrillation, characterized by the absence of clear P waves and an irregularly irregular ventricular response. One can appreciate the irregular, rapid undulations (F waves). Fibrillatory waves may not be visible in all leads and should be carefully sought in every tracing with irregular R-R intervals. Note that no two R-R intervals are the same.

enlargement or disease. Atrial fibrillation may be seen in older children with rheumatic mitral valve stenosis. It is also seen rarely as a complication of atrial surgery, in patients with left atrial enlargement secondary to left AV valve insufficiency, and in patients with WPW syndrome. Thyrotoxicosis, pulmonary embolism, pericarditis, or cardiomyopathy may be suspected in a previously normal older child or adolescent who presents with atrial fibrillation. Very rarely, atrial fibrillation may be familial and is usually an autosomal dominant disorder often affecting the potassium or sodium channel genes. The best initial treatment is **rate control**, most effectively with calcium channel blockers, to limit the ventricular rate during atrial fibrillation. Digoxin is not given if WPW syndrome is present. Normal sinus rhythm may be restored with intravenous procainamide, ibutilide, or amiodarone; DC cardioversion is the first choice in hemodynamically unstable patients. Patients with chronic atrial fibrillation are at risk for thromboembolism and stroke and should undergo anticoagulation with warfarin. Patients being treated by elective cardioversion should also undergo anticoagulation.

484.4 Ventricular Tachyarrhythmias

Aarti S. Dalal and George F. Van Hare

Ventricular tachycardia (VT) is much less common than SVT in pediatric patients. VT is defined as at least three PVCs at >120 beats/min (Fig. 484.10). It may be paroxysmal or incessant. VT can be seen in congenital or acquired heart disease, including inherited arrhythmia syndromes secondary to channelopathies, myopathies, or laminopathies. VT may be associated with structural disease such as myocarditis, anomalous origin of a coronary artery, mitral valve prolapse, primary cardiac tumors, arrhythmogenic cardiomyopathy (previously known as *arrhythmogenic right ventricular cardiomyopathy*), dilated or hypertrophic cardiomyopathy, and cardiac laminopathies (associated with lamin A/C gene pathogenic variants). Patients with laminopathies associated with a variant in the lamin A/C gene *(LMNA)*, as seen in Emery Dreifuss muscular dystrophy or 1B limb girdle muscular dystrophy are at risk of primary ventricular arrhythmias in addition to development of cardiomyopathies. VT can also be seen in patients with channelopathies such as catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, *TANGO2*-related encephalopathy and arrhythmias, and long QT syndrome. A prolonged QT interval of either congenital or acquired (proarrhythmic medication or hypokalemia, hypocalcemia, hypomagnesemia) causation can increase a patient's risk of arrhythmias. Other causes include WPW syndrome and drug use (cocaine, amphetamines). VT may develop years after intraventricular surgery (especially tetralogy of Fallot and related defects) or occur without obvious organic heart disease. VT must be distinguished from SVT with aberrancy or rapid conduction over an accessory pathway (Table 484.2). The presence of clear capture and fusion beats confirms the diagnosis of VT. Although some children tolerate rapid ventricular rates for many hours, this arrhythmia should be promptly treated because hypotension and degeneration into ventricular fibrillation may result. For patients who are hemodynamically stable, intravenous amiodarone, lidocaine, and procainamide are the initial drugs of choice. If treatment is to be successful, it is critical to search for and correct any underlying abnormalities, such as electrolyte imbalance, hypoxia, or drug toxicity. **Amiodarone** is the treatment of choice during cardiac arrest (see Chapter 79). Hemodynamically unstable patients with VT should be immediately treated with DC cardioversion. Overdrive ventricular pacing, through temporary pacing wires or a permanent pacemaker, may also be effective, although it may cause the arrhythmia to deteriorate into ventricular fibrillation. In the neonatal period, VT may be associated with an anomalous left coronary artery (see Chapter 481.2) or a myocardial tumor.

Unless a clearly reversible cause is identified, an electrophysiology study is usually indicated for patients in whom VT has developed, and depending on the findings, catheter ablation and/or implantable cardioverter-defibrillator (ICD) implantation may be indicated.

A related arrhythmia, **ventricular accelerated rhythm**, is occasionally seen in infants. It is defined the same way as VT, but the rate is only slightly faster than the coexisting sinus rate (within 10%). It is generally benign and resolves spontaneously.

Ventricular fibrillation (VF) is a chaotic rhythm that results in death unless an effective ventricular beat is rapidly reestablished. Usually, cardiopulmonary resuscitation and DC defibrillation are necessary. If defibrillation is ineffective or VF recurs, amiodarone or lidocaine may be given intravenously and defibrillation repeated (see Chapter 79). After recovery from VF, a search should be made for the

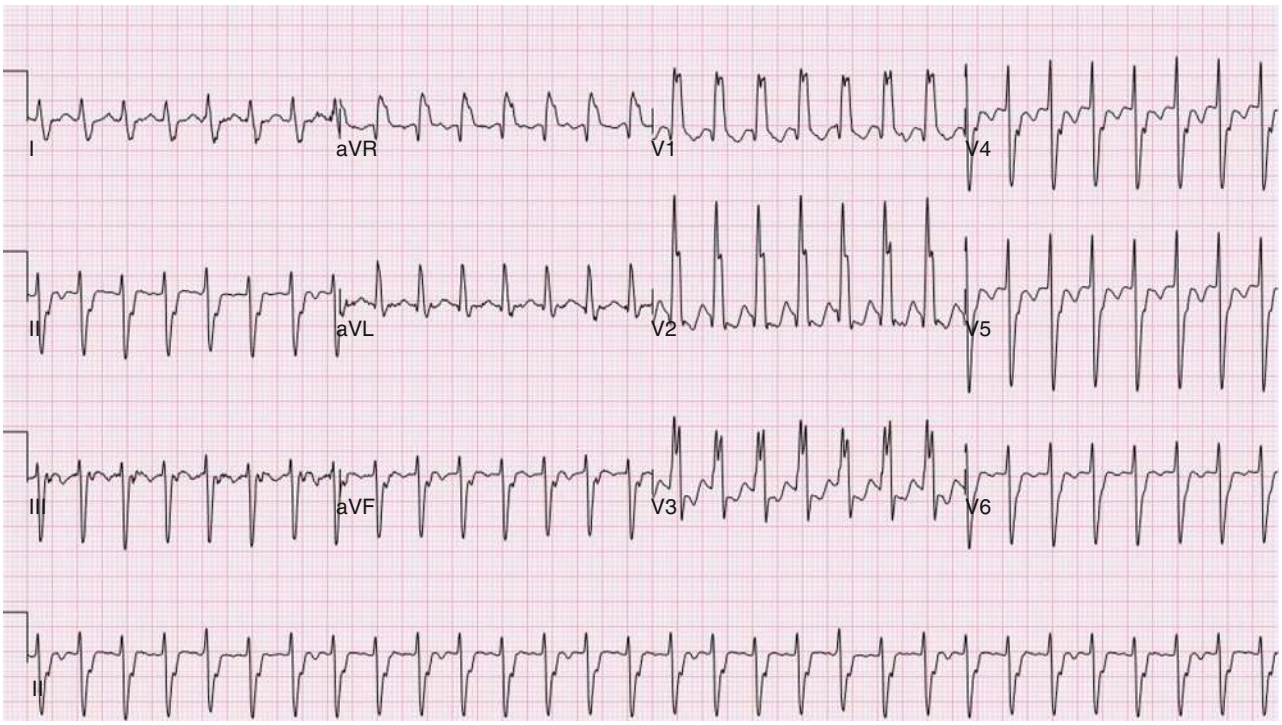

Fig. 484.10 Ventricular tachycardia. The QRS complexes are wide and abnormal. Atrioventricular dissociation can be best appreciated in the lead II rhythm strip at the bottom.

Table 484.2 Diagnosis of Tachyarrhythmias: Electrocardiographic Findings

	HEART RATE (BEATS/MIN)	P WAVE	QRS DURATION	REGULARITY
Sinus tachycardia	<230	Always present, normal axis	Normal	Rate varies with respiration
Atrial tachycardia	180-320	Present Abnormal P-wave morphology and axis	Normal or prolonged (with aberration)	Usually regular, but ventricular response may be variable because of Wenckebach conduction
Atrial fibrillation	120-180	Fibrillatory waves	Normal or prolonged (with aberration)	Irregularly irregular (no two R-R intervals alike)
Atrial flutter	Atrial: 250-400 Ventricular response variable: 100-320	Saw-tooth flutter waves	Normal or prolonged (with aberration)	Regular ventricular response (e.g., 2:1, 3:1, 3:2)
Junctional tachycardia	120-280	Atrioventricular dissociation with no fusion, and normal QRS capture beats	Normal or prolonged (with aberration)	Regular (except with capture beats)
Ventricular tachycardia	120-300	Atrioventricular dissociation with capture beats and fusion beats	Prolonged for age	Regular (except with capture beats)

underlying cause. EPS is indicated for patients who have survived VF unless a clearly reversible cause is identified. If WPW syndrome is noted, catheter ablation should be performed. For patients in whom no correctable abnormality can be found, an ICD is almost always indicated because of the high risk of sudden death.

484.5 Long QT Syndromes

Aarti S. Dalal and George F. Van Hare

Long QT syndrome is a genetic abnormality of ventricular repolarization, with an estimated incidence of about 1 per 10,000 births (Table 484.3; also includes other genetic arrhythmia syndromes). It presents as a long QT interval on the surface ECG and is associated with malignant ventricular arrhythmias (**torsades de pointes** and VF). Long QT syndrome can cause syncope and sudden death and may be the cause of some cases of sudden infant death syndrome, drowning, and intrauterine fetal demise (Fig. 484.11). In perhaps 80% of cases, there is an identifiable pathogenic variant. The distinction between dominant and recessive forms of the disease (Romano-Ward syndrome vs Jervell-Lange-Nielsen syndrome) is no longer made because the latter recessive condition is known to result from the homozygous state. **Jervell-Lange-Nielsen syndrome** is associated with congenital sensorineural deafness. Asymptomatic but at-risk patients carrying the gene variant may not all have a prolonged QT duration. QT interval prolongation may become apparent with exercise, position change or during catecholamine infusions.

Genetic studies have identified pathogenic variants in cardiac potassium and sodium channels (see Table 484.3). Additional forms (up to 13 variants) of long QT syndrome (LQTS) have been described, but these are much less common. Genotype may predict clinical manifestations;

LQTS type 1 (**LQT1**) events are usually induced by stress or exertion, whereas events in **LQT3** often occur at rest, especially during sleep (see Fig. 484.11). **LQT2** events have an intermediate pattern, often occurring in the postpartum period or with auditory triggers. LQT3 has the highest probability for sudden death, followed by LQT2 and then LQT1. Drugs may prolong the QT interval directly but more often do so when drugs such as erythromycin or ketoconazole inhibit their metabolism (Table 484.4).

The **clinical manifestation** of LQTS in children is most often a syncopal episode brought on by exercise, fright, or a sudden startle; some events occur during sleep (LQT3). Patients can initially be seen with seizures, presyncope, or palpitations; approximately 10% are initially in cardiac arrest. The diagnosis is based on electrocardiographic and clinical criteria. Not all patients with long QT intervals have LQTS, and patients with normal QT intervals on a resting ECG may have LQTS. A heart rate–corrected QT interval (QTc) of >0.47 second is highly indicative, whereas a QTc interval of >0.44 second is suggestive. Other features include notched T waves in three leads, T-wave alternans, a low heart rate for age, a history of syncope (especially with stress), and a familial history of either LQTS or unexplained sudden death. Exercise testing, provocative drug testing, and 24-hour Holter monitoring are adjuncts to the diagnosis. Genotyping is available and can identify the pathogenic variant in approximately 80% of patients known to have LQTS by clinical criteria. Genotyping is not useful in ruling out the diagnosis in individuals with suspected disease, but when positive is very useful in identifying asymptomatic affected relatives of the index case.

Short QT syndromes manifest with atrial or ventricular fibrillation and are associated with syncope and sudden death (see Table 484.3). They are often caused by a gain-of-function mutation in cardiac potassium channels.

Treatment of LQTS includes the use of β-blocking agents at doses that blunt sympathetic tone. Nonselective β blockers such as propranolol and nadolol seem to be more effective than atenolol and metoprolol for some genotypes. Some patients require a **pacemaker** because of drug-induced bradycardia. An **implantable cardiac defibrillator** (ICD) is indicated in patients with continued syncope despite treatment with β blockers and those who have experienced cardiac arrest. Genotype-phenotype correlative studies suggest that β blockers are not as effective in patients with LQT3, but these patients may respond to mexiletine with shortening of the QT interval.

484.6 Sinus Node Dysfunction

Aarti S. Dalal and George F. Van Hare

Sinus arrest and sinoatrial block may cause a sudden pause in the heartbeat. **Sinus arrest** is presumably caused by failure of impulse formation within the sinus node. **Sinoatrial block** results from a block between the sinus pacemaker complex and the surrounding atrium. These arrhythmias are rare in childhood except in patients who have had extensive atrial surgery.

Sick sinus syndrome is the result of abnormalities in the sinus node or atrial conduction pathways, or both. This syndrome may occur in the absence of CHD and has been reported in siblings, but it is most commonly seen after surgical correction of congenital heart defects,

Table 484.3 Heritable Arrhythmia Syndrome Susceptibility Genes

GENE	LOCUS	PROTEIN
LONG QT SYNDROME (LQTS)		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v7.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v11.1)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit (Na_v1.5)
Minor LQTS Genes (Listed Alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v1.2)
CALM1	14q32.11	Calmodulin 1
CALM2	2p21	Calmodulin 2
CALM3	19q13.2-q13.3	Calmodulin 3
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Kir3.4 subunit of I_{KACH} channel
SCN4B	11q23.3	Sodium channel $beta_4$ subunit
SNTA1	20q11.2	Syntrophin-$alpha_1$
TRIADIN KNOCKOUT (TKO) SYNDROME		
TRDN	6q22.31	Cardiac triadin
ANDERSEN-TAWIL SYNDROME (ATS)		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
TIMOTHY SYNDROME (TS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v1.2)
Cardiac-Only TS (COTS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v1.2)
SHORT QT SYNDROME (SQTS)		
KCNH2 (SQT1)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v11.1)
KCNQ1 (SQT2)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v7.1)

Continued

Table 484.3 Heritable Arrhythmia Syndrome Susceptibility Genes—cont'd

GENE	LOCUS	PROTEIN
KCNJ2 (SQT3)	17q23	I_{K1} potassium channel (Kir2.1)
CACNA1C (SQT4)	12p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNB2 (SQT5)	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
CACN2D1 (SQT6)	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)		
RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
KCNJ2 (CPVT3)	17q23	I_{K1} potassium channel (Kir2.1)
CALM1	14q32.11	Calmodulin 1
CALM3	19q13.2-q13.3	Calmodulin 3
TRDN	6q22.31	Cardiac triadin
BRUGADA SYNDROME (BRS)		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Minor Brs Genes (Listed Alphabetically)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
FGF12	3q28	Fibroblast growth factor 12
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1–like
KCND3	1p13.2	Voltage-gated potassium channel (I_{to}) subunit $K_v4.3$
KCNE3	11q13.4	Potassium channel $beta_3$ subunit (MiRP2)
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
HEY2	6q	Hes-related family BHLH transcription factor with YRPW motif 2
PKP2	12p11	Plakophilin-2
RANGRF	17p13.1	RAN guanine nucleotide release factor 1
SCN1B	19q13	Sodium channel $beta_1$
SCN2B	11q23	Sodium channel $beta_2$
SCN3B	11q24.1	Sodium channel $beta_3$
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit ($Na_v1.8$)
SLMAP	3p14.3	Sarcolemma-associated protein
EARLY REPOLARIZATION SYNDROME (ERS)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit ($Na_v1.8$)
IDIOPATHIC VENTRICULAR FIBRILLATION (IVF)		
ANK2	4q25-q27	Ankyrin B
CALM1	14q32.11	Calmodulin 1
DPP6	7q36	Dipeptidyl-peptidase-6
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
RYR2	1q42.1-q43	Ryanodine receptor 2
SCN3B	11q23	Sodium channel $beta_3$ subunit

Table 484.3 Heritable Arrhythmia Syndrome Susceptibility Genes—cont'd

GENE	LOCUS	PROTEIN
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
PROGRESSIVE CARDIAC CONDUCTION DISEASE/DEFECT (PCCD)		
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
TRPM4	19q13.33	Transient receptor potential cation channel, subfamily M, member 4
SICK SINUS SYNDROME (SSS)		
ANK2	4q25-q27	Ankyrin B
HCN4	15q24-q25	Hyperpolarization-activated cyclic nucleotide–gated channel 4
MYH6	14q11.2	Myosin, heavy chain 6, cardiac muscle, alpha
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
"ANKYRIN-B SYNDROME"		
ANK2	4q25-q27	Ankyrin B
FAMILIAL ATRIAL FIBRILLATION (FAF)		
ANK2	4q25-q27	Ankyrin B
GATA4	8p23.1-p22	GATA-binding protein 4
GATA5	20q13.33	GATA-binding protein 5
GJA5	1q21	Connexin 40
KCNA5	12p13	I_{Kur} potassium channel ($K_v1.5$)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNH2	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
KCNJ2	17q23	I_{K1} potassium channel (Kir2.1)
KCNQ1	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
NPPA	1p36	Atrial natriuretic peptide precursor A
NUP155	5p13	Nucleoporin 155 kD
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)

From Tester DJ, Ackerman MJ. Genetics of cardiac arrhythmias. In Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease*, 11th ed. Philadelphia: Elsevier; 2019, Table 33.1, p. 605.

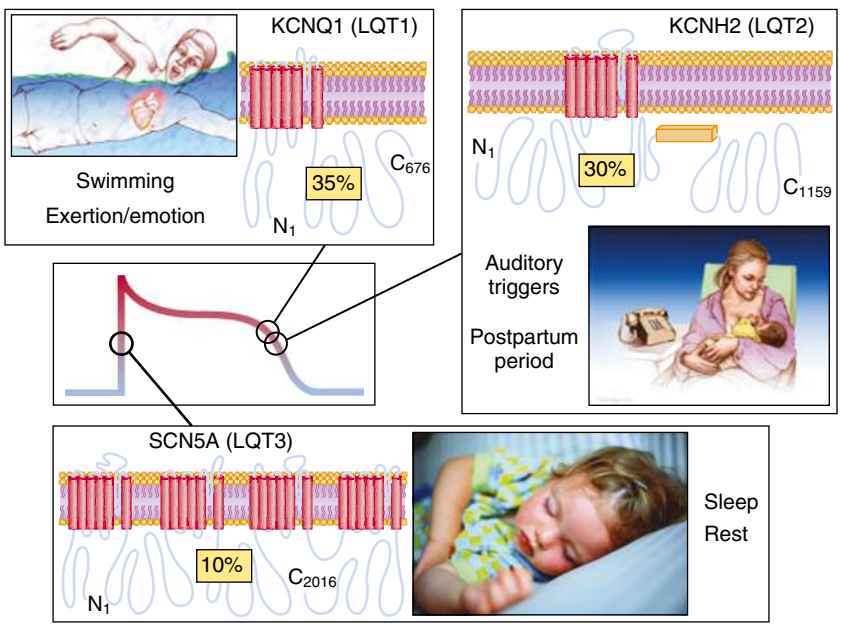

Fig. 484.11 Genotype-phenotype correlations in long QT syndrome (LQTS). About 75% of clinically strong LQTS is caused by mutations in three genes (35% *KCNQ1*, 30% *KCNH2*, and 10% *SCN5A*) encoding for ion channels that are critically responsible for the orchestration of the cardiac action potential. Observed genotype-phenotype correlations include swimming/exertion/emotion and LQT1, auditory triggers/postpartum period and LQT2, and sleep/rest and LQT3. *(From Tester DJ, Ackerman MJ. Genetics of cardiac arrhythmias. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig 33-3, p. 607.)*

Table 484.4 Acquired Causes of QT Prolongation*

DRUGS
Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones†
Antifungal agents†—fluconazole, itraconazole, ketoconazole
Antiprotozoal agents—pentamidine isethionate
Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)
Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)
Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors
Antiarrhythmic agents
Class 1A (sodium channel blockers)—quinidine, procainamide, disopyramide
Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, *N*-acetyl-procainamide, sotalol
Lipid-lowering agents—probucol
Antianginals—bepridil
Diuretics (through K^+ loss)—furosemide (Lasix), ethacrynic acid (bumetanide [Bumex])
Opiates—methadone, oxycodone
Oral hypoglycemic agents—glibenclamide, glyburide
Organophosphate insecticides
Motility agents—cisapride, domperidone
Vasodilators—prenylamine
Other drugs—ondansetron, HIV protease inhibitors, Chinese herbs
ELECTROLYTE DISTURBANCES
Hypokalemia—diuretics, hyperventilation
Hypocalcemia
Hypomagnesemia
UNDERLYING MEDICAL CONDITIONS
Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome
Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors
Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma
Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage
Nutritional—alcoholism, anorexia nervosa, starvation

*A more exhaustive updated list of medications that can prolong the QTc interval is available at the University of Arizona Center for Education and Research of Therapeutics website (www.crediblemeds.org).
†Combinations of quinolones plus azoles increase the risk of prolonged QT intervals.
From Park MY. *Pediatric Cardiology for Practitioners,* 5th ed. Philadelphia: Mosby; 2008: Box 24-1, p. 433.

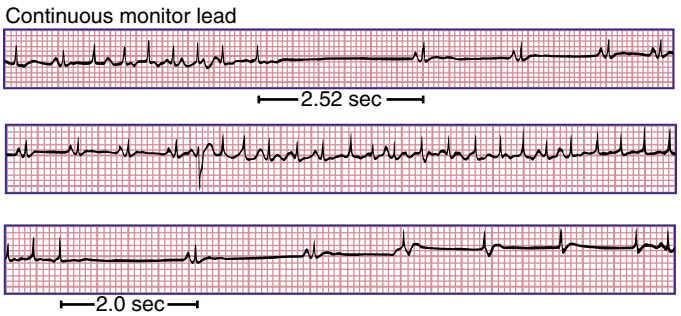

Fig. 484.12 The "tachy-brady" syndrome with sinus node dysfunction. Note the bursts of supraventricular tachycardia, probably multifocal atrial in origin, followed by long periods of sinus arrest and by sinus bradycardia. Often, symptoms are caused by the long sinus pauses after termination of tachycardia, rather than by the tachycardia itself.

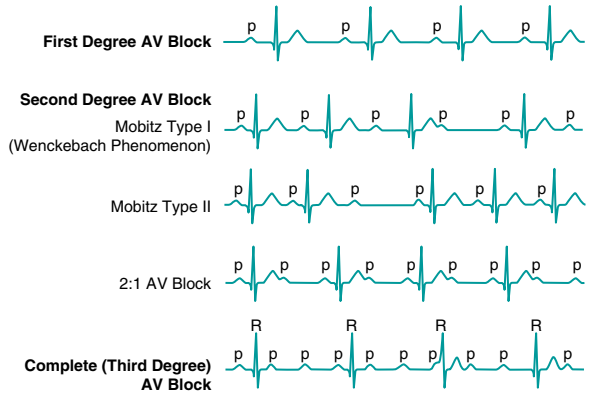

Fig. 484.13 Atrioventricular (AV) block. *(From Park MY. Pediatric Cardiology for Practitioners, 5th ed. Philadelphia: Mosby; 2008: Fig 25-1, p. 446.)*

especially the **Fontan procedure** and the **atrial switch** (Mustard or Senning) operation for transposition of the great arteries. Clinical manifestations depend on the heart rate. Most patients remain asymptomatic without treatment, but dizziness and syncope can occur during periods of marked sinus slowing with failure of junctional escape. Pacemaker therapy is indicated in patients who experience symptoms such as exercise intolerance or syncope.

Patients with sinus node dysfunction may also have episodes of SVT **("tachy-brady" syndrome)** with symptoms of palpitations, exercise intolerance, or dizziness (Fig. 484.12). Treatment must be individualized. Drug therapy to control tachyarrhythmias (propranolol, sotalol, amiodarone) may suppress sinus and AV node function to such a degree that further symptomatic bradycardia may be produced. Therefore insertion of a pacemaker in conjunction with drug therapy is usually necessary for such patients, even in the absence of symptoms ascribable to low heart rate.

484.7 Atrioventricular Block

Aarti S. Dalal and George F. Van Hare

Atrioventricular block may be divided into three forms (Fig. 484.13). In **first-degree AV block**, the PR interval is prolonged but all the atrial impulses are conducted to the ventricle. In **second-degree AV block**, not every atrial impulse is conducted to the ventricle. In the variant of second-degree block known as the **Wenckebach type** (also called **Mobitz type I**), the PR interval increases progressively until a P wave is not conducted. In the cycle following the dropped beat, the PR interval normalizes. In **Mobitz type II** there is no progressive conduction delay or subsequent shortening of the PR interval after a blocked beat. This conduction defect is less common but has more potential to cause syncope and may be progressive. A related condition is **high-grade second-degree AV block**, in which two or more P waves in a row fail to conduct. This is even more dangerous. In **third-degree AV block (complete heart block)**, no impulses from the atria reach the ventricles. An independent escape rhythm is usually present but may not be reliable, leading to syncope or even sudden death.

Congenital complete AV block in children is presumed to be caused by autoimmune injury of the fetal conduction system by maternally derived immunoglobulin G antibodies (anti-SSA/Ro, anti-SSB/La) in a mother with overt or, more often, asymptomatic systemic lupus erythematosus (SLE) or Sjögren syndrome. Autoimmune disease accounts for 60–70% of all cases of congenital complete AV block and 80% of cases in which the heart is structurally normal (Fig. 484.14). A pathogenic variant in *NKX2-5* is associated with congenital AV block and an atrial septal defect.

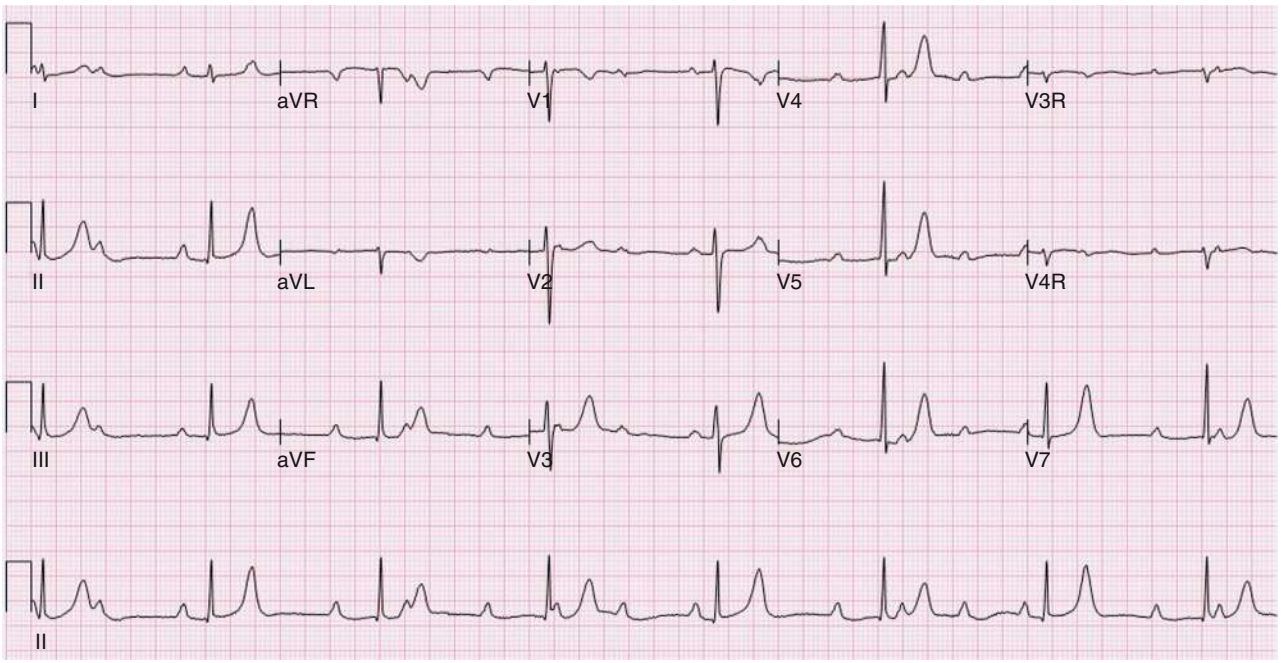

Fig. 484.14 Congenital complete atrioventricular (AV) block. The ventricular rate is regular at 44 beats/min. The atrial rate is approximately 100 beats/min and completely dissociated from the ventricle. The QRS morphology is normal, which is common in congenital complete AV block.

Complete AV block is also seen in patients with complex CHD and abnormal embryonic development of the conduction system. It has been associated with myocardial tumors and myocarditis. Acquired heart block (first, second, or third degree) is seen in Lyme disease and COVID-19–associated multisystem inflammatory syndrome. In these syndromes, first-degree heart block may progress to second- or third-degree heart block. Complete AV block is a known complication of myocardial abscess secondary to endocarditis. It is also seen in genetic conditions, including LQTS, Emery Dreifuss muscular dystrophy, and Kearns-Sayre syndrome. Postoperative AV block can be a complication of CHD repair—in particular, those repairs involving closure of a ventricular septal defect.

The incidence of congenital complete AV block is 1 per 20,000-25,000 live births; a high fetal loss rate may cause an underestimation of its true incidence. In some infants of mothers with SLE, complete AV block is not present at birth but develops within the first 3-6 months after birth. The arrhythmia is often diagnosed in the fetus (secondary to the dissociation between atrial and ventricular contractions seen on fetal echocardiography) and may produce hydrops fetalis. Maternal treatment with corticosteroids to halt progression or reverse AV block is controversial. Infants with associated CHD and heart failure have a high mortality rate.

In older children with otherwise normal hearts, complete AV block is often asymptomatic, although syncope and sudden death may occur. Infants and toddlers may have night terrors, tiredness with frequent naps, and irritability. The peripheral pulse is prominent because of the compensatory large ventricular stroke volume and peripheral vasodilation; systolic blood pressure is elevated. Jugular venous pulsations occur irregularly and may be large when the atrium contracts against a closed tricuspid valve (cannon wave). Exercise and atropine may produce an acceleration of 10-20 beats/min. Systolic murmurs are frequently audible along the left sternal border, and apical mid-diastolic murmurs are not unusual. The first heart sound is variable because of variable ventricular filing with AV dissociation. AV block may result in enlargement of the heart because of slow rates and increased diastolic ventricular filling.

The **diagnosis** is confirmed by electrocardiography; the P waves and QRS complexes have no constant relationship (see Fig. 484.14). The QRS duration may be prolonged, or it may be normal if the heartbeat is initiated high in the AV node or bundle of His.

The **prognosis** for congenital complete AV block is usually favorable; patients who have been observed to age 30-40 have lived normal, active lives. Some patients have episodes of exercise intolerance, dizziness, and syncope (Stokes-Adams attacks); syncope requires the implantation of a permanent cardiac pacemaker. Pacemaker implantation should be considered for patients who develop symptoms such as progressive cardiac dilation, prolonged pauses, or daytime average heart rates of ≤50 beats/min. In addition, prophylactic pacemaker implantation in adolescents is reasonable considering the low risk of the implant procedure and the difficulty in predicting who will develop sudden severe symptoms.

Cardiac pacing is recommended in neonates with low ventricular rates (≤55 beats/min), evidence of heart failure, wide complex rhythms, or CHD (with ventricular rates <70 beats/min). Isoproterenol, atropine, or epinephrine may be tried to increase the heart rate temporarily until pacemaker placement can be arranged. Transthoracic epicardial pacemaker implants have traditionally been used in infants; transvenous placement of pacemaker leads is available for young children. Postsurgical complete AV block can occur after any open heart procedure requiring suturing near the AV valves or crest of the ventricular septum. Postoperative heart block is initially managed with temporary pacing wires. The likelihood of a return of normal conduction after 10-14 days is low; a permanent pacemaker is recommended after that time.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 485

Sudden Death

Aarti S. Dalal and George F. Van Hare

Sudden death other than sudden infant death syndrome is rare in children. The causes of sudden death can be divided into traumatic versus nontraumatic in origin. *Traumatic* causes of sudden death are the most common in children; these include motor vehicle crashes, violent deaths, recreational deaths, and occupational deaths. *Nontraumatic* sudden deaths are often the result of specific cardiac causes. The incidence of sudden death varies from 0.8 to 6.2 per 100,000 per year in children and adolescents, in contrast to the higher incidence of **sudden cardiac death (SCD)** in adults of 1 per 1,000. Approximately 65% of sudden deaths are a result of heart-related problems in patients with either normal or congenitally (repaired, palliated, or unoperated) abnormal hearts. Competitive high school **sports** (basketball, soccer, football) are high-risk environmental factors. Common identifiable causes of death in competitive athletes include hypertrophic cardiomyopathy, with or without obstruction to left ventricular outflow, other cardiomyopathies, channelopathies, and anomalous coronary arteries; most are sudden *unexplained* deaths (Fig. 485.1). Table 485.1 lists other potential causes. These can be classified as *structural* abnormalities, including aortic stenosis and coronary artery abnormalities; myocardial disease, such as myocarditis; conduction system disease, including long QT syndrome; and miscellaneous causes, including seizures, pulmonary hypertension, and commotio cordis. Symptoms may be absent before the event but, if present, include syncope, chest pain, dyspnea, exercise intolerance, and palpitations. Patients may have a family history of heart disease (dilated or hypertrophic cardiomyopathy, long QT interval, arrhythmogenic [right ventricular] cardiomyopathy, Brugada or Marfan syndromes) or sudden unexplained death. Death often follows exertion or exercise. Some patients with sudden death during sports have anatomically normal hearts at autopsy; these patients should undergo genetic testing for hereditary arrhythmia syndromes.

MECHANISM OF SUDDEN DEATH

There are three recognized mechanisms of sudden death: *arrhythmic, nonarrhythmic cardiac* (circulatory and vascular causes), and *noncardiac*. **Ventricular fibrillation (VF)**, although the most common final cause of sudden death in adults, is only the final cause in 10–20% of children with SCD. More often, **bradycardia** leads either to VF or asystole (see Chapter 484).

CONGENITAL HEART DISEASE

Valvar aortic stenosis is the congenital defect most often associated with sudden death in children. Historically, approximately 5% of children with this disease die, although this has become quite rare in the modern era. A history of syncope, chest pain, and evidence of severe obstruction and left ventricular hypertrophy are risk factors (see Chapter 476.5).

Coronary artery anomalies are also frequently associated with sudden death in children and adolescents. The most common abnormality associated with sudden death is the origin of the left main coronary artery from the right sinus of Valsalva. The coronary artery takes an interarterial course between the aorta and pulmonary artery and may also have an intramural course, traveling within the ventricular myocardium. Exercise results in a rise in pulmonary and aortic pressure, and this is thought to compress the left main coronary artery and results in ischemia caused by compression or kinking. Anomalous origin of the right coronary artery from the left sinus of Valsalva is much more common, but only rarely is a cause of sudden death.

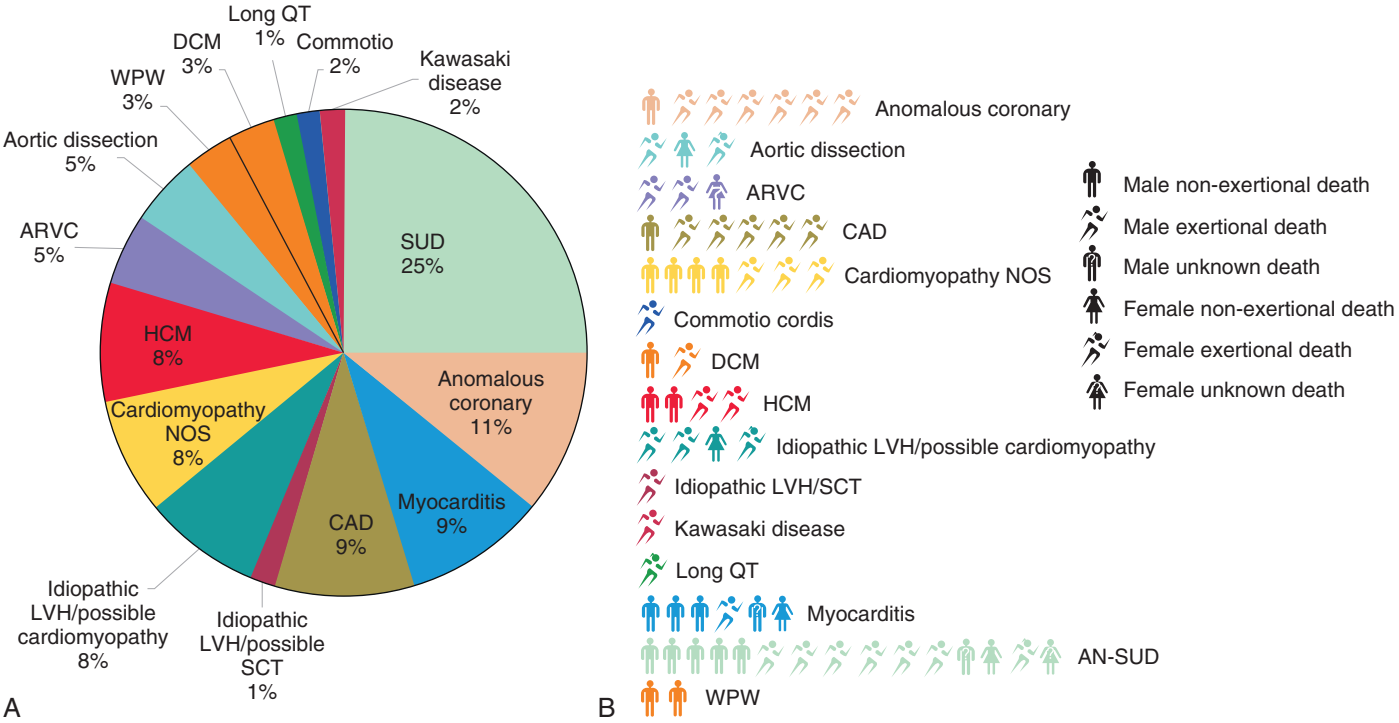

Fig. 485.1 A, Causes of sudden cardiac death in adolescent and young adult athletes. B, Cause and activity at time of death. One person figure equals one death; female figures follow male figures unless no male deaths were present. AN-SUD, Autopsy-negative sudden unexplained death; ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; NOS, not otherwise specified; SCT, sickle cell trait; SUD, sudden unexplained death; WPW, Wolff-Parkinson-White syndrome. *(From Harmon KG, Asif I, Maleszewski JJ, et al. Incidence, cause, and comparative frequency of sudden cardiac death in National Collegiate Athletic Association athletes. Circulation. 2015;132:10–19, Fig. 2.)*

CARDIOMYOPATHY

All three major types of cardiomyopathy (hypertrophic, dilated, and restrictive) are associated with sudden death in the pediatric population; cardiac arrest or sudden death may be the initial manifestation of the cardiomyopathy (see Chapter 488.1).

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the athletic adolescent in the United States. The annual risk of sudden death in young patients with HCM is 2% per year. Risk factors for sudden death include a history of syncope, symptoms, myocardial size, ventricular arrhythmias, and presentation at an early age. Many patients with HCM have left ventricular outflow tract obstruction (LVOTO). The mechanism of sudden death is arrhythmic and may be secondary to the development of dynamic obstruction with exercise and resultant loss of cardiac output, or may be related to cardiac ischemia. Thus patients without LVOTO are also at risk of sudden death. The **dilated cardiomyopathies** are also associated with SCD in children, although the risk is clearly lower than in adults.

Arrhythmogenic cardiomyopathy (also referred to as *arrhythmogenic right ventricular cardiomyopathy*) is a specific form of cardiomyopathy associated with exercise-induced ventricular arrhythmias and sudden death. It mainly affects the right ventricle, but the left can be involved as well. The diagnosis can be difficult; MRI, electrophysiology study, or endomyocardial biopsy is used with limited reliability. Pathologically, the disease is characterized by transmural fatty replacement of right ventricular myocardium, with patchy areas of fibrosis. Pathogenic variants are noted in ~60% of this autosomal dominant (with incomplete penetrance) disorder; associated genes include *PKP2, DSP, DSC2, DSG2, JUP, CTNNA3, PLN, TMEN43, SCN5A, CDH2,* and *DES*.

Myocarditis has often been found on pathology of patients with sudden death of unknown etiology. Symptoms before sudden death may be absent or may include overt heart failure or subtle findings such as a high heart rate. Pediatric patients with this disease may have complete atrioventricular block or ventricular arrhythmias.

Table 485.1 Potential Causes of Sudden Death in Infants, Children, and Adolescents

SIDS AND SIDS "MIMICS"
SIDS
Long QT syndromes*
Inborn errors of metabolism
Child abuse
Myocarditis
Ductal-dependent CHD
CORRECTED OR UNOPERATED CHD
Aortic stenosis
Tetralogy of Fallot
Transposition of great vessels (postoperative atrial switch)
Mitral valve prolapse
Hypoplastic left heart syndrome
Eisenmenger syndrome
CORONARY ARTERIAL DISEASE
Anomalous origin*
Anomalous tract (tunneled)
Kawasaki disease
Periarteritis
Arterial dissection
AORTOPATHIES (DISSECTION, RUPTURED AORTA)
Marfan syndrome
Loeys-Dietz syndrome
Takayasu aortitis
Smooth muscle dysfunction syndrome
Vascular Ehlers-Danlos syndrome
Familial thoracic aortic aneurysm and dissection syndrome
Mycotic aneurysm
MYOCARDIAL DISEASE
Myocarditis
Hypertrophic cardiomyopathy*
Dilated cardiomyopathy
Arrhythmogenic (right ventricular) cardiomyopathy
Lyme carditis
Takotsubo syndrome
Nonischemic left ventricular scar
Myocardial infarction
CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA
Long QT syndromes*
Brugada syndrome
Proarrhythmic drugs
Wolff-Parkinson-White syndrome
Complete AV block
Commotio cordis
Idiopathic ventricular fibrillation
Arrhythmogenic (right ventricular) cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Heart tumor
MISCELLANEOUS
Seizures
Pulmonary hypertension
Pulmonary embolism
Heat stroke
Cocaine and other stimulant drugs or medications
Anorexia nervosa
Electrolyte disturbances

*Common.
CHD, Congenital heart disease; SIDS, sudden infant death syndrome.

CARDIAC ARRHYTHMIA

A primary conduction system abnormality may result in sudden death. Causes include Wolff-Parkinson-White (WPW) syndrome, long QT syndrome, short QT syndrome, and Brugada syndrome. Besides causing supraventricular tachycardia, **WPW syndrome** can result in atrial fibrillation with rapid conduction across the accessory pathway, leading to VF and sudden death (Fig. 485.2). This is unusual in pediatric patients but has an increasing incidence in adolescence. In adults, there is an incidence of sudden death in asymptomatic patients of 1 per 1,000 patient-years, but this rate may well be higher in children, who have not yet survived to adulthood. As digoxin and verapamil can augment conduction down accessory pathways, these drugs are contraindicated in WPW syndrome.

Long QT syndrome (LQTS; see Chapter 484), a group of channelopathies that affect ventricular repolarization, is also associated with sudden death (Fig. 485.3). The mechanism of sudden death is polymorphic ventricular tachycardia **(torsades de pointes)** (Fig. 485.4). An initial presentation of SCD is found in 9% of patients. Thus treatment of asymptomatic patients with a long QT interval on electrocardiogram (ECG) and positive family history is advised.

Acquired long QT interval may be seen in patients with marked electrolyte abnormalities, central nervous system injury, or starvation (including bulimia and anorexia nervosa). Medications can also result in prolongation of the QT interval (see Table 484.4). These patients are also at risk of malignant ventricular arrhythmias, and correction of the underlying problem or withdrawal of the inciting medication may be necessary to reduce the risk of sudden death.

Brugada syndrome, an autosomal dominant disorder associated with SCD, often occurs with fever, drugs, nighttime electrolyte disorders, or after a large meal (Fig. 485.5). The most common pathogenic variant is a loss of function in *SCN5A,* seen in up to 30% of patients. Typical ECG findings include *coved* ST segment elevations in leads V_1-V_3; death results from either VF or ventricular tachycardia.

MISCELLANEOUS CAUSES

Commotio cordis is an often fatal condition that follows blunt nonpenetrating trauma to the chest (e.g., from a baseball or hockey puck). Occasionally, innocent-appearing chest blows incurred at home or at a playground may be fatal. Patients experience immediate VF in the absence of identifiable cardiac trauma (contusion, hematoma, lacerated coronary artery). This risk is highest in children before adolescence. Historically, death results from VF that is unresponsive to resuscitative efforts in 85–90% of children. Immediate direct current (DC) defibrillation may be effective, if available, particularly if employed

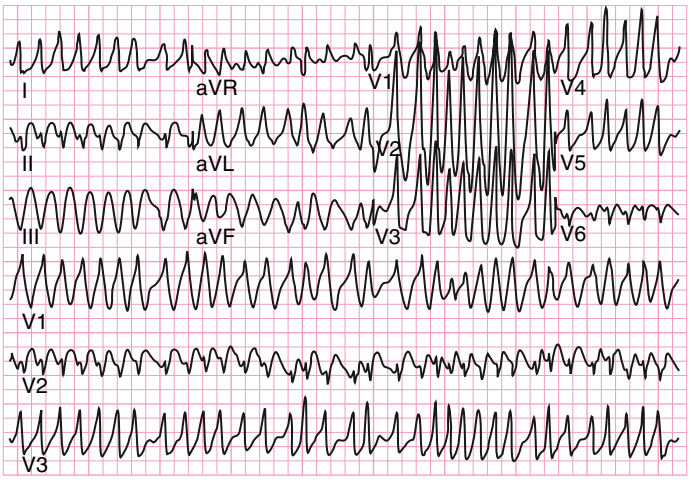

Fig. 485.2 Atrial fibrillation in a patient with Wolff-Parkinson-White syndrome and rapid conduction to the ventricle. Note the wide QRS complexes, a result of full preexcitation, and the irregularly irregular ventricular response, caused by the atrial fibrillation.

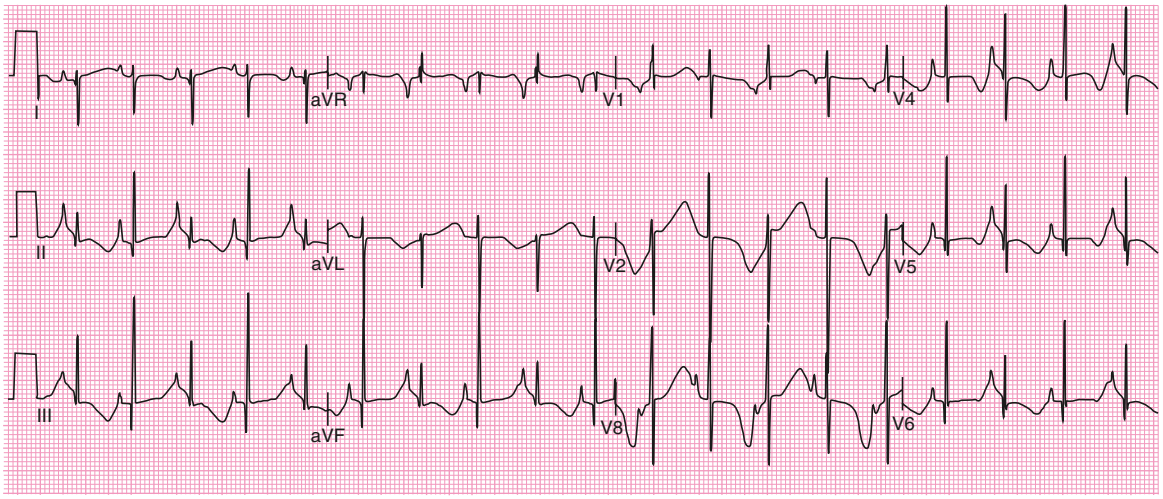

Fig. 485.3 Long QT syndrome in a neonate. QTc is markedly prolonged, and T-wave alternans is evident.

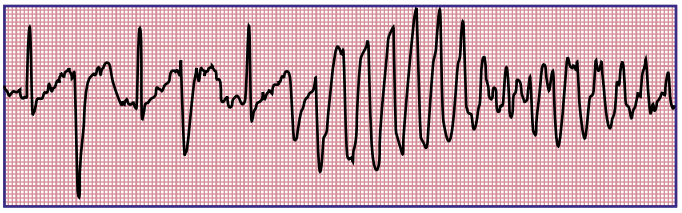

Fig. 485.4 Episode of torsades de pointes in a patient with long QT syndrome.

immediately; however, it is reported to be successful in only approximately 25% of cases.

EVALUATION AND THERAPY FOR RESUSCITATED PATIENTS

It is important to focus therapy on potentially reversible causes of sudden death. These include correction of major hemodynamic defects, pacing therapy for a patient with bradycardia, or supportive therapy for myocarditis. Unfortunately, reversible causes are not always found in young cardiac arrest survivors. Adding to this dilemma is the limited ability to predict antiarrhythmic drug response or risk of recurrence. The **implantable-cardioverter defibrillator** (ICD) is the therapy of choice for survivors of most forms of arrhythmic sudden death, with the exception of correctable causes such as WPW (see Chapter 484).

MEDICATION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Concern has been raised that stimulant medications prescribed for children with attention-deficit/hyperactivity disorder might increase the risk of sudden death (see Chapter 50). The concern arises from a limited number of reports to the U.S. Food and Drug Administration (FDA) of sudden death of unknown etiology in individuals taking stimulant medications, mostly adults. In a few cases, left ventricular hypertrophy caused by hypertension, coarctation of the aorta, or HCM has been identified at postmortem examination. No prospective studies support the notion that these medications increase the risk, and there is no evidence that ECG screening will reliably identify a subgroup at risk. Some have suggested ECG screening of children before starting these medications, but there is no consensus that such an approach is effective. The current recommendations do not support ECG screening before the initiation of stimulant medication in the absence of a positive cardiac history.

PREVENTION OF SUDDEN DEATH

The probability of survival to hospital discharge for a young patient who experiences an out-of-hospital cardiac arrest is <20%. The

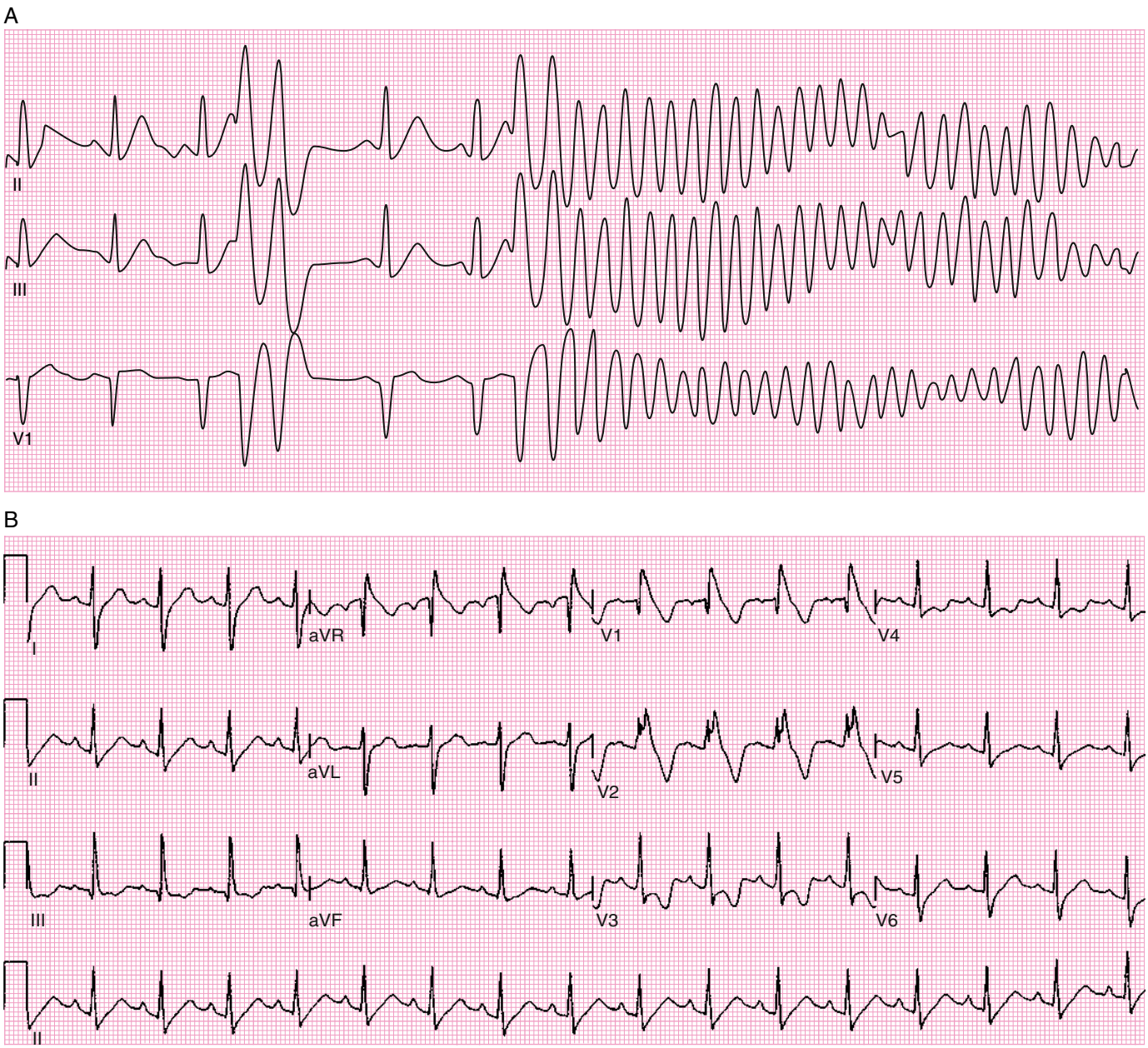

Fig. 485.5 Brugada syndrome. **A**, Frequent ventricular ectopy and sustained polymorphic ventricular tachycardia. **B**, Persistent coved-type ST segment elevation in lead V_1 and V_2 characteristic of Brugada type I. *(A from Talib S, van de Poll SE. Brugada syndrome diagnosed after Ramadan. Lancet. 2013;382:100.)*

presence of immediate **automatic external defibrillators** (AEDs), when combined with standard cardiopulmonary resuscitation (CPR) at the site of exercise (gym, track, basketball, or football arena), improves survival substantially. Thus identifying patients at risk is extremely important. The American Academy of Pediatrics Policy Statement on Sudden Death in the Young provides primary care providers with guidelines screening for life-threatening conditions, regardless of athletic status.

Some of the more common causes of sudden death in children and adolescents can be identified from the patient's history (prodromal symptoms), the family history, and physical examination. The American Heart Association (AHA) has a recommended 14-point preparticipation evaluation (PPE) that includes questions about personal and family history in addition to physical exam findings (Table 485.2). The screening for sudden cardiac arrest and SCD should be performed at the time of PPE or upon entry into middle school and high school. The AAP's Preparticipation Physical Evaluation form is available at https://www.aap.org/. Of paramount importance is the careful evaluation of any child who experiences **syncope** in association with **exercise** because this may be the last opportunity to diagnose a life-threatening condition in such a patient.

Patient avoidance of high-risk behavior (cocaine use, anorexia nervosa) and knowledge of drug side effects or drug interactions and contraindications are critical. Chest-protecting equipment has not been shown to prevent commotio cordis. Prompt bystander CPR and rapid defibrillation with an AED has the highest chance of leading to survival. Family survivors of victims of sudden death should also be evaluated for genetic etiologies of SCD (e.g., LQTS, HCM).

The 14-element screening checklist underperforms and may miss high-risk cardiac lesion. Depending on the population (elite vs recreational athletes) and the screening protocol (checklist, with ECG, with echocardiogram, with cardiac MRI), the incidence of

Table 485.2 Fourteen-Element Cardiovascular Screening Checklist for Congenital and Genetic Heart Disease

PERSONAL HISTORY
1. Chest pain/discomfort/tightness/pressure related to exertion
2. Unexplained syncope/near-syncope: Judged not to be of neurocardiogenic (vasovagal) origin; of particular concern when occurring during or after physical exertion
3. Excessive exertional and unexplained dyspnea/fatigue or palpitations, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
6. Prior restriction from participation in sports
7. Prior testing for the heart, ordered by a physician
FAMILY HISTORY
8. Premature death (sudden and unexpected, or otherwise) before age 50 attributable to heart disease in at least one relative
9. Disability from heart disease in close relative <50 yr of age
10. Hypertrophic or dilated cardiomyopathy, long QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of certain cardiac conditions in family members
PHYSICAL EXAMINATION
11. Heart murmur: Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both the supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction
12. Femoral pulses to exclude aortic coarctation
13. Physical stigmata of Marfan syndrome
14. Brachial artery blood pressure (sitting position): Preferably taken in both arms

From American College of Cardiology: ACC/AHA release recommendations for congenital and genetic heart disease screenings in youth. https://www.acc.org/latest-in-cardiology/articles/2014/09/15/14/24/acc-aha-release-recommendations-for-congenital-and-genetic-heart-disease-screenings-in-youth

at-risk cardiac lesions varies from 0.3–0.4% to 1.4%. The use of a preparticipation ECG for the detection of those athletes at risk for sudden death has long been controversial. Because many athletes either have no pre-event symptoms or are unwilling to admit to symptoms for concern of not being able to play, some have proposed that the ECG may identify a small but at-risk group with HCM or prolonged QT, Brugada, or WPW syndromes. These ECGs would fail to identify patients with phenotype-negative LQTS or catecholaminergic polymorphic ventricular tachycardia, as well as coronary artery anomalies. In addition, many false positives may be identified, requiring further evaluation to exclude worrisome diagnoses. Preparticipation ECG testing is mandatory in several European countries but not in the United States, although many athletic groups with varsity-level or professional membership (e.g., collegiate or professional sports organizations) require such testing as part of the medical evaluation. If the ECG is abnormal, **echocardiography** is performed. Cost-effectiveness studies suggest that the cost for implementation of a national program in the United States would be prohibitive because of the low incidence of sudden death in the pediatric population, the high rate of false-positive ECGs, and the difficulty in definitively excluding cardiac disease in patients with borderline ECG findings. Although studies of regional or national screening programs have suggested some benefit (e.g., the Veneto region of Italy), others have failed to demonstrate any effect of screening on the background incidence of sudden death in young individuals.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 5

Acquired Heart Disease

Chapter 486

Infective Endocarditis*

Erin Faherty and Thomas S. Murray

Infective endocarditis includes acute and subacute *bacterial* endocarditis, as well as *nonbacterial* endocarditis, caused by viruses, fungi, and other microbiologic agents. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents. The inability to eradicate infective endocarditis by prevention or early treatment stems from several factors. The disease represents a complex interplay between a pathogen and host factors such as endothelial disruption and immune function that is still not completely understood; the nature of the infecting organism changes over time; and diagnosis may be difficult during early stages and thus is often delayed until a more serious manifestation has developed. Special risk groups include intravenous drug users; survivors of cardiac surgery, especially those with mechanical prosthesis; patients taking immunosuppressant medications; and patients who require chronic intravascular catheters. Some patients have endocarditis on a native valve previously thought to be healthy but found to have mild structural abnormalities on surgical inspection.

ETIOLOGY

Viridans-type streptococci (α-hemolytic streptococci groups such as *Streptococcus mitis, S. anginosus, S. mutans, S. salivarius, S. bovis, S. sanguinis,* and *S. mitis*) and *Staphylococcus aureus* remain the leading causative agents for endocarditis in pediatric patients. Other organisms cause endocarditis less frequently, and in approximately 6% of cases, blood cultures are negative for any organisms (Table 486.1). No relationship exists between the infecting organism and the type of congenital defect, duration of illness, or age of the child. Staphylococcal endocarditis is more common in patients with no underlying heart disease. Viridans group streptococcal infection is more common after dental procedures; enterococci are seen more often after lower bowel or genitourinary manipulation.

Pseudomonas aeruginosa or *Serratia marcescens* is seen more frequently in intravenous drug users, and fungal organisms are encountered after open heart surgery. Coagulase-negative staphylococci are common in the presence of an indwelling central venous catheter.

EPIDEMIOLOGY

Infective endocarditis is often a complication of congenital or rheumatic heart disease but can also occur in children without any abnormal valves or cardiac malformations. In developed countries, congenital heart disease (CHD) is the overwhelming predisposing factor. Endocarditis is rare in infancy; in this age-group it usually follows open heart surgery or is associated with a central venous line.

Patients with congenital heart lesions where there is turbulent blood flow because of a hole or stenotic orifice, especially if there is a high-pressure gradient across the defect, are most susceptible to

* The authors would like to thank Dr Robert S. Baltimore for his work on previous editions of this chapter.

Table 486.1 Bacterial Agents in Pediatric Infective Endocarditis

COMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS
Viridans group streptococci *(S. mutans, S. sanguinis, S. mitis)*
Staphylococcus aureus
Group D streptococcus (enterococcus) *(S. bovis, S. faecalis)*
UNCOMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS
Streptococcus pneumoniae
Haemophilus influenzae
Coagulase-negative staphylococci
Abiotrophia defectiva (nutritionally variant streptococcus)
*Coxiella burnetii (Q fever)**
Neisseria gonorrhoeae
*Brucella**
*Chlamydia psittaci**
*Chlamydia trachomatis**
*Chlamydia pneumoniae**
Legionella*
Bartonella*
*Tropheryma whipplei** (Whipple disease)
HACEK group†
*Streptobacillus moniliformis**
*Pasteurella multocida**
Campylobacter fetus
Culture negative (6% of cases)
PROSTHETIC VALVE
Staphylococcus epidermidis
Staphylococcus aureus
Viridans group streptococcus
Pseudomonas aeruginosa
Serratia marcescens
Diphtheroids
*Legionella spp.**
HACEK group†
Fungi‡

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for >7 days, polymerase chain reaction on blood or valve for 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.
†The HACEK group includes Haemophilus spp. (H. paraphrophilus, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella spp.
‡Candida spp., Aspergillus spp., Pseudallescheria boydii, Histoplasma capsulatum.

endocarditis. This turbulent flow traumatizes the vascular endothelium, creating a substrate for deposition of fibrin and platelets, leading to the formation of a *nonbacterial thrombotic embolus (NBTE)* that is thought to be the initiating lesion for infective endocarditis. Biofilm forms on the surface of implanted mechanical devices such as valves, catheters, or pacemaker wires, which also serves as the adhesive substrate for infection. The development of transient bacteremia then colonizes this NBTE or biofilm, leading to proliferation of bacteria within the lesion. Bacterial surface proteins, such as the FimA antigen in viridans streptococci, act as adhesion factors to the NBTE or biofilm, after which bacteria can rapidly proliferate within the vegetation. Given the heavy colonization of mucosal surfaces (the oropharynx or gastrointestinal, vaginal, or urinary tracts) by potentially pathogenic bacteria, these surfaces are thought to be the origin of this transient bacteremia. There is controversy over the extent to which daily activities (e.g., brushing or flossing the teeth) vs invasive procedures (e.g., dental cleaning or surgery) contribute to this bacteremia. Transient bacteremia is reported to occur in 20–68% of patients after tooth brushing and flossing, and even in 7–51% of patients after chewing food. The magnitude of this bacteremia is also similar to that resulting from dental procedures. Maintenance of good oral hygiene may be a more important factor in decreasing the frequency and magnitude of bacteremia. Case reports suggest that body piercing and tattoos may be additional risk factors.

Children at **highest risk** of adverse outcome after infective endocarditis include those with prosthetic cardiac valves or other prosthetic material used for cardiac valve repair, unrepaired cyanotic CHD (including those palliated with shunts and conduits), completely repaired defects with prosthetic material or device during the first 6 months after repair, repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or device, valve stenosis or insufficiency occurring after heart transplantation, permanent valve disease from **rheumatic fever** (mitral stenosis, aortic regurgitation), and previous infective endocarditis. Patients with high-velocity blood flow lesions such as ventricular septal defects (VSDs) and aortic stenosis are also at high risk. In older patients, congenital bicuspid aortic valves and mitral valve prolapse with regurgitation pose additional risks for endocarditis. Surgical correction of CHD may reduce but does not eliminate the risk of endocarditis, except for the repair of a simple atrial septal defect or patent ductus arteriosus without prosthetic material.

In ~30% of patients with infective endocarditis, a predisposing factor is presumably recognized. Although a preceding dental procedure may be identified in 10–20% of patients, the time of the procedure may range from 1 to 6 months before the onset of symptoms—thus the continued controversy over the absolute risk of infective endocarditis after dental procedures. Primary bacteremia with *S. aureus* is thought to be another risk for endocarditis. The occurrence of endocarditis directly after most routine heart surgery is relatively low, but it can be an antecedent event, especially if prosthetic material is used. In the small group of patients with culture-negative endocarditis, epidemiologic or exposure factors may contribute to the diagnosis (Table 486.2).

CLINICAL MANIFESTATIONS

Table 486.3 outlines the manifestations of infective endocarditis. Early manifestations are usually mild, especially when viridans group streptococci are the infecting organisms. Prolonged fever without other manifestations (except occasionally weight loss) that persists for as long as several months may be the only symptom. Alternatively, with pathogenic organisms such as *S. aureus,* the onset may be acute and severe, with high intermittent fever and prostration. Usually, the onset and course vary between these two extremes. Fever in the absence of signs of URI in a patient with congenital heart disease must be considered as endocarditis. The symptoms are often nonspecific and consist of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and at times chills, nausea, and vomiting. The cardiac examination often depends on the underlying heart disease and the location of infection. A new pathologic murmur or changing heart murmur may be appreciated and can be associated with heart failure. Of note, children with palliated congenital heart disease, such as those palliated with a shunt, may not present with a change in murmur. Splenomegaly and petechiae are seen in <50% of patients. Serious neurologic complications such as embolic strokes, cerebral abscesses, mycotic aneurysms, and hemorrhage are most often associated with staphylococcal disease and may be late manifestations. Meningismus, increased intracranial pressure, altered sensorium, and focal neurologic signs are manifestations of these complications. Meningitis may be seen together with pneumococcal endocarditis. Myocardial abscesses may occur with staphylococcal disease and may damage the cardiac conducting system, causing heart block, or may rupture into the pericardium and produce purulent pericarditis. Pulmonary (with right-sided endocarditis) and systemic emboli (with left-sided lesions) are infrequent, except with fungal disease.

Many of the classic **skin findings** develop late in the disease; they are seldom seen in appropriately treated patients. Such manifestations include **Osler nodes** (tender, pea-size intradermal nodules in the pads of the fingers and toes), **Janeway lesions** (painless, small,

Table 486.2 Epidemiologic Clues in the Etiologic Diagnosis of Culture-Negative Endocarditis

EPIDEMIOLOGIC FEATURE	COMMON MICROORGANISM
Injection drug use (IDU)	*Staphylococcus aureus,* including community-acquired oxacillin-resistant strains Coagulase-negative staphylococci β-Hemolytic streptococci Fungi Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* Polymicrobial
Indwelling cardiovascular medical devices	*S. aureus* Coagulase-negative staphylococci Fungi Aerobic gram-negative bacilli *Corynebacterium* spp.
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus spp.* Group B streptococci *(S. agalactiae)* *Listeria monocytogenes* Aerobic gram-negative bacilli *Neisseria gonorrhoeae*
Chronic skin disorders, including recurrent infections	*S. aureus* β-Hemolytic streptococci
Poor dental health, dental procedures	Viridans group streptococci Nutritionally variant streptococci *Abiotrophia defectiva* *Granulicatella* spp. *Gemella* spp. HACEK organisms
Alcohol use, cirrhosis	*Bartonella spp.* *Aeromonas spp.* *Listeria spp.* *Streptococcus pneumoniae* *β-Hemolytic* streptococci
Burns	*S. aureus* Aerobic gram-negative bacilli, including *P. aeruginosa* Fungi
Diabetes mellitus	*S. aureus* β-Hemolytic streptococci *S. pneumoniae*
Early (≤1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Aerobic gram-negative bacilli Fungi *Corynebacterium* spp. *Legionella* spp.
Late (>1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* *Viridans group streptococci* *Enterococcus* spp. Fungi *Corynebacterium* spp.
Dog or cat exposure	*Bartonella spp.* *Pasteurella spp.* *Capnocytophaga spp.*
Contact with contaminated milk or infected farm animals	*Brucella spp.* *Coxiella burnetii* *Erysipelothrix spp.*
Homeless, body lice	*Bartonella spp.*
HIV/AIDS	*Salmonella spp.* *S. pneumoniae* *S. aureus*
Pneumonia, meningitis	*S. pneumoniae*
Solid-organ transplantation	*S. aureus* *Aspergillus fumigatus* *Enterococcus spp.* *Candida spp.*
Gastrointestinal lesions	*Streptococcus gallolyticus (bovis)* *Enterococcus spp.* *Clostridium septicum*

HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp.; HIV/AIDS, human immunodeficiency virus infection and acquired immunodeficiency syndrome.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. *Circulation.* 2015;132:1435–1486.

erythematous, or hemorrhagic lesions on the palms and soles), and **splinter hemorrhages** (linear lesions beneath the nails). These lesions may represent vasculitis produced by circulating antigen-antibody complexes. Retinal lesions are seen in 10–20%.

In the newborn infant the major risk factor for infective endocarditis is the presence of a central intravenous line. Thus prematurity is a risk, as are other severe congenital abnormalities. CHD is less likely to be the underlying condition than it is for older children. The clinical conditions are variable and may be indistinguishable from sepsis or congestive heart failure. Identification of infective endocarditis is most often based on a high index of suspicion during evaluation of an infection in a child with an underlying risk factor.

DIAGNOSIS

The critical information for appropriate treatment of infective endocarditis is obtained from blood cultures. All other laboratory data are secondary in importance (see Table 486.3). Blood specimens for culture should be obtained as promptly as possible, even if the child feels well and has no other physical findings. Although increased blood volume can increase the sensitivity of the blood culture, smaller volumes are reasonable in neonates and small children. When small volumes of blood are present, a single aerobic blood culture bottle should be inoculated. Ideally, for patients weighing 2-12.7 kg, the volume of the first blood culture is 4 mL (repeat culture is 2 mL); for patients 12.8-36.3 kg it is 10 mL for initial and repeat, and for patients >36.3 kg, 20-30 mL for both. Three to five separate blood collections should be obtained after careful preparation of the phlebotomy site. Contamination presents a special problem because bacteria found on the skin may cause infective endocarditis. The timing of collections is not important because bacteremia can be expected to be relatively constant. In 90% of cases of endocarditis, the causative agent is recovered from the first two blood cultures. Bacteremia is low grade in 80% (<100 colony-forming units/mL of blood). The laboratory should be notified that endocarditis is suspected so that, if necessary, the blood can be cultured on enriched media for longer than usual (>5 days) to detect nutritionally deficient and fastidious bacteria or fungi.

Table 486.3 Manifestations of Infectious Endocarditis

HISTORY
Prior congenital or rheumatic heart disease
Preceding dental, urinary tract, or intestinal procedure
Intravenous drug use
Central venous catheter
Prosthetic heart valve
SYMPTOMS
Fever
Chills
Chest and abdominal pain
Arthralgia, myalgia
Dyspnea
Malaise, weakness
Night sweats
Weight loss
CNS manifestations (stroke, seizures, headache)
SIGNS
Elevated temperature
Tachycardia
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)
Janeway lesions
New or changing murmur
Splenomegaly
Arthritis
Heart failure
Arrhythmias
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)
Clubbing
LABORATORY STUDIES
Positive blood culture
Elevated erythrocyte sedimentation rate; may be low with heart or renal failure
Elevated C-reactive protein
Anemia
Leukocytosis
Immune complexes
Hypergammaglobulinemia
Hypocomplementemia
Cryoglobulinemia
Rheumatoid factor
Hematuria
Renal failure: azotemia, high creatinine (glomerulonephritis)
Chest radiograph: bilateral infiltrates, nodules, pleural effusions
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, or new-onset valve insufficiency

CNS, Central nervous system.

Table 486.4 Diagnostic Approach to Uncommon Pathogens Causing Endocarditis

PATHOGEN	DIAGNOSTIC PROCEDURE
Brucella spp.	Blood cultures; serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Coxiella burnetii	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and mNGS of surgical material or blood/plasma
Bartonella spp.	Blood cultures; serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Chlamydia spp.	Serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Mycoplasma spp.	Serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Legionella spp.	Blood cultures; serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Tropheryma whipplei	Histology and mNGS of surgical material or blood/plasma

IgG, Immunoglobulin G; mNGS, metagenomic next-generation sequencing; PCR, polymerase chain reaction
From Moreillon P, Que YA. Infective endocarditis *Lancet*. 2004;363:139–148.

Although bacteremia may occur in the absence of endocarditis, bacteremia secondary to *S. mutans, S. bovis I*, *S. mitis, S. sanguinis,* and *S. aureus* (in the absence of focal musculoskeletal infection) is highly concerning for endocarditis. Antimicrobial pretreatment of the patient reduces the yield of blood cultures by 50–60%. Other specimens that may be cultured include scrapings from cutaneous lesions, urine, synovial fluid, abscesses, and in the presence of manifestations of meningitis, cerebrospinal fluid. Serologic diagnosis or metagenomic next-generation sequencing or polymerase chain reaction for 16S and 28S ribosomal RNA (rRNA) for bacteria and fungi, respectively, of resected valve tissues is necessary in patients with unusual or fastidious microorganisms when there is suspicion of culture-negative endocarditis or if the patient has received prior antibiotics (Table 486.4 and Fig. 486.1). Metagenomic next-generation sequencing on blood and plasma may help identify pathogens in patients with culture-negative endocarditis. Suspicion should be high when evaluating infection in a child with an underlying contributing factor.

Echocardiography remains the mainstay of diagnosis. Two-dimensional echocardiography can identify the size, shape, location, and mobility of the lesion; when combined with Doppler interrogation, the presence of valve dysfunction (regurgitation, obstruction) can be determined. (Fig. 486.2). In pediatric patients, transthoracic echocardiogram is usually adequate for detection of lesions, especially for children <60 kg. Transesophageal echocardiogram should be considered in pediatric patients with limited transthoracic views; it is superior to transthoracic echocardiogram in evaluating prosthetic valves or complications of infective endocarditis, such as aortic root abscess. Intracardiac echocardiography can be useful for patients with suspicion for an infected pacemaker lead or implanted percutaneous pulmonary valve. Cardiac MRI may be useful in suspected perivalvular complications, and PET-CT may aid in the diagnosis of endocarditis for those patients with prosthetic valves.

Echocardiography may also be helpful in predicting embolic complications, given that lesions >1 cm and fungating masses are at greatest risk for embolization. The absence of vegetations does not exclude endocarditis, and vegetations are often not visualized in the early phases of the disease or in patients with complex congenital heart lesions. Electrocardiography should be part of the evaluation and can demonstrate new rhythm disorders such as **ventricular**

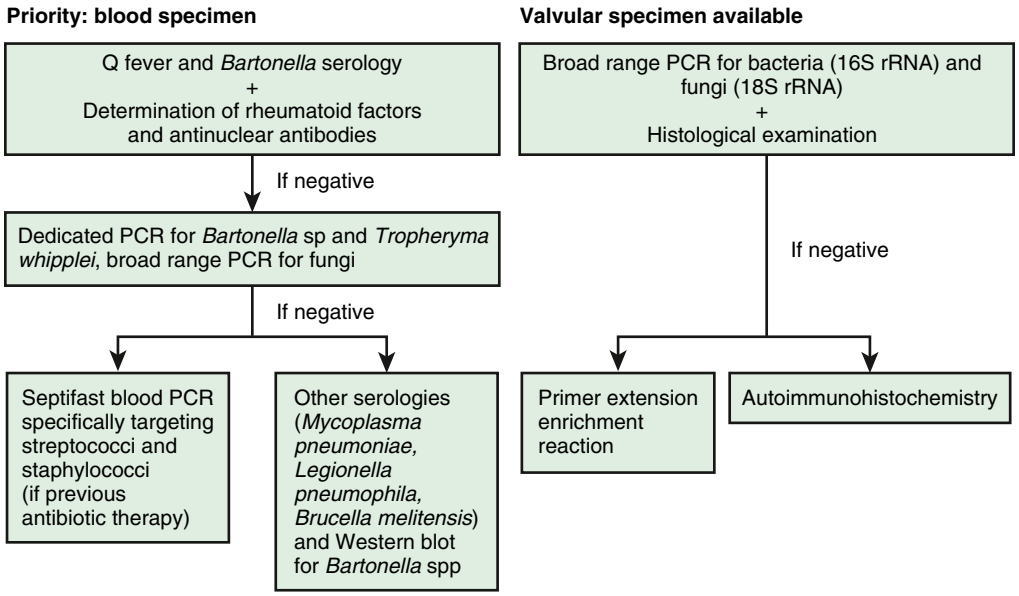

Fig. 486.1 Algorithm of diagnostic tests applied to clinical specimens for the identification of the causative agents of **blood culture–negative endocarditis**. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and *Bartonella* serologic analysis routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor be routinely done for the diagnosis of noninfective endocarditis. *(From Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. Lancet. 2012;379:965–975, Fig. 2.)*

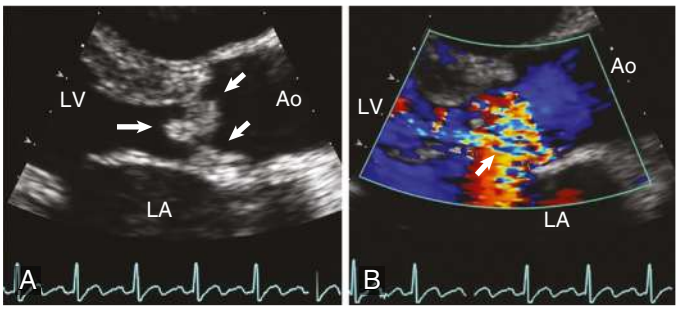

Fig. 486.2 Infective endocarditis of the native aortic valve. **A,** Transthoracic echocardiography shows vegetations *(small arrows)* attached to the left ventricular aspects of the valve cusps and prolapsing into the left ventricular outflow tract *(large arrow)* during diastole. **B,** Severe aortic regurgitation *(arrow)* is shown by color Doppler. Ao, Ascending aorta; LA, left atrium; LV, left ventricle. *(From Baddour LM, Freeman WK, Suri RM, Wilson WR. Cardiovascular infections. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 73-1, p. 1490.)*

ectopy and conduction disorders such as **complete heart block**. The presence of either of these findings, particularly heart block, may signal a serious or even life-threatening complication of endocarditis.

The **Duke criteria** help in the diagnosis of endocarditis (Table 486.5). Two major criteria, one major and three minor, or five minor criteria suggest definite endocarditis. Additional minor criteria to those listed include newly diagnosed clubbing, splenomegaly, splinter hemorrhages, or petechiae; high erythrocyte sedimentation rate or C-reactive protein level; presence of central nonfeeding or peripheral lines; and microscopic hematuria.

PROGNOSIS AND COMPLICATIONS

Despite the use of antibiotic agents, mortality remains high, up to 25%. Serious morbidity occurs in 50–60% of children with documented infective endocarditis; the most common is heart failure caused by worsening valvular regurgitation due to aortic or mitral valve vegetations, accompanied by ventricular dysfunction. Myocardial abscesses and toxic myocarditis may also lead to heart failure without characteristic changes in auscultatory findings and, occasionally, to life-threatening arrhythmias. Systemic emboli, often with central nervous system manifestations, are a major threat. Pulmonary emboli may occur in children with VSD or tetralogy of Fallot, although massive life-threatening pulmonary embolization is rare. Other complications include mycotic aneurysms, rupture of a sinus of Valsalva, obstruction of a valve secondary to large vegetations, acquired VSD, and heart block as a result of involvement (abscess) of the conduction system. Additional complications include meningitis, osteomyelitis, arthritis, renal abscess, purulent pericarditis, and immune complex–mediated glomerulonephritis.

TREATMENT

Antibiotic therapy should be instituted immediately once a definitive diagnosis of infectious endocarditis is made. When virulent organisms are responsible, small delays may result in progressive endocardial damage and are associated with a greater likelihood of severe complications. The choice of antibiotics, method of administration, and length of treatment should be coordinated with consultants from both cardiology and infectious diseases (Tables 486.6 and 486.7). Empirical therapy after appropriate blood cultures are drawn but before the identifiable agent is recovered may be initiated with vancomycin plus gentamicin in patients without a prosthetic valve and when there is a high risk of *S. aureus,* enterococcus, or viridans streptococci (the three most common organisms). High serum bactericidal levels must be maintained long enough to eradicate organisms that are growing in relatively inaccessible avascular vegetations. Between 5 and 20 times the in vitro minimal inhibitory concentration must be produced at the site of infection to destroy bacteria growing at the core of these lesions. Several weeks are required for a vegetation to organize completely; therapy must be continued through this period so that recrudescence can be avoided. A total of 4-6 weeks of treatment is usually recommended. Depending on the clinical and laboratory responses, antibiotic therapy may require modification, and some patients require more

Table 486.5 Definition of Infective Endocarditis (IE): Modified Duke Criteria

DEFINITE INFECTIVE ENDOCARDITIS

Pathologic Criteria

- Microorganisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; *or*
- Pathologic lesions; vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis

Clinical Criteria

- Two major criteria, *or*
- One major criterion and three minor criteria, *or*
- Five minor criteria

Possible Infective Endocarditis

- One major criterion and one minor criterion, *or*
- Three minor criteria

Rejected Diagnosis of Infective Endocarditis

- Firm alternative diagnosis explaining evidence of suspected IE, *or*
- Resolution of IE syndrome with antibiotic therapy for ≤4 days, *or*
- No evidence of IE at surgery or autopsy, on antibiotic therapy for ≤4 days, *or*
- Does not meet criteria for possible IE

DEFINITION OF TERMS USED IN MODIFIED DUKE CRITERIA

Major Criteria

- Blood culture findings positive for IE
  Typical microorganisms consistent with IE from two separate blood cultures:
  - Viridans streptococci, *Streptococcus gallolyticus* (formerly known as *S. bovis*), *Staphylococcus aureus,* HACEK group, *or*
  - Community-acquired enterococci, in the absence of a primary focus, *or*

  Microorganisms consistent with IE from persistently positive blood culture findings, defined as:
  - At least two positive culture findings of blood samples drawn >12 hr apart, *or*
  - Three or most of at least four separate culture findings of blood (with first and last sample drawn ≥1 hr apart)
  - Single positive blood culture for *Coxiella burnetii* or anti–phase I IgG titer ≥1:800
- Evidence of endocardial involvement
  Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least *possible* IE by clinical criteria or *complicated* IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, *or*
  - Abscess, *or*
  - New partial dehiscence of prosthetic valve

  New valvular regurgitation; worsening or changing of preexisting murmur not sufficient

Minor Criteria

- Predisposition, predisposing heart condition, or intravenous drug use
- Fever—temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture finding but does not meet a major criterion as noted earlier (excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

TEE, Transesophageal echocardiography; TTE, transthoracic echocardiography.
Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633.

prolonged treatment. With highly sensitive viridans group streptococcal infections, shortened regimens that include oral penicillin for some portion have been recommended for certain adults, but effectiveness studies in children are lacking. In *nonstaphylococcal* disease, bacteremia usually resolves in 24-48 hours, whereas fever resolves in 5-6 days with appropriate antibiotic therapy. Resolution with *staphylococcal* disease takes longer.

If the infection occurs on a valve and induces or increases symptoms and signs of heart failure, appropriate therapy should be instituted, including diuretics, inotropic medications, and afterload reducing agents. Surgical intervention for infective endocarditis is indicated for severe aortic, mitral, or prosthetic valve involvement with intractable heart failure (Table 486.8). Severe heart failure may be associated with acute valve regurgitation, obstruction of conduits or shunts, or periannular extension of infection, including fistula formation. Rarely, a mycotic aneurysm, rupture of an aortic sinus, intraseptal abscess causing complete heart block, or dehiscence of an intracardiac patch requires emergency surgery. Other surgical indications include failure to sterilize the blood despite adequate antibiotic levels in 7-10 days in the absence of extracardiac infection, myocardial abscess, recurrent emboli, and increasing size of vegetations while receiving therapy. Vegetations (aortic, mitral, prosthetic valve) >10-15 mm are at high risk of embolism. Although antibiotic therapy should be administered for as long as possible before surgical intervention, active infection is not a contraindication if the patient is critically ill as a result of severe hemodynamic deterioration from infective endocarditis. Emergent surgical intervention in patients with severe heart failure may improve the likelihood of survival. Removal of vegetations and, in some instances, valve replacement may be lifesaving, and sustained antibiotic administration will most often prevent reinfection. Replacement of infected prosthetic valves carries a higher risk.

Fungal endocarditis is difficult to manage and has a poorer prognosis. It has been encountered after cardiac surgery, in severely debilitated or immunosuppressed patients, and in patients on a prolonged course of antibiotics. The drugs of choice are amphotericin B (liposomal or standard preparation) and 5-fluorocytosine. Surgery to excise infected tissue is occasionally attempted, but often with limited success. Recombinant tissue plasminogen activation may help lyse intracardiac vegetations and avoid surgery in some high-risk patients.

PREVENTION

The American Heart Association (AHA) recommendations for antimicrobial prophylaxis before dental and other surgical procedures has resulted in a substantial reduction in the number of patients who require prophylactic treatment, and the procedures requiring coverage were recommended. The primary reasons for these revised recommendations were that (1) infective endocarditis is much more likely to result from exposure to the more frequent random bacteremias associated with daily activities than from a dental or surgical procedure, (2) routine prophylaxis may prevent "an exceedingly small" number of cases, and (3) the risk of antibiotic-related adverse events exceeds the benefits of prophylactic therapy. Improving general dental hygiene was thought to be a more important factor in reducing the risk of infective endocarditis resulting from routine daily bacteremias. The current recommendations limit the use of prophylaxis to those patients with cardiac conditions associated with the greatest risk of an adverse outcome from infective endocarditis (Table 486.9). Patients with permanently damaged valves from rheumatic heart disease should also be considered for prophylaxis. Prophylaxis for these patients is recommended for "all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa." Furthermore, "placement of removable prosthodontic or endodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa" are not indications for

Table 486.6 Therapy of Pediatric Native Valve Endocarditis Caused by Highly Penicillin-Susceptible[^] Viridans Group Streptococci and *Streptococcus bovis*

REGIMEN	DOSAGE*† AND ROUTE	DURATION	COMMENTS
Penicillin G	200,000-300,000 U/kg/24 hr IV given every 4 hr up to 12-24 million U/day	4 wk	Avoids nephrotoxicity of gentamicin
Or			
Ceftriaxone sodium	100 mg/kg/24 hr IV given every 12 hr **or** 80 mg/kg/24 hr given every 24 hr up to 4 g/day (If total amount is over 2 g/day then dosing should be every 12 hr)	4 wk	Avoids nephrotoxicity of gentamicin
Or			
Vancomycin hydrochloride¶	40 mg/kg/24 hr IV given every 8-12 hr up to 2g/day	4 wk	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain a trough concentration range of 10-15 μg/mL

[^]Defined as minimum inhibitory concentration (MIC) ≤0.10 μg/mL.
*Dosages recommended are for patients with normal renal function.
†Pediatric dose should not exceed that of a normal adult.
¶Vancomycin dosages should be infused during course of at least 1 hr to reduce risk of histamine release and facial flushing. Peak vancomycin levels should only be obtained to calculate the area under the curve to mean MIC ratio.
Data from Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update. A scientific statement from the American Heart Association. *Circulation.* 2015;132:1487–1515.

Table 486.7 Therapy for Pediatric Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSAGE*§ AND ROUTE	DURATION	COMMENTS
OXACILLIN-SUSCEPTIBLE STRAINS			
Nafcillin or oxacillin† ± gentamicin‡ for first 3-5 days	200 mg/kg/24 hr IV given every 4-6 hr up to 12 g/day AND consider gentamicin 3-6 mg/kg/24 hr IV every 8 hr	4-6 wk	Clinical benefit of aminoglycosides has not been established. Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).
For penicillin-allergic (non-anaphylactoid-type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin ± gentamicin‡ for first 3-5 days	100 mg/kg/24 hr IV given every 8 hr up to 12 g/day AND consider gentamicin 3-6 mg/kg/24 hr IV given every 8 hr	4-6 wk	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.§ Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).
OXACILLIN-RESISTANT STRAINS			
Vancomycin¶ ± gentamicin‡ for first 3-5 days	40 mg/kg/24 hr IV given every 8-12 hr up to 2 g/day AND consider gentamicin 3-6 mg/kg/24 hr IV given every 8 hr	6 wk	Adjust vancomycin dosage to achieve trough concentration of 10-15 μg/mL. Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).
Daptomycin ± gentamicin‡ for first 3-5 days	6 mg/kg/24 hr given every 24 hr <6 yr of age; 10 mg/kg/24 hr given every 24 hr AND consider gentamicin 3-6 mg/kg/24 hr IV given every 8 hr	4-6 wk	Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).

*Dosages recommended are for patients with normal renal function.
§Pediatric dose should not exceed that of a normal adult.
†Penicillin G 200,000-300,000 U/kg/24 hr IV given every 4 hr up to 12-24 million U/day may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase.
‡Gentamicin should be administered in close temporal proximity to nafcillin, or oxacillin dosing and blood levels monitored to reduce the risk of nephrotoxicity and ototoxicity.
¶For specific dosing adjustment and issues concerning vancomycin, see Table 464.6 footnotes.
IE, Infective endocarditis; IV, intravenously.
Data from Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update. A scientific statement from the American Heart Association. Circulation. 2015;132:1487–1515.

Table 486.8 Echocardiographic Features that Suggest Potential Need for Surgical Intervention

VEGETATION
Persistent vegetation after systemic embolization
Anterior mitral valve leaflet vegetation, particularly if it is highly mobile with size >10 mm*
One or more embolic events during the first 2 wk of antimicrobial therapy*
Increase in vegetation size despite appropriate antimicrobial therapy*†
VALVULAR DYSFUNCTION
Acute aortic or mitral insufficiency with signs of ventricular failure†
Heart failure unresponsive to medical therapy†
Valve perforation or rupture†
PERIVALVULAR EXTENSION
Valvular dehiscence, rupture, or fistula†
New heart block†‡
Large abscess or extension of abscess despite appropriate antimicrobial therapy†

*Surgery may be required because of risk of embolization.
†Surgery may be required because of heart failure or failure of medical therapy.
‡Echocardiography should not be the primary modality used to detect or monitor heart block.
From Baddour LM, Freeman WK, Suri RM, et al. Cardiovascular infections. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease*, 11th ed. Philadelphia: Elsevier, 2019: Table 73-5, p. 1492.

Table 486.9 Cardiac Conditions Associated with Highest Risk of Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable (2007 AHA Statement)

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Congenital heart disease (CHD)*
• Unrepaired cyanotic CHD, including palliative shunts and conduits
• Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 mo after the procedure†
• Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization)
• Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.
From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116:1736–1754.

prophylaxis. The 2023 recommendations of the European Society of Cardiology are noted in Table 486.10. Given that many invasive respiratory tract procedures do cause bacteremia, prophylaxis for many of these procedures is considered reasonable. In contrast to prior recommendations, prophylaxis for gastrointestinal or genitourinary procedures is no longer recommended in the majority of cases. Prophylaxis for patients undergoing cardiac surgery with placement of prosthetic material is still recommended. Given the highly individual nature of these recommendations, direct consultation with the child's cardiologist is still the best method for determining a specific patient's ongoing need for prophylaxis (Table 486.11).

Continuing education regarding both oral hygiene and, in appropriate cases, the need for prophylaxis is important, especially in teenagers and young adults. Vigorous treatment of sepsis and local infections and careful asepsis during heart surgery and catheterization reduce the incidence of infective endocarditis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 486-10 2023 European Recommendations for Antibiotic Prophylaxis in Patients with Cardiovascular Diseases Undergoing Oro-Dental Procedures at Increased Risk of Infective Endocarditis

• Antibiotic prophylaxis is recommended in patients with previous IE.
• Antibiotic prophylaxis is recommended in patients with surgically implanted prosthetic valves and with any material used for surgical cardiac valve repair.
• Antibiotic prophylaxis is recommended in patients with transcatheter implanted aortic and pulmonary valvular prostheses.
• Antibiotic prophylaxis should be considered in patients with transcatheter mitral and tricuspid valve repair.
• Antibiotic prophylaxis is recommended in patients with untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure.

From Delgado V, Marsan NA, de Waha S, et al: 2023 ESC Guidelines for the Management of endocarditis. *Eur Heart J* 2023;193:1-95 https://doi.org/10.1093/eurheartj/ehad193.

Table 486.11 Prophylactic Antibiotic Regimens for a Dental Procedure (2007 AHA Statement)

SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin *or* Cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin*† *or* Clindamycin *or* Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† *or* Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
IM, Intramuscularly; IV, intravenously.
From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association *Circulation*. 2007;116:1736–1754.

Chapter 487

Rheumatic Heart Disease

Michael R. Carr and Stanford T. Shulman

Rheumatic involvement of the cardiac valves is the most important sequela of **acute rheumatic fever (ARF)**, and the second most common major manifestation after arthritis (see Chapter 229.1). The definitions of three subgroups of rheumatic heart disease (RHD) are noted in Table 487.1. The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of one or more of the heart valves. The mitral valve is affected most often, followed in frequency by the aortic valve. Isolated aortic valve disease is rare and generally seen with concomitant mitral valve involvement. Right-sided heart manifestations are rarer and are virtually only associated with left-sided valve disease. As the inflammation subsides, the verrucae tend to disappear and leave scar tissue. With repeated attacks of rheumatic fever, new verrucae form near the previous ones and the mural endocardium and chordae tendineae become involved. A single episode of **acute rheumatic carditis** often results in complete healing of the valvular lesions, whereas *repeated* episodes, especially involving previously affected valves, result in chronic **RHD**, which is the rationale for secondary prophylaxis. The prevalence of RHD ranges from 3 to 4 cases per 100,000 population in nonendemic countries to >1,000 cases per 100,000 in endemic countries (Fig. 487.1). On a global scale, the sequelae of RHD is significant, with up to 300,000 deaths per year related to the disease process, as well as an exponential degree of related comorbidity.

The diagnosis of ARF requires the fulfillment of the **Jones criteria** (see Chapter 229.1), with carditis being a major criterion. The diagnosis of RHD was once only based on cardiac auscultatory findings of mitral or aortic valve involvement, which was insensitive for early valve involvement/injury. This was based on valvulitis being seen more frequently in ARF compared with pericarditis or myocarditis, both of which lack more readily apparent physical examination findings. Screening large, high-risk populations with echocardiography demonstrated a substantially greater number of patients with RHD than those detected by auscultation alone. Because access to echocardiography is often available, the current version of the Jones criteria focused on the concept of **subclinical carditis (SCC)** detected by echocardiography (see Table 487.1). SCC is defined as echocardiographic evidence of mitral or aortic valvulitis in the absence of auscultatory findings and not consistent with physiologic mitral or aortic insufficiency (Table 487.2). Echocardiography with Doppler should be performed for all cases of confirmed or suspected ARF (Table 487.3). Additional recommendations are that echocardiography should be performed in moderate- to high-risk patient populations if ARF is considered likely and that echocardiography can be used to exclude cardiac findings consistent with ARF in patients with cardiac murmurs thought to be suggestive of rheumatic carditis. Additionally, serial echocardiography should be considered in patients with diagnosed or suspected ARF even if there is no evidence of valvulitis by echocardiography at diagnosis. The echocardiographic finding of SCC fulfills the major criterion for carditis. The category of latent RHD is another approach to include patients with mild asymptomatic valve changes not typically detected on physical exam but identified by screening high-risk populations with echocardiography (see Table 487.1).

PATTERNS OF VALVULAR DISEASE

Mitral Insufficiency

Mitral insufficiency is the result of structural changes that may include some loss of valvular substance and/or changes to the subvalvular apparatus, including elongation of the chordae, both of which can lead to valve dysfunction. During ARF with severe cardiac involvement, heart failure is caused by a combination of mitral insufficiency coupled with a pancarditis involving the pericardium and myocardium in addition to the endocardium/valve. Because of the increased volume load from the mitral insufficiency and the inflammatory process, the left ventricle dilates. The left atrium also enlarges to accommodate the regurgitant volume. Increased left atrial pressure results in pulmonary congestion and symptoms of left-sided heart failure. Spontaneous improvement often occurs with time, even in patients in whom mitral insufficiency is severe at the onset. The resultant chronic lesion is most often mild or moderate in severity, and the patient is often asymptomatic. More than half of patients with acute mitral insufficiency no longer have an audible mitral insufficiency murmur 1 year later, although they still may demonstrate insufficiency on echocardiography. In patients with severe chronic mitral insufficiency, pulmonary artery pressure (PAP) becomes elevated, the right ventricle and atrium become enlarged, and right-sided heart failure subsequently develops.

Clinical Manifestations

Physical signs of mitral insufficiency depend on its severity. With mild disease, signs of heart failure are not present, the precordium is quiet, and auscultation reveals a high-pitched **holosystolic murmur** at the apex that radiates to the axilla. With severe mitral insufficiency, signs of acute or chronic heart failure may be noted. The heart is enlarged, with a heaving apical left ventricular (LV) impulse and often an apical systolic **thrill**. The second heart sound (S_2) may be accentuated if pulmonary hypertension is present. A third heart sound or **gallop** is generally prominent. A holosystolic murmur is heard at the apex with radiation to the axilla. A short mid-diastolic rumbling murmur is caused by increased blood flow across the mitral valve as a result of the significant insufficiency. Therefore auscultation of a diastolic murmur, often referred to as **relative mitral stenosis (Carey-Coombs murmur)**, does not necessarily mean that true mitral stenosis is present. The latter lesion takes many years to develop and is characterized by a diastolic murmur of greater length, usually with presystolic accentuation.

The electrocardiogram and chest radiographs are normal if the mitral insufficiency is mild. With more severe insufficiency, the ECG shows a prominent, longer duration and often bifid P waves, signs of LV hypertrophy, and associated right ventricular (RV) hypertrophy if pulmonary hypertension is present. On chest radiograph, prominence of the left atrium and ventricle can be seen, the former of which is better seen on lateral projections. Congestion of the perihilar vessels, a sign of pulmonary venous hypertension, may also be evident. Calcification of the mitral valve is rare in children. Echocardiography in the acute phase may demonstrate enlargement of the left atrium and ventricle. LV systolic function can be impaired if there is also a component of myocardial inflammation. Mitral annular dilation, chordal elongation, and at times, evidence of chordal rupture resulting in a flail leaflet may be noted. The leaflet tips demonstrate a nodular appearance, and prolapse of the anterior mitral valve leaflet tip (much more often than the posterior leaflet) is seen. Doppler evaluation demonstrates the severity of the mitral regurgitation. Chronic mitral insufficiency from RHD is characterized on echocardiography by leaflet and chordal thickening, chordal fusion, and restricted leaflet motion. These changes often lead to stenosis, but poor coaptation of the abnormal leaflets can also lead to variable degrees of regurgitation. Cardiac catheterization and left ventriculography are considered only if diagnostic questions are not completely resolved by noninvasive assessment or in rare cases with a concern for significantly elevated PAP.

Complications

Severe mitral insufficiency may result in cardiac failure that may be precipitated by progression of the rheumatic process, recurrent episodes of ARF, the onset of **atrial fibrillation (AF)** or other arrhythmias, or infective endocarditis. The effects of chronic mitral insufficiency may become manifest after many years and include LV and RV failure and atrial and ventricular arrhythmias.

Treatment

In patients with mild mitral insufficiency, **prophylaxis** against recurrences of rheumatic fever is all that is required in addition to the typical treatment for ARF (Table 487.4). For more significant insufficiency, corticosteroids are added in the acute phase. Treatment of complicating heart failure (see Chapter 491), arrhythmias (see Chapter 484), and infective endocarditis (see Chapter 486) is described elsewhere. Afterload-reducing

agents—angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)—may reduce the regurgitant volume, attenuate pathologic compensatory mechanisms, and preserve LV function, but these have not been proven to alter the natural history of the disease process. Diuretics may also provide some symptomatic and clinical benefit in select cases. In rare cases, phosphodiesterase inhibitors such as milrinone may be used in the acute stage because of their inotropic, lusitropic, and systemic vascular dilating effects. Surgical treatment is indicated for patients who, despite adequate medical therapy, have persistent heart failure, dyspnea with moderate activity, and progressive cardiomegaly, often with pulmonary hypertension. Although annuloplasty and other forms of mitral valve repair provide good results in some children and adolescents, mitral valve replacement may be required, which can be more complicated in younger children. In patients with a prosthetic mitral valve replacement, prophylaxis against bacterial endocarditis is warranted for dental procedures, as the routine antibiotics taken by these patients for rheumatic fever prophylaxis are insufficient to prevent endocarditis. Additionally, current recommendations suggest selecting a different class of antibiotic for such procedures, rather than increasing the dose of the antibiotic taken for rheumatic fever prophylaxis. Lastly, it is important to remember that all attempts should be made at maximizing medical management of severe mitral insufficiency during the acute phase of the disease process, before considering surgical intervention, because surgery carries a poorer prognosis and an increased risk for reoperation when performed during the acute phase.

Table 487.1 Proposed RHD Definitions

Latent RDH	All cases of RHD diagnosed through echocardiographic screening, to include previously unrecognized clinical RHD and subclinical RHD.
Clinical RDH	All cases of RHD that have clinical signs or symptoms, including pathologic heart murmur* diagnosed either through echocardiographic screening or clinical evaluation. Clinical RHD is typically more advanced than subclinical RHD.
Subclinical RDH	All cases of RHD that do not have clinical signs or symptoms, including heart murmur.* Subclinical RHD is only diagnosed by echocardiography and is typically less advanced than clinical RHD.

*Detection of a pathologic heart murmur without echocardiography has been shown to be poorly sensitive and specific in echocardiographic screening studies for RHD.
RHD, Rheumatic heart disease.
Modified from Beaton A, Engelman D, Mirabel M. Echocardiographic screening for rheumatic heart disease. In: Dougherty S, Carapetis J, Zühlke, Wilson N, eds. *Acute Rheumatic Fever and Rheumatic Heart Disease.* Philadelphia: Elsevier; 2021: Table 13.1.

Mitral Stenosis

Mitral stenosis of rheumatic origin results from fibrosis of the mitral ring, commissural adhesions, and contracture of the valve leaflets, chordae, and papillary muscles over time. This is a chronic process and often takes ≥10 years for the lesion to become fully established, although the process may occasionally be accelerated. In the developed world, rheumatic mitral stenosis is seldom encountered before adolescence and is not usually recognized until adult life. Significant mitral stenosis results in increased left atrial pressure and subsequent enlargement and hypertrophy of the left atrium, pulmonary venous hypertension, increased pulmonary vascular resistance, and eventually overt pulmonary hypertension (Fig. 487.2). RV hypertrophy and right atrial dilation ensue and are followed by RV dilation, tricuspid regurgitation, and clinical signs of right-sided heart failure.

Clinical Manifestations

Generally, the correlation between symptoms and the severity of obstruction is good. Patients with mild stenosis are asymptomatic. More severe degrees of obstruction are associated with exercise intolerance and dyspnea. Critical lesions can result in orthopnea, paroxysmal nocturnal dyspnea, and overt pulmonary edema, as well as atrial arrhythmias. When pulmonary hypertension has developed, RV dilation may result in functional tricuspid insufficiency, hepatomegaly, ascites, and edema. Hemoptysis caused by rupture of bronchial or pleurohilar veins and, occasionally, pulmonary infarction may occur.

Jugular venous pressure is increased in severe disease with heart failure, tricuspid valve disease/regurgitation, or severe pulmonary hypertension. In mild disease, the heart size is normal; however, moderate cardiomegaly is typical with severe mitral stenosis. Cardiac enlargement can be massive when AF and heart failure supervene. A parasternal RV lift is palpable when PAP is high. The principal auscultatory findings are a loud first heart sound, an opening snap of the mitral valve, and a long, low-pitched, rumbling mitral diastolic murmur with presystolic accentuation at the apex. The mitral diastolic murmur may be virtually absent in patients who are in significant heart failure from the elevated LV filling pressures. A holosystolic murmur secondary to tricuspid insufficiency may be audible at the left lower sternal border. In the presence of pulmonary hypertension, the pulmonic component of S_2 is accentuated. An early diastolic murmur may

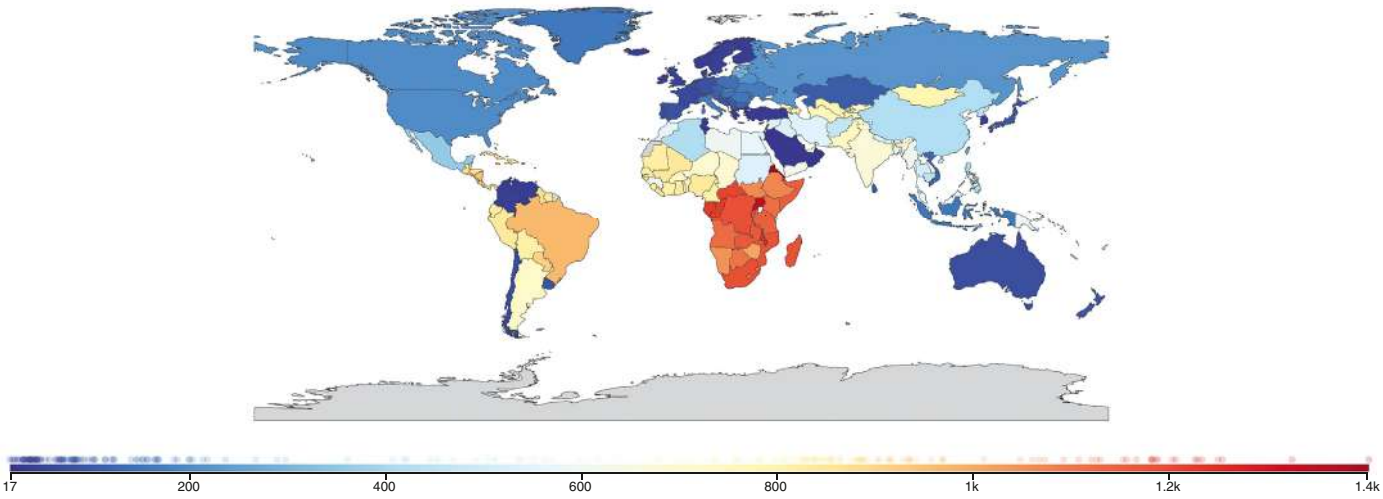

Fig. 487.1 Prevalence of rheumatic heart disease global map showing prevalence/100,000 population in 2017 by country. *(From the Institute for Health Metrics and Evaluation Global Burden of Disease 2019, Non-communicable disease data. Seattle: University of Washington IHME. https://www.healthdata.org/research-analysis/gbd.)*

be caused by associated rheumatic aortic insufficiency or pulmonary valvular insufficiency secondary to pulmonary hypertension.

ECGs and chest radiographs are normal if the stenosis is mild; as the severity increases, prominent and notched P waves and varying degrees of RV hypertrophy become evident. AF or other atrial arrhythmias are common late manifestations. Moderate to severe lesions are associated with radiographic signs of left atrial enlargement and prominence of the pulmonary artery and right-sided heart chambers; calcifications may be noted in the region of the mitral valve (see Fig. 487.2). Severe stenosis is associated with a redistribution of pulmonary blood flow so that the apices of the lung have greater perfusion (the reverse of normal). Lastly, horizontal lines in the lower lung periphery, called *Kerley B lines,* may be evident.

Echocardiography demonstrates thickening of the mitral valve and chordal apparatus, as well as restricted motion of the valve (Fig. 487.3). The typical "elbow" or "dog leg" appearance of the anterior leaflet of the mitral valve can aid in the distinction of a rheumatic valve from the various forms of congenital mitral stenosis. Left atrial dilation is common; color Doppler flow across the mitral valve shows a narrow jet with flow acceleration, and variable degrees of tricuspid insufficiency can be seen from left atrial hypertension. Doppler can estimate the transmitral pressure gradient but can underestimate the gradient if there is LV dysfunction. Estimates of the RV/PAP can be made by echocardiographic assessment of the tricuspid and pulmonary insufficiency, as well as changes in the RV size and function and the systolic septal position. Cardiac catheterization quantitates the diastolic gradient across the mitral valve well, allows for the calculation of cross-sectional valve area in older children, and assesses the degree of left atrial hypertension and PAP elevation.

Table 487.2 Echocardiographic Findings in Rheumatic Valvulitis

PATHOLOGIC MITRAL REGURGITATION*	PATHOLOGIC AORTIC REGURGITATION*
1. Seen in at least two views	1. Seen in at least two views
2. Jet length ≥2 cm in at least one view	2. Jet length ≥1 cm in at least one view
3. Peak velocity >3 meters/sec	3. Peak velocity >3 meters/sec
4. Pan-systolic jet in at least one envelope	4. Pan-diastolic jet in at least one envelope

*All four criteria need to be met.
Adapted from Gewitz MH, Baltimore RS, Tani LY, et al., On behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806–1818.

Table 487.3 Morphologic Findings in Echocardiogram in Rheumatic Vasculitis

ACUTE MITRAL VALVE CHANGES
Annular dilation
Chordal elongation
Chordal rupture resulting in flail leaflet with severe mitral regurgitation
Anterior (or, less commonly, posterior) leaflet tip prolapse
Beading/nodularity of leaflet tips
CHRONIC MITRAL VALVE CHANGES: NOT SEEN IN ACUTE CARDITIS
Leaflet thickening
Chordal thickening and fusion
Restricted leaflet motion
Calcification
AORTIC VALVE CHANGES IN EITHER ACUTE OR CHRONIC CARDITIS
Irregular or focal leaflet thickening
Coaptation defect
Restricted leaflet motion
Leaflet prolapse

From Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. *Circulation*. 2020;142(2):e337–e357, Supplemental Table 2.

Treatment

Intervention is indicated in patients with clinical signs and hemodynamic evidence of severe obstruction, but before the onset of severe manifestations. Pharmacologic therapy (diuretics and β blockers)

Table 487.4 Recommended Durations of Secondary Prophylaxis According to International Guidelines

GUIDELINE	SECONDARY PROPHYLAXIS DURATION RECOMMENDED
American (AHA)	ARF with carditis and residual heart disease: until age 40 yr or for 10 yr after last ARF (whichever is longer); lifetime prophylaxis may be needed
	ARF with carditis but no residual heart disease: until age 21 yr or for 10 yr after last ARF (whichever is longer)
	ARF without carditis: until age 21 yr or for 5 yr after last ARF (whichever is longer)
WHO Expert Consultation Geneva (2004)	Lifelong if severe valvular disease or after valve surgery
	For 10 yr after last ARF or until age 25 yr in patients with a previous diagnosis of carditis
	For 5 yr after last ARF or until age 18 yr in patients without proven carditis

AHA, American Heart Association; ARF, acute rheumatic fever; RHD, rheumatic heart disease; WHO, World Health Organization.
Modified from Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. *Circulation*. 2020;142(2):e337–e357, Table 2.

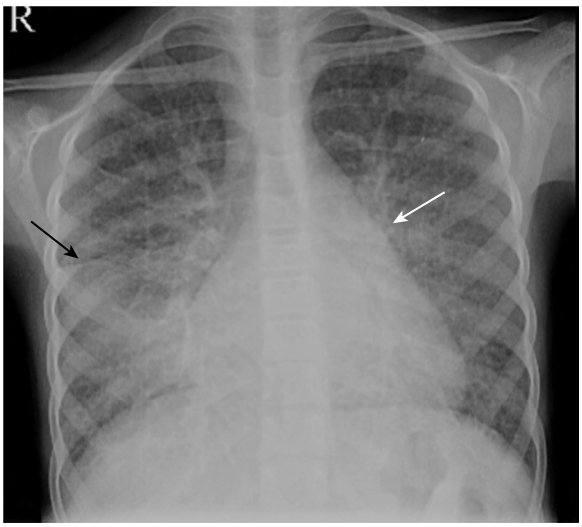

Fig. 487.2 Chest x-ray from an 8-yr-old child with advanced juvenile mitral valve stenosis. Severe pulmonary venous hypertension is shown by the prominent upper lobe vasculature, interstitial edema, and visible interlobar fissure *(black arrow)*. The left heart border is straightened, indicating enlargement of the main pulmonary artery and left atrial appendage *(white arrow)*. *(From Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. Circulation. 2020;142(2):e337–e357, Supplemental Fig. 3.)*

can be attempted but is generally used only for symptom control and much less often in children. However, it should not be considered adequate treatment in severe, symptomatic disease. Surgical valvotomy or balloon catheter mitral valvuloplasty generally yields good results (see Fig. 487.3); mitral valve replacement is avoided unless absolutely necessary. Balloon valvuloplasty is indicated for symptomatic, stenotic, pliable, noncalcified valves in patients without significant atrial arrhythmias or thrombi. Unfortunately, neither surgical nor interventional options may exist in areas of the world with high disease burden.

Aortic Insufficiency

In *acute* rheumatic aortic insufficiency, poor coaptation of the leaflets or leaflet prolapse is seen. *Chronic* rheumatic aortic insufficiency leads to sclerosis of the valve and results in distortion and retraction of the cusps. In both settings, regurgitation of blood leads to LV volume overload with dilation and hypertrophy of the left ventricle as it attempts to compensate for the excessive volume load. Concomitant mitral annular dilation accompanying LV dilation can further exacerbate mitral valve disease, specifically regurgitation. Combined mitral and aortic insufficiency in the acute phase of ARF is much more common than aortic involvement alone. However, in cases of isolated significant aortic insufficiency, RHD should not be discounted, even given the rare nature of this finding.

Clinical Manifestations

Symptoms are unusual except in severe aortic insufficiency or in the presence of significant concomitant mitral valve involvement or myocardial dysfunction. The large stroke volume and forceful LV contractions may result in palpitations. Sweating and heat intolerance are related to excessive vasodilation. Dyspnea on exertion can progress to orthopnea and pulmonary edema; angina may be precipitated by heavy exercise. Nocturnal attacks with sweating, tachycardia, chest pain, and hypertension may occur.

The pulse pressure is wide with bounding peripheral pulses (**water hammer** or **Corrigan pulse**). Systolic blood pressure is elevated, and diastolic pressure is lowered. In severe aortic insufficiency, the heart is enlarged, with an LV apical heave. A diastolic thrill may be present. The typical murmur begins immediately with S_2 and continues until late in diastole. The murmur is heard over the upper left and mid-left sternal border with radiation to the apex and upper right sternal border. Characteristically, it has a high-pitched blowing quality and is easily audible in full expiration with the diaphragm of the stethoscope placed firmly on the chest and the patient leaning forward. An aortic systolic ejection murmur is frequently heard because of the increased stroke volume. An apical presystolic murmur **(Austin Flint murmur)** resembling that of mitral stenosis is sometimes heard and is caused by the large regurgitant aortic flow in diastole preventing the mitral valve from opening fully.

Chest radiographs demonstrate enlargement of the left ventricle and aorta. The ECG may be normal, but in advanced cases it reveals signs of LV hypertrophy with a strain pattern and prominent P waves. Echocardiography shows a dilated left ventricle and diastolic mitral valve flutter or oscillations caused by aortic regurgitant flow hitting the valve leaflets. The aortic valve may demonstrate irregular or focal thickening, decreased systolic excursion, a coaptation defect, and leaflet prolapse. Doppler evaluation demonstrates the degree of aortic insufficiency. Cardiac magnetic resonance imaging/angiography (cMRI/MRA) can be useful in quantitating regurgitant volume and in assessing LV size and systolic function. Cardiac catheterization is generally only necessary when echocardiographic or axial imaging data are equivocal.

Prognosis and Treatment

Mild and moderate degrees of aortic insufficiency are well tolerated. Unlike mitral insufficiency, aortic insufficiency does not generally regress. Patients with combined lesions during the episode of ARF may have only aortic involvement 1-2 years later. Treatment consists of ACE inhibitors or ARBs and prophylaxis against ARF recurrence. Surgical intervention, which is typically aortic valve repair but occasionally can involve aortic valve prosthetic (biologic or mechanical) replacement, should be done well in advance of the onset of heart failure, pulmonary edema, and angina or when signs of decreasing myocardial performance become evident, as manifested by increasing LV dimensions and decreasing systolic function on echocardiography. Surgery is considered when early symptoms are present, significant ST-T wave changes are seen on the ECG, or evidence of decreasing LV ejection fraction is noted.

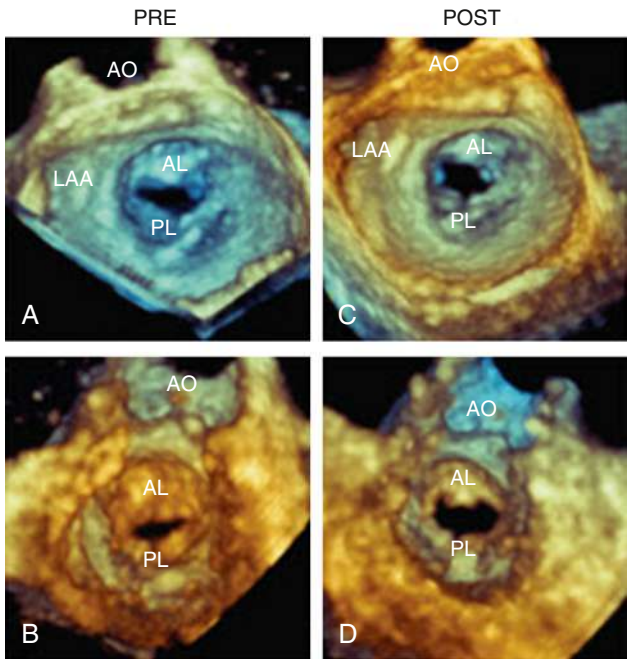

Fig. 487.3 Balloon mitral valvotomy. Real-time three-dimensional transesophageal echocardiographic images obtained before, during, and after balloon mitral valvotomy in a patient with mitral stenosis. A and B illustrate the stenotic mitral orifice as seen from the left atrium (A) and from the left ventricle (B) immediately prior to the procedure. C and D, obtained immediately after the procedure, show the commissure splitting and the larger mitral valve orifice. AL, anterior leaflet; AO, aorta; LAA, left atrial appendix; PL, posterior leaflet. *(From Salcedo EE, Carroll JD. Imaging guidance of transcatheter valve procedures. In Otto CM, Bonow RO (eds). Valvular Heart Disease: A Companion to Braunwald's Heart Disease. Philadelphia: Elsevier, 2013. Fig 16.11.)*

Tricuspid Valve Disease

Primary tricuspid valve involvement is rare during both the acute and chronic stages of rheumatic fever. Tricuspid insufficiency is more common secondary to RV dilation, resulting from significant left-sided cardiac lesions. The clinical signs of tricuspid insufficiency include prominent pulsations of the jugular veins, systolic pulsations of the liver, and a blowing holosystolic murmur at the lower left sternal border that increases in intensity during inspiration. Concomitant signs of mitral or aortic valve disease, with or without AF, are common. In these cases, signs of tricuspid insufficiency often decrease or even disappear when heart failure produced by the left-sided valvular lesions is successfully treated. Tricuspid valvuloplasty may be required in very rare cases.

Pulmonary Valve Disease

Pulmonary insufficiency secondary to ARF is rare and usually occurs on a functional basis secondary to pulmonary hypertension and is a late finding with severe mitral stenosis. The murmur **(Graham Steell murmur)** is similar to that of aortic insufficiency, but peripheral arterial signs (bounding pulses) are absent. The correct diagnosis is confirmed by two-dimensional echocardiography and Doppler studies demonstrating nonphysiologic pulmonary insufficiency, evidence of pulmonary hypertension, and the presence of mitral valve disease. Surgical intervention on the pulmonary valve is highly unusual.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 6

Diseases of the Myocardium and Pericardium

Chapter 488

Diseases of the Myocardium

John J. Parent and Stephanie M. Ware

The heterogeneous heart muscle diseases associated with structural remodeling and abnormalities of cardiac function **(cardiomyopathy)** are important causes of morbidity and mortality in the pediatric population. Several classification schemes have been formulated in an effort to provide logical, useful, and scientifically based etiologies for the cardiomyopathies. Insight into the molecular genetic basis of cardiomyopathies has increased exponentially, and etiologic classification schemes continue to evolve (Table 488.1).

Table 488.2 classifies the cardiomyopathies based on their anatomic (ventricular morphology) and functional pathophysiology. **Dilated cardiomyopathy**, the most common form of cardiomyopathy, is characterized predominantly by left ventricular (LV) dilation and decreased LV systolic function (Fig. 488.1). **Hypertrophic cardiomyopathy** demonstrates increased ventricular myocardial wall thickness, normal or increased systolic function, and often, diastolic (relaxation) abnormalities with fibrosis of varying degrees (Table 488.3 and Figs. 488.2 and 488.3). **Restrictive cardiomyopathy** is characterized by near-normal ventricular chamber size and wall thickness with preserved systolic function but dramatically impaired diastolic function leading to elevated filling pressures and atrial enlargement (Fig. 488.4). **Arrhythmogenic right ventricular (RV) cardiomyopathy** is characterized by fibrofatty infiltration and replacement of the normal RV myocardium and occasionally the left ventricle, leading to RV (and LV) systolic and diastolic dysfunction and arrhythmias. **Left ventricular noncompaction** is characterized by a hypertrabeculated LV apex and lateral wall, with a heterogeneous group of associated phenotypes (most often a dilated phenotype with LV dilation and dysfunction). Cardiomyopathies may be primary or associated with other organ involvement (Tables 488.4-488.6).

488.1 Dilated Cardiomyopathy

John J. Parent and Stephanie M. Ware

Dilated cardiomyopathy **(DCM)**, the most common form of cardiomyopathy in children, is the cause of significant morbidity and mortality and a common indication for cardiac transplantation. The etiologies are diverse. Unlike adult patients with DCM, ischemic etiologies are rare in children, although these include anomalous origin of the left coronary artery from the pulmonary artery, premature coronary atherosclerosis (homozygous familial hypercholesterolemia, rare genetic syndromic diseases such as progeria), and coronary inflammatory diseases such as Kawasaki disease. It is estimated that up to 50% of cases are **genetic** (usually autosomal dominant; some are autosomal recessive or X-linked), including some with metabolic causes (see Tables 488.1 and 488.2). Although the most common etiology of DCM remains **idiopathic**, it is likely that undiagnosed familial/genetic conditions and myocarditis predominate. The annual incidence of DCM in children younger than 18 years is 0.57 cases per 100,000 per year. The incidence is higher in males, Blacks, and infants <1 year old.

PATHOGENESIS

The pathogenesis of the ventricular dilation and altered contractility seen in DCM varies depending on the underlying etiology; systolic dysfunction and myocyte injury are common. Genetic abnormalities of several components of the cardiac muscle, including sarcomere proteins, the cytoskeleton, and the proteins that bridge the contractile apparatus to the cytoskeleton, have been identified in autosomal dominant and X-linked inherited disorders. DCM can occur after viral myocarditis. Although the primary pathogenesis varies from direct myocardial injury to viral-induced inflammatory injury, the resulting myocardial damage, ventricular enlargement, and poor function likely occur by a final common pathway similar to that in genetic disorders.

In 20–50% of cases, the DCM is familial, with autosomal dominant inheritance most common (see Table 488.3). **Duchenne and Becker muscular dystrophies** are X-linked cardiomyopathies that account for 5–10% of DCM cases (see Chapter 649.1). These dystrophinopathies result in an abnormal sarcomere-cytoskeleton connection, causing impaired myocardial force generation, myocyte damage/scarring, chamber enlargement, and altered function (see Table 488.6). Female carriers of dystrophinopathies may also manifest DCM.

Mitochondrial myopathies, as with the muscular dystrophies, may present clinically with a predominance of extracardiac findings, although in some children cardiomyopathy may be the first symptom. These are inherited in a recessive or mitochondrial pattern (see Tables 488.4 and 488.5). Disorders of **fatty acid oxidation** present with systemic derangements of metabolism (hypoketotic hypoglycemia, acidosis, and hepatic dysfunction), some with peripheral myopathy and neuropathy, and others with sudden death or life-threatening cardiac arrhythmias.

Anthracycline cardiotoxicity (doxorubicin [Adriamycin]) on rare occasion causes acute inflammatory myocardial injury, but more classically results in DCM and occurs in up to 30% of patients given a cumulative dose of doxorubicin exceeding 550 mg/m^2. The risk of toxicity appears to be exacerbated by concomitant radiation therapy.

CLINICAL MANIFESTATIONS

Although more prevalent in patients <1 year of age, all age-groups may be affected. Clinical manifestations of DCM are typically those of heart failure but can also include palpitations, syncope, and sudden death. Irritability or lethargy can be accompanied by additional nonspecific complaints of failure to thrive, nausea, vomiting, or abdominal pain. Respiratory symptoms (tachypnea, wheezing, cough, orthopnea, or dyspnea on exertion) are often present. Infrequently, patients may present acutely with pallor, altered mentation, hypotension, and shock. Patients can be tachycardic with narrow pulse pressure and may have hepatic enlargement and rales or wheezing. The precordial cardiac impulse is increased, and the heart may be enlarged to palpation or percussion. Auscultation may reveal a gallop rhythm in addition to tachycardia, and occasionally murmurs of mitral or, less often, tricuspid insufficiency may be present. The presence of hypoglycemia, acidosis, hypotonia, or signs of liver dysfunction suggests an inborn error of metabolism. Neurologic or skeletal muscle deficits are associated with mitochondrial disorders or muscular dystrophies (see Tables 488.4-488.6).

LABORATORY FINDINGS

Electrocardiographic screening reveals atrial or ventricular hypertrophy, nonspecific T-wave abnormalities, and occasionally, atrial or ventricular arrhythmias. The chest radiograph may demonstrate cardiomegaly and pulmonary vascular prominence or pleural effusions. The echocardiogram is often diagnostic, demonstrating the characteristic findings of LV enlargement, decreased ventricular contractility, and occasionally a globular (remodeled) LV contour (see Fig. 488.1).

Table 488.1 Classification of the Cardiomyopathies by Phenome and Genome

	PHENOTYPE				GENOME	
TYPE	**MORPHOLOGY**	**PHYSIOLOGY**	**PATHOLOGY**	**SYSTEMIC CONDITIONS, CLINICAL FEATURES, RISK FACTORS**	**NONSYNDROMIC, USUALLY SINGLE GENE**	**SYNDROMIC**
Dilated (DCM)	Dilation of LV and RV with minimal or no wall thickening	Reduced contractility is the primary defect; variable degree of diastolic dysfunction	Myocyte hypertrophy; scattered fibrosis	Hypertension, alcohol, thyrotoxicosis, myxedema, persistent tachycardia, toxins (e.g., chemotherapy, especially anthracyclines), radiation	Diverse gene ontology with >50 genes implicated	Diverse array of associated conditions, especially muscular dystrophies: Emery-Dreifuss, limb-girdle, Duchenne/Becker; Laing distal myopathy; Barth syndrome; Kearns-Sayre syndrome; other mitochondrial disorders; fatty acid oxidation disorders; Alstrom syndrome, others
Restrictive (RCM)	Usually normal chamber sizes; minimal wall thickening	Contractility normal or near-normal with a marked increase in end-diastolic filling pressure	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others	Endomyocardial fibrosis, amyloid, sarcoid, scleroderma, Churg-Strauss syndrome, cystinosis, lymphoma, pseudoxanthoma elasticum, hypereosinophilic syndrome, carcinoid	If not associated with systemic genetic disease, genetic cause usually from sarcomeric pathogenic gene variants	Gaucher disease, hemochromatosis, Fabry disease, familial amyloidosis, mucopolysaccharidoses, Noonan syndrome
Hypertrophic (HCM)	Usually normal or reduced internal chamber dimension; wall thickening pronounced, especially septal hypertrophy	Systolic function increased or normal	Myocyte hypertrophy, classically with disarray	Severe hypertension can confound clinical, morphologic diagnosis	Pathogenic variants of genes encoding sarcomeric proteins	Noonan syndrome, Noonan syndrome with multiple lentigines, Danon syndrome, Fabry disease, Wolff-Parkinson-White syndrome, Friedreich ataxia, MERRF, MELAS, other mitochondrial disorders, fatty acid oxidation disorders
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Scattered fibrofatty infiltration, classically of RV but also of LV; dilation of RV or LV, or both, is common but not universal	Ventricular arrhythmias (VT, VF) early or late, reduced contractility with progressive disease; can mimic DCM	Islands of fatty replacement; fibrosis	Palmoplantar keratoderma, wooly hair in Naxos syndrome	Pathogenic variants of genes encoding proteins of desmosome	Naxos syndrome
Left ventricular noncompaction (LVNC)	Ratio of noncompacted to compacted myocardium increased with normal LV or RV or any other phenotype	Normal to reduced systolic function	Myocardium normal and ranging to findings consistent with other coexisting cardiomyopathies	Phenotype observed in setting of other types of cardiomyopathy	Various cardiomyopathy genes associated, but uncertain whether genetic cause or developmental defect during organogenesis	

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 488.1 Classification of the Cardiomyopathies by Phenome and Genome—cont'd

	PHENOTYPE				GENOME	
TYPE	**MORPHOLOGY**	**PHYSIOLOGY**	**PATHOLOGY**	**SYSTEMIC CONDITIONS, CLINICAL FEATURES, RISK FACTORS**	**NONSYNDROMIC, USUALLY SINGLE GENE**	**SYNDROMIC**
Infiltrative	Usually thickened walls; occasional dilation	Restrictive physiology; systolic function usually mildly reduced	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others		See RCM earlier	See RCM earlier
Inflammatory	Normal or dilated without hypertrophy	Reduced systolic function	Inflammatory infiltrates	Hypereosinophilic syndrome, acute myocarditis		
Ischemic	Normal or dilated without hypertrophy	Reduced systolic function	Areas of infarcted myocardium	Hypercholesterolemia, hypertension, diabetes, cigarette smoking, family history	Familial hypercholesterolemia; other heritable lipid disorders	Familial hypercholesterolemia
Infectious	Normal or dilated without hypertrophy	Reduced systolic function	Specific to infection	Viral (especially acute myocarditis); protozoal (e.g., Chagas disease); bacterial, direct infection (e.g., Lyme disease), or from acute cellular toxicity as result of systemic toxins (e.g., *Streptococcus*, gram-negative, others)	Genetic predisposition to infection and/or variable response to infective agent	

LV, Left ventricle; MELAS, mitochondrial encephalopathy, lactic acidosis, and strokelike symptoms; MERRF, myoclonic epilepsy associated with ragged-red fibers; RV, right ventricle; VF, ventricular fibrillation; VT, ventricular tachycardia.
From Falk RH, Hershberger RE. The dilated, restrictive, and infiltrative cardiomyopathies. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease*, 11th ed. Philadelphia: Elsevier; 2019: Table 77.1.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 21, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 488.2 Etiology of Pediatric Myocardial Disease

CARDIOMYOPATHY	
Dilated Cardiomyopathy (DCM)	
Neuromuscular diseases	Muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, Emery-Dreifuss, congenital muscular dystrophy), myotonic dystrophy, myofibrillar myopathy
Inborn errors of metabolism	Fatty acid oxidation disorders (trifunctional protein, VLCAD, LCHAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia), Danon disease (DCM more common in females)
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic DCM
Genetic syndromes	Alström syndrome, Barth syndrome (phospholipid disorders)
Ischemic	Most common in adults
Chronic tachyarrhythmias	Atrial tachycardias (intractable reentrant supraventricular tachycardia [AVRT, AVNRT], multifocal atrial tachycardia, permanent junctional reciprocating tachycardia), ventricular tachycardia
Hypertrophic Cardiomyopathy (HCM)	
Inborn errors of metabolism	Mitochondrial disorders (including Friedreich ataxia, variants in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease); fatty acid oxidation disorders
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic HCM
Genetic syndromes	Noonan, Costello, cardiofaciocutaneous, and Beckwith-Wiedemann syndromes
Infant of a diabetic mother	Transient hypertrophy
Restrictive Cardiomyopathy (RCM)	
Neuromuscular disease	Myofibrillar myopathies
Metabolic	Storage disorders
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic RCM
Secondary	Rare in children; radiation therapy of thorax, amyloidosis, sarcoidosis, hemochromatosis, β-thalassemia
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic ARVC
Left Ventricular Noncompaction	
Genetic variants in cardiomyocyte structural apparatus	LVNC phenotype associated with HCM or DCM
Other	X-linked (Barth syndrome), autosomal recessive, mitochondrial inheritance, 1p36 deletion syndrome, and other chromosome abnormalities or genomic disorders; associated with congenital heart defects
SECONDARY OR ACQUIRED MYOCARDIAL DISEASE	
Myocarditis (see also Table 488.7)	**Viral:** parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV, SARS-CoV-2 (COVID-19), opportunistic infections **Rickettsial:** psittacosis, *Coxiella,* Rocky Mountain spotted fever, typhus **Bacterial:** diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis **Parasitic:** Chagas disease, toxoplasmosis, *Loa loa, Toxocara canis,* schistosomiasis, cysticercosis, echinococcus, trichinosis **Fungal:** histoplasmosis, coccidioidomycosis, actinomycosis
Systemic inflammatory disease	SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, periarteritis nodosa, hypereosinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease, multisystem inflammatory syndrome in children (COVID-19)
Nutritional deficiency	Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency)
Drugs, toxins	Doxorubicin (Adriamycin), cyclophosphamide, chloroquine, ipecac (emetine), sulfonamides, mesalazine, chloramphenicol, alcohol, hypersensitivity reaction, envenomations, irradiation, herbal remedy (blue cohosh), immune checkpoint inhibitors
Coronary artery disease	Kawasaki disease, medial necrosis, anomalous left coronary artery from pulmonary artery, other congenital coronary anomalies (anomalous right coronary artery, coronary ostial stenosis), familial hypercholesterolemia
Hematology-oncology	Anemia, sickle cell disease, leukemia
Endocrine-neuroendocrine	Hyperthyroidism, carcinoid tumor, pheochromocytoma, adrenal crisis
Stress (takotsubo) cardiomyopathy	Endocrine (see earlier) Neurologic (stroke, bleed) Induction of anesthesia Fright Medications/drugs (sympathomimetic agents, venlafaxine)

CPTI/CPTII, Carnitine palmitoyltransferase 1/2; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very-long-chain acyl-coenzyme A dehydrogenase.

RV enlargement and depressed function are occasionally noted. Echo Doppler studies can reveal evidence of pulmonary hypertension, mitral regurgitation, or other structural cardiac or coronary abnormalities. Cardiac MRI is useful for patients with suboptimal imaging echocardiographic windows or in patients with concern of acute myocarditis where, in contrast to echocardiography, recognition of inflammation of the myocardium is possible.

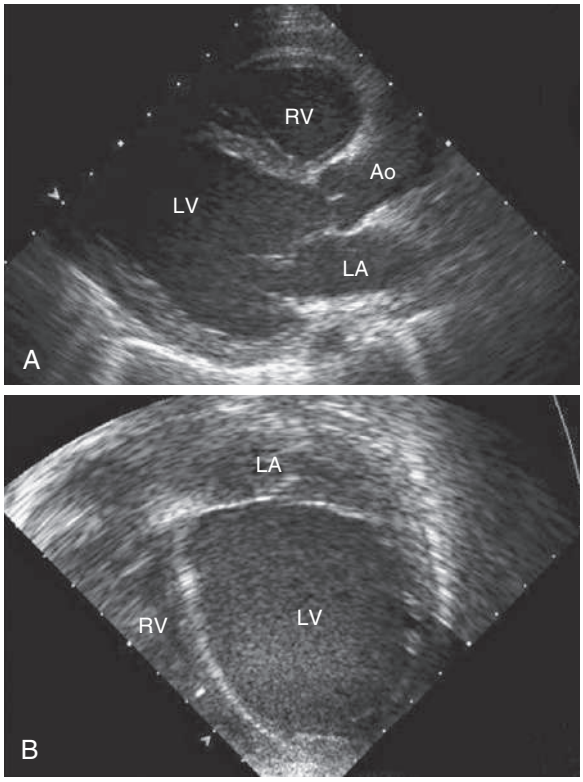

Fig. 488.1 Echocardiogram of a patient with dilated cardiomyopathy. **A,** Parasternal long-axis view showing the enlarged left ventricle. **B,** Apical four-chamber view showing the large left ventricle compressing the right ventricle. Ao, Ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

Additional testing may include complete blood count, renal and liver function tests, creatine phosphokinase (CPK), cardiac troponin I, lactate, brain natriuretic peptide (BNP) and pro-BNP, plasma amino acids, urine organic acids, and an acylcarnitine profile. Additional genetic testing is typically indicated, and enzymatic testing may be useful (see Table 488.3). Cardiac catheterization and endomyocardial biopsy are not routine but may be useful in patients with acute DCM. Biopsy samples can be examined histologically for the presence of mononuclear cell infiltrates, myocardial damage, storage abnormalities, and evidence of infection. It is considered standard of care to screen first-degree family members using echocardiography and electrocardiogram (ECG) in idiopathic and familial cases of DCM.

PROGNOSIS AND MANAGEMENT

The 1- and 5-year freedom from death or transplantation in patients diagnosed with DCM is 60–70% and 50–60%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation include older age, heart failure, lower LV fractional shortening *z* score, and underlying etiology. DCM is the most common cause for cardiac transplantation in pediatric and adult studies.

The therapeutic approach to patients with DCM includes a careful assessment to uncover possible treatable etiologies, screening of family members, and rigorous pharmacologic therapy. **Medications** aimed at reverse remodeling (improving ventricular size and function) include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) plus β-adrenergic blockade with carvedilol or metoprolol. The combination medication valsartan/sacubitril, which is an ARB/neprilysin inhibitor, respectively, that is FDA approved for patients 1 year of age and older, has been readily used in this setting in pediatrics in lieu of either an ACE or ARBs alone (see Chapter 491). Each of these medications have proved independently and in combination to improve survival and symptoms and reduce hospital admissions in adults with DCM. Additionally, furosemide may be used to reduce symptoms of pulmonary or systemic venous congestion. Digoxin therapy can also be considered in some patients. Implantable cardiac defibrillators may be considered for certain select patients with a high risk of sudden cardiac arrest. **Pacemakers**, including dual-chamber and biventricular pacing therapy, can improve patients with

Table 488.3 Cardiomyopathies

	DCM	HCM	RCM	LVNC	ARVC
Prevalence	50/100,000	1/500	Unknown	Unknown	1/2,000
Causes	Sarcomeric/ cytoskeletal/ desmosomal gene variant, neuromuscular disease, inborn error of metabolism, mitochondrial disease, genetic syndrome, infection	Sarcomeric/ cytoskeletal/ desmosomal gene variant, genetic syndrome, inborn error of metabolism/ mitochondrial disease	Sarcomeric gene variant, neuromuscular disease, genetic syndrome, storage or infiltrative disease	Sarcomeric-cytoskeletal-desmosomal gene mutation, neuromuscular disease, inborn error of metabolism, mitochondrial disease, genetic syndrome	Desmosomal gene variants
Inheritance	30–50% AD, AR, X-L, Mt	50% AD, Mt	AD, up to 50%	AD, X-L, Mt, % unknown	30–50% AD, rare AR (Naxos disease; Carvajal syndrome)
Sudden death	Yes	Yes	Yes	Yes	Yes
Arrhythmias	Atrial, ventricular, and conduction disturbances	Atrial and ventricular	Atrial fibrillation	Atrial, ventricular, and conduction disturbances	Ventricular and conduction disturbances
Ventricular function	Systolic and diastolic dysfunction	Diastolic dysfunction Dynamic systolic outflow obstruction	Diastolic dysfunction Normal systolic function	Systolic or diastolic dysfunction	Normal-reduced systolic and diastolic function

ACE, Angiotensin-converting enzyme; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVNC, left ventricular noncompaction; Mt, mitochondrial inheritance; RCM, restrictive cardiomyopathy; X-L, X-linked inheritance.

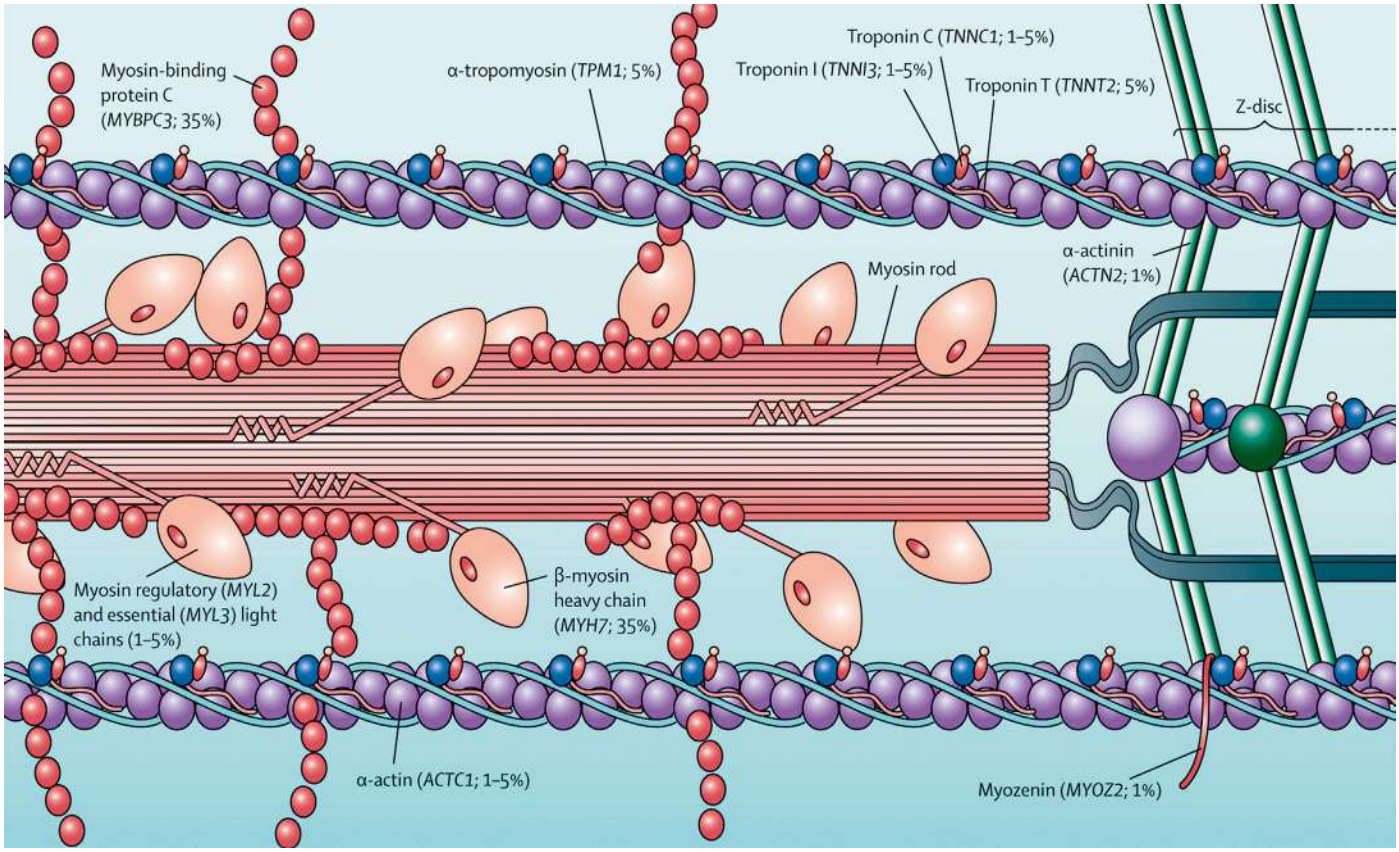

Fig. 488.2 Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy. Prevalence of every gene (derived from data of unrelated hypertrophic cardiomyopathy probands with positive genotyping) is shown in parentheses. *(From Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013;381:242–252, Fig 1.)*

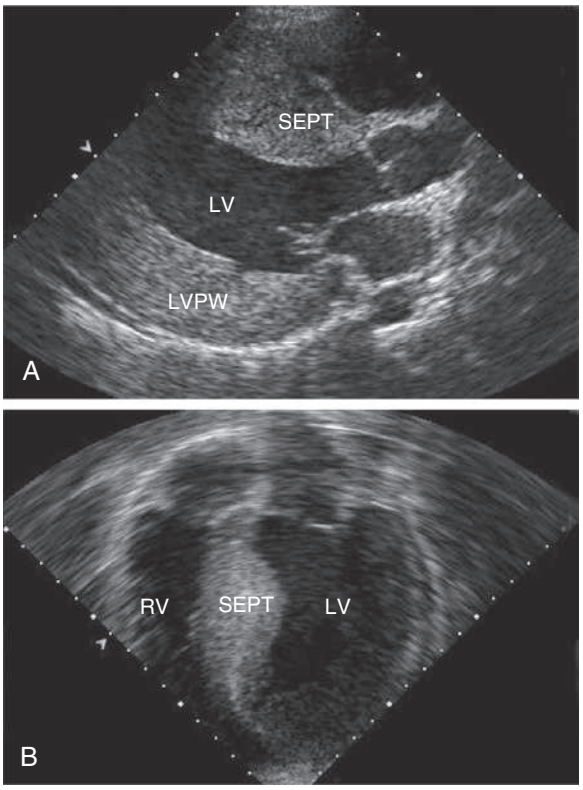

Fig. 488.3 Echocardiograms demonstrating hypertrophic cardiomyopathy. A, Parasternal long-axis view of a patient with severe concentric left ventricular hypertrophy. B, Four-chamber view of a patient with asymmetric septal hypertrophy. LV, Left ventricle; LVPW, left ventricular posterior wall; RV, right ventricle; SEPT, septum.

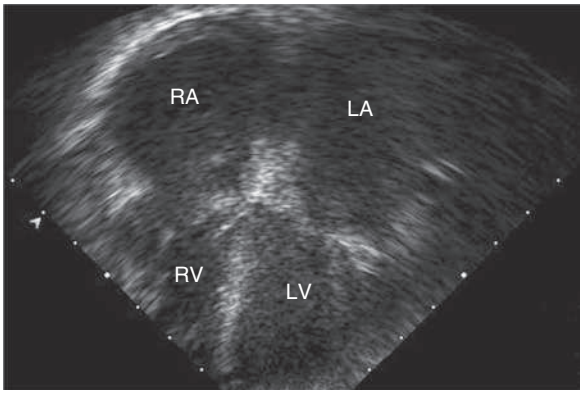

Fig. 488.4 Echocardiogram of a patient with restrictive cardiomyopathy. Apical four-chamber view shows the greatly enlarged right and left atria compared to the normal-size left and right ventricular chambers. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 488.4 Nuclear DNA Abnormalities Associated with Cardiomyopathy and Arrhythmias or Conduction Defects*

CONDITION	GENETIC DEFECT	HEART FINDINGS	OTHER CLINICAL FEATURES
ISOLATED COMPLEX DEFICIENCIES			
Complex I deficiency	Multiple complex I subunit genes, *ACAD9, FOXRED1*	HCM, DCM, LVNC, WPW	Leigh syndrome, FILA, MELAS, leukoencephalopathy, seizures, hypotonia, pigmentary retinopathy, optic atrophy, hearing loss, liver dysfunction
Complex II deficiency	*SDHA, SDHD*	HCM, DCM, LVNC, AF, heart block	Leukoencephalopathy, cerebellar atrophy, seizures, spasticity, myopathy, liver dysfunction, kidney dysfunction
Complex III deficiency	*BCS1L*	HCM	Developmental delay, psychosis, hearing loss
Complex IV deficiency	*SCO2, SURF1, C2orf64, Cl2orf62, COX6B1*	HCM, DCM	Leigh syndrome, encephalopathy, ataxia, liver dysfunction, kidney dysfunction
MITOCHONDRIAL TRANSLATION DEFECTS			
GTP-binding protein-3 deficiency	*GTPBP3*	HCM, DCM, heart block, WPW	Leigh syndrome, encephalopathy
Mitochondrial translational activator protein deficiency	*MTOI*	HCM, heart block	Encephalopathy, hypotonia
Alanyl-tRNA synthetase deficiency	*AARS2*	HCM	Leukoencephalopathy, myopathy
Tyrosyl-tRNA synthetase deficiency	*YARS2*	HCM	MLASA syndrome
tRNA methyltransferase-*5* deficiency	*TRMTS*	HCM	Developmental delay, hypotonia, peripheral neuropathy, renal tubulopathy
RNA processing defect	*ELAC2*	HCM, PSVE	Microcephaly, growth deficiency, hearing loss
Mitochondrial ribosomal subunit deficiencies	*MRPS22, MRPl3, MRPL44*	HCM, WPW	Leukoencephalopathy, seizures, liver dysfunction, renal tubulopathy
mtDNA DEPLETION SYNDROMES			
MNGIE	*TYMP*	Mild or asymptomatic HCM	Leukoencephalopathy, severe gastrointestinal dysmotility, ophthalmoplegia, hearing loss, peripheral neuropathy
F-box protein deficiency	*FBXL4*	Cardiomyopathy, unspecified	Encephalopathy, brain atrophy
Coenzyme Q_{10} biosynthesis defects	*COQ2, COQ4, COQ9*	HCM	Leigh syndrome, encephalomyopathy, retinitis pigmentosa, hearing loss, liver dysfunction, renal tubulopathy
3-METHYLGLUTACONIC ACIDURIAS			
Barth syndrome	*TAZ*	HCM, DCM, LVNC, EFE, VT, LQTS	Myopathy, short stature, neutropenia
Dilated cardiomyopathy and ataxia syndrome	*DNAJC19*	DCM, LVNC	Ataxia, optic ataxia, short stature, testicular abnormalities, liver disease
Complex V deficiency	*TMEM70*	HCM	Cataracts, leukodystrophy, ataxia, myopathy, short stature
Sengers syndrome	*AGK*	HCM	Cataracts, myopathy, exercise intolerance, short stature

*Examples of conditions that are associated with heart disease and feature abnormal nDNA are shown, along with the causative molecular defects and clinical findings. The genetic defects noted here are provided as major contributors to the various mitochondrial conditions but are not a comprehensive compilation.

AF, Atrial fibrillation; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; FILA, fatal infantile lactic acidosis; GTP, guanosine triphosphate; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MLASA, myopathy, lactic acidosis, sideroblastic anemia; MNGIE, mitochondrial neurogastrointestinal encephalopathy; nDNA, nuclear DNA; PSVE, paroxysmal supraventricular extrasystoles; LVNC, left ventricular noncompaction; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

From Enns GM. Pediatric mitochondrial diseases and the heart. *Curr Opin Pediatr*. 2017;29:541–551, Table 2.

certain underlying electrical derangements. In patients presenting with extreme degrees of heart failure or circulatory collapse, intensive care measures are often required, including intravenous inotropes and diuretics, mechanic ventilatory support, and on occasion, mechanical circulatory support, which may include a ventricular assist device (VAD), total artificial heart, extracorporeal membrane oxygenation (ECMO), and ultimately cardiac transplantation. In patients with DCM and atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be instituted.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 488.5 Mitochondrial DNA Abnormalities Associated with Cardiomyopathy and Arrhythmias or Conduction Defects*

CONDITION	GENETIC DEFECT	HEART FINDINGS	OTHER CLINICAL FEATURES
Kearns-Sayre syndrome	mtDNA deletion	HCM, DCM, heart block, PMVT	Progressive external ophthalmoplegia, pigmentary retinopathy, cerebellar ataxia, hearing loss, increased CSF protein, diabetes mellitus, renal tubulopathy
MELAS	$tRNA^{Lou}$ point variant	HCM, DCM, LVNC, RCM, heart block, WPW	Encephalopathy, seizures, strokelike episodes, headaches, hearing loss, myopathy
MERRF	$tRNA^{Lys}$ point variant	HCM, DCM, HiCM, WPW	Myoclonus, seizures, ataxia, optic atrophy, hearing loss, short stature
Complex I deficiency	Multiple complex I subunit genes	HCM, DCM	Leigh syndrome, leukoencephalopathy, seizures, optic atrophy
Complex III deficiency	*MTCYB*	HCM, DCM, HiCM	Exercise intolerance, myopathy, seizures, optic atrophy, short stature
Complex IV deficiency	*MT-CO1, MT-CO2, MT-CO3*	HCM, DCM, HiCM	Encephalopathy, seizures, pigmentary retinopathy, hearing loss, myopathy, liver dysfunction
Complex V deficiency	*MT-ATP6, MT-ATP8*	HCM	Ataxia, peripheral neuropathy

*Relatively common conditions that are associated with heart disease and feature abnormal mtDNA are shown, along with the most common molecular defects and clinical findings. Although the most common molecular defects are indicated in the table, in most cases, multiple genetic abnormalities can cause similar clinical presentations.

CSF, Cerebrospinal fluid; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HiCM, histiocytoid cardiomyopathy; LVNC, left ventricular noncompaction; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers; mtDNA, mitochondrial DNA; PMVT, polymorphic ventricular tachycardia; RCM, restrictive cardiomyopathy; WPW, Wolff-Parkinson-White syndrome.

From Enns GM. Pediatric mitochondrial diseases and the heart. *Curr Opin Pediatr.* 2017;29:541–551. Table 3.

Table 488.6 Gene Variants and Cardiac Manifestations of Neuromuscular Disorders

DISORDER	GENE VARIANT	CARDIOMYOPATHY	ECG	ARRHYTHMIA
Duchenne muscular dystrophy (DMD)	Dystrophin	Dilated	Short PR interval, prolonged QT interval, increased QT:PT ratio, right ventricular hypertrophy, deep Q waves II, III, aVF, V_5, V_6	Increased baseline HR, decreased rate variability, premature ventricular beats (58% of patients by 24 yr of age)
DMD—female carrier	Dystrophin	Dilated	None	Uncommon
Becker muscular dystrophy	Dystrophin	Dilated	Conduction system disease	Similar to DMD
Emery-Dreifuss autosomal dominant or proximal dominant limb-girdle muscular dystrophy IB	Lamin A/C	Dilated	Conduction abnormalities: prolonged PR interval, sinus bradycardia	Atrial fibrillation or flutter and atrial standstill; ventricular dysrhythmias
Limb-girdle muscular dystrophy	α, β, γ, δ sarcoglycans	Dilated	Incomplete right bundle branch block, tall R waves in V_1 and V_2, left anterior hemiblock	Uncommon
Congenital muscular dystrophy	Laminin α_2	Dilated	None	None
Limb-girdle muscular dystrophy 21	Fukutin	Dilated	AV node and bundle branch block; age at onset: late teens and early 20s	Atrial arrhythmias and/or ventricular arrhythmias
Emery-Dreifuss X-linked	Emerin	Rare	Conduction abnormalities: prolonged PR interval, sinus bradycardia	Atrial fibrillation or flutter and atrial standstill
Friedreich ataxia	Frataxin	Hypertrophic	T-wave inversion, left axis deviation, repolarization abnormalities	Ventricular arrhythmias
Myotonic dystrophy type 1, infantile	Myotonic dystrophy protein kinase gene	Hypertrophic	Conduction disease, prolonged PR interval, widening of QRS complex	Atrial fibrillation and flutter, complete heart block
Myotonic dystrophy type 1	Myotonic dystrophy protein kinase gene	LVNC	Conduction disease, prolonged PR interval, widening of QRS complex	Atrial fibrillation and flutter, complete heart block

AV, Atrioventricular; HR, heart rate; LVNC, left ventricular noncompaction.

From Hsu DT. Cardiac manifestations of neuromuscular disorders in children. *Pediatr Respir Rev.* 2010;11:35–38, Table 1.

488.2 Hypertrophic Cardiomyopathy

John J. Parent and Stephanie M. Ware

Hypertrophic cardiomyopathy **(HCM)** is a heterogeneous, relatively common, and potentially life-threatening form of cardiomyopathy. The causes of HCM include inborn errors of metabolism, neuromuscular disorders, syndromic conditions, and genetic abnormalities of the structural components of the cardiomyocyte (see Tables 488.1 and 488.2). Both the age of onset and the associated features are helpful in identifying the underlying etiology.

HCM is a genetic disorder and frequently occurs because of pathogenic variants in sarcomere or cytoskeletal components of the cardiomyocyte (see Fig. 488.2). Pathogenic variants of the genes encoding cardiac β-myosin heavy-chain *(MYH7)* and myosin-binding protein C *(MYBPC3)* are the most common (see Table 488.3). Pathogenic variants are inherited in an autosomal dominant pattern with a high penetrance but variable expressivity. Additional genetic causes for HCM include nonsarcomeric protein pathogenic variants, such as the γ_2-regulatory subunit of adenosine monophosphate–activated protein kinase *(PRKAG2)* and the lysosome-associated membrane protein 2α-galactosidase (**Danon disease**, a form of glycogen storage disease). Syndromic conditions, such as **Noonan syndrome**, may present with HCM at birth, and recognition of extracardiac manifestations is important in making the diagnosis. Medical therapy directed at the Ras signaling pathway is in the initial phases of use in patients with Noonan syndrome and related RASopathies.

Glycogen storage disorders such as **Pompe disease** often present in infancy with a heart murmur, abnormal ECG, systemic signs and symptoms, and occasionally heart failure. Many states have Pompe testing on the newborn screening, facilitating early diagnosis and therapy, which has improved the prognosis. The characteristic ECG in Pompe disease demonstrates prominent P waves, a *short* P-R interval, and massive QRS voltages. The echocardiogram confirms severe, often concentric, LV hypertrophy.

PATHOGENESIS

HCM is characterized by the presence of increased LV wall thickness in the absence of structural heart disease or hypertension. Often the interventricular septum is disproportionately involved, leading to the previous designation of *idiopathic hypertrophic subaortic stenosis* or the current term of **asymmetric septal hypertrophy**. In the presence of a resting or provocable outflow tract gradient, the term **hypertrophic obstructive cardiomyopathy** is used. Although the left ventricle is predominantly affected, the right ventricle may be involved, particularly in infancy. The mitral valve can demonstrate systolic anterior motion and mitral insufficiency. Left ventricular outflow tract (LVOT) obstruction occurs in 25% of patients, is dynamic in nature, and may in part be secondary to the abnormal position of the mitral valve as well as the obstructing subaortic hypertrophic cardiac muscle. The cardiac myofibrils and myofilaments demonstrate disarray and myocardial fibrosis.

Typically, systolic function is preserved or even hyperdynamic, although systolic dysfunction may occur late and is a predictor for death or need for cardiac transplant. LVOT obstruction with or without mitral insufficiency may be provoked by physiologic manipulations such as the Valsalva maneuver, positional changes, and physical activity. Frequently, the hypertrophic and fibrotic cardiac muscle demonstrates relaxation abnormalities (diminished compliance), and LV filling may be impaired (diastolic dysfunction).

CLINICAL MANIFESTATIONS

Many patients are asymptomatic; 50% of cases present with a heart murmur or during screening when another family member has been diagnosed with HCM. Symptoms of HCM may include palpitations, chest pain, easy fatigability, dyspnea, dizziness, and syncope. Sudden death is a well-recognized but uncommon manifestation that occurs during physical exertion but may also occur at rest or during sleep. Characteristic physical examination findings include an overactive precordial impulse with a lift or heave, a systolic ejection murmur in the aortic region *not* associated with an ejection click, and an apical blowing murmur of mitral insufficiency.

DIAGNOSIS

The ECG typically demonstrates LV hypertrophy with ST segment and T-wave abnormalities (particularly T-wave inversion in the left precordial leads). Intraventricular conduction delays and signs of ventricular preexcitation **(Wolff-Parkinson-White syndrome)** may be present and should raise the possibility of PRKAG2-related HCM, Danon disease, or Pompe disease. Chest radiography demonstrates normal or mildly increased heart size with a prominence of the left ventricle. Echocardiography is diagnostic in identifying, localizing, and quantifying the degree of myocardial hypertrophy (see Fig. 488.3). Doppler interrogation defines, localizes, and quantifies the degree of LVOT obstruction and demonstrates and quantifies the degree of mitral insufficiency and diastolic dysfunction.

Cardiac catheterization is rarely used in the diagnosis of HCM but may be helpful if there is concern for a **myocardial bridge** (when a coronary artery runs through vs on top of the myocardium) that may be causing intermittent coronary insufficiency during dynamic obstruction. Myocardial bridges can be seen on coronary angiography. Additionally, cardiac catheterization may occasionally be used to better define hemodynamics in patients.

Additional diagnostic studies include metabolic testing, genetic testing for specific syndromes, or genetic testing for pathogenic variants in genes known to cause isolated HCM (see Table 488.3). Clinical genetic testing panels continue to expand. Genetic diagnosis is also useful in identifying at-risk family members who require ongoing surveillance (Figs. 488.5 and 488.6).

PROGNOSIS AND MANAGEMENT

Children <1 year of age or with inborn errors of metabolism or malformation syndromes or those with a mixed HCM/DCM have a significantly poorer prognosis. The risk of sudden death in older patients is greater in those with a personal or family history of cardiac arrest, ventricular tachycardia, exercise hypotension, syncope, or excessive (>3 cm) ventricular wall thickness. Although intrafamilial variability in symptoms occurs, a family history of sudden death is a highly significant predictor of risk. Restriction from competitive sports and strenuous physical activity is highly recommended, and additional recreational exercise activities should be tailored to each individual based on their overall clinical status. β-Adrenergic blocking agents (propranolol, atenolol, metoprolol) or calcium channel blockers (verapamil) may be useful in diminishing LVOT obstruction, modifying LV hypertrophy, and improving ventricular filling. They also confer an antiarrhythmic benefit and may reduce symptoms. In patients with atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be used. Patients with documented, previously aborted sudden cardiac arrest, strong family histories of sudden death, ventricular wall end-diastolic dimensions of ≥3 cm, unexplained syncope, nonsustained ventricular tachycardia, apical aneurysm, ejection fraction ≤50%, or blunted or hypotensive blood pressure response to exercise should be considered for treatment with an **implantable cardioverter-defibrillator** (ICD). Early identification of HCM, family screening/surveillance, appropriate activity restriction, and use of ICDs have greatly reduced the mortality of HCM to approximately 0.5% per year in the modern era.

Innovative interventional procedures have been used to reduce the degree of LVOT obstruction anatomically or physiologically. Dual-chamber pacing, alcohol septal ablation, surgical septal

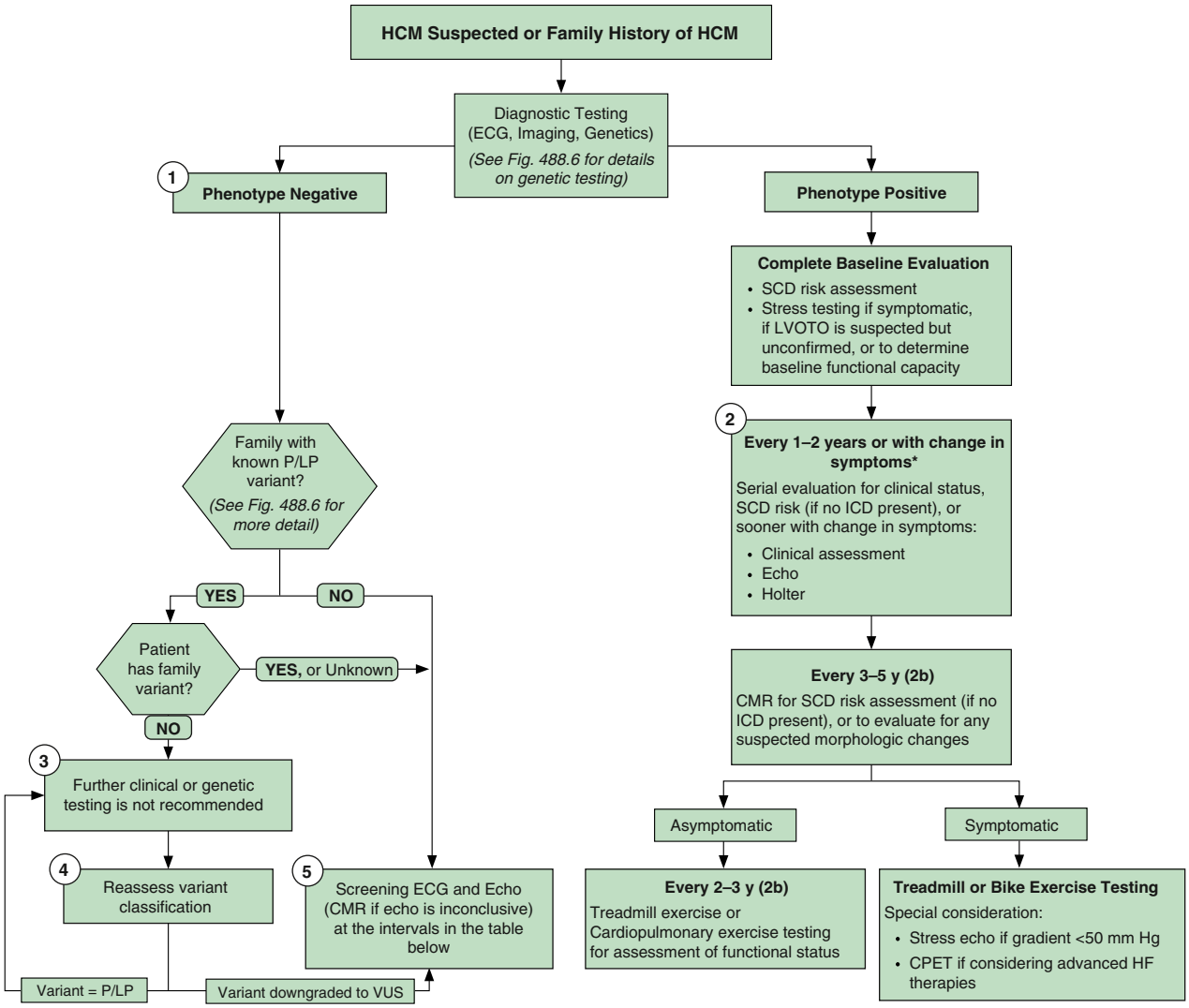

Screening Asymptomatic First-Degree Relatives of Patients With HCM		
Age of First-Degree Relative	**Initiation of Screening**	**Surveillance Interval**
Children and adolescents from genotype-positive family and/or family with early onset HCM	At the time of diagnosis in another family member	Every 1–2 y
All other children and adolescents	At any time after the diagnosis in the family, but no later than puberty	Every 2–3 y
Adults	At the time of diagnosis in another family member	Every 3–5 y

Fig. 488.5 Algorithm for recommended evaluation and testing modified for HCM. *The interval may be extended, particularly in adult patients who remain stable after multiple evaluations. CMR, Cardiovascular magnetic resonance; CPET, cardiopulmonary exercise test; ECG, electrocardiography/electrocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVOTO, left ventricular outflow tract obstruction; P/LP, pathogenic or likely pathogenic variant; SCD, sudden cardiac death; VUS, variant of unknown significance. *(Modified from Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. J Amer Coll Cardiol. 2020;142:e533–e557, Fig. 1.)*

myomectomy, and mitral valve replacement have all met with some success but are typically reserved for patients with significant symptoms despite medical therapy (Fig. 488.7). Mavacamten, a selective myosin inhibitor, has been an effective therapy in adults. Enzyme replacement therapy for Pompe disease is an effective therapy after birth (see Chapter 107.1). Preliminary trials of in utero enzyme replacement therapy for Pompe disease have also demonstrated efficacy.

First-degree relatives of patients identified as having HCM should be screened with ECG and echocardiogram. Genetic testing is available clinically and is of high utility. It is important first to test the affected individual in the family rather than "at-risk" individuals, because 20–50% of cases of HCM will not demonstrate pathogenic variants in currently available panels of genes. If a causative genetic variant is identified, at-risk members of the family can be effectively tested. In families with HCM without demonstrable pathogenic variants, repeat noninvasive cardiac screening with ECG and echocardiogram should be undertaken in at-risk individuals yearly until young adulthood (age 21 years) and then every 3 years if no prior evidence of HCM is present. Gene-positive but phenotype-negative pediatric patients may remain asymptomatic during childhood but require careful and frequent follow-up.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

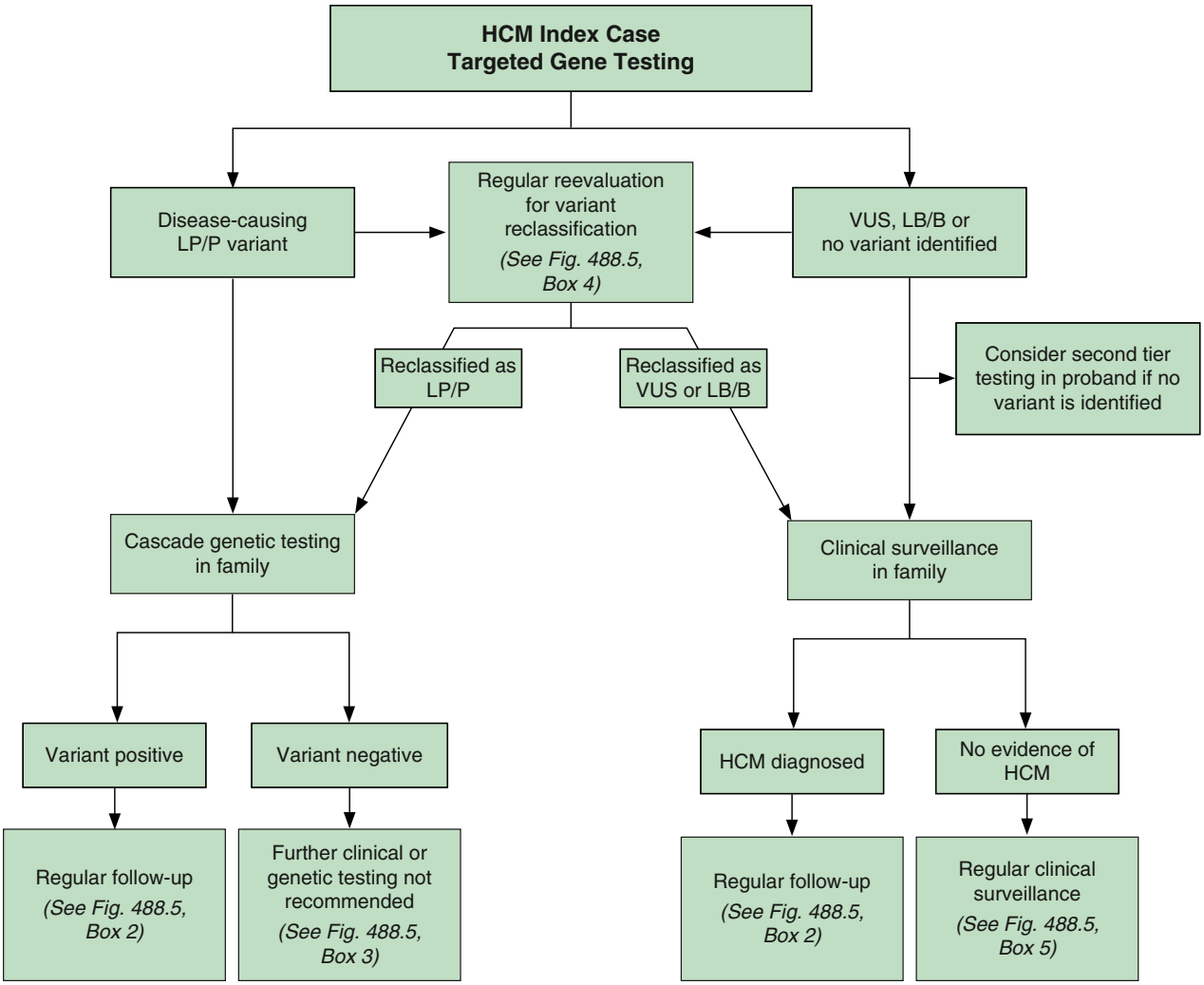

Fig. 488.6 Algorithm for genetic testing processes in HCM. HCM, Hypertrophic cardiomyopathy; LB/B, likely benign/benign; LP/P, likely pathogenic or pathogenic; VUS, variant of unknown significance. *(Modified from Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. J Amer Coll Cardiol. 2020;142:e533–e557, Fig. 2.)*

488.3 Restrictive Cardiomyopathy

John J. Parent and Stephanie M. Ware

Restrictive cardiomyopathy **(RCM)** accounts for <5% of cardiomyopathy cases. Incidence increases with age and is more common in females. In equatorial Africa, RCM accounts for a large number of deaths. Infiltrative myocardial causes and storage disorders frequently result in associated LV hypertrophy and may represent HCM with restrictive physiology. Noninfiltrative causes include pathogenic variants in genes encoding sarcomeric or cytoskeletal proteins. Although there has been significant success in discovering pathogenic gene variants causing RCM, the majority of cases are considered idiopathic. Potential etiologies include sarcoidosis and Gaucher, Hurler, or Fabry diseases.

PATHOGENESIS

RCM is characterized by normal ventricular chamber dimensions, normal myocardial wall thickness, and preserved systolic function. Dramatic atrial dilation can result from the abnormal ventricular myocardial compliance and high ventricular diastolic pressure. Autosomal dominant inheritance has been demonstrated for families with pathogenic gene variants in sarcomeric and cytoskeletal genes.

CLINICAL MANIFESTATIONS

Abnormal ventricular filling, sometimes referred to as *diastolic heart failure,* is manifest in the systemic venous circulation with edema, hepatomegaly, or ascites. Elevation of left-sided filling pressures results in cough, dyspnea, or pulmonary edema. With activity, patients may experience chest pain, shortness of breath, syncope/near-syncope, or even sudden death. Pulmonary hypertension and pulmonary vascular disease develop and may progress rapidly. Heart murmurs are typically absent, but a gallop rhythm may be prominent. In the presence of pulmonary hypertension, an overactive RV impulse and pronounced pulmonary component of the second heart sound (S_2) are present in RCM.

DIAGNOSIS

The characteristic electrocardiographic finding of prominent P waves (reflective of atrial enlargement) is usually associated with normal QRS voltages and nonspecific ST and T-wave changes. RV hypertrophy occurs in patients with pulmonary hypertension. The chest radiograph may be normal or may demonstrate a prominent atrial shadow and pulmonary vascular redistribution. The echocardiogram is often diagnostic, demonstrating normal-sized ventricles with preserved systolic function and dramatic enlargement of the atria (see Fig. 488.4). Flow and tissue Doppler interrogation reveal abnormal filling parameters. It is critical to differentiate RCM from **constrictive pericarditis**, which can be treated surgically (see Chapter 489.2). MRI may be necessary to demonstrate the thickened or calcified pericardium often present in constrictive pericardial disease.

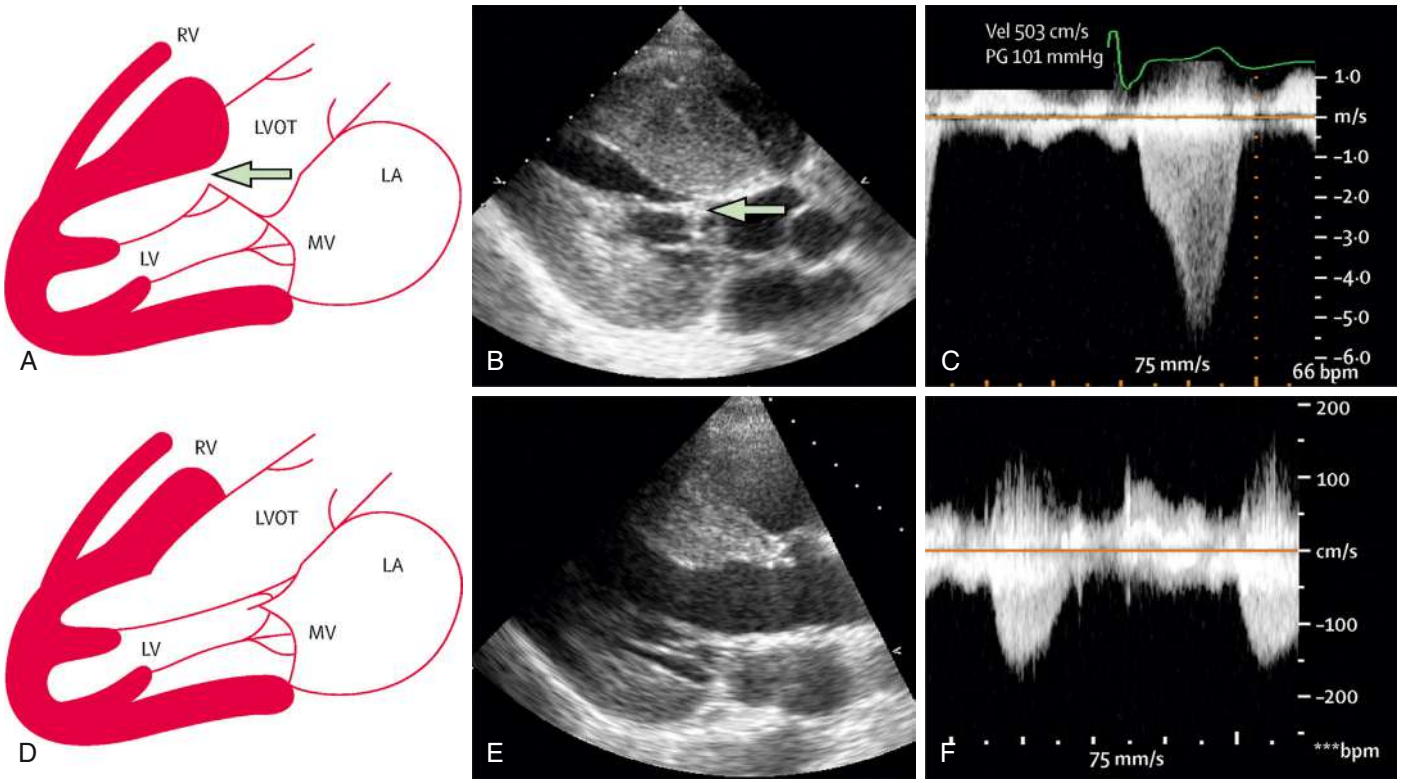

Fig. 488.7 Scheme of septal reduction therapy. **A,** Left ventricular outflow tract (LVOT) obstruction *(arrow)* created by hypertrophied basal septum and systolic anterior motion. **B,** Transthoracic echocardiography with systolic anterior motion *(arrow)*. **C,** Continuous-wave Doppler imaging of dynamic LVOT obstruction. **D,** Schematic finding after septal reduction. **E,** Transthoracic echocardiography after septal reduction procedure. **F,** Absence of LVOT obstruction in continuous-wave Doppler imaging after septal reduction therapy. LA, Left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. *(From Veselka J, Anavekar NS, Charron P. Hypertrophic obstructive cardiomyopathy. Lancet. 2017;389:1253–1264, Fig. 5, p. 1259.)*

PROGNOSIS AND MANAGEMENT

Pharmacologic modalities are of limited use, and the prognosis of patients with RCM is generally poor, with often progressive clinical deterioration. Sudden death is a significant risk, with a 2-year survival of 50%. When signs of heart failure exist, judicious use of diuretics can result in clinical improvement. As a result of the dramatic atrial enlargement and ventricular scarring, these patients are predisposed to the development of atrial tachyarrhythmias, complete heart block, and thromboemboli. Antiarrhythmic agents may be necessary, and anticoagulation with platelet inhibitors or warfarin (Coumadin) is indicated.

Cardiac transplantation is the treatment of choice in many centers for patients with RCM, and the results are excellent in patients without pulmonary hypertension, pulmonary vascular disease, or severe congestive heart failure. Some patients may need bridging to transplant with a VAD if they have elevated pulmonary pressures or significant heart failure.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

488.4 Left Ventricular Noncompaction, Arrhythmogenic Right Ventricular Cardiomyopathy, Endocardial Fibroelastosis, and Takotsubo Cardiomyopathy

John J. Parent and Stephanie M. Ware

Left ventricular noncompaction (LVNC) is characterized by a distinctive trabeculated or spongy-appearing left ventricle commonly associated with LV dysfunction and/or dilation and at times hypertrophy, diastolic dysfunction, and arrhythmias (Fig. 488.8). LVNC may be isolated or associated with structural congenital cardiac defects. Patients may present with signs of heart failure, arrhythmias, syncope, sudden death, or as an asymptomatic finding during screening of family members.

Imaging studies using ultrasound or MRI can demonstrate the characteristic pattern of deeply trabeculated LV myocardium, most characteristically within the apex. ECG findings are nonspecific and include chamber hypertrophy, ST and T-wave changes, or arrhythmias. In some patients, preexcitation is notable, and giant QRS voltages occur in approximately 30% of younger children. Metabolic screening should be considered, especially in young children. Elevated serum lactate and urine 3-methylglutaconic acid may be seen in **Barth syndrome**, an X-linked disorder of phospholipid metabolism caused by a pathogenic variant in the *TAZ* gene. Clinical testing for *TAZ* variants is available and should be considered, especially in males. Patients with mitochondrial disorders frequently demonstrate signs of LVNC. These children are at risk for atrial or ventricular arrhythmias and thromboembolic complications. Treatment includes anticoagulation, antiarrhythmic therapy if needed, and treatment of heart failure if present. In patients refractory to medical therapy, cardiac transplantation has been used successfully.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is relatively uncommon in North America compared with the high prevalence in Europe, especially Italy (see Chapter 484.4). Autosomal dominant inheritance is common. In addition, recessive forms associated with severe ARVC and skin manifestations are known. Comprehensive genetic screening has been reported to identify a cause in up to 50% of cases. ARVC is typically characterized by a dilated right ventricle with fibrofatty infiltration of the RV wall; increasingly, LV involvement is being recognized. Global and regional RV and LV dysfunction and ventricular tachyarrhythmias are the major clinical findings. Syncope or aborted sudden death can occur and should be treated with antiarrhythmic medications and placement of an ICD. In patients with ventricular dysfunction, heart failure management as indicated for patients with DCM may be of use.

Endocardial fibroelastosis (EFE), once an important cause of heart failure in children, is uncommon. The decline in primary EFE is likely related to the abolition of mumps virus infections by immunization practices. Rare familial cases exist, but the causative genes are unknown. Secondary EFE can occur with severe left-sided obstructive lesions such as aortic stenosis or atresia, hypoplastic left heart

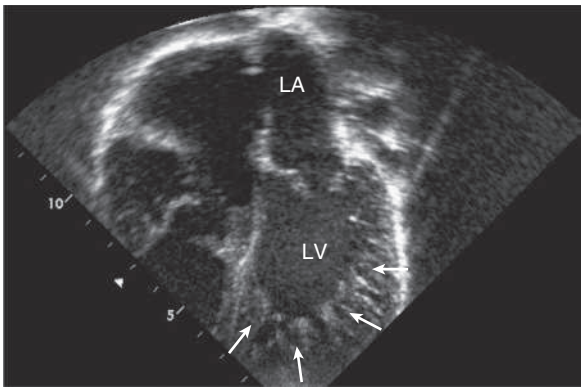

Fig. 488.8 Echocardiogram of a patient with left ventricular noncompaction cardiomyopathy. Apical view showing abnormal trabeculations of left ventricle at the apex *(arrows)*. For comparison, see the smooth-walled LV in Figure 488.2. LA, Left atrium; LV, left ventricle.

syndrome, or coarctation of the aorta. EFE is characterized by an opaque, white, fibroelastic thickening on the endocardial surface of the ventricle, which leads to systolic and/or diastolic dysfunction. Surgical removal of the endocardial fibrosis has been successfully done to improve cardiac function. Standard heart failure management, including transplantation, has been used in the management of EFE.

Takotsubo cardiomyopathy is a reversible stress-induced syndrome associated with transient systolic and diastolic dysfunction and regional ventricular wall motion abnormalities characterized by ventricular apical ballooning. Physical or emotional stress and associated etiologies (see Table 488.2) precipitate transient episodes of chest pain or heart failure. Treatment includes that for heart failure (β blockers, ACE inhibitors, diuretics) and addressing the precipitating event (thyrotoxicosis, pheochromocytoma, drug ingestion).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

488.5 Myocarditis

John J. Parent and Stephanie M. Ware

Acute or chronic inflammation of the myocardium is characterized by inflammatory cell infiltrates, myocyte necrosis, or myocyte degeneration and may be caused by infectious, connective tissue, granulomatous, toxic, immune, or idiopathic processes. There may be associated systemic manifestations of the disease, and occasionally the endocardium or pericardium is involved. Patients may be asymptomatic, have nonspecific prodromal symptoms, or present with overt congestive heart failure, compromising arrhythmias, or sudden death. It is assumed that viral infections are the most common etiology, although myocardial toxins, drug exposures, hypersensitivity reactions, and immune disorders may also lead to myocarditis (Table 488.7).

ETIOLOGY AND EPIDEMIOLOGY

Viral Infections

Coxsackievirus and other enteroviruses, adenovirus, parvovirus B19, Epstein-Barr virus, parechovirus, influenza virus, and cytomegalovirus are the most common causative agents in children. COVID-19 infections, particularly during multisystem inflammatory syndrome in children (MIS-C) and, rarely, after mRNA COVID-19 vaccinations, have been associated with myocarditis. In Asia, hepatitis C virus appears to be significant as well. The true incidence of viral myocarditis is unknown because mild cases probably go undetected. The disease is typically sporadic but may be epidemic. Manifestations are, to some degree, age dependent: in neonates and young infants, viral myocarditis can be fulminant; in children, it often occurs as an acute, myopericarditis with heart failure; and in older children and adolescents, it may present with signs and symptoms of acute or chronic heart failure or chest pain.

Table 488.7 Etiology of Myocarditis

INFECTIOUS CAUSES
Viral: adenoviruses, echoviruses, enteroviruses (e.g., coxsackieviruses), herpesviruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus, influenza virus, parvovirus B19, SARS-CoV-2 (COVID-19) disease and vaccine, smallpox vaccine
Bacterial: *Borrelia burgdorferi* (Lyme disease), *Chlamydia, Corynebacterium diphtheriae, Legionella, Mycobacterium tuberculosis, Mycoplasma, Staphylococcus,* streptococcus A, *Streptococcus pneumoniae,* Whipple disease
Fungal: *Actinomyces, Aspergillus, Candida, Cryptococcus*
Helminthic: *Echinococcus granulosus, Trichinella spiralis*
Protozoal: *Toxoplasma gondii, Trypanosoma cruzi*
Rickettsial: *Coxiella burnetii, Rickettsia typhi*
Spirochetal: *Borrelia burgdorferi, Leptospira, Treponema pallidum*
AUTOIMMUNE DISEASES
Rheumatic fever, celiac disease, Churg-Strauss syndrome, Crohn disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematosus, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis
HYPERSENSITIVITY REACTIONS
Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
TOXIC REACTIONS TO DRUGS
Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab, immune checkpoint inhibitors
TOXIC
Ethanol, snakebite, scorpion bite, electric shock, spider bite
OTHER CAUSES
Arsenic, copper, iron, radiotherapy, thyrotoxicosis, immune modulation

Adapted from Canter CE, Simpson KE. Diagnosis and treatment of myocarditis in children in the current era. *Circulation.* 2014;129:115–128, Table 1.

Bacterial Infections

Bacterial myocarditis has become much less common with the advent of advanced public health measures, which have minimized infectious causes such as diphtheria. Diphtheritic myocarditis is unique because bacterial toxin may produce circulatory collapse and toxic myocarditis characterized by atrioventricular block, bundle branch block, or ventricular ectopy (see Chapter 233). Lyme disease may present as myocarditis; rheumatic fever (poststreptococcal) may also manifest with valve, myocardium, and pericardium involvement. Any overwhelming systemic bacterial infection can manifest with circulatory collapse and shock with evidence of myocardial dysfunction, characterized by tachycardia, gallop rhythm, and low cardiac output. Additional nonviral infectious causes of myocarditis include rickettsiae, protozoa, parasitic infections, and fungal disease.

PATHOPHYSIOLOGY

Myocarditis is characterized by myocardial inflammation, injury or necrosis, and ultimately fibrosis. Cardiac enlargement and diminished systolic function are a direct result of the myocardial damage. Typical signs of congestive heart failure occur and may progress rapidly to shock, atrial or ventricular arrhythmias, and sudden death. Viral myocarditis may also become a chronic process, with persistence of viral nucleic acid in the myocardium and the perpetuation of chronic inflammation secondary to altered host immune response, including activated T lymphocytes (cytotoxic and natural killer cells) and antibody-dependent cell-mediated damage. Additionally, persistent viral infection may alter the expression of major histocompatibility complex (MHC) antigens with resultant exposure of neoantigens to the immune system. Some viral proteins share antigenic epitopes with host cells, resulting in autoimmune damage to the antigenically related myocyte. Cytokines such as tumor necrosis factor-α and interleukin-1 are inhibitors of myocyte response to adrenergic stimuli and result in diminished cardiac function. The final result of viral-associated inflammation can be DCM.

CLINICAL MANIFESTATIONS

Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end-organ involvement such as hepatitis or aseptic meningitis.

Patients with acute or chronic myocarditis may present with chest discomfort, fever, palpitations, easy fatigability, or syncope/near-syncope. Cardiac findings include overactive precordial impulse, gallop rhythm, and apical systolic murmur of mitral insufficiency. In patients with associated pericardial disease, a rub may be noted. Hepatic enlargement, peripheral edema, and pulmonary findings such as wheezes or rales may be present in patients with decompensated heart failure.

DIAGNOSIS

Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes, often suggestive of acute ischemia. Chest radiographs in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions. Echocardiography often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial infusion.

Cardiac MRI is a standard imaging modality for the diagnosis of myocarditis; information on the presence and extent of edema, gadolinium-enhanced hyperemic capillary leak, myocyte necrosis, LV dysfunction, and evidence of an associated pericardial effusion assist in the cardiac MRI diagnosis of myocarditis (Table 488.8 and Fig. 488.9).

Endomyocardial biopsy may be useful in identifying inflammatory cell infiltrates or myocyte damage and performing molecular viral analysis using polymerase chain reaction techniques. Catheterization and biopsy, although not without risk (perforation and arrhythmias), should be performed by experienced personnel in patients suspected to have myocarditis or if unusual forms of cardiomyopathy are strongly suspected, such as storage diseases or mitochondrial defects. Nonspecific tests include erythrocyte sedimentation rate, CPK isoenzymes, cardiac troponin I, and BNP levels. A novel microRNA derived from type 17 helper (Th17) cells may be another useful specific test for viral myocarditis.

DIFFERENTIAL DIAGNOSIS

The predominant diseases mimicking acute myocarditis include carnitine deficiency, other metabolic disorders of energy generation, hereditary mitochondrial defects, idiopathic DCM, pericarditis, EFE, and anomalies of the coronary arteries (see Table 488.2).

TREATMENT

Primary therapy for acute myocarditis is supportive. Acutely, the use of inotropic agents, preferably milrinone, should be considered but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with VAD implantation or ECMO may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, β blockers, ACE inhibitors, and ARBs are of use in patients with compensated congestive heart failure in the outpatient setting but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (e.g., amiodarone) should be administered and ICD placement considered if persistent after a period of recovery is observed.

Table 488.8 MRI Findings Suggestive of Myocarditis

- T2-weighted edema (global or regional)
- Regional hyperemia/capillary leak by early gadolinium enhancement ratio (EGEr)
- Myocardial fibrosis or necrosis on late gadolinium enhancement (LGE)
- Features often present in a midmyocardial, subepicardial, and nonvascular distribution
- Repeat MRI if no *early* MRI evidence present but clinical manifestation suggests myocarditis

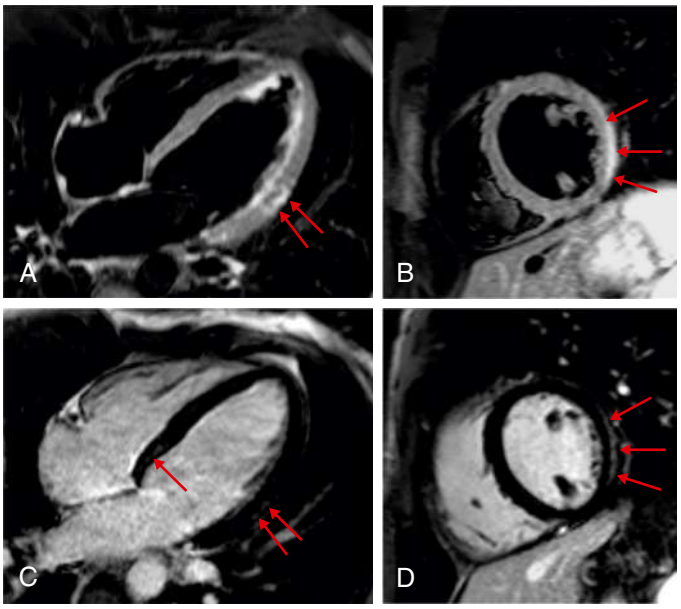

Fig. 488.9 MRI findings in patients with myocarditis. Cardiac MR images of a young patient presenting with acute chest pain syndrome caused by acute myocarditis. (**A**) Long-axis and (**B**) short-axis T2-weighted images demonstrating focal myocardial edema in subepicardium of left midventricular lateral wall *(red arrows)*. Corresponding (**C**) long-axis and (**D**) short-axis T1-weighted images demonstrate the presence of typical late gadolinium enhancement in subepicardium of left midventricular lateral wall and basal septum *(red arrows)*. *(From Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol. 2012;59:779–792, Fig. 3, p. 783.)*

Immunomodulation of patients with myocarditis is controversial. Intravenous immunoglobulin (IVIG) may have a role in the treatment of acute or fulminant myocarditis, and corticosteroids have been reported to improve cardiac function, but this remains controversial in children. Relapse has been noted in patients receiving immunosuppression who were weaned from therapy. There are no studies to recommend specific antiviral therapies for myocarditis.

If there is an identifiable and treatable condition, its specific therapy should be employed. If a medication is the etiology, it should be withdrawn and an alternative drug added if needed.

PROGNOSIS

The prognosis of symptomatic acute enteroviral myocarditis in newborns is poor, with a 75% mortality. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to the need for cardiac transplantation; recovery of ventricular function, however, has been reported in 10–50% of patients.

The prognosis for COVID-19 immunization–associated myocarditis is excellent with full recovery noted by 90 days. Patients with COVID-19 requiring intensive care unit (ICU) admission and those with MIS-C must be followed by a pediatric cardiologist (including follow-up echocardiography) and refrain from exercise for 3-6 months. Return to full activity requires clearance from a cardiologist.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 489
Diseases of the Pericardium

John J. Parent and Stephanie M. Ware

The heart is enveloped in a bilayer membrane, the *pericardium,* which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of

CLINICAL MANIFESTATIONS

Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end-organ involvement such as hepatitis or aseptic meningitis.

Patients with acute or chronic myocarditis may present with chest discomfort, fever, palpitations, easy fatigability, or syncope/near-syncope. Cardiac findings include overactive precordial impulse, gallop rhythm, and apical systolic murmur of mitral insufficiency. In patients with associated pericardial disease, a rub may be noted. Hepatic enlargement, peripheral edema, and pulmonary findings such as wheezes or rales may be present in patients with decompensated heart failure.

DIAGNOSIS

Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes, often suggestive of acute ischemia. Chest radiographs in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions. Echocardiography often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial infusion.

Cardiac MRI is a standard imaging modality for the diagnosis of myocarditis; information on the presence and extent of edema, gadolinium-enhanced hyperemic capillary leak, myocyte necrosis, LV dysfunction, and evidence of an associated pericardial effusion assist in the cardiac MRI diagnosis of myocarditis (Table 488.8 and Fig. 488.9).

Endomyocardial biopsy may be useful in identifying inflammatory cell infiltrates or myocyte damage and performing molecular viral analysis using polymerase chain reaction techniques. Catheterization and biopsy, although not without risk (perforation and arrhythmias), should be performed by experienced personnel in patients suspected to have myocarditis or if unusual forms of cardiomyopathy are strongly suspected, such as storage diseases or mitochondrial defects. Nonspecific tests include erythrocyte sedimentation rate, CPK isoenzymes, cardiac troponin I, and BNP levels. A novel microRNA derived from type 17 helper (Th17) cells may be another useful specific test for viral myocarditis.

DIFFERENTIAL DIAGNOSIS

The predominant diseases mimicking acute myocarditis include carnitine deficiency, other metabolic disorders of energy generation, hereditary mitochondrial defects, idiopathic DCM, pericarditis, EFE, and anomalies of the coronary arteries (see Table 488.2).

TREATMENT

Primary therapy for acute myocarditis is supportive. Acutely, the use of inotropic agents, preferably milrinone, should be considered but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with VAD implantation or ECMO may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, β blockers, ACE inhibitors, and ARBs are of use in patients with compensated congestive heart failure in the outpatient setting but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (e.g., amiodarone) should be administered and ICD placement considered if persistent after a period of recovery is observed.

Table 488.8 MRI Findings Suggestive of Myocarditis

- T2-weighted edema (global or regional)
- Regional hyperemia/capillary leak by early gadolinium enhancement ratio (EGEr)
- Myocardial fibrosis or necrosis on late gadolinium enhancement (LGE)
- Features often present in a midmyocardial, subepicardial, and nonvascular distribution
- Repeat MRI if no *early* MRI evidence present but clinical manifestation suggests myocarditis

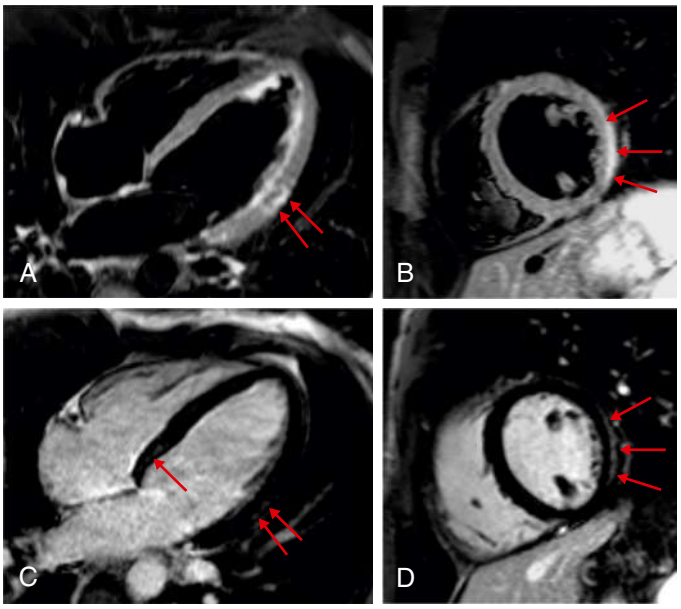

Fig. 488.9 MRI findings in patients with myocarditis. Cardiac MR images of a young patient presenting with acute chest pain syndrome caused by acute myocarditis. (**A**) Long-axis and (**B**) short-axis T2-weighted images demonstrating focal myocardial edema in subepicardium of left midventricular lateral wall *(red arrows)*. Corresponding (**C**) long-axis and (**D**) short-axis T1-weighted images demonstrate the presence of typical late gadolinium enhancement in subepicardium of left midventricular lateral wall and basal septum *(red arrows)*. *(From Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol. 2012;59:779–792, Fig. 3, p. 783.)*

Immunomodulation of patients with myocarditis is controversial. Intravenous immunoglobulin (IVIG) may have a role in the treatment of acute or fulminant myocarditis, and corticosteroids have been reported to improve cardiac function, but this remains controversial in children. Relapse has been noted in patients receiving immunosuppression who were weaned from therapy. There are no studies to recommend specific antiviral therapies for myocarditis.

If there is an identifiable and treatable condition, its specific therapy should be employed. If a medication is the etiology, it should be withdrawn and an alternative drug added if needed.

PROGNOSIS

The prognosis of symptomatic acute enteroviral myocarditis in newborns is poor, with a 75% mortality. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to the need for cardiac transplantation; recovery of ventricular function, however, has been reported in 10–50% of patients.

The prognosis for COVID-19 immunization–associated myocarditis is excellent with full recovery noted by 90 days. Patients with COVID-19 requiring intensive care unit (ICU) admission and those with MIS-C must be followed by a pediatric cardiologist (including follow-up echocardiography) and refrain from exercise for 3-6 months. Return to full activity requires clearance from a cardiologist.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 489
Diseases of the Pericardium

John J. Parent and Stephanie M. Ware

The heart is enveloped in a bilayer membrane, the *pericardium,* which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of

conditions, often as a manifestation of a systemic illness, and can result in serious, even life-threatening, cardiac compromise (Table 489.1).

489.1 Acute Pericarditis

John J. Parent and Stephanie M. Ware

Inflammation of the pericardium may have only minor pathophysiologic consequences in the absence of significant fluid accumulation in the pericardial space. When the amount of fluid in the nondistensible pericardial space becomes excessive, pressure within the pericardium increases and is transmitted to the heart, resulting in impaired filling by compressing the chambers (atria or ventricles). Although small to moderate amounts of **pericardial effusion** can be well tolerated and clinically silent, once the noncompliant pericardium has been distended maximally, any further fluid accumulation causes abrupt impairment of cardiac filling, and this can impair cardiac output and is termed **cardiac tamponade**. When untreated, tamponade can lead to shock and death. Pericardial effusions may be serous/transudative, exudative/purulent, fibrinous, or hemorrhagic.

Pericarditis may present without an obvious pericardial effusion on echocardiography. In addition, pericarditis may be associated with myocarditis (**myopericarditis**), in which case either pericarditis or myocarditis may be the dominant finding.

CLINICAL MANIFESTATIONS

The most common symptom of acute pericarditis is chest pain, typically described as sharp/stabbing, positional, radiating, worse with inspiration, and relieved by sitting upright, leaning forward, or prone. Cough, fever, dyspnea, abdominal pain, and vomiting are nonspecific symptoms associated with pericarditis. Additionally, signs and symptoms of organ system involvement may occur in the presence of generalized systemic disease.

Muffled or distant heart sounds, tachycardia, narrow pulse pressure, jugular venous distention, and a pericardial friction rub provide clues to the diagnosis of acute pericarditis. Cardiac tamponade is recognized by the excessive fall of systolic blood pressure (>10 mm Hg) with inspiration. This pulsus paradoxus can be assessed by careful auscultatory blood pressure determination (automated blood pressure cuffs are inadequate), arterial pressure line waveform, or pulse oximeter tracing inspection. Doppler assessment during echocardiography can also indirectly suggest pulsus paradoxus is present. Conditions other than cardiac tamponade that may result in pulsus paradoxus include severe dyspnea, obesity, and positive pressure ventilator support.

Table 489.1 Etiology of Pericardial Disease

CONGENITAL
Absence (partial, complete)
Cysts
Mulibrey nanism (*TRIM 37* gene variant)
Camptodactyly-arthropathy–coxa vara–pericarditis syndrome (*PRG4* gene variant)
Myhre syndrome (*SMAD4* gene variant)
INFECTIOUS
Viral: coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps, COVID-19, and mRNA COVID-19 and HPV vaccines
Bacterial: *Haemophilus influenzae,* streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, *Listeria,* leptospirosis, tuberculosis, Q fever, salmonella
Immune complex mediated: meningococcus, *H. influenzae*
Fungal: actinomycosis, histoplasmosis
Parasitic: toxoplasmosis, echinococcosis
NONINFECTIOUS
Idiopathic
Systemic inflammatory diseases: acute rheumatic fever, juvenile idiopathic arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis, Kawasaki disease, eosinophilic granulomatosis with polyangiitis, Behçet syndrome, sarcoidosis, familial Mediterranean fever and other recurrent fever syndromes, pancreatitis, granulomatosis with polyangiitis
Metabolic: uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency
Traumatic: surgical, catheter perforation, blunt trauma
Postpericardiotomy syndrome
Oncologic: lymphomas, leukemia, radiation therapy, primary pericardial tumors

DIAGNOSIS

The electrocardiogram is often abnormal in acute pericarditis, although the findings are nonspecific. Low-voltage QRS amplitude may be seen as a result of pericardial fluid accumulation. Tachycardia and abnormalities of the ST segments (diffuse ST segment elevation), PR segments, and T waves (inversion or flattening) may be present as well. Elevated troponin levels may be present in myopericarditis.

Although the chest x-ray findings in a patient with pericarditis without effusion are usually normal in the presence of a significant effusion, cardiac enlargement will be seen and the cardiac contour may be unusual (Erlenmeyer flask or water bottle appearance) (Fig. 489.1). Echocardiography is the most sensitive technique for identifying the size and location of a pericardial effusion. Compression and collapse of the right atrium and/or right ventricle are present with cardiac tamponade (Fig. 489.2). Abnormal diastolic filling parameters have also been described in cases of tamponade. Advanced imaging modalities like computed tomography or cardiac magnetic resonance imaging are useful for diagnosis in unclear cases (Fig. 489.3).

DIFFERENTIAL DIAGNOSIS

Chest pain similar to that present in pericarditis can occur with lung diseases, especially pleuritis, and with gastroesophageal reflux or costochondritis, with the latter being reproducible on palpation. Pain related to myocardial ischemia is usually more severe and prolonged and occurs with exercise, allowing distinction from pericarditis-induced pain. The presence of pericardial effusion on echocardiography is highly suggestive of pericarditis but does not determine the etiology.

Infectious Pericarditis

A number of viral agents are known to cause pericarditis, and the clinical course of the majority of these infections is mild and spontaneously resolving. The term *acute benign pericarditis* is synonymous for viral pericarditis. Agents identified as causing pericarditis include the enteroviruses, influenza, adenovirus, respiratory syncytial virus, and parvovirus. Because the course of this illness is usually benign, symptomatic treatment with nonsteroidal antiinflammatory drugs (NSAIDs) is often sufficient. Persistent or early recurrence episodes may need courses of colchicine or, rarely, corticosteroids. Anakinra and the interleukin-1

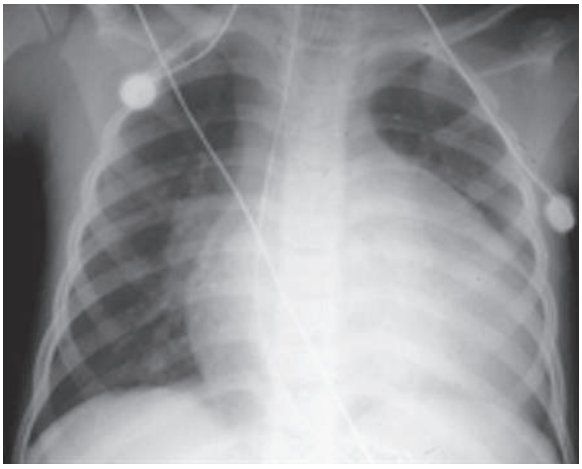

Fig. 489.1 "Water bottle" silhouette. This chest radiograph shows marked cardiomegaly, also known as a water bottle silhouette, which is seen in the presence of large pericardial effusions. Also note the associated pulmonary edema from associated high left atrial and left ventricular filling pressures. *(Courtesy Dr. Steven M. Selbst, Wilmington, DE; from Durani Y, Giordani K, Goudie BW. Myocarditis and pericarditis in children. Pediatr Clin North Am 2010;57:1281–1303, Fig. 7.)*

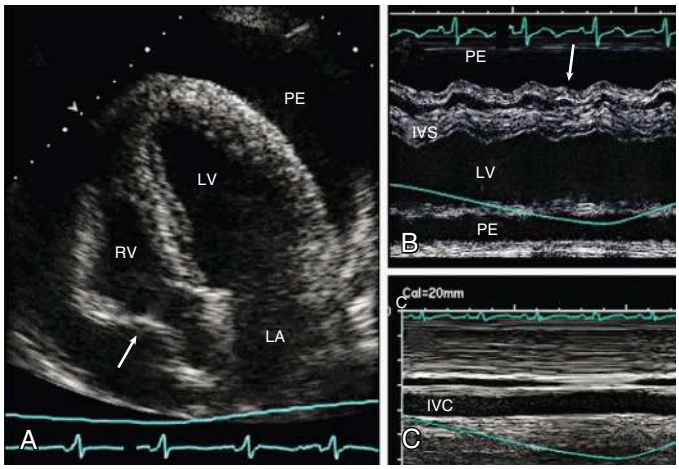

Fig. 489.2 Echocardiographic images of large pericardial effusion with features of tamponade. **A,** Apical four-chamber view of LV, LA, and RV that shows large PE with diastolic right atrial collapse *(arrow).* **B,** M-mode image with cursor placed through RV, IVS, and LV in parasternal long axis. The view shows circumferential PE with diastolic collapse of RV free wall *(arrow)* during expiration. **C,** M-mode image from subcostal window in the same patient that shows IVC plethora without inspiratory collapse. IVC, Inferior vena cava; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PE, pericardial effusion; RV, right ventricle. *(From Troughton RW, Asher CR, Klein AL. Pericarditis. Lancet. 2004;363:717–727.)*

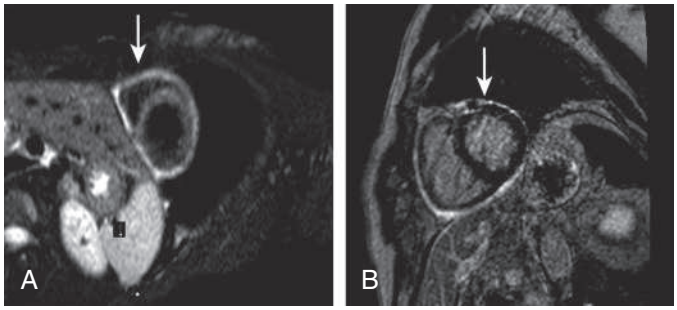

Fig. 489.3 Cardiac magnetic resonance T2 STIR (**A**) and delayed gadolinium (**B**) sequences showing enhancement of the pericardium signifying acute or active inflammation *(arrow). (Modified from Chetrit M, Xu B, Kwon DH, et al: Imaging-guided therapies for pericardial diseases. JACC: Cardiovascular Imaging. 2019;13(6):1422–1437; Fig. 1E and 1F, p. 1424.)*

cytokine trap agent rilonacept have been effective in colchicine-nonresponsive acute or recurrent pericarditis. Patients with large effusions and tamponade may require pericardiocentesis. Presumed viral but often idiopathic pericarditis may have an autoimmune component. Up to 30% of patients may have recurrences of pericarditis. Treatment *and* prevention of recurrences with colchicine improve symptoms and avoid recurrences in most of these patients. If the condition becomes chronic or relapsing, surgical pericardiectomy or creation of a pericardial window may be necessary.

Echocardiography is useful in differentiating pericarditis from *myocarditis,* which will show evidence of diminished myocardial contractility or valvular dysfunction (see Chapter 488.5). Pericarditis and myocarditis may occur together in some cases of viral infection.

Purulent pericarditis, often caused by bacterial infections, has become much less common with the advent of new immunizations for *Haemophilus influenzae* and pneumococcal disease. Historically, purulent pericarditis was seen in association with severe pneumonias, epiglottitis, meningitis, or osteomyelitis. Patients with purulent pericarditis are acutely ill. Unless the infection is recognized and treated expeditiously, the course can be fulminant, leading to tamponade and death. **Tuberculous pericarditis** is rare in developed countries but can be a relatively common complication of HIV infection in regions where tuberculosis is endemic and access to antiretroviral therapy is limited. **Immune complex–mediated pericarditis** is a rare complication that may result in a nonpurulent (sterile) effusion after systemic bacterial infections such as meningococcus or *Haemophilus.*

Noninfectious Pericarditis

Systemic inflammatory diseases such as autoimmune, rheumatologic, and connective tissue disorders may involve the pericardium and result in serous pericardial effusions. Pericardial inflammation may be a component of the type II hypersensitivity reaction seen in patients with acute rheumatic fever. It is often associated with rheumatic valvulitis and responds quickly to antiinflammatory agents, including corticosteroids. Tamponade is quite uncommon (see Chapters 229.1 and 487).

Juvenile idiopathic arthritis, usually systemic-onset disease, can manifest with pericarditis. Differentiating rheumatoid pericardial inflammation from that seen with systemic lupus erythematosus is difficult and requires careful rheumatologic evaluation. Aspirin and corticosteroids can result in rapid resolution of a pericardial effusion but may be needed on a chronic basis to prevent relapse. Many of the autoinflammatory recurrent fever syndromes present with pericarditis, usually with other manifestations of those disorders (see Chapter 204).

Patients with chronic renal failure or hypothyroidism may have pericardial effusions. Clinical suspicion warrants careful screening with physical examination and, if indicated, imaging studies during the course of their illness.

Especially common in referral centers with hematology/oncology units is the presence of pericardial effusion related to neoplastic disease. Conditions resulting in effusion include Hodgkin disease, lymphomas, and leukemia. Radiation therapy directed to the mediastinum of patients with malignancy can result in pericarditis and, later, constrictive pericardial disease.

The **postpericardiotomy syndrome** occurs in patients who have undergone cardiac surgery and is characterized by fever, lethargy, anorexia, irritability, and chest/abdominal discomfort beginning 1-4 weeks postoperatively (see Table 483.2 in Chapter 483). There can be associated pleural effusions. Postpericardiotomy syndrome is effectively treated with aspirin, NSAIDs, colchicine, and in severe cases, corticosteroids. Pericardial drainage is necessary in those patients with cardiac tamponade.

In many patients the etiology of pericarditis is not known. Approximately 30% of these patients have multiple occurrences and are treated with colchicine to reduce the risk of recurrent pericarditis. Other less frequently used treatments have included NSAIDs and corticosteroids. Refractory idiopathic recurrent pericarditis may require pericardiectomy; anakinra and rilonacept have demonstrated promise for difficult-to-treat patients.

489.2 Constrictive Pericarditis

John J. Parent and Stephanie M. Ware

Rarely, chronic pericardial inflammation can result in fibrosis, calcification, and thickening of the pericardium. Pericardial scarring may lead to impaired cardiac distensibility and filling and is termed *constrictive pericarditis.* Constrictive pericarditis can result from recurrent or chronic pericarditis, cardiac surgery, or radiation to the mediastinum as a treatment for malignancies, most often Hodgkin disease or lymphoma.

Clinical manifestations of systemic venous hypertension predominate in cases of restrictive pericarditis. Jugular venous distention, peripheral edema, hepatomegaly, and ascites may precede signs of more significant cardiac compromise, such as tachycardia, hypotension, and pulsus paradoxus. A pericardial knock, rub, and distant heart sounds might be present on auscultation. Abnormalities of liver function tests, hypoalbuminemia, hypoproteinemia, and lymphopenia may be present. On occasion, chest radiographs demonstrate calcifications of the pericardium.

Constrictive pericarditis may be difficult to distinguish clinically from restrictive cardiomyopathy because both conditions result in impaired myocardial filling (see Chapter 488.3). Echocardiography may be helpful in distinguishing constrictive pericardial disease from restrictive cardiomyopathy, but cardiac MRI and CT are more sensitive in detecting abnormalities of the pericardium. In rare cases, exploratory thoracotomy with direct examination of the pericardium may be required to confirm the diagnosis.

Although acute pericardial constriction is reported to respond to antiinflammatory agents, the more typical chronic constrictive pericarditis will respond only to pericardiectomy with extensive resection of the pericardium.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 490

Tumors of the Heart

John J. Parent and Stephanie M. Ware

Although cardiac tumors occur rarely in pediatric patients, they may result in serious hemodynamic or electrophysiologic abnormalities depending on tumor type and location.

The vast majority of tumors originating from the heart are benign. **Rhabdomyomas** are the most common pediatric cardiac tumors and are associated with tuberous sclerosis in 70–95% of cases (see Chapter 636.2). Rhabdomyomas may occur at any age, from fetal life through late adolescence. They are often multiple, can occur in any cardiac chamber, and originate within the myocardium, often extending into the atrial or ventricular cavities (Fig. 490.1). Depending on their location and size, rhabdomyomas can result in inflow or outflow obstruction, leading to cyanosis or cardiac failure; many are asymptomatic. Atrial and ventricular arrhythmias have been reported with rhabdomyomas, and on occasion, ventricular preexcitation (Wolff-Parkinson-White syndrome) is present on electrocardiogram (ECG).

Fibromas are the second most common pediatric cardiac tumor and, in contrast to rhabdomyomas, are usually solitary and intramyocardial. The size and location of fibromas can lead to heart failure, cyanosis, or rhythm disturbances. Loss of the tumor suppressor *PTCH1* is associated with the development of cardiac fibromas in sporadic cases. There is an increased incidence in patients with **Gorlin syndrome** (3%).

Myxomas, the most common cardiac tumor seen in adults, occur infrequently in the pediatric population. Myxomas are predominantly intraatrial, appear pedunculated, and are rather mobile (Fig. 490.2); however, they may also be ventricular (Fig. 490.3). They may cause obstruction to inflow or outflow and may present with a murmur, heart failure, or syncope. On occasion, atrial myxomas are associated with systemic symptoms of fever, malaise, and arthralgia. **Carney complex** is a familial autosomal dominant multiple neoplasia (often endocrine: pituitary adenoma, thyroid, testis, ovarian) and lentiginosis syndrome in which cardiac myxomas can occur at a young age in any or all cardiac chambers. Pathogenic variants in the *PRKAR1A* gene are causative in some families.

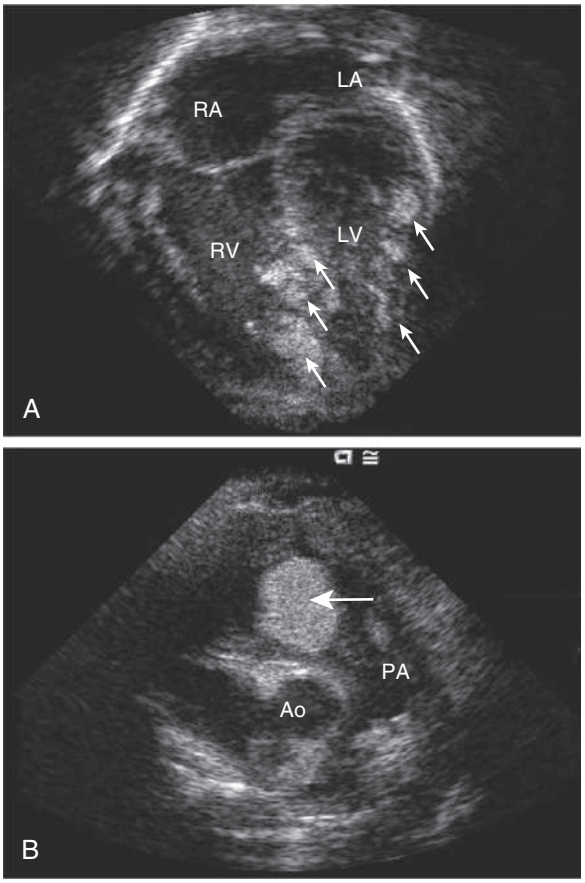

Fig. 490.1 Echocardiograms demonstrating rhabdomyomas. **A,** Apical four-chamber view showing multiple rhabdomyomas *(arrows)* within the septum and left ventricular myocardium. **B,** Short-axis view showing a large rhabdomyoma *(arrow)* extending into the right ventricular outflow tract. Ao, Ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

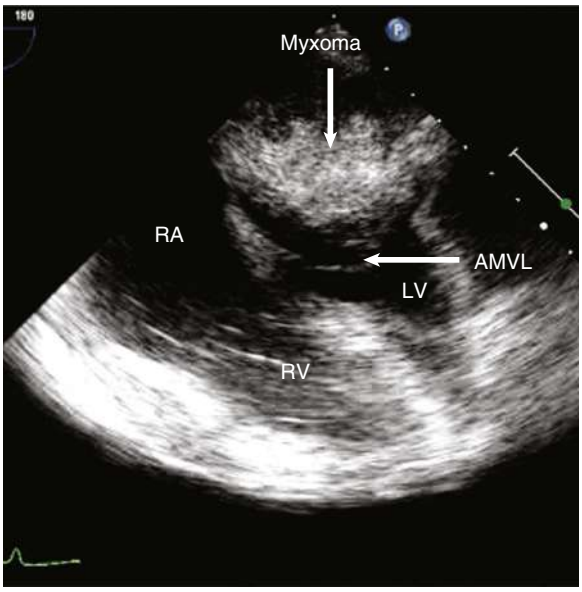

Fig. 490.2 A large left atrial myxoma prolapsing across the mitral valve, resulting in heart failure symptoms. AMVL, anterior mitral valve leaflet; LV, left ventricle; RA, right atrium; RV, right ventricle. *(From Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019, Fig. 95.8, p. 1871.)*

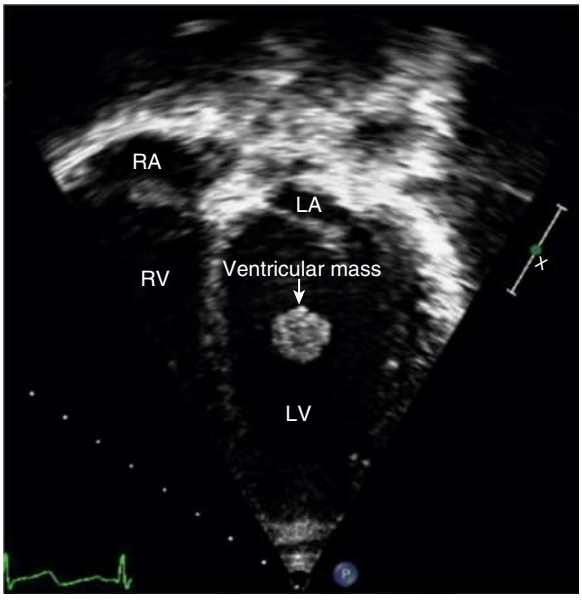

Fig. 490.3 Left ventricular myxoma. TTE apical four-chamber view of mass within the left ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. *(From Schroeder L, Zyblewski S, Forbus G, et al. Left ventricular myxoma. J Pediatr. 2016;168:249–249.e2, Fig. 1.)*

Other benign tumors include hemangiomas, Purkinje cell tumors, papillomas, lipomas, and mesotheliomas. Depending on their location, these benign tumors can result in valvular function abnormalities, myocardial dysfunction, or heart block and other arrhythmias.

Malignant pediatric cardiac tumors are much less common than benign tumors; the majority of such malignancies are sarcomas, including angiosarcomas, rhabdosarcomas, or fibrosarcomas. Lymphomas and pheochromocytomas are reported but rare. Tumors originating from noncardiac sources that invade, extend, or metastasize to the heart are more frequently seen than primary malignant cardiac tumors. In pediatric patients, Wilms tumor and lymphoma/leukemia are the most common causes of such secondary tumors.

Although the manifestations of cardiac tumors in pediatric patients are protean, when a tumor is suspected, noninvasive imaging with echocardiography and/or MRI may be diagnostic and can determine tumor type, location, extent, and hemodynamic impact. ECG and Holter studies are valuable adjuncts when rhythm abnormalities are suspected. Cardiac catheterization is rarely indicated but may be used to confirm tumor location, assess intracardiac hemodynamics, and perform biopsy for histologic assessment. Such risks as blood loss, perforation, arrhythmia, and vessel injury should be considered when discussing catheterization and biopsy.

Because the natural history of rhabdomyomas is one of spontaneous diminution or complete resolution, treatment of the majority of cardiac tumors in pediatric patients is usually unnecessary. *Everolimus,* an inhibitor of the mammalian target of rapamycin (mTOR), may enhance resolution in symptomatic patients with cardiac rhabdomyomas. Careful clinical follow-up and imaging are important. **Antiarrhythmic medications** may be prescribed to control rhythm disorders. Surgical removal of a cardiac tumor may be indicated to relieve obstruction, improve myocardial or valve function, or control arrhythmias. **Heart transplantation** has been performed in cases of unresectable tumors with significant hemodynamic compromise. Wilms tumors extending from the inferior vena cava into the atrium may require cardiopulmonary bypass support during the course of primary resection of the renal tumor. Radiation or chemotherapy can improve cardiac function in rare cases of lymphoma or leukemia compressing the heart with hemodynamic compromise.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 7

Cardiac Therapeutics

Chapter 491

Heart Failure

Danielle S. Burstein and Joseph W. Rossano

The International Society for Heart and Lung Transplantation (ISHLT) defines heart failure as follows:

> A clinical and pathological syndrome that results from ventricular dysfunction, volume, or pressure overload, alone or in combination. It leads to characteristic signs and symptoms, such as poor growth, feeding difficulties, respiratory distress, exercise intolerance, and fatigue, and is associated with circulatory, neurohormonal, and molecular abnormalities. Heart failure has numerous etiologies that are a consequence of cardiac and noncardiac disorders, either congenital or acquired.

PATHOPHYSIOLOGY

The heart can be viewed as a pump with an output proportional to its filling volume and inversely proportional to the resistance against which it pumps. As ventricular end-diastolic volume increases, a healthy heart increases cardiac output until a maximum is reached and cardiac output can no longer be augmented (the **Frank-Starling principle**; Fig. 491.1). The increased stroke volume obtained in this manner is a result of stretching of myocardial fibers, but it also results in increased wall tension, which elevates myocardial oxygen consumption. Hearts working under various types of stress function along different Frank-Starling curves. Cardiac muscle with compromised intrinsic contractility requires a greater degree of dilation to produce increased stroke volume and does not achieve the same maximal cardiac output as normal myocardium does. If a cardiac chamber is already dilated because of a lesion causing increased preload (e.g., a left-to-right shunt or valvular insufficiency), there is little room for further dilation as a means of augmenting cardiac output. The presence of lesions that result in increased afterload to the ventricle (e.g., aortic or pulmonic stenosis, coarctation of the aorta) decreases cardiac performance, thereby resulting in a depressed Frank-Starling relationship.

Systemic oxygen transport is calculated as the product of cardiac output and oxygen content of systemic blood. **Cardiac output** can be calculated as the product of heart rate and stroke volume. The primary determinants of stroke volume are the *afterload* (pressure work), *preload* (volume work), and *contractility* (intrinsic myocardial function). Abnormalities in heart rate can also compromise cardiac output; for example, tachyarrhythmias shorten the diastolic time interval for ventricular filling. Alterations in the oxygen-carrying capacity of blood (e.g., anemia or hypoxemia) also lead to a decrease in systemic oxygen transport and, if compensatory mechanisms are inadequate, can result in decreased delivery of substrate to tissues.

In some cases of heart failure, cardiac output is normal or increased, yet because of decreased systemic oxygen content (e.g., secondary to anemia) or increased oxygen demands (e.g., secondary to hyperventilation, hyperthyroidism, or hypermetabolism), an inadequate amount of oxygen is delivered to meet the body's needs. This condition, **high-output failure**, results in the development of signs and symptoms of heart failure when there is no basic abnormality in myocardial function and cardiac output is greater than normal. It is also seen with large systemic arteriovenous fistulas (e.g., vein of Galen malformation). These conditions reduce peripheral vascular resistance and cardiac afterload and increase myocardial contractility. Heart failure results when the demand for cardiac output exceeds the ability of the heart to respond.

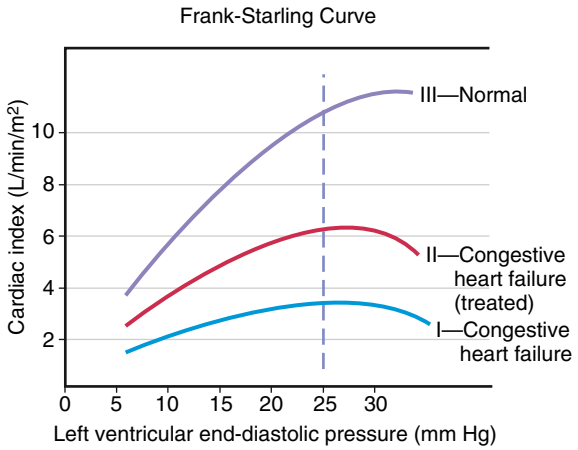

Fig. 491.1 The Frank-Starling relationship. As left ventricular end-diastolic (LVED) pressure increases, the cardiac index increases, even in the presence of congestive heart failure, until a critical level of LVED pressure is reached. Adding an inotropic agent (digoxin) shifts the curve from I to II. *(From Gersony WM, Steep CN. In: Dickerman JD, Lucey JF, eds. Smith's The Critically Ill Child: Diagnosis and Medical Management, 3rd ed. Philadelphia: Saunders; 1984.)*

Chronic severe high-output failure may eventually result in a decrease in myocardial performance as the metabolic requirements of the myocardium are not met.

Multiple systemic compensatory mechanisms are used by the body to adapt to chronic heart failure. Some are mediated at the molecular/cellular level, such as upregulation or downregulation of various metabolic pathway components leading to changes in efficiency of oxygen and other substrate utilizations. Others are mediated by neurohormones such as the renin-angiotensin system and the sympathoadrenal axis. One of the principal mechanisms for increasing cardiac output is an increase in sympathetic tone secondary to increased secretion of circulating epinephrine by the adrenals and increased release of norepinephrine at the neuromuscular junction. The *initial* beneficial effects of sympathetic stimulation include an increase in heart rate and myocardial contractility, mediated by these hormones' action on cardiac β-adrenergic receptors, increasing cardiac output. These hormones also cause vasoconstriction, mediated by their action on peripheral arterial α-adrenergic receptors. Some vascular beds may constrict more readily than others, so that blood flow is redistributed from the cutaneous, visceral, and renal beds to the heart and brain. Whereas these acute effects are beneficial, *chronically* increased sympathetic stimulation can have deleterious effects, including hypermetabolism, increased afterload, arrhythmogenesis, and increased myocardial oxygen requirements. Peripheral vasoconstriction can result in decreased renal, hepatic, and gastrointestinal tract function. Chronic exposure to circulating catecholamines leads to a decrease in the number of cardiac β-adrenergic receptors (downregulation) and also causes direct myocardial cell damage. Therapeutic agents for heart failure are directed at restoring balance to these neuroendocrine systems.

Based on these physiologic and clinical principles, heart failure has been described by different **classification** and **stage** definitions (Tables 491.1-491.3 and Fig. 491.2). These definitions help describe the degree of cardiac impairment and help direct therapy.

Table 491.1 Classification of Heart Failure Based on LVEF

HF CLASS ACCORDING TO LVEF (MUST HAVE SIGNS AND SYMPTOMS)	ACRONYM	LVEF, %
HF with reduced ejection fraction	HFrEF	≤40
HF with mildly reduced ejection fraction	HFmrEF	41–49
HF with preserved ejection fraction	HFpEF	≥50
HF with preserved ejection fraction, improved	HFpEF, improved	Prior <40, now ≥40

LVEF, Left ventricular ejection fraction.
From Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier; 2023: Table 2, p. 117.

Table 491.2 New York Heart Association (NYHA) Functional Classification (FC)

NYHA FC	FUNCTIONAL CAPACITY
I	No limitations. Can perform high level of activity without symptoms (for example, running, cycling, weightlifting).
II	Slight limitations. Tolerate lower or moderate level activities well, may have limitations with higher-level activities (for example, regular walking causes no symptoms, but a run may cause shortness of breath).
III	Significant limitations. Symptoms with low-level activities such as with daily activities such as walking and household chores.
IV	Symptoms at rest, dyspnea with any physical activity.

From Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier; 2023: Table 3, p. 117.

ETIOLOGY OF HEART FAILURE

There are many causes of heart failure in the pediatric population, and the etiologies of heart failure are age-dependent (Table 491.4). Pediatric heart failure can occur because of ventricular systolic or diastolic dysfunction caused by an underlying cardiomyopathy. This may be the result of a primary cardiomyopathy from an underlying genetic mutation in cardiac proteins or secondary due to conditions including metabolic and neuromuscular diseases. Ischemic cardiomyopathy caused by congenital coronary anomalies or acquired disease, such as Kawasaki disease, can also result in heart failure. Inflammatory or infectious diseases of the myocardium (e.g., myocarditis) can present with a range of heart failure severity from mild symptoms of chest pain to severe disease with fulminant cardiogenic shock. Persistent atrial and ventricular arrhythmias, particularly tachyarrhythmias, may also result in ventricular dysfunction and heart failure. High-output heart failure can occur in the setting of severe anemia or large arteriovenous malformations.

Heart failure in children can also occur in the setting of underlying congenital heart disease with outflow tract obstructive lesions, shunt lesions with overcirculation of the pulmonary vascular system (e.g., ventricular septal defect), or ventricular volume overload caused by significant valve regurgitation. Heart failure in children can also occur because of valvar heart disease resulting in significant valve regurgitation that causes ventricular volume overload and ventricular dilation with eventual systolic dysfunction. Single ventricle heart disease, including hypoplastic left heart syndrome, has increased the risk of developing heart failure due to multiple mechanisms that influence appropriate blood flow through the single ventricle palliated circulation.

CLINICAL MANIFESTATIONS

The clinical manifestations of heart failure depend in part on the degree of the child's cardiac reserve. A critically ill infant or child who has exhausted the compensatory mechanisms to the point that cardiac output is no longer sufficient to meet the basal metabolic needs of the body may present in **cardiogenic shock**. Other patients may be comfortable when quiet but are incapable of increasing cardiac output in response to even mild activity without experiencing significant symptoms. Conversely, it may take rather vigorous exercise to compromise cardiac function in children who have less severe heart disease.

A thorough **history** is extremely important in making the diagnosis of heart failure and in evaluating the possible causes. Parents or caregivers who observe their child on a daily basis may not recognize subtle changes that have occurred over the course of days or weeks. Gradually worsening perfusion or increasing respiratory effort may not be recognized as an abnormal finding, or may be misattributed to other diagnoses such as asthma. Edema, which is generally absent in infants and young children, may be passed off as normal weight gain, and exercise intolerance as lack of interest in an activity. The history of a young infant should also focus on **feeding**. An infant with heart failure often takes less volume per feeding, becomes dyspneic while sucking, and may perspire profusely. Eliciting a history of fatigue in an older child requires detailed questions about activity level and its course over several months.

In children and adolescents, the signs and symptoms of heart failure may be similar to those in adults and include fatigue, exercise intolerance, anorexia, nausea, vomiting, dyspnea, edema, wheezing, and cough. Many children, however, may have primarily abdominal symptoms (abdominal pain, nausea, vomiting, anorexia) and a surprising lack of respiratory complaints. Attention to the cardiovascular system may come only after an abdominal radiograph unexpectedly catches the lower end of an enlarged heart.

The **physical examination** for a child with suspected heart failure includes evaluation of vital signs and physical exam. Abnormal vital signs sometimes seen in pediatric heart failure include tachypnea, tachycardia, and desaturation caused by pulmonary edema. The elevation in systemic venous pressure may be gauged by clinical assessment of jugular venous pressure and liver enlargement. Orthopnea and

Table 491. 3 Classification of HF According to the American Heart Association (AHA) and American College of Cardiology (ACC)

HEART FAILURE STAGE		AHA/ACC DESCRIPTION
Stage A	At risk	Patients without identified structural or functional cardiac abnormality or ventricular function abnormality but at high risk of developing HF because of the presence of a condition (hypertension) strongly associated with the development of HF. Examples: anthracycline exposure, known pathogenic sarcomeric gene variant including dystrophinopathies.
Stage B	Pre-HF	Patients with structural heart disease or ventricular function abnormality that is strongly associated with the development of HF but without HF signs or symptoms, past or present. Examples: asymptomatic patient with CHD status postsurgical correction with residual lesion, isolated left ventricle noncompaction, elevated BNP or troponin if exposed to cardiotoxins.
Stage C	HF	Patients with current or prior symptoms of HF associated with underlying structural heart disease or ventricular function abnormality (elevated filling pressure, systolic dysfunction). Examples: acute myocarditis, dilated cardiomyopathy, mitral or aortic regurgitation.
Stage D	Advanced HF	Patients with advanced structural heart disease and refractory symptoms of HF requiring specialized interventions. Example: Inotropic dependency patient in end stage of dilated cardiomyopathy: may require VAD or transplant.

BNP, B-type natriuretic protein; CHD, congenital heart defect; VAD, ventricular assist devices; HF, heart failure
Modified from Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American college of cardiology/American heart association task force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure). *J Am Coll Cardiol.* 2001;38:2101–13.

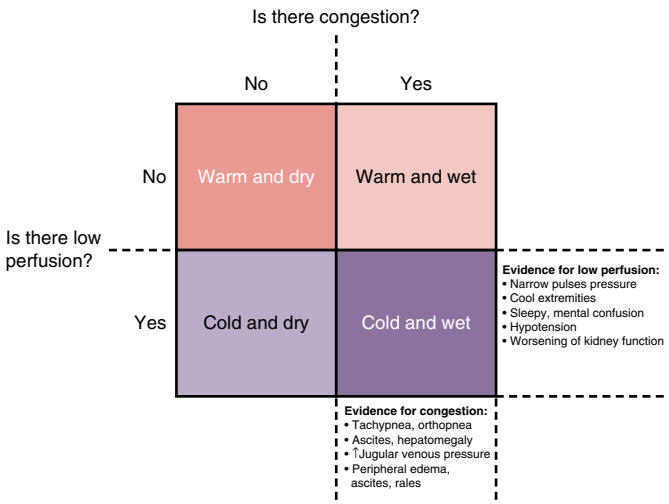

Fig. 491.2 Clinical assessment in acute decompensated heart failure should answer the two questions suggested by this diagram: First, does the patient present with significant congestion? Second, does the patient present with significant underperfusion? Using this construct, patients will segregate into one of four categories in accordance with clinical findings. Typically, patients move in a clockwise fashion through these categories, first becoming congested (warm and wet) and then vasoconstricted to maintain blood pressure (cold and wet). Once vasoactive support and diuresis are achieved, movement is generally counterclockwise, from cold and wet, to warm and wet, and then warm and dry. However, some patients will remain underperfused despite restoration of normovolemia, representing the cold and dry group, for whom mechanical support may be needed. *(Modified from Kantor PF, Mertens LL. Clinical practice: heart failure in children. Part I: clinical evaluation, diagnostic testing, and initial medical management. Eur J Pediatr. 2010;169[3]:269–279.)*

basilar rales are variably present; edema is usually discernible in dependent portions of the body, or anasarca may be present. Cardiomegaly is invariably noted based on a hyperactive precordium, ventricular heave, or displaced apical impulse. A **gallop rhythm** is common; when ventricular dilation is advanced, the **holosystolic murmur** of mitral or tricuspid valve regurgitation may be heard. **Pulsus alternans** is an ominous physical exam finding usually seeing in a state of low stroke volume with variable cardiac output with each ventricular contraction. Impaired systemic perfusion with poor capillary refill or decreased pulses is a concerning sign for cardiogenic shock.

In infants, heart failure may be difficult to distinguish from other causes of respiratory distress or gastrointestinal diseases. Prominent manifestations of heart failure include tachypnea, feeding difficulties, vomiting, poor weight gain, excessive perspiration, irritability, weak cry, and noisy, labored respirations with intercostal and subcostal retractions, as well as flaring of the alae nasi. The signs of cardiac-induced pulmonary congestion may be indistinguishable from those of bronchiolitis; wheezing is often a more prominent finding in young infants with heart failure than rales. Hepatomegaly usually occurs, and cardiomegaly is invariably present. Despite pronounced tachycardia, a gallop rhythm can frequently be recognized. The other auscultatory signs are those produced by the underlying cardiac lesion. Clinical assessment of jugular venous pressure in infants may be difficult because of the shortness of the neck and the difficulty of observing a relaxed state; palpation of an enlarged liver is a more reliable sign.

DIAGNOSIS

Chest radiograph (CXR) may be helpful in pediatric heart failure. It can assess the cardiac silhouette for cardiac enlargement. Pulmonary vascularity is variable and depends on the cause of the heart failure. Infants and children with large left-to-right shunts have exaggeration of the pulmonary arterial vessels to the periphery of the lung fields, whereas patients with cardiomyopathy may have a relatively normal pulmonary vascular bed early in the course of disease. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema are seen only with more severe degrees of heart failure. Pleural effusions may also be present. Cardiac enlargement as a marker of heart failure may be noted on a chest radiography performed to evaluate for a possible pulmonary infection, bronchiolitis, or asthma.

Electrocardiography (ECG) may be helpful in assessing the cause of heart failure but does not establish the diagnosis. In cardiomyopathies, exaggerated left or right ventricular voltages may be suggestive of underlying cardiomyopathy, and ischemic changes may correlate with other noninvasive parameters of ventricular function. Low-voltage QRS morphologic characteristics with ST-T–wave abnormalities may also suggest myocardial inflammatory disease (myocarditis) but can be seen with pericarditis as well. ECG is the best tool for evaluating rhythm disorders as a potential cause of heart failure, especially tachyarrhythmias. Ambulatory ECG monitoring can evaluate for occult arrhythmias that may be present in heart failure.

Echocardiography is the standard technique for assessing ventricular function (Fig. 491.3). Ventricular function can be quantitated simply and reliably with commonly used parameters such as fractional shortening (a single-dimensional variable) and an ejection fraction. The *fractional shortening* is determined as the difference between

Table 491.4 Etiology of Heart Failure

FETAL
Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19–induced anemia, hypoplastic anemia)
Supraventricular tachycardia
Ventricular tachycardia
Complete heart block
Severe Ebstein anomaly or other severe right-sided lesions
Myocarditis
PREMATURE NEONATE
Fluid overload
Patent ductus arteriosus
Ventricular septal defect
Cor pulmonale (bronchopulmonary dysplasia)
Hypertension
Myocarditis
Genetic/metabolic cardiomyopathy
FULL-TERM NEONATE
Asphyxial cardiomyopathy
Arteriovenous malformation (vein of Galen, hepatic)
Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart syndrome)
Large mixing cardiac defects (single ventricle, truncus arteriosus)
Myocarditis
Genetic/metabolic cardiomyopathy
Pheochromocytoma
Stress cardiomyopathy (Takotsubo)
Substance misuse
INFANT/TODDLER
Left-to-right cardiac shunts (ventricular septal defect)
Hemangioma (arteriovenous malformation)
Anomalous left coronary artery
Genetic/metabolic cardiomyopathy
Acute hypertension (hemolytic-uremic syndrome)
Supraventricular tachycardia
Kawasaki disease
Myocarditis
CHILD/ADOLESCENT
Congenital heart disease (various forms, including single ventricle heart disease)
Rheumatic fever
Acute hypertension (glomerulonephritis)
Myocarditis
Thyrotoxicosis
Hemochromatosis-hemosiderosis
Cancer therapy (radiation, doxorubicin)
Sickle cell anemia
Endocarditis
Cor pulmonale (cystic fibrosis)
Genetic/metabolic cardiomyopathy (hypertrophic, dilated)

end-systolic and end-diastolic diameter divided by end-diastolic diameter. Normal fractional shortening is between approximately 28% and 42%. The *ejection fraction* uses two-dimensional data to calculate a three-dimensional volume; the normal range is 55–65%. In children with right ventricular enlargement or other cardiac pathology resulting in flattening of the interventricular septum, ejection fraction is used because fractional shortening measured in the standard echocardiographic short-axis view will not be accurate. Doppler studies can also be used to estimate cardiac output. Doppler assessment of transmitral inflow and tissue characterization can also be used as a noninvasive assessment of diastolic function.

Cardiac magnetic resonance imaging (CMR) is also useful in quantifying left and right ventricular function, volume, and mass along with coronary artery anatomy. If valvular regurgitation is present, CMR can quantify the regurgitant fraction. CMR can also provide details about tissue characterization such as fibrosis and inflammation, which is helpful for assessing conditions such as myocarditis.

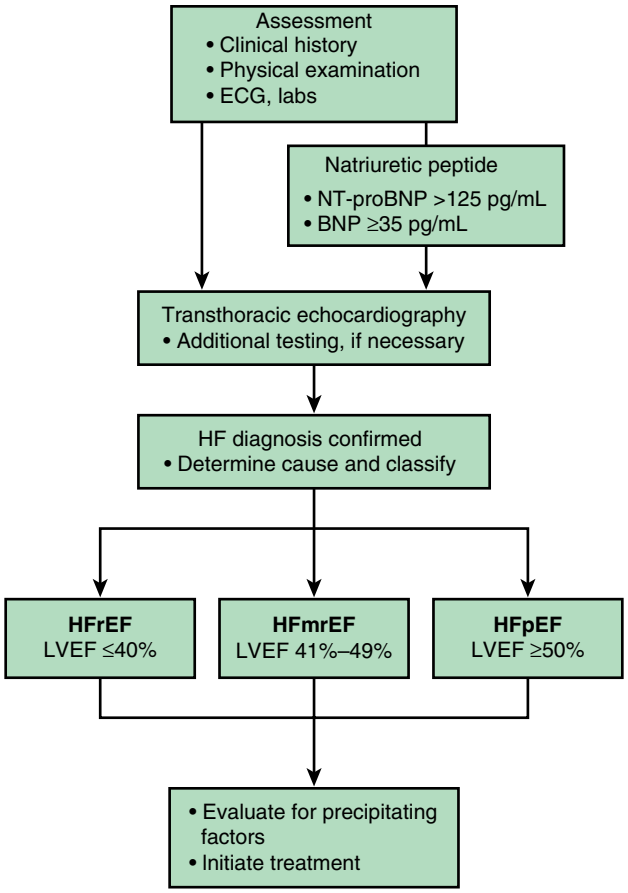

Fig. 491.3 Diagnostic algorithm for HF- and EF-based classification BNP, B-type natriuretic peptide; ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LV, left ventricular; NT-proBNP, N-terminal pro-B type natriuretic peptide. *(From Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Amer Coll Cardiol. 2022;79[17]:1757–1780, Fig. 4.)*

Cardiac catheterization is an invasive test that can be helpful for assessing heart failure by evaluating intracardiac hemodynamics and shunt lesions. Angiography can be performed to evaluate for structural heart defects. Endomyocardial biopsy may sometimes be performed as part of an evaluation of myocarditis.

Laboratory testing is important for evaluating end-organ function and systemic perfusion. This includes evaluating renal function, liver function, lactate levels, and electrolytes. Heart failure may result in hyponatremia caused by compensatory activation of the renin-angiotensin-aldosterone pathway with renal water retention, which may be compounded by further salt wasting due to chronic diuretic treatment. When heart failure is severe, respiratory acidosis or metabolic acidosis, or both, may be present. The cardiac serum **biomarker B-type (brain) natriuretic peptide (BNP)** (or N-terminal pro-BNP) is a cardiac neurohormone released in response to increased ventricular wall tension that is elevated in patients with heart failure. In children with heart failure, BNP may be elevated as a result of systolic dysfunction (e.g., cardiomyopathy) and in children with volume overload (e.g., left-to-right shunts such as ventricular septal defect). Table 491.5 lists other causes of an elevated BNP.

TREATMENT

The underlying cause of cardiac failure must be removed or alleviated if possible. If the cause is a congenital cardiac anomaly amenable to surgery, medical treatment of the heart failure is indicated to prepare the patient for surgery. With the current excellent outcomes of primary surgical repair of congenital heart defects, even in the neonatal period,

Table 491.5 Causes of Elevated Concentrations of Natriuretic Peptides

CARDIAC
Heart failure (HFpEF, HFrEF)
Acute coronary symptoms
Pulmonary embolism
Myocarditis
Left ventricular hypertrophy
Hypertrophic or restrictive cardiomyopathy
Valvular heart disease
Congenital heart disease
Atrial and ventricular tachyarrhythmias
Heart contusion
Cardioversion ICD shock
Surgical procedures involving the heart
Pulmonary hypertension
Toxic injury (chemotherapy)
NONCARDIAC
Ischemic stroke
Subarachnoid hemorrhage
Renal dysfunction
Liver dysfunction (mainly liver cirrhosis with ascites)
Paraneoplastic syndrome
Chronic obstructive pulmonary disease
Severe infections (including pneumonia and sepsis)
Severe burns
Anemia
Severe metabolic and hormone abnormalities (e.g., thyrotoxicosis, diabetic ketosis)

HFpEF, Heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator.

Adapted from McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in *Eur Heart J*. 2021 Oct 14]. *Eur Heart J*. 2021;42(36):3599–3726, Table 7.

few children require aggressive heart failure management to grow big enough for surgery. In contrast, if the cause of heart failure is cardiomyopathy, medical management provides temporary relief from symptoms and may allow the patient to recover if the insult is reversible (e.g., myocarditis). If the lesion is not reversible, heart failure management usually allows the child to return to normal activities for some period and to delay, sometimes for months or years, the need for heart transplantation.

General Measures

Heart failure management focuses on maintaining adequate cardiac output to allow for appropriate end-organ function while reducing volume overload and venous or pulmonary congestion. Encouraging regular physical activity is important for preventing acquired cardiovascular comorbidities, but it is important that the child be allowed to rest as needed and monitor for cardiac symptoms. Formal **cardiopulmonary exercise** testing can be used to assess the patient's ability to perform exercise in a controlled environment and is useful for providing exercise recommendations. Malnutrition is common in patients with heart failure because of gastrointestinal symptoms related to mesenteric venous congestion, and patients often require supplemental nutrition either with caloric fortification and/or nasogastric supplementation. For patients with pulmonary edema, positive pressure ventilation (PPV) may be required along with other drug therapies. For those in low-output heart failure, PPV can significantly reduce total body oxygen consumption by eliminating the work of breathing and help to reverse metabolic acidosis. Reverse remodeling agents, including β blockers, angiotensin-blockers, combination angiotensin receptor/neprilysin inhibitors, and aldosterone antagonists, can provide long-term myocardial reverse remodeling. Appropriate blood pressure control is important to reduce afterload and stress on the myocardium. In patients with advanced heart failure and/or cardiogenic shock, providing adequate cardiac output to meet the metabolic demands and provide adequate end-organ perfusion may require inotropic agents and, potentially, mechanical circulation support (Table 491.6).

Diet

Infants with heart failure usually fail to thrive because of a combination of increased metabolic demands and decreased caloric intake. Increasing daily calories is an important aspect of their management. Increasing the number of calories per ounce of infant formula (or supplementing breastfeeding) may be beneficial. Many infants do not tolerate an increase beyond 24 calories/oz because of diarrhea or because these formulas provide too large a solute load for compromised kidneys.

Severely ill infants and children may lack sufficient strength for effective sucking because of extreme fatigue, rapid respirations, and generalized weakness. In these circumstances, nasogastric feedings may be helpful. In many patients with cardiac enlargement, **gastroesophageal reflux** is a major problem. The use of continuous drip nasogastric feedings at night, administered by pump, may improve caloric intake while decreasing problems with reflux. Continued **malnutrition** may be an important factor in the decision to undertake earlier surgical intervention in patients who have an operable congenital heart lesion or to proceed with mechanical circulatory support and/or listing for transplantation in patients with cardiomyopathy. *Iron supplementation should be initiated in the presence of iron deficiency even in the absence of anemia.*

The use of low-sodium formulas in the routine management of infants with heart failure is not recommended because these preparations are often poorly tolerated and may exacerbate diuretic-induced hyponatremia. Human breast milk is the ideal low-sodium nutritional source. The use of more potent diuretic agents allows more palatable standard formulas to be used for nutrition while controlling salt and water balance by chronic diuretic administration. Most older children can be managed with generally heart-healthy diets that have low fat and sugar content, although caloric supplementation may be needed if there is significant malnutrition.

Diuretics

Diuretics are an important component of heart failure management by reducing volume overload and congestion. Diuretics interfere with reabsorption of water and sodium by the kidneys, which results in a reduction in circulating blood volume and thereby reduces pulmonary fluid overload and ventricular filling pressure. Diuretics are usually the first mode of therapy initiated in patients with congestive heart failure.

Loop diuretics, including Furosemide and bumetanide, are the most commonly used diuretics in pediatric patients with heart failure. It inhibits the reabsorption of sodium and chloride in the distal tubules and the loop of Henle. Patients requiring acute diuresis should be given intravenous (IV) furosemide at an initial dose of 1-2 mg/kg, which usually results in rapid diuresis and prompt improvement in clinical status, particularly if symptoms of pulmonary congestion are present. Chronic furosemide therapy is then prescribed at a dose of 1-4 mg/kg/24 hr given between 1 and 4 times a day. Careful monitoring of electrolytes is necessary with long-term furosemide therapy because of the potential for significant loss of potassium. Potassium chloride supplementation is usually required unless the potassium-sparing diuretics are given concomitantly. Chronic administration of furosemide may cause contraction of the extracellular fluid compartment and result in "contraction alkalosis" (see Chapter 73.7). Diuretic-induced hyponatremia may become difficult to manage in patients with severe heart failure.

Thiazide diuretics, including chlorothiazide, are also used for diuresis in children with heart failure. It is less immediate in action and less potent than furosemide, and it affects the reabsorption of electrolytes in the renal tubules only. The usual dose is 10-40 mg/kg/24 hr in two divided doses. Potassium supplementation is often required if chlorothiazide is used alone. **Sodium glucose cotransporter 2 (SGLT2) inhibitors** (dapagliflozin, empagliflozin) also produce a natriuresis and have other beneficial direct cardiac effects and have been recommended for some etiologies of heart failure.

Table 491.6 Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

DRUG	DOSAGE*
DIGOXIN	
Digitalization (1/2 initially, followed by 1/4 q12h × 2)	Premature: 20 μg/kg Full-term neonate (up to 1 mo): 20-30 μg/kg Infant or child: 25-40 μg/kg Adolescent or adult: 0.5-1 mg in divided doses *Note:* These doses are PO; IV dose is 75% of PO dose
Maintenance digoxin†	5-10 μg/kg/day, divided q12h *Note:* These doses are PO; IV dose is 75% of PO dose
DIURETICS	
Furosemide (Lasix)	IV: 0.5-2 mg/kg/dose PO: 1-4 mg/kg/day, divided qd-qid
Bumetanide (Bumex)	IV: 0.01-0.1 mg/kg/dose PO: 0.01-0.1 mg/kg/day q24-48h
Chlorothiazide (Diuril)	PO: 20-40 mg/kg/day, divided bid or tid
Spironolactone (Aldactone)	PO: 1-3 mg/kg/day, divided bid or tid
ADRENERGIC AGONISTS (ALL IV)	
Dobutamine	2-20 μg/kg/min
Dopamine	2-20 μg/kg/min
Epinephrine	0.01-1.0 μg/kg/min
PHOSPHODIESTERASE INHIBITORS (ALL IV)	
Milrinone	0.25-1.0 μg/kg/min
AFTERLOAD-REDUCING AGENTS	
Captopril (Capoten), all PO	Premature: start at 0.01 mg/kg/dose; 0.1-0.4 mg/kg/day, divided q6-24h Infant: start at 0.15-0.3 mg/kg/dose; 1.5-6 mg/kg/day, divided q6-12h Child: start at 0.3-0.5 mg/kg/dose; 2.5-6 mg/kg/day, divided q6-12h
Enalapril (Vasotec), all PO	0.08-0.5 mg/kg/day, divided q12-24h
Hydralazine (Apresoline)	IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg) PO: 0.75-5 mg/kg/day, divided q6-12h
Nitroglycerin	IV: 0.25-0.5 μg/kg/min start; increase to 20 μg/kg/min maximum
Nitroprusside (Nipride)	IV: 0.5-8 μg/kg/min
β-ADRENERGIC BLOCKERS	
Carvedilol (Coreg)	PO: initial dose: 0.1 mg/kg/day (maximum: 6.25 mg) divided bid (may use tid in infants), increase gradually (usually 2-wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximum dose: 50-100 mg/day
Metoprolol (Lopressor, Toprol-XL)	PO, non–extended-release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2-wk intervals) to maximum dose of 1-2 mg/kg/day PO, extended-release form (Toprol-XL): given once daily; adult initial dose: 25 mg/day, maximum: 200 mg/day

*Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.
†Maintenance digitalis therapy is started approximately 12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in two and given at 12-hr intervals. The oral maintenance dose is usually 20–25% higher than when digoxin is used parenterally. The normal daily dose of digoxin for older children (>5 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.
IV, Intravenous; PO, oral; bid, twice daily, tid, 3 times daily; qid, 4 times daily; qd, every day.

Cardiac Reverse Remodeling

Angiotensin Antagonists

The renin-angiotensin-aldosterone pathway becomes active as a compensatory response to heart failure, but these compensatory effects can result in increased afterload and adverse remodeling of the myocardium, including development of cardiac fibrosis. Angiotensin antagonists, including angiotensin-converting enzyme inhibitors (ACEIs) and aldosterone II receptor blockers (ARBs), reduce ventricular afterload by decreasing peripheral vascular resistance and thereby improving myocardial performance. Afterload reducers may be useful in children with heart failure secondary to cardiomyopathy and in patients with severe mitral or aortic insufficiency. They may also be effective in patients with heart failure caused by left-to-right shunts. ACEIs and ARBs may have additional beneficial effects on cardiac remodeling independent of their influence on afterload by directly influencing adverse cardiac intracellular signaling pathways and decreasing the formation of myocardial fibrosis. In adult patients with dilated cardiomyopathy, the addition of an ACEI to standard medical therapy reduces both morbidity and mortality.

The orally active ACEIs **captopril**, **enalapril,** and **lisinopril** produce arterial dilation by blocking the production of angiotensin II, thereby resulting in significant afterload reduction. Venodilation and consequent preload reduction also have been reported. In addition, these agents interfere with aldosterone production and therefore also help control salt and water retention. ACEIs have additional beneficial effects on cardiac structure and function that may be independent of

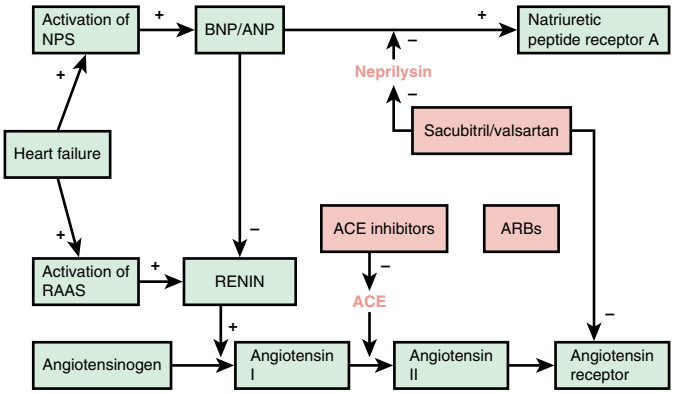

Fig. 491.4 Systems activated in heart failure and pathways blocked by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and neprilysin inhibitors (sympathetic nervous system activation pathway is not shown in the figure). ANP, Atrial natriuretic peptide; BNP, B-type natriuretic peptide; NPS, natriuretic peptide system; RAAS, renin angiotensin aldosterone system. *(From Arya A, Azad S, Sitaraman R. Angiotensin receptor and neprilysin inhibitor: a new drug in pediatric cardiologist's armamentarium. Ann Pediatr Cardiol. 2020;13[4]:334–336, Fig. 1.)*

Table 491.7 Valsartan/Sacubitril Recommended Dose* (Twice Daily)

	STARTING	SECOND	FINAL
Pediatric patients <40 kg** (mg/kg)	1.6	2.3	3.1
Pediatric patients at least 40 kg, <50 kg (mg)	24/26	49/51	72/78#
Pediatric patients at least 50 kg (mg)	49/51	72/78#	97/103

*Available as 24/26, 49/51, and 97/103 mg tablets, where the first drug is sacubitril and the second drug is valsartan.
#Doses of 72/78 mg can be achieved using three 24/26 mg tablets. Titration: titrate dose every 2 wk and target final dose.
**An oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.
From Arya A, Azad S, Sitaraman R. Angiotensin receptor and neprilysin inhibitor: a new drug in pediatric cardiologist's armamentarium. *Ann Pediatr Cardiol.* 2020;13(4):334–336, Table 1.

their effect on afterload. Adverse reactions to ACEIs include hypotension and its sequelae (weakness, dizziness, syncope) and hyperkalemia. A maculopapular pruritic rash is encountered in a small number of patients, but the drug may be continued because the rash often disappears spontaneously with time. Neutropenia, renal toxicity, and chronic cough also occur. Angioedema is a rare side effect of ACEIs and is related to inhibiting breakdown of bradykinin. If patients have had side effects related to bradykinin effect from ACEIs, including chronic cough, ARBs may be an alternative therapy and include **losartan** and **valsartan.**

An angiotensin receptor combined with neprilysin inhibition (ARNI) (valsartan/sacubitril) is approved for children 1-18 years of age with New York Heart Association class II-IV and a left ventricular ejection fraction ≤40%. The mechanism of action is noted in Figure 491.4 and the dosing in Table 491.7.

Aldosterone Antagonists

Spironolactone and **eplerenone** inhibit aldosterone and act both as a reverse remodeling agent and a weak diuretic. They also enhance potassium retention, often eliminating the need for oral potassium supplementation in patients receiving diuretics. Aldosterone antagonists blunt the adverse cardiac remodeling effects and may reduce cardiac fibrosis that results in heart failure. Spironolactone is usually given orally in two divided doses of 2 mg/kg/24 hr. Adults with heart failure have improved survival when an aldosterone inhibitor is included in the diuretic regimen, likely through multiple effects, including a favorable effect on cardiac fibrosis. Eplerenone is an alternative to spironolactone and does not have the side effect of gynecomastia.

β Blockers

Studies in adults with dilated cardiomyopathy show that β-adrenergic blocking agents, introduced gradually as part of a comprehensive heart failure treatment program, improve exercise tolerance, decrease hospitalizations, and reduce overall mortality. The agents most often used are **carvedilol**, with both α- and β-adrenergic receptor–blocking and free radical–scavenging effects, and **metoprolol**, a β_1-adrenergic receptor–selective antagonist. β Blockers are used for the chronic treatment of patients with heart failure and should not be administered when patients are still in the acute phase of heart failure (i.e., receiving IV adrenergic agonist infusions). Although highly efficacious in adults, clinical studies in children have shown mixed results, potentially from the significant heterogeneity of the populations being studied and differences in the types of β-blocking agents.

Although ACEIs/ARBs along with β-adrenergic–blocking agents and aldosterone antagonists have been shown in multiple prospective, randomized, controlled trials in adults to improve symptoms and mortality in adult heart failure patients, it is unclear if these medications improve the natural history of heart failure in children. Nonetheless, these medications are commonly used for the treatment of heart failure and are recommended by consensus guidelines from the ISHLT and Canadian Cardiovascular Society.

Afterload Reduction

Afterload reduction is an important component of heart failure management to reduce workload on the myocardium. Oral afterload-reducing agents, including ACEIs and ARBs, are often used for both cardiac reverse remodeling and afterload reduction benefits. If renal insufficiency is present, alternative oral afterload-reducing agents may be considered, including calcium channel blockers such as **amlodipine**, although they have potential side effects including peripheral edema and gingival hyperplasia.

Intravenously administered afterload-reducing agents, including **milrinone** (see later section on "Phosphodiesterase Inhibitors"), **nicardipine**, and **nitroprusside**, should be initiated only in a closely monitored clinical care setting. Nitroprusside's short IV half-life makes it ideal for titrating the dose in critically ill patients. Peripheral arterial vasodilation and afterload reduction are the major effects, but venodilation causing a decrease in venous return to the heart may also be beneficial. Blood pressure must be continuously monitored because sudden hypotension can occur. Consequently, nitroprusside is contraindicated in patients with preexisting hypotension. Because the drug is metabolized, small amounts of circulating cyanide are produced and detoxified in the liver to thiocyanate, which is excreted in urine. When high doses of nitroprusside are administered for several days, toxic symptoms related to *thiocyanate poisoning* may occur (fatigue, nausea, disorientation, acidosis, and muscular spasm). If nitroprusside use is prolonged, blood thiocyanate levels should be monitored.

Phosphodiesterase Inhibitors

Milrinone is useful in treating patients with low cardiac output who are refractory to standard therapy. It has been shown to be highly effective in managing the low-output state present in children after open heart surgery. It works by inhibiting phosphodiesterase, which prevents the degradation of intracellular cyclic adenosine monophosphate. Milrinone has both positive inotropic effects on the heart and peripheral vasodilatory effects and has generally been used as an adjunct to dopamine or dobutamine therapy in the intensive care unit. It is given by IV infusion at 0.25-1 μg/kg/min. A major side effect is **hypotension** secondary to peripheral vasodilation. The hypotension can generally be managed by the administration of IV fluids to restore adequate intravascular volume. Because of renal clearance of milrinone, caution must be used in the setting of renal insufficiency. Long-term milrinone

is often used to support patients while listed for heart transplantation, and in select patients can be used in the outpatient setting.

α- and β-Adrenergic Agonists

The α- and β-adrenergic receptor agonists may be needed for advanced heart failure with impaired cardiac output and are usually administered in an intensive care setting, where the dose can be carefully titrated to hemodynamic response. Continuous determinations of arterial blood pressure and heart rate are performed; measuring serial mixed venous oxygen saturations or cardiac output directly with a pulmonary thermodilution (Swan-Ganz) catheter may be helpful in assessing drug efficacy, although this technique is used much less in children than in adults. These agents increase myocardial oxygen consumption and are associated with increased arrhythmogenic burden and have been shown to increase morbidity and mortality in adults with heart failure; thus they are usually avoided as a long-term therapy.

Dopamine is a predominantly β-adrenergic receptor agonist, but it has α-adrenergic effects at higher doses. Dopamine has less chronotropic and arrhythmogenic effect than the pure β-agonist isoproterenol. At a dose of 2-10 μg/kg/min, dopamine results in increased contractility with little peripheral vasoconstrictive effect. If the dose is increased beyond 15 μg/kg/min, however, its peripheral α-adrenergic effects may result in vasoconstriction.

Dobutamine, a derivative of dopamine, is also useful in treating low cardiac output. It has direct inotropic effects and causes a moderate reduction in peripheral vascular resistance. Dobutamine can be used alone or as an adjunct to dopamine therapy to avoid the vasoconstrictive effects of higher-dose dopamine. Dobutamine is also less likely to cause cardiac rhythm disturbances.

Epinephrine is a mixed α- and β-adrenergic receptor agonist that is usually reserved for patients with cardiogenic shock and low arterial blood pressure. Although epinephrine can raise blood pressure effectively, it also increases systemic vascular resistance, and therefore increases the afterload against which the heart has to work and is associated with an increased risk of arrhythmia. Additionally, epinephrine is proarrhythmic and can result in direct cardiac toxicity, including myocardial necrosis and apoptosis.

Digitalis Glycosides

Digoxin, once the mainstay of heart failure management in both children and adults, is currently used less frequently as a result of the introduction of other therapies and the recognition of its potential toxicities. Some cardiologists will use digitalis as an adjunct to ACEIs and diuretics in patients with symptomatic heart failure, whereas others have stopped using it altogether. Despite multiple clinical studies, predominantly in adults, the controversy over digitalis remains. Some data suggest a beneficial effect of digoxin on reducing death among infants with single ventricle heart disease.

Digoxin is the digitalis glycoside used most often in pediatric patients. It has a half-life of 36 hours and is absorbed well by the gastrointestinal tract (60–85%), even in infants. An initial effect is seen as early as 30 minutes after administration, and the peak effect for oral digoxin occurs at 2-6 hours. When the drug is administered intravenously, the initial effect is seen in 15-30 minutes, and the peak effect occurs at 1-4 hours. The kidney eliminates digoxin, so dosing must be adjusted according to the patient's renal function. The half-life of digoxin may be up to 6 days in patients with anuria because slower hepatic excretion pathways are used in these patients.

Rapid digitalization of infants and children may be carried out intravenously. This should be done with caution in patients with severe heart failure. The dose depends on the patient's age (see Table 491.6). The recommended digitalization schedule is to give half the total digitalizing dose immediately and the succeeding two one-quarter doses at 12-hours intervals later. The ECG must be closely monitored and rhythm strips obtained before each of the three digitalizing doses. Digoxin should be discontinued if a new rhythm disturbance is noted. Prolongation of the P-R interval is not necessarily an indication to withhold digitalis, but a delay in administering the next dose or a reduction in the dosage should be considered, depending on the patient's clinical status. Minor ST segment or T-wave changes are frequently noted with digitalis administration and should not affect the digitalization regimen. Baseline serum electrolyte levels should be measured before and after digitalization. **Hypokalemia** and **hypercalcemia** exacerbate digitalis toxicity. Because hypokalemia is relatively common in patients receiving diuretics, potassium levels should be monitored closely in those receiving a potassium-wasting diuretic in combination with digitalis. In patients with active myocarditis, some cardiologists recommend avoiding digitalis altogether, and if used, maintenance digitalis should be started at half the normal dose without digitalization because of the increased risk of arrhythmia in these patients.

Patients who are not critically ill may be given digitalis initially by the oral route, and in most instances, digitalization is completed within 24 hours. When slow digitalization is desirable, for example, in the immediate postoperative period, initiation of a maintenance digoxin schedule without a previous loading dose achieves full digitalization in 7-10 days.

Measurement of serum digoxin levels is useful in the following circumstances: (1) when an unknown amount of digoxin has been administered or ingested accidently, (2) when renal function is impaired or if drug interactions are possible, (3) when questions regarding compliance are raised, and (4) when a toxic response is suspected. In suspected toxicity, elevated serum digoxin levels are not in themselves diagnostic of toxicity but must be interpreted as an adjunct to other clinical and electrocardiographic findings (rhythm and conduction disturbances). Hypokalemia, hypomagnesemia, hypercalcemia, cardiac inflammation secondary to myocarditis, and prematurity may all potentiate digitalis toxicity. A cardiac arrhythmia that develops in a child who is taking digitalis may also be related to the primary cardiac disease rather than the drug; however, any arrhythmia occurring after the institution of digitalis therapy must be considered to be drug related until proven otherwise. Many drugs interact with digoxin and may increase levels or risk of toxicity, so care should be taken when a patient receiving digoxin is being considered for any additional pharmacologic therapy.

Additional Therapies

Several medications that have shown promise in the treatment of adult patients with heart failure are being studied in pediatric patients. For chronic heart failure, **ivabradine** has been studied in patients with elevated heart rates despite optimized β blocker use. Ivabradine is a selective inhibitor of the I_f current in the sinus node and lowers heart rates without decreasing myocardial contractility. The use of ivabradine was associated with improved outcomes in adults with heart failure, and a recent study of children with heart failure caused by dilated cardiomyopathy demonstrated improved left ventricular systolic function and clinical status.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, which blocks reabsorption of glucose in the proximal renal tubule, are the newest class of adult heart failure medications and, though developed as a treatment for diabetes, have shown dramatic improvement in cardiac mortality and morbidity in adults with heart failure with reduced ejection fraction. Given the mechanism of action, which includes glucosuria, there is a risk for urinary tract infection and yeast infection. Additional possible side effects include acute kidney injury and bone fracture as well as development of diabetic ketoacidosis in patients with diabetes. Further studies are needed to determine what role, if any, these medications will have in the treatment of pediatric heart failure.

ELECTROPHYSIOLOGIC APPROACHES TO HEART FAILURE MANAGEMENT

Significant improvements in symptomatology and functional capacity have been achieved in select adult patients with cardiomyopathy using **biventricular resynchronization pacing**. This technique improves cardiac output by restoring normal synchrony between right and left ventricular contraction, which is often lost in patients with dilated cardiomyopathy (these patients usually manifest a left bundle branch block on ECG). There is growing experience with resynchronization pacing in children, but it remains uncertain which population of patients with heart failure benefit from this therapy.

Arrhythmias are a leading cause of sudden death in patients with severe cardiomyopathy (both dilated and hypertrophic). Although antiarrhythmic medications can sometimes reduce this risk, for patients at particularly high risk (e.g., those with a condition known to be associated with a high risk of ventricular arrhythmia or those who have already

Table 491.8 Treatment of Cardiogenic Shock*

	DETERMINANTS OF STROKE VOLUME		
	Preload	**Contractility**	**Afterload**
Parameters measured	CVP, PCWP, LAP, cardiac chamber size on echocardiography	CO, BP, fractional shortening or ejection fraction on echocardiography, MV O_2 saturation	BP, peripheral perfusion, SVR
Treatment to improve cardiac output	Volume expansion (crystalloid, colloid, blood)	β-Adrenergic agonists, phosphodiesterase inhibitors	Afterload-reducing agents: milrinone, nitroprusside, ACEIs

*The goal is to improve peripheral perfusion by increasing cardiac output, where cardiac output = heart rate × stroke volume.
ACEIs, Angiotensin-converting enzyme inhibitors; BP, blood pressure; CO, cardiac output (measured with a thermodilution catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV O_2 saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilution catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

experienced a "missed sudden death" episode), use of an **implantable cardioverter-defibrillator** can be lifesaving (see Chapter 485).

491.1 Cardiogenic Shock

Joseph W. Rossano and Danielle S. Burstein

Cardiogenic shock may be caused by (1) severe cardiac dysfunction before or after cardiac surgery, (2) septicemia, (3) severe burns, (4) anaphylaxis, (5) cardiomyopathy, (6) myocarditis, (7) myocardial infarction or stunning, and (8) acute central nervous system (CNS) disorders. It is characterized by low cardiac output and results in inadequate tissue perfusion (see Chapter 85).

Treatment is aimed at restoring adequate cardiac output to prevent the untoward effects of prolonged ischemia on vital organs, as well as management of the underlying cause. Under normal physiologic conditions, cardiac output is increased as a result of sympathetic stimulation, which increases both contractility and heart rate. If contractility is depressed, cardiac output may be improved by increasing the heart rate, increasing ventricular filling pressure (preload) through the Frank-Starling mechanism, or decreasing systemic vascular resistance (afterload). Optimal filling pressure is variable and depends on a number of extracardiac factors, including ventilatory support and intraabdominal pressure. The increased pressure necessary to fill a relatively noncompliant ventricle should also be considered, particularly after open heart surgery or in patients with restrictive or hypertrophic cardiomyopathies. If carefully administered incremental fluid does not result in improved cardiac output, abnormal myocardial contractility or an abnormally high afterload, or both, must be implicated as the cause of the low cardiac output. Although an increase in heart rate *may* improve cardiac output, an excessive increase in heart rate may reduce cardiac output because of decreased time for diastolic filling. Additionally, high heart rates will increase myocardial oxygen demand, which may be counterproductive in a state of limited tissue oxygen supply.

Myocardial contractility usually improves when treatment of the basic cause of shock is instituted, hypoxia is eliminated, and acidosis is corrected. β-Adrenergic agonists such as dopamine, epinephrine, and dobutamine improve cardiac contractility, increase heart rate, and ultimately increase cardiac output. However, some of these agents also have α-adrenergic effects, which cause peripheral vasoconstriction and increase afterload, so careful consideration of the balance of these effects in an individual patient is important. The use of cardiac glycosides and β blockers to treat acute low-cardiac-output states should be avoided.

Patients in cardiogenic shock may have a marked increase in systemic vascular resistance (SVR) resulting in high afterload and poor peripheral perfusion. If the increased SVR is persistent and the administration of positive inotropic agents alone does not improve tissue perfusion, the use of afterload-reducing agents may be appropriate, such as nitroprusside or milrinone in combination with a β-adrenergic agonist. Milrinone, a phosphodiesterase inhibitor (see earlier), is also a positive inotropic agent, and combined with a β-adrenergic agonist, it works synergistically to increase levels of myocardial cyclic adenosine monophosphate.

Sequential evaluation and management of cardiovascular shock are mandatory (see Chapter 85). Table 491.8 outlines the general treatment principles for acute cardiac circulatory failure under most circumstances. In addition to cardiac-specific medications, other treatments aimed at improving oxygen capacity (e.g., blood transfusion for patients with anemia) and decreasing oxygen demand (e.g., intubation, mechanical ventilation, sedation, antipyretics) can be beneficial. Treatment of infants and children with low cardiac output after cardiac surgery also depends on the nature of the operative procedure, any intraoperative complications, and the physiology of the circulation after repair or palliation (see Chapter 483). If cardiogenic shock does not respond rapidly to medical therapy, consideration of mechanical support is warranted.

MECHANICAL CIRCULATORY SUPPORT

Extracorporeal membrane oxygenation (ECMO), which can provide total cardiopulmonary support, is the most common *short-term* modality to support circulatory failure in children. In experienced centers, children can be placed on ECMO rapidly, and therefore the modality can be used in multiple settings, including low cardiac output syndrome (low-output heart failure) after cardiac surgery, rapidly deteriorating hemodynamics in several scenarios (e.g., myocarditis), and as resuscitation from refractory cardiac arrest. The modality is ideal for short-term support when the underlying disease requiring ECMO is expected to resolve within days to weeks. For multiple reasons, including the relatively high complication rate and decreased mobility of many patients on ECMO, it is not an ideal support modality for long-term myocardial support.

Given the limitations of ECMO, there is a need to develop long-term support options for children with refractory heart failure. **Ventricular assist devices (VADs)** include both short-term and long-term mechanical circulatory support and can be deployed either percutaneously or surgically. In children, most of these devices are used with the intention of subsequently performing a heart transplantation, although the devices can be removed if myocardial function recovers. This is in contrast to adult patients, many of whom are placed on these devices with no plan for heart transplantation, the so-called *destination therapy.* Successfully managing patients on VAD support requires a dedicated multidisciplinary team.

For infants and small children, the most commonly used VADs are paracorporeal devices, including paracorporeal pulsatile-flow VADs (e.g., Berlin Heart EXCOR) and paracorporeal continuous-flow VADs (e.g., Pedimag). These devices can be used for left, right, or biventricular support. They are classified as a paracorporeal device because the pump sits outside the body. In older children and adolescents, intracorporeal continuous flow devices (e.g., HeartMate3) are preferred. These VADs are completely internalized except for a drive line that connects to the power source (Fig. 491.5). These VADs have fewer complications and can provide long-term durable support outside the hospital. These devices are often used in older children and adolescents, with many of these patients discharged home on VAD support. Other types of devices, including **temporary percutaneous VAD** (e.g., Impella) for short-term support and the **total artificial heart** for long-term support, have also been used in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

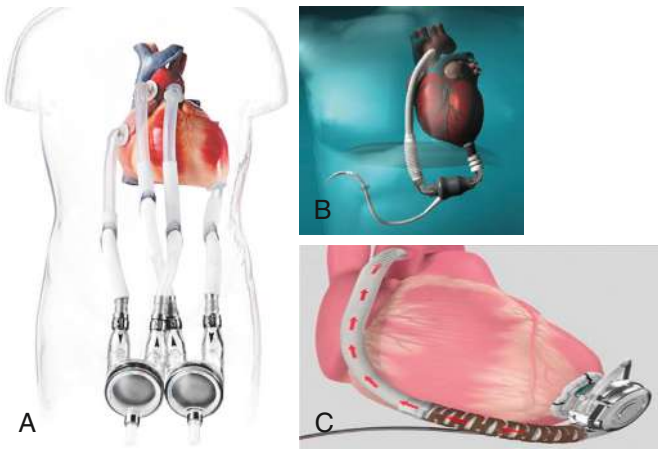

Fig. 491.5 Commonly used ventricular assist devices in children. **A,** Paracorporeal pneumatic pulsatile Berlin Heart EXCOR. **B** and **C,** Continuous flow devices: **(B)** HeartMate3; **(C)** HeartWare HVAD. *(A courtesy Berlin Heart, LLC; B from St. Jude Medical; C courtesy Medtronic, Inc.)*

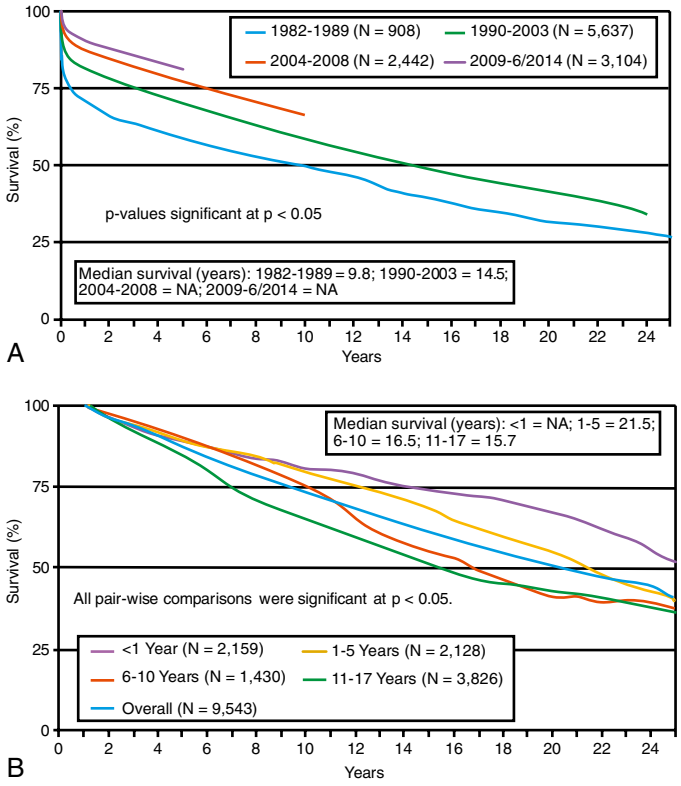

Fig. 492.1 A, Survival after pediatric heart transplantation comparing current and past eras. **B,** Long-term survival among patients that lived to 1-yr post-transplant. NA, Not applicable. *(From Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35[10]:1185–1195, Figs. 6 and 7.)*

Chapter 492

Pediatric Heart and Heart-Lung Transplantation

492.1 Pediatric Heart Transplantation

Danielle S. Burstein and Joseph W. Rossano

Pediatric heart transplantation is considered the standard therapy that offers long-term survival for end-stage heart disease in children. In adults, ventricular assist devices (VADs) are usually employed as a long-term therapy for patients not eligible for heart transplantation, but in children the vast majority of VADs are used as a *bridge* to transplantation as opposed to an alternative to transplantation. According to the International Society for Heart and Lung Transplantation, as of January 2019, over 14,000 heart transplants had been performed on children in the world, with about 400 transplants annually—a quarter of these in children <1 year of age. Survival rates have improved significantly over time, with most of the improvement occurring in the early period after transplant. This period continues to the associated with the greatest risk of death, and many patients who survive the first year after transplant are alive 20 years later (Fig. 492.1). Indeed, a growing number of patients receiving a heart transplant in childhood are approaching their 15-, 20-, and 30-year posttransplant anniversaries. Current (2011-2023) 1-year survival is ~90% and 5-year survival ~80%.

INDICATIONS

Heart transplantation is performed (1) in infants and children with end-stage cardiomyopathy who have become refractory to medical therapy, (2) in patients with previously repaired or palliated congenital heart disease (CHD) who have developed ventricular dysfunction or other nonoperable late-term complications, and (3) less frequently in patients with complex CHD—pulmonary atresia with intact septum and coronary arterial stenoses and some forms of hypoplastic left heart syndrome (HLHS)—for whom standard surgical procedures are extremely high risk. Additionally, **retransplantation** accounts for approximately 5% of transplants annually.

Cardiomyopathies account for >50% of heart transplants in pediatric patients older than 1 year, with the percentage of patients with previously repaired complex CHD at approximately 30%. In infants younger than 1 year, CHD previously represented >80% of transplants; this has decreased to 60% as standard surgical results for complex CHD (e.g., HLHS) have improved.

RECIPIENT AND DONOR SELECTION

Potential heart transplant recipients must be free of serious noncardiac medical problems such as neurologic disease, active systemic infection, severe hepatic or renal disease, and severe malnutrition. Many children with ventricular dysfunction are at risk for the development of **pulmonary vascular disease**, which, if severe enough, would also preclude heart transplantation. Therefore pulmonary vascular resistance (PVR) is measured at cardiac catheterization in heart transplant candidates, both at rest and, if elevated, in response to vasodilators. Patients with fixed elevated PVR above 6 index Wood units are at higher risk for heart transplantation and may be considered candidates for heart-lung transplantation (see Chapter 492.2). However, with advances in postoperative management of pulmonary hypertension (e.g., inhaled nitric oxide), many patients with moderate elevation in PVR can undergo heart transplant alone. A comprehensive social services evaluation is an important component of the recipient evaluation. Because of the complex posttransplantation medical regimen, the family must have a history of compliance. Detailed informed consent must be obtained, indicating that the family (and, if old enough, the patient) understand the lifelong commitment to immunosuppressive medication and careful monitoring.

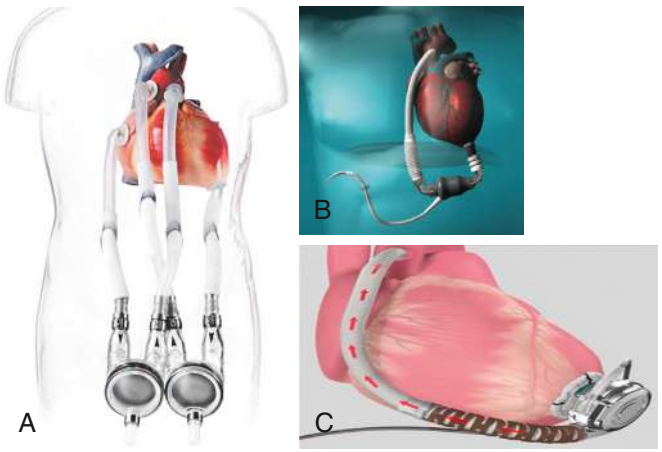

Fig. 491.5 Commonly used ventricular assist devices in children. **A,** Paracorporeal pneumatic pulsatile Berlin Heart EXCOR. **B** and **C,** Continuous flow devices: **(B)** HeartMate3; **(C)** HeartWare HVAD. *(A courtesy Berlin Heart, LLC; B from St. Jude Medical; C courtesy Medtronic, Inc.)*

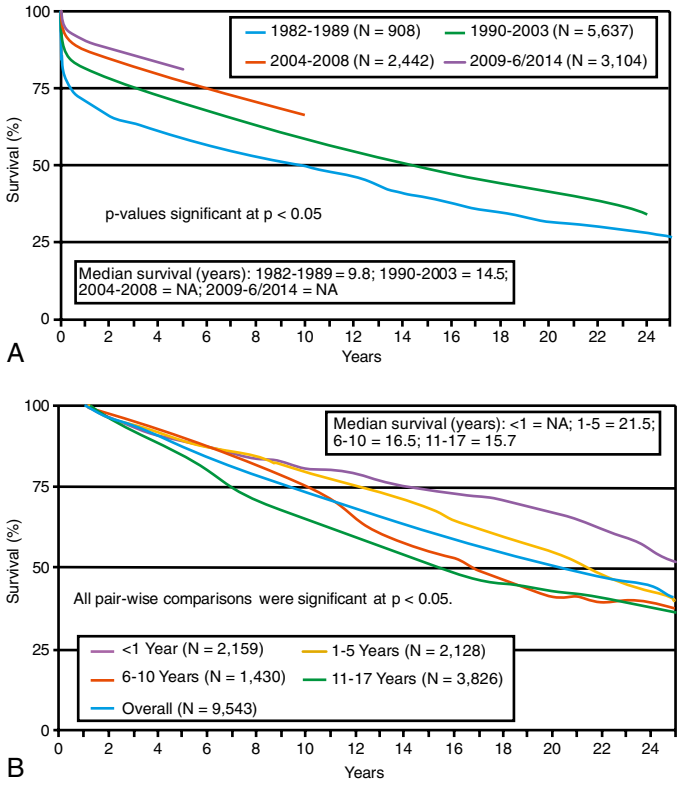

Fig. 492.1 A, Survival after pediatric heart transplantation comparing current and past eras. **B,** Long-term survival among patients that lived to 1-yr post-transplant. NA, Not applicable. *(From Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35[10]:1185–1195, Figs. 6 and 7.)*

Chapter 492

Pediatric Heart and Heart-Lung Transplantation

492.1 Pediatric Heart Transplantation

Danielle S. Burstein and Joseph W. Rossano

Pediatric heart transplantation is considered the standard therapy that offers long-term survival for end-stage heart disease in children. In adults, ventricular assist devices (VADs) are usually employed as a long-term therapy for patients not eligible for heart transplantation, but in children the vast majority of VADs are used as a *bridge* to transplantation as opposed to an alternative to transplantation. According to the International Society for Heart and Lung Transplantation, as of January 2019, over 14,000 heart transplants had been performed on children in the world, with about 400 transplants annually—a quarter of these in children <1 year of age. Survival rates have improved significantly over time, with most of the improvement occurring in the early period after transplant. This period continues to the associated with the greatest risk of death, and many patients who survive the first year after transplant are alive 20 years later (Fig. 492.1). Indeed, a growing number of patients receiving a heart transplant in childhood are approaching their 15-, 20-, and 30-year posttransplant anniversaries. Current (2011-2023) 1-year survival is ~90% and 5-year survival ~80%.

INDICATIONS

Heart transplantation is performed (1) in infants and children with end-stage cardiomyopathy who have become refractory to medical therapy, (2) in patients with previously repaired or palliated congenital heart disease (CHD) who have developed ventricular dysfunction or other nonoperable late-term complications, and (3) less frequently in patients with complex CHD—pulmonary atresia with intact septum and coronary arterial stenoses and some forms of hypoplastic left heart syndrome (HLHS)—for whom standard surgical procedures are extremely high risk. Additionally, **retransplantation** accounts for approximately 5% of transplants annually.

Cardiomyopathies account for >50% of heart transplants in pediatric patients older than 1 year, with the percentage of patients with previously repaired complex CHD at approximately 30%. In infants younger than 1 year, CHD previously represented >80% of transplants; this has decreased to 60% as standard surgical results for complex CHD (e.g., HLHS) have improved.

RECIPIENT AND DONOR SELECTION

Potential heart transplant recipients must be free of serious noncardiac medical problems such as neurologic disease, active systemic infection, severe hepatic or renal disease, and severe malnutrition. Many children with ventricular dysfunction are at risk for the development of **pulmonary vascular disease**, which, if severe enough, would also preclude heart transplantation. Therefore pulmonary vascular resistance (PVR) is measured at cardiac catheterization in heart transplant candidates, both at rest and, if elevated, in response to vasodilators. Patients with fixed elevated PVR above 6 index Wood units are at higher risk for heart transplantation and may be considered candidates for heart-lung transplantation (see Chapter 492.2). However, with advances in postoperative management of pulmonary hypertension (e.g., inhaled nitric oxide), many patients with moderate elevation in PVR can undergo heart transplant alone. A comprehensive social services evaluation is an important component of the recipient evaluation. Because of the complex posttransplantation medical regimen, the family must have a history of compliance. Detailed informed consent must be obtained, indicating that the family (and, if old enough, the patient) understand the lifelong commitment to immunosuppressive medication and careful monitoring.

Donor shortage is a serious problem for both adults and children. At the national registry of transplant recipients in the United States, the **United Network for Organ Sharing (UNOS)**, allografts are matched by ABO blood group and body weight. However, ABO matching may not be required for young infants less than 2 years of age because of the immaturity of the immune system. Patients, especially with a history of CHD, who have undergone prior operations may have antibodies against human leukocyte antigens (HLAs). Patients with elevated anti-HLA antibodies are at risk for a positive cross match and early graft dysfunction. These antibodies can also contribute to late graft dysfunction through antibody-mediated rejection and development of cardiac allograft vasculopathy. For patients with these elevated antibodies, there are strategies to avoid a positive cross match through a prospective cross match or a virtual cross match, although this may prolong the waiting list time. There are also desensitization therapies that may reduce circulating HLA antibody production, although they do not affect historical antibodies, and current data remain unclear how effective desensitization therapy is for reducing posttransplant rejection risk. Contraindications to organ donation include prolonged cardiac arrest with persistent moderate to severe cardiac dysfunction, ongoing systemic illness or infection, and preexisting severe cardiac disease. Physicians caring for a patient who may be a potential donor should always contact the organ donor coordinator at their institution, who can best judge the appropriateness of organ donation and has experience in interacting with potential donor families. A history of resuscitation alone or reparable CHD is not an automatic exclusion for donation.

The decision of when to place a patient on the transplant waiting list is based on many factors, including degree of ventricular function, markedly decreased exercise tolerance as determined by cardiopulmonary exercise testing (see Chapter 472.5), poor response to medical heart failure therapy, multiple hospitalizations for heart failure, arrhythmia, progressive deterioration in renal or hepatic function, early stages of pulmonary vascular disease, and poor nutritional status. Patients with severe ventricular dysfunction are often started on a regimen of anticoagulation to reduce the risk of mural thrombosis and thromboembolism. Patients with progressive heart failure resulting in decreases in end-organ (renal or hepatic) function unresponsive to standard pharmacologic treatment may be candidates for a VAD. The use of these devices has increased dramatically over the past decade, and currently over half of patients with dilated cardiomyopathy are on VAD support before transplant. VADs can improve hemodynamics and end-organ function, allow for rehabilitation, and allow some patients to be discharged home on VAD support (see Chapter 491).

PERIOPERATIVE MANAGEMENT

Heart transplantation in children can be performed either with a *biatrial* or *bicaval* anastomosis. In the *biatrial* anastomosis, both donor and recipient hearts are excised so that the posterior portions of the atria containing the venae cavae and pulmonary veins are left intact. The aorta and pulmonary artery are divided above the level of the semilunar valves. The anterior portions of the donor's atria are then connected to the remaining posterior portions of the recipient's atria, thereby avoiding the need for delicate suturing of the venae cavae or pulmonary veins. Previously, the donor and recipient great vessels were connected via end-to-end anastomoses. This has been supplanted in many centers by the *bicaval* anastomosis, with the donor right atrium (and sinus node) left intact and the suture lines at the superior and inferior vena cavae; the left atrial connection is still performed as in the *biatrial* anastomosis.

In the immediate postoperative period, **immunosuppression** is achieved with induction therapy that includes an antilymphocyte therapy for the first 5-7 days; common agents include antithymocyte globulin (ATG) and the humanized anti–interleukin-2 receptor antibodies (basiliximab). Steroids are also commonly used within the first 5-7 days and then are often weaned off or discontinued. Antiproliferative agents (mycophenolate mofetil [MMF]) are also started immediately after transplant and are transitioned to an oral compound once enteral medications are tolerated. The most common combinations of chronic immunosuppression are a *calcineurin inhibitor* (CNI; tacrolimus or cyclosporine) plus an *antiproliferative agent* (MMF or azathioprine). Mammalian target of rapamycin (mTOR) inhibitors (sirolimus or everolimus) may be added to decrease the dose of CNI if renal insufficiency occurs. Many centers do not use steroids as part of maintenance immunosuppression but do use them as bolus treatment for acute rejection episodes. Immunosuppression levels are usually reduced after the first year posttransplant if there are no significant concerns for rejection. An ongoing U.S. multicenter pediatric trial called the TEAMMATE trial is comparing conventional immunosuppression therapy (tacrolimus and mycophenolate) with low-dose tacrolimus with everolimus and mycophenolate to determine which combination of immunosuppression is better at improving long-term pediatric post–heart transplant outcomes.

Many pediatric heart transplant recipients can be extubated from endotracheal intubation and mechanical ventilation support within the first 48 hours after transplantation and are out of bed in several days. In patients with preexisting high-risk factors, postoperative recovery may be considerably prolonged. For those with preoperative pulmonary hypertension, the use of nitric oxide in the postoperative period can allow the donor right ventricle to hypertrophy in response to elevated pulmonary artery pressures. Occasionally, these patients will require extracorporeal membrane oxygenation (ECMO) for primary graft dysfunction.

DIAGNOSIS AND MANAGEMENT OF ACUTE GRAFT REJECTION

Posttransplantation management consists of adjusting medications to maintain a balance between the risk of rejection and the side effects of over-immunosuppression. **Acute graft rejection** is a leading cause of death in pediatric heart transplant recipients. The incidence of acute rejection is greatest in the first 3 months after transplantation and decreases considerably thereafter. Many pediatric patients experience at least one episode of acute rejection in the first 2 years after transplantation, although modern immunosuppressive regimens have decreased the frequency of severe rejection episodes. Because the symptoms of rejection can mimic many routine pediatric illnesses (e.g., pneumonia, gastroenteritis), the transplant center should be notified whenever a heart transplant recipient is seen in the pediatrician's office or emergency department for acute illnesses.

Clinical manifestations of acute rejection may include fatigue, fluid retention, fever, diaphoresis, abdominal symptoms, and a gallop rhythm. The electrocardiogram (ECG) may show reduced voltage, atrial or ventricular arrhythmias, or heart block but is usually nondiagnostic. X-ray examination may show an enlarged heart, effusions, or pulmonary edema but typically only in the more advanced stages of rejection. Natriuretic peptide levels are usually increased during episodes of acute rejection. Most rejection episodes occur without any detectable clinical symptoms. On echocardiography, indices of systolic left ventricular function may be decreased; however, these usually do not deteriorate until rejection is at least moderately severe. Techniques to evaluate wall thickening and left ventricular diastolic function have not fulfilled their promise as predictors of early rejection. Most transplant centers do not rely on echocardiography alone for rejection surveillance.

Myocardial biopsy is the most reliable method of monitoring patients for rejection. Biopsy specimens are taken from the right ventricular side of the interventricular septum and can be harvested relatively safely, even in small infants. In infants, surveillance biopsies are usually performed less often and may be as infrequent as once or twice per year. Children may have clinically unsuspected rejection episodes even 5-10 years after transplantation; most pediatric transplant centers continue routine surveillance biopsies, although at less frequent intervals. Cardiac MRI evaluation has been an effective noninvasive method to perform rejection surveillance and to diagnose actual rejection.

Gene expression profiling of peripheral blood mononuclear cells has been validated in adults as a highly sensitive, moderately selective method of rejection surveillance. These results have not been confirmed in children. Other promising current techniques include the profiling of donor cell–free DNA released in the serum of patients during episodes of graft injury. Progress has also been made in genetic profiling as a means to determine which patients are most at risk for rejection. Children who have single nucleotide polymorphisms (SNPs) leading to greater activity of inflammatory cytokines or decreased activity of regulatory cytokines are at increased risk of rejection.

Cardiac rejection can be classified as cellular, antibody-mediated, or mixed. Criteria for grading cellular rejection are based on a system developed by the **International Society for Heart and Lung Transplantation (ISHLT)** that considers the degree of cellular infiltration and whether myocyte necrosis is present. ISHLT rejection grade 1R is usually mild enough that it is often not treated with bolus steroids, and many of these episodes resolve spontaneously. For patients with ISHLT grade 2R rejection, treatment is instituted with either intravenous (IV) methylprednisolone or a "bump and taper" of oral prednisone. Asymptomatic patients further out from transplant with normal echocardiograms may be treated as outpatients. Patients with grade 3R, or anyone with hemodynamic instability, are admitted to the hospital for IV corticosteroid and potentially more aggressive antirejection therapy. For rejection episodes resistant to steroid therapy, additional therapeutic regimens include antilymphocyte preparation (antithymocyte globulin), methotrexate, or total lymphoid irradiation. Refractory rejection is often considered a contraindication for retransplantation because of the relatively poor outcomes compared with other indications for retransplantation.

Criteria for grading antibody-mediated rejection are based on a system developed by the ISHLT that considers histologic and immunopathologic findings. In contrast to cellular rejection, antibody-mediated rejection is mediated by circulating donor-specific antibodies (DSAs) and can be detected by immunostaining of the biopsy specimen for the complement component C4d, for macrophages expressing CD68, and for evidence of histologic damage. Antibody-mediated rejection is less responsive to standard therapies for acute cellular rejection (e.g., bolus corticosteroids) and has been treated with plasmapheresis, intravenous immunoglobulin (IVIG), the anti–CD20 monoclonal antibody rituximab, and the proteasome inhibitor bortezomib, all with mixed results. The long-term outcome of patients with persistent DSAs or antibody-mediated rejection is poor, with many having early graft failure and premature development of graft vasculopathy.

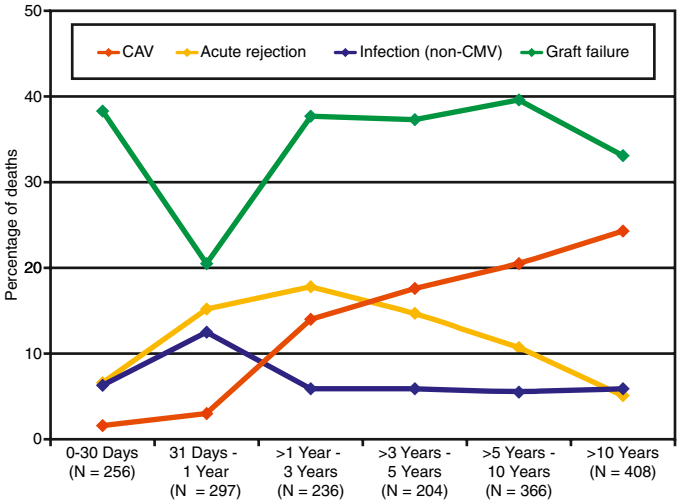

Fig. 492.2 Major causes of death after pediatric heart transplantation by time since transplant. CAV, Cardiac allograft vasculopathy; CMV, cytomegalovirus. *(From Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35[10]:1185–1195, Fig. 10.)*

COMPLICATIONS OF IMMUNOSUPPRESSION

Infection

Infection is also a leading cause of death in pediatric transplant patients (Fig. 492.2). The incidence of infection is greatest in the first 3 months after transplantation, when immunosuppressive doses are highest. **Viral** infections are most common and account for as many as 25% of infectious episodes. **Cytomegalovirus (CMV)** infection was once a leading cause of morbidity and mortality and may occur as a primary infection in patients without previous exposure to the virus or as a reactivation. Severe CMV infection can be disseminated or associated with pneumonitis or gastroenteritis and may provoke an episode of acute graft rejection or graft coronary disease. Most centers use IV ganciclovir or CMV immune globulin (Cytogam), or both, as prophylaxis in any patient receiving a heart from a donor who is positive for CMV or in any recipient who has serologic evidence of previous CMV disease. Oral preparations of ganciclovir with improved absorption profiles are available for chronic therapy, usually for 3-6 months after transplant, and have largely replaced IV preparations for prophylaxis. These regimens have significantly reduced the burden of CMV disease in heart transplant patients. Polymerase chain reaction (PCR) enhances the ability to diagnose CMV infection and monitor the efficacy of therapy serially.

Most normal childhood viral illnesses are well tolerated and do not usually require special treatment. Otitis media and routine upper respiratory tract infections can be treated in the outpatient setting, although fever or symptoms that last beyond the usual course require further investigation. **Gastroenteritis**, especially with vomiting, can result in greatly reduced absorption of immunosuppressive medications and provoke a rejection episode. In this setting, drug levels should be closely monitored and use of IV medications considered. Gastroenteritis can also be a sign of rejection, so a high index of suspicion must always be maintained. Varicella is another childhood illness of concern for immunosuppressed patients. If a heart transplant recipient acquires clinical varicella infection, treatment with IV acyclovir usually attenuates the illness.

Bacterial infections occur next in frequency after viral, with the lung the most common site of infection, followed by blood, urinary tract, and less often, the sternotomy site. Other sources of posttransplantation infection include fungi and protozoa. Many centers use trimethoprim-sulfamethoxazole for prophylaxis during the first several months after transplant to prevent *Pneumocystis jiroveci* infection.

Growth Stunting

Patients requiring chronic corticosteroid therapy usually have decreased linear growth. Thus many pediatric transplant programs aim for steroid-free immunosuppression within the first year after transplant. In patients who experience rejection when steroids are withdrawn, alternate-day corticosteroid regimens may result in improved linear growth. **Total lymphoid irradiation** has also shown promise as a steroid-sparing protocol. Despite these concerns, the majority of long-term survivors of pediatric heart transplantation have normal growth.

Hypertension

Hypertension is common in patients treated with CNIs, caused by a combination of plasma volume expansion and defective renal sodium excretion. Corticosteroids usually potentiate calcineurin-induced hypertension.

Renal Function

Chronic administration of cyclosporine or tacrolimus can lead to a tubulointerstitial nephropathy in adults, but severe renal dysfunction is less common in children. Most pediatric patients gradually have an increase in serum creatinine in the first year after transplantation; if renal dysfunction occurs, it usually responds to a decrease in CNI dosage. The addition of sirolimus, an mTOR inhibitor, allows a reduction in CNI dose in patients with renal dysfunction, although it is unclear whether this strategy leads to long-term improved renal function. Infection with BK virus, a growing problem in renal transplant patients, has been described as a source of renal dysfunction in heart transplant patients. Fortunately, pediatric heart transplant patients infrequently require dialysis or renal transplantation.

Neurologic Complications

Neurologic side effects of cyclosporine and tacrolimus include tremor, myalgias, paresthesias, and, rarely, seizures. These complications can be treated with reduced doses of medication and occasionally with oral magnesium supplementation. A rare form of encephalopathy known as **posterior reversible encephalopathy syndrome** (PRES) can occur in patients taking CNIs (cyclosporine or tacrolimus). PRES presents with hypertension, headaches, and seizures, requires MRI for diagnosis, and is usually managed by changing CNI or, in rare cases, eliminating CNIs totally in favor of other immunosuppressive agents (e.g., sirolimus, MMF).

Tumors

One of the serious complications limiting long-term survival in pediatric heart transplant patients is the risk of neoplastic disease. The most common is **posttransplant lymphoproliferative disease** (PTLD), a condition associated with Epstein-Barr virus (EBV) infection. Patients who are EBV seronegative at transplant (usually infants and young children) are at increased risk of developing PTLD if they subsequently seroconvert, acquiring the virus either from the donor organ or from primary infection. Unlike true cancer, many cases of PTLD respond to a reduction in immunosuppression. A monoclonal antibody directed against the CD20 antigen on activated lymphocytes (rituximab), in conjunction with steroids and cyclophosphamide therapy, has been effective against some forms of PTLD. However, PTLD can behave more aggressively, and many patients eventually require chemotherapy. An increased risk of skin cancer requires that children use appropriate precautions when exposed to sunlight.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is a disease of the coronary arteries that occurs in approximately 20% of children 5 years after transplant. The cause is still unclear, although it is thought to be a form of immunologically mediated vessel injury. Multiple factors, including rejection episodes, infections, hypercholesterolemia, and hyperglycemia, are thought to increase the risk of CAV. Unlike native coronary atherosclerosis, CAV is a diffuse process with a high degree of distal vessel involvement. Because the transplanted heart has been denervated, patients may not experience symptoms such as angina pectoris during ischemic episodes, and the initial manifestation may be cardiovascular collapse or sudden death. Most centers perform coronary angiography annually to screen for coronary abnormalities; some also perform coronary intravascular ultrasound in larger children and adolescents. Standard coronary artery bypass procedures are usually not helpful because of the diffuse nature of the process, although transcatheter stenting can sometimes be effective for isolated lesions. For patients with severe CAV, repeat heart transplantation has been the only effective treatment. Thus prevention has been the focus of most current research. The cell-cycle inhibitors sirolimus and everolimus have been shown to decrease coronary arterial intimal thickening in adult transplant patients. Cholesterol-lowering HMG-CoA (3-hydroxy-3-methyl-coenzyme A) reductase inhibitors (e.g., pravastatin, atorvastatin) have been associated with a lower risk of CAV.

Other Complications

Corticosteroids usually result in cushingoid facies, steroid acne, and striae. Cyclosporine can cause a subtle change in facial features, such as hypertrichosis and gingival hyperplasia. These cosmetic features can be particularly disturbing to adolescents and may be the motivation for noncompliance, one of the leading risks for late morbidity and mortality. Most of these cosmetic complications are dose related and improve as immunosuppressive medications are weaned. Tacrolimus does not have the cosmetic side effects of cyclosporine. Osteoporosis and aseptic necrosis are additional reasons for reducing the steroid dosage as soon as possible. Diabetes and pancreatitis are rare but serious complications.

Rehabilitation

Despite the potential risks of immunosuppression, the prospect for rehabilitation in pediatric heart transplant recipients is excellent; most have no functional limitations in their daily lives. They can attend daycare or school and participate in competitive sports and other age-appropriate activities. Standardized measurements of ventricular function are close to normal. Because the transplanted heart is denervated, the increase in heart rate and cardiac output during exercise is slower in transplant recipients, and maximal heart rate and cardiac output responses are mildly attenuated. These subtle abnormalities are rarely noticeable by the patient.

Growth of the transplanted heart is excellent, although a mild degree of ventricular hypertrophy is often seen, even years after transplantation. The sites of atrial and great vessel anastomoses usually grow without the development of obstruction. In neonates who undergo transplantation for HLHS, however, juxtaductal aortic coarctation may recur.

A serious problem with noncompliance may occur once patients reach adolescence, and life-threatening rejection may result. Early intervention by social workers, counselors, and psychologists may be able to reduce this risk.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

492.2 Heart-Lung and Lung Transplantation

Samuel B. Goldfarb, Danielle S. Burstein, and Joseph W. Rossano

More than 700 heart-lung and 2,500 lung (single or double) pediatric transplants have been performed and reported to ISHLT, with >100 procedures performed annually. The majority of these are lung transplantation, with only three heart-lung transplants reported in 2017. Only 16 heart-lung transplants have been performed in the United States in the past 5 years compared to over 140 lung transplants during this same time frame. Primary indications for lung transplantation include cystic fibrosis, pulmonary hypertension, interstitial lung disease, surfactant deficiencies, and retransplant. Indications for heart-lung transplant include complex CHD along with either pulmonary parenchymal or vascular disease. Patients with normal hearts are candidates for lung transplantation even in the setting of right ventricular dysfunction. This had led to the marked decline in heart-lung transplant procedures in the current era. In some patients with CHD, double-lung transplantation can be performed in combination with repair of intracardiac defects. Patients with cystic fibrosis are *not* candidates for single-lung grafts

because of the risk of infection from the diseased contralateral lung. Patients are selected according to many of the same criteria as for heart transplant recipients (see Chapter 492.1).

Posttransplant immunosuppression is usually achieved with a triple-drug regimen, combining a CNI (cyclosporine or tacrolimus) with an antiproliferative agent (MMF or azathioprine) and prednisone. Most patients receive induction therapy with an antithymocyte or anti–T-cell preparation. Unlike patients with isolated heart transplants, patients with lung or heart-lung transplants cannot be weaned totally off steroids. Prophylaxis against *P. jiroveci* infection is achieved with trimethoprim-sulfamethoxazole or aerosolized pentamidine. Ganciclovir and CMV immune globulin prophylaxis are used as in heart transplant recipients (see Chapter 492.1). Antifungal medications are used in the perioperative and posttransplant periods in patients who have pretransplant colonization.

Pulmonary rejection is common in lung or heart-lung transplant recipients, whereas heart rejection is encountered much less often than in patients with isolated heart transplants. Acute cellular rejection (ACR) occurs in approximately 10–30% of patients in the first year after transplant depending on the recipient's age. Younger recipients have a lower incidence of ACR. Antibody-mediated rejection (AMR) and chronic lung allograph dysfunction (CLAD) are other forms of rejection. Symptoms of lung rejection may include fever and fatigue, although many episodes are minimally symptomatic. Signs of rejection could include changes in lung function testing and radiographic findings. Surveillance for acute rejection is performed by monitoring pulmonary function (forced vital capacity; forced expiratory volume in 1 second [FEV_1]; forced expiratory flow, midexpiratory phase [$FEF_{25–75\%}$]), systemic arterial oxygen tension, chest radiographs, chest CT, transbronchial biopsy, and open lung biopsy. The gold standard for ACR is tissue diagnosis, generally performed with transbronchial biopsies. AMR is diagnosed based on findings of donor-specific antibodies and tissue biopsy often associated with graft dysfunction. CLAD is a form of chronic rejection. It can present as an obstructive lung disease in the form of obliterative bronchiolitis. CLAD can also present with significant pulmonary fibrosis in the form of restrictive allograft dysfunction (RAD). In heart-lung transplant recipients, hearts are assessed for rejection similar to the approach described in Chapter 492.1.

Actuarial survival rates after lung or heart-lung transplantation in children are currently 75–80% at 1 year and 50% at 5 years after transplant; improved patient selection and postoperative management are continually improving these survival statistics from prior eras. In the analysis of survival at 5 years conditional on survival at 12 months, rates significantly improve for both lung and heart-lung regardless of underlying condition. One year conditional survival rates at 5 years for both are roughly 70%. Some groups, such as patients with CHD in the absence of Eisenmenger syndrome, have particularly poor outcomes with transplant. Graft failure and infection are the leading cause of early death, whereas a form of chronic rejection in the form of CLAD or RAD accounts for almost 50% of cases of late mortality. Other causes of early morbidity and mortality include technical complications, multiorgan failure, primary graft dysfunction, and cardiovascular causes. Additional late complications include the development of late graft failure, malignancies, infection, and other side effects of chronic immunosuppression.

Postoperative indices of cardiopulmonary function and exercise capacity show significant improvement. Problems of donor availability are even more severe with lung transplantation than with isolated heart transplantation. However, significant advances in ex vivo lung perfusion have great potential to expand the number of organs available for transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 8

Diseases of the Peripheral Vascular System

Chapter 493

Diseases of the Blood Vessels (Aneurysms and Fistulas)

493.1 Aneurysms

Daniel Bernstein

See also Chapter 208.

Aneurysms of the coronaries and occasionally the systemic arteries may complicate Kawasaki disease and are the leading cause of morbidity in this disease (Figs. 493.1 and 493.2). Persistent moderate to large aneurysms carry several risks: embolism and thromboembolism (a clot developing in the aneurysm because of stagnant blood flow and obstructing flow and/or breaking off and traveling more distally down the coronary, resulting in myocardial ischemia/infarction) and stenosis (the distal end of the aneurysm tends to become narrowed over time, limiting downstream coronary blood flow). Management includes anticoagulation to prevent thrombosis and β blockers to reduce myocardial oxygen requirements (see Chapter 210).

COVID-19–associated multisystem inflammatory syndrome in children (MIS-C) typically occurs a few weeks after active SARS-CoV-2 infection and can cause coronary artery dilation and aneurysms, in addition to other significant cardiac manifestations (ventricular dysfunction, arrhythmias, and conduction abnormalities; see Chapters 311 and 449.1).

Other than in Kawasaki disease and MIS-C, aneurysms are not common in children and occur most frequently in the aorta in association with coarctation of the aorta, patent ductus arteriosus, Ehlers-Danlos syndrome type IV (vascular ecchymotic form), hyper-IgE syndrome, Marfan syndrome, and the four forms of Loeys-Dietz syndrome (see Chapter 641). Aneurysms may be seen in the arterial tortuosity syndrome and the multisystem smooth muscle dysfunction syndrome (MSMDS) (see Chapter 493.4). MSMDS is characterized by congenital mydriasis, patent ductus arteriosus, aortic and other arterial aneurysms, as well as moyamoya-like cerebrovascular disease and pulmonary hypertension. The affected gene is *ACTA2*. Aneurysms may also occur secondary to an infected embolus; infection contiguous to a blood vessel; trauma; congenital abnormalities of vessel structure, especially the medial wall; and arteritis, including polyarteritis nodosa, Behçet syndrome, and Takayasu arteritis (see Chapter 210.2).

493.2 Arteriovenous Fistulas

Daniel Bernstein

Arteriovenous fistulas may be limited and small or may be large and extensive, producing systemic complications (see Chapters 554 and 691). The most common sites in infants and children are within the

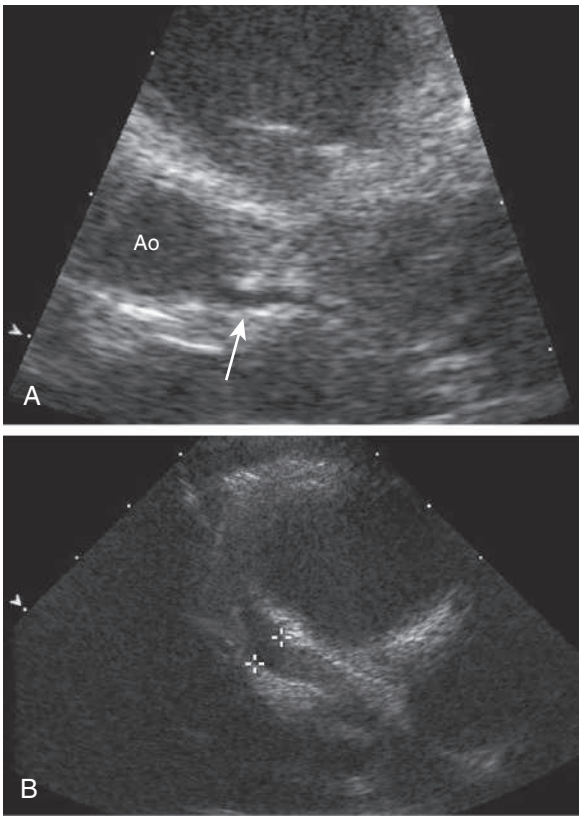

Fig. 493.1 Two-dimensional echocardiograms comparing a normal left main coronary artery (*arrow* in A) with a giant coronary artery aneurysm (outlined by *cross marks* in B) in a patient with Kawasaki disease. Ao, Aorta.

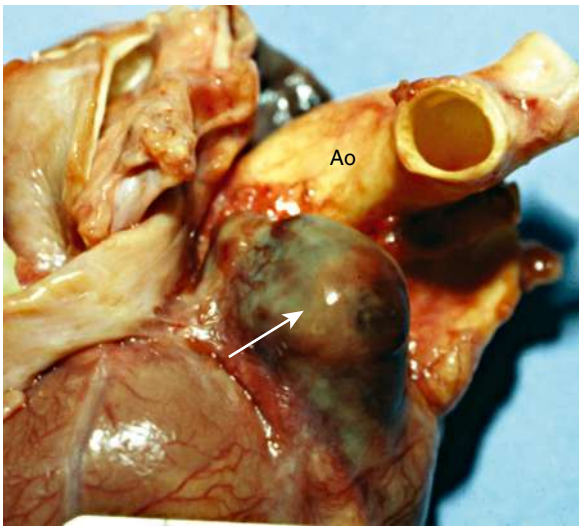

Fig. 493.2 Pathologic specimen showing giant aneurysm of left main coronary artery *(arrow)*. Ao, Ascending aorta.

cranium, in the liver, in the lung, in the extremities, and in vessels in or near the thoracic wall. These fistulas, although usually **congenital**, may follow trauma or may be a manifestation of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Femoral arteriovenous fistulas are a rare complication of percutaneous femoral catheterization.

CLINICAL MANIFESTATIONS

Clinical symptoms occur only in association with large arteriovenous communications when arterial blood flows into a low-pressure venous system without the resistance of the capillary bed; local venous pressure is increased, and arterial flow distal to the fistula is decreased. Systemic arterial resistance falls because of the runoff of blood through the fistula. Compensatory mechanisms include tachycardia and increased stroke volume so that cardiac output rises. Total blood volume is also increased. In large fistulas, left ventricular dilation, a widened pulse pressure, and high-output heart failure can occur. CT, MRI, or injection of contrast material into an artery proximal to the fistula confirms the diagnosis.

Large intracranial arteriovenous fistulas most often occur in newborn infants in association with a **vein of Galen malformation**. The large intracranial left-to-right shunt results in heart failure secondary to the demand for high cardiac output. Patients with smaller communications may not have cardiovascular manifestations but may later be disposed to hydrocephalus (see Chapter 631.9) or seizures. The diagnosis can often be made by auscultation of a continuous murmur over the cranium. Older children with more diffuse intracranial arteriovenous malformations may be recognized on the basis of intracranial calcification and high cardiac output without cardiac failure.

Coronary arteriovenous fistulas can develop between a coronary artery and any of the cardiac chambers **(coronary cameral fistula)** or great vessels. These fistulas can result in steal of blood away from the heart muscle downstream of the fistula resulting in ischemia and, in rare cases, can even cause obstruction of ventricular inflow caused by physical interference with atrioventricular valve function.

Hepatic arteriovenous fistulas may be generalized or localized in the liver and may be hemangioendotheliomas or cavernous hemangiomas. The fistula may be located between the hepatic artery and the ductus venosus or portal vein. Congenital hemorrhagic telangiectasia may also be present. Large arteriovenous fistulas are associated with increased cardiac output and heart failure. Hepatomegaly is usual, and systolic or continuous murmurs may be audible over the liver.

Peripheral arteriovenous fistulas generally involve the extremities and can be associated with disfigurement, swelling of the extremity, and visible hemangiomas. Their presence can be complicated by breathing difficulties if located near the upper airways and causing obstruction. Because only a small minority results in large arterial runoff, cardiac failure is uncommon.

TREATMENT

Medical management of heart failure is initially helpful in neonates with these conditions; with time, the size of the shunt may diminish and symptoms spontaneously regress. Hemangiomas of the liver often eventually disappear completely. Large liver hemangiomas have been treated with corticosteroids, β blockers, ε-aminocaproic acid, interferon, local compression, embolization, or local irradiation; the beneficial effects of these management options are not firmly established because individual patients display marked variation in clinical course without treatment. **Transcatheter closure** is becoming the treatment of choice for many patients with a symptomatic arteriovenous fistula. Embolic agents that have been used include detachable balloons, steel (Gianturco) coils, plugs, and liquid tissue adhesives (cyanoacrylate). Often, multiple procedures are necessary before flow is significantly reduced. **Gamma knife radiosurgery** has been used successfully in patients with cerebral arteriovenous malformations. Surgical removal of a large fistula may be attempted in patients with severe cardiac failure and lack of improvement with medical treatment. Surgical treatment may be contraindicated or unsuccessful when the lesion is extensive and diffuse or is located in a position where adjoining tissue may be injured during the surgery or related procedures. β-Adrenergic blockers such as propranolol have dramatically changed the treatment for cutaneous hemangiomas, with excellent results.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

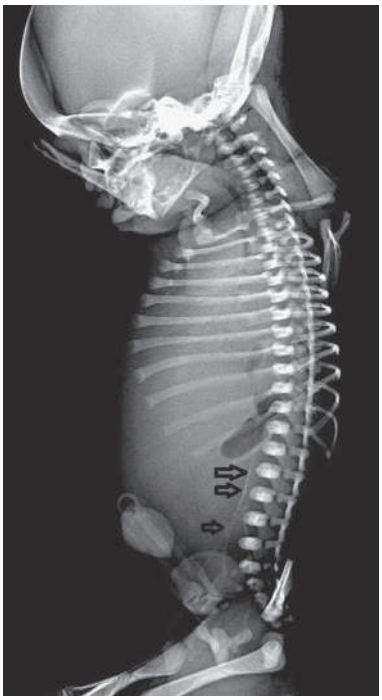

Fig. 493.3 Lateral radiograph of the neonate showing calcification of the descending aorta and its bifurcation *(arrows). (From Karthikeyan G. Generalized arterial calcification of infancy. J Pediatr. 2013;162:1074, Fig 3.)*

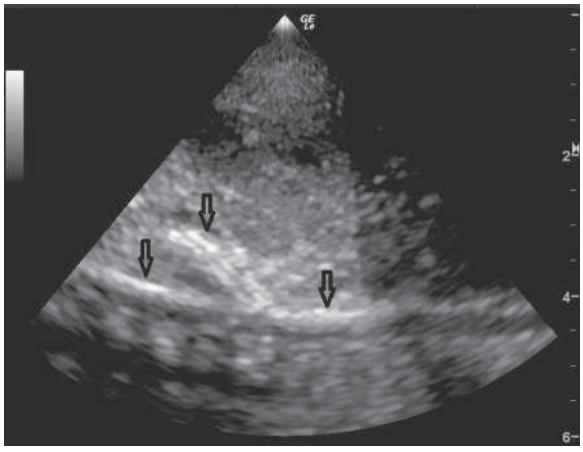

Fig. 493.4 Ultrasonography of abdominal aorta showing calcification of descending aorta and its branches *(arrows). (From Karthikeyan G. Generalized arterial calcification of infancy. J Pediatr. 2013;162:1074, Fig. 1.)*

493.3 Generalized Arterial Calcification of Infancy (Idiopathic Infantile Arterial Calcification)

Robert M. Kliegman

Generalized arterial calcification of infancy (GACI) is a rare and often lethal autosomal recessive disorder characterized by calcification of muscular arteries with fibrotic myointimal proliferation and subsequent vascular stenosis leading to tissue ischemia, poor function, or infarction. Diffuse arterial calcification may begin in utero, leading to hydrops fetalis; in the neonate, diffuse arterial calcification leads to respiratory distress and heart failure or myocardial infarction (coronary, pulmonary arteries), hypertension (renal arteries), and poor femoral pulses (aorta, femoral arteries).

Pathogenic variants in the ectonucleotide pyrophosphatase 1 gene (*ENPP1*) are noted in 75% of patients. Serum calcium, phosphate, and alkaline phosphatase levels are normal; the vascular calcification may be seen on plain x-ray films (Fig. 493.3), ultrasonography (Fig. 493.4), or CT scans (Fig. 493.5), which may reveal calcifications not visible on plain films.

A subset of patients with GACI have monoallelic or biallelic pathogenic variants in the adenosine triphosphate–binding cassette subfamily C number 6 gene (*ABCC6*), which is responsible for **pseudoxanthoma elasticum** (PXE). PXE, an autosomal recessive disorder, is classically associated with a later onset of ectopic mineralization of elastic fibers in the skin, eyes, joints, and arteries. In addition, some surviving infants with *ENPP1* variant develop PXE symptoms involving the skin and retina (angioid streaking).

Infants with GACI have been treated with bisphosphonates with variable success. In addition, some survivors with the *ENPP1* variant have developed hypophosphatemic-hyperphosphaturic rickets.

In the absence of stroke or encephalomalacia, most survivors are developmentally normal. In some survivors the vascular calcification resolves and is replaced by fibrosis. The differential diagnosis includes Singleton-Merten syndrome (aortic calcification, dental anomalies, osteopenia), hypervitaminosis D, hyperparathyroidism, congenital syphilis (aortitis), twin-twin transfusion syndrome (recipient), and idiopathic iliac artery calcification of infancy.

ARTERIAL CALCIFICATIONS CAUSED BY DEFICIENCY OF CD73

This rare autosomal recessive disorder, caused by pathogenic variants in the 5-exonucleotidase CD73 *(NT5E)*, results in joint and arterial (lower-extremity) calcification in adults. Patients present with intermittent claudication and joint pain. Onset is probably before adulthood, since patients may be undiagnosed with nonspecific findings during adolescence.

493.4 Arterial Tortuosity

Robert M. Kliegman

Arterial tortuosity may be seen in many different diseases and genes (Table 493.1). These disorders are usually recognized by their phenotype, and all may present during childhood. Tortuosity is best defined by magnetic resonance angiography (Fig. 493.6). When present, it often increases the risk for early cardiovascular morbidity for patients with Marfan or Loeys-Dietz syndrome.

Arterial tortuosity syndrome is another genetic arteriopathy caused by pathogenic variants in the *SCL2A10* gene. It has many features of other connective tissue diseases, including hyperextensible and soft velvety skin, high-arched palate, micrognathia, abdominal hernias, and joint hypermobility. The prognosis for patients with arterial tortuosity syndrome is quite variable, but the presence of vascular stenosis is associated with a poorer prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

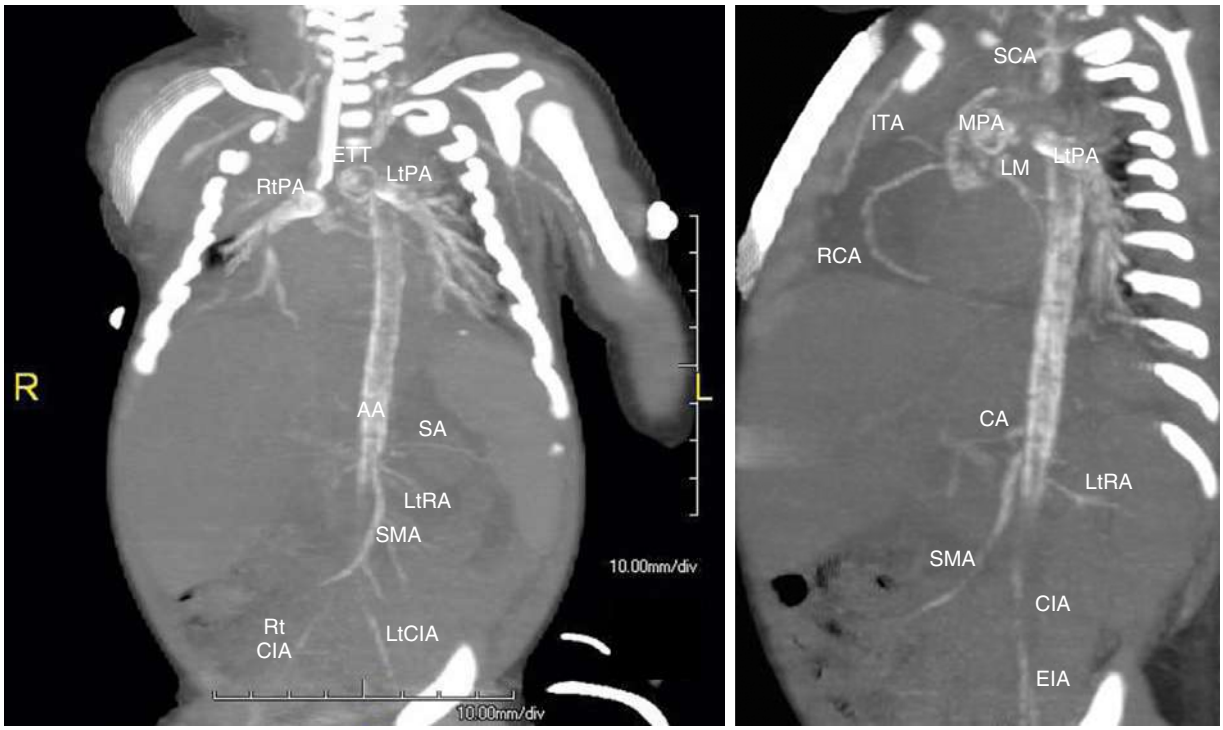

Fig. 493.5 Coronal maximum intensity projection (MIP) CT scans demonstrate an endotracheal tube (ETT) and extensive vascular calcifications. PA, Pulmonary artery; SA, splenic artery; RA, renal artery; CIA, common iliac artery; BA, brachial artery; CA, celiac axis; SMA, superior mesenteric artery; SCA, subclavian artery. *(From Bolster F, Ali Z, Southall P, et al. Generalized arterial calcification of infancy—findings at post-mortem computed tomography and autopsy. Forensic Sci Int. 2015;254:e7–e12, Fig 3.)*

Table 493.1 Genetic Disorders Associated with Aortic Disease and Arterial Tortuosity

GENE	DISORDER
TGFBR1	Loeys-Dietz syndrome, FTAAD
TGFBR2	Loeys-Dietz syndrome, FTAAD
FBN1	Marfan syndrome
SMAD3	Osteoarthritis-aneurysm syndrome, FTAAD
SLC2A10	Arterial tortuosity syndrome
TGFB2	FTAAD
PRKG1	FTAAD
FBLN4/EFEMP2	Cutis laxa
ATP7A	Occipital horn syndrome, Menkes syndrome
Monosomy X/mosaic monosomy X	Turner syndrome
FTAAD	Familial aortic aneurysm and dissection
ACTA2	Multisystem smooth muscle dysfunction syndrome

FTAAD, Familial thoracic aortic aneurysm and dissection.
Adapted from Morris SA. Arterial tortuosity in genetic arteriopathies. *Curr Opin Cardiol.* 2015;30:587–590, Table 1, p. 590.

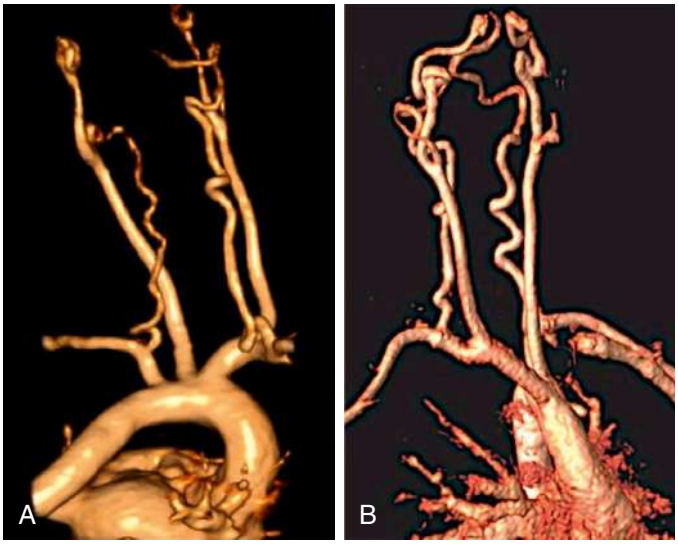

Fig. 493.6 Examples of vertebral artery tortuosity in Marfan syndrome with *FBN1* pathogenic variant (**A**) and Loeys-Dietz syndrome with a *TGFBR2* mutation (**B**). *(From Morris SA. Arterial tortuosity in genetic arteriopathies. Curr Opin Cardiol. 2015;30:587–593, Fig 1.)*

Chapter 494

Systemic Hypertension

Ian R. Macumber and Joseph T. Flynn

Hypertensive children, although frequently asymptomatic, already may manifest evidence of target organ damage. Up to 40% of hypertensive children have left ventricular hypertrophy, and hypertensive children have increased carotid intima-to-media thickness, a marker of early atherosclerosis. Primary (essential) hypertension occurring during childhood often continues into adulthood. Children with blood pressure (BP) >90th percentile exhibit a 2.4-fold greater risk of having hypertension as adults. Similarly, almost half of hypertensive adults had a BP >90th percentile as children. Adolescent hypertension is also an independent predictor of both end-stage kidney disease and left ventricular dysfunction in middle-age males.

PREVALENCE OF HYPERTENSION IN CHILDREN

In infants and young children, systemic hypertension is uncommon, with a prevalence of <1%, but, when present, often indicates an underlying disease process **(secondary hypertension)**. *Severe and symptomatic hypertension in children is usually caused by secondary hypertension.* In contrast, the prevalence of primary hypertension, mostly in older school-age children and adolescents, has increased in prevalence in parallel with the obesity epidemic. Estimates are variable, but data from the U.S. National Health and Nutrition Examination Survey (NHANES) show that approximately 9% of American youth have **elevated BP** and 3–4% have **hypertension**. A meta-analysis suggests a similar worldwide prevalence of hypertension in children. The normative data from the 2017 American Academy of Pediatrics (AAP) clinical practice guidelines have resulted in an overall trend of increased hypertension prevalence. The influence of obesity on elevated BP is evident in children as young as 2-5 years old. Approximately 20% of American youth have obesity, and up to 10% of these have hypertension.

DEFINITION OF HYPERTENSION

Normal BP in adults is <120/80 mm Hg. **Elevated** blood pressure is considered systolic BP of 120-129 *and* diastolic BP <80 mm Hg. **Stage 1** hypertension is systolic 130-139 *or* diastolic 80-89 mm Hg; **Stage 2** hypertension is systolic ≥140 *or* diastolic ≥90 mm Hg. This definition is based on potential outcomes because it relates degree of BP elevation with significant likelihood of subsequent cardiovascular events. Because hypertension-associated cardiovascular events (e.g., myocardial infarction, stroke) occur rarely in childhood, the definition of hypertension in children is statistical and based on the *distribution of BP in healthy children,* not outcomes. The AAP clinical practice guideline on childhood hypertension maintains the same statistical approach to defining and categorizing childhood BP as in previous guidelines from the **National High Blood Pressure Education Program (NHBPEP)**:

- **Normal BP:** BP <90th percentile for age, sex, and height or <120/<80 (systolic/diastolic) mm Hg for adolescents ≥13 years old
- **Elevated BP:** BP reading ≥90th percentile and <95th percentile for age, sex, and height or 120-129/<80 mm Hg for adolescents ≥13 years old
- **Hypertension:** BP >95th percentile for age, sex, and height or ≥130/80 mm Hg for adolescents ≥13 years old. Hypertensive-level BP is further staged as follows:
  - **Stage 1 hypertension:** BP >95th percentile for age, sex, and height up to the 95th percentile + 11 mm Hg or 130-139/80-89 mm Hg for adolescents ≥13 years of age
  - **Stage 2 hypertension:** BP ≥95th percentile + 12 mm Hg for age, sex, and height or >140/90 mm Hg for adolescents ≥13 years of age

The BP cut-points for adolescents ≥13 years old and use of the term *elevated BP* instead of prehypertension were chosen to align with revised BP cut-points and terminology found in the American Heart Association/American College of Cardiology (AHA/ACC) guideline for adult hypertension. The European Society of Hypertension (ESH) pediatric BP guideline also suggested that an absolute BP cutoff be used for adolescents age 16 and older, rather than using BP percentiles. For these older adolescents, the ESH guidelines define *high-normal* BP as 130-139/85-89 mm Hg and *hypertension* as ≥140/90 mm Hg.

The AAP guideline* also contains tables of normative BP values for children and adolescents based on a reanalysis of the NHBPEP database, removing all overweight and obese children. This revision results in BP values that are 2-3 mm Hg lower than the corresponding BP values in the 2004 NHBPEP Fourth Report, illustrating the impact of the childhood obesity epidemic on BP in young persons. The AAP guideline also contains a *simplified table* of BP values that may require further evaluation, which should be useful for screening (Table 494.1).

BLOOD PRESSURE MEASUREMENT IN CHILDREN

The AAP guideline recommends that children 3 years or older should have their BP measured during annual preventive visits, unless the child has risk factors such as obesity, chronic kidney disease (CKD), or diabetes, in whom it should be checked at every healthcare encounter. In contrast, the ESH pediatric guideline recommends checking BP at every healthcare encounter for all children >3 years old. Selected children <3 years old should also have their BP measured, including those with a history of prematurity, congenital heart disease, kidney disease, solid-organ transplant, cancer, treatment with drugs known to raise BP, other illnesses associated with hypertension (e.g., neurofibromatosis, tuberous sclerosis), or evidence of increased intracranial pressure. The preferred method is by auscultation using a sphygmomanometer (BP) with a cuff appropriate for the size of the child's arm.

Elevated readings should be confirmed on repeat visits before determining that a child is hypertensive. The BP should be measured with the child in the seated position after a period of quiet for at least 5 minutes, and it is recommended that the BP be checked 3 times, averaging the results. Careful attention to **cuff size** is necessary to avoid overdiagnosis, because a cuff that is too short or narrow artificially increases BP readings. An appropriate-sized cuff has an inflatable bladder whose length covers 80–100% of the upper arm circumference (measured midway between the acromion process and olecranon) and whose width is at least 40% of the arm circumference. A wide variety of cuff sizes should be available in any medical office where children are routinely seen.

Systolic blood pressure (SBP) is indicated by appearance of the *first* Korotkoff sound. Diastolic blood pressure (DBP) has been defined by consensus as the *fifth* Korotkoff sound, unless the Korotkoff sounds can be heard down to 0 mm Hg, in which case the *fourth* Korotkoff sound should be reported as the DBP. Palpation is useful for rapid assessment of SBP, although the palpated BP is generally about 10 mm Hg lower than that obtained by auscultation. Oscillometric techniques are used frequently in infants and young children, but they are susceptible to artifacts and are best for measuring mean arterial pressure (MAP). In addition, different devices use different proprietary algorithms to back-calculate SBP and DBP from the MAP, making comparison between devices difficult.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring **(ABPM)** is frequently used as a tool to assess pediatric hypertension. The patient wears a device that records BP every 20-30 minutes throughout a 24-hour period, during usual daily activities, including sleep. This monitoring allows calculation of the mean daytime BP, sleep BP, and mean

* https://publications.aap.org/pediatrics/article/140/3/e20171904/38358/Clinical-Practice-Guideline-for-Screening-and.

BP over 24 hours. The physician can also determine the proportion of BP measurements that are in the hypertensive range (BP load) and whether there is an appropriate decrease in BP during sleep (nocturnal dip), generally considered *normal* if there is a decrease in nocturnal BP of >10% from awake values. The cuff should be placed on the patient's nondominant arm. It is recommended that the patient keep a journal of sleep and awake times, medication timing, and other events that may be relevant to BP readings. Clinicians should only perform ABPM if they have had specific training in performing and interpreting the results.

ABPM readings are more strongly correlated with target-organ damage in children than casual/office BP readings and are more sensitive for a diagnosis of hypertension than either manual or automated office blood pressures. The 2017 AAP guideline strongly recommends that ABPM be performed on all patients with elevated office readings to confirm the diagnosis of hypertension. In addition, ABPM is necessary to diagnose **white coat hypertension** (elevated office BP but normal ambulatory BP) and **masked hypertension** (normal office BP but elevated ambulatory BP). It should be noted that white coat hypertension is not a benign condition, and children with white coat hypertension may be at increased risk of developing sustained hypertension in the future. In adults, white coat hypertension has been associated with higher all-cause and cardiovascular mortality compared to normotensive individuals. ABPM is also a useful tool for evaluating effectiveness of antihypertensive therapy. ABPM is recommended to assess BP patterns in high-risk patient populations, such as children with CKD, solid-organ transplant, diabetes mellitus, and severe obesity.

ABPM is an extremely useful tool for evaluating and managing hypertension in appropriate patient populations, but it does have limitations. Not every patient will tolerate APBM, including younger children (although there are reports of successful ABPM in toddlers 18 months old) and some children with developmental delay. Nonetheless, it is usually feasible to perform ABPM in children ≥6-7 years. The most accepted normative data come from the German Working Group on Pediatric Hypertension. However, there are concerns with this dataset: (1) it includes only Central European White children and thus might not be generalizable to other ethnicities; (2) there were relatively few shorter children included, which may limit its application to patients with chronic diseases such as CKD; and (3) there was very little variability in DBP values, which is not consistent with data from other BP measurement techniques showing that DBP varies with both age and height.

Table 494.1 Simplified Table of Screening Blood Pressure Values (mm Hg) Requiring Further Evaluation

	MALES		FEMALES	
AGE (YR)	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

From Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904, Table 6.

ETIOLOGY AND PATHOPHYSIOLOGY

Blood pressure is the product of cardiac output (CO) and peripheral vascular resistance (PVR). An increase in either CO or PVR results in an increase in BP; if either of these factors increases while the other decreases, BP may not increase. When hypertension is the result of another disease process, it is referred to as *secondary hypertension*. When no identifiable cause can be found, it is referred to as *primary hypertension*.

Secondary hypertension is most common in infants and younger children. It is most often caused by kidney abnormalities; additional etiologies include cardiovascular disease and endocrinopathies. Younger age, severely elevated BP, and symptomatic hypertension make a secondary cause of hypertension more likely. Many childhood diseases can be responsible for *chronic hypertension* (Table 494.2) or *acute/intermittent hypertension* (Table 494.3). The most likely cause varies with age. Hypertension in the premature infant is sometimes

Table 494.2 Conditions Associated with Chronic Hypertension in Children

RENAL
Recurrent pyelonephritis/renal scarring
Chronic glomerulonephritis
Prematurity
Congenital dysplastic kidney
Polycystic kidney disease
Vesicoureteral reflux nephropathy
Segmental hypoplasia (Ask-Upmark kidney)
Obstructive kidney disease
Renal tumors
Renal trauma
Systemic lupus erythematosus (other connective tissue diseases)
VASCULAR
Coarctation of thoracic or abdominal aorta
Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)
Umbilical artery catheterization with thrombus formation
Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)
Renal vein thrombosis
Vasculitis (ANCA associated, polyarteritis nodosa, Takayasu arteritis)
Arteriovenous shunt
Williams-Beuren syndrome
Moyamoya disease
ENDOCRINE
Hyperthyroidism
Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)
Cushing syndrome
Primary hyperaldosteronism
Apparent mineralocorticoid excess
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)
Glucocorticoid resistance (Chrousos syndrome)
Pseudohypoaldosteronism type 2 (Gordon syndrome)
Pheochromocytoma
Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
Liddle syndrome
Geller syndrome
CENTRAL NERVOUS SYSTEM
Intracranial mass
Hemorrhage
Residual after brain injury
Quadriplegia (dysautonomia)
Sleep disordered breathing

ANCA, Antineutrophil cytoplasmic antibody.

Table 494.3 Conditions Associated with Transient or Intermittent Hypertension in Children

RENAL
Acute postinfectious glomerulonephritis
Henoch-Schönlein purpura with nephritis
Hemolytic-uremic syndrome
Acute kidney injury
After renal transplantation (immediately and during episodes of rejection)
Hypervolemia
Pyelonephritis
Renal trauma
Leukemic infiltration of the kidney
DRUGS AND POISONS
Cocaine
Oral contraceptives
Sympathomimetic agents
Amphetamines
Phencyclidine
Corticosteroids and adrenocorticotropic hormone
Cyclosporine, sirolimus, or tacrolimus treatment after transplantation
Licorice (glycyrrhizic acid)
Lead, mercury, cadmium, thallium
Antihypertensive withdrawal (clonidine, methyldopa, propranolol)
Vitamin D intoxication
Ma-huang
CENTRAL AND AUTONOMIC NERVOUS SYSTEM
Increased intracranial pressure
Guillain-Barré syndrome
Burns
Familial dysautonomia
Stevens-Johnson syndrome
Posterior fossa lesions
Porphyria
Poliomyelitis
Encephalitis
Spinal cord injury (autonomic storm)
MISCELLANEOUS
Preeclampsia
Pain, anxiety
Hypercalcemia
After coarctation repair
White blood cell transfusion
Extracorporeal membrane oxygenation

associated with umbilical artery catheterization, renal artery thrombosis, or bronchopulmonary dysplasia. Hypertension during early childhood may be caused by kidney disease, coarctation of the aorta, endocrine disorders, or medications.

Kidney disease (e.g., acute or chronic glomerulonephritis, reflux or obstructive nephropathy, hemolytic-uremic syndrome, polycystic kidney disease, congenital anomalies of the kidney and urinary tract) and **renovascular hypertension** account for approximately 90% of children with secondary hypertension. Parenchymal kidney disease and renal artery stenosis lead to water and sodium retention thought to be, in part, secondary to increased renin secretion. **Coarctation of the aorta** must always be considered, even in adolescents. **Obstructive sleep apnea** is associated with hypertension in children, and patients with hypertension and symptoms of obstructive sleep apnea (snoring, daytime somnolence, insomnia, pauses in breathing) should be referred for polysomnography. Several **endocrinopathies** are associated with hypertension, usually those involving the thyroid, parathyroid, and adrenal glands. Systolic hypertension and tachycardia are common in hyperthyroidism; DBP is not usually elevated. **Hypercalcemia**, whether secondary to hyperparathyroidism or other causes, often results in mild elevation in BP because of an increase in vascular tone. **Adrenocortical disorders** (e.g., aldosterone-secreting tumors, sodium-retaining congenital adrenal hyperplasia, Cushing syndrome) may produce hypertension in patients with increased mineralocorticoid secretion. It is important to consider conditions associated with real or apparent **mineralocorticoid excess** and thus a *suppressed* renin level (with or without hypokalemia) form of secondary hypertension (Table 494.4 and Fig. 494.1). **Pheochromocytomas** are catecholamine-secreting tumors that give rise to hypertension because of the cardiac and peripheral vascular effects of epinephrine and norepinephrine. Children with pheochromocytoma usually have sustained rather than the intermittent or exercise-induced hypertension seen in adults. Pheochromocytoma develops in approximately 5% of patients with neurofibromatosis and can also be seen in certain genetic disorders such as von Hippel-Lindau disease. Rarely, secondary hypertension can be caused by **pseudohyperaldosteronism**, which leads to elevated BP in the face of a suppressed renin level. Such disorders include Liddle syndrome, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism. Altered sympathetic tone can be responsible for acute or intermittent elevation of BP in children with Guillain-Barré syndrome, poliomyelitis, burns, and Stevens-Johnson syndrome. Intracranial lesions also affect sympathetic outflow from the central nervous system.

A number of **drugs of misuse**, **therapeutic agents**, and **toxins** may cause hypertension (Table 494.5). Cocaine may provoke a rapid increase in BP and can result in seizures or intracranial hemorrhage. Phencyclidine causes transient hypertension that may become persistent in chronic abusers. Tobacco use may also increase BP. Sympathomimetic agents used as nasal decongestants, appetite suppressants, and stimulants for attention-deficit disorder produce peripheral vasoconstriction and varying degrees of cardiac stimulation. Individuals vary in their susceptibility to these effects. Oral contraceptives should be suspected as a contributor to elevated BP in adolescent girls, although the incidence is lower with the use of low-estrogen preparations. Immunosuppressant agents such as cyclosporine and tacrolimus cause hypertension in organ transplant recipients, and the effect is exacerbated by the coadministration of corticosteroids. BP may be elevated in patients with poisoning by a heavy metal (lead, cadmium, mercury).

In older school-age children and adolescents, **primary hypertension** becomes increasingly common. These patients often are overweight, have a strong family history of hypertension, and have BP values at, or only slightly above, the 95th percentile for age. Isolated systolic hypertension is also more consistent with primary hypertension, whereas diastolic hypertension may suggest a secondary cause. The cause of primary hypertension is likely to be multifactorial; obesity, genetic alterations in calcium and sodium transport, vascular smooth muscle reactivity, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system overactivity, and insulin resistance have been implicated in this disorder. Elevated uric acid levels may play a role in the pathophysiology of primary hypertension, and elevated uric acid levels have been associated with higher SBP and DBP in children. Proof-of-concept studies have confirmed that lowering of uric acid levels results in lower BP in overweight youth with hypertension or prehypertension. Some children and adolescents demonstrate *salt-sensitive hypertension*. This is more common in children with primary hypertension and may be ameliorated by weight loss and sodium restriction.

Normotensive children of hypertensive parents may show abnormal physiologic responses that are similar to those of their parents. When subjected to stress or competitive tasks, the offspring of hypertensive adults, as a group, respond with greater increases in heart rate and BP than do children of normotensive parents. Similarly, some children of hypertensive parents may excrete higher levels of urinary catecholamine metabolites or may respond to sodium loading with greater weight gain and increases in BP than do those without a family history of hypertension. The abnormal responses in children with affected parents tend to be greater in the Black population than among White individuals.

Table 494.4 Clinical Findings in Patients with Mineralocorticoid Excess

CONDITION	INVOLVED GENE	CLINICAL PRESENTATION
CAH: 11β-hydroxylase deficiency	*CYP11B1* (autosomal recessive)	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females
CAH: 17α-hydroxylase deficiency	*CYP17A1* (autosomal recessive)	Pseudohermaphroditism (male), sexual infantilism (female)
Apparent mineralocorticoid excess	*HSD11β;* deficiency of 11β hydroxysteroid dehydrogenase (autosomal recessive)	Growth stunting/short stature, nephrocalcinosis, hypokalemia, low renin, hypoaldosteronism
Liddle syndrome	*SCNN1A* *SCNN1B* *SCNN1G* (autosomal dominant)	Severe hypertension, hypokalemia, metabolic alkalosis, muscle weakness
Geller syndrome (exacerbated by pregnancy)	GOF variant in mineralocorticoid receptor gene *NR3C2* (autosomal dominant)	Early onset of hypertension (before age 20 yr), exacerbated in pregnancy: hypokalemia, low renin
Glucocorticoid remediable aldosteronism (GRA) (familial aldosteronism type 1)	Chimeric gene with ACTH responsive promoter of 11β hydroxylase fused with aldosterone synthase gene (autosomal dominant)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke
Pseudohypoaldosteronism type 2 (Gordon syndrome)	*WNK1* *WNK4* *KLHL3* *CUL3* (autosomal dominant)	Short stature, hyperkalemic and hyperchloremic metabolic acidosis, borderline blood pressure, low renin
Glucocorticoid resistance (children) (Chrousos syndrome)	*NR3C1* (autosomal dominant or sporadic)	Ambiguous genitalia, precocious puberty; women may have androgen excess: acne, excessive hair, oligo/anovulation, infertility

CAH, Congenital adrenal hyperplasia; GOF, gain of function.
Modified from Melcescu E, Phillips J, Moll G, et al. 11 Beta-hydroxylase deficiency and other syndromes of mineralocorticoid excess as a rare cause of endocrine hypertension. *Horm Metab Res.* 2012;44:867–878, Table 1.

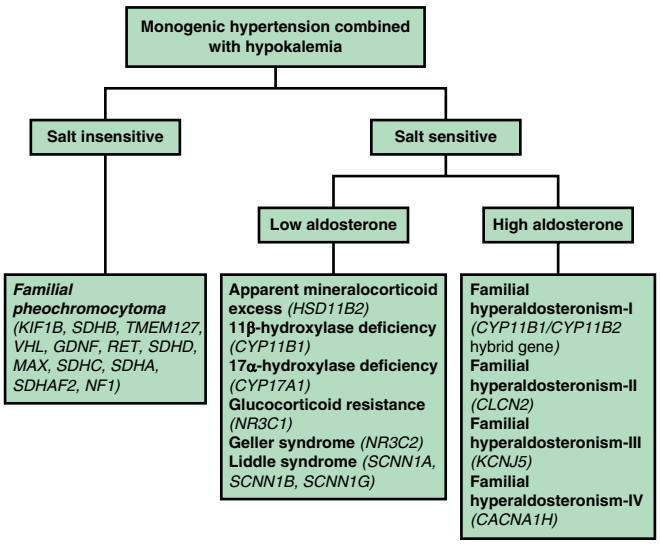

Fig. 494.1 Algorithm showing the overall categorization of monogenic hypertension combined with hypokalemia. Involved genes are italicized and in parentheses. *(From Lu YT, Fan P, Zhang D, et al. Overview of monogenic forms of hypertension combined with hypokalemia. Frontiers Pediatr. 2021;8:Article 543309, Fig. 1.)*

CLINICAL MANIFESTATIONS

Children and adolescents with primary hypertension are usually asymptomatic; the BP elevation is usually mild and is detected during a routine examination or evaluation before athletic participation. These children may also be obese. Children with secondary hypertension can have BP elevations ranging from mild to severe. Unless the BP has been sustained or is rising rapidly, hypertension does not usually produce symptoms. Therefore clinical manifestations may instead reflect the underlying disease process, such as growth failure in children with CKD. Children and adolescents with **acute severe hypertension**, in contrast, present with BP elevation well above stage 2 hypertension and severe symptoms that may represent acute target-organ injury.

Subclinical hypertensive **target-organ injury** is a common clinical manifestation in children with primary hypertension. Using echocardiography with pediatric normative data, left ventricular hypertrophy is detected in up to 40% of hypertensive children. Other markers of target-organ damage that have been demonstrated in hypertensive children include hypertensive retinopathy, increased carotid intima-to-media thickness, and increased vascular stiffness. Studies have shown that children with hypertension perform worse on tests of neurocognition than normotensive children and that these test results improve with successful treatment of hypertension. Target-organ effects of increased BP can be detected in adolescents even at BP levels below what is currently considered hypertensive.

Table 494.5 Drugs That May Elevate Blood Pressure

CLASS	DRUG
Antiinflammatory agents	COX-2 inhibitors (celecoxib) NSAIDs (ibuprofen, ketorolac)
Corticosteroids	Prednisone Hydrocortisone Dexamethasone
CNS stimulants	ADHD medications (methylphenidate, atomoxetine) Caffeine
Drugs of misuse	Amphetamines Cocaine MDMA Phencyclidine Tobacco
Estrogen- and progesterone-containing agents	HRT Oral contraceptives
Heavy metals	Cadmium Lead Mercury
Immunosuppressive agents	Cyclosporine Sirolimus Tacrolimus
Psychiatric agents	SNRI SSRI Tricyclic antidepressants
Supplements	Ephedra Guarana Ginseng Licorice St. John's wort Ma-huang
Sympathomimetic agents	Appetite suppressants Decongestants

COX-2, Cyclooxygenase-2; NSAID, nonsteroidal antiinflammatory drug; ADHD, attention-deficit/hyperactivity disorder; HRT, hormone replacement therapy; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

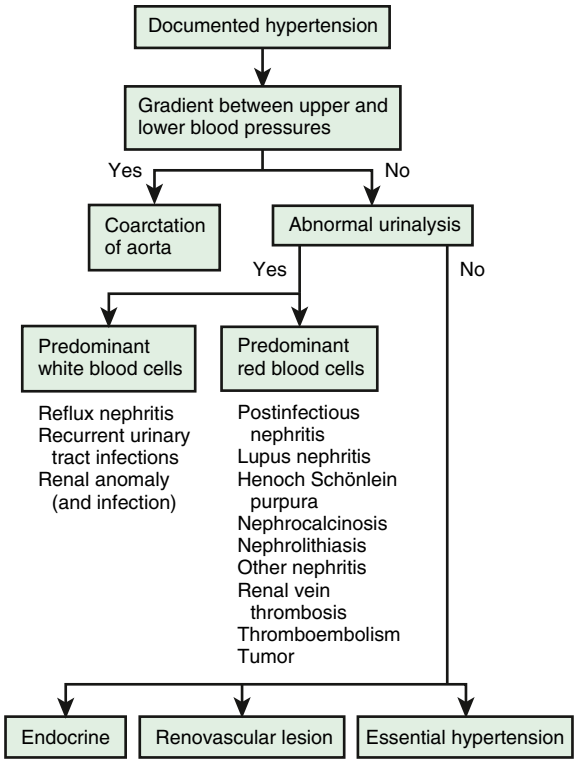

Fig. 494.2 Initial diagnostic algorithm in the evaluation of hypertension. *(From Kliegman RM, Greenbaum LA, Lye PS, eds. Practical Strategies in Pediatric Diagnosis and Therapy, 2nd ed. Philadelphia: Elsevier; 2004, p. 222.)*

DIAGNOSIS

The first step in diagnosing hypertension is recognition of elevated BP. BP readings taken in the office should be compared to normative BP tables (see 2017 AAP guidelines), indexed by height and sex, to ensure that the patient is normotensive. Multiple studies have shown substantial underrecognition of hypertension in children and adolescents, with less than half of elevated BP readings recognized, and even fewer with appropriate follow-up. This may be related to the complexity of the normative tables, although other factors such as provider experience and the presence or absence of obesity have also been shown to affect recognition of elevated BP readings. In addition to use of the simplified screening table found in the 2017 AAP guideline (see Table 494.1), this issue could also be overcome by building alerts into the electronic medical record. Elevated office BP readings should be confirmed using ABPM to identify children with white coat hypertension, who may not require further evaluation. This may require referral to an appropriate subspecialist.

Once the diagnosis of sustained hypertension is made, the evaluation should be directed toward uncovering potential underlying causes of the hypertension (Fig. 494.2), evaluating for comorbidities, and screening for evidence of target-organ damage. The extent of the evaluation for underlying causes of hypertension depends on the type of hypertension that is suspected. An extensive evaluation may be necessary when secondary hypertension is a strong consideration, such as in younger children, or in older children with severe, symptomatic hypertension. Alternatively, school-age children and adolescents with overweight/obesity and a family history of hypertension who have mild elevations of BP may only need limited testing.

In all patients, a careful **history** and **physical examination** are warranted. Birth history should be documented to screen for prematurity and other perinatal events that may affect later BP. A family history for metabolic disease, kidney disease, early cardiovascular events, and other forms of secondary hypertension should be obtained. Growth parameters should be determined to detect evidence of chronic disease. BP should be obtained in all four extremities to detect coarctation (thoracic or abdominal) of the aorta. Table 494.6 identifies other features of the physical examination that may provide evidence of an underlying cause of hypertension. Unless the history and physical examination suggest another cause, children with confirmed hypertension should have an evaluation to detect kidney disease, including urinalysis, electrolytes, blood urea nitrogen, creatinine, and complete blood count. Standard renal ultrasound should be considered in patients with a higher suspicion of secondary hypertension to assess for discrepancies in kidney size, structural abnormalities, and other potential causes of hypertension. Table 494.7 provides a more complete list of studies to consider in the clinical evaluation of a child with confirmed hypertension. Measuring serum potassium is essential because hypokalemia may be present in renovascular hypertension and many monogenic forms of hypertension (including Liddle syndrome, glucocorticoid remedial aldosteronism, and apparent mineralocorticoid excess), whereas hyperkalemia may be seen in Gordon syndrome (see Fig. 494.1). Hypokalemia may also be seen with a pheochromocytoma.

Renovascular hypertension is often associated with other diseases but may be isolated (Table 494.8). Magnetic resonance (MR) or computed tomography (CT) angiography can reveal renal artery stenosis, but formal intraarterial angiography may be needed to detect intrarenal vascular stenoses (Fig. 494.3) and in infants and young children, in whom noninvasive imaging techniques often are not helpful because of small vessel size. Doppler renal ultrasonography is of similar limited utility

Table 494.6 Physical Examination Findings in Patients with Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, upturned nose, short stature, cognitive impairment	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café-au-lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, "ash-leaf" spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep-disordered breathing
Webbed neck	Turner syndrome
CARDIOVASCULAR SIGNS	
Absent of diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure
Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia–associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
Jaundice	Alagille arteriohepatic dysplasia
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome (hypokalemic low renin hypertension)
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia (11β- or 17α-hydroxylase deficiencies)
SKELETAL	
Short metacarpal (fourth, fifth) bones, short stature	Autosomal dominant hypertension with brachydactyly (Bilginturan disease)

Table 494.7 Clinical Evaluation of Confirmed Hypertension

STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥90th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with signs of chronic kidney disease
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with signs or symptoms concerning for secondary cause of hypertension
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th to 94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs
Polysomnography	Identify sleep-disordered breathing	History of loud, frequent snoring, or daytime somnolence
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th to 94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th to 94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	All children with persistent BP ≥95th percentile
Renovascular imaging Magnetic resonance or CT angiography	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Arteriography: digital subtraction or classic		
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Patients with signs and symptoms concerning for pheochromocytoma

*Comorbid risk factors also include diabetes mellitus and kidney disease.
R/O, Rule out.
From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 Suppl 4th Report):562.

in children because of poor patient cooperation, imaging difficulties related to obesity, and operator inexperience. Doppler renal ultrasonography has a sensitivity of approximately 60–65% in patients with renovascular disease; specificity is 95%. CT angiography has a sensitivity and specificity of 88% and 81%, respectively, compared to 80% and 63% for MR angiography. *Doppler ultrasonography is not recommended when screening for renovascular hypertension in the 2017 AAP guideline except in selected patients.*

The presence of primary hypertension often clusters with other risk factors. All hypertensive children should be screened for comorbidities that may increase cardiovascular risk, including dyslipidemia and glucose intolerance. A nonfasting lipid panel is usually sufficient to screen for dyslipidemia but should be followed up by a fasting panel if abnormal. Similarly, a random fasting glucose level may be obtained initially but will need to be followed up with a fasting level if abnormal. In addition, a sleep history should be obtained in children with confirmed hypertension to screen for **sleep-disordered breathing**, an entity that is associated with high BP, particularly in overweight children. Patients with symptoms of sleep-disordered breathing should be referred to a sleep specialist for evaluation.

Left ventricular hypertrophy (LVH) is the most common manifestation of target-organ damage in hypertensive children. Left ventricular (LV) mass measurements should be indexed to height to account for the effect of body size and body surface area (BSA). LVH is defined as LV mass >51 g/m 2.7 in those 8 years of age and older, or LV mass >115 g/BSA for boys and >95 g/BSA for females <8 years of age. According to the 2017 AAP guideline, echocardiography should be obtained when treatment with antihypertensive medications is being considered.

PREVENTION

Prevention of high BP may be viewed as part of the prevention of cardiovascular disease and stroke, the leading cause of death in adults in the United States. Other risk factors for cardiovascular disease include

Table 494.8 Causes of Renovascular Hypertension in Children

Fibromuscular dysplasia
Syndromic causes
Neurofibromatosis type 1
Tuberous sclerosis
Williams syndrome
Marfan syndrome
Other syndromes
Vasculitis
Takayasu arteritis (disease)
Polyarteritis nodosa
Kawasaki disease
Other systemic vasculitides
Extrinsic compression
Neuroblastoma
Wilms tumor
Other tumors
Other causes
Radiation
Umbilical artery catheterization
Trauma
Congenital rubella syndrome
Transplant renal artery stenosis

From Tullus K, Brennan E, Hamilton G, et al. Renovascular hypertension in children. *Lancet*. 2008;371:1453–1463, Panel 1.

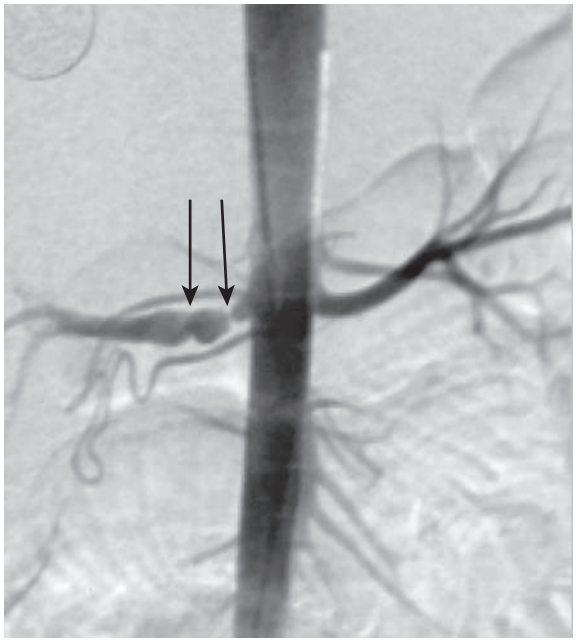

Fig. 494.3 Renal angiogram in 7-yr-old child with hypertension. Right renal artery is visible with a string-of-beads appearance characteristic of fibromuscular dysplasia *(arrows)*. The aorta and left renal artery appear normal. *(From Tullus K, Brennan E, Hamilton G, et al. Renovascular hypertension in children. Lancet. 2008;371:1453–1463, Fig 1.)*

obesity, elevated serum cholesterol levels, high dietary sodium intake, and a sedentary lifestyle, as well as alcohol and tobacco use. The increase in arterial wall rigidity and blood viscosity that is associated with exposure to the components of tobacco may exacerbate hypertension. Public health, population-based approaches to prevention of primary hypertension in both adults and children include a reduction in obesity, reduced sodium intake, avoidance of tobacco intake, and an increase in physical activity through school- and community-based programs.

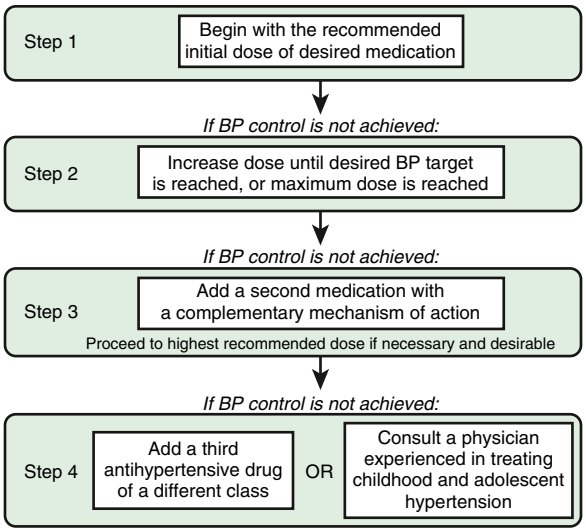

Fig. 494.4 Stepped-care approach to antihypertensive therapy in children and adolescents. BP, Blood pressure. *(From Flynn JT, Daniels SR. Pharmacologic treatment of hypertension in children and adolescents. J Pediatr. 2006;149:746–754, Fig 2.)*

TREATMENT

The mainstay of therapy for children with asymptomatic mild hypertension without evidence of target-organ damage is therapeutic **lifestyle modification** with dietary changes and regular exercise. **Weight loss** is the primary therapy in obesity-related hypertension. It is recommended that all hypertensive children have a diet increased in fresh fruits, fresh vegetables, fiber, and nonfat dairy and reduced in sodium. The **DASH** (Dietary Approaches to Stop Hypertension) diet has been suggested as a nutritional approach to prevent or treat hypertension (www.dashdiet.org). The diet focuses on lowering sodium intake and increasing potassium-, calcium-, and magnesium-containing foods, such as six to eight servings of whole grains, four to five servings of fruits, and four to five servings of vegetables per day and low-fat dairy foods. For adults, the standard DASH diet contains 2,300 mg of sodium (also recommended by the American Heart Association) and the low-sodium DASH diet recommends up to 1,500 mg of sodium per day. Studies suggest that although the DASH diet has potential beneficial effects on blood pressure, adherence to the diet remains low among adolescents. In addition, regular aerobic physical activity for at least 30-60 minutes on most days along with a reduction of sedentary activities to <2 hours a day is recommended.

Indications for **pharmacologic therapy** include symptomatic hypertension, stage 2 hypertension without a modifiable risk factor, hypertension in patients with comorbidities such as diabetes (types 1 and 2) or CKD, and persistent hypertension despite nonpharmacologic measures. When indicated, antihypertensive medication should be initiated as a single agent at a low dose (Fig. 494.4). The dose can then be increased until the goal BP is achieved. Once the highest recommended dose is reached, or if the child develops side effects, a second drug from a different class can be added.

Most classes of antihypertensive agents have been shown to reduce blood pressure in children and adolescents, although no data exist demonstrating one class to be superior. Per the 2017 AAP practice care guidelines, ACEIs, ARBs, thiazide diuretics, and calcium channel blockers are considered acceptable initial agents for use in children. The choice of antihypertensive agent for a patient should be tailored to the etiology of that patient's hypertension whenever possible. Table 494.9 gives recommended dosing information for antihypertensive agents in children and adolescents.

Table 494.9 Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

CLASS	DRUG	STARTING DOSE	INTERVAL	MAXIMUM DOSE*
Aldosterone receptor antagonist	Eplerenone	25 mg/day	qd-bid	100 mg/day
	Spironolactone†	1 mg/kg/day	qd-bid	3.3 mg/kg/day up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril†	0.2 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Captopril†	0.5 mg/kg/dose (0.05 mg/kg/dose in infants)	tid	6 mg/kg/day up to 450 mg/day
	Enalapril†	0.08 mg/kg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Lisinopril†	0.07 mg/kg/day up to 5 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5-10 mg/day	qd	80 mg/day
	Ramipril	1.6 mg/m^2/day	qd	6 mg/m^2/day up to 10 mg/day
Angiotensin receptor blockers	Candesartan	1-6 yr: 0.2 mg/kg/day 6-17 yr: <50 kg 4-8 mg qd >50 kg 8-16 mg qd	qd	1-6 yr: 0.4 mg/kg up to 4 mg/day 6-17 yr: <50 kg: 16 mg qd >50 kg: 32 mg qd
	Losartan†	0.75 mg/kg/day up to 50 mg/day	qd	1.4 mg/kg/day up to 100 mg/day
	Olmesartan	20 to <35 kg 10 mg qd; ≥35 kg 20 mg qd	qd	20 to <35 kg: 20 mg qd ≥35 kg: 40 mg qd
	Valsartan†	6-17 yr: 1.3 mg/kg/day up to 40 mg/day	qd	6-17 yr: 2.7 mg/kg/day up to 160 mg/day
α- and β-adrenergic antagonists	Labetalol†	2-3 mg/kg/day	bid	10-12 mg/kg/day up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 6.25 mg bid	bid	0.5 mg/kg/dose up to 25 mg bid
β-adrenergic antagonists	Atenolol†	0.5-1 mg/kg/day	qd-bid	2 mg/kg/day up to 100 mg/day
	Bisoprolol/HCTZ	2.5/6.25 mg/day	qd	10/6.25 mg/day
	Metoprolol	1-2 mg/kg/day	bid	6 mg/kg/day up to 200 mg/day
	Propranolol	1 mg/kg/day	bid-tid	8 mg/kg/day up to 640 mg/day
Calcium channel blockers	Amlodipine†	1-5 yr: 0.1 mg/kg/day ≥6 yr: 2.5 mg/day	qd	1-5 yr: 0.6 mg/kg/day up to 5 mg/day ≥6 yr: 10 mg/day
	Felodipine	2.5 mg/day	qd	10 mg/day
	Isradipine†	0.05-0.15 mg/kg/dose	tid-qid	0.6 mg/kg/day up to 10 mg/day
	Extended-release nifedipine	0.2-0.5 mg/kg/day	qd-bid	3 mg/kg/day up to 120 mg/day
Central α-agonist	Clonidine†	5-10 μg/kg/day	bid-tid	25 μg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5-10 mg/day	qd	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	qd	2 mg/kg/day up to 50 mg/day
	Chlorothiazide	10 mg/kg/day	bid	20 mg/kg/day up to 375 mg/day
	Furosemide	0.5-2.0 mg/kg/dose	qd-bid	6 mg/kg/day
	HCTZ	0.5-1 mg/kg/day	qd	3 mg/kg/day up to 37.5 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	tid-qid	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.1-0.2 mg/kg/day	bid-tid	1 mg/kg/day up to 50 mg/day

*The maximum recommended adult dose should never be exceeded.
†Information on preparation of a stable extemporaneous suspension is available for these agents.
bid, Twice daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.
Adapted from Flynn JT. Management of hypertension in the young: role of antihypertensive medications. *J Cardiovasc Pharmacol*. 2011;58(2):111–120.

There have been changes in the recommended BP goals for the treatment of hypertension in children and adolescents. Data from the SPRINT (SBP intervention) trial group suggests that stricter goals (SBP goal of 120 vs 140 mm Hg) improve cardiovascular outcomes in adults. In children with CKD, the ESCAPE (Effects of Strict BP Control and Angiotensin-Converting Enzyme Inhibition on the Progress of Chronic Renal Failure in Pediatric Patients) trial group showed slower progression of CKD if the 24-hour MAP was kept below the 50th percentile on ABPM compared to the 50th to 95th percentile. It is now recommended that treatment achieve BP <90th percentile for age or <130/80 mm Hg, whichever is lower. A lower goal based on ABPM (24-hour MAP <50th percentile) is recommended for children and adolescents with CKD. ACEIs or ARBs should be used for children with diabetes and microalbuminuria or proteinuric kidney disease.

Acute severe hypertension, sometimes referred to as *accelerated hypertension* or *hypertensive crisis*, is defined as severe hypertension (often with BP values well in excess of stage 2 hypertension) accompanied by symptoms such as headache, dizziness, or nausea/

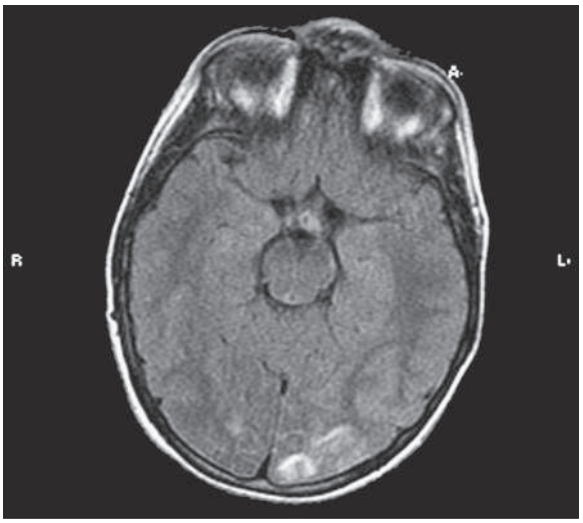

Fig. 494.5 MRI of the brain of a 6-yr-old child with end-stage kidney disease and hypertensive encephalopathy (i.e., posterior reversible leukoencephalopathy syndrome). Bilateral occipital high signal intensity is more pronounced on the left side. *(From Daroff RB, Fenichel GM, Jankovic J, et al., eds. Bradley's Neurology in Clinical Practice, 6th ed. Philadelphia: Saunders; 2012: Fig. 49B.4, p. 924.)*

vomiting, and in more severe cases, retinopathy, encephalopathy, cardiac failure, acute kidney injury, and seizures. These situations have also been described as *hypertensive urgency* and *hypertensive emergency,* respectively. This nomenclature can lead to confusion because there is often no absolute distinction between the two situations, and treatment will often depend on clinical judgment. *Hypertensive encephalopathy* (generalized or posterior reversible encephalopathy syndrome) is suggested by the presence of headache, vomiting, temperature elevation, visual disturbances, ataxia, depressed level of consciousness, imaging abnormalities, and seizures (Fig. 494.5); it is one of the more common presentations of acute severe hypertension in children and adolescents. Acute severe hypertension may also manifest with decreased vision (cortical blindness) and papilledema, congestive heart failure, or accelerated deterioration of kidney function.

For patients with acute severe hypertension and life-threatening symptoms, intensive care unit (ICU) admission and intravenous (IV) drug infusion are indicated so that decreases in BP can be carefully monitored and titrated (Table 494.10). Ideally, arterial lines should be used for continuous BP monitoring; if this is not available, oscillometric devices can be used for frequent/repeated BP measurement. Drug choices include labetalol, nicardipine, and sodium nitroprusside. Because too rapid a reduction in BP may interfere with adequate organ perfusion, a stepwise reduction in pressure should be planned. In general, BP should be reduced by

Table 494.10 Antihypertensive Drugs for Management of Severe Hypertension in Children Age 1-17 Years

DRUG	CLASS	DOSE	ROUTE	COMMENTS
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LIFE-THREATENING SYMPTOMS				
Esmolol	β-Adrenergic blocker	100-500 μg/kg/min	IV infusion	Very short acting—constant infusion preferred; may cause profound bradycardia
Hydralazine	Direct vasodilator	0.2-0.4 mg/kg/dose	IV, IM	Should be given every 4 hr when given IV bolus
Labetalol	α- and β-Adrenergic blocker	Bolus: 0.20-1.0 mg/kg/dose, up to 40 mg/dose Infusion: 0.25-3.0 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications
Nicardipine	Calcium channel blocker	Bolus: 30 μg/kg up to 2 mg/dose Infusion: 0.5-4 μg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Sodium nitroprusside	Direct vasodilator	0.5-10 μg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure or coadminister with sodium thiosulfate
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LESS SIGNIFICANT SYMPTOMS				
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Fenoldopam	Dopamine receptor agonist	0.2-0.8 μg/kg/min	IV infusion	Produced modest reductions in blood pressure in a pediatric clinical trial in patients up to age 12 yr
Hydralazine	Direct vasodilator	0.25 mg/kg/dose, up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05-0.15 mg/kg/dose, up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1-0.2 mg/kg/dose, up to 10 mg/dose	PO	Most potent oral vasodilator; long acting

IM, intramuscular; IV, intravenous; PO, oral.
Adapted from Flynn JT, Tullus K. Correction to severe hypertension in children and adolescents: pathophysiology and treatment. *Pediatr Nephrol.* 2012;27(3):503–504.

no more than 25% of the planned reduction over the first 8 hours, with a gradual normalization of BPs over the next 24-48 hours. For patients with less severe symptoms, such as headache or nausea/vomiting, oral medications such as clonidine or isradipine can be used if the patient can tolerate oral medications. Short-acting IV medications such as hydralazine or labetalol are acceptable if the patient cannot take oral drugs.

Treatment of secondary hypertension must also focus on the underlying disease, such as CKD, hyperthyroidism, pheochromocytoma, coarctation of the aorta, or renovascular hypertension. The treatment of renovascular hypertension includes antihypertensive medications, angioplasty, or surgery. If bilateral renovascular hypertension or renovascular disease in a solitary kidney is suspected, drugs acting on the RAAS are usually contraindicated because they may reduce glomerular filtration rate and lead to acute kidney injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Diseases of the Blood

PART XIX

Section 1

The Hematopoietic System

Chapter 495

Development of the Hematopoietic System

Stella T. Chou

HEMATOPOIESIS IN THE HUMAN EMBRYO AND FETUS

Hematopoiesis is the process by which the cellular elements of blood are formed. In the developing human embryo and fetus, hematopoiesis has three developmental waves and is conceptually divided into three anatomic stages: mesoblastic, hepatic, and myeloid. *Mesoblastic* hematopoiesis occurs in extraembryonic structures, principally in the yolk sac, and begins between the 10th and 14th days of gestation. By 6-8 weeks of gestation, the liver replaces the yolk sac as the primary site of blood cell production, and during this time, the placenta also contributes as a hematopoietic site. By 10-12 weeks, extraembryonic hematopoiesis has ceased. *Hepatic* hematopoiesis occurs through the remainder of gestation and then diminishes during the second trimester while bone marrow *(myeloid)* hematopoiesis increases. The liver is the predominant erythropoietic organ through 20-24 weeks of gestation.

Each hematopoietic organ houses distinct populations of cells. The yolk sac predominantly produces erythrocytes, megakaryocytes, and macrophages. The fetal liver is primarily an erythropoietic organ, while the bone marrow produces erythrocytes, megakaryocytes, and leukocytes. The types of leukocytes present in the fetal liver and marrow differ with gestation. Macrophages precede neutrophils in the marrow, and the ratio of macrophages to neutrophils decreases as gestation progresses. Regardless of gestational age or anatomic location, production of all hematopoietic tissues begins with multipotent cells capable of both self-renewal and clonal maturation into all blood cell lineages. Progenitor cells differentiate under the influence of transcription factors and hematopoietic growth factors.

The classical model of hematopoietic differentiation involves differentiation into increasingly lineage-specific progenitors, although there may also be alternate pathways that are used separately or in combination with classical pathways (Fig. 495.1). In the classical pathway, *long-term repopulating hematopoietic stem cells* (LTR-HSCs) are characterized by their ability to self-renew and differentiate into cells that are multipotent. *Multipotent progenitors* (MPPs) have reduced self-renewal capacity and differentiate into *common lymphoid progenitors* (CLPs) or *common myeloid progenitors* (CMPs). The CMP differentiates into all the blood lineages except for lymphoid. The commitment of hematopoietic cells to increasingly lineage-restricted cells requires cytokine stimulation and regulation by transcription factors.

Erythrocytes in the fetus are larger than in adults, and at 22-23 weeks' gestation, the mean corpuscular volume can be as high as 135 femtoliters (fL) (Fig. 495.2A). Similarly, the mean corpuscular hemoglobin is very high at 22-23 weeks and falls relatively linearly with advancing gestation (see Fig. 495.2B). In contrast, the mean corpuscular hemoglobin concentration is constant throughout gestation at 34 ±1 g/dL. While the size and quantity of hemoglobin in erythrocytes diminish during gestation, the hematocrit and blood hemoglobin concentration gradually increase (Fig. 495.3).

Platelet concentration in the blood increases gradually between 22 and 40 weeks' gestation (Fig. 495.4), but the platelet size, assessed by mean platelet volume, remains constant at 8 ±1 fL. No differences are observed between males and females in fetal and neonatal reference ranges for erythrocyte indices, hematocrit, hemoglobin, platelet counts, or mean platelet volume measurements.

FETAL GRANULOCYTOPOIESIS

Neutrophils are first observed in the human fetus about 5 weeks after conception as small clusters of cells around the aorta. The fetal bone marrow space begins to develop around the eighth week, and from 8-10 weeks, the marrow space enlarges, but no neutrophils appear there until 10.5 weeks. From 14 weeks through term, the most common granulocytic cell type in the fetal bone marrow space is the neutrophil. Neutrophils and macrophages originate from a common progenitor cell, but macrophages appear before neutrophils in the fetus, first in the yolk sac, liver, lung, and brain, all before the bone marrow cavity is formed.

Granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) are expressed in developing fetal bone as early as 6 weeks after conception, and both are expressed in the fetal liver as early as 8 weeks. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and stem cell factor (SCF) also are distributed widely in human fetal tissues. However, no changes in expression of any of these factors, or of their specific receptors, appear to be the signal for fetal production of neutrophils or macrophages.

Fetal blood contains few neutrophils until the third trimester. At 20 weeks' gestation, the blood neutrophil count is 0-500/mm^3. Although mature neutrophils are scarce, progenitor cells with the capacity to generate neutrophil clones are abundant in fetal blood. When cultured in vitro in the presence of recombinant G-CSF, they mature into large colonies of neutrophils. The physiologic role of G-CSF includes upregulating neutrophil production, and the low number of circulating neutrophils in the mid-trimester human fetus may be caused, in part, by low production of G-CSF. Monocytes isolated from the blood of adults produce G-CSF when stimulated with a variety of inflammatory mediators, such as bacterial lipopolysaccharide (LPS) or interleukin (IL)-1. In contrast, monocytes isolated from the blood or organs of fetuses up to 24 weeks' gestation generate only small quantities of G-CSF protein and messenger RNA (mRNA) after LPS or IL-1 stimulation. Despite this, G-CSF receptors on the surface of neutrophils of newborn infants are equal in number and affinity to those on adult neutrophils.

In the fetus, actions of the granulocytic factors (G-CSF, M-CSF, GM-CSF, and SCF) are not limited to hematopoiesis. Receptors for each of

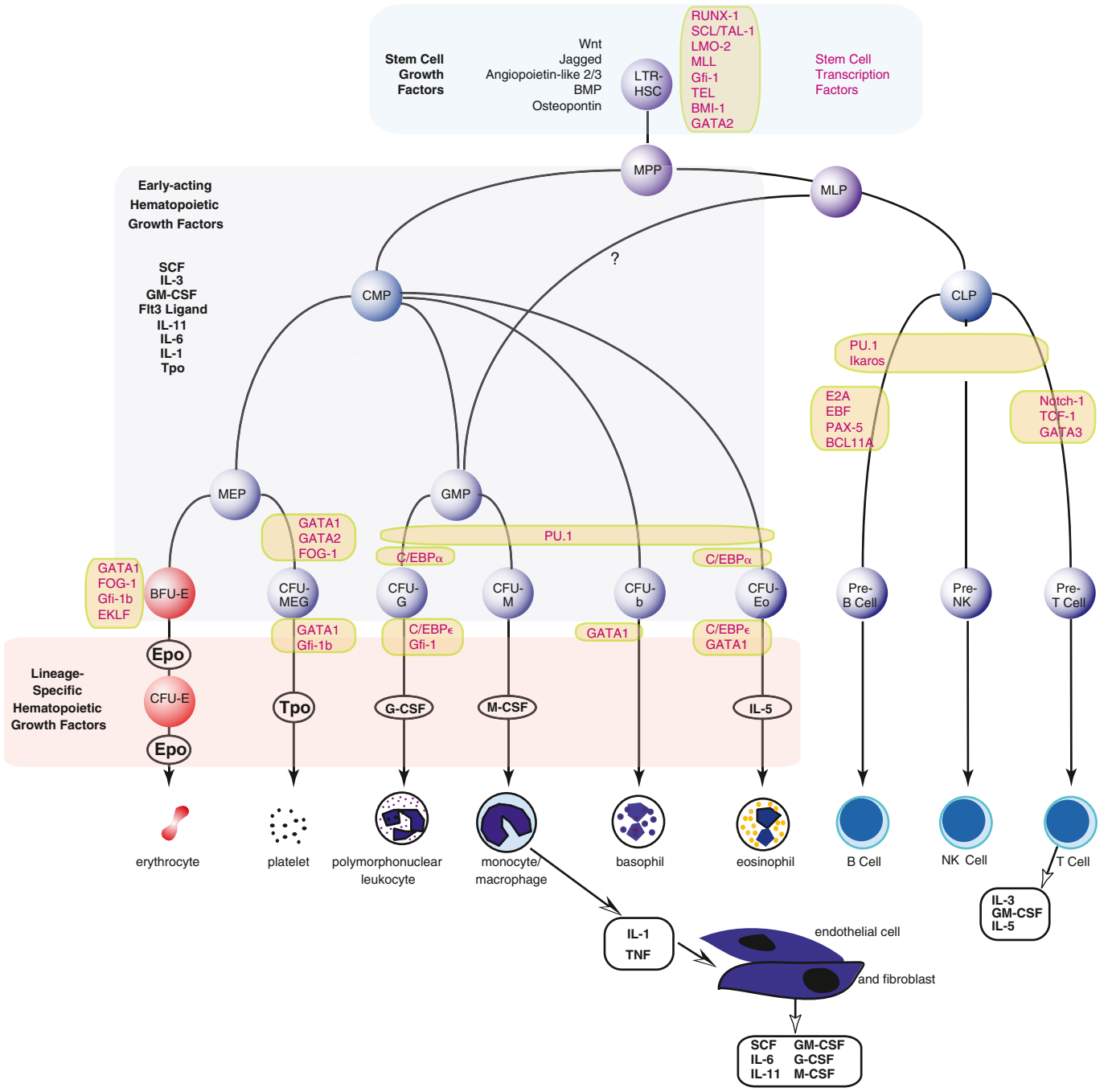

Fig. 495.1 Major cytokine sources and actions to promote hematopoiesis. Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblasts, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) after stimulation. These cytokines and others listed in the text have overlapping interactions during hematopoietic differentiation, as indicated; for all lineages, optimal development requires a combination of early- and late-acting factors. BFU, Burst-forming unit; BMP, bone morphogenic protein; CFU, colony-forming unit; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; Epo, erythropoietin; GMP, granulocyte-monocyte progenitor; IL, interleukin; LTR-HSC, long-term repopulating-hematopoietic stem cell; MEP, megakaryocyte-erythroid progenitor; MLP, multipotent lymphoid progenitor; MPP, multipotent progenitor; SCF, stem cell factor; TNF, tumor necrosis factor; Tpo, thrombopoietin. *(From Sieff CA, Daley GO, Zon LI. The anatomy and physiology of hematopoiesis. In Orkin SH, Fisher DE, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood, 8th ed. Philadelphia: Elsevier, 2015.)*

these are located in areas of the fetal central nervous system and gastrointestinal tract, where their patterns of expression change with development.

FETAL THROMBOPOIESIS

Several biologic differences exist between fetal, neonatal, and adult megakaryopoiesis and thrombopoiesis. There is a developmentally unique pattern of fetal/neonatal megakaryopoiesis characterized by rapid proliferation, followed by full cytoplasmic maturation without polyploidization. Fetal and neonatal megakaryocytes are significantly smaller, exhibit lower ploidy, and produce fewer platelets. However, fetal and neonatal megakaryocytes have a higher proliferative potential than adult progenitors. These differences allow fetuses and neonates to populate their rapidly expanding bone marrow space and blood volume while maintaining normal platelet counts.

Megakaryocyte progenitors are categorized as *burst-forming unit–megakaryocytes* (BFU-MK), which are primitive megakaryocyte

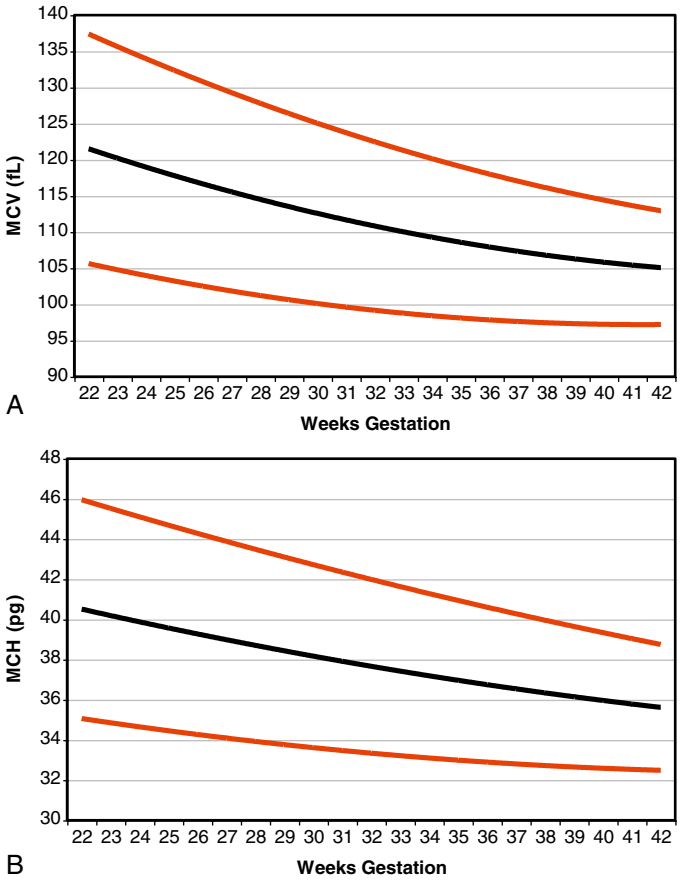

Fig. 495.2 A, Erythrocyte mean corpuscular volume (MCV), and B, mean corpuscular hemoglobin (MCH) from 22 weeks' gestation through term. The *lines* represent the 5th percentile, the mean, and the 95th percentile reference range. *(From Christensen RD, Jopling J, Henry E, et al. The erythrocyte indices of neonates, defined using data from over 12,000 patients in a multihospital healthcare system. J Perinatol 2008;28:24–28.)*

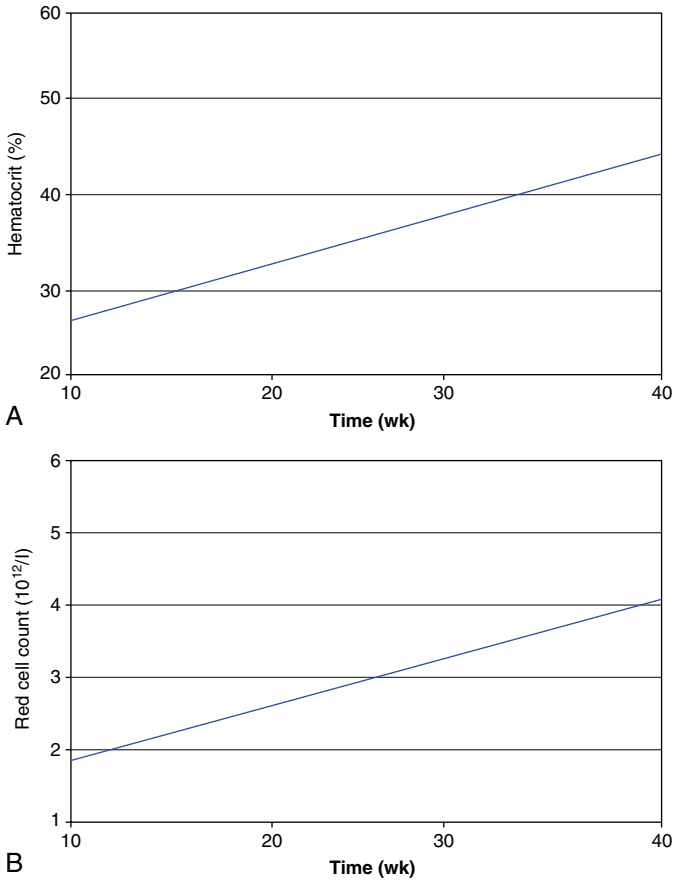

Fig. 495.3 Reference ranges of fetal hematocrit (A) and fetal red blood cell count (B) by cordocentesis throughout gestations.

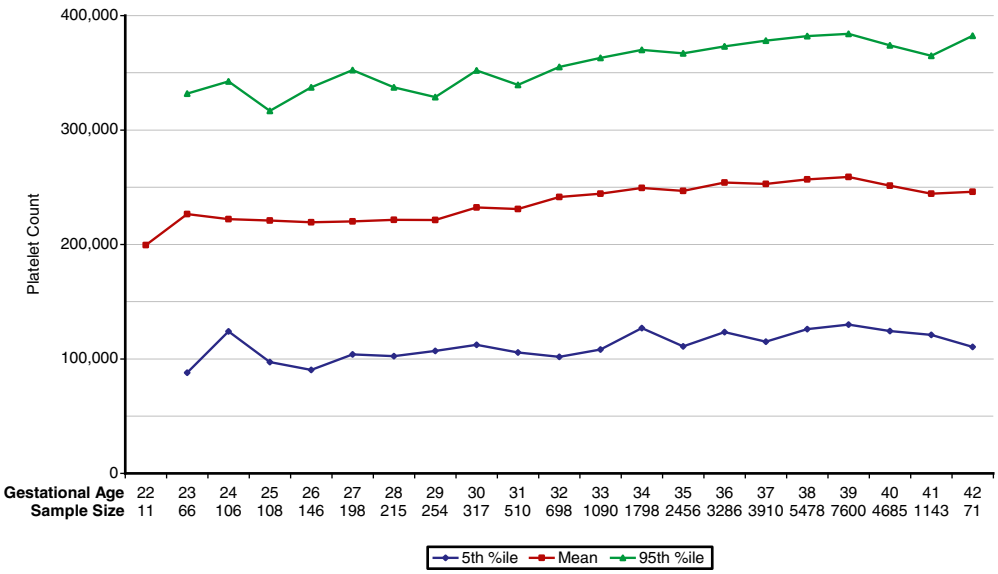

Fig. 495.4 Platelet count from 22 weeks' gestation through term. The *lines* represent the 5th percentile, the mean, and the 95th percentile reference range. *(From Wiedmeier SE, Henry E, Sola-Visner MC, et al. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. J Perinatol 2009;29:130–136.)*

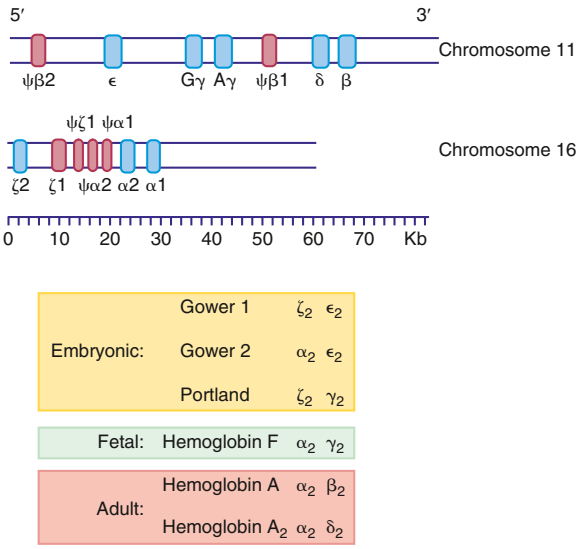

Fig. 495.5 Organization of the globin genes. The *bottom line* reflects the scale in kilobases. The *upper segment* represents the β-like globin genes on chromosome 11, and the *lower segment* the α-like genes on chromosome 16. Regions of the gene that code for primary globin proteins are shown as *blue segments*, and regions that code for pseudogenes ("ψ," nonexpressed remnants) are shown as *pink segments*. The composition of embryonic, fetal, and adult hemoglobins is listed. α, Alpha; β, beta; γ, gamma; δ, delta; ε, epsilon; ζ, zeta.

progenitors, and *colony-forming unit–megakaryocytes* (CFU-MK), which are more differentiated. BFU-MK produce large multifocal colonies containing ≥50 megakaryocytes, whereas CFU-MK generate smaller (3-50 cells/colony) unifocal colonies. Megakaryocytes are identified by their morphologic characteristics as they undergo endoreduplication, which results in large cells with polyploid nuclei. Megakaryocytes, unlike megakaryocyte progenitors, do not have the capacity to generate colonies. Rather, they undergo maturation, progressing from small mononuclear cells to large polyploid cells. The modal megakaryocyte *ploidy* (the number of sets of complete chromosomes) in normal adult marrow is 16N. In the fetus and neonate, ploidy is lower, primarily 2N and 4N, and mature megakaryocyte size is smaller. Large megakaryocytes generate more platelets than do small megakaryocytes; in vitro studies suggest that megakaryocytes of neonates produce fewer platelets than do their adult counterparts.

The exact mechanisms by which megakaryocytes release platelets into the circulation remain incompletely understood. In situ examination of this process suggests that mature megakaryocytes migrate to a perivascular site and extend a process through the endothelium, giving rise to proplatelets, which then release platelets. An alternate mechanism is that platelets are released from megakaryocytes in the lungs as a result of shear forces.

Thrombopoietin (TPO) is the dominant regulator of megakaryocyte development and platelet production. TPO is predominantly produced in the liver from early fetal to adult life but is also expressed by cells in the kidney, and, to a lesser extent, by smooth muscle and marrow cells. TPO concentrations are higher in healthy neonates of any gestational age than in healthy adults. TPO is a primary stimulator of megakaryocyte and platelet production, but SCF, IL-3, IL-11, IL-6, and erythropoietin also stimulate megakaryopoiesis and thrombopoiesis in vitro and in vivo. Importantly, TPO promotes expansion of hematopoietic stem cells (HSCs) and progenitor cells, and the TPO receptor is expressed on HSCs and erythroid progenitors in addition to megakaryocyte progenitors, megakaryocytes, and mature platelets.

FETAL ERYTHROPOIESIS

Similar to hematopoietic production of other cell lineages, fetal erythropoiesis is regulated by growth factors produced by the fetus, not by the mother. Erythropoietin (EPO) does not cross the human placenta. Stimulating maternal EPO production does not enhance fetal erythropoiesis, nor does suppressing maternal erythropoiesis by hypertransfusion.

EPO plays a central regulatory role on the proliferation and maturation of erythroid progenitors. Erythroid-committed progenitors consist of *burst-forming unit–erythroid* (BFU-E) and *colony-forming unit–erythroid* (CFU-E) cells. In colony-forming assays, human BFU-E cells are more proliferative, forming colonies of multiple clusters of erythroblasts, as compared with CFU-E cells, which form one or two clusters, with each containing 8-100 hemoglobinized erythroblasts. EPO is essential for erythrocyte production from CFU-E cells by inducing survival and proliferation of erythroblasts. EPO binds to specific receptors on the surface of committed erythroid precursors, and its expression is regulated by an oxygen-sensing mechanism through the hypoxia-inducible factor (HIF) family of proteins. HIF-1α and HIF-2α are regulated by oxygen tension, whereas HIF-1β is constitutively expressed. Together, HIF proteins maintain oxygen homeostasis and regulate erythropoiesis by inducing EPO under hypoxic conditions.

EPO is produced by monocytes and macrophages in the fetal liver during the first and second trimesters. After birth, the anatomic site of EPO production shifts to the kidney. The specific stimulus for this shift is unknown but may involve the increase in arterial oxygen tension that occurs at birth. Epigenetic modification of gene expression may also play a role because it appears that renal and hepatic EPO genes are methylated to different degrees. Although EPO mRNA and protein can be found in the human fetal kidney, it is not known whether this production is biologically relevant. It appears that renal production of EPO is not essential for normal fetal erythropoiesis, as evidenced by the normal serum EPO concentration and normal hematocrit of anephric fetuses.

Hemoglobins in the Fetus and Neonate

Hemoglobin is a tetramer of four *globin* chains with an iron-containing porphyrin ring called *heme* covalently bound to each chain. A dynamic interaction between heme and globin gives hemoglobin its unique properties in the reversible transport of oxygen. The hemoglobin molecule consists of two alpha (α)-like and two beta (β)-like polypeptide chains, with each chain having a heme group attached (Fig. 495.5). There are two β-globin genes and four α-globin genes. Within erythrocytes of an early embryo, fetus, child, and adult, six different hemoglobins may normally be detected (Fig. 495.6): the **embryonic** hemoglobins (Gower-1, Gower-2, and Portland), **fetal** hemoglobin (HbF), and the **adult** hemoglobins (HbA and HbA_2). The electrophoretic mobilities of hemoglobins vary with their chemical structures.

Expression and quantitative relationships among the hemoglobins are determined by complex developmental processes. Globin chain expression is developmental stage specific and occurs through two hemoglobin switches, mediated primarily through changes of the β-globin genes expressed. There are five functional β-like globin chain genes: embryonic *(HBE1)*, two fetal *(HBG1, HBG2)*, and two adult *(HBD, HBB)*; and three α-like globin chain genes: embryonic *(HBZ)* and two adult *(HBA1, HBA2)*. Primitive erythroid cells primarily express embryonic globins. The first β-globin switch occurs at approximately 6 weeks' gestation to fetal globin *(HBG)*, which coincides with the onset of definitive hematopoiesis. The major hemoglobin in the fetus (HbF) consists of two α and two gamma (γ) globin chains ($\alpha_2\gamma_2$). The second globin switch is responsible for the expression of the major hemoglobin of adults (HbA), consisting of two α and two β polypeptide chains ($\alpha_2\beta_2$) and is first expressed at mid-gestation. A key regulator of the fetal-to-adult hemoglobin switch is the transcription factor **BCL11A**, which binds to the β-globin gene and acts to silence γ-globin expression and thus HbF.

Embryonic Hemoglobins

The blood of early human embryos contains two slowly migrating hemoglobins, *Gower-1* and *Gower-2,* and *Hb Portland,* which has HbF-like mobility. The zeta (ζ) chains of Hb Portland and Gower-1 are structurally quite similar to α chains. Both Gower hemoglobins contain the epsilon (ε) β-like globin polypeptide chain. Hb Gower-1 has the structure $\zeta_2\varepsilon_2$, whereas Gower-2 has $\alpha_2\varepsilon_2$. Hb Portland has the structure $\zeta_2\gamma_2$. In embryos up to 6 weeks' gestation, the Gower hemoglobins predominate but are no longer detectable by 3 months of gestation.

Fetal Hemoglobin

By 6-8 weeks' gestation, HbF ($\alpha_2\gamma_2$) is the predominant hemoglobin; at 24 weeks' gestation, it constitutes 90% of the total hemoglobin. HbF

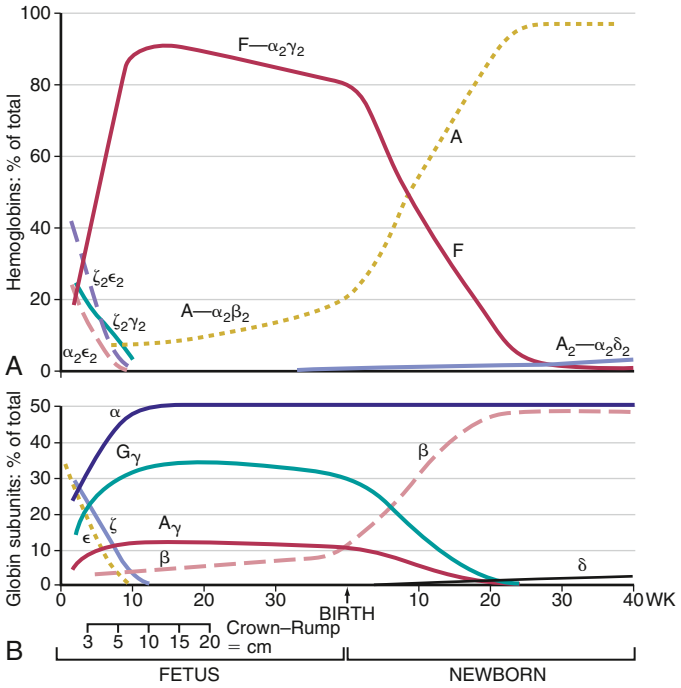

Fig. 495.6 Changes in hemoglobin tetramers (**A**) and in globin subunits (**B**) during human development from embryo to early infancy. *(From Polin RA, Fox WW. Fetal and Neonatal Physiology, 2nd ed. Philadelphia: Saunders, 1998: p. 1769.)*

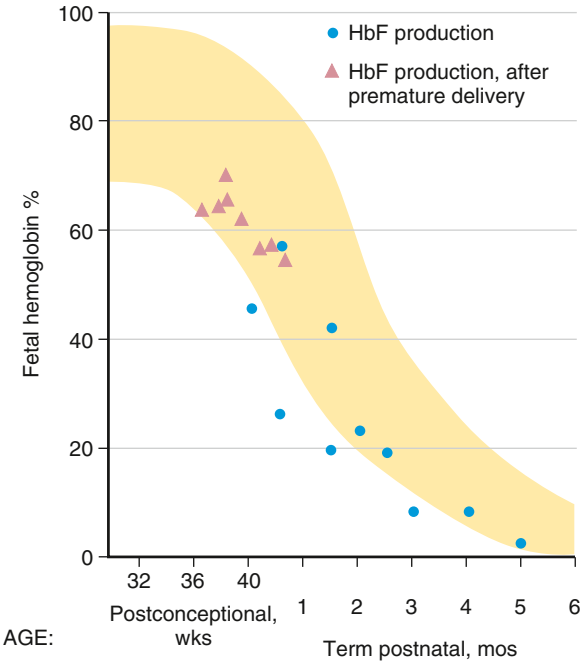

Fig. 495.7 Pre- and postnatal changes in the percentage of total hemoglobin represented by fetal hemoglobin (HbF) *(yellow)*. The *triangles* represent postnatal production by reticulocytes in premature infants, and the *circles* represent cord blood and postnatal reticulocyte production in term infants. *(From Brown MS. Fetal and neonatal erythropoiesis. In: Stockman JA, Pochedly C eds. Developmental and Neonatal Hematology. New York: Raven Press, 1988.)*

declines modestly in the third trimester, such that the HbF comprises 70–80% of the total hemoglobin. HbF production decreases rapidly postnatally (Fig. 495.7), and by 6-12 months of age declines to adult concentrations of <2%. Understanding the molecular basis of the fetal-to-adult hemoglobin switch is of interest because of the therapeutic benefits to patients with β-thalassemia and sickle cell disease, whose clinical severity is improved with modest elevation of HbF. The exact mechanisms by which BCL11A acts to repress HbF are not fully elucidated, but erythroid-specific enhancers of BCL11A have been identified and are potential targets for therapeutic HbF induction.

Adult Hemoglobins

HbA constitutes 5–10% of total hemoglobin at 24 weeks' gestation and steadily increases, so that at term, HbA averages 30% of total hemoglobin. By 6-12 months of age, individuals reach adult concentrations of HbA. The minor adult hemoglobin component, HbA_2, contains delta (δ) chains and has the structure $\alpha_2\delta_2$. At birth, <1.0% of HbA_2 is detected, but by 12 months of age the normal level is 2.0–3.4%. Throughout life, the normal ratio of HbA to HbA_2 is approximately 30:1.

Alterations of Hemoglobins

HbF levels may be elevated with hemoglobinopathies, hereditary persistence of HbF, or bone marrow failure syndromes or may be associated with stress erythropoiesis. Because the HbF level is elevated during the first years of life, knowledge of its normal pattern of decline is important (see Figs. 495.6 and 495.7). Two disorders resulting from pathogenic variants in the β-globin gene (HBB), β-thalassemia and sickle cell disease, become symptomatic postnatally as fetal γ-globin expression decreases and adult β-globin increases. In both these disorders, elevated HbF levels persist in childhood and later. In patients with the most severe type, β^0 thalassemia, except for a small amount of HbA_2, HbF is the only hemoglobin produced. At the other end of the spectrum, in individuals with β-thalassemia trait, the postnatal decrease of HbF is delayed and mildly elevated levels of HbF (>2%) may persist throughout life. Individuals with sickle cell disease, who also have a pathogenic variant in the *HBB* gene, typically demonstrate elevated levels of HbF, ranging from approximately 5% to up to 30%. In contrast, elevated HbF is not characteristic of α-thalassemia syndromes, but tetramers of γ chains (γ_4 or Hb Barts) may be found in the neonatal period. Because α-globin chains are expressed in fetal and adult hemoglobin, four α gene pathogenic variants leading to functional deletions are not compatible with life. Fetuses die in utero or shortly after birth from the severe anemia and hydrops fetalis. Inheritance of only one normal gene of the four (α –/–) results in **hemoglobin H disease**, which is usually associated with a moderate anemia. Inheritance of two or three normal α genes results in α-**thalassemia** trait or carrier status, respectively.

Hereditary persistence of HbF (HPFH) is a benign genetic condition caused by heterozygous deletions or nucleotide substitutions in regions of the β-globin locus that regulate transcription of *HBG1* and *HBG2*, causing persistent pancellular HbF expression levels of approximately 30% of total hemoglobins. Individuals with HPFH do not exhibit anemia.

Preterm infants treated with human recombinant EPO increase HbF production during active erythropoiesis. Moderate elevations of HbF may also occur in many diseases accompanied by hematologic stress, such as hemolytic anemias, leukemia, and bone marrow failure syndromes, such as Diamond Blackfan anemia.

The normal adult level of HbA_2 (2.0–3.4%) is seldom altered. Levels of HbA_2 > 3.4% are found in most persons with the β-thalassemia trait and in those with megaloblastic anemias secondary to vitamin B_{12} and folic acid deficiency. Decreased HbA_2 levels are found in those with iron-deficiency anemia (see Chapter 504) and α-thalassemia (see Chapter 511.10).

RED CELL LIFE SPAN IN THE FETUS AND NEONATE

In general, the highest hematocrit during a person's lifetime occurs at birth, and the lowest hematocrit occurs at the physiologic nadir that occurs 8-10 weeks postnatally. A shortened life span of fetal and neonatal red blood cells (RBCs) has been suggested as an important component. The average erythrocyte life span in normal adults is approximately 120 days. The life span of fetal/neonatal **erythrocytes** was once estimated to be considerably less, with an average of 60-90 days suggested by chromium (^{51}Cr)-labeled erythrocyte studies. However, newer studies indicate that the life span of fetal/neonatal RBCs is similar to that of adults. Neocytolysis is the active removal of young **erythrocytes** that were generated in relatively hypoxic conditions, after normoxic or hyperoxic conditions. This process has also been suggested as an explanation for the physiologic nadir of neonates.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 496

Anemias

Courtney D. Thornburg

Anemia is defined as a reduction of the hemoglobin concentration or red blood cell (RBC) volume below the range of values occurring in healthy persons. Normal ranges for hemoglobin and hematocrit (packed red cell volume) vary substantially with age and between males and females (Table 496.1) and by race and ethnicity (Table 496.2). Anemia is a significant global health problem affecting children and reproductive-age females (Figs. 496.1 and 496.2).

Physiologic responses to anemia include increased cardiac output, augmented oxygen extraction (increased arteriovenous oxygen difference), and shunting of blood flow toward vital organs and tissues. In addition, the concentration of 2,3-diphosphoglycerate increases within the RBC. The resultant "rightward shift" of the oxygen dissociation curve reduces the affinity of hemoglobin for oxygen and results in more complete transfer of oxygen to the tissues. This same shift in the oxygen dissociation curve can also occur at high altitude. Higher levels of erythropoietin (EPO) and consequent increased RBC production by the bone marrow further help the body to adapt.

HISTORY AND PHYSICAL EXAMINATION

A detailed history and thorough physical exam are essential when evaluating an anemic child. Important historical facts include demographics, diet, medications, chronic diseases, infections, travel, and exposures. A family history of anemia and associated difficulties (e.g., splenomegaly, jaundice, early-age onset of gallstones) is also important. Often, few physical symptoms or signs result solely from a low hemoglobin, particularly when the anemia develops slowly. Clinical findings generally do not become apparent until the hemoglobin level falls to <7-8 g/dL. Clinical features can include pallor, sleepiness, irritability, and decreased exercise tolerance. Pallor can involve the tongue, nail beds, conjunctiva, palms, or palmar creases. A flow murmur is often present. Ultimately, weakness, tachypnea, shortness of breath on exertion, tachycardia, cardiac dilation, and high-output heart failure results from increasingly severe anemia, regardless of its cause. Unusual physical findings linked to specific underlying disease etiologies are discussed in detail in sections describing the associated disorders and in Table 496.3.

Table 496.1 Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume

	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MEAN CORPUSCULAR VOLUME (fL)	
AGE (yr)	MEAN	LOWER LIMIT	MEAN	LOWER LIMIT	MEAN	LOWER LIMIT
0.5-1.9	12.5	11.0	37	33	77	70
2-4	12.5	11.0	38	34	79	73
5-7	13.0	11.5	39	35	81	75
8-11	13.5	12.0	40	36	83	76
12-14 female	13.5	12.0	41	36	85	78
12-14 male	14.0	12.5	43	37	84	77
15-17 female	14.0	12.0	41	36	87	79
15-17 male	15.0	13.0	46	38	86	78
18-49 female	14.0	12.0	42	37	90	80
18-49 male	16.0	14.0	47	40	90	80

From Brugnara C, Oski FJ, Nathan DG, eds. *Nathan and Oski's Hematology of Infancy and Childhood*, 7th ed. Philadelphia: Saunders, 2009: p. 456.

Table 496.2 NHANES-III Hemoglobin Values for Non-Hispanic Whites and Blacks Ages 2-18 Yr*

	WHITE NON-HISPANIC		BLACK	
AGE (yr)	MEAN	−2 SD	MEAN	−2 SD
2-5	12.21	10.8	11.95	10.37
6-10	12.87	11.31	12.40	10.74
11-15 male	13.76	11.76	13.06	10.88
11-15 female	13.32	11.5	12.61	10.85
16-18 male	15.00	13.24	14.18	12.42
16-18 female	13.39	11.61	12.37	10.37

*Sample size is 5,142 (White, 2,264; Black, 2,878).
NHANES-III, Third National Health and Nutrition Examination Survey; SD, standard deviation.
Adapted from Robbins EB, Blum S. Hematologic reference values for African American children and adolescents. *Am J Hematol* 2007;82:611–614.

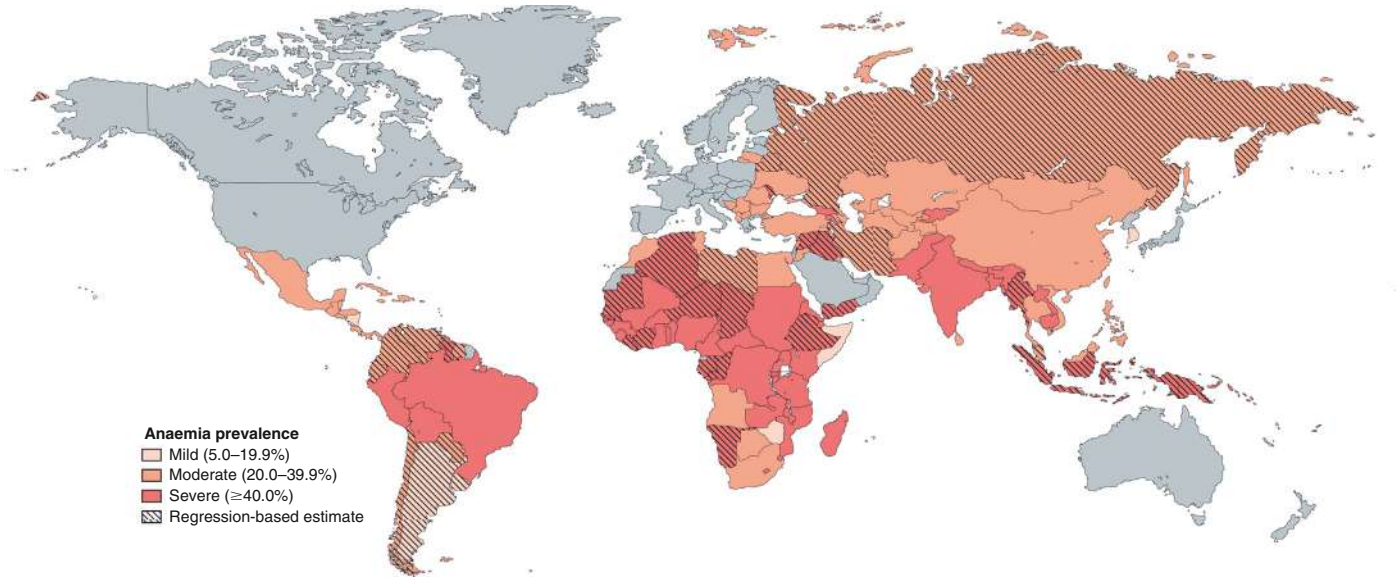

Fig. 496.1 Global prevalence of anemia in children of preschool age (0-5 yr). *(Adapted from Worldwide prevalence of anaemia 1993–2005. In WHO Global Database on Anaemia. Geneva: World Health Organization, 2008.)*

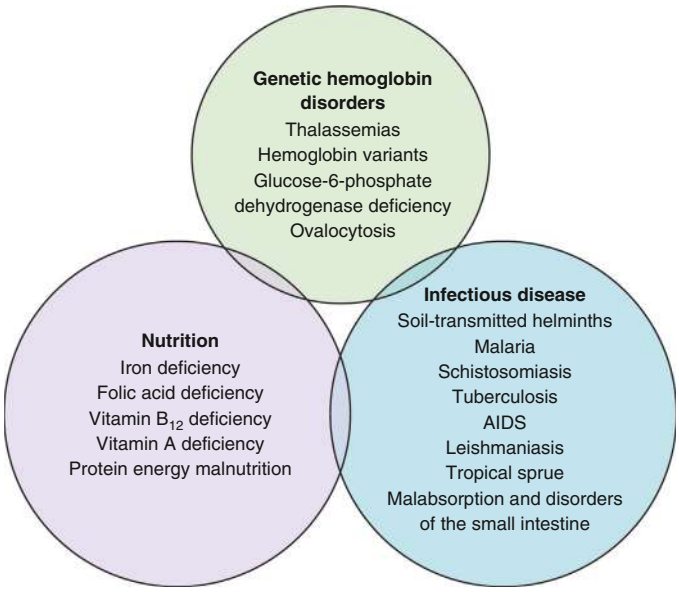

Fig. 496.2 Causes of anemia in countries with low- or middle-income populations. *(From Balarajan Y, Ramakrishnan U, Özaltin E, et al. Anaemia in low-income and middle-income countries. Lancet 2011;378:2123–2134; Fig 3.)*

LABORATORY STUDIES

Initial laboratory testing should include hemoglobin, hematocrit, RBC indices, white blood cell (WBC) count and differential, platelet count, reticulocyte count, and examination of the peripheral blood smear. The need for additional laboratory studies is dictated by the history, physical exam, and initial testing.

DIFFERENTIAL DIAGNOSIS

Anemia can result from many underlying pathologic processes. To narrow the diagnostic possibilities, anemias may be classified based on their morphology and physiology (Fig. 496.3).

Anemias may be morphologically categorized by red cell size (mean corpuscular volume [MCV]) and microscopic appearance. Anemias can be classified as *microcytic, normocytic,* or *macrocytic* based on whether the MCV is low, normal, or high, respectively (Table 496.4). RBC size also changes with age, and normal developmental changes in MCV should be accommodated before a designation is made (see Table 496.1). Examination of a peripheral blood smear often reveals changes in RBC appearance that will help to further narrow the diagnostic categories (Fig. 496.4 and Table 496.5). Details regarding morphologic changes associated with specific disorders are described in subsequent sections.

Anemias may also be further divided based on underlying pathophysiology. The two major categories are **decreased production** and **increased destruction** (or **loss**). These two groups are not always mutually exclusive. Decreased RBC production may be a consequence of either ineffective erythropoiesis or complete failure of erythropoiesis. Increased destruction or loss may be secondary to hemolysis, sequestration, or bleeding. The peripheral blood reticulocyte percentage or absolute number helps to distinguish between the two physiologic categories. The normal reticulocyte percentage of total RBCs during most of childhood is approximately 1%, with an absolute reticulocyte count of 25,000-75,000/mm^3. In the presence of anemia, EPO production and the absolute number of reticulocytes should rise. Low or normal numbers of reticulocytes generally represent an inadequate response to anemia that is associated with relative bone marrow failure or ineffective erythropoiesis. Increased numbers of reticulocytes represent a normal bone marrow response to ongoing RBC destruction (hemolysis), sequestration, or loss (bleeding).

Figure 496.3 presents a useful approach to assessing the common causes of anemia in the pediatric age group. Children with **microcytic anemia** and low or normal reticulocyte counts most often have defects in erythroid maturation or ineffective erythropoiesis. **Iron deficiency** is the most common cause (see Chapter 504). **Thalassemia trait** constitutes the primary differential diagnosis when iron deficiency is suspected (see Chapter 511). Distinctions between these entities are presented in Table 504.2. Chronic disease or inflammation (more often normocytic), lead poisoning, and sideroblastic anemias should also be considered and are discussed in other chapters. Microcytosis and elevated reticulocyte counts are associated with thalassemias and

Table 496.3 Physical Findings in the Evaluation of Anemia

SYSTEM	OBSERVATION	SIGNIFICANCE
Skin	Hyperpigmentation	Fanconi anemia, dyskeratosis congenita
	Café-au-lait spots	Fanconi anemia
	Vitiligo	Vitamin B_{12} deficiency
	Partial oculocutaneous albinism	Chédiak-Higashi syndrome
	Jaundice	Hemolysis, hepatitis
	Petechiae, purpura	Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia (Evans syndrome), hemolytic-uremic syndrome
	Erythematous rash	Parvovirus, Epstein-Barr virus
	Butterfly rash	Systemic lupus erythematosus
Head	Frontal bossing	Thalassemia major, severe iron deficiency, chronic subdural hematoma
	Microcephaly	Fanconi anemia Diamond-Blackfan anemia
Eyes	Microphthalmia	Fanconi anemia
	Retinopathy	Sickle cell disease, types SS and SC
	Optic atrophy, blindness	Osteopetrosis
	Blocked lacrimal gland	Dyskeratosis congenita
	Kayser-Fleischer ring	Wilson disease
	Blue sclera	Iron deficiency
Ears	Deafness	Osteopetrosis
Mouth	Glossitis	Vitamin B_{12} deficiency, iron deficiency
	Angular stomatitis	Iron deficiency
	Cleft lip, palate	Diamond-Blackfan anemia
	Pigmentation	Peutz-Jeghers syndrome (intestinal blood loss)
	Telangiectasia	Osler-Weber-Rendu syndrome (blood loss)
	Leukoplakia	Dyskeratosis congenital
Chest	Shield chest or widespread nipples	Diamond-Blackfan anemia
	Murmur	Endocarditis; prosthetic valve hemolysis
Abdomen	Hepatomegaly	Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis
	Splenomegaly	Acquired hemolytic anemia, inherited hemolytic anemia (hereditary spherocytosis, pyruvate kinase deficiency, sickle cell disease [age of presentation varies based on phenotype]), thalassemia, malaria, leukemia/lymphoma, Epstein-Barr virus, portal hypertension, hemophagocytic syndromes
	Nephromegaly	Fanconi anemia
	Absent kidney	Fanconi anemia
Extremities	Absent thumbs	Fanconi anemia
	Thenar eminence hypoplasia: triphalangeal thumb	Diamond-Blackfan anemia
	Spoon nails	Iron deficiency
	Beau line (nails)	Heavy metal intoxication, severe illness
	Mees line (nails)	Heavy metals, severe illness, sickle cell disease
	Dystrophic nails	Dyskeratosis congenita
	Edema	Milk-induced protein-losing enteropathy with iron deficiency, renal failure
Rectal	Hemorrhoids	Portal hypertension
	Heme-positive stool	Intestinal hemorrhage
Nerves	Irritable, apathy	Iron deficiency
	Peripheral neuropathy	Deficiency of vitamins B_1 and B_{12}, lead poisoning
	Dementia	Deficiency of vitamins B_{12} and E
	Ataxia, posterior column signs	Deficiency of vitamins B_{12} and E
	Stroke	Sickle cell disease, paroxysmal nocturnal hemoglobinuria

Adapted from Scott JP. Hematology. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics,* 2nd ed. Philadelphia: Saunders, 1994: p. 520.

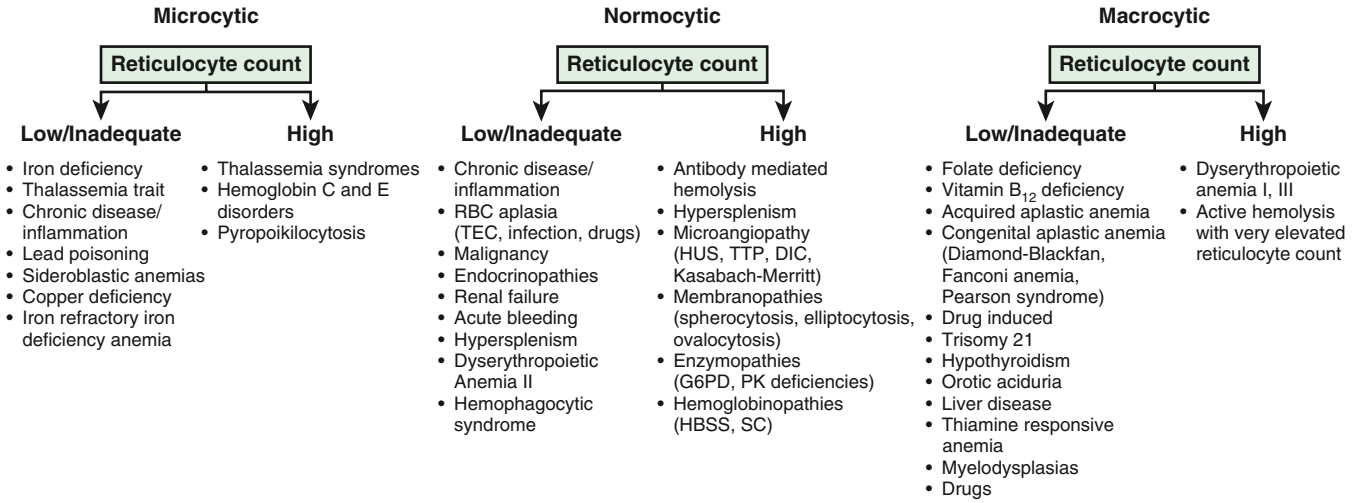

Fig. 496.3 Use of the mean corpuscular volume (MCV) and reticulocyte count in the diagnosis of anemia. *(Adapted from Brunetti M, Cohen J. The Harriet Lane Handbook, 17th ed. Philadelphia: Mosby, 2005. p. 338.)*

Table 496.4 Causes of High or Low Mean Corpuscular Volume

LOW MEAN CORPUSCULAR VOLUME
Iron deficiency
Thalassemias
Lead toxicity
Anemia of chronic disease
Copper deficiency
Sideroblastic anemia
Hemoglobin E
Hereditary pyropoikilocytosis
HIGH MEAN CORPUSCULAR VOLUME
Normal newborn
Elevated reticulocyte count
Vitamin B_{12} or folate deficiency
Diamond-Blackfan anemia (congenital hypoplastic anemia)
Fanconi anemia
Aplastic anemia
Down syndrome
Hypothyroidism (occasionally)
Orotic aciduria
Lesch-Nyhan syndrome
Drugs (zidovudine, chemotherapy)
Chronic liver disease
Paroxysmal nocturnal hemoglobinuria
Thiamine-responsive megaloblastic anemia
Myelodysplasias
Dyserythropoietic anemias

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis: Common Diseases and Their Mimics.* 2nd ed. Philadelphia: Elsevier, 2023: Table 49.5, p. 910.

hemoglobin C and E (see Chapter 511). Notably, thalassemias and hemoglobinopathies are most often seen in patients of Mediterranean, Middle Eastern, African, or Asian descent.

Normocytic anemia and low reticulocyte count characterize many anemias. The **anemia of chronic disease/inflammation** is usually normocytic (see Chapter 504). The anemia associated with renal failure, primarily a result of reduced EPO production, will invariably be associated with clinical and laboratory evidence of significant kidney disease. Decreased or absent RBC production secondary to transient erythroblastopenia of childhood (see Chapter 499), infection, medications, or endocrinopathy usually results in a normocytic anemia, as does bone marrow infiltration by malignancy. Normocytic anemia in combination with leukopenia (or significant leukocytosis with blasts) and/or thrombocytopenia should raise suspicion for malignancy. See Chapters 517 and 518 to review pancytopenias. Acute bleeding, hypersplenism, and congenital dyserythropoietic anemia type II are also normocytic (see Chapter 501).

In children with normocytic anemia and an appropriate (high) reticulocyte response, the anemia is usually caused by bleeding, hypersplenism, or ongoing hemolysis. In hemolytic conditions, reticulocytosis, indirect hyperbilirubinemia, and increased serum lactate dehydrogenase are indicators of accelerated erythrocyte destruction. Many causes of hemolysis result from conditions that are extrinsic (usually acquired) or intrinsic (usually congenital) to the erythrocyte. Abnormal RBC morphology (e.g., spherocytes, dacryocytes or sickle forms, and schistocytes) identified on the peripheral smear is often helpful in ascertaining the cause.

The anemia seen in children with macrocytic blood cells is sometimes megaloblastic, resulting from impaired DNA synthesis and nuclear development (see Chapter 503). The peripheral blood smear in **megaloblastic anemias** contains large macroovalocytes, and the neutrophils often show nuclear hypersegmentation. The major causes of megaloblastic anemia include folate deficiency, vitamin B_{12} deficiency, and rare inborn errors of metabolism. Other **macrocytic anemias** with low or normal reticulocyte counts include acquired and congenital (Diamond-Blackfan anemia and Fanconi anemia) aplastic anemias and hypothyroidism. Patients with trisomy 21 have macrocytic cells, although an accompanying anemia is generally not present. High MCV and reticulocytosis is seen in congenital dyserythropoietic anemias I and III and in situations where hemolysis results in such a large outpouring of young red cells that the MCV is abnormally high.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

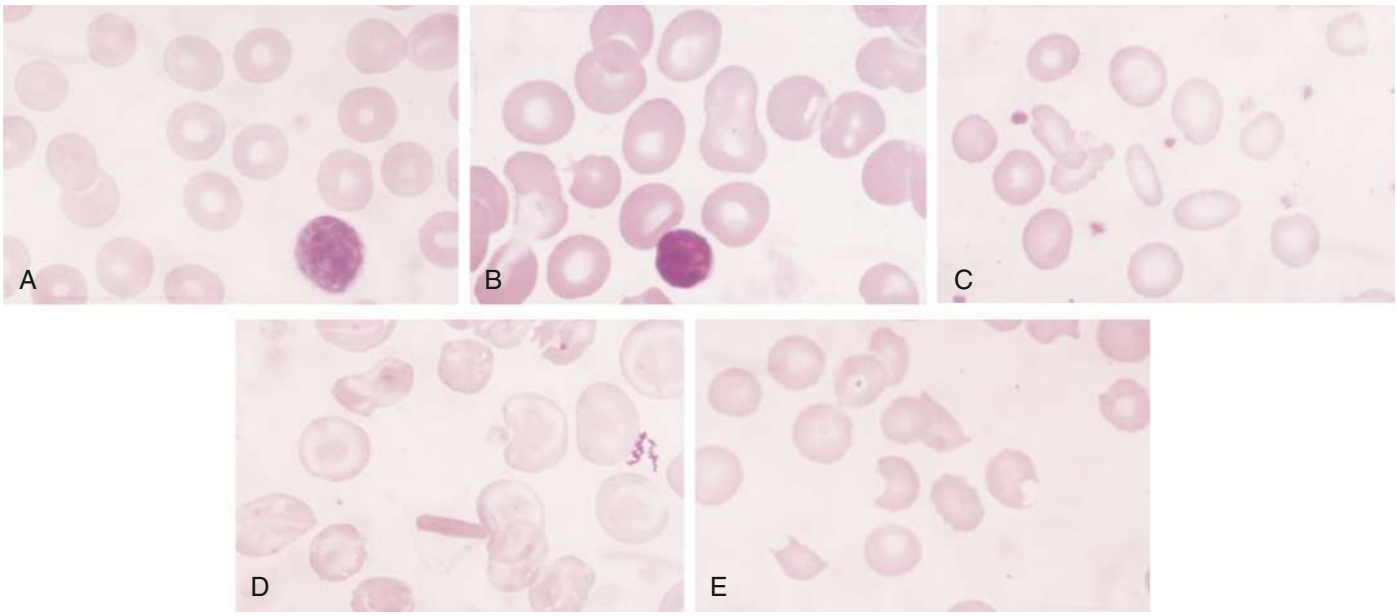

Fig. 496.4 Morphologic abnormalities of the red blood cell. **A,** Normal. **B,** Macrocytes (folic acid or vitamin B_{12} deficiency). **C,** Hypochromic microcytes (iron deficiency). **D,** Target cells (HbCC disease). **E,** Schistocyte (hemolytic-uremic syndrome). *(Courtesy Dr. Elias Schwartz, Children's Hospital of Philadelphia.)*

Table 496.5 Peripheral Blood Morphologic Findings in Various Anemias

MICROCYTES	**BASOPHIL STIPPLING**
Iron deficiency	Thalassemia
Thalassemias	Lead intoxication
Lead toxicity	Myelodysplasia
Anemia of chronic disease	
MACROCYTES	**RED BLOOD CELL FRAGMENTS, HELMET CELLS, BURR CELLS**
Newborns	Disseminated intravascular coagulation
Vitamin B_{12} or folate deficiency	Hemolytic uremic syndrome
Diamond-Blackfan anemia	Thrombotic thrombocytopenic purpura
Fanconi anemia	Kasabach-Merritt syndrome
Aplastic anemia	Waring blender syndrome (artificial heart valve)
Liver disease	Uremia
Down syndrome	Liver disease
Hypothyroidism	
SPHEROCYTES	**HYPERSEGMENTED NEUTROPHILS**
Hereditary spherocytosis	Vitamin B_{12} or folate deficiency
Immune hemolytic anemia (newborn or acquired)	
Hypersplenism	**BLASTS**
	Leukemia (ALL or AML)
SICKLED CELLS	Severe infection (rarely)
Sickle cell anemias (SS disease, SC disease, $S\beta^+$ thalassemia, $S\beta^0$ thalassemia)	**LEUKOPENIA/THROMBOCYTOPENIA**
	Fanconi anemia
ELLIPTOCYTES	Aplastic anemia
Hereditary elliptocytosis	Leukemia
Iron deficiency	Hemophagocytic histiocytosis
Megaloblastic anemia	
TARGET CELLS	**HOWELL-JOLLY BODIES**
Hemoglobinopathies (especially hemoglobin C and SC and thalassemia)	Asplenia, hyposplenia
	Severe iron deficiency
Liver disease	
Xerocytosis	**DACROCYTES (TEARDROP CELLS)**
	Myelodysplasia
	Leukemia
	Neuroblastoma

ALL, Acute lymphocytic leukemia; AML, acute myeloid leukemia; SC, sickle cell C disease; SS, sickle cell S disease.
From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis: Common Diseases and Their Mimics.* 2nd ed. Philadelphia: Elsevier, 2023: Table 49.7, p. 910.

Section 2

Anemias of Inadequate Production

Chapter 497

Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)

Courtney D. Thornburg

Diamond-Blackfan anemia (DBA) is a rare, congenital **bone marrow failure syndrome** that usually becomes symptomatic in early infancy. More than 90% of cases are recognized in the first year of life. The disorder is characterized by anemia, usually normochromic and macrocytic; reticulocytopenia; and insufficient or absent red blood cell (RBC) precursors in an otherwise normally cellular bone marrow. Up to 50% of affected individuals have additional, extrahematopoietic anomalies.

ETIOLOGY

The most common DBA-associated pathogenic variants are in *RPS19* (Fig. 497.1). This gene encodes a component protein of the small 40S ribosomal subunit and pathogenic variants are present in approximately 25–30% of patients with additional ribosomal protein (RP) genes, each encoding a different small (40S) or large (60S) ribosomal subunit protein, implicated as well. All of these pathogenic variants are inherited in an autosomal dominant fashion, with 40–45% of cases inherited from a parent and 55–60% with a de novo pathogenic variant. Less frequently, X-linked inherited cases of DBA involve pathologic genetic variants in *GATA1* or *TSR2*. Patients with *GATA1*-related DBA usually have no extra hematopoietic manifestations (Fig. 497.2). *TSR2*-related DBA is associated with mandibulofacial dysostosis. Approximately 20% of cases do not have an identified genetic variant. Because most causative variants are in ribosomal genes, the disorder is often referred to as a **ribosomopathy**.

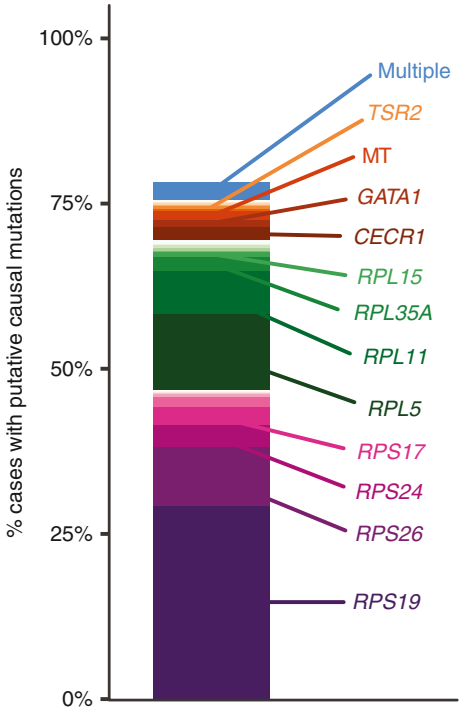

Fig. 497.1 Mutational spectrum of likely pathogenic variants in DBA. Percentage of putative causal mutations in each gene. A total of 78% of case subjects have a putative causal mutation. *(Modified from Ulirsch JC, Verboon JM, Kazerounian S, et al. The genetic landscape of Diamond-Blackfan anemia. Am J Hum Genetics 2018;103:930–947, Fig.1.)*

EPIDEMIOLOGY

DBA affects about 5-10 individuals per million live births. Notably, there is substantial phenotypic diversity in DBA, even in families whose members share the same pathologic genetic variant, suggesting that additional genetic modifiers affect phenotypic expression of the disease.

CLINICAL MANIFESTATIONS

Profound anemia usually becomes evident by 2-6 months of age, occasionally somewhat later. Approximately 25% of patients are anemic at birth, although hydrops fetalis occurs rarely; 92% are diagnosed within the first year of life. Approximately 40–50% of patients have congenital anomalies, and more than one anomaly is found in 25% of DBA patients (Table 497.1). Craniofacial abnormalities are the most common (50% of patients) and include a depressed nasal bridge and high-arched palate. Skeletal anomalies, mostly upper limb and hand, affect 30–40%. This includes thumb abnormalities, including flattening of the thenar eminence and triphalangeal thumb, that may be bilateral or unilateral. The radial pulse may be absent. Genitourinary (39%), cardiac (30%), ophthalmologic, and musculoskeletal anomalies have also been described. Short stature is common, but it is often unclear whether this characteristic results from the disease itself, related therapies, or both.

LABORATORY FINDINGS

The RBCs are usually macrocytic for age, but no hypersegmented neutrophils or other characteristics of megaloblastic anemia are appreciated on the peripheral blood smear. RBC characteristics are like those of a "fetal" RBC population, with increased expression of "i" antigen and elevated fetal hemoglobin (HbF). **Erythrocyte adenosine deaminase** (eADA) activity is increased in most patients with DBA, a finding that helps distinguish congenital RBC aplasia from acquired **transient erythroblastopenia of childhood** (TEC) (see Chapter 499). Because elevated eADA activity is not a fetal RBC feature, measurement of this enzyme may be particularly helpful when diagnosing DBA in very young infants. Thrombocytosis,

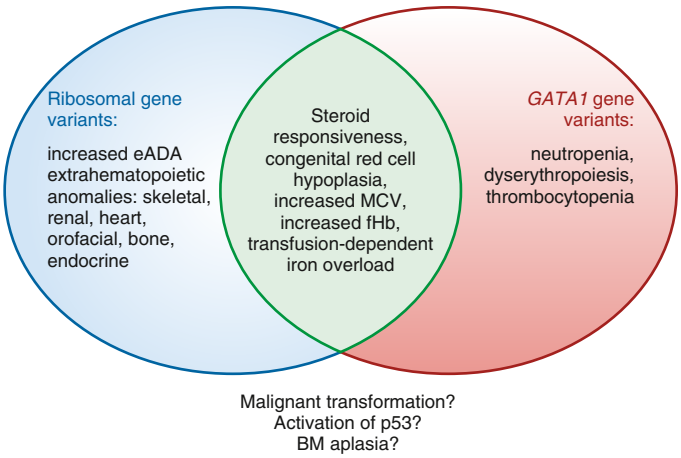

Fig. 497.2 Common and distinct phenotypes in congenital red cell aplasia caused by variants in *RP* genes and in *GATA1*. BM, Bone marrow; eADA, erythrocyte adenosine deaminase activity; fHb, fetal hemoglobin; MCV, mean corpuscular volume. *(Adapted from Weiss MJ, Mason PJ, Bessler M. What's in a name? J Clin Invest 2012;122:2346–2349.)*

or rarely thrombocytopenia, and occasionally neutropenia, may also be present. **Reticulocytopenia** is characteristic despite severe anemia. Bone marrow erythrocyte precursors are greatly reduced in most patients; other marrow elements are usually normal. Serum iron levels are elevated. Unlike Fanconi anemia, there is no increase in chromosomal breaks when lymphocytes are exposed to alkylating agents. Table 497.2 outlines suggested diagnostic criteria for "classical" DBA. Patients may be diagnosed with "nonclassical" DBA or "probable" DBA depending on their individual genetic test results, family history, and major and minor criteria.

Table 497.1 Range of Congenital Anomalies Observed in Diamond-Blackfan Anemia

TYPE/LOCATION	ANOMALIES
Craniofacial	Hypertelorism Broad, flat nasal bridge Cleft palate High-arched palate Microcephaly Micrognathia Microtia Low-set ears Low hairline Ptosis
Ophthalmologic	Congenital glaucoma Strabismus Epicanthal folds Congenital cataract
Neck	Short neck Webbed neck Sprengel deformity Klippel-Feil deformity
Thumbs	Triphalangeal Duplex or bifid Hypoplastic Flat thenar eminence Absent radial artery
Urogenital	Absent kidney Horseshoe kidney Hypospadias
Cardiac	Ventricular septal defect Atrial septal defect Coarctation of the aorta Complex cardiac anomalies
Other	Low birth weight Short stature Syndactyly Learning difficulties

Multiple anomalies, most often including craniofacial, are present in up to 25% of affected individuals. At least one anomaly is present in 40–50%.
From Vlachos A, Ball S, Dahl N, et al. Diagnosing and treating Diamond-Blackfan anaemia: Results of an international clinical consensus conference. *Br J Haematol* 2008;142:859–876, Table IV.

DIFFERENTIAL DIAGNOSIS

DBA must be differentiated from other anemias associated with reticulocytopenia. The syndrome of TEC is often the primary alternative diagnosis. Table 499.1 shows a useful comparison of findings in these two disorders (see Chapter 499). TEC often is differentiated from DBA by its relatively late onset, although it occasionally develops in infants younger than 6 months of age. Macrocytosis, congenital anomalies, fetal RBC characteristics, and elevated eADA are generally associated with DBA and not TEC.

Other inherited macrocytic bone marrow failure syndromes, particularly **Fanconi anemia** and **Shwachman-Diamond syndrome** (see Chapter 517), should also be considered, as should myelodysplastic syndrome. **Aase syndrome** includes congenital RBC aplasia with triphalangeal thumb, congenital heart disease, and cleft palate. **Hemolytic disease of the newborn** can also mimic features of DBA because it can have a protracted course and can be coupled with greatly reduced erythropoiesis. The anemia in this disorder usually resolves spontaneously at 5-8 weeks of age. Several types of chronic hemolytic diseases may be complicated by an **aplastic crisis**, characterized by reticulocytopenia and decreased numbers of RBC precursors. This event usually occurs after the first several months of life and is often caused by **parvovirus B19 infection** (see Chapter 499). Infection with parvovirus B19 in utero is also associated with pure RBC aplasia in infancy and even with hydrops fetalis at birth (see Chapter 298). When diagnosing DBA in young infants, it is important to rule out parvovirus B19 infection using a polymerase chain reaction assay because serologic testing may be inaccurate. Other infections, including HIV, as well as drugs, immune processes, and Pearson syndrome (see Chapter 498), should also be ruled out.

TREATMENT

Corticosteroids are a mainstay of therapy, and approximately 80% of patients initially respond. Because corticosteroids impair linear growth as well as physical and neurocognitive development, many hematologists maintain infants on chronic transfusion therapy and delay the start of steroids until after age 1 year. Prednisone or prednisolone in doses totaling 2 mg/kg/day is used as an initial trial. An increase in RBC precursors is usually seen in the bone marrow 1-3 weeks after therapy is begun and is followed by peripheral reticulocytosis. The hemoglobin can reach normal levels in 4-6 weeks, although the rate of response is quite variable. Once it is established that the hemoglobin concentration is increasing, the dose of corticosteroid may be reduced gradually by tapering and then by eliminating all except a single, lowest effective daily dose. This dose may

Table 497.2 Diagnostic Criteria for Diamond-Blackfan Anemia

DIAGNOSTIC CRITERIA	SUPPORTING CRITERIA	
	MAJOR CRITERIA	MINOR CRITERIA
Age younger than 1 yr	Pathogenic variant described in "classical DBA"	Elevated red cell adenosine deaminase
Macrocytic anemia with no other significant cytopenias	Positive family history	Congenital anomalies described in "classical" DBA
Reticulocytopenia		Elevated HbF
Normal marrow cellularity with paucity of bone marrow erythroid precursors		No evidence for another inherited bone marrow failure syndrome

"Classical DBA" diagnosis is made if all the diagnostic criteria are met.
DBA, Diamond Blackfan anemia, HbF, fetal hemoglobin.
From Vlachos A, Ball S, Dahl N, et al. Diagnosing and treating Diamond-Blackfan anaemia: results of an international clinical consensus conference. *Br J Haematol* 2008;142:859–876.

then be doubled, used on alternate days, and tapered still further while maintaining the hemoglobin level at ≥9 g/dL. The target maintenance dose should not exceed 0.5 mg/kg/day or 1 mg/kg every other day. In some patients, very small amounts of prednisone, as low as 2.5 mg twice a week, may be sufficient to sustain adequate erythropoiesis. Scheduled surveillance examinations and testing for corticosteroid side effects should be pursued in all patients, regardless of dose. Appropriate *Pneumocystis jiroveci* prophylaxis should be considered after the first month of high-dose steroids and continued until the patient is on low-dose alternate-day therapy. In the setting of illness, stress steroids should be considered for children on chronic corticosteroids. Many children with DBA stop taking corticosteroids, usually because of unacceptable side effects (i.e., cushingoid features, pathologic fractures, cataracts) or the evolution of corticosteroid refractoriness.

Chronic red cell transfusions are required in approximately 35% of patients, including patients who are never steroid responsive (30%), are steroid refractory (15%), or cannot be weaned to acceptable low dose (50%). Transfusions are given at intervals of 3-5 weeks to maintain a hemoglobin level >8 g/dL. Some younger children may require hemoglobin >9 g/dL to sustain normal growth and activities. Appropriate screening and ultimately the initiation of chelation therapy are required for transfusion-related iron overload.

L-leucine (700 mg/m^2 orally three times per day) has been evaluated in a phase I/II trial patients with DBA 2 years of age and older. In 43 evaluable patients, 16% had erythroid response, 36% had increase in weight, and 44% had an increase in linear growth velocity.

Spontaneous remission of anemia with independence from steroid or red cell transfusion therapy has been reported. The likelihood of remission is 25% by age 25 years, with most of these patients experiencing remission during the first decade. Mild macrocytic anemia and increased erythrocyte ADA levels persist in these circumstances.

Hematopoietic stem cell transplantation (HSCT) can be curative. Indications for HSCT include steroid resistance or unacceptable toxicity and transfusion dependence as well as significant complications of chronic red cell transfusions including iron overload and alloimmunizations. HLA-matched sibling HSCT is recommended for transfusion-dependent children with DBA. One recommendation is for HSCT between ages 3 and 9 years, and some advocate HSCT at a younger age to avoid iron overload and allosensitization from chronic red cell transfusions. It is important that sibling donors be carefully screened, including genotype if known, to ensure that the donor does not carry the pathologic genetic variant. Overall, outcomes are improving for matched-sibling and alternative donor HSCT.

PROGNOSIS

DBA has been identified as a **cancer predisposition syndrome** because of the higher risk of myelodysplastic syndrome, acute myeloid leukemia, colon carcinoma, osteogenic sarcoma, and female genital cancers. Patients are at risk for iron overload-related endocrine abnormalities (diabetes, hypogonadism), especially if transfused. Patients who have undergone HSCT are at risk of associated late effects (see Chapters 179, 180, and 181). The overall actuarial survival of all patients with DBA is approximately 75% at age 40 years, with approximately 87% for those maintained on corticosteroids and approximately 57% for transfusion-dependent patients. Of reported deaths, 67% were treatment related and 22% were DBA related (malignancy and severe aplastic anemia).

Treatment outcome and survival data are collected through the Diamond-Blackfan Anemia Registry (https://www.dbar.org).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 498

Pearson Syndrome

Courtney D. Thornburg

Pearson syndrome (PS) is a rare multisystem mitochondrial disorder that presents with a hypoplastic anemia that may be initially confused with Diamond-Blackfan syndrome (anemia) or transient erythroblastopenia of childhood (see Chapter 499). The marrow failure usually appears in the neonatal period and is characterized by a *sideroblastic macrocytic anemia* and, occasionally, neutropenia and thrombocytopenia. There are vacuolated erythroblasts and myeloblasts in the bone marrow (Fig. 498.1). PS is considered a unique variant of congenital sideroblastic anemia because the marrow also contains ringed sideroblasts. The hemoglobin F level is elevated. There is multiorgan involvement manifested by failure to thrive and symptoms of exocrine pancreas dysfunction, liver and renal tubular defects, malabsorption, and myopathy. Endocrine dysfunction (type 1 diabetes, adrenal insufficiency, hypoparathyroidism, and hypothyroidism) has also been reported. Children that survive early childhood typically develop **Kearns-Sayre syndrome**, an early-onset, mitochondrial disorder with lactic acidosis, progressive external ophthalmoplegia (impaired eye movement and ptosis), pigmentary retinitis, deafness, cerebellar ataxia, and heart block. Pearson syndrome is caused by a large heteroplasmic **mitochondrial DNA (mtDNA) deletion** (see Chapter 108) that predominates in the hematopoietic lineage. Subsequently, there is heterogeneity in different tissues and between patients, accounting for the variable clinical picture. The proportion of deleted mtDNA in the bone marrow correlates with the severity of the hematologic disease, and a reduction in the percentage of deleted mtDNA over time may be associated with spontaneous improvement of red blood cell hypoproliferation. PS may be misdiagnosed as Diamond-Blackfan anemia (DBA) based on the overlapping features, including severe anemia starting at a young age. Evaluation for mtDNA deletion differentiates PS from DBA (see Chapter 497).

Therapy for the hematologic manifestations of the disease includes red cell transfusions to correct anemia and granulocyte colony-stimulating factor in the setting of severe neutropenia. The hematologic manifestations may spontaneously resolve within the first few years of life and stem cell transplantation may be considered for persistent cytopenias.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

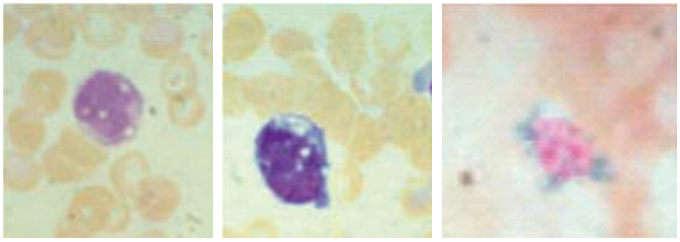

Fig. 498.1 Bone marrow morphology in Pearson syndrome. *Left,* Vacuoles in myeloid precursor. *Center,* Vacuoles in erythroid precursor. *Right,* Ringed sideroblast. (*From Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev 2010;24:101–122; Fig 14.*)

then be doubled, used on alternate days, and tapered still further while maintaining the hemoglobin level at ≥9 g/dL. The target maintenance dose should not exceed 0.5 mg/kg/day or 1 mg/kg every other day. In some patients, very small amounts of prednisone, as low as 2.5 mg twice a week, may be sufficient to sustain adequate erythropoiesis. Scheduled surveillance examinations and testing for corticosteroid side effects should be pursued in all patients, regardless of dose. Appropriate *Pneumocystis jiroveci* prophylaxis should be considered after the first month of high-dose steroids and continued until the patient is on low-dose alternate-day therapy. In the setting of illness, stress steroids should be considered for children on chronic corticosteroids. Many children with DBA stop taking corticosteroids, usually because of unacceptable side effects (i.e., cushingoid features, pathologic fractures, cataracts) or the evolution of corticosteroid refractoriness.

Chronic red cell transfusions are required in approximately 35% of patients, including patients who are never steroid responsive (30%), are steroid refractory (15%), or cannot be weaned to acceptable low dose (50%). Transfusions are given at intervals of 3-5 weeks to maintain a hemoglobin level >8 g/dL. Some younger children may require hemoglobin >9 g/dL to sustain normal growth and activities. Appropriate screening and ultimately the initiation of chelation therapy are required for transfusion-related iron overload.

L-leucine (700 mg/m^2 orally three times per day) has been evaluated in a phase I/II trial patients with DBA 2 years of age and older. In 43 evaluable patients, 16% had erythroid response, 36% had increase in weight, and 44% had an increase in linear growth velocity.

Spontaneous remission of anemia with independence from steroid or red cell transfusion therapy has been reported. The likelihood of remission is 25% by age 25 years, with most of these patients experiencing remission during the first decade. Mild macrocytic anemia and increased erythrocyte ADA levels persist in these circumstances.

Hematopoietic stem cell transplantation (HSCT) can be curative. Indications for HSCT include steroid resistance or unacceptable toxicity and transfusion dependence as well as significant complications of chronic red cell transfusions including iron overload and alloimmunizations. HLA-matched sibling HSCT is recommended for transfusion-dependent children with DBA. One recommendation is for HSCT between ages 3 and 9 years, and some advocate HSCT at a younger age to avoid iron overload and allosensitization from chronic red cell transfusions. It is important that sibling donors be carefully screened, including genotype if known, to ensure that the donor does not carry the pathologic genetic variant. Overall, outcomes are improving for matched-sibling and alternative donor HSCT.

PROGNOSIS

DBA has been identified as a **cancer predisposition syndrome** because of the higher risk of myelodysplastic syndrome, acute myeloid leukemia, colon carcinoma, osteogenic sarcoma, and female genital cancers. Patients are at risk for iron overload-related endocrine abnormalities (diabetes, hypogonadism), especially if transfused. Patients who have undergone HSCT are at risk of associated late effects (see Chapters 179, 180, and 181). The overall actuarial survival of all patients with DBA is approximately 75% at age 40 years, with approximately 87% for those maintained on corticosteroids and approximately 57% for transfusion-dependent patients. Of reported deaths, 67% were treatment related and 22% were DBA related (malignancy and severe aplastic anemia).

Treatment outcome and survival data are collected through the Diamond-Blackfan Anemia Registry (https://www.dbar.org).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 498

Pearson Syndrome

Courtney D. Thornburg

Pearson syndrome (PS) is a rare multisystem mitochondrial disorder that presents with a hypoplastic anemia that may be initially confused with Diamond-Blackfan syndrome (anemia) or transient erythroblastopenia of childhood (see Chapter 499). The marrow failure usually appears in the neonatal period and is characterized by a *sideroblastic macrocytic anemia* and, occasionally, neutropenia and thrombocytopenia. There are vacuolated erythroblasts and myeloblasts in the bone marrow (Fig. 498.1). PS is considered a unique variant of congenital sideroblastic anemia because the marrow also contains ringed sideroblasts. The hemoglobin F level is elevated. There is multiorgan involvement manifested by failure to thrive and symptoms of exocrine pancreas dysfunction, liver and renal tubular defects, malabsorption, and myopathy. Endocrine dysfunction (type 1 diabetes, adrenal insufficiency, hypoparathyroidism, and hypothyroidism) has also been reported. Children that survive early childhood typically develop **Kearns-Sayre syndrome**, an early-onset, mitochondrial disorder with lactic acidosis, progressive external ophthalmoplegia (impaired eye movement and ptosis), pigmentary retinitis, deafness, cerebellar ataxia, and heart block. Pearson syndrome is caused by a large heteroplasmic **mitochondrial DNA (mtDNA) deletion** (see Chapter 108) that predominates in the hematopoietic lineage. Subsequently, there is heterogeneity in different tissues and between patients, accounting for the variable clinical picture. The proportion of deleted mtDNA in the bone marrow correlates with the severity of the hematologic disease, and a reduction in the percentage of deleted mtDNA over time may be associated with spontaneous improvement of red blood cell hypoproliferation. PS may be misdiagnosed as Diamond-Blackfan anemia (DBA) based on the overlapping features, including severe anemia starting at a young age. Evaluation for mtDNA deletion differentiates PS from DBA (see Chapter 497).

Therapy for the hematologic manifestations of the disease includes red cell transfusions to correct anemia and granulocyte colony-stimulating factor in the setting of severe neutropenia. The hematologic manifestations may spontaneously resolve within the first few years of life and stem cell transplantation may be considered for persistent cytopenias.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

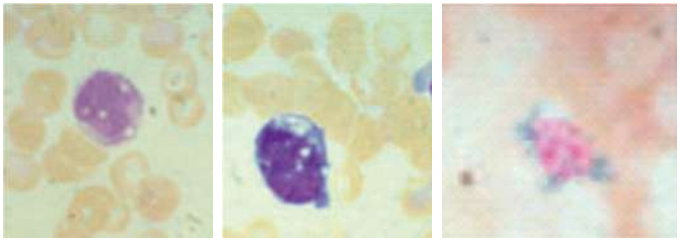

Fig. 498.1 Bone marrow morphology in Pearson syndrome. *Left,* Vacuoles in myeloid precursor. *Center,* Vacuoles in erythroid precursor. *Right,* Ringed sideroblast. (*From Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev 2010;24:101–122; Fig 14.*)

Chapter 499

Acquired Pure Red Blood Cell Anemia

Courtney D. Thornburg

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD

Transient erythroblastopenia of childhood **(TEC)** is the most common *acquired red cell aplasia* occurring in children. It is more prevalent than congenital hypoplastic anemia (Diamond-Blackfan anemia [DBA]). This syndrome of severe *transient hypoplastic anemia* occurs mainly in previously healthy children between 6 months and 3 years of age. Most children are older than 12 months at onset. Only 10% of affected patients are more than 3 years of age. The annual incidence is estimated to be 4.3 cases per 100,000 children, although it is likely higher, because TEC often resolves spontaneously with many cases undiagnosed. The suppression of erythropoiesis has been linked to IgG, IgM, and cell-mediated mechanisms. Familial cases have been reported, suggesting a hereditary component. TEC often follows a viral illness, although no specific virus has been consistently implicated.

The temporary suppression of erythropoiesis results in reticulocytopenia and moderate to severe normocytic anemia. Some degree of neutropenia occurs in up to 20% of cases. Platelet numbers are normal or elevated. Like the situation observed in iron-deficiency anemia and other red blood cell (RBC) hypoplasias, thrombocytosis is presumably caused by increased erythropoietin (EPO), which has homology to thrombopoietin (TPO). Mean corpuscular volume (MCV) is characteristically normal for age, and fetal hemoglobin (HbF) levels are normal before the recovery phase. RBC adenosine deaminase levels are normal in TEC, thus contrasting with the elevation noted in most cases of congenital hypoplastic anemia (Table 499.1). Differentiation from DBA is sometimes difficult, but differences in age at onset and in age-related MCV, HbF, and adenosine deaminase are usually helpful. The peak occurrence of TEC coincides with that of iron-deficiency anemia in infants receiving milk as their main caloric source; differences in MCV should help to distinguish between TEC and DBA.

Virtually all children recover within 1-2 months. RBC transfusions may be necessary for severe anemia in the absence of signs of early recovery. The anemia develops slowly, and significant symptoms usually develop only with severe anemia. *Corticosteroid therapy is of no value in this disorder.* Any child with presumed TEC who requires more than one transfusion should be reevaluated for another possible diagnosis. In rare instances, a prolonged case of apparent TEC may be caused by parvovirus-induced RBC aplasia, occurring in children with *hemolytic anemia* or *congenital* or *acquired immunodeficiencies.*

RED CELL APLASIA ASSOCIATED WITH PARVOVIRUS B19 INFECTION

Parvovirus B19 is a common infectious agent that causes **erythema infectiosum** (fifth disease) (see Chapter 298). It is also the most clearly documented viral cause of RBC aplasia in patients with chronic hemolytic anemia or an immunocompromised state. This single-stranded virus is cytotoxic to marrow erythroid progenitor cells, interacting specifically by binding to the red cell P antigen. In addition to decreased or absent erythroid precursors, characteristic nuclear inclusions in erythroblasts and giant pronormoblasts may be seen under light microscopy in bone marrow specimens. The virus does not cause significant anemia in immunocompetent individuals with a normal RBC life span.

Because parvovirus infection usually lasts less than 2 weeks, anemia may not develop or be appreciated in otherwise normal children whose peripheral RBC life span is 100-120 days. The RBC life span is much shorter in patients with **chronic hemolysis** secondary to conditions such as hereditary spherocytosis, immune hemolytic anemia, or sickle cell disease. In these children, a brief cessation of erythropoiesis can cause severe anemia, known as **aplastic crisis**. When a definitive diagnosis is required, the workup should include

Table 499.1 Comparison of Diamond-Blackfan Anemia and Transient Erythroblastopenia of Childhood

FEATURE	DBA	TEC
Male:female	1:1	1:3
AGE AT DIAGNOSIS, MALE (MO)		
Mean	10	26
Median	2	23
Range	0-408	1-120
AGE AT DIAGNOSIS, FEMALE (MO)		
Mean	14	26
Median	3	23
Range	0-768	1-192
Males >1 yr	9%	82%
Females >1 yr	12%	80%
Etiology	Genetic	Acquired, possibly familial
Antecedent history	None	Viral illness
Physical examination abnormal (congenital anomalies present)	25%	0%
LABORATORY		
Hemoglobin (g/dL)	1.2-14.8	2.2-12.5
WBCs <5,000/μL	15%	20%
Platelets >400,000/μL	20%	45%
Adenosine deaminase	Increased	Normal
MCV increased at diagnosis	80%	5%
MCV increased during recovery	100%	90%
MCV increased in remission	100%	0%
HbF increased at diagnosis	100%	20%
HbF increased during recovery	100%	100%
HbF increased in remission	85%	0%
i Antigen increased	100%	20%
i Antigen increased during recovery	100%	60%
i Antigen increased in remission	90%	0%

DBA, Diamond-Blackfan anemia; HbF, fetal hemoglobin; MCV, mean cell volume; TEC, transient erythroblastopenia of childhood; WBC, white blood cell.

From Nathan DG, Orkin SH, Ginsburg D, et al., eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 6th ed. Philadelphia: Saunders; 2003, p. 329. Adapted from Alter BP. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood.* 3rd ed. Philadelphia: Saunders; 1987. p 159; and Link MP, Alter BP. Fetal erythropoiesis during recovery from transient erythroblastopenia of childhood (TEC). *Pediatr Res* 1981;15:1036–1039.

serum parvovirus IgM and IgG titers. In young infants, a polymerase chain reaction (PCR) assay should be used since serologic testing may be inaccurate. Recovery from moderate to severe anemia is usually spontaneous, heralded by the appearance of nucleated RBCs and subsequent reticulocytosis in the peripheral blood. Nonetheless the parvovirus PCR may remain positive for months after recovery. An RBC transfusion may be necessary if the anemia is associated with significant symptoms. Parvovirus-induced aplastic crisis usually occurs only once in children with chronic hemolysis. In families with more than one child with a hemolytic disorder, parents should be warned that a similar aplastic episode can occur in the other children if they have not been previously infected. During the episode of aplastic crisis, the child is potentially contagious and should be isolated from at-risk patients.

Persistent parvovirus infection may occur in children with congenital immunodeficiency diseases, lymphoproliferative disorders, those being treated with immunosuppressive agents, and those with HIV/AIDS, because these children may be unable to mount an adequate antibody response. The resultant pure RBC aplasia may be severe, and affected children may be thought to have TEC. This type of RBC aplasia differs from TEC in that there is no spontaneous recovery, and more than one transfusion is often needed. The diagnosis of parvovirus infection is made by PCR of peripheral blood or bone marrow DNA because the usual serologic responses, reflected by parvovirus serum IgM or IgG titers, are impaired in immunodeficient children. In chronically infected patients, the disease may be treated with high doses of intravenous immunoglobulin, which contains neutralizing antibody to parvovirus and is effective in the short term.

Parvovirus infection and destruction of erythroid precursors can also occur in utero. Such events are associated with increased rates of fetal loss in the first and second trimesters. Infants may be born with **hydrops fetalis** and anemia (see Chapter 138). The presence of persistent congenital parvovirus infection is detected by PCR of peripheral blood and/or bone marrow DNA because immunologic tolerance to the virus can prevent the usual development of specific antibodies.

OTHER RED CELL APLASIAS IN CHILDREN

Acquired red cell aplasia in adults is usually mediated by a chronic antibody and often associated with disorders such as chronic lymphocytic leukemia, lymphoma, thymoma, lymphoproliferative disorders, and systemic lupus erythematosus. This chronic antibody-mediated type of RBC aplasia, often responsive to immunosuppressive therapy, is quite rare in childhood. Cases of acquired pure RBC aplasia attributable to T-cell suppression have also been described.

Infections other than parvovirus, such as cytomegalovirus, Epstein-Barr virus, and human herpes virus-6, may cause pure RBC aplasia. Certain drugs, such as chloramphenicol, also can inhibit erythropoiesis in a dose-dependent manner. Reticulocytopenia, erythroid hypoplasia, and vacuolated pronormoblasts in the bone marrow are reversible effects of this drug. These effects are distinct from the idiosyncratic and rare development of severe aplastic anemia in chloramphenicol recipients. Acquired antibody-mediated (to erythropoietin) pure RBC aplasia is a rare complication in chronic kidney disease patients treated with erythropoietin. In addition to discontinuing erythropoiesis-stimulating agents, therapy and addressing anemia with red cell transfusions, further treatment may require immunosuppression and eventually renal transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 500

Anemia of Chronic Disease and Renal Disease

500.1 Anemia of Chronic Disease

Courtney D. Thornburg

The anemia of chronic disease **(ACD)**, also referred to as **anemia of inflammation**, is found in conditions where there is ongoing immune activation. It occurs in a wide range of disorders, including infections, malignancies, chronic disease, autoimmunity, and graft-versus-host disease. A similar anemia is associated with chronic kidney disease. ACD is typically a mild to moderate normocytic, normochromic, hypoproliferative anemia associated with a decreased serum iron and low transferrin saturation.

ETIOLOGY

Decreased red cell life span, impaired erythropoiesis, and an increased uptake of iron in the reticuloendothelial system are important mechanisms contributing to ACD.

ACD-associated alterations in iron recycling are characterized by an accumulation of iron in reticuloendothelial macrophages despite low levels of serum iron. The diversion of iron from the circulation into the reticuloendothelial system results in *functional* iron deficiency, which causes the impaired heme synthesis and iron-restricted erythropoiesis that contribute to anemia. These alterations in iron metabolism have been attributed to inflammation-associated excess synthesis of hepcidin, a key regulatory protein that controls intestinal iron absorption and tissue distribution. Hepcidin, although mainly synthesized by hepatocytes, is expressed in other cells, including monocytes and macrophages. It functions by binding to and initiating the degradation of the iron exporter, ferroportin (Fig. 500.1).

CLINICAL MANIFESTATIONS

Although the important symptoms and signs associated with ACD are those of the underlying disease, the mild to moderate anemia can affect the patient's quality of life.

LABORATORY FINDINGS

Hemoglobin concentrations are generally 6-9 g/dL. The anemia is usually normochromic and normocytic, although some patients have modest hypochromia and microcytosis, particularly if there is concomitant iron deficiency. Absolute reticulocyte counts are normal or low, and leukocytosis is common. The serum iron level is low, without the increase in serum transferrin (the iron transport protein) that occurs in iron deficiency. This pattern of low serum iron and low-to-normal serum transferrin is a valuable diagnostic feature. *However, note that the serum ferritin level may be elevated secondary to inflammation*. Soluble transferrin receptor (sTfR) is a useful diagnostic test to distinguish ACD from iron-deficiency anemia (IDA) because sTfR levels are high in IDA and normal in ACD. A bone marrow biopsy typically shows normal cellularity with decreased or adequate red blood cell precursors; marrow hemosiderin may be increased and granulocytic hyperplasia may be present.

serum parvovirus IgM and IgG titers. In young infants, a polymerase chain reaction (PCR) assay should be used since serologic testing may be inaccurate. Recovery from moderate to severe anemia is usually spontaneous, heralded by the appearance of nucleated RBCs and subsequent reticulocytosis in the peripheral blood. Nonetheless the parvovirus PCR may remain positive for months after recovery. An RBC transfusion may be necessary if the anemia is associated with significant symptoms. Parvovirus-induced aplastic crisis usually occurs only once in children with chronic hemolysis. In families with more than one child with a hemolytic disorder, parents should be warned that a similar aplastic episode can occur in the other children if they have not been previously infected. During the episode of aplastic crisis, the child is potentially contagious and should be isolated from at-risk patients.

Persistent parvovirus infection may occur in children with congenital immunodeficiency diseases, lymphoproliferative disorders, those being treated with immunosuppressive agents, and those with HIV/AIDS, because these children may be unable to mount an adequate antibody response. The resultant pure RBC aplasia may be severe, and affected children may be thought to have TEC. This type of RBC aplasia differs from TEC in that there is no spontaneous recovery, and more than one transfusion is often needed. The diagnosis of parvovirus infection is made by PCR of peripheral blood or bone marrow DNA because the usual serologic responses, reflected by parvovirus serum IgM or IgG titers, are impaired in immunodeficient children. In chronically infected patients, the disease may be treated with high doses of intravenous immunoglobulin, which contains neutralizing antibody to parvovirus and is effective in the short term.

Parvovirus infection and destruction of erythroid precursors can also occur in utero. Such events are associated with increased rates of fetal loss in the first and second trimesters. Infants may be born with **hydrops fetalis** and anemia (see Chapter 138). The presence of persistent congenital parvovirus infection is detected by PCR of peripheral blood and/or bone marrow DNA because immunologic tolerance to the virus can prevent the usual development of specific antibodies.

OTHER RED CELL APLASIAS IN CHILDREN

Acquired red cell aplasia in adults is usually mediated by a chronic antibody and often associated with disorders such as chronic lymphocytic leukemia, lymphoma, thymoma, lymphoproliferative disorders, and systemic lupus erythematosus. This chronic antibody-mediated type of RBC aplasia, often responsive to immunosuppressive therapy, is quite rare in childhood. Cases of acquired pure RBC aplasia attributable to T-cell suppression have also been described.

Infections other than parvovirus, such as cytomegalovirus, Epstein-Barr virus, and human herpes virus-6, may cause pure RBC aplasia. Certain drugs, such as chloramphenicol, also can inhibit erythropoiesis in a dose-dependent manner. Reticulocytopenia, erythroid hypoplasia, and vacuolated pronormoblasts in the bone marrow are reversible effects of this drug. These effects are distinct from the idiosyncratic and rare development of severe aplastic anemia in chloramphenicol recipients. Acquired antibody-mediated (to erythropoietin) pure RBC aplasia is a rare complication in chronic kidney disease patients treated with erythropoietin. In addition to discontinuing erythropoiesis-stimulating agents, therapy and addressing anemia with red cell transfusions, further treatment may require immunosuppression and eventually renal transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 500

Anemia of Chronic Disease and Renal Disease

500.1 Anemia of Chronic Disease

Courtney D. Thornburg

The anemia of chronic disease **(ACD)**, also referred to as **anemia of inflammation**, is found in conditions where there is ongoing immune activation. It occurs in a wide range of disorders, including infections, malignancies, chronic disease, autoimmunity, and graft-versus-host disease. A similar anemia is associated with chronic kidney disease. ACD is typically a mild to moderate normocytic, normochromic, hypoproliferative anemia associated with a decreased serum iron and low transferrin saturation.

ETIOLOGY

Decreased red cell life span, impaired erythropoiesis, and an increased uptake of iron in the reticuloendothelial system are important mechanisms contributing to ACD.

ACD-associated alterations in iron recycling are characterized by an accumulation of iron in reticuloendothelial macrophages despite low levels of serum iron. The diversion of iron from the circulation into the reticuloendothelial system results in *functional* iron deficiency, which causes the impaired heme synthesis and iron-restricted erythropoiesis that contribute to anemia. These alterations in iron metabolism have been attributed to inflammation-associated excess synthesis of hepcidin, a key regulatory protein that controls intestinal iron absorption and tissue distribution. Hepcidin, although mainly synthesized by hepatocytes, is expressed in other cells, including monocytes and macrophages. It functions by binding to and initiating the degradation of the iron exporter, ferroportin (Fig. 500.1).

CLINICAL MANIFESTATIONS

Although the important symptoms and signs associated with ACD are those of the underlying disease, the mild to moderate anemia can affect the patient's quality of life.

LABORATORY FINDINGS

Hemoglobin concentrations are generally 6-9 g/dL. The anemia is usually normochromic and normocytic, although some patients have modest hypochromia and microcytosis, particularly if there is concomitant iron deficiency. Absolute reticulocyte counts are normal or low, and leukocytosis is common. The serum iron level is low, without the increase in serum transferrin (the iron transport protein) that occurs in iron deficiency. This pattern of low serum iron and low-to-normal serum transferrin is a valuable diagnostic feature. *However, note that the serum ferritin level may be elevated secondary to inflammation*. Soluble transferrin receptor (sTfR) is a useful diagnostic test to distinguish ACD from iron-deficiency anemia (IDA) because sTfR levels are high in IDA and normal in ACD. A bone marrow biopsy typically shows normal cellularity with decreased or adequate red blood cell precursors; marrow hemosiderin may be increased and granulocytic hyperplasia may be present.

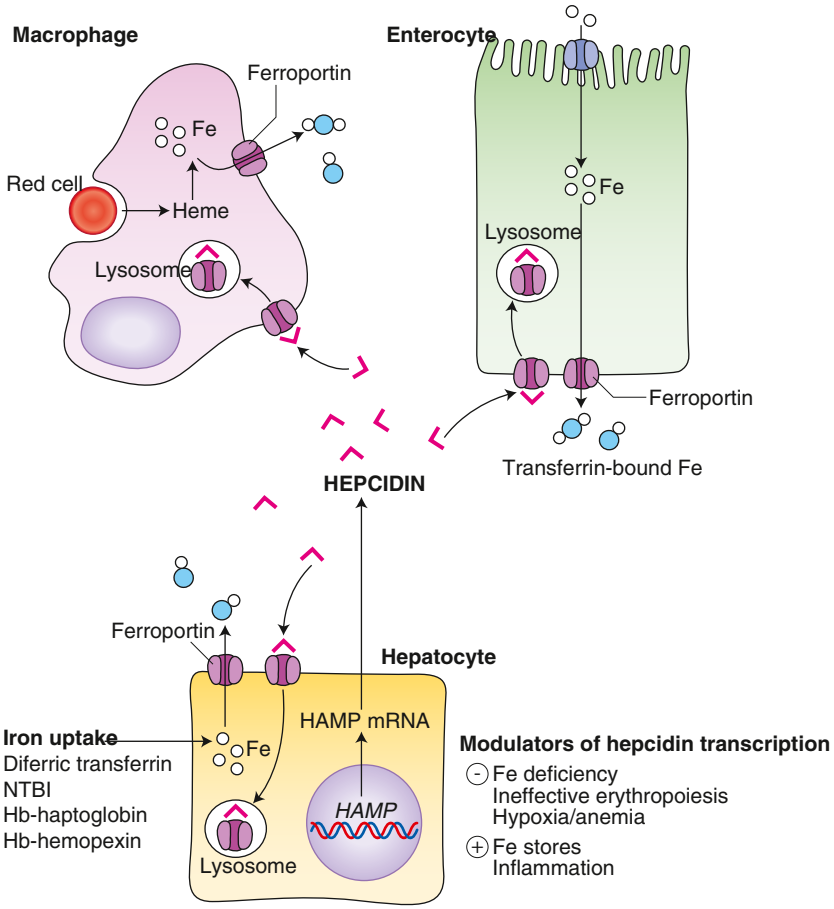

Fig. 500.1 Central role of hepcidin in iron metabolism. Hepcidin, produced by hepatocytes, downregulates iron export to circulating transferrin from iron "donor" cells (hepatocytes, macrophages, and duodenal enterocytes) by promoting the internalization and lysosomal degradation of ferroportin. Hepatocytes take up iron in several forms, whereas enterocytes obtain their iron predominantly from the gut lumen, and macrophages are specialized to deal with the high throughput of iron from senescent red cells. (*From Pippard M. Iron deficiency anemia, anemia of chronic disorders and iron overload. In Porwit A, McCullough J, Erber WN, eds. Blood and Bone Marrow Pathology, 2nd ed. London: Elsevier, 2011; Fig 11-5.*)

TREATMENT

Where possible, the best approach to ACD is the treatment of the underlying disorder. If the associated systemic disease can be controlled, the anemia typically improves or resolves. Transfusions raise the hemoglobin concentration temporarily but are rarely indicated. Erythropoiesis-stimulating agents (ESAs), such as recombinant human erythropoietin (EPO) or related extended half-life formulations, increase the hemoglobin level and improve activity and the sense of well-being. When using ESAs, *treatment with iron* is usually necessary to produce optimal effect. Response to these agents is highly variable, and poorly responsive patients may require high doses to reach target hemoglobin levels. In adults, high doses are associated with a higher incidence of adverse events, such as stroke, cardiovascular events, cancer progression, and death, leading the U.S. Food and Drug Administration (FDA) to require a "black box" warning on labels.

ACD does not respond to iron alone unless there is concomitant deficiency. Unfortunately, it is a common clinical challenge to identify iron deficiency in patients with an inflammatory disease (see Chapters 496 and 504). In this circumstance, a trial of iron therapy might be helpful, although there may be no response because persistent inflammation impairs iron absorption and utilization; intravenous iron may further increase hepcidin production.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

500.2 Anemia of Renal Disease

Courtney D. Thornburg

Anemia is common in children with chronic kidney disease (CKD). The anemia is usually normocytic, and the absolute reticulocyte count is normal or low. Although most patients with end-stage renal disease (ESRD) are anemic, earlier stages of CKD are also associated with a lower prevalence of anemia. In adults, a lower glomerular filtration rate (GFR) has been correlated with lower hemoglobin concentration, and hemoglobin has been reported to decline below a GFR threshold of 40-60 mL/min/1.73 m^2. In children with CKD, hemoglobin levels decline as the GFR decreases below 43 mL/min/1.73 m^2.

Decreased hemoglobin values are linked to increased incidence of left ventricular hypertrophy, impaired physical activity, and a reduced quality of life in pediatric patients with CKD. In those with ESRD on dialysis, anemia is also associated with increased risk of hospitalization and mortality.

ETIOLOGY

Although the anemia of CKD shares many features with anemia of chronic disease, its predominant cause is decreased erythropoietin (EPO) production by diseased kidneys. Other important causes include absolute and/or functional iron deficiency because of chronic blood loss (from blood sampling, surgeries, and dialysis) and disturbances in iron metabolism. Higher hepcidin levels have also been implicated in the anemia of CKD. Hepcidin is filtered by the glomerulus and excreted by the kidney; serum concentrations are increased in patients with decreased GFR. Inflammation may also be a contributing factor in pediatric dialysis patients who have elevated levels of proinflammatory cytokines. Hyperparathyroidism and deficiencies of vitamin B_{12}, folate, and carnitine may also have a role in anemia of CKD.

LABORATORY FINDINGS

Anemia in children with CKD is defined by age: hemoglobin <11.0 g/dL (0.5-5 years), <11.5 g/dL (5-12 years), <12 g/dL (12-15 years), <13.0 g/dL (males >15 years), and <12.0 g/dL (females >15 years). The anemia of CKD is hypoproliferative and usually normocytic and normochromic, unless there is concomitant iron deficiency or vitamin deficiency. The EPO level and absolute reticulocyte count are usually

low. White cell and platelet counts are generally normal. Ferritin will be low if there is accompanying iron deficiency and high if there is associated inflammation.

TREATMENT

Oral iron therapy is recommended for all pediatric CKD patients with anemia. Intravenous (IV) iron therapy may be considered for those receiving maintenance hemodialysis and those who to do not respond to oral iron. Current IV iron preparations (iron-gluconate, iron-sucrose, iron-carboxymaltose, iron-isomaltoside, ferumoxytol) have iron as a core within a carbohydrate stabilizer shell, thus preventing the uncontrolled release of free iron and thus reducing serious side effects.

Erythropoiesis-stimulating agents (ESAs) are the mainstay of therapy and, particularly for children with ESRD, have greatly reduced the need for frequent transfusions, decreasing the incidence of associated iron overload and alloimmunization.

Hemoglobin levels at which ESAs are initiated may be guided by individual patient characteristics, with a goal of 11-12 g/dL for children on maintenance ESA therapy. Dosing varies with age and dialysis modality. Darbepoetin, a synthetic form of EPO, appears to be equally effective as recombinant human EPO and has the benefit of less frequent dosing because of a longer half-life. Iron therapy should be prescribed when using ESAs because treatment demands additional iron for erythropoiesis. Infants and children require higher doses of ESAs.

In the rare case in which anti-EPO antibody-mediated pure red cell aplasia develops, ESA therapy should be stopped, and immunomodulatory therapy may be indicated to suppress the antibody response.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 501

Congenital Dyserythropoietic Anemias

Courtney D. Thornburg

The congenital dyserythropoietic anemias **(CDAs)** are a heterogeneous class of inherited disorders resulting from abnormalities of late erythropoiesis. These rare conditions are characterized by variable degrees of anemia, ineffective erythropoiesis, hyperbilirubinemia, gallstones, splenomegaly, and secondary hemochromatosis (iron overload). They may be misdiagnosed as other congenital anemias, such as hereditary spherocytosis or thalassemia. **Dyserythropoiesis** is the major cause of anemia but a shortened half-life of circulating red blood cells (RBCs) may also contribute. The CDAs have been classified into four major types (I, II, III, and IV) and variants based on distinctive bone marrow morphology, clinical features, and genetic mutations. **Genetic testing** is now the key method for achieving a timely accurate diagnosis (Fig. 501.1).

CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE I

Pathogenesis

Type I CDA **(CDA I)** is an autosomal recessive disorder. It is caused by pathogenic variants in *CDAN1,* the first gene to be implicated, which encodes Codanin-1, a cell-cycle regulated protein. Pathogenic variants in *CDIN1* (CDAN1-interacting nuclease 1, previously *C15orf41*) also cause CDA I. Proteins encoded by *CDAN1* and *CDIN1* likely contribute to DNA repair and/or chromatin reassembly after DNA replication.

Clinical Manifestations

CDA I may be diagnosed at any age, although most cases are recognized during childhood or adolescence in the setting of moderate to severe macrocytic anemia with relative reticulocytopenia. CDA I is rarely diagnosed in utero with severe anemia resulting in hydrops fetalis. Neonates with CDA 1 may have neonatal jaundice or pulmonary hypertension related to anemia. Type I CDA has been associated with **dysmorphic features** in 4–25% of patients, primarily involving the digits (syndactyly, absence of nails or curved toenails, supernumerary toes, skin pigmentation, café-au-lait spots, macrocephaly, dolichocephaly, spinal fusion, scoliosis, and short stature). Patients have progressive iron overload even in the absence of transfusions.

Laboratory Findings

Hemoglobin concentrations generally range between 7-11 g/dL. The anemia is usually macrocytic (mean corpuscular volume: 100-120 fL), but normocytic indices may be seen during childhood. **Anisopoikilocytosis** is appreciated on the peripheral blood smear. In some cases, normoblasts and basophilic stippling of RBCs may be seen. The reticulocyte count is inadequate for the degree of anemia **(reticulocytopenia)**. Elevated serum ferritin secondary to iron overload may be present. The bone marrow aspirate shows erythroid hyperplasia. Binucleate erythroblasts make up 2.5–10% of late erythroblasts. Incompletely divided cells with thin chromatin bridges between nuclei of pairs of erythrocytes are highly specific for type I CDA. Electron microscopy is the gold standard for clinical diagnosis, revealing erythroblasts with a characteristic "Swiss cheese" heterochromatin pattern.

Treatment

Treatment of this disorder includes transfusions, especially in the neonatal period and early childhood and in association with co-inherited disorders, such as thalassemia or RBC enzymopathy. However, adolescents and adults may require episodic transfusions only during aplastic crises, infection, or pregnancy. For patients with CDAN1 mutations, treatment with PEGylated interferon-α_2 can reduce transfusion requirements. Because of potential side effects of spastic diplegia and peripheral neuropathy, treatment initiation may be reserved for patients beyond early childhood requiring frequent transfusions. Patients do not respond to erythropoietin; splenectomy is generally not recommended. Cholecystectomy is often required for management of pigmented gallstones. Allogeneic stem cell transplantation may also be considered for severe cases.

The most important long-term complication is progressive **iron overload**, caused by increased intestinal absorption of iron and ineffective erythropoiesis and transfusion therapy. Regular phlebotomies is a treatment option as long as there is not significant anemia. If this approach is untenable, chelation therapy should be employed when repeated ferritin levels exceed 1,000 μg/L or liver iron is elevated as determined by hepatic magnetic resonance imaging T2*.

CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE II

Pathogenesis

CDA type II **(CDA II)**, the most common type of CDA, is an autosomal recessive disorder caused by biallelic pathogenic variants in *SEC23B*. This gene encodes a component of the cytoplasmic coat protein II (COPII) complex that is involved in endoplasmic reticulum vesicle trafficking.

Clinical Manifestations

CDA II presents with varying degrees of normocytic anemia and no or mild reticulocytosis. Approximately 20% of patients are transfusion dependent. CDA II may be initially misdiagnosed as hereditary spherocytosis due to overlapping symptoms of anemia, jaundice, splenomegaly, or hepatomegaly. Extramedullary hematopoiesis may result in

low. White cell and platelet counts are generally normal. Ferritin will be low if there is accompanying iron deficiency and high if there is associated inflammation.

TREATMENT

Oral iron therapy is recommended for all pediatric CKD patients with anemia. Intravenous (IV) iron therapy may be considered for those receiving maintenance hemodialysis and those who to do not respond to oral iron. Current IV iron preparations (iron-gluconate, iron-sucrose, iron-carboxymaltose, iron-isomaltoside, ferumoxytol) have iron as a core within a carbohydrate stabilizer shell, thus preventing the uncontrolled release of free iron and thus reducing serious side effects.

Erythropoiesis-stimulating agents (ESAs) are the mainstay of therapy and, particularly for children with ESRD, have greatly reduced the need for frequent transfusions, decreasing the incidence of associated iron overload and alloimmunization.

Hemoglobin levels at which ESAs are initiated may be guided by individual patient characteristics, with a goal of 11-12 g/dL for children on maintenance ESA therapy. Dosing varies with age and dialysis modality. Darbepoetin, a synthetic form of EPO, appears to be equally effective as recombinant human EPO and has the benefit of less frequent dosing because of a longer half-life. Iron therapy should be prescribed when using ESAs because treatment demands additional iron for erythropoiesis. Infants and children require higher doses of ESAs.

In the rare case in which anti-EPO antibody-mediated pure red cell aplasia develops, ESA therapy should be stopped, and immunomodulatory therapy may be indicated to suppress the antibody response.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 501

Congenital Dyserythropoietic Anemias

Courtney D. Thornburg

The congenital dyserythropoietic anemias **(CDAs)** are a heterogeneous class of inherited disorders resulting from abnormalities of late erythropoiesis. These rare conditions are characterized by variable degrees of anemia, ineffective erythropoiesis, hyperbilirubinemia, gallstones, splenomegaly, and secondary hemochromatosis (iron overload). They may be misdiagnosed as other congenital anemias, such as hereditary spherocytosis or thalassemia. **Dyserythropoiesis** is the major cause of anemia but a shortened half-life of circulating red blood cells (RBCs) may also contribute. The CDAs have been classified into four major types (I, II, III, and IV) and variants based on distinctive bone marrow morphology, clinical features, and genetic mutations. **Genetic testing** is now the key method for achieving a timely accurate diagnosis (Fig. 501.1).

CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE I

Pathogenesis

Type I CDA **(CDA I)** is an autosomal recessive disorder. It is caused by pathogenic variants in *CDAN1,* the first gene to be implicated, which encodes Codanin-1, a cell-cycle regulated protein. Pathogenic variants in *CDIN1* (CDAN1-interacting nuclease 1, previously *C15orf41*) also cause CDA I. Proteins encoded by *CDAN1* and *CDIN1* likely contribute to DNA repair and/or chromatin reassembly after DNA replication.

Clinical Manifestations

CDA I may be diagnosed at any age, although most cases are recognized during childhood or adolescence in the setting of moderate to severe macrocytic anemia with relative reticulocytopenia. CDA I is rarely diagnosed in utero with severe anemia resulting in hydrops fetalis. Neonates with CDA 1 may have neonatal jaundice or pulmonary hypertension related to anemia. Type I CDA has been associated with **dysmorphic features** in 4–25% of patients, primarily involving the digits (syndactyly, absence of nails or curved toenails, supernumerary toes, skin pigmentation, café-au-lait spots, macrocephaly, dolichocephaly, spinal fusion, scoliosis, and short stature). Patients have progressive iron overload even in the absence of transfusions.

Laboratory Findings

Hemoglobin concentrations generally range between 7-11 g/dL. The anemia is usually macrocytic (mean corpuscular volume: 100-120 fL), but normocytic indices may be seen during childhood. **Anisopoikilocytosis** is appreciated on the peripheral blood smear. In some cases, normoblasts and basophilic stippling of RBCs may be seen. The reticulocyte count is inadequate for the degree of anemia **(reticulocytopenia)**. Elevated serum ferritin secondary to iron overload may be present. The bone marrow aspirate shows erythroid hyperplasia. Binucleate erythroblasts make up 2.5–10% of late erythroblasts. Incompletely divided cells with thin chromatin bridges between nuclei of pairs of erythrocytes are highly specific for type I CDA. Electron microscopy is the gold standard for clinical diagnosis, revealing erythroblasts with a characteristic "Swiss cheese" heterochromatin pattern.

Treatment

Treatment of this disorder includes transfusions, especially in the neonatal period and early childhood and in association with co-inherited disorders, such as thalassemia or RBC enzymopathy. However, adolescents and adults may require episodic transfusions only during aplastic crises, infection, or pregnancy. For patients with CDAN1 mutations, treatment with PEGylated interferon-α_2 can reduce transfusion requirements. Because of potential side effects of spastic diplegia and peripheral neuropathy, treatment initiation may be reserved for patients beyond early childhood requiring frequent transfusions. Patients do not respond to erythropoietin; splenectomy is generally not recommended. Cholecystectomy is often required for management of pigmented gallstones. Allogeneic stem cell transplantation may also be considered for severe cases.

The most important long-term complication is progressive **iron overload**, caused by increased intestinal absorption of iron and ineffective erythropoiesis and transfusion therapy. Regular phlebotomies is a treatment option as long as there is not significant anemia. If this approach is untenable, chelation therapy should be employed when repeated ferritin levels exceed 1,000 μg/L or liver iron is elevated as determined by hepatic magnetic resonance imaging T2*.

CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE II

Pathogenesis

CDA type II **(CDA II)**, the most common type of CDA, is an autosomal recessive disorder caused by biallelic pathogenic variants in *SEC23B*. This gene encodes a component of the cytoplasmic coat protein II (COPII) complex that is involved in endoplasmic reticulum vesicle trafficking.

Clinical Manifestations

CDA II presents with varying degrees of normocytic anemia and no or mild reticulocytosis. Approximately 20% of patients are transfusion dependent. CDA II may be initially misdiagnosed as hereditary spherocytosis due to overlapping symptoms of anemia, jaundice, splenomegaly, or hepatomegaly. Extramedullary hematopoiesis may result in

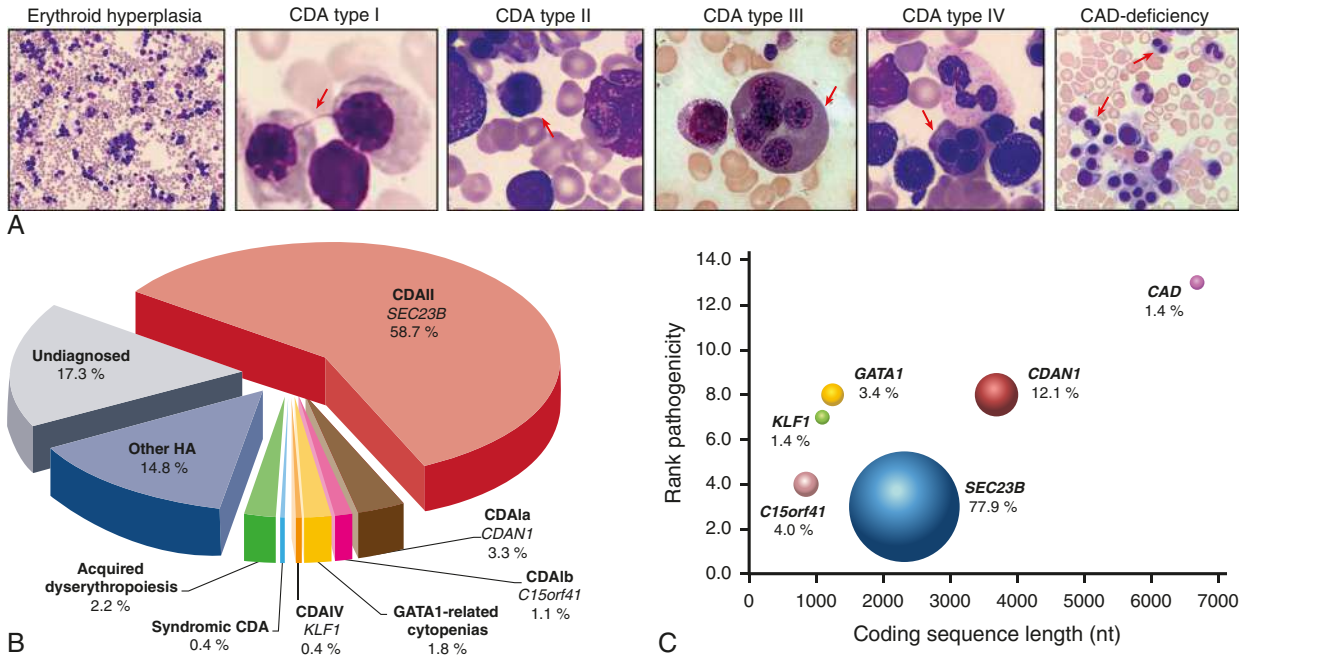

Fig. 501.1 Morphologic and molecular features of patients with congenital dyserythropoietic anemias (CDA). **A,** Light microscopy analysis of the bone marrow from patients with different CDA subtypes. CDA patients generally show erythroid hyperplasia. *Red arrows* indicate typical findings for each CDA subtype: CDAI, internuclear chromatin bridging; CDAII, binucleate erythroid precursors; CDAIII, giant multinucleated erythroblasts; CDAIV, multinucleate erythroblasts; and CAD deficiency, binucleate CDAII-like precursors. **B,** Pie chart showing the frequencies of the different CDA subtypes diagnosed after genetic testing in patients clinically suspected of having CDA. The frequency of each condition was calculated as the ratio between the number of patients in each CDA subtype and the overall count of patients tested (n = 218 patients [those included in our international registry of CDAs from 1995 to 2019]). Six patients originally suspected of CDA showed conclusive diagnosis of acquired dyserythropoiesis: two patients with liver failure, two with iron-deficiency anemia, one with erythrophagocytosis, and one with transient erythroblastopenia. Syndromic CDA refers to one patient with a mutation in the CAD gene. GATA1-related cytopenias include: X-linked thrombocytopenia with or without dyserythropoietic anemia; congenital erythropoietic porphyria; and idiopathic cytopenias of undetermined significance. Other hereditary anemias (HA) include: hereditary spherocytosis; hereditary dehydrated stomatocytosis; red cell enzymatic defects; and sideroblastic anemia. The undiagnosed cases were evaluated by analysis of the CDA gene panel, by extended targeted next-generation sequencing for hereditary anemias, or by whole-exome sequencing. **C,** Bubble chart defining the lengths of the coding sequences of each CDA-causative gene and their relative pathogenicity scores. These scores were calculated by combining the constraint metrics of each gene available at the ExAC database (http://exac.broadinstitute.org/). High pathogenicity scores identify increased constraints (intolerance to variation). The more intolerant to variation a gene is, the less likely it is to be mutated. The size of each bubble represents the frequency of the mutations in each gene, as calculated by the ratio of the number of mutated alleles for each gene and the overall count of disease alleles (n = 149, from 78 patients included in our international registry of CDAs from 2008 to 2019). (*From Iolascon A, Andolfo I, Russo R. Congenital dyserythropoietic anemias. Blood. 2020;136:1274–1281; Fig. 1.*)

posterior mediastinal or paravertebral masses. Iron overload occurs in both transfusion dependent and independent patients.

Laboratory Findings

The anemia is normocytic and is generally mild with inappropriately low reticulocytes. Hemoglobin levels are lower in children than adults and range from 8-11 g/dL. The peripheral blood smear shows anisopoikilocytosis, occasional basophilic stippling, as well as a few, sometimes binucleate, mature erythroblasts. The bone marrow aspirate is normoblastic but hypercellular, with erythroid hyperplasia. Binucleated and multinucleated erythroblasts with equal nuclei size (10–35%) and karyorrhexis (fragmentation of the nuclei) in >2% are characteristic. Electron micrographs demonstrate vesicles laden with endoplasmic reticulum proteins running beneath the plasma membrane (double membranes). Ninety-five percent of patients with CDA II have hypoglycosylated band 3, which has faster migration on the gel, and the diagnosis may be made by analyzing red blood cell membrane proteins with sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS PAGE).

Treatment

Most patients can lead a normal life and have a normal life expectancy if complications and consequences are managed appropriately. Approximately 10% of patients will require red cell transfusions in infancy and childhood but rarely during adulthood. Splenectomy may provide hematologic improvement and is currently recommended for patients with severe anemia and/or symptomatic splenomegaly. Splenectomy does not prevent further iron overloading, even in those patients whose hemoglobin is normalized, presumably because of persistent ineffective erythropoiesis in the bone marrow. Secondary iron overload is the most prominent long-term complication and should be approached as previously outlined.

Allogeneic stem cell transplantation may also be considered for severe cases.

CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE III

CDA type III **(CDA III)** is an extremely rare, poorly defined entity characterized by mild to moderate macrocytic anemia. It is inherited in an autosomal dominant or de novo fashion, although there have been cases that might represent other inheritance patterns. CDA III is caused by pathogenic variants in *KIF23*, which encodes a ubiquitous protein, mitotic kinesin-like protein 1, which regulates daughter cell separation during mitosis. Iron overload is not clinically significant (likely due to hemolysis being predominantly intravascular), and spleen size is generally normal. Patients can present with angioid streaks with macular degeneration. An association with monoclonal gammopathy and multiple myeloma is also reported. The blood smear shows macrocytes, anisopoikilocytosis, and occasional basophilic stippling. The bone marrow is notable for giant erythroid precursors that are often multinucleated, containing up to 12 nuclei per cell. Such multinucleated erythroblasts can also be seen in myelodysplasia and erythroleukemia. Transfusions are usually not required.

TRANSCRIPTION FACTOR–RELATED CDA

Transcription factor–related CDA includes CDA type IV (CDA IV) and X-linked thrombocytopenia with or without dyserythropoietic anemia (XLTDA). CDA IV has an autosomal dominant inheritance due to pathogenic variants in *KLF1*, which encodes an erythroid transcription factor that regulates fetal hemoglobin switching and is necessary for terminal erythroid differentiation. Patients have severe hemolytic anemia with no or mild reticulocytosis and very high fetal hemoglobin. Bone marrow morphology consists of hypercellularity and binucleate or multinucleate erythroblasts. Electron micrographs show immature red cell progenitors that have atypical inclusions within the cytoplasm, nuclear membrane invaginations, and heterochromatin.

XLTDA is an X-linked condition due to pathogenic variants in *GATA1*, a DNA-binding protein with two zinc fingers and a transactivation domain that plays a key role in development and maintenance of red cell and platelet lineages. The laboratory features of this condition include mild to severe anemia and macrothrombocytopenia with poorly granulated platelets. Bone marrow morphology shows dyserythropoiesis and megakaryocytes that are abnormal and reduced in number. Patients present with bleeding and anemia, and management includes transfusion and supportive care.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 502

Physiologic Anemia of Infancy

Courtney D. Thornburg

At birth, normal full-term infants have higher hemoglobin (Hb) levels and larger red blood cells (RBCs) than do older children and adults. However, within the first week of life, a progressive decline in Hb level begins and then persists for 6-8 weeks. The resulting anemia is known as the **physiologic anemia of infancy**.

With the onset of respiration at birth, considerably more oxygen becomes available for binding to Hb, and as a result the Hb-oxygen saturation increases from 50–95% or more. There is also a gradual, normal developmental switch from fetal to adult Hb synthesis after birth that results in the replacement of high-oxygen-affinity fetal Hb with lower-affinity adult Hb, capable of delivering more oxygen to tissues. The increase in blood oxygen content and delivery results in the downregulation of erythropoietin (EPO) production, leading to suppression of erythropoiesis. Because there is no erythropoiesis, aged RBCs that are removed from the circulation are not replaced, and the Hb level decreases. The Hb concentration continues to decline until tissue oxygen needs become greater than oxygen delivery. Normally, this point is reached between 8-12 weeks of age, when the Hb concentration is about 11 g/dL. In healthy term infants, the nadir rarely falls below 10 g/dL. At this juncture, EPO production increases and erythropoiesis resumes. The supply of stored reticuloendothelial iron, derived from previously degraded RBCs, remains sufficient for this renewed Hb synthesis, even in the absence of dietary iron intake, until approximately 20 weeks of age. In all, this "anemia" should be viewed as a physiologic adaptation to extrauterine life, reflecting the excess oxygen delivery relative to tissue oxygen requirements. There is no hematologic problem, and no therapy is required unless physiologic anemia of infancy is exacerbated by other ongoing processes including nutritional deficiency and blood loss. The degree of anemia at birth is correlated with maternal hemoglobin.

A late **hyporegenerative anemia**, with reticulocytopenia, can occur in infants with **hemolytic disease of the newborn**. The persistence of maternally derived anti-RBC antibodies in the infant's circulation can lead to an ongoing low-grade hemolytic anemia that can exaggerate the physiologic anemia. Lower-than-expected Hb at the "physiologic" nadir has also been seen in infants after intrauterine or neonatal RBC transfusions. When infants are transfused with adult blood containing HbA, the associated shift of the oxygen dissociation curve facilitates oxygen delivery to the tissues. Accordingly, the definition of anemia and the need for transfusion should be based not only on the infant's Hb level, but also on oxygen requirements and the ability of circulating RBCs to release oxygen to the tissues.

Premature infants also develop a physiologic anemia, known as **anemia of prematurity**. The Hb decline is both more extreme and more rapid. Hb levels of 7-9 g/dL usually are reached by 3-6 weeks of age, and levels may be even lower in very small premature infants (see Chapter 139). The same physiologic factors at play in term infants are exaggerated in preterm infants. In premature infants, the physiologic Hb decline may be intensified by blood loss from repeated phlebotomies obtained to monitor ill neonates. Demands on erythropoiesis are further heightened by the premature infant's presumed shortened RBC life span (40-60 days) and the accelerated expansion of RBC mass that accompanies the premature baby's rapid rate of growth. Nonetheless, plasma EPO levels are lower than would be expected for the degree of anemia, resulting in a suboptimal erythropoietic response. The reason for diminished EPO levels is not fully understood. During fetal life, EPO synthesis is handled primarily by the liver, and the liver's oxygen sensor is less sensitive to hypoxia compared with that of the kidney. The developmental switch from liver to kidney EPO production is not accelerated by early birth, and thus the preterm infant must rely on the liver as the primary site for synthesis, leading to diminished responsiveness to anemia. An additional mechanism thought to contribute to diminished EPO levels may be accelerated EPO metabolism. Because the pronounced decline in Hb that occurs in many very low birthweight infants may be associated with abnormal clinical signs, this "anemia of prematurity" is not considered benign and usually requires transfusions when symptomatic.

TREATMENT

In the **full-term infant**, physiologic anemia requires no therapy beyond ensuring that the infant's diet contains essential nutrients for normal hematopoiesis. For infants who are exclusively breastfed, iron supplementation is indicated beginning at 4 months of age and continued until oral iron intake via food is sufficient. In **premature infants**, an optimal Hb has not been established and is usually dictated by the infant's overall clinical condition. Transfusions may be needed to maintain the Hb at what is considered safe for that child. Premature infants who are feeding well and growing normally rarely need transfusion unless iatrogenic blood loss has been significant. Although factors such as poor weight gain, respiratory difficulties, and abnormal heart rate have prompted transfusion, the beneficial effect has not been documented. Laboratory tests such as blood lactate, EPO, and mixed venous oxygen saturation have poor predictive value. A restrictive strategy does not increase infant morbidity or mortality. Long-term neurodevelopmental outcomes have been found to be poorer in liberally transfused neonates. Exposure to packed RBCs may be related to the development of necrotizing enterocolitis, and early transfusions may be associated with the risk of intraventricular hemorrhage. Iron supplementation is indicated starting at 2 to 6 weeks of age until 6 to 12 months of age; dosing depends on birth weight and infants with smaller birth weights require higher doses.

Strategies to decrease anemia include delayed cord clamping, avoiding unnecessary phlebotomy, and providing adequate iron supplementation. Delayed cord clamping at birth results in fewer transfusions and a reduction in both intraventricular hemorrhage and necrotizing enterocolitis in preterm infants. Given the impact of phlebotomy losses during monitoring in the neonatal intensive care unit, attention to reducing unnecessary blood draws also has been advocated. Iron therapy is indicated for all neonates with anemia of prematurity starting at 1 month of age and continuing until about 1 year of age. Iron is prescribed as mg of elemental iron per kg/day and depends on birthweight.

When transfusions are necessary, an RBC volume of 10-15 mL/kg is recommended. It is good practice to split units derived from a single donor to minimize donor exposure if sequential transfusions are indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

TRANSCRIPTION FACTOR–RELATED CDA

Transcription factor–related CDA includes CDA type IV (CDA IV) and X-linked thrombocytopenia with or without dyserythropoietic anemia (XLTDA). CDA IV has an autosomal dominant inheritance due to pathogenic variants in *KLF1*, which encodes an erythroid transcription factor that regulates fetal hemoglobin switching and is necessary for terminal erythroid differentiation. Patients have severe hemolytic anemia with no or mild reticulocytosis and very high fetal hemoglobin. Bone marrow morphology consists of hypercellularity and binucleate or multinucleate erythroblasts. Electron micrographs show immature red cell progenitors that have atypical inclusions within the cytoplasm, nuclear membrane invaginations, and heterochromatin.

XLTDA is an X-linked condition due to pathogenic variants in *GATA1*, a DNA-binding protein with two zinc fingers and a transactivation domain that plays a key role in development and maintenance of red cell and platelet lineages. The laboratory features of this condition include mild to severe anemia and macrothrombocytopenia with poorly granulated platelets. Bone marrow morphology shows dyserythropoiesis and megakaryocytes that are abnormal and reduced in number. Patients present with bleeding and anemia, and management includes transfusion and supportive care.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 502

Physiologic Anemia of Infancy

Courtney D. Thornburg

At birth, normal full-term infants have higher hemoglobin (Hb) levels and larger red blood cells (RBCs) than do older children and adults. However, within the first week of life, a progressive decline in Hb level begins and then persists for 6-8 weeks. The resulting anemia is known as the **physiologic anemia of infancy**.

With the onset of respiration at birth, considerably more oxygen becomes available for binding to Hb, and as a result the Hb-oxygen saturation increases from 50–95% or more. There is also a gradual, normal developmental switch from fetal to adult Hb synthesis after birth that results in the replacement of high-oxygen-affinity fetal Hb with lower-affinity adult Hb, capable of delivering more oxygen to tissues. The increase in blood oxygen content and delivery results in the downregulation of erythropoietin (EPO) production, leading to suppression of erythropoiesis. Because there is no erythropoiesis, aged RBCs that are removed from the circulation are not replaced, and the Hb level decreases. The Hb concentration continues to decline until tissue oxygen needs become greater than oxygen delivery. Normally, this point is reached between 8-12 weeks of age, when the Hb concentration is about 11 g/dL. In healthy term infants, the nadir rarely falls below 10 g/dL. At this juncture, EPO production increases and erythropoiesis resumes. The supply of stored reticuloendothelial iron, derived from previously degraded RBCs, remains sufficient for this renewed Hb synthesis, even in the absence of dietary iron intake, until approximately 20 weeks of age. In all, this "anemia" should be viewed as a physiologic adaptation to extrauterine life, reflecting the excess oxygen delivery relative to tissue oxygen requirements. There is no hematologic problem, and no therapy is required unless physiologic anemia of infancy is exacerbated by other ongoing processes including nutritional deficiency and blood loss. The degree of anemia at birth is correlated with maternal hemoglobin.

A late **hyporegenerative anemia**, with reticulocytopenia, can occur in infants with **hemolytic disease of the newborn**. The persistence of maternally derived anti-RBC antibodies in the infant's circulation can lead to an ongoing low-grade hemolytic anemia that can exaggerate the physiologic anemia. Lower-than-expected Hb at the "physiologic" nadir has also been seen in infants after intrauterine or neonatal RBC transfusions. When infants are transfused with adult blood containing HbA, the associated shift of the oxygen dissociation curve facilitates oxygen delivery to the tissues. Accordingly, the definition of anemia and the need for transfusion should be based not only on the infant's Hb level, but also on oxygen requirements and the ability of circulating RBCs to release oxygen to the tissues.

Premature infants also develop a physiologic anemia, known as **anemia of prematurity**. The Hb decline is both more extreme and more rapid. Hb levels of 7-9 g/dL usually are reached by 3-6 weeks of age, and levels may be even lower in very small premature infants (see Chapter 139). The same physiologic factors at play in term infants are exaggerated in preterm infants. In premature infants, the physiologic Hb decline may be intensified by blood loss from repeated phlebotomies obtained to monitor ill neonates. Demands on erythropoiesis are further heightened by the premature infant's presumed shortened RBC life span (40-60 days) and the accelerated expansion of RBC mass that accompanies the premature baby's rapid rate of growth. Nonetheless, plasma EPO levels are lower than would be expected for the degree of anemia, resulting in a suboptimal erythropoietic response. The reason for diminished EPO levels is not fully understood. During fetal life, EPO synthesis is handled primarily by the liver, and the liver's oxygen sensor is less sensitive to hypoxia compared with that of the kidney. The developmental switch from liver to kidney EPO production is not accelerated by early birth, and thus the preterm infant must rely on the liver as the primary site for synthesis, leading to diminished responsiveness to anemia. An additional mechanism thought to contribute to diminished EPO levels may be accelerated EPO metabolism. Because the pronounced decline in Hb that occurs in many very low birthweight infants may be associated with abnormal clinical signs, this "anemia of prematurity" is not considered benign and usually requires transfusions when symptomatic.

TREATMENT

In the **full-term infant**, physiologic anemia requires no therapy beyond ensuring that the infant's diet contains essential nutrients for normal hematopoiesis. For infants who are exclusively breastfed, iron supplementation is indicated beginning at 4 months of age and continued until oral iron intake via food is sufficient. In **premature infants**, an optimal Hb has not been established and is usually dictated by the infant's overall clinical condition. Transfusions may be needed to maintain the Hb at what is considered safe for that child. Premature infants who are feeding well and growing normally rarely need transfusion unless iatrogenic blood loss has been significant. Although factors such as poor weight gain, respiratory difficulties, and abnormal heart rate have prompted transfusion, the beneficial effect has not been documented. Laboratory tests such as blood lactate, EPO, and mixed venous oxygen saturation have poor predictive value. A restrictive strategy does not increase infant morbidity or mortality. Long-term neurodevelopmental outcomes have been found to be poorer in liberally transfused neonates. Exposure to packed RBCs may be related to the development of necrotizing enterocolitis, and early transfusions may be associated with the risk of intraventricular hemorrhage. Iron supplementation is indicated starting at 2 to 6 weeks of age until 6 to 12 months of age; dosing depends on birth weight and infants with smaller birth weights require higher doses.

Strategies to decrease anemia include delayed cord clamping, avoiding unnecessary phlebotomy, and providing adequate iron supplementation. Delayed cord clamping at birth results in fewer transfusions and a reduction in both intraventricular hemorrhage and necrotizing enterocolitis in preterm infants. Given the impact of phlebotomy losses during monitoring in the neonatal intensive care unit, attention to reducing unnecessary blood draws also has been advocated. Iron therapy is indicated for all neonates with anemia of prematurity starting at 1 month of age and continuing until about 1 year of age. Iron is prescribed as mg of elemental iron per kg/day and depends on birthweight.

When transfusions are necessary, an RBC volume of 10-15 mL/kg is recommended. It is good practice to split units derived from a single donor to minimize donor exposure if sequential transfusions are indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 503

Megaloblastic Anemias

Courtney D. Thornburg

Megaloblastic anemia describes a group of disorders that are caused by impaired DNA synthesis. Red blood cells (RBCs) are larger than normal at every developmental stage, and there is maturational asynchrony between the nucleus and cytoplasm of erythrocytes. The delayed nuclear development becomes increasingly evident as cell divisions proceed. Myeloid and platelet precursors are also affected, and giant metamyelocytes and neutrophil bands are often present in the bone marrow. *There is often an associated thrombocytopenia and leukopenia*. The peripheral blood smear is notable for large, often oval RBCs with increased mean corpuscular volume (Fig. 503.1). Neutrophils are characteristically hypersegmented, with many having more than five lobes (see Fig. 503.1). Most cases of childhood megaloblastic anemia result from a deficiency of folic acid or vitamin B_{12} (cobalamin), vitamins essential for DNA synthesis (Table 503.1). Rarely, these anemias may be caused by inborn errors of metabolism. Megaloblastic anemias resulting from malnutrition are relatively uncommon in the United States but are important worldwide (see Chapters 62, 64, and 496).

503.1 Folic Acid Deficiency

Courtney D. Thornburg

Folates are essential for DNA replication and cellular proliferation. Humans cannot synthesize folate and must depend on dietary sources, including green vegetables, fruits, and animal organs (e.g., liver, kidney). Folates are heat labile and water soluble; consequently, boiling or heating folate sources leads to decreased amounts of the vitamin. Naturally occurring folates are in a polyglutamated form that is less efficiently absorbed than the monoglutamate species (i.e., folic acid). Dietary folate polyglutamates are hydrolyzed to simple folates that are absorbed primarily in the proximal small intestine by a specific carrier-mediated system. Folates travel in the bloodstream and are taken up in cells, primarily in the form of unconjugated methyltetrahydrofolate, which is subsequently reconjugated (polyglutamated) in the cell. There is an active enterohepatic circulation. Although rare, megaloblastic anemia because of folate deficiency has its peak incidence at 4-7 months of age, somewhat earlier than iron-deficiency anemia, although both conditions may be present concomitantly in infants with poor nutrition.

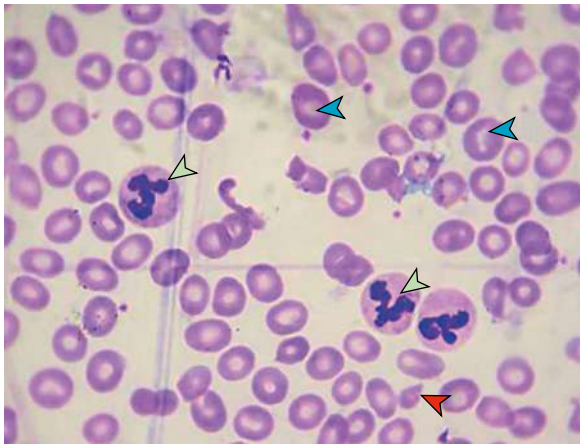

Fig. 503.1 Peripheral blood film shows hypersegmented neutrophils *(green arrowheads)*, macrocytes *(blue arrowheads)*, and a teardrop-shaped red blood cell *(red arrowhead)*. *(From Bawaskar HS, Bawaskar P, Bawaskar PH, Parekh PB. Tropical megaloblastic anemia. Lancet 2019;393:2261–2262.)*

ETIOLOGY

Folic acid deficiency can result from inadequate folate intake, decreased folate absorption, or acquired and congenital disorders of folate metabolism or transport (Table 503.2).

Inadequate Folate Intake

In the United States, anemia caused by insufficient folate intake usually occurs in the context of increased vitamin requirements associated with pregnancy, periods of accelerated growth, and chronic hemolysis (see Chapter 67.6). Folate requirements greatly increase during pregnancy, in part to meet fetal needs, and deficiencies are common in mothers, particularly those who are poor or malnourished. Folate supplementation is recommended from the start of pregnancy to prevent neural tube defects and to meet the needs of the developing fetus. Folate-deficient mothers generally do not give birth to infants with clinical folate deficiency because there is selective transfer of folate

Table 503.1 Causes of Red Blood Cell Macrocytosis

CAUSATIVE CONDITIONS	ACCOMPANYING HEMATOLOGIC FEATURES
MEGALOBLASTIC ANEMIA	
Cobalamin (vitamin B_{12}) deficiency	Megaloblastic changes, including hypersegmented neutrophils
Folate deficiency	Macrocytosis can become severe
Antifolate drugs (e.g., methotrexate)	Mild reticulocytopenia
Cytotoxic drugs (e.g., hydroxyurea, 5-FU)	Pancytopenia (when the megaloblastic process is severe)
Immunosuppressive drugs (e.g., azathioprine)	
Thiamine-responsive anemia	
Hereditary orotic aciduria	
DISORDERS OF ERYTHROID PRODUCTION	
Aplastic anemia, PRCA, Blackfan-Diamond anemia	Nonmegaloblastic
Some sideroblastic anemias	Some disorders feature dyserythropoiesis and sometimes hyposegmented neutrophils
CDA, non-CDA dyserythropoiesis, Fanconi anemia	
Myelodysplasia, myeloproliferative diseases	Macrocytosis can often be severe (e.g., aplastic processes)
	Reticulocytopenia (often severe)
RETICULOCYTOSIS	
Chronic hemolytic anemia	Nonmegaloblastic; no hypersegmented neutrophils
DRUGS AND TOXINS	
Alcohol abuse	Mechanism of macrocytosis is often unknown
Some antiviral drugs (e.g., nucleoside RT inhibitors)	No hypersegmented neutrophils
Some anticonvulsant drugs	
NONHEMATOLOGIC DISEASES	
Chronic liver diseases	Nonmegaloblastic; no hypersegmented neutrophils
Hypothyroidism	
Copper deficiency	Macrocytes are rarely oval
ARTIFACTS	
RBC clumping by cold agglutinins; some warm RBC antibodies	Nonmegaloblastic; no hypersegmented neutrophils
Severe hyperglycemia	Disparity between high MCV and normal morphologic examination
Hyponatremia	

CDA, Congenital dyserythropoietic anemia; MCV, mean corpuscular volume; PRCA, pure red cell aplasia; RBC, red blood cell; RT, reverse transcriptase; 5-FU, 5-fluorouracil.
From Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier, 2015; Table 10-3.

Table 503.2 Causes of Folate Deficiency* in Adults and Children

INADEQUATE NUTRITION
Poor diet†
Poor food preparation methods
Exclusive feeding with goat's milk
DEFECTS IN ABSORPTION
Gastric achlorhydria§
Diseases of the upper small intestine
Tropical sprue
Celiac disease
Dermatitis herpetiformis
Inflammatory bowel disease
Oral pancreatic replacement therapy§
Hereditary folate malabsorption
INCREASED REQUIREMENTS OR LOSSES
Pregnancy
Lactation§
Prematurity§,‖
Chronic hemolytic anemia§
Dialysis
Hyperthyroidism§
Lesch-Nyhan syndrome
DISORDERS OF TRANSPORT
Cerebral folate deficiency (genetic or acquired)¶
DISORDERS OF CELLULAR METABOLISM
Drugs inhibiting folate metabolism
Antifolates (e.g., methotrexate)
Pyrimethamine§; trimethoprim§
Sulfasalazine§
Valproic acid§,#
Inherited defects
Methylenetetrahydrofolate reductase (MTHFR) deficiency
Disorders of intracellular cobalamin metabolism
Dihydrofolate reductase deficiency
Methylenetetrahydrofolate dehydrogenase, cyclohydrolase, and formyltetrahydrofolate synthetase 1 (MTHFD1) deficiency
Others
MULTIFACTORIAL OR UNCERTAIN MECHANISMS
Alcohol use disorder‡
Anticonvulsants§
Oral contraceptives§

*Folate deficiency is often multifactorial.
†Relative dietary insufficiency (i.e., intake that is adequate under usual circumstances) is a particularly important cofactor that can convert borderline folate deficiency to clinically overt deficiency when other conditions coexist, such as increased requirements for folate or mild malabsorption.
§Megaloblastic anemia rarely results unless other limitations of folate status coexist.
‖Neonatal stores are low in premature infants.
¶Cerebral folate deficiency can occur on a genetic basis or an autoimmune basis; megaloblastic anemia does not occur because folate deficiency appears not to exist outside the central nervous system.
#Disrupts mitochondrial folate metabolism in utero.
‡Poor intake is often associated with alcoholism in adults.
From Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier, 2015; Box 10-2.

to the fetus via placental folate receptors. Rapid growth after birth increases demands for folic acid, and infants who are premature or ill and those with certain hemolytic disorders will have particularly high folate requirements. Human breast milk, infant formulas, and pasteurized cow's milk provide adequate amounts of folic acid. *Goat's milk is folate deficient, and supplementation must be given when it is the child's main food source.* Unless supplemented, powdered milk may also be a poor source of folic acid.

Malnutrition is the most common cause of folate deficiency in older children. In addition, children with chronic hemolytic anemias, infections, or malabsorption are at increased risk due to increased demand. Because body stores of folate are limited, deficiency can develop quickly in malnourished individuals. On a folate-free diet, megaloblastic anemia will occur after 2-3 months.

Decreased Folate Absorption

Malabsorption caused by chronic diarrheal states or diffuse inflammatory disease can lead to folate deficiency. In both situations, some of the decreased folate absorption may be caused by impaired folate conjugase activity. Chronic diarrhea also interferes with the enterohepatic circulation of folate, thereby enhancing folate losses because of rapid intestinal passage. Megaloblastic anemia caused by folic acid deficiency can occur in celiac disease or chronic infectious enteritis and in association with enteroenteric fistulas. Previous intestinal surgery is another potential cause of decreased folate absorption.

Certain anticonvulsant drugs (e.g., phenytoin, phenobarbital) can impair folic acid absorption, and many patients treated with these drugs have low serum levels. Frank megaloblastic anemia is rare and readily responds to folic acid therapy, even when administration of the offending drug is continued. Alcohol overuse also is associated with folate malabsorption.

Congenital Abnormalities in Folate Transport and Metabolism

Inborn errors of folate transport or metabolism are rare but can be life threatening. Those associated with megaloblastic anemia include hereditary folate malabsorption and certain extremely uncommon enzyme deficiencies.

Hereditary folate malabsorption (HFM) is an autosomal recessive disorder caused by loss-of-function pathogenic variants in the *SLC46A1* gene encoding the protein-coupled folate transporter. HFM is associated with an inability to absorb folic acid, 5-tetrahydrofolate, 5-methyltetrahydrofolate, or 5-formyltetrahydrofolate (folinic acid). It can become apparent at 2-6 months of age with megaloblastic anemia and other deficits, including infections and diarrhea. Neurologic abnormalities attributable to folate deficiency in the central nervous system (CNS) include seizures, developmental delay, and intellectual disability. Folate transport is impaired both in the intestine and at the brain's choroid plexus. Serum and cerebrospinal fluid (CSF) folate levels are very low, with a loss of the normal 3:1 ratio of CSF to serum folate.

Treatment for HFM involves parenteral (intramuscular) folate or high-dose oral 5-formyltetrahydrofolate (5-formylTHF), folinic acid, leucovorin, or the active isomer of 5-formylTHF (Isovorin or Fusilev) targeting normal or near normal trough levels in the CSF to ameliorate both the megaloblastic anemia and neurologic complications of folate deficiency.

Functional methionine synthase deficiency may result from pathologic genetic variants affecting the function of methionine synthase reductase or methionine synthase. These disorders are autosomal recessive and characterized not only by megaloblastic anemia but also by cerebral atrophy, nystagmus, blindness, and altered muscle tone. Both respond to hydroxocobalamin (OHCbl) plus betaine with variable clinical success. **Dihydrofolate reductase (DHFR) deficiency** is extremely rare and is associated with homozygous pathologic genetic variants in the *DHFR* gene. Clinical symptoms include megaloblastic anemia and neurologic manifestations. Although **methylenetetrahydrofolate reductase (MTHFR) deficiency** is the most common inborn error of folate metabolism, and severe cases can produce several neurologic and vascular complications, there is *no* associated megaloblastic anemia.

Drug-Induced Abnormalities in Folate Metabolism

Several drugs have anti–folic acid activity as their primary pharmacologic effect and regularly produce megaloblastic anemia. *Methotrexate* binds to dihydrofolate reductase and prevents formation of tetrahydrofolate, the active form of folate. *Pyrimethamine,* used in the therapy of toxoplasmosis, and *trimethoprim,* used for treatment of various infections, can induce folic acid deficiency and occasionally megaloblastic anemia. Therapy with folinic acid (5-formyltetrahydrofolate) is usually beneficial.

CLINICAL MANIFESTATIONS

In addition to the clinical features associated with anemia, folate-deficient infants and children may manifest irritability, chronic diarrhea, and poor weight gain. Hemorrhages from thrombocytopenia may occur in advanced cases. HFM and other rare etiologies of folate deficiency may be further associated with hypogammaglobulinemia, severe infections, failure to thrive, neurologic abnormalities, and cognitive delays.

LABORATORY FINDINGS

The anemia is macrocytic (mean corpuscular volume >100 fL). Variations in RBC shape and size are common (see Chapter 496, Fig. 496.4B). The reticulocyte count is low, and nucleated RBCs with megaloblastic morphology are often seen in the peripheral blood. Neutropenia and thrombocytopenia may be present, particularly in patients with long-standing and severe deficiencies. The neutrophils are large, some with *hypersegmented nuclei* (see Fig. 503.1). The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation are also seen.

Levels of RBC folate are a better indicator of chronic deficiency than serum folic acid levels. The normal RBC folate level is 150-600 ng/mL of packed cells. Levels of iron and vitamin B_{12} in serum usually are normal or elevated. Serum activity of lactate dehydrogenase, a marker of ineffective erythropoiesis, is markedly elevated.

TREATMENT

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. If the specific diagnosis is in doubt, smaller doses of folate (0.1 mg/day) may be used for 1 week as a diagnostic test because a hematologic response can be expected within 72 hours. Doses of folate >0.1 mg can correct the anemia of vitamin B_{12} deficiency but might aggravate any associated neurologic abnormalities. In most medical settings in developed countries, this therapeutic trial to distinguish the different causes of megaloblastic anemia is rarely necessary because vitamin B_{12} and folate blood levels are usually readily available. Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 weeks until a definite hematologic response has occurred. Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate. Parenteral or high doses of specific folate formulations are required in the setting of HFM. Transfusions are indicated only when the anemia is severe, or the child is very ill.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

503.2 Vitamin B_{12} (Cobalamin) Deficiency

Courtney D. Thornburg

Vitamin B_{12}, a generic term encompassing all biologically active cobalamins, is a water-soluble vitamin with a central, functional cobalt atom and a planar corrin ring. Methylcobalamin and adenosyl cobalamin are the metabolically active derivatives, serving as cofactors in two essential metabolic reactions: methylation of homocysteine to methionine (via methionine synthase) and conversion of methyl-malonyl-coenzyme A (CoA) to succinyl CoA (via L-methyl-malonyl-CoA mutase). The products and by-products of these enzymatic reactions are critical to DNA, RNA, and protein synthesis.

Cobalamin (Cbl) is synthesized *exclusively* by microorganisms, and humans must rely on dietary sources (animal products, including meat, eggs, fish, and milk) for their needs (see Chapter 67.7). Unlike folate, older children and adults have sufficient vitamin B_{12} stores to last 3-5 years. In young infants born to mothers with low vitamin B_{12} stores, clinical signs of Cbl deficiency can become apparent in the first 6-18 months of life.

METABOLISM

Under normal circumstances, cobalamin is released from food protein in the stomach through peptic digestion. Cbl then binds to *haptocorrin* (HC), a salivary glycoprotein. This complex moves into the duodenum, where HC is digested by pancreatic proteases and Cbl is liberated. Cbl then binds to *intrinsic factor* (IF), another glycoprotein that is produced by gastric parietal cells. The Cbl-IF complex subsequently enters mucosal cells of the distal ileum by receptor-mediated endocytosis. Through a complex series of protein interactions, Cbl is taken up into the blood stream and taken up into cells. Cobalamins are processed in the cytoplasm to a common intermediate that can be allocated to the methylcobalamin and adenosylcobalamin synthesis pathways to meet cellular needs.

ETIOLOGY

Vitamin B_{12} deficiency can result from inadequate dietary intake of Cbl, lack of IF, impaired intestinal absorption of IF-Cbl, inactivation, or absence of vitamin B_{12} transport protein (see Table 503.1).

Inadequate Vitamin B_{12} Intake

Vitamin B_{12} deficiency in infants is most often nutritional, resulting from low Cbl levels in the breast milk of B_{12}-deficient mothers. Associated **megaloblastic anemia** often appears during the first year of life. Maternal deficiency may be caused by **pernicious anemia** or gastrointestinal disorders such as *Helicobacter pylori* infection, celiac disease, Crohn disease, or pancreatic insufficiency. Previous gastric bypass surgery, treatment with proton pump inhibitors, and inadequate intake from a strict unsupplemented vegetarian diet have also been implicated. Fortunately, because of active placental Cbl transport in utero, most children of B_{12}-deficient mothers maintain Cbl levels sufficient to support adequate prenatal development. Such infants are born with low B_{12} stores, the depletion of which is associated with a gradual onset of clinical manifestations. *Vitamin B_{12} replacement often results in rapid improvement, but the longer the deficient period, the greater the likelihood of permanent disabilities.* Neonatal screening programs may detect maternal-neonatal nutritional B_{12} deficiency because of an increase in propionyl carnitine, but there is higher sensitivity using a measurement of methylmalonic acid. In high-income countries, dietary deficiency during childhood or adolescence is infrequent but can result from strict vegetarian or vegan diet. Daily requirements range from 0.4-2.4 μg.

Impaired Vitamin B_{12} Absorption

Gastric surgery or medications that impair gastric acid secretion may result in IF deficiency, leading to decreased vitamin B_{12} absorption. Pancreatic insufficiency can also lead to Cbl deficiency because of impaired cleavage and IF complex formation. Patients with neonatal necrotizing enterocolitis, inflammatory bowel disease, celiac disease, or surgical removal of the terminal ileum may also have impaired absorption of vitamin B_{12}. An overgrowth of intestinal bacteria within diverticula or duplications of the small intestine can cause vitamin B_{12} deficiency by consumption of (or competition for) the vitamin or by splitting of its complex with IF. In these cases, *hematologic response can follow appropriate antibiotic therapy.* In endemic areas, when the fish tapeworm *Diphyllobothrium latum* infests the upper small intestine, similar mechanisms may be operative. When megaloblastic anemia occurs in such situations, the serum vitamin B_{12} level is low, and the gastric fluid contains IF.

Hereditary intrinsic factor deficiency (HIFD) is a rare autosomal recessive disorder caused by a variety of pathologic genetic variants in the *IF* gene that produce a lack of gastric IF or a functionally abnormal IF. HIFD differs from typical adult pernicious anemia in that gastric acid is secreted normally and the stomach is histologically normal. It is not associated with antibodies or endocrine abnormalities. Unlike Imerslund-Grasbeck syndrome, described next, HIFD is only occasionally associated with proteinuria. Symptoms become prominent at an early age (6-24 months), consistent with exhaustion of vitamin B_{12} stores acquired in utero. As the anemia becomes severe, weakness, irritability, anorexia, and listlessness occur. The tongue is smooth, red, and painful. Neurologic manifestations include ataxia, paresthesias, hyporeflexia, Babinski responses, and clonus. Oral vitamin B_{12} is usually *ineffective*, and lifelong intramuscular (IM) or intranasal Cbl should be used to bypass the absorption defect. The natural form, OHCbl, is believed to be more effective than the synthetic form, cyanocobalamin (CNCbl).

Imerslund-Grasbeck syndrome is a rare, recessively inherited pediatric disorder resulting in selective vitamin B_{12} malabsorption in the ileum and consequent vitamin B_{12} deficiency. It usually becomes clinically apparent within the first 6 years of life. In addition to megaloblastic anemia, the patient may also have neurologic defects (e.g., hypotonia, developmental delay, brain atrophy, movement disorders, dementia) and/or proteinuria. Patients carry pathologic variants in genes *CUBN* or *AMN*, which encode proteins that form the cubam receptor for the ileal IF-Cbl complex. Because CUBN is also a key receptor for protein reabsorption in the kidney, impaired expression at this site results in associated proteinuria. The disease can be fatal if it remains untreated. Early diagnosis and treatment with IM or intranasal Cbl will reverse the hematologic and neurologic abnormalities. Proteinuria does not respond to therapy.

Classic pernicious anemia (autoimmune gastritis) usually occurs in older adults but can rarely affect children. This disorder **(juvenile pernicious anemia)** usually presents during adolescence. In such cases, the disease is associated with various detectable antibodies, including those against IF and the hydrogen-potassium adenosine triphosphatase proton pump in gastric parietal cells. These children can have additional immunologic abnormalities, cutaneous candidiasis, hypoparathyroidism, and other endocrine deficiencies; atrophy of the gastric mucosa and achlorhydria may occur. IM or intranasal vitamin B_{12} should be administered regularly.

Absence of Vitamin B_{12} Transport Protein Transcobalamin

Transcobalamin (TC) deficiency is a rare cause of megaloblastic anemia. A congenital deficiency is inherited as an autosomal recessive condition resulting in a failure to absorb and transport vitamin B_{12}. Most patients lack TC, but some have functionally defective forms. This disorder usually manifests in the first weeks of life. Characteristically, there is failure to thrive, diarrhea, vomiting, glossitis, neurologic abnormalities, and megaloblastic anemia. The diagnosis can be difficult given that total serum vitamin B_{12} levels are often normal because approximately 80% of serum Cbl is bound to HC. The diagnosis is suggested by the presence of severe megaloblastic anemia in the face of normal folate levels and no evidence of another inborn error of metabolism. Plasma homocysteine and methylmalonic acid levels are elevated. A definitive diagnosis is made by measuring plasma TC. The serum vitamin B_{12} levels must be kept high to force enough Cbl into cells and allow normal function using high-dose oral supplementation or IM or intranasal treatment. Symptoms and laboratory studies should be monitored, and doses adjusted as needed.

Disorders of Intracellular Cobalamin Metabolism

Disorders of intracellular cobalamin metabolism are associated with pathologic genetic variants in genes associated with lettered complementation groups. These include *MMACHC (cblC)*, *MMADHC* (*cblD*-combined and *cblD* homocystinuria), *MTRR (cblE), LMBRD1 (cblF), MTR (cblG), ABCD4 (cblJ), THAP11* (*cblX*-like), *ZNF143* (*cblX*-like), or *HCFC1* (*cblX*, which can show a cblC complementation class). The disorders present at a range of ages starting in utero and have a variable clinical presentation including complications of methylmalonic acidemia, homocystinuria, and megaloblastic anemia. Patients require care with a metabolic specialist to guide treatment with OHCbl, avoidance of agents that can cause metabolic decompensation, and surveillance for complications.

Vitamin B_{12} deficiency may develop by inactivation of vitamin B_{12}. This most often occurs in adolescents who chronically use "Whippets," which contain nitrous oxide, as a recreational agent to get high. Conversely, patients with underlying vitamin B_{12} deficiency may have an exacerbation after nitrous oxide anesthesia.

CLINICAL MANIFESTATIONS

Children with Cbl deficiency often present with nonspecific manifestations such as weakness, lethargy, feeding difficulties, failure to thrive, and irritability. Other common findings include pallor, glossitis, vomiting, diarrhea, and icterus. Hyperpigmentation is another feature that may mimic Addison disease. Neurologic symptoms can include paresthesia, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, neuropsychiatric changes, and brain/spine MRI changes. Neurologic problems from vitamin B_{12} deficiency may occur in the *absence* of any hematologic abnormalities. Thrombotic microangiopathy is a rare manifestation.

LABORATORY FINDINGS

The hematologic manifestations of folate and Cbl deficiency are identical. The anemia resulting from Cbl deficiency is macrocytic, with prominent macro-ovalocytosis of the RBCs (see Chapter 496, Fig. 496.2, and Fig. 503.1). The neutrophils may be large and hypersegmented (see Fig. 503.1). In advanced cases, neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia. Macrocytosis may not always be present. Serum vitamin B_{12} levels are low, and the serum concentrations of methylmalonic acid and homocysteine are elevated. Concentrations of serum iron and serum folic acid are normal or elevated. Serum lactate dehydrogenase activity is markedly increased, a reflection of ineffective erythropoiesis. Moderate elevations of serum bilirubin levels (2-3 mg/dL) also may be found. Excessive excretion of methylmalonic acid in the urine (normal: 0-3.5 mg/24 hr) is a reliable and sensitive index of vitamin B_{12} deficiency and is especially helpful when the serum vitamin B_{12} level is in the low-normal range.

DIAGNOSIS

A comprehensive medical history is essential to the clinical recognition of possible Cbl deficiency. Information regarding clinical symptoms, dietary history, diseases, surgeries, or medications and drugs is likely to provide important clues. The physical examination may reveal relevant findings such as irritability, pallor, pigmentation or specific neurologic symptoms. Screening laboratory findings offer important information, but more focused testing will be required to confirm a diagnosis of vitamin B_{12} deficiency and its cause. Cbl deficiency is usually identified by measuring total or TC-bound vitamin B_{12} in the blood. Although an extremely low level is generally diagnostic, this may not be the case because false negatives and false positives are reportedly common using currently available assays. As a result, it is wise not to discount vitamin B_{12} deficiency, particularly in the face of clinical symptoms, macrocytic anemia, an abnormal blood smear, and a normal folate level. In untreated patients, methylmalonic acid and total homocysteine levels are often helpful because they are greatly elevated in the majority of those with clinical signs of B_{12} deficiency. Excessive urinary methylmalonic acid excretion is also a sensitive test of B_{12} deficiency. Although modest increases occur with renal failure, elevated methylmalonic acid is otherwise quite specific for B_{12} deficiency. Notably, however, serum homocysteine is also elevated in folate deficiency, homocystinuria, and renal failure.

If vitamin B_{12} deficiency has been confirmed and there is no evidence of inadequate dietary intake or, in the case of an infant, inadequate maternal B_{12}, malabsorption should be investigated. Anti-IF antibodies and anti–parietal cell antibodies are useful for the diagnosis of pernicious anemia. Measurement of IF and testing from more specialized laboratories may be required for less common disorders.

TREATMENT

Treatment regimens in children have not been well studied. The cause of vitamin B_{12} deficiency should ultimately dictate treatment dosage and route of administration as well as the duration of therapy. Cyanocobalamin is available as a nasal spray as an alternative to parenteral injection. Dose adjustments should be made in response to clinical status and laboratory values. The physiologic requirement for vitamin B_{12} is about 1-3 µg/day. Hematologic responses have been observed with small doses, indicating that a mini-dose may be administered as a therapeutic test when the diagnosis of vitamin B_{12} deficiency is in doubt or in circumstances where the anemia is severe and higher initial doses might result in severe metabolic disturbances.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

503.3 Other Rare Megaloblastic Anemias

Courtney D. Thornburg

Orotic aciduria is a rare autosomal recessive disorder that usually appears in the first year of life and is characterized by growth failure, developmental delay, megaloblastic anemia, and increased urinary excretion of orotic acid (see Chapter 110). Rarely, orotic aciduria occurs without megaloblastic anemia. This defect is the most common metabolic error in the de novo synthesis of pyrimidines and therefore affects nucleic acid synthesis. The usual form of hereditary orotic aciduria is caused by a deficiency (in all body tissues) of orotic phosphoribosyl transferase and orotidine-5-phosphate decarboxylase, two sequential enzymatic steps in pyrimidine nucleotide synthesis. The diagnosis is suggested by the presence of severe megaloblastic anemia with normal serum B_{12} and folate levels and no evidence of TC deficiency. A presumptive diagnosis is made by finding increased urinary orotic acid. However, confirmation of the diagnosis requires assay of the transferase and decarboxylase enzymes in the patient's erythrocytes. Failure to thrive and intellectual disability often accompany this condition. The anemia is refractory to vitamin B_{12} or folic acid, but the anemia responds promptly to administration of uridine.

Thiamine-responsive megaloblastic anemia (Rogers syndrome) is a very rare autosomal recessive disorder characterized by megaloblastic anemia, sensorineural deafness, and diabetes mellitus. Congenital heart defects, arrhythmias, visual problems, short stature, trilineage myelodysplasia, and strokes are also described. Thiamine-responsive megaloblastic anemia usually presents in infancy but may occasionally develop in childhood and adolescence and occurs in several ethnically distinct populations. The bone marrow is characterized not only by megaloblastic changes but also by ringed sideroblasts. The defect is caused by biallelic pathologic genetic variants in *SCL19A2*, which encodes a high-affinity plasma membrane thiamine transporter. Continuous thiamine supplementation usually reverses the anemia and diabetes, but not existing hearing defects.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 504
Iron-Deficiency Anemia

Jennifer A. Rothman

Iron deficiency is the most widespread and common nutritional disorder in the world. It is estimated that 30–50% of the global population has iron-deficiency anemia, and most of these individuals live in developing countries. In the United States, 8–14% of children ages 12-36 months are *iron deficient*, and 30% of this group progresses to *iron-deficiency anemia*.

A full-term newborn infant contains about 0.5 grams of iron, compared with 5 grams of iron in adults. This change in quantity of iron from birth to adulthood means that an average of 0.8 mg of iron must be absorbed each day during the first 15 years of life. A small additional amount is necessary to balance normal losses of iron by shedding of cells. It is therefore necessary to absorb approximately 1 mg daily to maintain positive iron balance in childhood. Because <10% of dietary iron is usually absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels. During infancy, when growth is most rapid, the 1 mg/L of iron in cow's and breast milk makes it difficult to maintain body iron. Although breastfed infants have an advantage because they absorb iron 2-3 times more efficiently than infants fed cow's milk, breastfed infants nonetheless are at risk of developing iron deficiency without regular intake of iron-fortified foods by 6 months of age.

ETIOLOGY

Most iron in neonates resides in circulating hemoglobin. As the relatively high hemoglobin concentration of the newborn infant falls during the first 2-3 months of life, considerable iron is recycled. These iron stores are usually sufficient for blood formation in the first 6-9 months of life in term infants. Stores are depleted sooner in premature infants, low birthweight infants, or infants with perinatal blood loss, because their iron stores are smaller. Delayed (1-3 minute) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30 seconds) puts the infant at risk for iron deficiency. Dietary sources of iron are especially important in these infants. In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 months of age and is less common thereafter. The usual dietary pattern observed in infants and toddlers with nutritional iron-deficiency anemia in developed countries is excessive consumption of cow's milk (low iron content, blood loss from milk protein colitis) in a child who is often overweight or bottle feeding beyond 12 months of age. Worldwide, **undernutrition** is usually responsible for iron deficiency (Table 504.1).

Blood loss must be considered as a possible cause in every case of iron-deficiency anemia. Sources of blood loss, particularly in older children and adolescents, include menstrual losses, recurrent nosebleeds, or intravascular hemolysis with hemoglobinuria, as seen in diseases such as malaria or endurance athletics such as triathletes. Chronic iron-deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Infants can have chronic intestinal blood loss induced by exposure to cow's milk protein. Involved infants characteristically develop anemia that is more severe and occurs earlier than would be expected simply from an inadequate intake of iron. The ongoing loss of blood in the stools can be prevented either by breastfeeding or by delaying the introduction of whole cow's milk in the first years of life and then limiting the quantity to <24 oz/24 hours. *Infants and toddlers who have excessive raw milk intake with no iron supplementation and limited iron containing foods are at high risk of iron deficiency.* Unrecognized blood loss also can be associated with chronic diarrhea and, rarely, with pulmonary hemosiderosis. In developing countries, infections with hookworm, *Trichuris trichiura,* and *Plasmodium* often contribute to iron deficiency. Since iron is absorbed in the proximal duodenum with the assistance of gastric acid, gastric bypass procedures or *Helicobacter pylori* infection may interfere with iron absorption. Similarly, inflammation of the bowel from celiac disease and giardiasis may also interfere with iron absorption.

Approximately 2% of adolescent females have iron-deficiency anemia, largely as a result of their adolescent growth spurt and menstrual blood loss. The highest risk of iron-deficiency anemia (>30%) is among teenagers who are or have been pregnant.

CLINICAL MANIFESTATIONS

Most children with iron-deficiency anemia are asymptomatic and are identified by routine laboratory screening at 9-12 months of age. Normal hemoglobin values vary according to age, gender, ethnicity, and method of testing, such as capillary versus venous blood. Pallor is the

TREATMENT

Treatment regimens in children have not been well studied. The cause of vitamin B_{12} deficiency should ultimately dictate treatment dosage and route of administration as well as the duration of therapy. Cyanocobalamin is available as a nasal spray as an alternative to parenteral injection. Dose adjustments should be made in response to clinical status and laboratory values. The physiologic requirement for vitamin B_{12} is about 1-3 µg/day. Hematologic responses have been observed with small doses, indicating that a mini-dose may be administered as a therapeutic test when the diagnosis of vitamin B_{12} deficiency is in doubt or in circumstances where the anemia is severe and higher initial doses might result in severe metabolic disturbances.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

503.3 Other Rare Megaloblastic Anemias

Courtney D. Thornburg

Orotic aciduria is a rare autosomal recessive disorder that usually appears in the first year of life and is characterized by growth failure, developmental delay, megaloblastic anemia, and increased urinary excretion of orotic acid (see Chapter 110). Rarely, orotic aciduria occurs without megaloblastic anemia. This defect is the most common metabolic error in the de novo synthesis of pyrimidines and therefore affects nucleic acid synthesis. The usual form of hereditary orotic aciduria is caused by a deficiency (in all body tissues) of orotic phosphoribosyl transferase and orotidine-5-phosphate decarboxylase, two sequential enzymatic steps in pyrimidine nucleotide synthesis. The diagnosis is suggested by the presence of severe megaloblastic anemia with normal serum B_{12} and folate levels and no evidence of TC deficiency. A presumptive diagnosis is made by finding increased urinary orotic acid. However, confirmation of the diagnosis requires assay of the transferase and decarboxylase enzymes in the patient's erythrocytes. Failure to thrive and intellectual disability often accompany this condition. The anemia is refractory to vitamin B_{12} or folic acid, but the anemia responds promptly to administration of uridine.

Thiamine-responsive megaloblastic anemia (Rogers syndrome) is a very rare autosomal recessive disorder characterized by megaloblastic anemia, sensorineural deafness, and diabetes mellitus. Congenital heart defects, arrhythmias, visual problems, short stature, trilineage myelodysplasia, and strokes are also described. Thiamine-responsive megaloblastic anemia usually presents in infancy but may occasionally develop in childhood and adolescence and occurs in several ethnically distinct populations. The bone marrow is characterized not only by megaloblastic changes but also by ringed sideroblasts. The defect is caused by biallelic pathologic genetic variants in *SCL19A2*, which encodes a high-affinity plasma membrane thiamine transporter. Continuous thiamine supplementation usually reverses the anemia and diabetes, but not existing hearing defects.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 504
Iron-Deficiency Anemia

Jennifer A. Rothman

Iron deficiency is the most widespread and common nutritional disorder in the world. It is estimated that 30–50% of the global population has iron-deficiency anemia, and most of these individuals live in developing countries. In the United States, 8–14% of children ages 12-36 months are *iron deficient*, and 30% of this group progresses to *iron-deficiency anemia*.

A full-term newborn infant contains about 0.5 grams of iron, compared with 5 grams of iron in adults. This change in quantity of iron from birth to adulthood means that an average of 0.8 mg of iron must be absorbed each day during the first 15 years of life. A small additional amount is necessary to balance normal losses of iron by shedding of cells. It is therefore necessary to absorb approximately 1 mg daily to maintain positive iron balance in childhood. Because <10% of dietary iron is usually absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels. During infancy, when growth is most rapid, the 1 mg/L of iron in cow's and breast milk makes it difficult to maintain body iron. Although breastfed infants have an advantage because they absorb iron 2-3 times more efficiently than infants fed cow's milk, breastfed infants nonetheless are at risk of developing iron deficiency without regular intake of iron-fortified foods by 6 months of age.

ETIOLOGY

Most iron in neonates resides in circulating hemoglobin. As the relatively high hemoglobin concentration of the newborn infant falls during the first 2-3 months of life, considerable iron is recycled. These iron stores are usually sufficient for blood formation in the first 6-9 months of life in term infants. Stores are depleted sooner in premature infants, low birthweight infants, or infants with perinatal blood loss, because their iron stores are smaller. Delayed (1-3 minute) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30 seconds) puts the infant at risk for iron deficiency. Dietary sources of iron are especially important in these infants. In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 months of age and is less common thereafter. The usual dietary pattern observed in infants and toddlers with nutritional iron-deficiency anemia in developed countries is excessive consumption of cow's milk (low iron content, blood loss from milk protein colitis) in a child who is often overweight or bottle feeding beyond 12 months of age. Worldwide, **undernutrition** is usually responsible for iron deficiency (Table 504.1).

Blood loss must be considered as a possible cause in every case of iron-deficiency anemia. Sources of blood loss, particularly in older children and adolescents, include menstrual losses, recurrent nosebleeds, or intravascular hemolysis with hemoglobinuria, as seen in diseases such as malaria or endurance athletics such as triathletes. Chronic iron-deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Infants can have chronic intestinal blood loss induced by exposure to cow's milk protein. Involved infants characteristically develop anemia that is more severe and occurs earlier than would be expected simply from an inadequate intake of iron. The ongoing loss of blood in the stools can be prevented either by breastfeeding or by delaying the introduction of whole cow's milk in the first years of life and then limiting the quantity to <24 oz/24 hours. *Infants and toddlers who have excessive raw milk intake with no iron supplementation and limited iron containing foods are at high risk of iron deficiency.* Unrecognized blood loss also can be associated with chronic diarrhea and, rarely, with pulmonary hemosiderosis. In developing countries, infections with hookworm, *Trichuris trichiura,* and *Plasmodium* often contribute to iron deficiency. Since iron is absorbed in the proximal duodenum with the assistance of gastric acid, gastric bypass procedures or *Helicobacter pylori* infection may interfere with iron absorption. Similarly, inflammation of the bowel from celiac disease and giardiasis may also interfere with iron absorption.

Approximately 2% of adolescent females have iron-deficiency anemia, largely as a result of their adolescent growth spurt and menstrual blood loss. The highest risk of iron-deficiency anemia (>30%) is among teenagers who are or have been pregnant.

CLINICAL MANIFESTATIONS

Most children with iron-deficiency anemia are asymptomatic and are identified by routine laboratory screening at 9-12 months of age. Normal hemoglobin values vary according to age, gender, ethnicity, and method of testing, such as capillary versus venous blood. Pallor is the

serum transferrin levels that are accompanied by the deposition of non–transferrin-bound iron in parenchymal tissues. Because hepcidin production is induced by inflammatory stimuli, hepcidin elevation is also a feature of the **anemia of chronic disease** (ACD). However, in contrast to patients with IRIDA, in whom the hepcidin dysregulation is congenital, patients with ACD generally retain normal to high iron stores because of the acquired nature of their hepcidin elevation (see Chapter 500.1). Rare medical causes that may mimic IRIDA include vascular malformations of the GI tract, Castleman disease (where IL-6 overproduction causes hepcidin elevation), autoimmune gastritis, and pathogenic germline variants in *KCNQ1* (which regulates gastric acid secretion).

TREATMENT

Because of the underlying pathophysiology of IRIDA, *parenteral iron supplementation* is required to correct the anemia. Although parenteral iron therapy raises body iron stores, the hematologic response is usually slow and not completely corrective. This likely results from insufficient export of the processed iron from macrophages into the circulation, an expected consequence of hepcidin elevation. Serum ferritin levels increase with parenteral iron therapy in a dose-dependent manner and may raise concerns for iron overload, which would be expected to exhibit a reticuloendothelial rather than a parenchymal pattern of iron loading. Given the limited number of IRIDA cases reported to date, the optimal formulation and dosing of parenteral iron have not yet been established. Although oral iron supplementation does not appear to have a significant role in treatment of IRIDA, the addition of ascorbic acid to a ferrous sulfate oral supplement has been associated with hematologic responses in isolated cases. Treatment with recombinant erythropoietin has not been found to produce significant clinical benefit in patients with IRIDA.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 505

Other Microcytic Anemias

Jennifer A. Rothman

A number of rare microcytic anemias need to be considered when children with microcytic anemia fail to respond to oral iron (Table 504.5). These anemias include thalassemia or thalassemia trait (see Chapter 511), infantile poikilocytosis and hereditary pyropoikilocytosis (Chapter 508), and anemia of chronic disease (Chapter 500.1). Additionally, rare nutritional disorders and disorders of iron metabolism can cause microcytosis.

INFANTILE POIKILOCYTOSIS AND HEREDITARY PYROPOIKILOCYTOSIS

Infants with common **hereditary elliptocytosis** (see Chapter 508) may initially present with hemolytic anemia characterized by marked poikilocytosis with budding and fragmentation of the red blood cells (RBCs). These small RBC fragments reduce the overall mean corpuscular volume (MCV), resulting in microcytosis. By 2 years of age, the findings become typical of hereditary elliptocytosis. **Hereditary pyropoikilocytosis** is a much less common variant of hereditary elliptocytosis, in which the hemolytic anemia and RBC changes are more severe.

COPPER DEFICIENCY

Copper deficiency is a rare cause of microcytic anemia and neurologic dysfunction. Copper is absorbed in the stomach and proximal duodenum. Deficiency is associated with malabsorption; severe malnutrition, often with feeding of milk alone; gastric surgery or feedings that bypass the stomach and duodenum; or parenteral nutrition with inadvertent omission of supplemental copper. Zinc and copper are competitively absorbed from the gastrointestinal (GI) tract, so zinc excess may inadvertently lead to copper deficiency. Diagnosis is made by measuring a serum copper level, serum ceruloplasmin, and possibly a zinc level. Treatment includes either oral or parenteral supplementation, depending on the underlying cause.

DEFECTS OF IRON METABOLISM

Rare microcytic anemias may be associated with defects in iron trafficking and regulation. Most are inherited and usually identified in childhood, including defects of iron absorption, transport, utilization, and recycling. A *defect of iron absorption* is **iron-refractory iron-deficiency anemia** (see Chapter 504.1). *Defects of iron recycling* include aceruloplasminemia and atransferrinemia. **Aceruloplasminemia** is an autosomal recessive disorder in the *CP* gene that encodes ceruloplasmin. Iron cannot be appropriately transported from macrophages to plasma to be available for RBC production but accumulates instead in the brain and visceral organs, which can lead to an adult-onset neurodegenerative disorder. The diagnosis is made by a combination of absence of serum ceruloplasmin, low serum copper and iron, elevated ferritin, and increased liver iron concentration. Hypotransferrinemia or **atransferrinemia** is also an autosomal recessive disorder caused by pathogenic variants in the transferrin *(TF)* gene. Diagnosis is made by low or absent serum transferrin and liver iron overload. Genetic testing can confirm the diagnosis for both disorders. Treatment includes iron chelation therapy, limiting iron supplementation and dietary iron, and possibly fresh-frozen plasma to replace ceruloplasmin and/or transferrin. Purified transferrin (apotransferrin) infusions are available.

Defects of mitochondrial iron utilization are a diverse group of acquired and inherited defects known as **sideroblastic anemias** (Table 505.1). Several genes associated with these disorders have been described. Impaired heme synthesis leads to retention of iron within the mitochondria of marrow RBCs. The perinuclear distribution of mitochondria results in a pattern of iron staining surrounding the nucleus. These are *ringed sideroblasts* (Fig. 505.1), which are distinct from the more diffuse cytoplasmic distribution of iron in normal RBC precursors. The anemia is characterized by hypochromic, microcytic RBCs mixed with normal RBCs, so the complete blood count indicates a very high RBC distribution width. The serum iron concentration usually is elevated, and the transferrin saturation of iron is increased.

Congenital sideroblastic anemia (CSA) can be *syndromic* or *nonsyndromic*. The most common type of nonsyndromic CSA is an X-linked disorder and is most often a result of pathogenic variants in *ALAS2* that encodes erythrocytic isozyme 5-aminolevulinic acid synthetase, the rate-limiting enzyme reaction in heme synthesis. An important cofactor for 5-ALA synthetase is *pyridoxal phosphate,* with several pathogenic variants occurring near its binding site. Severe anemia is recognized in infancy or early childhood, whereas milder cases might not become apparent until early adulthood or later. Clinical findings include pallor, icterus, and moderate splenomegaly and/or hepatomegaly. The severity of the anemia varies such that some patients require no therapy and others need regular RBC transfusions. A subset of patients with hereditary sideroblastic anemia manifest a hematologic response to pyridoxine doses of 50-200 mg/day. Iron overload, as manifested by elevated serum ferritin, elevated serum iron, and increased transferrin saturation, is a major complication of this disorder. Clinical evidence of iron overload (e.g., diabetes mellitus, liver dysfunction) may be found in some patients who have little or no anemia, which may require iron chelation therapy. Stem cell transplantation has been used to treat affected children who are dependent on RBC transfusions.

A unique variant of congenital sideroblastic anemia is **Pearson syndrome** (see Chapter 498), but the anemia is usually *macrocytic* and not microcytic. Another rare variant of sideroblastic anemia is caused by pathogenic variants in *TRNT1* and manifests with developmental

Table 505.1 Clinical and Genetic Features of Congenital Sideroblastic Anemias

CATEGORY	DISORDER	INHERITANCE	SYNDROMIC	GENE	FREQUENCY	AGE AT PRESENTATION	ANEMIA SEVERITY	MCV	ASSOCIATED ABNORMALITIES
Heme synthesis defects	XLSA	X-linked	No	*ALAS2*	100s	Infancy to adulthood	Mild to severe	↓ males N/↑ female	Iron overload in the absence of transfusions
	SLC25A38 deficiency	AR	No	*SLC25A38*	40	Infancy	Severe	↓	Transfusional iron overload
	EPP	AR/PSD	No	*FECH*	100s	Childhood	Mild	↓	Acute photosensitivity
Fe-S biogenesis defects	GLRX5 deficiency	AR	No	*GLRX5*	2	Adulthood	Mild to severe	↓	Iron overload
	HSPA9 deficiency	AR/PSD	No	*HSPA9*	12	Childhood	Mild to severe	N/↓	Retinitis pigmentosa
	HSCB deficiency	AR	No	*HSCB*	1	Childhood	Moderate	N	None
	XLSA/A	X-linked	Yes	*ABCB7*	5	Childhood	Mild to moderate	↓	Cerebellar ataxia and hypoplasia, delayed motor development
Mitochondrial protein synthesis defects	PMPS	SP/M	Yes	*mtDNA*	100s	Early childhood	Severe	↑	Lactic acidosis, exocrine pancreatic insufficiency, failure to thrive, hepatic/renal failure
	MLASA1	AR	Yes	*PUS1*	10	Childhood	Mild to severe	N/↑	Myopathy, lactic acidosis, facial dysmorphism
	MLASA2	AR	Yes	*YARS2*	40	Childhood	Mild to severe	N/↑	Myopathy, lactic acidosis, cardiomyopathy
	LARS2 deficiency	AR	Yes	*LARS2*	1	Infancy	Severe	↑	Lactic acidosis, cardiomyopathy, hepatopathy, seizures
	SIFD	AR	Yes	*TRNT1*	30	Infancy	Severe		Immunodeficiency (B.T), aseptic febrile episodes, developmental delay, seizures, cardiomyopathy, retinitis pigmentosa, other
Mitochondrial respiratory protein mutations	MT-ATP6-SA	SP/M	Yes	*MT-ATP6*	4	Infancy to early childhood	Moderate to severe	N/↑	Lactic acidosis, myopathy, neurologic abnormalities
	NDUFB11-SA	X-linked	Yes	*NUDFB11*	5	Early childhood	Moderate	N	Lactic acidosis, myopathy
	Multifactorial TRMA	AR	Yes	*SLC19A2*	50	Early childhood	Mild to severe	↑	Sensorineural deafness, non-type 1 diabetes mellitus, optic atrophy, strokelike episodes

↑, increased; ↓, decreased; AR, autosomal recessive; EPP, erythropoietic protoporphyria; MCV, mean red blood cell volume; MLASA, mitochondrial myopathy lactic acidosis and sideroblastic anemia;. mtDNA, mitochondrial DNA; N, normal; PMPS, Pearson marrow pancreas syndrome; PSD, Pseudodominant; SIFD, sideroblastic anemia, immunodeficiency (B cell), periodic fevers, and developmental delay; SP/M, sporadic/mitochondrial; TRMA, thiamine responsive megaloblastic anemia; XLSA, X-linked sideroblastic anemia.

Adapted from Ducamp S and Fleming D. The molecular genetics of sideroblastic anemia. *Blood* 2019:133(1):59–69.

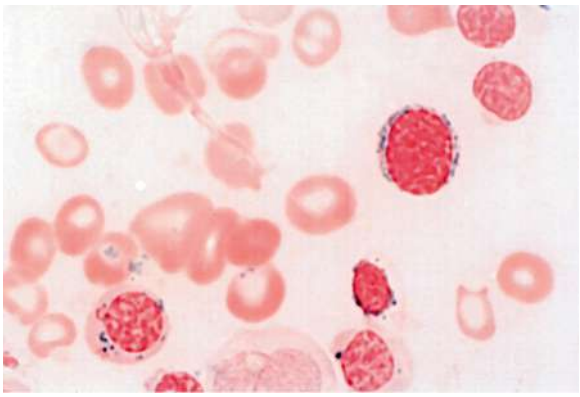

Fig. 505.1 Ring sideroblast in myelodysplastic syndrome (refractory anemia with ring sideroblasts)—iron stain. *(From Ryan DH, Cohen HJ. Bone marrow examination. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al., eds. Hematology, 4th ed. Philadelphia: Churchill Livingstone, 2005.)*

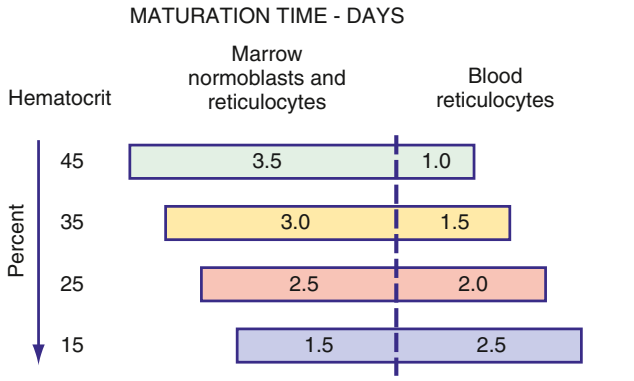

Fig. 506.1 Number of days for maturation of reticulocytes to mature erythrocytes in the marrow and blood. The duration of maturation as blood reticulocytes is taken as μ, which is used in the correction equation in this chapter. *(Modified from Hillman RS, Finch CA. Red cell manual. Philadelphia: FA Davis, 1983.)*

delay, periodic fevers, and B-cell immunodeficiency in addition to sideroblastic anemia.

Acquired sideroblastic anemias can be triggered by copper deficiency or drugs and toxins that disturb mitochondrial iron metabolism, including lead, chloramphenicol, penicillamine, ethanol, and isoniazid. The acquired neoplastic sideroblastic syndromes (myelodysplasias) seen in adults are very rare in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

Hemolytic Anemias

Chapter 506

Definitions and Classification of Hemolytic Anemias

Stephanie Prozora and Patrick G. Gallagher

Hemolysis is defined as the premature destruction of red blood cells (RBCs). Anemia results when the rate of destruction exceeds the capacity of the marrow to produce additional RBCs. Normal RBC survival time is 110-120 days (half-life: 55-60 days), and thus, approximately 0.85% of the most senescent RBCs are removed and replaced each day. During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and marrow erythropoietic activity is stimulated. This leads to compensatory erythroid hyperplasia with increased RBC production, reflected by an increase in the reticulocyte count. The marrow can increase its output twofold to threefold acutely, with a maximum of sixfold to eightfold in chronic hemolysis. The reticulocyte percentage can be corrected to measure the magnitude of marrow production in response to hemolysis as follows:

$$\text{Reticulocyte index} = \text{reticulocyte } \% \times \frac{\text{Observed hematocrit}}{\text{Normal hematocrit}} \times \frac{1}{\mu}$$

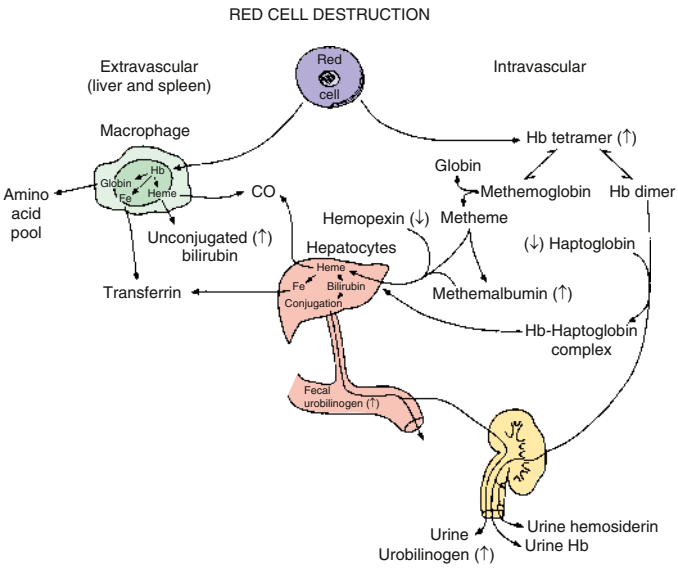

Fig. 506.2 Red cell destruction and catabolism of hemoglobin (Hb) based on the description by Hillman and Finch. Fe, Iron; CO, carbon monoxide. *(From Hillman RS, Finch CA. Red cell manual. Philadelphia: FA Davis, 1983.)*

where μ is a maturation factor of 1-3 related to the severity of the anemia (Fig. 506.1). The normal reticulocyte index is 1.0; therefore the index measures the fold increase in erythropoiesis (e.g., twofold, threefold). Because the reticulocyte index is essentially a measure of RBC production per day, the maturation factor μ provides this correction (see Fig. 506.1).

When hemolysis is chronic, compensatory erythroid hyperplasia may lead to significant expansion of the medullary spaces at the expense of cortical bone. This is particularly prominent in children with severe chronic hemolytic anemia such as thalassemia. These changes may be evident on physical examination or on radiographs of the skull and long bones. In severe cases, there is increased propensity for long bone fracture. Hemolysis also leads to increased degradation of hemoglobin. This process can result in indirect hyperbilirubinemia, increased biliary excretion of heme pigment derivatives, and formation of bilirubinate gallstones.

During hemolysis (Fig. 506.2), heme-binding proteins in the plasma are altered. Hemoglobin binds to haptoglobin and hemopexin, both of which are cleared more rapidly as heme-bound complexes. Oxidized heme binds to albumin to form methemalbumin, which is increased in the plasma during hemolysis. When the capacity of these heme-binding molecules is exceeded, free hemoglobin appears in the plasma. Free hemoglobin in the plasma is considered *prima facie* evidence of

serum transferrin levels that are accompanied by the deposition of non–transferrin-bound iron in parenchymal tissues. Because hepcidin production is induced by inflammatory stimuli, hepcidin elevation is also a feature of the **anemia of chronic disease** (ACD). However, in contrast to patients with IRIDA, in whom the hepcidin dysregulation is congenital, patients with ACD generally retain normal to high iron stores because of the acquired nature of their hepcidin elevation (see Chapter 500.1). Rare medical causes that may mimic IRIDA include vascular malformations of the GI tract, Castleman disease (where IL-6 overproduction causes hepcidin elevation), autoimmune gastritis, and pathogenic germline variants in *KCNQ1* (which regulates gastric acid secretion).

TREATMENT

Because of the underlying pathophysiology of IRIDA, *parenteral iron supplementation* is required to correct the anemia. Although parenteral iron therapy raises body iron stores, the hematologic response is usually slow and not completely corrective. This likely results from insufficient export of the processed iron from macrophages into the circulation, an expected consequence of hepcidin elevation. Serum ferritin levels increase with parenteral iron therapy in a dose-dependent manner and may raise concerns for iron overload, which would be expected to exhibit a reticuloendothelial rather than a parenchymal pattern of iron loading. Given the limited number of IRIDA cases reported to date, the optimal formulation and dosing of parenteral iron have not yet been established. Although oral iron supplementation does not appear to have a significant role in treatment of IRIDA, the addition of ascorbic acid to a ferrous sulfate oral supplement has been associated with hematologic responses in isolated cases. Treatment with recombinant erythropoietin has not been found to produce significant clinical benefit in patients with IRIDA.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 505

Other Microcytic Anemias

Jennifer A. Rothman

A number of rare microcytic anemias need to be considered when children with microcytic anemia fail to respond to oral iron (Table 504.5). These anemias include thalassemia or thalassemia trait (see Chapter 511), infantile poikilocytosis and hereditary pyropoikilocytosis (Chapter 508), and anemia of chronic disease (Chapter 500.1). Additionally, rare nutritional disorders and disorders of iron metabolism can cause microcytosis.

INFANTILE POIKILOCYTOSIS AND HEREDITARY PYROPOIKILOCYTOSIS

Infants with common **hereditary elliptocytosis** (see Chapter 508) may initially present with hemolytic anemia characterized by marked poikilocytosis with budding and fragmentation of the red blood cells (RBCs). These small RBC fragments reduce the overall mean corpuscular volume (MCV), resulting in microcytosis. By 2 years of age, the findings become typical of hereditary elliptocytosis. **Hereditary pyropoikilocytosis** is a much less common variant of hereditary elliptocytosis, in which the hemolytic anemia and RBC changes are more severe.

COPPER DEFICIENCY

Copper deficiency is a rare cause of microcytic anemia and neurologic dysfunction. Copper is absorbed in the stomach and proximal duodenum. Deficiency is associated with malabsorption; severe malnutrition, often with feeding of milk alone; gastric surgery or feedings that bypass the stomach and duodenum; or parenteral nutrition with inadvertent omission of supplemental copper. Zinc and copper are competitively absorbed from the gastrointestinal (GI) tract, so zinc excess may inadvertently lead to copper deficiency. Diagnosis is made by measuring a serum copper level, serum ceruloplasmin, and possibly a zinc level. Treatment includes either oral or parenteral supplementation, depending on the underlying cause.

DEFECTS OF IRON METABOLISM

Rare microcytic anemias may be associated with defects in iron trafficking and regulation. Most are inherited and usually identified in childhood, including defects of iron absorption, transport, utilization, and recycling. A *defect of iron absorption* is **iron-refractory iron-deficiency anemia** (see Chapter 504.1). *Defects of iron recycling* include aceruloplasminemia and atransferrinemia. **Aceruloplasminemia** is an autosomal recessive disorder in the *CP* gene that encodes ceruloplasmin. Iron cannot be appropriately transported from macrophages to plasma to be available for RBC production but accumulates instead in the brain and visceral organs, which can lead to an adult-onset neurodegenerative disorder. The diagnosis is made by a combination of absence of serum ceruloplasmin, low serum copper and iron, elevated ferritin, and increased liver iron concentration. Hypotransferrinemia or **atransferrinemia** is also an autosomal recessive disorder caused by pathogenic variants in the transferrin *(TF)* gene. Diagnosis is made by low or absent serum transferrin and liver iron overload. Genetic testing can confirm the diagnosis for both disorders. Treatment includes iron chelation therapy, limiting iron supplementation and dietary iron, and possibly fresh-frozen plasma to replace ceruloplasmin and/or transferrin. Purified transferrin (apotransferrin) infusions are available.

Defects of mitochondrial iron utilization are a diverse group of acquired and inherited defects known as **sideroblastic anemias** (Table 505.1). Several genes associated with these disorders have been described. Impaired heme synthesis leads to retention of iron within the mitochondria of marrow RBCs. The perinuclear distribution of mitochondria results in a pattern of iron staining surrounding the nucleus. These are *ringed sideroblasts* (Fig. 505.1), which are distinct from the more diffuse cytoplasmic distribution of iron in normal RBC precursors. The anemia is characterized by hypochromic, microcytic RBCs mixed with normal RBCs, so the complete blood count indicates a very high RBC distribution width. The serum iron concentration usually is elevated, and the transferrin saturation of iron is increased.

Congenital sideroblastic anemia (CSA) can be *syndromic* or *nonsyndromic*. The most common type of nonsyndromic CSA is an X-linked disorder and is most often a result of pathogenic variants in *ALAS2* that encodes erythrocytic isozyme 5-aminolevulinic acid synthetase, the rate-limiting enzyme reaction in heme synthesis. An important cofactor for 5-ALA synthetase is *pyridoxal phosphate,* with several pathogenic variants occurring near its binding site. Severe anemia is recognized in infancy or early childhood, whereas milder cases might not become apparent until early adulthood or later. Clinical findings include pallor, icterus, and moderate splenomegaly and/or hepatomegaly. The severity of the anemia varies such that some patients require no therapy and others need regular RBC transfusions. A subset of patients with hereditary sideroblastic anemia manifest a hematologic response to pyridoxine doses of 50-200 mg/day. Iron overload, as manifested by elevated serum ferritin, elevated serum iron, and increased transferrin saturation, is a major complication of this disorder. Clinical evidence of iron overload (e.g., diabetes mellitus, liver dysfunction) may be found in some patients who have little or no anemia, which may require iron chelation therapy. Stem cell transplantation has been used to treat affected children who are dependent on RBC transfusions.

A unique variant of congenital sideroblastic anemia is **Pearson syndrome** (see Chapter 498), but the anemia is usually *macrocytic* and not microcytic. Another rare variant of sideroblastic anemia is caused by pathogenic variants in *TRNT1* and manifests with developmental

Table 505.1 Clinical and Genetic Features of Congenital Sideroblastic Anemias

CATEGORY	DISORDER	INHERITANCE	SYNDROMIC	GENE	FREQUENCY	AGE AT PRESENTATION	ANEMIA SEVERITY	MCV	ASSOCIATED ABNORMALITIES
Heme synthesis defects	XLSA	X-linked	No	*ALAS2*	100s	Infancy to adulthood	Mild to severe	↓ males N/↑ female	Iron overload in the absence of transfusions
	SLC25A38 deficiency	AR	No	*SLC25A38*	40	Infancy	Severe	↓	Transfusional iron overload
	EPP	AR/PSD	No	*FECH*	100s	Childhood	Mild	↓	Acute photosensitivity
Fe-S biogenesis defects	GLRX5 deficiency	AR	No	*GLRX5*	2	Adulthood	Mild to severe	↓	Iron overload
	HSPA9 deficiency	AR/PSD	No	*HSPA9*	12	Childhood	Mild to severe	N/↓	Retinitis pigmentosa
	HSCB deficiency	AR	No	*HSCB*	1	Childhood	Moderate	N	None
	XLSA/A	X-linked	Yes	*ABCB7*	5	Childhood	Mild to moderate	↓	Cerebellar ataxia and hypoplasia, delayed motor development
Mitochondrial protein synthesis defects	PMPS	SP/M	Yes	*mtDNA*	100s	Early childhood	Severe	↑	Lactic acidosis, exocrine pancreatic insufficiency, failure to thrive, hepatic/renal failure
	MLASA1	AR	Yes	*PUS1*	10	Childhood	Mild to severe	N/↑	Myopathy, lactic acidosis, facial dysmorphism
	MLASA2	AR	Yes	*YARS2*	40	Childhood	Mild to severe	N/↑	Myopathy, lactic acidosis, cardiomyopathy
	LARS2 deficiency	AR	Yes	*LARS2*	1	Infancy	Severe	↑	Lactic acidosis, cardiomyopathy, hepatopathy, seizures
	SIFD	AR	Yes	*TRNT1*	30	Infancy	Severe		Immunodeficiency (B.T), aseptic febrile episodes, developmental delay, seizures, cardiomyopathy, retinitis pigmentosa, other
Mitochondrial respiratory protein mutations	MT-ATP6-SA	SP/M	Yes	*MT-ATP6*	4	Infancy to early childhood	Moderate to severe	N/↑	Lactic acidosis, myopathy, neurologic abnormalities
	NDUFB11-SA	X-linked	Yes	*NUDFB11*	5	Early childhood	Moderate	N	Lactic acidosis, myopathy
	Multifactorial TRMA	AR	Yes	*SLC19A2*	50	Early childhood	Mild to severe	↑	Sensorineural deafness, non-type 1 diabetes mellitus, optic atrophy, strokelike episodes

↑, increased; ↓, decreased; AR, autosomal recessive; EPP, erythropoietic protoporphyria; MCV, mean red blood cell volume; MLASA, mitochondrial myopathy lactic acidosis and sideroblastic anemia;. mtDNA, mitochondrial DNA; N, normal; PMPS, Pearson marrow pancreas syndrome; PSD, Pseudodominant; SIFD, sideroblastic anemia, immunodeficiency (B cell), periodic fevers, and developmental delay; SP/M, sporadic/mitochondrial; TRMA, thiamine responsive megaloblastic anemia; XLSA, X-linked sideroblastic anemia.

Adapted from Ducamp S and Fleming D. The molecular genetics of sideroblastic anemia. *Blood* 2019:133(1):59–69.

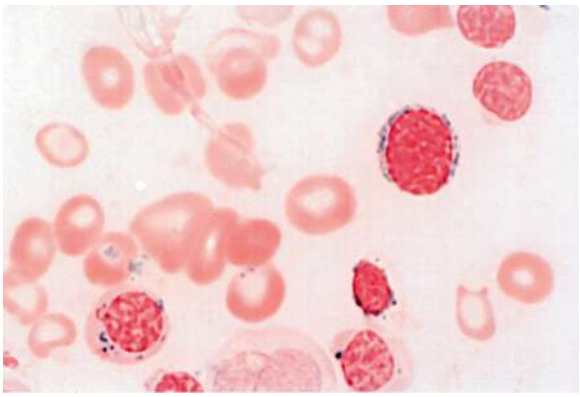

Fig. 505.1 Ring sideroblast in myelodysplastic syndrome (refractory anemia with ring sideroblasts)—iron stain. *(From Ryan DH, Cohen HJ. Bone marrow examination. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al., eds. Hematology, 4th ed. Philadelphia: Churchill Livingstone, 2005.)*

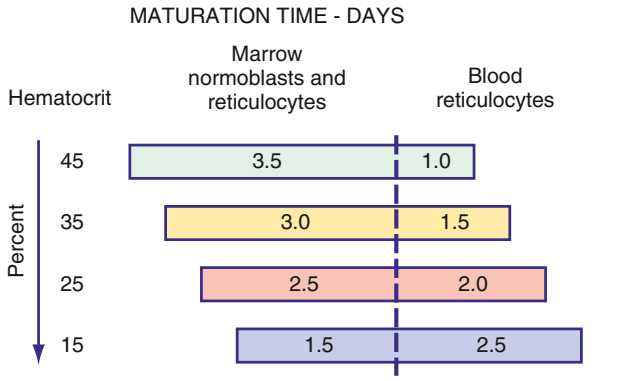

Fig. 506.1 Number of days for maturation of reticulocytes to mature erythrocytes in the marrow and blood. The duration of maturation as blood reticulocytes is taken as μ, which is used in the correction equation in this chapter. *(Modified from Hillman RS, Finch CA. Red cell manual. Philadelphia: FA Davis, 1983.)*

delay, periodic fevers, and B-cell immunodeficiency in addition to sideroblastic anemia.

Acquired sideroblastic anemias can be triggered by copper deficiency or drugs and toxins that disturb mitochondrial iron metabolism, including lead, chloramphenicol, penicillamine, ethanol, and isoniazid. The acquired neoplastic sideroblastic syndromes (myelodysplasias) seen in adults are very rare in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

Hemolytic Anemias

Chapter 506

Definitions and Classification of Hemolytic Anemias

Stephanie Prozora and Patrick G. Gallagher

Hemolysis is defined as the premature destruction of red blood cells (RBCs). Anemia results when the rate of destruction exceeds the capacity of the marrow to produce additional RBCs. Normal RBC survival time is 110-120 days (half-life: 55-60 days), and thus, approximately 0.85% of the most senescent RBCs are removed and replaced each day. During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and marrow erythropoietic activity is stimulated. This leads to compensatory erythroid hyperplasia with increased RBC production, reflected by an increase in the reticulocyte count. The marrow can increase its output twofold to threefold acutely, with a maximum of sixfold to eightfold in chronic hemolysis. The reticulocyte percentage can be corrected to measure the magnitude of marrow production in response to hemolysis as follows:

$$\text{Reticulocyte index} = \text{reticulocyte } \% \times \frac{\text{Observed hematocrit}}{\text{Normal hematocrit}} \times \frac{1}{\mu}$$

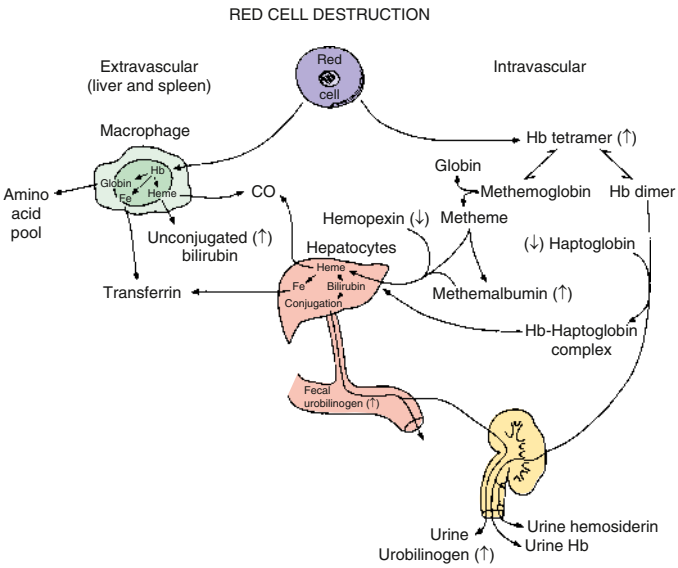

Fig. 506.2 Red cell destruction and catabolism of hemoglobin (Hb) based on the description by Hillman and Finch. Fe, Iron; CO, carbon monoxide. *(From Hillman RS, Finch CA. Red cell manual. Philadelphia: FA Davis, 1983.)*

where μ is a maturation factor of 1-3 related to the severity of the anemia (Fig. 506.1). The normal reticulocyte index is 1.0; therefore the index measures the fold increase in erythropoiesis (e.g., twofold, threefold). Because the reticulocyte index is essentially a measure of RBC production per day, the maturation factor μ provides this correction (see Fig. 506.1).

When hemolysis is chronic, compensatory erythroid hyperplasia may lead to significant expansion of the medullary spaces at the expense of cortical bone. This is particularly prominent in children with severe chronic hemolytic anemia such as thalassemia. These changes may be evident on physical examination or on radiographs of the skull and long bones. In severe cases, there is increased propensity for long bone fracture. Hemolysis also leads to increased degradation of hemoglobin. This process can result in indirect hyperbilirubinemia, increased biliary excretion of heme pigment derivatives, and formation of bilirubinate gallstones.

During hemolysis (Fig. 506.2), heme-binding proteins in the plasma are altered. Hemoglobin binds to haptoglobin and hemopexin, both of which are cleared more rapidly as heme-bound complexes. Oxidized heme binds to albumin to form methemalbumin, which is increased in the plasma during hemolysis. When the capacity of these heme-binding molecules is exceeded, free hemoglobin appears in the plasma. Free hemoglobin in the plasma is considered *prima facie* evidence of

Table 506.3 Clinical and Laboratory Features Suggestive of Hemolytic Anemia

Pallor	↑ RDW (caused by ↑ reticulocyte count)
Icterus	Abnormal RBC morphology
Splenomegaly	↑ Indirect bilirubin (normal direct bilirubin)
Gallstones	↓ Serum haptoglobin level
History of neonatal icterus	↑ Urinary urobilinogen level
Positive family history of anemia, splenectomy, cholecystectomy	Hemoglobinuria (+ dipstick test result for blood; no RBCs in urine)
↑ Reticulocyte count	↑ LDH level

LDH, Lactate dehydrogenase; RBC, red blood cell; RDW, red cell distribution width.
From Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis.* Philadelphia: Elsevier, 2018: 674; Table 37.12.

Table 506.4 Hemolytic Anemias: Diagnostic Clues Based on Red Blood Cell Shape

Sickle cells: sickle cell disease
Target cells: hemoglobinopathies (HbC, HbS, thalassemia), liver disease
Schistocytes/burr cells/helmet cells/RBC fragments: microangiopathic hemolytic anemia (DIC, HUS, TTP)
Spherocytes: hereditary spherocytosis, autoimmune hemolytic anemia
Cigar-shaped cells: hereditary elliptocytosis
"Bite" cells: G6PD deficiency
Poikilocytosis, microcytosis, fragmented erythrocytes, elliptocytes: hereditary pyropoikilocytosis

DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; HbC, hemoglobin C; HbS, sickle hemoglobin; HUS, hemolytic-uremic syndrome; RBC, red blood cell; TTP, thrombotic thrombocytopenia purpura.
From Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis.* Philadelphia: Elsevier, 2018: 674; Table 37.13.

Chapter 507

Hereditary Spherocytosis

Stephanie Prozora and Patrick G. Gallagher

Hereditary spherocytosis (HS) is a common cause of inherited hemolytic anemia, with a prevalence of approximately 1 in 2,000-5,000 persons. Described in patients of all ethnic groups, it is the most common inherited abnormality of the erythrocyte associated with inherited hemolytic anemia in persons of Northern European origin. HS is marked by wide variability in the associated clinical, laboratory, and genetic manifestations. Symptomatology ranges from asymptomatic patients with well-compensated anemia to severely affected patients with hemolytic anemia requiring regular blood transfusions.

ETIOLOGY

The pathophysiology underlying HS is twofold: an intrinsic defect of the erythrocyte membrane and an intact spleen that selectively retains, damages, and removes abnormal HS erythrocytes. Qualitative or quantitative defects of key membrane proteins lead to a multistep process of accelerated HS erythrocyte destruction. Abnormalities of ankyrin or spectrin are the most common molecular defects (Table 507.1). Defects in these membrane proteins result in uncoupling of the "vertical" interactions of the lipid bilayer with the underlying membrane skeleton with subsequent release of membrane microvesicles. The loss of membrane surface area without a proportional loss of cell volume causes decreased erythrocyte deformability. This impairs cell passage from the splenic cords to the splenic sinuses, leading to the trapping and premature destruction of HS erythrocytes by the spleen (Figs. 507.1 and 507.2). Splenectomy markedly improves erythrocyte life span and may be indicated in some patients with HS.

CLINICAL MANIFESTATIONS

Hereditary spherocytosis is usually transmitted as an autosomal dominant trait. However, as many as 25% of patients have no previous family history, representing either recessive inheritance or de novo gene variants.

In the neonatal period, HS is a significant cause of hemolysis and can manifest as anemia and/or hyperbilirubinemia severe enough to require phototherapy, transfusion, or exchange transfusions. Hemolysis may be more prominent in the newborn because hemoglobin F binds 2,3-diphosphoglycerate poorly, and the increased level of free 2,3-diphosphoglycerate destabilizes interactions among spectrin, actin, and protein 4.1 in the red blood cell (RBC) membrane (see Fig. 507.1). The need for transfusions in infancy is not indicative of more severe disease later in life because infants are typically slow to mount an adequate reticulocyte response for the first few months after birth.

Disease severity varies and can be used to clinically classify HS (Table 507.2). Mild cases (20–30% of all HS) are asymptomatic into adulthood and have well-compensated mild anemia where reticulocyte production and erythrocyte destruction are essentially balanced. Cases of moderate or "typical" HS (60–70%) have partially compensated hemolytic anemia with reticulocytosis, frequently with symptoms of fatigue, pallor, and intermittent jaundice. Splenomegaly is common after infancy, and it is present in almost all HS patients by young adulthood. Severe cases of HS (3–5%) have life-threatening anemia and are transfusion dependent.

Bilirubin gallstone formation is a function of age; they can form as early as 4-5 years of age and are present in most adult HS patients.

HS patients are susceptible to **aplastic crises** primarily as a result of parvovirus B19 infection, hypoplastic crises associated with other infections, and megaloblastic crises due to folate deficiency (Fig. 507.3). During these crises, high RBC turnover in the setting of erythroid marrow failure can result in profound anemia (hematocrit <10%), high-output heart failure, cardiovascular collapse, and death. Leukocyte and platelet counts may also fall.

Rare complications associated with HS include splenic sequestration crisis, gout, cardiomyopathy, priapism, leg ulcers, and neurologic or muscular abnormalities, including spinocerebellar degeneration.

Table 507.1 Common Gene Pathogenic Variants in Hereditary Spherocytosis

PROTEIN	GENE	COMMON PATHOGENIC VARIANTS	PREVALENCE	INHERITANCE	DISEASE SEVERITY
Ankyrin-1	*ANK1*	Frameshift Nonsense Splicing Missense Insertion/deletion Promoter region	50–67% 5–10% in Japan	Mostly dominant, rare recessive	Mild to moderate
Band 3	*AE1 (SLC4A1)*	Missense Nonsense	15–20%	Dominant	Mild to moderate
β-Spectrin	*SPTB*	Nonsense Missense Insertion/deletion	15–20%	Dominant	Mild to moderate
α-Spectrin	*SPTA1*	Splicing Nonsense Missense	<5%	Recessive	Severe
Protein 4.2	*EPB42*	Missense Nonsense Splicing Deletion	<5% 45–50% in Japan	Recessive	Mild to moderate

Modified from Bolton-Maggs PHB, Langer JC, Iolascon A, et al. Guidelines for the diagnosis and management of hereditary spherocytosis–2011 update. *Br J Haematol*. 2011;156:37–49.

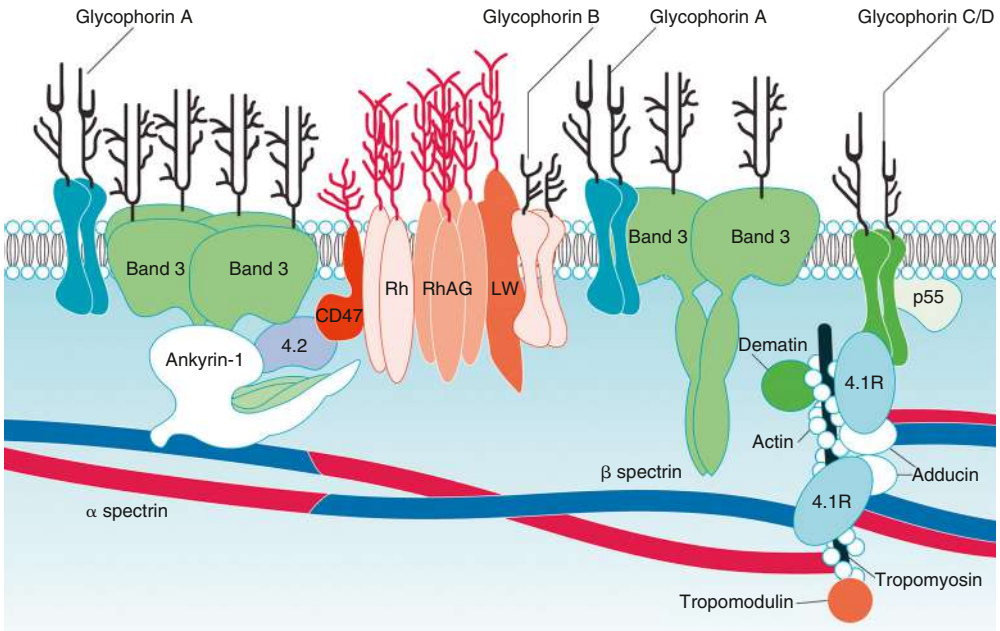

Fig. 507.1 A simplified cross-section of the red blood cell (erythrocyte) membrane. The lipid bilayer forms the equator of the cross-section with its polar heads (small circles) turned outward. 4.1R, protein; 4.2, protein 4.2; LW, Landsteiner-Wiener glycoprotein; Rh, Rhesus polypeptide; RhAG, Rh-associated glycoprotein. *(From Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. Lancet 2008;372:1411–1426.)*

DIAGNOSIS

Typically, there is evidence of hemolytic anemia with reticulocytosis and indirect hyperbilirubinemia. The mean corpuscular volume (MCV) of HS erythrocytes is low normal or even slightly decreased and the mean corpuscular hemoglobin concentration (MCHC) is usually increased (>35 g/dL). An MCHC > 35.4 g/dL combined with an RBC distribution width (RDW) <14% has been suggested as a screening test for HS. Erythroid cells on peripheral blood smear vary in size and include spherocytes and polychromatophilic reticulocytes. Spherocytes are smaller in diameter, hyperchromic due to elevated hemoglobin concentration from cellular dehydration, and lacking in central pallor (Fig. 507.4). Numbers of spherocytes are variable, with increased numbers likely reflecting the severity of disease. Other markers of hemolysis include decreased haptoglobin and elevated lactic dehydrogenase.

The diagnosis of HS can be established from a positive family history and the presence of typical clinical and laboratory features of the disease: splenomegaly, spherocytes on the blood smear,

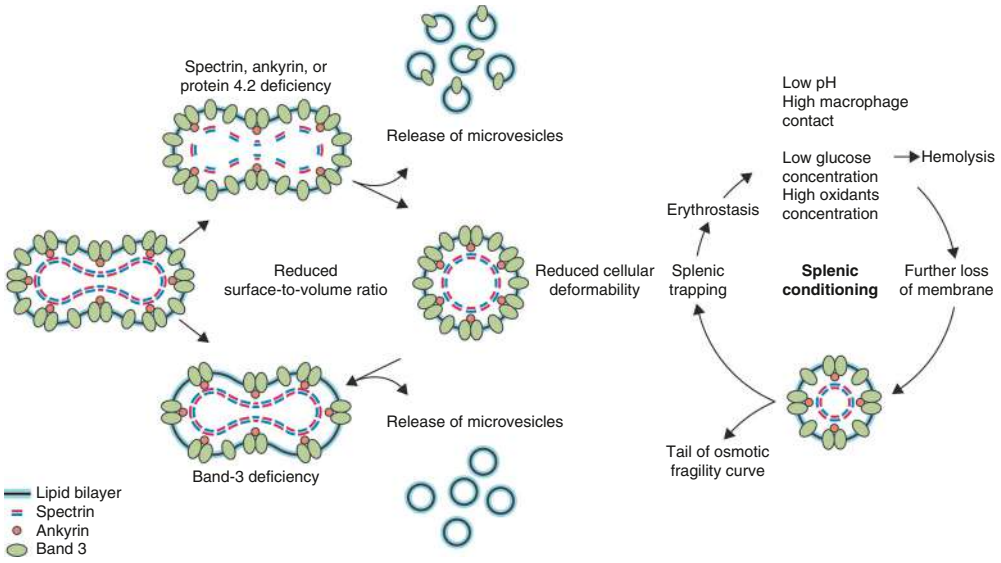

Fig. 507.2 Pathophysiologic effects of hereditary spherocytosis. *(From Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. Lancet 2008;372:1411–1426.)*

reticulocytosis, and an elevated MCHC. If these are present, no additional testing is necessary to confirm the diagnosis clinically. If the diagnosis is less certain, additional testing can be performed. Binding of fluorescently labeled eosin-5-maleimide (EMA) to band 3 and other membrane proteins is decreased in HS erythrocytes. This flow cytometry–based screening test is easy to perform and has good diagnostic sensitivity and specificity. In the classic incubated osmotic fragility test, HS erythrocytes are incubated in progressive dilutions of sodium chloride causing the cells to swell and lyse, with spherocytes lysing at a lower dilution due to their lower surface area to volume ratio. This test detects the presence of spherocytes in the blood, but it is not specific to HS and may be abnormal in other anemias with prominent spherocytosis. Osmotic fragility testing has poor sensitivity and may miss cases of mild HS where the numbers of spherocytes are few. Other assays such as the cryohemolysis test, the acidified glycerol lysis test, and the osmotic gradient ektacytometry have been used for diagnosis of HS, but they are not available in many laboratories. Genetic diagnosis is widely available on a commercial basis. The precise role of molecular testing in HS diagnosis and management is evolving. Some experts suggest molecular testing before splenectomy to verify the diagnosis of HS.

Diagnosis in the neonatal period requires a high index of suspicion as the disease presents differently than in older children, particularly in de novo and recessively inherited cases where family history is not available for guidance. Jaundice is frequently observed, and kernicterus can occur. Hemolytic anemia may be severe enough to require blood transfusion. In fact, HS is the leading cause of Coombs-negative hemolytic anemia, requiring transfusion in the first months of life. Splenomegaly is uncommon in neonates.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for spherocytosis on peripheral blood smear includes isoimmune and autoimmune hemolysis. Isoimmune hemolytic disease of the newborn, particularly when there is a result of ABO incompatibility, closely mimics the appearance of HS. The detection of antibody on an infant's RBCs using a direct antiglobulin (Coombs) test should establish the diagnosis of immune hemolysis. Autoimmune hemolytic anemias also are characterized by spherocytosis, but there will typically be evidence of previously normal values for hemoglobin, hematocrit, and reticulocyte count. Rare causes of spherocytosis include thermal injury, hemolytic transfusion reaction, clostridial sepsis, severe hypophosphatemia, Wilson disease, and snake, bee, or wasp envenomation, which all may manifest as transient spherocytic hemolytic anemia.

TREATMENT

General Supportive Care

Infants born to a parent with known HS should be monitored carefully because hyperbilirubinemia may peak several days after birth. Parents should be advised of the risk of neonatal anemia and jaundice and the potential need for transfusion, phototherapy, and/or exchange transfusion to treat anemia or hyperbilirubinemia. A subset of infants will be transfusion-dependent until development of adequate erythropoiesis to compensate for the ongoing hemolysis, usually between 6-12 months of age. Transfusion dependence after this time is rare and is most likely due to recessive HS.

Once the baseline level of disease severity is reached, an annual visit to the hematologist usually is sufficient follow-up. Growth should be monitored, and exercise tolerance and spleen size documented. Vaccinations should be up to date. Screening for gallbladder disease should begin at ~4 years of age, repeated every 3-5 years, or as indicated clinically. Documentation of parvovirus B19 susceptibility or immunity should be obtained in newly diagnosed patients. Similarly, HIV and hepatitis serology should be documented in patients who have received transfusions. Folic acid supplementation is recommended in cases of moderate and severe HS due to the demands of brisk erythropoiesis. Parents should receive anticipatory guidance regarding the risk of aplastic crisis secondary to parvovirus infection and hypoplastic crises with other infections. Parents and patients should be informed of an increased risk for gallstone development.

Guidelines for Splenectomy

Because spherocytes are destroyed almost exclusively in the spleen, splenectomy is curative in most patients because hemolysis, anemia, hyperbilirubinemia, and the incidence of gallstones are significantly lessened, if not completely eradicated, after splenectomy. Thus splenectomy became routine in the care of HS patients. However, splenectomy is associated with *short-term* risks, related to the operative procedure itself, and *long-term* risks, particularly increased lifelong

Table 507.2 Clinical and Laboratory Classification of Hereditary Spherocytosis

	NORMAL	MILD SPHEROCYTOSIS	MODERATE SPHEROCYTOSIS	MODERATELY SEVERE SPHEROCYTOSIS	SEVERE SPHEROCYTOSIS*
Inheritance	—	Autosomal dominant	Autosomal dominant, de novo variant	Autosomal dominant, de novo variant	Autosomal recessive
Proportion of hereditary spherocytosis cases	—	~20–30%	~60–70%	~10%	<5%
Hemoglobin (Hb, g/dL)†	11.5-16‡	10.5-15	8-12	6-8	<6
Reticulocytes (%)†	0.5-1.5	1.5-6	≥6	≥10	≥10
Bilirubin (mg/dL)†,‖	0-1	0.5-2	≥2	≥2	≥3
Peripheral smear*	Normal	Mild spherocytosis	Spherocytosis	Spherocytosis	Spherocytosis ± poikilocytosis
Osmotic fragility (fresh)	Normal	Normal or slightly increased	Increased	Increased	Greatly increased
Osmotic fragility (incubated)	Normal	Usually increased	Increased	Increased	Greatly increased
MCHC (g/dL)§	32-36	34-37	34-38	35-39	
RDW (%)§	11-14	12-19	16-23	20-30	
Hb/MCHC*	0.38-0.41	0.35-0.40	0.29-0.33	0.18-0.28	
Hb/RDW§	0.95-1.05	0.7-1.0	0.48-0.74	0.16-0.35	
Serum transferrin receptor (nmol/L)§	18-25	30-65	80-125	100-150	
Erythropoietin (mIU/mL)§	7-16	9-30	25-90	30-300	
Membrane protein patterns (SDS-PAGE)¶	—	"Normal"# Slight ↓ spectrin Slight ↓ spectrin and ankyrin Slight ↓ band 3 and 4.2 Absent protein 4.2 and ↓ CD47	↓ Spectrin ↓ Spectrin and ankyrin ↓ Band 3 and protein 4.2 Absent protein 4.2 and ↓ CD47	↓ Spectrin ↓ Spectrin and ankyrin ↓ Band 3 and protein 4.2	⇊ Spectrin ⇊ Spectrin and ankyrin ⇊ Band 3 and protein 4.2**
Transfusions	—	No	Sometimes required in infancy or with aplastic crisis	Occasionally with crises	Regular*
Splenectomy	—	Rarely, partial splenectomy††	Sometimes; consider partial splenectomy	Usually (6-9 yr)	Yes (>3 yr)

*Patients with severe disease are transfusion dependent by definition. Values are in untransfused patients or at nadir before transfusion.
†Data modified from Eber SW, Armbrust R, Schröter W. Variable clinical severity of hereditary spherocytosis: relation to erythrocytic spectrin concentration, osmotic fragility and autohemolysis. *J Pediatr.* 1990;177:409–416.
‡Varies with age.
§Ranges shown encompass the majority of individuals in each category. From Rocha S, Costa E, Rocha-Pereira P, et al. Complementary markers for the clinical severity classification of hereditary spherocytosis in unsplenectomized patients. *Blood Cells Mol Dis.* 2011;46:166–170.
‖Multiply by 17.1 to convert to μmol/L.
¶Indicates common patterns observed on SDS gels. Decreased spectrin alone is seen in α-spectrin or β-spectrin defects. Decreased spectrin and ankyrin arc observed with ankyrin defects. Decreased band 3 and protein 4.2 occur with band 3 defects. Absent protein 4.2 and decreased CD47 occur with protein 4.2 defects.
#Patients with mild spherocytosis who appear normal probably have small deficits (10–15%) that cannot be distinguished from normal findings on SDS gels.
**Rare patients with severe spherocytosis who are homozygous or compound heterozygous for band 3 defects.
††Consider in adolescents and adults who require a cholecystectomy or have disfiguring chronic jaundice.
CD, cluster of differentiation; MCHC, Mean corpuscular hemoglobin concentration; RDW, red cell distribution width (measure of variation in shape); SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; ↓, decreased.
From Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Elsevier, 2015:518; Table 16.3.

risk for sepsis, often caused by encapsulated bacteria. This risk is not eliminated but reduced with the requisite preoperative and postoperative vaccination against pneumococcus, meningococcus, and *Haemophilus influenzae* type b. In addition, there are increasing concerns regarding the emergence of penicillin-resistant pneumococci, as well as increased risk for cardiovascular diseases including thrombosis, pulmonary hypertension, and atherosclerosis, which have tempered the practice of routine splenectomy in HS.

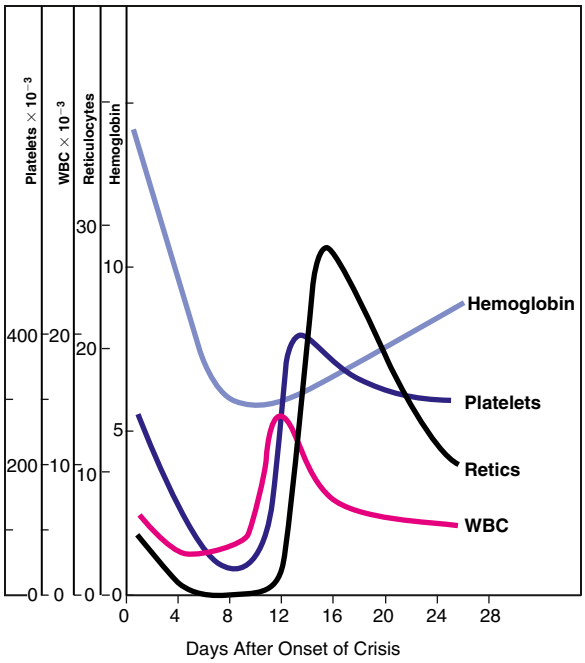

Fig. 507.3 Parvovirus-induced aplastic crisis. Progression of the changes in blood count is shown for a patient with hereditary spherocytosis and infection with parvovirus. Note that the fall in baseline reticulocytosis is associated with a rapid fall in hemoglobin. White blood cells (WBC) and platelets are also affected; Retics, reticulocytes. *(Adapted from Nathan DG, Orkin SH, Ginsburg D, et al., eds. Hematology of Infancy and Childhood, 6th ed. Philadelphia: Saunders, 2003.)*

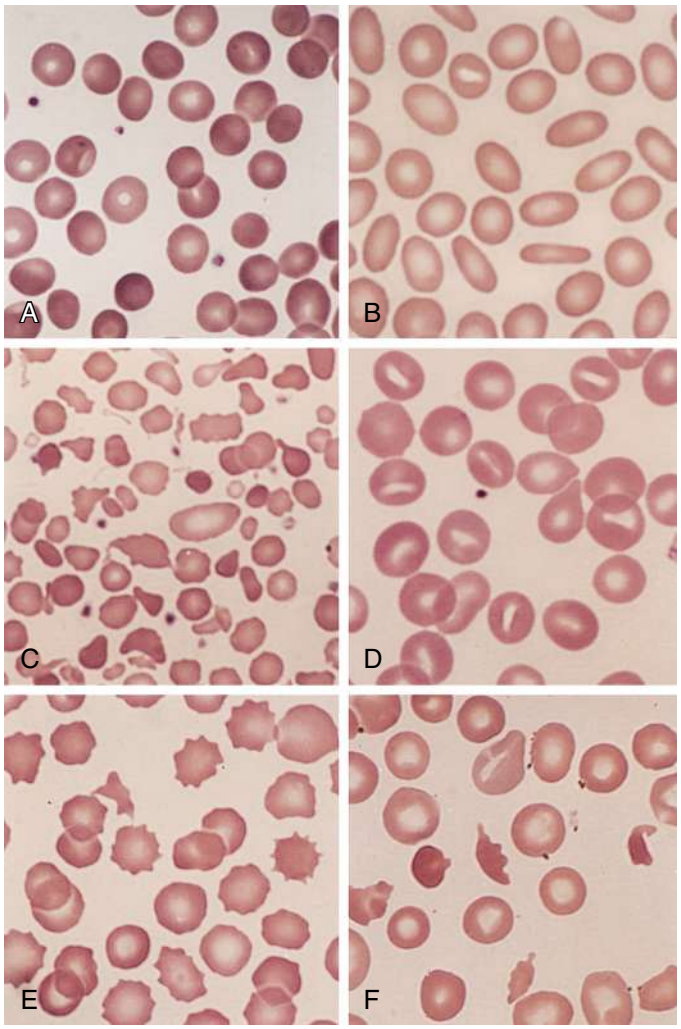

Fig. 507.4 Morphology of abnormal red cells. **A,** Hereditary spherocytosis. **B,** Hereditary elliptocytosis. **C,** Hereditary pyropoikilocytosis. **D,** Hereditary stomatocytosis. **E,** Acanthocytosis. **F,** Fragmentation hemolysis.

When considering splenectomy, the patient and the parents, together with their healthcare providers, should review and consider the risks and benefits. Individual-specific factors may confer additional risk after a splenectomy; time and distance from medical care in case of febrile illness and residence in or travel to areas where parasitic diseases such as malaria or babesiosis occur should be considered.

Most experts recommend splenectomy for patients with severe HS and believe it should be strongly considered for patients with moderate HS and frequent hypoplastic or aplastic crises, poor growth, or cardiomegaly. It is generally not recommended for patients with mild HS. When splenectomy is indicated, it should be performed after the age of 6 years, if possible, to avoid the heightened risk of postsplenectomy sepsis in younger children. The laparoscopic approach has less surgical morbidity and has become the technique of choice. Partial or subtotal splenectomy (removal of 85–95% of spleen volume) has been shown to decrease the hemolytic rate while preserving *some* splenic phagocytic function, although the decrease in hemolysis is less than that achievable with total splenectomy. Partial splenectomy is most attractive in children with severe HS requiring frequent transfusion early in childhood.

In children undergoing splenectomy, a concomitant cholecystectomy should be performed if there are gallstones. It is controversial whether to perform a concomitant splenectomy in less-severely ill patients who are undergoing cholecystectomy for gallstone disease. Postsplenectomy thrombocytosis is commonly observed but requires no treatment and usually resolves spontaneously. The patient should remain current on their vaccinations, as should household and frequent contacts. Prophylactic antibiotics are typically prescribed at least until the patient is 5 years of age or at least 2 years postsplenectomy. Folate supplementation should be continued if the hemoglobin level and reticulocyte count do not normalize.

Splenectomy failure may occur in cases of accessory spleen, accidental autotransplantation of splenic tissue into peritoneum at time of surgery, inaccurate diagnosis, or another co-inherited hemolytic anemia. Clues include return of hemolysis and disappearance of Howell-Jolly bodies on peripheral blood smear. The diagnosis can be made by radionucleotide studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 508

Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis, and Related Disorders

Stephanie Prozora and Patrick G. Gallagher

Hereditary elliptocytosis (HE), hereditary pyropoikilocytosis (HPP), and related disorders are characterized by the finding of elliptocytes on peripheral blood smear (Table 508.1). Whereas hereditary spherocytosis is thought of as a disorder of the vertical interactions coupling the erythrocyte membrane skeleton to the lipid bilayer, the HE syndromes interfere with the horizontal interactions that link spectrin molecules to each other and to membrane skeleton junctional complexes (see Chapter 507, Fig. 507.1), leaving the cell vulnerable to shear stress.

HE is the prototypical member of the group, in which abnormal shear stress over time results in elliptical deformation of the cell. It is much more common than hereditary spherocytosis, but it is much less likely to cause significant clinical symptomatology. The severity of HE varies markedly, with most patients experiencing little or no symptomatology beyond the finding of elliptocytes on peripheral blood smear. About 10% of patients have hemolytic HE with ongoing hemolysis and anemia. HE is often worse during infancy, with hemolytic anemia and hyperbilirubinemia that evolves to a well-compensated state with anemia that is absent, sporadic, or chronic. Hereditary elliptocytosis occurs worldwide and in all ethnic groups, but it is more common in patients with ancestry linked to areas of endemic malaria.

HPP is a subtype of HE characterized by severe hemolytic anemia with findings on peripheral blood smear reminiscent of a thermal burn (*pyro*, fire). HE and HPP are seen co-segregating in the same families because they involve overlapping pathogenic variants in spectrin. HPP occurs predominantly in patients of African descent.

Table 508.1 Clinical Subtypes of Hereditary Elliptocytosis and Related Disorders

CLINICAL MANIFESTATIONS	LABORATORY MANIFESTATION
TYPICAL HETEROZYGOUS HE	
Asymptomatic Dominant inheritance: one parent with HE No splenomegaly *Variants:* Some neonates have moderately severe hemolytic anemia and HPP-like smear; converts to typical HE by "1 yr." Some patients with typical HE have mild to moderate chronic hemolysis and some poikilocytosis, caused by co-inheritance of the low-expression variant α-spectrin^{LELY}, coexistence of chronic disease producing splenomegaly, or unknown factors.	Blood smear: elliptocytes, rod forms, few or no poikilocytes No anemia, little or no hemolysis (reticulocytes, 1–3%) Normal osmotic fragility Usually a defect in α-spectrin or β-spectrin leading to decreased spectrin self-association, or a defect in protein 4.1 leading to partial deficiency or dysfunction
HOMOZYGOUS HE OR HPP	
Moderate to severe hemolytic anemia Splenomegaly Intermittent jaundice Aplastic crises Recessive inheritance: typically one parent with HE and one with α-spectrin mutation, or both parents with HE Good improvement after splenectomy	Blood smear: bizarre poikilocytes, fragments, ± spherocytes, ± elliptocytes Reticulocytosis Decreased MCV because of red cell fragmentation Increased osmotic fragility, positive EMA test *α-Spectrin defects:* Decreased red cell and spectrin heat stability Marked defect in spectrin self-association In the more severe variants, partial spectrin deficiency (indicated by more spherocytes on the blood smear)
SPHEROCYTIC HE	
Mild to moderate hemolytic anemia Splenomegaly Intermittent jaundice Aplastic crises Dominant inheritance pattern Excellent response to splenectomy	Blood smear: rounded elliptocytes, ± spherocytes; may see variable morphology within a kindred Reticulocytosis Increased osmotic fragility *Variable molecular defects:* C-terminal truncation of β-spectrin Protein 4.2 deficiency (some patients); variable morphology: spherocytes, ovalocytes, stomatocytes, or spiculated cells, sometimes resembling spherocytic HE Glycophorin C deficiency (rare)
SOUTHEAST ASIAN OVALOCYTOSIS	
Anemia and jaundice in neonatal period; then asymptomatic Dominant inheritance Lowland Aboriginal tribes, especially in Melanesia, Malaysia, and the Philippines Very rigid red cells that resist invasion by malarial parasites in vitro and protect against cerebral malaria in vivo	Blood smear: rounded elliptocytes, some with a transverse bar that divides the central clear space (theta cells) No hemolysis or anemia after neonatal period Normal osmotic fragility, positive EMA test Mutant band 3 that lacks anion exchange function and tends to aggregate, leading to a rigid membrane

EMA, Eosin-5′-maleimide; HE, hereditary elliptocytosis; HPP, hereditary pyropoikilocytosis; MCV, mean cell volume.
Adapted from Wilensky ID, Narla M, Lux SF. Disorders of the red cell membrane. In: Handin RI, Lux SF, Stossel TP, eds. *Blood: Principles and Practice of Hematology*. Philadelphia: Lippincott, 2003.

Southeast Asian ovalocytosis (SAO) is a disorder characterized by the presence of ovalocytes (less elongated and plumper than elliptocytes), some with one or two transverse ridges on peripheral smear. SAO is found in individuals from New Guinea, Malaysia, Indonesia, and the Philippines. Unlike HE and HPP, SAO is due to a variant in a transmembrane protein, band 3, affecting vertical skeletal interactions and leading to increased red cell rigidity. These changes may lead to protection from malaria, particularly cerebral malaria.

ETIOLOGY

Various molecular defects have been described in HE. HE is inherited as an autosomal dominant disorder with occasional de novo cases. Most commonly, there are missense pathogenic variants of α- or β-spectrin that interfere with the formation of spectrin heterodimers into tetramers, the primary structural unit of the membrane skeleton (see Fig. 507.1). Erythrocytes carrying many of these spectrin pathogenic variants are resistant to malaria in vitro, hypothesized to explain the increased prevalence of HE in malaria-endemic areas. Less commonly, elliptocytosis results from pathogenic variants in protein 4.1 or glycophorin C, proteins of the junctional complex that link spectrin tetramers to the actin cytoskeleton. These defects in horizontal membrane skeleton protein interactions leave the cell susceptible to shearing forces, leading to the characteristic elliptical deformation of the cell and potentially membrane fragmentation.

In HPP, two abnormal spectrin alleles are inherited. Frequently, an HPP patient inherits an abnormal spectrin allele carrying a self-association site missense variant from one parent, who has mild or asymptomatic HE, and a production-defective allele that leads to quantitative deficiency of spectrin from the other parent, who is otherwise clinically well.

SAO is an autosomal dominant disorder associated with an in-frame, nine amino acid deletion in band 3.

CLINICAL MANIFESTATIONS

Most HE patients do not have clinically significant hemolysis (see Fig. 507.4B). HE may be an incidental finding on a blood film examination for an unrelated indication. The diagnosis of HE is established by the findings on the peripheral blood smear, the autosomal dominant inheritance pattern, and the absence of other causes of elliptocytosis. The differential diagnosis for other causes of elliptocytosis includes deficiencies of iron, folic acid, and vitamin B_{12}, thalassemia, myelodysplastic syndromes, and pyruvate kinase deficiency.

Interestingly, elliptocytes are not always present on the peripheral blood smear in the first few months of life. Even in hemolytic HE, which may lead to neonatal jaundice and anemia, the peripheral blood smear typically shows bizarre poikilocytes and pyknocytes with rare to no elliptocytes. Hemolysis and anemia are aggravated in the newborn period because of the increased presence of hemoglobin F, which binds poorly to 2,3-diphosphoglycerate. The increased free 2,3-diphosphoglycerate tends to destabilize the spectrin–actin–protein 4.1 complex, leading to membrane instability (see Fig. 507.1). The usual features of a chronic hemolytic process due to hemolytic HE manifest as anemia, jaundice, and splenomegaly. Cholelithiasis may occur in later childhood and aplastic crises have been reported. HPP is characterized by extreme microcytosis (mean corpuscular volume [MCV], 50-65 fL/cell), extraordinary variation in cell size and shape, and microspherocytosis with occasional elliptocytosis (see Fig. 507.4C). Hemolysis is chronic and significant.

SAO is associated with neonatal hyperbilirubinemia, but it is associated with little to no hemolysis later in life.

LABORATORY FINDINGS

Examination of the peripheral blood smear is essential to establish the diagnosis of HE (see Fig. 507.4*B*). HE elliptocytes are normochromic and normocytic with varying degrees of elongation. Because some HE patients may present with relatively low numbers of elliptocytes, there is no cutoff percentage that is useful diagnostically. In hemolytic HE, other abnormal RBC shapes may be present, depending on the severity of hemolysis, including spherocytes, pyknocytes, and other poikilocytes. In HPP, microspherocytes, red cell fragments, and occasional elliptocytes are seen. SAO is suggested when ovalocytes, which in contrast to elliptocytes are less elongated, are observed.

Reticulocyte levels and other markers of hemolysis, such as total bilirubin, lactate dehydrogenase, and haptoglobin, are helpful in establishing the severity of hemolysis, if present. In hemolytic HE and HPP, additional testing may include the eosin-5-maleimide (EMA) binding test, which detects binding to band 3 by flow cytometry, or incubated osmotic fragility testing. In cases of chronic hemolysis, splenomegaly and cholelithiasis can be assessed with abdominal ultrasound.

TREATMENT

If the presentation is that of typical HE (i.e., an isolated peripheral blood smear abnormality without clinically evident hemolysis), no treatment is necessary. For chronic HE and HPP, red blood cell transfusions are occasionally required. Splenectomy decreases the hemolysis and should be considered using criteria similar to that of hereditary spherocytosis. If hemolysis continues after splenectomy, patients should receive folic acid to prevent secondary folic acid deficiency. SAO does not require treatment beyond the newborn period.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 509

Hereditary Stomatocytosis Syndromes

Stephanie Prozora and Patrick G. Gallagher

The hereditary stomatocytosis syndromes are a group of heterogeneous, dominantly inherited disorders in which alterations in red cell cation permeability lead to alterations in intracellular water content (Table 509.1). A net increase in sodium and potassium ions allows water to enter the erythrocyte, creating stomatocytes or hydrocytes, whereas a net loss of sodium and potassium ions leads to water loss, creating dehydrated red cells, or xerocytes (Fig. 509.1).

HEREDITARY XEROCYTOSIS

Pathophysiology

Hereditary xerocytosis, the most common type of the hereditary stomatocytosis syndromes, is a dominant disorder of erythrocyte dehydration. The underlying defect is most commonly a missense variant in *PIEZO1*, a mechanosensory transduction protein, associated with delayed channel inactivation. In a few patients, pathogenic variants in the Gardos channel, important in erythrocyte dehydration in sickle cell disease, have been observed. Typically, there is a net loss of intracellular potassium that is not accompanied by a compensatory increase in sodium. Subsequently, the gradual loss of intracellular water leads to erythrocyte dehydration. Hereditary xerocytosis may be associated with a syndrome of hydrops fetalis with perinatal anemia and ascites. These findings are transient and remain unexplained.

Clinical Features

Affected patients exhibit a mild compensated macrocytic hemolytic anemia with variable degrees of splenomegaly and intermittent jaundice. The mean corpuscular hemoglobin concentration (MCHC) and mean cell volume (MCV) are elevated, and erythrocyte osmotic fragility is decreased, as are potassium concentration and total monovalent cation content. There are small numbers of stomatocytes, target cells, and contracted red blood cells (RBCs) with hemoglobin puddled to the side on peripheral blood smear. Treatment is supportive, similar

Southeast Asian ovalocytosis (SAO) is a disorder characterized by the presence of ovalocytes (less elongated and plumper than elliptocytes), some with one or two transverse ridges on peripheral smear. SAO is found in individuals from New Guinea, Malaysia, Indonesia, and the Philippines. Unlike HE and HPP, SAO is due to a variant in a transmembrane protein, band 3, affecting vertical skeletal interactions and leading to increased red cell rigidity. These changes may lead to protection from malaria, particularly cerebral malaria.

ETIOLOGY

Various molecular defects have been described in HE. HE is inherited as an autosomal dominant disorder with occasional de novo cases. Most commonly, there are missense pathogenic variants of α- or β-spectrin that interfere with the formation of spectrin heterodimers into tetramers, the primary structural unit of the membrane skeleton (see Fig. 507.1). Erythrocytes carrying many of these spectrin pathogenic variants are resistant to malaria in vitro, hypothesized to explain the increased prevalence of HE in malaria-endemic areas. Less commonly, elliptocytosis results from pathogenic variants in protein 4.1 or glycophorin C, proteins of the junctional complex that link spectrin tetramers to the actin cytoskeleton. These defects in horizontal membrane skeleton protein interactions leave the cell susceptible to shearing forces, leading to the characteristic elliptical deformation of the cell and potentially membrane fragmentation.

In HPP, two abnormal spectrin alleles are inherited. Frequently, an HPP patient inherits an abnormal spectrin allele carrying a self-association site missense variant from one parent, who has mild or asymptomatic HE, and a production-defective allele that leads to quantitative deficiency of spectrin from the other parent, who is otherwise clinically well.

SAO is an autosomal dominant disorder associated with an in-frame, nine amino acid deletion in band 3.

CLINICAL MANIFESTATIONS

Most HE patients do not have clinically significant hemolysis (see Fig. 507.4B). HE may be an incidental finding on a blood film examination for an unrelated indication. The diagnosis of HE is established by the findings on the peripheral blood smear, the autosomal dominant inheritance pattern, and the absence of other causes of elliptocytosis. The differential diagnosis for other causes of elliptocytosis includes deficiencies of iron, folic acid, and vitamin B_{12}, thalassemia, myelodysplastic syndromes, and pyruvate kinase deficiency.

Interestingly, elliptocytes are not always present on the peripheral blood smear in the first few months of life. Even in hemolytic HE, which may lead to neonatal jaundice and anemia, the peripheral blood smear typically shows bizarre poikilocytes and pyknocytes with rare to no elliptocytes. Hemolysis and anemia are aggravated in the newborn period because of the increased presence of hemoglobin F, which binds poorly to 2,3-diphosphoglycerate. The increased free 2,3-diphosphoglycerate tends to destabilize the spectrin–actin–protein 4.1 complex, leading to membrane instability (see Fig. 507.1). The usual features of a chronic hemolytic process due to hemolytic HE manifest as anemia, jaundice, and splenomegaly. Cholelithiasis may occur in later childhood and aplastic crises have been reported. HPP is characterized by extreme microcytosis (mean corpuscular volume [MCV], 50-65 fL/cell), extraordinary variation in cell size and shape, and microspherocytosis with occasional elliptocytosis (see Fig. 507.4C). Hemolysis is chronic and significant.

SAO is associated with neonatal hyperbilirubinemia, but it is associated with little to no hemolysis later in life.

LABORATORY FINDINGS

Examination of the peripheral blood smear is essential to establish the diagnosis of HE (see Fig. 507.4*B*). HE elliptocytes are normochromic and normocytic with varying degrees of elongation. Because some HE patients may present with relatively low numbers of elliptocytes, there is no cutoff percentage that is useful diagnostically. In hemolytic HE, other abnormal RBC shapes may be present, depending on the severity of hemolysis, including spherocytes, pyknocytes, and other poikilocytes. In HPP, microspherocytes, red cell fragments, and occasional elliptocytes are seen. SAO is suggested when ovalocytes, which in contrast to elliptocytes are less elongated, are observed.

Reticulocyte levels and other markers of hemolysis, such as total bilirubin, lactate dehydrogenase, and haptoglobin, are helpful in establishing the severity of hemolysis, if present. In hemolytic HE and HPP, additional testing may include the eosin-5-maleimide (EMA) binding test, which detects binding to band 3 by flow cytometry, or incubated osmotic fragility testing. In cases of chronic hemolysis, splenomegaly and cholelithiasis can be assessed with abdominal ultrasound.

TREATMENT

If the presentation is that of typical HE (i.e., an isolated peripheral blood smear abnormality without clinically evident hemolysis), no treatment is necessary. For chronic HE and HPP, red blood cell transfusions are occasionally required. Splenectomy decreases the hemolysis and should be considered using criteria similar to that of hereditary spherocytosis. If hemolysis continues after splenectomy, patients should receive folic acid to prevent secondary folic acid deficiency. SAO does not require treatment beyond the newborn period.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 509

Hereditary Stomatocytosis Syndromes

Stephanie Prozora and Patrick G. Gallagher

The hereditary stomatocytosis syndromes are a group of heterogeneous, dominantly inherited disorders in which alterations in red cell cation permeability lead to alterations in intracellular water content (Table 509.1). A net increase in sodium and potassium ions allows water to enter the erythrocyte, creating stomatocytes or hydrocytes, whereas a net loss of sodium and potassium ions leads to water loss, creating dehydrated red cells, or xerocytes (Fig. 509.1).

HEREDITARY XEROCYTOSIS

Pathophysiology

Hereditary xerocytosis, the most common type of the hereditary stomatocytosis syndromes, is a dominant disorder of erythrocyte dehydration. The underlying defect is most commonly a missense variant in *PIEZO1*, a mechanosensory transduction protein, associated with delayed channel inactivation. In a few patients, pathogenic variants in the Gardos channel, important in erythrocyte dehydration in sickle cell disease, have been observed. Typically, there is a net loss of intracellular potassium that is not accompanied by a compensatory increase in sodium. Subsequently, the gradual loss of intracellular water leads to erythrocyte dehydration. Hereditary xerocytosis may be associated with a syndrome of hydrops fetalis with perinatal anemia and ascites. These findings are transient and remain unexplained.

Clinical Features

Affected patients exhibit a mild compensated macrocytic hemolytic anemia with variable degrees of splenomegaly and intermittent jaundice. The mean corpuscular hemoglobin concentration (MCHC) and mean cell volume (MCV) are elevated, and erythrocyte osmotic fragility is decreased, as are potassium concentration and total monovalent cation content. There are small numbers of stomatocytes, target cells, and contracted red blood cells (RBCs) with hemoglobin puddled to the side on peripheral blood smear. Treatment is supportive, similar

Table 509.1 Features of Hereditary Stomatocytosis-Xerocytosis Syndromes

FEATURE (NORMAL VALUE)	OTHER HEREDITARY STOMATOCYTOSIS SYNDROMES			SOUTHEAST ASIAN OVALOCYTOSIS	HEREDITARY XEROCYTOSIS (DEHYDRATED STOMATOCYTOSIS)	
	OVERHYDRATED HEREDITARY STOMATOCYTOSIS	MILD HEREDITARY STOMATOCYTOSIS	HEREDITARY CRYOHYDROCYTOSIS		TYPICAL	PSEUDO-HYPERKALEMIA
Hemolysis	Severe	Mild to moderate	Mild to moderate	Mild (neonatal only)	Moderate	Mild or none
Anemia	Moderate to severe	Mild to moderate	Mild to moderate to completely compensated	Mild (neonatal only)	Mild to moderate to completely compensated	None
Blood smear	Stomatocytes; ± spherocytes	Stomatocytes; ± spherocytes	Stomatocytes, sometimes with curved or offset stoma; ± spherocytes; ± target cells	Rounded elliptocytes, some with a double central clearing and a theta (θ) shape; ± stomatocytes	Target cells; sometimes small numbers of echinocytes or stomatocytes	Target cells; few stomatocytes
MCV	Increased	Normal to increased	Normal to increased		High normal to increased	Normal to increased
MCHC	Decreased	Normal to decreased	Normal to increased		Normal to increased	Normal to increased
Unincubated osmotic fragility	Very increased	Variable	Variable	Unknown	Decreased to very decreased	Slightly decreased
RBC Na^+ (5-12 mEq/L)*	60-150	30-60	15-100	Normal	5-30	10-30
RBC K^+ (90-105 mEq/L)*	20-55	40-85	30-100	Normal	60-90	75-100
RBC $Na^+ + K^+$ (95-110 mEq/L)*	110-170	115-145	70-130	Normal	70-100	85-110
RBC passive membrane leak*†	20-40	~3-10	1-6	2-4	2-4	1-2
Cold hemolysis	No	Unknown	Yes	Yes	No	No
Pseudohyperkalemia	Sometimes	Unknown	Yes	Unknown	Sometimes	Yes
Perinatal ascites	No	Unknown	No	No	Sometimes	No
Stomatin markedly decreased	Yes	No	No (type 1) Yes (type 2)	No	No	No
Effect of splenectomy on hemolysis	Some benefit	Some benefit	Minimal or no effect	No significant hemolysis	No effect	No significant hemolysis
Thromboembolism risk after splenectomy	Yes	Unknown	?Yes	Unknown	Yes	Unknown
Genetics	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Defective gene(s)	*KHAG*	Band 3 *(SLC4A1)*	Type 1: Band 3 *(SLC4A1)* Type 2: Glut 1 *(SLC2A1)*	Band 3 *(SLC4A1)* in-frame deletion	*PIEZO1*	*PIEZO1, ABCR6*

*Based on a relatively small number of measurements reported in the literature.
†Times normal. Defined as the ouabain- and bumetanide-resistant $^{86}Rb^+$ influx at 37°C, and expressed as the ratio of patient residual leak to normal residual leak (normal: 0.06-0.10 mmol/L RBC/hr).
MCHC, Mean corpuscular hemoglobin concentration; MCV, mean cell volume; RBC, red blood cell.
From Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier, 2015: 561; Table 16.12.

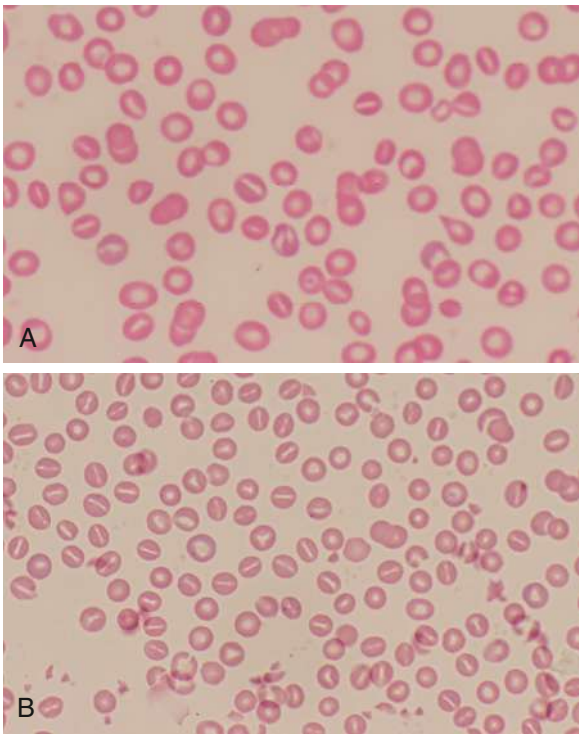

Fig. 509.1 Peripheral blood smears. A, Hereditary xerocytosis. B, Hereditary hydrocytosis.

to other disorders with congenital hemolytic anemia. Because of the apparent predisposition to major thromboses postsplenectomy, *splenectomy is not recommended in hereditary xerocytosis and related disorders.* Another unusual manifestation of hereditary xerocytosis is the propensity for iron overload, independent of transfusion history. Thus iron indices should be monitored at regular intervals.

HEREDITARY HYDROCYTOSIS

Pathophysiology

Hereditary hydrocytosis is a very rare, dominant disorder associated with large, swollen stomatocytic erythrocytes. The principal defect is an increase in Na^+ and K^+ permeability, leading to markedly increased intracellular sodium and water content. The molecular defect is unknown in most cases. In a subset of cases, missense variants in the Rh-associated glycoprotein (RhAG) have been identified.

Clinical Features

Hereditary hydrocytosis is the most clinically severe disorder of altered erythrocyte volume regulation. It is characterized by moderate to severe hemolysis and macrocytosis (110-150 fL), with a low MCHC (24–30%), elevated erythrocyte sodium concentration, reduced potassium concentration, increased total Na^+ and K^+ content, and increased erythrocyte osmotic fragility. There are large numbers (10–30%) of stomatocytes on peripheral blood smear. Patients typically develop jaundice, splenomegaly, and cholelithiasis.

Treatment is supportive. RBC transfusions are occasionally required. Patients should be followed for evidence of hematologic decompensation during acute illness. Interval ultrasonography to detect cholelithiasis should be obtained. When there is significant hemolysis, folate should be prescribed daily. Similar to hereditary xerocytosis, significant postsplenectomy major thromboses have been observed; thus splenectomy is not recommended in hereditary hydrocytosis.

INTERMEDIATE SYNDROMES AND OTHER VARIANTS

Hereditary xerocytosis and hereditary hydrocytosis are at the extremes of disorders with alterations in erythrocyte permeability. Patients with intermediate defects have been described with varying degrees of hemolysis and anemia. One of these intermediate syndromes is **cryohydrocytosis** in which affected patients typically suffer from mild anemia associated with stomatocytes, spherocytes, and sphero-stomatocytes on peripheral blood smear. Cryohydrocytosis erythrocytes are deficient in band 3 and demonstrate a significant cation leak upon cooling to low temperature (*kyros* = cold). This disorder is due to missense variants in band 3 that likely convert band 3 from an anion exchanger to a nonselective cation leak channel.

Rh deficiency syndrome, also known as Rh_{null} syndrome, is mild to moderate hemolytic anemia associated with markedly decreased (Rh_{mod}) or absent (Rh_{null}) Rh antigens on the erythrocyte membrane. Rh_{null} erythrocytes, which lack all Rh antigens, LW, and Fy5 antigens and have decreased reduced expression of Ss, U, and Duclos antigens, are dehydrated with decreased cell cation and water content. Findings on blood smear include reticulocytes, stomatocytes, and spherocytes. In response to immunization during pregnancy or after blood transfusion, Rh_{null} patients produce antibodies varying in specificity from reacting to anti-e or anti-C to reacting with all erythrocytes tested, an antibody called "anti-total Rh."

Familial deficiency of high-density lipoproteins (Tangier disease) is a rare recessive disorder that results from pathogenic variants in the cholesterol and phospholipid transport protein ABCA1, which lead to perturbations of cellular cholesterol transport and result in the accumulation of cholesterol esters in many tissues. Hematologic manifestations include a mild to moderate stomatocytic hemolytic anemia and thrombocytopenia. Affected patients can also have large orange tonsils, hepatosplenomegaly, lymphadenopathy, cloudy corneas, peripheral neuropathy, and premature atherosclerosis.

Sitosterolemia, also known as phytosterolemia, is a recessive disorder in which the absorption of sterols, both cholesterol and its plant-derived relatives (e.g., sitosterol), is unlimited and unselective. Clinical manifestations include early-onset xanthomatosis, short stature, and premature coronary artery disease. Hematologic abnormalities include macrothrombocytopenia and stomatocytic hemolytic anemia. The plasma cholesterol may or may not be abnormal, but mass spectrometry always shows a massive increase in plant sterol levels in the plasma and in the membranes of platelets and erythrocytes. Pathogenic variants in *ABCG5* or *ABCG8*, transporters that actively pump plant sterols out of intestinal cells back into the intestine and out of liver cells into bile ducts, lead to gastrointestinal hyperabsorption and decreased biliary elimination of plant sterols, as well as altered cholesterol metabolism. Treatment involves dietary restriction of cholesterol and plant sterols and prescription of ezetimibe, a sterol absorption inhibitor, and cholestyramine and other related bile acid–sequestering agents.

OTHER DISORDERS ASSOCIATED WITH STOMATOCYTOSIS

Acquired stomatocytosis may be seen with liver disease, alcoholism, malignancy, and cardiovascular disease and after vinca alkaloid administration. Stomatocytes can be seen as a blood smear–processing artifact.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 510

Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

Stephanie Prozora and Patrick G. Gallagher

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Etiology

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder of the cell membranes of multipotent bone marrow stem cells. The underlying somatic pathogenic variant propagates into a clonal population of stem cells so that all blood cells derived from these variant clonal progenitors, especially red blood cells (RBCs), are susceptible to complement-mediated destruction (Fig. 510.1). The pathogenic variant causes cell membranes to be deficient (either partially or completely) in proteins that impede complement-mediated lysis via the constitutively active alternative pathway. These complement regulating proteins include decay-accelerating factor (CD55), the membrane inhibitor of reactive lysis (CD59), and the C8 binding protein. The underlying defect involves the glycolipid anchor that maintains these protective proteins on the cell surface. Various pathogenic variants in the *PIGA* gene that encodes the glycosylphosphatidylinositol anchor protein have been identified in patients with PNH.

Clinical Manifestations

PNH is a rare disorder in children. Approximately 60% of pediatric patients have marrow failure, and the remainder have either intermittent or chronic anemia, often with prominent intravascular hemolysis (Tables 510.1 and 510.2). Nocturnal and morning hemoglobinuria is the classic finding in adults, but only a minority of PNH patients experience this. Most patients experience chronic hemolysis, often with thrombocytopenia and leukopenia. Hemoglobinuria is rarely seen in children compared with adults with PNH. *Thrombosis and thromboembolic phenomena* are serious complications that may be related to altered glycoproteins on the platelet surface and resultant platelet activation and production of procoagulant microparticles. Abdominal venous thrombosis presents as recurrent episodes of abdominal pain, Budd-Chiari syndrome (hepatic veins), or splenomegaly (splenic vein). Released free hemoglobin results in depletion of nitric oxide, fostering vasoconstriction, thrombosis, and pain. Back and head pain may also be prominent. Hypoplastic or aplastic pancytopenia can precede or follow the diagnosis of PNH; rarely, PNH may progress to acute myelogenous leukemia. At the time of presentation, more than 90% of patients with PNH have some blood abnormality (including ~35% with anemia alone, ~15% with anemia and thrombocytopenia, ~7% with anemia and neutropenia, and ~30% with pancytopenia), >10% have abdominal pain, and >5% have thrombosis. The mortality in PNH is related primarily to the development of aplastic anemia or thrombotic complications. The predicted survival rate for children before the development of eculizumab was 80% at 5 years, 60% at 10 years, and 28% at 20 years.

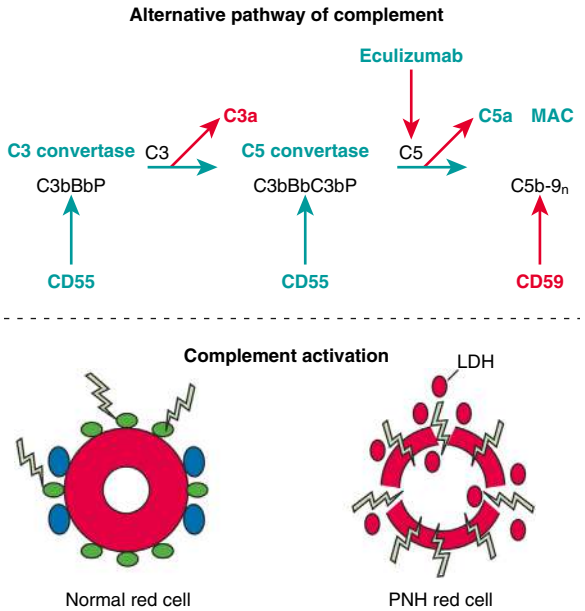

Fig. 510.1 Complement-mediated lysis in paroxysmal nocturnal hemoglobinuria (PNH). *Red circles* are hemoglobin. *Blue circles* are decay accelerating factor (CD55). *Green circles* are membrane inhibitor of reactive lysis (CD59). Bb, activated factor B; C3b, activated C3; C5b, activated C5; MAC, membrane attack complex (consisting of C5b, C6, C7, C8, and several molecules of C9 [9n]). *(From Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. Lancet 2009;373:759–767.)*

Laboratory Findings

Hemoglobin levels can range from normal to markedly decreased. Common findings reflect chronic intravascular hemolysis and include hemosiderinuria, an elevated reticulocyte percentage, a low serum haptoglobin, and increased lactic dehydrogenase. Initially, the anemia is normocytic, but if iron deficiency develops, it becomes microcytic. On the blood smear, poikilocytosis and anisocytosis may be present. Markedly reduced levels of RBC acetylcholinesterase activity and decay-accelerating factor are also found. *Flow cytometry is the diagnostic test of choice for PNH*. With the use of anti-CD59 for RBCs and anti-CD55 and anti-CD59 for granulocytes, flow cytometry is more sensitive than the classic RBC lysis (Ham or sucrose) tests in detecting these reduced glycolipid-bound membrane proteins. Fluorescently labeled aerolysin testing can heighten the sensitivity of detection by binding selectively to glycosylphosphatidylinositol anchors.

Treatment

Eculizumab therapy has resulted in sustained survival in the majority of patients. Eculizumab is a monoclonal antibody against complement component C5 that interrupts formation of the membrane attack complex, blocking downstream complement destruction of RBCs and activation of platelets. It decreases the rate of hemolysis, stabilizes hemoglobin levels, reduces the number of transfusions, reduces the risk of thrombosis, and improves quality of life. Eculizumab is an approved and effective treatment for PNH in adults. A recent phase I/II trial demonstrated safety and efficacy in patients 11-17 years of age. Because of the cost and duration of treatment (i.e., lifelong) required, particularly in children, it may be most useful in preventing thrombosis, anemia, and other symptoms while stem cell transplant is considered. Survival in adults with PNH treated with eculizumab may not be different from sex- and age-matched control patients from the general population. However, the medication does not improve the hematopoietic clonal expansion or prevent marrow failure. Before beginning eculizumab, it is recommended to immunize patients with the meningococcal vaccine if the patient hasn't already received this vaccine because a very serious risk of complement inhibition is increased susceptibility to *Neisseria* infections. If eculizumab therapy is desired to begin immediately for clinical reasons, the vaccine can be given at the same time, and prophylactic antibiotics can be given for a 2-week bridge. Headache is a common adverse effect after the first few doses but disappears subsequently. A poor response to eculizumab may be due to polymorphisms in the C5 gene that produce resistance to

Table 510.1 Suggested Criteria as Indications for PNH Testing

CATCH CRITERION	INDICATIONS FOR TESTING	SUPPORTING INFORMATION
Cytopenias	Patients for whom a bone marrow examination is considered for otherwise unexplained cytopenia(s)	Additional features such as elevated LDH, DAT-negative hemolysis, history of unexplained TE, and hemoglobinuria
AA/MDS	All patients with a diagnosis or suspicion of AA Testing should be done at diagnosis and monitored at least q6 months Low or intermediate-1 risk MDS, and especially if hypoplastic	Additional features such as elevated LDH, DAT-negative hemolysis, history of unexplained TE, and hemoglobinuria
Thrombosis	Unprovoked and/or unusual site TE (e.g.,, splenic, hepatic, CNS), especially if recurrent and/or despite anticoagulation	Additional features such as elevated LDH, DAT-negative hemolysis, otherwise-unexplained cytopenias, especially including anemia
Coombs-negative hemolysis	Hemolysis or hemolytic anemia (i.e., elevated LDH and indirect bilirubin, reduced haptoglobin, DAT/Coombs test negative) without other clear cause	Test in all patients unless a clear alternate explanation exists Supportive information may be helpful but is not necessary
Hemoglobinuria	Otherwise-unexplained hemoglobinuria or cases where "hematuria" has been identified without evidence of erythrocytes on microscopy	Test in all patients unless a clear alternate explanation exists Supportive information may be helpful but is not necessary

AA, Aplastic anemia; CNS, central nervous system; DAT, direct antiglobulin test (aka Coombs test); LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; TE, thromboembolic event.
From Patriquin CJ, Kiss T, Caplan S, et al. How we treat paroxysmal nocturnal hemoglobinuria: A consensus statement of the Canadian PNH Network and review of the national registry. *Eur J Haematol*. 2019;102:36–52: Table 2, p. 39.

Table 510.2 Classification of Paroxysmal Nocturnal Hemoglobinuria

CATEGORY	RATE OF INTRAVASCULAR HEMOLYSIS*	BONE MARROW	FLOW CYTOMETRY	BENEFIT FROM ECULIZUMAB
Classic clinical PNH	Florid (markedly abnormal LDH, often with episodic macroscopic hemoglobinuria)	Cellular marrow caused by erythroid hyperplasia and normal or near-normal morphology†	Large population (>50%) of GPI-AP– PMNs§	Yes
Clinical PNH in the setting of another bone marrow failure syndrome‡	Mild (often with minimal abnormalities of biochemical markers of hemolysis)	Evidence of a concomitant bone marrow failure syndrome‡	Although variable, the percentage of GPI-AP– PMNs is usually relatively small (<50%)	Typically no, but some patients have relatively large clones and clinically significant hemolysis and may benefit from treatment
Subclinical PNH	No clinical or biochemical evidence of intravascular hemolysis	Evidence of a concomitant bone marrow failure syndrome‡	Small (<1%) population of GPI-AP– PMNs detected by high-resolution flow cytometry	No

*Based on macroscopic hemoglobinuria, serum LDH concentration and reticulocyte count.
†Karyotypic abnormalities are uncommon.
‡Aplastic anemia or low-risk myelodysplastic syndrome.
§Analysis of PMNs is more informative than analysis of red blood cells because of selective destruction GPI-AP– RBCs.
GPI-AP–, Glycosylphosphatidylinositol–anchored protein–deficient; LDH, lactate dehydrogenase; PMNs, polymorphonuclear leukocytes.
From Parker CJ, Ware RE. Paroxysmal nocturnal hemoglobinuria. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier, 2015: Table 14-1.

eculizumab blockades. Patients on eculizumab therapy require regular monitoring, including complete blood counts with reticulocytes, lactate dehydrogenase, total bilirubin, and repeat flow cytometry every 6-12 months.

Hematopoietic stem cell transplantation (HSCT) is a key therapeutic consideration if a suitable donor exists, particularly in children. Severe aplastic anemia is a strong indication for transplant in PNH (Fig. 510.2). HSCT is the only potentially curative therapy available for PNH. Nonmyeloablative transplantation (with reduced intensity conditioning regimens) are often used to reduce transplant-related mortality and morbidity; because eradication of only the PNH clones is sought, total myeloablation is not necessary.

Glucocorticoids such as prednisone can be used for acute hemolytic episodes; the dosage should be tapered as soon as the hemolysis abates. Prolonged anticoagulation (heparin or low molecular weight heparin) therapy may be of benefit when thromboses occur. Because of chronic urinary loss of iron as hemosiderin, iron therapy may be necessary. Androgens (e.g., fluoxymesterone), antithymocyte globulin, cyclosporine, and growth factors (e.g., erythropoietin and granulocyte colony-stimulating factor) have been used to treat marrow failure.

ACANTHOCYTOSIS

Acanthocytosis is characterized by RBCs with irregular circumferential pointed projections (also known as spur cells) (see Fig. 507.4E).

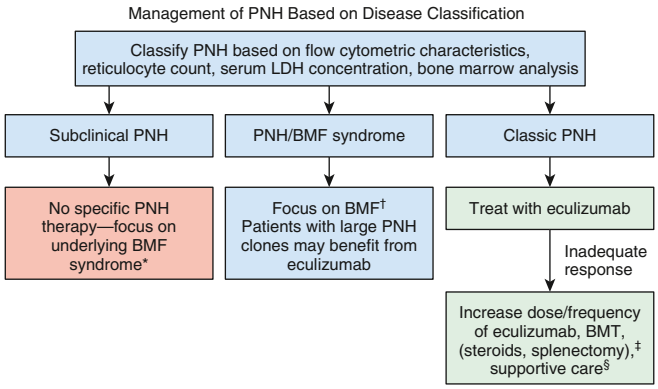

*Some, but not all, studies suggest a favorable response to immunosuppressive therapy (IST).
† BMT eradicates the PNH clone, and typically, treatment with IST does not affect PNH clone size.
‡ Consider for patients with clinically significant extravascular hemolysis.
§ Transfusion.

Fig. 510.2 Management algorithm for paroxysmal nocturnal hemoglobinuria (PNH). A management scheme based on classification of PNH into two categories: subclinical, PNH in the setting of another bone marrow failure syndrome (PNH/BMF), and classic PNH (see Table 510.2 for characteristics of each category.) *LDH*, Lactic dehydrogenase; *BMF*, bone marrow failure (aplastic anemia and low risk MDS); *BMT*, bone marrow transplant. *(From Orkin SH, Fisher DE, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood, 8th ed. Philadelphia: Elsevier, 2015. Fig 14-9.)*

Table 510.3 Hereditary Acanthocytosis Syndromes

SYNDROME	INHERITANCE	GENES
Chorea-acanthocytosis	Autosomal recessive	*VPS13A*
McLeod syndrome	X-linked recessive	*XK*
Huntington disease–like 2	Autosomal dominant	*JPH3*
Pantothenate kinase-associated neurodegeneration	Autosomal recessive	*PANK2*
Abetalipoproteinemia	Autosomal recessive	*MTTP*
Hereditary hypobetalipoproteinemia	Autosomal recessive	*APOB, MTP, PCSK9*
Aceruloplasminemia	Autosomal recessive	*CP*

This morphologic finding results from alterations in the membrane ratio of cholesterol to phospholipid, with the morphology attributed to an excess of lipid in the outer layer relative to the inner layer of the membrane bilayer. In liver disease, acanthocytes develop because of increased abundance of free cholesterol, as patients develop splenic congestion, hemolytic anemia, and jaundice. **Abetalipoproteinemia** is an inherited autosomal recessive disease in which acanthocytosis is associated with fat malabsorption, progressive ataxia, and retinitis pigmentosa. The fat malabsorption may become apparent in the first year of life, whereas the ataxia develops at school-age. The anemia is usually mild. **Hypobetalipoproteinemia** is a recessive familial disease that has a similar clinical spectrum, but with milder findings. Aceruloplasminemia leads to anemia, diabetes, ocular problems, tremors, chorea, ataxia, and facial abnormalities due to increased iron in the brain and other organs.

There are four genetically diverse **neuroacanthocytosis syndromes** (Table 510.3). *Chorea-acanthocytosis* is an adult-onset disease without anemia, variable numbers of acanthocytes on peripheral blood smear, with multiple neurologic findings such as limb chorea, tics, and hypotonia. The rare *X-linked McLeod syndrome* (marked by absence of the Kell antigen) presents with mild hemolytic anemia, late-onset myopathy, peripheral neuropathy, chorea, and splenomegaly. There are usually >3% acanthocytes on peripheral smear and caudate atrophy noted on MRI. McLeod syndrome is the only neuroacanthocytosis syndrome likely to present in childhood. Acanthocytes also are seen in *pantothenate kinase-associated neurodegeneration* (with dystonia, rigidity, chorea, dysarthria, spasticity, retinopathy) and *Huntington disease–like 2*.

In contrast to acanthocytes, echinocytes or "burr cells" have a more regular distribution of projections or serrations along the surface of the RBCs and will tend to a more spheroidal cell contour as they age. They are seen often as artifacts (e.g., due to elevated pH, contact with glass, or blood storage) and infrequently in end-stage renal disease, liver disease, uremia, pyruvate-kinase deficiency, long-distance runners, and patients with hypomagnesemia and hypophosphatemia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 511

Hemoglobinopathies

Kim Smith-Whitley and Janet L. Kwiatkowski

HEMOGLOBIN DISORDERS

Hemoglobin is a tetramer consisting of two pairs of globin chains. Abnormalities in these proteins are referred to as **hemoglobinopathies**.

More than 800 variant hemoglobins have been described. The most common and useful clinical classification of hemoglobinopathies is based on nomenclature associated with alteration of the involved *globin chain*. Two hemoglobin (Hb) gene clusters are involved in Hb production and are located at the end of the short arms of chromosomes 16 and 11. Their control is complex, including an upstream locus control region on each respective chromosome and an X-linked control site. On chromosome 16, there are three genes within the alpha (α) gene cluster: zeta (ζ), alpha 1 (α_1), and alpha 2 (α_2). On chromosome 11, there are five genes within the beta (β) gene cluster: epsilon (ε), gamma 1 (γ_1), gamma 2 (γ_2), delta (δ), and beta (β).

The order of gene expression within each cluster roughly follows the order of expression during the embryonic period, fetal period, and eventually childhood. After 8 weeks of fetal life, the embryonic hemoglobins, Gower-1 ($\zeta_2\varepsilon_2$), Gower-2 ($\alpha_2\varepsilon_2$), and Portland ($\zeta_2\gamma_2$), are formed. At 9 weeks of fetal life, the major hemoglobin is hemoglobin F (HbF; $\alpha_2\gamma_2$). Hemoglobin A (HbA; $\alpha_2\beta_2$) first appears at approximately 1 month of fetal life but does not become the dominant hemoglobin until after birth, when HbF levels start to decline. HbA_2 ($\alpha_2\delta_2$) is a minor hemoglobin that appears shortly before birth and remains at a low level after birth. The final hemoglobin distribution pattern that occurs in childhood is not achieved until at least 6 months of age and sometimes later. The normal hemoglobin pattern is ≥95% HbA, ≤3.5% HbA_2, and <2.5% HbF.

511.1 Sickle Cell Disease

Kim Smith-Whitley and Janet L. Kwiatkowski

Children with sickle cell disease should be followed by experts in the management of this disease, most often by pediatric hematologists. Children who receive disease-specific care that focuses on prevention of infectious complications and end-organ damage should have a

higher likelihood of survival to adult age. Medical care provided by a pediatric hematologist is also associated with a decreased frequency of emergency department (ED) visits and length of hospitalization compared to patients who were not seen by a hematologist within the last year.

PATHOPHYSIOLOGY

Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the 6th codon of the β-globin gene. This change encodes valine instead of glutamine in the sixth residue in the β-globin molecule. Sickle cell anemia (HbSS), homozygous HbSS, occurs when both β-globin alleles have the sickle cell pathogenic variant (βs). Sickle cell disease refers not only to patients with sickle cell anemia but also to compound heterozygotes where one β-globin allele includes the sickle cell pathogenic variant and the second β-globin allele includes a gene pathogenic variant other than the sickle cell pathogenic variant, such as HbC, β-thalassemia, HbD, and HbO^{Arab}. In sickle cell anemia, HbS is typically as high as 90% of the total hemoglobin, whereas in sickle cell disease, HbS is >50% of all hemoglobin.

In red blood cells (RBCs), the hemoglobin molecule has a highly specified conformation allowing for the transport of oxygen in the body. In the absence of globin-chain pathogenic variants, hemoglobin molecules do not interact with one another. However, the presence of HbS results in a conformational change in the Hb tetramer, and in the deoxygenated state, HbS molecules interact with each other, forming rigid polymers that give the RBC its characteristic "sickled" shape. Intraerythrocytic changes lead to a shortened RBC life span and hemolysis. Hemolysis leads to multiple changes, including altered nitric oxide metabolism and oxidant stress, which contribute to endothelial dysfunction. Intravascular sickling primarily occurs in the postcapillary venules and is a function of both mechanical obstruction by sickled erythrocytes, platelets, and leukocytes and increased adhesion between these elements and the vascular endothelium. Sickle cell disease is also an inflammatory disease based on nonspecific markers of inflammation, including, but not limited to, elevated baseline white blood cell (WBC) count and cytokines.

DIAGNOSIS AND EPIDEMIOLOGY

Every state in the United States has instituted a mandatory newborn screening program for sickle cell disease. Such programs identify newborns with the disease and provide prompt diagnosis and referral to providers with expertise in sickle cell disease for anticipatory guidance and the initiation of penicillin prophylaxis before 4 months of age.

The most commonly used procedures for newborn diagnosis include thin-layer/isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC). Some laboratories perform genetic testing on specimens demonstrating abnormal hemoglobins. A confirmatory step is recommended, with all patients who have initial abnormal screens being retested during the first clinical visit, which helps to account for potential administrative errors in specimen handling. In addition, a complete blood cell count (CBC) and Hb phenotype determination is recommended for both parents to provide an opportunity for genetic counseling and to better characterize disease genotype in the affected offspring if necessary. Infants who may have **HbS-hereditary persistence fetal hemoglobin (HbSHPFH)** but do not have full parental studies should have molecular testing for β-globin genotype before 12 months of age (or sooner if hydroxyurea is initiated). Table 511.1 correlates the initial hemoglobin phenotype at birth with the type of hemoglobinopathy.

In newborn screening programs, the hemoglobin with the greatest quantity is reported first, followed by other hemoglobins in order of decreasing quantity. Some states perform IEF initially on newborn blood samples, then use DNA probes to confirm abnormal hemoglobins found on IEF. In newborns with a hemoglobin analysis result of **HbFS**, the pattern supports HbSS, HbSHPFH, or $HbS\beta^0$-thalassemia. In certain situations, a newborn with a hemoglobin analysis of HbFS may have $HbS\beta^+$-thalassemia and the hemoglobin A may not be demonstrating on the electrophoresis in quantities high enough for detection. In a newborn with a hemoglobin analysis of **FSA**, the pattern is supportive of the diagnosis of $HbS\beta^+$-thalassemia. The diagnosis of $HbS\beta^+$-thalassemia is confirmed if at least 50% of the hemoglobin is HbS, HbA is present, and the amount of HbA_2 is elevated (typically >3.5%), although HbA_2 is not elevated in the newborn period. In newborns with a hemoglobin analysis of **FSC**, the pattern supports a diagnosis of HbSC. In newborns with a hemoglobin analysis of **FAS**, the pattern supports a diagnosis of HbAS (sickle cell trait); however, in this circumstance, care must be taken to confirm that the newborn has not received an RBC transfusion before testing.

A newborn with a hemoglobin analysis of **AFS** either has been transfused with RBCs before collection of the newborn screen to account for the greater amount of HbA than HbF, or there has been an error. The patient may have either sickle cell disease or sickle cell trait and

Table 511.1 Various Newborn Sickle Cell Disease Screening Results with Baseline Hemoglobin

NEWBORN SCREENING RESULTS: SICKLE CELL DISEASE*	POSSIBLE HEMOGLOBIN PHENOTYPE†	BASELINE HEMOGLOBIN RANGE AFTER AGE 5 YR
FS	SCD-SS	6-11 g/dL
	SCD-S β^0 thal	6-10 g/dL
	SCD-S β^+ thal	9-12 g/dL
	SCD-S $\delta\beta^-$ thal	10-12 g/dL
	S HPFH	12-14 g/dL
FSC	SCD-SC	10-15 g/dL
FSA‡	SCD-S β^+ thal	9-12 g/dL
FS other	SCD-S β^0 thal	6-10 g/dL
	SCD-SD, SO^{Arab}, SC^{Harlem}, S^{Lepore}	Variable
AFS‡§	SCD-SS	6-10 g/dL
	SCD-S β^+ thal	6-9 g/dL
	SCD-S β^0 thal	7-13 g/dL variable

*Hemoglobins are reported in order of quantity.
†Requires confirmatory hemoglobin analysis after at least 6 mo of age and, if possible, β-globin gene testing or hemoglobin analysis from both parents for accurate diagnosis of hemoglobin phenotype.
‡Sickle cell trait is another possible diagnosis.
§Impossible to determine the diagnosis because the infant most likely received a blood transfusion before testing.
A, Normal hemoglobin A; C, hemoglobin C; F, fetal hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; O^{Arab}, hemoglobin O^{Arab}; S, sickle hemoglobin; SC, sickle-hemoglobin C; SCD, sickle cell disease; SS, homozygous sickle cell disease; thal, thalassemia.

should be started on penicillin prophylaxis until the final diagnosis can be determined.

Given the implications of a diagnosis of sickle cell disease versus sickle cell trait in a newborn, the importance of repeating the Hb identification analysis in the patient and obtaining a Hb identification analysis and CBC to evaluate the peripheral blood smear and RBC parameters in the parents cannot be overemphasized. Unintended mistakes do occur in state newborn screening programs. Newborns who have the initial phenotype of HbFS but whose final true phenotype is HbSβ$^+$-thalassemia have been described as one of the more common errors identified in newborn screening hemoglobinopathy programs. Determining an accurate phenotype is important for appropriate genetic counseling for the parents. In addition, distinguishing HbSS from HbSHPFH in the newborn period usually requires parental or genetic testing. Infants who maintain HbF percentages above 25% after 12 months of age without evidence of hemolysis should have testing for β-globin gene deletions consistent with HPFH. These children have a much milder clinical course and do not require penicillin prophylaxis or hydroxyurea therapy.

If the parents are tested for sickle cell trait or hemoglobinopathy trait, full disclosure to the parent tested should be provided privately, and in some circumstances, the issue of paternity may be disclosed. For this reason and because of healthcare privacy, common practice is to always seek permission for the genetic testing and to report the hemoglobinopathy trait results back to each parent separately.

In the United States, sickle cell disease is the most common genetic disorder identified through the state-mandated newborn screening program, occurring in 1:2,647 births. The sickle hemoglobin gene is more prevalent in communities of color because descendants of people where malaria has been endemic are more likely to have been protected from the severe manifestations of malaria. Regarding ethnicity in the United States, sickle cell disease occurs in Black persons at a rate of 1:396 births and in Hispanics at a rate of 1:36,000 births. In the United States, an estimated 100,000 people have sickle cell disease, with an ethnic distribution of 90% Black and 10% Hispanic. The U.S. sickle cell disease population represents a fraction of the worldwide burden of the disease, with global estimates of 312,000 neonates born annually with HbSS disease.

CLINICAL MANIFESTATIONS AND TREATMENT OF SICKLE CELL ANEMIA

For a comprehensive discussion of the clinical management of children and adolescents with sickle cell disease, refer to the National Heart, Lung, and Blood Institute (NHLBI) 2014 Expert Panel Report on the Evidence-Based Management of Sickle Cell Disease (https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf).

Fever and Bacteremia

Fever in a child with sickle cell anemia is a medical emergency, requiring prompt medical evaluation and delivery of antibiotics because of the increased risk of serious bacterial infection and subsequent high mortality rate. As early as 6 months of age, infants with sickle cell anemia develop abnormal immune function because of splenic dysfunction. By 5 years of age, most children with sickle cell anemia have complete functional asplenia. Regardless of age, all patients with sickle cell anemia are at increased risk of infection and death from bacterial infection, particularly encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis,* as well as *Salmonella* spp.

Several clinical strategies have been developed to manage children with sickle cell disease who present with fever. These strategies range from hospital admission for intravenous (IV) antimicrobial therapy to administering a third-generation cephalosporin in an ED or outpatient setting to patients without established risk factors for occult bacteremia (Table 511.2). Given the observation that the average time for a positive blood culture is <20 hours in children with sickle cell anemia, admission for 24 hours is probably the most prudent strategy for children and families who live out of town or who are identified as high risk for poor follow-up.

Table 511.2 Clinical Factors Associated with Increased Risk of Acute Complications in Febrile Children with Sickle Cell Disease

Seriously ill appearance
Hypotension: systolic blood pressure <70 mm Hg at 1 yr of age or <70 mm Hg + 2 × age (yr) for older children
Poor perfusion: capillary refill time >4 sec
Temperature >40.0°C (104°F)
Hypoxia
Corrected white blood cell count >30,000/mm^3 or <5,000/mm^3
Platelet count <100,000/mm^3
History of pneumococcal sepsis*
Severe pain
Dehydration: poor skin turgor, dry mucous membranes, history of poor fluid intake, or decreased output of urine
Presence of acute chest syndrome (new infiltrate on chest radiograph)
Hemoglobin level <5.0 g/dL
No prophylactic antibiotics
Not immunized

*Or other serious infection requiring hospital admission.
Adapted from Williams JA, Flynn PM, Harris S et al. A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease. *N Engl J Med* 1993;329:472–476.

Outpatient management of fever without a source should be considered in children with the lowest risk of bacteremia and after appropriate cultures are obtained and IV ceftriaxone or another cephalosporin is given. Observation after antibiotic administration is important because children treated with ceftriaxone can develop severe, rapid, and life-threatening immune hemolysis. In the event that *Salmonella* spp. or *Staphylococcus aureus* bacteremia occurs, strong consideration should be given to an evaluation for osteomyelitis with an MRI, given the increased risk of osteomyelitis in children with sickle cell anemia compared to the general population. Screening laboratory and radiologic studies are strongly recommended to identify those at risk for transient red cell aplasia, acute splenic sequestration, and acute chest syndrome (ACS), because many children with these diagnoses present to acute care settings with isolated fever. Screening children and caregivers for psychosocial factors that could impede their return to the hospital in the case of a positive blood culture is essential.

Aplastic Crisis

Human parvovirus B19 infection poses a unique threat for patients with sickle cell disease because this infection results in temporary **red cell aplasia**, limiting the production of reticulocytes and causing profound anemia (see Fig. 507.3 in Chapter 507). Any child with sickle cell disease, fever, and *reticulocytopenia* should be presumed to have parvovirus B19 infection until proven otherwise. However, reticulocytopenia is not a requirement for the diagnosis of a recent parvovirus B19 infection because reticulocytosis and increased nucleated RBCs may be seen in the recovery phase. Diagnostic testing for the presence of human parvovirus B19 with polymerase chain reaction (PCR) testing is superior to using immunoglobulin M (IgM) and IgG titers. The acute exacerbation of anemia is treated conservatively using red cell transfusion when the patient becomes hemodynamically symptomatic or has a concurrent illness, such as ACS or acute splenic sequestration. Children with suspected aplastic crisis should be closely monitored because acute infection with parvovirus B19 is associated with pain, splenic sequestration, ACS, glomerulonephritis, arthropathy, and stroke. Patients with parvovirus-associated aplastic crisis are contagious, and infection precautions should be taken to avoid nosocomial spread of the infection and to avoid exposure of pregnant caregivers who may be at risk for adverse fetal outcomes with acute infection.

Splenic Sequestration

Acute splenic sequestration is a life-threatening complication occurring primarily in infants and young children with sickle cell anemia.

The incidence of splenic sequestration has declined from an estimated 30% to 12.6% with early identification by newborn screening and improved parental education. Sequestration can occur as early as 5 weeks of age but most often occurs in children between ages 6 months and 2 years. Patients with the SC and Sβ$^+$-thalassemia types of sickle cell disease can have acute splenic sequestration events throughout adolescence and adulthood.

Splenic sequestration is associated with rapid spleen enlargement causing left-sided abdominal pain and Hb decline from the patient's baseline. Sequestration may lead to signs of hypovolemia as a result of the trapping of blood in the spleen and profound anemia, with total Hb falling below 3 g/dL. A decrease in WBC and platelet count may also be present. Sequestration may be spontaneous or triggered by fever, bacteremia, or viral infections.

Treatment includes early intervention and maintenance of hemodynamic stability using isotonic fluid or transfusions. Careful blood transfusions with RBCs are recommended to treat both the sequestration and the resultant anemia. Blood transfusion aborts the RBC trapping in the spleen and allows release of the patient's blood cells that have become sequestered, often raising Hb above baseline values. A reasonable approach is to provide only 5 mL/kg of RBCs and/or a posttransfusion Hb target of 8 g/dL, keeping in mind that the goal of transfusion is to prevent hypovolemia. Blood transfusion that results in Hb levels >10 g/dL may put the patient at risk for **hyperviscosity syndrome** because RBCs may be released from the spleen after transfusion.

Repeated episodes of splenic sequestration are common, occurring in 65% of patients. Most recurrent episodes develop within 6 months of the previous episode. Prophylactic splenectomy performed after an acute episode has resolved is the only effective strategy for preventing future life-threatening episodes. Although blood transfusion therapy has been used with the goal of preventing subsequent episodes, evidence strongly suggests that this strategy does not reduce the risk of recurrent splenic sequestration compared to no transfusion therapy. However, a short course of regular RBC transfusions can be used until splenectomy is arranged. Children should be appropriately immunized with meningococcal and pneumococcal vaccines before surgery. Penicillin prophylaxis should be prescribed after splenectomy.

Hepatic and Gallbladder Involvement

See Chapters 408 and 414.

Sickle Cell Pain

Dactylitis, referred to as **hand-foot syndrome**, is often the first manifestation of pain in infants and young children with sickle cell anemia, occurring in 50% of children by their second year of life (Fig. 511.1). Dactylitis often manifests with symmetric or less often unilateral swelling of the hands and/or feet. Unilateral dactylitis can be confused with osteomyelitis, and careful evaluation to distinguish the two is important because treatment differs significantly. Dactylitis requires palliation with pain medications, whereas osteomyelitis requires at least 4-6 weeks of IV antibiotics. Feedback from the parents is needed to determine if pain therapy is successful in relieving pain.

The cardinal clinical feature of sickle cell disease is **acute vasoocclusive pain**. Acute sickle cell pain is characterized as unremitting discomfort that can occur in any part of the body but most often occurs in the chest, abdomen, or extremities. These painful episodes are often abrupt and cause disruption of daily life activities and significant stress for children and their caregivers. A patient with sickle cell anemia has approximately one painful episode per year that requires medical attention, but the frequency is extremely variable. The pattern of symptoms with subsequent episodes may resemble that of previous episodes.

The exact etiology of pain is unknown, but the pathogenesis may be initiated when blood flow is disrupted in the microvasculature by sickled RBCs and other cellular elements, resulting in tissue ischemia. Acute sickle cell pain may be precipitated by physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, and swimming for prolonged periods. However, most pain episodes occur without an identifiable trigger. Successful treatment of these episodes requires education of both caregivers and patients regarding the recognition of symptoms and the optimal management strategy. Given the absence of any reliable objective laboratory or clinical parameter associated with pain, trust between the patient and the treating physician is paramount to successful clinical management. Specific therapy for pain varies greatly but generally includes the use of acetaminophen or a nonsteroidal antiinflammatory drug (NSAID) early in the course of pain, followed by escalation to a combination analgesic regimen using a single-agent short-acting oral opioid, long-acting oral opioid, and continued nonopioid agent.

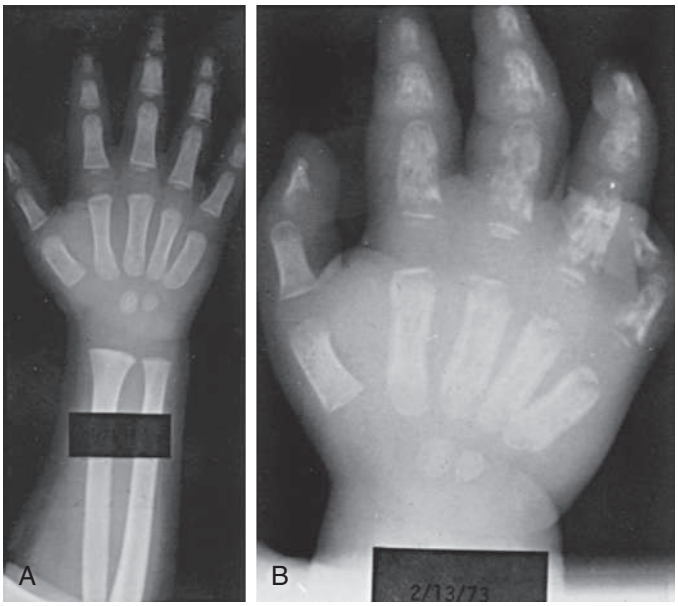

Fig. 511.1 Radiographs of an infant with sickle cell anemia and acute dactylitis. **A**, The bones appear normal at the onset of the episode. **B**, Destructive changes and periosteal reaction are evident 2 weeks later.

The majority of painful episodes in patients with sickle cell disease are managed at home with comfort measures, such as heating pad, relaxation techniques, massage, and oral pain medication. Some patients require treatment in an acute care setting with IV morphine or derivatives of morphine. The primary goal of treatment in these settings is timely administration of analgesics to provide relief of pain. The incremental increase and decrease in the use of the medication to relieve pain roughly parallels the eight phases associated with a chronology of pain and comfort in children (Table 511.3). When pain requires continued parenteral analgesic administration, hospitalization or prolonged stays in day hospitals are required. The average hospital length of stay for children admitted in pain is 4.4 days. The American Society of Hematology and NHLBI clinical guidelines for treating acute and chronic pain in children and adults with sickle cell disease are comprehensive and represent a starting point for treating pain.

The only measure for degree of pain is the patient. Healthcare providers working with children in pain should use a consistent, validated pain scale (e.g., Wong-Baker FACES Scale) for assessing pain. Although pain scales have proved useful for some children, other forms of pain assessment may be required to determine when opioid therapy should be initiated and decreased. Individualized pain plans provide important information for assessment and treatment that address patient preferences.

Several myths have been propagated regarding the treatment of pain in sickle cell disease. The concept that all painful episodes in children should be managed without opioids is without foundation and results in unwarranted suffering on the part of the patient. Blood transfusion therapy during an existing painful episode does not decrease the intensity or duration of the painful episode. Aggressive IV hydration does

Table 511.3 Phases of a Painful Episode in Patients with Sickle Cell Disease

PHASE	DESCRIPTION AND COMFORT MEASURES
DATA FROM CHILDREN	
I	*Baseline* No pain and no comfort measures
II	*Prepain phase* No evidence of pain Child begins to display some prodromal signs and symptoms of VOE (yellow eyes, fatigue) No comfort measures used Caregivers encouraged child to increase fluids to prevent the pain event from occurring
III	*Pain starting point* Child complained of mild "ache-ish" pain in one specific area, which gradually or rapidly increased or "waxed" Mild analgesics (ibuprofen and acetaminophen) given Child maintained normal activities and continued to attend school Caregivers hoped to prevent an increase in pain intensity
IV	*Pain acceleration* Pain continued to escalate; intensity increased from mild to moderate; pain appeared in more areas of the body; child was kept home from school; decreased level of activity; differences in behaviors, appearance, and mood Stronger oral analgesics may be combined with rest, rubbing, heat, distraction, and psychologic comfort
V	*Peak pain experience* Pain continued to escalate Some children were incapacitated and unable to obtain pain relief Pain described as "stabbing," "drilling," "pounding," "banging," "excruciating," "unbearable," or "throbbing" Caregivers sometimes decide to seek help from ED for stronger analgesics and protection from complications such as fever or respiratory distress Caregivers may be exhausted from caring for the child for several days with little or no rest All methods of comfort were used around the clock to reduce the pain and avoid going to the hospital Pain increased despite all efforts Decision is made to take the child to ED
VI	*Pain decrease starting point* Pain begins to resolve after the use of IV fluids and analgesics Analgesics sedate the child and allow the child to sleep for longer periods Pain described as "slowly decreasing" Pain is still sharp and throbbing
VII	*Steady pain decline* Pain decreased slowly or rapidly Child takes more interest in surroundings, roommates, and visitors Child is less irritable Level of activity increased—child may be taken to tub room for warm bath, may watch television, may play games with other children or hospital volunteers Mobility has improved Pain levels reported as "just a little" More animation in behaviors evident
VIII	*Pain resolution* Pain is at a tolerable level Child may be discharged from the hospital on mild oral analgesics; child is at or close to baseline conditions, with behavior, appearance, and mood more normal Caregiver and child attempt to regain, recapture, and catch up with life as it was before the pain event
DATA FROM ADULTS	
I	*Evolving/infarctive phase* 3 days ↓ RBC deformability ↓ Hemoglobin ↑ % of dense RBCs ↑ RDW, ↑ HDW S/S: fear, anorexia, anxiety, ↑ pain

Table 511.3 Phases of a Painful Episode in Patients with Sickle Cell Disease—cont'd

PHASE	DESCRIPTION AND COMFORT MEASURES
II	*Postinfarctive/inflammatory phase* 4-5 days ↓ Hemoglobin ↑ White blood cells (leukocytosis) ↑ Acute-phase reactants C-reactive protein ↑ Reticulocytes, ↑ LDH, ↑ CPK ↑ % dense RBCs ↑ RDW, ↑ HDW S/S: fever, severe steady pain, swelling, tenderness, joint stiffness, joint effusions
III	*Resolving/healing/recovery/postcrisis phase* ↑ RBC deformability Hemoglobin returns to precrisis level Retics return to precrisis levels ↓ % of dense RBCs ↓ RDW, ↓ HDW ↓ ISC Precursors to relapse that happens in phase III: ↑ platelets, ↑ acute-phase reactants (fibrinogen, α_1-acid glycoprotein, osmomucoid), ↑ viscosity, ↑ ESR ↑ Retics expressing the ↑ $\alpha_4\beta_1$-integrin complex ICAM-1

CPK, Creatinine phosphokinase; ED, emergency department; ESR, erythrocyte sedimentation rate; HDW, hemoglobin distribution width; ICAM, intracellular adhesion molecule; ISC, irreversibly sickled cells; IV, intravenous; LDH, lactate dehydrogenase; RBC, red blood cell; RDW, red cell distribution width; S/S, signs and symptoms; VOE, vasoocclusive episode.
Adapted from Jacob E. The pain experience of patients with sickle cell anemia. *Pain Manage Nurs* 2001;2:74–83; with data from Ballas SK, Smith ED. Red blood cell changes during the evolution of the sickle cell painful crisis. *Blood* 1992;79:2154–2163; and Beyer JE, Simmons L, Woods GM, Woods PM. A chronology of pain and comfort in children with sickle cell disease. *Arch Pediatr Adolesc Med* 1999;153:913–920.

not relieve or prevent pain and is appropriate when the patient is dehydrated or unable to drink as a result of the severe pain. *Opioid dependency in children with sickle cell disease is rare and should never be used as a reason to withhold pain medication.* However, patients with multiple painful episodes requiring hospitalization within 1 year or with pain episodes that require hospitalization for >7 days should be evaluated for comorbidities and environmental stressors that are contributing to the frequency or duration of pain. Children with chronic pain should be evaluated for other disease-related complications, including, but not limited to, presence of avascular necrosis, leg ulcers, and vertebral body compression fractures. A careful history is warranted to distinguish chronic pain that often is not relieved by opioids versus recurrent acute prolonged vasoocclusive pain episodes.

Skeletal pain (bone or bone marrow infarction) with or without fever must be differentiated from **osteomyelitis**. Both *Salmonella* spp. and *S. aureus* cause osteomyelitis in children with sickle cell disease, often involving the diaphysis of long bones (in contrast to children without sickle cell anemia, in whom osteomyelitis is in the metaphyseal region of the bone). Differentiating osteomyelitis from a vasoocclusive crisis is often difficult. Clinical signs and symptoms can be consistent with both osteomyelitis and vasoocclusive crises because low-grade fever pain, swelling of the affected area, high WBC counts, and elevated C-reactive protein levels can be present in both. Blood, fluid, and tissue cultures, when positive, are helpful. MRI may be useful for locating an area to obtain fluid for culture. Ultimately, aspiration with or with or without biopsy and culture will be needed to differentiate the two processes (see Chapter 725).

Avascular Necrosis

Avascular necrosis **(AVN)** occurs at a higher rate among children with sickle cell disease than in the general population and is a source of both acute and chronic pain. Most often, the femoral head is affected. AVN of the hip may cause limp and leg-length discrepancy. Other sites affected include the humeral head and mandible. Risk factors for AVN include HbSS disease with α-thalassemia trait, frequent vasoocclusive episodes, and elevated hematocrit (for patients with sickle cell anemia). Optimal treatment of AVN has not been determined, and individual management requires consultation with a sickle cell specialist, orthopedic surgeon, physical therapist, and primary care physician. Initial management should include referral to a pediatric orthopedist and a physical therapist to address strategies to increase strength and decrease weight-bearing daily activities that may exacerbate the pain associated with AVN as well as to determine whether surgical approaches may be beneficial. Opioids are often used but usually can be tapered after the acute pain has subsided. Regular blood transfusion therapy has not been demonstrated as an effective therapy to abate the acute and chronic pain associated with AVN.

Priapism

Priapism, defined as an unwanted painful erection of the penis, affects males of all sickle genotypes but most frequently affects males with sickle cell anemia. The mean age of first episode is 15 years, although priapism has been reported in children as young as 3 years. The actuarial probability of a patient experiencing priapism is approximately 90% by 20 years of age.

Priapism occurs in two patterns: *prolonged*, lasting >4 hours, or *stuttering*, with brief episodes that resolve spontaneously but may occur in clusters and herald a prolonged event. Both types occur from early childhood to adulthood. Most episodes occur between 3 AM and 9 AM. Priapism in sickle cell disease represents a low-flow state caused by venous stasis from RBC sickling in the corpora cavernosa. Recurrent prolonged episodes of priapism are associated with erectile dysfunction (impotence).

The optimal treatment for acute priapism is unknown. Supportive therapy, such as a hot shower, short aerobic exercise, or pain medication, is often used by patients at home. A prolonged episode lasting >4 hours should be treated by aspiration of blood from the corpora cavernosa, followed by irrigation with dilute epinephrine to produce immediate and sustained *detumescence.* Urology consultation is required to initiate this procedure, with appropriate input from a hematologist. Simple blood transfusion with exchange transfusion has been proposed for the acute treatment of priapism, but limited evidence supports this strategy as the initial management. If no benefit is obtained from surgical management, transfusion therapy should be considered. However, detumescence may not occur for up to 24 hours (much longer than with urologic aspiration) after transfusion, and transfusion for priapism has been associated with acute neurologic events. Consultation with a hematologist and urologist will help identify therapies to prevent recurrences.

Neurologic Complications

Neurologic complications associated with sickle cell disease are varied and complex, ranging from acute ischemic stroke with focal neurologic deficit to clinically *silent* abnormalities found on imaging. Before the development of transcranial Doppler ultrasonography to screen for stroke risk among children with sickle cell anemia, approximately 11% experienced an overt stroke before age 20. A functional definition of *overt stroke* is the presence of a focal neurologic deficit lasting for >24 hours and/or abnormal neuroimaging of the brain indicating a cerebral infarct on T2-weighted MRI corresponding to the focal neurologic deficit (Figs. 511.2 and 511.3). A *silent cerebral infarct* lacks focal neurologic findings and is diagnosed by abnormal imaging on T2-weighted MRI. The prevalence of silent infarct among children with HbSS is around 35%. Children with other types of sickle cell disease, such as HbSC or HbSβ$^+$-thalassemia, develop overt or silent cerebral infarcts as well, but at a lower frequency than children with HbSS and HbSβ^0-thalassemia. Other neurologic complications include transient ischemic attacks, headaches that may or may not correlate to degree of anemia, seizures, cerebral venous thrombosis, cerebral vasculopathy, and **posterior reversible encephalopathy syndrome (PRES)**. Chiari I malformations can occur in older children with sickle cell disease. **Fat embolism syndrome** (associated with bone marrow infarction) is a rapidly progressive, potentially fatal complication involving pain, respiratory distress, changes in mental status, and multiorgan system failure. When this syndrome is identified early, exchange transfusion therapy has improved patient survival in small case series. Skull infarction can lead to a subgaleal hematoma or epidural bleed, which may present as altered mental status.

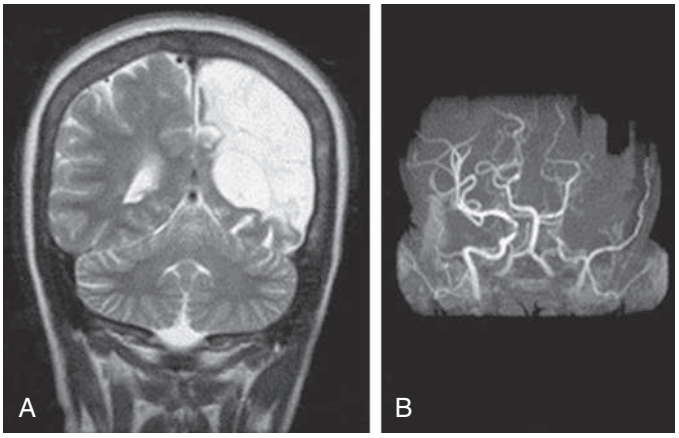

Fig. 511.2 MRI and magnetic resonance angiography (MRA) of the brain. **A**, T2-weighted MRI shows remote infarction of the territories of the left anterior cerebral artery and middle cerebral artery. **B**, MRA shows occlusion of the left internal carotid artery siphon distal to the takeoff of the ophthalmic artery.

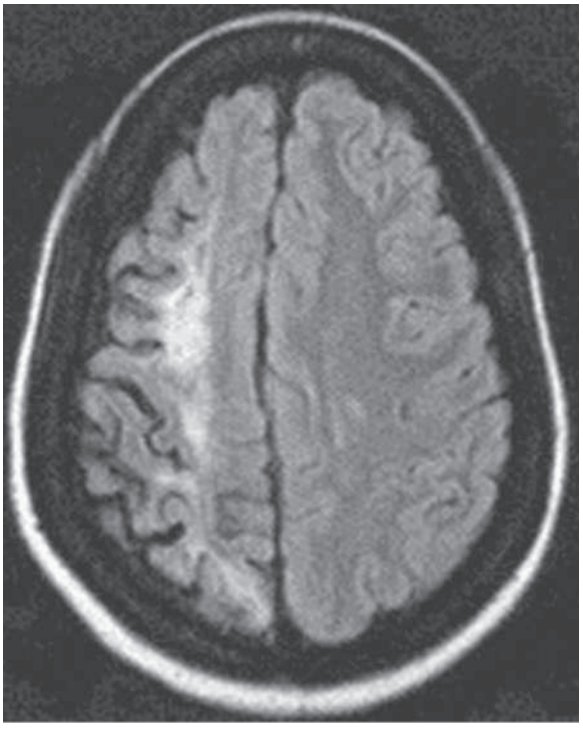

Fig. 511.3 Fast fluid-attenuated inversion recovery sequence MRI of the brain showing a right hemisphere border-zone cerebral infarction in a child with sickle cell anemia. *(From Switzer JA, Hess DC, Nichols F, et al. Pathophysiology and treatment of stroke in sickle-cell disease: present and future. Lancet Neurol 2006;5:501–512.)*

For patients presenting with acute focal neurologic deficit, a prompt pediatric neurologic evaluation and consultation with a pediatric hematologist is recommended. In addition, oxygen administration to keep oxygen saturation (So_2) >96% and blood transfusion within 2 hours of presentation, with a goal of increasing Hb to a maximum of 10 g/dL, is warranted. A timely simple blood transfusion is important because this is the most efficient strategy to dramatically increase oxygen content of the blood, particularly when exchange transfusion is not readily available. However, greatly exceeding this posttransfusion Hb limits oxygen delivery to the brain as a result of hyperviscosity by increasing the Hb significantly over the patient's baseline values. Subsequently, prompt treatment with an exchange transfusion is recommended, either manually or with automated erythrocytapheresis, to reduce the HbS percentage to <30%. Exchange transfusion at the time of acute stroke is associated with a decreased risk of second stroke compared to simple transfusion alone. CT of the head to exclude cerebral hemorrhage should be performed as soon as possible, and, if available, MRI of the brain with diffusion-weighted imaging to distinguish between ischemic infarcts and PRES. MR venography is useful to evaluate the possibility of **cerebral venous thrombosis**, a rare but potential cause of focal neurologic deficit in children with sickle cell disease. MR angiography may identify evidence of cerebral vasculopathy; these images are not critical in the initial time management of a child with sickle cell disease presenting with a focal neurologic deficit but are important for long-term management.

The clinical presentation of PRES or central venous thrombosis can mimic a stroke but would require a different treatment course. For both PRES and cerebral venous thrombosis, the optimal management has not been defined in patients with sickle cell disease, resulting in the need for consultation with both a pediatric neurologist and a pediatric hematologist. The primary approach for **prevention** of recurrent overt stroke is blood transfusion therapy aimed at keeping the maximum HbS concentration <30%. Despite regular blood transfusion therapy, approximately 20% of patients will have a second stroke and 30% of this group will have a third.

Transcranial Doppler Ultrasonography

Primary prevention of overt stroke can be accomplished using screening transcranial Doppler ultrasonography (TCD) assessment of the blood velocity in the terminal portion of the internal carotid and the proximal portion of the middle cerebral artery. Children with sickle cell anemia with an elevated *time-averaged mean maximum* (TAMM) blood flow velocity ≥200 cm/sec (abnormal study) are at increased risk for a cerebrovascular event. A repeat study should be performed within a week to confirm the result. However, a single value ≥220 cm/sec is concerning and does not require repeating before recommending an intervention. A TAMM measurement of <200 but ≥170 cm/sec represents a conditional threshold. A repeat measurement is suggested within a few months because of the high rate of conversion to a TCD velocity >200 cm/sec in this group of patients.

Two distinct methods of measuring TCD velocity are a nonimaging technique and an imaging technique. The *nonimaging* technique was the method used in the stroke prevention trial sponsored by the

National Institutes of Health, whereas most pediatric radiologists in practice use the *imaging* technique. When compared to each other, the imaging technique produces values that are 10–15% below those of the nonimaging technique. The imaging technique uses the *time-averaged mean of the maximum velocity* (TAMX), and this measure is believed to be equivalent to the nonimaging calculation of TAMM. A downward adjustment for the transfusion threshold is appropriate for centers using the imaging method to assess TCD velocity. The magnitude of the transfusion threshold in the imaging technique has not been settled, but a transfusion threshold of a TAMX of 185 cm/sec and a conditional threshold of TAMX of 165 cm/sec seem reasonable. Alternatively, some experts recommend using the same thresholds regardless of technique.

Children with abnormal TCD studies should begin chronic blood transfusion therapy to maintain HbS levels <30% to decrease the risk of first stroke. This strategy results in an over 90% reduction in the rate of overt strokes. Once transfusion therapy is initiated, a subset of patients at low risk for the development of increased TCD values, such as those without MRA-confirmed cerebral vasculopathy, may be able to transition from chronic transfusions to long-term hydroxyurea therapy. Acute stroke risk is decreased when hydroxyurea use and chronic transfusions overlap until a robust therapeutic response to hydroxyurea is achieved.

Pulmonary Complications

Lung disease in children with sickle cell disease is the second most common reason for hospital admission and is associated with significant mortality. **ACS** refers to a life-threatening pulmonary complication of sickle cell disease defined as a new radiodensity on chest radiography. Other clinical definitions include clinical features such as fever, respiratory distress, hypoxia, cough, and chest pain (Fig. 511.4). Even in the absence of respiratory symptoms, very young children with fever should receive a chest radiograph to identify evolving ACS because clinical examination alone is insufficient to identify patients with a new radiographic density. Early detection of ACS may alter clinical management. The radiographic findings in ACS are variable but may include single-lobe involvement, predominantly left lower lobe; multiple lobes, most often both lower lobes; and pleural effusions, either unilateral or bilateral. *ACS may progress rapidly from a simple infiltrate to extensive infiltrates and a pleural effusion.* Therefore continuous pulse oximetry and frequent clinical exams are required, and repeat chest x-ray films may be indicated for progressive hypoxia, dyspnea, tachypnea, and other signs of respiratory distress.

Most patients with ACS do not have a single identifiable cause. Infection is the most well-known etiology, yet only 30% of ACS episodes will have positive sputum or bronchoalveolar culture, and the most common bacterial pathogens are *S. pneumoniae*, *Mycoplasma pneumoniae,* and *Chlamydia* spp. The most frequent event preceding ACS is a painful episode requiring systemic opioid treatment. **Fat emboli** have also been implicated as a cause of ACS, arising from infarcted bone marrow, and can be life-threatening if large amounts are released to the lungs. Fat emboli can be difficult to diagnose but should be considered in any patient with sickle cell disease presenting with rapid onset of respiratory distress and altered mental status changes. Petechial rash may also occur but may be difficult to detect if not carefully sought.

Given that the causes of ACS are varied, recommended management is also multimodal (Table 511.4). The type of opioid, with overuse of morphine being more likely to cause ACS than nalbuphine

Table 511.4 Overall Strategies for the Management of Acute Chest Syndrome

PREVENTION
Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)
Cautious use of intravenous fluids
Intense education and optimum care of patients who have sickle cell anemia and asthma
DIAGNOSTIC TESTING AND LABORATORY MONITORING
Blood cultures, if febrile
Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza), depending on clinical setting
Complete blood counts every day and appropriate chemistries
Continuous pulse oximetry
Chest radiographs, for persistent or progressive illness
TREATMENT
Blood transfusion (simple or exchange), depending on clinical features; consider maintaining an active type and cross match
Supplemental O_2 for drop in pulse oximetry by 4% over baseline, or values <90%
Empirical antibiotics (third-generation cephalosporin and macrolide)
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)
Bronchodilators and corticosteroids for patients with asthma
Optimum pain control and fluid management

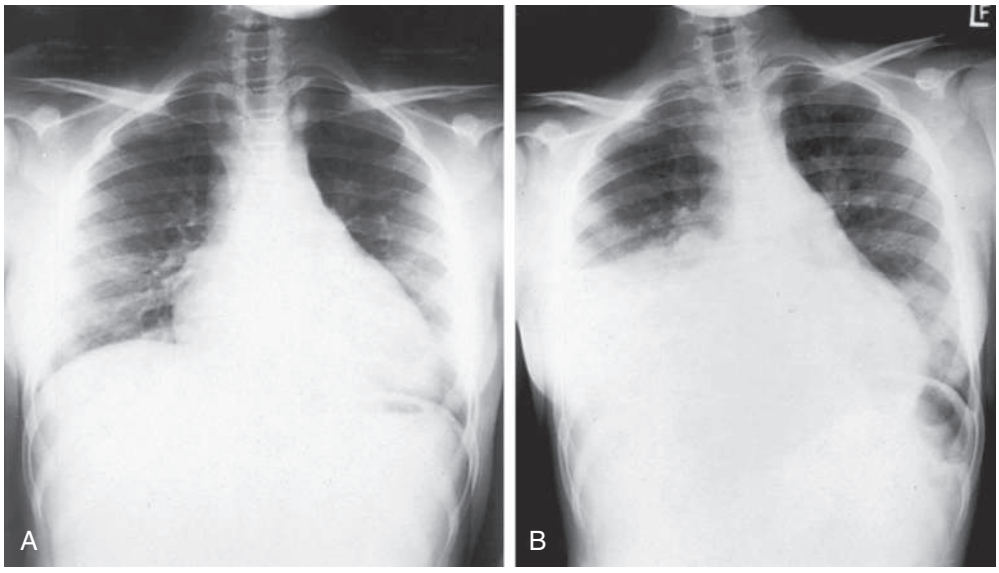

Fig. 511.4 Probable pulmonary infarction in a 15-year-old patient with HbSS. **A,** Frontal radiograph shows consolidation and a small pleural effusion posteriorly in the right lower lobe. **B,** Radiograph obtained <24 hr later shows massive right middle and lower lobe consolidation and effusion. No organisms could be cultured. The diagnosis of "probably pulmonary infarction" was established clinically. *(Courtesy Dr. Thomas L. Stovis, Children's Hospital of Michigan, Detroit. From Kuhn JP, Stovis TL, Haller JO: Caffey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby, 2004. p. 1087.)*

hydrochloride, is associated with an increase in the risk of ACS, in part because of sedation and hypoventilation. However, under no circumstance should opioid administration be limited to prevent ACS; rather, other measures must be taken to prevent ACS from developing. In patients with pain, regular use of an **incentive spirometer** at 10-12 breaths every 2 hours can significantly reduce the frequency of subsequent ACS episodes. Because of the clinical overlap between pneumonia and ACS, all episodes should be treated promptly with antimicrobial therapy, including at least a macrolide and a third-generation cephalosporin. A previous diagnosis of asthma or wheezing with ACS should prompt treatment following standard of care for an asthma exacerbation with bronchodilators. The diagnosis of ACS does not negate the recommended management of a patient with asthma exacerbation. Oxygen should be administered for patients who demonstrate hypoxia. Blood transfusion therapy using either simple or exchange (manual or automated) transfusion is the only method to abort a rapidly progressing ACS episode. The decision when to give blood and whether the transfusion should be a simple or exchange transfusion is less clearly defined. Usually, blood transfusions are given when at least one of the following clinical features are present: decreasing So_2, increasing work of breathing, rapidly changing respiratory effort either with or without a worsening chest radiograph, a dropping Hb of 2 g/dL below the patient's baseline, or previous history of severe ACS requiring admission to the intensive care unit.

Pulmonary hypertension has been identified as a major long time risk factor for death in adults with sickle cell anemia. The natural history of pulmonary hypertension in children with sickle cell anemia is unknown. Asymptomatic patients do not require screening for pulmonary hypertension. The initial diagnostic test is an echocardiogram and, depending on the severity of those findings, the echocardiogram should be followed by right-sided heart catheterization. Clinical findings suggestive of pulmonary hypertension include hypoxia or dyspnea at rest or with exertion, comorbid vascular complications (leg ulcers, priapism), elevated N-terminal, pro-B-type natriuretic peptide, or an abnormal 6-minute walk distance.

Renal Disease and Enuresis

Renal disease among patients with sickle cell disease is a major comorbid condition that can lead to premature death. Seven sickle cell disease nephropathies have been identified: gross hematuria, papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria, pyelonephritis, and renal medullary carcinoma. The presentation of these entities is varied but may include hematuria, proteinuria, renal insufficiency, concentrating defects, or hypertension.

The common presence of **nocturnal enuresis** occurring in children with sickle cell disease is not well defined but is troublesome for affected children and their parents. The overall prevalence of enuresis was 33% in the Cooperative Study of Sickle Cell Disease, with the highest prevalence (42%) among children 6-8 years old. Furthermore, enuresis may still occur in approximately 9% of older adolescents. Patients with sickle cell disease and nocturnal enuresis should have a systematic evaluation for recurrent urinary tract infections, kidney function, and possibly obstructive sleep apnea syndrome. Unfortunately, most children with nocturnal enuresis do not have an etiology, and targeted therapeutic interventions have been of limited success.

Cognitive and Psychologic Complications

Ongoing evaluation of the family unit and identification of the resources available to cope with a chronic illness are critical for optimal management. Children and adolescents with sickle cell disease have decreased quality of life, as measured on standardized assessments, compared to their siblings and children with other chronic diseases. Furthermore, children with sickle cell disease are at great risk for academic failure and have a 20% high school graduation rate, possibly because, among other reasons, approximately one third of children with sickle cell anemia have had a cerebral infarct, either silent or an overt stroke. Early school-age children with sickle cell anemia should have MRI without sedation to screen for silent cerebral ischemia. Children with cerebral infarcts require ongoing cognitive and school performance assessment so that education resources can be focused to optimize educational attainment. Participation in relevant support groups and group activities, such as camps for children with sickle cell disease, may be of direct benefit by improving self-esteem and establishing peer relationships.

Other Complications

In addition to the previous organ dysfunctions, patients with sickle cell disease can have other significant complications. These complications include, but are not limited to, sickle cell retinopathy, delayed onset of puberty, leg ulcers, and complications associated with pregnancy. Optimal treatment for each of these entities has not been determined, and individual management requires consultation with the hematologist and primary care physician. Reproductive health issues are prevalent in children and adolescents with sickle cell disease; therefore hematologists, adolescent medicine teams, and obstetrics/gynecology teams should co-manage patients to provide optimal care.

THERAPEUTIC CONSIDERATIONS

Hydroxyurea

Hydroxyurea is a well-established drug proven effective in reducing the frequency of acute pain episodes. In adults with sickle cell anemia, hydroxyurea decreases the rate of hospitalization for painful episodes by 50% and the rate of ACS and blood transfusion by almost 50%. In addition, adults taking hydroxyurea have shorter hospitalizations and require less analgesic medication during hospitalization.

In children with sickle cell anemia, hydroxyurea is safe and well tolerated. The primary toxicities are limited to myelosuppression that reverses on cessation of the drug. Infants treated with hydroxyurea experience fewer episodes of pain, dactylitis, and ACS; are hospitalized less frequently; and less often require a blood transfusion. Infants treated with hydroxyurea do not experience increased rates of bacteremia or serious infection.

Current recommendations are that all children with sickle cell anemia should be offered hydroxyurea beginning at 9 months of age. Hydroxyurea may be indicated for other sickle cell–related complications, especially in patients who are unable to tolerate other treatments. For patients who either will not or cannot continue blood transfusion therapy to prevent recurrent stroke, hydroxyurea therapy may be a reasonable alternative. The trial assessing the efficacy of hydroxyurea as an alternative to transfusions to prevent a *second* stroke was terminated early after the data safety and monitoring process found an increased stroke rate in the hydroxyurea arm compared to the transfusion arm. Hydroxyurea alone is inferior to transfusion therapy for secondary stroke prevention in patients who do not have contraindications to ongoing transfusions.

The long-term toxicity associated with initiating hydroxyurea in very young children has not yet been established. However, all evidence to date suggests that the benefits far outweigh the risks. For these reasons, very young children starting hydroxyurea require well-informed parents and medical care by pediatric hematologists, or at least co-management by a physician with expertise in immunosuppressive medications. The typical starting dose of hydroxyurea is 15-20 mg/kg once daily, with an incremental dosage increase every 8 weeks of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg per day. The infant hydroxyurea study found young children could safely be started at 20 mg/kg/day without increased toxicity. Achievement of the therapeutic effect of hydroxyurea can require several months, and for this reason, initiating hydroxyurea to address short-term symptom relief is not optimal. We prefer to introduce the concept to parents within the first year of life, preferably by 9 months; provide literature that describes both the pros and cons of starting hydroxyurea in children with severe symptoms of sickle cell disease; and educate parents on starting hydroxyurea in asymptomatic children as a preventive therapy for repetitive pain and ACS events. Other effects of hydroxyurea that may vary include an increase in the total Hb level and a decrease in the TCD velocity.

Other medications are available for long-term use in children and adults with sickle cell disease. **Oral L-glutamine** reduces hospitalizations and sickle cell crisis in children age 5 years and older. In addition, **crizanlizumab**, a humanized P-selectin inhibitor administered

monthly IV, is indicated for reducing acute pain in adults and children age 16 years and older. **Voxelotor**, a sickle hemoglobin polymerization inhibitor, is FDA-approved for adults and children 4 years and older. In clinical trials, Voxelotor demonstrated reduced hemolysis in patients with sickle cell disease.

Gene Therapy

The FDA (2023) has approved two different gene therapy approaches to ex vivo gene modification of autologous hematopoietic stem and progenitor cells following myeloablative conditioning. Both therapies are approved for patients ≥12 years of age with recurrent vasoocclusive crises.

Casgevy (exagamglogene autotemcel: exa-cel), involves *gene editing* with CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats / CRISPR associated nuclease 9). Exa-cel specifically targets and inactivates the red cell precursor *BCL11A* gene (a suppressor of fetal hemoglobin expression), which results in increased production of fetal hemoglobin (which does not sickle), resulting in decreased polymerization of sickle hemoglobin.

Lyfgenia (lovotibeglogene autotemcel: lovo-cel) is a *gene addition* approach using a lentiviral vector carrying a modified beta globin gene (beta-A-T87Q globin), thus increasing the levels of hemoglobin A.

Both have been successful in reducing or eliminating vasoocclusive crises after therapy. Lyfgenia has a black box warning for the risk of off target editing /insertional mutagenesis and the possibility of acute myeloid leukemia.

Hematopoietic Stem Cell Transplantation

The only currently approved cure for sickle cell anemia is transplantation with human leukocyte antigen (HLA)–matched hematopoietic stem cells from a sibling donor (allogenic) without sickle cell disease. Because of the limited availability of appropriate sibling donors, research is exploring a wide variety of curative regimens. Clinical trials are underway to explore unrelated and partially matched related donor stem cell transplants.

The most common indications for allogenic transplant are recurrent ACS, stroke, and abnormal TCD. Sibling-matched stem cell transplantation has a lower risk for graft-versus-host disease than unrelated donors. Surveys suggest that younger children may have lower morbidity and mortality. The decision to consider unrelated transplantation should involve appropriate consultation and counseling from physicians with expertise in sickle cell transplantation.

Stem cell transplantation for children with sickle cell disease who have a genetically matched sibling and *few complications* is less commonly performed. The use of hydroxyurea has dramatically decreased the disease burden for the patient and family, with far fewer hospitalizations for pain or ACS episodes and less use of blood transfusions. The field of stem cell transplantation is also progressing such that larger studies involving nonsibling donor and haploidentical donor transplantation. Transplant-related complications caused by conditioning regimens may be decreased by using low-intensity, nonmyeloablative HLA-matched sibling, allogenic stem cell transplantation.

Red Blood Cell Transfusions

RBC transfusions are used frequently both in the treatment of acute complications and to prevent acute or recurrent complications. Typically, short-term transfusions are used to prevent progression of acute complications such as ACS, aplastic crisis, splenic sequestration, and acute stroke, as well as to prevent surgery-related ACS. RBC transfusions are not recommended for uncomplicated acute pain events. Select RBC volumes judiciously to avoid high posttransfusion Hb levels and hyperviscosity. Long-term or chronic transfusion therapy is used to prevent first stroke in patients with abnormal TCD or MRI findings (silent stroke), recurrent stroke, or recurrent ACS. Patients with sickle cell disease are at increased risk of developing *alloantibodies* to less common RBC surface antigens after receiving even a single transfusion. In addition to standard cross matching for major blood group antigens (A, B, O, RhD), more *extended matching* should be performed to identify donor units that are C-, E-, and Kell-antigen matched. Full RBC antigen phenotyping or genotyping for all patients with sickle cell disease should be performed before RBC transfusion whenever possible to have the RBC units least likely to result in alloimmunization available for these patients.

Three methods of **blood transfusion therapy** are used in the management of acute and chronic complications associated with sickle cell disease: automated erythrocytapheresis, manual exchange transfusion (phlebotomy of a set amount of patient's blood followed by rapid administration of donated packed RBCs), and simple transfusion. The decision on which method to use depends on the patient's pretransfusion Hb level, the clinical indication, RBC alloimmunization, and transfusional iron overload. Exchange transfusion, manual or automated, is preferable for patients with new neurologic symptoms. *Automated erythrocytapheresis* is the preferred method for patients requiring chronic blood transfusion therapy because there is a minimum net iron balance after the procedure, followed by manual exchange transfusion. However, this method requires technical expertise, special machines, and good patient venous access. *Manual exchange* is more accessible. However, both methods may expose the patient to more RBC units and possible alloimmunization. *Simple transfusion* therapy may lower donor exposure and be more readily available but may result in higher net iron burden when compared to erythrocytapheresis or exchange transfusion.

Preparation for surgery for children with sickle cell disease requires a coordinated effort from the hematologist, surgeon, anesthesiologist, and primary care provider. Historically, ACS was associated with general anesthesia in patients with sickle cell disease. Blood transfusion before surgery for children with sickle cell disease is recommended to raise Hb level preoperatively to no more than 10 g/dL, to avoid ACS development. Because of better general perioperative care and the use of long-term therapies such as hydroxyurea and chronic transfusions, the decision to transfuse before general anesthesia should be made in conjunction with the medical team who provides sickle cell disease–related care for the patient. When preparing a child with sickle cell disease for surgery with a simple blood transfusion, caution must be used not to elevate Hb level beyond 10 g/dL because of the risk of hyperviscosity syndrome. For children with milder forms of sickle cell disease, such as HbSC or HbSβ-thalassemia, a decision must be made on a case-by-case basis as to whether an exchange transfusion is warranted because a simple transfusion may raise the hemoglobin to an unacceptable level.

Iron Overload

The primary toxic effect of blood transfusion therapy relates to excessive iron stores or iron overload, which can result in organ damage and premature death. Excessive iron stores develop after 100 mL/kg of RBC transfusion, or about 10 transfusions. The assessment of iron overload in children receiving regular blood transfusions is difficult. *The most common and least invasive method of estimating total body iron involves serum ferritin levels.* Ferritin measurements have significant limitations in their ability to estimate iron stores for several reasons, including, but not limited to, elevation during acute inflammation and poor correlation with excessive iron in specific organs, such as the heart and endocrine glands. MRI of the liver has proved to the most effective approach for assessment of iron stores. MRI T2* and MRI R2 and R2* sequences are used to estimate iron levels in the heart and liver. These imaging strategies are more accurate than serum ferritin in estimating heart and liver iron content. The standard for iron assessment previously was liver biopsy, which is an invasive procedure exposing children to the risk of general anesthesia, bleeding, and pain. Liver biopsy alone does not accurately estimate total body iron because iron deposition in the liver is not homogeneous and does not always correlate with iron levels in the heart and other organs. The major advantage of a liver biopsy is that histologic assessment of the parenchyma can be ascertained along with appropriate staging of suspected pathology, particularly cirrhosis.

The primary **treatment** of transfusion-related iron overload requires iron chelation using medical therapy. In the United States, three chelating agents are approved for use in transfusional iron overload. *Deferoxamine* is administered subcutaneously 5 of 7 nights/week over 8 to 12 hours a night. *Deferasirox* is taken by mouth daily, and *deferiprone* is available in tablet forms taken orally twice or three times a day and an oral solution taken three times a day. The FDA approved *deferasirox* for use in patients

age ≥2 years. A pill formulation of deferasirox is available that does not require mixing before oral administration. A sprinkle formulation that is mixed with a soft food such as applesauce also is available for young children who are unable to swallow pills. *Deferiprone* is an older oral chelator that has been widely used outside the United States for many years and was also approved as a first-line agent (see Table 511.8). Because of a 1–2% risk of agranulocytosis, weekly CBC monitoring is recommended, particularly in the first 6 months of treatment and with any febrile illness. Transfusion-related excessive iron stores in children with sickle cell disease should be managed by a physician with expertise in chelation therapy because of the need for close monitoring and due to the risk of significant toxicity from available chelation therapies.

OTHER SICKLE CELL SYNDROMES

The most common sickle cell syndromes besides HbSS are HbSC, HbSβ^0-thalassemia, and HbSβ^+-thalassemia. The other syndromes—HbSD, HbSO^{Arab}, HbSHPFH, HbSE, and other variants—are much less common. Patients with HbSβ^0-thalassemia have a clinical phenotype similar to those with HbSS. In the RBCs of patients with HbSC, crystals of HbC interact with membrane ion transport, dehydrating RBCs and inducing sickling. Children who have HbSC disease can experience the same symptoms and complications as those with severe HbSS disease, but less frequently. Children with HbSC have increased incidence of retinopathy, chronic hypersplenism, and acute splenic sequestration over the life span. The natural history of the other sickle cell syndromes is variable and difficult to predict because of the lack of systematic evaluation.

There is no validated model that can predict the clinical course of an individual with sickle cell disease. A patient with HbSC can have a more severe clinical course than a patient with HbSS. Management of end-organ dysfunction in children with sickle cell syndromes requires the same general principles as managing patients with sickle cell anemia; however, each situation should be managed on a case-by-case basis and requires consultation with a pediatric hematologist.

ANTICIPATORY GUIDANCE

Children with sickle cell disease should receive general health maintenance as recommended for all children, with special attention to disease-specific guidance and infection prevention education. In addition to counseling regarding adherence to penicillin and a vaccination schedule, patients, parents, and caregivers should be instructed to seek immediate medical attention for all febrile illness. In addition, early detection of acute splenic sequestration has been shown to decrease mortality. Therefore parents and caregivers should be educated early and repeatedly about the importance of daily penicillin administration and correct palpation of the spleen.

Prophylactic Penicillin

Children with sickle cell anemia should receive prophylactic oral penicillin VK until at least 5 years of age (125 mg twice daily up to age 3 years, then 250 mg twice daily thereafter). No established guidelines exist for penicillin prophylaxis beyond 5 years of age; some clinicians continue penicillin prophylaxis, and others recommend discontinuation. Penicillin prophylaxis should be continued beyond 5 years in children with a history of pneumococcal infection because of the increased risk of a recurrent infection. An alternative for children who are allergic to penicillin is erythromycin ethylsuccinate.

Immunizations

In addition to penicillin prophylaxis, routine childhood immunizations, as well as the annual administration of influenza vaccine, are highly recommended. Children with sickle cell disease develop functional asplenia and also require immunizations to protect against encapsulated organisms, including additional pneumococcal and meningococcal vaccinations. The U.S. Centers for Disease Control and Prevention (CDC) provides vaccination guidelines at https://www.cdc.gov/vaccines/hcp/acip-recs/index.html.

Spleen Palpation

Splenomegaly is a common complication of sickle cell disease, and splenic sequestration can be life threatening. Parents and primary caregivers should be taught how to palpate the spleen to determine if the spleen is enlarging starting at the first visit, with reinforcement at subsequent visits. Parents should also demonstrate spleen palpation to the provider.

Transcranial Doppler Ultrasound

Primary stroke prevention using TCD has resulted in a decrease in the prevalence of overt stroke among children with sickle cell anemia. Children with HbSS or HbSβ^0-thalassemia should be screened annually with TCD starting at age 2 years. TCD is best performed when the child is quietly awake and in their usual state of health. TCD measurements may be falsely elevated or decreased in the settings of acute anemia, sedation, pain, fever, or immediately after blood transfusions. Screening should occur annually from ages 2-16 years. Abnormal values should be repeated within a week to identify patients at greatest risk of overt stroke. Conditional values should be repeated within at least 3 months, and normal values should be repeated annually. Routine neuroimaging with MRI in asymptomatic patients requires consultation with a pediatric hematologist or neurologist with expertise in sickle cell disease.

Hydroxyurea

Recommendations include offering hydroxyurea therapy to all children with sickle cell anemia starting at 9 months of age regardless of clinical symptoms. Monitoring children receiving hydroxyurea is labor intensive. Hydroxyurea is a chemotherapeutic agent, and patients receiving this agent require the same level of nursing and physician oversight as any child with cancer receiving chemotherapy. The parents must be educated about the consequences of therapy, and when ill, children should be promptly evaluated. Starting doses should be approximately 20 mg/kg/day. CBC with differential and reticulocyte count should be checked within 4 weeks after initiation of therapy or any dose change to monitor for hematologic toxicity, then every 8-12 weeks. Dose escalation should be based on clinical and laboratory parameters. If appropriate, dose increases should be in 5 mg/kg/day increments to a maximum of 35 mg/kg/day.

While receiving hydroxyurea, steady-state absolute neutrophil count should be approximately 2,000/μL or higher and platelet count should be 80,000/μL or higher. However, children may tolerate lower absolute neutrophil counts while receiving hydroxyurea. Holding hydroxyurea and adjusting to lower doses may be required for neutropenia and thrombocytopenia. Hydroxyurea is a pregnancy class D medication, and adolescents should be counseled regarding methods to prevent pregnancy while taking this medication. Close monitoring of the patient requires a commitment by the parents and the patient as well as diligence by a physician to identify toxicity early. Information is scarce regarding the impact of hydroxyurea on fertility, although hydroxyurea has been shown to further reduce sperm count in males with sickle cell disease in several case reports; this effect may be reversible once hydroxyurea is discontinued.

Red Cell Transfusion Therapy

At the initiation of blood transfusion therapy, children with sickle cell disease should have testing to identify the presence of alloantibodies and RBC phenotyping or genotyping, which is performed to identify the best matched blood. RBC units selected should be extended antigen-matched for C, E, and K, when feasible. Goals of transfusion for acute events should be established before initiating therapy, including target posttransfusion Hb level and HbS percentage, or both. For children receiving chronic transfusion therapy, pretransfusion HbS goals should be defined; the most common goal is <30%. Posttransfusion Hb values should be targeted to avoid hyperviscosity. Children, parents, and caregivers should be educated about the symptoms of delayed hemolytic transfusion reactions. Any child with sickle cell disease with a recent history of RBC transfusion who presents with pain, dark urine, increased scleral icterus, or symptoms of worsening anemia should be screened for a delayed hemolytic transfusion reaction after consultation with the blood bank. Children meeting criteria for chronic transfusion therapy should receive annual evaluation for transfusion-transmitted infections, including hepatitis B, hepatitis C, and HIV. After receiving 100 mL/kg RBC transfusions, regular assessments of iron overload should begin, usually including measurements of serum ferritin and MRI assessments for hepatic iron every 1-2 years. Cardiac iron assessments should be

performed in children over 10 years old, especially if there is a history of poor adherence with iron chelation and/or liver iron concentration of 15 mg/g dry weight or higher. For children requiring chelation therapy, audiology and ophthalmology exams should be performed annually and monitoring of liver function and pituitary function performed regularly because of iron deposition.

Pulmonary and Asthma Screening

Pulmonary complications of sickle cell disease are common and life threatening. Asthma is common in children with sickle cell disease, and thus evaluation for asthma symptoms and asthma risk factors should be performed routinely, particularly given the high morbidity and mortality. All children should receive annual screening for signs and symptoms of lower airway disease, such as nighttime cough and exercise-induced cough. In children with symptoms consistent with lower airway disease, consultation with an asthma specialist should be considered. Pulse oximetry readings should be performed during well visits to identify children with abnormally low daytime oxygen saturation. For children with snoring, daytime somnolence, and symptoms associated with obstructive sleep apnea syndrome (OSAS), sleep studies should be performed as necessary.

Retinopathy

Effective therapy is available for retinopathy associated with sickle cell disease. Although all patients are at risk for development of retinopathy, those with sickle cell disease, type SC, are at very high risk. Patients should receive annual screening by an ophthalmologist to identify vascular changes that would benefit from laser therapy. Although changes may occur earlier, children with sickle cell disease should begin annual screenings no later than age 10 years.

Renal Disease

Sickle cell–associated renal disease starts in infancy and may not become clinically evident until adulthood. Chronic kidney disease is common in adults with sickle cell disease, with high morbidity and mortality. Screening protocols for early signs of sickle nephropathy in children have not been adopted due to lack of data. However, when creatinine elevation, microalbuminuria, or macroalbuminuria is detected, a nephrologist should be consulted to determine next steps for further evaluation and possible treatment. The age to begin screening for proteinuria has not been defined, but some experts recommend screening annually after at least 10 years, if not sooner. If proteinuria is detected, urine studies should be repeated with an early-morning urine collection; if the protein remains elevated, the patient should be referred to a pediatric nephrologist. Males with sickle cell disease should also receive counseling regarding the diagnosis and treatment of priapism. Because of the high frequency of enuresis beyond early childhood, approximately 9% between 18 and 20 years of age, parents and caregivers should be educated about the prolonged nature of enuresis in this disease. OSAS is associated with an increased prevalence of enuresis in sickle cell disease. Unfortunately, no evidence-based therapies have been developed to treat enuresis in children and young adults with sickle cell disease. In children with enuresis who have symptoms and clinical features of OSAS, referral to specialists for evaluation is recommended.

Echocardiography

Echocardiography is a screening tool to identify individuals with sickle cell disease who have pulmonary artery hypertension (see the section on "Pulmonary Hypertension"). Studies in adults with sickle cell disease have found that echocardiography is insensitive at identifying individuals truly at risk for pulmonary hypertension, although an elevated tricuspid velocity measurement may still be a risk factor for premature death in adults with sickle cell disease. Routine echocardiograms for pulmonary hypertension screening are not recommended in asymptomatic children; however, they are recommended in patients with leg ulcers, priapism, and connective tissue disease, as well as referral to a pulmonary hypertension specialist for patients with new steady-state cardiorespiratory symptoms, heart failure, or pulmonary embolus.

Additional Screening

Patients with sickle cell disease are at increased risk for behavioral health issues, including anxiety and depression. Screening should be performed at routine and acute visits. AVN of the hips and shoulders is increased in patients with sickle cell disease and may be identified early on routine physical exam. Plain radiographs may not detect early disease; thus, when AVN is suspected and plain films are normal, MRI should be obtained. When AVN is confirmed, patients should be referred promptly to orthopedics and physical therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

511.2 Sickle Cell Trait (Hemoglobin AS)

Kim Smith-Whitley and Janet L. Kwiatkowski

The prevalence of sickle cell trait varies throughout the world; in the United States, the incidence is 7–10% of the Black population. Because all state newborn screening programs include sickle cell disease, for most children, sickle cell trait is first identified on their newborn screen. Communication of sickle cell trait status from infancy to young adulthood for the affected individual, family, and healthcare providers is often inconsistent, and many young adults are unaware of their sickle cell trait status.

By definition, among individuals with sickle cell trait, the HbS level is <50%. The life span of people with sickle cell trait is normal, and serious complications are extremely rare. The CBC is within the normal range (Fig. 511.5B). Hemoglobin analysis is diagnostic, revealing a predominance of HbA, typically >50%, and HbS <50%. Rare complications of sickle cell trait may exist. Sickle cell trait is reported to be associated with exertional rhabdomyolysis in military recruits, and possibly with sudden death during rigorous exercise. However, whether these reports establish sickle cell trait as a risk factor that is nonmodifiable by other genetic factors remains unclear. Other complications reported with sickle cell trait include splenic infarction at high altitude, hematuria, hyposthenuria, deep vein thrombosis, and susceptibility to progressive eye injury after hyphema (Table 511.5). Renal medullary carcinoma has been reported almost exclusively in individuals with sickle cell trait and occurs predominantly in young people.

Children with sickle cell trait do not require limitations on physical activities as long as provisions are made for frequent rest and oral hydration, particularly when participating in physical conditioning or competitive sports. **Sudden death** in persons with sickle cell trait while exercising under extreme conditions is most likely associated with a second genetic factor and/or environmental factors and not the presence of sickle cell trait itself. However, if **exertional rhabdomyolysis** is identified, evaluation by neurology and cardiology should be considered. No causal pathway has been implicated for the presence of sickle cell trait and sudden death. All patients with sickle cell trait who participate in rigorous athletic activities should receive maximum hydration and appropriate rest during exertion, as would be the precautionary steps for all athletes, particularly when participating in hot, humid conditions. The presence of sickle cell trait should never be a reason to exclude a person from athletic participation but rather should serve as an indication that prudent surveillance is necessary to ensure appropriate hydration and prevention of exhaustion from heat or other strenuous exercise. If athletes are to be screened for sickle cell trait, the appropriate procedure is testing using a hemoglobin electrophoresis followed by genetic counseling, along with the knowledge that genetic information may provide opportunities to challenge paternity. Such situations are typically handled by a pediatrician or hematologist accustomed to providing both a balanced approach to genetic counseling and addressing the challenges about paternity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

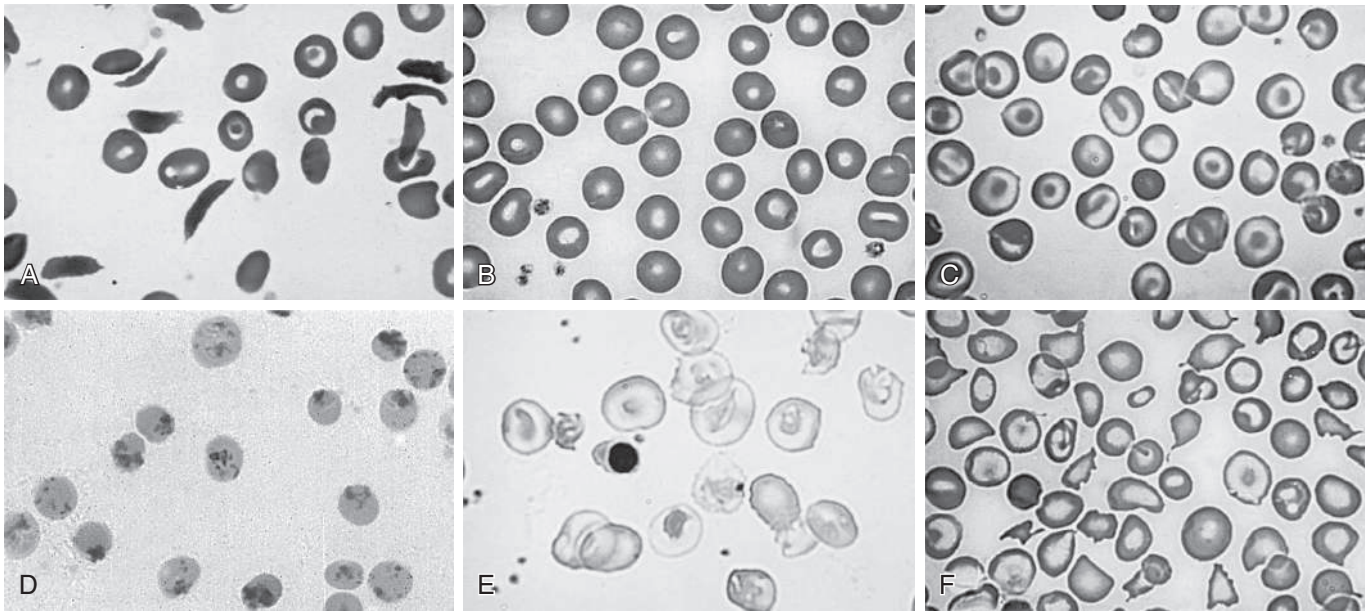

Fig. 511.5 Red blood cell morphology associated with hemoglobin disorders. **A,** Sickle cell anemia (HbSS): target cells and fixed (irreversibly sickled) cells. **B,** Sickle cell trait (HbAS): normal red blood cell (RBC) morphology. **C,** Hemoglobin CC: target cells and occasional spherocytes. **D,** Congenital Heinz body anemia (unstable hemoglobin): RBCs stained with supravital stain (brilliant cresyl blue) reveal intracellular inclusions. **E,** Homozygous β^0-thalassemia: severe hypochromia with deformed RBCs and normoblasts. **F,** Hemoglobin H disease (α-thalassemia): anisopoikilocytosis with target cells. *(Courtesy Dr. John Bolles, The ASH Collection, University of Washington, Seattle.)*

Table 511.5 Complications Reported with Sickle Cell Trait

Renal medullary cancer
Hematuria
Renal papillary necrosis
Hyposthenuria
Splenic infarction at high altitudes
Exertional rhabdomyolysis
Protection against severe complications of falciparum malaria
Microalbuminuria (adults)

From Tsaras G, Owusu-Ansah A, Boateng O, et al. Complications associated with sickle cell trait: a brief narrative review. *Am J Med* 2009;122:507–512.

511.3 Other Hemoglobinopathies

Kim Smith-Whitley and Janet L. Kwiatkowski

HEMOGLOBIN C

The pathogenic variant for HbC is at the same site as in HbS, with substitution of lysine instead of valine for glutamine. In the United States, hemoglobin C trait **(HbAC)** occurs in 1:40 and homozygous hemoglobin C disease **(HbCC)** occurs in 1:5,000 of the Black population. HbAC is asymptomatic. HbCC can result in mild anemia, splenomegaly, and cholelithiasis; rare cases of spontaneous splenic rupture have been reported. Splenic dysfunction does not occur. This condition is usually diagnosed through newborn screening programs. HbC crystallizes, disrupting the red cell membrane, and HbC crystals may be visible on peripheral smear (see Fig. 511.5C).

HEMOGLOBIN E

Hemoglobin E is an abnormal hemoglobin resulting from a qualitative pathogenic variant in the β-globin gene and is the second most common globin pathogenic variant worldwide. Patients may have asymptomatic hemoglobin E trait **(HbAE)** or benign homozygous hemoglobin E disease **(HbEE)**. Compound heterozygous hemoglobin E/β-thalassemia produces clinical phenotypes ranging from moderate to severe anemia, depending on the β-thalassemia pathogenic variant. In California, HbE/β-thalassemia is found almost exclusively in persons of Southeast Asian descent, with a prevalence of 1:2,600 births.

HEMOGLOBIN D

At least 16 variants of hemoglobin exist. HbD-Punjab (Los Angeles) is a rare hemoglobin that is seen in 1–3% of Western Indians and in some Europeans with Asian-Indian ancestry and produces symptoms of sickle cell disease when present in combination with HbS. Heterozygous HbD or hemoglobin D trait **(HbAD)** is clinically silent. Homozygous hemoglobin D disease **(HbDD)** produces a mild to moderate anemia with splenomegaly.

511.4 Unstable Hemoglobin Disorders

Kim Smith-Whitley and Janet L. Kwiatkowski

At least 200 rare unstable hemoglobins have been identified; the most common is **Hb Köln**. Most patients seem to have de novo pathogenic variants rather than inherited hemoglobin disorders. The best-studied unstable hemoglobins are the ones leading to hemoglobin denaturation from pathogenic variants affecting heme binding. The denatured hemoglobin can be visualized during severe hemolysis or after splenectomy as **Heinz bodies**. Unlike the Heinz bodies seen after toxic exposure, in unstable hemoglobins, Heinz bodies are present in reticulocytes and older RBCs (see Fig. 511.5D). Heterozygotes are asymptomatic.

Children with homozygous gene pathogenic variants can present in early childhood with anemia and splenomegaly or with unexplained hemolytic anemia. Hemolysis is increased with febrile illness and with the ingestion of oxidant medications (similar to glucose-6-phosphate dehydrogenase [G6PD] deficiency [see Chapter 512.3]) with some unstable hemoglobins. If the spleen is functional, the blood smear can appear almost normal or have only hypochromasia and basophilic stippling. A diagnosis may be made by demonstrating Heinz bodies, Hb instability, or an abnormal Hb analysis (although some unstable hemoglobins have normal mobility and are not detected on Hb analysis).

Treatment is supportive. Transfusion may be required during hemolytic episodes in severe cases. Oxidative drugs should be avoided, and folate supplementation may be helpful if dietary deficiency is a concern. Splenectomy may be considered in patients requiring recurrent transfusion or demonstrating poor growth, but the complications of splenectomy, including bacterial sepsis, risk of thrombosis, and risk of developing pulmonary hypertension, should be considered before surgery.

511.5 Abnormal Hemoglobins with Increased Oxygen Affinity

Kim Smith-Whitley and Janet L. Kwiatkowski

More than 110 high-affinity hemoglobins have been characterized. These pathogenic variants affect the state of Hb configuration during oxygenation and deoxygenation. Hemoglobin changes structure when in the oxygenated versus the deoxygenated state. The deoxygenated state is termed the **T (tense) state** and is stabilized by 2,3-diphosphoglycerate. When fully oxygenated, hemoglobin assumes the **R (relaxed) state**. The exact molecular interactions between these two states are unknown. High-affinity hemoglobins contain pathogenic variants that either stabilize the R form or destabilize the T form. The interactions between the R and T forms are complex, and the mechanisms of the pathogenic variants are not known. In most cases, the high-affinity hemoglobins can be identified by Hb analysis; approximately 20% must be characterized under controlled conditions where measurements are obtained with the P_{50} lowered to 9-21 mm Hg (normal: 23-29 mm Hg). The decreased P_{50} in these hemoglobins leads to an erythrocytosis with Hb levels of 17-20 g/dL. Levels of erythropoietin and 2,3-DPG are normal. Patients are usually asymptomatic and do not need phlebotomy. If phlebotomy is performed, oxygen delivery could be problematic because of the reduced number of Hb molecules to carry oxygen.

511.6 Abnormal Hemoglobins Causing Cyanosis

Kim Smith-Whitley

Abnormal hemoglobins causing cyanosis, also called **structural methemoglobinemias**, are rare. They are referred to as **M hemoglobins** and represent a group of hemoglobin variants that result from point pathogenic variants in one of the globin chains, α, β, or γ, located in the heme pocket; 13 known variants exist. These unstable hemoglobins lead to hemolytic anemia, most pronounced when the β-globin gene is affected. Clinically, these children are cyanotic from birth, without other signs or symptoms of disease, if the pathogenic variant is in the α-**globin** gene (HbM Boston, HbM Iwate, Hb Auckland). Infants with β-**globin** pathogenic variants become cyanotic later in infancy after the fetal hemoglobin switch (HbM Saskatoon, HbM Chile, HbM Milwaukee 1 and 2). The γ-**chain** pathogenic variants (HbF-M Fort Ripley, HbF-M Osaka, HbF Cincinnati, HbF Circleville, HbF Toms River, HbF Viseu) are all transient, presenting with cyanosis at birth, which resolves during the neonatal period after HbF production discontinues.

The abnormal M hemoglobins exhibit autosomal dominant inheritance and are diagnosed by Hb analysis. HbM variants may not be isolated reliably using Hb analysis (HPLC or IEF); consequently, diagnostic confirmation may require DNA sequencing or mass spectrometry. There is no specific treatment and affected patients do not respond to treatments used for *enzyme-deficient methemoglobinemia*. Beyond cyanosis, individuals are otherwise asymptomatic and do not require additional monitoring. Children with the β-globin form should avoid oxidant drugs. Individuals with all forms have a normal life expectancy and pregnancy course.

Low-affinity hemoglobins have less cyanosis than the M hemoglobins. The amino acid substitutions destabilize the oxyhemoglobin and lead to decreased oxygen saturation. The best characterized are Hb Kansas, Hb Beth Israel, and Hb Denver. Hb analysis (IEF and HPLC techniques) may be normal in affected individuals. When clinically suspected, oxygen affinity studies reveal a right-shifted dissociation curve, and heat testing demonstrates unstable hemoglobin. Children present with mild cyanosis only.

511.7 Hereditary Methemoglobinemia

Kim Smith-Whitley and Janet L. Kwiatkowski

Hereditary methemoglobinemia is a clinical syndrome caused by an increase in the serum concentration of methemoglobin either because of congenital changes in hemoglobin synthesis or of metabolism leading to imbalances in reduction and oxidation of hemoglobin. The iron molecule in hemoglobin is normally in the ferrous state (Fe^{2+}), which is essential for oxygen transport. Under physiologic conditions, there is a slow, constant loss of electrons to released oxygen, and the ferric (Fe^{3+}) form combines with water, producing **methemoglobin (MetHb)**. The newly formed MetHb has a reduced ability to bind oxygen.

Two pathways for MetHb reduction exist. The physiologic and predominant pathway is a reduced form of nicotinamide adenine dinucleotide (NADH)–dependent reaction catalyzed by cytochrome b5 reductase. This mechanism is >100-fold more efficient than the production of MetHb. The alternate pathway uses NAD phosphate generated by G6PD in the hexose monophosphate shunt and requires an extrinsic electron acceptor to be activated (i.e., methylene blue, ascorbic acid, riboflavin). In normal individuals, oxidation of hemoglobin to MetHb occurs at a slow rate, 0.5–3%, which is countered by MetHb reduction to maintain a steady state of 1% MetHb.

MetHb may be increased in the RBC because of exposure to toxic substances or to absence of reductive pathways, such as NADH-cytochrome b5 reductase deficiency. **Toxic methemoglobinemia** is much more common than hereditary methemoglobinemia (Table 511.6). Infants are exceptionally vulnerable to hemoglobin oxidation because their erythrocytes have half the amount of cytochrome b5 reductase seen in adults, hemoglobin F is more susceptible to oxidation than hemoglobin A, and the more alkaline infant gastrointestinal (GI) tract promotes the growth of nitrite-producing gram-negative bacteria. When MetHb levels are >1.5 g/24 hours, cyanosis is visible (15% MetHb); a level of 70% MetHb is lethal. The MetHb level is usually reported as a percentage of normal hemoglobin, and the toxic level is lower at a lower Hb level. Methemoglobinemia has been described in infants who ingested foods and water high in **nitrates**, who were exposed to aniline teething gels or other chemicals, and in some infants with severe gastroenteritis and acidosis. Methemoglobin can color the blood brown (Fig. 511.6). A patient with significant methemoglobinemia is cyanotic and does not respond to 100% oxygen. Arterial oxygen tension will be normal or elevated (if on high FiO_2) despite cyanosis, but blood oxygen saturation determined by multiwavelength co-oximetry will be low. Oxygen saturation calculated from arterial blood gas or pulse oximetry is misleading and inaccurate. Although pulse oximetry is usually lower than normal, it does not reflect the true degree of desaturation.

511.8 Hereditary Methemoglobinemia with Deficiency of NADH Cytochrome b5 Reductase

Kim Smith-Whitley

The first reported inherited disorder causing methemoglobinemia resulted from an enzymatic deficiency of NADH cytochrome b5

Table 511.6 Known Etiologies of Acquired Methemoglobinemia

MEDICATIONS
Benzocaine
Chloroquine
Dapsone
Doxycycline
EMLA (eutectic mixture of local anesthetics) topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)
Flutamide
Lidocaine
Metoclopramide
Nitrates
Nitric oxide
Nitroglycerin
Nitroprusside
Nitrous oxide
Phenazopyridine
Prilocaine
Primaquine
Riluzole
Silver nitrate
Sodium nitrate
Sulfonamides
MEDICAL CONDITIONS
Pediatric gastrointestinal infection, sepsis
Recreational drug overdose with amyl nitrate ("poppers")
Sickle cell disease–related painful episode
MISCELLANEOUS
Aniline dyes
Fume inhalation (automobile exhaust, burning of wood and plastics)
Herbicides
Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)
Pesticides
Gasoline octane booster
Nitrate rich vegetables (beets, borage, chard)
Well water

From Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia. *Medicine (Baltimore)* 2004;83:265–273.



Fig. 511.6 Normal arterial blood vs methemoglobinemia. Arterial whole blood with 1% methemoglobin *(left)* vs arterial whole blood with 72% methemoglobin *(right)*. Note the characteristic chocolate-brown color of the sample with an elevated methemoglobin level. Both samples were briefly exposed to 100% oxygen and shaken. This quick analysis is a good bedside test for methemoglobinemia. The sample on the *left* turned bright red, whereas the sample on the *right* remained chocolate-brown. *Methods:* Whole blood samples were drawn at the same time from the same person. The measured hemoglobin concentration was 11.7 g/dL. Calculated concentration of methemoglobin: 11.7 g/dL × 0.01 = 0.117 g/dL *(left)* and 11.7 g/dL × 0.72 = 8.42 g/dL *(right)*. An elevated methemoglobin level was made in vitro by adding 0.1 mL of a 0.144 molar solution of sodium nitrate *(right),* and 0.1 mL of normal saline was added as a control *(left)*. Co-oximetry measurements were taken on both samples shortly after the blood was drawn and 20 min after the addition of sodium nitrate solution. Both blood samples were exposed to 100% oxygen before the second measurement. *(Protocol based on personal communication with Dr. Ali Mansouri, December 2002.)*

reductase, which was classified into two distinct phenotypes. **In type I**, the most common form, the deficiency of NADH cytochrome b5 activity is found only in erythrocytes, with other cell types unaffected. In **type II,** the enzyme deficiency is present in all tissues and results in more significant symptoms beginning in infancy with encephalopathy, intellectual impairment, spasticity, microcephaly, and growth retardation, with death most often by 2 years of age. Both types exhibit an autosomal recessive inheritance pattern.

Cyanosis varies in intensity with season and diet. The time of cyanosis onset also varies, appearing in some patients at birth and others as late as adolescence. Although as much as 50% of the total circulating hemoglobin may be in the form of nonfunctional MetHb, little or no cardiorespiratory distress occurs in these patients, except on exertion.

Daily oral treatment with *ascorbic acid* (200-500 mg/day in divided doses) gradually reduces the MetHb to approximately 10% of the total pigment and alleviates the cyanosis as long as therapy is continued. Chronic high doses of ascorbic acid have been associated with hyperoxaluria and renal stone formation. Ascorbic acid should not be used to treat *acute toxic methemoglobinemia*. When immediately available, poison control should be contacted to verify the most up-to-date therapeutic strategies. As with ascorbic acid, *riboflavin* uses the alternate pathway of MetHb reduction and is most effective when given in high doses. *Methylene blue*, administered via IV (1-2 mg/kg initially), is used to treat toxic methemoglobinemia. An oral dose can be administered (100-300 mg/day) as maintenance therapy.

Methylene blue should not be used in patients with G6PD deficiency. This treatment is ineffective and can cause severe oxidative hemolysis. If methylene blue is given to a patient with G6PD deficiency, symptoms will not improve, and marked hemolysis can develop within 24 hours of administration. Because G6PD deficiency status is rarely known at the time of treatment, a careful history should be elicited. When the history is negative for symptoms of G6PD deficiency, treatment with methylene blue should be initiated judiciously, and the patient should be closely monitored for improvement.

511.9 Syndromes of Hereditary Persistence of Fetal Hemoglobin

Kim Smith-Whitley and Janet L. Kwiatkowski

Hereditary persistence of HbF **(HPFH)** syndromes are a form of thalassemia; pathogenic variants are associated with a decrease in the production of either or both β- and δ-globins. There is an imbalance in the α:non-α synthetic ratio characteristic of thalassemia. More than 20 variants of HPFH have been described. They are deletional, $\delta\beta^0$ (Black, Ghanaian, Italian), nondeletional (Tunisian, Japanese, Australian), linked to the β-globin–gene cluster (British, Italian-Chinese, Black), or unlinked to the β-globin–gene cluster (Atlanta, Czech, Seattle). The $\delta\beta^0$ forms have deletions of the entire δ- and β-globin gene sequences, and the most common form in the United States is the Black **(HPFH 1)** variant. As a result of the δ and β gene deletions, there is production only of γ-globin and formation of HbF. In the homozygous form, no manifestations of thalassemia are present. There is only HbF with very mild anemia and slight microcytosis. When inherited with other variant hemoglobins, HbF is elevated into the 20–30% range; when inherited with HbS, sickle cell disease is ameliorated, with fewer complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

511.10 Thalassemia Syndromes

Janet L. Kwiatkowski

Thalassemia refers to a group of genetic disorders of globin-chain production in which there is an imbalance between the α-globin and β-globin chain production. **β-thalassemia** syndromes result from a decrease in β-globin chains, which results in a relative excess of α-globin chains. There are >300 β-thalassemia pathogenic variants that have been characterized. These pathogenic variants can affect any step in the transcription of β-globin genes. **β^0-thalassemia** refers to the absence of production of the β-globin. When patients are homozygous for the β0-thalassemia gene, they cannot make any normal β-globin chains (HbA). **β+-thalassemia** indicates a pathogenic variant that makes decreased amounts of normal β-globin (HbA). Some β-thalassemia pathogenic variants have structural changes such as HbE. Others, such as δβ-thalassemia or HPFH, are variants of β-thalassemia that have decreased production of β-globin gene with increased compensatory production of HbF. β^0-thalassemia syndromes are generally more severe than β^+-thalassemia syndromes, but there is significant variability between the genotype and phenotype. β-thalassemia *major*, commonly called transfusion-dependent thalassemia, refers to severe β-thalassemia that requires early transfusion therapy. β-thalassemia *intermedia* (also known as non–transfusion-dependent thalassemia) is a clinical diagnosis of a patient with a less severe clinical phenotype that usually does not require regular transfusion therapy in childhood. Many of these patients have at least one β^+-thalassemia pathogenic variant. β-thalassemia syndromes usually require a β-thalassemia pathogenic variant in both β-globin genes. Carriers with a single β-globin pathogenic variant are generally asymptomatic, except for microcytosis and mild anemia.

In **α-thalassemia**, there is an absence or reduction in α-globin production usually due to deletions of α-globin genes. Normal individuals have four α-globin genes; the more genes affected, the more severe the disease. **α^0-thalassemia** indicates no α-chains produced from that chromosome (– –/). **α^+-thalassemia** produces a decreased amount of α-globin chain from that chromosome (-alpha/).

The primary pathology in the thalassemia syndromes stems from the *quantity* of globin produced, whereas the primary pathology in sickle cell disease is related to the *quality* of β-globin produced.

EPIDEMIOLOGY

There are >300 different pathogenic variants resulting in absent or decreased globin production. Although most are rare, the 20 most common abnormal alleles constitute 80% of the known thalassemias worldwide; 1.5% of the world's population carries alleles for β-thalassemia, and in Southeast Asia 5–10% of the population carry alleles for α-thalassemia. In the United States, an estimated 2,000 persons have β-thalassemia major.

PATHOPHYSIOLOGY

Two related features contribute to the sequelae of **β-thalassemia syndromes**: inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α- and β-globin chain production leading to ineffective erythropoiesis. In β-thalassemia α-globin chains are in excess to non–α-globin chains, and α-globin tetramers (α_4) are formed and appear as RBC inclusions. The free α-globin chains and inclusions are very unstable, precipitate in RBC precursors, damage the RBC membrane, and shorten RBC survival, leading to anemia and increased erythroid production (Table 511.7). This results in a marked increase in erythropoiesis, with early erythroid precursor death in the bone marrow. Clinically, this is characterized by a lack of maturation of erythrocytes and an inappropriately low reticulocyte count. This ineffective erythropoiesis and the compensatory massive marrow expansion with erythroid hyperactivity characterize β-thalassemia. Because of the low or absent production of β-globin, the α-chains combine with γ-chains, resulting in HbF ($\alpha_2\gamma_2$) being the dominant hemoglobin. In addition to the natural survival effect, the γ-globin chains may be produced in increased amounts, regulated by genetic polymorphisms. The δ-chain synthesis is not usually affected in β-thalassemia or β-thalassemia trait, and therefore patients have a relative or absolute increase in HbA_2 production ($\alpha_2\delta_2$).

In the **α-thalassemia syndromes**, there is a reduction in α-globin production. Normally, there are four α-globin genes (two from each parent) that control α-globin production. α-thalassemia syndromes vary from complete absence (hydrops fetalis) to only slightly reduced (α-thalassemia silent carrier) α-globin production. In the α-thalassemia syndromes, an excess of β- and γ-globin chains are produced. These excess chains form **hemoglobin Bart's (γ_4)** in fetal life and **HbH** (β_4) after birth. These abnormal tetramers are nonfunctional hemoglobins with very high oxygen affinity. They do not transport oxygen and result in extravascular hemolysis. A fetus with the most severe form of α-thalassemia **(hydrops fetalis)** develops in utero anemia and, without therapeutic intervention, the pregnancy usually results in fetal loss because HbF production requires sufficient amounts of α-globin. In contrast, infants with β-thalassemia major become symptomatic only after birth when HbA predominates and insufficient β-globin production manifests in clinical symptoms.

HOMOZYGOUS β-THALASSEMIA (TRANSFUSION-DEPENDENT BETA THALASSEMIA, BETA THALASSEMIA MAJOR, COOLEY ANEMIA)

Clinical Manifestations

If not treated, children with homozygous β^0-thalassemia usually become symptomatic from progressive anemia, with weakness, poor growth, and cardiac decompensation during the second 6 months of life. Depending on the pathogenic variant and degree of HbF production, regular transfusions are necessary beginning in the second month to second year of life, but rarely later. The decision to transfuse is multifactorial but is not determined solely by the degree of anemia. Persistent hemoglobin level below 7 g/dL in the absence of acute illness is an indication to start transfusions. In addition, the presence of signs of ineffective erythropoiesis, such as growth failure, bone deformities secondary to marrow expansion, and hepatosplenomegaly, are important variables in determining transfusion initiation.

The classic presentation of children with severe disease includes *thalassemic facies* (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, and cachexia and is primarily seen in countries without access to chronic transfusion therapy. Occasionally, patients with moderate anemia develop these features because of severe compensatory, ineffective erythropoiesis.

In nontransfused patients with severe ineffective erythropoiesis, marked **splenomegaly** can develop with hypersplenism and abdominal symptoms. The features of ineffective erythropoiesis include expanded medullary spaces (with massive expansion of the marrow of the face and skull), extramedullary hematopoiesis, and higher metabolic needs (Fig. 511.7). The chronic anemia and increased erythroid drive produce an increase in iron absorption from the GI tract and secondary hemosiderosis-induced organ injury.

Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia. Transfusion-induced **hemosiderosis** becomes the major clinical complication of transfusion-dependent thalassemia. Each mL of pure packed RBCs contains approximately 1 mg of iron. Physiologically, there is no mechanism to eliminate excess body iron. Iron is initially deposited in the liver and is followed by deposition in the endocrine organs and the heart. This leads to a high rate of hypothyroidism, hypogonadotropic gonadism, growth hormone deficiency, hypoparathyroidism, and diabetes mellitus. Iron deposition in the heart causes heart failure and arrhythmias, and heart disease is the leading cause of death in inadequately chelated patients. Eventually, most patients not receiving adequate iron chelation therapy die from cardiac failure or cardiac arrhythmias secondary to hemosiderosis. Hemosiderosis-induced morbidity can be prevented by adequate iron chelation therapy.

Laboratory Findings

In the United States, some children with β-thalassemia major will be identified on newborn screening because of the detection of only HbF on hemoglobin electrophoresis. However, infants with β^+ pathogenic variants might be missed on newborn screen if small amounts of hemoglobin

Table 511.7 The Thalassemias

THALASSEMIA	GLOBIN GENOTYPE	RED BLOOD CELL FEATURES	CLINICAL FEATURES	HEMOGLOBIN ANALYSIS
α-THALASSEMIA				
1 Gene deletion	−,α/α,α	Normal	Normal	Newborn: Bart's: 1–2%
2 Gene deletion (α-thalassemia trait)	−,α/−,α −, −/α,α	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart's: 5–10%
3 Gene deletion hemoglobin H	−,−/−,α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart's: 20–30%
2 Gene deletion + Constant Spring	$-,-/\alpha,\alpha^{\text{Constant Spring}}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2–3% Constant Spring, 10–15% HbH
4 Gene deletion	−,−/−,−	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89–90% Bart's with Gower-1, Gower-2, and Portland
Nondeletional	$\alpha,\alpha/\alpha,\alpha^{\text{variant}}$	Microcytosis, mild anemia	Normal	1–2% variant hemoglobin
β-THALASSEMIA				
β^0 or β^+ heterozygote: trait	β^0/A, β^+/A	Variable microcytosis, mild anemia	Normal	Elevated A_2, variable elevation of F
β^0 or β^+- homozygote or compound heterozygote Thalassemia severe	β^0/β^0, β^+/β^0, $\beta^+\beta^+$, E/β^0, E/β^+	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A_2 2%, E 30–40% (E/β^0); variably low HbA with β^+
β^0 or β^+ homozygote or compound heterozygote Thalassemia intermedia	β^0/β^0, β^+/β^0, $\beta^+\beta^+$, E/β^0, E/β^+	Hypochromic, microcytosis	Mild to moderate anemia, intermittent transfusions	A_2 2–5%, F 10–30%, HbA variably low levels
Dominant (rare)	B^0/A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
δ-Thalassemia	A/A	Normal	Normal	A_2 absent
$(\delta\beta)^0$-Thalassemia	$(\delta\beta)^0$/A	Hypochromic	Mild anemia	F 5–20%
$(\delta\beta)^+$-Thalassemia Lepore	β^{Lepore}/A	Microcytosis	Mild anemia	Lepore 8–20%
Homozygous Hb Lepore	$\beta^{\text{Lepore}}/\beta^{\text{Lepore}}$	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γδβ-Thalassemia	$(\gamma^A\delta\beta)^0$/A	Microcytosis, microcytic, hypochromic	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A_2 compared with δβ-thalassemia
γ-Thalassemia	$(\gamma^A\gamma^G)^0$/A	Microcytosis	Insignificant unless homozygote	Decreased F

A are present. An HbFE pattern can be consistent with hemoglobin E β^0-thalassemia, or the more benign hemoglobin EE disease, and needs to be followed up. The lack of standardized neonatal diagnosis of thalassemia disorders requires close follow-up of newborns with unclear thalassemia pathogenic variants and babies from high-risk ethnic groups.

Infants with serious β-thalassemia disorders have a progressive anemia after the newborn period. Microcytosis, hypochromia, and targeting characterize the RBCs. Nucleated RBCs, marked anisopoikilocytosis, and a relative reticulocytopenia are typically seen (see Fig. 511.5E). The Hb level falls progressively often to <6 g/dL unless transfusions are given. The reticulocyte count is commonly <8% and is inappropriately low compared to the degree of anemia caused by ineffective erythropoiesis. The unconjugated serum bilirubin level is usually elevated, but other chemistries may be initially normal. Even if the child does not receive transfusions, iron eventually accumulates with elevated serum ferritin and transferrin saturation. Evidence of bone marrow hyperplasia can be seen on radiographs (see Fig. 511.7).

Early definitive diagnosis is recommended. Newborn screening techniques such as hemoglobin electrophoresis are not definitive. DNA diagnosis of the β-thalassemia pathogenic variants, along with testing for common genetic modifiers of the clinical phenotype, is recommended. Co-inheritance of one or more α-thalassemia deletions is common, and it decreases the severity of the β-thalassemia disease as it improves the α:β chain imbalance. Some patients' pathogenic variants cannot be diagnosed by standard electrophoresis or common DNA probes. Referral of the samples to a tertiary laboratory is indicated, along with parental and family testing. After the definitive diagnosis, families should undergo detailed counseling.

Management and Treatment of Thalassemia

See Figure 511.8.

Transfusion Therapy

β-thalassemia major is a clinical diagnosis that requires the integration of laboratory findings and clinical features. Of patients with homozygous β^0-thalassemia (the most severe pathogenic variants), 15–20% may have a clinical course that is phenotypically consistent with thalassemia intermedia. In contrast, 25% of patients with homozygous β^+-thalassemia, typically a more benign genotype, may have transfusion-dependent thalassemia. Transient clinical events, such as a sudden fall in hemoglobin secondary to an episode of parvovirus requiring transfusion, do not necessarily indicate a transfusion-dependent patient. The long-term observation of the clinical characteristics, such as growth, bony changes, and hemoglobin, are necessary to determine chronic transfusion therapy.

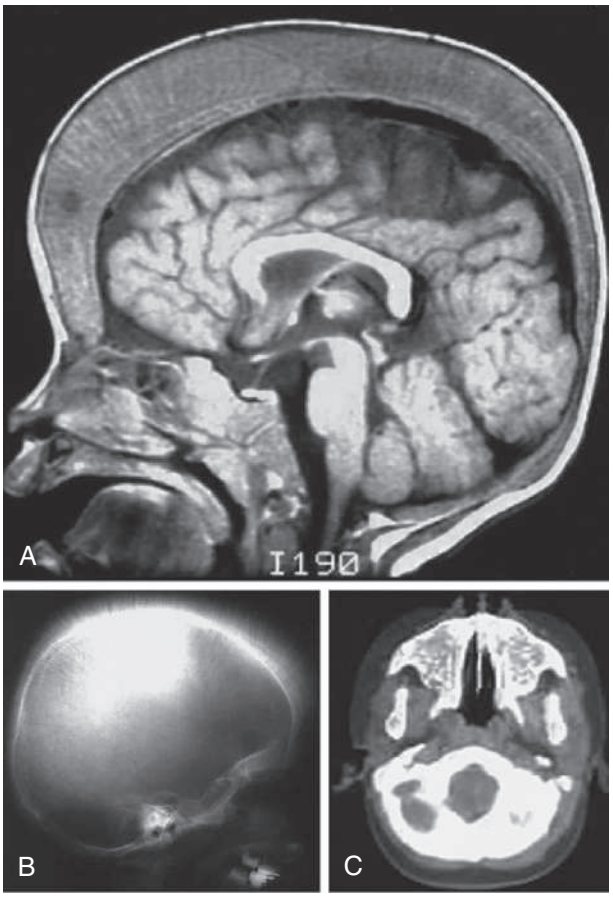

Fig. 511.7 Ineffective erythropoiesis in a 3-yr-old patient who has β-thalassemia major and has not received a transfusion. A, Massive widening of the diploic spaces of the skull as seen on MRI. B, Radiographic appearance of the trabeculae as seen on plain radiograph. C, Obliteration of the maxillary sinuses with hematopoietic tissue as seen on CT scan.

Guidelines for Transfusion Therapy. Patients who require transfusion therapy should have an extended RBC phenotype and/or genotype. Patients should receive RBCs depleted of leukocytes and matched for D, C, c, E, e, and Kell antigens at a minimum. Cytomegalovirus-safe units are indicated in stem cell transplantation candidates. Transfusions should generally be given at intervals of 3-4 weeks, with the goal being to maintain a pretransfusion Hb level of 9.5-10.5 g/dL. Ongoing monitoring for transfusion-associated transmitted infections (hepatitis A, B, and C, HIV), alloimmunization, annual blood transfusion requirements, and transfusion reactions is essential.

Iron Overload Monitoring

Excessive iron stores from transfusion cause many of the complications of β-thalassemia major. Accurate assessment of excessive iron stores is essential to optimal therapy. Serial serum ferritin levels provide a useful screening technique in assessing iron balance trends, but results may not accurately predict quantitative iron stores. Undertreatment or overtreatment of presumed excessive iron stores can occur in managing a patient based on serum ferritin alone. Quantitative measurements of liver iron and cardiac iron by MRI are standard noninvasive methods to assess tissue iron overload; estimation of pancreatic and gonadal iron is being studied. This technology, along with access to multiple chelators, enables targeted chelation therapy for patients with organ-specific hemosiderosis before the onset of overt organ failure. Integration of these imaging technologies with chelation therapy may prevent heart failure, diabetes, and other organ dysfunction.

Quantitative liver iron by approved R2 or R2* MRI is the best indicator of total body iron stores and should be obtained in patients after chronic transfusion therapy has been initiated. The liver iron results will help guide the chelation regimen. Cardiac iron estimation by T2* MRI, is usually obtained starting at 10 years old, but should be obtained earlier in the setting of severe iron overload or if the transfusion and chelation history is not known. There may be a discrepancy between the liver iron and the heart iron because of different rates of tissue loading and unloading and the differential effects of iron chelators on organ-specific iron removal.

Chelation Therapy

Iron-chelation therapy should start as soon as the patient becomes significantly iron-overloaded. In general, this occurs after 1 year of transfusion therapy and correlates with the serum ferritin >1,000 ng/mL and/or a liver iron concentration of >5,000 μg/g dry weight. Iron chelation is not currently labeled for use in children <2 years.

There are three available iron chelators (deferoxamine, deferasirox, and deferiprone); each varies in its route of administration, pharmacokinetics, adverse events, and efficacy (Table 511.8). Combination chelation therapy may be required for high iron burden. The overall goal is to prevent hemosiderosis-induced tissue injury and avoid chelation toxicity. This requires close monitoring of the patients. In general, chelation toxicity increases as iron stores decrease.

Deferoxamine (Desferal) is the most studied iron chelator; it has an excellent safety and efficacy profile. It requires subcutaneous or IV administration because of its poor oral bioavailability and short half-life of <30 minutes, necessitating administration as a continuous infusion over at least 8 hours daily, 5-7 days/week. Deferoxamine is initially started at 25 mg/kg and can be increased to 60 mg/kg in heavily iron-overloaded patients. The major problem with deferoxamine is poor adherence because of the difficult, time-consuming route of administration. Adverse side effects include local skin reactions, ototoxicity, retinal changes, and bone dysplasia with truncal shortening. Maintaining the therapeutic index (deferoxamine dose in mg/kg divided by the serum ferritin) below 0.025 limits these adverse effects.

The *oral* iron chelator **deferasirox** is commercially available in the United States. Of patients treated with deferoxamine, 70% have switched to deferasirox because it is orally available. Deferasirox has a half-life of >16 hours and requires once-daily administration. The drug was initially available as a dispersible tablet that is dissolved in water or juice. Subsequently, a film coated tablet that is swallowed whole and a granule form that is sprinkled on soft food and ingested became available. Dosing is different for the different deferasirox formulations. For the dispersible tablet form, the initial dose typically is 20 mg/kg/day and can be escalated to as high as 40 mg/kg/day based on the iron burden. The dosing for the film-coated tablet and granule forms is 30% lower than the dispersible tablet, with a starting dose of 14 mg/kg/day, which can be escalated to a maximum of 28 mg/kg/day. The most common side effects are GI symptoms, which may be lessened with the film-coated tablet and granule formulations because they do not contain lactose and sodium laureate, which are found in the dispersible tablet and are thought to be responsible for some of the GI symptoms. The most serious side effect of deferasirox is potential kidney damage. Up to 30% of patients have transient increases in creatinine that may require temporary modifications of dosing. This toxicity may occur more commonly in the setting of dehydration. Proteinuria also can develop and, less commonly, a renal Fanconi syndrome may occur. Long-term studies in thousands of patients have not demonstrated progressive renal dysfunction, but isolated cases of renal failure in patients have occurred. In addition, hepatic transaminitis may occur, with an increase to >5 times the upper limit of normal in approximately 8% of patients. All patients require monthly chemistry panels and ongoing monitoring for proteinuria.

Deferiprone, an oral iron chelator, is approved in the United States for use in individuals with transfusional iron overload 3 years and older. Deferiprone has a half-life of approximately 3 hours and requires dosing 3 times daily; a new longer-acting tablet form is available that is

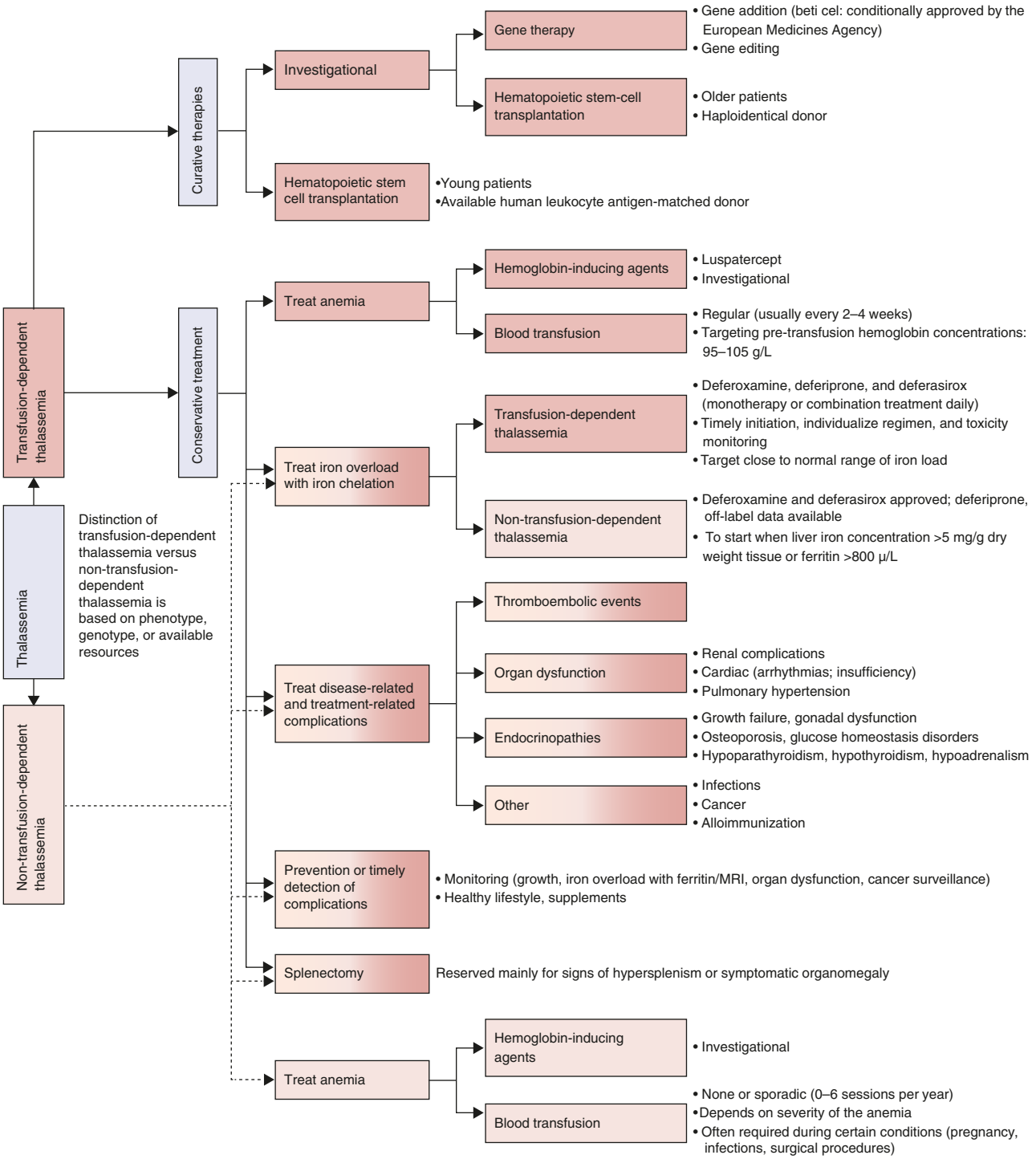

Fig. 511.8 Algorithm for the therapeutic management of thalassemia. *(From Kattamis A, Kwiatkowski JL, Aydinok Y. Thalassemia. Lancet. 2022;399:2310–2322; Fig. 3.)*

dosed twice daily. The starting dose is 75 mg/kg/day and can be escalated to 99 mg/kg/day based on the degree of iron overload. Deferiprone, a small molecule, effectively enters cardiac tissue and may be more effective than other chelators in reducing cardiac hemosiderosis. The most serious side effect of deferiprone is transient agranulocytosis, which occurs in 1-2% of patients and usually in the first year of treatment. It has been associated with rare deaths where patients were not adequately monitored. The use of deferiprone requires frequent CBC monitoring, typically weekly for at least the first 6 months of therapy. Most importantly, the drug should be held and the neutrophil count checked immediately with all febrile illnesses.

As thalassemia patients live longer, the iron chelation goals have changed. Aggressive treatment with combination chelation therapy is often used in heavily iron-overloaded patients to prevent or reverse organ dysfunction. Deferoxamine, in combination with deferiprone, is routinely used in patients with increased cardiac iron. Combination therapy of deferoxamine and deferasirox or with deferasirox and deferiprone may also be efficacious in patients with severe iron overload.

Luspatercept

Luspatercept is a recombinant fusion protein that binds TGFβ family ligands and thus blocks a signaling pathway involved in ineffective

Table 511.8 Properties of Iron Chelators

	DEFEROXAMINE	DEFERASIROX	DEFERIPRONE
Prototype trade name	Desferal	Exjade; Jadenu	Ferriprox
Route of administration	Subcutaneous; intravenous	Oral dispersible tablet; film-coated tablet; granules	Oral solution; oral tablet (3 times per day); oral tablet (twice per day)
Usual dose	Standard, 25–40 mg/kg per day over 8–12 h; low cardiac T2* or heart failure, 50–60 mg/kg per day over 12–24 h	Oral dispersible tablet, 20–40 mg/kg per day once daily; film-coated tablet and granules, 14–28 mg/kg per day once daily	75–100 mg/kg per day divided into 3 doses (oral solution or oral tablet, 3 times per day); 75–100 mg/kg per day divided into 2 doses (oral tablet, twice per day)
Excretion	Urinary (60%), defecation (40%)	Defecation (~90%)	Urinary (~75–90%)
Ability to remove liver iron	High	High	Moderate*
Ability to remove cardiac iron	Moderate†	Moderate‡	High
Adverse events	Local reactions, auditory, ophthalmologic, allergic reactions, bone defects, Yersinia or Klebsiella infections; high doses: pulmonary, neurologic, renal failure	Gastrointestinal, rash, renal impairment (increase in creatinine, proteinuria, proximal renal tubular dysfunction, renal insufficiency), elevated hepatic enzymes, gastrointestinal bleeding or ulcers, hepatic failure, auditory, ophthalmologic	Gastrointestinal, elevated hepatic enzymes, arthropathy, neutropenia or agranulocytosis
EU licensure	Licensed	Patients age 6 years and older with transfusion-dependent thalassemia; patients age 10 years and older with non-transfusion-dependent thalassemia (as a first-line treatment); patients age 2 years and older with transfusion-dependent thalassemia (as a second-line treatment)	Patients with thalassemia major when current chelation therapy is contraindicated or inadequate
USA licensure	Licensed	Patients age 2 years and older with transfusion-dependent thalassemia; patients age 10 years and older with nontransfusion-dependent thalassemia	Patients age 8 years and older with transfusional iron overload and thalassemia syndromes

*Reports of insufficient liver iron removal in some patients at doses of 75 mg/kg per day, but higher dosages, especially for patients with high transfusional iron burden, might be more effective.
†With continuous infusion.
‡Limited data show faster cardiac iron removal with modest hepatic iron loading, but this removal might be less effective in patients with more severe hepatic siderosis.
From Kattamis A, Kwiatkowski JL, Aydinok Y. Thalassemia. Lancet 2022;399:2310–2322; Table 1.

erythropoiesis and results in improved erythroid maturation. The drug is given by subcutaneous injection every 3 weeks at a starting dose of 1 mg/kg/dose, which can be escalated to 1.25 mg/kg/dose if no response after 6 weeks of treatment. In patients with transfusion-dependent β-thalassemia, use of luspatercept was associated with a reduction in RBC requirements in about 70% of treated patients. Luspatercept is approved by the FDA for use in adults with transfusion-dependent β-thalassemia. Adverse effects include bone pain, arthralgia, dizziness, hypertension, and hyperuricemia. The drug also is being studied in nontransfusion dependent thalassemia, where a 1 to 1.5 g/dL rise in hemoglobin has been seen.

Hydroxyurea

Hydroxyurea, a DNA antimetabolite, increases HbF production. It has been most successfully used in sickle cell disease and in some patients with β-thalassemia intermedia. Studies in β-thalassemia major are limited. In many parts of the world, hydroxyurea therapy is used in β-thalassemia intermedia patients. Even though increases in HbF levels are observed, they do not predictively correlate with increase in total Hb in these patients. In general, there appears to be a mean increase in Hb of 1 g/dL (range: 0.1-2.5 g/dL). Hydroxyurea therapy in thalassemia intermedia is associated with a reduced risk of leg ulcers, pulmonary hypertension, and extramedullary hematopoiesis. The initial starting dose for thalassemia intermedia is 10 mg/kg and may be escalated to 20 mg/kg/day. Patients with β-thalassemia are at increased risk of developing cytopenias with hydroxyurea use, which may prevent dose escalation. Close monitoring of the CBC with differential is required.

Hematopoietic Stem Cell Transplantation and Gene Therapy

Hematopoietic stem cell transplantation has cured >3,000 patients who had β-thalassemia major. In low-risk HLA-matched sibling patients, there is at least a 90% survival and an 80% event-free survival. In general, myeloablative conditioning regimens have been used to prevent graft rejection and thalassemia recurrence. Most success has been in children <14 years old without excessive iron stores and hepatomegaly who undergo sibling HLA-matched allogeneic transplantation. All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation. Outcomes of hematopoietic stem cell transplantation with a matched *unrelated donor* using molecular techniques for HLA typing have significantly improved, approaching outcomes with matched sibling donors, but with an increased risk of graft versus host disease. Alternative transplantation regimens for patients without appropriate donors are experimental and have variable success.

Gene therapy using gene addition or gene editing approaches are FDA approved for transfusion-dependent patients with β-thalassemia. Results with gene addition using lentiviral vectors containing a functional β-globin gene have been promising. **Betibeglogene autotemcel** is a rare gene-based, FDA- approved therapy for adults and pediatric patients (≥4 years) with transfusion dependent β-thalassemia. This one-time therapy transduces harvested autologous CD34+ cells with a replicant incompetent vector containing a modified β-globin gene. Approximately 90% of treated patients achieve transfusion independence.

A second approved approach to gene therapy involves gene editing to increase hemoglobin F levels. The first patient treated with transfusion-dependent thalassemia treated with a CRISPR-Cas9 gene editing approach was able to discontinue RBC transfusions while maintaining a normal hemoglobin level, mostly consisting of HbF. This gene approach is indicated for transfusion-dependent β-thalassemia patients ≥12 years of age.

Splenectomy

Splenectomy may be required in thalassemia patients who develop hypersplenism. These patients have a falling steady-state Hb level and/or a rising transfusion requirement. However, splenectomy is less frequently used as a therapeutic option; serious adverse effects of splenectomy are increasingly recognized beyond infection risk. In thalassemia intermedia, splenectomized patients have a marked increased risk of venous thrombosis, pulmonary hypertension, leg ulcers, and silent cerebral infarction compared to nonsplenectomized patients. All patients should be fully immunized against encapsulated bacteria and receive appropriate instructions regarding fever management. Prophylactic penicillin should be administered after splenectomy to prevent sepsis, and families need to be educated on the risk of fever and sepsis.

Preventive Monitoring of Thalassemia Patients

See Table 511.9.

Cardiac Disease

Cardiac disease is the major cause of death in thalassemia. Serial echocardiograms should be monitored to evaluate cardiac function and pulmonary artery pressure. Pulmonary hypertension frequently occurs in nontransfusion dependent thalassemia patients and may be an indication for transfusion therapy. After approximately 8 years of chronic transfusion therapy, cardiac hemosiderosis may occur; consequently, cardiac T2* MRI imaging studies are recommended, typically beginning at 10 years of age. Patients with cardiac hemosiderosis and decreasing cardiac ejection fraction require intensive combination chelation therapy. Periodic electrocardiogram studies also are obtained after age 10 years because of the risk of arrhythmia from cardiac iron overload.

Endocrine Disease

Endocrine function progressively declines with age secondary to hemosiderosis and nutritional deficiencies. Iron deposition in the pituitary and endocrine organs can result in multiple endocrinopathies, including hypothyroidism, growth hormone deficiency, delayed puberty, hypoparathyroidism, diabetes mellitus, osteoporosis, and adrenal insufficiency. Monitoring for endocrine dysfunction starts early, about 5 years of age, or after at least 3 years of chronic transfusions. All children require monitoring of their height, weight, pubertal assessment, and sitting height semiannually. Bone density scans should be obtained starting in the second decade of life given the high rate of osteopenia. Nutritional assessments are required. Most patients need vitamin D, vitamin C, and zinc replacement. Fertility is a growing concern among patients and should be assessed routinely.

Psychosocial Support

Thalassemia imposes major disruption in the family unit and significant obstacles to normal development. Culturally sensitive anticipatory counseling is necessary, and the early use of child life services decreases psychologic trauma of therapy. Early social service consultation to address financial and social issues is mandatory.

OTHER β-THALASSEMIA SYNDROMES

Non–Transfusion-Dependent Thalassemia: β-Thalassemia Intermedia

Non–transfusion-dependent thalassemia (thalassemia intermedia) includes a spectrum of patients who initially are not chronically transfused in infancy but may be sporadically transfused throughout their lifetime. The major determining characteristic of these patients is less α-β–globin chain imbalance than observed in thalassemia major. Sometimes, genetic modifiers alter the primary pathogenic variant severity and improve the globin-chain imbalance. Co-inheritance of α-thalassemia trait or polymorphisms of globin promoters such as BCL11A may lessen disease severity and result in a nontransfusion dependent thalassemia. HbE β-thalassemia is a common cause of both transfusion-dependent and non–transfusion-dependent thalassemia. These secondary

Table 511.9 Risk Factors of Thalassemia Comorbidities

CARDIOVASCULAR	
Left ventricle dysfunction	Anemia; cardiac iron overload
Pulmonary hypertension	Chronic hypoxia; splenectomy hypercoagulability; advanced age; nontransfusion-dependent thalassemia
Arrhythmia	Anemia; cardiac iron overload; thyroid disturbances
Thromboembolic events	Splenectomy; hypercoagulability; iron-induced endothelial damage
HEPATOBILIARY	
Viral hepatitis	Red cell transfusions
Fibrosis or cirrhosis	Liver iron overload
Gallstones	Chronic hemolysis
ENDOCRINOPATHIES	
Growth retardation; delayed puberty; hypogonadism	Pituitary iron deposition (thyroid hormone, hypothalamus-pituitary-gonadal axis, growth hormone-insulin like growth factor disturbances); nutrition; anemia
Glucose intolerance; diabetes	Liver iron overload; pancreatic iron deposition; family predisposition
Thyroid dysfunction	Anemia; thyroid iron deposition; hypopituitarism
Adrenal insufficiency	Anemia; adrenal iron deposition; hypopituitarism
Bone disease	Ineffective erythropoiesis, iron predisposition and chelator toxicity; hypogonadism; hypoparathyroidism
NEOPLASIA	
Hepatocellular carcinoma	Chronic hepatitis B or hepatitis C virus infections; liver iron overload
Thyroid cancer; renal cancer; gastrointestinal cancer; breast cancer; hematologic malignancies	Iron toxicity; chronic anemia; advanced age
OTHER	
Renal dysfunction; tubular dysfunction; nephrolithiasis	Anemia; renal iron deposition; and chelator (especially deferasirox) toxicity
Extramedullary hematopoiesis	Ineffective erythropoiesis
Leg ulcers	Anemia; hypercoagulability
Auditory disturbances	Chelator toxicity
Ophthalmologic disturbances	Chelator toxicity
Infectious complications	Splenic dysfunction; transfusion-related infections; iron overload; use of iron chelation therapy (especially deferoxamine)
Spleen (splenomegaly, hypersplenism)	Ineffective erythropoiesis; extramedullary hematopoiesis

From Kattamis A, Kwiatkowski JL, Aydinok Y. *Thalassemia*. Lancet 2022;399:2310–2322. Table 2.

genetic modifiers play a role in altering the severity of this disorder. Occasionally, patients with a single β-thalassemia pathogenic variant or autosomal dominant β-thalassemia trait have clinical features of thalassemia intermedia, or non–transfusion-dependent thalassemia. Genetic studies of these patients often uncover coinheritance of genetic modifiers that worsens the condition, such as α-gene triplication or an unstable β-globin variant.

Individuals with thalassemia intermedia have significant ineffective erythropoiesis that leads to microcytic anemia with hemoglobin of approximately 7 g/dL (range: 6-10 g/dL). These patients have some of the complications characterized in untransfused thalassemia major patients, but the severity varies depending on the degree of ineffective erythropoiesis. They can develop medullary hyperplasia, hepatosplenomegaly, hematopoietic pseudotumors, pulmonary hypertension, leg ulcers, thrombotic events, and growth failure. Many patients develop hemosiderosis secondary to increased GI absorption of iron requiring chelation. Extramedullary hematopoiesis can occur in the vertebral canal, compressing the spinal cord and causing neurologic symptoms; the latter is a medical emergency requiring immediate local radiation therapy to halt erythropoiesis. Transfusions are indicated in thalassemia intermedia patients with significant clinical morbidity.

Thalassemia trait is often misdiagnosed as iron deficiency in children because the two diagnoses produce similar hematologic abnormalities on CBC. However, *iron deficiency is much more prevalent.* A short course of iron and reevaluation is all that is required to identify children who will need further evaluation. Children who have β-thalassemia trait have a persistently normal RBC distribution width and low mean corpuscular volume (MCV), whereas patients with iron deficiency develop an elevated red cell distribution width (RDW) with treatment. On Hb analysis, patients with β-thalassemia trait have elevated levels of HbA_2 and variably increased HbF. There are "silent" forms of β-thalassemia trait, and if the family history is suggestive, further studies may be indicated.

α-THALASSEMIA SYNDROMES

The same evolutionary pressures that produced β-thalassemia and sickle cell disease produced α-thalassemia. Infants are identified in the newborn period by the increased production of hemoglobin Bart's (γ_4) during fetal life and its presence at birth. The α-thalassemia syndromes occur most frequently in Southeast Asia. Deletions are most common in α-thalassemia. In addition to deletional pathogenic variants, there are nondeletional α-globin gene pathogenic variants, the most common being Constant Spring ($\alpha^{CS}\alpha$); these variants cause a more severe anemia and clinical course than the deletional variants. Normally, there are four α-globin genes. The different phenotypes in α-thalassemia largely result from whether one (α^{+}-thalassemia) or both (α^{0}-thalassemia) α-globin genes are deleted in each of the two loci.

The deletion of one α-globin gene (silent carrier) is not identifiable hematologically. Specifically, no alterations are noted in the MCV and mean corpuscular hemoglobin (MCH). Persons with this deletion are usually diagnosed after the birth of a child with a two-gene deletion or HbH (β_4), but some newborn screening programs report even low concentrations of Hb Bart's. During the newborn period, <3% Hb Bart's is observed. The deletion of one α-globin gene is common in Black persons.

The deletion of two α-globin genes results in α-thalassemia trait. The α-globin alleles can be lost in a *trans* (–α/–α) or *cis* (α,α^{-SEA}) configuration. The *trans* or *cis* pathogenic variants can combine with other pathogenic variants or deletions and lead to HbH or α-thalassemia major. In persons from Africa or of African descent, the most common α-globin deletions are in the *trans* configuration, whereas in persons from or descended from Asia or the Mediterranean region, *cis* deletions are most common.

α-Thalassemia trait (two missing α-globin genes) manifests as a microcytic anemia that can be mistaken for iron-deficiency anemia (see Fig. 511.5F). The Hb analysis is normal, except during the newborn period, when Hb Bart's is typically <8% but >3%. Children with a deletion of two α-globin genes are commonly mistaken to have iron deficiency, given the presence of both low MCV and MCH. The simplest approach to distinguish between iron deficiency and α-thalassemia trait is with a good dietary history. Children with iron-deficiency anemia often have a diet that is low in iron and drink a significant amount of cow's milk. Alternatively, a brief course of iron supplementation along with monitoring of erythrocyte parameters might confirm the diagnosis of iron deficiency. If both parents of a child diagnosed with α-thalassemia trait are carriers in the *cis* conformation, they are at risk for a future hydrops fetalis pregnancy. Thus family screening and genetic counseling are indicated.

The deletion of three α-globin genes leads to the diagnosis of HbH disease. A more severe form of HbH disease may be caused by a nondeletional α-globin pathogenic variant in combination with two gene deletions. HbH Constant Spring ($-\alpha/\alpha,\alpha^{CS}$) is the most common type of nondeletional HbH disease.

In California, where a large population of persons of Asian descent resides, approximately 1:10,000 of all newborns have HbH disease. The simplest manner of diagnosing HbH disease is during the newborn period, when excess in γ-tetramers are present and Hb Bart's is commonly >25%. Obtaining supporting evidence from the parents is helpful. Later in childhood, there is an excess of β-globin chain tetramers that results in HbH. A definitive diagnosis of HbH disease requires DNA analysis. Brilliant cresyl blue can stain HbH, but it is rarely used for diagnosis. Patients with HbH disease have a marked microcytosis, anemia, mild splenomegaly, and, occasionally, scleral icterus or cholelithiasis. Chronic transfusion is not usually required for therapy because the Hb range is 7-11 g/dL, with MCV 51-73 fL, but intermittent transfusions for worsening anemia, particularly in the setting of acute infection, may be needed. Individuals with nondeletional HbH disease are more likely to require transfusions than individuals with deletional HbH disease.

The deletion of all four α-globin gene alleles causes profound anemia during fetal life, resulting in **hydrops fetalis**; the ζ-globin gene must be present for fetal survival. There are no normal hemoglobins present at birth (primarily Hb Bart's, with Hb Gower-1, Gower-2, and Portland). Intrauterine transfusions may rescue the fetus, but congenital abnormalities and neurodevelopmental delay often result. Infants with severe α-thalassemia will have lifelong transfusion dependence, and hematopoietic stem cell transplantation is the only cure.

Treatment of HbH disease requires ongoing monitoring of growth and organ dysfunction. Dietary supplement with folate and multivitamins without iron is indicated. Older patients may develop decreased bone density with calcium and vitamin D deficiency. Vitamin D supplementation is indicated if the level is low, and adequate dietary calcium intake should be encouraged to promote bone health. Iron supplementation should be avoided as patients are at risk of developing iron overload. Intermittent transfusion requirements during intercurrent infection may occur, particularly in nondeletional HbH. Splenectomy is occasionally indicated, and because of the high risk of postsplenectomy thrombosis, aspirin or other anticoagulant therapy after splenectomy should be considered. Hemosiderosis, secondary to GI iron absorption or transfusion exposure, may develop in older patients and require chelation therapy. Because HbH is an unstable hemoglobin sensitive to oxidative injury, oxidative medications should be avoided. At-risk couples for hydrops fetalis should be identified and offered molecular diagnosis on fetal tissue obtained early in pregnancy. Later in pregnancy, intrauterine transfusion can improve fetal survival, but chronic transfusion therapy or bone marrow transplantation for survivors will be required.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 512

Enzymatic Defects

512.1 Pyruvate Kinase Deficiency

Allison S. Remiker and Amanda M. Brandow

Congenital nonspherocytic hemolytic anemia occurs in persons homozygous or compound heterozygous for autosomal recessive genes that cause either a marked reduction in red blood cell (RBC) pyruvate kinase (PK) or production of an abnormal enzyme with decreased catalytic activity resulting in impaired conversion of phosphoenolpyruvate to pyruvate. Generation of adenosine triphosphate (ATP) within RBCs at this step is impaired, and low levels of ATP, pyruvate, and the oxidized form of nicotinamide adenine dinucleotide (NAD^+) are found (Fig. 512.1). The concentration of 2,3-diphosphoglycerate is increased; this isomer is beneficial in facilitating oxygen release from hemoglobin but detrimental in inhibiting hexokinase and enzymes of the hexose monophosphate shunt. This decrease of hemoglobin oxygen affinity leads to a rightward shift of the hemoglobin-oxygen dissociation curve and therefore improved oxygen delivery manifesting as tolerance of anemia more than expected for the degree of severity. In addition, an unexplained decrease occurs in the sum of the adenine (ATP, adenosine diphosphate, and adenosine monophosphate) and pyridine (NAD^+ and reduced form of NAD) nucleotides, further impairing glycolysis. Because of decreased ATP, RBCs cannot maintain their potassium and water content; the cells become rigid, and their life span is considerably reduced with precipitous destruction in the liver and/or spleen. This is more pronounced in reticulocytes, which require higher levels of ATP.

ETIOLOGY

There are two mammalian PK genes, but only the *PKLR* gene is expressed in RBCs. More than 300 pathogenic variants are reported in this structural gene, which codes for a 574–amino acid protein that forms a functional tetramer. There is some correlation of the type, location, and amino acid substitution with disease severity. The majority of patients have at least one missense pathogenic variant. Most affected patients are compound heterozygotes for two different PK gene defects. The many possible combinations likely account for the variability in clinical severity. The pathogenic variants 1456 C to T and 1529 G to A are the most common pathogenic variants in the White population.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

The clinical manifestations of **PK deficiency** vary from severe neonatal hemolytic anemia to mild, well-compensated hemolysis first noted in adulthood (Table 512.1). Perinatal complications include premature birth, prenatal anemia or fetal hydrops requiring transfusions, and preterm labor. Severe hyperbilirubinemia, anemia, and, in rare cases, hepatic failure may occur in the neonatal period, and kernicterus has been reported. The hemolysis in older children and adults varies in severity, with hemoglobin values ranging from 2-14 g/dL in various reports and associated pallor, jaundice, scleral icterus, splenomegaly, bone deformities due to extramedullary hematopoiesis, and hyperpigmentation. Reticulocyte counts are often extremely elevated, reflecting the severe ongoing hemolysis. Associated serum chemistries consistent with nonimmune hemolytic anemia are present, including an elevated indirect bilirubin, decreased haptoglobin, increased lactate dehydrogenase (LDH), negative direct antiglobulin test (DAT), and

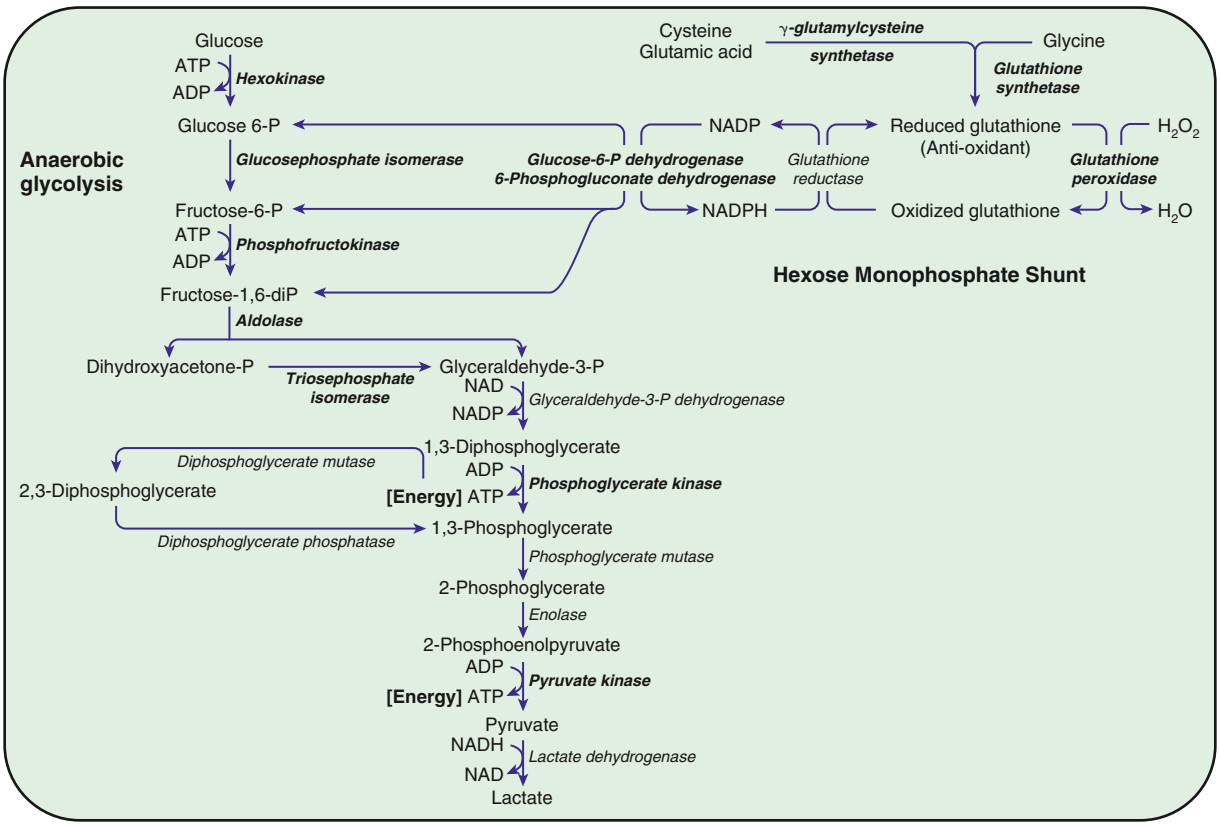

Fig. 512.1 Red blood cell metabolism: glycolysis and hexose monophosphate pathway. The enzyme deficiencies clearly associated with hemolysis are shown in **bold**. ATP, Adenosine triphosphate; ADP, adenosine diphosphate; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP.

Table 512.1 Hexokinase Variants Associated with Hemolytic Anemia

CLINICAL FEATURES			PROPERTIES OF RBC HEXOKINASE			
INHERITANCE	ANEMIA	OTHER	ACTIVITY	KINETIC ABNORMALITIES	STABILITY	MOBILITY
—	+	Congenital malformations	13-24*	0	—	—
Recessive	++		15-20*	+	Normal	Abnormal
Recessive	++		16*	0	—	Abnormal
Recessive	+++	Hydrops fetalis	17			
Recessive	+		20*	0	Normal	Normal
Recessive	++	Low platelet and fibroblast HK activity	20*	0	Low	Normal
Recessive	++	Low platelet HK activity	25*	+	Normal	Abnormal
Recessive	+		25*	0	Low	Normal
Dominant	+	Spherocytes, ovalocytes	30*	0	Low	Normal
Recessive	+	Developmental and cognitive delays	45†	+	Normal	Normal
Recessive	+		50*	0	Normal	Normal
—	+	Congenital malformations	33*	+	—	—
Recessive	+		40-53*	+	Low	Normal
—	+		50*	+	—	—
			53			
Dominant	+		45-91†	+	Normal	Abnormal
Dominant	++	WBC HK activity low	75*	+	Normal	Abnormal
Recessive	±		77†			

*Maximal enzyme activity (V_{max}) compared to reticulocytosis controls.
†Maximal enzyme activity (V_{max}) compared to normal red cells.
HK, Hexokinase; RBC, red blood cell; WBC, white blood cell.
From Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Elsevier, 2015: 583; Table 17.2.

negative indirect antiglobulin test. A severe form of the disease has a relatively high incidence among the Amish of the Midwestern United States (homozygous splicing pathogenic variant R479H). PK deficiency may possibly provide protection against falciparum malaria. There are long-term effects of chronic hemolysis, including folate deficiency, skin ulcers, gallstones, increased risk of bone fractures, and risk of transient bone marrow aplasia associated with certain viral infections.

Polychromatophilia and **mild macrocytosis** reflect the elevated reticulocyte count. Spherocytes are uncommon, but a few spiculated pyknocytes may be found. Diagnosis relies on demonstration of a marked reduction of RBC PK activity or an increase in the Michaelis-Menten dissociation constant (K_m) for its substrate, phosphoenolpyruvate (high K_m variant). Other RBC enzyme activity is normal or elevated, reflecting the reticulocytosis. No abnormalities of hemoglobin are noted. The white blood cells (WBCs) and platelets have normal PK activity and must be rigorously excluded from the RBC hemolysates used to measure PK activity. Fructose 1,6-disphosphate (FDP) must also be removed because it is an allosteric activator of PK. Heterozygous carriers usually have moderately reduced levels of PK activity. Molecular testing provides additional evidence for the disease. However, due to genotype-phenotype variability with unclear pathogenicity regarding variants, it is recommended to perform initial biochemical testing.

TREATMENT

Intrauterine RBC transfusions are performed in the setting of severe anemia associated with fetal hydrops. Phototherapy and exchange transfusions may be indicated for hyperbilirubinemia in newborns. Transfusions of packed RBCs are necessary for severe anemia or for aplastic crises. If the anemia is consistently severe and frequent transfusions are required, iron chelation may be necessary. Splenectomy should be considered after the child is 5-6 years of age to decrease the need for transfusions and minimize iron overload. Although not curative, splenectomy may be followed by higher Hb levels and by strikingly high (30–60%) reticulocyte counts. Death resulting from overwhelming pneumococcal sepsis has followed splenectomy; thus immunization with vaccines for encapsulated organisms should be given before splenectomy and prophylactic penicillin administered after the procedure. Splenectomy has also been associated with thrombosis and pulmonary hypertension. There is currently no standard curative therapy, although the role of gene therapy and hematopoietic cell transplant are actively being investigated. An oral allosteric PK activator (mitapivat) is being studied in clinical trials involving adults and is under review by the US Food and Drug Administration (FDA). The natural history of the disease is limited and is currently being studied through an international registry.

512.2 Other Glycolytic Enzyme Deficiencies

Allison S. Remiker and Amanda M. Brandow

Chronic nonspherocytic hemolytic anemias of varying severity have been associated with deficiencies of other enzymes in the glycolytic pathway, including hexokinase, glucose phosphate isomerase, and aldolase, which are inherited as autosomal recessive disorders. **Phosphofructokinase deficiency,** which occurs primarily in Ashkenazi Jews in the United States, results in hemolysis associated with a myopathy classified as **glycogen storage disease type VII** (see Chapter 107.1). Clinically, hemolytic anemia is complicated by

muscle weakness, exercise intolerance, cramps, and myoglobinuria. Erythrocyte production is increased to compensate for hemolysis. Enzyme assays for phosphofructokinase yield low values for RBCs and muscle.

Triose phosphate isomerase deficiency is an autosomal recessive disorder affecting many systems. Affected patients have hemolytic anemia, cardiac abnormalities, and lower motor neuron and pyramidal tract impairment, with or without evidence of cerebral impairment. They usually die in early childhood. The gene for triose phosphate isomerase has been cloned and sequenced and is located on chromosome 12.

Phosphoglycerate kinase (PGK) is the first ATP-generating step in glycolysis. At least 23 kindreds with PGK deficiency have been described. PGK is the only glycolytic enzyme inherited on the X chromosome. PGK is important in erythrocytes, the central nervous system (CNS), and skeletal muscle. The phenotype is quite variable and may affect one isolated tissue or a combination of all three. Affected males may present with dysfunction of the CNS with seizures, intellectual disability, and nonspherocytic hemolytic anemia; hemolytic anemia without CNS involvement; or myopathy, myoglobinuria, and progressive weakness. Some patients present with parkinsonism. Female heterozygotes have been shown to have partial symptoms depending on their degree of enzymatic activity, including signs of hemolysis. The gene for PGK is particularly large, spanning 23 kb, and various genetic abnormalities, including nucleotide substitutions, gene deletions, missense, and splicing pathogenic variants, result in PGK deficiency.

DEFICIENCIES OF ENZYMES OF HEXOSE MONOPHOSPHATE PATHWAY

The most important function of the hexose monophosphate pathway is to maintain glutathione in its reduced state (GSH) as protection against the oxidation of RBCs (see Fig. 512.1). Approximately 10% of the glucose taken up by RBCs passes through this pathway to provide the reduced form of NAD phosphate (NADPH) necessary for the conversion of oxidized glutathione to GSH. Maintenance of GSH is essential for the physiologic inactivation of oxidant compounds, such as hydrogen peroxide, that are generated within RBCs. If glutathione, or any compound or enzyme necessary for maintaining it in the reduced state, is decreased, the SH groups of the RBC membrane are oxidized, and the Hb becomes denatured and may precipitate into RBC inclusions called **Heinz bodies**. Once Heinz bodies have formed, an acute hemolytic process results from damage to the RBC membrane by the precipitated Hb, the oxidant agent, and the action of the spleen. The damaged RBCs then are rapidly removed from the circulation.

512.3 Glucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies

Allison S. Remiker and Amanda M. Brandow

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most frequent disease involving enzymes of the hexose monophosphate pathway, is responsible for two clinical syndromes: episodic *acute* hemolytic anemia and *chronic* nonspherocytic hemolytic anemia. The most common manifestations are neonatal jaundice and episodic acute hemolytic anemia, which is induced by infections, certain drugs, and, rarely, fava beans. This X-linked deficiency affects >400 million people worldwide, representing an overall 4.9% global prevalence. The global distribution of this disorder parallels that of malaria, representing an example of "balanced polymorphism," in which there is an evolutionary advantage of resistance to falciparum malaria in heterozygous females that outweighs the small negative effect of affected hemizygous males.

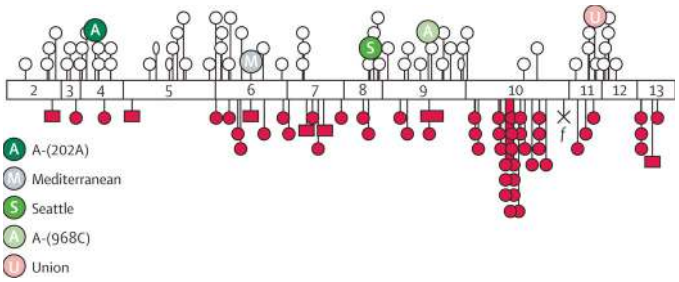

Fig. 512.2 Most common pathogenic variants along coding sequence of *G6PD* gene. Exons are shown as *open numbered boxes*. *Open circles* are pathogenic variants causing classes II and III variants. *Filled circles* represent sporadic pathogenic variants giving rise to severe variants (class I). *Open ellipses* are pathogenic variants causing class IV variants. X is a nonsense pathogenic variant; *f*, a splice site pathogenic variant; *filled squares*, small deletions. 202A and 968C are the two sites of base substitution in G6PD-A. *(From Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371:64–74.)*

The deficiency is caused by inheritance of any of a large number of abnormal alleles of the gene responsible for the synthesis of the G6PD protein. Over 200 pathogenic variants have been described in the gene responsible for the synthesis of the G6PD protein. Many of these pathogenic variants are missense point pathogenic variants leading to amino acid substitutions and destabilization of the G6PD enzyme. Figure 512.2 shows some of the pathogenic variants that cause episodic versus chronic hemolysis. Milder disease is associated with pathogenic variants near the *amino* terminus of the G6PD molecule, and chronic nonspherocytic hemolytic anemia is associated with pathogenic variants clustered near the *carboxyl* terminus near the G6P and NADP-binding sites. The normal enzyme found in most populations is designated G6PD B+. A normal variant, designated G6PD A+, is common in Americans of African descent.

EPISODIC OR INDUCED ACUTE HEMOLYTIC ANEMIA

Etiology

G6PD catalyzes the conversion of glucose 6-phosphate to 6-phosphogluconic acid. This reaction produces NADPH, which maintains GSH (glutathione in its reduced, functional state; see Fig. 512.1). GSH provides protection against **oxidant threats** from certain drugs and infections that would otherwise cause precipitation of hemoglobin (Heinz bodies) or damage the RBC membrane.

Synthesis of RBC G6PD is determined by a gene on the X chromosome. Thus heterozygous females have intermediate enzymatic activity and have two populations of RBCs: one is normal, and the other is deficient in G6PD activity. Because they have fewer susceptible cells, most heterozygous females do not have clinically evident hemolysis after exposure to oxidant drugs. Rarely, the majority of RBCs is G6PD deficient in heterozygous females because the inactivation of the normal X chromosome is random and sometimes exaggerated.

Disease involving this enzyme therefore occurs more frequently in males than in females. Approximately 13% of male Americans of African descent have a variant enzyme **(G6PD A–)** that results in a deficiency of RBC G6PD activity (5–15% of normal). Italians, Greeks, and other Mediterranean, Middle Eastern, African, and Asian ethnic groups also have a high incidence, ranging from 5–40%, of a variant designated **G6PD B– (G6PD Mediterranean)**. In these variants, the G6PD activity of homozygous females or hemizygous males is <5% of normal. Therefore the defect in Americans of African descent is *less severe* than that in Americans of European descent. A third variant enzyme with greatly reduced activity **(G6PD Canton)** occurs in approximately 5% of the Chinese population.

Clinical Manifestations

Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness unless triggered by infection, drugs, or ingestion of fava beans. Typically, hemolysis ensues in about 24-96 hours after a patient has ingested a substance with **oxidant properties**. In severe cases, hemoglobinuria and jaundice result, and the Hb concentration may fall precipitously. Drugs that elicit hemolysis in these individuals include fluoroquinolones, methylene blue, sulfonylureas, rasburicase, and antimalarials, such as primaquine and dapsone (Table 512.2). There is mixed evidence regarding the safety data of aspirin and sulfa-containing medications, which are generally thought to be safe. Chemical exposures to henna compounds and naphthalene (e.g., mothballs and deodorant) have also been implicated. The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency. In some individuals, ingestion of fava beans also produces an acute, severe hemolytic syndrome, known as **favism**. Fava beans contain divicine, isouramil, and convicine, which ultimately lead to production of hydrogen peroxide and other reactive oxygen products. Favism is thought to be more frequently associated with the G6PD Mediterranean and G6PD Canton variants.

In the G6PD A– variant, the stability of the folded protein dimer is impaired, and this defect is accentuated as the RBCs age. Thus hemolysis decreases as older RBCs are destroyed, even if administration of the drug is continued. This recovery results from the *age-labile enzyme*, which is abundant and more stable in younger RBCs (Fig. 512.3). The associated reticulocytosis produces a compensated hemolytic process in which the blood hemoglobin may be only slightly decreased, despite continued exposure to the offending agent.

G6PD deficiency can produce hemolysis in the neonatal period. In G6PD A–, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. In newborns with the G6PD B– and G6PD Canton varieties, hyperbilirubinemia and even kernicterus may occur. Neonates with co-inheritance of G6PD deficiency and a pathogenic variant of the promoter of uridine-diphosphate-glucuronyl transferase (UGT1A1), seen in **Gilbert syndrome**, have more severe neonatal jaundice. When a pregnant woman ingests oxidant drugs, they may be transmitted to her G6PD-deficient fetus, and hemolytic anemia and jaundice may be apparent at birth. Similarly, medications may be transmitted to a neonate through breast milk.

Laboratory Findings

The onset of acute hemolysis usually results in a precipitous fall in hemoglobin and hematocrit. If the episode is severe, the Hb-binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine. Hemolysis is intravascular and extravascular. Unstained or supravital preparations of RBCs reveal precipitated hemoglobin, or Heinz bodies. The RBC inclusions are not visible on the Wright-stained blood film. Cells that contain these inclusions are seen only within the first 3-4 days of illness because they are rapidly cleared from the blood. Also, the blood film may contain RBCs with what appears to be a bite taken from their periphery ("bite cells") and **polychromasia** (evidence of bluish, larger RBCs), representing reticulocytosis (Fig. 512.4).

Diagnosis

The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal, and the reduction of enzyme activity is more extreme in Americans of European descent and in Asians than in Americans of African descent. Satisfactory screening tests are based on decolorization of methylene blue, reduction of methemoglobin, or fluorescence of NADPH. Confirmatory testing is available using quantitative NADPH formation measured spectrophotometrically. Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells in the A– variety (African). *Testing may therefore have to be deferred for a few weeks before a diagnostically low*

Table 512.2 Agents Precipitating Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency

DEFINITE RISK OF AHA	"POSSIBLE" RISK OF AHA	POSSIBLE ASSOCIATION (LESS LIKELY)
ANTIMALARIAL DRUGS		
Dapsone	Chloroquine	
Pamaquine	Quinidine	
Primaquine	Quinine	
Tafenoquine		
OTHER DRUGS		
Ciprofloxacin	Aspirin*	Chloramphenicol
Glibenclamide	Menadiol sodium phosphate	Dimercaptosuccinic acid
Methylene blue	Sulfadiazine	Glibenclamide
Moxifloxacin	Sulfasalazine	Mepacrine
Nalidixic acid	Sulfonylureas	Vitamin K analogs
Nitrofurantoin	Tolonium chloride	
Norfloxacin		
Ofloxacin		
Phenazopyridine		
Rasburicase and pegloticase		
Sulfamethoxazole/cotrimoxazole		
Henna (cosmetic use)		

*Hemolysis is dose related. Typical 75 to 100 mg per day, widely used for prophylaxis of cardiovascular events, is safe for G6PD-deficient persons.
AHA, acute hemolytic anemia.
From Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. *Blood.* 2020;136:1225–1240; Table 1.

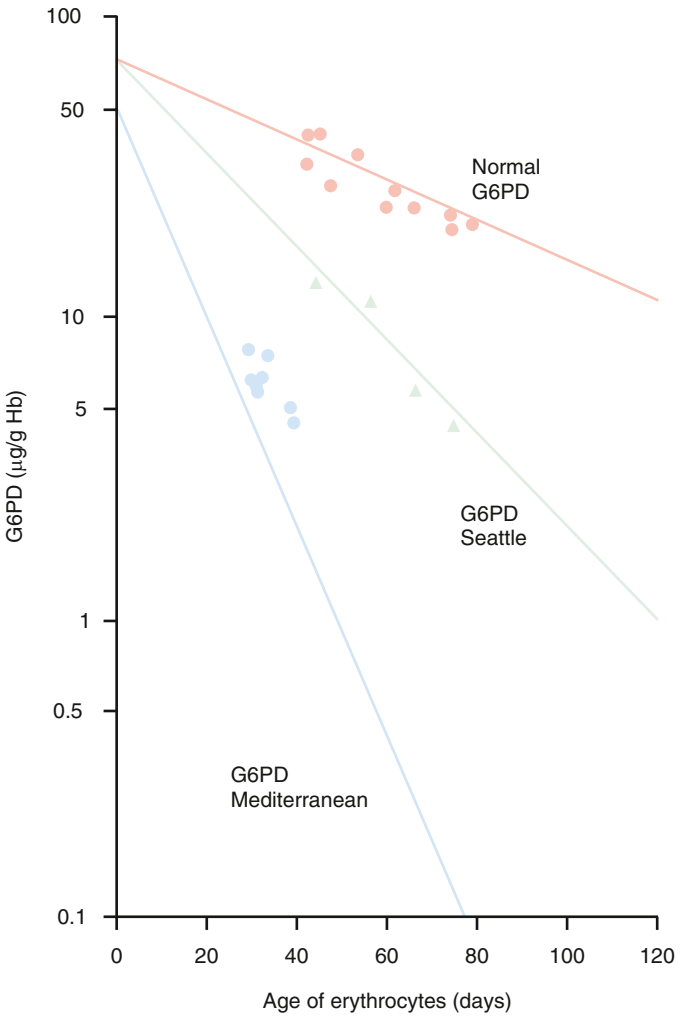

Fig. 512.3 Main mechanism of G6PD deficiency in RBCs is in vivo instability of mutant enzyme. For many G6PD variants, such as the two studied here, this is essentially acceleration of a process that takes place normally with the aging of RBCs in the circulation. Hb, Hemoglobin. *(Adapted from Morelli A, Benatti U, Gaetani GF, et al. Biochemical mechanisms of glucose-6-phosphate dehydrogenase deficiency. Proc Natl Acad Sci USA. 1978;75:1979–1983.)*

level of enzyme can be shown. The diagnosis can be suspected when G6PD activity is within the low-normal range in the presence of a high reticulocyte count. G6PD variants also can be detected by electrophoretic and molecular analysis. G6PD deficiency should be considered in any neonatal patients with hyperbilirubinemia and borderline low G6PD activity.

Prevention and Treatment

Prevention of hemolysis constitutes the most important therapeutic measure. When possible, males belonging to ethnic groups with a significant incidence of G6PD deficiency (e.g., Greeks, southern Italians, Sephardic Jews, Filipinos, southern Chinese, Black Americans, Thais) should be tested for the defect before known oxidant drugs are given.

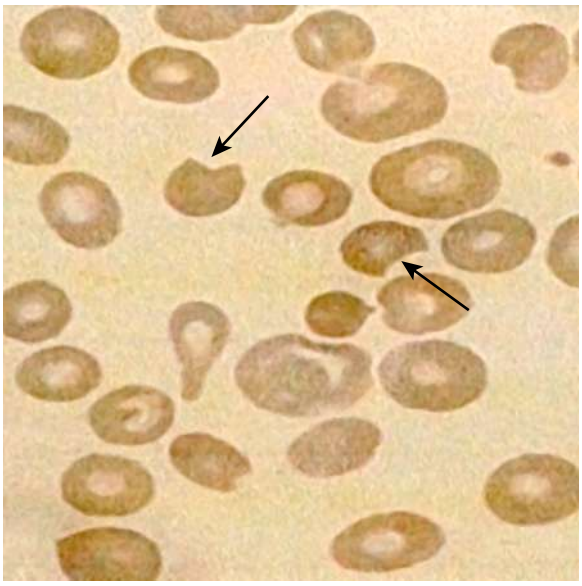

Fig. 512.4 Morphologic erythrocyte changes (anisopoikilocytosis, bite cells) during acute hemolysis in a G6PD-deficient patient. *Arrows* show bite cells. *Anisopoikilocytosis* is abnormality in the shape or size of erythrocytes. *(From Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371:64–74.)*

The usual doses of aspirin and trimethoprim-sulfamethoxazole do not cause clinically relevant hemolysis in the A– variety. Aspirin administered in doses used for acute rheumatic fever (50-100 mg/kg/24 hr) may produce a severe hemolytic episode. Infants with severe neonatal jaundice who belong to these ethnic groups also require testing for G6PD deficiency because of their heightened risk for this defect. If severe hemolysis has occurred, supportive therapy may require blood transfusions, although recovery is the rule when the oxidant agent is discontinued.

CHRONIC HEMOLYTIC ANEMIAS ASSOCIATED WITH DEFICIENCY OF G6PD OR RELATED FACTORS

Chronic **nonspherocytic hemolytic anemia** has been associated with profound deficiency of G6PD caused by enzyme variants, particularly those defective in quantity, activity, or stability. The gene defects leading to chronic hemolysis are located primarily in the region of the NADP-binding site near the carboxyl terminus of the protein (see Fig. 512.2). These include the Loma Linda, Tomah, Iowa, Beverly Hills, Nashville, Riverside, Santiago de Cuba, and Andalus variants. Persons with G6PD B– enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant drugs. Splenectomy is of little value in these types of chronic hemolysis.

Other enzyme defects may impair the regeneration of GSH as an oxidant "sump" (see Fig. 512.1). Mild, chronic nonspherocytic anemia has been reported in association with decreased RBC GSH, resulting from γ-glutamylcysteine or GSH synthetase deficiencies. Deficiency of 6-phosphogluconate dehydrogenase has been associated primarily with drug-induced hemolysis, and hemolysis with hyperbilirubinemia has been related to a deficiency of GSH peroxidase in newborn infants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 513

Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias

Allison S. Remiker and Amanda M. Brandow

IMMUNE HEMOLYTIC ANEMIAS

A number of extrinsic agents and disorders may lead to premature destruction of red blood cells (RBCs) at a rate where hemolysis exceeds hematopoietic replacement. Among the most clearly defined are antibodies associated with immune hemolytic anemias. The hallmark of this group of diseases is the positive result of the direct antiglobulin **(Coombs)** test (DAT), which detects a coating of immunoglobulin or components of complement on the RBC surface. The most important immune hemolytic disorder in pediatric practice is hemolytic disease of the newborn (erythroblastosis fetalis), caused by transplacental transfer of maternal antibody active against the RBCs of the fetus, that is, isoimmune hemolytic anemia (see Chapter 140).

Various other immune hemolytic anemias are **autoimmune** (Table 513.1). Often, no underlying cause can be found; this is the *primary* or idiopathic type. If the autoimmune hemolysis is associated with an underlying disease, including various infections (Epstein-Barr virus [EBV], rarely HIV, cytomegalovirus, and mycoplasma), autoimmune or inflammatory diseases (autoimmune lymphoproliferative disease [ALPS], systemic lupus erythematosus [SLE], rheumatoid arthritis, type 1 diabetes mellitus, ulcerative colitis), primary immunodeficiency diseases (common variable immunodeficiency [CVID], Wiskott-Aldrich syndrome), neoplasms (lymphoproliferative, solid tumors), or posttransplant (solid organ or allogeneic stem cell), it is considered *secondary* (Table 513.2). As many as 20% of episodes of autoimmune hemolysis are drug-induced (e.g.,

Table 513.1 Diseases Characterized by Immune-Mediated Red Blood Cell Destruction

AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY WARM-REACTIVE AUTOANTIBODIES
Primary (idiopathic)
Secondary
Lymphoproliferative disorders
Connective tissue disorders (especially systemic lupus erythematosus)
Nonlymphoid neoplasms (e.g., ovarian tumors)
Chronic inflammatory diseases (e.g., ulcerative colitis)
Immunodeficiency disorders
AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY COLD-REACTIVE AUTOANTIBODIES (CRYOPATHIC HEMOLYTIC SYNDROMES)
Primary (idiopathic) cold agglutinin disease
Secondary cold agglutinin disease
Lymphoproliferative disorders
Infections (*Mycoplasma pneumoniae*, Epstein-Barr virus)
Paroxysmal cold hemoglobinuria
Primary (idiopathic)
Viral syndromes (most common)
Congenital or tertiary syphilis
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA (SEE TABLE 513.2)
Hapten/drug adsorption (e.g., penicillin)
Ternary (immune) complex (e.g., quinine, quinidine)
True autoantibody induction (e.g., methyldopa)

Adapted from Packman CH. Autoimmune hemolytic anemias. In Rakel R (ed). *Conn's Current Therapy*. Philadelphia: Saunders, 1995: 305.

Table 513.2 Secondary Etiologies Causing Autoimmune Cytopenias in Children

DISEASES ASSOCIATED WITH AUTOIMMUNE CYTOPENIAS IN CHILDREN
Lymphoproliferative Disorders
Autoimmune lymphoproliferative syndrome (ALPS)*
Rosai-Dorfman disease
Castleman disease
Ras-associated leukoproliferative disorder
Immune Deficiencies
Common variable immune deficiency (CVID)*
Selective IgA deficiency
Chromosome 22q11.2 deletion (DiGeorge or velocardiofacial syndrome)
Severe combined immunodeficiency syndromes
IPEX syndrome
Rheumatologic Conditions
Systemic lupus erythematosus (SLE)*
Antiphospholipid antibody syndrome*
Juvenile idiopathic arthritis
Sjögren syndrome
Sarcoid
Malignancies
Non-Hodgkin lymphoma
Acute lymphoblastic leukemia
Myelodysplastic syndrome
Hodgkin lymphoma
Chronic Infections
EBV
HIV**
Helicobacter pylori
CMV
HCV
Other
Celiac disease
Inflammatory bowel disease
RECOMMENDED EVALUATION FOR CHILDREN WITH CHRONIC SINGLE LINEAGE AUTOIMMUNE CYTOPENIAS OR MULTI-LINEAGE AUTOIMMUNE CYTOPENIAS*
Flow cytometry for double negative T cells (ALPS)
ANA (SLE)
Anti-phospholipid antibodies
Quantitative immunoglobulins (CVID)
Specific antibody titers (CVID)
T cells subsets (CD3/CD4, CD3/CD8)
Ferritin
HIV**
FOXP3 testing (IPEX)
Exome or specific gene panels

*Consider screening for these conditions in children with chronic single lineage autoimmune cytopenias or multi-lineage autoimmune cytopenias.

**Consider also screening for HIV in adolescents with chronic single lineage or multi-lineage autoimmune cytopenias. Other diseases should be considered if the history or physical are suggestive of the underlying condition. It is extremely rare for the other conditions to present with autoimmune cytopenias and no other signs or symptoms suggestive of the underlying disease. Thus, the utility of routine screening is low.

EBV, Epstein-Barr virus; CMV, cytomegalovirus; HCV, hepatitis C virus; ANA, antinuclear antibody; IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked.

Modified from Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. *Pediatr Clin North Am*. 2013;60:1489–1511; Table 2.

methyldopa, L-dopa, checkpoint inhibitors). Other drugs (penicillins, cephalosporins) cause hemolysis by means of "drug-dependent antibodies"—antibodies directed toward the drug and in some cases toward an RBC membrane antigen as well.

Etiology

Autoimmune hemolytic anemia (AIHA) is caused by the production of anti-RBC autoantibodies generated by tissue and self-reactive B lymphocytes circulating in the periphery supported by T helper lymphocytes. The complement system induces sequential activation of the membrane attack complex (MAC) leading to erythrocyte lysis typically in the liver and circulation. RBCs are opsonized by the autoantibodies or complement then phagocytosed primarily in the spleen and lymph tissue. Antibody-dependent cell-mediated cytotoxicity (ADCC) induced by cytotoxic $CD8^+$ T lymphocytes and natural killer (NK) cells are an additional important mechanism contributing to AIHA also predominantly in lymphoid organs and the spleen.

The underlying cause of autoimmunity is loss of central self-tolerance in the early stages of lymphocyte differentiation, as well as loss of peripheral self-tolerance driven by Tregs and $CD8^+$ suppressor T lymphocytes. Loss of tolerance allows for autoreactive cells to avoid negative selection, and/or suppression of autoantibodies fails to occur appropriately in the periphery. It is theorized patients who develop AIHA have an underlying predisposition to losing such self-tolerance, which is stimulated by environmental factors.

The autoantibody may be produced as an inappropriate immune response to an RBC antigen or to another antigenic epitope similar to an RBC antigen, known as *molecular mimicry.* Alternatively, an infectious agent may alter the RBC membrane so that it becomes "foreign" or antigenic to the host.

The autoantibodies that form in AIHA have antibody class, antigenic reactivity, and thermal characteristics associated with binding and/or destroying erythrocytes. The temperature predilection is associated with corresponding nomenclature, including warm (wAIHA), cold (cold agglutinin disease [CAD]), paroxysmal cold hemoglobinuria (PCH), and rare mixed forms.

AUTOIMMUNE HEMOLYTIC ANEMIAS ASSOCIATED WITH "WARM" ANTIBODIES

Etiology

Warm autoimmune hemolytic anemia (wAIHA) is the most common form in children found in as many as 90% of cases. Autoantibodies are "warm-reactive" meaning they preferentially bind to erythrocytes at 37°C. Extravascular hemolysis occurs in the spleen. Typically, the antibodies are immunoglobulin (Ig) G, and react to epitopes (antigens) that are "public" or common to all human RBCs, such as Rh proteins. When IgG is present in exceptional quantity, it can fix complement, which results in intravascular hemolysis.

Clinical Manifestations

Patients with wAIHA present with symptoms consistent with anemia and nonspecific signs of hemolysis. Onset may be acute, with pallor, jaundice, icterus, hemoglobinuria, abdominal pain, fever, shortness of breath, and dizziness, or more gradual with primarily fatigue and pallor. Cardiovascular compromise is rare. The spleen is usually enlarged and is the primary site of destruction of IgG-coated RBCs.

Laboratory Findings

In many cases, anemia is profound with hemoglobin (Hb) levels <6 g/dL. Considerable spherocytosis and polychromasia (reflecting the reticulocyte response) are present. More than 50% of the circulating RBCs may be reticulocytes, and nucleated RBCs usually are present. In some cases, a *low reticulocyte count* may be found, particularly early in the episode due to similar epitopes on RBC precursors in the marrow, marrow suppression if there is concurrent infection, and/or a "shocked" marrow after a severe hemolytic event. Leukocytosis is common. The platelet count is usually normal, but concomitant immune thrombocytopenic purpura sometimes occurs (**Evans syndrome**). Patients with Evans syndrome often have or eventually develop a chronic disease, including SLE, an immunodeficiency syndrome (common variable immunodeficiency), or autoimmune lymphoproliferative syndrome.

Results of the **DAT (Coombs test)** are strongly positive, and free antibody can sometimes be demonstrated in the serum **(indirect Coombs test)**. These antibodies are active at 35–40°C (95–104°F) ("warm" antibodies) and most often belong to the IgG class. They do not require complement for activity. Antibodies from the serum and those eluted from the RBCs react with the RBCs of many persons in addition to those of the patient. They often have been regarded as nonspecific panagglutinins, but careful studies have revealed specificity for RBC antigens of the Rh system in 70% of patients (50% of adult patients). Complement, particularly fragments of C3b, may be detected on the RBCs in conjunction with IgG. The Coombs test result is *rarely* negative because of the sensitivity of the Coombs reaction. A minimum of 260-400 molecules of IgG per cell is necessary on the RBC membrane to produce a positive reaction. Special tests are required to detect the antibody in cases of "Coombs-negative" autoimmune hemolytic anemia. In warm antibody hemolytic anemia, the direct Coombs test may detect IgG alone, both IgG and complement fragments, or solely complement fragments if the level of RBC-bound IgG is below the detection limit of the anti-IgG Coombs reagent.

Treatment

Transfusions may provide only transient benefit but may be lifesaving in cases of severe anemia until the effects of other treatments are observed. All tested units for transfusion are serologically incompatible. It is important to identify the patient's ABO blood group to avoid a hemolytic transfusion reaction mediated by anti-A or anti-B. The blood bank should also test for the presence of an underlying alloantibody, which could cause rapid hemolysis of transfused RBCs. Patients who have been neither previously transfused nor pregnant are unlikely to harbor an alloantibody. Early consultation between the clinician and the blood bank physician is essential. Failure to transfuse a profoundly anemic infant or child may lead to serious morbidity and even death.

Patients with mild disease and compensated hemolysis may not require treatment. *If the hemolysis is severe and results in significant anemia or symptoms, treatment with glucocorticoids is initiated.* Glucocorticoids decrease the rate of hemolysis by blocking macrophage function through downregulating Fcγ receptor expression, decreasing the production of the autoantibody, and perhaps enhancing the elution of antibody from the RBCs. Initial dosing is dependent on the degree of anemia and symptoms. In patients who present with Hb <6 to 7 g/dL or severe symptoms, initial treatment with intravenous (IV) methylprednisolone 0.5-1 mg/kg every 6 to 8 hours in the first 24-72 hours is typically indicated. With rapid deterioration or severity of anemia, high-dose methylprednisolone 30 mg/kg with maximum 1 g daily for 3 days may be required. When hemolytic anemia remains severe despite glucocorticoid therapy, or if very large doses are necessary to maintain a reasonable Hb level, intravenous immunoglobulin (IVIG) may be tried. Long-term use of IVIG has not been shown to be effective in the majority of children. In children who present with mild to moderate anemia with Hg ≥7 to 8 g/dL and an appropriate reticulocyte count, oral prednisone 2 mg/kg/day may be started. Response is typically seen within 2-4 weeks after initiation of steroids and considered adequate with Hb concentration >9 to 10 g/dL. Hb, reticulocyte count, lactate dehydrogenase, and DAT should be monitored for response. Treatment should be continued until the rate of hemolysis decreases, with the dose then gradually reduced, typically over at least 4 months. The Coombs test result may remain positive even after the Hb level returns to normal. It is usually safe to discontinue prednisone once the direct Coombs test result becomes negative.

The majority of patients (approximately 80%) have an initial response to glucocorticoids within the first month of treatment; however, it is common to require prolonged or multimodal therapies over time. If a patient is unable to taper prednisone effectively within 1-2 months after diagnosis, addition of a second-line therapy should be considered.

Relapse occurs in 15–40% of patients with wAIHA, typically within the first 6-12 months after initial response to treatment. If this occurs, resumption of the lowest dose of prednisone that was effective in treating the patient is recommended. Because of the adverse effects of long-term steroid use, alternative agents could be considered if relapse continues to occur.

There are limited data in second-line therapies for wAIHA in children. **Rituximab**, a monoclonal antibody that targets B lymphocytes, the source of antibody production, *is useful in chronic cases refractory to conventional therapy.* Plasmapheresis has been used in refractory cases but generally is not helpful because most hemolysis is in the extravascular space. Splenectomy may be beneficial but is complicated by a heightened risk of infection with encapsulated organisms, particularly in patients <6 years old. Prophylaxis is indicated with appropriate vaccines (pneumococcal, meningococcal, and *Haemophilus influenzae* type b) before splenectomy and with oral penicillin after splenectomy. Thrombosis and pulmonary hypertension are also increasingly recognized problems after splenectomy. In refractory disease, several immunomodulating agents have been used in small case series or reports including azathioprine, 6-mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, and monoclonal antibodies (e.g., obinutuzumab, daratumumab, alemtuzumab, bortezomib).

Prognosis

Acute idiopathic autoimmune hemolytic disease in childhood varies in severity but is self-limited; death from untreatable anemia is rare. Approximately 30% of patients have chronic hemolysis, often associated with an underlying disease, such as SLE, immunodeficiency, or lymphoma. The presence of antiphospholipid antibodies in adult patients with immune hemolysis predisposes to thrombosis. Mortality in chronic cases depends on the primary disorder.

AUTOIMMUNE HEMOLYTIC ANEMIAS ASSOCIATED WITH "COLD" ANTIBODIES OR COLD AGGLUTININ DISEASE

"Cold" antibodies agglutinate RBCs at temperatures <37°C (98.6°F). They are primarily of the IgM class and require complement for hemolytic activity. The highest temperature at which RBC agglutination occurs is called the thermal amplitude. A higher thermal amplitude antibody—that is, one that can bind to RBCs at temperatures achievable in the body—results in hemolysis with exposure to a cold environment. High antibody titers are associated with high thermal amplitude.

Cold antibodies usually have specificity for the oligosaccharide antigens of the I/i system. They may occur in primary or idiopathic cold agglutinin disease, secondary to infections such as those from *Mycoplasma pneumoniae* and EBV, or secondary to lymphoproliferative disorders. After *M. pneumoniae* infection, the anti-I levels may increase considerably, and occasionally, enormous increases may occur to titers ≥1/30,000. The antibody has specificity for the I antigen and thus reacts poorly with human cord RBCs, which possess the i antigen but exhibit low levels of I. Patients with infectious mononucleosis occasionally have CAD, and the antibodies in these patients often have anti-i specificity. This antibody causes less hemolysis in adults than in children because adults have fewer i molecules on their RBCs. Spontaneous RBC agglutination is observed in the cold and in vitro, and RBC aggregates are seen on the blood film (rouleaux formation). Mean corpuscular volume (MCV) may be spuriously elevated because of RBC agglutination and reticulocytosis. The severity of the hemolysis is related to the thermal amplitude of the antibody, which itself partly depends on the IgM antibody titer.

When very high titers of cold antibodies are present and active near body temperature, severe intravascular hemolysis with hemoglobinemia and hemoglobinuria may occur and may be heightened on a patient's exposure to cold (external temperature or ingested foods). Each IgM molecule has the potential to activate a C1 molecule, so that large amounts of complement are found on the RBCs in CAD. These sensitized RBCs may undergo intravascular complement-mediated lysis or may be destroyed in the liver and spleen. Only complement, not IgM, is detected on RBCs because the IgM is removed during the washing steps of the DAT.

CAD is less common in children than in adults and more frequently results in an acute, self-limited episode of hemolysis. RBC transfusion is indicated based on symptoms and severity of anemia. If transfusion is required, blood should be warmed before administration. Glucocorticoids are much less effective in CAD than in hemolytic disease with warm antibodies. Patients should avoid exposure to cold and should be treated for any underlying disease. In the uncommon patient with severe hemolytic disease, immunosuppression and plasmapheresis can be used. Successful treatment of CAD has been reported with rituximab, which effectively depletes B lymphocytes. Splenectomy is not useful in CAD.

Paroxysmal Cold Hemoglobinuria

Paroxysmal cold hemoglobinuria is mediated by the Donath-Landsteiner (D-L) hemolysin, which is an IgG cold-reactive autoantibody with anti-P specificity. In vitro, the D-L antibody binds to RBCs in the cold, and the RBCs are lysed by complement as the temperature is increased to 37°C. A similar sequence is thought to occur in vivo as RBCs move from the cooler extremities to warmer parts of the circulation. Most reported cases are self-limited; many patients experience only one paroxysm of hemolysis. Congenital or acquired syphilis was once the most common underlying cause of paroxysmal cold hemoglobinuria, but currently, most cases are associated with nonspecific viral infections. Treatment includes transfusion for severe anemia and avoidance of cold ambient temperatures.

Drug-Induced Hemolytic Anemia

Drugs (penicillin or sometimes cephalosporins) that cause hemolysis through the "hapten" mechanism (immune but not autoimmune) bind tightly to the RBC membrane. Antibodies to the drug, either newly or previously formed, bind to the drug molecules on RBCs, mediating their destruction in the spleen. In other cases, certain drugs, such as quinine and quinidine, do not bind to RBCs, but rather form part of a "ternary complex," consisting of the drug, an RBC membrane antigen, and an antibody that recognizes both (see Table 513.3). Methyldopa and sometimes cephalosporins may, by unknown mechanisms, incite true autoantibodies to RBC membrane antigens, so that the presence of the drug is not required to cause hemolysis. Cephalosporins are the most common cause of drug-induced immune hemolytic anemia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 513.3 Selected Drugs That Cause Immune-Mediated Hemolysis

MECHANISM	DRUG ADSORPTION (HAPTEN)	TERNARY (IMMUNE) COMPLEX	AUTOANTIBODY INDUCTION
Direct antiglobulin test	Positive (anti-IgG)	Positive (anti-C3)	Positive (anti-IgG)
Site of hemolysis	Extravascular	Intravascular	Extravascular
Medications	Penicillins Cephalosporins 6-Mercaptopurine Tetracycline Oxaliplatin Hydrocortisone	Cephalosporins Quinidine Amphotericin B Hydrocortisone Rifampin (Rifadin) Metformin Quinine Probenecid Chlorpromazine Oxaliplatin	α-Methyldopa Cephalosporins Oxaliplatin L-Dopa Procainamide Ibuprofen Diclofenac (Voltaren) Interferon alfa

Adapted from Packman CH. Hemolytic anemia resulting from immune injury. In Kaushansky K, Lichtman MA, Beutler E, et al, (eds): *Williams Hematology*. 8th ed. New York: McGraw-Hill, 2010.

Chapter 514

Hemolytic Anemias Secondary to Other Extracellular Factors

Allison S. Remiker and Amanda M. Brandow

FRAGMENTATION HEMOLYSIS

See Table 506.2 in Chapter 506.

Red blood cell (RBC) destruction may occur in hemolytic anemias because of **mechanical injury** as the cells traverse a damaged vascular bed. Damage may be microvascular when RBCs are sheared by fibrin in the capillaries during intravascular coagulation or when renovascular disease accompanies the **hemolytic-uremic syndrome (HUS)** (see Chapter 560.5) or **thrombotic thrombocytopenic purpura (TTP)** (see Chapter 533.5). Larger vessels may be involved in **Kasabach-Merritt syndrome** (giant hemangioma and thrombocytopenia; see Chapter 554) or when a replacement heart valve is poorly epithelialized. The blood film shows many *schistocytes*, or fragmented cells, as well as polychromatophilia, reflecting the reticulocytosis (see Fig. 507.4F in Chapter 507 on Castleman disease). Secondary iron deficiency may complicate the intravascular hemolysis because of urinary hemoglobin and hemosiderin iron loss (see Fig. 506.2 in Chapter 506). **Treatment should be directed toward the underlying condition**, and the prognosis depends on the effectiveness of this treatment. The benefit of transfusion may be transient because the transfused cells are destroyed as quickly as those produced by the patient.

It is critical to determine the precise etiology of the fragmentation hemolysis because the treatment depends on the underlying problem (Table 514.1). **Acquired TTP** results from an antibody to an enzyme (ADAMTS13) that regulates the size of von Willebrand multimers. The lack of this enzyme results in a marked increase in multimer size and a resultant *thrombotic microangiopathy*. **Congenital TTP** can result in the inability to produce adequate amounts of the enzyme ADAMTS13 and results in the same pathophysiology. The treatment for acquired TTP involves plasma exchange (PEX) to remove the antibody and replace the ADAMTS13, in addition to immunosuppressive therapy with glucocorticoids. Treatment should be initiated as soon as possible when there is a high index of suspicion, even before confirmation of the diagnosis because of high morbidity and mortality. Once diagnosis has been confirmed, rituximab is suggested. Use of caplacizumab, an anti-von Willebrand factor monoclonal antibody, is used in adult patients with severe disease, although it has not been approved by the US Food and Drug Administration (FDA) in children. The treatment for congenital TTP involves scheduled plasma infusions to replace the ADAMTS13. Recombinant ADAMTS13 is under investigation for use in acquired and congenital TTP. In contrast, HUS results from *Shiga* toxin produced by *Escherichia coli* 0157 and may not be helped by plasmapheresis, and treatment is largely based on supportive measures. **Atypical HUS** involves activation of the alternative complement pathway and can be treated with *eculizumab* (anti-C5), an inhibitor of the complement pathway. Plasmapheresis may reduce the RBC fragmentation and improve the platelet count but has little effect on the tissue (kidney) vasculopathy, and thus is not usually recommended. **Pneumococcal-induced HUS** results from neuraminidase produced by the bacteria, which damages the membranes of the RBCs and the kidney, exposing the **T-antigen**. Plasma contains natural antibody to the T-antigen, producing hemolysis, renal damage, and a thrombotic microangiopathy. Thus, patients with T-antigen activation from suspected pneumococcal-induced HUS should not be given plasma infusions because this will significantly exacerbate the RBC hemolysis and can lead to life-threatening anemia.

THERMAL INJURY

Extensive burns may directly damage the RBCs and cause hemolysis that results in the formation of *spherocytes*. Blood loss and marrow suppression may contribute to anemia and require blood transfusion. Erythropoietin (EPO) has been used as treatment for diminished RBC production. There may be a role of early use of propranolol, which has been shown to restore erythrocyte progenitors.

Table 514.1 Thrombotic Microangiopathies

DISEASE*	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
Thrombotic thrombocytopenic purpura (TTP)	*Acquired:* Ab to ADAMTS13 *Congenital:* Inadequate ADAMTS13 production	Ab to ADAMTS13 ADAMTS13 <10%	*Acquired:* Plasma exchange (PEX) Glucocorticoids +/- Rituximab *Congenital:* Scheduled plasma infusions, recombinant ADAMTS13
Hemolytic-uremic syndrome (HUS)	*Escherichia coli* 0157, *Shiga* toxin	*E. coli* 0157, *Shiga* toxin	Supportive ? Value of plasmapheresis
Atypical HUS	Complement-mediated alternative pathway	ADAMTS13 >10% Decreased factors H and I (inhibitors of complement)†	Eculizumab (Ab to C5) Plasmapheresis not indicated
Pneumococcal-induced HUS	Neuraminidase-induced RBC, platelet, and kidney damage Exposure of T-antigen on RBC and kidney	Pneumococcal infection ADAMTS13 >10%	Plasmapheresis with albumin for neuraminidase and endogenous T Ab removal Avoid plasma infusions, which will exacerbate RBC hemolysis
Disseminated intravascular coagulation (DIC)	Sepsis, shock, endotoxin	Decreased fibrinogen, increased fibrin split products, decreased clotting factors and platelets	Treat underlying condition; replace factors and platelets if bleeding

*All show fragmentation hemolytic anemia, thrombocytopenia, and potential renal and other organ damage. An elevated lactate dehydrogenase and reduced haptoglobin usually are present secondary to hemolysis.
†May be related to inherited defect in factor H or I.
Ab, Antibody; RBC, red blood cell.

RENAL DISEASE

The anemia of uremia is multifactorial in origin. EPO production may be decreased, and the marrow suppressed by toxic metabolites. Furthermore, the RBC life span often is shortened because of retention of metabolites and organic acidemia. The use of EPO in chronic renal disease can decrease the need for blood transfusion. Abnormalities in the hepcidin-ferroportin pathway provide an additional pathway contributing to anemia associated with chronic kidney disease. Investigative use of medications targeting this pathway are being evaluated in patients. Hemodialysis is also implicated in causing fragmentation of erythrocytes.

LIVER DISEASE

A change in the ratio of cholesterol to phospholipids in the plasma may result in changes in the composition of the RBC membrane and shortening of the RBC life span. Some patients with liver disease have many target RBCs on the blood film, whereas others have a preponderance of *spiculated cells.* These morphologic changes reflect the alterations in the plasma lipid composition.

TOXINS AND VENOMS

Bacterial sepsis caused by *Haemophilus influenzae,* staphylococci, or streptococci may be complicated by accompanying hemolysis. Particularly severe hemolytic anemia has been observed in clostridial infections and results from a hemolytic clostridial toxin. Large numbers of spherocytes may be seen on the blood film. **Spherocytic hemolysis** also may be noted after bites by various snakes, including cobras, vipers, and rattlesnakes, which have phospholipases in their venom. Large numbers of bites by insects, such as bees, wasps, and yellow jackets, also may cause spherocytic hemolysis by a similar mechanism (see Chapter 768).

WILSON DISEASE

See Chapter 405.2.

An acute and self-limited episode of hemolytic anemia may precede by years the onset of hepatic or neurologic symptoms in Wilson disease. This event appears to result from the toxic effects of free copper on the RBC membrane. The blood film often (but not always) shows large numbers of spherocytes, and the Coombs test result is negative. Because early diagnosis of Wilson disease permits prophylactic treatment with penicillamine and prevention of hepatic and neurologic disease, correct assessment of this rare type of hemolysis is important.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Polycythemia (Erythrocytosis)

Chapter 515

Polycythemia

Allison S. Remiker and Amanda M. Brandow

Polycythemia exists when the hemoglobin concentration and/or hematocrit and total red blood cell (RBC) volume exceed the upper limits of normal in peripheral blood. In postpubertal individuals, an RBC mass >25% above the mean normal value (based on body surface area) or a hemoglobin level >16.5 g/dL (in males) or >16.0 g/dL (in females) and/or hematocrit >49% (in males) or >48% (in females) indicate **absolute erythrocytosis**. A decrease in plasma volume, such as occurs in acute dehydration and burns, may result in a high hemoglobin value. These situations are more accurately designated as **hemoconcentration** or **relative polycythemia** because the RBC mass is not increased, and normalization of the plasma volume restores hemoglobin to normal levels. Once the diagnosis of true polycythemia is made, sequential studies should be done to determine the underlying etiology (Fig. 515.1).

CLONAL POLYCYTHEMIA (POLYCYTHEMIA VERA)

Pathogenesis

Polycythemia vera is an acquired clonal myeloproliferative neoplastic disorder, which is rare in children and adolescents. The median age of diagnosis is >60 years. Although primarily manifesting as erythrocytosis, thrombocytosis and leukocytosis can also be seen. When isolated severe thrombocytosis exists in the absence of erythrocytosis, the myeloproliferative disorder is called **essential thrombocythemia**. A gain-of-function pathogenic variant involving exon 12 or 14 (V617F) of *JAK2,* a cytoplasmic tyrosine kinase, is found in >90% of adult patients with polycythemia vera, but in <30% of children with this condition. The erythropoietin receptor is normal, and serum erythropoietin levels are low. Patients without *JAK* pathogenic variants may have variants in the calreticulin or thrombopoietin receptor genes. Risk factors for development of polycythemia vera include a family history of polycythemia vera and presence of an autoimmune disorder.

Clinical Manifestations

Patients with polycythemia vera usually have splenomegaly. Erythrocytosis may cause hypertension, headache, early satiety, or neurologic symptoms and increases the risk of thrombosis. Granulocytosis may cause diarrhea or pruritus from histamine release. Thrombocytosis (with or without platelet dysfunction) may cause thrombosis or hemorrhage. Bleeding or acquired von Willebrand disease with extreme thrombocytosis, and complications of pregnancy may occur. Long-term effects include progression to myelofibrosis, myelodysplasia, and/or acute leukemia. These events are rare in children. Table 515.1 lists the diagnostic criteria for polycythemia vera.

Treatment

Phlebotomy and low-dose aspirin are the initial treatments of choice to alleviate symptoms of hyperviscosity and decrease the risk of thrombosis. Iron supplementation should be given to prevent viscosity problems from iron-deficient microcytosis or thrombocytosis. If these treatments are unsuccessful, the patient has progressive splenomegaly, thrombocytosis, or leukocytosis, or has high-risk features (i.e., age >60 or history of thrombosis), antiproliferative treatments (hydroxyurea, pegylated interferon, or busulfan) may be helpful. The use of ruxolitinib (a JAK2 inhibitor) is approved in hydroxyurea-resistant or hydroxyurea-intolerant adult patients, but the long-term effectiveness remains under investigation. There are limited data in the treatment of children, given the rarity of the condition. Often only phlebotomy is required. Transformation of the disease into myelofibrosis or acute leukemia is rare in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

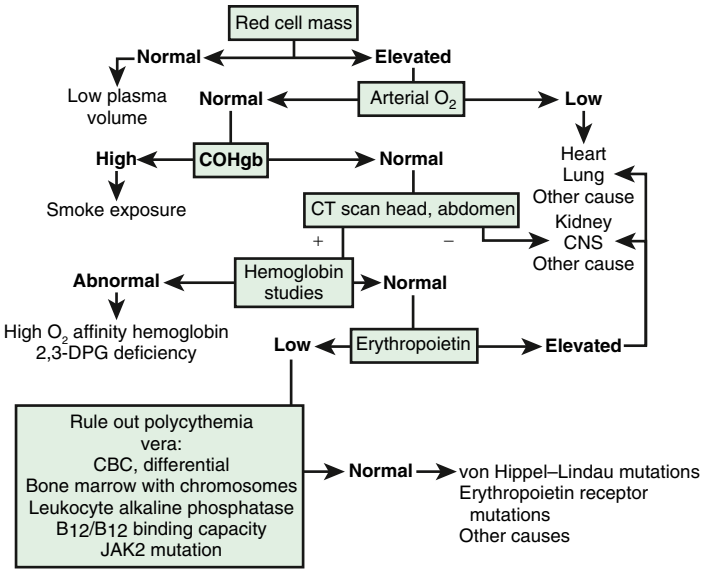

Fig. 515.1 Algorithm showing sequential studies in the evaluation of polycythemia. CBC, Complete blood count; CNS, central nervous system; COHgb, carboxyhemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.

Table 515.1 World Health Organization (WHO) Diagnostic Criteria for Polycythemia Vera

MAJOR CRITERIA
1. Hb >16.5 g/dL (males) or Hb >16.0 g/dL (females)
   or
   Hct >49% (males) or >48% (females)
   or
   Elevated red cell mass >25% above mean normal predicted value
2. Bone marrow (BM) biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic mature megakaryocytes (difference in sizes)
3. Presence of *JAK2* or JAK2 exon 12 mutation

MINOR CRITERIA
1. Subnormal serum erythropoietin level

DIAGNOSIS
All three major criteria
or
First two major criteria and the minor criterion*

*Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in males (hematocrit, 55.5%) or 16.5 g/dL in females (hematocrit >49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Hb, Hemoglobin; Hct, hematocrit.

Modified from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127: 2391–405.

Table 516.1 Differential Diagnosis of Polycythemia

CLONAL (PRIMARY)
Polycythemia vera

NONCLONAL
Congenital
High–oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, San Diego)
Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP])
Methemoglobin reductase deficiency
Hemoglobin M disease
2,3-Diphosphoglycerate deficiency

Acquired
Hormonal
- Adrenal disease: virilizing hyperplasia, Cushing syndrome
- Athletic performance enhancing substances (e.g., anabolic steroids, androgens, recombinant erythropoiesis stimulating agents)
- Malignant tumors: adrenal, cerebellar, hepatic, other
- Renal disease: cysts, hydronephrosis, renal artery stenosis

Hypoxia
- Altitude
- Cardiac disease
- Lung disease
- Sleep apnea
- Central hypoventilation
- Chronic carbon monoxide exposure including smoking

Neonatal: delayed cord clamping (placental-fetal transfusion)
- Normal intrauterine environment
- Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption)
- Twin-twin or maternal-fetal hemorrhage
- Perinatal asphyxia
- Infants of diabetic mothers
- Intrauterine growth restriction
- Trisomy 13, 18, or 21
- Adrenal hyperplasia
- Maternal-congenital hyperthyroidism

Spurious
Plasma volume decrease

Chapter 516

Nonclonal Polycythemia

Allison S. Remiker and Amanda M. Brandow

PATHOGENESIS

Nonclonal polycythemia is diagnosed when polycythemia is caused by a physiologic process that is not derived from a single cell (Table 516.1). Nonclonal polycythemia can be congenital or acquired (secondary).

Congenital Polycythemia

Lifelong or familial polycythemia should trigger a search for a congenital problem. These inherited conditions may be transmitted as dominant or recessive disorders instigating erythrocytosis

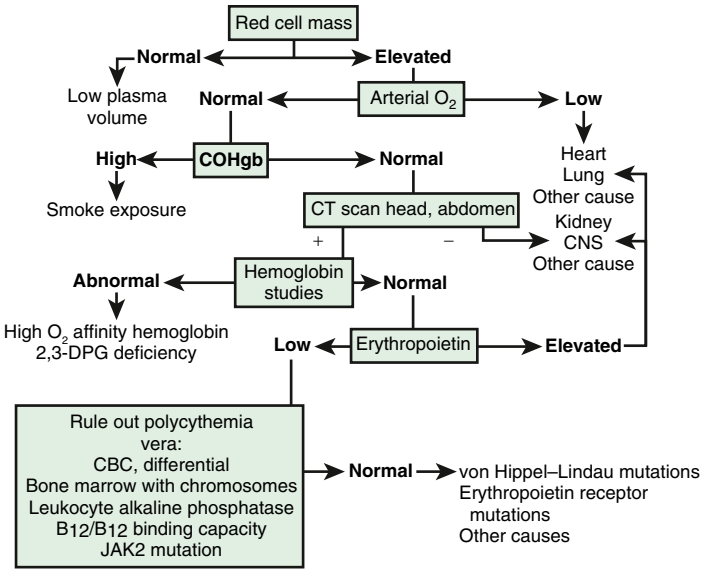

Fig. 515.1 Algorithm showing sequential studies in the evaluation of polycythemia. CBC, Complete blood count; CNS, central nervous system; COHgb, carboxyhemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.

Table 515.1 World Health Organization (WHO) Diagnostic Criteria for Polycythemia Vera

MAJOR CRITERIA
1. Hb >16.5 g/dL (males) or Hb >16.0 g/dL (females)
   or
   Hct >49% (males) or >48% (females)
   or
   Elevated red cell mass >25% above mean normal predicted value
2. Bone marrow (BM) biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic mature megakaryocytes (difference in sizes)
3. Presence of *JAK2* or JAK2 exon 12 mutation

MINOR CRITERIA
1. Subnormal serum erythropoietin level

DIAGNOSIS
All three major criteria
or
First two major criteria and the minor criterion*

*Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in males (hematocrit, 55.5%) or 16.5 g/dL in females (hematocrit >49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Hb, Hemoglobin; Hct, hematocrit.

Modified from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127: 2391–405.

Table 516.1 Differential Diagnosis of Polycythemia

CLONAL (PRIMARY)
Polycythemia vera

NONCLONAL
Congenital
High–oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, San Diego)
Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP])
Methemoglobin reductase deficiency
Hemoglobin M disease
2,3-Diphosphoglycerate deficiency

Acquired
Hormonal
- Adrenal disease: virilizing hyperplasia, Cushing syndrome
- Athletic performance enhancing substances (e.g., anabolic steroids, androgens, recombinant erythropoiesis stimulating agents)
- Malignant tumors: adrenal, cerebellar, hepatic, other
- Renal disease: cysts, hydronephrosis, renal artery stenosis

Hypoxia
- Altitude
- Cardiac disease
- Lung disease
- Sleep apnea
- Central hypoventilation
- Chronic carbon monoxide exposure including smoking

Neonatal: delayed cord clamping (placental-fetal transfusion)
- Normal intrauterine environment
- Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption)
- Twin-twin or maternal-fetal hemorrhage
- Perinatal asphyxia
- Infants of diabetic mothers
- Intrauterine growth restriction
- Trisomy 13, 18, or 21
- Adrenal hyperplasia
- Maternal-congenital hyperthyroidism

Spurious
Plasma volume decrease

Chapter 516

Nonclonal Polycythemia

Allison S. Remiker and Amanda M. Brandow

PATHOGENESIS

Nonclonal polycythemia is diagnosed when polycythemia is caused by a physiologic process that is not derived from a single cell (Table 516.1). Nonclonal polycythemia can be congenital or acquired (secondary).

Congenital Polycythemia

Lifelong or familial polycythemia should trigger a search for a congenital problem. These inherited conditions may be transmitted as dominant or recessive disorders instigating erythrocytosis

by augmenting hypoxia sensing or abnormalities in oxygen sensing. Autosomal dominant causes include hemoglobins that have increased oxygen affinity (P_{50} [partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated] <20 mm Hg), erythropoietin receptor pathogenic variants resulting in an enhanced effect of erythropoietin, or variants in the von Hippel–Lindau *(VHL), EGLN1*, or *EPAS1* genes that result in altered intracellular oxygen sensing. Another rare cause is autosomal recessive 2,3-diphosphoglyceric acid deficiency, which leads to a left shift of the oxygen dissociation curve, increased oxygen affinity, and consequent polycythemia.

Subtle decreases in oxygen delivery to tissues may cause polycythemia. Congenital **methemoglobinemia** resulting from an autosomal recessive deficiency of cytochrome b5 reductase may cause cyanosis and polycythemia (see Chapter 511.7). Most affected individuals are asymptomatic. Neurologic abnormalities may be present in patients whose enzyme deficits are not limited to hematopoietic cells. Hemoglobin M disease (autosomal dominant) causes methemoglobinemia and can lead to polycythemia. Cyanosis may occur in the presence of as little as 1.5 g/dL of methemoglobin but is uncommon in other hemoglobin variants unless hyperviscosity results in localized hypoxemia.

In rare cases, there is an undefined inherited lesion causing primary familial and congenital polycythemia (PFCP), which is described as an elevation of erythrocyte mass and hemoglobin, hypersensitivity to EPO, and low serum EPO in the setting of a normal hemoglobin-oxygen dissociation curve.

Acquired (Secondary) Polycythemia

Polycythemia may be present in clinical situations associated with chronic arterial oxygen desaturation. Cardiovascular defects involving right-to-left shunts and pulmonary diseases interfering with proper oxygenation are the most common causes of hypoxic polycythemia. Clinical findings usually include cyanosis, hyperemia of the sclerae and mucous membranes, and clubbing of the fingers. As the hematocrit rises to >65%, clinical manifestations of hyperviscosity, such as headache and hypertension, may require phlebotomy. Living at high altitudes also causes hypoxic polycythemia; the hemoglobin level increases approximately 4% for each rise of 1,000 m (~3,300 ft) in altitude. Smoking has been associated with polycythemia secondary to tissue hypoxia, elevation of carbon monoxide, and volume contraction. Partial obstruction of a renal artery rarely results in polycythemia. Polycythemia has also been associated with benign and malignant tumors that secrete paraneoplastic erythropoietin. Exogenous or endogenous excess of anabolic steroids also may cause polycythemia. A common spurious cause is a decrease in plasma volume, as occurs in moderate to severe dehydration.

DIAGNOSIS

See Chapter 515; Figure 515.1 outlines sequential studies to evaluate polycythemia.

TREATMENT

For mild disease, observation is sufficient. When the hematocrit is >65–70% (hemoglobin >23 g/dL), blood viscosity greatly increases. Periodic phlebotomy may prevent or decrease symptoms such as headache, dizziness, or exertional dyspnea. Apheresed blood should be replaced with plasma or saline to prevent hypovolemia in patients accustomed to a chronically elevated total blood volume. Increased demand for red blood cell production may cause iron deficiency. Iron-deficient microcytic red cells are more rigid, further increasing the risk of intracranial and other thromboses in patients with polycythemia. Periodic assessment of iron status should be performed, and iron deficiency should be treated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 5

The Pancytopenias

Chapter 517

Inherited Bone Marrow Failure Syndromes with Pancytopenia

Yigal Dror and Michaela Cada

Pancytopenia refers to a reduction below normal values of all three peripheral blood lineages: leukocytes, platelets, and erythrocytes. Identifying the etiology of pancytopenia usually requires microscopic examination of the peripheral blood smear, as well as bone marrow biopsy and aspirate specimens to assess overall cellularity and morphology. The three general categories of pancytopenia are related to bone marrow pathologies and can frequently be differentiated based on bone marrow findings.

Pancytopenia with hypocellular bone marrow on biopsy is seen with *inherited bone marrow failure syndromes* (IBMFSs) with pancytopenia, *acquired* aplastic anemia of varied etiologies, and the *hypoplastic* variant of *myelodysplastic syndrome* (MDS). **Pancytopenia with cellular bone marrow** is seen with primary bone marrow disease (e.g., acute leukemia, myelodysplasia) and secondary to autoimmune disorders (e.g., autoimmune lymphoproliferative syndrome, systemic lupus erythematosus), vitamin B_{12} or folate deficiency, storage diseases (e.g., Gaucher, Niemann-Pick), overwhelming infection, sarcoidosis, and hypersplenism. **Pancytopenia with bone marrow infiltration** can be seen in metastatic solid tumors, myelofibrosis, hemophagocytic lymphohistiocytosis, and osteopetrosis. It is important to note that exceptions exist with regard to this classification; IBMFSs can manifest as normocellular or hypercellular bone marrow at early stages of presentation or in cases where MDS develops.

Inherited pancytopenias with hypocellular bone marrow are IBMFSs that feature decreased bone marrow production of the three major hematopoietic lineages occurring on an inherited basis and resulting in anemia, neutropenia, and thrombocytopenia. Patients may have single-lineage or bi-lineage cytopenia at presentation and gradually develop pancytopenia over time. All disorders for which a genetic basis has been deciphered have thus far been shown to be monogenic. Transmission of pathogenic variant genes is mendelian and in an autosomal dominant, autosomal recessive, or X-linked manner (Table 517.1). Modifying genes and acquired factors may also be operative. Inherited pancytopenias account for approximately 30% of cases of pediatric bone marrow failure. Clinical features may help differentiate the IBMFS disorders (Table 517.2), but whole exome sequencing (WES) or specific bone marrow failure syndrome gene panels help to confirm the diagnosis.

FANCONI ANEMIA

Etiology and Epidemiology

Fanconi anemia (FA) is a rare multisystem hereditary disorder resulting in the development of bone marrow failure in those affected and a predisposition to malignancy, including myelodysplasia (MDS), acute myeloid leukemia (AML), and epithelial cancers. Individuals with FA

Table 517.1 Inherited Bone Marrow Failure Syndromes with Multilineage Cytopenia and Familial MDS/AML: Inheritance, Variant Genes, and Affected Pathways

DISORDER	INHERITANCE	GENE	AFFECTED PATHWAYS
Fanconi anemia	AR	*FANCA, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG/XRCC9, FANCI, FANCJ/BRIP1, FANCL/PHF9, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANCQ/ERCC4, FANCR/RAD51, FANCS/BRCA1, FANCT/UBE2T, FANCU/XRCC2, FANCV/REV7, FANCW/RFWD3*	DNA repair, homologous recombination, ribosome biogenesis *(FANCI)*
	XLR	*FANCB*	DNA repair, homologous recombination
Mixed Fanconi anemia/xeroderma pigmentosa/Cockayne syndrome	AR	*ERCC1/XPF*	DNA repair
Shwachman-Diamond syndrome	AR	*SBDS, DNAJC21, EFL1*	Ribosome biogenesis
	AD	*SRP54*	Co-translational protein modification
Dyskeratosis congenita	XLR	*DKC1*	Telomere maintenance, ribosome biogenesis
	AD	*TINF2, TERC, TERT, RTEL1, ACD(TPP1), PARN*	Telomere maintenance, RNA processing
	AR	*TERT, RTEL1, ACD(TPP1), WRAP53(TCAB1), CTC1, POT1, RPA1, PARN, NOP10, NHP2*	Telomere maintenance, RNA processing, ribosome biogenesis
Congenital amegakaryocytic thrombocytopenia	AR	*MPL*	Hematopoietic cytokine receptor
SRP72-associated hereditary aplastic anemia/MDS	AD	*SRP72*	Co-translational protein modification
ERCC6L2-associated hereditary aplastic anemia/MDS	AR	*ERCC6L2*	Transcription
THPO-associated hereditary aplastic anemia/MDS	AR/AD	*THPO*	Hematopoietic cytokine
Reticular dysgenesis	AR	*AK2*	Nucleotide metabolism
Cartilage-hair hypoplasia	AR	*RMRP, POP1, NEPRO*	rRNA and mitochondrial RNA processing
Pearson's syndrome	Maternal	*mDNA*	Mitochondrial DNA genes
Familial thrombocytopenia with predisposition to AML	AD	*RUNX1/CBFA2*	Hematopoietic cytokines
	AD	*ETV6*	Transcription repression
GATA2-associated disorders (MonoMac syndrome, Emberger syndrome, familial MDS syndrome)	AD	*GATA2*	Transcription
Bone marrow failure and diabetes		*DUT*	Nucleotide metabolism
Familial MDS/AML (others)		*CEBPA*	Transcription
Familial MDS/AML (others)		*DDX41*	RNA helicase
Seckel syndrome	AR	*CEP152, CENPJ, CEP63, NIN, PLK4, CDK5RAP2; ATR, RBBP8, ATRIP, DNA2*	Centriole/Centrosome duplication and function; DNA damage sensing and repair, and checkpoint signaling activation
Schimke immunoosseous dysplasia	AR	*SMARCAL1*	Chromatin remodeling
Dubowitz syndrome	AR	*NSUN2; LIG4*	Cytosine methylation in various RNA types; DNA non-homologous end joining repair
	AD	-14q32, -17q24, -19q13	
Rothmund-Thomson syndrome	AR	*RECQL4*	Chromosome segregation
Nijmegen breakage syndrome	AR	*NBN*	DNA repair

AD, Autosomal dominant; AML, acute myeloid leukemia AR, autosomal recessive; MDS, myelodysplastic syndrome; UK, unknown; XLR, X-linked recessive.

Table 517.2 Clinical Manifestations and Laboratory Findings in Inherited Bone Marrow Failure Syndrome

SYNDROME	NONHEMATOLOGICAL CLINICAL MANIFESTATIONS	LABORATORY FINDINGS
Fanconi anemia	Short stature, low birth weight, microcephaly, microphthalmia, hearing loss, triangular face, micrognathia, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, kidney anomalies, hypoplastic thenar eminence, clinodactyly, café-au-lait spots	Pancytopenia, macrocytosis, elevated Hb F, increased chromosome breakage in clastogenic assay
Dyskeratosis congenita	Mucocutaneous triad (skin pigmentation, nail dysplasia, oral leukoplakia), short stature, low birth weight, failure to thrive, pulmonary fibrosis, stenosis of the esophagus, liver fibrosis	Pancytopenia, macrocytosis, elevated Hb F, very short telomeres
Diamond-Blackfan anemia	Low birth weight, short stature, developmental delay, anomalies in craniofacial skeleton, eyes, heart, visceral organs, and limbs	Anemia, elevated red blood cell adenosine deaminase, macrocytosis, elevated Hb F
Shwachman-Diamond syndrome	Exocrine pancreatic insufficiency, failure to thrive, malabsorption, short stature, neurodevelopment and skeletal abnormalities	Neutropenia, low serum isoamylase, low serum trypsinogen
Severe congenital neutropenia	Recurrent infection	Neutropenia
Congenital amegakaryocytic thrombocytopenia	Nonsyndromic (occasionally, growth retardation, cardiac anomalies, psychomotor developmental delay)	Thrombocytopenia, reduced megakaryocytes
GATA2 deficiency	Lymphedema, immunodeficiency, atypical mycobacterial infections	Neutropenia, anemia, thrombocytopenia
SAMD9/SAMD9L disorders	MIRAGE (SAMD9): MDS, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy	Transient or permanent cytopenia
	Ataxia–pancytopenia syndrome (SAMD9L): cerebellar atrophy and white matter hyperintensities, gait disturbance, nystagmus	
MECOM-associated syndromes	Radioulnar synostosis, clinodactyly, hearing loss, cardiac/renal malformation	Thrombocytopenia
Pearson syndrome	Pancreatic insufficiency, failure to thrive, microcephaly, ptosis, Kearns-Sayre syndrome	Neutropenia, anemia, pancytopenia, lactic acidosis, hyperglycemia

Hb F, Hemoglobin F; MDS, myelodysplastic syndrome.
Modified from Park M. Overview of inherited bone marrow failure syndromes. *Blood Res.* 2022;57(S1):49–54. Table 1.

often have congenital malformations and high sensitivity to alkylating agents and radiation. The estimated frequency of FA is 1 in 200,000 in most populations but is higher in Ashkenazi Jews (1:30,000) and Afrikaners (1:22,000). Carrier frequency is approximately 1:200-300 in most populations. Pathogenic variants in 22 genes, designated *FANC* genes, have been reported to cause FA or FA-like disease. All pathogenic variants except for one are inherited in an autosomal recessive manner. One uncommon form of FA is X-linked recessive. FA occurs in all ethnic groups. At presentation, patients may have typical physical anomalies and abnormal hematologic findings (majority of patients), normal physical features but abnormal hematologic findings (about one third of patients), or physical anomalies and normal hematologic findings (unknown percentage of patients). There can be sibling discordance in clinical and hematologic manifestations, even in affected monozygotic twins.

Pathology

All FA genes code for proteins that play roles in various cellular pathways and most prominently in DNA cross linking and repair. Patients with FA have faulty DNA repair and increased chromosomal fragility caused by DNA interstrand cross-linking agents such as diepoxybutane (DEB) and mitomycin C (MMC). Cell fusion of FA cells with normal cells or with cells from some unrelated patients with FA produces a corrective effect on chromosomal fragility, a process called *complementation.* The classic FA phenotype that clearly defines the FA-associated genes *(FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ/BACH1/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCP/SLX4, FANCQ/ERCC4, UBE2T, REV7, RFWD3)* includes the triad of **bone marrow failure**, **congenital anomalies**, and **elevated chromosome fragility**. These genes can be mutated in patients who have one or all of the components of the triad. Genes that were found to be associated with one or two but not all three of the components are **FA-like genes** *(FANCO/RAD51C, RAD51, FANCS/BRCA1, FANCR/EXCC2). FANCA* accounts for approximately 64% of FA cases, *FANCC* for 14%, and *FANG* for 9%. *FANCB*, *FANCD1/BRCA2*, *FANCD2*, *FANCE,* and *FANCF* are collectively mutated in almost 13% of FA patients. The remaining genes are pathogenic variants in rare cases.

The proteins encoded by wild-type *FANC* genes are involved in the DNA damage recognition and repair biochemical pathway. Therefore aberrant proteins lead to genomic instability and chromosome fragility. FANC proteins are involved in other cellular activities, such as reactive oxygen species detoxification, energetic metabolism, and cytokine signaling. Thus FANC pathogenic variants likely affect several cellular and biochemical roles of the respective proteins, which eventually leads to the FA phenotype. The observed disease complexity and heterogeneity is likely caused by the involvement of multiple cellular and biochemical pathways both in unrelated individuals and in family members with the same genetic pathogenic variant.

Clinical Manifestations

The most common congenital anomalies in FA are skeletal and include absence of radii and/or thumbs that are hypoplastic, supernumerary, bifid, or absent. Anomalies of the feet, congenital hip dislocation, and leg abnormalities can also be seen (Fig. 517.1 and Table 517.3). Skin hyperpigmentation of the trunk, neck, and intertriginous areas;

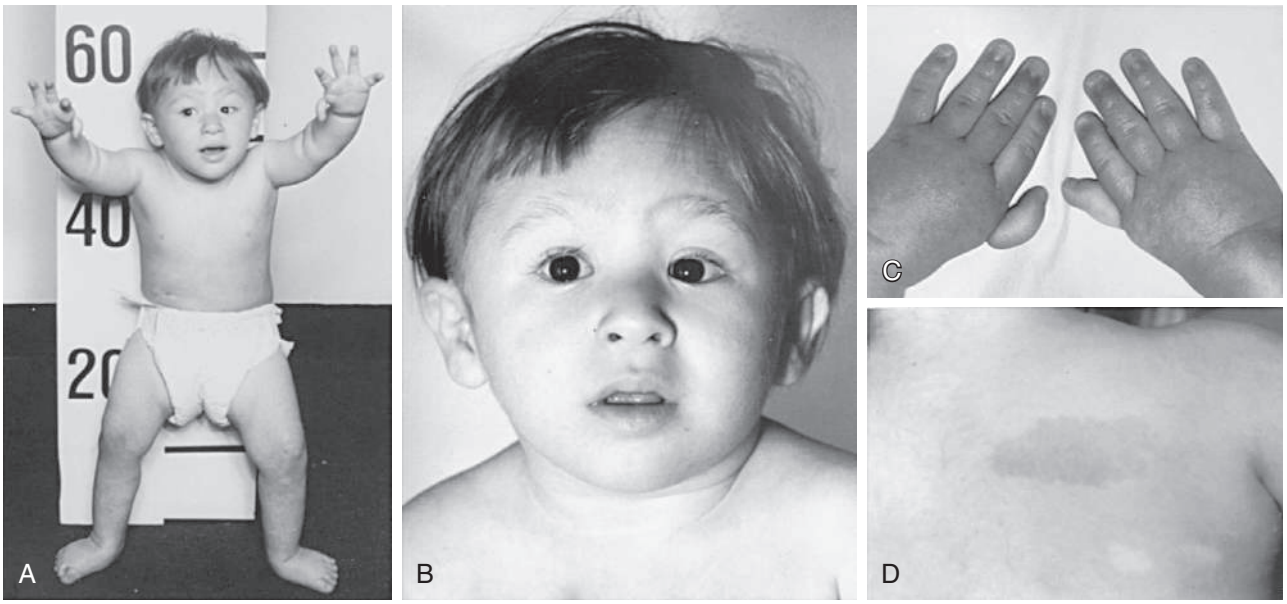

Fig. 517.1 A 3-year-old boy with Fanconi anemia who exhibits several classic phenotypic features. **A,** Front view. **B,** Face. **C,** Hands. **D,** Back right shoulder. The features to be noted include short stature, dislocated hips, microcephaly, a broad nasal base, epicanthal folds, micrognathia, thumbs attached by a thread, and café-au-lait spots with hypopigmented areas beneath. *(From Nathan DC, Orkin SH, Ginsburg D, et al, eds: Nathan and Oski's Hematology of Infancy and Childhood, 6th ed. Philadelphia: Saunders, 2003. p. 285.)*

Table 517.3 Specific Types of Anomalies in Fanconi Anemia

SKIN (40%) Generalized hyperpigmentation on the trunk, neck, and intertriginous areas; café-au-lait spots; hypopigmented areas	**EYES (20%)** Small eyes, strabismus, epicanthal folds, short or almond-shaped palpebral fissures, hypertelorism, ptosis, slanting, cataracts, astigmatism, blindness, epiphora, nystagmus, proptosis, small iris
BODY (40%) Short stature, delicate features, small size, underweight	**EARS (10%)** Deafness (usually conductive); abnormal shape; atresia; dysplasia; low set, large, or small; infections; abnormal middle ear; absent eardrum; dimples; rotated; canal stenosis
UPPER LIMBS (35%) *Thumbs (35%):* absent or hypoplastic; supernumerary, bifid, or duplicated; rudimentary; short, low set, attached by a thread; triphalangeal, tubular, stiff, hyperextensible *Radii (7%):* absent or hypoplastic (only with abnormal thumbs); absent or weak pulse *Hands (5%):* clinodactyly; hypoplastic thenar eminence; six fingers; absent first metacarpal; enlarged, abnormal fingers; short fingers; transverse crease *Ulnae (1%):* dysplastic or absent	**KIDNEY (20%)** Ectopic or pelvic; abnormal, horseshoe, hypoplastic, or dysplastic; absent; hydronephrosis or hydroureter; infections; duplicated; rotated; reflux; hyperplasia; no function; abnormal artery
LOWER LIMBS (5%) *Feet:* toe syndactyly, abnormal toes, flat feet, short toes, clubfeet, six toes, supernumerary toe *Legs:* congenital hip dislocation, Perthes disease, coxa vara, abnormal femur, thigh osteoma, abnormal legs	**GASTROINTESTINAL SYSTEM (5%)** High-arched palate, atresia (esophagus, duodenum, jejunum), imperforate anus, tracheoesophageal fistula, Meckel diverticulum, umbilical hernia, hypoplastic uvula, abnormal biliary ducts, megacolon, abdominal diastasis, Budd-Chiari syndrome
GONADS *Males (25%):* hypogenitalia, undescended testes, hypospadias, abnormal genitalia, absent testis, atrophic testes, azoospermia, phimosis, abnormal urethra, micropenis, delayed development *Females (2%):* hypogenitalia; bicornuate uterus; abnormal genitalia; aplasia of uterus and vagina; atresia of uterus, vagina, and ovary	**UROGENITAL** *Males (25%):* micropenis, penile-scrotal fusion, undescended or atrophic or absent testes, hypospadias, chordae, phimosis, azoospermia *Females (2%):* bicornuate uterus, aplasia or hypoplasia of vagina and uterus, atresia of vagina, hypoplastic uterus, hypoplastic or absent ovary, hypoplastic fused labia
OTHER SKELETAL ANOMALIES *Head (20%) and face (2%):* microcephaly, hydrocephalus, micrognathia, peculiar face, birdlike face, flat head, frontal bossing, scaphocephaly, sloped forehead, choanal atresia, dental abnormalities *Neck (1%):* Sprengel deformity; short, low hairline; webbed *Spine (2%):* spina bifida (thoracic, lumbar, cervical, occult sacral), scoliosis, abnormal ribs, sacral agenesis, sacrococcygeal sinus, Klippel-Feil syndrome, vertebral anomalies, extra vertebrae	**CARDIOPULMONARY SYSTEM (6%)** Patent ductus arteriosus, ventricular septal defect, abnormal heart, peripheral pulmonic stenosis, aortic stenosis, coarctation, absent lung lobes, vascular malformation, aortic atheromas, atrial septal defect, tetralogy of Fallot, pseudotruncus, hypoplastic aorta, abnormal pulmonary drainage, double aortic arch, cardiac myopathy
	CENTRAL NERVOUS SYSTEM (3%) Hyperreflexia, Bell palsy, central nervous system arterial malformation, moyamoya syndrome, Arnold-Chiari malformation, stenosis of internal carotid artery, small pituitary gland, absent corpus callosum Slow development (10%)

Abnormalities are listed in the approximate order of frequency within each category.
Adapted from Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. *Blood Rev.* 2010;24:101–122.

café-au-lait spots; and vitiligo, alone or in combination, occur with similar frequency. Short stature is common and in some patients is aggravated by subnormal growth hormone (GH) secretion or hypothyroidism. Male patients with FA may have an underdeveloped penis; undescended, atrophic, or absent testes; and hypospadias or phimosis, and all are infertile. Females can have malformations of the vagina, uterus, and ovary, and all have reduced fertility. Many patients have characteristic facial dysmorphisms, including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears (see Fig. 517.1). Kidneys may be ectopic, pelvic, horseshoe-shaped, hypoplastic, dysplastic, or absent. Cardiovascular (CV) and gastrointestinal (GI) malformations also occur. Approximately 10% of patients with FA are cognitively delayed. Neonates with FA usually have intrauterine growth restriction (IUGR) and low birthweight and may show malformations consistent with VACTERL/VACTERL-H association (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula with esophageal atresia, renal and limb structural abnormalities with hydrocephalus).

Bone marrow failure usually appears within the first decade of life. Thrombocytopenia, red blood cell (RBC) macrocytosis, and increased fetal hemoglobin (Hb F), as a result of bone marrow stress, often appear first. At these stages, bone marrow aspirate and biopsy often show a hypocellular specimen. Subsequently, patients develop neutropenia and then anemia. Severe aplasia develops in most cases, usually over a few years.

Cancer Risk and Other Complications

In addition to the low blood counts and physical anomalies, patients with FA have a high risk of developing cancer. The most frequent solid tumors are *squamous cell carcinomas* (SCCs) of the head and neck (600-fold higher risk than the general population) and carcinoma of the upper esophagus (2,000-fold higher risk), the vulva (3,000-fold higher risk), and/or anus, cervix, and lower esophagus. Onset of solid-tumor malignancy is much sooner than that seen in the general population, with median age of onset of SCC in the FA population occurring at 33 years vs 60–70 years in the general population. Human papillomavirus (HPV) is suspected in the pathogenesis of SCC. Benign and malignant liver tumors can occur (adenomas, hepatomas) and are usually associated with androgen therapy for aplastic anemia. Androgens are also implicated in the etiology of peliosis hepatis (blood-filled hepatic sinusoids), which is reversible when androgen therapy is discontinued. Clonal bone marrow cytogenetic abnormalities are common in FA and on follow-up can either be stable, intermittently detected, or progressive. The cumulative incidence of clonal and malignant myeloid transformation by age 18 years, which includes clonal cytogenetic marrow abnormalities, MDS, and AML, is approximately 75%. One study indicated that by age 40 years, the cumulative incidence of leukemia is 33%.

Diagnosis

FA should be considered in all children and young adults with unexplained cytopenias. Abnormal hematologic findings and characteristic physical anomalies suggest the diagnosis, which can be confirmed with a lymphocyte chromosomal breakage study done with and without the addition of cross-linking agents such as DEB and MMC. Increased chromosome fragility is indicated by spontaneously occurring chromatid breaks, rearrangements, gaps, endoreduplications, and chromatid exchanges in blood lymphocytes cultured with phytohemagglutinin, as well as in cultured skin fibroblasts, underscoring the constitutional nature of FA. With the addition of DEB or MMC, fragility is strikingly enhanced in lymphocyte cultures of patients with FA compared with those of controls. Abnormal chromosome breakage analysis and genetic testing for prenatal diagnosis can be performed on amniotic fluid cells or on tissue from a chorionic villus biopsy. No other inherited pancytopenia is associated with a prominent in vitro hypersensitivity to DEB or MMC by the chromosomal breakage study. However, 10–15% of patients with suspected FA have *somatic mosaicism* and may not show the characteristically high degree of chromosomal fragility in their lymphocytes, reflecting the presence of mixed populations of somatic cells, some with two abnormal alleles and some with only one. The latter population of lymphocytes derives from a portion of hematopoietic stem cells (HSCs) that underwent spontaneous somatic gene correction on one allele. Testing of skin fibroblasts should be performed if the suspicion of FA is high despite negative testing on peripheral blood lymphocytes.

Next-generation sequencing (NGS) gene panels and WES are the tests of choice for FA. NGS is an efficient and accurate method for diagnosing FA but can occasionally be limited by difficulties in interpreting previously unreported variants or in unraveling pathogenic variants due to reversion variants or technical matters. When no definite causative point pathogenic variants are found, high-resolution copy number variation analysis techniques are employed, followed by a genome-wide search for pathogenic variants in novel associated genes. Pathogenic variants in one of the 22 FA genes are found in over 95% of FA cases.

Extensive screening for potential medical problems is necessary after the diagnosis of FA is established. Imaging using radiation should be minimized as much as possible because of the carcinogenic risk inherent to this genetic instability disease; MRI should replace CT whenever possible. In addition to detailed review of the past medical history and thorough physical examination, the screen should include ultrasonographic examination of the abdomen and echocardiography to rule out internal congenital anomalies. Other imaging may be done as necessary and based on the initial screen. Subspecialty consultations for anomalies and disabilities that have been identified can be arranged during this interval. If growth velocity is below expectations, endocrine evaluation is needed to assess for GH and thyroid deficiency. Blood work should include evaluation of renal, liver, thyroid, metabolic, and immune systems.

Treatment

A hematologist, preferably one who specializes in IBMFSs, with a multidisciplinary team should manage patients with FA. At diagnosis, a detailed assessment of the patient's blood counts, bone marrow function, growth, development, and other organ function should be carried out.

If hematologic abnormalities are mild to moderate and stable and there is no transfusion requirement, patients can be observed closely with peripheral blood counts every 3 months and bone marrow aspiration surveillance every year for clonal cytogenetic abnormalities, MDS, and AML. Bone marrow biopsy might also be intermittently done during bone marrow testing to evaluate changes in percentage of cellularity and fibrosis. More frequent monitoring can be applied when deemed necessary, as when a decline in blood counts occurs. Glucose levels should be performed annually or biannually, depending on the degree of hyperglycemia found on initial testing. Screening for hypothyroidism should be performed yearly. Patients should be assessed for solid tumors at least annually, with a careful physical examination that includes comprehensive inspection of the skin, oral cavity, and other organs for unusual masses. After a certain age (e.g., 10 years) or after HSC transplant (HSCT), fluoroscopic examination of the orolaryngeal cavity and occult fecal blood testing are also recommended. Beginning at menarche, female patients should be screened annually for gynecologic cancer. Administration of HPV quadrivalent vaccine to decrease the risk of SCC is advised.

Chromosome fragility (and/or targeted genetic testing) should be offered to siblings and parents of affected patients for identification of other affected individuals. It is noteworthy that heterozygosity for several FA genes (e.g., *FANCN*, *FANCD1*, *FANCS*) is associated with cancer development. Human leukocyte antigen (HLA) typing of patients, biological parents, and full siblings for future HSCT should also occur early.

HSCT is the only curative therapy for the hematologic abnormalities observed in FA patients. Outcomes have improved because of modified reduced-intensity regimens that include fludarabine, low dose cyclophosphamide, and antithymocyte globulin with or without low-dose busulfan. Most regimens do not use radiation. These regimens have decreased the toxicities experienced by FA patients, who have high sensitivity to DNA-damaging agents such as alkylating drugs and irradiation. Those who undergo transplant using an HLA-identical sibling

donor without irradiation in the preparative regimen have an overall 3-5-year survival rate of >90%.

Traditionally, HSCT of FA patients with matched unrelated donors (MUD) or mismatched related donors have been a challenge because of the high degree of HSCT-related toxicity and death. However, major progress has been made in this regard. Several reports of radiation-free HSCT with in vivo or ex-vivo T-cell depleted, peripheral blood $CD34^+$ selected MUD graft and conditioning with fludarabine, rabbit antithymocyte globulin (ATG), low-dose cyclophosphamide, and low-dose busulfan demonstrated 80% or higher probabilities of overall and disease-free survival 1–5 years post HSCT. Improvement in high-resolution HLA typing contributes to better selection of unrelated-donor selection and a better outcome. Transplantation using haploidentical donors is on the rise and is showing promising outcomes, similar to those seen with unrelated donors.

Those transplanted before they receive multiple transfusions or develop clonal and malignant myeloid transformation (MDS or AML) do better. Survival rates are higher for patients who undergo transplant at <10 years of age. Molecular technology has led to preimplantation genetic diagnosis on parent-derived blastomeres, allowing for the unaffected ones to be implanted and resulting in the creation of an HLA-matched sibling donor without FA.

Androgens produce a response in approximately 70% of patients, heralded by reticulocytosis and a rise in hemoglobin within 1-2 months. White blood cell (WBC) counts may increase next, followed by platelet counts. After the initial response is seen, counts may continue to improve over many months until a maximum response is achieved. If a low dose is initially employed, the androgen dose can be increased every 3-4 weeks as long as no major side effects are seen and until the desired response is achieved. If a high dose is initially employed, androgen dosage can be slowly reduced to the minimum dose that maintains the required blood counts. Oral danazol and oxymetholone are currently the two most commonly used androgenic drugs. Patients typically stop responding to androgens after several months or years, as their bone marrow failure progresses or as they develop MDS or AML. Thus androgen therapy is not curative but is used rather as a bridge while waiting for a suitable donor for HSCT or while weighing the risks and benefits of transplant. Side effects of androgens include masculinization, increased linear growth, increased mood swings or aggressiveness, elevated hepatic enzymes, cholestasis, peliosis hepatis, and liver tumors. Screenings for these should be performed regularly.

The potential for recombinant growth factor (cytokine) therapy for FA has not been defined. Granulocyte colony-stimulating factor (G-CSF) can usually induce an increase in the absolute neutrophil count; however, there may be a heightened risk of expansion of bone marrow cells with clonal cytogenetic abnormalities such as monosomy 7. In one study, combination therapy consisting of G-CSF given subcutaneously daily or every 2 days along with erythropoietin given subcutaneously or intravenously 3 times per week resulted in improved neutrophil counts in most patients and a sustained rise in hemoglobin and platelet levels in approximately one third of patients. Most patients lost the response because of progression of bone marrow disease.

Prognosis

Improvements in supportive care, careful surveillance of known complications, prompt intervention, and improved transplant techniques have resulted in patients with FA surviving into their 30s. Unfortunately, there is an increased risk of solid tumors after HSCT. For example, head and neck cancer risk is increased 4.4-fold and is accelerated by approximately 15 years compared with nontransplanted patients. The cumulative incidence of malignancy 20 years after transplant is 35–40%. Some of the increased risk might be attributed to the use of DNA-damaging agents or the occurrence of graft-versus-host disease (GVHD).

SHWACHMAN-DIAMOND SYNDROME

Etiology and Epidemiology

Shwachman-Diamond syndrome (SDS) is an inherited disorder caused by pathogenic variants in one of four genes. It occurs in all racial and ethnic groups. SDS is a multisystem disorder. However, the nonhematologic manifestations of SDS are substantially different and usually include exocrine pancreatic insufficiency and skeletal abnormalities such as metaphyseal dysplasia (Table 517.4). SDS is a **ribosomopathy**, and the underlying defect is in ribosome assembly.

Table 517.4 Major Clinical Features of Shwachman-Diamond Syndrome

CLINICAL FEATURE	TOTAL/AVERAGE
Number of patients	225
Neutropenia	90%
Severe (≤500/μL)	46%
Anemia	46%
Thrombocytopenia	42%
Pancytopenia	21%
Exocrine pancreatic insufficiency	98%
Liver (elevated transaminases)	61%
Skeletal abnormalities	70%
Metaphyseal dysostosis	53%
Rib cage abnormalities	35%
Short stature (<3rd percentile)	66%

Data from Ginzberg H, Shin J, Ellis L, et al. Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar. *J Pediatr*. 1999;135:81–88; Cipolli M, D'Orazio C, Delmarco A, et al. Shwachman's syndrome: pathomorphosis and long-term outcome. *J Pediatr Gastroenterol Nutr*. 1999;29:265–272; and Kuijpers TW, Alders M, Tool AT, et al. Hematologic abnormalities in Shwachman-Diamond syndrome: lack of genotype-phenotype relationship. *Blood*. 2005;106:356–361.

Pathology

Four genes have been linked to SDS. *SBDS* is the first gene that was described to have biallelic variants in SDS in 2003. *SBDS* maps to chromosome 7q11 and accounts for 80–90% of SDS cases. *SBDS* plays a role in the late stage of the pre-60S ribosome subunit maturation, binding to the *EFL1* GTPase and facilitating the release of eIF6 to enable 80S monosome formation. *DNAJC21* is the second reported SDS gene. The function of the human *DNAJC21* is required for the release and recycling of the Arx1/Alb1 heterodimer from the pre-60S biogenesis factors. The third SDS gene discovered is *EFL1*. *DNAJC21* and *EFL1*-associated SDS are autosomal recessive. Monoallelic pathogenic variants in *SRP54*, a protein involved in co-translational protein modification, mainly cause severe congenital neutropenia phenotype. Nevertheless, a small proportion of the patients have partial or classical SDS phenotype. The underlying genetic defects of SDS indicate that the last step in ribosome biogenesis is associated with pancytopenia (most often neutropenia) and a hypoplastic bone marrow. Defects in ribosomal proteins that are involved in earlier stages of ribosome subunit maturation and are structural components of the ribosome are associated with predominantly anemia and pure red cell aplasia.

Exocrine pancreatic insufficiency is caused by failure of exocrine pancreatic acinar development in SDS, and fatty replacement of pancreatic tissue is prominent. **Bone marrow failure** is characterized by dysfunctional HSCs, accelerated apoptosis of bone marrow progenitors, and a defective bone marrow microenvironment that does not support and maintain normal hematopoiesis.

Clinical Manifestations

Most patients with SDS have symptoms of fat malabsorption from birth that are caused by pancreatic insufficiency, but steatorrhea is not always obvious. Approximately 50% of patients appear to exhibit an improvement in pancreatic enzyme secretion as they age. The clinical picture can be dominated by complications from neutropenia, anemia,

or thrombocytopenia. Bacterial and fungal infections secondary to neutropenia, neutrophil dysfunction, and immunodeficiency can occur. A major concern is the development of MDS and acute leukemia, most often AML.

Short stature is a consistent feature of SDS. Most patients show normal growth velocity yet remain consistently below the 3rd percentile for height and weight. The occasional SDS adult achieves the 25th percentile for height. Although skeletal abnormalities are variable, classic findings are metaphyseal dysplasia, osteopenia, delayed appearance of secondary ossification centers, short or flared ribs, and thoracic dystrophy.

Some patients have hepatomegaly and elevations of liver enzymes. Most patients have dental abnormalities and poor oral health. Many have neurocognitive problems and poor social skills.

Laboratory Findings

Exocrine pancreatic insufficiency in SDS is associated with reduced age-adjusted serum trypsinogen and pancreatic isoamylase levels. Because serum pancreatic isoamylase is physiologically low in the first 3 years of life, and because reduced serum trypsinogen is typically seen in young infants and often improves with age, testing both enzymes is helpful. Fecal elastase is often reduced in SDS patients. Fat-soluble vitamin (A, D, E, and K) absorption is impaired, and thus measurement of vitamin A, D, and E levels, as well as prothrombin time (or international normalized ratio [INR]), is helpful to assess the consequences of fat malabsorption. Ultrasound or CT scan can visualize fatty replacement of pancreatic tissue. Fat malabsorption can be proven by assay on a 72-hour stool collection.

Neutropenia is observed in about 70% of patients with SDS at presentation and is seen in close to 100% of patients on follow-up. It is chronic but can be persistent or intermittent and mild, moderate, or severe. It has been identified in some neonates during an episode of sepsis. Neutrophils may have a defect in mobility, migration, and chemotaxis because of alterations in neutrophil cytoskeletal or microtubular function. Anemia, thrombocytopenia, and pancytopenia are seen in 40–66%, 40–60%, and 21–44% of cases, respectively. Pancytopenia can be severe as a result of full-blown aplastic anemia. Bone marrow aspirate and biopsy specimens show varying degrees of bone marrow hypoplasia and fat infiltration. However, at a young age or when patients develop MDS or leukemia, the bone marrow can be normocellular or even hypercellular.

Patients may also have B-cell defects with one or more of the following: low immunoglobulin G (IgG) or IgG subclasses, low percentage of circulating B lymphocytes, decreased in vitro B-cell proliferation, and lack of specific antibody production. Patients may have a low percentage of circulating T cells, subsets, or natural killer cells and decreased in vitro T-cell proliferation.

Diagnosis

The clinical diagnosis of SDS relies on having evidence of two of the following: bone marrow dysfunction, exocrine pancreatic insufficiency, and metaphyseal dysplasia. However, atypical presentations have been identified, such as MDS without previous documentation of low blood counts. Up to 20% of patients lack clear evidence of exocrine pancreatic defects at diagnosis. Furthermore, 20–60% lack metaphyseal dysplasia at diagnosis because this bony anomaly often develops with age. Therefore it is recommended that all patients with either hypoplastic/aplastic bone marrow or exocrine pancreatic insufficiency or metaphyseal dysplasia of unknown etiology be considered for SDS genetic testing. Genetic analysis for *SBDS*, *DNAJC21*, and *EFL1* are definitive in all or almost all cases of SDS. A patient with neutropenia and an *SRP54* pathogenic variant who does not have exocrine pancreatic insufficiency or metaphyseal dysplasia should be considered as having severe congenital neutropenia.

Pearson syndrome, consisting of refractory sideroblastic anemia, cytoplasmic vacuolization of bone marrow precursors, metabolic acidosis, exocrine pancreatic insufficiency, and a diagnostic mitochondrial DNA pathogenic variant, is similar to SDS, but the clinical course, morphologic features of the bone marrow, and gene pathogenic variant are different. Severe anemia requiring transfusion, rather than neutropenia, is present in Pearson syndrome from birth to 1 year of age. SDS shares some manifestations with **Fanconi anemia**, such as bone marrow dysfunction and growth failure, but patients with SDS are readily distinguished because of pancreatic insufficiency with fat malabsorption, fatty changes within the pancreatic body visualized by imaging, characteristic skeletal abnormalities not seen in FA, and a normal chromosomal breakage study with DEB and MMC. Distinguishing SDS from **dyskeratosis congenita (DC)** may not be possible based solely on clinical findings and pancreatic enzyme levels; telomere length measurement may facilitate a correct diagnosis. *In difficult cases of IBMFSs that cannot be easily classified, comprehensive genetic testing using an NGS panel of all known IBMFS genes or unbiased testing using WES/genome sequencing is likely to assist in establishing a diagnosis.*

Predisposition to Cancer

Patients with SDS are predisposed to MDS and leukemic transformation. Approximately 25% of patients develop clonal marrow cytogenetic abnormalities, MDS, or leukemia by age 18 years. About one third of patients have been reported to develop leukemia by age 30 years. Isochromosome 7q [i(7q)] is particularly common and is rarely seen in other conditions. i(7q) might be related to the presence of pathogenic variant *SBDS* on 7q11 and likely confers a compensatory effect by increasing *SBDS* transcribing alleles (although they remain variant). Other clonal chromosome abnormalities include monosomy 7, i(7q) combined with monosomy 7, deletions or translocations involving part of 7q, and deletions of 20q [Del(20q)]. The i(7q) and del(20q) are associated with relatively low risk and very slow progression to MDS or leukemic transformation.

Treatment

Fat malabsorption responds to oral pancreatic enzyme replacement and supplemental fat-soluble vitamins, administered according to guidelines similar to those for cystic fibrosis. A long-term plan should be initiated to periodically monitor changes in peripheral blood counts that require corrective action and to look for early evidence of malignant myeloid transformation. The latter also requires periodic bone marrow aspirations for smears and cytogenetic testing, as well as bone marrow biopsy. A common recommendation is to perform bone marrow testing every 1-3 years and complete blood counts every 3 months.

Daily *subcutaneous G-CSF* for profound neutropenia is effective in inducing a sustained increase in neutrophils. Some patients require transfusion support for management of severe anemia or thrombocytopenia. Experience with erythropoietin is limited. Androgens have been used in few published cases (with and without steroids); some patients showed response, and some did not.

The only curative option for severe bone marrow failure and advanced MDS or leukemia in SDS is allogeneic HSCT. Traditional myeloablative HSCT results in treatment-related mortality in 35–50% of patients. Reduced-intensity conditioning regimens that incorporate *fludarabine* appear to be safer and have been shown to be effective in SDS. Graft failure poses a challenge, possibly due to a stromal cell defect that is not corrected by HSCT. Results of treatment for advanced MDS and AML are generally limited, and outcome is typically poor.

Prognosis

The accurate life expectancy of SDS patients is unknown; analysis of published cases revealed a median survival of 35 years. Because the number of undiagnosed patients with mild or asymptomatic disease is unknown, the overall prognosis may be better than previously thought.

Although all patients have some degree of hematologic cytopenia at diagnosis, the changes in most patients are mild to moderate and do not require therapeutic intervention. Severe neutropenia responds well to G-CSF, but there is a concern that G-CSF may promote the growth of evolving MDS or leukemia clones because of the agent's powerful

growth stimulus on bone marrow cells. HSCT for severe bone marrow failure has produced a 50–70% survival rate, but safer protocols need to be introduced. Malignant bone marrow transformation remains ominous.

Approximately 50% of patients experience spontaneous conversion from exocrine pancreatic insufficiency to pancreatic sufficiency as a result of improvement in pancreatic enzyme secretion.

DYSKERATOSIS CONGENITA

Etiology and Epidemiology

DC is an inherited multisystem telomere disorder. A diagnostic triad of mucocutaneous features was proposed when the disorder was first described and included **dysplastic nails**, lacy **reticular pigmentation** of the upper chest and/or neck, and **oral leukoplakia** (Fig. 517.2). *However, this triad is not present in all individuals.* If it occurs, skin and nail findings usually become apparent in the first 10 years of life, whereas oral leukoplakia may be noticed later. Manifestations tend to progress as patients age. Hematological manifestations are actually the most common features in this disease. Varying degrees of bone marrow failure are seen in approximately 90% of patients. Severe aplastic anemia occurs in approximately 50% of cases, with the age of onset varying according to the genetic group. In some genetic groups, the disease usually starts in the first decade of life (e.g., *DKC1*, *TINF2, PARN*), whereas in others, it typically starts after the first decade (e.g., *TERT, TERC*). In addition to progressive bone marrow failure, patients with DC are also at high risk for pulmonary and hepatic fibrosis, other congenital anomalies, and a predisposition to solid tumors and MDS or AML. DC is rare, with an incidence in childhood of approximately 4 cases per 1 million population per year.

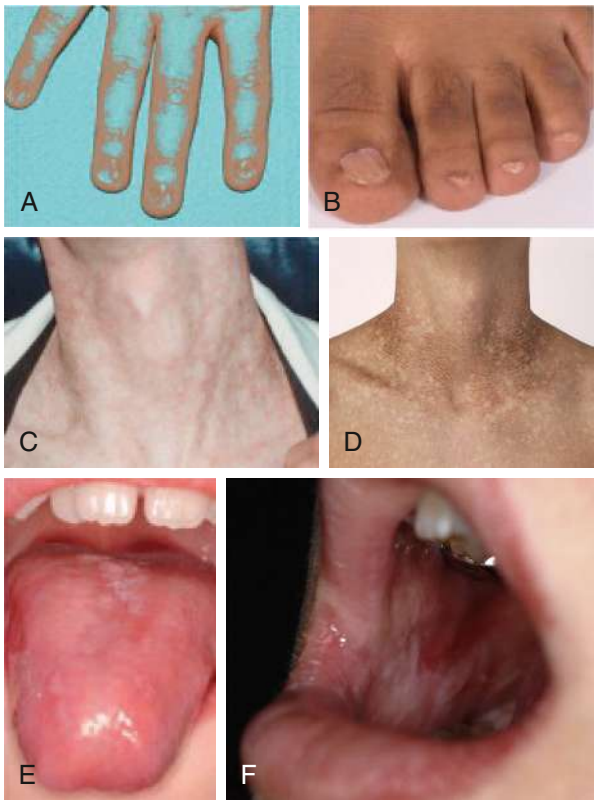

Fig. 517.2 Features of the diagnostic triad in dyskeratosis congenita. A and B, Dystrophic nails on hands and feet. C and D, Lacy reticular pigmentation on neck and upper thorax. E and F, Oral leukoplakia on tongue and buccal mucosa. *(A-C and E from Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev. 2010;24:101–122, Fig. 8; D and F from Savage SA, Alter BP. Dyskeratosis congenital. Hematol Oncol Clin North Am. 2009;23:215–231)*

Pathology

DC is genetically heterogeneous, and patients have pathogenic variants in genes that encode components of the telomerase complex *(TERT, TERC)*, telomere-capping complex *(CTC1, STN1)*, T-loop unwinding and telomere replication *(RTEL1, RPA1)*, telomerase trafficking *(WRAP53*/TCAB1*)*, TERC-associated factors that stimulate telomerase activity *(DKC1, NOP10, NHP2, NAF1)*, TERC-maturation factors *(PARN)*, and telomere-shelterin complex *(TINF2, POT1, ACD)*.

All components are critical for telomere maintenance. The **X-linked recessive** form of DC maps to Xq28, and many pathogenic variants have been identified in the *DKC1* gene, which codes for the nuclear protein dyskerin. The **autosomal dominant** form of disease is caused by pathogenic variants in *TINF2, TERC, TERT, RTEL1, ACD, NAF1,* and *RPA1*. **Autosomal recessive** DC is linked to pathogenic variants in *NOP10, NHP2, TCAB1/WRAP53, CTC1,* and *STN1,* as well as *TERT, TERC, RTEL1, PARN*, and *ACD*. Because of impaired telomere maintenance in all three inherited forms of DC, extremely short telomeres (<1st percentile for age) are demonstrated in the peripheral blood cells of all patients. Finding extremely short telomeres in lymphocytes performed by automated multicolor flow fluorescence in situ hybridization (FISH) has 97% sensitivity and 91% specificity for DC. Approximately 70% of individuals who meet clinical diagnostic criteria of DC have a pathogenic variant in one of the known DC-related genes. Pathogenic variants in *DKC1* are most common (20–25% of individuals), followed by *TINF2* (12–20% of individuals), *TERC* (5–10% of individuals), *RTEL1*, *TERT,* and *CTC1*. The remainder of the genetic pathogenic variants have been described in only a few families. Bone marrow failure is likely caused by progressive attrition and depletion of HSCs because of premature senescence, apoptosis, or chromosome instability, which manifests as pancytopenia.

Clinical Manifestations

The clinical criteria for classic DC include the presence of at least two of the four major features—abnormal skin pigmentation, nail dystrophy, leukoplakia, and bone marrow failure—and two or more of the other somatic features known to occur in DC. However, making a diagnosis continues to be challenging because individuals develop clinical features of DC at variable rates and ages, even within the same family. Further, some of the patients have only one complication (e.g., isolated bone marrow failure or isolated pulmonary fibrosis). In about one quarter of individuals with DC, pathogenic variants in the known DC-related genes cannot be identified. The spectrum ranges from individuals who develop bone marrow failure first, then years later develop other classic findings such as nail abnormalities, to others who have severe nail problems and abnormalities of skin pigmentation at presentation but normal bone marrow function. In classic disease, skin pigmentation and nail changes typically appear first, usually in the first decade of life. Bone marrow failure usually develops within the first two decades, with 80% of patients developing bone marrow failure by age 30 years and almost 90% of patients having bone marrow failure at some point in their life.

Lacy reticulated **skin pigmentation** affecting the face, neck, chest, and arms is a common finding (89%). The degree of pigmentation increases with age and can involve the entire skin surface. There may also be a telangiectatic erythematous component. Nail dystrophy of both hands and feet is the next most common finding (88%). It usually starts with longitudinal ridging, splitting, or pterygium formation and may progress to complete nail loss. **Leukoplakia** usually involves the oral mucosa (78%), especially the tongue, but may also be seen in the conjunctiva and the anal, urethral, or genital mucosa. Excessive tearing **(epiphora)** secondary to nasolacrimal duct obstruction is common and observed in about 30% of individuals. Approximately 25% of individuals have learning difficulties and/or developmental delay. Hyperhidrosis of the palms and soles, hair loss and graying, dental caries or loss, esophageal stricture, pulmonary disease with reduced diffusion capacity and/or a restrictive defect due to pulmonary fibrosis and abnormalities in pulmonary vasculature, and short stature are each seen in approximately 15–20% of individuals.

Ocular abnormalities include conjunctivitis, blepharitis, loss of eyelashes, strabismus, cataracts, and optic atrophy. **Skeletal** abnormalities include osteoporosis, avascular necrosis of the hips or shoulders, abnormal bone trabeculation, scoliosis, and mandibular hypoplasia. **Genitourinary** abnormalities include hypoplastic testes, hypospadias, phimosis, urethral stenosis, and horseshoe kidney. **GI** findings, such as vascular lesions causing bleeding, hepatomegaly, peptic ulceration, and fibrosis, are seen in 10% of cases.

Laboratory Findings

The initial hematologic change in DC is usually thrombocytopenia, anemia, or both, followed by pancytopenia and aplastic anemia. The red cells are often macrocytic, and the Hb F is elevated. Initial bone marrow specimens may be normocellular or hypercellular, but with time, a symmetric depletion of all hematopoietic lineages ensues. Some patients have immunologic abnormalities, including reduced or elevated immunoglobulin values, decreased B- and/or T-lymphocyte counts, and reduction or absence of lymphocyte proliferative responses to phytohemagglutinin. This is particularly common and severe in the *DKC1*-associated disease. Primary skin fibroblasts in culture have abnormal morphologic features and doubling rate and show numerous unbalanced chromosome rearrangements, such as dicentrics, tricentrics, and translocations, in the absence of DEB or MMC. These findings provide evidence of a defect that predisposes patient cells to chromosomal rearrangements and possibly to DNA damage.

The hallmark of DC is very short telomeres, below the first percentile for age. However, some patients do not have short telomeres. Further, adult patients tend to have telomere length at the low range of normal rather than below the first percentile.

Diagnosis

The diagnosis of DC can often be made based on medical and family history and physical examination. The following abnormalities are seen in patients with DC but not in those with FA: nail dystrophy, early-onset leukoplakia, tooth abnormalities, hyperhidrosis of the palms and soles, and hair loss. There are several relatively more severe forms of DC. **Hoyeraal-Hreidarsson syndrome** is a multisystem disorder that presents in early childhood, which requires the features of DC along with **cerebellar hypoplasia** to establish the diagnosis. Patients have the classic diagnostic DC triad, in addition to developmental delay, IUGR, and bone marrow failure. Hoyeraal-Hreidarsson syndrome is genetically heterogeneous and caused by X-linked recessive pathogenic variants in *DKC1*. Some patients may also have severe immunodeficiency. **Revesz syndrome** has many of the features of DC and presents in early childhood. Bilateral exudative retinopathy is required to establish a diagnosis. Patients may also have intracranial calcifications, IUGR, developmental delay, and bone marrow failure. Pathogenic variants of *TINF2* are involved in Revesz syndrome, making it mostly an autosomal dominant condition, but a few patients have been described without an identified pathogenic variant. Individuals with these severe forms of DC have even shorter telomere lengths than those with classic DC. **Coats plus syndrome** is caused by compound heterozygous pathogenic variants in the *CTC1* gene or the *STN1* gene and has overlapping features with DC, including sparse and graying hair, dystrophic nails, and anemia. Telomeres can be very short, but patients display variable telomere length. Coats plus syndrome is characterized by retinal telangiectasia and exudates, intracranial calcification, leukodystrophy, brain cysts, osteopenia, GI bleeding, and portal hypertension caused by the development of vasculature ectasias in the stomach, small intestine, and liver.

Laboratory testing and imaging are an important part in establishing a diagnosis but also evaluate the spectrum of patient organ involvement. These tests include, but are not limited to, the laboratory tests described in the section "Laboratory Findings," as well as ultrasound of the abdomen, pulmonary function tests, liver enzymes, and nutritional elements (such as ferritin, folic acid, and vitamin B12). MRI of the head is useful when the patient has developmental delay and ataxia. Baseline bone marrow testing is critical. Annual evaluation of the bone marrow and complete blood counts every 3 months are common practice.

Because of genomic instability, imaging involving radiation should be limited to those that may affect management.

Cancer Risk and Other Complications

Patients with DC are predisposed to MDS and AML, as well as to solid tumors. Cancer usually develops in the third and fourth decades of life. The cumulative incidence of solid cancers and leukemia by the age of 65–70 years were estimated as 20% and 5–10%, respectively. The cumulative incidence of MDS was predicted to be 20% by the age of 50 years. The actuarial risk of clonal and malignant myeloid disease is 25% by age 18 years.

Forty percent of the cancers in such patients are SCCs of the head and neck (tongue, mouth, pharynx). SCCs of the skin and GI tract (esophagus, stomach, colon), as well as anorectal adenocarcinoma, are common. Patients may develop multiple separate primaries in different sites involving the tongue and nasopharynx.

Other life-threatening complications include pulmonary fibrosis, liver fibrosis, and severe GI bleeding.

Treatment

Androgens can induce improvement of bone marrow function in approximately 70% of patients, and in some, this treatment can result in normal trilineage blood counts for a number of years. Patients with DC become refractory to androgens as aplastic anemia progresses due to HSC depletion. They also tend to be more sensitive to the side effects of androgens than FA patients, making it important to start with lower doses and to monitor for side effects frequently. When the response is maximal, the androgen dose can be slowly reduced to the minimum dose required to maintain desired and safe blood cell counts but cannot be stopped.

Cytokine therapy with granulocyte-macrophage colony stimulating factor (GM-CSF) or with G-CSF alone or combined with erythropoietin appears to offer potential benefit, at least in the short term. Use of cytokines needs to be balanced with a potential growth-promoting effect of these medications on as-yet undetected MDS or AML cells.

Allogeneic HSCT is the only curative option for severe bone marrow failure, MDS, and AML. Long-term survival, even with sibling HLA-matched HSC donors, has traditionally been poor at about 50%. Morbidity and mortality result from transplant-related complications such as graft failure, GVHD, sepsis, or venoocclusive disease or from emergence of DC-related complications, such as pulmonary fibrosis and GI bleeding related to vascular anomalies. The high morbidity and mortality rate after HSCT is likely caused by ongoing tissue sensitivity and aging because of the telomere maintenance defect.

Prognosis

Considerable heterogeneity exists in DC, and some data about genotype-phenotype correlations are available. Patients with certain genetic groups (e.g., monoallelic *TERC, TERT*) may develop severe aplastic anemia or fibrosis of the liver and lungs, but these complications may appear later on in life and may not be accompanied by multisystem involvement. Patients with other genetic groups (e.g., monoallelic pathogenic variants in *DKC1* or *TINF2 and biallelic pathogenic variants in PARN, ACD, RTEL1, TERC or TERT*) appear to have more physical anomalies and a higher incidence and earlier onset of aplastic anemia and cancer. The mean age of death for patients with DC who are diagnosed in childhood is approximately 30 years. However, patients who are diagnosed during adulthood may have a mild disease or be completely asymptomatic. The main causes of death are bone marrow failure, complications of HSCT, cancer, fatal pulmonary problems, and GI bleeding.

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA

Etiology and Epidemiology

Congenital amegakaryocytic thrombocytopenia **(CAMT)** is less common than FA, SDS, and DC. It is transmitted in an autosomal recessive manner. CAMT typically manifests in infancy as isolated thrombocytopenia caused by reduction or absence of bone marrow megakaryocytes

with initial preservation of granulopoietic and erythroid lineages. Pancytopenia due to aplastic anemia often ensues in the first few years of life. Development of MDS and AML was reported in patients with CAMT, as well as persistent aplastic anemia.

The defect in CAMT is directly related to pathogenic variants in *MPL*, the gene for the receptor of thrombopoietin (THPO). *THPO* is a growth factor that promotes HSC survival and stimulates megakaryocyte proliferation and maturation. Heterozygotes of the pathogenic variant gene have normal hematology, whereas affected individuals have pathogenic variants in both alleles. Genotype-phenotype correlations predict disease course and prognosis. **Nonsense pathogenic variants** cause a complete loss of function of the THPO receptor, resulting in persistently low platelet counts in early infancy due to absence of megakaryocytes and a fast progression to pancytopenia and aplastic anemia **(CAMT type I)**. Impaired stem cell survival with *MPL* nonsense pathogenic variants explains the evolution of CAMT into aplastic anemia because THPO also has an antiapoptotic and cell survival effect on HSCs. **Missense pathogenic variants** of *MPL* are associated with a milder disease course, a later presentation, a partial and transient increase in platelets during the first year of life after presentation, and a delayed onset, if any, of pancytopenia, indicating residual receptor function **(CAMT type II)**. Biologically active plasma THPO is consistently elevated in all patients with CAMT. A small proportion of patients with the clinical picture of CAMT have no pathogenic variants in *MPL*, but more recently have been found to have homozygous pathogenic variants in *THPO*.

Clinical Manifestations

Intracranial hemorrhage is a major risk; about 25% of the patients develop this complication either in utero (13%), at birth (4%), or within the first 4 weeks of life (7%). Patients with CAMT commonly have a petechial rash, bruising, or bleeding. Onset of symptoms may depend on the severity of pathogenic variants and ranges from birth to the first year of life. Most patients with CAMT have normal physical and imaging features. About 10–20% of published phenotypic CAMT cases involved physical anomalies. The most common anomalies are neurologic. Findings related to cerebellar and cerebral atrophy are frequent, and developmental delay is a prominent feature. Congenital heart disease is rare but includes atrial and ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta. Some of these occur in combinations. Other anomalies include abnormal hips or feet, kidney malformations, eye anomalies, and cleft or high-arched palate. Some patients have microcephaly and abnormal facies.

Laboratory Findings

Thrombocytopenia is the major laboratory finding in CAMT. At birth, most patients present with thrombocytopenia but not all. Typically, at first, thrombocytopenia appears with normal hemoglobin levels and WBC counts. Peripheral blood platelets are reduced or totally absent. As in other IBMFSs, RBCs may be macrocytic. Hemoglobin F may be elevated, and there may be increased expression of i antigen. Initial bone marrow aspirates and biopsy specimens show normal cellularity with marked reduction or absence of megakaryocytes. Most patients develop pancytopenia between 6 months to 2 years of age. In patients in whom aplastic anemia develops, bone marrow cellularity is decreased, with fatty replacement; erythropoietic and granulopoietic lineages are also symmetrically reduced.

Diagnosis

If thrombocytopenia persists beyond the neonatal period or is associated with adequate platelet transfusion response and no obvious precipitating cause such as infections or immunologic reactions, a bone marrow aspirate and biopsy are indicated. Deficient megakaryocytes in such cases suggest the diagnosis, and genetic analysis will confirm it. If CAMT occurs at birth or shortly after, it must be distinguished from other causes of inherited and acquired neonatal thrombocytopenia. Thrombocytopenia with absent radii **(TAR syndrome)** is distinguished from CAMT because radii are absent in TAR. The distinction from DC may be evident by a lack of mucocutaneous, neurologic, and immunologic findings that are characteristic of the early-onset forms of DC. Telomere lengths below the first percentile matched for age to healthy controls is characteristic of DC and not CAMT. CAMT blood lymphocytes do not show increased chromosomal breakage when exposed to DEB, distinguishing the disease from FA.

Cancer Predisposition

CAMT can evolve into MDS and AML, but the true risk cannot be defined because most patients undergo early transplantation. Typical course in patients with transformation includes thrombocytopenia, aplastic anemia, followed by MDS (e.g., with monosomy 7 or trisomy 8) and leukemia.

Therapy and Prognosis

The mortality rate from thrombocytopenic bleeding, complications of aplastic anemia, or leukemic transformation in patients with *MPL* **nonsense** pathogenic variants is close to 100% if bone marrow function is not improved. Patients with **missense** pathogenic variants have a milder course but may still have serious complications. HSCT is the only curative option. The majority of patients with CAMT who undergo HSCT are cured, especially if the procedure is performed with HLA-matched sibling donors. Before transplantation, platelet transfusion should be used carefully. Platelet count should not always be the sole indication for treatment, but symptoms such as clinical bleeding are an appropriate trigger. Single-donor, leuko-reduced platelets are preferred to minimize sensitization. In a patient who is a candidate for HSCT, all blood products should be irradiated and cytomegalovirus safe. The role of thrombomimetic agents such as eltrombopag or romiplostim might be suitable for some patients (CAMT type II) and need to be studied further. However, the promotion of fibrosis by these agents and the risk of MDS and leukemia in CAMT render HSCT the preferred treatment for patients with severe cytopenia. Romiplostim has shown good and sustained response in those with pathogenic variants in *THPO*, and there have been no reports of acute leukemia or MDS in this subgroup of CMPL patients, but the numbers of patients with pathogenic variants in *THPO* are small.

GATA2-RELATED DISORDERS

The *GATA2* gene codes for a hematopoietic transcription factor that is crucial for the proliferation and maintenance of early hematopoietic cells. Heterozygous germline pathogenic variants, inherited in an autosomal dominant fashion and that are spontaneous in the majority of cases, result in various phenotypes that range from mild cytopenia to severe immunodeficiency and myeloid neoplasia. Approximately two thirds of pathogenic variants in *GATA2* are null, and one third are missense substitutions. Germline pathogenic variants in *GATA2* have been recognized as a major MDS and AML predisposition syndrome. Approximately 150 unique *GATA2* germline pathogenic variants have been identified in about 550 patients.

Clinical manifestations include monocytopenia and *Mycobacterium avium* complex (MonoMAC syndrome) infections, MDS with lymphedema (Emberger syndrome), familial MDS/AML, primary MDS, and chronic neutropenia and dendritic cell, monocyte, and B and NK lymphoid deficiency (DCML deficiency). Hematologic presentation is variable. Some patients present with cytopenia, a hypocellular marrow and monocytopenia, whereas others have severe immunodeficiency, and others still present with MDS/AML and no preexisting relevant medical history or cytopenia. Immune deficiency results in HPV-related infections such as warts or generalized verrucosis, disseminated nontuberculous mycobacterial, and systemic bacterial and fungal infections. Recurrent respiratory tract infections can result in lung disease, such as pulmonary alveolar proteinosis. Few patients have autoimmune dysregulation manifesting as autoimmune cytopenia, arthritis, lupus, and others. Constitutional abnormalities, such as lymphedema, hydrocele, and congenital deafness, as well as abnormalities in pulmonary, CV, urogenital, and neurological systems have been observed in approximately 50% of patients (Fig. 517.3).

In children and adolescents with primary MDS, pathogenic variants in *GATA2* are a predominant germline predisposition accounting for 7% of all MDS cases, 15% of patients with advanced MDS, and 37% of patients

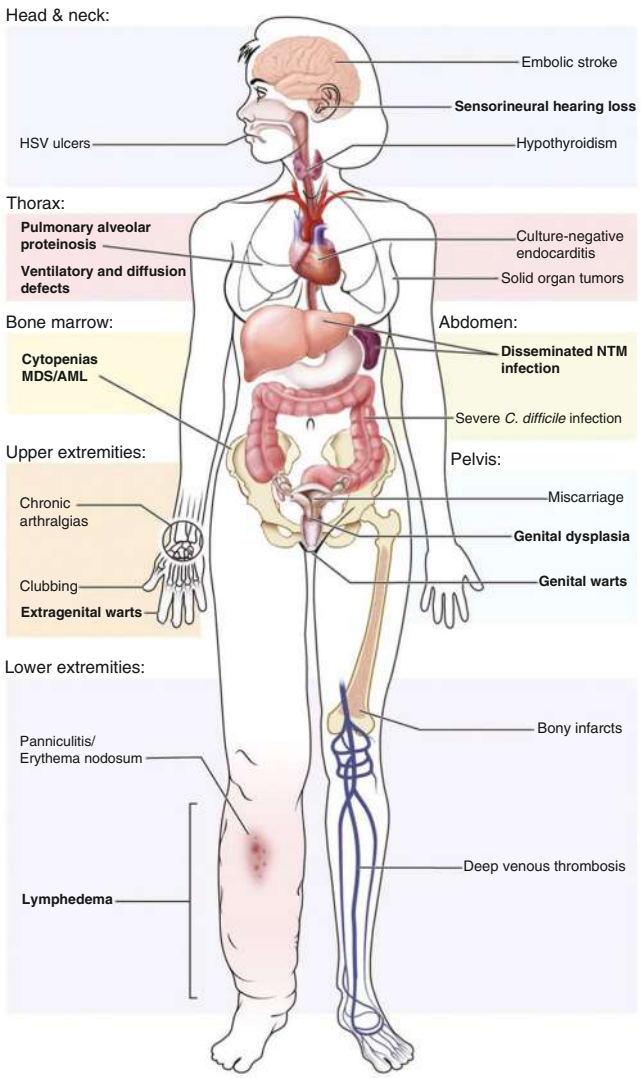

Fig. 517.3 Clinical features of GATA2 deficiency by organ system. Common clinical problems are indicated in bold. AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; NTM, non-tuberculous mycobacterium. *(From National Institute of Allergy and Infectious Diseases [NIAID] Health Information Fact Sheet.* https://www.niaid.nih.gov/sites/default/files/GATA2-Factsheet.pdf.*)*

with MDS and monosomy 7. Among children with MDS, the prevalence of *GATA2* pathogenic variants increases with age; 66% of adolescents with MDS and monosomy 7 carry germline *GATA2* pathogenic variants. Median age of diagnosis with *GATA2*-related MDS is approximately 10 years.

Patients should be followed by a hematologist with expertise in bone marrow failure/MDS and by an immunologist. Blood counts should be done every 3 months, and bone marrow aspirate and biopsy with cytogenetics should be carried out annually. HSCT is the only curative option for MDS and carries an overall survival ranging from 60–85% depending on donor type and MDS disease severity.

SAMD9/9L-RELATED DISORDER

Sterile alpha motif domain-containing protein 9 *(SAMD9)* and the paralogue gene *SAMD9*-like *(SAMD9L)* are located side-by-side on chromosome 7q21. They are interferon and tumor necrosis factor (TNF)-α responsive proteins that play a role in antiviral response, tumor suppression, inflammation, development, and endosomal fusion. Gain of function pathogenic variants, mostly missense, in these genes have variable penetrance. Thirty-eight pathogenic variants have been identified in approximately 110 patients.

Multiple organs can be affected in those with germline *SAMD9/9L* pathogenic variants, including the hematologic, immunologic, endocrine, and neurologic systems (see Table 517.2). The term **MIRAGE syndrome** was given to a constellation of abnormalities that include MDS, infection, restriction of growth (starting in utero), adrenal hypoplasia/insufficiency (with early onset), genital phenotypes (such as 46XY females and testicular dysgenesis), and enteropathy (often with reflux). Thrombocytopenia and anemia are often present at birth. In some patients, the anemia and thrombocytopenia resolve during infancy. Patients with *SAMD9L* pathogenic variants might show disease-specific neurological findings with very variable age of onset. Severe cerebellar ataxia is observed in some, whereas others have cerebellar atrophy, dysmetria, nystagmus, white matter abnormalities, and loss of Purkinje cells. The majority of patients in both syndromes have hematologic manifestations which range from single lineage cytopenia to pancytopenia with hypocellular marrow, MDS with monosomy 7, or deletion 7q. Some patients have nonsyndromic *SAMD9/9L* related MDS.

SAMD9/9L pathogenic variants are seen in 8–17% of pediatric MDS. The median age of presentation with SAMD9/9L related MDS is approximately 10 years. Ninety percent of children present in the early stage of MDS (refractory cytopenia of childhood), and another 10% present with advanced MDS. Transient monosomy 7 syndrome, the disappearance of monosomy 7 clones from the bone marrow, has been described in a few young children. It was hypothesized that pathogenic variants in the growth inhibitory genes, *SAMD9*/9L, confer gain of function that further suppress cell growth. Hence, monosomy 7, which depletes one allele of *SAMD9*/9L, reduces the growth inhibitory effect of the pathogenic variants. Somatic revertant mosaicism with expansion of benign, corrected hematopoiesis, has also been reported with normalization of blood counts and marrow cellularity for up to 20 years from diagnosis.

Monitoring and treatment depend on the degree of blood count abnormalities, the presence of MDS, and the presence of syndromic disease. Children who received HSCT for *SAMD9*/9L–related MDS showed an overall survival of 85% in one study.

OTHER INHERITED APLASTIC ANEMIAS

A substantial number of genes that are associated with bone marrow failure with pancytopenia have been identified with the emergence of whole genome screening methods (see Table 517.1). The specific gene-associated disorders may vary by phenotype but frequently include physical malformations, familial distribution, early age of disease onset, pancytopenia, and a risk of MDS and AML. Significant overlap exists between inherited pancytopenia syndromes and familial MDS and AML syndromes.

SRP72-Related Disorder

This autosomal dominant disorder is characterized by familial aplastic anemia and MDS. Some patients also have deafness. *SRP72* encodes for a signal recognition particle 72 protein. SRP72 is part of a ribonucleoprotein complex that mediates targeting of secretory proteins to the endoplasmic reticulum.

ERCC6L2-Related Disorder

This autosomal recessive disorder features multilineage cytopenia, MDS, and physical malformations. Neurological and cranial abnormalities are common in *ERCC6L2*-related disorder and include developmental delay, microcephaly, ataxia, dysmetria, generalized brain volume loss, retinal dystrophy, and low-set ears. ERCC6L2 regulates transcription by RNA Pol II through an interaction with DNA-PK; thereby, it promotes resolution of R loops and minimizes transcription-associated genome instability. The inherited BMF syndrome caused by biallelic pathogenic variants in ERCC6L2 is thus a primary transcription deficiency and may not cause a DNA repair defect.

Dubowitz Syndrome

Dubowitz syndrome is characterized by a peculiar facies, infantile eczema, small stature, and mild microcephaly. The face is small, with a shallow supraorbital ridge, a nasal bridge at the same level as the forehead, short palpebral fissures, variable ptosis, and micrognathia. There

is a predisposition to cancer in these patients. Approximately 10% of patients have hematopoietic disorders, including moderate pancytopenia, hypoplastic anemia, bone marrow hypoplasia, and full-blown aplastic anemia. Patients also have an increased risk of lymphoma and neuroblastoma. In about one third of patients, a genetic cause can be identified and includes biallelic pathogenic variants in *NSUN2* (an RNA methyltransferase), biallelic pathogenic variants in *LIG4* (a nuclear DNA ligase), or one copy deletion in several chromosome sites including 14q32, 17q24, -14q32, -17q24, and -19q13.

Seckel Syndrome

Seckel syndrome, sometimes called "bird-headed dwarfism," is a developmental disorder characterized by marked growth failure and mental deficiency, microcephaly, a hypoplastic face with a prominent nose, and low-set and/or malformed ears. Approximately 25% of patients have aplastic anemia or malignancies. The syndrome is genetically heterogeneous and is associated with biallelic pathogenic variants in *ATR*, *RBBP8*, *CENPJ*, *CEP152*, *CEP63*, *NIN,* or *ATRIP.* A deletion at the14q21-q22 locus has also been described.

Reticular Dysgenesis

Reticular dysgenesis is a severe form of immunodeficiency. It is mainly characterized by severe lymphopenia and neutropenia. Patients typically present with severe infections at birth or shortly thereafter. On physical examination, lymph nodes and tonsils are absent, and a thymic shadow on radiographs cannot be seen. Laboratory tests show absence of cellular and humoral immunity. Anemia, thrombocytopenia, and aplastic anemia may be evident. Bone marrow specimens show markedly reduced myeloid and lymphoid elements. Clonogenic assays of hematopoietic progenitors consistently show reduced to absent colony growth, suggesting that the disorder has its origins at the HSC level. The disease is inherited in an autosomal recessive fashion and is caused by biallelic pathogenic variants in mitochondrial *AK2*. The only curative therapy is HSCT.

Schimke Immunoosseous Dysplasia

Schimke immunoosseous dysplasia is an autosomal recessive disorder caused by pathogenic variants in the chromatin remodeling gene *SMARCAL1*. Patients have spondyloepiphyseal dysplasia with exaggerated lumbar lordosis and a protruding abdomen. There are pigmentary skin changes and abnormally discolored and configured teeth. T-cell immunodeficiency, progressive renal insufficiency, nephrotic syndrome, and early atherosclerosis are common causes of morbidity and mortality. Approximately 50% of patients have hypothyroidism; 50% have cerebral ischemia; 10% have bone marrow failure with neutropenia, thrombocytopenia, and anemia; and about 5% are predisposed to non-Hodgkin lymphoma. Eighty percent of patients have lymphopenia and altered cellular immunity. Bone marrow transplantation has been successfully applied to patients with bone marrow failure or immunodeficiency.

Cartilage Hair Hypoplasia

Cartilage-hair hypoplasia features metaphyseal dysostosis, short-limbed dwarfism, and fine sparse hair. Skeletal abnormalities may also include scoliosis, lordosis, chest deformity and varus lower limbs. GI abnormalities such as aganglionic megacolon have been reported. Most reported cases are of Finnish or Amish descent. In over 80% of patients, biallelic causal pathogenic variants in the noncoding RNA gene *RMRP* (RNA Component of Mitochondrial RNA Processing Endoribonuclease) can be found. Recently, biallelic pathogenic variants in *POP1* and in *NEPRO* have also been found to be associated with the disease. POP1 is a component of the RNAse-MRP endoribonuclease complex. NEPRO is a nucleolar and neural progenitor protein that interacts with multiple subunits of the RNase MRP complex. The complex plays a role in rRNA and in mitochondrial RNA processing by cleavage at a priming site during replication.

The hematological abnormalities include macrocytic anemia. In most cases the anemia is mild and self-limited, but a proportion of patients have severe and persistent anemia that requires regular RBC transfusions. Lymphopenia occurs in 65% of patients. Severe immunodeficiency can occur, often with severe anemia. Neutropenia has been reported in 25% of patients. HSCT has been used successfully to reconstitute the hemato/immunological system. Lymphomas and basal cell carcinoma occur at an increased frequency among these patients.

Pearson Syndrome

Pearson syndrome is a mitochondrial metabolic disorder with various bone marrow impairments. Insufficiency of the exocrine pancreas, caused by acinar cell atrophy and fibrosis, develops in 30% of cases. The syndrome is caused by a maternally inherited deletion of mitochondrial DNA (mtDNA) that encodes enzymes that are critical to oxidative phosphorylation. Severe macrocytic anemia requiring transfusions is commonly present within the first year of life, sometimes at birth. Bone marrow aspirate typically shows ringed sideroblasts and prominent vacuolization of erythroid and myeloid precursors. However, cases with pure red cell aplasia mimicking Diamond Blackfan anemia have been reported. Pancytopenia may occur alone or in association with hepatic failure, renal tubulopathy, and lactic acidosis. In such cases, platelet transfusions may also be required. Erythropoietin has been used for the anemia of renal failure. G-CSF is indicated to prevent infections in patients with severe neutropenia. HSCT is traditionally not recommended for the hematopoietic complications of Pearson syndrome due to their tendency to improve spontaneously in most cases; nonetheless, HSCT has been used in rare cases with Pearson syndrome, and engraftment was achieved. Interestingly, HSCT was associated not only with improved hematopoiesis but also with resolution of lactacidemia and acidosis. Patients may need pancreatic enzyme replacement if they develop malabsorption due to exocrine pancreatic insufficiency.

Immune-Related Pancytopenias

Primary immunodeficiency, autoimmune, lymphoproliferative, and hemophagocytic disorders can be associated with pancytopenia. Autoantibodies, hypersplenism, and bone marrow involvement are potential mechanisms. Recognizable disorders include common variable immunodeficiency syndrome (Chapter 165), hemophagocytic lymphohistiocytosis (Chapter 556.2), autoimmune lymphoproliferative syndrome (Chapter 174.7), and other lymphoproliferative disorders.

UNCLASSIFIED INHERITED BONE MARROW FAILURE SYNDROMES

Unclassified IBMFSs are heterogeneous disorders that in many cases were shown to present as new syndromes. In other cases, they may be atypical presentations of already characterized diseases. Unbiased approaches, such as study of comprehensive genetic panels of all known IBMFS genes regardless of the specific hematologic (e.g., isolated neutropenia or pancytopenia) or nonhematologic manifestations, or WES/genome sequencing, have proved this to be true. These disorders do not fit into classic genetic bone marrow failure diseases because all features of any one disease may not be evident at presentation. All are characterized by various cytopenias caused by underproductive bone marrow with or without physical manifestations. Compared with patients with classical disorders who present at a median age of 1 month, patients with unclassified disorders present later, at a median age of 9 months. Patients with unclassified IBMFSs can manifest single or multilineage cytopenia, aplastic anemia, MDS, or malignancy with variable expression of malformations. Table 517.5 lists criteria for the diagnosis, which include evidence of chronic bone marrow failure, in addition to factors that indicate a high likelihood of inherited disease (e.g., family history, congenital anomalies, young age at presentation).

When patients present later and without physical malformations, an acquired etiology cannot be ruled out. Detailed genetic testing for known IBMFS genes followed by approaches to discover novel genes and novel syndromes by WES/genome sequencing may identify an inherited etiology and define the disease.

Determining the actual genetic cause helps group patients according to diseases and guides counseling and proper medical care. Implementing a treatment plan is urgent in many cases. In such patients, the management should be according to the type of complications that the patient has at presentation and the lessons that can be learned from published experience on unclassified cases in the literature.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 517.5 The Canadian Inherited Marrow Failure Registry Criteria for Unclassified Inherited Bone Marrow Failure Syndromes

FULFILLS CRITERIA 1 AND 2:
1. Does not fulfill criteria for any categorized inherited bone marrow failure syndrome*
2. Fulfills both of the following:
FULFILLS AT LEAST TWO OF THE FOLLOWING:
a. Chronic cytopenia(s) detected on at least two occasions over at least 3 months†
b. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis‡
c. High fetal hemoglobin for age‡
d. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency)
FULFILLS AT LEAST ONE OF THE FOLLOWING:
a. Family history of bone marrow failure
b. Presentation at age <1 year
c. Anomalies involving multiple systems to suggest an inherited syndrome

*The criteria for most common syndromes are described in Tsangaris E, Klaasen R, Fernandez CV, et al. Genetic analysis of inherited bone marrow failure syndromes from one prospective, comprehensive, and population-based cohort and identification of novel mutations. *J Med Genet*. 2011;48:618–628.

†Cytopenia is defined according to the affected cell: neutropenia, neutrophil count of $<1.5 \times 10^9$/L; thrombocytopenia, platelet count of $<150 \times 10^9$/L; anemia, hemoglobin concentration of >2 standard deviations below mean, adjusted for age.

‡Hemoglobinopathies with ineffective erythropoiesis and high fetal hemoglobin should be excluded by clinical or laboratory testing.

Modified from Teo JT, Klaassen R, Fernandez CV, et al. Clinical and genetic analysis of unclassifiable inherited bone marrow failure syndromes. *Pediatrics*. 2008;22:e139–e148.

Table 518.1 Etiology of Acquired Aplastic Anemia

Radiation, Drug, and Chemicals
Predictable: chemotherapy, benzene
Idiosyncratic: chloramphenicol, antiepileptics, gold, 3,4-methylenedioxymethamphetamine, nonsteroidal antiinflammatory drugs (NSAIDs), antibiotics
See also Table 518.2
Viruses
Cytomegalovirus
Epstein-Barr
Hepatitis B
Hepatitis C
Hepatitis non-A, non-B, non-C (seronegative hepatitis)
HIV
COVID-19
Immune Diseases
Eosinophilic fasciitis
Hypoimmunoglobulinemia
Thymoma
Common variable immunodeficiency syndrome *(NFKB1)*
Pregnancy
Paroxysmal Nocturnal Hemoglobinuria
Marrow Replacement
Leukemia
Myelodysplasia
Myelofibrosis
Autoimmune
Nutritional
Vitamin B_{12}
Folate
Copper
Other
Cryptic dyskeratosis congenita (no physical stigmata)
Telomerase reverse transcriptase haploinsufficiency
Atypical presentation of genetic marrow failure syndromes
Leishmaniasis

Chapter 518

Acquired Pancytopenias

John H. Fargo and Jeffrey D. Hord

ETIOLOGY AND EPIDEMIOLOGY

Therapeutic and recreational drugs, environmental toxins, infectious agents, radiation, and immune disorders can result in pancytopenia by direct destruction of hematopoietic progenitors, disruption of the marrow microenvironment, or immune-mediated suppression of marrow elements (Tables 518.1 and 518.2). A careful history of exposure to known risk factors should be obtained for every child presenting with pancytopenia. Even in the absence of the classic associated physical findings, the possibility of a genetic predisposition to bone marrow failure must also be considered (see Chapter 517). Many cases of acquired marrow failure in childhood are idiopathic, in that no causative agent is identified. Many are probably immune mediated through cytotoxic T lymphocytes and cytokine destruction of marrow stem and progenitor cells. Patients with an initial diagnosis of acquired aplastic anemia may have developed somatic pathogenic variants in genes associated with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Clonal hematopoiesis resulting from these acquired somatic genetic variants may over time lead to the development of MDS or AML. The overall incidence of **acquired aplastic anemia** is relatively low, with an approximate incidence in both children and adults in the United States and Europe of 2–6 cases per 1 million population per year. The incidence is higher in Asia, with as many as 14 cases per 1 million per year in Japan.

Severe bone marrow suppression can develop after exposure to many different therapeutic drugs and environmental chemicals, including certain chemotherapeutic agents, insecticides, antibiotics, anticonvulsants, nonsteroidal antiinflammatory drugs (NSAIDs), and recreational drugs. Some of the most notable agents are benzene, chloramphenicol, gold, and 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy").

A number of viruses can either directly or indirectly result in bone marrow failure. Parvovirus B19 is classically associated with isolated red blood cell (RBC) aplasia, but in patients with sickle cell disease or immunodeficiency, it can result in transient pancytopenia (see Chapter 298). Prolonged pancytopenia can occur after infection with many of the hepatitis viruses, herpesviruses, Epstein-Barr virus (see Chapter 301), cytomegalovirus (see Chapter 302), and HIV (see Chapter 322).

Immune-mediated acquired pancytopenia is also found to be prominent among acute, sporadic cases of aplastic anemia. Immunologic conditions, such as seronegative hepatitis, eosinophilic fasciitis, and thymoma, have been implicated in aplastic anemia.

Patients with evidence of bone marrow failure should also be evaluated for inherited forms of marrow failure, **paroxysmal nocturnal hemoglobinuria** (PNH; see Chapter 510), and collagen vascular diseases. Pancytopenia without peripheral blasts may be caused by bone marrow replacement by malignant cells including leukemia and solid tumor cells, such as neuroblastoma.

Table 518.2 Drugs and Toxins Associated with Aplastic Anemia

DOSE DEPENDENT
Antineoplastic Agents
Antimetabolites: fluorouracil, mercaptopurine, 6-thioguanine, methotrexate, cytosine arabinoside, gemcitabine, fludarabine, cladribine, pentostatin, hydroxyurea
Alkylating and cross-linking agents: busulfan, cyclophosphamide, chlorambucil, nitrogen mustard, melphalan, cisplatin, carboplatin, ifosfamide, nitrosoureas (BCNU and CCNU), mitomycin C
Cytotoxic antibiotics: daunorubicin, doxorubicin, mitoxantrone
Plant alkaloids: vinblastine, paclitaxel
Topoisomerase inhibitors: etoposide
Antimicrobial Agents
Chloramphenicol, dapsone, fluorocytosine
Antiinflammatory and Antirheumatic Agent
Colchicine
Insecticides
Chlordane, chlorophenothane (DDT), lindane, parathion
Other Chemicals
Benzene
Benzene-containing chemicals: kerosene, chlorophenols, carbon tetrachloride

DOSE INDEPENDENT*
Idiosyncratic, likely immune mediated
Antimicrobial Agents
Chloramphenicol, dapsone, sulfonamides, tetracycline, methicillin, amphotericin, quinacrine, chloroquine, pyrimethamine
Anticonvulsants
Hydantoins, carbamazepine, phenacemide, primidone, ethosuximide
Antiinflammatory Agents
Phenylbutazone, indomethacin, ibuprofen, oxyphenbutazone, sulindac, naproxen
Antiarrhythmic Drugs
Quinidine, tocainide, procainamide
Metals
Gold, arsenic, mercury, bismuth
Antihistamines
Cimetidine, ranitidine, chlorpheniramine, pyrilamine, tripelennamine
Diuretics
Acetazolamide, furosemide, chlorothiazide, methazolamide
Hypoglycemic Agents
Chlorpropamide, tolbutamide
Antithyroid Drugs
Propylthiouracil, potassium perchlorate, methylthiouracil, methimazole, carbimazole
Antihypertensive Agents
Methyldopa, enalapril, captopril
Sedatives
Chlordiazepoxide, chlorpromazine, meprobamate, prochlorperazine

*Most agents listed in this group should be considered to be possibly associated with aplastic anemia.
From Bagby GC. Aplastic anemia and related bone marrow failure states. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier, 2020: Table 156.2.

PATHOLOGY AND PATHOGENESIS

The hallmark of aplastic anemia is peripheral pancytopenia, coupled with hypoplastic or aplastic bone marrow. The severity of the clinical course is related to the degree of myelosuppression. **Severe aplastic anemia** is defined as a condition in which ≥2 cell components have become seriously compromised (absolute neutrophil count <500/mm^3, platelet count <20,000/mm^3, reticulocyte count <1% after correction for hematocrit) in a patient whose bone marrow biopsy material has <30% cellularity. Approximately 65% of patients who first present with **moderate aplastic anemia** (absolute neutrophil count 500–1,500/mm^3, platelet count 20,000–100,000/mm^3, reticulocyte count <1%) eventually progress to meet the criteria for severe disease if they are simply observed. Bone marrow failure may be a consequence of a direct cytotoxic effect on hematopoietic stem cells (HSCs) from a drug or chemical or may result from either cell-mediated or antibody-dependent cytotoxicity. There is strong evidence that many cases of idiopathic aplastic anemia are caused by an immune-mediated process, with increased circulating cytotoxic T lymphocytes producing cytokines (interferon-γ) that suppress hematopoiesis. Abnormal telomere length and telomerase activity in granulocytic precursors of patients with aplastic anemia suggest that early apoptosis of hematopoietic progenitors may play a role in the pathogenesis of this disease.

Cytogenetic abnormalities associated with aplastic anemia include uniparental disomy of 6p, monosomy 7/deletion of 7q, and trisomy 8, 6, or 15. Genes associated with aplastic anemia include telomere complex genes *(TERT, TERC)* and *BCOR/BCORL, PIGA, DNMT3A,* and *ASXL1*.

CLINICAL MANIFESTATIONS, LABORATORY FINDINGS, AND DIFFERENTIAL DIAGNOSIS

Pancytopenia results in increased risks of cardiac failure, fatigue, infection, and bleeding. Acquired pancytopenia is typically characterized by anemia, leukopenia, and thrombocytopenia in the setting of elevated serum cytokine values. Other treatable disorders, such as cancer, collagen vascular disorders, PNH, and infections, that may respond to specific therapies (IV immunoglobulin for parvovirus), should be considered in the differential diagnosis. Careful examination of the peripheral blood smear for RBC, leukocyte, and platelet morphologic features is important. A reticulocyte count should be performed to assess erythropoietic activity. In children, the possibility of *congenital* pancytopenia must always be considered, and chromosomal breakage analysis should be performed to evaluate for **Fanconi anemia** (see Chapter 517) and telomere length to evaluate for telomeropathies. The presence of fetal hemoglobin suggests congenital pancytopenia but is not diagnostic. To assess for possible PNH, flow cytometric analysis of erythrocytes and granulocytes for CD55 and CD59 is the most sensitive test. Bone marrow examination should include both aspiration and biopsy, and the marrow should be carefully evaluated for morphologic features, cellularity, and cytogenetic abnormalities.

TREATMENT

The treatment of children with acquired pancytopenia requires comprehensive supportive care coupled with an attempt to treat the underlying etiology for marrow failure. For patients with a human leukocyte antigen (HLA)–matched family member donor, **allogeneic hematopoietic stem cell transplantation (HSCT)** offers a 90% chance of long-term survival. Preparative regimens vary but typically consist of cyclophosphamide, fludarabine, and horse antithymocyte globulin (ATG). Preliminary data also suggest that children with severe aplastic anemia can be successfully transplanted using *alemtuzumab* (humanized monoclonal antibody against CD52 on lymphocytes)–based conditioning. The risks associated with bone marrow transplantation include the immediate complications of transplantation, graft failure, and graft-versus-host disease. Late adverse effects associated with transplantation may include secondary cancers, cataracts, short stature, hypothyroidism, and gonadal dysfunction (see Chapters 179 and 180). Only approximately 20% of patients have an HLA-matched family member donor, so matched-related HSCT is not an option for the majority of patients.

For patients without a sibling donor, the major form of therapy is **immunosuppression** with horse ATG and cyclosporine, with a response rate of 60–70%. The median time to response is 6 months. As many as 30–60% of patient responders experience relapse after discontinuation of immunosuppression, and some patients must continue cyclosporine for several years to maintain a hematologic

response. Among those who relapse after immunosuppression, approximately 50% show response to a second course of ATG and cyclosporine. To accelerate neutrophil recovery, a hematopoietic colony-stimulating factor (e.g., granulocyte CSF, granulocyte-macrophage CSF) is sometimes added to ATG and cyclosporine for treatment of patients with very severe neutropenia (absolute neutrophil count <200/mm^3), but there is no clear evidence that this treatment influences response rate or survival. Higher baseline reticulocyte count correlates with a higher probability of response to immunosuppression and survival. There is an inverse correlation between telomere length and the probability of relapse after immunosuppression.

For patients who show no response to immunosuppression or who experience relapse after immunosuppression, **matched-unrelated HSCT and T-cell–depleted haploidentical family member–donor HSCT** are treatment options, with a response rate approaching 90%. Cord blood transplants have been performed in this refractory group of pediatric patients, with survival approximating 90%. Ongoing studies using **eltrombopag** (an oral thrombopoietin mimetic agent) have shown promise in patients ≥15 years of age (mostly adults) with refractory disease. The use of eltrombopag resulted in a hematologic response with improvements in platelet and neutrophil counts and hemoglobin levels in over half the patients. In patients who responded, bone marrow biopsies demonstrated trilineage normalization of hematopoiesis, with some showing a durable response. **High-dose cyclophosphamide** has been used successfully in the treatment of patients who are not good candidates for HSCT and have not had an adequate response to immunosuppression. This therapy leads to prolonged severe pancytopenia, increasing the risk of life-threatening infection, especially fungal infections. Other therapies that have been used in the past with inconsistent results include androgens, corticosteroids, and plasmapheresis. **Alemtuzumab** as monotherapy in relapsed disease showed improved response rates and 3-year survival compared to additional courses of ATG and cyclosporine.

COMPLICATIONS

The major complications of severe pancytopenia are predominantly related to the risk of life-threatening bleeding from prolonged thrombocytopenia or to infection secondary to protracted neutropenia. Patients with protracted neutropenia as a result of bone marrow failure are at risk not only for serious bacterial infections but also for invasive mycoses. Patients who have been transfused with RBCs regularly over a long period are at increased risk of developing alloantibodies to RBC antigens and may require iron chelation therapy for transfusional iron overload. The general principles of supportive care that have evolved from the use of chemotherapy-related myelosuppression to treat patients with cancer should be fully extended to the care of patients with acquired pancytopenia.

PROGNOSIS

Spontaneous recovery from pancytopenia rarely occurs. If left untreated, severe pancytopenia has an overall mortality rate of approximately 50% within 6 months of diagnosis and of >75% overall, with infection and hemorrhage being the major causes of morbidity and mortality. The majority of children with acquired severe aplastic anemia show response to allogeneic marrow transplantation or immunosuppression, leaving them with normal or near-normal blood cell counts.

PANCYTOPENIA CAUSED BY MARROW REPLACEMENT

Processes that either infiltrate or replace the bone marrow can manifest as acquired pancytopenia. Infiltration can be caused by malignancy (classically, neuroblastoma or leukemia) or result from myelofibrosis, MDS, or osteopetrosis. Although uncommon, evidence of hypoplastic anemia can precede the onset of acute leukemia, generally by a few months. This relationship is important to appreciate in evaluating and monitoring children who present with what appears to be acquired aplastic anemia. Morphologic examination of the peripheral blood and bone marrow and marrow cytogenetic studies are critically important in making the diagnoses of leukemia, myelofibrosis, and MDS.

Myelodysplasia is very rare in children, but when it occurs, its clinical course is more aggressive than the same category of MDS in adults. Pediatric MDS can be subdivided into **refractory cytopenia of childhood** (peripheral blasts <2% and marrow blasts <5%) and **MDS with excess blasts** (peripheral blasts 2–19% and/or marrow blasts 5–19%). Disease in children with >20% blasts is usually defined as AML.

Myelodysplastic syndromes are a heterogeneous group of bone marrow failure disorders that have in common ineffective hematopoiesis that leads to pancytopenia over time. In one group, there are somatic variants (in >25 genes) leading to MDS. In another group, usually in younger patients (<55 years), there is autoimmune suppression of hematopoiesis by clonal expansion of T lymphocytes, particularly in those patients who look similar to patients with idiopathic aplastic anemia. In all patients, other causes of MDS (medications and vitamin B_{12}, folate, or copper deficiencies) must be ruled out.

A number of inherited conditions are associated with an increased risk for development of MDS, including Down syndrome, severe congenital neutropenia, Noonan syndrome, Fanconi anemia, trisomy 8 mosaicism, neurofibromatosis, Shwachman-Diamond syndrome, and some familial MDS syndromes caused by pathogenic variants in *ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1,* and *SRP72* genes. Significant clonal abnormalities are found within the marrow of approximately 50% of patients with MDS, with monosomy 7 being most common but prognostically neutral. Those with a structurally complex karyotype have a very poor outcome (see Chapter 517).

The transition time from pediatric MDS to acute leukemia is relatively short, 14–26 months, so aggressive treatment such as HSCT must be considered shortly after diagnosis. With allogeneic HSCT, the survival rate is approximately 60%. One exception to such an aggressive therapeutic approach is MDS and AML in children with Down syndrome because these diseases in this specific population are very responsive to conventional chemotherapy, with long-term survival rates >80%.

The decision on how to treat a child with MDS who lacks a suitable HSC donor should be made with the specific clonal abnormality found within the child's marrow taken into consideration. Lenalidomide produces the best responses among patients who have the chromosomal abnormality 5q−. Immunosuppressive therapy with ATG and cyclosporine is most effective in patients with trisomy 8, especially in the presence of a PNH clone. Imatinib mesylate targets mutations in the tyrosine kinase receptor family of genes found in patients with t(5;12) and del(4q12). The DNA hypomethylating agents azacitidine and decitabine have also been used in treating MDS without a known molecular target and have some effect.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 6

Blood Component Transfusions

Chapter 519

Red Blood Cell Transfusions and Erythropoietin Therapy

Patricia E. Zerra and Cassandra D. Josephson

Red blood cells (RBCs) are transfused to increase the oxygen-carrying capacity of the blood, with the goal to increase or maintain satisfactory tissue oxygenation. This goal may not be achieved simply by increasing the hemoglobin (Hb) concentration or hematocrit (Hct) by an RBC transfusion because tissue oxygenation depends on several additional factors, including oxygen off-loading from RBCs, microvascular blood flow, and diffusion of oxygen into tissue cells. Although some attempts have been made to accurately relate posttransfusion Hb or Hct values to changes in posttransfusion tissue oxygenation (e.g., improvements in the ratio of cerebral vs mesenteric oxygenation patterns assessed by serial near-infrared spectroscopy measurements), decisions to transfuse RBCs per physiologic indications, rather than degree of anemia, remain investigational. This information can be applied to approaches for transfusion in both preterm infants/neonates and children/adolescents. However, neonates, especially extremely low birthweight infants (≤1,000 g), are not "small" children (i.e., RBC physiology and pathophysiology of anemia of prematurity are unique); thus RBC transfusions for neonates and children are considered separately.

RBC TRANSFUSION IN CHILDREN AND ADOLESCENTS

Guidelines for RBC transfusions in children and adolescents are based on maintaining a specified Hb or Hct level considered to be optimal (per the best evidence available) for the clinical condition present at the time of transfusion. The guidelines are similar to those for adults (Table 519.1). Transfusions may be given more stringently to children because normal Hb levels are lower in healthy children than in adults and, as is often the case, most children do not have the underlying multiorgan, cardiorespiratory, and vascular diseases that develop with aging in adults to suggest a need for RBC transfusions. As a result, children may compensate better for RBC loss than elderly adults, thus requiring less RBC transfusion support. In general, there is increasing enthusiasm for applying patient blood management strategies, encompassing conservative transfusion practices (i.e., accepting lower pretransfusion Hct values to "trigger" an RBC transfusion) to all patient ages with evidence-based support.

In the **perioperative period,** it is unnecessary for most children to maintain Hb of ≥8 g/dL, a level frequently desired for adults. Instead, Hb of ≥7 g/dL is an acceptable level, although the optimal value for individual patients is based on clinical and laboratory circumstances, as influenced by the following factors. The desired preoperative Hb level should consider the estimated blood loss for the surgical procedure planned and the rate of bleeding. There should be a compelling reason to prescribe any postoperative RBC transfusion, such as continued bleeding with hemodynamic instability because most children (without continued bleeding) can restore their RBC mass with iron therapy (in a relatively short time).

Table 519.1 Guidelines for Pediatric Red Blood Cell Transfusions*†

CHILDREN AND ADOLESCENTS
1. Maintain stable status with acute loss of >25% of circulating blood volume.
2. Maintain hemoglobin >7.0 g/dL† in the perioperative period.
3. Maintain hemoglobin >12.0 g/dL with *severe* cardiopulmonary disease.
4. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation.
5. Maintain hemoglobin >7.0 g/dL with *symptomatic* chronic anemia.
6. Maintain hemoglobin >7.0 g/dL with *marrow failure*.
INFANTS ≤4 MO OLD
1. Maintain hemoglobin >12.0 g/dL with *severe* pulmonary disease.
2. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation.
3. Maintain hemoglobin >10.0 g/dL with *moderate* pulmonary disease.
4. Maintain hemoglobin >12.0 g/dL with *severe* cardiac disease.
5. Maintain hemoglobin >10.0 g/dL preoperatively and during *major* surgery.
6. Maintain hemoglobin >7.0 g/dL postoperatively.
7. Maintain hemoglobin >7.0 g/dL with *symptomatic* anemia.

*Words in *italics* must be defined for local transfusion guidelines.
†Pretransfusion blood hemoglobin (Hb) level (convert to hematocrit values if preferred by multiplying Hb values by 3) "triggering" an RBC transfusion. Hb values to maintain vary among published reports, and the guideline values to maintain should be determined locally to fit the practices judged to be optimal by local physicians.

The most important measures in the treatment of **acute hemorrhage** are to control the hemorrhage and, if blood loss is modest, to restore the circulating blood volume and tissue perfusion with crystalloid or, less often, colloid solutions. If the estimated blood loss is >25% of the circulating blood volume (>15 mL/kg of an estimated 60 mL/kg total estimated blood volume) *and* the patient's condition is unstable despite initial intravenous (IV) fluids, RBC transfusions should be given without undue hesitation, along with plasma transfusions at a 1:1 ratio of RBC/plasma volumes. Some experts recommend transfusing platelets early if bleeding is sustained or "massive" (i.e., approximating one blood volume or 60 mL/kg, which may occur very quickly in infants and small pediatric patients). Details of combined RBC and plasma transfusions, the volume ratio transfused, and considerations for adding platelet transfusions to treat bleeding patients are controversial. Accordingly, each hospital should develop and follow a "massive transfusion" protocol to ensure consistent practices.

In critically ill children with severe cardiac or pulmonary disease requiring assisted ventilation, it is common practice to maintain the Hb level close to the normal range, although the efficacy of this practice has not been well documented. A similar approach is used for children with acute cardiac, pulmonary, or cardiopulmonary disorders managed with extracorporeal membrane oxygenation (ECMO).

The pretransfusion Hb level or Hct that should "trigger" an RBC transfusion remains controversial (i.e., restrictive or a low pretransfusion level vs liberal or a high pretransfusion level) despite a substantial amount of published information, including randomized clinical trials. The current trend in critical care settings is to transfuse RBCs conservatively, following restrictive guidelines, and to permit modest anemia because there appears to be no disadvantage to conservative/restrictive transfusion practices, and some patients with Hb levels maintained close to the normal range by RBC transfusions (i.e., liberal guidelines) have poorer outcomes. Studies in critically ill adults demonstrated better outcomes when Hb level was maintained at 7–9 g/dL vs 10–12 g/dL. Anemic adults with *significant cardiac disease* did better with Hb level maintained at 13 g/dL rather than 10 g/dL. A similar study in children admitted to intensive care units found no inferiority when RBC

transfusions were given by restrictive guidelines *(transfusion threshold of 7 g/dL)*. It must be remembered that the children studied were in stable clinical status and needed few transfusions. Therefore, results of the trial cannot be automatically generalized to all patients admitted to ICUs because unstable critically ill children (who were not included in the study) may need more liberal RBC transfusion approaches.

With **chronic anemia,** the decision to transfuse RBCs should not be based solely on blood Hb levels because children compensate well and may be asymptomatic despite low Hb levels. Patients with iron-deficiency anemia are often treated successfully with oral iron alone, even at Hb levels <5 g/dL. Factors other than Hb concentration to be considered in the decision to transfuse RBCs include (1) the patient's symptoms, signs, and compensatory capacities; (2) the presence of underlying cardiorespiratory, vascular, and central nervous system disease; (3) the cause and anticipated course of the anemia; and (4) alternative therapies, such as recombinant human erythropoietin (EPO) therapy, which is known to reduce the need for RBC transfusions and to improve the overall condition of children with chronic renal insufficiency (see Chapter 572.2). In anemias that are likely to be permanent, it is also important to balance the detrimental effects of the degree of long-standing anemia on growth and development against the potential toxicity associated with repeated transfusions (i.e., iron overload and risks of transfusion-transmitted diseases) given to maintain the Hb concentration at a specified level. RBC transfusions for disorders such as sickle cell anemia and thalassemia are discussed in Chapters 511.1 and 511.10.

RBC TRANSFUSION IN PRETERM INFANTS AND NEONATES

For neonates, almost all aspects of RBC transfusions remain controversial—the accepted indications for RBC transfusions, restrictive vs liberal pretransfusion Hb/Hct levels, optimal RBC product to be transfused, and fresh vs stored RBC units—and clinical practices vary greatly. Generally, RBCs are given to maintain an Hb value believed to be the most desirable for each neonate's clinical status. Restrictive guidelines (i.e., lower pretransfusion Hb/Hct levels) have been compared to more liberal transfusion practices, but both short-term and long-term results and outcomes have been inconsistent and controversial, particularly as to neurodevelopmental status. Two multicenter randomized controlled trials showed no difference in survival or neurodevelopmental outcome in premature infants receiving RBC transfusion based on liberal versus restrictive Hb thresholds. Importantly, a lower Hb threshold was *not inferior* to a higher threshold for RBC transfusion. However, these studies had limitations, and accordingly, conventional guidelines are recommended to avoid problems caused by undertransfusion or overtransfusion (see Table 519.1).

During the first few weeks of life, all neonates experience a decline in circulating RBC mass caused by physiologic factors and, in sick premature infants, by phlebotomy blood losses. In healthy term infants, the nadir Hb value rarely falls to <11 g/dL at age 10-12 weeks. This benign drop in Hb does not require transfusions. In contrast, the decline occurs earlier and is more pronounced in premature infants, in whom the mean Hb concentration falls to approximately 7 g/dL in infants weighing <1 kg at birth, resulting in the **anemia of prematurity**, for which there often is need for RBC transfusions, particularly when the anemia is worsened by blood draws for laboratory testing.

A key reason that the nadir Hb values of premature infants are lower than those of term infants is the premature infant's relatively diminished plasma EPO level in response to anemia (see Chapters 139 and 496). Another factor is the rapid disappearance of EPO from infant plasma (i.e., accelerated metabolism). Low plasma EPO levels provide a rationale for the possible use of recombinant EPO in the treatment of anemia of prematurity; treatment with EPO and iron effectively stimulate neonatal erythropoiesis. Recombinant EPO has not been widely accepted as a treatment for anemia of prematurity (see Chapter 139).

Many low birthweight preterm infants need RBC transfusions (see Table 519.1). Although the practice to maintain a very high Hb level >13 g/dL (or Hct >40%) was once widely recommended, currently more restrictive guidelines have been suggested. However, one prospective, observational, multisite, birth cohort study of very low birthweight infants (≤1500 g) found a sixfold increased risk of necrotizing enterocolitis (NEC) when an infant's hemoglobin was ≤8 g/dL. Importantly, RBC transfusion in a given week did not significantly increase the rate of NEC in this population. Consistent with the rationale for oxygen delivery in neonates with severe respiratory disease, it also seems appropriate to keep the Hb value relatively high in neonates with *severe cardiac disease* leading to either cyanosis or congestive heart failure, but convincing and consistent data are lacking.

The optimal Hb level for neonates facing major surgery has not been established. However, it seems reasonable to begin surgery in neonates with the Hb level no lower than 10 g/dL (hematocrit >30%) and to maintain that value during major surgery because even modest blood loss will have a relatively large effect on the small blood volume of the neonate. Neonates with underlying pulmonary problems have limited ability to compensate for anemia due to the inability to increase ventilation and the inferior off-loading of oxygen because of the diminished interaction between fetal Hb and 2,3-diphosphoglycerate. Postoperatively, a lower pretransfusion Hb value should be followed to "trigger" a transfusion.

Stable neonates do not require RBC transfusion, regardless of their blood Hb levels, unless they exhibit clinical symptoms attributable to anemia. Proponents of RBC transfusions for symptomatic anemia in preterm neonates believe that the low RBC mass contributes to tachypnea, dyspnea, tachycardia, apnea and bradycardia, feeding difficulties, and lethargy, which can be alleviated by transfusion of RBCs. However, anemia is only one of several possible causes of these problems, and RBC transfusions should only be given when clinical benefit seems likely.

RBC PRODUCT AND DOSE

The RBC product of choice to transfuse neonates, infants, children, and adolescents is prestorage *leukocyte-reduced* RBCs suspended in an anticoagulant/preservative storage solution at Hct of approximately 60–70% for storage up to 35–42 days. For those infants with birthweight <1,500 g, *irradiation* is recommended to prevent transfusion-associated graft-versus-host disease. Additionally, both leukoreduction and cytomegalovirus-seronegative RBC units have been recommended by some (estimated risk of *transfusion-transmission cytomegalovirus* [TT-CMV] infection: 0–0.3% per unit) as first-line therapy to prevent TT-CMV. However, given the low risks of TT-CMV with improvements in modern leukoreduction techniques, others have recommended use of leukoreduced blood without need for CMV antibody testing as an acceptably safe and low-risk alternative. RBC transfusion should not be delayed if CMV-negative blood is unavailable, and CMV-untested leukoreduced blood should be used because the risk of TT-CMV is relatively low, with possibly more harm to the patient if transfusion is withheld or delayed. The usual dose is 10–15 mL/kg, but transfusion volumes vary greatly depending on clinical circumstances (continued vs arrested bleeding, hemolysis). For neonates, some prefer a centrifuged RBC concentrate (Hct 70–90%). Unless transfusions are being given to treat rapid bleeding, RBCs are infused slowly (over 2–4 hours) at a dose of approximately 10–15 mL/kg. In this small-volume setting, because of the small quantity of extracellular fluid transfused and the slow rate of infusion, the type of RBC anticoagulant/preservative solution does not pose any risk for premature infants when the dose does not exceed 20 mL/kg. However, the additive solutions (e.g., AS-1, AS-3, AS-5) have not been studied by comparative randomized clinical trials in the setting of >20 mL/kg dosing or massive transfusion settings such as cardiopulmonary bypass, ECMO, or massive transfusion for trauma. Although a few anecdotal reports suggest RBCs in additive solutions are safe for large-volume transfusions while awaiting more definitive information, some hospitals that manage these complex neonates and children maintain separate inventories of different RBC products earmarked either for neonates and infants (e.g., citrate-phosphate-dextrose or citrate-phosphate-dextrose-adenine) or for older children (e.g., additive solutions).

STORAGE AGE OF RBC UNITS

The historical practice of transfusing fresh RBCs (<7 days of storage) for the small-volume (15 mL/kg) transfusions commonly given was supplanted several years ago in most centers by reserving a single unit of RBCs for an infant, from which multiple aliquots were obtained for transfusions as needed throughout the 42 days of storage. Concerns about high concentrations of extracellular potassium, loss of 2,3-diphosphoglycerate, altered RBC shape and deformability, and nitric oxide quenching were found not to pose clinically significant problems. Preterm neonates allocated to "fresh RBC" (<7 days' storage) transfusions vs "stored RBC" (up to 42 days' storage) transfusions have no advantage for fresh RBC transfusions in altering the composite clinical outcome of mortality, plus NEC, retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage, or of the individual disorders.

For children weighing >30 kg who are to undergo elective surgery for whom RBC transfusions are likely to be needed, autologous RBC transfusions offer an alternative to donor allogeneic RBCs. **Preoperative autologous** blood collections from the patient occur up to 6 weeks before the surgery and require careful considerations for the volume to be drawn, vascular access, and use of EPO and iron to help restore the donated RBCs. **Acute normovolemic hemodilution** occurs in the preoperative period, in which blood is withdrawn from the patient and replaced with saline, a task often difficult in centers without experience in the process. **Salvaged autologous blood** is collected from blood loss during the operation but is impractical unless the volume of blood salvaged is fairly large to permit washing and transfusion of a significant number of RBCs. Because of all these difficulties, plus the relative safety of the usual allogeneic blood supply, autologous RBC transfusions are not typically used in the pediatric setting.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 520

Platelet Transfusions

Patricia E. Zerra and Cassandra D. Josephson

CHILDREN AND ADOLESCENTS

Guidelines for platelet (PLT) support of children and adolescents with quantitative and qualitative PLT disorders are similar to those for adults, in whom the risk of life-threatening bleeding occurring after injury or spontaneously can be related to the severity of thrombocytopenia, although somewhat imprecisely (Table 520.1).

For children and adolescents with overt bleeding, therapeutic PLT transfusions should be given when the blood PLT count falls below 50×10^9/L and repeated as needed to maintain the PLT count $>50 \times 10^9$/L during bleeding and for 48 hours after bleeding ceases to allow the clot to "stabilize." Similarly, for a major invasive procedure (e.g., surgical), the PLT count should be maintained $>50 \times 10^9$/L until any bleeding that occurs ceases and the patient is stable. For minor invasive procedures (e.g., lumbar puncture, intravascular catheter placement), practices vary. It is reasonable to maintain the PLT count $>25 \times 10^9$/L, although these procedures often are performed in children with cancer or recent transplants, and it is important to be mindful of possible clotting abnormalities and anemia that may affect hemostasis beyond the effects of thrombocytopenia. Historical studies of patients with thrombocytopenia resulting from bone marrow failure suggest that the risk of spontaneous bleeding increases when blood PLT levels fall to $<20 \times 10^9$/L, particularly when hemorrhagic risk factors (infection, organ failure, clotting abnormalities, minor skin/mucosal bleeding, mucosal lesions, severe graft-versus-host disease [GVHD], anemia) are present. In this high-risk setting, prophylactic PLT transfusions are given to maintain a PLT count $>20 \times 10^9$/L. This threshold has been challenged by several studies of adult patients, who in many instances were carefully selected to be in relatively good clinical condition *without* hemorrhagic risk factors. Consequently, a lower PLT transfusion trigger of 10×10^9/L is recommended for stable (i.e., low-risk) patients.

Table 520.1 Guidelines for Pediatric Platelet (PLT) Transfusion*

CHILDREN AND ADOLESCENTS
1. Maintain PLT count $>50 \times 10^9$/L with bleeding.
2. Maintain PLT count $>50 \times 10^9$/L with *major invasive* procedure; $>25 \times 10^9$/L with minor.
3. Maintain PLT count $>20 \times 10^9$/L and *marrow failure* WITH hemorrhagic risk factors.
4. Maintain PLT count $>10 \times 10^9$/L and *marrow failure* WITHOUT hemorrhagic risk factors.
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure.
INFANTS ≤4 MO OLD
1. Maintain PLT count $>100 \times 10^9$/L with bleeding or during extracorporeal membrane oxygenation.
2. Maintain PLT count $>50 \times 10^9$/L and an invasive procedure.
3. Maintain PLT count $>20 \times 10^9$/L and *clinically stable.*
4. Maintain PLT count $>50 \times 10^9$/L and *clinically unstable and/or bleeding or not when on indomethacin, nitric oxide, antibiotics, etc., affecting PLT function.*
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure.

*Words in *italics* must be defined for local transfusion guidelines.

In practice, severe thrombocytopenia that is prolonged beyond 1 week usually becomes complicated by the development of risk factors, including fever, antimicrobial therapy, GVHD, active bleeding, need for an invasive procedure, disseminated intravascular coagulation, and liver or kidney dysfunction with clotting abnormalities. In these situations, prophylactic PLT transfusions are given to maintain relatively high PLT counts (e.g., at least $>30 \times 10^9$/L). Despite the desire by some physicians to elevate the blood PLT count to 80×10^9/L or 100×10^9/L, there are no definitive data to justify a true benefit of PLT transfusions given at a PLT count $>50 \times 10^9$/L, unless bleeding is ongoing despite a PLT count between 50 and 100×10^9/L *and* thrombocytopenia seems to be the only cause for the bleeding.

Qualitative PLT disorders may be *inherited* or *acquired,* as in advanced hepatic or renal insufficiency or when blood flows through an extracorporeal circuit, such as during extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. In patients with inherited disorders, PLT transfusions are justified only if the risk of significant bleeding is quite high or if bleeding is overt because inherited PLT dysfunction often is lifelong and repeated transfusions may lead to alloimmunization and refractoriness (i.e., poor response to PLT transfusions). Accordingly, prophylactic PLT transfusions are rarely justified unless an invasive procedure is planned, and therapeutic PLT transfusions must be given judiciously.

When managing patients with PLT dysfunction, it is important to remember that an abnormal test result with a modern PLT function device or, historically, a bleeding time more than twice the upper limit of normal provides diagnostic evidence of PLT dysfunction. However, an abnormal bleeding time or any other abnormal laboratory test is poorly predictive of hemorrhagic risk or the need to transfuse PLTs. Alternative therapies, particularly desmopressin acetate, should be considered to avoid PLT transfusions. Antiplatelet medications (nonsteroidal antiinflammatory drugs) should also be avoided.

INFANTS AND NEONATES

In neonates, thrombopoiesis and the risks of bleeding are substantially different from that in older children; the approach to thrombocytopenia and PLT transfusions likewise differs (see Table 520.1). **Thrombopoietin** (TPO) levels are higher in healthy neonates than in older individuals. Relative to adult PLT progenitors, *megakaryocyte* progenitors of neonates are more sensitive to TPO, have higher proliferative potential, and give rise to larger megakaryocyte colonies. Fetal/neonatal megakaryocytes are smaller in size and have lower ploidy than do their adult counterparts; this

information is important because small megakaryocytes of low ploidy produce fewer PLTs than do larger megakaryocytes of higher ploidy. Presumably, this allows the expanding marrow of the growing fetus and neonate to be supplied with sufficient numbers of megakaryocytes, yet not allowing blood PLT counts to become excessively high during proliferation because of the lower numbers of PLTs produced by each megakaryocyte.

An important contrasting point is that older children and adults respond to situations of increased demand for PLTs by first increasing megakaryocyte size and ploidy, which is followed in 3–5 days by increased megakaryocyte number. In thrombocytopenic neonates, megakaryocyte numbers but not size increase. Moreover, although cytoplasmic maturation is achieved per TPO stimulation, increases in ploidy are relatively diminished and actually appear to be inhibited by TPO, resulting in large numbers of small megakaryocytes that are cytoplasmically mature but with low ploidy and, consequently, lower PLT production.

PLT counts ≥150 × 10^9/L are present after 17 weeks' gestational age, and it is accepted that neonates have PLT counts in the same range as older children and adults (150,000–450,000/μL). However, other data suggest a lower limit of 120,000/μL for extremely small preterm infants. Approximately 1% of term infants demonstrate PLT counts <150 × 10^9/L, but bleeding in such infants is rare. In contrast, 18–35% of preterm neonates treated in intensive care units (ICUs) exhibit PLT counts <150 × 10^9/L at some time during admission, with approximately 4% overall receiving PLT transfusions. Notably, when only extremely low birthweight preterm infants (<1 kg) were considered in one report, 70% had PLT counts <150 × 10^9/L, and 5–9% of infants received platelet transfusions.

Debate continues in the United States as to the appropriate prophylactic platelet transfusion threshold for neonates, with a wide range in practice patterns. Multiple pathogenetic mechanisms underlie thrombocytopenia in these sick neonates, including predominantly accelerated PLT destruction plus diminished PLT production, as evidenced by decreased numbers of megakaryocyte progenitors and relatively low upregulation of TPO levels during thrombocytopenia, when compared with thrombocytopenic children and adults.

PLT counts <100 × 10^9/L pose significant clinical risks for premature neonates. Bleeding time may be prolonged at PLT counts <100 × 10^9/L in infants with birthweight <1,500 g, and PLT dysfunction is suggested by bleeding times (a test no longer performed) that are disproportionately long for the degree of thrombocytopenia. The risk of hemorrhage may be increased in thrombocytopenic infants. However, in a randomized trial, transfusing PLTs prophylactically whenever the PLT count fell to <150 × 10^9/L (i.e., at the lower limit of normal range) to maintain the average PLT count at >200 × 10^9/L, compared to not transfusing PLTs until the PLT count fell to <50 × 10^9/L to maintain the average PLT count at approximately 100 × 10^9/L, *did not result* in a lower incidence of intracranial hemorrhage (28% vs 26%, respectively). A U.S. multicenter observational study of very low birthweight infants in six neonatal ICUs found wide variation in PLT thresholds for transfusion, ranging from 10,000 to 139,000/μL in the first week of life and <10,000/μL to >50,000/μL after the first week. The most common thresholds were 80,000–89,000/μL in the first 7 days of life and 40,000–49,000/μL after the first 7 days. Furthermore, after controlling for severity of thrombocytopenia, the authors found PLT transfusions were not associated with a lower risk of intraventricular hemorrhage. Thus, there is no documented benefit for prophylactic PLT transfusions to maintain PLT counts within the normal range or to correct moderate thrombocytopenia (PLT count >50 × 10^9/L). As an exception, infants with inherited PLT dysfunction disorders *and* bleeding, as well as infants at high risk of bleeding because of acquired PLT dysfunction, such as during ECMO, typically receive transfusions to keep their PLT counts >100 × 10^9/L.

One randomized clinical trial reported a significantly higher rate of new major hemorrhage or death within 28 days of randomization in very low birthweight neonates given prophylactic PLT transfusions at a pretransfusion PLT count of 50,000/μL (26%) vs a pretransfusion PLT count of 25,000/μL (19%), irrespective of their baseline risk of bleeding. Results are too preliminary to permit changes in practice but support other published findings indicating no need to maintain normal PLT counts and add to the belief that a PLT count of 50,000/μL is too high to serve as the pretransfusion PLT count for transfusions in stable low birthweight neonates.

Table 520.1 lists pediatric PLT transfusion guidelines that are acceptable to many neonatologists. One particularly contentious issue is how to manage critically ill neonates receiving agents known to adversely affect PLT function (e.g., indomethacin, nitric oxide, antibiotics). Some reports suggest increased risk of bleeding for these neonates, but the efficacy of PLT transfusions has not been convincingly proven, particularly when given prophylactically. For optimal PLT transfusion practices, each hospital should modify their guidelines to comply with local practices, with audits and reviews done to avoid violations of the recommended practices.

PLATELET PRODUCTS AND DOSING

In the United States, two types/sources of PLT units are available, although any one blood bank or hospital may stock only one of these types. Whole blood–derived PLT units **(PLT concentrates)** and PLT units collected by apheresis **(apheresis PLTs)** differ in their PLT content and plasma volume. Although a PLT concentrate contains approximately 5.5-10 × 10^{10} PLTs in approximately 50 mL, and 1 apheresis PLT unit contains at least 3 × 10^{11} PLTs in 300–600 mL, the PLT content may vary considerably among different blood suppliers. Accordingly, it is prudent for hospital blood banks to confirm the composition of the PLT units they issue for transfusion, at the very least by contacting their blood supplier. It is often easier to use PLT concentrates for infants and small children because apheresis PLTs usually need to be prepared as *aliquots* to provide the correct dose (10–15 mL/kg). However, many blood centers exclusively provide only one type of PLT component. Platelet products generally have a 5-day expiration time, although 7-day storage has been approved for apheresis platelet units within certain stipulations to reduce the risk of bacterial contamination and are stored at room temperature with constant agitation.

The posttransfusion goal of most PLT transfusions is to raise the PLT count well above 50 × 10^9/L, hopefully to ≥100 × 10^9/L. These increases can be achieved consistently in children weighing up to 30 kg by infusion of 5–10 mL/kg of standard (unmodified) PLT concentrates, obtained either from PLT concentrates or apheresis PLTs. For larger children, the appropriate dose is 4-8 pooled PLT concentrates or 1 apheresis unit. Because PLT concentration/quantity varies in different PLT products made available for transfusion, each hospital should monitor posttransfusion PLT counts to determine the dose that works best locally. PLT concentrates may be transfused as rapidly as the patient's overall condition permits, certainly within 2 hours, but not longer than 4 hours. Neonates/infants requiring repeated PLT transfusions should receive leukocyte-reduced blood products to diminish HLA alloimmunization and PLT refractoriness and to reduce the risk of transfusion-transmission cytomegalovirus infection (TT-CMV). For those infants weighing <1,500 g at birth, *irradiation* is recommended to prevent transfusion associated GVHD. Additionally, some recommend both leukoreduction and CMV-seronegative RBC units (estimated risk of TT-CMV infection: 0–0.3% per unit) as first-line therapy to prevent TT-CMV. However, given the low risks of TT-CMV with improvements in modern leukoreduction techniques, others have recommended use of leukoreduced blood from CMV-untested donors as an acceptably safe and low-risk alternative. PLT transfusion should not be delayed if CMV-negative units are unavailable; CMV-untested leukoreduced units should be used because the risk of TT-CMV is relatively low and more harm may come to the patient if transfusion is withheld or delayed.

Routinely reducing the volume of PLT concentrates for infants and small children by additional centrifugation steps is both unnecessary and unwise. Transfusion of 10–15 mL/kg of an unmodified PLT concentrate is adequate because it adds approximately 10 × 10^9 PLTs to 70 mL of blood (estimated intravascular blood volume of 1 kg neonate), a dose/volume calculated to increase the PLT count by 100 × 10^9/L. This calculated increment is consistent with actual posttransfusion increment reported in patients. Moreover, 10–15 mL/kg is not an excessive transfusion volume, provided that the intake of other IV fluids, medications, and nutrients is monitored and adjusted.

It is important to select PLT units for transfusion with the donor ABO group identical to that of the neonate/infant and to avoid repeated transfusion of group O PLTs to group A or B recipients, because passive transfusion anti-A or anti-B in group O plasma can occasionally lead to intravascular hemolysis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 521

Neutrophil (Granulocyte) Transfusions

Patricia E. Zerra and Cassandra D. Josephson

Table 521.1 lists guidelines for granulocyte transfusion (GTX). GTX has been used sparingly in older infants and children. The current ability to collect markedly higher numbers of neutrophils from donors stimulated with combined recombinant granulocyte colony-stimulating factor (G-CSF) plus dexamethasone has led to renewed interest for patients with neutropenic infections, particularly when severe neutropenia is prolonged (e.g., in the setting of placental/cord blood hematopoietic progenitor cell transplantation). As a result, higher neutrophil yields are collected with this approach, making the addition of GTX to antibiotics a therapeutic consideration. This is especially true at institutions where neutropenic patients continue to die of progressive bacterial and fungal infections or to suffer substantial morbidity despite optimal antiinfection measures, including antibiotics and recombinant myeloid growth factors.

GRANULOCYTE TRANSFUSIONS FOR CHILDREN

The use of GTX added to antibiotics for children with **severe neutropenia** (neutrophil count $<0.5 \times 10^9$/L) because of bone marrow failure is similar to that for adults. Unfortunately, two randomized clinical trials comparing antibiotics plus GTX from donors stimulated with G-CSF plus dexamethasone vs antibiotics without GTX to treat neutropenic infections in children have not provided definitive guidelines. However, in practice, neutropenic patients with bacterial infections usually show response to antibiotics alone, provided bone marrow function recovers within the first 7–10 days of infection onset, so that severe neutropenia is relatively brief. Children with newly diagnosed acute lymphoblastic leukemia show rapid response to induction chemotherapy and are rarely candidates for GTX. In contrast, infected children with more sustained bone marrow failure and consequent severe neutropenia (e.g., acute myeloblastic leukemia, malignant neoplasms resistant to treatment, severe aplastic anemia, placental/cord blood hematopoietic progenitor cell transplant recipients) may benefit when GTX is added to antibiotics.

Currently, the efficacy of GTX obtained from G-CSF plus dexamethasone–stimulated donors for bacterial sepsis unresponsive to antibiotics in patients with severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) *is not well supported* by trials in children. Furthermore, GTX efficacy for yeast and fungal infections remains unproven, despite transfusing GTX with relatively large numbers of neutrophils.

Children with **qualitative neutrophil defects (neutrophil dysfunction)** usually have adequate or even increased numbers of blood neutrophils but develop serious infections because their neutrophils kill pathogenic microorganisms inefficiently. Neutrophil dysfunction syndromes are rare; accordingly, no definitive studies have established GTX efficacy. However, several patients with progressive life-threatening infections have shown striking improvement with the addition of GTX, often given for long periods, to antimicrobial therapy. These disorders are chronic and thus associated with an increased risk of alloimmunization to leukocyte antigens, specifically to Kell system antigens on the red blood cells in some patients with chronic granulomatous disease, and GTX is recommended only when serious infections are clearly unresponsive to antimicrobial drugs.

Table 521.1 Guidelines for Pediatric Granulocyte Transfusions*

CHILDREN AND ADOLESCENTS
1. Severe neutropenia (blood neutrophil count $<0.5 \times 10^9$/L) and infection (bacterial, yeast, or fungal) *unresponsive or progressive* despite appropriate antimicrobial therapy.
2. Qualitative neutrophil defect, neutropenia not required, and infection (bacterial or fungal) *unresponsive or progressive* to appropriate antimicrobial therapy.
INFANTS ≤4 MO OLD†
Blood neutrophil count $<3.0 \times 10^9$/L in first week of life or $<1.0 \times 10^9$/L thereafter and *fulminant* bacterial infection.

*Words in *italics* must be defined for local transfusion guidelines.
†No longer commonly used.

GRANULOCYTE TRANSFUSION FOR NEONATES

Neonates are unusually susceptible to severe bacterial infections, and a number of defects of neonatal defenses contribute to this susceptibility, including actual or "relative" neutropenia. Neonates with fulminant sepsis who exhibit *relative neutropenia* (blood neutrophil count $<3.0 \times 10^9$/L during the first week of life and $<1.0 \times 10^9$/L thereafter) and a severely diminished neutrophil marrow storage pool (with <10% of nucleated marrow cells being postmitotic neutrophils) are at risk of dying if treated only with antibiotics. Despite this risk, GTX has not provided the solution. GTX is rarely used in neonates because the results of clinical trials are mixed and not uniformly convincing, and it is difficult to obtain neutrophil apheresis concentrates in a timely fashion.

Current data are insufficient to conclude that recombinant myeloid growth factors have a role in treating septic neonates, despite demonstration that both G-CSF and granulocyte-macrophage CSF enhance myelopoiesis and raise neutrophil counts in infants. In contrast to the uncertain role of G-CSF and GM-CSF to treat infections in many clinical settings, it is important to remember that G-CSF is efficacious for the long-term treatment of several types of severe **congenital neutropenias**.

GRANULOCYTE PRODUCT

If the decision to provide a GTX has been made, an adequate dose of neutrophils/granulocytes collected by leukapheresis must be transfused as shortly after collection as possible. To facilitate this goal, experienced donors with recently performed negative testing for HIV and hepatitis (usually within the past 30 days) are selected. Granulocyte donors should be documented to be cytomegalovirus antibody negative (seronegative). These donors should also be ABO/Rh crossmatch compatible with the recipient because there is a large volume of red blood cells in the granulocyte product.

Granulocyte Product Dosing

Neonates and **infants** weighing <10 kg should receive $1\text{-}2 \times 10^9$/kg neutrophils per each GTX. **Larger infants** and **small children** should receive a minimal total dose of 1×10^{10} neutrophils per each GTX. The preferred dose for **adolescents** is $5\text{-}8 \times 10^{10}$ neutrophils per each GTX, a dose requiring donors to be stimulated with G-CSF plus dexamethasone. GTX should be given daily until either the infection resolves or the blood neutrophil count is sustained above 1.5×10^9/L for a few days. Because neutrophils transfused through the GTX often passively increase the blood neutrophil count, it may be necessary to skip 1-2 days of GTXs to accurately assess whether endogenous myelopoiesis and neutrophil production have recovered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 522

Plasma Transfusions

Patricia E. Zerra and Cassandra D. Josephson

Guidelines for plasma transfusion in pediatric patients are similar to those for adults but with the understanding that plasma levels of coagulant and anticoagulant proteins can be developmentally low in preterm infants (Table 522.1). Therefore transfusions of plasma and plasma-derived commercial concentrates should be determined by actual bleeding or a significant risk of bleeding, not simply by prolonged clotting time results. Plasma is transfused to replace clinically significant congenital or acquired deficiencies of plasma proteins for which more highly purified protein concentrates, treated to reduce infectious disease risks, or recombinant products are not available. Plasma and plasma derivatives are required to provide clotting proteins when bleeding is actually occurring or in settings when prevention of bleeding is deemed critical.

PLASMA PRODUCTS AND PATIENT TESTING

Two interchangeable plasma products are available for transfusion, plasma frozen within 8 hours of collection **(fresh-frozen plasma [FFP])** and plasma frozen within 24 hours of collection **(F24)**. Although levels of factors V and VIII are modestly reduced in F24 (generally, not more than 25% lower), they are equally efficacious for all indications for which plasma is transfused in infants and children (see Table 522.1). Recommendations for the volume of plasma to be transfused vary with the specific protein being replaced and the severity of the deficiency, but a starting dose of 15 mL/kg is usually sufficient to elevate plasma levels satisfactorily.

Transfusion of plasma is efficacious for the treatment of deficiencies of clotting factors II, V, X, and XI. Deficiencies of factor XIII and fibrinogen are treated either with cryoprecipitate or specific commercial concentrates; for patients being given large doses of plasma (e.g., in massive transfusion settings or to treat bleeding in liver failure), however, additional sources of fibrinogen may not be necessary because plasma contains large amounts of fibrinogen. It is always useful to include a measurement of plasma fibrinogen (a separate test) when performing clotting assays, including prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

PLASMA TRANSFUSION IN CHILDREN

Transfusion of plasma is not recommended for the treatment of patients with severe hemophilia A or B, von Willebrand disease, or factor VII deficiency because safer plasma-derived and recombinant factor products for VII, VIII, IX, and von Willebrand factor are available. Moreover, mild to moderate hemophilia A and certain types of von Willebrand disease can be treated with intranasal or intravenous desmopressin (see Chapter 526). An important use of plasma is for rapid reversal of the effects of warfarin in patients who are actively bleeding or who require emergency surgery (in whom functional deficiencies of vitamin K–dependent factors II, VII, IX, and X cannot be rapidly reversed by vitamin K administration). Plasma-derived and virally inactivated prothrombin "complex" concentrates can also be used for this purpose.

Results of screening coagulation tests (PT/INR, aPTT, thrombin time, and plasma fibrinogen level) should not be assumed to reflect the integrity of the coagulation system or be regarded as indications for plasma transfusions. This is particularly true for neonates. To justify plasma transfusions, coagulation test results must be related to the patient's clinical condition in regard to bleeding and the risk of bleeding. Transfusion of plasma in patients with chronic liver disease and prolonged clotting times is not recommended unless bleeding is present, or an invasive procedure is planned because prophylactic correction of the clotting factor deficiencies is brief and of questionable benefit.

Plasma also contains several anticoagulant proteins (antithrombin III, protein C, and protein S) whose deficiencies have been associated with thrombosis. In select situations, plasma as replacement therapy along with anticoagulant treatment may be appropriate in patients with these disorders; when available, purified concentrates are preferred. Other indications for plasma include replacement fluid during plasma exchange in patients with **thrombotic thrombocytopenic purpura** (i.e., thrombotic microangiopathies) or other disorders for which plasma is likely to be beneficial. This includes plasma exchange in a patient with overt bleeding caused by the underlying disorder (e.g., Goodpasture syndrome, vasculitis) or disorders with significant severe coagulopathy that would substantially worsen with replacement by albumin solutions only. *Plasma is not indicated for correction of hypovolemia or as immunoglobulin replacement therapy because safer alternatives exist (albumin or crystalloid solutions and IV immunoglobulin, respectively).*

PLASMA TRANSFUSION IN NEONATES

In neonates, clotting times are "physiologically" prolonged because of developmental deficiency of clotting proteins; plasma should be transfused only after reference to normal values is adjusted for the birthweight and age of the infant (*not* to normal ranges for older children and adults). The indications for plasma in neonates include (1) reconstitution of red blood cell (RBC) concentrates to simulate whole blood for use in massive transfusions (exchange transfusion, cardiac bypass surgery, and extracorporeal membrane oxygenation), (2) hemorrhage secondary to vitamin K deficiency, (3) disseminated intravascular coagulation *with* bleeding, and (4) bleeding in congenital coagulation factor deficiency when more specific treatment is either unavailable or inappropriate. The use of prophylactic plasma transfusion to prevent intraventricular hemorrhage in premature infants is not recommended. Plasma should not be used as a suspending agent to adjust the hematocrit values of RBC concentrates before small-volume RBC transfusions to neonates because it offers no apparent medical benefit over the use of sterile solutions such as crystalloid and albumin. Similarly, the use of plasma in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome is unnecessary because safer crystalloid or colloid solutions are available.

In the treatment of bleeding infants, *cryoprecipitate* is often considered because of its small infusion volume. However, cryoprecipitate contains significant quantities of only fibrinogen, von Willebrand factor, and factors VIII and XIII. Thus it is not effective for treating the usual clinical situation in bleeding infants with multiple clotting factor deficiencies. However, cryoprecipitate is an excellent source of fibrinogen (much more concentrated than frozen plasma), and with a dose of 1–2 units/kg, the patient's fibrinogen level can be quickly raised by 60–100 mg/dL.

In preliminary studies, infusions of very small volumes of recombinant activated factor VII have been lifesaving in patients with hemorrhage caused by several mechanisms. Because the efficacy and toxicity of factor VIIa have not been fully defined in these "off-label" uses (not approved by the U.S. Food and Drug Administration), it must be considered "experimental" therapy at this time.

Table 522.1 Guidelines for Children and Infants for Plasma Transfusions*

1. *Severe* clotting factor deficiency AND bleeding.
2. *Severe* clotting factor deficiency AND an invasive procedure.
3. *Emergency reversal* of warfarin effects.
4. Dilutional coagulopathy and bleeding (e.g., massive transfusion).
5. Anticoagulant protein (antithrombin III, proteins C and S) replacement.
6. Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura or for disorders with overt bleeding or in which there is risk of bleeding because of clotting protein abnormalities (e.g., liver failure).

*Words in *italics* must be defined for local transfusion guidelines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 523

Risks of Blood Transfusions

Patricia E. Zerra and Cassandra D. Josephson

The greatest risk of a blood transfusion is mistakenly receiving a transfusion intended for another patient. *Misidentification* is usually a result of mistakes made in labeling the patient's blood sample sent to the blood bank or not accurately matching the unit with the patient at the bedside when the blood is transfused. This risk is particularly high for infants, especially if ABO type-specific or type-compatible blood is transfused, because (1) identification bands may not be attached directly to their bodies, (2) difficulties in drawing blood samples for pretransfusion compatibility testing may lead to deviations from usual policies, and (3) infants cannot speak to identify themselves. Thus particular care must be taken to ensure accurate patient and blood sample identification.

INFECTIOUS RISKS OF TRANSFUSION

Although the infectious disease risks of allogeneic blood transfusions are extremely low, transfusions must be given judiciously because "emerging infections," such as Ebola or Zika virus, when they first arise, pose a potential threat until they are studied definitively and, accordingly, are of constant concern, and testing is not done for every microorganism possibly transmitted by blood transfusions (Table 523.1 and Fig. 523.1). Taking nucleic acid amplification testing (NAT) and all other donor-screening activities (antibody and epidemiology screening) into account, a current estimate of the risk of transfusion-associated **HIV** infection is approximately 1 per every 2 million donor exposures. Similarly, with NAT, the risk of hepatitis C virus **(HCV)** infection is 1 per every 1.5-2 million donor exposures (see Table 523.1). NAT identifies circulating microbial nucleic acids that appear in the window before antibodies develop, and NAT is used routinely to detect HIV, HCV, West Nile virus, hepatitis B virus, *Trypanosoma cruzi, Babesia microti,* and Zika virus.

Transfusion-associated cytomegalovirus **(CMV)** has been nearly eliminated by transfusion of leukocyte-reduced cellular blood products or by selection of blood collected from donors who are seronegative for antibody to CMV. Although it is logical to hypothesize that first collecting blood components from CMV-seronegative donors and then removing the white blood cells (WBCs) might further improve safety, little data are available to document the superior efficacy of this combined approach. However, in a recent prospective birth cohort study of premature infants with birthweight ≤1,500 g, a combined approach of leukoreduction and CMV-seronegative cellular blood components yielded 0% transfusion transmission of CMV (15.3% cumulative incidence at 12 weeks of maternal breast milk transmission from CMV-seropositive mothers) in >300 transfused infants studied. Similar uncontrolled reports of hematopoietic stem cell transplant patients found 0% transmission of CMV from leukoreduced blood products from donors of unknown CMV antibody status. Therefore considerable care must be taken not to place children at risk of delayed or missed transfusions while awaiting/searching for blood from CMV-seronegative donors, then to leukoreduce (i.e., risks must not be taken for practices with no established benefits).

Further data on these two mitigation strategies revealed that large quantities of CMV viral material are present "free" in the plasma of healthy-appearing donors during the early phase of primary infection (while CMV antibodies are either absent ["window" phase] or are newly emerging and at low, inconsistently detected levels in plasma), rather than being leukocyte associated, as occurs with CMV as substantial quantities of IgG antibodies appear. As a result of this biology of CMV primary infection, plasma "free" virus will not be removed by leukoreduction during early infection, and CMV-seronegative donors who may be asymptomatic or deny symptoms of infection during blood donor screening will be misclassified as being CMV safe. They are not necessarily as safe because antibody is below the limits of detection, while plasma "free" CMV is plentiful during early infection. Because almost all plasma "free" CMV disappears and becomes almost exclusively cell associated, once donors are CMV seropositive with antibody present for several months, some propose that the best method to reduce CMV risk may be leukoreduction of blood from donors known to be CMV seropositive for at least 1 year. However, data to prove the efficacy of this proposal are lacking, and in practice, several studies have shown that the most efficacious method currently available to prevent transfusion-transmitted CMV is to perform leukoreduction in the

Table 523.1 Estimated Risks in Transfusion per Unit Transfused in the United States

ADVERSE EFFECT (INFECTIOUS)	ESTIMATED RISK
Human immunodeficiency virus (HIV)-1 and HIV-2	1:2 million
Hepatitis B	1:2 million
Hepatitis C	1:2 million
Human T-cell lymphotropic virus (HTLV) I and II	1:3 million
Bacterial contamination (usually platelets)	1:100,000
Malaria	<1:3 million
Hepatitis A	Unknown
Parvovirus	Unknown
Dengue fever	Unknown
Cytomegalovirus	<1:3 million
Babesiosis	Unknown
West Nile virus	<1:3 million
Trypanosoma cruzi	<1:3 million
Leishmania spp.	Unknown
Variant Creutzfeldt-Jakob prion disease	Unknown
Zika virus	<1:3 million
Syphilis	Unknown
ADVERSE EFFECT (NONINFECTIOUS)	**ESTIMATED RISK**
Febrile nonhemolytic reaction	1:800
Mild-moderate allergic reaction	1:1,000
Severe allergic reactions	1:40,000
Transfusion-associated circulatory overload (TACO)	1:8,500
Hypotensive	1:11,000
Acute hemolytic transfusion reaction	1:95,000
Transfusion-associated dyspnea	1:15,000
Transfusion-related acute lung injury (TRALI)	1:70,000
Delayed hemolytic transfusion reaction	1:20,000
Transfusion-associated graft-versus-host disease	Uncommon
Immunomodulation	Unknown
Posttransfusion purpura	1:30,000
Life-threatening reactions, requiring major medical intervention	1:20,000

Adapted from Busch MP, Bloch EM, Kleinman S. Prevention of transfusion-transmitted infections. *Blood* 2019;133:1854–1864; and Savinkina AA, Haass KA, Sapiano MRP, et al. Transfusion-associated adverse events and implementation of blood safety measures – findings from the 2017 National Blood Collection and Utilization Survey. *Transfusion* 2020;60:S10–S16.

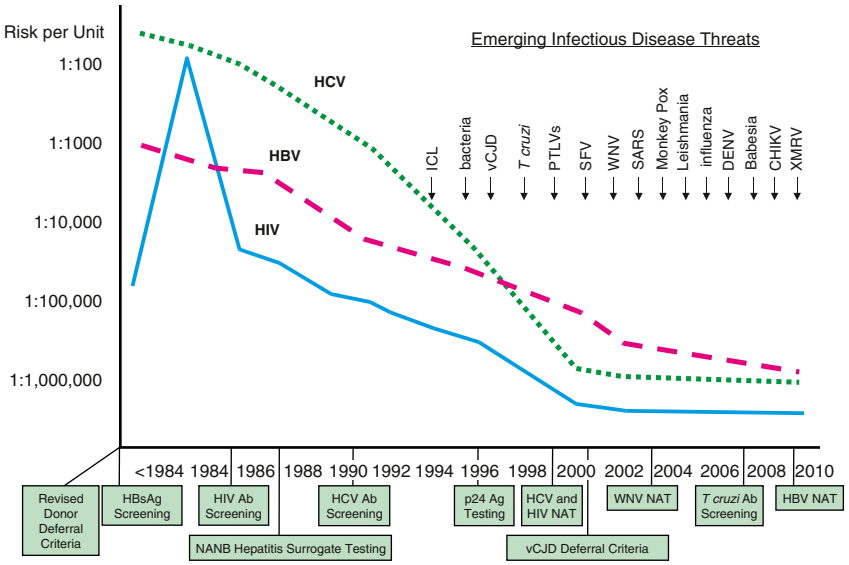

Fig. 523.1 Risks of major transfusion-transmitted viruses related to interventions and accelerating rate of emerging infectious diseases of concern to blood safety. Evolution of the risks of transmission by blood transfusion for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Major interventions to reduce risks are shown below the timeline on the *x* axis. Emerging infectious disease threats in the past 20 years are shown above in the *top right quadrant* of the figure. Ab, Antibody; Ag, antigen; CHIKV, chikungunya virus; DENV, dengue virus; HBsAg, hepatitis B surface antigen; ICL, idiopathic CD4 T-lymphocytopenia; NANB, non-A, non-B hepatitis; NAT, nucleic acid amplification testing; PTLVs, primate T-lymphotropic viruses; SARS, severe acute respiratory syndrome; SFV, simian foamy virus; vCJD, variant Creutzfeldt-Jakob disease; WNV, West Nile virus; XMRV, xenotropic murine leukemia virus–related virus. *(From Busch MP. Transfusion-transmitted viral infections: Building bridges to transfusion medicine to reduce risks and understand epidemiology and pathogenesis. 2005 Emily Cooley Award Lecture. Transfusion. 2006;46:1624–1640.)*

blood center/bank without regard for the CMV antibody status of the donor/unit (i.e., leukoreduction alone performed by the blood center/bank, not at the bedside, is sufficient in most cases).

Additional infectious risks include other types of **hepatitis** (A, B, E) and **retroviruses** (human T-cell lymphotropic virus types I and II, HIV-2), syphilis, parvovirus B19, Epstein-Barr virus, human herpesvirus 8, West Nile virus, yellow fever vaccine virus, malaria, babesiosis, *Anaplasma phagocytophilum*, Chagas disease, and Zika virus. Variant Creutzfeldt-Jacob disease has also been transmitted by blood transfusions in humans. All are reported very infrequently, but nonetheless provide the rationale to transfuse only when true benefits are likely.

NONINFECTIOUS RISKS OF TRANSFUSION

Transfusion-associated risks of a noninfectious nature that may occur include hemolytic and nonhemolytic transfusion reactions, circulatory fluid overload, **graft-versus-host disease** (GVHD), electrolyte and acid-base imbalances, iron overload if repeated red blood cell (RBC) transfusions are needed long term, increased susceptibility to oxidant damage, exposure to plasticizers, hemolysis with T-antigen activation of RBCs, posttransfusion purpura, **transfusion-related acute lung injury** (TRALI), posttransfusion immunosuppression and immunomodulation, and alloimmunization (Fig. 523.2; see Table 523.1). The risk of TRALI may be reduced by avoiding transfusion of plasma or platelets from female donors, who were possibly alloimmunized to leukocyte antigens during pregnancy or by selecting donors (e.g., males) who are likely to be negative for human leukocyte antigen (HLA) antibodies.

Immunologic adverse effects, including immunosuppression, immunomodulation, and alloimmunization, may be reduced by leukoreduction. Transfusion reactions and alloimmunization to RBC and leukocyte antigens seem to be uncommon in infants, perhaps because of developmental immaturity of the immune system or deficient cytokine production. When they do occur, adverse effects are seen primarily in massive transfusion settings, such as exchange transfusions and trauma or surgery, in which relatively large quantities of blood components are needed but are rare when small-volume transfusions are usually given.

Premature infants are known to have immune dysfunction, but their relative risk of posttransfusion GVHD is controversial. The postnatal age of the infant, the number of immunocompetent lymphocytes in the transfusion product, the degree of HLA compatibility between donor and recipient, and other, poorly described phenomena determine which infants are truly at risk for GVHD. Regardless, many centers caring for preterm infants transfuse exclusively irradiated cellular products. As an alternative, pathogen-reduction technology has been documented to prevent GVHD and can substitute for irradiation. Directed donations with blood drawn from blood relatives must always be irradiated because of the risk of engraftment with transfused HLA-homozygous, haploidentical lymphocytes. Cellular blood products given as intrauterine or exchange transfusions should be irradiated, as should transfusions for patients with severe congenital immunodeficiency disorders (severe combined immunodeficiency syndrome and DiGeorge syndrome requiring heart surgery) and transfusions for recipients of hematopoietic progenitor cell transplants. Other groups who are potentially at risk but for whom no conclusive data are available include patients given T-cell antibody therapy (antithymocyte globulin or OKT3), those with organ allografts, those receiving immunosuppressive drug regimens, and those infected with HIV.

As an alternative, pathogen-reduction technology has been documented to prevent T-cell proliferation, and thus TA-GVHD may be used as a substitute for irradiation. Current practice uses **irradiation** from a cesium, cobalt, or linear acceleration source at doses ranging from 1,500 to 2,500 centigray (cGy); a maximum dose of 2,500 cGy is required to hit the center of the irradiation field and a minimum of 1,500 cGy delivered to any other portion of the cannister. All cellular blood components should be irradiated, except those frozen without a cryoprotectant agent and to be rendered as "acellular" products, such as plasma and cryoprecipitate, which do not require irradiation. Leukocyte reduction cannot be substituted for irradiation to prevent GVHD. However, as mentioned, pathogen-reduction technologies have been demonstrated to be efficacious.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

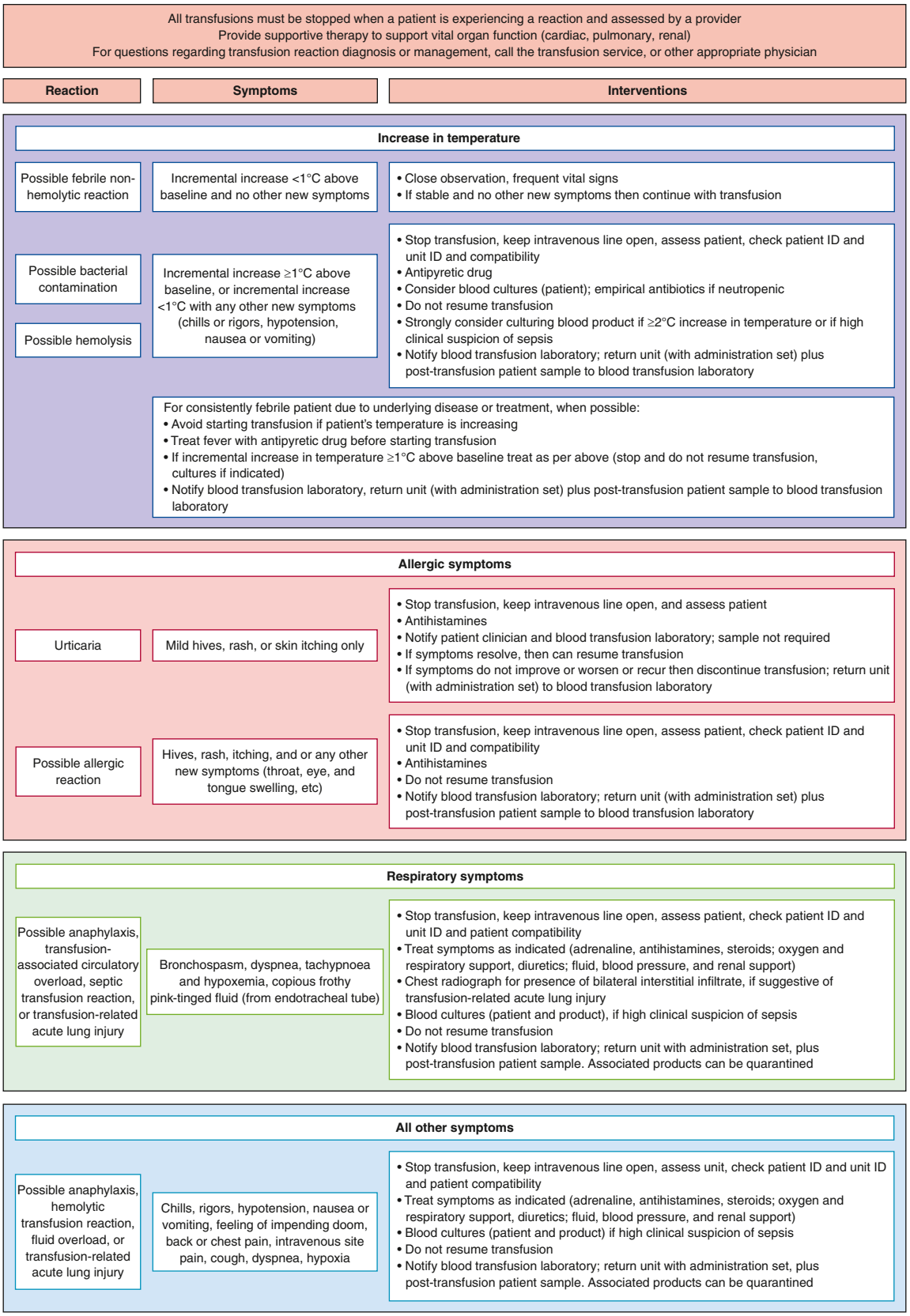

Fig. 523.2 Transfusion reaction decision tree. Algorithm to guide assessment and actions to take when a transfusion reaction is initially identified. Actions should proceed from left to right. *(From Delaney M, Wendel S, Bercovitz RS. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016;388:2825–2836. Fig 2.)*

Section 7

Hemorrhagic and Thrombotic Diseases

Chapter 524

Hemostasis

Brian R. Branchford, Benjamin J. Samelson-Jones, Leslie J. Raffini, and Veronica H. Flood

Hemostasis is the biological process that limits hemorrhage after blood vessel injury. An initial platelet plug (primary hemostasis) is bolstered by the product of the coagulation cascade: a factor XIII-cross-linked fibrin clot (secondary hemostasis). Extraneous fibrin is lysed by plasmin (fibrinolysis), and normal blood flow is restored through the previously damaged vessel. If hemostasis is impaired, varying degrees of bleeding may occur depending on the hemostatic defect and the site of injury. Excess coagulation activity can lead to thrombotic complications. The hemostatic response therefore needs to be rapid and locally regulated, such that trauma neither results in hemorrhage nor triggers a systemic thrombotic reaction. When a platelet adheres to a site of vascular injury, the activated platelet surface provides a phospholipid reaction surface where clotting factors bind and create a "thrombin burst." Active clotting is controlled by negative feedback loops that inhibit the clotting process when procoagulant products come in contact with intact endothelium. The main components of the hemostatic process are the **vessel wall, platelets, coagulation factors, anticoagulant proteins,** and **fibrinolytic system.** Many components of the hemostasis system are multifunctional. Fibrinogen serves as the ligand between platelets during platelet aggregation and as the substrate for thrombin to produce fibrin. Platelets provide the reaction surface on which clotting reactions occur, form the plug at the site of vessel injury, release procoagulant compounds from their granules, and contract to constrict and limit clot size.

THE HEMOSTATIC PROCESS

The intact vascular endothelium is the primary barrier against hemorrhage and thrombosis. The endothelial cells that line the vessel wall normally inhibit coagulation and provide a smooth surface that permits rapid blood flow.

After vascular injury, vasoconstriction occurs, and flowing blood comes in contact with the subendothelial matrix. **Von Willebrand factor (VWF)** tethers platelets to the site of injury by binding subendothelial matrix components such as collagen and platelets, via the glycoprotein Ib complex on platelet membranes. Platelet binding of VWF initiates complex cellular signaling, activating the platelets and triggering secretion of storage granules containing adenosine diphosphate (ADP), serotonin, and stored plasma and platelet membrane proteins. On activation, the platelet receptor for fibrinogen, $\alpha IIb\beta_3$, is switched on ("inside out" signaling) to bind fibrinogen and triggers the aggregation and recruitment of other platelets to form the platelet plug. Multiple physiologic agonists can trigger platelet activation and aggregation, including ADP, collagen, thrombin, and arachidonic acid. Aggregation involves the interaction of specific receptors on the platelet surface with plasma hemostatic proteins, primarily fibrinogen.

One of the subendothelial matrix proteins that is exposed after vascular injury is *tissue factor*. Exposed tissue factor binds to factor VII and activates the *clotting cascade* (Fig. 524.1). The activated clotting factor then initiates the activation of the next sequential clotting factor in a systematic manner. During the process of platelet activation, internalized platelet phospholipids (primarily phosphatidylserine) become externalized supporting membrane binding of the principal enzyme complexes of coagulation: the extrinsic and intrinsic Xase complexes and the prothrombinase complex. These complexes are localized to the platelet surface and bring together the active proteolytic enzyme, an activated cofactor, and the zymogen substrate that will form the next active enzyme in the cascade. This sequence of the coagulation cascade serves as a biochemical amplifier where a small amount of activated proteolytic enzyme can rapidly produce a large amount of downstream components, in a temporally and spatially controlled manner. In vivo, small amounts of activated factor VII (VIIa) are present, so the system is always poised to act. Near the bottom of the cascade, the multipotent enzyme *thrombin* is formed. Thrombin converts fibrinogen into fibrin, activates factors V, VIII, and XI, and aggregates platelets. Activation of factor XI by thrombin amplifies further thrombin generation and contributes to inhibition of fibrinolysis. Thrombin also activates factor XIII. The stable fibrin-platelet plug is ultimately formed through clot retraction and cross linking of the fibrin clot by factor XIIIa.

Virtually all procoagulant proteins are balanced by anticoagulant proteins that regulate or inhibit procoagulant function. Four clinically important, naturally occurring anticoagulants regulate the extension of the clotting process: antithrombin **(AT)**, protein C, protein S, and tissue factor pathway inhibitor **(TFPI)**. AT is a serine protease inhibitor (SERPIN) that regulates primarily factor Xa and thrombin and to a lesser extent, factors IXa, XIa, and XIIa. When thrombin encounters intact endothelium, thrombin binds to *thrombomodulin,* its endothelial receptor. The thrombin-thrombomodulin complex then converts **protein C** into activated protein C. In the presence of the cofactor **protein S**, activated protein C proteolyzes and inactivates factor Va and factor VIIIa. Inactivated factor Va is also a functional anticoagulant that inhibits clotting. TFPI limits activation of factor X by factor VIIa and tissue factor and shifts the activation site of tissue factor and factor VIIa to that of factor IX (Fig. 524.2).

Once a stable fibrin-platelet plug is formed, the fibrinolytic system limits its extension and proteolyzes the clot **(fibrinolysis)** to reestablish vascular integrity. Plasmin, generated from plasminogen by either urokinase-like or tissue-type plasminogen activator, degrades the fibrin clot. In the process of dissolving the fibrin clot, fibrin degradation products are produced. The fibrinolytic pathway is regulated by plasminogen activator inhibitors and α_2-antiplasmin, as well as by the thrombin-activatable fibrinolysis inhibitor (TAFI).

PATHOLOGY

Congenital deficiency of an individual procoagulant protein leads to a bleeding disorder, whereas deficiency of an anticoagulant (clotting factor inhibitor) predisposes the patient to thrombosis. In acquired hemostatic disorders, there are frequently multiple problems with homeostasis that perturb and dysregulate hemostasis. A primary illness (sepsis) and its secondary effects (shock and acidosis) activate coagulation and fibrinolysis and impair the host's ability to restore normal hemostatic function. When sepsis triggers **disseminated intravascular coagulation,** platelets, procoagulant clotting factors, and anticoagulant proteins are consumed, leaving the hemostatic system unbalanced and prone to bleeding or clotting (see Chapter 532). Similarly, newborn infants and patients with severe liver disease have synthetic deficiencies of both procoagulant and anticoagulant proteins. Such dysregulation causes the patient to be predisposed to both hemorrhage and thrombosis with mild or moderate triggers that result in major alterations in the hemostatic process.

In the laboratory evaluation of hemostasis, parameters are manipulated to allow assessment of isolated aspects of hemostasis and limit the multifunctionality of some of its components. The coagulation process is studied in plasma anticoagulated with citrate to bind calcium, with added phospholipid to mimic the reaction surface normally provided by the platelet membrane and with a stimulus to trigger clotting. Calcium is added to restart the clotting process. This process does not necessarily reflect the in vivo pathways of clot formation.

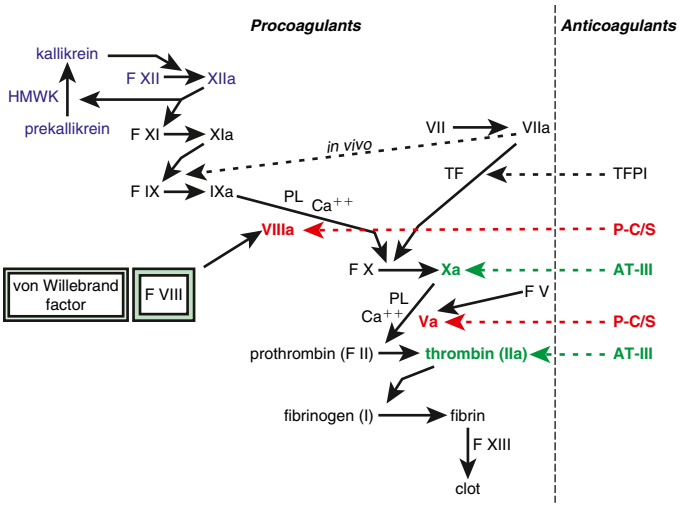

Fig. 524.1 The clotting cascade, with sequential activation and amplification of clot formation. Many of the factors (F) are activated by the clotting factors shown above them in the cascade. The activated factors are designated by the addition of an *a*. On the *right side*, the major anticoagulants and the sites that they regulate are shown. Tissue factor pathway inhibitor (TFPI) regulates tissue factor (TF); factor VIIa, protein C, and protein S (P-C/S) regulate factors VIII and V; and antithrombin III (AT-III) regulates factor Xa and thrombin (factor IIa). The *dotted line* shows that, in vivo, TF and factor VIIa activate both factors IX and X, but that, in vitro, only the activation of factor X is measured. Unactivated factor VIII, when bound to its carrier protein, von Willebrand factor (VWF), is protected from protein C inactivation. When thrombin, or factor Xa activates factor VIII, it becomes unbound from VWF, at which point it can participate with factor IXa in the activation of factor X in the presence of phospholipid (PL) and Ca^{++} (the "tenase" complex). Factor XIIIa cross-links the fibrin clot and thereby makes it more stable. Prekallikrein, high-molecular-weight kininogen (HMWK), and factor XII are shown in *purple* because they do not have a physiologic role in coagulation, although they contribute to the clotting time in partial thromboplastin time (PTT).

524.1 Clinical and Laboratory Evaluation of Hemostasis

Brian R. Branchford, Benjamin J. Samelson-Jones, Leslie J. Raffini, and Veronica H. Flood

CLINICAL HISTORY

For most hemostatic disorders, the clinical history provides the most useful information. To evaluate for a bleeding disorder, the history should determine the sites of bleeding, the severity and duration of hemorrhage, and the age at onset. Was the bleeding spontaneous, or did it occur after trauma? Was there a previous personal or family history of similar problems? Did the symptoms correlate with the degree of injury or trauma? Does bruising occur spontaneously? Are there lumps with bruises for which there is minimal trauma? If the patient had previous surgery or significant dental procedures, was there any increased bleeding? If a child or adolescent has had surgery that affects the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder. Delayed or slow healing of superficial injuries may suggest a hereditary bleeding disorder. In postpubertal females, it is important to take a careful menstrual history. Because some common bleeding disorders, such as **von Willebrand disease (VWD)**, have a fairly high prevalence, mothers and family members may have the same mild bleeding disorder and may not be cognizant that the child's menstrual history is abnormal. Females with mild VWD who have a moderate history of bruising frequently have a reduction in symptoms during pregnancy or after administration of oral contraceptives. Some medications, such as aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs), inhibit platelet function and increase bleeding symptoms in patients with a low platelet count or abnormal hemostasis. Standardized bleeding scores have been developed but have not been widely adopted in pediatrics.

Outside the neonatal period, thrombotic disorders are relatively rare until adulthood. In the neonate, physiologic deficiencies of procoagulants and anticoagulants place the hemostatic mechanism at greater risk for imbalance, and clinical events can lead to either hemorrhage or thrombosis. If a child or teenager presents with deep vein thrombosis

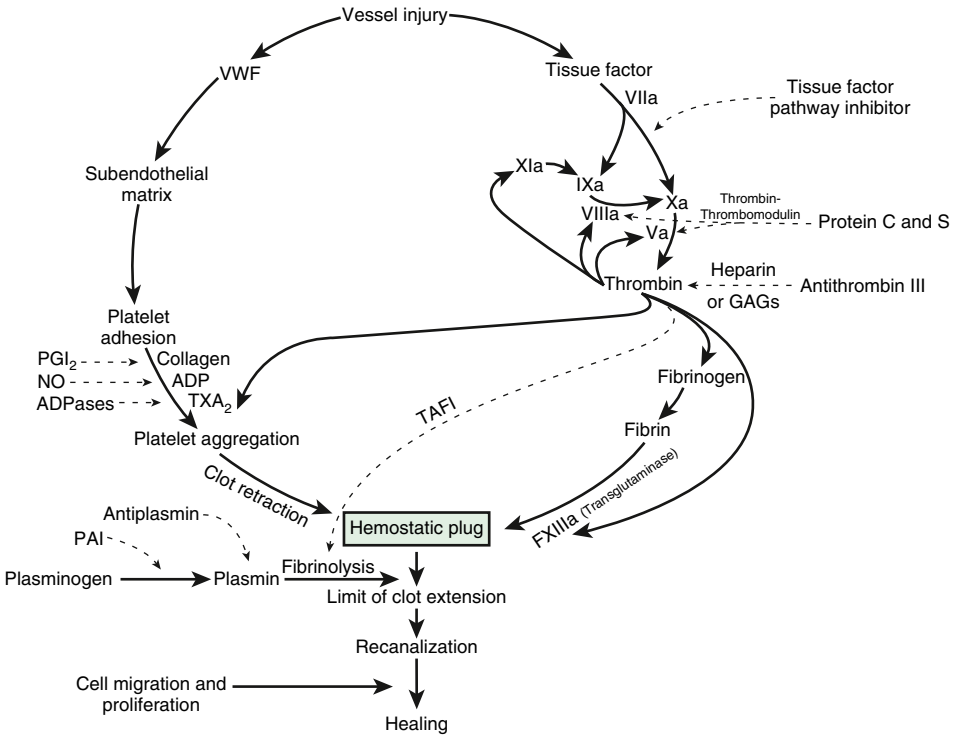

Fig. 524.2 The hemostatic mechanism. ADP, Adenosine diphosphate; GAGs, glycosaminoglycans; NO, nitric oxide; PGI_2, prostacyclin (prostaglandin I_2); PAI, plasminogen activator inhibitor; TAFI, thrombin-activated fibrinolytic inhibitor; TXA_2, thromboxane A_2; VWF, von Willebrand factor.

(DVT) or pulmonary embolism (PE), a detailed family history must be obtained to evaluate for DVT, PE, myocardial infarction (MI), or cerebrovascular accident (stroke) in other family members. The presence of **thrombosis**, especially in the absence of a provoking agent in the child or teenager, should induce the clinician to take a careful family history and consider an evaluation for a hereditary or acquired predisposition to thrombosis.

PHYSICAL EXAMINATION

The physical examination should focus on whether bleeding symptoms are associated primarily with the mucous membranes or skin (*mucocutaneous* bleeding) or with the muscles and joints (*deep* bleeding). The examination should determine the presence of petechiae, ecchymoses, hematomas, hemarthroses, or mucous membrane bleeding. Patients with defects in platelet–blood vessel wall interaction (VWD or platelet function defects) usually have mucocutaneous bleeding, which may include epistaxis, menorrhagia, petechiae, ecchymoses, occasional hematomas, and less frequently, hematuria and gastrointestinal bleeding. Individuals with a clotting deficiency of factor VIII or IX (hemophilia A or B) have symptoms of deep bleeding into muscles and joints, with much more extensive ecchymoses and hematoma formation. Patients with mild VWD or other mild bleeding disorders may have no abnormal findings on physical examination. Individuals with disorders of the collagen matrix and vessel wall may have loose joints and lax skin associated with easy bruising **(Ehlers-Danlos syndrome)**.

Patients undergoing evaluation for thrombotic disorders should be asked about swollen, warm, tender extremities (venous thrombosis), unexplained dyspnea or persistent "pneumonia," especially in the absence of fever (PE), and skin changes suggestive of chronic thrombosis (dilated collateral veins). Arterial thrombi usually cause an acute, dramatic impairment of organ function, such as stroke, MI, or a painful, white, cold extremity (Table 524.1).

LABORATORY TESTS

In patients who have a positive bleeding history or who are actively hemorrhaging, a platelet count, prothrombin time (PT), and partial thromboplastin time (PTT) should be performed as screening tests (Fig. 524.3). In individuals with abnormal screening tests, further evaluation should be based on those results (Table 524.2). In a patient with an abnormal bleeding history and a positive family history, normal screening tests should not preclude further laboratory evaluation, which may include a thrombin time, VWF testing, and platelet function studies. Historically, bleeding time and platelet function analysis **(PFA-100)** have been used as screening tests, but neither has proved to be useful in diagnosis of mild bleeding disorders.

There are no useful routine screening tests for *hereditary* thrombotic disorders. If the family history is positive or clinical thrombosis is unexplained, specific thrombophilia assays should be performed. Thrombosis is rare in children, and when it is present, the possibility of a hereditary predisposition should be considered (see Chapter 527).

Platelet Count

Platelet count is essential in the evaluation of the child with a positive bleeding history because thrombocytopenia is the most common acquired cause of a bleeding diathesis in children. Patients with a platelet count of $>50 \times 10^9$/L rarely have significant clinical bleeding. **Thrombocytosis** in children is usually reactive and is not associated with bleeding complications. Persistent, severe thrombocytosis in the absence of an underlying illness may require evaluation for the very rare pediatric presentation of essential thrombocythemia or polycythemia vera.

Prothrombin Time and Activated Partial Thromboplastin Time

Because clotting (coagulation) factors were named in the order of discovery, they do not necessarily reflect the sequential order of activation (Table 524.3; see also Table 524.2). Only two factors have commonly used names: fibrinogen (factor I) and prothrombin (factor II). The dual mechanisms of activating clotting have been termed the **intrinsic** (surface activation) and **extrinsic** (tissue factor–mediated) pathways. PT measures the activation of clotting by tissue factor (thromboplastin) in the presence of calcium. The tissue factor–factor VIIa complex activates factor X. Whether factor X is activated by the intrinsic or the extrinsic pathway, factor Xa on the platelet phospholipid surface complexes with factor Va and calcium (the "prothrombinase" complex) to activate prothrombin to thrombin (also referred to as *factor IIa*). Once thrombin is generated, fibrinogen is converted to a fibrin clot, the endpoint of the reaction (see Fig. 524.2). PT is not prolonged with deficiencies of factors VIII, IX, XI, and XII. In most laboratories, the normal PT value is 10-13 seconds. PT has been standardized using the international normalized ratio **(INR)** so that values can be compared from one laboratory or instrument to another. This ratio is used to determine similar degrees of anticoagulation with vitamin K antagonists, such as warfarin.

Partial Thromboplastin Time

The intrinsic pathway involves the initial activation of factor XII, which is accelerated by two other plasma proteins, prekallikrein and high-molecular-weight kininogen. In the clinical laboratory, factor XII is activated using a surface (silica or glass) or a contact activator, such as ellagic acid. Factor XIIa, in turn, activates factor XI to factor XIa, which then catalyzes factor IX to factor IXa. On the platelet phospholipid surface, factor IXa complexes with factor VIIIa and calcium to activate factor X ("tenase" complex).

This process is accelerated by interaction with phospholipid and calcium at the steps involving factors V and VIII. An isolated deficiency of

Table 524.1 Signs and Symptoms of Thrombosis

LOCATION OF CLOT	PRESENTING SYMPTOMS	RADIOGRAPHIC DIAGNOSIS
Venous thrombus in limbs	Swelling, pain, and/or redness	Venous ultrasonography with Doppler
Arterial thrombus in limbs	Cool limbs, diminished or absent pulse	Arterial ultrasonography with Doppler
Cerebral venous sinus thrombosis	Headache, nausea and/or vomiting, lethargy, change in mental status	CT venography or MR venography of head/brain
Pulmonary embolism	Chest pain, shortness of breath, pleuritis	CT angiography
Thrombus in the heart	Chest pain, shortness of breath, pleuritis	Echocardiogram
Portal vein thrombosis	Abdominal pain, nausea and/or vomiting, anorexia	Right upper quadrant ultrasonography with Doppler
Renal vein thrombosis	Hematuria, abdominal mass, abdominal pain, thrombocytopenia	Renal ultrasonography with Doppler or CT abdomen/pelvis with IV contrast

CT, Computed tomography; IV, intravenous; MR, magnetic resonance.
Modified from Han H, Hensch L, Hui SKR, Teruya J. Evaluation and management of coagulopathies and thrombophilias in pediatric patients. *Clin Lab Med.* 2021;41:83–100. Table 5.

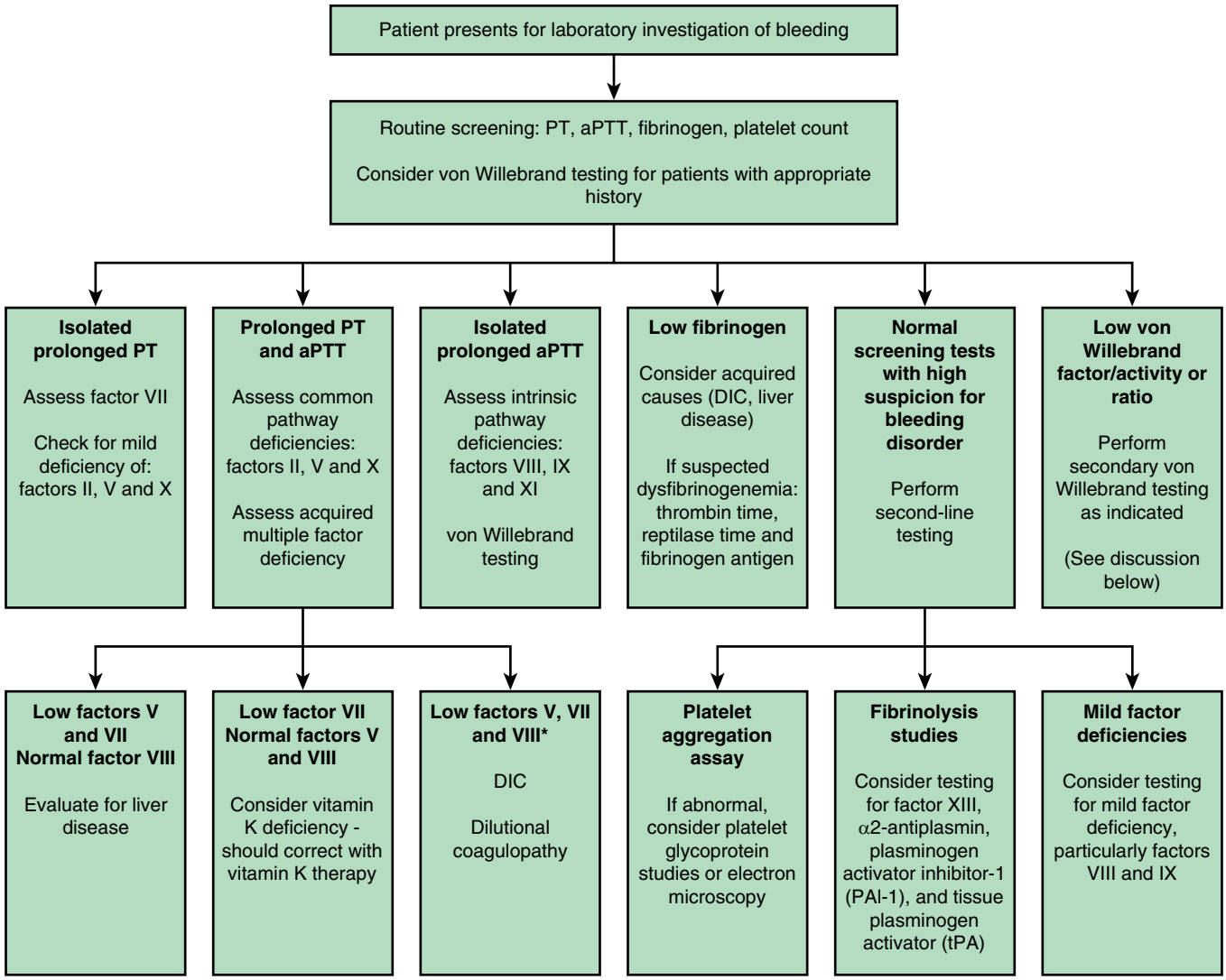

Fig. 524.3 Testing algorithm based on the screening tests (PT, aPTT, fibrinogen, and platelet count). DIC, disseminated intravascular coagulation. *Note: Factor VIII can be normal or increased in these settings secondary to the acute phase response. *(From Han H, Hensch L, Hui SKR, Teruya J. Evaluation and management of coagulopathies and thrombophilias in pediatric patients. Clin Lab Med. 2021;41:83–100. Fig. 1.)*

a single clotting factor may result in isolated prolongation of PT, PTT, or both, depending on the location of the factor in the clotting cascade. This approach is useful in determining hereditary clotting factor deficiencies; however, in acquired hemostatic disorders encountered in clinical practice, more than one clotting factor is frequently deficient, so the relative prolongation of PT and PTT must be assessed.

Measurement of PTT as performed in the clinical laboratory is actually "activated" PTT; most refer to it as **PTT**. This test measures the initiation of clotting at the level of factor XII through sequential steps to the final clot endpoint. It does not measure factor VII, factor XIII, or anticoagulants. PTT uses a contact activator (silica, kaolin, or ellagic acid) in the presence of calcium and phospholipid. Because of differences in reagents and laboratory instruments, the normal range for PTT varies among hospital laboratories. Normal ranges for PTT have much more interlaboratory variability than those for PT.

Thus the mechanisms studied by PT and PTT allow the evaluation of clotting factor deficiencies, even though these pathways may not be the same as those occurring physiologically. The PTT can be prolonged by deficiencies of factor XII, prekallikrein, and high-molecular-weight kininogen, yet these deficiencies do not result in bleeding,

Thrombin Time

Thrombin time (TT) measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin. The normal TT varies between laboratories but is usually 11-15 seconds. Prolongation of TT occurs with reduced fibrinogen levels (*hypofibrinogenemia* or *afibrinogenemia*), with dysfunctional fibrinogen *(dysfibrinogenemia)*, or in the presence of substances that interfere with fibrin polymerization, such as heparin and fibrin split products. If heparin contamination is a potential cause of prolonged TT, a reptilase time can be ordered.

Reptilase Time

Reptilase time uses snake venom to clot fibrinogen. Unlike thrombin time, reptilase time is not sensitive to heparin and is prolonged only by reduced or dysfunctional fibrinogen and fibrin split products. Therefore, if TT is prolonged but reptilase time is normal, the prolonged TT is caused by heparin and does not indicate the presence of fibrin split products or reduced concentration or function of fibrinogen.

Mixing Studies

If there is unexplained prolongation of PT or PTT, a mixing study is usually performed. Normal plasma is added to the patient's plasma, and the PT or PTT is repeated. Correction of PT or PTT by 1:1 mixing with normal plasma suggests deficiency of a clotting factor because a 50% level of individual clotting proteins is sufficient to produce normal PT or PTT. If the clotting time is not corrected or only partially corrected, an **inhibitor** is usually present. An inhibitor of clotting may be either a chemical similar to heparin that delays coagulation or an

Table 524.2 Causes of Bleeding Associated with Prolonged Prothrombin Time and Activated Partial Thromboplastin Time

ISOLATED PROLONGED PT	ISOLATED PROLONGED aPTT	PROLONGED PT AND aPTT	CAUSES OF BLEEDING WITHOUT PT/aPTT PROLONGATION
FVII deficiency	Hemophilia A (FVIII deficiency)	Disseminated intravascular coagulation	FXIII deficiency
Mild common pathway factor deficiency (II, V, and X), fibrinogen deficiency	Hemophilia B (FIX deficiency)	Dilutional coagulopathy	von Willebrand disease
Early vitamin K deficiency	Hemophilia C (FXI deficiency)	Liver synthetic dysfunction	Platelet dysfunction
Early liver synthetic dysfunction	von Willebrand disease	Marked vitamin K deficiency	Mild deficiency of FVIII, FIX, and FXI
Direct Xa inhibitor	Acquired FVIII, FIX, or FXI inhibitors	Common pathway factor deficiency (FII, FV, and FX), severe fibrinogen deficiency	α_2-antiplasmin deficiency and other causes of hyperfibrinolysis
—	Heparin	Warfarin or direct thrombin inhibitor, DOAC (not always)	Collagen vascular diseases (i.e., Ehlers-Danlos syndrome)
—	—	Increased tissue factor pathway inhibitor, FV Amsterdam or East Texas bleeding disorder	DOAC

DOAC, Direct oral anticoagulant.
From Han H, Hensch L, Hui SKR, Teruya J. Evaluation and management of coagulopathies and thrombophilias in pediatric patients. *Clin Lab Med.* 2021;41:83–100. Table 1.

Table 524.3 Coagulation (Clotting) Factors

CLOTTING FACTOR	SYNONYM	DISORDER
I	Fibrinogen	Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)
II	Prothrombin	Congenital deficiency or dysfunction
V	Labile factor, proaccelerin	Congenital deficiency (parahemophilia)
VII	Stable factor or proconvertin	Congenital deficiency
VIII	Antihemophilic factor	Congenital deficiency is hemophilia A (classic hemophilia)
IX	Christmas factor	Congenital deficiency is hemophilia B (sometimes referred to as Christmas disease)
X	Stuart-Prower factor	Congenital deficiency
XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

antibody directed against a specific clotting factor or the phospholipid used in clotting tests. In the inpatient setting the most common cause of a prolonged PTT is **heparin contamination** of the sample. The presence of heparin in the sample can be ruled in or out by adding *heparinase* to the sample and repeating the PTT. If the mixing study is not corrected or if its result becomes more prolonged and the patient has clinical bleeding, an inhibitor of a specific clotting factor (antibody directed against the factor), most often factor VIII, factor IX, or factor XI, may be present. If the patient has no bleeding symptoms and both PTT and the mixing study are prolonged, a **lupus-like anticoagulant** (see Chapter 531) is often present. Patients with these findings usually have a long PTT but do not bleed.

Platelet Aggregation

When a qualitative platelet function defect is suspected, platelet aggregation testing is usually ordered. Platelet-rich plasma from the patient is activated with a series of agonists (ADP, epinephrine, collagen, thrombin or thrombin-receptor peptide, and ristocetin). Some platelet aggregometers measure specific adenosine triphosphate release from the platelets, as measured by the generation of luminescence via lumi-aggregometry, and are more sensitive in detecting abnormalities of the platelet release reaction from storage granules. Repeat testing or testing of other symptomatic family members can help to determine the hereditary nature of the defect. Many medications, especially aspirin, other NSAIDs, and valproic acid, alter platelet function testing. Figure 524.1 provides an approach to the differential diagnosis of many common bleeding disorders based on screening tests.

Factor XIII

The PT and PTT reflect only fibrin formation and do not measure cross-linking by factor XIII. Therefore specific testing is required to identify factor XIII deficiency. Clot solubility testing can be performed but only identifies the most severely affected individuals. Quantitative measurement of factor XIII levels can also be performed.

Testing for Thrombotic Predisposition

Hereditary predisposition to thrombosis is associated with a reduction of anticoagulant function (protein C, protein S, AT III); the presence of

Table 524.4 Reference Values for Coagulation Tests in Healthy Children

PARAMETER	15 D-4 WK	1-5 MO	6-11 MO	1-5 YR	6-10 YR	11-17 YR	ADULT RANGES
SCREENING TESTS							
PT (sec)	11.2 (9.5-12.6)	11.0 (9.7-12.8)	11.0 (9.8-13.0)	11.3 (9.9-13.4)	11.7 (10.0-14.6)	11.8 (10.0-14.1)	10.9 (9.2-12.2)
PTT (sec)	35.4 (27.6-45.6)	33.5 (24.8-40.7)	32.4 (25.1-40.7)	31.6 (24.0-39.2)	31.6 (26.9-38.7)	31.0 (24.6-38.4)	31.7 (27.8-36.3)
COAGULATION PROTEINS							
Fibrinogen (g/L)	2.54 (1.43-4.02)	2.26 (1.50-3.76)	2.33 (1.57-3.60)	2.73 (1.88-4.13)	2.78 (1.89-4.75)	2.66 (1.77-4.20)	2.75 (2.17-3.42)
FII (IU/mL)	56 (45-74)	75 (47-111)	92 (74-117)	99 (49-130)	90 (68-132)	94 (48-119)	101 (75-132)
FV (IU/mL)	100 (69-124)	100 (60-147)	102 (59-160)	111 (73-188)	101 (82-141)	97 (62-125)	99 (61-142)
FVII (IU/mL)	76 (55-108)	88 (43-141)	88 (52-128)	82 (48-124)	77 (55-135)	82 (55-133)	95 (59-151)
FVIII (IU/mL)	96 (65-153)	85 (50-187)	75 (53-132)	95 (59-167)	87 (61-154)	93 (43-155)	97 (56-146)
FIX (IU/mL)	44 (30-77)	53 (29-105)	77 (51-107)	84 (53-129)	80 (55-156)	97 (60-138)	112 (70-131)
FX (IU/mL)	85 (66-92)	89 (68-122)	100 (76-134)	99 (60-153)	99 (71-162)	93 (64-131)	106 (73-150)
FXI IU/mL)	56 (33-75)	64 (28-126)	86 (61-126)	92 (58-154)	83 (32-154)	84 (55-139)	105 (49-139)
FXII (U/mL)	69 (25-81)	76 (38-137)	109 (48-156)	107 (50-175)	84 (49-154)	92 (49-154)	108 (47-157)
FXIII (IU/mL)	86 (78-100)	83 (55-133)	92 (51-137)	97 (49-137)	97 (54-142)	106 (64-133)	100 (68-138)
Von Willebrand antigen (IU/mL)	163 (46-220)	102 (36-217)	79 (48-199)	89 (41-186)	80 (45-141)	92 (56-123)	91 (43-144)
ANTICOAGULANT PROTEINS							
Antithrombin (IU/mL)	41 (33-63)	80 (29-120)	96 (63-122)	67 (61-128)	97 (64-136)	97 (64-136)	112 (83-126)
Protein C (IU/mL)	38 (30-115)	82 (28-128)	85 (44-151)	86 (61-144)	91 (39-170)	95 (66-127)	119 (69-149)
Protein S (IU/mL)	90 (29-115)	82 (33-154)	88 (52-1138)	97 (60-149)	105 (67-162)	99 (53-147)	102 (58-138)
Plasminogen (U/mL)	53 (41-83)	69 (38-110)	81 (49-126)	92 (60-178)	92 (52-158)	92 (58-131)	94 (63-135)
D-dimer (ng/mL)	530 (445-1200)	515 (90-878)	270 (133-844)	280 (88-780)	275 (60-567)	245 (69-580)	277 (109-560)

PT, Prothrombin time; PTT, partial thromboplastin time.
Data expressed as median (95% confidence interval).
Data adapted from Toulon P, Berruyer M, Brionne-François M, et al. Age dependency for coagulation parameters in paediatric populations. Results of a multicentre study aimed at defining the age-specific reference ranges. *Thromb Haemost.* 2016;116:9–16.

a factor V molecule that is resistant to inactivation by protein C (factor V Leiden); elevated levels of procoagulants (a pathogenic variant of the prothrombin gene); or a deficiency of fibrinolysis (plasminogen deficiency); and the rare metabolic disease homocystinuria (see Chapter 527).

Tests of the Fibrinolytic System

Euglobulin clot lysis time is a screening test used in some laboratories to assess fibrinolysis. More specific tests are available in most laboratories to determine the levels of plasminogen, plasminogen activator, and inhibitors of fibrinolysis. An increase in fibrinolysis may be associated with hemorrhagic symptoms, and a delay in fibrinolysis is associated with thrombosis.

DEVELOPMENTAL HEMOSTASIS

The normal newborn infant has reduced plasma concentrations of several procoagulants and anticoagulants compared to adults (see Table 524.4), and this is even more pronounced in preterm infants. During gestation, there is progressive maturation and increase of the clotting factors synthesized by the liver. The extremely premature infant has prolonged PT and PTT values, as well as a marked reduction in anticoagulant protein levels (protein C, protein S, and AT). Levels of fibrinogen, factors V and VIII, VWF, and platelets are near-normal throughout the later stages of gestation (see Chapter 142). Because protein C and protein S are physiologically reduced, factors V and VIII, which are present at normal levels at birth, are not balanced with their regulatory proteins. In contrast, the physiologic deficiency of vitamin K–dependent procoagulant proteins (factors II, VII, IX, and X) is partially balanced by the physiologic reduction of AT. The net effect is that newborns (especially premature infants) are at increased risk for complications of bleeding, clotting, or both. Establishing absolute cutoff values for normal ranges of coagulation proteins in newborn and preterm infants is challenging because of the age-dependent variation and heterogeneity among laboratory instruments and reagents. Repeat testing (or testing parents) may be necessary to confirm a diagnosis of an inherited deficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 525

Hereditary Clotting Factor Deficiencies (Bleeding Disorders)

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Inherited deficiencies in the coagulation factors responsible for forming cross-linked fibrin clots (as detailed in Chapter 524) can result in bleeding disorders. **Hemophilia A** (factor VIII deficiency) and **hemophilia B** (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies. The clinical findings in hemophilia A and hemophilia B are virtually identical. Factor XI deficiency is a rare autosomal bleeding disorder discussed in Chapter 525.2. Reduced levels of the *contact factors* (factor XII, high molecular weight kininogen, and prekallikrein) are associated with significant prolongation of *activated partial thromboplastin time* (aPTT; also referred to as **PTT**) but are not associated with clinical bleeding, as discussed in Chapter 525.3.

525.1 Factor VIII or Factor IX Deficiency (Hemophilia A or B)

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common severe inherited bleeding disorders.

PATHOPHYSIOLOGY

The activated forms of factors VIII and IX participate in the enzyme complex responsible for the sustained proteolytic activation of factor X during coagulation. Together with phospholipids and calcium, they form the intrinsic tenase (or factor X activating) complex. Hemophilia A and hemophilia B have similar clinical manifestations because, molecularly, both disorders result in a deficiency of factor X activation, which, in turn, results in insufficient thrombin generation (see Fig. 524.1 in Chapter 524 for a depiction of the in vitro clotting process as it occurs in the test tube). In hemostatically normal individuals, hemorrhage after an injury is constrained by the initial formation of the platelet plug, which is stabilized by the generation of a cross-linked fibrin clot. In people with hemophilia A or B, clot formation is delayed and ineffectual. Inadequate thrombin production leads to failure to form a tightly cross-linked fibrin to support the platelet plug. When untreated bleeding occurs in a closed space, such as a joint, bleeding may stop as the result of **tamponade**. With open wounds, in which tamponade cannot occur, even minor injuries may result in significant blood loss, with a highly friable clot forming slowly; rebleeding occurs during physiologic thrombolysis or with minimal new traumas.

CLINICAL MANIFESTATIONS

The severity of the bleeding phenotype in hemophilia A and B is strongly associated with the amount of residual factor VIII or factor IX, respectively. **Severe hemophilia** is characterized by having <1% normal factor activity, and bleeding is frequent and often spontaneous. Patients with **moderate hemophilia** have factor levels of 1–5% normal and bleed excessively with mild trauma. Individuals with **mild hemophilia** have factor levels 5–40% normal and usually only bleed abnormally after major trauma or surgery; people with mild hemophilia may go many years before the condition is diagnosed.

Because neither factor VIII nor factor IX crosses the placenta, bleeding symptoms may be present at birth. Between 1% and 4% of neonates with hemophilia have intracranial hemorrhages, mostly from birth trauma. However, about 35% and 70% of male infants with severe and nonsevere hemophilia, respectively, *do not bleed* with circumcision. Thus, in the absence of a positive family history (50% of cases), hemophilia may go undiagnosed in the newborn period. Obvious symptoms, such as easy bruising, intramuscular hematomas, and hemarthroses, begin when the child starts to cruise. Bleeding from minor traumatic lacerations of the mouth (torn frenulum) may persist for hours or days and may cause the parents to seek medical evaluation. Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by a year of age.

Although bleeding may occur in any area of the body, the hallmark of hemophilia bleeding is **hemarthrosis**, which can occur spontaneously or after minor trauma. The earliest joint hemorrhages appear most often in the ankles. In the older child and adolescent, hemarthroses of the knees and elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling and fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does: patients report a warm, tingling sensation in the affected joint as the first sign of a joint hemorrhage. Repeated bleeding episodes into the same joint may result in a "target" joint, which becomes more susceptible to recurrent bleeding because of the pathologic changes (see "Chronic Complications").

Although most **muscular hemorrhages** are clinically evident because of localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention. A patient may lose large volumes of blood into the iliopsoas muscle, verging on hypovolemic shock, with only a vague area of referred pain in the groin. The hip is held in a flexed, internally rotated position because of irritation of the iliopsoas. The diagnosis is made clinically from the inability to extend the hip but should be confirmed with ultrasonography, CT, or MRI (Fig. 525.1).

Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system [CNS], upper airway) or by exsanguination (external trauma, gastrointestinal [GI] or iliopsoas hemorrhage). Prompt treatment with clotting factor concentrate for these life-threatening hemorrhages is imperative. If head trauma is of sufficient concern to suggest radiologic evaluation, factor replacement should *precede* radiologic evaluation. Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL or 100%; see section below on "Treatment").

LABORATORY FINDINGS AND DIAGNOSIS

A reduced level of factor VIII or factor IX will often result in a *prolonged PTT*. In severe hemophilia, the PTT value is usually 2-3 times the upper limit of normal. However, depending on the PTT reagents, people with mild hemophilia can have a PTT in the normal range. Results of the other screening tests of the hemostatic mechanism (platelet count, bleeding time, prothrombin time [PT]) are normal. The specific activity assays for factors VIII and IX confirm the diagnosis of hemophilia. One IU of each factor activity is defined as that amount in 1 mL of normal plasma, referenced against a standard established by the World Health Organization (WHO). Thus 100 mL of normal plasma has 100 IU/dL (100% normal activity) of each factor. The term *% activity* refers to the percentage found in normal plasma (100% activity). Factor concentrates are also referenced against an international WHO standard, so treatment doses are usually referred to in IU.

In the newborn period, factor VIII activity values may be artificially elevated because of the acute-phase response elicited by the birth process. This artificial elevation may cause an infant with mild hemophilia A to have a normal or near-normal measured level. Patients with severe hemophilia A do not have detectable levels of factor VIII. In contrast, factor IX levels are physiologically low in all newborns and only reach adult values at about 6 months of age. If severe hemophilia is present in the family, an undetectable level of factor IX is diagnostic of severe hemophilia B. In some patients with mild factor IX deficiency, the presence of low factor IX activity can be confirmed only after several months of life.

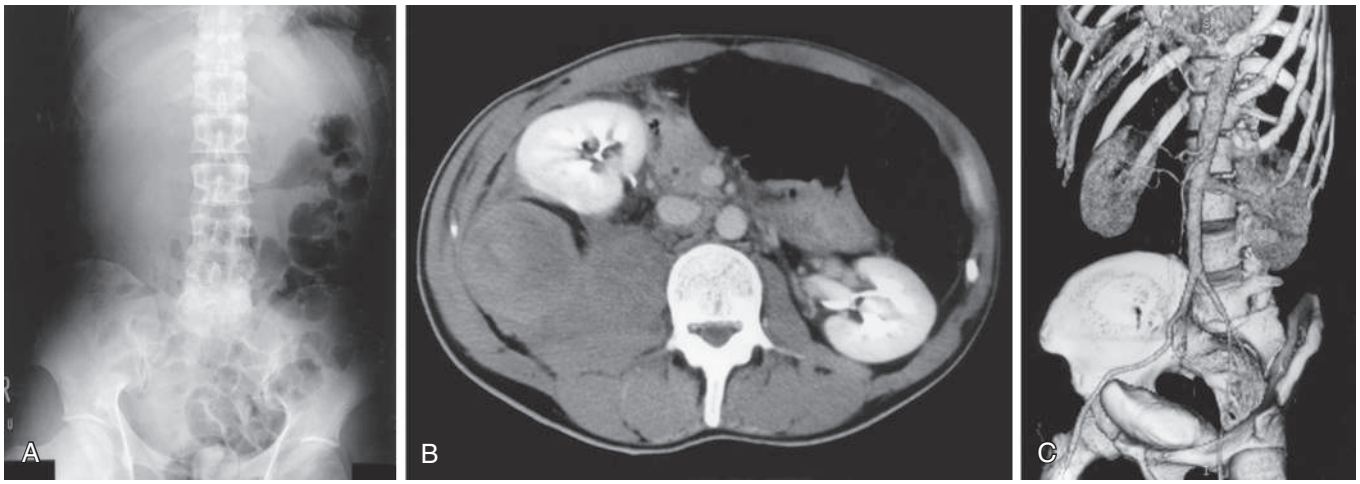

Fig. 525.1 Massive hematoma into the iliopsoas muscle in a patient with hemophilia B. A male with severe deficiency of factor IX (hemophilia B) was admitted for right lower abdominal pain of progressively increasing severity and tenderness. He had had a common cold with severe cough and loss of appetite for approximately 1 week. **A,** Abdominal radiograph shows presence of the psoas sign on the right side and left-shifted colon gas. **B,** CT scan shows massive hematoma in the right iliopsoas muscle, resulting in anterior translocation of the right kidney. **C,** Reconstructed 3-dimensional image shows more clearly the kidney translocation and the extended, but intact, large vessels. These are useful findings for the diagnostic procedures because progressive right lower abdominal pain may closely simulate acute appendicitis. The hemorrhage was successfully managed by replacement of factor IX for 1 week without any recurrence. The patient did not have any inhibitors to factor IX. *(From Miyazaki K, Higashihara M. Massive hemorrhage into the iliopsoas muscle. Intern Med. 2005;44:158–159.)*

The mixing of normal plasma with hemophilia plasma usually corrects PTT value, unless the patient has an inhibitor, as discussed later. An inhibitor titer can be quantified by the Bethesda assay, where 1 Bethesda Unit (BU) neutralizes 1 IU/mL of factor.

DIFFERENTIAL DIAGNOSIS

In young infants with severe bleeding manifestations, the differential diagnosis includes severe thrombocytopenia; severe platelet function disorders, such as Bernard-Soulier syndrome and Glanzmann thrombasthenia; type 3 (severe) von Willebrand disease; and vitamin K deficiency.

GENETICS

The genes for factor VIII and IX (*F8* and *F9*, respectively) are carried near the terminus of the long arm of the X chromosome, making hemophilia an X-linked disorder. It occurs in approximately 1/5,000 males, with 80% having factor VIII deficiency and 20% having factor IX deficiency. Hemophilia appears in all ethnic groups. A third of cases are estimated to be the result of a spontaneous pathogenic variant. Approximately 50% of cases of severe hemophilia A have a specific *F8* change, in which there is an internal inversion within the factor VIII gene (intron 22 inversion). Meanwhile, 98% of hemophilia patients have an identified genetic cause of their hemophilia, which can facilitate diagnosis, prenatal testing, and identification of female carriers.

Some **female carriers** (heterozygotes) have sufficiently low factor level to have abnormal bleeding. Factor levels should be determined in all known or potential carriers to assess the need for treatment in the event of surgery or clinical bleeding. Female carriers with factor levels <40% normal are considered to have hemophilia and should be treated as such. Notably, about 0.2% of people with severe and moderate hemophilia are female, mostly because of skewed lyonization or Turner syndrome. Female carriers with factor levels >40% normal can also have abnormal bleeding and are termed *symptomatic hemophilia carriers*. Historically, female carriers were thought to be asymptomatic, but newer data prove these individuals can also have significant bleeding.

TREATMENT

Disease-specific therapy started early in life is the hallmark of excellent hemophilia care (Table 525.1). Treatment can be divided into on-demand therapy (hemostatic interventions to stop bleeding) and prophylaxis therapy to prevent bleeding. *Prophylaxis is the standard of care for children with severe hemophilia* in countries with sufficient medical resources. Prophylaxis decreases catastrophic bleeding, prevents hemarthrosis, and preserves joint health. The types of hemostatic agents available for hemophilia A and hemophilia B are rapidly expanding, with several new classes of medications receiving regulatory approval (Table 525.2).

On-Demand Treatment

To treat acute bleeding, nothing works better than replacing the deficient coagulation factor. When mild to moderate bleeding occurs, values of factor VIII or factor IX must be raised to hemostatic levels, approximately 50% of normal activity. For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity. Both plasma-derived and recombinant factor VIII and factor IX concentrates are available. Replacement therapy requires intravenous administration, which patients and families often learn to do themselves. The half-lives of standard factor VIII and factor IX are 8-12 hours and 18-24 hours, respectively, although there is wide variability between patients with younger children often having shorter half-lives. There are also bioengineered factor VIII and factor IX products designed to have longer half-lives (termed *extended half-life products*), which reduce the frequency of intravenous administrations necessary to treat bleeds and provide prophylaxis.

Table 525.1 summarizes the treatment recommendations of some common types of hemorrhage in a patient with hemophilia. The calculation of the factor replacement dose is as follows, with the difference between factor VIII and factor IX being because of their different volumes of distribution:

$$\text{Factor VIII dose (IU)} = [\%\ \text{desired raise}] \times [\text{weight (kg)}] \times 0.5$$

$$\text{Factor IX dose (IU)} = [\%\ \text{desired raise}] \times [\text{weight (kg)}] \times 1.3$$

Therefore emergency dosing for factor VIII deficiency is approximately 50 units per kg and emergency dosing for factor IX deficiency is approximately 100-130 units/kg.

It is important to note that patients can have variable recoveries, and different factor products also have slightly different recoveries. Many patients will carry dosing cards detailing their recommended treatments. In general, doses are rounded up to vial size so as not to waste product.

For some patients with *mild* factor VIII deficiency, **desmopressin acetate** can be used to stimulate the cellular release of endogenously

Table 525.1 Treatment of Hemophilia *Without* Inhibitors

TYPE OF HEMORRHAGE	HEMOPHILIA A	HEMOPHILIA B
Hemarthrosis*	50-60 IU/kg factor VIII concentrate† on day 1, then 20 IU/kg the following day. Consider every other day until joint function is normal or back to baseline. Consider prophylaxis.	80-100 IU/kg factor IX concentrate‡ on day 1; then 40 IU/kg the following day. Consider every other day until joint function is normal or back to baseline. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every other day treatment may be needed until resolved.	80 IU/kg factor IX concentrate‡; 40 IU/kg every 2-3 days may be needed until resolved.
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate†; antifibrinolytic therapy§; remove loose deciduous tooth.	40 IU/kg factor IX concentrate‡; antifibrinolytic therapy§; remove loose deciduous tooth.
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy§; 20 IU/kg factor VIII concentrate† if this treatment fails.‖	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy§; 30 IU/kg factor IX concentrate‡ if this treatment fails.#
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate; then initiate 25 IU/kg q8-12h to maintain trough level >50 IU/dL for 5-7 days; then 50 IU/kg q24h to maintain trough >25 IU/dL for 7 days; monitor factor VIII levels.	80-120 IU/kg factor IX concentrate‡, then 50-60 IU/kg q12-24h to maintain factor IX at >40 IU/dL for 5-7 days, and then at >30 IU/dL for 7 days; monitor factor IX levels.
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate; then 25 IU/kg q12h until asymptomatic; then 20 IU/kg every other day, for a total of 10-14 days.**	100 IU/kg factor IX concentrate‡; then 50-60 IU/kg q12-24h to maintain factor IX at >40 IU/dL until patient is asymptomatic; then 40-50 IU every other day, for a total of 10-14 days.**
Hematuria	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected).	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; if not controlled, give prednisone (unless patient is HIV-infected).

*For hip hemarthrosis, orthopedic evaluation for possible aspiration is advisable to prevent avascular necrosis of the femoral head.
†For mild or moderate hemophilia, desmopressin 0.3 μg/kg can be used instead of factor VIII concentrate if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.
‡Stated doses apply for recombinant factor IX concentrate; different dosing may apply for long-acting recombinant factor IX concentrates or plasma-derived factor IX.
§Do not give antifibrinolytic therapy until 4-6 hr after a dose of prothrombin complex concentrate.
#Nonprescription coagulation-promoting products may be helpful.
**Repeat radiologic assessment should be performed before discontinuation of therapy.
HIV, Human immunodeficiency virus; IU, international units; q12-24h, every 12 to 24 hours.
Adapted from Di Paola J, Montgomery RR, Gill JC, Flood VH. Hemophilia and von Willebrand disease. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier, 2015: pp. 1028–1054.

Table 525.2 Strengths and Weaknesses of the Old and New Therapeutic Options for Hemophilia

	STRENGTHS	WEAKNESSES
Standard half-life clotting factor concentrates	Effective for both bleeding control and prevention; well established safety and effectiveness profile for decades; measurable FVIII and FIX concentrations as surrogate marker of effectiveness; can result in normal concentrations of FVIII and FIX	Frequent intravenous injections; inhibitor development
Extended half-life clotting factor concentrates	Effective for both bleeding control and prevention; a reduced number of injections; higher trough concentrations; measurable FVIII and FIX concentrations as surrogate markers of effectiveness; can result in normal concentrations of FVIII and FIX	Intravenous route; inhibitor development
Nonreplacement therapies (emicizumab, fitusiran, anti-tissue factor pathway inhibitor antibodies, SerpinPC)	Subcutaneous route; infrequent injections; standard doses for all patients	Need for adjunctive hemostatic treatment; steady state of coagulation activity not within the normal range; thrombotic risk
Gene therapy	Single intravenous injection; restoration of endogenous FVIII and FIX production	Preexisting immunity against adeno-associated viral vectors; immune response against vectors and transfected cells; unknown durability of transduction; need for immunosuppressive therapy; unknown long-term safety

FVIII, factor VIII; FIX, factor IX.
From Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet.* 2021;397:630–640. Table 5.

produced factor VIII to increase its plasma levels. In patients with moderate or severe factor VIII deficiency, the stored levels of factor VIII are inadequate, and desmopressin treatment is ineffective. Desmopressin can be administered intravenously or intranasally, with the latter facilitating home treatment. The intranasal formulation is a higher concentration of desmopressin than that used to treat enuresis or hypopituitarism; the dose is 150 μg (1 spray) for children weighing <50 kg and 300 μg (2 sprays) for children and young adults weighing >50 kg. Most centers administer a trial of desmopressin to determine if the factor VIII levels increase sufficiently for hemostasis. Because desmopressin triggers the release of cellularly stored factor VIII, usually it can only be given twice in a 1-2 day period. The most serious complication is hyponatremia, which can be mitigated by fluid restrictions for the 24 hours after administration. Desmopressin is not effective in the treatment of factor IX deficiency.

Mucosal bleeding often benefits from antifibrinolytic agents such as aminocaproic acid or tranexamic acid that can be given orally or intravenously.

PROPHYLAXIS

Many patients are given lifelong prophylaxis to prevent spontaneous joint bleeding. The World Federation of Hemophilia recommends prophylaxis for children with severe hemophilia and for adults with joint disease. Usually, such programs are initiated at the time of the first or second joint hemorrhage. Young children often require the insertion of a central catheter to ensure venous access for factor replacements. Such regimens are expensive but highly effective in preventing or greatly limiting the degree of joint pathology; complications include central line infection and thrombosis.

The goal of prophylaxis is generally to maintain a measurable plasma factor level (1–2%), when assayed just before the next infusion (trough level); this converts patients from severe to moderate hemophilia. For standard half-life products, this typically requires intravenous administration 2-4 times per week; this frequency is reduced with prophylaxis with extended half-life products.

Another class of hemophilia drugs that promotes hemostasis without factor VIII or factor IX is termed **nonfactor therapies**. Emicizumab is approved for prophylaxis for hemophilia A. Emicizumab is a bispecific, humanized monoclonal antibody that can bridge activated factor IX and factor X to restore factor X activation. It is administered subcutaneously and is given only 1-4 times per month after four weekly loading doses. Because emicizumab mimics some of the biochemistry of activated factor VIII, it dramatically shortens PTT times. It is not used to treat acute bleeds.

Efanesoctocog alfa, a modified extended half-life single recombinant factor VIII protein that decouples recombinant factor VIII from endogenous von Willebrand factor, has demonstrated efficacy in patients with severe hemophilia A. **Fitusiran**, a small interfering RNA molecule that reduces antithrombin synthesis, has been used successfully for prophylaxis in patients with hemophilia A or B with or without inhibitors. **Gene therapy** (valoctocogene roxaparvovec for hemophilia A; etranacogene dezaparvovec for hemophilia B) has demonstrated efficacy in reducing bleeding in adult patients with severe hemophilia.

SUPPORTIVE CARE

Effective measures to avoid trauma include anticipatory guidance, including the use of car seats, seatbelts, and bike helmets and the avoidance of high-risk behaviors. Older males should be counseled to avoid violent contact sports, but this issue is admittedly a challenge; however, active lifestyles are also encouraged to limit obesity. Early psychosocial intervention helps the family achieve a balance between overprotection and permissiveness. Patients with hemophilia should avoid aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) that affect platelet function.

Inhibitor Formation

The formation of neutralizing antibodies, termed *inhibitors*, is the major complication of factor VIII or factor IX replacement therapy. They develop in 20–30% of severe hemophilia A patients and 3–10% of severe hemophilia B patients that receive factor therapy, usually within 20 exposures to factor. Inhibitors may be identified during routine laboratory surveillance or become clinically apparent when bleeding episodes fail to respond to appropriate replacement therapy. There are both patient and product risk factors for inhibitor development, with the underlying hemophilia-causing gene pathogenic variant being the most important with the majority of people with large-gene deletions developing inhibitors. Prophylaxis with plasma-derived factor VIII products decreases the risk of inhibitor development about 1.7-fold compared to recombinant factor VIII products. Intensive early factor exposure during surgery or major trauma increases the risk of inhibitor development, likely through initiating immunologic danger signaling. Patients with inhibitors always require referral to a center that cares for many such patients and has a comprehensive hemophilia program.

Clinically, inhibitor titers are demarcated as low-titer (≤5 BU) and high-titer (>5 BU). Low-titer inhibitors can often be overcome by large amounts of factor, while high-titers necessitate the use of bypassing agents, which can circumvent the inhibitor to promote hemostasis. The two bypassing agents available that can treat acute bleeds are activated prothrombin complex concentrates and recombinant activated factor VII, both of which are administered intravenously. Prophylaxis regimens for bypassing agents have been described, but most hemophilia A patients with inhibitors currently use emicizumab prophylaxis because of its efficacy and ease of administration.

Inhibitor eradication has been prioritized, and it is still recommended since the advent of emicizumab. Low-titer or transient inhibitors often disappear with continued regular factor infusions. Higher titer inhibitors often require immune tolerance induction regimens, in which high doses of factor are administered to attempt to develop immune tolerance. This procedure is successful in about two-thirds of severe hemophilia A patients. Immune tolerance induction with factor IX products is complicated by allergic reactions and the development of nephrotic syndrome in some patients. Rituximab, corticosteroids, and other immunosuppressives have been used in patients with high-titer inhibitors in whom immune tolerance programs have failed, although the use of immunosuppressive therapy has declined with the use of emicizumab prophylaxis for factor VIII deficiency inhibitor patients.

CHRONIC COMPLICATIONS

Long-term complications of hemophilia A and B include chronic arthropathy and the risk of transfusion-transmitted infectious diseases, although both complications have been substantially mitigated with modern hemophilia care, including early initiation of prophylaxis and the use of recombinant protein products or plasma-derived products with advanced donor screening and highly active viricidal procedures.

Chronic arthropathy is the major long-term disability associated with hemophilia. The natural history of severe hemophilia without prophylaxis is one of cyclic recurrent hemorrhages into specific joints, including hemorrhages into the same (target) joint. In young children, the joint distends easily, and a large volume of blood may fill the joint until tamponade ensues or therapy intervenes. After joint hemorrhage, proteolytic enzymes are released by white blood cells into the joint space, and heme iron induces macrophage proliferation, leading to inflammation of the synovium. The synovium thickens and develops frondlike projections into the joint that are susceptible to being pinched and may induce further hemorrhage. The cartilaginous surface becomes eroded and ultimately may even expose raw bone, leaving the joint susceptible to articular fusion. In the older patient with advanced arthropathy, bleeding into the target joint, with its thickened synovium, causes severe pain, because the joint has little space to accommodate blood. Once a target joint develops, the patient is usually given short- or long-term prophylaxis to prevent progression of the arthropathy and reduce inflammation.

In the past, plasma-derived products tragically transmitted hepatitis B virus, hepatitis C virus, and HIV to large numbers of people with hemophilia. Modern plasma-derived products pose a very low risk of spreading identified bloodborne pathogens, but the risk of transmitting unidentified pathogens or emerging agents such as prions remains largely undefined.

COMPREHENSIVE CARE

Patients with hemophilia are best managed through comprehensive hemophilia care centers. Such centers are dedicated to patient and family education and the prevention and treatment of the complications of

hemophilia, including chronic joint disease and inhibitor development. Such centers involve a team that includes physicians, nurses, orthopedists, physical therapists, and psychosocial workers, all focused on hemophilia care. Education remains crucial in hemophilia care because patients who are receiving prophylaxis may be less experienced in recognizing bleeding episodes than affected children from previous eras.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.2 Factor XI Deficiency

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Factor XI deficiency (previously known as hemophilia C) is an autosomal disorder associated with mild to moderate bleeding symptoms. Bleeding is usually after trauma and surgery, with bleeding most commonly occurring at sites of high fibrinolytic activity, such as the oropharynx and urogenital tract. This focality is likely secondary to the role of factor XI in augmenting thrombin generation for the subsequent activation of *thrombin-activatable fibrinolysis inhibitor* (TAFI). Heavy menstrual bleeding is also common in females with factor XI deficiency. Factor XI deficiency can occur in any ethnic group but is frequently encountered in Ashkenazi Jews with a heterozygous frequency of 1 in 11 individuals. Factor XI deficiency usually (but not always) results in a prolonged PTT; specific factor XI activity assays are diagnostic.

The bleeding phenotype is poorly predicted by the measured factor XI activity. Some patients with severe deficiency (<20% normal activity) may have minimal or no symptoms, whereas other individuals with higher levels experience excessive surgical bleeding. Because spontaneous bleeding is very rare, treatment is focused on perioperative management. Although factor XI concentrates are available in other countries, in the United States, factor XI has to be replaced with fresh-frozen plasma (FFP). For minor surgeries or bleeds, antifibrinolytics such as aminocaproic acid or tranexamic acid are frequently used. For major surgeries, 15-25 mL/kg of FFP in combination with antifibrinolytics is recommended. The factor XI half-life is 50 hours.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.3 Deficiencies of the Contact Factors (Nonbleeding Disorders)

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Deficiency of the "contact factors"—factor XII, prekallikrein, and high molecular weight kininogen—causes a prolonged PTT but no bleeding symptoms. Because these contact factors function at the step of initiation of the intrinsic clotting system by the reagent used to determine PTT, the PTT is markedly prolonged when these factors are absent. Thus there is the paradoxical situation in which PTT is extremely prolonged with no evidence of clinical bleeding. It is important that individuals with these findings be well informed about the meaning of their clotting factor deficiency because they do not need treatment, even for major surgery.

525.4 Factor VII Deficiency

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Factor VII deficiency is a rare autosomal bleeding disorder that ranges in its presentation from mild to severe bleeding. There is a poor correlation between the clinical severity and the measured factor VII level, although major bleeding is more frequent in patients with <1% activity. Epistaxis and menorrhagia are the most common symptoms, although hemarthroses and intracranial hemorrhages also occur, with the latter reported in 1% of symptomatic cases.

Patients with this deficiency have greatly prolonged PT but normal PTT. Specific factor VII assays are diagnostic. Some recombinant factor VIIa products are approved for the treatment of factor VII deficiency at a dose of 15-30 mcg/kg, which is lower than the dose approved for hemophilia with inhibitors. The plasma half-life of factor VII is 2-6 hours and usually at least three doses at this frequency are required for major bleeding or surgery. Prophylaxis regimens with 2-3 administrations per week have been described in patients with severe bleeding.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.5 Factor X Deficiency

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Factor X deficiency is a rare autosomal recessive disorder with variable severity. Mild deficiency results in mucocutaneous and posttraumatic bleeding, whereas severe deficiency (<1–10% normal activity) is associated with joint, GI, and intracranial hemorrhages. Intracranial and umbilical bleeding can be the presenting symptom for neonates. Heterozygous carriers usually have activity >50% normal and are asymptomatic.

A reduced factor X level is associated with prolongation of both PT and PTT; factor X specific assays are diagnostic. Replacement treatment is with FFP or prothrombin complex concentrate (PCC) or plasma-derived factor X concentrates. The plasma half-life of factor X is approximately 40-60 hours, and prophylaxis regimens with PCC or factor X concentrates administered 1-2 times per week are described for patients with severe bleeding.

Although it is rarely a problem in pediatric patients, about 10% of cases of **light-chain amyloidosis** are associated with factor X deficiency, resulting from the adsorption of factor X on the amyloid protein. In the setting of amyloidosis, replacement therapy often is not successful because of the rapid clearance of factor X.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.6 Prothrombin (Factor II) Deficiency

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Prothrombin (factor II) deficiency is caused either by a markedly reduced prothrombin level (hypoprothrombinemia) or by functionally abnormal prothrombin (dysprothrombinemia). Laboratory testing in homozygous patients shows prolonged PT and PTT; specific prothrombin assays are diagnostic. Mucocutaneous bleeding in infancy and posttraumatic bleeding later are common. Patients are treated with either FFP or PCC at doses of 15-25 mL/kg or 20-40 U/kg, respectively. The half-life of prothrombin is 3-4 days, and once weekly prophylaxis regimens with PCC are reported.

Acquired factor II deficiency can be seen with a small percentage of patients with a lupus anticoagulant and is usually associated with significant bleeding. It is distinguished from inherited prothrombin deficiency by clinical history and the laboratory identification of antiphospholipid antibodies and abnormal PTT mixing studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.7 Factor V Deficiency

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Deficiency of factor V is an autosomal recessive, mild to moderate bleeding disorder. Factor V circulates with 80% in plasma and 20% in platelet α-granules; this platelet factor V pool has been suggested to ameliorate the bleeding that might be expected from low plasma factor V levels. The most common symptoms are epistaxis, oral cavity bleeding, heavy menstrual periods, and postoperative bleeding; joint, muscle, and intracranial hemorrhages occur rarely.

Laboratory evaluation shows prolonged PT and PTT. Specific assays for factor V show a reduction in factor V levels. FFP is the only currently available therapeutic product that contains factor V. Factor V is lost rapidly from stored FFP. Treatment for major surgery or bleeding is usually 15-25 mL/kg FFP followed by additional doses of 10 mL/kg every 12 hours. Twice weekly FFP prophylaxis regimens are sometimes used for patients with severe bleeding. Platelet transfusions are also an option for acute or prophylactic treatment. Rarely, a patient with a negative family history of bleeding has an *acquired antibody* to factor V, which can be identified in laboratory mixing studies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.8 Combined Deficiency of Factors V and VIII

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Combined deficiency of factors V and VIII is an autosomal recessive bleeding disorder that occurs secondary to the absence of intracellular transporters responsible for the shuttling of factors V and VIII from the endoplasmic reticulum to the Golgi compartments, as the result of pathogenic variants in the genes *LMAN1* or *MCFD2*. Factor V and VIII levels are usually between 5–20% of normal. Bleeding symptoms are often mild and most commonly mucocutaneous, traumatic, surgical bleeding. Treatment for major bleeding or surgery is 15-25 mL/kg of FFP.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.9 Congenital Fibrinogen Disorders

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Congenital fibrinogen disorders are a heterogenous group of rare autosomal recessive or dominant diseases because of qualitative **(dysfibrinogenemia)** or quantitative (**hypofibrinogenemia** or **afibrinogenemia**) reductions in functional fibrinogen. Fibrinogen cleavage by thrombin into fibrin is the final step of the coagulation cascade: polymerization follows cleavage and results in fibrin clot formation. Fibrinogen is also the major integrin ligand during platelet aggregation. Conversely, fibrin also sequesters thrombin to the site of clot formation and supports fibrinolysis by enhancing the activation of plasminogen. The multiple roles of fibrinogen and fibrin in hemostasis underlie the phenotypes of inherited fibrinogen disorders, which can have bleeding and clotting clinical manifestations, sometimes in the same patient. The most common bleeding symptoms are mucocutaneous, soft-tissue, joint, genitourinary, traumatic, surgical bleeding, and heavy menstrual periods. Both venous and arterial thrombosis are rare in the quantitative defects but occur in about 20% of cases of dysfibrinogenemia. Some congenital fibrinogen disorders also have nonhematologic manifestations, including liver disease due to retention of misfolded protein, poor wound healing, and splenic rupture.

Diagnosis is based on a decreased fibrinogen activity. Patients usually will also have a prolonged PT and PTT. Dysfibrinogenemia is defined as a decreased ratio of fibrinogen activity compared to fibrinogen antigen. Treatment for bleeding or major surgery is with FFP, cryoprecipitate, or fibrinogen concentrates, depending on local availability. Because of the variable clinical manifestations, including both bleeding and clotting complications, treatment is tailored to the personal and family history. The half-life of fibrinogen is 2-4 days.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.10 Factor XIII Deficiency (Fibrin-Stabilizing Factor or Transglutaminase Deficiency)

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Factor XIII deficiency is a rare autosomal bleeding disorder. Factor XIII is a heterotetramer composed of two catalytic A subunits and two carrier B subunits; activation of factor XIII by thrombin frees the activated A subunits, which covalently crosslink fibrin to increase clot strength and constrain fibrinolysis. The different biochemical roles of the A and B subunits result in distinct clinical manifestations. Inherited deficiencies in the factor XIII A-subunit results in soft tissue, umbilical, surgical, joint, and intracranial bleeding; the latter occurs in about a third of cases. Deficiencies in the B-subunit are associated with mild mucocutaneous and surgical bleeding. Because of its role in stabilizing the fibrin clot, factor XIII deficiency often presents with *delayed* abnormal bleeding or bruising symptoms where patients may have mild trauma and then present with an excessive hematoma on the following day. Extrahematologic clinical manifestation of factor XIII deficiency includes delayed umbilical cord separation, poor wound healing, and recurrent miscarriages.

Unlike the other severe inherited coagulation deficiencies, factor XIII deficiency will have normal PTT and PT. Specific activity assays are diagnostic and should be considered in infants with delayed umbilical cord separation, delayed bleeding symptoms, or unexplained intracranial hemorrhage. Treatment for bleeding or major surgery is 20-40 U/kg of factor XIII concentrate. Recombinant A-subunit protein is also available for A-subunit deficiencies. If specific factor XIII replacement therapies are not available, cryoprecipitate is preferred over FFP because of the substantially higher factor XIII content. The half-life of factor XIII is 9-12 days, which facilitates prophylaxis. Because of the high prevalence of intracranial hemorrhage, prophylaxis of 20-40 U/kg factor XIII concentrate every 4 weeks is recommended for patients with <10% normal activity. *Autoimmune acquired* factor XIII deficiency can be differentiated using specific mixing studies or activity assays of platelet lysates.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

525.11 Antiplasmin or Plasminogen Activator Inhibitor Deficiency

Benjamin J. Samelson-Jones, Brian R. Branchford, and Veronica H. Flood

Deficiency of either antiplasmin or plasminogen activator inhibitor, both of which are antifibrinolytic proteins, results in increased plasmin generation and premature lysis of fibrin clots. Affected patients have a mild-to-moderate bleeding disorder characterized by delayed bleeding symptoms, typically associated with trauma or surgery. Mucocutaneous bleeding and heavy menstrual bleeding are the most described symptoms, with rare reports of joint or intracranial hemorrhages.

Because results of the usual hemostatic tests are normal, further workup of a patient with a positive bleeding history (especially delayed bleeding) should include *euglobulin clot lysis time*, which measures fibrinolytic activity and yields a shortened result in the presence of these deficiencies. Specific assays for α_2-antiplasmin and plasminogen activator inhibitor are available, although the lower limit of normative values of these assays are not well defined. Antifibrinolytic therapies such as aminocaproic acid or tranexamic acid are the mainstay of treatments for controlling or preventing bleeding because they mitigate the hyperfibrinolysis. FFP can also be used to replace the deficient proteins.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 526

Von Willebrand Disease

Brian R. Branchford and Veronica H. Flood

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with an estimated prevalence cited at 1:100 to 1:10,000 depending on the criteria used for diagnosis. Patients with VWD typically present with mucosal bleeding. A family history of either VWD or bleeding symptoms and confirmatory laboratory testing are also required for the diagnosis of VWD.

PATHOPHYSIOLOGY

VWD is caused by a defect in, or deficiency of, von Willebrand factor (VWF). VWF has several functions in coagulation. VWF serves to tether platelets to injured subendothelium via binding sites for platelets and for collagen. VWF also serves as a chaperone, or carrier protein, for factor VIII (FVIII), protecting it from degradation in plasma. VWF is stored in endothelial cell Weibel-Palade bodies and platelet dense granules and circulates as a large, multimeric glycoprotein. Shear stress induces a conformational change in VWF that facilitates its ability to bind platelets through an exposed binding site on platelet glycoprotein Ib (GPIb). This enables VWF to recruit platelets to the site of clot formation, a function dependent on the high molecular weight (HMW) multimer forms of VWF.

VWD typically presents with mucocutaneous bleeding, similar to that seen with other platelet defects. **Epistaxis, easy bruising,** and **menorrhagia** in females are common complaints. However, symptoms are variable and do not necessarily correlate well with VWF levels. **Surgical bleeding**, particularly with dental extractions or adenotonsillectomy, is another common presentation. Severe type 3 VWD may present with joint and/or muscle bleeds. Most patients will have a family history of bleeding, but the VWD genetic variant demonstrates incomplete penetrance (not all carriers of the variant express bleeding symptoms) and variable expressivity (different VWF levels can be found in individuals with the same gene variant). Females are more likely to be diagnosed with VWD because of the potential for symptoms with menorrhagia, but males and females are equally likely to have VWD. However, diagnosis based on symptoms may be difficult, since minor bruising and epistaxis are not uncommon in childhood. Significant unexplained bruising, or bruising in unusual areas (stomach, back, face), in infants and toddlers is more often from nonaccidental trauma than from an underlying bleeding disorder. Gastrointestinal bleeding due to VWD may be complicated by associated angiodysplastic lesions anywhere in the gastrointestinal tract.

CLASSIFICATION

VWD may be caused by quantitative or qualitative defects in VWF. Mild to moderate quantitative defects are classified as type 1 VWD, whereas severe quantitative defects, in which there is no detectable VWF protein, are classified as type 3 VWD. The qualitative defects are grouped together as type 2 VWD.

Type 1 VWD is by far the most common type, accounting for 60–80% of all VWD patients. Typical symptoms include mucosal bleeding, such as epistaxis and menorrhagia, as well as easy bruising and potentially surgical bleeding. Diagnostic guidelines use a VWF level, as measured by the VWF antigen assay **(VWF:Ag)**, of <30 IU/dL for a clear diagnosis of VWD. Antigen and activity are usually symmetrically depressed in type 1 VWD. Patients with VWF:Ag <30 IU/dL are most likely to have a genetic defect in VWF. Patients with VWF:Ag between 30 and 50 IU/dL are said to have "low VWF." Whether or not this category truly represents VWD is a subject of some debate, and the joint guidelines suggest that the resolution should be based on presence or absence of bleeding symptoms. Because some patients with VWF levels in this range do experience bleeding, many physicians elect to treat them, especially perioperatively, for surgical procedures such as tonsillectomy.

Patients with type 1 VWD may have low VWF as a result of increased clearance of their VWF, known as **type 1C VWD**. Diagnosis of this subtype is important *because treatment of these patients with desmopressin is likely to be ineffective, necessitating administration of VWF-containing products instead.*

VWF levels can be influenced by external factors. Blood type has long been known to affect VWF, with lower VWF levels seen in people with blood group O. Stress, inflammation, exercise, menstrual cycle, and pregnancy all increase VWF levels; therefore a single normal VWF level does not necessarily rule out the presence of VWD. Certain diseases, such as **hypothyroidism** (see Chapter 603), and medications, such as valproic acid, can lower VWF levels in affected patients. Repeat testing is often required to confidently rule out or confirm a diagnosis of VWD.

Type 3 VWD is the most severe form and presents with symptoms similar to those seen in *mild hemophilia.* In type 3 VWD the VWF protein is completely absent, and the activity and antigen are both essentially zero. Type 3 VWD is seen at a frequency of approximately 1/1,000,000 members of the general population. In addition to mucosal bleeding, patients may experience joint bleeds, muscle bleeds, or central nervous system (CNS) hemorrhage. Some physicians elect to treat patients with prophylaxis, or modified prophylaxis, after injury, given that these patients typically have very low FVIII (<10 IU/dL). Because type 3 VWD is caused by a complete lack of VWF, *desmopressin is ineffective and treatment with VWF-containing concentrates is required.*

Type 2 VWD is often suspected when a discrepancy exists between the VWF antigen level (often normal) and the VWF activity (often low) because this type represents a qualitative defect, in which an abnormal protein is produced in normal amounts. A ratio of activity to antigen of less than 0.7 may raise concern for type 2 VWD, which itself has multiple subtypes. Multimer evaluation or other specialized testing can be used to discriminate the type 2 subtypes.

Type 2A VWD is characterized by a defect in VWF multimerization and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases. Type 2A VWD can result from variants that affect multimer assembly and processing, or variants that result in increased proteolysis of secreted VWF. Some variants affect both secretion and clearance of the VWF. Regardless of the mechanism, all type 2A VWD patients lack the HMW multimers, and therefore have reduced VWF activity, which results in bleeding. Symptoms are typically more severe than those seen in type 1 VWD. *Desmopressin may have clinical efficacy for treatment of minor bleeding, but significant surgical challenges or major bleeding symptoms generally require a VWF-containing concentrate for treatment.*

Type 2B VWD results from gain-of-function variants that increase the ability of VWF to bind platelets. This leads to increased clearance of both VWF and platelets from circulation and results in the loss of HMW multimers and decreased VWF activity, similar to that seen in type 2A VWD. Special testing is therefore required to diagnose type 2B VWD, either by direct measurement of the increased platelet binding or by an increased response to low dose ristocetin on platelet aggregation testing. Thrombocytopenia is not always present and may be more prominent during times of stress such as surgery or pregnancy. *Desmopressin is relatively contraindicated in type 2B VWD because it may accelerate VWF-platelet binding and clearance, so treatment with VWF-containing product is necessary.*

Platelet-type pseudo-VWD occurs when a variant in platelet GPIb causes spontaneous binding to VWF and also presents with decreased VWF activity, loss of HMW multimers, and thrombocytopenia similar to type 2B VWD. Specific testing is required to distinguish the two conditions. Because the defect involves platelets, treatment generally requires platelet transfusion.

Type 2M VWD includes those patients with decreased VWF activity but normal (or near normal) multimer distribution. This is generally caused by a defect in the ability of VWF to bind platelet GPIb, but this category also includes patients with defects in VWF-collagen interactions. *Some minor bleeding in type 2M VWD may respond to desmopressin, but because type 2M VWD is a functional defect, treatment with VWF-containing concentrates is usually required.*

Table 526.1 Laboratory Testing for von Willebrand Disease (VWD)

TEST	ABBREVIATION	PURPOSE
VWF antigen	VWF:Ag	Measures total amount of VWF protein present.
VWF activity	VWF:RCo*	Assesses interaction of VWF and platelets as mediated by ristocetin.
VWF activity/antigen ratio	VWF:RCo/VWF:Ag	A decreased ratio (<0.7) is found in type 2A, type 2B, and type 2M VWD.
Factor VIII activity	FVIII	Measures circulating FVIII, which will be very low in type 2N and type 3 VWD.
Multimer distribution	VWF multimers	Allows visualization of VWF multimers, used to identify high molecular weight multimers, which will be absent in types 2A and 2B VWD.

*In some laboratories a GPIb-binding assay, the VWF:GPIbM, is available.
VWF, Von Willebrand factor; GPIb, glycoprotein Ib; RCo, ristocetin cofactor.

Table 526.2 Classification of von Willebrand Disease

	TYPE 1	TYPE 3	TYPE 2A	TYPE 2B*	TYPE 2M	TYPE 2N
VWF:Ag	↓	Absent	↓	↓	↓	Normal or ↓
VWF:RCo	↓	Absent	⇊	⇊	⇊	Normal or ↓
FVIII	Normal	⇊	Normal or ↓	Normal or ↓	Normal or ↓	⇊
Multimer distribution	Normal	Absent	Loss of HMWM	Loss of HMWM	Normal	Normal

*Platelet count is also usually decreased in type 2B VWD.
FVIII, factor VIII; HMWM, high molecular weight multimers; VWF:Ag, von Willebrand factor antigen; VWF:RCo, VWF ristocetin cofactor activity.

Type 2N VWD is characterized by a defect in the ability of VWF to bind FVIII. Some patients with type 2N VWD may be misdiagnosed as mild hemophilia; therefore a high index of suspicion for this diagnosis is required in patients with low FVIII and an absent family history of FVIII deficiency. *Because the VWF in this case is dysfunctional, desmopressin is not usually helpful, and VWF-containing product infusion is typically required.*

LABORATORY DIAGNOSIS

There are no reliable screening tests for VWD. Patients with significant bleeding may present with anemia, and some patients with type 2B VWD or platelet-type pseudo-VWD may have thrombocytopenia. The partial thromboplastin time (PTT) may be prolonged if FVIII is low but especially in type 1 VWD it is often normal, precluding use of the PTT as a screening test. Platelet function analysis has been considered as a screening test for VWD, but suboptimal sensitivity and specificity render results difficult to interpret. Bleeding times are similarly unreliable in diagnosis of VWD.

Unfortunately, no single test can reliably diagnose VWD; therefore a panel of tests is usually required (Table 526.1). These include VWF:Ag, which measures the total amount of VWF protein present, and VWF activity test, typically using the *ristocetin cofactor* activity assay **(VWF:RCo)**, which provides a measure of the amount of functional VWF. FVIII activity is also usually included in the workup. Another test measures VWF binding to platelet GPIb without ristocetin **(VWF:GPIbM)**. This test is now FDA approved and its use is increasing. Collagen binding measures an additional function of VWF. Multimer distribution provides an assessment of HMW multimers (Table 526.2; Fig. 526.1).

Additional specialized testing may be employed to help determine the correct diagnosis. Specific testing for type 1C (clearance defects), type 2B, and type 2N VWD can confirm these diagnoses. Genetic diagnosis is not typically performed, partly because of the large size of the VWF gene and the high number of benign sequence variations. Large gene deletions are responsible for some cases of VWD and will not be detected on routine DNA sequencing. However, use of genetic diagnosis is increasing, particularly for types 2A, 2B, 2M, and 2N VWD.

TREATMENT

Treatment of VWD depends on the type of VWD present and the reason for treatment (Table 526.3). In general, type 1 VWD patients may be treated with **desmopressin**, which increases the amount of circulating VWF (and FVIII) by release from storage in endothelial cells. The exceptions are the rare type 1 patient who lacks a response to desmopressin and patients with type 1C VWD who do respond with an increase in VWF levels, but whose rapid clearance of circulating endogenous VWF results in a rapid return to baseline levels. Treatment of types 2 and 3 VWD requires **VWF-containing concentrates,** similar to the treatment of hemophilia. Dosing depends on the type of VWD and the reason for treatment. Careful monitoring of VWF and FVIII levels is recommended to tailor treatment for surgeries and major trauma. For all types of VWD, adjunct therapy should be considered when possible, such as the use of antifibrinolytics for oral surgery or hormonal treatment for menorrhagia.

Alternate treatment strategies should also be considered, particularly for difficult symptoms or severe VWD. Hormonal therapy for females with menorrhagia, although not specific to VWD, can be very helpful in managing symptoms and improving quality of life. Local treatment of epistaxis, such as nasal cautery or packing, may be helpful in some circumstances. Iron therapy for patients with iron-deficiency anemia may also be required.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

	Normal	Type 1	Type 1C (Vicenza)	Type 3	Type 2A	Type 2B	Type 2N	Type 2M	PT-VWD
VWF:Ag	N	↓	↓↓	absent	↓	↓	N or ↓	↓ or N	↓
VWF:RCo	N	↓	↓↓	absent	↓↓↓	↓↓	N or ↓	↓↓	↓↓
FVIII:C	N	N or ↓	↓	2-10 IU/dL	N or ↓	N or ↓	↓↓	N	N or ↓
VWFpp/VWF:Ag ratio	N	N	↑↑	absent	N or ↑	↑	N	N	↑
RIPA	N	often N	↓	absent	↓	often N	N	N or ↓	often N
LD-RIPA	absent	absent	absent	absent	absent	↑↑↑	absent	absent	↑↑↑
PFA'	N	N or ↑	↑	↑↑↑	↑	↑	N	↑	↑
BT'	N	N or ↑	↑	↑↑↑	↑	↑	N	↑	↑
Platelet count	N	N	N	N	N	↓ or N	N	N	↓
VWF multimers	N	N but ↓	N but ↓	absent	abnormal	abnormal	N but ↓	N but ↓	abnormal

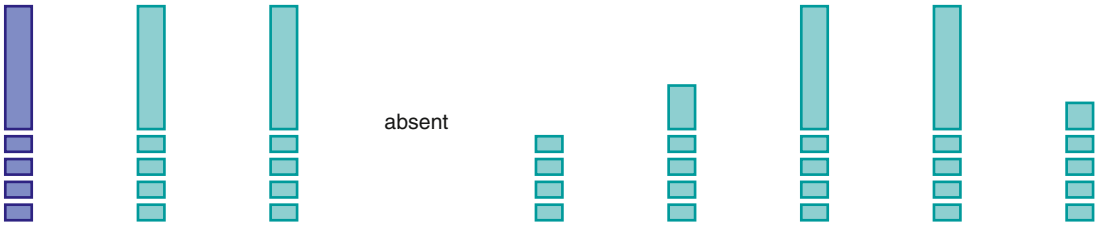

Fig. 526.1 Specialized laboratory testing for von Willebrand disease (VWD). ↓, ↓↓, ↓↓↓, Relative decrease; ↑, ↑↑, ↑↑↑, relative increase; BT, bleeding time; FVIII:C, factor VIII coagulant activity; LD-RIPA, low-dose ristocetin-induced platelet aggregation; N, normal; N but ↓, normal but decreased in intensity; PFA, platelet function analysis; PT-VWD, platelet-type VWD; RIPA, ristocetin-induced platelet aggregation; VWF:Ag, von Willebrand factor antigen; VWF:RCo, VWF activity by ristocetin cofactor; VWF pp, VWF propeptide. *(Courtesy Dr. Robert R. Montgomery.)*

Table 526.3 Treatment of Von Willebrand Disease

TREATMENT	VWD TYPES	ROUTE	DOSING
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN	0.3 μg/kg IV† 1 spray IN (<50 kg) 2 sprays IN (>50 kg)
Von Willebrand factor (VWF) concentrates‡	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV	40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level). If recombinant VWF used, may need to administer additional recombinant FVIII for emergency treatment.
Antifibrinolytics	Mucosal bleeding, all types of VWD	PO or IV	Aminocaproic acid: 100 mg/kg PO loading dose followed by 50 mg/kg every 6 hr§ Tranexamic acid: 1,300 mg PO 3 times daily for 5 days

*Recommended treatment with Stimate brand nasal spray because this form is concentrated to give 150 μg/spray. Other forms are much more dilute and will not result in desired increase in VWF.
†Maximum recommended dose is 20-30 μg/day.
‡Currently both Humate-P and Wilate are approved for treatment of VWD. Vonvendi is a recombinant VWF that is also approved for treatment of VWD but does not contain FVIII.
§Maximum recommended dose is 24 g/day.
IN, Intranasal; IV, intravenous; PO, oral administration.

Chapter 527

Hereditary Predisposition to Thrombosis

Benjamin J. Samelson-Jones and Leslie J. Raffini

Most children that develop clots have multiple risk factors, which may include inherited predispositions to thrombosis. The strength of the inherited prothrombotic risk factors varies. An estimated 30–60% of individuals with *strong* thrombophilias, such as antithrombin deficiency, protein C deficiency, and protein S deficiency, develop thromboembolic disease by age 60; in contrast, less than 10% of individuals with *weak* thrombophilias, such as heterozygous factor V Leiden variant or prothrombin *G20210A* gene variant, develop thromboembolic disease. The inherited thrombophilias with the best understood pathogenesis, population prevalence, and prothrombotic risks are listed in Table 527.1. Some of these disorders may also be acquired or mixed acquired and genetic (Table 527.2).

The inheritance of other thrombophilias is less well understood. Elevated levels of factor VIII (FVIII) and homocysteine are associated with thrombosis, but their levels are not necessarily genetically determined. Additional alterations in plasma proteins have also been associated with increased thrombotic risk, such as elevated concentrations of factors IX and XI, heparin cofactor II deficiency, elevated lipoprotein (a), and dysfibrinogenemia; however, these abnormalities have not gained widespread acceptance in routine testing of children for inherited thrombophilia.

In general, the prothrombotic tendency conferred by these defects is either a result of an increased procoagulant effect (prothrombin gene pathogenic variant, elevated FVIII, hyperhomocysteinemia) or a decreased anticoagulant effect (factor V Leiden, deficiency of protein C, protein S, or antithrombin). Although numerous inherited risk factors for thrombosis have been identified, the majority of individuals who inherit one of these risk factors, even strong thrombophilias, do not necessarily develop thrombosis during childhood. Before evaluating for these disorders, both the limitations of the testing and potential benefits need to be considered.

The **factor V Leiden pathogenic variant** is the result of a single base pair change at nucleotide 1765 within the factor V gene causing an R506Q amino acid substitution in the encoded protein. This pathogenic variant causes activated factor V to become resistant to inactivation by activated protein C. It is the most common inherited risk factor for thrombosis, although its prevalence varies across ethnicities. Individuals who are heterozygous have a 5-7–fold increased relative risk of venous thrombosis, whereas homozygous individuals have an even higher risk. There appears to be a synergistic prothrombotic risk enhancement with the inherited risk of factor V Leiden and the acquired risk of estrogen-containing contraceptives. The baseline annual risk of thrombosis for females of reproductive age is approximately 1/10,000 and increases to 1/2,500 for those taking estrogen-containing contraceptives. For young females who are heterozygous for the factor V Leiden pathogenic variant and on estrogen-containing contraceptives, the annual risk of venous thromboembolism (VTE) increases to 1 in 200. The **prothrombin 20210 gene pathogenic variant** is a G-to-A transition in the 3' untranslated region of the gene that results in increased levels of prothrombin. It is a weaker risk factor for venous thrombosis than factor V Leiden.

Deficiencies of the natural anticoagulation proteins (protein C, protein S, and antithrombin) are less common than the specific genetic pathogenic variants mentioned previously but are associated with a stronger risk of thrombosis. Although heterozygous deficiencies do not often present during childhood, homozygous defects may be embryonically lethal or result in significant symptoms in infancy. Neonates with *homozygous* deficiencies of protein C or protein S may present with **purpura fulminans**. This rare condition is characterized by rapidly spreading purpuric skin lesions resulting from thromboses of the small dermal vessels, followed by bleeding into the skin. In addition, these infants may also develop cerebral thrombosis, ophthalmic thrombosis, disseminated intravascular coagulation, and large-vessel thrombosis. An infant with purpuric skin lesions of unknown cause should receive empiric replacement with fresh-frozen plasma. Definitive diagnosis can be difficult in the sick premature neonate, who may have undetectable levels of these factors but not have a true genetic deficiency. Protein C and antithrombin concentrates are also available and have been demonstrated to be effective.

Elevated levels of homocysteine have been associated with venous *and* arterial thromboses, although the pathogenic mechanisms for thrombosis in homocystinemia are poorly understood. Thromboembolic complications are well described in children with **homocystinuria,** a rare inborn error of metabolism caused by deficiency of cystathione β-synthase that results in plasma levels of homocysteine

Table 527.1 Clinically Relevant Inherited Thrombophilias and Accompanying Diagnostic Laboratory Studies

THROMBOPHILIA	GENERAL POPULATION PREVALENCE (%)	VTE ADULT PATIENT PREVALENCE (%)	ANNUAL INCIDENCE OF VTE (%)	ODDS RATIO FOR FIRST VTE EPISODE IN CHILDHOOD	ODDS RATIO FOR RECURRENT VTE EPISODE IN CHILDHOOD	LABORATORY STUDIES
Antithrombin deficiency	0.02-0.04	1	1.8	9.4	3.4	Functional coagulation testing‡
Protein C deficiency	0.2	3	1.5	7.7	2.5	Functional coagulation testing‡
Protein S deficiency	0.03-0.13	2	1.9	5.8	3.8	Functional coagulation testing‡
Factor V Leiden variant*	3-7	20	0.5	3.8	0.8	Gene testing
Prothrombin 20210 variant*	1-4	5	0.3	2.6	2.2	Gene testing

*Values refer to heterozygous changes.
‡May be impacted by anticoagulation therapies.
VTE, Venous thromboembolism.

Table 527.2 Classification of Hypercoagulable States

HEREDITARY	MIXED	ACQUIRED
LOSS OF FUNCTION		
Antithrombin deficiency	Hyperhomocysteinemia	Previous venous thromboembolism Hepatic cirrhosis Severe liver disease Nephrotic syndrome L-asparaginase
Protein C deficiency	Obesity	Pregnancy, puerperium
Protein S deficiency	Cancer	
		Drug-induced: Heparin-induced thrombocytopenia Prothrombin complex concentrates L-asparaginase Hormonal therapy
GAIN OF FUNCTION		
Factor V Leiden	Postoperative	
Prothrombin FII G20210A	Myeloproliferative disorders	
Elevated factor VIII, IX, or XI		

Modified from Hoffman R, Benz Jr. EJ, Silberstein LE, et al., eds. *Hematology Basic Principles and Practice*, 7th ed. Philadelphia: Elsevier, 2018: Table 140.1, p. 2077.

that exceed 100 μmol/L. Much more common are mild to moderate elevations of homocysteine, which may be acquired or associated with a polymorphism in the methylenetetrahydrofolate reductase *(MTHFR)* gene. Although moderate elevations of homocysteine have been associated with both venous and arterial thrombotic events, testing for polymorphisms in the *MTHFR* gene is not indicated because these polymorphisms are common and by themselves (without homocystinemia) are not associated with thromboembolism.

Increased plasma concentrations of FVIII appear to be regulated by both genetic and environmental factors and are associated with an increased risk of thrombosis. High FVIII levels are usually polygenic, although rarely specific changes in the FVIII gene have been identified. FVIII is also an acute-phase reactant and may increase during periods of inflammation.

Although interpretation of gene testing is fairly straightforward, several challenges in interpretation of thrombophilia studies are unique to pediatric patients. Neonates have decreased concentrations of protein C, protein S, and antithrombin that increase rapidly over the first 6 months of life; protein C concentrations remain below adult levels throughout much of childhood. It is important to use pediatric normal ranges when evaluating these values and recognize that often the normal range overlaps with heterozygous defects and that retesting may be required, particularly in young children. Several nongenetic factors may also influence the results of inherited thrombophilia testing, including acute thrombosis, infection, inflammation, hepatic dysfunction, nephrotic syndrome, medication, and vitamin K deficiency. In some patients the hereditary nature may be confirmed by testing the parents.

Thrombophilia testing is considered during childhood when a child develops thrombosis or if a child has relatives with thrombosis or thrombophilia. Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. The majority of children who develop thrombosis have multiple, coexistent *acquired* risk factors (see Table 528.1 in Chapter 528). More than 90% of thromboses in children are associated with indwelling intravascular catheters; inherited thrombophilias are uncommon in this scenario, and testing is generally not warranted. However, inherited thrombophilia is more common in an otherwise healthy child or adolescent who develops a blood clot or in a child who develops unusual or recurrent thrombosis. Thrombophilia testing may be useful in these situations because it may help explain why the child developed a blood clot and inform on the duration of therapy. However, current treatment recommendations do not differ based on the presence or absence of an inherited thrombophilia. The identification of an inherited anticoagulant protein defect, such as antithrombin or protein C deficiency, may allow for replacement therapies while off anticoagulation, such as in the perioperative setting.

The decision to perform thrombophilia testing in an otherwise healthy child with a **family history** of thrombosis or thrombophilia should be carefully considered, weighing the potential advantages and limitations of such an approach. Given that the absolute risk of thrombosis in children is extremely low (0.07/100,000), it is unlikely that an inherited thrombophilia will have any impact on clinical decision-making for a young child. The risk of thrombosis increases with age, so identification of a thrombophilic defect in an adolescent may guide primary thromboprophylaxis in high-risk situations (lower-extremity casting or prolonged immobility), inform the discussion about estrogen-based contraceptives, and promote lifestyle modification to avoid behavioral risk factors (sedentary lifestyle, dehydration, obesity, and smoking). Limitations of such testing include the cost as well as the potential for causing unnecessary anxiety or false reassurance.

In most patients with inherited thrombophilia, the treatment is the same as for patients with no inherited disorders (see Chapter 528). In neonates with purpura fulminans caused by homozygous protein C or S deficiency or in patients with warfarin-induced skin necrosis, heparin-induced thrombocytopenias and severe antithrombin deficiency often require factor replacement (protein C, S or antithrombin concentrates or plasma) in addition to unfractionated heparin or low molecular weight heparin. In less severe antithrombin deficiency, higher than usual doses of heparin may be needed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 528

Thrombotic Disorders in Children

Leslie J. Raffini and Brian R. Branchford

Thromboembolic events (TEs) are seen in pediatric tertiary care centers and may result in significant acute and chronic morbidity. TEs in children are rare. Diagnosis and treatment are often extrapolated from adult data because of a current lack of high-quality data in the pediatric setting.

EPIDEMIOLOGY

Although the overall incidence of thrombosis in the general pediatric population is quite low (0.07/100,000), the rate of **venous thromboembolism (VTE)** in hospitalized children is 60/10,000 admissions. Infants <1 year old account for the largest proportion of pediatric VTEs, with a second peak during adolescence.

Most children who develop a TE have multiple risk factors that may be acquired, inherited, or anatomic (Table 528.1). The presence of a central venous catheter (CVC) or peripherally inserted central venous catheter (PICC) is the most important risk factor for VTE in pediatric patients, associated with approximately 90% of neonatal VTE and 60% of childhood VTE. PICC lines may be among the highest-risk CVC subtypes. CVCs are often necessary for the care of premature neonates and children with acute and chronic diseases and are used for intravenous (IV) hyperalimentation, chemotherapy, dialysis, antibiotics, or supportive therapy. CVCs may damage the endothelial lining and/or cause blood flow disruption, increasing the risk of thrombosis. Many other acquired risk factors are associated with thrombosis, including trauma, surgery, infection, inflammation, chronic medical conditions, and certain medications. Cancer, congenital heart disease, and prematurity are the most common medical conditions associated with TEs.

Antiphospholipid antibody syndrome (APS) is characterized by recurrent fetal loss and/or thrombosis (Table 528.2). Antiphospholipid antibodies are associated with venous and, less often, arterial thrombosis. The autoantibodies in APS include lupus anticoagulant, anticardiolipin antibodies, and anti-β_2 glycoprotein I. If all three antibodies are positive **(triple positive)**, the risk of thrombosis is increased. The mechanism by which these antibodies cause thrombosis is not well understood. A diagnosis of APS requires the presence of both clinical and laboratory abnormalities (see "Laboratory Testing"). The laboratory abnormalities must be identified on two separate occasions, at least 12 weeks apart. Because of the high risk of VTE recurrence, patients with APS often require long-term anticoagulation, at least until the antibodies have resolved; the type of antibodies and the presence of arterial thrombosis may have important implications for the type of anticoagulant therapy chosen. Up to 20% of healthy children may have a *transient* lupus anticoagulant, often diagnosed because of a prolonged partial thromboplastin time (PTT) on routine preoperative testing. In this setting, transient antibodies may be associated with a recent viral infection and are not a risk factor for thrombosis. APS is also noted in patients with **systemic lupus erythematosus** (see Chapter 199) and may also be associated with livedo reticularis, neuropsychiatric complications, thrombocytopenia, or anemia; these patients are often persistently positive for the antiphospholipid antibody. **Catastrophic antiphospholipid syndrome** is a rare and potentially fatal disorder characterized by rapid onset of multiorgan thrombosis and/or thrombotic microangiopathies (Table 528.3).

Anatomic abnormalities that impede blood flow also predispose patients to thrombosis at an earlier age. Atresia of the inferior vena cava has been described in association with acute and chronic lower-extremity deep vein thrombosis **(DVT)**. Compression of the left iliac vein by the overlying right iliac artery **(May-Thurner syndrome)** should be considered in patients who present spontaneously with left iliofemoral thrombosis, and thoracic outlet obstruction **(Paget-Schroetter syndrome)** frequently presents with effort-related axillary-subclavian vein thrombosis.

CLINICAL MANIFESTATIONS

Extremity Deep Vein Thrombosis

Children with acute DVT often present with extremity pain, swelling, and discoloration (see Table 524.1). A history of a current or recent CVC in that extremity should be very suggestive. Many times, symptoms of CVC-associated thrombosis are more subtle and chronic, including repeated CVC occlusion (potentially requiring clearance with tissue plasminogen activator [tPA]) or sepsis, or prominent venous collaterals on the chest, face, and neck.

Pulmonary Embolism

Signs and symptoms classically include shortness of breath, pleuritic chest pain, cough, hemoptysis, fever, tachypnea, tachycardia, and/or, in the case of massive pulmonary embolism (PE), hypotension and right-sided heart failure. Based on autopsy studies in pediatric centers, PE is often undiagnosed because young children are unable to describe their symptoms accurately, and their respiratory deterioration may be masked by other conditions (see Chapter 458.1).

Cerebral Sinovenous Thrombosis

Signs and symptoms of cerebral sinovenous thrombosis (CSVT) may be subtle and may develop over many hours or days (see Table 524.1). Neonates with CSVT often present with seizures, whereas older children often complain of headache, vomiting, seizures, visual changes, and/or focal neurologic signs. They may also have papilledema and abducens palsy. Older patients may have a concurrent sinusitis or mastoiditis that has contributed to the thrombosis. Other risk factors may include trauma, meningitis, or dehydration.

Renal Vein Thrombosis

Renal vein thrombosis (RVT) is the most common spontaneous VTE in neonates (see Table 524.1). Affected infants may present with hematuria, an abdominal mass, and thrombocytopenia. Infants of diabetic mothers are at increased risk for RVT, although the mechanism for the increased risk is unknown. Approximately 25% of cases are bilateral.

Portal Vein Thrombosis

Portal vein thrombosis (PVT) often occurs during the neonatal period and is often asymptomatic, only manifesting in those patients who develop symptomatic portal hypertension (e.g., gastrointestinal [GI] bleeding, splenomegaly) after the initial thrombotic event (see Table 524.1). The most common risk factor associated with PVT is an umbilical venous catheter, although sepsis, pancreatitis, cirrhosis, liver transplant, splenectomy, and sickle cell disease are also notable risk factors. A known complication of PVT is cavernous transformation, which confers a risk for variceal bleeding.

Peripheral Arterial Thrombosis

The majority of arterial TEs in children are associated with catheters, often related to umbilical artery lines in neonates or cardiac catheterization via the femoral artery (see Table 524.1). Less common etiologies of arterial thrombosis include homocystinuria and APS. Patients with an arterial thrombosis affecting blood flow to an extremity will present with a cold, pale extremity with poor or absent pulses, which can signify a limb-threatening emergency.

Acute Ischemic Stroke

Acute ischemic stroke (AIS) typically presents with hemiparesis, slurred speech, altered consciousness, or seizures. This condition may occur secondary to pathology that affects the intracranial arteries (e.g., sickle cell disease, vasculitis, vasculopathy, traumatic arterial dissection, or paradoxical embolism across a patent foramen ovale) or may result from venous thrombi that embolize to the arterial circulation (placental

Table 528.1 Risk Factors for Thrombosis

GENERAL
Indwelling catheter, especially PICC lines
Infection
Trauma
Surgery
Cancer
Immobility
Cardiac disease/prosthetic valve
Systemic lupus
Rheumatoid arthritis
Inflammatory bowel disease
Celiac disease
Polycythemia/dehydration
Nephrotic syndrome
Diabetes
Pregnancy
Obesity
Prematurity
Paroxysmal nocturnal hemoglobinuria
Thrombotic thrombocytopenic purpura (acquired)
COVID-19
Antiphospholipid antibody syndrome
INHERITED THROMBOPHILIA
Factor V Leiden pathogenic variant
Prothrombin pathogenic variant
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Homocystinuria
Elevated factor VIII
Dysfibrinogenemia
GATA-2 deficiency
Hereditary thrombotic thrombocytopenic purpura
ANATOMIC
Thoracic outlet obstruction (Paget-Schroetter syndrome)
Iliac vein compression syndrome (May-Thurner syndrome)
Absence of inferior vena cava
MEDICATIONS
Estrogen-containing contraceptives
Asparaginase
Heparin (heparin-induced thrombocytopenia)
Corticosteroids
Immune checkpoint inhibitors
Hemophilia bypassing agents

PICC, Peripherally inserted central venous catheter.

thrombi, children with congenital heart disease, or patent foramen ovale allowing right-to-left shunting of an embolic venous thrombosis).

Rapidly Progressive Thrombosis (Thrombotic Storm)

Rapid progression or multifocal thrombosis is a rare complication of APS **(catastrophic antiphospholipid syndrome)**, or heparin-induced thrombocytopenia with thrombosis (see Table 528.3). Multiorgan dysfunction develops in the presence of small vessel occlusion and elevated D-dimer levels, and this may progress to disseminated intravascular coagulation. Treatment includes aggressive anticoagulation, often with direct thrombin inhibitors or fondaparinux, followed by prolonged warfarin therapy. In rare cases, plasmapheresis and/or immunosuppression and/or antiinflammatory therapy may be warranted.

DIAGNOSIS

Compression ultrasound with Doppler flow is the most common imaging study for the diagnosis of extremity DVT and chest CT is used most frequently for the diagnosis of PE (Fig. 528.1). Echocardiogram is often used to detect and follow right atrial clots, most often detected in patients with central catheter tips in the right atrium. Other diagnostic imaging options include CT and MR venography, which are noninvasive, although the sensitivity and specificity of these studies is not known. These studies may be particularly helpful in evaluating proximal or abdominal thrombosis. For the diagnosis of CSVT and AIS, the most sensitive imaging study is brain MRI with venography or diffusion-weighted imaging.

Table 528.2 Sydney Investigational Criteria for the Diagnosis of the Antiphospholipid Syndrome

CLINICAL
• Vascular thrombosis (one or more episodes of arterial, venous, or small-vessel thrombosis). For histopathologic diagnosis, there should be no evidence of inflammation in the vessel wall.
• Pregnancy morbidities attributable to placental insufficiency, including: (a) three or more otherwise unexplained recurrent spontaneous miscarriages before 10 weeks of gestation, (b) one or more fetal losses after the 10th week of gestation, (c) stillbirth, and (d) episode of preeclampsia, preterm labor, placental abruption, intrauterine growth restriction, or oligohydramnios that are otherwise unexplained.
LABORATORY
• Medium- or high-titer aCL or anti-β_2GPI IgG and/or IgM antibody present on two or more occasions, at least 12 weeks apart, measured by standard ELISA.
• Lupus anticoagulant in plasma, on two or more occasions, at least 12 weeks apart, detected according to the guidelines of the ISTH SSC Subcommittee on Lupus Anticoagulants and Phospholipid-Dependent Antibodies.
"Definite APS" is considered present if at least one of the clinical criteria and one of the laboratory criteria are met.

aCL, Anticardiolipin; aPL, antiphospholipid; β_2GPI, β_2-glycoprotein I; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin.
Modified from Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *Thromb Haemost.* 2006;4:295–306. Table 2.

Table 528.3 Proposed Criteria for the Classification of Catastrophic Antiphospholipid Syndrome

1. Evidence of involvement of three or more organs, systems and/or tissues*
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue†
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)‡
DEFINITE CATASTROPHIC APS
• All four criteria
PROBABLE CATASTROPHIC APS
• All four criteria, except for only involvement of two organs, systems, and/or tissues
• All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart because of the early death of a patient never previously tested for aPL before the catastrophic APS event
• Criteria 1, 2, and 4
• Criteria 1, 3, and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

*Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (≥180/100 mm Hg) and/or proteinuria (≥500 mg/24 h).
†For histopathologic confirmation, significant evidence of thrombosis must be present, although, in contrast with Sydney criteria, vasculitis may coexist occasionally.
‡If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that the presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.
aPL, Antiphospholipid; APS, antiphospholipid syndrome
Modified from Asherson RA, Cevera R, de Groot PG et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;12:530–534.

LABORATORY TESTING

All children with a VTE should have a complete blood count and a baseline prothrombin time (PT) and PTT to assess their coagulation status in

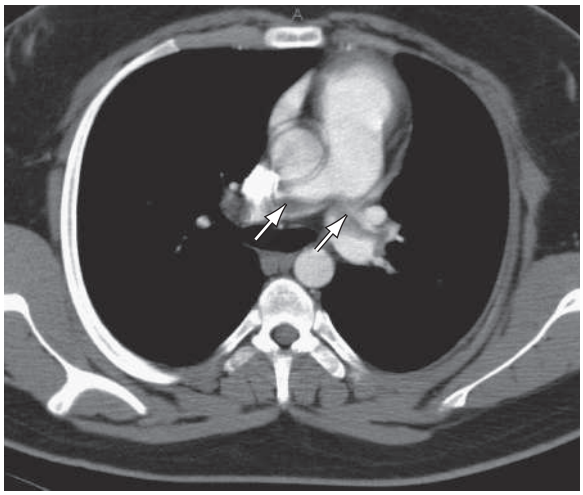

Fig. 528.1 Chest CT scan from a 15-yr-old male with a large pulmonary embolism. Large filling defects are present in the right and left main pulmonary arteries *(arrows)*.

anticipation of anticoagulation treatment. In adults with suspected DVT, the D-dimer level has a high negative predictive value, but the predictive value is not as well established for children. The D-dimer is a fragment produced when fibrin is degraded by plasmin and is a measure of both clot formation and subsequent fibrinolysis. Based on the clinical scenario, other laboratory studies, such as renal and hepatic function, may be indicated. Testing for APS includes evaluation for the lupus anticoagulant as well as anticardiolipin and anti–β_2-glycoprotein antibodies and should be considered in patients with inflammatory disorders, recent trauma, surgery, or infection, and those who present with thrombosis and no other obvious risk factors.

There is debate regarding which patients should have testing for inherited risk factors. Thrombophilia testing rarely influences the acute management of a child with a thrombotic event, and natural anticoagulants like protein C and S or antithrombin (AT) may appear to have low levels due to consumption during the acute phase of thrombosis, even if the patient does not have an existing deficiency of these proteins (see Chapter 527). Identification of an inherited thrombophilia may influence the duration of treatment, particularly for those with a *strong* thrombophilia, and may aid in counseling patients about their risk of recurrence. **Unprovoked** (absence of risk factors) thrombosis and a family history of thrombotic events may be a clue to an inherited thrombophilia, although they may coincide with a known risk factor.

The evaluation and interpretation of coagulation studies in pediatric patients may be complicated by the developing hemostatic system and the differences in normal ranges between infants and adults (see Chapter 527).

TREATMENT

Therapeutic options for children with thrombosis may include observation, anticoagulation, thrombolysis, and surgery. In premature neonates and critically ill children who are at high risk of bleeding, the potential benefits must be weighed against the risks, and close observation with repeat imaging may be an option. The majority of nonneonates with symptomatic thrombosis are treated with anticoagulant therapy. The goal of anticoagulation is to reduce the risk of embolism, halt clot extension, and prevent recurrence (see Chapter 528.1). Systemic or endovascular thrombolysis may be indicated for organ- or limb-threatening thrombosis. Surgery may be necessary for life- or limb-threatening thrombosis when there is a contraindication to thrombolysis. The optimal treatment for a child with AIS depends on the likely etiology and the size of the infarct and may include either anticoagulation or antiplatelet therapy such as aspirin. Children with sickle cell disease who develop stroke are treated acutely with erythrocytapheresis to rapidly lower the percentage of hemoglobin S and may also receive ongoing chronic red blood cell transfusions (or erythrocytapheresis) to reduce recurrence risk.

A summary of management recommendations for various types of VTE can be found in (Tables 528.4 and 528.5)

COMPLICATIONS

Complications of VTE include recurrent thrombosis (local or distant), and development of post-thrombotic syndrome (PTS). Over time, due to venous hypertension or damaged endovascular valves, patients may develop pain, swelling, edema, discoloration, and ulceration of the affected limb. Several prospective studies in adults have shown PTS to be present in 17–50% of patients with a history of thrombosis. The likelihood of developing PTS has been shown to increase with age, thrombus burden, and delay in anticoagulation therapy.

528.1 Anticoagulant and Thrombolytic Therapy

Leslie J. Raffini and Brian R. Branchford

Initial options for anticoagulation in children have generally included unfractionated heparin (UFH) or low molecular weight heparin (LMWH), followed by LMWH or warfarin for outpatient management (see Tables 528.4 and 528.5). Clinical trials of several direct oral anticoagulants (DOACs) have demonstrated the safety and efficacy of these drugs to treat VTE in children, and the landscape of treatment options for children with thrombosis is changing rapidly as these drugs gain regulatory approval. DOACs act by inhibiting factor Xa or thrombin (Table 528.6).

The optimal duration of anticoagulation for children with TEs is not well established. American Society of Hematology (ASH) guidelines recommend that pediatric patients with provoked DVT or PE receive ≤3 months of anticoagulation and those with unprovoked DVT or PE receive 6-12 months of therapy. Patients with strong inherited thrombophilia, recurrent thrombosis, and APS (or other nonmitigatable risk factors) may require indefinite anticoagulation.

UNFRACTIONATED HEPARIN

Both UFH and LMWH act by catalyzing the action of AT. UFH consists of large molecular weight polysaccharide chains that interact with AT, supporting the inhibition of factor Xa and thrombin, as well as other serine proteases.

Heparin Dosing

A therapeutic heparin dose achieves a prolongation of the PTT of 1.5-2.5 the upper limit of normal. A bolus dose of 75-100 units/kg results in a therapeutic PTT in the majority of children. This bolus should be followed by a continuous infusion. Initial dosing is based on age, with infants having the highest requirements. It is important to continue to monitor the PTT closely. In some situations, such as patients with a lupus anticoagulant, those with elevated factor VIII, or neonates, the PTT may not accurately reflect the degree of anticoagulation, and heparin can be monitored using a heparin anti-Xa level of 0.35-0.7 units/mL.

Heparin Complications

Maintaining the PTT in the therapeutic range can be difficult in young children. The bioavailability of heparin is difficult to predict and may be influenced by plasma proteins, including AT level. In many patients, this results in multiple dose adjustments requiring close monitoring with frequent venipuncture. UFH also requires continuous IV access, which may be difficult to maintain in young children.

The most common adverse effect related to heparin therapy is bleeding. There are case reports of life-threatening bleeding in children treated with heparin. The true frequency of bleeding in pediatric patients receiving heparin has not been well established and is reported as 1–24%. If the anticoagulant effect of heparin must be reversed immediately, protamine sulfate may be administered to neutralize the heparin. With an elimination half-life of approximately 30 minutes, the anticoagulant effect of this drug typically wears off in approximately 2-3 hours after stopping the infusion. UFH is cleared by the liver and kidney.

Other adverse effects include osteoporosis (with long-term use) and **heparin-induced thrombocytopenia (HIT)**. Although rare in pediatric populations, HIT is a prothrombotic, immune-mediated

Table 528.4 Management Considerations for Pediatric Thromboembolic Events

VTE	MANAGEMENT RECOMMENDATION	COMMENTS
Symptomatic DVT	Anticoagulation Provoked—treat <3 months (or until provoking factor is resolved) Unprovoked—treat 6-12 months, or longer based on risk/benefit analysis Thrombolysis considered if life- or limb-threatening VTE IVC filter considered if absolute contraindication to anticoagulation	Observation may be necessary or reasonable for premature neonates or critically ill children at high risk of bleeding Recommendations vary regarding utility of radiographic follow-up
Asymptomatic DVT	Anticoagulation or observation	Natural history is unclear, decision may vary based on VTE- and patient-specific factors
Massive PE (hemodynamic compromise)	Thrombolysis followed by anticoagulation	
Submassive PE (no hemodynamic compromise)	Anticoagulation alone	
CVC-related	Anticoagulation Removal of CVC if not functioning or no longer needed	Duration of anticoagulation needed before CVC removal is still being investigated, and recommendations vary
Renal vein thrombosis (RVT)	Unilateral: Anticoagulation alone Bilateral: Consider thrombolysis for bilateral RVT (life- or organ-threatening)	
Portal vein thrombosis (PVT)	Occlusive: Anticoagulation Nonocclusive: Observation (close radiologic follow-up)	Observe for cavernous transformation. Bleeding risk with anticoagulation increases in the setting of portal hypertension (and associated esophageal varices)
Cerebral Sinovenous Thrombosis (CSVT)	Anticoagulation (radiologic follow-up recommended) Acetazolamide if concomitant increased intracranial pressure	Decision in patients with intracranial hemorrhage needs to be individualized, but some patients may benefit from anticoagulation

CVC, Central venous catheter; DVT, deep vein thrombosis; IVC, inferior vena cava; PE pulmonary embolism; VTE, venous thromboembolism

Table 528.5 Comparison of Antithrombotic Agents

	rTPA	UNFRACTIONATED HEPARIN	WARFARIN	LMW HEPARIN (ENOXAPARIN)
Indication	Recent onset of life- or limb-threatening thrombus	Acute or chronic thrombus, prophylaxis	Subacute or chronic thrombosis, thromboprophylaxis for cardiac valves	Acute or chronic thrombus, prophylaxis
Administration	IV continuous infusion	IV continuous infusion	PO once daily	SC injection twice daily
Monitoring	"Lytic state": FDP or D-dimer	PTT	INR	Anti–factor Xa activity
Other	Higher risk of bleeding	Difficult to titrate; requires frequent dose adjustments; higher dose required in newborns	Heavily influenced by other drugs and diet	More stable and easy to titrate; concern of osteopenia with long-term use

FDP, Fibrin degradation products; INR, international normalized ratio; IV, intravenous; LMW, low-molecular-weight; PO, oral; PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator; SC, subcutaneous.

complication in which antibodies develop to a complex of heparin and platelet factor-4. These antibodies result in platelet activation, stimulation of coagulation, thrombocytopenia, and in some cases, life-threatening thrombosis. If HIT is strongly suspected, heparin must be discontinued immediately. An alternative parenteral anticoagulant, including the direct thrombin inhibitors argatroban or bivalirudin, may be used in this situation.

LOW MOLECULAR WEIGHT HEPARIN

In contrast to UFH, LMWH contains smaller molecular weight polysaccharide chains. The interaction of the smaller chains with AT results primarily in the inhibition of factor Xa, with less of an effect on thrombin. The several LMWHs available have variable inhibitory effects on thrombin. For this reason, the PTT is not a reliable measure of the anticoagulant effect of LMWH, and the anti–factor Xa activity is used instead. Because of the ease of dosing and need for less monitoring, *LMWH is the most frequently used anticoagulant in pediatric patients.* Although dalteparin was the first (and currently only) LMWH approved by the Food and Drug Administration (FDA) for use in children (older than 1 month of age), enoxaparin is the LMWH that has been studied and used more often in pediatric patients.

Enoxaparin Dosing

The recommended standard starting dose of enoxaparin for infants <2 months old is 1.5 mg/kg/dose subcutaneously every 12 hours and for patients >2 months old, 1 mg/kg every 12 hours, although many

Table 528.6 Pharmacologic Properties of Direct Oral Anticoagulants

	DABIGATRAN	APIXABAN	BETRIXABAN	EDOXABAN	RIVAROXABAN
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Bioavailability, %	6–7%	50%	34%	62%	66%*
Protein binding, %	35%	87%	60%	40–59%	92–95%
Time to maximum concentration, hr	2	1–3	3–4	1–2	2–4
Half-life, hr	12–14	8–15	19–27	9–14	9–13
Renal elimination, %	>80%	25%	6–13%	50%	33%
Metabolism via cytochrome P450 enzymes, %	<2%	<32%	<1%	<5%	57%
Drug interactions	Inhibitors and inducers of P-gp	Dual inhibitors and inducers of CYP3A4 and P-gp	Inhibitors and inducers of P-gp	Inhibitors and inducers of P-gp	Dual inhibitors and inducers of CYP3A4 and P-gp
Specific reversal agents	Idarucizumab	Andexanet alfa	Andexanet alfa†	Andexanet alfa†	Andexanet alfa

*Applies to the 15 mg and 20 mg doses given once a day without food; bioavailability is 80–100% when these doses are given with food.
†Expected to be effective on the basis of its mechanism of action, although not approved for these agents.
P-gp, P-glycoprotein.
From Chan N, Sobieraj-Teague M, Eikelboom JW. Direct oral anticoagulants: evidence and unresolved issues. Lancet 2020;396:1767–1776. Table 1.

centers use slightly higher doses for children <2 years old. In general, peak levels are achieved 3-6 hours after injection. A therapeutic anti–factor Xa level, drawn 4 hours after the second or third dose, should be 0.5-1.0 IU/mL; the dose can be titrated to achieve this range. The elimination half-life of enoxaparin is 4-6 hours. Enoxaparin is cleared by the kidney and should be used with caution in patients with renal insufficiency. It should be avoided in patients with renal failure.

After an initial period of anticoagulation with heparin or LMWH, patients may continue to receive LMWH as an outpatient for the duration of therapy or may be transitioned to an oral anticoagulant such as warfarin.

Direct Thrombin Inhibitors

Argatroban and bivalirudin are IV direct thrombin inhibitors that are used in the setting of HIT, complex heart disease/failure cases with ventricular assist devices, or other relatively uncommon situations in pediatrics. They have short half-lives but cannot be fully reversed. Dosing has not been well established in children.

WARFARIN

Warfarin is an oral anticoagulant that competitively interferes with vitamin K metabolism, exerting its action by decreasing concentrations of the vitamin K–dependent coagulation factors II, VII, IX, and X, as well as protein C and protein S. Therapy should be started while a patient is anticoagulated with heparin or LMWH because of the risk of warfarin-induced skin necrosis. This transient hypercoagulable condition may occur when levels of protein C drop more rapidly than the procoagulant factors.

Dosing

Warfarin therapy is often initiated with a weight-based loading dose, with subsequent dose adjustments made according to a nomogram. When initiating warfarin therapy, UFH or LMWH should be continued until the international normalized ratio (INR) is therapeutic for 2 days. In most patients, this takes 5-7 days. The PT is used to monitor the anticoagulant effect of warfarin. Because the thromboplastin reagents used in PT assays have widely varying sensitivities, the PT performed in one laboratory cannot be compared with that performed in another laboratory. As a result, the INR was developed as a mechanism to standardize the variation in the thromboplastin reagent. The target INR range depends on the clinical situation. In general, a range of 2.0-3.0 is the target for the treatment of VTE. High-risk patients, such as those with mechanical heart valves, APS, or recurrent thrombosis, may require a higher target range.

Polymorphisms in *CYP2C9* and *VKORC1* affect the pharmacokinetics and pharmacodynamics of warfarin. Pharmacogenetic testing can identify wild-type responders, as well as those who are more sensitive (increased risk of bleeding). Genotyping in adults may help select warfarin dose, monitor for bleeding, or choose a DOAC instead of warfarin for patients highly sensitive and at risk for hemorrhage.

Complications

Bleeding is the most common adverse effect of warfarin. The risk of serious bleeding in children receiving warfarin for the treatment of VTE has been reported at 0.5% per year. Children who have supratherapeutic INR are at higher risk. There is considerable interpatient variation in dose. Diet, medications, and illness may influence the metabolism of warfarin, requiring frequent dose adjustments and laboratory studies. Numerous medications can affect the pharmacokinetics of warfarin by altering its clearance or rate of absorption. These effects can have a profound impact on the INR and must be considered when monitoring a patient receiving warfarin.

The strategies used to reverse warfarin therapy depend on the clinical situation and whether there is bleeding. Vitamin K can be administered to reverse the effect of warfarin but takes some time to have an effect. If the patient is having significant bleeding, a nonactivated plasma-derived 4-factor prothrombin complex concentrate (PCC) or fresh-frozen plasma (FFP, 15 mL/kg) should be given along with the vitamin K. PCCs have not been well investigated in children.

Nonhemorrhagic complications are uncommon in children, although hair loss has been reported. Warfarin is a teratogen, particularly in the first trimester. **Warfarin embryopathy** is characterized by bone and cartilage abnormalities known as *chondrodysplasia punctata*. Affected infants may have nasal hypoplasia and excessive calcifications in the epiphyses and vertebrae.

DIRECT ORAL ANTICOAGULANTS

Oral direct thrombin inhibitors (dabigatran) or inhibitors of factor Xa (apixaban, rivaroxaban, edoxaban) are approved for the prevention or treatment of thrombosis in patients >18 years old (see Table 528.6), and dabigatran is FDA-approved for children older than 3 months of age. Fixed dosing, oral administration, no dietary interference with vitamin

Table 528.7 Guidelines for Therapeutic Anticoagulation Treatment Duration

INDICATION	RISK FACTOR	THERAPEUTIC ANTICOAGULATION TREATMENT DURATION
First VTE episode	Provoked, reversible	3 mo
	Provoked, chronic	3 mo, then continue anticoagulation with either therapeutic or prophylaxis regimens until the risk factor is resolved
	Unprovoked	6–12 mo
Recurrent VTE	Reversible	3 mo
	Chronic	If recurrence occurs while the patient was on prophylaxis regimen, after first VTE episode, restart therapeutic regimen until risk factor is resolved
	Unprovoked	Restart therapeutic regimen for at least 3 mo and then switch to lifelong VTE prophylaxis regimen

VTE, Venous thromboembolism.
From Shoag J, Davis JA, Corrales-Medina FF. Venous thromboembolism in pediatrics. *Pediatr Rev.* 2021;42:78–87.

K, and no need to monitor laboratory tests, as well as initial results suggesting noninferiority to warfarin and fewer bleeding episodes, have favored the use of DOACs. Clinical trials have demonstrated the safety and efficacy of dabigatran and rivaroxaban in children. Drugs are available to *reverse* the effects of DOACs if indicated. DOACs should be avoided in patients with APS in the presence of arterial thrombosis.

THROMBOLYTIC THERAPY

Although anticoagulation alone is often effective at managing thrombosis while awaiting natural fibrinolysis, more rapid clot resolution may sometimes be necessary or desirable. In these situations, a thrombolytic agent that can activate the fibrinolytic system is of potential benefit. The pharmacologic activity of thrombolytic agents depends on the conversion of endogenous plasminogen to plasmin. Plasmin is then able to degrade several plasma proteins, including fibrin and fibrinogen. Because of the high risk of bleeding, thrombolytic therapy is generally reserved for patients with life- or limb-threatening thrombosis.

tPA is available as a recombinant product and has become the primary agent used for thrombolysis in children, although proper dose finding studies have not been performed. Depending on the situation, tPA may be used systemically or locally with catheter-directed thrombolysis, sometimes with the addition of mechanical clot lysis devices operated by interventional radiologists.

Dosing

An extremely wide range of doses of tPA has been used for systemic therapy, and no consensus exists as to the optimal dose. Systemic tPA doses of 0.1-0.6 mg/kg/hr were previously recommended, although recent reports indicate successful therapy with fewer bleeding complications using prolonged infusions with very low doses—0.01-0.06 mg/kg/hr.

Monitoring

There is no specific laboratory test to document a "therapeutic range" for thrombolytic therapy. It is important to maintain the fibrinogen >100 mg/dL and the platelet count >75,000 × 10^9/L during treatment. Supplementation of plasminogen using FFP is generally recommended in neonates before initiating thrombolysis because of their low baseline levels.

The clinical and radiologic response to thrombolysis should be closely monitored. The duration of therapy depends on the clinical response. Invasive procedures, including urinary catheterization, arterial puncture, and rectal temperatures, should be avoided.

The role of adjuvant UFH during thrombolytic therapy is controversial. Animal models have demonstrated that thrombolytic therapy can induce a procoagulant state with activation of the coagulation system, generation of thrombin, and extension or reocclusion of the thrombosis. In pediatric patients thought to be at low risk for bleeding, adjuvant UFH should be considered using doses of 10-20 units/kg/hr. The recommended duration of therapy is noted in Table 528.7.

Complications

The most serious complication from thrombolysis is bleeding, which has been reported in 0–40% of patients. Absolute contraindications to thrombolysis include major surgery within 7 days, history of significant bleeding (intracranial, pulmonary, or GI), peripartum asphyxia with brain damage, uncontrolled hypertension, and severe thrombocytopenia. In the event of serious bleeding, thrombolysis should be stopped, and cryoprecipitate should be given to replace fibrinogen.

THROMBOPROPHYLAXIS

There have been no formal trials of VTE prevention in children, although many institutions are starting to develop and use risk-guided algorithms to identify children who may benefit from mechanical (sequential compression devices) or pharmacologic (low-dose anticoagulant) prevention strategies in the absence of concomitant bleeding risk. Hospitalized adolescents with multiple risk factors for thrombosis who are immobilized for a prolonged period are a group that expert consensus would suggest may benefit from prophylactic treatment with enoxaparin, 0.5 mg/kg every 12 hours (maximum 30 mg).

ANTIPLATELET THERAPY

Inhibition of platelet function using agents such as aspirin is more likely to be protective against arterial TEs than VTEs. Aspirin, or acetylsalicylic acid (ASA), exerts its antiplatelet effect by irreversibly inhibiting cyclooxygenase, preventing platelet thromboxane A_2 production. Aspirin is used routinely in children with Kawasaki disease and may also be useful in children with stroke, ventricular assist devices, and single-ventricle cardiac defects. The recommended dose of aspirin to achieve an antiplatelet effect in children is 1-5 mg/kg/day.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 529

Postneonatal Vitamin K Deficiency

Brian R. Branchford, Benjamin J. Samelson-Jones, and Veronica H. Flood

Vitamin K deficiency occurring after the neonatal period is usually secondary to insufficient vitamin K intake, malabsorption, or alterations in the intestinal flora as a consequence of antibiotics. The biologic activity of the "vitamin K–dependent factors" (coagulation factors II, VII, IX, and X, as well as the natural anticoagulants protein C and protein S) requires vitamin K for their posttranslational carboxylation. In the absence of vitamin K, only nonfunctional forms of these proteins are synthesized, which are ineffective for hemostasis. Severe vitamin K deficiency will result in a prolonged prothrombin time (PT) and partial thromboplastin time (PTT), although early deficiency may only demonstrate a prolonged PT because of the short half-life of factor VII. Plasma levels of uncarboxylated factor II are measured in the PIVKA-II (proteins induced by vitamin K absence) test and elevated levels are diagnostic of vitamin K deficiency, although clinical history and basic coagulation labs are usually sufficient to make the diagnosis. It can often be clinically helpful to distinguish between deficiencies of the vitamin K–dependent factors and deficiencies in the clotting factors synthesized by hepatocytes due to liver disease (see Chapter 530), which includes the vitamin K–dependent factors as well as factors V and XI.

Intestinal malabsorption of fats may accompany cystic fibrosis, biliary atresia, or other liver diseases and results in a deficiency of fat-soluble dietary vitamins including vitamin K.

Prophylactic administration of water-soluble vitamin K orally is indicated in these patients (2-5 mg/24 hr for children and 5-10 mg/24 hr for adolescents and adults). Vitamin K may also be administered at 1-2 mg intravenously. Broad-spectrum antibiotics can alter the intestinal flora, reducing the vitamin K that is produced in the gastrointestinal tract. Patients have only a few weeks of vitamin K stores. The anticoagulant properties of warfarin (Coumadin) depend on interference with vitamin K, with a concomitant reduction of the vitamin K–dependent clotting factors. **Rat poison** (superwarfarin) produces a similar deficiency that should be considered in young children presenting with bleeding and bruising with a history compatible with ingestion. There are also cases of illicit drugs being adulterated with vitamin K antagonists. Vitamin K is a specific antidote for these substances. Four factor prothrombin complex concentrates contain all the vitamin K–dependent clotting factors; they are available for warfarin reversal and have been used to rapidly replace vitamin K–dependent clotting factors in urgent scenarios. Dosing is based on the international normalized ratio (INR), and vitamin K should also be administered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 530

Coagulopathy in Liver Disease

Brian R. Branchford and Veronica H. Flood

Because all the clotting factors *except* factor VIII (which is synthesized in liver sinusoids and extrahepatic endothelium) are produced exclusively in hepatocytes, coagulation abnormalities are very common in patients with severe liver disease (Table 530.1). Only 15% of such patients have significant clinical bleeding states, possibly because of concomitant reduction in anticoagulation proteins (protein C and S). The severity of the coagulation abnormality appears to be directly proportional to the extent of hepatocellular damage. The most common mechanism causing the hemostasis defect is decreased synthesis of coagulation factors. Patients with severe liver disease characteristically have normal to increased (not reduced) levels of factor VIII activity in plasma. In some instances, **disseminated intravascular coagulation** (DIC; see Chapter 510), hypofibrinogenemia, or hyperfibrinolysis may complicate liver disease, making laboratory differentiation of severe liver disease from DIC-related clotting factor consumption difficult. These entities, as well as vitamin K deficiency (see Chapter 529), may be distinguished by comparing levels of a hepatically synthesized factor (such as factor V), a hepatically synthesized vitamin K–dependent factor (such as factor VII), and a nonhepatically synthesized factor that could be subject to consumption (such as factor VIII).

Treatment of the coagulopathy of liver disease should be reserved for patients with clinical bleeding rather than used to normalize the lab values. Because a reduction in vitamin K–dependent coagulation factors is common in those with acute or chronic liver disease, a trial of vitamin K supplementation can be given. Vitamin K can be given orally, subcutaneously, or preferably intravenously (not intramuscularly) at a dose of 1 mg/24 hr for infants, 2-5 mg/24 hr for children, and 5-10 mg/24 hr for adolescents and adults. Inability to correct coagulopathy with vitamin K indicates that the coagulopathy may be caused by reduced levels of clotting factors that are not vitamin K–dependent and/or by inadequate production of precursor vitamin K proteins. Treatment for bleeding consists of factor replacement with **fresh-frozen plasma** (FFP) or **cryoprecipitate**. FFP (10-15 mL/kg) contains all clotting factors, but replacement of fibrinogen for severe hypofibrinogenemia may require cryoprecipitate at a dose of 1 unit per 5-10 kg body weight, or a fibrinogen concentrate if a patient is unable to tolerate excess fluid volume. In severe liver disease, it is often difficult to attain correction of abnormal clotting studies despite vigorous therapy with FFP and cryoprecipitate, and such attempts are often complicated by volume overload concerns. Some patients with bleeding as a result of liver disease have responded to therapy with desmopressin (DDAVP), whereas others have responded to treatment with recombinant factor VIIa, albeit at a dose lower than typically given for hemophilia. Recombinant factor VIIa is contraindicated in DIC.

Desmopressin (0.3 μg/kg intravenously) is effective in shortening bleeding time, prompts endothelial cell release of von Willebrand factor and factor VIII, promotes platelet activation, and is therefore used effectively to augment hemostasis before diagnostic liver biopsy in the setting of hepatic insufficiency/failure. In clinical trials of adults, recombinant factor VIIa has not been shown to be effective for the treatment of bleeding caused by severe liver disease, possibly because of its short half-life (3-6 hours). Frequently, severe liver disease is associated with moderate prolongation of coagulation disorder screening tests (partial thromboplastin time [PTT]; prothrombin time [PT]) that is not corrected by vitamin K or plasma replacement. Another diagnostic clue may be a low serum albumin level because this protein is also synthesized in the liver.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 530.1 Coagulation Changes in Liver Disease

CHANGES IN PROCOAGULANT PROTEINS	CHANGES IN ANTICOAGULANT PROTEINS	CHANGES IN ANTIFIBRINOLYTIC PROTEINS
Decreased fibrinogen and factors FII, FV, FVII, FIX, FX, and FXI	Decreased protein C	Decreased α_2-antiplasmin and thrombin-activatable fibrinolysis inhibitor
Increased FVIII	Decreased protein S	FXIII decreased in some patients
Increased VWF, decreased ADAMTS-13	Decreased antithrombin	Increased tissue plasminogen activator

ADAMTS-13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.
From Han H, Hensch L, Hui SKR, Teruya J. Evaluation and management of coagulopathies and thrombophilias in pediatric patients. *Clin Lab Med.* 2021;41:83–100. Table 4.

Chapter 531

Acquired Inhibitors of Coagulation

Brian R. Branchford and Veronica H. Flood

Acquired circulating anticoagulants **(inhibitors)** are antibodies that react, or cross-react, with clotting factors or components used in coagulation screening tests (phospholipids), thereby prolonging screening tests, such as prothrombin time (PT) and partial thromboplastin time (PTT), although not all of them result in a clinical bleeding state. Some of these anticoagulants are autoantibodies that react with phospholipid and thereby interfere with clotting in vitro *but not in vivo.* This group comprises anticardiolipin and anti-beta(2)-glycoprotein-Ib antibodies, but the most common subtype of these **antiphospholipid antibodies** has been referred to as the *lupus anticoagulant* (see Chapter 528.1). This unfortunately named antibody is neither found exclusively in patients with systemic lupus erythematosus (SLE; see Chapter 199), nor does its presence consistently signify the concomitant presence of SLE in a patient. It can also be seen in those with other collagen vascular diseases and in association with HIV infection. In otherwise healthy children, spontaneous lupus-like inhibitors have developed transiently after incidental viral infection and can be seen in up to 26% of screening tests in asymptomatic subjects. These transient inhibitors are usually not associated with either bleeding or thrombosis.

Although the classic lupus anticoagulant is more often associated with a predisposition to thrombosis than with bleeding symptoms, bleeding symptoms in a patient with the lupus anticoagulant may be caused by **thrombocytopenia**, which may be a manifestation of the antiphospholipid syndrome or of lupus itself (alone or occasionally in context with Evans syndrome), or, rarely, by a coexistent specific autoantibody against prothrombin (factor II). The antiprothrombin antibody does not inactivate prothrombin but rather causes accelerated clearance of the protein, resulting in low levels of prothrombin and subsequent inadequate hemostasis.

Rarely, antibodies may arise spontaneously against a specific clotting factor, such as *factor VIII* or *von Willebrand factor*, leading to acquired hemophilia A or von Willebrand disease (VWD), but this is usually seen more frequently in adult patients. These patients are prone to excessive hemorrhage and may require specific treatment. In patients with a hereditary deficiency of a clotting factor (factor VIII or factor IX), antibodies may develop after exposure to transfused factor concentrates. These hemophilic inhibitory antibodies are discussed in Chapter 525.1.

LABORATORY FINDINGS

Inhibitors against specific coagulation factors usually affect factors VIII, IX, and XI, or, rarely, prothrombin (factor II). Depending on the target of the antibody and the target's participation in the intrinsic, extrinsic, or common coagulation cascade pathway, the PT and/or PTT may be prolonged. The mechanism by which the inhibitory antibody functions determines whether mixing patient plasma with normal plasma will normalize (correct) the clotting time. Patient plasma that contains antibodies directed against the active site of a clotting factor (factor VIII or factor IX) will not correct on 1:1 mixing with normal plasma, whereas antibodies that lead to increased clearance of the factor (such as antiprothrombin antibodies) will correct on such mixing studies. Specific factor assays are used to determine which factor is involved, and the pattern of abnormalities in PT, PTT, and/or thrombin time (TT) is used to guide initial investigation.

TREATMENT

Management of the bleeding patient with an acquired inhibitory autoantibody against factor VIII or IX is the same as for the patient with congenital hemophilia who has an alloantibody against factor VIII or factor IX. Infusions of recombinant factor VIIa or activated prothrombin complex concentrate may be needed to control significant bleeding. Occasionally, high-dose coagulation factor VIII or IX concentrates may be effective. Immunosuppressive agents have been used "off label" to treat the inhibitor or reduce titers. Acute bleeding caused by an antiprothrombin antibody can often be treated with a plasma infusion and may resolve with a short course of corticosteroid therapy.

Asymptomatic spontaneous inhibitors that arise after a viral infection tend to disappear within a few weeks to months. Inhibitors seen with an underlying disease, such as those associated with SLE, often resolve during the treatment of the underlying disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 532

Disseminated Intravascular Coagulation

Benjamin J. Samelson-Jones and Leslie J. Raffini

Disseminated intravascular coagulation (DIC) is an acquired clinicopathologic syndrome characterized by the widespread pathologic activation of the coagulation system, which results in both microvascular thrombi and the consumption of clotting factors, anticoagulant proteins, and platelets. Microvasculature injury can contribute to organ dysfunction, while hemorrhage can be life-threatening in a minority of cases. The diagnosis of DIC is based on the laboratory findings and clinical manifestations within the appropriate clinical context. The

simultaneous occurrence of bleeding and clotting is clinically challenging, with management starting from appropriately recognizing this syndrome.

ETIOLOGY

DIC is always a secondary complication of an underlying disorder (Table 532.1) and never an isolated diagnosis. The complex pathogenesis involves the loss of localization and excessive activation of coagulation leading to unregulated thrombin generation and microvascular fibrin deposition. Dysfunction of the vascular endothelium can both precipitate and amplify this process. The excessive activation consumes platelets, procoagulant clotting factors (factor V, factor VIII, prothrombin, and fibrinogen), and anticoagulant proteins (protein C, protein S, and antithrombin). The fibrinolytic system can also become dysregulated with endothelial injury and plasma protein consumption.

Table 532.1 Causes of Disseminated Intravascular Coagulation in Children

INFECTIONS
Meningococcemia (purpura fulminans)
Bacterial sepsis (staphylococcal, streptococcal, *Escherichia coli*, *Salmonella*)
Rickettsia (Rocky Mountain spotted fever)
Viruses (cytomegalovirus, herpes simplex, hemorrhagic fevers)
Malaria
Fungi
TISSUE INJURY
Central nervous system trauma (massive head injury)
Fat embolism
Crush injury
Profound shock or asphyxia
Hypothermia or hyperthermia (heat shock)
Massive burns
MALIGNANCY
Acute promyelocytic leukemia
Acute monoblastic leukemia
Disseminated solid tumors (rhabdomyosarcoma, neuroblastoma)
VENOM OR TOXINS
Toxic shock syndrome
Snakebites
Spider bites
MICROANGIOPATHIC DISORDERS
Severe thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome
Vascular malformations
GASTROINTESTINAL DISORDERS
Fulminant hepatitis
Ischemic bowel
Pancreatitis
HEREDITARY THROMBOTIC DISORDERS
Homozygous/compound heterozygous protein C, protein S, or antithrombin deficiency
PERINATAL
Maternal toxemia
Abruptio placentae
Severe respiratory distress syndrome
Meconium aspiration syndrome
Necrotizing enterocolitis
Erythroblastosis fetalis
Fetal demise of a twin
MISCELLANEOUS
Severe acute graft rejection
Acute hemolytic transfusion reaction
Severe collagen-vascular disease
Kawasaki disease
Heparin-induced thrombosis
Infusion of activated prothrombin complex concentrates
Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome

Adapted from Montgomery RR, Scott IP. Hemostasis: diseases of the fluid phase. In Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood*, 4th ed. Philadelphia: Saunders, 1993.

LABORATORY FINDINGS

Although DIC is characterized by a number of abnormal laboratory findings, none are specific for the diagnosis. The consumption of coagulation factors and platelets often results in a prolonged prothrombin time (PT), an increased partial thromboplastin time (PTT), and low platelet counts. Low fibrinogen is seen in severe disease, but as an acute-phase reactant, fibrinogen may be high or normal early in the disease process; declining fibrinogen levels, even within the normal range, can suggest DIC. Fibrinogen degradation products and D-dimer levels are frequently highly elevated. Factors V and VIII are usually both reduced in DIC, whereas in acute hepatic disease, factor VIII may be normal or elevated. Thrombi in the microvasculature can lead to red blood cell fragmentation and a **microangiopathic hemolytic anemia** with elevated lactate dehydrogenase and characteristic blood smear morphology, including schistocytes, helmet cells, and microspherocytes.

CLINICAL MANIFESTATIONS

DIC may be subclinical with only laboratory abnormalities, termed *nonovert DIC*. Clinical manifestations include thrombotic and hemorrhagic complications, as well as organ dysfunction. Bleeding frequently first occurs from sites of venipuncture or surgical incision, and the skin may show petechiae, purpura, and ecchymoses. Localized large-vessel arterial or venous thromboembolic events can occur. Tissue necrosis may involve many organs and can be most spectacularly seen as infarction of large areas of skin and subcutaneous tissue. A compromised blood supply can lead to organ dysfunction including organ failure, especially to the lungs, kidneys, liver, and brain.

MANAGEMENT

The primary treatment of DIC is resolving the underlying triggering disease process. Blood components support is recommended for active hemorrhage or in patients requiring invasive procedures; this may consist of platelet infusions (for thrombocytopenia), cryoprecipitate (for hypofibrinogenemia), and fresh-frozen plasma (for replacement of other coagulation factors and anticoagulant proteins). Blood product support in the absence of bleeding should not be based solely on laboratory abnormalities, but clinical practice varies on the importance of minor bleeding symptoms. Hemostatic products with activated clotting factors such as recombinant factor VIIa (FVIIa) and activated prothrombin complex concentrate (aPCC) theoretically may worsen the widespread and unregulated generation of thrombin. Likewise, systemic antifibrinolytics are generally contraindicated except in clinical scenarios associated with hyperfibrinolysis such as acute promyelocytic leukemia and early trauma.

DIC patients with overt thromboembolic complications should receive therapeutic anticoagulation, usually with unfractionated heparin, as outlined in Chapter 528.1; stringent attention to replacement therapy is warranted to maintain an adequate platelet count to limit bleeding. Prophylactic anticoagulation may be carefully used in patients with DIC at high risk of thromboembolic events that are not actively bleeding. Most patients should receive mechanical thromboprophylaxis such as sequential compression devices.

The prognosis of patients with DIC is primarily dependent on the outcome of the treatment of the primary disease and prevention of end-organ damage.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 533

Platelet and Blood Vessel Disorders

Brian R. Branchford, Benjamin J. Samelson-Jones, and Veronica H. Flood

MEGAKARYOPOIESIS

Platelets are anuclear cellular fragments produced by megakaryocytes (large polyploid cells) within the bone marrow, lung, and other tissues. When the megakaryocyte approaches maturity, budding of the cytoplasm occurs, and large numbers of platelets are liberated. Platelets circulate with a life span of 7-10 days. **Thrombopoietin (TPO)** is the primary growth factor that controls platelet production (Fig. 533.1). Levels of TPO appear to correlate inversely with platelet number and megakaryocyte mass, with highest expression in the thrombocytopenic states associated with decreased marrow megakaryopoiesis, and may be variable in states of increased platelet production.

The platelet plays multiple hemostatic roles. The platelet surface possesses a number of important receptors for adhesive proteins, including **von Willebrand factor (VWF)** and fibrinogen, as well as receptors for agonists that trigger platelet aggregation, such as thrombin, collagen, and adenosine diphosphate (ADP). After injury to the blood vessel wall, the extracellular matrix containing adhesive and procoagulant proteins is exposed. Subendothelial collagen binds VWF, which then undergoes a conformational change that induces binding of the platelet glycoprotein Ib (GPIb) complex, the VWF receptor. This process is called *platelet adhesion.* Platelets then undergo activation. During the process of activation, the platelets generate thromboxane A_2 from arachidonic acid via the enzyme cyclooxygenase. After activation, platelets release agonists, such as ADP, adenosine triphosphate (ATP), calcium ions (Ca^{2+}), serotonin, and coagulation factors, into the surrounding milieu from dense and alpha granules. Binding of VWF to the GPIb complex triggers a complex signaling cascade that results in activation of the fibrinogen receptor, the major platelet integrin glycoprotein αIIb-β_3 (GPIIb-IIIa). Circulating fibrinogen binds to this receptor on activated platelets, linking platelets in a process called *aggregation.* This series of events forms a hemostatic plug at the site of vascular injury. The serotonin and histamine that are liberated during activation increase local vasoconstriction. In addition to acting in concert with the vessel wall to form the platelet plug, the platelet provides the catalytic phospholipid surface on which coagulation factors assemble and eventually generate thrombin through a sequential series of enzymatic cleavages. Lastly, the platelet contractile proteins and cytoskeleton mediate clot retraction.

THROMBOCYTOPENIA

The normal platelet count is 150-450 × 10^9/L. *Thrombocytopenia* refers to a reduction in platelet count to <150 × 10^9/L, although clinically significant bleeding is not seen until counts drop well below 50 × 10^9/L. Causes of thrombocytopenia include decreased production on either a congenital or an acquired basis, sequestration of the platelets within an enlarged spleen or other organ, and increased destruction of normally synthesized platelets on either an immune or a nonimmune basis (Tables 533.1-533.3, Fig. 533.2, and Chapter 524).

533.1 Immune Thrombocytopenia

Brian R. Branchford and Veronica H. Flood

The most common cause of acute onset of thrombocytopenia in an otherwise-well child is immune thrombocytopenia **(ITP)** (also called immune or idiopathic thrombocytopenic purpura).

EPIDEMIOLOGY

In a small number of children, estimated at 1/20,000, 1-4 weeks after exposure to a common viral infection, an autoantibody directed against the platelet surface develops with resultant sudden onset of thrombocytopenia. A recent history of viral illness is described in 50–65% of children with ITP. The peak age is 1-4 years, although the age ranges from early in infancy to elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness. Approximately 5–10% of ITP may recur more than 3 months after initial disease resolution.

PATHOGENESIS

The exact antigenic target for most such antibodies in most cases of childhood acute ITP remains undetermined, although in chronic ITP, many patients demonstrate antibodies against αIIb-β_3 and GPIb. After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the Fc receptor on splenic macrophages, ingested, and destroyed. The most common identifiable viruses that have been described in association with ITP include Epstein-Barr

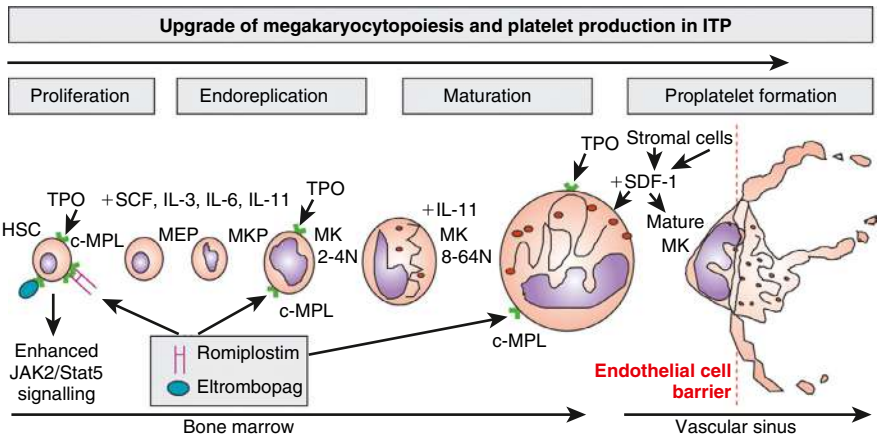

Fig. 533.1 Scheme of megakaryocytopoiesis and platelet production in immune thrombocytopenia (ITP). Hematopoietic stem cells (HSC) are mobilized, and megakaryocyte (MK) and erythroid progenitors (MEP) accumulate with MK-committed progenitors (MKP), giving rise to mature MKs under control of thrombopoietin (TPO) working with chemokines, cytokines, and growth factors, including stem cell factor (SCF) and interleukin (IL)-3, IL-6, and IL-11. Endoreplication results in ploidy changes in MKs and increased chromosome number (up to 64N). Mature MKs migrate to the endothelial cell barrier delimiting the vascular sinus and, under the influence of stromal-derived factor-1 (SDF-1), give rise to proplatelets that protrude into the circulation and produce large numbers of platelets under hemodynamic determinants. Therapeutically given romiplostim and eltrombopag enter the marrow and join with TPO to stimulate megakaryocytopoiesis and platelet production. *(From Nurden AT, Viallard JF, Nurden P. New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura. Lancet 2009;373:1563–1569.)*

Table 533.1 Differential Diagnosis of Thrombocytopenia in Children and Adolescents

DESTRUCTIVE THROMBOCYTOPENIAS
Primary Platelet Consumption Syndromes
Immune thrombocytopenias
- Acute and chronic ITP
- Autoimmune diseases with chronic ITP as a manifestation
  - Cyclic thrombocytopenia
  - Autoimmune lymphoproliferative syndrome and its variants
  - Systemic lupus erythematosus
  - Evans syndrome
  - Antiphospholipid antibody syndrome
  - Neoplasia-associated immune thrombocytopenia
- Thrombocytopenia associated with HIV
- Neonatal immune thrombocytopenia
  - Alloimmune
  - Autoimmune (e.g., maternal ITP)
- Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)
- Posttransfusion purpura
- Allergy and anaphylaxis
- Posttransplant thrombocytopenia

Nonimmune thrombocytopenias
- Thrombocytopenia of infection
  - Bacteremia or fungemia
  - Viral infection
  - Protozoan
- Thrombotic microangiopathic disorders
  - Hemolytic-uremic syndrome
  - Eclampsia, HELLP syndrome
  - Thrombotic thrombocytopenic purpura
  - Bone marrow transplantation–associated microangiopathy
  - Drug induced (quinine, etc.)
- Platelets in contact with foreign material
- Congenital heart disease
- Drug-induced via direct platelet effects (ristocetin, protamine)
- Type 2B VWD or platelet-type VWD

Combined Platelet and Fibrinogen Consumption Syndromes
Disseminated intravascular coagulation
Kasabach-Merritt syndrome
Hemophagocytic lymphohistiocytosis (inherited or acquired)

IMPAIRED PLATELET PRODUCTION
Hereditary disorders (see Table 533.2)
Acquired disorders
- Aplastic anemia
- Myelodysplastic syndrome
- Marrow infiltrative process—neoplasia
- Osteopetrosis
- Nutritional deficiency states (iron, folate, vitamin B12, anorexia nervosa)
- Drug- or radiation-induced thrombocytopenia
- Neonatal hypoxia or placental insufficiency

SEQUESTRATION
Hypersplenism
Hypothermia
Burns

ASSOCIATION WITH OTHER DISEASES
Fanconi anemia
Congenital amegakaryocytic thrombocytopenia
Shwachman-Diamond syndrome
Hemophagocytic lymphohistiocytosis
TAFRO syndrome

HELLP, Hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; TAFRO, thrombocytopenia, ascites, myelofibrosis renal dysfunction, organomegaly (a variant of multicentric Castleman disease); VWD, von Willebrand disease.
From Wilson DB. Acquired platelet defects. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier, 2015: Box 34.1, p. 1077.

virus (EBV; see Chapter 301) and HIV (see Chapter 322), and ITP is also noted as a rare occurrence after measles, mumps, and rubella (MMR) vaccination. EBV-related ITP is usually of short duration and follows the course of infectious mononucleosis. HIV-associated ITP is usually chronic. In some patients, ITP appears to arise in children infected with *Helicobacter pylori* or rarely after vaccines. The SARS-CoV-2 virus responsible for the COVID-19 infection has been associated with development of ITP, as have some of the vaccines for this virus.

CLINICAL MANIFESTATIONS

The classic presentation of ITP is a previously healthy 1–4-year-old child who has sudden onset of generalized petechiae and purpura. The parents often state that the child was fine the previous day but is now covered with bruises and purple dots. There may be bleeding from the gums and mucous membranes, particularly with *profound thrombocytopenia* (platelet count $<10 \times 10^9$/L). There is a history of a preceding viral infection 1-4 weeks before the onset of thrombocytopenia. Findings on physical examination are typically normal, other than petechiae and purpura. *Splenomegaly, lymphadenopathy, bone pain, and pallor are rare.* A simple classification system to characterize the severity of bleeding in ITP on the basis of symptoms and signs rather than platelet count includes:

1. No symptoms
2. Mild symptoms: Bruising and petechiae, occasional minor epistaxis, very little interference with daily living
3. Moderate symptoms: More severe skin and mucosal lesions, more troublesome epistaxis, and menorrhagia
4. Severe symptoms: Bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization, symptoms interfering seriously with the quality of life

The presence of abnormal findings such as hepatosplenomegaly, bone or joint pain, remarkable lymphadenopathy, other cytopenias, or congenital anomalies suggests other diagnoses (e.g., leukemia, genetic syndromes). When the onset is insidious, especially in an adolescent, chronic ITP or the possibility of a systemic illness, such as **systemic lupus erythematosus** (SLE), is more likely. In addition, presentation at an atypical age (neonates, adolescents) should suggest an underlying disease.

OUTCOME

Severe bleeding is rare (<3% of cases in one large international study). In 70–80% of children who present with acute ITP, spontaneous resolution occurs within 6 months. Therapy does not appear to affect the natural history of the illness. Fewer than 1% of patients develop an **intracranial hemorrhage** (ICH). Proponents of interventional therapy argue that the objective of early therapy is to raise the platelet count to $>20 \times 10^9$/L and prevent the rare development of ICH. There is no evidence that therapy prevents serious bleeding. Approximately 20% of children who present with acute ITP go on to have chronic ITP. The outcome/prognosis may be related more to age; ITP in younger children is more likely to resolve, whereas development of chronic ITP in adolescents approaches 50%.

LABORATORY FINDINGS

Severe thrombocytopenia (platelet count $<20 \times 10^9$/L) is common, and platelet size is normal or increased, reflective of increased platelet turnover (Fig. 533.3). In acute ITP, the hemoglobin value, white blood cell (WBC) count, and differential count are usually normal. Hemoglobin may be decreased in the context of profuse nosebleeds (epistaxis) or menorrhagia. Bone marrow examination, *which is not routinely indicated in this disease*, shows normal granulocytic and erythrocytic series, with characteristically normal or increased numbers of megakaryocytes. Some of the megakaryocytes may appear to be immature and reflect increased platelet turnover. *Indications for bone marrow aspiration/biopsy* include an abnormal WBC count or differential or unexplained anemia, as well as history and physical examination findings suggestive of a bone marrow failure syndrome or malignancy. Other laboratory tests should be performed as indicated by the history and examination. HIV studies should be done in at-risk populations, especially sexually active teens. Platelet antibody testing is seldom useful in acute ITP. A direct antiglobulin test (Coombs) should be done if there is unexplained anemia to rule out **Evans syndrome** (autoimmune hemolytic anemia and thrombocytopenia; see Chapter 506). Evans syndrome may be idiopathic or an early sign of SLE, autoimmune lymphoproliferative syndrome, or common variable immunodeficiency

Table 533.2 Inherited Platelet Disorders

PLATELET DEFECT	GENE DEFECT (CHROMOSOMAL LOCATION)	CLINICAL AND LABORATORY CHARACTERISTICS	BLEEDING TREATMENT
DEFECTS IN PLATELET ADHESION			
Bernard-Soulier syndrome (BSS)	Autosomal recessive: *GP1BA* (17p13) *GP1BB* (22q11) *GP9* (3q21) Autosomal dominant: Ala156Val, GP1BA - Bolzano variant	• Often severe bleeding phenotype • Thrombocytopenia • Large platelets • Platelet aggregation: absent ristocetin-induced response • Flow cytometry: reduced or absent CD42a (GPIX)/CD42b (GP1bα) • *GP1BA* & *GP1BB* gene sequencing	• Supportive care • Platelet transfusion (risk of alloantibodies) • Antifibrinolytics • rFVIIa
Velocardiofacial/DiGeorge syndrome (VCFS)	22q11.2 deletion including *GP1BB*	• Thrombocytopenia • Large platelets and α-granules • Cardiac, thymus, parathyroid, facial, and cognitive abnormalities	• Supportive care
Platelet-type von Willebrand disease (PT-VWD)	Autosomal dominant: gain of function variants in *GP1BA*	• Thrombocytopenia • Large platelets • Platelet clumping • Decreased VWF:Ag, VWF multimers • Platelet aggregation: low dose ristocetin-induced platelet agglutination • *GP1BA* gene sequencing	• Supportive care • Platelet transfusion • Antifibrinolytics • rFVIIa
DEFECTS OF PLATELET AGGREGATION			
Glanzmann thrombasthenia (GT)	Autosomal recessive: *ITGA2B* (17Q21.32) *ITGB3* (17q21.32)	• Often severe bleeding phenotype • Normal platelet count and morphology • Platelet aggregation: absent response to all agonists except ristocetin • Flow cytometry: absent or reduced CD41 and CD61	• Supportive care • rFVIIa (considered the first line) • Platelet transfusion (risk of HPA alloantibodies) • Antifibrinolytics
DEFECTS IN AGONISTS RECEPTORS			
Thromboxane-prostanoid (TP) receptor defects	Autosomal recessive *TBXA2R* (19p13.3)	• Mild bleeding phenotype • Platelet aggregation: abnormal response to arachidonic acid and U46619 • *TBXA2R* gene sequencing	• Supportive care
ADP receptor defects P2Y12	Autosomal recessive *P2RY12* (3q23–25)	• Mild bleeding phenotype • Platelet aggregation: abnormal response to ADP • *P2RY12* gene sequencing	• Supportive care
Collagen receptor defects GPVI	Autosomal recessive *GP6* (19q13.4)	• Mild bleeding phenotype • Platelet aggregation: abnormal response to collagen • *GP6* gene sequencing	• Supportive care
PLATELET GRANULES DEFECTS (A-GRANULES)			
Gray platelet syndrome (GPS)	Autosomal recessive *NBEAL2* (3p21)	• Progressive myelofibrosis • Thrombocytopenia • Large pale platelets on blood smears • Absent α-granules on TEM • *NBEAL2* gene sequencing	• Supportive care • Antifibrinolytics • DDVAP • Platelet transfusion • Splenectomy
Arthrogryposis, renal dysfunction, and cholestasis syndrome (ARC syndrome)	Autosomal dominant *VPS33B* (15q26) *VIPAS39* (14q24)	• Thrombocytopenia • Large pale platelets on blood smears • Absent α-granules on TEM • Lethal early in life • *VPS33B* & *VIPAS39* sequencing	• Supportive care • Platelet transfusion • Antifibrinolytics

Continued

Table 533.2 Inherited Platelet Disorders—cont'd

PLATELET DEFECT	GENE DEFECT (CHROMOSOMAL LOCATION)	CLINICAL AND LABORATORY CHARACTERISTICS	BLEEDING TREATMENT
Quebec platelet disorder (QPD)	Autosomal recessive Tandem duplication of *PLAU* (10q22.2)	• Delayed-onset bleeding not responding to platelet transfusion • Variable thrombocytopenia • Abnormal urokinase in platelets detected with immunoblot or ELISA • *PLAU* duplication testing	• Supportive care • Antifibrinolytics
Paris-Trousseau/Jacobsen syndrome (PTS)	Autosomal dominant Deletion of chromosome 11q23–24 Hemizygous deletion of *FLI1* (11q24.1 – q24.3)	• Thrombocytopenia • Large platelets • Giant α-granules on TEM • Immature megakaryocytes in the bone marrow • Cognitive, cardiac, and facial abnormalities	• Supportive care • Antifibrinolytics • Platelet transfusion
PLATELET GRANULES DEFECTS (δ-GRANULES)			
Hermansky-Pudlak syndrome (HPS)	Autosomal recessive HPS1–10 (*HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S6,* and *AP3D1*)	• Decreased to absent δ-granules • Lumiaggregometry: decreased/absent ATP release • Whole-mount EM • Gene sequencing of 10 candidate genes • Oculocutaneous albinism	• Supportive care • Antifibrinolytics • Platelet transfusion • DDAVP
Chediak-Higashi syndrome (CHS)	Autosomal recessive *LYST* (1q42 – 1q42.2)	• Giant eosinophilic inclusions in neutrophils • Decreased to absent δ-granules • Lumiaggregometry: decreased/absent ATP release • Hypopigmentation and immunodeficiency	• Supportive care
PLATELET CYTOSKELETAL DEFECTS			
Wiskott-Aldrich syndrome (WAS) / X-linked thrombocytopenia	X-linked *WAS* (Xp11.23 – p11.22) encoding WAS protein	• Thrombocytopenia • Small platelets • Recurrent infections and eczema • Decreased/absent intracellular • WASp per immunoblot/ELISA • *WAS* gene sequencing	• Supportive care • Platelet transfusion • Antifibrinolytics • Splenectomy (not recommended)
ARPC1B deficiency	Autosomal recessive *ARPC1B* (7q22.1)	• Small platelets • Inflammatory disease, recurrent infections, small vessel vasculitis, abnormal platelet function • Decreased/absent intracellular • ARPC1B per immunoblot • *ARPC1B* gene sequencing	• Supportive care • Antifibrinolytics • Platelet transfusion
MYH9-related disease (MYH9-RD)	Autosomal dominant *MYH9* (22q12–13) encoding nonmuscle myosin heavy chain IIA	• Thrombocytopenia • Large platelets • Döhle-like inclusions in neutrophils • Myosin IIA aggregates in neutrophils - immunofluorescence microscopy • Variable degree of renal disease, sensorineural hearing loss, presenile cataract	• Supportive care • Platelet transfusion • Antifibrinolytics • THPO receptor agonists

VWF, Von Willebrand factor; HPA, human platelet antigen; ADP, adenosine diphosphate; TEM, transmission electron microscopy; EM, electron microscopy; ELISA, enzyme-linked immunosorbent assay; DDAVP, desmopressin; THPO, thrombopoietin.
Modified from Al-Huniti A, Kahr WHA. Inherited platelet disorders: diagnosis and management. *Transfu Med Rev* 2020;34:277–285. Table 1.

syndrome. An antinuclear antibody should be considered in adolescents, especially with other features of SLE (see Chapter 199).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The well-appearing child with moderate to severe thrombocytopenia, an otherwise normal complete blood cell count (CBC), and normal exam findings has a limited differential diagnosis that includes exposure to medication inducing drug-dependent antibodies, splenic sequestration because of previously unappreciated portal hypertension, and, rarely, early aplastic processes, such as Fanconi anemia (see Chapter 517). Other than congenital thrombocytopenia syndromes (see Chapter 533.8), such as thrombocytopenia–absent radius (TAR) syndrome and MYH9-related thrombocytopenia, most marrow processes that interfere with platelet production eventually cause abnormal synthesis of red blood cells (RBCs) and WBCs and therefore manifest diverse abnormalities on the CBC. Disorders that cause increased platelet destruction on a nonimmune basis are usually serious systemic illnesses with obvious clinical findings such as **hemolytic-uremic syndrome** (HUS) and **disseminated intravascular**

Table 533.3	Classification of Fetal and Neonatal Thrombocytopenias*
Fetal	**Alloimmune thrombocytopenia**
	Congenital infection (CMV, toxoplasma, rubella, HIV, syphilis)
	Aneuploidy (trisomy 18, 13, or 21, triploidy, Turner syndrome)
	Autoimmune condition (maternal ITP, SLE)
	Severe Rh hemolytic disease
	Congenital/inherited (Wiskott-Aldrich, Noonan, Cornelia deLange, Jacobsen syndromes)
Early-onset neonatal (<72 hr)	**Placental insufficiency** (PET, IUGR, diabetes)
	Perinatal asphyxia
	Perinatal infection (*Escherichia coli*, GBS, herpes simplex)
	DIC
	Alloimmune thrombocytopenia
	Autoimmune condition (maternal ITP, SLE)
	Congenital infection (CMV, toxoplasma, rubella, HIV)
	Thrombosis (aortic, renal vein)
	Bone marrow disease (congenital leukemia, HLH)
	Kasabach-Merritt syndrome
	Metabolic disease (propionic and methylmalonic acidemia)
	Congenital/inherited (TAR, CAMT)
Late-onset neonatal (>72 hr)	**Late-onset sepsis**
	NEC
	Congenital infection (CMV, toxoplasma, rubella, HIV)
	Autoimmune
	Kasabach-Merritt syndrome
	Metabolic disease (propionic and methylmalonic acidemia)
	Congenital/inherited (TAR, CAMT)

*The most common conditions are shown in **bold**.
CAMT, Congenital amegakaryocytic thrombocytopenia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; GBS, group B streptococcus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; ITP, immune thrombocytopenic purpura; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PET, preeclampsia; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absent radii.
From Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F359–F364.

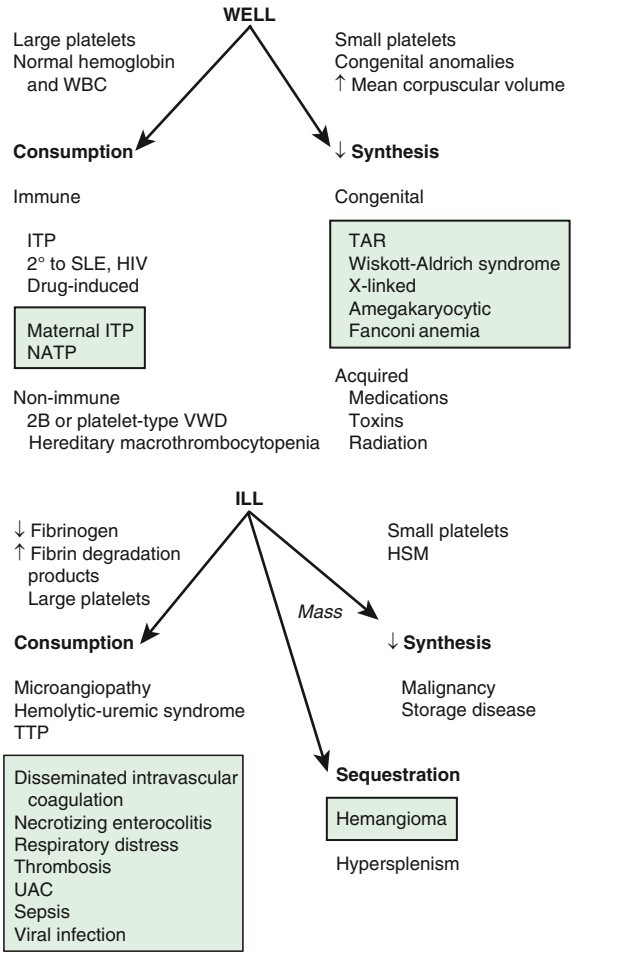

Fig. 533.2 Differential diagnostic algorithm of childhood thrombocytopenic syndromes. The syndromes initially are separated by their clinical appearance. Clues leading to the diagnosis are shown in *italics*. The mechanisms and common disorders leading to these findings are shown in the *lower part* of the figure. Disorders that commonly affect neonates are listed in the *shaded boxes*. HSM, Hepatosplenomegaly; ITP, immune thrombocytopenia; NATP, neonatal alloimmune thrombocytopenic purpura; SLE, systemic lupus erythematosus; TAR, thrombocytopenia–absent radius; TTP, thrombotic thrombocytopenic purpura; UAC, umbilical artery catheter; VWD, von Willebrand disease; WBC, white blood cell. *(From Scott JP. Bleeding and thrombosis. In Kliegman RM, ed. Practical Strategies in Pediatric Diagnosis and Therapy. Philadelphia: Saunders, 1996. p. 849; and Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. Nelson Essentials of Pediatrics, 5th ed. Philadelphia: Saunders, 2006. p. 716.)*

coagulation (DIC) (see Fig. 533.2, and Table 532.1 in Chapter 532). Patients receiving heparin may develop heparin-induced thrombocytopenia. Isolated enlargement of the spleen suggests the potential for hypersplenism caused by liver disease or portal vein thrombosis. Autoimmune thrombocytopenia may be an initial manifestation of SLE, HIV infection, common variable immunodeficiency, and, rarely, lymphoma or autoimmune lymphoproliferative syndrome. Wiskott-Aldrich syndrome (WAS) must be considered in young males found to have thrombocytopenia with *small* platelets, particularly if there is a history of eczema and recurrent infection (see Chapter 165.2). Bernard-Soulier syndrome, on the other hand, involves a macrothrombocytopenia. Gray platelet syndrome is usually associated with splenomegaly and pale-colored platelets on peripheral smear.

TREATMENT

A number of treatment options exist (Table 533.4), but there are no current high-quality data showing that treatment affects either short- or long-term clinical outcome of ITP in children. Many patients with new-onset ITP have mild symptoms, with findings limited to petechiae and purpura on the skin, despite severe thrombocytopenia. Compared with untreated controls, treatment appears to be capable of inducing a more rapid rise in platelet count to the presumed safe level of >20 $\times$ 10^9/L, although no data indicate that early therapy prevents ICH.

Antiplatelet antibodies bind to transfused platelets as well as they do to autologous platelets. Thus platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present. Management guidelines for ITP in children and adults reinforce existing emphasis on prioritizing watchful waiting for spontaneous resolution or outpatient therapy in the uncommon cases for which treatment is needed. Initial approaches to the management of pediatric ITP include the following:

1. No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun. This approach is much less costly, and side effects are minimal. Observation is recommended for children with no bleeding or *only* mild bleeding symptoms such as bruising or petechiae.
2. Treatment with either intravenous immunoglobulin (IVIG) or corticosteroids, particularly for children who present with *mucocutaneous* bleeding. IVIG at a dose of 0.8-1.0 g/kg/day for 1-2 days induces a rapid rise in platelet count (usually >20 × 10^9/L) in 95% of patients within 48 hours. IVIG appears to induce a response by downregulating Fc-mediated phagocytosis of antibody-coated platelets. IVIG therapy is both expensive and time-consuming and typically requires inpatient admission. Additionally, after infusion, there is a risk of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.
3. Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Doses of prednisone at 1-4 mg/kg/day appear to induce a more rapid rise in platelet count than in untreated patients with ITP. Corticosteroid therapy is usually continued for a short course (approximately 5 days) until a rise in platelet count to >20 × 10^9/L has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.

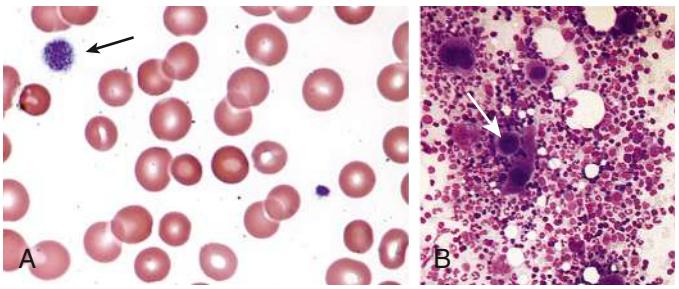

Fig. 533.3 Blood and marrow aspirate from child with immune thrombocytopenia. **A**, Blood smear shows large platelets. **B**, Bone marrow aspirate shows increased numbers of megakaryocytes, many of which appear immature. *(From Blanchette V, Bolton-Maggs P: Childhood immune thrombocytopenic purpura: diagnosis and management. Pediatr Clin North Am 2008;55:393–420. Fig 4.)*

Each of these medications may also be used to treat subsequent ITP exacerbations/recurrences, which usually occur several weeks after an initial course of therapy in 5–10% of patients. In the special case of ICH, multiple modalities should be used, including platelet transfusion (although not recommended in other bleeding manifestations), IVIG, high-dose corticosteroids, and prompt consultation by neurosurgery and general surgery (splenectomy).

Patients who are bleeding significantly (<5% of children with ITP) should be treated. ICH remains rare, and there are no data showing that treatment actually reduces its incidence. *Mucosal bleeding* in particular is the most significant in terms of predicting severe bleeding, but specific predictive indices, such as positive or negative predictive values, are not currently well established.

The role of **splenectomy** in ITP should be reserved for one of two circumstances: (1) the older child (≥4 years) with severe ITP that has lasted >1 year **(chronic ITP)** and whose symptoms are not easily controlled with therapy and/or (2) when life-threatening hemorrhage (e.g., ICH) complicates acute ITP if the platelet count cannot be corrected rapidly with transfusion of platelets and administration of IVIG and corticosteroids. Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms, increased risk of thrombosis, and the potential development of pulmonary hypertension in adulthood. As an alternative to splenectomy**, rituximab** has been used in children to treat chronic ITP. In 30–40% of children, rituximab has induced a partial or complete remission. TPO receptor agonists have also been used to increase platelet count and are approved for pediatric use.

CHRONIC AUTOIMMUNE THROMBOCYTOPENIC PURPURA

Approximately 20% of patients who present with acute ITP have persistent thrombocytopenia for >12 months and are said to have *chronic* ITP. At that time, a careful reevaluation for associated disorders should be performed, especially for autoimmune disease (e.g., SLE), chronic infectious disorders (e.g., HIV), and nonimmune causes of chronic thrombocytopenia, such as type 2B and platelet-type von Willebrand disease (VWD), X-linked thrombocytopenia, autoimmune lymphoproliferative syndrome, common variable immunodeficiency syndrome, autosomal macrothrombocytopenia, and WAS. The presence of coexisting *H. pylori* and hepatitis C infection should be considered and, if found, treated. Therapy should be aimed at controlling symptoms and

Table 533.4 Treatment Options for Immune Thrombocytopenia (ITP)

	PROS	CONS	COST
Observation	Does not expose patient to unnecessary medications	May increase parent and physician anxiety	Relatively inexpensive
IVIG	Rapid response in most cases	IV administration, side effects	Expensive
Corticosteroids	Oral, effective in 70–80% of patients, minimal side effects with short courses	Side effects, may not affect long term outcome	Inexpensive
Rituximab	Long-term remission in 40–60% of patients	IV administration, immune suppression, potential for reactivation of hepatitis	Very expensive
Splenectomy	Curative in 80% of patients	Requires surgery and anesthesia, lifelong risk of infection	Expensive
Thrombopoietin receptor agonists	Potential for oral administration, 40–60% of patients respond	Not curative, usually required long term, can cause elevated liver enzymes	Very expensive

IV, Intravenous; IVIG, intravenous immunoglobulin.
Adapted from Flood VH, Scott JP. Bleeding and thrombosis. In: Kliegman R, Lye P, Bordini B, et al. eds. *Nelson Pediatric Symptom-Based Diagnosis.* Philadelphia: Elsevier, 2017.

preventing serious bleeding. In ITP, the spleen is the primary site of both antiplatelet antibody synthesis and platelet destruction. Splenectomy is successful in inducing complete remission in 64–88% of children with chronic ITP. This effect must be balanced against the lifelong risk of overwhelming postsplenectomy infection and/or thrombosis. This decision is often affected by quality-of-life issues, as well as the ease with which the child can be managed using medical therapy, such as IVIG, corticosteroids, IV anti-D, or rituximab. Two effective agents that act to stimulate thrombopoiesis, **romiplostim** and **eltrombopag** (see Fig. 533.1), are approved to treat adults and children with chronic ITP. Although these do not address the mechanism of action of ITP, the increase in platelet count may be enough to compensate for the increased destruction and allow the patient to have resolution of bleeding and maintain a platelet count >50 × 10^9/L.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.2 Drug-Induced Thrombocytopenia

Brian R. Branchford and Veronica H. Flood

A number of drugs are associated with immune thrombocytopenia as the result of either an immune process or megakaryocyte injury. Some common drugs used in pediatrics that cause thrombocytopenia include valproic acid, phenytoin, carbamazepine, sulfonamides, vancomycin, and trimethoprim-sulfamethoxazole. Most of these drugs may affect platelet function as well as the count itself. Heparin-induced thrombocytopenia (and rarely an associated thrombosis) is seldom seen in pediatrics, but it occurs when, after exposure to heparin, the patient has an antibody directed against the heparin–platelet factor 4 complex. Recommended treatment for heparin-induced thrombocytopenia includes direct thrombin inhibitors such as argatroban or bivalirudin and removal of all sources of heparin, including central venous catheter line flushes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.3 Nonimmune Platelet Destruction

Brian R. Branchford and Veronica H. Flood

The syndromes of DIC (see Chapter 532), HUS (see Chapter 560.5), and thrombotic thrombocytopenic purpura (see Chapter 533.5) share the hematologic picture of a thrombotic microangiopathy in which there exists RBC destruction and consumptive thrombocytopenia caused by platelet and fibrin deposition in the microvasculature. The microangiopathic hemolytic anemia is characterized by the presence of RBC fragments, including helmet cells, schistocytes, spherocytes, and burr cells.

533.4 Hemolytic-Uremic Syndrome

See Chapter 560.5.

533.5 Thrombotic Thrombocytopenic Purpura

Brian R. Branchford and Veronica H. Flood

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy characterized by the pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, abnormal renal function, and central nervous system (CNS) changes; TTP is clinically similar to HUS (Table 533.5). Although TTP can be congenital, the acquired form is more common and usually presents in adults and occasionally in adolescents. Microvascular thrombi within the CNS cause subtle, shifting neurologic signs that vary from changes in affect and orientation to aphasia, blindness, and seizures. Initial manifestations are often nonspecific (weakness, pain, emesis), and prompt recognition of this disorder is critical. Laboratory findings provide important clues to the diagnosis and show microangiopathic hemolytic anemia characterized by morphologically abnormal RBCs, with schistocytes, spherocytes, helmet cells, and an elevated reticulocyte count in association with thrombocytopenia. Coagulation studies are usually nondiagnostic. Blood urea nitrogen and creatinine are sometimes elevated. The **treatment** of acquired TTP is plasmapheresis (plasma exchange), which is effective in 80–95% of patients. Treatment with plasmapheresis should be instituted on the basis of thrombocytopenia and microangiopathic hemolytic anemia even if other symptoms are not yet present because of the high mortality (80–90%) in patients without timely intervention. Rituximab, corticosteroids, and splenectomy are reserved for refractory cases. *Caplacizumab,* an anti-VWF humanized immunoglobulin, blocks the interaction of ultralarge (i.e., most likely to bind platelets) VWF multimers with platelets, and many result in rapid resolution of acute TTP.

The majority of cases of TTP are acquired, caused by an autoantibody-mediated **deficiency of ADAMTS13** (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13) that is responsible for cleaving the high-molecular-weight multimers of VWF and appears to play a pivotal role in the evolution of the thrombotic microangiopathy (Fig. 533.4) that results in a preponderance of ultralarge multimers that more adeptly bind platelets, triggering the microangiopathy. In contrast, levels of ADAMTS13 in HUS are usually normal.

Congenital ADAMTS13 deficiency causes rare familial cases of TTP/HUS, usually manifested as recurrent episodes of thrombocytopenia, hemolytic anemia, jaundice, and renal involvement, with or without neurologic changes, that often present in infancy in the context of an intercurrent illness. Treatment of hereditary TTP with recombinant ADAMTS13 has been successful when patients are refractory to fresh frozen plasma therapy. Abnormalities of the complement system have now also been implicated in rare cases of familial TTP. ADAMTS13 deficiency can be treated by repeated infusions of fresh-frozen plasma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.6 Kasabach-Merritt Syndrome

Brian R. Branchford and Veronica H. Flood

See also Chapter 691.

The association of a giant hemangioma with localized intravascular coagulation causing consumptive thrombocytopenia and hypofibrinogenemia is called Kasabach-Merritt syndrome. In most patients, the site of the hemangioma is obvious, but retroperitoneal and intra-abdominal hemangiomas may require body imaging for detection. Platelet trapping and activation of coagulation occurs inside the hemangioma, with fibrinogen consumption and generation of fibrin(ogen) degradation products. Arteriovenous malformation within the lesions can cause heart failure. Pathologically, Kasabach-Merritt syndrome appears to develop more often as a result of a kaposiform hemangioendothelioma or tufted hemangioma rather than a simple hemangioma. The peripheral blood smear shows microangiopathic changes.

Multiple modalities have been used to treat Kasabach-Merritt syndrome, including propranolol, surgical excision (if possible), laser photocoagulation, high-dose corticosteroids, local radiation therapy, antiangiogenic agents such as interferon-α_2, and vincristine. Over time, most patients who present in infancy have regression of the hemangioma. Treatment of the associated coagulopathy may benefit from a trial of antifibrinolytic therapy with ε-aminocaproic acid (Amicar) or anticoagulation with low molecular weight heparin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 533.5 ADAMTS13 Deficiency and Thrombotic Thrombocytopenic Purpura

DISEASE	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
Thrombotic thrombocytopenic purpura (TTP)	*Acquired*: Ab to ADAMTS13 *Congenital*: Inadequate ADAMTS13 production	Ab to ADAMTS13 ADAMTS13 <10%	*Acquired*: Plasmapheresis with plasma *Congenital*: Scheduled plasma infusions

Autoimmune TTP may be transient, recurrent, drug (ticlopidine, clopidogrel) associated, or seen in some pregnancy-associated cases of TTP.
ADAMTS13 pathogenic variants are often familial and chronic-relapsing RRP.

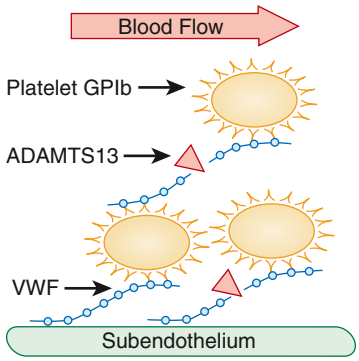

Fig. 533.4 Pathogenesis of thrombotic thrombocytopenic purpura (TTP). The von Willebrand factor (VWF) multimers facilitate platelet adhesion to the subendothelium by binding to exposed connective tissue and then to platelet glycoprotein Ib (GPIb). In flowing blood shear stress unfolds ultralarge VWF multimers in the platelet-rich thrombus and enables ADAMTS13 to cleave a specific Tyr-Met bond in the second of the three A domains in VWF subunits. Cleavage reduces VWF multimer size and limits thrombus growth. In the absence of ADAMTS13, VWF-dependent platelet accumulation continues and eventually results in microvascular thrombosis and TTP. *(Courtesy Dr. J. Evan Sadler, Washington University.)*

533.7 Sequestration

Brian R. Branchford and Veronica H. Flood

Thrombocytopenia develops in individuals with massive splenomegaly, such as those with portal vein thrombosis or liver disease, because the spleen acts as a reservoir for platelets and may sequester a large number of them. Most such patients also have mild leukopenia and anemia on CBC. Individuals who have thrombocytopenia caused by splenic sequestration should undergo a workup to diagnose the etiology of splenomegaly, including infectious, inflammatory, infiltrative, neoplastic, obstructive, and hemolytic causes.

533.8 Congenital Thrombocytopenic Syndromes

Brian R. Branchford and Veronica H. Flood

See Table 533.2.

Congenital amegakaryocytic thrombocytopenia (CAMT) usually manifests within the first few days to week of life, when the child presents with petechiae and purpura caused by profound thrombocytopenia. CAMT is caused by a rare defect in hematopoiesis as a result of pathogenic variants in the *MPL* gene that encodes the stem cell TPO receptor. Other than skin and mucous membrane abnormalities, findings on physical examination are normal. Examination of the bone marrow shows an absence of megakaryocytes. These patients often progress to marrow failure (aplasia). Hematopoietic stem cell transplantation (HSCT) is curative.

Thrombocytopenia–absent radius (TAR) syndrome consists of thrombocytopenia (absence or hypoplasia of megakaryocytes) that presents in early infancy with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening (Fig. 533.5). Many such individuals also have other skeletal abnormalities of the ulna, radius, and lower extremities. *Present thumbs help to differentiate this disorder from Fanconi anemia.* Intolerance to cow's milk formula (present in 50%) may complicate management by triggering gastrointestinal (GI) bleeding, increased thrombocytopenia, eosinophilia, and a leukemoid reaction. The thrombocytopenia of TAR syndrome frequently remits over the first few years of life. The molecular basis of TAR syndrome is linked to *RBM8A*. A few patients have been reported to have a syndrome of **amegakaryocytic thrombocytopenia with radioulnar synostosis** caused by a pathogenic variant in the *HOXA11* gene. In contrast to TAR syndrome, this clinical disorder presents with marrow aplasia.

WAS is characterized by microthrombocytopenia, with tiny platelets, eczema, and recurrent infection as a consequence of immune deficiency (see Chapter 165.2). WAS is inherited as an X-linked disorder, and the gene implicated in WAS has been identified. The WAS protein appears to play an integral role in regulating the cytoskeletal architecture of both platelets and T lymphocytes in response to receptor-mediated cell signaling. The WAS protein is common to all cells of hematopoietic lineage. Molecular analysis of families with X-linked thrombocytopenia has shown that many affected members have a single nucleotide pathogenic variant within the WAS gene, whereas individuals with the full manifestation of WAS have large gene deletions. Examination of the bone marrow in WAS shows the normal number of megakaryocytes, although they may have bizarre morphologic features. Transfused platelets have a normal life span in these patients. Splenectomy often corrects the thrombocytopenia, suggesting that the platelets formed in WAS have accelerated destruction. After splenectomy, these patients are at increased risk for overwhelming infection and require lifelong antibiotic prophylaxis against encapsulated organisms. Approximately 5–15% of patients with WAS develop lymphoreticular malignancies (involving mostly leukemias and lymphomas). Successful HSCT from an unaffected donor cures WAS. **X-linked macrothrombocytopenia** and **dyserythropoiesis** have been linked to pathogenic variants in *GATA1*, which encodes an erythroid and megakaryocytic transcription factor.

MYH9-related thrombocytopenias include a number of diverse hereditary thrombocytopenia syndromes (e.g., Sebastian, Epstein, May-Hegglin, Fechtner) characterized by autosomal dominant macrothrombocytopenia, neutrophil inclusion bodies, and a variety of physical anomalies, including sensorineural deafness, renal disease, and eye disease. These have all been shown to be caused by different pathogenic variants in the *MYH9* gene (nonmuscle myosin-IIa heavy chain 9). The thrombocytopenia is usually mild and not progressive. Some other individuals with recessively inherited macrothrombocytopenia have abnormalities in chromosome 22q11. Pathogenic variants in the gene for glycoprotein Ibβ, an essential component of the platelet VWF receptor, can result in **Bernard-Soulier syndrome** (see Chapter 533.13), a macrothrombocytopenic disease. A diagnostic approach to genetic platelet disorders is noted in Figure 533.6.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

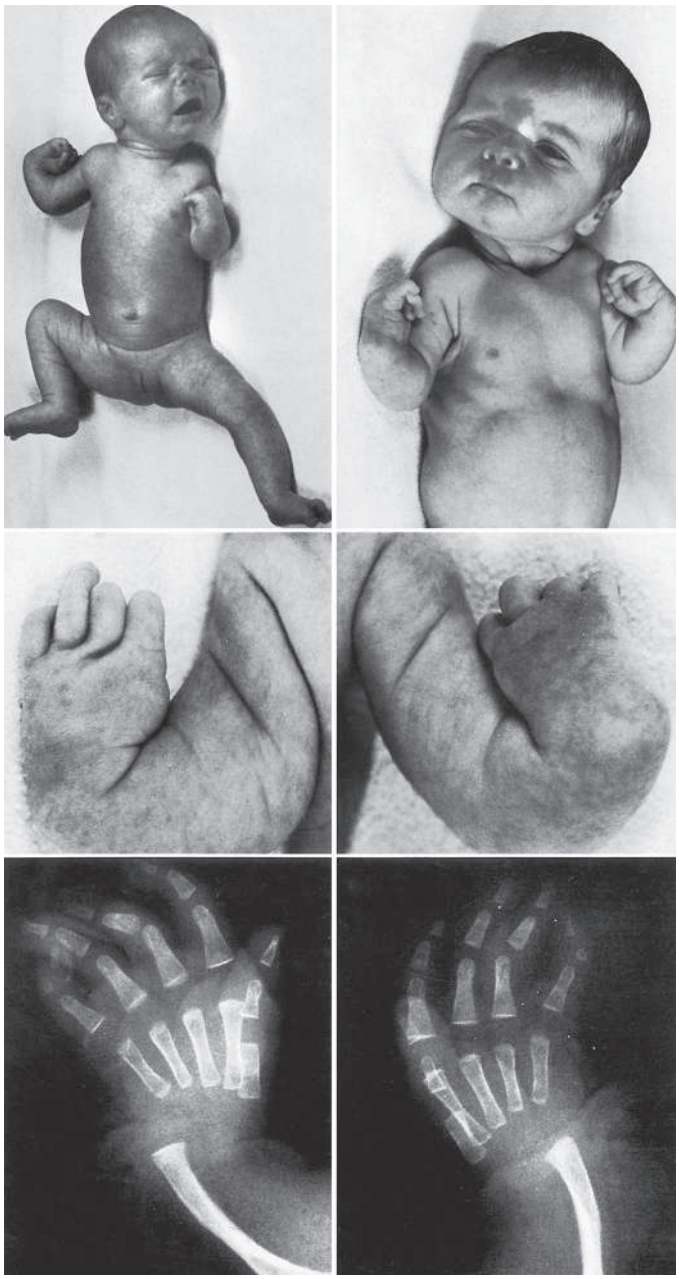

Fig. 533.5 A newborn, the first child of young, healthy parents, with fully expressed thrombocytopenia–absent radius (TAR) syndrome, including hypereosinophilia and anemia. Hypoplasia of the distal humeri and the shoulder girdles, bilateral hip dysplasia, mild talipes calcaneus, and clinodactyly of both little fingers are seen. This patient had a pronounced allergy to cow's milk, with exposure followed by diarrhea, vomiting, and decreased weight and platelet count, making a cow's milk–free diet mandatory. A persistent depressed nasal bridge and development of pronounced bowed legs are seen. *(From Wiedemann H-R, Kunze J, Grosse F-R, eds. Clinical Syndromes, 3rd ed. [English translation]. London: Mosby-Wolfe, 1997. p. 430.)*

533.9 Neonatal Thrombocytopenia

Brian R. Branchford and Veronica H. Flood

Thrombocytopenia in the newborn rarely is indicative of a primary disorder of megakaryopoiesis. It is usually the result of systemic illness or transfer of maternal antibodies directed against fetal platelets (see Table 533.3). Neonatal thrombocytopenia often occurs in association with congenital viral infections, especially rubella, cytomegalovirus, protozoal infection (e.g., toxoplasmosis), and syphilis, and perinatal bacterial infections, especially those caused by gram-negative bacilli. Thrombocytopenia associated with DIC may be responsible for severe spontaneous bleeding. The constellation of marked thrombocytopenia and abnormal abdominal findings is common in necrotizing enterocolitis and other causes of necrotic bowel. Thrombocytopenia in an ill child requires a prompt search for viral and bacterial pathogens.

Antibody-mediated thrombocytopenia in the newborn occurs because of transplacental transfer of maternal antibodies directed against fetal platelets. **Neonatal alloimmune thrombocytopenia (NAIT)** is caused by the development of maternal antibodies against paternally inherited antigens present on fetal platelets that are recognized as foreign by the maternal immune system. The incidence of NATP is 1/4,000-5,000 live births. The clinical manifestations of NAIT are those of an apparently well child who, within the first few days after delivery, has generalized petechiae and purpura. Laboratory studies show a normal maternal platelet count but moderate to severe thrombocytopenia in the newborn. Detailed review of the history should show no evidence of maternal thrombocytopenia. Up to 30% of infants with severe NAIT may have ICH, either prenatally or in the perinatal period. Unlike Rh disease, first pregnancies may be severely affected. Subsequent pregnancies are often more severely affected than the first.

The **diagnosis** of NAIT is made by checking for the presence of maternal alloantibodies directed against the father's platelets. Specific studies can be done to identify the target alloantigen. The most common cause is incompatibility for the platelet alloantigen HPA-1a. Specific DNA sequence polymorphisms have been identified that permit informative prenatal testing to identify at-risk pregnancies. The differential diagnosis of NAIT includes transplacental transfer of maternal IgG antiplatelet autoantibodies (maternal ITP), and, more commonly, viral or bacterial infection.

Treatment of NAIT requires the administration of IVIG prenatally to the mother if the status is known before birth. Therapy usually begins in the second trimester and is continued throughout the pregnancy. Fetal platelet count can be monitored by percutaneous umbilical blood sampling. Delivery should be performed by cesarean section to reduce risk for ICH from vaginal delivery. After delivery, if severe thrombocytopenia persists, transfusion of platelets that share the maternal alloantigens (e.g., washed maternal platelets) will cause a rise in platelet counts to provide effective hemostasis. However, a random donor platelet transfusion is more likely to be readily available. Some centers have units available that may lack the antigens most often involved. After there has been one affected child, genetic counseling is critical to inform the parents of the high risk of thrombocytopenia in subsequent pregnancies.

Children born to mothers with immune thrombocytopenic purpura **(maternal ITP)** appear to have a lower risk of serious hemorrhage than infants born with NAIT, although severe thrombocytopenia may occur. The mother's preexisting platelet count may have some predictive value in that severe maternal thrombocytopenia before delivery appears to predict a higher risk of fetal thrombocytopenia. In mothers who have had splenectomy for ITP, the maternal platelet count may be normal and is not predictive of fetal thrombocytopenia.

Treatment includes prenatal administration of corticosteroids to the mother and IVIG and sometimes corticosteroids to the infant after delivery. Thrombocytopenia in an infant, whether a result of NAIT or maternal ITP, usually resolves within 2-4 months after delivery. The period of highest risk is the immediate perinatal period.

Two syndromes of congenital failure of platelet production often present in the newborn period. In **CAMT** the newborn manifests petechiae and purpura shortly after birth. Findings on physical examination are otherwise normal. Megakaryocytes are absent from the bone marrow. This syndrome is caused by a pathogenic variant in the megakaryocyte TPO receptor that is essential for development of all hematopoietic cell lines. Pancytopenia eventually develops, and HSCT is curative. **TAR syndrome** consists of thrombocytopenia that presents in early infancy, with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening. It frequently remits over the first few years of life (see Chapter 533.8 and Fig. 533.5).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

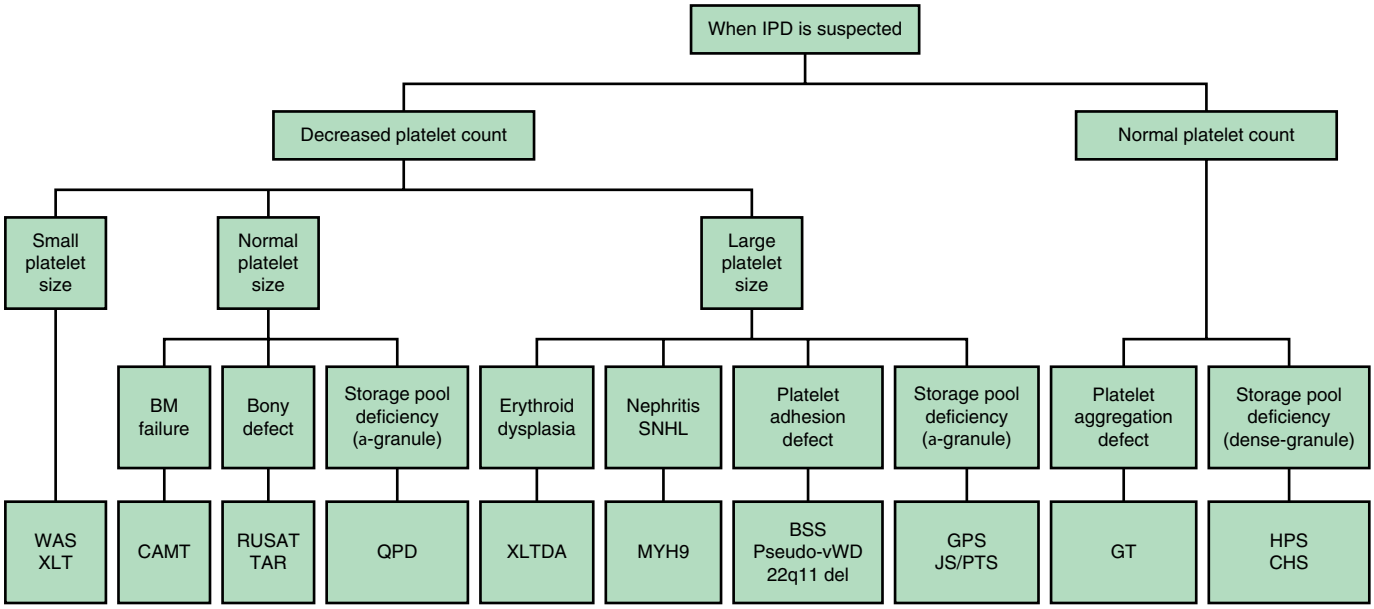

Fig. 533.6 Diagnostic algorithm for sequence and flow in inherited platelet disorders (IPDs). BM, bone marrow; WAS, Wiskott-Aldrich syndrome; XLT, X-linked thrombocytopenia; CAMT, congenital amegakaryocytic thrombocytopenia; RUSAT, radioulnar synostosis with amegakaryocytic thrombocytopenia; TAR, thrombocytopenia-absent radius; QPD, Quebec platelet disorder; XLTDA, X-linked thrombocytopenia with or without dyserythropoietic anemia; MYH9, MYH9-related disorders; BSS, Bernard-Soulier syndrome; vWD, von Willebrand disease; 22q11 del, 22q11 deletion syndrome; GPS, gray platelet syndrome; JS, Jacobsen syndrome; PTS, Paris-Trousseau syndrome; GT, Glanzmann thrombasthenia; HPS, Hermansky-Pudlak syndrome; CHS, Chediak-Higashi syndrome. *(From Shim YJ. Genetic classification and confirmation of inherited platelet disorders: current status in Korea. CEP 2020;63:79–87. Fig. 2.)*

533.10 Thrombocytopenia From Acquired Disorders Causing Decreased Production

Brian R. Branchford and Veronica H. Flood

Disorders of the bone marrow that inhibit megakaryopoiesis usually affect RBC and WBC production. Infiltrative disorders, including malignancies, such as acute lymphocytic leukemia, histiocytosis, lymphomas, and storage disease, usually cause either abnormalities on physical examination (lymphadenopathy, hepatosplenomegaly, or masses), abnormalities of the WBC count, or anemia. Aplastic processes may present as isolated thrombocytopenia, although there are usually clues on the CBC (leukopenia, neutropenia, anemia, or macrocytosis). Children with constitutional aplastic anemia (Fanconi anemia) often (but not always) have abnormalities on examination, including radial and/or thumb anomalies, other skeletal anomalies, short stature, microcephaly, and hyperpigmentation. Bone marrow examination should be performed when thrombocytopenia is associated with abnormalities found on physical examination or on examination of the other blood cell lines.

533.11 Platelet Function Disorders

Brian R. Branchford and Veronica H. Flood

There is no simple and reliable test to screen for abnormal platelet function. Bleeding time and the platelet function analyzer (PFA-100) have been used, but neither has sufficient sensitivity or specificity to rule in or rule out a platelet defect, especially one with mild-moderate phenotypic expression. Bleeding time measures the interaction of platelets with the blood vessel wall and thus is affected by both platelet count and platelet function. The predictive value of bleeding time is problematic because bleeding time is dependent on other factors, including the technician's skill and the patient's cooperation, often a challenge in the infant or young child; it is not recommended in high resource settings. The PFA-100 measures platelet adhesion and aggregation in whole blood at high shear when the blood is exposed to either collagen-epinephrine or collagen-ADP. Results are reported as the closure time in seconds. The use of the PFA-100 as a screening test remains controversial. For patients with a positive history of bleeding suggestive of VWD or platelet dysfunction, specific VWF testing and platelet function studies should be done, irrespective of the results of the bleeding time or PFA-100.

Platelet function in the clinical laboratory is measured using platelet aggregometry. In the aggregometer, agonists, such as collagen, ADP, ristocetin, epinephrine, arachidonic acid, and thrombin (or the thrombin receptor peptide), are added to platelet-rich plasma, and the clumping of platelets over time is measured by an automated machine through either light transmission or electric impedance. At the same time, other instruments measure the release of granular contents, such as ATP, from the platelets after activation. The ability of platelets to aggregate and their metabolic activity can thus be assessed simultaneously. When a patient is being evaluated for possible platelet dysfunction, it is critically important to exclude the presence of other exogenous agents and to study the patient, if possible, off all medications for 2 weeks, especially those with any potential antiplatelet effects. Further evaluation using flow cytometric analysis of surface receptors or molecular and/or genetic testing is often necessary to make a more definitive diagnosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.12 Acquired Disorders of Platelet Function

Brian R. Branchford and Veronica H. Flood

A number of systemic illnesses are associated with platelet dysfunction, most frequently liver disease, kidney disease (uremia), and disorders that trigger increased amounts of fibrin degradation products. These disorders frequently cause prolonged bleeding time and are often associated with other abnormalities of the coagulation mechanism. *The most important element of management is to treat the primary illness.* If treatment of the primary process is not feasible, infusions of

desmopressin have been helpful in augmenting hemostasis and correcting bleeding time. In some patients, transfusions of platelets and cryoprecipitate have also been helpful in improving hemostasis.

Many medications alter platelet function. The most common drug in adults that alters platelet function is acetylsalicylic acid *(aspirin)*. Aspirin irreversibly acetylates the enzyme cyclooxygenase, which is critical in the formation of thromboxane A_2. Aspirin usually causes moderate platelet dysfunction that becomes more prominent if there is another abnormality of the hemostatic mechanism. In children, common drugs that reversibly inhibit platelet function include other nonsteroidal anti-inflammatory drugs (NSAIDs), valproic acid, and high-dose penicillin. Specific agents to inhibit platelet function therapeutically include those that block the platelet ADP receptor (clopidogrel) and αIIb-β_3 receptor antagonists, as well as aspirin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.13 Congenital Abnormalities of Platelet Function

Brian R. Branchford and Veronica H. Flood

Severe platelet function defects usually present with petechiae and purpura shortly after birth, especially after vaginal delivery (see Table 533.2). Defects in the platelet GPIb complex (the VWF receptor) or the αIIb-β_3 complex (the fibrinogen receptor) cause severe congenital platelet dysfunction. Although laboratory tests of platelet function are available, molecular characterization by genetic testing is rapidly progressing for platelet disorders.

Bernard-Soulier syndrome, a severe congenital platelet function disorder, is caused by absence or severe deficiency of the GPIb complex (VWF receptor) on the platelet membrane. This syndrome is characterized by a macrothrombocytopenia, with giant platelets and greatly prolonged bleeding time (>20 min) or PFA-100 closure time. Patients may have significant mucocutaneous and GI bleeding. Platelet aggregation tests classically demonstrate absent ristocetin-induced platelet aggregation but normal aggregation to all other agonists. Ristocetin induces the binding of VWF to platelets and agglutinates platelets. Results of studies of VWF antigen and activity are normal. The GPIb complex interacts with the platelet cytoskeleton; a defect in this interaction is believed to be the cause of the large platelet size. This receptor deficiency can also be detected by flow cytometry. Bernard-Soulier syndrome is inherited as an autosomal recessive disorder. Causative pathogenic variants are usually identified in the genes encoding the GPIb complex of glycoproteins Ibα, Ibβ, V, and IX.

Glanzmann thrombasthenia is a congenital disorder associated with severe platelet dysfunction that yields prolonged bleeding time and a normal platelet count. Platelets have normal size and morphologic features on the peripheral blood smear, and closure times for PFA-100 or bleeding time are extremely abnormal. Aggregation studies classically demonstrate abnormal or absent aggregation with all agonists used except ristocetin because ristocetin agglutinates platelets and does not require a metabolically active platelet. This disorder is caused by deficiency of the platelet fibrinogen receptor αIIb-β_3, the major integrin complex on the platelet surface that undergoes conformational changes by inside-out signaling when platelets are activated. This receptor deficiency can also be detected by flow cytometry. Fibrinogen binds to this complex when the platelet is activated and causes platelets to aggregate. Glanzmann thrombasthenia is caused by pathogenic variants in the genes for αIIb or β_3 and is inherited in an autosomal recessive manner. For both Bernard-Soulier syndrome and Glanzmann thrombasthenia, the **diagnosis** is confirmed by flow cytometry of the patient's platelet glycoproteins. Bleeding in Glanzmann thrombasthenia may be quite severe and is typically mucocutaneous, including epistaxis, gingival, and GI bleeding. There are reports of curative therapy using stem cell transplant.

Hereditary deficiency of platelet storage granules occurs in two well-characterized but rare syndromes that involve deficiency of intracytoplasmic granules. **Dense granule deficiency** is characterized by absence of the granules that contain ADP, ATP, Ca^{2+}, and serotonin. This disorder is diagnosed by the finding that ATP is not released on platelet aggregation studies and ideally is characterized by transmission electron microscopic studies. **Hermansky-Pudlak syndrome** (with nine subtypes) is a dense granule deficiency caused by defects in lysosomal storage. Affected patients present with oculocutaneous albinism and hemorrhage caused by the platelet defect; some patients also develop granulomatous colitis resembling

Table 533.6 Comparison of Nine Types of Hermansky-Pudlak Syndrome

	1	2	3	4	5	6	7	8	9
Oculocutaneous albinism	Variable, mild-moderate: brown to white hair	Severe: lack of hair and iris pigment	Mild-moderate: light skin pigment	Severe: blonde hair, gray iris	Variable: light-brown hair, brown iris	Variable: iris heterochromia	Variable	Variable: tan skin, silver hair, brown iris	Pale skin, silver-blonde hair, pale-blue iris
Platelet defect/bruising	+	+	+	+	+	+	+	+	+
Granulomatous colitis	+	–	–	+	–	+	+	–	–
Pulmonary fibrosis/ILD	+	+	–	+	–	–	–	–	–
Other symptoms		Neutropenia Failure to thrive Hypothyroidism CAH		Depression	High cholesterol				Cutaneous infections

+, Present; –, absent; CAH, congenital adrenal hyperplasia; ILD, interstitial lung disease.

Crohn disease or pulmonary fibrosis/interstitial lung disease (Table 533.6). **Chédiak-Higashi syndrome** also presents with a dense granule defect, immune dysfunction, and albinism. **Gray platelet syndrome** is caused by the absence of platelet α granules, resulting in large platelets that are large and appear gray on Wright stain of peripheral blood. In this rare syndrome, aggregation and release are absent with most agonists other than thrombin and ristocetin. Transmission electron microscopic studies are diagnostic. Autosomal recessive gray platelet syndrome is caused by defects in the *NBEAL2* gene, while autosomal dominant disease is associated with a pathogenic variant in *GFI1B*. This disorder may also be associated with familial leukemia. **Quebec platelet syndrome** is caused by degradation of platelet α granules caused by defects in *PLAU*, which encodes a urokinase-type plasminogen activator. Treatment usually involves antifibrinolytic therapy.

OTHER HEREDITARY DISORDERS OF PLATELET FUNCTION

Abnormalities in the pathways of platelet signaling/activation and release of granular contents cause a heterogeneous group of platelet function defects that are usually manifested as increased bruising, epistaxis, and menorrhagia. Symptoms may be subtle and are often made more obvious by high-risk surgery, such as tonsillectomy or adenoidectomy, or by administration of NSAIDs. In the laboratory, bleeding time is variable, and closure time as measured by the PFA-100 is frequently, but not always, prolonged. Platelet aggregation studies show deficient aggregation with one or two agonists and/or abnormal release of granular contents.

The formation of thromboxane from arachidonic acid (AA) after the activation of phospholipase is critical to normal platelet function. Deficiency or dysfunction of enzymes, such as cyclooxygenase and thromboxane synthase, which metabolize AA, causes abnormal platelet function. In the aggregometer, platelets from such patients do not aggregate in response to AA.

The most common platelet function defects are those characterized by variable bleeding time/PFA closure times and abnormal aggregation with one or two agonists, usually ADP and/or collagen. Some of these individuals have only decreased release of ATP from intracytoplasmic granules; the significance of this finding is debated.

TREATMENT OF PATIENTS WITH PLATELET DYSFUNCTION

Successful treatment depends on the severity of both the diagnosis and the hemorrhagic event. In all but severe platelet function defects, desmopressin, 0.3 μg/kg intravenously, may be used for mild to moderate bleeding episodes. In addition to its effect on stimulating levels of VWF and factor VIII, desmopressin corrects bleeding time and augments hemostasis in many individuals with mild to moderate platelet function defects. Antifibrinolytic therapy may be useful for mucosal bleeds. For individuals with Bernard-Soulier syndrome or Glanzmann thrombasthenia, platelet transfusions of 0.5-1 unit single donor platelets correct the defect in hemostasis and may be lifesaving. Rarely, alloantibodies develop to the deficient platelet protein, rendering the patient refractory to the transfused platelets. In such patients, the use of recombinant factor VIIa has been effective, and this treatment was recently approved for platelet-refractory Glanzmann's thrombasthenia. In both conditions, HSCT has been curative.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.14 Disorders of the Blood Vessels

Brian R. Branchford and Veronica H. Flood

Disorders of the vessel walls or supporting structures mimic the findings of a bleeding disorder, although coagulation studies are usually normal. The findings of petechiae and purpuric lesions in such patients are often attributable to an underlying vasculitis or vasculopathy. Skin biopsy can be particularly helpful in elucidating the type of vascular pathology.

IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA)

See Chapter 210.1.

EHLERS-DANLOS SYNDROME

See Chapter 744.

OTHER ACQUIRED DISORDERS

Scurvy, chronic corticosteroid therapy, and severe malnutrition are associated with "weakening" of the collagen matrix that supports the blood vessels. Therefore these factors are associated with easy bruising, and, particularly in the case of scurvy, bleeding gums and loosening of the teeth. Lesions of the skin that initially appear to be petechiae and purpura may be seen in vasculitic syndromes, such as SLE. Leukocytoclastic vasculitis may present with nonthrombocytopenic purpura (see Chapter 210). A unique variant of leukocytoclastic vasculitis is associated with exercise.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 8
The Spleen

Chapter 534
Anatomy and Function of the Spleen

Allison S. Remiker and Amanda M. Brandow

ANATOMY

The splenic precursor is recognizable by 5 weeks of gestation. At birth, the spleen weighs approximately 11 g. Thereafter, it enlarges until puberty, reaching an average weight of 150 g, and then diminishes in size during adulthood. Approximately 15% of patients will have an accessory spleen. The major splenic components are a lymphoid compartment *(white pulp)* and a filtering system *(red pulp)*. The white pulp consists of periarterial lymphatic sheaths (PALS; T-zone) of T lymphocytes with embedded germinal centers containing B lymphocytes. The red pulp has a skeleton of fixed reticular cells, mobile macrophages, partially collapsed endothelial passages (cords of Billroth), and splenic sinuses. A *perifollicular zone (PFZ)* (known as the marginal zone in murine models) is rich in dendritic (antigen-presenting) cells and natural killer cells and separates the red pulp from the white pulp. The splenic capsule contains smooth muscle and contracts in response to epinephrine. Approximately 10% of the blood delivered to the spleen flows rapidly through a closed vascular network. The other 90% flows more slowly through an open system (the *splenic cords*), where it is filtered through 1-5 μm slits before entering the splenic sinuses.

FUNCTION

The unique anatomy and blood flow of the spleen enable it to perform reservoir, filtering, and immunologic functions. The spleen

Crohn disease or pulmonary fibrosis/interstitial lung disease (Table 533.6). **Chédiak-Higashi syndrome** also presents with a dense granule defect, immune dysfunction, and albinism. **Gray platelet syndrome** is caused by the absence of platelet α granules, resulting in large platelets that are large and appear gray on Wright stain of peripheral blood. In this rare syndrome, aggregation and release are absent with most agonists other than thrombin and ristocetin. Transmission electron microscopic studies are diagnostic. Autosomal recessive gray platelet syndrome is caused by defects in the *NBEAL2* gene, while autosomal dominant disease is associated with a pathogenic variant in *GFI1B*. This disorder may also be associated with familial leukemia. **Quebec platelet syndrome** is caused by degradation of platelet α granules caused by defects in *PLAU*, which encodes a urokinase-type plasminogen activator. Treatment usually involves antifibrinolytic therapy.

OTHER HEREDITARY DISORDERS OF PLATELET FUNCTION

Abnormalities in the pathways of platelet signaling/activation and release of granular contents cause a heterogeneous group of platelet function defects that are usually manifested as increased bruising, epistaxis, and menorrhagia. Symptoms may be subtle and are often made more obvious by high-risk surgery, such as tonsillectomy or adenoidectomy, or by administration of NSAIDs. In the laboratory, bleeding time is variable, and closure time as measured by the PFA-100 is frequently, but not always, prolonged. Platelet aggregation studies show deficient aggregation with one or two agonists and/or abnormal release of granular contents.

The formation of thromboxane from arachidonic acid (AA) after the activation of phospholipase is critical to normal platelet function. Deficiency or dysfunction of enzymes, such as cyclooxygenase and thromboxane synthase, which metabolize AA, causes abnormal platelet function. In the aggregometer, platelets from such patients do not aggregate in response to AA.

The most common platelet function defects are those characterized by variable bleeding time/PFA closure times and abnormal aggregation with one or two agonists, usually ADP and/or collagen. Some of these individuals have only decreased release of ATP from intracytoplasmic granules; the significance of this finding is debated.

TREATMENT OF PATIENTS WITH PLATELET DYSFUNCTION

Successful treatment depends on the severity of both the diagnosis and the hemorrhagic event. In all but severe platelet function defects, desmopressin, 0.3 μg/kg intravenously, may be used for mild to moderate bleeding episodes. In addition to its effect on stimulating levels of VWF and factor VIII, desmopressin corrects bleeding time and augments hemostasis in many individuals with mild to moderate platelet function defects. Antifibrinolytic therapy may be useful for mucosal bleeds. For individuals with Bernard-Soulier syndrome or Glanzmann thrombasthenia, platelet transfusions of 0.5-1 unit single donor platelets correct the defect in hemostasis and may be lifesaving. Rarely, alloantibodies develop to the deficient platelet protein, rendering the patient refractory to the transfused platelets. In such patients, the use of recombinant factor VIIa has been effective, and this treatment was recently approved for platelet-refractory Glanzmann's thrombasthenia. In both conditions, HSCT has been curative.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

533.14 Disorders of the Blood Vessels

Brian R. Branchford and Veronica H. Flood

Disorders of the vessel walls or supporting structures mimic the findings of a bleeding disorder, although coagulation studies are usually normal. The findings of petechiae and purpuric lesions in such patients are often attributable to an underlying vasculitis or vasculopathy. Skin biopsy can be particularly helpful in elucidating the type of vascular pathology.

IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA)

See Chapter 210.1.

EHLERS-DANLOS SYNDROME

See Chapter 744.

OTHER ACQUIRED DISORDERS

Scurvy, chronic corticosteroid therapy, and severe malnutrition are associated with "weakening" of the collagen matrix that supports the blood vessels. Therefore these factors are associated with easy bruising, and, particularly in the case of scurvy, bleeding gums and loosening of the teeth. Lesions of the skin that initially appear to be petechiae and purpura may be seen in vasculitic syndromes, such as SLE. Leukocytoclastic vasculitis may present with nonthrombocytopenic purpura (see Chapter 210). A unique variant of leukocytoclastic vasculitis is associated with exercise.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 8
The Spleen

Chapter 534
Anatomy and Function of the Spleen

Allison S. Remiker and Amanda M. Brandow

ANATOMY

The splenic precursor is recognizable by 5 weeks of gestation. At birth, the spleen weighs approximately 11 g. Thereafter, it enlarges until puberty, reaching an average weight of 150 g, and then diminishes in size during adulthood. Approximately 15% of patients will have an accessory spleen. The major splenic components are a lymphoid compartment *(white pulp)* and a filtering system *(red pulp)*. The white pulp consists of periarterial lymphatic sheaths (PALS; T-zone) of T lymphocytes with embedded germinal centers containing B lymphocytes. The red pulp has a skeleton of fixed reticular cells, mobile macrophages, partially collapsed endothelial passages (cords of Billroth), and splenic sinuses. A *perifollicular zone (PFZ)* (known as the marginal zone in murine models) is rich in dendritic (antigen-presenting) cells and natural killer cells and separates the red pulp from the white pulp. The splenic capsule contains smooth muscle and contracts in response to epinephrine. Approximately 10% of the blood delivered to the spleen flows rapidly through a closed vascular network. The other 90% flows more slowly through an open system (the *splenic cords*), where it is filtered through 1-5 μm slits before entering the splenic sinuses.

FUNCTION

The unique anatomy and blood flow of the spleen enable it to perform reservoir, filtering, and immunologic functions. The spleen

receives 5–6% of the cardiac output but normally contains only 25 mL of blood. It can retain much more when it enlarges, leading to **cytopenias**. Hematopoiesis in the red pulp is a major splenic function at 3-6 months of fetal life but subsequently disappears. *Splenic hematopoiesis* can be resumed in patients with myelofibrosis or severe hemolytic anemia. Factor VIII, iron, plasmablasts, plasma cells, and one third of the circulating platelet mass are sequestered in the spleen and can be released by stress or epinephrine stimulation. **Thrombocytosis** and **leukocytosis** occur with loss of the splenic reservoir function. A high platelet count after the loss of splenic function or splenectomy is not associated with an increased risk of thrombosis in children.

Slow blood flow past macrophages and through small openings in the sinus walls facilitates the filtering functions of the spleen removing any particles >1 micron in size from the circulation. Excess membrane is removed from young red blood cells (RBCs) and loss of this function is characterized by target cells, poikilocytosis, and decreased osmotic fragility. The spleen is the primary site for destruction of old RBCs, and this function is assumed by other reticuloendothelial cells after splenectomy. The spleen also removes damaged/abnormal RBCs (e.g., spherocytes, antibody-coated RBCs) and damaged/senescent platelets. Intracytoplasmic inclusions may be removed from RBCs without cell lysis. Functional or anatomic hyposplenia is characterized by continued circulation of cells containing nuclear remnants **(Howell-Jolly bodies)**, denatured hemoglobin **(Heinz bodies)**, and other debris in RBCs. This debris may appear as "pits" on indirect microscopy.

The spleen plays a large role in host defense against infection. Mechanical filtration occurs removing parasitized erythrocytes, as well as unopsonized bacteria. The spleen is the largest lymphoid organ in the body and contains almost half the body's total immunoglobulin-producing B lymphocytes. The spleen processes foreign material to stimulate production of opsonizing antibody. Upon antigenic challenge, B and T cells are developed in the spleen, with subsequent release of immunoglobulins. Production of immune-mediating proteins important in bacterial clearance occurs in the spleen including complement, opsonins, properdin, and tuftsin. Thus young (nonimmune) or hyposplenic individuals are at increased risk for **sepsis** caused by pneumococci and other encapsulated bacteria. The spleen can also use phagocytosis to trap and destroy intracellular parasites. The spleen has a minor role in antibody response to intramuscularly or subcutaneously injected antigens but is required for early antibody production after exposure to intravenous antigens. Additionally, the spleen is important in the pathogenesis of immune-mediated cytopenias (IMCs). Antibody-coated platelets or erythrocytes are phagocytosed via mechanisms associated with splenic macrophages. The spleen also serves as a reservoir for antibody producing plasma cells involved in IMCs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 535

Splenomegaly

Allison S. Remiker and Amanda M. Brandow

CLINICAL MANIFESTATIONS

A soft, thin spleen is palpable in 15% of neonates, 10% of normal children, and 5% of adolescents. In most individuals, the spleen must be 2-3 times its normal size before it is palpable. The spleen is best examined when standing on the right side of a supine patient by palpating across the abdomen as the patient inspires deeply or with the patient in the right lateral decubitus position. A splenic edge felt more than 2 cm below the left costal margin is abnormal. An enlarged spleen might descend into the pelvis; when splenomegaly is suspected, the abdominal examination should begin at a lower starting point. Superficial abdominal venous distention may be present when splenomegaly is a result of portal hypertension. Patients may also complain of left upper quadrant pain as the spleen enlarges. Radiologic detection or confirmation of splenic enlargement is done with ultrasonography, CT, MRI, positron emission tomography, or technetium-99m sulfur colloid scan. The latter also assesses splenic function.

DIFFERENTIAL DIAGNOSIS

Table 535.1 lists specific causes of splenomegaly. A thorough history with a focus on systemic complaints (e.g., fever, night sweats, malaise, weight loss) and a complete physical examination (with special attention to lymphadenopathy, jaundice, hepatomegaly, rashes, joint swelling, petechiae, ecchymoses), in combination with a complete blood count and careful review of the peripheral smear, can help guide diagnosis.

Pseudosplenomegaly

Abnormally long mesenteric connections may produce a *wandering* or ptotic spleen. An enlarged left lobe of the liver, a left upper quadrant mass, or a splenic hematoma may be mistaken for splenomegaly. Splenic **cysts** may contribute to splenomegaly or mimic it; these may be congenital (epidermoid) or acquired (pseudocyst) after trauma or infarction. Cysts are usually asymptomatic and are found on radiologic evaluation. **Splenosis** after splenic rupture or an accessory spleen (present in 15% of normal individuals) may also mimic splenomegaly; most are not palpable. The syndrome of **congenital polysplenism** includes cardiac defects, left-sided organ anomalies, bilobed lungs, biliary atresia, and pseudosplenomegaly (see Chapter 480.11).

Hypersplenism

Increased splenic function (sequestration or destruction of circulating cells) can result in peripheral blood **cytopenias** (thrombocytopenia, neutropenia, anemia), increased bone marrow activity, and splenomegaly. It is usually secondary to another disease and may be cured by treatment of the underlying condition or, if absolutely necessary, may be moderated by splenectomy. Table 535.1 lists the most common diseases associated with massive splenomegaly.

Congestive Splenomegaly

Splenomegaly may result from obstruction in the hepatic, portal, or splenic veins leading to hypersplenism. Wilson disease (see Chapter 405.2), galactosemia (see Chapter 107.2), biliary atresia (see Chapter 404.1), and α_1-antitrypsin deficiency (see Chapter 405) may result in hepatic inflammation, fibrosis, and vascular obstruction. Congenital abnormalities (absence or hypoplasia) of the portal or splenic veins may cause vascular obstruction. Septic omphalitis or thrombophlebitis (spontaneous or as a result of umbilical venous catheterization in neonates) may result in secondary obliteration of these vessels. Splenic venous flow may be obstructed by masses of sickled erythrocytes leading to infarction. When the spleen is the site of vascular obstruction, splenectomy cures hypersplenism. However, because obstruction usually is in the hepatic or portal systems, **portacaval shunting** may be more helpful since both portal hypertension and thrombocytopenia contribute to variceal bleeding.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 535.1 Differential Diagnosis of Splenomegaly by Pathophysiology

ANATOMIC LESIONS
Cysts, pseudocysts
Hamartomas
Polysplenia syndrome
Hemangiomas and lymphangiomas
Hematoma or rupture (traumatic)
Peliosis

HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS
*Acute and Chronic Hemolysis**
Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins)‡
Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)
Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)
Immune hemolysis (autoimmune and isoimmune hemolysis)
Paroxysmal nocturnal hemoglobinuria
Chronic Iron Deficiency
Extramedullary Hematopoiesis
Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera
Osteopetrosis
Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors

INFECTIONS†
Bacterial
Acute sepsis: *Salmonella typhi*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus aureus*
Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease
Local infections: splenic abscess (*S. aureus*, streptococci, less often *Salmonella* spp., polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, gram-negative enteric bacteria), cholangitis

*Viral**
Acute viral infections
Congenital CMV, herpes simplex, rubella
Hepatitis A, B, and C; CMV
EBV
Viral hemophagocytic syndromes: CMV, EBV, HHV-6
HIV‡

Spirochetal
Syphilis, especially congenital syphilis
Leptospirosis

Rickettsial
Rocky Mountain spotted fever
Q fever
Typhus

Fungal/Mycobacterial
Miliary tuberculosis
Disseminated histoplasmosis
South American blastomycosis
Systemic candidiasis (in immunosuppressed patients)

Parasitic
Malaria‡
Toxoplasmosis, especially congenital
Toxocara canis, *Toxocara cati* (visceral larva migrans)
Leishmaniasis (kala-azar)‡
Schistosomiasis (hepatic-portal involvement)
Trypanosomiasis
Fascioliasis
Babesiosis

IMMUNOLOGIC AND INFLAMMATORY PROCESSES*
Systemic lupus erythematosus
Juvenile idiopathic arthritis
Mixed connective tissue disease
Systemic vasculitis
Serum sickness
Drug hypersensitivity, especially to phenytoin
Graft-versus-host disease
Sjögren syndrome
Cryoglobulinemia
Amyloidosis
Sarcoidosis
Autoimmune lymphoproliferative syndrome‡
Castleman disease‡
Posttransplant lymphoproliferative disease
Large granular lymphocytosis and neutropenia
Histiocytosis syndromes‡
Macrophage activation syndrome
Hemophagocytic lymphohistiocytosis (genetic, acquired)‡

MALIGNANCIES
Primary: leukemia (acute, chronic)‡, lymphoma‡, angiosarcoma, mastocytosis
Metastatic

STORAGE DISEASES
Lipidosis (Gaucher disease‡, Niemann-Pick disease, infantile GM1 gangliosidosis)
Mucopolysaccharidoses (Hurler, Hunter-type)
Mucolipidosis (I-cell disease, sialidosis, multiple sulfatase deficiency, fucosidosis)
Defects in carbohydrate metabolism: galactosemia, fructose intolerance, glycogen storage disease IV
Sea-blue histiocyte syndrome
Tangier disease
Wolman disease
Hyperchylomicronemia type I, IV

CONGESTIVE DISEASE*
Heart failure
Intrahepatic cirrhosis or fibrosis
Extrahepatic portal (thrombosis), splenic, and hepatic vein obstruction (thrombosis, Budd-Chiari syndrome)

*Common.
†Chronic or recurrent infection suggests underlying immunodeficiency.
‡Associated with hypersplenomegaly.
CML, Chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

Chapter 536

Hyposplenism, Splenic Trauma, and Splenectomy

Allison S. Remiker and Amanda M. Brandow

HYPOSPLENISM

Congenital absence (asplenia) or underdevelopment (hyposplenia) of the spleen is associated with complex cyanotic heart defects, dextrocardia, bilateral trilobed lungs, and heterotopic abdominal organs (**Ivemark syndrome**; see Chapter 480.11). Patients with isolated congenital asplenia have pathogenic variants in *RPSA* in ~40% of cases. Right atrial isomerism (Ivemark syndrome), a form of heterotaxy, may have asplenia associated with pathogenic variants of *GDF1*. Splenic function is usually normal in children with congenital polysplenia. **Functional hyposplenism** may occur in normal neonates, especially premature infants. Children with sickle cell hemoglobinopathies (see Chapter 511.1) may have splenic hypofunction as early as 6 months of age. In this setting, the spleen eventually autoinfarcts and becomes fibrotic and permanently nonfunctional. Functional hyposplenism may also occur in malaria (see Chapter 334), after irradiation to the left upper quadrant, and when the reticuloendothelial function of the spleen is overwhelmed (as in severe hemolytic anemia or metabolic storage disease). Thrombosis of the splenic/celiac arteries or splenic vein is associated with functional hyposplenism. Splenic hypofunction has been reported occasionally in patients with autoimmune diseases (i.e., juvenile idiopathic arthritis, lupus, sarcoidosis), nephritis, inflammatory bowel disease, celiac disease, chronic hepatitis, Pearson syndrome, Fanconi anemia, those with use of high-dose corticosteroids, and graft-versus-host disease (Table 536.1).

Splenic hypofunction is characterized by **red blood cell (RBC) inclusions** in peripheral blood smears (Howell-Jolly or Heinz bodies), "pits" on interference microscopy, and poor uptake of technetium or other spleen scans (Table 536.2 and Fig. 536.1). Reduced immunoglobulin M memory B cells may also be detected and is a risk factor for overwhelming **sepsis**. Patients with functional hyposplenism or asplenia are at increased risk for sepsis from **encapsulated bacteria** and benefit from antibiotic prophylaxis and urgent evaluation when febrile.

Table 536.1 Diseases Associated with Hyposplenism or Splenic Atrophy

CONGENITAL FORMS	**AUTOIMMUNE DISORDERS**
Normal and premature neonates	Systemic lupus erythematosus
Isolated congenital hypoplasia	Juvenile idiopathic arthritis
Ivemark syndrome	Glomerulonephritis
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome	Granulomatosis with polyangiitis
	Goodpasture syndrome
	Sjögren syndrome
Hypoparathyroidism syndrome	Polyarteritis nodosa
Stormorken syndrome	Thyroiditis
Heterotaxia syndromes	Sarcoidosis
GASTROINTESTINAL DISORDERS	**INFECTIOUS DISEASES**
Celiac disease	Pneumococcal meningitis
Inflammatory bowel disease	HIV/AIDS
Whipple disease	Malaria
Dermatitis herpetiformis	**IATROGENIC FORMS**
Intestinal lymphangiectasia	Exposure to methyldopa
Idiopathic chronic ulcerative enteritis	High-dose steroids
	Total parenteral nutrition
	Splenic irradiation
HEPATIC DISORDERS	**ALTERATION IN SPLENIC CIRCULATION**
Active chronic hepatitis	Thrombosis of splenic artery
Primary biliary cirrhosis	Thrombosis of splenic vein
Hepatic cirrhosis and portal hypertension	Thrombosis of celiac artery
Alcoholism and alcoholic hepatopathy	**MISCELLANEOUS**
	Amyloidosis
HEMATOLOGIC AND ONCOLOGIC DISORDERS	
Sickle cell disease (all genotypes)	
Bone marrow transplantation	
Chronic graft-versus-host disease	
Acute leukemia	
Chronic myeloproliferative disorders	
Fanconi syndrome	
Splenic tumors	
Mastocytosis	

From Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet* 2011;378:86–97.

SPLENIC TRAUMA

Injury to the spleen may occur with abdominal trauma. Small splenic capsular tears may cause abdominal or referred left shoulder pain as a result of diaphragmatic irritation by blood. Larger tears result in more severe blood loss, with similar pain and signs of **hypovolemic shock**. Previously enlarged spleens (as in patients with infectious mononucleosis) are more likely to rupture with minor trauma. *Patients with splenomegaly should avoid contact sports and other activities that increase the risk of splenic trauma.* CT scan with intravenous contrast is the best imaging modality to assess splenic trauma in a hemodynamically stable patient. In emergent situations extended focused assessment with sonography in trauma (E-FAST) should be considered as an initial evaluation, although the sensitivity and specificity in children is variable.

Treatment of a small capsular injury should include careful observation with attention to changes in vital signs or abdominal findings, serial hemoglobin determinations, and the availability of prompt surgical intervention if a patient's condition deteriorates (see Chapter 80). RBC transfusion requirements should be minimal (<25 mL/kg/48 hr). These patients are usually hospitalized for 10-14 days and have their activities restricted for months. Laparotomy, with or without splenectomy, is indicated for more marked abdominal bleeding, in patients who have clinical instability or deterioration, or when other organ damage is suspected. Partial splenectomy and splenic repair should be substituted for total splenectomy when feasible to maintain some splenic immune function. Nonoperative management is typically possible in >90% of patients. Delayed splenic rupture is quite rare in children.

SPLENECTOMY

Splenectomy should be limited to specific indications where medical therapy is (or has been) ineffective. These include traumatic splenic rupture, anatomic defects, splenic malignancy (i.e., splenic marginal zone lymphoma [SMZL]), severe transfusion-dependent hemolytic anemia, refractory and severe immune-mediated cytopenias, metabolic storage diseases, and secondary hypersplenism. There are certain conditions where splenectomy should be avoided because of increased risk of complications and/or better alternative treatments. These include autoimmune lymphoproliferative syndrome (ALPS), hereditary stomatocytosis (HSt), hereditary xerocytosis (HX), cold agglutinin disease (CAD), paroxysmal cold hemoglobinuria (PCH), Gaucher disease, and thrombocytopenia in hepatic cirrhosis. *The major long-term risk of splenectomy is sudden, overwhelming postsplenectomy infections (sepsis or meningitis).* This risk is especially high in children <5 years old at surgery. The risk of sepsis is less when splenectomy is performed for trauma, RBC membrane defects, and immune thrombocytopenia (2–4%) than when there is sickle cell anemia, thalassemia, or a preexisting immune deficiency (Wiskott-Aldrich syndrome, Hodgkin disease) or reticuloendothelial blockade (storage disease, severe hemolytic anemia) (8–30%). The overall risk is 2-5 per 1,000 asplenic patient-years,

Table 536.2 Diagnostic Techniques for and Features of Spleen Dysfunction

	DESCRIPTION	COMMENTS
Immunoglobulin M memory B cells	Cells dependent on spleen for survival. Produced in marginal zone.	Special tests required.
Technetium-99m–labeled sulfur colloidal scintiscan	Quantitation of splenic uptake of colloidal sulfur particles enables a fairly accurate static assessment of spleen function.	Hypertrophy of the left hepatic lobe might be a limiting factor (this technique does not clearly show whether the mass originated in the liver or the spleen in the presence of an overlapping hypertrophic left hepatic lobe).
Technetium-99m–labeled or rubidium-81–labeled heat-damaged autologous erythrocyte clearance	Measurement of clearance time allows a dynamic evaluation of spleen function.	Preexisting erythrocyte defects, difficult erythrocyte incorporation of the radioisotope, and false-positive or false-negative results in relation to excessive or insufficient heat damage make the test not suitable for clinical practice.
Detection of Howell-Jolly bodies by staining	Erythrocytes with nuclear remnants Flow cytometry	No need for special equipment; inaccurate in the quantitation of splenic hypofunction.
Detection of pitted erythrocytes by phase-interference microscopy	Erythrocytes with membrane indentations (4% upper limit of the normal range)	Need for phase-interference microscopy; counts enable a wide range of measurements and correlate with radioisotopic methods.

From Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet* 2011;378:86–97. Table 1.

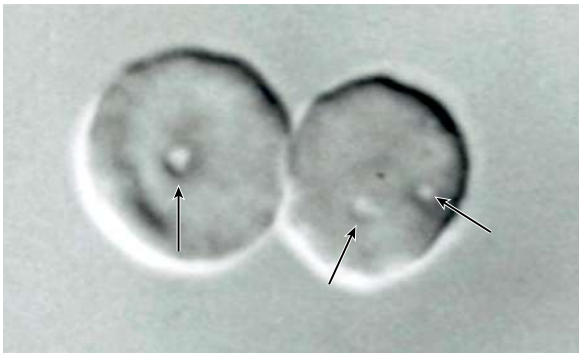

Fig. 536.1 Characteristic pitted erythrocytes in hyposplenism. A pitted erythrocyte is recognizable on phase-interference microscopy by the characteristic "pit" on the cell membrane *(arrows). (From Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. Lancet. 2011;378:86–97. Fig 2.)*

with a lifelong risk of overwhelming postsplenectomy infections of 5%; more than half occur within 2 years after splenectomy, although the risk remains lifelong. The use of laparoscopic splenectomy has decreased surgical morbidity and hospitalization time.

Encapsulated bacteria, such as *Streptococcus pneumoniae* (>60% of cases), *Haemophilus influenzae,* and *Neisseria meningitidis,* account for >80% of cases of postsplenectomy sepsis. Because the spleen is responsible for filtering the blood and for early antibody responses, sepsis (with or without meningitis) can progress rapidly, leading to death within 12-24 hours of onset. Febrile splenectomized patients should be evaluated and treated promptly with antibiotics to cover the organisms previously mentioned. This treatment should be initiated at home if access to definitive medical care will be delayed. Common empiric antibiotics include amoxicillin-clavulanate or cefdinir. A broad-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended until specific antibiotic susceptibility and presence, or absence of meningitis is known. Vancomycin (to cover penicillin-resistant pneumococci) should be initiated, depending on the illness severity and susceptibilities of pneumococci at the institution. Splenectomized patients are also at increased risk for contracting protozoal infections, such as malaria and babesiosis. Serious infections may occur after an animal bite or lick (particularly dogs) and is caused by *Capnocytophaga canimorsus* or *C. cynodegmi*. Prophylactic antibiotics should be given after a bite potentially to prevent sepsis caused by these organisms (see Chapter 765).

Preoperative, intraoperative, and postoperative management may decrease the risk of postsplenectomy infection. It is important to be certain of the need for splenectomy and, if possible, to postpone the operation until the patient is ≥5 years of age. *Pneumococcal, meningococcal, and H. influenzae conjugate vaccines given at least 14 days before splenectomy may reduce postsplenectomy sepsis.* The 7-valent (PCV7) was replaced by the 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13). Thus, depending on what primary pneumococcal vaccine was given, a single dose of PCV13 may be recommended. In addition, the 23-valent pneumococcal polysaccharide vaccine (Pneumovax) should be given at age ≥2 years and a second dose 5 years later. Yearly influenza vaccine should also be given because influenza infection is a risk factor for secondary pneumococcal infections. Prophylaxis with oral penicillin VK (125 mg twice daily for children <5 years old; 250 mg twice daily for children ≥5 years) should be given until at least 5 years of age and for at least 2 years after splenectomy. Although the greatest risk is in the immediate postoperative period, reports of deaths occurring years after splenectomy suggest that the risk (and the need for prophylaxis) may be lifelong. Lifelong prophylaxis should be strongly considered in patients who have had an invasive pneumococcal infection or who have an underlying immune deficiency. In children with sickle cell disease, penicillin prophylaxis should be started as soon as the diagnosis is made. Prophylaxis may be continued into adulthood for higher-risk patients, including those with a history of pneumococcal sepsis, but effectiveness in this older group has not been well documented.

In patients with traumatic injury, splenic repair or partial splenectomy should be considered in an attempt to preserve splenic function. Partial splenectomy or partial *splenic embolization* may be sufficient to ameliorate some forms of hemolytic anemia. Up to 50% of children whose spleen is removed because of trauma have spontaneous splenosis; *surgical splenosis* (distributing small pieces of spleen throughout the abdomen) may decrease the risk of sepsis in patients whose splenectomy is necessitated by trauma. However, in both these settings, the splenic tissue that regrows frequently has poor function.

In addition to postsplenectomy sepsis, splenectomized patients may be at risk for **thromboembolic complications**, including arterial and venous thrombosis and pulmonary hypertension. These findings have been reported regardless of the underlying reason for splenectomy and the postsplenectomy platelet count. Proposed mechanisms include loss of filtering function of the spleen, allowing abnormal RBCs to remain in the circulation and activate the coagulation cascade. Portal vein thrombosis has been reported as a complication of laparoscopic splenectomy. The etiology of pulmonary hypertension is not well understood. It has been described in chronic hemolytic conditions including thalassemia, sickle cell disease, and hereditary spherocytosis, indicating there may be a relation to ongoing chronic hemolysis postsplenectomy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 9

The Lymphatic System

Chapter 537

Anatomy and Function of the Lymphatic System

Michael E. Kelly and Richard L. Tower

The lymphatic system participates in many biologic processes, including fluid homeostasis, absorption of dietary fat, and initiation of specific immune responses. Besides these well-known, classical functions, several novel and unexpected physiologic and pathophysiologic functions of the lymphatics have been recently discovered, including blood pressure regulation, reverse cholesterol transport, association with metabolic diseases and obesity, and an important role in the preparation for neonatal respiration. This system includes circulating lymphocytes, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and thymus. **Lymph** is an ultrafiltrate of blood and is collected by lymphatic capillaries that are present in all organs where blood flows except the bone marrow and retina. Lymphatic capillaries form progressively larger vessels that drain regions of the body. The lymphatic vessels carry lymph to the lymph nodes, where it is filtered through sinuses, particulate matter and infectious organisms are phagocytosed, and antigens are presented to surrounding lymphocytes. These actions stimulate antibody production, T-cell responses, and cytokine secretion (see Chapter 165). Lymph is ultimately returned to the intravascular circulation.

The composition of lymph can vary with the site of lymph drainage. It is usually clear, but lymph drained from the intestinal tract may be milky **(chylous)** because of the presence of fats. The protein content is intermediate between an exudate and a transudate. The protein level may be increased with inflammation and in lymph drained from the liver or intestines. Lymph also contains variable numbers of lymphocytes and antigen-presenting cells.

Embryonic lymphatic development is a stepwise process that starts in the embryonic veins, where lymphatic endothelial cell (LEC) progenitors are initially specified. The differentiation and maturation of these progenitors continues as they bud from the veins to produce scattered primitive lymph sacs, from which most of the lymphatic vasculature is derived. *PROX1* gene expression is important to LEC specification, and studies have shown the critical importance of bone morphogenetic protein (BMP), Wnt, Notch, and vascular endothelial growth factor (VEGF) signaling pathways in lymphatic system development.

Little is known about the establishment of organ-specific lymphatics at later stages. Studies using lineage-tracing technology suggest a venous and nonvenous origin of LECs giving rise to organ-specific lymphatics in the mesentery, skin, and heart. Lymphatic vessels also run parallel to the dural sinuses in the central nervous system. The embryonic origin of the meningeal lymphatics has not been determined.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 538

Abnormalities of Lymphatic Vessels

Michael E. Kelly and Richard L. Tower

LYMPHATIC MALFORMATIONS

Developmental lymphatic anomalies including **lymphatic malformations (LMs) and complex lymphatic anomalies (CLAs)** manifest as localized or multifocal lesions of the lymphatic vasculature, respectively (see International Society for the Study of Vascular Anomalies [**ISSVA**] classification; www.issva.org).

Cystic LMs are the most common *congenital* lymphatic anomalies. They occur as solitary lesions of variable size that are classified as macrocystic, microcystic, or mixed cystic LM. LMs commonly infiltrate soft tissues and can be found anywhere on the body, although they occur more frequently on the head, neck, and axilla.

CLAs are multifocal lymphatic vascular lesions involving both soft tissue and bone and often result in disruption of central collecting lymphatic channels. They include **generalized lymphatic anomaly (GLA), Gorham-Stout disease (GSD)** (Fig. 538.1), **kaposiform lymphangiomatosis (KLA), and central conducting lymphatic anomalies (CCLA)** (Fig. 538.2). CLAs are rare diseases with overlapping and variable clinical features. Common features include bone involvement, lymphatic leakage into the thoracic (chylous effusion) and abdominal (chylous ascites) cavities and mesenteric involvement leading to protein losing enteropathy. In addition to common features, GSD is uniquely associated with progressive cortical bone loss (see Fig. 538.1). KLA can be distinguished by the presence of spindle cells on histology, an aggressive clinical course, and evidence of consumptive coagulopathy and hemorrhage. CCLA, or channel type anomaly is characterized by dilation, malformation, and dysfunction of the major abdominal or thoracic lymphatic vessels.

LMs can also occur as combined malformations with other blood vessel types like capillaries (capillary-lymphatic malformation) or veins (lymphatic-venous malformation). LMs are commonly associated with **PIK3CA-related overgrowth spectrum (PROS) disorders**, which include **Klippel-Trenaunay syndrome (KTS), CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies) and Proteus syndrome** (Fig. 538.3).

Genetics

Somatic, activating variants in the *PIK3CA* gene that encodes the p110α catalytic subunit of PI3K are present at variable frequencies in most (80%) isolated LMs and LMs associated with PROS. These activating *PIK3CA* variants are identical to those found in venous malformations and in many human cancers. The genetics of CLAs are far more diverse. Activating *PIK3CA* gene variants have been identified in several patients diagnosed with GLA. In addition, pathologic genetic variants in genes involved in the RAS-MAPK signaling pathway have been implicated in other CLAs. Activating *NRAS* gene variants are associated with KLA while two patients with GSD were found to have activating gene variants in *KRAS*. Somatic, pathologic genetic variants in both the *ARAF* and *CBL* genes have been found in patients diagnosed with CCLA as have inactivating germline pathogenic variants in *EPHB4*. The role of RAS/MAPK pathway activation in CLAs is further reinforced by the observation that patients with known RASopathies, including Noonan and Noonan-like syndrome, can present with central conducting lymphatic anomalies.

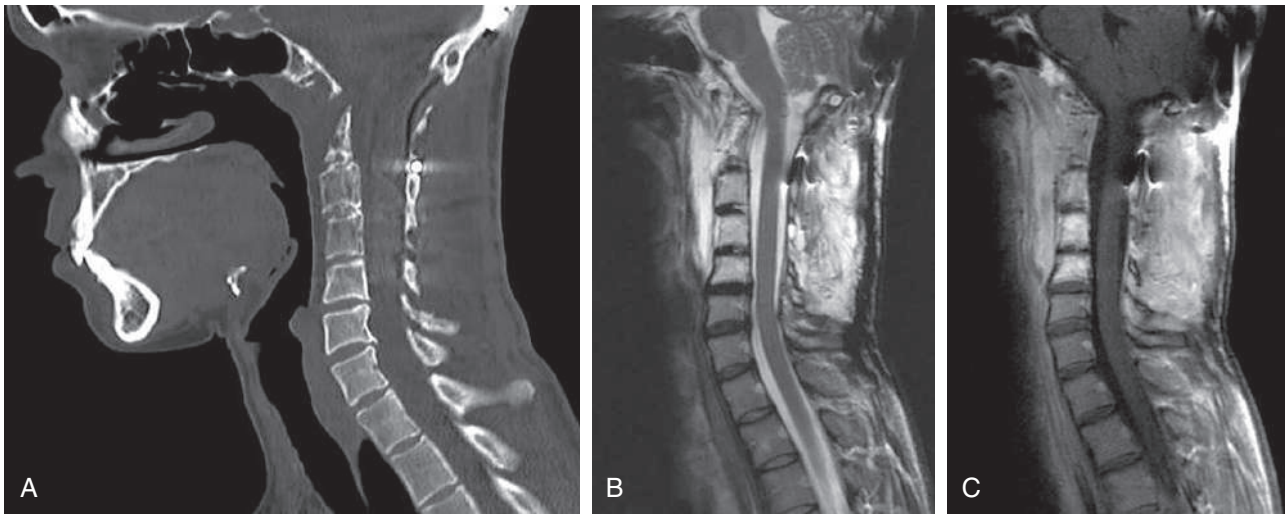

Fig. 538.1 Gorham–Stout disease. **A,** CT sagittal reformat. Multiple erosive changes in the occiput, clivus, and the cervical spine. (**B**) Sagittal T2-weighted fat-saturated (FS) MRI sequence. High signal is seen in the clivus and C 1–5 vertebral and the surrounding soft tissue. **C,** Postgadolinium T1 FS MRI. Enhancement is seen in the areas of osseous and soft tissue abnormalities. *(From Trenor III CC, Chaudry G. Complex lymphatic anomalies. Sem Pediatr Surg 2014;23:186–190. Fig. 3.)*

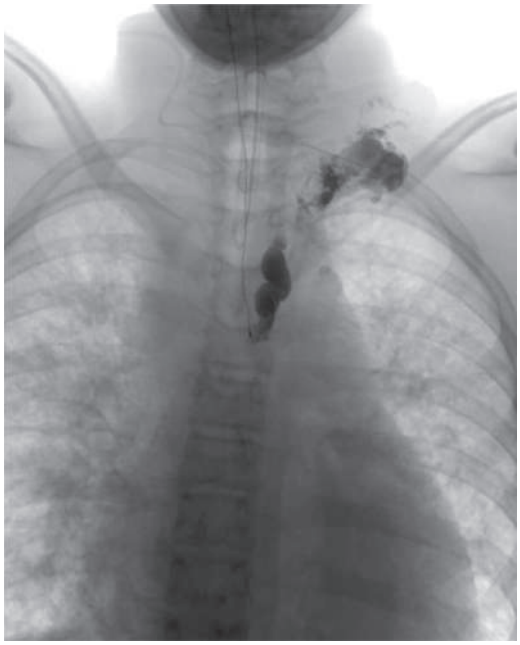

Fig. 538.2 Intranodal lymphangiogram in 15-year-old male with central conducting lymphatic anomaly and recurrent pericardial effusions. Stagnant flow is seen in the patulous superior portion of the thoracic duct. Direct puncture of the terminal portion demonstrates marked dilation with no spontaneous emptying.

Treatment

A decision to treat an LM depends on the anatomic location, involvement of local structures, and symptoms. Referral to a specialized vascular anomalies clinic with the expertise to guide appropriate imaging and treatment decisions is recommended. For localized macrocystic LMs, **interventional radiology (IR) administration of sclerosing agents** (OK432, ethanol, bleomycin) is most effective. For lesions involving skin and mucosa, **laser treatments** may be used.

Most patients with CLAs have extensive and invasive disease, necessitating systemic therapeutic approaches. The mTOR inhibitor **sirolimus** has had excellent effects in patients with vascular anomalies, including those patients with CLAs. A majority of CLA patients showed improvements in functional impairment and quality of life measures, whereas fewer showed evidence of decreased disease burden by imaging. **Combining sirolimus with bisphosphonates** may be even more effective in CLA patients with significant bone disease. **Alpelisib,** a *PIK3CA* inhibitor, has been used with success in patients with PROS and in a growing number of GLA patients with a known *PIK3CA* pathologic variant. Small numbers of patients with KLA who were known to have pathogenic variants in either NRAS or CBL experienced clinical improvement with **trametinib**, a MEK inhibitor. Trametinib also induced remodeling of the central lymphatics and induced symptom resolution in a patient with CCLA who had an *ARAF* pathogenic variant, as well a patient with Noonan syndrome and a *SOS1* pathogenic variant with severe lymphatic abnormalities.

LYMPHEDEMA

Lymphedema is a localized swelling caused by impaired lymphatic flow and can be primary (congenital) or acquired. **Primary lymphedemas** are grouped as LMs because they result from dysgenesis of lymphatic networks during early development. Primary lymphedema may be found in Turner syndrome, Noonan syndrome, autosomal dominantly inherited Milroy disease, and other chromosomal abnormalities. Pathologic variants in multiple genes, including the vascular endothelial growth factor receptor–3 gene *(VEGFR3), GJC2*, *PTPN14*, and *GATA2,* are associated with primary lymphedema (www.issva.org) (Table 538.1). Autosomal recessive, dominant or de novo pathogenic variants of *VEGFR3* produce Milroy disease. Pathologic variants in other genes are associated with specific syndromes: *CCBE1* (Hennekam), *FOXC2* (lymphedema distichiasis), *SOX18* (hypotrichosis-telangiectasia-lymphedema), *KMT2D/MLL2,* and *KDM6A* (Kabuki). Unilateral or bilateral lower extremity lymphedema in an adolescent may be Meige disease.

Acquired obstruction of the lymphatics is much more common than primary disorders and result from tumor, postirradiation fibrosis, and postinflammatory scarring. **Filariasis** is an important cause of lymphedema in Africa, Asia, and Latin America. One third of the 120 million infected persons (primarily older adolescents and adults) have lymphedema or a hydrocele. Injury to the major lymphatic vessels can cause



Fig. 538.3 Photographs and MRIs of participants with isolated LM, CLOVES, KTS, and FAVA. **A,** An 8-month-old male with isolated LM. Note swelling in deltoid region without cutaneous vascular signs. Coronal and sagittal fat-saturated T2-weighted MRI demonstrates macrocystic LM (a multilocular cystic mass) involving the anterolateral aspects of the right shoulder without muscular infiltration *(arrows)*; humeral head *star*. **B,** A 19-month-old female with CLOVES syndrome. Note asymmetric distribution of truncal lipomatous masses and bilateral lower extremity involvement. Coronal fat-saturated T1-weighted MRI after contrast administration demonstrates moderate heterogeneous enhancement of the bilateral truncal masses *(arrows)*. Axial T1-weighted MRI without contrast depicts truncal lipomatous overgrowth *(arrows)*; segment VI of the liver *(asterisk)*.

Continued

Fig. 538.3, cont'd **C,** A 3-yr-old male (KT4) with KTS. Note capillary-lymphatic malformation and overgrowth involving right lower extremity. Coronal and axial fat-saturated T2-weighted MRI shows the persistent marginal vein system *(bent arrows)* and marked enlargement of the subcutaneous tissues because of a combination of lymphatic fluid and fat *(straight arrow)*. There are also intramuscular venous malformations. **D,** A 9-yr-old male (F8) with FAVA of the left gastrocnemius muscle; note absence of overgrowth and cutaneous vascular anomalies. Sagittal fat-saturated T1-weighted MRI after contrast administration demonstrates the longitudinal distribution of the diffuse, fibro-adipose vascular anomaly *(arrows)*. Axial fat-saturated T2-weighted MRI with (upper) and without (lower) contrast. Note right head of the gastrocnemius muscle is diffusely replaced by a contrast enhancing heterogeneous soft tissue lesion *(arrows)*. CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis; FAVA, fibro-adipose vascular anomaly; KTS, Klippel-Trenaunay syndrome; LM, lymphatic malformations. *(From Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. J Pediatr. 2015;166:1048–1054.)*

Table 538.1 Chromosomal, Gene, and Syndromes Associated with Lymphedema

	SYNDROMES	KNOWN GENES, CHROMOSOMAL LOCI, INHERITANCE PATTERN
Primary lymphedema	Milroy disease	*VEGFR3* AR, AD
	Meige disease	Familial lymphedema
		No known gene
Chromosomal aneuploidy	Turner syndrome	45,X
	Klinefelter syndrome	47,XXY
	Trisomy 21	47,XX+21; 47,XY+21
	Trisomy 13	47,XX+13; 47,XY+13
	Trisomy 18	47,XX+18; 47,XY+18
Other genetic and syndromic disorders	Emberger syndrome (primary lymphedema with myelodysplasia)	*GATA2*(3q21.3), AD
	Lymphedema-distichiasis syndrome	*FOXC2*(16q24.1), AD
	Hennekam lymphangiectasia-lymphedema syndrome 1 (HKLLS1)	*CCBE1*(18q21.32), AR
	Hennekam lymphangiectasia-lymphedema syndrome 2 (HKLLS2)	*FAT4*(4q28.1), AR
	Hypotrichosis-lymphedema-telangiectasia ± renal defect syndrome (HLTRS)	*SOX18*(20q13.33), AR/AD
	Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR)	*KIF11*(10q23.33), AD
	Microcephaly and chorioretinopathy, 1 (MCCRP1)	*TUBGCP6*(22q13.33), AR
	Noonan syndrome	*PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, AD
	Cholestasis-lymphedema syndrome (Aagenaes syndrome)	*LSC1*, AR
	Ectodermal dysplasia, hypo/anhidrotic, lymphedema and immunodeficiency; immunodeficiency 33	*IKBKG*, (Xq28), XLR

AD, Autosomal dominant; AR, Autosomal recessive; XLR, X-linked recessive.
Modified from Unolt M, Barry J, Digilio MC, et al. Primary lymphedema and other lymphatic anomalies are associated with 22q11.2 deletion syndrome. *Eur J Med Genetics.* 2018;61:411–415. Table 1.

collection of lymph fluid in the abdomen (chylous ascites) or chest (chylothorax).

Untreated lymphedema can be disabling and is associated with immune dysfunction, inflammation, fibrosis, adipose tissue overgrowth, and lymphangiosarcoma. Treatment modalities attempt to reduce localized swelling through massage, exercise, and compression. Lymphatic reconstructive procedures, including lymphovenous bypass and lymphatico-lymphatic anastomosis are increasingly used to achieve lymphatic decongestion, especially in the early stages of disease.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis **(LAM)** is characterized by proliferation of lymphatic endothelial cells and smooth muscle cells in the lungs, leading to airway and lymphatic obstruction, cyst formation, pneumothorax, and respiratory failure. It may initially be mistaken for asthma. LAM occurs in young females and is associated with pathogenic variants in the tuberous sclerosis tumor-suppressor gene *TSC2* in one third of cases. **Sirolimus** stabilizes lung function, reduces symptoms, and improves life quality. Lung transplantation may be required.

LYMPHANGITIS

Lymphangitis is an inflammation of the lymphatics that drain an area of infection. Tender, erythematous streaks extend proximally from the infected area. Regional nodes may also be tender. Group A streptococci and *Staphylococcus aureus* are the most common pathogens, and therapy should include antibiotics that treat these organisms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Bibliography

Adams DM, et al. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. *Pediatrics*. 2016;137:e20153257.

Chang DW, Dayan J, Greene AK, et al. Surgical treatment of lymphedema: a systematic review and meta-analysis of controlled trials. Results of a consensus conference. *Plast Reconstr Surg*. 2021;1(4):975–993. 147.

Dentici ML, Di Pede A, Lepri FR, et al. Kabuki syndrome: clinical and molecular diagnosis in the first year of life. *Arch Dis Child*. 2015;100:158–164.

Frosk P, Chodirker B, Simard L, et al. A novel *CCBE1* pathogenic variant leading to a mild form of hennekam syndrome: case report and review of the literature. *BMC Med Genet*. 2015;16:28.

Iacobas I, et al. Multidisciplinary guidelines for initial evaluation of complicated lymphatic anomalies—expert opinion consensus. *Pediatric Blood & Cancer*. 2020;67:e28036.

Kuentz P, et al. Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. *Genet Med*. 2017;19:989–997.

Li D, et al. ARAF recurrent pathogenic variant causes central conducting lymphatic anomaly treatable with a MEK inhibitor. *Nature Medicine*. 2019;25:1116–1122.

Mäkinen T, Boon LM, Vikkula M, Alitalo K. Lymphatic Malformations: Genetics, Mechanisms and Therapeutic Strategies. *Circ Res*. 2021;129(1):136–154.

Ricci KW, et al. Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham–Stout disease. *Pediatric Blood & Cancer*. 2019;66:e27614.

Rodriguez-Laguna L, et al. Somatic activating pathogenic variants in PIK3CA cause generalized lymphatic anomaly. *J Exper Med*. 2018;216:407–418.

Trenor II CC, Chaudry G. Complex lymphatic anomalies. *Semin Pediatr Surg*. 2014;23:186–190.

Section 9

The Lymphatic System

Chapter 537

Anatomy and Function of the Lymphatic System

Michael E. Kelly and Richard L. Tower

The lymphatic system participates in many biologic processes, including fluid homeostasis, absorption of dietary fat, and initiation of specific immune responses. Besides these well-known, classical functions, several novel and unexpected physiologic and pathophysiologic functions of the lymphatics have been recently discovered, including blood pressure regulation, reverse cholesterol transport, association with metabolic diseases and obesity, and an important role in the preparation for neonatal respiration. This system includes circulating lymphocytes, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and thymus. **Lymph** is an ultrafiltrate of blood and is collected by lymphatic capillaries that are present in all organs where blood flows except the bone marrow and retina. Lymphatic capillaries form progressively larger vessels that drain regions of the body. The lymphatic vessels carry lymph to the lymph nodes, where it is filtered through sinuses, particulate matter and infectious organisms are phagocytosed, and antigens are presented to surrounding lymphocytes. These actions stimulate antibody production, T-cell responses, and cytokine secretion (see Chapter 165). Lymph is ultimately returned to the intravascular circulation.

The composition of lymph can vary with the site of lymph drainage. It is usually clear, but lymph drained from the intestinal tract may be milky **(chylous)** because of the presence of fats. The protein content is intermediate between an exudate and a transudate. The protein level may be increased with inflammation and in lymph drained from the liver or intestines. Lymph also contains variable numbers of lymphocytes and antigen-presenting cells.

Embryonic lymphatic development is a stepwise process that starts in the embryonic veins, where lymphatic endothelial cell (LEC) progenitors are initially specified. The differentiation and maturation of these progenitors continues as they bud from the veins to produce scattered primitive lymph sacs, from which most of the lymphatic vasculature is derived. *PROX1* gene expression is important to LEC specification, and studies have shown the critical importance of bone morphogenetic protein (BMP), Wnt, Notch, and vascular endothelial growth factor (VEGF) signaling pathways in lymphatic system development.

Little is known about the establishment of organ-specific lymphatics at later stages. Studies using lineage-tracing technology suggest a venous and nonvenous origin of LECs giving rise to organ-specific lymphatics in the mesentery, skin, and heart. Lymphatic vessels also run parallel to the dural sinuses in the central nervous system. The embryonic origin of the meningeal lymphatics has not been determined.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 538

Abnormalities of Lymphatic Vessels

Michael E. Kelly and Richard L. Tower

LYMPHATIC MALFORMATIONS

Developmental lymphatic anomalies including **lymphatic malformations (LMs) and complex lymphatic anomalies (CLAs)** manifest as localized or multifocal lesions of the lymphatic vasculature, respectively (see International Society for the Study of Vascular Anomalies [**ISSVA**] classification; www.issva.org).

Cystic LMs are the most common *congenital* lymphatic anomalies. They occur as solitary lesions of variable size that are classified as macrocystic, microcystic, or mixed cystic LM. LMs commonly infiltrate soft tissues and can be found anywhere on the body, although they occur more frequently on the head, neck, and axilla.

CLAs are multifocal lymphatic vascular lesions involving both soft tissue and bone and often result in disruption of central collecting lymphatic channels. They include **generalized lymphatic anomaly (GLA), Gorham-Stout disease (GSD)** (Fig. 538.1), **kaposiform lymphangiomatosis (KLA), and central conducting lymphatic anomalies (CCLA)** (Fig. 538.2). CLAs are rare diseases with overlapping and variable clinical features. Common features include bone involvement, lymphatic leakage into the thoracic (chylous effusion) and abdominal (chylous ascites) cavities and mesenteric involvement leading to protein losing enteropathy. In addition to common features, GSD is uniquely associated with progressive cortical bone loss (see Fig. 538.1). KLA can be distinguished by the presence of spindle cells on histology, an aggressive clinical course, and evidence of consumptive coagulopathy and hemorrhage. CCLA, or channel type anomaly is characterized by dilation, malformation, and dysfunction of the major abdominal or thoracic lymphatic vessels.

LMs can also occur as combined malformations with other blood vessel types like capillaries (capillary-lymphatic malformation) or veins (lymphatic-venous malformation). LMs are commonly associated with **PIK3CA-related overgrowth spectrum (PROS) disorders**, which include **Klippel-Trenaunay syndrome (KTS), CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies) and Proteus syndrome** (Fig. 538.3).

Genetics

Somatic, activating variants in the *PIK3CA* gene that encodes the p110α catalytic subunit of PI3K are present at variable frequencies in most (80%) isolated LMs and LMs associated with PROS. These activating *PIK3CA* variants are identical to those found in venous malformations and in many human cancers. The genetics of CLAs are far more diverse. Activating *PIK3CA* gene variants have been identified in several patients diagnosed with GLA. In addition, pathologic genetic variants in genes involved in the RAS-MAPK signaling pathway have been implicated in other CLAs. Activating *NRAS* gene variants are associated with KLA while two patients with GSD were found to have activating gene variants in *KRAS*. Somatic, pathologic genetic variants in both the *ARAF* and *CBL* genes have been found in patients diagnosed with CCLA as have inactivating germline pathogenic variants in *EPHB4*. The role of RAS/MAPK pathway activation in CLAs is further reinforced by the observation that patients with known RASopathies, including Noonan and Noonan-like syndrome, can present with central conducting lymphatic anomalies.

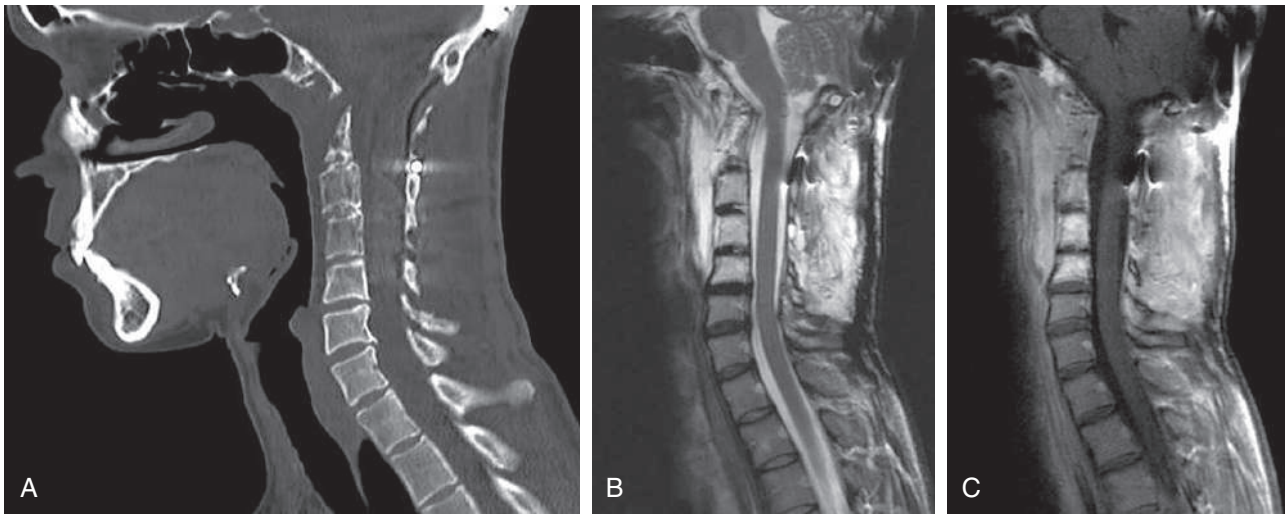

Fig. 538.1 Gorham–Stout disease. **A,** CT sagittal reformat. Multiple erosive changes in the occiput, clivus, and the cervical spine. (**B**) Sagittal T2-weighted fat-saturated (FS) MRI sequence. High signal is seen in the clivus and C 1–5 vertebral and the surrounding soft tissue. **C,** Postgadolinium T1 FS MRI. Enhancement is seen in the areas of osseous and soft tissue abnormalities. *(From Trenor III CC, Chaudry G. Complex lymphatic anomalies. Sem Pediatr Surg 2014;23:186–190. Fig. 3.)*

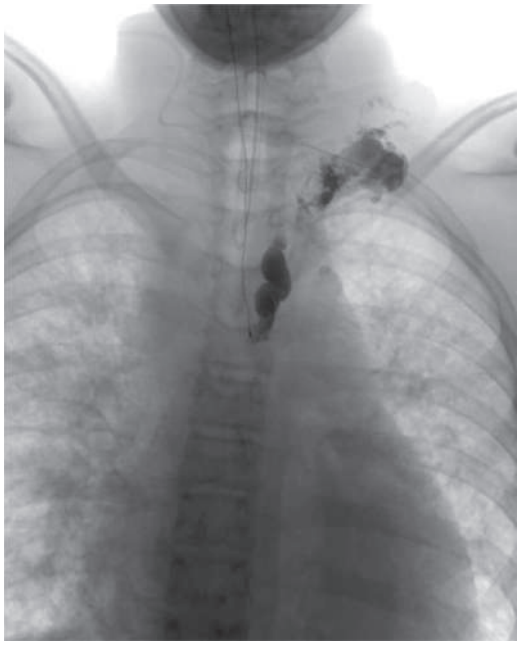

Fig. 538.2 Intranodal lymphangiogram in 15-year-old male with central conducting lymphatic anomaly and recurrent pericardial effusions. Stagnant flow is seen in the patulous superior portion of the thoracic duct. Direct puncture of the terminal portion demonstrates marked dilation with no spontaneous emptying.

Treatment

A decision to treat an LM depends on the anatomic location, involvement of local structures, and symptoms. Referral to a specialized vascular anomalies clinic with the expertise to guide appropriate imaging and treatment decisions is recommended. For localized macrocystic LMs, **interventional radiology (IR) administration of sclerosing agents** (OK432, ethanol, bleomycin) is most effective. For lesions involving skin and mucosa, **laser treatments** may be used.

Most patients with CLAs have extensive and invasive disease, necessitating systemic therapeutic approaches. The mTOR inhibitor **sirolimus** has had excellent effects in patients with vascular anomalies, including those patients with CLAs. A majority of CLA patients showed improvements in functional impairment and quality of life measures, whereas fewer showed evidence of decreased disease burden by imaging. **Combining sirolimus with bisphosphonates** may be even more effective in CLA patients with significant bone disease. **Alpelisib,** a *PIK3CA* inhibitor, has been used with success in patients with PROS and in a growing number of GLA patients with a known *PIK3CA* pathologic variant. Small numbers of patients with KLA who were known to have pathogenic variants in either NRAS or CBL experienced clinical improvement with **trametinib**, a MEK inhibitor. Trametinib also induced remodeling of the central lymphatics and induced symptom resolution in a patient with CCLA who had an *ARAF* pathogenic variant, as well a patient with Noonan syndrome and a *SOS1* pathogenic variant with severe lymphatic abnormalities.

LYMPHEDEMA

Lymphedema is a localized swelling caused by impaired lymphatic flow and can be primary (congenital) or acquired. **Primary lymphedemas** are grouped as LMs because they result from dysgenesis of lymphatic networks during early development. Primary lymphedema may be found in Turner syndrome, Noonan syndrome, autosomal dominantly inherited Milroy disease, and other chromosomal abnormalities. Pathologic variants in multiple genes, including the vascular endothelial growth factor receptor–3 gene *(VEGFR3), GJC2*, *PTPN14*, and *GATA2,* are associated with primary lymphedema (www.issva.org) (Table 538.1). Autosomal recessive, dominant or de novo pathogenic variants of *VEGFR3* produce Milroy disease. Pathologic variants in other genes are associated with specific syndromes: *CCBE1* (Hennekam), *FOXC2* (lymphedema distichiasis), *SOX18* (hypotrichosis-telangiectasia-lymphedema), *KMT2D/MLL2,* and *KDM6A* (Kabuki). Unilateral or bilateral lower extremity lymphedema in an adolescent may be Meige disease.

Acquired obstruction of the lymphatics is much more common than primary disorders and result from tumor, postirradiation fibrosis, and postinflammatory scarring. **Filariasis** is an important cause of lymphedema in Africa, Asia, and Latin America. One third of the 120 million infected persons (primarily older adolescents and adults) have lymphedema or a hydrocele. Injury to the major lymphatic vessels can cause



Fig. 538.3 Photographs and MRIs of participants with isolated LM, CLOVES, KTS, and FAVA. **A,** An 8-month-old male with isolated LM. Note swelling in deltoid region without cutaneous vascular signs. Coronal and sagittal fat-saturated T2-weighted MRI demonstrates macrocystic LM (a multilocular cystic mass) involving the anterolateral aspects of the right shoulder without muscular infiltration *(arrows)*; humeral head *star*. **B,** A 19-month-old female with CLOVES syndrome. Note asymmetric distribution of truncal lipomatous masses and bilateral lower extremity involvement. Coronal fat-saturated T1-weighted MRI after contrast administration demonstrates moderate heterogeneous enhancement of the bilateral truncal masses *(arrows)*. Axial T1-weighted MRI without contrast depicts truncal lipomatous overgrowth *(arrows)*; segment VI of the liver *(asterisk)*.

Continued

Fig. 538.3, cont'd **C,** A 3-yr-old male (KT4) with KTS. Note capillary-lymphatic malformation and overgrowth involving right lower extremity. Coronal and axial fat-saturated T2-weighted MRI shows the persistent marginal vein system *(bent arrows)* and marked enlargement of the subcutaneous tissues because of a combination of lymphatic fluid and fat *(straight arrow)*. There are also intramuscular venous malformations. **D,** A 9-yr-old male (F8) with FAVA of the left gastrocnemius muscle; note absence of overgrowth and cutaneous vascular anomalies. Sagittal fat-saturated T1-weighted MRI after contrast administration demonstrates the longitudinal distribution of the diffuse, fibro-adipose vascular anomaly *(arrows)*. Axial fat-saturated T2-weighted MRI with (upper) and without (lower) contrast. Note right head of the gastrocnemius muscle is diffusely replaced by a contrast enhancing heterogeneous soft tissue lesion *(arrows)*. CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis; FAVA, fibro-adipose vascular anomaly; KTS, Klippel-Trenaunay syndrome; LM, lymphatic malformations. *(From Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. J Pediatr. 2015;166:1048–1054.)*

Table 538.1 Chromosomal, Gene, and Syndromes Associated with Lymphedema

	SYNDROMES	KNOWN GENES, CHROMOSOMAL LOCI, INHERITANCE PATTERN
Primary lymphedema	Milroy disease	*VEGFR3* AR, AD
	Meige disease	Familial lymphedema
		No known gene
Chromosomal aneuploidy	Turner syndrome	45,X
	Klinefelter syndrome	47,XXY
	Trisomy 21	47,XX+21; 47,XY+21
	Trisomy 13	47,XX+13; 47,XY+13
	Trisomy 18	47,XX+18; 47,XY+18
Other genetic and syndromic disorders	Emberger syndrome (primary lymphedema with myelodysplasia)	*GATA2*(3q21.3), AD
	Lymphedema-distichiasis syndrome	*FOXC2*(16q24.1), AD
	Hennekam lymphangiectasia-lymphedema syndrome 1 (HKLLS1)	*CCBE1*(18q21.32), AR
	Hennekam lymphangiectasia-lymphedema syndrome 2 (HKLLS2)	*FAT4*(4q28.1), AR
	Hypotrichosis-lymphedema-telangiectasia ± renal defect syndrome (HLTRS)	*SOX18*(20q13.33), AR/AD
	Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR)	*KIF11*(10q23.33), AD
	Microcephaly and chorioretinopathy, 1 (MCCRP1)	*TUBGCP6*(22q13.33), AR
	Noonan syndrome	*PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, AD
	Cholestasis-lymphedema syndrome (Aagenaes syndrome)	*LSC1*, AR
	Ectodermal dysplasia, hypo/anhidrotic, lymphedema and immunodeficiency; immunodeficiency 33	*IKBKG*, (Xq28), XLR

AD, Autosomal dominant; AR, Autosomal recessive; XLR, X-linked recessive.
Modified from Unolt M, Barry J, Digilio MC, et al. Primary lymphedema and other lymphatic anomalies are associated with 22q11.2 deletion syndrome. *Eur J Med Genetics.* 2018;61:411–415. Table 1.

collection of lymph fluid in the abdomen (chylous ascites) or chest (chylothorax).

Untreated lymphedema can be disabling and is associated with immune dysfunction, inflammation, fibrosis, adipose tissue overgrowth, and lymphangiosarcoma. Treatment modalities attempt to reduce localized swelling through massage, exercise, and compression. Lymphatic reconstructive procedures, including lymphovenous bypass and lymphatico-lymphatic anastomosis are increasingly used to achieve lymphatic decongestion, especially in the early stages of disease.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis **(LAM)** is characterized by proliferation of lymphatic endothelial cells and smooth muscle cells in the lungs, leading to airway and lymphatic obstruction, cyst formation, pneumothorax, and respiratory failure. It may initially be mistaken for asthma. LAM occurs in young females and is associated with pathogenic variants in the tuberous sclerosis tumor-suppressor gene *TSC2* in one third of cases. **Sirolimus** stabilizes lung function, reduces symptoms, and improves life quality. Lung transplantation may be required.

LYMPHANGITIS

Lymphangitis is an inflammation of the lymphatics that drain an area of infection. Tender, erythematous streaks extend proximally from the infected area. Regional nodes may also be tender. Group A streptococci and *Staphylococcus aureus* are the most common pathogens, and therapy should include antibiotics that treat these organisms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 539

Lymphadenopathy

Zachary T. Graff and Richard L. Tower

Palpable lymph nodes are common in pediatrics and often pose a diagnostic challenge. Lymph node enlargement can be caused by proliferation of normal lymphoid elements or by infiltration with malignant or other phagocytic cells. In most patients, a careful history and a complete physical examination suggest the proper diagnosis.

DIAGNOSIS

What Is the Site of the Mass?

The differential diagnosis of a mass varies greatly based on anatomic location. Although pathologic masses can occur in any site, masses occurring in the supraclavicular and lower half of the neck are more likely to reflect pathologic lymphadenopathy than in other sites of the body.

Is the Mass a Lymph Node?

Nonlymphoid masses (cervical rib, thyroglossal cyst, branchial cleft cyst or infected sinus, cystic hygroma, goiter, thyroiditis, sternomastoid muscle tumor of infancy, neurofibroma) occur frequently in the neck and less often in other areas.

Is the Node Enlarged?

Lymph nodes are not usually palpable in the newborn. With antigenic exposure, lymphoid tissue increases in volume. They are not considered enlarged until their diameter exceeds 1 cm for cervical and axillary nodes, 1.5 cm for inguinal nodes, and epitrochlear >0.5 cm. Other lymph nodes usually are not palpable or visualized with plain radiographs.

What are the Characteristics of the Node?

Acutely infected nodes are usually tender. There may also be erythema and warmth of the overlying skin. Fluctuance suggests abscess formation. *Tuberculous* nodes may be matted. With chronic infection, many of these signs are not present. A firm, fixed, nonmobile (to adjacent or underlying tissues), nontender node should always raise the question of malignancy, regardless of the presence or absence of systemic symptoms or other abnormal physical findings. Tumors or tumor-involved nodes are often present for >2 weeks and may be associated with local extension (voice change, dysphagia, otalgia) or systemic signs (fever, weight loss, night sweats).

Is the Lymphadenopathy Localized or Generalized?

Generalized adenopathy (enlargement of >2 noncontiguous node regions) is caused by systemic disease (Table 539.1) and is often accompanied by abnormal physical findings in other systems. In contrast, *regional adenopathy* is most frequently the result of infection in the involved node and/or its drainage area (Table 539.2). When caused by infectious agents other than bacteria, adenopathy may be characterized by atypical anatomic areas, a prolonged course, a draining sinus, lack of prior pyogenic infection, and unusual clues in the history (cat scratches, tuberculosis exposure, venereal disease). The histopathologic pattern may also help with a differential diagnosis (Table 539.3).

Table 539.1 Differential Diagnosis of Generalized Lymphadenopathy

NEONATE	CHILD	ADOLESCENT
COMMON CAUSES		
CMV	Nonspecific viral infections	Viral infections
HIV	EBV	EBV
Syphilis	CMV	CMV
Toxoplasmosis	HIV	HIV
	Toxoplasmosis	Measles
	Measles	Toxoplasmosis
		Syphilis
RARE CAUSES		
Chagas disease (congenital)	Serum sickness	Serum sickness
Congenital leukemia	SLE, JIA	SLE, JIA
Congenital tuberculosis	Leukemia/lymphoma	Leukemia/lymphoma
Reticuloendotheliosis	Tuberculosis (miliary)	Tuberculosis
Metabolic storage disease	Sarcoidosis	Sarcoidosis
Histiocytic disorders	DRESS	DRESS
Listeria sepsis	Fungal infections	Fungal infections
	Plague	Plague
	Leptospirosis	Leptospirosis
	Brucellosis	Brucellosis
	Langerhans cell histiocytosis	Drug reaction (immune)
	Macrophage activation syndrome	Castleman disease
	Hemophagocytic lymphohistiocytosis	Rickettsial infection
	Castleman disease (very rare in this age group)	
	Chronic granulomatous disease	
	Sinus histiocytosis (Rosai-Dorfman disease)	
	Kikuchi-Fujimoto disease	
	Autoimmune lymphoproliferative disease (ALP)	
	Rickettsial infection	

CMV, Cytomegalovirus; DRESS, drug reaction, eosinophilia, systemic symptoms; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis (as Still disease); SLE, systemic lupus erythematosus.

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis: Common Diseases and Their Mimics*, 2nd ed. Philadelphia: Elsevier, 2023: Table 48.3, p. 891.

TREATMENT

Evaluation and treatment of lymphadenopathy is guided by the probable etiologic factor, as determined from the history and physical examination. Many patients with **cervical adenopathy** have a history compatible with viral infection and are observed without intervention. If bacterial infection is suspected, antibiotic treatment covering at least streptococci and staphylococci is indicated. Those who do not respond to oral antibiotics, as demonstrated by persistent swelling and fever, require intravenous (IV) antistaphylococcal antibiotics. If there is no response in 1-2 days, or if there are signs of airway obstruction or significant toxicity, ultrasound, CT, or MRI of the neck with contrast should be obtained. If *pus* is present, it may be aspirated, or if it is extensive, it may require incision and drainage. Gram stain and culture of the pus should be obtained. The sizes of involved nodes should be documented before treatment. Failure to decrease in size within 14 days also suggests the need for further evaluation. This evaluation may include a complete blood cell count (CBC) with differential; Epstein-Barr virus, cytomegalovirus, *Toxoplasma,* and *Bartonella henselae* titers; anti–streptolysin O or anti-DNase B serologic tests; tuberculin skin test or gamma interferon assay; and chest radiograph to evaluate for mediastinal adenopathy. If these are not diagnostic, consultation with an infectious diseases or oncology specialist may be helpful. Biopsy should be considered if there is persistent or unexplained fever, weight loss, night sweats, supraclavicular location, mediastinal mass, hard nodes, or fixation of the nodes to surrounding tissues. Biopsy may also be indicated if there is an increase in size over baseline in 2 weeks, no decrease in size in 4-6 weeks, no regression to "normal" in 8-12 weeks, or if new signs and symptoms develop.

Table 539.2 Sites of Regional Lymphadenopathy and Associated Diseases

CERVICAL
Oropharyngeal infection (viral, group A streptococcal, staphylococcal, or fusobacterial)
Scalp infection (tinea)
Mycobacterial lymphadenitis (tuberculous and nontuberculous mycobacteria)
Viral infection (EBV, CMV, HHV-6, measles)
Cat-scratch disease
Kawasaki disease
Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19
Thyroid disease
Kimura disease
Rosai-Dorfman (sinus histiocytosis)
Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome
Kikuchi-Fujimoto disease
Unicentric Castleman disease
ANTERIOR AURICULAR
Conjunctivitis or other eye infections
Oculoglandular tularemia, cat-scratch disease, EBV, adenovirus
POSTERIOR AURICULAR
Otitis media
Viral infection (especially rubella, parvovirus)
SUPRACLAVICULAR
Malignancy or infection in the mediastinum (right)
Metastatic malignancy from abdomen (left)
Lymphoma
Tuberculosis
EPITROCHLEAR
Hand infection, arm infection*
Lymphoma†
Sarcoidosis
Syphilis
EBV
HIV
INGUINAL
Urinary tract infection
Sexually transmitted infection (especially syphilis or lymphogranuloma venereum)
Lower extremity suppurative infection
Plague
HILAR (NOT PALPABLE, FOUND ON CHEST RADIOGRAPH OR CT) (SEE TABLE 539.1)
Tuberculosis†
Histoplasmosis†
Blastomycosis†
Coccidioidomycosis†
Leukemia/lymphoma†
Hodgkin disease†
Metastatic malignancy*
Sarcoidosis†
Castleman disease
AXILLARY
Cat-scratch disease
Arm infection
Malignancy of chest wall
Leukemia/lymphoma
Brucellosis

*Unilateral.
†Bilateral.
CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.
From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis: Common Diseases and Their Mimics*, 2nd ed. Philadelphia: Elsevier, 2023: Table 48.2, p. 890.

Differentiating benign disorders from a malignancy may initially be difficult. Hard, nontender, nonerythematous nodes involving multiple regions (including mediastinum and abdomen), hepatic or splenic enlargement, fever, night sweats, and weight loss suggest malignancy or a granulomatous process. Persistence of symptoms and lymphadenopathy >2 weeks and certain locations (supraclavicular, mediastinal, abdominal) also suggest malignancy. Cytopenias and elevated blood lactate dehydrogenase are associated with malignancy and certain infectious and inflammatory disorders. Ultrasound is useful in distinguishing malignancy from reactive nodes. CT with contrast is helpful in identifying other affected nodes and organs. Although fine needle aspiration (FNA) is sometimes used as an initial approach to diagnosis, excisional biopsies are often needed and are the preferred diagnostic approach to fully appreciate the lymph node architecture and genomic profiling when malignant conditions are being considered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

539.1 Kikuchi-Fujimoto Disease (Histiocytic Necrotizing Lymphadenitis)

Zachary T. Graff and Richard L. Tower

Kikuchi-Fujimoto disease is a rare, usually self-limiting disease that is seen in all ethnic groups; children and adults may be affected. Familial cases have been reported. The etiology is unknown, although infectious and autoimmune diseases such as systemic lupus erythematosus (SLE) have been associated. The differential diagnosis includes infectious lymphadenitis, lymphoma, tuberculosis, and SLE.

Presentation is varied but most often presents as firm, painful unilateral posterior cervical adenopathy evolving over several weeks. Fever is frequently reported. Labs are often normal; however, elevated erythrocyte sedimentation rate (ESR), elevated CRP, atypical lymphocytosis, and leukopenia can be seen. Nodes range in size from 0.5-6.0 cm, are painful or tender in only 50% of cases, may be multiple, and must be differentiated from lymphoma. Node involvement may occasionally be bilateral or rarely present in axillary, supraclavicular, or intraabdominal lymph nodes. Ultrasound usually shows multiple conglomerated, unilateral cervical lymphadenopathy with perinodal fat swelling and even size distribution. Aseptic meningitis is an uncommon associated feature.

The diagnosis is made by lymph node biopsy. Histologic features include paracortical lymph node expansion with patchy, well-circumscribed areas of necrosis showing karyorrhexis, an absence of neutrophils and eosinophils, a CD68+/MPO+ histiocytic infiltrate, and CD123+/TCL1+ plasmacytoid dendritic cells. Kikuchi-Fujimoto disease usually resolves within 6 months, although relapses have occurred up to 16 years later. Treatment is typically symptomatic including rest and analgesics. Therapy with systemic steroids is reserved for patients with severe symptoms. Recurrences occur in ~5-20% depending on site (higher recurrences with bone, CNS, or skin involvement). Patients should be followed for the possible development of systemic lupus erythematosus. Rarely, the disease has been fatal.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

539.2 Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Zachary T. Graff and Richard L. Tower

The uncommon, benign, and usually self-limited Rosai-Dorfman disease (RDD) is a non-Langerhans cell histiocytosis that has a worldwide distribution but is more common in individuals of African descent. The etiology is unknown, but immune dysfunction is suspected. Lesional histiocytes are $S100^+$, $CD68^+$, and $CD1a^-$. It is not a single entity, but a

Table 539.3 Differential Diagnosis for the Histologic Patterns Seen in Pediatric Lymphadenopathies

HISTOLOGIC PATTERN	DIFFERENTIAL DIAGNOSIS	KEY FEATURES
Isolated follicular hyperplasia	Nonspecific reactive pattern Viral infections HIV lymphadenitis Measles Follicular lymphoma Primary immunodeficiencies	Multinucleated Warthin-Finkeldey cells seen in both HIV and measles Expansile irregular follicles in acute HIV Normal polarization of germinal center cells and phenotyping helpful to rule out follicular lymphoma
Follicular hyperplasia with PTGC	Nonspecific reactive pattern Nodular lymphocyte predominant Hodgkin lymphoma	Cytologically atypical cells seen in nodular lymphocyte predominant Hodgkin lymphoma are absent in PTGC
Paracortical hyperplasia	EBV infectious mononucleosis HSV1/2 CMV Varicella Measles Classic Hodgkin lymphoma Drug-induced lymphadenopathy Primary immunodeficiencies Non-Hodgkin B-cell and T-cell lymphoma	Polymorphic with numerous immunoblasts RS-like cells express CD20, unlike RS cells of classic Hodgkin lymphoma Warthin-Finkeldey cells may be seen in measles and HSV lymphadenitis Well-delineated necrosis in HSV Intranuclear inclusions may be seen in CMV, HSV, and varicella Associated monocytoid B-cell hyperplasia seen in CMV lymphadenitis
Suppurative	Bacterial lymphadenitis, Staphylococcus, Streptococcus, Haemophilus, Yersinia, *Francisella tularensis*, Brucella HSV lymphadenitis Kawasaki	Poorly formed granulomas also may be seen in bacterial infections Necrotic foci beneath the capsule seen in Kawasaki
Necrotizing granulomas	Mycobacteria, tuberculous, and nontuberculous Fungal infections CSD Kikuchi-Fujimoto lymphadenitis/SLE	Acellular (caseating) necrosis with numerous giant cells seen in mycobacterial and fungal infections CSD palisading histiocytes with neutrophilic microabscesses Kikuchi-Fujimoto lymphadenitis/SLE necrosis with nuclear debris and absence of neutrophils; C-shaped histiocytes; clusters of immunoblasts and plasmacytoid dendritic cells
Nonnecrotizing granulomas	Sarcoidosis; infections; nonspecific	
Histiocytoses	HLH, Rosai-Dorfman disease	
Miscellaneous	Toxoplasmosis • Triad: follicular hyperplasia, monocytoid B-cell hyperplasia, epithelioid histiocytes extend into lymphoid follicles • Kimura • Follicular hyperplasia and interfollicular eosinophils	

CMV, cytomegalovirus; CSD, cat-scratch disease; EBV, Epstein Barr virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; PTGC, progressive transformation of germinal centers; SLE, systemic lupus erythematosus.
From Faraz M, Rosando FGN. Reactive lymphadenopathies. *Clin Lab Med.* 2021;41:433–451. Table 1.

pattern, and can be associated with neoplasia or autoimmune disease. It can be sporadic or associated with inherited conditions. Some patients have somatic pathogenic variants in *NRAS*, *KRAS*, and *MAP2K1*. Familial RDD has been noted in patients with pathogenic variants in *SLC29A3*. RDD may coexist with SLE, JIA, and autoimmune hemolytic anemia.

Patients can be classified as classical (nodal) RDD or extranodal RDD. **Classical RDD** patients present with massive *bilateral*, painless, mobile cervical adenopathy with or without fever, night sweats, and weight loss. Other lymph node involvement can include mediastinal, axillary, and inguinal, although retroperitoneal involvement is rare. **Extranodal RDD** occurs in 43% of cases. Soft tissue involvement has been reported in many organ systems. The most common sites are the skin, followed by the nasal cavity and sinuses, palate, orbit, bone, and central nervous system. Lab abnormalities can include normocytic anemia, leukocytosis (typically neutrophilia), elevated ESR, and polyclonal elevation of immunoglobulin G (hypergammaglobulinemia). Initial imaging studies are determined by symptoms and sites of suspected disease.

A biopsy that demonstrates histiocytes with hypochromatic nuclei with pale cytoplasm containing engulfed erythrocytes, plasma cells, and lymphocytes (emperipolesis), and immunoreactivity to S100 protein, in conjunction with expected clinical features, is diagnostic. IgG4-positive cells are often abundant. Occasionally, autoantibodies to erythrocytes or synovium may be present. The differential diagnosis includes Langerhans cell histiocytosis, myeloproliferative disorders, lymphoma, and hyper-IgG4 syndrome. After diagnosis, whole-body imaging with MRI or PET scan is recommended to evaluate for extranodal RDD.

Observation alone is a reasonable treatment choice for patients with uncomplicated nodal/cutaneous disease, as spontaneous remissions are seen in 20–50% of these patients. Symptomatic patients may benefit from surgical resection or debulking with the presence of single-site disease. Systemic therapy is typically reserved for severe, refractory, multifocal, or unresectable disease. Steroids are helpful in reducing nodal size; however, durable responses are often not seen with steroids alone. Various immunomodulatory (sirolimus) and chemotherapy regimens have been used successfully in severe disease, with treatment courses ranging from 6-12 months followed by close observation. Targeted therapies, including MEK inhibitors, have shown promising early results with studies ongoing. Radiation therapy has modest efficacy in RDD but has been used successfully in emergent therapy with visual or airway compromise. RDD may recur for many years with an unpredictable clinical course.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

539.3 Castleman Disease (Angiofollicular Lymph Node Hyperplasia)

Zachary T. Graff and Richard L. Tower

Castleman disease (CD) is an uncommon nonmalignant B-cell lymphoproliferative disorder and is also called **angiofollicular lymph node hyperplasia**. CD causes lymph node enlargement and is classified as either unicentric (involving a single lymph node or lymph node region) or multicentric (involving multiple lymph node regions). **Unicentric CD** typically presents with enlargement of a single bulky lymph node, most often in the mediastinum, neck, or abdomen, which can be asymptomatic or present with locally compressive symptoms. Patients may have fever, night sweats, weight loss, and fatigue. Diagnosis is made by an excisional lymph node biopsy. Staging imaging is performed with CT scan of chest/abdomen/pelvis or PET-CT scan to evaluate for multicentric disease. Management includes surgical resection when possible and is associated with a benign course, although patients should be educated on an increased risk of lymphoma.

Multicentric CD is subclassified based on the etiologic driver of the disease, either human herpes virus-8 (HHV-8), peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS) syndrome, or idiopathic. An underlying immunocompromised state is the primary risk factor for HHV-8 CD, particularly patients with HIV. Other forms of multicentric CD have no known risk factors. HHV-8 and idiopathic multicentric CD are driven by the excessive production of interleukin-6 (IL-6). Lymphadenopathy is often small volume and is present in peripheral and central lymph node chains. Constitutional symptoms such as fever, night sweats, and weight loss are more common at presentation compared to unicentric CD. Fluid collections including ascites, cytopenias, and liver/kidney dysfunction are also seen and indicate more aggressive disease. Diagnosis is again made by excisional lymph node biopsy as well as consistent clinical features. To determine type of multicentric CD, testing for HIV, HHV-8, and evaluation for POEMS (polyneuropathy, organomegaly, edema/endocrinopathy, monoclonal-protein, skin) syndrome is needed. Serum inflammatory markers are often tested at baseline and used to track disease. The differential diagnosis is broad even after lymph node biopsy, including infection, autoimmune disease, and malignancy. There is no standard treatment for multicentric Castleman disease. For symptomatic HHV-8+ multicentric CD, rituximab +/- etoposide with antiretroviral therapy for HIV+ patients have achieved excellent relapse-free survival. Idiopathic multicentric CD is managed with anti-IL-6 directed therapy (siltuximab) and steroids. Even after initial responses, symptoms can return after stopping therapy. Rituximab, steroids, and additional immunomodulatory medications (particularly the mTOR inhibitor sirolimus) are used next in patients that have had an inadequate response to therapy. Cytotoxic chemotherapy can be used for severe disease with organ dysfunction after failure of first-line therapy.

TAFRO (thrombocytopenia, anasarca, fever, reticulum fibrosis, organomegaly) syndrome is thought to be a subtype of multicentric Castleman disease based on the histologic appearance of the lymph node. Although there are overlapping features, TAFRO may be a distinct entity (Fig. 539.1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

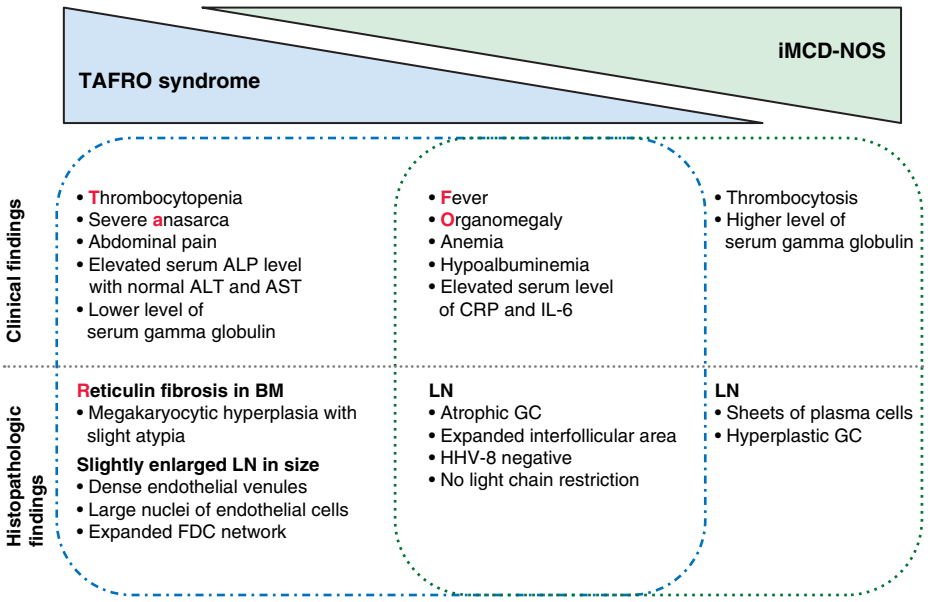

Fig. 539.1 Summary of the clinical and histopathologic features of TAFRO syndrome and iMCD-NOS. Although TAFRO syndrome and iMCD-NOS have clinicopathologic features in common, TAFRO syndrome has unique characteristics that can distinguish it from iMCD-NOS. ALP, alkaline phosphatase; ALT, Alanine transaminase; AST, aspartate transaminase; BM, bone marrow; CRP, C-reactive protein; FDC, follicular dendritic cell; GC, germinal center; HHV, human herpes virus; LN, lymph node; iMCD, idiopathic multicentric Castleman disease; NOS, not otherwise specified; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly. *(From Igawa T, Sato Y. TAFRO syndrome. Hematol Oncol Clin N Am. 2018;32:107–118. Fig. 4.)*

Cancer and Benign Tumors

PART XX

Chapter 540

Epidemiology of Childhood and Adolescent Cancer

Barbara L. Asselin

Cancer in patients younger than 20 years is uncommon, with an age-adjusted annual incidence of 19.6 per 100,000 children age 0-19 years, representing only approximately 1% of all new cancer cases in a year in the United States, or an estimated 16,000 new cases in 2021. This translates to nearly a 1 in 300 chance of developing cancer by age 20 years. Although the relative 5-year survival rates have improved from 61% in 1975–1977 to 85.1% in 2011–2017 in all age-groups 0-19 years (Fig. 540.1), **malignant neoplasms** remain the leading cause of disease-related (noninjury) mortality (9%) among persons 1-19 years of age, with 1,800-1,900 cancer-related deaths annually in the United States among children and adolescents 0-19 years of age. The relative contribution of cancer to the overall mortality in infants 0-1 year old and adolescents 15-19 years old is lower than for children age 1-14 years. The impressive improvements in survival over the last four decades are attributed primarily to advances in treatment, supportive care, and enrollment in clinical trials for the majority of patients. Ongoing multi-institutional cooperative clinical trials are investigating novel therapies and ways to improve survival rates further while decreasing treatment-related long-term complications. Because increasingly more patients survive their disease, clinical investigations also are focusing on the quality of life among survivors and the late outcomes of therapy for pediatric and adult survivors of childhood cancer. The **National Cancer Institute** (NCI; https://www.cancer.gov/types/childhood-cancers/) estimated that as of January 1, 2018, there were approximately 483,000 persons alive (in all age-groups) who had survived childhood cancer (diagnosed at ages 0-19 years). Given the overall improvement in survival rates coupled with the increased incidence of childhood cancer observed in recent decades, the number of survivors will continue to increase.

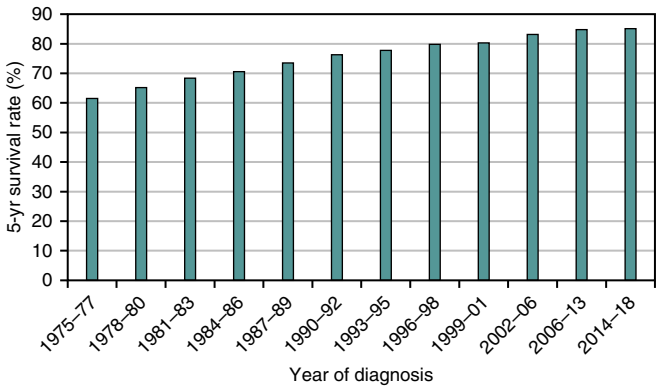

Fig. 540.1 The 5-year relative survival rates (%) by year of diagnosis of all cancers in children ≤19 years old. The difference between the periods 1975–1977 and 2014–2018 is statistically significant ($p < .05$). Rates based on follow-up of patients into 2018 from Surveillance, Epidemiology, and End Results (SEER) database. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2018. Bethesda, MD: National Cancer Institute. https://seer.cancer.gov/csr/1975_2018/. Based on November 2020 SEER data submission, posted to the SEER website, April 2021.)*

Pediatric malignancies differ greatly from adult malignancies in both prognosis and distribution by histology and tumor site. **Lymphohematopoietic cancers** (i.e., acute lymphoblastic leukemia, myeloid leukemia, Hodgkin and non-Hodgkin lymphomas) account for approximately 40%, **central nervous system cancers** for approximately 30%, and **embryonal tumors** and **sarcomas** for approximately 10% among the broad categories of childhood cancers (Table 540.1). In contrast, the **epithelial tumors** (or **adenocarcinomas**) of organs such as lung, colon, breast, and prostate often seen among adults, are rare malignancies in children. Incidence patterns in the pediatric age-group show two peaks, in early childhood and in adolescence (Fig. 540.2). During the first year of life, *embryonal tumors* such as neuroblastoma, nephroblastoma (Wilms tumor), retinoblastoma, rhabdomyosarcoma, hepatoblastoma, and medulloblastoma are most common (Figs. 540.3 and 540.4). These tumors are much less common in older children and adults after cell differentiation processes have slowed considerably. Embryonal tumors, acute leukemias, non-Hodgkin lymphomas, and gliomas peak in incidence from 2-5 years of age. As children age, bone malignancies, Hodgkin disease, gonadal germ cell malignancies (testicular and ovarian carcinomas), and other carcinomas increase in incidence. Adolescence is a transitional period between the common early childhood malignancies and characteristic carcinomas of adulthood (see Fig. 540.4).

Incidence rates also vary by *gender* (generally higher in males vs females), *ethnicity* (leukemia more common in Hispanic children than White or Black children; brain tumors more common in White children), and between countries (data assembled by the International Agency for Research in Cancer in Lyon, France, http://www.iarc.who.int/). These variations are not fully understood but likely reflect differences in genetic susceptibility and environmental exposures related to both known and unknown causes and risk factors for cancer (Table 540.2). Over the past four decades, 1975–2018, the U.S. Surveillance, Epidemiology, and End Results Program (SEER) data show some increases in the incidence of children and adolescents diagnosed with cancer (annual percent change about 1%), particularly in occurrence of leukemia, brain, and lymphoma and among adolescents. Interestingly, a similar increased incidence of malignancies diagnosed in childhood was observed between 1980 and 2010 in an international population-based registry study involving 62 countries. Reasons postulated to explain these increases include, but are not limited to, improved diagnosis, better record keeping, and development of data registries. Further analysis of trends among subpopulations, geographic variations, and incidence rates in high-income vs low-income countries are needed to clarify the role of *genetic ancestry, environmental factors,* and *technology* as explanations of these time trends in cancer in children.

Table 540.1 Age-Adjusted Incidence and Survival Rates of Malignant Neoplasms by Tumor Type in U.S. Children

	ANNUAL INCIDENCE RATES PER 1 MILLION CHILDREN, 2014–2018					5-YR SURVIVAL (%), AGE ≤19 YR AT DIAGNOSIS, 2011–2017
	AGE <1 YR	AGE 1-4 YR	AGE 5-9 YR	AGE 10-14 YR	AGE 15-19 YR	
All malignancies combined	265	227	137	164	252	85.1
All Leukemias (ALL/AML)	51 (18/20)	93 (78/11)	4.5 (37/4)	36 (24/8)	37 (19.5/10)	85 (89/68)
Lymphoma (Hodgkin)	— (—)	9 (1)	17 (3.5)	28 (13)	54 (33)	94 (98)
CNS tumors	46	54	50	52	64	74
Neuroblastoma	56	21	4	1	1	82
Nephroblastoma/Wilms (renal cell carcinoma)	16 (—)	19 (—)	6 (—)	1 (1)	— (1.5)	93
Bone	—	2	7	16	15	71
Soft tissue sarcomas	14	11	9	13	17	74
Retinoblastoma	31.5	8	—	—	—	96
Hepatoblastoma (hepatic carcinoma)	14 (—)	6 (—)	0.8 (—)	0.4 (0.7)	— (1.5)	82
Germ cell tumors	20	4	3	9	29	92
Malignant epithelial cancer	2.5	2	6	24	68.5	94
Thyroid / melanoma	–*/–†	–*/1†	2*/2†	11*/3†	35*/9†	(99*/94†)

*Thyroid carcinoma.
†Malignant melanoma.
—, Indicates that the rate could not be calculated with <16 cases for the time interval.
ALL, Acute lymphoid leukemia; AML, acute myeloid leukemia; CNS, central nervous system.
Data compiled from Howlader N, Noone AM, Krapcho M, et al., eds. SEER cancer statistics review, 1975-2018. Bethesda, MD: National Cancer Institute, 2020. Based on November 2020 SEER data submission, posted to SEER website, April 2021.
Based on the International Classification of Childhood Cancer (ICCC). Rates are per 1 million children and are age-adjusted to the 2000 U.S. standard population.

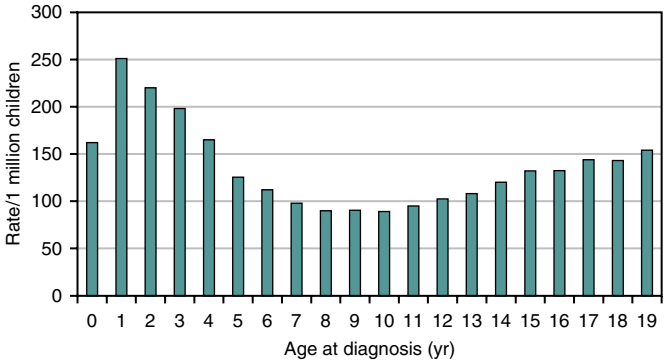

Fig. 540.2 Age-specific cancer incidence rates per 1 million children within the United States. *(Rates based on data from 2000–2017 from Surveillance, Epidemiology, and End Results [SEER] database http://seer.cancer.gov/csr/1975_2018/ and data compiled from Marcotte EL, Domingues AM, Sample JM, et al. Racial and ethnic disparities in pediatric cancer incidence among children and young adults in the United States by single year of age. Cancer 2021;127[19]:3651–3663. http://seer.cancer.gov/csr/1975_2018/.)*

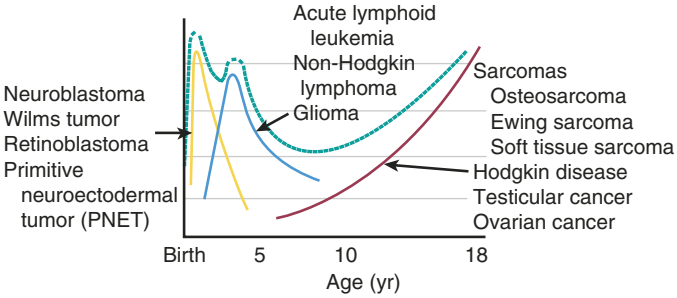

Fig. 540.3 Generalized incidence of the most common types of cancer in children by age. The cumulative incidence of all cancers is shown as a *dashed green line. (Courtesy Archie Bleyer, MD.)*

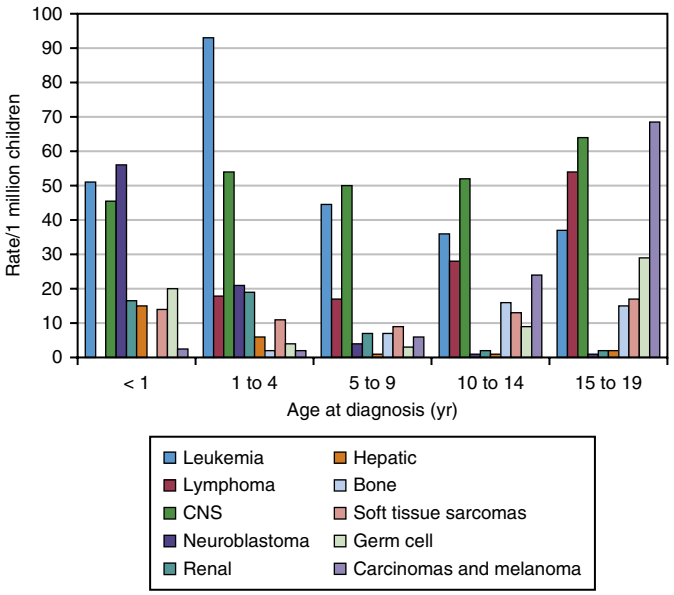

Fig. 540.4 Surveillance, Epidemiology, and End Results (SEER) cancer incidence rates per 1 million children by International Classification of Childhood Cancer (ICCC) and age <20 years. CNS, Central nervous system. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al., eds. SEER cancer statistics review, 1975-2018. Bethesda, MD: National Cancer Institute, 2020. http://seer.cancer.gov/csr/1975_2018/. Based on November 2020 SEER data submission, posted to the SEER website, April 2021.)*

Table 540.2 Known Risk Factors for Selected Childhood Cancers

CANCER TYPE	RISK FACTOR	COMMENTS
Acute lymphoid leukemia	Ionizing radiation	Therapeutic irradiation for cancer treatment
	Ethnicity	Hispanic children have higher incidence compared with White or Black children White children have a higher rate than Black children
	Immunodeficiency	SCID, Wiskott-Aldrich syndrome
	Genetic factors*	Down syndrome is associated with an estimated 10-20–fold increased risk NF1 Li-Fraumeni syndrome (*TP53* pathogenic variants) Noonan syndrome Chromosome breakage syndromes Bloom syndrome Ataxia-telangiectasia
Acute myeloid leukemias/ myelodysplastic syndrome	Chemotherapeutic agents	Alkylating agents and epipodophyllotoxins associated with risk of secondary leukemia
	Genetic factors*	Down syndrome (particularly acute megakaryocytic leukemia) NF1 Fanconi anemia and other inherited marrow failure syndromes Li-Fraumeni syndrome GATA2 deficiency Noonan syndrome Familial monosomy 7 and other chromosomal pathogenic variants
Brain cancers	Therapeutic ionizing radiation to the head	Radiation therapy as part of cancer treatment
	Genetic factors*	NF1 is strongly associated with optic gliomas, and, to a lesser extent, with other central nervous system tumors Li-Fraumeni syndrome Tuberous sclerosis Noonan syndrome Von Hippel-Landau syndrome FAP syndrome
Hodgkin disease	Family history	Monozygotic twins and siblings of cases are at increased risk
	Infections	EBV is associated with increased risk
Non-Hodgkin lymphoma	Immunodeficiency	Congenital immunodeficiency disorders (e.g., SCID and Wiskott-Aldrich syndrome) Immunosuppressive therapy for other conditions associated with increased risk
	Infections	EBV is associated with Burkitt lymphoma PTLD-EBV plays role in development of B-cell lymphoproliferative disease seen in immunocompromised hosts, especially those on immunosuppression following organ transplantation
Osteosarcoma	Ionizing radiation	Cancer radiation therapy
	Chemotherapy	Alkylating agents increase risk
	Genetic factors*	Li-Fraumeni syndrome Second malignancy in hereditary retinoblastoma with *RB1* pathogenic variant
Ewing sarcoma	Ethnicity	White children have about a ninefold higher incidence rate than Black children in the United States
Neuroblastoma		Beckwith-Wiedemann syndrome Li-Fraumeni
Retinoblastoma	Genetic factors*	Familial; pathogenic variant of *RB1* without other syndromic features—also with high risk of second malignancies
Wilms tumor	Genetic factors*	WAGR syndrome *WT1* germline pathogenic variant Beckwith-Wiedemann syndrome Li-Fraumeni syndrome
	Ethnicity	Asian children reportedly have about half the rates of White and Black children
Rhabdomyosarcoma	Genetic factors*	Li-Fraumeni syndrome NF1 Beckwith-Wiedemann syndrome DICER1 syndrome Gorlin syndrome

Continued

Table 540.2 Known Risk Factors for Selected Childhood Cancers—cont'd

CANCER TYPE	RISK FACTOR	COMMENTS
Hepatoblastoma	Genetic factors*	Beckwith-Wiedemann syndrome Gardner syndrome; FAP
Malignant germ cell tumors	Cryptorchidism	Cryptorchidism is a risk factor for testicular germ cell tumors

*See Chapter 541 for additional information.
SCID, Severe combined immunodeficiency syndrome; NF1, neurofibromatosis type1; FAP, familial adenomatous polyposis; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder; WAGR, Wilms, aniridia, genitourinary anomalies, and retardation syndrome.
From Ripperger T, Bielack SS, Borkhardt A, et al. Childhood cancer predisposition syndromes – a concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet.* 2017;173:1017–1037, with data compiled from Porter CC, Druley TE, Erez A, et al. Recommendations for surveillance for children with leukemia-predisposing conditions. *Clin Cancer Res.* 2017;23(11):e14–e22.

Childhood cancer includes a diverse array of malignant tumors, termed "cancers," and nonmalignant tumors arising from disorders of genetic processes involved in control of cellular growth and development. Although many genetic conditions are associated with increased risks for childhood cancer, such conditions are believed to account for 8–10% of all occurrences (see Chapter 541). The most notable germline genetic conditions that impart susceptibility to childhood cancer are Li-Fraumeni *(P53)* syndrome, neurofibromatosis types 1 and 2, Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis, von Hippel-Landau disease, Noonan syndrome, ataxia-telangiectasia, and familial adenomatous polyposis syndrome and associated conditions (see Table 540.2). Consensus guidelines for surveillance screening in pediatric cancer predisposition syndromes were developed during a workshop of the Pediatric Cancer Working Group of the **American Association for Cancer Research** (AACR) and are available online through the AACR Open Access journal website (http://clincancerres.aacrjournals.org/content/23/11).

Compared with adult epithelial tumors, an extremely small fraction of pediatric cancers appears to be explained by known **environmental exposures** (see Table 540.2). Ionizing radiation exposure and several chemotherapeutic agents explain only a small number of pediatric cases (see Chapter 758). The association between fetal exposures and pediatric cancer is largely not established, with the exception of maternal diethylstilbestrol intake during pregnancy and subsequent vaginal adenocarcinoma in adolescent daughters. Environmental exposures that have been studied without convincing evidence for a causal role include nonionizing power frequency electromagnetic fields, pesticides, parental occupational chemical exposures, dietary factors, in vitro fertilization, and tobacco smoke exposure. Viruses associated with certain pediatric cancers include **polyomaviruses** (BK, JC, SV40) associated with brain cancer and **Epstein-Barr virus** (EBV) associated with certain subtypes of non-Hodgkin lymphoma.

The etiology of cancer in children still is poorly understood, and epidemiology studies demonstrate that the likely mechanisms are multifactorial, possibly resulting from potential interactions between genetic susceptibility traits and environmental exposures. Ongoing studies are investigating the role of **polymorphisms** of genes encoding enzymes, which function in the activation or metabolism of xenobiotics, protection of cells against oxidative stress, DNA repair, and/or immune modulation.

Curative therapy with chemotherapy, radiation, and/or surgery can adversely affect a child's development and result in serious long-term medical and psychosocial effects in childhood and adulthood. Potential adverse late effects include subsequent second malignancy, early mortality, infertility, reduced stature, cardiomyopathy, pulmonary fibrosis, osteoporosis, neurocognitive impairment, affective disorders, and altered social functioning (see Chapter 542). Much has been learned about the incidence of late effects from large, multisite cohort studies such as the **Childhood Cancer Survivor Study**, an ongoing study of medical and psychosocial outcomes in survivors, which has provided data for the development of clinical care guidelines for survivors (http://www.survivorshipguidelines.org).

Given the relative rarity of specific types of childhood cancer and the sophisticated technology and expertise required for diagnosis, treatment, and monitoring of late effects, all children with cancer should be treated with standardized clinical protocols in pediatric clinical research settings whenever possible. Promoting such treatment, the **Children's Oncology Group** is an international multi-institutional research consortium that facilitates cooperative clinical, biologic, and epidemiologic research in more than 200 affiliated institutions in the United States, Canada, and other countries (http://childrensoncologygroup.org/). Coordinated participation in such research trials has been a major factor in the increased survival for many children with cancer.

INFLUENCING THE INCIDENCE OF CANCER

There are only a few recognized environmental causes of childhood cancer that can be avoided or counteracted. One example is immunization against **hepatitis B**, which decreases the risk of hepatocellular carcinoma in adolescence and adulthood, and **human papillomavirus** vaccination, which prevents cervical cancer and HPV-positive oropharyngeal cancers and anal cancers. Associations between cumulative radiation exposure from common diagnostic radiologic tests such as CT scans and an increased risk of malignancy later in life are of great concern for pediatricians. Guidelines to ensure the safe clinical use of diagnostic imaging are being evaluated (http://www.imagegently.org/). An objective of pediatric medicine is *to teach children how to adopt healthy lifestyles to reduce their risk of cancer during adulthood,* such as avoiding tobacco, alcohol, high-fat diets, and obesity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 541

Molecular and Cellular Biology of Cancer

Kristopher R. Bosse and Stephen P. Hunger

Cancer is a complex of diseases arising from alterations that can occur in a wide variety of genes. Multiple pathogenic gene variants and other genetic aberrations, some germline but most acquired (somatic), are required for cells to become fully malignant. These genetic changes lead to alterations in normal cellular processes that control cell proliferation and survival, including signal transduction, cell-cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence, and apoptosis (programmed cell death).

GENES INVOLVED IN ONCOGENESIS

Two major classes of genes are implicated in the development of cancer: oncogenes and tumor-suppressor genes. **Protooncogenes** are cellular genes that are important for normal cellular function and code for various proteins, including transcription factors, growth factors, and growth factor receptors. These proteins are vital components in the networks of signal transduction that regulate cell growth, division, and differentiation. Protooncogenes can be altered to form **oncogenes**—genes that, when translated, can contribute to malignant transformation of a cell.

Oncogenes can be divided into five different classes based on their mechanisms of action. Changes in any of these normal cellular components can result in unchecked cell growth. Some oncogenes code for **growth factors** that bind to a receptor and stimulate the production of a protein. Other oncogenes code for **growth factor receptors**, which are proteins on the cell surface. When growth factors bind to a growth factor receptor, they can turn the receptor on or off. Pathogenic genetic variants or posttranslational modifications of the receptor can result in it being permanently turned on, with consequent unregulated growth. **Signal transducers** or effectors make up another class. Signal transducers are responsible for taking the signal from the cell surface receptor to the cell nucleus. **Transcription factors** are molecules that bind to specific areas of the DNA and control transcription. **MYC** and **MYCN** are examples of transcription factors that when activated by pathogenic variants or amplification cause overstimulation of cell division. The final class of oncogenes **interferes with apoptosis**, or programmed cell death. Cells that no longer respond to the signal to die can lead to uncontrolled cell proliferation.

The three main mechanisms by which protooncogenes are activated are **amplification**, **pathogenic variants**, and **translocation** or **interstitial deletion** (Table 541.1). *MYC* or *MYCN,* which code for proteins that regulate transcription, are examples of protooncogenes that are activated by amplification. Patients with neuroblastoma in which the *MYCN* gene is amplified 10-300–fold have a poorer clinical outcome. Point pathogenic genetic variants can also activate protooncogenes. The *NOTCH1* protooncogene codes for a membrane-bound receptor integral to cell fate and differentiation pathways during normal development that undergoes proteolytic cleavage on ligand-induced activation, so that the protein can enter the nucleus and activate target gene transcription. *NOTCH1* has pathogenic variants in approximately 75% of **T-cell acute lymphoblastic leukemias** (ALLs), resulting in a *constitutively activated* protein important in leukemogenesis.

The third mechanism by which protooncogenes become activated is chromosomal translocation or interstitial deletion. In some leukemias and lymphomas, transcription factor–controlling sequences are relocated adjacent to transcriptionally active T-cell receptors or immunoglobulin genes, resulting in dysregulated transcription of these genes and leukemogenesis. A prominent example are translocations that bring *c-MYC* under control of the immunoglobulin heavy-chain gene *(IGH)* or kappa *(IGκ)* or lambda *(IGλ)* light-chain genes in **Burkitt lymphoma**. Chromosomal translocations that join genes from two different chromosomes or interstitial deletions or inversions within a chromosome can also result in **fusion genes**; transcription of the fusion gene results in production of a chimeric protein with new and potentially oncogenic activity. Examples of cancers associated with fusion genes include the childhood solid tumors **Ewing sarcoma [t(11;22)]** and **alveolar rhabdomyosarcoma [t(2;13)** or **t(1;13)]**. These translocations result in novel messenger RNA transcripts that are useful as diagnostic markers. The best-described translocation in leukemia is the **Philadelphia chromosome t(9;22)**, which produces the BCR-ABL1 protein found in **chronic myelogenous leukemia** and specific subtypes of **ALL**. BCR-ABL1 is a constitutively active tyrosine kinase. In addition, the protein is localized to the cytoplasm instead of the nucleus, exposing the kinase to a new spectrum of substrates.

Alteration in the regulation of **tumor-suppressor genes** is another mechanism involved in oncogenesis. Tumor-suppressor genes are important regulators of cellular growth and apoptosis. They have been called *recessive* oncogenes because the inactivation of both alleles of a tumor-suppressor gene is typically required for expression of a malignant phenotype.

Knudson's "2-hit" model of cancer development was based on the eye tumor **retinoblastoma** developing at a significantly younger age in children with the familial versus the sporadic form of the disease, and that tumors were often multifocal in familial cases but were almost always unifocal in sporadic cases. Knudson postulated that sporadic cases of retinoblastoma required somatic pathogenic variants to inactivate both copies of a gene, whereas in familial cases, children must inherit an inactivated allele from one parent and consequently only require the somatic inactivation of the remaining normal allele. This hypothesis was confirmed 15 years later following the discovery of the ***RB*** tumor-suppressor gene.

Another major tumor-suppressor protein is **TP53**, which is known as the "guardian of the genome" because it detects the presence of chromosomal damage and prevents the cell from dividing until repairs have been made. In the presence of damage beyond repair, TP53 initiates apoptosis and the cell dies. More than 50% of all tumors have abnormal TP53 proteins. Pathogenic variants in the *TP53* gene are important in many cancers, including breast, colorectal, lung, esophageal, stomach, ovarian, and prostatic carcinomas, as well as gliomas, sarcomas, and some leukemias.

SYNDROMES PREDISPOSING TO CANCER

Several syndromes are associated with an increased risk of developing malignancies, which can be characterized by different mechanisms (Table 541.2). One mechanism involves the *inactivation of tumor-suppressor genes* such as *RB* in **familial retinoblastoma**. Interestingly, patients with retinoblastoma in which one of the alleles is inactivated throughout the patient's body are also at a very high risk for developing osteosarcoma. A familial syndrome, **Li-Fraumeni syndrome**, in which one *TP53* pathogenic variant allele is inherited, also has been described in patients who develop sarcomas, leukemias, adrenocortical carcinoma, and cancers of the breast, bone, lung, and brain. **Neurofibromatosis** (NF) is a condition characterized by the proliferation of cells of neural crest origin. NF patients are at a higher risk of developing nervous system tumors, breast cancer, leukemia, pheochromocytomas, and other tumors. NF is inherited in an autosomal dominant manner, although 50% of cases present without a family history and occur secondary to the high rate of spontaneous pathogenic variants of the *NF1* gene.

A second mechanism responsible for an inherited predisposition to develop cancer involves *defects in DNA repair.* Syndromes associated with an excessive number of broken chromosomes caused by repair defects include **Bloom syndrome** (short stature, photosensitive telangiectatic erythema), **ataxia-telangiectasia** (childhood ataxia with progressive neuromotor degeneration, ocular telangiectasias), and **Fanconi anemia** (short stature, skeletal and renal anomalies, pancytopenia). As a result of the decreased ability to repair chromosomal defects, cells accumulate

Table 541.1 Oncogene Activators of Pediatric Tumors

MECHANISM	CHROMOSOME	GENES	PROTEIN FUNCTION	TUMOR
Chromosomal translocation	t(9;22)	*BCR::ABL1*	Chimeric tyrosine kinase	CML, ALL
	t(1;19)	*TCF3 (E2A)::PBX1*	Chimeric transcription factor	ALL
	t(8;14)	*MYC::IGH*	Transcription factor	Burkitt lymphoma
	t(15;17)	*PML::RARA*	Chimeric transcription factor	APML
	11q23 and others (over 50 fusions partners)	*KMT2A (MLL)*	Regulation of gene expression	Infant leukemia, ALL, AML, treatment-related leukemias
	t(12;21)	*ETV6::RUNX1*	Chimeric protein	ALL
	t(2;13) or t(1;13)	*PAX3* or *PAX7::FOXO1*	Transcription factor	Rhabdomyosarcoma
	t(11;22)	*EWS::FLI1*	Transcription factor	Ewing sarcoma
Gene amplification	2p	*MYCN*	Transcription factor	Neuroblastoma
	7p	*EGFR*	Growth factor receptor, tyrosine kinase	Glioblastoma, lung cancer
Point pathogenic gene variant	1p or 12p	*NRAS* or *KRAS*	Guanosine triphosphatase	AML, ALL, JMML, rhabdomyosarcoma, neuroblastoma
	10q	*RET*	Tyrosine kinase	MEN2
	2p	*ALK*	Tyrosine kinase	Neuroblastoma
	9q	*NOTCH1*	Transmembrane receptor	ALL

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; JMML, juvenile myelomonocytic leukemia; MEN2, multiple endocrine neoplasia, type 2.

Table 541.2 Familial or Genetic Susceptibility to Malignancy

DISORDER	TUMOR/CANCER	COMMENT
CHROMOSOMAL DELETION/ANEUPLOIDY SYNDROMES		
Chromosome 11p13 deletion syndrome	Wilms tumor	Also known as WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, mental retardation); deletion typically includes *WT1* gene
Chromosome 13q14 deletion syndrome	Retinoblastoma, sarcoma	Associated with intellectual disability, characteristic craniofacial abnormalities; deletion typically includes *RB1* gene
Trisomy 21	ALL, AML, AMKL, TMD	Risk of ALL is increased 20-fold, risk of AMKL is increased 500-fold; high cure rates; more prone to chemotherapy toxicity; AMKL associated with *GATA1* pathogenic variants
Klinefelter syndrome (47,XXY)	Breast cancer, extragonadal germ cell tumors	
Trisomy 8	Myeloid neoplasms	Most commonly mosaic trisomy 8
Monosomy 5 or 7	AML, MDS	
CHROMOSOMAL INSTABILITY SYNDROMES		
Xeroderma pigmentosum	Basal cell and squamous cell carcinomas, melanoma	Autosomal recessive; failure to repair UV-damaged DNA; *XP/POLH* pathogenic variants
Fanconi anemia	AML, MDS, rare head, neck, and skin tumors, GI and GU cancers	Autosomal recessive; chromosome fragility; positive diepoxybutane (DEB) test result; pathogenic variants in *FANCX* gene family (includes at least 21 members)
Bloom syndrome	AML, MDS, ALL, lymphoma, and solid tumors	Associated with growth deficiency, malar rash; autosomal recessive; increase sister chromatid exchange (SCE); pathogenic variants in *BLM* gene; member of the RecQ helicase gene (unwinds DNA)
Ataxia-telangiectasia	Lymphoma, leukemia, less often central nervous system and other solid tumors	Associated with progressive ataxia, oculocutaneous telangiectasias; autosomal recessive; sensitive to radiation-induced DNA damage; increased risk of treatment-related morbidity; biallelic pathogenic variant in *ATM* tumor-suppressor gene
Nijmegen breakage syndrome	Leukemia, lymphoma	Associated with microcephaly, characteristic facies, immunodeficiency; biallelic pathogenic variants in *NBN* gene
Werner syndrome (progeria)	Soft tissue sarcomas, osteosarcoma, melanoma	Associated with accelerated aging; autosomal recessive; pathogenic variants in *WRN* gene

Table 541.2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
IMMUNODEFICIENCY SYNDROMES		
Wiskott-Aldrich syndrome	Lymphoma, leukemia	Associated with thrombocytopenia, eczema, and recurrent infections; X-linked recessive; *WASP* pathogenic variants
X-linked lymphoproliferative syndrome (XLP)	B-cell lymphoproliferative disease, lymphomas, HLH	Associated with fulminant and often fatal EBV infection; X-linked; pathogenic variants in the *SH2D1A* gene
X-linked agammaglobulinemia (XLA)	Lymphoproliferative disorders, colorectal cancer	Associated with absence of B cells; X-linked; pathogenic variants in *BTK* gene
Severe combined immunodeficiency (SCID)	Leukemia, lymphoma	X-linked or autosomal recessive; pathogenic variants in *IL2RG* and *ADA* genes
SYNDROMES ARISING FROM PATHOGENIC VARIANTS IN TUMOR SUPRESSORS OR ONCOGENES		
Neurofibromatosis 1	Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, rhabdomyosarcoma, MPNST, neuroblastoma, leukemias	Associated with café-au-lait macules, axillary/inguinal freckling, Lisch nodules; autosomal dominant; pathogenic variants in tumor-suppressor gene *NF1*
Neurofibromatosis 2	Bilateral acoustic neuromas, meningiomas	Autosomal dominant; pathogenic variants in tumor-suppressor gene *NF2*
Tuberous sclerosis	Facial angiofibromas, renal cell carcinoma, renal angiomyolipomas, myocardial rhabdomyoma	Autosomal dominant; pathogenic variants in tumor-suppressor gene *TSC1* or *TSC2*
Noonan syndrome	JMML, ALL, neuroblastoma, brain tumors	Associated with distinct facial features, short stature, and heart defects; autosomal dominant; caused by RAS/MAPK pathway pathogenic variants (most frequently *PTPN11*)
Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome)	Multiple basal cell carcinomas, medulloblastoma	Associated with odontogenic keratocysts, skeletal and skin anomalies; autosomal dominant; pathogenic variants in *PTCH1 or SUFU* gene
Li-Fraumeni syndrome	Osteosarcoma, soft tissue sarcoma, acute leukemias, breast and brain cancer, adrenal cortical tumors	Autosomal dominant; pathogenic variants in *TP53* tumor-suppressor gene
Beckwith-Wiedemann syndrome (BWS)	Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma	Associated with macrosomia, macroglossia, hemihypertrophy, omphalocele; epigenetic/genomic alterations of chromosome 11p15
Von Hippel-Landau syndrome	Hemangioblastomas of the brain and retina, pheochromocytoma, renal cell carcinoma	Autosomal dominant; pathogenic variants of tumor-suppressor *VHL* gene
Multiple endocrine neoplasia, type 1 (Wermer syndrome)	Parathyroid, pancreatic islet cell and pituitary tumors	Associated with hyperparathyroidism, ZES; autosomal dominant; pathogenic variants in *MEN1* tumor-suppressor gene
Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)	Medullary thyroid carcinoma, parathyroid tumors, pheochromocytoma	Associated with hyperparathyroidism; autosomal dominant; pathogenic variants in *RET* gene
Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)	Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma	Associated with Marfan habitus, neuropathy; autosomal dominant; pathogenic variants in *RET* gene
Familial adenomatous polyposis (FAP)	Colorectal, thyroid, stomach and small intestinal cancer, hepatoblastoma	Associated with multiple colon polyps; autosomal dominant; pathogenic variants in *APC* gene
Juvenile polyposis syndrome	Colorectal, stomach, small intestinal and rectal cancer	Autosomal dominant; pathogenic variants in *BMPR1A* and *SMAD4* gene
Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome)	Colorectal cancer, endometrial and stomach cancer, many other cancers	Autosomal dominant; pathogenic variants in DNA mismatch repair genes *MSH2, MLH1, PMS1, PMS2,* and *MSH6*
Turcot syndrome	Colorectal cancer, brain tumors (glioblastoma, medulloblastoma)	Autosomal dominant; pathogenic variants in *APC* or *MLH1* gene
Gardner syndrome	Colorectal cancer, other tumors similar to FAP	Subtype of FAP; autosomal dominant; pathogenic variants in *APC* gene
Constitutional mismatch repair deficiency syndrome (CMMRD)	Many different types of hematologic malignancies and brain and CNS tumors, colorectal carcinomas, and several other rare tumors	Autosomal recessive; homozygous germline pathogenic variants in the *MLH1, MSH2, MSH6,* or *PMS2* genes; tumors with very high variant burden, pathogenic variants of only one allele of the same genes results in Lynch syndrome
Peutz-Jeghers syndrome	Breast cancer, colorectal cancer, pancreatic cancer	Associated with hamartomatous polyps of GI tract; freckling of mouth, lips, fingers, and toes; autosomal dominant; pathogenic variants in *STK11* gene

Continued

Table 541.2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
Hereditary hemochromatosis	Hepatocellular carcinoma	Autosomal dominant; pathogenic variants in the *HFE* gene; malignancy associated with cirrhotic liver
Glycogen storage disease type 1 (von Gierke disease)	Hepatocellular carcinoma, liver adenomas	Autosomal recessive; pathogenic variants in *G6PC* or *SLC37A4* gene
Diamond-Blackfan anemia (DBA)	Colorectal and other GI cancers, AML, MDS, osteogenic sarcoma	Autosomal dominant; pathogenic variants in the small or large subunit-associated ribosomal protein genes (most often *RPS19*)
Shwachman-Diamond syndrome	AML, MDS	Associated with neutropenia, diarrhea, and failure to thrive; autosomal recessive; pathogenic variants in *SBDS* gene
DICER1 syndrome	Pleuropulmonary blastoma (PPB), cystic nephromas, ovarian Sertoli-Leydig tumors, multinodular goiter	Autosomal dominant; associated with pathogenic variants in *DICER1* gene
Familial neuroblastoma	Neuroblastoma	Autosomal dominant; pathogenic variants in *ALK* or *PHOX2B* gene
Hereditary paraganglioma-pheochromocytoma syndrome (PGL/PCC)	PGL, PCCs	Autosomal dominant; pathogenic variants in the mitochondrial enzyme succinate dehydrogenase protein family (*SDHA, B, C,* or *D*)
Severe congenital or cyclic neutropenia	AML, MDS	Associated with increased bacterial infections; typically autosomal dominant; pathogenic variants in *ELANE* or *HAX1* (Kostmann syndrome) gene
Rhabdoid predisposition syndrome 1 and 2	Atypical teratoid rhabdoid tumors, rhabdoid tumor of kidney, medulloblastoma, choroid plexus tumor	*SMARCB1/SMARCA4* tumor suppression genes
Predisposition to medulloblastoma	Medulloblastoma	*SUFU,* tumor suppression gene
Rothmund-Thomson syndrome	Skin, bone	*ANAPC1/RECQL4* stability gene
Multiple exostosis	Chondrosarcoma	*EXT1/EXT2,* tumor suppression gene
PTEN Hamartoma tumor syndromes: Cowden, Bannayan-Riley-Ruvalcaba, proteus, proteus-like syndromes	Breast, thyroid, renal, colon, melanoma	*PTEN, AKT1, PIK3CA, AKT3, PIK3R2, WWP1* germline or somatic pathogenic variants
BRCA1/2	Brain, solid tumors in children	Heterozygous pathogenic variants increase risk

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; AMKL, acute megakaryocytic leukemia; CNS, central nervous system; EBV, Epstein-Barr virus; GI, gastrointestinal; GU, genitourinary; HLH, hemophagocytic lymphohistiocytosis; JMML, juvenile myelomonocytic leukemia; MAPK, mitogen-activated protein kinase; MDS, myelodysplastic syndrome; MPNST, malignant peripheral nerve sheath tumor; PTEN, phosphatase and tensin homolog; TMD, transient myeloproliferative disorder; UV, ultraviolet; ZES, Zollinger-Ellison syndrome.

abnormal DNA that results in significantly increased rates of cancer, especially leukemia. **Xeroderma pigmentosum** likewise increases the risk of skin cancer because of defects in repair to DNA damaged by ultraviolet light. **Constitutional mismatch repair deficiency syndrome** (CMMRD) is a disorder that results from the loss of both alleles of genes integral in repairing errors that occur during DNA replication, leading to the accumulation of multiple potentially pathogenic genetic alterations. These disorders display an autosomal recessive pattern.

The third category of inherited cancer predisposition is characterized by *defects in immune surveillance.* This group includes patients with **Wiskott-Aldrich syndrome**, severe combined immunodeficiency, common variable immunodeficiency, and the X-linked lymphoproliferative syndrome. The most common types of malignancy in these patients are lymphoma and leukemia. Cure rates for immunodeficient children with cancer are much poorer than for immunocompetent children with similar malignancies, suggesting a role for the immune system in cancer treatment as well as in cancer prevention.

Genome-wide association studies (GWAS) in a diverse array of childhood tumors, including ALL and neuroblastoma, have defined common **single nucleotide polymorphisms (SNPs)** in genes that are associated with cancer predisposition and collectively define regions of the genome that are critical in tumorigenesis. These alterations may occur in the coding or noncoding regions of the genome and typically lead to a relatively modest increase in cancer risk (2-10–fold over background) compared to the cancer susceptibility syndromes previously discussed, which may be associated with a lifetime risk of 50–100% of developing cancer. Furthermore, **whole genome sequencing** efforts across diverse pediatric cancers have identified that at least 8% of children who develop malignancy have a germline cancer-predisposing gene pathogenic variant. Many of these predisposing pathogenic variants occur in children without a family history of cancer or a known cancer predisposition syndrome.

OTHER FACTORS ASSOCIATED WITH ONCOGENESIS

Viruses

Several viruses have been implicated in the pathogenesis of malignancy. The association of the **Epstein-Barr virus (EBV)** with Burkitt lymphoma and nasopharyngeal carcinoma was identified more than 40 years ago, although EBV infection alone is not sufficient for malignant transformation. EBV is also associated with mixed cellularity and lymphocyte-depleted Hodgkin disease, as well as some T-cell lymphomas, which is particularly intriguing because EBV normally does not infect T lymphocytes. The most conclusive evidence for a role of EBV in lymphogenesis is the direct causal role of EBV for **B-cell lymphoproliferative disease** in immunocompromised persons, especially those with HIV infection or those receiving immunosuppression after organ

transplantation. **Human herpesvirus 8 (HHV-8)** is associated with the development of Kaposi sarcoma.

Children who are chronically infected with **hepatitis B virus** (hepatitis B surface antigen positive) have a 100-fold increased risk of developing **hepatocellular carcinoma**. In adults the latency period between viral infection and development of hepatocellular carcinoma approaches 20 years. However, in children who acquire the viral infection through perinatal transmission, the latency period can be as short as 6-7 years. The additional factors that are required for the malignant transformation of virally infected hepatocytes are not clear. **Hepatitis C virus** infection is another risk factor for hepatocellular carcinoma and is also associated with a subset of B-cell non-Hodgkin lymphomas such as splenic lymphoma.

Almost all cervical carcinomas are caused by **human papillomaviruses (HPVs)**. High-risk HPVs include types 16 and 18 but also types 31, 33, 34, 45, 52, and 58, which together cause >90% of cervical cancers. Vaccines against the major oncogenic subtypes are now available and are likely to save hundreds of millions of lives worldwide. The low-risk HPVs, including 6 and 11, which are commonly found in genital warts, are almost never associated with malignancies. Like other virus-associated cancers, the presence of HPV alone is not sufficient to cause malignant transformation. The mechanism by which the HPV-associated **oncoproteins HPV E6** and **E7** induce malignant transformation is thought to involve both the TP53 and the RB tumor-suppressor proteins, as well as other pathways that are critical in cell cycle progression, maintenance of telomerase and genomic stability, and apoptosis.

Radiation

Children who are exposed to ionizing radiation, either via environmental factors or from medical diagnostics or treatment, are also at an increased of developing cancer over their lifetime, especially leukemias, brain, breast, skin, or thyroid malignancies. This increased pediatric cancer risk is likely due both to the enhanced radiosensitivity of the developing organs of children and their longer postexposure life expectancy. Diagnostic imaging (e.g., CT scans) and therapeutic radiation for children with cancer are a major source of childhood radiation exposure. However, CT scan dose-reduction strategies, the increased use of MRI in pediatric medical centers, and the shift in therapeutic practice in oncology to proton radiotherapy all have been integral in lowering the exposure of children to ionizing radiation.

Genomic Imprinting

The development of cancer has also been linked to *genomic imprinting*, which is the selective inactivation of one of two alleles of certain genes depending on parental origin. **Beckwith-Wiedemann syndrome (BWS)** (see Chapter 113), the most commonly identified imprinting disorder, is an overgrowth syndrome characterized by macrosomia, macroglossia, hemihypertrophy, omphalocele, and renal anomalies that is also associated with an increased risk of Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma, and adrenocortical carcinoma. This increased risk in developing cancer is directly associated with changes in the promoter methylation patterns (or loss of heterozygosity) of imprinted genes on chromosome 11p15.5. Normally, the maternally derived *IGF2* (insulin-like growth factor receptor 2) allele at this genomic locus is inactivated, thus suppressing *IGF2* expression. However, children with BWS show a gain of methylation in this promoter region, which allows for expression from both maternal and paternal *IGF2* alleles, leading to growth factor overexpression. Concurrently, the neighboring maternal *H19* gene (which encodes ncRNA and miRNA critical in growth suppression) is silenced by this hypermethylation, ultimately resulting in a progrowth phenotype and predisposition to tumor development.

Telomerase

Telomeres are a series of tens to thousands of TTAGGG DNA sequence repeats at the ends of chromosomes that are important for stabilizing the chromosomal ends and limiting breakage, translocation, and loss of DNA material. With DNA replication there is a progressive shortening of telomere length, which is a hallmark of cellular aging and acts as a replicative senescence signal. In a majority of cancers, **telomerase** (encoded by the *TERT* gene), an enzyme that adds telomeres to the ends of chromosomes, becomes activated, usually through pathologic variants in the *TERT* promoter. The telomerase-driven maintenance of telomere length in tumors enables unrestrained cellular proliferation by relieving a main checkpoint to cellular life span.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 542

Principles of Cancer Diagnosis

Julia C. Meade, Erika D. Friehling, and A. Kim Ritchey

Childhood cancer is uncommon and can manifest with symptoms seen with nonmalignant illnesses. The challenge for the pediatrician is to be alert to the clues suggesting a diagnosis of cancer. In addition to the classic manifestations, any persistent, unexplained symptom or sign should be evaluated as potentially emanating from a cancerous or precancerous condition.

SIGNS AND SYMPTOMS

The symptoms and signs of cancer are variable and nonspecific in pediatric patients. The types of cancer that occur during the first 20 years of life vary dramatically as a function of age—more so than at any other comparable age range (see Chapter 540). Unlike cancers in adults, childhood cancers usually originate from the deeper, visceral structures and from the parenchyma of organs rather than from the epithelial layers that line the ducts and glands of organs and compose the skin. In children, dissemination of disease at diagnosis is common, and presenting symptoms or signs are often caused by systemic involvement. **Pain was one of the initial presenting symptoms in >50% of children with cancer in one study.** Infants and young children cannot express or localize their symptoms well.

Solid tumors may produce **mass effects** that are nonspecific, such as compression of the thoracic airways or superior vena cava (lymphoma), the optic chiasm and hypothalamic-pituitary region (craniopharyngioma), and the fourth ventricle (cerebellar astrocytoma). Another factor is the variability in the physiology and biology of the host related to growth and development during infancy, childhood, and adolescence.

The signs of cancer in children are often attributed to other causes before the malignancy is recognized. Delays in diagnosis are particularly problematic during late adolescence and are the result of a variety of factors prominent in this age-group, including historic lack and complexity of health insurance coverage.

Although there is no clearly established set of warning signs of cancer in young people, the most common cancers in children suggest some guidelines that may be helpful in early recognition of signs and symptoms of cancer (Table 542.1). Most of the symptoms and signs are not specific and might represent other possibilities in a differential diagnosis. Nonetheless, these clues encompass the common cancers of childhood and have been very useful in early detection.

PHYSICAL EXAMINATION

Physical examination findings in a child with malignancy are dependent on whether the cancer is systemic or localized. The cancers most common in children involve the lymphoid and hematopoietic system. When the bone marrow is compromised by malignancy (e.g., leukemia, disseminated neuroblastoma), typical findings include pallor from anemia; bleeding, petechiae, or purpura from thrombocytopenia or coagulopathy; cellulitis or other localized infection from leukopenia; and skin nodules (especially in infants) and hepatosplenomegaly

Table 542.1 Common Manifestations of Childhood Malignancies

	SIGNS AND SYMPTOMS	POTENTIAL ETIOLOGY AND POSSIBLE DIAGNOSIS
Constitutional/ systemic	Fever, persistent or recurrent infection, neutropenia	Bone marrow infiltration from leukemia, neuroblastoma
	Fever of unknown origin, weight loss, night sweats	Hodgkin and non-Hodgkin lymphoma
	Painless, persistent lymphadenopathy	Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma
	Hypertension	Renal or adrenal tumor such as neuroblastoma, pheochromocytoma, or Wilms tumor
	Soft tissue mass	Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis
	Pain	Bone marrow involvement (ALL) or metastatic disease (neuroblastoma), primary bone tumors, Langerhans cell histiocytosis
Neurologic/ ophthalmologic	Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies	Increased intracranial pressure from primary brain tumor or metastasis
	Leukocoria (white pupil)	Retinoblastoma
	Periorbital ecchymosis	Neuroblastoma
	Miosis, ptosis, heterochromia	Horner syndrome: compression of cervical sympathetic nerves from neuroblastoma
	Opsoclonus myoclonus, ataxia	Paraneoplastic syndrome from neuroblastoma
	Exophthalmos, proptosis	Mass effect from rhabdomyosarcoma, lymphoma, or Langerhans cell histiocytosis
Respiratory/ thoracic	Cough, stridor, pneumonia, tracheal-bronchial compression; superior vena cava syndrome	Anterior mediastinal mass due to germ cell tumor, non-Hodgkin lymphoma, or Hodgkin lymphoma
	Vertebral or nerve root compression; dysphagia	Posterior mediastinal mass from neuroblastoma or Ewing sarcoma
Gastrointestinal	Abdominal mass	Neuroblastoma, Wilms tumor, lymphoma
	Diarrhea	Vasoactive intestinal peptide secretion from neuroblastoma, ganglioneuroma
Hematologic	Pallor, anemia	Bone marrow infiltration from leukemia, neuroblastoma
	Petechiae, thrombocytopenia	Bone marrow infiltration from leukemia, neuroblastoma
Musculoskeletal	Bone pain, limp, arthralgia	Osteosarcoma, Ewing sarcoma, leukemia, metastatic neuroblastoma
Endocrine	Diabetes insipidus	Pituitary tumor, Langerhans cell histiocytosis
	Poor growth	Diencephalic syndrome from hypothalamic tumor
	Galactorrhea	Pituitary tumor/prolactinoma
	Precocious puberty	Germ cell tumor (cranial or extracranial), adrenocortical carcinoma, hepatoblastoma

ALL, Acute lymphoblastic leukemia
Adapted from Marcdante KJ, Kliegman RM, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011. p. 588.

from malignant leukocytosis. Abnormalities found in lymphatic malignancies include peripheral **adenopathy** (Fig. 542.1) and signs of superior vena cava syndrome from an anterior **mediastinal mass** (Fig. 542.2), including respiratory distress, and facial and neck plethora and edema. Enlargement of cervical lymph nodes is common in children, but when persistent, progressive, and painless, it often suggests **lymphoma**. Supraclavicular adenopathy suggests underlying malignancy.

Abnormalities of the central nervous system (CNS) that can indicate cancer include headaches, vomiting, cranial nerve palsies, ataxia, afebrile seizures, ptosis, decreased visual activity, neuroendocrine deficits, and increased intracranial pressure, which may be diagnosed by the presence of papilledema (Fig. 542.3). Any focal neurologic deficit in the motor or sensory system, especially a decrease in cranial nerve function, should prompt further investigation for malignancy.

Ophthalmologic presentation of malignancy includes a **white pupillary reflex** (Fig. 542.4) rather than the usual red reflection from incident light. A white pupillary reflex is essentially pathognomonic for retinoblastoma, although some benign conditions can mimic this finding. **Proptosis** can be produced by rhabdomyosarcoma, neuroblastoma, lymphoma, and Langerhans cell histiocytosis. In the few first years of life, Horner syndrome, periorbital ecchymosis, iris heterochromia, and opsoclonus-myoclonus all suggest a diagnosis of neuroblastoma.

Abdominal masses can be divided into upper and lower locations. Malignancies in the upper abdomen include Wilms tumor, neuroblastoma, and hepatoblastoma. Enlargement of the liver or spleen

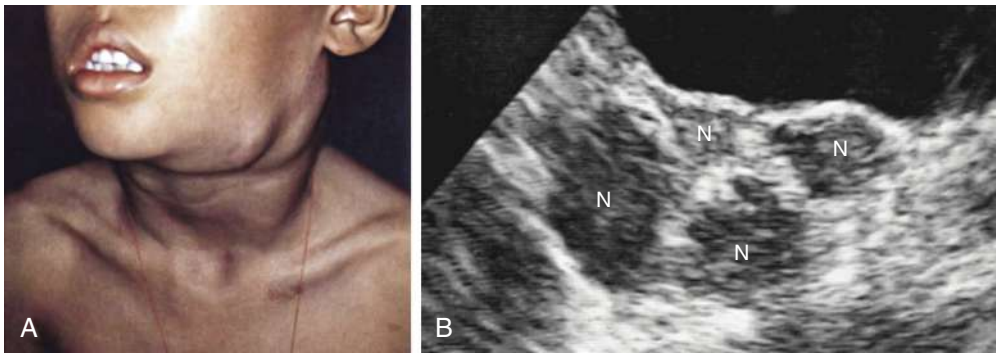

Fig. 542.1 Cervical lymphadenopathy. Manifestations on physical examination (**A**), and ultrasound examination (**B**). N, Abnormally enlarged lymph nodes. *(From Sinniah D, D'Angio GJ, Chatten J, et al. Atlas of Pediatric Oncology. London: Arnold; 1996.)*

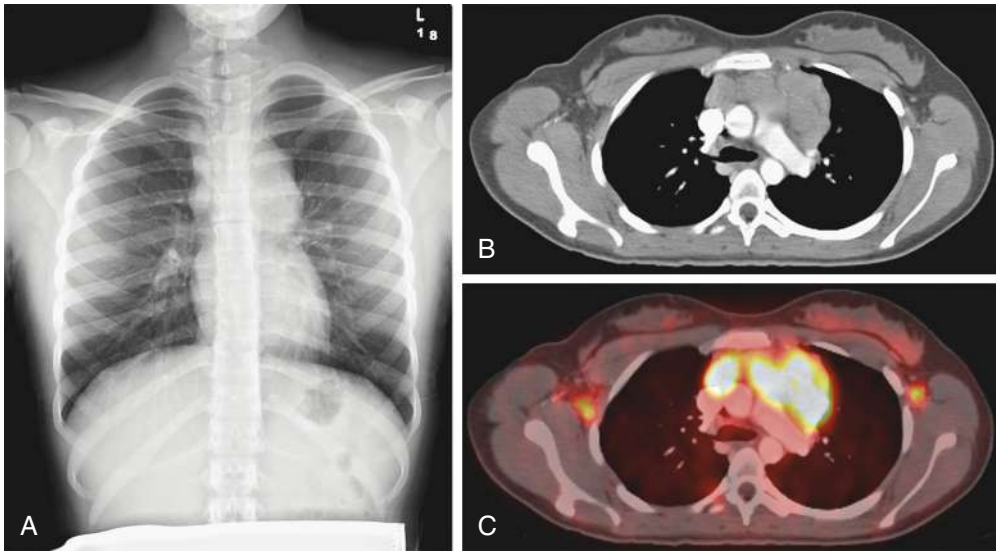

Fig. 542.2 Anterior upper mediastinal mass from non-Hodgkin lymphoma. **A,** Plain chest radiograph. **B,** CT scan. **C,** PET scan.



Fig. 542.3 Papilledema on fundoscopic examination. *(From Sinniah D, D'Angio GJ, Chatten J, et al. Atlas of Pediatric Oncology. London: Arnold; 1996.)*



Fig 542.4 White pupillary reflex in the left eye. *(From Sinniah D, D'Angio GJ, Chatten J, et al. Atlas of Pediatric Oncology. London: Arnold; 1996.)*

from leukemia can be mistaken for an upper abdominal mass. Lower abdominal masses non-Hodgkin lymphoma, neuroblastoma, germ cell tumors (ovarian), and sarcomas.

Rhabdomyosarcoma can occur as an extremity mass, particularly in adolescents, but also as a mass in the head and neck region (e.g., orbit, nasopharynx, and others). These tumors can be deceptively benign in

appearance, but as with all unexplained masses, require immediate attention. Sacrococcygeal masses in neonates are usually **teratomas**, which are usually benign but can undergo malignant transformation if not removed promptly. **Neuroblastoma** can present as "blueberry muffin" spots on the skin of neonates or as periorbital ecchymosis in older children.

AGE-RELATED MANIFESTATIONS

Because various types of cancer in children occur at specific ages, the physician should tailor the history and physical examination based on the age of the child. The **embryonal tumors**, including neuroblastoma, retinoblastoma, and hepatoblastoma usually occur during the first 2 years of life (see Fig. 540.4). The peak age for presentation of **Wilms tumor** is 3-4 years. Two thirds of patients with **rhabdomyosarcoma** present before age 6 with another smaller peak in adolescence. From 1-4 years of age, **acute lymphoblastic leukemia** peaks in incidence. **Brain tumors** have a peak incidence in the first decade of life. **Non-Hodgkin lymphomas** are uncommon earlier than 5 years of age but steadily increase thereafter. During adolescence, bone tumors, Hodgkin lymphoma, and gonadal and soft tissue sarcomas predominate. Hence, for infants and toddlers, special attention should be paid to the possibility of embryonal and intraabdominal tumors. Preschool-age and early school-age children showing compatible signs and symptoms should be specifically evaluated for **leukemia**. School-age children might present with lymphoma or with brain tumors. Adolescents require assessment for bone and soft tissue sarcomas and gonadal malignancies, as well as for Hodgkin lymphoma.

EARLY DETECTION

The prognosis of malignancy in children depends primarily on tumor type, extent of disease at diagnosis, and rapidity of response to treatment. Early diagnosis helps to ensure that appropriate therapy is given in a timely manner and thus optimizes the chances of cure. Because most physicians in general practice rarely encounter children with undiagnosed cancer, they should remember to investigate the possibility of malignancy, especially when they encounter an atypical course of a common childhood condition, unusual manifestations that do not fit common conditions, and any persistent symptom that defies diagnosis. It is also good practice to obtain a three-generation family pedigree with specific attention to a family history of cancer. A strong family history of cancer would suggest a referral for a cancer predisposition evaluation.

Delays in diagnosis are particularly likely in certain clinical situations. The cardinal symptom of both **osteosarcoma** and **Ewing sarcoma** is localized and usually persistent pain. Because these tumors occur during the second decade of life, a time of increased physical activity, patients often assume the pain results from trauma. Prompt radiologic evaluation can help confirm the diagnosis. **Lymphoma**, especially during adolescence, often manifests as an anterior mediastinal mass. Symptoms such as chronic cough, unexplained shortness of breath, or "new-onset asthma" are typical with this presentation and are often overlooked. Tumors of the nasopharynx or middle ear can mimic infection. Prolonged, unexplained ear pain, nasal discharge, retropharyngeal swelling, and trismus should be investigated as possible signs of malignancy.

Early symptoms of **leukemia** may be limited to prolonged or unexplained low-grade fever. Bone and joint pain may present with refusal to walk. Blood counts with abnormalities in two or more cell lines might indicate the need for bone marrow examination, even when leukemic blast cells are not seen in the blood smear (see Table 542.1).

Mass screening for children with malignancy is not feasible. A screening program to detect early-stage neuroblastoma was successful in documenting more cases of the disease but had no impact on overall outcome. However, certain children are at increased risk for cancer and require an individualized plan to ensure early detection of malignancy. Select examples include children with certain chromosome abnormalities, such as Down syndrome, Klinefelter syndrome, and WAGR syndrome (Wilms tumor, *a*niridia, *g*enital abnormalities, mental *r*etardation); children with overgrowth syndromes, such as Beckwith-Wiedemann syndrome or hemihypertrophy; and children with certain inherited single-gene disorders, including hereditary retinoblastoma, Li-Fraumeni syndrome, familial adenomatous polyposis, and neurofibromatosis (see Table 541.2).

ENSURING THE DIAGNOSIS

When a malignant neoplasm is suspected, the immediate goal is to confirm the diagnosis. A tentative diagnosis can often be established based on the patient's age, symptoms, and location of masses. Selected imaging techniques and tumor markers can facilitate the diagnostic approach (Table 542.2 and Fig. 542.5). Especially when a solid tumor is present, the pediatric oncologist, surgeon, and pathologist should work as a team to determine the site of biopsy, amount of tissue required, and whether percutaneous image-guided biopsy, incisional biopsy, or excisional biopsy and tumor resection are indicated. For select situations, at the time of the initial diagnostic procedure, plans for bone marrow aspiration and biopsy and placement of central venous access may be appropriate.

Pathologic evaluation of pediatric malignancies requires appropriate handling of tissue so that multiple different techniques can be used to obtain a diagnosis. It is important that some fresh tissue not be placed in formalin. Along with routine light microscopy, pathologic evaluation may include immunochemistry, flow cytometry, cytogenetics, molecular genetic studies (e.g., fluorescence in situ hybridization, tumor whole exome sequencing, and evaluation of circulating tumor genes with cell-free DNA detection in blood). Additional technologies include DNA microarray analysis and cancer genome sequencing that can identify specific gene expression patterns and sequences in tumors, which can facilitate more accurate classification and treatment.

STAGING

Once a specific diagnosis is confirmed, studies to define the extent of the malignancy are necessary to determine prognosis and treatment. Table 542.2 outlines the minimum evaluation required for common pediatric malignancies. In addition, for many tumors (e.g., Wilms tumor, neuroblastoma, rhabdomyosarcoma), a surgical staging system is used. Surgical stage can be determined at the time of the initial diagnostic procedure or subsequently. For example, a patient who has abdominal surgery for possible Wilms tumor should have careful evaluation and biopsy of all adjacent lymph nodes. A child with rhabdomyosarcoma can require a subsequent biopsy of sentinel lymph nodes as determined by scintigraphy or dye injection adjacent to the primary tumor. The pathologist facilitates staging by examining margins of the specimen to determine residual tumor.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 542.2 Workup of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY FILM	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Leukemia	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	—	—	—	—	Yes	—	—
Non-Hodgkin lymphoma	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	Yes	—	Yes	Yes (selected cases)	Yes	—	—
Hodgkin lymphoma	Yes (in advanced stage)	Yes	Yes	—	Yes	—	—	—	—
CNS tumors	—	—	—	Yes	—	—	Yes (selected cases)	Yes (selected cases)	—
Neuroblastoma	Yes (includes cytogenetics, molecular studies)	—	Yes	Yes	—	—	—	Urine VMA, HVA	MIBG or PET scan; bone x-rays
Wilms tumor	—	Yes	Yes	—	—	—	—	—	—
Rhabdomyo-sarcoma	Yes	Yes	Yes	Yes (select sites)	—	Yes (selected cases)	Yes (for paramenin-geal tumors only)	—	—
Osteosarcoma	—	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes (selected cases)	—	—	—
Ewing sarcoma	Yes (selected cases)	Yes	Yes (of chest)	Yes (for primary tumors)	Yes	Yes (selected cases)	—	—	—
Germ cell tumors	—	Yes	Yes	Consider MRI of brain	—	—	—	AFP, HCG	—
Liver tumors	—	Yes	Yes	—	—	—	—	AFP, HCG	—
Retinoblastoma	Selected cases	—	Yes	Yes (includes brain)	—	Yes (selected cases)	Selected cases	—	—

AFP, α-Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; VMA, vanillylmandelic acid.

Modified from Marcdante KJ, Kliegman RM, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011. p. 589.

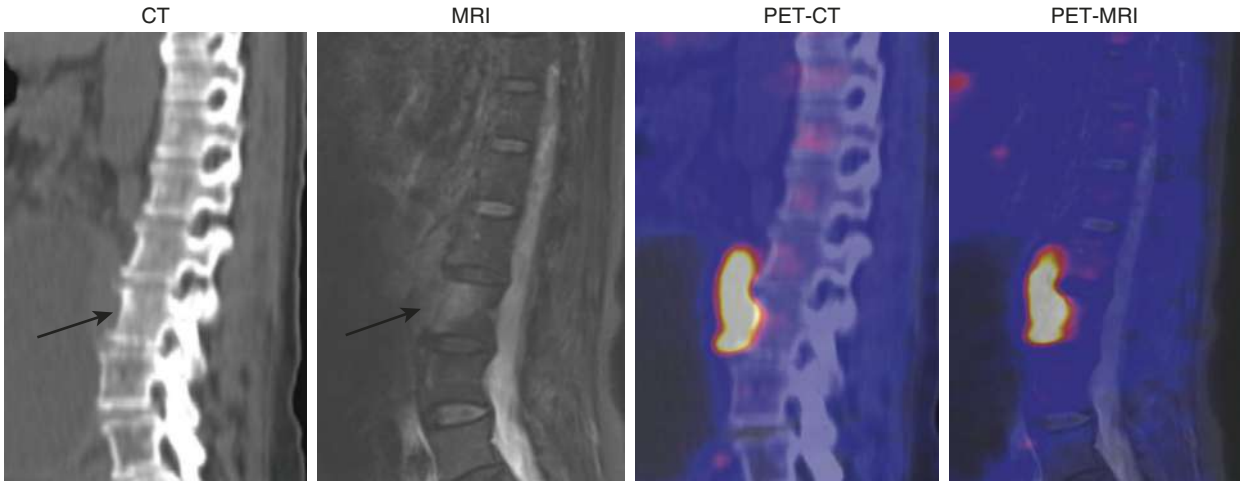

Fig. 542.5 Neuroblastoma PET/CT sagittal fused image demonstrated partial mis-registration of avid disease, occult on the low-dose noncontrast CT. PET/MRI sagittal fused image demonstrated correct image co-registration with corresponding T2-weighted hyperintensity in L3 vertebra, confirming L3 marrow involvement, delineated on the MR and not on the CT *(arrow). (From Sepehrizadeh T, Jong I, DeVeer M, Malhotra A. PET/MRI in paediatric disease. Eur J Radiol. 2021;144:109987. Fig. 2.)*

Chapter 543

Principles of Cancer Treatment

Erika D. Friehling, Julia C. Meade, Archie Bleyer, and A. Kim Ritchey

Treatment of children with cancer begins with an absolute requirement for the *correct diagnosis* (including subtype), proceeds through accurate and thorough *staging* of the extent of disease and determination of *prognostic subgroup*, provides appropriate multidisciplinary and usually multimodal therapy, and requires assiduous evaluation for possible recurrent disease and late effects of the disease and the therapies rendered. Throughout treatment, every child with cancer should have the benefit of the expertise of specialized teams of providers of pediatric cancer care, including pediatric oncologists, pathologists, radiologists, surgeons, radiation oncologists, nurses, and support staff, including nutritionists, social workers, psychologists, pharmacists, other medical specialists, and teachers trained to work with seriously ill children.

The best chance for cure of cancer is during the initial course of treatment; the cure rates for patients with recurrent disease are much lower than those for patients with primary disease. All patients with cancer should be referred to an appropriate specialized center as soon as possible when the diagnosis of cancer is suspected. All such centers in North America are identified on the **Children's Oncology Group** website (http://www.childrensoncologygroup.org) and on the **National Cancer Institute** (NCI) cancer trials website (http://www.clinicaltrials.gov). In the United States, the NCI's Clinical Trials Cooperative Groups Program is associated with a >80% reduction in the incidence of mortality from childhood cancer over 40 years despite an overall increase in cancer incidence during this interval (Fig. 543.1). After what appeared to be a plateau in the rate of decline in mortality in the early 2000s, there is evidence that the mortality rate continues to decline. Notably, a greater decline in mortality has been seen in the adolescent and young adult population when compared with children <15 years old, reversing prior trends (Fig. 543.2). The most current information on treatment of all types of childhood cancer is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/pediatrictreatment).

DIAGNOSIS AND STAGING

Accurate diagnosis and staging of the extent of disease are imperative because the nature of therapy depends strongly on the type of cancer. In addition, **prognostic subgroups** based on the stage of disease have been established for most cancers that occur in children. Accordingly, children with a better prognosis are treated with less intensive therapy, including lower doses of chemotherapy or radiation therapy, a shorter duration of treatment, or elimination of at least one treatment modality (radiation therapy, chemotherapy, surgery). Accurate staging thus reduces the risk of excessive acute toxicity and long-term effects of therapy in patients whose prognosis indicates that less therapy is required for cure. **Overtreatment** of patients with a more favorable prognosis is a definite risk if the patient is not referred to a cancer treatment center. Conversely, **undertreatment** also is a clear risk if the diagnosis and stage are not correct, resulting in a compromise of an otherwise high potential for cure.

Diagnostic imaging is a critical phase of evaluation in most children with solid tumors. MRI, CT, ultrasonography, scintigraphy (nuclear medicine scans), positron emission tomography (PET), and spectroscopy, as appropriate, all serve a clear purpose in the evaluation of children with cancer, not only before treatment to determine the extent of disease and the appropriate therapy but also during follow-up to determine whether the therapy was effective (see Chapter 542). In addition, response to treatment as determined by imaging techniques is being increasingly used to guide changes in the therapy.

Expertise in pathology and laboratory medicine provides critical diagnostic support and guides therapy in most children with cancer. Relatively noninvasive methods of obtaining tumor tissue such as percutaneous image-guided biopsy can be performed in pediatric centers with appropriate expertise in diagnostic imaging, interventional radiology, cytology, and anesthesia support. Sentinel node mapping is helpful in the staging of some children's cancers. Determining the adequacy of surgery by evaluating frozen sections of the surgical margins for tumor cells is essential in many tumor operations.

A MULTIMODAL, MULTIDISCIPLINARY APPROACH

Many pediatric subspecialists are involved in the evaluation, treatment, and management of children with cancer, including provision of primary therapy and supportive care services (Fig. 543.3). More than two of the primary modalities are often used together, with chemotherapy the most widely used, followed in order of use by surgery, radiation therapy, and biologic agent therapy (Fig. 543.4).

The **leukemias** that occur in childhood usually are managed with chemotherapy alone, with a small proportion of patients receiving cranial radiation therapy to prevent or treat overt central nervous system (CNS) leukemia. Children with **non-Hodgkin lymphoma** also are treated with chemotherapy alone, except for radiation therapy for CNS involvement. Localized therapy with surgery or irradiation, or both, is an important component of treatment of most solid tumors, including **Hodgkin lymphoma**, but systemic multiagent chemotherapy usually is necessary because tumor dissemination generally is present even if undetectable. Chemotherapy alone usually is not adequate to eradicate gross residual tumors. Therefore it is not unusual for children with malignant tumors to require treatment with all three modalities (see Fig. 543.4). Unfortunately, most treatments that are effective in children with cancer have a narrow therapeutic index (a low ratio of efficacy to toxicity). The acute and late effects of these treatments can be minimized but not entirely avoided.

Biologic agent therapy is an important modality in a few childhood cancers (see Fig. 543.4). This type of treatment generally refers to immunotherapy, biologic response modifiers, or endogenously occurring molecules that have therapeutic effects in supraphysiologic doses. Examples are retinoic acid therapy in acute promyelocytic leukemia, monoclonal antibody therapy for neuroblastoma and certain non-Hodgkin lymphomas, tyrosine kinase inhibitors such as imatinib mesylate for chronic myelogenous and Philadelphia chromosome–positive leukemias, and radioactive metaiodobenzylguanidine (MIBG) therapy for neuroblastoma. In addition, immune therapy directed at tumor cell antigens with modification of T-cell receptors (TCRs) or chimeric antigen receptors (CARs) have improved survival in patients with chemotherapy-resistant diseases (leukemia, lymphoma) and have shown promise in solid tumors and brain tumors.

Chemotherapy is used more widely in children than in adults because children better tolerate the acute adverse effects, and the malignant diseases that occur in childhood are more responsive to chemotherapy than are malignant diseases of adults. **Radiation therapy** is used sparingly in children because of its association with growth impairment and with the development of second malignant neoplasms.

Whenever possible, treatment is given on an outpatient basis. Children should remain living at home and in school as much as possible throughout treatment. Increasingly, pediatric cancer therapies are being administered to ambulatory patients, with the advent of such innovations as programmable infusion pumps, oral chemotherapeutic regimens, early discharge from hospital with intensive outpatient supportive care, and home healthcare services. Some patients miss a considerable amount of school in the first year after diagnosis because of the intensity of therapy or its adverse effects and the ensuing complications of the disease or therapy. Tutoring should be encouraged so that children do not fall behind in their schooling; counseling should be provided as appropriate. In-hospital school services should be provided for patients who must spend much of their time as inpatients receiving therapy for disease or for managing adverse effects. Upon completion of therapy, referral for pediatric neuropsychiatric testing in a specialized center is often recommended to ensure they are well supported in their education.

De novo or acquired resistance to chemotherapy and radiation therapy remains an obstacle to cure. Ongoing discoveries of molecular and cellular

mechanisms that explain the cancer process have led to increasingly specific antineoplastic therapies, generally referred to as **molecularly targeted therapies**. Their most prominent feature is a relative lack of normal tissue toxicity, such that the additional therapeutic benefit occurs with minimum additional toxicity. Many biologic agent therapies, such as imatinib and selumetinib, fall into this category (Table 543.1). **Complementary** and **alternative** therapies are increasingly being provided by parents to their children with cancer, with or without knowledge of the medical professionals entrusted with the child's care (see Chapter 7). Collaboration with the family and a pharmacist specializing in chemotherapy can minimize unwanted interactions from supplements.

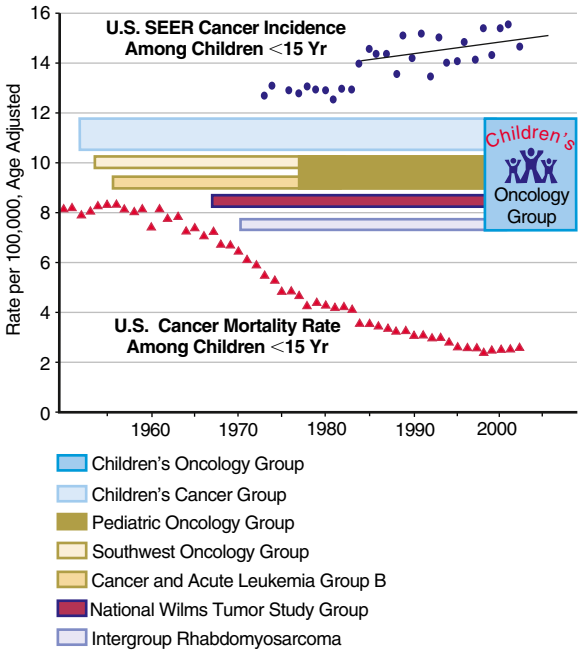

Fig. 543.1 Reduction in the national cancer mortality rate among children younger than 15 years of age *(triangles)* in the United States as a direct consequence of the National Cooperative Group Program sponsored by the National Cancer Institute and compared with the rising incidence of cancer before age 15 *(circles)*. The *horizontal bars* indicate the duration of the existence of the national pediatric cancer cooperative groups, beginning with the Children's Cancer Group in 1955. Other groups are the Pediatric Oncology Group, which was derived from the Pediatrics Divisions of the Southwest Oncology Group and the Cancer and Acute Leukemia Group B; the National Wilms Tumor Study Group; and the Intergroup Rhabdomyosarcoma Study Group. In 2000 the four pediatric cooperative groups merged into the Children's Oncology Group. *(Incidence and mortality rate data from Ries LAG, Eisner MP, Kosary CL, et al., eds. SEER Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute; http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER [Surveillance, Epidemiology, and End Results] data submission. The mortality rate data are national rates, and the incidence data are derived from the SEER program, representing approximately 15% of the United States. The most current information on treatment of all types of childhood cancer is available in the PDQ [Physician Data Query] on the NCI website, http://www.cancer.gov/cancertopics/pdq/pediatrictreatment.)*

DISCUSSING THE TREATMENT PLAN WITH THE PATIENT AND FAMILY

The diagnostic and treatment plan must be carefully explained to parents and, if the child is old enough to understand, to the patient. Children should be given as much information as they can understand and would be useful to them. All questions should be answered openly and honestly. Effects of treatment, such as loss of hair during chemotherapy, the possible need to amputate a limb, and possible temporary or permanent functional impairment, must be anticipated and fully discussed. The possibility and probability of death from cancer should be covered in an age-appropriate manner. It usually is necessary to repeat explanations several times before

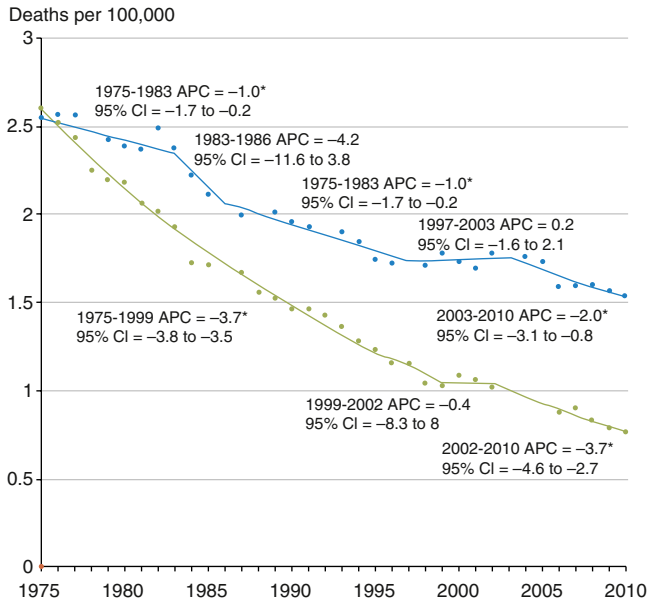

Fig. 543.2 Age-adjusted mortality trends for all malignant cancers among children <20 yr old in the United States from 1975 through 2010, along with annual percentage changes (APCs) for join point segments. *Asterisk* indicates that the slope of the join point segment is statistically different from zero ($p < .05$). The *green line* indicates leukemias and lymphomas, and the *blue line* indicates all other cancer sites; CI, confidence interval. *(From Smith MA, Altekruse SF, Adamson PC, et al. Declining childhood and adolescent cancer mortality. Cancer. 2014;120:2497–2506.)*

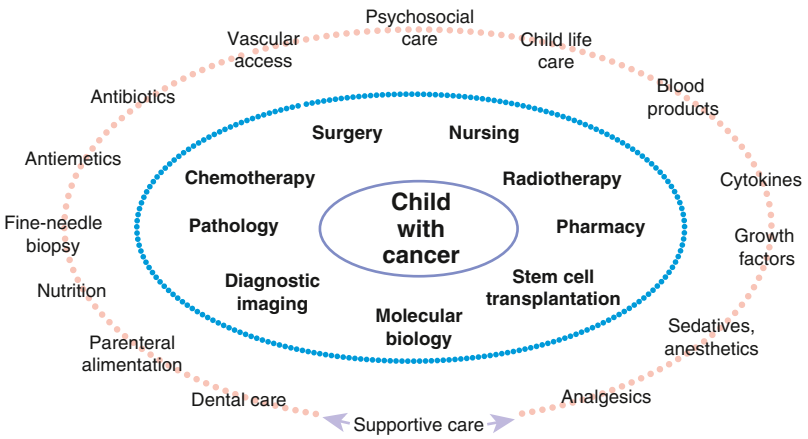

Fig. 543.3 Multidisciplinary care of children with cancer. The *inner circle* designates primary modalities, and the *outer ring* identifies supportive care elements to which all children with cancer have access.

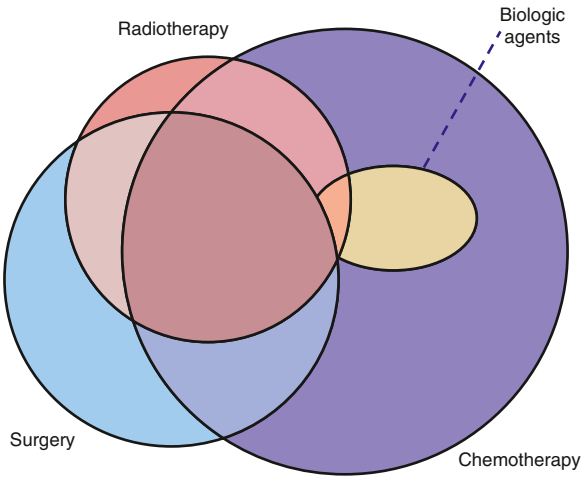

Fig. 543.4 The primary modalities of therapy used in the treatment of children with cancer. The relative sizes of the circles designate the approximate proportion of overall role in the management of pediatric cancers.

Table 543.1 Tyrosine Kinase Inhibitors and Monoclonal Antibodies for Pediatric Cancers

AGENT	TARGET	MALIGNANCY
Imatinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
	PDGFRα cKIT	Hypereosinophilic syndrome Gastrointestinal stromal tumor
Dasatinib, nilotinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
Brentuximab	CD30	Hodgkin lymphoma
Rituximab	CD20	Non-Hodgkin lymphoma
Selumetinib	MAPK/MEK	Plexiform neurofibroma Low-grade glioma
Bevacizumab	VEGFR-1, -2	Low-grade glioma
Crizotinib, lorlatinib	ALK/ROS	Neuroblastoma Anaplastic large cell lymphoma Inflammatory myofibroblastic tumor
Dinutuximab	GD2	Neuroblastoma
Blinatumomab	CD19	Leukemia Lymphoma

ALL, Acute lymphoblastic leukemia; CML, chronic myelogenous leukemia.

distraught family members fully understand. Throughout treatment, parents, patients, siblings, and medical staff will all need help in expressing feelings of anxiety, depression, guilt, and anger. The pediatrician, pediatric oncologist, and nurses should call on experienced professionals, including pediatric social workers, child psychologists and psychiatrists, child life specialists, and teachers with special expertise in managing students with cancer, to assist when needed.

TREATMENTS

Chemotherapy

The most widely used modality in pediatric cancer therapy is chemotherapy (see Fig. 543.4). Therapy usually involves a combination of drugs with different mechanisms of action and nonoverlapping toxicities. Sequential single-drug therapy rarely results in complete responses, and partial responses usually are infrequent, transient, and grow progressively shorter in duration with each drug used. Most of the cytotoxic drugs for childhood cancer are selected from several classes of agents, including alkylating agents, antimetabolites, antibiotics, hormones, plant alkaloids, and topoisomerase inhibitors (Table 543.2). The increased metabolic and cell cycle activity of malignant cells makes them more susceptible to the cytotoxic effects of these types of agents (Fig. 543.5).

Because most antineoplastic agents are cell cycle dependent, their adverse effects usually are related to the proliferation kinetics of individual cell populations. Most susceptible are tissues or organs with high rates of cell turnover: bone marrow, oral and intestinal mucosa, epidermis, liver, and spermatogonia. The most common acute adverse effects are **myelosuppression** (with neutropenia and thrombocytopenia the most problematic), immunosuppression, nausea and vomiting, hepatic dysfunction, upper and lower gastrointestinal mucositis, dermatitis, and alopecia. Fortunately, the tissues affected also recover relatively quickly, so that the acute adverse effects are usually reversible. Life-threatening effects of many chemotherapy agents include severe neutropenia with infection, fungemia, or fungal pneumonia as a result of immunosuppression, and septicemia, not infrequently linked to indwelling intravascular devices (Table 543.3; see Chapters 223 and 224). **Cardiomyopathy** caused by anthracyclines (e.g., doxorubicin, daunorubicin) and **renal failure** from platinum-containing agents also may be life-threatening or disabling. Assistance from a supportive care team can also provide safe and effective support for toxicities associated with chemotherapy, such as pain and nausea.

Least susceptible to chemotherapy and radiation therapy are cells that do not replicate or that replicate slowly, such as neurons, muscle cells, connective tissue, and bone. Children are not exempt from toxicities of these tissues, probably because they are still undergoing proliferation, although at a slower pace than other tissues, during growth and growth spurts.

Physically, children can endure the acute adverse effects of chemotherapy better than adults can in many ways. The maximum tolerated dosage in children, when expressed based on body surface area or body weight, typically is greater than that in adults. A comparison of anticancer drugs tested in phase I trials in both adult and pediatric patients showed that the maximum tolerated dosage in children was greater than that in adults for 70% of the agents, equal to that in adults for 15%, and less than the adult dose for only 15% of the agents. For all the drugs that were compared, the mean pediatric maximum tolerated dosage was greater than the adult mean.

Pharmacogenomics

Interindividual variability in the response to similar doses of a given medication is an inherent characteristic of both adult and pediatric populations. Variations in the germline genome can lead to differences in drug response at the level of individual patients. **Pharmacogenomics** represents the combination of pharmacology and genomics and is defined as the broader application of genetic testing strategies to identify factors predictive of drug efficacy and risk of adverse drug reactions.

Thiopurine *S*-methyltransferase **(TPMT)** is an enzyme that catalyzes the methylation of the chemotherapy 6-mercaptopurine (6MP) used in the treatment of acute lymphoblastic leukemia (ALL). To exert its cytotoxic effects, 6MP requires metabolism to thioguanine nucleotides, and this reaction is prevented by TPMT. Of the general population, 89% has normal TPMT activity, 11% has intermediate activity, and 0.3% has low activity. In patients with low or intermediate activity variants of TPMT, there is accumulation of cytotoxic thioguanine nucleotides (Fig. 543.6). These patients are at increased risk for **severe myelosuppression** if treated with routine doses of thiopurines and require a 10-15–fold reduction in dose to minimize this risk.

TPMT genotype is not the only determinant of intolerance to thiopurines; genetic variation in *NUDT15,* a nucleotide diphosphatase that reduces the incorporation of thioguanine into DNA, may also be involved. Reduction or loss of *NUDT15* activity results in increased cytotoxicity. Patients who have inherited reduced-function *NUDT15* alleles tolerate thiopurine doses that are much lower (10%) than normal. It is reasonable to expect that both *TPMT* and *NUDT15* genotypes will need to be considered for individualized thiopurine treatment, identifying patients who will benefit from specific dosing regimens and those who will be at risk for short-term and long-term toxicities.

Immunotherapy

Tumor-directed immune therapies employ and enhance the patient's immune system to kill malignant cells. Tumor antigen–specific monoclonal antibodies have been incorporated into the standard therapy of

Table 543.2 Common Chemotherapeutic Agents Used in Pediatric Cancer

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase	ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma	Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration, osteopenia and bone fractures With high-dose administration, renal and CNS toxicity With intrathecal administration, arachnoiditis, leukoencephalopathy, and leukomyelopathy	Systemic administration may be PO, IM, or IV; also may be administered intrathecally Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly
6-Mercaptopurine (Purinethol)	Purine analog; inhibits purine synthesis	ALL	Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity	Allopurinol inhibits metabolism
Cytarabine (cytosine arabinoside; Ara-C)	Pyrimidine analog; inhibits DNA polymerase	ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration, arachnoiditis, leukoencephalopathy, and leukomyelopathy	Systemic administration may be PO, IM, or IV; may also be administered intrathecally
Cyclophosphamide (Cytoxan)	Alkylates guanine; inhibits DNA synthesis	ALL, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis	Requires hepatic activation and thus is less effective in presence of liver dysfunction Mesna prevents hemorrhagic cystitis
Ifosfamide (IFEX)	Alkylates guanine; inhibits DNA synthesis	Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis	Mesna prevents hemorrhagic cystitis
Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)	Binds to DNA, intercalation	ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma	Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia	Dexrazoxane reduces risk of cardiotoxicity
Dactinomycin	Binds to DNA, inhibits transcription	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma	Nausea, vomiting tissue necrosis on extravasation, myelosuppression, radiation dermatitis, mucosal ulceration	
Bleomycin (Blenoxane)	Binds to DNA, cleaves DNA strands	Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors	Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis	
Vincristine (Oncovin)	Inhibits microtubule formation	ALL, non-Hodgkin lymphoma, Hodgkin disease, Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma	Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression	IV administration only; must not be allowed to extravasate
Vinblastine (Velban)	Inhibits microtubule formation	Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors	Local cellulitis, leukopenia	IV administration only; must not be allowed to extravasate
L-Asparaginase	Depletion of L-asparagine	ALL; AML, when used in combination with cytarabine	Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy	Pegaspargase now preferred to L-asparaginase
Pegaspargase (Oncaspar) Calaspargase-pegol-mknl (Asparlas)	Polyethylene glycol conjugate of L-asparagine	ALL	Indicated for prolonged asparagine depletion and for patients with allergy to L-asparaginase	

Continued

Table 543.2 Common Chemotherapeutic Agents Used in Pediatric Cancer—cont'd

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Prednisone and dexamethasone (Decadron)	Lymphatic cell lysis	ALL; Hodgkin lymphoma, non-Hodgkin lymphoma	Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis	
Carmustine (BiCNU)	Carbamylation of DNA; inhibits DNA synthesis	CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis	Phenobarbital increases metabolism, decreases activity
Carboplatin and cisplatin (Platinol)	Inhibits DNA synthesis	Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors	Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis	Aminoglycosides may increase nephrotoxicity
Etoposide (Vepesid)	Topoisomerase inhibitor	ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma	Nausea, vomiting, myelosuppression, secondary leukemia	
Tretinoin (all *trans*-retinoic acid) and isotretinoin (*cis*-retinoic acid; Accutane)	Enhances normal differentiation	Acute promyelocytic leukemia; neuroblastoma	Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects	

ADH, Antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; IM, intramuscular; IV, intravenous; PO, oral.

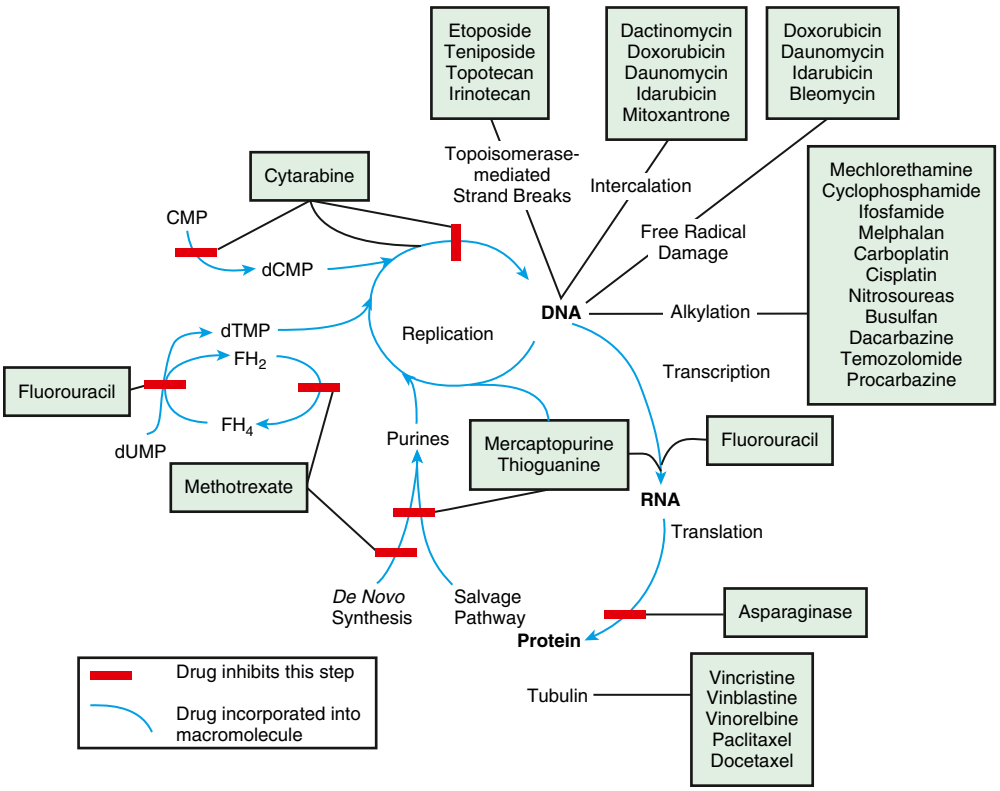

Fig. 543.5 Site of action of the commonly used anticancer drugs. CMP, Cytidine monophosphate; dCMP, deoxycytidine monophosphate; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2, dihydrofolate; FH_4, tetrahydrofolate. *(Redrawn from Adamson PC, Balis FM, Blaney SM. General principles of chemotherapy. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011: p. 283.)*

neuroblastoma (anti–ganglioside GD_2). The antiangiogenic agent bevacizumab (monoclonal antibody against vascular endothelial growth factor A) is used in the treatment of low-grade gliomas.

Chimeric antigen receptor T cells (CAR-T cells) are genetically engineered to make new TCRs that can recognize and attach to an antigen on the tumor cell. This results in T-cell proliferation, cytolysis, and cytokine release with subsequent tumor cell death (Fig. 543.7). The B-cell antigen CD19 is the antigen targeted in children with ALL and some adults with lymphoma. The response to therapy in children with chemotherapy-resistant ALL is dramatic. Other antigens may be targeted, including CD22, CD30 (lymphomas), CD171, GD2 (neuroblastoma), EGFR, and HER2 (glioblastoma).

Side effects of CAR-T therapy are common and potentially serious and are caused by the **cytokine release syndrome (CRS)**. Manifestations

Table 543.3 Infectious Complications of Malignancy

PREDISPOSING FACTOR	ETIOLOGY	SITE OF INFECTION	INFECTIOUS AGENTS
Neutropenia	Chemotherapy, bone marrow infiltration	Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis	Viridans group streptococcus, *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus,* anaerobic oral and rectal bacteria
Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction	Chemotherapy, corticosteroid	Pneumonia, meningitis, disseminated viral infection	*Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma,* varicella-zoster virus, cytomegalovirus, herpes simplex
Indwelling central venous catheter	Nutrition, administration of chemotherapy	Line sepsis, tract of tunnel, exit site	*S. epidermidis, S. aureus, Candida albicans, P. aeruginosa, Aspergillus, Corynebacterium, Enterococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes*

Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011.

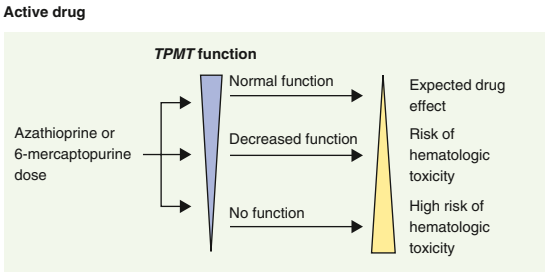

Fig. 543.6 The impact of variable pharmacokinetic gene function on the effect of bioactivation of prodrug versus inactivation of an active drug. *(From Roden DM, McLeod HL, Relling MV, et al. Pharmacogenomics. Lancet. 2019;394[10197]:521–532. Fig. 2)*

of CRS include hypotension, vascular leak, myalgias, cerebral edema, seizures, and confusion. Symptoms correlate with the extent of the tumor burden and require supportive care. Tocilizumab, an anti–interleukin-6 receptor monoclonal antibody, is the treatment of choice for CRS. B-cell aplasia may also develop and requires immune globulin replacement.

Immune checkpoint inhibitors are drugs (monoclonal antibodies) which enhance the ability of T-cells to attack cancer cells. Checkpoints on T-cells and cancer cells include PD-1/PD-L1 (programed death protein and programed death ligand-1), which normally dampen the T-cell response. CTLA-4 and LAG-3 are additional immune checkpoint molecules. Thus checkpoint inhibitors allow the T-cell to kill the cancer cells more effectively. Immune-related adverse events (irAEs) due to activated T cells include autoimmune-like disorders affecting many tissues including skin, liver, lung, CNS, and gastrointestinal and endocrine organs.

Surgery

Superb pediatric surgical and anesthesia services are indispensable for children with cancer. The pediatric surgeon's role varies depending on the type of tumor. For **solid tumors**, complete resection with documented evidence of negative margins often is required for cure or long-term control. Considerable prolongation of life usually depends on the tumor's resectability and the actual extent of resection.

Except for pontine gliomas and retinoblastoma, all solid tumors in children require a tissue diagnosis; therefore biopsy of the suspected neoplasm is paramount. Staging with sentinel node biopsies has become the standard of care for several pediatric malignancies. Surgical expertise is essential for implantation of vascular access devices and removal and replacement of such devices when infection or thrombosis supervenes (see Chapter 224).

Minimally invasive endoscopic surgical techniques are being used when indicated and, if the patient's condition permits, for biopsy and resection of tumor, direct ascertainment of residual disease and assessment of response, lysis of adhesions, and splenectomy.

Radiation Therapy

Radiation therapy is used sparingly in children, who are more susceptible than adults to the adverse delayed effects of ionizing radiation. A major advance in pediatric radiation therapy is the application of **conformal radiation** to children with cancer. This technique, most often applied as **intensity-modulated radiation therapy**, spares normal tissue by conforming the radiation volume to the shape of the tumor, thereby enabling delivery of higher doses to the tumor with lower exposure of normal tissue adjacent to the tumor or in the path of the radiation beam. Another example is **proton-beam radiotherapy**. With more focused beams and better sedation and immobilization techniques, radiation therapy is becoming more common in children. Acute adverse effects from radiation therapy depend on which part of the body is irradiated and the means of administration. **Dermatitis** is the most common general adverse effect because skin is always in the treatment field. Nausea and diarrhea are common subacute adverse effects with abdominal radiation therapy. **Mucositis** typically occurs to some extent whenever oral or intestinal mucosa is in the treatment volume. **Somnolence** is common with cranial irradiation. **Alopecia** occurs where hair is in the radiation field.

Most radiation therapy schedules require treatment 5 days per week for 4-7 weeks, depending on the dose needed to control the tumor and the amount and nature of normal tissue in the field. Most adverse effects are not noted until the second half of the course of irradiation. Late effects can occur months to years after radiation therapy and usually are dose-dependent manifestations. The type of delayed toxicity also depends on the site of irradiation. Examples are impaired growth resulting from cranial or vertebral irradiation, endocrine dysfunction from hypothalamic irradiation, pulmonary or cardiac insufficiency from chest irradiation, strictures and adhesions from abdominal irradiation, and infertility from pelvic irradiation. Second malignancy can also develop in the radiation field, such as breast cancer from chest irradiation and brain tumors from CNS irradiation.

ACUTE TOXIC EFFECTS AND SUPPORTIVE CARE

Adverse treatment effects that occur early in therapy can result in oncologic emergencies. These include metabolic disorders, bone marrow suppression, and compression by tumors on vital structures (Table 543.4). In **tumor lysis syndrome (TLS)**, uric acid, phosphate, and potassium are released in the circulation in large quantities from death of tumor cells. Hyperuricemia can lead to impairment of renal function, which further exacerbates the metabolic abnormalities. TLS can occur before therapy in patients with a large tumor burden (e.g., Burkitt lymphoma, lymphoblastic lymphoma, and leukemia presenting with a high white blood cell count), but it is usually seen within 12-48 hours of initiating chemotherapy. TLS is infrequently reported in other tumors (Hodgkin lymphoma, neuroblastoma, hepatoblastoma). Before therapy is initiated, the serum levels of uric acid, electrolytes, calcium, phosphorus, and creatinine should be measured, and adequate hydration ensured. Allopurinol (a xanthine oxidase inhibitor) should be started to prevent further accumulation of uric acid. In patients with established TLS with high uric acid levels or those at high risk for TLS, rasburicase (an enzyme that degrades uric acid) should be given. Symptomatic hyperkalemia and hyperphosphatemia with subsequent hypocalcemia can develop in the setting of inadequate renal function.

Virtually all chemotherapy regimens can produce **myelosuppression**, as can malignancies that invade and replace bone marrow. **Anemia** can

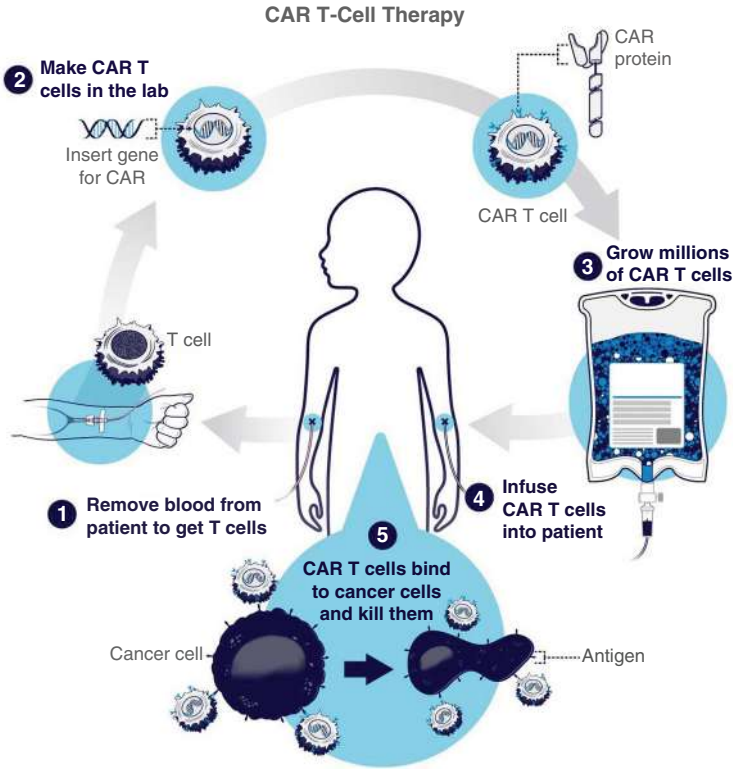

Fig. 543.7 Chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy is a type of treatment in which a patient's T cells are genetically engineered in the laboratory so they will bind to specific proteins (antigens) on cancer cells and kill them. *(1)* A patient's T cells are removed from their blood. Then *(2)* the gene for a special receptor called a chimeric antigen receptor is inserted into the T cells in the laboratory. The gene encodes the engineered CAR protein that is expressed on the surface of the patient's T cells, creating a CAR T cell. *(3)* Millions of CAR T cells are grown in the laboratory. *(4)* They are then given to the patient by intravenous infusion. *(5)* The CAR T cells bind to antigens on the cancer cells and kill them. *(Courtesy National Institutes of Health, National Cancer Institute, Bethesda, Maryland. https://www.cancer.gov/about-cancer/treatment/research/car-t-cell-therapy-infographic)*

Table 543.4 Oncologic Emergencies

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
METABOLIC				
Hyperuricemia	Uric acid nephropathy	Tumor lysis syndrome	Lymphoma, leukemia	Allopurinol, hydration, rasburicase
Hyperkalemia	Arrhythmias, cardiac arrest	Tumor lysis syndrome	Lymphoma, leukemia	Kayexalate, sodium bicarbonate, calcium gluconate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube
Hyperphosphatemia	Hypocalcemic tetany; metastatic calcification, photophobia, pruritus	Tumor lysis syndrome	Lymphoma, leukemia	Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate
Hyponatremia	Seizure, lethargy (may also be asymptomatic)	SIADH; fluid, sodium losses in vomiting	Leukemia, CNS tumor	Restrict free water for SIADH; replace sodium if depleted
Hypercalcemia	Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval	Bone resorption; ectopic parathormone, vitamin D, or prostaglandins	Metastasis to bone, rhabdomyosarcoma, leukemia	Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates
HEMATOLOGIC				
Anemia	Pallor, weakness, heart failure	Bone marrow suppression or infiltration; blood loss	Any with chemotherapy	Packed red blood cell transfusion
Thrombocytopenia	Petechiae, hemorrhage	Bone marrow suppression or infiltration	Any with chemotherapy	Platelet transfusion
Disseminated intravascular coagulation	Shock, hemorrhage	Sepsis, hypotension, tumor factors	Promyelocytic leukemia, others	Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder
Neutropenia	Infection	Bone marrow suppression or infiltration	Any with chemotherapy	If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate

Table 543.4 Oncologic Emergencies—cont'd

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
Hyperleukocytosis (>100,000/mm^3)	Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome	Leukostasis; vascular occlusion	Leukemia	Leukapheresis; chemotherapy; hydroxyurea
Graft versus host disease	Dermatitis, diarrhea, hepatitis	Immunosuppression and nonirradiated blood products; bone marrow transplantation	Any with immunosuppression	Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin
SPACE-OCCUPYING LESIONS				
Spinal cord compression	Back pain ± radicular *Cord above T10:* symmetric weakness, increased deep tendon reflex; sensory level present; toes up *Conus medullaris (T10-L2):* symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down *Cauda equina (below L2):* asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down	Metastasis to vertebra and extramedullary space	Neuroblastoma, ewing, glioma	Corticosteroids, surgery, chemotherapy, radiotherapy
Increased intracranial pressure	Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerve III and VI palsies	Primary or metastatic brain tumor	Medulloblastoma, glioma	Corticosteroids, ventriculostomy, radiotherapy, chemotherapy
Superior vena cava syndrome	Distended neck veins, plethora, edema of head and neck, cyanosis, Horner syndrome	Superior mediastinal mass	Lymphoma Germ cell tumor	Chemotherapy, radiotherapy
Tracheal compression	Respiratory distress	Mediastinal mass compressing trachea	Lymphoma Neuroblastoma	Radiation, corticosteroids

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Adapted from Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011. p. 590.

be corrected by transfusions of packed erythrocytes, and **thrombocytopenia** can be corrected by platelet infusions. Patients receiving immunosuppressive therapy should receive irradiated blood products to prevent graft-versus-host disease and leukoreduced blood products to prevent transfusion-associated reactions and infections. **Neutropenia** (neutrophil counts <500/μL) poses a risk of life-threatening infection. Patients with febrile neutropenia should be hospitalized and treated with empirical broad-spectrum intravenous antimicrobial therapy pending the results of appropriate cultures of blood, urine, or any obvious sites of infection (see Chapter 223). Treatment is continued until fever resolves and the neutrophil count rises. If fever persists for more than 3-5 days while the patient is receiving broad-spectrum antibiotics, the possibility of fungal infection must be considered. Fungal infections caused by *Candida* and *Aspergillus* are common in immunosuppressed patients. Opportunistic organisms such as *Pneumocystis jiroveci* can produce fatal pneumonia. Prophylactic treatment with trimethoprim-sulfamethoxazole is given when severe or prolonged immunosuppression is anticipated.

Viruses of low pathogenicity can produce serious disease in the setting of immunosuppression caused by malignancy or its treatment. Patients should not be given live-virus vaccines. Children who are receiving chemotherapy and who are exposed to chickenpox should receive varicella-zoster immunoglobulin, or if varicella-zoster immunoglobulin is not available, oral acyclovir should be considered. If clinical disease develops, the child should be hospitalized and treated with intravenous acyclovir.

Depending on the type of cancer therapy, patients can lose >10% body weight. Patients sometimes reduce their food intake because of temporary, treatment-associated nausea, stomatitis, and vomiting. Appetite loss is not a cause for alarm. **Malnutrition** is a particular risk in patients receiving radiation therapy involving the abdomen or the head and neck, intensive chemotherapy, or total body irradiation and high-dose chemotherapy before marrow transplantation. If oral supplementation proves inadequate, such patients may require enteral tube feedings or parenteral hyperalimentation.

Adequate **pain management** is critical. The World Health Organization (WHO) guidelines are particularly useful in the management of pain associated with cancer and cancer therapy (see Chapter 93). Assistance from a **supportive care** team can provide safe and effective support for toxicities associated with chemotherapy, such as pain and nausea.

LATE EFFECTS

Late effects of therapy can cause substantial morbidity (Table 543.5). The type of late effects depends on the child's age at treatment, the location(s) of the cancer, and the therapy administered. These effects can be either from the tumor or its treatment. For example, a brain or spinal tumor can leave the child with a permanent paresis or autonomic dysfunction; anthracycline-induced cardiomyopathy usually produces refractory cardiac dysfunction; and the leukoencephalopathy caused by intrathecal methotrexate and CNS radiation therapy often is only partially reversible.

Successful surgical resection can result in loss of important functional structures. Irradiation can produce irreversible organ damage, with symptoms and functional limitations depending on the organ involved and the severity of the damage. Many problems related to radiation therapy do not become obvious until the patient is fully grown, such as asymmetry between irradiated and nonirradiated areas or extremities. Irradiation of fields that include endocrine organs can cause hypothyroidism, pituitary dysfunction, or infertility. In sufficient doses, cranial irradiation can produce neurologic dysfunction, and spinal irradiation can produce growth deficiency.

Chemotherapy also carries the risk of long-lasting organ damage. Of particular concern are **leukoencephalopathy** after high-dose

methotrexate therapy; **infertility** in patients treated with alkylating agents (e.g., cyclophosphamide); **myocardial damage** caused by anthracyclines; **pulmonary fibrosis** caused by bleomycin; **renal dysfunction** caused by ifosfamide, nitrosourea, or platinum agents; and **hearing loss** from cisplatin. Development of these sequelae may be dose related and usually is irreversible. Appropriate baseline and intermittent testing should be performed before these drugs are administered to ensure that there is no preexisting damage to the organs likely to be affected and to permit monitoring of the effects of treatment-induced changes.

Perhaps the most serious late effect is the occurrence of **second cancers** in patients successfully cured of a first malignancy. The risk

Table 543.5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
NEUROCOGNITIVE			
Neurocognitive deficits Functional deficits in: • Executive function • Sustained attention • Memory • Processing speed • Visual-motor integration Learning deficits Diminished IQ Behavioral change	Chemotherapy: • Methotrexate Radiation affecting brain: • Cranial • Ear/infratemporal • Total body irradiation (TBI)	Age <3 yr old at time of treatment Female Supratentorial tumor Premorbid or family history of learning or attention problems Radiation doses >24 Gy Whole-brain irradiation	Acute lymphoblastic leukemia Brain tumor Sarcoma (head and neck or osteosarcoma)
NEUROSENSORY			
Hearing loss, sensorineural	Chemotherapy: • Cisplatin • Carboplatin Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher cisplatin dose (360 mg/m^2) Higher radiation dose impacting ear (>30 Gy) Concurrent radiation and cisplatin	Brain tumor Germ cell tumor Sarcoma (head and neck) Neuroblastoma Hepatoblastoma
Hearing loss, conductive Tympanosclerosis Otosclerosis Eustachian tube dysfunction	Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher radiation dose affecting ear (>30 Gy)	Brain tumor Sarcoma (head and neck)
Visual impairment Cataracts Lacrimal duct atrophy Xerophthalmia Retinopathy Glaucoma	Chemotherapy: • Busulfan • Glucocorticoids Radiation affecting eye: • Cranial • Orbital/eye • TBI	Higher radiation dose impacting eye (≥15 Gy for cataracts; >45 Gy for retinopathy and visual impairment)	Brain tumor Acute lymphoblastic leukemia Retinoblastoma Rhabdomyosarcoma (orbital) Allogeneic HSCT
Peripheral neuropathy, sensory	Chemotherapy: • Vincristine • Vinblastine • Cisplatin • Carboplatin Brentuximab vedotin	Higher cisplatin dose (≥300 mg/m^2)	Acute lymphoblastic leukemia Brain tumor Hodgkin lymphoma Germ cell tumor Non-Hodgkin lymphoma Sarcoma Neuroblastoma Wilms tumor Carcinoma
NEUROMOTOR			
Peripheral neuropathy, motor	Chemotherapy: • Vincristine • Vinblastine Brentuximab vedotin		Acute lymphoblastic leukemia Hodgkin lymphoma Non-Hodgkin lymphoma Sarcoma Brain tumor Neuroblastoma Wilms tumor
ENDOCRINE			
GH deficiency Precocious puberty	Radiation affecting HPA: • Cranial • Orbital/eye	Female Radiation dose to HPA >18 Gy	Acute lymphoblastic leukemia Sarcoma (facial) Carcinoma (nasopharyngeal)
Obesity	Ear/infratemporal Nasopharyngeal	Female Younger age (<4 yr)	Acute lymphoblastic leukemia
Hypothyroidism, central Gonadotropin deficiency Adrenal insufficiency, central	TBI	Radiation dose to HPA >18 Gy	Brain tumor Sarcoma (facial) Carcinoma (nasopharyngeal)
Hypothyroidism, primary	Neck, mantle irradiation	Radiation dose to thyroid >20 Gy	Hodgkin lymphoma

Table 543.5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment—cont'd

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
REPRODUCTIVE			
Gonadal dysfunction Delayed or arrested puberty Premature menopause Germ cell dysfunction or failure Infertility	Chemotherapy, alkylating: • Busulfan • Carmustine (BiCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine Radiation affecting reproductive system: • Whole abdomen (females) • Pelvic • Lumbar/sacral spine (females) • Testicular (males) • TBI	Higher alkylating agent dose Alkylating agent conditioning for HSCT Radiation dose ≥15 Gy in prepubertal females Radiation dose ≥10 Gy in pubertal females For germ cell failure in males, any pelvic irradiation For androgen insufficiency, gonadal irradiation, ≥20-30 Gy in males	Acute lymphoblastic leukemia, high risk Brain tumor Hodgkin lymphoma, advanced or unfavorable Non-Hodgkin lymphoma, advanced or unfavorable Sarcoma Neuroblastoma Wilms tumor, advanced Autologous or allogeneic HSCT
CARDIAC			
Cardiomyopathy Arrhythmias	Chemotherapy: • Daunorubicin • Doxorubicin • Idarubicin	Female Age <5 yr old at time of treatment Higher doses of chemotherapy (≥300 mg/m^2) Higher doses of cardiac radiation (≥30 Gy) Combined-modality therapy with cardiotoxic chemotherapy and irradiation	Hodgkin lymphoma Leukemia Non-Hodgkin lymphoma Sarcoma Wilms tumor Neuroblastoma
Cardiomyopathy Arrhythmias Pericardial fibrosis Valvular disease Myocardial infarction Atherosclerotic heart disease	Radiation affecting heart: • Chest • Mantle • Mediastinum • Axilla • Spine • Upper abdomen		
PULMONARY			
Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Chemotherapy: • Bleomycin • Busulfan • Carmustine (BiCNU) • Lomustine (CCNU) Radiation impacting lungs: • Mantle • Mediastinum • Whole lung • TBI	Higher doses of chemotherapy Combined modality therapy with pulmonary toxic chemotherapy and irradiation	Brain tumor Germ cell tumor Hodgkin lymphoma Sarcoma (chest wall or intrathoracic) Autologous or allogeneic HCST
GASTROINTESTINAL			
Chronic enterocolitis Strictures Bowel obstruction	Radiation affecting GI tract (≥30 Gy) Abdominal surgery	Higher radiation dose to bowel (≥45 Gy) Combined modality therapy with abdominal irradiation and radiomimetic chemotherapy (dactinomycin or anthracyclines) Combined modality therapy with abdominal surgery and irradiation	Sarcoma (retroperitoneal or pelvic primary)
HEPATIC			
Hepatic fibrosis Cirrhosis	Radiation affecting liver	Higher radiation dose or treatment volume (20-30 Gy to entire liver or ≥40 Gy to at least one third of liver)	Sarcoma Neuroblastoma
RENAL			
Renal insufficiency Hypertension Glomerular injury Tubular injury	Chemotherapy: • Ifosfamide • Cisplatin • Carboplatin Radiation affecting kidneys: • Whole abdomen • Upper abdominal fields • TBI	Higher ifosfamide dose (≥60 g/m^2) Higher cisplatin dose (≥200 mg/m^2) Renal radiation dose (≥15 Gy) Combined modality therapy with above agents	Brain tumor Germ cell tumor Sarcoma Wilms tumor Neuroblastoma Hepatoblastoma Carcinoma Autologous or allogeneic HSCT

GH, Growth hormone; HPA, hypothalamic-pituitary-adrenal axis; HSCT, hematopoietic stem cell transplantation; IQ, intelligence quotient.
From Kurt BA, Armstrong GT, Cash DK, et al. Primary care management of the childhood cancer survivor. *J Pediatr*. 2008;152:458–466.

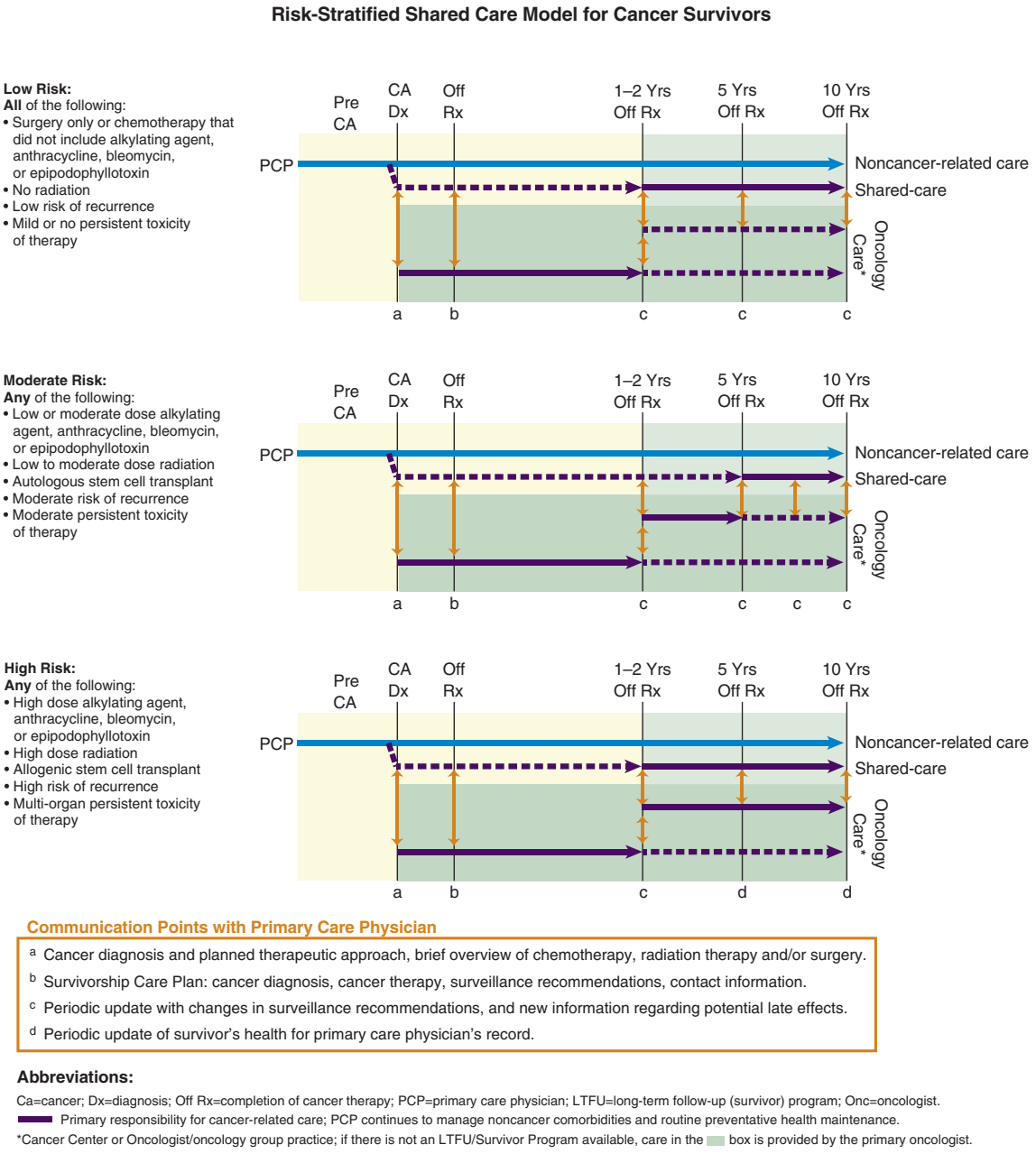

Fig. 543.8 Proposed risk-stratified shared care model for childhood cancer survivors. *Purple solid line* denotes primary responsibility cancer-related care; risk stratification is based on determination of the long-term follow-up staff. *(Adapted from McCabe MS, Partridge A, Grunfeld, E, Hudson MM. Risk-based health care, the cancer survivor, the oncologist, and the primary care physician. Semin Oncol. 2013;40:804–812; with data from Oeffinger KC, McCabe MS. Models for delivering survivorship care. J Clin Oncol. 2006;24:5117–5124.)*

appears to be cumulative, increasing by approximately 0.5% per year, resulting in approximately a 12% incidence at 25 years after treatment. Patients who have been treated for childhood cancer should be examined annually with particular attention to possible late effects of therapy, including second malignancies (Fig. 543.8).

Risk-stratified therapy over the past few decades has been shown to reduce late morbidity and mortality. A good resource for the pediatrician, patient, and family who must anticipate the possibilities is available at http://www.survivorshipguidelines.org.

PALLIATIVE CARE

At all stages of caring for children with cancer, principles of palliative care should be applied to relieve pain and suffering and to provide comfort (see Chapter 8). Early involvement of palliative or supportive care teams is beneficial. **Pain** is a serious cause of suffering among patients with cancer. It may be the result of organ obstruction or compression or bone metastasis, or it may be neuropathic. Pain should be managed in a stepwise manner, as recommended by the WHO, in accordance with the principles of selecting the appropriate analgesic, prescribing the appropriate dosage, administering the drug by the appropriate route, and choosing an appropriate dosing schedule to prevent persistent pain and to relieve breakthrough pain (see Chapter 93). In addition, the dosage should be titrated aggressively while attempts are made to prevent, anticipate, and manage side effects. Adjuvant drugs and sequential trials of analgesic drugs should be considered.

The goals in the care of dying patients are to avoid distress for the patient, family, and caregivers; to provide care consistent with the patient's and family's wishes; and to comply with and advocate for clinical, cultural, and ethical standards.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 544

The Leukemias

A. Kim Ritchey, Erika D. Friehling, Julia C. Meade, David G. Tubergen, and Archie Bleyer

INTRODUCTION

The leukemias are the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies that occur in children younger than 15 years old. Each year, leukemia is diagnosed in approximately 3,100 children and adolescents <20 years old in the United States, an annual incidence of 4.8 cases per 100,000 children. Acute lymphoblastic leukemia (ALL) accounts for approximately 77% of cases of childhood leukemia, acute myelogenous leukemia (AML) for approximately 11%, chronic myelogenous leukemia (CML) for 2–3%, and juvenile myelomonocytic leukemia (JMML) for 1–2%. The remaining cases consist of a variety of acute and chronic leukemias that do not fit classic definitions for ALL, AML, CML, or JMML.

The leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The progeny of these cells have a growth advantage over normal cellular elements because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and, ultimately, marrow failure. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia.

544.1 Acute Lymphoblastic Leukemia

Erika D. Friehling, A. Kim Ritchey, Julia C. Meade, and Archie Bleyer

Leukemia (ALL) was the first disseminated cancer shown to be curable. It is a heterogeneous group of malignancies with distinctive genetic abnormalities that result in varying clinical behaviors and responses to therapy.

EPIDEMIOLOGY

Acute lymphoblastic leukemia is diagnosed in approximately 3,100 children and adolescents <20 years old in the United States each year. It has a striking peak incidence at 2-3 years of age and occurs more in males than in females at all ages. The disease is more common in children with certain chromosomal abnormalities, such as Down syndrome, Li-Fraumeni, Bloom syndrome, and ataxia-telangiectasia. Among identical twins, the risk to the second twin if one twin develops leukemia is greater than that in the general population. The risk is >70% if ALL is diagnosed in the first twin during the first year of life and the twins shared the same (monochorionic) placenta. If the first twin develops ALL by 5-7 years of age, the risk to the second twin is at least twice that of the general population, regardless of zygosity.

ETIOLOGY

In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia (Table 544.1). Most cases of ALL are thought to be caused by post-conception somatic pathogenic gene variants in lymphoid cells. However, the identification of the leukemia-specific fusion-gene sequences in archived neonatal blood spots of some children who develop ALL at a later date indicates the importance of in utero events in the initiation of the malignant process in some cases. The long lag period before the onset of the disease in some children, reported to be as long as 14 years, supports the concept that additional genetic modifications are required for disease expression. Moreover, those same pathogenic variants have been found in neonatal blood spots of children who *never* go on to develop leukemia.

Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased incidence of ALL (see Chapter 758). In addition, published descriptions and investigations of geographic clusters of cases have raised concern that environmental factors can increase the incidence of ALL. Thus far, no such factors other than radiation have been identified in the United States. In certain developing countries, there is an association between B-cell ALL (B-ALL) and Epstein-Barr virus (EBV) infections.

CELLULAR CLASSIFICATION

The classification of ALL depends on characterizing the malignant cells in the bone marrow to determine the morphology, phenotype as measured by cell membrane markers, and cytogenetic and molecular genetic features. **Morphology** is usually adequate alone to establish a diagnosis, but the other studies are essential for disease classification, which can have a major influence on the prognosis and the choice of appropriate therapy. The current system used is the World Health Organization (WHO) classification of leukemias. Phenotypically, surface markers show that approximately 85% of cases of ALL are classified as **B-lymphoblastic leukemia** (previously termed precursor B-ALL or pre–B-ALL), approximately 15% are **T-lymphoblastic leukemia**, and approximately 1% are derived from mature B cells. The rare leukemia of mature B cells is termed **Burkitt leukemia** and is one of the most rapidly growing cancers in humans, requiring a different therapeutic approach than other subtypes of ALL. A small percentage of children with leukemia have a disease characterized by surface markers of both lymphoid and myeloid derivation.

Chromosomal abnormalities are used to subclassify ALL into prognostic groups (Table 544.2). Many genetic alterations, including inactivation of tumor-suppressor genes and pathogenic gene variants that activate the *JAK-STAT* or *RAS* pathways, have been discovered (Fig. 544.1).

The polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) techniques offer the ability to pinpoint molecular genetic abnormalities and can be used to detect small numbers of malignant cells at diagnosis as well as during follow-up (**minimal residual disease [MRD]**, see later) and are of proven clinical utility. DNA microarray and whole genome sequencing make it possible to analyze the expression of thousands of genes in the leukemic cell.

Table 544.1 Predisposing Factors of Acute Lymphoblastic Leukemia

GENETIC SUSCEPTIBILITY
Congenital syndromes: Down syndrome, Fanconi anemia, ataxia telangiectasia, Bloom syndrome, Nijmegen breakage syndrome
Inherited gene variants: *ARID5B, IKZF1, CEBPE, CDKN2A,* or *CDKN2B, PIP4K2A, ETV6*
Constitutional Robertsonian translocation between chromosomes 15 and 21, rob(15;21)(q10;q10)
Single nucleotide polymorphisms: rs12402181 in miR-3117 and rs62571442 in miR-3689d2
ENVIRONMENTAL FACTORS
Pesticide exposure
Ionizing radiation
Childhood infections

From Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–1158. Panel, p. 1147.

CLINICAL MANIFESTATIONS

The initial presentation of ALL usually is nonspecific and relatively brief. Anorexia, fatigue, malaise, irritability, and intermittent low-grade fever are often present. Bone or joint pain, particularly in the lower extremities, may be present. Less often, symptoms may be of several months' duration, may be localized predominantly to the bones or joints, and may include joint swelling. Bone pain is severe and can wake the patient at night. As the disease progresses, signs and symptoms of **bone marrow failure** become more obvious with the occurrence of pallor, fatigue, exercise intolerance, bruising, oral mucosal bleeding or epistaxis, and fever, which may be caused by infection or the leukemia. Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures). Respiratory distress may be caused by severe anemia or mediastinal node compression of the airways.

On **physical examination,** findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage can reflect bone marrow failure (see Chapter 542). The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less often, hepatomegaly. Patients with bone or joint pain may have exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Nonetheless, with marrow involvement, deep bone pain may be present, but tenderness will not be elicited. Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the CNS. These include papilledema (see Fig. 542.3), retinal hemorrhages, and cranial nerve palsies. Respiratory distress usually is related to anemia but can occur in patients as the result of a large anterior mediastinal mass (e.g., in the thymus or nodes). This problem is most frequently seen in adolescent males with T-cell ALL (T-ALL). **T-ALL** also usually has a higher leukocyte count.

B-lymphoblastic leukemia is the most common immunophenotype, with onset at 1-10 years of age. The median leukocyte count at presentation is 33,000/μL, although 75% of patients have counts <20,000/μL; thrombocytopenia is seen in 75% of patients and hepatosplenomegaly in 30–40% of patients. In all types of leukemia, CNS symptoms are seen at presentation in 5% of patients. Leukemia cells can be seen in the cerebrospinal fluid (CSF) of 10–15% of patients, but only 3–5% are diagnosed with CNS leukemia, defined as >5 WBCs/μL with blasts present. Testicular involvement is rarely evident at diagnosis, but prior studies indicate occult involvement in 25% of males. There is no indication for testicular biopsy.

DIAGNOSIS

The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. Anemia and thrombocytopenia are seen in most patients. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations. Many patients with ALL present with total leukocyte counts of <10,000/μL. In such cases, the leukemic cells often are reported initially to be "atypical lymphocytes," and it is only on further evaluation that the cells are

Table 544.2 Main Genetic Subtypes of B-Cell Acute Lymphoblastic Leukemia

	FREQUENCY	PATHOGENIC VARIANTS	PROGNOSIS
High hyperdiploid (gain of ≥5 chromosomes)	25% children; 3% AYAs and adults	RTK-RAS signaling pathway, histone modifiers	Favorable
Near-haploid (24-31 chromosomes)	2% children; <1% AYAs and adults	RAS-activating, *IKZF3*	Poor
Low-hypodiploid (32-39 chromosomes)	<1% children; 5% AYAs; >10% adults	*TP53, IKZF2, RB1*	Very poor
MLL (KMT2A) rearrangements	>80% infants; <1% children; 4% AYAs; 15% adults	*MLL (KMT2A)* rearrangement, few additional pathogenic variants (PI3K-RAS signaling pathway)	Very poor
ETV6-RUNX1 translocation, t(12;21)(q13;q22)	30% children; <5% AYAs and adults	*ETV6-RUNX1*	Favorable
TCF3-PBX1 translocation, t(1;19)(q23;p13)	5% children, AYAs and adults	*TCF3-PBX1*	Favorable
TCF3-HLF variant of t(1;19)(q23;p13)	<1% acute lymphoblastic leukemia	*TCF3-HLF*	Poor
BCR-ABL1 Philadelphia chromosome, t(9;22)(q34;q11)	2–5% children, 6% AYAs; >25% adults	*BCR-ABL1* fusion gene, common deletions of *IKZF1, CDKN2A, CDKN2B,* and *PAX5*	Poor (improved with tyrosine kinase inhibitors)
Philadelphia chromosome-like acute lymphoblastic leukemia	10% children; 25–30% AYAs; 20% adults	Rearrangements of *CRLF2* (about 50%), *ABL*-class tyrosine kinase genes (12%) and *JAK2* (10%); pathogenic variants of *EPOR* (3–10%); pathogenic variants activating JAK-STAT (10%) and RAS (2–8%) signaling pathways	Poor
DUX4 and *ERG*-deregulated acute lymphoblastic leukemia	5–10% acute lymphoblastic leukemia	*DUX4* rearrangement and overexpression, *ERG* deletions	Favorable, including if coexistence of *IKZF1* pathogenic variants (about 40% of patients)
MEF2D-rearranged acute lymphoblastic leukemia	4% children; 7% AYAs and adults	*MEF2D* is fused to *BCL9* (most frequent fusion event), *HNRNPUL1, SS18, FOXJ2, CSF1R,* or *DAZAP1*	Poor
ZNF384-rearranged acute lymphoblastic leukemia	5% children; 10% AYAs and adults	*ZNF384* rearranged with a transcriptional regulator or chromatin modifier (*EP300, CREBBP, TAF15, SYNRG,* EWSR1, *TCF3, ARID1B, BMP2K,* or *SMARCA2*)	Intermediate

AYAs, Adolescents and young adults.
From Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–1158. Table 1, p. 1148.

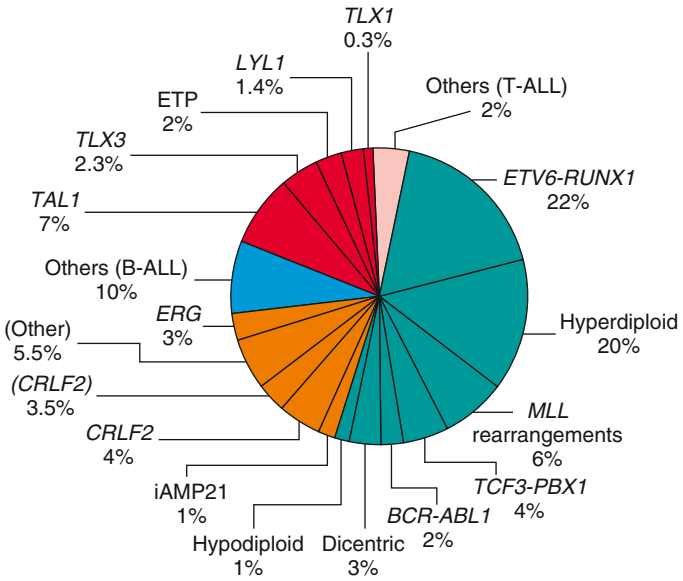

Fig. 544.1 Estimated frequency of specific genotypes in childhood acute lymphoblastic leukemia (ALL). *Teal wedges* refer to B-cell ALL (B-ALL), *orange* to recently identified subtypes of B-ALL, and *red wedges* to T-cell ALL (T-ALL). *(From Mullighan CG. Genomic characterization of childhood acute lymphoblastic leukemia. Semin Hematol. 2013;50:314–324.)*

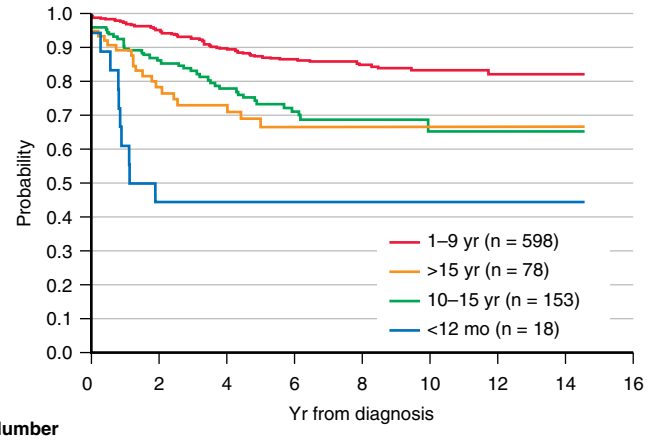

Number at risk									
<12 mo	18	11	8	8	6	1	1	0	0
1–9 yr	598	528	378	295	213	149	85	31	4
10–15 yr	153	130	100	77	50	26	11	6	1
>15 yr	78	60	40	29	20	7	1	0	0

Fig. 544.2 Kaplan-Meier estimates of event-free survival according to age at diagnosis of acute lymphoblastic leukemia. *(From Pui CH, Robinson LL, Look AT. Acute lymphoblastic leukaemia. Lancet. 2008;371:1030–1042.)*

found to be part of a malignant clone. When the results of an analysis of peripheral blood suggest the possibility of leukemia, flow cytometry can rapidly facilitate the diagnosis. The bone marrow should be examined promptly to confirm the diagnosis. It is important that all studies necessary to confirm a diagnosis and adequately classify the type of leukemia be performed, including bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.

ALL is diagnosed by a bone marrow evaluation that demonstrates >25% of the bone marrow cells as a homogeneous population of lymphoblasts. Initial evaluation also includes CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or

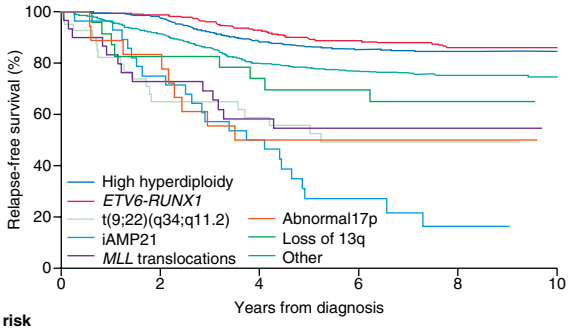

Number at risk						
High hyperdiploidy	551	529	470	434	249	98
ETV6-RUNX1	365	355	331	301	167	47
t(9;22)(q34;q11.2)	42	22	19	14	8	2
iAMP21	28	21	14	6	1	0
MLL translocations	30	20	16	14	9	1
Abnormal17p	18	15	9	8	7	2
Loss of 13q	24	19	17	15	9	4
Other	644	567	483	440	258	105

Fig. 544.3 Kaplan-Meier analysis of relapse-free survival according to biologic subtype of leukemia. *(From Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Results from the UK Medical Research Council ALL97/99 randomised trial. Lancet Oncol. 2010;11:429–438.)*

meningeal leukemia is present. This finding reflects a poorer stage and indicates the need for additional CNS and systemic therapies. The staging lumbar puncture (LP) may be performed in conjunction with the first dose of intrathecal chemotherapy, if the diagnosis of leukemia was previously established from bone marrow evaluation. An experienced proceduralist should perform the initial LP, because a traumatic LP is associated with an increased risk of CNS relapse.

DIFFERENTIAL DIAGNOSIS

The diagnosis of leukemia is readily made in the patient with typical signs and symptoms, anemia, thrombocytopenia, and elevated WBC count with blasts present on smear. Elevation of the lactate dehydrogenase (LDH) is often a clue to the diagnosis of ALL. When pancytopenia is present without peripheral blasts, aplastic anemia (congenital or acquired), marrow infiltration from metastatic disease, and hemophagocytic lymphohistiocytosis should be considered. Failure of a single cell line, as seen in transient erythroblastopenia of childhood, immune thrombocytopenia, and congenital or acquired neutropenia, is rarely the presenting feature of ALL. A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from juvenile idiopathic arthritis in patients with fever, bone pain but often no tenderness, and joint swelling. These presentations also can require bone marrow examination.

ALL must be differentiated from AML and other malignant diseases that invade the bone marrow and can have clinical and laboratory findings similar to ALL, including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma.

TREATMENT

The single most important prognostic factor in ALL is the treatment: without effective therapy, the disease is fatal. Considerable progress has been made in overall survival for children with ALL through use of multiagent chemotherapeutic regimens, intensification of therapy, and selection of treatment based on relapse risk. Survival is also related to age (Fig. 544.2) and biologic subtype (Fig. 544.3).

Risk-stratified therapy is the standard of current ALL treatment and accounts for age at diagnosis, initial WBC count, immunophenotypic and cytogenetic characteristics of blast populations, rapidity of early treatment response (i.e., how quickly the leukemic cells can be cleared from the marrow or peripheral blood), and assessment of MRD at the end of induction therapy (Table 544.3). Different

Table 544.3 Prognostic Factors for Acute Lymphoblastic Leukemia

	FAVORABLE FACTOR	ADVERSE FACTOR
DEMOGRAPHIC AND CLINICAL FEATURES		
Age	1 year to <10 years	<1 year or ≥10 years
Sex	Female	Male
Ethnicity	White, Asian	Black, Hispanic
CLINICAL, BIOLOGIC, OR GENETIC FEATURES OF LEUKEMIA		
CNS involvement	No	Yes
Blood count at diagnosis	Low blood count; $<50 \times 10^9$ cells/L for B-cell acute lymphoblastic leukemia and $<100 \times 10^9$ cells/L for T-cell acute lymphoblastic leukemia	High blood count; $\geq 50 \times 10^9$/L for B-cell acute lymphoblastic leukemia and $\geq 100 \times 10^9$ cells/L for T-cell acute lymphoblastic leukemia
Immunophenotype	B-cell lineage	T-cell lineage
Cytogenetic features	Hyperdiploidy, *ETV6-RUNX*, *TCF3-PBX1*, and trisomy of chromosomes 4, 10, or 17	Hypodiploidy, *BCR-ABL1* Philadelphia chromosome-positive, *MLL* rearrangements, *TCF3-HLF*, and complex karyotype (≥5 chromosomal abnormalities)
Genomic features	*DUX4*-rearrangement (*ERG* deletion)	*IKZF1* deletions or pathogenic variants, Philadelphia chromosome-like, *MEF2D*-rearrangement
RESPONSE TO TREATMENT		
Minimal residual disease at specified time points	Low minimal residual disease $<10^{-3}$ nucleated cells or undetectable	Persistence of minimal residual disease $\geq 10^{-3}$ nucleated cells, the higher this value the worse the prognosis

From Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–1158. Table 2, p. 1150.

study groups use various factors to define risk, but age 1-10 years and a leukocyte count <50,000/μL are used by the National Cancer Institute (NCI) to define standard risk. Children who are younger than 1 year or older than 10 years or who have an initial leukocyte count of >50,000/μL are considered to be high risk. Additional characteristics that adversely affect outcome include T-cell immunophenotype or a slow response to initial therapy. Chromosomal abnormalities, including hypodiploidy, the Philadelphia chromosome, and *KMT2A (MLL)* gene rearrangements, portend a poorer outcome. Other genetic pathogenic variants, such as in the *IKZF1* gene, have been shown to be associated with a poor prognosis and may become important in treatment algorithms in the future. More favorable characteristics include a rapid response to therapy, hyperdiploidy, trisomy of specific chromosomes (4, 10, and 17), and rearrangements of the *ETV6-RUNX1* (formerly *TEL-AML1*) genes.

The outcome for patients at higher risk can be improved by administration of more intensive therapy despite the greater toxicity of such therapy. Infants with ALL, along with patients who present with specific chromosomal abnormalities, such as t(4;11), have an even higher risk of relapse despite intensive therapy. However, the poor outcome of Philadelphia chromosome–positive ALL with t(9;22) has been dramatically changed by the addition of imatinib to an intensive chemotherapy backbone. **Imatinib** is an agent specifically designed to inhibit the BCR-ABL kinase resulting from the translocation. With this approach, the event-free survival has improved from 30% to 70%. Clinical trials demonstrate that the prognosis for patients with a slower response to initial therapy may be improved by therapy that is more intensive than the therapy considered necessary for patients who respond more rapidly.

Most children with ALL are treated in clinical trials conducted by national or international cooperative groups. Standard treatment involves chemotherapy for 2-3 years, and most achieve remission at the end of the induction phase. Patients in clinical remission can have MRD that can only be detected with specific molecular probes to translocations and other DNA markers contained in leukemic cells or specialized flow cytometry. MRD can be quantitative and can provide an estimate of the burden of leukemic cells present in the marrow. Higher levels of MRD present at the end of induction suggest a poorer prognosis and higher risk of subsequent relapse. MRD of >0.01% on the marrow on day 29 of induction is a significant risk factor for shorter event-free survival for all risk categories, compared with patients with negative MRD. Therapy for ALL intensifies treatment in patients with evidence of MRD at the end of induction.

Initial therapy, termed **remission induction**, is designed to eradicate the leukemic cells from the bone marrow. During this phase, therapy is given for 4 weeks and consists of vincristine weekly, a corticosteroid such as dexamethasone or prednisone, and usually a single dose of a long-acting, pegylated asparaginase preparation. Patients at higher risk also receive daunorubicin at weekly intervals. With this approach, 98% of patients are in remission, as defined by <5% blasts in the marrow and a return of neutrophil and platelet counts to near-normal levels after 4-5 weeks of treatment. Intrathecal chemotherapy is always given at the start of treatment and at least once more during induction.

The second phase of treatment, **consolidation**, focuses on intensive CNS therapy in combination with continued intensive systemic therapy to prevent later CNS relapses. Intrathecal chemotherapy is given repeatedly by LP. The likelihood of later CNS relapse is thereby reduced to <5%, from historical incidence as high as 60%. A small percentage of patients with features that predict a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. This includes patients who at diagnosis have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsy.

Subsequently, many regimens provide 14-28 weeks of therapy, with the drugs and schedules used varying depending on the risk group of the patient. This period of treatment is often termed **intensification** and includes phases of aggressive treatment **(delayed intensification)** as well as relatively less toxic phases of treatment **(interim maintenance)**. Multiagent chemotherapy, including such medications as cytarabine, methotrexate, asparaginase, and vincristine, is used during these phases to eradicate residual disease.

Finally, patients enter the **maintenance** phase of therapy, which lasts for 2-3 years, depending on the protocol used. Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid.

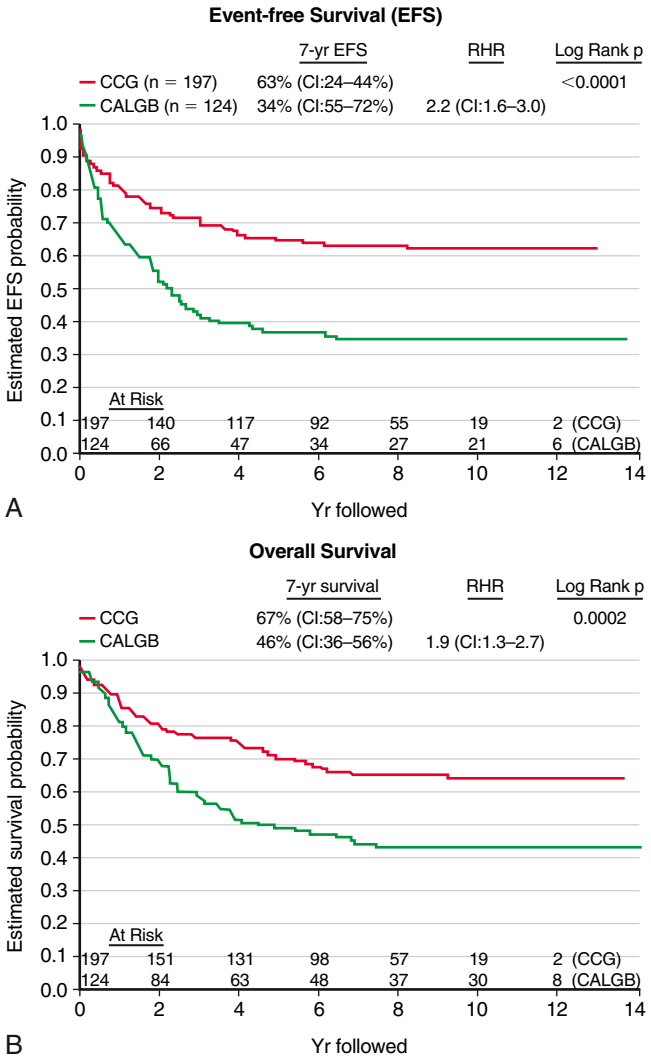

Fig. 544.4 Comparison of event-free survival (A) and overall survival (B) among Cancer and Leukemia Group B (CALGB) (adult protocol, *green line*) and Children's Cancer Group (CCG) (pediatric protocol, *red line*) patients. CI, Confidence interval; EFS, event-free survival; RHR, relative hazard rate. *(From Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112:1646–1654.)*

A small number of patients with particularly poor prognostic features, such as those with induction failure or extreme hypodiploidy, may undergo bone marrow transplantation during the first remission.

Adolescents and **young adults** with ALL have a poor prognosis compared to children <15 years old. They often have adverse prognostic factors and require more intensive therapy. Patients in this age-group have a superior outcome when treated with pediatric rather than adult treatment protocols (Fig. 544.4). Although the explanation for these findings may be multifactorial, it is important that these patients be treated with pediatric treatment protocols, ideally in a pediatric cancer center.

Genetic polymorphisms of enzymes important in drug metabolism may impact both the efficacy and the toxicity of chemotherapeutic medications. **Pharmacogenetic testing** of the thiopurine *S*-methyltransferase *(TPMT)* gene, which encodes one of the metabolizing enzymes of mercaptopurine, can identify patients with varying levels of TPMT enzyme activity. Decreased TPMT enzyme activity results in accumulation of a toxic metabolite of mercaptopurine and severe myelosuppression, requiring dose reductions of the chemotherapy (see Chapter 543).

Treatment of Relapse

The major impediment to a successful outcome is **relapse** of the disease. Outcomes remain poor among those who relapse, with the most important prognostic indicators being time from diagnosis and site of relapsed disease. In addition, other factors, such as immunophenotype (T-ALL worse than B-ALL) and age at initial diagnosis, have prognostic significance.

Relapse occurs in the bone marrow in 15–20% of patients with ALL and has the most serious implications, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient followed by allogeneic stem cell transplantation can result in long-term survival for some patients with bone marrow relapse (see Chapter 177). **Chimeric antigen receptor** (CAR) T-cell technology will have an increasing role in the treatment of patients who have experienced a relapse of ALL (see Chapter 543). In addition, therapy targeted to the possible underlying pathogenic pathways (tyrosine kinase inhibitors) or cell receptors (blinatumomab) have demonstrated promising results in patients with relapsed or refractory disease (Fig. 544.5)

The incidence of **CNS relapse** has decreased to <5% since introduction of preventive CNS therapy. CNS relapse may be discovered at a routine LP in the asymptomatic patient. Symptomatic patients with relapse in the CNS usually present with signs and symptoms of increased intracranial pressure and can present with isolated cranial nerve palsies. The diagnosis is confirmed by demonstrating the presence of leukemic cells in the CSF. The treatment includes intrathecal medication and cranial or craniospinal irradiation. Systemic chemotherapy also must be used, because these patients are at high risk for subsequent bone marrow relapse. Most patients with leukemic relapse confined to the CNS do well, especially those in whom the CNS relapse occurs longer than 18 months after initiation of chemotherapy.

Testicular relapse occurs in <2% of males with ALL, usually after completion of therapy. Such relapse occurs as painless swelling of one or both testes. The diagnosis is confirmed by biopsy of the affected testis. Treatment includes systemic chemotherapy and possibly local irradiation. A high proportion of males with a testicular relapse can be successfully retreated, and the survival rate of these patients is good.

The most current information on treatment of childhood ALL is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/treatment/childALL/healthprofessional/).

SUPPORTIVE CARE

Close attention to the medical supportive care needs of the patients is essential in successfully administering aggressive chemotherapeutic programs. Patients with high WBC counts are especially prone to **tumor lysis syndrome** as therapy is initiated. The kidney failure associated with very high levels of serum uric acid can be prevented or treated with allopurinol or urate oxidase. Chemotherapy often produces severe myelosuppression, which can require erythrocyte and platelet transfusion and always requires a high index of suspicion and aggressive empirical antimicrobial therapy for sepsis in febrile children with neutropenia. Patients must receive prophylactic treatment for *Pneumocystis jiroveci* pneumonia during chemotherapy and for several months after completing treatment.

The successful therapy of ALL is a direct result of intensive and often toxic treatment. However, such intensive therapy can incur substantial academic, developmental, and psychosocial costs for children with ALL and considerable financial costs and stress for their families. Both long-term and acute toxicity effects can occur. An array of cancer care professionals with training and experience in addressing the myriad of problems that can arise is essential to minimize the complications and achieve an optimal outcome.

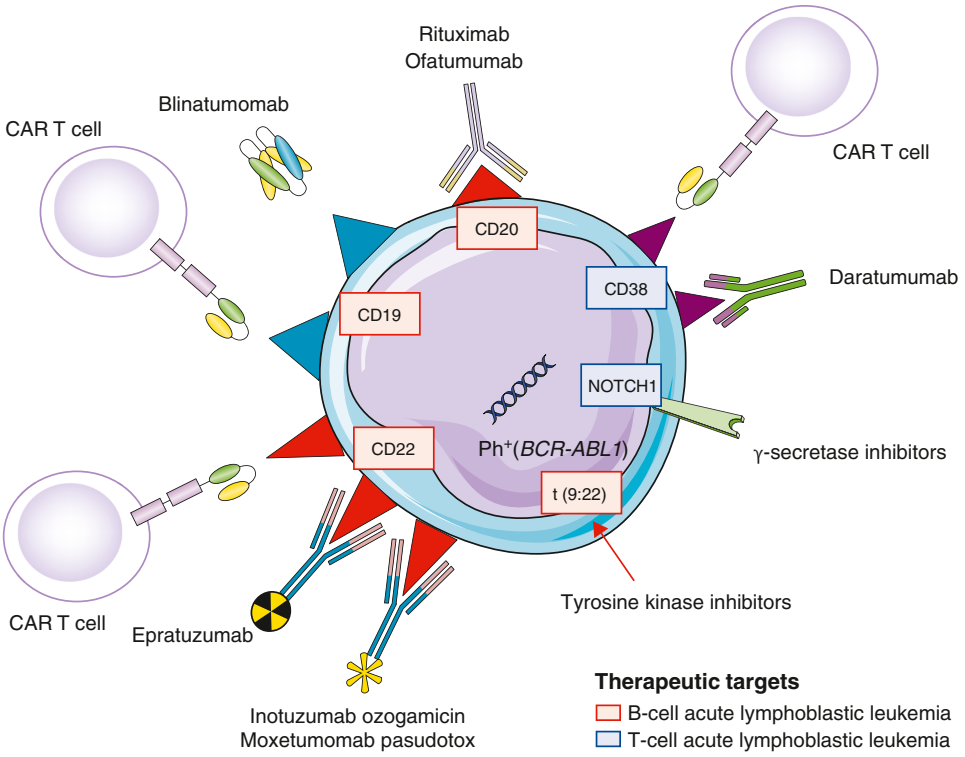

Fig. 544.5 New targeted therapy for acute lymphoblastic leukemia. CAR, Chimeric antigen receptor. *(From Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet. 2020;395:1146–1158. Fig. 2, p. 1153.)*

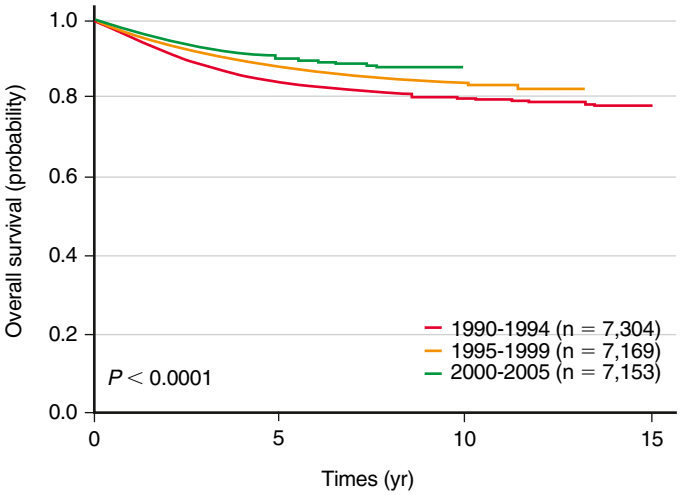

Fig. 544.6 Overall survival probabilities by treatment era for patients with acute lymphoblastic leukemia (ALL) in Children's Oncology Group trials in 1990–1994, 1995–1999, and 2000–2005. *(From Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. J Clin Oncol. 2012;30:1663–1669.)*

PROGNOSIS

Improvements in therapy and risk stratification have resulted in significant increases in survival rates, with current data showing overall 5-year survival of approximately 90% (Fig. 544.6). Although survivors are more likely to experience significant chronic medical conditions compared with siblings, including musculoskeletal, cardiac, and neurologic conditions, risk-adapted therapy has resulted in a decrease in late effects. Overall, long-term management following ALL should be conducted in a clinic where children and adolescents can be followed by a variety of specialists to address the challenges of these unique patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

544.2 Acute Myelogenous Leukemia

Julia C. Meade, Erika D. Friehling, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

EPIDEMIOLOGY

AML accounts for 11% of the cases of childhood leukemia in the United States; it is diagnosed in approximately 370 children annually. The relative frequency of AML increases in adolescence, representing 36% of cases of leukemia in 15-19 year olds. **Acute promyelocytic leukemia (APL)** is a subtype that is more common in certain regions of the world, but the incidence of the other types is generally uniform. Environmental risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), and organic solvents (benzene). Approximately 10% of children with AML are found to have a germline pathogenic variant predisposing them to leukemia. Certain syndromes are also known to increase the risk of leukemia: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1 (see Table 544.1).

CELLULAR CLASSIFICATION

The characteristic feature of AML is that >20% of bone marrow cells on bone marrow aspiration or biopsy touch preparations constitute a fairly homogeneous population of blast cells, with features similar to those that characterize early differentiation states of the myeloid-monocyte-megakaryocyte series of blood cells. Current practice requires the use of flow cytometry to identify cell surface antigens and use of chromosomal and molecular genetic techniques for additional diagnostic precision and to aid the choice of therapy. The WHO has proposed a new classification system that incorporates morphology, chromosome abnormalities, and specific gene pathogenic variants. This system provides significant biologic and prognostic information (Table 544.4).

CLINICAL MANIFESTATIONS

The production of symptoms and signs of AML is a result of replacement of bone marrow by malignant cells and caused by secondary bone

marrow failure. Patients with AML can present with any or all of the findings associated with marrow failure in ALL. In addition, patients with AML may present with signs and symptoms that are uncommon in ALL, including **subcutaneous nodules** or "blueberry muffin" lesions (especially in infants), infiltration of the gingiva (especially in monocytic subtypes), signs and laboratory findings of **disseminated intravascular coagulation** (especially indicative of APL), and discrete masses, known as **chloromas** or **granulocytic sarcomas**. These masses can occur in the absence of apparent bone marrow involvement and typically are associated with a t(8;21) translocation. Chloromas also may be seen in the orbit and epidural space.

DIAGNOSIS

Analysis of bone marrow aspiration and biopsy specimens of patients with AML typically reveals the features of a hypercellular marrow consisting of a monotonous pattern of cells. Flow cytometry and special stains assist in identifying myeloperoxidase-containing cells, thus confirming both the myelogenous origin of the leukemia and the diagnosis. Some chromosomal abnormalities and molecular genetic markers are characteristic of specific subtypes of disease (Table 544.5).

Table 544.4 WHO Classification of Acute Myeloid Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with *PML-RARA*
- AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
- AML with t(6;9)(p23;q34.1); *DEK-NUP214*
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
- *Provisional entity: AML with BCR-ABL1*
- AML with variant NPM1
- AML with biallelic pathogenic variants of CEBPA
- *Provisional entity: AML with variant RUNX1*

AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma
Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

AML, Acute myelogenous leukemia; APL, acute promyelocytic leukemia.
Adapted from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127:2391–2405.

PROGNOSIS AND TREATMENT

Aggressive multiagent chemotherapy is successful in inducing remission in approximately 85–90% of patients. Survival has increased dramatically since the 1970s, when only 15% of newly diagnosed patients survived, compared with a current survival rate of 60–70% with modern therapy (Fig. 544.7). Various induction chemotherapy regimens exist, typically including an anthracycline in combination with high-dose cytarabine. Targeting therapy to genetic markers may be beneficial (see Table 544.5). Up to 5% of patients die of either infection or bleeding before a remission can be achieved. Post-remission therapy is chosen based on a combination of cytogenetic and molecular markers of the leukemia as well as the response to induction chemotherapy (MRD assessment). Selected patients with favorable prognostic features [t(8;21); t(15;17); inv(16); *NPM1* pathogenic variants] and robust response to induction chemotherapy have improved outcomes with chemotherapy alone, with stem cell transplantation only recommended after a relapse. However, patients with unfavorable prognostic features (e.g., monosomies 7 and 5, 5q−, and 11q23 abnormalities) who have inferior outcomes with chemotherapy might benefit from stem cell transplant in first remission. With improvements in supportive care, there is no longer a substantial difference in mortality when comparing matched-related stem cell transplants to matched-unrelated stem cell transplants for AML.

Acute promyelocytic leukemia, characterized by a gene rearrangement involving the retinoic acid receptor [t(15;17); PML-RARA], is very responsive to **all-*trans*-retinoic acid (ATRA, tretinoin)** combined with anthracyclines and cytarabine. The success of this therapy makes marrow transplantation in first remission unnecessary for patients with this disease. Arsenic trioxide is an effective noncytotoxic therapy for APL. Data from trials in adults and children show that the use of combined ATRA and arsenic without cytotoxic drugs for initial therapy for selected patients is feasible and highly effective.

Increased **supportive care** is needed in patients with AML because the intensive therapy they receive produces prolonged bone marrow suppression with a very high incidence of serious infections, especially viridans streptococcal sepsis and fungal infection. These patients require prolonged hospitalization and prophylactic antimicrobials.

The most current information on treatment of AML is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/treatment/childAML/healthprofessional/).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 544.5 Prognostic Implications of Common Chromosomal Abnormalities in Pediatric Acute Myelogenous Leukemia

CHROMOSOMAL ABNORMALITY	GENETIC ALTERATION	USUAL MORPHOLOGY	PROGNOSIS
t(8;21)	*RUNX1-RUNX1T1*	Myeloblasts with differentiation	Favorable
inv(16)	*CBFB-MYHII*	Myeloblasts plus abnormal eosinophils with dysplastic basophilic granules	Favorable
t(15;17)	*PML-RARA*	Promyelocytic	Favorable
11q23 abnormalities	*KMT2A(MLL)* rearrangements	Monocytic	Unfavorable
FLT3 alterations	*FLT3*-ITD	Any	Unfavorable
del(7q), −7	Unknown	Myeloblasts without differentiation	Unfavorable

Adapted from Nathan DG, Orkin SH, Ginsburg D, et al., eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 6th ed. Philadelphia: Saunders; 2003: p. 1177.

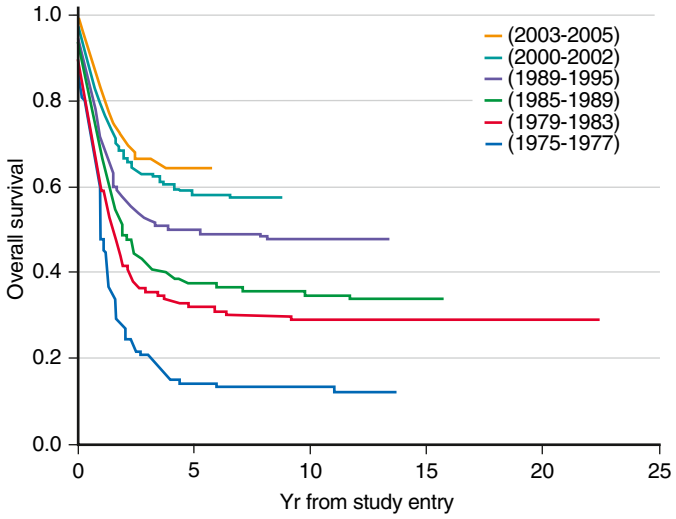

Fig. 544.7 Overall survival showing incremental improvements over the last 40 years in Children's Oncology Group and legacy trials in childhood acute myelogenous leukemia (AML). *(From Gamis AS, Alonzo TA, Perentesis JP, Meshinchi S. On behalf of the COG Acute Myeloid Leukemia Committee: Children's Oncology Group's 2013 blueprint for research: acute myeloid leukemia. Pediatr Blood Cancer. 2013;60:964–971.)*

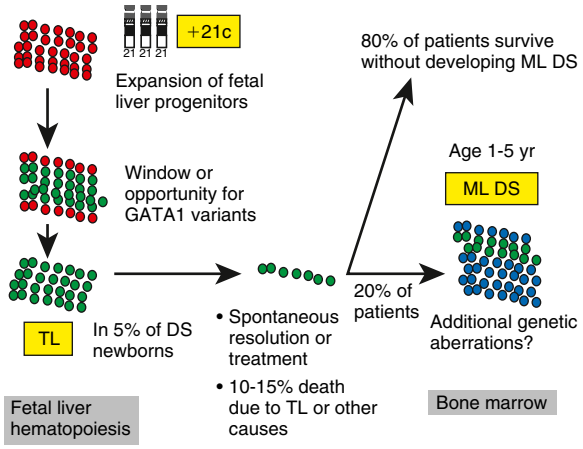

Fig. 544.8 Stepwise development of myeloid leukemia in Down syndrome (ML DS) following transient leukemia (TL). TL arises from expanded fetal liver progenitors as a result of constitutional trisomy 21, providing a window of opportunity for the occurrence of acquired mutations in the hematopoietic transcription factor GATA1. In most cases, TL spontaneously disappears, but some children need treatment because of severe TL-related symptoms. Approximately 20% of children with TL subsequently develop ML DS, which requires additional hits. *(From Zwaan MC, Reinhardt D, Hitzler J, Vyas P. Acute leukemias in children with Down syndrome. Pediatr Clin North Am. 2008;55:53–70.)*

544.3 Down Syndrome and Acute Leukemia and Transient Abnormal Myelopoiesis

A. Kim Ritchey, Julia C. Meade, Erika D. Friehling, David G. Tubergen, and Archie Bleyer

Acute leukemia occurs about 15-20 times more frequently in children with Down syndrome than in the general population (see Chapters 57 and 541). The ratio of ALL to AML in patients with Down syndrome is the same as that in the general population. The exception is during the first 3 years of life, when AML is more common. In children with Down syndrome who have ALL, the expected outcome of treatment has been slightly inferior to that for other children, a difference that can be partially explained by a lack of good prognostic characteristics, such as *ETV6-RUNX1* and trisomies, as well as the presence of genetic abnormalities associated with an inferior prognosis, such as *IKZF1*. However, studies of patients with Down syndrome and standard risk ALL show a 94% 10-year event-free survival. Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, resulting in substantial toxicity if standard doses are administered. However, in the case of AML, patients with Down syndrome have much better outcomes than children without Down syndrome, with a >90% long-term survival rate. After induction therapy, these patients receive therapy that is less intensive to decrease toxicity while maintaining excellent cure rates.

Approximately 10% of neonates with Down syndrome develop a **transient abnormal myelopoiesis (TAM)**, a unique myeloproliferative disorder characterized by high leukocyte counts, blast cells in the peripheral blood, and associated anemia, thrombocytopenia, jaundice, and hepatosplenomegaly. Hydrops fetalis is an uncommon manifestation of TAM and is associated with pleural effusions, ascites, cardiac infiltration, hepatic dysfunction, and anemia. Mortality is rare from TAM but is associated with hyperleukocytosis, prematurity, ascites, coagulopathy, and renal or hepatic dysfunction. These features usually resolve within the first 3 months of life. Although these neonates can require temporary transfusion support, they usually do not require chemotherapy. Low-dose cytarabine has been used to decrease mortality in patients with high WBC counts and life-threatening complications. Patients who have Down syndrome and who develop TAM require close follow-up, because 20–30% will develop typical leukemia (often **acute megakaryocytic leukemia**) by 3 years of age (mean onset, 16 months). *GATA1* variants (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome who have TAM and also in those with leukemia (Fig. 544.8). The presence of flow cytometry minimal residual disease at 3 months after a diagnosis of TAM is a risk factor for the development of myeloid leukemia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

544.4 Chronic Myelogenous Leukemia

Erika D. Friehling, Julia C. Meade, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

Chronic myelogenous leukemia (**CML**) is a clonal disorder of the hematopoietic tissue that accounts for 2–3% of all cases of childhood leukemia. Approximately 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the **Philadelphia chromosome**, resulting in a *BCR-ABL* fusion protein.

The presenting symptoms of CML are nonspecific and can include fever, fatigue, weight loss, and anorexia. Splenomegaly also may be present, resulting in pain in the left upper quadrant of the

abdomen. The diagnosis is suggested by a high WBC count with myeloid cells at all stages of differentiation in the peripheral blood and bone marrow. It is confirmed by cytogenetic and molecular studies that demonstrate the presence of the characteristic Philadelphia chromosome and the *BCR-ABL* gene rearrangement. This translocation, although characteristic of CML, is also found in a small percentage of patients with ALL.

The disease is characterized by an initial **chronic phase** in which the malignant clone produces an elevated leukocyte count with a predominance of mature forms but with increased numbers of immature granulocytes. In addition to leukocytosis, blood counts can reveal mild anemia and thrombocytosis. Typically, the chronic phase terminates 3-4 years after onset, when the CML moves into the **accelerated** or "blast crisis" **phase**. At this point, the blood counts rise dramatically, and the clinical picture is indistinguishable from acute leukemia. Additional manifestations can occur, including neurologic symptoms from hyperleukocytosis, which causes increased blood viscosity with decreased CNS perfusion.

Imatinib (Gleevec), an agent designed specifically to inhibit the *BCR-ABL* tyrosine kinase, has been used in adults and children and has shown an ability to produce major cytogenetic responses in >70% of patients (see Table 542.1). Experience in children suggests it can be used safely with results comparable to those seen in adults. Second-generation tyrosine kinase inhibitors, such as **dasatinib and nilotinib**, have improved remission rates in adults and are now included in the first-line therapy in that population. Both agents have been studied in children and have been found to be effective and safe. While waiting for a response to the tyrosine kinase inhibitor, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which gradually returns the leukocyte count to normal. **Treatment with a tyrosine kinase inhibitor is the current standard for pediatric CML.** Although not considered curative at this time, prolonged responses can be seen, and studies in adults have shown that, in select cases, treatment with the tyrosine kinase inhibitor can be stopped. The role of potentially curative human leukocyte antigen (HLA)-matched family donor stem cell transplant in management of pediatric CML is debated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

544.5 Juvenile Myelomonocytic Leukemia

Julia C. Meade, Erika D. Friehling, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

JMML, formerly termed **juvenile chronic myelogenous leukemia,** is a clonal proliferation of hematopoietic stem cells that typically affects children <2 years old. JMML is rare, constituting <1% of all cases of childhood leukemia. Patients with this disease do not have the Philadelphia chromosome characteristic of CML. Patients with JMML present with rashes, lymphadenopathy, splenomegaly, and hemorrhagic manifestations. Analysis of the peripheral blood often shows an elevated leukocyte count with increased monocytes, thrombocytopenia, and anemia with the presence of erythroblasts. The bone marrow shows a myelodysplastic pattern, with blasts accounting for <20% of cells. Most patients with JMML have been found to have pathogenic variants that lead to activation of the ***RAS* oncogene pathway**. About 90% have molecular changes in *NRAS, KRAS, NF1, CBL,* and *PTPN11*. Patients with **neurofibromatosis type 1** and **Noonan syndrome** have a predilection for this type of leukemia because they have germline mutations involved in *RAS* signaling. JMML in the setting of Noonan syndrome and CBL syndrome is unique, with most patients having a spontaneous resolution. However, for other patients with JMML, stem cell transplantation offers the best opportunity for cure, although outcomes are still poor.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

544.6 Infant Leukemia

A. Kim Ritchey, Erika D. Friehling, Julia C. Meade, David G. Tubergen, and Archie Bleyer

The incidence of infant acute leukemia is about 40 cases per million, or about 160 cases per year in the United States. Approximately 2% of cases of childhood leukemia occur before age 1 year. In contrast to the situation in older children, the ratio of ALL in infants to AML is 2:1. Leukemic clones have been noted in cord blood at birth before symptoms appear, and in one case, the same clone was noted in maternal cells (maternal-to-fetal transmission). Chromosome translocations can also occur in utero during fetal hematopoiesis, leading to malignant clone formation.

Several unique biologic features and a particularly poor prognosis are characteristic of ALL during infancy. Almost all are B cell with infrequent T cell. Seventy to 80% of the cases demonstrate rearrangements of the *KMT2A (MLL)* gene, found at the site of the 11q23 band translocation, the majority of which are the t(4;11). This subset of patients largely accounts for the very high relapse rate. These patients often present with hyperleukocytosis and extensive tissue infiltration producing organomegaly, including CNS disease. Subcutaneous nodules, known as **leukemia cutis**, and tachypnea caused by diffuse pulmonary infiltration by leukemic cells are observed more often in infants than in older children. The leukemic cell morphology is usually that of large, irregular lymphoblasts, with a phenotype negative for the CD10 (common ALL antigen) marker (pro-B), unlike most older children with B-ALL, who are $CD10^+$.

Very intensive chemotherapy programs, including stem cell transplantation, are being explored in infants with *KMT2A (MLL)* gene rearrangements, but none has yet proved satisfactory. Infants defined as high risk (*KMT2A*, age <6 months and WBC ≥300,000) have survival of only 30%, whereas infants with the *KMT2A* without other high-risk features have survival of 58%. Infants with leukemia who lack the *KMT2A* rearrangement have a prognosis somewhat inferior to that of older children with ALL.

Infants with AML often present with CNS or skin involvement and have a subtype known as **acute myelomonocytic leukemia.** The treatment may be the same as that for older children with AML, with similar outcome. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 545

Lymphoma

Jessica Hochberg, Stanton C. Goldman, and Mitchell S. Cairo

INTRODUCTION

Lymphoma is the third most common cancer among U.S. children (≤14 years old), with an annual incidence of 15 cases per 1 million children. It is the most common cancer in adolescents, accounting for >25% of newly diagnosed cancers in those 15-19 years old. The two broad categories of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), have different clinical manifestations and treatments.*

545.1 Hodgkin Lymphoma

Stanton C. Goldman, Jessica Hochberg, and Mitchell S. Cairo

Hodgkin lymphoma (HL) is a malignant process involving the lymphoreticular system that accounts for 6% of childhood cancers. In the United States, HL accounts for approximately 5% of cancers in children ≤14 years old; it accounts for approximately 15% of cancers in adolescents (15-19 years), making HL the most common malignancy in this age-group.

EPIDEMIOLOGY

The worldwide incidence of HL is approximately 2-4 new cases per 100,000 population per year. There is a bimodal age distribution, with peaks at 15-35 years of age and again after 50 years. HL is the most common cancer seen in adolescents and young adults and the third most common in children <15 years old. In developing countries, the early peak tends to occur before adolescence. A male predominance is found among young children but lessens with age. Infectious agents may be involved, such as human herpesvirus 6, cytomegalovirus, and Epstein-Barr virus (EBV). The role of EBV is supported by prospective serologic studies. Infection with EBV confers a fourfold higher risk of developing HL and may precede the diagnosis by years. EBV antigens have been demonstrated in HL tissues, particularly type II latent membrane proteins 1 and 2. Some studies have suggested that elevated copies of EBV by polymerase chain reaction correspond to worse prognosis. The EBV antigens latent membrane protein 1 and 2 have been used as targets for cytotoxic T-lymphocyte therapy in patients with relapsed/refractory HL.

PATHOGENESIS

The **Reed-Sternberg (RS) cell,** a pathognomonic feature of HL, is a large cell (15-45 μm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL, although similar cells are seen in infectious mononucleosis, NHL, and other conditions. The RS cell is clonal in origin and arises from the germinal center B cells but typically has lost most B-cell gene expression and function. There is no single simple genetic aberration that leads to malignant transformation of the RS cell; rather, a combination of somatic pathogenic variants, chromosomal instability, and complex chromosomal rearrangements has been reported with no particular pattern or frequency. This typically leads to cell regulation defects such as constitutive activation of the nuclear factor (NF)-κB pathway or abnormal regulation of the Bcl-2 family of proteins. HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, macrophages, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype. The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is important in the development and progression of HL. Reactive infiltration of eosinophils and $CD68^+$ macrophages and increased concentrations of cytokines, such as interleukin (IL)-1 and IL-6 and tumor necrosis factor, are all associated with an unfavorable prognosis. Other factors associated with a worse prognosis include advanced stage, the presence of systemic symptoms, decreased response to therapy, and slow response to therapy. In addition, evidence of $CD8^+$ T cells surrounding the RS cell offers evidence of an important role in T-cell promotion of malignant cell survival, perhaps through the CD30 and CD40 ligands found on RS cells as well as immune checkpoint inhibition pathways. Other features that distinguish the histologic subtypes include various degrees of fibrosis and the presence of collagen bands, necrosis, or malignant reticular cells (Fig. 545.1). The distribution of subtypes varies with age.

The **Revised World Health Organization Classification of Lymphoid Neoplasms** includes two modifications of the older Rye system. HL appears to arise in lymphoid tissue and spread to adjacent lymph node areas in a relatively orderly manner (Table 545.1). Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow (BM), or brain, and is usually associated with systemic symptoms.

CLINICAL MANIFESTATIONS

Patients typically present with painless, nontender, firm, rubbery cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. Clinically detectable hepatosplenomegaly may be encountered. Depending on the extent and location of nodal and extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or BM infiltration (anemia, neutropenia, or thrombocytopenia). Systemic symptoms, classified as **B symptoms**, that are considered important in staging are unexplained fever >38°C (100.4°F), weight loss >10% total body weight over 6 months, and drenching night sweats. Less common and not considered of prognostic significance are symptoms of pruritus, lethargy, anorexia, or pain. Patients also exhibit immune system deficiencies that often persist during and after therapy.

DIAGNOSIS

Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should undergo chest radiography to identify the presence of a large mediastinal mass before undergoing lymph node biopsy (Fig. 545.2). Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies. Once the diagnosis of HL is established, extent of disease (stage) should be determined to allow selection of appropriate therapy (Table 545.2). Evaluation includes history, physical examination, and imaging studies, including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and PET scan (Fig. 545.3). Laboratory studies should include a CBC to identify abnormalities that might suggest marrow involvement, ESR, and measurement of serum ferritin, which is of some prognostic significance and, if abnormal at diagnosis, serves as a baseline to evaluate the effects of treatment. A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax (see Fig. 545.2). This determines "bulk" disease and becomes prognostically significant. Chest CT more clearly defines the extent of a mediastinal mass if present and identifies hilar nodes and pulmonary parenchymal involvement, which may not be evident on chest radiographs (see Fig. 545.3). BM aspiration and biopsy should be performed to rule out advanced disease. Bone scans are performed in patients with bone pain and/or elevation of alkaline phosphatase. Fluorodeoxyglucose (FDG) PET imaging has advantages over traditional gallium scanning, with higher resolution, better dosimetry, less intestinal activity, and the potential to quantify disease (Table 545.3).

* The views expressed are the result of independent work and do not necessarily represent the views or findings of the U.S. Food and Drug Administration or the United States.

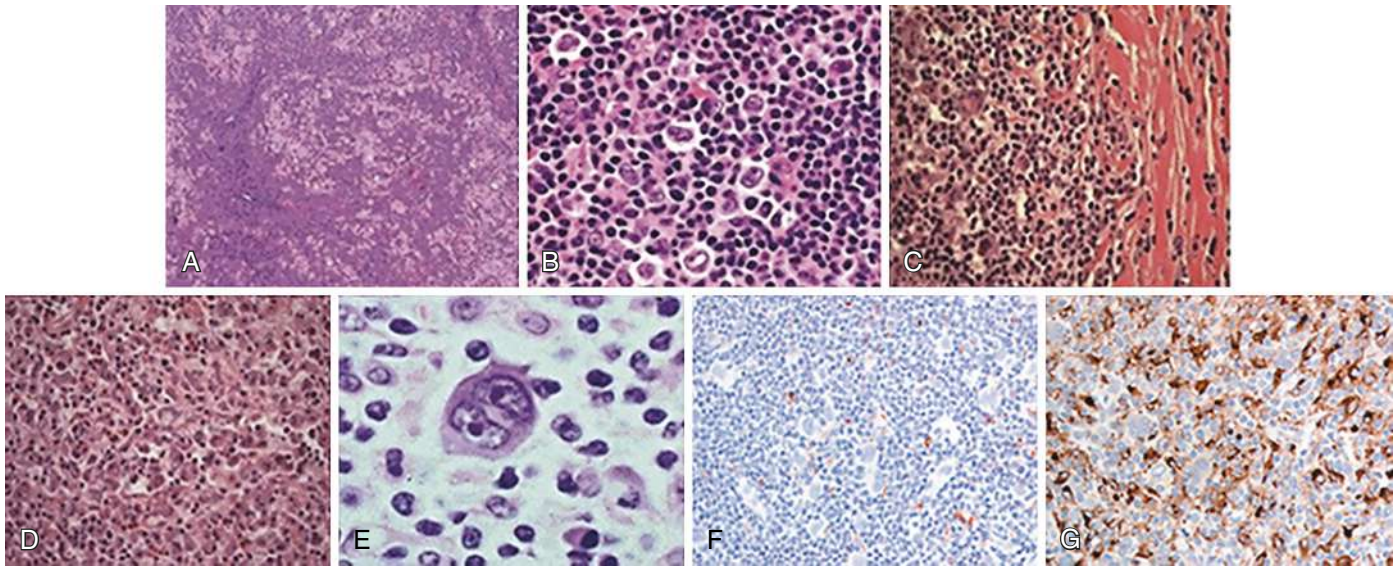

Fig. 545.1 Histologic subtypes of Hodgkin lymphoma. **A,** Hematoxylin and eosin (H&E) stains of nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) demonstrating a nodular proliferation with a moth-eaten appearance. **B,** High-power view demonstrating the neoplastic L and H cells found in NLPHL. **C,** Classic Hodgkin lymphoma, nodular sclerosis subtype. Large mononuclear and binucleate Reed-Sternberg cells are seen admixed in the inflammatory cell background. **D,** Classic Hodgkin lymphoma, mixed cellularity subtype, demonstrating increased numbers of Reed-Sternberg cells in a mixed inflammatory background without sclerotic changes. **E,** High-power view of a classic Reed-Sternberg cell showing binucleate cells with prominent eosinophilic nucleoli and relatively abundant cytoplasm. **F,** Few $CD68^+$ macrophages in a patient with successful treatment. **G,** Many $CD68^+$ macrophages in a treatment failure patient.

Table 545.1 New World Health Organization/Revised European–American Classification of Lymphoid Neoplasms for Hodgkin Lymphoma

Nodular lymphocyte predominance
Classical Hodgkin lymphoma
Lymphocyte rich
Mixed cellularity
Nodular sclerosis
Lymphocyte depletion

From Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. *Histopathology*. 2000;36:69–87.

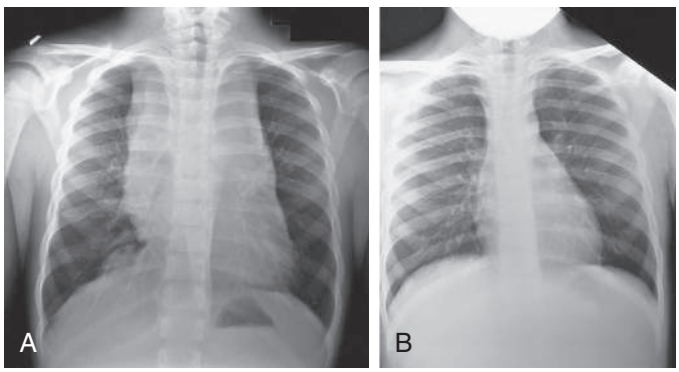

Fig. 545.2 **A,** Anterior mediastinal mass in a patient with Hodgkin disease before therapy. **B,** After 2 months of chemotherapy, the mediastinal mass has disappeared.

PET scans are essential as a prognostic tool in HL, enabling therapy to be reduced in those predicted to have a good outcome and identifying those at risk of relapse.

The staging classification currently used for HL was initially adopted at the **Ann Arbor Conference** in 1971 and was revised in 1989. The **Lugano classification** was developed in 2014 and incorporates standardized staging and response criteria for FDG-PET–avid lymphomas (see Table 545.2). HL can be subclassified into A or B categories: *A* is used to identify asymptomatic patients, and *B* is used for patients who exhibit any B symptoms. Extralymphatic disease resulting from direct extension of an involved lymph node region is designated by category *E*. A *complete response* in HL is defined as the complete resolution of disease on clinical examination and imaging studies, or at least 70–80% reduction of disease and a change from initial positivity to negativity on PET scanning, reflecting residual fibrosis, which is common.

Table 545.2 Lugano Classification for Hodgkin Lymphoma*

STAGE	INVOLVEMENT	EXTRANODAL STATUS
I	One node or group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Lung, liver, bone marrow, bone marrow, bone

*The absence or presence of fever >38°C (100.4°F) for 3 (some suggest 7) consecutive days, drenching night sweats, or unexplained loss of >10% of body weight in the 6 months preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

From *Cheson* BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059–3067.

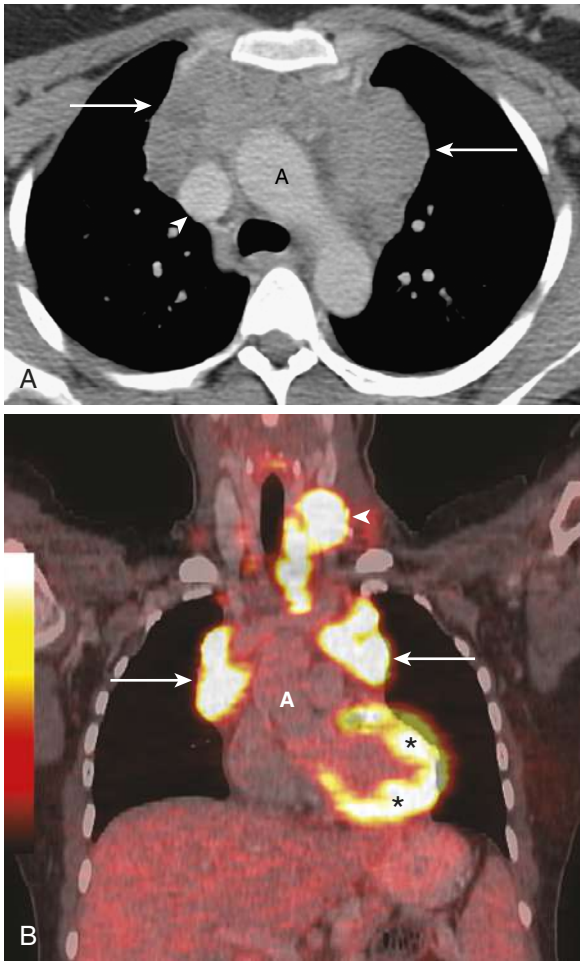

Fig. 545.3 Hodgkin lymphoma in a young individual. **A,** CT shows a homogeneous anterior mediastinal mass *(arrows)*. The *arrowhead* points to the superior vena cava. **B,** PET/CT in the coronal plane. The mass shows marked fluorodeoxyglucose (FDG) activity *(arrows)*. Note the associated left neck mass *(arrowhead)*. The left ventricle activity *(asterisks)* is normal. A, Ascending aorta. *(From Haaga JR, Boll DT, et al., eds. CT and MRI of the Whole Body [Vol, 1]. Philadelphia: Elsevier; 2017: Fig. 38-89, p. 1065.)*

Table 545.3 TEP Evaluation After Two Chemotherapy Cycles Using Deauville Criteria 5-Point Scale

	^{18}F-FDG UPTAKE
1	No uptake
2	Uptake lower than or equal to that of mediastinal blood pool
3	Uptake higher than that of mediastinum and lower than or equal to that of the liver
4	Uptake moderately higher than that of the liver at any site
5	Uptake markedly higher than that of the liver at any site or at new sites of disease, or both
X	New areas of uptake unlikely to be related to lymphoma

^{18}F-FDG, fluorodeoxyglucose F^{18}; TEP, technical expert panel.
From Brice P, de *Kerviler* E, Friedberg JW. Classical Hodgkin lymphoma. *Lancet.* 2021;398:1518–1526. Table 2.

TREATMENT

Multiple agents allow different mechanisms of action to have nonoverlapping toxicities so that full doses can be given to each patient. Chemotherapy and radiation therapy are both effective in the treatment of HL. Treatment of HL in pediatric patients is **risk adapted** and involves the use of combined chemotherapy with or without low-dose involved-field radiation therapy based on response. Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of *bulky nodal disease*. The development of effective multiagent combination **chemotherapy** and **immunotherapy** is a major milestone in the treatment of HL, resulting in a complete response rate of 70–80% and cure rate of 40–50% in patients with advanced-stage disease. However, this regimen also led to significant acute and long-term toxicity. The desire to reduce side effects and morbidity has stimulated attempts to reduce the intensity of chemotherapy, as well as radiation dose and volume. Combinations of chemotherapy have reduced the risk of secondary cancers. Also, current radiation therapy uses lower amounts of overall radiation in addition to narrowing the radiation treatment field to either involved-field or even involved-node irradiation. The current **Children's Oncology Group** and other trials are investigating whether radiation therapy can be eliminated altogether in patients who have a very good rapid early response to induction chemotherapy.

Chemotherapy agents used to treat children and adolescents with HL include cyclophosphamide, procarbazine, vincristine or vinblastine, prednisone or dexamethasone, doxorubicin, bleomycin, dacarbazine, etoposide, methotrexate, and cytosine arabinoside. The combination chemotherapy regimens in current use are based on **COPP** (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) or **ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), with the addition of prednisone, cyclophosphamide, and etoposide (**ABVE-PC** and **BEACOPP**) or **BAVD** (brentuximab vedotin, doxorubicin [Adriamycin], vincristine, dacarbazine) in various combinations for intermediate- and high-risk groups (Table 545.4). *Risk-adapted protocols* are based on both staging criteria and rapidity of response to initial chemotherapy. The aim is to reduce total drug doses and treatment duration and to eliminate radiation therapy, if possible.

Agents such as those that disrupt the NF-κB pathway or monoclonal antibodies (mAbs) that target RS tumor cells, as well as the benign reactive cells that surround them, are being investigated. Ongoing clinical trials report encouraging results with anti-CD20 antibody **(rituximab)**, particularly in nodular lymphocyte-predominant HL, for which trials in relapsed disease have shown an overall response rate of 94%. In addition, anti-CD30 agents are being used that target the RS cells themselves, where CD30 is abundantly expressed. **Brentuximab vedotin** is an antibody–drug conjugate approved by the U.S. Food and Drug Administration to treat HL. It combines the chimeric anti-CD30 antibody brentuximab linked to the antimitotic agent monomethyl auristatin E. This agent shows impressive efficacy as single-agent therapy in refractory HL and is being tested as part of up-front therapy combined with chemotherapy in patients with newly diagnosed disease where pediatric trials incorporating brentuximab to replace vincristine in the OEPA/COPDac backbone have demonstrated overall safety, tolerability, and efficacy with 97% event-free survival (EFS) and the ability to limit radiation to involved node radiation sites only. Furthermore, the combination of both brentuximab and rituximab, together with **AVD** chemotherapy in newly diagnosed patients, has shown 100% efficacy while allowing for the elimination of toxic alkylator agents, topoisomerase inhibitors, bleomycin, and any radiation in the majority of patients. **EBV-specific cytotoxic T lymphocytes (CTLs)** can also be generated from allogeneic donors for patients with advanced HL. In clinical trials, these cells show promising results, with enhanced antiviral activity and stabilization of disease. EBV-CTLs have been developed and are currently being investigated. These enhanced EBV-CTLs are designed to be latent membrane protein 1 and 2 specific and can be generated from second-party (in the case of BM transplant recipients) or even third-party donors for patients with refractory disease. These approaches represent an exciting direction in adoptive cellular tumor

Table 545.4 Chemotherapy Regimens for Children, Adolescents, and Young Adults with Hodgkin Lymphoma

CHEMOTHERAPY REGIMEN	CORRESPONDING AGENTS
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ABVD-Rituxan	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab
ABvVD	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine
ABvVD-R	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine, rituximab
AEPA/CAPDac	Brentuximab, etoposide, prednisone, and doxorubicin/cyclophosphamide, brentuximab, prednisone, and dacarbazine
ABVE (DBVE)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide
VAMP	Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone
OPPA ± COPP (females)	Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
OEPA ± COPP (males)	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP/ABV	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine
BEACOPP (advanced stage)	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone
ABVE-PC (DBVE-PC)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
ICE ± (Brentuximab)	Ifosfamide, carboplatin, etoposide ± brentuximab
Ifos/Vino ± (Brentuximab)	Ifosfamide, vinorelbine ± brentuximab

immunology, and it remains to be determined whether CTLs will have improved cytotoxicity that can overcome inhibitory signals.

RELAPSE

Most relapses occur within the first 3 years after diagnosis, but relapses as late as 10 years have been reported. Relapse cannot be predicted accurately with this disease. Poor prognostic features include tumor bulk, stage at diagnosis, extralymphatic disease, and presence of B symptoms. Patients who achieve an initial chemosensitive response but relapse or progress before 12 months from diagnosis are candidates for myeloablative chemotherapy and autologous stem cell transplantation (SCT), with or without radiation therapy. Retrospective studies show a significant decrease in relapse in patients with HL following allogeneic vs autologous SCT. Reduced-intensity conditioning or nonmyeloablative regimens are successful at reducing regimen-related morbidity and mortality associated with myeloablative allogeneic SCT while still achieving a strong graft versus HL effect. For more difficult-to-treat refractory cases, radioimmunotherapy agents such as Zevalin and Bexxar are being trialed, often in combination with SCT strategies. Both are monoclonal anti-CD20 antibodies to which a radioactive isotope is directly linked. Clinical trials show each to be more effective than rituximab in NHL patients, and there is some interest in studying their use in the CD20 subpopulation of HL patients. Tumors can evade the host immune system by exploiting immune checkpoint pathways, such as the CTL-associated protein four (CTLA-4) and **programmed-death protein 1 (PD-1)** pathways. PD-1 is a negative co-stimulatory receptor with increased expression reported on T cells. PD-1 is critical for suppression of T-cell activation, with binding of **programmed-death ligand 1 (PD-L1)** resulting in "T-cell exhaustion." Blockade of this interaction renders previously anergic T cells responsive to antigen. Evidence has shown that antitumor immune responses can be improved by blocking immune checkpoint inhibitors in the tumor microenvironment. Phase I trials of the PD-1 blocking mAbs **nivolumab** and **pembrolizumab** have shown significant promise in refractory patients. Phase II clinical trials suggest that combining immunotherapy such as rituximab or brentuximab with PD-1 checkpoint blockade will be highly effective against relapsed lymphomas and well tolerated, without treatment-related adverse events. With the success seen in relapsed or refractory patients, PD-1 blockade likely will have a role in frontline therapy as well where studies have shown promise in combination with chemotherapy in adults, with pediatric trials currently under investigation.

PROGNOSIS

With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an EFS of 85–90% and an overall survival (OS) at 5 years of >95%. Patients with advanced-stage disease have slightly lower EFS (80–85%) and OS (90%), respectively, although OS has approached 100% with dose-intense chemotherapy (Table 545.5). Prognosis after relapse depends on the time from completion of treatment to recurrence, site of relapse (nodal vs extranodal), and presence of B symptoms at relapse. Patients whose disease relapses >12 months after chemotherapy alone or combined-modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60–70%. A myeloablative autologous SCT in patients with refractory disease or relapse within 12 months of therapy results in a long-term survival rate of only 40–50%. Allogeneic SCT has shown promise in patients with poor-risk features at relapse/progression.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

545.2 Non-Hodgkin Lymphoma

Stanton C. Goldman, Jessica Hochberg, and Mitchell S. Cairo

Non-Hodgkin lymphoma (**NHL**) accounts for approximately 60% of lymphomas in children and is the second most common malignancy between ages 15 and 35 years. The annual incidence of pediatric NHL in the United States is 750-800 cases per year. In contrast to adult NHL, which is predominantly indolent, pediatric NHL is usually *high grade*. Although >70% of patients present with advanced disease, the prognosis has improved dramatically, with survival rates of 90–95% for localized disease and 80–95% for advanced disease.

EPIDEMIOLOGY

Although most children and adolescents with NHL present with de novo disease, a small number of patients have NHL secondary to specific etiologies, including inherited or acquired immunodeficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), virus-associated malignancy (e.g., HIV, EBV), and as part of genetic syndromes (e.g., ataxia-telangiectasia, Bloom syndrome).

Table 545.5 Treatment Regimens and Outcome by Disease Staging

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Hodgkin lymphoma	**Treatment**	*POG study 9426/GPOH-HD 95:* ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)	*Stanford/DAL-HD-90:* COPP-based or dose-intense multiagent chemotherapy + low-dose RT *POG 9426/CCG 5942:* ABVD-type therapy ± IFRT (risk adapted) *ABvVD-R*	*POG 8725/DAL-HD-90:* Dose-intense multiagent chemotherapy + low-dose RT *HD9/HD12/CCG 59704:* Dose-intense BEACOPP ± IFRT *AEPA/CAPDac* *ABvVD-R*
	Prognosis	5-yr EFS: 85–90% 5-yr OS: 95%	*Stanford/DAL-HD-90:* 5-yr EFS: 89–92% *POG 9426/CCG 5942:* 5-yr EFS: 84% 5-yr OS: 91% *ABvVD-R:* 5-yr EFS/OS: 100%	*POG 8725:* 5-yr EFS: 72–89% (age-based) *DAL-HD-90:* 5-yr EFS: 86% 5-yr OS: 85–90% *HD9/HD12/CCG 59704:* 5-yr EFS/OS: 88-93/~100% *AEPA/CAPDac:* 3 yr EFS/OS: 97.4%/98.7% *ABvVD-R:* 5-yr EFS/OS: 100%
Burkitt lymphoma and diffuse large B-cell lymphoma	**Treatment**	*FAB/LMB 96 Group A therapy:* Complete surgical resection followed by two cycles of chemotherapy	*FAB/LMB 96 Group B therapy:* Reduced cyclophosphamide and no maintenance therapy *COG ANHL01P1*: FAB/LMB Group B therapy + rituximab	*FAB/LMB 96 standard-intensity Group C therapy*: Reduction, induction, intensification, and maintenance therapy *COG ANHL01P1*: FAB/LMB Group C therapy + rituximab
	Prognosis	4-yr EFS: 98% (CI_{95} 94-99.5%) 4-yr OS: 99% (CI_{95} 96-99.9%)	*FAB/LMB96:* 4-yr EFS: 92% (CI_{95} 90–94%) 4-yr OS: 95% (CI_{95} 93–96%) *PMB DLBCL has worse prognosis (EFS/OS: 66/73%) *COG ANHL01P1:* 3-yr EFS 93% (CI_{95} 79-98%) 3-yr OS 95% (CI_{95} 83–99%)	*FAB/LMB96:* 4-yr FS:BM−/CNS−: 91% ± 3%BMCNS+: 85% ± 6%BM+/CNS+: 66% ± 7% *COG ANHL01P1:* 3-yr EFS/OS:BM+ or CNS+: 90% (CI_{95} 75–96%) CNS+: 93% (CI_{95} 61–99%)
Lymphoblastic lymphoma	**Treatment**	*NHL-BFM86/90/95:* Two cycles of ALL-type therapy *COG A5971:* ALL-type therapy × 2 yr without prophylactic cranial RT	No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)	*NHL-BFM86/90/95:* ALL-type therapy × 2 yr ± px CRT *CCG 5941:* Intensive chemotherapy × 1 yr + cranial RT if CNS + at diagnosis
	Prognosis	*COG A5971:* 5-yr EFS: 90 (CI_{95} 78–96%) 5-yr OS: 96 (CI_{95} 84–99%)	No intermediate group; see above	*NHL-BFM95:* 5-yr EFS: 90% ± 3% (III), 95 ± 5% (IV) *CCG 5941:* 5-yr EFS/OS: 78% ± 5%/85% ± 4%
Anaplastic large cell lymphoma	**Treatment**	*EICHNL ALCL 99:* Short intensive chemotherapy + HD MTX Completely resected stage I disease may be treated with surgery alone	No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)	*ALCL 99, CCG 5941:* Short intensive chemotherapy + HD MTX *COG ANHL0131*: APO (doxorubicin, prednisone, vincristine) ± vinblastine
	Prognosis	*EICHNL database:* 5-yr PFS: 89% (CI_{95} 82–96%) 5-yr OS: 94% (CI_{95} 89–99%)	No intermediate group; see above	*ALCL 99:* 2-yr EFS: 71% (CI_{95} 75–77%) 2-yr OS: 94% (CI_{95} 89-95%) *COG 5941:* 5-yr EFS 68% (CI_{95} 57–78%) 5-yr OS: 80% (CI_{95} 69–87%) *COG ANHL0131:* 2-yr EFS 79% (CI_{95} 71–88%) 2-yr OS 89% (CI_{95} 83–95%)

ABVD, Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ABvVD-R, doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine rituximab; AEPA/CAPDac, Adcetris (brentuximab vedotin), etoposide, prednisone, doxorubicin (adriamycin), cyclophosphamide, adcetris (brentuximab vedotin), prednisone, cacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; ANHL, Children's Oncology Group non-hodgkin lymphoma study; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children's Cancer Group; CI_{95}, 95% confidence interval; CNS, central nervous system (involvement); COG, Children's Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; DAL-HD, German-Austrian Lymphoma Froup Hodgkin 90 Study; EFS, event-free survival; EICHNL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved-field radiation therapy; LMB, Lymphome Malins de Burkitt; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.

However, most children in North America and Europe in whom NHL develops have no obvious genetic or environmental etiology.

PATHOGENESIS

Three most prevalent subtypes of childhood and adolescent NHL with different treatment approaches are **lymphoblastic lymphoma (LBL), mature B-cell lymphoma**, and **anaplastic large cell lymphoma** (**ALCL**; Figs. 545.4 and 545.5). LBL arises from precursor T lymphocytes and less often from precursor B lymphocytes, with biology and treatment approaches similar to acute lymphoblastic leukemia. Mature B-cell lymphomas comprise two main pathologies, **Burkitt lymphoma (BL)** and **diffuse large B-cell lymphoma (DLBCL)**. DLBCL is further divided into several subtypes: the *germinal center B-cell–like* subtype, which carries a favorable prognosis and accounts for most pediatric cases of DLBCL, and the subtypes with poorer prognosis, including *activated B-cell–like* and *primary mediastinal B-cell* subtypes. Primary mediastinal B-cell subtype of DLBCL shares molecular signature more akin to HL then germinal center–derived DLBCL. Most cases of ALCL are of mature T-cell origin, with a smaller percentage of null-cell and B-cell origin. Cellular surface markers can aid in differentiating NHL subtypes and present opportunities for specific antibody-targeted treatments. BL and DLBCL express the mature B-cell antigens CD20 (the target of rituximab) and CD22, whereas ALCL expresses the CD30 antigen (the target of the antibody conjugate brentuximab vedotin). Some pathologic subtypes have specific cytogenetic aberrations. Children with BL frequently have a driver genetic change involving the *MYC* gene juxtaposed to an immunoglobulin chain in the form of translocations: t(8;14) (90%) or, less often, a t(2;8) or t(8;22) translocation (10%). Children with BL who have additional chromosomal aberrations such as 13q deletion or complex karyotype have a poorer prognosis. Unlike adult DLBCL, a higher proportion of pediatric DLBCL may also have c-myc dysregulation with t(8;14) translocation (30%) and often have a complex (80%) and aneuploid (80%) karyotype. In recent years a Burkitt morphology lymphoma (Burkitt-like) that lacks a c-myc driver has been categorized by findings of 11q aberrations and several target genes such as chromatin remodeling complex pathogenic variants (INO80) that likely contribute to lymphomagenesis (Fig. 545.6). Patients with ALCL usually have a driver t(2;5) translocation (90%), which results in the formation of a fusion gene encoding the constitutively active nucleophosmin–anaplastic lymphoma kinase (ALK) tyrosine kinase and can be targeted by the oral agent, crizotinib. T-cell LBL harbors many of the same cytogenetic abnormalities as T-cell acute lymphoblastic leukemia (T-ALL), including rearrangements with breakpoints at 14q11.2 involving the T-cell receptor and multiple other rearranged genes. Loss of heterozygosity at chromosome 6q defines a poor-risk subgroup of T-LBL patients.

Genomic studies have offered insights into NHL pathogenesis as well as elucidated potential targets for novel therapies. Gene expression profiling of T-LBL and T-ALL has implicated the activation of oncogenic transcription factors as a result of aberrant T-cell receptor gene rearrangement. One of the most frequently activated signaling pathways is NOTCH1, which may be amenable to therapeutic targeting with γ-secretase inhibitors. In BL and DLBCL, extensive genomic work has identified unique gene expression signatures that

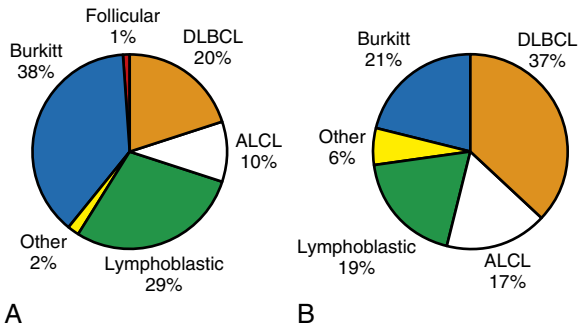

Fig. 545.4 Incidence of non-Hodgkin lymphoma subtypes. **A,** In 0- to 14-yr-old children. **B,** In 15- to 19-yr-old adolescents. ALCL, Anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma. *(Adapted from Hochberg J, Waxman IM, Kelly KM, et al. Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science. Br J Haematol. 2008;144:24–40.)*

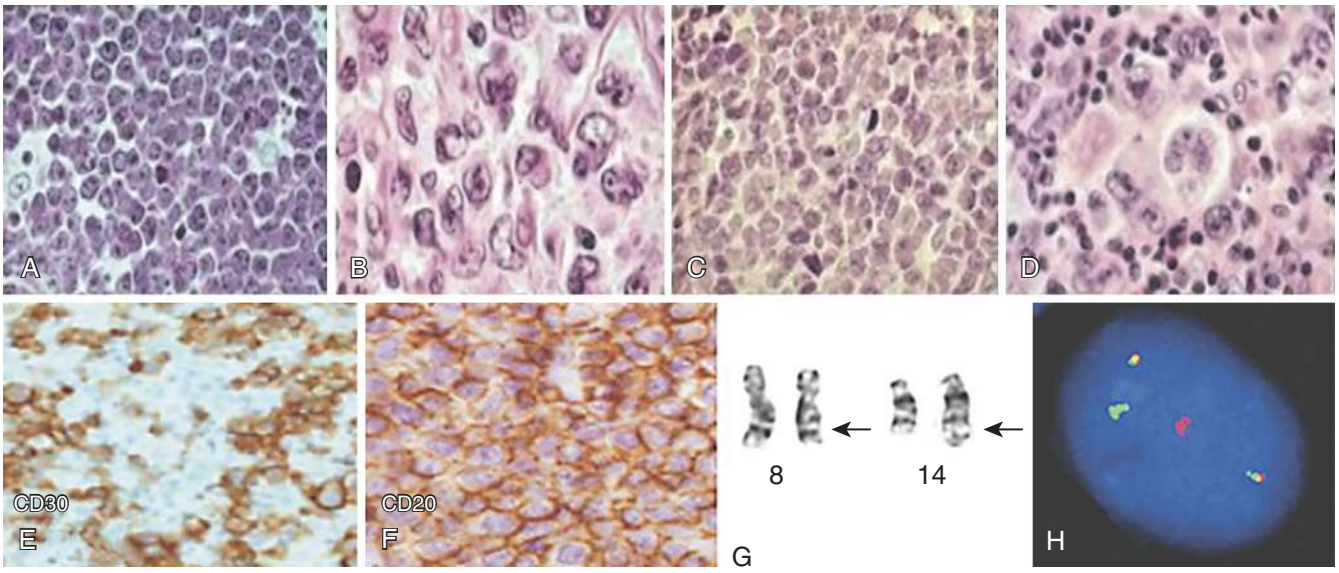

Fig. 545.5 Histologic subtypes of childhood and adolescent non-Hodgkin lymphoma. **A-D,** Hematoxylin and eosin (H&E) stains showing morphology of Burkitt lymphoma (**A,** high power), diffuse large B-cell lymphoma (**B,** high power), precursor T-lymphoblastic lymphoma (**C,** high power), and anaplastic large cell lymphoma (**D,** high power). **E** and **F,** Characteristic surface markers for anaplastic large cell lymphoma (ALCL) (CD30; **E**) and BL (CD20; **F**). **G** and **H,** Cytogenetic analysis of Burkitt lymphoma (BL) demonstrating t(8;14). **G,** Karyotype showing the conventional t(8;14)(q24;q32). **H,** Interphase fluorescence in situ hybridization showing a balanced translocation involving MYC and immunoglobulin (Ig) H loci. The chromosome eight centromere is labeled with spectrum aqua, MYC probe is labeled with spectrum orange, and IgH is labeled with spectrum green. Two fusion signals are seen, as well as one red and one green, representing the normal chromosomes. *(**A-D** from Cairo MS, Raetz E, Lim MS, et al. Childhood and adolescent non-Hodgkin lymphoma: new insights in biology and critical challenges for the future. Pediatr Blood Cancer. 2005;45:753–769; **E-H** from Giulino-Roth, Cesarman E. Molecular biology of Burkitt lymphoma. In Robertson ES, ed. Burkitt's Lymphoma. New York: Springer; 2012.)*

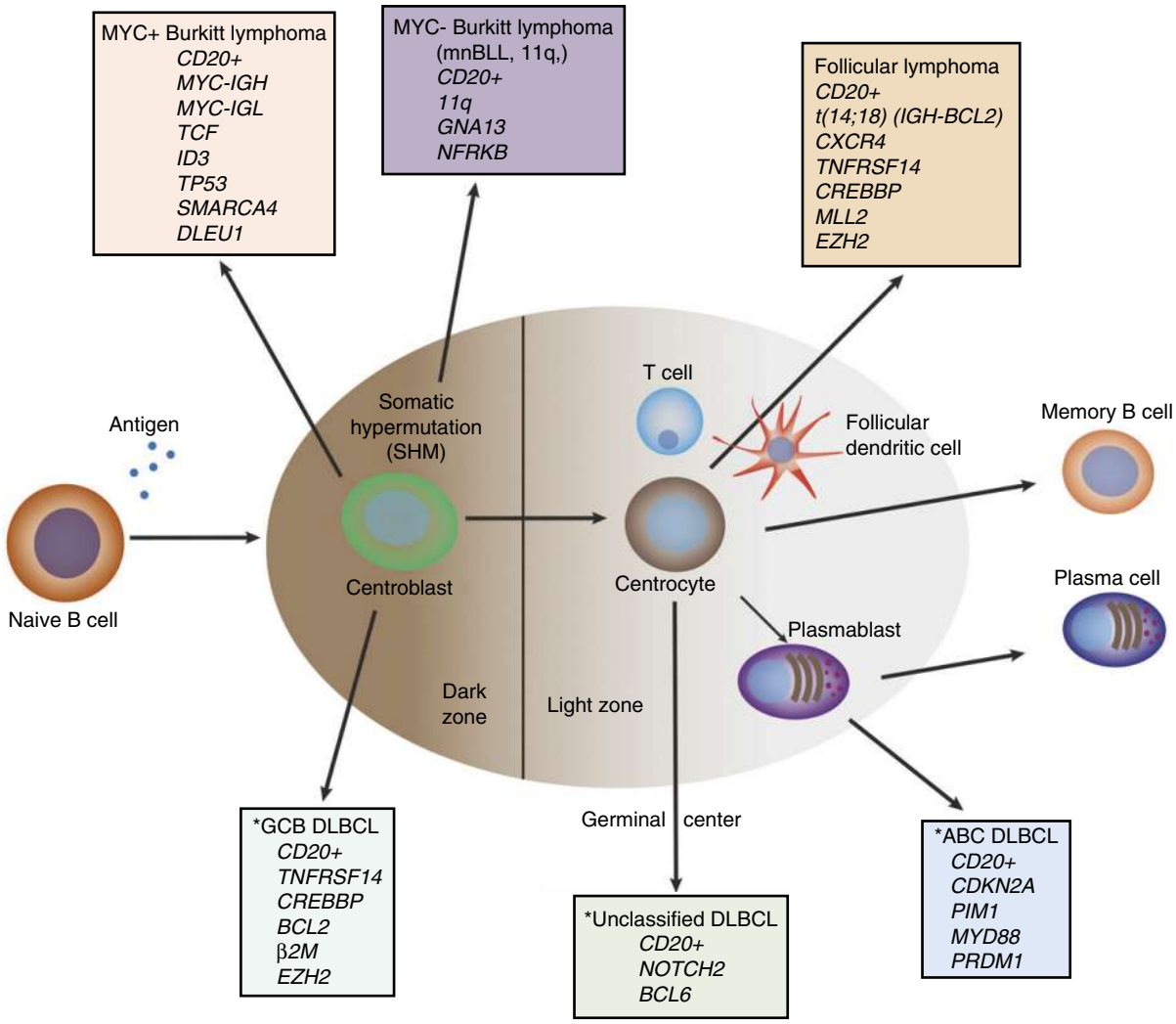

Fig. 545.6 Germinal center–derived B-cell lymphomagenesis. *Diffuse large B-cell lymphoma (DLBCL), recently subclassified as MCD, BNS, N1, and EZB subgroups. *(From Cairo, MS. A new Burkitt "look-alike" lymphoma. Blood. 2019;133[9]:889–891.)*

differentiate these two mature B-cell neoplasms. In addition, next-generation sequencing of BL has identified genetic lesions in *TCF3* and *ID3,* which lead to activation of the AKT/PI3 kinase pathway. Other genetic lesions that have been described in BL include loss of function of the chromatin remodeling genes *ARID1A* and *SMARCA4.* Importantly, many of these alterations are potentially targetable by agents that are in development.

CLINICAL MANIFESTATIONS

The clinical manifestations of childhood and adolescent NHL depend primarily on pathologic subtype and sites of involvement. The current revised staging system used for NHL is the **International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS),** which reflects our increasing ability to diagnose lower levels of organ involvement with disease. For instance, the older staging system (St. Jude/Murphy classification) did not account for molecular or flow cytometry involvement of BM, which is now reflected in the new system (Tables 545.6 and 545.7). Patients are further classified based on risk categories according to pediatric international cooperative group trials. Approximately 70% of patients with NHL present with advanced disease (stage III or IV), including extranodal disease with BM and CNS involvement. B symptoms of fever, weight loss, and night sweats can be seen, particularly in ALCL, but unlike HL, are not prognostic.

The primary site of tumor involvement and the pattern of metastasis vary by pathologic subtype. LBL typically manifests as a symptomatic mediastinal mass and also has a predilection for spreading to the BM, CNS, and testes in males. BL commonly manifests as a diffuse leukemia presentation or massive abdominal (*sporadic* type) or head and neck (*endemic* type) tumor and can metastasize to the BM or CNS. DLBCL usually manifests as either an abdominal or a mediastinal primary tumor and, rarely, disseminates to the BM or CNS. ALCL manifests either as a primary cutaneous manifestation (10%) or as systemic disease (90%) with dissemination to liver, spleen, lung, or mediastinum. BM or CNS disease is rare in ALCL. Site-specific manifestations of NHL include painless, rapid lymph node enlargement; cough or dyspnea with thoracic involvement; superior mediastinal syndrome; ascites, increased abdominal girth or intestinal obstruction with an abdominal mass; nasal congestion, earache, hearing loss, or tonsil enlargement with Waldeyer ring involvement; and localized bone pain.

NHL can present as a life-threatening **oncologic emergency**. These manifestations are important to recognize because these patients require intensive supportive care and, in some cases, alternative treatment. **Superior mediastinal syndrome** can occur as a consequence of a large mediastinal mass causing obstruction of blood flow or respiratory airways. Spinal cord tumors can cause cord compression and acute paraplegias requiring emergent radiation therapy. **Tumor lysis syndrome** (TLS) can occur from rapid cell turnover, which is especially common in BL. TLS can result in severe metabolic abnormalities, including hyperuricemia, hyperphosphatemia, hyperkalemia, and

Table 545.6 International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS)*

STAGE I
- A single tumor with the exclusion of the mediastinum and abdomen (N: nodal; EN: extranodal; bone (B) or skin (S): EN-B, EN-S)

STAGE II
- A single extranodal tumor with regional node involvement
- Two or more nodal areas on the same side of the diaphragm
- A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of the tumor to adjacent organs, it should be regarded as stage III)

STAGE III
- Two or more extranodal tumor(s) (including bone or skin: EN-B, EN-S) above and/or below the diaphragm
- Two or more nodal areas above and below the diaphragm
- Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic)
- Intraabdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except a primary gastrointestinal tract tumor [usually in the ileocecal region], with or without involvement of associated mesenteric nodes, that is completely resectable)
- Any paraspinal or epidural tumor, whether or not other sites are involved
- Single bone lesion with concomitant involvement of extranodal and/or nonregional nodal sites

STAGE IV
- Any of the previous findings with initial involvement of the central nervous system (stage IV CNS), bone marrow (stage IV BM), or both (stage IV combined) based on conventional methods, see Table 545.7
- For each stage, type of examination and degree of BM and CNS involvement should be specified, using the abbreviations listed in Table 545.7 to identify involvement

*Based on the classification proposed by Murphy (Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol*. 7:332–339, 1980.)
From Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. *J Clin Oncol*. 2015;33(18):2112–2118.

Table 545.7 Additional IPNHLSS Information*

BONE MARROW (BM) INVOLVEMENT

Stage IV disease, caused by BM involvement, is currently defined by morphologic evidence of ≥5% blasts or lymphoma cells by bone marrow aspiration. This applies to any histologic subtype and will be maintained in the IPNHLSS.

However, for each stage, type and degree of BM involvement (by bone marrow aspiration) should be specified, using the abbreviations below to identify involvement:
- BMm = BM positive by morphology (specify % lymphoma cells).
- BMi = BM positive by immunophenotypic methods (immunohistochemical/flow cytometry analysis) (specify % lymphoma cells).
- BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells).
- BMmol = BM positive by molecular techniques (PCR based) (specify level of involvement).

Same approach should be used for peripheral blood (PB) involvement (i.e., PBm, PBi, PBc, PBmol).

Note: Definition of BM involvement should be obtained from analysis of bilateral BM aspirates and BM biopsy.

CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT

CNS is considered involved in case of:
1. Any CNS tumor mass (identified by imaging techniques; i.e., CT, MRI).
2. In case of cranial nerve palsy that cannot be explained by extradural lesions.
3. In case of blasts morphologically identified in the cerebrospinal fluid (CSF).

Condition that defines CNS positivity should be specified: CNS positive/mass; CNS positive/palsy; CNS positive/blasts.

CSF status: CSF positivity is based on morphologic evidence of lymphoma cells.

CSF should be considered positive when any number of blasts is detected.

CSF unknown (e.g., not performed, technical difficulties).

Similar to BM, type of CSF involvement should be described whenever possible:
- CSFm = CSF positive by morphology (specify the number of blasts per microliter).
- CSFi = CSF positive by immunophenotype methods (immunohistochemical/flow cytometry analysis) (specify % lymphoma cells).
- CSFc = CSF positive by cytogenetic/FISH analysis (specify % lymphoma cells).
- CSFmol = CSF positive by molecular techniques (PCR based) (specify level of involvement).

*Until sufficient data are available, PET should be used with caution for staging, and PET results should be compared and discussed in light of other, more consolidated imaging approaches.
IPNHLSS, International Pediatric Non-Hodgkin Lymphoma Staging System Information; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction.
From Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. *J Clin Oncol*. 2015;33(18):2112–2118.

hypocalcemia. This can rapidly lead to renal insufficiency/failure, as well as cardiac abnormalities, if not aggressively treated.

LABORATORY FINDINGS

Recommended laboratory and radiologic testing includes CBC; measurements of electrolytes, lactate dehydrogenase, uric acid, calcium, phosphorus, BUN, creatinine, bilirubin, alanine aminotransferase, and aspartate aminotransferase; BM aspiration and biopsy; lumbar puncture with cerebrospinal fluid cytology, cell count, and protein; chest radiographs; and abdominal ultrasound for initial diagnosis. Staging relies on more detailed anatomic imaging, with CT for neck, chest, abdomen, and pelvic imaging and MRI the preferred modality for suspected CNS disease of brain and spine (Fig. 545.7). PET scan, usually with radioactive FDG for functional imaging, is more sensitive and has replaced gallium imaging. It is also an excellent modality for judging treatment response to therapy. Tumor tissue (i.e., biopsy, BM, cerebrospinal fluid, pleurocentesis/paracentesis fluid) should be tested by flow cytometry for immunophenotypic origin (T, B, or null) and cytogenetics (karyotype). Additional tests might include fluorescent in situ hybridization (FISH) or quantitative reverse-transcription polymerase chain reaction (RT-PCR) for specific genetic translocations, T- and B-cell gene rearrangement studies, and molecular profiling by oligonucleotide microarray or next-generation sequencing.

TREATMENT

The primary modality of treatment for childhood and adolescent NHL is *multiagent systemic chemotherapy and/or immunotherapy with intrathecal chemotherapy* (see Table 545.5). An international pediatric NHL response classification has been developed (IPNHLRC) (Tables 545.8 and 545.9). Surgery is used mainly for diagnosis. Radiation therapy is used only in special circumstances, such as CNS involvement in LBL or the presence of acute superior mediastinal syndrome or paraplegias. Newly diagnosed patients, especially those with BL or LBL, are at high risk for TLS. These patients require vigorous hydration, frequent electrolyte monitoring, and either a xanthine oxidase inhibitor (e.g., allopurinol, 10 mg/kg/day orally in three divided doses daily) or a recombinant urate oxidase (e.g., rasburicase, 0.2 mg/kg/day intravenously once daily for up to 5 days). Recombinant urate oxidase is preferred in patients with a high risk of tumor lysis but is *contraindicated* in patients with a history of G6PD deficiency.

Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma

Pediatric BL and DLBCL (except mediastinal primary B cell) are treated with the same mature B-cell NHL chemoimmunotherapy regimens

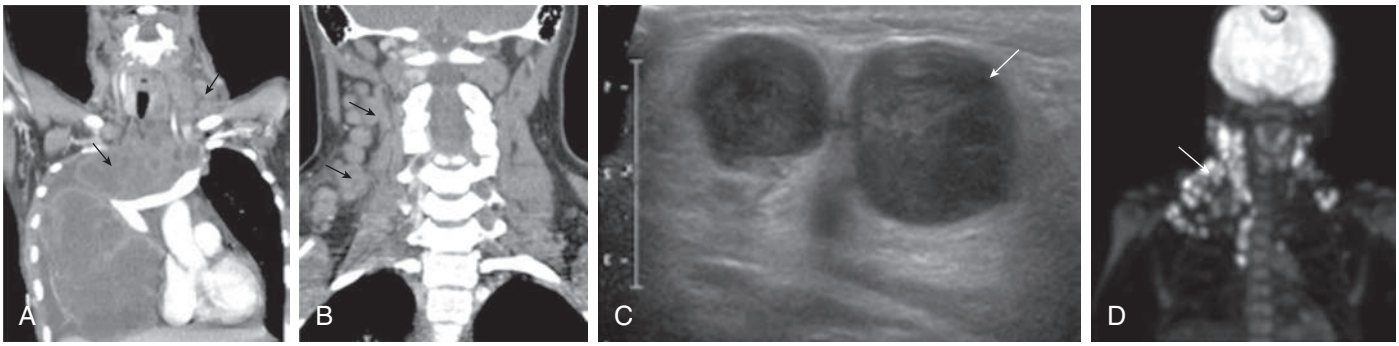

Fig. 545.7 Lymphoma. Coronal postcontrast CT images demonstrate extensive cervical (**A**) and mediastinal (**B**) lymphadenopathy *(arrows)*. **C,** Sonographic image demonstrates two enlarged lymph nodes with abnormal internal morphology *(arrow)*. **D,** PET scan demonstrates metabolically active conglomeration of right-sided cervical lymph nodes *(arrow)*. *(From Haaga JR, Boll DT, et al., eds. CT and MRI of the Whole Body (Vol. 1). Philadelphia: Elsevier; 2017: Fig. 26-15, p. 768.)*

Table 545.8 International Pediatric Non-Hodgkin Lymphoma Response Criteria (IPNHLRC)

Complete Response (CR): disappearance of all disease (three designations)

1. Complete (CR):
   a. CT or MRI reveals no residual disease or new lesions.
   b. Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques, as described in "supporting data," Table 545.9).
   c. Bone marrow (BM) and cerebrospinal fluid (CSF) morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 545.9).
2. Complete Response, biopsy negative (CRb):
   a. Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques, as described in Table 545.9) with no new lesions by imaging examination.
   b. BM and CSF morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 545.9).
   c. No new and/or progressive disease elsewhere.
3. Complete Response, unconfirmed (CRu):
   a. Residual mass is negative by FDG-PET; no new lesions by imaging examination.
   b. BM and CSF morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 545.9).
   c. No new and/or progressive disease elsewhere.

Partial Response (PR): 50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) on CT or MRI. FDG-PET may be positive (Deauville score of 4 or 5 with reduced lesional uptake compared with baseline). No new and/or PD. Morphologic evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques, as described in Table 545.9); however, there should be a 50% reduction in the percentage of lymphoma cells.

Minor Response (MR): Decrease in SPD is >25% but <50% on CT or MRI. No new and/or PD. Morphologic evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques, as described in Table 545.9); however, there should be a 25–50% reduction in the percentage of lymphoma cells.

No Response (NR): For those who do not meet CR, PR, MR, or PD criteria.

Progressive Disease (PD): For those with >25% increase in the SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with an increase in lesional uptake from baseline, or the development of new morphologic evidence of disease in the BM or CSF.

FDG-PET, Fluorodeoxyglucose positron emission tomography.
From Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. *J Clin Oncol.* 2015;33(18):2106–2111.

Table 545.9 Supporting IPNHLRC Data

BONE MARROW (BM) INVOLVEMENT

BM involvement is currently defined by morphologic evidence of lymphoma cells. This applies to any histologic subtypes.
Type and degree of BM involvement should be specified, using the following abbreviations:
- BMm = BM positive by morphology (specify % lymphoma cells).
- BMi = BM positive by immunophenotypic methods (histochemical/flow cytometry analysis) (specify % lymphoma cells).
- BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells).
- BMmol= BM positive by molecular techniques.

Same approach should be used for peripheral blood (PB) involvement (i.e., PBm, PBi, PBc, PBmol).

CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT

Cerebrospinal fluid (CSF) status: CSF positivity is based on morphologic evidence of lymphoma cells.
CSF should be considered positive when any number of blasts is detected.
CSF unknown (e.g., not performed, technical difficulties).
Similar to BM, type of CSF involvement should be described whenever possible:
- CSFm = CSF positive by morphology (specify the number of blasts/μL).
- CSFi = CSF positive by immunophenotypic methods (histochemical/flow cytometry analysis) (specify % lymphoma cells).
- CSFc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells).
- CSFmol = CSF positive by molecular techniques.

RESIDUAL MASS (RM)

RMm = Tumor detected by standard morphologic evaluation.
RMi = Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometry analysis).
RMc = Tumor detected by cytogenetic/FISH analysis.
RMmol = Tumor detected by molecular techniques.

FISH, Fluorescence in situ hybridization.
From Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. *J Clin Oncol.* 2015;33(18):2106–2111.

based on stage and risk stratification. For patients with localized disease, multiagent chemotherapy is given over 6 weeks, and the prognosis is excellent. In the international French-American-British Lymphoma, mature B cell [FAB/LMB 96] trial, patients with localized, completely resected disease received two cycles of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin), resulting in a 4-year OS of 99%. Advanced disease is usually treated with a 4- to 6-month regimen of multiagent chemoimmunotherapy, such as FAB/LMB 96 protocol therapy or

NHL-Berlin-Frankfurt-Mulnster-95 (BFM 95) protocol therapy with the addition of rituximab, with an OS of 79–90%. A subset of patients who likely require a different treatment approach have **primary mediastinal B-cell lymphoma (PMBCL)**. PMBCL is a histologic subtype that represents 2% of mature B-NHLs. Pediatric patients with PMBCL had an inferior outcome when treated with standard mature B-NHL protocols (EFS of only 66%). Alternative treatment strategies, including prolonged infusional chemotherapy, rituximab, and chimeric antigen receptor T cells expressing anti-CD19 mAbs, may benefit this group (see Chapter 543).

Rituximab is a mAb directed at CD20 that, when combined with standard chemotherapy, improves outcomes in adult patients with aggressive B-NHL (usually DLBCL). A window study of rituximab given to pediatric patients with newly diagnosed BL and DLBCL demonstrated its activity as a single agent with a response rate of 41%. Additionally, a Children's Oncology Group study examined the safety and pharmacokinetics of rituximab when added to standard chemotherapy for intermediate-risk patients. Rituximab was found to be safe, and survival in this cohort was the best reported to date (3-year OS of 95%). In a similar cohort of CNS-positive patients, the addition of rituximab to the chemotherapy backbone resulted in a 93% EFS. Based on this pilot data, an international randomized study of rituximab added to standard multiagent chemotherapy in advanced-stage pediatric patients enrolled over 300 patients. The randomized trial demonstrated that the addition of rituximab markedly prolonged EFS and OS. The EFS at 3 years was 94% compared to 82% in patients who received chemotherapy alone. As expected with an antibody to a protein on the surface of normal mature B cells, there was a higher incidence of low immunoglobulin levels in rituximab-treated patients up to 1 year poststudy entry. Rituximab is standard-of-care therapy for pediatric mature B-NHL with advanced disease at presentation. These patients make up roughly ~30% of all mature B-NHL. A study of dose substitution of anthracycline (doxorubicin) intensity with rituximab in children and adolescents with good-risk mature B-cell lymphoma noted reduction of anthracycline dramatically reduced mucositis and febrile admissions during the intensive induction phases of therapy and was associated with 100% EFS and OS. With the success of rituximab in pediatric mature B-NHL and the poor outcome of recurrent or refractory disease, there is interest in improving immunotherapy in up-front patients. Polatuzumab vedotin is a CD79b-directed antibody conjugated to an antimitotic agent. The therapy has been approved in conjunction with rituximab and chemotherapy for adult refractory DLBCL. A study to determine the feasibility and safety of the addition of polatuzumab vedotin in combination with rituximab and FAB chemotherapy in patients with intermediate and high-risk mature B-NHL is in progress.

Lymphoblastic Lymphoma

Localized or advanced LBL requires 12-24 months of therapy, including chemotherapy, intrathecal therapy, and cranial radiation in CNS-positive lymphomas. The best results in advanced LBL have been obtained using therapeutic approaches mirroring those for childhood acute leukemia, including induction, consolidation, interim maintenance, and reinduction (advanced disease only) phases, as well as a year-long maintenance phase with 6-mercaptopurine and methotrexate. For patients with relapsed disease, the outcome is poor (OS of 10%), and novel treatments are needed. *Nelarabine,* a purine analog with significant T-lymphocyte toxicity, has completed testing in primary therapy for T-LBL in conjunction with a much larger cohort of T-ALL patients. Nelarabine was demonstrated in the trial to improve disease-free survival at 4 years and to reduce the risk of CNS relapses. The smaller subset of patients with advanced LBL did not have a benefit demonstrated to nelarabine, but this subset was underpowered, and most U.S. centers are now including nelarabine in the up-front treatment of all T-LBL patients.

Anaplastic Large Cell Lymphoma

For patients who present with localized disease, surgical resection alone is sufficient. The majority of patients, however, have advanced disease, which requires multiagent chemotherapy. Various chemotherapy regimens have been studied, with similar outcomes and survival of 70–79%. CNS prophylaxis consists of intrathecal chemotherapy, although this may be omitted with the substitution of high-dose methotrexate.

Two novel targeted agents have shown substantial promise in early-phase trials in ALCL. The CD30 antibody–drug conjugate **brentuximab vedotin** and the ALK inhibitor **crizotinib** both have impressive activity and minimal toxicity in patients with relapsed ALCL. A trial piloted the addition of brentuximab vedotin in newly diagnosed advanced ALCL patients with impressive 2-year EFS of 79% and OS of 97% among ~70 patients. There were no toxic deaths with combination brentuximab and chemotherapy and no severe neurotoxicity.

Relapsed Non-Hodgkin Lymphoma

Patients with NHL in whom progressive or relapsed disease develops require reinduction chemotherapy and may require either allogeneic or autologous SCT. A notable exception is ALCL, where low-dose approaches such as prolonged vinblastine have been efficacious for some patients. The specific reinduction regimen or transplantation type depends on the pathologic subtype, previous therapy, site of reoccurrence, and stem cell donor availability. Novel reinduction approaches are being investigated, including a type II CD20 antibody, *obinutuzumab,* alone and in combination with chemotherapy, *ibrutinib,* a BTK inhibitor alone and in combination with chemotherapy, and *idelalisib,* a PI3K delta inhibitor alone and in combination with chemotherapy. Although there are no randomized trials examining autologous versus allogeneic SCT for relapsed NHL, data from retrospective studies suggest that outcomes are similar, with the exception of LBL and ALCL, for which allogeneic SCT is superior, perhaps because of a graft versus lymphoma effect.

Native (autologous) patient T cells have been genetically manipulated to produce a T-cell vs leukemia or lymphoma response. Tisagenlecleucel (Kymriah) is a CD19-directed genetically modified autologous T-cell immunotherapy first approved for patients under 25 years with precursor B-ALL. The immunotherapy has been approved in adults with relapsed mature DLBCL after two prior lines of systemic therapy. An additional CD19-directed immunotherapy, axicabtagene ciloleucel, has been approved for recurrent adult mature B-NHL. The responses have been less impressive in adult DLBL to those seen in childhood adolescent and young adult ALL, but continued work with different target antigens and genetic manipulation of the constructs is ongoing. These T-cell–modified products, although autologous, can lead to a cytokine release syndrome and CNS toxicities that can be severe.

Because relapsed NHL can be difficult to treat, efforts have been made to identify patients at higher risk of relapse to tailor initial therapy. The measurement of **minimal residual disease** may serve as a prognostic marker and aid in risk stratification. Minimal residual disease is prognostic in ALCL and LBL. In ALCL, there is also evidence that a humoral response to the ALK kinase can be used to predict outcome, with a superior outcome in patients who mount an antibody titer to ALK.

COMPLICATIONS

Patients receiving multiagent chemotherapy for advanced disease are at acute risk for mucositis, infections, cytopenias that require red blood cell and platelet blood product transfusions, electrolyte imbalances, and poor nutrition. Long-term complications include the risk of growth retardation, cardiac toxicity, gonadal toxicity with infertility, and secondary malignancies.

PROGNOSIS

The prognosis is excellent for most forms of childhood and adolescent NHL (see Table 545.5). Patients with localized disease have a 90–100% survival rate, and those with advanced disease have an 80–95% survival rate. Because outcomes for pediatric patients with NHL have improved substantially, the focus has now shifted to minimizing the *long-term toxicity of therapy.* Novel targeted agents are desirable because they have the potential to improve outcomes and decrease the reliance on toxic conventional chemotherapy. An ongoing multi-institutional study is testing the reduction of anthracycline to decrease short-term (mucositis) and long-term (cardiac health) complications of therapy by incorporation of immunotherapy in mature B-NHL, with promising results to date.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

545.3 Late Effects in Children and Adolescents with Lymphoma

Jessica Hochberg, Stanton C. Goldman, and Mitchell S. Cairo

The majority of patients with newly diagnosed HL and NHL have OS rates >90%. There are approximately 270,000 survivors of childhood cancer in the United States, or about one of every 640 adults between ages 20 and 40. However, this survival has often been achieved at the expense of an increased relative risk of long-term complications, including solid tumors, leukemia, cardiac disease, pulmonary complications, thyroid disease, and infertility. An analysis of >1,000 long-term childhood NHL survivors found increased rates of death >20 years after treatment. A review of the National Cancer Institute Surveillance, Epidemiology, and End Results data over a 25-year follow-up demonstrates that the relative survival curves do not plateau after 10 years following diagnosis of HL, but rather accelerate. This finding highlights the importance of late morbidity and mortality among survivors of lymphoma. The incidence of Grade 3-5 adverse health conditions is >15% in adult survivors of childhood HL treated with chemoradiotherapy regimens. Radiation therapy has been shown to further compound the risk for late mortality, obesity, and organ dysfunction with worsening effects on cardiovascular, pulmonary, and thyroid function. The first **Childhood Cancer Survivor Study**, a retrospective cohort study of 10,397 cancer survivors, shows that 62.3% of survivors report at least one chronic condition, with 27.5% reporting severe or life-threatening conditions. The survivor's adjusted relative risk of a severe or life-threatening chronic condition, compared with that of a sibling, was 8.2 (95% confidence interval, 6.9-9.7). Studying disease-specific health outcomes, both HL and NHL were found to be associated with a cumulative incidence of chronic health conditions **approaching 70–80%, with severe conditions reported in ~50% of HL survivors** (Fig. 545.8).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

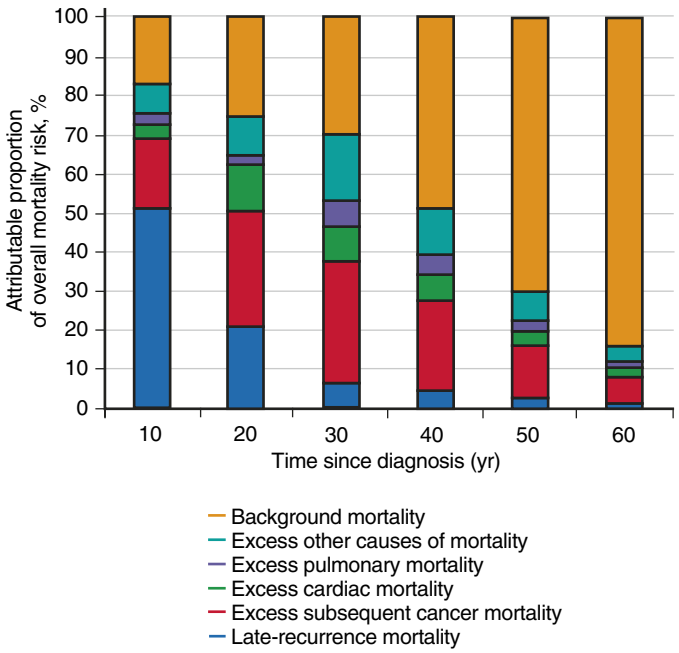

Fig. 545.8 Percentage of attributable proportions of overall mortality risk in survivors of childhood cancer. *(Adapted from Yeh JM, Nekhlyudov L, Goldie SJ, et al. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. Ann Intern Med. 2010;152[7]:409– 417.)*

Chapter 546

Central Nervous System Tumors in Childhood

Wafik Zaky

Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the most common malignancy in childhood and adolescence. The overall mortality among this group approaches 30%. Patients with CNS tumors have the highest morbidity, primarily neurologic, of all children with malignancies. Outcomes have improved with innovations in neurosurgery, imaging, and radiation therapy as well as the introduction of chemotherapy and biologic agents as a therapeutic modality. The treatment approach for the majority of these tumors is multimodal. Surgery with complete resection, if feasible, is the foundation, with radiation therapy and chemotherapy utilized according to the diagnosis, patient age, and other factors.

ETIOLOGY

The etiology of pediatric CNS tumors is not well defined. An overall female predominance exists in the incidence of CNS tumors, but male predominance is noted in the incidence of high-grade tumors like glioblastoma multiforme, medulloblastoma, and ependymoma. Familial syndromes associated with an increased incidence of brain tumors account for approximately 5% of cases (Table 546.1). Cranial exposure to ionizing radiation also is associated with a higher incidence of CNS tumors. There are sporadic reports of CNS tumors within families without evidence of a heritable syndrome.

EPIDEMIOLOGY

Approximately 5,550 primary brain tumors are diagnosed each year in children and adolescents in the United States, with an average annual age adjusted incidence rate of 5.65 per 100,000 population. It is the most common cancer in patients 0-14 years of age and the leading cause of cancer-related death in this age-group.

PATHOGENESIS

More than 100 histologic categories and subtypes of primary brain tumors are described in the World Health Organization (WHO) classification of tumors of the CNS. In children 0-14 years of age, the most common tumors are pilocytic astrocytomas (PAs) and embryonal tumors (i.e., medulloblastoma/primitive neuroectodermal tumors [PNETs]). In adolescents (15-19 years), the most common tumors are pituitary/craniopharyngeal tumors and PAs (Fig. 546.1).

There is a slight predominance of infratentorial tumor location (43.2%), followed by the supratentorial region (40.9%), spinal cord (4.9%), and multiple sites (11%) (Fig. 546.2, Table 546.2). There are age-related differences in the primary location of tumor. During the first year of life, supratentorial tumors predominate and include, most commonly, choroid plexus complex tumors and germ cell tumors. In children 1-10 years of age, infratentorial tumors predominate, due to the high incidence of juvenile PA and medulloblastoma. After 10 years of age, supratentorial tumors predominate, with diffuse astrocytomas (DAs) most common. Tumors of the optic pathway and hypothalamus region, the brainstem, and the pineal–midbrain region are more common in children and adolescents than in adults. Additionally, some tumors are more common in males (astrocytic and germ cell tumors), whereas meningioma and craniopharyngiomas are more common in females. Malignant tumors are more common in White children (embryonal and astrocytic neoplasms), whereas low-grade tumors are more common in Black children (meningiomas and craniopharyngiomas).

545.3 Late Effects in Children and Adolescents with Lymphoma

Jessica Hochberg, Stanton C. Goldman, and Mitchell S. Cairo

The majority of patients with newly diagnosed HL and NHL have OS rates >90%. There are approximately 270,000 survivors of childhood cancer in the United States, or about one of every 640 adults between ages 20 and 40. However, this survival has often been achieved at the expense of an increased relative risk of long-term complications, including solid tumors, leukemia, cardiac disease, pulmonary complications, thyroid disease, and infertility. An analysis of >1,000 long-term childhood NHL survivors found increased rates of death >20 years after treatment. A review of the National Cancer Institute Surveillance, Epidemiology, and End Results data over a 25-year follow-up demonstrates that the relative survival curves do not plateau after 10 years following diagnosis of HL, but rather accelerate. This finding highlights the importance of late morbidity and mortality among survivors of lymphoma. The incidence of Grade 3-5 adverse health conditions is >15% in adult survivors of childhood HL treated with chemoradiotherapy regimens. Radiation therapy has been shown to further compound the risk for late mortality, obesity, and organ dysfunction with worsening effects on cardiovascular, pulmonary, and thyroid function. The first **Childhood Cancer Survivor Study**, a retrospective cohort study of 10,397 cancer survivors, shows that 62.3% of survivors report at least one chronic condition, with 27.5% reporting severe or life-threatening conditions. The survivor's adjusted relative risk of a severe or life-threatening chronic condition, compared with that of a sibling, was 8.2 (95% confidence interval, 6.9-9.7). Studying disease-specific health outcomes, both HL and NHL were found to be associated with a cumulative incidence of chronic health conditions **approaching 70–80%, with severe conditions reported in ~50% of HL survivors** (Fig. 545.8).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

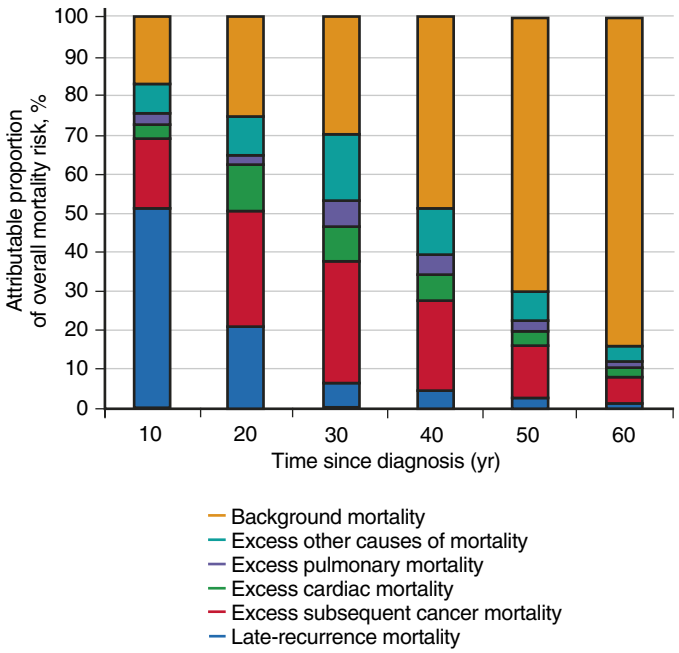

Fig. 545.8 Percentage of attributable proportions of overall mortality risk in survivors of childhood cancer. *(Adapted from Yeh JM, Nekhlyudov L, Goldie SJ, et al. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. Ann Intern Med. 2010;152[7]:409– 417.)*

Chapter 546

Central Nervous System Tumors in Childhood

Wafik Zaky

Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the most common malignancy in childhood and adolescence. The overall mortality among this group approaches 30%. Patients with CNS tumors have the highest morbidity, primarily neurologic, of all children with malignancies. Outcomes have improved with innovations in neurosurgery, imaging, and radiation therapy as well as the introduction of chemotherapy and biologic agents as a therapeutic modality. The treatment approach for the majority of these tumors is multimodal. Surgery with complete resection, if feasible, is the foundation, with radiation therapy and chemotherapy utilized according to the diagnosis, patient age, and other factors.

ETIOLOGY

The etiology of pediatric CNS tumors is not well defined. An overall female predominance exists in the incidence of CNS tumors, but male predominance is noted in the incidence of high-grade tumors like glioblastoma multiforme, medulloblastoma, and ependymoma. Familial syndromes associated with an increased incidence of brain tumors account for approximately 5% of cases (Table 546.1). Cranial exposure to ionizing radiation also is associated with a higher incidence of CNS tumors. There are sporadic reports of CNS tumors within families without evidence of a heritable syndrome.

EPIDEMIOLOGY

Approximately 5,550 primary brain tumors are diagnosed each year in children and adolescents in the United States, with an average annual age adjusted incidence rate of 5.65 per 100,000 population. It is the most common cancer in patients 0-14 years of age and the leading cause of cancer-related death in this age-group.

PATHOGENESIS

More than 100 histologic categories and subtypes of primary brain tumors are described in the World Health Organization (WHO) classification of tumors of the CNS. In children 0-14 years of age, the most common tumors are pilocytic astrocytomas (PAs) and embryonal tumors (i.e., medulloblastoma/primitive neuroectodermal tumors [PNETs]). In adolescents (15-19 years), the most common tumors are pituitary/craniopharyngeal tumors and PAs (Fig. 546.1).

There is a slight predominance of infratentorial tumor location (43.2%), followed by the supratentorial region (40.9%), spinal cord (4.9%), and multiple sites (11%) (Fig. 546.2, Table 546.2). There are age-related differences in the primary location of tumor. During the first year of life, supratentorial tumors predominate and include, most commonly, choroid plexus complex tumors and germ cell tumors. In children 1-10 years of age, infratentorial tumors predominate, due to the high incidence of juvenile PA and medulloblastoma. After 10 years of age, supratentorial tumors predominate, with diffuse astrocytomas (DAs) most common. Tumors of the optic pathway and hypothalamus region, the brainstem, and the pineal–midbrain region are more common in children and adolescents than in adults. Additionally, some tumors are more common in males (astrocytic and germ cell tumors), whereas meningioma and craniopharyngiomas are more common in females. Malignant tumors are more common in White children (embryonal and astrocytic neoplasms), whereas low-grade tumors are more common in Black children (meningiomas and craniopharyngiomas).

Table 546.1 Familial Syndromes Associated with Pediatric Brain Tumors

SYNDROME	CENTRAL NERVOUS SYSTEM MANIFESTATIONS	CHROMOSOME	GENE
Neurofibromatosis type 1 (autosomal dominant)	Optic pathway gliomas, astrocytoma, malignant peripheral nerve sheath tumors, neurofibromas	17q11	*NF1*
Neurofibromatosis type 2 (autosomal dominant)	Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma, hamartomas	22q12	*NF2*
von Hippel-Lindau (autosomal dominant)	Hemangioblastoma	3p25-26	*VHL*
Tuberous sclerosis (autosomal dominant)	Subependymal giant cell astrocytoma, cortical tubers	9q34 16q13	*TSC1* *TSC2*
Li-Fraumeni (autosomal dominant)	Astrocytoma, primitive neuroectodermal tumor	17q13	*TP53*
Cowden (autosomal dominant)	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)	10q23	*PTEN*
Turcot (autosomal dominant)	Medulloblastoma	5q21	*APC*
	Glioblastoma	3p21 7p22	*hMLH1* *hPSM2*
Nevoid basal cell carcinoma Gorlin (autosomal dominant)	Medulloblastoma	9q31	*PTCH1*

Modified from Kleihues P, Cavenee WK. *World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Nervous System*. Lyon: IARC Press, 2000.

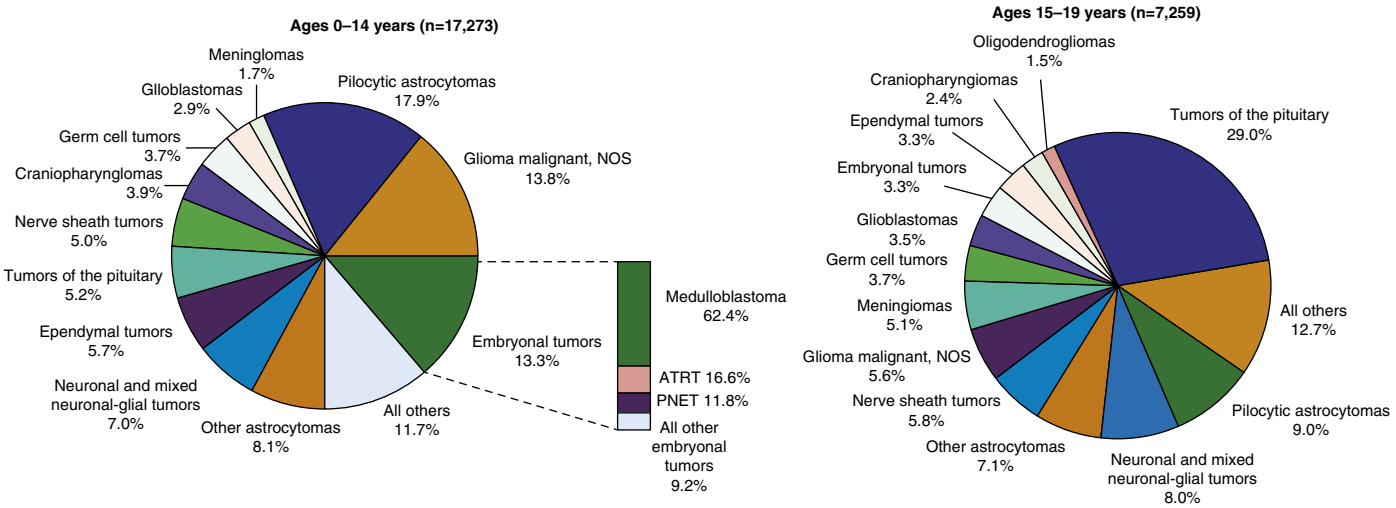

Fig. 546.1 Distribution of childhood primary brain and central nervous system (CNS) tumors by histology. ATRT, Atypical teratoid rhabdoid tumor; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor. *(From Ostrom QT, Patil N, Cioffi G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013-2017. Neuro Oncol. 2020;30;22:iv1–iv96.)*

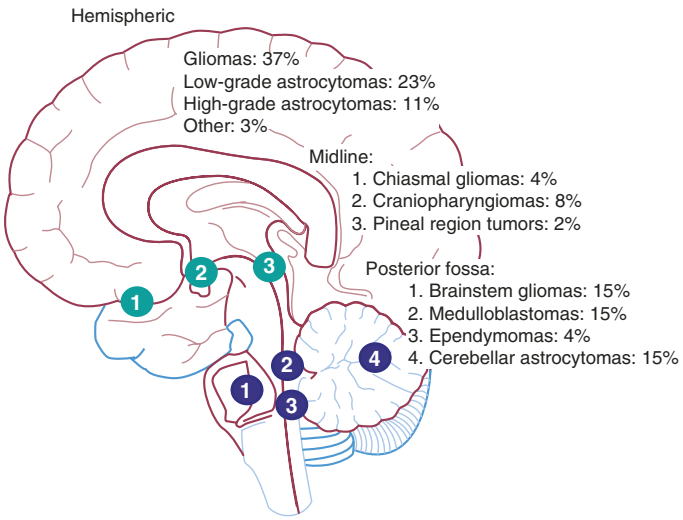

Fig. 546.2 Childhood brain tumors occur at any location within the central nervous system. The relative frequency of brain tumor histologic types and the anatomic distribution are shown. *(Redrawn from Albright AL. Pediatric brain tumors. CA Cancer J Clin 1993;43:272–288.)*

CLINICAL MANIFESTATIONS

The clinical presentation of the patient with a brain tumor depends on the tumor location, the tumor type, and the age of the child. Signs and symptoms are related to obstruction of cerebrospinal fluid (CSF) drainage paths by the tumor, leading to **increased intracranial pressure (ICP)** or causing focal brain dysfunction. In young children, the diagnosis of a brain tumor may be delayed because the symptoms are similar to those of more common illnesses, such as gastrointestinal disorders, with associated vomiting. Infants with open cranial sutures may present with signs of increased ICP, such as vomiting, lethargy, and irritability, as well as the later finding of macrocephaly. The **classic triad** of headache, nausea, and vomiting as well as papilledema is associated with midline or infratentorial tumors. Disorders of equilibrium, gait, and coordination occur with infratentorial tumors. **Torticollis** may occur in cases of cerebellar tonsil herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors. Tumors of the brainstem region may be associated with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g., hemiparesis, hyperreflexia, and clonus). **Supratentorial tumors** are more commonly associated with focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry. Infants with supratentorial tumors may present

Table 546.2 Posterior Fossa Tumors of Childhood

TUMOR	RELATIVE INCIDENCE (%)	PRESENTATION	DIAGNOSIS	PROGNOSIS
Medulloblastoma	35-40	2-3 mo of headaches, vomiting, truncal ataxia	Heterogeneously or homogeneously enhancing fourth ventricular mass; may be disseminated	65–85% survival; dependent on stage/type; poorer (20–70%) in infants
Cerebellar astrocytoma	35-40	3-6 mo of limb ataxia; secondary headaches, vomiting	Cerebellar hemisphere mass, usually with cystic and solid (mural nodule) components	90–100% survival in totally resected pilocytic type
Brainstem glioma	10-15	1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities	Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomedullary lesion	>90% mortality in diffuse tumors; better in localized
Ependymoma	10-15	2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry	Usually enhancing, fourth ventricular mass with cerebellopontine predilection	>75% survival in totally resected lesions
Atypical teratoid/rhabdoid	5–10% of infantile malignant tumors	As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus	As in medulloblastoma, but often more laterally extended	≤20% survival in infants

Modified from Packer RJ, MacDonald T, Vezina G. Central nervous system tumors. *Pediatr Clin North Am.* 2008;55:121–145.

with premature hand preference. **Optic pathway tumors** manifest as visual and/or afferent oculomotor disturbances, such as decreased visual acuity, Marcus Gunn pupil (afferent pupillary defect), nystagmus, and/or visual field defects. Suprasellar region tumors and third ventricular region tumors may manifest initially as **neuroendocrine deficits,** such as subacute development of obesity, abnormal linear growth velocity, diabetes insipidus, galactorrhea, precocious puberty, delayed puberty, and hypothyroidism. In fact, signs of endocrine dysfunction preceded symptoms of neuroophthalmologic dysfunction by an average of 1.9 years, and their recognition as a possible sign of hypothalamic or pituitary neoplasm can hasten diagnosis and improve outcome. The **diencephalic syndrome,** which manifests as failure to thrive but normal linear growth, emaciation despite normal caloric intake, and inappropriately normal or happy (euphoric) affect, occurs in infants and young children with tumors (most often low-grade hypothalamic or thalamic glioma). **Parinaud syndrome** is seen with pineal region tumors and is manifested by paresis of upward gaze, pupillary caliber reactive to accommodation but not to light (pseudo-Argyll Robertson pupil), nystagmus to convergence or retraction, and eyelid retraction. **Spinal cord tumors** and spinal cord dissemination of brain tumors may manifest as long nerve tract motor and/or sensory deficits often localized to below a specific spinal level, bowel and bladder deficits, resistance to back flexion, scoliosis, bowel and bladder dysfunction, and back or radicular pain. The signs and symptoms of meningeal metastatic disease from brain tumors or leukemia include head or back pain and symptoms referable to compression of cranial nerves or spinal nerve roots.

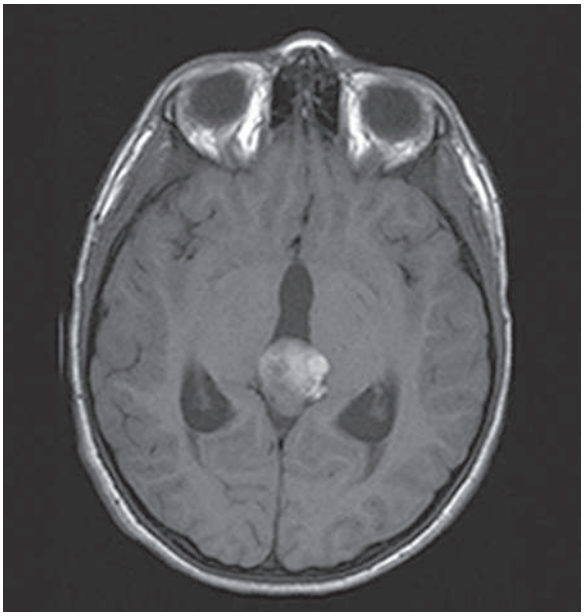

Fig. 546.3 Axillary T1 weighted MR image with gadolinium of a 10-yr-old male presenting with **mixed germ cell tumor** of the pineal region, with early onset of puberty, headaches, and elevated α-fetoprotein and β-human chorionic gonadotropin in the spinal fluid and serum.

DIAGNOSIS

The evaluation of a patient when a CNS tumor is suspected is an emergency. Initial evaluation should include a complete history (including endocrine), physical (including ophthalmic) examination, and full neurologic assessment with neuroimaging. For primary brain tumors, **MRI** with and without gadolinium is the neuroimaging standard. Tumors in the pituitary/suprasellar region, optic pathway, and infratentorium are better delineated with MRI than with CT. Patients with tumors of the midline and the pituitary/suprasellar/optic chiasmal region should undergo evaluation for **neuroendocrine dysfunction.** Formal ophthalmologic examination is beneficial in patients with optic path region tumors to document the impact of the disease on oculomotor function, visual acuity, and fields of vision. The suprasellar and pineal regions are preferential sites for germ cell tumors (Fig. 546.3). Both serum and CSF measurements of β-**human chorionic gonadotropin** and α-**fetoprotein** can assist in the diagnosis of germ cell tumors. In tumors with a propensity for spreading to the leptomeninges, such as medulloblastoma/PNET, ependymoma, and germ cell tumors, lumbar puncture with cytologic analysis of the CSF is indicated; lumbar puncture is contraindicated in individuals with newly diagnosed hydrocephalus secondary to CSF flow obstruction, in tumors that cause supratentorial midline shift, and in individuals with

infratentorial tumors. Lumbar puncture in these individuals may lead to brain herniation, resulting in neurologic compromise and death. Therefore, in children with newly diagnosed intracranial tumors and signs of increased ICP, the lumbar puncture usually is delayed until surgery or shunt placement.

SPECIFIC TUMORS

Astrocytoma

Astrocytomas are a heterogeneous group of tumors that account for approximately 40% of pediatric CNS malignancies. These tumors occur throughout the CNS.

Low-grade astrocytomas (LGAs), the predominant group of astrocytomas in childhood, are characterized by an indolent clinical course. **PA** is the most common astrocytoma in children, accounting for approximately 15.2% of all brain tumors (Fig. 546.4). Based on clinicopathologic features using the WHO Classification System, PA is classified as a WHO grade I tumor. Although PA can occur anywhere in the CNS, the classic sites are the **cerebellum followed by the optic pathway region** (Fig. 546.5A-B). The classic but not exclusive neuroradiologic finding in PA is the presence of a contrast-enhancing nodule within the wall of a cystic mass (Fig. 546.5A). The microscopic findings include the biphasic appearance of bundles of compact fibrillary tissue interspersed with loose microcystic, spongy areas. The presence of **Rosenthal fibers,** which are condensed masses of glial filaments occurring in the compact areas, with low mitotic potentials helps establish the diagnosis. A small proportion of these tumors can progress and develop leptomeningeal spread, particularly in the optic path region and very rarely transform to higher grade aggressive type. A PA of the optic nerve and chiasmal region is a relatively common finding in patients with neurofibromatosis type 1 (15% incidence). Molecularly, PA has activation of the **MAPK** pathway in the form of **BRAF** fusion or duplication and less commonly BRAF pathogenic variant (V600E) (see Fig. 546.4). Other low-grade tumors occurring in the pediatric age-group with clinic pathologic characteristics similar to PA include pleomorphic xanthoastrocytoma, pilomyxoid astrocytoma, and subependymal giant cell astrocytoma.

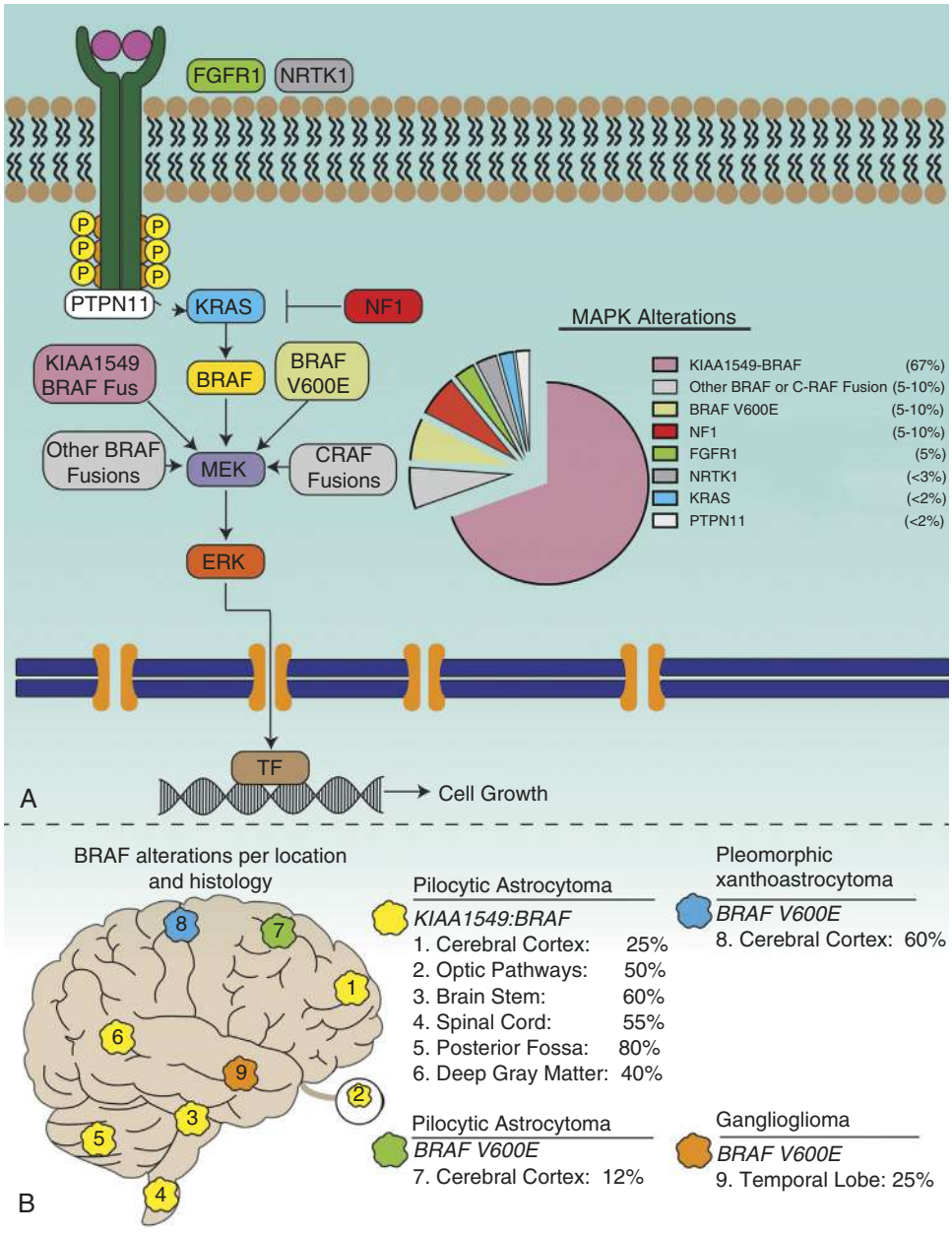

Fig. 546.4 A, Schematic of the frequency of MAPK pathway alterations detected by biopsy of pilocytic astrocytomas. This underestimates the frequency of NF1 pathogenic variants among children with low-grade gliomas (LGGs) because the tumors in patients affected by NF1 often do not undergo biopsy. Although BRAF fusions (BRAF Fus) constitute the majority of alterations in pilocytic astrocytoma, BRAF pathogenic variants are more commonly observed in pleomorphic xanthoastrocytomas and gangliogliomas. B, Frequency of the different BRAF abnormalities as a function of tumor location and histological diagnosis. *(From Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr. 2019;23:261–273. Fig. 1.)*

The second most common astrocytoma is **DA,** which consists of a group of tumors characterized by a pattern of diffuse infiltration of tumor cells amidst normal neural tissue. Histologically, these low-grade tumors demonstrate greater cellularity, with few mitotic figures, nuclear pleomorphism, and microcysts. They occur anywhere in the CNS with predilection to supratentorial location. The characteristic MRI finding is a lack of enhancement after contrast agent infusion. Molecular genetic abnormalities found in DA include pathogenic variants of *P53* and overexpression of platelet-derived growth factor receptor-α. Evolution of DA into malignant astrocytoma is associated with cumulative acquisition of multiple molecular abnormalities. Overactivation of the MAPK pathway has been detected in DA in the form of the ***BRAF V600E*** pathogenic variant and **FGFR1** duplication.

Pilomyxoid astrocytoma occurs most commonly in the hypothalamic/optic chiasmic region and carries a high risk of local as well as cerebrospinal spread. This astrocytoma affects young children and infants. It is classified as a WHO grade II tumor.

The clinical management of LGAs focuses on a multimodal approach incorporating surgery if feasible as the primary treatment as well as radiation therapy and chemotherapy. With complete surgical resection, the overall survival approaches 80–100%. In patients with partial resection, overall survival varies from 50–95%, depending on the anatomic location of the tumor. In the patient who has undergone partial tumor resection and has stable neurologic status, the current approach is to follow the patient closely by examination and imaging. With evidence of progression, a second surgical resection should be considered. In patients in whom a second procedure was less than complete or is not feasible, radiation therapy is beneficial. Radiation therapy is delivered to the tumor bed at a total cumulative dose ranging from 50-55 Gy. Modern surgical techniques and innovative radiation therapy methodology, *including proton-beam radiation,* may have a positive impact on the survival and clinical outcome of these patients. Chemotherapy for LGAs has become the standard of care for progressive LGAs. Because of concerns regarding morbidity from radiation therapy in young children, several chemotherapy approaches have been evaluated, especially in children younger than 10 years of age. Complete response to chemotherapy is uncommon; however, these approaches have yielded durable control of disease in 70–100% of patients with clinical improvement. Patients with midline tumors in the hypothalamic/optic chiasmatic region (see Fig. 546.5B) have tended to do less well. The chemotherapy approaches have permitted delay and, potentially, avoidance of radiation therapy. Chemotherapy agents given singly or in combination for LGA include carboplatin, vincristine, lomustine, procarbazine, temozolomide, and vinblastine. Observation is the primary approach in clinical management of selected patients with LGAs that are biologically indolent (neurofibromatosis type 1 and tectal gliomas and indolent LGA variants like angiocentric gliomas). *Astrocytomas associated with tuberous sclerosis have responded to everolimus, a mammalian target of rapamycin inhibitor.*

Malignant astrocytomas are less common in children and adolescents than in adults, accounting for 7–10% of all childhood brain tumors. Among this group, **anaplastic astrocytoma** (WHO grade III; Fig. 546.6) is more common than **glioblastoma multiforme** (WHO grade IV). The histopathology of anaplastic astrocytomas demonstrates greater cellularity than that of LGA, with cellular and nuclear atypia, and the presence of mitoses. Characteristic histopathologic findings in glioblastoma multiforme include dense cellularity, high mitotic index, microvascular proliferation, and foci of tumor necrosis with pseudopalisading. Genome-wide DNA methylation patterns have identified five molecular subgroups of pediatric high-grade glioma. These subgroups appear to have distinct cellular origins and biological drivers. Common genetic alterations include gene pathogenic variants in ***histone H3.3*** or ***H3.1, p53,*** and ***BRAF*** in addition to focal amplifications of oncogene (***PDGFRA*** and ***EGFR***) and deletions of tumor-suppressor genes ***(CDKN2A, CDKN2B, PTEN).***

Optimal therapeutic approaches for malignant astrocytomas have yet to be defined. Standard therapy continues to be surgical resection followed by involved-field radiation therapy with evolving role of maintenance alkylator chemotherapy (temozolomide ± lomustine). A study of adult glioblastoma showed significantly better survival with temozolomide during and after irradiation than with irradiation alone. Current therapeutic approaches incorporate novel chemotherapeutic agents with radiation therapy.

Oligodendrogliomas are uncommon tumors of childhood. These infiltrating tumors occur predominantly in the cerebral cortex and originate in the white matter. Histologically, oligodendrogliomas consist of rounded cells with little cytoplasm and microcalcifications. Observation of a **calcified cortical mass** on CT in a patient presenting with a seizure is suggestive of oligodendroglioma. The definition of oligodendroglioma requires two diagnostic genotypic features: pathogenic gene variants in isocitrate dehydrogenase (IDH) and the co-deletions of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). Treatment approaches are similar to those for infiltrating astrocytomas.

Ependymal Tumors

Ependymal tumors are derived from the ependymal lining of the ventricular system. Cellular ependymoma (WHO grade II) is the most common of these neoplasms, accounting for 5% of childhood CNS tumors. Approximately 70% of ependymomas in childhood occur in the posterior fossa. The mean age of patients is 6 years, with approximately

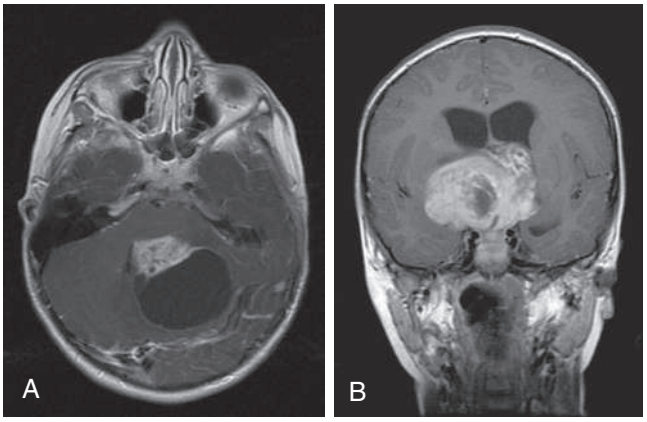

Fig. 546.5 A, Gadolinium-enhanced axial T1-weighted MR image in a 4-yr-old child with cerebellar **pilocytic astrocytoma** presenting with headaches, emesis, and ataxia demonstrates a predominantly cystic mass with enhancement of the solid component and enhancement of the capsule. B, Gadolinium-enhanced coronal view of a cystic juvenile pilocytic astrocytoma of the suprasellar region from a 4-yr-old child presenting with visual loss and headaches.

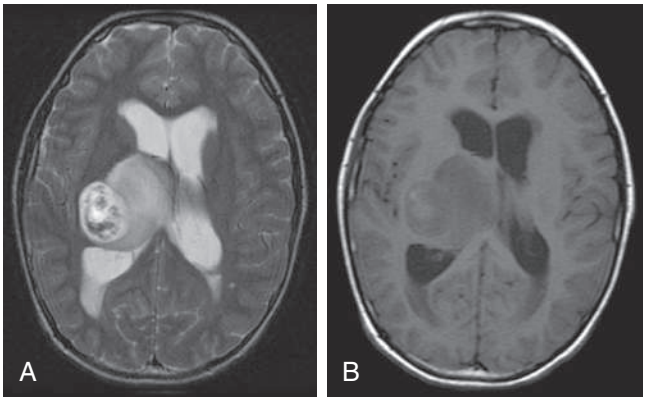

Fig. 546.6 A, Nonenhanced axial T2-weighted MR image of **grade III astrocytoma** of the right thalamus demonstrating diffuse hyperintensity and area of necrotic cyst formation. B, Gadolinium-enhanced sagittal T1-weighted MR image showing slight enhancement and hypodensity of **grade III astrocytoma** of the thalamus. This 14-yr-old child presented with left arm and leg numbness and weakness and right-sided headaches.

40% of cases occurring in children younger than 4 years of age. The incidence of leptomeningeal spread approaches 10% overall. Clinical presentation can be insidious and often depends on the anatomic location of the tumor. MRI demonstrates a well-circumscribed tumor with variable and complex patterns of gadolinium enhancement, with or without cystic structures (Fig. 546.7). These tumors usually are noninvasive, extending into the ventricular lumen and/or displacing normal structures, sometimes leading to significant obstructive hydrocephalus. Histologic characteristics include perivascular pseudorosettes, ependymal rosettes, monomorphic nuclear morphology, and occasional nonpalisading foci of necrosis. Other histologic subtypes include **anaplastic ependymoma** (WHO grade III), which is much less common in childhood and is characterized by a high mitotic index and histologic features of microvascular proliferation and pseudopalisading necrosis. **Myxopapillary ependymoma** (WHO grade II) is a slow-growing tumor arising from the filum terminale and conus medullaris and appears to be a biologically different subtype. Preliminary studies suggest that there are genetically distinct subtypes of ependymoma, exemplified by an association between alterations in the ***NF2*** gene and spinal ependymoma. Surgery is the primary treatment modality, with extent of surgical resection a major prognostic factor. Two other major prognostic factors are age, with younger children having poorer outcomes, and tumor location, with localization in the posterior fossa, which often is seen in young children, associated with poorer outcomes. Surgery alone is rarely curative. Multimodal therapy incorporating irradiation with surgery has resulted in long-term survival in approximately 40% of patients with ependymoma undergoing gross total resection. Recurrence is predominantly local. The role of chemotherapy in multimodal therapy of ependymoma is still unclear. Current investigations are directed toward identification of optimal radiation dose, surgical questions addressing the use of second-look procedures after chemotherapy, and further evaluation of classic as well as novel chemotherapeutic agents. Genome-wide DNA methylation patterns have identified nine molecular subgroups in these tumors across three anatomic compartments including supratentorial (ST), posterior fossa (PF), and the spinal locations (Fig. 548.8). Two subgroups (group A and B) of PF ependymoma have been identified with distinct molecular and clinical characteristics, and the use of targeted chemotherapy against these subtypes is being evaluated.

Choroid Plexus Tumors

Choroid plexus tumors account for 2–4% of childhood CNS tumors. They are the most common CNS tumors in children younger than 1 year of age and account for 10–20% of CNS tumors in infants. These tumors are intraventricular epithelial neoplasms arising from the choroid plexus. Children present with signs and symptoms of increased ICP. Infants may present with macrocephaly and focal neurologic deficits. In children, these tumors predominantly occur supratentorially in the lateral ventricles. The group of choroid plexus tumors is made up of **choroid plexus papillomas** (WHO grade I), **atypical choroid plexus papillomas** (WHO grade II), and **choroid plexus carcinomas** (WHO grade III). Choroid plexus papilloma, the *most common of this group*, is a well-circumscribed lesion with focal calcification on neuroimaging. *Choroid plexus carcinoma* is a malignant tumor with metastatic potential to seed into the CSF pathways. This malignancy has the following histologic characteristics: nuclear pleomorphism, high mitotic index, necrosis, and increased cell density. MRI typically demonstrates a large, hyperdense, contrast-enhancing, intraventricular mass with peritumoral edema, hemorrhage, and hydrocephalus. The tumor suppressor p53 is crucially involved in the biology of this cancer and may contribute to aggressive tumor behavior. Molecular data subclassify choroid plexus tumors into three distinct subgroups with different molecular aberrations and clinical outcomes. These tumors are associated with the Li-Fraumeni syndrome. After complete surgical resection, the frequency of cure for choroid plexus *papilloma* approaches 100%, whereas the frequency of cure for choroid plexus *carcinoma* approaches 20–40%. Reports suggest that radiation therapy and/or chemotherapy may lead to better disease control for choroid plexus carcinoma.

Embryonal Tumors

Embryonal tumors or **primitive neuroectodermal tumors (PNETs)** are one of the most common groups of *malignant* CNS tumors of childhood, accounting for approximately 9% of pediatric CNS tumors. They have the potential to metastasize to the neuraxis and extracranial tissues. The group includes medulloblastoma, supratentorial PNET, atypical teratoid/rhabdoid tumor, and other rare embryonal tumors, all of which are histologically classified as WHO grade IV tumors.

Medulloblastoma, which accounts for ~62% of embryonal CNS tumors, is a cerebellar tumor occurring predominantly in males and at a median age of 5-7 years. CT and MRI demonstrate a solid, homogeneous, contrast medium–enhancing mass in the PF causing fourth ventricular obstruction and hydrocephalus (Fig. 546.9). Up to 30% of patients with medulloblastoma present with neuroimaging evidence of leptomeningeal spread. Among a variety of diverse histologic patterns of this tumor, the most common is a monomorphic sheet of undifferentiated cells classically noted as small, blue round cells. Neuronal differentiation is more common among these tumors and is characterized

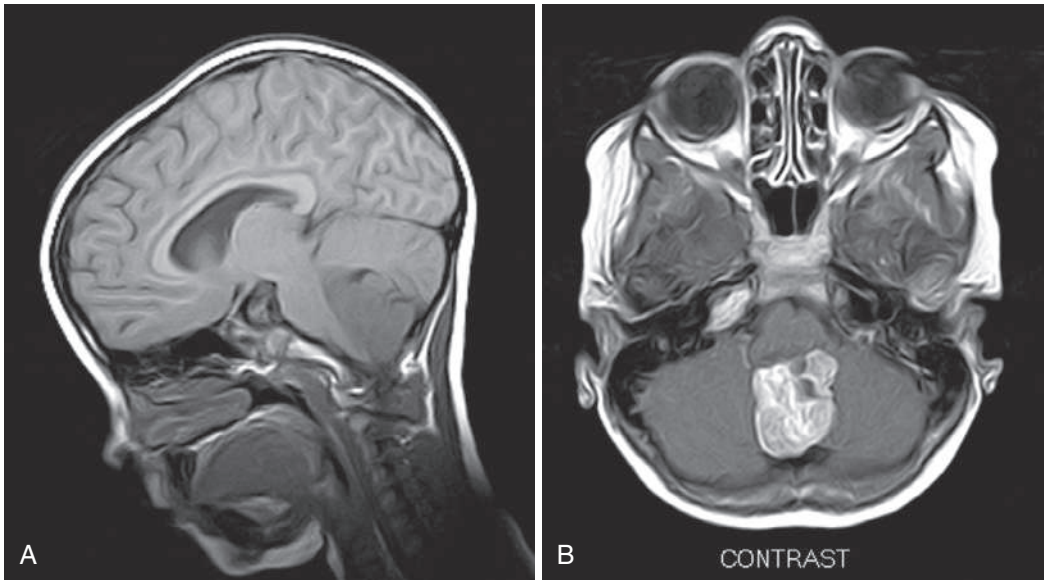

Fig. 546.7 A, Sagittal T1-weighted MR image of a 6-yr-old patient with **ependymoma**, demonstrating a hypointense mass within the fourth ventricle compressing the brainstem. B, Gadolinium-enhanced axial T1-weighted image of an ependymoma showing an enhancing mass within the fourth ventricle.

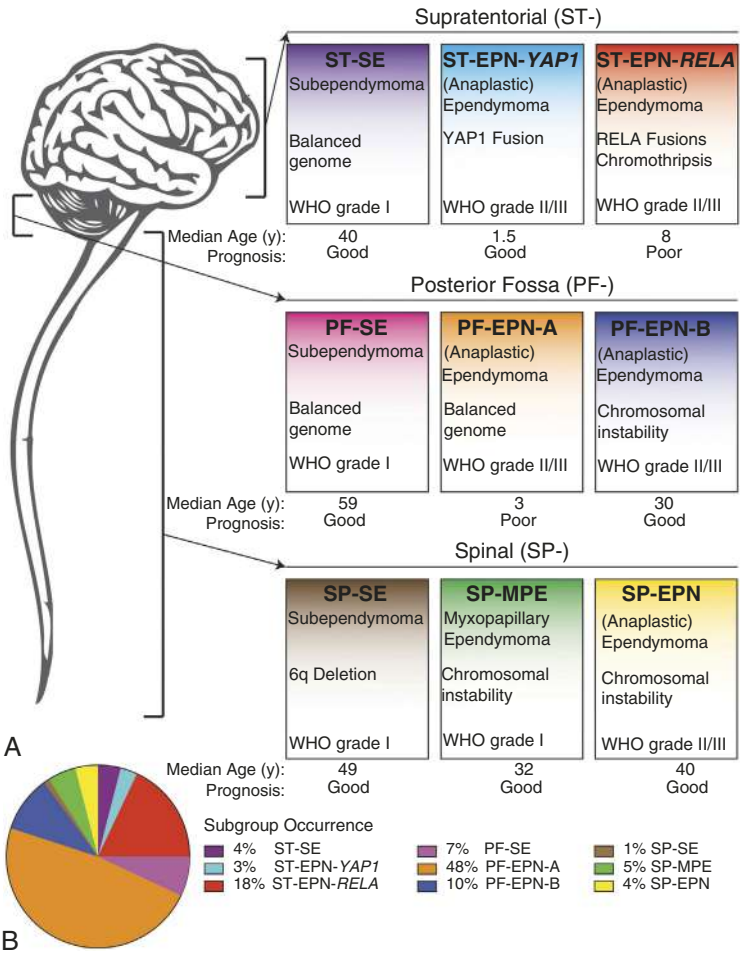

Fig. 546.8 A, Illustration of the nine recognized subsets of **ependymomas**. Only four of these subsets (ST-EPN-YAP1, ST-EPN-RELA, PF-EPN-A, and PF-EPN-B) typically occur during the childhood years. The subependymoma (SE) groups typically affect middle-age or older adults, and the spinal lesions, although occasionally encountered in children, are largely seen in adults. B, Estimate of the overall frequency of the different subtypes of ependymomas. *(From Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr. 2019;23:261–273. Fig. 3.)*

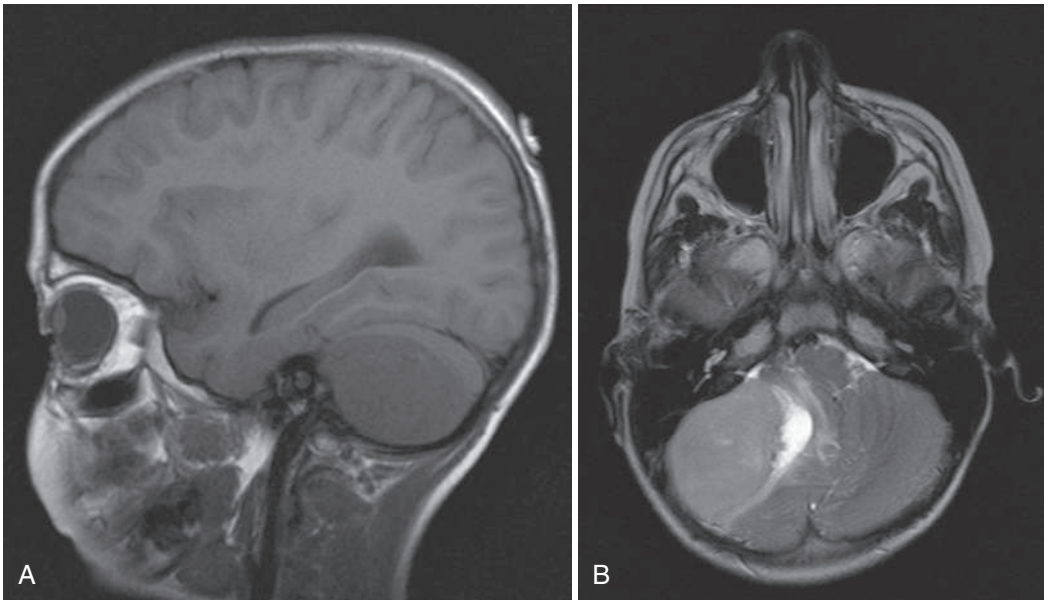

Fig. 546.9 A, Sagittal T1-weighted MR image shows hypointense mass involving the cerebellar hemisphere in a 6-yr-old child with desmoplastic variant of **medulloblastoma**. B, Axial T2-weighted image of the same child shows hyperintense mass involving the cerebellar hemisphere.

histologically by the presence of Homer Wright rosettes and by immunopositivity for synaptophysin. An anaplastic variant is often more aggressive and may be associated with poorer prognosis. Patients present with signs and symptoms of increased ICP (i.e., headache, nausea, vomiting, blurring of vision, mental status changes, and hypertension) and cerebellar dysfunction (i.e., ataxia, poor balance, dysmetria, dysarthria). Clinical staging evaluation includes MRI of the brain and spine, both preoperatively and postoperatively, as well as lumbar puncture after the increased ICP has resolved. Clinical features that have consistently demonstrated prognostic significance include age at diagnosis,

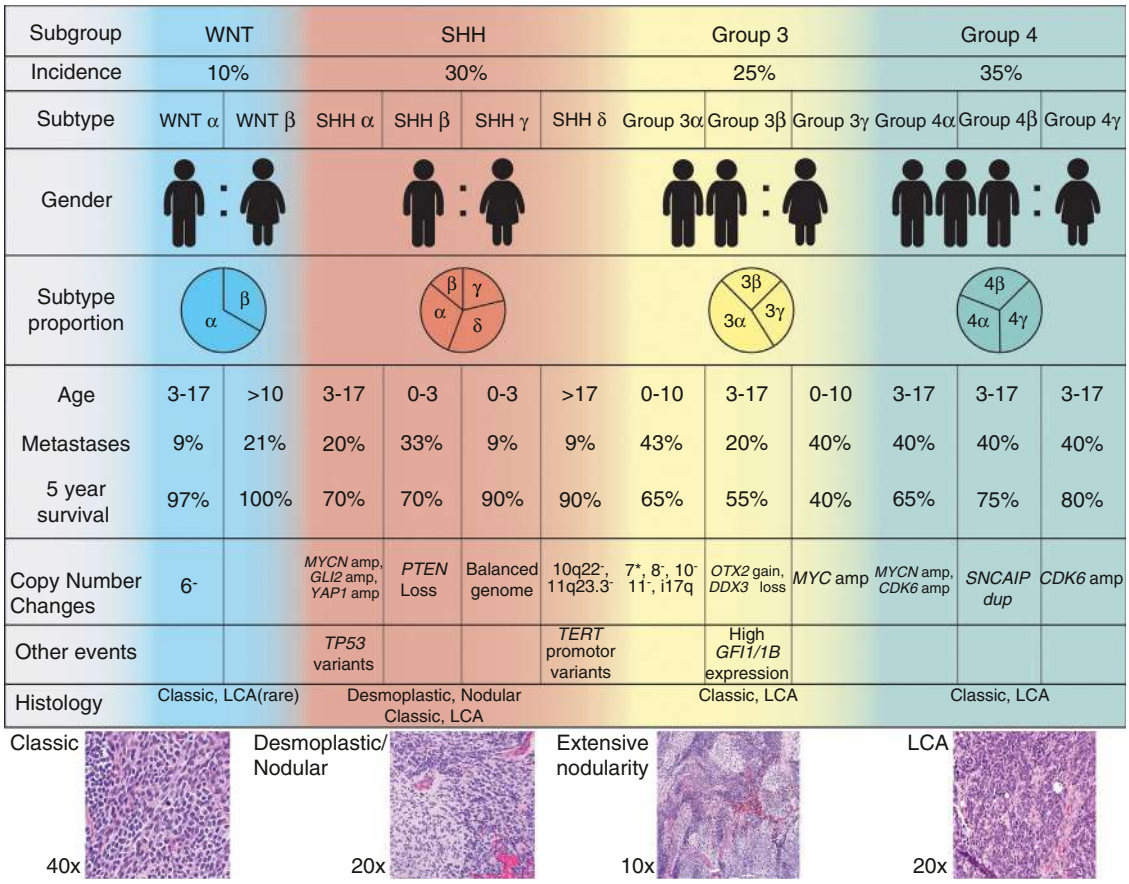

Fig. 546.10 Schematic *(upper)* depicting the four WHO-recognized subgroups of medulloblastoma, as well as the additional subtypes noted more recently and their distinguishing characteristics in terms of amplifications (amp) and duplications (dup). The figure *(lower)* also depicts the histological diversity of medulloblastomas: WNT tumors most commonly have a classic histology, whereas SHH tumors have desmoplastic histology with varying degrees of nodularity. Large cell/anaplastic (LCA) histology is most commonly seen in group 3 and less commonly in group 4 tumors. *(From Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr. 2019;23:261–273. Fig. 2.)*

extent of disease, and extent of surgical resection. Patients younger than 4 years of age have a poor outcome, partly as the result of a higher incidence of disseminated disease on presentation and past therapeutic approaches that have used less intense therapies. Patients with disseminated disease at diagnosis (M > 0), including positive CSF cytologic result alone (M1), have a markedly poorer outcome than those patients with no dissemination (M0). Similarly, patients with gross residual disease after surgery have poorer outcomes than those in whom surgery achieved gross total resection of disease.

Cytogenetic and molecular genetic studies have demonstrated multiple abnormalities in medulloblastoma (Fig. 546.10). The most common abnormality involves chromosome 17p deletions, which occur in 30–40% of all cases. Several signaling pathways have been shown to be active in medulloblastomas, including the sonic hedgehog **(SHH)** pathway, predominately associated with the desmoplastic variants, and the **WNT** pathway, which can occur in up to 15% of cases and has been associated with improved survival. Integrative genomic studies have identified at least four distinct molecular subgroups of medulloblastoma—**WNT**, **SHH**, **group 3**, and **group 4**—that exhibit highly discriminate transcriptional, cytogenetic, and mutational spectra, in addition to divergent patient demographics and clinical behavior (see Fig. 546.10). These prognostic groups still must be validated in larger prospective studies, though the WNT subgroup is known to have the most favorable outcome. A multimodal treatment approach is pursued in medulloblastoma, with surgery as the starting point of treatment. Medulloblastoma is sensitive to both chemotherapy and radiation therapy. With technologic advances in neurosurgery, neuroradiology, and radiation therapy, as well as identification of chemotherapy as an effective modality, the overall outcome among all patients approaches 60–70%. Standard radiation treatment in standard risk medulloblastoma incorporates craniospinal radiation at a total cumulative dose of 24 Gy, with a cumulative dose of 50-55 Gy to the tumor bed. Craniospinal radiation at this dose in children younger than 3 years of age results in severe late neurologic sequelae, including microcephaly, learning disabilities, cognitive impairment, neuroendocrine dysfunction (growth failure, hypothyroidism, hypogonadism, and absence/delay of puberty), and/or second malignancies. Similarly, in older children, late sequelae, such as learning disabilities, neuroendocrine dysfunction, and/or second malignancies, can occur. These observations have resulted in stratification of treatment approaches into the following three strata: (1) patients younger than 3 years of age, (2) standard-risk patients older than 3 years of age with surgical total resection and no disease dissemination (M0), and (3) high-risk patients older than 3 years of age with disease dissemination (M > 0) and/or bulky residual disease after surgery. With the risk-based approach to treatment, children with high-risk medulloblastoma receive high-dose cranial–spinal radiation (36 Gy) with chemotherapy during and after radiation therapy. As the dose of radiation depends on the risk stratification, complete staging with MRI of the spine before starting treatment is essential for the best chance of survival. Approaches in young children (usually younger than 3 years of age) incorporate high-dose chemotherapy with peripheral stem cell reinfusion to avoid radiation therapy.

Overall survival in children with nonmetastatic medulloblastoma and gross total tumor resection approaches 85%. The presence of bulky residual tumor (56% survival) or metastases (38% survival) confers a poor prognosis. The molecular classification is being evaluated to stratify risk groups and tailor therapy accordingly. The WNT subgroup and nonmetastatic group 4 tumors are recognized as low-risk tumors that may qualify for reduced therapy. High-risk groups were defined as patients with metastatic SHH or group 4 tumors, where intensification of therapy is being profiled.

Supratentorial primitive neuroectodermal tumors (SPNETs) account for approximately 1% of childhood CNS tumors, primarily in children within the first decade of life. These tumors are similar histologically to medulloblastoma and are composed of undifferentiated or poorly differentiated neuroepithelial cells. Historically, patients with SPNETs have had poorer outcomes than those with medulloblastoma after combined-modality therapy. Children with SPNETs are considered among the high-risk group and receive dose-intense chemotherapy with craniospinal radiation therapy.

Atypical teratoid/rhabdoid tumor is a very aggressive embryonal malignancy that occurs predominantly in children younger than 5 years of age and can occur at any location in the neuraxis. The histology demonstrates a heterogeneous pattern of cells, including rhabdoid cells that express epithelial membrane antigen and neurofilament antigen. The characteristic cytogenetic pattern is partial or complete deletion of chromosome 22q11.2 that is associated with pathogenic variants in the *INI1* gene. The relation between this variant and tumorigenesis is unclear. Though the overall prognosis remains poor, intensive chemotherapy, focal radiation, and high-dose chemotherapy with stem cell rescue have shown a trend toward improved survival. This is noted more in patients who undergo complete resection of tumor and focal radiation.

Pineal Parenchymal Tumors

The pineal parenchymal tumors are the most common malignancies after germ cell tumors that occur in the pineal region. These include **pineoblastoma**, occurring predominantly in childhood, **pineocytoma**, and the **mixed pineal parenchymal tumors**. The therapeutic approach in this group of diseases is multimodal. There was significant concern regarding the location of these masses and the potential complications of surgical intervention. With developments in neurosurgical technique and surgical technology, the morbidity and mortality associated with these approaches have markedly decreased. Stereotactic biopsy of these tumors may be adequate to establish diagnosis; however, consideration should be given to total resection of the lesion before institution of additional therapy. Pineoblastoma, the more malignant variant, is considered a subgroup of childhood PNETs. Chemotherapy regimens incorporate cisplatin, cyclophosphamide (Cytoxan), etoposide (VP-16), and vincristine and/or lomustine. The survival outcome of combined chemotherapy and radiation therapy in pineal-region PNETs approaches 70% at 5 years. Pineocytoma usually is approached with surgical resection.

Craniopharyngioma

Craniopharyngioma (WHO grade I) is a common tumor of childhood, accounting for 3–10% of all CNS childhood tumors. Two histological subtypes have been identified, adamantinomatous and papillary craniopharyngiomas (CP), each with specific origin and genetic alterations. ***BRAFV600E*** pathogenic variants are solely found in the papillary CP subgroup, which is the common type in adults, whereas ***CTNNB1*** pathogenic variants are exclusively detected in adamantinomatous CP, which is common in children. Children with CP often present with endocrinologic abnormalities (growth failure and delayed sexual maturation) and/or visual changes (decreased acuity or visual field abnormalities). These tumors are often large and heterogeneous, displaying both solid and cystic components, and occur within the suprasellar region. They are minimally invasive, adhere to adjacent brain parenchyma, and engulf normal brain structures. MRI demonstrates the solid tumor with cystic structures containing fluid of intermediate density, and CT may show calcifications. Surgery is the primary treatment modality, with gross total resection being curative. Controversy exists regarding the relative roles of surgery and radiation therapy in large, complex tumors. Significant morbidity (panhypopituitarism, growth failure, visual loss) is associated with these tumors and their therapy, owing to the anatomic location.

Germ Cell Tumors

Germ cell tumors of the CNS are a heterogeneous group of tumors that are primarily tumors of childhood, arising predominantly in midline structures of the pineal and suprasellar regions (see Fig. 546.3). They account for 3–5% of pediatric CNS tumors. The peak incidence of these tumors is in children 10-12 yr of age. Overall, there is a male preponderance, although there is a female preponderance for suprasellar tumors. Germ cell tumors occur multifocally in 5–10% of cases. This group of tumors is much more prevalent in Asian populations than European populations. Delays in diagnosis can occur because these tumors have a particularly insidious course; the initial presenting symptoms may be subtle. Similar to peripheral germ cell tumors, the analysis of protein markers, **α-fetoprotein,** and **β-human chorionic gonadotropin** may be useful in establishing the diagnosis and monitoring treatment response. Surgical biopsy is recommended to establish the diagnosis; however, secreting **germinomas** and **nongerminomatous germ cell tumors** may be diagnosed based on protein marker elevations. Therapeutic approaches to germinomas and nongerminomatous germ cell tumors are different. The survival proportion among patients with pure germinoma exceeds 90%. The postsurgical treatment of pure germinomas is somewhat controversial in defining the relative roles of chemotherapy and radiation therapy. Clinical trials have investigated the use of chemotherapy and reduced-dose radiation and field after surgery in pure germinomas. The therapeutic approach to nongerminomatous germ cell tumors is more aggressive, combining more intense chemotherapy regimens with craniospinal radiation therapy. Survival rates among patients with these tumors are markedly lower than those noted in patients with germinoma, ranging from 70–80% at 5 years. Trials have shown the benefit of the use of high doses of chemotherapy with peripheral blood stem cell rescue specially at metastatic and relapse groups.

Tumors of the Brainstem

Tumors of the brainstem are a heterogeneous group of tumors that account for 10.9% of childhood primary CNS tumors. Outcome depends on tumor location, imaging characteristics, and the patient's clinical status. Patients with these tumors may present with motor weakness, cranial nerve dysfunction, cerebellar dysfunction, and/or signs of increased ICP. On the basis of MRI evaluation and clinical findings, tumors of the brainstem can be classified into four types: focal (5–10% of patients), dorsally exophytic (5–10%), cervicomedullary (5–10%), and diffuse intrinsic pontine glioma **(DIPG)** (70–85%) (Fig. 546.11). Surgical resection is the primary treatment approach for focal and dorsally exophytic tumors and leads to a favorable outcome. Histologically, these two groups usually are low-grade gliomas. *Cervicomedullary tumors, because of their location, may not be amenable to surgical resection but are sensitive to radiation therapy*. DIPG, characterized by the diffuse infiltrating grade II-IV glioma, is associated with a very poor outcome independent of histologic diagnosis. These tumors are not amenable to surgical resection. Biopsy in children in whom MRI shows DIPG is controversial and is not recommended unless there are atypical radiographic findings suspicious for another diagnosis, such as infection, vascular malformation, myelination disorder, or metastatic tumor. Studies have identified the unique genetic makeup of this fatal brain cancer, with nearly 80% found to harbor pathogenic variants in histone ***H3.3*** or ***H3.1 (H3-K27M)*** and 20% pathogenic variants affecting the activin receptor gene ***(ACVR1);*** three molecularly distinct subgroups have been identified (H3-K27M, silent and MYCN).

The standard treatment approach has been palliative radiation therapy, and median survival with this treatment is 12 months, at best. Use

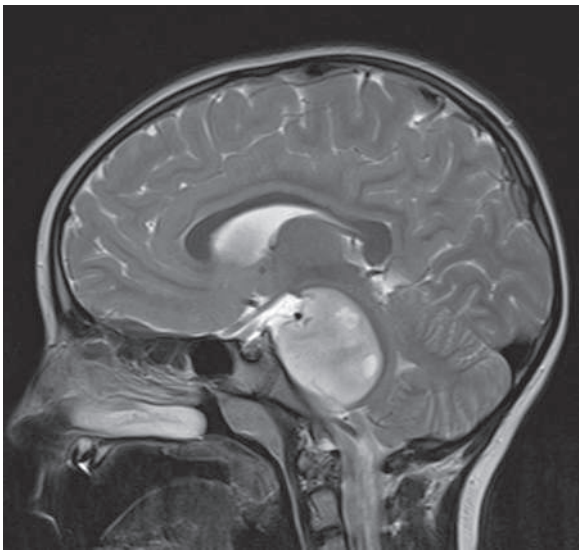

Fig. 546.11 T2-weighted sagittal MR image of a diffuse infiltrating pontine glioma in a 5-yr-old child presenting with headaches, left facial droop, and lethargy.

of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Experimental approaches have included the use of immunotherapy with oncolytic herpes simplex virus (HSV) or adenoviruses.

Metastatic Tumors

Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. **Chloromas,** which are collections of myeloid leukemia cells, can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal administration of chemotherapy, and/or systemic administration of chemotherapy. Medulloblastoma is the childhood brain tumor that most commonly metastasizes extraneurally. Less commonly, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

COMPLICATIONS AND LONG-TERM MANAGEMENT

Data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program indicate that more than 70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits such as focal motor and sensory abnormalities, seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay or absence of puberty). These patients are also at significant risk for secondary malignancies, hearing deficit, and early cataract from radiation therapy. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions may enhance the childhood brain tumor survivor's quality of life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 547

Neuroblastoma

Fiorela N. Hernandez Tejada and Douglas J. Harrison

Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. The causes of most cases remain unknown. Advances have been made in the treatment of children with these tumors, which have improved outcomes, although many with aggressive forms of neuroblastoma still succumb to their disease despite intensive therapy.

EPIDEMIOLOGY

Neuroblastoma is the most common extracranial solid tumor in children and is the most commonly diagnosed malignancy in the first year of life. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8–10% of childhood malignancies and one-third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 18 months, and 90% of cases are diagnosed in children who are <10 years of age. The incidence is slightly higher in males and in the White population.

PATHOLOGY

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other **small, round blue cell tumors,** such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor as dictated by the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

PATHOGENESIS

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma is rare but accounts for 1–2% of all cases, is associated with a younger age at diagnosis, and is linked to germline gain-of-function pathogenic variants in the *ALK* gene. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Germline gain-of-function pathogenic variants in *PHOX2B* predisposes to most of the syndromic neuroblastoma cases, including Hirschsprung disease and central congenital hypoventilation syndrome. Neuroblastoma is associated with other neural crest disorders, such as neurofibromatosis type 1, and potentially congenital cardiovascular malformations (Table 547.1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, maternal drug use, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN (N-myc)* protooncogene and tumor cell DNA content, or ploidy (Tables 547.2-547.4). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Other genetic alterations have been identified

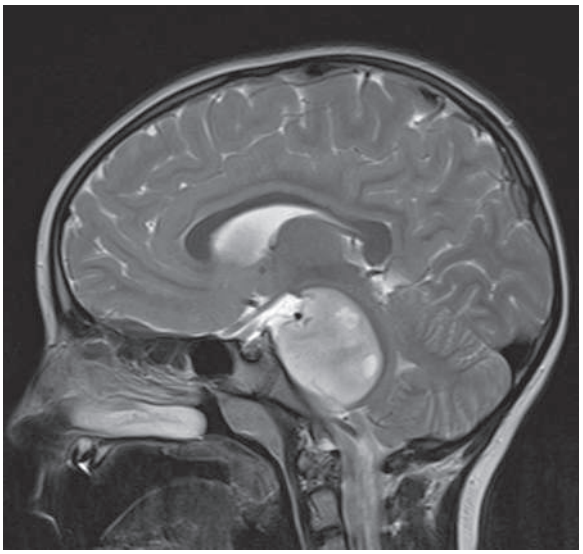

Fig. 546.11 T2-weighted sagittal MR image of a diffuse infiltrating pontine glioma in a 5-yr-old child presenting with headaches, left facial droop, and lethargy.

of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Experimental approaches have included the use of immunotherapy with oncolytic herpes simplex virus (HSV) or adenoviruses.

Metastatic Tumors

Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. **Chloromas,** which are collections of myeloid leukemia cells, can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal administration of chemotherapy, and/or systemic administration of chemotherapy. Medulloblastoma is the childhood brain tumor that most commonly metastasizes extraneurally. Less commonly, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

COMPLICATIONS AND LONG-TERM MANAGEMENT

Data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program indicate that more than 70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits such as focal motor and sensory abnormalities, seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay or absence of puberty). These patients are also at significant risk for secondary malignancies, hearing deficit, and early cataract from radiation therapy. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions may enhance the childhood brain tumor survivor's quality of life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 547

Neuroblastoma

Fiorela N. Hernandez Tejada and Douglas J. Harrison

Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. The causes of most cases remain unknown. Advances have been made in the treatment of children with these tumors, which have improved outcomes, although many with aggressive forms of neuroblastoma still succumb to their disease despite intensive therapy.

EPIDEMIOLOGY

Neuroblastoma is the most common extracranial solid tumor in children and is the most commonly diagnosed malignancy in the first year of life. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8–10% of childhood malignancies and one-third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 18 months, and 90% of cases are diagnosed in children who are <10 years of age. The incidence is slightly higher in males and in the White population.

PATHOLOGY

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other **small, round blue cell tumors,** such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor as dictated by the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

PATHOGENESIS

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma is rare but accounts for 1–2% of all cases, is associated with a younger age at diagnosis, and is linked to germline gain-of-function pathogenic variants in the *ALK* gene. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Germline gain-of-function pathogenic variants in *PHOX2B* predisposes to most of the syndromic neuroblastoma cases, including Hirschsprung disease and central congenital hypoventilation syndrome. Neuroblastoma is associated with other neural crest disorders, such as neurofibromatosis type 1, and potentially congenital cardiovascular malformations (Table 547.1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, maternal drug use, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN (N-myc)* protooncogene and tumor cell DNA content, or ploidy (Tables 547.2-547.4). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Other genetic alterations have been identified

Table 547.1 Syndromes Due to or Associated with Neuroblastoma

EPONYM	FEATURES
SYNDROMES CAUSED BY NEUROBLASTOMA	
Pepper syndrome	Massive involvement of the liver with metastatic disease with or without respiratory distress
Horner syndrome	Unilateral ptosis, myosis, and anhidrosis associated with a thoracic or cervical primary tumor; symptoms do not resolve with tumor resection
Hutchinson syndrome	Limping and irritability in young child associated with bone and bone marrow metastases
Opsoclonus-myoclonus-ataxia syndrome	Myoclonic jerking and random conjugate eye movements with or without cerebellar ataxia; often associated with a biologically favorable and differentiated tumor; the condition is likely immune mediated, may not resolve with tumor removal, and often exhibits progressive neuropsychologic sequelae
Kerner-Morrison syndrome	Intractable secretory watery diarrhea due to tumor secretion of vasointestinal peptides; tumors are generally biologically favorable
ROHHAD	Approximately 40% may have neural crest-derived tumors. Obesity and neurologic issues may be part of a paraneoplastic syndrome
SYNDROMES PREDISPOSING TO NEUROBLASTOMA	
Neurocristopathy syndrome	Neuroblastoma associated with other neural crest disorders, including congenital hypoventilation syndrome or Hirschsprung disease; germline pathogenic variants in the paired homeobox gene *PHOX2B* have been identified in a subset of patients with this disease
Beckwith-Wiedemann syndrome	Macrosomia, hyperinsulinemic hypoglycemia, omphalocele
Costello syndrome (faciocutaneo-skeletal syndrome)	Autosomal dominant, pathogenic variant in *HRAS*, intellectual disability, delayed development, cardiomyopathy
Familial pheochromocytoma/paraganglioma syndrome	Autosomal dominant, pathogenic variant in *MAX* and other genes
Fanconi anemia	Autosomal recessive, congenital anomalies, aplastic anemia, pathogenic variants in *FANCA*, *FANCC*, *FANCG*
Neurofibromatosis type 1	*NF1* pathogenic variants
Noonan syndrome	Ras-MAPK pathway (RASopathies) pathogenic variant
Turner syndrome	Partial or complete deletion of X chromosome, short-webbed neck, short stature

ROHHAD, Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation.
Modified from Park JR, Eggert A, Caron H. *Neuroblastoma*: biology, prognosis, and treatment. *Pediatr Clin North Am*. 2008;55:97–120.

Table 547.2 Children's Oncology Group Neuroblastoma Risk Stratification

RISK GROUP	STAGE	AGE	*MYCN* AMPLIFICATION STATUS	PLOIDY	SHIMADA
Low	1	Any	Any	Any	Any
Low	2A/2B	Any	Not amplified	Any	Any
High	2A/2B	Any	Amplified	Any	Any
Intermediate	3	<547 days	Not amplified	Any	Any
Intermediate	3	≥547 days	Not amplified	Any	FH
High	3	Any	Amplified	Any	Any
High	3	≥547 days	Not amplified	Any	UH
High	4	<365 days	Amplified	Any	Any
Intermediate	4	<365 days	Not amplified	Any	Any
High	4	365 to <547 days	Amplified	Any	Any
High	4	365 to <547 days	Any	DNA index = 1	Any
High	4	365 to <547 days	Any	Any	UH
Intermediate	4	365 to <547 days	Not amplified	DNA index > 1	FH
High	4	≥547 days	Any	Any	Any
Low	4S	<365 days	Not amplified	DNA index > 1	FH
Intermediate	4S	<365 days	Not amplified	DNA index = 1	Any
Intermediate	4S	<365 days	Not amplified	Any	UH
High	4S	<365 days	Amplified	Any	Any

FH, Favorable histology; UH, unfavorable histology.
Data from Irwin MS, Naranjo A, Zhang FF, et al. Revised neuroblastoma risk classification system: a report From the Children's Oncology Group. *J Clin Oncol*. 2021;39(29):3229–3241.

Table 547.3 International Neuroblastoma Staging System

STAGE	DEFINITION	INCIDENCE (%)	SURVIVAL AT 5 YR* (%)
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)	5	≥90
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically	10	70-80
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically	10	70-80
3	Unresectable unilateral tumor infiltrating across the midline,† with or without regional lymph node involvement; *or* localized unilateral tumor with contralateral regional lymph node involvement; *or* midline tumor with bilateral extension by infiltration (resectable) or by lymph node involvement	25	40-70
4	Any primary tumor with dissemination to distant lymph nodes; bone, bone marrow, liver, skin, and other organs (except as defined for stage 4S)	60	85-90¶ 30-40#
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and bone marrow‡ (limited to infants <1 yr of age)	5	>80

*Survival is influenced by other characteristics, such as *MYCN* amplification. Percentages are approximate.
†The *midline* is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the other side of the vertebral column.
‡Marrow involvement in stage 4S should be minimal (i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). More extensive marrow involvement would be considered stage 4. Results of the metaiodobenzylguanidine (MIBG) scan (if performed) should be negative in the marrow.
¶If age at diagnosis is <18 mo.
#If age at diagnosis is >18 mo.
Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 5th ed. Philadelphia: WB Saunders; 2006. p 746; and Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol*. 1993;11:1466–1477.

Table 547.4 Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category

	PROGNOSTIC CATEGORY*			
VARIABLE	LOW RISK	INTERMEDIATE RISK	HIGH RISK	TUMOR STAGE 4S
Pattern of disease	Localized tumor	Localized tumor with locoregional lymph node extension; metastases to bone marrow and bone in infants	Metastases to bone marrow and bone (except in infants)	Metastases to liver and skin (with minimal bone marrow involvement) in infants
Tumor genomics	Whole-chromosome gains	Whole-chromosome gains	Segmental chromosomal aberrations	Whole-chromosome gains
Treatment	Surgery†	Moderate-intensity chemotherapy; surgery†	Dose-intensive chemotherapy, surgery, and external-beam radiotherapy to primary tumor and resistant metastatic sites; myeloablative chemotherapy with autologous hematopoietic stem cell rescue; isotretinoin with anti-ganglioside GD2 immunotherapy	Supportive care‡
Survival rate	>98%	90–95%	40–50%	>90%

*Patients are assigned to prognostic groups according to risk, as described by the Children's Oncology Group, with the level of risk defining the likelihood of death from disease. Stage 4S disease is considered separately here because of the unique phenotype of favorable biologic features and relentless early progression but ultimately full and complete regression of the disease.
†The goal of surgery is to safely debulk the tumor mass and avoid damage to surrounding normal structures while obtaining sufficient material for molecular diagnostic studies. Some localized tumors may spontaneously regress without surgery.
‡Low-dose chemotherapy or radiation therapy, or both, is used in patients with life-threatening hepatic involvement, especially in infants <2 mo of age, who are at much higher risk for life-threatening complications from massive hepatomegaly.
From Maris JM. Recent advances in neuroblastoma. *N Engl J Med*. 2010;362:2202–2210.

in patients with neuroblastoma using whole genome sequencing such as loss of function in *ATRX* and *TERT*. Hyperdiploidy confers better prognosis if the child is younger than 18 months of age at diagnosis if amplification of *MYCN* is not present. Other chromosomal abnormalities, including loss of heterozygosity of 1p, 11q, and 14q, and gain of 17q, may be found in neuroblastoma tumors and have been associated with worse outcomes. In addition, many other biologic factors are associated with neuroblastoma outcomes, including tumor vascularity and the expression levels of nerve growth factor receptors (TrkA, TrkB), ferritin, lactate dehydrogenase, ganglioside GD2, neuropeptide Y, chromogranin A, CD44, multidrug resistance–associated protein, and telomerase.

CLINICAL MANIFESTATIONS

Neuroblastoma may develop at any site of sympathetic nervous system tissue. Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia. Metastatic spread, which is more common in children older than 1 year of age at diagnosis, occurs via local invasion or distant hematogenous or lymphatic routes. The most common sites

of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin. Lung and brain metastases are rare, occurring in less than 3% of cases.

The signs and symptoms of neuroblastoma reflect the tumor site and extent of disease and may mimic other disorders, which can result in a delayed diagnosis. Metastatic disease can cause a variety of signs and symptoms, including fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and periorbital ecchymoses (Fig. 547.1). Localized disease can manifest as an asymptomatic mass or can cause symptoms due to mass effect, which can in certain cases result in spinal cord compression, bowel obstruction, and superior vena cava syndrome.

Children with neuroblastoma can also present with associated neurologic signs and symptoms (see Table 547.1). Neuroblastoma originating in the superior cervical ganglion can result in **Horner syndrome.** Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed **opsoclonus-myoclonus-ataxia syndrome**, in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination, and cognitive dysfunction. Some tumors produce catecholamines that can cause increased sweating and hypertension, and some release vasoactive intestinal peptide, causing a profound secretory diarrhea. Children with extensive tumors can also experience tumor lysis syndrome and disseminated intravascular coagulation. Infants younger than 18 months of age also can present in unique fashion, termed *stage MS* (previously 4S; see later), with widespread subcutaneous tumor nodules, massive liver involvement, limited bone marrow disease, and a small primary tumor without bone involvement or other metastases. The stage MS disease can spontaneously regress. The enigmatic characteristics of neuroblastoma with paraneoplastic syndromes and spontaneous regression under some circumstances have led some researchers to suggest that neuroblastoma may originate as a neurodevelopmental disorder.



Fig. 547.1 Neuroblastoma. Periorbital ecchymosis, proptosis, and subconjunctival hemorrhage of the left eye. *(From Mota EB, Penna CRR, Marchiori E. Metastatic dissemination of a neuroblastoma. J Pediatr. 2017;189:232–232.e1. Fig. 1.)*

DIAGNOSIS

Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, CT, or MRI (Fig. 547.2A). The mass often contains calcification and hemorrhage that can allow it to be appreciated on plain radiography or CT (Fig. 547.3). Prenatal diagnosis of perinatal neuroblastoma on maternal ultrasound scans is sometimes possible. Tumor markers, including catecholamine metabolites homovanillic acid and vanillylmandelic acid, are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis. A pathologic diagnosis is established from tumor tissue obtained by biopsy. Neuroblastoma can be confirmed without a primary tumor biopsy if small, round, blue tumor cells are observed in bone marrow samples (Fig. 547.4) and the levels of vanillylmandelic acid or homovanillic acid are elevated in the urine.

Evaluations for metastatic disease should include CT or MRI of the chest and abdomen, bone scans to detect cortical bone involvement, and at least two independent bone marrow aspirations and biopsies to evaluate for marrow disease. **Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG)** studies should be used when available to better define the extent of disease. Some centers use gallium-68 dotatate PET/MRI or CT scans, especially if the MIBG scan is negative (Fig. 547.5). MRI of the spine should be performed in cases with suspected or potential spinal cord compression, but imaging of the brain with

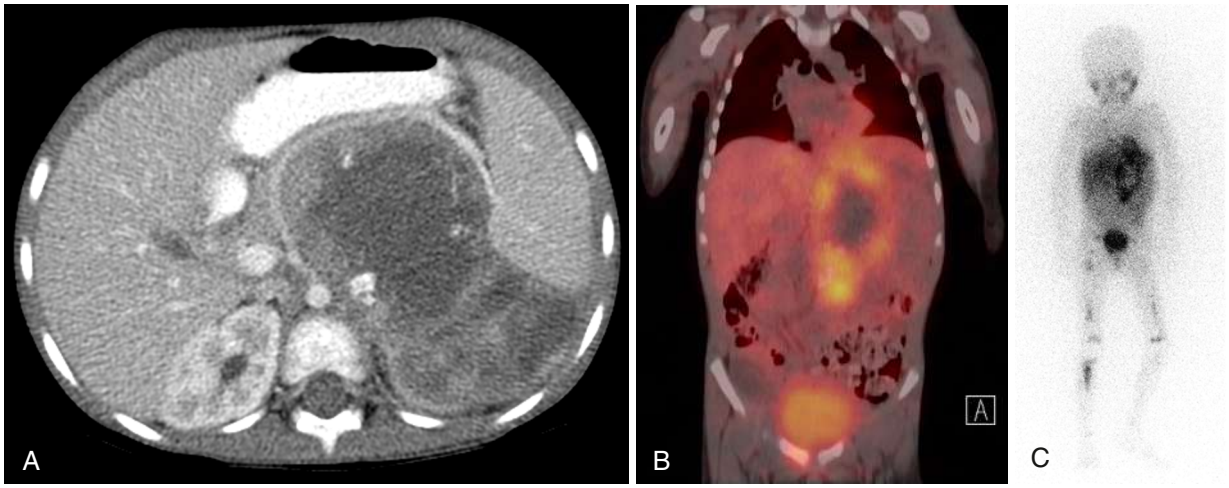

Fig. 547.2 A, CT scan of an abdominal neuroblastoma with central necrosis at diagnosis. B, Coronal fused CT and metaiodobenzylguanidine (MIBG) image of the same child with extensive retroperitoneal mass and central necrosis, probably an adrenal primary with extensive lymph node involvement. C, MIBG avid neuroblastoma with increased uptake of radiolabeled tracer can be detected in multiple sites of disease, including bone and soft tissue.

either CT or MRI is not routinely performed unless dictated by the clinical presentation.

The **International Neuroblastoma Risk Group (INRG) Staging System (INSS)** is currently used to stage patients with neuroblastoma and is based on the extent of disease as determined by imaging at diagnosis. Extent of locoregional disease is based on specific local image-defined risk factors (IDRFs) (see Table 547.3). L1 tumors (previously classified as INSS stage 1) are localized and confined to one body compartment without any IDRFs. L2 tumors (previously classified as INSS stages 2 and 3) refer to localized tumors with the presence of IDRFs. Disseminated tumors with metastases to bones, bone marrow, liver, distant lymph nodes, and/or other organs are staged as M (previously classified as INSS stage 4). Stage MS (previously stage 4S) refers to neuroblastoma in children younger than 18 months of age with dissemination to liver, skin, and/or bone marrow without bone involvement and with a primary tumor that would otherwise be staged as L1 or L2. This new INSS was recently developed to allow for more effective comparisons of treatments and outcomes worldwide.

TREATMENT

Treatment strategies for neuroblastoma have changed with significant reduction in treatment intensity for children who have localized low-risk tumors and with continued increased treatment intensity and the addition of novel agents for treatment of children who have high risk or recurrent disease. The patient's age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient (see

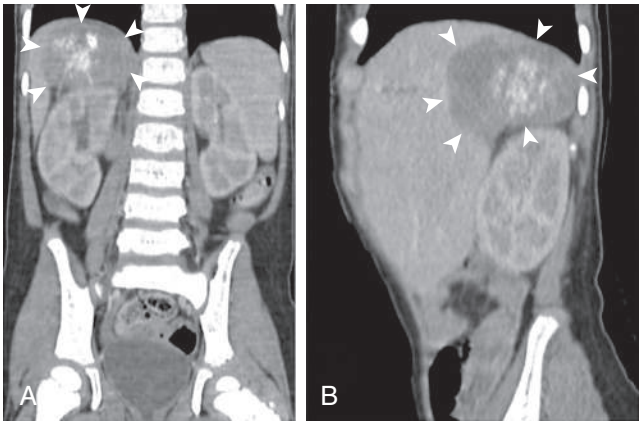

Fig. 547.3 Neuroblastoma. CT images of the abdomen with coronal (**A**) and sagittal (**B**) reconstructions showing a large low-density tumor in the right suprarenal region *(arrowheads)*. Note the neoplastic calcifications inside the mass. *(From Mota EB, Penna CRR, Marchiori E. Metastatic dissemination of a neuroblastoma. J Pediatr. 2017;189:232–232.e1. Fig. 3.)*

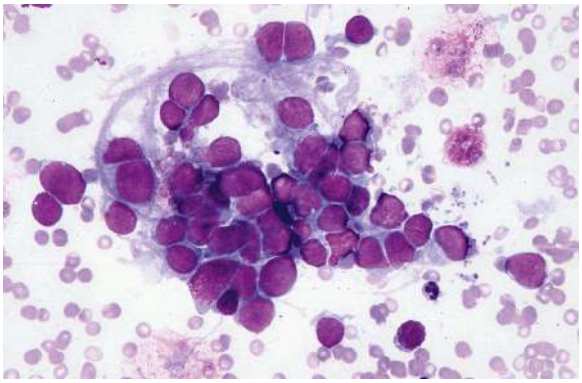

Fig. 547.4 Neuroblastoma cells aspirated from the bone marrow. Clumps of cells often contain ≥3 cells with or without evidence of rosette formation. Rosettes of cells surrounding an inner mass of fibrillary material are characteristic of neuroblastoma.

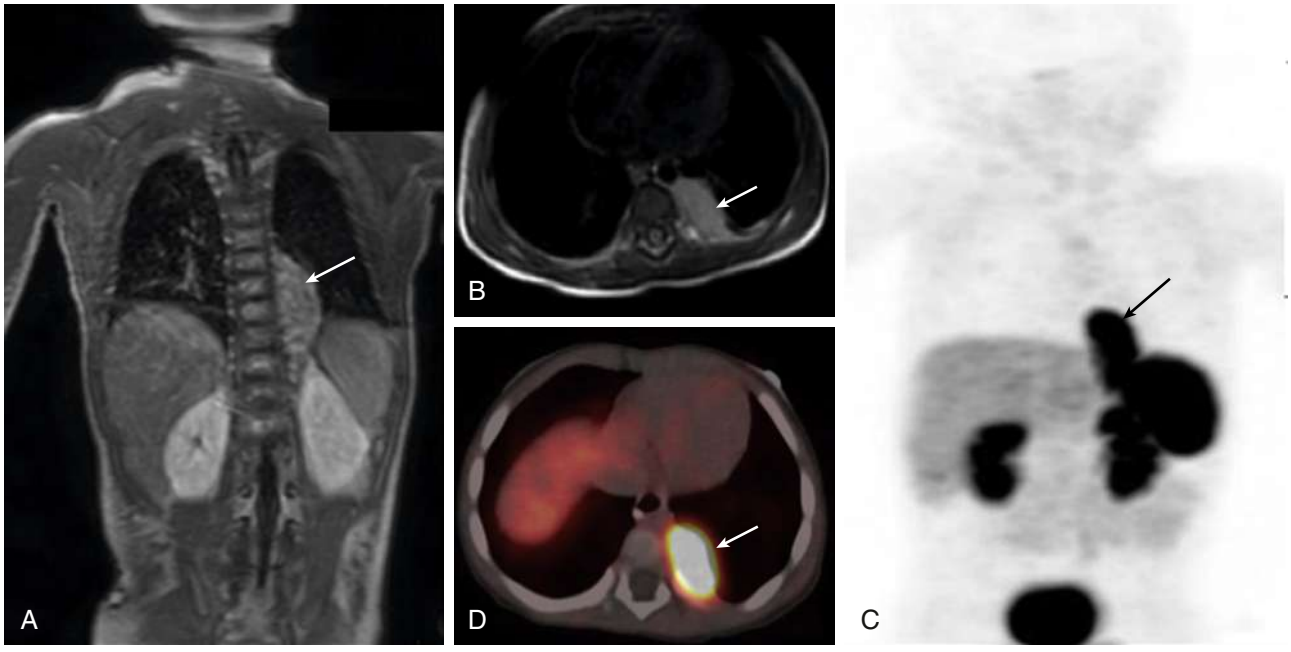

Fig. 547.5 Neuroblastoma. MRI and gallium-68 DOTANOC PET/CT scan of chest and abdomen reveal a mass in left posterior mediastinum (likely neuroblastoma). **A**, Coronal T1-weighted postcontrast image (**A**) and axial T2-weighted image (**B**) reveal a well-defined isointense lesion (42 × 26 × 27 mm) in the left posterior mediastinum extending from D7-D11 vertebrae. **C**, PET/CT maximum intensity projection image shows increased uptake in left lower thoracic paraspinal region. **D**, Axial fused PET-CT image shows somatostatin-receptor expressing mass (maximum standardized uptake value, 21; *arrow in A–D*) in the same location. *(From Kaur A, Bhagwat C, Madaan P, et al. Dancing eyes. J Pediatr. 2019;214:231.)*

Tables 547.2-547.4). Treatment for children with low-risk neuroblastoma typically includes surgery for stages L1 and L2 and observation for asymptomatic stage MS with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic damage. Stage MS neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, chemotherapy or radiation is used to alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given over several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with L2 disease and infants with M disease both with favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and *MYCN* gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with high-risk neuroblastoma historically have had poor long-term survival rates of 25–35% despite intensive treatment consisting of induction chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-*cis*-retinoic acid. Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of the differentiating agent, 13-*cis*-retinoic acid, following autologous stem cell transplantation, resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18 **(dinutuximab)** to 13-*cis*-retinoic acid therapy. This monoclonal antibody targets a disialoganglioside, GD2, which has ubiquitous expression on neuroblastoma cells. In this large, randomized, clinical trial of high-risk neuroblastoma patients sponsored by the Children's Oncology Group, incorporation of the antibody into consolidative therapy following autologous stem cell transplant improved the 2-year event-free survival from 46.5–66.5%. The incorporation of tandem autologous stem cell transplant (two separate autologous stem cell transplants with differing conditioning regimens) may further improve outcomes for patients with high-risk disease.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents as well as novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as *therapeutic* ^{131}I-MIBG), immunotherapy, and antitumor vaccines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 548
Neoplasms of the Kidney

548.1 Wilms Tumor

Najat C. Daw and Dristhi S. Ragoonanan

Wilms tumor **(nephroblastoma)** is the most common primary malignant *renal* tumor of childhood. It is the second most common malignant abdominal tumor in childhood after neuroblastoma. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic Wilms tumor is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The use of multimodality treatment and multi-institutional cooperative group trials has dramatically improved the cure rate of Wilms tumor from <30% to >90% (Table 548.1).

EPIDEMIOLOGY

Wilms tumor accounts for 6% of pediatric malignancies and >95% of kidney tumors in children. In the United States, incidence of Wilms tumor is approximately 7 cases per 1 million children <15 years of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children <5 years old, with a peak incidence at 2-3 years. It can arise in one or both kidneys; the incidence of bilateral Wilms tumors is 7%. The male/female ratio is 0.92 to 1 in unilateral disease and 0.6 to 1 in bilateral disease. Most cases are sporadic, but approximately 2% of patients have a family history. In 8–10% of patients, Wilms tumor is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies, and a variety of rare syndromes, including **Beckwith-Wiedemann syndrome (BWS)** and **Denys-Drash syndrome** (Table 548.2). An earlier age at diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

ETIOLOGY: GENETICS AND MOLECULAR BIOLOGY

Wilms tumor is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme **(nephrogenic rests)** that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population but are present in up to 90% of children who have a family history of Wilms tumor, develop bilateral tumors, or display features of Wilms tumor–related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

Wilms tumor has been associated with genetic abnormalities. The first identified Wilms tumor gene, *WT1*, located at 11p13, is a homozygous gene variant in 10–15% of tumors, resulting in loss of function of the encoded zinc finger transcription factor. The majority of *WT1* pathogenic variants are somatic; however, *WT1* pathogenic variants can also be germline. The type of WT1 pathogenic variant affects the disease phenotype. Germline truncating variants are usually associated with Wilms tumor in the context of genitourinary anomalies or the **WAGR syndrome** (Wilms tumor, aniridia, genitourinary anomalies, mental retardation) as it involves the deletion of several contiguous genes at 11p13. Missense germline variants are usually observed in children with Denys-Drash syndrome, resulting in early-onset renal failure. In instances of germline variant, the wild-type allele present in the germline is altered or lost in the tumor, resulting in loss of *WT1* function.

Tables 547.2-547.4). Treatment for children with low-risk neuroblastoma typically includes surgery for stages L1 and L2 and observation for asymptomatic stage MS with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic damage. Stage MS neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, chemotherapy or radiation is used to alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given over several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with L2 disease and infants with M disease both with favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and *MYCN* gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with high-risk neuroblastoma historically have had poor long-term survival rates of 25–35% despite intensive treatment consisting of induction chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-*cis*-retinoic acid. Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of the differentiating agent, 13-*cis*-retinoic acid, following autologous stem cell transplantation, resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18 **(dinutuximab)** to 13-*cis*-retinoic acid therapy. This monoclonal antibody targets a disialoganglioside, GD2, which has ubiquitous expression on neuroblastoma cells. In this large, randomized, clinical trial of high-risk neuroblastoma patients sponsored by the Children's Oncology Group, incorporation of the antibody into consolidative therapy following autologous stem cell transplant improved the 2-year event-free survival from 46.5–66.5%. The incorporation of tandem autologous stem cell transplant (two separate autologous stem cell transplants with differing conditioning regimens) may further improve outcomes for patients with high-risk disease.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents as well as novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as *therapeutic* ^{131}I-MIBG), immunotherapy, and antitumor vaccines.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 548
Neoplasms of the Kidney

548.1 Wilms Tumor

Najat C. Daw and Dristhi S. Ragoonanan

Wilms tumor **(nephroblastoma)** is the most common primary malignant *renal* tumor of childhood. It is the second most common malignant abdominal tumor in childhood after neuroblastoma. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic Wilms tumor is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The use of multimodality treatment and multi-institutional cooperative group trials has dramatically improved the cure rate of Wilms tumor from <30% to >90% (Table 548.1).

EPIDEMIOLOGY

Wilms tumor accounts for 6% of pediatric malignancies and >95% of kidney tumors in children. In the United States, incidence of Wilms tumor is approximately 7 cases per 1 million children <15 years of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children <5 years old, with a peak incidence at 2-3 years. It can arise in one or both kidneys; the incidence of bilateral Wilms tumors is 7%. The male/female ratio is 0.92 to 1 in unilateral disease and 0.6 to 1 in bilateral disease. Most cases are sporadic, but approximately 2% of patients have a family history. In 8–10% of patients, Wilms tumor is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies, and a variety of rare syndromes, including **Beckwith-Wiedemann syndrome (BWS)** and **Denys-Drash syndrome** (Table 548.2). An earlier age at diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

ETIOLOGY: GENETICS AND MOLECULAR BIOLOGY

Wilms tumor is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme **(nephrogenic rests)** that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population but are present in up to 90% of children who have a family history of Wilms tumor, develop bilateral tumors, or display features of Wilms tumor–related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

Wilms tumor has been associated with genetic abnormalities. The first identified Wilms tumor gene, *WT1*, located at 11p13, is a homozygous gene variant in 10–15% of tumors, resulting in loss of function of the encoded zinc finger transcription factor. The majority of *WT1* pathogenic variants are somatic; however, *WT1* pathogenic variants can also be germline. The type of WT1 pathogenic variant affects the disease phenotype. Germline truncating variants are usually associated with Wilms tumor in the context of genitourinary anomalies or the **WAGR syndrome** (Wilms tumor, aniridia, genitourinary anomalies, mental retardation) as it involves the deletion of several contiguous genes at 11p13. Missense germline variants are usually observed in children with Denys-Drash syndrome, resulting in early-onset renal failure. In instances of germline variant, the wild-type allele present in the germline is altered or lost in the tumor, resulting in loss of *WT1* function.

Table 548.1 Treatment and Four-Year Outcomes for Patients with Wilms Tumor

STUDY	STAGE/HISTOLOGY	TREATMENT	EFS (%)	OS (%)
NWTS-5	Stage I or II FH; no LOH	Regimen EE4A	91	98
COG AREN0532	Stage I FH (age <24 mo, tumor weight <550 g)	Nephrectomy alone	90	100
	Stage I or II FH; +LOH	Regimen DD4A	87	100
	Stage III FH; no LOH	Regimen DD4A Flank radiation*	88	97
COG AREN0533	Stage III or IV FH; +LOH	Regimen M Radiation to flank per local stage Radiation to metastatic sites	90	96
	Stage IV FH with lung metastases only and complete response at 6 weeks; no LOH	Regimen DD4A Radiation to flank per local stage Omit radiation to whole lung	80	96
	Stage IV FH with lung metastases only and incomplete response at 6 weeks; no LOH	Regimen M Radiation to flank per local stage Radiation to whole lung	89	95
COG AREN0534	Stage V FH	Chemotherapy Radiation per local stage	82	95
COG AREN0321	Stage I FA + DA	Regimen DD4A Radiation to flank	100	100
	Stage II DA	Regimen UH-1 Radiation to flank	87	86
	Stage III DA	Regimen UH-1 Radiation to flank*	81	89
	Stage IV DA	Regimen UH-1/UH-2 Radiation to flank per local stage Radiation to metastatic sites	42	49
COG AREN0534	Stage V DA	Chemotherapy Radiation to flank per local stage Radiation to metastatic sites	58	68
	Unilateral Wilms tumor with bilateral predisposition	EE4A followed by treatment per stage/histology Radiation to flank per local stage	94	100

*Whole-abdomen radiation therapy indicated for patients with diffuse intraperitoneal tumor rupture, peritoneal tumor seeding, and cytology-positive ascites

NWTS-5, National Wilms Tumor Study-5; COG, Children's Oncology Group; EFS, event-free survival; OS, overall survival; FH, favorable histology; LOH, loss of heterozygosity at both 1p and 16q; FA, focal anaplasia; DA, diffuse anaplasia; EE4A, vincristine/dactinomycin × 19 weeks; DD4A, vincristine/dactinomycin/doxorubicin × 25 weeks; M, vincristine/dactinomycin/doxorubicin/cyclophosphamide/etoposide × 31 weeks; revised UH-1, vincristine/doxorubicin/cyclophosphamide/carboplatin/etoposide × 30 weeks; revised UH-2, revised UH-1 with vincristine/irinotecan × 36 weeks.

Table 548.2 Wilms Tumor Predisposing Conditions

SYNDROME	GENETIC LESION	ESTIMATED WT RISK	PHENOTYPE
WT1-ASSOCIATED WILMS TUMOR PREDISPOSITION SYNDROMES			
Denys-Drash syndrome (DDS)	*WT1* pathogenic variant affecting exon 8 or 9	~75%	Ambiguous genitalia, diffuse mesangial sclerosis
Frasier syndrome	*WT1* pathogenic variant affecting intron 9 donor splice site	Low; 1 case reported	Ambiguous genitalia, streak gonads, focal segmental glomerulosclerosis
WAGR syndrome (Wilms tumor, aniridia, genital anomalies, retardation)	Deletion of 11p13 containing *WT1*	~50%	Aniridia, genitourinary anomalies, delayed-onset renal failure
WT1-associated WT predisposition	*WT1* pathogenic variant	~30%	Median age at WT diagnosis is 1.3 yr (range: 0.6-4.5)
OTHER SYNDROMES THAT PREDISPOSE TO WILMS TUMOR			
Beckwith-Wiedemann syndrome (BWS)	LOM at maternal IC2 at 11p15.5 GOM at maternal IC1 at 11p15.5 Paternal UPD at 11p15.5 Pathogenic variant in *CDKN1C* Negative molecular test	~0.2% ~24% ~8% ~1.4% ~4%	Organomegaly, large birth weight, macroglossia, omphalocele, hemihypertrophy, ear pits and creases, neonatal hypoglycemia
Bloom syndrome	Biallelic *BLM* pathogenic variants	~3%	Short stature, microcephaly, growth deficiency, immune abnormalities, sensitivity to sunlight

Continued

Table 548.2 Wilms Tumor Predisposing Conditions—cont'd

SYNDROME	GENETIC LESION	ESTIMATED WT RISK	PHENOTYPE
Fanconi anemia	Biallelic *BRCA2* or *PALB2* pathogenic variants	20–40%	Short stature, abnormal skin pigmentation, skeletal malformations, microcephaly, bone marrow failure
Hyperparathyroid-jaw tumor syndrome	*CDC73* pathogenic variant	~3%	Primary hyperparathyroidism, ossifying fibroma of the maxilla and/or mandible
Mosaic variegated aneuploidy	Biallelic *BUB1B* or *TRIP13* pathogenic variants	>85%	Microcephaly, growth deficiency, developmental delay, eye anomalies, mild dysmorphism
Perlman syndrome	Biallelic *DIS3L2* pathogenic variants	~65%	Organomegaly, large birth weight, developmental delay
Simpson-Golabi-Behmel syndrome	*GPC3* pathogenic variant	4–9%	Overgrowth, congenital heart defects
CLOVES syndrome	*PIK3CA* pathogenic variant	<5%	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal/spine anomalies
Sotos syndrome	*NSD1* pathogenic variant	<5%	Cerebral giantism, macrocephaly, intellectual disability, advanced bone age, poor coordination
Trisomy 18	Trisomy 18	<5%	Cognitive impairment, hypertonia, overlapping fingers, congenital heart disease, micrognathia
GENETIC VARIANTS THAT PREDISPOSE TO NONSYNDROMIC WILMS TUMOR			
CTR9-associated WT predisposition	*CTR9* pathogenic variant	4 families reported; 9/14 individuals with a pathogenic *CTR9* variant developed WT	Median age at WT diagnosis is 1.3 yr (range: 0.6-3.3). All reported variants are paternally inherited
DICER1 syndrome	*DICER1* pathogenic variant	Low; 5 families in which 6/22 individuals with a pathogenic *DICER1* variant developed WT	Lung cysts, cystic nephroma, nodular hyperplasia of the thyroid, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma and increased cancer risks including pleuropulmonary blastoma (PPB), ovarian sex cord-stromal tumors, pineoblastoma, and pituitary blastoma
Li-Fraumeni syndrome (LFS)	*TP53* pathogenic variant	Low; 12 cases reported	Around 50% of individuals with LFS develop cancer by the age of 30 yr, with a lifetime risk of >70% The tumors most closely associated with LFS include soft tissue sarcomas, osteosarcoma, premenopausal breast cancer, brain tumors, and adrenocortical carcinoma
REST-associated WT predisposition	*REST* pathogenic variant	4 families reported; 7/14 individuals with a pathogenic *REST* variant developed WT Ten presumed sporadic cases reported	Median age at WT diagnosis is 3 yr (range: 0.5-6) Other clinical features reported include primary ovarian failure, café-au-lait macules, and mild developmental delay
TRIM28-associated WT predisposition	*TRIM28* pathogenic variant	9 families reported; 18/24 individuals with a pathogenic *TRIM28* variant developed WT; however, few unaffected family members were tested 17 presumed sporadic cases reported	Median age at WT diagnosis is 1.1 yr (range: 0.4-9.8) All reported variants are maternally inherited Histology is frequently epithelial type

GOM, Gain of methylation; IC, imprinting center; LOM, loss of methylation; UPD, uniparental disomy; WT, Wilms tumor.
Modified from Maciaszek JL, Oak N, Nichols KE. Recent advances in Wilms' tumor predisposition. *Hum Mole Genetics.* 2020;29(R2):R138–R149. Table 1, p. R139–R140.

Consistent with the etiology of Wilms tumor being grounded in aberrant kidney development, genes that regulate the proliferation and differentiation of kidney progenitors have been identified to be mutated in tumors. One class of genes that encodes proteins essential for the biogenesis of mature miRNAs are altered in one fifth to one third of Wilms tumors. These include *DROSHA* missense variants that occur in approximately 10% of tumors, and *DICER, DGCR8, XPO5*, and *TARBP2* variants. Of note, germline *DICER1* variants are observed, albeit infrequently, in Wilms tumor families and, more frequently, in families with pleuropulmonary blastoma (see Table 548.2).

The **Wnt signaling pathway** plays a critical role in regulating the differentiation of the fetal kidney. Somatic pathogenic variants in *CTNNB1* and *WTX*, both of which play a role in the Wnt pathway regulation, are observed in approximately 15% and 20% of Wilms tumors,

Table 548.3 Differential Diagnosis of Abdominal and Pelvic Tumors in Children

TUMOR	PATIENT AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms tumor	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria, polycythemia, thrombocytosis, elevated partial thromboplastin time
Neuroblastoma	Preschool	Gastrointestinal/genitourinary obstruction, raccoon eyes, myoclonus-opsoclonus, diarrhea, skin nodules	Increased urinary vanillylmandelic acid, homovanillic acid, or ferritin; stippled calcification in the mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in >2 yr old	Increased lactate dehydrogenase; blood cytopenia caused by bone marrow involvement
Rhabdomyosarcoma	All	Gastrointestinal/genitourinary obstruction, abdominal pain, vaginal bleeding, paratesticular mass	Hypercalcemia; blood cytopenia caused by bone marrow involvement
Germ cell tumor/ teratoma	Preschool, teenage	*Females:* Abdominal pain, vaginal bleeding *Males:* Testicular mass, new-onset hydrocele, sacrococcygeal mass/dimple	Increased β-human chorionic gonadotropin, increased α-fetoprotein
Hepatoblastoma	Birth-3 yr	Right upper quadrant mass, jaundice Early puberty in males	Increased α-fetoprotein
Hepatocellular carcinoma	School age, teenage	Right upper quadrant mass, jaundice, hepatitis B, cirrhosis	Increased α-fetoprotein

respectively. Somatic variants in genes that are critical for regulating progenitor proliferation and differentiation (*MYCN, SIX1,* and *SIX2*) are observed in approximately 10% of tumors. Other somatic variants, including *MLLT1, ARID1A,* and *SMARCA4,* occur at a frequency of approximately 4–5% each. Importantly a somatic variant of the p53 gene, *TP53*, is observed in approximately 5% of tumors and is associated with **anaplastic tumor** histology, a poor prognostic feature of Wilms tumor.

Loss of heterozygosity (LOH; usually copy number neutral) or loss of imprinting at imprinted loci at 11p15 is observed in approximately 70% of Wilms tumors. This epigenetic alteration often results in biallelic expression of *IGF2,* a normally imprinted gene that encodes insulin-like growth factor 2, in addition to the loss of imprinting of other 11p15 genes. BWS, a somatic overgrowth syndrome with predisposition to embryonal tumors (including Wilms tumor), has been linked to 11p15, and microdeletions within the *IGF2* imprinting control region are present in BWS families in whom Wilms tumor is observed.

Allelic imbalances have been identified in Wilms tumors, particularly LOH at 1p and 16q, which has been associated with increased risk of recurrence. Gain of chromosome 1q was found to be associated with inferior survival in unilateral favorable-histology Wilms tumor.

In patients with a family history of Wilms tumor, predisposition is inherited as an autosomal dominant trait with incomplete penetrance. Predisposition to other tumor types or other phenotypes is not observed in most of these families. Germline pathogenic variants have been identified in a minority of families, and each of those genes identified (e.g., *WT1, DICER1, MYCN, REST, BRCA2*) is altered in <5% of Wilms tumor families.

CLINICAL PRESENTATION

The most common initial clinical presentation for Wilms tumor is the incidental discovery of an asymptomatic **abdominal mass** by parents while bathing or clothing an affected child or by a physician during a routine physical examination (Table 548.3). At presentation, the mass can be quite large, because retroperitoneal masses can grow unhampered by strict anatomic boundaries. Functional defects in paired organs such as the kidney, with good functional reserve, are also unlikely to be detected early. Physical exam findings include a firm, nontender, smooth abdominal mass that rarely crosses the midline. Care should be taken to avoid vigorous palpation to prevent the risk of renal capsule rupture. Children with direct access to pediatricians vs generalists as primary caregivers are more likely to be diagnosed early and to have smaller tumors and less advanced stage at diagnosis. Hypertension is present in about 25% of patients at presentation and has been attributed to increased renin activity. Abdominal pain (40%), gross painless hematuria (18%), and constitutional symptoms such as fever, anorexia, and weight loss are other findings at diagnosis. Occasionally, rapid abdominal enlargement and anemia occur because of bleeding into the renal parenchyma or pelvis. Wilms tumor thrombus extends into the inferior vena cava (IVC) in 4–10% of patients and rarely into the right atrium; dislodgment of the intravascular tumor may produce a fatal occlusive **pulmonary embolism**. Patients might also have microcytic anemia from iron deficiency or anemia of chronic disease, polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor or factor VII deficiency.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

An abdominal mass in a child should be considered malignant until diagnostic imaging, laboratory findings, and pathology can define its true nature (see Table 548.3). Imaging studies include plain abdominal radiography, abdominal ultrasonography (US), and CT of the abdomen to define the intrarenal origin of the mass and differentiate it from adrenal masses (e.g., neuroblastoma) and other masses in the abdomen. Abdominal US helps differentiate solid from cystic masses. Wilms tumor might show focal areas of necrosis or hemorrhage and hydronephrosis because of obstruction of the renal pelvis by the tumor. US with Doppler imaging of renal veins and the IVC is a useful first study to identify Wilms tumor, evaluate the collecting system, and demonstrate tumor thrombi in the renal veins and IVC. However, its routine use after CT has been performed is not required.

CT is useful to define the extent of the disease, integrity of the contralateral kidney, and metastasis (Figs. 548.1 and 548.2). MRI requires sedation in young children and is not routinely used. However, MRI may be helpful in defining an extensive tumor thrombus that extends up to the level of the hepatic veins, or even into the right atrium, and to distinguish Wilms tumor from nephrogenic rests. Chest CT is more sensitive than chest radiography to screen for pulmonary metastasis and is preferably performed before surgery because effusions and atelectasis can confound the interpretation of postoperative imaging studies. A bone scan is performed if the histologic diagnosis confirms clear cell sarcoma of the kidney (CCSK) or rhabdoid tumor of the kidney, to look for bone metastasis. Brain imaging with CT or MRI is also obtained in cases of clear cell sarcoma or rhabdoid tumor of the kidney because these tumors can spread to the brain.

Wilms tumor lesions are metabolically active and concentrate fluorodeoxyglucose (FDG). Regional spread and metastatic lesions can

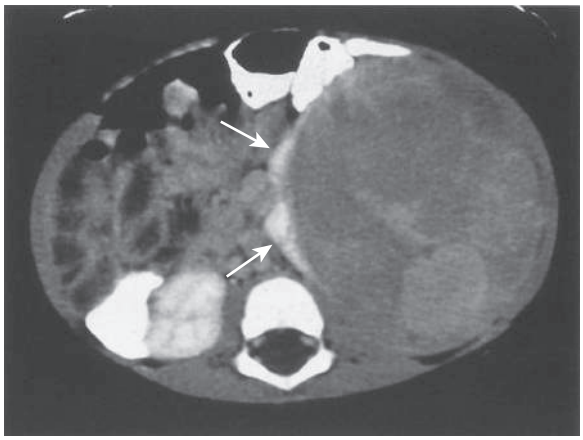

Fig. 548.1 Large heterogeneous Wilms tumor in left kidney. The residual renal parenchyma is displaced medially *(arrows). (From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017: Fig. 54-84, p. 1816.)*

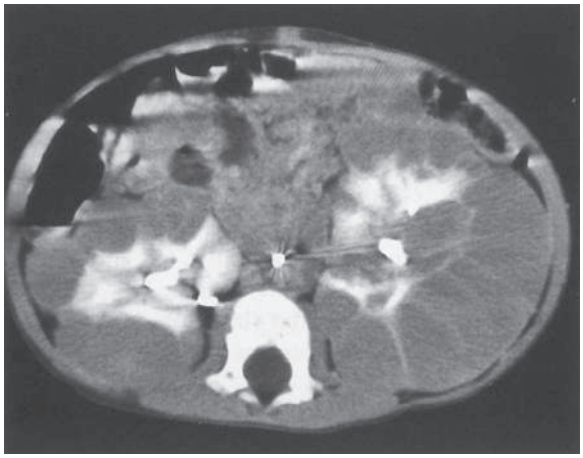

Fig. 548.2 Multicentric and bilateral Wilms tumors. The tumors have a low density and compress residual enhancing renal tissue. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017: Fig. 54-86, p. 1817.)*

be visualized on PET/CT scanning. The diagnosis is usually made by imaging studies and confirmed by histology at the time of nephrectomy. Although biopsy is a reliable diagnostic tool, it is discouraged because it results in disease upstaging according to the Children's Oncology Group (COG) staging system. A core needle biopsy obtained through a posterior approach (to limit contamination of the peritoneal cavity) should be performed in cases of unusual presentation (>10 years old, signs of infection, inflammation) or unusual imaging findings (significant adenopathy, no renal parenchyma seen, intratumoral calcification).

Patients with Wilms tumor associated syndromes should undergo routine screening with serial abdominal US to allow for early detection and treatment.

TREATMENT

The COG protocols and the **International Society of Pediatric Oncology (SIOP)** protocols differ in their initial treatment approach. *COG advocates upfront surgery* prior to initiating treatment, whereas *SIOP recommends preoperative chemotherapy.* Each approach has advantages and limitations, but they have similar outcomes. Early surgery provides accurate diagnosis and staging and can facilitate *risk-adapted therapy*. Preoperative chemotherapy can make surgery easier and reduces the risk of intraoperative tumor rupture and hemorrhage. Surgery entails a radical nephrectomy, with meticulous dissection to avoid rupture of the tumor capsule, and lymph node sampling despite the absence of abnormal nodes on preoperative imaging studies or intraoperative assessment. Partial nephrectomy is performed in patients with bilateral disease or those with unilateral Wilms tumor and predisposing syndrome such as the Denys-Drash and WAGR syndromes to minimize the risk of future renal failure.

Table 548.4 Children's Oncology Group Staging of Wilms Tumor

STAGE	DESCRIPTION
I	Tumor *confined to the kidney* and completely resected Renal capsule or sinus vessels not involved Tumor not ruptured or biopsied Regional lymph nodes examined and negative
II	Tumor extends *beyond the kidney* but is completely resected with negative margins and lymph nodes At least one of the following has occurred: (a) penetration of renal capsule, (b) invasion of renal sinus vessels
III	*Residual tumor* present following surgery confined to the abdomen, including gross or microscopic tumor; spillage of tumor preoperatively or intraoperatively; biopsy prior to nephrectomy, regional lymph node metastases; tumor implants on the peritoneal surface; extension of tumor thrombus into the inferior vena cava, including thoracic vena cava and heart
IV	*Hematogenous metastases* (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
V	*Bilateral* renal involvement by tumor

Prognostic factors for risk-adapted therapy include age, stage, histology, tumor weight, LOH at chromosomes 1p and 16q, and metastatic lung nodule response (Table 548.4). Histology plays a major role in risk stratification of Wilms tumor. Absence of anaplasia is considered a favorable histologic finding. Presence of anaplasia is further classified as focal or diffuse, both of which are unfavorable histologic findings.

The COG has very specific drug dose and schedule recommendations for risk-adapted treatment of Wilms tumor. Patients with *favorable-histology* Wilms tumor have a good outcome and are generally treated in the outpatient setting. Nephrectomy alone is sufficient for patients with very low risk disease (<2 years old with stage I disease and a tumor weight <550 g), resulting in a 4-year event-free survival of 90% and a 4-year overall survival of 100%. Patients with stage I and II disease receive chemotherapy with two drugs, vincristine and actinomycin D (also called dactinomycin), every 1-3 weeks for a total of 18 weeks (regimen **EE4A**). Patients with stage III or stage IV disease receive chemotherapy with three drugs (vincristine, doxorubicin, and actinomycin D) every 1-3 weeks for a total of 24 weeks (regimen **DD4A**) and radiation therapy. Patients with regional lymph node metastases, residual disease after surgery, or tumor rupture receive radiation therapy to the flank or abdomen, and those with lung metastases receive radiation therapy to the lungs. Rapid response of lung metastases to chemotherapy may eliminate the need for lung radiation. In patients with stage III or stage IV disease and LOH at both 1p and 16q or in those with lung metastases only who have incomplete response at 6 weeks of DD4A, therapy is augmented by adding cyclophosphamide/etoposide to DD4A (Regimen M). The LOH of both 1p and 16q and gain of 1q confers an adverse prognosis and deserves treatment intensification.

For patients with bilateral Wilms tumor, three-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis, and histology-based postoperative therapy improves survival outcomes and feasibility of nephron-sparing surgery.

Anaplastic histology (focal and diffuse) accounts for approximately 11% of Wilms tumor cases. Patients with *diffuse anaplasia* have worse outcome than patients with favorable histology and receive more

intensive therapy. Patients with stage 1 anaplastic Wilms tumor treated with regimen DD4A and flank radiation had excellent survival outcomes. Patients with stage II-IV disease are treated more intensively with multiagent chemotherapy including vincristine, cyclophosphamide, doxorubicin, etoposide, carboplatin, and irinotecan, in addition to radiotherapy. Despite some improvement in survival outcomes, patients with stage IV disease continue to fare poorly.

RECURRENT DISEASE

Approximately 15% of favorable-histology and 50% of anaplastic-histology Wilms tumors relapse; most relapses occur early (within 2 years of diagnosis). Factors associated with a favorable outcome after relapse include low stage (I/II) at diagnosis, treatment with vincristine and actinomycin D only, no prior radiotherapy, favorable histology, relapse to lung only, and interval from nephrectomy to relapse ≥12 months. Patients with recurrent Wilms tumor who previously received only vincristine and actinomycin D had a 4-year survival of approximately 80%, whereas those who previously received the three-drug regimen of vincristine, actinomycin D, and doxorubicin had a 4-year survival of only 50%. Other agents used to treat recurrent Wilms tumor include doxorubicin, carboplatin, cyclophosphamide, ifosfamide, etoposide, irinotecan, and topotecan. *Metachronous* Wilms tumor may not represent tumor relapse but development of a new tumor in the opposite kidney.

PROGNOSIS

Despite some adverse risk factors that decrease prognosis (presence of metastasis, unfavorable histology, recurrent disease, incomplete lung nodule response at 6 weeks of chemotherapy, LOH of both 1p and 16q and gain of 1q), most children with Wilms tumor have a very favorable prognosis. Overall survival of children with Wilms tumor exceeds 90%, with some prognostic factors (low stage, favorable histology, young age, low tumor weight) conferring even better outcomes. Wilms tumor tops the list of common pediatric solid tumors in terms of favorable outcome.

LATE EFFECTS

Current strategies are successful with relatively few long-term effects of therapy. Generally, late complications are a consequence of treatment type and intensity; the use of radiotherapy and anthracyclines increase the risk of these complications. Clinically significant late sequelae include musculoskeletal effects, cardiac toxicity, pulmonary disease, reproductive problems, renal dysfunction, and development of second malignant neoplasms such as leukemia and cancer of the digestive organs and breast (in females).

548.2 Other Pediatric Renal Tumors

Najat C. Daw and Dristhi S. Ragoonanan

MESOBLASTIC NEPHROMA

Mesoblastic nephroma is the most common solid renal tumor identified in the *neonatal period* and the most frequent benign renal tumor in childhood. It represents approximately 5% of all pediatric renal tumors. ETV6-NTRK3 fusion pathogenic variant is the most common molecular alteration seen in these tumors. Many cases are diagnosed with prenatal US and can manifest as polyhydramnios, hydrops, and premature delivery. Most patients are diagnosed before 3 months of age, whereas Wilms tumor is *rarely diagnosed* before 6 months. Male/female ratio is 1.5:1. Radical nephrectomy is the treatment of choice and may be sufficient by itself. Local recurrence is uncommon. Although rare, malignant variants do occur, marked by metastases to the lung, liver, heart, and brain.

CLEAR CELL SARCOMA OF THE KIDNEY

CCSK is an uncommon renal neoplasm of childhood, with approximately 20 new cases diagnosed each year in North America. Peak incidence is between 1 and 4 years of age with a male/female ratio of 2:1. It usually presents with abdominal distention, abdominal mass, or gross hematuria. Gene expression profiles of CCSK suggest the cell of origin to be a renal mesenchymal cell with neural markers, and *BCOR* gene duplication is the most common molecular alteration seen. Bone is the most common site of distant metastasis, followed by lung, abdomen, retroperitoneum, brain, and liver. Therefore the staging workup should include a bone scan. With modern therapy, patients with stage I and II disease have an excellent prognosis (4-year overall survival of 97–100%), whereas those with stage III and IV disease have a 4-year overall survival of 89% and 45%, respectively.

RHABDOID TUMOR OF THE KIDNEY

Malignant rhabdoid tumor of the kidney **(MRTK)** has rhabdomyoblast-like morphology and is a rare but aggressive cancer. The median age of presentation is 11 months, and hematuria is a common presenting feature. Both rhabdoid tumor of the kidney and central nervous system (CNS) atypical teratoid/rhabdoid tumors have deletions and pathogenic variants of the *SMARCB1/hSNF5/INI1* gene and are considered related. Germline pathogenic variants in *SMARCA4* or *SMARCB1* have been linked to rhabdoid tumor predisposition syndrome, an autosomal dominant disorder that results in the increased risk of developing rhabdoid tumors predominantly in infants and children younger than 3 years of age. MRTKs tend to metastasize to the lungs and brain. Prognosis is poor with current therapeutic protocols. Younger age at diagnosis, advanced-stage disease, and CNS involvement are associated with a worse prognosis. The outcome of patients with MRTK is poor. Both the 4-year relapse-free survival and overall survival for patients treated on the National Wilms Tumor Study-5 (NWTS-5) were 50% for stage I, 33% for stages II and III, and 21% for stage IV.

RENAL CELL CARCINOMA

Although renal cell carcinoma **(RCC)** is the most prevalent renal tumor in adults, it is extremely rare in children, accounting for <10% of pediatric renal tumors. The annual incidence rate is approximately four cases per 1 million children. Although Wilms tumor is the predominant renal tumor in childhood, it is rare past early childhood, and RCC is the most prevalent renal malignancy during the second decade of life. Several **genetic disorders** are associated with a predisposition to RCC, including von Hippel-Lindau disease, tuberous sclerosis, and hereditary leiomyomatosis. The most common subtype of RCC in children, the **translocation-type RCC**, is characterized by translocations most frequently involving the *TFE3* gene on chromosome Xp11.2 or the *TFEB* gene on chromosome 6p21. *Renal medullary carcinoma is seen typically in young patients with sickle cell trait.*

Children with RCC may present with frank hematuria, flank pain, and/or a palpable mass, although RCC can be asymptomatic and detected incidentally. RCC has a propensity to metastasize to the lungs, liver, and bone. Although local lymph node involvement is a poor prognostic indicator in adult RCC, the importance of nodal status in pediatric RCC is controversial. Nephrectomy alone may be adequate for early-stage RCC. Along with surgery, there is no established optimal treatment for childhood RCC; neither chemotherapy nor radiation therapy has demonstrated significant activity. Localized pediatric RCC has an excellent outcome without adjuvant therapy; however, the outcomes remain poor for metastatic RCC and renal medullary carcinoma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 549

Soft Tissue Sarcomas

Wendy A. Allen-Rhoades and Carola A.S. Arndt

The annual incidence of soft tissue sarcomas is 11 cases per 1 million children younger than 14 years of age and 17.4 cases per 1 million adolescents age 15-19 years. Rhabdomyosarcoma accounts for more than 50% of soft tissue sarcomas. The prognosis most strongly correlates with age and extent of disease at diagnosis, primary tumor site and histology, and presence of translocations involving the *FOXO1* and *PAX* genes.

RHABDOMYOSARCOMA

Epidemiology

The most common pediatric soft tissue sarcoma, rhabdomyosarcoma, accounts for approximately 3.5% of childhood cancers. These tumors may occur at any anatomic site (Table 549.1) including the head and neck, orbit, genitourinary tract, and extremities; retroperitoneal and other sites account for the remainder of primary sites. The incidence at each anatomic site is related to both patient age and tumor type. Extremity lesions are more likely to occur in older children and to have alveolar histology and harbor a fusion oncoprotein. Rhabdomyosarcoma occurs with increased frequency in patients with neurofibromatosis, Costello syndrome, and other family cancer predisposition syndromes such as Li-Fraumeni syndrome (Table 549.2).

Table 549.1 Common Presenting Signs and Symptoms by Primary Site

PRIMARY SITE (%)	SYMPTOMS AND SIGNS
Head and neck (40%)	Painless or painful swelling Proptosis Ptosis Ophthalmoplegia Headache Vomiting Cranial nerve palsy Other cranial nerve palsies Nasal discharge Nasal/sinus congestion Trismus Systemic hypertension
Limbs/trunk (30%)	Asymptomatic swelling
Genitourinary tract/pelvis (20%)	Painless scrotal lesions Hematuria Urinary retention/dribbling Vulval nodule Polypoid vaginal lesions Vaginal bleeding/discharge Constipation
Abdomen/liver/biliary (~10%)	Asymptomatic swelling Abdominal pain Intestinal obstruction Jaundice Cholangitis
Metastatic disease (20% at diagnosis) Bone Bone marrow Lung Lymph nodes	Otherwise unexplained: Poor feeding Seizures Pain Irritability Pancytopenia

Modified from Rogers TN, Dasgupta R. Management of rhabdomyosarcoma in pediatric patients. *Surg Oncol Clin N Am.* 2021;30(2):339–353. Table 2.

Pathogenesis

Rhabdomyosarcoma is thought to arise from the same embryonic mesenchyme as striated skeletal muscle although a large percentage of these tumors arise in areas lacking skeletal muscle (e.g., bladder, prostate, vagina). On the basis of light microscopic appearance, it belongs to the general category of small, round, blue cell tumors that includes Ewing sarcoma, neuroblastoma, and non-Hodgkin lymphoma. Definitive diagnosis of a pathologic specimen requires immunohistochemical studies using antibodies to skeletal muscle (desmin, muscle-specific actin, myogenin) and reverse transcription polymerase chain reaction, next generation sequencing, or fluorescent in situ hybridization for *FOXO1* rearrangements.

Determination of the specific histologic subtype and fusion status is important in treatment planning and assessment of prognosis. There are four recognized histologic subtypes. The **embryonal type** accounts for approximately 60% of all cases and does not typically harbor a genetic translocation. The rare **spindle/sclerosing** subtype that accounts for approximately 3–4% of all children with rhabdomyosarcoma. It is characterized by a sclerosing (microalveolar) pattern that can mimic the alveolar subtype, but it does not harbor the characteristic PAX/FOXO translocation seen in the alveolar subtype. The **alveolar type** accounts for approximately 25–40% of cases and is characterized by the presence of a chromosomal translocation. Over 80% of *FOXO1* translocations in the alveolar subtype involve a translocation between *FOXO1* and *PAX3*, but other rare variants exist such as *PAX3-NCOA2*. The tumor cells tend to grow in nests that often have cleft-like spaces resembling alveoli. Alveolar tumors occur most often in the trunk and extremities and carry the poorest prognosis. The **pleomorphic type** (adult form) is rare in childhood, accounting for <1% of cases.

Table 549.2 Genetic Disorders Associated with Rhabdomyosarcoma

DISORDER	GENETIC VARIANTS
Beckwith-Wiedemann syndrome	Deletions and loss of heterozygosity at chromosome 11p15, particularly affecting *IGF2, CDKAIC, H19,* and/or *LIT1*
Gorlin syndrome (basal cell nevus syndrome)	*PTCH*
Costello syndrome	*H-RAS*
Neurofibromatosis 1	*NF1*
Li-Fraumeni syndrome	*TP53*
Mosaic variegated aneuploidy syndrome	*BUB1B*
Nijmegen breakage syndrome (ataxia-telangiectasis syndrome variant 1)	*NBS*
Rubinstein-Taybi syndrome	*CREBBP*
Constitutional mismatch-repair/deficiency syndrome	*PSM2*
Adenomatous polyposis coli	*APC*
Hereditary retinoblastoma	*RB1*
Familial pleuropulmonary blastoma syndrome	*DICER1*
Noonan syndrome	*PTPN11*
Werner syndrome	*RECOL2*

From Parham DM, Alaggio R, Coffin CM. Myogenic tumors in children and adolescents. *Pediatr Dev Pathol.* 2012;15(1):S211–S236. Table 3.

Clinical Manifestations

The most common presenting feature of rhabdomyosarcoma is a mass that may or may not be painful. Symptoms are caused by displacement or obstruction of normal structures. Origin in the **nasopharynx** may be associated with nasal congestion, mouth breathing, epistaxis, and difficulty with swallowing and chewing. Regional extension into the cranium can produce cranial nerve paralysis, blindness, and signs of increased intracranial pressure with headache and vomiting. When the tumor develops in the face or cheek, there may be swelling, pain, trismus, and, as extension occurs, paralysis of cranial nerves. Tumors in the **neck** can produce progressive swelling with neurologic symptoms after regional extension. **Orbital** primary tumors are usually diagnosed early in their course because of associated proptosis, periorbital edema, ptosis, change in visual acuity, and local pain. When the tumor arises in the **middle ear**, the most common early signs are pain, hearing loss, chronic otorrhea, or a mass in the ear canal; extensions of the tumor produce cranial nerve paralysis and signs of an intracranial mass on the involved side. An unremitting croupy cough and progressive stridor can accompany rhabdomyosarcoma of the **larynx**. Because most of these signs and symptoms also are associated with common childhood conditions, clinicians must be alert to the possibility of tumor.

Rhabdomyosarcoma of the trunk or extremities often is first noticed after trauma and initially may be regarded as a hematoma. If the swelling does not resolve or increases, malignancy should be suspected. Involvement of the genitourinary tract can produce hematuria, obstruction of the lower urinary tract, recurrent urinary tract infections, incontinence, or a mass detectable on abdominal or rectal examination. Paratesticular tumor usually manifests as a painless, rapidly growing mass in the scrotum. Vaginal rhabdomyosarcoma may manifest as a grapelike mass of tumor tissue bulging through the vaginal orifice, known as **sarcoma botryoides**, and can cause urinary tract or large bowel symptoms. Vaginal bleeding or obstruction of the urethra or rectum may occur. Similar findings can be noted with tumors arising from the uterus.

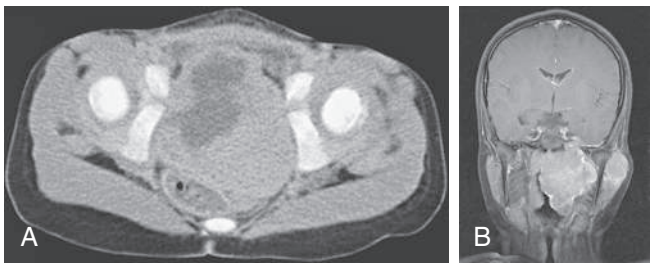

Fig. 549.1 A, Pelvic CT scan of a child with a bladder rhabdomyosarcoma. B, MR image of a child with a parameningeal rhabdomyosarcoma.

Tumors in any location may disseminate early and cause symptoms of pain or respiratory distress associated with pulmonary metastases. Extensive bone involvement can produce symptomatic hypercalcemia or bony pain. In such cases, it may be difficult to identify the primary lesion.

Diagnosis

Early diagnosis of rhabdomyosarcoma requires a high index of suspicion. The microscopic appearance is that of a small, round blue cell tumor. Neuroblastoma, lymphoma, and Ewing sarcoma also are **small, round blue cell tumors** from which suspected rhabdomyosarcomas must be differentiated. The differential diagnosis depends on the site of presentation. Definitive diagnosis is established by biopsy, microscopic appearance, and results of immunohistochemical stains and analysis of *PAX/FOXO1* expression. A lesion in an extremity may be thought to be a hematoma or hemangioma, an orbital lesion resulting in proptosis may be treated as an orbital cellulitis, or bladder-obstructive symptoms may be missed. Adolescents may ignore or be embarrassed to mention paratesticular lesions for a long time. Unfortunately, several months often elapse between initial symptoms and biopsy. Diagnostic procedures are determined mainly by the area of involvement. CT or MRI is necessary for evaluation of the primary tumor site. With signs and symptoms in the head and neck area, MRI should be performed to identify intracranial extension or meningeal involvement and also to reveal bony involvement or erosion at the base of the skull. For abdominal and pelvic tumors, CT with a contrast agent or MRI can help delineate the tumor (Figs. 549.1 and 549.2). A radionuclide bone or fluorodeoxyglucose PET (FDG-PET) scan, chest CT, and bilateral bone marrow aspiration and biopsy should be performed to evaluate the patient for the presence of metastatic disease and to plan treatment. Some low-risk patients may not need bone marrow evaluation. The most critical element of the diagnostic workup is examination of tumor tissue by an experienced sarcoma pathologist, which includes the use of special histochemical stains and immunostains along with molecular genetics to detect fusion transcripts as described earlier. Lymph nodes also should be sampled for the presence of disease spread, especially in tumors of the extremities and in males older than 10 years of age with paratesticular tumors.

Treatment

Treatment is multidisciplinary and includes the pediatric oncologist, pediatric surgeon or other surgical subspecialist, and often a radiation oncologist. Only if the tumor is able to be completely resected, with negative margins, without loss of function or major cosmetic deformity, should this be attempted initially. Unfortunately, most rhabdomyosarcomas are not completely resectable at initial diagnosis. Treatment is based on risk classification of the tumor, which is determined by the stage of tumor, the tumor histology and/or fusion status, and the amount of tumor that was surgically resected prior to chemotherapy ("surgical group"). Stage is dependent on primary site

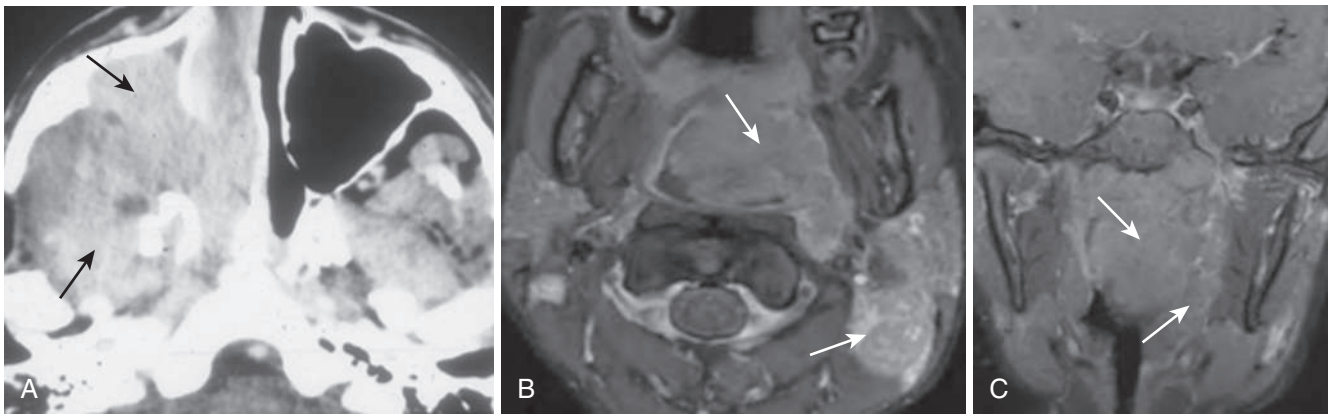

Fig. 549.2 Rhabdomyosarcoma. A, Axial contrast-enhanced CT scan at the level of the nasal cavity demonstrates a large, enhancing aggressive soft tissue mass involving the right maxillary sinus and the infratemporal fossa *(arrows)*. Axial MR image (B) and coronal contrast-enhanced T1-weighted MR image (C) demonstrate an infiltrative mass involving the pharyngeal mucosal space, left infratemporal masticator space, skull base, and sphenoid sinus *(arrows)*. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017: Fig. 26-16, p. 769.)*

(favorable vs unfavorable), tumor invasiveness (T1 or T2), lymph node status, tumor size, and presence of metastasis. Favorable sites include female genital, paratesticular, and head and neck (nonparameningeal) regions; all other sites are considered unfavorable. Table 549.3 shows the Children's Oncology Group staging system for rhabdomyosarcoma.

Patients should be offered enrollment in clinical trials. Table 549.4 shows current risk stratification and outcome based on results of recent studies. Patients with low-risk disease can be cured with minimal therapy consisting of vincristine and actinomycin with or without lower doses of cyclophosphamide; radiation therapy can be used in the case of residual disease after initial surgery. Treatment for patients with intermediate-risk disease consists of vincristine, actinomycin, and cyclophosphamide along with radiation. The addition of irinotecan has recently been studied in intermediate risk rhabdomyosarcoma, and the current trial for patients with intermediate risk disease is exploring the role of maintenance chemotherapy. For patients with high-risk disease, approaches using intensive multiagent chemotherapy have not improved the outcome and new approaches are being investigated.

Prognosis

Prognostic factors include age, stage, histology/fusion status, and primary site. Among patients with resectable tumor and favorable histology, 80–90% have prolonged disease-free survival. Unresectable tumor localized to certain favorable sites, such as the orbit, also has a high likelihood of cure. Approximately 65–70% of patients with incompletely resected tumor also achieve long-term disease-free survival. Patients with disseminated disease have a poor prognosis; only approximately 50% achieve remission, and fewer than 50% of these are cured. Older children have a poorer prognosis than younger children. For all patients, surveillance for late effects of cancer treatment is extremely important. Some examples of late effects include infertility from cyclophosphamide, late effects in the radiation field such as bladder dysfunction, infertility, cataracts, impaired bone growth, and secondary malignancies.

OTHER SOFT TISSUE SARCOMAS

The nonrhabdomyosarcoma soft tissue sarcomas constitute a heterogeneous group of tumors that account for 3% of all childhood malignancies (Table 549.5). Because they are relatively rare in children, much of the information about their natural history and treatment has been derived from studies in adult patients. In children, the median age at diagnosis is 12 years, with a male:female ratio of 2.3:1. These tumors commonly arise in the trunk or lower extremities. The most common histologic types are synovial sarcoma (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%). Molecular genetic studies often prove useful in diagnosis, because several of these tumors have characteristic chromosomal translocations. Tumor size, stage (clinical group), invasiveness, and histologic grade correlate with survival.

Surgery remains the mainstay of therapy, but a careful search for lung and bone metastases should be undertaken before surgical excision. Chemotherapy and radiation therapy should be considered for large, high-grade, and/or unresectable tumors. The role of chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas is not as well defined as for rhabdomyosarcoma. Patients with large (>5 cm) high-grade, or unresectable or metastatic disease are treated with multiagent chemotherapy in addition to irradiation and/or surgery. Patients with completely resected small (<5 cm) tumors are generally treated with surgery alone and can be expected to have an excellent outcome regardless of whether the tumor is high or low grade.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 549.3 Staging System for Rhabdomyosarcoma

STAGE	SITE	T STAGE	SIZE	NODE STATUS	METASTASIS
1	Favorable	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a b	N1 N0 or N1 or Nx	M0
4	Any	T1 or T2	a or b	N0 or N1 or Nx	M1

T1, confined to anatomic site of origin; T2, extension and/or fixative to surrounding tissue.
Size: a, <5 cm in diameter; b, ≥5 cm in diameter.
Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional node status unknown.
Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in cerebrospinal, pleural, or peritoneal fluid).

Table 549.4 Risk Groups and Outcome for Rhabdomyosarcoma, Children's Oncology Group

RISK GROUP	STAGE	CLINICAL GROUP	MOLECULAR FINDINGS	AGE	LONG-TERM EFS (%)*
Very Low	1	I	FOXO1 -, wildtype P53, wildtype MYOD1	Any	92
Low	1	II, III (orbit only)	FOXO1-, wildtype P53, wildtype MYOD1	Any	87
Low	2	I, II	FOXO1 -, wildtype P53, wildtype MYOD1	Any	87
Intermediate	1	III (non orbit)	FOXO1-	Any	70-85
Intermediate	1, 2, 3	I, II, III	FOXO1+	Any	63-93
Intermediate	2, 3	III	FOXO1 -	Any	63-93
Intermediate	3	I, II	FOXO1-	Any	63-93
Intermediate	4	IV	FOXO1-	<10 yr	60-64
High	4	IV	FOXO1-	≥10 yr	35
High	4	IV	FOXO1+	Any	9†

*4–5-year EFS based on D9602, D9803, ARST0331, ARST0431, and ARST0531 studies.
†From Rudzinski ER, Anderson JR, Chi YY, et al. Histology, fusion status, and outcome in metastatic rhabdomyosarcoma: A report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2017;64(12):10.1002/pbc.26645.
EFS, event-free survival,
Modified from Oberoi, S, Crane, JN, Haduong, JH, et al. Children's Oncology Group's 2023 blueprint for research: Soft tissue sarcomas. *Pediatr Blood Cancer.* 2023;70(Suppl. 6):e30556. https://doi.org/10.1002/pbc.30556.

Table 549.5 Clinical and Biological Features of the Nonrhabdomyosarcoma Soft Tissue Sarcomas

TUMOR*	CELL ORIGIN AND CYTOGENETICS/ PRODUCT	COMMON SITES	COMMON AGES	GOOD PROGNOSTIC FACTORS†	OUTCOME	THERAPY
Synovial sarcoma	Mesenchymal cells/t(X;18) (p11q11)/*SSX1–SYT*(seen in biphasic tumors) *SSX2–SYT*(seen in monophasic tumors)/ translocation present in >90%, MYCN over-expression	Extremities (lower twice as common as upper extremity)	Adolescence/ young adult-hood, accounts for 30% of pedi-atric NRSTS	Age ≤14 years, size <5 cm, calcification, chemosensi-tive	Stages I and II, 70%; stages III and IV, poor	WLE with/without RT chemo: ifosfa-mide/doxorubicin
Dermatofibrosar-coma protuber-ans (DFSP)	Dermis/t(17;22) (q21;q13) ring chromosome/*COL1A1–PDGFB*	Trunk and proximal limbs, rare head and neck	20-50 years, rare in childhood	Complete exci-sion, local recurrence 60% with incomplete resection		WLE (3 cm) margin pseudopod-like projections with Mohs micrographic surgery; RT has been used when WLE not possible, imatinib for unresectable; locally advanced, recurrent, or metastatic disease
MFH aka undif-ferentiated pleomorphic sarcoma	Unknown/19p+, complex abnormalities	Lower extremity, trunk, head and neck	In children, 10-20 years, 40-60 years common radiation-induced sarcoma	Extremity site	5-year survival, 27–53%	WLE chemo: ifosfamide/ doxorubicin
Angiomatoid fibrous histiocy-toma	Fibroblast/t(2;22)(q34;q12) t(12;16)(q13;p11) t(12;22) (q13;q12)/*EWSR1–CREB1 TLS–ATF1 EWSR1–ATF1*	Extremity, trunk and head and neck (subcutis may infiltrate dermis or muscle)	Young children and young adults	Much less aggressive than MFH	Excellent with surgery alone	WLE
MPNST	Schwann cell or fibroblast/17q;22q loss or rearrangement, complex abnormalities in high-grade tumors	Extremity, retroperito-neum trunk	Younger patients with neurofi-bromatosis (NF1) develop in 10% patients with *NF1* and 20–60% cases of MPNST occur in association with *NF1*	Size <5 cm, no *NF1*	53% survival without NF, 16% with NF	WLE with/without RT chemo: neoadjuvant role, ifosfamide/ doxorubicin
Fibrosarcoma	Fibroblast/t(X;18), t(2;5), t(7;22)	Truncal/proxi-mal site	Adolescence		5-year survival 34–60%	WLE with/without RT chemo: no established role
Infantile fibro-sarcoma	Fibroblast/t(12;15) (p13;q25)/*ETV6–NTRK3*	Distal extremity	Most <2 years	<5 years	5-year survival 84%	WLE, RT/chemo if WLE not possible historically, neoad-juvant chemo-therapy (with VA ± C). However, the use of molecular targeting with NTRK inhibitor for up to 26 cycles has had dramatic results and should be considered first-line therapy

Table 549.5 Clinical and Biological Features of the Nonrhabdomyosarcoma Soft Tissue Sarcomas—cont'd

TUMOR*	CELL ORIGIN AND CYTOGENETICS/ PRODUCT	COMMON SITES	COMMON AGES	GOOD PROGNOSTIC FACTORS†	OUTCOME	THERAPY
Leiomyosarcoma	Deletion 1p, other complex abnormalities, smooth muscle-uterine t(12;14)(q15;q24); *HMGA2* rearrangement	Retroperitoneum GI tract, any soft-tissue or vascular area	40-70 years, when in children, any age, associated with human immunodeficiency virus related to EBV infection, reported in patients who received RT for retinoblastoma and Carney triad‡	<5 cm	33% disease-free survival at 1-5 years	WLE chemo: ifosfamide/ doxorubicin or gemcitabine/ docetaxel
Alveolar soft part sarcoma	der(17)t(X;17)(p11;25)/*ASPSCR1–TFE3*	Orbit, head and neck, lower extremity	15-35 years	Young age, orbital site, <5 cm	5-year survival 27–59% (indolent; death from disease after 10-20 years) 79% metastatic disease, including brain	WLE chemo or RT only after recurrence chemo: no clear role Possible role of vascular endothelial growth factor inhibitors being explored
Hemangiopericytoma infantile form (<1 year of age)	Pericytes/t(12;19)(q13;q13)/t(13;22)(q22;q11)	Extremity, retroperitoneum head and neck extremity, trunk	20-70 years, when in children, 10-20 years rare, but typically 1 year	Low stage, <5 cm, infantile form	Stages I and II, 30–70% 5-year survival with adjuvant therapy stages III and IV, poor infantile—excellent with surgery alone	WLE, with/without RT chemo: no established role but can be chemoresponsive, infantile form responds more favorably to chemotherapy
Liposarcoma (myxoid)	Primitive mesenchyme/t(12;16)(q13p11)/*FUS–DDIT3*	Extremity, retroperitoneum	0-2 years and second decade; sixth decade most common	Child, myxoid type	Very good with WLE, rarely metastasizes	WLE, with/without RT RT important in retroperitoneal lesion chemo: no established role
Clear cell sarcoma	Mesoderm, melanin deposits t(12;22)(p13;q12)/*EWSR1–ATF1*	Tendons and aponeuroses of lower extremity	Young adults, females	<5 cm, no necrosis, nonmetastatic	Adverse prognosis; 5-year survival rates of 60–70%. However, only 30–40% are long-term survivors due to late recurrences	WLE with sentinel node biopsy no clear role for adjuvant chemotherapy Potential role for immunotherapy (e.g., translocation-targeted vaccines, interferon, GM-CSF-secreting vaccine)
Epithelioid sarcoma	Inactivation of INI1 (hSNF5/SMAR CB1) located on chromosome 22q11.2	Distal extremities (especially hands)	Young adult	Younger age, distal tumor location, no necrosis or vascular invasion, negative nodal status, and microscopic complete resection	Tumor is highly aggressive and has a propensity for lymph node metastases Localized smaller tumors have better prognosis	WLE with sentinel lymph node biopsy ± RT and/or chemo: ifosfamide/ doxorubicin Clinical trial for use of tazemetostat recently completed Approval for patients with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection

*Listed in order of decreasing incidence.
†Low histologic grade and low stage are good prognostic factors.
‡Carney triad: A condition consisting of gastric epithelioid leiomyosarcoma, pulmonary chondroma, functioning extraadrenal paraganglioma.
NRST, Nonrhabdomyosarcoma soft tissue sarcoma; GI, gastrointestinal; EBV, Epstein-Barr virus; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; NF, neurofibromatosis; V, vincristine; C, cyclophosphamide; NTRK, neurotrophic tyrosine receptor kinase; RT, radiation therapy; WLE, wide local excision; GM-CSF, granulocyte-macrophage colony-stimulating factor.
From Amin S, Levy CF. Rhabdomyosarcoma and other soft-tissue sarcomas. In: Fish JD, Lipton JM, Lanzkowsky P, eds. *Lanzowsky's Manual of Pediatric Hematology and Oncology*. 7th ed. London: Elsevier; 2022: Table 25.1, p. 543–544.

Chapter 550
Neoplasms of Bone

550.1 Malignant Tumors of Bone

Wendy A. Allen-Rhoades and Carola A.S. Arndt

The annual incidence of malignant bone tumors in the United States is approximately 8.2 cases per 1 million children younger than 14 years and 14.7 per 1 million for adolescents age 15-19. **Osteosarcoma** is the most common primary malignant bone tumor in children and adolescents, followed by **Ewing sarcoma** (Table 550.1, Fig. 550.1). In children <10 years old, Ewing sarcoma is more common than osteosarcoma. Both tumor types are most likely to occur in the second decade of life.

OSTEOSARCOMA

Epidemiology

The annual incidence of osteosarcoma in the United States is 5.7 cases per 1 million children 0-19 years old. The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation. Patients with osteosarcoma are taller than their peers of similar age.

Pathogenesis

Although the cause of osteosarcoma is unknown, certain genetic or acquired conditions predispose patients to development of osteosarcoma. Patients with **hereditary retinoblastoma** have a significantly increased risk for development of osteosarcoma. The sites of osteosarcoma in these patients include previously irradiated areas but also sites far from the original retinoblastoma radiation field. Predisposition to development of osteosarcoma in these patients may be related to loss of heterozygosity of the *RB* gene. Osteosarcoma also occurs in **Li-Fraumeni syndrome**, which is a familial cancer syndrome associated with germline pathogenic variants of the *P53* gene. Kindreds with Li-Fraumeni syndrome have a spectrum of malignancies in first-degree relatives, including carcinoma of the breast, soft tissue sarcomas, brain tumors, leukemia, adrenocortical carcinoma, and other malignancies. **Rothmund-Thomson syndrome** is a rare condition associated with short stature, skin telangiectasia, small hands and feet, hypoplasticity or absence of the thumbs, and a high risk of osteosarcoma. **Diamond-Blackfan anemia** is also a risk factor for osteosarcoma. Osteosarcoma can also be induced by irradiation for Ewing sarcoma, craniospinal irradiation for brain tumors, or high-dose irradiation for other malignancies. Other benign conditions that can be associated with malignant transformation to osteosarcoma include Paget disease, enchondromatosis, multiple hereditary exostoses, and fibrous dysplasia (see Chapter 550.2).

The pathologic diagnosis of osteosarcoma is made by demonstration of a highly malignant, pleomorphic, spindle cell neoplasm associated with the formation of malignant osteoid and bone. There are four pathologic subtypes of conventional high-grade osteosarcoma: osteoblastic, fibroblastic, chondroblastic, and telangiectatic. No significant differences in outcome are associated with the various subtypes, although the chondroblastic component of that subtype may not respond as well to chemotherapy.

Telangiectatic osteosarcoma may be confused with aneurysmal bone cyst (ABC) because of its lytic appearance on radiography. High-grade osteosarcoma typically arises in the diaphyseal region of long bones and invades the medullary cavity. It also may be associated with a soft tissue mass. Two variants of osteosarcoma, parosteal and periosteal, should be distinguished from conventional osteosarcoma because of their characteristic clinical features. **Parosteal osteosarcoma** is a low-grade, well-differentiated tumor that does not invade the medullary cavity and most frequently is found in the posterior aspect of the distal femur. Surgical resection alone often is curative in this lesion, which has a low propensity for metastatic spread. **Periosteal osteosarcoma** is a rare variant that arises on the surface of the bone but has a higher rate of metastatic spread than the parosteal type and an intermediate prognosis.

Clinical Manifestations

Pain, limp, and swelling are the most common presenting manifestations of osteosarcoma. Because these tumors occur most often in active

Table 550.1 Comparison of Features of Osteosarcoma and the Ewing Family of Tumors

FEATURE	OSTEOSARCOMA	EWING FAMILY OF TUMORS*
Age	Second decade	Second decade
Ethnicity	All	Primarily Whites
Sex (M:F)	1.5:1	1.5:1
Predisposition	Retinoblastoma, Li-Fraumeni syndrome, Rothmund-Thomson syndrome, Paget disease, radiotherapy	None known
Site	Metaphyses of long bones	Diaphyses of long bones, flat bones, soft tissues
Presentation	Local pain and swelling; often history of injury; pathologic fracture	Local pain and swelling; fever, palpable mass, pathologic fracture
Radiographic findings	Sclerotic destruction (less often lytic); sunburst pattern, Codman triangle	Primarily lytic, multilaminar periosteal reaction ("onion-skinning"), "moth-eaten," Codman triangle
Differential diagnosis	Ewing sarcoma, osteomyelitis, hematoma	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma, FUO
Metastasis	Lungs, bones	Lungs, bones, bone marrow
Treatment	Chemotherapy	Chemotherapy
	Ablative surgery of primary tumor	Radiotherapy and/or surgery of primary tumor
Outcome	Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival	Without metastases, 65–75% cured; with metastases at diagnosis, 20–30% survival

FUO, Fever of unknown origin.
*Ewing family of tumors includes: (1) Ewing sarcoma of bone; (2) extraosseous (extraskeletal) Ewing tumor; (3) peripheral primitive neuroectodermal tumor (PPNET). A PPNET arising from the chest wall is an Askin tumor.

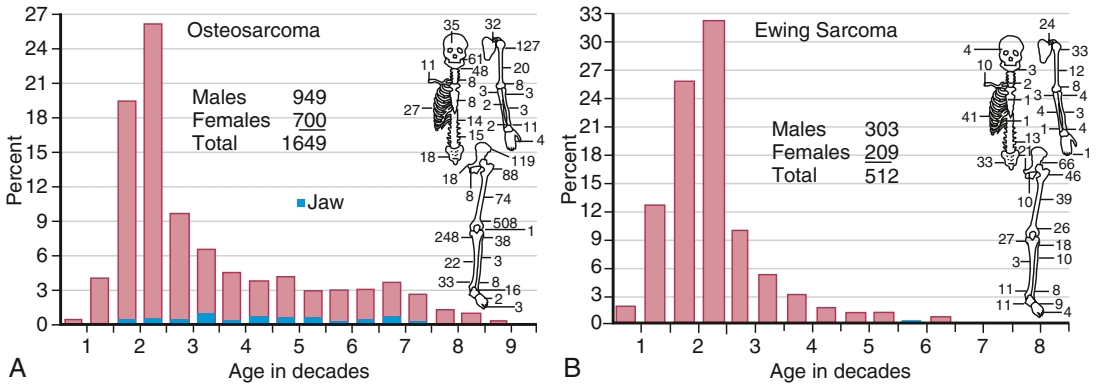

Fig. 550.1 A, Age and skeletal distribution of 1,649 cases of osteosarcoma in the Mayo Clinic files. B, Age and skeletal distribution of 512 cases of Ewing sarcoma in the Mayo Clinic files. *(From Unni KK, ed. Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases. 5th ed. Philadelphia: Lippincott-Raven; 1996. Reprinted by permission of the Mayo Foundation.)*

adolescents, initial complaints may be attributed to a sports injury or sprain; any bone or joint pain not responding to conservative therapy within a reasonable time should be investigated thoroughly. Additional clinical findings may include limitation of motion, joint effusion, tenderness, and warmth. Results of routine laboratory tests, such as a complete blood cell count and chemistry panel, are usually normal, although alkaline phosphatase or lactate dehydrogenase values may be elevated.

Diagnosis

Bone tumor should be suspected in a patient who presents with deep bone pain, often causing nighttime awakening, and has a palpable mass with radiographs that demonstrate a lesion. The lesion may be mixed lytic and blastic in appearance, but new bone formation is usually visible. The classic radiographic appearance of osteosarcoma is the *sunburst pattern* (Fig. 550.2). When osteosarcoma is suspected, the patient should be referred to a center with experience in managing bone tumors. The biopsy and the surgery should be performed by the same surgeon so that the incisional biopsy site can be placed in a manner that will not compromise the definitive surgical procedure. Tissue usually is obtained for molecular and biologic studies at the time of the initial biopsy. Before biopsy, MRI of the primary lesion and the entire bone should be performed to evaluate the tumor for its proximity to nerves and blood vessels, soft tissue and joint extension, and skip lesions. The metastatic workup includes CT of the chest and radionuclide bone scanning or positron emission tomography (PET) scan to evaluate for lung and bone or soft tissue metastases, respectively. The **differential diagnosis** of a lytic bone lesion includes histiocytosis, Ewing sarcoma, lymphoma, and bone cyst.



Fig. 550.2 Radiograph of an osteosarcoma of the femur with typical sunburst appearance of bone formation.

Treatment

With chemotherapy and surgery, 5-year disease-free survival of patients with nonmetastatic extremity osteosarcoma is 65–75%. Complete surgical resection of the tumor is important for cure. The current approach is to treat patients with preoperative chemotherapy in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately. Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy. It is important to resume chemotherapy as soon as possible after surgery. Lung metastases present at diagnosis should be resected by thoracotomies at some time during treatment. Active agents in use in multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.

One of the most important prognostic factors in osteosarcoma is the *histologic response to chemotherapy;* a poor histologic response is ≥10% viable tumor (<90% necrosis in resected tissue). **MAP** (methotrexate, doxorubicin, cisplatin) is the standard chemotherapy regimen for osteosarcoma. After limb salvage surgery, intensive rehabilitation and physical therapy are necessary to ensure maximal functional outcome. Intensification of therapy by addition of ifosfamide and etoposide in patients with poor histologic response after induction chemotherapy with MAP has not improved outcome.

For patients who require amputation, early prosthetic fitting and gait training are essential to enable patients to resume normal activities as soon as possible. Before definitive surgery, patients with tumors on weight-bearing bones should be instructed to use crutches to avoid stressing the weakened bones and causing pathologic fracture. The role of chemotherapy in parosteal and periosteal osteosarcomas is not well defined, and chemotherapy is generally reserved for use in patients with tumors that have a high-grade microscopic appearance.

Prognosis

Surgical resection alone is curative only for patients with low-grade parosteal osteosarcoma. Conventional high-grade osteosarcoma requires multiagent chemotherapy. Up to 75% of patients with nonmetastatic extremity osteosarcoma are cured with current multiagent treatment protocols. The prognosis is not as favorable for patients with pelvic tumors as for those with primary tumors in the extremities. From 20–30% of patients who have limited numbers of pulmonary metastases also can be cured with aggressive chemotherapy and resection of lung nodules. Patients with bone metastases and those with widespread lung metastases have an extremely poor prognosis. Long-term follow-up of patients with osteosarcoma is important to monitor for late effects of chemotherapy, such as cardiotoxicity from anthracycline and hearing loss from cisplatin. Patients in whom late, isolated lung metastases develop may be cured with surgical resection of the metastatic lesions alone.

EWING SARCOMA

Epidemiology

The incidence of Ewing sarcoma in the United States is 3.1 cases per 1 million children ages 0-19 years. It is rare among Black children. Ewing sarcoma, an undifferentiated sarcoma of bone, also may arise from soft tissue. Treatment protocols for these tumors are the same whether the tumors arise in bone or soft tissue. Anatomic sites of primary tumors arising in bone are distributed evenly between the extremities and the central axis (pelvis, spine, and chest wall). Primary tumors arising in the chest wall are often referred to as **Askin tumors**.

Pathogenesis

Immunohistochemical staining assists in the diagnosis of Ewing sarcoma to differentiate it from **small, round, blue cell tumors** such as lymphoma, rhabdomyosarcoma, and neuroblastoma. Histochemical stains may react positively with certain neural markers on tumor cells (neuron-specific enolase and S-100), especially in peripheral primitive neuroectodermal tumors. Reactivity with muscle markers (e.g., desmin, actin) is absent. Additionally, MIC-2 (CD99) staining is usually positive. A specific chromosomal translocation, t(11;22) (q24;q12), or a variant is found in most of the Ewing sarcoma family of tumors. Analysis for the translocation by next generation sequencing, fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR) analysis for the chimeric fusion gene products *EWS*/*FLI1* or *EWS*/*ERG* (or other variants) are used routinely in diagnosis.

Clinical Manifestations

Symptoms of Ewing sarcoma are similar to those of osteosarcoma. Pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue are common presenting symptoms. Patients with large chest wall primary tumors may present with respiratory distress. Patients with paraspinal or vertebral primary tumors may present with symptoms of cord compression. Ewing sarcoma often is associated with **systemic manifestations**, such as fever and weight loss, and may be accompanied by elevated inflammatory markers; patients may have undergone treatment for a presumptive diagnosis of osteomyelitis or a fever of unknown origin. Patients also may have a delay in diagnosis when their pain or swelling is attributed to a sports injury. Biopsy and tissue diagnosis should be considered for patients presenting with suspicious bone lesions, because even the gross appearance of Ewing sarcoma can appear similar to infection and the time course can be rapid. Surgical procedures for treatment of infection can contaminate the surgical field and impact treatment outcomes.

Diagnosis

The diagnosis of Ewing sarcoma should be suspected in a patient who presents with pain and swelling, with or without systemic symptoms, and with a radiographic appearance of a primarily lytic bone lesion with periosteal reaction, the characteristic **onion-skinning** (Fig. 550.3). A large, associated soft tissue mass often is visualized on MRI or CT (Fig. 550.4). The **differential diagnosis** includes osteosarcoma,



Fig. 550.3 Radiograph of tibial Ewing sarcoma showing periosteal elevation or "onion-skinning."



Fig. 550.4 MR image of tibial Ewing sarcoma showing a large associated soft tissue mass.

osteomyelitis, Langerhans cell histiocytosis, primary lymphoma of bone, metastatic neuroblastoma, or rhabdomyosarcoma in the case of a pure soft tissue lesion. Patients should be referred to a center with experience in managing bone tumors for evaluation and biopsy. Thorough evaluation for metastatic disease includes CT of the chest, radionuclide bone scan, or PET scan. Bone marrow aspiration and biopsy specimens from at least two sites are generally required but can be omitted for certain lower risk patients. MRI of the tumor and the entire length of involved bone should be performed to determine the exact extension of the soft tissue and bony mass and the proximity of tumor to neurovascular structures. Studies are also using fluorodeoxyglucose (FDG) PET to evaluate response to therapy.

To avoid compromising an ultimate potential for limb salvage by a poorly planned biopsy incision, the same surgeon should perform the biopsy and the surgical procedure. CT-guided biopsy of the lesion often provides diagnostic tissue. It is important to obtain adequate tissue for special stains and molecular studies.

Treatment

Tumors of the Ewing sarcoma family are best managed with a comprehensive multidisciplinary approach in which the surgeon, chemotherapist, and radiation oncologist plan therapy. Multiagent chemotherapy is important because it can shrink the tumor rapidly and is usually given before local control is attempted. In North America, standard **chemotherapy** for nonmetastatic Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide. Chemotherapy usually causes dramatic shrinkage of the soft tissue mass and rapid, significant pain relief. Patients with nonmetastatic Ewing sarcoma have a better outcome when treated on a 14-day rather than on a 21-day schedule. An international cooperative group trial found that myeloablative chemotherapy and stem cell rescue was not superior to chemotherapy with lung irradiation for patients with pulmonary metastases.

Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with **irradiation** or **surgery**. Radiation therapy is associated with a risk of radiation-induced second malignancies, especially osteosarcoma, as well as failure of bone growth in skeletally immature patients. It is important to provide the patient with crutches if the tumor is in a weight-bearing bone to avoid a pathologic fracture before definitive local control. Many centers prefer surgical resection, if possible, to achieve local control. Chemotherapy should be resumed as soon as possible after surgery.

Prognosis

Patients with small, nonmetastatic, distally located extremity tumors have the best prognosis, with a cure rate of up to 75%. Patients with pelvic tumors have, until recently, had a much worse outcome. Patients with metastatic disease at diagnosis, especially bone or bone marrow metastases, have a poor prognosis, with <30% surviving long term.

Long-term follow-up of patients with Ewing sarcoma is important because of the potential for late effects of treatment, such as anthracycline-induced cardiotoxicity, infertility, and second malignancies, especially in the radiation field, and late relapses, even as long as 10 years after initial diagnosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

550.2 Benign Tumors and Tumor-Like Processes of Bone

Carola A.S. Arndt and A. Noelle Larson

Benign bone lesions in children are common compared with the relatively rare malignant neoplasms of bone. A broad range of diagnostic possibilities must be considered when the physician is confronted with an undiagnosed bone lesion (Table 550.2). Some, although histologically benign, can be life-threatening, while others can be locally destructive to bone. Many represent an incidental finding that, if asymptomatic, can be observed. A group of benign characteristic lesions including osteochondroma, nonossifying fibroma, unicameral bone cyst, and enchondroma may occur in 19% of children in a historic cohort of children and can readily be diagnosed on standard radiographs without additional imaging studies. Other conditions require further study to determine a diagnosis where no single element in the history or diagnostic test is sufficient to rule out malignancy. Benign lesions are usually painless but may be painful, especially if the lesion is causing local bone destruction or there is an impending pathologic fracture. Night pain that awakens a child suggests malignancy, but relief of such pain with aspirin is common with osteoid osteomas. Rapidly enlarging lesions usually are associated with malignancy, but several benign lesions, such as ABCs, can enlarge faster than most malignancies. Several conditions, such as osteomyelitis, can simulate the appearance of bone tumors.

Many benign bone tumors are diagnosed incidentally or after pathologic fracture. Initial management of these fractures is similar to that of nonpathologic fractures in the same location. It is unusual for benign bone tumors to interfere with fracture healing, but the area of weakness typically remains, and refracture is common. Fractures rarely result in resolution of the tumor, which usually is treated after the fracture has healed. Fractures around the hip, however, frequently require immediate treatment to stabilize the femoral neck and restore anatomic alignment.

Radiographs of any suspected bone lesion should always be obtained in two planes. Additional studies may be necessary to help arrive at the correct diagnosis and to guide treatment. Although these lesions are benign, selected lesions require intervention. If biopsy is performed, both microbiology and pathology evaluations should always be obtained.

Osteochondroma (exostosis) is one of the most common benign bone tumors in children. Because many are completely asymptomatic and unrecognized, the true incidence of this lesion is unknown. Osteochondromas develop in childhood, arising from the metaphysis of a long bone, particularly the distal femur, proximal humerus, and proximal tibia. The lesion enlarges with the child until skeletal maturity. Children commonly present at 5-15 years of age, when the child or parent notices a bony, nonpainful mass. Some are discovered because they are irritated by soft tissues rubbing over the lesion during athletic or other activities. Fracture is rare. Osteochondromas appear radiographically as stalks or broad-based projections from the surface of the bone, usually in a direction away from the adjacent joint (Fig. 550.5A). The bone is in continuity with the medullary canal. Invariably, the lesion is radiographically smaller than suggested by palpation because the cartilage cap covering the lesion is not seen. This cartilage cap may be up to 1 cm thick. Both the cortex of the bone and the marrow space of the involved bone are continuous with the lesion. Malignant degeneration of a chondrosarcoma is rare in children but occurs in as many as 1% of adults. Routine removal is not performed unless the lesion is large enough to cause symptoms, such as pain or nerve compression, most commonly presenting as foot drop. Osteochondromas can be diagnosed by radiographs alone, and unless patients present with unusual symptoms such as night pain, further studies such as CT or MRI are not typically indicated. Patients should be referred to an orthopedic practice for counseling, but routine radiographic follow-up and treatment should be based on symptoms.

Multiple hereditary osteochondrosis (exostoses) is a related but rare condition characterized by the presence of multiple osteochondromas (see Fig. 550.5B). This is an autosomal dominant disorder due to pathogenic variants in *EXT1* or *EXT2*. Severely involved children can have short stature, limb-length inequality, premature partial physeal arrests, deformity of both the upper and lower extremities including genu valgum, dislocation of the radial head at the elbow, and neurovascular impingement or entrapment in areas adjacent to the tumor and neurovascular compartments. These children must be monitored carefully during growth by a pediatric orthopedist. Malignant transformation may occur but is rare. Screening MRI of the entire spine is recommended during childhood to detect bony lesions growing into the

Table 550.2 Features of Pediatric Benign Bone Tumors

LESION	TYPICAL COURSE	MOST COMMON WORKUP TO CONFIRM DIAGNOSIS
Fibroma (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect)	Observation; surgery to treat fracture/impending fracture (rare, large lesions)	Radiographs
Enchondroma	Observation; treat if symptomatic	Radiographs, occasionally MRI
Osteochondroma	Observation; excise if symptomatic	Radiographs
Subungual exostosis	Symptoms warrant excision for most patients	Radiographs
Unicameral/simple bone cyst	Observation; treat if fracture occurs to prevent further fractures	Radiographs, occasionally MRI
Osteoid osteoma	NSAIDs; but symptoms warrant percutaneous ablation for most patients	Radiographs, CT
Heterotopic ossification	Observation; if symptomatic, excise after bone is mature (>6 mo)	Radiographs, ± MRI, CT
Fibrous dysplasia	Observation; treat if pain or bony deformities	Radiographs, ± MRI, ± biopsy
Chronic regional multifocal osteomyelitis (reactive bone condition)	Observation; medical treatment available if symptomatic; pathology is identical to osteomyelitis	Radiographs, MRI; bone scan to look for other lesions; antibiotics to rule out osteomyelitis; biopsy
Langerhans cell histiocytosis	Variable; depends on extent of disease	Skeletal survey, MRI, biopsy, workup to rule out systemic disease
Infection	Treat with prolonged antibiotics, typically some intravenously; surgery for joint/growth plate involvement, abscess, and chronic disease	CRP, sedimentation rate, CBC with differential, blood cultures, radiographs, ± MRI, ± biopsy
Osteoblastoma	Locally aggressive, treat	Radiographs, CT, MRI, biopsy
Aneurysmal bone cyst	Locally aggressive, treat	Radiographs, MRI, biopsy
Chondroblastoma	Locally aggressive, treat	Radiographs, MRI, biopsy
Chondromyxoid fibroma	Locally aggressive, treat	Radiographs, MRI, biopsy
Osteofibrous dysplasia	Possibly locally aggressive; variable	Radiographs, MRI, biopsy
Adamantinoma	Malignant, treat	Radiographs, MRI, biopsy

CBC, Complete blood count; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs.

canal, which can result in spinal cord compression which may occur in up to 20–30% of patients (see Fig. 550.5C).

SUBUNGUAL EXOSTOSIS

This lesion is an osteochondroma that forms underneath the nailbed in an otherwise healthy child. The nailbed may become discolored or raised, and the condition is typically painful (Fig. 550.6). It can be differentiated from a paronychia or ingrown toenail by findings of an osteochondroma on radiographs. Radiographs should be taken, which will show a bony protuberance under the nailbed. Treatment should be nailbed removal and surgical excision with nailbed repair. Despite surgical excision, recurrence can occur up to 5% of the time.

Enchondroma is a benign lesion of hyaline cartilage that occurs centrally in the bone. These lesions are asymptomatic and frequently occur in the hands. Most are discovered incidentally, although pathologic fractures often lead to the diagnosis. Radiographically, the lesions occupy the medullary canal, are radiolucent, and are sharply marginated. Punctate or stippled calcification may be present within the lesion, but this is much more common in adults than in children. Almost all enchondromas in children are solitary and small. Most can simply be observed, with curettage and bone grafting reserved for lesions that are symptomatic or large enough to weaken the bone structurally. Large lesions with extensive involvement may represent low-grade chondrosarcoma. Multifocal involvement is referred to as **Ollier disease** and can result in bone dysplasia, short stature, limb-length inequality, and joint deformity. Surgery may be necessary to correct or prevent such deformities. When multiple enchondromas are associated with angiomas of the soft tissue, the condition is referred to as **Maffucci syndrome**. A high rate of malignant transformation has been reported in both of these multifocal conditions.

Chondromyxoid fibroma is an uncommon benign bone tumor in children. This metaphyseal lesion usually causes pain and local tenderness. The lesion occasionally is asymptomatic. Chondromyxoid fibroma appears radiographically as eccentric, lobular metaphyseal radiolucency with sharp, sclerotic, and scalloped margins. The lower extremity is involved most often. Treatment usually consists of curettage and bone grafting or en bloc resection.

Osteoid osteoma is a small benign bone tumor typically found in the proximal tibia and femur and the posterior elements of the spine. Most of these tumors are diagnosed between 5 and 20 years of age. The clinical pattern is characteristic, consisting of unremitting and gradually increasing pain that often is worst at night and is relieved by NSAIDs. Boys are affected more often than girls. Vertebral lesions can cause scoliosis or symptoms that mimic a neurologic disorder. Examination can reveal a limp, atrophy, and weakness when the lower extremity is involved. Palpation and range of motion do not alter the discomfort. Radiographs may show cortical thickening, and CT shows distinctive findings, with a round or oval metaphyseal or diaphyseal lucency (0.5-1.0 cm in diameter) surrounded by dense sclerotic bone (Fig. 550.7). The central lucency, or nidus, shows intense uptake on bone scan. Approximately 25% of osteoid osteomas are not visualized on plain radiographs but can be identified with CT. Because of the small size of the lesion and its location adjacent to thick cortical bone, MRI is poor at diagnosing osteoid osteomas, revealing only extensive T2

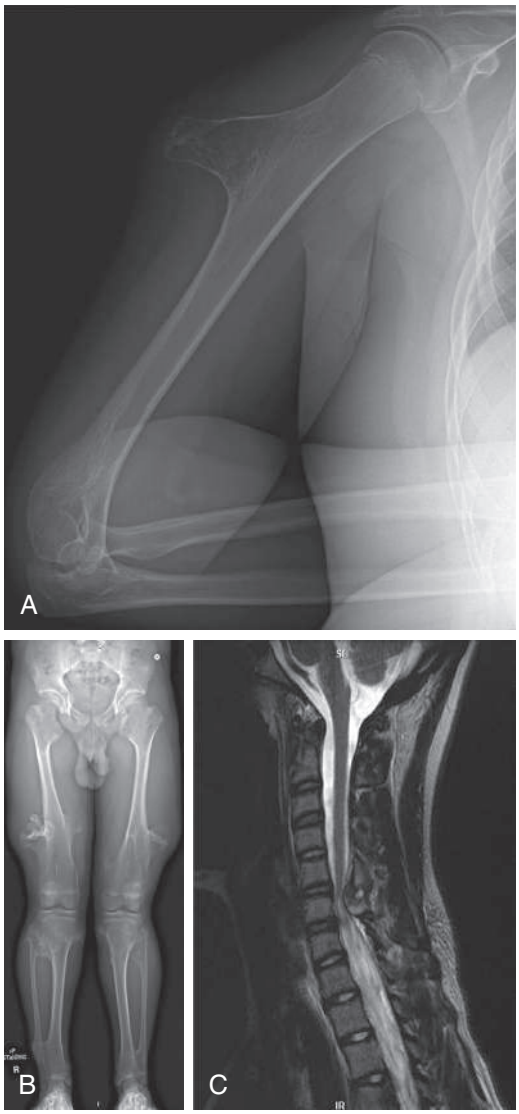

Fig. 550.5 A, Lateral radiograph of the right humerus showing isolated osteochondroma. Bone lesion is in continuity with the medullary canal and points away from the growth plate. B, Hip-to-ankle radiograph in a child with multiple hereditary exostoses (MHE) showing many osteochondromas about the knees and ankles. C, Sagittal T2 weighted MR image of the cervical spine in a 15-yr-old female with MHE who underwent routine cervical screening MRI, which detected asymptomatic spinal stenosis caused by C6 osteochondroma. She underwent urgent decompression.

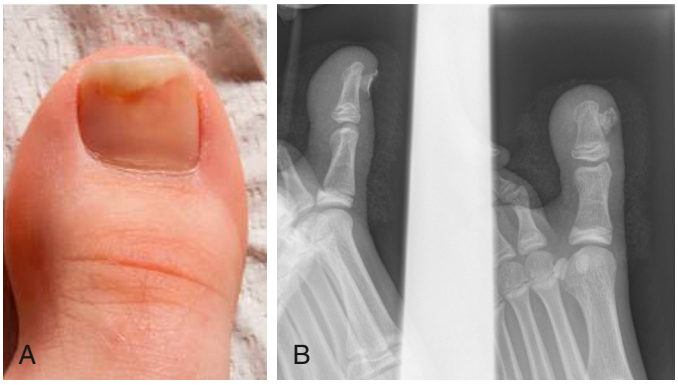

Fig. 550.6 A, Photograph of the great toe showing nailbed abnormality. B, Lateral and oblique views of the left great toe showing subungual exostosis. These lesions are typically painful and require surgical removal.

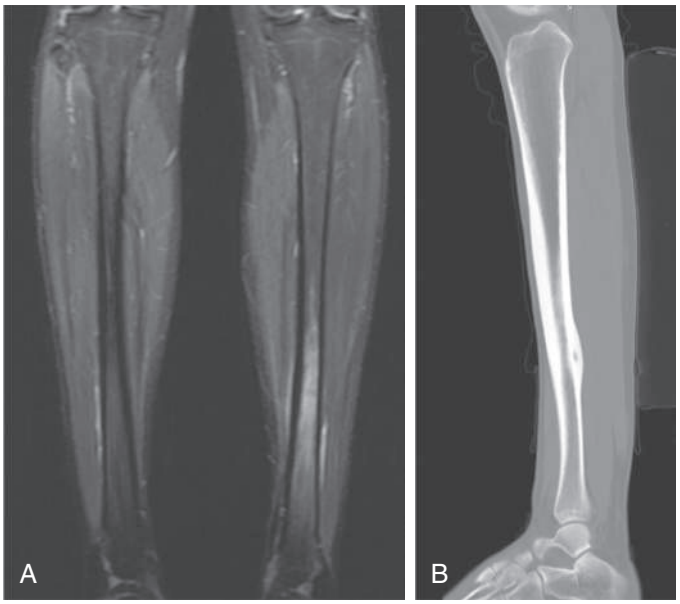

Fig. 550.7 MRI and CT in 15-yr-old female with left tibial night pain. A, Coronal T2 weighted MR of the bilateral tibias shows increased T2 signal change in the left tibia diaphysis. B, Sagittal CT scan shows cortically based lesion <1 cm typical for osteoid osteoma. Patient was treated with percutaneous radiofrequency ablation.

signal change throughout the region. Treatment is directed at removing the lesion. Patients may be treated with NSAIDs, and the symptoms typically resolve within 1-2 years. Most patients and families elect for treatment. Percutaneous treatments such as radiofrequency ablation and cryoablation have become the standard of care for routine lesions. There is still an occasional role for open surgical resection, if there is concern for osteomyelitis (Brodie's abscess), or the lesion is in close proximity to articular cartilage or neurovascular structures.

Osteoblastoma is a locally destructive, progressively growing lesion of bone with a predilection for the vertebrae, although almost any bone may be involved. Most patients note the insidious onset of dull aching pain, which may be present for months before patients seek medical attention. Spinal lesions can cause neurologic symptoms or deficits. The radiographic appearance is variable and less distinctive than that of other benign bone tumors. CT or MRI is indicated. Approximately 25% show features suggesting a malignant neoplasm, making biopsy necessary in many cases. Expansile spinal lesions often involve the posterior elements. Treatment involves curettage and bone grafting or en bloc excision; care must be taken to preserve nerve roots when treating spinal lesions. Surgical stabilization of the spine may be necessary.

Fibromas (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect) are fibrous lesions of bone that occur in up to 40% of children older than 2 years of age. They most likely represent a defect in ossification rather than a neoplasm and usually are asymptomatic. Most are discovered incidentally when radiographs are taken for other reasons, usually to rule out a fracture after trauma. Occasional pathologic fractures can occur through large lesions. Physical examination usually is unrevealing. Radiographs show a sharply marginated eccentric lucency in the metaphysis or metaphyseal cortex (Fig. 550.8). Lesions may be multilocular and expansile, with extension from the cortex into the medullary bone. The long axis of the lesion runs parallel to that of the bone. Approximately 50% are bilateral or multiple. Because of the characteristic radiographic appearance, most lesions do not require axial imaging, biopsy, or treatment. If the child is asymptomatic, no further monitoring is needed for characteristic lesions. Spontaneous regression can be expected after skeletal maturity. Curettage and bone grafting may be considered for symptomatic lesions or lesions occupying >50% of the bone diameter due to the risk of a pathologic fracture.



Fig. 550.8 Anteroposterior radiograph of the knee showing nonossifying fibroma, which was discovered incidentally.



Fig. 550.9 External rotation view of the left humerus in a 9-yr-old female who presented with pain after falling off her bicycle. Imaging is consistent with simple bone cyst.

Unicameral bone cysts can occur at any age in childhood but are rare in children younger than 3 years of age and after skeletal maturity. The cause of these fluid-filled lesions is unknown. Spontaneous resolution after skeletal maturity is expected, although pathologic fracture can be a significant problem in the interim. Diagnosis usually follows a pathologic fracture (Fig. 550.9). Such fractures can occur with relatively minor trauma, such as with throwing or catching a ball. Unicameral bone cysts appear radiographically as solitary, centrally located lesions within the medullary portion of the bone. These cysts are most common in the proximal humerus or femur. They often extend to (but not through) the physis and are sharply marginated. The cortex expands, but that does not exceed the width of the adjacent physis. Treatment involves allowing the pathologic fracture to heal. Subsequently, humerus lesions can be observed or treated. Proximal femoral lesions are typically treated due to the risk of pathologic fracture. Treatments include aspiration and injection with methylprednisolone or calcium phosphate. A randomized controlled trial (RCT) showed 42% healing rate with steroid injections (1-3, mean 1.7 injections) compared with injection of bone marrow aspirate (23% healing rate, 1-3 injections, 2.1 mean). Open biopsy and bone grafting with or without internal fixation can also be performed. Recurrence is common despite surgical treatment. Repeat injections are frequently necessary to treat recurrent lesions. Healing rates are higher with injection or surgical treatment compared with observation, and internal fixation is recommended for proximal femoral lesions given the high risk of fracture.

Fibrous dysplasia is a developmental abnormality characterized by fibrous replacement of cancellous bone. Lesions may be solitary or multifocal (polyostotic). Lesions may progress over time or may be stable. Some children are asymptomatic, although others have bone pain. Those with skull involvement might have swelling or exophthalmos. Pain and limp are characteristic of proximal femoral involvement, which also may indicate impending pathologic fracture. Limb-length discrepancy, bowing of the tibia or femur, and pathologic fractures may be presenting complaints. The triad of polyostotic disease, precocious puberty, and cutaneous pigmentation is known as McCune-Albright syndrome. Radiographic features of fibrous dysplasia include a lytic or ground-glass expansile lesion of the metaphysis or diaphysis. The lesion is sharply marginated and often is surrounded by a thick rim of sclerotic bone. Bowing, especially of the proximal femur, may be present. Treatment usually involves observation for asymptomatic lesions. Surgery is indicated for patients with progressive deformity, pain, or impending pathologic fractures. Bone grafting is not as successful in the treatment of fibrous dysplasia, because the lesion recurs within the grafted bone. Reconstructive surgical techniques with metal implants often are necessary to provide stability and treat pain, particularly in the proximal femur. In addition to surgical stabilization, bisphosphonate therapy has been used to treat bone pain, although a recent RCT showed improvement in regional bone mineral density but no change in pain scores.

LOCALLY AGGRESSIVE LESIONS

Aneurysmal bone cyst (ABC) is a reactive lesion of bone seen in persons younger than 20 years of age. The lesion is characterized by cavernous spaces filled with blood and solid aggregates of tissue. Although the femur, tibia, and spine are commonly involved, this progressively growing, expansile lesion can develop in any bone. Radiographs show eccentric lytic destruction and expansion of the metaphysis surrounded by a thin sclerotic rim of bone. Expansion of the bone frequently extends beyond the diameter of the physis. Pain and swelling are common. Spinal involvement can lead to cord or nerve root compression and associated neurologic symptoms, including paralysis. Posterior elements of the spine are involved more commonly than the vertebral body. Unlike most other benign bone tumors, which usually are confined to a single bone, ABCs can involve adjacent vertebrae. Spinal lesions can require stabilization after excision. As with other benign tumors, attempts are made to preserve nerve roots and other vital structures. Rapid growth is characteristic and can lead to confusion with malignant neoplasms (Fig. 550.10). ABCs can occur with concomitantly with neoplasms, confounding pathology results from biopsy. Treatment consists of percutaneous injection, curettage and bone grafting, or excision. Recurrence after surgical treatment occurs in 20–30% of patients, is more common in younger than older children, and usually occurs in the first 1-2 years after treatment. Treatment approaches also include percutaneously treatment with polidocanol or doxycycline, which targets the specific matrix metalloproteinase upregulation pathway seen in ABCs and has shown promising results.

CHARACTERISTIC LESIONS OF THE TIBIA

Osteofibrous dysplasia affects the tibia in children. Most children present with anterior swelling or enlargement of the leg. Radiographs show solitary or multiple lucent cortical diaphyseal lesions surrounded by sclerosis. Anterior bowing of the tibia often is present, and pathologic fracture can occur. The radiographic appearance closely resembles that

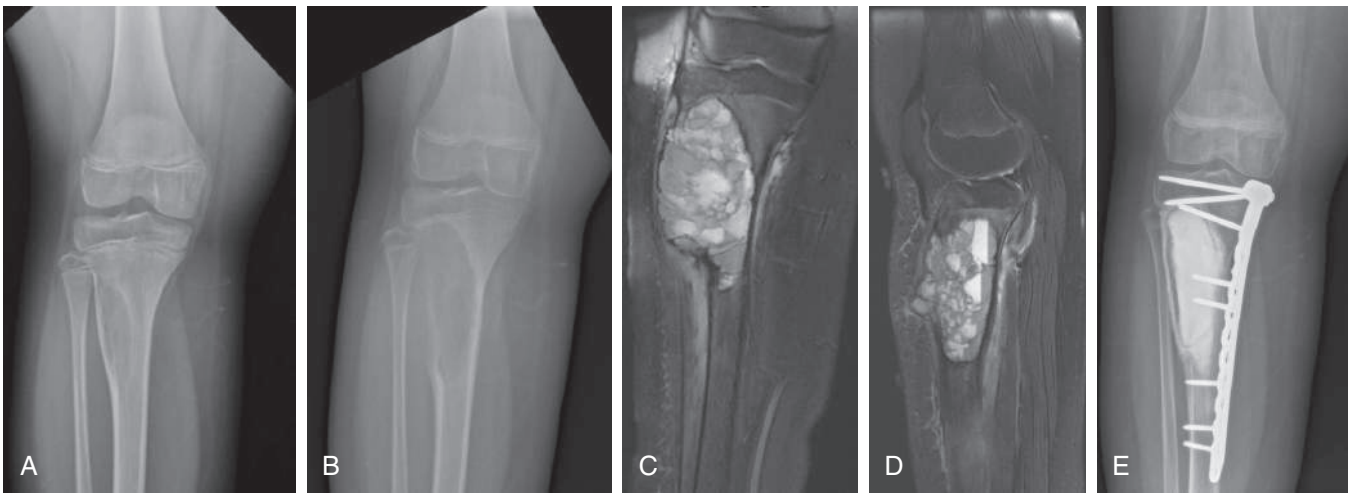

Fig. 550.10 Aneurysmal bone cyst. **A**, A 10-yr-old female presents with right tibia pain after playing softball. PA radiograph of the right proximal tibia reveals an eccentric, lytic lesion. **B**, Repeat imaging 4 months later shows rapid expansion. **C**, Coronal T2 MR image. **D**, Sagittal T2 MR image shows fluid-fluid levels classically seen with aneurysmal bone cysts. **E**, The patient was treated with curettage, bone grafting, and plate fixation to prevent fracture.

Table 550.3 Summary of Prognosis and Treatment of Vascular Bone Tumors

CLASSIFICATION	ENTITY	PROGNOSIS	TREATMENT
Benign	Hemangioma	100% survival, 0% metastasis	Treat symptoms
Intermediate	Epithelioid hemangioma	100% survival, 2% metastases, 9% local recurrence	Curettage or marginal excision
	Pseudomyogenic hemangioendothelioma	Limited follow-up, stable or progressive osseous disease	
Malignant	Epithelioid hemangioendothelioma	85% survival, 25% metastases	Wide resection
	Angiosarcoma	30% survival	Wide resection, consider systemic therapy

From van IJzendoorn DGP, Bovee JVMG. Vascular tumors of bone: the evolvement of a classification based on molecular developments. *Surg Pathol Clin.* 2017;10:621–635. Table 1.

of adamantinoma, a malignant neoplasm, making biopsy more common than with other benign bone tumors. Some believe osteofibrous dysplasia is a precursor lesion to adamantinoma. Treatment options include observation, excision and bone grafting, or wide resection.

Adamantinoma is a rare malignancy, typically found in adults, but occasionally in children. In contrast to osteofibrous dysplasia, the lesion involves the medullary canal. Resection is indicated, as there are no known benefits to radiation or chemotherapy for this slow-growing tumor.

Langerhans cell histiocytosis is a monostotic or polyostotic disease that can also involve the skin, liver, or other organs. Single-site disease should be distinguished from the other forms of Langerhans cell histiocytosis (Hand-Schüller-Christian or Letterer-Siwe variants), which can have a less favorable prognosis (see Chapter 556.1). Langerhans cell histiocytosis usually occurs during the first 3 decades of life and is most common in males 5-10 years of age. The skull is commonly affected, but any bone may be involved. Patients usually present with local pain and swelling. Marked tenderness and warmth often are present in the area of the involved bone. Spinal lesions can cause pain, stiffness, and occasional neurologic symptoms. Vertebra plana with uniform compression or flattening of the vertebral body is commonly but not always associated with Langerhans cell histiocytosis. The radiographic appearance of the skeletal lesions is similar in all forms of Langerhans cell histiocytosis but is variable enough to mimic many other benign and malignant lesions of bone as well as infection. The radiolucent lesions have well-defined or irregular margins with expansion of the involved bone and periosteal new bone formation. A skeletal survey is warranted as lesions may not be apparent on bone scan. Polyostotic involvement and the typical skull lesions strongly suggest the diagnosis of eosinophilic granuloma. Biopsy often is necessary to confirm the diagnosis because of the broad radiographic differential diagnosis. Treatment for isolated bone lesions includes curettage and bone grafting, or observation for asymptomatic lesions because most osseous lesions heal spontaneously and do not recur. All children with bone lesions should be evaluated for visceral involvement because multisystem organ disease may exist with the bone lesion and may not be obvious. Treatment of multisystem disease is more complex and often systemic and may require chemotherapy. For multisystem disease, bone lesions frequently improve with systemic chemotherapy, and operative treatment may not be necessary.

VASCULAR TUMORS OF BONE

There is a wide spectrum of vascular bone tumors (Table 550.3), which, depending on severity, may produce local sclerosis or osteopenia (see also Chapter 554). More severe lesions are locally aggressive and result in cortical destruction.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 551

Retinoblastoma

Cynthia E. Herzog

Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children. Although the survival rate of children with retinoblastoma in the United States and developed countries is extremely high, retinoblastoma progresses to metastatic disease and death in >40% of children in low income countries. Furthermore, the associated loss of vision and side effects of therapy are significant problems that remain to be addressed.

EPIDEMIOLOGY

Approximately 200-300 new cases of retinoblastoma are diagnosed each year in the United States, with no known racial or gender predilection. The cumulative lifetime incidence of retinoblastoma is approximately 1 in 20,000 live births, and retinoblastoma accounts for 2% of all pediatric malignancies. The median age at diagnosis is approximately 2 years, and >90% of cases are diagnosed in children <5 years old. Overall, 66–75% of children with retinoblastoma have unilateral tumors, with the remainder having bilateral retinoblastoma. Bilateral involvement is more common in younger children, particularly in those diagnosed before age 1 year, and is always heritable. Risk of retinoblastoma may be increased in children conceived by in vitro fertilization.

Retinoblastoma can be either hereditary or sporadic. **Hereditary** cases usually are diagnosed at a younger age and are multifocal and bilateral, whereas **sporadic** cases are usually diagnosed in older children who tend to have unilateral, unifocal involvement. The hereditary form is associated with loss of function of the **retinoblastoma gene *(RB1)*** via a pathogenic variant or deletion. *RB1* is located on chromosome 13q14 and encodes the retinoblastoma protein, a tumor-suppressor protein that controls cell cycle phase transition and has roles in apoptosis and cell differentiation. Children with **13q deletion syndrome** are at increased risk to develop retinoblastoma. Many different causative pathogenic variants have been identified, including translocations, deletions, insertions, point pathogenic variants, and epigenetic modifications such as gene methylation. The nature of the predisposing pathogenic variant can affect the penetrance and expressivity of retinoblastoma development.

According to Knudson's "2-hit" model of oncogenesis, two pathogenic variant events are required for retinoblastoma tumor development (see Chapter 541). In the hereditary form of retinoblastoma, the first pathogenic variant in *RB1* is inherited through germinal cells, and a pathogenic variant occurs subsequently in somatic retinal cells. Second pathogenic variants that lead to retinoblastoma often result in the loss of the normal allele and concomitant loss of heterozygosity. Parents and siblings of a child with a germline pathologic genetic variant should be referred to a genetic specialist for testing; most children with hereditary retinoblastoma have spontaneous new germinal pathogenic variants, and both parents have wild-type retinoblastoma genes. All first-degree relatives of children with known or suspected hereditary retinoblastoma should have retinal examinations to identify retinomas or retinal scars, which may suggest hereditary retinoblastoma even though malignant retinoblastoma did not develop. In the sporadic form of retinoblastoma, the two pathogenic variants occur in somatic retinal cells. Heterozygous carriers of oncogenic *RB1* pathogenic variants demonstrate variable phenotypic expression.

PATHOGENESIS

Histologically, retinoblastoma appears as a small, round blue cell tumor with rosette formation **(Flexner-Wintersteiner rosettes)**. It may arise in any of the nucleated layers of the retina and exhibit various degrees of differentiation. Retinoblastoma tumors tend to outgrow their blood supply, resulting in necrosis and calcification.

Endophytic tumors arise from the inner surface of the retina and grow into the vitreous and can also grow as tumors suspended within the vitreous itself, known as **vitreous seeding**. *Exophytic* tumors grow from the outer retinal layer and can cause retinal detachment. Diffuse infiltrating tumors grow intraretinally and remain flat; these are less common and can cause iris neovascularization. Tumors can also be both endophytic and exophytic. These tumors can also spread by direct extension to the choroid or along the optic nerve beyond the lamina cribrosa to the central nervous system, or by hematogenous or lymphatic spread to distant sites, including bones, bone marrow, and lungs.

SCREENING

Children with a positive family history of retinoblastoma should undergo a dilated eye examination under general anesthesia early in life and at regular intervals until genetic testing is performed and results are available. Infants with a negative genetic test require no further screening; infants with a positive genetic test require regular screening ophthalmologic examinations until age 7 years.

CLINICAL MANIFESTATIONS

Retinoblastoma classically presents with **leukocoria,** a *white pupillary reflex*, which often is first noticed when a red reflex is not present at a routine newborn or well-child examination or in a flash photograph of the child (Fig. 551.1). Strabismus often is an initial presenting complaint. Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease. Pain can occur if secondary glaucoma is present. Only about 10% of retinoblastoma cases are detected by routine ophthalmologic screening in the context of a positive family history.

DIAGNOSIS

The diagnosis is established by the characteristic ophthalmologic findings of a chalky, white-gray retinal mass with a soft, friable consistency. Imaging studies are not diagnostic, and biopsies are contraindicated. Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma tumors, but a complete evaluation requires an examination

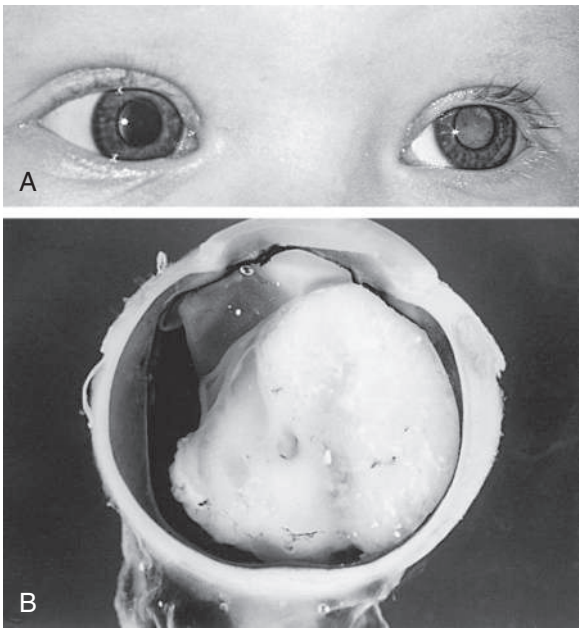

Fig. 551.1 A, Leukocoria noted in the left eye of a child presenting with retinoblastoma. B, A large white tumor mass noted within the posterior chamber of the enucleated eye. *(From Shields JA, Shields CL. Current management of retinoblastoma. Mayo Clin Proc. 1994;69:50–56.)*

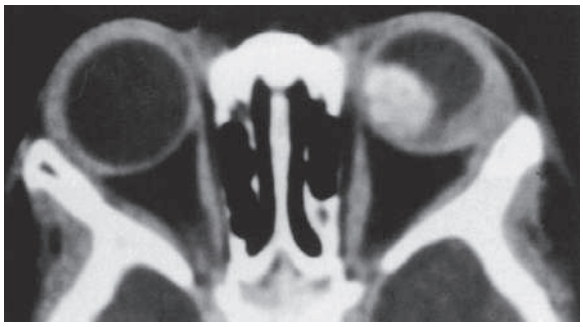

Fig. 551.2 Axial contrast-enhanced CT scan shows calcified retinoblastoma of the left eye. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017. Fig. 20-32.)*

under general anesthesia by an experienced ophthalmologist to obtain complete visualization of both eyes, which also facilitates photographing and mapping of the tumors. Retinal detachment or vitreous hemorrhage can complicate the evaluation.

Orbital ultrasonography, CT, or MRI is used to evaluate the extent of intraocular disease and extraocular spread (Fig. 551.2). In approximately 5% of cases, a pineal area (primitive neuroectodermal) tumor is detected in a child with hereditary and bilateral retinoblastoma, a phenomenon known as **trilateral retinoblastoma**. MRI allows for better evaluation of optic nerve involvement. Metastatic disease is rarely present at diagnosis; evaluation of the cerebrospinal fluid and bone marrow for tumor metastasis and radionuclide bone scan are required only if indicated by other clinical, laboratory, or imaging findings.

The **differential diagnosis** of retinoblastoma includes other causes of leukocoria, including persistent hyperplastic primary vitreous, Coats disease, vitreous hemorrhage, cataract, endophthalmitis from *Toxocara canis*, choroidal coloboma, retinopathy of prematurity, and familial exudative vitreoretinopathy.

TREATMENT

Treatment is determined by the size and location of the tumors, if the disease is localized to the eye or has spread either to the brain or to the rest of the body, and whether the child has hereditary or sporadic disease. The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies. With current modalities for local control of intraocular tumors and more effective systemic chemotherapy, primary enucleation is being performed less often.

Most unilateral disease presents with a solitary, large tumor. **Enucleation** is performed if useful vision cannot be salvaged. With bilateral disease, chemoreduction in combination with **focal therapy** (laser photocoagulation or cryotherapy) has replaced the traditional approach of enucleation of the more severely affected eye and irradiation of the remaining eye. If feasible, small tumors can be treated with focal therapy with careful follow-up for recurrence or new tumor growth. Larger tumors often respond to multiagent **chemotherapy**, including carboplatin, vincristine, and etoposide given intravenously. However, systemic therapy is generally reserved for patients with unilateral disease when high-risk features are noted after enucleation, or in very young patients with bilateral disease that are at higher risk of complications with intraarterial chemotherapy. The delivery of chemotherapy via the ophthalmic artery is becoming more common, as is delivery of intravitreal chemotherapy. If these approaches fail, **external-beam irradiation** should be considered, although this approach may result in significant orbital deformity and increased incidence of second malignancies in patients with germline *RB1* pathologic genetic variants. **Brachytherapy**, or *episcleral plaque radiotherapy,* is an alternative with less morbidity. Enucleation may be required for unresponsive or recurrent tumors. Intense multiagent chemotherapy with autologous stem cell rescue may be used for patients with metastatic disease.

PROGNOSIS

Approximately 95% of U.S. children with retinoblastoma are cured with modern treatment. Current efforts using chemotherapy in combination with focal therapy are intended to preserve useful vision and avoid external-beam radiation or enucleation. Unfortunately, the diagnosis of retinoblastoma in many children from resource-poor countries is delayed, resulting in spread of the tumor outside the orbit. The prognosis for children with retinoblastoma that has spread outside the eye is poor. Trilateral retinoblastoma, disease involving both eyes and the pineal region, is almost universally fatal.

Children with germline *RB1* pathologic genetic variants are at significant risk for development of *second malignancies*, especially osteosarcoma, as well as soft tissue sarcomas and malignant melanoma. The risk of second malignancies is further increased by the use of radiation therapy. Other radiation-related late adverse effects include cataracts, orbital growth deformities, lacrimal dysfunction, and late retinal vascular injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 552

Gonadal and Germ Cell Neoplasms

Cynthia E. Herzog and Winston W. Huh

EPIDEMIOLOGY

Malignant **germ cell tumors (GCTs)** and gonadal tumors are rare, with an incidence of 12 cases per 1 million persons younger than 20 years. Most malignant tumors of the gonads in children are GCTs. The incidence varies according to age and sex, although the incidence of GCTs in adolescent males has increased over time. **Sacrococcygeal** tumors occur predominantly in infant females. **Testicular** GCTs occur predominantly before age 4 years and after puberty. Klinefelter syndrome is associated with an increased risk of **mediastinal** GCTs. Trisomy 21, undescended testes, infertility, testicular atrophy, testicular microlithiasis, testicular dysgenesis syndrome, and inguinal hernias are associated with an increased risk of **testicular cancer**. The risk of testicular cancer in patients with cryptorchidism is reduced but not eliminated if orchiopexy is performed before 13 years of age. The risk of testicular GCT is increased in first-degree relatives and is highest among monozygotic twins.

PATHOGENESIS

The GCTs and non-GCTs arise from primordial germ cells and coelomic epithelium, respectively. Testicular and sacrococcygeal GCTs arising during early childhood characteristically have deletions at chromosome arms 1p and 6q and gains at 1q, and they lack the isochromosome 12p that is highly characteristic of malignant GCTs of adults. Testicular GCTs also may demonstrate loss of imprinting. Ovarian GCTs from older females characteristically have deletions at 1p and gains at 1q and 21. Dysregulation of microRNAs have been linked to GCTs. Because GCTs may contain benign and mixed malignant elements in different areas of the tumor, extensive sectioning is essential to confirm the correct diagnosis. The many histologically distinct subtypes of GCTs include **teratoma** (mature and immature), endodermal sinus tumor, and embryonal carcinoma (Fig. 552.1). Non-GCTs of the

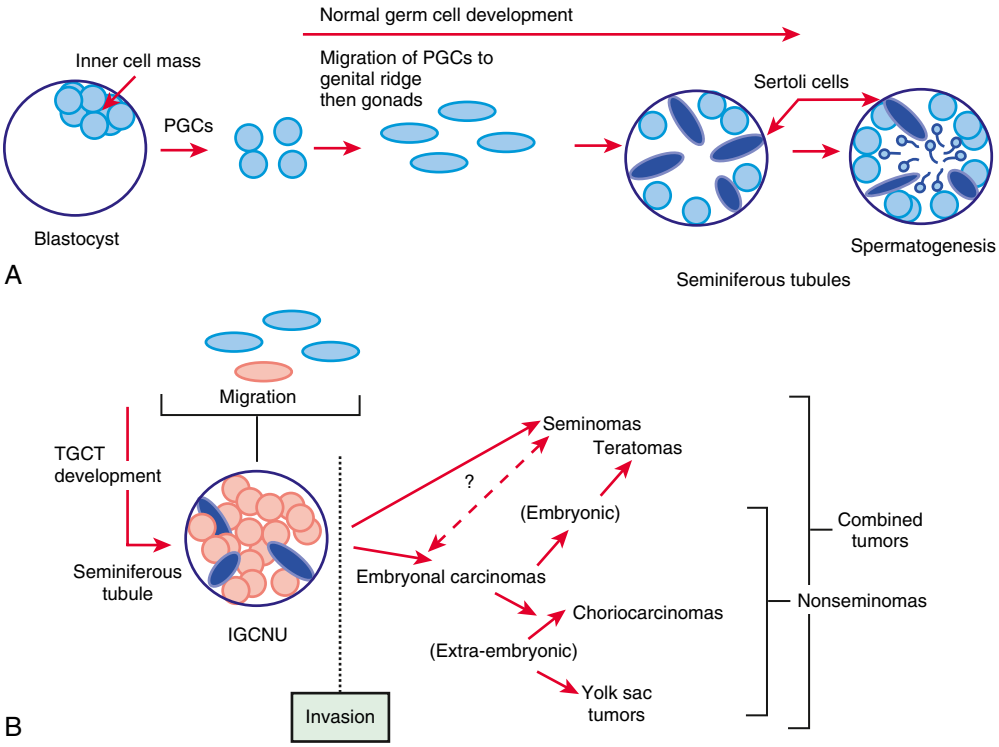

Fig. 552.1 A, Normal germ cell development. B, Model for the origin and histogenesis of different subtypes of testicular germ cell tumors. IGCNU, Intratubular germ cell neoplasia unclassified; PGCs, primary germ cells; TGCT, testicular germ cell tumor.

Table 552.1 Main Histologic Types of Testicular Germ Cell Tumors*

NONINVASIVE GERM CELL NEOPLASIA
Germ cell neoplasia in situ (GCNIS; previous synonyms: carcinoma in situ testis, intratubular germ cell neoplasia unclassified)
Gonadoblastoma (in patients with disorders of sex development; tumor also contains sex cord–stromal elements)
GERM CELL TUMORS DERIVED FROM GCNIS
Seminoma
Nonseminoma (nonseminomatous germ cell tumors)
Embryonal carcinoma
Teratoma (postpubertal type)
Yolk sac tumor (postpubertal type)
Choriocarcinoma and other trophoblastic tumors
GERM CELL TUMORS UNRELATED TO GCNIS
Childhood tumors
Teratoma (prepubertal type)
Yolk sac tumor (prepubertal type)
Spermatocytic tumor (median age at diagnosis: approximately 50 yr)

*Based on updated WHO classification of tumors of the testis and paratesticular tissue. Adapted from Raypert-De Meyts E, McGlynn KA, Okamoto, et al. Testicular germ cell tumours, *Lancet* 2016;387:1762–1770.

ovary include epithelial (serous and mucinous) and sex cord–stromal tumors; non-GCTs of the testicle include sex cord–stromal (e.g., Leydig cell, Sertoli cell) tumors. *DICER1* pathogenic variants have been observed in nonepithelial ovarian cancers, especially in Sertoli-Leydig tumors. Table 552.1 provides a histologic classification of testicular GCTs.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of germ cell neoplasms depends on location (Table 552.2). Ovarian tumors often are quite large by the time they are diagnosed (Fig. 552.2). Extragonadal GCTs occur in the midline, including the suprasellar region, pineal region, neck, mediastinum, and retroperitoneal and sacrococcygeal areas (Fig. 552.3). Symptoms relate to mass effect, but the intracranial GCTs often present with anterior and posterior pituitary deficits (see Chapter 546).

The serum α-fetoprotein **(AFP)** level is elevated with endodermal sinus tumors and may be minimally elevated with teratomas (Table 552.3). Infants normally have higher levels of AFP, which usually falls to normal adult levels by about age 8 months; consequently, high AFP levels must be interpreted with caution in this age-group. Elevation of the β subunit of human chorionic gonadotropin (β-**hCG**), which is secreted by syncytiotrophoblasts, is seen with choriocarcinoma and germinomas. Lactate dehydrogenase, although nonspecific, may be a useful marker. If elevated, these markers provide important confirmation of the diagnosis and provide a means for risk stratification and to monitor the patient for tumor response and recurrence. Both serum and cerebrospinal fluid (CSF) should be assayed for these markers in patients with intracranial lesions. MicroRNA-371 is a superior tumor marker in GCT, but its use is still limited.

Diagnosis begins with physical examination and imaging studies, including plain radiographs of the chest and ultrasonography of the abdomen. CT or MRI can further delineate the primary tumor. If germ cell malignancy is strongly suggested, preoperative staging with CT of the chest and bone scan is appropriate. Primary surgical resection is indicated for tumors deemed resectable. For older patients with testicular tumors, ipsilateral retroperitoneal lymph node sampling may be required to determine extent of the disease and aid in treatment planning. Ovarian tumors also require detailed surgical evaluation, including lymph node removal and pelvic washings for cytologic analysis for peritoneal spread. Diagnosis of intracranial lesions can be established with imaging and AFP or β-hCG determinations of serum and CSF.

Gonadoblastomas often occur in patients with gonadal dysgenesis and all or parts of a Y chromosome. **Gonadal dysgenesis** is characterized by failure to fully masculinize the external genitalia. If this syndrome is diagnosed, imaging of the gonad with ultrasonography or CT is performed, and surgical resection of the tumor usually is curative. Prophylactic resection of dysgenetic gonads at the time of diagnosis is recommended, because gonadoblastomas, some of which contain malignant GCT elements, often develop. Gonadoblastomas may produce abnormal amounts of estrogen.

Table 552.2 Clinical Features of Germ Cell Tumors

CLINICAL FEATURES		
TUMOR TYPE	**FEMALE**	**MALE**
Mature/immature teratoma	Abdominal pain, abdominal mass 10% bilateral Gliomatosis peritonei does not affect prognosis	Nontender scrotal mass Excellent survival with surgery alone in prepubertal males
Dysgerminoma/seminoma	Rapidly developed intraabdominal mass 20% bilateral 14–25% mixed with other germ cell elements	Virtually not seen in children, most common testicular tumor in adult males. Most patients present in their 30s
YST	Most common malignant histology 75% stage I	Most common malignant histology, most pediatric tumors are pure YST 85% stage I
Embryonal carcinoma	Associated with precocious puberty, amenorrhea, and hirsutism	Higher incidence of metastatic disease at presentation, patients can present with retroperitoneal mass
Choriocarcinoma	Rare in children, when present in infants related to maternal metastatic disease	Frequent pulmonary metastatic disease at presentation, patients can present with hemoptysis due to hemorrhage of metastases
Gonadoblastoma	Associated with gonadal dysgenesis Presents mostly in phenotypical females with a Y chromosome	Very rare

YST, Yolk sac tumor.
Modified from Fonseca A, Olson TA. Extracranial germ cell tumors. In: Fish JD, Liptin JM, Lanzkowsky P, eds. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*. 7th ed. London: Elsevier; 2022: Table 28.2, p. 600.

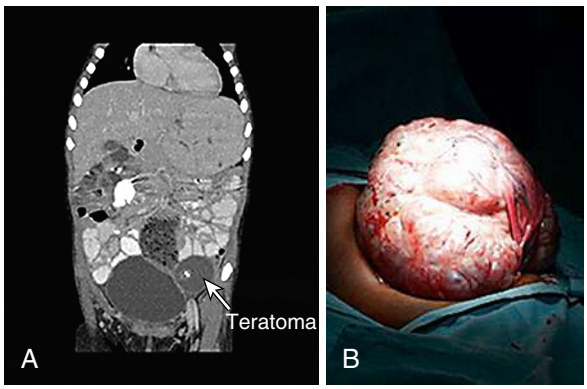

Fig. 552.2 A, Postnatal MR image showing a left ovarian teratoma with bony calcification. B, Massive ovarian teratoma. *(From Lakhoo K. Neonatal teratomas. Early Hum Dev. 2010;86:643–647.)*

Table 552.3 Serum Tumor Marker Levels for Pediatric GCTs

GCT TYPE	AFP	β-hCG	LDH
MT	-	-	-
IT	+/–	-	+/–
Seminoma/dysgerminoma	-	-	+
Yolk sac tumor	+	-	-
Choriocarcinoma	-	+	-
Embryonal carcinoma	+	+	+/–

+, Usually elevated; +/–, may be elevated; -, usually not elevated.
GCT, Germ cell tumor; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; MT, mature teratoma; IT, immature teratoma.
From Weil BR, Billmire DF. Management of germ cell tumors in pediatric patients. *Surg Oncol Clin N Am*. 2021;30:325–338. Table 1.

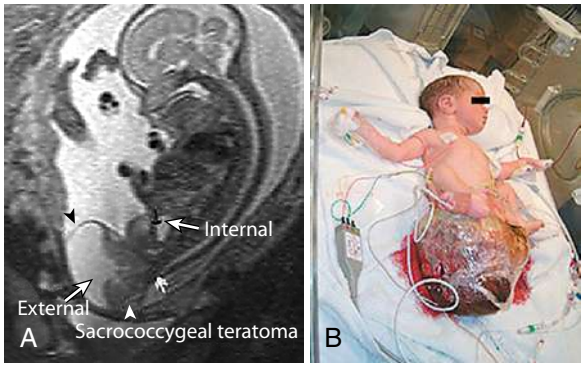

Fig. 552.3 A, Prenatal MR image showing sacrococcygeal teratoma with a small internal and large external component. B, Postnatal large, bleeding sacrococcygeal teratoma. *(From Lakhoo K. Neonatal teratomas. Early Hum Dev. 2010;86:643–647.)*

Teratomas occur in many locations, presenting as masses. They are not associated with elevated markers unless malignancy is present. The sacrococcygeal region is the most common site for teratomas. Sacrococcygeal teratomas occur most commonly in infants and may be diagnosed in utero or at birth, with most found in girls. The rate of malignancy in this location varies, ranging from <10% in children younger than 2 months to >50% in children older than 4 months.

Germinomas occur intracranially, in the mediastinum, and in the gonads. In the ovary, they are called **dysgerminomas,** and in the testis, they are called **seminomas.** They usually are tumor-marker–negative masses despite being malignant. Endodermal sinus or yolk sac tumor and choriocarcinoma appear highly malignant by histologic criteria. Both occur at gonadal and extragonadal sites. Embryonal carcinoma most often occurs in the testes. Choriocarcinoma and embryonal carcinoma rarely occur in the pure form and are usually found as part of a mixed malignant GCT.

Non–germ cell gonadal tumors are very uncommon in pediatrics and occur predominantly in the ovary. Epithelial carcinomas (usually an adult tumor), Sertoli-Leydig cell tumors, and granulosa cell

tumors may occur in children. Carcinomas account for ~30% of ovarian tumors in females <20 years old; most of these occur in older teens and are of the serous or mucinous subtype. **Sertoli-Leydig cell tumors** and **granulosa cell tumors** produce hormones that can cause virilization, feminization, or precocious puberty, depending on pubertal stage and the balance between Sertoli cells (estrogen production) and Leydig cells (androgen production). Diagnostic evaluation usually focuses on the chief complaint of inappropriate sex steroid effect and includes hormone measurements, which reflect gonadotropin-independent sex steroid production. Appropriate imaging also is performed to rule out a functioning gonadal tumor. Surgery usually is curative. No effective therapy for nonresectable disease has been found.

TREATMENT

Complete surgical excision of the tumor usually is indicated, except for patients with intracranial tumors, for whom the primary therapy consists of radiation therapy and chemotherapy. For testicular tumors, an inguinal approach is indicated, and complete resection should include the entire spermatic cord. When complete excision cannot be accomplished, preoperative chemotherapy is indicated, with second-look surgery, especially if retroperitoneal lymph node enlargement persists. For teratomas, both mature and immature, and completely resected malignant tumors of the testes and ovary, surgery alone is the treatment. For ovarian tumors, unless the contralateral ovary is obviously also involved by tumor, a fertility-sparing surgery should be performed. Cisplatin-based chemotherapy regimens usually are curative in GCTs that cannot be completely resected, even if metastases are present. However, sex cord–stromal tumors tend to be refractory to chemotherapy. Except for GCTs of the central nervous system, radiation therapy is limited to those tumors that are not amenable to complete excision and are refractory to chemotherapy. High-dose chemotherapy followed by autologous stem cell rescue is an option in those with refractory disease.

PROGNOSIS

The overall cure rate for children with GCTs is >80%. Age is the most predictive factor of survival for extragonadal GCTs. Children >12 years old have a fourfold higher risk of death and a sixfold higher risk if the tumor is thoracic. Histology has minimal effect on prognosis. Patients with nonresected extragonadal GCTs have a slightly worse prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 553

Neoplasms of the Liver

Fiorela N. Hernandez Tejada and Cynthia E. Herzog

Hepatic tumors are rare in children. Primary tumors of the liver account for approximately 1% of malignancies in children younger than 15 years, with an annual incidence of 1.5 cases per 1 million children in the United States (Table 553.1). Between 50% and 60% of hepatic tumors in children are malignant, with >65% of these malignancies being **hepatoblastomas** and most of the remainder being **hepatocellular carcinomas (HCCs)**. Rare **hepatic malignancies** include embryonal sarcoma, angiosarcoma, malignant germ cell tumor, rhabdomyosarcoma of the liver, and undifferentiated sarcoma. More common childhood malignancies, such as neuroblastoma, Wilms tumor, and lymphoma, can metastasize to the liver. **Benign liver tumors**, which usually present in the first 6 months of life, include hemangiomas, hamartomas, and hemangioendotheliomas.

Table 553.1 Pediatric Liver Tumors Consensus Classification

Epithelial tumors Hepatocellular	**Benign:** Hepatocellular adenoma, focal nodular hyperplasia (FNH), regenerative nodules, and dysplastic nodules **Malignant:** Hepatoblastoma (various types), hepatocellular carcinoma (classic HCC and fibrolamellar HCC), hepatocellular malignant neoplasm not otherwise specified (NOS)
Biliary	**Benign:** Bile duct adenoma, biliary hamartoma **Malignant:** Cholangiocarcinoma, combined HCC-cholangiocarcinoma
Mesenchymal tumors	**Benign:** Hemangioma, mesenchymal hamartoma **Malignant:** Embryonal sarcoma, rhabdomyosarcoma, malignant vascular tumors (epithelioid hemangioendothelioma, angiosarcoma)
Other rare malignancies	Malignant rhabdoid tumor, germ cell tumors, desmoplastic small round cell tumor, peripheral primitive neuroectodermal tumor
Metastases (and secondary)	From solid tumors: neuroblastoma, Wilms, acute myeloid leukemia, Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis

Modified from Chavhan GB, Siddiqui I, Ingley KM, Gupta AA. Rare malignant liver tumors in children. *Pediatr Radiol*. 2019;49:1404–1421. Table 1.

HEPATOBLASTOMA

Epidemiology

Approximately 100 new cases of hepatoblastoma are diagnosed each year in the United States. The incidence of hepatoblastoma has increased over the last 30 years by as much as 2.7% per year, probably related to increasing survival of very low birthweight premature infants. Hepatoblastoma occurs predominantly in children <3 years old, and the median age of diagnosis is 1 year. The etiology is unknown. Hepatoblastomas are associated with **familial adenomatous polyposis**. Alterations in the antigen-presenting cell/β-catenin pathway have been found in most of the tumors evaluated. Hepatoblastomas are also associated with **Beckwith-Wiedemann syndrome** (BWS), **hemihyperplasia**, and other somatic overgrowth syndromes. Increased expression of insulin-like growth factor 2 secondary to genetic pathogenic variants or epigenetic changes is implicated in hepatoblastoma development in patients with BWS. All children with BWS or hemihyperplasia should be routinely screened with α-fetoprotein (AFP) levels and abdominal ultrasounds. Prematurity/low birthweight is associated with increased incidence of hepatoblastoma, with the risk increasing as birthweight decreases. Aicardi syndrome, trisomy 18, other trisomies, Li-Fraumeni syndrome, Prader-Willi syndrome, Alagille syndrome, glycogen storage disease (type 1), Simpson-Golabi-Behmel syndrome, and fetal alcohol syndrome have also been associated with increased risk of hepatoblastoma.

Pathogenesis

Hepatoblastoma arises from precursors of hepatocytes and is histologically classified as *whole epithelial* type, containing fetal or embryonal malignant cells (either as a mixture or as pure elements), and *mixed* type, containing both epithelial and mesenchymal elements. Histologic classification has a direct correlation with clinical outcome. *Pure fetal histology* and low mitotic activity predicts the best outcome, and the *small cell undifferentiated* subtype associated with normal AFP levels predicts the worse outcome.

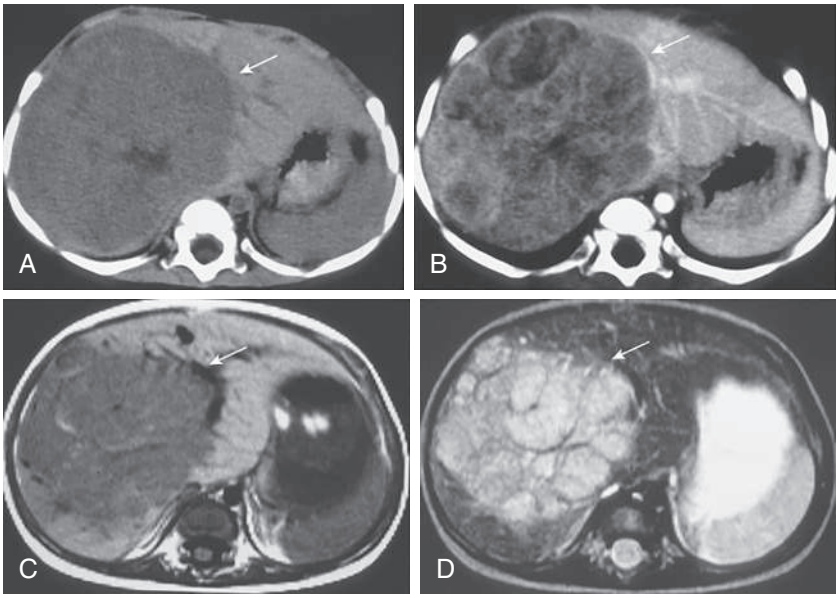

Fig. 553.1 Hepatoblastoma in a 3-yr-old child. **A,** Precontrast CT scan shows well-demarcated, heterogeneous hypodense mass *(arrow).* **B,** Postcontrast CT scan shows heterogeneous internal enhancement *(arrow).* **C** and **D,** The mass *(arrow)* demonstrates heterogeneous hypointensity on T1-weighted **(C)** and hyperintensity on T2-weighted **(D)** MR images.

Clinical Manifestations

Hepatoblastoma usually presents as a large, asymptomatic abdominal mass, with no associated systemic symptoms. Jaundice is uncommon. It arises from the right lobe three times more often than the left and usually is unifocal. When the disease progresses, fatigue, fever, weight loss, anorexia, vomiting, and abdominal pain may ensue. Rarely, hepatoblastoma presents with hemorrhage secondary to trauma or spontaneous rupture. Metastatic spread of hepatoblastoma most often involves regional lymph nodes and the lungs.

Diagnosis

A biopsy of liver tumors is necessary to establish the diagnosis. A valuable serum tumor marker, AFP, is used in the diagnosis and monitoring of hepatic tumors. AFP is normally elevated in the newborn period and then declines to <10 ng/mL by 1 year of age. The AFP levels are elevated in almost all hepatoblastomas. Bilirubin and liver enzymes usually are normal. Anemia is common, and thrombocytosis occurs in approximately 30% of patients. Serologic testing for hepatitides B and C should be performed, but the results usually are negative in hepatoblastoma.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. US can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest (Fig. 553.1).

Treatment

Treatment is guided by the degree of local tumor burden determined by the pre- and posttreatment extent of disease. In general, the cure of malignant hepatic tumors in children depends on complete resection of the primary tumor (Fig. 553.2); as much as 85% of the liver can be resected, with hepatic regeneration noted within 3-4 months after surgery. Treatment of hepatoblastoma is based on surgery and **systemic chemotherapy** using cisplatin in combination with vincristine and 5-fluorouracil (5-FU), and for intermediate- and high-risk patients, doxorubicin is also used. The role of **radiation therapy** is questionable, because the effective antitumor dose exceeds the hepatic tolerance. Radiation therapy may have a role in shrinking unresectable disease or managing incompletely resected tumors. In 30% of cases, tumors are resectable at diagnosis; a safe attempt for initial gross total resection should be made, followed by adjuvant chemotherapy. Unresectable tumors with or without metastatic disease at presentation usually respond to chemotherapy; preresection chemotherapy is indicated, and excision of the primary tumor and

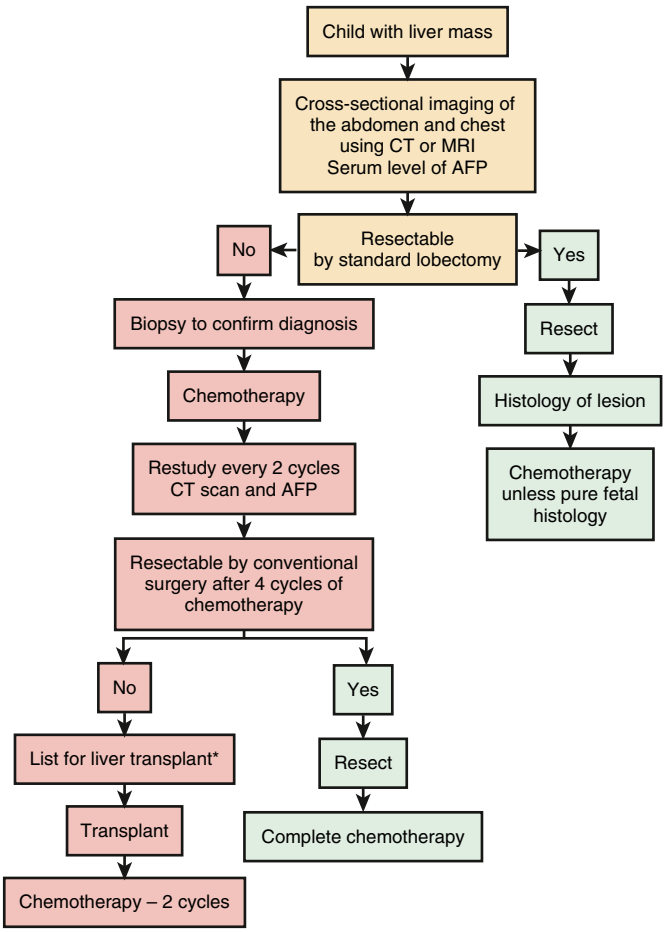

*Consider continuation of chemotherapy or living-related liver transplantation if cadaveric liver transplant not available in a timely fashion

Fig. 553.2 Algorithm for the management of a child who presents with a hepatoblastoma. AFP, α-Fetoprotein. *(From Tiao GM, Bobey N, Allen S, et al. The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. J Pediatr. 2005;146:204–211.)*

extrahepatic disease should be attempted as soon as it becomes feasible, followed by additional chemotherapy. Orthotopic **liver transplant** is a viable option for unresectable primary hepatic malignancies and results in good long-term survival. The pretransplant medical condition is an important predictor of outcome, and thus transplant is much more effective as the primary surgery than as salvage therapy. Alternative treatment options currently under investigation include other systemic chemotherapy agents such as carboplatin, ifosfamide, etoposide, irinotecan, and temsirolimus. Other treatment approaches include transarterial chemoembolization, cryoablation, and radiofrequency ablation (RFA).

Prognosis

In low-stage tumors, survival rates >90% can be achieved with multimodal treatment, including surgery and adjuvant chemotherapy. With tumors unresectable at diagnosis, survival rates of approximately 60% can be obtained. Metastatic disease further reduces survival, but complete regression of disease often can be obtained with chemotherapy and surgical resection of the primary tumor and isolated pulmonary metastatic disease, resulting in survival rates of approximately 25%. Treatment-related long-term adverse effects include cardiac toxicity with doxorubicin and renal and ototoxicity with cisplatin.

HEPATOCELLULAR CARCINOMA

Epidemiology

HCC occurs mostly in adolescents and often is associated with perinatal acquired hepatitis B infection and tyrosinemia. It is more common in East Asia and other areas where hepatitis B is endemic; the incidence has decreased following the introduction of hepatitis B vaccination. In these areas, HCC also tends to occur in a bimodal pattern, with the younger age peak overlapping the age of hepatoblastoma presentation. HCC also occurs in the chronic form of glycogen storage disease, α_1-antitrypsin deficiency, biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, congenital portosystemic shunts, Budd-Chiari syndrome, status postirradiation for liver metastatic Wilms tumor, and with other liver diseases producing chronic inflammation or cirrhosis (Fig. 553.3).

Pathogenesis

Pediatric HCC arises in cirrhotic and noncirrhotic backgrounds and presents as a multicentric, invasive tumor consisting of large pleomorphic cells of epithelial origin. Compared to adults, cirrhosis in children is less common, and congenital liver disorders are more common. HCCs are classified as **classical** or **fibrolamellar**. The fibrolamellar variant occurs more often in adolescent and young adult patients, is not associated with cirrhosis, and represents one fourth of the pediatric

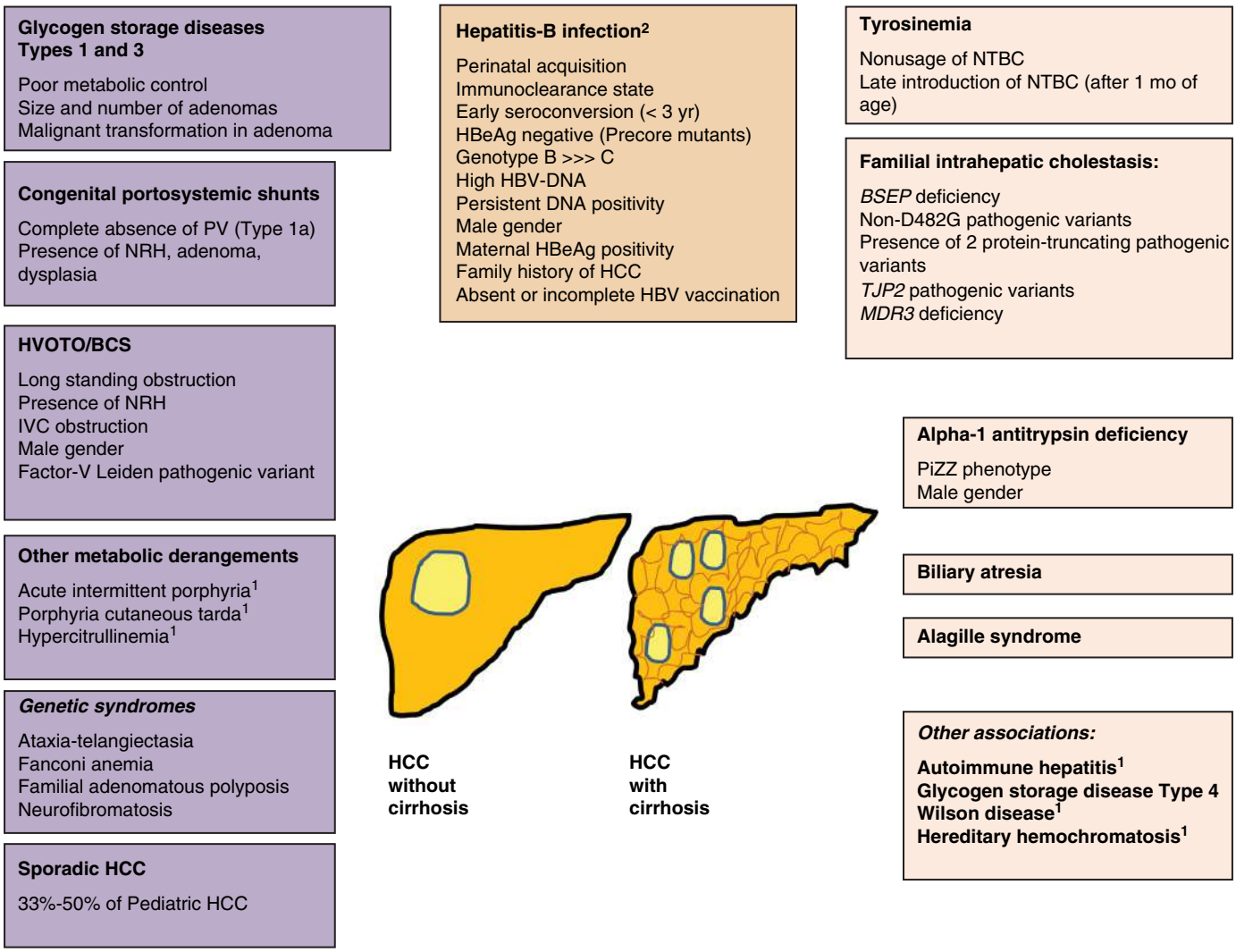

Fig. 553.3 Risk factors for pediatric hepatocellular carcinoma (HCC). [1]Conditions cause HCC in adults, and very rarely in children; [2]Hepatitis B virus (HBV)-related HCC may occur in the presence or absence of cirrhosis. BCS, Budd-Chiari syndrome; HVOTO, hepatic venous outflow tract obstruction; IVC, inferior vena cava; NRH, nodular regenerative hyperplasia; BSEP, bile salt export pump; MDR3, multidrug resistance protein-3; NTBC, [2-(2-nitro4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (Nitisinone); PiZZ, homozygous PiZ phenotype of α_1-antitrypsin; PV, Portal vein; TJP: tight junction protein. *(From Khanna R, Verma SK. Pediatric hepatocellular carcinoma. World J Gastroenterol. 2018;24[35]:3980–3999. Fig. 1.)*

HCC cases. This variant has been reported to have a distinct translocation, *DNAJB1-PRKACA*. A rare subtype called **transitional liver tumor** occurs in older children and has clinical and histopathologic findings of both hepatoblastoma and HCC.

Clinical Manifestations

HCC usually presents as a hepatic mass with abdominal distention and symptoms of anorexia, weight loss, jaundice, and abdominal pain. HCC can present as an acute abdominal crisis with rupture of the tumor and hemoperitoneum. Metastatic spread usually involves regional lymph nodes and the lungs. The AFP level is elevated in approximately 60% of children with conventional HCC, but not in the fibrolamellar variant. Evidence of hepatitis B usually is found in endemic areas but not in Western countries or with the fibrolamellar type. Liver enzymes may be abnormal.

Diagnostic imaging should include plain radiographs and US of the abdomen to characterize the hepatic mass. US can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

Treatment

Complete tumor resection is crucial for curative treatment. Because of the multicentric origin of HCC and underlying liver disease, complete resection is accomplished in only 20–30% of cases. A gross total resection should be attempted at diagnosis when possible; if not, neoadjuvant chemotherapy should be given to convert nonresectable tumors into resectable ones. Combination chemotherapy following surgery is necessary. For unresectable tumors, **chemotherapy** followed by surgical assessment is essential, and **liver transplant** should be decided individually for each patient with HCC. Chemotherapy, including cisplatin, carboplatin, doxorubicin, and etoposide, has shown activity against this tumor, but improved long-term outcome has been difficult to achieve if tumor is not completed resected. **Sorafenib**, a small inhibitor of several tyrosine protein kinase showed antitumoral activity in adult patients with HCC, and initial studies have been published in the pediatric population with encouraging results. Other techniques are under study in adults, including cryosurgery, RFA, transarterial chemoembolization, and radiation therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 554

Complex Vascular Anomalies

Alexandra J. Borst and Denise M. Adams

Vascular anomalies in children encompass a spectrum of disorders that may be divided into **vascular malformations** and vascular tumors (Tables 554.1-554.4; see Chapter 691). **Vascular malformations** are developmental disorders of blood vessel formation. Malformations do not regress; rather, they slowly enlarge. They should be named after the predominant vessel(s) forming the lesion: arterial, capillary, lymphatic, or venous, or combinations of these (see Table 554.1). Vascular tumors exhibit endothelial cell hyperplasia and proliferation. The International Society for the Study of Vascular Anomalies (ISSVA) continues to update the classification structure for vascular disorders as new disorders are identified and as the biology and genetic causes for established disorders are found. The complete classification, associated syndromes, and causative pathogenic variants can be found at www.issva.org. The discovery of the molecular basis of many **vascular malformations** and tumors has allowed for improved understanding of the etiology of these disorders as well as new **targeted therapeutic approaches** for management.

GENETIC BASIS FOR VASCULAR ANOMALIES

Two key intracellular signaling pathways have been implicated in the pathogenesis of most **vascular malformations**, syndromes, and tumors. The RAS/MAPK and PI3K/AKT/mTOR pathways are crucial for cell cycle regulation, proliferation, and migration (Fig. 554.1). Pathogenic, *somatic* variants in the *PIK3CA* gene have been identified in patients with **venous malformations**, **lymphatic malformations**, and several vascular anomalies and overgrowth syndromes (see Table 554.4). Pathogenic variants in the RAS/MAPK pathway have been identified in **capillary and arteriovenous malformations (AVMs)**, central conducting lymphatic anomalies, as well as many of the vascular tumors.

Discovery of the molecular basis for **vascular malformations** and tumors has led to the ability to find **targeted therapies** for management of these conditions. **Sirolimus** has been utilized successfully in vascular malformations and tumors. The identification of the crucial role of *PIK3CA* pathogenic variants in vascular anomalies has led to the investigation of **PI3K inhibitors** as important targeted therapies. Agents that target the RAS/MAPK pathway, such as **MEK inhibitors**, have also been trialed in complicated AVMs as well as Kaposiform lymphangiomatosis (KLA).

COMPLEX LYMPHATIC ANOMALIES

Lymphatic anomalies represent a rare disease entity, with an estimated incidence of 1:10,000 for the most common form of lymphatic malformations, but with only a few hundred case reports in the literature for *complex* lymphatic anomalies. Lymphatic anomalies arise from developmental defects in lymphangiogenesis. They carry significant risk for comorbidities, including pain, infection, disfigurement, and life-threatening organ dysfunction. Lymphatic anomalies encompass a broad range of developmental and functional defects in lymphatic vessels that range from discrete malformations to complex anomalies (generalized lymphatic anomaly [GLA], KLA, and Gorham-Stout disease [GSD]) and primary lymphedema syndromes.

Most lymphatic anomalies are thought to arise from *somatic* pathogenic variants in genes involved in lymphangiogenesis, but germline predispositions also exist. Pathogenic variants in the PIK3CA/AKT/mTOR and VEGFC/VEGFR3 pathways have been found in many isolated lymphatic malformations; variants in the RAS/MAPK pathway have been identified in patients with *complex lymphatic anomalies* (Fig. 554.2). However, most patients remain without a genetic diagnosis.

Generalized Lymphatic Anomaly

Previously known as lymphangiomatosis, GLA is characterized by a nonneoplastic, multicentric proliferation of dilated lymphatic vessels, with multiple sites resembling common lymphatic malformations (Fig. 554.3). The lesions are present since birth but generally become clinically apparent within the first 2 decades of life. The lesions can affect the bones, liver, spleen, mediastinum, lung, and soft tissues. Bone involvement is typically osteolytic, with punched out lesions and intact cortex. Clinical response depends on location and extent of disease, with thoracic involvement having the poorest prognosis. Patients with GLA most commonly have pathogenic somatic variants in *PIK3CA* leading to overactivity in the PI3K/AKT/mTOR pathway and disrupted lymphatic development and growth. Many patients have been successfully managed with sirolimus.

Gorham-Stout Disease

GSD (also known as *vanishing bone disease*) has significant clinical overlap with GLA but tends to involve a single site or adjacent sites. Patients may present with adjacent soft tissue mass or small areas of

Table 554.1 Overview of Vascular Anomalies

VASCULAR TUMORS	VASCULAR MALFORMATIONS			
	SIMPLE	COMBINED*	OF MAJOR NAMED VESSELS	ASSOCIATED WITH OTHER ANOMALIES
Benign	Capillary malformations Lymphatic malformations	CMV, CLM LVM, CLVM	See Table 554.2	See Table 554.3
Locally aggressive or borderline	Venous malformations Arteriovenous malformations†	CAVM† CLAVM†		
Malignant	Arteriovenous fistula†	Others		

*Defined as two or more vascular malformations found in one lesion.
†High-flow lesions.
A list of casual genes and related vascular anomalies is available in Tables 554.3 and 554.4
CVM, Capillary venous malformation; CLM, capillary lymphatic malformation, LVM, lymphatic venous malformation, CLVM, capillary lymphatic venous malformation, CAVM, capillary arteriovenous malformation; CLAVM, capillary lymphatic arteriovenous malformation.
From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

Table 554.2 Anomalies of Major Named Vessels (Also Known as "Channel Type" or "Truncal" Vascular Malformations)

Affect
Lymphatics
Veins
Arteries
Anomalies of
Origin
Course
Number
Length
Diameter (aplasia, hypoplasia, stenosis, ectasia / aneurysm)
Valves
Communication (AVF)
Persistence (of embryonal vessel)

AVF, Arteriovenous fistula.
From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

microcystic lymphatic malformation. The upper axial skeleton is commonly affected, and there is osteolysis of both the medullary and cortical bone (Fig. 554.4). This osteolysis can be profound and result in significant morbidity, including dysfunction of an appendage or even spinal column instability. Some molecular findings in patients with GSD have suggested that somatic activating variants in *KRAS* and dysfunction of the RAS/MAPK signaling pathway drive the pathogenesis of GSD. Many patients have been treated with sirolimus with adjunctive bisphosphonate therapy.

Kaposiform Lymphangiomatosis

KLA has been considered an aggressive subtype of GLA but is histologically and molecularly distinct. Many patients with KLA harbor *somatic* activation variants in the RAS pathway, rather than the PI3K/AKT/mTOR pathway identified as causative in GLA. KLA presents with distinct foci of spindled endothelial cells on a background of malformed lymphatic vessels. KLA can affect multiple organs and sites but primarily affects the thoracic cavity with patients presenting with life-threatening, and frequently hemorrhagic, pleural effusions (Fig. 554.5). Patients often have a coagulopathy at presentation due to the same **Kasabach-Merritt phenomenon (KMP)** seen in patients with **Kaposiform hemangioendothelioma**. Patients typically present at a younger age than those with GLA or GSD; the mortality has been reported as high as 50–60% prior to the introduction of sirolimus.

Central Conducting Lymphatic Anomaly

Central conducting lymphatic anomaly (CCLA), also known as *lymphangiectasia*, is classified as a channel-type lymphatic anomaly. CCLA is caused by lymphatic channel dysmotility and distal obstruction/malformation affecting lymphatic drainage and leading to recurrent effusions (Fig. 554.6). Patients with other complex lymphatic anomalies may have a component of CCLA. Pathogenic variants in *EPHB4* and *ARAF* have been identified in patients with CCLA and both mTOR and MEK inhibition have been used in its management with mixed success. Patients frequently needed targeted interventional procedures to embolize abnormal lymphatic vessels.

Treatment of Complex Lymphatic Anomalies

Management of complex lymphatic anomalies is principally aimed at control, not cure. This can include a variety of medical, surgical, and interventional procedures to control symptoms and prevent morbidity. Sirolimus, an mTOR inhibitor, has been shown to decrease symptoms of lymphatic leak such as lymphatic blebs, decrease the size of macrocystic and microcystic malformations, decrease chylous production, and may slow the pathologic dissolution of bone by lymphatic malformation. MEK inhibition has shown promise in the management of KLA and CCLA, both found to be driven more by perturbations affecting RAS/MAPK signaling. Adjunctive therapy with bisphosphonates is often used in GSD and in patients with GLA and KLA with bony vertebral lesions.

COMPLEX VENOUS ANOMALIES

Venous anomalies are slow-flow lesions that represent abnormal or excessive growth of venous structures. **Venous malformations** are the most common vascular malformations with an incidence of 1 in 5,000 to 10,000. Due to the slow and sometimes turbulent flow, they commonly are associated with pain, swelling, and intralesional thrombosis. Venous malformations have been found to have *somatic* pathogenic variants in both *PIK3CA* and *TIE2/TEK*, an endothelial cell–specific tyrosine kinase receptor that functions through the PI3K/AKT/mTOR pathway (see Fig. 554.1).

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome (BRBNS) is characterized by multiple cutaneous and internal venous malformations, primarily hepatic and intestinal (Fig. 554.7). Many cases have been found to be due to gain-of-function

Table 554.3 Vascular Malformations Associated with Other Anomalies

SYNDROME	LESIONS	GENES
Klippel-Trenaunay syndrome*:	CM + VM +/– LM + limb overgrowth	*PIK3CA*
Parkes-Weber syndrome:	CM + AVF + limb overgrowth	*RASA1*
Servelle-Martorell syndrome:	limb VM + bone undergrowth	
Sturge-Weber syndrome:	facial + leptomeningeal CM + eye anomalies +/– bone and/or soft tissue overgrowth	*GNAQ*
Limb CM + congenital nonprogressive limb overgrowth		*GNA11*
Maffucci syndrome:	VM +/– spindle-cell hemangioma + enchondroma	*IDH1/IDH2*
Macrocephaly-CM (M-CM/MCAP)*		*PIK3CA*
Microcephaly-CM (MICCAP)		*STAMBP*
CLOVES syndrome*:	LM + VM + CM +/– AVM + lipomatous overgrowth	*PICK3CA*
Proteus syndrome:	CM, VM, and/or LM + asymmetrical somatic overgrowth	*AKT1*
Bannayan-Riley-Ruvalcaba syndrome:	AVM + VM + macrocephaly, lipomatous overgrowth	*PTEN*
CLAPO syndrome*:	lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth	*PIK3CA*

*These lesions belong to the PIK3CA-related overgrowth spectrum (PROS)
CM, Capillary malformation; VM, venous malformation; LM, lymphatic malformation; AVF, arteriovenous fistula; M-CM, macrocephaly-capillary malformation; MCAP, megalocephaly-capillary-malformation-polymicrogyria; MICCAP, microcephaly-capillary malformation; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/scoliosis/spinal anomalies; CLAPO, lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth.
From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

Table 554.4 PIK3CA-Related Overgrowth Spectrum

PIK3CA-related overgrowth spectrum (PROS) group lesions with heterogeneous segmental overgrowth phenotypes with or without vascular anomalies due to somatic PIK3CA activating variants.

This spectrum includes:

- Fibroadipose hyperplasia or overgrowth (FAO)
- Hemihyperplasia multiple lipomatosis (HHML)
- Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal, and spinal (CLOVES) syndrome
- Macrodactyly
- Fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis
- Megalencephaly-capillary malformation (MCAP or M-CM)
- Dysplastic megalencephaly (DMEG)
- Klippel-Trenaunay syndrome

From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

TIE2/TEK pathogenic variants; both sporadic and autosomal dominant inheritance have been described. Significant morbidity can arise due to intestinal venous malformations, which can lead to severe bleeding and secondary iron deficiency anemia. Patients must be monitored closely for signs and symptoms of bleeding. The mainstay of management is control of disease with sirolimus and supportive care for anemia.

Glomuvenous Malformation (Glomangioma)

Glomuvenous malformations, also known as *glomangiomas* or *glomus tumors*, are one of the rare germline conditions in vascular anomalies. Glomuvenous malformations result from an autosomal dominant loss-of-function variant in the *GLMN* gene, which encodes a protein essential for normal vascular development. Patients present with multiple superficial cutaneous lesions with a cobblestone appearance (Fig. 554.8). There is 100% penetrance but variable expressivity. Painful lesions can be treated with surgical resection, laser, or sclerotherapy.

SYNDROMES ASSOCIATED WITH VASCULAR ANOMALIES

PIK3CA-Related Overgrowth Spectrum Disorders

PIK3CA-related overgrowth spectrum (PROS) encompasses a group of disorders caused by somatic mosaic mutations in the PI3K/AKT/mTOR pathway (see Table 554.4). The *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α) gene encodes a group of lipid kinases (PI3 kinases) that are key to regulating cell proliferation and survival via the PI3K/AKT/mTOR pathway. Patients with PROS present with a wide spectrum of clinical phenotypes, but progressive segmental overgrowth and vascular malformations are key components.

Klippel-Trenaunay Syndrome

Klippel-Trenaunay syndrome (KTS) is characterized by overgrowth of one lower extremity in combination with combined slow-flow vascular malformation (capillary, venous, and/or lymphatic). Complications include lymphatic overgrowth, infection, oozing and/or bleeding from lymphatic blebs, and thromboembolism (Fig. 554.9). Patients with KTS have an anomalous venous return system composed of dilated and incompetent veins, often with a larger marginal vein. The deep venous system may also be poorly developed. Patients can have lymphatic involvement of the skin, musculature, and intestinal tract. Venous malformation may affect the bladder and urethra. Due to variability in diagnostic criteria and identification of KTS over the years, the genetic etiology of KTS is not completely confirmed, but many patients have been identified to have a *somatic* variants in *PIK3CA*; KTS is considered part of PROS disorders. Surgical and interventional procedures may be important for some patients with KTS. Medical management currently includes sirolimus and anticoagulation therapy.

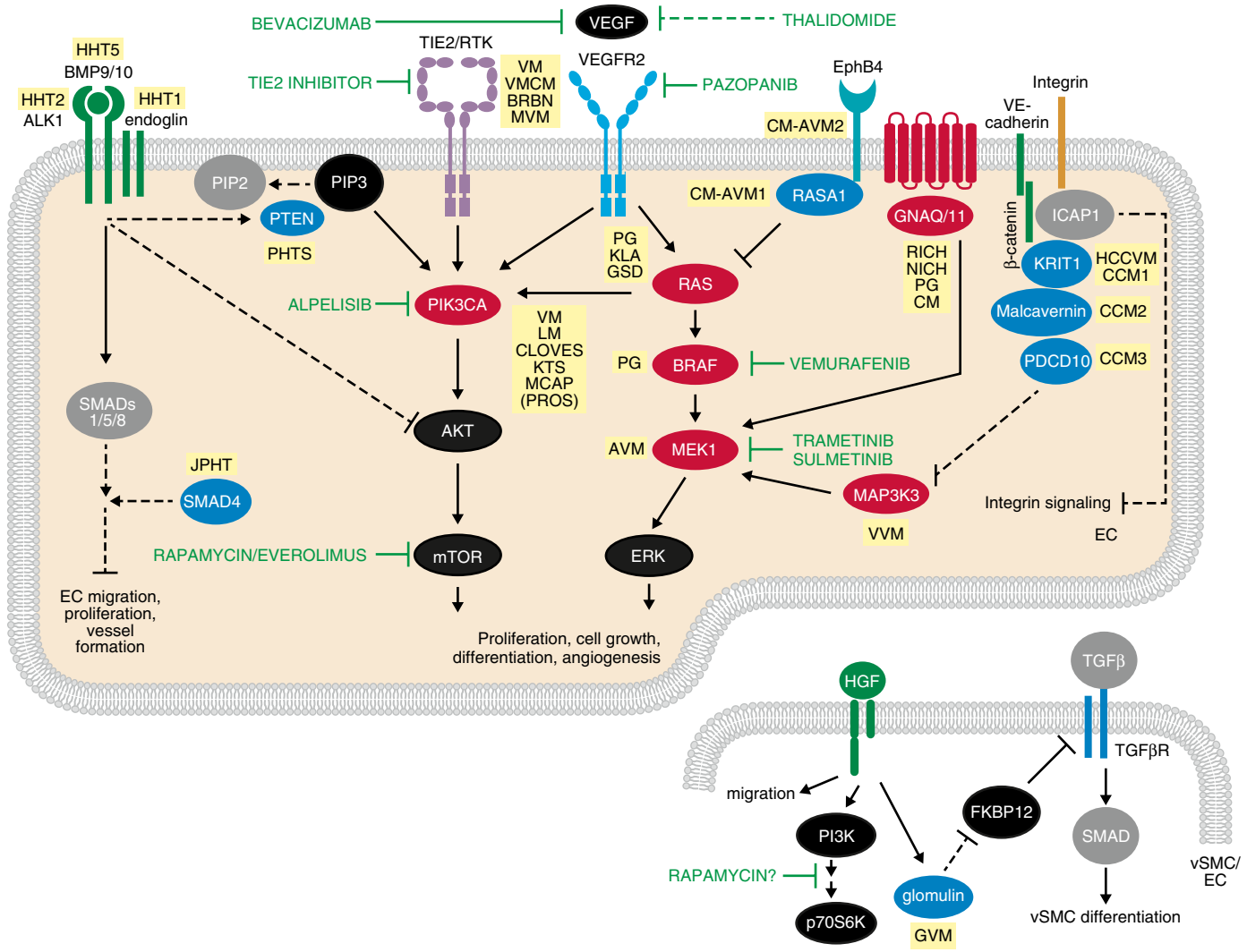

Fig. 554.1 PI3K/AKT/mTOR signaling and RAS/MAPK signaling in vascular anomalies. Red, gain of function; blue, loss of function; black, enhanced signaling; gray, decreased signaling. *(From Queisser A, Seront E, Boon LM, Vikkula M. Genetic basis and therapies for vascular anomalies. Circ Res. 2021;129[1]:155–173. Fig. 3.)*

CLOVES

CLOVES, or congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/spinal/skeletal anomalies, is a disorder that results from an early embryonic pathogenic variant in *PIK3CA*. In addition to extremity hypertrophy, patients can have significant fatty lipomatous overgrowth (Fig. 554.10). Spinal involvement is common. Patients with vascular malformations usually have a combination of capillary, venous, and lymphatic malformations. AVMs are less common but have been reported with spinal involvement. Deep venous anomalies increase the risk for venous thromboembolism. Patients with CLOVES have an increased risk of Wilms tumor and require serial monitoring with abdominal ultrasonography in early childhood. Patients may require sclerotherapy, surgery, and other interventional procedures depending on symptoms. Patients have also been successfully managed with sirolimus.

Macrocephaly-Capillary Malformation

Macrocephaly-capillary malformation (M-CM) syndrome is a PROS disorder characterized by macrocephaly, brain abnormalities, CM (often in a reticular pattern), overgrowth, and developmental delays (Fig. 554.11). Neurologic manifestations can include hydrocephalus, cortical dysplasia, polymicrogyria, and posterior fossa crowding with cerebellar tonsillar herniation. Patients require supportive care for overgrowth and other vascular anomalies, as well as close monitoring of brain growth and development.

AKT-RELATED OVERGROWTH SPECTRUM

Proteus Syndrome

Proteus is an overgrowth disorder caused by a *somatic* mosaic pathogenic variant in the PI3K/AKT/mTOR pathway. Clinical features include overgrowth (including lipomatous), bony abnormalities, cerebriform connective tissue nevus, vascular malformations (capillary, venous, lymphatic), epidermal nevi, cerebral abnormalities and accompanying intellectual disability, and increased risk for secondary neoplasms and venous thromboembolism. Management of proteus disorders has primarily been supportive, although use of AKT1 inhibition is currently being evaluated.

RASopathies

RASopathies refers to a group of medical conditions caused by pathogenic variants in the RAS/MAPK pathway. It includes both germline conditions, as well as *somatic* variants. The RAS/MAPK pathway is important in cell cycle regulation, proliferation, migration, and stress response. RAS/MAPK pathway pathogenic variants have been identified in patients with solitary CMs and AVMs, GLA, KLA, verrucous venous malformation, cerebral CM, pyogenic granuloma (PG), and congenital hemangiomas.

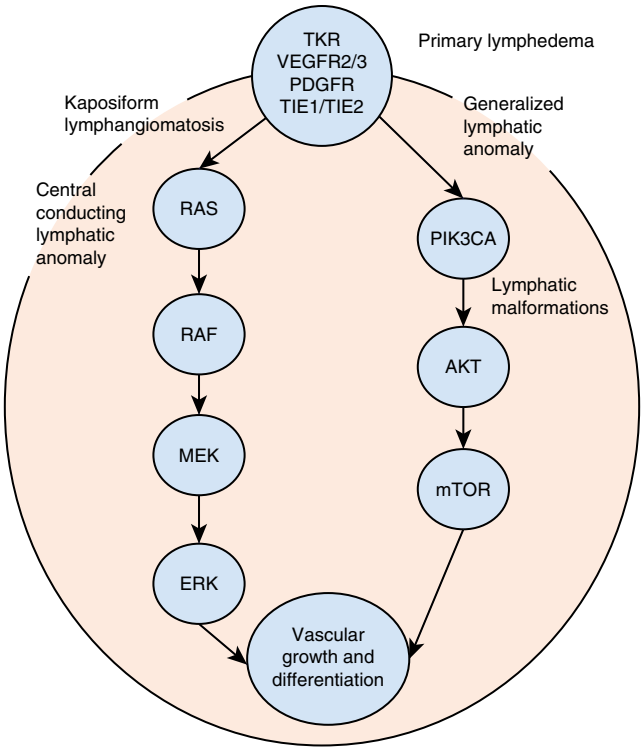

Fig. 554.2 Molecular pathways identified in lymphatic anomalies.

Capillary Malformation-Arteriovenous Malformation Syndrome

Capillary malformation-arteriovenous malformation (CM-AVM) is an autosomal dominant disorder characterized by diffuse, circumscribed CMs and increased risk for intra- or extracranial AVMs. AVMs are found in ~80% of patients. The CMs have a distinct appearance with a round or ovoid shape and surrounding pale halo. Most cases of CM-AVM are caused by a loss-of-function pathogenic variant in *RASA1*, but variants in *EPHB4* have also been reported (CM-AVM type 2). Familial penetrance is high, and screening is important due to the high risk for life-threatening complications from AVMs. AVMs may require treatment with a combination of interventional and surgical procedures.

Parkes-Weber Syndrome

Parkes-Weber syndrome (PKWS) is associated with pathogenic variants in *RASA1*. The syndrome includes multiple microscopic arteriovenous fistulae in association with a CM. PKWS is also associated with soft tissue and bony overgrowth of an extremity.

KAPOSIFORM HEMANGIOENDOTHELIOMA

Kaposiform hemangioendothelioma (KHE) is a rare and potentially life-threatening vascular tumor. KHE classically presents as a red to purple firm plaque on the lateral neck, axilla, trunk, or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. **Tufted angioma,** once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 554.12). The main complication of these tumors is the development of **KMP**, which may be fatal; therefore early diagnosis and treatment is important. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

Kasabach-Merritt Phenomenon

KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only

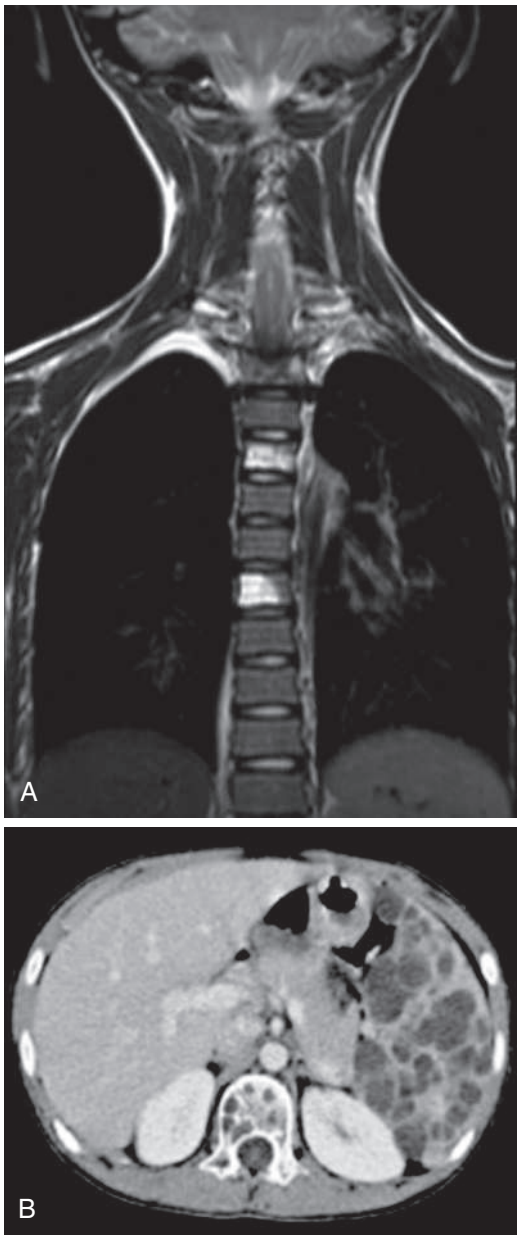

Fig. 554.3 **A**, MRI imaging of vertebral body **lymphatic malformations** in a patient with generalized lymphatic anomaly (GLA). **B**, Splenic and vertebral body lesions in a patient with GLA. (***B*** *from Joshi M, Phansalkar DS. Simple lymphangioma to generalized lymphatic anomaly: role of imaging in disclosure of a rare and morbid disease. Case Rep Radiol. 2015;2015:603859.)*

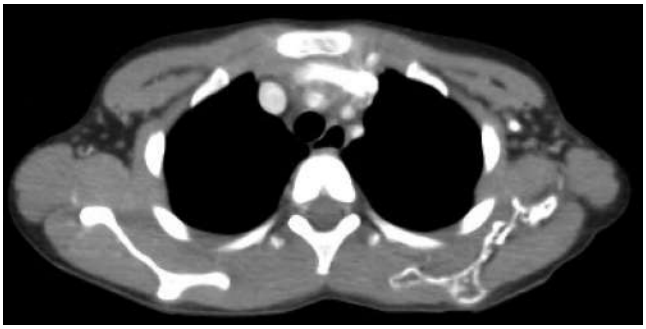

Fig. 554.4 Osteolytic destruction of the left scapula in a patient with Gorham-Stout disease (GSD). Axial CT image of the left scapula demonstrates intramedullary lucent lesions with cortical thinning.

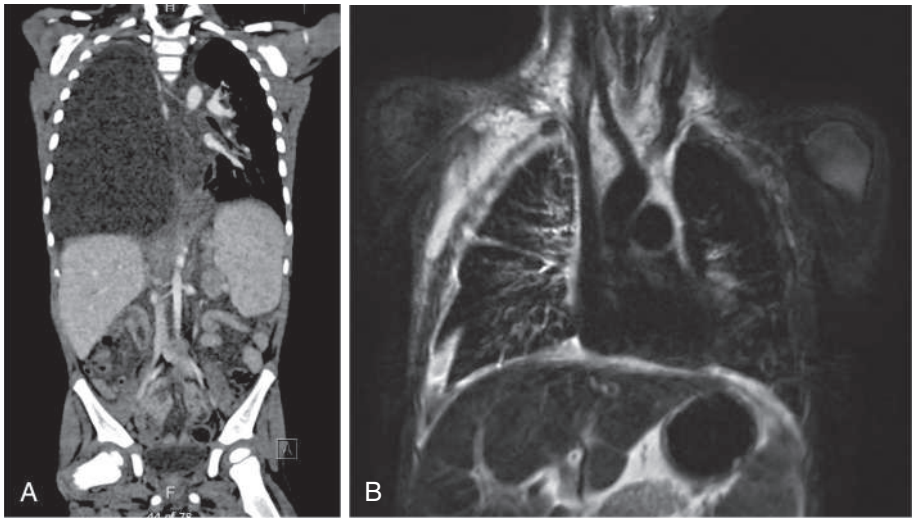

Fig. 554.5 A, Large hemorrhagic pleural effusion in a patient with Kaposiform lymphangiomatosis (KLA). B, Abnormal lymphatic fluid distribution and central lymphatic drainage in a patient with KLA.



Fig. 554.6 MR lymphangiography study showing a dilated and malformed thoracic duct and central lymphatics with retrograde flow into the mediastinum and pericardium *(arrows)* in a patient with central conducting lymphatic anomaly (CCLA).



Fig. 554.7 Multiple **venous malformations** on the tongue (A) and subcutaneous tissues of the foot (B) in a patient with blue rubber bleb nevus syndrome (BRBNS).

rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 533.6). KMP is seen in KHE or tufted angioma, as well as to a milder extent in very large congenital and hepatic hemangiomas *but not* in infantile hemangiomas.

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy and the infiltrative nature of the tumor. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. mTOR inhibition with sirolimus has been found to be successful as an alternative first-line treatment for KHE. The optimal initial combination of medical therapies is not yet known. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. The mortality rate overall once patients have KMP is high.

OTHER RARE VASCULAR TUMORS

Benign Tumors (Other Than Infantile Hemangiomas) (see Chapter 691)

Epithelioid Hemangiomas

Epithelioid hemangioma (EH) is a very rare vascular tumor, usually occurring in the skin or subcutaneous tissues, but occasionally occurring



Fig. 554.8 Cobblestoned appearance of a patient with a glomangioma, or glomuvenous malformation, caused by a germline pathogenic variant in the glomulin gene *(GLMN)*. Family members all with similar appearing lesions.



Fig. 554.9 Overgrown right lower extremity with **capillary-venous-lymphatic malformation** in a patient with Klippel-Trenaunay syndrome.

in other sites such as bone. They may be mistaken for infantile hemangiomas or PGs and can be reactive due to trauma or infection. EHs are well-circumscribed proliferations of capillaries that stain for endothelial cell and lymphatic markers but are without any cytologic atypia or mitoses. Primary treatment is with surgical excision, though they can recur locally. *FOS* gene rearrangements have been identified in some EHs.

Pyogenic Granuloma (Lobular Capillary Hemangioma)

A PG is a small red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (see Fig. 691.16). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauterization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with **pulsed dye laser** therapy.

Spider Angioma

A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (see Fig. 691.17). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region, lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.

Maffucci Syndrome

The association of spindle cell hemangiomas with nodular enchondromas in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as Maffucci syndrome. Maffucci syndrome is caused by *somatic* mosaic pathogenic variants in the *IDH1* and *IDH2* genes. Vascular lesions are typically soft, compressible, asymptomatic blue to purple subcutaneous masses that grow in proportion to a child's growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 550).

LOCALLY AGGRESSIVE RARE VASCULAR TUMORS

Retiform Hemangioendothelioma

Retiform hemangioendothelioma (RHE) is an intermediate, or rarely metastasizing, vascular tumor. They usually present as a slow-growing mass with plaque-like or nodular appearance. They can involve the entire dermis and extend into the subcutaneous tissue. Histologically, hobnail endothelial cells are found, but only variably lymphatic endothelial cell markers. Treatment is with surgical excision, though local recurrence is common and regional lymph node metastases have been reported.

Papillary Intralymphatic Angioendothelioma

Papillary intralymphatic angioendothelioma (PILA), also referred to as *Dabska tumor,* is a locally aggressive hemangioendothelioma. PILA occur within the dermis and superficial soft tissues of the head, neck, trunk, or extremities. On occasion they have been reported to arise from preexisting lymphatic or venolymphatic malformations, or within an extremity affected by lymphedema. They appear as violaceous nodules similar to RHE but histologically appear similar to lymphatic malformations and contain hobnail endothelial cells. Primary treatment is with excision, but regional lymph node metastasis and even death due to distant metastasis have been reported. Systemic chemotherapy based on sarcoma treatment may be used in recurrent or refractory cases.

Composite Hemangioendothelioma

Composite hemangioendotheliomas (CHE) contain overlapping histologic features with epithelioid, retiform, and spindle-cell hemangioendotheliomas. Some also contain angiosarcoma-like features within the same tumor. Fewer than 40 cases have been reported in the literature, and they can present at any age and in association with other vascular anomalies. Treatment options include surgical excision, chemotherapy, and radiation therapy.



Fig. 554.10 A, Soft tissue and bony overgrowth of the digits of the bilateral hands in a patient with CLOVES. Also noted is overlying capillary malformation (CM). B, Overgrowth of digits of the feet and right sandal-toe gap deformity in a patient with CLOVES. Also noted are CM and dilated venous pattern from underlying bilateral **venous malformation** of the lower extremities.



Fig. 554.11 Infant with macrocephaly, prominent forehead, depressed nasal bridge, short neck, bluish white iris, and reticulated port-wine stains over body, consistent with macrocephaly-capillary malformation (M-CM). *(From Panigrahi I, Bhushan M, Yadav M, Khandelwal N, Singhi P. Macrocephaly-capillary malformation syndrome: three new cases. J Neurol Sci. 2012;313:178–181. Fig. 5.)*

Pseudomyogenic Hemangioendothelioma (Epithelioid Sarcoma-Like Hemangioendothelioma)

Pseudomyogenic hemangioendothelioma (PMH) is a rare vascular tumor that presents more commonly in males than females (4:1 predominance) and usually in young adulthood (<40 years). The typical presentation is multifocal presentation within one extremity, and it does frequently have bony involvement. Histologically, it shares some features with epithelioid sarcoma, with myoid-appearing spindle cells, but has very low metastatic potential. Primary treatment is with surgical resection, but local recurrence is common, and mTOR inhibition with sirolimus has shown promise in its management.

MALIGNANT TUMORS

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is variant of *angiosarcoma,* which is locally aggressive and has metastatic potential. It usually occurs in middle-age adults and presents as a solitary mass in the soft tissues, viscera, or bone, with liver as the most common site. Thirty



Fig. 554.12 A, Patient with **Kaposiform hemangioendothelioma** (KHE) of the thigh who presented with **Kasabach-Merritt phenomenon** (KMP) with thrombocytopenia and hypofibrinogenemia unresponsive to all therapy until introduction of sirolimus. B, Premature infant with KHE of the arm who presented with KMP.

percent present with metastases, and occasionally patients present with hemolytic anemia or consumptive coagulopathy. EHE is characterized by the WWTR1/CAMTA1 translocation, with some also expressing a *YAP1-TFE3* gene fusion. Histologically, EHE are epithelioid tumors arranged in nests or cords. They may contain spindle endothelial cells and express Fli-1 and CD31. Treatment depends on location and metastatic pattern but includes surgery, radiotherapy, and chemotherapy. Overall survival for those with progressive disease is quite poor.

Angiosarcoma

Angiosarcomas account for ~2% of all soft tissue sarcomas, occur mostly in adults, and very rarely affect children. In children, they may be cutaneous or in the deep tissues or viscera. Angiosarcomas present as rapidly enlarging purplish plaques or nodules that ulcerate and can leak serosanguinous fluid. Necrosis and hemorrhage within the tumor are common. Due to risk for rapid progression and metastasis, multimodal therapy including resection and intensive chemotherapy is generally pursued. Combined treatment with mTOR and MEK inhibition has shown some promise, but progression-free and overall survival remain very poor.

Hepatic angiosarcomas appear to be a distinct subtype of angiosarcoma, presenting in earlier childhood, usually between age 1 and 5 years (Fig. 554.13). There is sometimes a history of infantile hepatic hemangioma, although cutaneous infantile hemangiomas do not appear to progress to angiosarcoma. Patients can present with anemia and thrombocytopenia due to intratumoral bleeding. Liver function tests may be abnormal, but α-fetoprotein is normal or only minimally elevated. Risk of local invasion and metastasis is quite high, so rapid diagnosis, surgical resection, and initiation of sarcoma-based chemotherapy is important. Unfortunately, complete cure is very rare.

Lymphangiosarcoma is a distinct subtype of angiosarcoma arising from the lymphatic endothelium of a site of lymphedema. Lymphangioma resembles angiosarcoma both clinically and histologically and appears to harbor the same c-myc amplification seen in postradiation angiosarcoma of the breast. Similar to the "hemangiosarcoma" form of angiosarcoma, lymphangiosarcomas are managed similarly and have similar overall poor prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 554.13 Angiosarcoma of the liver. *(From Potanos KM, Hodgkinson N, Fullington NM, et al. Long-term survival in pediatric hepatic angiosarcoma (PHAS): a case report and review of the literature. J Pediatr Surg Case Rep. 2015;3:410–413. Fig. 1.)*

Chapter 555
Rare Tumors

555.1 Thyroid Tumors

Jonathan D. Wasserman

See Chapter 607.

BENIGN THYROID TUMORS

Benign thyroid tumors represent approximately 75% of all thyroid nodules presenting in the pediatric population and generally require no treatment unless they result in compressive symptoms or thyroid hormone hypersecretion. The workup of a suspected thyroid nodule includes the laboratory assessment of thyroid function (thyroid-stimulating hormone [TSH]), ultrasound (US) to assess characteristics of the nodule(s) and regional lymph nodes, and US-guided fine-needle aspiration biopsy (of the primary nodule and suspicious lymph nodes) for cytopathologic diagnosis if imaging is suspicious for malignancy. Nuclear scintigraphy using radioactive iodine (^{123}I) or technetium 99m (^{99m}Tc)-pertechnetate are not recommended in the initial diagnostic evaluation, except in the event of a suppressed TSH level.

MALIGNANT THYROID TUMORS

Pediatric thyroid malignancies are rare tumors that include medullary thyroid carcinoma (MTC) and the differentiated thyroid carcinomas (DTCs), namely, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma. Findings suggestive of a thyroid malignancy are noted in Table 555.1.

PTC represents the majority of thyroid cancers in children. The incidence of pediatric thyroid cancer has been rising, with the highest rate in adolescence, and a female predominance emerges around the time of puberty. With few exceptions, children with PTC have a highly favorable prognosis, with anticipated survival over decades, even in the presence of distally metastatic disease at diagnosis. *The major established risk factor for development of PTC is exposure to ionizing radiation, typically in the context of antineoplastic therapy.*

MTC is an uncommon disease in childhood that usually occurs in the context of **multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B),** autosomal dominant, hereditary endocrine tumor syndromes that arise secondary to activating variants in the *RET* proto-oncogene. In addition to the almost complete penetrance of MTC in patients with the most common *RET* variants, patients with MEN2A and MEN2B have up to a 50% lifetime risk of developing pheochromocytomas (PHEOs). Up to 20% of MEN2A patients also develop primary hyperparathyroidism. Patients with MEN2B do not develop hyperparathyroidism but have a distinct clinical phenotype that includes a characteristic facial appearance, marfanoid body habitus, aerodigestive tract ganglioneuromatosis, and **oral and ocular mucosal neuromas** (Fig. 555.1). The diagnosis of MEN2B is often delayed (usually after the MTC has already metastasized) because its pathognomonic features are not apparent in very early childhood, although an inability to cry tears (alacrimia) and constipation represent the earliest clues to diagnosis. MTC may be sporadic or familial without features of MEN 2A or 2B; it may also be associated with **Hirschsprung disease**.

Children with sporadic **DTC** typically present with an asymptomatic thyroid mass and/or cervical lymphadenopathy. Lymph node metastases are present in most PTC cases, and lung metastases are identified in up to 20% of patients, primarily in those children with a high burden of neck disease. In contrast, children with MEN2-related **MTC** are often diagnosed only after a positive genetic test result or, in the case of MEN2B, after the clinical phenotype is recognized. When

Table 555.1	Clinical Findings Associated with Malignant Thyroid Nodules
HISTORIC FEATURES	
Neck irradiation during childhood or adolescence	
Rapid growth	
Recent, persistent changes in speaking, breathing, or swallowing	
Family history of multiple endocrine neoplasia type 2	
PHYSICAL EXAMINATION	
Firm, fixed, and irregular consistency of nodule	
Vocal cord paralysis or hoarseness	
Persistent regional lymph adenopathy	

Modified from Melmed S, Auchus RJ, Goldfine AB, et al., eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2020: Table 14.3, p. 439.



Fig. 555.1 Classic appearance of oral mucosal neuromas on the tongue in a boy with multiple endocrine neoplasia type 2b (MEN2B) secondary to the typical M918T variant in the *RET* protooncogene.

a family history is known, presymptomatic surveillance may identify MTC at earlier stages. As with PTC, MTC also frequently metastasizes to cervical lymph nodes.

There are well-documented genotype-phenotype correlations in MEN2, and the biologic aggressiveness of MTC depends on the hereditary setting in which it develops. With the availability of genetic testing for *RET* variants, MTC has become one of the few malignancies that can be prevented by *prophylactic thyroidectomy*.

The age at which prophylactic thyroidectomy is recommended is determined based on the specific *RET* variant, serum calcitonin levels, and parent and child preference.

The **primary therapy** for thyroid cancer, regardless of histologic type, is thyroidectomy and, if there is evidence of lymph node metastasis, a compartment-oriented lymph node dissection performed by a highly experienced thyroid cancer surgeon. In **DTC**, adjuvant radioactive iodine (^{131}I) may be used postoperatively to treat iodine-avid distant metastasis and unresectable residual neck disease. The use of ^{131}I is limited to children at higher risk for residual or recurrent disease who are most likely to benefit from treatment. Children with **MTC** do not require ^{131}I therapy.

In children with DTC, the TSH level is initially suppressed by giving supraphysiologic levothyroxine, because TSH may stimulate DTC tumor growth; the TSH level is kept normal in MTC.

Oral multikinase inhibitors and oncogene-targeted therapy (for children with tumors driven by *BRAF*, *RET*, or *NTRK* substitutions or oncogenic fusions) have demonstrated benefit for the treatment of advanced MTC and DTC in adults. These are rarely indicated in pediatric patients but may be considered for symptomatic and/or progressive disease.

Long-term follow-up of thyroid cancer survivors involves monitoring of tumor markers (thyroglobulin/thyroglobulin antibody in DTC, calcitonin/carcinogenic embryonic antigen in MTC) and routine imaging, primarily neck US.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

555.2 Nasopharyngeal Carcinoma

Cynthia E. Herzog

Nasopharyngeal carcinoma is rare in the pediatric population, but it is one of the most common nasopharyngeal tumors in pediatric patients. In adults, the incidence is highest in South China, but it is also high among the Inuit people and in North Africa and Northeast India. In China, this diagnosis is rare in the pediatric population, but in other populations, a substantial proportion of cases occur in the pediatric age-group, primarily in adolescents. It occurs in males twice as often as in females and is more common in Black people. In the pediatric population, the tumors are more frequently of undifferentiated histology and associated with **Epstein-Barr virus (EBV)**. Nasopharyngeal carcinoma is associated with specific human leukocyte antigen (HLA) types; other genetic factors may play a role, especially in low-incidence populations.

Most pediatric patients present with advanced locoregional disease manifesting as cervical lymphadenopathy. Epistaxis, trismus, and cranial nerve deficits also may be present. The diagnosis is established from biopsy of the nasopharynx or cervical lymph nodes. In most cases the lactate dehydrogenase level is elevated, but this finding is nonspecific. CT or MRI evaluation of the head and neck is performed to determine the extent of locoregional disease. Chest radiography, CT, bone scan, and liver scan are used to evaluate for metastatic disease. PET scans appear to be useful for monitoring primary disease and looking for metastases. EBV DNA levels correlate with disease stage, have prognostic value, and can be used to monitor for recurrence.

Treatment is a combination of chemotherapy and irradiation. Cisplatin, given concurrently with radiation, with either neoadjuvant or adjuvant cisplatin-based chemotherapy, is the standard treatment. The outcome depends on the extent of disease; patients with distant metastases have a very poor prognosis. Using intensity-modulated radiation therapy improves local control and reduces the late adverse effects associated with radiation therapy, including hormonal dysfunction, dental caries, fibrosis, and second malignancies. Use of proton therapy may result in further reduction of adverse effects.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

555.3 Adenocarcinoma of the Colon and Rectum

Cynthia E. Herzog and Winston W. Huh

Colorectal carcinoma (CRC) is rare in the pediatric population, with an estimated incidence rate of approximately one case per 1 million. Even in patients with predisposing conditions, CRC usually does not present until late adolescence or adulthood; only 35–40% of CRC in this age-group are association with a known predisposition factor. **Hereditary nonpolyposis colon cancer (HNPCC) (Lynch Syndrome)** is an autosomal dominant disorder, with germline pathogenic variants in DNA mismatch repair genes *(MMR)* causing DNA repair errors and microsatellite instability (MSI). *MYH*-associated polyposis, Peutz-Jeghers syndrome, and juvenile polyposis also predispose to CRC.

Genetic testing is available, and screening for cancer in HNPCC and familial adenomatous polyposis (FAP) should begin during childhood or adolescence. Likewise, genetic evaluation for these conditions should be pursued in young patients presenting with colon cancer, even when there is no history of predisposing genetic conditions.

Presenting symptoms include bloody stools or melena, abdominal pain, weight loss, and changes in bowel patterns. In many cases, signs are vague, often resulting in a delay in diagnosis, sometimes not until the disease has reached an advanced stage. The histologic subtype differs from that seen in adults, with most pediatric tumors being either mucinous adenocarcinoma or signet ring cell carcinoma. Pediatric patients tend to have tumors with MSI and tend to present with more advanced disease. Treatment is based on guidelines used in adults with CRC and consists of surgical resection when possible with chemotherapy for unresectable tumors. Adequate lymph node removal should be performed at surgical resection of primary tumor. Radiation therapy is useful in select cases. Pediatric patients have a worse overall prognosis compared with adult patients, but the reasons for this discrepancy are not clear.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

555.4 Adrenal Tumors

Jonathan D. Wasserman

See Chapters 617-621.

The adrenal gland is comprised of two embryologically distinct layers, the steroid-secreting outer cortex and the catecholamine-secreting inner medulla. **Adrenocortical tumors (ACTs)** arise from the cortex, whereas pheochromocytomas (**PHEOs**) derive from the chromaffin cells of the adrenal medulla. Additionally, catecholaminergic tumors arising from the parasympathetic and sympathetic ganglia *outside* the adrenal medulla are called **paragangliomas (PGLs)**. Both ACTs and PHEOs are strongly associated with hereditary tumor predisposition syndromes, and thus diagnosis of either in childhood should initiate a thorough family history and referral to an expert in cancer genetics for counseling and germline testing.

ACTs are very rare and, in children, tend to present before age 10 years. They have a female predominance and are functional (hormone secreting) in >90% of cases, primarily producing androgens and/or glucocorticoids and causing clinically apparent **virilization** with or without **Cushing syndrome** (see Chapter 619). ACTs may also present as an abdominal mass or pain. In children, ACTs are most frequently associated with **Li-Fraumeni syndrome** (germline inactivating variants in the *TP53* tumor-suppressor gene) and **Beckwith-Wiedemann syndrome** (BWS), but they can also be seen in hemihyperplasia other than that seen as part of BWS, MEN1, McCune-Albright syndrome, FAP, and very rarely, congenital adrenal hyperplasia. Unusual causes of bilateral nodular adrenocortical disease, which also typically present with Cushing syndrome, include the Carney complex and macronodular adrenocortical hyperplasia.

PHEOs/PGLs are rare tumors that are more likely to be bilateral, malignant, and secondary to a heritable tumor syndrome when diagnosed in childhood compared with adulthood (see Chapter 621). **Von Hippel-Lindau disease** is the most common genetic association in the pediatric population, followed by the **familial PGL syndromes (1, 2, 3, 4)** caused by variants in the succinate dehydrogenase *(SDHx)* genes. MEN2 (types 2A and 2B) and neurofibromatosis type 1 *(NF1)* are also included in the differential diagnosis but are more often associated with a PHEO diagnosis during adulthood (Table 555.2). Overall, germline pathogenic variants in at least 16 different genes have been associated with predisposition to PHEO/PGL. PHEO/PGL is also associated with congenital cyanotic heart disorders (somatic gain-of-function variant in *EPAS1*). *Hypertension is usually sustained* in pediatric patients with PHEO/PGL, who may also lack the triad of intermittent headache, palpitations, and diaphoresis typically seen in adults. Nonetheless, PHEO/PGL accounts for <1% of pediatric hypertension. Additional manifestations may include chest pain, pallor, tremor, fever, cardiomyopathy, or exacerbations with exercise; flushing is not typical of PHEO/PGL. The differential diagnosis is noted in Table 555.3. The most appropriate screening test for PHEO/PGL is measurement of fractionated plasma and/or urine **metanephrine** levels. Initial imaging studies, when metanephrine levels are elevated, include CT or MRI. When indicated, to confirm abnormal biochemistry and/or cross-sectional imaging, ^{18}F-DOPA and ^{68}Ga-DOTATATE (DOTA-octreotate) PET/MRIs are the functional imaging modalities of choice given greater sensitivity and specificity than earlier radioisotopes (Fig. 555.2). ^{131}I-Metaiodobenzyguanidine (MIBG) imaging may also be considered in such circumstances.

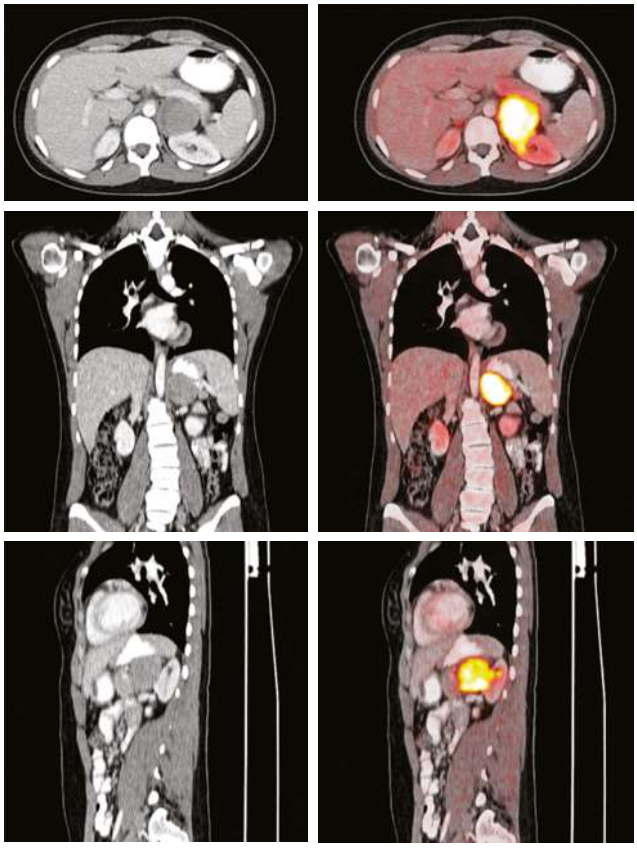

Fig. 555.2 Appearance of pheochromocytoma on functional imaging (^{18}F-l -dihydroxyphenylalanine [^{18}F-DOPA] PET/CT). Focal uptake is seen in the left suprarenal fossa. *(From Duh QY, Livhits M, Yeh MW. The adrenal glands. In: Mattox KL, Townsend CM, Beauchamp RD, Evers BM, eds. Sabiston Textbook of Surgery. 21st ed. Philadelphia: Elsevier; 2022. Fig. 40.18A.)*

Table 555.2 Germline Pathogenic Variants Associated with Pheochromocytoma and Paraganglioma

SYNDROME/NAME	GENE	TYPICAL TUMOR LOCATION AND OTHER ASSOCIATIONS
HYPOXIC PATHWAY: CLUSTER 1*		
SDHD (familial paraganglioma type 1)†	*SDHD*	Primarily skull base and neck; occasionally adrenal medulla, mediastinum, abdomen, pelvis; GIST; possible pituitary adenoma
SDHAF2 (familial paraganglioma type 2)†	*SDHAF2*	Primarily skull base and neck; occasionally abdomen and pelvis
SDHC (familial paraganglioma type 3)	*SDHC*	Primarily skull base and neck; occasionally abdomen, pelvis, or chest; GIST; possible pituitary adenoma
SDHB (familial paraganglioma type 4)	*SDHB*	Abdomen, pelvis, and mediastinum; rarely adrenal medulla, skull base, and neck; GIST; renal cell carcinoma; possible pituitary adenoma
SDHA	*SDHA*	Primarily skull base and neck; occasionally abdomen and pelvis; GIST; possible pituitary adenoma
VHL disease	*VHL*	Adrenal medulla, frequently bilateral; occasionally paraganglioma that may be localized from skull base to pelvis
Hereditary leiomyomatosis and renal cell carcinoma (Reed syndrome)—fumarate hydratase variant	*FH*	Multifocal and metastatic; associated with hereditary leiomyomatosis, uterine fibroids, and renal cell cancer
Hypoxia-inducible factor (HIF) 2α	*HIF2A*	Paraganglioma, polycythemia, and rarely somatostatinoma
Familial erythrocytosis associated with pathogenic variant in prolyl hydroxylase isoform 1 (PDH1)	*EGLN2*	Polycythemia associated with pheochromocytoma and paraganglioma
Familial erythrocytosis associated with pathogenic variant in prolyl hydroxylase isoform 2 (PDH2)	*EGLN1*	Polycythemia associated with pheochromocytoma and paraganglioma
KIF1B	*KIF1B*	Neuroblastoma
KINASE SIGNALING PATHWAY: CLUSTER 2‡		
MEN2A and MEN2B	*RET*	Adrenal medulla, frequently bilateral
Neurofibromatosis type 1 (NF1)	*NF1*	Adrenal or periadrenal
MAX†	*MAX*	Adrenal medulla
Familial pheochromocytoma	*TMEM127*	Adrenal medulla; possible renal cell carcinoma

*Cluster 1 tumors are mostly extraadrenal paragangliomas (except in VHL, where most tumors are localized to the adrenal) and nearly all have a noradrenergic biochemical phenotype.
†Associated with maternal imprinting.
‡Cluster 2 tumors are usually adrenal pheochromocytomas with an adrenergic biochemical phenotype.
GIST, Gastrointestinal stromal tumor; MEN, multiple endocrine neoplasia; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease.
Modified from Melmed S, Auchus RJ, Goldfine AB, et al., eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2020: Table 16.4, p. 550.

Table 555.3 Differential Diagnosis of Pheochromocytoma-Type Spells

ENDOCRINE CAUSES
Carbohydrate intolerance
Hyperadrenergic spells
Hypoglycemia
Pancreatic tumors (e.g., insulinoma)
Pheochromocytoma
Thyrotoxicosis
CARDIOVASCULAR CAUSES
Orthostatic hypotension
Paroxysmal cardiac arrhythmia
Pulmonary edema
Renovascular disease
Syncope (e.g., vasovagal reaction)
PSYCHOLOGIC CAUSES
Factitious (e.g., drugs, Valsalva maneuver)
Hyperventilation
Severe anxiety and panic disorders
Somatization disorder
PHARMACOLOGIC CAUSES
Chlorpropamide-alcohol flush
Combination of a monoamine oxidase inhibitor and a decongestant
Illegal drug ingestion (cocaine, phencyclidine, lysergic acid diethylamide)
Sympathomimetic drug ingestion
Vancomycin (red man syndrome)
Withdrawal of adrenergic inhibitor
NEUROLOGIC CAUSES
Autonomic neuropathy
Diencephalic epilepsy (autonomic seizures)
Migraine headache
Postural orthostatic tachycardia syndrome
Stroke
OTHER CAUSES
Carcinoid syndrome
Mast cell disease
Recurrent idiopathic anaphylaxis
Unexplained flushing spells

Modified from Melmed S, Auchus RJ, Goldfine AB, et al., eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2020: Table 16.3, p. 547.

The initial treatment of ACT and PHEO/PGL is *resection by a surgeon experienced in the management of these tumors.* Children with suspected or confirmed PHEO/PGL require preoperative medical management with α-adrenergic blockade (and sometimes β-blockade) to mitigate risk of hypertensive crisis.

Medical therapy for metastatic ACT includes mitotane and chemotherapy with cisplatin, etoposide, and doxorubicin. Endocrine therapy targeting hormonal overproduction may also be needed to palliate symptoms and improve quality of life. Metastatic PHEO/PGL has historically been poorly responsive to cytotoxic chemotherapy. Kinase inhibitor therapy and peptide-receptor radiotherapy (such as ^{177}Lu-DOTATATE) have demonstrated promise in some studies.

Long-term follow-up is warranted for both ACTs and PHEOs to monitor for recurrence, particularly in the context of hereditary tumor predisposition syndromes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

555.5 Desmoplastic Small Round Cell Tumor

Cynthia E. Herzog

Desmoplastic small round cell tumor **(DSRCT)** is a very rare and aggressive mesenchymal tumor that occurs predominantly in adolescent and young adult males. It is associated with a diagnostic chromosomal translocation between the Ewing tumor gene and the Wilms tumor gene, t(11;22) (p13;q12), creating a chimeric gene *(EWS-WT1)* that encodes a chimeric protein with oncogenic properties. Patients typically present at advanced stage with a bulky abdominal mass, multiple peritoneal and omental implants, and symptoms of abdominal sarcomatosis, including pain, ascites, intestinal obstruction, hydronephrosis, and weight loss. DSRCT mainly involves the abdominal cavity but can spread to the lymph nodes, liver, lungs, and bones, and in ~10% of cases, arise outside of the abdomen. There is no standard treatment approach. Aggressive treatment with combination chemotherapy, debulking surgery, and whole abdominopelvic irradiation results almost universally in a poor outcome. Median survival ranges between 17 and 25 months, and the 5-year overall survival remains <20%. Hyperthermic intraperitoneal chemotherapy may be of benefit but requires further study. Novel targeted agents and radioimmunotherapy with monoclonal antibodies targeting different surface antigens on tumor cells are being studied.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 556
Histiocytosis Syndromes of Childhood

Stephan Ladisch

INTRODUCTION

Childhood histiocytoses constitute a diverse group of disorders that are frequently severe in their clinical expression. These disorders are individually rare and are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte-macrophage system of bone marrow (myeloid) origin. Although these disorders sometimes are difficult to distinguish clinically, accurate diagnosis is essential for facilitating progress in treatment. A current systematic classification of histiocytoses is based on histopathologic, clinical, and genetic findings (Tables 556.1-556.3) A thorough, comprehensive evaluation of a biopsy specimen obtained at diagnosis is critical. This evaluation includes studies such as immunostaining, molecular genetic analyses, and electron microscopy that may require special sample processing.

CLASSIFICATION AND PATHOLOGY

Three classes of childhood histiocytosis are defined, based on histopathologic findings. The first and best known is **Langerhans cell histiocytosis (LCH)**, previously called *histiocytosis X.* LCH includes the clinical entities of bone or skin limited disease (**eosinophilic granuloma**), **Hand-Schüller-Christian disease,** and **Letterer-Siwe disease.** The normal Langerhans cell is an antigen-presenting cell (APC) of the skin. The hallmark of LCH in all forms is the presence of a clonal proliferation of cells of the monocyte–dendritic cell lineage containing the characteristic electron microscopic findings of a Langerhans cell, the **Birbeck granule**. This tennis racket–shaped bilamellar granule, when seen in the cytoplasm of lesional cells in LCH, is diagnostic of the disease. The Birbeck granule expresses a newly characterized antigen, *langerin* (CD207), which itself is involved in antigen presentation to T lymphocytes. CD207 expression has been established to be uniformly present in LCH lesions and thus becomes an additional reliable diagnostic marker. However, it is now clear that the LCH cell is not actually a (differentiated) Langerhans cell but rather an immature cell of myeloid origin, possibly in an arrested state of development. The definitive diagnosis of LCH is established by demonstrating CD1a positivity of lesional cells, which can be done using fixed tissue (Fig. 556.1). Lesional cells must be distinguished from normal Langerhans cells of the skin, which are also CD1a positive but are only sparsely distributed and are not diagnostic of LCH. The peripheral lesions usually leading to the diagnosis of LCH (e.g., skin, lymph node, bone) contain various proportions of Birbeck granule–containing CD1a-positive cells, lymphocytes, granulocytes, monocytes, and eosinophils.

Clonality of individual lesions exists in some cases of LCH. Importantly, an activating *somatic* pathogenic variant of the *BRAF* gene *(V600E)* (part of the mitogen-activated protein kinase [MAPK] cell signaling pathway: Fig. 556.2) has been identified in many patients with LCH. Studies in patients negative for *BRAFV600E* have revealed pathogenic variants in other genes of the MAPK pathway, including *MAP2K1* and *ARAF.* With the majority of LCH patients having one or another of these activating variants in the MAPK pathway (see Fig. 556.2), it has been suggested that LCH is driven by a disorder in MAPK signaling affecting cell migration and resulting in an accumulation of LCH cells in the lesions.

In contrast to the prominence of an APC in LCH, the other common form of histiocytosis is characterized by accumulation of activated macrophages and lymphocytes and is known as **hemophagocytic lymphohistiocytosis (HLH)**. This diagnosis is the result of uncontrolled hemophagocytosis and uncontrolled activation (upregulation) of inflammatory cytokines driven by an abnormality of T cells. It has some similarities to the **macrophage activation syndrome**. Tissue infiltration by activated CD8 T lymphocytes, activated macrophages, and hypercytokinemia are classic features (Fig. 556.3). With the characteristic morphology of normal macrophages by light microscopy, these phagocytic cells (see Fig. 556.1) are CD163 positive but negative for the markers that are characteristic of LCH cells (Birbeck granules, CD1a, CD207).

The two major forms of HLH, primary and secondary, have indistinguishable pathologic findings but are important to differentiate because of implications for treatment and prognosis. **Primary HLH**, originally named *familial erythrophagocytic lymphohistiocytosis,* is now known as **familial hemophagocytic lymphohistiocytosis (FHLH)**. This disease is an autosomal recessive disorder and represents approximately 25% of patients with HLH (see Table 556.3).

Table 556.1 Main Types of Histiocytosis Disease

DISEASE	HISTIOCYTOSIS CLASSIFICATION GROUP
LANGERHANS CELL HISTIOCYTOSIS	L
Single system	L
Pulmonary	L
Multisystem with no risk organ involvement	L
Multisystem with risk organ involvement	L
ERDHEIM-CHESTER DISEASE	L
Mixed H	L
Indeterminate H	L
Extracutaneous/disseminated JXG with MAPK pathogenic variant (including LALK + H. and other genetic alterations)	L
ROSAI-DORFMAN-DESTOMBES DISEASE	R
Familial	R
Sporadic classical with or without IgG4 infiltration	R
Sporadic extranodal with or without IgG4 infiltration	R
MALIGNANCY HISTIOCYTOSES	M
Primary, phenotypic subtypes	M
Secondary, phenotypic subtypes	M
Histiocytoses with cutaneous or mucosal involvement	C
LYMPHOHISTIOCYTOSES	M
Primary	M
Sporadic	M
Unknown	M

L, Langerhans; R, Rosai-Dorfman-Destombes; M, Malignant, C, cutaneous; H, hemophagocytic; JXG, juvenile xanthogranuloma; MAPK: mitogen-activated kinase.
From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. *Lancet*. 2021;398:157–168. Supplementary Appendix, Table 1.

Genes are known for four of five familial HLH syndromes and other hereditary causes of HLH; these pathogenic variants affect the ability of T lymphocytes and natural killer (NK) cells to synthesize and release perforin and granzymes, thus reducing cytotoxic granule formation (Fig. 556.4). **Secondary HLH** includes other forms of the syndrome triggered by a separate pathologic process, such as infection *(infection-associated hemophagocytic syndrome),* tumor *(malignancy-associated HLH),* or primary immunodeficiency diseases and metabolic disorders (Tables 556.4 and 556.5). Both primary and secondary HLH affect multiple organs and are characterized by massive infiltrates of hyperactivated lymphocytes and activated phagocytic macrophages in the involved organs, with the lymphocytes serving as the driver of the resulting disease process.

In primary HLH, genetic pathogenic variants in multiple different steps in granule formation and release by cytotoxic T cells have been identified (Fig. 556.5, *bottom*). Pathogenic variants in the *PRF1* perforin gene or the *MUNC13-4* gene are the most common causes of defective function of the cytotoxic lymphocytes whose activity is inhibited in primary HLH. In an analogous way, a trigger can result in secondary HLH (see Fig. 556.5, *top*). A myriad of both infectious and noninfectious processes can trigger secondary HLH (Fig. 556.6; see Table 556.4 and Fig. 556.11). Examples of noninfectious triggers include drugs (e.g., phenytoin, Lamictal, highly active antiretroviral therapy), hematopoietic stem cell transplantation, chemotherapy, autoimmune diseases, inflammatory bowel disease, cancer, and immunodeficiency states (e.g., DiGeorge syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, chronic granulomatous disease). A complicating factor in diagnosis is the realization that there are also both mixed genetic variants causing primary HLH and heterozygotic variants (therefore not strictly primary HLH) also causing disease, particularly triggered by infection.

In addition to these two most common forms of childhood histiocytosis (LCH and HLH), rarer diseases are included under this rubric (see Table 556.2). **Juvenile xanthogranuloma (JXG)** is characterized by vacuolated histiocytes with foamy cytoplasm in lesions that evolve into mixed granulomas also containing eosinophils, lymphocytes, and other cells. **Erdheim-Chester disease (ECD)** predominantly affects adults. Surface markers suggest a link among LCH, JXG, and ECD; all three are dendritic cell diseases, and represent a spectrum, or continuum, of differentiation stages of the abnormal dendritic cell precursors, frequently with *BRAFV600E* pathogenic variants in the affected cells. Another rare form of histiocytosis is **Rosai-Dorfman disease**, also known as **sinus histiocytosis** with massive lymphadenopathy. Rosai-Dorfman disease is characterized by packing of sinusoids of the lymph nodes with hemophagocytic histiocytes, although extranodal involvement may also be present. Last, there is a group of unequivocal **malignancies** of cells of monocyte–macrophage lineage. By this definition, acute monocytic leukemia and true malignant histiocytosis are included among the class III histiocytoses (see Chapter 544). True neoplasms of Langerhans cells have been reported but are extremely rare.

556.1 Langerhans Cell Histiocytosis

Stephan Ladisch

CLINICAL MANIFESTATIONS

LCH has an extremely variable presentation. The skeleton is involved in 80% of patients and may be the only affected site, especially in children >5 years old. **Bone lesions (eosinophilic granuloma)** may be single or multiple and are seen most often in the skull (Fig. 556.7). Other sites include the pelvis, femur, vertebra, maxilla, and mandible. Lesions may be asymptomatic or associated with pain and local swelling. Involvement of the spine may result in collapse of the vertebral body, which can be seen radiographically and may cause secondary compression of the spinal cord. In flat and long bones, osteolytic lesions with sharp borders occur, and no evidence exists of reactive new bone formation until the lesions begin to heal. Lesions that involve weight-bearing long bones may result in pathologic fractures. Chronically draining, infected ears are usually associated with destruction in the mastoid area. Bone destruction in the mandible and maxilla may result in teeth that appear to be free floating on radiographs. With response to therapy, healing of bone lesions is usually complete.

Approximately 50% of patients experience **skin involvement** (isolated or part of multisystem disease) at some time during the course of disease. This is a frequently difficult-to-treat scaly, papular, seborrheic dermatitis of the scalp, diaper, axillary, or posterior auricular regions (see Fig. 556.7; Figs. 556.8 and 556.9). The lesions may spread to involve the back, palms, and soles. The exanthem may be petechial or hemorrhagic, even in the absence of thrombocytopenia. Localized or disseminated **lymphadenopathy** is present in approximately 33% of patients. **Hepatosplenomegaly** occurs in approximately 20% of patients. Various degrees of hepatic malfunction may occur, including jaundice and ascites.

Gastrointestinal involvement, more common than previously appreciated**,** can present as vomiting, abdominal pain, bloody diarrhea, and/or failure to thrive.

Exophthalmos, when present, may be bilateral and is caused by retroorbital accumulation of granulomatous tissue. Gingival mucous membranes may be involved with infiltrative lesions that appear superficially like candidiasis. Otitis media is present in 30–40% of patients; deafness may follow

Table 556.2 Clinical Features, Investigations, and Treatment of Langerhans Cell Histiocytosis, Erdheim-Chester Disease, and Rosai-Dorfman-Destombes Disease

	MOST FREQUENT REVEALING CLINICAL FEATURES	INITIAL INVESTIGATIONS* WHEN DIAGNOSIS IS CONFIRMED BY BIOPSY	MOST FREQUENT FIRST-LINE SYSTEMIC THERAPIES FOR MULTIORGAN OR DISSEMINATED FORMS	MOST FREQUENT SYSTEMIC SECOND-LINE AND SALVAGE THERAPIES
Childhood Langerhans cell histiocytosis	Bone pain or fracture; vertebra plana†; skin papules; lymphadenomegaly; palpable tumor; diabetes insipidus†; exophthalmos†; deafness or chronic otorrhea; systemic symptoms with fever, hepatosplenomegaly, or hematologic cytopenia (risk organs); pneumothorax	For all patients: blood tests (full blood count, erythrocyte sedimentation rate or CRP, albumin, renal function tests, liver function tests, coagulation tests); chest and skeletal radiographs According to initial investigations: CT scan or MRI focused on involved area; brain MRI when diabetes insipidus or any sign of CNS involvement or visual or hearing dysfunction; chest high-resolution CT scan when signs of lung involvement	Vinblastine combined with corticosteroids	Should be decided according to initial extension and risk-organ involvement status, as assessed by a trained team With risk organ involvement: BRAF or MEK inhibitors‡ Without risk organ involvement: monotherapy or combined chemotherapies with cladribine, and, in less documented approaches, cytarabine or clofarabine
Adult Langerhans cell histiocytosis	Bone pain or fracture; skin papules; lymphadenopathy; palpable tumor; diabetes insipidus†; exophthalmos†; repeated dental loss; pneumothorax; dyspnea, dry cough	^{18}F-FDG-PET (full body); chest, abdomen, and pelvis CT scan; brain MRI; blood tests (full blood count, CRP, albumin, renal function tests, liver function tests)	Cytarabine, alone or combined with methotrexate; vinblastine combined with corticosteroids; cladribine	BRAF or MEK inhibitors
Erdheim-Chester disease	Lower limb pain; general symptoms (fatigue, weight loss, fever); xanthelasma; diabetes insipidus†; exophthalmos†; dyspnea, dry cough; signs of cardiac involvement (e.g., tamponade); signs of CNS involvement (degenerative or tumoral)	^{18}F-FDG-PET (full body); chest, abdomen, and pelvis CT scan; brain MRI; cardiac MRI; blood tests (full blood count, CRP, albumin, renal function tests, liver function tests)	Interferon alfa-2a or pegylated interferon alfa-2a; other potential options are anakinra, infliximab, or sirolimus plus corticosteroids; BRAF or MEK inhibitors for life-threatening cases (e.g., CNS or heart involvement)	BRAF or MEK inhibitors
Rosai-Dorfman-Destombes disease	Lymphadenopathy; skin nodules; nasal obstruction, epistaxis, nasal dorsum deformity; dyspnea, dry cough; signs of CNS or nerve root involvement; testicular enlargement	Children: chest x-ray with neck and abdominal ultrasound scans Adults: neck, chest, abdomen, and pelvis CT scan; ^{18}F-FDG-PET is recommended by some experts All patients: brain MRI when signs of orbital or CNS involvement; blood tests (full blood count, CRP, albumin, renal function tests, liver function tests)	Corticosteroids; sirolimus; methotrexate; azathioprine	Several drugs or combined chemotherapies or MEK inhibitors reported to be active in case reports or small case series

^{18}F-FDG-PET, ^{18}F-fluorodeoxyglucose PET; CNS, central nervous system..
*Aimed to determine the extent of the disease; thus each clinical feature drives specific investigation of the potentially involved organ(s), including for any signs of endocrine dysfunction or autoimmunity.
†Features that are suggestive of the disease.
‡BRAF inhibitors: vemurafenib, dabrafenib, encorafenib. MEK inhibitors: cobimetinib, trametinib, binimetinib, selumetinib.
From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. *Lancet*. 2021;398:157–168. Fig. 1, p. 158.

destructive lesions of the middle ear. In 10–15% of patients, **pulmonary infiltrates** are found on radiography. The lesions may range from diffuse fibrosis and disseminated nodular infiltrates to diffuse cystic changes (Fig. 556.10). Rarely, pneumothorax is a complication. If the lungs are severely involved, tachypnea and progressive respiratory failure may result.

Pituitary dysfunction or hypothalamic involvement in patients often presents as diabetes insipidus and may also cause growth retardation. Patients suspected of having LCH should demonstrate the ability to concentrate their urine before going to the operating room for a biopsy. Rarely, panhypopituitarism may occur, as may primary hypothyroidism as a result of thyroid gland infiltration.

Patients with multisystem disease who are affected more severely are those who have systemic manifestations, including fever, weight loss, malaise, irritability, and failure to thrive. These systemic manifestations will distinguish patients at high risk of mortality (i.e., risk organ–positive, or RO+, patients) from patients at low risk of mortality (i.e., without systemic

Table 556.3 Hemophagocytic Lymphohistiocytosis

DISEASE	GENE	PROTEIN	PERCENTAGE OF FHLH	IMMUNE IMPAIRMENT	UNIQUE CLINICAL CHARACTERISTICS
FHLH-1	Unknown		Rare	Cytotoxicity	
FHLH-2	*PRF1*	Perforin	~20–37, 50delT mainly in African American/ African descent	Cytotoxicity; forms pores in APCs	
FHLH-3	*UNC13D*	Munc13–4	20–33	Cytotoxicity; vesicle priming	Increased incidence of CNS HLH
FHLH-4	*STX11*	Syntaxin	<5	Cytotoxicity; vesicle fusion	Mild recurrent HLH, colitis
FHLH-5	*STXBP2*	Syntaxin-binding protein 2	5–20	Cytotoxicity; vesicle fusion	Colitis, hypogammaglobulinemia
SYNDROMES WITH PARTIAL OCULOCUTANEOUS ALBINISM					
Griscelli syndrome	*RAB27A*	Rab27A	~5	Cytotoxicity; vesicle docking	Partial albinism, silver-gray hair
Chédiak-Higashi syndrome	*LYST*	Lyst	~2	Cytotoxicity; heterogeneous defects in NK cells	Partial albinism, bleeding tendency, recurrent infections
Hermansky-Pudlak syndrome type II	*AP3B1*	AP-3 complex subunit β_1	Rare	Cytotoxicity; vesicle trafficking	Partial albinism, bleeding tendency
EBV-DRIVEN AND RARE CAUSES					
XLP1	*SH2D1A*	SAP	~7	Signaling in cytotoxic NK and T cells	Hypogammaglobulinemia, lymphoma
XLP2	*BIRC4*	XIAP	~2	NK T-cell survival and NF-κB signaling	Mild recurrent HLH, colitis
ITK deficiency	*ITK*	ITK	Rare	IL-2 signaling in T cells	Hypogammaglobulinemia, autoimmunity, Hodgkin lymphoma
CD27 deficiency	*CD27*	CD27	Rare	Signal transduction in lymphocytes	Combined immunodeficiency, lymphoma
XMEN syndrome	*MAGT1*	MAGT1	Rare	Magnesium transporter, induced by TCR stimulation	Lymphoma, recurrent infections, CD4 T-cell lymphopenia
NLRC4 GOF	*NLRC4* Somatic or germline variants	NLRC4 inflammasome	Rare	↑ IL-18	Responds to recombinant IL-18BP
CDC42	*CDC42*	CDC42	Rare	↑ IL-18, variants interfere with binding and localization of CDC42	Neonatal cytopenias, hepatosplenomegaly, fevers, urticaria-like rashes, facial dysmorphisms
CD70	*CD70*	CD70 interaction with CD27	Rare	↓ expression and ↓ cytotoxicity of T cells	EBV susceptibility to HLH
CTPS1	*CTPS1*	Cytidine nucleotide triphosphate synthesis	Rare	Impaired proliferation of NKT cells	EBV susceptibility
RASGRP1	*RASGRP1*	RASGRP1	Rare	Activates RAS; defects in T-cell activation, migration, proliferation ↓ cytotoxicity ↓ NKT cells	EBV susceptibility to HLH

APCs, Antigen-presenting cells; CNS, central nervous system; EBV, Epstein-Barr virus; FHLH, familial hemophagocytic lymphohistiocytosis; GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; ITK, interleukin (IL)-2–inducible T-cell kinase; NF-κB, nuclear factor–kappa B; NK, natural killer; TCR, T-cell receptor; XLP-1, 2-X-linked lymphoproliferative diseases.

Adapted from Erker C, Harker-Murray, Talano JA. Usual and unusual manifestations of familial hemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. *Pediatr Clin North Am.* 2017;64:91–109. Table 1.

manifestations; risk organ–negative patients). The **risk organs** are liver, spleen, and the hematopoietic (bone marrow) system. The lung is not considered a risk organ. The distinction of risk-organ involvement is important for deciding the intensity of the treatment approach and has been addressed in standard treatment approaches for LCH, as delineated in the Histiocyte Society protocols. Bone marrow involvement may cause anemia and thrombocytopenia. Two uncommon but serious manifestations of LCH are hepatic involvement (leading to fibrosis and cirrhosis) and a peculiar central nervous system (CNS) involvement characterized by ataxia, dysarthria, and other neurologic symptoms. **Hepatic involvement** is associated with multisystem disease that is often already present at diagnosis. In contrast, neurodegenerative **CNS involvement**, which is progressive and

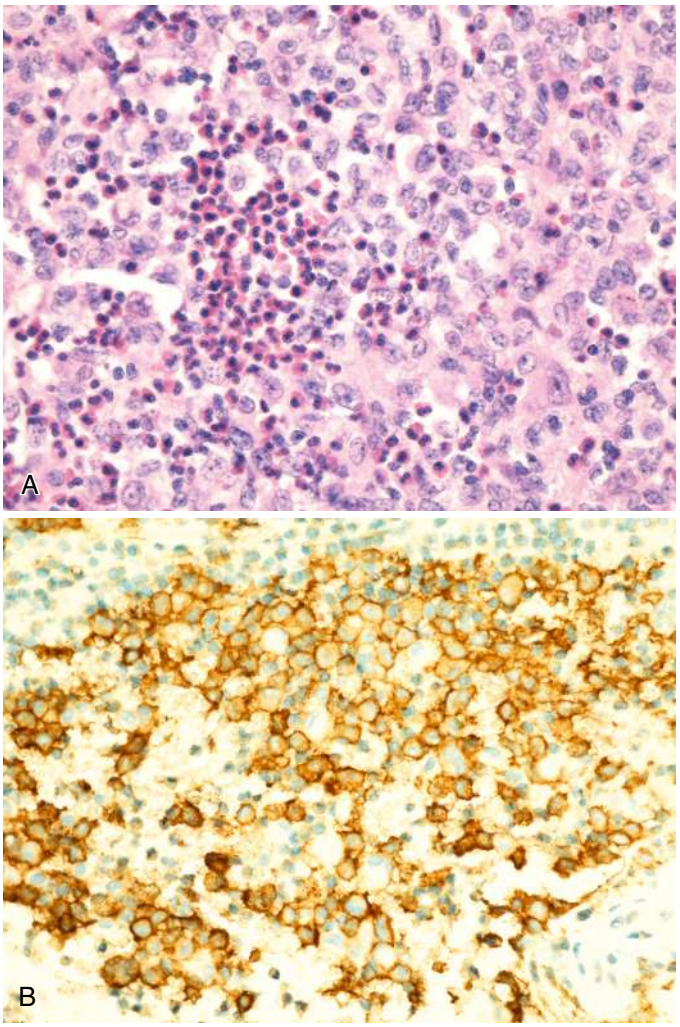

Fig. 556.1 A, Histopathology of Langerhans cell histiocytosis (LCH) shows eosinophilic granuloma of a lytic bone lesion of the femoral head. Multiple LCH cells with characteristic grooved nuclei, as well as numerous eosinophils, are visible in this mixed infiltrate. B, CD1a staining, characteristic and diagnostic of lesions with LCH cells.

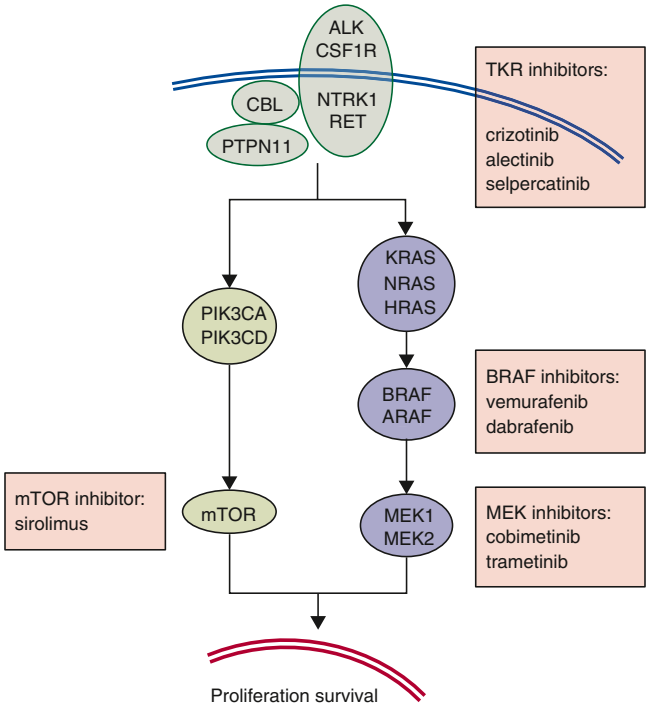

Fig. 556.2 Proteins of the MAP kinase cell-signaling pathway involved by activating pathogenic variants, and inhibitors already reported to benefit patients with histiocytosis. *(From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. Lancet. 2021;398:157–168. Fig. 1.)*

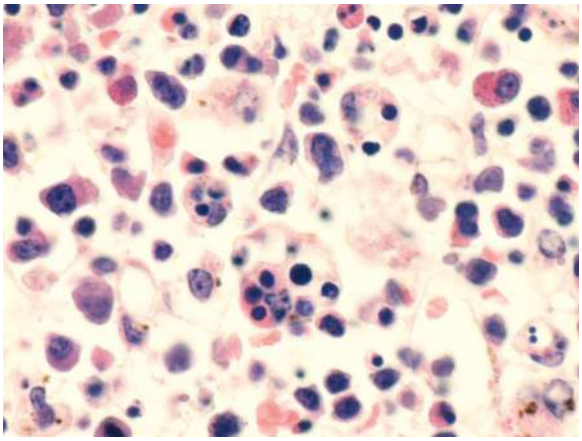

Fig. 556.3 Bone marrow aspirate of a child with familial (genetically confirmed) hemophagocytic lymphohistiocytosis. Numerous characteristic hemophagocytic cells (which are CD163-positive macrophages) are seen ingesting various blood elements.

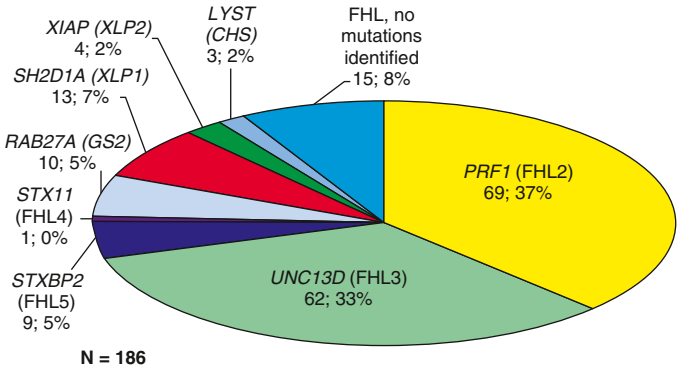

Fig. 556.4 Different genetic subtypes in 171 patients with familial hemophagocytic lymphohistiocytosis (FHL) or FHL-related disease. For each subtype, the name of the gene, the abbreviation of the disease subtype, the absolute number, and the percentage are shown. Furthermore, we include as FHL one subgroup of 15 patients with either familial recurrence or refractory/recurrent disease despite specific therapy and/or repeatedly documented severe functional defect in degranulation or cytotoxicity assays. *(From Cetica V, Sieni E, Pende D, et al. Genetic predisposition to hemophagocytic lymphohistiocytosis: Report on 500 patients from the Italian registry. J Allergy Clin Immunol. 2016;137:188–196. Fig. 2, p. 191.)*

histopathologically characterized by gliosis and has no definitive treatment, may be observed only many years after the initial diagnosis of LCH. These manifestations are not known to be associated with LCH cells, Birbeck granules, CD1a positivity, or any other indication of LCH cell infiltration, raising questions about their pathogenesis and the suggestion that they may be cytokine-mediated.

After tissue biopsy, which is diagnostic of LCH and is easiest to perform on skin or bone lesions, a comprehensive clinical and laboratory evaluation is essential and should be undertaken. This should include a series of studies in all patients: CBC, liver function tests, coagulation studies, skeletal survey, chest radiograph, and measurement of urine osmolality. In addition, detailed evaluation of any organ system shown to be involved by physical examination or by these studies should be performed to establish the extent of disease before initiation of treatment.

TREATMENT AND PROGNOSIS

The clinical course of **single-system disease** (usually bone, lymph node, or skin) generally is benign, with a high chance of spontaneous remission. Therefore treatment should be minimal and should be directed at arresting the progression of a bone lesion that could result in permanent damage before it resolves spontaneously. Curettage or, less often but especially

Table 556.4 Infections Associated with Hemophagocytic Syndrome

VIRAL
Adenovirus
Cytomegalovirus (CMV)
Dengue virus
Epstein-Barr virus (EBV)
Enteroviruses
Herpes simplex viruses (HSV1, HSV2)
Human herpesviruses (HHV6, HHV8)
HIV
Influenza viruses
Parvovirus B19
Varicella-zoster virus (VZV)
Hepatitis viruses
Measles
Parechovirus
BACTERIAL
Babesia microti
Brucella abortus
Enteric gram-negative rods
Haemophilus influenzae
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae
Ehrlichia chaffeensis
FUNGAL
Candida albicans
Cryptococcus neoformans
Histoplasma capsulatum
Fusarium
MYCOBACTERIAL
Mycobacterium tuberculosis
RICKETTSIAL
Coxiella burnetii
Other rickettsial diseases
PARASITIC
Leishmania donovani
Plasmodium

From Nathan DG, Orkin SH, Ginsburg D, et al., eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia: Saunders; 2003, p. 1381.

Table 556.5 Other Primary Immunodeficiency and Inherited Metabolic Diseases That May Be Complicated (Rarely) by Hemophagocytic Lymphohistiocytosis

PRIMARY IMMUNODEFICIENCY DISEASES
SCID
CIDs
DiGeorge syndrome
Wiskott-Aldrich syndrome
Ataxia telangiectasia
Dyskeratosis congenita
ORAI-1 deficiency
Chronic granulomatous disease
Other PIDs
X-linked agammaglobulinemia
Autoimmune lymphoproliferative syndrome
STAT1 gain of function
CTLA4
GATA2
TRAPS
FMF
NEMO
TIM3
DOCK8
STAT2
STAT3
PIK3CD
INBORN ERRORS OF METABOLISM
Lysinuric protein intolerance
Multiple sulfatase deficiency
Biotinidase deficiency
Lysosomal acid lipase deficiency/Wolman disease
Methylmalonic acidemia
Galactosemia
Gaucher disease
Pearson syndrome
Galactosialidosis
Propionic acidemia
Cobalamin C disease
Niemann-Pick disease
LCHAD deficiency
CONGENITAL DISORDERS OF GLYCOSYLATION
COG6

From Canna SW, March RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332–1343. Table 5.

when a weight-bearing bone is involved, corticosteroid injection or low-dose local radiation therapy (5-6 Gy) may accomplish this goal.

In contrast, **multisystem disease** requires treatment with systemic multiagent chemotherapy. Several different regimens have been proposed, but central elements are the inclusion of vinblastine and corticosteroids, both of which have been found to be very effective in treating LCH. Etoposide has been excluded from the standard treatment of multisystem LCH, which is treated with multiple agents, designed to reduce mortality, reactivation of disease, and long-term consequences. The response rate to therapy is quite high, and mortality in severe LCH has been substantially reduced by multiagent chemotherapy, especially if the diagnosis is made accurately and expeditiously. The most recent treatment results associated with lengthened continuation therapy (HS LCH-III) show a greater than 85% survival rate in severe (RO+) multisystem disease and a reduced rate of reactivation.

Experimental therapies are suggested only for unresponsive disease (often in very young children with multisystem disease and organ dysfunction who have not responded to multiagent initial treatment) and reactivation of RO+ disease in risk organs but not in reactivation of mild disease (any risk organ–negative reactivations) (see Fig. 556.2). The approaches include immunosuppressive therapy with cyclosporine/antithymocyte globulin and possibly imatinib, 2-chlorodeoxyadenosine, and clofarabine. With the discovery of the *BRAFV600E* pathogenic variant causing hyperactivation of the MAPK pathway in LCH cells, pharmacologic inhibition of BRAF and pharmacologic inhibition of MEK are currently the subject of clinical trials as therapeutic approaches for resistant disease.

Late (fibrotic) complications, whether hepatic or pulmonary, are irreversible and require organ transplantation to be definitively treated. Current treatment approaches and experimental protocols for both LCH and HLH can be obtained at the Histiocyte Society website (http://www.histiocytesociety.org). An unresolved problem is treatment of the (usually late-onset) severe, progressive, and intractable LCH-associated **neurodegenerative** syndrome. This is also under investigation for response to experimental therapies, including the pharmacologic inhibitors of the MAPK pathway. Regarding current treatment recommendations for LCH as well as HLH, the continuing rapid advances in understanding of their pathogeneses is likely to result in further rapid development and validation of new therapeutic approaches.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

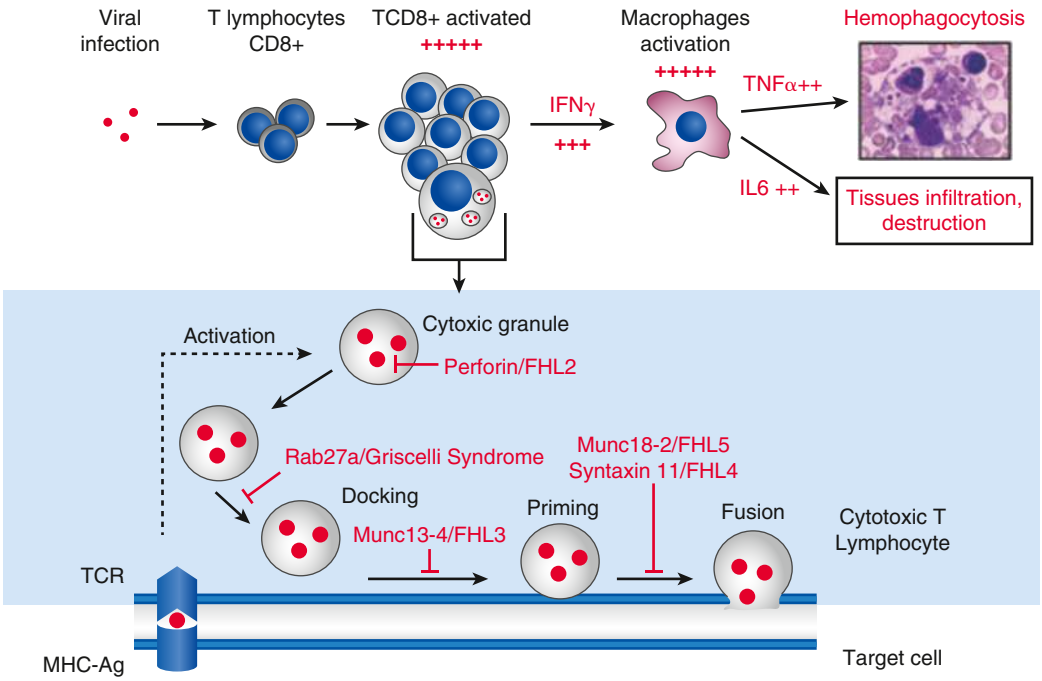

Fig. 556.5 Inborn errors in the cytotoxic activity of lymphocytes. **Top,** Immune mechanisms leading to the occurrence of a hemophagocytic syndrome. Following a viral infection, antigen-specific $CD8^+$ T lymphocytes undergo massive expansion and activation and secrete high levels of interferon (IFN)-γ. The overwhelming activated effector cells induce excessive macrophage activation and proinflammatory cytokine production, including tumor necrosis factor (TNF)-α and interleukin-6 (IL-6). Macrophages spontaneously phagocytose blood elements (platelets, red blood cells, and a polymorphonuclear cell shown here). Activated lymphocytes and macrophages infiltrate various organs, resulting in massive tissue necrosis and organ failure. **Bottom,** Genetic variants causing hemophagocytic lymphohistiocytic syndrome (HLH) affect a precise step of the cytotoxic machinery: granule content, docking, priming, or fusion. Only the defects causing Griscelli syndrome and familial hemophagocytic lymphohistiocytosis (FHL) are shown. MHC-Ag, Major histocompatibility complex antigen; TCR, T-cell receptor. *(From Pachlopnik Schmid J, Cote M, Menager MM, et al. Inherited defects in cytotoxic lymphocyte activity. Immunol Rev. 2010;235:10–23.)*

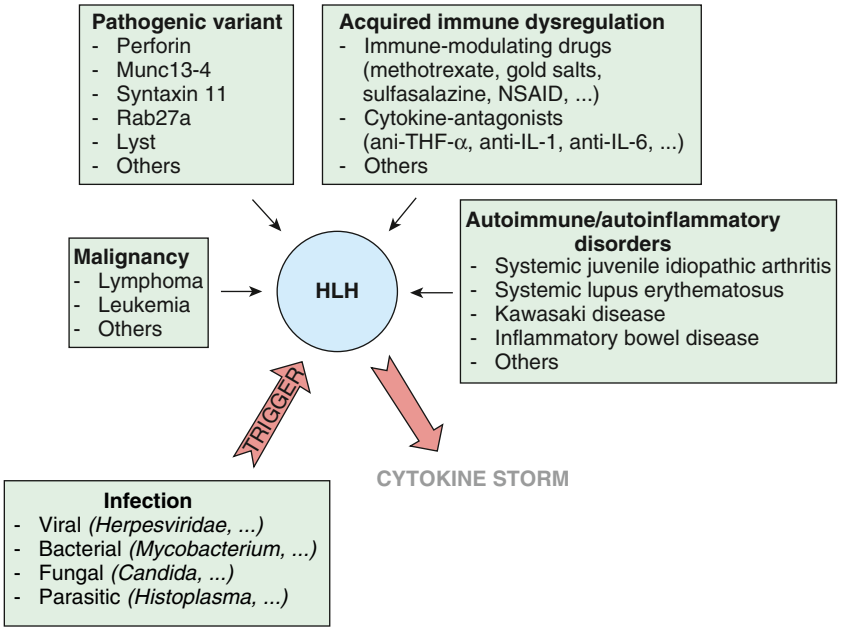

Fig. 556.6 Hemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous spectrum of disorders that all present with severe cytokine storm and life-threatening immunopathology. HLH can be caused by pathogenic variants in genes involved in granule-mediated cytotoxicity but can also be acquired on a multitude of underlying autoimmune/autoinflammatory diseases or malignancies, with possible facilitation by immunomodulating therapies. Clinical manifestations of HLH are generally precipitated by an infection. IL, Interleukin; NSAID, nonsteroidal antiinflammatory drugs. *(From Brisse E, Wouters CH, Matthys P. Hemophagocytic lymphohistiocytosis (HLH): a heterogeneous spectrum of cytokine-driven immune disorders. Cytokine Growth Factor Rev. 2015;26:263–280. Fig. 2, p. 267.)*

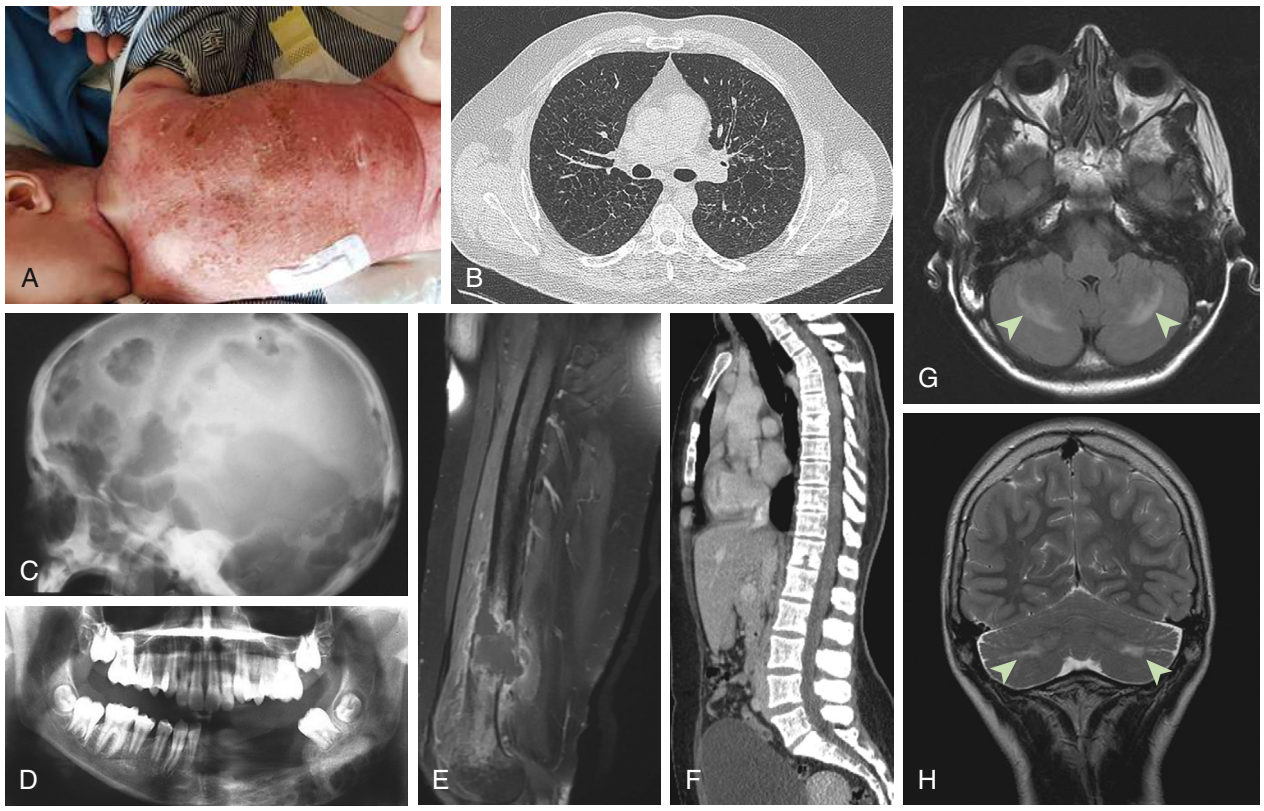

Fig. 556.7 Langerhans cell histiocytosis. **A,** Young child with disseminated Langerhans cell histiocytosis (LCH) skin lesions. **B,** Chest CT scan showing multiple cysts. **C,** X-rays showing LCH involvement of the skull. **D,** X-rays showing LCH involvement of the mandible, as revealed by so-called floating teeth. **E,** MRI showing a femoral lesion revealed by a fracture. **F,** CT scan showing the spinal column. **G and H,** MRI showing degenerative neuro-LCH on axial T2 spin echo-weighted images, which reveal symmetrical hyperintensities within the cerebellar corpus medullare *(arrows). (From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. Lancet. 2021;398:157–168. Fig. 2.)*

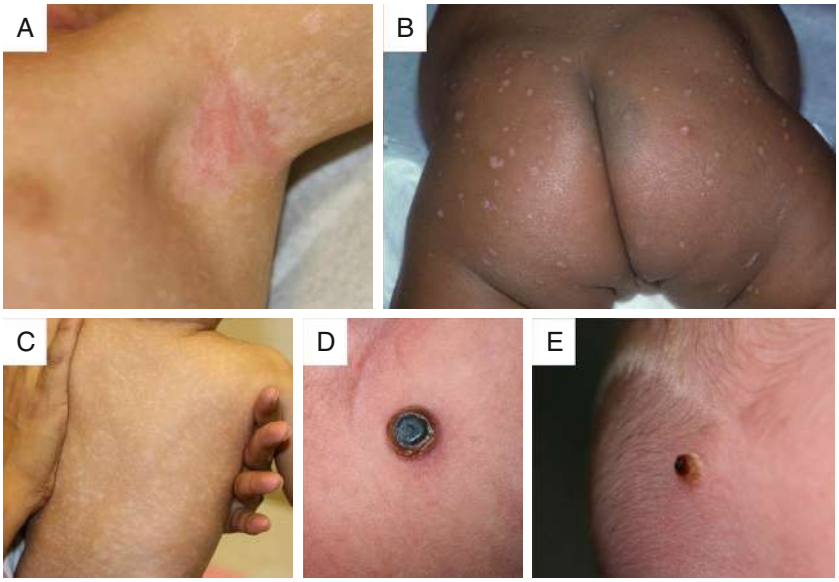

Fig. 556.8 Variable appearance of Langerhans cell histiocytosis of skin. **A,** Eczematous dermatitis. **B,** Hypopigmented, eroded papules. **C,** Hypopigmented macules. **D** and **E,** Crusted papulonodules. Presentation does not reflect presence or absence of multisystem disease. Despite similar appearance, the patient in **D** had a single lesion, whereas the patient in **E** had organ involvement. *(From Simko SJ, Garmezy B, Abhyankar H, et al. Differentiating skin-limited and multisystem Langerhans cell histiocytosis. J Pediatr. 2014;165:990–996. Fig. 3.)*



Fig. 556.9 Langerhans cell histiocytosis presenting as "blueberry muffin" rash in neonate. Multiple firm, nonblanching, purple papules affecting the head and neck (A) and the body (B). *(From Schmitt AR, Wetter DA, Camilleri MJ, et al. Langerhans cell histiocytosis presenting as a blueberry muffin rash. Lancet. 2017;390:155.)*

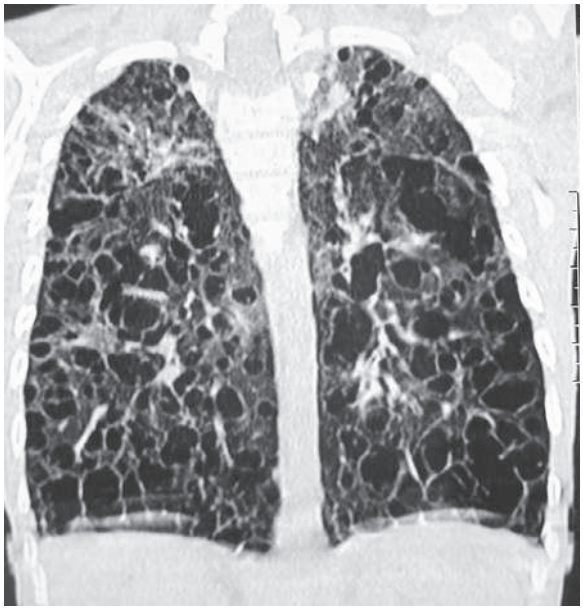

Fig. 556.10 High-resolution coronal CT image (lung window) reveals diffuse lung cysts with parenchymal destruction in bilateral lung fields. *(From Chauhan L, Aggarwal N. Honey-comb Langerhans cell histiocytosis. J Pediatr. 2016;168:248. Fig. 2.)*

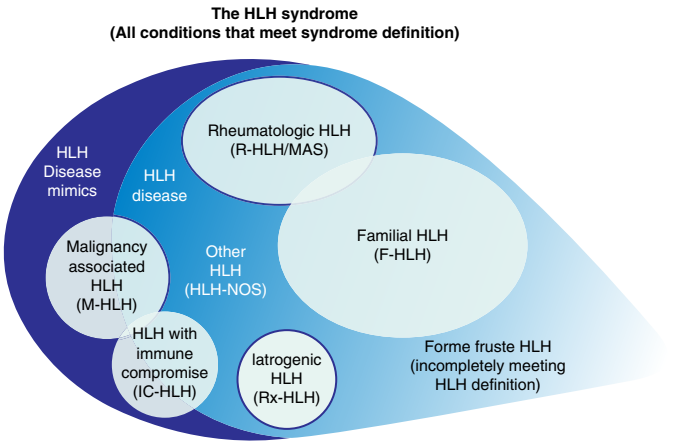

Fig. 556.11 Spectrum of the hemophagocytic lymphohistiocytosis (HLH) syndrome. The HLH syndrome includes all conditions meeting consensus diagnostic criteria. This syndrome includes conditions that would benefit from HLH-directed immunosuppressive therapies, which are termed "HLH disease," and those conditions that would not benefit from such therapy or require entirely different treatments, termed "HLH disease mimics." HLH disease includes recognizable subgroups: familial HLH with clear genetic etiology, HLH associated with malignancy, HLH associated with rheumatologic conditions (also called MAS), HLH observed after immune-activating therapies (iatrogenic HLH, also called cytokine release syndrome), HLH associated with immune compromise (either primary immune deficiency or treatment-related immune suppression), and HLH not associated with other specific conditions. Recognition of these subcategories is valuable as this may alter treatment. *(From Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium (NACHO). Pediatr Blood Cancer. 2019;66:e27929.)*

556.2 Hemophagocytic Lymphohistiocytosis

Stephan Ladisch

See the previous section on "Classification and Pathology," Table 556.3, and Chapter 174.

CLINICAL MANIFESTATIONS

Primary FHLH and secondary HLH have a remarkably similar, clinically indistinguishable presentation (Fig. 556.11). It consists of a generalized disease process, most often with fever (90–100%), maculopapular and/or petechial rash (10–60%), weight loss, and irritability. The initial clinical presentation can vary but is usually severe. In the case of secondary HLH, onset may be camouflaged by a primary disease process. Acute presentations of HLH include a hyperferritinemic septic shock–like picture, acute respiratory distress, seizures, ataxia, focal lesions, or coma (because of CNS infiltration). Other features that are frequently present result from bone marrow involvement and pancytopenia or hepatic dysfunction.

Children with primary HLH are generally <1-2 years old, and children with secondary HLH typically present at an older age, but both forms may present at any age. **Physical examination** often reveals hepatosplenomegaly (70–100%), lymphadenopathy (20–50%), respiratory distress (40–90%), jaundice, and symptoms of CNS involvement (50%) that are not unlike those of aseptic meningitis, CNS vasculitis, or acute demyelinating encephalomyelitis. MRI may demonstrate systemic T2 weighted/fluid-attenuated inversion recovery (FLAIR) hyperintensities in gray and white matter and in supratentorial and infratentorial regions (Fig. 556.12). The cerebrospinal fluid (CSF) pleocytosis (50–90%) associated with CNS involvement in primary HLH is characterized by cells that are the same phagocytic macrophages found in the peripheral blood or bone marrow. HLH may initially or only manifest CNS symptoms. Isolated neuroinflammation may be present in the absence of cytopenias, splenomegaly, or other systemic features. Approximately 35% will eventually develop diagnostic features of HLH (Table 556.6). The interval from neurologic onset to eventual diagnosis often exceeds 2 years. In CNS isolated disease, the diagnosis of familial HLH is often made by whole exome sequencing for other diseases.

The **diagnosis** of HLH is arrived at in two stages. The first stage is based on a set of eight clinical and laboratory findings, with the presence of five of the eight being diagnostic of HLH. The eight findings, formulated by the Histiocyte Society, are fever, splenomegaly, cytopenia of two cell lines (in 90–100%), hypertriglyceridemia (80–100%) or hypofibrinogenemia (65–85%), hyperferritinemia (≥500 but often >10,000), extremely elevated soluble CD25 (interleukin-2 receptor), reduced or absent NK cell activity, and bone marrow, CSF, or lymph node evidence of hemophagocytosis (see Table 556.6). The second stage involves genetic analysis and is undertaken as quickly as possible but generally requires ~2 weeks to complete and should not interfere with initiation of treatment (Fig. 556.13). The genetic findings and family history will determine whether the diagnosis is (autosomal

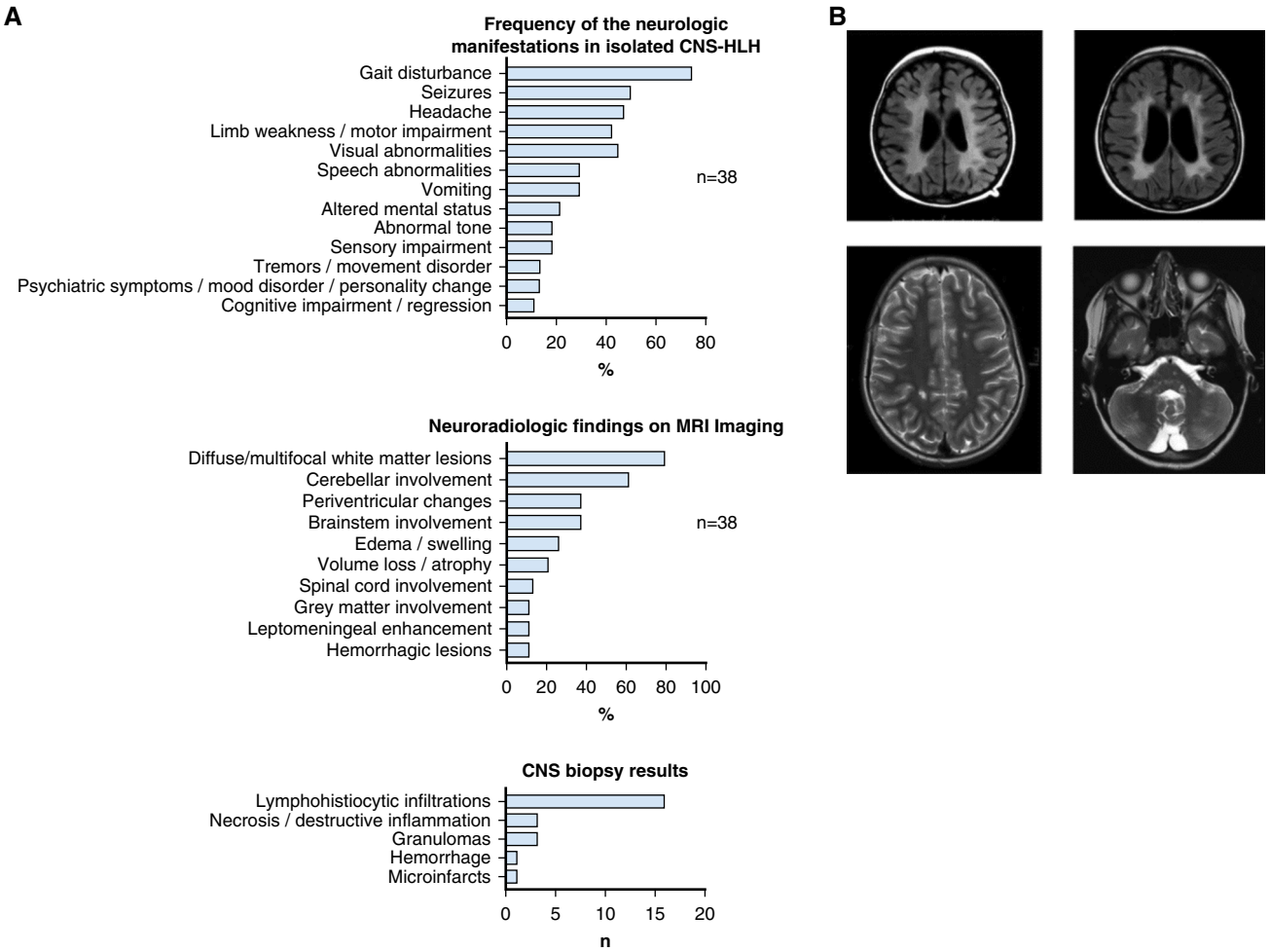

Fig. 556.12 A, Frequencies of neurologic manifestations, neuroradiologic findings, and histopathologic central nervous system (CNS) biopsy results in 38 patients with isolated CNS hemophagocytic lymphohistiocytosis (HLH). B, Examples of CNS MRI imaging in patients with isolated CNS-HLH. *Upper panels*, T2 images in one patient from 2016 *(left)* and 2017 *(right)* demonstrate cerebral atrophy with diffuse white matter involvement. Neuroradiologic findings on MRI show imaging abnormalities. *Lower panels*, T2 images from another patient reveal multiple nodular lesions in the pons, cerebellum, and white matter. *(From Blincoe A, Heeg M, Campbell PK, et al. Neuroinflammatory disease as an isolated manifestation of hemophagocytic lymphohistiocytosis. J Clin Immunol. 2020;40:901–916. Fig. 1.)*

recessive) primary HLH, secondary HLH, or a genetic hybrid form of HLH.

Hemophagocytosis is not specific for HLH and should be considered only in the context of the diagnostic criteria. No absolute clinical or laboratory distinction can be made between primary HLH and secondary HLH. In some subgroups of HLH, perforin assays may be normal. Similarly, some patients with primary FHLH have no known identifiable pathogenic variant, while new genetic variants associated with HLH continue to be discovered.

In the absence of either (1) a documented genetic defect coupled with defective NK cell cytotoxicity or (2) frank hemophagocytosis, care should be taken in making the diagnosis of secondary HLH, given the implication to use cytotoxic chemotherapy. The nonspecific criteria (indicative of inflammation) used to diagnose HLH can also be seen in diseases that are not always associated with hemophagocytosis (e.g., overwhelming acute viral infection with appropriate T-cell activation), in which the cytotoxic and immunosuppressive therapy used in treating HLH might be contraindicated.

Macrophage activation syndrome, particularly in the context of systemic-onset juvenile idiopathic arthritis (JIA) or infection, has many similarities to HLH (see Chapter 196). Indeed, whole exome sequencing of patients with systemic-onset JIA or those with fatal influenza has revealed a higher than expected incidence of HLH genes.

TREATMENT AND PROGNOSIS

Therapy for **primary HLH** (autosomal recessive genetic disease or familial occurrence) consists of a combination of etoposide, dexamethasone, cyclosporine, and intrathecal methotrexate. It should be stressed that pancytopenia and the presence of an infection are *not* contraindications to cytotoxic or immunosuppressive therapy (etoposide and steroid, cyclosporine or antithymocyte globulin for maintenance therapy). Paradoxically they ameliorate the HLH. Emapalumab, a monoclonal antibody against interferon-γ, is approved for recurrent, refractory, or progressive familial HLH or for patients who cannot tolerate chemotherapy. The goal for all therapies is to reach the point of initiating **stem cell transplantation,** to date the only known potentially curative treatment for primary HLH, effective in achieving cure in >60% of patients. Chemotherapy is inadequate for sustained cure of primary HLH, which is ultimately fatal without transplantation.

In **secondary HLH**, it is critical that the underlying disease (e.g., infection, malignancy) be identified and successfully treated. The diagnostic distinction between primary HLH and secondary HLH sometimes can be based on the acute onset of secondary HLH in the presence of an already documented infection or cancer, including leukemia, and certain autoimmune or immunodeficiency disorders. In this case, treatment of the underlying infection is coupled with supportive care. If the diagnosis is made in the setting of iatrogenic immunodeficiency, immunosuppressive

Table 556.6 Diagnostic Criteria for the HLH-2004 Trial and Their Relevance for Clinical Diagnosis

HLH2004 ENTRY CRITERIA	COMMENT
A. Molecular diagnosis consistent with HLH: Pathogenic variants of *PRF1, UNC13D, STXBP2,* Rab27a, *STX11, SH2D1A,* or *XIAP* or	In a patient with known variants, treatment before full development of HLH may be appropriate, but genetic studies usually just help to define HLH recurrence risk, not the presence of an active disease state.
B. Five of the eight criteria listed below are fulfilled	
1. Fever ≥38.3°C	Nearly universal in untreated HLH.
2. Splenomegaly	Although splenomegaly and hepatomegaly are very common in HLH, adenopathy is not.
3. Cytopenias (affecting at least two of three lineages in the peripheral blood): Hemoglobin <9 g/dL (in infants <4 wk: hemoglobin <10 g/dL), platelets <100 × 10^3/mL, neutrophils <1 × 10^3/mL	Cytopenias are ubiquitous in HLH. Lack of cytopenias should make one doubt a diagnosis of HLH, except in the special case of isolated, CNS-only disease.
4. Hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)	Low fibrinogen in the context of inflammation is paradoxical and one of the more distinctive features of HLH.
5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver	Not specific to HLH, or essential for the diagnosis, but helpful as a disease marker. Of note, it is often not evident early after disease onset.
6. Low or absent NK-cell activity	More modern and robust assays measuring perforin levels and its degranulation should replace this assay for reliable diagnosis of HLH. This assay is not specific for primary HLH.
7. Ferritin >500 ng/mL	Most patients have much higher levels than this threshold suggests.
8. Elevated soluble CD25 (soluble IL-2 receptor α)	As HLH is a T-cell driven disease, this assay is extremely informative for diagnosis and response to therapy.

HLH, Hemophagocytic lymphohistiocytosis; NK, natural killer; IL, interleukin; CNS, central nervous system.
From Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium (NACHO). *Pediatr Blood Cancer.* 2019;66(11):e27929. Table 1.

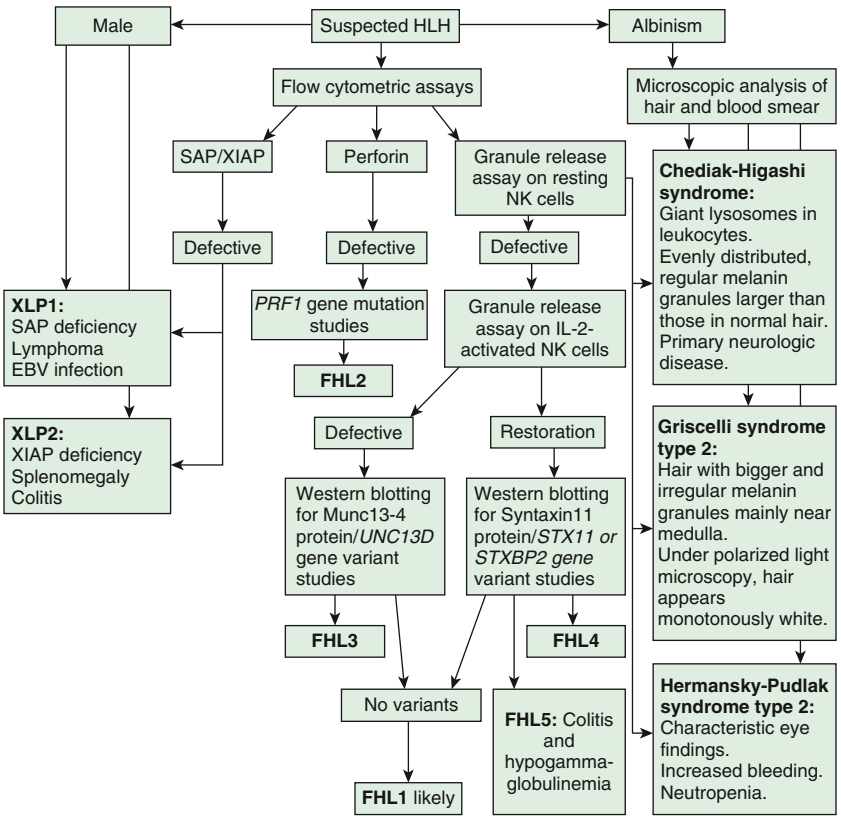

Fig. 556.13 Algorithm for identification of genetic causes of hemophagocytic lymphohistiocytosis (HLH). The HLH algorithm is based on flow cytometry assays: all the patients fitting into HLH criteria, irrespective of age and clinical presentations, should be screened for perforin expression and granule release assay. All male patients should be screened for signaling lymphocyte activation molecule–associated protein (SAP) and X-linked inhibitor of apoptosis protein (XIAP) expression. For patients clinically presenting with albinism, microscopic analysis of hair and blood smear is essential for differential diagnosis of Chédiak-Higashi syndrome, Griscelli syndrome, and Hermansky-Pudlak syndrome. Based on the defect in expression of a particular protein identified, molecular characterization for the respective gene should be performed for confirmation of diagnosis. EBV, Epstein-Barr virus; FHL, familial hemophagocytic lymphohistiocytosis; IL, interleukin; NK, natural killer. *(Adapted from Madkaikar M, Shabrish S, Desai M. Current updates on classification, diagnosis and treatment of hemophagocytic lymphohistiocytosis (HLH). Indian J Pediatr. 2016;83:434–443.)*

treatment should be withdrawn and supportive care instituted along with specific therapy for the underlying infection. In many patients the prognosis is excellent without additional specific treatment other than treating the triggering infection. However, when a treatable infection or other cause cannot be documented, and when the clinical presentation is severe, the prognosis for secondary HLH is as poor as for primary HLH. These patients should receive the identical initial 8-week chemotherapeutic approach, including etoposide, even in the face of cytopenias. In both primary and secondary HLH, the cytotoxic effect of etoposide on macrophages interrupts cytokine production and the consequent cytokine storm, the hemophagocytic process, and the accumulation of macrophages, all of which may contribute to the pathogenesis of **infection-associated hemophagocytic syndrome**. A broad spectrum of infectious agents, including viruses (e.g., cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), fungi, protozoa, and bacteria, may trigger secondary HLH, often in the setting of immunodeficiency (see Table 556.3). A thorough evaluation for infection should be undertaken in immunodeficient patients with hemophagocytosis. The same syndrome may be identified in conjunction with a rheumatologic disorder (e.g., systemic lupus erythematosus, Kawasaki disease) or a neoplasm (e.g., leukemia). In these patients, effective treatment of the underlying disease (e.g., infection, cancer) is critical and may itself lead to ultimate resolution of the hemophagocytosis. In addition anakinra or ruxolitinib (JAK inhibitors) has been used in patients with secondary HLH.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

556.3 Other Histiocytoses

Stephan Ladisch

Other rare histiocytoses that have been named for their clinical presentation include xanthogranuloma in JXG, ECD, and striking lymphadenopathy in Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy). JXG and ECD may require systemic treatment with cytotoxic chemotherapy or potentially MAPK pathway inhibitors, reflecting the presence of a *BRAF* pathogenic variant. Rosai-Dorfman disease usually is not treated, although the massive lymphadenopathy may require intervention because of its tendency to cause physical obstruction.

Rare histiocytic malignancies include acute monocytic leukemia, true malignant histiocytosis, and histiocytic sarcoma. Also included is the more recently identified histiocytic malignancy, ALK+ histiocytosis, which is a systemic histiocytic proliferation presenting as disseminated disease in infants. The cells bear histiocytic markers (CD68, CD163) but not those of LCH (CD1a, BRAF V600E). Whereas all these rare histiocytic malignancies are referred to as histiocytoses because of their monocyte-macrophage lineage, they are better considered under the rubric of true proliferative malignancies of the monocyte–macrophage lineage.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Nephrology

PART XXI

Section 1

Glomerular Disease

Chapter 557

Introduction to Glomerular Diseases

557.1 Anatomy of the Glomerulus

Edward J. Nehus

The kidneys lie in the retroperitoneal space slightly above the level of the umbilicus. They range in length and weight, respectively, from approximately 6 cm and 24 g in a full-term newborn to ≥12 cm and 150 g in an adult. The kidney (Fig. 557.1) has an outer layer, **the cortex,** which contains the glomeruli, proximal and distal convoluted tubules, and collecting ducts, and an inner layer, **the medulla,** which contains the straight portions of the tubules, the loops of Henle, the vasa recta, and the terminal collecting ducts (Fig. 557.2).

The blood supply to each kidney usually consists of a main renal artery that arises from the aorta, although multiple renal arteries can occur. The main artery divides into segmental branches within the medulla, becoming the interlobar arteries that pass through the medulla to the corticomedullary junction. At this point, the interlobar arteries branch to form the arcuate arteries, which run parallel to the surface of the kidney. Interlobular arteries originate from the arcuate arteries and give rise to the afferent arterioles of the glomeruli. Specialized muscle cells in the wall of the afferent arteriole and specialized distal tubular cells adjacent to the glomerulus (macula densa) form the juxtaglomerular apparatus that controls the secretion of renin. The afferent arteriole divides into the glomerular capillary network, which then recombines into the efferent arteriole (see Fig. 557.2). The juxtamedullary efferent arterioles are larger than those in the outer cortex and provide the blood supply, as the vasa recta, to the tubules and medulla.

Each kidney contains approximately one million **nephrons** (each consisting of a glomerulus and associated tubules). There is a large distribution of normal nephron numbers in humans, ranging from 200,000 to 1.8 million nephrons per kidney. This variation can have major pathophysiologic significance as a risk factor for the later development of hypertension and progressive renal dysfunction. In humans, the formation of nephrons is complete at 34-36 weeks of gestation, but functional maturation with tubular growth and elongation continues during the first decade of life. Because new nephrons cannot be formed after birth, any disease that results in progressive loss of nephrons can lead to renal insufficiency. A decreased number of nephrons secondary to low birthweight, prematurity, and/or unknown genetic or environmental factors has been implicated as a significant risk factor for the development of primary hypertension and progressive renal dysfunction in adulthood. A low nephron number presumably results in hyperfiltration and eventual sclerosis of *overworked* nephron units.

The glomerular network of specialized capillaries serves as the filtering mechanism of the kidney. The glomerular capillaries are lined by endothelial cells (Fig. 557.3) and have very thin cytoplasm that contains many holes (fenestrations). The **glomerular basement membrane** (GBM) forms a continuous layer between the endothelial and mesangial cells on one side and the epithelial cells on the other. The membrane has three layers: a central electron-dense lamina densa; the lamina rara interna, which lies between the lamina densa and the endothelial cells; and the lamina rara externa, which lies between the

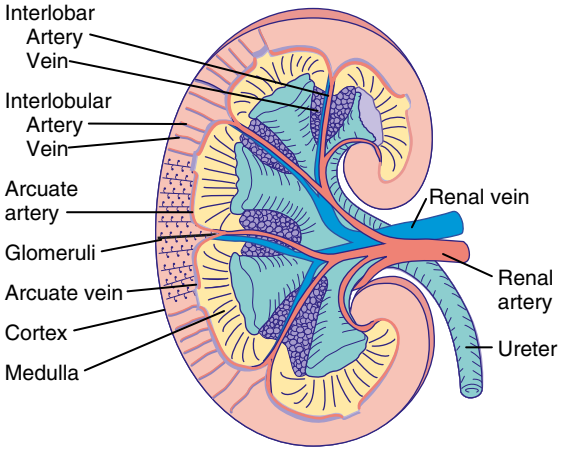

Fig. 557.1 Gross morphology of the renal circulation. *(From Pitts RF. Physiology of the Kidney and Body Fluids, 3rd ed. Chicago: Year Book Medical Publishers; 1974.)*

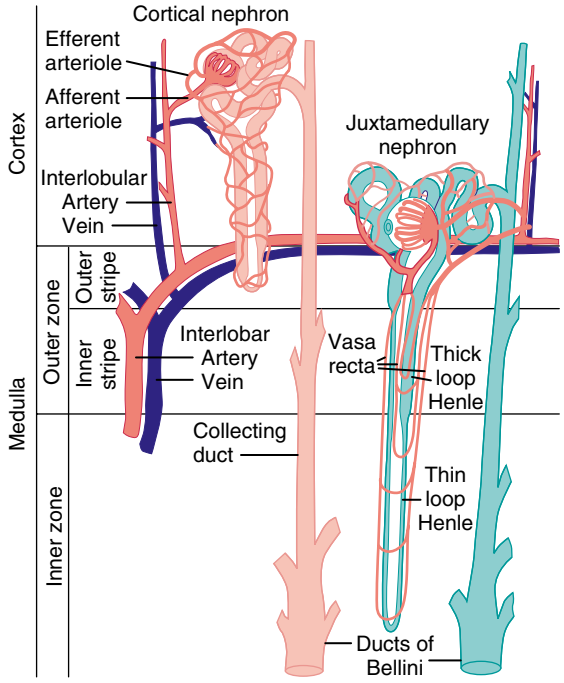

Fig. 557.2 Comparison of the blood supplies of cortical and juxtamedullary nephrons. *(From Pitts RF. Physiology of the Kidney and Body Fluids, 3rd ed. Chicago: Year Book Medical Publishers; 1974.)*

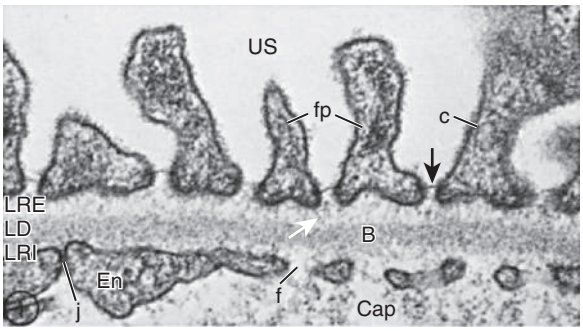

Fig. 557.3 Electron micrograph of the normal glomerular capillary *(Cap)* wall demonstrating the endothelium *(En)* with its fenestrations *(f)*; the glomerular basement membrane *(B)* with its central dense layer, the lamina densa *(LD)*, and adjoining lamina rara interna *(LRI)* and externa *(LRE) (white arrow)*; and the epithelial cell foot processes *(fp)* with their thick cell coat *(c)*. The glomerular filtrate passes through the endothelial fenestrae, crosses the basement membrane, and passes through the filtration slits *(black arrow)* between the epithelial cell foot processes to reach the urinary space *(US)* (×60,000). *j*, Junction between two endothelial cells. *(From Farquhar MG, Kanwar YS. Functional organization of the glomerulus: state of the science in 1979. In: Cummings NB, Michael AF, Wilson CB, eds. Immune Mechanisms in Renal Disease. New York: Plenum; 1982.)*

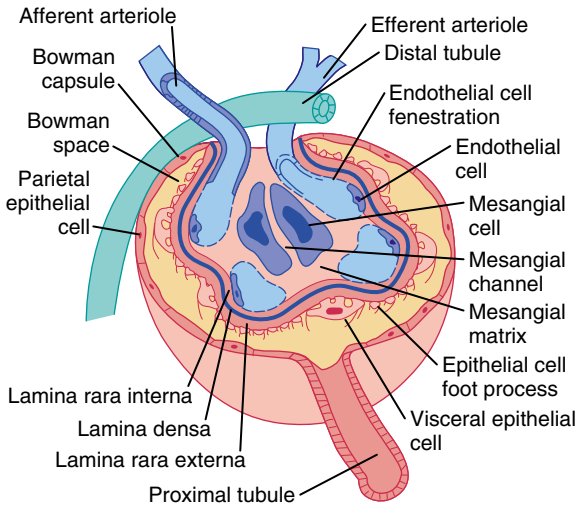

Fig. 557.4 Schematic depiction of the glomerulus and surrounding structures.

lamina densa and the epithelial cells. The visceral epithelial cells cover the capillary and project cytoplasmic foot processes, which attach to the lamina rara externa. Between the foot processes are spaces or filtration slits. The **mesangium** (mesangial cells and matrix) lies between the glomerular capillaries on the endothelial cell side of the GBM and forms the medial part of the capillary wall. The mesangium may serve as a supporting, stalk-like structure for the glomerular capillaries and probably has a role in the regulation of glomerular blood flow, filtration, and the removal of macromolecules (such as immune complexes) from the glomerulus. The Bowman's capsule, which surrounds the glomerulus, is composed of a basement membrane, which is continuous with the basement membranes of the glomerular capillaries and the proximal tubules, and the parietal epithelial cells, which are adjacent to the visceral epithelium (Fig. 557.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

557.2 Glomerular Filtration

Edward J. Nehus

Kidney function is best measured as the **glomerular filtration rate (GFR)**. As the blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. Small plasma molecules filter freely (e.g., electrolytes, glucose, phosphate, urea, creatinine, peptides, low molecular weight proteins), whereas larger molecules are retained in the circulation (such as albumin and globulins). The filtrate is collected in Bowman's space and enters the tubules. There its composition is modified by tightly regulated secretion and absorption of solute and fluid by the multiple tubular segments of the nephron and the ductal system, until it exits the kidney, via the ureter, as urine.

Glomerular filtration is the net result of opposing forces applied across the capillary wall. The force for ultrafiltration (glomerular capillary hydrostatic pressure) is a result of systemic arterial pressure, modified by the tone of the afferent and efferent arterioles. The major force opposing ultrafiltration is glomerular capillary oncotic pressure, created by the gradient between the high concentration of plasma proteins within the capillary and the almost protein-free ultrafiltrate in Bowman's space. Filtration may be modified by the rate of glomerular plasma flow, the hydrostatic pressure within Bowman's space, and/or the permeability of the glomerular capillary wall.

Although glomerular filtration begins at approximately the sixth week of fetal life, kidney function is not necessary for normal intrauterine homeostasis because the placenta serves as the major fetal excretory organ. After birth, the GFR increases until renal growth ceases (by age ~18-20 years in most people). To compare GFRs of children and adults, the GFR is standardized to the body surface area (1.73 m^2) of an "ideal" 70-kg adult. Even after correction for surface area, the GFR of a child does not approximate adult values until the second to third year of life (Fig. 557.5). The GFR may be estimated by measurement of the serum creatinine level. Creatinine is derived from muscle metabolism. Its production is typically constant, and its excretion is primarily through glomerular filtration, although tubular secretion can become important as the serum creatinine rises in renal insufficiency. In contrast to the concentration of blood urea nitrogen, which is affected by the state of hydration and nitrogen balance, the serum creatinine level is primarily influenced by muscle mass and the level of glomerular function.

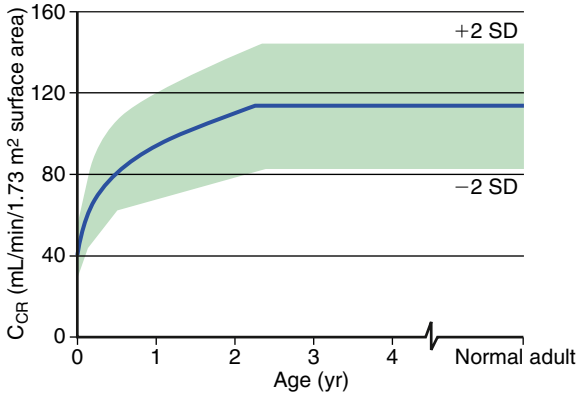

Fig. 557.5 Changes in the normal value of the glomerular filtration rate, as measured by the creatinine clearance *(Ccr)*, when standardized to mL/min/1.73 m^2 of body surface area. The *solid line* depicts the mean, and the *shaded area* includes 2 standard deviations (SDs). *(From McCrory W. Developmental Nephrology. Cambridge, MA: Harvard University Press; 1972.)*

The serum creatinine is of value only in estimating the GFR under steady-state conditions. A patient can have a normal serum creatinine level with decreased renal function very shortly after the onset of acute kidney injury. In this clinical setting, serum creatinine may take days to reach the steady state. Furthermore, kidney function may fall significantly before a noticeable rise in serum creatinine occurs.

The precise measurement of the GFR is accomplished by quantitating the clearance of a substance that is freely filtered across the capillary wall and is neither reabsorbed nor secreted by the tubules. The clearance (C_s) of such a substance is the volume of plasma that, when completely cleared of the contained substance, would yield an equal quantity of that substance excreted in the urine over a specified time. Renal clearance is calculated by the following formula:

$$C_s\left(\text{mL/min}\right) = U_s\left(\text{mg/mL}\right) \times \left(V\left(\text{mL/min}\right) / P_s\left(\text{mg/mL}\right)\right)$$

where C_s equals the clearance of substance s, U_s reflects the urinary concentration of s, V represents the urinary flow rate, and P_s equals the plasma concentration of s. To correct the clearance for individual body surface area, the formula is:

$$\text{Corrected clearance}\left(\text{mL/min/1.73 m}^2\right) = C_s\left(\text{mL/min}\right) \times \frac{1.73}{\text{Surface area}\left(\text{m}^2\right)}$$

The GFR is optimally measured by the clearance of inulin, a fructose polymer having a molecular weight of approximately 5.7 kDa. Because the inulin clearance technique is cumbersome, radioisotopes are commonly used to measure GFR in clinical practice. GFR can be accurately determined by a single intravenous injection of a radioisotope, most commonly ^{99m}TC-DTPA, followed by timed monitoring of serum samples.

Because true measurement of the GFR is expensive and time-consuming, the GFR is commonly estimated (eGFR) by the clearance of endogenous creatinine. Formulas that estimate creatinine clearance accurately in clinical settings have been useful tools in patient care. The "bedside" Schwartz formula is the most widely used pediatric formula and is based on the serum creatinine (S_{cr}), patient height, and an empirical constant:

$$\text{eGFR} = 0.413\,\text{height}\left(\text{cm}\right) / S_{cr}\left(\text{mg/dL}\right)$$

The accuracy of GFR-estimating equations can be further improved utilizing an additional endogenous marker, cystatin C, in addition to serum creatinine. Cystatin C is a 13.6-kDa protease inhibitor produced by nucleated cells that is freely filtered by the kidney. It continues to gain popularity as a clinical tool to provide an alternative to creatinine-based formulas because it has distinct advantages in estimating the GFR. Unlike creatinine, cystatin C is not secreted by the renal tubules under any conditions. Furthermore, it is less affected by sex, age, and muscle mass than serum creatinine. Several cystatin C-based formulas have been developed, including a multivariable eGFR equation that combines both cystatin C and creatinine in addition to height, BUN, and gender:

$$\text{eGFR} = 39.8 \times \left[\text{height}\left(\text{m}\right)/S_{cr}\left(\text{mg/dl}\right)\right]^{0.456} \times \left[1.8/\text{cystatin C}\left(\text{mg/L}\right)\right]^{0.418} \times \left[30/\text{BUN}\left(\text{mg/dl}\right)\right]^{0.079} \times \left[1.076\right]^{\text{male}} \times \left[\text{ht}\left(\text{m}\right)/1.4\right]^{0.179}$$

However, cystatin C assays are not available in many laboratories and lack standardization. Therefore the creatinine-based bedside Schwartz equation remains the most widely used assessment of kidney function in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for a Bibliography.

557.3 Glomerular Diseases

Edward J. Nehus

PATHOGENESIS

Glomerular injury may be the result of a genetic, immunologic, perfusion, or coagulation disorder. Genetic disorders of the glomerulus may result from pathogenic variants in genes encoding proteins located within the glomerulus, interstitium, or tubular epithelium; pathogenic variants in regulatory genes controlling DNA transcription; abnormal posttranscriptional modification of RNA transcripts; or abnormal posttranslational modification of proteins. Immunologic injury to the glomerulus results in **glomerulonephritis,** which is a generic term for several diseases but more precisely is a histopathologic term defining inflammation of the glomerular capillaries. Evidence that glomerulonephritis is caused by immunologic injury includes morphologic and immunopathologic similarities to experimental immune-mediated glomerulonephritis, the demonstration of immune reactants (immunoglobulin, complement) in glomeruli, abnormalities in serum complement, and the finding of autoantibodies (anti-GBM) in some of these diseases (Fig. 557.6). There appear to be two major mechanisms of immunologic injury: glomerular deposition of circulating antigen-antibody immune complexes and direct interaction of antibody with specific glomerular antigens in situ. In the former, antibody is produced against and combines with a circulating antigen that is usually unrelated to the kidney (see Fig. 557.6). The immune complexes accumulate in GBMs and activate the complement system, leading to immune injury. Immunofluorescence microscopy often demonstrates granular or irregular deposits containing immunoglobulin and complement in the glomerular capillary wall. Electron microscopic studies may show these deposits in the GBM and in the mesangium. Examples of circulating immune complex–mediated glomerulonephritis include postinfectious glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, and lupus nephritis. In situ immune complex formation occurs when an antibody reacts with antigen(s) of the GBM. Immunopathologic studies reveal linear deposition of immunoglobulin and complement along the GBM. This type of immune complex injury occurs in Goodpasture syndrome and membranous nephropathy.

The inflammatory reaction that follows immunologic injury results from activation of one or more mediator pathways. The most important of these is the complement system, which has two initiating sequences: the classic pathway, which is activated by antigen-antibody immune complexes, and the alternative or properdin pathway, which occurs by autoactivation of C3 by a process known as C3 tick over. These pathways converge at C3; from that point on, the same sequence leads to lysis of cell membranes (see Chapter 173). The major noxious products of complement activation are produced after activation of C3 and include anaphylatoxin (which stimulates contractile proteins within vascular walls and increases vascular permeability) and chemotactic factors (C5a) that recruit neutrophils and perhaps macrophages to the site of complement activation, leading to consequent damage to vascular cells and basement membranes.

PATHOLOGY

The glomerulus may be injured by several mechanisms, but it has only a limited number of histopathologic responses; different disease states can produce similar microscopic changes.

Proliferation of glomerular cells occurs in most forms of glomerulonephritis and may be generalized (involving all glomeruli) or focal (involving only some glomeruli and sparing others). Within a single glomerulus, proliferation may be diffuse (involving all parts of the glomerulus) or segmental (involving only one or more tufts, but not others). Proliferation commonly involves the endothelial and mesangial cells and is often associated with an increase in the mesangial matrix (see Fig. 557.6). Mesangial proliferation can result from deposition of

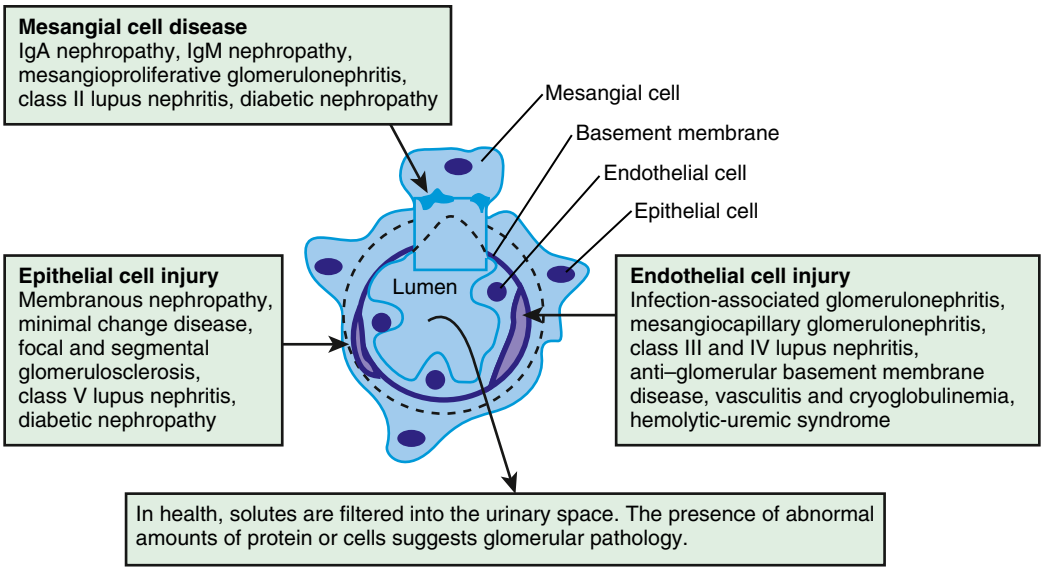

Fig. 557.6 Cellular location of injury during glomerulonephritis. Mesangial cells are directly exposed to the circulation. Deposition of immune complexes within these cells is typically seen in disorders such as immunoglobulin A *(IgA)* nephropathy; it results in proliferation and expansion of the cells, leading to hematuria, proteinuria, and renal impairment. Epithelial cells, in conjunction with basement membrane, allow filtration of plasma solutes but retard passage of cells and plasma proteins. Disease related to these cells is typified by the presence of subepithelial deposits and flattening of the foot processes that engage the basement membrane, resulting in disruption of the filtration barrier and proteinuria. Endothelial cell disease can result from deposition of immune complex (as occurs in mesangiocapillary glomerulonephritis), attachment of antibody to the basement membrane (Goodpasture disease), or trauma and activation of coagulation (hemolytic-uremic syndrome). Endothelial cell proliferation and necrosis are accompanied by leukocyte accumulation; rupture of the basement membrane, crescent formation, and disruption of glomerular architecture can develop. A nephritic or rapidly progressive presentation ensues. *(From Chadban SJ, Atkins RC. Glomerulonephritis. Lancet. 2005;365:1797–1806.)*

immune complex within the mesangium. The resultant increase in cell size and number, and production of mesangial matrix, can increase the glomerular size and narrow the lumens of glomerular capillaries, leading to renal insufficiency.

Crescent formation in Bowman's space (capsule) is a result of proliferation of parietal epithelial cells and is often associated with clinical signs of renal dysfunction. Crescents develop in several forms of glomerulonephritis (termed **rapidly progressive** or **crescentic;** see Chapter 559.7) and are a characteristic response to deposition of fibrin in Bowman's space. Newly formed crescents contain fibrin, the proliferating epithelial cells of Bowman's space, basement membrane–like material produced by these cells, and macrophages that might have a role in the genesis of glomerular injury. Over subsequent days to weeks, the crescent is invaded by connective tissue and becomes a fibroepithelial crescent. This process generally results in glomerular obsolescence and the clinical development of chronic renal failure. Crescent formation is often associated with glomerular cell death. The necrotic glomerulus has a characteristic eosinophilic appearance and usually contains nuclear remnants. Crescent formation is usually associated with generalized proliferation of the mesangial cells and with either immune complex or anti-GBM antibody deposition in the glomerular capillary wall.

Certain forms of acute glomerulonephritis show glomerular exudation of blood cells, including neutrophils, eosinophils, basophils, and mononuclear cells. The thickened appearance of GBM can result from a true increase in the width of the membrane (as seen in membranous glomerulopathy; see Chapter 559.5), from massive deposition of immune complexes that have staining characteristics similar to the membrane (as seen in systemic lupus erythematosus; see Chapter 560.2), or from the interposition of mesangial cells and matrix into the subendothelial space between the endothelial cells and the GBM. The last can give the basement membrane a split appearance, as seen in membranoproliferative glomerulonephritis (see Chapter 559.6) and other diseases.

Sclerosis refers to obliteration of capillary loops within the glomerulus caused by increased mesangial matrix. Glomerulosclerosis may be caused by a putative circulating factor, as occurs in primary focal segmental glomerulosclerosis (FSGS), or it may be secondary to a variety of conditions including pathogenic variants, obesity, infection, certain medications, or any condition that results in reduced renal mass.

Tubulointerstitial fibrosis is present in all patients who have glomerular disease and who develop progressive renal injury. This fibrosis is initiated by injury to either the glomeruli, which, if severe, may secondarily involve the tubules, or direct injury to the tubules themselves. Tubular injury recruits mononuclear cell infiltrate, which releases a variety of soluble factors that have fibrosis-promoting effects. Matrix proteins of the renal interstitium begin to accumulate, leading to eventual destruction of renal tubules and peritubular capillaries.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

Conditions Particularly Associated with Hematuria

Chapter 558

Clinical Evaluation of the Child with Hematuria

Francisco X. Flores

Hematuria, defined as the persistent presence of more than five red blood cells (RBCs)/high-power field (hpf) in uncentrifuged urine, occurs in 4–6% of urine samples from school-aged children. Quantitative studies demonstrate that normal children can excrete more than 500,000 RBCs per 12-hour period; this increases with fever and/or exercise. In the clinical setting, qualitative estimates are provided by a urinary dipstick that uses a very sensitive peroxidase chemical reaction between hemoglobin (or myoglobin) and a colorimetric chemical indicator impregnated on the dipstick. Chemstrip (Boehringer Mannheim), a common commercially available dipstick, is very sensitive and capable of detecting 3-5 RBCs/hpf of unspun urine. The presence of 10-50 RBCs/μL may suggest underlying pathology, but significant hematuria is generally considered as >50 RBCs/hpf. False-negative results can occur in the presence of formalin (used as a urine preservative) or high urinary concentrations of ascorbic acid (i.e., in patients with vitamin C intake >2,000 mg/day). False-positive results may be seen in a child with an alkaline urine (pH >8), or more commonly following contamination with oxidizing agents such as hydrogen peroxide used to clean the perineum before obtaining a specimen. Microscopic analysis of 10-15 mL of freshly voided and centrifuged urine is essential in confirming the presence of RBCs suggested by >10 RBCs/hpf, or a 1+ positive urinary dipstick reading.

Red urine *without* RBCs is seen in a number of conditions (Table 558.1). Clinically significant heme-positive urine without RBCs may be caused by the presence of either hemoglobin or myoglobin. **Hemoglobinuria** without hematuria can occur in the presence of acute or chronic hemolysis. **Myoglobinuria** without hematuria occurs in the presence of rhabdomyolysis resulting from skeletal muscle injury and is generally associated with a fivefold increase in the plasma concentration of creatine kinase. Clinically innocuous heme-negative urine can appear red, cola colored, or burgundy, due to ingestion of various drugs, foods (blackberries, beets), or dyes used in food and candy, whereas dark brown (or black) urine can result from various urinary metabolites.

Evaluation of the child with hematuria begins with a careful history, physical examination, and microscopic urinalysis. This information is used to determine the level of hematuria (upper vs lower urinary tract) and to determine the urgency of the evaluation based on symptomatology. Special consideration needs to be given to the family history, identification of anatomic abnormalities and malformation syndromes, presence of gross hematuria, and manifestations of hypertension, edema, or heart failure.

Table 558.2 lists causes of hematuria. Upper urinary tract sources of hematuria originate within the nephron (glomerulus, tubular system, or interstitium). Lower urinary tract sources of hematuria originate from the pelvicalyceal system, ureter, bladder, or urethra. Hematuria from within the glomerulus is often associated with brown, cola- or tea-colored, or burgundy urine, proteinuria >100 mg/dL via dipstick, urinary microscopic findings of RBC casts, and deformed urinary RBCs (particularly acanthocytes). Hematuria originating within the tubular system may be associated with the presence of leukocytes or renal tubular casts. Lower urinary tract sources of hematuria may be associated with gross hematuria that is bright red or pink, terminal hematuria (gross hematuria occurring at the end of the urine stream), blood clots, normal urinary RBC morphology, and minimal proteinuria on dipstick (<100 mg/dL).

Patients with hematuria can present with a number of symptoms suggesting specific disorders. Tea- or cola-colored urine, facial or body edema, hypertension, and oliguria are classic symptoms of **glomerulonephritis.** Diseases commonly manifesting as glomerulonephritis include postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), IgA vasculitis nephritis (formerly Henoch-Schönlein purpura nephritis), systemic lupus erythematosus (SLE) nephritis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiitis, Goodpasture syndrome, and hemolytic-uremic syndrome. A history of recent upper respiratory, skin, or gastrointestinal infection suggests postinfectious glomerulonephritis, hemolytic-uremic syndrome, or IgA vasculitis nephritis. Rash and joint complaints suggest IgA vasculitis or SLE nephritis.

Hematuria associated with glomerulonephritis is typically painless but can be associated with flank pain when acute or unusually severe. Frequency, dysuria, and unexplained fevers suggest a urinary tract infection, whereas renal colic suggests nephrolithiasis. A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, or tumor. Hematuria associated with headache, mental status changes, visual changes (diplopia), epistaxis, or heart failure suggests associated severe hypertension. Patients with hematuria and a history of trauma require immediate evaluation (see Chapter 80). Child abuse must always be suspected in the child presenting with unexplained perineal bruising and hematuria.

A careful family history is critical in the initial assessment of the child with hematuria given the numerous genetic causes of renal disorders. Hereditary glomerular diseases include hereditary nephritis (isolated Alport syndrome or with leiomyomatosis or macrothrombocytopenia); thin glomerular basement membrane disease; SLE nephritis; hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC); and IgA nephropathy (Berger disease). Other hematuric renal disorders with a hereditary component include both autosomal recessive and autosomal dominant polycystic kidney diseases, atypical hemolytic-uremic syndrome, urolithiasis, and sickle cell disease/trait.

Physical examination may also suggest possible causes of hematuria. The presence of hypertension, edema, or signs of heart failure suggests acute glomerulonephritis. Several malformation syndromes are associated with renal disease, including VATER (*v*ertebral body anomalies, *a*nal atresia, *t*racheo*e*sophageal fistula, and *r*enal dysplasia) syndrome. Abdominal masses may be caused by bladder distention in posterior urethral valves, hydronephrosis in ureteropelvic or ureterovesical junction obstruction, polycystic kidney disease, or Wilms tumor. Hematuria seen in patients with neurologic or cutaneous abnormalities may be the result of a number of syndromic renal disorders, including tuberous sclerosis, von Hippel-Lindau syndrome, and Zellweger (cerebrohepatorenal) syndrome. Anatomic abnormalities of the external genitalia may be associated with hematuria and/or renal disease.

Patients with gross hematuria present additional challenges because of the associated parental anxiety. The most common cause of gross hematuria is bacterial or viral urinary tract infection. **Urethrorrhagia,** which is urethral bleeding in the absence of urine, is associated with

Table 558.1 Other Causes of Red Urine

HEME POSITIVE
Hemoglobin
Myoglobin
HEME NEGATIVE
Drugs
Adriamycin
Chloroquine
Deferoxamine
Hydroxocobalamin
Ibuprofen
Iron sorbitol
Levodopa
Metronidazole
Nitrofurantoin
Phenazopyridine (Pyridium)
Phenolphthalein
Phenothiazines
Phenytoin
Quinine
Rifampin
Salicylates
Sulfasalazine
Dyes (Vegetable/Fruit)
Beets
Blackberries
Blueberries
Food and candy coloring
Paprika
Rhubarb
Metabolites
Homogentisic acid
Melanin
Methemoglobin
Porphyrin
Tyrosinosis
Urates

Table 558.2 Causes of Hematuria in Children

UPPER URINARY TRACT DISEASE
Isolated Renal Disease
Immunoglobulin (Ig) A nephropathy (Berger disease)
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane nephropathy
Postinfectious GN (poststreptococcal GN)*
Membranous nephropathy
Membranoproliferative GN*
Rapidly progressive GN
Focal segmental glomerulosclerosis
Anti–glomerular basement membrane disease
Hereditary angiopathy with nephropathy, aneurysms, muscle cramps (HANAC)
Multisystem Disease
Systemic lupus erythematosus nephritis*
IgA vasculitis nephritis†
Granulomatosis with polyangiitis‡
Microscopic polyangiitis
Goodpasture syndrome
Hemolytic-uremic syndrome
Sickle cell glomerulopathy
HIV nephropathy
Tubulointerstitial Disease
Pyelonephritis
Interstitial nephritis
Papillary necrosis
Acute tubular necrosis
Vascular Disorders
Arterial or venous thrombosis
Malformations (aneurysms, hemangiomas)
Nutcracker syndrome
Hemoglobinopathy (sickle cell trait/disease)
Crystalluria
Anatomic Disorders
Hydronephrosis
Cystic-syndromic kidney disease
Polycystic kidney disease
Multicystic dysplasia
Tumor (Wilms tumor, rhabdomyosarcoma, angiomyolipoma, medullary carcinoma)
Trauma
LOWER URINARY TRACT DISEASE
Inflammation (infectious and noninfectious)
Cystitis
Urethritis
Urolithiasis
Trauma
Coagulopathy
Heavy exercise
Bladder tumor
Factitious syndrome, factitious syndrome by proxy§

*Denotes glomerulonephritides presenting with hypocomplementemia.
†Formerly Henoch-Schönlein purpura.
‡Formerly Wegener granulomatosis.
§Formerly Munchausen syndrome and Munchausen syndrome by proxy.
GN, Glomerulonephritis.

dysuria and blood spots on underwear after voiding. This condition, which often occurs in prepubertal boys at intervals several months apart, has a benign self-limited course. Less than 10% of patients have evidence of glomerulonephritis. Recurrent episodes of gross hematuria suggest IgA nephropathy, Alport syndrome, or thin glomerular basement membrane disease. Dysuria and abdominal or flank pain are symptoms of idiopathic hypercalciuria, or urolithiasis. Table 558.3 lists common causes of gross hematuria; Figure 558.1 outlines a general approach to the laboratory and radiologic evaluation of the patient with glomerular or nonglomerular hematuria. Asymptomatic patients with isolated microscopic hematuria should not undergo extensive diagnostic evaluation, because such hematuria is often transient and benign.

The child with completely asymptomatic isolated microscopic hematuria that persists on at least three urinalyses observed over a minimum of a 2-week period poses a dilemma in regard to the degree of further diagnostic testing that should be performed. Significant disease of the urinary tract is uncommon with this clinical presentation. The initial evaluation of these children should include a urine culture followed by a spot urine for hypercalciuria with a calcium:creatinine ratio in culture-negative patients. In Black patients, a sickle cell screen should be included. If these studies are normal, urinalysis of all first-degree relatives is indicated. Renal and bladder ultrasonography should be considered to rule out structural lesions such as tumor, cystic disease, hydronephrosis, or urolithiasis. Ultrasonography of the urinary tract is most informative in patients presenting with gross hematuria, abdominal pain, flank pain, or trauma. If these initial studies are normal, assessment of serum creatinine and electrolytes is recommended.

The finding of certain hematologic abnormalities can narrow the differential diagnosis. **Anemia** in this setting may be caused by

Table 558.3 Common Causes of Gross Hematuria

Urinary tract infection
Meatal stenosis with ulcer
Perineal irritation
Trauma
Urolithiasis
Hypercalciuria
Obstruction
Coagulopathy
Tumor
Glomerular disease
Postinfectious glomerulonephritis
IgA vasculitis nephritis*
IgA nephropathy
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane disease
Systemic lupus erythematosus nephritis

*Formerly Henoch-Schönlein purpura.

hypervolemia with dilution associated with acute kidney injury; decreased RBC production in chronic kidney disease; hemolysis from hemolytic-uremic syndrome, a chronic hemolytic anemia, or SLE; blood loss from pulmonary hemorrhage, as seen in Goodpasture syndrome; or melena in patients with IgA vasculitis or hemolytic-uremic syndrome. Inspection of the peripheral blood smear might reveal a **microangiopathic** process consistent with the hemolytic-uremic syndrome. The presence of autoantibodies in SLE can result in a positive Coombs test, the presence of antinuclear antibody, leukopenia, and multisystem disease. **Thrombocytopenia** can result from decreased platelet production (malignancies) or increased platelet consumption (SLE, idiopathic thrombocytopenic purpura, hemolytic-uremic syndrome, renal vein thrombosis, or congenital hepatic fibrosis with portal hypertension secondary to autosomal recessive polycystic kidney disease). Although urinary RBC morphology may be normal with lower tract bleeding and dysmorphic from glomerular bleeding, it is not sensitive enough to unequivocally delineate the site of hematuria. A bleeding diathesis is an unusual cause of hematuria, and coagulation studies are not routinely obtained unless a personal or family history suggests a bleeding tendency.

A voiding cystourethrogram is only required in patients with a urinary tract infection, renal scarring, hydroureter, or pyelocaliectasis. Cystoscopy is an unnecessary and costly procedure in most pediatric patients with hematuria and carries the associated risks of anesthesia. This procedure should be reserved for evaluating the rare child with a bladder mass noted on ultrasound, urethral abnormalities caused by trauma, posterior urethral valves, or tumor. The finding of unilateral gross hematuria localized by cystoscopy is rare, but it can indicate a vascular malformation or another anatomic abnormality.

Children with persistent asymptomatic isolated hematuria and a completely normal evaluation should have their blood pressure and urine checked every 3 months until the hematuria resolves. Referral to a pediatric nephrologist should be considered for patients with persistent asymptomatic hematuria greater than 1 year in duration and is recommended for patients with nephritis (glomerulonephritis, tubulointerstitial nephritis), hypertension, renal dysfunction, urolithiasis or nephrocalcinosis, or a family history of renal disease such as polycystic kidney disease or hereditary nephritis. Renal biopsy is indicated for some children with persistent microscopic hematuria and for most children with recurrent gross hematuria associated with decreased renal function, proteinuria, or hypertension.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

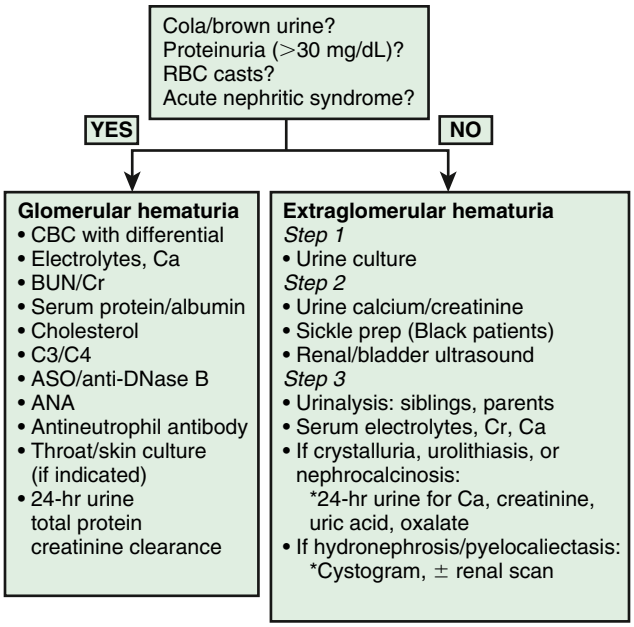

Fig. 558.1 Diagnostic algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, Antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.

Chapter 559

Isolated Glomerular Diseases Associated with Recurrent Gross Hematuria

Francisco X. Flores

INTRODUCTION

Approximately 10% of children with gross hematuria have an acute or a chronic form of glomerulonephritis that may be associated with a systemic illness. The gross hematuria, which is usually characterized by brown or cola-colored urine, may be painless or associated with vague flank or abdominal pain. A presentation with gross hematuria is common within 1-2 days after the onset of an apparent viral upper respiratory tract infection in immunoglobulin (Ig) A nephropathy and typically resolves within 5 days. This relatively short period contrasts with a latency period of 7-21 days occurring between the onset of a streptococcal pharyngitis or impetiginous skin infection and the development of postinfectious acute glomerulonephritis. Gross hematuria in these circumstances can last as long as 4-6 weeks. Gross hematuria can also be seen in children with glomerular basement membrane (GBM) disorders such as hereditary nephritis (Alport syndrome [AS]) and thin GBM disease. These glomerular diseases can also manifest as microscopic hematuria and/or proteinuria without gross hematuria.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.1 Immunoglobulin A Nephropathy (Berger Nephropathy)

Francisco X. Flores

IgA nephropathy is the most common chronic glomerular disease in children. It is characterized by a predominance of IgA within mesangial glomerular deposits in the absence of systemic disease. Its diagnosis requires a renal biopsy, which is performed when clinical features warrant confirmation of the diagnosis or characterization of the histologic severity, which might affect therapeutic decisions.

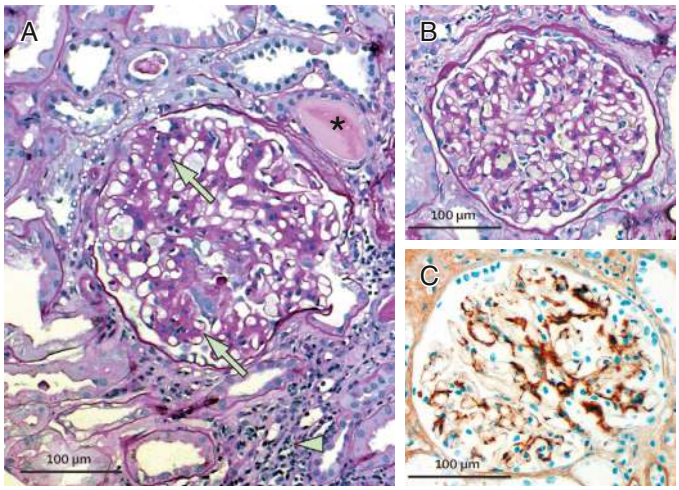

Fig. 559.1 IgA nephropathy. **A,** In IgA nephropathy, segmental areas *(arrows)* of mesangial hypercellularity and matrix expansion occur, characteristic of mesangioproliferative glomerulonephritis. Part of the glomerular tuft adheres to Bowman's capsule *(white dashed oval)*, constituting the starting point of a secondary focal segmental glomerulosclerosis lesion. Tubulointerstitial damage with leukocyte infiltrates, tubular atrophy and fibrosis *(arrowhead)*, and tubular protein casts *(asterisk)* is also present. Periodic acid–Schiff (PAS) stain. **B,** Other glomeruli in the same patient exhibit few pathologic abnormalities on light microscopy (PAS stain), but the characteristic mesangial granular IgA deposition (**C**) can be found in these glomeruli as well. *(From Floege J, Amann K. Primary glomerulonephritides. Lancet. 2016;387:2036–2046. Fig. 2.)*

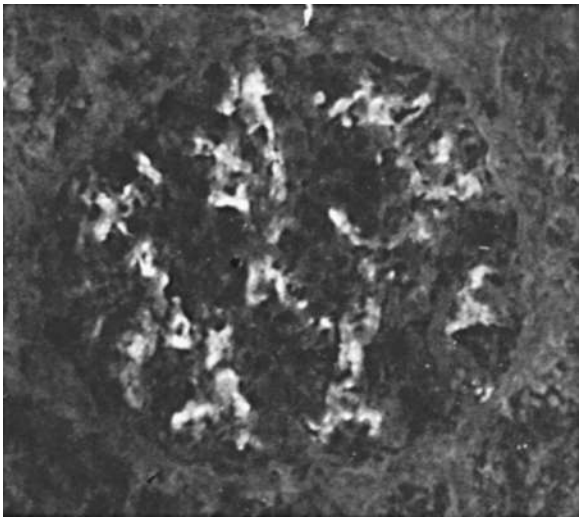

Fig. 559.2 Immunofluorescence microscopy of the biopsy specimen from a child with episodes of gross hematuria demonstrating mesangial deposition of IgA (×150).

PATHOLOGY AND PATHOLOGIC DIAGNOSIS

Focal and segmental mesangial proliferation and an increased mesangial matrix are seen in the glomerulus (Fig. 559.1). Renal histology demonstrates mesangial proliferation that may be associated with epithelial cell crescent formation and sclerosis. IgA deposits in the mesangium are often accompanied by C3 complement (Fig. 559.2).

IgA nephropathy is an immune complex disease initiated by excessive amounts of poorly galactosylated IgA_1 in the serum, causing the production of IgG and IgA autoantibodies. The abnormalities identified in the IgA system have also been observed in patients with IgA vasculitis (formerly known as Henoch-Schönlein purpura), and this finding lends support to the hypothesis that these two diseases are part of the same disease spectrum. Familial clustering of IgA nephropathy cases suggests the importance of genetic factors. Genome-wide linkage analysis suggests the linkage of IgA nephropathy to 6q22-23 in multiplex IgA nephropathy kindreds. Additional genomic studies demonstrate a high predisposition to IgA nephropathy in Southeast Asia.

CLINICAL AND LABORATORY MANIFESTATIONS

IgA nephropathy is seen more often in male than in female patients. Although there are rare cases of rapidly progressive forms of the disease, the clinical presentation of childhood IgA nephropathy is often benign compared with that of adults. IgA nephropathy is an uncommon cause of end-stage renal failure during childhood. A majority of children with IgA nephropathy in the United States and Europe present with gross hematuria, whereas microscopic hematuria and/or proteinuria is a more common presentation in Japan. Other presentations include acute nephritic syndrome, nephrotic syndrome, or a combined nephritic-nephrotic picture. Gross hematuria often occurs within 1-2 days of onset of an upper respiratory or gastrointestinal infection, in contrast with the longer latency period observed in acute postinfectious glomerulonephritis and may be associated with loin pain. Proteinuria is often <1,000 mg/24 hr in patients with asymptomatic microscopic hematuria. Mild to moderate hypertension is most often seen in patients with nephritic or nephrotic syndrome but is rarely severe enough to result in hypertensive emergencies. Normal serum levels of C3 in IgA nephropathy help to distinguish this disorder from postinfectious glomerulonephritis. Serum IgA levels have limited diagnostic value because they are elevated in only 50% of pediatric patients.

PROGNOSIS AND TREATMENT

Although IgA nephropathy does not lead to significant kidney damage in most children, progressive disease develops in 20–30% of adult patients 15-20 years after disease onset. Therefore most children with IgA nephropathy do not display progressive renal dysfunction until adulthood, prompting the need for careful long-term follow-up. Poor

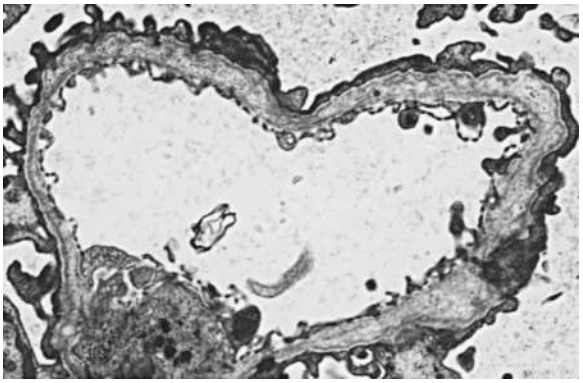

Fig. 559.3 Electron micrograph of a biopsy specimen from a child with Alport syndrome depicting thickening, thinning, splitting, and layering of the glomerular basement membrane (GBM; ×1,650). *(From Yum M, Bergstein JM. Basement membrane nephropathy. Hum Pathol. 1983;14:996–1003.)*

prognostic indicators at presentation or follow-up include persistent hypertension, diminished renal function, and significant, increasing, or persistent proteinuria. A more severe prognosis is correlated with histologic evidence of diffuse mesangial proliferation, extensive glomerular crescents, glomerulosclerosis, and diffuse tubulointerstitial changes, including inflammation and fibrosis.

The primary treatment of IgA nephropathy is appropriate blood pressure control and management of significant proteinuria. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are effective in reducing proteinuria and slowing the rate of disease progression when used individually or in combination. Fish oil, which contains antiinflammatory omega-3 polyunsaturated fatty acids, may decrease the rate of disease progression in adults. If a renin-angiotensin system (RAS) blockade proves ineffective and significant proteinuria persists, then addition of immunosuppressive therapy with corticosteroids is recommended. Corticosteroids reduce proteinuria and improve renal function in those patients with a glomerular filtration rate >60 mL/min/m^2. It remains unclear if the effects of glucocorticoids deter progression to end-stage renal failure to a degree to offset their significant side effects. Additional immunosuppression with cyclophosphamide or azathioprine has not appeared to be effective. Tonsillectomy has been used as a treatment for IgA nephropathy in many countries, including Japan. Performing a tonsillectomy in the absence of significant tonsillitis in association with IgA nephropathy is currently not recommended. Targeted-release oral budesonide is approved by the FDA to reduce proteinuria in adult patients with IgA nephropathy. Patients with IgA nephropathy may undergo successful kidney transplantation. Although recurrent disease is frequent, allograft loss caused by IgA nephropathy occurs in only 15–30% of patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.2 Alport Syndrome

Francisco X. Flores

Alport syndrome (AS), or hereditary nephritis, is a genetically heterogeneous disease caused by pathogenic variants in the genes coding for type IV collagen, a major component of basement membranes. These genetic alterations are associated with marked variability in the clinical presentation, natural history, and histologic abnormalities.

GENETICS

Approximately 70–80% of patients have X-linked inheritance caused by a mutation in the *COL4A5* gene encoding the α5 chain of type IV collagen. Patients with a subtype of X-linked AS and diffuse **leiomyomatosis** demonstrate a contiguous pathogenic variant within the *COL4A5* and *COL4A6* genes that encodes the α5 and α6 chains, respectively, of type IV collagen. Autosomal recessive forms of AS in approximately 5% of patients are caused by pathogenic variants in the *COL4A3* and *COL4A4* genes on chromosome 2 encoding the α3 and α4 chains, respectively, of type IV collagen. An autosomal dominant form of AS linked to the *COL4A3-COL4A4* gene locus occurs in 19–31% of cases.

Fechtner syndrome (AS with macrothrombocytopenia) and **Epstein syndrome** are autosomal dominant disorders due to pathogenic variants in *MYH9*. **Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)** may initially resemble AS. HANAC is due to pathogenic variants in the *COL4A1* gene.

PATHOLOGY

Kidney biopsy specimens during the first decade of life will show only a few changes on light microscopy. Later, the glomeruli may develop mesangial proliferation and capillary wall thickening, leading to progressive glomerular sclerosis. Tubular atrophy, interstitial inflammation and fibrosis, and lipid-containing tubular or interstitial cells, called *foam cells,* develop as the disease progresses. Immunopathologic studies are usually nondiagnostic.

In most patients, electron microscopy reveals diffuse thickening, thinning, splitting, and layering of the glomerular and tubular basement membranes (Fig. 559.3). To confound the diagnosis, the ultrastructural analysis of the GBM in all genetic forms of AS may be completely normal, display nonspecific alterations, or demonstrate only uniform thinning.

CLINICAL MANIFESTATIONS

All patients with AS have *asymptomatic* microscopic hematuria, which may be *intermittent* in females and younger males. Single or recurrent episodes of gross hematuria commonly occurring 1-2 days after an upper respiratory infection are seen in approximately 50% of patients. Proteinuria is often seen in males but may be absent, mild, or intermittent in females. Progressive proteinuria, often exceeding 1 g/24 hours, is common by the second decade of life and can be severe enough to cause nephrotic syndrome.

Bilateral **sensorineural hearing loss,** which is never congenital, develops in 90% of hemizygous males with X-linked AS, 20% of heterozygous females with X-linked AS, and 67% of patients with autosomal recessive AS. This deficit begins in the high-frequency range but progresses to involve the hearing associated with normal speech, prompting the need for hearing aids. This progression of hearing loss seems to run parallel to the loss of renal function. **Ocular abnormalities**, which occur in 30–40% of patients with X-linked AS, include anterior lenticonus (extrusion of the central portion of the lens into the anterior chamber), macular flecks, and corneal erosions. **Leiomyomatosis** of the esophagus, tracheobronchial tree, and female genitals has been reported but is rare.

DIAGNOSIS

A combination of a thorough family history, a screening urinalysis of first-degree relatives, an audiogram, and an ophthalmologic examination are critical in making the diagnosis of AS. The presence of anterior lenticonus is pathognomonic. AS is highly likely in the patient who has hematuria and at least two of the following characteristic clinical features: macular flecks, recurrent corneal erosions, GBM thickening and thinning, or sensorineural deafness. The absence of epidermal basement membrane staining for the α5 chain of type IV collagen in male hemizygotes and discontinuous epidermal basement membrane staining in female heterozygotes on skin biopsy is pathognomonic for X-linked AS and can preclude a diagnostic renal biopsy. Genetic testing is clinically available for X-linked AS and *COL4A5* pathogenic variants. Prenatal diagnosis is available for families with members who have X-linked AS and who carry an identified pathogenic variant.

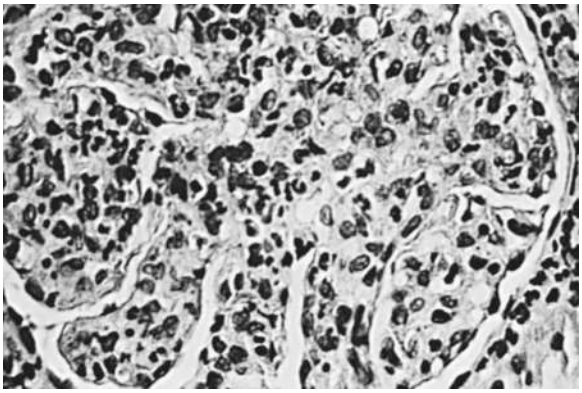

Fig. 559.4 Glomerulus from a patient with poststreptococcal glomerulonephritis appears enlarged and relatively bloodless and shows mesangial proliferation and exudation of neutrophils (×400).

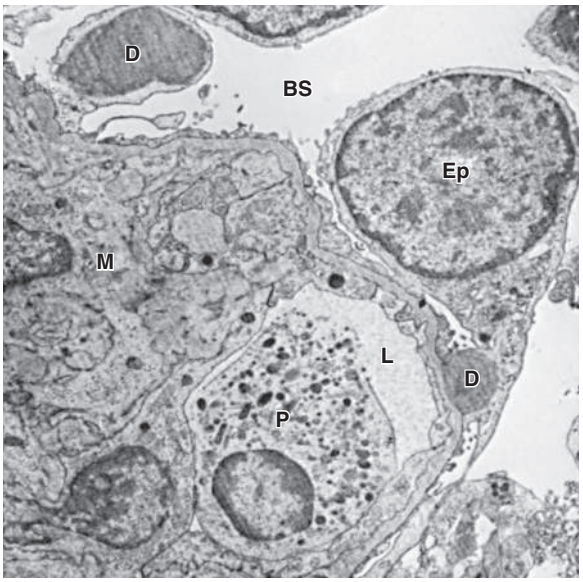

Fig. 559.5 Electron micrograph in poststreptococcal glomerulonephritis demonstrating electron-dense deposits *(D)* on the epithelial cell *(Ep)* side of the glomerular basement membrane. A polymorphonuclear leukocyte *(P)* is present within the lumen *(L)* of the capillary. BS, Bowman's space; M, mesangium.

PROGNOSIS AND TREATMENT

The risk of progressive renal dysfunction leading to end-stage kidney disease (ESKD) is highest among hemizygotes and autosomal recessive homozygotes. ESKD occurs before age 30 years in approximately 75% of hemizygotes with X-linked AS. The risk of ESKD in X-linked heterozygotes is 12% by age 40 years and 30% by age 60 years. Risk factors for progression are gross hematuria during childhood, nephrotic syndrome, and prominent GBM thickening. An intrafamilial variation in phenotypic expression results in significant differences in the age of ESKD among family members. No specific therapy is available to treat AS, although angiotensin-converting enzyme inhibitors (and possibly angiotensin II receptor inhibitors) can slow the rate of progression. Careful management of renal failure complications, such as hypertension, anemia, and electrolyte imbalance, is critical. Patients with ESKD are treated with dialysis and kidney transplantation (see Chapter 573). Approximately 5% of kidney transplantation recipients develop anti-GBM nephritis, which occurs primarily in males with X-linked AS who develop ESKD before age 30 years.

Pharmacologic treatment of proteinuria with angiotensin-converting enzyme inhibition or angiotensin II receptor blockade has proven effective in other glomerular diseases and has also shown promise in AS. Screening of heterozygote carriers for significant renal disease in later adulthood and possible treatment of significant proteinuria is also recommended.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.3 Thin Basement Membrane Disease

Francisco X. Flores

Thin basement membrane disease (TBMD) is defined by the presence of persistent microscopic hematuria and isolated thinning of the GBM (and, occasionally, tubular basement membranes) on electron microscopy. Microscopic hematuria is often initially observed during childhood and may be intermittent. Episodic gross hematuria can also be present, particularly after a respiratory illness. Isolated hematuria in multiple family members without renal dysfunction is referred to as **benign familial hematuria.** Although most of these patients will not undergo renal biopsy, it is often presumed that the underlying pathology is TBMD. TBMD may be sporadic or transmitted as an autosomal dominant trait. Heterozygous pathogenic variants in the *COL4A3* and *COL4A4* genes, which encode the α3 and α4 chains of type IV collagen present in the GBM, result in TBMD. Rare cases of TBMD progress, and such patients develop significant proteinuria, hypertension, or renal insufficiency. Homozygous pathogenic variants in these same genes result in autosomal recessive AS. Therefore in these rare cases, the absence of a positive family history for renal insufficiency or deafness would not necessarily predict a benign outcome. Consequently, monitoring patients with benign familial hematuria for progressive proteinuria, hypertension, or renal dysfunction is important throughout childhood and young adulthood.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.4 Acute Poststreptococcal Glomerulonephritis

Francisco X. Flores

Group A β-hemolytic streptococcal infections are common in children and can lead to the postinfectious complication of acute GN. Acute poststreptococcal glomerulonephritis (APSGN) is a classic example of the **acute nephritic syndrome** characterized by the sudden onset of gross hematuria, edema, hypertension, and renal dysfunction. It is one of the most common glomerular causes of gross hematuria in children and is a major cause of morbidity in group A β-hemolytic streptococcal infections.

ETIOLOGY AND EPIDEMIOLOGY

APSGN follows infection of the throat or skin by certain *nephritogenic* strains of group A β-hemolytic streptococci. Epidemics and clusters of household (camps, military) cases occur throughout the world, and 97% of cases occur in less-developed countries. The overall incidence has decreased in industrialized nations, presumably as a result of improved hygienic conditions and the near eradication of streptococcal pyoderma. Poststreptococcal GN commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months. Although epidemics of nephritis have been described in association with throat (serotypes M1, M4, M25, and some strains of M12) and skin (serotype M49) infections, this disease is most commonly sporadic.

PATHOLOGY

Glomeruli appear enlarged and relatively bloodless and show a diffuse mesangial cell proliferation, with an increase in mesangial matrix (Fig. 559.4). Polymorphonuclear leukocyte infiltration is common in glomeruli during the early stage of the disease. Crescents and interstitial inflammation may be seen in severe cases, but these changes are not specific for poststreptococcal GN. Immunofluorescence microscopy reveals a pattern of "lumpy-bumpy" deposits of immunoglobulin and complement on the glomerular basement membrane and in the mesangium. On electron microscopy, electron-dense deposits, or "humps," are observed on the epithelial side of the glomerular basement membrane (Fig. 559.5).

PATHOGENESIS

Morphologic studies and a depression in the serum complement (C3) level provide strong evidence that ASPGN is mediated by immune complexes. Circulating immune complex formation with streptococcal antigens and subsequent glomerular deposition is thought less likely to be a pathogenic mechanism. Molecular mimicry, whereby circulating antibodies elicited by streptococcal antigens react with normal glomerular antigens, in situ immune complex formation of antistreptococcal

Table 559.1 Summary of Primary Renal Diseases that Manifest as Acute Glomerulonephritis

DISEASES	POSTSTREPTOCOCCAL GLOMERULONEPHRITIS	IGA NEPHROPATHY	GOODPASTURE SYNDROME	IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS
CLINICAL MANIFESTATIONS				
Age and sex	All ages, mean 7 yr, 2:1 male	10-35 yr, 2:1 male	15-30 yr, 6:1 male	Adults, 2:1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	5–10%	Rare	Rare	10–20%
Hypertension	60%	30–50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive Streptozyme (95%) ↓ C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in some
Immunogenetics	HLA-B12, D "EN" (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
RENAL PATHOLOGY				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposits
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25–50%	75% stabilize or improve if treated early	75% stabilize or improve if treated early
Treatment	Monitor for oliguria, hypertension; treat appropriately	Uncertain (options include steroids, and ACE inhibitors); sparsentan (adults)	Plasma exchange, steroids, cyclophosphamide	Steroid pulse therapy

*Relative risk.
ACE, Angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.
From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004.

antibodies with glomerular deposited antigen, and complement activation by directly deposited streptococcal antigens, continues to be considered as a probable mechanism of immunologic injury.

Group A streptococci possesses M proteins, and nephritogenic strains are related to the M protein serotype. The search for the precise nephritogenic antigen(s) that cause disease suggests that streptococcal pyogenic exotoxin (SPE) B and nephritis-associated streptococcal plasmin receptor are promising candidates. Both have been identified in glomeruli of affected patients, and in one study, circulating antibodies to SPE B were found in all patients. Cross reactivity of SPE B and other M proteins with various components of the glomerular basement membrane also give evidence for molecular mimicry.

CLINICAL MANIFESTATIONS

Poststreptococcal GN is most common in children ages 5-12 years and uncommon before the age of 3 years. The typical patient develops an acute nephritic syndrome 1-2 weeks after an antecedent streptococcal pharyngitis or 3-6 weeks after a streptococcal pyoderma. The history of a specific infection may be absent because symptoms may have been mild or have resolved without patients receiving specific treatment or seeking the care of a medical provider.

The severity of kidney involvement varies from asymptomatic microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Depending on the severity of renal involvement, patients can develop various degrees of edema, hypertension, and oliguria. Patients are at risk for developing encephalopathy and/or heart failure secondary to hypertension or hypervolemia. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status, or new seizures. The effects of acute hypertension not only depend on the severity of hypertension but also the absolute change in comparison with the patient's baseline blood pressure and the rate at which it has risen. Respiratory distress, orthopnea, and cough may be symptoms of pulmonary edema and heart failure. Peripheral edema typically results from salt and water retention and is common; nephrotic syndrome develops in a minority (<5%) of childhood cases. Atypical presentations of APSGN include those with subclinical disease and those with severe symptoms but an absence of initial urinary abnormalities; in individuals who present with a purpuric rash, it is difficult to distinguish APSGN from IgA vasculitis without a renal biopsy.

The acute phase generally resolves within 6-8 weeks. Although urinary protein excretion and hypertension usually normalize by 4-6 weeks after onset, persistent microscopic hematuria can persist for 1-2 years after the initial presentation.

DIAGNOSIS

Urinalysis demonstrates red blood cells, often in association with red blood cell casts, proteinuria, and polymorphonuclear leukocytes. A mild normochromic anemia may be present from hemodilution and low-grade hemolysis. The serum C3 level is significantly reduced in >90% of patients in the acute phase and returns to normal 8-10 weeks

Table 559.2 Secondary Causes of Membranoproliferative Glomerulonephritis

ASSOCIATED WITH INFECTION
Hepatitis B and C
Visceral abscesses
Infective endocarditis
Shunt nephritis
Quartan malaria
Schistosoma nephropathy
Mycoplasma infection
ASSOCIATED WITH RHEUMATOLOGIC DISEASE
Systemic lupus erythematosus
Scleroderma
Sjögren syndrome
Sarcoidosis
Mixed essential cryoglobulinemia with or without hepatitis C infection
Anti–smooth muscle syndrome
ASSOCIATED WITH MALIGNANCY
Carcinoma
Lymphoma
Leukemia
ASSOCIATED WITH AN INHERITED DISORDER
α_1-Antitrypsin deficiency
Complement deficiency (C2 or C3), with or without partial lipodystrophy

From Saha MK, Pendergraft WF III, Jennette JC, et al. Primary glomerular disease. In: Yu AS, Chertow GM, Luyckx VA, et al., eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Box 31.7.

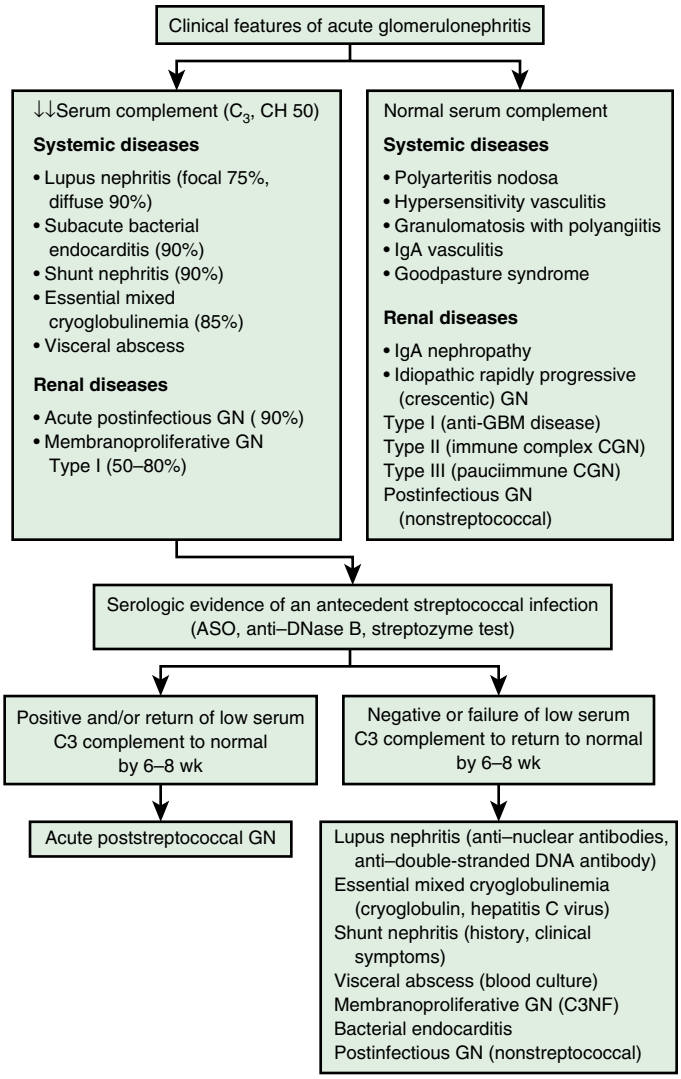

Fig. 559.6 Differential diagnostic algorithm of acute glomerulonephritis *(GN).* ASO, Anti–streptolysin O; CGN, crescentic glomerulonephritis; GBM, glomerular basement membrane; NF, nuclear factor. *(Adapted from Sulyok E. Acute proliferative glomerulonephritis. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric Nephrology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004: Fig. 30-4.)*

after the onset. Although serum CH_{50} is commonly depressed, *C4 is most often normal in APSGN,* or only mildly depressed.

Confirmation of the diagnosis requires clear evidence of a prior streptococcal infection. A positive throat culture report might support the diagnosis or might represent the carrier state. A rising antibody titer to streptococcal antigen(s) confirms a recent streptococcal infection. The antistreptolysin O titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections. The best single antibody titer to document cutaneous streptococcal infection is the antideoxyribonuclease B level. If available, a positive Streptozyme screen (which measures multiple antibodies to different streptococcal antigens) is a valuable diagnostic tool. Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and far more sensitive than positive bacterial cultures obtained at the time of onset of acute nephritis.

MRI of the brain is indicated in patients with severe neurologic symptoms and can demonstrate **posterior reversible encephalopathy syndrome** in the parietooccipital areas on T2 weighted images. Chest x-ray is indicated in those with signs of heart failure or respiratory distress, or physical exam findings of a heart gallop, decreased breath sounds, rales, or hypoxemia.

The clinical diagnosis of poststreptococcal GN is quite likely in a child presenting with acute nephritic syndrome, evidence of recent streptococcal infection, and a low C3 level. However, it is important to consider other diagnoses such as systemic lupus erythematosus, endocarditis, membranoproliferative GN, and an acute exacerbation of chronic GN. Renal biopsy should be considered only in the presence of acute renal failure, nephrotic syndrome, absence of evidence of streptococcal infection, or normal complement levels. In addition, renal biopsy is considered when hematuria and proteinuria, diminished renal function, and/or a low C3 level persist more than 2 months after onset. Persistent hypocomplementemia can indicate a chronic form of postinfectious GN or another disease such as membranoproliferative GN.

The differential diagnosis of poststreptococcal GN includes many of the causes of hematuria listed in Table 559.1 and Table 558.2, and algorithms to help with the diagnosis are presented in Figs. 559.6 and 559.7. Acute postinfectious GN can also follow other infections with coagulase-positive and coagulase-negative staphylococci, *Streptococcus pneumoniae,* and gram-negative bacteria. The clinical course, histopathology, and laboratory features are similar to those described for APSGN. For some, the terms APSGN and acute postinfectious GN are used synonymously. Acute GN can occur after certain fungal, rickettsial, protozoan, parasitic, or viral diseases. Among the latter, influenza and parvovirus infections are particularly notable.

COMPLICATIONS

Acute complications result from hypertension and acute renal dysfunction. Hypertension is seen in 60% of patients and is associated with hypertensive encephalopathy in 10% of cases. Although the

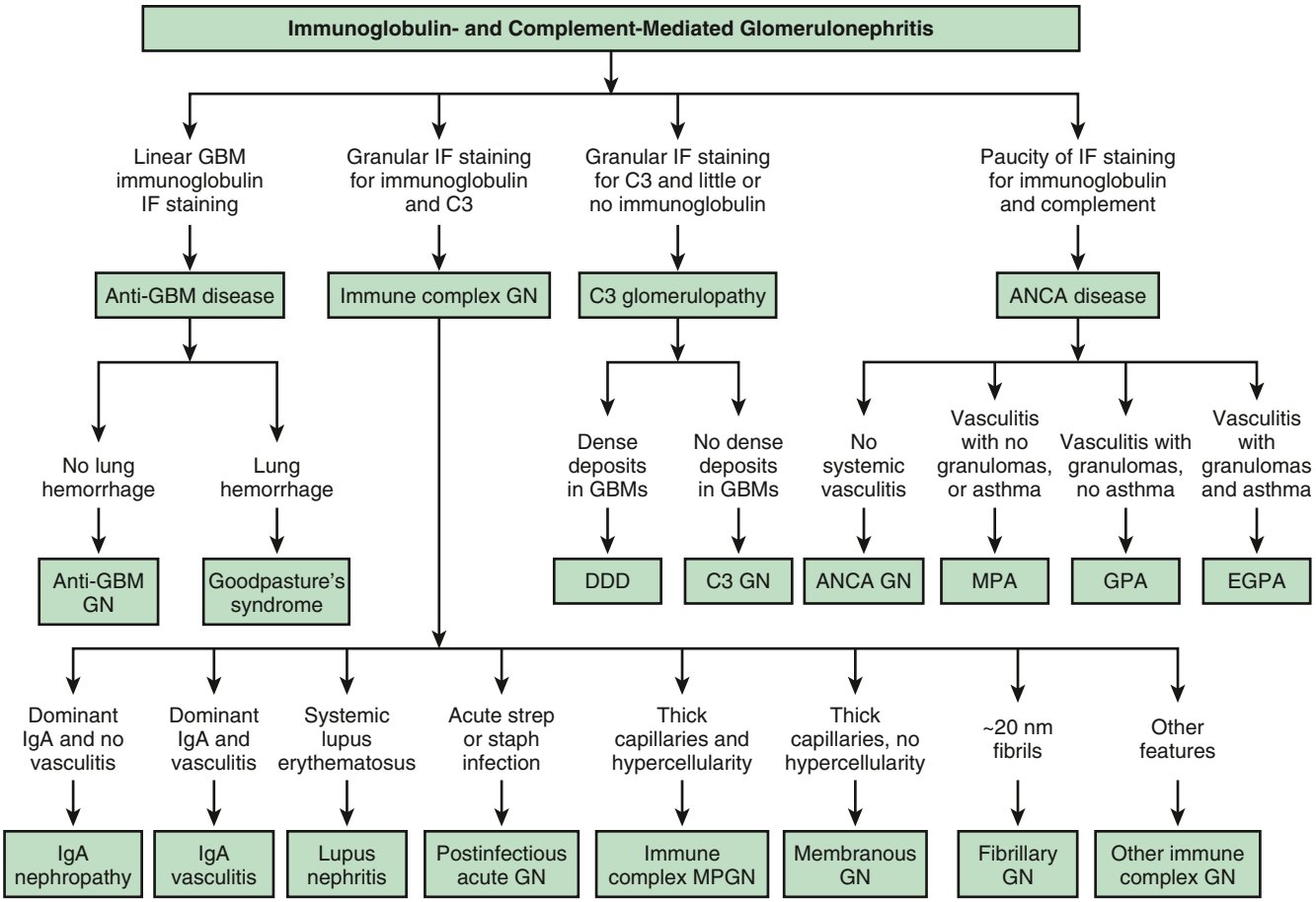

Fig. 559.7 Algorithm for diagnostic classification of glomerulonephritis *(GN)* that is known or suspected of being mediated by antibodies and complement. Note that the integration of light microscopy, immunofluorescence *(IF)* microscopy, electron microscopy, laboratory data, and clinical manifestations is required to precisely diagnose GN. ANCA, Anti–neutrophil cytoplasmic autoantibody; DDD, dense deposit disease; EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; MPA, microscopic polyangiitis; MPGN, membranoproliferative glomerulonephritis. *(From Saha MK, Pendergraft WF III, Jennette JC, et al. Primary glomerular disease. In Yu AS, BChir GM, Chertow GM, et al., eds. Brenner & Rector's The Kidney, 11th ed. Philadelphia: Elsevier; 2020: Fig. 31-35.)*

neurologic sequelae are often reversible with appropriate management, severe prolonged hypertension can lead to intracranial bleeding. Other potential complications include heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia. Acute renal failure can require treatment with dialysis.

PREVENTION

Early systemic antibiotic therapy for streptococcal throat and skin infections does not eliminate the risk of GN. Family members of patients with acute GN, especially young children, should be considered at risk and be cultured for group A β-hemolytic streptococci and treated if positive. Family pets, particularly dogs, have also been reported as carriers.

TREATMENT

Management is directed at treating the acute effects of renal dysfunction and hypertension (see Chapter 572.1). Although a 10-day course of systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms, antibiotic therapy does not affect the natural history of APSGN. This is unlike the GN seen in the context of ongoing or chronic infections, as noted in Chapter 560.1. Sodium and fluid restriction, diuretics, and pharmacotherapy with calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors are standard therapies used to treat hypertension.

PROGNOSIS

Complete recovery occurs in >95% of children with APSGN. Recurrences are extremely rare. Mortality in the acute stage can be avoided by appropriate management of acute renal failure, cardiac failure, and hypertension. Infrequently, the acute phase is severe and leads to glomerulosclerosis and chronic renal disease in <2% of affected children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.5 Membranous Nephropathy

Francisco X. Flores

Membranous nephropathy (MN), among the most common causes of nephrotic syndrome in adults, is a rare cause of nephrotic syndrome in children. MN is classified as the primary, idiopathic form, where there is isolated renal disease, or secondary MN, where nephropathy is associated with other identifiable systemic diseases or medications. In children, *secondary* MN is far more common than primary, idiopathic MN. The most common etiologies of secondary

MN are systemic lupus erythematosus or chronic infections. Among the latter, chronic hepatitis B infection and congenital syphilis are the best characterized and recognized causes of MN. Other chronic infections have also been associated with MN, including malaria, which is likely the most common cause of nephrotic syndrome worldwide. Certain medications, such as penicillamine and gold, or chronic factor replacement in patients with hemophilia, can also cause MN. Rare causes associated with MN include tumors, such as neuroblastoma, or other idiopathic systemic diseases. Identification of secondary causes of MN is critical, because removal of the offending agent or treatment of the causative disease often leads to resolution of the associated nephropathy and improves patient outcome.

PATHOLOGY

Glomeruli have diffuse thickening of the glomerular basement membrane (GBM), without significant cell proliferative changes. Immunofluorescence and electron microscopy typically demonstrate granular deposits of IgG and C3 located on the epithelial side of the GBM. The GBM thickening presumably results from the production of membrane-like material in response to deposition of immune complexes (Fig. 559.8).

PATHOGENESIS

MN is believed to be caused by in situ immune complex formation. Therefore antigens from the infectious agents or medications associated with secondary MN directly contribute to the pathogenesis of the renal disease. The causative antigen in idiopathic MN is not established, but the podocyte phospholipase A2 receptor (PLA2R), present on normal podocytes, may be a target antigen in idiopathic MN. Antigen from this receptor is found in immune deposits extracted from glomeruli in patients with idiopathic MN. The majority of idiopathic MN patients have circulating antibody against this podocyte membrane antigen, as well as against several podocyte cytoplasmic antigens. Childhood MN may be associated with anticationic bovine serum albumin antibodies. In addition, neutral endopeptidase antigen may be the antigen in neonatal onset MN.

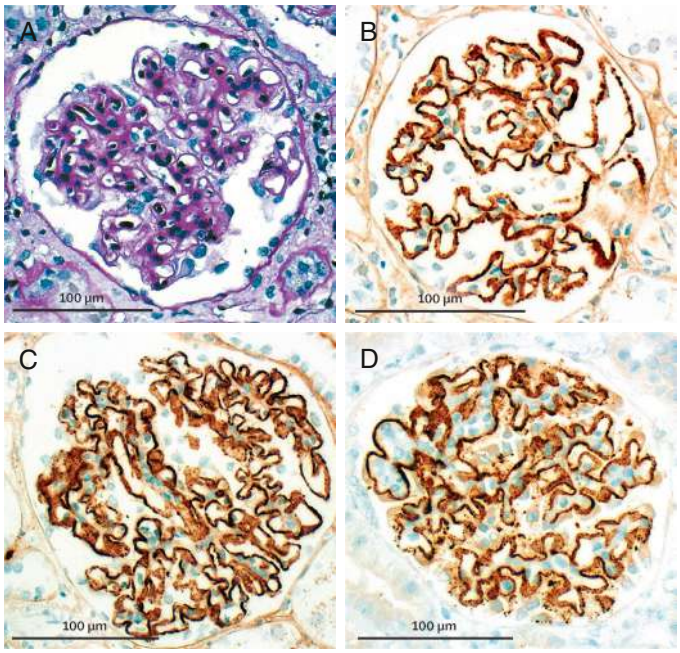

Fig. 559.8 Membranous glomerulonephritis. The periodic acid–Schiff (PAS) stain (A) shows slightly thickened glomerular basement membranes and prominent podocytes. On immunohistology, granular deposits of IgG (B) and C3c (C) can be found along the glomerular basement membrane, and pronounced de novo expression of phospholipase A2 receptor (PLA2R) (D) is present on the podocytes. *(From Floege J, Amann K. Primary glomerulonephritides. Lancet. 2016;387:2036–2046. Fig. 3.)*

CLINICAL MANIFESTATIONS

In children, MN is most common in the second decade of life, but it can occur at any age, including infancy. The disease usually manifests as nephrotic syndrome and accounts for 2–6% of all cases of childhood nephrotic syndrome. Most patients also have microscopic hematuria and only rarely present with gross hematuria. Approximately 20–30% of children have hypertension at presentation. A subset of patients with MN present with a major venous thrombosis, commonly **renal vein thrombosis**. This complication of nephrotic syndrome (see Chapter 567) is particularly common in patients with MN. Serum C3 and CH_{50} levels are normal, except in secondary forms such as in systemic lupus erythematosus, where levels may be depressed (see Fig. 559.6).

DIAGNOSIS

MN might be suspected on clinical grounds, particularly in the setting of known risk factors for secondary forms of the disease. In the past, the diagnosis could be established only by renal biopsy, but testing for PLA2R antibodies has allowed a noninvasive way to make the diagnosis, to differentiate primary vs secondary MN, and to guide treatment decisions. Common indications for renal biopsy leading to the diagnosis of MN include presentation with nephrotic syndrome in a child >10 years old or unexplained persistent hematuria with significant proteinuria.

PROGNOSIS AND TREATMENT

The clinical course of idiopathic membranous glomerulopathy is variable. Children presenting with asymptomatic, low-grade proteinuria can enter remission spontaneously. Retrospective reports of children 1-15 years after diagnosis treated with a variety of regimens indicate that 20% progress to chronic renal failure, 40% continue with active disease, and 40% achieve complete remission. Poor prognostic factors include male gender, high levels of proteinuria, reduced kidney function, and findings of glomerulosclerosis and tubular damage in the renal biopsy. Although no controlled trials have been performed in children, immunosuppressive therapy with an extended course of prednisone can be effective in promoting complete resolution of symptoms. The addition of chlorambucil or cyclophosphamide provides further benefit to those not responding to steroids alone. Rituximab has shown significant promise in adults and has been proposed by some as the first-line treatment but has yet to be studied in a randomized controlled trial in any age-group. For those unresponsive to immunosuppression, or with mild clinical features, proteinuria can be reduced with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.6 Membranoproliferative Glomerulonephritis

Francisco X. Flores

Membranoproliferative glomerulonephritis (MPGN), also known as **mesangiocapillary glomerulonephritis**, most commonly occurs in older children or young adults. MPGN can be classified into *primary* (idiopathic) and *secondary* forms of glomerular disease. Secondary forms of MPGN are most commonly associated with subacute and chronic infection, including hepatitis B and C, syphilis, endocarditis, and infected shunts, especially ventriculoatrial

shunts (shunt nephritis) (Table 559.2). MPGN can also be one of the glomerular lesions seen in lupus nephritis (see Chapter 560.2).

PATHOLOGY

Primary MPGN is defined by the histologic pattern of glomeruli as seen by light, immunofluorescence, and electron microscopy. Two subtypes have been defined on histologic criteria and are associated with different clinical phenotypes. **Type I MPGN** is most common. Glomeruli have an accentuated lobular pattern from diffuse mesangial expansion, endocapillary proliferation, and an increase in mesangial cells and matrix. The glomerular capillary walls are thickened, often with splitting from interposition of the mesangium. Crescents, if present, indicate a poor prognosis. Immunofluorescence microscopy reveals C3 and lesser amounts of immunoglobulin in the mesangium and along the peripheral capillary walls in a lobular pattern. Electron microscopy confirms numerous deposits in the mesangial and subendothelial regions.

Far less common is **type II MPGN,** also called **dense deposit disease,** which has similar light microscopic findings as type I MPGN. Differentiation from type I disease is by immunofluorescence and electron microscopy. In type II disease, C3 immunofluorescence typically is prominent, without concomitant immunoglobulin. By electron microscopy, the lamina densa in the GBM undergoes a very dense transformation, without evident immune complex–type deposits.

C3 glomerulonephritis (C3GN) is a related but separate diagnostic category. By light and electron microscopy C3GN usually has features indistinguishable from classic MPGN. Immunofluorescence studies distinguish between the two, with C3GN having only C3 deposition and MPGN having both C3 and immunoglobulin fluorescence.

PATHOGENESIS

Although the histology of type I MPGN produced by primary and secondary forms is indistinguishable, it appears that type I disease occurs when circulating immune complexes become trapped in the glomerular subendothelial space, which then causes injury, resulting in the characteristic proliferative response and mesangial expansion. Further evidence confirming this pathway to glomerular injury is the finding of complement activation through the classic pathway in as many as 50% of affected patients.

Type II MPGN appears *not* to be mediated by immune complexes. The pathogenesis of the disease is not known, but the characteristic finding of severely depressed serum complement levels suggests that deranged complement regulation might play a major role in the disease. A typical finding is markedly depressed serum C3 complement levels, with normal levels of other complement components. In many patients with type II MPGN, **C3 nephritic factor** (ant–C3 convertase antibody) is present. This factor activates the alternative complement pathway. In unusual cases, patients with type II MPGN demonstrate an associated systemic disease called **partial lipodystrophy,** where there is diffuse loss of adipose tissue and decreased complement in the presence of C3 nephritic factor. The correlation between the presence of C3 nephritic factor, complement levels, and disease presence or severity is not strong, indicating that the complement abnormalities alone are not sufficient to cause the disease.

Type II MPGN (dense deposit disease) is considered part of the broader spectrum of C3GN. The latter, as defined previously pathologically, appears to be caused by primary dysregulation of the alternative or terminal cascade complement pathways.

CLINICAL MANIFESTATIONS

MPGN is most common in the second decade of life, equally affects males and females, and is more common in White individuals. Systemic features may provide clues to which type of MPGN may be present, but the two histologic types of idiopathic MPGN are indistinguishable in terms of their renal manifestations. Patients present in equal proportions with nephrotic syndrome, acute nephritic syndrome (hematuria, hypertension, and some level of renal dysfunction), or persistent asymptomatic microscopic hematuria and proteinuria. Serum C3 complement levels are low in the majority of cases (see Fig. 559.6).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes all forms of acute and chronic glomerulonephritis, including idiopathic and secondary forms, along with postinfectious glomerulonephritis. Postinfectious glomerulonephritis, far more common than MPGN, usually does not have nephrotic features but typically has hematuria, hypertension, renal dysfunction, and transiently low C3 complement, all features that may be seen with MPGN or C3GN. In contrast to MPGN and C3GN, where C3 levels usually remain persistently low, C3 returns to normal within 8-10 weeks after the onset of postinfectious glomerulonephritis (see Chapter 559.4). The diagnosis of MPGN is made by renal biopsy. Indications for biopsy include nephrotic syndrome in an older child, significant proteinuria with microscopic hematuria, and hypocomplementemia lasting >2 months in a child with acute nephritis. If C3 but no immunoglobulin deposition is found in glomeruli with MPGN, genetic testing and functional assays to define defects of complement cascade regulation should be pursued.

PROGNOSIS AND TREATMENT

It is important to determine whether MPGN is idiopathic or secondary to a systemic disease, particularly lupus or chronic infection, because treatment of the causative disease can result in resolution of the MPGN. Untreated, idiopathic MPGN, regardless of type, has a poor prognosis. By 10 years following onset, 50% of patients with MPGN have progressed to end-stage renal disease. By 20 years following onset, up to 90% have lost renal function. Those with nephrotic syndrome and hypertension at the time of presentation progress to renal failure more rapidly. No definitive therapy exists, but several reports, including a randomized controlled trial, indicate that extended courses of alternate-day prednisone (for years) provide benefit. Some patients treated with steroids enter a complete clinical remission of their disease, but many have ongoing disease activity. Nevertheless, an extended course of prednisone is associated with significant preservation of renal function when compared with patients receiving no such treatment.

The prognosis of C3GN, separate from dense deposit disease (considered a part of C3GN by some) and other forms of classically defined MPGN, is as yet hard to define because reports of the outcome of such patients previously had been grouped in studies of all forms of MPGN (types I and II, and even a poorly characterized type III form not considered earlier). The apparent pathophysiology of C3GN promises that treatments targeting the interruption of complement activation pathways, such as complement factor H replacement or shutting down the terminal complement cascade by blocking C5 activation with eculizumab (anti–C5 antibody), could be beneficial in preventing the progression of renal disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

559.7 Rapidly Progressive (Crescentic) Glomerulonephritis

Francisco X. Flores

Rapidly progressive describes the clinical course of several forms of glomerulonephritis (GN) that have the unifying feature of a histopathologic finding of crescents in the majority of glomeruli (Fig. 559.9). The terms *rapidly progressive glomerulonephritis* (RPGN) and *crescentic glomerulonephritis* (CGN) are synonymous. The natural history of most forms of CGN is the rapid loss of the renal function.

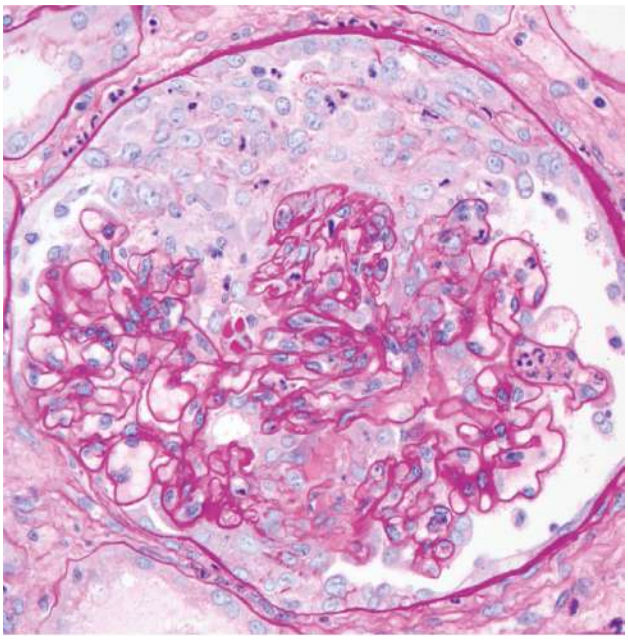

Fig. 559.9 Light micrograph showing a cellular crescent in Bowman's space. The underlying glomerular tuft is delineated by the glomerular basement membranes. (Periodic acid-Schiff stain, x500.) *(From Saha MK, Pendergraft WF, Jennette JC, Falk RJ. Primary glomerular dsease. In Yu AS, Chertow, G, et al, eds. Brenner and Rector's The Kidney, 11th edition. Philadelphia: Elsevier; 2020: Fig. 31.34.)*

CLASSIFICATION

CGN can be a severe manifestation of essentially every defined primary and secondary GN, but particular forms of GN are more likely to present as, or evolve into, RPGN (Table 559.3). If no underlying cause is identified by systemic features, serologic testing, or histologic examination, the disease is classified as idiopathic CGN. The incidence of specific etiologies of CGN in children varies widely; certain common themes are shared in all such reports. Patients with systemic vasculitis appear to be particularly prone to develop CGN. Patients with IgA vasculitis, antineutrophil cytoplasmic antibody (ANCA)-mediated GN (microscopic polyangiitis and granulomatosis with polyangiitis), and systemic lupus erythematosus account for the majority of patients with CGN. Postinfectious GN or endocarditis rarely progresses to CGN, but because it is the most common form of GN in childhood, it accounts for a significant percentage of patients with CGN in most reports. MPGN and idiopathic disease make up most of the remaining cases of CGN. IgA nephropathy, a common GN, only rarely is rapidly progressive. Goodpasture disease often has rapidly progressive GN as a component of the syndrome, but its rarity in childhood results in only a small percentage of children with CGN.

PATHOLOGY AND PATHOGENESIS

The hallmark of CGN is the histopathologic finding of epithelial crescents involving 50% or more glomeruli (see Fig. 559.9). Crescent formation, through proliferation of parietal epithelial cells in Bowman's space, may be the final pathway of any severe inflammatory glomerular injury. Podocytes and renal progenitor cells are involved in the pathogenesis of CGN. Fibrous crescents, in which proliferative cellular crescents are replaced by collagen, are a late finding. The immunofluorescence findings, as well as the pattern of any deposits by electron microscopy, can delineate the underlying glomerulopathy in CGN secondary to lupus, IgA vasculitis nephritis, MPGN, postinfectious GN, IgA nephropathy, or Goodpasture disease. Rare or absent findings by immunofluorescence and electron microscopy typify pauciimmune GN (granulomatosis with polyangiitis and microscopic polyangiitis) and idiopathic crescentic GN.

Table 559.3 Classification of Rapidly Progressive (Crescentic) Glomerulonephritis

PRIMARY
Anti–glomerular basement membrane antibody disease
Goodpasture syndrome (with pulmonary disease)
Immune complex mediated
Pauci-immune (usually antineutrophil cytoplasmic antibody positive)
SECONDARY
Membranoproliferative glomerulonephritis
Immunoglobulin A nephropathy, IgA vasculitis
Poststreptococcal glomerulonephritis
Systemic lupus erythematosus

CLINICAL MANIFESTATIONS

Most children present with acute nephritis (hematuria, various degrees of renal dysfunction, and hypertension) and usually have concomitant proteinuria, often with nephrotic syndrome. Occasional patients present late in the course of disease with oliguric renal failure. Extrarenal manifestations, such as pulmonary involvement, joint symptoms, or skin lesions, can help lead to the diagnosis of the underlying systemic disease causing the CGN.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of CGN is made by obtaining a kidney biopsy. Delineation of the underlying etiology is reached by a combination of additional biopsy findings (described earlier), extrarenal symptoms and signs, and serologic testing, including the evaluation of antinuclear and anti-DS DNA antibodies, serum complement levels, anti-GBM antibodies, and ANCA titers. If the patient has no extrarenal manifestations and a negative serologic evaluation, and if the biopsy has no immune or electron microscopy deposits, the diagnosis is idiopathic, rapidly progressive CGN.

PROGNOSIS AND TREATMENT

The natural course of CGN is far more severe in the setting of other etiologies, including the idiopathic category, and progression to end-stage kidney disease within weeks to months from the onset is common. Having a majority of fibrous crescents on a renal biopsy portends a poor prognosis, because the disease usually has progressed to irreversible damage. Although there are few controlled data, the consensus of most nephrologists is that the combination of high-dose corticosteroids and cyclophosphamide may be effective in preventing progressive renal failure in patients with systemic lupus erythematosus, IgA vasculitis nephritis, granulomatosis with polyangiitis, and IgA nephropathy if given early in the course when acute cellular crescents predominate. Although such therapy can also be effective in the other diseases causing RPGN, renal outcomes in those settings are less favorable. Progression to end-stage kidney disease often occurs despite aggressive immunosuppressive therapy. In combination with immunosuppression, plasmapheresis has been reported to benefit patients with Goodpasture disease. Plasmapheresis may also benefit patients with ANCA-associated CGN, in particular those with the most severe renal dysfunction and pulmonary hemorrhage at presentation. The possible benefits of plasmapheresis in other forms of RPGN are unclear.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 560

Multisystem Disease Associated with Hematuria

Prasad Devarajan

Gross or microscopic hematuria may be associated with several multisystem disorders, including chronic systemic infections, systemic lupus erythematosus (SLE), IgA vasculitis nephritis (formerly known as Henoch-Schönlein purpura nephritis), Goodpasture disease, hemolytic uremic syndrome (HUS), nephrotoxicity, and renal cortical necrosis. In most of these conditions, the presenting complaints pertain primarily to the underlying systemic illness, and hematuria often heralds or portends renal involvement (see Chapters 560.1-560.8).

560.1 Chronic Infections

Prasad Devarajan

Glomerulonephritis (GN) with hematuria is a recognized complication of various chronic infections. Examples include bacterial endocarditis caused by viridans group streptococci and other organisms, and ventriculoatrial shunts infected with *Staphylococcus epidermidis*. Other infections, observed less commonly in children than in adults, include those due to HIV, hepatitis B virus (HBV), or hepatitis C virus; syphilis; and renal candidiasis. Parasitic infections associated with glomerular disease include malaria, schistosomiasis, leishmaniasis, filariasis, hydatid disease, trypanosomiasis, and toxoplasmosis. In each condition, the infecting organism has a low virulence, and the host is chronically infected with a microbial antigen. In the presence of high levels of circulating antigen, the host's antibody response leads to the formation of **immune complexes** that are deposited in the kidneys and initiate glomerular inflammation. Foreign antigens can also stimulate an autoimmune response through the production of antibodies that cross react with such antigens incorrectly recognized as glomerular structural components.

The kidney histopathology in GN due to chronic infections can resemble poststreptococcal GN, membranous GN, or membranoproliferative GN. The clinical manifestations are generally those of an acute nephritic syndrome (active urinary sediment with hematuria, proteinuria, and granular and/or red blood cell (RBC) casts, edema, hypertension) or nephrotic syndrome (proteinuria, edema, hypoalbuminemia). *The serum C3 and CH_{50} complement levels are often decreased due to activation of the classic complement pathway.*

In **HIV-associated nephropathy,** direct viral infection of nephrons occurs because renal cells express a variety of lymphocyte chemokine receptors that are essential for and facilitate viral invasion. The kidney expression of HIV infection is quite variable and includes an immune complex injury and a direct cytopathic effect. The classic histopathologic lesion of HIV-associated nephropathy is *focal segmental glomerulosclerosis.* In the era of antiretroviral therapy, the decline in mortality from HIV disease has led to the increased recognition of renal disorders as an important long-term complication in children who survive perinatal HIV infection.

HBV infection is a global public health problem. It is estimated that there are more than 350 million HBV carriers in the world.

Prompt eradication of any infection before severe glomerular injury occurs usually results in resolution of the GN associated with chronic infections. Progression to end-stage kidney disease has been described but is uncommon. Spontaneous resolution of hepatitis B infection is common in children (30–50%) and results in remission of the glomerulopathy. Widespread use of hepatitis B vaccines has decreased the incidence of HBV-related renal diseases. Also, with the new availability of direct-acting antivirals for hepatitis C virus, a sustained virologic response, successful remission, and even regression of glomerular lesions can be achieved if treatment is initiated at an early stage. Similarly, in patients with HIV-associated nephropathy, several clinical studies have demonstrated the overall improvement in kidney function with early initiation of antiretroviral therapy. Particularly in children, modern antiretroviral therapy has improved the outcome and decreased the prevalence of childhood HIV-associated nephropathy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.2 Glomerulonephritis Associated with Systemic Lupus Erythematosus

Prasad Devarajan

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by fever, weight loss, dermatitis, hematologic abnormalities, arthritis, and involvement of the heart, lungs, central nervous system (CNS), and kidneys (see Chapter 199). Although SLE is less frequent in children, kidney involvement (lupus nephritis) is more common and is more severe than that seen in adults. Lupus nephritis is the most important cause of morbidity and mortality in SLE.

PATHOGENESIS AND PATHOLOGY

The hallmark of SLE is the abnormal production of pathogenic autoantibodies to self-antigens such as DNA (anti–double stranded DNA antibody [anti-dsDNA]) and nuclear proteins (antinuclear antibodies [ANA]), driven by immune dysregulation and loss of self-tolerance. The antigen-antibody complexes accumulate in small vessels of many organs, where they incite a local inflammatory response by activating complement pathways and by binding to Fc receptors. Lupus nephritis is a result of the deposition of circulating immune complexes, as well as the direct binding of autoantibodies to glomerular components with resultant complement stimulation.

Kidney biopsy and evaluation of kidney histopathology remain the gold standard for establishing the diagnosis of SLE nephritis and determining specific therapeutic regimens. The World Health Organization (WHO) classification of lupus nephritis has been employed in clinical trials and is based on a combination of features, including light microscopy, immunofluorescence, and electron microscopy. In patients with **WHO class I nephritis** (minimal mesangial lupus nephritis), no histologic abnormalities are detected on light microscopy, but mesangial immune deposits are present on immunofluorescence or electron microscopy. In **WHO class II nephritis** (mesangial proliferative nephritis), light microscopy shows both mesangial hypercellularity and an increased matrix, along with mesangial deposits containing immunoglobulin and complement.

WHO class III nephritis and **WHO class IV nephritis** are interrelated lesions characterized by both mesangial and endocapillary lesions. Class III nephritis is defined by <50% glomeruli with involvement, and class IV has ≥50% glomerular involvement. Immune deposits are present in both the mesangium and subendothelial areas. A **subclassification** scheme helps grade the severity of the proliferative lesion based on whether the glomerular lesions are segmental (<50% glomerular tuft involved) or global (≥50% glomerular tuft involved). The WHO classification scheme also delineates whether there is a predominance of chronic disease versus active disease. Chronic injury results in glomerular sclerosis and is felt to be the consequence of significant proliferative disease seen in classes III and IV. Other signs of active disease include capillary walls that are thickened secondary to subendothelial deposits (creating the characteristic wire-loop lesion), necrosis, and crescent formation. WHO class IV nephritis is associated with poorer outcomes but can be successfully treated with aggressive immunosuppressive therapy.

WHO class V nephritis (membranous lupus nephritis) is less commonly seen as an isolated lesion and resembles idiopathic membranous nephropathy with subepithelial immune deposits. This lesion is often seen in combination with class III or IV proliferative nephritis, and if the membranous lesion is present in >50% glomeruli, both classes are noted in the designation. This classification scheme also identifies cases with combinations of mixed classes III, IV, and V lesions, directing appropriate treatment for such patients.

Another classification scheme proposed by both the International Society of Nephrology and the Renal Pathology Society differs mainly in its subclassification of class IV into diffuse global and diffuse segmental lesions (Table 560.1). Although this classification is widely preferred, it should be noted that most available results of clinical trials are based on the WHO classification.

Transformation of the histologic lesions of lupus nephritis from one class to another is common. This is more likely to occur among inadequately treated patients and usually results in progression to a more severe histologic lesion.

Immunofluorescence microscopy is an essential component of the pathologic evaluation. Lupus nephritis is characterized by the granular deposition of all immunoglobulin isotypes (IgG, IgM, and IgA—also referred to as "full house"), as well as complements (C3, C4, and C1q) in the glomerular mesangium and capillary walls. This pattern of extensive glomerular immune deposition is referred to as full-house immune staining and is diagnostic of lupus nephritis.

CLINICAL MANIFESTATIONS

Most children with SLE are adolescent females (female-to-male ratio of 5:1) and present with extrarenal manifestations. The relative risk of SLE is three- to sevenfold higher in Asian, Black, and Hispanic females compared with White females. Lupus nephritis in Black and Hispanic populations also typically displays an increased severity and worse prognosis. Lupus nephritis affects 80% of pediatric patients with SLE, and although it commonly presents within the first year of diagnosis, may occur at any time during the disease. The clinical findings in patients having milder forms of lupus nephritis (all class I and II, some class III) include hematuria, normal renal function, and proteinuria <1 g/24 hr. Some patients with class III and all patients with class IV nephritis have hematuria and proteinuria, active urinary sediment with cellular casts, hypertension, reduced kidney function, nephrotic syndrome, or acute kidney injury. The urinalysis may be normal on rare occasions in patients with proliferative lupus nephritis. Patients with class V nephritis commonly present with nephrotic syndrome.

Table 560.1 Classification of Lupus Nephritis

CLASS	CLINICAL FEATURES
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN (<50% glomeruli involved) A. Active A/C. Active and chronic C. Chronic	More active sediment changes; often active serology; increased proteinuria (>25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment; chronic do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active A/C. Active and chronic C. Chronic	Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active; active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active lupus serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents renal failure

LN, Lupus nephritis.
From Radhakrishnan J, Appel GB. Glomerular disorders and nephrotic syndromes. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020: Table 113.7.

DIAGNOSIS

The diagnosis of SLE is confirmed by the detection of circulating ANA and by demonstrating antibodies that react with native anti-dsDNA. In most patients with active disease, C3 and C4 levels are depressed. In view of the lack of a clear correlation between the clinical manifestations and the severity of the kidney involvement, kidney biopsy should be performed in all patients with SLE who display even minor urinary abnormalities or other clinical evidence for renal disease. Histopathologic findings are used to determine the classification, severity, prognosis, and selection of specific immunosuppressive therapies.

TREATMENT

Current therapies are largely based on the histology, clinical severity, and lessons learned from clinical trials of adults with lupus nephritis. Immunosuppression remains the cornerstone of therapy. The goal of immunosuppressive therapy in lupus nephritis is to produce both a clinical remission, defined as normalization of renal function and proteinuria, and a serologic remission, defined as normalization of anti-DNA antibody, C3, and C4 levels. Therapy is initiated in all patients with prednisone at a dose of 1-2 mg/kg/day in divided doses, followed by a slow steroid taper over 4-6 months beginning 4-6 weeks after achieving a serologic remission.

For patients with more severe forms of nephritis (WHO classes III and IV), more aggressive immunosuppressive regimens are required because corticosteroid therapy alone is insufficient to induce a remission. In general, such regimens are separated into two phases, namely, induction and maintenance. The most commonly employed induction therapy has been six consecutive monthly intravenous infusions of cyclophosphamide at a dose of 500-1,000 mg/m^2. Pulse intravenous methylprednisolone (1,000 mg/m^2) is also used in addition to oral corticosteroids. Maintenance therapy previously consisted of additional cyclophosphamide infusions every 3 months for 18 months, which reduced the risk of progressive renal dysfunction. Serious side effects of cyclophosphamide have included infections, hair loss, hemorrhagic cystitis, and gonadal failure.

As an alternative induction therapy, in adult and pediatric clinical trials, mycophenolate mofetil was as efficacious as, or even superior to, cyclophosphamide, and is increasingly considered for use in children at a dosage of 600 mg/m^2 per dose twice daily. Maintenance therapy using mycophenolate mofetil or azathioprine is also as efficacious as intravenous cyclophosphamide and results in less serious side effects. Mycophenolate mofetil is particularly more efficacious than cyclophosphamide in Black patients. Major side effects of mycophenolate mofetil have included diarrhea, leukopenia, and teratogenicity. Azathioprine, at a single daily dose of 1.5-2.0 mg/kg, may be used as a steroid-sparing agent in patients with WHO class I or II lupus nephritis.

Rituximab, a chimeric monoclonal antibody specific for human CD20, is an alternative that has been shown to induce a remission in adults and children with proliferative lupus nephritis refractory to steroids and other immunosuppressants. Rituximab is used in cases where resistance to conventional treatment is demonstrated. Plasmapheresis is ineffective in lupus nephritis unless there is accompanying thrombotic thrombocytopenic purpura (TTP) or antineutrophilic cytoplasmic antibody (ANCA)-associated disease. Other therapies include belimumab, a fully humanized monoclonal antibody against a type II transmembrane protein that functions in the normal survival and differentiation of B cells; it has been approved by the FDA for use

in SLE. Its role in lupus nephritis, either in combination with current therapies or to replace them, requires further study.

The optimal treatment for class V lupus nephritis remains unclear. On the one hand, the low risk of progression to end-stage kidney disease when compared with proliferative forms of lupus nephritis has encouraged a less aggressive approach. On the other hand, patients with uncontrolled nephrotic syndrome due to class V lupus nephritis are at a high risk of morbidity and may require more aggressive immunosuppression.

Hydroxychloroquine is prescribed for most patients with SLE for extrarenal manifestations but is thought to have a beneficial effect in maintaining the remission in lupus nephritis. It is a rational choice given its low side effect profile. Use of antihypertensive drugs to aggressively treat hypertension, as well as the specific use of drugs that block the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) to reduce proteinuria, are also important adjuvant therapies that appear to decrease the long-term progression of renal disease.

PROGNOSIS

Overall, kidney survival (defined as chronic kidney disease without progression to end-stage kidney disease therapy) is seen in 80% of patients 10 years after the diagnosis of SLE nephritis. Patients with diffuse proliferative WHO class IV lupus nephritis, poor kidney function at presentation, or persistent nephrotic-range proteinuria exhibit the highest risk for progression to end-stage kidney disease. Concerns regarding the side effects of chronic immunosuppressive therapy and the risk of recurrent disease are lifelong. Close monitoring for the relapse of disease is critical to ensure maximally successful renal outcomes. Special care must be taken to minimize the risks of infection, osteoporosis, obesity, poor growth, hypertension, and diabetes mellitus associated with chronic corticosteroid therapy. Patients require counseling regarding the risk of malignancy or infertility, which may be increased in those receiving a cumulative dose of >20 g of cyclophosphamide or other immunosuppressant therapies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.3 IgA Vasculitis Nephritis

Prasad Devarajan

IgA vasculitis (formerly known as Henoch-Schönlein purpura) is an idiopathic systemic immune complex–mediated vasculitis associated with IgA deposition within small-vessel walls. It is the most common small-vessel vasculitis in children, with a peak incidence in early childhood (4-6 years of age). Ninety percent of cases occur in children, with about half the cases preceded by an upper respiratory infection. It is characterized by a purpuric rash and commonly accompanied by arthritis and abdominal pain (see Chapter 210.1). Approximately 50% of patients with IgA vasculitis develop kidney manifestations, which vary from asymptomatic microscopic hematuria to severe, progressive GN. IgA vasculitis nephritis shares a similar pathogenesis and nearly identical kidney histology with IgA nephropathy. Although the two are considered as distinct entities, many consider IgA vasculitis nephritis and IgA nephropathy as part of the same clinical spectrum and IgA nephropathy as one of the sequelae of IgA vasculitis nephritis.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of IgA vasculitis nephritis appears to be mediated by the deposition of **polymeric IgA** in glomeruli. This is analogous to the same type of IgA deposits seen in systemic small vessels in IgA vasculitis, primarily those of the skin and intestine. Studies have identified defective glycosylation of the hinge region of IgA1 in patients with both IgA vasculitis nephritis and IgA nephropathy. Recognition of the exposed hinge region of IgA1 by naturally occurring autoantibodies leads to formation of immune complexes that are deposited in the glomerular mesangium. Any mucosal infection or food antigen may trigger the increased production of pathogenic IgA1. IgA immune complexes are deposited throughout the body and activate pathways leading to necrotizing vasculitis. A skin biopsy characteristically shows leukocytoclastic vasculitis with IgA, C3, and fibrin deposition. The glomerular findings can be indistinguishable from those of IgA nephropathy. Pathognomonic IgA deposits are detected by immunofluorescence as the dominant immunoglobulin in the glomerular mesangium. Histologically, a broad spectrum of glomerular lesions that can range from mild mesangial and endocapillary proliferation to necrotic and crescentic changes from extracapillary proliferation can be seen.

CLINICAL AND LABORATORY MANIFESTATIONS

The classic tetrad of IgA vasculitis nephritis includes a palpable purpura, arthritis or arthralgia, abdominal pain, and evidence for kidney disease. *These may develop over a period of days to weeks and may vary in their order of presentation.* Notably, not all of the tetrad are present in all patients. The nephritis associated with IgA vasculitis usually *follows* the onset of the rash, often presenting weeks or even months after the initial nonkidney manifestations have resolved. Nephritis can be manifest at the initial presentation but only rarely before onset of the rash. Some degree of kidney involvement occurs in approximately 50% of IgA vasculitis cases, more commonly in older children (age >8 years confers a threefold greater risk for kidney involvement). Most patients (80%) initially display only mild renal involvement, principally isolated microscopic hematuria without significant proteinuria. About 20% of patients can present with a more severe kidney involvement, including a combined acute nephritic and nephrotic picture (hematuria, hypertension, renal insufficiency, significant proteinuria, and nephrotic syndrome). Older children (and adults) have a greater risk for more severe involvement. Initial mild kidney involvement can also occasionally progress to more severe nephritis despite resolution of all other features of IgA vasculitis. The severity of the systemic manifestations is not correlated with the severity of the nephritis. *Most patients who develop nephritis have urinary abnormalities by 1 month, and nearly all have abnormalities by 3-6 months after the onset of IgA vasculitis.* Therefore a urinalysis (and blood pressure checks) should be performed weekly in patients with IgA vasculitis during the period of active clinical disease (usually during the first 4 weeks). Thereafter, a urinalysis (and blood pressure checks) should be performed once a month for up to 6 months. If all urinalyses and blood pressures are normal during this follow-up interval, nephritis is unlikely to develop. If proteinuria, kidney insufficiency, or hypertension develops along with hematuria, consultation with a pediatric nephrologist is indicated. Indications for a kidney biopsy in children with IgA vasculitis nephritis include significant proteinuria (urine protein >1 g/day or urine protein/creatinine ratio >1.0), significant hypertension, or elevated serum creatinine.

Mimics of IgA vasculitis include endocarditis (skin, renal) and granulomatosis with polyangiitis (skin, renal).

PROGNOSIS AND TREATMENT

The prognosis of IgA vasculitis nephritis for most patients is excellent. Spontaneous and complete resolution of the nephritis typically occurs in many patients with mild initial manifestations (isolated hematuria with insignificant proteinuria). However, such patients uncommonly can progress to severe kidney involvement, including development of chronic kidney disease. Patients with acute nephritic or nephrotic syndrome at presentation have a guarded kidney prognosis, particularly if they are found to have concomitant necrosis or substantial crescentic changes on kidney biopsy. Untreated, the risk of developing chronic kidney disease, including end-stage kidney disease, is 2–5% in all patients with IgA vasculitis, but almost 50% in those with the most severe early kidney clinical and histologic features.

No controlled studies have demonstrated any efficacy of short courses (weeks) of oral corticosteroids administered promptly after the onset of IgA vasculitis in either preventing the development of nephritis or decreasing the severity of subsequent kidney involvement. Tonsillectomy has been proposed as an intervention for IgA vasculitis nephritis, but it also does not appear to have any measurable effect on

the renal outcome. Mild IgA vasculitis nephritis does not require treatment because it usually resolves spontaneously.

The efficacy of treatment for moderate or severe IgA vasculitis nephritis, which is far more likely to progress to chronic kidney disease, is more difficult to assess. Several uncontrolled studies have reported a significant benefit from aggressive immunosuppression (high-dose and extended courses of corticosteroids with azathioprine, mycophenolate mofetil, or cyclophosphamide) in patients with poor prognostic features on kidney biopsy; such patients are at high risk of progressing to chronic kidney disease. Reports of the treatment of high-risk patients with either plasmapheresis or rituximab have also indicated a potential benefit. Balancing the absence of controlled data with the severe side effects of aggressive therapies in patients with poor renal prognostic factors is difficult. Aggressive therapy with careful monitoring may be reasonable in those with the most severe IgA vasculitis nephritis (>50% crescents on biopsy). One common approach in children with severe clinical kidney involvement (nephrotic range proteinuria, elevated serum creatinine, hypertension) is the use of oral prednisone (1 mg/kg/day for 3 months), along with angiotensin-converting enzyme inhibitors, followed by azathioprine or mycophenolate mofetil if severe clinical involvement persists. For children with severe histologic manifestations (>50% glomerular crescents), treatment with intravenous methylprednisolone pulses for 3 days, followed by a combination of oral prednisone (for 3 months) and azathioprine or mycophenolate mofetil (extended course) may be considered. For children with the most severe histology (>75% glomerular crescents) and progressive kidney disease, intravenous steroids plus plasmapheresis may be considered. If progression to end-stage kidney disease occurs, renal transplantation is the treatment of choice. Deposition of IgA in the transplanted kidney is common, but most cases are subclinical, and the overall graft survival is similar to that for other renal transplant recipients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.4 Goodpasture Disease

Prasad Devarajan

Goodpasture disease is an autoimmune disease characterized by pulmonary hemorrhage, **rapidly progressive glomerulonephritis**, and elevated **anti–glomerular basement membrane (anti-GBM) antibody** titers. The disease results from an attack on these organs by antibodies directed against certain epitopes of type IV collagen, located within the alveolar basement membrane in the lung and glomerular basement membrane (GBM) in the kidney. An acquired conformational change in the noncollagenous 1 domain of the alpha 3-chain of type IV collagen leads to the production of pathologic autoantibodies. The high affinity of these antibodies to the GBM results in the characteristic rapidly progressive kidney disease. Infusion of human anti-GBM antibodies into animals reproduces the rapidly aggressive glomerulonephritis, confirming the high pathogenicity of these antibodies.

PATHOLOGY

Kidney biopsy shows proliferative crescentic glomerulonephritis in most patients. Immunofluorescence microscopy demonstrates the pathognomonic continuous linear deposition of immunoglobulin G along the GBM (Fig. 560.1).

CLINICAL MANIFESTATIONS

Goodpasture disease is rare in childhood. Patients usually present with hemoptysis from pulmonary hemorrhage that can be life-threatening. Concomitant renal manifestations include acute glomerulonephritis with hematuria, nephritic urinary sediment with cellular casts, proteinuria, and hypertension, which usually follow a rapidly progressive course. Kidney failure commonly develops within days to weeks of the clinical presentation. Although fever may be present, other systemic complaints such as malaise or arthralgia are usually absent; their presence should raise suspicion for a systemic vasculitis. *Less commonly, patients can have anti-GBM nephritis manifesting as isolated, rapidly progressive glomerulonephritis without pulmonary hemorrhage.* In essentially all cases, anti-GBM antibody is present in the serum and/or the kidney, and the serum complement C3 level is normal. **Antineutrophilic cytoplasmic antibody (ANCA)** levels can be found to be elevated in 10–40% of patients, along with the anti-GBM antibody; such patients doubly positive for these autoantibodies have more severe disease at presentation. In general, anti-GBM antibody titers are correlated with the severity of the renal involvement. However, a kidney biopsy should be performed (unless contraindicated) because the accuracy of anti-GBM serology is variable, and renal biopsy provides additional histologic information that can guide therapy.

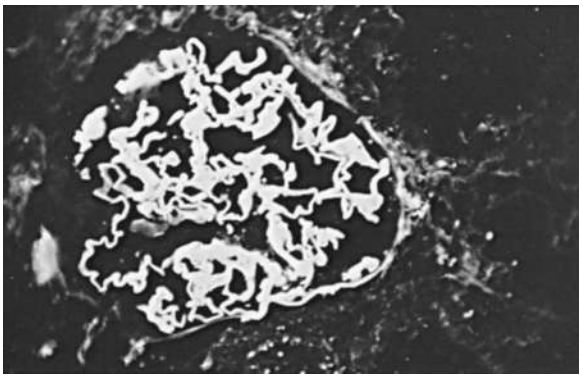

Fig. 560.1 Immunofluorescence micrograph demonstrating the continuous linear staining of immunoglobulin G along the glomerular basement membrane in Goodpasture disease (×250).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made by a combination of the clinical presentation of pulmonary hemorrhage with acute glomerulonephritis, the presence of serum antibodies directed against GBM (anti–type IV collagen in GBM), and characteristic renal biopsy findings. Other diseases that can cause a **pulmonary-renal syndrome** need to be considered and include SLE, IgA vasculitis, nephrotic syndrome–associated pulmonary embolism, and ANCA-associated vasculitis (such as granulomatosis with polyangiitis and microscopic polyangiitis). These diseases are ruled out by the absence of other characteristic clinical features, kidney biopsy findings, and negative serologic studies for antibodies against nuclear (ANA), DNA (anti-dsDNA), and neutrophil cytoplasmic components (ANCA antibody).

PROGNOSIS AND TREATMENT

Untreated, the prognosis of Goodpasture disease is poor. Treatment must be initiated emergently as soon as the diagnosis is suspected. The prompt institution of plasmapheresis, high-dose intravenous methylprednisolone, and cyclophosphamide often induces remission and improves survival times. Initial therapy with plasmapheresis removes circulating anti-GBM antibodies, and initial immunosuppression with steroids and cyclophosphamide inhibits ongoing antibody production. Rituximab may be used as a substitute in cases where cyclophosphamide toxicity is encountered. Initial treatment is guided by the clinical response and serial anti-GBM antibody titers. Retrospective cohort studies suggest that when this combination of treatments is started early, most patients will have a good kidney outcome. However, an initial presentation with oligoanuria, a high proportion of glomerular crescents, or kidney failure requiring dialysis predicts worse kidney and patient survival rates. After the induction of remission, maintenance therapy with lower doses of prednisone and azathioprine (or mycophenolate mofetil) is continued for 6-9 months. However, patients who survive the acute pulmonary hemorrhage and rapidly progressive glomerulonephritis can still progress to end-stage kidney disease despite ongoing immunosuppressive therapy. For patients who

progress, kidney transplantation is the treatment of choice. Relapse and recurrent disease after kidney transplantation are both uncommon.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.5 Hemolytic-Uremic Syndrome

Prasad Devarajan

Hemolytic-uremic syndrome (HUS) is a common cause of community-acquired acute kidney injury in young children. It is the most common form of **thrombotic microangiopathy (TMA)** in children (Fig. 560.2). Like all TMAs, HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and kidney insufficiency. HUS has clinical features in common with thrombotic thrombocytopenic purpura (TTP) (see Chapter 533.5). The etiology and pathophysiology of the more common forms of HUS clearly delineate typical childhood HUS as separate from idiopathic TTP.

ETIOLOGY

The various etiologies of HUS and other related thrombotic microangiopathies allow classification into infection-induced, genetic, drug-induced, and HUS associated with systemic diseases characterized by microvascular injury (Table 560.2; see Fig. 560.2). The most common form of HUS is caused by **Shiga toxin–producing *Escherichia coli* (STEC)**, which causes prodromal acute enteritis and is commonly termed STEC-HUS or *diarrhea-associated HUS*. In the subcontinent of Asia and in southern Africa, the toxin of *Shigella dysenteriae* type 1 is causative, whereas in Western countries, verotoxin or STEC is the usual cause. STEC-HUS accounts for about 90% of all HUS cases in childhood.

Several serotypes of *E. coli* can produce the toxin. O157:H7 is most common in Europe and the Americas; other serotypes include O26, O111, O121, O145, O91, O103, O104, and O80. The reservoir of STEC is the intestinal tract of domestic animals, usually cows. Disease commonly is transmitted by undercooked meat or unpasteurized (raw) milk and apple cider. Local outbreaks have followed the ingestion of undercooked, contaminated hamburger or other foods cross-contaminated on unwashed cutting boards at fast food restaurants; contaminated municipal water supplies; petting farms; and swimming in contaminated ponds, lakes, or pools. With broad food distribution, wider epidemics have been traced to lettuce, raw spinach, and bean sprouts contaminated with STEC. Less often, STEC has been spread by person-to-person contact within families or childcare centers.

A rare but distinct entity of infection-triggered HUS is related to neuraminidase-producing *Streptococcus pneumoniae* (Sp-HUS). Sp-HUS, typically severe, develops during acute infection with this organism, typically manifesting as pneumonia with empyema. Compared with the prevaccine era, Sp-HUS incidence seems to be decreasing after the introduction of 7-serotype valent and 13-serotype valent pneumococcal vaccines. However, severe Sp-HUS cases continue to occur secondary to vaccine failure and emergence of nonvaccine/replacement serotypes. A TMA, similar to HUS or TTP, also can occur in patients with untreated HIV infection and influenza infection.

Genetic forms of HUS (atypical, nondiarrheal) compose the second major category of the disease (see Table 560.2 and Fig. 560.2). Inherited deficiencies of either von Willebrand factor–cleaving protease (ADAMTS13) or complement factor H, I, or B can cause HUS. A specific genetic defect has not been identified in approximately 50% of familial cases transmitted in classic Mendelian autosomal dominant or

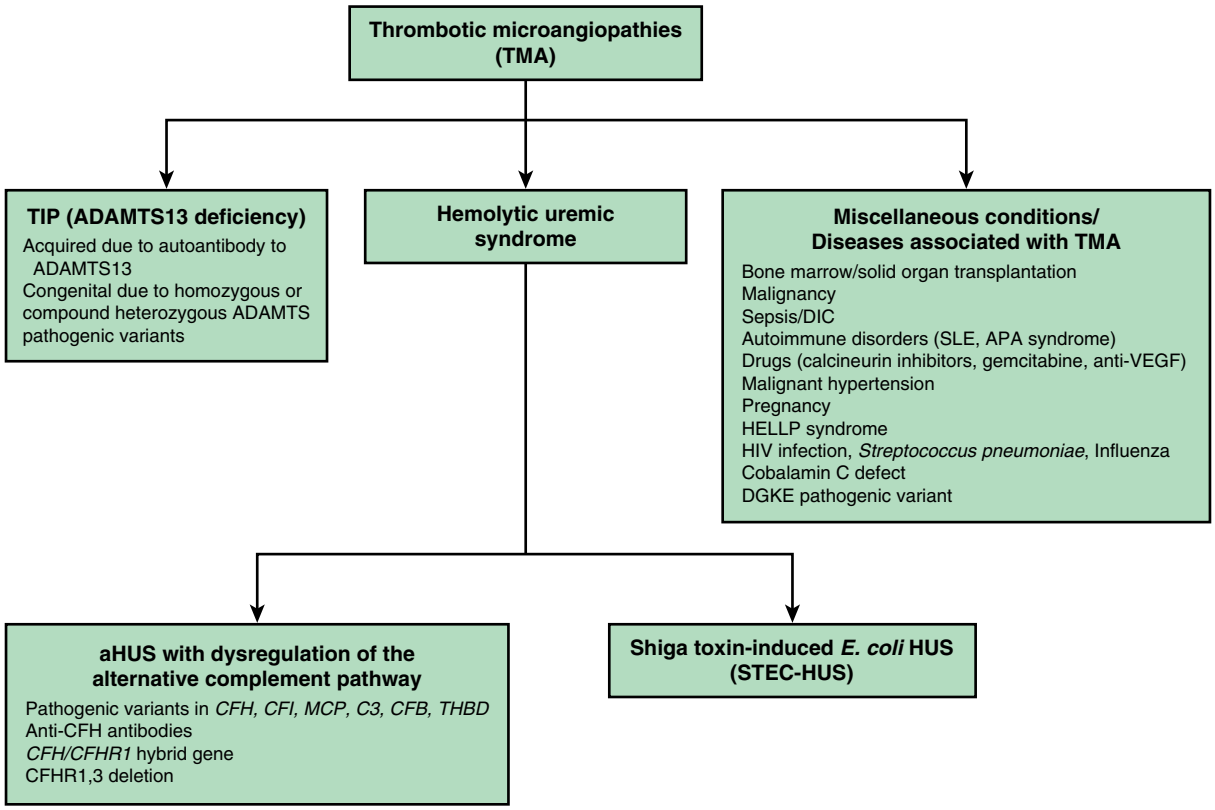

Fig. 560.2 Classification algorithm for the thrombotic microangiopathies based on etiology. ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; APA, antiphospholipid antibody syndrome; CFB, complement Factor B; CFH, complement Factor H; CFI, complement Factor I; DGKE, diacylglycerol kinase ε; DIC, disseminated intravascular coagulation; HELLP syndrome, hemolysis, elevated liver enzymes and low platelet count syndrome; MCP, membrane cofactor protein (CD46); SLE, systemic lupus erythematosus; THBD, thrombomodulin gene; VEGF, vascular endothelial growth factor. *(From Dixon BP, Gruppo RA. Atypical hemolytic uremic syndrome. Pediatr Clin N Am. 2018;65:509–525. Fig. 2.)*

Table 560.2 Current Classification of Hemolytic Uremic Syndromes and Thrombotic Microangiopathies

DIARRHEA-ASSOCIATED HUS
STEC (*Escherichia coli* O157:H7)
STEC (*E .coli* 0121 and 0104:H4)
Non-STEC (*Shigella dysenteriae* type 1)
HUS SECONDARY TO SYSTEMIC INFECTIONS
Neuraminidase (*Streptococcus pneumoniae*)
HIV
Influenza
Human herpes virus 6
Parvovirus B19
Malaria
ATYPICAL HUS DUE TO COMPLEMENT DYSREGULATION
Factor H deficiency (pathogenic variants, autoantibodies)
Factor I deficiency (pathogenic variants)
Factor B (gain-of-function pathogenic variants)
Membrane cofactor (MCP) deficiency (pathogenic variants)
C3 deficiency (pathogenic variants, autoantibodies)
Thrombomodulin deficiency (pathogenic variants)
Anti–complement factor H antibody
Unknown
THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)
Inherited ADAMTS13 deficiency (pathogenic variants)
Acquired ADAMTS13 deficiency (antibody-mediated)
Pregnancy-associated
Vitamin B_{12} deficiency
DRUG INDUCED
Cyclosporine
Tacrolimus
Bleomycin
Mithramycin
Cisplatin
Quinine
Cocaine
Anti–vascular endothelial growth factor (anti-VEGF) drugs
SYSTEMIC DISEASE ASSOCIATED
Systemic lupus erythematosus
Coexisting nephropathies
Malignant hypertension
Malignancies
Cobalamin C defect
Diacylglycerol kinase epsilon pathogenic variant
TRANSPLANT ASSOCIATED
Stem cell transplant
Bone marrow transplant
Renal
Heart
Intestinal

recessive patterns. Some of these may be due to cobalamin C pathogenic variants. A major feature characteristic of genetic forms of HUS is the *absence* of a preceding diarrheal prodrome, although the presence of a diarrheal prodrome does not rule out atypical HUS. Genetic forms of HUS can be indolent and unremitting once they become manifest, or they can have a relapsing pattern precipitated by an infectious illness. The latter feature likely explains the association of many infectious agents with HUS, particularly in reports published before the recognition of the unique pathophysiology of STEC and neuraminidase-producing pneumococci in causing HUS.

HUS can be superimposed on any disease associated with microvascular injury, including malignant hypertension, SLE, and antiphospholipid syndrome. It can also occur after bone marrow or solid organ transplantation and may be triggered by the use of the calcineurin inhibitors cyclosporine and tacrolimus in that setting. Several other medications also can induce HUS (see Table 560.2 and Fig. 560.2).

PATHOLOGY

Kidney biopsies are only rarely performed in HUS because the diagnosis is usually established by clinical criteria, and the risks of biopsy are significant during the active phase of the disease. Early glomerular changes include thickening of the capillary walls caused by swelling of endothelial cells and accumulation of fibrillar material between endothelial cells and the underlying basement membrane, causing narrowing of the capillary lumens. Platelet-fibrin thrombi are often seen in glomerular capillaries. Thrombi are also seen in afferent arterioles and small arteries with fibrinoid necrosis of the arterial wall, leading to kidney cortical necrosis from vascular occlusion. Late findings include glomerular sclerosis and obsolescence secondary to either severe direct glomerular involvement or glomerular ischemia from arteriolar involvement.

PATHOGENESIS

Microvascular injury with endothelial cell damage is characteristic of all forms of TMA, including HUS. In the diarrhea-associated form of HUS, enteropathic organisms produce either Shiga toxin or the highly homologous Shiga-like verotoxin. These toxins are easily absorbed from the colonic mucosa into the systemic circulation, bind to endothelial cells in the glomerulus and elsewhere, and directly cause endothelial cell damage. Shiga toxin can also directly activate platelets to promote their aggregation. Mechanical injury to RBCs passing through the thrombotic microvasculature results in a severe nonimmune anemia with a negative direct Coombs test. In pneumococcal-associated HUS, neuraminidase cleaves sialic acid on membranes of endothelial cells, red cells, and platelets to expose the underlying cryptic Thomsen-Friedenreich (T) antigen. Endogenous IgM antibodies recognize and react with the T antigen to trigger hemolysis and anemia with a positive direct Coombs test.

The *familial* recessive and dominant forms of HUS, including the inherited deficiencies of ADAMTS13 and regulators of the complement cascade, probably predispose patients to developing HUS but do not cause the disease per se because these patients might not develop HUS until later childhood or even adulthood. In such cases, HUS is often triggered by an inciting event such as an infectious disease. The absence of ADAMTS13 impairs cleavage of von Willebrand factor multimers, which enhances platelet aggregation. Factor H plays a central role in complement regulation, primarily arresting the amplification and propagation of complement activation. It is possible that mild endothelial injury that would normally resolve instead evolves to an aggressive microangiopathy because of the inherited deficiencies of these factors.

In each form of HUS, capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic hemolytic anemia results from mechanical damage to RBCs as they pass through the damaged and thrombotic microvasculature.

CLINICAL MANIFESTATIONS

Typical HUS (diarrhea form) is most common in preschool- and school-age children, but it can occur in adolescents and adults. In HUS caused by toxigenic *E. coli,* the onset of HUS occurs 5-7 days after the onset of gastroenteritis with fever, vomiting, abdominal pain, and diarrhea. The prodromal intestinal symptoms may be severe and require hospitalization, but they can also be relatively mild and considered trivial. Not all infected patients will develop HUS. The diarrhea is often bloody but not necessarily so. After the prodromal illness, the sudden onset of pallor, weakness, and lethargy heralds the onset of HUS, and it reflects the development of microangiopathic hemolytic anemia. Oliguria can be present in early stages but may be masked by ongoing diarrhea because the prodromal enteritis often overlaps the onset of HUS, particularly with ingestion of large doses of toxin. Thus patients with HUS can present with either significant dehydration or volume overload, depending on whether the enteritis or kidney insufficiency from HUS predominates and the amount of fluid that has been administered.

Patients with pneumococci-associated HUS usually are quite ill with pneumonia, empyema, and bacteremia when they develop HUS. The onset can be insidious in patients with the genetic forms of HUS, with HUS triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections.

HUS can be relatively mild or can progress to a severe and fatal multisystem disease. Leukocytosis, severe prodromal enteritis, hyponatremia, and antibiotic use portend a severe course, but no presenting features reliably predict the severity of HUS in any given patient. Patients with HUS who appear mildly affected at presentation can rapidly develop severe, multisystem, life-threatening complications. Kidney insufficiency can be mild but also can rapidly evolve into severe oliguric or anuric kidney failure. The combination of rapidly developing kidney failure and severe hemolysis can result in life-threatening hyperkalemia. Severe acute kidney injury requiring dialysis develops in about 50% of patients with STEC-HUS. The duration of the dialysis requirement is usually about 2 weeks. Volume overload, hypertension, and severe anemia can all develop soon after the onset of HUS and together can precipitate heart failure. Direct **cardiac involvement** is rare, but pericarditis, myocardial dysfunction, or arrhythmias can occur without predisposing features of hypertension, volume overload, or electrolyte abnormalities.

The majority of patients with HUS have some **CNS involvement**. Most have mild manifestations, with significant irritability, lethargy, or nonspecific encephalopathic features. Severe CNS involvement occurs in ≤20% of cases. Seizures and significant encephalopathy are the most common manifestations in those with severe CNS involvement, resulting from focal ischemia secondary to microvascular CNS thrombosis. Small infarctions in the basal ganglion and cerebral cortex have also been reported, but large strokes and intracranial hemorrhage are rare. Hypertension may produce an encephalopathy and seizures. Intestinal complications can be protean and include severe inflammatory colitis, ischemic enteritis, bowel perforation, intussusception, and pancreatitis. Patients can develop petechiae, but significant or severe bleeding is rare despite very low platelet counts.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made by the combination of microangiopathic hemolytic anemia with schistocytes, thrombocytopenia, and some degree of kidney involvement. The anemia can be mild at presentation, but it rapidly progresses. Thrombocytopenia is an invariable finding in the acute phase, with platelet counts usually 20,000-100,000/mm^3. Partial thromboplastin and prothrombin times are usually normal. The Coombs test is negative, except in pneumococci-induced HUS, where the Coombs test is usually positive. Leukocytosis is often present and significant. Urinalysis typically shows microscopic hematuria and low-grade proteinuria. The kidney insufficiency can vary from mild elevations in serum BUN and creatinine to acute, anuric kidney failure.

The etiology of HUS is often clear with the presence of a diarrheal prodrome or pneumococcal infection. The presence or absence of toxigenic organisms on stool culture has little role in making the diagnosis of diarrhea-associated STEC-HUS. Only a minority (~10%) of patients infected with those organisms develops HUS, and the organisms that cause HUS may be rapidly cleared. Therefore the stool culture may be negative in patients who have diarrhea-associated HUS. If no history of diarrheal prodrome or pneumococcal infection is obtained, then evaluation for genetic forms of HUS should be considered because those patients are at risk for recurrence, have a severe prognosis, and can benefit from specific therapy. Other causes of acute kidney injury associated with a microangiopathic hemolytic anemia and thrombocytopenia should be considered and excluded, such as SLE, malignant hypertension, and bilateral renal vein thrombosis. A kidney biopsy is rarely indicated to diagnose HUS.

PROGNOSIS AND TREATMENT

With early recognition and intensive supportive care, the mortality rate for diarrhea-associated HUS is <5%. Up to half of patients may require dialysis support during the acute phase of the disease. Recovery of platelet counts usually occurs first, followed by kidney recovery about 5 days later, and finally by resolution of anemia. Most recover kidney function completely, but of surviving patients, 5% remain dependent on dialysis, and up to 30% are left with some degree of chronic kidney disease. The prognosis for HUS not associated with diarrhea is more severe. Pneumococci-associated HUS causes increased patient morbidity (>80% require dialysis), with the mortality rate reported as 20%. The familial, genetic forms of HUS can be insidiously progressive or relapsing diseases and have a poor prognosis. Identification of specific factor deficiencies in some of these genetic forms provides an opportunity for directed therapy to improve the outcome.

The primary approach that has substantially improved an acute outcome in HUS is early recognition of the disease, monitoring for potential complications, and meticulous supportive care. Supportive care includes careful management of fluid and electrolytes, including prompt correction of a volume deficit, control of hypertension, and early institution of dialysis if the patient becomes significantly oliguric or anuric, particularly with hyperkalemia. Early intravenous volume expansion before the onset of oliguria or anuria may be nephroprotective in diarrhea-associated HUS. Red cell transfusions are usually required because hemolysis can be brisk and recurrent until the active phase of the disease has resolved. In pneumococci-associated HUS, it is critical that any administered red cells be washed before transfusion to remove residual plasma, because endogenous IgM directed against the revealed T antigen can play a role in accelerating the pathogenesis of the disease. Platelets should generally not be administered, regardless of the platelet count, to patients with HUS because they are rapidly consumed by the active coagulation and theoretically can worsen the clinical course. Despite low platelet counts, serious bleeding is very rare in patients with HUS.

There is no evidence that any therapy directed at arresting the disease process of the most common, diarrhea-associated STEC-HUS provides benefit, and some can cause harm. Attempts have been made using anticoagulants, antiplatelet agents, fibrinolytic therapy, plasma therapy, immune globulin, and antibiotics. Anticoagulation, antiplatelet, and fibrinolytic therapies are specifically contraindicated because they increase the risk of serious hemorrhage. Antibiotic therapy to clear enteric toxigenic organisms (STEC) can result in increased toxin release, potentially exacerbating the disease; therefore it is not recommended. However, prompt treatment of causative pneumococcal infection is important. The European experience with *E. coli* O104:H4 in adults who were treated with azithromycin demonstrated more rapid elimination of the organism. Furthermore, in vitro evidence suggests that meropenem, rifaximin, and azithromycin downregulate the release and expression of Shiga toxin. Nonetheless, *in children with E. coli O157:H7–associated HUS, antibiotics are still considered contraindicated.*

Plasma infusion or plasmapheresis has been proposed for patients suffering severe manifestations of HUS with serious CNS involvement. There are no controlled data demonstrating the effectiveness of this approach, and it is specifically contraindicated in those with pneumococcal-associated HUS because it could exacerbate the disease. The use of plasma therapy in STEC-HUS was one of many treatment strategies during one of the largest reported outbreaks of STEC-HUS. This outbreak was caused by an uncommon serotype (O104:H4) that had unique virulence factors. Thought initially to cause more severe disease, it differed epidemiologically from other STEC-HUS serotypes by affecting primarily healthy adults, rather than the usual pattern of affecting children and the elderly. Treatment in this epidemic included plasma exchange in most of the adult patients, as well as the use of eculizumab.

Eculizumab is an anti-C5 antibody that inhibits complement activation, a pathway that contributes to active disease in some forms of atypical familial HUS; this pathway may also contribute to the process in STEC-HUS. Eculizumab is approved by the FDA for the treatment of *atypical HUS*. Because of the risk of meningococcal disease in patients with defects in terminal complement components, it is recommended to give the meningococcal vaccine before giving eculizumab (if the patient has not been primarily immunized). Although initial reports suggested that eculizumab provided benefit in patients with

diarrhea-associated HUS, subsequent systematic analysis showed no benefit from either plasma exchange or eculizumab.

Plasma therapy can be of substantial benefit to patients with identified deficits of ADAMTS13 or factor H. It may also be considered in patients with other genetic forms of HUS, such as the undefined familial (recessive or dominant) form or sporadic but recurrent HUS. In contrast to its use in STEC-HUS, eculizumab shows great promise in the treatment of atypical HUS, including HUS occurring following renal transplantation. Whether it should be combined with plasma therapy or used as a primary treatment of atypical HUS is still undetermined.

Most patients with diarrhea-associated HUS recover completely, with little risk of long-term sequelae. Patients with hypertension, any level of kidney insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS (particularly significant proteinuria) require careful follow-up. Patients who have recovered completely with no residual urinary abnormalities after 1 year are less likely but may still manifest long-term sequelae. In a multicenter pooled analysis of 3,476 children with hemolytic uremic syndrome followed up for a mean of 4.4 years, the combined average death and end-stage kidney disease rate was 12%, and the combined average kidney sequelae rate (chronic kidney disease, proteinuria, hypertension) was 25%. Because of reports of late sequelae in such patients, annual examinations with a primary physician are still warranted.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.6 Toxic Nephropathy

Prasad Devarajan

Aberrant renal function often results from purposeful or accidental exposure to any number of diagnostic, biologic, or therapeutic agents that are potential or actual nephrotoxins. Among diagnostic agents, **contrast-induced nephropathy** is a common and generally reversible form of **acute kidney injury** that results from administration of radiocontrast media in predisposed individuals. Iodinated radiocontrast agents are generally well tolerated by most patients without significant adverse consequences. In volume-depleted patients or patients with underlying chronic kidney disease, their use poses a risk for the development of acute kidney injury with significant attendant morbidity and mortality. Contrast agents can lead to renal vasoconstriction as well as direct tubule cell injury. Contrast-induced nephropathy usually manifests as an increase in serum creatinine 1-2 days following exposure; most patients are not oliguric. In most cases, the serum creatinine normalizes in the next 3-7 days, and treatment is supportive. The overall risk of radiocontrast agents to cause acute kidney injury remains controversial but appears to be low in children with normal kidney function and with the dominant current practice of using low osmolar contrast agents. Biologic nephrotoxins include venomous exposures from insects, reptiles, amphibians, and a wide variety of sea-dwelling animals. The most common forms of toxic nephropathy unfortunately relate to the exposure of children to pharmacologic agents, accounting for close to 20% of episodes of acute kidney injury occurring in children and adolescents. Age, underlying medical condition, genetics, exposure dose, and the concomitant use of other drugs all influence the likelihood of developing acute kidney injury. One common scenario is the use of nonsteroidal antiinflammatory agents (NSAIDs) in febrile children with concomitant dehydration. In this situation, NSAIDs can inhibit the production of intrarenal vasodilatory prostaglandins, thereby leading to decreased renal perfusion and acute kidney injury.

Table 560.3 summarizes the agents that commonly cause acute kidney injury and some of their clinical manifestations. A combination of multiple drugs amplifies the risk. Mechanisms of injury often help to explain the presentation; however, multiple toxic exposures in patients with complicated clinical histories often limit the ability to clearly establish clinical cause and effect. For example, diminished urine output may be the clinical hallmark of tubular obstruction caused by agents such as methotrexate or agents that cause acute tubular necrosis, such as amphotericin B or pentamidine. Alternatively, nephrogenic

Table 560.3 Renal Syndromes Produced by Nephrotoxins

NEPHROTIC SYNDROME
- Angiotensin-converting enzyme inhibitors
- Gold salts
- Interferon
- Mercury compounds
- Nonsteroidal antiinflammatory drugs
- Penicillamine

NEPHROGENIC DIABETES INSIPIDUS
- Amphotericin B
- Cisplatin
- Colchicine
- Demeclocycline
- Lithium
- Methoxyflurane
- Propoxyphene
- Vinblastine

RENAL VASCULITIS
- Hydralazine
- Isoniazid
- Penicillins
- Propylthiouracil
- Sulfonamides
- Numerous other drugs that can cause a hypersensitivity reaction

THROMBOTIC MICROANGIOPATHY
- Cyclosporine A
- Oral contraceptive agents
- Mitomycin C

NEPHROCALCINOSIS OR NEPHROLITHIASIS
- Allopurinol
- Bumetanide
- Ethylene glycol
- Furosemide
- Melamine
- Methoxyflurane
- Topiramate
- Vitamin D

ACUTE KIDNEY INJURY
- Acetaminophen
- Acyclovir
- Aminoglycosides
- Amphotericin B
- Angiotensin-converting enzyme inhibitors
- Biologic toxins (snake, spider, bee, wasp)
- Cisplatin
- Cyclosporine
- Ethylene glycol
- Halothane
- Heavy metals
- Ifosfamide
- Lithium
- Methoxyflurane
- Nonsteroidal antiinflammatory drugs
- Radiocontrast agents
- Tacrolimus
- Vancomycin with or without piperacillin-tazobactam

OBSTRUCTIVE UROPATHY
- Sulfonamides
- Acyclovir
- Methotrexate
- Protease inhibitors
- Ethylene glycol
- Methoxyflurane

FANCONI SYNDROME
- Aminoglycosides
- Chinese herbs (aristolochic)
- Cisplatin
- Heavy metals (cadmium, lead, mercury, and uranium)
- Ifosfamide
- Lysol
- Outdated tetracycline

RENAL TUBULAR ACIDOSIS
- Amphotericin B
- Lead
- Lithium
- Toluene

INTERSTITIAL NEPHRITIS
- Amidopyrine
- *p*-Aminosalicylate
- Carbon tetrachloride
- Cephalosporins
- Cimetidine
- Cisplatin
- Colistin
- Copper
- Cyclosporine
- Ethylene glycol
- Foscarnet
- Gentamicin
- Gold salts
- Indomethacin
- Interferon-α
- Iron
- Kanamycin
- Lithium
- Mannitol
- Mercury salts
- Mitomycin C
- Neomycin
- Nonsteroidal antiinflammatory drugs
- Penicillins (especially methicillin)
- Pentamidine
- Phenacetin
- Phenylbutazone
- Poisonous mushrooms
- Polymyxin B
- Radiocontrast agents
- Rifampin
- Salicylate
- Streptomycin
- Sulfonamides
- Tacrolimus
- Tetrachloroethylene
- Trimethoprim-sulfamethoxazole

STEC, Shiga toxin–producing *Escherichia coli*.

diabetes insipidus may be the critical clinical manifestation of agents that cause interstitial nephritis, such as lithium or cisplatin. Acute kidney injury due to nephrotoxins is frequently polyuric. Nephrotoxicity is often reversible if the noxious agent is promptly removed.

Clinical use of potential nephrotoxins should be judicious. Necessity of exposure, dosing parameters, and the use of drug levels or pharmacogenomic data, when available, should always be considered. Caution is particularly mandated for patients with complex medical conditions that include preexisting renal disease, cardiac disease, diabetes, and/or complicated surgeries. Alternative approaches to imaging or the use of different pharmacologic options should be considered when possible. Imaging modalities such as ultrasonography, radionuclide scanning, or MRI may be preferable to contrast studies in some patients. Alternatively, a judicious volume expansion with or without the administration of *N*-acetylcysteine might offer renoprotection when radioiodinated contrast studies are critical, especially in children with chronic kidney disease or those who are already on other nephrotoxic agents. Pharmacologic agents with no known kidney effects can often be substituted for known nephrotoxins with equal clinical efficacy. In all cases, simultaneous use of known nephrotoxins should be avoided whenever possible. The use of nephrotoxic agents represents one of the few modifiable risk factors for acute kidney injury, and promising new biomarkers for the early detection and modification of nephrotoxic injuries are currently becoming available. Use of the electronic health record for systematic surveillance for nephrotoxic medication exposure and acute kidney injury can also lead to sustained reductions in avoidable kidney injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.7 Cortical Necrosis

Prasad Devarajan

BACKGROUND

Renal cortical necrosis is a rare cause of severe acute kidney injury occurring secondary to extensive ischemic damage of the renal cortex. Ischemic necrosis is due to markedly decreased renal arterial perfusion as a result of vascular spasm, microvascular injury, or intravascular coagulation. Renal cortical necrosis is usually bilateral and extensive, although focal and patchy forms have also been described. The medulla, the juxtamedullary cortex, and a thin rim of subcapsular cortex are usually spared. It occurs most commonly in neonates and in adolescents of childbearing age.

ETIOLOGY

In newborns, cortical necrosis is most associated with hypoxic or ischemic insults caused by perinatal asphyxia, placental abruption, and twin–twin or fetal–maternal transfusion. Other causes include renal vascular thrombosis and severe congenital heart disease. After the neonatal period, cortical necrosis is most commonly seen in children with septic shock or severe hemolytic-uremic syndrome. In adolescents and women, cortical necrosis occurs in association with obstetric complications, including prolonged intrauterine fetal death, placental abruption, septic abortion, or amniotic fluid embolism.

Less common causes of cortical necrosis include malaria, extensive burns, snakebites, infectious endocarditis, and medications (e.g., nonsteroidal antiinflammatory agents). Acute renal cortical necrosis has also been reported to occur in SLE-associated antiphospholipid antibody syndrome.

PATHOGENESIS

The presumed initiating factor in many cases is intense vasospasm of the small vessels. When prolonged, this leads to necrosis and thrombosis of the distal arterioles and glomeruli, with ensuing cortical necrosis. In hemolytic-uremic syndrome and septic abortion, endotoxin-mediated endothelial damage contributes to worsening vascular thrombosis.

CLINICAL MANIFESTATIONS

Cortical necrosis clinically presents as severe acute kidney injury in patients with predisposing causes. Urine output is diminished and gross, and/or microscopic hematuria may be present. Hypertension is common, and thrombocytopenia may be present because of renal microvascular injury.

LABORATORY AND RADIOLOGIC FINDINGS

Laboratory results are consistent with acute kidney injury: an elevated BUN and creatinine, hyperkalemia, and metabolic acidosis. Anemia and thrombocytopenia are common. Urinalysis reveals hematuria with red cell or granular casts, and proteinuria.

Ultrasound examination with Doppler flow studies demonstrates decreased perfusion to both kidneys. Kidneys are enlarged in the initial stages, but cortical tissue becomes shrunken in the later stages. Thin cortical shells of calcification (tram lines) are a radiologic hallmark, but they develop only 4-5 weeks after the initial insult.

CT scanning with contrast is the most sensitive imaging modality in renal cortical necrosis. Diagnostic features include absent opacification of the renal cortex and enhancement of subcapsular and juxtamedullary regions and of the medulla with absent excretion of contrast medium.

A radionuclide renal scan shows decreased uptake with significantly delayed or absent function. Renal scanning is the imaging technique of choice if contrast-enhanced CT scanning is not available or is contraindicated.

TREATMENT

The cornerstones of therapy for renal cortical necrosis are to restore hemodynamic stability, institute early dialysis, and treat the underlying cause. Most cases of renal cortical necrosis require initial treatment in an intensive care setting. It is important to prevent or treat the underlying cause of acute cortical necrosis, when possible. Therapy involves medical management of acute renal failure, often with the initiation of dialysis as indicated. Management is otherwise supportive and involves volume repletion, correction of asphyxia, and treatment of sepsis.

PROGNOSIS

The most important prognostic factors include the extent of necrosis, duration of oligoanuria, and severity of the overall associated conditions. Untreated, renal cortical necrosis has a high mortality rate, exceeding 50%. Early initiation of dialysis significantly diminishes the mortality rate. Most patients require dialysis for variable but extended periods of time. Twenty to 40% of patients have partial recovery of renal function, the extent of which depends on the amount of preserved cortical tissue. All patients require long-term follow-up for chronic kidney disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

560.8 Coagulopathies and Thrombocytopenia

Prasad Devarajan

Gross or microscopic hematuria may be associated with inherited or acquired disorders of coagulation (hemophilia, disseminated intravascular coagulation, thrombocytopenia). In these cases, however, hematuria is not usually the presenting complaint or a major factor affecting the clinical management or outcome (see Chapters 524-533).

Chapter 561

Tubulointerstitial Disease Associated with Hematuria

Prasad Devarajan

Gross or microscopic hematuria may be associated with several disorders of the renal tubules and the interstitium (pyelonephritis, tubulointerstitial nephritis, papillary necrosis, acute tubular necrosis). However, except for papillary necrosis, hematuria is not usually the presenting complaint or a major factor affecting the clinical management or outcome (see Chapters 561.2-561.4).

561.1 Pyelonephritis

See Chapter 575, Urinary Tract Infections.

561.2 Tubulointerstitial Nephritis

Prasad Devarajan

Tubulointerstitial nephritis (TIN, also called interstitial nephritis) is the term applied to conditions characterized by tubulointerstitial inflammation and damage with relative sparing of glomeruli and vessels. Both acute and chronic primary forms exist. **Acute TIN** is characterized by an acute extensive lymphocytic inflammatory response and a rapid decline in renal function. **Chronic TIN** usually displays a protracted onset and a chronic patchy lymphocytic infiltrate, interstitial fibrosis, and a slow deterioration in renal function. Secondary forms of interstitial nephritis can be associated with primary glomerular diseases, as well as systemic diseases affecting the kidney.

ACUTE TUBULOINTERSTITIAL NEPHRITIS

The hallmarks of acute TIN are an extensive lymphocytic infiltration of the tubulointerstitium, interstitial edema, and varying degrees of tubular necrosis and regeneration. Eosinophils may be present, particularly in drug-induced TIN; occasionally, interstitial granulomas with giant cells occur. Glomeruli are usually normal in primary TIN. The pathogenesis is not fully understood, but a T-cell–mediated immune mechanism has been postulated. *Drugs are the most common cause of acute TIN in children.* Many medications, especially antimicrobials, anticonvulsants, and analgesics, have been implicated as etiologic agents (Table 561.1). Nonsteroidal antiinflammatory drugs (NSAIDs), penicillins, and sulfonamides account for most cases. Drug-induced TIN is an idiosyncratic reaction that occurs in only a very small subset of patients who ingest the medication, typically with repeated exposure. Drugs of abuse (including synthetic cannabinoids, bath salts, ecstasy, anabolic steroids, inhaled solvents, heroin, and cocaine) are an increasingly common problem in certain populations. Other causes of acute TIN include infections, primary glomerular diseases, and systemic diseases such as systemic lupus erythematosus.

Clinical Manifestations

The classic presentation of acute TIN is fever, rash, and arthralgia in the setting of a rising serum creatinine. Acute TIN accounts for about 5% of pediatric acute kidney injury cases. Although the full clinical triad may be noted in drug-induced TIN, most patients with acute TIN do not demonstrate all the typical features. The rash can vary from maculopapular to urticarial and is often transient. Patients often have nonspecific constitutional symptoms of nausea, vomiting, fatigue, and weight loss. Flank pain may be present, presumably secondary to stretching of the renal capsule from acute inflammatory enlargement of the kidney. If acute TIN is caused by a systemic disease such as systemic lupus erythematosus, the clinical presentation will be consistent with specific signs and symptoms of the underlying disease. Unlike the typical presentation of oliguric **acute kidney injury (AKI)** seen with glomerular diseases, 30–40% of patients with acute TIN are nonoliguric, and hypertension is less common. Peripheral eosinophilia can occur, especially with drug-induced TIN. Microscopic hematuria is invariably present, but significant hematuria or proteinuria >1.5 g/day is uncommon. One exception is patients whose TIN is caused by NSAIDs, who can present with nephrotic syndrome. Urinalysis can reveal white blood cell, granular, or hyaline casts, but red blood cell casts (a characteristic of glomerular disease) are absent. The presence of urine eosinophils is neither sensitive nor specific, being detected in only 25% of cases. Because of pyuria, the initial diagnosis may be a urinary tract infection.

Diagnosis

The diagnosis is usually based on the clinical presentation and laboratory findings. A renal biopsy will establish the correct diagnosis in cases where the etiology or clinical course confounds the diagnosis. A careful history of the timing of disease onset in relation to drug exposure is essential in suspected drug-induced TIN. Because of the immune-mediated nature of TIN, signs or symptoms generally appear within 1-2 weeks following exposure. In children, antimicrobials are a common inciting agent. NSAIDs are an important cause of acute TIN in children, and volume depletion or underlying chronic kidney disease can increase the risk of occurrence. Urinalysis and serial measurements of serum creatinine and electrolytes should be monitored. Renal ultrasonography, though not diagnostic, can demonstrate enlarged, echogenic kidneys. Removal of a suspected offending agent followed by spontaneous improvement in kidney function is highly suggestive of the diagnosis, and additional testing is generally not performed in this setting. In more severe cases, in which the cause is unclear, or the patient's kidney function deteriorates rapidly, a renal biopsy is indicated.

Treatment and Prognosis

Treatment of acute TIN starts with eliminating the suspected causative drug or agent. Most patients with mild ATN recover kidney function when the inciting agent is discontinued. Other treatment includes supportive care directed at addressing complications of AKI, such as hyperkalemia or volume overload (see Chapter 572.1). Corticosteroid administration within 2 weeks of the discontinuation of certain offending agents (e.g., NSAIDs or antibiotics) can hasten the recovery and improve the long-term prognosis in drug-induced TIN. Current recommendations favor the use of oral prednisone in children whose kidney function fails to improve soon after stopping the suspected agent. IV methylprednisolone is used in severe cases. Mycophenolate mofetil has been found to be beneficial in steroid-unresponsive cases. Whether such therapies are indicated in other causes of TIN is not clear. For patients with prolonged kidney insufficiency, the prognosis remains guarded, and severe acute TIN from any cause can progress to chronic TIN.

CHRONIC TUBULOINTERSTITIAL NEPHRITIS

In children, chronic TIN most commonly occurs in the context of (1) an underlying congenital urologic kidney disease, such as obstructive uropathy or vesicoureteral reflux, or (2) an underlying metabolic disorder affecting the kidneys (see Table 561.1). Some commonly used drugs such as cyclosporine and tacrolimus also cause chronic TIN. Chronic TIN can occur as an idiopathic disease, although this is more common in adults.

The **juvenile nephronophthisis (JN)–medullary cystic kidney disease complex (MCKD)** is a group of inherited, genetically determined cystic renal diseases that share the common histologic finding of chronic TIN. At least 20 different genes are associated with JN, usually

Table 561.1 Etiology of Interstitial Nephritis

ACUTE INTERSTITIAL NEPHRITIS

Drugs

- **Antimicrobials**
  - Penicillin derivatives
  - Cephalosporins
  - Sulfonamides
  - Trimethoprim-sulfamethoxazole
  - Ciprofloxacin
  - Tetracyclines
  - Vancomycin
  - Erythromycin derivatives
  - Rifampin
  - Amphotericin B
  - Acyclovir
- **Anticonvulsants**
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Sodium valproate

Drugs of Abuse

- Synthetic cannabinoids
- Bath salts
- Ecstasy
- Anabolic steroids
- Inhaled solvents
- Heroin
- Cocaine

Other Drugs

- Allopurinol
- All-trans-retinoic acid
- 5-Aminosalicylic acid
- Cimetidine
- Cyclosporine
- Diuretics
- Escitalopram
- Interferon
- Mesalazine
- Quetiapine
- Olanzapine
- Nonsteroidal antiinflammatory drugs
- Protease inhibitors
- Proton pump inhibitors
- Aristolochic acid (traditional Chinese herb)

Infections

- Adenovirus
- Bacteria associated with acute pyelonephritis
- BK virus
- *Brucella*
- Streptococcal species
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B virus
- Histoplasmosis
- Human immunodeficiency virus
- Hantavirus
- Leptospirosis
- *Toxoplasma gondii*

Disease-Associated

- Glomerulonephritis (e.g., systemic lupus erythematosus)
- Acute allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome

Idiopathic

CHRONIC INTERSTITIAL NEPHRITIS

Drugs and Toxins

- Analgesics
- Cyclosporine
- Lithium
- Heavy metals (including lead)

Infections (See Acute Interstitial Nephritis)

- **Disease-associated causes**
  - Metabolic and hereditary
  - Cystinosis
  - Oxalosis
  - Fabry disease
  - Wilson disease
  - Sickle cell nephropathy
  - Alport syndrome
  - Juvenile nephronophthisis, medullary cystic disease

Immunologic

- Systemic lupus erythematosus
- Crohn disease
- Chronic allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome
- Anti-tubular basement disease

Urologic

- Posterior urethral valves
- Eagle-Barrett syndrome
- Ureteropelvic junction obstruction
- Vesicoureteral reflux

Miscellaneous

- Balkan nephropathy
- Radiation
- Sarcoidosis
- Neoplasm

Idiopathic

inherited as an autosomal recessive disease (Table 561.2). These genes only define 30% of cases, and new genes are being identified at a rapid pace. Although uncommon in the United States, JN causes 10–20% of pediatric cases of end-stage kidney disease (ESKD) in Europe. Patients with JN typically present with polyuria, growth failure, unexplained anemia, and chronic kidney disease in late childhood or adolescence.

JN is a **ciliopathy** and is often associated with extrarenal features such as retinal degeneration, hepatobiliary disease, cerebellar vermis hypoplasia, laterality defects, intellectual disability, and shortening of bones (see Chapter 101.3). These features are represented in several syndromes, such as **Senior-Løken syndrome (retinitis pigmentosa), Joubert syndrome (cerebellar vermis hypoplasia;** 22 subtypes),

Table 561.2 Juvenile Nephronophthisis: Summary of the *NPHP1* to *NPHP18, NHPH1L,* and *NPHP2L* Genes, Gene Products, Chromosomal Localization, Phenotypes, Extrarenal Symptoms, and Interaction Partners

GENE (PROTEIN)	CHROMOSOME	PHENOTYPE (MEDIAN AGE AT ESRD)	EXTRARENAL SYMPTOMS	INTERACTION PARTNERS
NPHP1 (nephrocystin-1)	2q13	NPHP (13 yr)	RP (10%), OMA (2%), JBTS (rarely)	Inversin, nephrocystin-3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B
NPHP2/INVS (inversin)	9q31	Infantile NPHP (<4 yr)	RP (10%), LF, situs inversus, CHD	Nephrocystin-1, calmodulin, catenins, β-tubulin, APC2
NPHP3 (nephrocystin-3)	3q22	Infantile and adolescent NPHP	LF, RP (10%), situs inversus, MKS, CHD	Nephrocystin-1
NPHP4 (nephrocystin-4)	1p36	NPHP (21 yr)	RP (10%), OMA, LF	Nephrocystin-1, BCAR1, PTK2B
NPHP5/IQCB1 (nephrocystin-5)	3q21	NPHP (13 yr)	Early-onset RP	Calmodulin, RPGR, nephrocystin-6
NPHP6/CEP290 (nephrocystin-6/CEP290)	12q21	NPHP	JBTS, MKS	ATF4, nephrocystin-5, CC2D2A
NPHP7/GLIS2 (nephrocystin-7/GLIS2)	16p	NPHP	—	—
NPHP8/RPGRIP1L (nephrocystin-8/RPGRIP1L)	16q	NPHP	JBTS, MKS	Nephrocystin-1
NPHP9/NEK8 (nephrocystin-9/NEK8)	17q11	Infantile NPHP	—	—
NPHP10/SDCCAG8 (nephrocystin-10/SDCCAG8)	1q43	Juvenile NPHP	RP (SLS), BBS-like	OFD1
TMEM67/MKS3/NPHP11 (nephrocystin-11/meckelin)	8q22.1	NPHP	JBTS, MKS, LF	MKS1, nephrocystin-1, nephrocystin-4, nephrocystin-6, nesprin-2, TMEM216
TTC21B//JBTS11/NPHP12 (nephrocystin-12/IFT139)	2q24.3	Early-onset NPHP, juvenile NPHP	JATD, MKS, JBTS, BBS-like	Ciliopathy modifier
WDR19/NPHP13 (nephrocystin-13/IFT144)	4p14	NPHP	JATD, SBS, CED, RP, Caroli, BBS-like	—
ZNF423/NPHP14 (nephrocystin-14/ZNF423)	16q12.1	Infantile NPHP, PKD	JBTS, situs inversus	PARP1, nephrocystin-6,
CEP164/NPHP15 (nephrocystin-15 centrosomal protein 164 kDa)	11q23.3	NPHP (8 years)	RP, JBTS, LF, obesity	ATRIP, CCDC92, TTBK2, nephrocystin-3, nephrocystin-4, Dvl3
ANKS6/NPHP16 (nephrocystin-16/ANKS6)	9q22.33	NPHP, PKD	LF, situs inversus, cardiovascular abnormalities	INVS, nephrocystin-3, NEK8, HIF1AN, NEK7, BICC1
IFT172/NPHP17 (nephrocystin-17/IFT172)	2p23.3	NPHP	JATD, MZSDS, JBTS	IFT140, IFT80
CEP83/NPHP18 (nephrocystin-18/centrosomal protein 83 kDa)	12q22	Early-onset NPHP (3 yr)	Learning disability, hydrocephalus, LF	CEP164, IFT20
NPHP1L/XPNPEP3 (nephrocystin-1L/XPNPEP3)	22q13	NPHP	Cardiomyopathy, seizures	Cleaves LRRC50, ALMS1, nephrocystin-6
NPHP2L/SLC41A1 (nephrocystin-2L/SLC41A1)	1q32.1	NPHP	Bronchiectasis	—

ATF4, Activating transcription factor 4; APC2, anaphase-promoting complex 2; BBS, Bardet-Biedl syndrome; BCAR1, breast cancer antiestrogen resistance 1; CC2D2A, coiled-coil and C2 domain containing 2A; CED, cranioectodermal dysplasia; CHD, congenital heart disease; JATD, Jeune asphyxiating thoracic dysplasia; JBTS, Joubert syndrome; LF, liver fibrosis; MKS, Meckel-Gruber syndrome; MZSDS, Mainzer-Saldino syndrome; NPHP, nephronophthisis; OMA, oculomotor apraxia; PKD, polycystic kidney disease; PTK2B, protein tyrosine kinase 2B; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; SBS, Sensenbrenner syndrome; SLS, Senior-Løken syndrome.

From Wolf MTF. Nephronophthisis and related syndromes. *Curr Opin Pediatr.* 2015;27:201–211. Table 1.

Bardet-Biedl syndrome (intellectual disability, obesity; 17 subtypes), **Jeune asphyxiating thoracic dystrophy** (shortening of the long bones, narrow rib cage; 11 subtypes), and many others. **MCKD** is an autosomal dominant disease that typically manifests in adulthood, characterized by tubulointerstitial sclerosis leading to ESKD. Because at least four different gene pathogenic variants may give rise to the condition, the name **autosomal dominant tubulointerstitial kidney disease (ADTKD)** has been proposed for this condition. The two best known forms of ADTKD include mucin-1 kidney disease 1 (MKD1) and mucin-2 kidney disease/uromodulin kidney disease (MKD2), based on the pathogenic variant identified. **TIN with uveitis (TINU syndrome)** is a rare autoimmune syndrome of chronic TIN with bilateral anterior uveitis and bone marrow granulomas that occurs primarily in adolescent girls. Clinical manifestations include photophobia, ocular pain and redness, and visual impairment. Chronic TIN is seen in all forms of progressive kidney disease, regardless of the underlying cause, and the severity of interstitial disease is the single most important factor predicting progression to ESKD.

Pathogenesis and Pathology

The pathophysiology of chronic TIN is undefined, but data suggest that, other than the abnormal cilia structure and function in JN and MCKD, in other cases it is immune mediated. Cells making up the interstitial infiltrate appear to be a combination of native interstitial cells, inflammatory cells recruited from the circulation, and resident tubular cells that undergo epithelial-mesenchymal transformation. Grossly, kidneys can appear pale and small for age. Microscopically, tubular atrophy and "dropout" with interstitial fibrosis and a patchy lymphocytic interstitial inflammation are seen. Patients with JN often have characteristic small cysts in the corticomedullary region. In primary chronic TIN, glomeruli are relatively spared until late in the disease course. Patients with chronic TIN secondary to a primary glomerular disease have histologic evidence of the primary disease. Chronic TIN due to cyclosporine or tacrolimus use is characterized by tubular atrophy, "stripe" interstitial fibrosis, and vascular sclerosis.

Clinical Manifestations

The clinical features of chronic TIN are often nonspecific and can reflect signs and symptoms of slowly progressive chronic kidney disease (see Chapter 572). Fatigue, growth failure, polyuria, polydipsia, and enuresis are often present. Anemia that is seemingly disproportionate to the degree of kidney insufficiency is common and is a particularly prominent feature in JN. Because tubular damage often leads to salt wasting by the kidney, significant hypertension is unusual. Fanconi syndrome, proximal renal tubular acidosis, distal renal tubular acidosis, and hyperkalemic distal renal tubular acidosis can occur.

Extrarenal manifestations of **nephronophthisis** include ophthalmic, neurologic, hepatic, and skeletal disorders (Table 561.3).

Table 561.3 Extrarenal Manifestations Associated with Nephronophthisis and Resulting Syndromes Associated with *NPHP* Pathogenic Variants

DISORDER	SYNDROME
OPHTHALMOLOGIC	
Retinitis pigmentosa	Senior-Løken syndrome (SLSN)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Alstrom (RP, obesity, DM type 2, hearing impairment)
	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Oculomotor apraxia	Cogan syndrome
Nystagmus	Joubert syndrome/Joubert syndrome–related disorders
Coloboma	Joubert syndrome/Joubert syndrome–related disorders
NEUROLOGIC	
Encephalocele	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
Vermis aplasia	Joubert syndrome/Joubert syndrome–related disorders
Hypopituitarism	RHYNS
HEPATIC	
Liver fibrosis	Boichis syndrome
	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Joubert syndrome/Joubert syndrome–related disorders
SKELETAL	
Short ribs	Jeune syndrome/asphyxiating thoracic dystrophy
Cone-shaped epiphysis	Mainzer-Saldino syndrome
Postaxial polydactyly	Joubert syndrome/Joubert syndrome–related disorders
	Bardet-Biedl syndrome (NPHP, RP, obesity, deafness)
	Ellis van Creveld
Skeletal abnormalities	Sensenbrenner syndrome/ cranioectodermal dysplasia
	Ellis van Creveld
OTHERS	
Situs inversus	
Cardiac malformation	
Bronchiectasis	
Ulcerative colitis	

RP, Retinitis pigmentosa; DM, diabetes mellitus; NPHP, nephronophthisis.
From Wolf MT, Hildebrandt F. Nephronophthisis. *Pediatr Nephrol*. 2011;26:181–194.

Diagnosis

The diagnosis is suggested by signs or symptoms of kidney tubular damage such as polyuria and an elevated serum creatinine value, coupled with a history suggestive of a chronic disease, such as long-standing enuresis or the presence of anemia resistant to iron therapy. Radiographic studies, in particular ultrasonography, can give additional evidence of chronicity, such as small, echogenic kidneys, corticomedullary microcysts suggesting JN, or findings of obstructive uropathy. A voiding cystourethrogram can demonstrate the presence of vesicoureteral reflux or bladder abnormalities. If JN is suspected, a specific genetic diagnosis is available. In instances in which the cause is unclear, a kidney biopsy may be performed. In cases of advanced disease, a kidney biopsy might not be diagnostic. Many ESKDs display a common histologic appearance of tubular fibrosis and inflammation.

Treatment and Prognosis

Therapy is directed at maintaining the fluid and electrolyte balance and avoiding further exposure to nephrotoxic agents. Patients with obstructive uropathies can require salt supplementation and treatment with potassium-binding resin. Prevention of infection by antibiotic prophylaxis can slow the progression of renal damage in appropriate patients. The prognosis in patients with chronic TIN depends in large part on the nature of the underlying disease. Patients with obstructive uropathy or vesicoureteral reflux can have a variable degree of kidney damage and thus a variable course. ESKD can develop over months to years. Patients with JN uniformly progress to ESKD by adolescence. Patients with metabolic disorders can benefit from treatment when available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

561.3 Papillary Necrosis

Prasad Devarajan

Renal papillary necrosis (RPN) is a descriptive term applied to conditions that result in necrosis of the kidney medullary pyramids and papillae. The hypoxic and hypertonic environment that normally prevails in the kidney medullary region renders it especially vulnerable to ischemic necrosis. Common precipitating factors in children include shock, hypovolemia, hypoxia, pyelonephritis, urinary tract obstruction, and sickle cell hemoglobinopathies, Analgesic abuse and diabetes mellitus are additional important causes in adults. RPN can result in secondary infection, deposition of stones, and sloughing of papillae with resultant urinary tract obstruction. Both an acute progressive clinical course and a more chronic protracted form have been described. Patients most commonly present with flank pain and hematuria. Radiologic studies are key to establishing the diagnosis. Management is directed toward treating the underlying cause, ameliorating kidney ischemia with hydration, and surgical relief of obstruction.

PATHOGENESIS AND PATHOLOGY

RPN may be focal (involving only the papillary tips) or diffuse (involving the whole papilla and the innermost areas of the medulla). RPN may affect a single papilla or multiple papillae. Histologically, the tissue typically reveals classic coagulative necrosis, surrounded by an inflammatory response.

Under normal conditions, the medullary region of the kidney subsists on a hypoxic precipice due to low blood flow and countercurrent exchange of oxygen, although paradoxically housing nephron segments with very high energy requirements. The blood flow decreases even further as one approaches the innermost regions of the medulla and becomes marginal toward the apex and tips of the papillae. The already compromised blood supply is further attenuated in several pathophysiologic states, including the hypoxia from shock and dehydration, the intraluminal stasis of sickle cell nephropathy, the inflammation of pyelonephritis, the increased pressure of urinary tract obstruction, the microvascular changes of diabetes, and the direct damage from analgesics (including NSAIDs). Approximately 15–30% of patients with sickle cell disease will encounter episodes of RPN during their lifetime.

CLINICAL MANIFESTATIONS

The classic presentation of acute RPN is flank pain and renal colic, gross hematuria with clots and tissue debris, and fever with chills. AKI, an increase in the serum creatinine, and oliguria are not common but may accompany the rapidly progressive form. Patients with the chronic indolent form may be asymptomatic and may first present with the passage of sloughed papillae in the urine.

DIAGNOSIS

The diagnosis of RPN is usually based on the history, clinical presentation, laboratory findings, and radiologic investigations. Contrast-enhanced CT scanning is the imaging modality of choice. In the acute phase, this method depicts several typical features, including clefts in the medulla, pelvic filling defects, nonenhanced lesions surrounded by rings of excreted material, medullary calcifications, and the presence of obstruction. If IV contrast is contraindicated, CT scanning without contrast or renal ultrasonography may be performed. These modalities are now replacing IV urography, which was the imaging method of choice in the past.

TREATMENT AND PROGNOSIS

Treatment of acute RPN starts with ameliorating the kidney ischemia with IV hydration. In addition, it is important to treat the underlying cause, including appropriate medical management of shock, sepsis, pyelonephritis, or sickle cell disease. Cessation of any analgesics (including NSAIDs) is critical. Patients with acute obstruction may require surgical intervention for relief.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography

561.4 Acute Tubular Necrosis

Prasad Devarajan

Acute tubular necrosis (ATN) is a descriptive term applied to conditions that result in necrosis of the renal tubular epithelial cells. The hypoxic environment that normally prevails in the kidney medullary region renders its nephron segments especially vulnerable to necrotic cell death. ATN frequently coexists with other forms of cell death, as well as cellular regeneration. Common precipitating factors in children include prolonged renal ischemia, sepsis, shock, hypovolemia, and nephrotoxic medications. ATN is the most common cause of *intrinsic* **acute kidney injury (AKI)** (see Chapter 572). ATN is clinically characterized by a rapid (within hours to days) decline in kidney function that leads to retention of waste products such as BUN and creatinine, fluid overload, and reduced urine output in many cases. Patients with hospital-acquired ATN frequently have no specific symptoms, and the diagnosis requires a high index of suspicion in predisposed individuals. Laboratory tests and radiologic studies are the key to establishing the diagnosis. Management is directed toward treating the underlying or precipitating cause, correction of imbalances in fluid, electrolyte, and acid-base status, avoidance of nephrotoxic medications, and treatment of complications.

PATHOGENESIS AND PATHOLOGY

The pathologic findings are highly variable, depending on the etiology and the region of the kidney affected. In children with predominantly ischemic ATN, necrosis is relatively inconspicuous, whereas it is more widespread in nephrotoxic ATN. Because the medullary region of the kidney (including the straight segment of the proximal tubule and the medullary thick ascending limb of the loop of Henle) normally subsists in a hypoxic environment due to low blood flow and countercurrent exchange of oxygen, these nephron segments are usually the most severely affected. Typical findings include patchy areas of tubule cell necrosis with resultant loss of tubule epithelial cells and exposure of denuded basement membrane. Other forms of cell death, including apoptosis, necroptosis, and ferroptosis, occur simultaneously. Surviving proximal tubule cells show diffuse effacement and loss of the brush border and apical blebs. The distal nephron segments exhibit tubular dilatation with intraluminal casts. There is concomitant evidence for cellular regeneration and repair among freshly damaged tubule epithelial cells. Injury is aggravated by several pathophysiologic states, including the ischemia from sepsis, shock, and dehydration and the direct damage from nephrotoxic medications.

The significant decline in kidney function is often out of proportion to the observed patchy histologic changes. In addition to tubule cell necrosis, several other factors contribute to the decline in the glomerular filtration rate (GFR). First, a single collecting tubule drains multiple nephrons, such that obstruction of even a small number of collecting tubules results in failure of filtration from several nephrons. Second, obstruction aggravates the backflow of filtered tubular fluid into the vascular space across the denuded epithelium. Third, loss of the proximal tubular reabsorptive capacity results in increased delivery of sodium chloride to the macula densa, with activation of the tubuloglomerular feedback mechanisms that worsens the afferent arteriolar constriction. Fourth, many additional factors contribute to the pathogenesis of ATN, including changes in the microvascular blood flow, endothelial damage, and the activation of inflammatory pathways.

The pathophysiology and clinical course of ATN may be divided into three sequential phases, namely, initiation, maintenance, and recovery. The *initiation* phase occurs during the initial exposure to ischemia or nephrotoxins. Tubule cell damage begins to evolve, and the sloughed tubular cell debris results in obstruction of the tubular lumen. The combination of hypoperfusion and obstruction to the tubular fluid flow results in a fall in the GFR and urine output and a rise in serum creatinine levels. During the *maintenance* phase of ATN, renal tubule injury is established at its highest severity, the GFR and urine output become stabilized at a very low level, and the BUN and serum creatinine peak. It should be noted that ATN due to nephrotoxic

medications is typically nonoliguric. This phase typically lasts for 1-2 weeks but may extend to several weeks. Complications (e.g., metabolic, fluid, and electrolyte imbalances) typically occur during this phase. The *recovery* phase, also called the diuretic phase, is characterized by regeneration of lost tubule epithelial cells, repair of sub-lethally injured cells, and removal of intratubular casts by reestablishment of tubular fluid flow. It is clinically heralded by polyuria and a slow recovery of the GFR. Diuresis occurs because the rapidly increasing GFR precedes the complete recovery of the tubule cell structure and function and can result in volume depletion if not recognized and treated promptly.

The most prevalent causes of ATN in neonates and older children are shown in Tables 561.4 and 561.5, respectively.

CLINICAL MANIFESTATIONS

ATN is largely asymptomatic, and the clinical diagnosis depends on having a high index of suspicion in children with etiologic risk factors. ATN most frequently manifests with a progressive accumulation of fluid, a serial elevation in the BUN and serum creatinine, and a reduction in urine output, in a predisposed patient who has been exposed to either ischemic or nephrotoxic injury. The evaluation requires a complete history directed toward the known causes of ATN, physical examination, laboratory testing, and renal imaging. A detailed history of all ingested drugs and medications is especially important. Although ATN is technically a histologic diagnosis, kidney biopsies are only rarely performed in children with this condition.

Signs of ATN on physical examination include edema, hypertension, and evidence of heart failure. Children with intravascular volume depletion exhibit tachycardia, hypotension, decreased skin turgor, and dry mucous membranes.

Table 561.4 Prevalent Causes of Acute Tubular Necrosis in Neonates

MECHANISM	CAUSES
Ischemia	Perinatal asphyxia, respiratory distress syndrome, hemorrhage, congenital heart disease, sepsis, shock
Exogenous toxins	Aminoglycosides, maternal ingestion of angiotensin-converting enzyme inhibitors or nonsteroidal antiinflammatory drugs
Endogenous toxins	Hemoglobin (hemolysis), myoglobin (seizures)
Primary kidney disease	Renal vein thrombosis, renal artery thrombosis, polycystic kidney disease

Table 561.5 Prevalent Causes of Acute Tubular Necrosis in Older Children

MECHANISM	CAUSES
Ischemia	Severe dehydration, hemorrhage, shock, sepsis, burns, major surgery, severe cardiac disease, prolonged cold ischemia time in kidney transplant
Exogenous toxins	Aminoglycosides, cisplatin, contrast agents, cyclosporine, tacrolimus, angiotensin-converting enzyme inhibitors, nonsteroidal antiinflammatory drugs
Endogenous toxins	Hemoglobin (hemolysis, extracorporeal circulation), myoglobin (crush injuries, seizures, influenza)
Primary kidney disease	Hemolytic uremic syndrome, crescentic glomerulonephritis

DIAGNOSIS

The diagnosis of ATN is aided by laboratory findings and radiologic investigations. A freshly voided urine is typically positive for blood and protein, and microscopy reveals red blood cells and broad, muddy-brown granular casts. Heme-positive urine in the absence of red blood cells in the sediment should raise the suspicion for hemolysis or rhabdomyolysis. In ATN, the impaired kidney reabsorptive and concentrating capacity typically results in a low urine specific gravity and a high urinary sodium and fractional excretion of sodium. The hallmark of ATN is a progressive increase in the serum creatinine and BUN. Urine biomarkers, such as neutrophil gelatinase associated lipocalm (NGAL) and cystatin C, usually increase before creatinine levels and are helpful in predicting acute tubular injury. A mild to moderate anemia is common due to dilution and decreased erythropoiesis. A high anion gap metabolic acidosis results from impaired renal excretion of acids and decreased tubular reabsorption of bicarbonate. Several electrolyte disturbances may be encountered, including hyponatremia (usually dilutional), hyperkalemia, hyperphosphatemia, hypocalcemia, and hypomagnesemia. If rhabdomyolysis is suspected, the diagnosis can be confirmed by the detection of urine myoglobin and elevated levels of serum creatine kinase. The diagnosis of nephrotoxicity may be aided by the determination of serum drug levels. Renal ultrasonography in ATN typically reveals enlarged echogenic kidneys. Prolonged severe ATN results in renal cortical necrosis and a reduction in kidney size.

TREATMENT AND PROGNOSIS

See Chapter 572.1

Treatment of ATN starts with ameliorating the kidney ischemia by restoring and maintaining the intravascular volume with IV hydration. In addition, it is important to treat the underlying cause, including with appropriate medical management of shock, sepsis, or cardiac disease. Cessation of any potential nephrotoxic agent (including NSAIDs) is critical. Dosages of all medications should be chosen based on the estimated GFR. Children with oliguria and volume overload may require fluid restriction and the judicious use of furosemide. Although furosemide can convert the clinical picture from an oliguric to a nonoliguric one (which can facilitate medical management), there is little evidence that it changes the clinical course of ATN. Children with established ATN may not respond to furosemide and are at higher risk for ototoxicity. Common indications for dialysis in ATN include fluid overload that is unresponsive to diuretics or is a hindrance to the provision of adequate nutrition, hyperkalemia unresponsive to medical management, symptomatic acid-base imbalances, and refractory hypertension.

In the absence of multiorgan failure, most children with ATN eventually regain renal function to a large extent. In the context of severe multiorgan dysfunction, renal recovery is limited, and morbidity and mortality rates remain high. Patients who recover from severe ATN remain at risk for subsequently developing chronic kidney disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for a Bibliography.

Chapter 562

Vascular Diseases Associated with Hematuria

562.1 Vascular Abnormalities

Prasad Devarajan

Hemangiomas, hemangiolymphangiomas, angiomyomas, and arteriovenous malformations of the kidneys and lower urinary tract are rare causes of hematuria. They can present clinically with microscopic hematuria or gross hematuria with clots. When associated cutaneous vascular malformations are present, they can offer a clue to these underlying causes of hematuria. **Angiomyolipomas,** the most common benign solid tumors of the kidney, are composed of vascular, smooth muscle, and fatty tissue elements. They can rupture on occasion to cause severe hemorrhage. Angiomyolipomas are an important component of the **tuberous sclerosis complex** (see Chapter 636.2), which includes developmental delay, facial angiofibromas, and lung cysts. Renal colic can develop with any upper tract vascular abnormality that obstructs urinary drainage, induces an inflammatory response, or distends the renal capsule. The diagnosis may be confirmed by angiography or endoscopy.

Unilateral bleeding of varicose veins of the left ureter, resulting from compression of the left renal vein between the aorta and superior mesenteric artery (mesoaortic compression), is referred to as the **nutcracker syndrome.** Patients with this syndrome typically present with persistent microscopic hematuria (and, occasionally, recurrent gross hematuria) that may be accompanied by proteinuria, left lower abdominal pain, left flank pain, or orthostatic hypotension. The diagnosis requires a high degree of suspicion and is confirmed by Doppler ultrasonography, CT scanning, phlebography of the left renal vein, or MRI.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

562.2 Renal Vein Thrombosis

Prasad Devarajan

EPIDEMIOLOGY

Renal vein thrombosis (RVT) occurs in two distinct clinical settings: (1) In newborns and infants, RVT is commonly associated with asphyxia, dehydration, shock, sepsis, congenital hypercoagulable states, central venous catheters, and maternal diabetes or preeclampsia. (2) In older children, RVT is seen in patients with nephrotic syndrome, cyanotic heart disease, inherited hypercoagulable states, sepsis, sickle cell nephropathy, Behcet syndrome, antiphospholipid syndrome following kidney transplantation, and following exposure to angiographic contrast agents.

PATHOGENESIS

RVT begins in the intrarenal venous circulation and can then extend to the main renal vein and even the inferior vena cava. Thrombus formation is mediated by endothelial cell injury resulting from hypoxia, endotoxin, or contrast media. Other contributing factors include hypercoagulability from either nephrotic syndrome or pathogenic variants in genes that encode clotting factors (e.g., deficiencies of protein C, protein S, antithrombin, and factor V Leiden); hypovolemia and decreased venous blood flow associated with septic shock, dehydration, or nephrotic syndrome; and intravascular sludging caused by polycythemia.

CLINICAL MANIFESTATIONS

The development of RVT is classically heralded by the sudden onset of gross hematuria and unilateral or bilateral flank masses. However, patients can also present with any combination of microscopic hematuria, flank pain, hypertension, or a microangiopathic hemolytic anemia with thrombocytopenia or oliguria. RVT is usually unilateral. Bilateral RVT results in acute kidney injury.

DIAGNOSIS

The diagnosis of RVT is suggested by the development of hematuria and flank masses in patients seen in the high-risk clinical settings or with the predisposing clinical features noted previously. Ultrasonography shows marked renal enlargement, and radionuclide studies reveal little or no renal function in the affected kidney(s). Doppler flow studies of the inferior vena cava and renal vein are essential to confirm the diagnosis. Contrast studies should be avoided to minimize the risk of further vascular damage.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RVT includes other causes of hematuria that are associated with rapid development of microangiopathic hemolytic anemia or enlargement of the kidney(s). These include hemolytic uremic syndrome, hydronephrosis, polycystic kidney disease, Wilms tumor, and intrarenal abscess or hematoma. All patients with RVT should be evaluated for congenital and acquired hypercoagulable states.

TREATMENT

The primary treatment of RVT starts with aggressive supportive intensive care, including correction of fluid and electrolyte imbalance and treatment of renal insufficiency. Recommendations include additional initial treatment of bilateral RVT with tissue plasminogen activator and unfractionated heparin followed by continued anticoagulation with unfractionated or low molecular weight heparin. Treatment recommendations for unilateral RVT with inferior vena cava extension include either unfractionated or low molecular weight heparin. There is no consensus as to whether unilateral RVT without extension should be managed with heparin or with supportive therapy alone. Aggressive treatment with thrombolytic agents in all these clinical settings, as well as antithrombotic prevention of patients with documented thrombotic risk, remains controversial despite such recommendations given the significant risks of bleeding. Evidence-based data, particularly in children, do not exist despite such best practice recommendations. Children with severe hypertension secondary to RVT who are refractory to antihypertensive medications may require nephrectomy.

PROGNOSIS

Perinatal mortality rates from RVT have decreased significantly over the past 20 years. Partial or complete renal atrophy is a common sequela of RVT in the neonate, leading to an increased risk of chronic kidney disease, renal tubular dysfunction, and systemic hypertension. These complications are also seen in older children. However, recovery of kidney function is not uncommon in older children with RVT resulting from nephrotic syndrome or cyanotic heart disease with correction of the underlying etiology. Long-term follow-up of infants and children with RVT by pediatric nephrologists is recommended for the monitoring of kidney function and the early detection of hypertension and chronic kidney disease

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

562.3 Sickle Cell Nephropathy

Prasad Devarajan

Gross or microscopic hematuria may be seen in children with sickle cell disease or sickle trait. Hematuria tends to resolve spontaneously in most children. Clinically apparent kidney involvement occurs more commonly in patients with sickle cell disease than in those with sickle

cell trait with the exception of an association with **renal cell carcinoma**, which is more common in patients with sickle cell trait.

ETIOLOGY

The kidney manifestations of sickle cell nephropathy (SCN) are generally related to microthrombosis secondary to sickling in the relatively hypoxic, acidic, hypertonic kidney medulla, where vascular stasis is normally present. Analgesic use, volume depletion with consequent prerenal acute kidney injury, infection, and iron-related hepatic disease are independent contributing factors. Glomerular hyperfiltration, mediated by the intrarenal production of prostaglandins and synthesis of nitric oxide, is involved in the pathogenesis of proteinuria and kidney injury in SCN.

PATHOLOGY

Ischemia, papillary necrosis, and interstitial fibrosis are common pathologic findings in SCN. The specific sickle cell glomerular lesion consists of glomerular hypertrophy, with glomerulomegaly and distended capillaries. In addition, a variety of glomerular lesions are also found in SCN; most commonly these include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and thrombotic microangiopathy. The pathophysiology of these specific glomerulonephritic lesions in SCN is poorly understood.

CLINICAL MANIFESTATIONS

Clinical manifestations of SCN include polyuria caused by a urinary concentrating defect, renal tubular acidosis, and proteinuria associated with the glomerular lesions noted previously.

Approximately 20–30% of patients with sickle cell disease develop proteinuria. Nephrotic-range proteinuria with or without clinically apparent nephrotic syndrome occurs in up to 30% of patients with SCN, and when present, generally heralds progressive kidney disease.

TREATMENT

Tubular manifestations have no specific treatment other than those recommended generally for patients with sickle cell disease. However, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor inhibitors can be used to reduce the urine protein excretion in patients with daily amounts exceeding 500 mg and may slow the progression of chronic kidney disease. Gross hematuria secondary to papillary necrosis may respond to treatment with ε-aminocaproic acid or desmopressin acetate. Hydroxyurea and newer treatments for sickle cell disease (see Chapter 511.1) have decreased the manifestations of SCN in proportion to the other complications of the primary hemoglobinopathy.

PROGNOSIS

SCN can eventually lead to hypertension, chronic kidney disease, and progressive kidney failure. Dialysis and eventual kidney transplantation are successful treatment modalities when kidney failure is irreversible.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

562.4 Idiopathic Hypercalciuria

Prasad Devarajan

Idiopathic hypercalciuria, which may be inherited as an autosomal dominant disorder, can clinically present as recurrent *gross* hematuria, persistent microscopic hematuria, dysuria, crystalluria, or abdominal pain with or without **kidney stone** formation. Hypercalciuria can also accompany conditions resulting in hypercalcemia, such as hyperparathyroidism (see Chapter 613), vitamin D intoxication, immobilization, and sarcoidosis (see Chapter 209). Hypercalciuria may be associated with Cushing syndrome (see Chapter 619), corticosteroid therapy, tubular dysfunction secondary to Fanconi syndrome as occurs with Wilson disease (see Chapter 405.2), oculocerebrorenal (Lowe) syndrome, William syndrome, distal renal tubular acidosis, or Bartter syndrome (see Chapter 571.1). Hypercalciuria may also be seen in patients with Dent disease, which is an X-linked form of nephrolithiasis associated with hypophosphatemic rickets. Although microcrystal formation with consequent tissue irritation is believed to mediate symptoms, the precise mechanism by which hypercalciuria causes hematuria or dysuria is unknown.

DIAGNOSIS

Hypercalciuria is diagnosed by a 24-hour urinary calcium excretion >4 mg/kg. A screening test for hypercalciuria may be performed on a random urine specimen by measuring the calcium and creatinine concentrations. A spot urine calcium:creatinine ratio (mg/dL:mg/dL) >0.2 suggests hypercalciuria in an older child. Normal ratios may be as high as 0.8 in infants <7 months of age.

TREATMENT

Left untreated, hypercalciuria leads to nephrolithiasis in approximately 15% of cases. Hypercalciuria has also been associated with an increased risk for development of low bone mineral density, as well as an increased incidence of urinary tract infections. Idiopathic hypercalciuria has been identified as a risk factor in 40% of children with kidney stones, and a low urinary citrate level has been associated as a risk factor in approximately 38% of this group. Oral thiazide diuretics can normalize urinary calcium excretion by stimulating calcium reabsorption in the proximal and distal tubules. Such therapy can lead to the resolution of gross hematuria or dysuria and can prevent nephrolithiasis. The precise indications for thiazide treatment (including its duration if initiated) remain controversial.

In patients with persistent gross hematuria or dysuria, therapy is initiated with hydrochlorothiazide at a dose of 1-2 mg/kg/24 hours as a single morning dose. The dose is titrated upward until the 24-hour urinary calcium excretion is <4 mg/kg and clinical manifestations resolve. After 1 year of treatment, hydrochlorothiazide is usually discontinued, but it may be resumed if gross hematuria, nephrolithiasis, or dysuria recurs. During hydrochlorothiazide therapy, the serum potassium level should be monitored periodically to avoid hypokalemia. Potassium citrate at a dose of 1 mEq/kg/24 hours may also be beneficial, particularly in patients with low urinary citrate excretion, a low urine pH, and symptomatic dysuria or crystalluria.

Sodium restriction is important because urinary calcium excretion parallels sodium excretion. Importantly, *dietary calcium restriction is not recommended* (except in children with a massive calcium intake >250% of the recommended dietary allowance by dietary history) because calcium is a critical requirement for growth, and no evidence supports a relationship between decreased calcium intake and decreased urinary calcium levels. This is particularly important given the association of hypercalciuria in some patients with reduced bone mineral density. A number of uncontrolled, small-scale studies support a role for bisphosphonate therapy, which leads to a reduction in urinary calcium excretion and improvement in bone mineral density. Controlled studies are necessary to establish a clear role for such therapy in children with hypercalciuria.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

562.5 Nephrocalcinosis

See Chapter 584.

Chapter 563

Anatomic Abnormalities Associated with Hematuria

563.1 Congenital Anomalies

Prasad Devarajan

Gross or microscopic hematuria may be associated with many different types of malformations of the urinary tract. The sudden onset of gross hematuria after minor trauma to the flank is often associated with ureteropelvic junction obstruction, cystic kidneys, or enlarged kidneys from any cause (see Chapter 577).

563.2 Autosomal Recessive Polycystic Kidney Disease

Prasad Devarajan

Autosomal recessive polycystic kidney disease (ARPKD) (also known as ARPKD-congenital hepatic fibrosis [CHF]) is an autosomal recessive disorder occurring with an incidence of 1:20,000 and a gene carrier rate in the general population of 1/70. The gene for ARPKD ***(PKHD1** [polycystic kidney and hepatic disease 1])* encodes **fibrocystin**, a large protein (>4,000 amino acids) with multiple isoforms.

PATHOLOGY

Both kidneys are markedly enlarged and grossly show innumerable small cysts throughout the cortex and medulla. Microscopic studies demonstrate dilated, ectatic collecting ducts radiating from the medulla to the cortex. The development of progressive interstitial fibrosis and tubular atrophy during the advanced stages of the disease eventually leads to end-stage kidney disease (ESKD). ARPKD causes dual-organ disease, hence, the term *ARPKD/CHF*. Liver involvement is characterized by a basic ductal plate abnormality that leads to bile duct proliferation and ectasia, as well as progressive hepatic fibrosis.

PATHOGENESIS

Fibrocystin may form a multimeric complex with proteins of other primary genetic cystic diseases. Altered intracellular signaling from these complexes, located at epithelial apical cell surfaces, intercellular junctions, and basolateral cell surfaces in association with the focal adhesion complex, is a critical feature of the disease pathophysiology.

Over 300 pathogenic variants in *PKHD1* (without identified specific hot spots) cause disease, and the same pathogenic variant can give variable degrees of disease severity in the same family. This clinical observation is consistent with preclinical data demonstrating many environmental and unknown genetic factors affecting disease expression. The false-negative rate for genetic diagnosis is approximately 10%. Limited available information suggests only a gross genotype–phenotype correlation: pathogenic variants that modify fibrocystin appear to cause less severe disease than those that truncate fibrocystin.

CLINICAL MANIFESTATIONS

The diagnosis of ARPKD is often made antenatally by the demonstration of oligohydramnios and bilateral enlarged kidneys on prenatal ultrasound. The typical infant presents with bilateral flank masses during the neonatal period or in early infancy. ARPKD may be associated with respiratory distress and spontaneous pneumothorax in the neonatal period. Perinatal demise (25–30%) appears to be associated with truncating pathogenic variants. Severe bilateral cases often result in the **oligohydramnios complex (Potter syndrome),** which is marked by low-set ears, micrognathia, flattened nose, limb-positioning defects, intrauterine growth restriction, and pulmonary hypoplasia (see Chapter 574). Respiratory distress may also be secondary to large kidneys that compromise the diaphragm function. Hypertension is usually noted within the first few weeks of life, is often severe, and requires aggressive multidrug therapy for control. Oliguria and acute kidney injury are uncommon, but transient hyponatremia may be seen, which often responds to diuresis. Kidney function is usually impaired but may be initially normal in 20–30% of patients. Approximately 50% of patients with a neonatal-perinatal presentation develop ESKD by age 10 years.

ARPKD is increasingly recognized in infants (and, rarely, in adolescents and young adults) with a mixed renal-hepatic clinical picture. Such children and young adults often present with predominantly hepatic manifestations in combination with variable degrees of kidney disease. **Hepatic fibrosis** manifests as portal hypertension, hepatosplenomegaly, gastroesophageal varices, episodes of ascending cholangitis, prominent cutaneous periumbilical veins, reversal of portal vein flow, and thrombocytopenia. CHF may manifest with cholangiodysplastic changes or a frank **Caroli type** with marked intrahepatic bile duct dilation, affecting the whole liver or just one segment; biliary tract disease increases the risk of ascending cholangitis. Kidney findings in patients with a hepatic presentation may range from asymptomatic abnormal renal ultrasonography to systemic hypertension and chronic kidney disease. In the newborn, clinical evidence of liver disease by radiologic or clinical laboratory assessment is present in approximately 50% of children and believed to be universal by microscopic evaluation. Natural history studies of ARPKD patients presenting as infants and young children have classified this group in terms of the severity of their dual-organ phenotype: 40% have the severe kidney/severe liver phenotype, and 20% each have the severe kidney/mild liver, severe liver/mild kidney, and mild kidney/mild liver phenotype.

DIAGNOSIS

The diagnosis of ARPKD is strongly suggested by bilateral palpable flank masses in an infant with pulmonary hypoplasia, oligohydramnios, hypertension, and the absence of renal cysts by sonography of the parents (Fig. 563.1). Markedly enlarged and uniformly hyperechogenic kidneys with poor corticomedullary differentiation are commonly seen on ultrasonography (Fig. 563.2). The diagnosis is supported by clinical and laboratory signs of hepatic fibrosis, pathologic findings of ductal plate abnormalities seen on liver biopsy, anatomic and pathologic proof of ARPKD in a sibling, or parental consanguinity. The diagnosis can be confirmed by genetic testing. The differential diagnosis includes other causes of bilateral renal enlargement and/or cysts, such as multicystic dysplasia, hydronephrosis, Wilms tumor, and bilateral renal vein thrombosis (Tables 563.1 and 563.2).

Nephronophthisis, an autosomal recessive disorder with kidney fibrosis, tubular atrophy, and cyst formation, is a common cause of ESKD in children and adolescents (see Tables 563.1 and 563.2) (see also Chapter 561). Associated external findings include retinal degeneration (Senior-Løken syndrome), cerebellar ataxia (Joubert syndrome), and hepatic fibrosis (Boichis disease). Symptoms include polyuria (salt wasting, poor concentrating ability), failure to thrive, and anemia. Hypertension and edema are seen later when ESKD develops. Prenatal diagnostic testing using genetic linkage analysis or direct pathogenic variant analysis is available in families with a previously affected child.

Preimplantation genetic diagnosis with in vitro fertilization is available for families with a child affected with ARPKD.

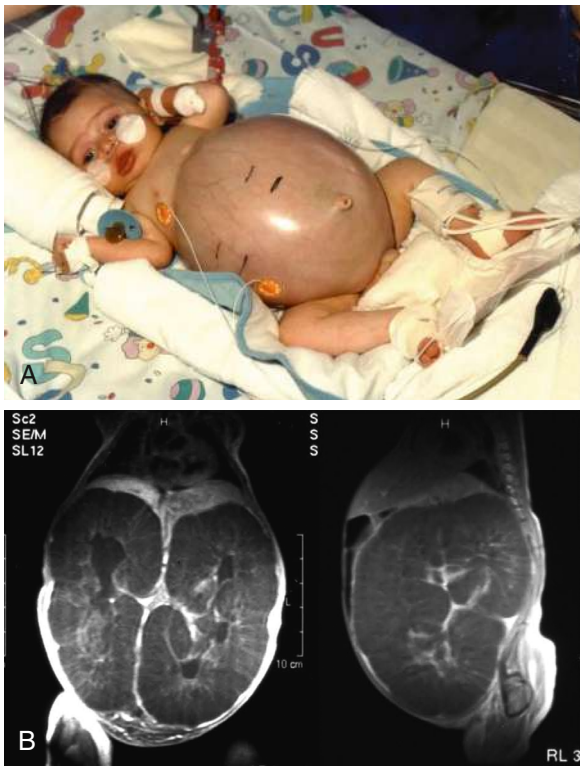

Fig. 563.1 A, Severe nephromegaly in a 3-mo-old infant with autosomal recessive polycystic kidney disease, with x-rays (B). *(From Bakkaloglu SA, Schaefer F. Disease of the kidney and urinary tract in children. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. Brenner & Rector's The Kidney. 10th ed. Philadelphia: Elsevier; 2016: Fig. 74-6, p. 2320.)*

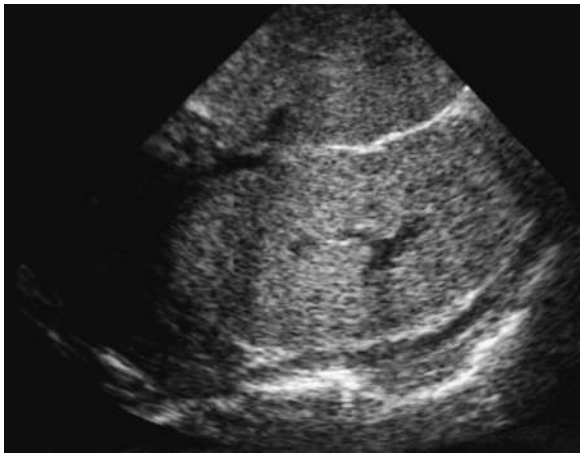

Fig. 563.2 Ultrasound examination of a neonate with autosomal recessive polycystic kidney disease demonstrating renal enlargement (9 cm) and increased diffuse echogenicity with complete loss of corticomedullary differentiation resulting from multiple small cystic interfaces.

TREATMENT

The treatment of ARPKD is supportive. Aggressive ventilatory support is often necessary in the neonatal period secondary to pulmonary hypoplasia, hypoventilation, and the respiratory illnesses of prematurity. Careful management of hypertension (angiotensin-converting enzyme inhibitors, and other antihypertensive medications as needed), fluid and electrolyte abnormalities, osteopenia, and clinical manifestations of kidney insufficiency are essential. Children with severe respiratory failure or feeding intolerance from enlarged kidneys can require unilateral or, more commonly, bilateral nephrectomies, prompting the need for renal replacement therapy. For many children approaching ESKD therapy, significant portal hypertension is present. This in combination with the dramatic improvement in liver transplantation survival has led to consideration of dual kidney and liver transplantation in a carefully selected group of patients. Dual transplantation thus avoids the later development of end-stage liver disease despite successful kidney transplantation.

PROGNOSIS

Mortality rates have improved dramatically, although approximately 30% of patients die in the neonatal period from complications of pulmonary hypoplasia. Neonatal respiratory support and renal replacement therapies have increased the 10-year survival of children surviving beyond the first year of life to >80%. The 15-year survival rate is currently estimated at 70–80%. Consideration of dual kidney and liver transplantation and the development of disease-specific therapies for pediatric clinical trials will further positively impact the natural history of ARPKD. An important resource for families of patients is the ARPKD/CHF Alliance (www.arpkdchf.org).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

563.3 Autosomal Dominant Polycystic Kidney Disease

Prasad Devarajan

Autosomal dominant polycystic kidney disease (ADPKD), also known as adult-onset polycystic kidney disease, is the most common hereditary human kidney disease, with an incidence of 1/400 to 1/1,000. It is a systemic disorder with possible cyst formation in multiple organs (liver, pancreas, spleen, brain) and the possible development of saccular cerebral aneurysms.

PATHOLOGY

Both kidneys are enlarged and show large cortical and medullary cysts originating from all regions of the nephron.

PATHOGENESIS

Approximately 85% of patients with ADPKD have pathogenic variants that map to the *PKD1* gene on the short arm of chromosome 16, which encodes polycystin, a transmembrane glycoprotein. Another 10–15% of ADPKD pathogenic variants map to the *PKD2* gene on the long arm of chromosome 4, which encodes polycystin 2, a proposed nonselective cation channel. The majority of pathogenic variants appear to be unique to a given family. At present, a pathogenic variant can be found in 85% of patients with well-characterized disease.

Approximately 8–10% of patients will have de novo, disease-causing pathogenic variants. Pathogenic variants of *PKD1* are associated with more severe renal disease than pathogenic variants of *PKD2*. The pathophysiology of the disease appears to be related to the disruption of normal multimeric cystoprotein complexes, with consequent abnormal intracellular signaling resulting in abnormal proliferation, tubular secretion, and cyst formation. Abnormal growth factor expression, coupled with low intracellular calcium and elevated cyclic adenosine monophosphate, appear to be important features leading to formation of cysts and progressive enlargement. Pathogenic variants in *GANAB* have been reported in *PKD1*- and *PKD2*-negative patients.

CLINICAL PRESENTATION

The severity of renal disease and the clinical manifestations of ADPKD are highly variable. Symptomatic ADPKD most commonly occurs in the fourth or fifth decade of life. However, symptoms, including gross

Table 563.1 Differential Diagnosis in ARPKD and ADPKD Genotypes

	ASSOCIATED DISEASE	RENAL PHENOTYPE	EXTRARENAL PHENOTYPE
CLASSIC ARPKD			
	PKHD1, possibly *DZIP1L*	Bilateral nephromegaly, heterogenous parenchymal echogenicity with salt and pepper pattern Prenatal onset: bilateral nephromegaly, oligohydramnios, Potter-like syndrome	Progressive hepatic fibrosis, Caroli syndrome, portal hypertension
CLASSIC ADPKD			
PKD1	ADPKD-*PKD1* with truncating variant	Innumerable bilateral kidney cysts causing progressive kidney enlargement and reduction in eGFR; median age at ESKD about 55 years	Polycystic liver disease, mild to severe, SAH-CNS aneurysms*
PKD1	ADPKD-*PKD1* with nontruncating variant	Innumerable bilateral kidney cysts causing progressive kidney enlargement and reduction in eGFR; median age at ESKD about 67 years	Polycystic liver disease, mild to severe, SAH-CNS aneurysms*
PKD2	ADPKD-*PKD2*	Innumerable bilateral kidney cysts causing progressive kidney enlargement and reduction in eGFR; median age at ESKD about 79 years	Polycystic liver disease, mild to severe, SAH-CNS aneurysms*
ADPKD-LIKE PHENOTYPE			
GANAB	ADPKD-*GANAB*	Bilateral renal cysts, preserved kidney function	Polycystic liver disease, mild to severe
DNAJB11	ADPKD-*DNAJB11*	Normal or small-sized kidneys with multiple small renal cysts; possible evolution to ESKD after 60 years	Polycystic liver disease, absent to moderate
ADTKD-ASSOCIATED GENES			
HNF1B	ADTKD-*HNF1B*	Bilateral renal cysts in about 45% of affected individuals, occasionally mimics ADPKD imaging presentation; evolution to ESKD is highly variable, from childhood-onset ESKD to preserved kidney function throughout life	Diabetes, gout, hyperuricemia, hypomagnesaemia, elevated liver enzymes, bicornate uterus, solitary kidney
MUC1	ADTKD-*MUC1*	Normal or small-sized kidneys, few small renal cysts in half of patients; evolution to ESKD highly variable, age 20-70 years	Gout
SEC61A1	ADTKD-*SEC61A1*	Normal or small-sized kidneys, bilateral small renal cysts in about 50% of individuals	Congenital anemia, intrauterine growth retardation, neutropenia
UMOD	ADTKD-*UMOD*	Normal or small-sized kidneys, few small renal cysts in a third of patients, unilateral or bilateral; evolution to ESKD highly variable, age 20-70 years	Gout
ADPLD-ASSOCIATED GENES			
PRKCSH	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to severe
SEC63	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to severe
ALG8	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to moderate
SEC61B	ADPLD	No renal cysts observed to date in the two families reported with a pathogenic variant in this gene	Polycystic liver disease, mild to moderate
LRP5	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to moderate
RECESSIVE INHERITANCE			
PKHD1	ARPKD	Antenatally enlarged hyperechogenic kidneys; multiple bilateral millimeter-sized cysts; ESKD in the first decade of life in about 50% of individuals but milder renal presentation with diagnosis in adulthood possible	Congenital hepatic fibrosis, Caroli syndrome, small liver cysts in heterozygous patients
DZIP1L	ARPKD	Antenatal enlarged hyperechogenic kidneys; multiple bilateral millimeter-sized cysts; progression to ESKD variable (second and third decade of life)	No obvious extrarenal manifestations reported in the seven patients identified to date

Continued

Table 563.1 Differential Diagnosis in ARPKD and ADPKD Genotypes—cont'd

	ASSOCIATED DISEASE	RENAL PHENOTYPE	EXTRARENAL PHENOTYPE
PMM2	Hyperinsulinemic hypoglycemia with PKD	Antenatal enlarged hyperechogenic kidneys, enlarged kidneys with multiple cysts; progression to ESKD variable, from infancy to early adulthood	Hyperinsulinemic hypoglycemia; small liver cysts in some patients
SYNDROMIC FORMS OF PKD			
TSC1 or *TSC2*	Tuberous sclerosis	Multiple and bilateral angiomyolipomas and renal cysts; kidney function usually preserved; possible evolution to ESKD, either by destruction of the renal parenchyma by multiple angiomyolipomas or following nephrectomies for hemorrhagic angiomyolipomas; if there is contiguous gene deletion of *TSC2* and *PKD1*, severe PKD with evolution to ESKD occurs before age 30 years	CNS (cortical tubers, astrocytomas, epilepsy, and intellectual disabilities); skin lesions (facial angiofibromas and hypopigmented spots); pulmonary lymphangioleiomyomatosis; cardiac rhabdomyoma and retinal hamartoma; polycystic liver disease if contiguous deletion of both *PKD1* and *TSC2*
VHL	Von Hippel-Lindau disease	Bilateral renal cysts, renal cell carcinoma	Hemangioblastomas of the retina, spine, or brain; pheochromocytoma; neuroendocrine tumor of the pancreas
COL4A1	HANAC syndrome or *COL4A1*-related disease	Bilateral renal cysts occasionally reported; patients can develop renal insufficiency after about age 50-60 years	Microscopic hematuria, aneurysms, muscle cramps, elevated creatine phosphokinase, tortuosity of the retinal arteries
OFD1	Oro-facial-digital syndrome type 1	X-linked, embryonically lethal in males, PKD in females	Cleft palate, facial dysmorphy; syndactyly, clinodactyly, or polydactyly; intellectual disabilities; polycystic liver disease

*Intracranial aneurysms in 9–12% of patients with ADPKD.
ADPKD, Autosomal dominant PKD; ADPLD, autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CNS, central nervous system; eGFR, estimate glomerular filtration rate; ESKD, end-stage kidney disease; HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; PKD, polycystic kidney disease; SAH, subarachnoid hemorrhage.
From Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393:919–932. Table 1.

Table 563.2 Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies

DISEASE	GENE(S)	RENAL DISEASE	HEPATIC DISEASE	SYSTEMIC FEATURES
ARPKD	*PKHD1*	Collecting duct dilation	CHF; Caroli disease	No
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	Yes: adults
NPHP	*NPHP1-NPHP16*	Cysts at the corticomedullary junction	CHF	+/–
Joubert syndrome and related disorders	*JBTS1-JBTS20*	Cystic dysplasia; NPHP	CHF; Caroli disease	Yes
Bardet-Biedl syndrome	*BBS1-BBS18*	Cystic dysplasia; NPHP	CHF	Yes
Meckel-Gruber syndrome	*MKS1-MKS10*	Cystic dysplasia	CHF	Yes
Oral-facial-digital syndrome, type I	*OFD1*	Glomerular cysts	CHF (rare)	Yes
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with PKD1 pathogenic variants)	+/–
Jeune syndrome (asphyxiating thoracic dystrophy)	*IFT80 (ATD2) DYNC2H1 (ADT3) ADT1, ADT4, ADT5*	Cystic dysplasia	CHF; Caroli disease	Yes
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	Yes
Zellweger syndrome	*PEX1-3;5-6;10-11;13;14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Yes

ADPKD, Autosomal dominant PKD; ARPKD, autosomal recessive polycystic kidney disease; CHF, congenital hepatic fibrosis; NPHP, nephronophthisis.
Modified from Guay-Woodford LM, Bissler JJ, Braun MC, et al. Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. *J Pediatr*. 2014;165:611–617.

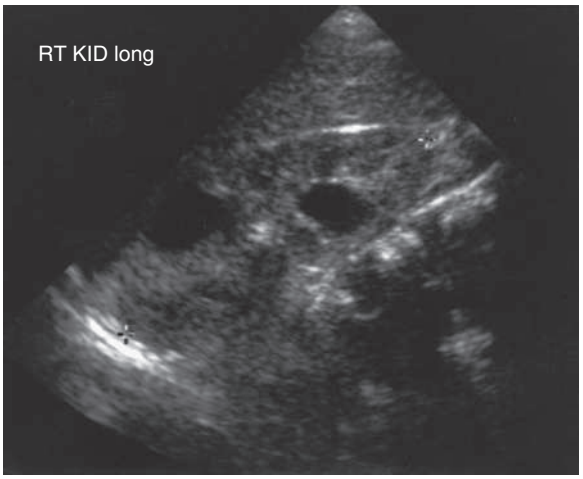

Fig. 563.3 Ultrasound examination of an 18-mo-old male with autosomal dominant polycystic kidney disease demonstrating renal enlargement (10 cm) and two large cysts.

or microscopic hematuria, bilateral flank pain, abdominal masses, hypertension, and urinary tract infection, may be seen in neonates, children, and adolescents. With the increased utilization of abdominal sonography in the pediatric population, as well as ADPKD families requesting possible screening in their asymptomatic, at-risk offspring, most children with ADPKD are diagnosed by abnormal renal sonography in the absence of symptoms. Renal ultrasonography usually demonstrates multiple bilateral macrocysts in enlarged kidneys (Fig. 563.3), although normal kidney size and unilateral disease may be seen in the early phase of the disease in children.

ADPKD is a multiorgan disorder affecting many tissue types. Cysts may be asymptomatic but present within the liver, pancreas, spleen, and ovaries and, when present, help confirm the diagnosis in childhood. **Intracranial aneurysms,** which appear to segregate within certain families, have an overall prevalence of 15% and are an important cause of mortality in adults but only occasionally occur in children. Mitral valve prolapse is seen in approximately 12% of children; aortic and coronary artery aneurysms and aortic valve insufficiency are noted in affected adults. Hernias, bronchiectasis, and intestinal diverticula can also occur in these children.

DIAGNOSIS

ADPKD is confirmed by the presence of enlarged kidneys with bilateral macrocysts in a patient with an affected first-degree relative. De novo pathogenic variants occur in 8–10% of patients with newly diagnosed disease. The diagnosis might be made in children before their affected parent, making parental renal sonography an important diagnostic test to be performed in families with no apparent family history. Among patients with genetically defined ADPKD, screening renal ultrasonography results may be normal in ≤20% by 20 years of age and <5% by 30 years of age.

Prenatal diagnosis is suggested from the presence of enlarged kidneys with or without cysts on ultrasonography in families with known ADPKD. Prenatal DNA testing is available in families with affected members whose disease is caused by identified pathogenic variants in the *PKD1* or *PKD2* genes.

The differential diagnosis includes renal cysts associated with glomerulocystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease, which may be inherited in an autosomal dominant pattern (see Table 563.1). The neonatal manifestations of ADPKD and ARPKD may rarely be indistinguishable.

TREATMENT AND PROGNOSIS

Treatment of ADPKD is primarily supportive. Control of blood pressure is critical because the rate of disease progression in ADPKD correlates with the presence of hypertension. Angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists are agents of choice. Obesity, dietary salt and protein excess, caffeine ingestion, smoking, multiple pregnancies, and male gender appear to accelerate the disease progression. Older patients with a family history of intracranial aneurysm rupture should be screened for cerebral aneurysms. Although the approach remains controversial, most nephrologists now recommend initial screening for cerebral aneurysms with an MR angiogram around 18 years of age in asymptomatic patients with a family history of ADPKD and associated aneurysms.

Although neonatal ADPKD may be fatal, long-term survival of the patient and the kidneys is possible for children surviving the neonatal period. ADPKD that occurs initially in older children has a favorable prognosis, with normal kidney function during childhood seen in >80% of children. Pain may be a manifestation of infection, hemorrhage, cyst rupture, stones, or tumors and should be managed appropriately with pain medications and specifically based on its etiology.

Although disease-specific therapy is not yet available, clinical trials are in progress based on promising preclinical laboratory investigations. These potential therapies include renin-angiotensin blockade, vasopressin V_2 receptor antagonism (tolvaptan), statins (to reduce pain), and somatostatin analogues. Tolvaptan has been effective in adults in slowing the progression of renal impairment. A valuable resource for patients and their families is the Polycystic Kidney Disease Foundation (www.pkdcure.org).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

563.4 Trauma

Prasad Devarajan

Infants and children are more susceptible to kidney injury following blunt or penetrating injury to the back or abdomen because of their decreased muscle mass "protecting" the kidney. Gross or microscopic hematuria, flank pain, and abdominal rigidity can occur; associated injuries may be present (see Chapter 80). In the absence of hemodynamic instability, most kidney trauma can be managed nonoperatively. Urethral trauma can result from crush injury, often associated with a fractured pelvis or from direct injury. Such injury is suspected in the appropriate clinical setting when gross blood appears at the external urethral meatus. Rhabdomyolysis and consequent acute kidney injury is another complication of crush injury that can be ameliorated by vigorous fluid resuscitation. There may be a relationship between microscopic hematuria and recreational accidents in individuals >16 years of age, none of whom exhibited hypotension or required surgical intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

563.5 Renal Tumors

See Chapters 547 and 548.

Chapter 564

Lower Urinary Tract Causes of Hematuria

564.1 Infectious Causes of Cystitis and Urethritis

Prasad Devarajan

Gross or microscopic hematuria may be associated with bacterial, mycobacterial, or viral infections of the bladder (see Chapter 575).

564.2 Hemorrhagic Cystitis

Prasad Devarajan

Hemorrhagic cystitis is defined as the presence of sustained hematuria and lower urinary tract symptoms (e.g., dysuria, frequency, urgency) in the absence of other bleeding conditions such as vaginal bleeding, a generalized bleeding condition, or a bacterial urinary tract infection. Depending on the severity, patients can present with microscopic or gross hematuria, often with clots. In severe forms, bleeding can lead to a significant decrease in blood hemoglobin levels and symptoms of lower urinary tract obstruction.

Hemorrhagic cystitis can occur in response to chemical toxins (cyclophosphamide, penicillins, busulfan, thiotepa, dyes, insecticides), viruses (adenovirus types 11 and 21 [see Chapter 309] and influenza A [see Chapter 305]), radiation, and amyloidosis. The polyoma **BK virus** (see Chapter 321), present latently in immunocompetent hosts, is associated with the development of drug-induced cystitis in immunosuppressed patients. The pediatric bone marrow transplantation population is particularly susceptible to hemorrhagic cystitis.

For chemical irritation related to the use of cyclophosphamide, hydration, bladder washes, and the use of mesna disulfide, which inactivates urinary cyclophosphamide metabolites, helps to protect the bladder. Administration of oral cyclophosphamide in the morning followed by aggressive oral hydration throughout the remainder of the day is very effective in minimizing the risk of hemorrhagic cystitis. Treatment of hemorrhagic cystitis consists of a combination of intensive intravenous hydration, forced diuresis, analgesia, and spasmolytic drugs. Consultation with a urologist is recommended for more invasive measures if the cystitis does not respond to conservative measures. Gross hematuria associated with viral hemorrhagic cystitis usually resolves within 1 week.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

564.3 Vigorous Exercise

Prasad Devarajan

Gross or microscopic hematuria can follow vigorous exercise. **Exercise-induced hematuria** is less common in females and can be associated with dysuria. Approximately 30–60% of runners completing marathons have dipstick-positive urine for blood. In limited follow-up, none appeared to have any significant kidney or urinary tract abnormalities. The color of the urine following vigorous exercise can vary from red to black. Blood clots may be rarely present in the urine. Findings on urine culture, intravenous pyelography, voiding cystourethrography, and cystoscopy are normal in most patients. This seems to be a benign condition, and the hematuria generally resolves within 48 hours after cessation of exercise. The absence of red blood cell casts or evidence of renal disease and the presence of dysuria and blood clots in some patients suggest that the source of bleeding lies in the lower urinary tract. **Rhabdomyolysis** with **myoglobinuria** or hemoglobinuria must be considered in the differential diagnosis when the condition is associated with symptoms in the appropriate clinical context. Hydronephrosis or other anatomic abnormalities must be considered in any child who presents with hematuria (particularly gross hematuria) after mild exercise or following mild trauma. Appropriate imaging studies are indicated in this setting.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

Conditions Particularly Associated With Proteinuria

Chapter 565

Clinical Evaluation of the Child with Proteinuria

Francisco X. Flores

NORMAL PHYSIOLOGY

The charge and size selective properties of the glomerular capillary wall prevent significant amounts of albumin, globulin, and other large plasma proteins from entering the urinary space (see Chapter 557). Smaller proteins (low molecular weight proteins) do cross the capillary wall but are reabsorbed by the proximal tubule. A very small amount of protein that normally appears in the urine is the result of normal tubular secretion. The normally excreted protein mostly consists of **Tamm-Horsfall protein (uromodulin)**, a protective glycoprotein secreted by the tubules that inactivates cytokines.

PATHOPHYSIOLOGY OF PROTEINURIA

Abnormal amounts of protein may appear in the urine from three possible mechanisms: *glomerular proteinuria,* which occurs as a result of disruption of the glomerular capillary wall; *tubular proteinuria,* a tubular injury or dysfunction that leads to ineffective reabsorption of mostly low molecular weight proteins; and *increased production of plasma proteins* (in multiple myeloma, rhabdomyolysis, or hemolysis), which may cause the production or release of very large amounts of protein that are filtered at the glomerulus and overwhelm the absorptive capacity of the proximal tubule.

MEASUREMENT OF URINE PROTEIN

Urine protein can be measured in random collected samples or in timed (e.g., 24-hour or overnight) samples. Tests to accurately quantify the urine protein concentration rely on precipitation with sulfosalicylic acid and measurement of turbidity (Table 565.1).

Table 565.1 Quantification of Proteinuria in Children

METHOD	INDICATIONS	NORMAL RANGE	COMMENTS
Dipstick testing	Routine screening for proteinuria performed in the office	Negative or trace in a concentrated urine specimen (specific gravity: ≥1.020) Test interpretation: 1+ ~30 mg/dL 2+ ~100 mg/dL 3+ ~300 mg/dL	False-positive test can occur if urine is very alkaline (pH >8.0) or very concentrated (specific gravity: >1.025), or when there is pus, vaginal secretions, or semen present
24-hr urine for protein and creatinine*excretion	Quantitation of proteinuria (as well as creatinine clearances)	<150 mg/m^2/24 hr	More accurate than spot urine analysis; inconvenient for patient; the creatinine content should be measured to determine whether the specimen is truly a 24-hr collection. The amount of creatinine in a 24-hr specimen can be estimated as follows: females, 15-20 mg/kg; males, 20-25 mg/kg
Spot urine for protein/creatinine ratio, preferably on first morning urine specimen	Semiquantitative assessment of proteinuria	<0.2 mg protein/mg creatinine in children older than 2 yr old <0.5 mg protein/mg creatinine in those 6-24 mo old	Simplest method to quantitate proteinuria; less accurate than measuring 24-hr proteinuria
Microalbuminuria	Assess risk of progressive glomerulopathy in patients with diabetes mellitus	<30 mg urine albumin per gram of creatinine on first morning urine	Therapy should be intensified in diabetics with microalbuminuria

*Note that in a 24-hr urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24-hr collection. The amount of creatinine in a 24-hr specimen can be estimated as follows: females, 15-20 mg/kg and males, 20-25 mg/kg.

Adapted from Hogg RJ, Portman RJ, Milliner D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE). *Pediatrics.* 2000;105(6):1242–1249.

Urine Dipstick Measurement of Protein

The total protein concentration in urine can be estimated with chemically impregnated plastic strips that contain a pH-sensitive colorimetric indicator that changes color when negatively charged proteins, such as albumin, bind to it. Dipsticks primarily detect albuminuria and are less sensitive for other forms of proteins (low molecular weight proteins, Bence-Jones protein, gamma globulins). Visual changes in the color of the dipstick are a semiquantitative measure of urinary protein concentration. The dipstick is reported as negative, trace (10-29 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1,000 mg/dL), and 4+ (>1,000 mg/dL). False-positive results can occur with a very high urine pH (>7.0), a highly concentrated urine specimen, contamination of the urine with blood, and the presence of pyuria or prolonged dipstick immersion. False-negative test results can occur in patients with a low urine pH (<4.5), dilute urine or a large volume of urine output, or in disease states in which the predominant urinary protein is not albumin.

Positive urine dipstick test for protein is considered to be present if there is more than a trace (10-29 mg/dL) in a urine sample in which the specific gravity is <1.010. If the specific gravity is >1.015, the dipstick must read ≥1+ (>30 mg/dL) to be considered clinically significant.

Because the dipstick reaction offers only a qualitative measurement of urinary protein excretion, children with persistent proteinuria should have proteinuria quantitated more precisely. **Timed (24-hour) urine collections** offer more precise information regarding urine protein excretion than a randomly performed dipstick test. Urinary protein excretion in the normal child is <100 mg/m^2/day or a total of 150 mg/day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2, because of reduced reabsorption of filtered proteins. A reasonable upper limit of normal protein excretion in healthy children is 150 mg/24 hr. More specifically, normal protein excretion in children is defined as ≤4 mg/m^2/hr, abnormal proteinuria is defined as excretion of 4-40 mg/m^2/hr, and nephrotic-range proteinuria is defined as > 40 mg/m^2/hr.

Timed urine collections are cumbersome to obtain, and the sensitivity and specificity of the test can be influenced by fluid intake, the volume of urine output, and the importance of including a complete collection without missed voids.

Urine Protein-to-Creatinine Ratio Measurement

Urine protein-to-creatinine ratio measurement of an untimed (spot) urine specimen has largely replaced timed urine collection. In children, urine protein-to-creatinine ratios have been shown to be significantly correlated with measurements of 24-hour urine protein and are useful to screen for proteinuria and to longitudinally monitor urine protein levels.

This ratio is calculated by dividing the urine protein concentration (mg/dL) by the urine creatinine concentration (mg/dL) to provide a simple measure. It should be ideally performed on a first morning voided urine specimen to eliminate the possibility of orthostatic (postural) proteinuria (see Chapter 566.2). A ratio of <0.5 in children <2 years of age and <0.2 in children >2 years of age suggests normal urinary protein excretion. A ratio >2 suggests nephrotic-range proteinuria.

CLINICAL CONSIDERATIONS

The finding of proteinuria in children and adolescents in a single, non–first morning urine specimen is common, varying between 5% and 15%. The prevalence of persistent proteinuria on repeated testing is much less common. The challenge is to differentiate the child with proteinuria related to renal disease from the otherwise healthy child with transient or other benign forms of proteinuria. When proteinuria is detected, it is important to determine whether it is transient, orthostatic, or fixed in nature.

Microalbuminuria is defined as the presence of albumin in the urine above the normal level but below the detectable range of conventional urine dipstick methods. In adults, persistent microalbuminuria (defined as a urinary albumin excretion of 30-300 mg/g creatinine on at least two to three samples) is accepted as evidence of diabetic nephropathy and also a predictor of cardiovascular and renal disease. The mean level of urinary albumin excretion falls between 8 and 10 mg/g of creatinine in children >6 years of age. Similar to adults, microalbuminuria in children has been found to be associated with obesity and to predict, with reasonable specificity, the development of diabetic nephropathy in type 1 diabetes mellitus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 566

Conditions Associated with Proteinuria

566.1 Transient Proteinuria

Francisco X. Flores

The majority of children found to have positive tests for protein on urinary dipsticks will have negative evaluations on repeated dipsticks and normal urinary protein if formally quantitated. Approximately 10% of children who undergo random urinalysis have proteinuria by a single dipstick measurement. Across the school-age spectrum, this finding occurs more commonly in adolescents than in younger children. In most cases, serial testing of the patient's urine demonstrates resolution of the abnormality. This phenomenon defines **transient proteinuria,** and its cause remains elusive. Defined contributing factors include a temperature >38.3°C (101°F), exercise, dehydration, cold exposure, heart failure, recent use of epinephrine, seizures, or stress. Transient proteinuria usually does not exceed 1-2+ on the dipstick. No evaluation or therapy is needed for children with this benign condition, and it resolves spontaneously or as the cause resolves. Persistence of proteinuria, even if low grade, is not consistent with the diagnosis and suggests the need for additional evaluation (Fig. 566.1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

566.2 Orthostatic (Postural) Proteinuria

Francisco X. Flores

Orthostatic proteinuria is the most common cause of *persistent* proteinuria in school-age children and adolescents, occurring in up to 60% of children with persistent proteinuria. Children with this condition are usually asymptomatic, and the condition is discovered by routine urinalysis. Patients with orthostatic proteinuria excrete normal or minimally increased amounts of protein in the supine position. In the upright position, urinary protein excretion may be increased 10-fold, up to 1,000 mg/24 hr (1 g/24 hr). *Hematuria, hypertension, hypoalbuminemia, edema, and renal dysfunction are absent.*

In a child with persistent asymptomatic proteinuria, the initial evaluation should include an assessment for orthostatic proteinuria. It begins with the collection of a first morning urine sample, with subsequent testing of any urinary abnormalities by a complete urinalysis and determination of a spot urine protein-to-creatinine ratio (see Fig. 566.1). The correct collection of the first morning urine sample is critical. The child must fully empty the bladder before going to bed and then collect the first voided urine sample immediately upon arising in the morning. The absence of proteinuria (dipstick negative or trace for protein; and a normal ratio of urinary protein [uPr; mg/dL] to urinary creatinine [uCr; mg/dL] = [uPr/uCr] <0.2) on the first morning urine sample for 3 consecutive days confirms the diagnosis of orthostatic proteinuria. No further evaluation is necessary, and the patient and family should be reassured of the benign nature of this condition. However, if there are other abnormalities of the urinalysis (e.g., hematuria), or if the urine uPr:uCr ratio is >0.2, the patient should be referred to a pediatric nephrologist for a complete evaluation.

The cause of orthostatic proteinuria is unknown, although altered renal hemodynamics and partial left renal vein obstruction in the upright, lordotic position have been proposed as possible causes. An increased body mass index is recognized as a strong correlate of orthostatic proteinuria. Long-term follow-up studies in young adults suggest that orthostatic proteinuria is a benign process, but similar data are not available for children. Therefore long-term follow-up of children is prudent. Patients should be monitored for the development of nonorthostatic proteinuria, particularly in the presence of hematuria, hypertension, or edema. Such findings may herald underlying kidney disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

566.3 Fixed Proteinuria

Francisco X. Flores

Children found to have fixed proteinuria on a first morning urine sample on three separate occasions should be further investigated. Fixed proteinuria is defined as a first morning urine sample that is ≥1+ on dipstick testing with a urine specific gravity >1.015 or with a urine protein-to-creatinine ratio of ≥0.2. Fixed proteinuria indicates a potential kidney disease caused by either glomerular or tubular disorders.

GLOMERULAR PROTEINURIA

The glomerular capillary wall consists of three layers: the fenestrated capillary endothelium, the glomerular basement membrane, and the podocytes (with foot processes and intercalated slit diaphragms) (Fig. 566.2). Glomerular proteinuria results from alterations in the permeability of any of the layers of the glomerular capillary wall to normally filtered proteins and occurs in a variety of renal diseases (Table 566.1). Glomerular proteinuria can range widely from <1 g to >30 g of protein in a 24-hour period. The podocyte is the predominant cell of injury in most glomerular diseases characterized by heavy proteinuria.

Glomerular proteinuria should be suspected in any patient with a first morning urine protein-to-creatinine ratio >1.0, or significant proteinuria of any degree, accompanied by hypertension, hematuria with active urine sediment, edema, or renal dysfunction. Disorders characterized primarily by proteinuria include idiopathic (minimal change disease) nephrotic syndrome, secondary causes of nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, diabetic nephropathy, and obesity-related glomerulopathy. Other renal disorders that can include proteinuria as a prominent feature include acute postinfectious glomerulonephritis, immunoglobulin A nephropathy, systemic lupus erythematosus nephritis, IgA vasculitis (formerly Henoch-Schönlein purpura) nephritis, and Alport syndrome.

The initial evaluation of a child with fixed proteinuria should include the measurement of serum creatinine and an electrolyte panel, first morning urine protein-to-creatinine ratio, serum albumin level, complement levels, and antinuclear antibodies (ANA). The child should be referred to a pediatric nephrologist for further evaluation and management. Renal biopsy is often necessary to establish a diagnosis and guide therapy.

In asymptomatic patients with low-grade proteinuria (urine protein-to-creatinine ratio between 0.2 and 1.0) in whom all other findings are normal, renal biopsy might not be indicated, because the underlying process may be transient or resolving or because specific pathologic

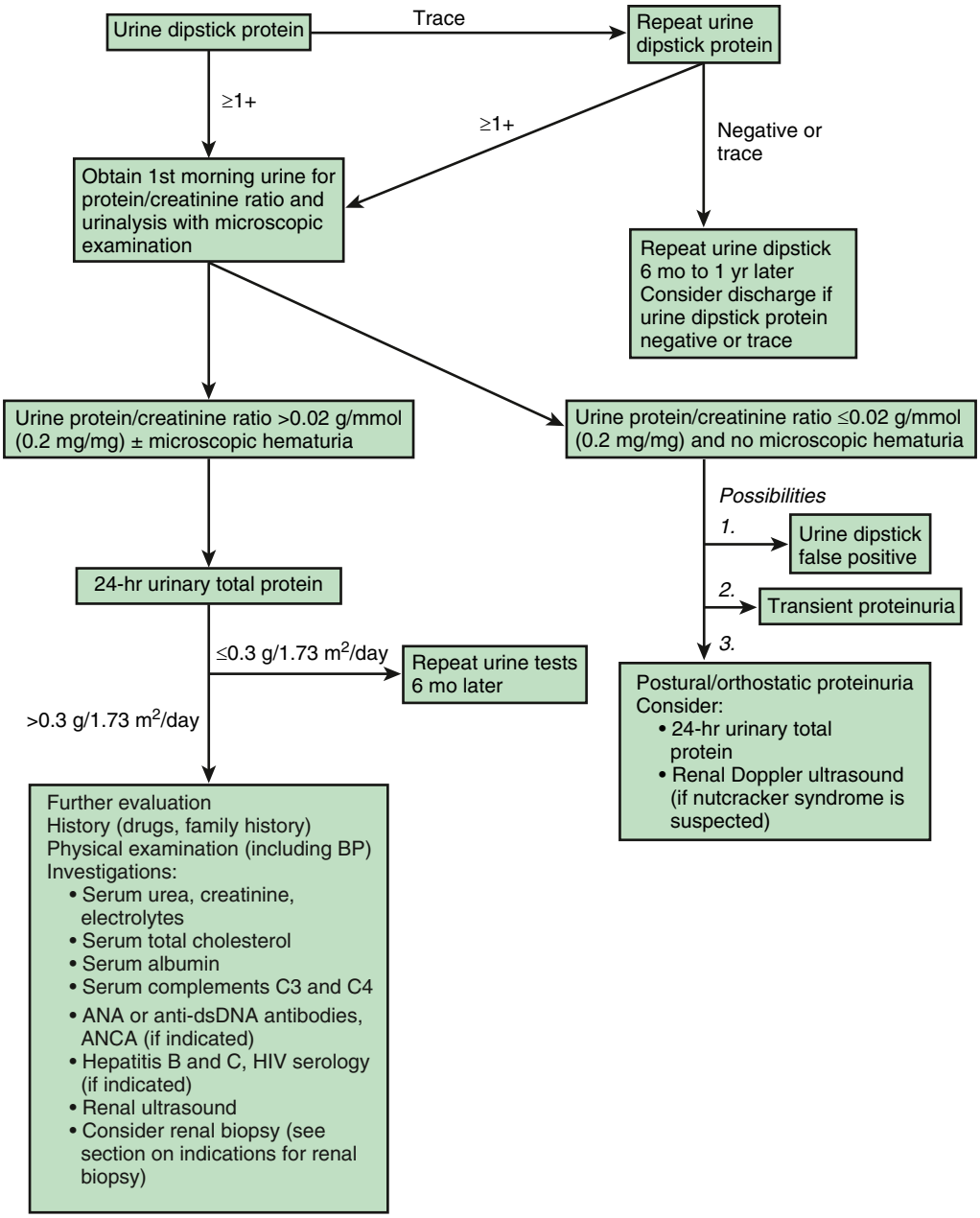

Fig 566.1 Algorithm for investigating proteinuria. ANA, Antinuclear antibody; ANCA, antinuclear cytoplasmic antibody; anti-dsDNA, anti–double-stranded DNA; BP, blood pressure. *(From Yap HK, Lau PYW. Hematuria and proteinuria. In: Geary DF, Scharfer F, eds. Comprehensive Pediatric Nephrology. Philadelphia: Elsevier; 2008: p. 190.)*

features of a chronic kidney disease might not yet be apparent. Such patients should have periodic reevaluation (ideally every 4-6 months unless the patient is or becomes symptomatic). The evaluation should consist of a physical examination with accurate blood pressure measurement, urinalysis, measurement of serum creatinine, and a repeat first morning urine protein-to-creatinine ratio. Indications for renal biopsy include increasing proteinuria (urine protein-to-creatinine ratio >1.0) or the development of hematuria with active urine sediment, hypertension, or reduced renal function.

TUBULAR PROTEINURIA

A variety of renal disorders that primarily involve the tubulointerstitial compartment of the kidney can cause low-grade fixed proteinuria (urine protein-to-creatinine ratio 0.2:1.0). In the healthy state, large amounts of proteins of lower molecular weight than albumin are filtered by the glomerulus and reabsorbed in the proximal tubule. Injury to the proximal tubules can result in diminished reabsorptive capacity and the loss of these low molecular weight proteins in the urine.

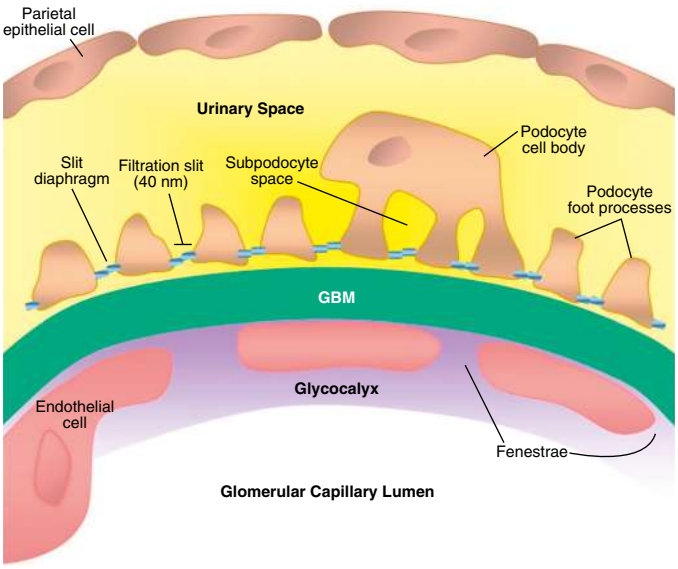

Fig. 566.2 Glomerular capillary wall. The three layers of the capillary wall (glomerular endothelial cell, glomerular basement membrane [GBM], and podocyte) act as the glomerular filtration barrier (GFB), preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies within the urinary space, and the cell is attached to the GBM through foot processes. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the GFB leads the passage of protein across the capillary wall, leading to proteinuria. *(From Jefferson JA, Nelson PJ, Najafian B, et al. Podocyte disorders: core curriculum 2011. Am J Kidney Dis. 2011;58:666–677. Fig. 1.)*

Tubular proteinuria (see Table 566.1) may be seen in acquired and inherited disorders and may be associated with other defects of proximal tubular function, such as Fanconi syndrome (glycosuria, phosphaturia, bicarbonate wasting, and aminoaciduria). Tubular proteinuria is a consistent finding among patients with the X-linked tubular syndrome, Dent disease, caused by pathogenic variants of the renal chloride channel.

Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by protein electrophoresis of the urine. In tubular proteinuria, little or no albumin is detected, whereas in glomerular proteinuria, the major protein is albumin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 566.1 Causes of Proteinuria

TRANSIENT PROTEINURIA
Fever
Exercise
Dehydration
Cold exposure
Congestive heart failure
Seizure
Stress
Recent use of epinephrine
ORTHOSTATIC (POSTURAL) PROTEINURIA
GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA
Idiopathic (minimal change) nephrotic syndrome
Focal segmental glomerulosclerosis
Secondary causes of nephrotic syndrome (see Chapter 567)
Mesangial proliferative glomerulonephritis
Membranous nephropathy
Membranoproliferative glomerulonephritis
Amyloidosis
Diabetic nephropathy
Sickle cell nephropathy
GLOMERULAR DISEASES WITH PROTEINURIA AS A PROMINENT FEATURE
Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV)
Immunoglobulin A nephropathy
IgA vasculitis nephritis
Lupus nephritis
Serum sickness
Alport syndrome
Vasculitic disorders
Reflux nephropathy
TUBULAR DISEASES
Cystinosis
Fanconi syndrome
Wilson disease
Lowe syndrome
Dent disease (X-linked recessive nephrolithiasis)
Galactosemia
Tubulointerstitial nephritis
Acute tubular necrosis
Renal dysplasia
Polycystic kidney disease
Reflux nephropathy
Renal transplant rejection
Drugs (aminoglycosides, cisplatin, penicillamine, lithium, nonsteroidal antiinflammatory drugs, cyclosporine)
Heavy metals (lead, gold, mercury)

Chapter 567

Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic range) proteinuria. Nephrotic-range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein:creatinine ratio >2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).

Nephrotic syndrome affects 1-3 per 100,000 children <16 years of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Fortunately, 80% of children with nephrotic syndrome respond to corticosteroid therapy. Although glucocorticoid therapy is standard therapy for nephrotic syndrome, neither the target cell nor the mechanism of action of steroids has been determined. Early referral to a pediatric nephrologist is recommended for initial management

of nephrotic syndrome. However, continued care of these children is always a collaborative effort between the nephrologist and the primary care physician.

ETIOLOGY

Most children with nephrotic syndrome have a form of **primary** or idiopathic nephrotic syndrome (Table 567.1). Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (most common), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (Table 567.2). These etiologies have different age distributions (Fig. 567.1). Nephrotic syndrome may also be **secondary** to systemic diseases such as systemic lupus erythematosus, IgA vasculitis (formerly Henoch-Schönlein purpura), malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria) (see Table 567.1). A number of **hereditary** proteinuria syndromes are caused by pathogenic variants in genes that encode critical protein components of the glomerular filtration apparatus (Table 567.3).

PATHOGENESIS

Role of the Podocyte

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and the progression of glomerulosclerosis (Fig. 567.2). The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop. Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters; they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α-actinin 4. Podocyte injury or pathogenic variants of genes producing podocyte proteins may cause nephrotic-range proteinuria (see Table 567.3). Genetic screening of 1,655 patients with steroid-resistant nephrotic syndrome and congenital nephrotic syndrome in the European PodoNet Registry Cohort has shown that pathogenic variants in *NPHS1, WT1,* and *NPHS2* were the most common. The proportion of patients with pathogenic variants of podocyte genes decreased by age; it was 66% in patients with congenital nephrotic syndrome and 15–16% in school-age patients and adolescents.

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein leakiness across the glomerular capillary wall into the urinary space.

Role of the Immune System

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine and provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

Considering the recurrence rate of 30% after kidney transplantation, a permeability factor was implicated in pathophysiology of FSGS. Rat glomeruli exposed to patient sera with FSGS has demonstrated increased permeability to albumin. A subset of adult and pediatric patients was found to have circulating nephrin autoantibodies, suggesting the role of circulating antibodies in the pathogenesis of MCNS.

CLINICAL CONSEQUENCES OF NEPHROTIC SYNDROME

Edema

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are two opposing theories, the *underfill hypothesis* and the *overfill hypothesis,* that have been proposed as mechanisms causing nephrotic edema.

The *underfill hypothesis* is based on nephrotic-range proteinuria that leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, results in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis without the concomitant use of diuretics. Also, reducing the renin-aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increased urine output before their urinary protein excretion is measurably reduced.

The *overfill hypothesis* postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of IV albumin infusions, if indicated.

Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoproteins, and very low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as well as decreased catabolism of lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon.

Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and

Table 567.1 Causes of Childhood Nephrotic Syndrome

IDIOPATHIC NEPHROTIC SYNDROME
Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Glomerulonephritis associated with nephrotic syndrome–membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy

GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME (SEE ALSO TABLE 567.3)

Nephrotic Syndrome (Typical)
Finnish-type congenital nephrotic syndrome (absence of nephrin)
Focal segmental glomerulosclerosis (pathogenic variants in nephrin, podocin, *MYO1E*, α-actinin 4, TRPC6)
Diffuse mesangial sclerosis (pathogenic variants in laminin β_2 chain)
Denys-Drash syndrome (pathogenic variants in WT1 transcription factor)
Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 pathogenic variant)
Mitochondrial disorders

Proteinuria With or Without Nephrotic Syndrome
Nail–patella syndrome (pathogenic variant in LMX1B transcription factor)
Alport syndrome (pathogenic variant in collagen biosynthesis genes)

Multisystem Syndromes With or Without Nephrotic Syndrome
Galloway-Mowat syndrome
Charcot-Marie-Tooth disease
Jeune syndrome
Cockayne syndrome
Laurence-Moon-Biedl-Bardet syndrome

Metabolic Disorders With or Without Nephrotic Syndrome
Alagille syndrome
α_1-Antitrypsin deficiency
Fabry disease
Glutaric acidemia
Glycogen storage disease
Hurler syndrome
Partial lipodystrophy
Mitochondrial cytopathies
Sickle cell disease

SECONDARY CAUSES OF NEPHROTIC SYNDROME

Infections
Endocarditis
Post-streptococcal
Hepatitides B, C
HIV-1
Infectious mononucleosis
Cytomegalovirus
Malaria
Syphilis (congenital and secondary)
Toxoplasmosis
Tuberculosis
Schistosomiasis
Filariasis

Drugs
Captopril
Penicillamine
Gold
Nonsteroidal antiinflammatory drugs
Pamidronate, other bisphosphonates
Interferon
Mercury
Heroin
Lithium
Rifampicin
Sulfasalazine

Immunologic or Allergic Disorders
Vasculitis syndromes
Castleman disease
Kimura disease
Bee sting
Snake venom
Food allergens
Serum sickness
Poison ivy, poison oak

ASSOCIATED WITH MALIGNANT DISEASE

Wilms Tumor
Lymphoma
Pheochromocytoma
Leukemia
Thymoma
Solid tumors

Glomerular Hyperfiltration
Oligomeganephronia
Morbid obesity
Adaptation to nephron reduction

Adapted from Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;362:629–638.

Table 567.2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				TYPE I	TYPE II
DEMOGRAPHICS					
Age (years)	2-6, some adults	2-10, some adults	40-50	5-15	5-15
Sex (male:female)	2:1	1.3:1	2:1	1:1	1:1
CLINICAL MANIFESTATIONS					
Nephrotic syndrome	100%	90%	80%	60%*	60%*
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria (microscopic or gross)	10–20%	60–80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%

Table 567.2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome—cont'd

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				TYPE I	TYPE II
Rate of progression to renal failure	Does not progress	10 years	50% in 10-20 years	10-20 years	5-15 years
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors	None	Partial lipodystrophy
GENETICS	None except in congenital nephrotic syndrome (see Table 567.3)	Podocin, α-actinin 4, TRPC6 channel, INF-2, MYH-9	None	None	None
LABORATORY FINDINGS	Manifestations of nephrotic syndrome ↑ BUN in 15–30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20–40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels: C1, C4, C3-C9	Normal complement levels: C1, C4, low C3-C9
RENAL PATHOLOGY					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY	90%	15–20%	Resistant	Not established/ resistant	Not established/ resistant

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.
↑, Elevated; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.
Modified from Couser WG. Glomerular disorders. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine,* 19th ed. Philadelphia: WB Saunders; 1992. p. 560.

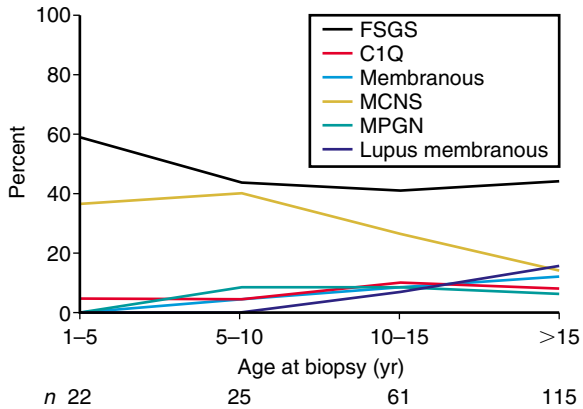

Fig. 567.1 Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, Nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; *n*, number of patients. *(From Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124:747–757.)*

bacteremia. This occurs as a result of many factors, particularly hypoglobulinemia, as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms. Children with nephrotic syndrome are at significantly increased risk for infection with encapsulated bacteria and, in particular, pneumococcal disease. **Spontaneous bacterial peritonitis** presents with fever, abdominal pain, and peritoneal signs. Although pneumococcus is the most frequent cause of peritonitis, gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn, and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts >250 cells/μL are highly suggestive of spontaneous bacterial peritonitis.

Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2–5%) compared with adults but has the potential for serious consequences.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 567.3 Causative Genes and Histologic Patterns of Nephrotic Syndrome by Time of Disease Onset

	CAUSE	INHERITANCE/ LOCUS	GENE/PROTEIN	HISTOLOGIC FEATURES
CONGENITAL ONSET (0-3 MO)				
Isolated	Congenital nephrotic syndrome of the Finnish type (CNF)	AR	*NPHS1*/nephrin	Radial dilation of proximal tubule
	Recessive SRNS, type 2	AR	*NPHS2*/podocin	FSGS/MGC
	Recessive SRNS, type 3	AR	*NPHS3*/PLCE1	DMS
	Isolated DMS	AR	WT1	DMS
	Recessive SRNS	AR	COQ2	FSGS, collapsing
	Recessive SRNS + deafness	AR	COQ6	FSGS
	Dominant SRNS + deafness	AD/11q24	Unknown	FSGS
	DMS + neurologic findings	AR	ARHGDIA/Rho GDP dissociation inhibitor (GDI) alpha	DMS
	NS + lung and skin disease	AR	*ITGA3*/integrin alpha 3	DMS
	Steroid-sensitive nephrotic syndrome	AR/2p12-13.2	Unknown	MGC/FSGS
Syndromic	Denys-Drash syndrome	AD	WT1	DMS
	Pierson syndrome	AR	*LAMB2*/laminin-β2	FSGS
	Nail–patella syndrome	AD	*LMX1B*/LIM homeobox transcription factor-1β	
	Frasier syndrome	AD	WT1	FSGS
	Schimke immunoosseous dysplasia	AR	SMARCAL1	FSGS
	Epidermolysis bullosa + FSGS	AR	*ITGB4*/integrin-β4	FSGS
	Galloway-Mowat syndrome	AR	Unknown	MGC to FSGS
INFANCY-CHILDHOOD ONSET				
Genetic	Recessive SSNS	AR	*EMP2*/epithelial membrane protein 2	
	Recessive SRNS	AR	*NPHS2*/podocin	FSGS/MGC
	Recessive SRNS	AR	*NPHS1*/nephrin	FSGS/MGC
	Recessive SRNS	AR	*NPHS3*/PLCE1	DMS
	Isolated DMS	AD	WT1	DMS
	Recessive SRNS + deafness or intellectual disability	AR	ARHGDIA	DMS
	SRNS	AR	*MYOE1*/nonmuscle class I myosin E	FSGS
	SRNS	AR	*PTPRO/GLEPP1* protein tyrosine phosphatase receptor type O/glomerular epithelial protein-1	FSGS
JUVENILE-ADULT ONSET				
Genetic	SRNS	AR or sporadic	*NPHS2* (p.R229Q)	FSGS
	Familial SRNS	AD	*INF2*/formin family of actin-regulating proteins	FSGS
	FSGS, type 1	AD/19q13	*ACTN4*/α-actinin-4	FSGS
	FSGS, type 2	AD/11q21-22	*TRPC6*/transient receptor potential cation channel, subfamily C, member 6	FSGS
	FSGS, type 3	AR-AD/6p12	*CD2AP*/CD2-associated protein	FSGS
	SRNS	AR	*PTPRO/GLEPP1* protein tyrosine phosphatase receptor type O/glomerular epithelial protein-1	FSGS
	SRNS	AR	*ADCK4*/aarF domain-containing kinase 4	FSGS
	SRNS (no extrarenal symptoms)	AD or sporadic	*LMX1B* encodes homeodomain-containing transcription factor	FSGS

AD, Autosomal dominant; AR, autosomal recessive; DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; MGC, minimal glomerular changes; NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.
From Bakkaloglu SA, Schaefer F. Diseases of the kidney and urinary tract in children. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney*, 10th ed. Philadelphia: Elsevier; 2016: Table 74-2.

567.1 Idiopathic Nephrotic Syndrome

Elif Erkan

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

PATHOLOGY

In **minimal change nephrotic syndrome (MCNS)** (approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the

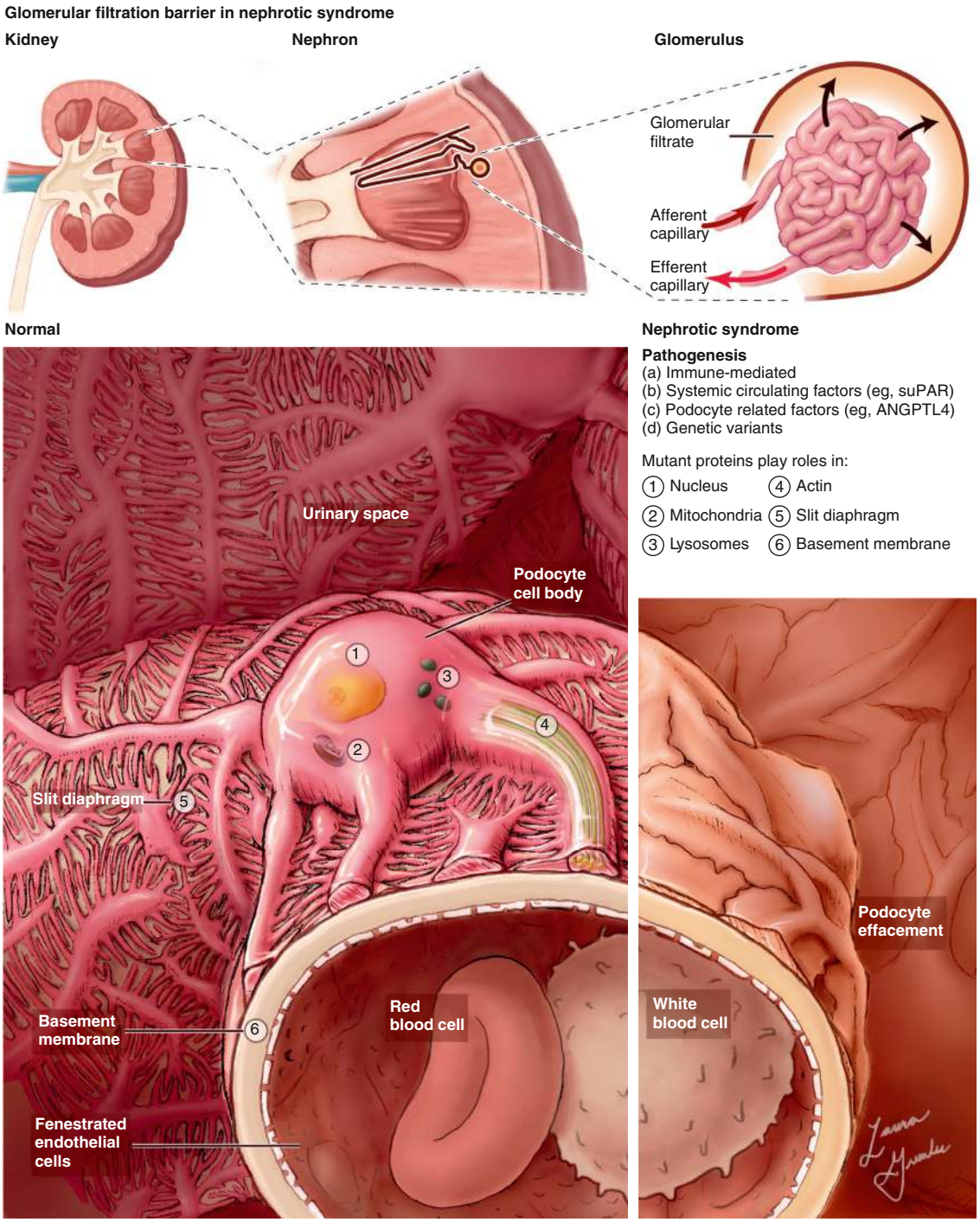

Fig. 567.2 The glomerular filtration barrier and pathogenesis of idiopathic nephrotic syndrome. Within the kidney is the glomerulus, a capillary tuft that filters the blood. The podocyte, glomerular basement membrane, and fenestrated glomerular endothelium form the glomerular filtration barrier, allowing the ultrafiltrate to enter the urinary space. The podocyte has extensive cellular extensions that interdigitate, and these foot processes are connected by the slit diaphragm. In nephrotic syndrome, there is extensive effacement of the podocytes and loss of this barrier to protein, allowing excessive serum albumin to leak into the urine. The pathogenesis of idiopathic nephrotic syndrome is hypothesized to be either immune mediated, due to a systemic podocyte-derived circulating factor, or, in rarer or familial forms, a genetic variant. Numerous pathogenic variants are associated with steroid-resistant nephrotic syndrome that affect various parts of the podocyte itself or the other constituents of the glomerular basement membrane. These include pathogenic variants affecting the podocyte nucleus, mitochondria or lysosomes, the slit diaphragm or actin cytoskeleton, and the glomerular basement membrane. Nephrin, podocin, and CD2AP, for example, are essential components of a zipper-like structure spanning the interdigitating foot processes of the podocyte and the slit diaphragm and link directly with the podocyte actin cytoskeleton. The actin cytoskeleton is further supported by microfilaments that maintain structural stability and facilitate the dynamic nature of the podocyte structure and function. The importance of these microfilaments is evident because pathogenic variants in both α-actinin 4 and INF2, which are involved in actin regulation and polymerization, lead to FSGS. *(From Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018;392:61–72. Fig. 2.)*

epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In **focal segmental glomerulosclerosis (FSGS),** glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy (Fig. 567.3; see Table 567.2). Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen. The tip variant of FSGS is more common in Caucasians and is associated with better renal survival; by contrast, the collapsing variant of FSGS has a faster progression rate to end-stage kidney disease and is more common in Black patients.

Lesions consistent with FSGS may be seen secondary to HIV infection, vesicoureteral reflux, and IV use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli with end-stage kidney disease in most patients.

MINIMAL CHANGE NEPHROTIC SYNDROME

Clinical Manifestations

Idiopathic nephrotic syndrome is more common in males than in females (2:1) and most commonly appears between the ages of 2 and 6 years (see Fig. 567.1). However, it has been reported as early as 6 months of age and throughout adulthood. MCNS is present in 85–90% of patients <6 years of age. In contrast, only 20–30% of adolescents who present for the first time with nephrotic syndrome have MCNS. The more common cause of idiopathic nephrotic syndrome in this older age group is FSGS. The incidence of FSGS is increasing; it may be more common in Black, Hispanic, and Asian patients. FSGS is the most common cause of end-stage kidney disease in adolescents.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and, uncommonly, reactions to insect bites, bee stings, or poison ivy.

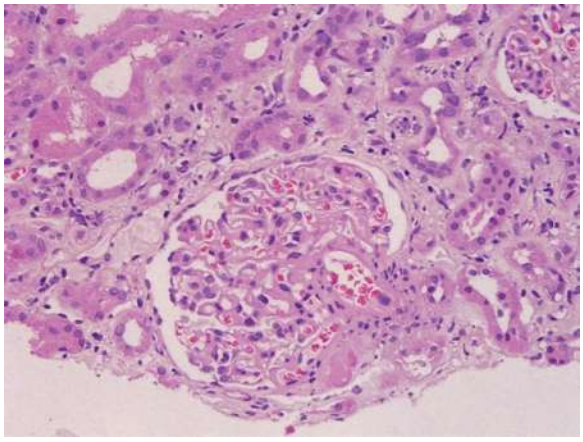

Fig. 567.3 Steroid-resistant nephrotic syndrome (SRNS). Kidney biopsy image of patient with SRNS shows focal segmental glomerulosclerosis. Segmental sclerosis is noted in a perihilar location with hyalinosis. Evidence of tubular atrophy and interstitial fibrosis is also present. H&E magnification 20×. *(From Tullus K, Webb H, Bagga A. Management of steroid-resistant nephrotic syndrome in children and adolescents. Lancet Child Adolesc Health. 2018;2:880–888. Fig. 1B, p. 881.)*

Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common. Important features of MCNS are the absence of hypertension and gross hematuria (the so-called nephritic features).

The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition. A diagnosis other than MCNS should be considered in children <1 year of age, with a positive family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Diagnosis

Recommendations for the Initial Evaluation of Children with Nephrotic Syndrome

Confirming the Diagnosis of Nephrotic Syndrome. The initial workup for a child with nephrotic syndrome is shown in Table 567.4. Labs should be obtained including urinalysis with the first morning urine protein:creatinine ratio, CBC, serum electrolytes, BUN, creatinine, glomerular filtration rate, albumin, complement C3 and C4 levels, antinuclear and anti-streptococcal antibodies, and antineutrophil cytoplasmic antibodies.

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children. A spot urine protein:creatinine ratio should be >2.0. The serum creatinine value is usually normal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume. The serum albumin level is <2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. Kidney ultrasound may be considered to exclude renal malformations and venous thrombosis but is not mandatory. A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Treatment

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Such outpatient management is not practiced in all major centers, because the time required for successful education of the family regarding all aspects of the condition can require a short period of hospitalization. The child's parents must be able to recognize the signs and symptoms of the complications of the disease and may be taught how to use a dipstick and interpret the results to monitor for the degree of proteinuria. Tuberculosis must be ruled out before starting immunosuppressive therapy with corticosteroids by placing a purified protein derivative skin test or obtaining an interferon-gamma release assay and confirming a negative result.

Children with onset of uncomplicated nephrotic syndrome between 1 and 12 years of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, sustained hypertension, acute kidney injury, low C3 levels, arthritis and/or rash to suggest glomerulonephritis, or age <1 year or >12 years) should be considered for renal biopsy before treatment.

Use of Corticosteroids to Treat Minimal Change Nephrotic Syndrome

Corticosteroids are the mainstay of therapy for MCNS. The treatment guidelines for corticosteroid use presented in the following sections are adapted from and based on the 2021 Kidney Disease: Improving

Table 567.4 Investigations in a Child with Nephrotic Syndrome (NS)

BASELINE INVESTIGATIONS
1. Urinalysis and urine microscopy
2. Urine albumin or protein:creatinine ratio
3. 24-hr timed collection of urine for protein quantification
4. Serum electrolytes, albumin, total protein, renal function, and cholesterol
ADDITIONAL TESTING IF THERE IS A SUSPICION OF A GLOMERULONEPHRITIS
1. Serum complement C3 and C4 concentrations
2. Serum immunoglobulins
3. Antistreptolysin titers
4. Anti-DNase B antibodies
5. Antinuclear antigen antibodies
6. Anti–double-stranded DNA antibodies
7. Anti-neutrophil cytoplasmic antibodies
INFECTIOUS WORKUP DEPENDING ON CLINICAL CONTEXT
1. Hepatitis B and C, HIV, syphilis, or tuberculosis can also be considered depending on the clinical context
CONSIDERATION OF GENETIC TESTING
1. A positive family history of NS
2. Congenital NS
3. Failure to respond to steroid therapy
4. Persistent kidney dysfunction
5. Features suggestive of a known syndrome (appendix)
RENAL BIOPSY CONSIDERED IN THE FOLLOWING SITUATIONS
1. Age <1 or >12 years
2. Persistent or sustained elevation in creatinine
3. Significant hematuria or gross hematuria
4. Hypocomplementemia
5. Findings indicative of another autoimmune disease
6. Infection with hepatitis B or C, HIV, or tuberculosis
7. Hypertension
8. Glucocorticoid resistance

From Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet.* 2018;392:61–72. Panel 3.

Global Outcomes (KDIGO) clinical practice guidelines on glomerulonephritis (Fig. 567.4).

Treatment of the Initial Episode of Nephrotic Syndrome

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m^2/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 weeks followed by alternate-day prednisone (starting at 40 mg/m^2 every other day or 1.5 mg/kg every other day) for a period ranging from 4-6 weeks. The issue of the duration of steroid treatment has been controversial, but current evidence suggests that prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes. Approximately 80–90% of children respond to steroid therapy.

Response is defined as the attainment of remission within the initial 4 weeks of corticosteroid therapy. **Remission** consists of a urine protein:creatinine ratio of <0.2 or <1+ protein on urine dipstick testing for 3 consecutive days. Most children who respond to prednisone therapy do so within the first 5 weeks of treatment.

Managing the Clinical Sequelae of Nephrotic Syndrome

Edema. Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1,500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, *although extreme caution should be exercised.* Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/dose IV) is sometimes necessary. Such therapy should be used only in collaboration with a pediatric nephrologist and mandates close monitoring of volume status, blood pressure, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension, heart failure, and pulmonary edema, is a potential complication of parenteral albumin therapy, particularly when it is administered as a rapid infusion.

Dyslipidemia. Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with a saturated fat intake of <10% calories. Dietary cholesterol intake should be <300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylgluataryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia.

Infections. Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is a suspicion of infection, a blood culture should be drawn before starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include pneumococcus and gram-negative bacteria. A third-generation cephalosporin is a common choice of IV antibiotic.

Thromboembolism. Children who present with the clinical signs of thromboembolism should be evaluated with appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. In children with thrombotic events, anticoagulation therapy including heparin, low molecular weight heparin, and warfarin are therapeutic options that appear to be effective.

Obesity and Growth. Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

Relapse of Nephrotic Syndrome. Relapse of nephrotic syndrome is defined as a urine protein:creatinine ratio of >2 or ≥3+ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated similar to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission, and the regimen is then switched to alternate-day therapy. The duration of alternate-day therapy varies depending on the frequency of relapses of the individual child. Children are classified as infrequent relapsers or frequent relapsers, and as being steroid dependent, based on the number of relapses in a 12-month period or their inability to remain in remission following discontinuation of steroid therapy.

Steroid Resistance. Steroid resistance is defined as the failure to achieve remission after 4 weeks of corticosteroid therapy. Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy and genetic testing. Steroid-resistant nephrotic syndrome is usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Implications of Steroid-Resistant Nephrotic Syndrome. Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 years of diagnosis if patients do not achieve a partial or complete remission. Persistent nephrotic syndrome is associated with a poor

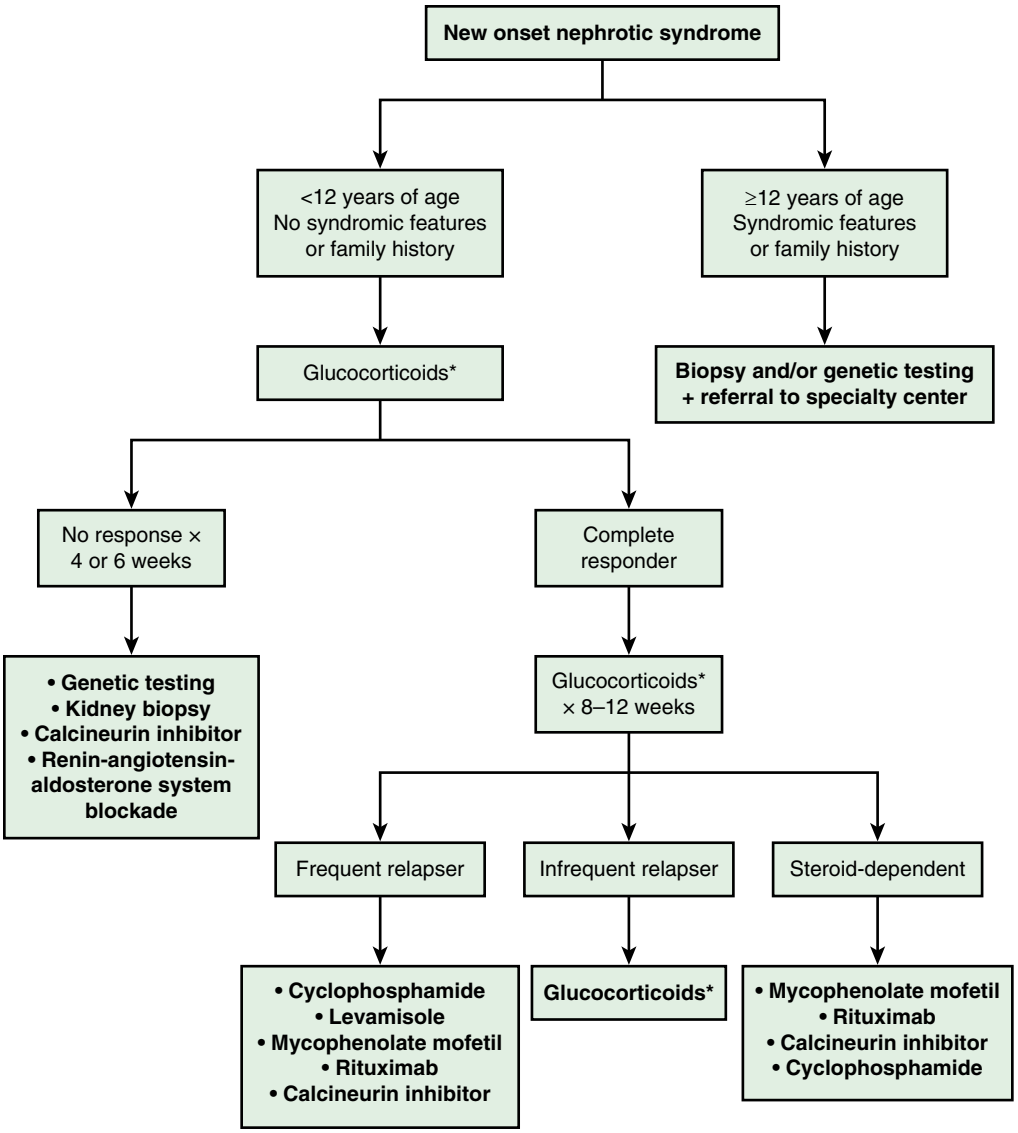

Fig. 567.4 Treatment algorithm for new-onset nephrotic syndrome (NS). Therapeutic approach to NS in children from onset. *Glucocorticoids include PO prednisone or prednisolone. NS, Nephrotic syndrome. *(From Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100[4S]:S1–S276. Fig. 40.)*

patient-reported quality of life, hypertension, serious infections, and thromboembolic events. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared with their peers.

Alternative Therapies to Corticosteroids in the Treatment of Nephrotic Syndrome. Steroid-dependent patients, frequent relapsers, and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). **Cyclophosphamide** prolongs the duration of remission and reduces the number of relapses in children with **frequently relapsing** and **steroid-dependent** nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. Cyclophosphamide (2 mg/kg) is given as a single oral dose for a total duration of 8-12 weeks. Alternate-day prednisone therapy is often continued during cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly, and the drug should be withheld if the count falls below 5,000/mm^3. The cumulative threshold dose above which oligospermia or azoospermia occurs in males is >250 mg/kg.

Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with **steroid-resistant** nephrotic syndrome. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. **Mycophenolate** can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. **Levamisole**, an anthelmintic agent with immunomodulating effects that has been shown to reduce the risk of relapse when compared with prednisone, is not available in the United States.

Rituximab, the chimeric monoclonal antibody against CD20-targeting B cells, was found to be effective in children by maintaining remission and decreasing the number of relapses in steroid-dependent and/or steroid-resistant nephrotic syndrome. Randomized trials with rituximab have shown promising results of an up to 80% drug-free remission rate at 1 year in patients with steroid-dependent nephrotic syndrome. However, rituximab is less effective in patients treated with calcineurin inhibitors and steroids and with multidrug-resistant nephrotic syndrome.

Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

Immunizations in Children with Nephrotic Syndrome. To reduce the risk of serious infections in children with nephrotic syndrome, give the full pneumococcal vaccination (with the 13-valent conjugant vaccine and 23-valent polysaccharide vaccine) and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. Following close contact with varicella infection, give immunocompromised children taking immunosuppressive agents varicella-zoster immune globulin if available; immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 weeks after vaccination.

Table 567.5 provides monitoring recommendations for children with nephrotic syndrome.

Prognosis

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Although there is no proven way to predict an individual child's course, children who respond rapidly to steroids and those who have no relapses during the first 6 months after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile. To minimize the psychologic effects of the condition and its therapy, children with idiopathic nephrotic syndrome should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted diet when in remission.

Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage kidney disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30–50% of transplant recipients with FSGS.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

567.2 Secondary Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome can occur as a secondary feature of many forms of glomerular disease. Membranous nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, and IgA vasculitis nephritis (formerly Henoch-Schönlein purpura nephritis) can all have a nephrotic component (see Tables 567.1 and 567.3). Secondary nephrotic syndrome should be suspected in patients >12 years and those with sustained hypertension, hematuria, renal dysfunction, extrarenal symptoms (e.g., rash, arthralgias, fever), or depressed serum complement levels. In certain areas of the world, malaria and schistosomiasis are the leading causes of nephrotic syndrome. Other infectious agents associated with nephrotic syndrome include hepatitis B virus, hepatitis C virus, filaria, leprosy, and HIV.

Nephrotic syndrome has been associated with malignancy, particularly in the adult population. In patients with solid tumors, such as carcinomas of the lung and gastrointestinal tract, the renal pathology often resembles membranous glomerulopathy. Immune complexes composed of tumor antigens and tumor-specific antibodies presumably mediate the renal involvement. In patients with lymphomas, particularly Hodgkin lymphoma, the renal pathology most often resembles MCNS. The proposed mechanism of

Table 567.5 Monitoring Recommendations for Children with Nephrotic Syndrome

DISEASE AND TREATMENT	HOME URINE PROTEIN	WEIGHT, GROWTH, BMI	BP	CR	ELECTROLYTES	SERUM GLUCOSE	CBC	LIPID PROFILE	DRUG LEVELS	LFTS	UA	CPK
DISEASE TYPE												
Mild (steroid responsive)	•	•	•								•	
Moderate (frequent relapsing, steroid dependent)	•	•	•	•				•			•	
Severe (steroid resistant)	•	•	•	•				•			•	
THERAPY												
Corticosteroids		•	•			•		•				
Cyclophosphamide				•			•				•	
Mycophenolate mofetil							•			•		
Calcineurin inhibitors			•	•	•	•		•	•			
ACEIs/ARBs			•	•	•		•					
HMG-CoA reductase inhibitors								•		•		•

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CPK, creatine phosphokinase; Cr, creatinine; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LFTs, liver function tests; UA, urinalysis.

From Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. *Pediatrics*. 2009;124:747–757.

the nephrotic syndrome is that the lymphoma produces a lymphokine that increases permeability of the glomerular capillary wall. Nephrotic syndrome can develop before or after the malignancy is detected, resolve as the tumor regresses, and return if the tumor recurs.

Nephrotic syndrome has also developed during therapy with numerous drugs and chemicals. The histologic picture can resemble membranous glomerulopathy (penicillamine, captopril, gold, nonsteroidal antiinflammatory drugs, mercury compounds), MCNS (probenecid, ethosuximide, methimazole, lithium), or proliferative glomerulonephritis (procainamide, chlorpropamide, phenytoin, trimethadione, paramethadione).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

567.3 Congenital Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) has a poorer prognosis when it occurs in the first year of life, when compared with nephrotic syndrome manifesting in childhood. **Congenital nephrotic syndrome** is defined as nephrotic syndrome manifesting at birth or within the *first 3 months of life.* Congenital nephrotic syndrome may be classified as primary or as secondary to a number of etiologies such as in utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitides B and C, HIV), infantile systemic lupus erythematosus, or mercury exposure.

Primary congenital nephrotic syndrome is due to a variety of syndromes inherited as autosomal recessive disorders (see Table 567.3). A number of structural and functional abnormalities of the glomerular filtration barrier causing congenital nephrotic syndrome have been elucidated. In a large European cohort of children with congenital nephrotic syndrome, 85% carried pathogenic variants in four genes *(NPHS1, NPHS2, WT1,* and *LAMB2),* the first three of which encode components of the glomerular filtration barrier. The Finnish type of congenital nephrotic syndrome is caused by pathogenic variants in the *NPHS1* or *NPHS2* gene, which encodes nephrin and podocin, critical components of the slit diaphragm. Affected infants most commonly present at birth with edema caused by massive proteinuria, and they are typically delivered with an enlarged placenta (>25% of the infant's weight). Severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia result from loss of filtering selectivity at the glomerular filtration barrier. Prenatal diagnosis can be made by the presence of elevated maternal and amniotic α-fetoprotein levels.

Denys-Drash syndrome is caused by pathogenic variants in the *WT1* gene, which results in abnormal podocyte function. Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumor.

Pathogenic variants in the *LAMB2* gene, seen in **Pierson syndrome,** lead to abnormalities of β_2-laminin, a critical component of the glomerular and ocular basement membranes. In addition to congenital nephrotic syndrome, affected infants display bilateral microcoria (fixed narrowing of the pupil).

Galloway-Mowat syndrome is characterized by microcephaly with hiatal hernia and congenital nephrotic syndrome. Patients have distinctive kidney biopsy findings with loss of or poor basement membrane formation or permeation of their basement membranes with fibrils.

Regardless of the etiology of congenital nephrotic syndrome, the diagnosis is made clinically in newborns or infants who demonstrate severe generalized edema, poor growth and nutrition with hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and an increased risk of thrombotic events (urinary loss of antithrombin). Most infants have progressive renal insufficiency.

Table 567.6 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year of Age

SECONDARY CAUSES
Infections
Syphilis
Cytomegalovirus
Toxoplasmosis
Rubella
Hepatitis B or C
HIV
Malaria
Drug Reactions
Toxins
Mercury
Syndromes with Associated Renal Disease
Nail–patella syndrome
Lowe syndrome
Nephropathy associated with congenital brain malformation
Denys-Drash syndrome: Wilms tumor
Hemolytic uremic syndrome
Systemic lupus erythematosus
PRIMARY CAUSES (SEE TABLE 567.3)
Congenital nephrotic syndrome
Diffuse mesangial sclerosis
Minimal change disease
Focal segmental sclerosis
Membranous nephropathy

From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004: p. 418.

Albumin and diuretic infusions, providing high amounts of protein (3-4 g/kg), lipids, and a high caloric intake to maintain nutrition, along with vitamin and thyroid hormone replacement, have been the mainstream therapy for congenital nephrotic syndrome. Treatment of the congenital syndrome also consists of unilateral nephrectomy and use of angiotensin-converting enzyme inhibitors and/or indomethacin to decrease the proteinuria and glomerular filtration rate. Some centers prefer more aggressive therapy, including bilateral nephrectomy at 1-2 years of age, weight >7 kg, and initiation of peritoneal dialysis with subsequent kidney transplantation.

Secondary congenital nephrotic syndrome can resolve with treatment of the underlying cause, such as syphilis (Table 567.6). The management of primary congenital nephrotic syndrome includes intensive supportive care with IV albumin and diuretics, regular administration of IV γ-globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails and patients suffer from persistent anasarca or repeated severe infections, bilateral nephrectomies are performed, and chronic dialysis is initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome, though recurrence of the nephrotic syndrome has been reported to occur after transplantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Tubular Disorders

Chapter 568

Tubular Function

Eliza Blanchette and Bradley P. Dixon

Water and electrolytes are freely filtered at the level of the glomerulus. Thus the electrolyte content of ultrafiltrate at the beginning of the proximal tubule is similar to that of plasma. Carefully regulated processes of tubular reabsorption and/or tubular secretion determine the final water content and electrolyte composition of urine. Bulk movement of solute tends to occur in the proximal portions of the nephron, and fine adjustments tend to occur distally (see Chapter 73).

SODIUM

Sodium is essential in maintaining extracellular fluid balance and, thus, volume status. The kidney is capable of effecting large changes in sodium excretion in a variety of normal and pathologic states.

There are four main sites of sodium transport. Approximately 60% of sodium is absorbed in the proximal tubule by coupled transport with glucose, amino acids, and phosphate; 25% in the ascending loop of Henle (mediated by NKCC2, the loop diuretic-sensitive sodium-potassium-2 chloride transporter); and 15% in the distal tubule (mediated by NCCT, the thiazide-sensitive sodium chloride co-transporter) and collecting tubule (mediated by ENaC, the epithelial sodium channel).

The urinary excretion of sodium normally approximates the sodium intake of 2-6 mEq/kg/24 hr for a child consuming a typical American diet, minus 1-2 mEq/kg/24 hr required for normal metabolic processes. However, in states of volume depletion (dehydration, blood loss) or decreased effective circulating blood volume (septic shock, hypoalbuminemic states, heart failure), there may be a dramatic decrease in urinary sodium excretion to as low as 1 mEq/L. Changes in systemic volume status are detected by (1) baroreceptors in the atria, afferent arteriole, and carotid sinus and (2) by the macula densa, which detects changes in chloride delivery.

The major hormonal mechanisms mediating sodium balance include the renin-angiotensin-aldosterone axis, atrial natriuretic factor, and norepinephrine. Angiotensin II and aldosterone increase sodium reabsorption in the proximal tubule and distal tubule, respectively. Norepinephrine, released in response to volume depletion, does not directly act on tubular transport mechanisms but affects sodium balance by decreasing renal blood flow, thus decreasing the filtered load of sodium as well as stimulating renin release. With more severe volume depletion, antidiuretic hormone is also released (see Chapter 570). Sodium excretion is promoted by atrial natriuretic factor and suppression of renin.

POTASSIUM

Extracellular potassium homeostasis is regulated because small changes in plasma potassium concentrations have dramatic effects on cardiac, neural, and neuromuscular function (see Chapter 73.4). Essentially, all filtered potassium is fully reabsorbed in the proximal tubule and ascending loop of Henle. Therefore urinary excretion of potassium is completely dependent on tubular secretion by potassium channels (renal outer medullary potassium [ROMK] and big potassium [BK] channels) present in the principal cells of the collecting tubule. Factors that promote potassium secretion include aldosterone, increased sodium delivery to the distal nephron, and increased urine flow rate.

CALCIUM

A significant portion of filtered calcium (70%) is reabsorbed in the proximal tubule. Additional calcium is reabsorbed in the ascending loop of Henle (20%) and the distal tubule and collecting duct (5–10%). Calcium is reabsorbed by passive movement between cells (paracellular absorption) in a process driven by sodium chloride reabsorption and potassium recycling into the lumen. In addition, calcium uptake is actively regulated by calcium receptors, specific transporters, and calcium channels. Factors that promote calcium reabsorption include parathyroid hormone (released in response to hypocalcemia), calcitonin, vitamin D, thiazide diuretics, and volume depletion (see Chapter 610). Factors that promote calcium excretion include volume expansion, increased sodium intake, and diuretics such as mannitol and furosemide.

PHOSPHATE

The majority of filtered phosphate is reabsorbed in the proximal tubule by active transport coupled with sodium through the NaPi2a, NaPi2c, and PiT-2 channels. Reabsorption is increased by dietary phosphorus restriction, volume contraction, and growth hormone. Fibroblast growth factor 23 (FGF-23), parathyroid hormone, and volume expansion increase phosphate excretion.

MAGNESIUM

Approximately 25% of filtered magnesium is reabsorbed in the proximal tubule. Modulation of renal magnesium excretion occurs primarily in the ascending loop of Henle, with some contribution of the distal convoluted tubule. Magnesium is transported by the paracellular route similar to calcium, as well as through the transcellular route. Although specific magnesium transporters for transcellular absorption have been identified such as TRPM6, the precise mechanisms by which they are regulated remain unclear.

ACIDIFICATION AND CONCENTRATING MECHANISMS

Acidification and concentration are addressed in the sections on renal tubular acidosis and nephrogenic diabetes insipidus, respectively (see Chapters 569 and 570).

DEVELOPMENTAL CONSIDERATIONS

The tubular transport capabilities of neonates (especially premature infants) and young infants are less than those of adults. Although nephrogenesis (the formation of new glomerular/tubular units) is complete by about 36 weeks of gestation, significant tubular maturation occurs during infancy. Renal tubular immaturity, a reduced glomerular filtration rate, a decreased concentrating gradient, and a diminished responsiveness to antidiuretic hormone are characteristic of young infants. These factors can contribute to impaired regulation of water, solute, and electrolyte and acid-base homeostasis, particularly during times of acute illness.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 569

Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

Renal tubular acidosis (RTA) is a disease state characterized by a non–anion gap (hyperchloremic) metabolic acidosis in the setting of a normal or near-normal glomerular filtration rate. There are four main types of RTA: proximal (type II), classic distal (type I), hyperkalemic (type IV), and a combined proximal and distal (type III). Proximal RTA (pRTA) results from impaired bicarbonate reabsorption and distal RTA (dRTA) from failure to secrete acid. These defects may be inherited and persistent from birth or acquired, as is seen more commonly in clinical practice.

NORMAL URINARY ACIDIFICATION

Kidneys contribute to the acid-base balance by reabsorption of filtered bicarbonate (HCO_3^-) and excretion of hydrogen ion (H^+) produced every day. Hydrogen ion secretion from tubule cells into the lumen is key in the reabsorption of HCO_3^- and the formation of titratable acid (H^+ bound to buffers such as HPO_4^{2-}) and ammonium ions (NH_4^+). Because loss of filtered HCO_3^- is equivalent to the addition of H^+ to the body, all filtered bicarbonate should be absorbed before dietary H^+ can be excreted. Approximately 90% of filtered bicarbonate is absorbed in the proximal tubule and the remaining 10% in the distal segments, mostly the thick ascending limb and outer medullary collecting tubule (Fig. 569.1). In the proximal tubule and thick ascending limb of the loop of Henle, H^+ from water is secreted by the Na^+-H^+ exchanger on the luminal membrane. H^+ combines with filtered bicarbonate, resulting in the formation of H_2CO_3, which decomposes into water and CO_2 in the presence of carbonic anhydrase IV. CO_2 diffuses freely back into the cell, combines with OH^- (from H_2O) to form HCO_3^- in the presence of carbonic anhydrase II, and returns to the systemic circulation via a Na^+-HCO_3^- co-transporter situated at the basolateral membrane of the cell. In the collecting tubule, H^+ is secreted into the lumen by H^+ATPase (adenosine triphosphatase), and HCO_3^- is returned to the systemic circulation by the HCO_3^--Cl^- exchanger located on the basolateral membrane. The H^+ secreted proximally and distally in excess of the filtered HCO_3^- is excreted in the urine either as titratable acid ($H_2PO_4^-$) or as NH_4^+.

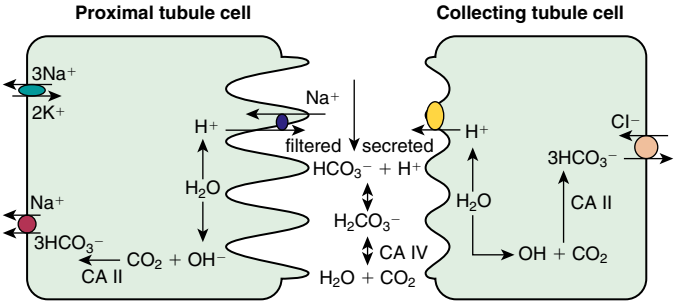

Fig. 569.1 Major cellular luminal events in acid-base regulation in the proximal and collecting tubule cells. In the proximal tubule, H^+, split from H_2O, is secreted into the lumen via the Na^+/H^+ exchanger, and HCO_3^-, formed by a combination of OH^- (split from H_2O) with CO_2 in the presence of carbonic anhydrase (CA) II, is returned to the systemic circulation by an Na^+-$3HCO_3^-$ co-transporter. Similarly, in the collecting tubule, H^+ is secreted into the lumen by an active H^+-ATPase (adenosine triphosphatase), and HCO_3^- is returned to the systemic circulation via an HCO_3^--Cl^- exchanger. H^+ secreted into the lumen combines with filtered HCO_3^- to form carbonic acid (H_2CO_3) and then CO_2 and H_2O in the presence of CA IV, which can be passively reabsorbed. *(Modified from Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed. New York: McGraw-Hill; 2001.)*

569.1 Proximal (Type II) Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

pRTA can be inherited and persistent from birth or occur as a transient phenomenon during infancy. Although rare, it may be primary and isolated. Typically, however, pRTA occurs as a component of global proximal tubular dysfunction or **Fanconi syndrome,** which is characterized by low molecular weight proteinuria, glycosuria, phosphaturia, aminoaciduria, and pRTA. Table 569.1 outlines the causes of pRTA and Fanconi syndrome. Many of these causes are inherited disorders. In addition to **cystinosis** and **Lowe syndrome,** autosomal recessive and dominant pRTA are addressed further in this section. Other inherited forms of Fanconi syndrome include galactosemia (see Chapter 107.2), hereditary fructose intolerance (see Chapter 107.3), tyrosinemia (see Chapter 105.2), and Wilson disease (see Chapter 405.2). Dent disease, or X-linked nephrolithiasis, is discussed in Chapter 571.3. In children, an important form of secondary Fanconi syndrome is exposure to medications such as the chemotherapy agents ifosfamide and cisplatin.

AUTOSOMAL RECESSIVE DISEASE

Isolated autosomal recessive pRTA is caused by pathogenic variants in *SLC4A4* encoding the sodium bicarbonate co-transporter NBC1. It manifests with ocular abnormalities (band keratopathy, cataracts, and glaucoma, often leading to blindness), short stature, enamel defects of the teeth, intellectual impairment, and occasionally basal ganglia calcification along with pRTA. An autosomal dominant pattern of inheritance has also been identified but is rare; these patients present with hyperchloremic metabolic acidosis, a normal ability to acidify urine, normal renal function, and growth retardation.

CLINICAL MANIFESTATIONS OF PROXIMAL RTA AND FANCONI SYNDROME

Patients with isolated, sporadic, or inherited pRTA present with growth failure in the first year of life. Additional symptoms can include polyuria, dehydration (from sodium loss), anorexia, vomiting, constipation, and hypotonia. Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets. Those with systemic diseases present with additional signs and symptoms specific to their underlying disease. Urinalysis in patients with isolated pRTA is generally unremarkable. The urine pH is acidic (<5.5) because distal acidification mechanisms are intact in these patients. Urinary studies in patients with Fanconi syndrome demonstrate varying degrees of phosphaturia, aminoaciduria, glycosuria, uricosuria, and elevated urinary sodium or potassium. Depending on the nature of the underlying disorder, laboratory evidence of chronic kidney disease (CKD), including elevated serum creatinine, may be present.

Cystinosis

Cystinosis is an autosomal recessive, systemic lysosomal storage disease caused by a defect in the transport of cystine out of lysosomes resulting in the accumulation of cystine crystals in most of the major organs of the body, notably the kidney, liver, eye, and brain. It occurs at an incidence of 1:100,000 to 1:200,000. At least three clinical patterns have been described. The most severe form of the disease, infantile or nephropathic cystinosis, presents in the first or second

Table 569.1 Disorders with Dysfunction of Renal Acidification—Defective HCO_3^- Reclamation: Proximal Renal Tubular Acidosis

ISOLATED PURE BICARBONATE WASTING (UNASSOCIATED WITH FANCONI SYNDROME)
Primary
Autosomal recessive with ocular abnormalities (pathogenic variant of *SLC4A4*/NBC1)
Autosomal dominant with short stature (pathogenic variant of *SLC9A3*/ NHE3)
Carbonic anhydrase deficiency, inhibition, or alteration
Drugs
Acetazolamide
Topiramate
Sulfanilamide
Mafenide acetate
Carbonic anhydrase II deficiency with osteopetrosis (mixed proximal and distal RTA type III)
GENERALIZED (ASSOCIATED WITH FANCONI SYNDROME)
Primary (Without Associated Systemic Disease)
Genetic
Sporadic
Genetically Transmitted Systemic Diseases
Cystinosis
Lowe syndrome
Wilson syndrome
Fanconi-Bickel syndrome
Tyrosinemia
Galactosemia
Hereditary fructose intolerance (during fructose ingestion)
Metachromatic leukodystrophy
Pyruvate carboxylase deficiency
Methylmalonic acidemia
Dysproteinemic States
Multiple myeloma
Monoclonal gammopathy
Secondary Hyperparathyroidism with Chronic Hypocalcemia
Vitamin D deficiency or resistance
Vitamin D dependency
Drugs or Toxins
Ifosfamide
Cisplatin
Outdated tetracycline
3-Methylchromone
Streptozotocin
Valproate
Topiramate
Lead
Mercury
Amphotericin B (historical)
Tubulointerstitial Diseases
Sjögren syndrome
Medullary cystic disease
Renal transplantation
Other Renal and Miscellaneous Diseases
Nephrotic syndrome
Amyloidosis
Paroxysmal nocturnal hemoglobinuria

From DuBose TD Jr. Disorders of acid-base balance. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 17-7.

year of life with severe tubular dysfunction and growth failure. If the disease is not treated, the children develop end-stage kidney disease by the end of their first decade. A milder form of the disease manifests by adolescence called juvenile or intermediate nephropathic cystinosis, and it is characterized by less severe tubular abnormalities and a slower progression to renal failure. A nonnephropathic adult form also exists called ocular cystinosis and has isolated ocular involvement.

Cystinosis is caused by pathogenic variants in *CTNS,* which encodes the protein cystinosin, a lysosomal cystine transporter. Genotype-phenotype studies demonstrate that patients with severe nephropathic cystinosis carry variants that lead to complete loss of cystinosin function. Patients with milder clinical disease have variants that lead to the expression of partially functional protein. Patients with nephropathic cystinosis present with clinical manifestations reflecting their pronounced tubular dysfunction and Fanconi syndrome, including polyuria and polydipsia, growth failure, and rickets. Fever, caused by dehydration or diminished sweat production, is common. Patients are typically fair skinned and blond because of diminished pigmentation. Ocular presentations include photophobia, retinopathy, and impaired visual acuity. Patients also can develop hypothyroidism, hepatosplenomegaly, and delayed sexual maturation. With progressive tubulointerstitial fibrosis, CKD is invariant.

The diagnosis of cystinosis is suggested by the detection of cystine crystals in the cornea and confirmed by measurement of increased leukocyte cystine content and genetic testing for biallelic pathogenic variants in the *CTNS* gene. Prenatal testing is available for at-risk families.

Treatment of cystinosis is directed at correcting the metabolic abnormalities associated with Fanconi syndrome. In addition, lifelong therapy is required with cysteamine, a therapy which converts cystine to cysteine and a cysteine-cysteamine heterodimer. This facilitates lysosomal transport and decreases tissue cystine. Oral cysteamine does not achieve adequate levels in ocular tissues, so additional therapy with cysteamine eyedrops is required. Early initiation of cysteamine can prevent or delay deterioration of renal function and the need for renal replacement therapy. Patients with growth failure that does not improve with cysteamine may benefit from treatment with growth hormone. Kidney transplantation is a viable option in patients with renal failure. With prolonged survival, additional complications may become evident, including central nervous system abnormalities, muscle weakness, swallowing dysfunction, and pancreatic insufficiency. It is unclear whether long-term cysteamine therapy will decrease these complications.

Lowe Syndrome

Lowe syndrome (oculocerebrorenal syndrome of Lowe) is a rare X-linked disorder characterized by congenital cataracts, developmental delay, and Fanconi syndrome. The disease is caused by pathogenic variants in *OCRL1,* which encodes the phosphatidylinositol polyphosphate 5-phosphatase protein. The abnormalities seen in Lowe syndrome are thought to be caused by abnormal transport of vesicles within the Golgi apparatus. Kidneys show nonspecific tubulointerstitial changes. Thickening of glomerular basement membrane and changes in proximal tubule mitochondria are also seen.

Patients with Lowe syndrome typically present in infancy with cataracts, progressive growth failure, hypotonia, and Fanconi syndrome. Significant low molecular weight proteinuria is common. Blindness and CKD often develop. Characteristic behavioral abnormalities are also seen, including tantrums, stubbornness, stereotypy (repetitive behaviors), and obsessions. There is no specific therapy for the renal disease or neurologic deficits. Cataract removal is generally required.

569.2 Distal (Type I) Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

dRTA can be sporadic or inherited. It can also occur as a complication of inherited or acquired diseases of the distal tubules. Primary or secondary causes of dRTA can result from damaged or impaired

functioning of one or more transporters or proteins involved in the acidification process, including the H^+/ATPase, the HCO_3^-/Cl^- anion exchangers, or the components of the aldosterone pathway. Because of impaired hydrogen ion excretion, the urine pH cannot be reduced to <5.5, despite the presence of severe metabolic acidosis. Loss of sodium bicarbonate distally, due to lack of H^+ to bind to in the tubular lumen (see Fig. 569.1), results in increased chloride absorption and hyperchloremia. Inability to secrete H^+ is compensated for by increased K^+ secretion distally, leading to hypokalemia. **Hypercalciuria** is usually present and can lead to nephrocalcinosis or nephrolithiasis. Chronic metabolic acidosis also impairs urinary citrate excretion. **Hypocitraturia** further increases the risk of calcium deposition in the tubules. Bone disease is common, resulting from mobilization of organic components from bone to serve as buffers to chronic acidosis.

CLINICAL MANIFESTATIONS OF DISTAL RTA

dRTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of dRTA include nephrocalcinosis and hypercalciuria. The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent. Table 569.2 lists the causes of primary and secondary dRTA. Although inherited forms are rare, three specific inherited forms of dRTA have been identified, including an autosomal recessive form associated with sensorineural deafness.

Medullary sponge kidney is a relatively rare sporadic disorder in children, although not uncommon in adults. *HNF1B* pathogenic variants have been implicated in some patients. It is characterized by cystic dilation of the terminal portions of the collecting ducts as they enter the renal pyramids. On ultrasound studies, patients often have medullary nephrocalcinosis. Although patients with this condition typically maintain normal renal function through adulthood, complications include nephrolithiasis, pyelonephritis, hyposthenuria (inability to concentrate urine), and dRTA. Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome or hemihypertrophy have been reported.

569.3 Hyperkalemic (Type IV) Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

Type IV RTA occurs as the result of impaired aldosterone production *(hypoaldosteronism)* or impaired renal responsiveness to aldosterone *(pseudohypoaldosteronism)*. Acidosis results because aldosterone has a direct effect on the H^+/ATPase responsible for hydrogen secretion. In addition, aldosterone is a potent stimulant for potassium secretion in the collecting tubule; consequently, lack of aldosterone results in hyperkalemia. This further affects the acid-base status by inhibiting ammoniagenesis and, thus, H^+ excretion. Aldosterone deficiency typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia. In children, aldosterone unresponsiveness is a more common cause of type IV RTA. This can occur transiently, during an episode of acute pyelonephritis or acute urinary obstruction, or chronically, particularly in infants and children with a history of obstructive uropathy. The latter patients can have significant hyperkalemia, even in instances when renal function is normal or only mildly impaired. Rare examples of inherited forms of type IV RTA have been identified (Table 569.3).

CLINICAL MANIFESTATIONS OF TYPE IV RTA

Patients with type IV RTA can present with growth failure in the first few years of life. Polyuria and dehydration (from salt wasting) are common. Rarely, patients (especially those with pseudohypoaldosteronism type 1) present with life-threatening hyperkalemia.

Table 569.2 Disorders with Dysfunction of Renal Acidification—Selective Defect in Net Acid Excretion: Classic Distal Renal Tubular Acidosis

PRIMARY DISORDERS
Familial
Autosomal dominant
SLC4A1 gene
Autosomal recessive
With deafness (*rdRTA1* or *ATP6V1B1* gene)
Without deafness (*rdRTA2* or *ATP6V0A4*)
Sporadic
ENDEMIC DISORDERS
Northeastern Thailand
DISORDERS SECONDARY TO SYSTEMIC DISORDERS
Autoimmune Diseases
Hyperglobulinemic purpura
Fibrosing alveolitis
Cryoglobulinemia
Chronic active hepatitis
Sjögren syndrome
Primary biliary cirrhosis
Thyroiditis
Polyarteritis nodosa
HIV nephropathy
Hypercalciuria and Nephrocalcinosis
Primary hyperparathyroidism
Hyperthyroidism
Medullary sponge kidney
Fabry disease
X-linked hypophosphatemia
Vitamin D intoxication
Idiopathic hypercalciuria
Wilson disease
Hereditary fructose intolerance
DRUG- AND TOXIN-INDUCED DISEASE
Amphotericin B
Toluene
Cyclamate
Mercury
Hepatic cirrhosis
Vanadate
Ifosfamide
Lithium
Foscarnet
Classic analgesic nephropathy
TUBULOINTERSTITIAL DISEASES
Balkan nephropathy
Kidney transplantation
Chronic pyelonephritis
Leprosy
Obstructive uropathy
Vesicoureteral reflux
Jejunoileal bypass with hyperoxaluria
DISORDERS ASSOCIATED WITH GENETICALLY TRANSMITTED DISEASES
Ehlers-Danlos syndrome
Hereditary elliptocytosis
Sickle cell anemia
Marfan syndrome
Medullary cystic disease
Hereditary sensorineural deafness
Jejunal bypass with hyperoxaluria
Osteopetrosis with carbonic anhydrase II deficiency (mixed proximal and distal RTA type III)
Carnitine palmitoyltransferase deficiency

From Hamm LL, DuBose TD Jr. Disorders of acid-base balance. In: Yu AS, Chertow GM, Luyckx VA, et. Al., eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 16.9.

Table 569.3 Disorders with Dysfunction of Renal Acidification: Generalized Abnormality of Distal Nephron with Hyperkalemia

MINERALOCORTICOID DEFICIENCY

Primary Mineralocorticoid Deficiency

- Combined deficiency of aldosterone, desoxycorticosterone, and cortisol
  - Addison disease
  - Bilateral adrenalectomy
  - Bilateral adrenal destruction
  - Hemorrhage or carcinoma
- Congenital enzymatic defects
  - 21-Hydroxylase deficiency
  - 3β-Hydroxydehydrogenase deficiency
  - Desmolase deficiency
- Isolated (selective) aldosterone deficiency
  - Chronic idiopathic hypoaldosteronism
  - Heparin (low molecular weight or unfractionated) administration in critically ill patient
  - Familial hypoaldosteronism
  - Corticosterone methyl oxidase deficiency types 1 and 2
  - Primary zona glomerulosa defect
  - Transient hypoaldosteronism of infancy
  - Persistent hypotension and/or hypoxemia
- Angiotensin-converting enzyme inhibition
  - Endogenous
  - Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Secondary Mineralocorticoid Deficiency

- Hyporeninemic hypoaldosteronism
  - Diabetic nephropathy
  - Tubulointerstitial nephropathies
  - Nephrosclerosis
  - Nonsteroidal antiinflammatory agents
  - Acquired immunodeficiency syndrome
  - Immunoglobulin M monoclonal gammopathy
  - Obstructive uropathy

MINERALOCORTICOID RESISTANCE

- PHA I: autosomal dominant (human mineralocorticoid receptor defect)

Renal Tubular Dysfunction (Voltage Defect)

- PHA I: autosomal recessive
- PHA II: autosomal dominant
- Drugs that interfere with Na^+ channel function in the CCT
  - Amiloride
  - Triamterene
  - Trimethoprim
  - Pentamidine
- Drugs that interfere with Na^+-K^+-ATPase in the CCT
  - Cyclosporine
  - Tacrolimus
- Drugs that inhibit aldosterone effect on the CCT
  - Spironolactone
  - Eplerenone
- Disorders associated with tubulointerstitial nephritis and renal insufficiency
  - Lupus nephritis
  - Methicillin nephrotoxicity
  - Obstructive nephropathy
  - Kidney transplant rejection
  - Sickle cell disease
  - Williams syndrome with uric acid nephrolithiasis

ATPase, Adenosine triphosphatase; CCT, cortical collecting tubule; PHA I, PHA II, pseudohypoaldosteronism types 1 and 2.

From Hamm LL, DuBose TD Jr. Disorders of acid-base balance. In: Yu AS, Chertow GM, Luyckx VA, et al., eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 16.11.

Patients with obstructive uropathies can present acutely with signs and symptoms of pyelonephritis, such as fever, vomiting, and foul-smelling urine. Laboratory tests reveal a hyperkalemic non–anion gap metabolic acidosis. Urine may be alkaline or acidic. Elevated urinary sodium levels with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

DIAGNOSTIC APPROACH TO RENAL TUBULAR ACIDOSIS

The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis, identify electrolyte abnormalities, assess renal function, and rule out other causes of bicarbonate loss such as diarrhea (Table 569.4). Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with correction of volume depletion. Patients with protracted diarrhea can deplete their total-body bicarbonate stores and can have persistent acidosis despite apparent restoration of volume status. In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores. If acidosis persists beyond a few days in this setting, additional studies are indicated.

Serum electrolytes, BUN, calcium, phosphorus, creatinine, and venous blood gas for pH should be obtained by venipuncture. Traumatic blood draws (such as heel-stick specimens), small volumes of blood in adult-size specimen collection tubes, or a prolonged specimen transport time at room temperature can lead to falsely low bicarbonate levels, often in association with an elevated serum potassium value. True hyperkalemic acidosis is consistent with type IV RTA, whereas the finding of normal or low potassium suggests type I or II RTA. The **blood anion gap** should be calculated using the formula $[Na^+] - [Cl^- + HCO_3^-]$. Typically, values of <12 demonstrate the absence of an anion gap. Values of >20 indicate the presence of an anion gap and other diagnoses (lactic acidosis, diabetic ketoacidosis, inborn errors of metabolism, ingested toxins) should be investigated. If tachypnea is noted, evaluation of an arterial blood gas may be appropriate to evaluate the possibility of a mixed acid-base disorder primarily involving respiratory and metabolic components. A detailed history, with particular attention to growth and development, recent or recurrent diarrheal illnesses, a family history of developmental delay, failure to thrive, end-stage kidney disease, infant deaths, or miscarriages is essential. The physical examination should determine growth parameters and volume status as well as the presence of any dysmorphic features suggesting an underlying syndrome.

Once the presence of a non–anion gap metabolic acidosis is confirmed, the urine pH can help distinguish distal from proximal causes. A urine pH <5.5 in the presence of acidosis suggests pRTA, whereas patients with dRTA typically have a urine pH >6.0. The **urine anion gap** ([urine Na^+ + urine K^+] – urine Cl^-) is sometimes calculated to confirm the diagnosis of dRTA. A positive gap suggests a deficiency of ammoniagenesis and, thus, the possibility of a dRTA. A negative gap is consistent with proximal tubule bicarbonate wasting (or gastrointestinal bicarbonate wasting). A urinalysis should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction. Random or 24-hour urine calcium and creatinine measurements will identify hypercalciuria. Renal ultrasonography should be performed to identify underlying structural abnormalities such as obstructive uropathies, as well as to determine the presence of nephrolithiasis or nephrocalcinosis (Fig. 569.2).

TREATMENT AND PROGNOSIS

The mainstay of therapy in all forms of RTA is bicarbonate replacement. Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution (Bicitra or Shohl solution). The base requirement for dRTA is generally in the range of 2-4 mEq/kg/24 hr, although individual patient requirements can vary. Patients with Fanconi syndrome usually require phosphate supplementation. Patients with dRTA should be monitored for the development of hypercalciuria. Those with symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis may require

Table 569.4 Contrasting Features and Diagnostic Studies in Renal Tubular Acidosis

	TYPE OF RENAL TUBULAR ACIDOSIS		
FINDING	**PROXIMAL**	**CLASSIC DISTAL**	**GENERALIZED DISTAL DYSFUNCTION**
Plasma [K^+]	Low	Low	High
Urine pH with acidosis	<5.5	>5.5	<5.5 or >5.5
Urine net charge	Negative	Positive	Positive
Fractional bicarbonate excretion	>10–15% during alkali therapy	2–5%	5–10%
U−BPco_2	Normal	Low	Low
Response to therapy	Least responsive	Responsive	Less responsive
Associated features	Fanconi syndrome	Nephrocalcinosis/ hyperglobulinemia	Renal insufficiency

U−BPco_2, urine minus blood CO_2 pressure.
Modified from DuBose TD Jr. Disorders of acid-base balance. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 17-17.

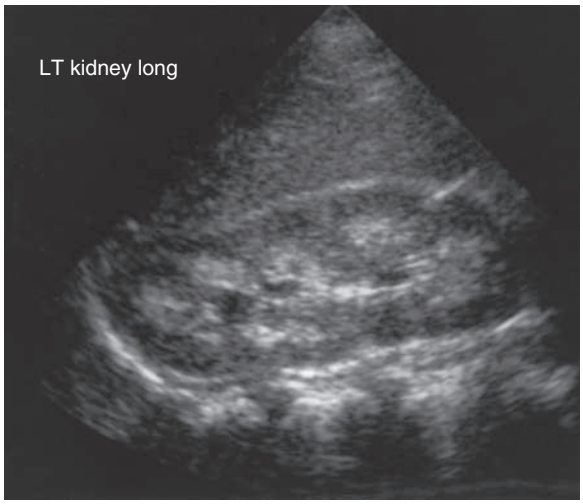

Fig. 569.2 Ultrasound examination of a child with distal RTA, demonstrating medullary nephrocalcinosis.

thiazide diuretics to decrease urine calcium excretion. Patients with type IV RTA can require chronic treatment for hyperkalemia with a sodium-potassium exchange resin (i.e., sodium polystyrene sulfonate or patiromer).

The prognosis of RTA depends to a large extent on the nature of any existing underlying disease. Patients with treated isolated proximal or dRTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range. Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

569.4 Rickets Associated with Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

Rickets may be present in primary RTA, *particularly in pRTA,* due to the added features of hypophosphatemia and phosphaturia from generalized proximal tubular dysfunction. Bone demineralization without overt rickets usually is detected in distal (type I) RTA. This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures. Bone demineralization in dRTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA.

Administration of sufficient bicarbonate to reverse acidosis reverses bone dissolution and the hypercalciuria that is common in dRTA. pRTA is treated with both bicarbonate and oral phosphate supplements to heal rickets. Doses of phosphate similar to those used in familial hypophosphatemia or Fanconi syndrome may be indicated. Vitamin D is required to offset the secondary hyperparathyroidism that complicates oral phosphate therapy. Following therapy, growth in patients with type II (proximal) RTA is greater than in patients with primary Fanconi syndrome.

Chapter 570 Nephrogenic Diabetes Insipidus

Margret E. Bock and Bradley P. Dixon

Nephrogenic diabetes insipidus (NDI) is a rare congenital or, more commonly, acquired, disorder of water metabolism characterized by an inability of the kidneys to concentrate urine, even in the presence of antidiuretic hormone (ADH). The most common pattern of inheritance in congenital NDI is as an X-linked recessive disorder (90% of cases of congenital NDI). Rarely, affected females are seen, presumably secondary to nonrandom X-chromosome inactivation. Approximately 10% of cases of congenital NDI are inherited as autosomal dominant or recessive disorders, with males and females affected equally. The clinical phenotype of autosomal recessive forms is similar to that of the X-linked form. Secondary (acquired) forms of NDI, either partial or complete, are not uncommon. They may be seen in many disorders affecting renal tubular function, including obstructive uropathies, acute kidney injury or chronic kidney disease, cystic kidney diseases, interstitial nephritis,

nephrocalcinosis, or toxic nephropathy caused by hypokalemia, hypercalcemia, lithium, or amphotericin B.

PATHOGENESIS

The ability to concentrate urine (and thus absorb water) requires three components: (1) the delivery of urine to the collecting tubule, (2) an intact concentrating gradient in the renal medulla, and (3) the ability to modulate water permeability in the collecting tubule by ADH. ADH (also called arginine vasopressin [AVP]) is synthesized in the hypothalamus and stored in the posterior pituitary. Under basal situations, the collecting tubule is impermeable to water. However, in response to increased serum osmolality (as detected by osmoreceptors in the hypothalamus) and/or severe volume depletion, ADH is released into the systemic circulation. It then binds to its receptor, vasopressin V2R (AVPR2), on the basolateral membrane of the collecting tubule cell. Binding of the hormone to its receptor activates a cyclic adenosine monophosphate–dependent cascade that results in insertion of preformed water channels (aquaporin 2 [AQP2]) into the luminal membrane of the collecting duct, rendering it permeable to water.

Pathogenic variants in *AVPR2* cause the more common X-linked form of NDI. Pathogenic variants in *AQP2* have been identified in patients with the rarer autosomal dominant and recessive forms. Pathogenic variants in *STIM1* (stromal interaction molecular 1) have also been identified in a mouse model exhibiting partial NDI, due to abnormalities in intracellular calcium regulation by the endoplasmic reticulum. Prenatal testing is available for families at risk for X-linked NDI. Patients with secondary forms of NDI can have ADH resistance due to defective aquaporin expression (as seen in lithium intoxication). Most often, secondary ADH resistance occurs as the result of loss of the hypertonic medullary gradient as a result of solute diuresis or tubular damage, resulting in the inability to absorb sodium or urea.

CLINICAL MANIFESTATIONS

Patients with congenital NDI typically present in the newborn period with massive polyuria, volume depletion, hypernatremia, and hyperthermia. Irritability and inconsolability are common features. Constipation and poor weight gain are also seen. After multiple episodes of **hypernatremic dehydration** in infancy, patients may develop intellectual disabilities, although this has become less common with cautious fluid resuscitation and gradual correction of hypernatremia. Toddlers and older children often display a marked thirst and a preference particularly for cold water. Mediated by the intact thirst mechanism, the need to consume large volumes of water during the day is profound, and patients often have diminished appetite and poor food intake, which may contribute to failure to thrive. However, even with adequate caloric supplementation, patients still exhibit growth abnormalities. Daytime and nighttime enuresis, caused by large urine volumes, is common. Patients with congenital NDI also may exhibit behavioral problems, including hyperactivity and short-term memory problems. Patients with the secondary form generally present later in life, primarily with hypernatremia and polyuria. Associated symptoms such as developmental delay and behavioral abnormalities are less common in this latter group.

DIAGNOSIS

The diagnosis is suggested in a male infant with polyuria, hypernatremia, and dilute urine. Simultaneous serum and urine osmolality measurements should be obtained. *If the serum osmolality value is ≥290 mOsm/kg with a simultaneous urine osmolality value of <290 mOsm/kg, a formal water-deprivation test is not necessary.* Because the differential diagnosis includes causes of **central diabetes insipidus,** the inability to respond to ADH (and thus the presence of NDI) should be confirmed by the administration of vasopressin (10-20 μg intranasally) followed by serial urine and serum osmolality measurements hourly for 4 hours. In patients with possible "partial" or secondary diabetes insipidus, in whom the initial serum osmolality value may be <290 mOsm/kg, a water-deprivation test should be considered. Fluids should be withheld and urine and serum osmolalities measured periodically until the serum osmolality value is >290 mOsm/kg; vasopressin is then given as before. Criteria for premature termination of a water-deprivation test include a decrease in body weight of >3%. These evaluations typically require an inpatient admission, given the need for serial laboratory monitoring and prompt intervention/response to results. If NDI is confirmed or suspected, an additional evaluation should include a detailed history to assess possible toxic exposures, determination of renal function by serum creatinine and BUN levels, and renal ultrasonography to identify obstructive uropathies or cystic kidney disease. Because of the massive urine output, patients with congenital NDI can have *nonobstructive hydronephrosis* of varying severity.

TREATMENT AND PROGNOSIS

Treatment of NDI includes maintenance of adequate fluid intake and access to free water, minimizing the urine output by limiting the solute load with a low-osmolar, low-sodium diet, and administering medications directed at decreasing the urine output. For infants, human milk or a low-solute formula, such as Similac PM 60/40, is preferred. Most infants with congenital NDI require gastrostomy or nasogastric feedings to ensure adequate fluid administration throughout the day and night. Sodium intake in older patients should be <0.7 mEq/kg/24 hr**.** Thiazide diuretics (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water. Potassium-sparing diuretics, in particular, amiloride (0.3 mg/kg/24 hr in three divided doses), are often additionally indicated. Patients who have an inadequate response to diuretics alone might benefit from the addition of prostaglandin synthetase inhibitors such as indomethacin (2 mg/kg/24 hr), which has an additive effect in reducing water excretion in some patients. Renal function must be monitored closely in such patients because indomethacin can cause deterioration in renal function over time. Patients with secondary NDI may not require medications but should have access to free water. Such patients should have the serum electrolytes and volume status monitored closely, particularly during periods of superimposed acute illnesses. Amiloride may also play a role in managing lithium-induced NDI by blocking entry of lithium into the tubular cell through the epithelial sodium channel (ENaC).

Prevention of recurrent dehydration and hypernatremia in patients with congenital NDI has significantly improved the neurodevelopmental outcome of these patients. However, behavioral issues remain a significant problem. In addition, chronic use of nonsteroidal antiinflammatory drugs can predispose patients to chronic kidney disease. The prognosis of patients with secondary NDI generally depends on the nature of the underlying disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 571

Inherited Tubular Transport Abnormalities

571.1 Bartter Syndrome

Danielle E. Soranno and Bradley P. Dixon

Bartter syndrome is a group of disorders characterized by hypokalemic hypochloremic metabolic alkalosis with hypercalciuria and salt wasting (see Chapter 73). These disorders are currently classified by the anatomic site affected by the pathogenic variant (Tables 571.1 and 571.2). **Antenatal Bartter syndrome** (types I, II, and IV; also called hyperprostaglandin E syndrome) typically manifests in infancy and has a more severe phenotype than **classic Bartter syndrome** (type III). The perinatal onset includes maternal polyhydramnios, neonatal salt wasting, and severe episodes of recurrent dehydration. The milder phenotype, classic Bartter syndrome, manifests in childhood with failure to thrive and a history of recurrent episodes of dehydration. A phenotypically related disease, **Gitelman syndrome**, has a distinct genetic defect and is discussed in Chapter 571.2 (see Table 571.1). One distinct variant of antenatal Bartter syndrome is associated with sensorineural deafness (type IV). Bartter-like phenotypes have been noted in other diseases such as Kearns-Sayre syndrome.

PATHOGENESIS

The biochemical features of Bartter syndrome, such as hypokalemic hypochloremic metabolic alkalosis with hypercalciuria, resemble those seen with chronic use of loop diuretics and reflect a defect in sodium, chloride, and potassium transport in the ascending loop of Henle. The urinary loss of sodium and chloride, with resultant volume contraction, stimulates the renin-angiotensin II-aldosterone axis. Aldosterone promotes distal sodium uptake and potassium secretion, exacerbating the hypokalemia. It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis. Hypokalemia stimulates prostaglandin synthesis, which further activates the renin-angiotensin II-aldosterone axis. Bartter syndrome has been associated with at least five distinct genetic defects in transporters along the loop of Henle (see Table 571.1). Each contributes, in some manner, to sodium and chloride transport. Pathogenic variants in the genes that encode the $Na^+/K^+/2Cl^-$ transporter (NKCC2, the site of action of furosemide), the luminal potassium channel (ROMK), combined chloride channel (CLC-Ka, CLC-Kb), or subunit of chloride channels (barttin) cause neonatal Bartter syndrome. Isolated defects in the genes that produce a specific basolateral chloride channel (ClC-Kb) cause classic Bartter syndrome.

CLINICAL MANIFESTATIONS

A history of maternal polyhydramnios with or without prematurity may be elicited. Dysmorphic features, including triangular facies, protruding ears, large eyes with strabismus, and drooping mouth may be present on physical examination. Consanguinity suggests the presence of an autosomal recessive disorder. Older children can have a history of recurrent episodes of polyuria with dehydration, failure to thrive, nonspecific fatigue, dizziness, and chronic constipation. Older children may also present with muscle cramps and weakness secondary

Table 571.1 Types of Bartter Syndrome, Gitelman Syndrome, and Related Conditions

DISORDER	OMIM, GENE	GENE PRODUCT	INHERITANCE	FEATURES
BS VARIANTS				
BS I (ABS, HPES)	601678, *SLC12A1*	NKCC2	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS II (ABS with transient hyperkalemia and acidosis, HPES)	241200, *KCNJ1*	ROMK1	AR	Polyhydramnios, prematurity, transient hyperkalemia and acidosis, then hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS III (CBS)	607364, *CLCNKB*	ClC-Kb	AR; many sporadic	Variable age at presentation with severity corresponding to type of gene pathogenic variant; hypokalemic hypochloremic alkalosis
BS IVa and BS IVb (ABS or HPES with sensorineural deafness)	602522, *BSND CLCNKA, CLCNKB*	Bartter ClC-Ka and ClC-Kb	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, sensorineural deafness, with or without concentrating defect
BS V (transient ABS)	300971, *MAGED2*	MAGED2	XR	Severe polyhydramnios, hypokalemic hypochloremic alkalosis with symptoms resolving within the first few months of life
AD hypocalcemic hypercalciuria	601199, *L125P*	CaSR	AD	Hypocalcemic hypocalciuria, hypokalemic hypochloremic alkalosis, suppressed PTH
GS VARIANTS				
GS	263800, *SLC12A3*	NCC	AR	Present in later childhood or adulthood with weakness, lethargy, carpopedal spasm, hypokalemic alkalosis, hypomagnesemia, hypermagnesuria and hypocalciuria
EAST syndrome (SeSAME)	612780, *Kir4.1*	KCNJ10	AR	Epilepsy, ataxia, sensorineural deafness, hypokalemic hypochloremic alkalosis
OTHER VARIANTS				
CLDN10 pathogenic variants	617579, *CLDN10*	Claudin-10	AR	Hypokalemic metabolic alkalosis with hypocalciuria but normal to elevated magnesium

ABS, Antenatal Bartter syndrome; AD, autosomal dominant; AR, autosomal recessive; BS, Bartter syndrome; CaSR, calcium-sensing receptor; CBS, classic Bartter syndrome; ClC-Ka, chloride channel-Ka; ClC-Kb, chloride channel-Kb; GS, Gitelman syndrome; HPES, hyperprostaglandin E syndrome; MAGED, melanoma-associated antigen-D2; NCC, thiazide-sensitive NaCl cotransporter; NKCC2, furosemide-sensitive Na-K-2Cl cotransporter; OMIM, Online Mendelian Inheritance in Man; PTH, parathyroid hormone; ROMK, renal outer medullary K channel; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalances; XR, X-linked recessive.
From Fulchiero R, Seo-Mayer P. Bartter syndrome and Gitelman syndrome. *Pediatr Clin North Am*. 2019;66:121–134. Box 1.

Table 571.2 Features That Distinguish Bartter and Gitelman Syndrome Variants

VARIANT	AGE OF ONSET	SERUM K	SERUM CL	SERUM MG	SERUM RENIN, ALDOSTERONE	URINE CA/CR	OTHER DISTINCT FEATURES
BS I	AN	Low	Low	Normal	High, high	High	—
BS II	AN	High, then low	Low	Normal	High, high	High	Transient hyperkalemia
BS III	N, C, A	Low	Very low	Normal	High, high	Low, normal, or high	—
BS IVa, IVb	AN	Low	Low	Normal	High, high	Normal or high	Sensorineural deafness
BS V	AN	Low	Low	Normal	High, high	—	Transient features
Hypocalcemic hypercalciuria	—	Low	Low	Normal	High, high	High	Family history, hypocalcemia, suppressed PTH
GS	C, A	Low	Low	Low	High, high	Low	—
EAST syndrome	—	Low	Low	Low	High, high	Low	Epilepsy, ataxia, sensorineural deafness

A, Adult; AN, antenatal; BS, Bartter syndrome; C, child; Ca/Cr, spot calcium to creatinine ratio; GS, Gitelman syndrome; Mg, magnesium; N, neonate; PTH, parathyroid hormone.
From Fulchiero R, Seo-Mayer P. Bartter syndrome and Gitelman syndrome. *Pediatr Clin North Am*. 2019;66:121–134. Box 3.

to chronic hypokalemia. Blood pressure is usually preserved, although patients with the antenatal form can have severe salt wasting, resulting in dehydration and hypotension. Serum chemistry reveals the classic biochemical abnormalities of a **hypokalemic hypochloremic metabolic alkalosis.** Renal function is typically normal. Urinary calcium levels are typically elevated, as are urinary potassium and sodium levels. Serum renin, aldosterone, and prostaglandin E levels are often markedly elevated, particularly in the more severe antenatal form. Nephrocalcinosis, resulting from hypercalciuria, may be seen on ultrasound examination (types I and II).

DIAGNOSIS

The diagnosis is usually made based on the clinical presentation and laboratory findings. The diagnosis in the neonate or infant is suggested by severe hypokalemia, usually <2.5 mmol/L, with metabolic alkalosis. Hypercalciuria is typical; hypomagnesemia is seen in a minority of patients but is more common in Gitelman syndrome. Because features of Bartter syndrome resemble the chronic use of loop diuretics, diuretic abuse should be considered in the differential diagnosis, even in young children. Chronic vomiting and cystic fibrosis can also present a similar clinical picture but can be distinguished by the measurement of **urinary chloride,** which is elevated in Bartter syndrome and low in patients with chronic vomiting and cystic fibrosis. Kidneys demonstrate hyperplasia of the juxtaglomerular apparatus, although renal biopsy is rarely performed to diagnose this condition.

TREATMENT AND PROGNOSIS

Treatment of Bartter syndrome is directed at preventing dehydration, maintaining nutritional status, and correcting hypokalemia. Potassium supplementation, usually in the form of potassium chloride to correct the concomitant chloride depletion and often at very high doses, is required. Potassium-sparing diuretics (such as spironolactone) are also often used to inhibit distal potassium secretion. Even with appropriate therapy, serum potassium values might not normalize, particularly in patients with the neonatal form. Infants and young children require a high-sodium diet and, at times, sodium supplementation. Indomethacin, a prostaglandin inhibitor, can also be effective. If hypomagnesemia is present, magnesium supplementation is required. With close attention to electrolyte balance, volume status, and growth, the long-term prognosis is generally good. Routine monitoring is necessary, particularly during periods of growth, to ensure that electrolytes are maintained in a safe range. Strict return/call precautions are needed in times of illness with extrarenal volume loss such as vomiting or diarrhea. In a minority of patients, chronic hypokalemia, nephrocalcinosis, and chronic indomethacin therapy can lead to chronic interstitial nephritis and chronic renal failure.

571.2 Gitelman Syndrome

Danielle E. Soranno and Bradley P. Dixon

Gitelman syndrome (often called a *Bartter syndrome variant*) is a rare autosomal recessive cause of hypokalemic hypochloremic metabolic alkalosis, with distinct features of **hypocalciuria** and **hypomagnesemia.** Patients with Gitelman syndrome are typically diagnosed incidentally in late childhood or early adulthood (see Tables 571.1 and 571.2).

PATHOGENESIS

The biochemical features of Gitelman syndrome resemble those of chronic use of thiazide diuretics. Thiazides act on the sodium chloride cotransporter NCCT, present in the distal convoluted tubule. Through linkage analysis and mutational studies, defects in the gene encoding NCCT have been demonstrated in patients with Gitelman syndrome.

CLINICAL MANIFESTATIONS

Patients with Gitelman syndrome typically present at a later age than those with Bartter syndrome and may have symptoms similar to older children with Bartter syndrome (see Chapter 571.1). Patients often have a history of salt craving, recurrent muscle cramps and spasms, presumably caused by low serum magnesium levels, nocturia, polyuria, and occasional hypotension. They usually do not have a history of recurrent episodes of dehydration. Biochemical abnormalities include hypokalemia, metabolic alkalosis, and hypomagnesemia. The urinary calcium level is usually very low (in contrast to the elevated urinary calcium level often seen in Bartter syndrome), and the urinary magnesium level is elevated. Renin and aldosterone levels are usually normal, and prostaglandin E secretion is not elevated. Growth failure is less prominent in Gitelman syndrome than in Bartter syndrome.

DIAGNOSIS

The diagnosis of Gitelman syndrome is suggested in an adolescent or adult presenting with hypokalemic hypochloremic metabolic alkalosis, hypomagnesemia, and hypocalciuria. The diagnosis is often made incidentally after hypokalemia is noted on bloodwork, spurring further evaluation.

TREATMENT

Therapy is directed at correcting hypokalemia and hypomagnesemia with supplemental potassium and magnesium. Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume

depletion or elevated prostaglandin E excretion. Recently, SGLT2 inhibitors have begun to be utilized in adults with refractory hypomagnesemia; however, further studies are needed to investigate their utility in the treatment of Gitelman syndrome.

571.3 Other Inherited Tubular Transport Abnormalities

Danielle E. Soranno and Bradley P. Dixon

Inherited abnormalities in distinct transporters in each segment of the nephron have now been identified and the molecular defects have been characterized. Renal tubular acidosis and nephrogenic diabetes insipidus are discussed in detail in Chapters 569 and 570, respectively. **Cystinuria** is an autosomal recessive disorder seen primarily in patients of Middle Eastern descent and is characterized by recurrent stone formation. The disease is caused by a defective high-affinity transporter for L-cystine and dibasic amino acids present in the proximal tubule; affected females form fewer stones than males. Treatment focuses on stone prevention via hydration, sodium restriction, urine alkalinization, and cystine-binding therapy.

Dent disease is an X-linked proximal tubulopathy with characteristic abnormalities that include low molecular weight proteinuria, hypercalciuria, and variably other features of Fanconi syndrome, such as glycosuria, aminoaciduria, and phosphaturia. Although some patients develop nephrocalcinosis, nephrolithiasis, progressive renal failure, and hypophosphatemic rickets, patients with Dent disease typically do not have proximal renal tubular acidosis or extrarenal manifestations. Loss-of-function pathogenic variants of *CLCN5,* which encodes a renal Cl^-/H^+ antiporter (ClC-5), are reported in ~50–60% of patients with Dent disease. The genetic heterogeneity of Dent disease in some patients who exhibit pathogenic variants in the gene for OCRL1 (responsible for Lowe syndrome) also meet the criteria for Dent disease (~15% of patients) called Dent 2 disease. Dent disease includes X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and idiopathic low molecular weight proteinuria seen in Japanese children.

Pathogenic variants in an extracellular basolateral calcium-sensing receptor, normally present in the loop of Henle, can cause a **dominant Bartter syndrome–like picture** (also known as Bartter syndrome type V). These patients' predominant symptoms are hypocalcemia and suppressed parathyroid hormone function, which differentiates them from patients with Bartter syndrome.

In the distal convoluted tubule, gain-of-function pathogenic variants in *WNK1* and loss-of-function pathogenic variants in *WNK4,* both serine threonine kinases, lead to excessive NCCT-mediated salt reabsorption with the clinical picture of pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension, or **Gordon syndrome**), including volume expansion with hypertension, hyperkalemia, hyperchloremic metabolic acidosis, and hypercalciuria. Due to the excessive activation of the thiazide-sensitive NCCT, this disorder can be effectively treated with thiazide diuretics.

In the collecting duct, gain-of-function pathogenic variants of the gene that encodes the epithelial sodium channel (ENaC) cause an inherited form of hypertension, **Liddle syndrome.** Patients with this disorder have constitutive sodium uptake in the collecting duct, with hypokalemia and suppressed aldosterone. Due to the excessive activation of ENaC, potassium-sparing diuretics (specifically amiloride) are an effective treatment for Liddle syndrome. Conversely, loss-of-function pathogenic variants cause **pseudohypoaldosteronism,** characterized by severe sodium wasting and hyperkalemia as well as a distal (type IV) RTA (also discussed in Chapter 569.3). A variant of the latter disorder is associated with systemic abnormalities, including defects in sweat chloride, and can resemble cystic fibrosis.

Renal hypouricemia, a defect in *SLC22A12,* presents with low serum uric acid levels and is complicated by exercise-induced acute kidney injury. Patients have elevated urine uric acid levels and present with loin pain, nausea, and vomiting after exercise. Treatment is for acute kidney injury and reducing the intensity of exercise.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 572 Renal Failure

572.1 Acute Kidney Injury

Prasad Devarajan

Acute kidney injury (AKI) has been traditionally defined as an abrupt loss of kidney function leading to a rapid decline in the glomerular filtration rate (GFR), accumulation of waste products such as blood urea nitrogen (BUN) and creatinine, and dysregulation of extracellular volume and electrolyte homeostasis. The term AKI has replaced acute renal failure (ARF); AKI embodies a continuum of renal dysfunction that ranges from a small increase in serum creatinine to complete anuric renal failure. The incidence of AKI varies from 5–10% of all hospitalizations to >25% in critically ill infants and children. The etiology of AKI varies widely according to age, geographic region, and clinical setting. Functional AKI induced by dehydration is usually reversible with early fluid therapy. However, the prognosis for patients with structural AKI in the intensive care setting with multiorgan failure remains guarded.

A classification system proposed by the Kidney Disease Improving Global Outcomes (KDIGO) AKI Consensus Conference takes both serum creatinine and urine output criteria into account to define and stage AKI (Table 572.1). Thus AKI is defined as

Increase in serum creatinine by ≥0.3 mg/dL from baseline within 48 hours, *or*

Increase in serum creatinine to ≥1.5 times baseline within the prior 7 days, *or*

Urine volume ≤0.5 mL/kg/hr for 6 hours

PATHOGENESIS

AKI has been conventionally classified into three categories: prerenal, intrinsic renal, and postrenal (Table 572.2 and Fig. 572.1).

Prerenal AKI, also called *prerenal azotemia,* is characterized by a diminished effective circulating arterial volume, which leads to inadequate kidney perfusion and a decreased GFR. Evidence of structural kidney damage is largely absent. Common causes of prerenal AKI include dehydration, sepsis, hemorrhage, severe hypoalbuminemia, and cardiac failure. If the underlying cause of the kidney hypoperfusion is reversed promptly, kidney function returns to normal. If hypoperfusion is sustained, intrinsic kidney parenchymal damage can develop.

Intrinsic renal AKI includes a variety of disorders characterized by kidney parenchymal damage, including sustained hypoperfusion and ischemia. Ischemic/hypoxic injury and nephrotoxic insults are the most common causes of intrinsic AKI in high-resource countries and are more common with an underlying comorbid condition; most are associated with cardiac, oncologic, urologic, kidney, and genetic disorders or prematurity (Table 572.3). Many forms of **glomerulonephritis,**

Table 572.1 Kidney Disease Improving Global Outcomes Staging of Acute Kidney Injury

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5-1.9 times baseline, OR ≥0.3 mg/dL increase	<0.5 mL/kg/hr for 6-12 hr
2	2.0-2.9 times baseline	<0.5 mL/kg/hr for ≥12 hr
3	3.0 times baseline, OR SCr ≥4.0 mg/dL, OR Initiation of renal replacement therapy, OR eGFR <35 mL/min per 1.73 m^2 (<18 yr)	<0.3 mL/kg/hr for ≥24 hr, OR Anuria for ≥12 hr

SCr, Serum creatinine; eGFR, estimated glomerular filtration rate.

Table 572.2 Common Causes of Acute Kidney Injury

PRERENAL
Dehydration (hypovolemia)
Gastroenteritis (hypovolemia)
Hemorrhage (hypovolemia)
Burns
Sepsis
Shock
Capillary leak/systemic inflammatory response syndrome
Hypoalbuminemia
Cirrhosis
Abdominal compartment syndrome
Cardiac failure
Anaphylaxis
INTRINSIC RENAL
Glomerulonephritis
Postinfectious/poststreptococcal
Lupus erythematosus
IgA vasculitis
Membranoproliferative
Anti–glomerular basement membrane
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Acute tubular necrosis
Cortical necrosis
Renal vein thrombosis
Infarction
Rhabdomyolysis
Acute interstitial nephritis
Tumor infiltration
Toxin and drugs (see Table 572.3)
Tumor lysis syndrome
Vasculitis
POSTRENAL
Posterior urethral valves
Ureteropelvic junction obstruction
Ureterovesical junction obstruction
Ureterocele
Tumors
Urolithiasis
Urethral strictures
Hemorrhagic cystitis (blood clots)
Neurogenic bladder
Anticholinergic drugs

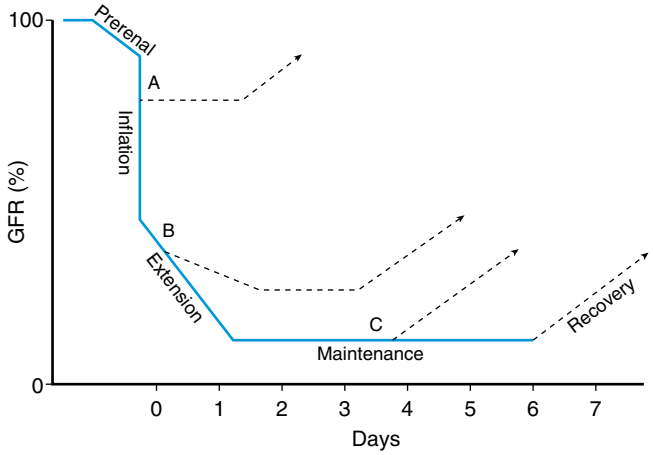

Fig. 572.1 Phases of acute kidney injury. GFR, Glomerular filtration rate. *(From Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. Kidney Int. 2002;62:1539–1549.)*

Table 572.3 Major Endogenous and Exogenous Toxins Causing Acute Tubular Injury

ENDOGENOUS TOXINS	EXOGENOUS TOXINS
MYOGLOBULINURIA	**ANTIBIOTICS**
Muscle breakdown: trauma, compression, electric shock, hypothermia, hyperthermia, seizures, exercise, burns	Aminoglycosides
Metabolic: hypokalemia, hypophosphatemia	Amphotericin B
Infections: tetanus, influenza	Antiviral agents: acyclovir, cidofovir, indinavir, foscarnet, tenofovir
Toxins: isopropyl alcohol, ethanol, ethylene glycol, toluene, snake and insect bites, cocaine, heroin	Pentamidine
Drugs: HMG-CoA reductase inhibitors (statins), amphetamines, fibrates	Piperacillin tazobactam**
Inherited disease: deficiency of myophosphorylase, phosphofructokinase, carnitine palmitoyltransferase	Vancomycin
Autoimmune: polymyositis, dermatomyositis	**CHEMOTHERAPY**
	Cisplatin
	CAR-T cell therapy*
	Ifosfamide
	Plicamycin
	5-Fluorouracil
	Cytarabine
	6-Thioguanine
	Methotrexate
	Immune checkpoint inhibitors
	CALCINEURIN INHIBITORS
	Cyclosporine
	Tacrolimus
HEMOGLOBINURIA	**ORGANIC SOLVENTS**
Mechanical: prosthetic valves, microangiopathic hemolytic anemia, extracorporeal circulation	Toluene
Drugs: hydralazine, methyldopa	Ethylene glycol
Chemicals: benzene, arsine, fava beans, glycerol, phenol	Mannitol
Immunologic: transfusion reaction	**POISONS**
Genetic: G6PD deficiency, PNH	Snake venom
	Paraquat
	MISCELLANEOUS
	Radiocontrast media
	Intravenous immune globulin
	ACE inhibitors
	Nonsteroidal antiinflammatory drugs
	Allopurinol
	Oral phosphate bowel preparations
	Synthetic cannabinoids
INTRATUBULAR OBSTRUCTION FROM CRYSTALLURIA OR PARAPROTEINS	
Tumor lysis syndrome	
HGPRT deficiency	
Multiple myeloma	
Oxalate (ethylene glycol)	

*Associated cytokine release syndrome, tumor lysis syndrome.
**Controversial
ACE, Angiotensin-converting enzyme; CAR-T, chimeric antigen receptor T cells; G6PD, glucose-6-phosphate dehydrogenase; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PNH, paroxysmal nocturnal hemoglobinuria.
Modified from Weisbord SD, Palevsky PM. Acute kidney injury. In: Yu AS, Chertow GM, Luyckx VA, et al, eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 29.3.

including postinfectious glomerulonephritis, lupus nephritis, IgA vasculitis nephritis (formerly Henoch-Schönlein purpura nephritis), membranoproliferative glomerulonephritis, and anti–glomerular basement membrane nephritis, can also cause intrinsic AKI. Severe and prolonged ischemic/hypoxic injury and nephrotoxic insult lead to **acute tubular**

necrosis (ATN), seen most often in critically ill infants and children. Mechanisms leading to ischemic AKI include hypotension/intravascular volume depletion (hemorrhage, third-space fluid losses, diarrhea), decreased effective intravascular volume (heart failure, cirrhosis, hepatorenal syndrome, peritonitis, abdominal compartment syndrome), vasodilation/vasoconstriction (sepsis, hepatorenal syndrome), renal artery obstruction (thrombosis, embolization, stenosis), intrarenal artery disease (vasculitis, hemolytic uremic syndrome [HUS], sickle cell anemia, transplant rejection), and impaired renal blood flow (cyclosporine, tacrolimus, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blocking agents, radiocontrast agents).

The typical pathologic feature of ATN is tubular cell necrosis, although significant histologic changes are not consistently seen in patients with clinical ATN. The mechanisms of injury in ATN can include alterations in intrarenal hemodynamics, tubular obstruction, and passive back leak of the glomerular filtrate across injured tubular cells into the peritubular capillaries.

Tumor lysis syndrome is a specific form of AKI related to spontaneous or chemotherapy-induced cell lysis in patients with lymphoproliferative malignancies. This disorder is primarily caused by obstruction of the tubules by uric acid crystals (see Chapters 544 and 545). **Acute interstitial nephritis** is another common cause of AKI and is usually a result of a hypersensitivity reaction to a therapeutic agent or various infectious agents (see Chapter 561.2).

Postrenal AKI includes a variety of disorders characterized by obstruction of the urinary tract. In neonates and infants, congenital conditions, such as posterior urethral valves and bilateral ureteropelvic junction obstruction, account for most cases of AKI. Other conditions, such as urolithiasis, tumor (intraabdominal lesion or within the urinary tract), hemorrhagic cystitis, and neurogenic bladder, can cause AKI in older children and adolescents. In a patient with two functioning kidneys, obstruction must be bilateral to result in AKI. Relief of the obstruction usually results in recovery of renal function, except in patients with associated renal dysplasia or prolonged urinary tract obstruction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A carefully taken history is critical in defining the cause of AKI. An infant with a three day history of vomiting and diarrhea most likely has prerenal AKI caused by volume depletion, but hemolytic-uremic syndrome (HUS) must also be a consideration. A 6-year-old child with a recent pharyngitis who presents with periorbital edema, hypertension, and gross hematuria most likely has intrinsic AKI related to acute postinfectious glomerulonephritis. A critically ill child with a history of protracted hypotension or with exposure to nephrotoxic medications most likely has ATN. A neonate with a history of hydronephrosis seen on prenatal ultrasound studies and a palpable bladder most likely has congenital urinary tract obstruction, probably related to posterior urethral valves.

The physical examination must be thorough, with careful attention to volume status. Tachycardia, dry mucous membranes, and poor peripheral perfusion suggest an inadequate circulating volume and the possibility of prerenal AKI. Hypertension, peripheral edema, rales, and a cardiac gallop suggest volume overload and the possibility of intrinsic AKI from glomerulonephritis or ATN. The presence of a rash and arthritis might indicate systemic lupus erythematosus (SLE) or IgA vasculitis nephritis. Palpable flank masses may be seen with renal vein thrombosis, tumors, cystic disease, or urinary tract obstruction.

LABORATORY FINDINGS

Laboratory abnormalities can include anemia (the anemia is usually dilutional or hemolytic, as in SLE, renal vein thrombosis, HUS); leukopenia (SLE, sepsis); thrombocytopenia (SLE, renal vein thrombosis, sepsis, HUS); hyponatremia (dilutional); metabolic acidosis; elevated serum concentrations of blood urea nitrogen (BUN), creatinine, uric acid, potassium, and phosphate (diminished kidney function); and hypocalcemia (hyperphosphatemia).

The serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis), and antibodies may be detected in the serum to streptococcal (poststreptococcal glomerulonephritis), nuclear (SLE), neutrophil cytoplasmic (granulomatosis with polyangiitis, microscopic polyarteritis), or glomerular basement membrane (Goodpasture disease) antigens.

The presence of hematuria, proteinuria, and red blood cell or granular urinary casts suggests intrinsic AKI, in particular glomerular disease and ATN. The presence of white blood cells and white blood cell casts with low-grade hematuria and proteinuria suggests tubulointerstitial disease. Urinary eosinophils may be present in some children with drug-induced tubulointerstitial nephritis.

Urinary indices may be useful in differentiating prerenal AKI from intrinsic AKI (Table 572.4). Patients whose urine shows an elevated specific gravity (>1.020), elevated urine osmolality (UOsm >500 mOsm/kg), low urine sodium (UNa <20 mEq/L), and fractional excretion of sodium <1% (<2.5% in neonates) most likely have prerenal AKI. Those with a specific gravity of <1.010, low urine osmolality (UOsm <350 mOsm/kg), high urine sodium (UNa >40 mEq/L), and fractional excretion of sodium >2% (>10% in neonates) most likely have intrinsic AKI.

Table 572.4 Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury

	HYPOVOLEMIA	ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	GLOMERULONEPHRITIS	OBSTRUCTION
Sediment	Bland, may have hyaline casts	Broad, brownish granular casts	White blood cells, eosinophils, cellular casts	Red blood cells, red blood cell casts	Bland or bloody
Protein	None or low	None or low	Minimal but may be increased with NSAIDs	Increased, >100 mg/dL	Low
Urine sodium (mEq/L)*	<20	>40	>30	<20	<20 (acute) >40 (few days)
Urine osmolality (mOsm/kg)	>400	<350	<350	>400	<350
Fractional excretion of sodium %†	<1	>2‡	Varies	<1	<1 (acute) >1 (few days)

*The sensitivity and specificity of urine sodium of <20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.
†Fractional excretion of sodium is the urine:plasma (U:P) ratio of sodium divided by U:P of creatinine × 100. The sensitivity and specificity of fractional excretion of sodium of <1% in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.
‡The fractional excretion of sodium may be <1% in acute tubular necrosis secondary to radiocontrast material or rhabdomyolysis.
NSAIDs, Nonsteroidal antiinflammatory drugs.
From Singri N, Ahya SN, Levin ML. Acute renal failure. *JAMA*. 2003;289:747–751.

Chest radiography may reveal cardiomegaly, pulmonary congestion (fluid overload), or pleural effusions. Renal ultrasonography can reveal hydronephrosis and/or hydroureter, which suggest urinary tract obstruction, or nephromegaly, consistent with intrinsic renal disease. Renal biopsy may ultimately be required to determine the precise cause of AKI in patients who do not have clearly defined prerenal or postrenal AKI.

Although serum creatinine is used to measure kidney function, it is an insensitive and delayed measure of decreased kidney function following AKI. Tissue inhibitor of metallopritinase-2 (TIMP2) and insulin-like growth factor binding protein-7 (IGFBP7) are biomarkers for early tubular injury and the risk for the development of AKI used mostly in critically ill adult patients.

TREATMENT

Medical Management

Complications of AKI are noted in Table 572.5. In infants and children with urinary tract obstruction, such as in a newborn with suspected posterior ureteral valves, a bladder catheter should be placed immediately to ensure adequate drainage of the urinary tract. The placement of a bladder catheter may also be considered in nonambulatory older children and adolescents to accurately monitor urine output during AKI; however, precautions to prevent iatrogenic infection should be taken.

Determination of the volume status is of critical importance when initially evaluating a patient with AKI. If there is no evidence of volume overload or cardiac failure, the intravascular volume should be expanded by intravenous (IV) administration of isotonic saline, 20 mL/kg over 30 minutes. In the absence of blood loss or hypoproteinemia, colloid-containing solutions are not required for volume expansion. Severe hypovolemia may require additional fluid boluses (see Chapters 74, 75, and 85). Determination of the central venous pressure may be helpful if adequacy of the blood volume is difficult to determine. After volume resuscitation, hypovolemic patients generally void within 2 hours; failure to do so suggests intrinsic or postrenal AKI. Hypotension caused by sepsis requires vigorous fluid resuscitation followed by a continuous infusion of vasopressors.

Diuretic therapy should be considered only after the adequacy of the circulating blood volume has been established. Furosemide (2-4 mg/kg) may be administered as a single IV dose. Bumetanide (0.1 mg/kg) may be given as an alternative to furosemide. If urine output is not improved, then a continuous diuretic infusion may be considered. To increase renal cortical blood flow, many clinicians administer dopamine (2-3 μg/kg/min) in conjunction with diuretic therapy, although no controlled data support this practice. *There is little evidence that diuretics or dopamine can prevent AKI or hasten recovery*. Mannitol may be effective in the prevention of pigment (myoglobin, hemoglobin)-induced renal failure. Atrial natriuretic peptide may be of value in preventing or treating AKI, although there is little pediatric evidence to support its use.

If there is no response to a diuretic challenge, diuretics should be discontinued and fluid restriction is essential. Patients with a relatively normal intravascular volume should initially be limited to 400 mL/m^2/24 hr (insensible losses) plus an amount of fluid equal to the urine output for that day. Extrarenal (blood, GI tract) fluid losses should be replaced, milliliter for milliliter, with appropriate fluids. Markedly hypervolemic patients can require further fluid restriction, omitting the replacement of insensible fluid losses, urine output, and extrarenal losses to diminish the expanded intravascular volume. Fluid intake, urine and stool output, body weight, and serum chemistries should be monitored daily.

In AKI, rapid development of **hyperkalemia** (serum potassium level >6 mEq/L) can lead to cardiac arrhythmia, cardiac arrest, and death. The earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves. This may be followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest (see Chapter 472.2). Procedures to deplete body potassium stores should be initiated when the serum potassium value rises to >6.0 mEq/L. Exogenous sources of potassium (dietary, IV fluids, total parenteral nutrition) should be eliminated. Sodium polystyrene sulfonate (SPS) resin (Kayexalate), 1 g/kg, should be given orally or by retention enema. This resin exchanges sodium for potassium and can take several hours to take effect. A single dose of 1 g/kg can be expected to lower the serum potassium level by about 1 mEq/L. Resin therapy may be repeated every 2 hours, the frequency being limited primarily by the risk of sodium overload.

More severe elevations in serum potassium (>7 mEq/L), especially if accompanied by electrocardiographic changes, require emergency measures in addition to Kayexalate. The following agents should be administered:

- Calcium gluconate 10% solution, 100 mg/kg/dose (maximum 3,000 mg/dose)
- Sodium bicarbonate, 1-2 mEq/kg IV, over 5-10 minutes
- Regular insulin, 0.1 units/kg, with glucose 50% solution, 1 mL/kg, over 1 hour

Calcium gluconate counteracts the potassium-induced increase in myocardial irritability but does not lower the serum potassium level. Administration of sodium bicarbonate, insulin, or glucose lowers the serum potassium level by shifting potassium from the extracellular to the intracellular compartment. A similar effect has been reported with the acute administration of β-adrenergic agonists in adults, but there are no controlled data in pediatric patients. Because the duration of action of these emergency measures is just a few hours, persistent hyperkalemia should be managed by dialysis.

Mild **metabolic acidosis** is common in AKI because of the retention of hydrogen ions, phosphate, and sulfate, but it rarely requires treatment. If acidosis is severe (arterial pH <7.15; serum bicarbonate <8 mEq/L) or contributes to significant hyperkalemia, treatment is indicated. The acidosis should be corrected partially by the IV route, generally by giving enough bicarbonate to raise the arterial pH to 7.20 (which approximates a serum bicarbonate level of 12 mEq/L). The remainder of the correction may be accomplished by oral administration of sodium bicarbonate after normalization of the serum calcium and phosphorus levels. Correction of metabolic acidosis with IV bicarbonate can precipitate tetany in patients with renal failure because rapid correction of acidosis reduces the ionized calcium concentration.

Hypocalcemia is primarily treated by lowering the serum phosphorus level. Calcium should not be given IV, except in cases of tetany, to avoid deposition of calcium salts into tissues. Patients should

Table 572.5 Common Complications of Acute Kidney Injury

METABOLIC	CARDIOPULMONARY	GASTROINTESTINAL	NEUROLOGIC	HEMATOLOGIC	INFECTIOUS	OTHER
Hyperkalemia Metabolic acidosis Hyponatremia Hypocalcemia Hyperphosphatemia Hypermagnesemia Hyperuricemia	Pulmonary edema Arrhythmias Pericarditis Pericardial effusion Hypertension Myocardial infarction Pulmonary embolism	Nausea Vomiting Malnutrition Hemorrhage	Neuromuscular irritability Asterixis Seizures Mental status changes	Anemia Bleeding	Pneumonia Septicemia Urinary tract infection	Hiccups Elevated parathyroid hormone level Low total triiodothyronine and thyroxine levels Normal thyroxine level

From Weisbord SD, Palevsky PM. Acute kidney injury. In: Yu AS, Chertow GM, Luyckx VA, et al, eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 29.6.

be instructed to follow a low-phosphorus diet, and phosphate binders should be orally administered to bind any ingested phosphate and increase the GI phosphate excretion. Common agents include sevelamer (Renagel), calcium carbonate (Tums tablets or Titralac suspension), and calcium acetate (PhosLo). Aluminum-based binders, commonly employed in the past, should be avoided because of the risk of aluminum toxicity.

Hyponatremia is most commonly a dilutional disturbance that must be corrected by fluid restriction rather than sodium chloride administration. Administration of hypertonic (3%) saline should be limited to patients with symptomatic hyponatremia (seizures, lethargy) or those with a serum sodium level <120 mEq/L. Acute correction of the serum sodium to 125 mEq/L (mmol/L) should be accomplished using the following formula:

$$\text{mEq sodium required} = 0.6 \times \text{weight in kg} \times (125 - \text{serum sodium in mEq/L}).$$

AKI patients are predisposed to **GI bleeding** because of uremic platelet dysfunction, increased stress, and heparin exposure if treated with hemodialysis (HD) or continuous renal replacement therapy (CRRT). Oral or IV H_2 blockers such as ranitidine are commonly administered to prevent this complication.

Hypertension can result from hyperreninemia associated with the primary disease process and/or expansion of the extracellular fluid volume and is most common in AKI patients with acute glomerulonephritis or HUS. Salt and water restriction is critical, and diuretic administration may be useful (see Chapter 494). Isradipine (0.05-0.15 mg/kg/dose, maximum dose 5 mg 4 times per day) may be administered for a relatively rapid reduction in blood pressure (BP). Longer-acting oral agents such as calcium channel blockers (amlodipine, 0.1-0.6 mg/kg/24 hr daily or divided twice daily) or β blockers (labetalol, 4-40 mg/kg/24 hr divided 2 or 3 times daily) may be helpful in maintaining control of the BP. Children with severe symptomatic hypertension (hypertensive urgency or emergency) should be treated with continuous infusions of nicardipine (0.5-5.0 μg/kg/min), sodium nitroprusside (0.5-10.0 μg/kg/min), labetalol (0.25-3.0 mg/kg/hr), or esmolol (150-300 μg/kg/min) and converted to intermittently dosed antihypertensives when more stable.

Neurologic symptoms in AKI can include headache, seizures, lethargy, and confusion (encephalopathy). Potential etiologic factors include hypertensive encephalopathy, hyponatremia, hypocalcemia, cerebral hemorrhage, cerebral vasculitis, and the uremic state. Benzodiazepines are the most effective agents in acutely controlling seizures, and subsequent therapy should be directed toward the precipitating cause.

The **anemia** of AKI is generally mild (hemoglobin 9-10 g/dL) and primarily results from volume expansion (hemodilution). Children with HUS, SLE, active bleeding, or prolonged AKI can require transfusion of packed red blood cells if their hemoglobin level falls below 7 g/dL. In hypervolemic patients, blood transfusion carries the risk of further volume expansion, which can precipitate hypertension, heart failure, and pulmonary edema. Slow (4- to 6-hour) transfusion with packed red blood cells (10 mL/kg) diminishes the risk of hypervolemia. The use of fresh, washed red blood cells minimizes the acute risk of hyperkalemia, and the chronic risk of sensitization if the patient becomes a future candidate for renal replacement therapy. In the presence of severe hypervolemia or hyperkalemia, blood transfusions are most safely administered during dialysis or ultrafiltration.

Nutrition is of critical importance in children who develop AKI. In most cases, sodium, potassium, and phosphorus should be restricted. Protein intake should be moderately restricted while maximizing the caloric intake to minimize the accumulation of nitrogenous wastes. In critically ill patients with AKI, parenteral hyperalimentation with essential amino acids should be considered.

Dialysis

Indications for dialysis in AKI include the following:

- Anuria/oliguria with fluid overload
- Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
- Persistent hyperkalemia
- Severe metabolic acidosis unresponsive to medical management
- Uremia (encephalopathy, pericarditis, neuropathy)
- Calcium:phosphorus imbalance, with hypocalcemic tetany that cannot be controlled by other measures

An additional important practical indication for dialysis is the inability to provide adequate nutritional intake because of the need for severe fluid restriction. In patients with AKI, dialysis support may be necessary for days or for up to 12 weeks. Many patients with AKI require dialysis support for 1-3 weeks. Table 572.6 lists the advantages and disadvantages of the three types of dialysis.

Intermittent HD is useful in patients with a relatively stable hemodynamic status. This highly efficient process accomplishes both fluid and electrolyte removal in sessions of 3-4 hours using a pump-driven extracorporeal circuit and large central venous catheter. Intermittent HD may be performed 3-7 times per week based on the patient's fluid and electrolyte balance.

Peritoneal dialysis (PD) is most employed in neonates and infants with AKI, although this modality may be used in children and adolescents of all ages. Hyperosmolar dialysate is infused into the peritoneal cavity via a surgically or percutaneously placed PD catheter. The fluid is allowed to dwell for 45-60 minutes and is then drained from the patient by gravity (manually or with the use of machine-driven cycling), accomplishing fluid and electrolyte removal. Cycles are repeated for 8-24 hours per day based on the patient's fluid and electrolyte balance. Anticoagulation is not necessary. PD is contraindicated in patients with significant abdominal pathology.

Continuous renal replacement therapy (CRRT) is useful in patients with an unstable hemodynamic status, increased intracranial pressure, cerebral edema, concomitant sepsis, or multiorgan failure (including

Table 572.6 Comparison of Peritoneal Dialysis, Intermittent Hemodialysis, and Continual Renal Replacement Therapy

	PD	IHD	CRRT
BENEFITS			
Fluid removal	+	++	++
Urea and creatinine clearance	+	++	+
Potassium clearance	++	++	+
Toxin clearance	+	++	+
COMPLICATIONS			
Abdominal pain	+	–	–
Bleeding	–	+	+
Dysequilibrium	–	+	–
Electrolyte imbalance	+	+	+
Need for heparinization	–	+	+/–
Hyperglycemia	+	–	–
Hypotension	+	++	+
Hypothermia	–	–	+
Central line infection	–	+	+
Inguinal or abdominal hernia	+	–	–
Peritonitis	+	–	–
Protein loss	+	–	–
Respiratory compromise	+	–	–
Vessel thrombosis	–	+	+

PD, Peritoneal dialysis; IHD, intermittent hemodialysis; CRRT, continual renal replacement therapy.
Adapted from Rogers MC. *Textbook of Pediatric Intensive Care*. Baltimore: Williams & Wilkins; 1992.

hepatic failure) in the intensive care setting. CRRT is an extracorporeal therapy in which fluid, electrolytes, and small- and medium-size solutes are continuously removed from the blood (24 hours/day) using a specialized pump-driven machine. Usually, a double-lumen catheter is placed into the internal jugular or femoral vein. The patient is then connected to the pump-driven CRRT circuit, which continuously passes the patient's blood across a highly permeable filter.

CRRT may be performed in three basic fashions. In continuous venovenous **hemofiltration**, a large volume of fluid is driven by systemic or pump-assisted pressure across the filter, bringing with it by *convection* other molecules, such as urea, creatinine, phosphorus, and uric acid. The blood volume is reconstituted by an IV infusion of a replacement fluid having a desirable electrolyte composition similar to that of blood. Continuous venovenous **HD** uses the principle of diffusion by circulating dialysate in a countercurrent direction on the ultrafiltrate side of the membrane. No replacement fluid is used. Continuous **hemodiafiltration** employs both replacement fluid and dialysate, offering the most effective solute removal of all forms of CRRT.

Table 572.6 compares the relative risks and benefits of the various renal replacement therapies. CRRT has similar outcomes for recovery of renal function when compared with intermittent HD.

PROGNOSIS

The mortality rate in children with AKI is variable and depends entirely on the nature of the underlying disease process rather than on the renal failure itself. Children with AKI caused by a kidney-limited condition such as postinfectious glomerulonephritis have a very low mortality rate (<1%); those with AKI related to multiorgan failure have a very high mortality rate (>50%).

The prognosis for recovery of kidney function depends on the disorder that precipitated AKI. Recovery is likely after AKI resulting from prerenal causes, ATN, acute interstitial nephritis, or tumor lysis syndrome. Complete recovery of renal function is unusual when AKI results from most types of rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis. Medical management may be necessary for a prolonged period to treat the sequelae of AKI, including chronic renal insufficiency, hypertension, renal tubular acidosis, and urinary concentrating defect.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

572.2 Chronic Kidney Disease

Donna J. Claes

Chronic kidney disease (CKD) is determined by the presence of kidney damage and level (or severity) of kidney function (GFR; Tables 572.7 and 572.8). **End-stage kidney disease (ESKD)** is an administrative term in the United States; it is used to define patients who are treated with dialysis or kidney transplantation and is a subset of patients with stage 5 CKD.

Table 572.7 Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

Patient has chronic kidney disease (CKD) if either of the following criteria are present:

1. Kidney damage for ≥3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by one or more of the following features:
   - Abnormalities in the composition of the blood or urine
   - Abnormalities in imaging tests
   - Abnormalities on kidney biopsy
2. GFR < 60 mL/min/1.73 m^2 for ≥3 mo, with or without the other signs of kidney damage described previously

GFR, Glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 572.8 Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)

STAGE	DESCRIPTION	GFR (ML/MIN/1.73 M²)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 or on dialysis

GFR, Glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

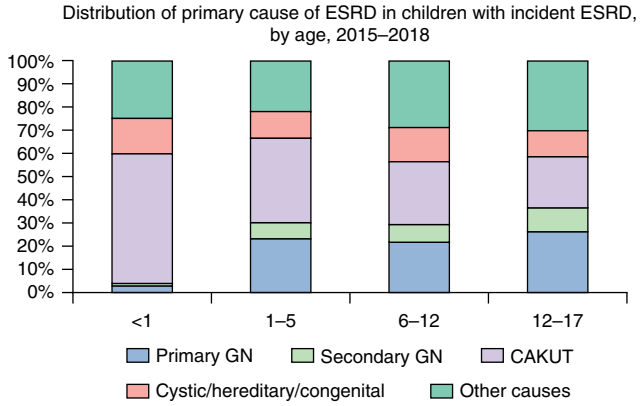

Fig. 572.2 Distribution of primary cause of end-stage renal disease (ESRD), by age, in incident pediatric dialysis patients reported to United States Renal Data System (USRDS) in 2016–2020. CAKUT, Congenital anomalies of the kidney and urinary tract; GN, glomerulonephritis. *(Adapted from the United States Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. Fig. 8.4. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/8-esrd-among-children-and-adolescents)*

Pediatric CKD prevalence is approximately 18 per 1 million children. The prognosis for the infant, child, or adolescent with CKD has improved secondary to improved medical management, dialysis techniques, and kidney transplantation. Childhood-onset ESKD still carries significant morbidity and a 30-fold increased mortality rate as compared with healthy peers.

ETIOLOGY

The etiology of pediatric CKD may be the result of congenital, acquired, inherited, or metabolic renal disease; however, the common etiology is having a reduction in nephron mass (Fig. 572.2). Causes of kidney disease in children are typically subdivided as being non-glomerular vs glomerular in origin (Table 572.9). The underlying cause correlates with the age at the time of diagnosis. **Congenital anomalies of the kidney and urinary tract** (CAKUT; i.e., renal hypoplasia, dysplasia, obstructive uropathy) are predominantly diagnosed in children less than 5 years of age; in many cases, CAKUT is diagnosed with prenatal ultrasonography. Cystic kidney disease (due to single gene pathogenic variants associated with cilia function, or ciliopathies) can be diagnosed prenatally, during childhood, or as a young adult depending on the underlying genetic variant and disease phenotype. After 5 years of age, acquired or inherited forms of glomerulonephritis predominate.

Table 572.9 Etiologies of Pediatric Chronic Kidney Disease

NONGLOMERULAR	GLOMERULAR
Aplastic, hypoplastic, and dysplastic kidneys	Chronic glomerulonephritis (including focal segmental glomerulonephritis [FSGS])
Cystinosis	Congenital nephrotic syndrome (CNS)
Medullary cystic kidney disease/ juvenile nephronophthisis	Hemolytic uremic syndrome (HUS)
Obstructive uropathy (e.g., PUV, cloaca, neurogenic bladder)	Idiopathic crescentic glomerulonephritis
Oxalosis	IgA nephritis
Autosomal dominant and autosomal recessive polycystic kidney disease (ADPKD, ARPDK)	IgA nephropathy (IGAN)
Pyelonephritis/interstitial nephritis/reflux nephropathy	Membranoproliferative glomerulonephritis (MPGN)
Renal infarct	Membranous nephropathy
Syndrome of agenesis of abdominal musculature (Eagle-Barrett syndrome)	Sickle cell nephropathy
Wilms tumor	Systemic immunologic disease (e.g., SLE, granulomatosis with polyangiitis)
	Hereditary nephritis (Alport syndrome)

PUV, Posterior urethral valve; SLE, systemic lupus erythematosus.

PATHOGENESIS

In addition to progressive injury with ongoing structural or metabolic genetic diseases, renal injury can progress despite removal of the original insult.

Hyperfiltration injury may be an important final common pathway of glomerular destruction, independent of the underlying cause of renal injury. As nephrons are lost, the remaining nephrons undergo structural and functional hypertrophy characterized by an increase in glomerular blood flow. The driving force for glomerular filtration is thereby increased in the surviving nephrons. Although this compensatory hyperfiltration temporarily preserves total renal function, it can cause progressive damage to the surviving glomeruli, possibly by a direct effect of the elevated hydrostatic pressure on the integrity of the capillary wall and/or the toxic effect of increased protein traffic across the capillary wall. Over time, the remaining nephrons suffer an increased excretory burden, resulting in a vicious cycle of increasing glomerular blood flow and hyperfiltration injury.

Other pathologic etiologies of CKD include proteinuria, hypertension, hyperphosphatemia, and hyperlipidemia. **Proteinuria**, secondary to either damage to the glomerular capillary wall and/or decreased tubular reabsorption, contributes to renal functional decline. Proteinuria can exert a direct toxic effect on tubular cells and initiate many inflammatory and pro-fibrotic cellular pathways that recruit monocytes and macrophages, enhancing the process of glomerular sclerosis and tubulointerstitial fibrosis. Podocyte injury can also result from proteinuria, although the mechanism is less understood. Uncontrolled **hypertension** can exacerbate disease progression by causing arteriolar nephrosclerosis and by increasing the hyperfiltration injury. **Hyperphosphatemia** can increase progression of disease by leading to calcium phosphate deposition in the renal interstitium and blood vessels. **Hyperlipidemia,** a common condition in CKD patients, can adversely affect glomerular function through oxidant-mediated injury.

CKD is viewed as a continuum of disease, with increasing biochemical and clinical manifestations as renal function deteriorates (Fig. 572.3). Regardless of etiology, the progression of tubulointerstitial fibrosis is the primary determinant of CKD progression.

CLINICAL MANIFESTATIONS

Table 572.10 outlines the pathophysiologic manifestations of CKD. The clinical presentation of CKD is varied and depends on the underlying etiology and CKD stage (Fig. 572.4). CAKUT and some genetic forms of renal disease (i.e., familial nephronophthisis) demonstrate growth failure, vomiting, and polyuria with associated polydipsia. Patients with cystic kidney disease due to a ciliopathy can have a wide range of extrarenal anomalies of the kidneys, liver, pancreas, skeletal system, eyes, central nervous system, and/or cardiac system that can assist with disease diagnosis. Urinary tract infection can also be common in those with urologic abnormalities. Glomerular forms of CKD often present with edema, hypertension, hematuria, and proteinuria; in severe forms of glomerulonephritis, malnutrition can be seen. As renal deterioration advances in severity, patients can develop uremic symptoms (i.e., worsening fatigue, weakness, nausea, vomiting, anorexia, and poor sleep patterns) and edema, hypertension, and other findings of fluid overload, regardless of CKD etiology.

Physical examination in CKD should focus on overall growth and development, with special attention and/or evaluation of BP, as well as the skin (pallor) and the extremities (edema; bony abnormalities of rickets seen in untreated renal osteodystrophy).

LABORATORY FINDINGS

Laboratory findings can include elevations in BUN and serum creatinine in addition to hyperkalemia, hyponatremia (secondary to either renal salt wasting vs volume overload), hypernatremia (loss of free water), acidosis, hypocalcemia, hyperphosphatemia, and an elevation in uric acid. Patients with heavy proteinuria can have hypoalbuminemia. A complete blood cell count may show a normochromic, normocytic anemia. Dyslipidemia is commonly seen. In children with glomerulonephritis, the urinalysis (UA) shows hematuria and proteinuria, whereas, in children with congenital lesions such as renal dysplasia, the UA often has a low specific gravity with minimal other abnormalities.

Renal function can be measured or estimated by GFR. Inulin clearance is the gold standard to measure GFR, but it is no longer readily available. Other methods to measure GFR in clinical practice include using iohexol or various radioisotopes (^{99m}Tc-DTPA, ^{51}Cr-EDTA, or ^{125}Iothalamate). However, estimating GFR by endogenous markers (such as creatinine and/or cystatin C) is the most utilized method to understand severity of renal disease. A "bedside" creatinine-based estimating equation [estimated GFR (mL/min/1.73 m^2) = 0.413 × height (cm)/serum creatinine (mg/dL)] has been validated in a pediatric CKD population of children age 1-16 years whose GFR was between 15 and 90 mL/min/1.73 m^2; however, this formula has less accuracy in the very young (<5 years of age) and young adults (18-25 years of age). Newer estimation formulas ("Chronic Kidney Disease in Children [CKID] study under 25," or U25) have been developed that allow for age- and gender-based corrections of creatinine and cystatin C with improved accuracy of GFR estimation. Although these newer formulas are more complex in regard to the mathematical corrections of age and gender for both creatinine and cystatin C, they are accessible by an online calculator, which allows for ease in their clinical use.

TREATMENT/MANAGEMENT

CKD treatment is supportive, with an aim to screen for and treat various metabolic complications of CKD in hopes of improving quality of life and potentially slowing the progression of renal dysfunction. Children with CKD should be treated at a pediatric center capable of supplying multidisciplinary services, including medical, nursing, social service, nutritional, and psychologic support.

CKD management requires close monitoring of blood studies, urine studies (including quantitative measurement for proteinuria using either a spot urine protein/urine creatinine ratio or 24-hour urine collection), and overall clinical symptomatology. Ambulatory blood pressure monitoring (ABPM) over 24 hours, the gold standard of BP evaluation, is recommended in patients with renal disease to diagnose and treat hypertension, especially masked hypertension. **Masked hypertension** (defined as a normal office BP but abnormal ABPM) is seen in up to 35% of pediatric predialysis CKD patients and carries a fourfold increased risk of having left ventricular hypertrophy (LVH).

Nutrition

Nutritional management by a dietician experienced in pediatric renal patients is recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Patients should

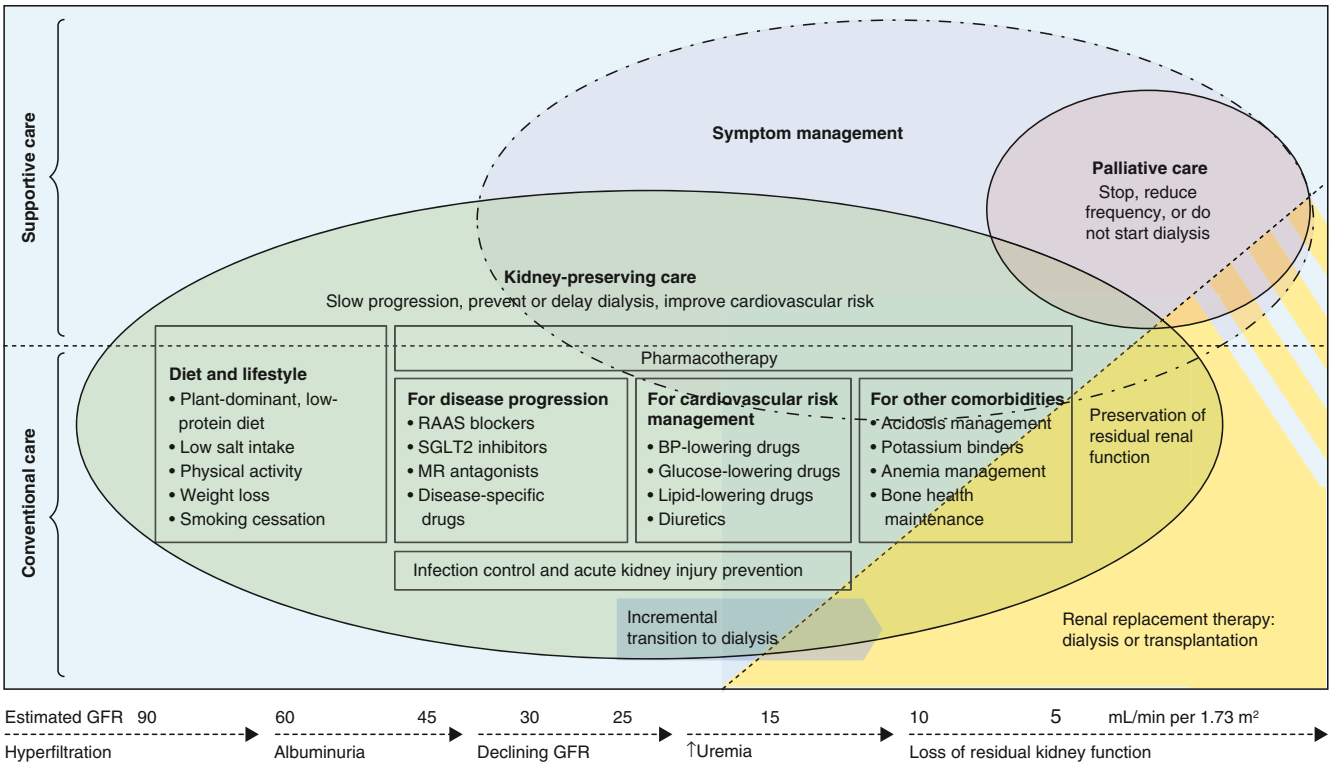

Fig. 572.3 Conservative and preservative management of chronic kidney disease without dialysis or renal transplantation. This chart highlights the role of preservative management and its goals *(green domain)* within the overall conservative management of chronic kidney disease without dialysis *(blue zone)*, juxtaposing renal replacement therapy including dialysis and kidney transplantation *(yellow zone)*. The X-axis (showing chronic kidney disease progression) should be read exclusively from left to right. The bottom half of the chart represents conventional (life-prolonging and kidney-prolonging) strategies, whereas the top half represents supportive care, including palliative and hospice care, in which dialysis is often avoided or withdrawn *(violet domain)*. The *oblique dotted line* between the two main zones (conservative management vs renal replacement therapy) suggests that there is variability in transitioning to dialysis therapy (moving from bottom left to top right), including timing (early vs late vs never), level of care (life-prolonging vs supportive care), and type of dialysis (conventional vs incremental). The symptom management *(purple)* domain provides wide ranges of interventions to encompass the goals of care under both kidney-preserving care and palliative and hospice care. Preservative management can preserve residual kidney function for longer, especially after incremental transition to dialysis. BP, Blood pressure; GFR, glomerular filtration rate; MR, mineralocorticoid receptor; RAAS, renin-angiotensin-aldosterone system. *(From Kalantar-Zadeh K, Jafar TH, Nitsch D, et al. Chronic kidney disease. Lancet. 2021;398:786–798. Fig. 1, p. 787.)*

receive 100% of estimated energy requirement for age, individually adjusted for physical activity level, body mass index, and response in the rate of weight gain or loss. When oral supplemental nutrition with increased calories or fluid volume is insufficient, tube feeding (by nasogastric tubes or gastrostomy tubes) should be considered. Calories should be balanced between carbohydrate, unsaturated fat in physiologic ranges (per dietary reference intake [DRI]), and protein. Dietary protein restriction is not suggested for children with CKD because of the concern about adverse effects on growth and development; in fact, recommended protein intake is often 100% (or more for those receiving dialysis) of the DRI for ideal weight for children. Children with CKD stages 2-5 should receive 100% of DRI of vitamins and trace elements; water-soluble vitamin supplements are often required for patients receiving dialysis.

CKD Mineral and Bone Disorder (CKD-MBD)

CKD is characterized by systemic disorders of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism that can lead to bone disorders (**renal osteodystrophy**) but also *vascular and soft tissue calcification* (Fig. 572.5). Efforts have focused on the role of the hormone fibroblast growth factor 23 (FGF-23) and its cofactor, Klotho, in CKD-mineral and bone disorder (MBD). Elevated FGF-23 results in increased urinary phosphate excretion and suppression of 1-α-hydroxylase activity, leading to reduced 1,25-dihydroxycholecalciferol ($1,25OH_2D$) values and increased PTH secretion. Elevated FGF-23 is the first sign of altered osteocyte function in pediatric and adult CKD, is seen as early as CKD stage 2 (GFR 60-90 mL/min/1.73 m^2), and occurs despite normal calcium, phosphorus, PTH, and $1,25OH_2D$ levels. With continued loss of renal function, further FGF-23 elevation results in the development of secondary hyperparathyroidism (low $1,25OH_2D$ with hypocalcemia, hyperphosphatemia, and elevated PTH values).

Renal osteodystrophy is characterized by abnormalities in *bone turnover* (high vs low), *mineralization,* and *bone volume.* High-turnover bone disease, or **osteitis fibrosa cystica**, is the most common condition seen in advanced pediatric CKD, with characteristic laboratory (hypocalcemia, hyperphosphatemia, and elevated alkaline phosphatase and PTH values) and radiographic (subperiosteal bone resorption, metaphyseal widening) findings. Clinical manifestations may include bone pain, fractures with minor trauma, and various bony abnormalities (rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses [SCFE]). In contrast, low-turnover bone disease **(adynamic renal osteodystrophy)** is associated with PTH over-suppression, hypercalcemia, and low alkaline phosphatase activity; it is more commonly seen in pediatric dialysis patients receiving treatment for secondary hyperparathyroidism. Defective bone mineralization occurs in states of either high bone turnover (mixed lesion) or low to normal bone turnover (osteomalacia). In terms of bone volume, most pediatric CKD patients have normal to high bone volume on bone histomorphometry unless they were exposed to prolonged corticosteroid use.

Vascular calcification in CKD-MBD typically occurs within the vascular media, which is in contrast to the atherosclerotic plaques that form within the vascular intima in patients with traditional cardiovascular risk factors (hypertension, diabetes/obesity, cigarette smoking,

Table 572.10 Pathophysiology of Chronic Kidney Disease

MANIFESTATION	MECHANISMS
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol ($1,25OH_2D$) Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron, folate, and/or vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Decreased academic achievement, attention regulation, or executive functioning	Hypertension Low birth weight
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity Abnormal HDL-C
Cardiomyopathy	Hypertension Anemia Fluid overload
Glucose intolerance	Tissue insulin resistance

HDL-C, High-density lipoprotein cholesterol.

and dyslipidemia). Vascular calcification in CKD has been associated with hypercalcemia, hyperphosphatemia, and an elevated calcium-phosphorus product ($Ca \times PO_4$); yet, studies of adult and pediatric patients with mild to moderate CKD have noted findings of vascular calcification despite normal serum calcium and phosphorus values. The cause of vascular calcification in CKD is not completely understood and is being actively studied. The proposed pathophysiologic etiology involves the transition of vascular smooth muscle cells to osteoblast-like cells in response to trigger(s) that are currently unknown.

Treatment for CKD-MBD is guided by clinical assessment of calcium, phosphorus, 25OH vitamin D, and PTH. The goals of treatment are to normalize mineral metabolism with the goal of improving growth, reducing bone deformities and fragility, and reducing vascular and other soft tissue calcification. This is typically accomplished with reduced phosphorus intake, normalization of 25OH vitamin D, and use of active vitamin D sterols.

CKD patients of all ages should typically follow a low-phosphorus diet with the goal to maintain age-appropriate serum phosphorus values. Infants should be provided with a low-phosphorus formula (Similac PM 60/40). **Phosphate binders** (given with meals) are used to enhance GI phosphate excretion, and at present are recommended to be started at the onset of hyperphosphatemia. Phosphate binders should be adjusted to maintain normal serum calcium and phosphorus levels and to ensure that the recommended total daily intake of calcium is not exceeded. Phosphate binders can be either calcium based (calcium carbonate, calcium acetate) or non–calcium based (sevelamer). Because aluminum may be absorbed from the GI tract and can lead to aluminum toxicity (manifested by anemia, various bony abnormalities, and neurologic abnormalities including seizures), aluminum-based binders should be avoided.

Correcting 25OH vitamin D insufficiency can delay the onset of secondary hyperparathyroidism in predialysis CKD patients and improves bone mineralization. 25OH vitamin D provides a substrate for the formation of $1,25OH_2D$ and has been shown to directly suppress PTH production at the level of the parathyroid gland. U.S.-based pediatric CKD treatment guidelines define 25OH vitamin D sufficiency as a serum value of ≥30 ng/mL; **ergocalciferol** or **cholecalciferol** are typically recommended to treat insufficient 25OH vitamin D.

Active vitamin D sterols have been traditionally indicated when (1) $1,25OH_2D$ levels fall below the established goal range for the child's particular stage of CKD, (2) PTH levels increase above the established goal range for CKD stage (after correcting for insufficient 25OH vitamin D), or (3) patients have elevated PTH levels and hypocalcemia. Vitamin D sterols increase calcium and phosphorus absorption from the GI tract and are effective in reducing PTH values. Calcitriol is the most well-known and studied active vitamin D sterol; other agents such as paricalcitol and doxercalciferol have less intestinal calcium and phosphorus reabsorption and are used in CKD patients predisposed to hypercalcemia. The ideal PTH target to initiate and monitor active vitamin D sterol therapy is debated, particularly in the predialysis CKD population.

Fluid and Electrolyte Management

Infants and children with renal dysplasia may be polyuric with significant urinary sodium and free water losses. These children benefit from high-volume, low-caloric-density feedings with sodium supplementation. Children with high BP or edema benefit from sodium restriction and diuretic therapy. Fluid restriction is necessary in severe cases of nephrotic syndrome or when renal function worsens to the point of requiring dialysis.

Hyperkalemia can develop with severe deterioration in renal function, as well as in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, or hyporeninemic hypoaldosteronism (related to destruction of the renin-secreting juxtaglomerular apparatus). Hyperkalemia may be treated by restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or use of **cation exchange resins**. The most commonly utilized cation exchange resin, SPS (Kayexalate) has many severe adverse drug events, including but not limited to GI abnormalities (including intestinal necrosis), hypernatremia, hypocalcemia, and hypomagnesemia, that can limit its use or result in significant morbidity. Newer cation exchange resins (such as sodium zirconium cyclosilicate and patiromer) are more selective for potassium ion exchange and have a more favorable side effect profile compared with SPS. Patiromer is approved for ages ≥12 years in the United States, and sodium cyclosilicate is currently approved for adults; pediatric studies are ongoing.

Metabolic acidosis develops as a result of decreased net acid excretion by the failing kidneys. Either Bicitra (1 mEq sodium citrate/mL) or sodium bicarbonate tablets (650 mg = 7.7 mEq of sodium and 7.7 mEq of bicarbonate) may be used to maintain the serum bicarbonate level ≥22 mEq/L.

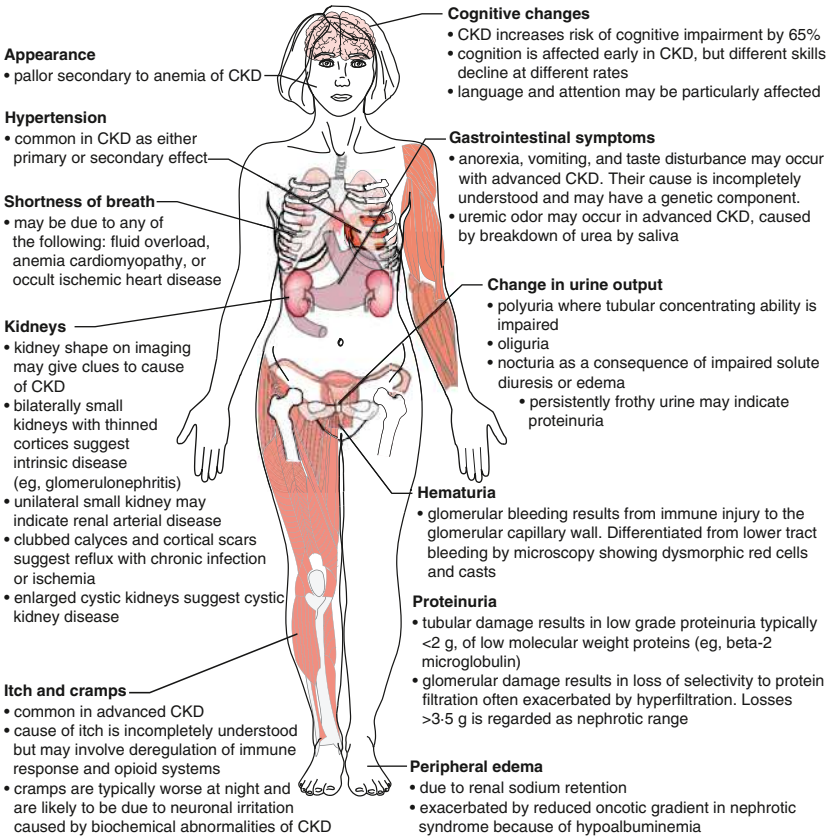

Fig. 572.4 Symptoms and signs of CKD. *(From Webster AC, Navler EV, Morton RL, et al. Chronic kidney disease. Lancet. 2017;389:1238–1252. Fig. 2.)*

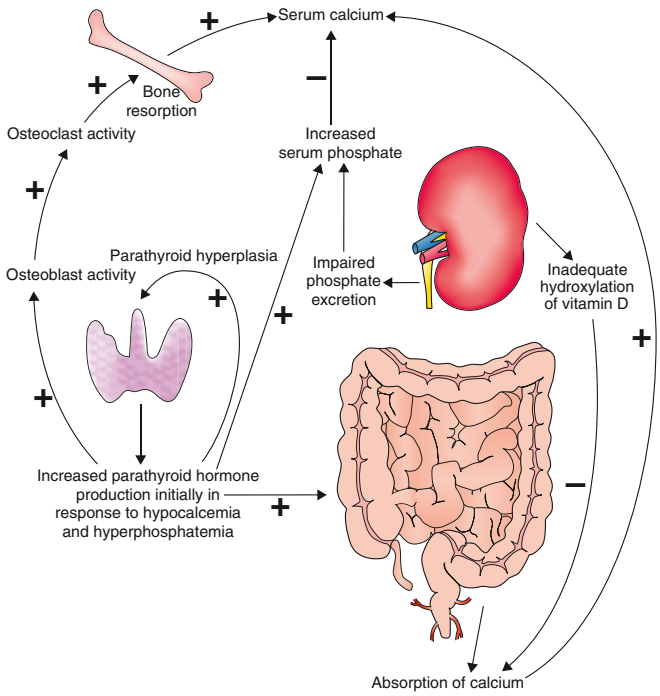

Fig. 572.5 Pathophysiology of CKD mineral bone disease. *(From Webster AC, Navler EV, Morton RL, et al. Chronic kidney disease. Lancet. 2017;389:1238–1252. Fig. 4.)*

Linear Growth

Short stature is a significant long-term sequela of childhood CKD. CKD results in an apparent growth hormone–resistant state, with elevated growth hormone levels but decreased insulin-like growth factor-1 levels and abnormalities of insulin-like growth factor–binding proteins.

Children with CKD who remain less than −2 SD for height and/or have a growth velocity of <25% over a minimum of 6 months despite optimal medical support (adequate caloric intake and effective treatment of renal osteodystrophy, anemia, and metabolic acidosis) may benefit from treatment with recombinant human growth hormone (rHuGH). rHuGH is given by daily, subcutaneous injections and continues until the patient reaches the 50th percentile for mid-parental height, achieves a final adult height, or undergoes kidney transplantation (with the caveat that rHuGH can be restarted 1 year after kidney transplantation if there are concerns for ongoing short stature despite kidney transplantation). Long-term rHuGH treatment significantly improves final adult height and induces persistent catch-up growth; some patients are able to achieve normal adult height.

Anemia

Anemia in patients with CKD is primarily the result of inadequate erythropoietin production by the peritubular interstitial cells of the kidneys and typically manifests when renal function falls below 40 mL/min/1.73 m^2. Other contributory factors for anemia in CKD include iron, folic acid, and/or vitamin B_{12} deficiency, and decreased erythrocyte survival secondary to uremia.

Anemia in pediatric CKD patients is defined when the hemoglobin falls to <5% for age and gender; alternatively, anemia can also be defined when the hemoglobin falls to <11g/dL (ages 0.5-5 years of age), <11.5 g/dL (5-12 years of age), <12 g/dL (females >12 years of age, males 12-15 years of age), and <13 g/dL (males >15 years of age). Once anemia is diagnosed, the recommendation is to investigate for deficiencies in iron and/or other vitamins (i.e., vitamin B_{12}, folate). Iron supplementation (oral or IV) is recommended for patients who demonstrate a transferrin saturation (TSAT) ≤20% and ferritin ≤100 ng/mL.

Erythropoiesis-stimulating agents (ESAs) have decreased the need for transfusions in CKD patients, especially those receiving HD. Erythropoietin and darbepoetin alfa are commonly prescribed ESAs. All patients receiving ESA therapy should be provided with either oral or IV iron supplementation. Patients who appear to be resistant to ESA should be evaluated for iron deficiency, occult blood loss, a chronic infection or inflammatory state, vitamin B_{12} or folate deficiency, or bone marrow fibrosis related to secondary hyperparathyroidism.

Emerging therapies for anemia of CKD are being directed toward the hypoxia-inducible signaling factor (HIF) pathway. HIF stabilizers prevent degradation of the HIF alpha subunit and allow for erythropoietin production. These agents are currently being studied for clinical use in adult CKD patients.

Hypertension and Proteinuria

Hypertension in pediatric CKD can be secondary to volume overload and/or excessive renin production due to glomerular disease. Both hypertension and proteinuria have been independently associated with more rapid CKD progression in various pediatric CKD observational studies. The ESCAPE trial demonstrated that more aggressive BP control delays CKD progression. In this study, participants with 24-hour mean arterial pressure (MAP) <50th percentile for age and sex by ABPM had a 35% lower risk of reaching the composite outcome (doubling of serum creatinine, estimated GFR (eGFR) of <10 mL/min/1.73 m^2, or need for dialysis or kidney transplant) compared with those randomized to a conventional BP target (MAP of 50–95% by ABPM); this effect was more notable in those with significant proteinuria.

Therapy for hypertension involves both dietary interventions and often pharmacologic agents. **Dietary sodium restriction** (<2 g of sodium/24 hr) and lifestyle modifications that promote achieving a healthy weight are both important aspects of achieving good BP control. Treatment guidelines recommend initiating pharmacologic antihypertensive therapy when systolic or diastolic BPs are >90% for age, gender, and height. Once therapy is started, it is recommended to titrate medications to achieve a systolic and diastolic BP <50% for age, gender, and height, especially in those patients with proteinuria. **ACE inhibitors** (such as enalapril, lisinopril) and **angiotensin II receptor blockers** (ARBs; such as losartan) are the antihypertensive medications of choice in all children with pediatric CKD, irrespective of the level of proteinuric renal disease, because of their potential ability to slow CKD and their superiority in controlling BP as noted in various observational and research studies. It is important to closely monitor renal function and electrolyte balance while using ACE inhibitors or ARBs, particularly in those with advanced CKD. **Thiazide** (hydrochlorothiazide, chlorothiazide, metolazone, and chlorthalidone) or **loop diuretics** (furosemide) can be helpful to control hypertension related to salt and fluid retention. Historical guidelines recommend the cessation of thiazide diuretics when a patient's eGFR falls below 30 mL/min/1.73 m^2 due to concerns of decreased efficacy; however, many adult studies support continued thiazide use either alone or in conjunction with loop diuretics for BP control in advanced (non-ESKD) CKD. Calcium channel blockers (amlodipine), β blockers (propranolol, atenolol), and centrally acting agents (clonidine) may be useful as adjunctive agents in children with CKD whose BP cannot be controlled using dietary sodium restriction, ACE inhibitors, and diuretics.

Immunizations

Children with CKD should receive all standard immunizations according to the schedule used for healthy children, with an exception to withhold live virus vaccines (such as measles, mumps, rubella, varicella) from those receiving immunosuppressive medications (i.e., kidney transplant recipients, and in some patients with glomerulonephritis). It is critical to make every attempt to administer live virus vaccines before kidney transplantation. All children with CKD should receive a yearly influenza vaccine; children with CKD are also eligible for pneumococcal vaccination with PPSV-23. Data from a number of studies suggest that children with CKD might respond suboptimally to immunizations.

Adjustment in Drug Dose

Drugs excreted by the kidneys may need to be dose adjusted in CKD patients to maximize effectiveness and minimize the risk of toxicity. Strategies in dosage adjustment include lengthening of the interval between doses, decreasing the absolute dose, or both.

Progression of Disease

The timing of CKD progression from minimal renal injury to onset of ESKD is variable. The median loss of GFR in children enrolled in the CKID study is 1.5 (non-glomerular CKD etiology) vs 4.3 (glomerular CKD etiology) mL/min/1.73 m^2/year. Nonmodifiable risk factors associated with more rapid CKD progression include older age, glomerular etiology of renal disease, CKD severity, and onset of puberty. In terms of potential modifiable risk factors, in addition to elevated BP, persistent nephrotic range proteinuria, anemia, dyslipidemia, and no ACE inhibitor/ARB use were important predictors of CKD progression.

In addition to addressing and treating the risk factors as noted previously, prompt treatment of infectious complications (especially urinary tract infection [UTI]) and episodes of dehydration can minimize additional loss of renal parenchyma. Other potentially beneficial recommendations include tobacco avoidance; prevention of obesity; and avoidance of potential nephrotoxic medications, which includes over-the-counter medications (such as nonsteroidal antiinflammatory medicines), pharmacologic agents, various illegal street drugs, and herbal and/or homeopathic medications or supplements.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

572.3 End-Stage Kidney Disease

Donna J. Claes

Kidney failure, also termed end-stage kidney disease (ESKD), represents the state in which a patient's kidney dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained despite maximal medical management. At this point, kidney replacement therapy (KRT; which is either dialysis or kidney transplantation) becomes necessary. The ultimate goal for children with ESKD is successful kidney transplantation (see Chapter 573) because it provides the most normal lifestyle and improved mortality and morbidity.

In the United States, 75% of children with ESKD require dialysis before transplantation. It is recommended discussions and plans for eventual KRT be initiated when a child reaches stage 4 CKD (GFR <30 mL/min/1.73 m^2). Indications for initiating maintenance dialysis include diuretic-resistant fluid overload, severe fluid restrictions that inhibit the ability to provide appropriate nutrition sufficient for linear growth, uncontrolled electrolyte abnormalities (hyperkalemia, hyperphosphatemia, metabolic acidosis), and subjective findings of uremia (fatigue, weakness, nausea, vomiting, anorexia, and poor sleep patterns), especially if these symptoms are negatively affecting academic performance. Although dialysis initiation should be considered as the GFR approaches 10-15 mL/min/1.73m^2, multiple adult and pediatric studies have indicated increased risk of mortality in those who start dialysis with a higher GFR compared to a lower GFR. Thus it is recommended to maximize medical management of CKD for as long as possible until concerns of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms make medical management unsafe and/or impossible. Dialysis modality selection must be individualized to fit the needs of each child.

In the United States, peritoneal dialysis (PD) is still the most utilized dialysis modality (55.7%) compared to hemodialysis (44.3%); however, there is a temporal trend toward greater use of hemodialysis (HD) as the initial maintenance dialysis therapy. Age is a defining factor in dialysis modality selection: 85% of infants and children from birth to 5 years of age initiate maintenance dialysis treatment using PD, whereas 50% of children ≥13 years of age initiate maintenance dialysis treatment with HD.

Peritoneal dialysis utilizes the patient's peritoneal membrane to transport fluid and solutes. Excess body water is removed by an osmotic gradient created by the relatively high dextrose concentration in the dialysis fluid; wastes are removed by diffusion from the peritoneal capillaries into the dialysis fluid. Access to the peritoneal cavity is achieved by a surgically inserted tunneled catheter. PD may be provided either as continuous ambulatory peritoneal dialysis (CAPD) or as an automated therapy using a cycler (APD), which allows exchanges of peritoneal fluid to be performed automatically during sleep by a cycler machine. APD is the PD modality of choice in countries without cost restraints. Cycler-driven PD therapy allows the child and family an

uninterrupted day of activities (including decreased school interruption), a reduction in the number of dialysis catheter connections and disconnections (which decreases the risk of peritonitis), often less strict fluid and dietary restrictions, and a reduction in the time required by patients and parents to perform dialysis, reducing the risk of caregiver fatigue and burnout. Because PD is not as efficient as HD, it must often be performed 6-7 days per week. Contraindications to PD use include anatomic abnormalities (e.g., significant surgical adhesions, omphalocele, gastroschisis, or bladder exstrophy), peritoneal injury (including injury secondary to previous severe peritoneal infections), or lack of an appropriate caregiver who can reliably perform PD in the home.

Hemodialysis, unlike PD, is usually performed in a hospital or outpatient clinic setting; home pediatric HD programs or programs that provide intensified HD are available but uncommon. Access to the child's circulation is achieved by a surgically created arteriovenous fistula (AVF), arteriovenous graft (AVG), or tunneled dual lumen catheter. The internal jugular vein is the preferred catheter site because indwelling subclavian catheters can cause subclavian stenosis that limits that ability to utilize future AVF and AVG in the ipsilateral arm. Each HD treatment is typically prescribed to provide appropriate solute clearance and fluid removal. HD has historically been provided 3 times per week; however, more frequent dialysis treatments (up to 4-5 times per week) are seen in the United States. Intensified HD programs (such as short daily HD, intermittent nocturnal HD, and daily nocturnal HD) have demonstrated improved control of BP, fluid overload, phosphorus, anemia, and improved growth. Contraindications to HD include inadequate vascular access.

Pediatric patients on dialysis have a death rate 30 times higher than the general pediatric population, with cardiovascular disease and infections as the leading causes of mortality. Dialysis-associated infections (peritonitis, HD-related bloodstream infections) are also the leading causes of hospitalization in pediatric dialysis patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 573

Renal Transplantation

David K. Hooper and Charles D. Varnell Jr.

Kidney transplantation is the optimal therapy for children with end-stage kidney disease (ESKD). The life expectancy in children who receive a kidney transplant has steadily increased and is substantially better than for those who remain on dialysis (Fig. 573.1). Children and adolescents with ESKD have special needs that differ from adults, including the need to achieve normal growth and cognitive development. Successful transplantation leads to accelerated linear growth, allows for regular school attendance, and often eliminates the need for dietary restrictions. Improvements in surgical techniques and a reduction in the early complications such as thrombosis have given young children the best long-term outcomes of all age-groups among transplant recipients. Following kidney transplantation, the most commonly encountered complications include acute or chronic allograft rejection, an increased risk for infections with both community-acquired and opportunistic organisms, and cardiovascular disease (hypertension, obesity, dyslipidemia). Providers must also be aware of the risks for malignancy and sequelae of chronic kidney disease (CKD).

INCIDENCE AND ETIOLOGY OF ESKD

The incidence of ESKD in pediatric patients in the United States varies by age-group (Table 573.1), with an adjusted incident rate of 11 per million population in 2020. The etiology of ESKD in children also varies

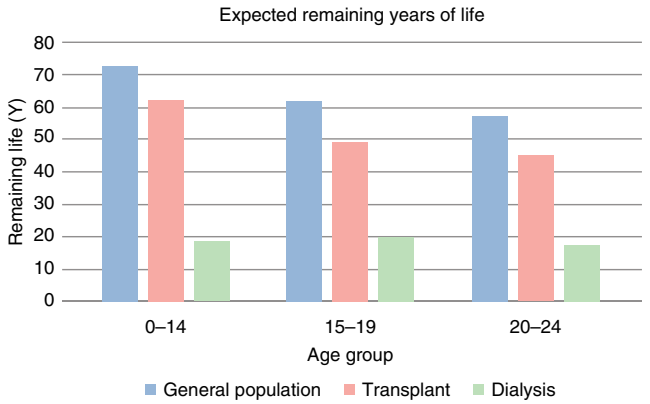

Fig. 573.1 Expected remaining years of life by end-stage renal disease treatment modality. Patients on dialysis or with a kidney transplant are compared to healthy children by age. *(Adapted from United States Renal Data System. 2020 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.)*

Table 573.1 Incident Rates of Reported ESKD in the United States

AGE RANGE (YEAR)	ADJUSTED INCIDENT RATES PER MILLION POPULATION
<1	26
1-5	7
6-12	8
13-17	16

Data from United States Renal Data System. 2022 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. Fig. 8.2. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/8-esrd-among-children-and-adolescents.

by age (Table 573.2; see Fig. 572.2 in Chapter 572). **Cystic or hereditary diseases** account for more than 24% of children wait-listed for a kidney transplant, whereas **congenital anomalies of the kidney and urinary tract (CAKUT)** account for 18% of such children. In 2020, there were 710 kidney transplants performed in children <18 years of age in the United States, with 184 performed in children ≤5 years old, 129 in children ages 6-10 years, and 397 in children ages 11-17 years. That same year, of the 6,177 children in the United States with ESKD, 4,577 (74.1%) had a functioning kidney transplant.

INDICATIONS FOR RENAL TRANSPLANTATION

Renal transplantation is generally considered for any child when chronic renal replacement therapy is indicated. There are few absolute contraindications for pediatric kidney transplantation, yet relative contraindications arise when the combined risks of the transplant procedure itself and lifelong immunosuppression outweigh the benefits of improved health, longevity, and/or quality of life. Such relative contraindications include preexisting malignancy, primary or secondary immunodeficiency, chronic severe infection, inability to receive appropriate posttransplant care, or severe neurologic dysfunction where improvement in the quality of life and/or longevity is unlikely. In each scenario, the multidisciplinary team must weigh the risks and benefits of transplantation while accounting for the values of patients and caregivers. For instance, patients who have remission of malignancy for a minimum of 1-2 years may be considered on an individual basis for kidney transplantation. Similarly, patients with autoimmune diseases resulting in ESKD (e.g., systemic lupus erythematosus) are candidates for transplantation after a period of immunologic quiescence of the primary disease.

Table 573.2 Characteristics of Children with Incident End-Stage Kidney Disease, by Primary Cause of End-Stage Kidney Disease, 2016–2020

PRIMARY CAUSES OF ESKD	%
All Etiologies	100
Primary Glomerular Disease	21.5
Glomerulonephritis (GN) (histologically not examined)	5.4
Focal glomerulosclerosis, focal sclerosing	11.4
Membranous nephropathy	0.4
Membranoproliferative GN (MPGN) type 1, diffuse MPGN	0.4
Dense deposit disease, MPGN type 2	0.3
IgA nephropathy, Berger's disease (proven by immunofluorescence)	0.5
With lesion of rapidly progressive GN	0.8
Other proliferative GN	2.5
Secondary Glomerular Disease	8.3
Systemic lupus erythematosus (SLE nephritis)	2.6
Hemolytic uremic syndrome	1.9
Polyarteritis and other vasculitis	1.5
Associated vasculitis	1.8
CAKUT1	28.1
Congenital obstructive uropathies	10.1
Renal hypoplasia, dysplasia, oligonephronia	15.0
Chronic pyelonephritis, reflux nephropathy	3.0
Cystic/Hereditary/Congenital Diseases	11.9
Polycystic kidneys, adult type (dominant)	0.5
Polycystic, infantile (recessive)	3.0
Medullary cystic disease, including nephronophthisis	1.7
Hereditary nephritis, Alport syndrome	1.2
Cystinosis	1.0
Primary oxalosis	0.4
Congenital nephrotic syndrome	2.0
Other (congenital malformation syndromes)	1.9
Tubulointerstitial Diseases	4.9
Chronic interstitial nephritis	2.3
Acute interstitial nephritis	0.4
Tubular necrosis	2.1
Transplant Complications	1.5
Other transplant complication	1.4
Diabetes	0.6
Neoplasms/Tumors	0.8
Renal tumor	0.7
Hypertensive/Large Vessel Disease	1.6
Renal artery stenosis	0.3
Renal artery occlusion	1.2
Miscellaneous Conditions	14.0
Acquired obstructive uropathy	4.5
Unspecified with renal failure	2.3
Traumatic or surgical loss of kidney(s)	1.1
Other renal disorders	5.1
Nephropathy caused by other agents	0.9
Etiology Uncertain	4.0
Etiology Missing	2.9

IgA, Immunoglobulin A; CAKUT, congenital anomalies of the kidney and urinary tract. Modified from the United States Renal Data System. 2022 *USRDS* Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. Table 8.1. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/8-esrd-among-children-and-adolescents.

In children, dialysis may be required before transplantation to optimize the nutritional and metabolic conditions, allow for quiescence of an underlying autoimmune disorder, achieve an appropriate size, or keep a patient stable until a suitable donor is available. Although successful transplantation with an adult-sized kidney has occurred in children <10 kg and <6 months of age, recipients usually must weigh at least 8-10 kg to minimize the risk for vascular thrombosis and accommodate an adult-size kidney. This may require a period of dialysis support until the child is 12-18 months of age.

Preemptive transplantation (i.e., transplantation without prior dialysis) accounts for ~25% of all pediatric renal transplants. It is the preferred approach when possible because of a small but incremental decrease in patient and allograft survival for every year spent on dialysis before transplant. Preemptive renal transplantation can and should therefore be considered in any child with stage 4 or 5 CKD who is likely to require dialysis within 6-12 months and/or has evidence of the adverse effects of CKD on their health or neurocognitive development. This requires early referral to a transplant center for evaluation of the candidate and potential donors. The transplant team must work with the recipient and caregivers to determine the optimal time for transplantation considering the risks and benefits posed to the recipient.

CHARACTERISTICS OF KIDNEY DONORS AND RECIPIENTS

Approximately 30–40% of pediatric kidney transplants come from **living donors.** Because the Organ Procurement and Transplantation Network (OPTN) gives preference to children waiting for a **deceased-donor** renal transplant, children have a higher rate of transplantation than adults. In 2020, children less than 17 years of age on dialysis were transplanted at a rate of 43.7 transplants per 100 patient-years (29.9 deceased donor, 13.8 living donor), whereas adults were transplanted at a rate of 8.3 transplant per 100 patient-years. The current allocation policy was implemented to allocate priority to children based on projected organ survival using the **Kidney Donor Profile Index (KDPI),** which computes the projected allograft survival from 12 important donor characteristics. Under this system, the top 35% of kidneys (KDPI <35%) are preferentially allocated to children. Additional factors that determine the allocation include the time on dialysis or since listing (whichever is longest), a zero human leukocyte antigen (HLA)-antigen mismatch, calculated panel-reactive antibody (cPRA), prior living donor, and 0 or 1 HLA-DR (HLA–antigen D–related) mismatch. In 2021, a new allocation system was implemented based on a 250-nautical mile radius rather than allocation based on local organ procurement organizations, and children were given even higher priority on the wait-list. Because of such policies, the time on the wait-list for children is shorter than that for adults. Median wait time is approximately 7-8 months for children nationally compared with 4-5 years or more for adults.

EVALUATION AND PREPARING FOR KIDNEY TRANSPLANTATION

A comprehensive transplant evaluation includes a transplant surgeon, nephrologist, dietitian, social worker, psychologist, pharmacist, financial counselor, pretransplant nurse coordinator, and anesthesiologist. A urologist familiar with transplantation is also essential for patients with lower urinary tract anomalies. Important considerations for the transplant evaluation include considering the primary diagnosis and risk of recurrence; ensuring an adequate lower urinary tract for drainage of the transplanted kidney; diagnosing and treating infections; the presence of cardiovascular disease, anemia, and other sequelae of ESKD; and preparing the patient with immunizations before starting lifelong immunosuppression.

Understanding the primary renal disease is essential before kidney transplantation. For instance, a number of primary renal diseases can recur in a transplanted kidney, but this is not a contraindication to transplantation. Recurrent disease accounts for graft loss in almost 7% of primary transplantations and 10% of repeat transplants. **Primary focal segmental glomerulosclerosis (FSGS)** is known to recur in 30–60% of cases and substantially decreases allograft survival. Because **primary hyperoxaluria** is caused by enzymatic defects in the liver, traditionally kidney transplantation has been accompanied by liver transplantation to prevent recurrent disease in the kidney allograft. However, advancements in pharmacotherapy have led to development of **lumasiran**, the first medication approved by the U.S.

Food and Drug Administration (FDA) to treat primary hyperoxaluria. It is not yet known how these medications will affect progression to ESKD in children and/or the need for liver transplantation. Primary **membranoproliferative glomerulonephritis (MPGN)** carries a high risk of disease recurrence (>50%) and decreased allograft survival. Attempts to classify MPGN into immune vs complement-mediated disease may facilitate research that provides insight into prognosis and options for prevention and treatment, but data are still limited. Histologic recurrence with mesangial immunoglobulin (Ig) A deposits is common and occurs in about half of the patients with **IgA nephropathy** and in approximately 30% of patients with **IgA vasculitis** (formerly Henoch-Schönlein purpura), yet it may not necessarily lead to premature allograft failure. **Congenital nephrotic syndrome** rarely recurs after transplantation, although patients can develop **antinephrin antibodies** and present with nephrotic syndrome. **Membranous nephropathy** occurs very rarely in children. The recurrence rate after kidney transplantation for patients who have been treated for **Wilms tumor** is approximately 13%. Although **Alport syndrome** does not recur following transplantation, approximately 3–4% of patients with Alport syndrome can develop de novo **anti–glomerular basement membrane (anti-GBM) glomerulonephritis** that may lead to graft loss. Certain forms of **complement-mediated thrombotic microangiopathy (TMA)** (commonly referred to as **atypical hemolytic uremic syndrome**) caused by inherited defects in complement regulation can recur posttransplant with devastating consequences for the new allograft. These conditions must be evaluated with genetic testing and analysis of the complement system before transplant so appropriate monitoring and therapy with complement inhibition can be applied to prevent recurrent disease.

Due to the high risk of developing Wilms tumor, patients with **Denys-Drash syndrome** should undergo bilateral nephrectomy before transplantation. Other indications for unilateral or bilateral native nephrectomies include hyposthenuria with polyuria, significant proteinuria leading to coagulopathy, recurrent infection of the native kidneys, and severe hypertension resistant to medical management. Nephrectomies are also indicated in cases such as **polycystic kidney disease,** where the native kidneys may become so large that they cause feeding intolerability in infants or prevent space for a transplanted kidney. Finally, it is important to perform bilateral native nephrectomy or ureteral ligation in patients with **primary FSGS** who produce significant amounts of urine protein to allow for surveillance of proteinuria and early identification and treatment of **recurrent FSGS.**

Urologic problems, such as **vesicoureteral reflux, posterior urethral valves,** and/or abnormal bladders as seen in **Eagle-Barrett syndrome**, should be addressed before surgery. Malformations and voiding abnormalities (e.g., neurogenic bladder, bladder dyssynergia, remnant posterior urethral valves, and urethral strictures) should be identified and repaired if possible. Children with urologic disease and renal dysplasia often require multiple operations to optimize the urinary tract anatomy and function. Such procedures include ureteric reimplantation to correct vesicoureteral reflux, bladder augmentation or reconstruction, urinary diversion (vesicostomy, ureterostomy, ileal conduit, continent appendicovesicostomy), and excision of ureteroceles. Good outcomes have been achieved in posterior urethral valve bladders by following a staged procedure of initial valve resection and bladder rehabilitation by a process of regimented double voiding and/or bladder cycling before transplantation. Following transplantation, bladder function in these patients should be followed for the long term because they can become less compliant over time and lead to premature failure of the transplanted allograft.

A comprehensive nutritional assessment should be performed to ensure that an optimal nutritional status is achieved before transplant. Many children with ESKD require nutritional supplements to provide them with sufficient protein and calories. Infants and young children on dialysis often require nasogastric or gastrostomy tube feedings to overcome decreased oral intake from nausea and anorexia due to uremia.

Bone disease should be evaluated for and bone health optimized before transplantation. Uncontrolled secondary hyperparathyroidism may lead to urinary phosphate wasting, hypercalcemia, hypercalciuria, and/or nephrolithiasis posttransplant. A high calcium phosphorus product before transplantation leads to vascular stiffness and calcifications, increasing the risk for cardiovascular disease and difficult-to-control hypertension in the perioperative and posttransplant period.

In the United States, >25% of the deaths in children on maintenance dialysis are a result of cardiovascular disease. Cardiac death is the leading cause of mortality in young adults after transplant in childhood. Therefore evaluation of cardiac function, including echocardiography and electrocardiography, is required before kidney transplantation to ensure sufficient cardiac function to tolerate the large fluid load that accompanies kidney transplantation. Hypertension is common in ESKD and should be treated before transplant. If medical management is insufficient, bilateral nephrectomy may be considered to control the hyperreninemic response from the failing kidneys. Finally, patients with a history of obstructive uropathy and oligohydramnios in utero who survive to kidney transplant may have undiagnosed/unrecognized pulmonary hypertension, which should be evaluated before transplantation.

Anemia needs to be treated before transplantation. Most patients receive erythropoietin, folate, and iron to maintain goals for hemoglobin levels between 11 and 13 g/dL. Blood transfusions should be avoided if possible due to concerns about sensitizing the patient to HLAs before transplant. If a blood transfusion is required, patients should receive leukoreduced red blood cells.

Evaluation for hypercoagulable states is important before renal transplantation because venous thrombosis is an important cause of graft failure. Risk factors for graft thrombosis include history of prior thrombosis, surgical technique, perfusion and reperfusion injury of the graft, young donor age (<6 years), young recipient (<5 years), cold ischemia time >24 hours, arterial hypotension, prior history of peritoneal dialysis, and/or hypoperfusion of an adult allograft transplanted into a small child. Particularly in the young recipient, there must be an evaluation for thrombosis of the iliac vessels and inferior vena cava, especially if there is a history of previous surgery or central line placement. Children who have large protein losses, such as from nephrotic syndrome and/or peritoneal dialysis, can be at an increased risk for thrombosis because of protein loss, such as protein S, protein C, and antithrombin III. Doppler ultrasound, CT angiography, and MR angiography have all been used to evaluate vessels. To minimize the risk of contrast-induced nephropathy associated with CT contrast, patients with advanced CKD or ESKD not yet on dialysis should receive intravenous hydration before and after the study and acidosis should be corrected before giving contrast medium. While MR angiography has traditionally been avoided in patients with CKD or ESKD because of the risk of nephrogenic systemic fibrosis from early forms of gadolinium, the more recent broad availability of newer, more stable gadolinium preparations makes contrast-enhanced MRI a valid and reasonably safe option. Collaboration between radiology and nephrology is important when determining which gadolinium agents to use and when contrast MRI is appropriate in children with CKD and ESKD.

Infections must be identified, prevented, and treated before transplantation. Infectious disease screening includes obtaining a complete history of the following: current or previous infections, all vaccinations, any occupational risks among family members (e.g., healthcare worker), household or other contacts with treatment for tuberculosis, travel within the past 2 years or significant time spent in another country, bacille Calmette-Guérin administration, animal and/or insect exposure, sexual activity, and consumption of high-risk foods such as unpasteurized products. Screening includes a tuberculosis skin test (purified protein derivative) or interferon gamma release assay, cytomegalovirus IgG, Epstein-Barr virus (EBV) antibody panel, varicella titer, measles antibody, hepatitis B serologies, hepatitis C antibody, HIV, and toxoplasmosis. Additional testing for patients who live in or have visited endemic areas might include *Coccidioides* immunodiffusion, serology for *Strongyloides,* and/or antibody for *Histoplasma* antibody. Sexually active patients should also be screened for syphilis, gonorrhea, and *Chlamydia.*

It is recommended that all immunizations be current before transplantation. All live vaccines (measles, mumps, rubella [MMR] and varicella) should be given before transplantation, and antibody titers should be checked for a response because these vaccines should not be given to immunosuppressed patients. MMR may be given as early as 6 months of age. Inhaled (live-attenuated virus) influenza vaccine should not be given to transplant patients, family members, or healthcare providers.

Psychiatric evaluation should be performed before transplantation to evaluate the ability of patients and families to cope with the substantial stressors that accompany caring for a child with a kidney transplant. This evaluation should include screening for depression, substance abuse, and adherence so that problems can be identified and managed before kidney transplantation. If nonadherence is identified or anticipated, interventions should be in place before transplantation.

The ABO blood type must be confirmed twice before a patient is listed for kidney transplantation. Donors and recipients are currently matched for HLA-A, HLA-B, and HLA-DR antigens. In general, better matched organs have improved survival times following kidney transplantation. Matching at the DR locus appears to be especially advantageous, though in the modern era of immunosuppression, successful six-antigen mismatched transplants are performed routinely. All patients must be screened for preformed anti-HLA antibodies before kidney transplantation. The most common, sensitive, and specific method uses flow cytometry and single HLA-antigen beads. In this manner, a patient's PRA can be assessed and is reported as the percentage of the population against which a recipient has anti-HLA antibodies. Patients can become sensitized by a prior transplant, blood transfusions, and/or pregnancy. Highly sensitized patients (PRA >80%) may undergo desensitization with plasmapheresis, anti-CD 20 antibody, and/or proteasome inhibitors to expand the donor pool from which they can safely receive an organ.

IMMUNOSUPPRESSION

Most pediatric kidney transplant centers employ induction immunosuppression at the time of transplant followed by lifelong maintenance immunosuppression with a calcineurin inhibitor and an antiproliferative agent with or without steroids.

Induction Therapy

Induction therapy is used in nearly all pediatric renal transplants to prevent early acute rejection. The OPTN Scientific Registry of Transplant Recipients (OPTN/SRTR) 2020 Annual Report indicates that 60% of patients receive T-cell–depleting induction therapy (rabbit antithymocyte globulin). Use of an interleukin (IL)-2 receptor antagonist (basiliximab) has been stable at between 30% and 40% for the past 5 years, and the rates of no induction therapy have declined to below 10%.

T-Cell Antibodies

Antithymocyte globulin is comprised of rabbit- or horse-derived polyclonal antibodies against human T-lymphocyte antigens that results in a rapid depletion of T lymphocytes. The infusion is generally started in the operating room before reperfusion of the transplant kidney. Most centers use this for standard induction therapy, but some limit its use to induction of sensitized high-risk patients or patients who have concerns for delayed graft function and want to avoid high calcineurin inhibitor levels in the early postoperative period. The standard dosage is 1.5 mg/kg/dose for three to five doses, with daily monitoring of lymphocyte, neutrophil, and platelet counts. Some centers monitor $CD3^+$ subsets and hold the dose if the $CD3^+$ count is below 20 cells/mm^3.

Interleukin-2 Receptor Antibodies

Basiliximab is currently the only monoclonal anti-CD25 antibody on the market. This chimeric (murine/human) anti-CD25 antibody prevents T-cell proliferation but does not cause T-cell depletion. Basiliximab is given in two doses of 10 mg for patients <35 kg and 20 mg for patients ≥35 kg. The first dose should be given within 2 hours before the transplant surgery and the second dose on day 4. Patients tend to tolerate IL-2 receptor antagonists well with few side effects.

Other Induction Therapies

Alemtuzumab (Campath-1H) is a monoclonal antibody against CD52 present on T and B cells, monocytes, and natural killer cells. Some centers have used this induction antibody in steroid and calcineurin inhibitor-sparing protocols, but pediatric data are limited as has been its use.

Other induction therapies for highly sensitized patients include targeting B cells and/or removing neutralizing antibodies by using rituximab against the CD20 epitope on early-lineage and intermediate-lineage B cells, proteasome inhibitors, and plasmapheresis and/or high-dose intravenous immunoglobulin for removing donor-specific antibodies.

Maintenance Immunosuppression

Lifelong maintenance immunosuppression is required in nearly all patients following kidney transplantation. The most common regimens include a calcineurin inhibitor (predominantly tacrolimus vs cyclosporine) and an antiproliferative agent (predominantly mycophenolate mofetil [MMF] vs azathioprine) with or without corticosteroids. The mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus are sometimes used in place of the calcineurin inhibitor or antiproliferative agent. The rationale for combination therapy in children is to provide effective immunosuppression while minimizing the toxicity of any single drug.

Calcineurin Inhibitors

Despite the search for immunosuppression regimens that minimize calcineurin inhibitor exposure, **tacrolimus** remains the centerpiece of maintenance immunosuppression for most pediatric patients in North America. According to OPTN/SRTR in 2020, >90% of children in the United States were placed on tacrolimus-based immunosuppression at the time of transplant. The increasing use of tacrolimus in place of **cyclosporine** can be attributed to studies demonstrating better efficacy (fewer rejections and less reliance on steroids) and less severe cosmetic side effects, such as hypertrichosis, gingival hyperplasia, and coarsening of facial features. This is especially relevant for adolescents for whom unwanted cosmetic side effects can become a barrier to immunosuppression adherence. Tacrolimus also appears to cause less dyslipidemia, though other side effects such as **new-onset diabetes after transplant (NODAT),** tremor, seizure, alopecia, and sleep disturbance seem to be more common in patients treated with tacrolimus. Despite the nearly complete replacement of cyclosporine with tacrolimus, there are select cases when cyclosporine is the preferred agent (e.g., to treat posttransplant recurrence of FSGS or conversion therapy in patients who develop NODAT).

Unfortunately, both calcineurin inhibitors have a narrow therapeutic index and can cause acute and chronic kidney injury. Additionally, many foods and drugs interact with the calcineurin inhibitor metabolism, requiring frequent therapeutic drug monitoring. A usual starting dose of tacrolimus is 0.1-0.15 mg/kg twice a day on the day of the transplant, targeting trough levels above 10 ng/mL for the first month and then tapering down to trough levels of 4-8 ng/mL by 6 months. Patients with CYP3A5 expression (80–90% of patients from African descent vs 20–30% of patients with Caucasian ancestry) often require doses nearly twice as high. Pharmacogenetic testing of CYP3A5 polymorphisms is available and may assist with personalized dosing. The recent development of long-acting tacrolimus preparations (Envarsus XR and Astagraf XL) have provided the opportunity for a simplified, once daily medication regimen. Most long-term immunosuppressive regimens attempt to limit calcineurin inhibitor dosing as much as possible, and the search for calcineurin inhibitor–sparing drug regimens remains an area of intense research.

Antiproliferative Agents

Most immunosuppression regimens for children following kidney transplantation include an antiproliferative agent. **MMF** is the

morpholinoethyl ester prodrug of mycophenolic acid, an inhibitor of de novo purine synthesis, and is part of the initial maintenance immunosuppression regimen in at least two thirds of U.S. pediatric renal transplant recipients. The absence of nephrotoxicity, cardiovascular risk (hypertension, dyslipidemia), and hepatotoxicity make it an attractive option for immunosuppression, and the fact that it has greater efficacy than azathioprine has enabled the use of lower doses of corticosteroids and/or calcineurin inhibitors. Primary toxicities include diarrhea and upset stomach, as well as leukopenia and anemia, affecting up to 40% of patients. These side effects are often transient and can be treated with a temporary dosage reduction, but persistent dose reductions have been associated with an increased risk of rejection. MMF is also associated with a high risk for birth defects, so its use in adolescent females necessitates two forms of birth control and regular pregnancy screening. The usual dose of MMF is 600 mg/m^2 in patients treated with cyclosporine. MMF metabolism is slower in patients treated concomitantly with tacrolimus, allowing for lower doses (450 mg/m^2) to be used.

Azathioprine, an analog of **6-mercaptopurine**, is an alternative to MMF that also inhibits de novo purine synthesis and contributes to cell cycle arrest. It was the first medication approved for immunosuppression in kidney transplantation, yet in the past 2 decades, its use has declined because of the advent of newer immunosuppressive medications with purported greater efficacy. It is inexpensive and, unlike MMF, it can be administered once daily, so it is an attractive alternative for patients who struggle to take twice-daily medications. Usual dosage is 1.5-3 mg/kg once daily. Bone marrow suppression is the primary toxicity, but gastrointestinal side effects are less common than with MMF, with the exception of pancreatitis, which has rarely been reported. Unlike MMF, it is not associated with birth defects and is an important alternative in pregnant patients. Enteric-coated mycophenolic acid is another alternative to MMF that may decrease upper gastrointestinal side effects in some patients.

Mammalian Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors (sirolimus more commonly than everolimus) are used primarily as adjunctive immunosuppression in combination with MMF to avoid tacrolimus toxicity or with tacrolimus and MMF to spare steroids. However, they are used in only 5–10% of pediatric kidney transplant recipients 1 year posttransplant, perhaps due to evidence suggesting a high rate of donor-specific antibodies and antibody-mediated rejection (AMR) in patients taking mTOR inhibitors. Other toxicities, including a high rate of aphthous ulcers, dyslipidemia, poor wound healing, proteinuria, and diarrhea, have limited their use.

Corticosteroids

Corticosteroids remain integral to most immunosuppressive protocols despite their multifaceted toxicities. According to the 2020 OPTN/SRTR report, 54% of patients are treated with steroids at the time of transplant. The adverse effects of steroids are especially pronounced in children, for whom retarded skeletal growth, hypertension, obesity, diabetes mellitus, hyperlipidemia, osteopenia, and aseptic necrosis of bone (particularly the femoral heads) can have dire long-term consequences. Cosmetic side effects, such as cushingoid facies and acne, also become barriers to adolescents taking their medication. For these reasons, steroid-based regimens in children seek to minimize steroid exposure by starting with high-dose steroids as induction therapy and tapering down over several months to a lowest dose of 5-10 mg or 0.1 mg/kg daily. Other protocols call for a more rapid steroid taper lasting from 1 week to several months before stopping them altogether.

Several well-designed randomized controlled trials in children and adults have demonstrated that complete steroid avoidance can be safely achieved in patients with a low immunologic risk by using induction therapy with dual-maintenance immunosuppression comprised of tacrolimus and MMF. In general, steroid avoidance is associated with higher rates of rejection but also carries significant benefits for growth, hypertension, and dyslipidemia with no decrease in long-term allograft survival. Importantly, this approach appears to be safe and without increases in the generation of donor-specific antibody or histologic injury. Despite this evidence, data from the OPTN network suggest that steroid use is largely dependent on the center where the transplant is performed rather than the characteristics of the patient.

Other Agents

Belatacept is a fusion protein composed of the Fc fragment of a human IgG_1 linked to the extracellular domain of CTLA-4 (a molecule crucial for T-cell costimulation), which selectively blocks the process of T-cell activation. Belatacept is attractive for maintenance immunosuppression because it is a quick monthly infusion rather than a daily oral medication, and it does not have many of the untoward side effects associated with calcineurin inhibitors, including and especially nephrotoxicity. Adult studies of belatacept have demonstrated similar rejection rates but significantly improved kidney function up to 10 years following kidney transplantation compared with cyclosporine. Unfortunately, there is an unacceptably high rate of **posttransplant lymphoproliferative disorder (PTLD)** in EBV-naïve patients, which are most of the children receiving a kidney transplant.

FLUID MANAGEMENT IN INFANTS AND SMALL CHILDREN AFTER KIDNEY TRANSPLANTATION

Maintenance of adequate blood flow to an adult-sized kidney in an infant or small child is crucial to avoid acute tubular necrosis (ATN) and graft loss from vascular thrombosis. The recipient aortic blood flow early after transplantation of an adult-size kidney more than doubles from the pretransplantation aortic blood flow. The maximum blood flow that can be obtained in an adult-size kidney transplanted into a small child is approximately 65% of what was in the donor. Low blood flow states, such as those with hypovolemia or hypotension, increase the risk for ATN, graft thrombosis, and graft nonfunction. Thus, in the postoperative period, patients are maintained on high fluid volumes.

Close attention is paid to the blood pressure and hydration status in the operating room in an attempt to reduce the incidence of delayed graft function. Typically, a central venous catheter is inserted to monitor the central venous pressure throughout the operation. A central venous pressure of 12-15 cm H_2O should be achieved before removing the vascular clamps; a higher central venous pressure may be desirable in the case of a small infant receiving an adult-size kidney. Dopamine may be started in the operating room and continued for 24-48 hours postoperatively to maintain a mean arterial blood pressure (MAP) >55 mm Hg. A blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin can drop as a result of sequestration of approximately 150-250 mL of blood in the transplanted kidney. Because an adult kidney transplanted into a small child can produce enormous amounts of urine, a fluid strategy that provides a constant rate for insensible losses (D10W at a rate of 400 mL/m^2/day) and urine replacements helps to ensure adequate hydration of the adult kidney. Some transplant centers continue to provide infants with aggressive fluid management by nasogastric or gastrostomy tube feedings of at least 2,500 mL/m^2/day for up to 6 months following transplant if the child is unable to take in sufficient volume by mouth.

REJECTION OF KIDNEY TRANSPLANT

Hyperacute rejection, caused by preformed antibodies against the donor HLA, ABO, or other antigens, occurs immediately on reperfusion of the allograft. The practice of prospective cross matching using complement-dependent cytotoxicity has virtually eliminated hyperacute rejection.

Acute T-cell-mediated rejection (TCMR) must be identified and treated promptly, although this may not be straightforward in the very young transplant recipient. Because most small children receive adult-size kidneys with a large renal reserve compared with their body mass, significant allograft dysfunction may be present with little or no increase in serum creatinine. Therefore even subtle findings such as hypertension or new proteinuria can indicate acute TCMR and must be investigated. Late diagnosis and treatment of rejection are associated with a higher incidence of resistant rejections and graft loss. Most cases of acute TCMR can be treated if detected early by using a short course (3-5 days) of high-dose intravenous steroids

(10-30 mg/kg) followed by an oral steroid taper over the next several weeks and either increased maintenance immunosuppression or improved adherence, whichever is most appropriate. Steroid-resistant or high-grade rejection can be treated with thymoglobulin (1.5 mg/kg/day) for 7-14 days, high-dose tacrolimus (trough levels >20 ng/dL for 1-2 weeks), or local allograft irradiation. Following treatment for rejection, it is important to consider 3-12 months of prophylaxis with trimethoprim/sulfamethoxazole to prevent *Pneumocystis jirovecii* pneumonia (PJP pneumonia), valganciclovir/valacyclovir to prevent cytomegalovirus/herpes reactivation, and nystatin or fluconazole to prevent oral candidiasis.

Active AMR consisting of anti-HLA donor-specific antibodies is an important cause of kidney function decline and allograft loss. It can present acutely in the few weeks following transplantation in previously sensitized patients or may develop chronically due to inadequate immunosuppression or poor adherence. Unlike acute TCMR, acute AMR is much more difficult to treat and may require plasmapheresis, intravenous immunoglobulin (IVIG), anti-CD20 antibody infusions, and/or proteasome inhibitors. Treatment is most likely to be successful if initiated within a few months of identifying new donor-specific antibodies.

Chronic rejection (T-cell mediated or antibody mediated) is the leading cause of graft loss. Children often have a gradual decline in their renal function and often have fixed proteinuria and hypertension. Despite initial excitement about the potential of MMF and sirolimus mitigating chronic graft injury, this has not translated readily into observable clinical benefits. Chronic TCMR, chronic AMR, and the impact of non-HLA antibodies are areas of active investigation.

Kidney Biopsy

Kidney biopsy is the gold standard for the diagnosis of TCMR or AMR. Despite attempts to develop noninvasive biomarker panels, none has proven sensitive enough to rule out rejection. Many centers perform **surveillance biopsies** at specific time points following transplantation to detect **subclinical rejection**, which has been reported in <10% of such surveillance biopsies.

GRAFT SURVIVAL OF KIDNEYS

Survival rates for live-donor kidney allografts are superior to those for deceased-donor allografts. Living-donor kidneys generally have fewer HLA mismatches, lower cold ischemia time, and require less immunosuppression than deceased-donor kidneys. Furthermore, deceased-donor transplant requires children to wait several weeks to a few years on the deceased-donor wait-list before receiving an organ. The OPTN/SRTR 2021 annual report showed that the death-censored, 5-year allograft survival rate was 85.2% for deceased-donor kidney transplants performed in 2014–2016, whereas the death-censored, 5-year allograft survival rate for living-donor transplants was 93.1% over the same time period. For these reasons and because it expands the donor pool, living donation should be advocated at every opportunity.

Children <10 years of age have the best long-term graft and patient survival rates of all age-groups, and adolescents and young adults have the worst. Among patients with at least 1 year of graft function, graft failure rates are stable at around 1.4 per 100 person-years until 10 years of age, when rates increase, peaking at a maximum of 6.3 per 100 person-years at age 19 years, regardless of the age at transplantation. A variety of factors likely account for such poor outcomes in adolescents and young adults, including the patient's changing physiology, a transition from pediatric to adult care, and a greater number of barriers to taking immunosuppressives.

COMPLICATIONS OF IMMUNOSUPPRESSION

Since the mid-1990s, the incidence of acute rejection has decreased, but the incidence of infection after transplantation has increased.

Pneumonia and urinary tract infection are the most common post-transplant bacterial infections. Urinary tract infections can progress rapidly to urosepsis and may be confused with episodes of acute rejection. Trimethoprim-sulfamethoxazole is used for urinary tract infection antibiotic prophylaxis as well as PJP prophylaxis for 3-6 months after transplant (see Chapter 290).

The herpesviruses (cytomegalovirus, herpesvirus, varicella-zoster virus, and EBV) pose a special problem in view of their common occurrences in childhood (see Chapters 299-302). Many young children have not yet been exposed to these viruses, and because they lack protective immunity, their predisposition to serious primary infection is high. The incidence of cytomegalovirus seropositivity is approximately 30% in children >5 years of age and rises to approximately 60% in teenagers. Thus the younger child is at a greater potential risk for serious infection when a cytomegalovirus-positive donor kidney is transplanted. About half of children are seronegative for EBV; most of them will become infected shortly after transplant. Most EBV infections are clinically silent but put transplant recipients at risk for PTLD in the presence of immunosuppression. The incidence of these infections is higher in children who receive antibody induction therapy and after treatment of acute rejection. Antiviral prophylaxis with ganciclovir or valganciclovir for 3-12 months after transplantation, especially in the higher-risk groups (recipient-negative, donor-positive), has been effective in reducing the incidence of clinical cytomegalovirus disease. Serial surveillance for these viruses by quantitative polymerase chain reaction (PCR) for the viral load in the peripheral blood has also allowed educated minimization of immunosuppression with a resultant reduction in the viral burden. It is important to monitor for PTLD with routine examinations for lymphadenopathy, hepatosplenomegaly, and EBV screening.

Polyomavirus nephropathy is an important cause of allograft dysfunction; almost 30% of children have BK viruria (see Chapter 321), although allograft dysfunction occurs only in a small subset of patients (~5%). Early protocols focusing on screening for BK virus in the urine have proven ineffective at distinguishing patients who will develop BK nephropathy; rather, plasma BK monitoring has become the standard of care. Ultimately, a renal biopsy, with identification of BK virus by immunoperoxidase staining, is required to make the diagnosis of BK virus nephropathy with certainty. Reducing immunosuppression when plasma BK PCR levels start to rise is the main form of therapy. Cidofovir, leflunomide, and IVIG have all been used as adjunctive therapies.

Oral candidiasis is another important infection following kidney transplantation and can be prevented with oral nystatin 4 times daily or fluconazole once daily for the first 3 months after transplant. Careful monitoring of calcineurin inhibitor levels is important when starting or stopping treatment with fluconazole as it interferes with calcineurin inhibitor metabolism.

Pediatric solid organ transplant patients are generally considered to be at increased risk for infections and worse outcomes compared with their nonimmunosuppressed peers. This concern was brought to the forefront during the global COVID-19 pandemic. Despite their immunosuppressed state, studies have not shown that children with a solid organ transplant are at increased risk for complications from COVID-19 infection. Early studies indicate that short-term outcomes from COVID-19 in pediatric kidney transplant recipients are generally favorable, without increased risk of graft loss, respiratory failure, or death compared with nonimmunosuppressed peers. Nonetheless, COVID-19 vaccination is recommended before transplantation to minimize risk of complications and spread.

Hypertension, dyslipidemia, obesity, and posttransplant diabetes mellitus are other complications of immunosuppression and kidney transplantation that have been underrecognized and undertreated. Cardiovascular disease is the primary cause of premature death in young adults who had a kidney transplant in childhood, and uncontrolled blood pressure leads to premature allograft failure. Up to 80% of children have hypertension and up to 60% are uncontrolled despite multiple available therapies. The 24-hour ambulatory blood pressure monitoring (ABPM) is the gold standard for assessing blood pressure control because isolated nocturnal hypertension and masked hypertension are common following kidney transplantation and can only be diagnosed with ABPM. Guidelines for CKD recommend treating blood pressure to achieve a MAP below the 50th percentile for age, gender, and height on ABPM, though recommendations for children with a kidney transplant have not been as aggressive. Blood pressure

should be treated to at least below the 90th percentile for age, gender, and height and below 130/80 mm Hg. Angiotensin-converting enzyme (ACE) inhibitors are the preferred first-line agents in patients with proteinuria; otherwise, either calcium channel blockers or ACE inhibitors can be used with other agents added as needed to achieve blood pressure control.

Although growth improves after transplantation, chronic steroid use does not allow a child to reach their full potential height. The use of recombinant human growth hormone in pediatric renal transplant recipients significantly improves the growth velocity and standard deviation score (SDS). Steroid minimization and withdrawal protocols have demonstrated growth benefits, and the steroid-avoidance data in children show significant catch-up growth at 5 years after transplantation. It is thus likely that with a well-functioning kidney and no maintenance steroids, children might now be able to realize their full height potential.

Malignancy is an important problem following kidney transplantation for children. Lifelong immunosuppression confers at least a twofold lifetime risk of developing cancer for solid-organ transplant recipients compared with the general population. The most common cancer to develop within 10 years following kidney transplantation in children is **PTLD.** It occurs in 1–5% of pediatric kidney transplant recipients and is the most likely cancer to be encountered in childhood. Over the long term, skin cancers (basal cell carcinoma, cutaneous squamous cell carcinoma) are the most common malignancies, with an incidence of close to 15% by 15 years posttransplant and increasing from there. Carcinomas other than skin carcinomas also arise at a rate far higher than in the general population. The prognosis is generally good for most of these malignancies when they are diagnosed early and treated appropriately. Any kidney transplant recipient must be assessed regularly for signs of malignancy and practice preventative measures such as using appropriate sunscreen products.

Developing good adherence behaviors with immunosuppressive medications is one of the most important challenges facing children and adolescents following kidney transplantation. Up to 43% of adolescents display some decreased adherence to their immunosuppressive regimen, which is thought to contribute to decreased allograft survival rates compared with other age-groups. A child's normal development, which includes establishing more independence, spending more time away from home, feeling invincible, and being vulnerable to cosmetic medication side effects, increases the barriers to taking immunosuppression medications. Systems-based approaches, in which clinicians partner with patients to identify and address adherence barriers, are most likely to improve adherence over the long term.

LONG-TERM OUTCOME OF KIDNEY TRANSPLANTATION

With advances in transplant care and treatment modalities and with diligent attention to the pediatric patient's psychosocial, educational, vocational, and developmental rehabilitation, the social and emotional functioning of the child and the child's family appears to return to the same level as before the illness within 1 year of successful transplantation. Renal transplantation leads to improvement in linear growth in children. School function tests improve after renal transplantation. Most patients can reenter school and social activities after a short recovery time of 6-12 weeks following surgery. Surveys of 10-year survivors of pediatric kidney transplants report that most patients consider their health to be good, and they engage in appropriate social, educational, and sexual activities while experiencing a very good to excellent quality of life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Urologic Disorders in Infants and Children

PART XXII

Chapter 574

Congenital Anomalies and Dysgenesis of the Kidneys

Heather N. Di Carlo and Chad B. Crigger

EMBRYONIC AND FETAL DEVELOPMENT

The kidney is derived from reciprocal interaction between the ureteral bud and the metanephric blastema. During the fifth week of gestation, the ureteral bud arises from the mesonephric (Wolffian) duct and penetrates the metanephric blastema, which is an area of undifferentiated mesenchyme on the nephrogenic ridge. The ureteral bud undergoes a series of approximately 15 generations of divisions and by the 20th week of gestation forms the entire collecting system, including the ureter, renal pelvis, calyces, papillary ducts, and collecting tubules. Signals from the mesenchymal cells induce ureteric bud formation from the Wolffian duct as well as ureteric bud branching. Reciprocal signals from the ureteric bud and, later, from its branching tips induce mesenchymal cells to condense, proliferate, and convert into epithelial cells. Under the inductive influence of the ureteral bud, nephron differentiation begins during the seventh week of gestation.

By the 20th week of gestation, when the collecting system is developed, approximately 30% of the nephrons are present. Nephrogenesis continues at a nearly exponential rate and is complete by the 36th week of gestation. During nephrogenesis, the kidneys ascend to a lumbar site just below the adrenal glands. At least 16 signaling agents have been identified that regulate renal development. Defects in any of the signaling activities could cause a kidney not to form **(renal agenesis)** or to differentiate abnormally **(renal dysgenesis)**. Dysgenesis of the kidney includes **aplasia, dysplasia, hypoplasia,** and certain forms of **renal cystic disease.**

The fetal kidneys play a minor role in the maintenance of fetal salt and water homeostasis. The rate of urine production increases throughout gestation; at term, volumes have been reported to be 50 mL/hr. The glomerular filtration rate is 25 mL/min/1.73 m^2 at term and triples by 3 months postpartum. The increase in the glomerular filtration rate is caused by a reduction in intrarenal vascular resistance and redistribution of intrarenal blood flow to the cortex, where more nephrons are located.

RENAL AGENESIS

Renal agenesis, or absent kidney development, can occur secondary to a defect of the Wolffian duct, ureteric bud, or metanephric blastema. Unilateral renal agenesis has an incidence of 1 in 450-1,000 births. Unilateral renal agenesis often is discovered during the course of an evaluation for other congenital anomalies such as VACTERL association (vertebral defects, anal atresia, congenital heart disease, tracheoesophageal fistula, renal and limb defects; see Chapter 100.1). Its incidence is increased in newborns with a single umbilical artery. In true agenesis, the ureter and the ipsilateral bladder hemitrigone are absent. The contralateral kidney undergoes compensatory hypertrophy to some degree prenatally, but primarily after birth. Approximately 15% of these children have contralateral vesicoureteral reflux, and most males have an ipsilateral absent vas deferens because the Wolffian duct is absent. Because the Wolffian and müllerian ducts are contiguous, müllerian abnormalities in females also are common.

The **Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome** (1 in 4,000 to 1 in 5,000 female births) is a group of associated findings that may include vaginal aplasia, uterine maldevelopment, and normal ovaries. Two types are described. In **type I**, only müllerian aplasia occurs, whereas in **type II**, there are associated anomalies, most commonly unilateral renal agenesis, or a horseshoe kidney, with skeletal anomalies present in 10% (see Chapter 591). **Zinner syndrome** is considered the male counterpart of MRKH syndrome (Fig. 574.1). In this condition, males with unilateral renal agenesis (or a regressed **multicystic dysplastic kidney** [MCDK]) have an ipsilateral seminal vesicle cyst and a possible epididymal cyst and dilated distal ureteral segment. These patients typically present in adolescence. Expectant management is usually followed with interim ultrasonography unless symptoms develop, including hematuria, hematospermia, or dysuria.

Renal agenesis is distinguished from aplasia, in which a nubbin of nonfunctioning tissue is seen capping a normal or abnormal ureter. This distinction may be difficult but usually is clinically insignificant. Unilateral renal agenesis is diagnosed in some patients based on the finding of an absent kidney on ultrasonography or renal scintigraphy (renal scan). Some of these patients were born with a hypoplastic kidney or a MCDK that underwent complete cyst regression. Although the specific diagnosis is not critical, if the finding of an absent kidney is based on an ultrasound, a functional imaging study such as a renal scan should be considered because some of these patients have an ectopic kidney in the pelvis. If there is a normal contralateral kidney, long-term renal function usually remains normal.

Bilateral renal agenesis is incompatible with extrauterine life and produces **Potter syndrome.** Death occurs shortly after birth from pulmonary hypoplasia. The newborn has a characteristic facial appearance, termed **Potter facies** (Fig. 574.2). The eyes are widely separated with epicanthal folds, the ears are low set, the nose is broad and compressed flat, the chin is receding, and there are limb anomalies. Bilateral renal agenesis should be suspected when maternal ultrasonography demonstrates **oligohydramnios,** nonvisualization of the bladder, and absent kidneys. The incidence of this

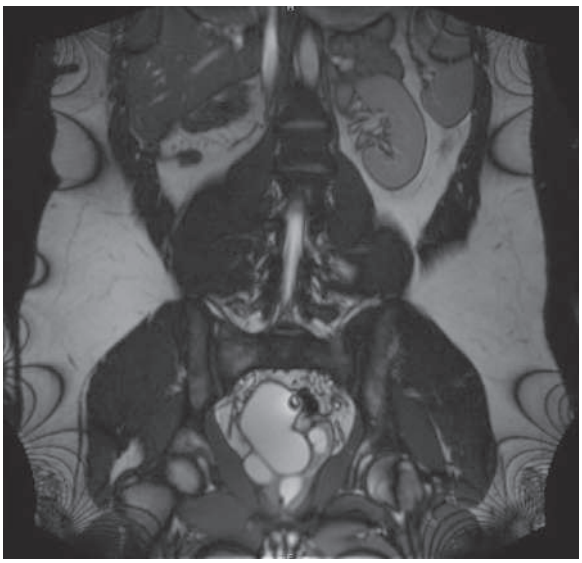

Fig. 574.1 Zinner syndrome. A 17-yr-old male with regressed right multicystic dysplastic kidney and dilated ectopic distal ureter draining into seminal vesicle cyst.



Fig. 574.2 Stillborn infant with renal agenesis exhibiting characteristic Potter facies.

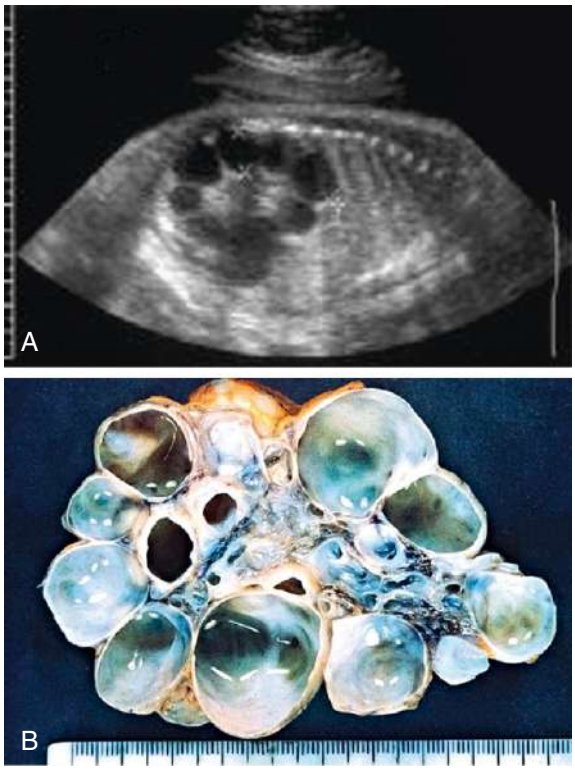

Fig. 574.3 A, Prenatal sonogram demonstrating multicystic dysplastic kidney. B, Surgical specimen.

disorder is 1 in 5,000 births, with a male predominance, and represents 20% of newborns with the Potter phenotype. Other common causes of neonatal renal failure associated with the Potter phenotype include cystic renal dysplasia and obstructive uropathy. Less common causes are autosomal recessive polycystic kidney disease (infantile), renal hypoplasia, and medullary dysplasia. Neonates with bilateral renal agenesis die of pulmonary insufficiency from pulmonary hypoplasia rather than renal failure (see Chapter 444).

The term **familial renal adysplasia** describes families in which renal agenesis, renal dysplasia, multicystic kidney (dysplasia), or a combination occurs in a single family. This disorder has an autosomal dominant inheritance pattern with a penetrance of 50–90% and variable expression. Because of this association, many clinicians advise screening first-degree relatives of persons who have renal agenesis or dysplasia.

The American Academy of Pediatrics recommends that children with a single kidney or single functioning kidney be allowed to play most sports. In fact, sports are less likely to cause kidney injury than motor vehicle crashes, horseback riding, or bicycle accidents. Children with one kidney are not at higher risk for renal injury during contact sports. Despite this, families should be made aware of the potential complications of injury to the patient's single kidney including potential need for dialysis or a renal transplant. Protective padding may be worn during sports, but there is no evidence that this prevents renal injury.

RENAL DYSGENESIS: DYSPLASIA, HYPOPLASIA, AND CYSTIC ANOMALIES

Renal dysgenesis refers to maldevelopment of the kidney that affects its size, shape, or structure. The three principal types of dysgeneses are dysplastic, hypoplastic, and cystic. Although dysplasia always is accompanied by a decreased number of nephrons (hypoplasia), the converse is not true: hypoplasia can occur in isolation. When both conditions are present, the term **hypodysplasia** is preferred. The term **dysplasia** is technically a histologic diagnosis and refers to focal, diffuse, or segmentally arranged primitive structures, specifically primitive ductal structures, resulting from abnormal metanephric differentiation. Nonrenal elements, such as cartilage, may also be present. The condition can affect all or only part of the kidney. If cysts are present, the condition is termed **cystic dysplasia.** If the entire kidney is dysplastic with a preponderance of cysts, the kidney is referred to as a **MCDK** (Fig. 574.3).

The pathogenesis of dysplasia is multifactorial. The "bud" theory proposes that if the ureteral bud arises in an abnormal location, such as an ectopic ureter, there is abnormal penetration and induction of the metanephric blastema, which causes abnormal kidney differentiation, resulting in dysplasia. Renal dysplasia also can occur with severe obstructive uropathy early in gestation, as with the most severe cases of posterior urethral valves or in a MCDK, in which a portion of the ureter is absent or atretic.

MCDK is a congenital condition in which the kidney is replaced by cysts and does not function; it can result from ureteral atresia. Kidney size is highly variable. The incidence is approximately 1 in 2,000. Some clinicians incorrectly use the terms *multicystic kidney* and *polycystic kidney* interchangeably. However, polycystic kidney disease is an inherited disorder that may be autosomal recessive or autosomal dominant and affects both kidneys (see Chapter 563). MCDK usually is unilateral and generally is not inherited. Bilateral MCDKs are incompatible with life.

MCDK is the most common cause of an abdominal mass in the newborn, but the vast majority are nonpalpable at birth. In most cases, it is discovered incidentally during prenatal ultrasound. In some patients, the cysts are identified prenatally, but the cysts regress in utero, and no kidney is identified on imaging at birth. Contralateral hydronephrosis is present in 5–10% of patients. Sonography shows the characteristic appearance of a kidney replaced by multiple cysts of varying sizes that do not communicate, and no identifiable parenchyma is present. In some patients, usually males, a small nonobstructing ureterocele is present in the bladder (see Chapter 577). Although 15% have contralateral vesicoureteral reflux, it is

usually low grade, and obtaining a voiding cystourethrogram is unnecessary unless there is significant contralateral hydronephrosis or the child develops an upper urinary tract infection. *Management is controversial.* Complete cyst regression occurs in nearly half of MCDKs by age 7 years. The risk of associated hypertension is 0.2–1.2%, and the risk of Wilms tumor arising from a MCDK is approximately 1 in 1,200. Because neoplasms arise from the stromal rather than the cystic component, even if the cysts regress completely, the likelihood that the kidney could develop a neoplasm is not altered.

Because of the occult nature of these potential problems, many clinicians advise follow-up with ultrasound and blood pressure measurement every 6 months to a year. The most important aspect of follow-up is being certain that the solitary kidney is functioning normally. *If there is an abdominal mass, the cysts enlarge, the stromal core increases in size, or hypertension develops, nephrectomy is recommended.* In lieu of follow-up screening, laparoscopic nephrectomy may be performed.

Renal hypoplasia refers to a small nondysplastic kidney that has fewer than the normal number of calyces and nephrons. The term encompasses a group of conditions with an abnormally small kidney and should be distinguished from aplasia, in which the kidney is rudimentary. If the condition is unilateral, the diagnosis usually is made incidentally during evaluation for another urinary tract problem or hypertension. Bilateral hypoplasia usually manifests with signs and symptoms of chronic renal failure and is a leading cause of end-stage renal disease during the first decade of life. A history of polyuria and polydipsia is common. Urinalysis results may be normal. In a rare form of bilateral hypoplasia called **oligomeganephronia,** the number of nephrons is markedly reduced, and those present are markedly hypertrophied.

The **Ask-Upmark kidney,** also termed **segmental hypoplasia,** refers to small kidneys, usually weighing less than 35 g, with one or more deep grooves on the lateral convexity, underneath which the parenchyma consists of tubules resembling those in the thyroid gland. It is unclear whether the lesion is congenital or acquired. Most patients are 10 years or older at diagnosis and have severe hypertension. *Nephrectomy usually controls the hypertension.*

Table 574.1 Cystic Diseases of the Kidney

INHERITABLE
Autosomal recessive (infantile) polycystic kidney disease (ARPKD)
Autosomal dominant (adult) polycystic kidney disease (ADPKD)
Juvenile nephronophthisis and medullary cystic disease complex
Juvenile nephronophthisis (autosomal recessive)
Medullary cystic disease (autosomal dominant)
Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive)
Familial hypoplastic glomerulocystic disease (autosomal dominant)
Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease)
Glomerulocystic kidney disease
Familial
Meckel-Gruber syndrome
Tuberous sclerosis
Zellweger syndrome
Trisomy 13
Jeune syndrome
Lissencephaly
Nephronophthisis
Orofacialdigital syndrome
NONHERITABLE
Multicystic kidney (multicystic dysplastic kidney)
Benign multilocular cyst (cystic nephroma)
Simple cysts
Medullary sponge kidney
Sporadic glomerulocystic kidney disease
Acquired renal cystic disease
Calyceal diverticulum (pyelogenic cyst)

Modified from Glassberg KI, Stephens FD, Lebowitz RL, et al. Renal dysgenesis and cystic disease of the kidney: a Report of the Committee on Terminology, Nomenclature and Classification, Section on Urology, American Academy of Pediatrics. *J Urol.* 1987;138:1085–1092. Table 2.

RENAL CYSTS IN CHILDREN

Although rare, there are many renal cystic disorders in children (Table 574.1). The most common is the **simple renal cyst** with a mean incidence of 0.22%. They are usually discovered incidentally during urinary tract imaging. Most are small and asymptomatic and do not require treatment, although follow-up imaging is recommended. If there are septations, irregular margins, calcifications, or a cluster of cysts, further evaluation may be indicated. The **Bosniak classification** of simple and complex renal cysts places various cystic lesions into four risk categories and helps guide a decision on whether removal of a lesion is necessary. A **calyceal diverticulum** is an outpouching of the collecting system into the corticomedullary region of the kidney, and it usually arises from the fornix of a calyx, usually in the upper or lower pole. Typically, the infundibulum between the diverticulum and renal pelvis is narrow. Occasionally, calculi form within the lesion, or it causes symptoms of flank pain, necessitating removal of the diverticulum.

A **multilocular cyst (multilocular cystic nephroma)** is a lesion in the kidney that falls in a spectrum of diseases, along with multilocular cyst with partially differentiated Wilms tumor, multilocular cyst with nodules of Wilms tumor, or cystic Wilms tumor. The multilocular cyst is considered benign and is unrelated to the MCDK. More than 95% occur in children <4 years, and most are discovered during evaluation for an abdominal or flank mass. The lesion should be removed.

ANOMALIES IN SHAPE AND POSITION

During renal development, the kidneys normally ascend from the pelvis into their normal position within the retroperitoneum. The normal process of ascent and rotation of the kidney may be incomplete,

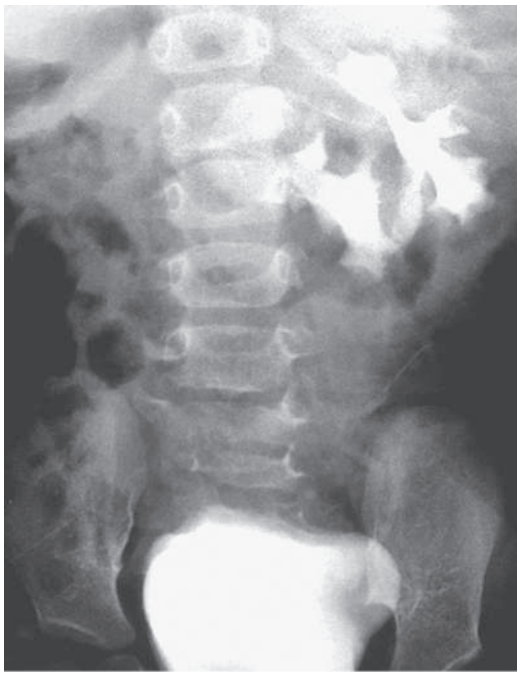

Fig. 574.4 Crossed renal ectopia. Intravenous urography shows both renal collecting systems to the left of the spine. Segmentation anomalies of the sacrum, which are subtle in this child, are one of the skeletal anomalies associated with renal ectopia. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Elsevier; 2008. Fig. 145-23A, p. 2244.)*

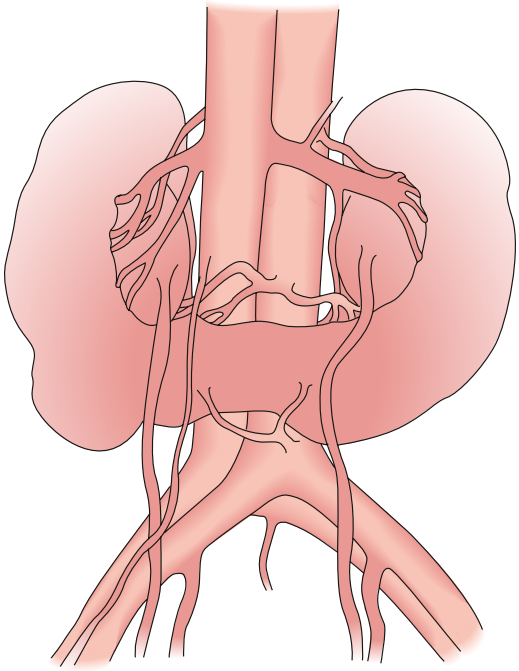

Fig. 574.5 Horseshoe kidney.

resulting in renal ectopia or malrotation. The ectopic kidney may be in a pelvic, iliac, thoracic, or contralateral position. Ectopia may be bilateral; the kidneys fuse in 90% of these cases. The incidence of renal ectopia is approximately 1 in 900 (Fig. 574.4).

Renal fusion anomalies are more common. The lower poles of the kidneys can fuse in the midline, resulting in a horseshoe kidney (Fig. 574.5); the fused portion is termed the *isthmus* and may be thick functioning parenchyma or a thin fibrous strand. Horseshoe kidneys occur in 1 in 400-500 births and are seen in 14–20% of patients with Turner syndrome (see Chapter 626); horseshoe kidneys are also associated with VACTERL and caudal regression syndromes, as well as trisomies 18 and 21. Wilms tumors are four times more common in children with horseshoe kidneys than in the general population. Stone disease, hydronephrosis secondary to ureteropelvic junction obstruction, and vesicoureteral reflux are other potential complications. The incidence of MCDK affecting one of the two sides of a horseshoe kidney also is increased. With crossed fused ectopia, one kidney crosses over to the other side, and the parenchyma of the two kidneys is fused. Renal function usually is normal. Most commonly, the left kidney crosses over and fuses with the lower pole of the right kidney. The insertion of the ureter to the bladder does not change, and the adrenal glands remain in their normal positions. The clinical significance of this anomaly is that if renal surgery is necessary, the blood supply is variable and can make partial nephrectomy more difficult.

ASSOCIATED PHYSICAL FINDINGS

Upper urinary tract anomalies are more common in children with certain physical findings. The incidence of renal anomalies is increased if there is a single umbilical artery and an abnormality of another organ system (e.g., congenital heart disease). External ear anomalies, imperforate anus, and scoliosis are also associated with renal anomalies. Infants with these physical findings should undergo a renal ultrasound.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 575

Urinary Tract Infections

Marie E. Wang and Pearl W. Chang

PREVALENCE AND ETIOLOGY

Urinary tract infections (UTIs) commonly occur in children of all ages, though the prevalence varies with age. UTIs are most common in children under 1 year of age. The prevalence in *febrile* infants and children less than 24 months is 7%, and the prevalence in older children less than 19 years presenting with urinary symptoms and/or fever is 8%. During the first 3 months of life, UTIs are most common in uncircumcised febrile males with a prevalence of 20%, which is eight times higher than circumcised males and 2-3 times higher than females. After 6 months of age, UTIs are much more likely in females, with peaks during infancy, toilet training, and onset of sexual activity.

UTIs are caused primarily by colonic bacteria. *Escherichia coli* (see Chapter 246) causes the majority of UTIs, followed by *Klebsiella* spp. and *Proteus* spp., *Enterococcus,* and *Pseudomonas* (see Chapter 148). Other bacteria known to cause UTIs include *Staphylococcus saprophyticus,* group B streptococcus, and, less commonly, *Staphylococcus aureus, Candida* spp., and *Salmonella* spp.

CLINICAL MANIFESTATIONS AND CLASSIFICATION

The two basic forms of UTIs are **pyelonephritis** and **cystitis.** Focal pyelonephritis (lobar nephronia) and renal abscesses are less common.

Pyelonephritis

Pyelonephritis is characterized by any or all of the following: abdominal, back, or flank pain; fever; malaise; nausea; vomiting; and, occasionally, diarrhea. *Fever may be the only manifestation, especially in young children; particular consideration should occur for a temperature ≥39°C (102.2°F) without another source lasting more than 48 hours in infants*. Newborns can also show nonspecific symptoms, such as poor feeding, irritability, jaundice, or weight loss. Pyelonephritis is the most common bacterial infection in infants younger than 24 months of age who have fever without an obvious focus (see Chapters 220 and 221). Involvement of the renal parenchyma is termed acute pyelonephritis (Figs. 575.1 and 575.2), whereas if there is no parenchymal involvement, the condition may be termed **pyelitis**. Acute pyelonephritis can result in renal injury, termed **pyelonephritic scarring**.

Acute lobar nephronia (acute focal bacterial nephritis) is a localized renal parenchymal mass caused by acute focal infection without liquefaction; it more commonly occurs in older children. It may be an early stage in the development of a renal abscess (Fig. 575.3). Manifestations are identical to those of pyelonephritis and include fever and flank pain. The epidemiology of the causative organism is also similar to that of pyelonephritis. **Renal abscess** can occur following a pyelonephritic infection caused by the usual uropathogens or less commonly following hematogenous spread with *S. aureus.* Most abscesses are unilateral and right-sided and can affect children of all ages (Fig. 575.4). Both acute lobar nephronia and renal abscess are associated with an increased risk of renal scarring. **Perinephric abscess** can occur secondary to contiguous infection in the perirenal area (e.g., vertebral osteomyelitis, psoas abscess) or pyelonephritis that dissects to the renal capsule. It differs from renal abscess in that it is diffuse throughout the capsule and is not walled off, although it can develop septations. As with renal abscesses, the most common organisms are *S. aureus* and *E. coli.* A perinephric abscess may not communicate with the collecting system, and, thus, abnormal findings may not be seen on urinalysis or culture.

Xanthogranulomatous pyelonephritis is a rare type of chronic renal infection characterized by granulomatous inflammation with

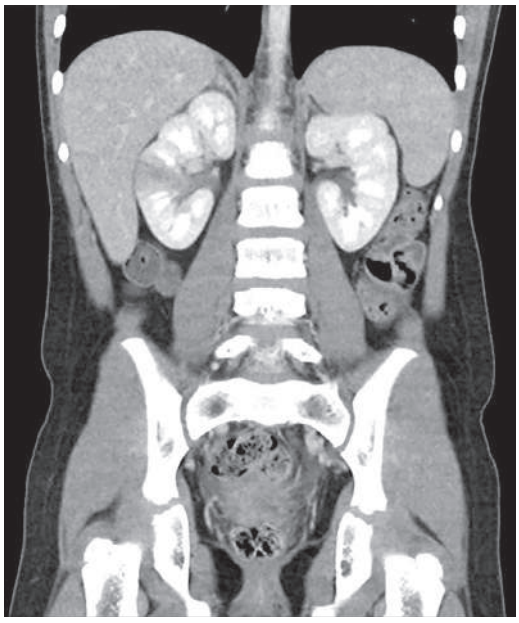

Fig. 575.1 Acute pyelonephritis seen as an area of decreased perfusion by CT scan done for abdominal pain and fever in a child who subsequently was shown to have no reflux by VCUG.

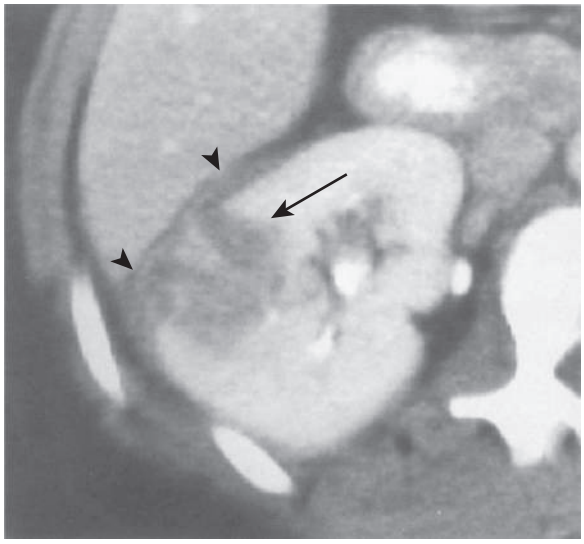

Fig. 575.2 Acute pyelonephritis with focal mass formation. The kidney shows a rounded heterogeneous mass *(arrow)* with a poorly defined margin. Inflammatory changes in the adjacent perinephric fat and renal fascial thickening *(arrowheads)* are also present. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017. Fig. 54-131, p. 1833.)*

giant cells and foamy histiocytes. It can manifest clinically with a renal mass and nonspecific symptoms including fever, flank pain, weight loss, and malaise. Dysuria and other urinary symptoms are less common. Renal calculi, obstruction, and infection with *Proteus* spp. or *E. coli* contribute to the development of this lesion, which usually requires total or partial nephrectomy.

Alkaline encrusted pyelitis/cystitis is a rare chronic obstruction UTI caused by *Corynebacterium urealyticum*. The organism creates an alkaline urine (converting urea to ammonia), precipitating struvite and calcium phosphate resulting in stone formation and pyuria with

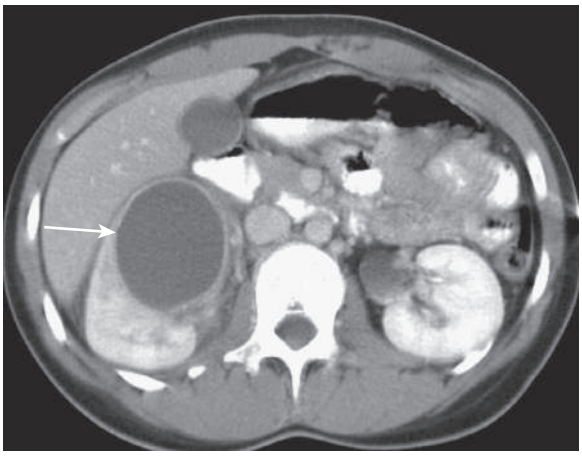

Fig. 575.3 Right renal abscess *(arrow)* shows a thick wall and low density (30 HU). Inflammatory stranding is present in the perinephric fat. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017. Fig. 55.3, p. 1834.)*

hematuria. Risk factors include urinary tract instrumentation, congenital uropathies/anomalies, chronic illness, and immune suppression.

Cystitis

Cystitis indicates that there is only bladder involvement; symptoms include dysuria, urgency, frequency, suprapubic pain, incontinence, and possibly malodorous urine. Cystitis does not cause high fever and does not result in renal injury. Malodorous urine is suggestive but not specific for a UTI.

Acute hemorrhagic cystitis, though uncommon in immunocompetent children, is often caused by *E. coli;* it also has been attributed to adenovirus types 11 and 21. It is self-limiting, with hematuria lasting approximately 4 days. Patients receiving immunosuppressive therapy (e.g., solid-organ or bone marrow transplantation) are at higher risk for hemorrhagic cystitis; adenoviruses and polyomaviruses (i.e., JC virus and BK virus) are important causes in immunocompromised populations (see Chapter 321). Other rare types of cystitis that may be confused with infection include *eosinophilic cystitis* or *interstitial cystitis.* Eosinophilic cystitis may present with hematuria, whereas interstitial cystitis may present with irritative voiding symptoms but a negative urine culture.

PATHOGENESIS AND PATHOLOGY

Nearly all UTIs are ascending infections. The bacteria arise from the fecal flora, colonize the perineum, and enter the bladder via the urethra. In uncircumcised males, the bacterial pathogens arise from the flora beneath the prepuce. In some cases, the bacteria causing cystitis ascend to the kidney to cause pyelonephritis. Rarely, renal infection occurs by hematogenous spread, as in endocarditis or in bacteremic neonates.

If bacteria ascend from the bladder to the kidney, acute pyelonephritis can occur. Normally, the simple and compound papillae in the kidney have an antireflux mechanism that prevents urine in the renal pelvis from entering the collecting tubules. However, some compound papillae, typically in the upper and lower poles of the kidney, allow intrarenal reflux. Infected urine stimulates an immunologic and inflammatory response that can cause renal injury and scarring (Figs. 575.5 and 575.6).

Table 575.1 and Figure 575.7 outline the host risk factors for UTI. Vesicoureteral reflux (VUR) is discussed in Chapter 576. If there is grade III, IV, or V VUR and a febrile UTI, 90% of patients have evidence of acute pyelonephritis on renal scintigraphy or other imaging studies. In females, UTIs often occur at the onset of toilet training because of bowel-bladder dysfunction that occurs at that age. The child is trying to retain urine to stay dry, yet the bladder may have uninhibited contractions forcing urine out. The resulting high-pressure, turbulent urine flow and incomplete bladder emptying both increase

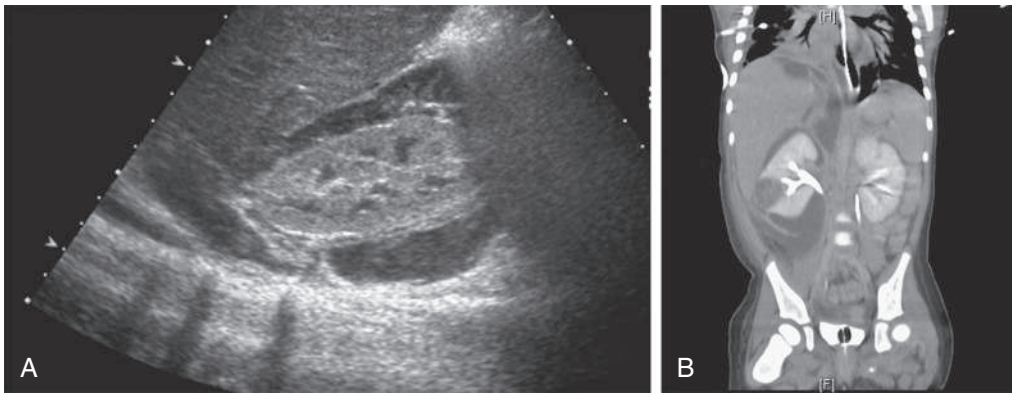

Fig. 575.4 A, Renal sonogram, 19-mo-old infant with perirenal abscess secondary to methicillin-resistant *Staphylococcus aureus*. B, CT scan demonstrates extensive perinephric and focal intrarenal abscess. Patient underwent incision and drainage.

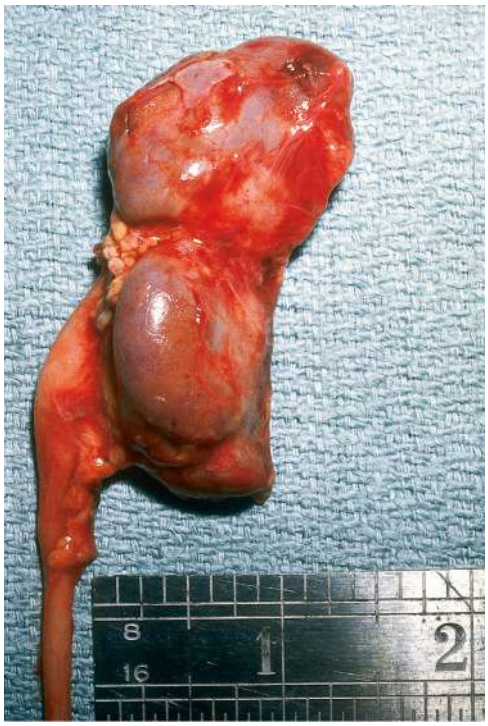

Fig. 575.5 Scarred kidney from recurrent pyelonephritis.

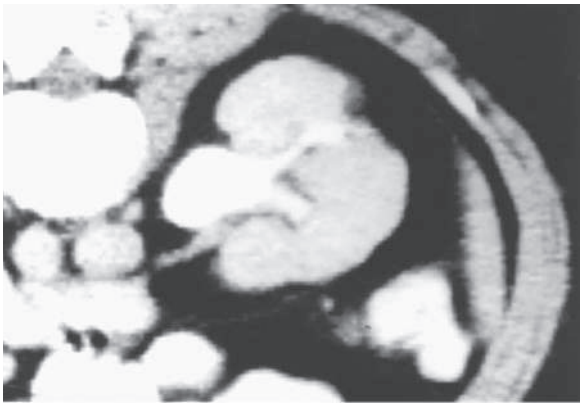

Fig. 575.6 CT scan showing an area of parenchymal thinning corresponding to an underlying calyx, characteristic of pyelonephritic scarring or reflux nephropathy.

Table 575.1 Risk Factors for Urinary Tract Infection

Female anatomy	Obstructive uropathy
Uncircumcised male	Urethral instrumentation
Age ≤1 years	Constipation
Vesicoureteral reflux	Anatomic abnormality (labial adhesion)
Toilet training	Neurogenic bladder
Voiding dysfunction	Sexual activity
Sources of external irritation (such as tight clothing, pinworm infestation)	Pregnancy

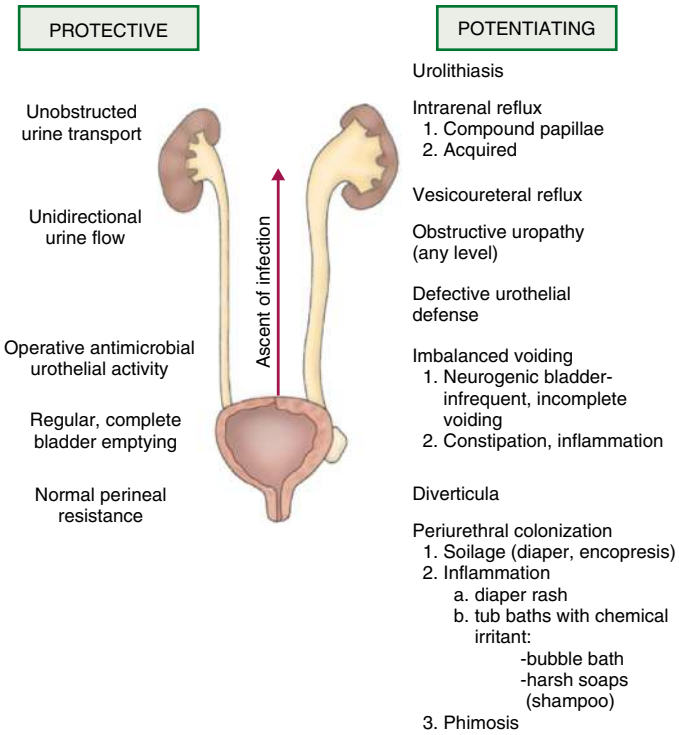

Fig. 575.7 Host factors that protect the urinary tract from infection and abnormalities that potentiate the establishment of invasive bacterial infection. *(From Holcomb III GW, Murphy JP, Ostlie DJ, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020. Fig. 55-3, p. 855.)*

Table 575.2 Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

TEST	SENSITIVITY (RANGE) %	SPECIFICITY (RANGE) %
Leukocyte esterase test	83 (67–94)	78 (64–92)
Nitrite test	53 (15–82)	98 (90–100)
Leukocyte esterase or nitrite positive	93 (90–100)	72 (58–91)
Microscopy (white blood cells)	73 (32–100)	81 (45–98)
Microscopy (bacteria)	81 (16–99)	83 (11–100)
Leukocyte esterase test, nitrite, or microscopy positive	99.8 (99–100)	70 (60–92)

From Finnell SM, Carroll AE, Downs SM, Subcommittee on Urinary Tract Infection. Technical report—diagnosis and management of an initial UTI in febrile infants and young children. *Pediatrics.* 2011;128:e749–e770.

the likelihood of bacteriuria. *Bowel-bladder dysfunction* can arise in school-age children who refuse to use the school bathroom, creating a state of urinary retention. Obstructive uropathy resulting in hydronephrosis increases the risk of UTI because of urinary stasis. Constipation with fecal impaction can increase the risk of UTI because it can cause bladder dysfunction.

Other host factors for UTI include anatomic abnormalities precluding normal micturition, such as a labial adhesion. This lesion acts as a barrier and causes vaginal voiding. A neurogenic bladder can predispose to UTI if there is incomplete bladder emptying and/or detrusor-sphincter dyssynergia or a resultant need for frequent catheterization. Sexual activity is associated with UTI in females due to introduction of bacteria near the urinary tract, which can be exacerbated in part because of urethral irritation and incomplete bladder emptying following intercourse.

The pathogenesis of UTI is based in part on the presence of bacterial pili or fimbriae on the bacterial surface, which allow for attachment to the uroepithelial cells. For *E. coli,* this attachment occurs through the type 1 fimbriae and P-fimbriae, which may result in bacterial uptake and replication and formation of intracellular bacterial communities. These intracellular organisms may evade the immune response, form quiescent reservoirs protected from antibiotics, and be a source of recurrent infections. Current research is attempting to prevent the initial attachment of bacteria to the bladder wall that can lead to intracellular bacterial communities and quiescent reservoirs.

DIAGNOSIS

Among children 2-24 months of age, risk factors for UTI include age younger than 12 months, being a female or uncircumcised male, temperature ≥39°C (102.2°F), fever for at least 2 days, and absence of another source of infection. Urine testing is recommended when the pretest probability of a UTI is ≥2%, and an online UTI calculator can provide probability estimates (https://uticalc.pitt.edu/). In older verbal children, urine testing should be considered when there are UTI symptoms. A positive urinalysis suggestive of infection (i.e., presence of pyuria) plus a urine culture with ≥50,000 colony-forming units (CFU)/mL of a single uropathogen are recommended for diagnosis of a UTI in a symptomatic child. In the appropriate clinical context, ≥10,000 CFU/mL may be sufficient for diagnosis, especially if the laboratory does not categorize counts between 10,000 and 100,000 CFU/mL.

There are several ways to obtain a urine sample; some are more accurate than others. In toilet-trained children, a midstream urine sample usually is satisfactory; the introitus should be cleaned before obtaining the specimen. In uncircumcised males, the prepuce must be retracted; if the prepuce is not retractable, a voided sample may be unreliable and contaminated with skin flora. For children 2-24 months who are not toilet trained, a catheterized urine sample should be obtained. Alternatively, the application of an adhesive, sealed, sterile collection bag after disinfection of the skin of the genitals can be useful only if the urinalysis and culture are negative; the negative predictive value for urinalysis from a "bag" specimen is 99%. However, a positive culture can result from skin contamination, particularly in females and uncircumcised males. If treatment is planned immediately after obtaining the urine sample, a bagged specimen *should not* be the method because of a high rate of contamination, often with mixed organisms. A suprapubic aspirate generally is unnecessary.

Inclusion of pyuria in the diagnostic criteria along with a positive urine culture helps to distinguish true UTI from asymptomatic bacteriuria or contamination. **Pyuria** is defined as ≥5 white blood cells (WBCs)/high-power field on a centrifuged specimen, ≥10 WBC/mm^3 on an enhanced urinalysis, or any **leukocyte esterase** on a dipstick. Additional urinalysis findings that support a UTI diagnosis include presence of **nitrites**. Bacteria generally require 4 hours for metabolism of nitrates to nitrites. Thus nitrites may not be detected in cases of UTI where the organism does not convert nitrates to nitrites (most notably *Enterococcus*) or if the child has urinary frequency, where there may not be enough time for the conversion to nitrites. Findings of leukocyte esterase, WBC on microscopy, or nitrites has a high sensitivity for UTI, including in febrile infants <60 days of age (Table 575.2). Microscopic hematuria is common in acute cystitis, but microhematuria alone does not suggest UTI. WBC casts in the urinary sediment suggest renal involvement, but in practice these are rarely seen.

Sterile pyuria (positive leukocytes, negative culture) may occur in partially treated bacterial UTI, viral infections, urolithiasis, renal tuberculosis, renal abscess, UTI in the presence of urinary obstruction, urethritis as a consequence of a sexually transmitted infection (see Chapter 163), inflammation near the ureter or bladder (appendicitis, Crohn disease), Kawasaki disease (see Chapter 493.1), COVID-19–associated multisystem inflammatory syndrome in children (MIS-C; see Chapter 311), schistosomiasis, neoplasm, renal transplant rejection, or interstitial nephritis (eosinophils). Prompt plating of the urine sample for culture is important, because if the urine sits at room temperature for more than 60 minutes, overgrowth of a minor contaminant can suggest a UTI when the urine might not be infected. Refrigeration is a reliable method of storing the urine until it can be cultured.

With acute renal infection, leukocytosis and neutrophilia are noted on the CBC; an elevated ESR, procalcitonin level, and CRP are common. However, these are all nonspecific markers of inflammation; thus their elevation does not prove that the child has acute pyelonephritis, and they do not need to be routinely obtained. Bacteremia in the setting of pyelonephritis is reported to occur in 3–20% of patients and is most common in infants <60 days old (with rates decreasing with increasing age in the first 60 days). For infants <60 days old or ill-appearing patients at presentation, blood cultures should be drawn before starting antibiotics, if possible.

IMAGING FINDINGS

Imaging is not needed to make the diagnosis of UTI. If there is concern about acute lobar nephronia or renal abscess (e.g., patient not responding to appropriate antibiotics), imaging should be considered. Ultrasound is the first-line imaging for screening and will likely demonstrate an enlarged kidney with a possible mass in the case of acute lobar nephronia or renal abscess. CT scan is more sensitive and specific for lobar nephronia and will typically show a wedge-shaped, lower-density area after contrast administration.

TREATMENT

Acute cystitis should be treated promptly to prevent possible progression to pyelonephritis. If the symptoms are severe, and the urinalysis shows pyuria, presumptive treatment should be started while awaiting urine culture results. If the symptoms are mild or the diagnosis is doubtful, treatment can be delayed until the results of culture are known, and the urinalysis and culture can be repeated if the results are uncertain. In **acute febrile UTI**, the clinical symptoms of cystitis and pyelonephritis are difficult to differentiate. Given the presence of systemic symptoms, it is reasonable to consider that the infection has likely progressed to the kidneys and treat for pyelonephritis. A UTI can be treated safely and effectively with oral antibiotics in the outpatient setting, including in younger children. Thus route of therapy should be based on practical considerations. Parenteral therapy should be used in children who are dehydrated, are vomiting, are unable to drink fluids, have complicated infection, or in whom urosepsis is a possibility. Infants less than 1 month of age with suspected febrile UTI are typically hospitalized and started on parenteral antibiotics while awaiting results of a sepsis evaluation and can be converted to oral therapy if there is no concern for meningitis and they are otherwise clinically well. Infants 1-2 months of age can be managed as an outpatient unless hospitalization is indicated for other reasons (e.g., emesis, dehydration). Although infants with bacteremic UTI are often treated with longer parenteral courses, duration of therapy has not been associated with UTI relapse.

Local antimicrobial sensitivity patterns should be considered when selecting empiric antibiotic treatment. For oral treatment, cephalexin is a commonly used narrow-spectrum empiric option, as overall rates of *E. coli* resistance to first-generation cephalosporins are low. In areas with high rates of *E. coli* resistance to first-generation cephalosporins, oral third-generation cephalosporins such as cefixime can be appropriate empiric options and are effective against a variety of gram-negative organisms. Trimethoprim-sulfamethoxazole (TMP-SMX) may also be used, though resistance is increasing in some areas. Nitrofurantoin can be used for cystitis but should not be used routinely in children with a febrile UTI, because it does not achieve significant renal tissue levels. The oral fluoroquinolone ciprofloxacin can be considered for UTI caused by *P. aeruginosa* or resistant microorganisms when there are no other oral antibiotic options. However, clinical treatment with fluoroquinolones in young children should be used with caution because of potential cartilage damage. For parenteral treatment in hospitalized children 1 month and older, ceftriaxone is a reasonable choice until culture results are available to determine whether a narrower-spectrum antibiotic can be used. Ampicillin plus either gentamicin or a third-generation cephalosporin are often used empirically in neonates. If prior urine culture results have grown resistant or atypical organisms, other antibiotic choices may be prudent on a case-by-case basis.

A repeat urine culture after the termination of UTI treatment is not routinely needed. Urine cultures are typically negative within 24 hours of initiation of antibiotic therapy; therefore a urine culture during treatment is almost invariably negative. Most children exhibit clinical improvement (afebrile) within 48-72 hours of antibiotic initiation. Recommended duration of therapy is generally 3-5 days for cystitis and 7-10 days for uncomplicated pyelonephritis. Atypical features include failure to respond within 48-72 hours of appropriate antibiotics; poor urine flow; an abdominal, flank, or suprapubic mass; sepsis; or an elevated creatinine level. Atypical features should prompt further evaluation.

Acute Lobar Nephronia, Renal Abscess, and Perinephric Abscess

Acute lobar nephronia is treated with the same antibiotics as pyelonephritis. The recommended duration of treatment is 14-21 days; one study suggested higher treatment failure in the group treated for shorter duration. Children with a renal or perirenal abscess or with infection in obstructed urinary tracts can require percutaneous or surgical drainage in addition to antibiotic therapy and other supportive measures (see Fig. 575.4). Percutaneous drainage is typically attempted prior to surgical intervention. Medical management alone has been successful in treating small-to-moderate renal abscesses. Although some studies have commented that resolution with antibiotics alone are more likely in abscesses 3 cm or less, some patients with abscesses >3 cm have been managed successfully with IV antibiotics only. Thus a 48-hour trial of IV antibiotics prior to percutaneous drainage may be warranted in otherwise stable children. Few studies address the role of oral antibiotic therapy for renal abscess. Traditionally, patients received 10-14 days of IV antibiotics, followed by 2-4 weeks of oral antibiotic therapy targeted against the known organism (or the likely causes of *E. coli* and *S. aureus* if the organism was unknown). The increasing use of oral antibiotics for other serious infections (e.g., osteomyelitis) suggests that an earlier transition to oral therapy for renal abscess is likely feasible. Kidney loss is reported to occur in 10–20% of cases of renal abscess. Perinephric abscesses may be managed with IV antibiotics alone or with percutaneous drainage if the area is large or causing impaired kidney function. Identification of a causative organism can be an additional advantage of percutaneous drainage of a perinephric abscess because the infection may remain isolated from the collecting system based on the location.

Other Potential Treatment or Prevention Options

There is interest in probiotic therapy as well as cranberry juice to *prevent* UTIs. Studies are ongoing and a probiotic containing a non-uropathogenic *E. coli* called Nissle 1917 is available in Europe and other parts of the world. These bacteria may inhibit growth of other bacteria. Cranberry juice may prevent bacterial adhesion and biofilm formation, hypothesized to be via proanthocyanidin (PAC). Currently there is insufficient evidence regarding the use of these therapies in children to reduce UTIs.

The main consequences of chronic renal damage caused by pyelonephritis are arterial hypertension and end-stage renal insufficiency; when they are found, they should be treated appropriately (see Chapters 494 and 572). Even without chronic renal damage, the consequences of infections include lost days from school and work, uncomfortable symptoms, and exposure to antibiotics that change the healthy microbiome.

IMAGING STUDIES IN CHILDREN WITH A FEBRILE UTI

The primary goal of imaging studies in children with a febrile UTI is to identify anatomic abnormalities that predispose to future infection, such as high-grade VUR, posterior urethral valves, or other obstructive uropathy. Imaging is usually unnecessary in children with afebrile cystitis. Historically, children either underwent a renal sonogram plus a voiding cystourethrogram (VCUG) in a "bottom-up" approach, or a dimercaptosuccinic acid (DMSA) renal scan first to identify areas of acute pyelonephritis (Fig. 575.8) in a "top-down" approach. If the DMSA scan was positive, then a VCUG was performed (Fig. 575.9) because up to 90% of children with dilating reflux have a positive DMSA scan. In the past decade, with increasing evidence that most children with first-time UTI have normal genitourinary tracts and the unclear benefit of early detection of VUR, most national guidelines recommend selective imaging for children with UTI. Though the sensitivity of renal-bladder ultrasounds for detecting VUR is poor, there is no established harm of nondetection of VUR after a first UTI.

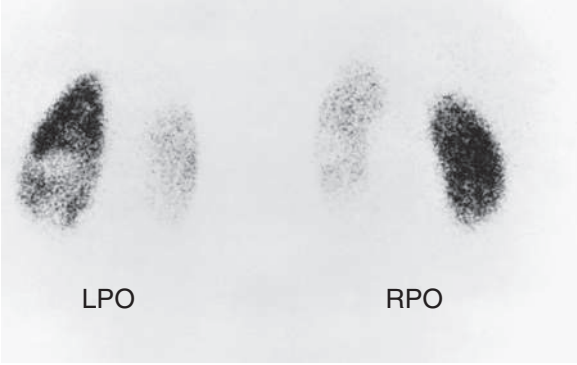

Fig. 575.8 DMSA renal scan showing bilateral photopenic areas indicating acute pyelonephritis and renal scarring. LPO, left posterior oblique; RPO, right posterior oblique.

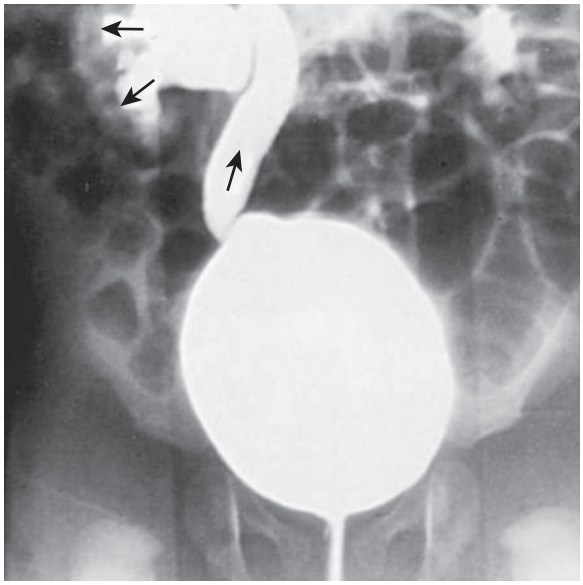

Fig. 575.9 Intrarenal reflux. VCUG in an infant boy with a history of a UTI. Note the right VUR with ureteral dilation, with opacification of the renal parenchyma representing intrarenal reflux.

Most experts still recommend initial ultrasound of the kidneys, ureters, and bladder for children 2-24 months with a first febrile UTI. VCUG should be obtained if the ultrasound study indicates hydronephrosis, scarring, or other findings suggestive of high-grade (e.g., grades IV-V) reflux or obstructive uropathy, or if the patient has other atypical complex features. Further, a VCUG should be obtained if the child has a recurrent febrile UTI (Table 575.3). The rate of renal scarring increases between days 2 and 3 of fever; this makes the prompt evaluation and appropriate treatment of a recurrent UTI important. The risk of scarring also increases with the number of episodes of pyelonephritis and with higher grades of reflux.

The NICE (National Institute for Health and Care Excellence, UK) guidelines for diagnosis, management, and imaging after UTI were released in 2022 (Table 575.4). These recommendations divided children into those younger than 6 months, 6 months to younger than 3 years, and 3 years and older. An initial renal-bladder ultrasound is recommended for all children younger than 6 months, and a VCUG only if atypical features (including non–*E. coli* infection, sepsis or bacteremia, failure to respond to antibiotics within 48 hours), recurrent UTI, or abnormal ultrasound findings. For children age 6 months to younger than 3 years who have a UTI with atypical features or recurrent UTI, an ultrasound is recommended, and if risk factors are present, then also a VCUG should also be obtained (see Table 575.4). No imaging is suggested for otherwise first-time, typical UTI in this age group. When ultrasound is recommended, the optimal timing for obtaining it is unclear. Most national guidelines recommend an ultrasound during the acute infection if there is concern for obstruction (e.g., not responding to antibiotics, elevated creatinine, poor urine flow) but otherwise nonurgently within 2-6 weeks after the UTI as routine ultrasound during the acute infection rarely changes management.

PREVENTION OF RECURRENCES

In a child with recurrent UTIs, identification of predisposing factors is beneficial. Bowel and bladder dysfunction is a very important contributor to recurrent UTIs and is one of the main reasons for an increase in UTIs around the time of toilet training. Bladder dysfunction is manifested by urgency, wetting, and especially "Vincent's curtsy" (children squat on their heels in response to an uninhibited bladder contraction) (see Chapter 580). In toilet-trained children, a thorough history and use of urodynamic studies and measurement of postvoid residual volumes may be helpful in

Table 575.3 Guideline Recommendations for Diagnostic Evaluation Following a Febrile Urinary Tract Infection in Infants

GUIDELINE	ULTRASONOGRAPHY	VCUG	LATE DMSA SCAN
National Institute for Health and Care Excellence (NICE)	See Table 575.4		
American Academy of Pediatrics (retired)	Yes	If abnormal ultrasonogram or febrile recurrence	No
Italian Society for Paediatric Nephrology (ISPN)	Yes	If abnormal ultrasonogram, non-*Escherichia coli* infection, or febrile recurrence	If grade IV-V VUR
Spanish Association of Paediatrics	Yes, if age <6 months, atypical infection,* or recurrence	If abnormal ultrasonogram, atypical infection,* or recurrence	If atypical infection* or recurrence
Swiss consensus recommendations	Yes	If abnormal ultrasonogram, atypical infection,† or febrile recurrence	No

*Defined as fever >48 hours after appropriate antibiotics, sepsis, non–*E. coli* infection, acute kidney injury, or abdominal or vesical mass.
†Defined as failure to respond to appropriate antibiotics within 48 hours, non–*E. coli* infection, increased creatinine, abnormal electrolytes, hypertension, or poor urine flow.
VCUG, Voiding cystourethrogram; DMSA, dimercaptosuccinic acid; VUR, vesicoureteral reflux.

Table 575.4 NICE Recommended Imaging Schedule for Children with Urinary Tract Infection

CHILD AGE AND TESTS	TYPE OF INFECTION		
	RESPONDS WELL TO TREATMENT WITHIN 48 HR	ATYPICAL INFECTION*	RECURRENT INFECTION
CHILDREN YOUNGER THAN 6 MO OLD			
Ultrasound scan during acute infection	No	Yes	Yes
Ultrasound scan within 6 wk of infection	Yes	No	No
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
VCUG	Consider if ultrasound scan abnormal	Yes	Yes
CHILDREN 6 MO TO YOUNGER THAN 3 YR OLD			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
VCUG	No	Not routine; consider if dilation on ultrasound, poor urine flow, non–*E. coli* infection, or family history of vesicoureteral reflux	
CHILDREN 3 YR OR OLDER			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	No	Yes
VCUG	No	No	No

*Defined as seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, sepsis or bacteriemia, failure to respond to appropriate antibiotics within 48 hours, or infection with non–*E. coli* organisms.

NICE, National Institute for Health and Care Excellence; DMSA, Dimercaptosuccinic acid; VCUG, voiding cystourethrogram.

Adapted from National Institute for Health and Clinical Excellence. Urinary tract infection in children: Diagnosis, treatment, and long-term management. NICE clinical guidelines, no. 224. London: RCOG Press; 2022. Tables 4–6.

identifying children with bladder dysfunction that may contribute to UTI. Tightening the pelvic floor during urination can sometimes be seen on a VCUG as a **spinning-top urethra** (Fig. 575.10). An ultrasound may document residual urine and possibly a thick bladder wall. Urodynamics may show an intermittent stream with increased activity in the pelvic floor muscles. Some children with UTI may also have constipation (see Chapter 378.3). Behavioral modification, with treatment of constipation as described in Chapter 580, often is effective at reducing recurrent UTI from constipation.

Routine use of antibiotic prophylaxis is not recommended for children with a first episode of pyelonephritis and an otherwise anatomically normal urinary tract. Urologic conditions that can cause recurrent UTIs that might benefit from long-term antibiotic prophylaxis include neurogenic bladder, urinary tract stasis and obstruction, severe VUR (see Chapter 576), and urinary calculi. The RIVUR study was a randomized trial of TMP-SMX prophylaxis for patients with a history of UTI and diagnosed grades I-IV VUR. Although the UTI recurrence rate was decreased by half from 30% in the group not receiving prophylaxis to 15% in those receiving prophylaxis, rates of renal scarring were the same in both groups. Additionally, the rates of UTI caused by resistant organisms increased in the group receiving prophylaxis. Although the use of prophylaxis can decrease rates of recurrence, routine prophylaxis is not recommended for children with VUR (especially lower-grade VUR) due to the increase in antibiotic resistance, need for daily medication in children, and lack of change in renal scarring.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 575.10 VCUG shows contraction of the pelvic floor and external sphincter during voiding, leading to a dilated posterior urethra and bilateral reflux.

Chapter 576

Vesicoureteral Reflux

Heather N. Di Carlo and Chad B. Crigger

Vesicoureteral reflux (VUR) describes the retrograde flow of urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder normally is oblique, between the bladder mucosa and detrusor muscle, creating a flap-valve mechanism that prevents VUR (Fig. 576.1). VUR occurs when the submucosal tunnel between the mucosa and detrusor muscle is short or absent. Affecting 1–2% of children, VUR usually is congenital and often is familial. VUR is present in approximately 30% of females who had a urinary tract infection and in 5–15% of infants with antenatal hydronephrosis.

VUR predisposes to kidney infection **(pyelonephritis)** by facilitating the transport of bacteria from the bladder to the upper urinary tract (see Chapter 575). The inflammatory reaction caused by pyelonephritis can result in renal injury or scarring, also termed **reflux-related renal injury** or **reflux nephropathy.** In children with a febrile urinary tract infection, those with VUR are three times more likely to develop renal injury compared with those without VUR. Extensive **renal scarring** impairs renal function and can result in renin-mediated hypertension (see Chapter 494), renal insufficiency or end-stage renal disease (see Chapter 572), impaired somatic growth, and morbidity during pregnancy. Scarring associated with reflux may be present at birth or develop in the absence of infection if there is significant bladder-sphincter discoordination during voiding.

In the past, reflux nephropathy accounted for as much as 15–20% of end-stage renal disease in children and young adults. With greater attention to the management of UTIs and a better understanding of VUR, end-stage renal disease secondary to reflux nephropathy is uncommon. Reflux nephropathy remains a common cause of hypertension in children. VUR in the absence of infection or elevated bladder pressure (e.g., neuropathic bladder, posterior urethral valves) rarely causes renal injury.

CLASSIFICATION

VUR severity is graded using the International Reflux Study (IRS) classification of I-V and is based on the appearance of the urinary tract on a contrast **voiding cystourethrogra**m (VCUG) (Figs. 576.2 and 576.3). The higher the VUR grade the greater the likelihood of renal injury. VUR severity is an indirect indication of the degree of abnormality of the ureterovesical junction.

VUR may be primary or secondary (Table 576.1). **Bladder-bowel dysfunction (BBD)** can worsen preexisting VUR if there is a marginally competent ureterovesical junction. In the most severe cases, there is such massive VUR into the upper tracts that the bladder becomes overdistended. This condition, the **megacystis-megaureter syndrome,** occurs primarily in males and may be unilateral or bilateral (Fig. 576.4). Reimplantation of the ureters into the bladder to correct VUR corrects the condition.

Primary VUR appears to be an autosomal dominant inherited trait with variable penetrance. Approximately 35% of siblings of children with VUR also have VUR, and VUR is found in nearly half of newborn siblings. The likelihood of a sibling having VUR is independent of the grade of VUR or sex of the index child. Approximately 12% of asymptomatic siblings with VUR have evidence of renal scarring. In addition, 50% of children born to women with a history of VUR also have VUR. The American Urological Association Vesicoureteral Reflux Guidelines Panel stated that, *in siblings of individuals with VUR, a VCUG or radionuclide cystogram is recommended if there is evidence of a renal cortical abnormality or renal size asymmetry on sonography, or if the sibling has a history of febrile UTI*. Otherwise, screening is optional. VUR may be suggested on a prenatal ultrasound that demonstrates hydronephrosis or hydroureteronephrosis.

Approximately 1 in 125 children has a **duplication** of the upper urinary tract, in which two ureters rather than one drain the kidney. Duplication may be partial or complete. In partial duplication, the

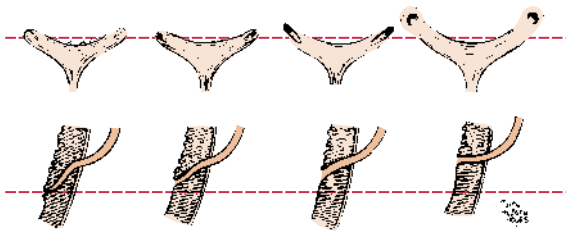

Fig. 576.1 Normal and abnormal configuration of the ureteral orifices. Shown from *left* to *right*, progressive lateral displacement of the ureteral orifices and shortening of the intramural tunnels. *Top*, Endoscopic appearance. *Bottom*, Sagittal view through the intramural ureter.

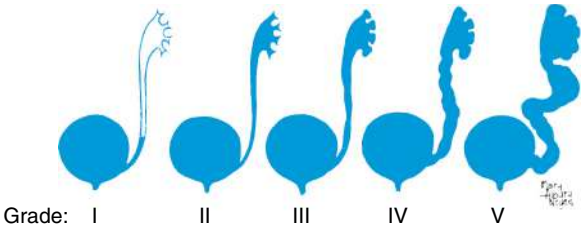

Fig. 576.2 Grading of VUR. Grade I: VUR into a nondilated ureter. Grade II: VUR into the upper collecting system without dilation. Grade III: VUR into a dilated ureter and/or blunting of the calyceal fornices. Grade IV: VUR into a grossly dilated ureter. Grade V: massive VUR, with significant ureteral dilation and tortuosity and loss of the papillary impression.

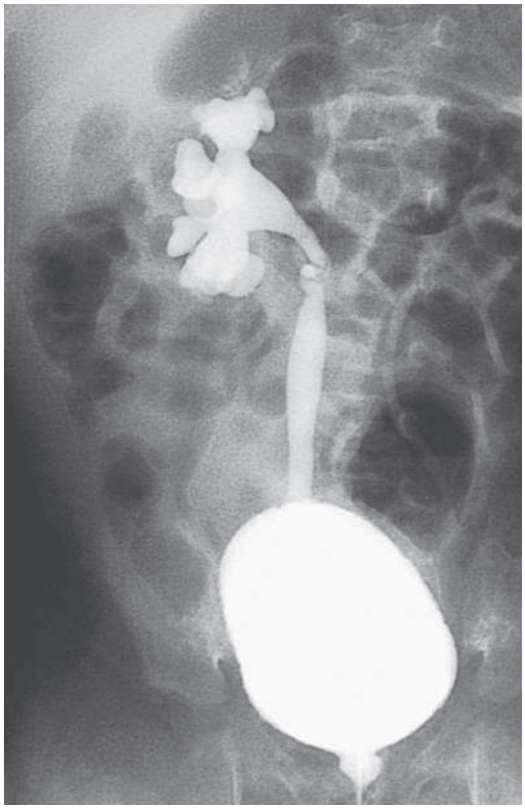

Fig. 576.3 VCUG showing grade IV right VUR.

Table 576.1 Classification of Vesicoureteral Reflux

TYPE	CAUSE
Primary	Congenital incompetence of the valvular mechanism of the vesicoureteral junction
Primary associated with other malformations of the ureterovesical junction	Ureteral duplication Ureterocele with duplication Ureteral ectopia Paraureteral diverticula
Secondary to increased intravesical pressure	Neuropathic bladder Nonneuropathic bladder dysfunction Bladder outlet obstruction
Secondary to inflammatory processes	Severe bacterial cystitis Foreign bodies Vesical calculi Clinical cystitis
Secondary to surgical procedures involving the ureterovesical junction	Surgery

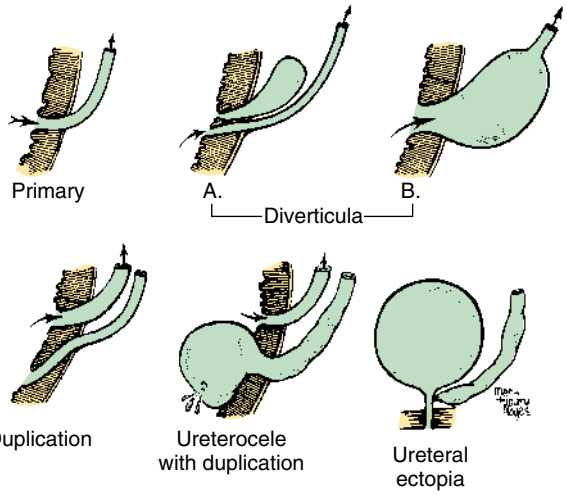

Fig. 576.5 Various anatomic defects of the ureterovesical junction associated with VUR.

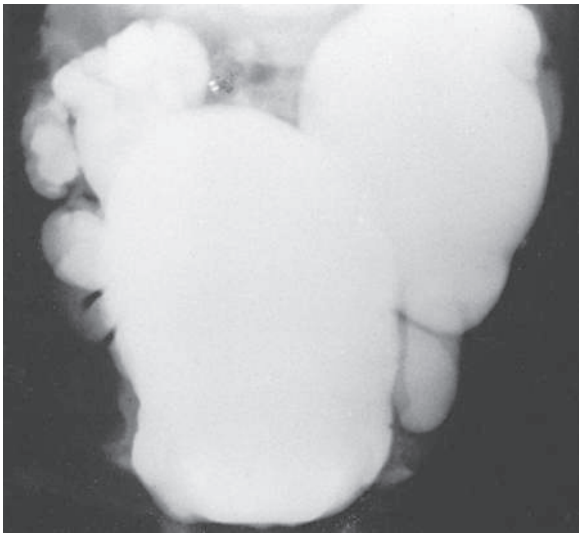

Fig. 576.4 VCUG in a newborn with megacystis-megaureter syndrome. Note the massive ureteral dilation caused by high-grade VUR. The bladder is very distended. There was no urethral obstruction or neuropathic dysfunction.



Fig. 576.6 VUR and bladder diverticulum. The VCUG demonstrates left VUR and a paraureteral diverticulum.

ureters join above the bladder, and there is one ureteral orifice. In complete duplication, the attachment of the lower pole ureter to the bladder is superior and lateral to the upper pole ureter. The valvelike mechanism for the lower pole ureter often is marginal, and VUR into the lower ureter occurs in as many as 50% of cases (Fig. 576.5). VUR occurs into both the lower and upper systems in some persons. With a duplication anomaly, some patients have an **ectopic ureter**, in which the upper pole ureter drains outside the bladder (see Chapter 577 and Figs. 577.6 and 577.7). If the ectopic ureter drains into the bladder neck, typically it is obstructed and refluxes. Duplication anomalies also are common in children with a **ureterocele**, which is a cystic swelling of the intramural portion of the distal ureter. These patients often have VUR into the associated lower pole ureter or the contralateral ureter. In addition, generally VUR is present when the ureter enters a bladder diverticulum (Fig. 576.6).

VUR is present at birth in 25% of children with **neuropathic bladder,** as occurs in myelomeningocele (see Chapters 579 and 631.4), sacral agenesis, and many cases of high imperforate anus. VUR is seen in 50% of males with posterior urethral valves. VUR with increased intravesical pressure (as in detrusor-sphincter discoordination or bladder outlet obstruction) can result in renal injury because of increased intravesical pressure transmitted to the upper urinary tract, even in the absence of infection.

Primary VUR occurs in association with several congenital urinary tract abnormalities. Of children with a multicystic dysplastic kidney or renal agenesis (see Chapter 574), 15% have VUR into the contralateral kidney, and 10–15% of children with a ureteropelvic junction obstruction have VUR into either the hydronephrotic kidney or the contralateral kidney. As such, a diagnosis of VUR should prompt complete investigation to rule out concomitant pathology contralaterally.

CLINICAL MANIFESTATIONS

VUR usually is discovered during evaluation for a UTI (see Chapter 575). Among these children, 80% are female, with an average age at diagnosis of 2-3 years. In other children, a VCUG is performed during evaluation of BBD, renal insufficiency, hypertension, or other suspected pathologic process of the urinary tract. Primary VUR also may be discovered during evaluation for antenatal hydronephrosis. In this select population, 80% of affected children are male, and the VUR

grade usually is higher than in females whose VUR is diagnosed following a UTI. The UTI may be symptomatic, an isolated febrile event, or more often both febrile and symptomatic (abdominal pain, dysuria). BBD (constipation) may be present in 50% of children with reflux and a UTI.

DIAGNOSIS

Diagnosis of VUR requires catheterization of the bladder, instillation of a solution containing iodinated contrast or a radiopharmaceutical, and radiologic imaging of the lower and upper urinary tract (a contrast VCUG or radionuclide cystogram, respectively). The bladder and upper urinary tracts are imaged during bladder filling and voiding. VUR occurring during bladder filling is termed *low-pressure* VUR; VUR during voiding is termed *high-pressure* VUR. *VUR in children with low-pressure VUR is significantly less likely to resolve spontaneously than in children who exhibit only high-pressure VUR.* Radiation exposure during a radionuclide cystogram is significantly less than that from a contrast VCUG. Low-dose radiation contrast VCUG provides more anatomic information, such as demonstration of a duplex collecting system, ectopic ureter, paraureteral (bladder) diverticulum, bladder outlet obstruction in males, upper urinary tract stasis, and signs of voiding dysfunction, such as a **spinning-top** urethra in females. The VUR grading system is based on the appearance on contrast VCUG, and the grade reported is the maximum grade observed during the study. For follow-up evaluation, some prefer the radionuclide cystogram because of the lower radiation exposure (Fig. 576.7), although it is difficult to determine whether the VUR severity has changed and the grading system for the radionuclide study is different than the standard IRS grading system.



Fig. 576.7 Radionuclide cystogram shows bilateral VUR.

Children undergoing cystography may be psychologically traumatized by the catheterization. Careful preparation by caregivers, use of Child Life specialists, or administration of oral or nasal midazolam (for sedation and amnesia) or propofol before the study can result in a less-distressing experience.

Indirect cystography is a technique of detecting VUR without catheterization that involves injecting an intravenous radiopharmaceutical that is excreted by the kidneys, waiting for it to be excreted into the bladder, and imaging the lower urinary tract while the patient voids. This technique detects only 75% of VUR cases. Another technique, which avoids radiation exposure, involves instilling sonographic contrast medium through a urethral catheter. The kidneys are imaged sonographically to determine whether any of the material refluxes. This technique is currently investigational only.

After VUR is diagnosed, assessment of the upper urinary tract is important. The goal of upper tract imaging is to assess whether renal scarring and associated urinary tract anomalies are present. Renal imaging typically is performed with a renal sonogram and/or renal scintigraphy (Fig. 576.8; see Chapter 575).

The child should be evaluated for BBD, including urgency, frequency, diurnal incontinence, infrequent voiding, or a combination of these (see Chapter 575). Children with an overactive bladder often undergo a regimen of behavioral modification with timed voiding, treatment of constipation, and, on occasion, anticholinergic therapy.

After diagnosis, the child's height, weight, and blood pressure should be measured and monitored. If upper tract imaging shows renal scarring, a serum creatinine measurement should be obtained. The urine should be assessed for infection and proteinuria.

NATURAL HISTORY

The incidence of reflux-related renal scarring increases with VUR grade. With bladder growth and maturation, the VUR grade often resolves or improves. *Lower grades of VUR are much more likely to resolve than are higher grades.* For grade I and II VUR, the likelihood of resolution is similar regardless of age at diagnosis and whether it is unilateral or bilateral. For grade III, a younger age at diagnosis and unilateral VUR usually are associated with a higher rate of spontaneous resolution (Fig. 576.9). Bilateral grade IV VUR is much less likely to resolve than is unilateral grade IV VUR. Grade V VUR rarely resolves. The mean age at VUR resolution is 6 years. *BBD and grade III-V VUR are the most common risk factors for recurrent febrile UTI and new renal scarring.*

Sterile VUR does not usually cause renal injury in the absence of infection, but in situations with high-pressure VUR, as in children with posterior urethral valves, neuropathic bladder, and nonneurogenic neurogenic bladder (i.e., **Hinman syndrome**), sterile VUR can cause significant renal damage. Children with high-grade VUR who acquire



Fig. 576.8 A, VCUG in a 3-yr-old child with two febrile UTIs shows bilateral grade III VUR. B, At 5 years, repeat VCUG shows worsening VUR and calyceal clubbing, indicating renal scarring. C, At 11 years, renin-mediated hypertension has developed. Dimercaptosuccinic acid (DMSA) renal scan shows significant VUR-related renal scarring.

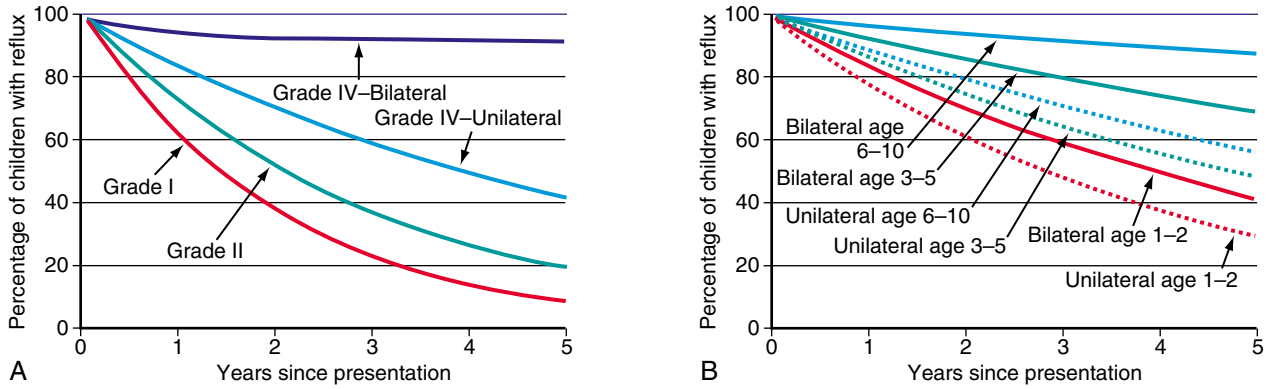

Fig. 576.9 A, Percentage chance of VUR persistence, grades I, II, and IV, for 1-5 years after presentation. B, Percentage chance of VUR persistence by age at presentation, grade III, for 1-5 years after presentation. *(From Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol. 1997;157:1846–1851.)*

a UTI are at significant risk for acute and recurrent pyelonephritis and new renal scarring (see Fig. 576.8).

TREATMENT

The goals of treatment are to prevent pyelonephritis, VUR-related renal injury, and other complications of VUR. Medical therapy is based on the principle that VUR often resolves over time and that if UTIs can be prevented, the morbidity or complications of VUR may be avoided without surgery. Medical therapy includes observation with behavioral modification or behavioral modification with antimicrobial prophylaxis in some patients. The basis for surgical therapy is that in selected children, ongoing VUR has caused or has significant potential for causing renal injury or other VUR-related complications, and that elimination of VUR minimizes the risk of these problems. Therapy for VUR should be individualized based on a particular patient's risk factors.

Observation

In children undergoing observation, therapeutic emphasis is directed at minimizing the risk of UTI by behavioral modification. These methods include timed voiding during the day, ensuring regular fecal elimination, increased fluid intake, periodic assessment of satisfactory bladder emptying, and prompt assessment and treatment of UTIs, particularly febrile UTIs. This approach is most appropriate for children with grade I and II VUR, and perhaps older children with persistent VUR and normal kidneys who have not experienced clinical pyelonephritis.

Antimicrobial Prophylaxis

In the past, daily antimicrobial prophylaxis was recommended as an initial approach to most children with VUR. However, several prospective clinical trials question the benefit of prophylaxis in children with VUR. The risk of recurrent UTI is highest in patients with grade III or IV reflux, those with BBD, and those whose first reflux-associated UTI was *febrile* rather than just symptomatic without fever. Antibiotic prophylaxis after a reflux-associated UTI decreases the risk of recurrent UTI but may increase the risk of developing resistant bacteria. In one study, antibiotic prophylaxis reduced the risk of new renal scars in children with grade III or IV reflux, while in another larger study, antibiotic prophylaxis did not affect the incidence of new renal scars in those with severe reflux (approximately 10% developed new scars regardless of prophylaxis).

Surgery

The purpose of surgical therapy is to minimize the risk of febrile UTI from ongoing VUR and nonsurgical therapy (observation or prophylaxis with follow-up testing). VUR can be corrected through a lower abdominal or inguinal incision (open), laparoscopically (with or without robotic assistance), or endoscopically with subureteral injection of a bulking agent.

Surgical management involves modifying the abnormal ureterovesical attachment. The operation can be performed from either outside (extravesical) or inside the bladder (intravesical). When VUR is associated with severe ureteral dilation (i.e., megaureter), the ureter must be tailored or narrowed to a more normal size to allow a smaller length:width ratio for the intramural tunnel, and a corner of the bladder is attached to the psoas tendon, forming a *psoas hitch.* Most children can be discharged 1-2 days following the surgical procedure. If the refluxing kidney is poorly functioning, nephrectomy or nephroureterectomy is indicated. Minimally invasive approaches with **laparoscopic** and **robotic-assisted laparoscopic ureteral reimplantation** offer alternatives to open surgical management; as experience with these procedures grows, success rates are approaching that of open surgery.

The success rate of conventional open ureteral reimplantation in children with primary VUR is >95–98% for grades I-IV, with 2% experiencing persistent VUR and 1% having ureteral obstruction that requires correction. The success rate is so high that many pediatric urologists do not perform a postoperative VCUG unless the child develops clinical pyelonephritis. For grade V VUR, the success rate is approximately 80%. In lower grades of VUR, a failed reimplantation is most likely to occur in children with undiagnosed BBD. In children with secondary VUR (posterior urethral valves, neuropathic bladder), the success rate is slightly lower than with primary VUR. The risk of pyelonephritis in children with grade III and IV VUR is significantly lower following open surgical correction compared with medical management. *Surgical repair will not reverse renal scarring or lead to improvement in renal function.*

Endoscopic repair of VUR involves injection of a bulking agent through a cystoscope just beneath the ureteral orifice, creating an effective flap-valve (Figs. 576.10 and 576.11). In 2001, the US Food and Drug Administration (FDA) approved the use of a biodegradable material, dextranomer microspheres suspended in hyaluronic acid (Dx-HA) (Deflux), for subureteral injection. The advantage of subureteral injection is that it is a noninvasive outpatient procedure (performed under general anesthesia) with no recovery time. The success rate is 70–80% and is highest for lower grades of VUR. If the first injection is unsuccessful, one or two repeat injections can be performed. The VUR recurrence rate is approximately 10–20%. In other areas of the world, a polyacrylamide hydrogel is used for endoscopic injection. The success rate with this product, which is not approved in the United States, is similar to Dx-HA, but the risk of reflux recurrence is significantly less.

CURRENT VESICOURETERAL REFLUX GUIDELINES

The long-standing belief regarding the benefit of antibiotic prophylaxis in children with VUR has been questioned. Multiple randomized, controlled prospective trials suggested that the risk of UTI in children with VUR is not reduced by prophylaxis. Most of the children in these trials had grade I-III VUR, and few younger than 1 year of age were studied.

In contrast, the PRIVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts) trial from Australia showed significant benefit to prophylaxis in children with VUR. The Swedish VUR Trial in Children studied children younger than 2 years of age with grades III and IV VUR; they compared antibiotic prophylaxis (nitrofurantoin) with observation and endoscopic injection therapy. Females in the surveillance group had a significantly higher incidence of febrile UTI and new renal scarring compared with the other treatment groups. The largest randomized trial (RIVUR [Randomized Intervention for Children with Vesicoureteral Reflux]) enrolled more than 600 children and demonstrated a reduction in the recurrence rate of UTIs with no reduction in the occurrence of renal scarring with antibiotic prophylaxis, but the prevalence of renal scarring at study entry was low.

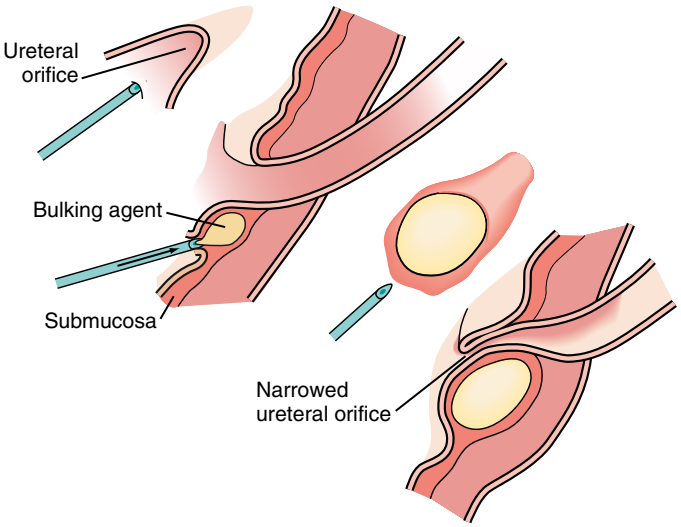

Fig. 576.10 Endoscopic correction of VUR. Through a cystoscope, a needle is inserted into the submucosal plane deep to the ureteral orifice, and a bulking agent is injected, creating a flap-valve to prevent VUR. *(Adapted from Ortenberg J. Endoscopic treatment of vesicoureteral reflux in children. Urol Clin North Am. 1998;25:151–156.)*

Prophylaxis is recommended by the American Urologic Association (AUA) in children at greatest risk for VUR-related renal injury (i.e., those <1 year of age). In addition, evaluation for bladder and bowel dysfunction is considered a standard part of initial and ongoing patient evaluation in children with VUR. Because children with BBD and VUR are much more likely to have recurrent UTIs and renal scarring, prophylaxis is recommended for these children. In children with VUR who are being managed by surveillance, if a febrile UTI occurs, prophylaxis is recommended. The decision whether to recommend observation, medical therapy, or surgery is based on the risk of VUR to the patient, the likelihood of spontaneous resolution, and the parents' and patient's preferences; the family should understand the risks and benefits of each treatment approach.

Another aspect of VUR management pertains to screening. VUR is known to be a familial disorder with autosomal dominant transmission with variable penetrance. The advantage of early VUR detection is to implement treatment before a potentially damaging episode of clinical pyelonephritis. In siblings of an index patient with VUR, optional management includes screening of asymptomatic siblings or offspring with a renal ultrasound or VCUG. The AUA recommends that a VCUG should be obtained if a screening ultrasound demonstrated a renal abnormality or if the sibling had a UTI.

The AUA also determined that female newborns with renal pelvic dilation were more likely than male newborns to have VUR. The AUA recommends that a VCUG be performed in neonates with grade III-IV *antenatal* hydronephrosis (moderate to severe pelvicalyceal dilation), hydroureter, or an abnormal bladder. In children with less severe renal pelvic dilation, an observational approach without screening for VUR, with prompt treatment of any UTI, is appropriate. However, the AUA also indicated that obtaining a VCUG is considered an appropriate option for neonates with lesser grades of hydronephrosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

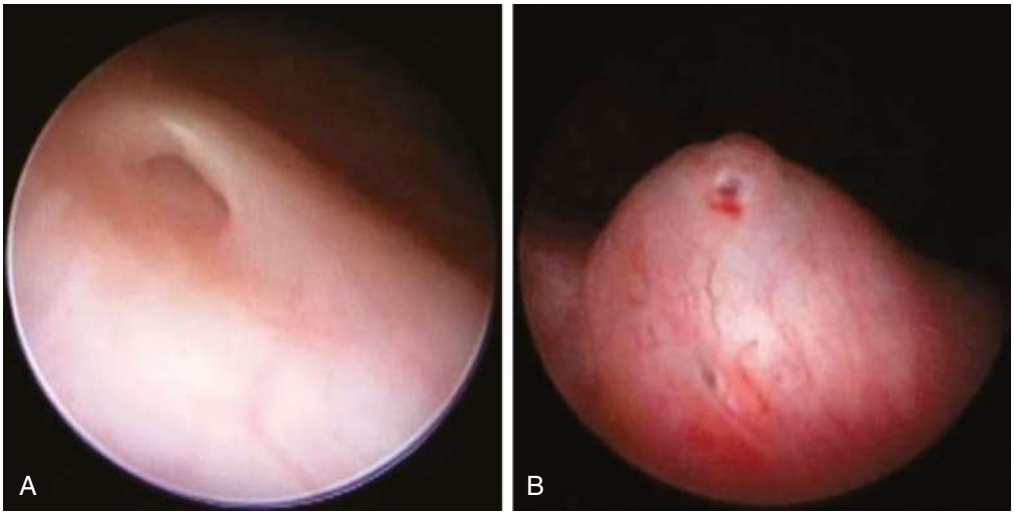

Fig. 576.11 A, Endoscopic view of right vesicoureteral refluxing ureter. B, The same ureter after subureteral injection of dextranomer microspheres.

Chapter 577

Obstruction of the Urinary Tract

Heather N. Di Carlo and Chad B. Crigger

Most childhood obstructive lesions are congenital, although urinary tract obstruction can be caused by trauma, neoplasia, calculi, inflammatory processes, or surgical procedures. Obstructive lesions occur at any level from the urethral meatus to the calyceal infundibula (Table 577.1). The pathophysiologic effects of obstruction depend on its level, the extent of involvement, the child's age at onset, and whether it is acute or chronic.

ETIOLOGY

Severe ureteral obstruction early in fetal life results in renal dysplasia, ranging from multicystic kidney, which is associated with ureteral or ureteropelvic junction (UPJ) atresia (see Fig. 574.3), to various degrees of histologic renal cortical dysplasia that are seen with less severe obstruction. **Chronic ureteral obstruction** in late fetal life or after birth results in dilation of the ureter, renal pelvis, and calyces with alterations of renal parenchyma ranging from minimal tubular changes to dilation of Bowman's space, glomerular fibrosis, and interstitial fibrosis. After birth, infection can complicate obstruction and worsen renal damage.

Prenatal screening with ultrasonography (US) may detect **antenatal hydronephrosis** (ANH), which is graded by the trimester and the anterior-posterior diameter of the renal pelvis (Table 577.2); most are mild. Table 577.3 notes the eventual etiology. Risk stratification for prenatal (Fig. 577.1) and postnatal (Fig. 577.2) urinary tract dilation (UTD) helps plan for further evaluation and treatment.

CLINICAL MANIFESTATIONS

Obstruction of the urinary tract generally causes **hydronephrosis,** which typically is asymptomatic in its early phases. An obstructed kidney secondary to a **ureteropelvic junction (UPJ) obstruction** or **ureterovesical junction obstruction** can manifest as a unilateral mass or cause upper abdominal or flank pain on the affected side. Pyelonephritis can occur because of urinary stasis. An upper urinary tract stone can occur, causing abdominal and flank pain and hematuria. With bladder outlet obstruction, the urinary stream may be weak; urinary tract infection (UTI; see Chapter 575) is common. Many of these lesions are identified by antenatal US; an abnormality involving the genitourinary tract is suspected in as many as 1 in 50 fetuses (see Table 577.3).

Obstructive renal insufficiency can manifest itself by failure to thrive, vomiting, diarrhea, or other nonspecific signs and symptoms. In older children, **infravesical obstruction** can be associated with overflow urinary incontinence or a poor urine stream. **Acute ureteral obstruction** causes flank or abdominal pain; there may be nausea and vomiting. Chronic ureteral obstruction can be silent or can cause vague abdominal or typical flank pain with increased fluid intake (such as in Dietl's crisis).

DIAGNOSIS

Urinary tract obstruction may be diagnosed prenatally by US, which typically shows hydronephrosis and occasionally a distended bladder. More complete evaluation, including imaging studies, should be undertaken in these children in the neonatal period.

A multidisciplinary consensus group has standardized the fetal evaluation and early postnatal management of babies with ANH. The US parameters include the anterior-posterior renal pelvic diameter (APRPD), **calyceal dilation,** whether the ANH involves the major and/or minor calyces, the parenchymal thickness and appearance, whether the ureter is normal or abnormal, and whether the bladder is normal or abnormal. Normal values for UTD are based on the APRPD:

Antenatal	16-27 weeks	<4 mm
	≥28 weeks	<7 mm
Postnatal	(>48 hours)	<10 mm

Assuming there is no calyceal dilation, the kidneys have a normal appearance, and the ureter and bladder are normal, the study is considered normal.

The consensus group then categorized ANH into antenatal and postnatal risk groups. For antenatal ANH, there are two risk groups: low and high (see Fig. 577.1). For postnatal ANH, there are three risk groups: low,

Table 577.1 Types and Causes of Urinary Tract Obstruction

LOCATION	CAUSE
Infundibula	Congenital Calculi Inflammatory (tuberculosis) Traumatic Postsurgical Neoplastic
Renal pelvis	Congenital (infundibulopelvic stenosis) Inflammatory (tuberculosis) Calculi Neoplasia (Wilms tumor, neuroblastoma)
Ureteropelvic junction	Congenital stenosis Calculi Neoplasia Inflammatory Postsurgical Traumatic
Ureter	Congenital obstructive megaureter Midureteral structure Ureteral ectopia Ureterocele Retrocaval ureter Ureteral fibroepithelial polyps Ureteral valves Calculi Postsurgical Extrinsic compression Neoplasia (neuroblastoma, lymphoma, and other retroperitoneal or pelvic tumors) Inflammatory (Crohn disease, chronic granulomatous disease) Hematoma, urinoma Lymphocele Retroperitoneal fibrosis
Bladder outlet and urethra	Neurogenic bladder dysfunction (functional obstruction) Posterior urethral valves Anterior urethral valves Diverticula Urethral strictures (congenital, traumatic, or iatrogenic) Urethral atresia Ectopic ureterocele Meatal stenosis (males) Calculi Foreign bodies Phimosis Extrinsic compression by tumors Urogenital sinus anomalies

Table 577.2 Definition of Antenatal Hydronephrosis by Anterior-Posterior Diameter

DEGREE OF ANTENATAL HYDRONEPHROSIS	SECOND TRIMESTER	THIRD TRIMESTER
Mild	4–6 mm	7 to 9 mm
Moderate	7–10 mm	10–15 mm
Severe	>10 mm	>15 mm

From Nguyen HT, Herndon CDA, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol.* 2010;6:212–231. Table 2.

Table 577.3 Etiology of Antenatal Hydronephrosis

ETIOLOGY	INCIDENCE
Transient hydronephrosis	41–88%
Ureteropelvic junction obstruction	10–30%
Vesicoureteral reflux	10–20%
Ureterovesical junction obstruction/ megaureters	5–10%
Multicystic dysplastic kidney	4–6%
Posterior urethral valve/urethral atresia	1–2%
Ureterocele/ectopic ureter/duplex system	5–7%
Others: prune-belly syndrome, cystic kidney disease, congenital ureteric strictures, megalourethra	Uncommon

From Nguyen HT, Herndon CDA, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol.* 2010;6:212–231. Table 5.

intermediate, and high (see Fig. 577.2). The panel recommended that all seven urinary tract parameters be described in a written report.

For antenatal presentation, if the APRPD is 4-7 mm at 16-27 weeks or 7-10 mm at ≥28 weeks and there is central or no calyceal dilation, the fetus is categorized as having **UTD A1**, **Low Risk**. In follow-up for UTD A1, the panel suggested one additional antenatal US at ≥32 weeks, and after birth, a renal US at >48 hours to 1 month of age and a second renal US 6 months later. Genetic screening is not indicated unless there are associated congenital malformations.

If the APRPD is ≥7 mm at 16-27 weeks or ≥10 mm at ≥28 weeks, with any peripheral calyceal dilation or any other upper urinary tract abnormality, the fetus is classified as having **UTD A2-3,** or **Increased Risk**. The assigned risk is based on the most concerning feature. For UTD A2-3, the panel recommends a follow-up US in 4-6 weeks, although with suspected **posterior urethral valves** (PUVs) or severe bilateral hydronephrosis, more frequent follow-up was recommended until delivery. Following delivery, a renal US after 48 hours but before 1 month is suggested, again with more immediate evaluation if PUV is suspected or there is significant bilateral hydronephrosis. In addition, specialist consultation with pediatric urology or nephrology is recommended.

For postnatal presentation, at >48 hours an APRPD <10 mm is **Normal.** If the APRPD is 10-15 mm and there is central calyceal dilation, but all other parameters are normal, the infant is classified as having **UTD P1, Low Risk**. Society of Fetal Urology (SFU) hydronephrosis grades 1 and 2 correspond to UTD P1. The panel recommends a follow-up renal US in 1-6 months. *A voiding cystourethrogram (VCUG) and antibiotic prophylaxis are optional and at the discretion of the clinician. A renal scan is not recommended.*

If the postnatal APRPD is ≥15 mm and there is peripheral calyceal dilation and/or abnormal ureters, the infant is classified as having **UTD P2, Intermediate Risk**. SFU hydronephrosis grade 3 corresponds to UTD P2. The panel recommends a follow-up renal US in 1-3 months.

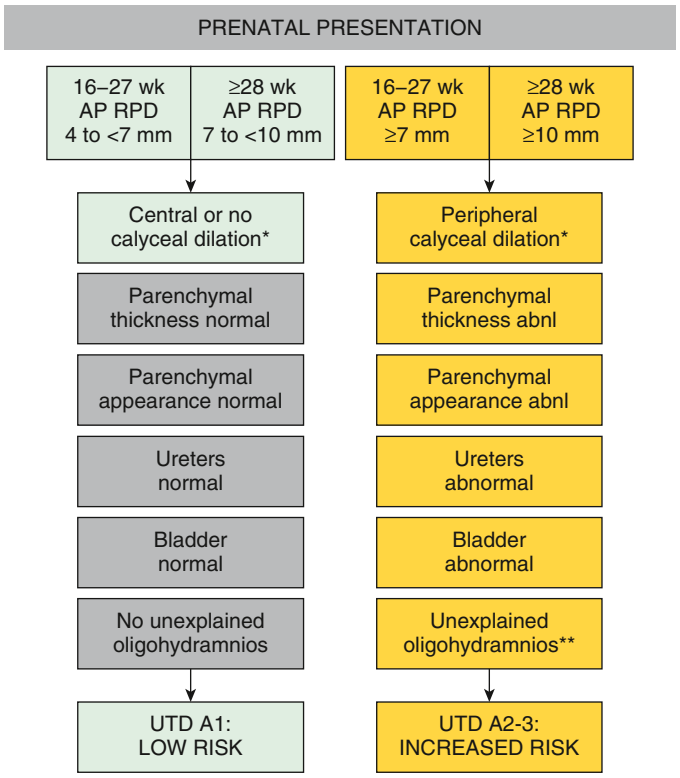

*Central and peripheral calyceal dilation may be difficult to evaluate early in gestation

**Oligohydramnios is suspected to result from a GU cause

Fig. 577.1 Urinary tract dilation (UTD) risk stratification: prenatal presentation for UTD A1 (low risk) and UTD A2-3 (increased risk). Note: Classification is based on the presence of the most concerning feature. For example, a fetus with an APRPD within the UTD A1 range but with peripheral calyceal dilation would be classified as UTD A2-3. GU, Genitourinary. *(From Nguyen HT, Benson CB, Bromley B, et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation [UTD classification system]. J Pediatr Urol. 2014;10:982–998. Fig. 3.)*

VCUG, antibiotic prophylaxis, and a functional renal scan are optional and at the discretion of the clinician.

If the APRPD is ≥15 mm and there is peripheral calyceal dilation, abnormal parenchymal thickness, abnormal parenchymal appearance, abnormal ureters, and/or abnormal bladder, the infant is classified as having **UTD P3, High Risk**. SFU hydronephrosis grade 4 corresponds to UTD P3. The panel recommends a follow-up renal US in 1 month. *A VCUG and antibiotic prophylaxis are recommended. A functional renal scan is optional and at the discretion of the clinician (but is virtually always recommended).*

PHYSICAL FINDINGS

Urinary tract obstruction is often silent. In the newborn infant, a palpable abdominal mass most commonly is a hydronephrotic or multicystic dysplastic kidney. With PUVs, which constitute an infravesical obstructive lesion in males, a walnut-sized mass representing the bladder is palpable just above the pubic symphysis. A **patent draining urachus** also can suggest urethral obstruction. **Urinary ascites** in the newborn usually is caused by renal or bladder urinary extravasation secondary to PUVs. Infection and sepsis may be the first indications of an obstructive lesion of the urinary tract. The combination of infection and obstruction poses a serious threat to infants and children and generally requires parenteral administration of antibiotics and drainage of the obstructed kidney. Renal US should be performed in all children during the acute stage of an initial febrile UTI.

IMAGING STUDIES

Renal Ultrasound

Hydronephrosis is the most common characteristic of obstruction (Fig. 577.3). Upper UTD is not diagnostic of obstruction and often

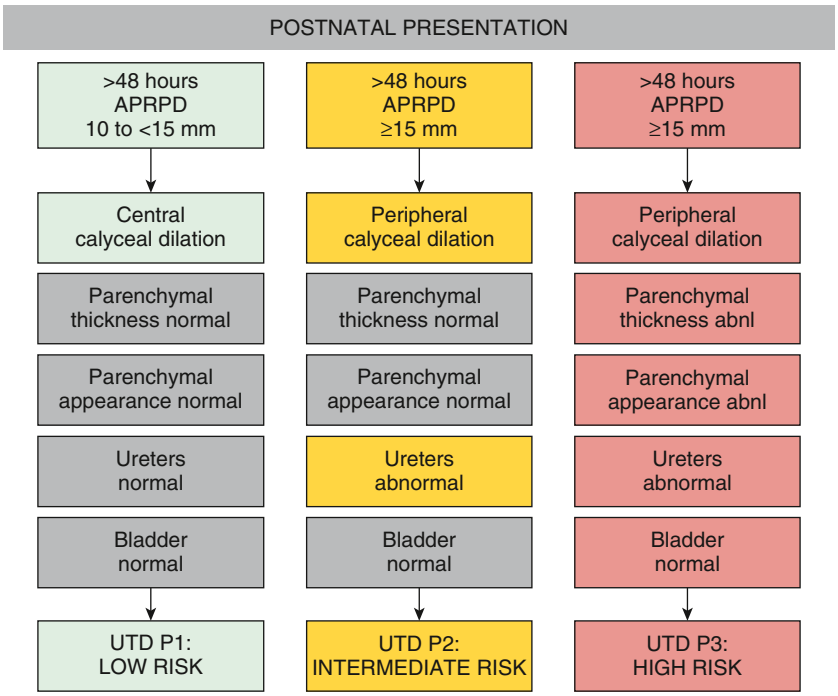

Fig. 577.2 Urinary tract dilation (UTD) risk stratification: postnatal presentation for UTD P1 (low risk), UTD P2 (intermediate risk), and UTD P3 (high risk). Note: Stratification is based on the most concerning ultrasound finding. For example, if the APRPD is in the UTD P1 range but there is peripheral calyceal dilation, the classification is UTD P2. Similarly, the presence of parenchymal abnormalities (abnl) denotes a UTD P3 classification, regardless of APRPD measurement. *(From Nguyen HT, Benson CB, Bromley B, et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation [UTD classification system]. J Pediatr Urol. 2014;10:982–998. Fig. 6.)*

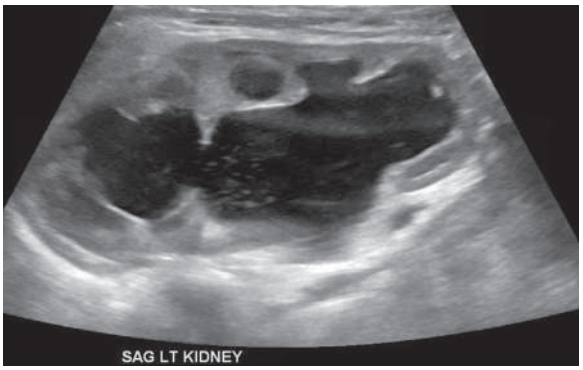

Fig. 577.3 US image of the left kidney with marked pelvic and calyceal dilation (grade 4 hydronephrosis) in a newborn with ureteropelvic junction obstruction.

persists after surgical correction of a significant obstructive lesion. Dilation can result from vesicoureteral reflux (VUR), or it may be a manifestation of abnormal development of the urinary tract, even when there is no obstruction. Renal length, degree of caliectasis and parenchymal thickness, and presence or absence of ureteral dilation should be assessed. In addition to the UTD system, most pediatric urologists also grade the severity of hydronephrosis from 1-4 using the SFU grading scale (Table 577.4). The clinician should ascertain that the contralateral kidney is normal, and the bladder should be imaged to see whether the bladder wall is thickened, the lower ureter is dilated, and bladder emptying is complete. In acute or intermittent obstruction, the dilation of the collecting system may be minimal, and US may be misleading.

Voiding Cystourethrogram

In neonates and infants with congenital grade 3 or 4 hydronephrosis and in any child with ureteral dilation, a **contrast VCUG** should be obtained, because the dilation is secondary to VUR in 15% of cases.

Table 577.4 Society for Fetal Urology Grading System for Hydronephrosis

GRADE OF HYDRONEPHROSIS	RENAL IMAGE	
	CENTRAL RENAL COMPLEX	RENAL PARENCHYMAL THICKNESS
0	Intact	Normal
1	Slight splitting	Normal
2	Evident splitting, complex confined within renal border	Normal
3	Wide splitting, pelvis dilated outside renal border, calyces uniformly dilated	Normal
4	Further dilation of pelvis and calyces (calyces may appear convex)	Thin

After Maizels M, Mitchell B, Kass E, et al. Outcome of nonspecific hydronephrosis in the infant: a report from the registry of the Society for Fetal Urology. *J Urol.* 1994;152:2324–2327.

In males, the VCUG also is performed to rule out urethral obstruction, particularly in cases of suspected PUVs. In older children, the urinary flow rate can be measured noninvasively with a urinary flowmeter. Decreased flow with a normal bladder contraction suggests infravesical obstruction (e.g., PUVs, urethral stricture). When the urethra cannot be catheterized to obtain a VCUG, the clinician should suspect a urethral stricture or an obstructive urethral lesion. Retrograde urethrography with contrast medium injected into the urethral meatus helps delineate the anatomy of the urethral obstruction.

Radioisotope Studies

Renal scintigraphy is used to assess renal anatomy and function. The two most commonly used radiopharmaceuticals are mercaptoacetyl triglycine (MAG-3) and technetium-99m–labeled dimercaptosuccinic acid (DMSA). MAG-3, which is excreted by renal tubular secretion, is used to assess differential renal function, and when furosemide is administered, drainage also can be measured. DMSA is a renal cortical imaging agent and is used to assess differential renal function and to demonstrate whether renal scarring is present. It is used infrequently in children with obstructive uropathy.

In a MAG-3 diuretic renogram, a small dose of technetium-labeled MAG-3 is injected intravenously (Figs. 577.4 and 577.5). During the first 2-3 minutes, renal parenchymal uptake is analyzed and compared, allowing computation of differential renal function.

Subsequently, excretion is evaluated. After 20 minutes, furosemide 1 mg/kg is injected intravenously, and the rapidity and pattern of drainage from the kidneys to the bladder are analyzed. If no obstruction is present, half of the radionuclide should be cleared from the renal pelvis within 10-15 minutes, termed the half-time ($t_{1/2}$). If there is significant upper tract obstruction, the $t_{1/2}$ usually is longer than 20 minutes. A $t_{1/2}$ of 15-20 minutes is indeterminate. An elevated $t_{1/2}$ is suggestive but not diagnostic of obstruction. The images generated usually provide an accurate assessment of the site of obstruction. Numerous variables affect the outcome of the diuretic renogram. Newborn kidneys are functionally immature, and, in the first month of life, normal kidneys might not demonstrate normal drainage after diuretic administration. Patient dehydration prolongs parenchymal transit and can blunt the diuretic response. As such, renal scintigraphy is usually performed after 8 weeks of life in an appropriately hydrated infant. Giving an insufficient dose of furosemide can result in slow drainage. If VUR is present, continuous bladder drainage is mandatory to prevent the radionuclide from refluxing from the bladder into the dilated upper tract, which would prolong the washout phase.

Magnetic Resonance Urography

Magnetic resonance (MR) urography is also used to evaluate suspected upper urinary tract pathology. The child is hydrated and given intravenous furosemide. Gadolinium-diethylene tetrapentaacetic acid is injected, and routine T1 weighted and fat-suppressed fast spin-echo T2 weighted imaging is performed through the kidneys, ureters, and bladder. This study provides superb images of the pathology, and methodology permits assessment of differential renal function and drainage (Fig. 577.6). There is no radiation exposure; however, young children need sedation or anesthesia. It is used primarily when renal US and radionuclide imaging fail to delineate complex pathology.

Computed Tomography

In children with a suspected ureteral calculus (see Chapter 584), noncontrast, low-dose spiral CT of the abdomen and pelvis is a standard method of demonstrating whether a calculus is present, its location, and whether there is significant proximal hydronephrosis. This study may be ordered when a renal/bladder US is inconclusive. The disadvantage of CT is the significant radiation exposure, and it should be used only when the results will direct management decisions.

Ancillary Studies

In unusual cases, an **antegrade pyelogram** (insertion of a percutaneous nephrostomy tube and injection of contrast agent) can be performed to assess the anatomy of the upper urinary tract. This procedure usually requires general anesthesia. In addition, an **antegrade pressure-perfusion flow study** (Whitaker test) may be performed, in which fluid is infused at a measured rate, usually 10 mL/min. The pressures

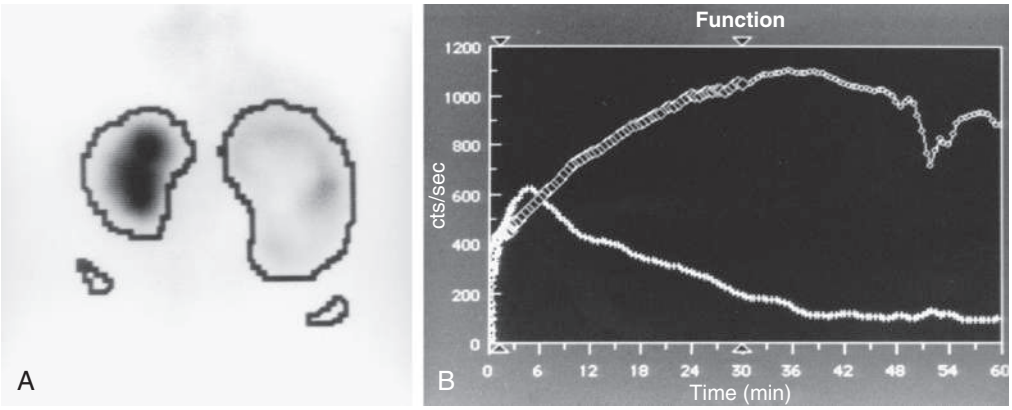

Fig. 577.4 MAG-3 diuretic renogram of a 6-wk-old infant with severe right hydronephrosis. The right kidney is on the *right* side of the image. A, Differential renal function: left kidney 70%, right kidney 30%. B, After administration of furosemide, drainage from the left kidney was normal and drainage from the right kidney was slow, consistent with right UPJ obstruction. Pyeloplasty was performed on the right kidney.

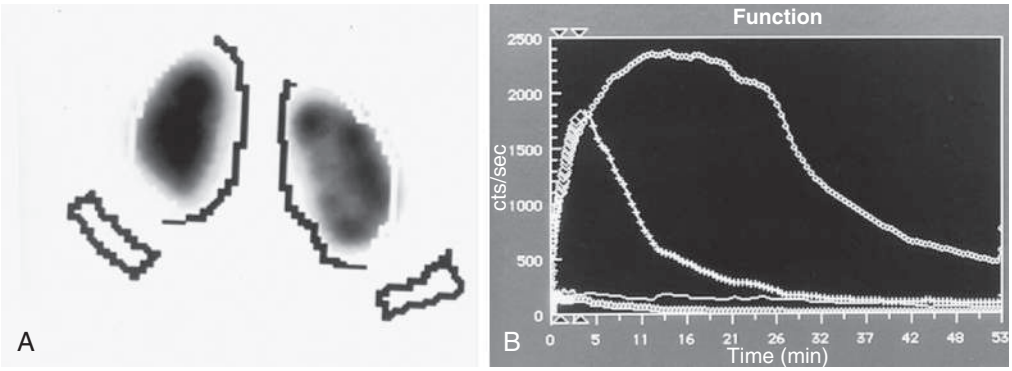

Fig. 577.5 A, MAG-3 diuretic renogram at 14 mo of age shows equal function in the two kidneys. B, Prompt drainage after the administration of furosemide.

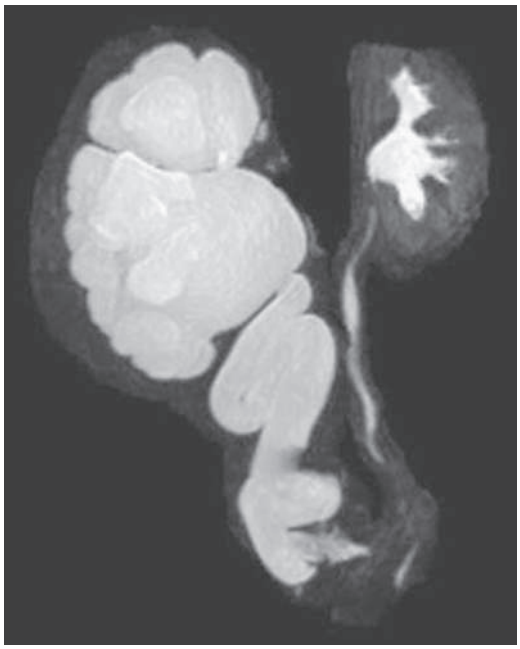

Fig. 577.6 MR urogram in boy with distal ureterovesical obstruction.

in the renal pelvis and the bladder are monitored during this infusion, and pressure differences exceeding 20 cm H_2O suggest obstruction. In other cases, cystoscopy with retrograde pyelography provides excellent images of the upper urinary tract (Fig. 577.7).

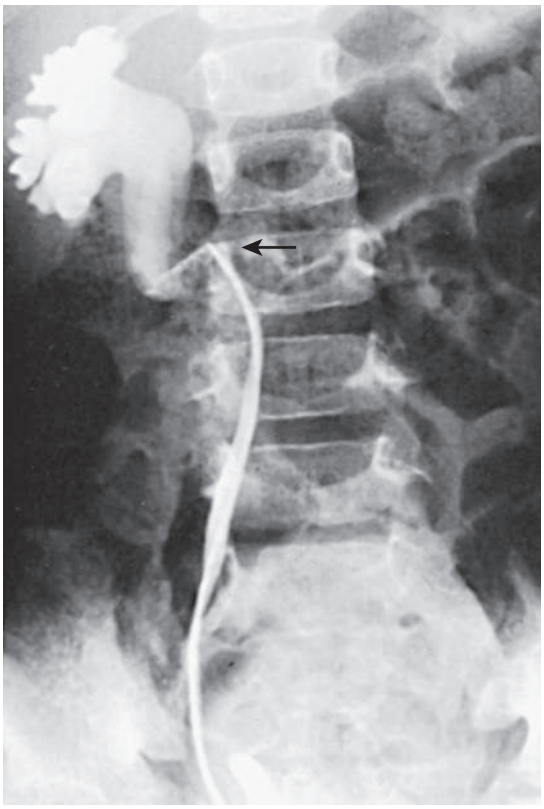

Fig. 577.7 Retrograde pyelogram showing medial deviation of a dilated upper ureter to the level of the third lumbar vertebra *(arrow)*, characteristic of a retrocaval ureter.

SPECIFIC TYPES OF URINARY TRACT OBSTRUCTION AND THEIR TREATMENT

Hydrocalycosis

Hydrocalycosis refers to a localized dilation of the calyx caused by obstruction of its infundibulum, termed **infundibular stenosis.** This condition can be developmental in origin or secondary to inflammatory processes, such as UTI. It usually is discovered during evaluation for pain or UTI. The diagnosis of infundibular stenosis is usually established by sonograph and CT scan or MR urography.

Ureteropelvic Junction Obstruction

UPJ obstruction is the most common obstructive lesion in childhood and usually is caused by intrinsic stenosis (see Figs. 577.3-577.5). An accessory artery to the lower pole of the kidney can also cause extrinsic obstruction. The typical appearance on US is grade 3 or 4 hydronephrosis without a dilated ureter and a clear transition point. UPJ obstruction may present on antenatal sonography revealing fetal hydronephrosis; as a palpable renal mass in a newborn or infant; as abdominal, flank, or back pain; as a febrile UTI; or as hematuria after minimal trauma. Approximately 60% of cases occur on the left side; the male:female ratio is 2:1. *UPJ obstruction is bilateral in only 10% of cases*. In kidneys with UPJ obstruction, renal function may be significantly impaired from pressure atrophy, but approximately half of affected kidneys have relatively normal glomerular function. The anomaly is corrected by performing a **pyeloplasty**, in which the stenotic segment is excised, and the normal ureter and renal pelvis are reattached. Success rates are 91–98%. Pyeloplasty can be performed using laparoscopic techniques, often robotic assisted using the da Vinci robot.

Lesser degrees of UPJ narrowing might cause mild hydronephrosis, which usually is nonobstructive, and typically these kidneys function normally. The spectrum of UPJ abnormalities has been referred to as **anomalous UPJ**. Another cause of mild hydronephrosis is fetal folds of the upper ureter, which also are nonobstructive.

The diagnosis can be difficult to establish in an asymptomatic infant in whom dilation of the renal pelvis is found incidentally in a prenatal US. After birth, the sonographic study is repeated to confirm the prenatal finding. A VCUG is necessary because 10–15% of patients have ipsilateral vesicoureteral reflux. Because neonatal oliguria can cause temporary decompression of a dilated renal pelvis, it is ideal to perform the first postnatal US after the third day of life. Delaying the US may be impractical. *If no dilation is found on the initial US, a repeat study should be performed at 1 month of age*. If the kidney shows grade 1 or 2 hydronephrosis and the renal parenchyma appears normal, a period of observation usually is appropriate, with sequential renal US studies to monitor the severity of hydronephrosis, and the hydronephrosis usually disappears. Antibiotic prophylaxis is *not* indicated for children with mild hydronephrosis. If the hydronephrosis is grade 3 or 4, spontaneous resolution is less likely, and obstruction is more likely to be present, particularly if the renal pelvic diameter is 3 cm. A diuretic renogram with MAG-3 is performed at 4-6 weeks of age. If there is poor upper tract drainage or the differential renal function is poor, pyeloplasty is recommended. After pyeloplasty the differential renal function often improves, and improved drainage with furosemide stimulation is expected.

If the differential function on renography is normal and drainage is satisfactory, the infant can be followed with serial US studies, even with grade 4 hydronephrosis. If the hydronephrosis remains severe with no improvement, a repeat diuretic renogram after 6-12 months can help in the decision between continued observation and surgical repair. Prompt surgical repair is indicated in infants with an abdominal mass, bilateral severe hydronephrosis, a solitary kidney, or diminished function in the involved kidney. In unusual cases in which the differential renal function is <10% but the kidney has some function, insertion of a percutaneous nephrostomy tube allows drainage of the hydronephrotic kidney for a few weeks to allow reassessment of renal function. In older children who present with symptoms, the diagnosis of UPJ obstruction usually is established by US and diuretic renography.

The differential diagnosis includes megacalycosis, a congenital nonobstructive dilation of the calyces without pelvic or ureteric dilation; VUR with marked dilation and kinking of the ureter; midureteral or

distal ureteral obstruction when the ureter is not well visualized on the urogram; and retrocaval ureter.

Midureteral Obstruction

Congenital ureteral stenosis or a ureteral valve in the midureter is rare. It is corrected by excision of the strictured segment and reanastomosis of the normal upper and lower ureteral segments. A **retrocaval ureter** is an anomaly in which the upper right ureter travels posterior to the inferior vena cava. In this anomaly, the vena cava can cause extrinsic compression and obstruction. A retrograde pyelogram or MR urogram shows the right ureter to be medially deviated at the level of the third lumbar vertebra (see Fig. 577.7). Surgical treatment consists of transection of the upper ureter, moving it anterior to the vena cava, and reanastomosing the upper and lower segments. Repair is necessary only when obstruction is present. Retroperitoneal tumors, fibrosis caused by surgical procedures, inflammatory processes (as in chronic granulomatous disease), and radiation therapy can cause acquired midureteral obstruction.

Ectopic Ureter

A ureter that drains outside the bladder is referred to as an ectopic ureter. This anomaly is three times as common in females as in males and usually is detected prenatally. The ectopic ureter typically drains the upper pole of a duplex collecting system (two ureters).

In females, approximately 35% of these ureters enter the urethra at the bladder neck; 35% enter the urethrovaginal septum; 25% enter the vagina; and a few drain into the cervix, uterus, Gartner duct, or a urethral diverticulum. Often the terminal aspect of the ureter is narrowed, causing **hydroureteronephrosis**. Apart from the ectopic ureter entering the bladder neck, in females an ectopic ureter causes continuous urinary incontinence from the affected renal moiety. UTI is common because of urinary stasis.

In males, ectopic ureters enter the posterior urethra (above the external sphincter) in 47%, the prostatic utricle in 10%, the seminal vesicle in 33%, the ejaculatory duct in 5%, and the vas deferens in 5%. Consequently, in males, an ectopic ureter does not cause incontinence, and most patients present with a UTI or epididymitis.

Evaluation includes a renal US, VCUG, and renal scan, which demonstrates whether the affected segment has significant function. The US shows the affected hydronephrotic kidney or dilated upper pole and ureter down to the bladder (Fig. 577.8). If the ectopic ureter drains into the bladder neck (female), a VCUG usually shows reflux into the ureter. Otherwise, there is no reflux into the ectopic ureter, but there may be reflux into the ipsilateral lower pole ureter or contralateral collecting system.

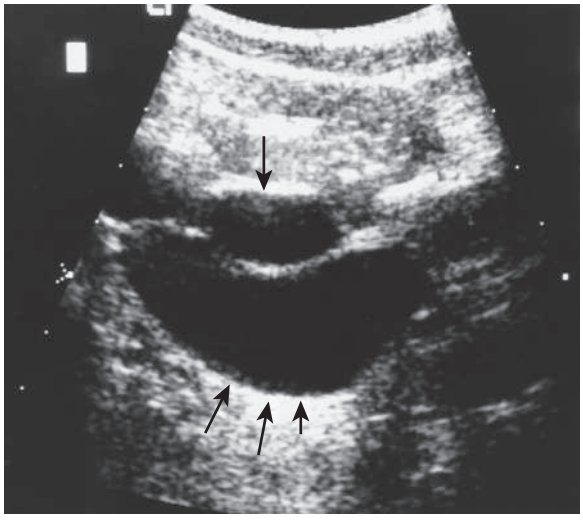

Fig. 577.8 US image of the right dilated ureter *(bottom arrows)* extending behind and caudal to a nearly empty bladder *(top arrow)* in a female with urinary incontinence and ectopic ureter draining into the vagina.

Treatment depends on the status of the renal unit drained by the ectopic ureter. If there is satisfactory function, ureteral reimplantation into the bladder or **ureteroureterostomy** (anastomosing the ectopic upper pole ureter into the normally inserting lower pole ureter) is indicated. If function is poor, partial or total nephrectomy is indicated. In many centers this procedure is done laparoscopically, often with robotic assistance.

Ureterocele

A ureterocele is a cystic dilation of the terminal ureter and is obstructive because of a pinpoint ureteral orifice. Ureteroceles are much more common in females than in males. Affected children usually are discovered by prenatal US, but some present with a febrile UTI. Ureteroceles may be ectopic, in which case the cystic swelling extends through the bladder neck into the urethra, or orthotopic, in which case the ureterocele is entirely within the bladder. Both orthotopic and ectopic ureteroceles can be bilateral.

In females, ureteroceles nearly always are associated with ureteral duplication (Fig. 577.9), whereas in 50% of affected males there is only one ureter. When associated with a duplication anomaly, the ureterocele drains the upper renal moiety, which commonly functions poorly or is dysplastic because of congenital obstruction. The lower pole ureter drains into the bladder superior and lateral to the upper pole ureter and may reflux.

An **ectopic ureterocele** extends submucosally through the bladder neck into the urethra. Rarely, large ectopic ureteroceles can cause bladder outlet obstruction and retention of urine with bilateral hydronephrosis. In females, the ureterocele can prolapse from the urethral meatus. US is effective in demonstrating the ureterocele and whether the associated obstructed system is duplicated or single. VCUG usually shows a filling defect in the bladder, sometimes large, corresponding to the ureterocele, and it often shows reflux into the adjacent lower pole collecting system with typical findings of a "drooping lily" appearance to the kidney. Nuclear renal scintigraphy is most accurate in demonstrating whether the affected renal moiety has significant function.

Treatment of ectopic ureteroceles depends on whether the upper pole functions on renal scan and whether there is reflux into the lower pole ureter. If there is nonfunction of the upper pole of the kidney and there is no reflux, treatment usually involves laparoscopic, robotic, or open excision of the obstructed upper pole and most of the associated ureter. If there is function in the upper pole or significant reflux into the lower pole ureter, or if the patient is septic from infection of the hydronephrotic kidney, then transurethral incision with cautery is appropriate initial therapy to decompress the ureterocele. Reflux into the incised ureterocele is common, and subsequent excision of the ureterocele and ureteral reimplantation usually is necessary. An alternative method is to perform an upper-to-lower ureteroureterostomy, allowing the obstructed upper pole ureter to drain through the normal lower ureter; this procedure often is performed with minimally invasive laparoscopic (robotic) technique or through a small incision.

Orthotopic ureteroceles are associated with duplicated or single collecting systems, and the orifice is in the expected location in the bladder (Fig. 577.10). These anomalies usually are discovered during an investigation for prenatal hydronephrosis or a UTI. US is sensitive for detecting the ureterocele in the bladder and hydroureteronephrosis. Transurethral incision of the ureterocele effectively relieves the obstruction, but it can result in VUR, necessitating ureteral reimplantation later. Some prefer open excision of the ureterocele and reimplantation as the initial form of treatment. Small, simple ureteroceles discovered incidentally without upper tract dilation generally do not require treatment. Rarely, a large ureterocele occupying much of the bladder lumen can result in bilateral hydronephrosis by obstructing drainage of the contralateral ureteral orifice.

Megaureter

Table 577.5 presents a classification of megaureters (dilated ureter). Numerous disorders can cause ureteral dilation, and many are nonobstructive.

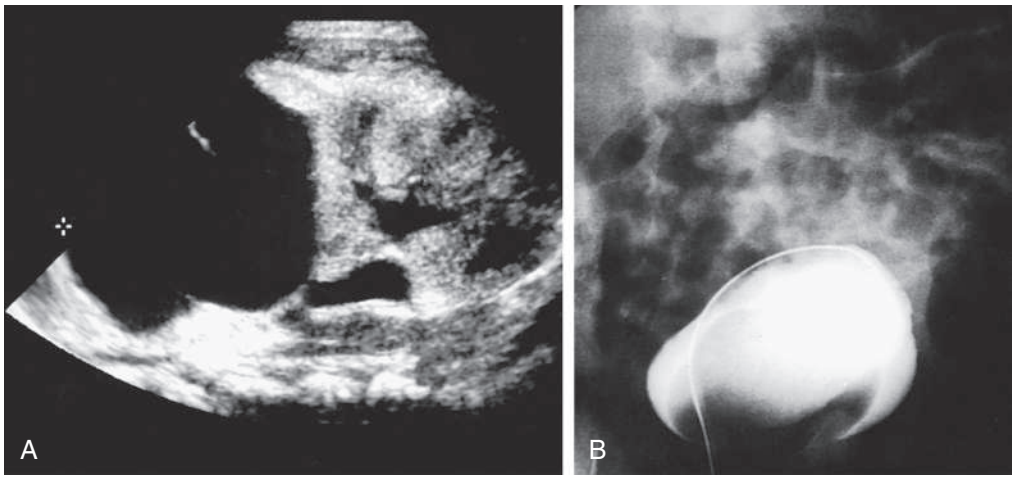

Fig. 577.9 A, Infant with ectopic ureterocele. US of the left kidney shows massive dilation of the upper pole and a normal lower pole. B, VCUG shows large ureterocele, draining the left upper pole, in the bladder. No reflux is present.

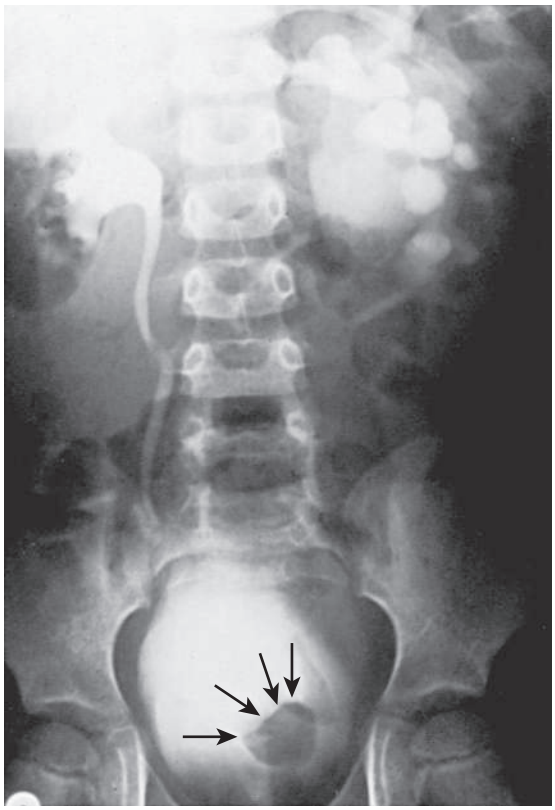

Fig. 577.10 Simple intravesical ureterocele. The excretory urogram shows left hydronephrosis and a round filling defect *(arrows)* on the left side of the bladder corresponding to a simple ureterocele causing left ureteral obstruction. This lesion was treated by transurethral incision and drainage of the ureterocele.

Megaureters usually are discovered during antenatal US or during workup for postnatal UTI, hematuria, or abdominal pain. A careful history, physical examination, and VCUG identify causes of secondary megaureters and refluxing megaureters, as well as the prune-belly syndrome. Primary obstructed megaureters and nonobstructed megaureters represent varying degrees of severity of the same anomaly.

The **primary obstructed nonrefluxing megaureter** results from abnormal development of the distal ureter, with collagenous tissue replacing the muscle layer. Normal ureteral peristalsis is disrupted, and the proximal ureter widens. In most cases there is not a true stricture. On intravenous pyelogram or an MR urogram, the distal ureter is more dilated in its distal segment and tapers abruptly at or above the junction of the bladder (Fig. 577.11). The lesion may be unilateral or bilateral. Significant hydroureteronephrosis suggests obstruction. Megaureter predisposes to UTI, urinary stones, hematuria, and flank pain because of urinary stasis. In most cases, diuretic renography and sequential sonographic studies can reliably differentiate obstructed from nonobstructed megaureters. In most nonobstructed megaureters, the hydroureteronephrosis diminishes gradually (Fig. 577.12). Truly obstructed megaureters require surgical treatment, with excision of the narrowed segment, ureteral tapering, and reimplantation of the ureter. The results of surgical reconstruction usually are good, but the prognosis depends on preexisting renal function and whether complications develop.

If differential renal function is normal (>45%) and the child is asymptomatic, it is safe to manage the patient with observation with serial US and periodic diuretic renography to monitor renal function and drainage. In children with grade 4 hydroureteronephrosis, prophylactic antimicrobial therapy should be prescribed, as these children are prone to upper UTI. If renal function deteriorates, upper urinary tract drainage slows, or UTI occurs, ureteral reimplantation is recommended. Approximately 25% of children with a nonrefluxing megaureter undergo ureteral reimplantation.

Prune-Belly Syndrome

Prune-belly syndrome, also called **triad syndrome** (lax abdominal wall muscles, urinary tract distention, intrabdominal testis) or **Eagle-Barrett syndrome,** occurs in approximately 1 in 40,000 births; 95% of affected children are male. The characteristic association occurs in a wide spectrum with deficient (hypoplastic) abdominal muscles, undescended testes, and urinary tract abnormalities (Fig. 577.13 and Table 577.6). Oligohydramnios and pulmonary hypoplasia are common complications in the perinatal period. Urinary tract abnormalities include massive (usually unobstructed) dilation of the ureters and upper tracts and a very large hypotonic bladder, with a patent urachus or a urachal diverticulum. Most patients have VUR. The prostatic urethra is usually dilated, and the prostate is hypoplastic. The anterior urethra may be dilated, resulting in a **megalourethra**. In severe cases, there is urethral stenosis or atresia. The kidneys show various degrees of dysplasia, and the testes are typically intraabdominal. Malrotation of the bowel is often present. Cardiac abnormalities occur in 10% of cases; >50% have abnormalities of the musculoskeletal system, including limb abnormalities and scoliosis. In the females, rare anomalies of the urethra, uterus, and vagina usually are present. Pathogenic variants in *FLNA* and possibly *MYOCD* or *HNF1β* have been reported; the disorder is usually sporadic, although rare instances of familial cases occur.

Many neonates with prune-belly syndrome have difficulty with effective bladder emptying because the bladder musculature is poorly

Table 577.5 Classification of Megaureter

REFLUXING		OBSTRUCTED		NONREFLUXING AND NONOBSTRUCTED	
PRIMARY	**SECONDARY**	**PRIMARY**	**SECONDARY**	**PRIMARY**	**SECONDARY**
Primary reflux	Neuropathic bladder	Intrinsic (primary obstructed megaureter)	Neuropathic bladder	Nonrefluxing, nonobstructive	Diabetes insipidus
Megacystic-megaureter syndrome	Hinman syndrome	Ureteral valve	Hinman syndrome		Infection
Ectopic ureter	Posterior urethral valves	Ectopic ureter	Posterior urethral valves		Persistent after relief of obstruction
Prune-belly syndrome	Bladder diverticulum Postoperative	Ectopic ureterocele	Ureteral calculus Extrinsic Postoperative		

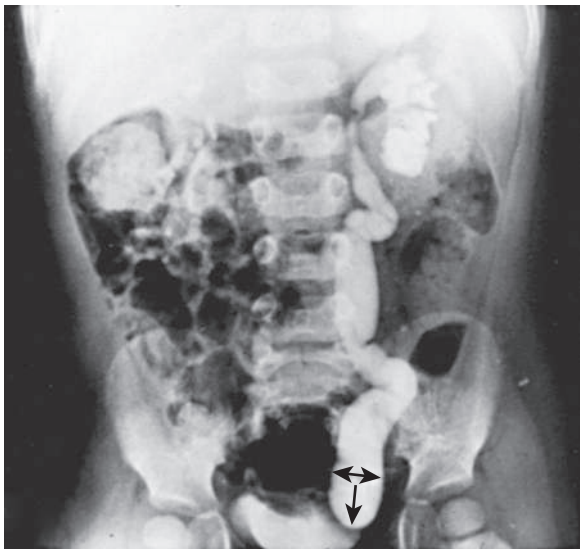

Fig. 577.11 Obstructed nonrefluxing megaureter. Excretory urogram in a female with a history of a febrile UTI. The right side is normal. The left side reveals hydroureteronephrosis with predominant dilation of the distal ureter. Note the characteristic appearance of the distal ureter. There was no vesicoureteral reflux. The diagnosis of obstruction was confirmed by diuretic renography.

developed, and the urethra may be narrowed. When no obstruction is present, the goal of treatment is the prevention of UTI with antibiotic prophylaxis. When obstruction of the ureters or urethra is demonstrated, temporary drainage procedures, such as a vesicostomy, can help to preserve renal function until the child is old enough for surgical reconstruction. Some children with prune-belly syndrome have been found to have classic or atypical PUVs. UTIs occur often and should be treated promptly. Correction of the undescended testes by orchidopexy can be difficult in these children because the testes are located high in the abdomen and surgery is best accomplished in the first 6 months of life. Reconstruction of the abdominal wall offers cosmetic and functional benefits.

The prognosis depends on the degree of pulmonary hypoplasia and renal dysplasia. One third of children with prune-belly syndrome are stillborn or die in the first few months of life because of pulmonary hypoplasia. As many as 30% of the long-term survivors develop end-stage renal disease from dysplasia or complications of infection or reflux and eventually require renal transplantation. Renal transplantation in these children offers good results.

Megacystis-microcolon-intestinal hypoperistalsis syndrome manifests with a dilated unobstructed bladder in the context of the more dominant gastrointestinal manifestations of intestinal pseudoobstruction (see Table 378.11 and Figs. 378.6 and 378.7). The abdominal muscles are normal, but abdominal distention is prominent. Associated pathogenic gene variants include *ACTG2* (~45%) as well as *MYH11*, *LOMD1*, *MYL9*, and *MYLK*; ~20% are unknown. Hydronephrosis is common, and most patients are female.

Bladder Neck Obstruction

Bladder neck obstruction usually is secondary to ectopic ureterocele, bladder calculi, or a tumor of the prostate (rhabdomyosarcoma). The manifestations include difficulty voiding, urinary retention, UTI, and bladder distention with overflow incontinence. Apparent bladder neck obstruction is common in cases of PUVs, but it seldom has any functional significance. Primary bladder neck obstruction is extremely rare.

Posterior Urethral Valves

The most common cause of severe obstructive uropathy in children is PUVs, affecting 1 in 8,000 males. The urethral valves are tissue leaflets fanning distally from the prostatic urethra to the external urinary sphincter. A slitlike opening usually separates the leaflets. Valves are of unclear embryologic origin and cause varying degrees of obstruction. Approximately 30% of patients experience end-stage renal disease or chronic renal insufficiency. The prostatic urethra dilates, and the bladder muscle undergoes hypertrophy. VUR occurs in 50% of patients, and distal ureteral obstruction can result from a chronically distended bladder or bladder muscle hypertrophy. Renal changes range from mild hydronephrosis to severe renal dysplasia; their severity depends on the severity of the obstruction and its time of onset during fetal development. As in other cases of obstruction or renal dysplasia, there may be oligohydramnios and pulmonary hypoplasia.

Affected males with PUVs often are discovered prenatally when maternal US reveals bilateral hydronephrosis, a distended bladder, and, if the obstruction is severe, oligohydramnios. Prenatal bladder decompression by percutaneous vesicoamniotic shunt or open fetal surgery has been reported. Experimental and clinical evidence of the possible benefits of fetal intervention is lacking, and few affected fetuses are candidates. Prenatally diagnosed PUVs, particularly when discovered in the second trimester, carry a poorer prognosis than those detected in the third trimester following a normal second-trimester fetal US. In the male neonate, PUVs are suspected when there is a palpably distended bladder and the urinary stream is weak. If the obstruction is severe and goes unrecognized during the neonatal period, infants can present later in childhood with failure to thrive because of uremia or sepsis caused by infection in the obstructed urinary tract. With lesser degrees of obstruction, children present later in life with difficulty in achieving diurnal urinary continence or with UTI. The diagnosis is established with a VCUG (Fig. 577.14) or by perineal US.

After the diagnosis is established, renal function and the anatomy of the upper urinary tract should be carefully evaluated. In the healthy neonate, a small polyethylene feeding tube (No. 5 or No. 8 French) is inserted in the bladder and left for several days. Passing the feeding tube may be difficult because the tip of the tube can coil in the prostatic

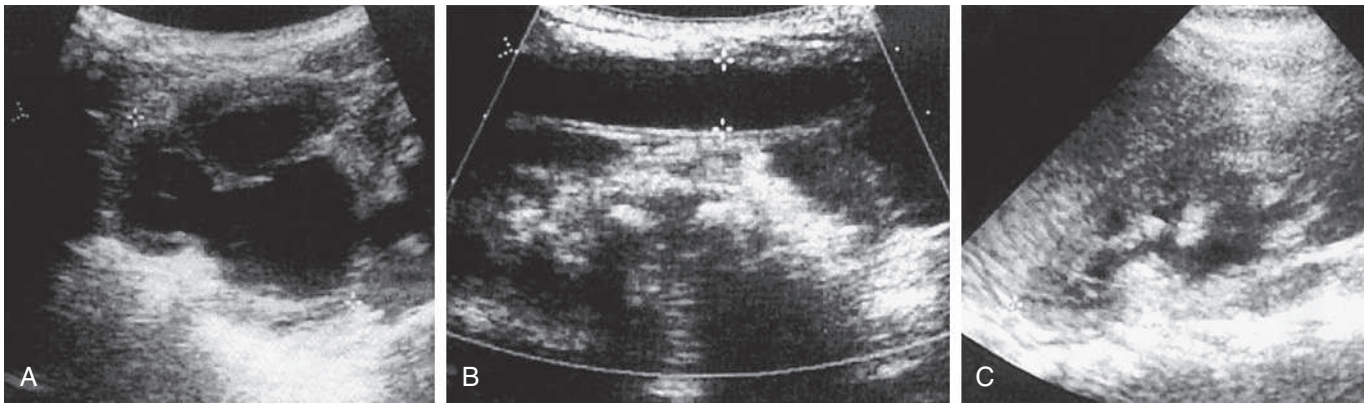

Fig. 577.12 Neonate with primary nonrefluxing megaureter. **A,** Renal US shows grade 4 hydronephrosis. **B,** Dilated ureter. Renal scan showed equal function with the contralateral kidney and satisfactory drainage with diuresis stimulation. **C,** Follow-up US at 10 mo shows complete resolution of hydronephrosis.



Fig. 577.13 Abdominal wall features of prune-belly syndrome, with increasing flaccidity and cutaneous wrinkles, including pot-belly appearance in older age. *(From Lopes RI, Baker LA, Dénes FT. Modern management of and update on prune belly syndrome. J Pediatr Urol. 2021;17:548–554. Fig. 1.)*

urethra. A sign of this problem is that urine drains around the catheter rather than through it. A Foley (balloon) catheter *should not be used*, because the balloon can cause severe bladder spasm, which can produce severe ureteral obstruction.

If the serum creatinine level remains normal or returns to normal, treatment consists of transurethral ablation of the valve leaflets, which is performed endoscopically under general anesthesia. If the urethra is too small for transurethral ablation, temporary vesicostomy is preferred, in which the dome of the bladder is exteriorized on the lower abdominal wall. When the child is older, the valves may be ablated and the vesicostomy closed.

If the serum creatinine level remains high or increases despite bladder drainage by a small catheter, secondary ureteral obstruction, irreversible renal damage, or renal dysplasia should be suspected. In such cases, a vesicostomy should be considered. Cutaneous pyelostomy rarely affords better drainage compared with cutaneous vesicostomy, and the latter also allows continued bladder growth and gradual improvement in bladder wall compliance.

In the septic and uremic infant, lifesaving measures must include prompt correction of the electrolyte imbalance and control of the infection by appropriate antibiotics. Drainage of the upper tracts by percutaneous nephrostomy and hemodialysis may be necessary. After the patient's condition becomes stable, evaluation and treatment may be undertaken. PUVs are diagnosed in some older males because of a poor stream, diurnal incontinence, or a UTI; these males are treated by primary valve ablation.

Favorable prognostic factors include a normal prenatal US between 18 and 24 weeks of gestation, a serum creatinine level <0.8-1.0 mg/dL after bladder decompression, and visualization of the corticomedullary junction on renal sonography. In several situations, a "popoff valve" can occur during urinary tract development, which preserves the integrity of one or both kidneys. For example, 15% of males with PUVs have unilateral reflux into a nonfunctioning dysplastic kidney, termed the **VURD syndrome** (valves, unilateral reflux, dysplasia). In these males, the high bladder pressure is dissipated into the nonfunctioning kidney, allowing normal development of the contralateral kidney. In newborn males with urinary ascites, the urine leaks out from the obstructed collecting system through the renal fornices, allowing normal development of the kidneys. Unfavorable prognostic factors include the presence of oligohydramnios in utero, identification of hydronephrosis before 24 weeks of gestation, a serum creatinine level >1.0 mg/dL after bladder decompression, identification of cortical cysts in both kidneys, and persistence of diurnal incontinence beyond 5 years of age.

The prognosis in the newborn is related to the child's degree of pulmonary hypoplasia and potential for recovery of renal function. Severely affected infants often are stillborn. Of those who survive the neonatal period, approximately 30% eventually require kidney transplantation, and 15% have renal insufficiency. In some series, kidney transplantation in children with PUVs has a lower success rate than does transplantation in children with normal bladders, presumably because of the adverse influence of altered bladder function on graft function and survival.

After valve ablation, antimicrobial prophylaxis is beneficial in preventing UTI, because hydronephrosis to some degree often persists for many years. These males should be evaluated annually with a renal US, physical examination including assessment of somatic growth and blood pressure, urinalysis, and determination of serum levels of electrolytes. Many individuals have significant polyuria resulting from a concentrating defect secondary to prolonged obstructive uropathy. If these children acquire a systemic illness with vomiting and/or diarrhea, urine output cannot be used to assess their hydration status. They

Table 577.6 The PBS RUBACE Severity Scoring Rubric

Eagle-Barrett syndrome PBS triad ("RUBAC") Max score: 16					Extra-genitourinary manifestations ("E") Max score: 15				
No subcategory points are awarded for normal anatomy with absent pathology					No subcategory points are awarded for normal anatomy with absent pathology				
Renal Max score: 6	**Ureteral Max score: 3**	**Bladder/outlet Max score: 3**	**Abdominal wall Max score: 2**	**Cryptorchidism Max score: 2**	**Neurologic Max score: 3**	**Cardiac Max score: 3**	**Gastrointestinal Max score: 3**	**Musculoskeletal Max score: 3**	**Respiratory Max score: 2**
1 pt: G1-G2: Structural damage (dilation, dysplasia, scarring) with preserved GFR ≥ 60	**1 pt**: Low grade or absent VUR, or distal ureter 4–10mm	**1 pt**: Urotherapy required to empty bladder, or bladder size is 100–200% of normal	**1 pt**: Can do "sit-up" exercise before or after abdomino-plasty, musculature mostly intact, minimal laxity, or mild/nonconvincing prune appearance	**1 pt**: History of or current unilateral or palpable undescended testicle(s), or patient is female		**1 pt**: Congenital septal defects (PDA, ASD, VSD) which are spontaneously resolved	**1 pt**: Mild to moderate constipation, managed with diet or laxatives	**1 pt**: Mild facies, abnormally shaped fingers or toes (no loss of function), or rib flaring	**1 pt**: Minimal respiratory support at birth, some difficulty coughing, mild intermittent asthma, or mild reactive airway disease
2 pts: G3a-b: Kidney damage with decreased GFR 30–59 **3 pts**: G4: Severe loss of kidney function with GFR 15–29	**2 pts**: Persistent high grade VUR (no surgery), s/p lower tract ureteral reconstruction, or distal ureter 1–2 cm	**2 pts**: Urethral-catheterization or pharm required to empty, bladder size >200% normal, or patient takes antibiotic prophylaxis for recurrent UTI	**2 pts**: Severe abdominal laxity with obvious thinning of abdominal wall, classic prune appearance, or s/p abdominoplasty + cannot do a "sit-up"	**2 pts**: History of or current bilateral nonpalpable testes		**2 pts**: Small septal defects which are not spontaneously resolved, minimal L to R shunting, or PDA requiring surgical management	**2 pts**: MACE/cecostomy required, or malrotation s/p Ladd's	**2 pts**: Scoliosis, hip dysplasia, club or rockerbottom foot, genu valgum, pectus excavatum or carinum	**2 pts**: Persistent/ moderate asthma, frequent respiratory tract infections (≥3/year), or ≥2 hospitalizations for pneumonia
					PBS-plus or congenital/genetic syndrome or association				
4 pts: Renal failure with GFR <15, or on dialysis or s/p renal transplant **Additional points for young age:** If patient is <2 years, add +2 pts and if patient is <13 years, add +1 pt	**3 pts**: Persistent high grade VUR despite surgery, distal ureter 2+ cm girth, or current diverting ureterostomy or nephrostomy	**3 pts**: Current surgical diversion (e.g., s/p tube, vesicostomy, APV), urethral atresia, or megalourethra requiring repair			**3 pts**: Seizures, tethered cord, spina bifida, hearing loss, intellectual delay, autism, or severe neurologic condition not otherwise specified	**3 pts**: Severe congenital or cyanotic heart disease-Tetralogy of Fallot, left-sided obstructive lesions, reversed shunt, CHF or severe cardiologic conditions not otherwise specified	**3 pts**: Required surgical bowel diversion (e.g., imperforate anus, anal atresia), gastrointestinal malignancy (e.g., hepatoblastoma), or severe GI condition not otherwise specified	**3 pts**: Arthrogryposis, muscular dystrophy, or severe musculoskeletal malformation not otherwise specified	**3 pts**: Ventilator-dependent >1 week, tracheostomy, history of pneumothorax, or severe asthma
Total triad RUBAC score: _____					**Total E score: _____**				
Total triad RUBAC score _____ + Total E score _____ = Total RUBACE score _____									

PBS, Prune-belly syndrome; RUBACE, renal-ureter-bladder-abdominal wall-cryptorchidism-extra GU anomalies.
From Wong DG, Arevalo MK, Passoni NM, et al. Phenotypic severity scoring system and categorization for prune belly syndrome: application to a pilot cohort of 50 living patients. *BJU Int.* 2019;123:130–139. Table 1.



Fig. 577.14 VCUG in an infant with posterior urethral values. Note the dilation of the prostatic urethra and the transverse linear filling defect corresponding to the valves *(arrows)*.

can become dehydrated quickly, and there should be a low threshold for hospital admission for intravenous rehydration. Some of these patients have renal tubular acidosis, requiring oral bicarbonate therapy. If there is any significant degree of renal dysfunction, growth impairment, or hypertension, the child should be followed closely by a pediatric nephrologist. When VUR is present, expectant treatment and prophylactic doses of antibacterial drugs are advisable. If breakthrough UTI occurs, surgical correction should be undertaken.

After treatment, males with PUVs often do not achieve diurnal urinary continence as early as other males. Incontinence can result from a combination of factors, including uninhibited bladder contractions, poor bladder compliance, bladder atonia, bladder neck dyssynergia, or polyuria. Often these males require urodynamic evaluation with urodynamics or videourodynamics to plan therapy. Individuals with a poorly compliant bladder are at significant risk for ongoing renal damage, even in the absence of infection. Overnight catheter drainage has been shown to be beneficial in males with polyuria and can help preserve renal function. Urinary incontinence usually improves with age, particularly after puberty. Meticulous attention to bladder compliance, emptying, and infection can improve results in the future.

Urethral Atresia

The most severe form of obstructive uropathy in males is urethral atresia, a rare condition. In utero there is a distended bladder, bilateral hydroureteronephrosis, and oligohydramnios. In most cases, these infants are stillborn or succumb to pulmonary hypoplasia. Rare males with prune-belly syndrome also have urethral atresia. If the urachus is patent, oligohydramnios is unlikely, and the infant usually survives.

Urethral reconstruction is difficult, and most patients are managed with continent urinary diversion.

Urethral Hypoplasia

Urethral hypoplasia is a rare form of obstructive uropathy in males that is less severe than urethral atresia. In urethral hypoplasia, the urethral lumen is extremely small. Neonates with urethral hypoplasia typically have bilateral hydronephrosis and a distended bladder. Passage of a small pediatric feeding tube through the urethra is difficult or impossible. Usually a cutaneous vesicostomy must be performed to relieve upper urinary tract obstruction, and the severity of renal insufficiency is variable. The most severely affected males have end-stage renal disease. Treatment includes urethral reconstruction, gradual urethral dilation, or continent urinary diversion.

Urethral Stricture

Urethral strictures in males usually result from urethral trauma, either iatrogenic (catheterization, endoscopic procedures, previous urethral reconstruction) or accidental (straddle injuries, pelvic fractures). Because these lesions can develop gradually, the decrease in force of the urinary stream is seldom noticed by the child or the parents. More commonly, the obstruction causes symptoms of bladder instability, hematuria, or dysuria. Catheterization of the bladder usually is impossible. The diagnosis is made by a **retrograde urethrogram,** in which contrast is injected toward the bladder through a catheter inserted into the distal urethra. US also has been used to diagnose urethral strictures. Endoscopy is confirmatory. Endoscopic treatment of short strictures by direct vision urethrotomy is often successful initially and results in a profoundly improved urinary stream, but strictures are prone to recur. Longer strictures surrounded by periurethral fibrosis often require urethroplasty. Repeated endoscopic procedures should be avoided as they cause additional urethral damage. Noninvasive measurement of the urinary flow rate and pattern is useful for diagnosis and follow-up.

In females, true urethral strictures are rare because the female urethra is protected from trauma, particularly in childhood.

Anterior Urethral Valves and Urethral Diverticula in the Male

Anterior urethral valves are rare. The obstruction is not obstructing valve leaflets, as occurs in the posterior urethra. Rather, it is a urethral diverticulum in the penile urethra that expands during voiding. Distal extension of the diverticulum causes extrinsic compression of the distal penile urethra, causing urethral obstruction. There is usually a soft mass on the ventral surface of the penis at the penoscrotal junction. In addition, the urinary stream is typically weak, and the physical findings associated with PUVs are often present. The diverticulum may be small and minimally obstructive or, in other cases, may be severely obstructive and cause renal insufficiency. The diagnosis is suspected on physical examination and is confirmed by VCUG. Treatment involves open excision of the diverticulum or transurethral excision of the distal urethral cusp. Urethral diverticula occasionally occur after extensive hypospadias repair.

Fusiform dilation of the urethra or megalourethra can result from underdevelopment of the corpus spongiosum and support structures of the urethra. This condition is commonly associated with prune-belly syndrome.

Male Urethral Meatal Stenosis

See Chapter 581 for information on urethral meatal stenosis in males.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 578

Anomalies of the Bladder

Heather N. Di Carlo and Chad B. Crigger

BLADDER EXSTROPHY

Exstrophy of the urinary bladder occurs in approximately 1 in 35,000-40,000 births with a male:female ratio of 2:1. The severity ranges from simple **epispadias** (in males) to complete exstrophy of the cloaca involving exposure of the entire hindgut and the bladder **(cloacal exstrophy)**.

Considering the range of defects associated with exstrophy, prenatal diagnosis is challenging. Accurately diagnosing exstrophy (and its subtypes) is paramount in properly counseling families. Proper prenatal diagnosis allows for planning that may optimize postnatal medical and surgical management. Classically, the diagnosis was suspected on prenatal ultrasound. For instances in which the diagnosis remains uncertain, as for midline abdominal defects such as exstrophy versus gastroschisis or omphalocele, fetal magnetic resonance imaging (fMRI) may help elucidate the correct diagnosis.

Clinical Manifestations

Anomalies of the bladder are hypothesized to result when the mesoderm fails to invade the cephalad extension of the cloacal membrane; the timing and extent of this failure determines the degree of the anomaly. In classic bladder exstrophy (Fig. 578.1), the bladder protrudes from the abdominal wall, and its mucosa is exposed. The umbilicus is displaced downward, the pubic rami are widely separated in the midline, and the rectus muscles are separated. In males, there is complete epispadias with dorsal chordee, and the overall penile length is approximately half that of unaffected males. The scrotum typically is separated slightly from the penis and is wide and shallow. Undescended testes and inguinal hernias are common. Females may also have epispadias, with separation of the two halves of the clitoris and wide separation of the labia. The anus is displaced anteriorly in both sexes, and there may be rectal prolapse. The pubic rami are widely separated.

The consequences of untreated bladder exstrophy are total urinary incontinence and an increased incidence of bladder cancer, usually adenocarcinoma. The external and internal genital deformities cause sexual disability in both sexes, particularly in males. The wide separation of the pubic rami causes a characteristic broad-based gait but no significant lasting disability. In classic bladder exstrophy, the upper urinary tracts usually are normal at birth.



Fig. 578.1 Classic bladder exstrophy in a newborn male. The bladder is exposed in the midline, the umbilical cord is displaced caudad, the penis is epispadiac, and the scrotum is broad.

Treatment

Management of bladder exstrophy should start at birth. The bladder should be covered with plastic wrap to keep the bladder mucosa moist. Saline may be gently irrigated as needed to moisten the bladder template. *Application of gauze or petroleum-gauze to the bladder mucosa should be avoided, because significant inflammation will result.* The infant should be transferred promptly to a center with pediatric urology and pediatric anesthetic support for newborns with complex anomalies. These children are prone to *latex allergy,* and latex precautions should be practiced from birth, both in the nursery and in the operating room.

There are two surgical approaches: staged reconstruction and total single-stage reconstruction. Most babies also undergo bilateral iliac osteotomy, which allows the pubic symphysis to be approximated, which supports the bladder closure. In a staged reconstruction, the initial stage is bladder closure, the second stage (in males) is epispadias repair, and the final stage is bladder neck reconstruction. The single-stage reconstruction attempts to reconstruct the entire malformation in a single procedure. When this operation is performed in the newborn, there is an increased risk of intraoperative penile injury and postoperative hydronephrosis compared with the staged reconstruction. The complication rate is high with both approaches, and there is no consensus on which is better.

Although bladder closure within the first 48 hours of life has been the historical standard, many centers of excellence now defer the procedure until 1-2 weeks of life to ensure that the appropriate multidisciplinary surgical and anesthetic teams are available. During bladder exstrophy closure, the abdominal wall is mobilized and the pubic rami are brought together in the midline following pelvic osteotomy. Early bladder closure can be performed in almost all neonates with classic bladder exstrophy. Treatment should be deferred in select situations including when surgical therapy would be excessively risky or complex, such as a premature baby, or if performed by inexperienced surgeons. In the staged approach, in males, epispadias repair usually is performed around age 1 or 2 years. At this point the child has total urinary incontinence because there is no functional external urinary sphincter. Most infants with bladder exstrophy have vesicoureteral reflux and should receive antibiotic prophylaxis. Typically, the bladder capacity is monitored every 12-24 months using cystoscopy with cystogram under anesthesia. The final stage of reconstruction involves creation of a sphincter muscle for bladder control and correction of vesicoureteral reflux. This is usually performed when the child is 3-6 years old with a bladder capacity of at least 80-90 mL, and the child must have gained rectal sphincter control.

Total single-stage reconstruction includes newborn closure of the bladder and bladder neck narrowing, abdominal wall closure, and, in males, correction of epispadias using a technique of penile disassembly. This involves separating the two corpora cavernosa and the midline urethra into three parts via radical mobilization. Postoperatively, the infant's upper urinary tract is monitored closely for possible development of hydronephrosis and infection. Comparison of outcomes between the multistage and single-stage approaches is ongoing.

At puberty pubic hair is often distributed to the sides of the external genitals. A monsplasty can be performed during adolescence to provide a normal escutcheon.

Long-Term Prognosis

Long-term management of individuals born with bladder exstrophy includes monitoring the upper urinary tract appearance and function for any deterioration and infection, as well as assessing continence. As these patients age, erectile function is assessed in males, and, later on in adults, sexual function and fertility are evaluated.

The previously described plan of treatment has yielded a continence rate of 60–70% in a few centers, with <15% risk of deterioration of the upper urinary tract. This continence rate reflects not only successful reconstruction but also the quality and size of the bladder. From a functional standpoint, the reconstructed bladder neck does not relax during voiding as in a normal child; instead the patient must void by assisted techniques such as the Valsalva maneuver or Credé maneuver.

Children who remain incontinent for more than 1 year after bladder neck reconstruction or those who are ineligible for bladder neck reconstruction because of small bladder capacity are candidates for an alternative reconstructive procedure to achieve dryness. In select cases, cystoscopic injection of bulking agents such as dextranomer or polydimethylsiloxane microspheres into the bladder neck can provide sufficient bladder neck coaptation and resistance to establish continence. Alternatively, if the child is not a candidate for endoscopic therapy, options include:

- Augmentation cystoplasty, in which the bladder is enlarged with a patch of small or large bowel to increase its capacity.
- Creation of a neobladder out of a small or large bowel segment with placement of a continent abdominal stoma through which clean, intermittent catheterization can be performed.
- Placement of an artificial urinary sphincter, with possible combined augmentation cystoplasty.
- Ureterosigmoidostomy, in which the ureters are detached from the bladder and sutured to the sigmoid colon; individuals void urine and stool from the rectum and rely on their anal sphincter for continence. This approach does not require many resources in surgical technique or long-term care (such as ostomy supplies).
- Mainz II procedure, in which the sigmoid colon is reconfigured into a "bladder" into which the ureters are connected; the patient voids 3-6 times daily through the rectum, and the stool tends to be more solid.

Ureterosigmoidostomy carries a significant risk of chronic pyelonephritis (see Chapter 575), upper urinary tract damage, metabolic acidosis resulting from absorption of hydrogen ion and chloride in the intestine, and at least a 15–22% long-term risk of colon carcinoma. Patients from less-developed countries often undergo the Mainz II procedure because the continence rate is high and pyelonephritis and upper tract changes are relatively uncommon.

Late follow-up has shown that although adult males with exstrophy have a penis that is half the normal length, they usually experience satisfactory sexual function. Fertility has been low, possibly because of iatrogenic injury to the secondary sexual organs during reconstruction. With artificial reproductive technology, nearly all affected men can be fertile. In adult females, fertility is not affected, but uterine prolapse during pregnancy is a problem. In adult females who have undergone a continent urinary diversion, delivery by cesarean section is usually necessary.

OTHER EXSTROPHY ANOMALIES

More rarely, children have a more severe form of exstrophy, cloacal exstrophy, which occurs in 1 in 400,000 live births. In addition to an exposed bladder, gastrointestinal manifestations typically include omphalocele, an imperforate anus, and a short bowel, resulting in short bowel syndrome (see Chapter 385.6). It is the most devastating anomaly managed by pediatric urologists. Approximately 50% of patients have an upper urinary tract anomaly, and 50% have spina bifida (see Chapter 631.2). Children with cloacal exstrophy do not achieve normal urine or stool continence. Reconstructive techniques result in a satisfactory outcome in most patients with permanent urinary diversion (either ileal conduit or continent urinary diversion) and a colostomy. Because the penis in males with cloacal exstrophy usually is diminutive, genital reconstruction in males with cloacal exstrophy has been unsatisfactory. Until recently, many specialists recommended assigning a female gender to such infants, but currently there is debate as to whether these children, who have a 46,XY karyotype and brain androgen imprinting in utero, can have a satisfactory female gender identity (see Chapter 153). Decisions regarding gender assignment should be made jointly by the physicians caring for the infant (surgical team, pediatric endocrinologist, child psychiatrist, and ethicist) and the family. Current practice by pediatric urologists is to reconstruct genitalia in a manner congruent with the genotype when at all possible, and after extensive counseling with the patient's family.

Epispadias is at the less severe end of the spectrum of exstrophy anomalies, affecting approximately 1 in 117,000 males and 1 in 480,000 females. In males, the diagnosis is obvious because the prepuce is distributed primarily on the ventral aspect of the penile shaft and the urethral meatus is on the dorsum of the penis. Distal epispadias in males (Fig. 578.2) usually is associated with normal urinary control and normal upper urinary tracts and should be repaired by 6-12 months of age. In females, the clitoris is bifid, and the urethra is split dorsally (Fig. 578.3). In more severely affected males and in all females with



Fig. 578.2 Adolescent male with penopubic epispadias.

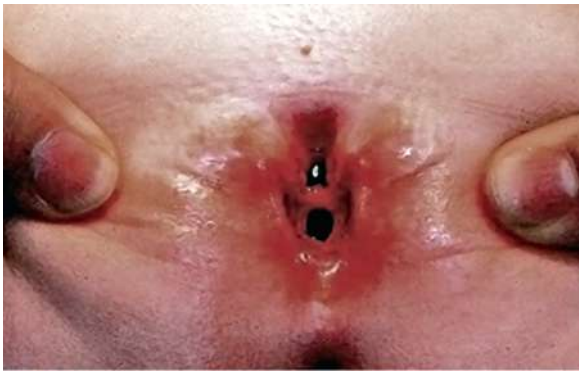

Fig. 578.3 Female with complete epispadias. *(From Gearhart JP, Rink RC, Mouriquand PDE, eds. Pediatric Urology, 2nd ed. Philadelphia: Saunders; 2010.)*

epispadias, there is total urinary incontinence because the sphincter is incompletely formed along with a wide separation of the pubic rami. These children require surgical reconstruction of the bladder neck, similar to the final management stage in children with classic bladder exstrophy.

BLADDER DIVERTICULA

Bladder diverticula develop as herniations of the bladder mucosa between defects of bladder smooth muscle fibers. Primary bladder diverticula usually develop at the ureterovesical junction and may be associated with vesicoureteral reflux, because the diverticulum interferes with the normal flap-valve attachment between the ureter and bladder. In rare circumstances, the diverticulum is so large that it interferes with normal micturition by obstructing the bladder neck. Bladder diverticula also commonly are associated with distal urethral obstructions such as posterior urethral valves or neurogenic bladder dysfunction. They occur commonly in children with connective tissue disorders, including Williams syndrome, Ehlers-Danlos syndrome, and Menkes syndrome (Fig. 578.4). Small diverticula require no treatment other than that of the primary disease, whereas large diverticula can contribute to inefficient voiding, residual urine, urinary stasis, and urinary tract infections and should be excised.

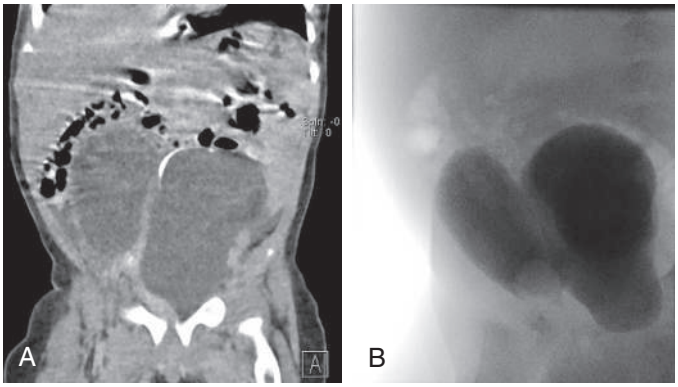

Fig. 578.4 Six-mo-old male with abdominal mass. Ultrasound showed a large fluid-filled mass and normal kidneys. **A,** CT scan shows large bladder diverticulum on right side with ureter coursing between the diverticulum and the bladder. **B,** Voiding cystourethrogram demonstrates no reflux and large diverticulum on left side. Managed with diverticulectomy.

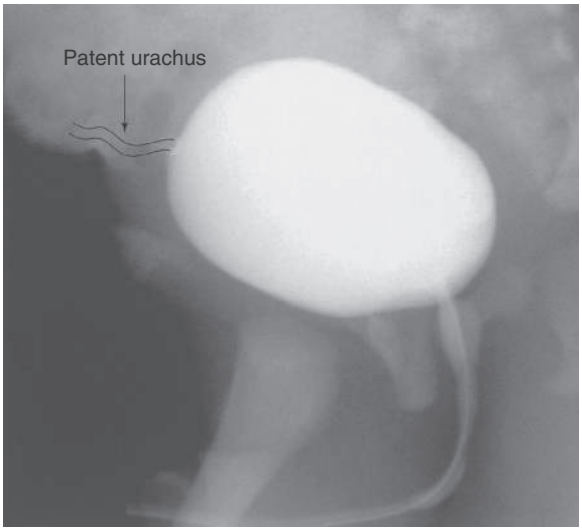

Fig. 578.5 Patent urachus. Vesicourethrogram image of patent urachus in a newborn. Retrograde contrast filling of patent canal with contrast pooling in umbilicus. *(From Partin AW, Dmochowski RR, Kavoussi LR, Peters C., eds. Campbell-Walsh Urology, 12th ed. Philadelphia: Elsevier; 2021. Fig. 30-7.)*

URACHAL ANOMALIES

The urachus is an embryologic canal connecting the dome of the fetal bladder with the allantois, a structure that contributes to the formation of the umbilical cord. The lumen of the urachus is normally obliterated during embryonic development, transforming the urachus into a solid cord. Urachal abnormalities are more common in males than in females. A **patent urachus** can occur as an isolated anomaly, or it may be associated with prune-belly syndrome or posterior urethral valves (see Chapter 577; Fig. 578.5). A patent urachus results in continuous urinary drainage from the umbilicus and treatment involves excising the tract. Another urachal anomaly is the **urachal cyst,** which can become infected. Typical symptoms and physical findings include suprapubic pain, fever, irritative voiding symptoms, and an infraumbilical mass, which can be erythematous. Diagnosis is made by ultrasonography or CT (Fig. 578.6). Treatment is intravenous antibiotic therapy and drainage and excision. Other urachal anomalies include the **vesicourachal diverticulum,** which is a diverticulum of the bladder dome, and **umbilical-urachal sinus,** which is a blind external sinus that opens at the umbilicus. These lesions should be excised.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

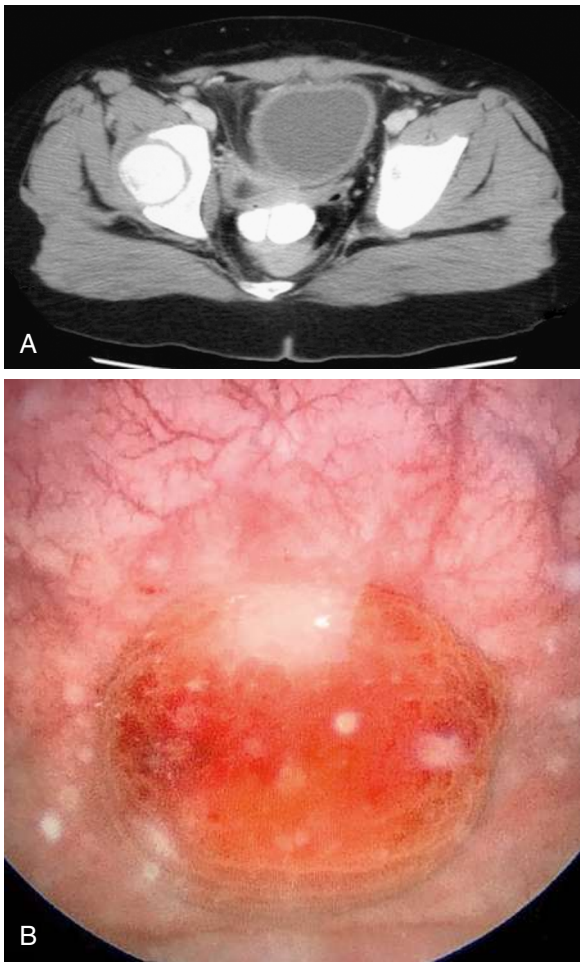

Fig. 578.6 A, CT scan demonstrating infected urachal abscess in an 8-yr-old child. The condition was managed by drainage and excision. B, Cystoscopic view of 10-yr-old child with new-onset daytime frequency and incontinence secondary to infected urachal cyst.

Chapter 579

Neuropathic Bladder

Heather N. Di Carlo and Chad B. Crigger

Neuropathic bladder dysfunction in children is usually congenital, generally resulting from neural tube defects or other spinal abnormalities (see Chapter 754). Acquired diseases and traumatic lesions of the spinal cord are less common (see Chapter 751). Central nervous system tumors, sacrococcygeal teratoma, spinal abnormalities associated with imperforate anus (see Chapter 392), and spinal cord trauma also can result in abnormal innervation of the bladder and/or sphincter (Table 579.1).

NEURAL TUBE DEFECTS

Neural tube defects, resulting from failure of the neural tube to close spontaneously between the third and fourth week in utero, result in abnormalities of the vertebral column that affect spinal cord function, including **spina bifida occulta**, **myelomeningocele,** and **meningocele**

Table 579.1 Causes of Neuromuscular Dysfunction of the Lower Urinary Tract

CONGENITAL
Neural tube defect
Occult forms of neural tube defect (lipomeningocele and other spinal dysraphisms)
Sacral agenesis
Anorectal malformations
ACQUIRED
Extensive pelvic surgery
Central nervous system disorders
Cerebral palsy
Conditions of the brain (tumors, infarcts, encephalopathies)
Spinal cord insults
Trauma
Transverse myelitis

From Partin AW, Dmochowski RR, Kavoussi LR, Peters CW, eds. *Campbell-Walsh Urology*, 12th ed. Philadelphia: Elsevier; 2021: Box 34-1.

(see Chapters 631.2, 631.3, and 631.4). Specialized medical centers in the United States have performed antenatal myelomeningocele closure. Long-term results from one large clinical trial of **in utero closure** have not shown a definite improvement in lower urinary tract function, although some children have demonstrated nearly normal bladder function. Overall, this trial has demonstrated a significant reduction in the need for ventriculoperitoneal shunting and improved performance on measures of self-care, motor function, and mobility.

Clinical Manifestations and Diagnosis

The most important urologic consequences of neuropathic bladder dysfunction associated with neural tube defects are urinary incontinence (see Chapter 580), urinary tract infections (UTIs; see Chapter 575), and hydronephrosis from vesicoureteral reflux (see Chapter 576) or detrusor-sphincter dyssynergia (see Chapter 580). Pyelonephritis and renal functional deterioration (see Chapter 575) are common causes of premature death in affected patients.

In the neonate, renal ultrasonography, assessment of postvoiding residual urine volumes, and a voiding cystourethrogram are performed after closure of the myelomeningocele as approximately 10–15% of newborns with myelomeningocele have hydronephrosis, and renal malformations are common; 25% have vesicoureteral reflux. A **urodynamic** study also should be performed. In this study, the bladder is filled with saline, and the bladder volume, bladder pressure, abdominal pressure, and sphincter tone are measured until the patient voids. During bladder filling, the bladder might show (1) uninhibited (premature) contractions (termed hyperreflexia) at low volumes, (2) normal bladder volume with contraction at an appropriate volume, or (3) atonia (lack of bladder contraction). Bladder compliance or elasticity also may be abnormal (i.e., abnormally high bladder pressure during bladder filling). The sphincter can show (1) normal tonicity with relaxation during bladder contraction, (2) reduced or absent tonicity, or (3) normal or increased tonicity that increases significantly during a bladder contraction (termed **detrusor-sphincter dyssynergia**; Fig. 579.1).

Renal Damage

Renal damage usually results from detrusor-sphincter dyssynergia. This dyssynergia causes functional obstruction of the bladder outlet, leading to bladder muscle hypertrophy and trabeculation, high intravesical pressure, and transmission of this high pressure into the upper urinary tracts, causing hydronephrosis (Fig. 579.2). Vesicoureteral reflux and UTI compound this problem, but severe hydronephrosis can result without reflux. Treatment includes reduction of bladder pressure with anticholinergic drugs (e.g., oxybutynin, 0.2 mg/kg/dose up to three times per day) and **clean intermittent catheterization** every 3-4 hours. If the child has vesicoureteral reflux or UTI, antimicrobial prophylaxis also is prescribed.

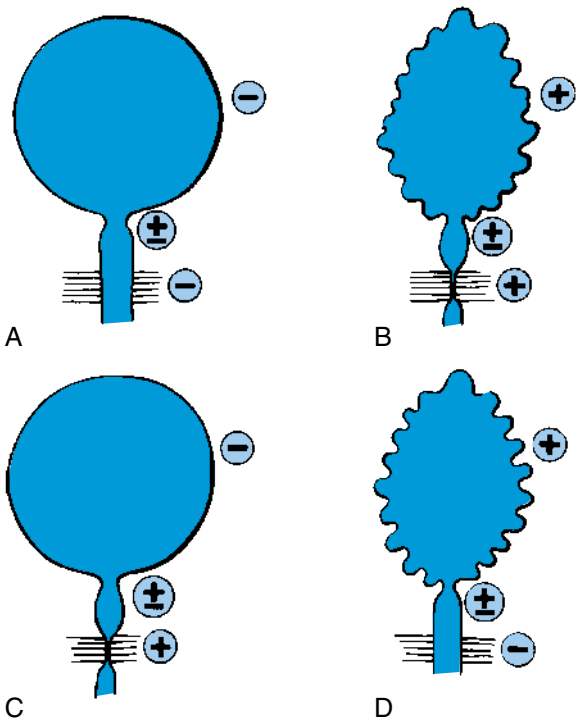

Fig. 579.1 Grouping of neuropathic bladder dysfunction according to the innervation, tonicity, and coordination of the detrusor and sphincters described by Guzman. This grouping is based on data from imaging studies, cystometrography, and electromyography of the sphincters. Patients in group B are at risk of developing reflux and hydronephrosis. For guidance in the treatment of incontinence, group A patients benefit from procedures that increase outlet resistance, group B patients from anticholinergics or bladder augmentation surgery, and group C patients from intermittent catheterization. Group D patients require both increased outlet resistance and pharmacologic or surgical bladder enlargement. Most patients require intermittent catheterization to empty. *(Modified from Gonzalez R. Urinary incontinence. In Kelalis PK, King LR, Belman AB, eds. Clinical Pediatric Urology. Philadelphia: Saunders; 1992. p. 387.)*



Fig. 579.2 Voiding cystourethrogram in an infant with myelodysplasia shows a severely trabeculated bladder with multiple diverticula and grade V (out of V) right vesicoureteral reflux. Evaluation showed severe detrusor-sphincter dyssynergia.

Temporary urinary diversion by cutaneous vesicostomy is an alternative in the newborn or infant with severe reflux, if intermittent catheterization is difficult, or if anticholinergic medications are not well tolerated. Another option for treating the severely trabeculated bladder is transurethral injection of botulinum toxin (Botox) into the detrusor muscle, which reduces bladder hypertonicity for approximately 6 months and often needs to be repeated. A different approach in these children is to temporarily inactivate the tight sphincter by urethral overdilation or transurethral injection of botulinum toxin into the sphincter. In children with upper tract changes, continuous overnight bladder drainage allows significant bladder relaxation and can reduce bladder wall thickening and lessen hydronephrosis.

Clean intermittent catheterization and anticholinergic therapy cure reflux in up to 80% of children with grade I or II reflux. Children with more severe reflux often require subureteral endoscopic injection therapy (see Chapter 576) or open antireflux surgery followed by intermittent catheterization and anticholinergic drugs. In older children with myelomeningocele with high-grade reflux, UTI, and hydronephrosis, augmentation enterocystoplasty (enlarging the bladder with a patch of intestine) with intermittent catheterization may be necessary. This intervention allows a normal-capacity bladder with low bladder pressure and effective drainage of the bladder.

Urinary Incontinence

Incontinence in the child with neuropathic bladder can result from total or partial denervation of the sphincter, bladder hyperreflexia, poor bladder compliance, chronic urinary retention, or a combination of these factors.

Incontinence is often addressed at 4-5 years of age and is tailored to the individual child. Nearly all children require clean intermittent catheterization to stay dry. This technique allows efficient bladder emptying with minimal risk of symptomatic UTI. *The urinary tract should be reevaluated with renal ultrasonography, a voiding cystourethrogram, and a urodynamic study (including bladder capacity) prior to initiation of an intermittent catheterization regimen*. If the external sphincter tone is sufficient and the bladder has adequate compliance, intermittent catheterization every 3-4 hours is often successful in keeping the child socially dry. If there are unstable bladder contractions, an anticholinergic medication such as oxybutynin chloride, hyoscyamine, or tolterodine is prescribed to increase bladder capacity. If there is sphincteric incompetence, α-adrenergic medications are prescribed to enhance outlet resistance. Bacteriuria is seen in up to 50% of children using intermittent self-catheterization, but it seldom causes symptoms. In the absence of reflux, there seems to be little cause for concern. Performing intermittent catheterization with a new catheter (hydrophilic or standard silicone) each time is also quite effective in preventing bacteriuria and avoids the need for antibiotic prophylaxis. With this treatment plan, 40–85% of patients are dry, depending on the definition of continence; some children wear a pad in their underwear or a diaper for security but feel that they are dry.

If there is persistent incontinence despite medical therapy, reconstructive urinary tract surgery nearly always provides complete or satisfactory continence. If urethral resistance is low, bladder neck reconstructive procedures such as a periurethral sling are often successful. Alternatively, implantation of an artificial sphincter is usually successful. This sphincter consists of an inflatable cuff that is placed around the bladder neck, a pressure-regulating balloon implanted in the extraperitoneal space, and a pump mechanism that is implanted in the scrotum of boys and in the labia majora of girls. Squeezing the pump 3-4 times moves the fluid out of the inflatable urethral cuff, and then the cuff slowly refills over the next 2-3 minutes.

If the bladder capacity or bladder compliance is low, or if there are persistent uninhibited contractions despite anticholinergic therapy, enlargement of the bladder with a patch of small or large intestine,

termed augmentation cystoplasty or **enterocystoplasty**, is effective. These patients still need to perform clean intermittent catheterization. If urethral catheterization is difficult, a continent urinary stoma may be incorporated into the urinary tract reconstruction. A common method is the **Mitrofanoff procedure** (appendicovesicostomy), in which the appendix is isolated from the cecum on its vascular pedicle and is interposed between the bladder and abdominal wall to allow intermittent catheterization through a dry stoma. An ileal conduit with a bag on the abdominal wall is rarely used.

Complications of Augmentation Cystoplasty

Urinary Tract Infection

The urine may be colonized with gram-negative bacteria, and attempts to sterilize the urine for prolonged periods usually fail. There is no evidence that chronic bacteriuria in patients who have had enterocystoplasty is associated with renal damage; therefore only symptomatic UTIs should be treated.

Metabolic Acidosis

The enteric mucosal surface in contact with the urine absorbs ammonium, chloride, and hydrogen ions and loses potassium. *Hyperchloremic metabolic acidosis can result, possibly requiring medical treatment* (see Chapter 73). Chronic acidosis can compromise skeletal growth. This condition is common with colocystoplasty but is uncommon with ileocystoplasty. Metabolic acidosis is also common in patients with compromised renal function. To overcome this limitation of enterocystoplasty in patients with chronic renal insufficiency, a composite augmentation using the stomach and a small or large bowel gastric segment can be used. The stomach secretes chloride and hydrogen ions; thus preexisting metabolic acidosis remains stable or improves. However, augmentation with a gastric segment remains rare.

Spontaneous Perforation

Perforation of the augmented bladder is a life-threatening complication that results most often from acute or chronic overdistention of the augmented bladder. Patients with this complication typically present with severe abdominal pain and signs of peritonitis. Prompt diagnosis and treatment with exploratory laparotomy and bladder closure are necessary. Meticulous adherence to the prescribed program of intermittent catheterization to avoid bladder overdistention is important.

Bladder Calculi

Bladder calculi have developed in as many as 70% of children followed for 10 years after enterocystoplasty. The calculi develop in response to mucus that accumulates in the bladder and serves as a nidus for stone formation. This complication can be prevented by daily irrigation of the bladder with sterile saline.

Malignant Neoplasm

Invasive transitional cell carcinoma has been reported in nearly 4.6% of patients undergoing enterocystoplasty (compared with a 2.6% risk in spina bifida patients without enterocystoplasty). The pathogenesis is uncertain, but there is speculation that it is related to bacteriuria and the bowel-bladder contact. The risk is highest following gastrocystoplasty. The risk increases 10 years following enterocystoplasty. Although there are no formal guidelines or recommendations regarding screening, it seems appropriate to advise yearly endoscopic examinations or urine cytologic studies beginning in the tenth postoperative year.

ASSOCIATED DISORDERS

Constipation

Many patients with spina bifida also have bowel problems with constipation, and a vigorous bowel regimen is important. Some benefit from the **Malone antegrade continence enema (MACE) procedure**, in which the appendix is brought out to the skin to allow a catheter to be inserted into the cecum for antegrade enema. The stoma is continent, and an antegrade enema can be performed with tap water each day. This form of management allows the patient to be continent of stool and be more self-sufficient. An alternative to the MACE procedure is a percutaneous cecostomy, in which a button is placed into the cecum to allow an antegrade flush. The MACE and percutaneous cecostomy procedures can be performed laparoscopically.

Latex Allergy

Latex allergy is a very serious problem encountered by as many as half of patients with spina bifida and other urologic conditions who require clean intermittent catheterization and urinary tract reconstructive procedures. This immunoglobulin E–mediated allergy is acquired and is secondary to repeated exposure to the latex allergen. Latex allergy can manifest as watery eyes, sneezing, itching, hives, or anaphylaxis when blowing up a balloon or if an examiner is using latex gloves. Intraoperatively, a sensitized patient can experience anaphylactic shock. A latex-free environment should be provided for all children with spina bifida in the office, during hospitalization, and during operative procedures. Affected children also should wear a medical alert bracelet.

Occult Spinal Dysraphism

Approximately 1 in 4,000 patients have occult spinal dysraphism, a category that includes lipomeningocele, intradural lipoma, diastematomyelia, tight filum terminale, dermoid cyst-sinus, aberrant nerve roots, anterior sacral meningocele, and cauda equina tumor. More than 90% of patients have a cutaneous abnormality overlying the lower spine, including a **sacral dimple**, tuft of hair, dermal vascular malformation, or subcutaneous lipoma (Fig. 579.3). Often these children have high-arched feet, discrepancy in muscle size and strength between the legs,

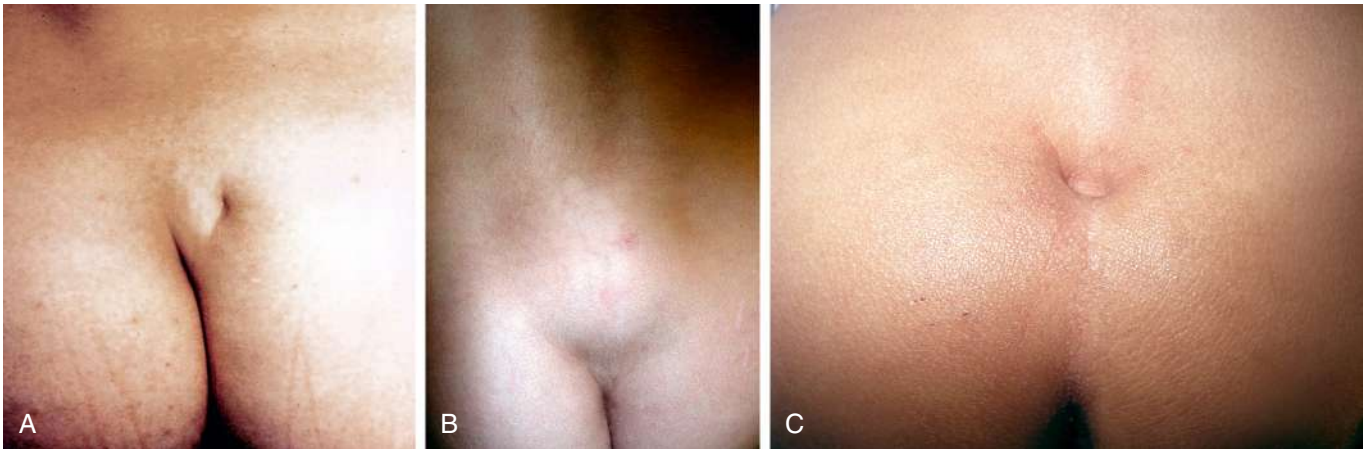

Fig. 579.3 A, Buttocks of teenage boy with tethered cord secondary to lipomeningocele. Note sacral dimple and deviation of gluteal fold to the left. B, Fat deposit over sacrum in girl with tethered cord secondary to lipomeningocele. C, Deep sacral pit in child with neuropathic bladder.

and a gait abnormality. Newborns and young infants often have a normal neurologic examination. Older children often have absent perineal sensation and back pain. Lower urinary tract function is abnormal in 40% of patients, including incontinence, recurrent UTI, and fecal soiling. The likelihood of a normal examination is inversely related to the child's age at surgical correction of the spinal lesion. In infants with abnormal urodynamics, 60% revert to normal; in older children, only 27% become normal. Management of the urinary tract in other children is similar to that described earlier for neural tube defects.

Sacral Agenesis

Sacral agenesis is defined as the absence of part or all of two or more lower vertebral bodies. *This condition is more common in the offspring of women with diabetes.* These children have a flattened buttock and a low, short gluteal cleft but usually have no orthopedic deformity, although some have high-arched feet. Palpation of the coccygeal area detects the absent vertebrae. Approximately 20% of cases are undetected until the age of 3-4 years; many are diagnosed after unsuccessful toilet training. Urodynamic studies in these children show a variety of patterns, and most need clean intermittent catheterization and pharmacotherapy to stay dry.

Imperforate Anus

Approximately 30–45% of children with a high imperforate anus have a neuropathic bladder, often because of sacral agenesis. Newborns with imperforate anus should undergo a spinal ultrasound during their initial evaluation, and if these children have difficulty with toilet training, complete urologic evaluation with upper and lower urinary tract imaging and urodynamics should be performed (see Chapter 392).

Cerebral Palsy

Children with cerebral palsy (see Chapter 638.1) often have reasonable bladder control. However, they achieve continence at a later age than unaffected children. Overall, 25–50% are incontinent, and the risk is directly related to the severity of physical impairment. Their upper urinary tracts are usually normal. Urodynamic studies have shown that most have uninhibited bladder contractions. Timed voiding and anticholinergic therapy are usually effective. Upper urinary tract deterioration is uncommon, and clean intermittent catheterization is rarely necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 580

Enuresis and Voiding Dysfunction

Heather N. Di Carlo and Chad B. Crigger

NORMAL VOIDING AND TOILET TRAINING

Fetal voiding occurs by reflex bladder contraction in concert with simultaneous contraction of the bladder and relaxation of the sphincter. Urine storage results from sympathetic and pudendal nerve-mediated inhibition of detrusor contractile activity accompanied by closure of the bladder neck and proximal urethra with increased activity of the external sphincter. The infant has coordinated reflex voiding as often as 15-20 times/day. Over time, bladder capacity increases. In children up to the age of 14 years, the mean bladder capacity in milliliters is equal to the ([age (in years) + 2] times 30) (e.g., the bladder capacity of a 6 year old should be [6 + 2] × 30 or 240 mL).

At 2-4 years, the child is developmentally ready to begin toilet training. To achieve conscious bladder control, several conditions must be present: awareness of bladder filling, cortical inhibition (suprapontine modulation) of reflex (unstable) bladder contractions, ability to consciously tighten the external sphincter to prevent incontinence, normal bladder growth, and motivation by the child to stay dry. The transitional phase of voiding refers to the period when children are acquiring bladder control. *Females typically acquire bladder control before males, and bowel control typically is achieved before bladder control.*

DIURNAL INCONTINENCE

Daytime incontinence not secondary to neurologic abnormalities is common in children. At 5 years of age, 95% have been dry during the day at some time and 92% are dry consistently. At 7 years of age, 96% are dry, although 15% have significant **urgency** at times. At 12 years, 99% are dry consistently during the day. The most common causes of daytime incontinence are **overactive bladder (urge incontinence)** and bladder-bowel dysfunction (BBD). Table 580.1 lists the causes of diurnal incontinence in children; Table 580.2 categorizes four types of voiding dysfunction.

The patient history should assess the pattern of incontinence, including the frequency of voiding, frequency of day and night urinary leakage, volume of urine lost during incontinent episodes, whether the incontinence is associated with urgency or giggling, whether it occurs after voiding, and whether the incontinence is continuous. In addition, whether the patient has a strong continuous urinary stream and sensation of incomplete bladder emptying should be assessed. A diary of when the child voids and whether the child is wet or dry is helpful. Other urologic problems, such as urinary tract infections (UTIs), vesicoureteral reflux, neurologic disorders, or a family history of renal duplication anomalies, should be assessed. Bowel habits also should be evaluated because incontinence is common in children with constipation and/or encopresis. Diurnal incontinence can occur in children with a history of sexual abuse or following bullying. Physical examination is directed at identifying signs of organic causes of incontinence. Short stature, hypertension, enlarged kidneys and/or bladder, constipation, labial adhesion, ureteral ectopy, back or sacral anomalies (see Fig. 579.4), and neurologic abnormalities should be documented.

Assessment tools include urinalysis, with culture if indicated; bladder diary (recorded times and volumes voided, whether wet or dry); postvoid residual urine volume (generally obtained by bladder scan); and the **Dysfunctional Voiding Symptom Score** (Fig. 580.1). An alternative to the Dysfunctional Voiding Symptom Score is the **Vancouver Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome** questionnaire. This questionnaire is a validated tool that consists of 14 questions scored on a 5-point Likert scale to assess lower urinary tract and bowel dysfunction. In most cases, a

Table 580.1 Causes of Urinary Incontinence in Childhood

Overactive bladder (urge incontinence or diurnal urge syndrome)
Infrequent voiding (underactive bladder)
Voiding postponement
Detrusor-sphincter discoordination
Nonneurogenic neurogenic bladder (Hinman syndrome)
Vaginal voiding
Giggle incontinence
Cystitis
Bladder outlet obstruction (posterior urethral valves)
Ectopic ureter and fistula
Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality)
Neuropathic
Overflow incontinence
Traumatic
Iatrogenic
Behavioral
Combinations

Table 580.2 Symptoms and Signs of Four Main Subtypes of Lower Urinary Tract Dysfunction

	SYMPTOMS	SIGNS
Overactive bladder	(Cystometric) detrusor overactivity, frequency, voiding urgency, incontinence, constipation, enuresis	Holding maneuvers, normal flow pattern, thick bladder wall, low-volume voids
Dysfunctional voiding	Failure to relax the sphincter during voiding, normal micturition frequency, incontinence, constipation, urinary tract infections, enuresis	Post-void residue, staccato or interrupted flow pattern, normal frequency of voids
Underactive bladder	(Cystometric) weak detrusor contractions, low micturition frequency incontinence, constipation, urinary tract infections	Post-void residue, staccato or interrupted flow pattern, frequent large volume voids
Voiding postponement	Low micturition frequency, incontinence	Normal flow pattern

Classification of daytime lower urinary tract dysfunction, assessment, and documentation should be based on the following parameters: incontinence (presence or absence and symptom frequency), voiding frequency, voiding urgency, voided volumes, and fluid intake.
From Nieuwhof-Leppink AJ, Schroeder RPJ, van de Putte EM, et al. Daytime urinary incontinence in children and adolescents. *Lancet Child Adolesc Health.* 2019;3:492–500.

Patient name:
Hospital number:
Reason for referral:
Date:

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.	0	1	2	3	NA
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	No (0)			Yes (3)	
Total*					

- New baby.
- New home.
- New school.
- School problems.
- Abuse (sexual/physical).
- Home problems (divorce/death).
- Special events (birthday).
- Accident/injury.
- Others.

*Females with a score ≥6 and males with a score ≥9 are most likely to have dysfunctional voiding.

Fig. 580.1 Dysfunctional Voiding Symptom Score questionnaire. *(From Farhat W, Bagli DJ, Capolicchio G, et al. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol. 2000;164:1011–1015.)*

uroflow study with electromyography (noninvasive assessment of urinary flow pattern and measurement of external sphincter activity) is indicated. Another item that may be useful in children older than age 5 years is the **Pediatric Symptom Checklist (PSC)**, a brief screening questionnaire that may reveal psychosocial stressors contributing to incontinence (see Chapter 32).

Bowel function should also be assessed. The **Bristol Stool Form Score** (Fig. 580.2) should be recorded. In addition, the clinician should utilize the Rome III diagnostic criteria, which classify functional gastrointestinal disorders that do not have underlying structural or tissue-based causes. Children 4 years of age or older are diagnosed as being constipated if they fulfill two or more of the following criteria over a period of 2 months: two or fewer defecations in the toilet per week, at least one episode of fecal incontinence per week, a history of retentive posturing or excessive volitional stool retention, a history of painful or hard bowel movements, the presence of a large fecal mass in the rectum, and a history of large-diameter stools that obstruct the toilet.

Imaging (renal-bladder ultrasound with or without a voiding cystourethrogram) is indicated in children with diurnal incontinence who have significant physical findings, those who have a family history of urinary tract anomalies or UTIs, and those who do not respond to therapy appropriately. Urodynamics should be performed if there is evidence of neurologic disease and may be helpful if empirical therapy is ineffective. *If there is any evidence of a neurologic disorder or if there is a sacral abnormality on physical examination, an MRI of the lower spine should be obtained.*

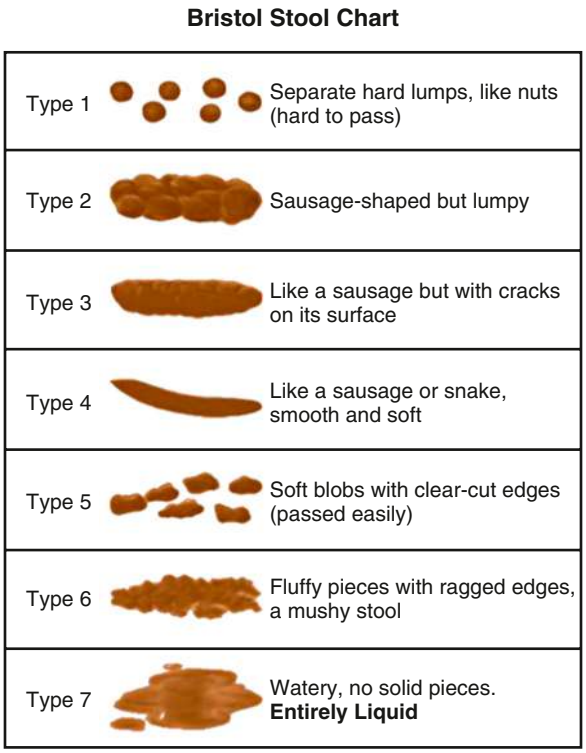

Fig. 580.2 Bristol Stool Chart for evaluating bowel function.

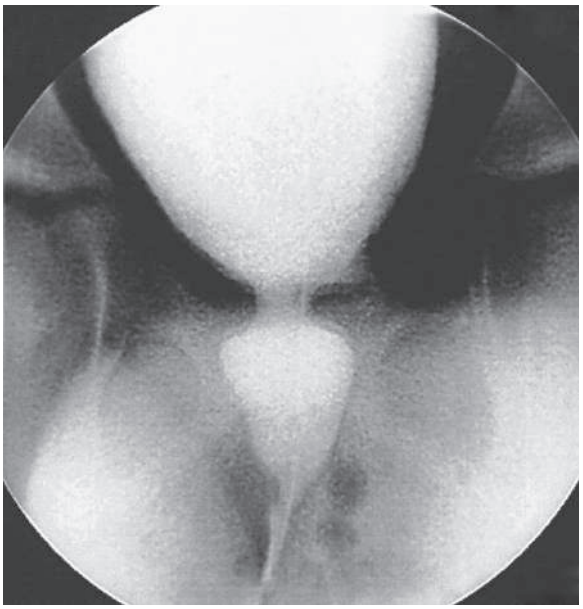

Fig. 580.3 Spinning-top deformity. Voiding cystourethrogram demonstrating dilation of the urethra with distal urethral narrowing and contraction of the bladder neck.

OVERACTIVE BLADDER (DIURNAL URGE SYNDROME)

Children with an overactive bladder typically exhibit urinary frequency, urgency, and urge incontinence. Often a female will squat down on her foot to try to prevent incontinence (termed *Vincent's curtsy*). The bladder in these children is functionally, but not anatomically, smaller than normal and exhibits strong uninhibited contractions. Approximately 25% of children with nocturnal enuresis also have symptoms of an overactive bladder. Many children indicate they do not feel the need to urinate, even just before they are incontinent. In females, a history of recurrent UTI is common, but incontinence can persist long after infections are brought under control. It is unclear if the voiding dysfunction is a sequela of the UTIs or if the voiding dysfunction predisposes to recurrent UTIs. In some females, voiding cystourethrography shows a dilated urethra (**spinning-top deformity**; Fig. 580.3) and narrowed bladder neck with bladder wall hypertrophy. The urethral finding results from inadequate relaxation of the external urinary sphincter.

The overactive bladder nearly always resolves, but the time to resolution is highly variable, occasionally not until the teenage years. Initial therapy is timed voiding, every 1.5-2 hours. Treatment of constipation and UTIs is important. Another treatment is **biofeedback**, in which children are taught pelvic floor exercises **(Kegel exercises),** because daily performance of these exercises can reduce or eliminate unstable bladder contractions. Biofeedback often consists of 8-10 1-hour sessions and may include participation with animated computer games. Biofeedback also may include periodic uroflow studies with sphincter electromyography to be certain that the pelvic floor relaxes during voiding, and assessment of postvoid residual urine volume by sonography. **Anticholinergic** therapy often is helpful if bowel function is normal. **Oxybutynin chloride** and **tolterodine** are the only U.S. Food and Drug Administration (FDA)-approved medications in children, but hyoscyamine, trospium, solifenacin, and mirabegron have also demonstrated safety in this population; these medications reduce bladder overactivity and may help the child achieve dryness. Adequate hydration should be emphasized to combat constipation as oxybutynin can induce constipation in some patients. Treatment with an α-adrenergic blocker such as terazosin or doxazosin can aid in bladder emptying by promoting bladder neck relaxation; these medications also have mild anticholinergic properties. If pharmacologic therapy is successful, the dosage should be tapered periodically to determine its continued need. Children who do not respond to therapy should be evaluated with urodynamic studies to rule out other possible forms of bladder or sphincter dysfunction. In refractory cases, other procedures such as **sacral neuromodulation** (InterStim), percutaneous tibial nerve stimulation, and intravesical botulinum toxin injection have been effective in children.

If the child has constipation based on the criteria described earlier, treatment generally is initiated with polyethylene glycol powder, which has been shown to be safe in children and is generally more effective than other laxative preparations (see Chapter 378.3).

NONNEUROGENIC NEUROGENIC BLADDER (HINMAN SYNDROME)

Hinman syndrome is a very serious but uncommon disorder involving failure of the external sphincter to relax during voiding in children without neurologic abnormalities. Children with this syndrome, also called **nonneurogenic neurogenic bladder**, typically exhibit a staccato stream, day and night wetting, recurrent UTIs, constipation, and encopresis. Evaluation of affected children often reveals vesicoureteral reflux, a trabeculated bladder, and a decreased urinary flow rate with an intermittent pattern (Fig. 580.4). In severe cases, hydronephrosis, renal insufficiency, and end-stage renal disease can occur. The pathogenesis of this syndrome is thought to involve learning abnormal voiding habits during toilet training; the syndrome is rarely seen in infants. Urodynamic studies and MRI of the spine are indicated to rule out a neurologic cause for the bladder dysfunction.

The treatment usually is complex and can include anticholinergic and α-adrenergic blocker therapy, timed voiding, treatment of constipation, behavioral modification, and encouragement of relaxation during voiding. Biofeedback has been used successfully in older children to teach relaxation of the external sphincter. Botulinum toxin injection into the external sphincter can provide temporary sphincteric paralysis and thereby reduce outlet resistance. In severe cases, intermittent catheterization is necessary to ensure bladder emptying. In selected patients, external urinary diversion is necessary to protect the upper urinary tract. These children require long-term treatment and careful follow-up.

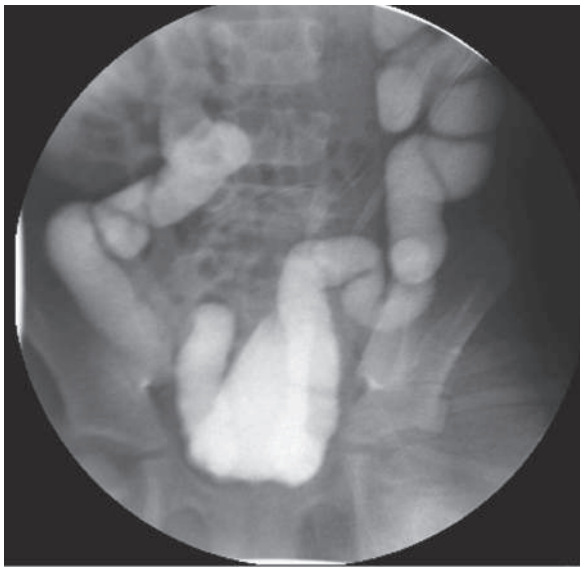

Fig. 580.4 Voiding cystourethrogram demonstrating severe bladder trabeculation and vesicoureteral reflux in a 12-yr-old male with Hinman syndrome. The patient presented with day and night incontinence, had chronic renal failure, and underwent kidney transplantation.

INFREQUENT VOIDING (UNDERACTIVE BLADDER)

Infrequent voiding is a common disorder of micturition. Affected children, usually females, often void only 1-2 times a day rather than the normal 4-7 times. Poor detrusor contraction strength and/or duration lead to bladder overdistention and prolonged retention of urine and ultimately bacterial growth that can lead to recurrent UTIs. Some of these children are constipated. Some also have occasional episodes of incontinence from overflow or urgency. The disorder is behavioral. If the child has UTIs, treatment includes antibacterial prophylaxis and encouragement of frequent voiding and complete emptying of the bladder by double voiding until a normal pattern of micturition is reestablished.

VAGINAL VOIDING

In females with vaginal voiding, incontinence typically occurs after urination after the female stands up. The volume is usually minimal, about 5-10 mL, and characterized as dribbling. One of the most common causes is **labial adhesion** (Fig. 580.5). This lesion, typically seen in young females, can be managed either by topical application of estrogen or steroid cream to the adhesion or manual separation (this should only be done after ensuring adequate anesthesia and potentially sedation; see Chapter 586). Some females experience vaginal voiding because they do not separate their legs widely during urination. These females typically are overweight and/or do not pull their underwear down to their ankles when they urinate. Management involves encouraging the female to separate the legs as widely as possible during urination. The most effective way to do this is to have the child sit backward on the toilet seat during micturition.

OTHER CAUSES OF INCONTINENCE IN FEMALES

Ureteral ectopia, usually associated with a duplicated collecting system in females, refers to a ureter that drains outside the bladder, often into the vagina or distal urethra. It can produce urinary incontinence characterized by constant urinary dribbling all day, even though the child voids regularly. Sometimes the urine production from the renal segment drained by the ectopic ureter is small, and urinary drainage is confused with watery vaginal discharge. Children with a history of vaginal discharge or incontinence and an abnormal voiding pattern require careful study. The ectopic orifice is usually difficult to find. On ultrasonography or intravenous urography, one may suspect duplication of the collecting system (Fig. 580.6), but the upper collecting system drained by the ectopic ureter usually has poor or delayed function.



Fig. 580.5 A, Labial adhesion. Note the inability to visualize the urethral meatus and vagina. B, Normal female external genitals following lysis of labial adhesion.

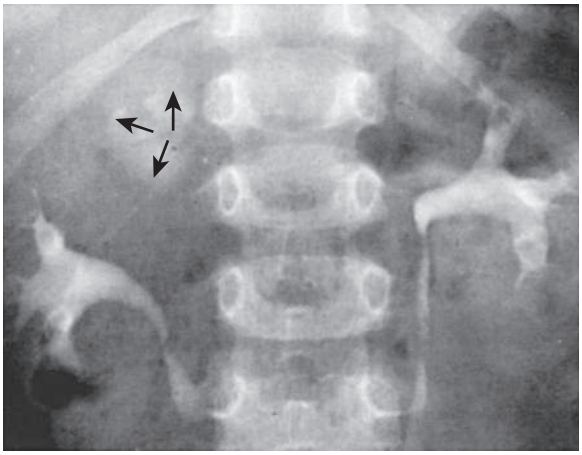

Fig. 580.6 Duplication of the right collecting system with ectopic ureter. Excretory urogram in a female presenting with a normal voiding pattern and constant urinary dribbling. The left kidney is normal, and the right side, well visualized, is the lower collecting system of a duplicated kidney. On the upper pole opposite the first and second vertebral bodies, note the accumulation of contrast material *(arrows)* corresponding with a poorly functioning upper pole drained by a ureter opening in the vestibule.

CT scanning of the kidneys or an MR urogram should demonstrate subtle duplication anomalies. Examination under anesthesia for an ectopic ureteral orifice in the vestibule or the vagina may be necessary (Fig. 580.7). Treatment in these cases is either partial nephrectomy, with removal of the upper pole segment of the duplicated kidney and its ureter down to the pelvic brim, or ipsilateral ureteroureterostomy, in which the upper pole ectopic ureter is anastomosed to the normally positioned lower pole ureter. These procedures often are performed by minimally invasive laparoscopy with or without robotic assistance.

Giggle incontinence typically affects females 7-15 years of age. The incontinence occurs suddenly during giggling, and the entire bladder volume is lost. The pathogenesis is thought to be sudden relaxation of the urinary sphincter. Anticholinergic medication and timed voiding occasionally are effective. The most effective treatment is low-dose methylphenidate, which seems to stabilize the external sphincter.

Total incontinence in females may be secondary to **epispadias** (see Fig. 578.2). This condition, which affects only 1 in 480,000 females, is characterized by separation of the pubic symphysis, separation of the right and left sides of the clitoris, and a patulous urethra. Treatment is bladder neck reconstruction; an alternative surgical therapy is



Fig. 580.7 An ectopic ureter entering the vestibule next to the urethral meatus. The thin ureteral catheter with transverse marks has been introduced into this ectopic ureter. This female had a normal voiding pattern and constant urinary dribbling.

Table 580.3 Nocturnal Enuresis

CAUSES
Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex
Defective sleep arousal
Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)
Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis
Bladder factors (lack of inhibition, reduced capacity, overactive)
Constipation
Organic factors, such as urinary tract infection, obstructive uropathy, or sickle cell anemia nephropathy
Sleep disorders
Sleep-disordered breathing secondary to enlarged adenoids
Psychologic factors more often implicated in secondary enuresis
OTHER FEATURES
Enuresis can occur in any stage of sleep (but usually non–rapid eye movement sleep)
All children are most difficult to arouse in the first third of the night and easiest to awaken in the last third, but enuretic children are more difficult to arouse than those with normal bladder control
Enuretic children often are described as "soaking the bed"
Family history in enuretic children often positive for enuresis
Risk increased with developmental delay, attention-deficit/hyperactivity disorder, autism spectrum disorders

placement of an artificial urinary sphincter to repair the incompetent urethra.

A short, incompetent urethra may be associated with certain urogenital sinus malformations. The diagnosis of these malformations requires a high index of suspicion and a careful physical examination of all incontinent females. In these cases, urethral and vaginal reconstruction often restores continence.

VOIDING DISORDERS WITHOUT INCONTINENCE

Some children have abrupt onset of severe urinary frequency, voiding as often as every 10-15 minutes during the day, without dysuria, UTI, daytime incontinence, or nocturia. The most common age for these symptoms to occur is 4-6 years, after the child is toilet trained; males are more often affected. This condition is termed the **daytime frequency syndrome of childhood,** or **pollakiuria**. The condition is functional without associated anatomic problems. Often the symptoms occur just before a child starts kindergarten or if the child is having emotional family stress-related problems. These children should be checked for UTIs, and the clinician should ascertain that the child is emptying the bladder satisfactorily. Another contributing cause is constipation. Occasionally, pinworms cause these symptoms. The condition is self-limited, and symptoms generally resolve within 2-3 months. Anticholinergic therapy is rarely effective.

Some children have **dysuria-hematuria syndrome,** in which the child has dysuria without UTI but with microscopic or total gross hematuria (blood throughout the stream). This condition affects children who are toilet-trained and is often secondary to hypercalciuria. A 24-hour urine sample should be obtained and calcium and creatinine excretion assessed. A 24-hour calcium excretion of >4 mg/kg is abnormal and deserves treatment with thiazides, because some of these children are at risk for urolithiasis. **Terminal hematuria** (blood at the end of the stream) occurs in males and typically is secondary to BBD or urethral meatal stenosis. Cystoscopy is not indicated, and the condition usually resolves with treatment for constipation.

NOCTURNAL ENURESIS

By 5 years of age, 90–95% of children are nearly completely continent during the day, and 80–85% are continent at night. Nocturnal enuresis refers to the occurrence of involuntary voiding at night after 5 years old, the age when volitional control of micturition is expected. Enuresis may be **primary** (estimated 75–90% of children with enuresis; nocturnal urinary control never achieved) or **secondary** (10–25%; the child was dry at night for at least a few months and then enuresis developed). Overall, 75% of children with enuresis are wet only at night, and 25% are incontinent day and night. This distinction is important, because children with both forms are more likely to have an abnormality of the urinary tract. *Monosymptomatic enuresis* is more common than *polysymptomatic enuresis* (associated urgency, hesitancy, frequency, daytime incontinence).

Epidemiology

Approximately 60% of children with nocturnal enuresis are males. The family history is positive in 50% of cases. Although primary nocturnal enuresis may be polygenetic, candidate genes have been localized to chromosomes 6, 12, and 13. If one parent was enuretic, each child has a 44% risk of enuresis; if both parents were enuretic, each child has a 77% likelihood of enuresis. Nocturnal enuresis without overt daytime voiding symptoms affects up to 20% of children at the age of 5 years; it ceases spontaneously in approximately 15% of involved children every year thereafter. Its frequency among adults is <1%.

Pathogenesis

The pathogenesis of primary nocturnal enuresis (normal daytime voiding habits) is multifactorial (Table 580.3).

Clinical Manifestations and Diagnosis

A careful history should be obtained, especially with respect to fluid intake at night and the pattern of nocturnal enuresis. Children with diabetes insipidus (see Chapter 596), diabetes mellitus (see Chapter 629), and chronic renal disease (see Chapter 572) can have a high obligatory urinary output and a compensatory polydipsia. The family should be asked whether the child snores loudly at night. Many children with enuresis sleepwalk or talk in their sleep. A complete physical examination should include palpation of the abdomen and possibly a rectal examination after voiding to assess the possibility of a chronically distended bladder and constipation. The child with nocturnal enuresis should be examined carefully for neurologic and spinal abnormalities. There is an increased incidence of bacteriuria in enuretic females, and, if found, it should be investigated and treated (see Chapter 575), although this does not always lead to resolution of bed-wetting. A urine sample should be obtained after an overnight fast and evaluated

for specific gravity or osmolality to exclude polyuria as a cause of frequency and incontinence and to ascertain that the concentrating ability is normal. The absence of glycosuria should be confirmed. If there are no daytime symptoms, the physical examination and urinalysis are normal, and the urine culture is negative, further evaluation for urinary tract pathology generally is not warranted. A renal ultrasound is reasonable in an older child with enuresis or in children who do not respond appropriately to therapy.

Treatment

The best approach to treatment is to reassure the child and parents that the condition is self-limited and to avoid punitive measures that can affect the child's psychologic development adversely. Fluid intake should be restricted to 2 oz after 6 or 7 PM. The parents should be certain that the child voids at bedtime. Avoiding extraneous sugar and caffeine after 5 PM is also beneficial. If the child snores and the adenoids are enlarged, referral to an otolaryngologist should be considered, because adenoidectomy can cure the enuresis in some cases.

Active treatment should be avoided in children younger than 6 years of age, because enuresis is extremely common in younger children. Treatment is more likely to be successful in children approaching puberty compared with younger children. In addition, treatment is most likely to be effective in children who are motivated to stay dry and is less successful in children who are overweight. Treatment should be viewed as a facilitator that requires active participation by the child (e.g., a coach and an athlete).

The simplest initial measure is **motivational therapy** and includes a star chart for dry nights. Waking children a few hours after they go to sleep to have them void often allows them to awaken dry, although this measure is not curative. Some have recommended that children try holding their urine for longer periods during the day, but there is no evidence that this approach is beneficial. **Conditioning therapy** involves use of a loud auditory or vibratory alarm attached to a moisture sensor in the underwear. The alarm activates when voiding occurs and is intended to awaken children and alert them to void. This form of therapy has a reported success of 30–60%, although the relapse rate is significant. Often the auditory alarm wakes up other family members and not the enuretic child; persistent use of the alarm for several months often is necessary to determine whether this treatment is effective. Conditioning therapy tends to be most effective in older children. Another form of therapy to which some children respond is self-hypnosis. The primary role of psychologic therapy is to help the child deal with enuresis psychologically and help motivate the child to void at night if he or she awakens with a full bladder.

Pharmacologic therapy is intended to treat the symptom of enuresis and thus is regarded as second line and is not curative. Direct comparisons of the moisture alarm with pharmacologic therapy favor the former because of lower relapse rates, although initial response rates are equivalent.

One form of pharmacologic treatment is **desmopressin acetate,** a synthetic analog of antidiuretic hormone that reduces urine production overnight. This medication is FDA-approved in children and is available as a tablet, with a dosage of 0.2-0.6 mg orally 2 hours before bedtime. A nasal spray formulation is available but is no longer recommended for nocturnal enuresis due to increased risk of hyponatremia and convulsions. Hyponatremia has not been reported in children using oral tablets. Fluid restriction at night is important, and the drug should not be used if the child has a systemic illness with vomiting or diarrhea or if the child has polydipsia. Desmopressin acetate is effective in as many as 40% of children and is most effective in those approaching puberty. If effective, it should be used for 3-6 months, and then an attempt should be made to taper the dosage. Some families use it intermittently (sleepovers, school trips, vacations) with success. If tapering results in recurrent enuresis, the child should return to the higher dosage. Few adverse events have been reported with the long-term use of desmopressin acetate.

For therapy-resistant enuresis or children with symptoms of an overactive bladder, anticholinergic therapy is indicated. Oxybutynin 5 mg or tolterodine 2 mg at bedtime is often prescribed. If the medication is ineffective, the dosage may be doubled. The clinician should monitor constipation as a potential side effect.

A third-line treatment is **imipramine,** which is a tricyclic antidepressant. This medication has mild anticholinergic and α-adrenergic effects, reduces the urine output slightly, and might alter the sleep pattern. The dosage of imipramine is 25 mg in children age 6-8 years, 50 mg in children age 9-12 years, and 75 mg in teenagers. Reported success rates are 30–60%. Side effects include anxiety, insomnia, dry mouth, and heart rhythm changes. If there is any history of palpitations or syncope in the child, or sudden cardiac death or unstable arrhythmia in the family, long QT syndrome in the patient needs to be excluded prior to prescribing imipramine. The drug is one of the most common causes of poisoning by prescription medication, so it is also important to emphasize safe storage.

In unsuccessful cases, combining therapies often is effective. Alarm therapy plus desmopressin is more successful than either alone. The combination of oxybutynin chloride and desmopressin is more successful than a single agent. Desmopressin and imipramine also may be combined.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 581

Anomalies of the Penis and Urethra

Heather N. Di Carlo and Chad B. Crigger

HYPOSPADIAS

Hypospadias is a urethral opening on the ventral surface of the penile shaft affecting 1 in 200 male newborns. Typically an isolated defect, its incidence is increased in many males with chromosomal abnormalities, anorectal malformation, and congenital heart disease. Usually, there is incomplete development of the prepuce, called a **dorsal hood,** in which the foreskin is on the sides and dorsal aspect of the penile shaft and deficient or absent ventrally. Some males with hypospadias, particularly those with proximal hypospadias, have **chordee,** in which there is ventral penile curvature during erection. The incidence of hypospadias appears to be increasing, possibly because of in utero exposure to estrogenic or antiandrogenic endocrine-disrupting chemicals (e.g., polychlorobiphenyls, phytoestrogens).

Clinical Manifestations

Hypospadias is classified according to the position of the urethral meatus after considering whether chordee is present (Fig. 581.1). The deformity is described as distal (further broken down into glanular [on the glans penis], coronal, or subcoronal), midpenile (distal penile, midshaft, or proximal penile), or proximal (penoscrotal, scrotal, or perineal). Approximately 65% of cases are distal, 25% are subcoronal or midpenile, and 10% are proximal. In the most severe cases, the scrotum is bifid, and sometimes there is moderate **penoscrotal transposition.** As many as 10% of affected males have a **megameatal variant of hypospadias** in which the foreskin is developed normally (megameatus intact prepuce variant), and there is either glanular or subcoronal hypospadias with a "fish mouth" meatus. These cases might not be diagnosed until after a circumcision is performed.

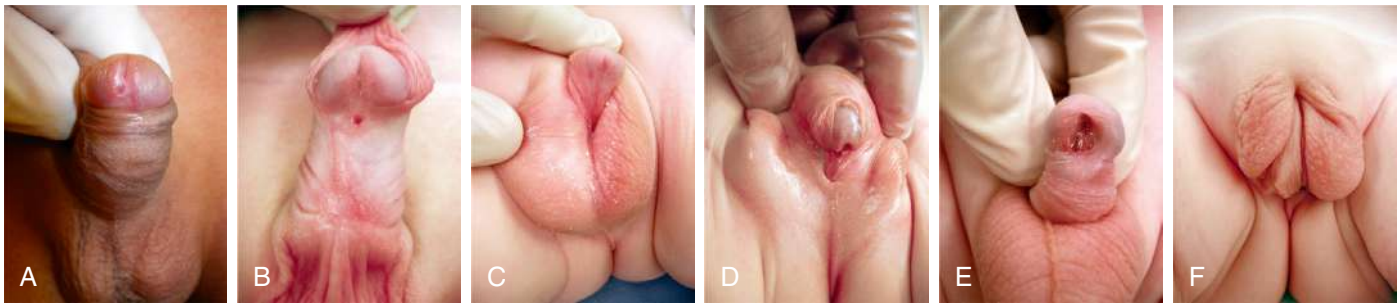

Fig. 581.1 Varying forms of hypospadias. A, Glanular hypospadias. B, Subcoronal hypospadias. Note the dorsal hood of foreskin. C, Penoscrotal hypospadias with chordee. D, Perineal hypospadias with chordee and partial penoscrotal transposition. E, Megameatal variant of hypospadias diagnosed following circumcision; note absence of hooded foreskin. F, Complete penoscrotal transposition with scrotal hypospadias.

Approximately 10% of males with hypospadias have an undescended testis; inguinal hernia(s) also are common. In the newborn, the differential diagnosis of midpenile or proximal hypospadias associated with an undescended testis should include forms of a **disorder of sex development,** particularly mixed gonadal dysgenesis, partial androgen insensitivity, true hermaphroditism, and congenital adrenal hyperplasia in a female (see Chapter 616). In the latter condition, neither gonad is palpable. *A karyotype should be obtained in patients with midpenile or proximal hypospadias and cryptorchidism* (see Chapter 628). In males with proximal hypospadias, a voiding cystourethrogram should be considered because 5–10% of these children have a dilated **prostatic utricle,** which is a remnant of the müllerian system (see Chapter 591). The incidence of upper urinary tract abnormalities is low unless there are abnormalities of other organ systems.

Complications of untreated hypospadias include deformity of the urinary stream, typically ventral deflection or severe splaying; sexual dysfunction secondary to penile curvature; infertility if the urethral meatus is proximal; meatal stenosis (congenital), which is uncommon; and cosmetic appearance. The goal of hypospadias surgery is to correct the functional and cosmetic deformities. Whereas hypospadias repair is recommended for all males with midpenile and proximal hypospadias, some males with distal hypospadias have no functional abnormality and do not need surgical correction.

Treatment

Management begins in the newborn period. *Circumcision should be avoided because the foreskin often is used in the repair in most cases.* The ideal age for repair in a healthy infant is 6-12 months because the risk of general anesthesia at this age is similar to older children; penile growth over the next several years is slow; the child does not remember the surgical procedure; and postoperative analgesic needs are less than in older children. With the exception of proximal hypospadias, virtually all cases are repaired in a single operation on an ambulatory basis. The most common repair involves tubularization of the urethral plate distal to the urethral meatus, with coverage by a vascularized flap from the foreskin, termed a tubularized incised plate repair. Proximal cases might require a two-stage repair.

The complication rate parallels severity: 5% for distal hypospadias, 10% for midpenile hypospadias, and 40% for proximal hypospadias. The most common complications include urethrocutaneous fistula and meatal stenosis. Other complications include a deformed urinary stream, persistent or recurrent penile curvature, and dehiscence of the hypospadias repair. Treatment of these complications generally is straightforward. In complex cases, a buccal mucosa graft from the mouth is used to create urethral mucosa. Repair of hypospadias is a technically demanding operation and should be performed by a surgeon with specialty training in pediatric urology and extensive experience.

CHORDEE WITHOUT HYPOSPADIAS

In some males, there is mild or moderate ventral penile curvature **(chordee)** and incomplete development of the foreskin **(dorsal hood),** but the urethral meatus is at the tip of the glans (Fig. 581.2). In most of these males, the urethra is normal, but there is insufficient ventral penile skin or prominent, inelastic ventral bands of dartos fascia that prevent a straight erection. In some cases, the urethra is hypoplastic, and a formal urethroplasty is necessary for repair. The only sign of this anomaly in the neonate may be the hooded foreskin, and delayed repair under general anesthesia after 6 months of age is recommended. **Lateral penile curvature** usually is caused by overgrowth or hypoplasia of a corporal (erectile) body and usually is congenital. Surgical repair is also recommended at age 6-12 months.

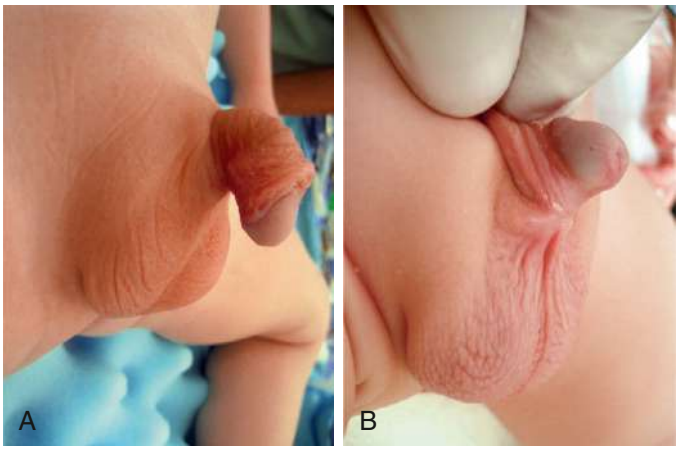

Fig. 581.2 A and B, Two examples of chordee without hypospadias. Note hooded foreskin and normal location of urethral meatus.

PHIMOSIS AND PARAPHIMOSIS

Phimosis refers to the inability to retract the prepuce. At birth, phimosis is physiologic. Over time, the adhesions between the prepuce and glans lyse and the distal phimotic ring loosens. In 80% of uncircumcised males, the prepuce becomes retractable by 3 years of age. Accumulation of epithelial debris under the infant's prepuce is physiologic and does not mandate circumcision. In older males, phimosis may be physiologic or may be pathologic from **lichen sclerosus (balanitis xerotica obliterans)** at the tip of the foreskin (Fig. 581.3A) and can also affect the meatus (see Fig. 581.3B). The prepuce might have been retracted forcefully on one or two occasions in the past, which can result in a cicatricial scar that prevents subsequent retraction of the foreskin. In males with persistent physiologic or pathologic phimosis, application of corticosteroid ointment to the tip of the foreskin twice daily for 1 month loosens the phimotic ring in two thirds of cases. *If there is ballooning of the foreskin during voiding or phimosis beyond 10 years of age and topical corticosteroid therapy is ineffective, circumcision is recommended.*

Paraphimosis occurs when the foreskin is retracted proximal to the coronal sulcus and the prepuce cannot be pulled back over the glans (Fig. 581.4). Painful venous stasis in the retracted foreskin results, with

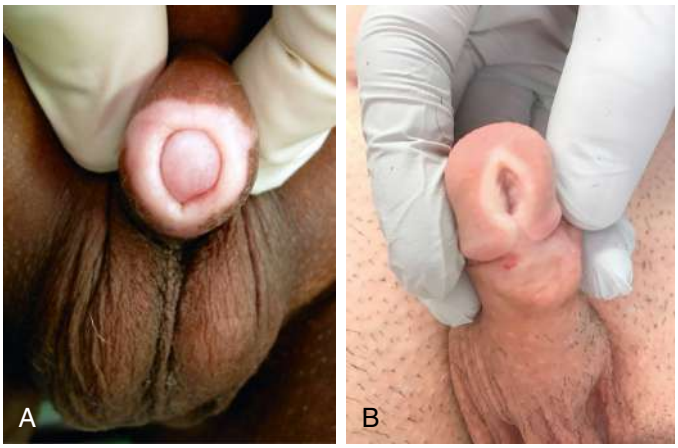

Fig. 581.3 A, Balanitis xerotica obliterans. Note whitish cicatricial plaque. B, Involvement of the urethral meatus necessitated a meatoplasty.



Fig. 581.4 Paraphimosis. The foreskin has been retracted proximal to the glans penis and is markedly swollen secondary to venous congestion.

edema leading to severe pain and inability to reduce the foreskin (pull it back over the glans). Treatment includes lubricating the foreskin and glans and then simultaneously compressing the glans and placing distal traction on the foreskin to try to push the phimotic ring past the coronal sulcus. Topical application of granulated sugar has been reported to aid in reduction of edema by creation of an osmotic gradient, facilitating reduction of paraphimosis. In addition, injection of hyaluronidase into the edematous skin has been reported to result in immediate reduction in swelling. In rare cases, emergency circumcision under general anesthesia is necessary.

CIRCUMCISION

In the United States, circumcision usually is performed for cultural reasons, but several health benefits have been identified that may outweigh the risks of the procedure. Specific benefits include prevention of urinary tract infections (UTIs) and penile cancer and reducing the risk and transmission of some sexually transmitted infections, including HIV.

UTIs are 10-15 times more common in uncircumcised *infant* males than in circumcised infants, with the urinary pathogens arising from bacteria that colonize the space between the prepuce and glans. The risk of febrile UTI (see Chapter 575) is highest between birth and 6 months, but there is an increased risk of UTI until at least 5 years of age, or age of completion of toilet training. Many recommend circumcision in infants who are predisposed to UTI, such as those with congenital hydronephrosis and vesicoureteral reflux. Circumcision reduces the risk of sexually transmitted infections in adults (see Chapter 163), in particular HIV (see Chapter 322). There have been only a handful of reports of adult males who were circumcised at birth and subsequently acquired penile carcinoma, but in Scandinavian countries, where few males are circumcised and hygiene is good, the incidence of penile cancer is low.

Circumcision should be performed by trained providers under sterile conditions. When performing a neonatal circumcision, local analgesia, such as a dorsal or penile ring block or application of EMLA (eutectic mixture of local anesthetics) cream (lidocaine 2.5% and prilocaine 2.5%) is recommended. Early and late complications after neonatal circumcision include bleeding, wound infection, meatal stenosis, secondary phimosis, removal of insufficient foreskin, and fibrous penile adhesions (skin bridge; Fig. 581.5); 0.2–3.0% of patients undergo a subsequent operative procedure. Males with a large hydrocele or hernia are at particular risk for secondary phimosis because the scrotal swelling tends to displace the penile shaft skin over the glans. Serious complications of newborn circumcision include sepsis, amputation of the distal part of the glans, removal of an excessive amount of foreskin, and urethrocutaneous fistula. Circumcision should not be performed in neonates with hypospadias, chordee without hypospadias, or a dorsal hood deformity (relative contraindication) or in those with a small penis (Fig. 581.6). In males with a "wandering raphe," in which the median raphe deviates to one side, there may be underlying penile torsion or hypospadias, and evaluation by a pediatric urologist is suggested before performing a circumcision.

PENILE TORSION

Penile torsion, a rotational defect of the penile shaft, usually occurs in a counterclockwise direction, usually to the left side (see Fig. 581.6D). In most cases, penile development is normal, and the condition is unrecognized until circumcision is performed or the foreskin is retractable. In many cases, the midline raphe of the penile shaft is deviated. Penile torsion also occurs in some males with hypospadias. The defect has primarily cosmetic significance, and correction is unnecessary if the rotation is <60 degrees from the midline. The severity of penile torsion may lessen during infancy.

INCONSPICUOUS PENIS

The term *inconspicuous penis* refers to a penis that appears to be small. A **webbed penis** is a condition in which the scrotal skin extends onto the ventral penile shaft. This deformity represents an abnormality of the attachment between the penis and scrotum. Although the deformity might appear mild, if a routine circumcision is performed, the penis can retract into the scrotum, resulting in secondary phimosis **(trapped penis).** The concealed **(hidden or buried)** penis is a normally developed penis that is camouflaged by the suprapubic fat pad (Fig. 581.7). This anomaly may be congenital, iatrogenic after circumcision, or a result of obesity. Surgical correction is indicated for cosmetic reasons or if there is a functional abnormality with a splayed stream.

A **trapped penis** is an acquired form of inconspicuous penis and refers to a phallus that becomes embedded in the suprapubic fat pad after circumcision (Fig. 581.8). This deformity can occur after neonatal circumcision in an infant who has significant scrotal swelling from a large hydrocele or inguinal hernia or after routine circumcision in an infant with a webbed penis. This complication can predispose to UTIs and can cause urinary retention. Initial treatment of a trapped penis should include topical corticosteroid cream, which often loosens the phimotic ring. In some cases, secondary repair is necessary at 6-9 months.

MICROPENIS

Micropenis is defined as a normally formed penis that is at least 2.5 standard deviations (SD) below the mean in size (Fig. 581.9). Typically, the ratio of the length of the penile shaft to its circumference is normal.

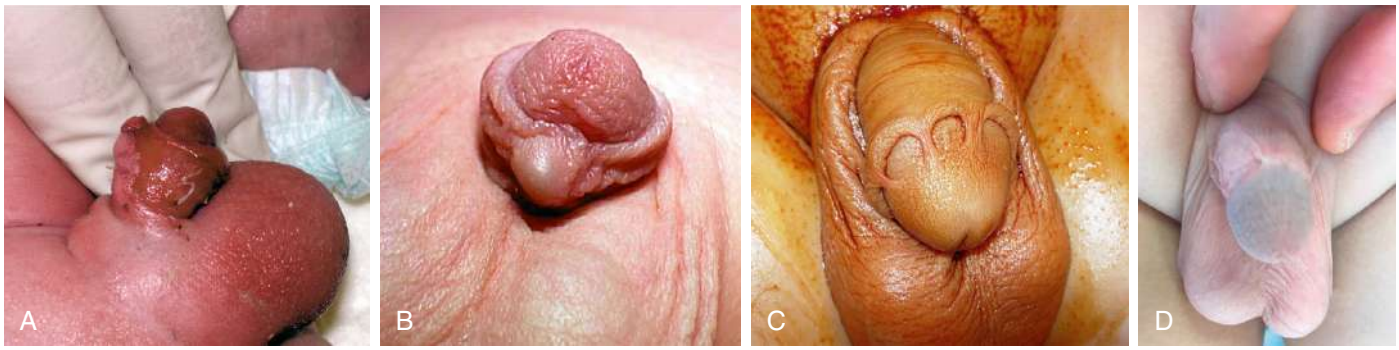

Fig. 581.5 Complications of circumcision. **A,** Denuded penile shaft. With local care, the penis healed and appeared normal. **B,** Midline epithelial inclusion cyst. **C** and **D,** Fibrous penile skin bridges.

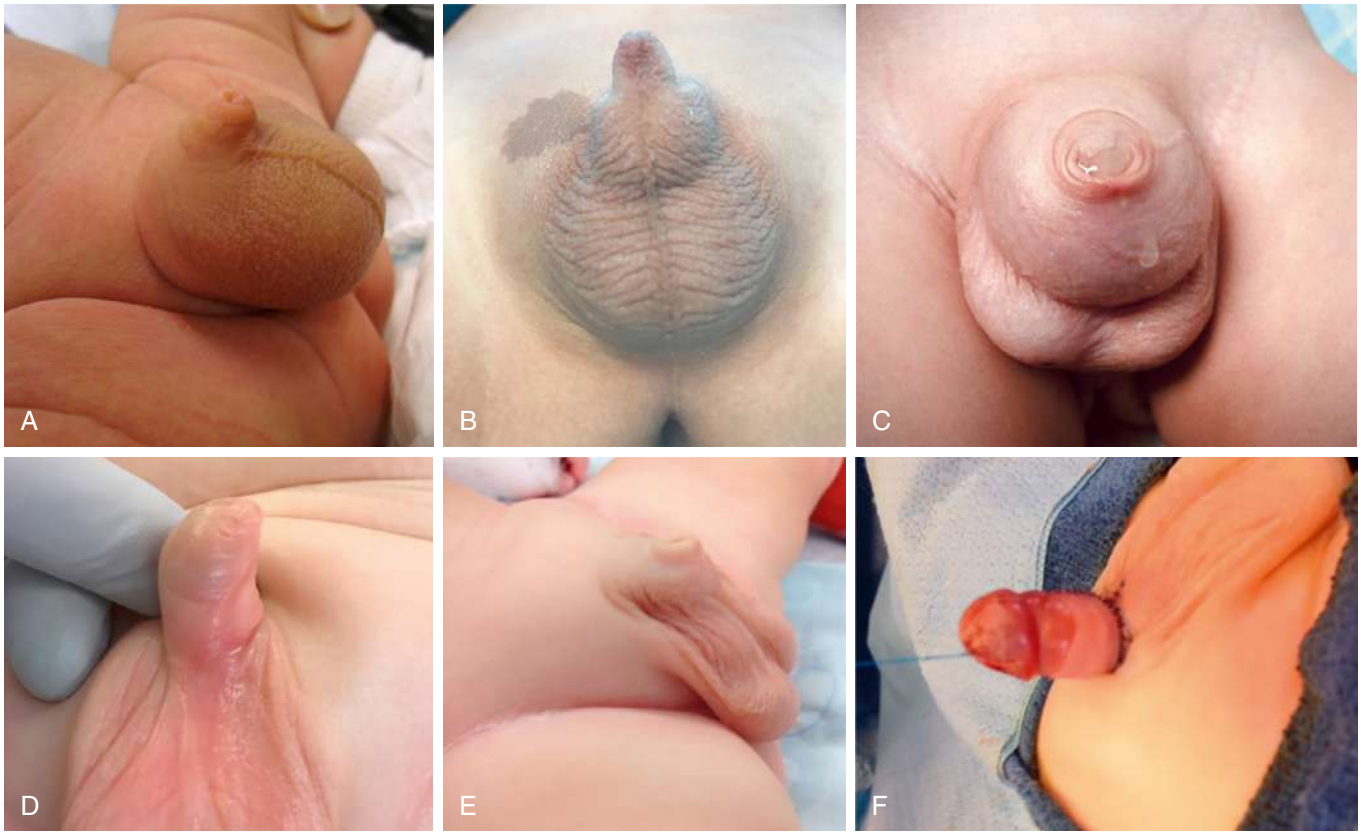

Fig. 581.6 Examples of congenital deformities in which neonatal circumcision is contraindicated. **A** and **B,** Hidden penis. **C,** Megaprepuce. **D,** Penile torsion to left side; note "wandering raphe." **E,** Webbed penis; note scrotal attachment to penile shaft. **F,** Same patient as in **E** following reconstruction at 6 mo.

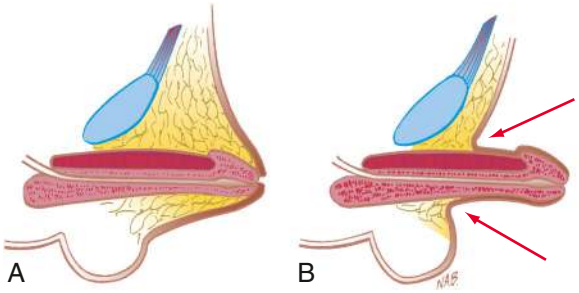

Fig. 581.7 Concealed penis **(A)**, which may be visualized by retracting skin lateral to penile shaft **(B)**. *(From Wein AJ, Kavoussi LR, Novick AC, et al., eds. Campbell-Walsh Urology, 9th ed. Philadelphia: WB Saunders; 2007: Fig. 126-4, p. 2339.)*

The pertinent measurement is the **stretched penile length**, which is measured by stretching the penis and measuring the distance from the penile base under the pubic symphysis to the tip of the glans. The mean length of the term newborn penis is 3.5 ± 0.7 cm and the diameter is 1.1 ± 0.2 cm. The diagnosis of micropenis in a male newborn is if the stretched length is <1.9 cm.

Micropenis usually results from a hormonal abnormality that occurs after the 14th week of gestation. Common causes include hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic micropenis. If growth hormone deficiency is also present, neonatal hypoglycemia can occur. The most common cause of micropenis is failure of the hypothalamus to produce an adequate amount of gonadotropin-releasing hormone, as typically occurs in Kallmann syndrome (see Chapter 623), Prader-Willi syndrome (see Chapter 99), and Lawrence-Moon-Bardet-Biedl

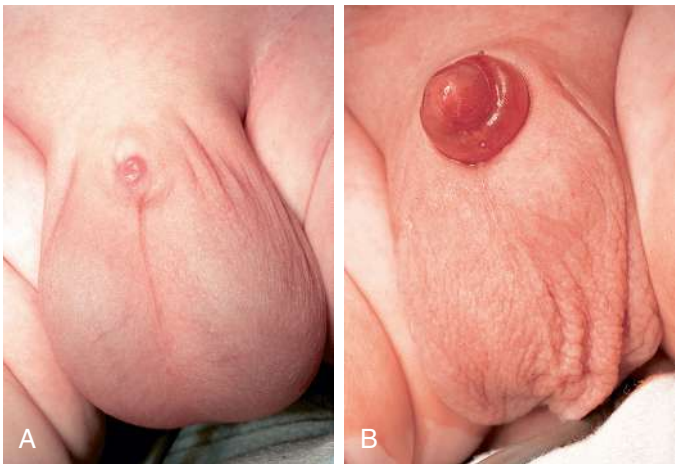

Fig. 581.8 A, Trapped (concealed) penis resulting from circumcision. B, Same patient after revision of circumcision. *(From Wein AJ, Kavoussi LR, Novick AC, et al., eds. Campbell-Walsh Urology, 9th ed. Philadelphia: WB Saunders; 2007: Fig. 126-2, p. 2340.)*



Fig. 581.9 Micropenis secondary to hypopituitarism in an 8-yr-old male. *(From Wein AJ, Kavoussi LR, Novick AC, et al., eds. Campbell-Walsh Urology, 9th ed. Philadelphia: WB Saunders; 2007: Fig. 126-5a, p. 2341.)*

syndrome. In some cases, there is growth hormone deficiency. Primary testicular failure can result from gonadal dysgenesis or rudimentary testes syndrome and also occurs in **Robinow syndrome** (characterized by hypoplastic genitals, shortening of the forearms, frontal bossing, hypertelorism, wide palpebral fissures, short broad nose, long philtrum, small chin, brachydactyly, and a normal karyotype).

A pediatric endocrinologist, geneticist, and pediatric urologist should examine all children with these syndromes, with participation by medical ethics. *Evaluation includes a karyotype, assessment of anterior pituitary function and testicular function, and MRI* to determine the anatomic integrity of the hypothalamus and the anterior pituitary gland as well as the midline structure of the brain. One of the difficult questions is whether androgen therapy is essential during childhood, because androgenic stimulation of penile growth in a prepubertal male can limit the growth potential of the penis in puberty. Studies of small groups of men with micropenis suggest that many, although not all, have satisfactory sexual function. Consequently, a decision for gender surgery in infancy is infrequently made.

PRIAPISM

Priapism is a persistent penile erection at least 4 hours in duration that continues beyond, or is unrelated to, sexual stimulation. Typically, only the corpora cavernosa is affected. There are three subtypes:

- Ischemic (venoocclusive, low-flow) priapism is characterized by little or no cavernous blood flow, and cavernous blood gases are hypoxic, hypercapnic, and acidotic. The corpora are rigid and tender to palpation. Immediate intervention is warranted.
- Nonischemic (arterial, high-flow) priapism is caused by unregulated cavernous arterial inflow. Typically, the penis is neither fully rigid nor painful. There is often a history of antecedent trauma resulting in a cavernous artery–corpora cavernosa fistula. Most cases resolve without intervention and expectant management is typical.
- Stuttering (intermittent) priapism is a recurrent form of ischemic priapism with painful erections with intervening periods of detumescence.

The most common cause of priapism in children is sickle cell disease, which is characterized by a predominance of sickle cell hemoglobin (see Chapter 511.1). As many as 29% of male patients with sickle cell disease develop priapism. The priapism is generally related to a low-flow state, secondary to sickling of red blood cells within the sinusoids of the corpora cavernosa during normal erection, resulting in venous stasis. This situation results in decreased local oxygen tension and pH, which potentiates further stasis and sickling. Priapism typically occurs during sleep, when mild hypoventilatory acidosis depresses oxygen tension and pH in the corpora. There is typically significant corporal engorgement with sparing of the glans penis. If the spongiosum is involved, voiding may be impaired. Evaluation may include a complete blood count. If the sickle cell status is unknown, hemoglobin electrophoresis should be performed. Corporal blood gas can help distinguish between a high-flow and low-flow state; ultrasound may also be used to differentiate these diagnoses. Other causes of low-flow priapism include sildenafil ingestion and leukemia.

In priapism secondary to sickle cell disease, medical therapy includes intravenous hydration, oxygen, alkalinization, and pain management with morphine. The American Urological Association guideline on priapism recommends concurrent intracavernous treatment beginning with corporal aspiration and irrigation with a sympathomimetic agent, such as phenylephrine. For patients with sickle cell disease, exchange transfusion may be considered but often takes several hours to arrange; therefore it is used when intracavernous treatment is not successful. If priapism has been present for >48 hours, ischemia and acidosis impair the intracavernous smooth muscle response to sympathomimetics. If irrigation and medical therapy are unsuccessful, a corporoglanular shunt should be considered. For stuttering priapism, administration of an oral α-adrenergic agent (pseudoephedrine) once or twice daily is first-line therapy. If this treatment is unsuccessful, an oral β-agonist (terbutaline) is recommended; a gonadotropin-releasing hormone analog plus flutamide is recommended as third-line therapy. Long-term follow-up of adults treated for sickle cell disease as children shows that satisfactory erectile function is inversely related to the patient's age at the onset of priapism and duration of priapism.

Nonischemic (high-flow) priapism most commonly follows perineal trauma, such as a straddle injury, that results in laceration of the cavernous artery. Typically, the aspirated blood is bright red, and the aspirate is similar to arterial blood. Color Doppler ultrasonography often demonstrates the fistula. The priapism spontaneously resolves in most cases. If it does not, angiographic embolization is indicated.

OTHER PENILE ANOMALIES

Aphallia (agenesis of the penis) affects approximately 1 in 10 million males. The karyotype is almost always 46, XY, and the usual appearance is that of a well-developed scrotum with descended testes and an absent penile shaft. Upper urinary tract abnormalities are common. In most cases, gender assignment surgery is recommended in the newborn period. **Diphallia** (duplication of the penis) ranges from a small accessory penis to complete duplication.

MEATAL STENOSIS

Meatal stenosis is a condition that almost always is acquired and occurs after neonatal circumcision. It most likely results from inflammation of

the denuded glans and is difficult to prevent. If the meatus is pinpoint, males void with a forceful, fine stream that goes a great distance. These males can experience dysuria, frequency, hematuria, or a combination of these conditions, typically around age 3-8 years. UTI is uncommon. Other males have dorsal deflection of the urinary stream. Although the meatus may be small, hydronephrosis or voiding difficulty is extremely rare unless there is associated balanitis xerotica obliterans (see Fig. 581.3; chronic dermatitis of unknown etiology, generally involving the glans and prepuce, occasionally extending into the urethra). Treatment is meatoplasty, in which the urethral meatus is opened surgically; this procedure can be performed either under anesthesia as an outpatient or in the office using local anesthesia (EMLA cream) with or without sedation. Routine cystoscopy is unnecessary.

OTHER MALE URETHRAL ANOMALIES

Parameatal urethral cyst manifests as an asymptomatic small cyst on one side of the urethral meatus. Treatment is excision under anesthesia. **Congenital urethral fistula** is a rare deformity in which a fistula is present from the penile urethra. It usually is an isolated abnormality. Treatment is fistula closure. **Megalourethra** is a large urethra that usually is associated with abnormal development of the corpus spongiosum. This condition is most commonly associated with prune-belly syndrome (see Chapter 577). **Urethral duplication** is a rare condition in which the two urethral channels lie in the same sagittal plane. There are many variations with complete and incomplete urethral duplication. These males often have a double stream. Most commonly, the dorsal urethra is small, and the ventral urethra is of normal caliber. Treatment involves excision of the small urethra. **Urethral hypoplasia** is a rare condition in which the entire male urethra is extremely small but patent. In some cases, a temporary cutaneous vesicostomy is necessary for satisfactory urinary drainage. Either gradual enlargement of the urethra or major urethroplasty is necessary. **Urethral atresia** refers to maldevelopment of the urethra and nearly always is fatal unless the urachus remains patent throughout gestation.

URETHRAL PROLAPSE (FEMALE)

Urethral prolapse occurs predominantly in females 1-9 years of age. The most common signs are bloody spotting on the underwear or diaper, although dysuria or perineal discomfort also can occur (Fig. 581.10). An inexperienced examiner can mistake the finding for sexual abuse. Initial therapy consists of application of estrogen cream 2-3 times daily for 3-4 weeks and sitz baths. Surgical repair is recommended for females that fail medical therapy and is curative. In some cases, this can be performed in the office under local anesthesia.



Fig. 581.10 Urethral prolapse in a 4-yr-old female who had bloody spotting on her underwear.



Fig. 581.11 Paraurethral cyst in a newborn female.



Fig. 581.12 Prolapsed ectopic ureterocele in a female infant. She had a nonfunctioning upper pole collecting system connected to the ureterocele.

OTHER FEMALE URETHRAL LESIONS

Paraurethral cyst results from retained secretions in the Skene glands secondary to ductal obstruction (Fig. 581.11). These lesions are present at birth, and most regress in size during the first 4-8 weeks, although occasionally incision and drainage is necessary. A **prolapsed ectopic ureterocele** appears as a cystic mass protruding from the urethra and is a presenting symptom in 10% of females with a ureterocele, which is a cystic swelling of the terminal ureter (Fig. 581.12). Ultrasonography should be performed to visualize the upper urinary tracts to confirm the diagnosis. Usually, either the ureterocele is incised or an upper urinary tract reconstructive procedure is necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 582

Disorders and Anomalies of the Scrotal Contents

Heather N. Di Carlo and Chad B. Crigger

UNDESCENDED TESTIS (CRYPTORCHIDISM)

The absence of a palpable testis in the scrotum indicates that the testis is undescended, absent, atrophic, or retractile.

Epidemiology

An undescended **(cryptorchid)** testis is the most common congenital genitourinary tract disorder in males. At birth, approximately 4.5% of males have an **undescended testis.** Because testicular descent occurs at 7-8 months of gestation, 30% of premature male infants have an undescended testis; the incidence is 3.4% at term. As many as 50% of congenital undescended testes descend spontaneously during the first 3 months of life, and by 6 months the incidence decreases to 1.5%. Spontaneous descent occurs secondary to a temporary testosterone surge (termed a *minipuberty*) during the first 2 months, which also results in significant penile growth. If the testis has not descended by 4 months, it will remain undescended. Cryptorchidism is bilateral in 10% of cases. There is some evidence that the incidence of cryptorchidism is increasing; this is attributed to increase in utero exposure to endocrine disrupting chemicals. Although cryptorchidism usually is considered to be congenital, some older males have a scrotal testis that "ascends" to a low inguinal position and therefore requires an orchiopexy. In addition, 1–2% of neonatal and young males undergoing hernia repair develop secondary cryptorchidism from scar tissue along the spermatic cord.

Pathogenesis

The process of testicular descent is regulated by an interaction among genetic, hormonal, and mechanical factors, including testosterone, dihydrotestosterone, müllerian-inhibiting factor, the gubernaculum, intraabdominal pressure, and the genitofemoral nerve (Table 582.1). The testis develops in the abdomen at 7-8 weeks of gestation. Insulin-like factor 3 controls the transabdominal phase. At 10-11 weeks, the Leydig cells produce testosterone, which stimulates differentiation of the Wolffian (mesonephric) duct into the epididymis, vas deferens, seminal vesicle, and ejaculatory duct. At 32-36 weeks, the testis, which is anchored at the internal inguinal ring by the gubernaculum, begins its process of descent and is controlled in part by a calcium gene-related peptide produced by the genitofemoral nerve. The gubernaculum descends the inguinal canal and guides the testis into the scrotum. Following testicular descent, the patent processus vaginalis (hernia sac) normally closes.

Clinical Manifestations

Undescended testes are classified as **abdominal** (which are nonpalpable), **peeping** (abdominal but can be pushed into the upper part of the inguinal canal), **inguinal, gliding** (can be pushed into the scrotum but retracts immediately to the pubic tubercle), and **ectopic** (superficial inguinal pouch or, rarely, perineal). Most undescended testes are palpable just distal to the inguinal canal over the pubic tubercle.

A **disorder of sex development** should be suspected in a newborn phenotypic male with bilateral nonpalpable testes, as the child could be a virilized female with congenital adrenal hyperplasia (see Chapter 616). *In a male with midpenile or proximal hypospadias and a palpable undescended testis, the risk of a disorder of sexual development is 15%; the risk is 50% if the testis is nonpalpable.*

The potential **consequences of cryptorchidism** include poor testicular growth, infertility, testicular malignancy, associated hernia, torsion of the cryptorchid testis, and the possible psychologic effects of an empty scrotum.

The undescended testis is normal at birth histologically with a plethora of germ cells, but pathologic changes occur by 6-12 months of age. Delayed germ cell maturation, germ cell depletion, hyalinization of the seminiferous tubules, and reduced Leydig cell number are typical; these changes are progressive over time if the testis remains undescended. At puberty, an undescended testis has no viable sperm components. Although less severe, changes may occur in the contralateral descended testis after 4-7 years. After treatment for a unilateral undescended testis, 85% of patients are fertile, which is slightly less than the 90% rate of fertility in an unaffected population of adult males. In contrast, following bilateral orchiopexy, only 50–65% of patients are fertile.

The risk of a **germ cell malignancy** (see Chapter 552) developing in an undescended testis is four times higher than in the general population and is approximately 1 in 80 with a unilateral undescended testis and 1 in 40-50 for bilateral undescended testes. Testicular tumors are less common if orchiopexy is performed before 10 years of age, but they still occur, and adolescents should be instructed in testicular self-examination. The peak age for developing a malignant testis tumor is 15-45 years of age. The most common tumor developing in an undescended testis in an adolescent or adult is a **seminoma** (65%); after orchiopexy, nonseminomatous tumors represent 65% of testis tumors. Orchiopexy seems to reduce the risk of testicular cancer; it is uncommon for testis tumors to occur if the orchiopexy was performed before the age of 2 years. The contralateral scrotal testis may also be at a slightly increased risk for malignancy.

An indirect inguinal hernia usually accompanies a congenital undescended testis but rarely is symptomatic. Torsion and infarction of the cryptorchid testis also are uncommon but can occur because of excessive mobility of undescended testes. Consequently, inguinal pain and/or swelling in a male with an undescended testis should raise the suspicion of an inguinal hernia or torsion of the undescended testis.

An *acquired* or **ascending undescended testis** occurs when a male has a descended testis at birth, but during childhood, usually between ages 4-10 years, the testis does not remain in the scrotum. Such males often have a history of a retractile testis. With testicular ascent on physical examination, the testis can often be manipulated into the upper scrotum, but there is obvious tension on the spermatic cord. This condition is speculated to result from incomplete involution of the processus vaginalis, restricting spermatic cord growth and resulting in the testis gradually moving out of its scrotal position during a male's somatic growth.

On physical examination of the scrotum, the child should be encouraged to relax. Careful consideration of a hypoplastic ipsilateral scrotum may clue the examiner in to a diagnosis of an undescended testicle. The examiner should examine the patient's scrotum and inguinal canal using their dominant hand. The nondominant hand is positioned over the pubic tubercle and is pushed inferiorly toward the scrotum. The examiner's dominant hand is used to try to palpate the testis. If the testis is nonpalpable, the *soap test* often is useful; soap is applied to the inguinal canal and the examiner's hand, significantly reducing friction and facilitating identification of an inguinal testis. In addition, pulling on the scrotum can pull a high inguinal testis into a palpable position. One soft sign that a testis is absent is contralateral testicular hypertrophy, but this finding is not 100% diagnostic.

Retractile testes may be misdiagnosed as undescended testes. Males older than 1 year of age often have a brisk cremasteric reflex, and if the child is anxious or ticklish during scrotal examination, the testis may be difficult to manipulate into the scrotum. Males should be examined with their legs in a relaxed frog-leg position, and if the testis can be manipulated into the scrotum comfortably, it is probably retractile. It should be monitored every 6-12 months with follow-up physical examinations, because it can become an acquired undescended testis. Overall, as many as one third of males with a retractile testis develop an acquired undescended testis requiring orchiopexy, and males younger than 7 years of age at diagnosis of a retractile testis are at greatest risk. Although definitive data are not available, it is generally thought that males with a retractile testis are not at increased risk for infertility or malignancy.

Approximately 10% of undescended testes are **nonpalpable testes.** Of these, 50% are viable testes in the abdomen or high in the inguinal canal, and 50% are atrophic or absent, almost always in the scrotum,

Table 582.1 Conditions Associated with Cryptorchidism

DISEASES OR SYNDROMES ASSOCIATED WITH DECREASED ANDROGEN LEVELS
Disorders of Sex Development (DSD)
Sex chromosome DSD 47,XXY (Klinefelter syndrome and variants) 45,X/46,XY (mixed gonadal dysgenesis) 46,XX/46,XY (chimerism)
46,XY DSD
Disorders of testicular development Complete or partial gonadal dysgenesis Variations in *ARX, ATRX, CBX2, DAX1 (NROB1), DHH, DHX37, DMRT1, EMX2, ESR2, FGFR2, GATA4, HHAT, MAP3K1, NR5A1, SF1, SOX9, SRY, TSPYL1, WNT4, WT1*(WAGR syndrome, Denys-Drash syndrome, Frasier syndrome), *ZFPM2*, and *ZNRF3* genes
Disorders in androgen synthesis or action Androgen biosynthetic defect • Abnormal LH (*LHB*) • Steroidogenic acute regulatory protein (StAR deficiency) (*STAR*) • 7-Dehydro-cholesterol desmolase deficiency (Smith-Lemli-Opitz syndrome) • Cholesterol desmolase deficiency (*CYP11A1*) • 3β -hydroxysteroid dehydrogenase type 2 deficiency (*HSD3B2*) • 17,20-lyase deficiency or combined 17 hydroxylase/17,20-lyase deficiency (*CYP17A1*) • P450-oxidoreductase deficiency (*POR*) • 17β -Hydroxysteroid-dehydrogenase type 3 (*HSD17B3*) • 5-α reductase type 2 enzyme deficiency (*SRD5A2*) • Cytochrome b5 deficiency (*CYB5A*) • Backdoor steroidogenetic enzyme deficiency (*AKR1C2, AKR1C4*) Defect in androgen action • Partial androgen insensitivity (*AR*) • Infantile onset X-linked spinal muscular atrophy LH receptor defects • Inactivating mutation of LH receptor gene (*LHCGR*) (Leydig cell hypoplasia, aplasia)
46,XX DSD Ovotesticular DSD Testicular DSD (e.g. *SRY*+, dup *SOX9*, *RSP01*) 46,XX male
Congenital Hypogonadotropic Hypogonadism in 46,XY
Isolated hypogonadotropic hypogonadism with anosmia (Kallmann syndrome) *KAL1, FGFR1/FGF8, PROK2/PROKR2, KAL1, NELF, HS6ST1, WDR11*, and *SEMA3A* gene variants *CHD7* gene variant (CHARGE syndrome)
Normosmic isolated hypogonadotropic hypogonadism Variants in *KISS1, GPR54, LEP, LEPR, TAC3/TACR3*, and *GNRH1/GNRHR* genes (also reported variants in *FGFR1/FGF8, PROKR2, CHD7*, and *WDR11* genes)
Multiple pituitary hormone deficiencies Variants in *PROP1* genes, *HESX1* gene (septo-optic dysplasia)
Congenital Hypergonadotropic Hypogonadism
Down syndrome Noonan syndrome
Syndromes Associated with Both Primary and Secondary Hypogonadism
Prader-Willi syndrome Bardet-Biedl syndrome
CONDITIONS ASSOCIATED WITH DECREASED INSL3 OR AMH LEVELS OR ACTIONS
INSL3 or *RXFP2* variants Persistent Müllerian duct syndrome: AMH and AMH receptor (*AMH, AMHR2*)
OTHER CONDITIONS RELATED WITH CRYPTORCHIDISM
Multiple syndromes not specifically involving pituitary-gonadal development or function

AMH, anti-Müllerian hormone; CHARGE, coloboma, heart defects, atresia choanal, growth restriction, genital abnormalities, ear abnormalities; INSL3, insulin like peptide 3;.LH, luteinizing hormone.

Modified from Rodprasert W, Virtanen HE, Mäkekä JA, Toppari J: Hypogonadism and cryptorchidism. *Front Endocrinol (Lausanne)*. 2020;10:906.

secondary to spermatic cord torsion in utero **(vanishing testis).** If the nonpalpable testis is abdominal, it will not descend after 3 months of age. *Although sonography often is performed to try to identify whether the testis is present, it rarely changes clinical management, because the abdominal testis and atrophic testis are not identified on sonography.* Inguinal/scrotal sonography might be beneficial in obese males with a nonpalpable testis; in this clinical setting, the undescended testis often is nonpalpable, and an inguinal/scrotal sonogram can be beneficial in surgical planning. Computed tomographic imaging is relatively accurate in demonstrating the presence of the testis, but the radiation exposure is significant. MRI is even more accurate, but the disadvantage is that general anesthesia or sedation is necessary in most young children.

None of these imaging studies are 100% accurate and in general do not add significantly to clinical decision-making by the pediatric urologist or pediatric surgeon. Consequently, routine use of imaging is discouraged. A diagnostic approach is noted in Figure 582.1.

Treatment

The congenital undescended testis that does not descend by 6 months (corrected for gestational age) should be treated surgically within the next 12 months. Most testes can be brought down to the scrotum with an orchiopexy, which involves an inguinal incision, mobilization of the testis and spermatic cord, and correction of an indirect inguinal hernia. The procedure is typically performed on an outpatient basis and has a success rate of 98%. In some males with a testis that is close to the scrotum, a prescrotal orchiopexy can be performed. In this procedure, the entire operation is performed through a high scrotal incision. Often the associated inguinal hernia also can be corrected through this incision. Advantages of this approach over the inguinal approach include shorter operative time and less postoperative discomfort.

In males with a nonpalpable testis, an exam under anesthesia should be done to reassess for palpability; if testes are still nonpalpable, diagnostic laparoscopy is performed in most centers. This procedure allows safe and rapid assessment of whether the testis is intraabdominal. In most cases, orchiopexy of the intraabdominal testis located adjacent to the internal inguinal ring is successful, but orchiectomy should be considered in more difficult cases or when the testis appears to be atrophic. A two-stage orchiopexy sometimes is needed in males with a high abdominal testis. Males with abdominal testes are managed with laparoscopic techniques at many institutions. Testicular prostheses are available for older children and adolescents when the absence of the gonad in the scrotum might have an undesirable psychologic effect. The FDA has approved a saline testicular implant. Solid silicone "carving block" implants also are used (Fig. 582.2). Placement of testicular prostheses early in childhood is recommended for males with anorchia (absence of both testes).

The American Urological Association guidelines for the evaluation and treatment of males with an undescended testis are summarized in Table 582.2.

SCROTAL SWELLING

Scrotal swelling may be acute or chronic and painful or painless (Table 582.3). Abrupt onset of painful scrotal swelling necessitates prompt evaluation because some conditions, such as testicular torsion and incarcerated inguinal hernia, require emergency surgical management. Tables 582.4 and 582.5 show the differential diagnosis.

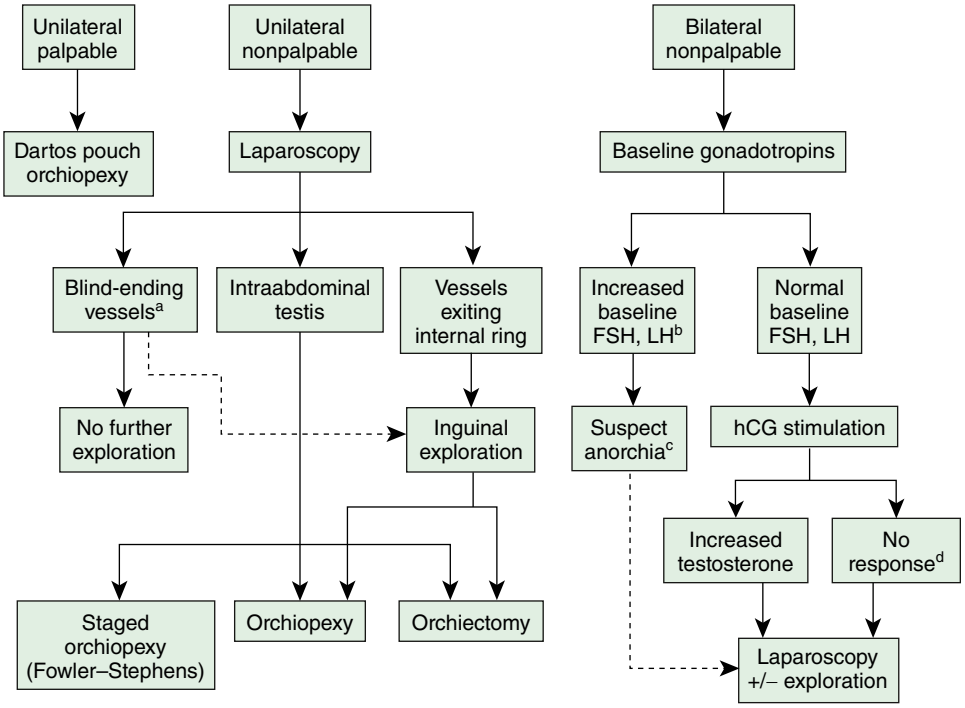

Fig. 582.1 Management algorithm for undescended testis. [a]If blind-ending vas deferens vessels are unequivocally identified, then there is no need for further exploration. [b]Baseline FSH and LH levels are elevated if values are 3 SD above the mean. *c*, Increased suspicion of anorchia with elevated baseline FSH and LH levels; however, exploration is still warranted. *d*, Testicular remnant tissue may be present despite a negative hCG stimulation test; therefore exploration for testicular remnant tissue should still be performed. *(From Bowlin PR, Lorenzo AJ. Undescended testes and testicular tumors. In: Holcomb III GW, Murphy JP, St. Peter SD, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020: Fig. 51-2, p. 808.)*

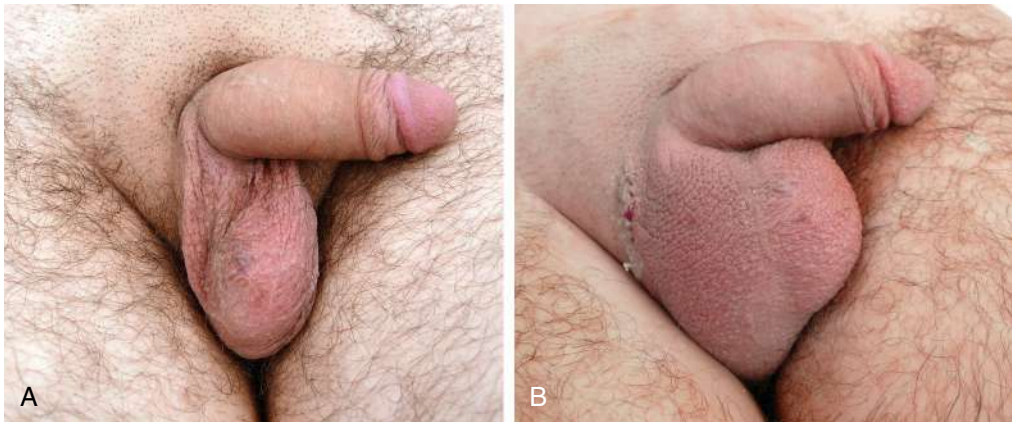

Fig. 582.2 A, Adolescent with solitary left testis. B, Appearance following implantation of right testicular prosthesis.

Table 582.2 American Urological Association Guidelines for Evaluation and Treatment of Males with an Undescended Testis

DIAGNOSIS

- Providers should obtain gestational history at initial evaluation of males with suspected cryptorchidism. *(Standard)*
- Primary care providers should palpate testes for quality and position at each recommended well-child visit. *(Standard)*
- Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by 6 months (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. *(Standard)*
- Providers should refer males with the possibility of newly diagnosed (acquired) cryptorchidism after 6 months (corrected for gestational age) to an appropriate surgical specialist. *(Standard)*
- Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). *(Standard)*
- Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of males with cryptorchidism before referral because these studies rarely assist in decision making. *(Standard)*
- Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. *(Recommendation)*
- In males with bilateral, nonpalpable testes who do not have congenital adrenal hyperplasia (CAH), providers should measure Mullerian Inhibiting Substance (MIS or Anti-Mullerian Hormone [AMH] level), and consider additional hormone testing, to evaluate for anorchia. *(Option)*
- In males with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. *(Standard)*

TREATMENT

- Providers should not use hormonal therapy to induce testicular descent because evidence shows low response rates and lack of evidence for long-term efficacy. *(Standard)*
- In the absence of spontaneous testicular descent by 6 months (corrected for gestational age), specialists should perform surgery within the next year. *(Standard)*
- In prepubertal males with palpable, cryptorchid testes, surgical specialists should perform scrotal or inguinal orchidopexy. *(Standard)*
- In prepubertal males with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. *(Standard)*
- At the time of exploration for a nonpalpable testis in boys, surgical specialists should identify the status of the testicular vessels to help determine the next course of action. *(Clinical Principle)*
- In males with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a male has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. *(Clinical Principle)*
- Providers should counsel males with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. *(Clinical Principle)*

Adapted from Kolon TF, Herndon CDA, Baker LA, et al. Evaluation and treatment of cryptorchidism (2018): AUA Guideline. https://www.auanet.org/guidelines-and-quality/guidelines/cryptorchidism-guideline

Clinical Manifestations

A detailed history is helpful in determining the cause of the swelling and includes the rapidity of onset of pain. With testicular torsion, the pain often is sudden in onset and may be associated with exercise or minor genital trauma, duration of pain, and radiation of pain. Inguinal discomfort is common with testicular torsion, inguinal hernia, or epididymitis, and associated flank pain can occur with passage of a ureteral calculus; previous episodes of similar pain, which are common in males with intermittent testicular torsion or inguinal hernia; nausea and vomiting, which

Table 582.3 Differential Diagnosis of Pediatric Adolescent Acute Scrotal Pain

- Appendage torsion
  - Appendix testis
  - Other appendage (epididymis, paradidymis, vas aberrans)
- Spermatic cord torsion
  - Intravaginal, acute or intermittent
  - Extravaginal
- Epididymitis
  - Infectious
    - Urinary tract infection
    - Sexually transmitted infection
    - Viral including COVID-19
  - Sterile or traumatic
- Scrotal edema or erythema
  - Diaper dermatitis, insect bite, or other skin lesions
  - Idiopathic scrotal edema
  - IgA vasculitis (Henoch-Schönlein purpura)
- Orchitis
  - Associated with epididymitis with or without abscess
  - Vasculitis (e.g., IgA vasculitis)
  - Viral illness (mumps, COVID-19)
- Trauma
  - Hematocele or scrotal contusion or testis rupture
- Hernia or hydrocele
  - Inguinal hernia with or without incarceration
  - Communicating hydrocele
  - Encysted hydrocele with or without torsion
  - Associated with acute abdominal pathology (e.g., appendicitis, peritonitis)
- Varicocele
- Intrascrotal mass
  - Cystic dysplasia or tumor of testis
  - Epididymal cyst, spermatocele or tumor
  - Other paratesticular tumors
- Musculoskeletal pain from inguinal tendinitis or muscle strain
- Ilioinguinal neuropathy
- Genitofemoral nerve entrapment
- Referred pain (e.g., ureteral calculus or anomaly)

Modified from Palmer LS, Palmer JS. Management of abnormalities of the external genitalia in boys. In: Partin AW, Dmochowski RR, Kavoussi LR, Peters CW, eds. *Campbell-Walsh Urology,* 12th ed. Philadelphia: Elsevier; 2021: Box 44-2.

Table 582.4 Differential Diagnosis of Scrotal Masses in Male Children and Adolescents

PAINFUL	PAINLESS
Testicular torsion	Hydrocele
Torsion of appendix testis	Inguinal hernia*
Epididymitis	Varicocele*
Trauma: ruptured testis, hematocele	Spermatocele*
	Testicular tumor*
Inguinal hernia (incarcerated)	IgA vasculitis*
Mumps orchitis	Idiopathic scrotal edema
Testicular vasculitis	

*May be associated with discomfort.

Table 582.5 Differential Diagnosis of Scrotal Swelling in Newborn Males

- Hydrocele
- Inguinal hernia (reducible)
- Inguinal hernia (incarcerated)*
- Testicular torsion*
- Scrotal hematoma
- Testicular tumor
- Meconium peritonitis
- Epididymitis*

*May be associated with discomfort.

are associated with testicular torsion and inguinal hernia; and irritative urinary symptoms, such as dysuria, urgency, and frequency, which indicate a urinary tract infection that can cause epididymitis. Some males report a recent history of scrotal trauma. There are multiple reports of familial testicular torsion related to inheritance of bell clapper deformity (discussed later). Males with lower urinary tract pathology such as urethral stricture or neuropathic bladder may be prone to epididymitis.

Physical examination may be difficult in males with a painful scrotum. Some have advocated performing a spermatic cord block or administering intravenous analgesia to facilitate the examination, but such measures are often unnecessary. Scrotal wall erythema is common in testicular torsion, epididymitis, torsion of the appendix testis, and an incarcerated hernia. In males with a normal cremasteric reflex, testicular torsion is unlikely. Absence of a cremasteric reflex is nondiagnostic.

Laboratory Findings and Diagnosis

Pertinent laboratory studies include urinalysis and culture. A positive urinalysis suggests bacterial epididymitis (uncommon before adolescence). Serum studies are not helpful in establishing a diagnosis unless a testicular malignancy is suspected. After initial evaluation in males with testicular pain, color Doppler ultrasonography often is helpful in establishing the diagnosis because it assesses whether testicular blood flow is normal, reduced, or increased (Fig. 582.3). If a hydrocele is present and the testis is nonpalpable, or if an abnormality of the testis is found, sonography also is indicated. *Imaging studies are not 100% accurate; they should not be used to decide whether a male with testicular pain should be referred for urologic evaluation.* As such, torsion is a clinical diagnosis.

Color Doppler ultrasonography allows assessment of testicular blood flow and testicular morphologic features. Accuracy is >95% if the ultrasonographer is experienced and the patient is older than 2 years of age. The "whirlpool" sign is pathognomonic. A false-negative study (demonstrates normal testicular blood flow) can occur in a male with testicular torsion if the degree of torsion is <360 degrees and the duration of torsion is short, because there may be continued testicular perfusion. In males <1 year of age, including neonates, blood flow may be difficult to demonstrate in 15% of normal testes.

TESTICULAR (SPERMATIC CORD) TORSION

Etiology

Testicular torsion requires prompt diagnosis and treatment to salvage the testis. Torsion is the most common cause of severe testicular pain in males 12 years of age and older and is uncommon before age 10. It is caused by inadequate fixation of the testis within the scrotum, resulting from a redundant tunica vaginalis and abnormal gubernacular attachment, allowing excessive mobility of the testis. The abnormal attachment is termed a **bell clapper deformity** and may be bilateral. Following spermatic cord torsion, venous congestion occurs, and subsequently arterial flow is interrupted. The likelihood of testis survival depends on the duration and severity of torsion. After 6 hours of absent blood flow to the testis, irreversible loss of spermatogenesis can occur. Torsion is familial in 10% of males.

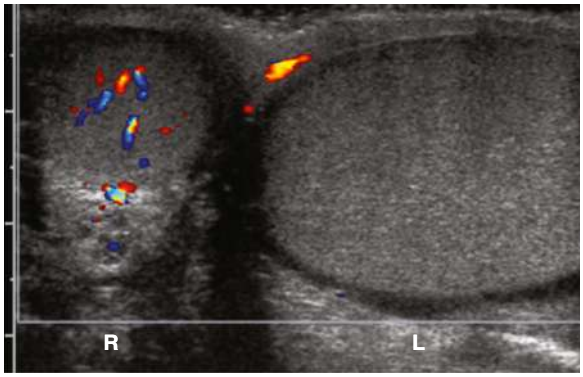

Fig. 582.3 Testicular torsion and axis change. A color Doppler ultrasound in the transverse plane shows color flow in the right testicle. The right testicle is oval to circular because it has been evaluated in the transverse plane. The left testicle is elongated as if it is in the longitudinal plane, indicating an abnormal lie within the scrotum worrisome for torsion. Lack of color Doppler flow in the left testicle confirms left testicular torsion. *(From Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 125-13, p. 1195.)*

Diagnosis

Testicular torsion produces acute pain and swelling of the scrotum. On examination, the scrotum is swollen, and the testis is exquisitely tender and often difficult to examine. The cremasteric reflex is nearly always absent, though this may be absent at baseline in a proportion of males. The position (lie) of the testis is abnormal, and the testis is often located high in the scrotum. In addition, nausea and vomiting often occur. The condition can be differentiated from an incarcerated hernia because swelling in the inguinal area typically is absent with torsion. The Testicular Workup for Ischemia and Suspected Torsion (TWIST) score is a clinical tool that can be used determine the likelihood of testicular torsion. The score consists of testicular swelling (2 points), hard testis (2 points), high-riding testis (1 point), absent cremasteric reflex (1 point), and nausea/vomiting (1 point). Patients can then be stratified into low (0 points), intermediate (1-5), and high risk (6-7), which aids in determining further imaging and/or surgical consultation.

For patients who are high risk or meet the clinical diagnosis of testicular torsion, prompt surgical consultation should be obtained. If the pain duration is <4-6 hours, manual detorsion may be attempted. In 65% of cases the torsed testis rotates inward, so detorsion should be attempted in the opposite direction (e.g., the left testis is rotated clockwise). Successful manual detorsion results in dramatic pain relief. In the emergency department, patients with an intermediate risk TWIST score should undergo immediate scrotal ultrasound. In some centers, this is performed as a point of care procedure by the emergency department staff.

Some adolescents experience **intermittent testicular torsion**. These males report episodes of severe unilateral testicular pain that resolves spontaneously after 30-60 minutes. Treatment is elective bilateral scrotal orchiopexy. Close follow-up and clear return instructions are requisite in such cases until elective orchiopexy is performed.

Treatment

Treatment is prompt surgical exploration and detorsion. If the testis is explored within 6 hours of torsion, up to 90% will survive. Testicular salvage decreases rapidly with a delay of more than 6 hours. If the degree of torsion is 360 degrees or less, the testis might have sufficient arterial flow to allow the gonad to survive, even after 24-48 hours. Following detorsion, the testis is fixed in the scrotum with nonabsorbable sutures, termed **scrotal orchiopexy,** to prevent torsion in the future. The contralateral testis also should be fixed in the scrotum because the predisposing anatomic condition (bell clapper deformity) often is bilateral. If the testis appears nonviable, orchiectomy is performed (Fig. 582.4A). The detorsed testis may undergo compartment syndrome,



Fig. 582.4 A, Left testicular torsion in adolescent with acute scrotum; the testis is necrotic. B, "Late-phase torsion" in an adolescent with severe testicular pain 1 month prior. Note absence of inflammation and high position of testis in scrotum.

and following detorsion, despite blood flow to the testis, high intratesticular pressure may cause ischemia and necrosis. This condition has been treated intraoperatively by incising the tunica vaginalis (similar to a blunt testicular rupture) and placing a tunica vaginalis flap over the exposed tunica. Some adolescents do not undergo prompt evaluation and treatment and present with *late phase testicular torsion,* in which there is delayed diagnosis of torsion. Often the testis is high in the scrotum and nontender (see Fig. 582.4B). While males with torsion of longer duration prior to treatment may exhibit reduced spermatogenesis, current evidence shows pregnancy rates of couples in which the male has a history of acute testicular torsion to be similar to the general population.

Spermatic cord torsion can also occur in the fetus or neonate. This condition results from incomplete attachment of the tunica vaginalis to the scrotal wall and is "extravaginal." When torsion occurs just before delivery, the baby usually is born with a large, firm, nontender testis. Usually the ipsilateral hemiscrotum is ecchymotic (Fig. 582.5). In these cases, the testis rarely is viable because torsion was a remote event. However, the contralateral testis is at increased risk for torsion until 1-2 months beyond term. The pediatric urology community is divided regarding whether immediate exploration is necessary in a male newborn who has suspected testicular torsion at birth, but if observation is recommended, the family needs to be counseled regarding the risk of contralateral spermatic cord torsion. If the initial exam is normal and the newborn subsequently develops scrotal swelling and erythema, and imaging is consistent with spermatic cord torsion, emergency scrotal exploration is indicated.

TORSION OF THE APPENDIX TESTIS/EPIDIDYMIS

Torsion of the appendix testis is the most common cause of testicular pain in males age 4-10 years but is uncommon in adolescents. The appendix testis is a stalklike structure that is a vestigial embryonic remnant of the müllerian (paramesonephric) ductal system that is attached to the upper pole of the testis. When it undergoes torsion, progressive inflammation and swelling of the testis and epididymis occurs, resulting in testicular pain and scrotal erythema. The onset of pain is typically gradual. Palpation of the testis usually reveals a 3-5 mm tender indurated mass on the upper pole (Fig. 582.6A). In some cases, the appendage that has undergone torsion may be visible through the scrotal skin, termed the **"blue dot"** sign. In some males, distinguishing torsion of the appendix from testicular torsion is difficult. In such cases, color Doppler ultrasonography is useful because testicular blood flow is normal and shows hyperemia to the upper pole of the testis. In such cases, the radiologist often recognizes epididymal enlargement and makes the diagnosis of epididymitis, reflecting the inflammatory reaction (see Fig. 582.6B).

The natural history of torsion of the appendix testis is for the inflammation to resolve in 3-10 days. Nonoperative treatment is recommended, including bed rest for 24 hours and analgesia with nonsteroidal antiinflammatory medication for several days. If the diagnosis is uncertain, scrotal exploration is recommended.



Fig. 582.5 A and B, Right testicular torsion in a newborn. The right hemiscrotum is darker, and the testis was indurated and enlarged.

EPIDIDYMITIS

Acute bacterial inflammation of the epididymis is an ascending retrograde infection from the urethra, through the vas deferens into the epididymis. This condition causes acute scrotal pain, erythema, and swelling. It is rare before puberty and should raise the question of a congenital abnormality of the Wolffian duct, such as an ectopic ureter entering the vas. In younger males, the responsible organism is often *Escherichia coli* (see Chapter 246). After puberty, bacterial epididymitis becomes progressively more common and can cause acute painful scrotal swelling in young sexually active males. Urinalysis usually reveals pyuria. Epididymitis can be bacterial (usually gonococcus or *Chlamydia*; see Chapters 238 and 272) or viral (mumps, enterovirus, or adenovirus; see Chapters 295, 297, and 309), but often the organism remains undetermined. Familial Mediterranean fever is another cause. Treatment consists of bed rest and antibiotics as indicated. Differentiation from torsion is straightforward with scrotal ultrasonography.

IgA vasculitis, previously known as Henoch-Schönlein purpura, (see Chapter 210.1) is a systemic vasculitis that involves multiple organ systems and that can involve the kidney and spermatic cord. When the spermatic cord is involved, typically there is bilateral painful scrotal swelling with purpuric lesions involving the scrotum. Scrotal sonography should show normal testicular blood flow. Treatment is directed toward systemic treatment of the IgA vasculitis. Isolated testicular vasculitis is less common in IgA vasculitis and, in such cases, polyarteritis nodosa should be suspected.

VARICOCELE

A **varicocele** is a congenital condition in which there is abnormal dilation of the pampiniform plexus in the scrotum, often described as a "bag of worms" (Fig. 582.7). Dilation of the pampiniform venous plexus results from valvular incompetence of the internal spermatic vein. Approximately 15% of adult males have a varicocele; of these, approximately 10–15% are subfertile. Varicocele is the most common (and virtually the only) surgically correctable cause of infertility in males. A varicocele is found in 10–15% of adolescent males, but it rarely is diagnosed in males younger than 10 years old, because the varicocele becomes distended only after the increased blood flow associated with

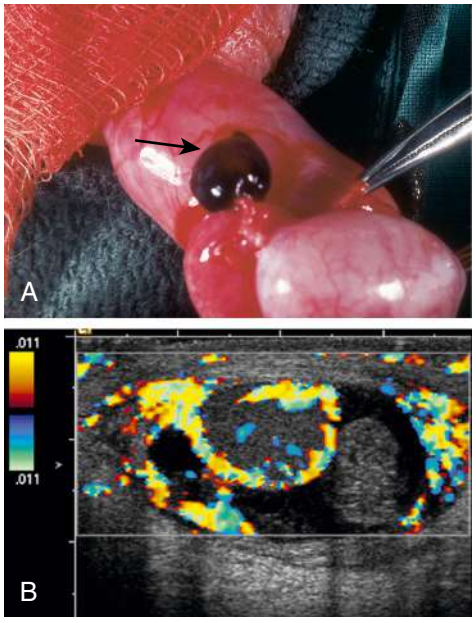

Fig. 582.6 A, Torsion of the appendix testis; the appendix testis is necrotic *(arrow)*. B, Color Doppler scrotal sonogram showing hyperemia to the testis and absent flow to the appendix testis *(right side)*. Symptoms resolved with medical therapy.

puberty occurs. Varicoceles occur predominantly on the left side, are bilateral in 2% of cases, and rarely involve the right side only. A varicocele in a male younger than 10 years or on the right side might indicate an abdominal or retroperitoneal mass; an abdominal ultrasound or CT scan should be performed in such cases.

A varicocele typically is a painless paratesticular mass. Occasionally patients describe a dull ache in the affected testis. Usually the varicocele is not apparent when the patient is supine because it is decompressed; in contrast, the varicocele becomes prominent when the patient is standing and enlarges with a Valsalva maneuver. Many pediatricians do not routinely screen adolescents for a varicocele. Varicoceles typically are graded from 1-3 with the male standing: **grade 1** is palpable only with Valsalva (clinically insignificant); **grade 2** is palpable without Valsalva but is not visible on inspection; and **grade 3** is visible with inspection. Males with a grade 3 varicocele are at greatest risk for testicular growth arrest, particularly if the varicocele is larger than the testis. Testicular size should be documented with calipers, an orchidometer, or scrotal sonography, because if the affected left testis is significantly smaller than the right testis, spermatogenesis probably has been adversely affected. A **semen analysis** should be considered in sexually mature adolescents who are Tanner stage V.

The goal of varicocelectomy is to maximize future fertility. Surgical treatment of varicoceles is indicated in males with a significant disparity in testicular size, with pain in the affected testis, if the contralateral testis is diseased or absent, or with oligospermia on semen analysis. Following treatment, typically the involved testis enlarges and catches up with the normal testis over the following 1-2 years. Varicocelectomy should also be considered in males with a large grade 3 varicocele, even if there is no disparity in testicular size. Surgical repair is accomplished with a variety of techniques by ligation of the veins of the pampiniform plexus laparoscopically or through an inguinal or subinguinal incision (with or without an operating microscope) or by ligating the internal spermatic vein in the retroperitoneum. The operation is performed on an ambulatory basis.

SPERMATOCELE

A **spermatocele** is a cystic lesion that contains sperm and is attached to the upper pole of the sexually mature testis. Spermatoceles usually are painless and are incidental findings on physical examination. Enlargement of the spermatocele or significant pain is an indication for removal.



Fig. 582.7 Left varicocele in an adolescent male.

HYDROCELE

Etiology

A hydrocele is an accumulation of fluid in the tunica vaginalis (Fig. 582.8). Between 1% and 2% of neonates have a hydrocele. In most cases, the hydrocele is noncommunicating (the processus vaginalis was obliterated during development). In such cases, the hydrocele fluid disappears by 1 year of age. If there is a persistently patent processus vaginalis, the hydrocele persists. It is typically small in the morning and may become larger during the day due to upright positioning. A rare variant of a hydrocele is the **abdominoscrotal hydrocele,** in which there is a large, tense hydrocele that extends into the lower abdominal cavity. In some older males, a noncommunicating hydrocele can result from an inflammatory condition within the scrotum, such as testicular torsion, torsion of the appendix testis, epididymitis, or testicular tumor. The long-term risk of a communicating hydrocele is the development of an inguinal hernia. Some older males and adolescents also develop a hydrocele. In some cases, hydroceles develop acutely after an episode of scrotal trauma or epididymoorchitis, whereas others develop more insidiously.

Diagnosis

On examination, hydroceles are smooth and nontender. Transillumination of the scrotum confirms the fluid-filled nature of the mass. It is important to palpate the testis, because some young males develop a hydrocele in association with a testis tumor. If the testis is nonpalpable, a scrotal ultrasound should be performed to confirm that the testis is present and normal. If compression of the fluid-filled mass completely reduces the hydrocele, an inguinal hernia/hydrocele is the likely diagnosis.

Treatment

Most congenital hydroceles resolve by 12 months of age following reabsorption of the hydrocele fluid. If the hydrocele is large and tense, however, early surgical correction should be considered, because it is difficult to verify that the child does not have a hernia, and large hydroceles rarely disappear spontaneously. Hydroceles persisting beyond 12-18 months often are communicating and should be repaired. Surgical correction is similar to a herniorrhaphy (see Chapter 394). Through an inguinal incision, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed. If an older male has a large hydrocele, often diagnostic laparoscopy can be performed to determine whether there is a patent processus vaginalis, and if the internal ring is closed, then the hydrocele may be corrected with a scrotal incision.



Fig. 582.8 Newborn with large right hydrocele.

INGUINAL HERNIA

Inguinal hernia is discussed in Chapter 394.

TESTICULAR MICROLITHIASIS

Approximately 2–3% of pediatric scrotal ultrasound examinations demonstrate calcific depositions in the testis, termed testicular microlithiasis. Typically, it is found in males undergoing an examination for testicular pain, varicocele, or scrotal swelling. In adults, it is a common finding in males with infertility and with a germ cell tumor of the testis. In pediatric patients with microlithiasis, there are no guidelines for monitoring, but the condition should be monitored for changes in testicular size or induration, with follow-up ultrasound studies as indicated.

TESTICULAR TUMOR

Testicular and paratesticular tumors can occur at any age, even in the newborn. Approximately 35% of prepubertal testis tumors are malignant; most commonly they are yolk sac tumors, although rhabdomyosarcoma and leukemia also can occur in this age group. In adolescents, 98% of painless solid testicular masses are malignant (see Chapter 552). Most manifest as a painless, hard testicular mass that does not transilluminate. Scrotal ultrasonography should be performed to confirm the finding of a testicular mass, and it can help to delineate the type of testis tumor. Serum tumor markers, including *α-fetoprotein* and *β-human chorionic gonadotropin,* should be drawn. Definitive therapy includes surgical exploration through an inguinal incision. In most cases, a radical orchiectomy, consisting of removal of the entire testis and spermatic cord, is performed. In a prepubertal male, if the ultrasonographic study or surgical exploration suggests that the tumor is localized and benign, such as a teratoma or an epidermoid cyst, testis-sparing surgery with removal only of the mass may be appropriate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 583

Trauma to the Genitourinary Tract

Heather N. Di Carlo and Chad B. Crigger

Most injuries to the genitourinary tract in children result from blunt trauma during falls, athletic activities, or motor vehicle crashes (see Chapter 80). *Children are at greater risk of blunt renal injury than adults, because they have less body fat and because the kidneys are not located directly behind the ribs.* Children with a preexisting renal anomaly, such as hydronephrosis secondary to a ureteropelvic junction obstruction, horseshoe kidney, or renal ectopia, also are at increased risk for renal injury. Blunt abdominal or flank trauma often causes a renal injury. Falling can cause a deceleration injury that results in an injury to the renal pedicle, interrupting blood flow to the kidney. If the bladder is full, blunt lower abdominal trauma can cause a bladder rupture. Rupture of the membranous urethra occurs in 5% of pelvic fractures. Straddle injuries usually are associated with trauma to the bulbous urethra.

Symptoms and signs of urinary tract injury include gross or microscopic hematuria, bleeding from the urethral meatus, abdominal or flank pain, a flank mass, fractured lower ribs or lumbar transverse processes, and a perineal or scrotal hematoma.

In more than 50% of cases, there also are major injuries to the brain, spinal cord, skeleton, lungs, or abdominal organs.

DIAGNOSIS

Evaluation of the patient begins after an adequate airway has been established and the patient is hemodynamically stable (see Chapters 78 and 79). With significant abdominal injury, gross hematuria or >50 red blood cells per high-power field, or suspicion of renal injury (deceleration injury, flank pain, or bruise), renal imaging is indicated (Fig. 583.1). The bladder should be catheterized unless blood is dripping from the urethral meatus, which is an indication of potential urethral injury. Passing the catheter in the presence of a urethral injury can increase the extent of the damage and convert a partial membranous urethral tear into a total disruption. In these patients, a retrograde urethrogram should be performed by injecting radiopaque contrast medium into the urethral meatus under fluoroscopy. Oblique radiographs demonstrate the extent of the injury and whether urethral continuity is preserved or has been disrupted.

A three-phase spiral CT scan should be performed to evaluate the kidneys, ureters, and bladder. The delayed images are important to detect renal extravasation of blood or urine. Prompt function of both kidneys without extravasation usually excludes significant renal injury. Renal injuries are classified according to the grading scale presented in Table 583.1. Minor renal injuries are most common; these include contusion of the renal parenchyma and shallow cortical lacerations not involving the collecting system. Major renal injuries include deep lacerations involving the collecting system, shattered kidney, and renal pedicle injuries (Fig. 583.2). Complete absence of function of one kidney without contralateral compensatory hypertrophy (indicating congenital absence) should be regarded as an indication of major injury to the renal pedicle. Renal angiography, once used for further evaluation of renal injuries, particularly if a renal pedicle injury is suspected, now is rarely used because such patients are often hemodynamically unstable, and management is not significantly affected by the findings. In some cases, a preexisting renal anomaly is demonstrated on the study. A ruptured ureteropelvic junction obstruction may be apparent if the kidney is intact, but the distal ureter is not visualized.

If there is a pelvic fracture, a urethral transection injury should be suspected, particularly in males. The risk is directly related to the number of broken pubic rami and whether there is separation of the pubic symphysis or displacement of the posterior pubic arch. Radiographic evaluation with retrograde urethrography should be performed if there is blood at the urethral or vaginal meatus, inability to void, and a perineal or penile hematoma.

TREATMENT

Minor renal injuries such as contusions are managed by bed rest and monitoring of vital signs until abdominal or flank discomfort and gross hematuria have resolved. Children with a major renal injury usually are admitted to an intensive care unit for continuous monitoring of vital signs and urine output. Intravenous antibiotics are also administered. These injuries also are managed nonoperatively, because Gerota's fascia often causes tamponade of bleeding from the kidney, and dramatic healing of the injured parenchyma can occur even with significant urinary extravasation.

Approximately 10% of children with a major renal injury undergo surgical exploration because of associated abdominal injuries, hemodynamic instability, persistent extravasation, or persistent hematuria or to correct a congenital renal deformity. It can be difficult to identify normal and devitalized parenchyma, and the likelihood of having to remove the kidney is significant. If the child is undergoing exploration for other abdominal injuries, the injured kidney is examined. If there is persistent extravasation because of intermittent ureteral obstruction from a blood clot, passage of a temporary double-J stent endoscopically between the bladder and kidney might allow resolution. If the renal pedicle is injured, nephrectomy is necessary. The kidney can be salvaged by

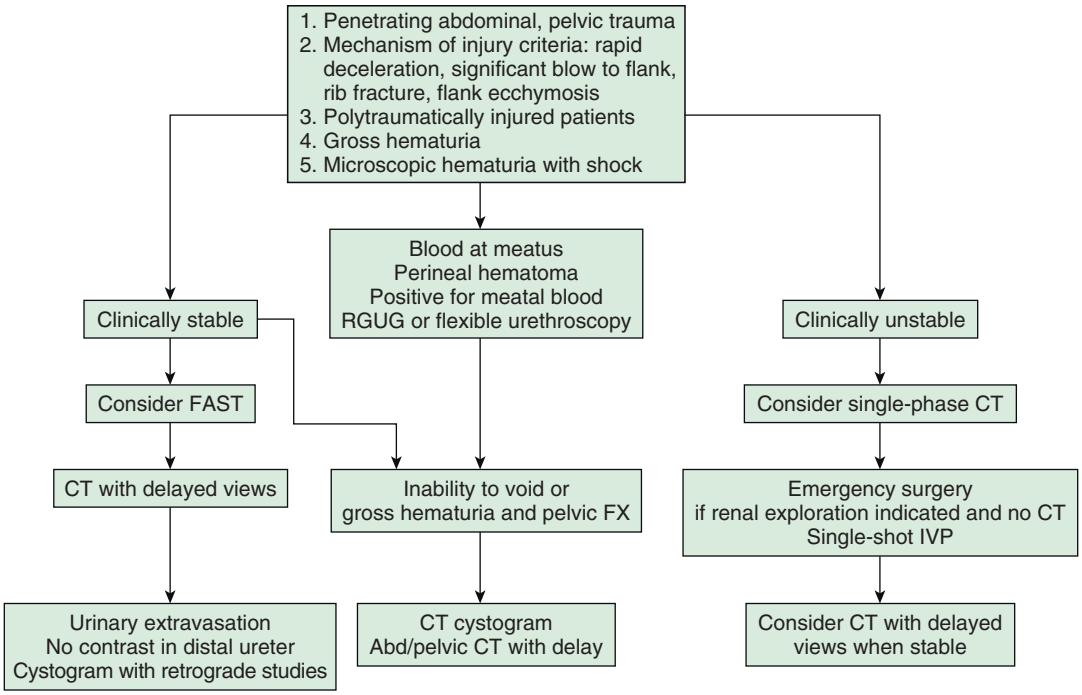

Fig. 583.1 Algorithm showing the recommended evaluation protocol for patients with a medical history or physical findings consistent with possible genitourinary injury. Abd, Abdominal; FAST, focused assessment with sonography for trauma; FX, fracture; IVP, intravenous pyelography; RGUG, retrograde urethrogram. *(From Husmann DA. Pediatric genitourinary trauma. Modified from Wein AJ, Kavoussi LR, Partin AW, Peters CA, eds. Campbell-Walsh Urology. 11th ed. Philadelphia: Elsevier; 2016: Fig. 154-6, p. 3546.)*

Table 583.1 Grading of Renal Injuries

GRADE	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, <1 cm parenchymal laceration, no urinary extravasation; all renal fragments viable; confined to renal retroperitoneum
3	Nonexpanding perirenal hematoma, >1 cm parenchymal laceration, no urinary extravasation; renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation; renal fragments may be vital or devitalized *or* Injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney; by definition, multiple major lacerations >1 cm associated with multiple devitalized fragments *or* Injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion

emergency renal revascularization only if the kidney is explored within 2-3 hours of the injury. Virtually all penetrating injuries of the kidneys should be explored.

In addition to loss of renal function, the main long-term complication of renal injury is renin-mediated hypertension. Children who sustain significant renal injuries should have periodic measurement of blood pressure if they have any residual renal abnormality.

Ureteral injuries usually are iatrogenic. Injuries of the ureter by blunt or penetrating trauma require immediate surgical attention.

When the bladder can be catheterized, a static cystogram is obtained, infusing a contrast solution through the catheter by gravity, ideally using fluoroscopy. Flat and oblique views are often obtained; a postvoid film also should be obtained because, in some cases, extravasation may be hidden by the full bladder. An alternative is a CT cystogram, which is highly accurate in demonstrating a bladder injury.

Bladder ruptures can be intraperitoneal or extraperitoneal. All intraperitoneal ruptures require surgical repair. Minor extraperitoneal near-ruptures might be treated by catheter drainage but generally require surgical treatment.

Treatment of a **membranous urethral injury** is controversial. Erectile dysfunction, urethral stricture, and urinary incontinence are the major late complications of rupture of the membranous urethra, and therapy is directed at minimizing the risk of these problems. A large pelvic hematoma with tamponade often is present, and an immediate attempt to repair the injury can be technically difficult and result in significant hemorrhage. Many such injuries are managed initially by temporary suprapubic cystostomy, with continuous bladder drainage for 3-6 months. Subsequently, open or endoscopic urethroplasty can be performed. Alternatively, some try to achieve urethral continuity under anesthesia and leave a urethral catheter for several months. These patients typically require subsequent open urethroplasty.

Penile injury is uncommon. Partial or complete glans amputation is a risk of newborn circumcision with a Mogen clamp. With immediate surgical repair, often the excised glans tissue can be replaced as a free graft. Some males who are in the process of toilet training sustain an injury to the glans penis if the lid of the toilet falls while they are urinating. These males often have a hematoma covering the distal half of the glans. Typically, they have no difficulty urinating and do not need extensive evaluation. Some male infants develop an inadvertent **hair tourniquet** or strangulation injury. Typically,

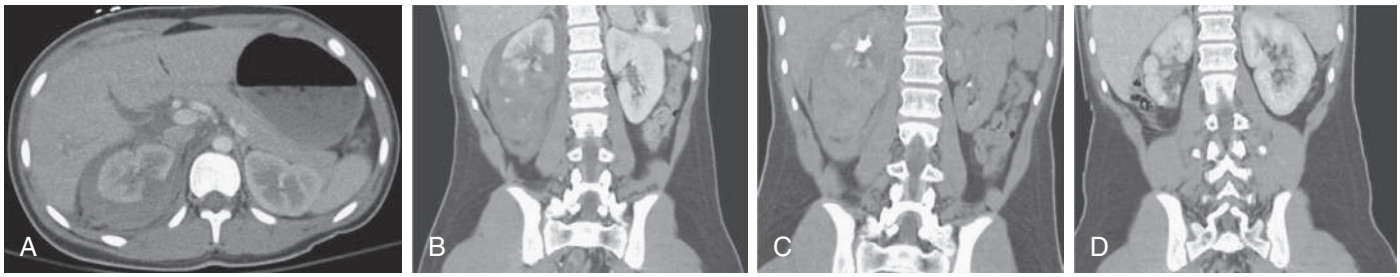

Fig. 583.2 CT images of grade 3 right renal trauma: acute, delayed, and at 3-month follow-up. **A,** Acute CT image of grade 3 renal trauma showing laceration of more than 1 cm of midrenal pole with perinephric hematoma. **B,** Acute CT image coronal reconstruction of grade 3 renal trauma, with possible devitalization of the entire lower pole of the kidney. **C,** Two-hour delayed CT image coronal reconstruction of grade 3 renal trauma, with no urinary extravasation noted and lower pole with questionable devitalization versus contusion. **D,** CT image coronal reconstruction 3 months after traumatic injury revealing parenchymal scarring at site of laceration with scarred but functional lower pole consistent with healed parenchyma following severe renal contusion. Scarring of lower pole was believed to have occurred with impoverished blood supply because of severe contusion. *(From Husmann DA. Pediatric genitourinary trauma. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA, eds. Campbell-Walsh Urology. 11th ed. Philadelphia: Elsevier; 2016: Fig. 154-3, p. 3542.)*

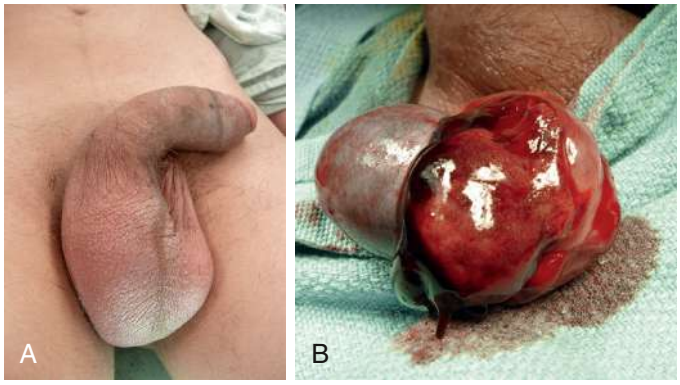

Fig. 583.3 **A,** Adolescent male with blunt right testicular injury. **B,** Tunica albuginea of testis is ruptured; the patient underwent debridement and closure of testicular capsule.

a very narrow constriction is noted with severe distal penile swelling and pain. Identification and incision of the hair allows prompt resolution of the edema. The urethra and penile vascularity should be assessed after release of the hair tourniquet. Adolescent males who indulge in extremely vigorous sexual intercourse may sustain rupture of one of the corporal bodies, resulting in penile fracture. These males have severe swelling of the penile shaft and require emergency exploration and repair. Males with penetrating injuries of the penis also require emergency debridement and repair.

Testicular injuries are relatively uncommon in children because of the small size of the testes and their mobility within the scrotum. Such injuries usually result from blunt trauma during athletic activity. Typically, these males have significant scrotal swelling, testicular pain, and tenderness (Fig. 583.3A). Ultrasonography demonstrates rupture of the tunica albuginea, which is the capsule of the testis, and surrounding hemorrhage. Prompt surgical treatment of testicular injuries increases the salvage rate (see Fig. 583.3B). An uncommon injury is the **zipper injury,** which can affect either the scrotum or foreskin. This problem generally occurs in males who do not wear underwear. The zipper can be cut with bone cutters or metal cutters. Sedation generally is unnecessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 584

Urinary Lithiasis

Heather N. Di Carlo and Chad B. Crigger

Urinary lithiasis in children is related to genetic, climatic, dietary, and socioeconomic factors. The incidence increased steadily over the past several decades. Adolescents are 10 times more likely to have a symptomatic calculus compared with children age 0-3 years. The increase in stone disease in the United States is attributed to obesity and changes in dietary habits, such as increased sodium and fructose intake, and decreased calcium and water intake.

Urolithiasis is less common in the United States than in other parts of the world. In the United States, 1 in 685 pediatric hospital admissions is for stone disease. Approximately 7% of urinary calculi occur in children younger than 16 years of age. In the United States, many children with stone disease have a metabolic abnormality. The exceptions are patients with a neuropathic bladder (see Chapter 579), who are prone to infection-initiated renal stones, and those who have urinary tract reconstruction with small or large intestine, which predisposes to bladder calculi. The incidence of metabolic stones is similar in males and females; they are most common in the southeastern United States. Racial and ethnic differences have been noted, with the highest prevalence among Whites. In Southeast Asia, urinary calculi are endemic and are related to dietary factors.

STONE FORMATION

Nearly 90% of urinary stones contain calcium as a major constituent, and 60% are composed of calcium oxalate. Most *spontaneous* stones are composed of calcium oxalate, or calcium phosphate crystals; others are caused by uric acid, cystine, ammonium crystals, or phosphate crystals, or a combination of these substances (Table 584.1). The risk of stone formation increases in the presence of increasing concentrations of these crystals and is reduced with increasing concentrations of urinary inhibitors. Renal calculi develop from crystals that form on the calyx and aggregate to form a calculus. Bladder calculi may be stones that formed in the kidney and traveled down the ureter, or they can form primarily in the bladder.

Table 584.1 Classification of Urolithiasis

CALCIUM STONES (CALCIUM OXALATE AND CALCIUM PHOSPHATE)*
Hypercalciuria
Absorptive: increased Ca absorption from gut; types I and II
Renal leak: decreased tubular reabsorption of Ca
Resorptive
Primary hyperparathyroidism (rare in children)
Iatrogenic
Loop diuretics
Ketogenic diet
Corticosteroids
Adrenocorticotropic hormone administration
Methylxanthines (theophylline, aminophylline)
Distal renal tubular acidosis, type 1 (calcium phosphate)
Hypocitraturia—citrate most important inhibitor of Ca crystallization
Vitamin D excess
Immobilization
Sarcoidosis
Cushing disease
Hyperuricosuria
Heterozygous cystinuria
Hyperoxaluria (calcium oxalate)
Primary hyperoxaluria, types 1 and 2
Secondary hyperoxaluria
Enteric hyperoxaluria
CYSTINE STONES
Cystinuria
STRUVITE STONES (MAGNESIUM AMMONIUM PHOSPHATE)
Urinary tract infection (urea-splitting organism)
Foreign body
Urinary stasis
URIC ACID STONES
Hyperuricosuria
Lesch-Nyhan syndrome
Myeloproliferative disorders
After chemotherapy
Inflammatory bowel disease
OTHER
Indinavir stones
Melamine
Nephrocalcinosis

*Most common.

Low urine volume, low urine pH, calcium, sodium, oxalate, and urate are known to promote stone formation. Many inorganic (e.g., citrate, magnesium) and organic (e.g., glycosaminoglycans, osteopontin) substances are known to inhibit stone formation. Organic inhibitory compounds adsorb to the surface of the crystal, thereby inhibiting crystal growth and nucleation.

Stone formation depends on four factors: matrix, precipitation-crystallization, epitaxy, and the absence of inhibitors of stone formation in the urine. **Matrix** is a mixture of protein, nonamino sugars, glucosamine, water, and organic ash that makes up 2–9% of the dry weight of urinary stones and is arranged within the stones in organized concentric laminations. **Precipitation-crystallization** refers to supersaturation of the urine with specific ions composing the crystal. Crystals aggregate by chemical and electrical forces. Increasing the saturation of urine with respect to the ions increases the rate of nucleation, crystal growth, and aggregation and increases the likelihood of stone formation and growth. **Epitaxy** refers to the aggregation of crystals of different composition but similar lattice structure, thus forming stones of a heterogeneous nature. The lattice structures of calcium oxalate and monosodium urate have similar structures, and calcium oxalate crystals can aggregate on a nucleus of monosodium urate crystals. Urine also contains **inhibitors of stone formation,** including citrate, diphosphonate, and magnesium ion.

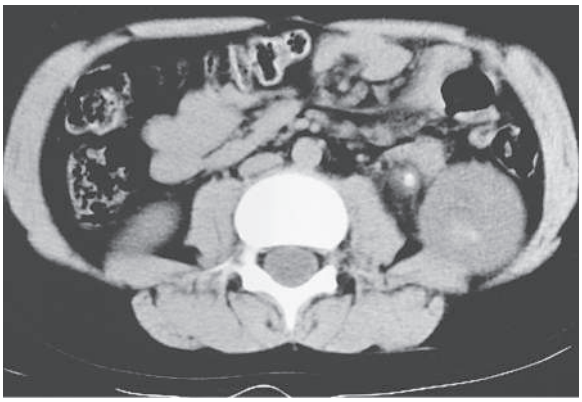

Fig. 584.1 Noncontrast CT scan of the midabdomen in a male infant with cystinuria shows a left-sided calculus at the ureteropelvic junction with proximal hydronephrosis.

CLINICAL MANIFESTATIONS

Children with urolithiasis usually have gross or microscopic hematuria. If the calculus causes ureteral or renal pelvic obstruction, then severe flank pain (renal colic) or abdominal pain occurs. The calculus typically causes obstruction at areas of narrowing of the urinary tract—the ureteropelvic junction, where the ureter crosses the iliac vessels, and the ureterovesical junction. The ureter progressively narrows distally, and its most narrow segment is the ureterovesical junction. The pain typically radiates anteriorly to the scrotum or labia. Often the pain is intermittent, corresponding to periods of obstruction of urine flow, which increases the pressure in the collecting system. If the calculus is in the distal ureter, the child can have irritative symptoms of dysuria, urgency, and frequency. If the stone passes into the bladder, the child usually becomes asymptomatic. If the stone is in the urethra, dysuria and difficulty voiding can result, particularly in males. Some children pass small amounts of gravel-like material. Stones can also be asymptomatic, although it is uncommon to pass a ureteral calculus without symptoms.

DIAGNOSIS

Approximately 90% of urinary calculi are calcified to some degree and are radiopaque on a plain abdominal film. However, many calculi are only a few millimeters in diameter and are difficult to see, particularly if they are in the ureter. Struvite (magnesium ammonium phosphate) stones are radiopaque. Cystine, xanthine, and uric acid calculi may be radiolucent but often are slightly opacified. Some children have **nephrocalcinosis,** which is calcification of the renal tissue itself. Nephrocalcinosis is seen most commonly in premature neonates receiving furosemide, which causes **hypercalciuria**, and in children with medullary sponge kidney.

In a child with suspected renal colic, there are multiple imaging options, including ultrasound, CT, and plain radiographs. The American Urological Association recommends ultrasound as the *initial* imaging modality in children as it avoids radiation. Ultrasound has high specificity (97%) but only moderate sensitivity (67%) in the diagnosis of urolithiasis; thus CT should be considered when clinical suspicion for stones is high, but ultrasound is negative. CT scan of the abdomen and pelvis is the most accurate study in diagnosis of stones with both sensitivity and specificity exceeding 96% (Fig. 584.1). This study takes only a few minutes to perform, is useful in delineating the number and location of calculi, and demonstrates whether the involved kidney is hydronephrotic. *Most pediatric imaging centers use low-dose CT to reduce radiation exposure.* A plain radiograph of the abdomen and pelvis is sometimes used to detect radiopaque stones but cannot identify obstruction and rarely visualizes renal calculi <3 mm.

In a child with a previously diagnosed calculus, renal ultrasonography can be used to follow the status of the calculus, such as whether it has grown or diminished in size or has moved. If a child has a renal pelvic calculus, a ureteropelvic junction obstruction should be suspected.

Table 584.2 Laboratory Tests Suggested for Evaluation of Urolithiasis

SERUM
Calcium
Phosphorus
Magnesium
Uric acid
Electrolytes and anion gap
Creatinine
Alkaline phosphatase
URINE
Urinalysis
Urine culture
Spot test for cystinuria
Stone analysis
If toilet-trained, 24 hour collection for:
Creatinine clearance
Calcium
Phosphate
Oxalate
Uric acid
Dibasic amino acids (if cystine spot test result is positive)
If not toilet-trained, random urine sample for:
Calcium
Creatinine
Oxalate
Citrate

In some cases, it can be difficult to determine whether hydronephrosis in such a child is secondary to an obstructing stone, ureteropelvic junction obstruction, or both.

Any material that resembles a calculus should be sent for analysis by a laboratory that specializes in identifying the components of urinary calculi.

METABOLIC EVALUATION

A metabolic evaluation for the most common predisposing factors should be undertaken in all children with urolithiasis, bearing in mind that structural, infectious and metabolic factors often coexist. This evaluation should not be undertaken in a child who is in the process of passing a stone, because the altered diet and hydration status, as well as the effect of obstruction on the kidney, can alter the results of the study. Table 584.2 lists the basic laboratory studies required, and Table 584.3 shows the normal values for 24-hour urine collections. In children with hypercalciuria, further studies of calcium excretion with dietary calcium restriction and calcium loading are necessary.

PATHOGENESIS OF SPECIFIC RENAL CALCULI

Calcium Oxalate and Calcium Phosphate Calculi

Most urinary calculi in children in the United States are composed of calcium oxalate and/or calcium phosphate. The most common metabolic abnormality in these patients is **normocalcemic hypercalciuria.** Between 30% and 60% of children with calcium stones have hypercalciuria without hypercalcemia. Other metabolic aberrations that predispose to stone disease include hyperoxaluria, hyperuricosuria, hypocitraturia, heterozygous cystinuria, hypomagnesuria, hyperparathyroidism, and **renal tubular acidosis** (RTA; see Chapter 569).

Hypercalciuria may be absorptive, renal, or resorptive. The primary disturbance in *absorptive hypercalciuria* is intestinal hyperabsorption of calcium. In some children, an increase in 1,25-dihydroxyvitamin D is associated with the increased calcium absorption, whereas in others, the process is independent of vitamin D. *Renal hypercalciuria* refers to impaired renal tubular reabsorption of calcium (see Chapter 562.4). Renal leak of calcium causes mild hypocalcemia, which triggers an increased production of parathyroid hormone, with increased intestinal absorption of calcium and increased mobilization of calcium stores. *Resorptive hypercalciuria* is uncommon and is found in patients with primary hyperparathyroidism. Excess parathyroid hormone secretion stimulates intestinal absorption of calcium and mobilization of calcium stores. Table 584.4 summarizes the metabolic evaluation of children with hypercalciuria.

Hyperoxaluria is another potentially important cause of calcium stones. Oxalate increases the solubility of calcium oxalate crystallization 7-10 times more than calcium. Consequently, hyperoxaluria significantly increases the likelihood of calcium oxalate precipitation. Oxalate is found in high concentrations in tea, coffee, spinach, and rhubarb. Primary hyperoxaluria is a rare autosomal recessive disorder that can be subclassified into glycolic aciduria and L-glyceric aciduria. Most patients with primary hyperoxaluria have glycolic aciduria; oxalic and glycolic acids are increased in the urine of affected persons. Both defects cause increased endogenous production of oxalate, with hyperoxaluria, urolithiasis, nephrocalcinosis, and injury to the kidneys. Death from renal failure occurs by age 20 in untreated patients. **Oxalosis,** defined as extrarenal deposition of calcium oxalate, occurs when renal insufficiency is present with elevated plasma oxalate. Calcium oxalate deposits appear first in blood vessels and bone marrow, and with time they appear throughout the body. Secondary hyperoxaluria is more common and can occur in patients with increased intake of oxalate and oxalate precursors such as vitamin C, in those with pyridoxine deficiency, and in children with intestinal malabsorption.

Enteric hyperoxaluria refers to disorders such as inflammatory bowel disease (see Chapter 382), pancreatic insufficiency (see Chapter 398), and biliary disease (see Chapter 404), in which there is gastrointestinal malabsorption of fatty acids, which bind intraluminal calcium and form salts that are excreted in the feces. Normally, calcium forms a complex with oxalate to reduce oxalate absorption, but if calcium is unavailable, there is increased absorption of unbound oxalate.

Hypocitraturia refers to a low excretion of citrate, which is an important inhibitor of calcium stone formation. Citrate acts as an inhibitor of calcium urolithiasis by forming complexes with calcium, increasing the solubility of calcium in the urine, and inhibiting the aggregation of calcium phosphate and calcium oxalate crystals. Disorders such as chronic diarrhea, intestinal malabsorption, and RTA can cause hypocitraturia. It may also be idiopathic.

Renal tubular acidosis (RTA) is a syndrome involving a disturbance of acid-base balance within the kidney that can be classified into three types, one of which predisposes to renal calculi that typically are calcium phosphate (see Chapter 569). In type 1 RTA, the distal nephron does not secrete hydrogen ion into the distal tubule. The urine pH is never <5.8, and hyperchloremic hypokalemic acidosis results. Patients acquire nephrolithiasis, nephrocalcinosis, muscle weakness, and osteomalacia. Type 1 RTA can be an autosomal dominant disorder, but more often it is acquired and associated with systemic diseases such as Sjögren syndrome, Wilson disease, primary biliary cirrhosis, and lymphocytic thyroiditis, or it results from amphotericin B, lithium, or toluene (an organic solvent associated with glue sniffing).

From 5–8% of patients with **cystic fibrosis** (see Chapter 454) have urolithiasis. Typically, the stones are calcium, and they often manifest in adolescence or young adulthood. Microscopic nephrocalcinosis also occurs in younger children with the disease. These patients do not have hypercalciuria, and the propensity for urolithiasis has been speculated to result from an inability to excrete a sodium chloride load or from intestinal malabsorption.

Other disorders can play a role in causing calcium stones. **Hyperuricosuria** may be related to the epitactic growth of calcium oxalate crystals around a nucleus of uric acid crystals or to the action of uric acid, which counteracts urinary mucopolysaccharides that then inhibit calcium oxalate crystallization. Heterozygous **cystinuria** is found in some patients with calcium stones. The mechanism is unknown but may be similar to that of uric acid. Sarcoidosis (see Chapter 209) causes an increased sensitivity to vitamin D_3 and thus an increased absorption of calcium from the gastrointestinal tract. In Lesch-Nyhan syndrome (see Chapter 110), there is excessive uric acid synthesis. These patients are more likely to form uric acid stones, but some of these stones may be calcified. **Immobility** can cause hypercalciuria by mobilization of calcium stores. High-dose

Table 584.3 Urine Chemistry: Normal Values

URINE CONSTITUENT	AGE	RANDOM	TIMED	COMMENTS
Calcium	0-6 mo	<0.8 mg/mg creat	<4 mg/kg/24 hours	Prandial variation
	7-12 mo	<0.6 mg/mg creat		Sodium-dependent
	≥2 yr	<0.21 mg/mg creat		
Oxalate*	<1 yr	0.15-0.26 mmol/mmol creat	≥2 yr: <0.5 mmol/1.73 m^2/24 hr	Random urine mmol/mmol highly age dependent
	1-<5 yr	0.11-0.12 mmol/mmol creat		Excretion rate/1.73 m^2 constant through childhood and adulthood
	5-12 yr	0.006-0.15 mmol/mmol creat		
	>12 yr	0.002-0.083 mmol/mmol creat		
Uric acid	Term infant	3.3 mg/dL GFR†	<815 mg/1.73 m^2/24 hr	Excretion rate/1.73 m^2 from >1 yr age; constant through childhood
	>3 yr	<0.53 mg/dL GFR		
Magnesium	>2 yr	<0.12 mg/mg creat	<88 mg/1.73 m^2/24 hr	Excretion rate/1.73 m^2 constant through childhood
Citrate		>400 mg/g creat		Limited data available for children
Cystine		<75 mg/g creat	<60 mg/1.73 m^2/24 hr	Cystine >250 mg/g creat suggests homozygous cystinuria

*Oxalate oxidase assay.
†(mg/dL uric acid) (serum creatinine concentration/urine creatinine concentration).
creat, Creatinine; GFR, glomerular filtration rate.
From Milliner DS. Urolithiasis. In: Avner ED, Harmon WE, Naiudet P, eds. Pediatric Nephrology. 6th ed. Berlin: Springer-Verlag; 2009: p. 1409, with permission.

Table 584.4 Metabolic Evaluation of Children with Hypercalciuria

TYPE	SERUM CALCIUM	RESTRICTED CALCIUM (URINE)	FASTING CALCIUM (URINE)	CALCIUM LOAD (URINE)	PARATHYROID HORMONE (SERUM)
Absorptive	N or I	N or I	N	I	D or N
Renal	N	I	I	I	I
Resorptive	I	I	I	I	I

I, Increased; N, normal; D, decreased

corticosteroids can cause hypercalciuria and calcium oxalate precipitation. Furosemide, which is often administered in the neonatal intensive care unit, also can cause severe hypercalciuria, urolithiasis, and nephrocalcinosis.

In some children, calcium calculi are idiopathic. A complete metabolic evaluation must be performed before this diagnosis is made.

Cystine Calculi

Cystinuria accounts for 1% of renal calculi in children. The condition is a rare autosomal recessive disorder of the epithelial cells of the renal tubule that prevents absorption of the four dibasic amino acids (cystine, ornithine, arginine, lysine) and results in excessive urinary excretion of these products. The only known complication of this familial disease is the formation of calculi, because of the low solubility of cystine. The patients usually have acidic urine, which leads to a higher rate of precipitation. In the homozygous patient, the daily excretion of cystine usually exceeds 500 mg, and stone formation occurs at an early age. Heterozygotes excrete 100-300 mg/day and typically do not have clinical urolithiasis. The sulfur content of cystine gives these stones their faint radiopaque appearance.

Struvite Calculi

Urinary tract infections (see Chapter 575) caused by urea-splitting organisms (most often *Proteus* spp., and occasionally *Klebsiella* spp., *Escherichia coli, Pseudomonas* spp., and others) result in urinary alkalinization and excessive production of ammonia, which can lead to the precipitation of magnesium ammonium phosphate (struvite) and calcium phosphate. In the kidney, these calculi often have a staghorn configuration, filling the calyces. The calculi act as foreign bodies, causing obstruction, perpetuating infection, and causing gradual kidney damage. Patients with struvite stones also can have metabolic abnormalities that predispose to stone formation. These stones often are seen in children with neuropathic bladder, particularly those who have undergone a urinary tract reconstructive procedure (see Chapter 579). Struvite stones also can form in the reconstructed bladder of children who have undergone augmentation cystoplasty or continent urinary diversion.

Uric Acid Calculi

Calculi containing uric acid represent <5% of all cases of lithiasis in children in the United States but are more common in less-developed areas of the world. Hyperuricosuria with or without hyperuricemia is the common underlying factor in most cases. The stones are radiolucent on x-ray. The diagnosis should be suspected in a patient with persistently acidic urine and urate crystalluria.

Hyperuricosuria can result from various inborn errors of purine metabolism that lead to overproduction of uric acid, the end product of purine metabolism in humans. Children with Lesch-Nyhan syndrome and patients with glucose-6-phosphatase deficiency (see Chapter 107) form urate calculi as well. In children with short-bowel syndrome (see Chapter 385.7), and particularly those with ileostomies, chronic dehydration and acidosis sometimes are complicated by uric acid lithiasis.

One of the most common causes of uric acid lithiasis is the rapid turnover of purine with some tumors and myeloproliferative diseases. The risk of uric acid lithiasis is especially great when treatment of these diseases causes rapid breakdown of nucleoproteins. Uric acid calculi or "sludge" can fill the entire upper collecting system and cause renal failure and even anuria. Urate is also present within calcium-containing stones. In these cases, more than one predisposing factor for stone formation can exist.

Indinavir Calculi

Indinavir sulfate is a protease inhibitor approved for treating HIV infection (see Chapter 322). Up to 4% of patients acquire symptomatic nephrolithiasis. Most of the calculi are radiolucent and are composed of indinavir-based monohydrate, although calcium oxalate and/or phosphate have been present in some. After each dose, 12% of the drug is excreted unchanged in the urine. The urine in these patients often contains crystals of characteristic rectangles and fan-shaped or starburst crystals. Indinavir is soluble at a pH of <5.5. Consequently, dissolution therapy by urinary acidification with ammonium chloride or ascorbic acid should be considered.

Nephrocalcinosis

Nephrocalcinosis refers to calcium deposition within the renal tissue. Often nephrocalcinosis is associated with urolithiasis. The most common causes are furosemide (administered to premature neonates), distal RTA, hyperparathyroidism, medullary sponge kidney, hypophosphatemic rickets, sarcoidosis, cortical necrosis, hyperoxaluria, prolonged immobilization, Cushing syndrome, hyperuricosuria, monogenetic causes of hypertension, and renal candidiasis.

TREATMENT

In a child or adolescent with a renal or ureteral calculus, the decision whether to remove the stone depends on its location, size, and composition (if known) and whether obstruction and/or infection is present. Pain is managed with nonsteroidal antiinflammatory drugs or, less often, opiates. Small ureteral calculi often pass spontaneously, although the child might experience severe renal colic. The narrowest segment of the ureter is the ureterovesical junction. Calculi <5 mm will pass 80–90% of the time. An α-adrenergic blocker, such as tamsulosin, 0.4 mg at bedtime, may facilitate stone passage by decreasing ureteral pressure below the stone and decreasing the frequency of the peristaltic contractions of the obstructed ureter. This intervention is termed **medical expulsive therapy**. In many cases, passage of a ureteral stent past the stone endoscopically relieves pain and dilates the ureter sufficiently to allow the calculus to pass. In cases such as children with a uric acid calculus or an infant with a furosemide-associated calculus, dissolution alkaline therapy may be effective. Fluid management with a forced diuresis is controversial and may not improve stone passage. Nonetheless, dehydration (from anorexia or emesis) must be corrected, and intravenous fluids may offset contrast-induced renal injury if CT contrast imaging is anticipated.

If the calculus does not pass or seems unlikely to pass or if there is associated urinary tract infection, removal is necessary (Table 584.5). Lithotripsy of bladder, ureteral, and small renal pelvic calculi using the holmium laser through a flexible or rigid ureteroscope is quite effective. Extracorporeal shock wave lithotripsy has been successfully applied to children with renal and ureteral stones, with a success rate of >75%. Another alternative is percutaneous nephrostolithotomy, in which access to the renal collecting system is obtained percutaneously and the calculi are broken down by ultrasonic lithotripsy. In cases in which these modalities are unsuccessful, an alternative is laparoscopic removal; this procedure can be performed using the da Vinci robot.

STONE PREVENTION

In children with urolithiasis, the underlying metabolic disorder should be addressed (Table 584.6). Because lithiasis results from elevated concentrations of specific substances in the urine, maintaining a continuous high urine output by maintaining a high fluid intake often is an effective method of preventing further stones. The high fluid intake should be continued at night, and usually it is necessary for the child to get up at least once at night to urinate and drink more water. A daily fluid intake of 2-2.5 L in adolescent stone formers is recommended, with greater intake during summer months.

Dietary sodium intake in children has increased significantly because of increased consumption of salty, processed foods. High sodium intake increases urinary excretion of calcium and may result in hypocitraturia. In addition, increased salt intake induces metabolic acidosis. To compensate for the acid load, the kidneys conserve anions, including urinary citrate, which contributes to hypocitraturia. Reduction in dietary intake of sodium and increased potassium intake is indicated.

Although counterintuitive, low-calcium diets are less effective in the treatment of calcium stones than diets containing normal amounts of calcium and limited amounts of sodium and animal protein. Low-sodium, low-protein diets reduce urinary calcium and oxalate excretion. Children with stone disease should avoid excess calcium intake. However, children require calcium for bone development, and

Table 584.5 Primary Surgical Treatment Options vs Stone Size and Location

STONES	SHOCK WAVE LITHOTRIPSY	URETEROSCOPY	PERCUTANEOUS NEPHROLITHOTOMY
RENAL			
<1 cm	Most common	Optional	Optional
1-2 cm	Most common	Optional	Optional
>2 cm	Optional	Rare	Most common
LOWER POLE			
<1 cm	Most common	Optional	Optional
>1 cm	Optional	Optional	Most common
URETERAL			
Proximal	Most common	Optional	Occasional
Distal	Optional	Most common	Rare

From Durkee CT, Balcom A. Surgical management of urolithiasis. Pediatr Clin North Am. 2006;53:465–477.

Table 584.6 Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities

METABOLIC ABNORMALITY	INITIAL TREATMENT	SECOND-LINE TREATMENT
Hypercalciuria	Reduction of dietary Na^+	Potassium citrate
	Dietary calcium at RDA	Thiazides
	Thiazides*	Neutral phosphate
Hyperoxaluria	Reduce dietary oxalate	Neutral phosphate†
	Potassium citrate	Magnesium
		Pyridoxine†
Hypocitric aciduria	Potassium citrate	Bicarbonate
Hyperuricosuria	Alkalinization	Allopurinol
Cystinuria	Alkalinization	Tiopronin (Thiola)
	Reduction of dietary Na^+	D-Penicillamine
		Captopril

*If hypercalciuria is severe or there is osteopenia.
†Initial therapy in primary hyperoxaluria.
RDA, Recommended dietary allowance.
From Milliner DS. Urolithiasis. In: Avner ED, Harmon WE, Naiudet P, eds. Pediatric Nephrology. 6th ed. Berlin: Springer-Verlag; 2009: p. 1412, with permission.

recommendations for daily calcium intake vary by age. *Consequently, calcium restriction in children should be avoided.* Thiazide diuretics also reduce renal calcium excretion. The addition of potassium citrate, an inhibitor of calcium stones, with a dosage of 1-2 mEq/kg/24 hours is beneficial. An excellent source of citrate is lemonade, because 4 oz of lemon juice contains 84 mEq of citric acid. A daily mixture of 4 oz of reconstituted lemon juice in 2 L of water and sweetened to taste should significantly increase the urinary citrate level. In difficult cases, neutral orthophosphate should be given, although it is poorly tolerated.

In patients with uric acid stones, allopurinol is effective. Allopurinol is an inhibitor of xanthine oxidase and is effective in reducing the production of both uric acid and 2,8-dihydroxyadenine and can help control the recurrence of both types of stones. In addition, urinary alkalinization with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family.

Maintaining a high urine pH can also prevent the recurrence of cystine calculi. Cystine is much more soluble when the urinary pH is >7.5, and alkalinization of urine with sodium bicarbonate or sodium citrate is effective. Another important medication is D-penicillamine, which is a chelating agent that binds to cysteine or homocysteine, increasing the solubility of the product. Although poorly tolerated by many patients, it has been reported to be effective in dissolving cystine stones and in preventing recurrences when hydration and urinary alkalinization fail. *N*-Acetylcysteine appears to have low toxicity and may be effective in controlling cystinuria, but long-term experience with it is lacking.

Treatment of type 1 RTA involves correcting the metabolic acidosis and replacing lost potassium and sodium. Sodium or potassium citrate therapy, or both, is necessary. When the metabolic acidosis is corrected, the urinary citrate excretion returns to normal.

Treatment of primary hyperoxaluria involves liver transplantation because the defective enzymes are hepatic. Ideally, this procedure is performed before renal failure occurs. In the most severe cases, kidney transplantation is also necessary. A U.S. Food and Drug Administration (FDA)-approved agent (lumasiran) greatly decreases oxalate production in children with primary hyperoxaluria type 1. It is hoped that it will prevent end-stage renal disease in this disorder.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Gynecologic Problems of Childhood

PART XXIII

Chapter 585

Gynecologic History and Physical Examination

Kathryn C. Stambough and Alla Vash-Margita

HISTORY

For the young patient, developmentally appropriate social questions directed to the patient can put them at ease and help to develop cooperation and rapport that will facilitate a subsequent examination. Specific patient, caregiver, or provider concerns about vaginal discharge or bleeding, pruritus, external genital lesions, or abnormalities should direct a problem-focused history. In a patient presenting with vaginal bleeding, questions should focus on recent growth and development, signs of pubertal progression, trauma, vaginal discharge, medication exposure, and any history of foreign objects in the vagina. For complaints of vulvovaginal irritation, pruritus, or discharge, questions should concentrate on perineal hygiene, the onset and duration of symptoms, the presence and quality of discharge, exposure to skin irritants, recent antibiotic use, travel, presence of medical comorbidities or infections in the patient and their family members, and other systemic symptoms of illness or skin conditions. Throughout the history, the patient should be encouraged to ask their own questions. Occasionally, the child is brought to the clinician because they or their parents have concerns about anatomic findings, developmental changes, or congenital anomalies. It helps to understand the family's concerns and if a specific reason, event, or family history raised the need for a gynecologic consultation.

GYNECOLOGIC EXAMINATION

The physical examination of the patient should be tailored to the child's age, complaint, and any other concerns elicited in the history. The date of onset of the last menstrual period should be included with an assessment of other vital signs as age appropriate.

Neonates

At the time of delivery, a brief examination of the external genitalia of female infants to visually confirm the patency of the vagina and assess the presence of any obvious genital anomalies should be performed. The newborn examination should note any abnormal findings, such as ambiguous genitalia, imperforate hymen, urogenital abnormalities, abdominal mass, or inguinal hernia, that might herald a gynecologic problem.

Placing the infant in the supine position with thighs flexed against the abdomen allows visualization of the neonate's external genitalia. Estrogenic effects commonly notable in neonates include prominence of the labia majora and a white vaginal discharge. The labia minora and hymen may protrude slightly from the vestibule. A small amount of neonatal vaginal bleeding from endometrial sloughing after maternal hormone withdrawal might occur. Bleeding that is excessive or persistent beyond the first month of life requires further evaluation. Breast buds may be palpable at the time of the neonatal examination but should regress in the first 3 months of life; occasionally, nipple discharge occurs.

The vaginal orifice may be difficult to see. Gentle lateral traction on the labia majora usually allows complete visualization of the hymen and vaginal orifice. The hymen should be evaluated for patency. Most hymenal variations—imperforate, microperforate, septate—do not require treatment during the neonatal period (Fig. 585.1). Variations should be noted and readdressed in subsequent visits. The hymen originates from the urogenital sinus. The uterus and upper vagina originate from the Müllerian ducts. The concomitant renal malformations seen with Müllerian anomalies are not associated with hymenal anomalies because of different embryologic origin of the two structures. Similarly, uterine anomalies are typically not observed with hymenal anomalies (see Chapter 591). Hymenal polyps seen in newborns typically regress in size as the maternal estrogen effects subside. Cervicovaginal mucus secretions can accumulate behind the blocked outflow tract of an imperforate hymen and manifest as a mucocolpos. *In this instance and if urinary obstruction occurs, correction of the imperforate hymen in the neonatal period is indicated.* In the absence of any concern for urinary obstruction, the imperforate hymen and associated mucocolpos can be observed for resolution, and the imperforate hymen is ideally repaired surgically after onset of puberty, specifically thelarche. This allows for improved healing of tissue in the presence of endogenous estrogen production.

The clitoris may appear large in proportion to the other genital structures, especially in premature infants. If the clitoris appears enlarged, the clitoral width and length should be measured; width values >6 mm or length values >6.5 mm in a newborn indicate a need for further evaluation. *If clitoromegaly and ambiguous genitalia are present, the provider should immediately obtain expert (endocrine) consultation for evaluation of the infant and to counsel the parents.* Congenital adrenal hyperplasia is the most common cause of ambiguous genitalia (accounting for >90% of cases), and the salt-wasting forms can lead to rapid dehydration with subsequent fluid and electrolyte imbalance (see Chapter 616). Delay in the diagnosis and treatment of congenital adrenal hyperplasia may be life-threatening.

In the neonate, the ovaries are <1 cm in diameter and average 1 cm^3 in volume. Antenatal or postnatal abdominopelvic ultrasound might reveal small simple ovarian cysts, which represent normal follicles. Because of the abdominal location of ovaries in the neonate, ovarian enlargement can manifest as a palpable abdominal mass. Large cysts (>4-5 cm) or those of a complex nature pose the risk of ovarian torsion, hemorrhage into the cyst, or, uncommonly, an ovarian tumor. A nonresolving or enlarging neonatal ovarian cyst warrants pediatric surgery or pediatric gynecology consultation. Percutaneous decompression has been described in cases where benign nature can be reliably ascertained. Cyst aspiration can provide temporary relief but is not recommended if cystectomy can safely be performed because the aspirated fluid may not be reliable for diagnosis and may reaccumulate. If a cystectomy is done for appropriate clinical indications, the cyst wall should be surgically excised to prevent reaccumulation of fluid and to provide a pathologic diagnosis, the remaining ovarian tissue should be left in situ, and the contralateral ovary should be inspected. Preservation of normal ovarian tissue is recommended for all benign lesions, and salpingo-oophorectomy should not be performed unless clinically indicated.

Infants and Prepubertal Girls

When the maternal estrogen effect subsides, the genitalia of the female infant change in appearance. The labia begin to flatten. The hymenal membrane loses its redundancy and becomes translucent. The hypoestrogenic prepubertal vaginal epithelium appears thin, red, and sensitive to the touch. The vaginal mucosa of young children can have longitudinal ridges running along the axis of the vagina at 3 o'clock, 6 o'clock, and 9 o'clock, which can cause small protrusions on the hymen at these locations. The cervix usually appears flat and flush with the vaginal vault. During infancy, the uterus regresses in size and does not return to its birth size until the child is 5-6 years old. The prepubertal cervix:fundus ratio is 2:1.

When puberty approaches, the child experiences increasing endocrine activity of the hypothalamus, pituitary gland, adrenal

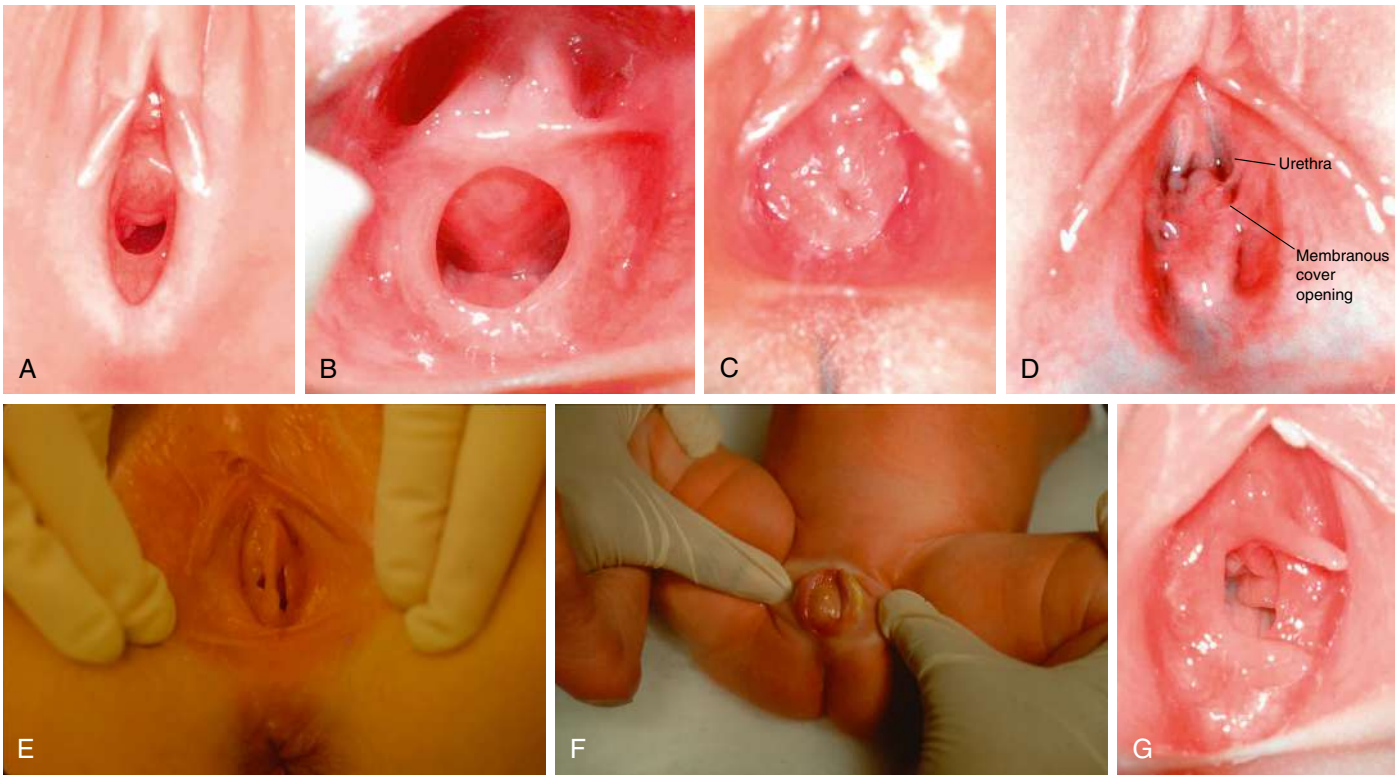

Fig. 585.1 Types of hymens. **A,** Crescentic. **B,** Annular. **C,** Redundant. **D,** Microperforate. **E,** Septated. **F,** Imperforate. **G,** Hymeneal tags. *(A–F from Perlman SE, Nakajima ST, Hertweck SP, eds: Clinical Protocols in Pediatric Adolescent Gynecology. Parthenon Publishing Group, 2004; G, from McCann JJ, Kerns DL [eds]: The Child Abuse Atlas. St Louis: Evidentia Learning, 2021, www.childabuseatlas.com.)*

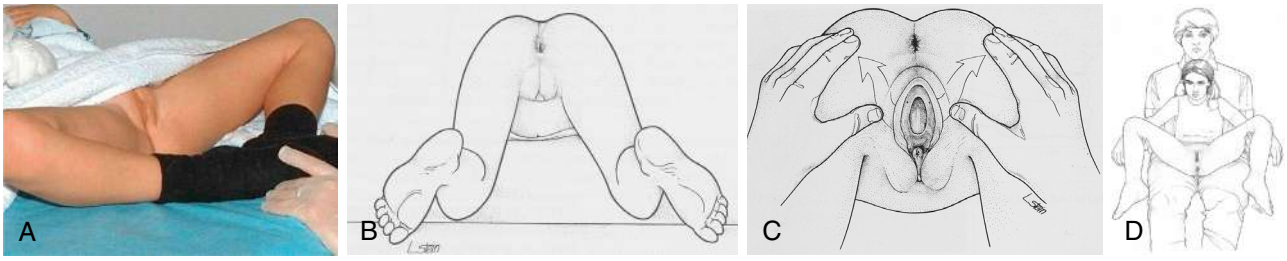

Fig. 585.2 Different exam positions for performing a gynecologic exam on a child. **A,** Frog-leg position. **B,** Knee-chest position. **C,** Prone position. **D,** Sitting on caregiver's lap. *(A from McCann JJ, Kerns DL, eds : The Child Abuse Atlas. St Louis: Evidentia Learning, 2021, www.childabuseatlas.com; B–D from Finkel MA, Giardino AP [eds]: Medical Examination of Child Sexual Abuse: A Practical Guide. Elk Grove Village, Illinois: American Academy of Pediatrics Publications, 2009;46–64.)*

gland, and ovaries (see Chapter 599). The labia majora begin to fill out, and the labia minora thicken and elongate as a result of increased estrogen levels. The hymen thickens and becomes more redundant. Clear or white physiologic secretions may be present. Breast buds begin to appear, either bilateral or initially unilateral with subsequent development of the contralateral breast. Pubic hair begins to appear.

Indications for Genital Examination

Genitourinary complaints or suspected genitourinary pathology warrants assessment of the external and internal genitalia of pediatric patients, specifically in cases of vaginal bleeding, vaginal discharge, vulvar trauma, presence of a foreign body, perineal or pelvic masses, vulvovaginal ulcerative or inflammatory lesions, congenital anomalies, or suspected sexual abuse.

Preparation

An examination of the external genitalia in prepubertal females requires a gentle, patient approach to maximize cooperation and minimize fear and embarrassment. A clear, simple explanation of what the examination involves can facilitate the child's comfort and cooperation. The presence of a parent or caregiver during the entire examination provides reassurance for most children. For the older prepubertal patient, the physician may discuss whether the patient wishes to have a family member present during the examination. Even in the presence of the caregiver, the examiner should speak directly to the child. Before initiating any part of the examination, the provider should explicitly verify with both the patient and their caregiver that the caregiver has given permission for the examination. This provides an opportunity to explain to the child the privacy of body parts and who may examine or touch those areas. It is useful to educate the patient and caregiver about the basic anatomy and hygiene of the external genital area. Before each step of the examination, the physician should explain what will occur. Allowing an older child the option of watching their examination with a handheld mirror may contribute to their comfort and understanding. Forcible restraint is never indicated; if optimal evaluation is not possible, the clinician must assess the acuity of the complaint and pathology and determine the potential need for multiple visits to complete the examination or an examination under anesthesia.

Positioning

A variety of techniques and positions can facilitate the genital examination in prepubertal patients. Children younger than 4 years of age can be placed on the parent or caregiver's lap with the child's legs straddling the caregiver's thighs (Fig. 585.2). If the child permits, they may be positioned on the table in the supine position with the hips fully abducted and the feet together in the frog-leg (diamond or butterfly) position. Older children may prefer to use the stirrups. The head of the examination table should be raised so that eye contact can be maintained with the patient throughout the examination. When the child is supine, grasping the labia majora along the inferior portion between the thumb and index finger and gently pulling outward and posteriorly (labial traction) allows visualization of the vaginal introitus. Alternatively, the child may be placed in the knee-chest position with elevation of the buttocks and hips (see Fig. 585.2). This position provides exposure of the inferior portion of the hymen, the lower vagina, and possibly the upper vagina and cervix but has the disadvantage of having the child face away from the examiner.

Some extremely cooperative children tolerate a vaginoscopic examination in an outpatient office setting for better intravaginal assessment. The endoscope (either a cystoscope or a hysteroscope) is placed in the vagina, and the labia are gently opposed, allowing the vagina to distend with water. This technique permits visualization of the vagina and cervix, allowing for the evaluation of an injury, lesion, and anatomic variant or for the presence of a foreign body. Application of 2% lidocaine gel at the introitus makes the insertion easier and less irritating for the patient. If a more complete examination is indicated or if the child is too young, frightened, or unable to cooperate, an examination under anesthesia is recommended.

Documentation

Clinicians should thoroughly and accurately document the genital examination findings in the medical record, reserving conclusions and diagnostic terms for the impression and plan portion of the documentation rather than in the description of exam findings. Each structure visualized should be noted (e.g., clitoris, labia majora, labia minora, urethra, vestibule, and rectum) with attention to describing normal appearance and any anatomic variations (e.g., the configuration of the hymen as annular, crescentic, and so forth). Describing any findings or lesions using a clock-face method provides a consistent reference point; a sketch or magnified photograph may also be helpful. Future examiners will rely on this documentation as a record with which they compare their findings and note any variances. Changes should be noted in any follow-up examinations.

Adolescents

Some teens prefer to initially meet and discuss the reason for their visit with the provider without their parent or guardian present, and this request should be honored (see Chapter 151). Obtaining a history from an adolescent usually begins with meeting the patient and parent or caregiver together to review their history and the reason for the visit and to explain the concepts of confidentiality and privacy. Care should be taken to ask the patient their preferred name and pronouns when addressing them. Familiarity with local laws governing limitations to confidential services should guide the protection of the adolescent and their parents' rights to information access and privacy. The Guttmacher Institute provides an up-to-date listing of state and federal laws in the United States affecting access to medical care (https://www.guttmacher.org/geography/united-states). Brief discussions of normal pubertal development and menstruation can reassure both patients and their parents or guardians and provide valuable education on appropriate menstrual flow, menstrual hygiene, and the duration and frequency of bleeding. Introducing the menstrual diary as an invaluable tool for the teen can help patients, parents, and clinicians identify abnormal bleeding patterns that might require further evaluation. Many applications are available for tracking menstrual periods on a smart phone or computer.

After the initial interview with the teen and their parent or caregiver, the confidential and sensitive portion of the history, particularly sexual history and alcohol, tobacco, and drug use, is taken with the teen alone. Such a request could be phrased as follows: "I would like to give your child an opportunity to ask any questions they might have privately, so would you mind stepping out of the room for a moment?" After obtaining the teen's assent for the confidential interview, questions regarding gender identity, sexual orientation, mental health, safety, and use of illicit substances should be asked. Any concerns regarding parent or caregiver access to personal electronic health records should be addressed. Concerns for the presence of vaginal discharge, the potential for sexually transmitted infections, pregnancy, or menstrual aberration should be explored. Teens and their parents should be informed of the proper use and accessibility of condoms, all contraceptive methods, and emergency contraception.

Resources for educating adolescents regarding their first pelvic examination and in-depth sexual history and psychosocial screening tools are available. These include the North American Society for Pediatric and Adolescent Gynecology (http://www.naspag.org), the American Academy of Pediatrics (http://www.aap.org), the Society for Adolescent Health and Medicine (http://www.adolescenthealth.org), and the American College of Obstetricians and Gynecologists (http://acog.org/Patients).

Individuals with Special Needs

Special care should be taken in the approach to individuals with both physical and cognitive disabilities (see Chapter 592). The assistance of Child Life services can be beneficial in decreasing patient anxiety.

Pelvic Examination

Table 585.1 presents the indications for the first pelvic examination in adolescents. If an adolescent does not meet one of the criteria listed in Table 585.1, the American College of Obstetricians and Gynecologists (ACOG) recommends that the first gynecologic encounter occur between the ages of 13-15 years (Table 585.2), with attention toward anticipatory guidance focusing on normal pubertal development and menstruation. All sexually active patients age

Table 585.1 Suggested Indications for Pelvic Examination in Adolescents

Age 21 yr of age for initial Papanicolaou test (Pap smear)
Unexplained menstrual irregularities, including pubertal aberrations (especially delayed puberty)
Severe dysmenorrhea
Unexplained abdominal or pelvic pain
Unexplained dysuria
Abnormal vaginal discharge
Concern for pelvic inflammatory disease
Placement of intrauterine device
Removal of foreign body
Inability to place tampons

Data from American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. The initial reproductive health visit: ACOG Committee Opinion, Number 811. *Obstet Gynecol*. 2020;136: e70–e80.

Table 585.2 Recommendations for First Gynecologic Evaluation

Occurs between 13 and 15yr of age
Focuses on patient education
Increases comfort with issues regarding adolescent sexuality
Ensures opportunity for adolescent to speak 1-on-1 with the provider
Makes the adolescent aware of limitations of confidentiality (including issues related to mandatory reporting, insurance billing, electronic health record notifications, and legal requirements)
Pelvic examination with Papanicolaou test (Pap smear) is generally not indicated until 21 yr of age, unless otherwise indicated by Table 585.1

Data from American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. The initial reproductive health visit: ACOG Committee Opinion, Number 811. *Obstet Gynecol*. 2020;136: e70–e80.

<25 years should undergo annual screening for sexually transmitted infections (STIs). This testing can also be obtained 3 months after treatment of a positive screening, with new symptoms, or with each new sexual partner. With the availability of urine and vaginal swab nucleic acid amplification testing for chlamydia, gonorrhea, and trichomoniasis, STI screening does not necessitate a speculum exam. Extragenital (rectal or pharyngeal) chlamydia and gonorrhea testing can be considered for patients based on self-reported sexual behaviors through shared clinical decision-making between the patient and the provider. Expedited partner treatment may be used according to the state law.

Before the initiation of a physical examination, all patients should be offered the choice of having a medical attendant, family member, or friend present during their examination. Presence of the chaperone is advised based on the laws of the state and the policies of the institution. At the initial gynecologic exam, the physician should explain the process in understandable terms. A thorough evaluation begins with an assessment of body mass index, blood pressure, menstruation status, thyroid, lymph nodes, breast development, abdominal exam, and skin. The external genitalia should be examined with the patient in the dorsal lithotomy position while communication is maintained between the physician and patient. Elevating the head of the examination table allows the teen and their examiner to maintain eye contact. The teen can hold a mirror to follow along with the examination, and they should be encouraged to ask questions. Inspection of the vulva is followed by inspection of the Bartholin, urethral, and Skene glands. The clitoris, normally 2-4 mm in width, is then assessed; a clitoris wider than 10 mm, especially in the presence of other signs of virilization, suggests a need for further evaluation. The hymenal anatomy should also be evaluated. Throughout the examination, the proper nomenclature for genital anatomy should be emphasized with the teen to empower them to use proper wordage with the avoidance of slang when referring to their body.

Because the initial Papanicolaou (Pap) test is deferred until 21 years of age except in certain immunocompromised patients and cultures for STIs can be obtained from urine or vaginal swabs, the need for a speculum exam is decreasing in this age group. If a speculum exam is indicated, use an appropriately sized speculum, such as the Huffman (½ in wide × 4 in long) or Pedersen (⅞ in wide × 4 in long) speculum. Shorter speculums will not allow visualization of the entire vaginal canal. The adolescent patient should be reassured that the exam may be uncomfortable but should not be painful and that their request to stop or wait will be honored. Encouraging the patient to watch with a handheld mirror facilitates patient education and can be empowering. They may be told before the insertion of the speculum that they will experience a pressure sensation. Before touching the introitus, it may be useful to touch the inner thigh with the speculum. Compression of the urethra anteriorly should be avoided. Gentle pressure with a finger for displacement of the fourchette posteriorly further facilitates proper speculum placement. After visualization of the vagina and cervix, specimens should be obtained as indicated. A bimanual examination, sometimes with a single digit, allows palpation of the vaginal walls and cervix and bimanual assessment of the uterus and adnexa. Reassurance of normal findings throughout the examination should be provided, and normal variants to anatomy should be pointed out to the teen as they are encountered (e.g., asymmetric labia minora).

After the examination, it is appropriate to review the exam findings with the teen (and parents or caregivers as appropriate) and initiate a collaborative discussion of the management plan. Encouraging the adolescent to participate in decision-making empowers them to undertake responsibility for their health, may strengthen compliance with the medical plan, and will acknowledge them as a unique individual.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 586

Vulvovaginitis

Helen M. Oquendo Del Toro and Holly R. Hoefgen

Vulvovaginitis is the most common gynecologic-based problem for prepubertal children, with a reported incidence of 17–50%. It is most typically caused by either inadequate or excessive hygiene or chemical irritants. The age of presentation peaks at 4-8 years of age. The condition is usually improved by hygiene measures and education of the caregivers and child.

ETIOLOGY

Vulvitis refers to external genital pruritus, burning, redness, or rash. **Vaginitis** denotes inflammation of the vagina, which can manifest as a discharge with or without an odor or bleeding. If these occur simultaneously, the term vulvovaginitis is used. When a child presents with vulvovaginitis, the history should include questions on hygiene (wiping from front to back) and information about possible exposure to chemical irritants (bath soaps, bubble bath, bath bombs, laundry detergents, swimming pools, or hot tubs). A detailed history of recent diarrhea, perianal itching, or nighttime itching is important. The possibility of foreign objects being placed into the vagina should also be asked, although the young child is unlikely to recall. Approximately 75% of cases of vulvovaginitis in children are nonspecific for a variety of reasons, including their lack of vaginal estrogenization and resulting atrophy and alkalinic pH, poor perianal hygiene, and the proximity of the anus to the vagina, which is without geographic barriers given the flattened labia and lack of pubic hair. Table 586.1 lists other vulvovaginal disorders commonly seen in children.

EPIDEMIOLOGY

Infectious vulvovaginitis, where a specific pathogen is isolated as the cause of symptoms, is commonly associated with fecal or respiratory pathogens, and cultures may reveal *Escherichia coli* (see Chapter 246), *Streptococcus pyogenes* (Chapter 229), *Staphylococcus aureus* (see Chapter 227), *Haemophilus influenzae* (see Chapter 240), *Enterobius vermicularis* (see Chapter 340), and, rarely, *Candida spp*. (see Chapter 280). These organisms may be transmitted by the child using improper toilet hygiene or manually from the nasopharynx to the vagina. Typical presentation includes perianal redness, introital inflammation, and often a yellow-green or mildly bloody discharge. Children may be observed to be grabbing their genital area or "digging" in their underwear, which is usually stained with yellow-brown discharge. Attempts to treat these bacterial etiologies with antifungal medication will fail, and often the antifungal product will lead to more irritation. Table 586.2 gives specific treatment recommendations based on the bacteria identified.

Neisseria gonorrhoeae or *Chlamydia trachomatis* are also causes of specific infectious vulvovaginitis (see Chapter 163). If acquired after the neonatal period, some diseases (e.g., gonorrhea, syphilis, and chlamydia) are virtually 100% indicative of sexual contact. Management of prepubertal children who have **sexually transmitted infections** requires close cooperation between clinicians and child-protection authorities. Official investigations for sexual abuse, when indicated, should be initiated promptly (see Chapter 17). For some diseases (e.g., human papillomavirus infection and herpes simplex virus), the association with sexual contact is not as clear. Presumptive treatment for prepubertal children who have been sexually assaulted or abused is not recommended, because (1) the incidence of most sexually transmitted infections in children is low after abuse/assault, (2) prepubertal females appear to be at lower risk for ascending infection than adolescent or adult women, and (3) regular follow-up of children usually can be ensured. Although *Trichomonas vaginalis* can be transmitted vertically

Table 586.1 Specific Vulvar Disorders in Children

CONDITION	PRESENTATION	DIAGNOSIS	TREATMENT
Molluscum contagiosum (Fig. 586.8)	1- to 5-mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug	Diagnosis usually made by visual inspection	• Disease is generally self-limited and the lesions can resolve spontaneously. • Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curettage, podophyllotoxin, and topical silver nitrate. • Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects.
Condyloma acuminata	Skin-colored papules, some with a shaggy, cauliflower-like appearance	• Diagnosis is usually made by visual inspection. • Biopsy should be reserved for when the diagnosis is in question. • Human papilloma-virus DNA testing is not helpful.	• Many lesions in children resolve spontaneously, with "wait and see" often used in children (60 days). • Topical treatment with imiquimod cream (3 times/wk at bedtime × 16 wk, wash 6-10 hr after application) and podophyllotoxin (bid × 3 days followed by 4 day break; typical treatment duration is 4 wk) is the most studied. • General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery); reserve for symptomatic or large lesions. • Other treatments have been used in adults, including trichloroacetic acid, 5-fluorouracil, sine catechins, topical cidofovir, and cimetidine. • The efficacy and safety of these treatments in children has not been established.
Herpes simplex	Blisters that break, leaving tender ulcers	Visual inspection confirmed by culture from lesion	• *Infants*: Acyclovir 20 mg/kg body weight IV q8 hr × 21 days for disseminated and central nervous system disease or × 14 days for disease limited to the skin and mucous membranes. • *Genital/mucocutaneous disease:* • *Age 3 mo-2 yr:* 15 mg/kg/day IV divided q8h × 5-7 days. • *Age 2-12 yr (first episode):* Same as above or 40-80 mg/kg/day PO divided tid-qid × 7-10 days (max 1,000-1,200 mg/day). • *Age 2-12 yr (recurrence):* 1,000 mg/day PO in 5 divided doses × 5 days or 1,600 mg/day PO divided bid × 5 days or 2400 mg PO divided q8 × 2 days.
Labial adhesions (see Fig. 586.1)	May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis	Diagnosis made by visual inspection of the adherent labia, often with a central semitranslucent line.	• Does not require treatment if the patient is asymptomatic. • Symptomatic patients: Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction. • Estrogen should be interrupted if breast budding occurs. • Mechanical or surgical separation of the adhesions is rarely indicated. • The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, recurrence is common. • To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime.
Lichen sclerosus (see Fig. 586.4)	A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin; subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma. The patient can experience perineal itching, soreness, or dysuria.	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question.	• Ultrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk. • Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up. • In many females, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up. • Immunomodulators can be used: tacrolimus 1% (applied once daily) and pimecrolimus 1% (applied twice daily for 3 mo, then every other day).
Psoriasis	Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetric plaques. The classic extragenital lesions are similar but with a silver scaly appearance.	Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears.	Vulvar lesions may be treated with low- to medium-potency topical corticosteroids, increasing strength as necessary.
Atopic dermatitis	Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema. Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection.	May be seen in vulvar area but characteristically affects the face, neck, chest, and extremities	Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups. If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing.

Continued

Table 586.1 Specific Vulvar Disorders in Children—cont'd

CONDITION	PRESENTATION	DIAGNOSIS	TREATMENT
Contact dermatitis	Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed	Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components	Avoidance of irritant; topical corticosteroids for flare-ups
Seborrheic dermatitis	Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face	Diagnosis usually made by visual inspection	Gentle cleaning, topical clotrimazole with 1% hydrocortisone added
Vitiligo (see Fig. 586.6)	Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions; may be present in periphery at body orifices and extensor surfaces	Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus).	If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions.

Table 586.2 Antibiotic Recommendations for Specific Vulvovaginal Infections

ETIOLOGY	TREATMENT
Streptococcus pyogenes *Streptococcus pneumoniae*	• Penicillin V, 250 mg PO bid-tid for children < 27 kg, and 500 mg bid-tid for children > 27 kg × 10 days • Amoxicillin, 50 mg/kg/day (max: 500 mg/dose) PO divided tid × 10 days • Erythromycin ethyl succinate, 30-50 mg/kg/day (max: 400 mg/dose) PO divided qid • TMP-SMX, 6-10 mg/kg/day (TMP component) PO divided bid × 10 days • Clarithromycin, 7.5 mg/kg bid (max: 1 g/day) PO × 5-10 days • Recurrence most likely from asymptomatic pharyngeal carriage in child or family member; however, failure of penicillin regimens can occur • For penicillin resistance: Rifampin 10 mg/kg PO every 12 hr × 2 days
Staphylococcus aureus	• Topical mupirocin 2% tid to the affected skin area • If systemic therapy required: Amoxicillin-clavulanate, 45 mg/kg/day (amoxicillin) PO divided bid-tid × 7 days (first-line treatment because of high penicillin resistance) • Extensive resistance to common antibiotics noted; recommend susceptibility testing for further antibiotic use • MRSA: TMP-SMX double-strength 8-10 mg/kg/day; culture abscesses, incision and drainage
Haemophilus influenzae	• Amoxicillin, 40 mg/kg/day PO divided tid × 7 days • For cases of treatment failure or nonencapsulated *H. influenzae*, amoxicillin–clavulanate is recommended.
Yersinia	• TMP-SMX 6 mg/kg (TMP component) daily for 3 days
Shigella	• TMP-SMX 10/50 mg/kg/day (max: 160/600) PO divided bid × 5 days • Ampicillin 50-100 mg/kg/day PO divided qid (adult max: 4 g/day) × 5 days • Azithromycin 12 mg/kg (max: 500) PO × 1 day, then 6 mg/kg/day (max: 250 mg) × 4 days (in areas of high resistance to above regimens or when sensitivities are unknown) • For resistant organisms: Ceftriaxone 50-75 mg/kg/day IV or IM divided into 1 or 2 doses (max: 2 g/day) × 2-5 days

Chlamydia trachomatis	• Children weighing < 45 kg: Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided qid × 14 days
	• Children weighing > 45 kg but age younger than 8 yr: Azithromycin 1 g PO in a single dose
	• Children age older than 8 yr: Azithromycin 1 g PO in a single dose or Doxycycline 100 mg PO bid × 7 days
	• Adolescents and Adults:
	  • *Preferred*: Doxycycline 100 mg PO bid × 7 days
	  • *Alternative*: Azithromycin 1 g PO in single dose or Levofloxacin 500 mg PO once daily × 7 days

Neisseria gonorrhoeae	• Children weighing < 45 kg: Ceftriaxone, 25-50 mg/kg body weight IV or IM in a single dose (max 250 mg IM) • Children weighing ≥ 45 kg: Treat with adult regimen of 500 mg IM in a single dose; add azithromycin 1 g PO in a single dose if chlamydia has not been excluded. In persons > 150 kg, provide 1 g ceftriaxone.
Trichomonas	• Metronidazole, 15-30 mg/kg/day PO bid (max: 500 mg/dose) × 7 days or Tinidazole 50 mg/kg (max 2 g) PO as a single dose for children older than 3 yr
Pinworms (*Enterobius vermicularis*)	• Mebendazole, 100 mg chewable tablet once, repeated in 2 wk or Albendazole, 200 mg PO for child younger than age 2 yr or 400 mg PO for older child once, repeated in 2 wk • Pyrantel pamoate 11 mg/kg PO once (max 1 g), repeated in 2 wk

MRSA, Methicillin-resistant *Staphylococcus aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

and can be seen in children up to 1 year of age, it is an uncommon cause of specific infectious vulvovaginitis in the unestrogenized prepubertal female.

Other causes of specific infectious vulvovaginitis include *Shigella* (see Chapter 245), which often manifests with a blood-tinged purulent discharge, and *Yersinia enterocolitica* (see Chapter 249). Candida infections (yeast) commonly cause diaper rash (diaper dermatitis), but they are unlikely to cause vaginitis in children because the alkaline pH of the prepubertal vagina does not support fungal infections. Diabetic or immunocompromised children and children taking prolonged antibiotics may be at increased risk for fungal vaginitis. Pinworms are the most common helminthic infestation in the United States, with the highest rates in school-age and preschool children. Perianal itching can lead to excoriation and, rarely, bleeding.

CLINICAL MANIFESTATIONS

Diaper Dermatitis

Diaper dermatitis is the most common dermatologic problem in infancy and occurs in half of all diaper-wearing infants and children. The moisture and contact with urine and feces irritates the skin, and colonization with *Candida spp*. increases the severity of the dermatitis. First-line treatment includes hygiene measures such as increasing the frequency of diaper changes, allowing the infant to be diaper free, frequent bathing, and application of water-repellant barriers such as zinc oxide. If diaper dermatitis persists after these conservative measures, or if the classic satellite lesions of *Candida* are present, treatment with a topical antifungal can decrease the inflammation.

Physiologic Leukorrhea

Neonates and peripubertal children can present with a white, clear, or mucus discharge, which is physiologic in nature and secondary to exposure to estrogen. Some patients may complain of the moisture and mucus. Hygiene measures, including plain warm water baths, may help decrease symptomatology, but education should also be provided to reassure the patient and their parents.

Labial Agglutination

Labial agglutination (**labial adhesions**) are described most frequently in infants and young children (Fig. 586.1). This phenomenon is thought to be secondary to an inflammatory response in the labia minora in combination with a hypoestrogenic state. Diagnosis is made on routine genital examination. Asymptomatic patients usually require no intervention. Most common symptoms include urinary frequency, vaginitis, and postvoidal dribbling; labial adhesions also increase a patient's susceptibility to urinary tract infections. First-line therapy in symptomatic patients includes topical estrogen (estradiol cream 0.01%) or a topical steroid (betamethasone dipropionate 0.05% ointment) applied twice daily to the midline raphe under gentle traction. Surgical correction is rarely necessary, but recurrence is common until the age of puberty. Liberal use of bland emollients for 6-12 months after resolution of adhesions can limit recurrences.

Genital Ulcers

Acute genital ulceration of the vulva (Fig. 586.2) is described in young adolescents who are not sexually active and can occur in association with oral aphthous ulcers. Although linked to infectious causes such as Epstein-Barr virus, cytomegalovirus, mycoplasma, mumps, and influenza A, these ulcers may also be idiopathic vulvar aphthoses. Other potential etiologies include Crohn disease, Behçet disease, pemphigoid, Stevens-Johnson syndrome, fixed drug eruption, or mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, which has combined features of relapsing polychondritis and Behçet disease.

These lesions usually appear on the mucosal surfaces of the introitus as painful red or white lesions that evolve into sharply demarcated, red-rimmed ulcers with a necrotic or eschar-like base. The time course is generally 10-14 days until remission occurs. The lesions are painful; dysuria and vulvar pain are common complaints as well. Patients with acute genital ulcers show a fairly consistent picture of flulike prodromal symptoms, including fever, nausea, and abdominal pain. One



Fig. 586.1 Labial adhesions. *(Photo courtesy Diane F. Merritt, MD.)*

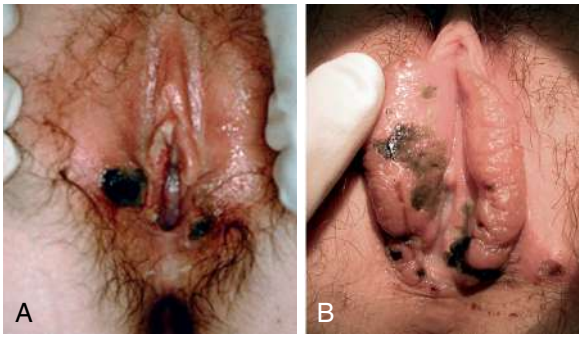

Fig. 586.2 Aphthous ulcers. *(Photo courtesy Diane F. Merritt, MD.)*

third of patients present with a history of or develop oral ulcerations. Evaluation includes culture or polymerase chain reaction (PCR) test for herpes simplex virus to exclude this etiology. Special testing for systemic disease depends on the history. Biopsies are usually nondiagnostic because they yield acute and chronic inflammatory changes. Figure 586.3 outlines the suggested evaluation and management of initial and recurrent disease. Evaluation for Behçet disease (see Chapter 202) using the International Study Group diagnostic guidelines should be considered with recurrent or severe cases (see Table 586.1 for other common etiologies). Treatment of acute genital ulcers should include topical lidocaine 2% jelly, sitz baths, good hygiene, and acetaminophen. Nonsteroidal antiinflammatory drug *avoidance* is suggested because of a possible causative link. Hospitalization may be required for pain management not controlled with oral narcotics or urinary retention requiring Foley catheterization, or for whirlpool debridement should hygiene become difficult. Antibiotic treatment is not required, unless evidence of bacterial superinfection exists or the patient is immunocompromised. Insufficient evidence exists to recommend whether oral steroid treatment is effective, but this may be helpful in the setting of recurrent outbreaks and extensive disease. Ultrapotent topical steroids (clobetasol 0.05% ointment) are beneficial in oral aphthous ulcers and may prove helpful in acute genital ulcers as well.

Dermatoses

Dermatologic conditions often affect the vulvar area in children; it is important to determine if the child presenting with vulvar irritation has a skin condition elsewhere on the body. **Lichen sclerosus** is commonly seen in the anogenital region and has a characteristic appearance of thinning and whitened skin changes associated with areas of erosion, ulceration, and petechiae. This disease can cause severe discomfort and most commonly presents with vulvar or perianal pruritus, dysuria, and constipation. Patients may also present without any symptoms, which may lead to underrecognition and undertreatment. If untreated, lichen sclerosus can lead to destruction and scarring of

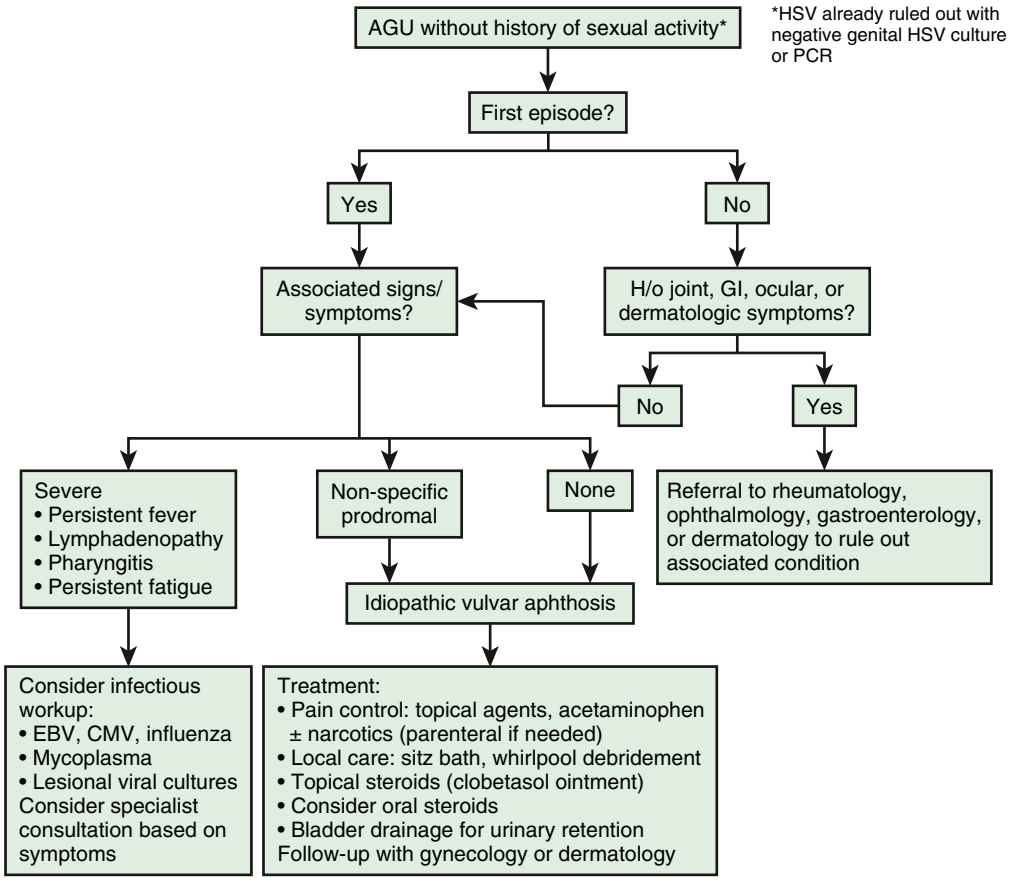

Fig. 586.3 Algorithm for evaluation and management of acute genital ulcers in non–sexually active young girls. AGU, Acute genital ulcer; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GI, gastrointestinal; HSV, herpes simplex virus; PCR, polymerase chain reaction. *(From Rosman IS, Berk DR, Bayliss SJ, et al. Acute genital ulcers in nonsexually active young girls: Case series, review of the literature, and evaluation and management recommendations. Pediatr Dermatol. 2012;29[2];147-153.)*



Fig. 586.4 Lichen sclerosus. *(Photo courtesy Diane F. Merritt, MD.)*

normal genital architecture, including labial resorption, obliteration of the clitoris, narrowing of the introitus, and painful fissures that may become secondarily infected. Once thought to resolve with puberty, this theory is now controversial, and many postmenarchal adolescents still suffer from disease (Fig. 586.4). Lichen sclerosus may be treated with potent topical steroids, such as clobetasol propionate 0.05% applied once or twice daily until the symptoms resolve, and then tapered down through lower-dose topical steroids. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus have been used in the treatment of lichen sclerosus. Patients should be followed every 6-12 months to evaluate for recurrence (Fig. 586.5).

Vitiligo is an acquired skin depigmentation resulting from an autoimmune process directed at epidermal melanocytes. Lesions appear as sharply demarcated patches of pigment loss, often symmetrically located around the vagina and anal area. Similar lesions of hypopigmentation can be found surrounding body orifices and extensor surfaces (Fig. 586.6). Although the diagnosis is clinical, there is an association with other autoimmune or endocrine disorders (hypothyroidism, Graves disease, Addison disease, pernicious anemia, insulin-dependent diabetes mellitus), and the workup should include evaluation for thyroid dysfunction. Mild topical corticosteroid cream or ointment may be prescribed for children. Dermatologists may offer immunomodulators (tacrolimus) and phototherapy.

Vulvar psoriasis presents as pruritic, well-demarcated, erythematous, symmetric plaques that involve the vulva, perineum, and/or gluteal folds. Lesions on the mons pubis may have the more characteristic scaly appearance. The classic signs of psoriasis may also be appreciated with pitting nailbeds, posterior auricular erythema, or a silvery scaling rash found elsewhere on the body. Many of the treatments used in adults may not be appropriate in children. Psoriasis may be treated with moisturizers, topical steroids, and light therapy. Teens may be treated with coal tar, retinoids, tacrolimus, and calcipotriene, which is a derivative of vitamin D_3.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Children with symptoms of vulvovaginitis often have had previous evaluations and treatment failures. Cultures with sensitivities to test for specific pathogens may be obtained with cotton swabs or urethral (Calgiswab) swabs moistened with nonbacteriostatic saline. Use of a swab can cause discomfort or, rarely, minimal bleeding. The

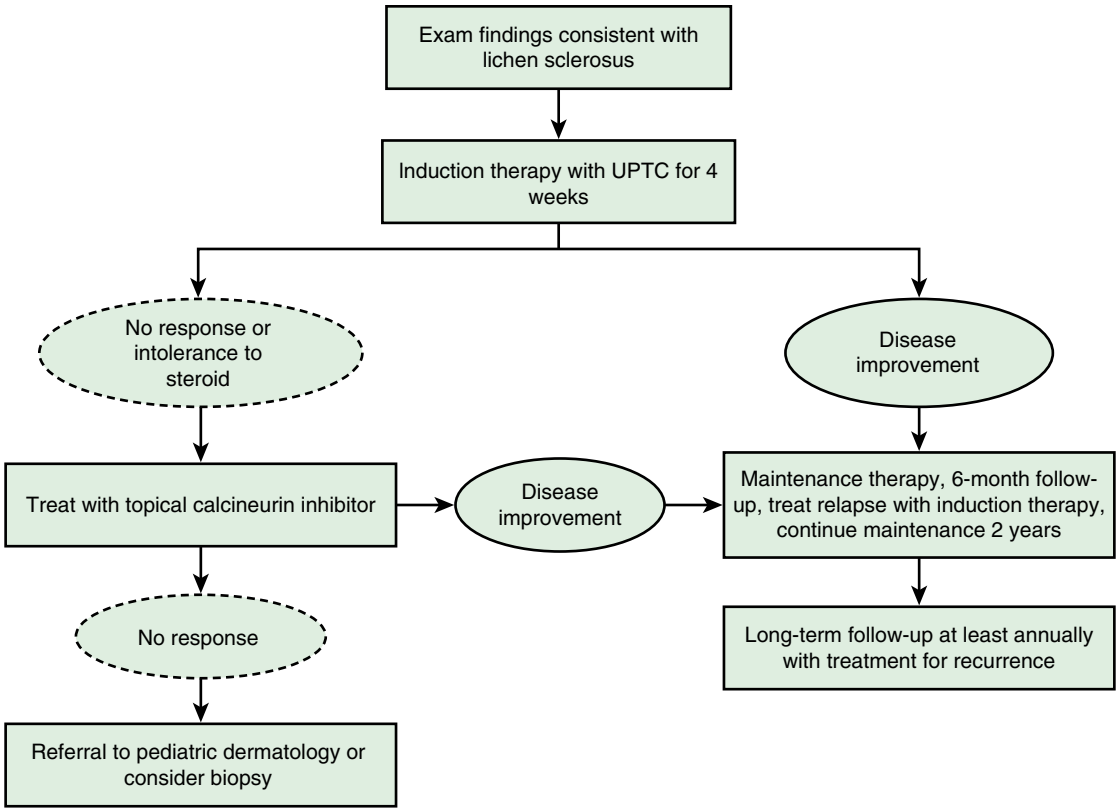

Fig. 586.5 Management algorithm for lichen sclerosus. UPTC, Ultrapotent topical corticosteroids. *(From Simms-Cendan J, Hoover K, Marathe K, Tyler K. NASPAG clinical opinion: Diagnosis and management of lichen sclerosis in pediatric and adolescent patients. J Pediatr Adolesc Gynecol. 2022;35[2]:112-120; Fig. 6.)*



Fig. 586.6 Vitiligo. *(Photo courtesy Diane F. Merritt, MD.)*

premoistened swab can be placed vertically between the labia minora to collect secretions, as it is not necessary to place the swab into the vagina. Testing for gonorrhea and chlamydia may be done by culture or by nucleic acid amplification testing, depending on institutional or state and Centers for Disease Control and Prevention guidelines. Tests for *Shigella* and *H. influenzae* might require special media and collection procedures.

If pinworms (see Chapter 340) are suspected, transparent adhesive tape or an anal swab should be applied to the anal region in the morning before defecation or bathing and then placed on a slide. Eggs seen on microscopic examination confirm the diagnosis, and sometimes the pinworms can be seen at the anal verge. Clinical history is often more indicative of disease than physical examination, and a negative tape test does not rule out this pathogen as a cause.

If the vaginal discharge is serosanguineous, if a foul odor is present, or if the discharge fails to respond to hygiene measures, presence of a vaginal foreign body (Fig. 586.7) should be considered. If inspection suggests the presence of a foreign body, the vagina can be irrigated, or an examination under anesthesia may reveal the foreign body. Vaginal irrigation may occasionally lead to expulsion of the foreign body; in cases where this does not occur, vaginoscopy is an excellent diagnostic tool and can be performed in an unsedated cooperative patient in an outpatient setting, or under general anesthesia if necessary. Using a cystoscope with saline or water irrigation to gravity, insert the endoscopic device into the vagina and gently oppose the labia; the vagina will distend, and the entire vaginal cavity and cervix may be easily assessed.

TREATMENT AND PREVENTION

The treatment of specific vulvovaginitis should be directed at the disorder or organism causing the symptoms (see Tables 586.1 and 586.2). Treatment of nonspecific vulvovaginitis includes sitz baths

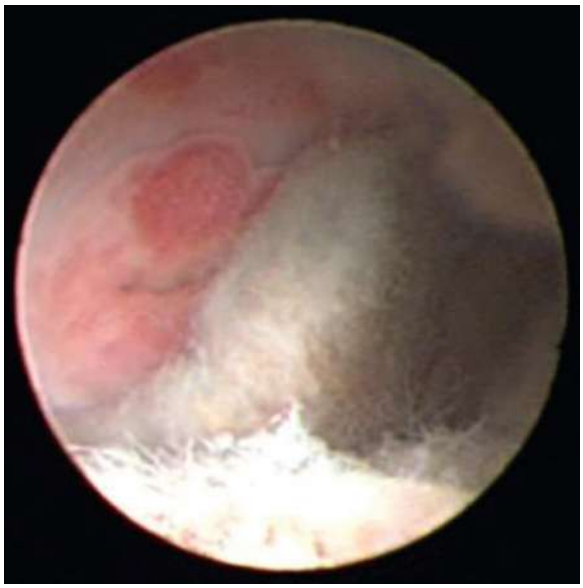

Fig. 586.7 Vaginal foreign body as seen through vaginoscope. *(Photo courtesy Diane F. Merritt, MD.)*



Fig. 586.8 Molluscum contagiosum. *(Photo courtesy Diane F. Merritt, MD.)*

and avoidance of irritating or harsh soaps and chemicals and tight clothing that abrades the perineum. External application of bland emollient barriers such as nonprescription diaper rash medications and petroleum jelly may be helpful. Proper perineal hygiene is critical for long-term improvement. Younger children need supervised perineal hygiene, and caregivers should be advised to wipe the genital area from front to back. Use of a warm moistened washcloth or diaper wipe is helpful after initially wiping with toilet tissue. Children should wear cotton underwear and limit time spent in tights, leotards, leggings, tight jeans, and wet swimsuits. Soaking in warm clean bathwater for 15-minute intervals (no shampoo or bubble bath) is soothing and helps with cleaning the area. Parents should be counseled to avoid all scented, antiseptic, and deodorant-based soaps, and to eliminate the use of fabric softeners or dryer sheets when laundering undergarments.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 587

Vaginal Bleeding in the Prepubertal Child

Kathryn C. Stambough and Christina Davis-Kankanamge

Newborn females may experience physiologic bleeding (**neonatal withdrawal bleeding**) in the first week of life secondary to diminished circulating maternal estrogen and stimulation of endometrial sloughing; this bleeding resolves in 3-4 days. Vaginal bleeding in infants lasting longer than a few days and all other vaginal bleeding in prepubescent children should be promptly evaluated because there are many pathologic etiologies that require expeditious workup. Common causes include vulvovaginitis, dermatologic conditions, vaginal foreign bodies, and urethral prolapse; less common are the effects of endogenous or exogenous estrogen; and the least common but most worrisome sources include neoplasms and trauma.

Although many cases of pediatric vaginal bleeding are idiopathic, many can be attributed to **vulvovaginitis** (see Chapter 586) stemming from transmission of respiratory, oral, fecal, or sexually communicated pathogens. Vulvovaginitis may present with serosanguineous vaginal drainage (e.g., *Streptococcus, Shigella*) or vulvar irritation. Age-appropriate anatomic and physiologic factors put prepubertal females at higher risk of developing vulvovaginitis. The protective barrier of fully developed labia is absent, leaving the vaginal introitus exposed to the external environment. The hypo-estrogenized vagina is marked by an alkaline milieu prone to infection because of lack of the protective acidic pH afforded by the lactobacilli colonization that occurs with puberty. Routine handwashing, improved perineal hygiene (e.g., wiping from front to back, use of wet wipes after bowel movements, proper cleansing of genitalia during baths), and avoidance of topical irritants, chemicals, and perfumed or deodorant soaps and bubble baths reduces nonspecific vulvovaginitis. Topical application of bland emollient barriers (e.g., over-the-counter diaper rash ointments, petroleum jelly) may be protective against and mitigate symptoms of external irritation. Antibiotics should be employed in the event of recurrent or persistent infections where a specific pathogen has been identified (see Table 586.2).

Vulvar dermatoses may initially present with bleeding. **Lichen sclerosus** (see Table 586.1 and Fig. 586.4) is characterized by chronic inflammation, intense pruritus, loss of normal architecture, and thinning and whitening of vulvar and perianal skin, often in a butterfly or keyhole distribution. Petechiae or blood blisters can complicate the classic clinical picture, leading to a mistaken assumption of sexual trauma. A tissue biopsy can provide a definitive diagnosis but is not usually necessary in prepubertal children and, if needed, is most appropriately performed under anesthesia. The first-line treatment is ultrapotent topical steroids (e.g., clobetasol propionate 0.05%). Appropriate timing and duration of application is practitioner dependent, but guidelines suggest treating children similarly to adults by starting with once or twice daily application for 4 weeks. Tapering of topical corticosteroid use can then occur with symptom control and include a decrease in the frequency of corticosteroid application, potency of the corticosteroid used, or both. Follow-up evaluations for response should start at 1 month after initiation of treatment. In the event of flare-ups, long-term maintenance therapy with a lower potency steroid may be initiated with appropriate counseling because side effects are rare.

Vaginal foreign bodies are a common finding in children presenting with blood-tinged and foul-smelling discharge. Quick identification and removal of the foreign body avoids potential complications, including recurrent urinary tract infections, dermatologic

abnormalities, vaginal perforation, or fistula formation. The most common object found in the prepubertal vagina is retained toilet paper. If physical exam in knee-chest or frog-leg position reveals the object, an attempt at removal in the office can be made using warm water flushes through a small feeding tube. If the object is not visible, irrigation is unlikely to remove it, and examination under anesthesia and vaginoscopy are often required. Direct visualization via vaginoscopy facilitates extraction of an object, as well as evaluation for potential sites of injury or unrelated sources of bleeding. In-office vaginoscopy may also be a possibility in the appropriate patient (see Chapter 585).

Several urologic conditions may have a mixed clinical picture suspicious for vaginal bleeding, including **gross hematuria** (see Chapter 558) and **urethral prolapse** (see Chapter 581) (Fig. 587.1). Prolapse involves protrusion of urethral mucosa through the external meatus, resulting in a friable hemorrhagic mass that often obscures the adjacent vaginal introitus. Predisposing factors include hypoestrogenic state, neuromuscular diseases, urethral anomalies, fascial defects, trauma, and chronic increases in intraabdominal pressure (e.g., recurrent Valsalva related to constipation or forceful coughing). Treatment of prolapse is conservative, involving twice-daily sitz baths followed by topical application of estrogen cream (e.g., Estradiol 0.01%) at the affected area for 2 weeks. If on reevaluation the prolapse remains, application should be continued until complete resolution is achieved. Surgical excision is rarely necessary and reserved primarily for management of necrotic tissue.

Vaginal bleeding may be a presenting sign of **precocious puberty** (see Chapter 600), defined as premature pubertal development occurring 2.0-2.5 standard deviations earlier than the average age in the general population. A formal evaluation should be conducted if pubic hair or breast development occurs rapidly or initiates before age 8 years in a female child. The most common source of premature development is **gonadotropin-dependent** or **central precocious puberty** (see Chapter 600.1), resulting in early enhancement of pulsatile release of hypothalamic gonadotropic-releasing hormone (GnRH) that stimulates ovarian follicular growth and subsequent estrogen production. **Gonadotropin-independent** or **peripheral precocious puberty** occurs less commonly and in the absence of hypothalamic influence, with estrogen being a product of ovarian or adrenal tumors, or McCune-Albright syndrome (see Chapter 600.6). In both instances, elevated estrogen levels lead to a thickened endometrium capable of shedding as in menses.

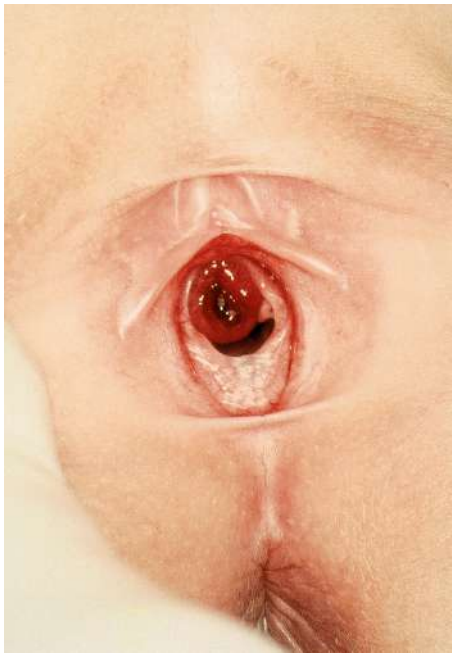

Fig. 587.1 Prepubertal urethral prolapse with high crescent-shaped hymen. *(From Lara-Torre E, Valea FA. Pediatric and adolescent gynecology: Gynecologic examination, infections, trauma, pelvic mass, precocious puberty. In Lobo RA, Gershenson DM, Lentz GM, Valea FA [eds]: Comprehensive Gynecology. Elsevier, 2022: 227; Fig. 12.6.)*

Evaluation of precocious puberty starts by examining for secondary sex characteristics and documenting the Tanner stage of breast and pubic hair development using the **Sexual Maturation Index** (see Chapter 150). Plotting height and weight on a growth chart may assist in identifying accelerated growth velocity. Supportive laboratory findings include elevated serum luteinizing hormone levels, but the gold standard remains measurement of gonadotropin levels after stimulation with GnRH or a GnRH receptor agonist. Estradiol levels greater than 100 pg/mL can indicate either the presence of premature ovarian follicles or a peripheral tumor (e.g., ovarian germ cell tumor). A pelvic ultrasound should be used to evaluate for ovarian or adrenal pathology, as well as uterine maturation in response to estrogen. However, premature ovarian follicles typically produce estrogen for a very short period, in quantities just sufficient to stimulate growth and shedding of the endometrium. Follicular involution and return of estrogen to prepubertal levels may occur before an ultrasound can be obtained. An x-ray for bone maturity is simple and noninvasive. Other supportive radiologic findings include a brain MRI demonstrating a mass in the context of central precocious puberty. If indicated, central precocious puberty can be suppressed with GnRH agonist therapy. Peripheral tumors (i.e., ovarian germ cell tumors) are treated by surgical excision with staging and chemotherapy as indicated by oncologic protocols.

Differential diagnoses of vaginal bleeding attributed to premature estrogenization must also include exposure to **exogenous estrogens,** including hormonal contraceptives, certain foods (soy), beauty products (lavender, tea tree oil), and plastics with endocrine disruptors. Ingesting large quantities of Bisphenol A (BPA), a product that may leach into the contents of plastic cups and bottles, is known to convey an estrogenic effect, although the impact remains unknown. Treatment involves elimination of any problematic sources of estrogen from the patient's daily use.

Juvenile hypothyroidism (see Chapter 603) commonly causes pubertal delay, but severe cases may present with premature breast development, vaginal bleeding, and abdominal distention secondary to ovarian enlargement and ascites. The mechanism for this condition is unclear, but it has been proposed that elevated levels of thyroid-stimulating hormone cross-react with follicle-stimulating hormone receptors, resulting in follicle maturation and estradiol production. Treatment with thyroid hormone replacement (e.g., levothyroxine) results in improvement and ultimately reversal of symptoms.

Neoplasms of the vulva and vagina (see Chapter 590) are rare causes of bleeding in the pediatric patient. **Infantile hemangiomas** are the most common benign vascular neoplasm of infancy, affecting up to 5% of all infants. Most lesions initially proliferate before resolving spontaneously and seldom require intervention. However, on identifying a perineal hemangioma, a neurologic assessment should be performed due to an association with spinal dysraphism. If a persistent lesion is superficial, application of topical β blockers (e.g., Timolol 0.5%) 2-3 times daily for 6-12 months has demonstrated good response rates. Oral β blocker use and intralesional corticosteroids may be used as well. If conservative therapies fail, laser therapy and surgical excision may be beneficial. Vaginal polyps may result in bleeding, and vaginoscopy for evaluation of any upper vaginal or cervical etiologies for bleeding with expedient excision and pathologic evaluation is recommended.

Malignant gynecologic neoplasms (see Chapter 590) are a source of pediatric genital bleeding that requires scrupulous evaluation and timely management. **Rhabdomyosarcoma** is the most common soft tissue sarcoma of childhood; 3% arise from the uterus or vagina. The embryonal variant is responsible for uterine sarcomas, whereas the embryonal subvariant sarcoma botryoides is found in the vagina. Primary **endodermal sinus** (i.e., yolk sac) **tumors** of the vagina are exceedingly rare, but early diagnosis is imperative given the malignancy's aggressive nature and poor prognosis. Both sarcomatous and endodermal sinus tumors arise primarily in the first 3 years of life, presenting on examination with a cystic or polypoid mass, bloody discharge, and occasionally urinary retention. Treatment consists of a multimodal approach, including surgery, radiation, and chemotherapy per oncologic guidelines.

Vulvovaginal trauma is an especially concerning cause of pediatric genital bleeding. Most traumatic injuries are accidental, but physical and sexual abuse must be ruled out (see Chapter 17.1). **Straddle injuries** are commonly seen after falls at home, particularly after slipping on a wet surface in the bathroom; they may result in bruising, hematomas, or lacerations (Fig. 587.2). Accidental trauma usually spares the hymen and vagina, instead affecting the external impact-absorbing tissue of the mons and labia. *However, a physical finding consistent with external injuries does not exclude the need to rule out involvement of internal genital structures. If there are no eyewitnesses to the injury, if the history does not clarify or support the clinical findings, and especially if there is a hymenal laceration, abuse must be considered in the differential diagnosis and a forensic interview of the patient and family conducted.* If after initial inspection a penetrative injury is suspected, further examination and imaging are necessary to assess for potential damage to the urethra, bladder, anus, or intraabdominal structures. An examination under anesthesia may be needed to fully assess and repair extensive injuries, while minor lacerations in a cooperative child may potentially be repaired using local anesthesia and/or conscious sedation. If the patient can void spontaneously, nonexpanding hematomas can be observed and treated with ice, pressure, and pain medications. Large expanding hematomas may require drainage, ligation of bleeding vessels, and placement of a closed suction drain if the overlying skin is showing signs of necrosis. A Foley catheter should be placed in all children who are having difficulty with voiding secondary to the injury.

Vaginal bleeding in the infant or prepubertal female is distressing to the patient and their family and can result from a wide spectrum of pathologic conditions or traumatic incidents. A detailed history and thorough physical examination must be done to identify the source of bleeding and for a management plan to be established efficiently. Presentations suspicious for trauma or abuse should involve the appropriate healthcare staff and authorities from an early stage, with findings meticulously documented. If an intervention is indicated to manage bleeding, regardless of its source, the risks and benefits of any therapy should be reviewed carefully with the family before initiation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 587.2 Vulvar hematoma in an adolescent female as a result of a straddle injury. *(From Mok-Lin EY, Laufer MR. Management of vulvar hematomas: Use of a Word catheter. J Pediatr Adolesc Gynecol. 2009; 22:e156-e158.)*

Chapter 588

Breast Health

Marcene R. McVay-Gillam and Amy D. DiVasta

Breast complaints in pediatric patients typically include concerns about breast appearance or development, pain, nipple discharge, or a lump/mass. Although the development of breast cancer is very rare during childhood and adolescence, this patient population should be evaluated by practitioners who have experience with the immature and developing breast to avoid overtreatment with unnecessary diagnostic or invasive procedures.

BREAST DEVELOPMENT

Prenatal breast development begins around the fifth week of gestation, when the ectoderm on the anterior body wall thickens into two **mammary ridges.** These ridges extend from the axilla to the region of the inguinal canal (Fig. 588.1). The ridge above and below the area of the pectoralis muscle recedes in utero, leaving the **mammary primordium**, which is the origin of the lactiferous ducts. The lactiferous ducts form between weeks 10 and 20 and become interspersed through the developing mesenchyme, which develops into the fibrous and fatty portions of the breast. The **breast bud**, under the stimulation of maternal estrogen, becomes palpable at week 34 of gestation. This breast bud regresses within the first month of life once estrogen stimulation is no longer present. The **areola** appears at 5 months of gestation, and the nipple is seen shortly after birth. It is initially depressed or inverted, and later becomes elevated.

Thelarche, the onset of pubertal breast development, is hormonally mediated. It occurs when the hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (see Chapter 599). FSH and LH then stimulate the ovaries to produce estradiol, which leads to breast development. Thelarche typically occurs between ages 8 and 13 years. Age at thelarche is affected by familial predisposition and varies by ethnicity.

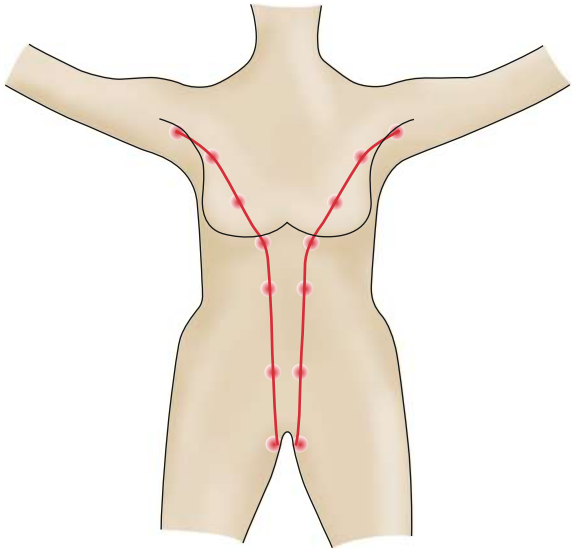

Fig. 588.1 Milk lines or mammary ridges. *(From Gao Y, Saksena MA, Brachtel EF, terMeulen DC, Rafferty EA. How to approach breast lesions in children and adolescents. Eur J Radiol. 2015;84:1350-1364; Fig. 1.)*

Breast development continues over a 2-4 year period after thelarche and is classified by the **Sexual Maturity Rating (SMR) system** (also known as **Tanner staging**) into five stages (see Chapter 150). Lack of breast development (**amastia**) by age 13 years is considered delayed and warrants evaluation. **Menarche** (onset of menses) usually occurs 2-3 years after thelarche.

BREAST EXAMINATION

Breast examination should be included in the routine healthcare maintenance examinations of all children and adolescents. Assessment of the newborn includes breast size, nipple position, presence of accessory nipples, and nipple discharge. Assessment of the prepubertal female includes inspection and palpation of the chest wall for masses, pain, nipple discharge, and signs of **premature thelarche.** Examination of the adolescent is performed with the patient in the supine position; the arm ipsilateral to the breast that is being examined should be placed next to the patient's head. The breast tissue is examined with the flat pads of the middle fingers, and the examiner should palpate all of the breast tissue in a uniform manner. The SMR should be noted and the axillary, supraclavicular, and infraclavicular nodes evaluated for lymphadenopathy. The areola should be gently compressed to assess for nipple discharge.

BREAST SELF-AWARENESS

Controversy exists as to the utility of breast self-examination in the adolescent population. Experts believe that it might be ill-advised to encourage breast self-examination in the adolescent because of a potential for unnecessary anxiety and possible unwarranted treatment in a population that is at low risk for malignant disease. The American College of Obstetricians and Gynecologists (ACOG) endorses breast self-awareness, which is defined as a female's awareness of the normal appearance and feel of their breasts. Breast self-awareness may increase an adolescent's understanding of their body, increase their comfort with exams, and provide opportunities for questions or discussion. Instruction in self-exam techniques should be considered for high-risk patients, such as those with a family history of conditions that may increase breast cancer risk or those at risk of secondary tumors. Adolescents should be educated to report any changes in their breasts or concerns to their healthcare providers.

Neonatal Breast Hypertrophy

Breast bud enlargement is a common condition in term newborns of either gender. It occurs as a result of elevated circulating maternal steroid hormones in late gestation. As maternal estrogen levels fall, prolactin levels can increase, and the breasts may produce a clear or cloudy (milk like) nipple discharge ("witch's milk") in male and female infants. Repeated manipulation of the breast can exacerbate the condition and should be discouraged.

ABNORMAL DEVELOPMENT

Premature Thelarche

Premature thelarche is defined as isolated unilateral or bilateral breast development in a female child under age 8 years without other signs of puberty; this is commonly seen in children under 3 years of age. Patient assessment includes a careful review of medications (including creams, ointments), home exposures to potential estrogens, review of growth charts, and x-ray for determination of bone age. Treatment consists of reassurance and follow-up to confirm that thelarche remains benign. Serial examinations, with particular emphasis on growth velocity, secondary sex characteristics such as pubic hair, pigmentation of the labia or areola, or vaginal bleeding, are imperative. Occasionally, patients with premature thelarche eventually develop true **central precocious puberty** (see Chapter 600.1). If puberty progresses, further workup should be performed to exclude central nervous system disorders or possible adrenal or gonadal neoplasm.

Amastia and Athelia

Complete absence of the breast, or **amastia,** is rare and is thought to occur from lack of formation of or obliteration of the mammary ridge. Amastia is usually unilateral and can be congenital or associated with systemic disorders (e.g., ectodermal dysplasia), endocrine disorders (e.g., congenital adrenal hyperplasia, gonadal dysgenesis, hypogonadotropic hypogonadism), or novel pathogenic gene variants. It can be associated with anomalies of the underlying mesoderm, such as the absence or hypoplasia of the pectoralis muscles seen in **Poland syndrome** (aplasia of the pectoralis muscles, rib deformities, webbed fingers, and radial nerve aplasia) (Fig. 588.2). Amastia or hypomastia can also be iatrogenic, resulting from injuries sustained during thoracotomy, chest tube placement, radiotherapy, severe burns, or incisional/excisional procedures on the breast bud. Surgical correction is individualized to the patient and the etiology. **Athelia**, the absence of a nipple either unilaterally or bilaterally, is rare and can be familial. It is also associated with exposure to endogenous androgens during pregnancy.

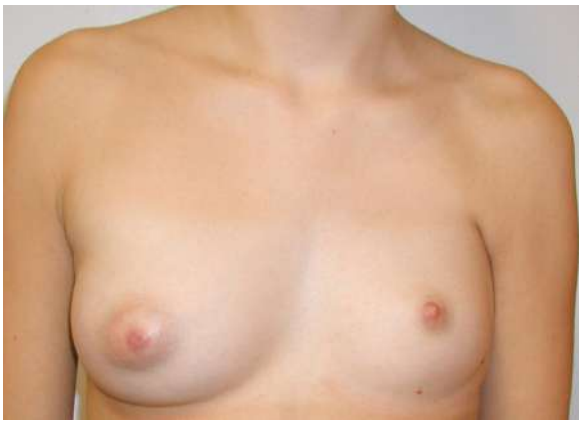

Fig. 588.2 Preoperative frontal view of a patient with left breast hypoplasia secondary to Poland syndrome. *(From Laberge LC, Bortoluzzi PA. Correction of breast asymmetry in teenagers. In: Hall-Findlay EJ, Evans GRD, eds. Aesthetic and Reconstructive Surgery of the Breast. London: Elsevier, 2010. Fig 39.14.)*



Fig. 588.3 Accessory nipple located inferior to the right breast. *(From Swartz MH. Textbook of Physical Diagnosis. Philadelphia: Elsevier, 2014; Fig 13-5.)*

Polymastia and Polythelia

Accessory breast tissue **(polymastia)** or accessory nipples **(polythelia)** occur in approximately 1–6% of the population (Fig. 588.3). The abnormally placed tissue can be seen anywhere along the mammary ridges ("milk lines") as a result of incomplete involution but is usually noted on the chest, axilla, or just inferior to the normally positioned breast. Polythelia has been reported in association with congenital malformations, particularly renal anomalies; it is therefore reasonable to perform a genitourinary ultrasound in an infant with supernumerary nipples. Surgical excision of the accessory breast or nipple is usually performed for pain (mastodynia), nipple discharge, or cosmesis.

Breast Hypoplasia and Asymmetry

Breast hypoplasia varies in degree from a near-total absence of breast tissue to well-formed breasts that are considered by the patient to be too small. Poor or absent breast development may simply be a delay in the development of normal secondary sex characteristics; the breasts develop slowly but are normal in all other respects. Family history may reveal other family members with a similar pattern. Other causes include ovarian dysfunction, hypothyroidism, eating disorders, chest wall irradiation, or surgery. Hypoplastic breast tissue can also be associated with a **tuberous breast** anomaly. Tuberous breasts are characterized by hypoplasia, a narrow breast base, and the appearance of herniation of the glandular tissue through enlarged areolae (Fig. 588.4).

More commonly, patients complain of *breast asymmetry*. Some degree of breast asymmetry is normal; it may be more pronounced during puberty while the breasts are developing. In asymmetry, the goals of evaluation are twofold. First, it is essential to exclude a neoplasm as the cause of the larger breast. Other etiologies may include a solitary large fibroadenoma, multiple fibroadenomas, or a parenchymal abscess. Alternatively, the possibility of tuberous breast development or Poland syndrome should be considered when evaluating the smaller side. Treatment depends on the underlying cause. Patients with mild asymmetry and no other associated pathology should be reassured. If a child has marked breast asymmetry, they may be initially offered cosmetic options, such as use of bra inserts or prostheses for the underdeveloped breast. Surgical correction may be pursued after breast development is complete. The American Society of Plastic Surgeons generally recommends that uncommon chest deformities or congenital breast asymmetry are the only cases in which a board-certified plastic surgeon should deem breast augmentation appropriate for a teenager. It is important that patients undergoing surgery have a realistic understanding of the potential results as well as the possible need for additional surgery. Saline-filled implants are the only type of implant approved by the U.S. Food and Drug Administration for females <22 years; saline-filled implants typically have a life span of about 10 years.

Macromastia

Adolescents may develop very large breasts **(macromastia)**, leading to both physical and psychologic symptoms. Common complaints include back pain, postural kyphosis, breast pain, intertrigo, limitation of physical activities, unwanted negative attention, diminished self-esteem, and eating disordered behaviors. Strong emotional support should be provided because macromastia can affect an adolescent's self-esteem at a vulnerable time in their psychologic development. The differential diagnosis for macromastia includes obesity, pregnancy, fibrocystic disease, end organ hormonal hypersensitivity, or lesions described in the previous paragraphs. Options for treatment of simple macromastia include surgical and nonsurgical interventions. Bras that provide maximal support can help correct symptoms. Alternatively, breast reduction mammoplasty may be desired. When adolescents are seeking breast surgery, ACOG first recommends education and reassurance regarding normal variations in anatomy, growth, and development for the patient and her family. Nonsurgical alternatives for comfort and appearance should be emphasized, and knowledge regarding indications and timing of surgical intervention and referral should be provided. Assessment of the adolescent's physical and emotional maturity level must be performed, as well as screening for **body dysmorphic disorder.**

Juvenile hypertrophy, or spontaneous massive growth of one or both breasts, is rare and should be distinguished from simple adolescent macromastia. This rapid growth of breast tissue may occur any time after thelarche but more commonly occurs abruptly over a several month period, after a preceding sustained period of normal breast development. Circulating estradiol levels are normal. Juvenile hypertrophy can cause extreme mastalgia, skin hyperemia or necrosis, and even damage to normal breast parenchyma due to compromised vascular supply. It can be unilateral or bilateral (Fig. 588.5). The etiology has not been elucidated; therefore treatment options include both pharmacologic and surgical interventions. The key to management is prompt recognition and intervention before the development of complications. Reduction mammoplasty is often the treatment of choice, with pharmacologic treatment (e.g., tamoxifen) or even mastectomy reserved for recurrence following surgery.

Infections

Mastitis is the most common infection of the breast and can occur any time from the neonatal period through adolescence and into adulthood. **Neonatal mastitis** is an infection that usually occurs in the first 2 months after delivery in term or near-term infants. Breast infections in adolescents occur most commonly with lactation. Adolescents can also develop **nonlactational mastitis** or a **breast abscess** as a result of irritation of the skin (e.g., acne lesions of the chest, shaving, or nipple stimulation), trauma, a foreign body (e.g., piercing), or ductal abnormality (such as ductal ectasia). *Staphylococcus aureus* is the cause of nearly all breast infections, but anaerobic bacilli *(Bacteroides)* may also be involved in the adolescent population. Methicillin-resistant *S. aureus* (MRSA) coverage should be considered in communities where the prevalence is high,



Fig. 588.5 Juvenile hypertrophy in a 12-year-old female. *(From Al-Saif AA, Al-Yahya GM, Al-Qattan MM. Juvenile mammary hypertrophy: is reduction mammaplasty always feasible? J Plast Reconstr Aesthet Surg. 2009;62:1470-1472; Fig. 1.)*



Fig. 588.4 Bilateral tuberous breast anomaly. *(Adapted from Pacifico MD, Kang NV. The tuberous breast revisited. J Plast Reconstr Aesthet Surg. 2007;60:455-464; Fig. 5.)*

especially for infants. Mastitis may be initially treated with warm compresses, analgesics, and oral antibiotics for 7-10 days. Antibiotic options include dicloxacillin, clindamycin, trimethoprim-sulfamethoxazole, or amoxicillin-clavulanic acid. If symptoms fail to resolve after a course of antibiotics, ultrasonography may reveal an abscess and can be used to guide needle aspiration. Incision and drainage should be reserved for failure of aspiration, and a periareolar incision is most cosmetic. Follow-up ultrasonography should be considered in adolescents to ensure that there is no remaining parenchymal lesion (e.g., cyst).

Trauma and Inflammation

Breast trauma is common in adolescent girls participating in contact sports. The trauma usually takes the form of contusion or **hematoma** and can resolve spontaneously or may be associated with late cystic changes in the breast, **fat necrosis** with calcium deposition over time, or fibrosis with retraction of the skin or the nipple over the injured area. When diagnosed with a hematoma, or when a palpable mass is present at the area of injury, serial follow-up by ultrasound is recommended until complete resolution. Persistent calcifications lasting more than 18 months after injury may require additional investigation by advanced imaging or biopsy.

Nipple Discharge

Nipple discharge must be carefully evaluated and characterized. Discharge may be milky and white **(galactorrhea)**, bloody, purulent, or serous (Table 588.1). A careful history and physical examination will help the practitioner determine the etiology. Examination of the discharge assists in diagnosis. Infection is usually associated with a purulent discharge; **ductal ectasia** (dilated subareolar ducts and periductal inflammation) may present with sticky, green or brown, or serosanguineous discharge. Discharge from the ducts of Montgomery (coming from the areola itself rather than through the nipple) may appear clear or brownish.

Galactorrhea is a specific type of nipple discharge that appears milky and is usually bilateral. Causes of galactorrhea are listed in Table 588.2. Cytologic evaluation of milky nipple discharge is not recommended. Laboratory evaluation should include a pregnancy test, prolactin, estradiol, and thyroid-stimulating hormone (TSH); these measures are obtained to rule out pregnancy, a pituitary prolactinoma, and/or the presence of a thyroid abnormality. If the prolactin level is elevated, visual field studies and a brain MRI might reveal the presence of a pituitary adenoma (see Chapter 598). Treatment is directed by results of the history, physical exam, and lab and imaging studies. Patients should be instructed to avoid nipple stimulation and stop any offending drugs, if appropriate to do so. Hypothyroidism should be treated and prolactin-releasing tumors managed with appropriate medical or surgical care. Medical treatment of galactorrhea consists primarily of dopamine agonists such as bromocriptine or cabergoline. Surgical intervention, usually transsphenoidal hypophysectomy, is rarely required.

Bloody discharge may be due to chronic nipple irritation (such as from **jogger's nipple**), ductal ectasia, phyllodes tumor, or intraductal papilloma (a rare, benign proliferative tumor). Unless the etiology of the bloody discharge is superficial (i.e., from obvious skin breakdown related to jogger's nipple), cytologic assessment of bloody discharge should be performed. Breast ultrasound may also be obtained to determine whether a mass or cyst is present.

Table 588.1 Common Causes of Nipple Discharge

DISCHARGE CHARACTERISTICS	POTENTIAL ETIOLOGY
Milky (galactorrhea)	Pregnancy or postpartum Medication use/drug use Herbal supplements Hypothyroidism Prolactinoma Chest wall trauma
Serous, serosanguineous	Ductal ectasia Intraductal papilloma
Sticky	Ductal ectasia Fibrocystic changes
Purulent	Mastitis Abscess
Bloody	Intraductal papilloma Phyllodes tumor Ductal ectasia Trauma ("jogger's nipple")
Episodic, clear to brown	Montgomery tubercles

Mastalgia

Mastalgia, or breast tenderness, is common in reproductive-age females. Mastalgia may be due to exercise, medications, early pregnancy, or benign breast changes **(fibrocystic changes)**. Physiologic swelling and tenderness can occur on a cyclic basis, most commonly during the premenstrual phase, and are secondary to hormonal stimulation and resulting proliferative changes. Hormonal imbalance can cause exaggerated responses in the breast tissue, especially in the upper and outer quadrants. Evaluation should include a pregnancy test and a breast examination. Nodularity,

Table 588.2 Etiologies of Hyperprolactinemia

PITUITARY DISEASE
Prolactinomas
Acromegaly
Empty sella syndrome
Lymphocytic hypophysitis
Cushing disease
HYPOTHALAMIC DISEASE
Craniopharyngiomas
Meningiomas
Dysgerminomas
Nonsecreting pituitary adenomas
Other tumors/metastatic disease
Sarcoidosis
Eosinophilic granuloma
Chiari-Frommel syndrome
Encephalitis
Pituitary stalk section or compression
MEDICATIONS
Anesthetics, including cocaine
Opiates
Selective serotonin reuptake inhibitors
Phenothiazines
Benzodiazepines
Protease inhibitors
Prostaglandins
Tricyclic antidepressants
Atypical antipsychotics
α-Methyldopa
Reserpine
Metoclopramide
Marijuana
Herbal supplements (fennel, anise, fenugreek)
NEUROGENIC DISORDERS
Chest wall lesions/surgery
Spinal cord lesions
Breast stimulation
OTHER CAUSES
Pregnancy, postpartum, and postabortion
Hypothyroidism
ROHHAD
Chronic renal failure
Cirrhosis
Stress
Idiopathic disorders

ROHHAD, rapid-onset obesity, hypothalamic dysregulation, hypoventilation, and autonomic dysregulation.
Modified from Chanson P, Maiter D. Prolactinoma. In Melmed S (ed). *The Pituitary*. 4th ed. Philadelphia: Elsevier, 2017; 467-514.

poorly localized tenderness, and soreness radiating to the axilla and arm are usual accompanying findings. Treatments for mastalgia include utilization of a firm, supportive sports-type bra, heat, and analgesics (oral or topical). Low-dose combined estrogen/progestin oral contraceptives often improve the breast pain. A course of NSAIDs is also typically effective. The effect of caffeine and chocolate on mastalgia is controversial, but if pain is worsened with increased intake, they should be avoided. Evening primrose oil, vitamin E, and chamomile extract are popular but unproven treatments.

BREAST MASSES

Peripubertal Masses

Initial breast development at the onset of thelarche can be unilateral and asymmetric, with the developing breast bud being mistaken for a "mass." Such asynchronous thelarche should be recognized to avoid unnecessary biopsy and potential injury to the maturing breast. If there is any question as to the etiology of the lump, ultrasound can be used to evaluate for a mass.

Adolescent Breast Masses

The differential diagnosis for breast masses in the adolescent patient is broad (Table 588.3). The patient should be questioned about variations associated with the menstrual cycle, associated symptoms such as nipple discharge, recent trauma to the breast, family history of breast masses or cancer, and personal history of chest radiation or malignancy. Physical examination should characterize the mass location, size, and firmness and determine whether tenderness, skin changes, nipple discharge, or lymphadenopathy is present. Because breast cancer in the adolescent is extremely rare (3.2 cases per million person-years for women <25 years), masses in this population can often be expectantly managed for extended periods of time.

Fibroadenomas are the most common solid mass found in the adolescent breast. Fibroadenomas are slow-growing, hormonal dependent masses most often located in the upper, outer quadrant of the breast. The average size at diagnosis is 2-3 cm; 10–25% of patients have multiple lesions. On examination, these lesions are well circumscribed, rubbery, mobile, and not tender. Given the slow-growing nature and lack of malignant potential, conservative management is recommended for most patients. If expectant management is chosen, serial exams and/or ultrasounds every 6-12 months may be done to prove lack of progression or rapid growth. Fibroadenomas have defined sonographic characteristics; biopsy is not required to make the diagnosis. A subset of fibroadenomas behave differently and can be distinguished from their routine counterparts by rapidity of growth and excisional biopsy alone. **Juvenile fibroadenomas** (or **giant fibroadenomas**) grow rapidly over 3-6 months to >5 cm and can replace the breast tissue or cause skin necrosis. The distinction between these and **phyllodes tumor** on core needle biopsy is difficult, so excisional biopsy is the recommended intervention. The only true histologic difference between juvenile and routine fibroadenomas is hypercellularity. Surgical excision of fibroadenomas is recommended when a mass has complex ultrasonographic signs, is >5 cm or rapidly growing, or causes anxiety to the patient or their family. The presence of five or more fibroadenomas in an adolescent should prompt a genetic evaluation for *PTEN* pathogenic variant.

Breast cysts are common, often arising from ductal ectasia, glands of Montgomery, or lymphatic malformations. Ultrasound is used for diagnosis and surveillance. Simple cysts are usually self-limited. If a simple cyst persists, it may be aspirated with a needle. Aspirated fluid that is clear may be discarded. Bloody fluid and other aspirated material should be sent for cytologic examination. Cysts that resolve with aspiration should be reevaluated in 3 months by ultrasound. If they recur, biopsy or excision should be considered.

Table 588.3 Breast Masses in the Adolescent Female

Developmental	Unilateral thelarche Macromastia, simple Juvenile hypertrophy or gigantomastia Intramammary lymph node
Infectious	Mastitis Abscess
Traumatic	Fat necrosis Hematoma
Cystic	Fibrocystic change Vascular malformation (hemangioma, lymphatic malformation) Galactocele
Benign tumors	Fibroadenoma (simple or juvenile/giant) Lipoma Hamartoma Intraductal papilloma Juvenile papillomatosis
Malignant tumors	Cystosarcoma phyllodes Breast carcinoma (secretory or ductal) Metastatic disease (lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia)

Malignant Masses

Phyllodes tumors are classified as sarcomas and are the most common nonepithelial tumor of the breast. They are classified as benign, borderline, or malignant based on histopathology and are characterized by asymmetric breast enlargement in association with a firm, mobile, circumscribed mass. The tumor often grows rapidly and can become quite large, mimicking a giant or juvenile fibroadenoma. The majority of these tumors have a favorable prognosis, but malignant phyllodes can recur locally or with metastases. Excision with 1 cm margins is the preferred initial therapy in adolescent patients, regardless of the histologic classification of the lesion. Survival at 10 years approaches 90% after complete excision.

Juvenile papillomatosis is a rare proliferative tumor that often presents as a discrete mass. It is a marker for increased breast cancer risk in family members, and in patients with this condition, up to 15% may have a juvenile secretory carcinoma. Treatment of juvenile papillomatosis is total resection of the lesion with preservation of the breast. Family members of these patients should be screened.

Primary breast carcinoma is extremely rare in adolescents. Surveillance Epidemiology and End Results (SEER) data from 2015–2019 established an age-specific rate for female invasive breast cancer of 0.1/100,000 for ages <20 years. Although malignancy is rare, suspicion may be raised if a lesion is enlarging, hard, immobile, and poorly circumscribed. Biopsy of lesions with suspicious imaging findings (e.g., irregular shape or microlobulated/spiculated margins) or progressive growth is imperative. Contrary to adults with primary ductal carcinoma, 10-year survival is only slightly better than 50% in adolescents.

Rather than primary breast cancer, **secondary** cancers or **metastatic** tumors are more prevalent. Adolescents with previous *therapeutic radiation* to the chest or with malignancies with the potential to metastasize to the breast should be monitored more closely for breast masses. Rhabdomyosarcoma is the most common to metastasize to the breast. Other malignancies with risk of breast metastases include neuroblastoma, melanoma, renal cell carcinoma, and Ewing sarcoma. Breast tumors also may be the first manifestation of relapse (extramedullary) in acute lymphoblastic leukemia. Those with previous radiation therapy have increased risk of developing breast cancer at a young age and require careful ongoing surveillance.

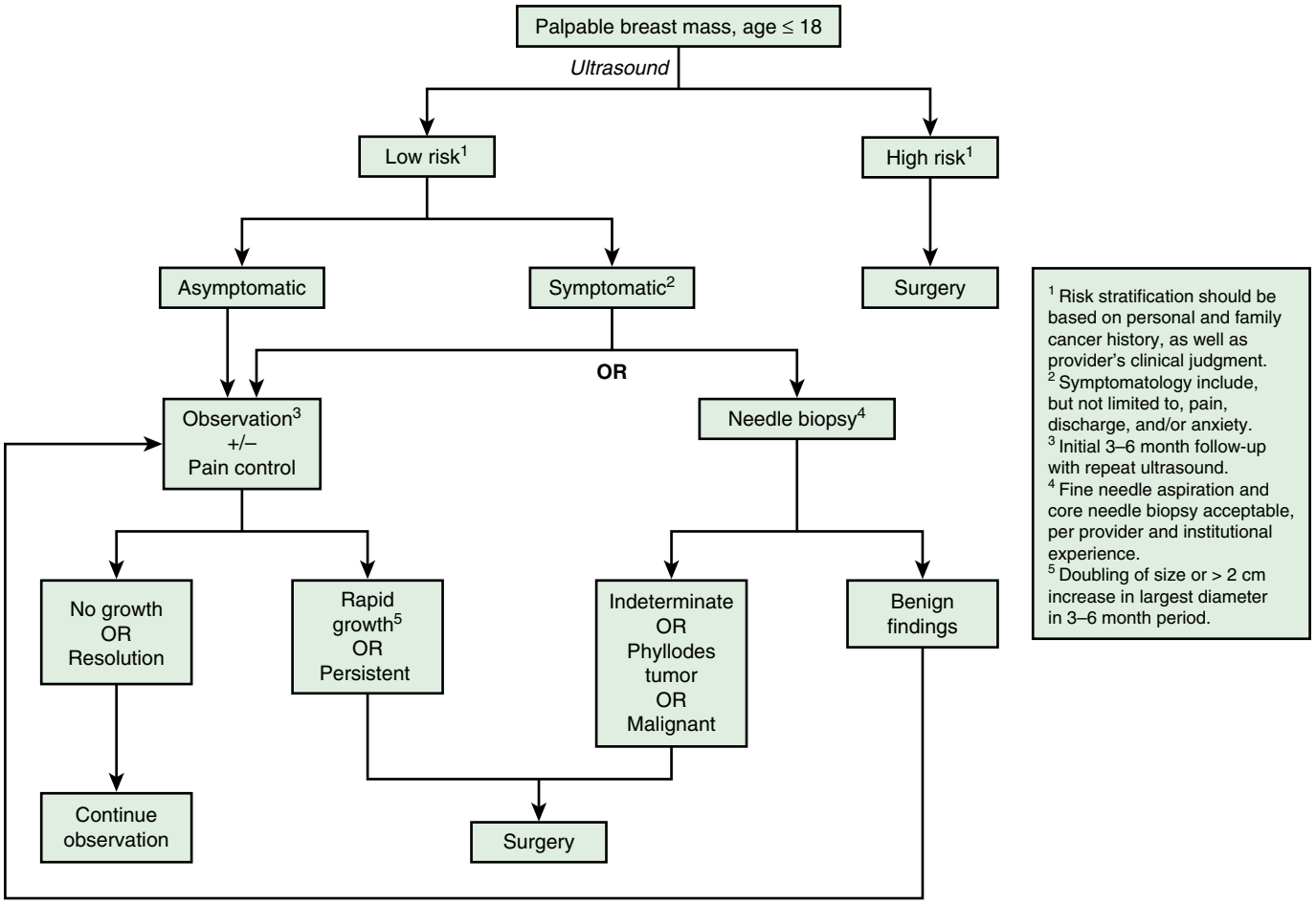

Fig. 588.6 Suggested clinical care algorithm for children presenting with a palpable breast mass. *(From McLaughlin CM, Gonzalez-Hernandez J, Bennett M, Piper HG. Pediatric breast masses: An argument for observation. J Surg Res. 2018;228:247-252; Fig 3.)*

Imaging of Breast Masses

Ultrasonography is the imaging modality of choice for palpable abnormalities in the pediatric and adolescent breast, given the diagnostic specificity and lack of ionizing radiation. MRI may be useful in select disease processes, but its use should be guided by a surgeon or oncologist. Because of the dense breast tissue in this patient population, there is no role for mammography.

MANAGEMENT OF BREAST MASSES

Figure 588.6 represents management algorithms for pediatric patients undergoing imaging for an identified breast mass. Core needle biopsy as a diagnostic tool is very sensitive but lacks specificity in distinguishing the hypercellular stroma of a juvenile fibroadenoma from a phyllodes tumor. Core needle biopsy should be recommended only for indeterminate masses, and based on co-decision-making between the patient, family, and clinician. Generally, observation and ultrasound surveillance should be the initial management for masses under 4 cm in size and excisional biopsy considered for those >4-5 cm.

Recommendations for Daughters of Women with Breast Cancer

Risk Reduction

There are a limited number of things that young people can do to lower their risk of breast cancer. The American Cancer Society recommends regular physical activity, limiting alcohol, eliminating cigarette smoking, and maintaining a healthy weight. Some studies have shown that breastfeeding for at least 1 year may slightly lower the breast cancer risk.

Screening Procedures

Screening mammography and/or ultrasound are not currently recommended in adolescents, regardless of family history. Routine testing of children and adolescents for the *BRCA1* and *BRCA2* pathogenic variants in families with a known history is also not typically recommended, because there are no guidelines for additional screening or treatment at this age, and *children* are very unlikely to develop a cancer related to an inherited *BRCA* variant.

Even in high-risk families, development of breast cancer below the age of 18 years is extremely rare. The American Cancer Society recommends a breast-screening regimen including mammography and MRI beginning at age 30 years for females with a known *BRCA* pathogenic variant or history of chest radiation between the ages of 10 and 30 years. Patients with an identified familial predisposition for malignancy should be referred for genetic evaluation to determine whether and/or when screening tests should occur. Any adolescent patient with a known primary breast malignancy should also be referred to a geneticist to be screened for pathogenic variants such as Li-Fraumeni (p53) or Cowden syndrome (*PTEN*).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 589

Polycystic Ovary Syndrome and Hirsutism

Heather G. Huddleston, Molly M. Quinn, and Mark Gibson

POLYCYSTIC OVARY SYNDROME

Etiology and Definition

Polycystic ovary syndrome (PCOS) is a common disorder of reproductive hormone function. The most widely accepted approach to the diagnosis of PCOS in adult females is the Rotterdam criteria, which require two out of three of the following features: **oligomenorrhea**, clinical or biochemical **hyperandrogenism**, and ovaries with a **polycystic morphology** on ultrasound examination (≥20 follicles in one ovary and/or ovarian volume >10 mm^3). Increased levels of antimüllarian hormone may be a marker of ovarian dysfunction and antral follicle count. Alternative criteria, such as the Androgen Excess Society and National Institutes of Health, place a greater emphasis on requiring hyperandrogenism be present (Table 589.1). The disorder, affecting 5–10% of females of reproductive age, depending on the diagnostic criteria used, typically emerges in adolescence when a normal menstrual pattern is not established and there is clinical evidence of androgen excess. Although not part of the *diagnostic* schemes, PCOS is often accompanied by cardiovascular disease risk factors, including insulin resistance, obesity, and dyslipidemia. Depression and anxiety have also been found to be more prevalent in females with PCOS.

Pathology, Pathogenesis, and Genetics

PCOS has a high concordance rate in twins, and in some studies either epigenetic or dominant inheritance patterns are observed. Nonetheless, a consistent hereditary pattern has not been identified.

Gonadotropic dysregulation with increased luteinizing hormone (LH) pulsatility and abnormally high ratios of circulating LH to follicle-stimulating hormone (FSH) are found in many patients with PCOS. Increased *ovarian* production of androgen in response to LH and impaired folliculogenesis owing to lower FSH are attributed to this gonadotropic pattern (Fig. 589.1). An increased ratio of circulating levels of LH:FSH is *not* a diagnostic criterion for PCOS.

Alterations in activities of steroidogenic enzymes that would explain *ovarian androgenic* hyperfunction are seen in PCOS subjects, but they are not consistently present in all patients, and it is unclear whether these alterations are a cause of PCOS or are a consequence of ovarian dysregulation. The size of ovarian stromal cells responsible for androgen production is increased; surgery that reduces this ovarian component (ovarian wedge resection or laparoscopic ablative procedures) reduces circulating androgen levels and often restores ovarian cyclicity. Patients with hyperandrogenic congenital or adult-onset adrenal hyperplasia exhibit PCOS-like ovarian dysfunction that can be reversed by reducing the *adrenal-derived* androgens with glucocorticoid therapy. A primary role for androgen excess in the pathophysiology of all instances of PCOS seems unlikely; many patients have minimal hyperandrogenism, and elimination of androgen excess (with gonadotropin-releasing hormone agonists) does not affect associated insulin resistance.

Measures of **insulin resistance** are greater and more prevalent among females with PCOS than controls even when accounting for body mass index (BMI). Insulin enhances ovarian androgen production directly and contributes to elevation of free testosterone levels through its suppression of hepatic production of sex steroid–binding globulin. Treatment with insulin sensitivity–enhancing agents that can reduce insulin levels is associated with modest reductions in measures of androgen excess and, in some patients, restoration of regular ovulation. The association of insulin resistance with weight might explain the appearance of features of PCOS among some females who gain weight, as well as the resolution of PCOS among affected females who lose weight.

Clinical Manifestations

PCOS, a lifelong disorder, commonly manifests as puberty progresses, but its onset can occur later, in young adulthood. Clinical hallmarks are menstrual abnormalities and manifestations of hyperandrogenism, but the severity of the disorder is variable (Table 589.2). Ovulation is typically irregular or absent, and menses are consequently irregular or absent. When menstrual bleeding does occur, it may be *anovulatory* bleeding, which is often heavy and/or protracted, resulting from an extended period of unopposed endometrial growth. Alternatively, bleeding can be relatively normal in character as a consequence of a preceding ovulation. Protracted spells of anovulation, with accompanying unopposed estrogen, are a risk factor for endometrial hyperplasia, and more severe premalignant and frankly malignant changes may eventuate. Hyperandrogenism is most commonly manifest as **hirsutism**, which is graded by the extent and locations of excessive male pattern hair growth (Fig. 589.2).

Obesity is common among individuals with PCOS. In some patients, the expression of features of PCOS is conditional on elevation of BMI and is reversible with weight loss. However, there is a subset of patients who present with a lean PCOS phenotype, and thus normal or low weight should not preclude consideration of the PCOS diagnosis. PCOS is associated with an increased prevalence of insulin resistance and type 2 diabetes independent of the tendency for many affected patients to have an elevated BMI. Additionally, PCOS confers a substantial and specific increase in risk for **metabolic syndrome** (hyperlipidemia, insulin resistance, type 2 diabetes) in adults as well as adolescent females after accounting for BMI.

Laboratory Findings, Diagnosis, and Differential Diagnosis

The diagnosis of PCOS requires exclusion of disorders that would otherwise account for hyperandrogenism and anovulation. Serum 17-hydroxyprogesterone should be measured when there is clear androgen excess to screen for adult-onset 21-hydroxylase deficiency (see Chapter 616). In the adolescent with amenorrhea but minimal hyperandrogenic findings, consideration should be given to functional hypothalamic suppression as a result of excessive exercise and/or dieting, and a careful history taken to rule out such behavioral patterns. All patients should be clinically evaluated for Cushing syndrome, and biochemical evaluation is indicated when clinical findings, including

Table 589.1 Diagnostic Criteria for Polycystic Ovary Syndrome in Adult Females*

NATIONAL INSTITUTES OF HEALTH CRITERIA	ROTTERDAM CRITERIA**	ANDROGEN EXCESS SOCIETY
Oligoovulation or anovulation *and* Clinical or biochemical hyperandrogenism	Two of three of the following: • Oligoovulation or anovulation • Polycystic ovaries on ultrasonography (20 or more follicles in a single ovary or ovarian volume of > 10 mm^3 in one ovary) • Clinical and/or biochemical hyperandrogenism	Clinical or biochemical hyperandrogenism and at least one of the following: • Polycystic ovaries *or* • Oligoovulation or anovulation

**In adolescents, diagnosis should be made when both hyperandrogenism and oligomenorrhea are present, with ultrasound criteria not required/recommended.

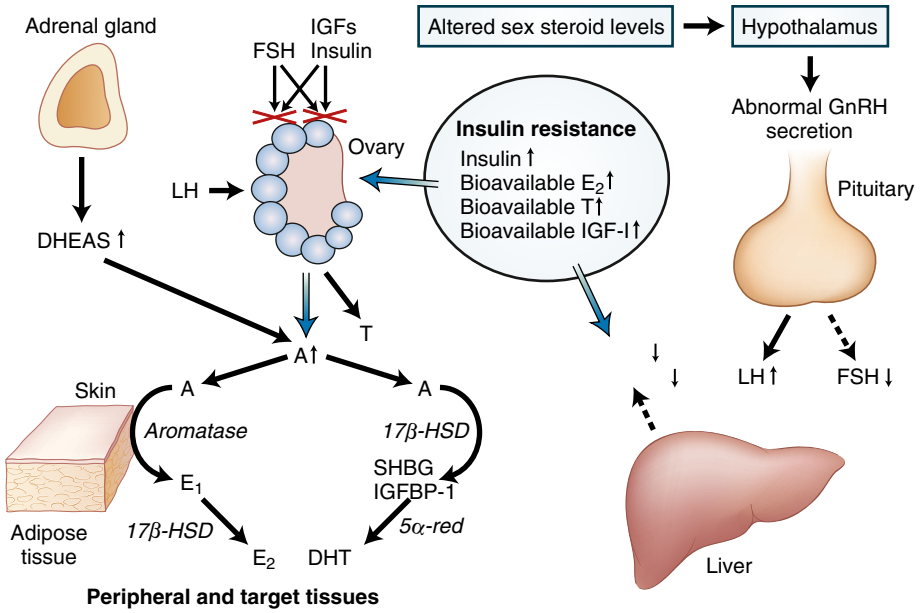

Fig. 589.1 Pathologic mechanisms in polycystic ovary syndrome (PCOS). A deficient in vivo response of the ovarian follicle to physiologic quantities of follicle-stimulating hormone (FSH), possibly because of an impaired interaction between signaling pathways associated with FSH and insulin-like growth factors (IGFs) or insulin, may be an important defect responsible for anovulation in PCOS. Insulin resistance associated with increased circulating and tissue levels of insulin and bioavailable estradiol (E_2), testosterone (T), and IGF-I gives rise to abnormal hormone production in a number of tissues. Oversecretion of luteinizing hormone (LH) and decreased output of FSH by the pituitary, decreased production of sex hormone–binding globulin (SHBG) and IGF-binding protein 1 (IGFBP-1) in the liver, increased adrenal secretion of dehydroepiandrosterone sulfate (DHEAS), and increased ovarian secretion of androstenedione (A) all contribute to the feed-forward cycle that maintains anovulation and androgen excess in PCOS. Excessive amounts of E_2 and T arise primarily from the conversion of A in peripheral and target tissues. T is converted to the potent steroids estradiol or DHT (dihydrotestosterone). Reductive 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme activity may be conferred by protein products of several genes with overlapping functions; 5α-reductase (5α-red) is encoded by at least two genes, and aromatase is encoded by a single gene. GnRH, Gonadotropin-releasing hormone. *(From Bulun SE. Physiology and pathology of the female reproductive axis. In Melmed S, Auchus RJ, Goldfine AB, eds. Williams Textbook of Endocrinology, 14th ed. Philadelphia: Elsevier, 2020. Fig 17-30.)*

Table 589.2 Phenotypes for Polycystic Ovary Syndrome Based on 2003 Rotterdam Criteria

SIGNS, RISKS, AND PREVALENCE	SEVERE PCOS	HYPERANDROGENISM AND CHRONIC ANOVULATION	OVULATORY PCOS	MILD PCOS
Periods	Irregular	Irregular	Normal	Irregular
Ovaries on ultrasonography	Polycystic	Normal	Polycystic	Polycystic
Androgen concentrations	High	High	High	Mildly raised
Insulin concentrations	Increased	Increased	Increased	Normal
Risks	Potential long term	Potential long term	Unknown	Unknown
Prevalence in affected females	61%	7%	16%	16%

PCOS, Polycystic ovary syndrome.
From Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007;370(9588):685-697.

hypertension and/or characteristic exam features, are suggestive (see Chapter 619). The two disorders have in common a tendency for overweight and varying degrees of insulin resistance and androgen excess, but they differ in that Cushing syndrome demonstrates muscle wasting as a result of catabolism.

Evidence for androgen excess that is *rapid in onset and/or severe,* especially if masculinizing, warrants measurement of androgens (total testosterone, dehydroepiandrosterone [DHEAS]) to exclude the possibility of an androgen-secreting adrenal or ovarian tumor. The laboratory evaluation is completed with the exclusion of hyperprolactinemia, premature ovarian failure, and thyroid disease as causes of anovulation by measurement of prolactin, FSH, and thyroid-stimulating hormone, respectively.

The diagnosis of PCOS in reproductively mature females (at 8 years post menarche) is confirmed by the constellation of oligoovulation or anovulation, androgen excess (clinically or with biochemical confirmation), and typical ovarian morphology on ultrasound. Various experts weigh these three features differently and do not, as a rule, require the presence of all (see Table 589.1). Antimüllarian hormone levels are elevated in PCOS and may be a marker for ovarian dysfunction and cyst formation. Other recommendations have clarified that ultrasound features need not be assessed in adolescents, because normative values for ovarian anatomy have not been established. Indeed, young females often exhibit the multifollicular ovaries without any evidence of hyperandrogenism or oligomenorrhea, and not all patients with PCOS by the criteria of hyperandrogenism and ovulatory disruption exhibit ovarian changes typical of PCOS. *Therefore in the adolescent, diagnosis should only be made when both oligomenorrhea and hyperandrogenism are present and other causes of these symptoms have been ruled out.* Findings of anovulatory cycles and hyperandrogenism, particularly acne, may accompany the normal pubertal transition.

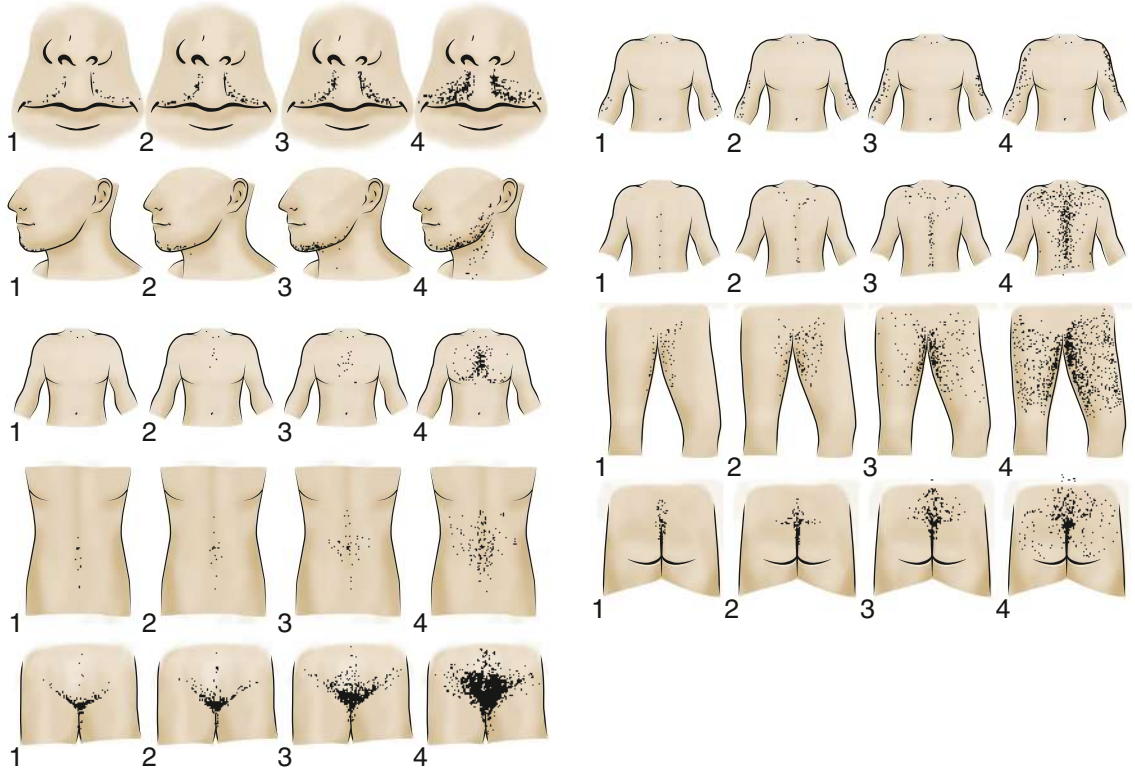

Fig. 589.2 Gender-neutral modified Ferriman-Gallwey (mFG) diagram. *(From Grimstad F, Moyer Q, Williams CR, Kremen J. A body-neutral and gender-neutral modified Ferriman-Gallwey diagram. J Pediatr Adolesc Gynecol. 2021;S1083-318800334-X. Fig 2.)*

For this reason, it is recommended that a formal PCOS diagnosis not be considered until at least 2 years post menarche. Adolescents with features of PCOS before this time can be considered "at risk" for PCOS, and a plan can be made for reevaluation in the future.

Insulin resistance is common among females with PCOS, and although not requisite for diagnosis, it should be considered when PCOS is identified. Adults, as well as adolescents, with hyperandrogenemia and anovulation should be evaluated for diabetes or impaired glucose tolerance with a 2-hour (75-g glucose load) glucose tolerance test.

Complications and Long-Term Outlook

Management of the features of hyperandrogenism, assistance with fertility, prevention of endometrial cancer, and reduction in the likelihood and severity of the common accompanying risk for the metabolic syndromes are long-term tasks for the PCOS patient and their healthcare providers (Table 589.3). Although there is a tendency for symptoms to ameliorate as menopause approaches, PCOS usually requires management throughout the reproductive years. Young patients should be counseled that modern fertility management allows most affected females to have children without great difficulty, and they should also know that the disorder does not confer reliable protection from unintended pregnancy. Endometrial cancer can develop as early as the third decade in females with PCOS who are not managed with progestins or ovulation induction; thus patients should understand the importance of long-term strategies for endometrial protection. Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome are more common in females with PCOS compared to weight-matched controls. Metabolic disturbance can manifest as early as adolescence, and the prevalence increases over time. Weight control through diet and lifestyle measures, detection and management of impaired glucose tolerance and diabetes, and management of abnormal lipids are targets for long-term management.

Table 589.3 Lifelong Health Complications of Polycystic Ovary Syndrome

PRENATAL OR CHILDHOOD	ADOLESCENCE, REPRODUCTIVE YEARS	POST-MENOPAUSAL
REPRODUCTIVE		
Premature adrenarche Early menarche	Menstrual irregularity Hirsutism Acne Infertility Endometrial cancer Miscarriage Pregnancy complications	Delayed menopause
METABOLIC		
Abnormal fetal growth	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes
OTHER		
	Sleep apnea Fatty liver Depression	Cardiovascular disease risk factors

From Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007;370(9588):685-697.

Treatment

The management of PCOS is multifaceted and depends on the specific complaints of the patient. Primary goals include management of menstrual abnormalities, treatment of symptoms of androgen excess, and optimization of metabolic health. Weight loss through lifestyle

change, use of hormonal contraceptive agents for menstrual regulation as well as androgen suppression, antiandrogens as adjuncts for hirsutism treatment, and insulin-sensitizing agents are common components of treatment.

Lifestyle Changes

Comprehensive lifestyle programs for overweight and obese adults with PCOS aimed at fitness and weight loss can yield restoration of normal menstrual function in some patients. Lifestyle changes also lead to a reduction in the free androgen index, reduction in measures of insulin resistance, and improvement in serum lipids. Limited data show similar benefits from such interventions for obese adolescents with PCOS. Successful weight loss programs for adolescents with PCOS using both psychologic and nutritional counseling may result in improved menstrual function.

Hormonal Contraceptives

Combined (estrogen and progestin) hormonal contraceptive medications are considered first-line therapy for patients not desiring fertility (see Chapter 160). Avoidance of hyperplastic endometrial states resulting from unopposed estrogen and management of abnormal uterine bleeding in anovulatory episodes can be accomplished with the use of combined hormonal contraceptives. The progestational component inhibits endometrial proliferation, and the schedule of pill administration predictably regulates menstrual bleeding. The estrogenic component of the combined oral contraceptive elevates circulating sex hormone–binding globulin (SHBG), which reduces free and bioavailable testosterone levels. Both of the hormonal elements in oral contraceptives combine to suppress gonadotropic (particularly LH) stimulation of ovarian androgen production. DHEAS levels, often contributory to hyperandrogenemia in PCOS, are usually decreased by combined contraceptive use. Products with less androgenic progestational components (drospirenone, desogestrel) may provide better relief from androgenic symptoms.

Using hormonal contraception that is well tolerated in long-term use is more important than using a product with a particular progestational component. Products with reduced frequency and duration of pill-free intervals can provide superior androgen suppression and a welcome decrease in the frequency of bleeding episodes. Depot medroxyprogesterone acetate for contraception, endometrial protection, and androgen suppression may be a suitable alternative to combined hormonal contraceptives; it provides even more profound suppression of ovarian androgen production, but it does not elevate SHBG. Low-dose progestin-only regimens (oral minipills, implantable progestational contraceptives, and progestin-releasing intrauterine devices) also provide effective endometrial protection but would be expected to provide only partial and/or inconsistent androgen suppression and would not elevate SHBG.

Patients without the need for management of hyperandrogenic symptoms or contraception are often treated with periodic use of oral progestins to induce predictable menstrual bleeding and prevent endometrial hyperplasia and malignancy. Twelve-day courses of medroxyprogesterone acetate 10 mg daily or norethindrone acetate 5 mg daily are effective and safe for this purpose when taken every 1-2 months.

Oral contraceptives also provide the added benefit of contraception. Given the relative infrequency of ovulation, fertility in females with PCOS would be expected to be reduced relative to that of their peers, but they are still at risk for pregnancy and should be counseled accordingly.

Metformin

Metformin is a biguanide medication used to treat type 2 diabetes, which is its only FDA-approved indication. It has been used in a variety of settings and with differing objectives for patients with PCOS. Metformin exerts its principal effect by reducing hepatic production of glucose and limiting intestinal absorption of glucose. A subset of females with PCOS resume regular ovulation and menses when treated with metformin, obviating the need for progestational therapy to protect endometrial health or medications to induce ovulation. For some patients, the resulting normal reproductive function is appealing regardless of interest in fertility.

Metformin reduces insulin resistance and the levels of androgens. Its extended use can reduce the likelihood of development of impaired glucose tolerance or the progression of impaired glucose tolerance to type 2 diabetes; these effects are not yet proven for patients with PCOS. It should not be used in the presence of renal or hepatic impairment. Typical dosing is 1,500-2,000 mg/day, achieved through gradual increments because gastrointestinal intolerance is common. Long-acting preparations are helpful when gastrointestinal intolerance is a problem. The use of metformin in the treatment of PCOS depends on the patient's goals and preference. For the treatment of hyperandrogenic symptoms, metformin effects may be modest compared with other available agents. There are no empirical data supporting the theoretical benefits of long-term use of metformin in adolescents with PCOS and obesity compared with the outcomes achieved with weight loss and oral contraceptive medications. Use of metformin as a first-line agent is favored by some experts, in part for improvement in serum measures of intermediate outcomes, and in part because of evidence in other populations of reduced progression of insulin resistance. There is no evidence for a long-term benefit for clinical outcomes of adding metformin to treatment for patients managed primarily with oral contraceptives. For adolescents receiving metformin as a first-line medication, some element of progestational management (combined contraceptives or periodic progestins) will still be necessary for those not resuming ovulatory function, and oral contraceptives may still be an important adjunct for management of clinical hyperandrogenism and/or contraception. Metformin side effects include nausea, emesis, and diarrhea; more serious effects include lactic acidosis and vitamin B12 deficiency. Glucagon-like peptide receptor agonists are being studied as a possible add on therapy to metformin or as a single agent to treat PCOS.

Antiandrogens

Antiandrogenic medications may be added to other therapies or used alone for the treatment of hirsutism. These agents are usually used adjunctively with ovarian hormonal suppression, in part because of better reduction in hirsutism when antiandrogens are combined with ovarian suppression but also to reduce the risk of unintended embryonic or fetal exposure. The highly active androgen antagonist and progestin, cyproterone, is available in Europe and in Canada as a single agent for treatment of hirsutism or in combination with ethinyl estradiol as an oral contraceptive with enhanced antiandrogenic profile. In the United States, spironolactone is the most commonly used antiandrogen. Spironolactone antagonizes androgens at their receptor and also impairs androgen synthesis. Doses of 100-200 mg daily are commonly used. Other agents that have been studied are finasteride, a 5α-reductase inhibitor, and flutamide, a nonsteroidal and highly specific androgen receptor antagonist. These are rarely used because of lack of evidence of superior effectiveness, cost, and, in the case of flutamide, the potential for hepatotoxicity.

HIRSUTISM

Hirsutism is defined as abnormally increased terminal (mature, heavy, dark) hair growth in areas of the body where hair growth is normally androgen dependent (see Chapter 703). Its presence is a result of the combination of the extent of androgenic stimulation and familial regional follicle sensitivity to androgens, which varies considerably among ethnic groups. Patients' cosmetic concerns generally determine whether findings of hirsutism are a matter for clinical investigation and treatment. Hirsutism as an isolated finding is to be distinguished from **masculinization.** The latter includes alteration in muscle mass, clitoral enlargement, and voice change, generally manifesting as a rapid

Table 589.4	Treatment of Hirsutism
SYSTEMIC THERAPIES	
Suppression of androgen production	
Combined oral contraceptives (ethinyl estradiol + progestin with low androgenic activity)	
Androgen blockers	
Spironolactone	
Finasteride	
Flutamide	
Cyproterone acetate (not available in the United States)	
COSMETIC STRATEGIES	
Temporary measures	
Shaving, bleaching, chemical depilation	
Permanent measures	
Electrolysis	
Laser therapy	

evolution (over months). *Masculinization mandates a search for a neoplastic source of androgen.* Elevations of testosterone or DHEAS commonly indicate an ovarian or adrenal androgen source, respectively; specific imaging and occasionally selective catheterization studies are indicated (see Chapters 590 and 617).

Hirsutism without masculinization is common. The potential causes to consider are PCOS (when there is hyperandrogenism and anovulation), benign functional androgen excess (measurable hyperandrogenism without anovulation), idiopathic hirsutism (increased hair in androgen-dependent areas without measurable androgen excess), and adult-onset adrenal hyperplasia. Patients can be primarily distinguished by evidence of an ovulatory disorder by menstrual history, and for those with absent or irregular menses, a diagnosis of PCOS can be made. The remainder, for whom adult-onset adrenal hyperplasia and PCOS have been excluded, either have normal androgen levels with enhanced end-organ sensitivity owing to familial or ethnic predisposition or have a functional and benign overproduction of ovarian androgens. Measures of androgens (testosterone, DHEAS) may be normal or mildly elevated in the latter group. Testosterone suppresses circulating sex-steroid binding globulin, so states of testosterone overproduction might not be accompanied by elevated measures of total testosterone, although estimates of "free" or "bioavailable" testosterone reveal hyperandrogenism. Measures of unbound testosterone distinguish idiopathic hirsutism from mild benign hyperandrogenic states; making this distinction contributes little to patient management and adds cost. Idiopathic hirsutism (without evidence of androgen excess) usually responds to antiandrogen or androgen suppression therapy similarly to hirsutism associated with elevated androgens and anovulation (PCOS) and benign hyperandrogenism not associated with PCOS.

If hirsutism is present, and clinical evaluation excludes neoplasm, adult-onset adrenal hyperplasia, and Cushing syndrome, then management for symptoms of hyperandrogenism (regardless of whether measures of circulating androgens are elevated or not) can proceed as for patients with PCOS (Table 589.4). Estrogen and progestin suppression of ovarian function, with or without added antiandrogen treatment, is the mainstay of therapy for these patients. Androgen suppression and/or antagonism results in gradual regression of the size and productivity of follicles in androgen-sensitive areas of the face and body, and these changes will evolve over successive and months-long generations of hair growth and shedding. Patients should therefore be advised that the effects of medical therapy accrue slowly, over many months.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 590

Gynecologic Neoplasms and Prevention Methods for Human Papillomavirus Infections in Adolescents

Joan R. Tymon-Rosario, Levent Mutlu, and Alla Vash-Margita

OVERVIEW OF GYNECOLOGIC MALIGNANCIES IN CHILDREN AND ADOLESCENTS

Cancer is the second most common cause of death in children and adolescents, surpassed only by childhood injuries. The highest death rate is in the 5- to 14-year-old age group. Although rare, gynecologic malignancies can result in long-term sequelae such as infertility, depression, and a poor self-image, which may cause significant morbidity.

In children and adolescents younger than 18 years, ovarian cancer accounts for 87.5% of gynecologic malignancies, vaginal cancer for 4.5%, cervical cancer for 3.9%, uterine cancer for 2.5%, and vulvar cancer comprises 1.6% of all gynecologic cancers.

Ovarian cancers usually manifest as an abdominal or pelvic mass with acute or chronic lower abdominal pain and/or menstrual irregularities. The diagnostic workup includes a physical exam and laboratory tests such as a urine pregnancy test, hormone levels, and tumor markers. The preferred initial method of imaging is transabdominal pelvic ultrasonography. The differential diagnosis includes gynecologic tumors, other abdominal and pelvic organ-based tumors, and functional, physiologic, inflammatory/infectious, or pregnancy-related ovarian pathology. Although the majority of ovarian neoplasms are benign, approximately 9–33% of all pediatric or adolescent ovarian neoplasms are malignant. Ovarian neoplasms constitute 1.3% of all childhood malignancies but account for 60–70% of all gynecologic malignancies in this age group. Germ cell tumors are the most common type of neoplasm. Less often, the vagina or cervix is a site of malignant lesions in children, with a few specific tumors having their greatest incidence in this population. Vulvar and endometrial malignancies in children and adolescents are exceedingly rare.

IMPACT OF CANCER THERAPY ON FERTILITY

The treatment of gynecologic cancer, depending on the type and extent of disease, may include fertility-sparing cytoreductive surgery with adjuvant chemotherapy, definitive surgery including bilateral salpingo-oophorectomy, and comprehensive surgical staging, radiation, and/or secondary salvage surgery. Fertility-sparing surgery is defined as unilateral salpingo-oophorectomy, lymph node sampling, and omentectomy, whereas maximal cytoreduction includes hysterectomy and contralateral salpingo-oophorectomy. For malignant ovarian germ cell tumors, the most common adolescent gynecologic malignancy, the use of fertility-sparing surgery, is seen as the gold standard. This approach achieves a good prognosis, and the majority of patients achieve normal hormonal function and future pregnancies. Importantly, it does not seem to be associated with lower progression-free survival, overall survival, or mortality rates compared with radical surgery.

Platinum-based chemotherapeutic regimens are most often used for malignant ovarian tumors. The need for chemotherapy and radiation therapy is associated with acute ovarian failure, premature menopause, and infertility (Table 590.1). Risk factors include older age, abdominal or spinal radiation, and certain chemotherapeutic drugs, such as

Table 590.1 Effect of Cancer Treatment on the Development of Amenorrhea

TREATMENT	AGENT/MODALITY	IMPACT	TREATMENT FOR
Protocols containing nonalkylating agents or lower levels of alkylating agents	ABVD, CHOP, COP, multiagent therapies for leukemia	LOWER RISK <20% of women develop amenorrhea posttreatment	Non-Hodgkin lymphoma Leukemia
Protocols containing	Multiagent therapies using vincristine	VERY LOW/NO RISK No effect on menses	Leukemia Lymphomas
Protocols containing	Procarbazine MOPP and BEACOPP 3 cycles >6 cycles	HIGH RISK More than 80% develop amenorrhea posttreatment	Hodgkin lymphoma
Protocols containing	Temozolomide or BCNU + cranial radiation	HIGH RISK More than 80% develop amenorrhea posttreatment	Brain tumor
Abdominal or pelvic radiation	10-15 Gy in prepubertal females 5-10 Gy in postpubertal females	INTERMEDIATE RISK 30–70% of women develop amenorrhea posttreatment	Acute lymphoblastic leukemia Brain tumor Neuroblastoma Non-Hodgkin lymphoma Hodgkin lymphoma Spinal tumor Wilms tumor
Whole abdominal or pelvic radiation	>15 Gy in prepubertal females >10 Gy in postpubertal females >6 Gy in adult women	HIGH RISK More than 80% develop amenorrhea posttreatment	
Total cyclophosphamide	5 g/m^2 in women >30 yr 7.5 g/m^2 in women and females <20 yr	HIGH RISK More than 80% develop amenorrhea posttreatment	Non-Hodgkin lymphoma
Any alkylating agent + pelvic radiation	Busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine	HIGH RISK More than 80% develop amenorrhea posttreatment	Ovarian cancer Sarcoma
Any alkylating agent + total body irradiation	Busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine	HIGH RISK More than 80% develop amenorrhea posttreatment	Lymphomas Myelomas Choriocarcinoma Ewing sarcoma, neuroblastoma
Any cancer requiring bone marrow transplant/stem cell transplant		HIGH RISK More than 80% develop amenorrhea posttreatment	Hodgkin lymphoma Non-Hodgkin lymphoma Acute myeloid leukemia Chronic myeloid leukemia Myeloma Acute lymphoid lymphoma Chronic lymphoid lymphoma Some solid tumors (e.g., breast, ovarian, kidney, brain)

ABVD, Doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COP, cyclophosphamide, vincristine, prednisone; MOPP, mechlorethamine, vincristine, prednisone, procarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BCNU, carmustine; Gy, gray.

Adapted from Female Fertility Preservation LIVESTRONG, a registered trademark of the LIVESTRONG Foundation. https://www.livestrong.org/we-can-help/just-diagnosed/female-fertility-preservation.

alkylating and platinum-based agents (cisplatin, cyclophosphamide, busulfan). Uterine irradiation is associated with infertility, spontaneous pregnancy loss, and intrauterine growth restriction. The vagina, bladder, ureters, urethra, and rectum can also be injured by radiation. Vaginal shortening, vaginal stenosis, urinary tract fistulas, and diarrhea are potential side effects of pelvic irradiation.

Advancements in oncologic treatments of gynecologic and systemic tumors have led to improvements in childhood cancer survival rates. Unfortunately, with these advances come an increase in short- and long-term adverse effects, which include gonadotoxicity and infertility. Approximately 15% of *all* childhood cancer survivors experience infertility, and pregnancy outcomes appear to be influenced by prior chemotherapy and radiation treatment (see Chapter 543). Cancer survivors have an increased rate of spontaneous abortion, premature delivery, and low birthweight infants compared with their healthy siblings. No data support an increased incidence of congenital malformations in offspring. Individualized risk of infertility should be discussed before gonadotoxic therapies and options for fertility preservation should be made available to all patients, with referrals to reproductive specialists and mental health professionals as appropriate. Multiple recommendations specifically address the pediatric population, stating that parents/guardians should be allowed to act for and consent in the interest of their minor children.

Mature oocyte and embryo cryopreservation are both standard of care preservation options available to postpubertal females with ample time before treatment to allow for ovarian stimulation (2-6 weeks). Ovarian tissue cryopreservation (OTC) is the only available option for prepubertal females. OTC is also an option for fertility preservation for postpubertal females with time-limiting treatment plans. The safety and feasibility of OTC and transplantation after nonsterilizing chemotherapy and in select leukemia survivors have been favorable, and there have been over 130 live births reported after orthotopic transplantation

of previously cryopreserved and thawed ovarian tissue as of 2017. Laparoscopic ovarian transposition can be used before radiation therapy where a high risk of ovarian radiation exposure in its anatomic position is expected. Hormone suppression with gonadotropin-releasing hormone (GnRH) analogs has been investigated as a means of fertility preservation, but evidence is lacking as to its efficacy.

Gonadotoxicity can also lead to primary ovarian insufficiency, which is associated with an increased risk for cardiovascular complications, osteoporosis, and difficulties with sexual function. Risks and benefits of hormone replacement therapy should be addressed as appropriate.

NEONATAL AND PEDIATRIC OVARIAN CYSTS

Normal follicles or physiologic ovarian cysts can be seen by ultrasound examination of the ovaries in healthy neonates, infants, and prepubertal females. The true incidence of neonatal cysts is unknown, but most are physiologic. Ovarian cysts are often detected during prenatal imaging and should be differentiated from masses originating from the urinary or gastrointestinal (GI) tract. Ovarian cysts that are less than 2 cm, sonolucent, and have a simple appearance on ultrasound are most likely physiologic. Simple neonatal ovarian cysts will resolve spontaneously and should be followed with observation. Larger cysts may be seen; in these cases, the interval to complete resolution is usually longer. Because of the risk of **ovarian torsion** and resultant autoamputation of the ovary, treatment modalities have been developed to prevent ovarian torsion, including ultrasound-guided aspiration, laparoscopic cystectomy, and detorsion, with the goal of ovarian preservation. Oophorectomy should be avoided. Treatment is usually reserved for the postnatal period unless the cyst is large enough to prevent embryonic development. Similarly, intervention might be necessary if the cyst is large enough to complicate delivery or if there is concern for compromise of the other organs because of the mass effect. If a conservative approach is chosen, serial ultrasonographic evaluation is reasonable until resolution in the prenatal and neonatal period. In the neonatal period, aspiration is an option for cysts that are larger than 6 cm and persistent over 4 months. Surgical exploration is generally reserved for complex, symptomatic, or enlarging cysts, with a great deal of effort exerted to preserve the surrounding normal ovary.

In **prepubertal** children, ovarian cysts are rare and, if present, usually asymptomatic and hormonally inactive. However, a careful exam is indicated because prepubertal ovarian cysts may be associated with peripheral precocious puberty. If symptomatic, cysts might present as an abdomino-pelvic mass resulting in pain, constipation, or urinary frequency. In **adolescents**, ovarian cysts are common and usually represent normal follicular development.

Cysts that are simple appearing, without septations or internal echogenicity, and less than 10 cm on transabdominal ultrasound are almost always benign, and observation is preferred (Fig. 590.1). Careful counseling and patient education should be provided for early recognition of complications related to ovarian cysts, such as cyst rupture and ovarian torsion. Unless associated with intractable symptoms or intraabdominal bleeding because of cyst rupture, cysts can be managed conservatively. Large ovarian cysts pose a risk of ovarian torsion. *Ovarian torsion* is a surgical emergency and can happen with ovarian cysts of any size, although the risk increases in adnexal masses larger than 5 cm. Rarely, torsion of the adnexa can occur without presence of an ovarian cyst, which is more common in prepubertal patients.

Functional Cysts

Over the course of several menstrual cycles, a **dominant follicle** forms and increases in size. After ovulation, the dominant follicle becomes a corpus luteum that, if it bleeds, is termed a **hemorrhagic corpus luteum**. These can become symptomatic owing to size or peritoneal irritation, and they have a characteristic complex appearance on ultrasound. Expectant and symptomatic management for a presumed functional or hemorrhagic cyst is appropriate. Physiologic cysts are usually ≤5 cm and resolve over the course of 6-8 weeks or several menstrual cycles without the need for any intervention. Monophasic oral contraceptives can be used to suppress future follicular development and prevent formation of additional cysts. When a cyst is found on ultrasound, a pregnancy test should be obtained because an adnexal mass on imaging could represent either a corpus luteum cyst that physiologically supports a normal pregnancy or an abnormal pregnancy state such as an ectopic pregnancy in the adnexa.

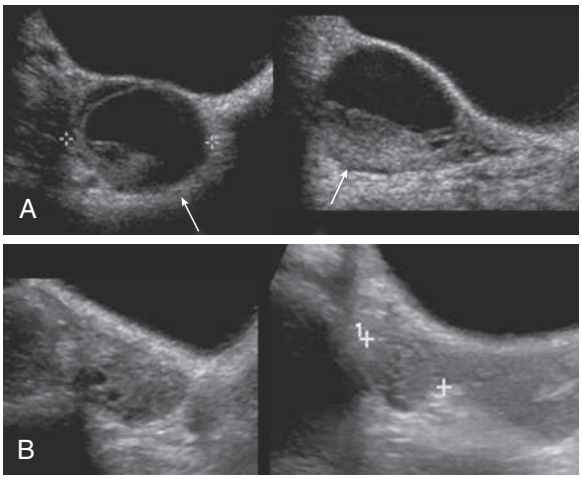

Fig. 590.1 Ovarian cyst. 14-yr-old female with pelvic pain. **A,** Transverse and sagittal images from a transabdominal pelvic ultrasound demonstrate a well-circumscribed cystic lesion in the right adnexa with a fluid–debris level *(arrows).* **B,** Follow-up imaging 6 weeks later demonstrates complete resolution of the cyst. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017:186; Fig. 6.70.)*

OVARIAN NEOPLASMS

Teratomas

Ovarian teratomas are the most common pediatric ovarian neoplasm and account for 25% of all pediatric teratomas. Aberrant migration and differentiation of primordial germ cells from the yolk sac to the gonadal ridge during embryogenesis is considered to be the embryologic origin of teratomas. Ovarian teratomas are usually asymptomatic but may become quite large and present with abdomino-pelvic pain and a palpable mass; ovarian torsion may be the initial presenting symptom. Ovarian teratomas are usually unilateral, but about 10% of cases are bilateral. **Mature cystic teratomas** (**dermoid cysts**) account for more than 95% of all teratomas. Depending on the germ layers, teratomas can be polydermal or monodermal and may contain mature tissue of ectodermal (skin, hair, sebaceous glands, neuroectodermal tissue), mesodermal (muscle, bone, cartilage, fat, teeth), and/or endodermal (thyroid, salivary, respiratory, GI) origin (Fig. 590.2). Mature teratomas are usually benign; malignant transformation is reported in less than 2% of the cases. Although any of the components of the mature teratoma can undergo malignant transformation, the most common secondary neoplasm arising from mature teratoma is squamous cell carcinoma. Teratomas have a characteristic sonographic appearance that includes findings such as fluid-fluid levels, Rokitansky nodules (a solid protuberance projecting from an ovarian cyst), echogenic sebaceous material, calcification, and hyperechoic regions. On abdominal radiograph, calcification is often a hallmark for teratomas. Ultrasound has a high sensitivity and specificity for diagnosing dermoid cysts with excellent diagnostic accuracy. Monodermal teratomas are rare and contain elements originating from a single germ cell layer. **Struma ovarii** is a monodermal teratoma that is composed of mature thyroid tissue that may result in clinically overt hyperthyroidism. **Ovarian carcinoid tumors** are another example of a monodermal teratoma. These rare tumors are generally associated with a mature teratoma but can be encountered in a pure form as a monodermal teratoma in a minority of cases. Approximately 30% of the time, clinical signs of carcinoid syndrome such as diarrhea, flushing, abdominal pain, and wheezing

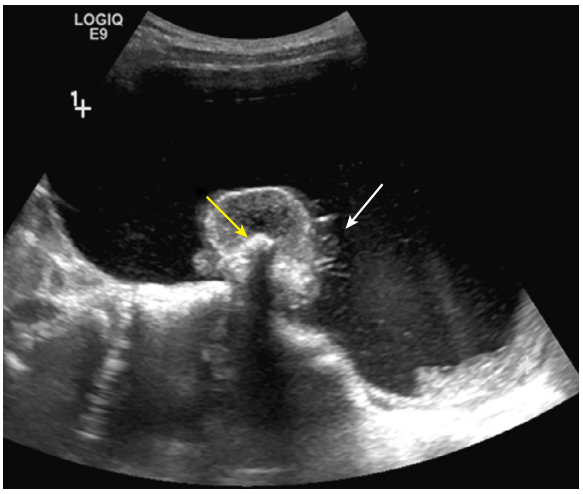

Fig. 590.2 Mature teratoma. 12-yr-old female with increasing abdominal girth. Transabdominal pelvic ultrasound image demonstrates a large pelvic mass with cystic and solid components. There is a rounded echogenic area in the center of the large, hypoechoic cystic portion. A central dense echogenic focus *(yellow arrow)* demonstrates posterior acoustic shadowing, consistent with calcification. Tiny linear echogenic foci *(white arrow)* are also associated with the central echogenic mass, representing hair. This constellation of findings is seen with a mature teratoma or dermoid cyst. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017: 187; Fig. 6.71.)*

may be present because of vasoactive amines secreted by the carcinoid tumors.

Benign teratomas can be observed if they are asymptomatic and small (<5 cm). However, when they are large or symptomatic, they should be surgically resected to prevent torsion or rupture, with preservation of the surrounding healthy ovarian parenchyma. Cystectomy is the treatment of choice, and minimally invasive techniques are increasingly used. Rupture of the cyst should be avoided as much as possible because of concerns for chemical peritonitis secondary to fatty acids of a teratoma and the rare risk of inadvertent upstaging of an occult carcinoma. During surgery, both ovaries should be evaluated for lesions. Intraoperative concern for a malignant lesion should prompt an evaluation of both the gross specimen and frozen section by pathology because malignant transformation of mature teratomas can occasionally occur.

An **immature teratoma (IT)** of the ovary is an uncommon tumor, accounting for <1% of ovarian teratomas. In contrast to the mature cystic teratoma, which is encountered most often during the reproductive years but occurs at all ages, IT has a specific age incidence, occurring most commonly in the first 2 decades of life. IT contain cells originating from three germ cell layers, but in contrast to mature teratomas, these elements have varying degrees of maturation. IT are histologically separated into three categories based on the proportion of the immature neural elements. Grade 3 IT have the highest percentage of immature neural elements, which correlates with the greatest risk of extraovarian spread. The presence of a yolk sac component also confers a higher risk of extraovarian spread. Clinically, IT present similarly to mature teratomas with pelvic pain or a mass. There is an association of dermoid tumors with neural elements and *anti–N-methyl-D-aspartase receptor (anti-NMDAR) encephalitis*. Patients may present with flu-like symptoms and progress to psychiatric and cognitive symptoms, autonomic instability, and seizure activity (see Chapter 638). The sonographic appearance of IT is nonspecific but is typically a heterogenous, partially solid mass with coarse calcifications.

Although the data are scant in the pediatric population, the stage and grade of the IT ultimately determines the treatment approach. Surgical staging for germ cell tumors in the pediatric population may differ from the adult population, and surgical staging in pediatric patients include collection of ascites and pelvic washings, examination of peritoneal surfaces with biopsy and excision of any nodules, examination of lymph nodes with sampling of any firm/enlarged lymph nodes, inspection/palpation of omentum with biopsy of any abnormal areas, and unilateral oophorectomy with preservation of the fallopian tube if uninvolved. It should be emphasized that grossly normal lymph nodes on palpation and normal appearing omentum may not need to be routinely removed. Stage I and grade 1 ITs can be managed with serial monitoring of associated tumor markers and pelvic imaging after initial fertility-sparing surgery. Grade 2-3 or stage II-IV IT are typically treated with systemic treatment in the form of the BEP chemotherapy regimen (bleomycin, etoposide, cisplatin).

Cystadenomas

Serous, mucinous, and mixed serous/endometrioid or mucinous/endometrioid cystadenomas are the second most common benign ovarian tumor in adolescents, representing 10–28% of adolescent tumors (Fig. 590.3). These tumors are usually thin walled, cystic, and may be associated with mild elevation of tumor markers such as carcinoembryonic antigen (CEA), CA-125, and CA 19-9, but high levels of these markers should raise suspicion for malignancy. These cystic lesions can become very large, yet, with care, these tumors can be resected, preserving normal ovarian tissue for future reproductive potential. Recurrence rates may be as high as 9%, and thus patients and providers may choose to continue surveillance postoperatively with pelvic ultrasound.

Endometriomas

Endometriosis is a syndrome defined by the presence of ectopic endometrial tissue usually located within the pelvis and abdomen but outside of the uterus. The principal clinical symptoms in adolescents consist of severe menstrual pain and pelvic pain but may also include abnormal uterine bleeding and GI, genitourinary, or constitutional symptoms. Diagnosis is often delayed, and a high clinical suspicion should be maintained. Although endometriosis has a variable presentation, it is associated with endometriomas in approximately 17–44% of adolescent cases; they may be unilateral or bilateral. **Endometriomas (chocolate cysts)** form when collections of old blood and hemosiderin deposit within an endometrium-lined cyst within or on the ovary. They have a typical homogeneous "ground glass" echogenic appearance on ultrasound and are more common in adults than in adolescents. Conservative management (suppressive therapy with ovulation suppression, nonsteroidal antiinflammatory drugs, combined oral contraceptives, or progestin therapy) is recommended for adolescents. An ovarian-sparing cystectomy should be performed if conservative care fails to control the symptoms or the size of the endometrioma is concerning for torsion. Recurrence of endometriosis occurs more commonly in adolescents than adults, and future fertility is associated with stage of disease. Early diagnosis and initiation of menstrual suppression with estrogen-progesterone, progesterone-only formulations, GnRH agonist, or GnRH antagonist may prevent progression of the disease.

Pelvic Inflammatory Disease and Tuboovarian Abscess

Pelvic inflammatory disease (PID) complicated by a tuboovarian abscess (TOA) should be considered in a sexually active adolescent with an adnexal mass and pain on examination (see Chapter 163). PID is a spectrum of upper genital tract inflammation and includes some combination of endometritis, salpingitis, and TOA. Rarely, TOA can occur in nonsexually active adolescents, particularly in association with obstructive Müllerian anomalies, ruptured appendicitis, obesity, and severe constipation. Patients with PID and TOA typically exhibit fever with leukocytosis, cervical motion, uterine or adnexal tenderness, vaginal discharge, nausea, peritoneal signs, and abnormal vaginal bleeding. TOAs are usually demonstrated on transvaginal ultrasound, but pelvic CT imaging may be used for uncertain cases. Treatment of PID with TOA consists of inpatient administration of intravenous (IV) antibiotics. After 48-72 hours of treatment with antibiotics

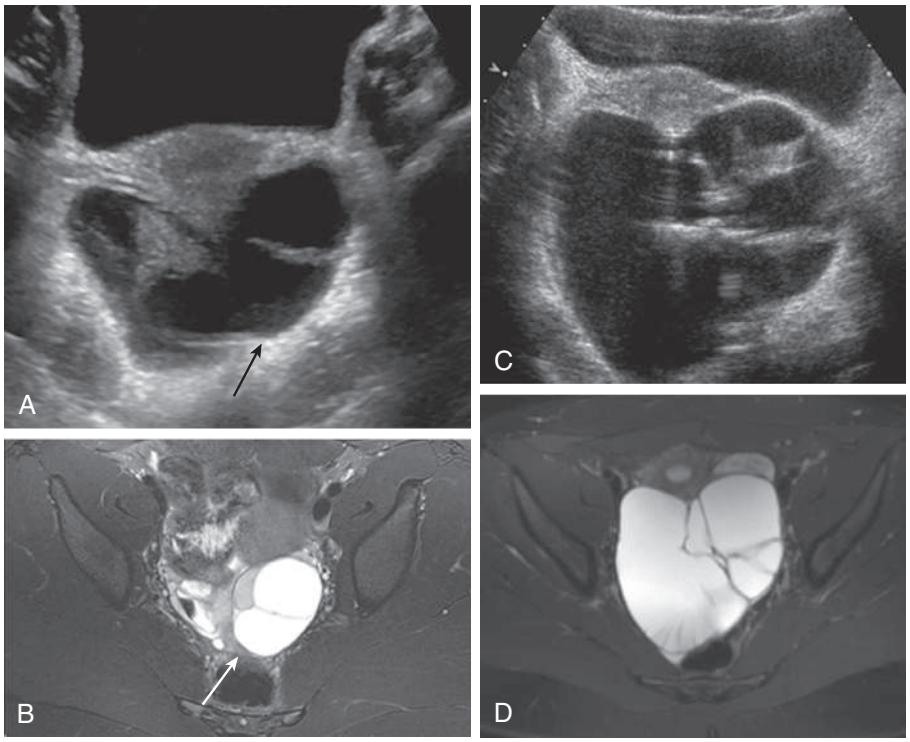

Fig. 590.3 Serous cystadenoma and mucinous cystadenoma. **A** and **B**, 20-yr-old female with pelvic pain. **A**, Transverse ultrasound and (**B**) axial T2 fat-saturated magnetic resonance images (MRIs) demonstrate a complex cystic mass with septations in the left adnexa *(arrows)*. This was removed and found to be a serous cystadenoma. **C** and **D**, 15-yr-old female with pelvic pain. **C**, Transverse ultrasound and (**D**) axial T2 fat-saturated MRIs demonstrate a cystic, septated mass posterior to the uterus. After surgical resection, pathology confirmed a mucinous cystadenoma. Note that the imaging appearances of serous and mucinous cystadenoma are similar. A specific diagnosis is difficult to discern based on imaging alone. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017; 188: Fig. 6.72.)*

alone, patients with TOAs who do not respond or who worsen should undergo imaging-guided abscess drainage. Conservative management with IV and then oral antibiotics and/or image-guided drainage is recommended as long as the patient continues to improve. TOAs that are large (>7-8 cm in the largest diameter) are associated with the need for surgical intervention and/or radiologically guided drainage. Clinical deterioration is an indication for surgical exploration, and a familiarity with bowel surgery is important with any attempt at resection of a pelvic abscess because of the challenges of encountering anatomic distortion, other organ involvement, and friable tissue planes.

Adnexal Torsion

Adnexal torsion of the ovary and/or fallopian tube is the fifth most common gynecologic emergency and occurs more often in children and adolescents than in adults. If ovarian torsion is suspected, timely surgical intervention is necessary to preserve ovarian function and future fertility. About 60% of ovarian torsions are on the right side; this is possibly because the right utero-ovarian ligament is longer than the left and/or due to the protective effect of the descending colon to the left adnexa. The most common presentation is *sudden*-onset abdominal pain, which is typically intermittent and nonradiating, with associated nausea and vomiting. Abdominal tenderness is common on physical exam and may be accompanied by peritoneal signs. Ultrasound with Doppler is the imaging modality of choice (Fig. 590.4). In adnexal torsion, ovarian venous flow is obstructed, and the fallopian tube and/or ovary become enlarged. Pelvic ultrasound findings include an edematous appearance of the ovary with subsequent hyperechogenicity, increase in size, "whirlpool" sign (twisted vascular pedicle of the ovary), and peripherally displaced follicles. Doppler studies in the evaluation of torsion are limited because of low sensitivity, and the presence of arterial flow does not rule out torsion. Therefore Doppler flow alone should not guide clinical decision-making. Prompt surgical intervention (i.e., diagnostic laparoscopy and laparoscopic ovarian detorsion) is essential to preserve ovarian function. Appearance of the ovary during surgery is not a reliable indicator for ovarian viability as even devascularized-appearing ovaries during laparoscopy have been reported to regain normal perfusion and function in several days. The goal of surgery should be to preserve the ovary regardless of the color and time from onset of symptoms to intervention. A torsed ovary should not be removed in adolescents unless it is severely necrotic and is disintegrating.

Although adnexal torsion may occur in individuals with normal ovaries, torsion occurs more commonly in adnexa enlarged by cystic changes or ovarian neoplasms. The rate of malignancy among premenarchal adolescents with ovarian torsion ranges from 0.4–5%. If an ovarian cyst is easily identified at the time of detorsion, it is reasonable to proceed with concomitant cystectomy; however, it should be noted that the concomitant cystectomy could be challenging because of the friable edematous ovary, which can result in ovarian damage and bleeding leading to oophorectomy. Given that most cysts are benign, drainage of the cyst's fluid is reasonable, and repeat ultrasound in 6-12 weeks usually demonstrates resolution of the cyst. Another approach may include detorsion and second-stage surgery at delayed interval for cystectomy. Oophoropexy is controversial, and the two most compelling reasons are the absence of a contralateral ovary and a history of recurrent ovarian torsion. Initiation of ovarian suppression is reasonable to prevent recurrent ovarian cysts.

OVARIAN MALIGNANCIES

Ovarian cancer is very uncommon in children; only 1.3% of all ovarian cancers are diagnosed in patients < 20 years old. Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence rates for 2016–2020 are 1.35/100,000 for females 15–19 years; mortality rates for this age group are 0.05/100,000.

Germ Cell Tumors

Germ cell tumors are the most common ovarian malignancy and originate from primordial germ cells that develop into a number of heterogeneous tumor types. **Dysgerminomas** are the most common malignant germ cell tumor of the ovary and have the best prognosis (Table 590.2). They may contain syncytiotrophoblastic cells that produce alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH), making these serum proteins useful tumor markers for monitoring disease activity during surveillance (Table 590.3). Because of rapid growth and expansion, dysgerminomas may present as large abdomino-pelvic masses, and hemoperitoneum may result due to capsular rupture. Dysgerminomas are the most common bilateral ovarian germ cell tumor, occurring bilaterally in 10–15% of patients. **Yolk sac tumors**, also

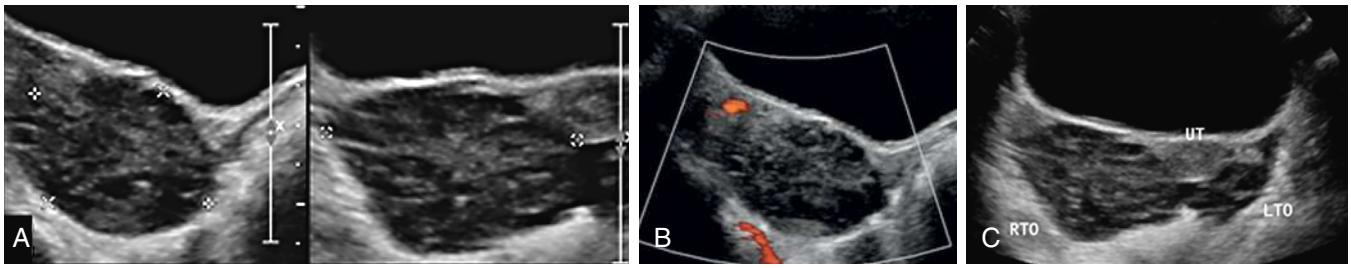

Fig. 590.4 Ovarian torsion. 15-yr-old female with acute-onset pelvic pain. **A,** Sagittal and transverse transabdominal pelvic ultrasound images demonstrate a rounded appearance of the right ovary, which is displaced medially and positioned posterior to the uterus. There is peripheralization of the ovarian follicles. **B,** Power Doppler imaging shows no demonstrable flow within the ovarian parenchyma. **C,** Transverse image of the pelvis shows marked asymmetric enlargement of the right ovary (RTO) in comparison with the normal left ovary (LTO). This patient went to surgery, and right ovarian torsion was confirmed. UT, Uterus. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017; 189: Fig. 6.74.)*

Table 590.2 Malignant Ovarian Tumors in Children and Adolescents

TUMOR	OVERALL 5-YR SURVIVAL	CLINICAL FEATURES
GERM CELL TUMORS		
Dysgerminoma	85%	10–20% bilateral Most common ovarian malignancy Gonadal dysgenesis/androgen insensitivity Sensitive to chemotherapy/radiation
Immature teratoma	97–100%	All three germ layers present
Endodermal sinus tumor	80%	Almost always large (>15cm) Schiller-Duval bodies
Choriocarcinoma	30%	Rare Can mimic ectopic pregnancy
Embryonal carcinoma	25%	Endocrinologic symptoms (precocious puberty) Highly malignant
Gonadoblastoma	100%	Primary amenorrhea Virilization 45,X or 45,X/46,XY mosaicism
SEX CORD STROMAL TUMORS		
Juvenile granulosa stroma cell tumor	92%	Produce estrogen Menstrual irregularities Isosexual precious pseudopuberty Call-Exner bodies rare
Sertoli-Leydig cell tumor	70–90%	Virilization in 40% Produce testosterone
Lipoid cell tumors	~80%	Rare heterogeneous group with lipid-filled parenchyma
Gynandroblastoma	90% or greater	Rare low-grade mixed tumors that produce either estrogen or androgen

referred to as **endodermal sinus tumors**, clinically present similarly to dysgerminomas with a rapidly enlarging pelvic mass and associated abdominal pain. Schiller Duval bodies are pathognomonic on pathology and contain a central blood vessel surrounded by cuboidal tumor cells. AFP is a useful marker for monitoring response to treatment and for surveillance. Immature teratomas and yolk sac tumors are more aggressive malignancies than dysgerminomas. Embryonal carcinomas are a relatively undifferentiated product of the primordial germ cells and are one of the most malignant germ cell tumors of the ovary. They may secrete β-hCG and AFP. **Gonadoblastomas** are almost always associated with chromosomal abnormalities; therefore chromosomal analysis is essential. Polyembryoma is a very aggressive ovarian malignancy and contains embryoid bodies. The treatment for stage Ia dysgerminomas and stage I immature teratomas is resection. For stage Ic and higher, treatment is surgical excision followed by postoperative chemotherapy. Radiotherapy may be administered for disease recurrence in dysgerminomas, but it is not included in routine treatment. For unresectable tumors or for patients who cannot undergo surgery, neoadjuvant chemotherapy is an option. Recurrences are treated with chemotherapy. Germ cell tumors may recur in up to 10% of cases, and thus yearly follow-up ultrasound is recommended.

Sex-Cord Stromal Tumors

Sex-cord stromal tumors (SCSTs) originate from the stromal component of the gonads and include benign **thecomas** and **fibromas,** as well as malignant **Sertoli-Leydig cell tumors** and **juvenile granulosa cell tumors**. Individuals with Peutz-Jeghers syndrome are at increased risk for developing SCSTs. SCSTs clinically present as an abdomino-pelvic mass, pain, and symptoms of excess sex steroid hormone production, such as hirsutism, virilization, and heterosexual or isosexual precocious puberty. When an SCST is suspected, serum levels of inhibin B, AFP, estradiol and testosterone should be obtained. SCSTs usually present as a unilateral solid mass on imaging, but some degree of necrosis could lead to a heterogenous appearance (Figs 590.5 and 590.6).

Most **juvenile granulosa** cell tumors have an intact capsule and therefore are associated with a good prognosis; however, in the case of capsular rupture or invasion, they potentially have an aggressive course. Juvenile granulosa cell tumors are usually associated with excess estrogen and precocious puberty in prepubertal females. Approximately 20% of the SCSTs in the pediatric population are **Sertoli-Leydig cell tumors,** which may be associated with clinical signs and symptoms of androgen excess. The *DICER1* pathogenic variant is associated with Sertoli-Leydig cell tumors, and the presence of the variant increases the risk of metachronous tumor in the contralateral ovary. Karyotype and referral to genetics is recommended for patients with SCSTs.

Epithelial Ovarian Cancers

Epithelial ovarian cancers are less common than germ cell tumors in the pediatric and adolescent population, comprising only 12.4% of ovarian malignancies in this group. Borderline ovarian tumors are similarly exceedingly rare in adolescents. Individuals with *BRCA1* and *BRCA2* pathogenic variants are at higher risk of developing epithelial ovarian cancer at younger ages compared with females without *BRCA* variants. Similarly, low-grade epithelial ovarian carcinomas tend to occur at younger ages compared with high-grade ovarian carcinomas. Common presenting symptoms include dysmenorrhea, abdominal pain, abdominal distention, nausea and vomiting, and vaginal

Table 590.3 Serum Tumor Markers

TUMOR	CA-125	AFP	β-HCG	LDH	E2	T	INHIBIN	MIS	VEGF	DHEA
Epithelial tumor	+									
Immature teratoma	+	+			+					+
Dysgerminoma			+	+	+					
Endodermal sinus tumor		+								
Embryonal carcinoma		+	+		+					
Choriocarcinoma			+							
Mixed germ cell		+	+	+						
Granulosa cell tumor	+				+		+	+		
Sertoli-Leydig						+	+			
Gonadoblastoma					+	+	+			+
Theca-fibroma									+	

AFP, α-Fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrostenedione; E2, estradiol; β-hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone; MIS, Müllerian-inhibiting substance; VEGF, vascular endothelial growth factor.

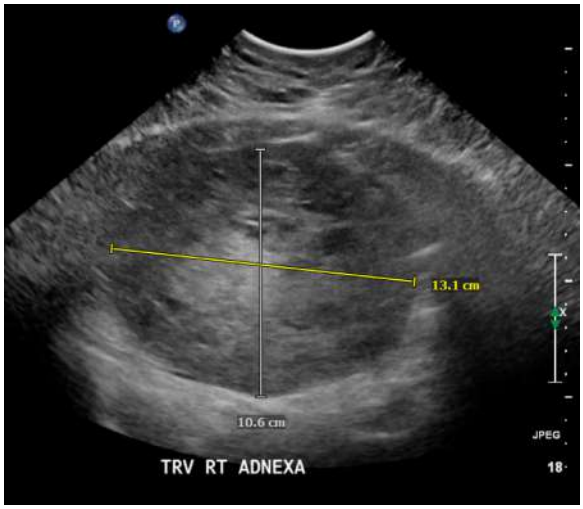

Fig. 590.5 Complex 13.1 × 8.1 × 10.6 cm solid mass with smaller cystic foci, arising from the right ovary. Final pathology demonstrated juvenile granulosa cell tumor. *(Image courtesy Alla Vash-Margita, MD.)*

discharge; CA-125 is almost always elevated. Treatment involves surgical salpingo-oophorectomy, pelvic washings, and biopsies of suspicious omental, peritoneal, and lymph node lesions, with adjuvant chemotherapy for patients with Federation of Gynecology and Obstetrics (FIGO) stage II-IV disease. Given the young age of this population, although this is not the standard of care for adult patients, fertility-sparing surgery is recommended for stage I cancer to conserve the contralateral ovary and uterus if they appear normal. Data suggest that in patients with early-stage disease, such an approach with appropriate surgical staging results in optimal outcomes but is not recommended for stage II-IV disease due to the high rate of recurrence. The number of term pregnancies and use of oral combined hormonal contraceptive pills decrease the risk of invasive epithelial ovarian cancer. Young females with a family history of ovarian cancer should consider the use of long-term oral combined hormonal contraceptive pills for the preventive benefits when pregnancy is not being sought.

UTERINE MALIGNANCIES

Uterine malignancies account for 2.5% of all gynecologic malignancies of children and adolescents less than 18 years of age. The most common types are sarcomas (34%), followed by adenocarcinomas (34%) and squamous cell carcinomas (10%). **Rhabdomyosarcomas** are the most common type of soft tissue sarcoma occurring in patients <20 years of age (see Chapter 549). They can develop in any organ or tissue in the body except bone, and roughly 3% originate from the uterus or vagina. Of the various histologic subtypes, embryonal rhabdomyosarcomas in the female patient most often occur in the genital tract of infants or young children. They are rapidly growing entities that can cause the tumor to be expelled through the cervix, with subsequent complications such as uterine inversion or large cervical polyps. Irregular vaginal bleeding may be another presenting clinical symptom. They are defined histologically by the presence of mesenchymal cells of skeletal muscle in various stages of differentiation intermixed with myxoid stroma. A genetic link has been found between Li-Fraumeni cancer susceptibility syndrome, Beckwith-Wiedemann syndrome, pleuropulmonary blastoma, Costello syndrome, Noonan syndrome, and neurofibromatosis type I. Treatment recommendations are based on protocols coordinated by the Intergroup Rhabdomyosarcoma Study Group and consist of a multimodal approach including radiation therapy and chemotherapy. Vincristine, Adriamycin-D, and cyclophosphamide (VAC) with or without radiation therapy make up the first line of treatment. Intensity-modulated radiation therapy and proton beam radiotherapy are used to reduce the therapy burden and long-term toxicity. Resection rates are very low because of the risk of losing the form and function of local tissue; chemotherapy with restrictive surgery and adjunctive irradiation has enabled many patients to retain the uterus while achieving excellent long-term survival rates.

Leiomyosarcomas and **leiomyomas** are extremely rare, occurring in <2 in 10 million individuals in the pediatric and adolescent age-groups, although their numbers are increasing among pediatric patients with AIDS. They usually involve the spleen, lung, or GI tract, but they could also originate from uterine smooth muscle. Epstein-Barr virus pathogenesis has been shown in AIDS and solid-organ transplant patient populations (see Chapter 301). Despite treatment that demands complete surgical resection (and chemotherapy for the sarcomas), they tend to recur frequently.

Endometrial stromal sarcoma and **endometrial adenocarcinoma** of the uterine corpus are extremely rare in children and adolescents. A comprehensive review described 19 cases of endometrial cancer (EC) among adolescent females younger than 21 years in which five subjects (26.3%) had a genetic condition (Cowden syndrome and Turner syndrome). This emphasizes the consideration of genetic evaluation in very young patients with EC. In most cases, patients presented with abnormal uterine bleeding and had associated comorbidities such as obesity and polycystic ovary syndrome. Standard of care for treatment of EC consists of hysterectomy, removal of both ovaries and fallopian tubes and surgical staging, followed by adjunctive radiotherapy and/

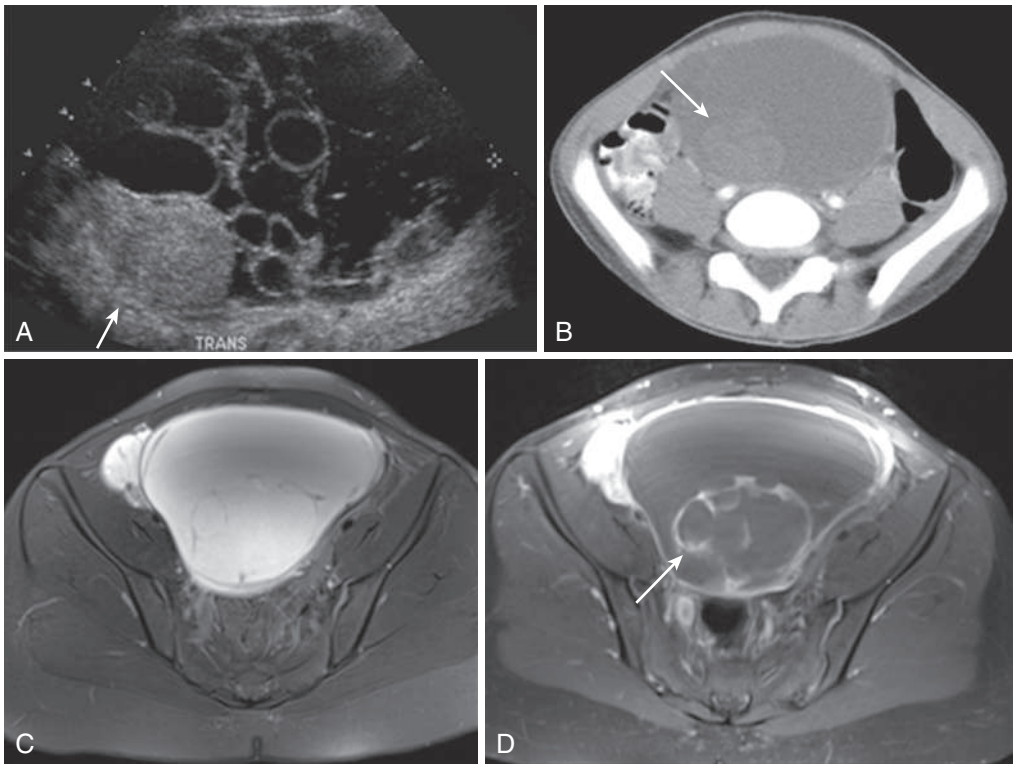

Fig. 590.6 Sertoli-Leydig cell tumor. 2-yr-old female with a palpable pelvic mass and secondary sex characteristics. **A**, Transabdominal pelvic ultrasound demonstrates a complex cystic, septated mass, with a solid component posteriorly *(arrow)*. **B**, Contrast-enhanced computed tomography shows a predominantly cystic mass, with an enhancing mural nodule along the posterior margin *(arrow)*. **C**, T2-weighted and **D**, contrast-enhanced magnetic resonance images in a different patient demonstrate a T2 hyperintense lesion in the pelvis, with enhancing internal solid components noted after contrast administration *(arrow)*. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017; 188: Fig. 6.73.)*

or chemotherapy as indicated by final pathology and stage. In young patients who desire childbearing, fertility-sparing approaches with preservation of the uterus have been increasingly utilized. Per National Comprehensive Cancer Network (NCCN) guidelines, candidates for this approach are patients with grade 1 endometrioid adenocarcinoma on dilation and curettage, patients with disease confined to endometrium by MRI (preferred imaging modality) or ultrasound, absence of metastatic disease on imaging, and no contraindications to medical therapy or pregnancy. Patients should undergo counseling that fertility-sparing options are not standard of care for the treatment of endometrial carcinoma. Existing data on hormonal therapy come from observational studies and have variable rates of outcomes. Although there is no standard follow-up protocol, patients with EC treated with hormonal therapies should be reexamined with endometrial sampling every 3-6 months.

VAGINAL MALIGNANCIES

Vaginal tumors are rare with a variable clinical presentation that may include abdomino-pelvic pain, an abdominal mass, bloody vaginal discharge, genital ulceration, or tissue protruding from the vagina. **Embryonal rhabdomyosarcoma (RMS)** is the most common vaginal malignancy followed by germ cell tumor (GCT) and clear cell adenocarcinoma (CCA). The management of pediatric vaginal tumors consists of neoadjuvant chemotherapy followed by local control with surgery or radiotherapy.

Embryonal rhabdomyosarcoma (RMS) or **sarcoma botryoides** typically arises in the anterior wall of the vagina or within the wall of the bladder and presents as an edematous grapelike mass protruding from the vagina. Overall, RMS arising in the female genital tract accounts for less than 4% of all pediatric RMS. Approximately 90% of these sarcomas present before age 5 years. Embryonal RMS of the vagina is managed with multimodality treatment. A series of Intergroup Rhabdomyosarcoma Study Group (IRSG) reports demonstrated survival rates in excess of 85% employing the use of combination chemotherapy treatment with vincristine, actinomycin-D, and cyclophosphamide (VAC) and wide excision with or without adjuvant radiation treatment. This approach spares most patients from exenterative surgery. Because of the high rates of local recurrences in patients who did not receive radiation, the Soft Tissue Sarcoma committee of the Children's Oncology Group recommends local radiation treatment unless potential toxicity is considered unacceptable.

Endodermal sinus tumors or **yolk sac tumors** are the most common subtype of pediatric germ cell tumor of the vagina but are still quite rare. These tumors present almost exclusively in children under the age of 3 years with vaginal bleeding. Typically, patients have a markedly elevated serum AFP, which can be used to monitor treatment effect and disease recurrence. Management involves combination of surgery and chemotherapy (either carboplatin/etoposide/bleomycin, BEP regimen, or VAC regimen). Unfortunately, survival rates are low despite treatment.

There is an increased incidence of **clear cell adenocarcinoma** (CCA) of the vagina in young females related to in utero exposure to diethylstilbestrol (DES) during the first 16 weeks of pregnancy. The suggested mechanism of carcinogenesis involves the retention of nests of abnormal cells of Müllerian duct origin that, after stimulation by endogenous hormones during puberty, are promoted into adenocarcinomas. Most cases involve the anterior upper third of the vaginal wall. Treatment of CCA of the vagina includes a surgery and/or radiation treatment depending on the extent of disease. Fortunately, the incidence of CCA of the vagina has decreased since the practice of prescribing DES during pregnancy has been eliminated.

VULVAR MALIGNANCIES

Pediatric vulvar malignancies are rare. Patients typically present with an ulcerated or raised lesion and/or a mass. It is imperative that any concerning vulvar lesion be biopsied and submitted for pathologic evaluation. Vulvar malignancies that have been described in the literature include invasive squamous cell carcinomas, yolk sac tumors, Ewing sarcoma/primitive neuroectodermal tumors (ES/PNET), and melanomas. Each of these entities make up approximately 10% of reported cases. Cases of pediatric vulvar squamous cell carcinoma include those lesions that are **human papillomavirus (HPV)**-mediated and HPV-independent. Possible risk factors include HPV infection, immunosuppression, Fanconi anemia, and lichen sclerosis. Extragonadal germ cell tumors involving the vulva are very uncommon, and the leading hypothesis behind their pathogenesis is possible aberrant germ cell migration along the gubernaculum. These are aggressive tumors, and treatment options include various combinations of excisional

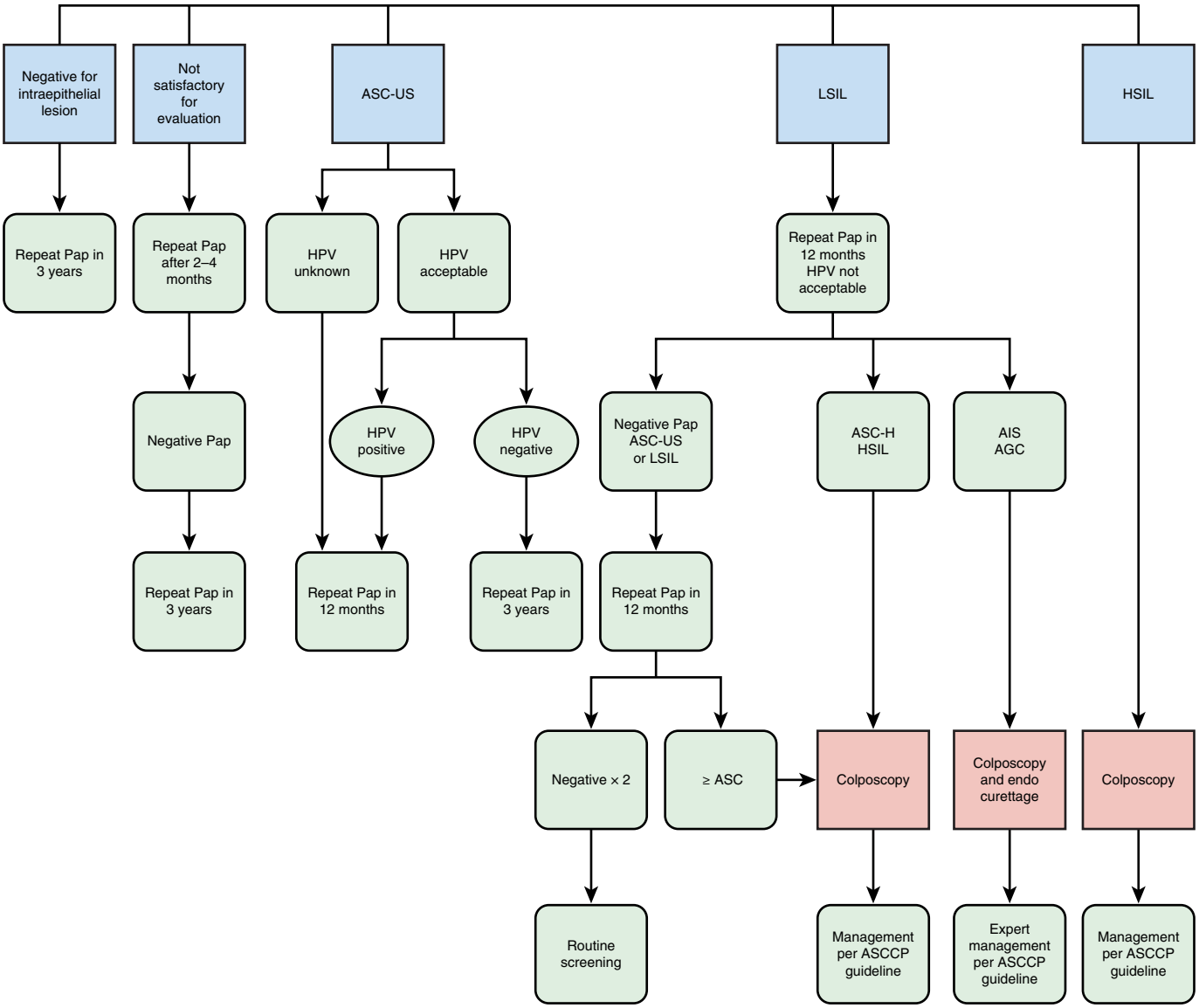

Fig. 590.7 Algorithm for the management of Pap smear results in women between age 21-24. AIS, adenocarcinoma in situ; AGC, atypical glandular cells; ASC, atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-H, atypical squamous cells that cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion *(From Trotman GE, Vash-Margita A, Kahn JA, et al. Human papillomavirus infection and cervical cancer screening and prevention in adolescents. In: Emans SJ, Laufer MR, Di Vasta DP, eds. Pediatric and Adolescent Gynecology. Philadelphia: Lippincott Williams & Wilkins, 2020; 330–348: Fig 20.9.)*

procedures and neoadjuvant or adjuvant chemotherapy. **Malignant melanoma** of the vulva represents 2.4–10% of all vulvar malignancies, second to invasive squamous cell carcinomas in frequency. Early-stage melanoma treatment involves surgical excision followed by possible radiation treatment. Treatment of advanced stage melanoma involves systemic chemotherapy and/or targeted treatment agents such as checkpoint inhibitor immunotherapy. **Rhabdomyosarcomas** are the most common vulvar sarcomas reported in pediatric patients. The second most common sarcoma of the vulva in pediatric patients is ES/PNET. Management of both vulvar sarcomas includes surgical excision, multi-agent chemotherapy, and radiation treatment. ES/PNET cases often present in the advanced stage and have a poor prognosis.

Condyloma acuminata are common, raised, verrucous lesions of the vulva that result from squamous cell proliferation associated with HPV infection (most common genotypes HPV 6 and 11). Prevention of HPV infection and subsequent formation of condyloma acuminata has been achieved through HPV vaccination. *In young children with condyloma acuminata, sexual abuse must be ruled out.* These lesions are benign and can spontaneously regress. If lesions are bothersome, treatment modalities consist of topical podophyllin resin, imiquimod, trichloroacetic acid, local cryotherapy, electrocautery, excision, and laser ablation. Imiquimod is approved by the U.S. Food and Drug Administration (FDA) for individuals 12 years of age and above.

CERVICAL MALIGNANCIES AND THEIR PREVENTION

In 2020, cervical cancer accounted for an estimated 604,000 new cancer cases and 342,000 deaths worldwide, making it the fourth most common cancer in females of all ages. From 2016 to 2020, the United States age-adjusted incidence of cervical cancer in females under age 20 was <0.1 per 100,000. The adolescent population is at greatest risk of HPV infection, which predisposes them to development of cervical cancer because about half of HPV infections occur before the age of 24. Thus prevention of initial infection in the adolescent population is critical to decreasing cervical cancer rates.

Primary prevention of HPV infection includes vaccination before the onset of sexual activity with the HPV vaccine. The HPV vaccine is approved for males and females ages 9-26. The Centers for Disease Control and Prevention (CDC) recommends two doses of the HPV 9-valent vaccine for patients before age 15 years (typically between ages 11-12) given 6-12 months apart (see Chapter 215). For those initiating the vaccine series at 15 years of age or older, three doses of the HPV vaccine should be given at 0, 1-2, and 6 months. Three doses are also recommended for patients who are immunocompromised (i.e., solid organ transplant recipient, HIV infection). Children with a history of sexual abuse should start immunization at age 9. In 2018, the FDA approved the use of the HPV 9-valent vaccine to include adults age 27-45 years; while the vaccine is not routinely recommended in this group, it may be given after shared clinical decision-making between a patient and their healthcare provider. The HPV vaccine can be administered despite prior infection with HPV. Cervical cancer screening via Papanicolaou (Pap) testing and HPV co-testing are important secondary prevention strategies. ACOG recommends cervical cancer screening for females starting at age 21 years in immunocompetent females regardless of onset of penetrative vaginal intercourse or primary prevention with HPV vaccination. Separate guidelines describe cervical cancer screening recommendations for immunocompromised individuals. Briefly, sexually active immunocompromised adolescents (such as solid organ or hematopoietic stem cell transplant recipients, patients with inflammatory bowel disease on immunosuppressive therapy, and patients with systemic lupus erythematosus) should start screening 1 year after of onset of sexual activity and thereafter annually for 3 years. If consecutive screening is negative, patients may follow the guidelines for immunocompetent females. HIV positive patients should start screening at age 21 regardless of sexual activity. Additionally, condom use, limiting the number of sexual partners, and smoking cessation are recommended to lower the risk for cervical cancer.

Because of the high prevalence of HPV infection in the adolescent population and because HPV-associated lesions typically regress, HPV screening should be not done before age 21 years in immunocompetent patients. If an inadvertent HPV test is done in adolescents, the results should not be acted on. Guidelines on management of the abnormal results of cervical cancer screening (Pap smear) for females age 21-24 are shown in Figure 590.7. Overall, data shows that prevention strategies such as widespread implementation of HPV vaccine translates into reduced incidence of cervical cancer in the future. Pediatric providers should educate patients and caregivers about benefits of the HPV vaccine and offer it at the recommended age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 591

Vulvovaginal and Müllerian Anomalies

Laura L. Hollenbach, Emanuele Pelosi, Miranda Margetts, and Alla Vash-Margita

EMBRYOLOGY

The formation of a normal reproductive system occurs in the developing embryo and early fetus and is regulated by several processes, including cellular differentiation, duct elongation, fusion, resorption, canalization, and programmed cell death. Numerous Müllerian and/or vulvovaginal anomalies can result from interruption of the intricate sequence or functions of any one of these processes during formation of the reproductive system (Table 591.1). Genetic, epigenetic, and environmental factors all have been described as playing some role in these processes (Table 591.2).

Table 591.1 Congenital Müllerian Anomalies

MÜLLERIAN ANOMALY	DESCRIPTION
Agenesis	Absence of uterus, cervix, and upper portion of vagina
Hypoplasia	Incomplete development of uterus, cervix, and upper portion of vagina
Unicornuate uterus	One cervix and one uterine horn, the result of failure of one Müllerian duct to descend
Septate uterus	Septum dividing the uterus, partially or completely
Didelphic uterus	Two cervices, each associated with one uterine horn
Bicornuate uterus	One cervix associated with two uterine horns
OHVIRA (obstructed hemivagina and ipsilateral renal anomaly)	Double uterus with unilateral obstructed hemivagina and ipsilateral renal agenesis
CONDITIONS ASSOCIATED WITH MÜLLERIAN ANOMALIES	**DESCRIPTION**
Hydrocolpos	Accumulation of mucus or nonsanguineous fluid in the vagina
Hematocolpos	Accumulation of blood in the vagina
Hematometra	Accumulation of blood in the uterus
Hydrosalpinx	Accumulation of serious fluid in the fallopian tube, often a result of pyosalpinx

Table 591.2 Genetic Conditions Associated with Müllerian Anomalies

MODE OF INHERITANCE	SYNDROME	ASSOCIATED MÜLLERIAN DEFECT
Autosomal dominant	Camptobrachydactyly	Longitudinal vaginal septum
	Hand-foot-genital	Incomplete Müllerian fusion
	Denys-Drash	Persistent Müllerian duct derivatives
Autosomal recessive	McKusick-Kaufman	Vaginal atresia, transverse vaginal septum
	Johanson-Blizzard	Longitudinal vaginal septum
	Renal-genital-middle ear anomalies	Vaginal atresia
	Fraser	Incomplete Müllerian fusion
	Persistent Müllerian duct	Persistent Müllerian duct derivatives
	Urioste syndrome	Persistent Müllerian duct derivatives
Polygenic/ multifactorial	Mayer-Rokitansky-Küster-Hauser	Müllerian aplasia
X-linked	Persistent Müllerian duct	Persistent Müllerian duct derivatives

Phenotypic sexual differentiation, especially during formation of the vulvovaginal and Müllerian systems, is determined from genetic, gonadal, and hormonal influences (see Chapter 622). Gonadal development determines the hormonal production regulating progression or regression of the genital ducts and subsequently the external genitalia.

In 46,XY embryos, the *SRY* (sex-determining region of Y-chromosome) gene is one of the first regulators driving the formation of a testis from a primitive gonad and triggering the expression of a cascade of additional factors responsible for testis development as well as spermatogenesis. The testis begins to develop between 6-7 weeks of gestation, first with Sertoli cells, which produce anti-Müllerian hormone (AMH), followed by Leydig cells, which produce testosterone starting at approximately 8 weeks of gestation. The genital tract in both male and female embryos initially includes both the Wolffian and the Müllerian (or paramesonephric) ducts and begins to differentiate later than the gonads. The differentiation of the Wolffian ducts, the primordia of the male reproductive tract, is regulated by testosterone, and the local action of testosterone activates development of the epididymis, vas deferens, and seminal vesicle. Concomitantly, the anti-Müllerian hormone (or Müllerian-inhibiting substance) will cause regression of the Müllerian ducts. Further male genital duct and external genital structures depend on the conversion of testosterone to dihydrotestosterone. Failure of Müllerian duct regression results in retention of Müllerian derivatives in males. One example is **persistent Müllerian duct syndrome (PMDS)**, which is characterized by the presence of Müllerian structures usually associated with undescended testes. The majority of PMDS cases are due to pathogenic variants in the *AMH* gene or its receptor *AMHR2*. Other conditions featuring the presence of Müllerian derivatives in males are **Denys-Drash syndrome** (characterized by gonadal dysgenesis), nephropathy, and Wilms tumor, each caused by pathogenic variants in the *WT1* gene, and Müllerian derivatives-lymphangiectasia-polydactyly syndrome **(Urioste syndrome)**, a condition of unknown etiology.

In a 46,XX embryo, female sexual differentiation occurs about 2 weeks later than gonadal differentiation in the male. The regression of the Wolffian ducts results from the lack of local gonadal testosterone production, and the persistence of the Müllerian ducts results from the absence of anti-Müllerian hormone production. The Müllerian ducts continue to differentiate into the fallopian tubes, uterus, and upper one-third of the vagina without interference from anti-Müllerian hormone. Because the ovaries develop separately from the Müllerian ducts, females with Müllerian ductal anomalies usually have normal ovaries and steroid hormone production. There are complex interactions among the Wolffian, Müllerian, and metanephric ducts (the latter giving rise to the urinary tract) early in embryonic development, and normal development of the Müllerian system depends on such interaction. If this process is interrupted, coexisting Müllerian and renal anomalies are often discovered in the female patient at the time of evaluation. Although most Müllerian defects seem sporadic, familial recurrence or clustering has been observed, which strongly supports the influence of genetic factors. The molecular processes underlying the developmental program of the female reproductive tract are extremely intricate and are regulated by numerous gene products, including *WNT4*, *WNT5*, *WNT7A*, *WNT9B*, *LIM1*, *HNF1B*, *EMX2*, *PAX8*, and *HOX*. The WNT family plays crucial roles in both the formation and differentiation of the Müllerian ducts, providing inductive signals for the correct patterning of the developing tract. Homeobox genes *LIM1* and *HNF1B* are expressed in duct epithelial cells and are necessary for the development of the entire urogenital tract. Similarly, *EMX2* and *PAX8* play fundamental roles in the initial steps of urogenital development by regulating the formation of the Wolffian and Müllerian ducts. The family of *HOXA* genes is one of the most well described and comprises regulatory molecules that encode highly conserved transcription factors regulating the developmental axis of the female reproductive tract. These genes display a characteristic expression pattern along the developing reproductive tract (Fig. 591.1). A role for environmental factors in Müllerian anomalies has also been proposed. During gestation, the Müllerian ducts develop in an estrogen-free environment because of the presence of α-fetoprotein

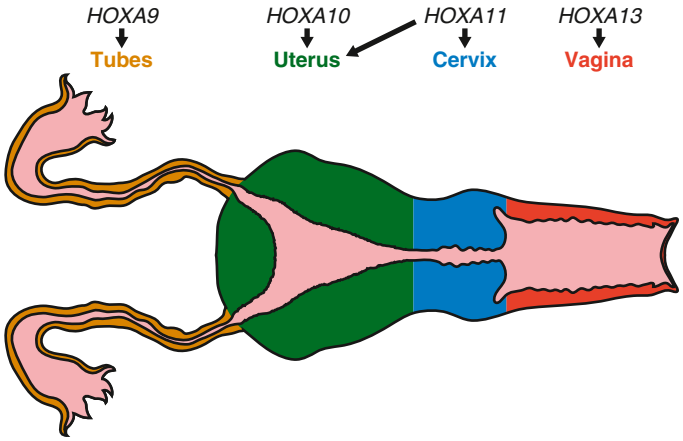

Fig. 591.1 Expression of *HOXA* genes in the developing Müllerian system. *(Adapted from Taylor HS. The role of HOX genes in the development and function of the female reproductive tract. Semin Reprod Med. 2000;18:81-89.)*

peptides that sequester estrogen molecules. Therefore attention has been turned to **endocrine-disrupting chemicals (EDCs)**, especially compounds with estrogenic activity, for their potential teratogenic role in Müllerian anomalies. A striking example is provided by diethylstilbestrol (DES), an estrogen agonist once given to pregnant patients to prevent pregnancy-related complications, including miscarriage. However, DES was found to induce epigenetic modifications and cause reproductive malformations, including a T-shaped uterus ultimately associated with higher spontaneous abortion rates.

By 10 weeks of gestation, the caudal portions of the Müllerian ducts fuse together in the midline to form the uterus, cervix, and upper vagina, in a Y-shaped structure, with the open upper arms of the Y forming the primordial fallopian tubes. Initially, the Müllerian ducts are solid cords that gradually canalize as they grow along and cross the mesonephric ducts ventrally and fuse in the midline. The Müllerian ducts caudally open into the **urogenital sinus,** where proliferation of the cells at the point of contact form the Müllerian tubercle. Cells between the Müllerian tubercle and the urogenital sinus continue to proliferate, forming the vaginal plate. At the same time of the midline fusion of the Müllerian ducts, the medial walls—forming the septum—begin to degenerate, forming the central cavity of the uterovaginal canal. Uterine septal resorption is thought to occur in a caudal to rostral direction and to be complete at approximately 20 weeks of gestation. This theory has been scrutinized because some anomalies do not fit the standard classification system; it is possible that septal resorption starts at some point in the middle and proceeds in both directions. At approximately 16 weeks of gestation, the central cells of the vaginal plate desquamate, and resorption occurs, forming the vaginal lumen. The lumen of the vagina is initially separated from the urogenital sinus by a thin hymenal membrane. The hymenal membrane undergoes apoptosis and central resorption and is usually perforate before birth.

EPIDEMIOLOGY

Müllerian anomalies can include abnormalities in portions or all of the fallopian tubes, uterus, cervix, and vagina (Fig. 591.2). True estimates of prevalence are difficult because of the varied presentations and asymptomatic nature of some of the anomalies, use of different diagnostic procedures, subjectivity of the diagnostic criteria, and the inconsistent interpretation of the classification of Müllerian anomalies.

It is estimated that Müllerian anomalies are present in 6.7% of the general female population. The prevalence of Müllerian anomalies increases in females with a history of adverse pregnancy outcomes or infertility: 8% of females who are infertile, 15% of females with primary amenorrhea, 16.7% of females with recurrent pregnancy loss, and 24.5% of females with both miscarriage and infertility have Müllerian defects.

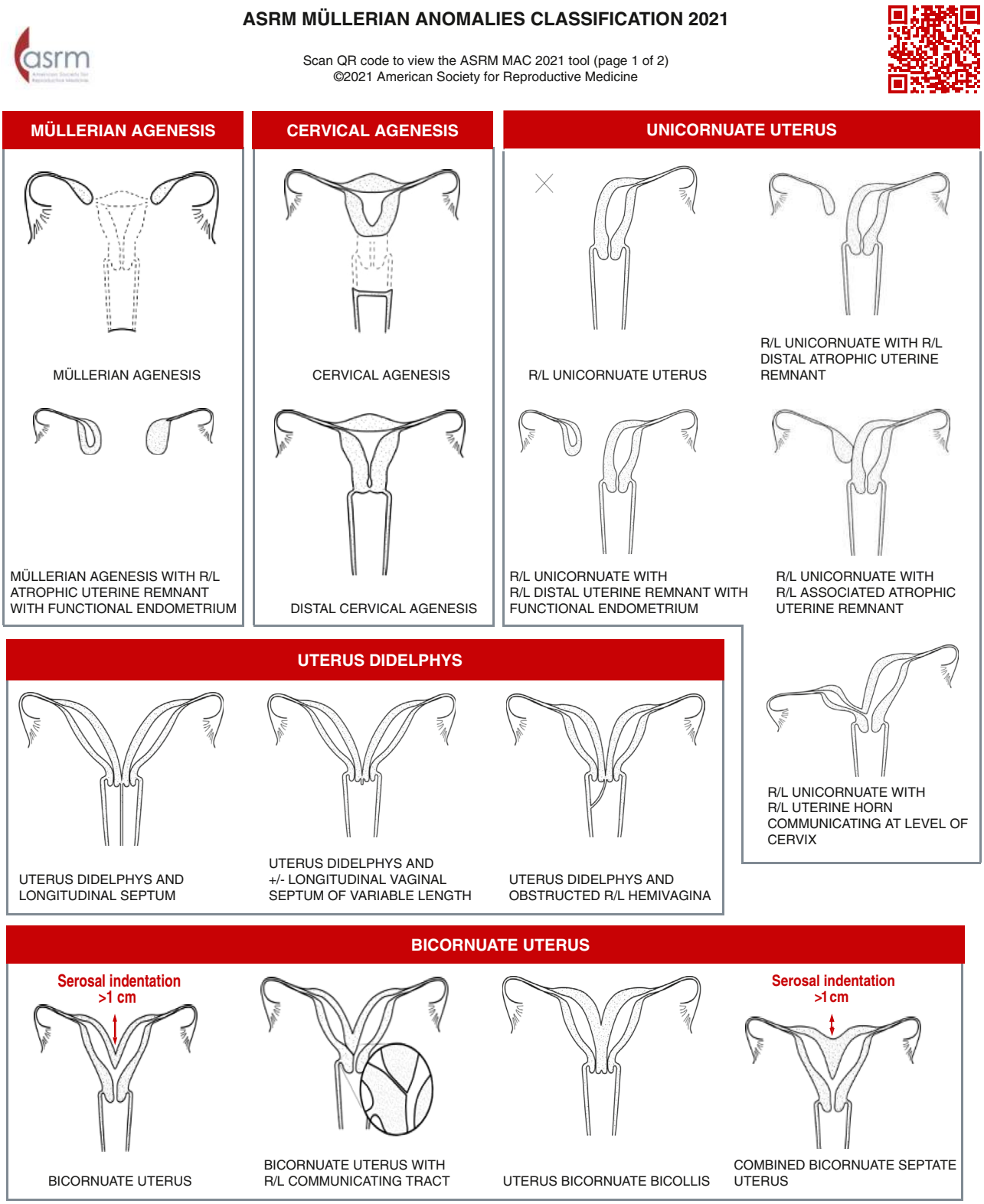

Fig. 591.2 Classification system of Müllerian duct anomalies developed by the American Society of Reproductive Medicine. *(From Pfeifer SM, Attaran M, Goldstein J, et al. ASRM Müllerian anomalies classification 2021. Fertil Steril. 2021;116:1238-1252; Fig 1.)*

SEPTATE UTERUS

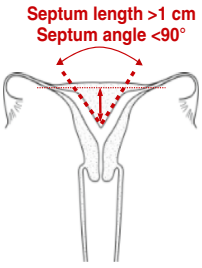

PARTIAL SEPTATE UTERUS

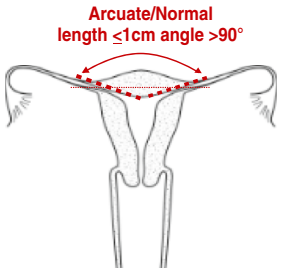

NORMAL/ARCUATE UTERUS

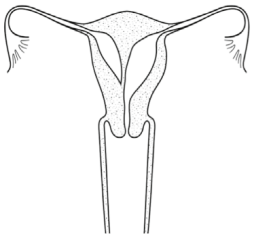

ROBERT'S UTERUS

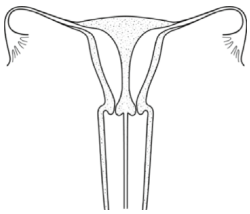

COMPLETE SEPTATE UTERUS WITH DUPLICATED CERVICES AND LONGITUDINAL VAGINAL SEPTUM

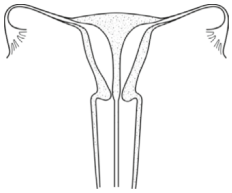

COMPLETE SEPTATE UTERUS WITH SEPTATE CERVIX AND LONGITUDINAL VAGINAL SEPTUM

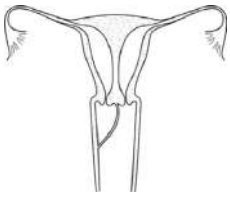

COMPLETE SEPTATE UTERUS, DUPLICATED CERVICES, AND OBSTRUCTED R/L HEMIVAGINA

TRANSVERSE VAGINAL SEPTUM

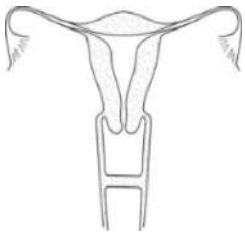

MID VAGINAL SEPTUM

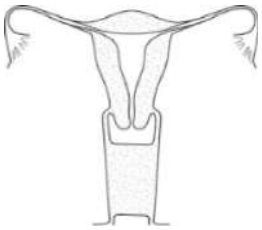

DISTAL VAGINAL AGENESIS

LONGITUDINAL VAGINAL SEPTUM

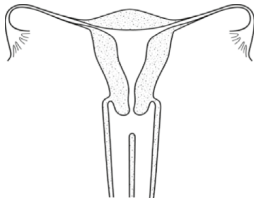

LONGITUDINAL VAGINAL SEPTUM OF VARIABLE LENGTH

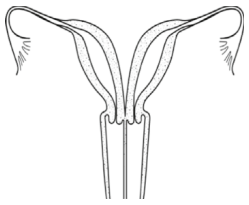

LONGITUDINAL VAGINAL SEPTUM OF VARIABLE LENGTH AND UTERUS DIDELPHYS

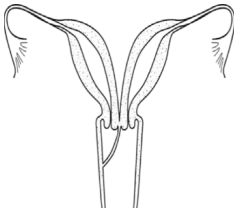

OBSTRUCTED R/L HEMIVAGINA AND UTERUS DIDELPHYS

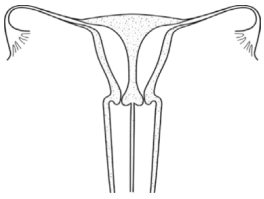

LONGITUDINAL VAGINAL SEPTUM OF VARIABLE LENGTH AND COMPLETE SEPTATE UTERUS WITH DUPLICATED CERVIX

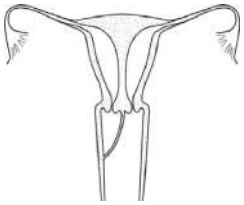

OBSTRUCTED R/L HEMIVAGINA AND COMPLETE SEPTATE UTERUS WITH DUPLICATED CERVICES

COMPLEX ANOMALIES

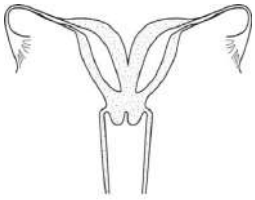

BICORNUATE UTERUS WITH BILATERAL OBSTRUCTED ENDOMETRIAL CAVITIES

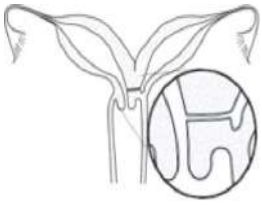

UTERUS DIDELPHYS WITH COMMUNICATING HEMIUTERI AND UNILATERAL R/L CERVICO-VAGINAL ATRESIA

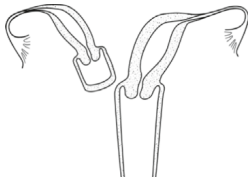

OBSTRUCTED R/L HEMIVAGINA, HEMIUTERUS AND SINGLE CERVIX WITH SEPARATE CONTRALATERAL R/L PATENT HEMIUTERUS, CERVIX AND VAGINA

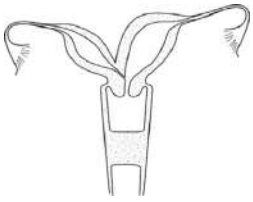

BICORNUATE UTERUS WITH R/L COMMUNICATING TRACT AND TRANSVERSE VAGINAL SEPTUM

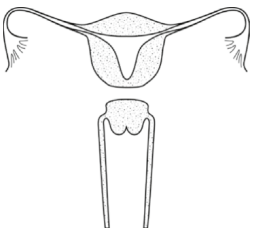

UTERUS ISTHMUS AGENESIS

Scan QR code to view the ASRM MAC 2021 tool (page 2 of 2)
©2021 American Society for Reproductive Medicine

Fig. 591.2 cont'd

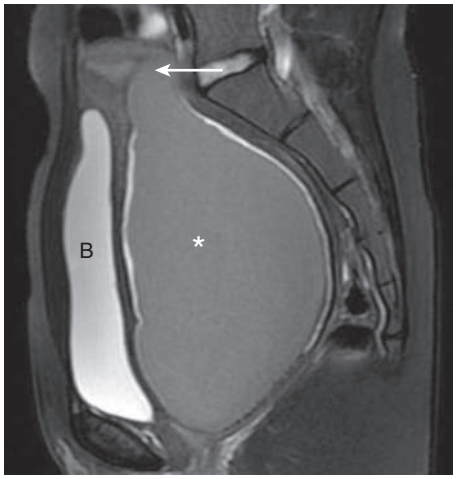

Fig. 591.3 Sagittal MRI of pelvis showing large volume hematocolpos (*asterisk*). *B,* Bladder; *arrow*, hematometra.

Combinations of congenital anomalies in other organ systems are prevalent in females with Müllerian anomalies. Renal and musculoskeletal abnormalities are the most common. An estimated 29% of females with a renal anomaly will have an associated Müllerian abnormality. Concomitant congenital malformations are also prevalent in approximately 54.4% of females with **Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome**.

CLINICAL MANIFESTATIONS

Vulvovaginal and Müllerian anomalies can manifest at a variety of chronological time points during a female's life: from infancy, through childhood and adolescence, and during adulthood (see Table 591.1). The majority of external genitalia malformations manifest at birth, and often even subtle deviations from normal in either a male or female newborn warrant evaluation. Structural reproductive tract abnormalities can be seen at birth or can cluster at menarche or any time during a patient's reproductive life. Some Müllerian anomalies such as arcuate uterus are asymptomatic and have no implications clinically, whereas others can cause gynecologic, obstetric, or fertility issues.

Clinical manifestations and treatments depend on the specific type of Müllerian anomaly and are varied. There may be a pelvic mass, which may or may not be associated with symptoms. A mass bulging at the introitus or within the vagina indicates complete or partial **outflow tract obstruction.** A newborn can present with no evidence of a vaginal opening. An adolescent can present with cyclic pelvic pain either in association with **primary amenorrhea** or several months after the onset of menarche. Patients also may be asymptomatic until they present with miscarriage, pregnancy loss, or preterm delivery. When presentation is acutely symptomatic, emergency management may be required. Obstruction can result from a number of distinct anomalies, including an **imperforate hymen,** a **transverse vaginal septum,** a distal **vaginal agenesis,** or a **noncommunicating rudimentary horn.** As menstrual fluid accumulates proximal to the obstruction, the resulting **hematocolpos** (Fig. 591.3) and **hematometra** cause cyclic pain, pelvic mass and, occasionally, urinary dysfunction.

Prenatal or neonatal presentation of hydrometrocolpos from distal vaginal obstruction produces fluid accumulation in the vagina and uterus and presents as a lower abdominal mass with or without associated acute urinary tract obstruction. Hydrometrocolpos with polydactyly may be a result of two autosomal recessive disorders: **McKusick-Kaufman syndrome** (with associated congenital heart disease) and **Bardet-Biedl syndrome** (with associated obesity, learning disabilities, retinitis pigmentosa, and renal anomalies).

Adolescent patients can present with acute obstruction of the outflow tract because of a Müllerian anomaly, which requires emergency evaluation and surgical treatment. A small percentage of females can present with concomitant urinary retention caused by an altered urethral angle or pressure on the sacral plexus. Urinary hesitancy and incomplete emptying symptoms may be present before abdominopelvic pain increases from the obstruction in a patient of any age. Some menstruating adolescents may present with increasing cyclic abdominopelvic pain with their menses due to an obstructed hemivagina with uterine didelphys and ipsilateral renal agenesis (OHVIRA).

LABORATORY AND RADIOGRAPHIC FINDINGS

Laboratory evaluation in the setting of primary amenorrhea would include hormonal evaluation with assessment of the beta chorionic gonadotropin (beta-hCG) to rule out pregnancy, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and thyroid-stimulating hormone (TSH). Androgen evaluation may be done if virilization is seen on physical examination. The patient's karyotype may be obtained based on clinical presentation. Other hormonal testing might be indicated in specific cases. Several radiographic studies have been used, often in combination, to aid in diagnosis including ultrasound, hysterosalpingogram, sonohysterography (saline-infusion sonography), and MRI. The least invasive initial study for a young adolescent with cyclic pain, a pelvic mass, or amenorrhea is a transabdominal pelvic ultrasound; transvaginal pelvic ultrasound can be used in sexually active teens. MRI is considered the gold standard of care and best suited for complex anomalies because of its noninvasive, high-quality capabilities. MRI is the most sensitive and specific imaging technique used for evaluating Müllerian anomalies because it can image nearly all reproductive structures, blood flow, external contours, junctional zone resolution on T2-weighted images, and associated renal and other anomalies. MRI also has a high correlation with surgical findings because of its multiplanar capabilities and high spatial resolution. Three-dimensional ultrasound is another useful diagnostic tool and may be superior to traditional pelvic ultrasound and hysterosalpingogram but may not be easily accessible. Evaluation of the external contour of the uterus is important for differentiating types of uterine anomalies. This often requires a combination of radiologic modalities for the uterine cavity, external contour, and possible tubal patency. Diagnostic laparoscopy or hysteroscopy may be necessary depending on the presentation, but it is less common with advancement of MRI and other imaging modalities.

Diagnosis of Müllerian anomalies should include a complete history, including family history, with special attention to history of infertility for female relatives and renal and skeletal abnormalities. A complete physical exam including skeletal inspections for associated anomalies should be performed in addition to the radiology studies discussed above. Renal anomalies are noted in 30–40% and skeletal anomalies are associated in 10–15% of patients with Müllerian anomalies. Unilateral renal agenesis occurs in 15% of patients. The most common skeletal anomaly is scoliosis. Patients usually have a normal female karyotype (46, XX), and most malformations are sporadic, with a polygenic mechanism and multifactorial etiology (Table 591.2).

UTERINE ANOMALIES

Anomalous development of the uterus may be symmetric or asymmetric and/or obstructed or nonobstructed. Patients can present with primary amenorrhea or have either irregular or regular menstrual cycles. There may be an asymptomatic pelvic mass or dysmenorrhea. In adolescents and adults, pregnancy loss can cause the first suspicion of a uterine anomaly. Treatment is tailored to the specific anomaly.

Septate Uterus

Uterine septum (also known as a septate uterus) is the most common Müllerian anomaly, accounting for just over half of all abnormalities, and it is the most common structural uterine anomaly. After the two Müllerian ducts fuse in the midline, resorption must occur to unify the endometrial cavities; failure of this process results in some degree of uterine septum. It can vary in length from just below the fundus to beyond the cervix, depending on the amount of caudal resorption, but is generally defined as >1 cm. A septate uterus has a normal external uterine contour, which is what distinguishes it from a bicornuate or

didelphic uterus. An MRI can help delineate between a predominantly fibrous septum and a muscular or myometrial septum. There is insufficient evidence between an association of the uterine septum and infertility. Controversy still exists regarding whether a female should have such surgical removal of the septum as part of infertility treatment. A previous recommendation for surgical septum resection has been challenged by recent research, which demonstrated that septum resection did not improve live birth rates compared with expectant management. Limited data exist on the influence of the thickness and the length of the septum on the choice of treatment and reproductive outcomes. Differentiating precisely between bicornuate and septate uteri is extremely important to determine effective and safe treatment plans.

Bicornuate Uterus

Both Müllerian ducts develop and elongate in this anomaly, but they do not completely fuse in the midline. The vagina and external cervix are normal, but the extent of division of the two endometrial cavities can vary, depending on the extent of failed fusion between the cervix and the fundus. Bicornuate uteri are also associated with increased preterm labor and delivery, malpresentation, and miscarriage. This anomaly accounts for approximately 10–20% of Müllerian anomalies. Presently there is no pregnancy outcome data to provide evidence to support unification of a uterine duplication, and expectant management should be encouraged.

Unicornuate Uterus and Rudimentary Horns

A unicornuate uterus results from the normal creation of a fallopian tube, functional uterus, cervix, and vagina from one Müllerian duct. The other side fails to develop, resulting in either absence of the contralateral Müllerian duct or a rudimentary horn. There is a 30–40% association of renal anomalies. If a rudimentary horn is identified, it is important to determine whether functional endometrium is present (usually with T2-weighted MRI images). About two-thirds of rudimentary horns are noncommunicating, some with a fibrous band connecting the two structures. Rudimentary horns can also communicate with the contralateral uterus. A fertilized ovum can implant and develop within a rudimentary horn. Pregnancies within a rudimentary horn are incompatible with expectant management, and rupture of the horn could be life-threatening. Rupture tends to occur at a later gestation than with an ectopic pregnancy, and hemorrhage is severe. Patients with rudimentary horns with functioning endometrium can also present with pain caused by accumulating menses. Because the contralateral uterine horn has a normal outflow pathway, these patients present with cyclic pain and/or a mass, not primary amenorrhea. Pregnancies that arise in a unicornuate uterus are associated with increased preterm labor and delivery, malpresentation, and miscarriage. The patient should be counseled regarding these increased obstetric risks and be offered a preconception consult with a high-risk obstetric physician to best manage pregnancy.

Uterus Didelphys

A uterus didelphys is the result of a complete failure of fusion and represents 5% of Müllerian anomalies. There are two fallopian tubes, two separate uterine cavities, two cervices, and often two vaginal canals or two partial canals because of an associated longitudinal vaginal septum (75% of the time). At times, the longitudinal septum attaches to one sidewall and obstructs one side of the vagina (or hemivagina) (Fig. 591.4). Evaluation for renal anomalies should be pursued because they are common as well. The combination of uterine didelphys, obstructed hemivagina, and ipsilateral renal agenesis is a variant of the broad spectrum of Müllerian anomalies that is referred to as **obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome** or **Herlyn-Werner-Wunderlich syndrome.** Adolescents with this disorder usually present with abdominal pain shortly after menarche. Although there still may be a risk of adverse pregnancy outcomes with a uterine didelphys (preterm labor, malpresentation), overall pregnancy outcomes are good and are associated with less risk than in other uterine anomalies, but preconception counseling and a consult with a high-risk obstetric physician should be offered.

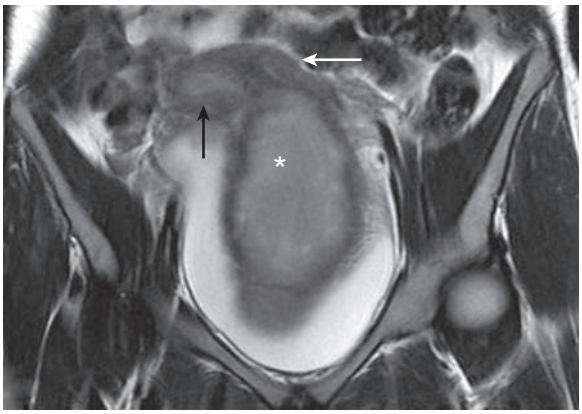

Fig. 591.4 Coronal MRI demonstrating large volume hematocolpos (*asterisk*) in a case of uterine didelphys with longitudinal vaginal septum. *Black arrow,* obstructed right uterus resulting in hematometra; white arrow, unobstructed left uterus.

Arcuate Uterus

An arcuate uterus is a uterine cavity that has a small midline septum from lack of a small amount of resorption (<1 cm), and sometimes a slight indentation of the uterine fundus. An arcuate uterus might represent a variant of normal rather than a Müllerian anomaly. Untoward pregnancy outcomes are rare, and *surgical correction is not warranted.*

Treatment

Treatment depends on the specific diagnosis and should be determined by a clinician with expertise in management of Müllerian anomalies. Most treatments focus on relief of obstruction and consider a patient's reproductive goals and history. Hysteroscopic surgical resection of the uterine septa was widely employed in the past, but a Cochrane systematic review shows no evidence to support surgical excision of the septum. Each individual case should be discussed with the patient, and a shared decision approach should be exercised based on the evidence of the benefit of such surgery.

A noncommunicating horn with functional endometrium should be resected to improve the quality of life or prevent future complications. Opinions vary as to whether resection of a communicating horn or one with no functional endometrium is warranted. Any surgical resection of a rudimentary horn requires careful surgical technique to protect the ipsilateral ovarian blood supply and the myometrium of the remaining unicornuate uterus.

Although metroplasty (also known as the Strassman unification method) had been employed with didelphic and bicornuate uteri in the past, currently most clinicians feel there is not enough evidence to support such a complicated procedure. Any obstruction to the outflow tract must be relieved; this can necessitate creation of a vaginal window or excision of the vaginal septum.

VAGINAL ANOMALIES

Abnormalities of the Hymen

An imperforate hymen is the most common obstructive anomaly, and familial occurrences have been reported (see Fig. 591.1). Its incidence is approximately 1 in 1,000. In the newborn period and early infancy, it may be diagnosed by a bulging membrane caused by a **mucocolpos** from maternal estrogen stimulation of the vaginal mucosa. This can eventually reabsorb if it is not too large or symptomatic. More often, it is diagnosed at the time of menarche when menstrual fluid accumulates **(hematocolpos)**. The clinical manifestations often are a bulging blue-black membrane, pain, and/or primary amenorrhea in a setting of normal secondary sex

characteristics. A mucocolpos or hematocolpos may obstruct urinary outflow. Depending on the circumstance, patients might have cyclic abdominal pain or a pelvic mass. Other hymenal variations can occur such as annular (most common) or crescentic configurations. In some cases, the hymenal membrane does not undergo complete resorption or perforation, resulting in a microperforate, cribriform, or septate-shaped hymen. Age of recognition varies, but hymenal variations are often discovered after menarche when it is difficult for an adolescent to place or remove a tampon.

Congenital Absence of the Vagina and Mayer-Rokitansky-Küster-Hauser Syndrome

Vaginal agenesis or atresia results when the vaginal plate fails to canalize. On physical exam, it appears as an extremely foreshortened vagina, sometimes referred to as a *vaginal dimple.* Isolated (partial) vaginal agenesis involves an area of aplasia between the distal vaginal portion and a normal upper vagina, cervix, and uterus. These patients present with cryptomenorrhea and eventually have cyclic pain caused by obstructed outflow. Each subsequent menses distends the upper vagina with menstrual blood. On initial presentation it may be confused with a low transverse septum or imperforate hymen, and therefore clear delineation of the anomaly with appropriate imaging is critical before attempting surgical repair. Surgical repair and reconstruction are complicated and best performed with consultation of specialists with expertise in managing these anomalies.

Uterine and **vaginal agenesis/aplasia** often occur together because of their close association during development, when Müllerian ductal development fails early in the process. The most common cause of uterovaginal agenesis/aplasia is **Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome,** with an incidence reported at 1 in 5,000 female births. The etiology is believed to be multigenetic and multifactorial. This condition is present at birth but often not diagnosed until mid-adolescence. Females with MRKH syndrome have normal ovarian function and undergo normal secondary sexual development at puberty but do not have a menstrual cycle (primary amenorrhea). The range and severity of MRKH syndrome can vary greatly and the disorder may be type I (isolated uterovaginal anomaly) or type II, involving additional organ systems, including the renal, skeletal, auditory, or cardiac systems. Absence of the vagina and uterus has significant anatomic, physiologic, and psychologic implications for the patient and family, and counseling is recommended. Although most patients with Müllerian agenesis have small rudimentary Müllerian bulbs, approximately 2–7% of patients can have active endometrium within these uterine structures. These patients will often present with cyclic pelvic pain. MRI may be necessary to determine if any small uterine remnant is present (often located on the pelvic sidewall or near the ovaries) and to clearly delineate the anomaly. Laparoscopy is not necessary to diagnose Müllerian agenesis but may be useful in the treatment of rudimentary uterine horns, particularly when removal of obstructed uterine structures or associated endometriosis is indicated for pelvic pain. Any diagnosis of Müllerian agenesis must be differentiated from **androgen insensitivity**; karyotype, serum testosterone levels, and pubic hair distribution help distinguish between the two because testosterone levels and adrenarche will be normal in females with MRKH syndrome.

Abnormalities involving other organ systems occur in association with MRKH type II, or Müllerian duct aplasia, renal dysplasia, and cervical somite anomalies (MURCS) association. The most common are urinary tract anomalies (15–40%) primarily involving unilateral absence of a kidney; a horseshoe or pelvic kidney; and skeletal anomalies (5–10%), which primarily involve vertebral development but can also include cardiac anomalies and hearing impairment, and these should be evaluated at the time of diagnosis.

Longitudinal Vaginal Septum

Longitudinal vaginal septa represent failure of complete canalization of the vagina. These often occur in the presence of uterine anomalies. These septa can vary in length from the cervix or cervices caudally and at times extend fully to the introitus. Patients may report menstruation that overflows their tampon because they only have a single side of the vagina occluded.

Transverse Vaginal Septum (Vertical Fusion Defects)

Vertical fusion defects can result in a transverse septum, which may be imperforate and associated with hematocolpos or hematometra in adolescents or with mucocolpos in infants. These are uncommon anomalies, reportedly found in 1 in 80,000 females. Patients commonly present with primary amenorrhea and cyclical abdominal pain around the time of menarche. However, patients who have a small opening in the transverse septa might present with prolonged vaginal drainage and mucopurulent or sanguineous discharge. Transverse vaginal septa can vary in location (15–20% occur in the lower third, but the majority are in the middle or upper third of the vagina) and thickness (but are generally ≤1 cm). High locations, thicker septa (>1 cm), and narrow vaginal orifices present challenging surgical cases.

Transverse vaginal septa may be associated with other congenital anomalies, although this occurs less often than with Müllerian agenesis. These patients have a functional normal uterus, unlike females with MRKH syndrome. In the majority of cases with outflow obstruction, there is also an increased incidence of endometriosis secondary to retrograde menstruation.

Evaluation of transverse vaginal septa includes careful pelvic examination and pelvic imaging, usually with MRI and ultrasound, to delineate the anatomic abnormalities. MRI is especially helpful to determine the thickness of the septum and verify the presence of a cervix for surgical planning. Diagnosis and treatment plans should be made as soon as possible after menarche because significant accumulation of hematometra and/or hematosalpinx could affect future reproductive success by negatively affecting uterine and/or tubal function. Alternately, menstrual suppression is another option to provide adolescent patients time to mature psychologically and participate in the treatment phase of the resection of the transverse septum.

Treatment

An imperforate hymen requires resection to prevent or relieve the outflow tract obstruction. Many approach it with a horizontal, lunate, or cruciate incision; excision of excess tissue; and approximation of the mucosal edges. Repair should be done at time of diagnosis if the patient is symptomatic, although the lesion may be repaired any time during infancy, childhood, or adolescence. Elective surgery with general anesthesia is discouraged in the very young. Elective hymenal excision in the prepubertal child may have improved healing if topical estrogen is placed at the site postoperatively. Elective excision of an imperforate hymen can be performed after onset of thelarche but ideally before menses. Variants in the hymen with microperforations or hymenal septa may interfere with tampon use, and resection of this tissue is usually electively performed using local anesthesia or sedation according to patient preference.

Treatment of congenital absence of the vagina is usually delayed until the patient is mature enough to discuss and participate in the treatment. The nonsurgical approach using vaginal dilation is the most common first-line therapy because it is safer, patient-controlled, more cost effective than surgery, and successful in 90–96% of patients. If done correctly, it is possible to achieve a functional vaginal length (6-8 cm), width, and physiologic angle for intercourse in about 6-8 months of therapy. When the ultimate size that accommodates coitus is reached, the patient must use the dilator or have coitus with a frequency that maintains adequate length.

Surgical approaches require expertise and often some postoperative vaginal dilation to ensure a functional result. Controversy exists as to when creation of a neovagina should occur. Surgery is indicated at any age if there is a medical indication such as mucocolpos that causes urinary obstruction or any other surgical emergency.

However, literature reports better outcomes with delaying creation of the neovagina to when the patient is interested in sexual activity and can participate in the decision to have surgery and in their own postoperative recovery. There is no consensus as to the best surgical option. Surgery should be reserved for the rare patient for whom primary dilator therapy was unsuccessful or for those who request surgery after a thorough informed consent. Referral to centers with expertise should be offered.

Future options for having children should be addressed, including adoption and gestational surrogacy. Assisted reproductive techniques using ovum retrieval, fertilization, and implantation of embryos into gestational carriers (surrogates) have been successful. Female offspring usually have normal reproductive tracts. Uterine transplantation has resulted in live births, but this procedure remains rare. Opportunities for family building enable patients and their families to appreciate the potential for becoming parents and help cope with the diagnosis and its implications.

Surgical resection of transverse vaginal septa should be undertaken only by surgeons with expertise. Some surgeons advocate waiting for one or more menstrual cycles or using preoperative dilators from below to increase the depth and circumference of the distal vagina and to allow menstrual blood to accumulate and dilate the upper portion of the vagina. Complete resection of the septum, with primary anastomosis of the upper and lower mucosal segments, should be attempted. A vaginal stent is sometimes placed postoperatively in the vagina to maintain patency and allow squamous epithelialization of the upper vagina and cervix. Follow-up dilation may be necessary after the stent is removed. Careful preoperative assessment is important because surgeons who begin a case believing they are operating on an imperforate hymen can find themselves in entirely different and more complex surgical planes. Regardless of the approach, vaginoplasty is often best deferred until the patient is mature and physically and psychologically prepared to participate in the healing process and postoperative dilator treatments. It can be challenging to differentiate a low transverse septum from distal vaginal agenesis. If the distal vagina cannot be palpated close to the anal sphincter by rectal examination, the patient should be allowed to continue to menstruate to distend the upper vagina to within 3 cm of the anal sphincter. This enables the surgeon to dissect up to the lower vagina and perform a pull-through procedure, anastomosing the upper vagina to the introitus. Proper timing and surgical execution yield excellent outcomes.

Longitudinal vaginal septa themselves do not lead to adverse reproductive outcomes but may be symptomatic in a patient, causing dyspareunia, traumatic bleeding with intercourse, difficulties with tampon insertion, or impedance during vaginal birth. Such complaints can warrant a resection of the vaginal septa. A carefully planned incision and resection of the oblique septum to maintain patency of the upper tract is performed in cases of OHVIRA (Herlyn-Werner-Wunderlich syndrome).

CERVICAL ANOMALIES

Congenital atresia or complete agenesis of the uterine cervix is extremely rare and often manifests at puberty with amenorrhea and pelvic pain. It is associated with significant renal anomalies in 5–10% of patients. A pelvic MRI is often warranted to completely define the abnormality. Usually, pain and obstruction are significant, and a hysterectomy is necessary. Attempts to reconnect the uterus to the vagina are rarely successful and are associated with significant morbidity and reoperation rates. The ovaries usually have normal function, and future reproduction can still occur using in vitro fertilization and a gestational carrier.

VULVAR AND OTHER ANOMALIES

Complete Vulvar Duplication

Duplication of the vulva is a rare congenital anomaly that is seen in infancy and consists of two vulvas, two vaginas, and two bladders, a didelphic uterus, a single rectum and anus, and two renal systems. Treatment is individualized and requires a multidisciplinary approach with gynecology, urology, and plastic surgery.

Labial Asymmetry and Hypertrophy

With the onset of puberty, the labia minora enlarge and grow to an adult size. A female's labia can vary in size and shape. Asymmetry of the labia, where the right and left labia are different in size and appearance, is a normal variant. Some patients are uncomfortable with what they perceive to be their asymmetric or enlarged labia minora and complain about self-consciousness and discomfort while wearing tight clothing, exercising, or having sex. The mature labia minora can protrude beyond the labia majora, and this normal variant can be functionally or psychologically bothersome. Local irritation, problems of personal hygiene with bowel movements or menses, or interference with sexual intercourse or while sitting or exercising have resulted in requests for labial reduction. Patients may find online procedures advertised to reduce uneven or enlarged labia minora. Education and reassurance are very important for adolescents who have concerns about the appearance of their labia. Surgery is not recommended unless there is significant congenital malformation or persistent symptoms directly related to the labia. Surgical alteration of the labia that is not necessary to the health of the adolescent less than age 18 is considered a violation of federal law in the United States. Complications of labial surgery include loss of sensation, keloid formation, and dyspareunia.

Clitoral Abnormalities

Agenesis of the clitoris is rare. Clitoral duplication has been reported, often associated with cloacal and bladder exstrophy. Exposure to male hormones will result in clitoral enlargement and is often a sign of a difference of sex development, a testosterone-producing tumor, or use of exogenous steroids.

Cloacal Anomalies

Cloacal anomalies are rare lesions representing a common urogenital sinus into which the gastrointestinal, urinary, and vaginal canals all exit. Usually there is an abnormality in all or some of the processes of fusion of the Müllerian ducts, development of the sinovaginal bulbs, or development of the vaginal plate. The single opening (cloaca) requires surgical correction, which is often done very early in life, preferably by a multidisciplinary pediatric surgical team.

Ductal Remnants

Even though the opposite duct regresses in both sexes, there can sometimes be a small portion of either the Müllerian or Wolffian duct that remains in either the male or female, respectively. Such remnants can form cysts, which are what make them clinically visible during surgery, examination, or imaging. Most do not cause pain, although torsion of some has been reported, and small asymptomatic ones usually do not require resection. The most commonly reported are hydatid of Morgagni cysts (remnant of a Wolffian duct arising from the fallopian tube), cysts of the broad ligament, and Gartner's duct cysts, which can form an ectopic ureter or be found along the cervix or vaginal walls.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 592

Gynecologic Care for Adolescents with Special Needs

Elisabeth H. Quint and Melina L. Dendrinos

Adolescence presents challenges for all children and their families but particularly for teens with special needs and their families. The start of menstrual periods, the mood changes associated with puberty, the concerns about sexual activity with possible unplanned pregnancies, and worries about safety and abuse present teens with disabilities and their families with additional issues.

SEXUALITY AND SEXUAL EDUCATION

Adolescents with special needs can have physical and/or developmental disabilities. These young people are often seen as asexual by their families, care providers, and society and, therefore, sexual education might not have been provided or considered necessary, even though physically disabled teens report being sexually active. The care provider needs to assess the teen's knowledge of anatomy and sexuality, gender identity, social knowledge of relationships, ability to consent to sexual and intimate activities, and sexual orientation, as well as any previous sexual activity. Education regarding HIV and other sexually transmitted infections, disease prevention, and contraception, including emergency contraception, should be offered at a developmentally appropriate level.

ABUSE

The risk for sexual abuse in teens with disabilities is difficult to estimate. Teens with disabilities may be more at risk for isolation and depression during adolescence, leading to vulnerability.

Teens with disabilities are just as sexually active or even more so than their nondisabled counterparts, but more of their activity is nonvoluntary. Patients with cognitive impairment are often taught to be cooperative, which may make them more vulnerable to coercion. Abuse prevention education can include the No! Go! Tell! model. For teens with limited verbal capacity or developmental delay, abuse may be very hard to detect; thus screening for abuse is extremely important. The care provider needs to be vigilant in looking for signs on physical exam, such as unexplained bruises or scratches, or changes in behavior, such as regression, which may be indications of sexual abuse (see Chapters 17.1 and 162).

PELVIC EXAMINATION

An internal pelvic exam is rarely indicated in teens, as Papanicolaou smears are not recommended to start until age 21. An external genital exam can be performed if there are vulvovaginal issues such as discharge, irregular bleeding, suspicion for abuse, or foreign body. The frog-leg position is usually favored over the use of stirrups. If the vagina or cervix needs to be clearly visualized for a medical indication, an exam under anesthesia by a gynecologist can be considered. Testing for sexually transmitted infections can be accomplished by urine testing or vaginal swabs (see Chapter 163).

MENSTRUATION

Irregular menstruation is common in teenagers, especially during the first 5 years after menarche, because of immaturity of the hypothalamic-pituitary-ovarian axis and subsequent anovulation (see Chapter 159). Several conditions in teens with disabilities are associated with an even higher risk of irregular cycles. Thyroid disease is more common in teens with Down syndrome. There is a higher incidence of reproductive issues, including polycystic ovarian syndrome, in teens with epilepsy or those taking certain antiepileptic drugs. Antipsychotic medication can lead to hyperprolactinemia, which can affect menstruation.

For teens with disabilities, the main issue with menstrual cycles, whether they are regular, irregular, or heavy, is the impact of menstruation on the patient's life, health, and ability to perform their normal activities. The history should focus on this aspect, and menstrual calendars may be helpful to document the cycles, behavior, and impact of treatments. Most adolescents who self-toilet can learn to use menstrual hygiene products appropriately. Menstrual underwear have been very helpful for many teens. Premenarchal anticipatory guidance is recommended, but hormonal treatment before menarche should be avoided.

The medical evaluation for abnormal bleeding is the same as for all teens (see Chapter 159.2). Areas requiring particular attention for the teen with special needs are the consideration of menstrual suppression for hygiene or cyclical behavioral issues, like crying, tantrums, or withdrawal.

Treatment of Menstruation

If the impact of cycles, whether regular, irregular, or heavy, on the patient's well-being is significant (often documented through menstrual or behavioral charting for several months), the care provider, patient, and family may decide on menstrual intervention. Menstrual regulation or suppression is not much different from that in the nondisabled teenager in general, although there are some special considerations. Goals for treatment can be to decrease the heaviness of flow, regulate cycles to predictable bleeding, relieve pain or cyclical behavior symptoms, provide contraception, and/or obtain amenorrhea. Menstrual suppression leading to complete amenorrhea is usually difficult to obtain and infrequent scheduled bleeds may be easier to manage than unpredictable spotting, a common side effect of any suppressive treatment, for certain patients. After treatment has started, providers should continue to monitor outcomes, ideally with continued menstrual or behavioral calendars to assess efficacy and need for changes.

Nonhormonal Methods

If menorrhagia or dysmenorrhea (occasionally leading to cyclical behavior changes in nonverbal teens) is the main concern, the patient can be started on scheduled nonsteroidal anti-inflammatory drugs. These can decrease the flow by up to 20% in adequate doses and can be used alone or in combination with other treatments. Use of tranexamic acid during the first 5 days of menses can also be used to decrease heavy bleeding.

Estrogen-Containing Methods

All estrogen-containing medication can be used in a cyclical fashion with scheduled medication breaks to allow for monthly menses; in a more extended fashion, where the active hormonal method is used for 3 months with a scheduled break; or a more flexible schedule, where the hormones are used until bleeding starts, and a break for withdrawal bleeding can be done at that time.

Oral Contraceptives

Cyclical oral contraceptives usually lead to regular, lighter cycles with less cramping. Continuous daily use of active oral contraceptives can suppress cycles, with amenorrhea rates improving with time. Some unpredictable spotting is usually unavoidable, and often teens with special needs prefer to have predictable cycles several times a year. Chewable oral contraceptives are available for those with swallowing issues.

Contraceptive Ring
The contraceptive ring can be used in a pattern of 3 weeks in and 1 week out, but it can also be used (off-label) in a continuous 4-week pattern, which leads to less bleeding. However, the contraceptive ring may be difficult to use for a teen with dexterity problems, and help with placement has obvious privacy issues.

Contraceptive Patch
The weekly patch can also be used in a cyclic or extended fashion. Some teens with developmental disabilities and sensory issues may remove their patch erratically, and placement out of reach (e.g., on buttocks or shoulder) is advised.

Estrogen Use, Venous Thromboembolism, and Mobility Issues
Whether immobility and wheelchair use can lead to an increased risk of venous-thromboembolic events (VTEs) in association with estrogen-containing contraceptives remains controversial. The risk of thrombosis in young females is very low overall, but the use of combined hormonal contraceptives by adolescents who are immobile or who have limited mobility has not been studied. Immobility per se is not a contraindication to estrogen-containing contraceptives; however, it may increase the risk of VTE. There are limited data to support the concern that higher-dose oral estrogen and the third- and fourth-generation progestin preparations may have a higher risk for VTE. It is important to assess for other VTE risk factors in the patient's history before initiating estrogen therapy. Careful use of lower-dose (30 or 20 μg) ethinyl estradiol preparations after appropriate counseling may be advisable, and third-generation progestin combinations should only be used if second-generation medications have failed.

Progestin-Only Methods
Intramuscular Medroxyprogesterone Acetate
Intramuscular depot medroxyprogesterone acetate (DMPA) has long been used for menstrual suppression. Two issues are particularly relevant to teens with disabilities. Studies documenting a decrease in bone density associated with longer-term use of DMPA and a black box warning by the FDA have raised concerns about use of these products in young females, although research indicates that the bone density improves after the medication is stopped. For teens with mobility issues or those with very low body weight who are already at risk for low bone density, decreased bone density is a real concern, although the risk of fractures is unclear. Adequate calcium and vitamin D is recommended. The second issue for teens with mobility issues is weight gain associated with DMPA, especially among obese teens, which can lead to transfer and mobility issues. The potential health risks associated with the effects of DMPA on bone density and weight must be balanced against the need for menstrual suppression and the likelihood of unintended pregnancy. Weight should be monitored closely. Routine bone density scanning (DEXA) is not recommended in adolescents.

Oral Progestins
Continuous oral progestins can also be very effective in obtaining amenorrhea. The contraceptive progestin-only pill (norethindrone 0.35 mg) can cause significant irregular spotting, so if full suppression is the goal, then other progestins can be used daily, such as drospirenone 4 mg, norethindrone 2.5 or 5 mg, or micronized progesterone 200 mg.

Progesterone Intrauterine Device
The 8-year levonorgestrel-intrauterine device is used for many teenagers for contraception, as well as heavy menses and dysmenorrhea (off-label use). Teens with special needs might require anesthesia for insertion if the exam is difficult because of discomfort, contractures, or a narrow vagina. Checking for strings in a clinic setting may be challenging; however, the intrauterine device location can be confirmed by sonography. There may be a significant amount of irregular bleeding and spotting in the first several months, but there is 20% rate of amenorrhea after insertion and up to 50% rate of amenorrhea after 1 year of use. The bleeding profile of the smaller and lower dose 3-5 year levonorgestrel-intrauterine devices may not be as helpful for menstrual suppression; the amenorrhea rates from the initial studies by the manufacturer are 8–12% at 1 year, but more studies are needed.

Implants
Progestin subdermal implants have relatively low amenorrhea rates and higher rates of unscheduled bleeding; therefore they are often less desirable for menstrual suppression for teens with special needs. They also require significant patient cooperation for insertion.

Hormones and Antiepileptic Drugs
Certain enzyme-inducing seizure medications can interfere with estrogen-containing contraceptives, change their contraceptive effectiveness, and/or lead to intermittent bleeding. Higher estrogen dose or shorter injection intervals for DMPA may be considered. The only antiepileptic medication that is affected by combined oral contraceptives is lamotrigine; consequently, the dose of that medication may need to be adjusted if used in conjunction with hormones, so discussion with other providers is needed.

Surgical Methods
Surgical procedures, such as endometrial ablation, a procedure where the lining of the uterus is surgically removed, and hysterectomy, are available for treatment of abnormal and heavy bleeding in adults, but they should only rarely be used in extreme situations for teenagers where all other methods have failed, and the patient's health is severely compromised by their cycles. Endometrial ablation only leads to amenorrhea approximately 30% of the time, has a higher failure rate in females younger than 40 years of age, and is not recommended in the adolescent population. Ethical considerations around these methods leading to infertility and consent issues are complicated, and state law varies on this topic.

CONTRACEPTION
See also Chapter 160.

The menstrual management methods discussed above can also be used for contraception. A request for birth control, especially coming from a caregiver and not the teen, requires an evaluation of the teen's ability to consent to sexual activity and the safety of their environment. The method chosen should be the safest method for their situation with the highest protection rate. Therefore a long-acting reversible contraceptive method may be advisable. Sexually transmitted infections and condom use should be addressed with the teen and specific guidelines on how to obtain condoms and negotiate their use may be needed. A discussion about emergency contraception is recommended, as well as ways to help the teen obtain this if indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 593

Female Genital Mutilation

Deborah Hodes and Sarah M. Creighton

Female genital mutilation (FGM) is a worldwide human rights issue that constitutes violence against women and children. It is defined by the World Health Organization (WHO) as procedures that involve partial or total removal of the external female genitalia, or other injury to the female genital organs for nonmedical reasons. In September 2015 the United Nations adopted the Sustainable Development Goals (SDGs), which includes the elimination of FGM by 2030. UNICEF (United Nations International Children's Emergency Fund) estimates that at least 200 million women and young females in 30 countries have undergone FGM. There has been a decline in the prevalence of FGM, but current trends suggest that actual numbers will rise because of population growth. FGM is commonly performed in Africa, the Middle East, and Asia, with data suggesting an estimated 40 million young females in Indonesia have undergone FGM. According to the UNICEF report 2020, the COVID-19 pandemic has caused disruption to the protection of young females from FGM leading to an estimated 2 million additional cases than would otherwise have occurred.

The migration of FGM-practicing communities means that FGM is a global problem, although there are scant data on the practice in high-income countries. Despite estimates, a British pediatric surveillance unit study found low numbers presenting to pediatricians; there were very few illegal cases and only one successful prosecution in the UK by 2021. FGM is almost always carried out on children, and pediatricians must be familiar with the identification of FGM, the impact on health, and ways to protect young females from this widespread form of child abuse.

FGM has no health benefits and can cause lifelong damage to physical and psychologic health. The WHO has classified FGM into four types, depending on the extent and type of genital tissue removed (Table 593.1). The traditional practitioner performs FGM without anesthetic or sterile conditions, and in some countries, it is done as part of a wider ritual related to early child marriage. The child is restrained whilst the external genitalia are removed or damaged using a knife, scalpel, or other sharp instrument. An increasing number of procedures are performed at a younger age, and the United Nations Population Fund (UNFPA) estimates that around one in five young females subjected to FGM were cut by a trained healthcare provider. Table 593.2 lists potential risks and protective factors for FGM.

COMPLICATIONS

Immediate complications of FGM include hemorrhage and infection. Deaths have been reported, although numbers are unknown. Infections include immediate wound infection, tetanus, and gangrene. FGM has been implicated in the transmission of blood-borne infections because of the use of shared and unsterile tools. Although procedure-related blood-borne infection is probable, there are no good studies to confirm this; infections such as hepatitis B and HIV are endemic in areas where FGM is prevalent. FGM leads to obstetric, gynecologic, and psychologic consequences in adult women. Gynecologic symptoms include painful and unsightly scarring, clitoral cysts, and recurrent urinary infections. Menstrual difficulties and infertility are reported, although the underlying mechanisms of these are unclear apart from type 3 FGM, where the vagina is narrowed. FGM damages sexual function by removing sensitive sexual tissue and narrowing the vagina. Mental health problems such as anxiety and depression have been linked to FGM. FGM also has a detrimental impact on obstetric outcomes for both the mother and baby, leading to increased risks of postpartum hemorrhage, perineal trauma, and perinatal death.

Table 593.1 Summary of WHO Classification of FGM

Type 1: Clitoridectomy: Partial or total removal of the clitoris (a small sensitive and erectile part of the female genitals) and, in rare cases, only the prepuce (the fold of skin surrounding the clitoris).
Type 2: Excision: Partial or total removal of the clitoris and labia minora with or without removal of the labia majora (the labia are the "lips" that surround the vagina).
Type 3: Infibulation: Narrowing of the vaginal opening through the creation of a covering seal. The seal is formed by cutting and repositioning the labia minora or majora with or without removal of the clitoris.
Type 4: Other: All other harmful procedures to the genitalia for nonmedical reasons (e.g., pricking, piercing, incision, scraping, and cauterizing the genital area).

From the World Health Organization Female Genital Mutilation Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/female-genital-mutilation

CLINICAL MANAGEMENT OF FGM

Most pediatricians will not see a child who is acutely unwell due to FGM. Management of FGM in the acute situation should include assessment for blood loss, sepsis, and urinary retention and treatment with antibiotics, analgesia, tetanus toxoid, and urinary catheterization. Pediatricians are more likely to see a child in whom FGM has been found during the investigation of other often vague symptoms as well as recurrent urinary tract infections and vulvovaginitis. FGM may also be alleged by the child or family member, or concerns may be raised by other health and social care professionals, particularly if the mother herself has undergone FGM and has little support from the husband (see Table 593.2). Pediatricians may be asked to confirm FGM on genital examination; it should be performed using a colposcope for magnification and video documentation, which can be used for peer review and in a court of law. The examination must be done in a sensitive and gentle manner by an appropriately trained clinician and in an age-appropriate setting. It is often assumed that FGM will be obvious. However, whilst type 3 FGM, in which the vagina is sealed, is usually easy to detect, other types of FGM can be more difficult to diagnose. This is particularly true for type 4 FGM, which may involve a prick or small scratch on or adjacent to the clitoris and may heal without a trace. General assessment of the child's health should include screening for blood-borne viruses.

If the child has type 3 FGM, then a deinfibulation procedure will be required at some point. Deinfibulation is a minor surgical procedure to divide any scar tissue that obscures the vaginal introitus. If the child is asymptomatic, this can be deferred until adolescence or before sexual activity. Deinfibulation procedures are usually performed under a local anesthetic in adult women, but in children a brief general anesthetic is more appropriate. The psychologic impact of FGM on a child may be severe, and flashbacks and nightmares have been reported. Input from a child psychologist or psychotherapist with experience in working with children with FGM and their families should be available. If a child is confirmed to have FGM, then other children in the family may be at risk, and local safeguarding pathways should be activated. Pediatricians must be advocates against FGM and contribute to training

Table 593.2 Factors That Influence Whether or Not a Child May Have FGM

RISK FACTORS
Mother or sister cut
Isolated mother
Grandmother influential
Little information and discussion about FGM
PROTECTIVE FACTORS
Discussing with husband or friend
Knowing the law has been implemented
TV, global debate, media
Men's attitude and knowledge
Knowing an uncut person

healthcare workers who may treat patients. In developed countries, there are concerns that the emphasis on prosecution has stigmatized and alienated communities in the diaspora who have abandoned the practice; because of this, experts emphasize the need for a more community-centric approach to current and future FGM prevention efforts.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

The Endocrine System

PART XXIV

Section 1

Disorders of the Hypothalamus and Pituitary Gland

Chapter 594

Hormones of the Hypothalamus and Pituitary

Eric I. Felner and Briana C. Patterson

The pituitary and hypothalamus are the major regulators of an elaborate hormonal system. The pituitary gland receives signals from the hypothalamus and responds by sending pituitary hormones to target glands. The target glands produce hormones that provide negative feedback at the level of the hypothalamus and pituitary (Figs. 594.1 and 594.2). This feedback mechanism enables the pituitary to regulate the amount of hormone released into the bloodstream by the target glands. The pituitary's central role in this hormonal system and its ability to interpret and respond to a variety of signals have led to its designation as the *master gland*. Table 594.1 lists the hypothalamic and pituitary hormones and their functions.

ANATOMY

The pituitary gland is located at the base of the skull in a saddle-shaped cavity of the sphenoid bone called the **sella turcica**. The bony structure protects and surrounds the pituitary bilaterally and inferiorly. The dura, a dense layer of connective tissue, forms the roof of the sella turcica. An external layer of the dura continues into the sella turcica to form its lining. As a result, the pituitary is extradural and is not normally in contact with cerebrospinal fluid. The pituitary gland is connected to the hypothalamus by the pituitary stalk. The pituitary gland is composed of an anterior (adenohypophysis) and a posterior (neurohypophysis) lobe. The anterior lobe constitutes approximately 80% of the gland.

EMBRYOLOGY

The anterior pituitary gland originates from Rathke's pouch as an invagination of the oral ectoderm. It then detaches from the oral epithelium and becomes an individual structure of rapidly proliferating cells. By 6 weeks of gestation, the connection between **Rathke's pouch** and oropharynx is completely obliterated. The pouch establishes a direct connection with the downward extension of the hypothalamus, which gives rise to the pituitary stalk. Persistent remnants of the craniopharyngeal duct, the original connection between Rathke's pouch and the oral cavity, can develop into adamantinous **craniopharyngiomas** (see Chapter 546).

VASCULAR SUPPLY

The arterial blood supply of the pituitary gland originates from the internal carotid via the inferior, middle, and superior **hypophyseal arteries**. This network of vessels forms a unique portal circulation connecting the hypothalamus and pituitary. The branches of the superior hypophyseal arteries penetrate the stalk and form a network of vessels that traverse the pituitary stalk and terminate in a network of capillaries within the anterior lobe. It is through this portal venous system that hypothalamic hormones are delivered to the anterior pituitary gland. Anterior pituitary hormones, in turn, are secreted into a secondary plexus of portal veins that drain into the dural venous sinuses.

ANTERIOR PITUITARY CELL TYPES

A series of sequentially expressed transcriptional activation factors directs the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. The consequences of pathogenic variants in several of these genes are evident in human forms of multiple pituitary hormone deficiency. Five cell types in the anterior pituitary produce six peptide hormones. **Somatotropes** produce growth

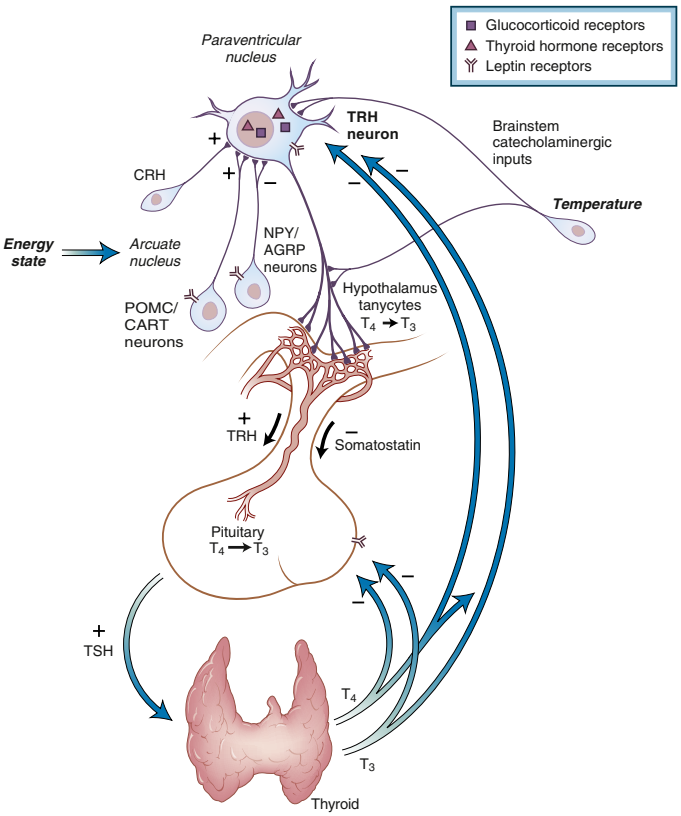

Fig. 594.1 Regulation of the hypothalamic-pituitary-thyroid axis. AGRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin. *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.9.)*

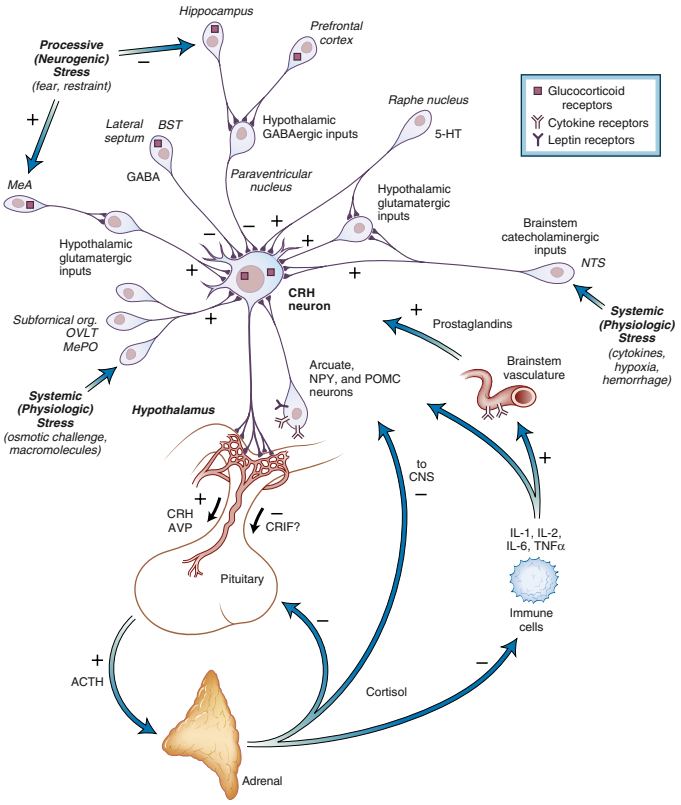

Fig. 594.2 Regulation of the hypothalamic-pituitary-adrenal axis. ACTH, Adrenocorticotropic hormone; AVP, arginine vasopressin; BST, bed nucleus of the stria terminalis; CNS, central nervous system; CRH, corticotropin-releasing hormone; CRIF, corticotropin release–inhibiting factor; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; IL-1, interleukin 1; MeA, medial amygdala; MePO, medial preoptic nucleus; NPY, neuropeptide Y; NTS, nucleus of the tractus solitarius; OVLT, organum vasculosum of the lamina terminalis; POMC, proopiomelanocortin; TNF-α, tumor necrosis factor-α. *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.18.)*

hormone (GH), **lactotropes** produce prolactin (PRL), **thyrotropes** make thyroid-stimulating hormone (TSH), **corticotropes** express proopiomelanocortin (POMC), the precursor of adrenocorticotropic hormone (ACTH), and **gonadotropes** express luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Growth Hormone

Human GH is a 191–amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotropes in the pituitary. Its gene *(GH1)* is the first in a cluster of five closely related genes on the long arm of chromosome 17 (q22-24). The other four genes *(CS1, CS2, GH2,* and *CSP)* have >90% sequence identity with the *GH1* gene.

GH is secreted in a pulsatile fashion under the regulation of hypothalamic hormones. The alternating secretion of GH-releasing hormone (GHRH), which stimulates GH release, and somatostatin, which inhibits GH release, accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of GHRH coincide with troughs of somatostatin. **Ghrelin**, a peptide produced in the arcuate nucleus of the hypothalamus and in much greater quantities by the stomach, also stimulates GH secretion. In addition to these three hypothalamic hormones, physiologic factors play a role in stimulating and inhibiting GH. Sleep, exercise, physical stress, trauma, acute illness, puberty, fasting, and hypoglycemia stimulate the release of GH, whereas hyperglycemia, hypothyroidism, and glucocorticoids inhibit GH release (Fig. 594.3).

GH binds to receptor molecules on the surface of target cells. The GH receptor is a 620–amino acid, single-chain molecule with an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. Proteolytically cleaved fragments of the extracellular domain circulate in plasma and act as a GH-binding protein. Similar to other members of the cytokine receptor family, the cytoplasmic domain of the GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated Janus kinase (Jak2). Phosphorylation of the kinase and other protein substrates initiates a series of events that leads to alterations in nuclear gene transcription. The signal transducer and activator of transcription 5b (STAT5b) plays a critical role in linking receptor activation to changes in gene transcription.

The biologic effects of GH include increases in linear growth, bone thickness, soft tissue growth, protein synthesis, fatty acid release from adipose tissue, insulin resistance, and blood glucose. The mitogenic actions of GH are mediated through increases in the synthesis of **insulin-like growth factor** 1 (IGF-1), formerly named *somatomedin C*, a 70–amino acid single-chain peptide coded for by a gene on the long arm of chromosome 12 with considerable homology to insulin. Circulating IGF-1 is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells, particularly in the growth plates of children, where its effect is exerted by paracrine or autocrine mechanisms. Circulating levels of IGF-1 are bound to several different binding proteins and are related to blood levels of GH and nutritional status. The major binding protein is a 150-kDa complex (IGF-BP3) that is low in GH-deficient children. Human recombinant IGF-1 has been developed as a therapeutic in conditions characterized by primary IGF-1 deficiency, end-organ resistance to GH (e.g., **Laron syndrome**), and the development of antibodies for those individuals administered GH. **Insulin-like growth factor** 2 (IGF-2) is a 67–amino acid single-chain protein that is coded for by a gene on the short arm of chromosome 11 that is also homologous to insulin and IGF-1. Less is known about its physiologic role, but it appears to be an important mitogen in bone cells, where it occurs in a concentration many times higher than that of IGF-1.

Prolactin

PRL is a 199–amino acid peptide made in pituitary lactotropes. The regulation of PRL is unique because PRL is constitutively secreted by the pituitary unless it is actively inhibited by dopamine, a peptide produced by neurons in the hypothalamus. Disruption of the hypothalamus or pituitary stalk can result in elevated PRL levels. Dopamine antagonists, states of primary hypothyroidism, administration of thyrotropin-releasing hormone (TRH), hypothalamic injury secondary to radiation therapy, and pituitary tumors result in increased serum levels of PRL. Dopamine agonists and processes causing destruction of the anterior pituitary gland can reduce levels of PRL.

The primary physiologic role for PRL is the initiation and maintenance of lactation. PRL prepares the breasts for lactation and stimulates milk production postpartum. During pregnancy, PRL stimulates the development of the milk secretory apparatus, but lactation does not occur because of the high levels of estrogen and progesterone. After delivery, the estrogen and progesterone levels drop, and physiologic stimuli such as suckling and nipple stimulation signal PRL release and initiate lactation.

Thyroid-Stimulating Hormone

TSH consists of two glycoprotein chains (α, β) linked by hydrogen bonding: the α-subunit, which is composed of 89 amino acids and is identical to other glycoproteins (FSH, LH, and human chorionic gonadotropin), and the β-subunit, composed of 112 amino acids, that is specific for TSH.

TSH is stored in secretory granules and released into circulation primarily in response to TRH, which is produced by the hypothalamus. TRH is released from the hypothalamus into the hypothalamic-pituitary portal system and ultimately stimulates TSH release from

Table 594.1 Hormones of the Hypothalamus and Pituitary Gland

HORMONES	LOCATION	S/I	FUNCTION
ACTH	Anterior pituitary	S	Production and secretion of GCs, MCs, and androgens from adrenal gland
ADH	Posterior pituitary	S	Reabsorption of water into the bloodstream via renal collecting ducts
CRH	Hypothalamus	S	Secretion of ACTH
Dopamine	Hypothalamus	I	Secretion of PRL
FSH (females)	Anterior pituitary	S	Secretion of estrogen from ovary
FSH (males)	Anterior pituitary	S	Production of sperm from testis
GH	Anterior pituitary	S	Secretion of IGF-1
GHRH	Hypothalamus	S	Secretion of GH
Ghrelin	Hypothalamus	S	Secretion of GH
GnRH	Hypothalamus	S	Secretion of FSH and LH
LH (females)	Anterior pituitary	S	Ovulation and development of the corpus luteum
LH (males)	Anterior pituitary	S	Production and secretion of testosterone
Oxytocin	Posterior pituitary	S	Contractions of uterus at birth and release of milk from breast
PRL	Anterior pituitary	S	Promotion of milk synthesis
Somatostatin	Hypothalamus	I	Secretion of GH and TSH
TRH	Hypothalamus	S	Secretion of TSH and PRL
TSH	Anterior pituitary	S	Secretion of T_4 and T_3

ACTH, Adrenocorticotropic hormone; ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GCs, glucocorticoids; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-derived growth factor 1; LH, luteinizing hormone; MCs, mineralocorticoids; PRL, prolactin; S/I, stimulate/inhibit; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

pituitary thyrotropes. TSH stimulates release of thyroxine (T_4) and triiodothyronine (T_3) from the thyroid gland through the formation of cyclic adenosine monophosphate and the G protein second messenger system. In addition to the negative feedback inhibition by T_3, the release of TRH and TSH is inhibited by dopamine, somatostatin, and glucocorticoids.

Deficiency of TSH results in inactivity and atrophy of the thyroid gland, whereas excess TSH results in hypertrophy and hyperplasia of the thyroid gland.

Adrenocorticotropic Hormone

ACTH is a 39–amino acid single-chain peptide that is derived by proteolytic cleavage from POMC, which is a 240–amino acid precursor glycoprotein product of the pituitary gland. POMC also contains the sequences for the lipotropins, melanocyte-stimulating hormones (α, β, γ), and β-endorphin.

Secretion of ACTH is regulated by corticotropin-releasing hormone (CRH), a 41–amino acid peptide found predominantly in the median eminence but also in other areas in and outside of the brain. ACTH is secreted in a diurnal pattern. It acts on the adrenal cortex to stimulate cortisol synthesis and secretion. ACTH and cortisol levels are highest in the morning at the time of waking, are low in the late afternoon and evening, and reach their nadir within the first 2 hours after beginning sleep. Similar to TRH and TSH, CRH and ACTH function through the formation of cyclic adenosine monophosphate and the G protein second messenger system. Although CRH is the primary regulator of ACTH secretion, other hormones play a role. Arginine vasopressin, oxytocin, angiotensin II, and cholecystokinin stimulate release of CRH and ACTH, whereas atrial natriuretic peptide and opioids inhibit release of CRH and ACTH. Similar to the feedback inhibition T_3 has on TRH and TSH, cortisol also inhibits CRH and ACTH. Physiologic conditions, such as stress, fasting, and hypoglycemia, also stimulate release of CRH and ACTH.

Luteinizing Hormone and Follicle-Stimulating Hormone

Gonadotropic hormones include two glycoproteins: LH and FSH. They contain the same α subunit as TSH and human chorionic gonadotropin but distinct β subunits. Receptors for FSH on the ovarian granulosa cells and on testicular Sertoli cells mediate FSH stimulation of follicular development in the ovary and of gametogenesis in the testis. On binding to specific receptors on ovarian theca cells and testicular Leydig cells, LH promotes luteinization of the ovary and Leydig cell function of the testis (Fig. 594.4). The receptors for LH and FSH belong to a class of receptors with seven membrane-spanning protein domains. Receptor occupancy activates adenylyl cyclase through the mediation of G proteins.

LH-releasing hormone, a decapeptide, has been isolated, synthesized, and widely used in clinical studies. Because it leads to the release of LH and FSH from the same gonadotropic cells, it appears that it is the only gonadotropin-releasing hormone (GnRH).

Secretion of LH is inhibited by androgens and estrogens, and secretion of FSH is suppressed by gonadal production of inhibin, a 31-kDa glycoprotein produced by ovarian granulosa cells (females) and testicular Sertoli cells (males). Inhibin consists of α and β subunits joined by disulfide bonds. The β-β dimer activin also exists, and its actions generally oppose that of inhibin by stimulating FSH secretion. In addition to its endocrine effect, activin has paracrine effects in the testis. It facilitates LH-induced testosterone production, indicating a direct effect of Sertoli cells on Leydig cells.

POSTERIOR PITUITARY CELL TYPES

The posterior lobe of the pituitary is part of a functional unit, the neurohypophysis, that consists of the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe. Vasopressin (antidiuretic hormone

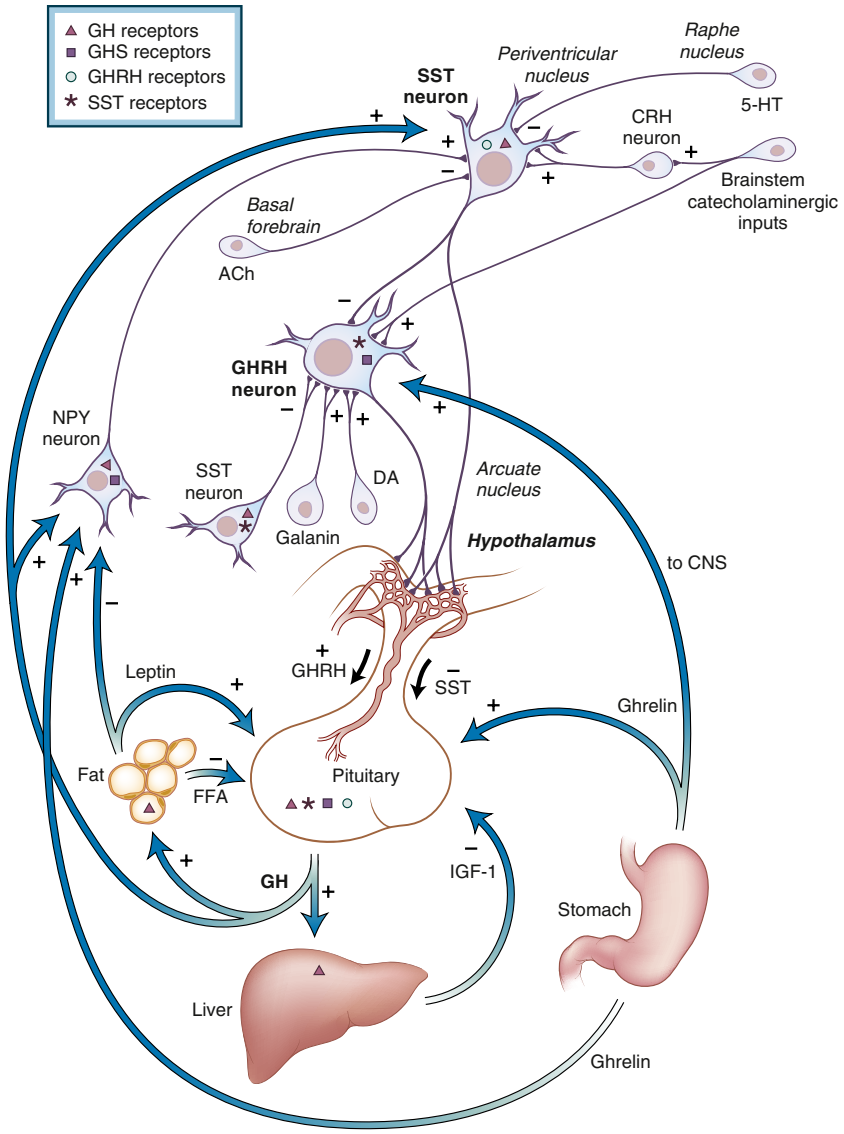

Fig. 594.3 Regulation of the hypothalamic-pituitary-growth hormone (GH) axis. GH secretion by the pituitary is stimulated by GH-releasing hormone (GHRH) and is inhibited by somatostatin (SST). Negative feedback control of GH secretion is exerted at the pituitary level by insulin-like growth factor 1 (IGF-1) and by free fatty acids (FFAs). GH itself exerts a short-loop negative feedback through activation of SST neurons in the hypothalamic periventricular nucleus. These SST neurons directly synapse on arcuate GHRH neurons and project axon collaterals to the median eminence. Neuropeptide Y (NPY) neurons in the arcuate nucleus also indirectly modulate GH secretion by integrating peripheral GH, leptin, and ghrelin signals and projecting to periventricular SST neurons. Ghrelin is secreted from the stomach and is a natural ligand for the GH secretagogue (GHS) receptor that stimulates GH secretion at both the hypothalamic and pituitary levels. On the basis of indirect pharmacologic data, it appears that release of GHRH is stimulated by galanin, γ-aminobutyric acid (GABA), and α_2-adrenergic and dopaminergic inputs and inhibited by SST. Secretion of SST is inhibited by muscarinic acetylcholine (ACh) and 5-HT-1D receptor ligands and increased by β_2-adrenergic stimuli and corticotropin-releasing hormone (CRH). CNS, Central nervous system; DA, dopamine; 5-HT, serotonin (5-hydroxytryptamine). *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.22.)*

[ADH]) and oxytocin are the two hormones produced by neurosecretion in the hypothalamic nuclei and released from the posterior pituitary. They are octapeptides and differ by only two amino acids.

Vasopressin

Vasopressin (ADH) regulates water conservation at the level of the kidney by increasing the permeability of the renal collecting duct to water. It stimulates translocation of water channels through its interaction with vasopressin 2 (V2) receptors in the collecting duct, which act through G proteins to increase adenylyl cyclase activity and increase permeability to water. These V2 receptors also mediate von Willebrand factor and tissue plasminogen activator. At higher concentrations, ADH activates vasopressin 1 (V1) receptors in smooth muscle cells and hepatocytes and exerts pressor and glycogenolytic effects through mobilization of intracellular calcium stores. Separate vasopressin 3

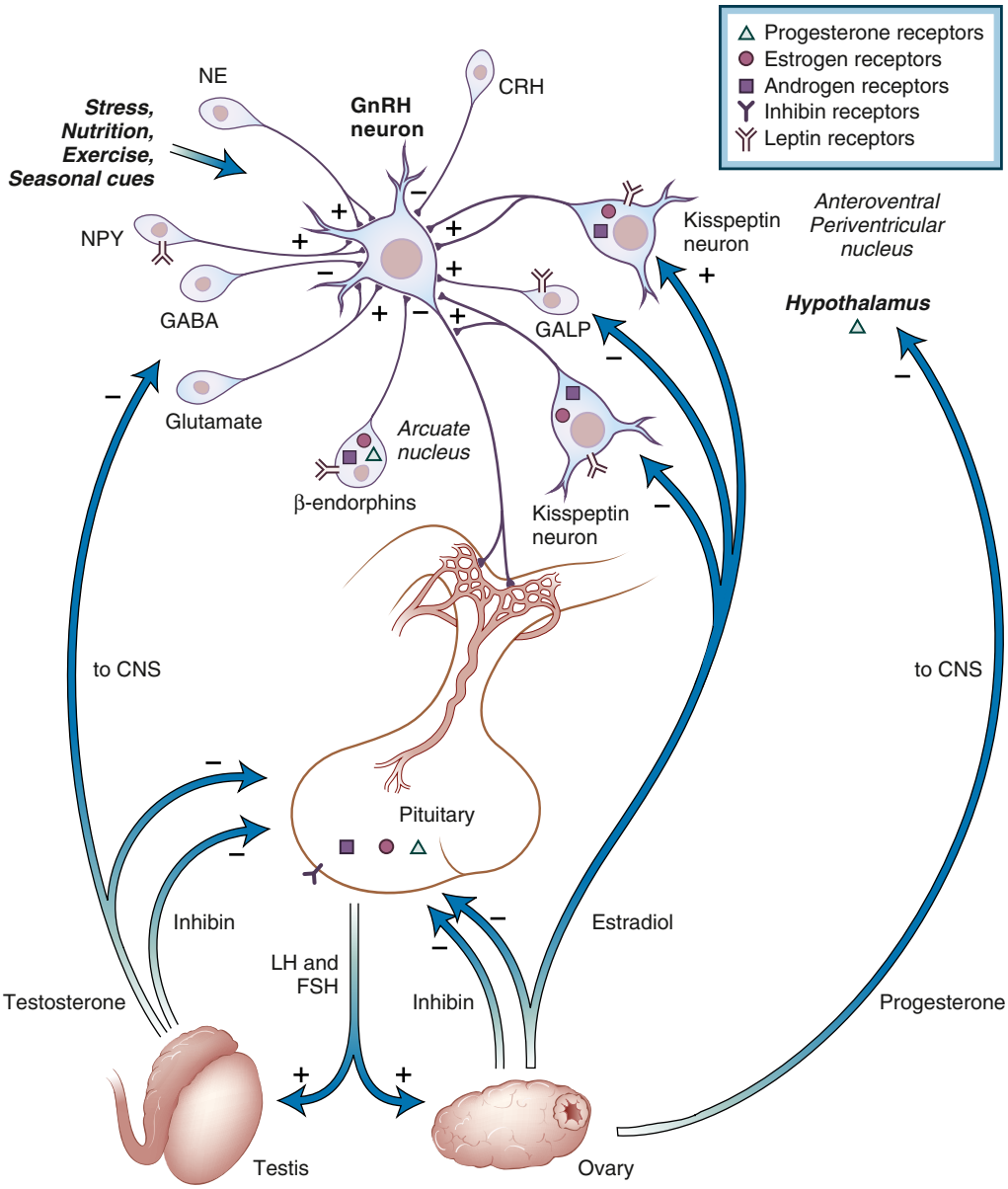

Fig. 594.4 Regulation of the hypothalamic-pituitary-gonadal axis. Schematic diagram of the hypothalamic-pituitary-gonadal axis showing neural systems that regulate gonadotropin-releasing hormone (GnRH) secretion and feedback of gonadal steroid hormones at the level of the hypothalamus and pituitary. CNS, Central nervous system; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GABA, γ-aminobutyric acid; GALP, galanin-like peptide; LH, luteinizing hormone; NE, norepinephrine; NPY, neuropeptide Y. *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.30.)*

(V3) receptors mediate stimulation of ACTH secretion. These effects involve phosphatidylinositol hydrolysis rather than cyclic adenosine monophosphate production.

Vasopressin and its accompanying protein neurophysin II are encoded by the same gene. A single preprohormone is cleaved, and both are transported to neurosecretory vesicles in equimolar amounts in the posterior pituitary.

Vasopressin has a short half-life and responds quickly to changes in hydration. The stimuli for its release are increased plasma osmolality, perceived by osmoreceptors in the hypothalamus, and decreased blood volume, perceived by baroreceptors in the carotid sinus of the aortic arch.

Oxytocin

Oxytocin stimulates uterine contractions at the time of labor and delivery in response to distention of the reproductive tract and stimulates smooth muscle contraction in the breast during suckling, which results in milk letdown. Studies suggest that oxytocin also plays a role in orgasm, social recognition, pair bonding, anxiety, trust, love, and maternal behavior. Most recently, through the interaction with its G protein–coupled receptor in pancreatic and adipose tissue, oxytocin appears to play a significant role in appetite regulation and obesity by inducing anorexia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 595

Hypopituitarism

Briana C. Patterson and Eric I. Felner

Hypopituitarism denotes underproduction of one or more pituitary hormones. Affected children have postnatal growth impairment and other endocrine deficiencies that are specifically corrected by hormone replacement. The incidence of *congenital* hypopituitarism is thought to be between 1 in 4,000 and 1 in 10,000 live births. An epidemiologic association between hypopituitarism and breech delivery has been reported, but the causal relationship is not understood. With expanding knowledge of the genes that direct pituitary development or hormone production, an increasing proportion of cases can be attributed to specific genetic alterations. Monogenic causes can only be identified in about 10% of persons with congenital hypopituitarism. The likelihood of finding a genetic alteration is increased by consanguinity and occurrence in siblings or across generations; however, in *most* cases of *isolated* **growth hormone deficiency (GHD)** and *sporadic* **multiple pituitary hormone deficiency (MPHD)**, no specific single-gene cause can be identified. It is likely that polygenic and/or environmental factors regularly play a role in the development of congenital hypopituitarism. The genes, hormonal phenotypes, associated abnormalities, and modes of transmission of several single-gene disorders causing congenital MPHD are shown in Table 595.1. Causes of *acquired* hypopituitarism, which usually has a later onset, has different causes (Table 595.2). Single-gene alterations causing disruption of the GH axis primarily are shown in Table 595.3.

MULTIPLE PITUITARY HORMONE DEFICIENCY

Genetic Forms (see Table 595.1)

Sequentially expressed transcriptional activation factors direct the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. Alterations in different genes may produce different manifestations of MPHD. The *PROP1* and *POU1F1* genes are expressed later in pituitary development only in cells of the anterior pituitary and result in hypopituitarism without anomalies in other organ systems. The *HESX1, LHX3, LHX4, OTX2, SOX3,* and *PITX2* genes are expressed at earlier stages and are not restricted to the pituitary. Pathogenic alterations in these genes tend to produce phenotypes that extend beyond hypopituitarism to include abnormalities in other organs, and the degree of hypopituitarism is typically variable.

PROP1

PROP1 is found in the nuclei of somatotropes, lactotropes, and thyrotropes. Its roles include turning on *POU1F1* expression and downregulating *HESX1* expression. Although no genetic alteration can be identified in most patients with MPHD, pathogenic variants of *PROP1* are the most common explanation for recessive MPHD and are 10 times as common as the combined total of alterations in other pituitary transcription factor genes. Deletions of one or two base pairs in exon 2 are most common, followed by missense, nonsense, and splice-site pathogenic mutations. Anterior pituitary hormone deficiencies may not be evident in the neonatal period. The median age at diagnosis of GHD is around 6 years. Recognition of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adrenocorticotropic hormone (ACTH) deficiencies is delayed relative to recognition of GHD. Anterior pituitary size is small in most patients, but in others there is progressive enlargement of the pituitary.

POU1F1 (PIT1)

POU1F1 (formerly *PIT1*) is a nuclear protein that binds to the GH and prolactin promoters. It is necessary for the emergence and mature function of somatotropes, lactotropes, and thyrotropes. Dominant and recessive pathogenic variants in *POU1F1* are responsible for complete deficiencies of growth hormone (GH) and prolactin and variable TSH deficiency. Affected patients exhibit nearly normal fetal growth but experience severe growth failure in the first year of life. With normal production of LH and FSH, puberty develops spontaneously, although at a later-than-normal age. These patients are not at risk for development of ACTH deficiency. Anterior pituitary size is normal to small.

HESX1

The *HESX1* gene is expressed in precursors of all five cell types of the anterior pituitary early in embryologic development. Pathogenic genetic variations in *HESX1* result in heterogeneous phenotypes with differences in development of the optic nerve and pituitary. The anterior pituitary may be hypoplastic or aplastic, and the posterior pituitary may be orthotopic or ectopic. Patients may have isolated GHD or MPHDs, with or without the **optic nerve hypoplasia syndrome**, historically called *septo-optic dysplasia* (incomplete development of the septum pellucidum with optic nerve hypoplasia and pituitary insufficiency). However, the majority of patients with optic nerve hypoplasia syndrome do not have *HESX1* gene alterations.

LHX3 and *LHX4*

The phenotype produced by recessive loss-of-function alterations of the *LHX3* gene resembles that produced by *PROP1* genetic variants. There are deficiencies of GH, prolactin, TSH, LH, and FSH but not ACTH. Some affected persons show enlargement of the anterior pituitary. The first patients to be described had the unusual findings of a short neck and a rigid cervical spine. Dominantly inherited pathogenic variations in the structurally similar *LHX4* gene consistently produce GH deficiency, with the variable presence of TSH and ACTH deficiencies. Additional findings can include a very small V-shaped pituitary fossa, **Chiari I malformation**, and an ectopic posterior pituitary.

Other Congenital Forms

Pituitary hypoplasia can occur as an isolated phenomenon or in association with more extensive developmental differences such as anencephaly or holoprosencephaly. Midline facial anomalies (cleft lip, palate; see Chapter 356) or the finding of a solitary maxillary central incisor may indicate a higher likelihood of GH or other anterior or posterior hormone deficiency (Fig. 595.1). At least 12 genes have been implicated in the complex genetic etiology of **holoprosencephaly**.

Hall-Pallister syndrome is caused by dominant loss-of-function alterations in the *GLI3* gene. Absence of the pituitary gland is accompanied by hypothalamic hamartoma, polydactyly, nail dysplasia, bifid epiglottis, imperforate anus, and anomalies of the heart, lungs, and kidneys. The combination of **anophthalmia** and **hypopituitarism** has been associated with pathogenic variants in the *SIX6, SOX2,* and *OTX2* genes.

Optic nerve hypoplasia syndrome may be detected as a result of clinical observation of nystagmus and visual impairment in infancy. Neuroimaging demonstrates optic nerve and brain abnormalities and is associated with anterior and/or posterior pituitary hormone deficiencies in up to 75% of cases (Fig. 595.2). Although these patients often show the triad of a small anterior pituitary gland, an attenuated pituitary stalk, and an ectopic posterior pituitary bright spot, the primary etiology of the hypopituitarism in this condition is thought to be hypothalamic dysfunction. GH deficiency is the commonly observed hormone deficiency, and other anterior pituitary hormone deficiencies are less common. Diabetes insipidus is reported in only about 5% of cases. The etiology is likely multifactorial and may involve interaction between genetic and environmental factors. In most cases, no single-gene alteration can be identified.

Severe, early-onset MPHD, including deficiency of ACTH, is often associated with the triad of anterior pituitary hypoplasia, absence or attenuation of the pituitary stalk, and an ectopic posterior pituitary bright spot seen on MRI. Most cases are sporadic, and there is a male predominance. Some are caused by pathogenic variants of the *SOX3* gene, located on the X chromosome.

Table 595.1 Etiologic Classification of Congenital and Genetic Forms of Multiple Pituitary Hormone Deficiency

GENE OR LOCATION	PHENOTYPE	INHERITANCE
GENETIC FORMS		
POU1F1 (PIT1)	GH, PRL deficiencies, variable TSH deficiency	AR, AD
PROP1	GH, TSH, PRL, LH, FSH deficiencies, variable ACTH deficiency, variable AP	AR
LHX3	GH, TSH, PRL, LH, FSH deficiencies, variable AP, ± short neck, limited neck rotation, sensorineural deafness	AR
LHX4	GH, TSH, ACTH deficiencies, small AP, EPP, variable Arnold-Chiari, cerebellar abnormalities	AD
TPIT	ACTH deficiency, severe neonatal form	AR
HESX1	GH deficiency, variable for others, small AP, EPP, optic nerve hypoplasia; septo-optic dysplasia	AR, AD
SOX2	LH, FSH deficiencies, variable GH deficiency, anophthalmia, microphthalmia, esophageal atresia, sensorineural hearing loss	AD
SOX3	Variable deficiencies, ± MR, EPP, small AP and stalk, developmental delay	XL
PITX2	Axenfeld-Rieger syndrome: hypogonadotropic hypogonadism, pituitary hypoplasia, anterior chamber abnormalities of the eye, dental hypoplasia	AD
GLI2	Hypopituitarism, holoprosencephaly, midline defects, polydactyly	AD
GLI3	Hall-Pallister syndrome, hypopituitarism	AD
SHH (Sonic Hedgehog)	GH deficiency with single central incisor	AD
OTX2	GH or combined deficiencies, anophthalmia or microphthalmia, coloboma, developmental delay	AD
TBX19	ACTH deficiency, neonatal hypoglycemia or cholestatic jaundice	AR
PC1	Hypogonadotropic hypogonadism, ACTH deficiency	AR
GIF, SHHT, SIX3	Pituitary stalk interruption syndrome: thin or absent pituitary stalk, hypoplasia of adenohypophysis, ectopic neurohypophysis, neonatal hypoglycemia, cholestasis, micropenis	Holoprosencephaly related gene group
FGF8	Hypopituitarism, holoprosencephaly	AD
FGFR1	Hypopituitarism, pituitary hypoplasia, agenesis of the corpus callosum, ocular defects	AD
PROKR2	GH, TSH and ACTH deficiencies, micropenis and neonatal hypoglycemia	AD, AR
UNKNOWN OR POLYGENETIC ETIOLOGY		
Congenital absence of pituitary gland		
Optic nerve hypoplasia syndrome/septo-optic dysplasia	Optic nerve hypoplasia, nystagmus, absent septum pellucidum, pituitary hypoplasia	

ACTH, Adrenocorticotropic hormone; AP, anterior pituitary; AD, autosomal dominant; EPP, ectopic posterior pituitary; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; MR, mental retardation; PRL, prolactin; AR, autosomal recessive; TSH, thyroid-stimulating hormone; XL, X-linked.

Acquired Forms

Any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary can cause pituitary hormone deficiency (see Table 595.2). Because such lesions are not selective, multiple hormonal deficiencies are usually observed. Diabetes insipidus is more frequent in *acquired* than in congenital hypopituitarism. The most common structural lesion of the pituitary causing childhood-onset acquired MPHD is craniopharyngioma (see Chapter 546). Central nervous system germinoma, optic pathway or hypothalamic glioma, histiocytosis, tuberculosis, sarcoidosis, toxoplasmosis, meningitis, pituitary abscess, and aneurysms can also cause hypothalamic-hypophyseal damage and dysfunction. Additionally, children treated with radiation therapy for central nervous system or nasopharyngeal tumors are at increased risk for GHD and other pituitary hormone deficiencies to the extent that the radiation field includes the hypothalamus and/or pituitary, even if the tumor itself is anatomically remote from the pituitary and hypothalamus. The magnitude of the risk and the timing of the emergence of pituitary hormone deficiencies depend on the dose of radiation to the hypothalamic-pituitary axis and the duration of elapsed time after radiotherapy is complete. High doses of radiation (>50 Gy) are likely to produce GH deficiency sooner than 1 year after irradiation, whereas other anterior pituitary hormone deficiencies may not appear until later. GH production appears to be particularly vulnerable to the effects of irradiation, even at lower doses, whereas deficiencies of ACTH, gonadotropins, and thyrotropin-releasing hormone (TRH)/TSH occur with declining frequency and typically occur at higher doses of radiation. Irradiation alone does not typically result in diabetes insipidus. Traumatic brain injury, including abusive head trauma, motor vehicle accidents, and chronic repetitive head injury, is an increasingly recognized cause of pituitary dysfunction related to damage to the pituitary, its stalk, or the hypothalamus.

ISOLATED GROWTH HORMONE DEFICIENCY AND INSENSITIVITY

Genetic Forms of Growth Hormone Deficiency

Isolated GHD is caused by abnormalities of the GH-releasing hormone receptor, GH genes, and certain genes located on the X chromosome (see Table 595.3).

Growth Hormone–Releasing Hormone Receptor

Recessive loss-of-function alterations in the receptor for GH-releasing hormone interfere with proliferation of somatotropes during pituitary development and disrupt the most important signals for release of GH. The anterior pituitary is small, in keeping with the observation that

Table 595.2 Causes of Acquired Pituitary Insufficiency

TRAUMATIC
Surgical resection
Radiation damage
Traumatic brain injury
INFILTRATIVE/INFLAMMATORY
Primary hypophysitis
Lymphocytic
Granulomatous
Xanthomatous
Secondary hypophysitis
Sarcoidosis
Langerhans cell histiocytosis
Granulomatosis with polyangiitis
Takayasu disease
Hemochromatosis
INFECTIONS
Tuberculosis
Pneumocystis jirovecii infection
Fungal (histoplasmosis, aspergillosis)
Parasites (toxoplasmosis)
Viral (cytomegalovirus)
VASCULAR
Pregnancy related
Aneurysm
Apoplexy
Diabetes
Hypotension
Arteritis
Sickle cell disease
NEOPLASTIC
Pituitary adenoma
Parasellar mass
Rathke cyst
Dermoid cyst
Meningioma
Germinoma
Suprasellar/optic pathway glioma
Craniopharyngioma
Hypothalamic hamartoma
Pituitary metastatic deposits
Hematologic malignancy
Leukemia
Lymphoma
FUNCTIONAL
Nutritional
Caloric restriction
Malnutrition
Excessive exercise
Nonspecific illness
Acute critical illness
Chronic renal failure
Chronic liver failure
Hormonal
Hyperprolactinemia
Hypothyroidism
Drugs
Anabolic steroids
Glucocorticoid excess
GnRH agonists
Estrogen
Dopamine
Somatostatin analog
Immune check-point inhibitors

Modified from Kaiser U, Ho KKY. Pituitary physiology and diagnostic evaluation. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology,* 13th ed. Philadelphia: Elsevier; 2016: Table 8.5, p. 193.

somatotropes normally account for >50% of pituitary volume. There is some compromise of fetal growth followed by severe compromise of postnatal growth.

GH1

The *GH1* gene is one of a cluster of five genes on chromosome 17q22-24. This cluster arose through successive duplications of an ancestral GH gene. Unequal crossing over at meiosis has produced a variety of gene deletions. Small deletions (<10 kb) remove only the *GH1* gene, whereas large deletions (45 kb) remove one or more of the adjacent genes (*CSL, CS1, GH2,* and *CS2*). The growth phenotype is identical with deletion of *GH1* alone or *GH1* together with one or more of the adjacent genes. Loss of the *CS1, GH2,* and *CS2* genes without loss of *GH1* causes deficiency of chorionic somatomammotropin and placental GH in the maternal circulation, but it does not result in fetal or postnatal growth retardation. Most children with *GH1* gene deletions respond very well to recombinant GH treatment, but some develop *antibodies* to GH and cease growing despite treatment.

Recessively transmitted pathogenic variants in the *GH1* gene produce a similar phenotype. Missense, nonsense, and frameshift alterations have been described. Autosomal dominant isolated GHD is also caused by variants in *GH1*. These alterations usually involve splice-site errors in intron 3 and result in a variant protein that lacks the amino acids normally encoded by exon 3. Accumulation of this protein interferes with the processing, storage, and secretion of the normal GH protein and may result in additional deficiencies of TSH and/or ACTH. There are several reports of alterations in *GH1* that lead to variant proteins with reduced biologic activity.

X-Linked Isolated Growth Hormone Deficiency

Two loci on the X chromosome have been associated with hypopituitarism. The first lies at Xq21.3-q22 in the region of the *BTK* gene. Pathogenic variants in this region produce hypogammaglobulinemia and isolated GHD. The second locus maps farther out on the long arm, at Xq24-q27.1, a region containing the *SOX2* transcription factor gene. Abnormalities in this locus have been linked to isolated GHD with intellectual disability and to MPHD with the triad of pituitary hypoplasia, missing pituitary stalk, and ectopic posterior pituitary gland.

Acquired Forms

The GH axis is more susceptible to disruption by acquired conditions than are other hypothalamic-pituitary axes. Recognized causes of acquired GHD include the use of radiotherapy for malignancy, meningitis, histiocytosis, and trauma.

Children who receive radiotherapy for central nervous system tumors, leukemia, or total body irradiation before hematopoietic stem cell transplant are at risk for developing GHD. Spinal irradiation results in disproportionately poor growth of the axial skeleton relative to the appendicular skeleton; this problem is not remediable with GH treatment. Growth typically slows during radiation therapy or chemotherapy, may improve for 1-2 years after cancer treatment, and then declines with the development of GHD. The dose and frequency of radiotherapy are important determinants of hypopituitarism. GHD is almost universal 5 years after therapy with a total dose ≥35 Gy. More subtle defects are seen with doses around 20 Gy. Deficiency of GH is the most common defect, but deficiencies of TSH and ACTH can also occur. The evaluation of GHD is more complicated when radiation-associated precocious puberty is also present. The clinician is likely to encounter children in the 8- to 10-year age range who are growing at rates that are normal for chronological age but subnormal for stage of pubertal development.

GROWTH HORMONE INSENSITIVITY

Abnormalities of the Growth Hormone Receptor

GH insensitivity is caused by disruption of pathways distal to the production of GH (Table 595.4). **Laron syndrome** involves pathogenic genetic variations in the GH receptor. Children with this condition clinically resemble those with severe isolated GHD. Birth length tends to be about 1 standard deviation (SD) below the mean, and severe short stature with lengths >4 SD below the mean is present by 1 year of age. Resting and stimulated GH levels tend to be high, and insulin-like growth factor (IGF) 1 levels are low. The GH receptor has an extracellular GH-binding domain, a transmembrane domain, and an

Table 595.3 Established Genetic Defects of the GH-IGF Axis Resulting in Isolated GH Deficiency, GH Insensitivity, or IGF-1 Deficiency

GENE	INHERITANCE	PHENOTYPE
ISOLATED GROWTH HORMONE DEFICIENCY		
GHRHR	AR	Type IB form of isolated **GHD**; low levels of GH production, but less severe than type 1A isolated **GHD**; may also be caused by pathogenic variants in GH1
GHS-R	AD	**GHD** and ISS
GH1	AR	Type IA form of isolated **GHD**, in utero growth retardation; absent GH production caused by gene deletion, antibodies to GH develop over time during treatment
GH1	AR	Type IB form of isolated **GHD**; low levels of GH production, but less severe than type 1A isolated **GHD**; may also be caused by pathogenic variants in GHRHR
GH1	AD	Type II form of isolated **GHD**; dominant negative pathogenic variants in GH1, which decrease GH secretion
BTK	XL	Type III form of isolated **GHD**; hypogammaglobulinemia
GH1	AD	Bioinactive GH molecule; rare, dominant negative pathogenic variant in GH1 that interferes with GHR signaling
GROWTH HORMONE INSENSITIVITY		
GHR	AR, AD	IGF-I deficiency; high GH level; normal, decreased or increased GHBP (depending on which domain of the receptor is affected); unresponsive to GH treatment
IGF-1 DEFICIENCY		
IGF1	AR	IGF-1 deficiency; IUGR and postnatal growth failure, sensorineural deafness, insulin resistance, microcephaly
STAT5b	AR	IGF-1 deficiency, variable immune defect, hyperprolactinemia, chronic pulmonary infections, eczema
ALS	AR	IGF-1 deficiency; variable postnatal growth failure, delayed puberty

AD, Autosomal dominant; ALS, acid-labile subunit; AR, autosomal recessive; GH, growth hormone; GHBP, GH-binding protein; GHD, growth hormone deficiency; GHRHR, GH-releasing hormone receptor; IGF, insulin-like growth factor; ISS, idiopathic short stature; IUGR, intrauterine growth retardation; XL, X-linked.
Modified from Sperling MA. *Pediatric Endocrinology,* 4th ed. Philadelphia: Elsevier; 2014: Table 10.3, p. 333.



Fig. 595.1 Solitary median maxillary central incisor at age 16 mo. *(From Giannopoulou EZ, Rohrer T, Hoffmann P, et al. Solitary median maxillary central incisor. J Pediatr. 2015;167:770, Fig. 2.)*



Fig. 595.2 Septo-optic dysplasia with agenesis of the septum pellucidum. Sagittal T1 weighted MR image shows that fornices are inferiorly positioned *(long arrow)*. The optic apparatus is hypoplastic *(short arrow)*; there is no identifiable neurohypophysis. *(From Rollins N. Congenital brain malformations. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 31.13.)*

intracellular signaling domain. Pathogenic alterations in the extracellular domain interfere with binding of GH. Serum GH-binding protein activity, representing the circulating form of the membrane receptor for GH, is generally low. Variants in the transmembrane domain can interfere with anchoring of the receptor to the plasma membrane. In these cases, circulating GH-binding protein activity is normal or high. Alterations in the intracellular domain interfere with JAK/STAT signaling.

Post-Receptor Forms of Growth Hormone Insensitivity

Some children with severe growth failure, high GH and low IGF-1 levels, and normal GH-binding protein levels have abnormalities distal to the GH binding and activation of the GH receptor. Several have been found to have pathogenic variations in the gene-encoding signal transducer and activator of transcription 5b (STAT5b). Disruption of this key intermediate connecting receptor activation to gene transcription produces growth failure similar to that seen in Laron syndrome. These patients also suffer from *immunodeficiency* and chronic pulmonary

Table 595.4 Proposed Classification of Growth Hormone Insensitivity

PRIMARY GH INSENSITIVITY (HEREDITARY DEFECTS)
GH receptor defect (may be positive or negative for GH-binding protein)
• Extracellular alteration (e.g., Laron syndrome)
• Cytoplasmic alteration
• Intracellular alteration
GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
• Stat5b pathogenic variants
Insulin-like growth factor-1 defects
• IGF-1 gene deletion
• IGF-1 transport defect (pathogenic variant in ALS)
• IGF-1 receptor defect
Bioinactive GH molecule (responds to exogenous GH)
SECONDARY GH INSENSITIVITY (ACQUIRED DEFECTS)
Circulating antibodies to GH that inhibit GH action
Antibodies to the GH receptor
GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
Other conditions that cause GH insensitivity

ALS, Acid-labile subunit; GH, growth hormone; IGF, insulin-like growth factor.
From Sperling MA. *Pediatric Endocrinology,* 4th ed. Philadelphia: Elsevier; 2014: Box 10.4.

infections, consistent with important roles for STAT5b in interleukin cytokine signaling.

IGF-1 Gene Abnormalities

Pathogenic alterations of the *IGF-1* gene produce severe prenatal and postnatal growth impairment. Microcephaly, intellectual disability, and deafness are present in patients with exon deletion and a missense variant. These patients can be expected to respond to recombinant IGF-1 treatment.

Insulin-Like Growth Factor–Binding Protein Abnormalities

Pathogenic variants in the gene encoding the acid-labile subunit of the circulating 165-kDa IGF-1, IGF-BP3, acid-labile subunit complex has been associated with short stature. Total IGF-1 levels were very low. The index case, with homozygosity for an acid-labile subunit alteration, did not show an increase in IGF-1 levels or an increase in growth rate during GH treatment.

IGF-1 Receptor Gene Abnormalities

Pathogenic variants in the gene encoding the IGF-1 receptor also compromise prenatal and postnatal growth. The phenotype does not appear to be as severe as that seen with the absence of IGF-1. Adult heights are closer to the normal range, and affected patients do not have intellectual disability or deafness.

CLINICAL MANIFESTATIONS

Congenital Hypopituitarism

The child with congenital hypopituitarism is usually of normal size and weight at birth, although those with MPHD and those with pathogenic genetic variants in the *GH1* or *GHR* gene have birth lengths that average 1 SD below the mean. Children with severe deficits in GH production or action typically fall more than 4 SD below the mean for length by 1 year of age. Those with less severe deficiencies grow at rates below the 25th percentile for age and gradually diverge from normal height percentiles. Delayed closure of the epiphyses permits growth beyond the normal age when growth should be complete. Features of GH insensitivity, including Laron syndrome, are somewhat distinct from GHD and MPHD and are noted in Table 595.5.

Infants with congenital dysfunction of the pituitary or hypothalamus may present with neonatal emergencies such as apnea, cyanosis, or severe hypoglycemia with or without seizures. Prolonged neonatal cholestatic jaundice is common. It involves elevation of conjugated and unconjugated bilirubin and may be associated with giant cell neonatal hepatitis. Nystagmus can suggest optic nerve hypoplasia syndrome (see Chapter 671). Micropenis with or without testicular maldescent in males provides an additional diagnostic clue. Deficiency of GH may be accompanied by hypoadrenalism (see Chapter 615.2) and hypothyroidism (see Chapter 603), along with gonadotropin deficiency (see Chapters 623.2 and 626.2).

Table 595.5 Clinical Features of Growth Hormone Insensitivity, Including Classic Laron Syndrome

GROWTH AND DEVELOPMENT
Near-normal birthweight
Slightly decreased birthweight
Severe postnatal growth failure
Delayed bone age (may be advanced relative to height age)
Micropenis in childhood; normal for body size in adults
Puberty may be delayed 3-7 yr
Normal sexual function and fertility
OTHER PHYSICAL CHARACTERISTICS
Sparse hair (before age 7 yr)
Frontal bossing
Normal head circumference
Small facies (resulting in craniofacial disproportion)
Hypoplastic nasal bridge
Shallow orbits
Delayed dentition
Blue sclerae
High-pitched voice
Hip dysplasia
Limited extension in elbows
LATE FINDINGS/OTHER COMPLICATIONS
Hypoglycemia in infants and children (fasting symptoms in some adults)
Delayed walking and motor milestones
Avascular necrosis of femoral head
Thin, prematurely aged skin
Osteopenia

From Sperling MA. *Pediatric Endocrinology,* 4th ed. Philadelphia: Elsevier; 2014: Box 10.5.

Toddlers and school-age children tend to present with proportionate short stature. On physical examination, the head may be round and the face short and broad. The frontal bone may be prominent, and the bridge of the nose is often depressed and saddle shaped. The nose may be small, but the nasolabial folds are well developed. The mandible and the chin may be underdeveloped, and the teeth, which erupt late, are often crowded. The neck is short, and the larynx is small. The voice is high-pitched and remains high after puberty. The extremities are well proportioned, with small hands and feet. Weight for height is often normal, but there may be an imbalance of lean mass and adipose tissue. The genitals are usually small for age in males, and sexual maturation may be delayed or absent as the child ages.

In teens with undiagnosed congenital hypopituitarism, short stature is expected. Additionally, facial, axillary, and pubic hair may be decreased, and the scalp hair is fine. Intelligence is usually normal for age, unless there are other structural brain abnormalities, and the children may seem precocious compared with younger children of a similar size.

Acquired Hypopituitarism

The child is normal initially, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress. When complete or almost complete destruction of the pituitary gland occurs, signs of pituitary insufficiency are present. Atrophy of the adrenal cortex, thyroid, and gonads results in loss of weight, asthenia, sensitivity to cold, mental torpor, and absence of sweating. Sexual maturation fails to take place or regresses if already present. There may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia. Growth slows dramatically. Diabetes insipidus (see Chapter 596) may be present but can by obscured by the development of yet untreated central adrenal insufficiency.

If the lesion is an **expanding tumor**, symptoms such as headache, vomiting, visual disturbances, pathologic sleep patterns, decreased school performance, seizures, polyuria, and growth failure can occur. Documented slowing of growth can antedate neurologic signs and symptoms, especially with craniopharyngioma, yet neurologic and ophthalmologic complaints are more often the presenting problems. In other cases, evidence of pituitary insufficiency may first appear after surgical intervention. In children with craniopharyngioma, visual field defects, optic atrophy, papilledema, obesity, and cranial nerve palsy are common. Skeletal age may be delayed in acquired MPHD but may be relatively normal if the pituitary dysfunction is of very recent onset.

LABORATORY FINDINGS

MPHD and/or GHD should be suspected in infants with hypoglycemia, micropenis, congenital nystagmus, and prolonged conjugated hyperbilirubinemia and in older children with severe postnatal growth failure (Table 595.6). Criteria for short stature include height below the first percentile for age and sex or height >2 SD below sex-adjusted mid-parent height. Acquired GHD can occur at any age, and when it is of acute onset, height may be within the normal range. In both congenital and acquired GH deficiency, height velocity will be low relative to sex- and bone age–matched peers. A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity. Random GH levels are not helpful in the evaluation of toddlers and older children because of the pulsatile secretion of GH, *whereas measurement of GH may be useful in the first 2 weeks of life when levels are tonically increased.* Observation of low serum levels of IGF-1 and the GH-dependent IGF-BP3 can be helpful, but IGF-1 and IGF-BP3 levels should be matched to normal values for skeletal age and sexual maturity rating, rather than chronological age. Values in the upper part of the normal range for age effectively exclude GHD. IGF-1 values in the lower part of the normal range may occur in normally growing children, children with impaired nutrition, or those with hypopituitarism. The expected range for IGF-1 in normal and GH-deficient children overlaps somewhat during infancy and early childhood. IGF-1 levels in isolation should not be used to diagnose GH deficiency.

Table 595.6 Evaluation of Suspected Growth Hormone Deficiency

History	• Birthweight and length • Obstetric complications • Breech presentation • Neonatal hypoglycemia • Prolonged neonatal jaundice/cholestasis • Review of systems for systemic illness • Diet history
Physical exam	• Linear growth failure (may be the only clinical feature present) Proportionate short stature Low height velocity • Weight for length appropriate or increased • Micropenis with or without testicular maldescent in males • Small midface • Cleft palate • High-pitched voice • Delayed dental eruption • Optic nerve hypoplasia
Imaging	• Radiologic evaluation of bone age • Central nervous system imaging to evaluate the hypothalamus/pituitary and to exclude other conditions
Laboratory evaluation	• Measurements of IGF-1 and IGF-binding protein levels • Assess thyroid function • Exclude chronic medical illness CBC, metabolic profile, inflammatory markers, celiac testing, urinalysis • Determination of peak GH levels after stimulation test
Treatment considerations	• Replacement with rhGH • Dosage adjustment IGF-1 Height velocity Pubertal status Body weight • Predictors of improved response to treatment Early initiation of treatment Higher rhGH dose • Monitor during treatment Height velocity IGF-1 levels Glucose metabolism Skeletal age Thyroid function, adrenal function

GH, Growth hormone; IGF, insulin-like growth factor; rhGH, recombinant human growth hormone.

After infancy, a definitive diagnosis of GHD traditionally requires demonstration of absent or low levels of GH in response to stimulation, but provocative testing may be omitted if the patient has the expected auxologic findings, a documented hypothalamic or pituitary defect, and at least one other pituitary hormone deficiency. A variety of provocative tests have been devised that rapidly increase the level of GH in normal children. These include administration of insulin, arginine, clonidine, levodopa, or glucagon. Macimorelin is an oral ghrelin agonist approved in the United States for growth hormone stimulation testing in adults, but not in children. *Because thyroid hormone is a prerequisite for normal GH synthesis, it must always be assessed and replaced, if needed, before provocative GH testing.* In chronic GHD, the demonstration of subnormal linear growth, a delayed skeletal age, and low peak levels of GH (<10 ng/mL) in each of two provocative tests are compatible with the diagnosis. In acute GHD, a high clinical suspicion of GHD and low peak levels of GH (<10 ng/mL) in each of two provocative tests are compatible with the diagnosis. This rather arbitrary cutoff point is higher than the criteria used for diagnosis of adult GHD. There is no consensus regarding adoption of criteria that account for age, sex, and GH assay characteristics. Some studies indicate that many GH-sufficient prepubertal children fail to achieve GH values >10 ng/mL with two pharmacologic tests; pretest, short-term sex steroid priming has been proposed to increase the diagnostic specificity of this testing.

In addition to establishing the diagnosis of GHD, it is necessary to examine other pituitary functions. Levels of TSH, free thyroxine or total thyroxine with T_3 resin uptake, ACTH, cortisol, gonadotropins, and gonadal steroids might provide evidence of other pituitary hormonal deficiencies. Antidiuretic hormone deficiency may be established by appropriate studies (see Chapter 596). Infants with clear clinical and biochemical evidence of multiple pituitary hormone deficiencies and supportive anatomic variants demonstrated on MRI of the brain may not require provocative GH testing.

RADIOLOGIC FINDINGS

Neurologic imaging should be obtained when the cause of hypopituitarism is not known. CT is appropriate for recognizing suprasellar calcification associated with craniopharyngiomas and bony changes accompanying histiocytosis. However, MRI is usually used as the initial test to anatomically characterize the pituitary and hypothalamus, as MRI provides a much more detailed view of the relevant anatomy. Many cases of severe early-onset MPHD show the triad of a small anterior pituitary gland, a missing or attenuated pituitary stalk, and an ectopic posterior pituitary bright spot at the base of the hypothalamus (Fig. 595.3). Subnormal anterior pituitary height, implying a small anterior pituitary, is common in genetic and idiopathic causes of isolated GHD. Craniopharyngiomas are rare tumors in childhood, but common causes of acquired hypopituitarism, whereas pituitary adenomas rarely cause hypopituitarism in children. Both hypoplastic and

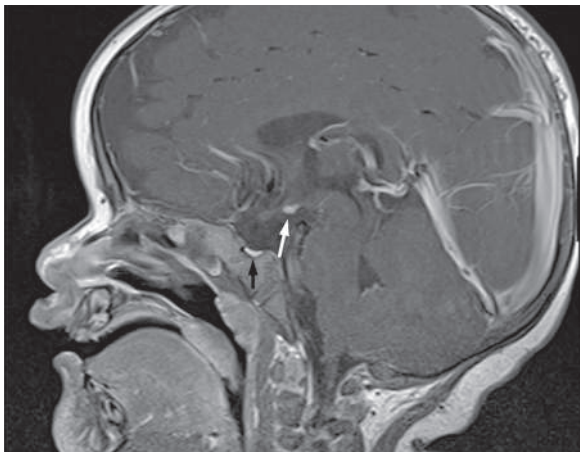

Fig. 595.3 Sagittal T1 weighted MRI shows an ectopic posterior pituitary *(white arrow)* and a small anterior pituitary *(black arrow). (From Giannopoulou EZ, Rohrer T, Hoffmann P, et al. Solitary median maxillary central incisor. J Pediatr. 2015;167:770, App Fig. 1.)*

markedly enlarged anterior pituitary glands are seen in patients with *PROP1* or *LHX3* gene alterations. Structural lesions causing isolated, acquired GHD are not common, but are important from a therapeutic perspective, such that MRI is usually recommended at the time of the diagnosis of GHD.

Skeletal maturation may be assessed with a plain film of the hand (bone age) and is delayed in patients with isolated GHD and may be even more delayed when there is combined GH and TSH deficiency. Importantly, in very recent or acute onset of hypopituitarism, initial assessment of skeletal age may not demonstrate the delay classically reported in congenital or long-standing hypopituitarism. Further, comorbid *central precocious puberty* may accelerate skeletal development when both precocious puberty and GHD are present, as may be seen in some patients with GHD after cranial irradiation. Dual-photon x-ray absorptiometry shows deficient bone mineralization, deficiencies in lean body mass, and a corresponding increase in adiposity, but it is not routinely recommended in the initial evaluation of pediatric GHD.

DIFFERENTIAL DIAGNOSIS

The causes of growth disorders are numerous. The differential diagnosis can be summarized broadly as follows: hormonal disorders, chronic illness, undernutrition, genetic conditions, nonsyndromic family trait, and constitutional delay of growth and development. Hormonal disorders include primary hypothyroidism and Cushing disease. Systemic conditions, such as inflammatory bowel disease, celiac disease, occult renal disease, and anemia, must be considered. Patients with systemic conditions often have a greater deficit of weight than length. Severe psychosocial deprivation may result in growth failure that mimics GH deficiency. Numerous **syndromic genetic** conditions include short stature as a manifestation, among other findings, whereas some specific genetic alterations may present with isolated short stature. These include Turner syndrome (see Chapter 99.4), pathogenic variants and deletions in *SHOX, ACAN, PTPN11,* and *IHH,* the skeletal dysplasias (see Chapter 735), and identifiable syndromes including Donohue *(INSR),* Kabuki *(KMT2D, KDM6A),* Noonan (RASopathy), Smith-Lemli Opitz *(DHCR7),* and Cornelia de Lange *(NIPBL, SMC1A, HDAC8, RAD21, SMC3).* Prenatal-onset short stature associated with being small for gestational age that persists during childhood may also be syndromic. Whole exome sequencing is helpful in identifying the specific syndrome.

Some otherwise normal children are short (i.e., >2.25 SD below the mean for age) and grow 5 cm/year or less but have normal levels of GH in response to provocative tests and normal spontaneous episodic secretion; this is often termed **idiopathic short stature**. Most of these children show increased rates of growth when treated with GH in doses comparable with those used to treat children with hypopituitarism. Plasma levels of IGF-1 in these patients may be normal or low. Several groups of treated children have achieved final or near-final adult heights. Different studies have found changes in adult height that range from −2.5 to +7.5 cm compared with pretreatment predictions. There are no methods that can reliably predict which of these children will become taller in adulthood as a result of GH treatment and which will have compromised adult height despite treatment.

Diagnostic strategies for distinguishing between permanent GH deficiency and other causes of impaired growth are imperfect. Children with a combination of genetic short stature and constitutional delay of growth have short stature, below-average growth rates, and delayed bone ages. Many of these children exhibit minimal GH secretory responses to provocative stimuli and may be treated with GH therapy. When children in whom idiopathic or acquired isolated GHD is diagnosed are treated with recombinant human GH and retested as adults, the majority have peak GH levels within the normal range.

Constitutional Growth Delay

Constitutional growth delay is one of the variants of normal growth commonly encountered by the pediatrician. Length and weight measurements of affected children are normal at birth, and growth is normal for the first 4-12 months of life. Height is sustained at a lower percentile during childhood. The pubertal growth spurt is delayed, so their growth rates persist at a lower prepubertal rate after their classmates have begun to accelerate. Detailed questioning often reveals other family members (often one or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature. IGF-1 levels tend to be low for chronological age but within the normal range for bone age and sexual maturation rating. GH responses to provocative testing tend to be lower than in children with a more typical timing of puberty. The prognosis for these children to achieve normal adult height is guarded. Predictions based on height and bone age tend to overestimate eventual height to a greater extent in males than in females. Males with >2 years of pubertal delay can benefit from a short course of testosterone therapy to hasten puberty after 14 years of age. The cause of this variant of normal growth is thought to be persistence of the relative hypogonadotropic state of childhood.

TREATMENT

Although well-established treatments are available to replace the classical anterior pituitary hormone deficiencies, treatment must take into account patient age, pubertal maturation, and patient goals. Lifelong attention to correct administration of hormone replacement and monitoring for comorbidities are needed to optimize patient outcomes.

Recombinant human GH (rhGH) has been available by prescription since the 1980s. Multiple brands are marketed in the United States, which are therapeutically equivalent, with the major differences consisting of proprietary devices for subcutaneous injection and availability of solubilized liquid forms versus powders needing reconstitution before injection. Long-acting forms are under development and will need to demonstrate comparable efficacy, safety, and tolerability to the daily injections currently available.

The U.S. Food and Drug Administration (FDA) has approved eight pediatric indications for rhGH treatment to promote linear growth. They are GHD, Turner syndrome, chronic renal

failure before transplantation, idiopathic short stature, small-for-gestational-age short stature, Prader-Willi syndrome, *SHOX* gene abnormality, and Noonan syndrome. In the United States, FDA approval for a given indication does not ensure that a patient's insurance carrier will approve payment for the drug. Treatment should be started as soon as possible to narrow the gap in height between patients and their classmates during childhood and to have the greatest effect on mature height. For some infants with MPHD, initiation of rhGH treatment may be urgent to reduce the frequency and severity of episodes of hypoglycemia. The recommended initial dose of rhGH for treatment of GHD is 0.16-0.24 mg/kg/wk (22-35 μg/kg/day). Higher doses have been used during puberty and for non-GHD indications. Most currently available forms of rhGH are administered subcutaneously once daily, but a weekly preparation has been recently FDA approved for use in the United States.

Maximal response to rhGH occurs in the first year of treatment. Growth velocity during this first year is typically above the 95th percentile for age. With each successive year of treatment, the growth rate tends to decrease until it approximates a typical height velocity for skeletal age. If the growth rate drops below the 25th percentile, adherence should be evaluated before the dose is increased. IGF-1 may be measured as an objective assessment of adherence. GH therapy should be continued until near-final height is achieved. Criteria for stopping GH treatment include a decision by the adolescent that they are tall enough, a growth rate less than 1 inch per year, and a bone age greater than 14 years in females and greater than 16 years in males. Adolescents who have completed treatment for promotion of adult stature should be reevaluated for GHD based on adult criteria after treatment is complete. Some adolescents or young adults, particularly those with profound GHD and/or MPHD, may benefit from continuation of rhGH treatment as adults. The dose of rhGH is much lower in adults relative to growing teens. Children with hypopituitarism require coordinated transition to adult care and lifelong attention to their endocrine deficiencies.

Concurrent treatment with rhGH and a gonadotropin-releasing hormone agonist has been used in the hope that interruption of puberty will delay epiphyseal fusion and prolong growth. This strategy may increase adult height. Risks include increasing the discrepancy in physical maturity between GH-deficient children and their age peers, decreasing the upper to lower segment ratio, and impairing bone mineralization. There have also been attempts to forestall epiphyseal fusion in males by giving aromatase inhibitors, which inhibit the enzyme responsible for converting androgens to estrogens. These agents are not approved for this purpose in the United States, but some clinical trials have demonstrated an increase in predicted adult height with this approach.

Some patients develop either primary or central hypothyroidism while under treatment with GH. Similarly, there is a risk of developing adrenal insufficiency as an associated component of **hypopituitarism**. If unrecognized, this can be fatal. Periodic evaluation of thyroid and adrenal function is indicated for all patients diagnosed with GHD.

rhGH treatment may enhance the growth of non-GHD children as well. Intensive investigation is in progress to determine the full spectrum of short children who may benefit from treatment with GH. The FDA approval for use of GH in idiopathic short stature specifies a height below the 1.2 percentile (−2.25 SD) for age and sex, a predicted height below the 5th percentile, and open epiphyses. Studies of the effect of GH treatment on adult height suggest a median gain of 2-3 inches, depending on dose and duration of treatment.

In children with MPHD, replacement should also be directed at other hormonal deficiencies. In TSH-deficient patients, thyroid hormone replacement (levothyroxine) is given in full replacement doses. In ACTH-deficient patients, hydrocortisone should be prescribed in physiologic doses, about 8-12 mg/m^2/day. In patients deficient in both TSH and ACTH, initiation of adrenal replacement before thyroid hormone replacement is mandatory to reduce the risk of adrenal crisis. Individualized dose adjustment of hydrocortisone is needed to minimize the risk of side effects associated with excess glucocorticoid administration and prevent symptoms of adrenal insufficiency. *Increased doses of hydrocortisone are required to support vital functions and prevent adrenal crisis during illness or during and after surgical procedures (so-called "stress dosing.")*

In patients with a deficiency of gonadotropins, gonadal steroids are given at the appropriate time. Consideration of chronological age, height age, bone age, and psychosocial development may all play a role in determining the timing of initiation of low-dose sex steroid replacement in young adolescents. For infants with micropenis, one or two 3-month courses of monthly intramuscular injections of 25 mg of testosterone cypionate or testosterone enanthate can bring the penis to near-normal size without an inordinate effect on osseous maturation.

Recombinant IGF-1 (mecasermin) is approved for use in the United States for primary IGF-1 deficiency. It is given subcutaneously twice a day. Side effects are similar to rhGH, except that mecasermin can cause hypoglycemia. The risk of hypoglycemia is reduced by giving the injections concurrently with a meal or snack. In some situations, its use may be more efficacious than use of GH. These conditions include abnormalities of the GH receptor and *STAT5b* genes that alter GH signaling downstream. It may have utility for severe GHD in the rare patients who have developed clinically significant antibodies to administered rhGH. However, mecasermin is not an indicated treatment for most patients with GHD.

COMPLICATIONS AND ADVERSE EFFECTS OF GROWTH HORMONE TREATMENT

GH treatment influences glucose homeostasis. Fasting and postprandial insulin levels are characteristically low before treatment, and they normalize during GH replacement. GH treatment is associated with an increase in the risk for type 2 diabetes and no significant increase in the risk for type 1 diabetes.

Concerns have been raised about the safety of GH treatment in children who become deficient after treatment of brain tumors, leukemia, and other neoplasms. Long-term studies show no increase in risk of recurrence of craniopharyngioma, other brain tumors, or leukemia. Some studies indicate an increased risk of second neoplasms in cancer survivors treated with GH. However, other studies have found no increased risk for secondary brain tumors after adjustment for radiation therapy. Looking more broadly at young adults treated in childhood with GH for a variety of indications, the Safety and Appropriateness of Growth hormone treatments in Europe consortium (SAGhE) has reported an increase in cause-specific mortality due to circulatory and hematologic conditions, but no increase in all-cause mortality for youth treated with GH.

Other reported side effects include pseudotumor cerebri, slipped capital femoral epiphysis, gynecomastia, coarsening of features, and worsening of scoliosis. The risk of late development of Creutzfeldt-Jakob disease was limited to recipients of contaminated lots of extracted pituitary GH. No comparable risks have been seen with rhGH, which is the only pharmacologic form of hGH currently in clinical use.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 596

Diabetes Insipidus

Carmen L. Soto-Rivera, David T. Breault, and Joseph A. Majzoub

Diabetes insipidus (DI) manifests clinically with polyuria and polydipsia and can result from either vasopressin deficiency (central DI, also known as arginine vasopressin [AVP] deficiency) or vasopressin insensitivity at the level of the kidney (nephrogenic DI [NDI], also known as AVP resistance). Both central DI and NDI can arise from inherited defects of congenital or neonatal onset or can be secondary to a variety of causes (Table 596.1).

PHYSIOLOGY OF WATER BALANCE

The control of extracellular tonicity (osmolality) and volume within a narrow range is critical for normal cellular structure and function (see Chapter 73.2). Extracellular fluid tonicity is regulated almost exclusively by water intake and excretion, whereas extracellular volume is regulated by sodium intake and excretion. The control of plasma tonicity and intravascular volume involves a complex integration of endocrine, neural, behavioral, and paracrine systems (Fig. 596.1). Vasopressin, secreted from the posterior pituitary, is the principal regulator of tonicity, with its release largely stimulated by increases in plasma osmolality over 283 mOsm/kg H_2O. Volume homeostasis is largely regulated by the renin-angiotensin-aldosterone system, with contributions from both vasopressin and the natriuretic peptide family.

Vasopressin, a 9–amino acid peptide, has both antidiuretic and vascular pressor activity and is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is transported to the posterior pituitary via axonal projections, where it is stored awaiting release into the systemic circulation. The half-life of vasopressin in the circulation is 5-10 minutes, as it is rapidly degraded by a cysteine aminoterminal peptidase. The carboxyterminus of the vasopressin precursor, **copeptin**, is more stable than vasopressin, and blood concentrations of the two peptides are highly correlated when evaluating response to osmotic stimuli.

In addition to responding to osmotic stimuli, vasopressin is secreted in response to significant decreases in intravascular volume and pressure (minimum of 8% decrement) via afferent baroreceptor pathways arising from the aortic arch (carotid sinus) and volume receptor pathways in the cardiac atria and pulmonary veins. Osmotic and hemodynamic stimuli interact synergistically. Nausea is also a potent stimulus for vasopressin secretion.

The sensation of thirst and the release of vasopressin are regulated by cortical and hypothalamic neurons. The thirst threshold is approximately 10 mOsm/kg H_2O higher (i.e., 293 mOsm/kg H_2O) than the osmotic threshold for vasopressin release. Consequently, under conditions of hyperosmolality, vasopressin is released before thirst is initiated, allowing ingested water to be retained. Subsequently, anticipation of water ingestion by cortical and vasopressin-secreting neurons leads to a decrease in vasopressin release immediately before water ingestion, presumably to prevent subsequent hyponatremia. Chemoreceptors present in the oropharynx also downregulate vasopressin release after water ingestion. In addition, thirst drive decreases even before the ingested fluid lowers blood osmolality, presumably to prevent overdrinking leading to hyponatremia.

Vasopressin exerts its principal effect on the kidney via V2 (AVPR2) receptors located primarily in the collecting tubule, the thick ascending limb of the loop of Henle, and the periglomerular tubules. The human V2 receptor gene *(AVPR2)* is located on the long arm of the X chromosome (Xq28) at the locus associated with **congenital, X-linked, vasopressin-resistant DI**. Activation of the V2 receptor results in increases in intracellular cyclic adenosine monophosphate, which leads to the insertion of the aquaporin-2 water channel into the apical (luminal) membrane. This allows water movement along its osmotic gradient into the hypertonic inner medullary interstitium from the tubule lumen and excretion of concentrated urine. In contrast to aquaporin-2, aquaporin-3 and aquaporin-4 are expressed on the basolateral membrane of the collecting duct cells, and aquaporin-1 is expressed in the proximal tubule. These channels may also contribute to urinary concentrating ability.

Atrial natriuretic peptide, initially isolated from cardiac atrial muscle but also expressed in the brain, has several important effects on salt and water balance, including stimulation of natriuresis, inhibition of sodium resorption, inhibition of vasopressin secretion, and inhibition of vasopressin and aldosterone action in the renal tubules. Atrial natriuretic peptide is expressed in endothelial cells and vascular smooth muscle, where it appears to regulate relaxation of arterial smooth muscle. **Brain natriuretic peptide (BNP)**, synthesized and secreted by cardiac ventricular tissue, similarly induces natriuresis, whereas the physiologic role of C-type natriuretic peptide (CNP) has yet to be defined.

Table 596.1 Causes of Hypotonic Polyuria

CENTRAL (NEUROGENIC) DIABETES INSIPIDUS (DI)
Congenital (congenital malformations, autosomal dominant, arginine vasopressin [AVP] neurophysin pathogenic variants)
Drug or toxin induced (ethanol, diphenylhydantoin, snake venom)
Granulomatous (histiocytosis, sarcoidosis)
Neoplastic (craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary tumor, metastases)
Infectious (meningitis, tuberculosis, encephalitis)
Inflammatory, autoimmune (lymphocytic infundibuloneurohypophysitis, immune check point inhibitors)
Trauma (neurosurgery, deceleration injury)
Vascular (cerebral hemorrhage or infarction, brain death)
Idiopathic
OSMORECEPTOR DYSFUNCTION
Granulomatous (histiocytosis, sarcoidosis)
Neoplastic (craniopharyngioma, pinealoma, meningioma, metastases)
Vascular (anterior communicating artery aneurysm or ligation, intrahypothalamic hemorrhage)
Other (hydrocephalus, ventricular or suprasellar cyst, trauma, degenerative diseases)
Idiopathic
INCREASED AVP METABOLISM
Pregnancy
NEPHROGENIC DIABETES INSIPIDUS
Congenital (X-linked recessive, AVP V2 receptor pathogenic variants, autosomal recessive or dominant, aquaporin-2 water channel pathogenic variants)
Drug induced (lithium, demeclocycline, cisplatin, methoxyflurane)
Hypercalcemia
Hypokalemia
Infiltrating lesions (sarcoidosis, amyloidosis)
Vascular (sickle cell anemia)
Mechanical (polycystic kidney disease, bilateral ureteral obstruction)
Solute diuresis (glucose, mannitol, sodium, radiocontrast dyes)
Idiopathic
PRIMARY POLYDIPSIA
Psychogenic (schizophrenia, obsessive-compulsive behaviors)
Dipsogenic (downward resetting of thirst threshold, idiopathic or similar lesions, as with central DI)

From Verbalis JG. Disorders of water balance. In Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 16.2.

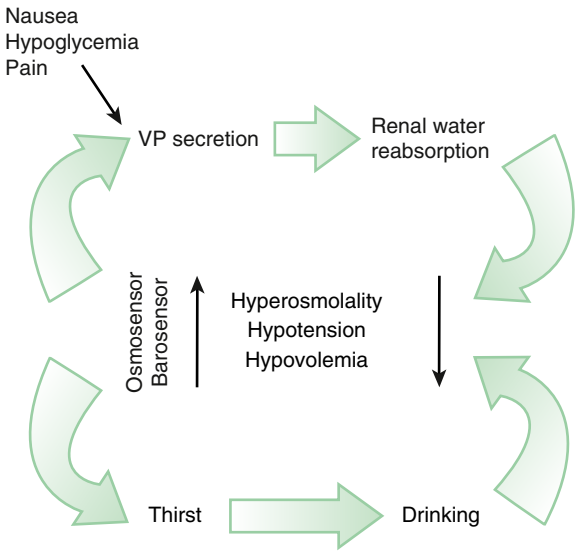

Fig. 596.1 Regulation of vasopressin secretion and serum osmolality. Hyperosmolality, hypovolemia, and hypotension are sensed by osmosensors, volume sensors, and barosensors, respectively. These stimulate both vasopressin secretion and thirst. Vasopressin, acting on the kidney, causes increased reabsorption of water (antidiuresis). Thirst causes increased water ingestion. The results of these dual negative feedback loops cause a reduction in hyperosmolality or in hypotension or hypovolemia. Additional stimuli for vasopressin secretion include nausea, hypoglycemia, and pain. *(From Srivasta A, Majzoub JA. Disorders of the posterior pituitary. In: Sperling MA, ed. Pediatric Endocrinology, 5th ed. Philadelphia: Elsevier; 2020: Fig. 12.6.)*

APPROACH TO THE PATIENT WITH POLYURIA, POLYDIPSIA, AND HYPERNATREMIA

The cause of pathologic polyuria or polydipsia (exceeding 2 L/m^2/24 hr) may be difficult to establish in children. Infants can present with irritability, failure to thrive, and intermittent fever. Patients with suspected DI should have a careful history taken, which should quantify the child's daily fluid intake and output and establish the voiding pattern, nocturia, and primary or secondary enuresis. A complete physical examination should establish the patient's hydration status, and the physician should search for evidence of visual and central nervous system dysfunction, as well as for other pituitary hormone deficiencies.

If pathologic polyuria or polydipsia is present, the following should be obtained: serum for osmolality, sodium, potassium, blood urea nitrogen, creatinine, glucose, hemoglobin A_{1c}, and calcium and urine for osmolality, specific gravity, and glucose determination. The diagnosis of DI is established if the serum osmolality is >300 mOsm/kg H_2O and the urine osmolality is <300 mOsm/kg. A baseline copeptin level above 20 pmol/L in this setting can confirm *nephrogenic* DI.

DI is unlikely if the serum osmolality is <270 mOsm/kg H_2O or the urine osmolality is >600 mOsm/kg. If the patient's serum osmolality is <300 mOsm/kg H_2O (but >270 mOsm/kg H_2O) and pathologic polyuria and polydipsia are present, a water deprivation test is indicated to establish the diagnosis of DI and to differentiate central from nephrogenic causes by assessing response to aqueous vasopressin at the end of the test.

Now that copeptin measurement is clinically available, test protocols aim to measure copeptin instead of AVP during water deprivation. Hypertonic saline infusion (3% saline) can also be given as an osmotic stimulus for copeptin secretion (instead of water deprivation tests), with a potentially higher diagnostic accuracy than water deprivation alone. In the inpatient postneurosurgical setting, central DI is likely if hyperosmolality (serum osmolality >300 mOsm/kg) is associated with urine osmolality less than serum osmolality. It is important to distinguish between polyuria resulting from postsurgical central DI and polyuria resulting from the normal diuresis of fluids received intraoperatively. Both cases may be associated with a large volume (>200 mL/m^2/hr) of dilute urine, although in patients with DI, the serum osmolality is high in comparison with patients undergoing postoperative diuresis.

CAUSES OF HYPERNATREMIA

Hypernatremia is discussed in Chapter 73.3.

Central Diabetes Insipidus

Central DI can result from multiple etiologies, including pathogenic variants in the vasopressin *(AVP)* gene; trauma (accidental or surgical) to vasopressin neurons; congenital malformations of the hypothalamus or pituitary; neoplasms; infiltrative, autoimmune, and infectious diseases affecting vasopressin neurons or fiber tracts; and increased metabolism of vasopressin. In approximately 10% of children with central DI, the etiology is idiopathic. Other pituitary hormone deficiencies may be present (see Chapter 595). *Over time, up to 35% of those with idiopathic central DI will develop other hormone deficiencies or have an underlying etiology identified.*

Autosomal dominant central DI usually occurs within the first 5 years of life and results from pathogenic variants in *AVP*. A number of these genetic variants can cause gene-processing defects in a subset of vasopressin-expressing neurons, which have been postulated to result in endoplasmic reticulum stress and cell death. **Wolfram syndrome**, which includes DI, diabetes mellitus, optic atrophy, and deafness, also results in vasopressin deficiency. Autosomal recessive pathogenic variants in the *WFS1* (most common) or *WFS2* (CISD2) genes, which give rise to endoplasmic reticulum proteins, are associated with this condition. Congenital brain abnormalities (see Chapter 631) such as **optic nerve hypoplasia syndrome** with agenesis of the corpus callosum, **Niikawa-Kuroki syndrome**, holoprosencephaly, and familial pituitary hypoplasia with absent stalk may be associated with central DI and defects in thirst perception (adipsia). Empty sella syndrome, possibly resulting from unrecognized pituitary infarction, can be associated with DI in children.

Trauma to the base of the brain and neurosurgical intervention in the region of the hypothalamus or pituitary are common causes of central DI. The **triphasic response** after surgery refers to an initial phase of transient DI, lasting 12-48 hours, followed by a second phase of syndrome of inappropriate antidiuresis (SIAD), lasting up to 10 days, which may be followed by permanent (or partial) DI. The initial phase may be the result of local edema interfering with normal vasopressin secretion; the second phase results from unregulated vasopressin release from dying neurons, whereas in the third phase, permanent DI results if more than 90% of the neurons have been destroyed.

Given the anatomic distribution of vasopressin neurons over a large area within the hypothalamus, **tumors** causing DI must either be very large and infiltrative or be strategically located near the base of the hypothalamus, where vasopressin axons converge before their entry into the posterior pituitary. Germinomas and pinealomas typically arise in this region and are among the most common primary brain tumors associated with DI. Germinomas can be very small and undetectable by MRI for several years after the onset of polyuria. Quantitative measurement of α-fetoprotein and β-human chorionic gonadotropin, often secreted by germinomas, should be performed in children with idiopathic or unexplained DI in addition to serial MRI scans. Craniopharyngiomas and optic gliomas can also cause central DI when they are very large, although this is more often a postoperative complication of the treatment for these tumors (see Chapter 546). Hematologic malignancies, such as acute myelocytic leukemia, can cause DI via infiltration of the pituitary stalk and sella.

Langerhans cell histiocytosis (see Chapter 556.2) and lymphocytic hypophysitis are common types of infiltrative disorders causing central DI, with **hypophysitis** as the cause in 50% of cases of "idiopathic" central DI. Infections involving the base of the brain (see Chapter 643), including meningitis (meningococcal, cryptococcal, listerial, toxoplasmal), congenital cytomegalovirus infection, and nonspecific

inflammatory diseases of the brain, may give rise to central DI that is often transient. Drugs associated with the inhibition of vasopressin release include ethanol, phenytoin, opiate antagonists, halothane, and α-adrenergic agents.

Nephrogenic Diabetes Insipidus

NDI can result from genetic or acquired causes. Genetic causes are less common but more severe than acquired forms of NDI. The polyuria and polydipsia associated with genetic NDI usually occur within the first several weeks of life but may become apparent only after weaning or with longer periods of nighttime sleep. Many infants initially present with fever, vomiting, and dehydration. Failure to thrive may be secondary to the ingestion of large amounts of water, resulting in caloric malnutrition. Long-standing ingestion and excretion of large volumes of water can lead to nonobstructive hydronephrosis, hydroureter, and megabladder.

Congenital X-linked NDI results from inactivating pathogenic variants of the vasopressin V2 receptor, *AVPR2*. **Congenital autosomal recessive NDI** results from defects in the aquaporin-2 gene, *AQP2*. An **autosomal dominant form of NDI** is associated with processing variants of the *AQP2* gene.

Acquired NDI can result from hypercalcemia or hypokalemia and is associated with lithium, demeclocycline, foscarnet, clozapine, amphotericin, methicillin, and rifampin. Impaired renal concentrating ability can also be seen with ureteral obstruction, chronic renal failure, polycystic kidney disease, medullary cystic disease, Sjögren syndrome, and sickle cell disease. Decreased protein or sodium intake or excessive water intake, as in primary polydipsia, can lead to diminished tonicity of the renal medullary interstitium, which impairs water reabsorption and thus the ability to concentrate the urine, leading to NDI.

TREATMENT OF CENTRAL DIABETES INSIPIDUS

Fluid Therapy

With an intact thirst mechanism and free access to oral fluids, a person with complete DI can maintain plasma osmolality and sodium in the high-normal range, although at great inconvenience. Neonates and young infants are often best treated solely with fluid therapy, given their requirement for large volumes (~3 L/m^2/24 hr) of nutritive fluid. The use of vasopressin analogs in patients with obligate high fluid intake is difficult given the risk of life-threatening hyponatremia. Although not FDA approved, the use of DDAVP (desmopressin) administered to infants with central DI, both as the diluted parenteral form given subcutaneously and as the diluted intranasal form given via the buccal mucosa, has been successful without causing severe hyponatremia. Patients with both central DI and NDI should ingest a diet without excessive solute (e.g., sodium chloride) to help decrease urine output when vasopressin action wanes.

Vasopressin Analogs

Treatment of central DI in older children is best accomplished with the use of DDAVP. DDAVP is available in an intranasal preparation (onset 5-10 minutes) and more commonly as tablets (onset 15-30 minutes). The intranasal preparation of DDAVP (10 μg/0.1 mL) can be administered by rhinal tube (allowing dose titration) or by nasal spray (10 μg/puff). Use of DDAVP oral tablets requires at least a 10-fold increase in the dosage compared with the intranasal preparation. Oral dosages of 25-300 micrograms every 8-12 hours are safe and effective in children. The appropriate dosage and route of administration are determined empirically based on the desired length of antidiuresis and patient preference. The use of oral DDAVP for the treatment of enuresis in older children should be regarded as a temporizing measure, given that it does not affect the underlying condition, and should be used with great caution given the risk of hyponatremia if water intake exceeds the capacity for renal clearance. To prevent water intoxication, patients should have at least 1 hour of urinary breakthrough between doses each day and be advised to drink only in response to thirst sensation, if present. The use of DDAVP nasal spray for childhood enuresis is no longer approved because of its risk of causing hyponatremia.

Aqueous Vasopressin

Central DI of acute onset after neurosurgery is best managed with continuous administration of synthetic aqueous vasopressin (Pitressin). Under most circumstances, total fluid intake must be limited to 1 L/m^2/24 hr during antidiuresis. A typical dosage for intravenous vasopressin therapy is 1.5 mU/kg/hr, which results in a blood vasopressin concentration of approximately 10 pg/mL. On occasion, after hypothalamic (but not transsphenoidal) surgery, higher initial concentrations of vasopressin may be required to treat acute DI, which has been attributed to the release of a vasopressin inhibitory substance. *Vasopressin concentrations >1,000 pg/mL should be avoided because they can cause cutaneous necrosis, rhabdomyolysis, cardiac rhythm disturbances, and hypertension.* Post-neurosurgical patients treated with vasopressin infusion should be switched from intravenous to oral fluids as soon as possible to allow thirst sensation, if intact, to help regulate osmolality.

Individuals with central DI caused by intracranial tumors that require chemotherapy often need hyperhydration with large amounts of intravenous fluids to prevent nephrotoxicity during treatment. Using a low-dose vasopressin continuous infusion to minimally concentrate urine above baseline can allow infusion of fluids over 1 L/m^2/day, while preventing the discomfort of full diuresis if done under careful monitoring of volume status and sodium levels.

TREATMENT OF NEPHROGENIC DIABETES INSIPIDUS

The treatment of acquired NDI focuses on eliminating, if possible, the underlying disorder, such as offending drugs, hypercalcemia, hypokalemia, or ureteral obstruction. Congenital NDI is often difficult to treat. The main goals are to ensure the intake of adequate calories for growth and to avoid severe dehydration. Foods with the highest ratio of caloric content to osmotic load (Na <1 mmol/kg/24 hr) should be ingested to maximize growth and to minimize the urine volume required to excrete the solute load. However, even with the early institution of therapy, growth failure and developmental disabilities are common.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria. High-dose DDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment could prove useful in patients with genetic defects in the V2 receptor associated with a reduced binding affinity for vasopressin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 597

Other Abnormalities of Arginine Vasopressin Metabolism and Action

Carmen L. Soto-Rivera, David T. Breault, and Joseph A. Majzoub

Hyponatremia (serum sodium <130 mEq/L) in children is usually associated with severe systemic disorders and is most often a result of intravascular volume depletion, excessive salt loss, or hypotonic fluid overload, especially in infants (see Chapter 73).

The initial approach to the patient with hyponatremia begins with determination of the volume status. A careful review of the patient's history, physical examination (including changes in weight), and vital signs helps to determine whether the patient is hypovolemic or hypervolemic. Supportive evidence includes laboratory data such as serum electrolytes, blood urea nitrogen, creatinine, uric acid, urine sodium, specific gravity, and osmolality (Tables 597.1 and 597.2; see Chapter 73).

CAUSES OF HYPONATREMIA

Systemic Dehydration

The initial manifestation of systemic dehydration is often hypernatremia and hyperosmolality, which subsequently lead to the activation of vasopressin secretion and a decrease in water excretion. As dehydration progresses, hypovolemia and/or hypotension become a major stimulus for vasopressin release, further decreasing free water clearance. Excessive free water intake (orally or intravenous infusion of hypotonic fluids) with ongoing salt loss can produce hyponatremia. Urinary sodium excretion is low (usually <20 mEq/L), owing to a low glomerular filtration rate and concomitant activation of the renin-angiotensin-aldosterone system unless primary renal disease or diuretic therapy is present.

Table 597.1 Differential Diagnosis of Hyponatremia

DISORDER	INTRAVASCULAR VOLUME STATUS	URINE SODIUM
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss (nonrenal)	Low	Low
Primary salt loss (renal)	Low	High
Adrenal insufficiency	Low	High
SIAD	High	High
Cerebral salt wasting	Low	Very high
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Runner's hyponatremia	Low	Low
NSIAD	High	High
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

NSIAD, Nephrogenic syndrome of inappropriate antidiuresis; SIAD, syndrome of inappropriate antidiuresis.

Runner's Hyponatremia

Excess hypotonic fluid ingestion during long-distance running (e.g., marathon running) can result in severe hyponatremia from hypovolemia-induced activation of arginine vasopressin secretion coupled with excessive water ingestion and is correlated with weight gain, long racing time, and extremes of body mass index.

Decreased Effective Plasma Volume

Hyponatremia can result from decreased effective plasma volume, as found in congestive heart failure, cirrhosis, nephrotic syndrome, positive pressure mechanical ventilation, severe burns, bronchopulmonary dysplasia in neonates, cystic fibrosis with obstruction, and severe asthma. The resulting decrease in cardiac output leads to reduced water and salt excretion, as with systemic dehydration, and an increase in vasopressin secretion. In patients with impaired cardiac output and elevated atrial volume (congestive heart failure, lung disease), atrial natriuretic peptide concentrations are elevated further, leading to hyponatremia by promoting natriuresis. However, owing to the marked elevation of aldosterone in these patients, their urine sodium remains low (<20 mEq/L) despite this. Unlike dehydrated patients, these patients also have excess *total body* sodium from activation of the renin-angiotensin-aldosterone system and can demonstrate peripheral edema as well.

Syndrome of Inappropriate Antidiuresis

The syndrome of inappropriate antidiuresis (SIAD) is characterized by hyponatremia, an inappropriately concentrated urine (often >800 mOsm/kg H_2O), normal or slightly elevated plasma volume, normal-to-high urine sodium, and low serum uric acid. SIAD is uncommon in children, and most cases result from excessive administration of vasopressin in the treatment of central diabetes insipidus (vasopressin deficiency). It can also occur with increased intracranial pressure, encephalitis, brain tumors, head trauma, psychiatric disease, prolonged nausea, pneumonia, tuberculous and bacterial meningitis, AIDS, and in the postictal phase after generalized seizures (Table 597.3). SIAD is the cause of the hyponatremic second phase of the triphasic response seen after hypothalamic-pituitary surgery. It is found in up to 35% of patients 1 week after surgery and can result from retrograde neuronal degeneration with cell death and vasopressin release. Common drugs that have been shown to increase vasopressin secretion or mimic vasopressin action, resulting in hyponatremia, include oxcarbazepine, carbamazepine, chlorpropamide, vinblastine, vincristine, and tricyclic antidepressants.

Nephrogenic Syndrome of Inappropriate Antidiuresis

Gain-of-function pathogenic variants in the V2 vasopressin receptor gene, *AVPR2,* on chromosome Xq28 have been described in male

Table 597.2 Clinical Parameters to Distinguish Among Syndrome of Inappropriate Antidiuresis (SIAD), Cerebral Salt Wasting, and Central Diabetes Insipidus (DI)

CLINICAL PARAMETER	SIAD	CEREBRAL SALT WASTING	CENTRAL DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Blood pressure	Normal	Decreased/ orthostatic hypotension	Decreased/ orthostatic hypotension
Vasopressin level	High	Low	Low
BUN	Low	High	High

Table 597.3 Disorders Associated with Syndrome of Inappropriate Antidiuresis

CANCER	PULMONARY DISORDERS	CENTRAL NERVOUS SYSTEM DISORDERS	OTHER DISORDERS
Thymoma	Viral pneumonia	Encephalitis (viral or bacterial)	AIDS
Lymphoma	Bacterial pneumonia	Meningitis (viral, bacterial, tuberculous, fungal)	Prolonged exercise
Ewing sarcoma	Pulmonary abscess	Head trauma	Idiopathic (in older individuals)
Oropharyngeal tumor	Tuberculosis	Brain abscess	Nephrogenic
	Aspergillosis	Guillain-Barré syndrome	Acute intermittent porphyria
	Positive pressure ventilation	Subarachnoid hemorrhage or subdural hematoma	
	Asthma	Cerebellar and cerebral atrophy	
	Pneumothorax	Cavernous sinus thrombosis	
	Cystic fibrosis	Neonatal hypoxia	
		Shy-Drager syndrome	
		Rocky Mountain spotted fever	
		Delirium tremens	
		Cerebrovascular accident (cerebral thrombosis or hemorrhage)	
		Acute psychosis	
		Peripheral neuropathy	
		Multiple sclerosis	

Modified from Verbalis JG. Disorders of water balance. In Skorecki K, Chertow GM, Marsden PA, et al., eds, *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 16.6.

neonates with an SIAD-like clinical picture with undetectable vasopressin levels. Females are most often asymptomatic carriers. It is most commonly treated by fluid restriction, but oral urea has also been used to promote osmotic diuresis and increase water clearance. Germline activating pathogenic variants in *GNAS* have also been found in infants presenting with hyponatremia. Activating variants in the aquaporin-2 gene *(AQP2)* also give rise to the same syndrome.

Cerebral Salt Wasting

Cerebral salt wasting appears to be the result of hypersecretion of natriuretic peptides and is seen primarily with central nervous system disorders, including brain tumors, head trauma, hydrocephalus, neurosurgery, cerebrovascular accidents, and brain death. Hyponatremia is accompanied by elevated urinary sodium excretion (often >150 mEq/L), excessive urine output, hypovolemia, normal or high uric acid, and elevated atrial natriuretic peptide concentrations (>20 pmol/L). Thus it is distinguished from SIAD, in which normal or decreased urine output, normal or elevated blood volume, only modestly elevated urine sodium concentration, and an elevated vasopressin level occur. The distinction between cerebral salt wasting and SIAD is important because the treatment of the two disorders differs markedly. The existence of cerebral salt wasting has been controversial; however, current data support this entity as different from SIAD.

Primary Polydipsia (Increased Water Ingestion)

In patients with normal renal function, the kidney can excrete dilute urine with an osmolality as low as 50 mOsm/kg H_2O. To excrete a daily solute load of 500 mOsm/m^2 under these circumstances, the kidney must produce 10 L/m^2 of urine per day. Therefore to avoid hyponatremia, the maximum amount of water a person with normal renal function can consume daily is 10 L/m^2, or less if solute intake is lower. However, neonates cannot dilute their urine to this degree, putting them at risk for water intoxication if water intake exceeds 4 L/m^2/day (approximately 60 mL/hr in a newborn). Infants may develop transient hyponatremic seizures after being fed pure water without electrolytes rather than breast milk or formula.

Primary Salt Loss

Hyponatremia can result from the primary loss of sodium chloride, as seen in specific disorders of the kidney (congenital polycystic kidney disease, acute interstitial nephritis, chronic renal failure), gastrointestinal tract (gastroenteritis), and sweat glands (cystic fibrosis). The hyponatremia is not solely caused by salt loss, as it is often associated with hypovolemia, leading to an increase in vasopressin. Mineralocorticoid deficiency (hypoaldosteronism), pseudohypoaldosteronism (genetic or sometimes seen in children with urinary tract obstruction or infection), and diuretics can also result in loss of sodium chloride (Table 597.4). Low aldosterone states, such as primary adrenal insufficiency (Addison disease), are associated with salt wasting, hypovolemia, hyponatremia, hyperkalemia, and failure to thrive.

Decreased Free Water Clearance

Hyponatremia as a consequence of decreased renal free water clearance, even in the absence of an increase in vasopressin secretion, can result from adrenal insufficiency or thyroid deficiency or can be related to a direct effect of drugs on the kidney. Glucocorticoids are required for normal free water clearance in a vasopressin-independent manner. In patients with unexplained hyponatremia, adrenal and thyroid insufficiency should be considered. Patients with coexisting adrenal failure and diabetes insipidus might have no symptoms of the latter until glucocorticoid therapy unmasks the need for vasopressin replacement. Certain drugs can inhibit renal water excretion through direct effects on the nephron, thus causing hyponatremia; these drugs include high-dose cyclophosphamide, vinblastine, cisplatinum, carbamazepine, and oxcarbazepine.

Pseudohyponatremia and Other Causes of Hyponatremia

Pseudohyponatremia can result from hypertriglyceridemia (see Chapter 73.3). Elevated lipid levels result in a relative decrease in serum water content. As electrolytes are dissolved in the aqueous phase of the serum, they appear low when expressed as a fraction of the total serum volume. However, as a fraction of serum water, electrolyte content is normal. Modern laboratory methods that measure sodium concentration directly, independent of sample volume, do not cause this anomaly. Factitious hyponatremia can result from obtaining a blood sample downstream to the site of intravenous hypotonic fluid infusion.

Hyponatremia is also associated with hyperglycemia, which causes the influx of water into the intravascular space. Serum sodium decreases by ~1.6 mEq/L for every 100 mg/dL increment in blood glucose >100 mg/dL. Glucose is not ordinarily an osmotically active agent and does not stimulate vasopressin release, probably because it can equilibrate freely across plasma membranes. However, in the presence of insulin deficiency and hyperglycemia, glucose acts as an osmotic agent, presumably because its normal intracellular access to osmosensor sites is prevented. Under these circumstances, an osmotic gradient exists, stimulating vasopressin release.

TREATMENT

Patients with systemic dehydration and hypovolemia should be rehydrated with salt-containing fluids such as normal saline or lactated Ringer's solution. Because of activation of the renin-angiotensin-aldosterone system, the administered sodium is avidly conserved, and water diuresis quickly

Table 597.4 Pathogenic Gene Variants Associated with Hypoaldosteronism/ Pseudohypoaldosteronism (Type IV Renal Tubular Acidosis)

GENE CHROMOSOME OMIM	PATHOPHYSIOLOGY	PATHOGENIC VARIANT–CLINICAL MANIFESTATIONS–OMIM–INHERITANCE
PRIMARY HYPOALDOSTERONISM		
CYP21A2—cytochrome P450, subfamily XXIA, polypeptide 2 6p21.3 613815	P450c21—steroid 21-hydroxylase that converts 17 α-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata	Loss-of-function pathogenic variants decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classic congenital adrenal hyperplasia, AR–201910
CYP11B2—cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080	P450c11B2—aldosterone synthase/corticosterone methyloxidase types I and II expressed only in the zona glomerulosa; hydroxylates deoxycorticosterone at carbon-11 and corticosterone at carbon-18 and oxidizes 18-hydroxycorticosterone to aldosterone	Loss-of-function pathogenic variants associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMOI 203400; CMOII 610600)
PSEUDOHYPOALDOSTERONISM TYPE I (PHA1)		
NR3C2—nuclear receptor subfamily 3, group C, member 2 (MR-mineralocorticoid receptor), 4q31.1 600983	Ligand-activated nuclear transcription factor that transmits aldosterone-mediated control of gene expression by binding to the mineralocorticoid response element in the promoter region of the target gene	Loss-of-function pathogenic variants in the MR lead to mineralocorticoid resistance and salt wasting, PHA1A, AD–177735
SCNN1A—sodium channel, non–voltage-gated, α-subunit 12p13.31 600228	Inactivating pathogenic variant of α-subunit of the epithelial sodium channel	Loss-of-function pathogenic variants in the epithelial sodium channel lead to mineralocorticoid resistance and salt wasting, PHA1B, AR–264350
SCNN1B—sodium channel, non–voltage-gated, β-subunit 16p12.2 600760	Inactivating mutation of β-subunit of the epithelial sodium channel	Loss-of-function pathogenic variants in the epithelial sodium channel lead to mineralocorticoid resistance and salt wasting, PHA1B, AR–264350
SCNN1G—sodium channel, non–voltage-gated, γ-subunit 16p12.2 600761	Inactivating mutation of γ-subunit of the epithelial sodium channel	Loss-of-function pathogenic variants in the epithelial sodium channel lead to mineralocorticoid resistance and salt wasting, PHA1B AR–264350
PSEUDOHYPOALDOSTERONISM TYPE II (PHA2) (GORDON SYNDROME)		
WNK4—protein kinase, lysine-deficient 4 17q21.31 601844	Multifunctional serine-threonine protein kinase whose substrate is SLC12A3, the thiazide-sensitive sodium/chloride co-transporter (NCCT)—OMIM 600968—that also regulates lysosomal degradation of NCCT and endocytosis of the KCNJ1 potassium channel	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2B, AD–614491
WNK1—protein kinase, lysine-deficient 1 12p13.33 605232	Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2C, AD–614492
KLH3—Kelch-like 3 5q31.2 605775	Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2D, AD/AR–614495
CUL3—Cullin 3 2q36.2 603136	Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2E, AD–614496

AD, Autosomal dominant; AR, autosomal recessive; CMO, corticosterone methyloxidase; OMIM, Online Mendelian Inheritance in Man.
From Root AW. Disorders of aldosterone synthesis, secretion, and cellular function. *Curr Opin Pediatr.* 2014;26:480–486, Table 1.

ensues as volume is restored and vasopressin concentrations decrease. Under these conditions, caution must be taken to prevent a too-rapid correction of hyponatremia (with a goal increase of <0.5 mEq/L/hr), which can result in central pontine myelinolysis characterized by discrete regions of axonal demyelination and the potential for irreversible brain damage.

Hyponatremia from a decrease in effective plasma volume caused by cardiac, hepatic, renal, or pulmonary dysfunction is more difficult to reverse. The most effective therapy is treatment of the underlying systemic disorder. Patients weaned from positive pressure ventilation undergo a prompt water diuresis and resolution of hyponatremia as cardiac output is restored and vasopressin concentrations decrease. Vaptans are a class of small-molecule arginine vasopressin V2 receptor antagonists (aquaretics) useful for the treatment of hypervolemic hyponatremia associated with severe congestive heart failure and chronic liver failure. Although these agents successfully increase plasma sodium, they also lead to increased thirst and plasma vasopressin levels, which can limit their effectiveness, can increase serum sodium more rapidly than is safe, and may cause hepatoxicity.

Patients with hyponatremia from primary salt loss require supplementation with sodium chloride and fluids. Initially, intravenous replacement with isotonic fluids containing sodium chloride (150 mEq/L) may be necessary. Hypertonic fluids (450 mEq/L sodium choride) should be reserved for treatment of acute neurologic deterioration caused by severe hyponatremia. Oral salt supplementation may be required subsequently. This treatment contrasts with that of SIAD, in which water restriction without sodium supplementation is the mainstay.

Emergency Treatment of Hyponatremia

The development of acute hyponatremia (onset <12 hr) or a serum sodium concentration <120 mEq/L may be associated with lethargy,

psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia can cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. *The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and can require rapid correction with hypertonic 3% sodium chloride*. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to cause an improvement in mental status and, in no case, faster than 0.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of Syndrome of Inappropriate Antidiuresis

Chronic SIAD is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg H_2O), a normal daily obligate renal solute load of 500 mOsm/m^2 would be excreted in 500 mL/m^2 water. This, plus a daily nonrenal water loss of 500 mL/m^2, would require that oral fluid intake be limited to 1,000 mL/m^2/24 hr to avoid hyponatremia. In young children, this degree of fluid restriction might not provide adequate calories for growth. In this situation, a vaptan such as tolvaptan, although not FDA approved in children and may cause initial correction of hyponatremia too rapidly, may allow sufficient fluid intake for normal growth without concomitant hyponatremia. Urea has also been safely used to induce an osmotic diuresis in infants and children.

Treatment of Cerebral Salt Wasting

Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as for the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually the result of acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine and sodium losses volume for volume.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 598

Hyperpituitarism

Omar Ali

Hyperpituitarism is defined as the excessive secretion or production of one or more of the hormones produced by the pituitary gland. The anterior pituitary normally produces prolactin, growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and the gonadotropin hormones (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]); overproduction of any of these hormones is possible, though all are relatively rare. The posterior pituitary stores and releases antidiuretic hormone (ADH) and oxytocin, both produced by neurons in the hypothalamus. Although extremely rare cases of hypothalamic neurocytomas producing excess ADH have been reported (mostly in adults), these are vanishingly rare and will not be considered any further. *Hyperpituitarism refers to the overproduction of one or more of the anterior pituitary hormones.*

SECONDARY HYPERPITUITARISM

Several of the anterior pituitary hormones (all except GH and prolactin) act on other endocrine glands and regulate their secretion. They are regulated by negative feedback loops from their target glands, and their secretion increases if the end organ is not producing enough hormone. This can lead in extreme cases to severe hypertrophy of the relevant anterior pituitary cells and is a normal physiologic response to target hormone deficiencies resulting in decreased hormonal feedback, such as in hypogonadism, hypoadrenalism, or hypothyroidism. In these cases of *secondary hyperpituitarism,* chronic pituitary hypersecretion occurs in response to target hormone deficiencies that leads to pituitary hyperplasia; in extreme cases this can even enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such enlargements should not be confused with *primary* pituitary tumors; they disappear, and elevated pituitary hormone levels readily suppress to normal when the underlying hormone deficiency is treated by replacement of end-organ hormones.

Primary hypersecretion of pituitary hormones is uncommon in childhood. The most commonly diagnosed adenoma during childhood is prolactinoma, followed by corticotropinoma, and then somatotropinoma, which secrete prolactin, corticotropin, and GH, respectively. There are a handful of case reports of **thyrotropinoma** in children and adolescents. There are no pediatric reports of gonadotropinoma, but hypothalamic hamartomas that secrete excess gonadotropin-releasing hormone are one cause of precocious puberty. In very rare cases, pituitary hyperplasia can also occur in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome secondary to corticotropin-releasing hormone excess or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

The monoclonal nature of most pituitary adenomas implies that most originate from a clonal event in a single cell. In some cases, the pituitary tumors result from stimulation with hypothalamic-releasing hormones and in other instances, as in **McCune-Albright syndrome** (MAS), the tumor is caused by activating pathogenic variants of the *GNAS1* gene that codes for the α subunit of $G_s\alpha$, a guanine nucleotide-binding protein. The clinical presentation typically depends on the pituitary hormone that is hypersecreted. In addition, disruptions of growth regulation and/or sexual maturation are common as a result of either hormone hypersecretion or local compression by the tumor. MAS also features polyostotic fibrous dysplasia of bone and café-au-lait spots in a distinct distribution.

EXCESS GROWTH HORMONE SECRETION AND PITUITARY GIGANTISM

In young persons with open epiphyses, overproduction of GH results in **gigantism**; in persons with closed epiphyses, the result is **acromegaly**. Often some acromegalic features are seen with gigantism, even in children and adolescents. After closure of the epiphyses, the acromegalic features become more prominent.

Gigantism is rare, with only several hundred reported cases worldwide to date. It must be emphasized that the vast majority of patients with tall stature will not have gigantism. The normal distribution of height predicts that 2.3% of the population will be taller than 2 standard deviations (SD) (97.7%) above the mean, and many cases of tall stature will therefore be normal-variant familial tall stature; if their growth is in line with their midparental height and no other concerning features are present, then no further investigation is needed. In cases where the tall stature is unexpected or extreme, other etiologies of rapid linear growth such as precocious puberty and hyperthyroidism should be carefully excluded. Coexisting findings (e.g., dysmorphic facial features, neurocognitive problems, hemihypertrophy) may suggest syndromic or chromosomal causes of tall stature, such as Sotos, Weaver, Klinefelter, or XYY syndrome.

The cardinal clinical feature of gigantism is longitudinal growth acceleration secondary to GH excess. The usual manifestations consist of coarse facial features and enlarging hands and feet. In young children, rapid growth of the head can precede linear growth. Some patients have behavioral and visual problems. In most recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period. Giants have rarely been reported to grow to a height of over 8 feet. In some cases, the patient may present with local effects of the pituitary tumor (headache, visual field defects, and other pituitary hormone deficiencies) as the main complaint, and there is at least one report of a patient presenting with diabetic ketoacidosis induced by GH excess. The presentation of gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults.

Pituitary adenomas secreting GH are more common in males, but females may present at an earlier age. Tumors with *AIP* pathogenic

psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia can cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. *The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and can require rapid correction with hypertonic 3% sodium chloride*. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to cause an improvement in mental status and, in no case, faster than 0.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of Syndrome of Inappropriate Antidiuresis

Chronic SIAD is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg H_2O), a normal daily obligate renal solute load of 500 mOsm/m^2 would be excreted in 500 mL/m^2 water. This, plus a daily nonrenal water loss of 500 mL/m^2, would require that oral fluid intake be limited to 1,000 mL/m^2/24 hr to avoid hyponatremia. In young children, this degree of fluid restriction might not provide adequate calories for growth. In this situation, a vaptan such as tolvaptan, although not FDA approved in children and may cause initial correction of hyponatremia too rapidly, may allow sufficient fluid intake for normal growth without concomitant hyponatremia. Urea has also been safely used to induce an osmotic diuresis in infants and children.

Treatment of Cerebral Salt Wasting

Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as for the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually the result of acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine and sodium losses volume for volume.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 598

Hyperpituitarism

Omar Ali

Hyperpituitarism is defined as the excessive secretion or production of one or more of the hormones produced by the pituitary gland. The anterior pituitary normally produces prolactin, growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and the gonadotropin hormones (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]); overproduction of any of these hormones is possible, though all are relatively rare. The posterior pituitary stores and releases antidiuretic hormone (ADH) and oxytocin, both produced by neurons in the hypothalamus. Although extremely rare cases of hypothalamic neurocytomas producing excess ADH have been reported (mostly in adults), these are vanishingly rare and will not be considered any further. *Hyperpituitarism refers to the overproduction of one or more of the anterior pituitary hormones.*

SECONDARY HYPERPITUITARISM

Several of the anterior pituitary hormones (all except GH and prolactin) act on other endocrine glands and regulate their secretion. They are regulated by negative feedback loops from their target glands, and their secretion increases if the end organ is not producing enough hormone. This can lead in extreme cases to severe hypertrophy of the relevant anterior pituitary cells and is a normal physiologic response to target hormone deficiencies resulting in decreased hormonal feedback, such as in hypogonadism, hypoadrenalism, or hypothyroidism. In these cases of *secondary hyperpituitarism,* chronic pituitary hypersecretion occurs in response to target hormone deficiencies that leads to pituitary hyperplasia; in extreme cases this can even enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such enlargements should not be confused with *primary* pituitary tumors; they disappear, and elevated pituitary hormone levels readily suppress to normal when the underlying hormone deficiency is treated by replacement of end-organ hormones.

Primary hypersecretion of pituitary hormones is uncommon in childhood. The most commonly diagnosed adenoma during childhood is prolactinoma, followed by corticotropinoma, and then somatotropinoma, which secrete prolactin, corticotropin, and GH, respectively. There are a handful of case reports of **thyrotropinoma** in children and adolescents. There are no pediatric reports of gonadotropinoma, but hypothalamic hamartomas that secrete excess gonadotropin-releasing hormone are one cause of precocious puberty. In very rare cases, pituitary hyperplasia can also occur in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome secondary to corticotropin-releasing hormone excess or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

The monoclonal nature of most pituitary adenomas implies that most originate from a clonal event in a single cell. In some cases, the pituitary tumors result from stimulation with hypothalamic-releasing hormones and in other instances, as in **McCune-Albright syndrome** (MAS), the tumor is caused by activating pathogenic variants of the *GNAS1* gene that codes for the α subunit of $G_s\alpha$, a guanine nucleotide-binding protein. The clinical presentation typically depends on the pituitary hormone that is hypersecreted. In addition, disruptions of growth regulation and/or sexual maturation are common as a result of either hormone hypersecretion or local compression by the tumor. MAS also features polyostotic fibrous dysplasia of bone and café-au-lait spots in a distinct distribution.

EXCESS GROWTH HORMONE SECRETION AND PITUITARY GIGANTISM

In young persons with open epiphyses, overproduction of GH results in **gigantism**; in persons with closed epiphyses, the result is **acromegaly**. Often some acromegalic features are seen with gigantism, even in children and adolescents. After closure of the epiphyses, the acromegalic features become more prominent.

Gigantism is rare, with only several hundred reported cases worldwide to date. It must be emphasized that the vast majority of patients with tall stature will not have gigantism. The normal distribution of height predicts that 2.3% of the population will be taller than 2 standard deviations (SD) (97.7%) above the mean, and many cases of tall stature will therefore be normal-variant familial tall stature; if their growth is in line with their midparental height and no other concerning features are present, then no further investigation is needed. In cases where the tall stature is unexpected or extreme, other etiologies of rapid linear growth such as precocious puberty and hyperthyroidism should be carefully excluded. Coexisting findings (e.g., dysmorphic facial features, neurocognitive problems, hemihypertrophy) may suggest syndromic or chromosomal causes of tall stature, such as Sotos, Weaver, Klinefelter, or XYY syndrome.

The cardinal clinical feature of gigantism is longitudinal growth acceleration secondary to GH excess. The usual manifestations consist of coarse facial features and enlarging hands and feet. In young children, rapid growth of the head can precede linear growth. Some patients have behavioral and visual problems. In most recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period. Giants have rarely been reported to grow to a height of over 8 feet. In some cases, the patient may present with local effects of the pituitary tumor (headache, visual field defects, and other pituitary hormone deficiencies) as the main complaint, and there is at least one report of a patient presenting with diabetic ketoacidosis induced by GH excess. The presentation of gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults.

Pituitary adenomas secreting GH are more common in males, but females may present at an earlier age. Tumors with *AIP* pathogenic

variants **(familial isolated pituitary adenoma)** are more common in males, are larger and invasive, and secrete GH or prolactin. **X-LAG syndrome (X-linked acrogigantism)** is a recognized cause of familial pituitary adenomas, and in these patients the rapid growth begins in infancy and is more frequent in females. Patients with MAS will usually exhibit other features, including polyostotic fibrous dysplasia, café-au-lait spots, and precocious puberty.

Pituitary tumors secrete extremely high levels of GH; approximately 50% of pituitary adenomas also exhibit hyperprolactinemia because they secrete both GH and prolactin. Adenomas can compromise other anterior pituitary function through growth or cystic degeneration. Secretion of gonadotropins, thyrotropin, or corticotropin may be impaired. Delayed sexual maturation or hypogonadism can occur. When GH hypersecretion is accompanied by gonadotropin deficiency, accelerated linear growth can persist for decades. In some cases, the tumor spreads outside the sella, invading the sphenoid bone, optic nerves, and brain. GH-secreting tumors in pediatric patients are more likely to be locally invasive or aggressive than are those in adults.

Acromegalic features consist chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. Visual field defects and neurologic abnormalities are common; signs of increased intracranial pressure appear later. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. GH levels are elevated and occasionally exceed 100 ng/mL. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test, and insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels are consistently elevated in acromegaly and pituitary gigantism.

Diagnosis

GH hypersecretion should be screened for by testing IGF1 and IGFBP-3 levels. An elevated IGF1 level in a patient with appropriate clinical suspicion usually indicates GH excess. Potential confusion can arise in the evaluation of normal adolescents because significantly higher IGF1 levels occur during puberty than in adulthood; the IGF1 level must be age and gender matched. Serum IGFBP-3 levels are also sensitive markers of GH elevations and will be elevated in almost all cases. If IGF1 and/or IGFBP-3 levels are elevated, then the next step is to test for GH excess by doing an oral glucose-suppression test. The gold standard for the diagnosis of GH excess in adults is the failure to suppress serum GH levels to <1 ng/dL at any time during a 2-hour oral glucose tolerance test with 1.75 g/kg oral glucose challenge (maximum: 75 g). GH levels may not be suppressed to this level in normal adolescents, and a cutoff of 5 ng/mL may be more appropriate in this age-group. If laboratory findings suggest GH excess, the presence of a pituitary adenoma should be confirmed by MRI of the brain. In rare cases, a pituitary mass is not identified. This might be from an occult pituitary microadenoma or ectopic production of GHRH or GH. CT is acceptable when MRI is unavailable.

Genetic causes: Genetic pathogenic variants are recognized as being present in ~50% of cases, though many are sporadic. In a large series, detailed genetic testing revealed pathogenic variants in *AIP* in 29% of cases, X-LAG due to microdeletions at Xq26.3 in 10% of the cases, and MAS in 5% of the cases. No genetic abnormality was identified in 54% of the cases. Although GH-secreting adenomas eventually develop in up to 60% of patients with multiple endocrine neoplasia 1 (MEN1), most of these occur in adults and therefore cause acromegaly rather than gigantism. Increased GH secretion and GH-secreting adenomas may also be seen in neurofibromatosis; tuberous sclerosis; MEN4; Carney complex; and the paraganglioma, pheochromocytoma, and pituitary adenoma association known as *3PA*.

A genetics consultation and appropriate genetic testing is therefore indicated in all cases of pituitary gigantism.

Treatment

The goals of therapy are to remove or shrink the pituitary mass, to restore GH and secretory patterns to normal, to restore IGF1 and IGFBP-3 levels to normal, to retain the normal pituitary secretion of other hormones, and to prevent recurrence of disease.

For well-circumscribed pituitary adenomas, trans-sphenoidal surgery is the treatment of choice and may be curative. The tumor should be removed completely. The likelihood of surgical cure depends greatly on the surgeon's expertise and on the size and extension of the mass. Intraoperative GH measurements can improve the results of tumor resection. Trans-sphenoidal surgery to resect the tumors is as safe in children as in adults. At times, a transcranial approach might be necessary. The primary goal of treatment is to normalize GH and IGF1 levels. GH levels (<1 ng/mL within 2 hours after a glucose load) and serum IGF1 levels (age-adjusted normal range) are the best tests to define a biochemical cure.

If GH secretion and IGF1 levels are not normalized by surgery, the options include pituitary irradiation and medical therapy. Further growth of the tumor is prevented by irradiation in >99% of patients. The main disadvantage is the delayed efficacy in decreasing GH levels. GH is reduced by approximately 50% from the initial concentration by 2 years, by 75% by 5 years, and approaches 90% by 15 years. Multiple pituitary hormone deficiency is a predictable result of pituitary radiation, occurring in 40–50% of patients 10 years after irradiation.

Surgery fails to cure a significant number of patients, and radiotherapy may not work fast enough, so medical therapy has an important role in treating patients with GH excess. Treatment is effective and well tolerated with GH antagonists, long-acting somatostatin analogs, and in some cases, by dopamine agonists.

Pegvisomant is a GH-receptor antagonist that competes with endogenous GH for binding to the GH receptor. It effectively suppresses GH and IGF1 levels in patients with acromegaly caused by pituitary tumors and ectopic GHRH hypersecretion. Normalization of IGF1 levels occurs in up to 90% of patients treated daily with this drug for 3 months or longer. The adult dosage is 10-40 mg via subcutaneous injection once daily, although twice-weekly protocols have also been reported as highly successful. IGF1 levels and hepatic enzymes must be monitored. Combined therapy with somatostatin analogs and weekly pegvisomant injections also is effective. Pediatric experience is limited, but case reports indicate that it can successfully suppress IGF1 levels when used in doses of 10-30 mg/day.

The **somatostatin analogs** are frequently effective in the treatment of patients with GH excess. Octreotide suppresses GH to <2.5 ng/mL in 65% of patients with acromegaly and normalizes IGF1 levels in 70%. The effects of octreotide are well sustained over time. Tumor shrinkage also occurs with octreotide but is generally modest. Consistent GH suppression can be obtained with a continuous subcutaneous (SC) pump infusion of octreotide or with long-acting formulations, including long-acting octreotide and lanreotide. Octreotide injection in the pediatric population has been used at doses of 1-40 μg/kg/24 hr. In adults the long-acting form is used in a dose of 10-40 mg every month, but no pediatric dose range has been established.

For patients with both GH and prolactin oversecretion, **dopamine agonists, such as bromocriptine and cabergoline**, which bind to pituitary dopamine type 2 receptors and may also suppress GH secretion, can also be considered. Prolactin levels are often adequately suppressed, but GH levels and IGF1 levels are rarely normalized with this treatment modality alone. Tumor shrinkage occurs in a minority of patients. The effectiveness of these agents may be additive to that of octreotide. Cabergoline therapy at doses of 0.25-4.0 mg/wk (given 1-2 times per week) has been used in adults with acromegaly, and because of its less frequent dosing and lower incidence of side effects as compared to bromocriptine, this is now considered the dopamine agonist of choice in both adults and children. Side effects can include nausea, vomiting, abdominal pain, arrhythmias, nasal stuffiness, orthostatic hypotension, sleep disturbances, and fatigue.

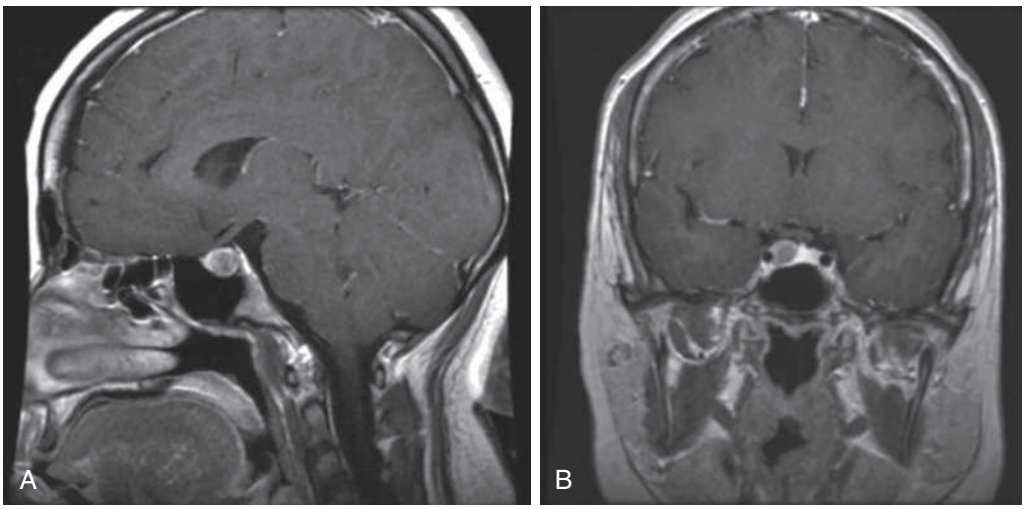

Fig. 598.1 Sagittal (A) and coronal (B) post-gadolinium T1-weighted MRI scans of a female with a microprolactinoma on the right side of the sella, who presented with amenorrhea and galactorrhea. Her serum prolactin was 89 ng/mL. *(From Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. J Clin Neurosci. 2015;22:1562–1567, Fig. 1, p. 1563.)*

TREATMENT OF NORMAL-VARIANT TALL STATURE

Patients who have **familial tall stature** and no other underlying pathology usually require no treatment other than reassurance. The use of the bone age to predict adult height might provide some comfort for them, as will general supportive discussions on the social acceptability of this condition. Although treatment is possible for females and males with excessive growth, its use should be restricted to patients with predicted adult height >3-4 SD above the mean (79 inches or 200 cm in males, 73 inches or 185 cm in females) *and* evidence of significant psychosocial impairment.

Sex steroids have been used in the treatment of tall stature and are designed to accelerate puberty and to promote epiphyseal fusion; these are therefore of little benefit when given in late puberty. The lack of extensive experience with this form of therapy and the risks of estrogen or androgen treatment for tall stature should be carefully weighed and discussed with the family, and treatment should be discouraged except in the most extreme cases. Detailed discussion with the child at the child's level is also advisable, as up to 40% of those who underwent such treatments are dissatisfied as adults and feel they were not sufficiently consulted about this course of action. Therapy is initiated ideally before puberty or in early puberty (no later than bone age of 14). In the extremely rare instances where treatment is desired, testosterone enanthate is used at a dose of 250-500 mg intramuscularly every 2 weeks for 6 months in males. In females, oral estrogens in various doses have been used to reduce the predicted height, but average height reduction may be only 1.1-2.4 cm. Therapy must begin before the bone age has reached 12 years. In the rare case where treatment is advised, oral ethinyl estradiol has been used at a dose of 0.15-0.5 mg/day until cessation of growth occurs**.** Short-term side effects have included benign breast disease, cholelithiasis, hypertension, menstrual irregularities, weight gain, nausea, limb pain, galactorrhea, and thrombosis. Reduced fertility later in life may be a potential long-term complication. An alternative to sex-steroid therapy is the use of epiphysiodesis (destruction of the growth plates) around the knee to limit linear growth, but this intervention also remains controversial, and its long-term safety profile and psychologic risks and benefits remain unknown.

HYPERSECRETION OF OTHER PITUITARY HORMONES

Prolactinoma

Prolactin-secreting pituitary adenomas are the most common pituitary tumors in adolescents. With the use of MRI, more of these tumors, particularly microadenomas (<1 cm in diameter), are being detected (Fig. 598.1). The most common presenting manifestations are headache, primary or secondary amenorrhea, and galactorrhea. The disorder affects more than twice as many females as males; most patients have undergone normal puberty before becoming symptomatic. Only a few have delayed puberty. In some kindreds with **type I multiple endocrine neoplasia syndrome**, prolactinomas are the presenting feature during adolescence. Familial cases and sporadic cases with de novo pathogenic variants of the *AIP* gene and X-LAG are being recognized more often as genetic testing becomes more common.

Prolactin levels may be elevated mildly (40-50 ng/mL) or markedly (10,000-15,000 ng/mL), and there is a correlation between tumor size and prolactin levels. Most prolactinomas in children are large (macroadenomas), cause the sella to enlarge, and, in some cases, cause visual field defects. Approximately 30% of patients with macroadenomas develop other pituitary hormone deficiencies, particularly GH deficiency. Alternatively, prolactin-secreting adenomas might also stain for and secrete excess GH and/or TSH.

Prolactinomas should not be confused with the hyperprolactinemia and pituitary hyperplasia that can occur in patients with **primary hypothyroidism**, which is readily treated with thyroid hormone (see Chapter 603). Moderate elevations (<200 ng/mL) of prolactin are also associated with a variety of medications (antipsychotics, metoclopramide, phenothiazines, verapamil, opioids), with pituitary stalk dysfunction such as can occur with craniopharyngioma, with chronic renal failure, with chronic stress (rarely >40 ng/mL), and with nipple stimulation; hyperprolactinemia may also remain idiopathic in some cases (Table 598.1).

Drug-induced hyperprolactinemia is especially common, and in most cases the level is less than 100 ng/mL, though risperidone can cause elevations up to 300 ng/mL. No further investigation is needed if elevations in these ranges are seen in patients on antipsychotic medications who do not have any other suspicious features.

In extremely rare cases, prolactin may be produced by tumors outside the pituitary; in these cases there will be hyperprolactinemia with no sign of a pituitary tumor on imaging and no response to cabergoline treatment.

In some cases, extreme hyperprolactinemia is associated with a *hook effect* that leads to factitiously low values on blood tests. In cases where clinical features are compatible with hyperprolactinemia, serial dilution of the laboratory specimen should be done to rule out this kind of measurement error. On the other hand, patients may have factitiously elevated prolactin levels on immunoassay as a result of the presence of prolactin polymers and dimers **(macroprolactinemia)** that are not physiologically active. In cases where an elevated prolactin is detected in an asymptomatic patient, unnecessary diagnostic workup and treatment can be avoided by performing polyethylene glycol precipitation to exclude the presence of macroprolactinemia, which is clinically benign.

Table 598.1 Causes of Hyperprolactinemia

PHYSIOLOGIC
Pregnancy and lactation/nipple stimulation
Stress
Exercise
Sexual intercourse
PHARMACOLOGIC
Antipsychotics
Typical
Phenothiazines
Haloperidol
Atypical
Risperidone
Clozapine
Olanzapine
Antidepressants
Tricyclics
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Antihypertensives
Verapamil
Reserpine
α-Methyldopa
Antiemetics
Metoclopramide
Domperidone
H2 blockers
Cimetidine
Ranitidine
Opiates
Morphine
Methadone
Others
Estrogens
Cocaine
Heroin
Alcohol
Anesthetics
Marijuana
PATHOLOGIC
Prolactinoma
Nonfunctioning pituitary adenoma causing stalk effect
Craniopharyngioma
Meningioma
Germinoma
Empty sella syndrome
Lymphocytic hypophysitis
Hypothalamic-pituitary disease
Infiltrative diseases
Sarcoidosis
Histiocytosis X
Tuberculosis
Metastasis
OTHER DISEASE STATES
ROHHAD
Primary hypothyroidism
Chronic renal failure
Cirrhosis, severe hepatic insufficiency
Ectopic secretion of prolactin
Chest-wall lesions (trauma, surgery, herpes zoster virus)

ROHHAD, rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

From Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. *J Clin Neurosci.* 2015;22:1562–1567, Table 2.

It should be noted that there are occasional cases of galactorrhea where the prolactin level is completely normal (even after serial dilution to rule out the hook effect); the galactorrhea is usually mild in such cases and is not associated with any other clinical finding. No further treatment or investigation is indicated in these cases, and minimal galactorrhea can be left untreated. If the amount of milk discharge is bothersome, then low-dose cabergoline (0.25 mg once or twice weekly) may be effective even if elevated prolactin levels are not present.

In most patients where the hyperprolactinemia is secondary to an adenoma, it can be effectively treated with dopamine agonists. Treatment leads to lowering of prolactin levels and tumor shrinkage in the vast majority of patients and even large adenomas can usually be treated without surgical intervention. Because of its greater efficacy and lower incidence of side effects, cabergoline is considered the drug of choice for treatment of hyperprolactinemia. The usual protocol is to begin with 0.25 mg twice weekly and then increase as needed to 1 mg twice weekly. Even higher doses may be needed in some patients but should be carefully monitored; high doses of cabergoline used for long periods in older patients with parkinsonism are associated with cardiac valvular abnormalities, though this has not been reported with the doses used in pediatric hyperprolactinemia; monitoring of cardiac valves with echocardiography may be advisable if high doses are used for a prolonged period.

When dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or the size of the adenoma, and when symptoms or signs attributable to hyperprolactinemia or adenoma size persist during treatment, trans-sphenoidal surgery may be considered. Very rare cases of malignant prolactinomas may require chemotherapy with temozolomide, but a cure is difficult in such cases.

Corticotropinoma

Corticotropinoma is very rare in children, but unlike other types of pituitary adenomas, its incidence is higher in younger children and decreases with age. **Cushing disease** refers specifically to an ACTH-producing pituitary adenoma that stimulates excess cortisol production and secretion (see Chapter 619). It is more common than primary adrenal causes of Cushing syndrome, except in younger children (younger than 5 years of age), in whom adrenal carcinomas and adrenal activating variants of MAS are rare but dominant causes of the syndrome. Adenomas causing Cushing disease are almost always microadenomas with a diameter of <5 mm and are significantly smaller than all other types of adenomas at presentation. The most sensitive indicator of excess glucocorticoid secretion in children is growth failure, which generally precedes other manifestations. Patients develop weight gain that may be centripetal rather than generalized. Pubertal arrest, hypertension, large purplish striae, fatigue, and depression are also common. In prepubertal children, males are more frequently affected than females.

Midnight salivary cortisol measurements can be used as a screening test for cortisol excess, but confirmation requires at least one additional test (either 24-hour urinary free cortisol or an overnight dexamethasone suppression test). Location of the microadenoma is usually determined by MRI, and bilateral inferior petrosal sinus sampling may be needed in difficult cases. Trans-sphenoidal surgery is the treatment of choice for Cushing disease in children. Initial remission rates of 70–98% of patients and long-term success rates of 50–98% are reported. Residual transient hypoadrenalism is often observed after surgery, lasting as long as 30 months. Pituitary radiotherapy is used if cortisol levels remain elevated and/or ACTH levels continue to be detectable. Successful treatment may not correct the height deficit, and GH deficiency may be present after treatment and should be treated as required.

Thyrotropinomas are extremely rare, with only a few cases reported in the pediatric age-group. They present with symptoms of hyperthyroidism as well as local symptoms such as headaches and visual field defects. Laboratory testing reveals elevated thyroid hormone levels with inappropriately unsuppressed TSH levels. Treatment consists of trans-sphenoidal surgery in most cases, though radiation may be needed if surgery is unsuccessful.

598.1 Overgrowth Syndromes

Jennifer M. Kalish

OVERGROWTH IN THE FETUS AND NEONATE

Maternal diabetes is the most common cause of infants being large for gestational age. Even in the absence of clinical symptoms or a family history, the birth of a large-for-gestational-age infant should lead to evaluation for maternal (or gestational) diabetes.

Overgrowth syndromes: A group of disorders associated with excessive somatic growth and growth of specific organs has been described and is collectively referred to as *overgrowth syndromes.* These disorders are caused in many cases by excess production and availability of IGF2 encoded by the gene *IGF2.* The best described of these syndromes is **Beckwith-Wiedemann syndrome** (BWS), which is an overgrowth malformation syndrome that occurs with an incidence of 1:10,340 births, equal in males and females. It is caused by genetic or epigenetic abnormalities in the 11p15 chromosomal region, with most cases being the result of epigenetic abnormalities (loss or gain of DNA methylation) of two imprinting control regions, IC1 and IC2. Other causes include pathogenic variants, duplications, deletions, and loss of heterozygosity in this region. The imprinted genes involved in BWS and associated childhood tumors include, in addition to *IGF2,* the noncoding RNA *H19,* which is involved in *IGF2* suppression, cyclin-dependent kinase inhibitor 1C *(CDKN1C),* potassium channel voltage-gated KQT-like subfamily member 1 *(KCNQ1),* and *KCNQ1*-overlapping transcript 1 (*KCNQ1OT1*, or long QT intronic transcript 1, *LIT1*). Approximately 10% of cases are familial, whereas the rest appear to be sporadic. Cardinal clinical features of BWS include macroglossia, omphalocele, lateralized overgrowth (hemihypertrophy), bilateral Wilms tumor, hyperinsulinism, and pathologic findings (adrenal cytomegaly, pancreatic adenomatosis, and mesenchymal dysplasia). Suggestive features include macrosomia, mid-glabellar capillary malformation (nevus flammeus), earlobe creases and pits, umbilical hernia or diastasis recti, hepatomegaly, nephromegaly, transient hypoglycemia, and embryonal tumors (hepatoblastoma and unilateral Wilms tumor) (Fig. 598.2). The hyperinsulinemia is a result of pancreatic β-cell hyperplasia. These children are predisposed to embryonal tumors, including Wilms tumor, hepatoblastoma, neuroblastoma, and adrenocortical carcinoma. Management focuses on the omphalocele, airway issues (a result of macroglossia), neonatal hyperinsulinism/hypoglycemia, leg length differences, and tumor screening. Because of the cancer risk, screening is recommended until the seventh birthday. Screening includes complete abdominal ultrasound and measurement of α-fetoprotein every 3 months through the fourth birthday and renal ultrasounds every 3 months until the seventh birthday. Thereafter, renal ultrasound is recommended in cases of renal malformation such as medullary sponge kidney and nephrocalcinosis.

Pathogenic variants in *GPC3* and *GPC4,* glypican genes (which code for an IGF2–neutralizing membrane receptor), cause **Simpson-Golabi-Behmel** syndrome (Fig. 598.3). Other syndromic causes of fetal overgrowth include **Costello syndrome**, **Weaver syndrome**, **Sotos syndrome** (Fig. 598.4), and **Perlman syndrome** (Tables 598.2 and 598.3 and Fig. 598.5).

Overgrowth in Childhood or Adolescence

Normal-variant, familial, or constitutional tall stature is by far the most common cause of tall stature. Almost invariably, a family history of tall stature can be obtained, and no organic pathology is present. The child is often taller than the child's peers throughout childhood and has typical health. There are no abnormalities in the physical examination, and laboratory studies, if obtained, are negative.

Exogenous obesity is associated with rapid linear growth and relatively early onset of puberty (more so in girls). Bone age is accelerated, leading to relative tall stature in childhood but adult height is typically normal.

Klinefelter syndrome (XXY syndrome) is a relatively common (1 in 500-1,000 live male births) chromosomal abnormality associated with tall stature, learning disabilities (including requirement for speech therapy), gynecomastia, and decreased upper body:lower body segment ratio. Affected boys can have hypotonia, clinodactyly, and hypertelorism. The testes are invariably small, although androgen production by Leydig cells is often in the low-normal range. Spermatogenesis and Sertoli cell function are defective and lead to infertility. Other genital abnormalities include relatively small phallus and an increased incidence of hypospadias and cryptorchidism.



Fig. 598.2 Beckwith-Wiedemann syndrome in newborn infants. *(Courtesy Dr. Michael Cohen, Dalhousie University, Halifax, Nova Scotia. From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022, Fig. 1, p. 221.)*



Fig. 598.3 Simpson-Golabi-Behmel syndrome. Affected 16-yr-old male. Note the ocular hypertelorism, broad flat nose, 2-3 syndactyly, and nail hypoplasia. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier, 2022. Fig. 1, p. 225.)*



Fig. 598.4 Cerebral gigantism (Sotos syndrome) in an 8-yr-old male. The height age was 12 yr, and the bone age was 12 yr. IQ was 60. The electroencephalogram had abnormal findings. Note the prominence of the forehead and jaw and the large hands and feet. Sexual development was consistent with chronologic age. Hormone study results were normal. The adult height was 208 cm (6 ft 10 in); his sexual development was normal. He wears size 18 shoes.

Table 598.2 Differential Diagnosis of Tall Stature and Overgrowth Syndromes

FETAL OVERGROWTH
Maternal diabetes mellitus
Sotos syndrome *(NSD1)*
Weaver syndrome *(EZH2)*
Beckwith-Wiedemann syndrome (11p15 alterations)
Marshall-Smith syndrome *(NFIX)*
POSTNATAL OVERGROWTH LEADING TO CHILDHOOD OR ADULT TALL STATURE
Nonendocrine Causes
Familial (constitutional) tall stature
Exogenous obesity
Sotos syndrome *(NSD1)*
Weaver syndrome *(EZH2)*
Perlman syndrome *(DIS3L2)*
Simpson-Golabi-Behmel syndrome *(GPC3, GPC4)*
Marfan syndrome *(FBN1)*
Homocystinuria
Beckwith-Wiedemann syndrome (11p15 alterations)
Klinefelter syndrome (XXY)
Other syndromes with extra X or Y chromosomes
Overgrowth syndromes with intellectual disability *(DNMT3A, CHD8, HIST1H1E, EED)*
Endocrine Causes
Excess GH secretion caused by adenomas (pituitary gigantism)
X-linked acrogigantism (Xq26.3 duplication)
McCune-Albright syndrome or MEN associated with excess GH secretion
Aromatase deficiency and estrogen receptor defects
Precocious puberty (initial acceleration, ultimate short stature)
Hyperthyroidism (acceleration, but not adult tall stature)

GH, Growth hormone; MEN, multiple endocrine neoplasia.

XYY syndrome is associated with tall stature, severe acne in adolescence, increased incidence of learning disabilities, and behavioral problems, particularly impulsivity. Intelligence is usually in the normal range but may be 10-15 IQ points lower than their siblings. Other rare chromosomal abnormalities in which an excess number of X or Y chromosomes are present (e.g., XXX, XXXY, XYYY) are also associated with increased height.

Marfan syndrome is an autosomal dominant connective tissue disorder consisting of tall stature, arachnodactyly, thin extremities, increased arm span, and decreased upper body:lower body segment ratio (see Chapter 743). Additional abnormalities include ocular abnormalities (e.g., lens subluxation), hypotonia, kyphoscoliosis, cardiac valvular deformities, and aortic root dilation.

Homocystinuria is an autosomal recessive inborn error of amino acid metabolism caused by a deficiency of the enzyme cystathionine synthetase. It is characterized by intellectual disability when untreated, and many of its clinical features resemble Marfan syndrome, particularly ocular manifestations (see Chapter 105).

SOTOS SYNDROME

Children with Sotos syndrome (see Fig. 598.4) are typically above the 90th percentile for both length and weight at birth and may also have an increased head size. In other cases, macrocephaly becomes more apparent postnatally. Most cases of Sotos syndrome are caused by pathogenic variants in *NSD1*, but in the Japanese population most cases are attributable to microdeletions of the 5q35 region that includes this gene. Inheritance is autosomal dominant, but 95% of cases are a result of de novo (new) mutations. Incidence is estimated to be approximately 1 in 14,000 live births. The *NSD1* gene is thought to play a role in epigenetic regulation, but the exact mechanisms by which mutations lead to the features of Sotos syndrome are not yet understood.

Although it is characterized by rapid growth, there is no evidence that Sotos syndrome is caused by endocrine dysregulation. Growth is markedly rapid; by 1 year of age, affected infants are often taller than the 97th percentile in height. Accelerated growth continues for the first 4-5 years and then returns to a normal rate. Puberty usually occurs at the expected time but may occur slightly early. Adult height is usually in the upper-normal range.

Clinically the syndrome is characterized by a large (macrocephaly) dolichocephalic head, prominent forehead and jaw, hypertelorism, downslant of the palpebral fissures, high-arched palate, and large hands and feet with thickened subcutaneous tissue. Clumsiness and awkward gait are also noted, and affected children may have difficulty in sports, in learning to ride a bicycle, and in other tasks requiring coordination. Some degree of developmental disability affects most patients; in some affected children, perceptual deficiencies may predominate. Many different types of nonfebrile seizures have been reported, and up to 25% of patients with Sotos syndrome have seizures at some point in their life. Hyperinsulinism can also occur. Affected patients may be at somewhat increased risk for neoplasms, including neuroblastoma, hepatoblastoma, and leukemia, with a lifetime risk of between 2% and 4%. Osseous maturation is usually compatible with the patient's height, although

Table 598.3 Overgrowth Syndromes

SYNDROME	CLINICAL FEATURES	GENETIC ETIOLOGY	TUMOR SURVEILLANCE
Beckwith-Wiedemann syndrome (BWS)	Hypoglycemia, macroglossia, ear pits, omphalocele or umbilical hernia, lateralized overgrowth, organomegaly, high risk of embryonal tumors until age 7	Various genetic and epigenetic abnormalities in 11p15, most commonly in the IC2 region	Tumor surveillance until at least age 7 yr
Perlman syndrome	Macrosomia, unusual facies, nephroblastosis, severe hypotonia, very high risk of Wilms tumor	*DIS3L2* (DIS3 Like 3′-5′ exoribonuclease 2) (autosomal recessive)	Routine tumor surveillance recommended
Simpson-Golabi-Behmel syndrome	Coarse facial features, macroglossia, central groove lower lip, supernumerary nipples, cardiac and skeletal defects	*GPC3* (glypican 3) (X-linked recessive)	Tumor surveillance justified (per BWS protocol)
Sotos syndrome	Excessive growth in first 4 yr, dolichocephaly, macrocrania, typical facies, long limbs, seizures, hypotonia	*NSD1* deletion or variant (autosomal dominant) Rare familial cases *NFIX* (Nuclear Factor I X) may cause related Malan syndrome	Routine tumor screening not recommended
Tatton-Brown syndrome	Round face, heavy/horizontal eyebrows, narrow palpebral fissures, intellectual disability, and increased height	*DNMT3A* (DNA Methyltransferase 3 Alpha)	Routine tumor screening not recommended
Weaver syndrome	Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, redundant nuchal skin, heart and brain defects	*EZH2* (Enhancer of zeste homolog 2) gene in some cases	Routine tumor screening not recommended
PTEN-hamartoma syndromes (including Bannayan-Ruvalcaba-Riley)	Macrocephaly, hypotonia, pigmented skin, penile macules, lipomas, seizures	*PTEN* (phosphatase and TENsin homolog)(sporadic or autosomal dominant)	Tumor surveillance recommended
PIK3CA-related overgrowth spectrum	Brain overgrowth (megalencephaly), microgyria, cutaneous vascular malformations, syndactyly, seizures, developmental delay	Pathogenic variants in various PIK3 related genes, including *PIl3R2, AKT3, CCND2, PIK3CA,* etc.	Tumor surveillance is debated
Marfan syndrome	Facial gestalt, lens dislocation, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation	*FBN1* (Fibrillin 1) (autosomal dominant)	None
Loeys-Dietz syndrome	Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy (more aggressive than Marfan syndrome)	TGF-β pathway genes including *TGFBR1, TGFBR2, SMAD3,* and *TGFB2* (autosomal dominant)	None
Homocystinuria	Marfan-like habitus, developmental delay, lens dislocation	*CBS* gene (Cystathionine β-synthase) (autosomal recessive)	None
Lujan syndrome	Marfan-like habitus, intellectual disability, no eye or cardiovascular anomalies	*MED12* (Mediator Complex Subunit 12) gene (X-linked recessive)	None

advanced bone age has been reported. Scoliosis develops in up to 30% of cases, usually starting in school-age children. GH, IGF1, and other endocrine studies are usually normal; there is no distinctive laboratory or radiologic marker for the syndrome. Abnormal electroencephalograms are common; imaging studies often reveal an enlarged ventricular system, but intracranial pressure is normal. Genetic testing for *NSD1* pathogenic variants (or fluorescence in situ hybridization for 5q35 microdeletions in Japanese patients) is available and should be routinely used. Management is symptomatic and includes paying special attention to developmental and behavioral problems (which tend to improve with age), scoliosis, and seizure disorder. No specific treatment is needed for the overgrowth itself. There is no consensus on the need for cancer surveillance at this time.

Tatton-Brown Syndrome

Tatton-Brown syndrome is characterized by distinctive facial appearance (round face, heavy/horizontal eyebrows, and narrow palpebral fissures), intellectual disability, and increased height. It is caused by pathogenic variants in *DNMT3A*, a methyltransferase. Pathogenic variants in *DNMT3A* are also seen in hematologic malignances, which like *NSD1* and *EZH2*, show dual-gene functionality in overgrowth syndromes and myeloid neoplasms.

Hyperthyroidism in adolescents is associated with rapid growth but normal final adult height. It is almost always caused by Graves disease and is much more common in girls (see Chapter 606).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

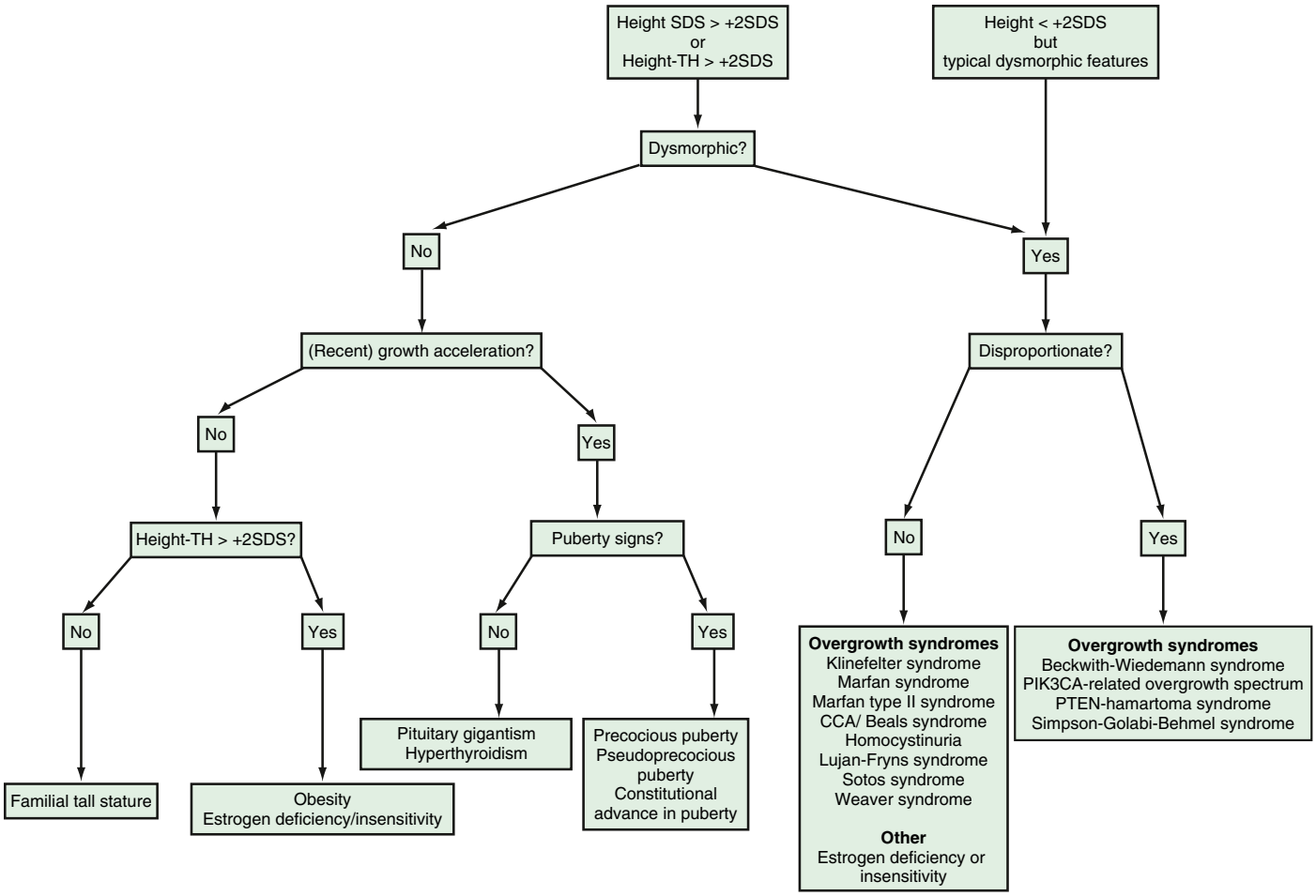

Fig. 598.5 Diagnostic algorithm for the differential diagnosis of tall stature and overgrowth syndromes. CCA, congenital contractural arachnodactyly; Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; *SDS*, standard deviation score. *(Adapted from Neylon OM, Werther GA, Sabin MA. Overgrowth syndromes. Curr Opin Pediatr. 2012;24:505–511, Fig. 1.)*

Chapter 599

Physiology of Puberty

Luigi R. Garibaldi and Wassim Chemaitilly

Between early childhood and approximately 8-9 years of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in females, testosterone in males). One to 3 years before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep-entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin-releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among the hypothalamus, pituitary, and gonads in the peripubertal period. By mid-puberty, LH pulses become evident even during the daytime and occur at about 90- to 120-minute intervals. A second critical event occurs in middle or late adolescence in females in whom cyclicity and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The *GnRH pulse generator* is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, neurokinin-B (stimulatory); γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). Pathogenic variants of *KISS1R* (previously known as *GPR54,* a G protein–coupled receptor gene whose ligand is kisspeptin) are a rare cause of autosomal recessive hypogonadotropic hypogonadism (loss-of-function pathogenic variants) or precocious puberty (gain-of-function pathogenic variants). The imprinted paternally expressed gene makorin RING finger protein 3 *(MKRN3)* has been described as a *brake* for the onset of puberty. Loss-of-function pathogenic variants of this gene are responsible for paternally transmitted familial precocious puberty in both sexes.

The interpretation of the hormonal changes of puberty is complex. Challenges with interpreting LH and follicle-stimulating hormone (FSH) measurements include the presence of multiple gonadotropin isoforms, immunoassay-related variability, and problems inherent to their pulsatile secretion, which mandate serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland because serum LH concentrations tend to increase earlier in the course of the pubertal process in males than in females. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 years of age, before any increase in LH or sex hormones

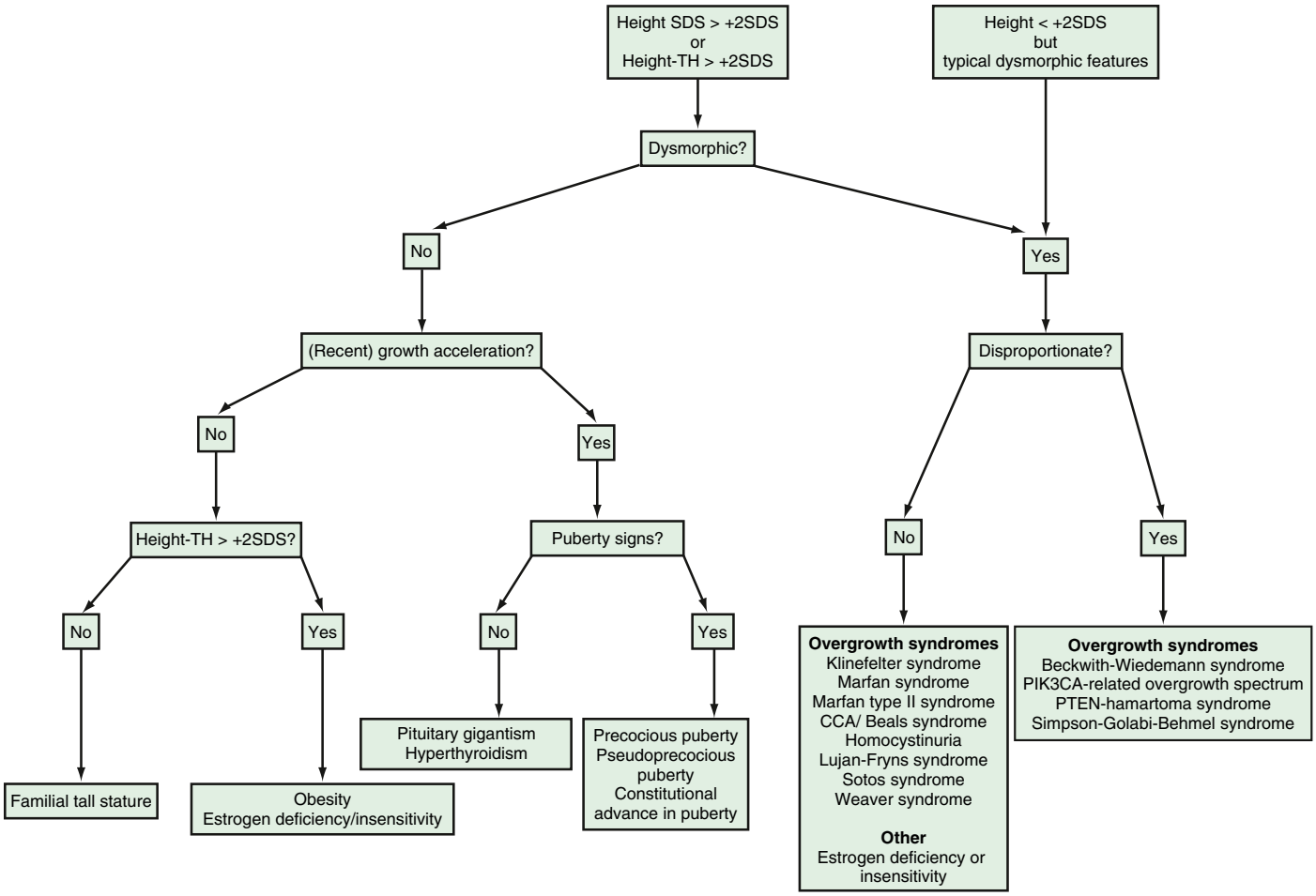

Fig. 598.5 Diagnostic algorithm for the differential diagnosis of tall stature and overgrowth syndromes. CCA, congenital contractural arachnodactyly; Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; *SDS*, standard deviation score. *(Adapted from Neylon OM, Werther GA, Sabin MA. Overgrowth syndromes. Curr Opin Pediatr. 2012;24:505–511, Fig. 1.)*

Chapter 599

Physiology of Puberty

Luigi R. Garibaldi and Wassim Chemaitilly

Between early childhood and approximately 8-9 years of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in females, testosterone in males). One to 3 years before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep-entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin-releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among the hypothalamus, pituitary, and gonads in the peripubertal period. By mid-puberty, LH pulses become evident even during the daytime and occur at about 90- to 120-minute intervals. A second critical event occurs in middle or late adolescence in females in whom cyclicity and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The *GnRH pulse generator* is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, neurokinin-B (stimulatory); γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). Pathogenic variants of *KISS1R* (previously known as *GPR54,* a G protein–coupled receptor gene whose ligand is kisspeptin) are a rare cause of autosomal recessive hypogonadotropic hypogonadism (loss-of-function pathogenic variants) or precocious puberty (gain-of-function pathogenic variants). The imprinted paternally expressed gene makorin RING finger protein 3 *(MKRN3)* has been described as a *brake* for the onset of puberty. Loss-of-function pathogenic variants of this gene are responsible for paternally transmitted familial precocious puberty in both sexes.

The interpretation of the hormonal changes of puberty is complex. Challenges with interpreting LH and follicle-stimulating hormone (FSH) measurements include the presence of multiple gonadotropin isoforms, immunoassay-related variability, and problems inherent to their pulsatile secretion, which mandate serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland because serum LH concentrations tend to increase earlier in the course of the pubertal process in males than in females. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 years of age, before any increase in LH or sex hormones

and before the earliest physical changes of puberty are apparent; this process has been called *adrenarche*. DHEAS is the most abundant adrenal C-19 steroid in the blood, and its serum concentration remains fairly stable over 24 hours. A single measurement of this hormone is commonly used as a marker of adrenal androgen secretion. Although adrenarche typically precedes the onset of gonadal activity (gonadarche) by a few years, the two processes do not seem to be causally related, as evidenced by adrenarche and gonadarche being dissociated in conditions such as central precocious puberty and adrenocortical failure.

The effects of gonadal steroids (testosterone in males, estradiol in females) on bone growth and osseous maturation are critical. Both aromatase deficiency and estrogen receptor defects result in delayed epiphyseal fusion and tall stature in affected males. These observations suggest that estrogens, rather than androgens, are responsible for the process of bone maturation that ultimately leads to epiphyseal fusion and cessation of growth. Estrogens also mediate the increased production of growth hormone, which along with a direct effect of sex steroids on bone growth, is responsible for the pubertal growth spurt.

The age of onset of puberty varies and is more closely correlated with osseous maturation than with chronologic age (see Chapter 150). In females, the **breast bud** (thelarche) is usually the first sign of puberty (10-11 years), followed by the appearance of **pubic hair** (pubarche) 6-12 months later. The interval to the onset of **menstrual activity** (menarche) is usually 2-2.5 years but may be as long as 6 years. In the United States, at least one sign of puberty is present in approximately 95% of females by 12 years of age and in 99% of females by 13 years of age. Peak height velocity occurs early (at breast stage II-III, typically between 11 and 12 years of age) in females and always precedes menarche. The mean age of menarche is about 12.75 years. However, there are wide variations in the sequence of changes involving growth spurt, breast bud, pubic hair, and maturation of the internal and external genitalia.

In males, **growth of the testes** (≥4 mL in volume or 2.5 cm in longest diameter) and thinning of the scrotum are the first signs of puberty (11-12 years). These are followed by pigmentation of the scrotum and growth of the penis and by **pubarche**. Appearance of **axillary hair** usually occurs in mid-puberty. In males, unlike in females, acceleration of growth begins after puberty is well underway and is maximal at genital stage IV-V (typically between 13 and 14 years of age). In males, the growth spurt occurs approximately 2 years later than in females, and growth may continue beyond 18 years of age.

Genetic and environmental factors affect the timing for the onset of puberty. Population-based studies in the United States and Europe have suggested secular trends for earlier onset of puberty over the past few decades in females and, to a lesser degree, in males. African American, and to a lesser extent Hispanic, females *appear* to be more advanced in the development of secondary sex characteristics for age than White females. However, the timing of menarche has advanced only marginally (2.5-4 months) in White females and slightly more so (up to 6 months) in African American females. The Copenhagen Puberty Study showed that the earlier onset of breast development observed in females examined in 2006–2008 than those seen in 1991–1993 (means 10.9 years vs 9.9 years) *was not* associated with different levels of gonadotropins or estradiol when females of similar chronologic ages were compared between the two groups. Hence earlier breast development may not simply reflect earlier activation or maturation of the hypothalamic-pituitary-gonadal axis but could also stem from other factors such as increased adiposity or increased exposure to certain environmental agents. Positive correlations between the degree of adiposity and earlier pubertal development in females have been reported. Conversely, female athletes in whom leanness and strenuous physical activity have coexisted from early childhood frequently exhibit a marked delay in puberty or menarche, and they frequently have oligomenorrhea or amenorrhea as adults (see Chapter 732). Pubertal delay is also prevalent in males who are physically very active. Thus energy balance is closely related to the activity of the GnRH pulse generator and the mechanisms initiating and sustaining puberty, possibly via hormonal signals such as leptin; other adipokines; or by way of the central melanocortin-4 receptor (MC4R), which controls appetite, food intake, and energy expenditure.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 600

Disorders of Pubertal Development

Luigi R. Garibaldi and Wassim Chemaitilly

INTRODUCTION

Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 years in females and 9 years in males. The variation in the age of the onset of puberty in normal children, particularly of different ethnicities, makes this definition somewhat arbitrary. It remains in use by most clinicians.

Depending on the primary source of the hormonal production, precocious puberty may be classified as **central** (also known as **gonadotropin dependent**, or **true**) or **peripheral** (also known as **gonadotropin independent**) (Table 600.1). **Central** precocious puberty (CPP) is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation. In **peripheral** precocious puberty, some of the secondary sex characteristics appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (see Chapters 622-628).

Peripheral precocious puberty can also induce maturation of the hypothalamic-pituitary-gonadal axis and trigger the onset of central puberty at a later time. This mixed type of precocious puberty occurs in congenital adrenal hyperplasia, particularly after adrenal androgens are suppressed by treatment; McCune-Albright syndrome; and familial male-limited precocious puberty, when the bone age reaches the pubertal range (10.5-12.5 years).

600.1 Central Precocious Puberty

Luigi R. Garibaldi and Wassim Chemaitilly

CPP is defined by the onset of pubertal development due to the early activation of the hypothalamic-pituitary-gonadal axis before the ages of 8 and 9 years in females and males, respectively. It occurs 5- to 10-fold more frequently in females than in males and is usually sporadic. Although at least 90% of females have an idiopathic form, a structural central nervous system (CNS) abnormality may occur in 25–75% of males with CPP. **Genetic forms of CPP**, such as the paternally transmitted types due to pathogenic variants of *MKRN3* gene or, more rarely *DLK1,* may account for 5–10% of all cases of CPP. A high prevalence of CPP has been reported in females adopted from developing countries, particularly if adopted several months or years after birth, possibly related to undefined nutritional or environmental factors.

CLINICAL MANIFESTATIONS

In females, CPP should be suspected when breast development is noted before the age of 8 years. In males who have not been exposed to gonadotoxic agents, CPP usually manifests first via increased testicular size (volume ≥4 mL) and scrotal thinning before the age of 9 years. Sexual development in affected individuals generally follows the sequence observed in normal puberty. In females, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported as early as 5.5 years of age (Fig. 600.1). In males, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed as early as 5-6 years of age. In affected females and males, height, weight, and height velocity are accelerated. The increased rate of bone maturation results in early closure of the epiphyses and compromised adult height, particularly

Table 600.1 Classification of Sexual Precocity

TRUE PRECOCIOUS PUBERTY OR COMPLETE ISOSEXUAL PRECOCITY
(GNRH-Dependent Sexual Precocity or Premature Activation of the Hypothalamic GNRH Pulse Generator)

Idiopathic true precocious puberty
CNS tumors
Optic glioma associated with neurofibromatosis type 1
Hypothalamic astrocytoma
Other CNS disorders
Developmental abnormalities including hypothalamic hamartoma of the tuber cinereum
Encephalitis
Static encephalopathy
Brain abscess
Sarcoid or tubercular granuloma
Head trauma
Hydrocephalus
Arachnoid cyst
Myelomeningocele
Vascular lesion
Cranial irradiation
True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroids
True precocious puberty caused by pathogenic variants in the following genes:
KISS1R/GPR54
KISS1
MKRN3
DLK1

INCOMPLETE ISOSEXUAL PRECOCITY (HYPOTHALAMIC GNRH-INDEPENDENT)

Males
Gonadotropin-secreting tumors
hCG-secreting CNS tumors (e.g., chorioepitheliomas, germinoma, teratoma)
hCG-secreting tumors located outside the CNS (hepatoma, teratoma, choriocarcinoma)
Increased androgen secretion by adrenal or testis
Congenital adrenal hyperplasia (CYP21 and CYP11B1 deficiencies)
Virilizing adrenal neoplasm
Leydig cell adenoma
Familial male-limited precocious puberty (FMPP, "testotoxicosis") (autosomal dominant gonadotropin-independent precocious Leydig cell and germ cell maturation)
Cortisol resistance syndrome

Females
Ovarian cyst
Estrogen-secreting ovarian or adrenal neoplasm
Peutz-Jeghers syndrome with sex cord tumor with annular tubules (SCTAT)

Both Sexes
McCune-Albright syndrome
Hypothyroidism
Iatrogenic or exogenous sexual precocity (including inadvertent exposure to estrogens in food, drugs, or cosmetics)

VARIATIONS OF PUBERTAL DEVELOPMENT
Premature thelarche
Premature isolated menarche
Premature adrenarche
Adolescent gynecomastia in males
Macroorchidism

HETEROSEXUAL PRECOCITY

Feminization in Males
Adrenal neoplasm
Chorioepithelioma
Testicular neoplasm (Peutz-Jeghers syndrome)
Increased extraglandular conversion of circulating adrenal androgens to estrogen
Iatrogenic (exposure to estrogens)

Virilization in Females
Congenital adrenal hyperplasia
CYP21 deficiency
CYP11B1 deficiency
3β-HSD deficiency
Virilizing adrenal neoplasm (with or without Cushing syndrome)
Virilizing ovarian neoplasm (e.g., arrhenoblastoma)
Iatrogenic (exposure to androgens)
Cortisol resistance syndrome
Aromatase deficiency

CNS, Central nervous system; CYP11B1, 11-hydroxylase; CYP21, 21-hydroxylase; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; 3β-HSD, 3β-hydroxysteroid dehydrogenase 4,5-isomerase; KISS1R/GPR54, kisspeptin receptor/G protein–coupled receptor 54.
Modified from Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology,* 13th ed. Philadelphia: Elsevier; 2016: Table 25.25, p. 1163.

if puberty begins at a very early age. Historically, approximately 30% of females and an even larger percentage of males achieved a height below the fifth percentile as adults *without* treatment. Mental development is usually compatible with chronological age. Emotional behavior and mood swings are common, but serious psychologic problems are rare.

Although the clinical course is variable, three main patterns of pubertal progression can be identified. Most females (particularly those younger than 6 years of age at the onset) and a large majority of males have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential. An increasing percentage of females (older than 6 years of age at the onset with an idiopathic form) and, rarely, males have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. Very rarely, central puberty may regress spontaneously (*unsustained* CPP). This variability in the natural course of sexual precocity underscores the need for longitudinal observation at the onset of sexual development before treatment is considered.

LABORATORY FINDINGS

Sex hormone concentrations are usually appropriate for the stage of puberty in both sexes (Table 600.2). Despite the availability of sensitive and specific assays for sex hormones, random serum estradiol concentrations are low or undetectable in the early phase of sexual precocity in females, as they are in normal puberty. In males, serum testosterone levels are usually detectable or elevated by the time the parents seek medical attention, provided that an early morning blood sample is obtained. With the use of highly sensitive assays, serum LH concentrations are undetectable in prepubertal children in random blood samples but become detectable in 50–75% of females and a higher percentage of males with CPP. Unfortunately, a number of hospitals use only moderately sensitive immunoenzymatic assays for LH and often insensitive assays for estradiol and testosterone, which decreases the diagnostic yield of these measurements. Measurement of LH in serial blood samples obtained during sleep has very

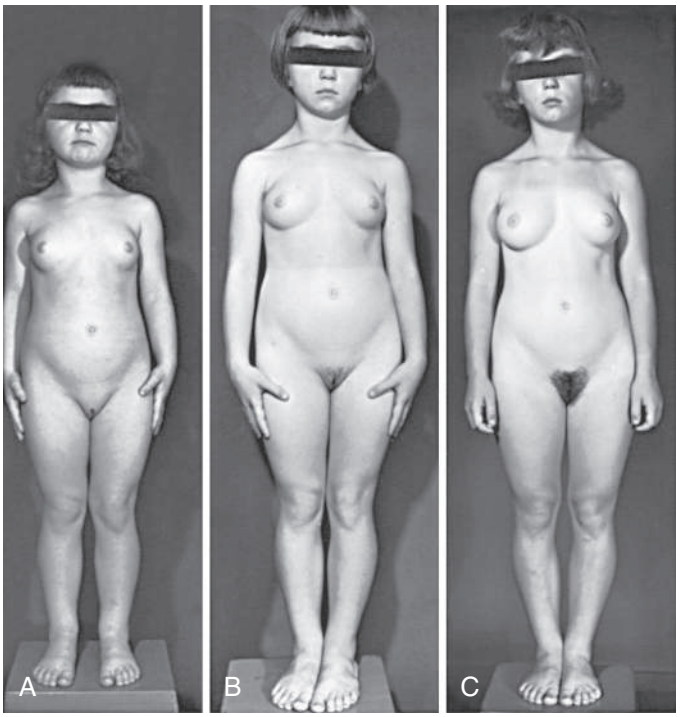

Fig. 600.1 Natural course of untreated idiopathic central precocious puberty. Patient (A) at 3 11/12, (B) at 5 8/12, and (C) at 8½ yr of age. Breast development and vaginal bleeding began at 2½ yr of age. Bone age was 7½ yr at 3 11/12 and 14 yr at 8 yr of age. Intelligence and dental age were normal for chronological age. Growth was completed at 10 yr; ultimate height was 142 cm (56 in). No effective therapy was available at the time this patient sought medical attention.

good diagnostic power and typically reveals a well-defined pulsatile secretion of LH in early puberty; it is, however, difficult to implement in a clinical setting. Dynamic tests using gonadotropin-releasing hormone (GnRH, intravenously; unavailable in the United States) or a GnRH agonist (leuprolide, subcutaneously) are helpful diagnostic tools, particularly for males, in whom a pubertal LH response (LH peak >5 IU/L) with predominance of LH over follicle-stimulating hormone (FSH) tends to occur early in the course of precocious puberty. In females with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast stages II to early III (LH peak, <5 IU/L), and the LH to FSH ratio may remain low until mid-advanced puberty. In such females with low LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL) 20-24 hours after stimulation with leuprolide.

Osseous maturation is variably advanced, often more than 2-3 standard deviations (SD). Pelvic ultrasonography in females reveals progressive enlargement of the ovaries, enlargement of the fundus, and then of the whole uterus to pubertal size. An MRI scan usually demonstrates physiologic enlargement of the pituitary gland, as seen in normal puberty; it may also reveal CNS pathology.

DIFFERENTIAL DIAGNOSIS

Organic CNS causes of central sexual precocity are more likely in males and in females who have rapid breast development, estradiol greater than 30 pg/mL, or are younger than 6 years of age. All children in these categories, and children with neurologic symptoms or signs, should undergo MRI scans of the brain and pituitary gland. Criteria for brain imaging in females older than 6 years are controversial, although some authorities recommend MRI scans for *all children* with CPP.

Gonadotropin-independent causes of isosexual precocious puberty must be considered in the differential diagnosis (see Tables 600.1 and 600.2). For females, these include tumors of the ovaries, autonomously functioning ovarian cysts, feminizing adrenal

Table 600.2 Differential Diagnosis of Sexual Precocity

DISORDER	PLASMA GONADOTROPINS	LH RESPONSE TO GNRH	SERUM SEX STEROID CONCENTRATION	GONADAL SIZE	MISCELLANEOUS
GONADOTROPIN DEPENDENT					
True (central) precocious puberty	Prominent LH pulses (premature reactivation of GnRH pulse generator), initially during sleep	Pubertal LH response	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement	MRI of brain to rule out CNS tumor or other abnormality
GONADOTROPIN INDEPENDENT					
Males					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; MRI of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	High testosterone	Irregular, asymmetric enlargement of a testis	Testicular US
Familial, male-limited precocious puberty (FMPP, testotoxicosis)	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetric and length >2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Activating pathogenic variant of the LHCG receptor; autosomal dominant transmission
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive, variable severity/age of onset; may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency

Continued

Table 600.2 Differential Diagnosis of Sexual Precocity—cont'd

DISORDER	PLASMA GONADOTROPINS	LH RESPONSE TO GNRH	SERUM SEX STEROID CONCENTRATION	GONADAL SIZE	MISCELLANEOUS
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS, DHEA, and/or androstenedione values	Testes prepubertal	CT or MRI of abdomen
Females					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Tumor often palpable on physical examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Single or recurrent episodes of menses and/or breast development; exclude McCune-Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol, variable DHEAS increase	Ovaries prepubertal	Unilateral adrenal mass on CT or MRI
Nonclassical congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or in corticotropin-stimulated state	Ovaries prepubertal	Autosomal recessive
In Both Sexes					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroid pubertal; estradiol may be quite high in girls	Ovarian enlargement (asymmetrical) on US; slight (usually symmetrical) testicular enlargement	Skeletal survey/bone scan for polyostotic fibrous dysplasia and skin examination for café-au-lait macules
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal; flat FSH, LH response	Estradiol often pubertal	Testicular enlargement; ovaries macrocystic	TSH very high, prolactin mildly elevated; T_4 low
INCOMPLETE PRECOCITY/VARIATIONS OF PUBERTY					
Premature thelarche	Prepubertal	Prepubertal LH	Prepubertal or early pubertal estradiol response	Ovaries prepubertal	Onset usually before 3 yr of age
Premature adrenarche (males)	Prepubertal	Prepubertal LH response	Prepubertal testosterone; DHEAS value appropriate for pubic hair stage	Testes prepubertal	Onset usually after 6 yr of age; more frequent in CNS-injured children
Premature adrenarche (females)	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS value appropriate for pubic hair stage	Ovaries prepubertal	Onset usually after 6 yr of age; more frequent in brain-injured children

CNS, Central nervous system; CT, computed tomography; CYP, P450 cytochrome isoenzyme; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; 17-OHP, 17-hydroxyprogesterone; T_4, thyroxine; TSH, thyrotropin; US, ultrasonography.

Modified from Styne DM, Grumbach MM. Physiology and disorders of puberty. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 13th ed. Philadelphia: Elsevier; 2016: Table 25.41, pp. 1196–1197.

tumors, McCune-Albright syndrome, and exogenous sources of estrogens. In males, congenital adrenal hyperplasia, adrenal tumors, Leydig cell tumors, human chorionic gonadotropin (hCG)–producing tumors, exposure to exogenous androgens, and familial male precocious puberty should be considered.

TREATMENT

Virtually all males and the large subgroup of females with *rapidly progressive precocious puberty,* including CPP beginning *before age 6 years,* are candidates for treatment. Females with slowly progressive idiopathic CPP do not seem to benefit in terms of height prognosis from GnRH agonist therapy. Former small-for-gestational-age infants may be at greater risk of short stature as adults and may require more aggressive treatment of precocious puberty, possibly in conjunction with human growth hormone (hGH) therapy. Certain patients require treatment predominantly for psychologic or social reasons, including children with special needs.

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for treatment of CPP. By virtue of being more potent and having a longer duration of action than native GnRH, these GnRH agonists (after a brief period of stimulation) desensitize the gonadotropic cells of the pituitary to the stimulatory effect of endogenous GnRH and effectively halt the progression of central sexual precocity.

Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentration of the drug for weeks or months, constitute the preparations of choice for treatment of CPP. In the United States, the available preparations include (1) **leuprolide acetate** (Lupron Depot Ped), in a dose of 0.2-0.3 mg/kg (7.5-15 mg) intramuscularly (IM) every 28 days; (2) longer-acting preparations of depot-leuprolide, including Lupron-Depot Ped 90-day, 11.25 or 30 mg IM every 3 months, or Fensolvi 45 mg subcutaneously every 24 weeks; (3) **histrelin** (Supprelin LA), a subcutaneous 50-mg implant with effects lasting at least 12 months; and (4) **triptorelin** (Triptodur), 22.5 mg IM every 24 weeks. Other preparations

are approved for treatment of precocious puberty in other countries. Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1–3% of patients treated with IM depot-leuprolide. Breakage or malfunction of the histrelin implant is rare. Other available treatment options for children who cannot tolerate the products listed previously include subcutaneous injections of aqueous leuprolide, given once or twice daily (total dose 60 mcg/kg/24 hr), or intranasal administration of the GnRH agonist **nafarelin** (Synarel), 800 mcg bid. The potential for irregular compliance with daily administration, as well as the variable absorption of the intranasal route for nafarelin, may limit the efficacy and long-term benefit of the latter preparations. GnRH antagonists, including novel oral compounds, have not been investigated sufficiently in children and are not FDA approved.

Treatment results in decrease of the growth rate, generally to age-appropriate values, and an even greater decrease of the rate of osseous maturation. Some children, particularly those with greatly advanced (pubertal) bone age, may show marked deceleration of their growth rate and an arrest in the rate of osseous maturation. Treatment results in enhancement of the predicted height, more so in younger patients at diagnosis, male patients, and those children with more rapidly progressive CPP. In females, breast size may regress in those with Tanner stage II-III development but tends to remain unchanged in females with late stage III-V development or may even increase slightly because of progressive adipose tissue deposition. The amount of glandular tissue decreases. Pubic hair usually remains stable in females or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens. Menses, if present, cease. Pelvic sonography demonstrates a decrease of the ovarian and uterine size. In males, there is a decrease of testicular size, variable regression of pubic hair, and decrease in the frequency of erections. Except for a reversible decrease in bone density (of uncertain clinical significance) and a reversible increase in body mass index (BMI) percentiles in some females, no serious adverse effects of GnRH analogs have been reported in children during or after treatment for sexual precocity. If treatment is effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone <10-20 ng/dL in males; estradiol <5-10 pg/mL in females). The serum LH and FSH concentrations, as measured by sensitive immunometric assays, decrease to less than 1 IU/L in most patients, although rarely does the LH return to truly prepubertal levels (<0.1 IU/L). Moreover, the incremental FSH and LH responses to GnRH stimulation decrease to less than 2-3 IU/L. Serum LH, FSH, and sex hormone levels are suppressed more completely and evenly by the histrelin implant than by GnRH agonist injections. Therapy is typically discontinued at a pubertal chronological age, after which puberty resumes promptly. In females, menarche generally appears at an average of 18 months (range 6-24 months) after cessation of IM therapy and somewhat earlier after removal of the histrelin implant. The addition of hGH to GnRH agonists has been used on an investigational basis in children with precocious puberty, markedly advanced bone age, and prediction of short stature. The available, albeit limited, data indicate that combined therapy may increase the adult height.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.2 Precocious Puberty Resulting from Organic Brain Lesions

Wassim Chemaitilly and Luigi R. Garibaldi

Hypothalamic hamartoma is the most common brain lesion causing CPP (Fig. 600.2). This congenital malformation consists of ectopically located neural tissue, within which glial cells can produce transforming growth factor-α (TGF-α), which has the potential to activate the GnRH pulse generator. On MRI, it appears as a small pedunculated mass attached to the tuber cinereum or the floor of the third ventricle or, less often, as a sessile mass (Fig. 600.3) that remains static in size over years.

A wide variety of other CNS lesions or insults, usually involving the hypothalamus by scarring, invasion, or pressure, have been associated with CPP (see Table 600.1). These include postencephalitic scars, tuberculous meningitis, tuberous sclerosis, severe head trauma, and hydrocephalus, either isolated or associated with myelomeningocele. Gonadotropin-dependent precocious puberty occurs in 26–29% of children with tumors developing within or near the hypothalamus or optic pathways. Low-grade gliomas, the most common types of such neoplasms, are highly prevalent (15–20%) in children with neurofibromatosis type 1 (NF-1) and constitute the main etiologic factor for the central sexual precocity encountered in a small subset (approximately 3%) of children with NF-1.

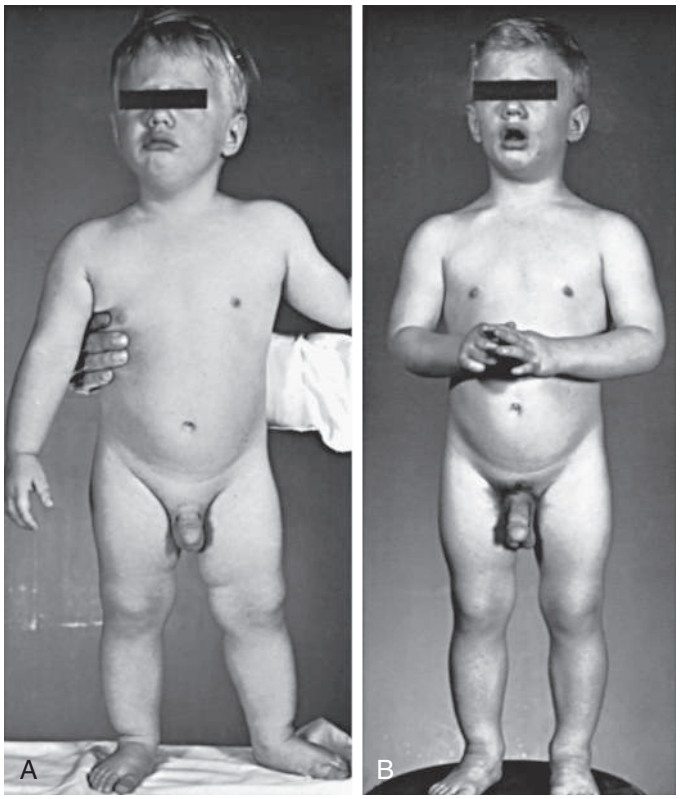

Fig. 600.2 Natural course of untreated precocious puberty with central nervous system lesion. Photographs at 1½ (A) and 2½ (B) yr of age. Accelerated growth, muscular development, osseous maturation, and testicular development were consistent with the degree of secondary sexual maturation. In early infancy, the patient began having frequent spells of rapid, purposeless motion; later in life, he had episodes of uncontrollable laughing with ocular movements. At 7 yr, he exhibited emotional lability, aggressive behavior, and destructive tendencies. Although a hypothalamic hamartoma had been suspected, it was not established until CT scanning became available when the patient was 23 yr of age. Epiphyses fused at 9 yr of age; final height was 142 cm (56 in). At 24 yr of age, he developed an embryonal cell carcinoma of the retroperitoneum.

About 50% of the tumors in the pineal region are germ cell tumors or astrocytomas; the remainder consists of a wide variety of histologically distinct tumor types. Pineal or hypothalamic germ cell tumors can cause CPP in males by secreting hCG, which stimulates the luteinizing hormone (LH) receptors in the Leydig cells of the testes (see Chapter 600.5).

CLINICAL MANIFESTATIONS

Hypothalamic hamartomas remain static in size or grow slowly and can be associated with gelastic or psychomotor seizures, but most often produce no signs other than precocious puberty. This is often rapidly progressive sexual precocity in very young children. For other lesions causing neurologic symptoms, the neuroendocrine manifestations may be present for 1-2 years before the tumor can be detected radiologically. Hypothalamic signs or symptoms such as diabetes insipidus, adipsia, hyperthermia, unnatural crying or laughing, obesity, and cachexia should suggest the possibility of an intracranial lesion. Visual signs (proptosis, decreased visual acuity, visual field defects) may be the first manifestation of an optic glioma.

The sexual precocity is always *isosexual,* and the endocrine patterns are generally those found in children without demonstrable organic



Fig. 600.3 MRI of a central nervous system lesion in a child with central precocious puberty. A 6-yr-old female was referred for stage IV breast development and growth acceleration. Serum luteinizing hormone and estradiol concentrations were in the adult range. The midsagittal T1-weighted image shows an isointense hypothalamic mass *(arrowheads)*, typical of a hamartoma. *(From Sharafuddin M, Luisiri A, Garibaldi LR, et al. MR imaging diagnosis of central precocious puberty: importance of changes in the shape and size of the pituitary gland. Am J Roentgenol. 1994;162:1167–1173.)*

lesions. In conditions other than hypothalamic hamartoma, growth hormone (GH) deficiency can occur and may be masked by the growth-promoting effect of the increased sex hormone levels. The pubertal staging of males treated with gonadotoxic modalities such as high-dose alkylating agents or testicular radiotherapy should not rely on testicular volume measurements because these are affected by treatment-induced germ cell and Sertoli depletion. Pubic hair development, scrotal thinning, and penile size may be better indicators, and providers should not hesitate to measure serum LH and testosterone levels when in doubt.

TREATMENT

GnRH agonists (depot forms or implant) are the treatment of choice of tumor-induced CPP. Neurosurgical treatment has been shown to have limited efficacy and to be associated with high complication rates in a subset of patients with hypothalamic hamartoma and associated intractable gelastic or psychomotor seizures. Stereotactic radiation therapy (gamma knife surgery) and, more recently, MRI-guided laser therapy, have been proposed as possible alternatives in these instances. For other neurologic lesions, therapy depends on the nature and location of the pathologic process. Combined GH therapy should be considered for patients with associated GH deficiency. The final height outcome will also depend on other factors such as the burden of disease from the primary tumor, side effects of cancer treatments, and associated chronic health conditions

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.3 Precocious Puberty After Irradiation of the Brain

Wassim Chemaitilly and Luigi R. Garibaldi

Children treated with cranial radiotherapy at a wide range of doses (18-50 Gy) are at an increased risk for gonadotropin-dependent precocious puberty. The prevalence of this condition in children treated with radiotherapy for tumors located outside of the hypothalamic pituitary or optic pathways region has been reported at 6.6%. Hydrocephalus, young age at exposure to radiation (<5 years), being female, and increased BMI are additional risk factors. This condition is often *associated with GH deficiency* and at times with other conditions (spinal irradiation, hypothyroidism) adversely affecting the adult height prognosis. Unless careful attention is paid to early signs of pubertal development in these children, the combination of GH deficiency and the growth-promoting effect of sex steroids often results in a normal growth rate at the expense of a rapidly advancing bone age and impaired adult height potential. The pubertal staging of males treated with gonadotoxic modalities such as high-dose alkylating agents or testicular radiotherapy should not rely on testicular volume measurements (see Chapter 600.2).

TREATMENT

GnRH analogs are effective in arresting pubertal progression, but concomitant GH (and/or thyroid hormone) deficiency should be diagnosed and treated promptly to improve the adult height prognosis.

Paradoxically, hypopituitarism with gonadotropin deficiency may subsequently develop as a late effect of high-dose CNS irradiation in patients with or without a history of precocious puberty, and it may require substitution therapy with sex steroids.

600.4 Syndrome of Precocious Puberty and Hypothyroidism

Wassim Chemaitilly and Luigi R. Garibaldi

The onset of puberty is usually delayed in children with mild forms of hypothyroidism. However, up to 50% of children with profound, untreated hypothyroidism of long duration may paradoxically develop precocious puberty (a condition known as **VanWyk-Grumbach syndrome**). **Hashimoto thyroiditis** is frequently the cause of such forms of hypothyroidism. Patients have the usual manifestations of hypothyroidism (see Chapter 603); the symptoms may be difficult to recognize in children with special needs. Children with precocious puberty caused by hypothyroidism have, contrary to other children with sexual precocity, decreased growth velocity and delayed bone age. Females may present with breast development and menstrual bleeding; the latter may occur even in females with minimal breast enlargement. Pelvic sonography may reveal large, multicystic ovaries. Males have testicular enlargement associated with modest or no penile enlargement. No pubic hair development occurs in either females or males. Enlargement of the sella, which is typical of long-standing primary hypothyroidism, may be demonstrated by skull film or MRI. Plasma levels of thyroid-stimulating hormone (TSH) are markedly elevated, often greater than 500 μU/mL, and those of prolactin and estradiol are mildly elevated. Although serum FSH is low and LH is undetectable, when measured by specific assays, the massively elevated concentrations of TSH appear to interact with the FSH receptor (specificity spillover), thus inducing FSH-like effects in the absence of LH effects on the gonads. The FSH-like effect suffices to induce estradiol secretion by the ovaries, whereas in males, testicular enlargement occurs without substantial testosterone secretion. Treatment of the hypothyroidism results in rapid return to normal of the biochemical and clinical manifestations. Possible progression to central puberty with rapid bone age advancement may occur in the months after the initiation of thyroid hormone replacement, a complication that would justify delaying puberty with GnRH analogs. Macroorchidism (testicular volume >30 mL) may persist in adult males despite adequate levothyroxine therapy. Children with a high risk of primary hypothyroidism, especially those with special needs such as patients with trisomy 21, should be screened at least annually via measurement of serum free T_4 and TSH levels.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.5 Chorionic Gonadotropin-Secreting Tumors: Paraneoplastic Precocious Puberty

Wassim Chemaitilly and Luigi R. Garibaldi

hCG-secreting tumors are a rare cause of precocious puberty in males. Secretion of hCG activates luteinizing hormone/choriogonadotropin (LHCG) receptors in the Leydig cells causing testosterone production and virilization with minimal testicular enlargement. Testicular histology reveals interstitial cell hyperplasia with no spermatogenesis. Plasma levels of testosterone are elevated, whereas those of FSH and LH, as measured by specific assays, are low. Females with **hCG-secreting tumors** do not present with precocious puberty because the ovarian production of estradiol cannot occur in the absence of FSH stimulation.

HEPATIC TUMORS

All reported cases of hepatoblastoma causing isosexual precocious puberty have been in males, with the average age of onset of 2 years (range 4 months to 8 years). An enlarged liver or mass in the right upper quadrant should suggest the diagnosis. Plasma levels of hCG and α-fetoprotein (AFP) are usually markedly elevated and serve as useful markers for following the effects of therapy. As with other carcinomas of the liver, the prognosis for survival beyond 1-2 years from the time of diagnosis is poor.

INTRACRANIAL TUMORS

Nongerminomatous or mixed germ cell tumors, choriocarcinomas, teratomas, teratocarcinomas, and others account for <5% of intracranial tumors; are usually located in the neurohypophyseal area or the pineal area; and may cause precocious puberty in males if they secrete hCG—the mass effect can infrequently cause precocious puberty in females. Marked elevations of hCG and AFP often occur in the cerebrospinal fluid, although elevations in the blood may be modest. Treatment includes radiation, chemotherapy, and debulking surgery.

TUMORS IN OTHER LOCATIONS

Very rare locations include mediastinum, gonads, or even adrenal glands. Mediastinal germ cell tumors have been reported to cause precocious puberty in males with Klinefelter syndrome.

PERIPHERAL PRECOCIOUS PUBERTY

The adrenal causes of peripheral precocious puberty are discussed in Chapter 616, and the gonadal causes are discussed in Chapters 624 and 627.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.6 McCune-Albright Syndrome

Luigi R. Garibaldi and Wassim Chemaitilly

McCune-Albright syndrome, or precocious puberty with *polyostotic fibrous dysplasia* and abnormal pigmentation, is a syndrome of endocrine dysfunction associated with patchy cutaneous pigmentation and fibrous dysplasia of the skeletal system. It is a rare condition with a prevalence between 1/100,000 and 1/1,000,000, characterized by autonomous hyperfunction of one or more glands (which may include pituitary, thyroid, and adrenal glands). An activating missense pathogenic variant in the *GNAS1* gene encoding the α-subunit of G_S, the G protein that stimulates cyclic adenosine monophosphate (cAMP) formation, results in activation of receptors (adrenocorticotropic hormone [ACTH], TSH, FSH, and LH receptors) that operate via a cAMP-dependent mechanism, as well as cell proliferation. Because the pathogenic variant is postzygotic rather than genomic, it is present variably in different tissues (somatic mosaicism) and hence results in variable clinical expression and limited diagnostic sensitivity of genetic testing from leukocyte DNA or unaffected tissues. The diagnostic sensitivity may improve with new techniques, however. Precocious puberty has been described predominantly in females (Fig. 600.4) and is characterized by recurrent ovarian cysts, bouts of estrogen secretion, and vaginal bleeding in the context of modest breast development. The age at onset in females is usually 3-6 years but has been reported as early as 4-6 months of age. Serum levels of LH and FSH are suppressed, with no response to GnRH stimulation. Estradiol levels fluctuate from low to markedly elevated (>300 pg/mL), are often cyclic, and may correlate with the size of the cysts. Precocious puberty is less commonly reported in males with McCune-Albright syndrome. Testicular enlargement is often symmetric and is followed by the appearance of phallic enlargement and pubic hair development, as in normal puberty. Testicular histology has shown foci or nodules (often sonographically detectable) of Leydig cell hyperplasia. In females and males, when the bone age reaches the usual pubertal age range, gonadotropin secretion begins and CPP ensues and overrides the antecedent (gonadotropin-independent) puberty. In females, menses become more regular, but often not completely so, and fertility has been documented.

Pubertal progression is variable in these patients. Functioning ovarian cysts often disappear spontaneously; aspiration or surgical excision of cysts is rarely indicated. For those females with persistent or recurrent estradiol secretion, **aromatase inhibitors** (which inhibit the final step of estrogen biosynthesis) such as **letrozole** (1.25-2.5 mg/day PO) have proven safe and effective in limiting the estrogen effects on pubertal and osseous maturation. The same compounds have also been used in males in combination with **antiandrogens**. These medications are not approved by the FDA for this indication. Associated therapy with **long-acting analogs of GnRH** is indicated only for young children whose puberty has shifted from a gonadotropin-independent to a predominantly gonadotropin-dependent mechanism. Ovarian torsion is a severe complication of large ovarian cysts.

EXTRAGONADAL MANIFESTATIONS

The hyperthyroidism that occurs in this condition is usually clinically mild or subclinical, unlike that observed in **Graves disease**. Mildly elevated triiodothyronine levels, suppressed TSH levels, and nodular abnormalities on ultrasound have been reported. Thyroidectomy is rarely necessary.

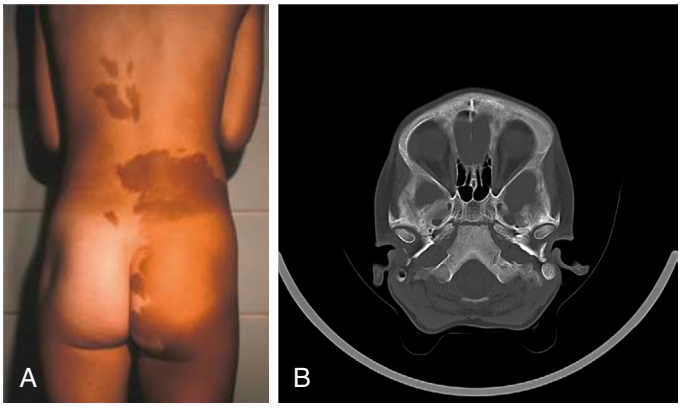

Fig. 600.4 Precocious puberty with McCune-Albright syndrome (MAS). **A,** A girl presented at 5 yr of age with early stage III breast development and vaginal bleeding. Note the extensive café-au-lait skin patches, some of which did not cross the midline. **B,** A girl presented with recurring episodes of mild breast enlargement and vaginal bleeding associated with ovarian cysts, starting at age 7 mo. She had no skin lesions and a negative skeletal survey and bone scan at age 4 yr. The diagnosis of MAS was established at 5 yr of age, when prominence of her left forehead and supraorbital ridge prompted a CT scan, which revealed unilateral thickening of the skull bones **(B)**. Skull lesions are often hyperostotic, whereas long bone lesions usually have a lytic, "ground-glass" appearance.

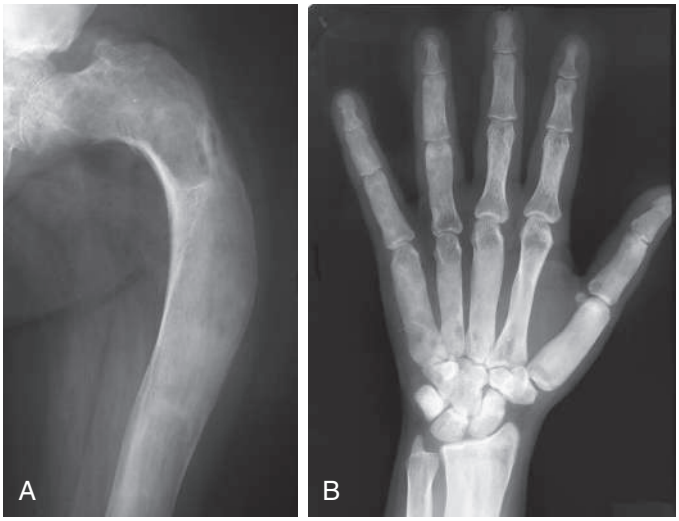

Fig. 600.5 Polyostotic fibrous dysplasia in a 22-yr-old female. A, The femur is expanded and bowed with a "shepherd's crook" deformity. The femoral trabeculae are replaced by a "ground-glass" matrix. B, Diffuse sclerosis is seen in the hand and wrist with mild expansion and indistinct transition from the cortex to medullary space. *(From Thapa MM, Kaste SC, Meyer JS. Soft tissue bone tumors. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 138.31.)*

Cushing syndrome caused by bilateral nodular adrenocortical hyperplasia has occurred only in neonates or young infants. ACTH levels are low, and cortisol is elevated and not suppressible by dexamethasone. The condition may resolve spontaneously; if not, treatment is bilateral adrenalectomy.

Increased secretion of GH occurs uncommonly and is manifested clinically by **gigantism** or **acromegaly**. The growth rate is increased (even in the absence of precocious puberty); serum levels of GH are elevated, increase during sleep, and are poorly suppressed by oral glucose. Serum levels of prolactin are increased in most patients. Less than 50% of the patients have a demonstrable pituitary tumor. Treatment includes octreotide or lanreotide—long-acting somatostatin analogs—to lower the elevated GH levels or pegvisomant to antagonize the effect of GH at the receptor level.

Fibrous dysplasia of (usually) multiple bones (polyostotic) represents a major cause of morbidity in this syndrome (Fig. 600.5). The base of the skull and the proximal femurs are most commonly involved, but any bone can be affected. Even in the absence of deformities, a CT scan of the cranium is recommended by several investigators. The prognosis is favorable for longevity, but deformities, repeated fractures, pain, and occasional cranial nerve compression may result from the bony lesions. Bone pain often responds to IV pamidronate or other bisphosphonates. Extensive bony lesions may be associated with phosphaturia because of oversecretion of FGF23, leading to rickets or osteomalacia. Extraglandular manifestations of this syndrome are rare, but cardiovascular and hepatic involvement (severe neonatal cholestasis) may be life threatening.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.7 Familial Male-Limited Gonadotropin-Independent Precocious Puberty

Wassim Chemaitilly and Luigi R. Garibaldi

This rare, autosomal dominant form of peripheral precocious puberty is transmitted from affected males and unaffected female carriers of the pathogenic variant to their male offspring. Signs of puberty appear by 2-3 years of age. The testes are only slightly enlarged. Testicular biopsies show Leydig cell maturation and, sometimes, marked hyperplasia. Maturation of seminiferous tubules may be present. Testosterone levels are variably elevated, often markedly so, even above the adult male range; however, baseline levels of LH are prepubertal, pulsatile secretion of LH is absent, and LH does not respond to stimulation with GnRH or a GnRH agonist. The cause for activation of Leydig cells independently of gonadotropin stimulation is a missense pathogenic variant of *LHCGR*, which encodes the LHCG receptor leading to constitutive activation of cAMP production. Osseous maturation may be markedly advanced; when it reaches the pubertal age range, hypothalamic maturation shifts the mechanism of pubertal development to a gonadotropin-dependent one. This sequence of events is similar to that occurring in children with McCune-Albright syndrome (see Chapter 600.6) or in those with congenital adrenal hyperplasia (see Chapter 616).

Gonadotropin-independent precocious puberty has been diagnosed in a few unrelated males with **type IA pseudohypoparathyroidism** with a specific pathogenic variant of *GNAS* that encodes the $G_s\alpha$ protein. This pathogenic variant is inactivating at normal body temperature and causes pseudohypoparathyroidism, but in the cooler temperature of the testes, it is constitutionally activating, resulting in adenyl cyclase stimulation and production of testosterone. Although this pathogenic variant differs from the constitutive LH receptor pathogenic variant, which usually causes familial male gonadotropin-independent precocious puberty, the end result is the same.

TREATMENT

Young males have been treated with ketoconazole (10-15 mg/kg/day in 8-hour divided doses), an antifungal drug that inhibits C-17,20-lyase and testosterone synthesis. Complications of ketoconazole include liver toxicity and tachyphylaxis. A combination of antiandrogens (such as spironolactone 50-100 mg bid, flutamide 125-250 mg daily or bid, or bicalutamide 25-50 mg daily) and **aromatase inhibitors** (letrozole 2.5 mg/day or anastrozole 1 mg/day) has been used—the latter compounds to suppress estrogens derived from androgens, which potently stimulate bone maturation. These medications are unable to revert the serum testosterone to normal (prepubertal) concentrations or completely offset the unfavorable effects of the elevated sex hormones. They slow down, but do not halt, the progression of puberty and may not improve the height prognosis. Males whose GnRH pulse generator has matured require combined therapy with GnRH agonists.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.8 Incomplete (Partial) Precocious Development

Wassim Chemaitilly and Luigi R. Garibaldi

Isolated development of the breasts in females and growth of sexual hair in both sexes without other signs of puberty are the two most common forms of incomplete precocity and are not unusual in a pediatric practice.

PREMATURE THELARCHE

This term applies to a sporadic, transient condition of isolated breast development that most often appears in the first 2 years of life. In some females, breast development is present at birth and persists. It may be unilateral or asymmetric and often fluctuates in degree. Growth and osseous maturation are normal or slightly advanced. The genitalia show no evidence of estrogenic stimulation. Breast development may regress after 2 years, often persists for 3-5 years, and is rarely progressive. Menarche generally occurs at a normal age, and reproduction is also normal. Basal serum levels of FSH and the FSH response to GnRH stimulation may be greater than that seen in normal controls. Plasma levels of LH and estradiol are typically undetectable. Pelvic ultrasound reveals normal-sized ovaries, but a few small (<9 mm) cysts are not uncommon.

In some females, breast development may be associated with definite evidence of systemic estrogen effects, such as growth acceleration or bone age advancement. Pelvic sonography may reveal enlarged ovaries and/or uterus. This condition, referred to as **exaggerated or atypical thelarche**, differs from CPP because it spontaneously regresses. Leuprolide or GnRH stimulation elicits a robust FSH response, a low LH response, and (after leuprolide only) a moderate estradiol increment at 24 hours (average 60-90 pg/mL). The pathogenesis of typical and exaggerated forms of thelarche is unclear. Delayed inactivation of the hypothalamic-pituitary-ovarian axis, which is active during the prenatal and early postnatal period, increased peripheral sensitivity to estrogens, and other possibilities are unproven hypotheses. In addition to a detailed history, a bone age should be obtained if there are any unusual features. Random serum concentrations of FSH, LH, and estradiol are generally low and not diagnostic. Pelvic ultrasound examination or leuprolide stimulation testing is occasionally indicated. Continued observation is important because the condition cannot be readily distinguished from true precocious puberty. Regression and recurrence suggest functioning **follicular cysts**. Occurrence of thelarche in children older than 3 years of age most often is caused by a condition other than **benign premature thelarche**.

PREMATURE PUBARCHE (ADRENARCHE)

This term has traditionally applied to the appearance of sexual hair before the age of 8 years in females or 9 years in males without other evidence of maturation. It is much more frequent in females than in males. The higher prevalence of this condition in African American and, to a smaller extent, Latino females in comparison to White females may suggest that the cutoff age for the definition of *premature* should be adjusted for different ethnic groups on epidemiologic data. Hair appears on the mons and labia majora in females and perineal and scrotal area in males; axillary hair generally appears later. Adult-type axillary odor is common. Affected children are often slightly advanced in height and osseous maturation. **Premature adrenarche** is an early maturational event of adrenal androgen production. It coincides with precocious maturation of the zona reticularis, traditionally believed to be associated with a decrease in 3β-hydroxysteroid dehydrogenase activity and an increase in C-17,20-lyase activity. These enzymatic changes result in increased basal and ACTH-stimulated serum concentrations of the Δ^5-steroids (17-hydroxypregnenolone and dehydroepiandrosterone [DHEA]) and, to a lesser extent, of the Δ^4-steroids (particularly androstenedione) compared with age-matched control subjects. One class of androgens, the 11-oxygenated steroids, have been reported to play an important role in adrenal physiology and pathology, including adrenarche. **Idiopathic premature adrenarche** is a slowly progressive condition that requires no therapy. However, a subset of patients presents with **atypical premature adrenarche** characterized by one or more features of systemic androgen effects, such as marked growth acceleration, clitoral (females) or phallic (males) enlargement, cystic acne, and advanced bone age (2 SD greater than the mean for age). In this subgroup, an ACTH stimulation test with measurement of serum 17-hydroxyprogesterone concentration is indicated to rule out **nonclassical congenital adrenal hyperplasia** due to 21-hydroxylase deficiency. The prevalence of nonclassical 21-hydroxylase deficiency is approximately 3–6% of unselected children with precocious pubarche; other enzyme defects (i.e., 3β-hydroxysteroid dehydrogenase or 11β-hydroxylase deficiencies) are extremely rare. Although idiopathic premature adrenarche has been considered a benign condition, longitudinal observations suggest that approximately 50% of females with premature adrenarche are at high risk for hyperandrogenism and **polycystic ovary syndrome**, alone or more often in combination with other components of so-called metabolic syndrome (insulin resistance possibly progressing to type 2 diabetes mellitus, dyslipidemia, hypertension, increased visceral fat) as adults. Whether the unfavorable progression to pubertal hyperandrogenism can be prevented by insulin-sensitizing agents (metformin 850-2000 mg/day) or lifestyle interventions (diet, exercise) remains to be proven in large studies. An increased risk of premature adrenarche and **metabolic syndrome** has been documented in children born small for their gestational age. This appears to be associated with insulin resistance and decreased β-cell reserve, perhaps as a consequence of fetal undernutrition.

PREMATURE MENARCHE

This is a rare entity, much less frequent than premature thelarche or premature adrenarche, and is a diagnosis of exclusion. In females with isolated vaginal bleeding in the absence of other secondary sexual characteristics, more common causes, such as vulvovaginitis, a foreign body (typically associated with malodorous discharge), or sexual abuse, and uncommon causes, such as urethral prolapse and sarcoma botryoides, must be carefully excluded. Most females with idiopathic premature menarche have only one to three episodes of bleeding; puberty occurs at the usual time, and menstrual cycles are normal. Plasma levels of gonadotropins are low, but estradiol levels may be occasionally elevated, probably owing to episodic ovarian estrogen secretion associated with ovarian follicular cysts that can be sometimes detected on ultrasound.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.9 Medicational Precocity

Luigi R. Garibaldi and Wassim Chemaitilly

Various medicaments can induce the appearance of secondary sexual characteristics (i.e., peripheral precocious puberty). Examples include the accidental ingestion of estrogens (including contraceptive pills) and the administration of anabolic steroids. Exogenous estrogens may produce a darkening of the areola that is not usually seen in central sexual precocity. The most common cause of medicational precocity is currently related to the widespread use of **testosterone gels or creams**, which are applied to the skin for treatment of male hypogonadism. Systemic absorption from the skin area of a male relative where the gel/cream was applied may result in elevated serum testosterone levels (50-100 mg/dL or higher), with ensuing virilization of exposed children and women. Intense application of diaper rash creams or ointments has recently been reported to cause mild pubarche, with an unclear mechanism.

Less commonly, estrogens in cosmetics, hair creams, and breast augmentation creams cause breast development in females and gynecomastia in males via percutaneous absorption. Lavender and tea tree oils have been associated with prepubertal gynecomastia in several reports. Genistein, a compound from soy, has estrogenic activity in mice, but data in humans are conflicting. The physical changes disappear after cessation of exposure to the hormones. A careful history focused on exploring the possibility of accidental exposure to, or ingestion of, sex hormones is important.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

600.10 Delayed or Absent Puberty

Peter M. Wolfgram

For hypofunction of testis, see Chapter 623. For hypofunction of ovaries, see Chapter 626.

Delayed puberty is the failure of development of any pubertal feature by 13 years of age in females or by 14 years of age in males. A lower cutoff may be appropriate in a child with a strong familial pattern of early puberty.

DIFFERENTIAL DIAGNOSIS

Delay or absence of puberty is caused by:

- Constitutional delay: A variant of normal.
- Hypogonadotropic hypogonadism: Low gonadotropin levels as a result of a defect of the hypothalamus and/or pituitary gland (Tables 600.3, 600.4, and 600.5).
- Hypergonadotropic hypogonadism: High gonadotropin levels as a result of a lack of negative feedback because of a gonadal problem (see Tables 600.3, 600.4, and 600.5). Females may have evidence of adrenarche with absence of normal breast development.

Table 600.3 Classification of Delayed Puberty and Sexual Infantilism

IDIOPATHIC (CONSTITUTIONAL) DELAY IN GROWTH AND PUBERTY (DELAYED ACTIVATION OF HYPOTHALAMIC GNRH PULSE GENERATOR)

HYPOGONADOTROPIC HYPOGONADISM: SEXUAL INFANTILISM RELATED TO GONADOTROPIN DEFICIENCY

CNS Disorders

Tumors
- Craniopharyngiomas
- Germinomas
- Other germ cell tumors
- Hypothalamic and optic gliomas
- Astrocytomas
- Pituitary tumors (including MEN-1, prolactinoma)

Other Causes
- Langerhans histiocytosis
- Postinfectious lesions of the CNS
- Vascular abnormalities of the CNS
- Radiation therapy
- Congenital malformations especially associated with craniofacial anomalies
- Head trauma
- Lymphocytic hypophysitis

Isolated Gonadotropin Deficiency

Kallmann syndrome (with hyposmia or anosmia; without anosmia)
GnRH receptor pathogenic variant
Congenital adrenal hypoplasia (*DAX1* pathogenic variant)
Isolated LH deficiency
Isolated FSH deficiency
Prohormone convertase 1 deficiency (PCI)

Idiopathic and Genetic Forms of Multiple Pituitary Hormone Deficiencies Including PROP1 Pathogenic Variant

Miscellaneous Disorders

See Table 600.4 for syndromic etiologies
Functional gonadotropin deficiency
- Chronic systemic disease and malnutrition
- Sickle cell disease
- Cystic fibrosis
- Acquired immunodeficiency syndrome (AIDS)
- Chronic gastroenteric disease
- Chronic renal disease
- Malnutrition

Miscellaneous Disorders (continued)
- Anorexia nervosa
- Bulimia
- Psychogenic amenorrhea
- Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea)
- Hypothyroidism
- Diabetes mellitus
- Cushing disease
- Hyperprolactinemia
- Marijuana use
- Gaucher disease

HYPERGONADOTROPIC HYPOGONADISM

Males

The syndrome of seminiferous tubular dysgenesis and its variants (Klinefelter syndrome)
Other forms of primary testicular failure
- Chemotherapy
- Radiation therapy
- Testicular steroid biosynthetic defects
- Sertoli-only syndrome
- LH receptor mutation
- Anorchia and cryptorchidism
- Trauma/surgery

Females

The syndrome of gonadal dysgenesis (Turner syndrome) and its variants
XX and XY gonadal dysgenesis
- Familial and sporadic XX gonadal dysgenesis and its variants
- Familial and sporadic XY gonadal dysgenesis and its variants

Aromatase deficiency
Other forms of primary ovarian failure
- Premature menopause
- Radiation therapy
- Chemotherapy
- Autoimmune oophoritis
- Galactosemia
- Glycoprotein syndrome type 1
- Resistant ovary
- FSH receptor pathogenic variant
- LH/hCG resistance
- Polycystic ovarian disease
- Trauma/surgery
- Noonan or pseudo-Turner syndrome
- Ovarian steroid biosynthetic defects

CNS, Central nervous system; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin.
From Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 13th ed. Philadelphia: Elsevier; 2016: Table 25.15, p. 1129.

Table 600.4 Syndromes Associated with Pubertal Delay

	PHENOTYPE	GENETIC DEFECT
Prader-Willi syndrome	Cognitive impairment, morbid obesity, hypotonia	Deletions within paternally imprinted 15q 11.2-12 region
Bardet-Biedl syndrome	Cognitive impairment, obesity, retinitis pigmentosa, postaxial polydactyly	*BBS 1-11* (multiple loci) 20p12, 16q21, 15q22.3-23, 14q32.1
Biemond syndrome	Iris coloboma, polydactyly, short stature	
CHARGE anomaly	Coloboma, heart malformations, choanal atresia, growth retardation, genital anomalies and ear anomalies, HH, olfactory bulb aplasia, hypoplasia	*CHD7*
Adrenohypoplasia congenita	Primary adrenal deficiency	*NR0B1*
Septo-optic dysplasia	Small, dysplastic pale optic discs, pendular nystagmus, midline hypothalamic defect with diabetes insipidus, GH, ACTH, TSH, and LH/FSH deficiency, absent septum pellucidum	*HESX1*
Solitary median maxillary incisor syndrome	Prominent midpalatal ridge	*SHH 7q3*
Börjeson-Forssman-Lehmann syndrome	Cognitive impairment, gynecomastia, moderate short stature, truncal obesity	*PHF6*
Gordon Holmes syndrome	Cerebellar ataxia, dementia, chorioretinopathy, anterior hypopituitarism	*RNF216/OTUD4* *PNPLA6*

Modified from Howard SR, Dunkel L. Delayed puberty – phenotype diversity, molecular genetic mechanisms, and recent discoveries. *Endocrine Rev.* 2019;40:1285–1317, Table 3, p. 1301.

Table 600.5 Molecular Basis for Developmental Disorders Associated with Hypogonadotropic Hypogonadism

GENE	PHENOTYPE	COMPLEX PHENOTYPE
ISOLATED HYPOGONADOTROPIC HYPOGONADISM		
Kallmann Syndrome or Normosmic IHH (With the Same Pathogenic Gene Variant)		
KAL1 (Xp22.3)	X-linked Kallmann syndrome	Anosmia/hyposmia, renal agenesis, dyskinesia
FGFR1 (KAL2) (8p11.2)	Autosomal dominant Kallmann syndrome (± recessive)	Anosmia/hyposmia, cleft lip/palate
FGF8 (ligand for FGFR1) (10q25)		
NELF (9p34.3)	Autosomal dominant (?) Kallmann syndrome	
PROK2 (3p21.1)	Autosomal recessive Kallmann syndrome	
*PROKR2** (20p12.3)		
CHD7 (8p12.1)	Autosomal dominant (some)	CHARGE syndrome includes hyposmia
Normosmic Isolated Hypogonadotropic Hypogonadism		
GNRH1 (8p21-11.2)	Autosomal recessive	
*GNRHR** (4q13.2-3)	Autosomal recessive (± dominant)	
*GPR54** (19p13.3)	Autosomal recessive	
SNRPN		Prader-Willi syndrome
Lack of function of paternal 15q11-q13 region or maternal uniparental disomy		Obesity
LEP (7q31.3)	Autosomal recessive	Obesity
LEPR (1p31)	Autosomal recessive	Obesity
NR0B1 (DAX1) (X21.3-21.2)	X-linked recessive	Adrenal hypoplasia
TAC3 (12q13-12)	Autosomal recessive	
TACR3 (4q25)	Autosomal recessive	
Multiple Pituitary Hormone Deficiencies		
PROP1 (POU1F1)	Autosomal recessive GH, PRL, TSH, and LH/FSH (less commonly, later-onset ACTH deficiency)	
HESX1 (RPX)	Autosomal recessive; and heterozygous mutations Multiple pituitary deficiencies including diabetes insipidus, but LH/FSH uncommon	Septo-optic dysplasia
LHX3	Autosomal recessive GH, PRL, TSH, FSH/LH	Rigid cervical spine
PHF6	X-linked; GH, TSH, ACTH, LH/FSH	Börjeson-Lehmann syndrome: mental retardation; facies

*A G-protein–coupled receptor.
ACTH, Adrenocorticotropic hormone; CHD7, chromatin-remodeling factor; DAX1, dosage-sensitive sex reversal-adrenal hyperplasia congenita critical region on the X chromosome, gene 1; FGF, fibroblast growth factor; FSH, follicle-stimulating hormone; GH, growth hormone; GNRH, gonadotropin-releasing hormone; GPR54, kisspeptin G protein–coupled receptor 54; HESX1, homeobox gene expressed in ES cells; IHH, idiopathic hypogonadotropic hypogonadism; LEP, leptin; LH, luteinizing hormone; LHX3, lim homeobox gene 3; NELF, nasal embryonic luteinizing hormone–releasing factor; NR0B1, nuclear receptor family 0, group B, member 1; PHF6, plant homeodomain–like finger gene; PRL, prolactin; PROK2, prokineticin 2; PROP1, prophet of Pit-1; R, receptor; SNRPN, small nuclear ribonucleoprotein polypeptide SmN; TAC3, neurokinin 3; TSH, thyroid-stimulating hormone.
From Styne DM, Grumbach MM. Physiology and disorders of puberty. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 13th ed. Philadelphia: Elsevier; 2016: Table 25.19, p. 1138.

Constitutional Delay of Growth and Puberty

This is the most common cause of delayed puberty and a normal variant of pubertal timing. It is predominately diagnosed in males, likely as a result of ascertainment bias from referral patterns. The cause is unknown, but approximately 50% of affected patients have a first-degree relative with delayed puberty and/or late growth. This tendency can occur in a child of the same gender as the affected parent or in a child of the opposite gender. An affected child typically presents in early adolescence, when peers are beginning to develop and having growth spurts but the patient is not. The patient's height is usually at or below the third percentile. In a classic patient, the affected child had a normal length at birth, followed by a slowdown in height velocity between 6 months and 2 years of age that resulted in a decreased height percentile, and then normal or near-normal height velocity thereafter along this decreased height percentile. The physical examination findings are unremarkable, except at the typical age of puberty the child will have delayed pubertal development and growth. The cardinal diagnostic finding is a bone age that is moderately delayed (or younger appearing) than the typical bone age for the patient's actual chronological age. There may also be a history of delayed dentition. Without intervention, final adult heights usually reach or approximate the genetic target height range. However, rarely, children with constitutional delay may have a blunted pubertal growth spurt in relation to their peers and therefore may not reach their target height range.

Hypogonadotropic Hypogonadism

A variety of CNS anomalies or injuries may disrupt production of gonadotropins. The GnRH pulse generator may be disrupted by an interfering substance, such as excess prolactin, chronic illness, malnutrition, or excessive physical activity. The hypothalamic arcuate nucleus may be damaged by trauma, radiation, infection, infiltration, increased intracranial pressure, or surgery. The most common mass lesions are craniopharyngiomas, gliomas, and cysts. Of note, congenital conditions or malformations may have allowed enough GnRH, LH, and FSH for infantile development but may not be enough later to begin and sustain puberty.

Kallmann Syndrome

This is the combination of a deficiency of gonadotropins with an impaired or absent sense of smell. Other features may include color blindness, atrial septal defects, and renal structural anomalies (unilateral renal agenesis). The X-linked form is caused by a pathogenic variant of *KAL*; there are autosomal recessive and autosomal dominant forms.

LH and FSH deficiencies may be isolated or accompanied by multiple pituitary hormone deficiencies. The deficiency may be a result of pituitary damage from trauma, radiation, infection, sickle cell disease, compression by infiltrate or tumor, or autoimmune processes. In differentiating primary pituitary deficiency from that secondary to hypothalamic deficiency, the clinician should remember that all pituitary hormones, except prolactin, are stimulated by hypothalamic-releasing hormones; however, prolactin is inhibited by hypothalamic prolactin inhibitory factor (dopamine). Therefore if all pituitary hormones, including prolactin, are deficient, the problem is in the pituitary gland. If prolactin levels are present or even elevated but the other pituitary hormones are deficient, the problem is above the pituitary gland, in the stalk or hypothalamus. In the case of isolated LH and FSH deficiencies, the primary abnormality may lie within the pituitary-hypothalamic neurons producing GnRH or farther upstream of the GnRH-secreting neurons. In particular, defects in molecules required for proper migration of GnRH neurons (including the *KAL* gene) or lack of necessary signaling to GnRH-producing neurons (defects in kisspeptin or neurokinin B and their receptors) can result in LH and FSH deficiency through inappropriate GnRH secretion.

Hypergonadotropic Hypogonadism: Males

If the testes are small, they may have been damaged by torsion, sickle cell disease, infection, autoimmune disease, chemotherapy, or radiation and may not be able to respond to LH and FSH stimulation. If the male is of pubertal age (bone age is greater than 10 years) and the hypothalamus has matured, the serum LH and FSH will be high because of lack of testicular response. Also, if there is a problem with testicular LH receptors, the LH can be high but the testosterone will not appropriately increase.

Klinefelter Syndrome

This occurs in 1:500 males and is often associated with a 47,XXY karyotype; common features include reduced intelligence, adolescent gynecomastia (often severe), and small, firm testes. The testes rarely exceed 5 mL in volume (approximately 25% of the average adult volume). Patients are often tall and thin with an eunuchoid habitus and may have delayed puberty with high FSH and LH. Virilization may be incomplete, the phallus is often smaller than average, and infertility approaches 100%.

Hypergonadotropic Hypogonadism: Females

In this condition, the ovary may be unable to synthesize estrogen (an inherited metabolic defect), the ovary may not be formed normally (dysgenesis), or the ovary may have been damaged by any of the factors listed for testicular damage and by galactosemia.

The ovary may be intact but may not be stimulated by gonadotropins—for example, FSH is present but there is an FSH receptor problem, so estradiol is not made appropriately.

Turner Syndrome

The two most common features of Turner syndrome are short stature (involving the limbs to a greater degree than the trunk) and ovarian insufficiency with high FSH. Lymphedema and a webbed neck are diagnostic features present in a neonate. Additional features include shield chest, increased carrying angle (cubitus valgus), short fourth metacarpal, hypoplastic nails, renal anomalies, and left-sided heart defects (coarctation of the aorta, bicuspid aortic valve). Approximately 50% of affected females have no stigmata except short stature and thus are typically identified later. About 20% may have spontaneous puberty with functioning ovaries for at least a short period, which is in large part dependent on the child's karyotype; the infertility rate is greater than 99%.

Females with Delayed or Absent Adrenarche

If a female has advanced breast development but no androgen signs, she may have a disorder of androgen activity as occurs in **androgen insensitivity syndrome** (testicular feminization). In females, the androgens come predominantly from the adrenal glands (adrenarche). If the bone age is less than 8 years, adrenarche may simply be delayed (delayed adrenarche). However, if the bone age is older, there may be an inherited problem in androgen synthesis from an enzyme deficiency, or the adrenal may be damaged secondary to autoimmune, infectious, or hypoxic injury. In these latter conditions of adrenal damage, other signs of adrenal insufficiency would be evident.

DIAGNOSTIC APPROACH TO DELAYED PUBERTY

A normal growth rate with delayed, but not absent, puberty and a family history of late puberty suggest the diagnosis of constitutional delay of growth and puberty, which is the most commonly encountered cause. A bone age that correlates with the patient's current pubertal status but is delayed for their chronological age confirms the clinical impression; no other testing is necessary.

Initial evaluation should include:

- Medical history: trauma, illness, medications (e.g., stimulants, chemotherapy), radiation, infection, malnutrition, autoimmune problems, sickle cell disease status, stresses, growth records, galactosemia
- Review of symptoms: vision problems, headache, vomiting, inability to detect odors (hyposmia or anosmia), age at onset of androgen signs, age at onset of estrogen signs, small genitalia at birth, signs of primary adrenal insufficiency such as hyperpigmentation, need for deodorant, need to wash hair more frequently
- Family history: timing of maternal and paternal growth and pubertal development; siblings and cousins with delayed development
- Physical examination: signs of chronic disease, temperature, blood pressure, height, weight, head circumference, dental age, hyperpigmentation, pubic and axillary hair, adult body odor, evidence of skin and hair oils, visual fields, optic discs, ability to detect odors, breast development, vaginal cornification/discharge, penis size, scrotal development, testicular volume, pubic hair stages, neurologic status, affect or mood, intellectual ability, dysmorphic features

Initial laboratory evaluation screens for chronic disease (complete blood cell count, chemistry profile, sedimentation rate), hypothyroidism (free thyroxine and TSH), and hyperprolactinemia (prolactin level) should be obtained. If growth is slow, the clinician should measure insulin-like growth factor-1 level (marker of basal GH activity) and consider GH testing. The clinician should measure testosterone levels in males and estradiol levels in females.

Measurements of random FSH and LH and results of a GnRH stimulation test may differentiate between hypogonadotropic hypogonadism and primary gonadal failure (Figs. 600.6 and 600.7). Elevated gonadotropin levels support a diagnosis of primary gonadal failure. A random LH or an LH after GnRH is not typically helpful in distinguishing between constitutional delay and hypogonadotropic hypogonadism because with both diagnoses the LH will be low. However, the child with constitutional delay eventually develops an appropriate pubertal development and LH values. If there are elevated gonadotropins, chromosomal karyotyping can be performed (Klinefelter syndrome in males and Turner syndrome in females).

If Kallmann syndrome is being considered, an MRI scan may show abnormalities in the olfactory region. If a 46,XX female has unexplained ovarian failure, antiovarian antibodies and müllerian-inhibiting substance can assess ovarian follicle reserve and potential fertility. In males, an hCG stimulation test to evaluate ability to produce testosterone and a serum level of müllerian-inhibiting substance (secreted by

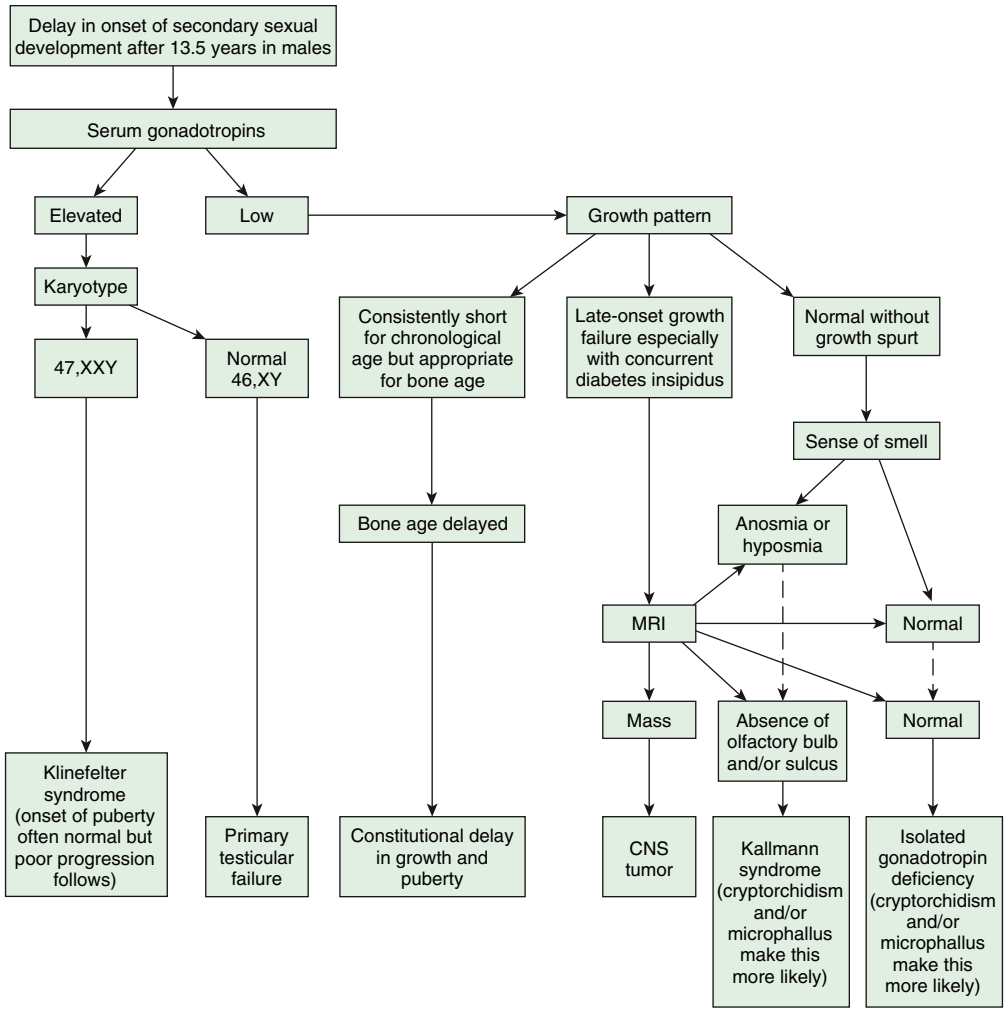

Fig. 600.6 Diagnostic algorithm for the evaluation of delayed puberty in males. CNS, Central nervous system; MRI, magnetic resonance imaging. *(From Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 25.48.)*

Sertoli cells) are useful for determining whether functional testicular tissue is present.

TREATMENT OF DELAYED PUBERTY

If delayed puberty is a normal physiologic variant (constitutional delay of growth and puberty), sex steroid replacement is not medically necessary. Watchful waiting is usually the appropriate course of action. However, adolescent males with constitutional delay of growth and puberty who are short, underdeveloped, and psychologically compromised may benefit from a short course of testosterone therapy. This is usually given as long-acting intramuscular testosterone, at a dosage of 50-100 mg every 4 weeks for a course ranging between 6 and 12 months. Treatment is generally begun at about 14 years of age and, if possible, when the testes have enlarged to about 6-8 mL in volume. These doses stimulate height and weight gain, allow adequate virilization (increased pubic and axillary hair growth and penile enlargement), and do not typically suppress pituitary FSH and LH secretion, thereby allowing simultaneous endogenous pubertal progression (testicular enlargement). This narrows the physical gap between the patient and peers without causing undue advancement of bone age. Acne is the principal side effect, and the adult height is not altered. It is the hope that at the conclusion of treatment, the male will continue to grow and develop rapidly, with the testosterone treatment perceived as a jump starter of endogenous puberty. Additionally, a short course of a low-dose anabolic steroid, such as oxandrolone, can also be used in prepubertal and pubertal males, and low-dose estradiol has been used in prepubertal and pubertal females with constitutional delay.

Treatment of hypogonadism aims to mimic normal physiology with stepwise replacement of testosterone in males and estrogen and progesterone in females. For males with hypogonadism, low-dose parenteral testosterone is initiated at 50 mg every 4 weeks, with increases in 50-mg increments made over a 2- to 3-year period. Most adult males receive 200 mg every 2-4 weeks, which is based on the daily adult male testosterone production rate of 6 mg. Adult men can receive testosterone by patch, which is often associated with local irritation, or by gel, but, typically in growing adolescents, intramuscular testosterone is prescribed to allow more reliable control of testosterone activity.

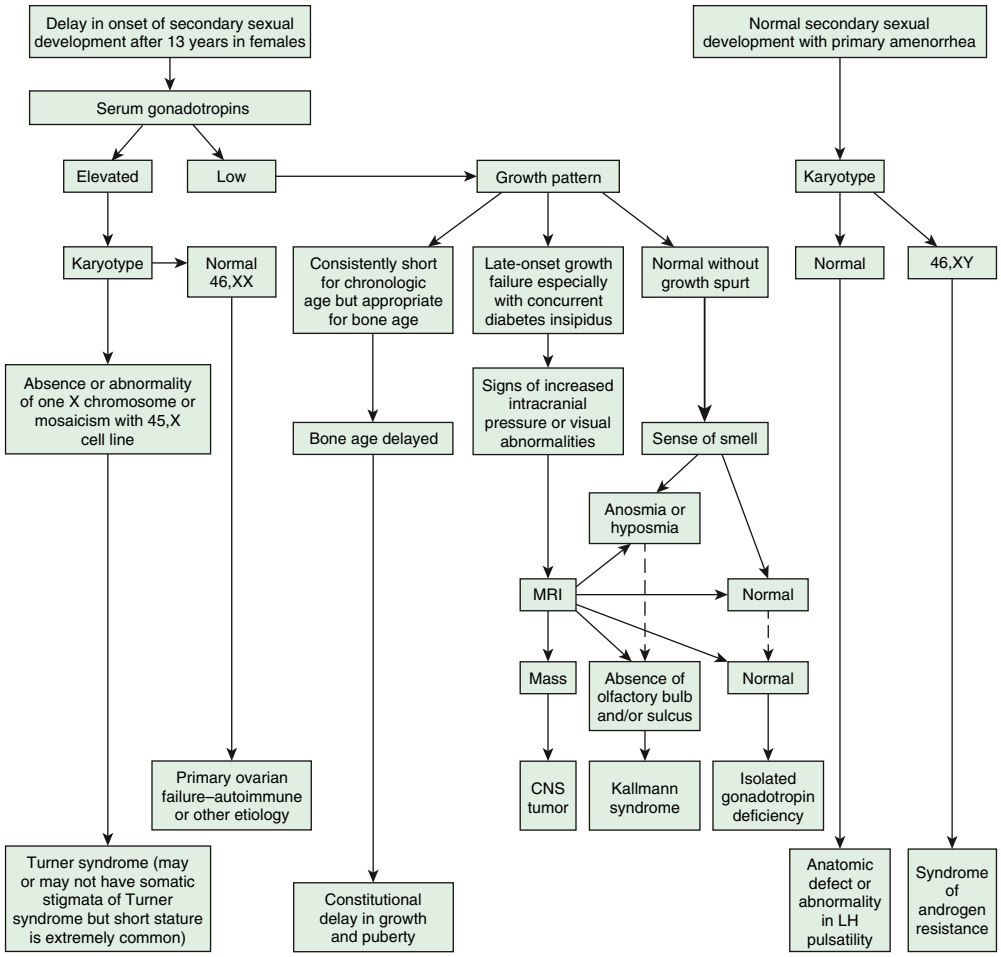

Fig. 600.7 Diagnostic algorithm for the evaluation of delayed puberty in females. CNS, Central nervous system; MRI, magnetic resonance imaging. *(From Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 25.49, p. 1157.)*

For females with hypogonadism, daily estrogen therapy typically is provided through a transdermal 17β-estradiol patch 25 mcg/24 hr patch, which is more physiologic than oral preparations of the estrogens (conjugated estrogens [Premarin] or ethinyl estradiol) because transdermal therapy avoids initial first-pass hepatic metabolism. The transdermal or oral dose of estrogen (Premarin starts at 0.3 mg daily) is increased over the course of about 2 years. Two years of estrogen therapy without progesterone does not place the uterus at undue risk for hyperplasia and malignancy, but after 2 years (or sooner if spotting occurs prior), progesterone should be added. Options to consider when adding progesterone include continuing the 17β-estradiol patches or estrogen-only–containing pills (conjugated estrogens or ethinyl estradiol) in conjunction with oral medroxyprogesterone acetate (Provera), a progesterone eluting intrauterine device (IUD), or switching the patient to conventional oral contraceptives. If the patient is not put on a conventional oral contraceptive or a progesterone-eluting IUD, the estrogen (pill or patch) is prescribed on days 1-23 of the calendar month with the addition of medroxyprogesterone acetate on days 10-23. With this approach, withdrawal bleeding generally occurs between day 23 and the end of the month, although there can be some variability in the timing between patients.

Patients of either sex with hypogonadotropic hypogonadism are potentially fertile, but sex-steroid therapy alone is ordinarily not sufficient to initiate gametogenesis, although there are rare cases in males in which testosterone replacement alone has stimulated spermatogenesis. The general approach to fertility induction in either sex involves the addition of either cyclical gonadotropin therapy or pump-driven GnRH therapy at the age of desired conception. *When hypogonadotropic hypogonadism is present as one component of hypopituitarism, it is critical to adequately replace all deficient hormones* (see Chapter 595). In contrast, patients with primary hypogonadism have intrinsic gonadal damage and are normally infertile.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2

Disorders of the Thyroid Gland

Chapter 601

Thyroid Development and Physiology

Ari J. Wassner and Jessica R. Smith

FETAL DEVELOPMENT

The fetal thyroid arises from an outpouching of the foregut at the base of the tongue (foramen cecum) and migrates to its normal location below the cricoid cartilage by 8-10 weeks of gestation. The thyroid's bilobed shape is apparent by 7 weeks of gestation, and thyroid follicular cells capable of forming colloid are present by 10 weeks. Thyroglobulin synthesis begins at 4 weeks, iodine trapping occurs by 8-10 weeks, and synthesis and secretion of thyroxine (T_4) and, to a lesser extent, triiodothyronine (T_3) occur from 12 weeks of gestation. Several transcription factors, including NKX2.1, FOXE1, and PAX8, are important in thyroid gland morphogenesis and differentiation and possibly also in its caudal migration. Thyrotropin (TSH) secretion is evident by 10-12 weeks of gestation. Maturation of the hypothalamic-pituitary-thyroid axis occurs during the second half of gestation, but normal hormonal feedback relationships are not mature until 1-3 months of postnatal life. Other transcription factors, including PROP1 and POU1F1, are important for the differentiation and growth of pituitary thyrotrophs, along with somatotrophs and lactotrophs.

THYROID PHYSIOLOGY

The primary function of the thyroid gland is to synthesize T_4 and T_3, of which iodine is a critical component. The only known physiologic role of iodine is in the synthesis of these hormones, and iodine deficiency results in hypothyroidism. The daily recommended dietary allowance of iodine is 110-130 μg for infants, 90-120 μg for children, and 150 μg for adolescents and adults (see Chapter 605.3).

Ingested iodine reaches the thyroid gland as its ionized form, iodide [I^-]. Thyroid tissue has a unique avidity for iodide and can take up and concentrate it in the follicular lumen to synthesize thyroid hormone. Transport of iodide from the circulation into the thyroid follicular cell is facilitated by the transmembrane sodium–iodide symporter (NIS). Once taken up, iodide diffuses across the cell and is transported across the apical membrane into the colloid by pendrin (and likely another unidentified transporter).

To form thyroid hormone, trapped inorganic iodide is organified onto tyrosine residues of thyroglobulin in the follicular lumen, a reaction catalyzed by thyroperoxidase (TPO). This reaction requires the H_2O_2 produced by the enzyme DUOX2, which is expressed in conjunction with dual oxidase maturation factor 2 (DUOXA2). Thyroglobulin is a large homodimeric glycoprotein that contains 138 tyrosine residues. Iodination of specific tyrosine residues forms monoiodotyrosines (MITs) and diiodotyrosines (DITs), which are further coupled by TPO to produce T_4 or T_3. Once formed, T_4 and T_3 remain stored as part of thyroglobulin in the thyroid colloid until they are secreted through a process of follicular cell endocytosis of colloid followed by endolysosomal degradation of thyroglobulin to release T_4 and T_3.

The thyroid secretes T_4 and T_3 in a ratio of about 12 to 1. Although T_3 circulates at about one-fiftieth the concentration of T_4, T_3 is the physiologically active thyroid hormone because it binds the thyroid hormone receptor with 10- to 15-fold greater affinity than T_4. Only 20% of circulating T_3 is secreted directly by the thyroid, and the remainder is produced by conversion from T_4 in extrathyroidal tissues by iodotyrosine deiodinases (types 1 and 2).

Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism. Entry of T_4 and T_3 into cells is facilitated by specific thyroid hormone transporters, of which the most important is monocarboxylate transporter 8 (MCT8). Once inside the cell, T_4 is converted to T_3 by type 1 or 2 deiodinase. Intracellular T_3 enters the nucleus and binds to thyroid hormone receptors. Thyroid hormone receptors are members of the steroid hormone receptor superfamily, and three thyroid hormone receptor isoforms (α_1, β_1, and β_2) are expressed in different tissues. Binding of T_3 to a thyroid hormone receptor causes recruitment of co-activator molecules, transcription of messenger RNA, and protein synthesis. Deiodination, transmembrane transport, and thyroid hormone receptor expression provide multiple levels of tissue-specific modulation of thyroid hormone action in the face of a given level of circulating T_4.

Approximately 70% of circulating T_4 and 50% of T_3 are bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only 0.03% of serum T_4 and 0.3% of T_3 are unbound (free T_4 and free T_3, respectively). Because the concentration or binding of TBG is altered in many clinical circumstances, its status must be considered when interpreting total T_4 or T_3 levels.

THYROID REGULATION

The thyroid is regulated by TSH, a glycoprotein hormone secreted by the anterior pituitary thyrotrophs. Binding of TSH to its receptor in the thyroid gland activates adenylate cyclase and stimulates all steps of thyroid hormone biosynthesis (see Fig. 594.1). TSH is a heterodimer composed of α and β subunits. The α subunit is common to luteinizing hormone, follicle-stimulating hormone, and chorionic gonadotropin, and the specificity of each hormone is conferred by its unique β subunit. TSH synthesis and release are stimulated by TRH, a tripeptide synthesized in the hypothalamus and secreted into the pituitary. In states of decreased thyroid hormone, TSH and TRH are increased, and increased thyroid hormone inhibits TSH and TRH production. TSH levels can be measured in serum, whereas circulating levels of TRH are not clinically measurable.

Further control of the level of circulating thyroid hormones occurs in the periphery. In many nonthyroidal illnesses, circulating T_3 levels fall because of decreased extrathyroidal production of T_3 by type 1 deiodinase and increased inactivation of T_4 (to reverse T_3) and T_3 (to T_2) by type 3 deiodinase. These changes may be induced by factors such as fasting, chronic malnutrition, acute illness, and certain drugs. Although levels of T_3 may be significantly decreased, levels of free T_4 and TSH may remain normal. The decreased levels of T_3 may be a physiologic adaptation, resulting in decreased rates of oxygen consumption, substrate use, and other catabolic processes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

601.1 Thyroid Hormone Studies

Ari J. Wassner and Jessica R. Smith

SERUM THYROID HORMONES

Methods are available to measure many thyroid hormones in serum, including T_4, free T_4, T_3, and free T_3. The metabolically inert reverse T_3 (rT_3) is present in serum, but measuring rT_3 is rarely useful clinically. Direct assays for free T_4 are widely available and are reliable in healthy patients, but these assays may be less reliable during acute illness or with severe abnormalities of thyroid hormone binding. Therefore in such situations it may be preferable to measure total T_4 as an index of TBG binding or to measure free T_4 by the gold standard technique of equilibrium dialysis. The clinical utility of many free T_3 assays is limited by their poor standardization. Because normal thyroid function changes over time, age-specific reference ranges should be used when interpreting thyroid hormone testing in children, particularly in neonates and infants.

Measuring serum levels of TSH and free T_4 can diagnose most clinical thyroid disorders. Serum TSH is the most sensitive test for primary thyroid dysfunction, and it is elevated in primary hypothyroidism and suppressed in primary thyrotoxicosis. In central (secondary) hypothyroidism, serum TSH is low or inappropriately in the normal range despite low serum T_4 and free T_4 levels. Biotin supplements may cause a false elevation of T_4 and T_3 and a false decrease of TSH.

Thyroglobulin is a glycoprotein secreted through the apical surface of the thyroid follicular cell into the colloid. Thyroglobulin is measurable in the serum, and levels of thyroglobulin increase with TSH stimulation and in proportion to functional thyroid mass. Athyreotic infants have markedly reduced levels of thyroglobulin. In contrast, thyroglobulin levels may be increased in neonates and in patients with Graves disease and other forms of autoimmune thyroid disease, differentiated thyroid carcinoma, or endemic goiter.

FETAL AND NEWBORN THYROID

Fetal serum T_4 and free T_4 increase from midgestation to approximately 9.5 μg/dL and 1.4 ng/dL, respectively, at term. Fetal levels of T_3 are low before 20 weeks and then gradually increase to approximately 60 ng/dL at term. Reverse T_3 levels, however, are high in the fetus (300 ng/dL at 30 weeks) and decrease to 200 ng/dL at term. Serum levels of TSH gradually increase to 6 mIU/L at term. Approximately one third of fetal T_4 at term is derived from the transplacental passage of maternal T_4. Maternal T_4 plays a key role in fetal development, especially that of the brain, beginning before fetal synthesis of thyroid hormone begins. Therefore a fetus with congenital hypothyroidism may be partially protected by maternal T_4 if the mother is euthyroid but may be at risk for neurodevelopmental injury if the mother is hypothyroid.

Immediately after birth there is an acute release of TSH, with peak serum concentrations reaching 70-100 mIU/L 30 minutes after delivery in full-term infants. TSH declines rapidly over the ensuing 24 hours and more gradually over the next 5 days to <10 mIU/L. After the first 1-3 months of life, normal levels of TSH are <5 mIU/L. The postnatal surge in TSH stimulates an increase in levels of T_4 to approximately 16 μg/dL and of T_3 to approximately 300 ng/dL in about 4 hours. T_4 levels gradually decrease during the first 2 weeks of life to 10-12 μg/dL. T_3 levels decline during the first week of life to below 200 ng/dL. Reverse T_3 levels remain high for 2 weeks (200 ng/dL) and decrease by 4 weeks to around 50 ng/dL. In preterm infants, changes in thyroid function after birth are qualitatively similar to but quantitatively smaller than in full-term infants. Serum T_4 and T_3 levels are decreased in proportion to gestational age and birthweight.

SERUM THYROXINE-BINDING GLOBULIN

The thyroid hormones are transported in plasma bound primarily to TBG, a glycoprotein synthesized in the liver. TBG binds approximately 70% of T_4 and 50% of T_3. Estimating TBG binding is occasionally necessary because changes caused by various clinical conditions can affect measured levels of total (but not free) T_4 and T_3. TBG levels increase in pregnancy; in the newborn period; with hepatitis; and with the administration of estrogens (oral contraceptives), selective estrogen receptor modulators, heroin or methadone, mitotane, and 5-fluorouracil. TBG levels decrease with androgens, anabolic steroids, glucocorticoids, nicotinic acid, and L-asparaginase. These effects are the result of altered hepatic synthesis of TBG. Severe TBG deficiency may be caused by genetic variants, decreased production with hepatocellular disease, or massive protein loss in the gut (protein-losing enteropathies) or the urine (congenital nephrotic syndrome) (see Chapter 602). Some medications, including furosemide, salicylates, nonsteroidal antiinflammatory drugs, heparin, and free fatty acids, can elevate levels of free T_4 by inhibiting binding to TBG.

THYROID ULTRASONOGRAPHY

The primary clinical uses of thyroid ultrasound are to assess thyroid morphology and to evaluate the characteristics of thyroid nodules. In infants with congenital hypothyroidism, evaluation of the size and location of the thyroid may clarify the diagnosis of thyroid dysgenesis; however, the sensitivity of ultrasound is user-dependent, and it will not reliably detect ectopic thyroid glands. Ultrasound is more accurate than physical examination for estimating thyroid gland size and assessing thyroid nodules. Certain characteristics of thyroid nodules, such as irregular margins, microcalcifications, hypoechogenicity, and taller-than-wide shape, increase the likelihood that a thyroid nodule is malignant and guide decisions about the need for fine-needle aspiration. In children with autoimmune thyroiditis or Graves disease, ultrasound may reveal heterogeneous echotexture or changes in vascularity. However, ultrasound generally is not clinically useful in these conditions unless a thyroid nodule is suspected. Ultrasound may also be useful to evaluate thyroglossal duct cysts.

RADIONUCLIDE STUDIES

The availability of highly sensitive tests of thyroid function has decreased the necessity for radioiodine uptake studies except in specific clinical situations. The ability of the thyroid to take up and organify iodine can be evaluated by measuring the uptake of radioactive isotope ^{123}I (half-life: 13 hours). Technetium (^{99m}Tc) is also a useful radioisotope for children because it is trapped but not organified by the thyroid and has a half-life of only 6 hours. Thyroid scintigraphy can demonstrate the anatomic distribution of tracer uptake by thyroid tissue and may be indicated to assess for possible thyroid dysgenesis or ectopic thyroid tissue or to evaluate possible autonomous (hot) thyroid nodules. ^{131}I may be used to treat hyperthyroidism or thyroid cancer, but its use generally should be avoided for thyroid uptake and scintigraphy because of its cytotoxic effect.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 602

Disorders of Thyroxine-Binding Globulin

Ari J. Wassner and Jessica R. Smith

Approximately 70% of circulating thyroxine (T_4) and 50% of triiodothyronine (T_3) are bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only the unbound (free) fractions of these hormones, comprising 0.03% of serum T_4 and 0.3% of T_3, can exert biologic activity. Because regulation of the hypothalamic-pituitary-thyroid axis is mediated by the concentrations of free thyroid hormones, abnormalities of thyroid hormone binding tend to alter concentrations of total, but not free, thyroid hormones. *Therefore abnormalities in levels of TBG are not associated with clinical disease and do not require treatment.* They are usually discovered as an incidental finding of abnormally low or high levels of T_4 and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

Congenital TBG deficiency is an X-linked recessive trait that occurs in 1 in 1,700 male newborns. It is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T_4 as the primary screening test. Affected males have low levels of total T_4 (usually <4 μg/dL) and elevated T_3 resin uptake, but levels of free T_4 and thyrotropin (TSH) are normal. The diagnosis is confirmed by the measurement of absent or low serum levels of TBG, although rare cases may have normal concentrations of TBG with reduced affinity for T_4. No treatment is required, but testing may be indicated in potentially affected family members to avoid the incorrect diagnosis of hypothyroidism in the future. More than 40 different pathogenic variants have been reported in the TBG gene. **Acquired** causes of TBG deficiency are listed in Table 602.1.

TBG excess is a benign X-linked dominant variant that occurs in approximately 1 in 25,000 individuals. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T_4 is elevated, T_3 is variably elevated, TSH and free T_4 are normal, and T_3 resin uptake is decreased. Elevated serum levels of TBG confirm the diagnosis. Affected neonates have been found to have levels of T_4 as high as 95 μg/dL, which decrease to 20-30 μg/dL after 2-3 weeks. Affected patients are euthyroid, but family studies may be indicated to alert other affected family members. Acquired causes of TBG excess are listed in Table 602.1.

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant variant caused by an abnormal albumin with a markedly increased affinity for T_4. This leads to increased serum concentrations of T_4 (and in some cases T_3) that can be mistaken for thyrotoxicosis. However, levels of free T_4, free T_3, and TSH are normal, and affected patients are euthyroid.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 602.1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG
Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Nephrotic syndrome	Heroin, methadone
Protein-losing enteropathy	Mitotane
Nicotinic acid	5-Fluorouracil
L-Asparaginase	Perphenazine

Chapter 603

Hypothyroidism

Ari J. Wassner and Jessica R. Smith

Hypothyroidism is a state of insufficient thyroid hormone action at the tissue level. Hypothyroidism most often results from deficient production of thyroid hormone caused either by a defect in the thyroid gland itself (primary hypothyroidism) or by reduced thyrotropin (TSH) stimulation (central or secondary hypothyroidism; Table 603.1). Hypothyroidism may be present from birth (congenital) or may be acquired, although some acquired cases are due to congenital defects in which the onset of hypothyroidism is delayed.

CONGENITAL HYPOTHYROIDISM

Most cases of congenital hypothyroidism are caused by abnormal formation of the thyroid gland **(thyroid dysgenesis)**, and ~30% of cases are due to inborn errors of thyroid hormone synthesis **(dyshormonogenesis)** or other causes. Most infants with congenital hypothyroidism are detected by newborn screening programs in the first week after birth, before significant clinical signs or symptoms develop. In regions without newborn screening, severely affected infants usually manifest features within the first week of life, but in infants with milder hypothyroidism, the clinical manifestations may not be evident for weeks or months.

Epidemiology

The incidence of congenital hypothyroidism was initially reported to be 1 in 4,000 infants based on the earliest established neonatal screening programs. The incidence of diagnosis has increased to about 1 in 2,000, primarily because more stringent screening algorithms have resulted in the detection of milder cases of hypothyroidism, mostly in patients with a eutopic thyroid gland.

Etiology

See Table 603.1.

Primary Hypothyroidism

Thyroid Dysgenesis. Thyroid dysgenesis is the most common cause of permanent congenital hypothyroidism, accounting for 80–85% of cases. In approximately one third of cases of dysgenesis, no thyroid tissue is present **(agenesis)**. In the other two thirds of infants, rudiments of thyroid tissue are present, either in the normal position **(hypoplasia)** or in an **ectopic** location along the embryologic path of descent of the thyroid from the base of the tongue (lingual thyroid) to the normal position. Thyroid dysgenesis occurs twice as common in females as in males.

The cause of thyroid dysgenesis is largely unknown. The condition is usually sporadic, but familial cases have been reported rarely. Thyroid developmental anomalies, such as thyroglossal duct cysts and thyroid hemiagenesis, are present in 8–10% of first-degree relatives of infants with thyroid dysgenesis. However, most thyroid dysgenesis is unlikely to be genetic given the high degree of discordance among monozygotic twins.

A small minority (2–5%) of thyroid dysgenesis is caused by genetic defects in one of several transcription factors essential for thyroid morphogenesis and differentiation, including NKX2.1 (formerly TTF1), FOXE1 (formerly TTF2), and PAX8. NKX2.1 is expressed in the thyroid, lung, and central nervous system, and recessive pathogenic variants in *NKX2-1* cause thyroid dysgenesis, respiratory distress, and neurologic problems (chorea and ataxia) **(brain-lung-thyroid syndrome)**. Recessive pathogenic variants in *FOXE1* cause thyroid dysgenesis, spiky or curly hair, cleft palate, and sometimes choanal atresia and bifid epiglottis **(Bamforth-Lazarus syndrome)**. PAX8 is expressed in the thyroid and kidney, and dominant *PAX8* variants are associated with thyroid dysgenesis and kidney and ureteral malformations.

Chapter 602

Disorders of Thyroxine-Binding Globulin

Ari J. Wassner and Jessica R. Smith

Approximately 70% of circulating thyroxine (T_4) and 50% of triiodothyronine (T_3) are bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only the unbound (free) fractions of these hormones, comprising 0.03% of serum T_4 and 0.3% of T_3, can exert biologic activity. Because regulation of the hypothalamic-pituitary-thyroid axis is mediated by the concentrations of free thyroid hormones, abnormalities of thyroid hormone binding tend to alter concentrations of total, but not free, thyroid hormones. *Therefore abnormalities in levels of TBG are not associated with clinical disease and do not require treatment.* They are usually discovered as an incidental finding of abnormally low or high levels of T_4 and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

Congenital TBG deficiency is an X-linked recessive trait that occurs in 1 in 1,700 male newborns. It is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T_4 as the primary screening test. Affected males have low levels of total T_4 (usually <4 μg/dL) and elevated T_3 resin uptake, but levels of free T_4 and thyrotropin (TSH) are normal. The diagnosis is confirmed by the measurement of absent or low serum levels of TBG, although rare cases may have normal concentrations of TBG with reduced affinity for T_4. No treatment is required, but testing may be indicated in potentially affected family members to avoid the incorrect diagnosis of hypothyroidism in the future. More than 40 different pathogenic variants have been reported in the TBG gene. **Acquired** causes of TBG deficiency are listed in Table 602.1.

TBG excess is a benign X-linked dominant variant that occurs in approximately 1 in 25,000 individuals. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T_4 is elevated, T_3 is variably elevated, TSH and free T_4 are normal, and T_3 resin uptake is decreased. Elevated serum levels of TBG confirm the diagnosis. Affected neonates have been found to have levels of T_4 as high as 95 μg/dL, which decrease to 20-30 μg/dL after 2-3 weeks. Affected patients are euthyroid, but family studies may be indicated to alert other affected family members. Acquired causes of TBG excess are listed in Table 602.1.

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant variant caused by an abnormal albumin with a markedly increased affinity for T_4. This leads to increased serum concentrations of T_4 (and in some cases T_3) that can be mistaken for thyrotoxicosis. However, levels of free T_4, free T_3, and TSH are normal, and affected patients are euthyroid.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 602.1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG
Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Nephrotic syndrome	Heroin, methadone
Protein-losing enteropathy	Mitotane
Nicotinic acid	5-Fluorouracil
L-Asparaginase	Perphenazine

Chapter 603

Hypothyroidism

Ari J. Wassner and Jessica R. Smith

Hypothyroidism is a state of insufficient thyroid hormone action at the tissue level. Hypothyroidism most often results from deficient production of thyroid hormone caused either by a defect in the thyroid gland itself (primary hypothyroidism) or by reduced thyrotropin (TSH) stimulation (central or secondary hypothyroidism; Table 603.1). Hypothyroidism may be present from birth (congenital) or may be acquired, although some acquired cases are due to congenital defects in which the onset of hypothyroidism is delayed.

CONGENITAL HYPOTHYROIDISM

Most cases of congenital hypothyroidism are caused by abnormal formation of the thyroid gland **(thyroid dysgenesis)**, and ~30% of cases are due to inborn errors of thyroid hormone synthesis **(dyshormonogenesis)** or other causes. Most infants with congenital hypothyroidism are detected by newborn screening programs in the first week after birth, before significant clinical signs or symptoms develop. In regions without newborn screening, severely affected infants usually manifest features within the first week of life, but in infants with milder hypothyroidism, the clinical manifestations may not be evident for weeks or months.

Epidemiology

The incidence of congenital hypothyroidism was initially reported to be 1 in 4,000 infants based on the earliest established neonatal screening programs. The incidence of diagnosis has increased to about 1 in 2,000, primarily because more stringent screening algorithms have resulted in the detection of milder cases of hypothyroidism, mostly in patients with a eutopic thyroid gland.

Etiology

See Table 603.1.

Primary Hypothyroidism

Thyroid Dysgenesis. Thyroid dysgenesis is the most common cause of permanent congenital hypothyroidism, accounting for 80–85% of cases. In approximately one third of cases of dysgenesis, no thyroid tissue is present **(agenesis)**. In the other two thirds of infants, rudiments of thyroid tissue are present, either in the normal position **(hypoplasia)** or in an **ectopic** location along the embryologic path of descent of the thyroid from the base of the tongue (lingual thyroid) to the normal position. Thyroid dysgenesis occurs twice as common in females as in males.

The cause of thyroid dysgenesis is largely unknown. The condition is usually sporadic, but familial cases have been reported rarely. Thyroid developmental anomalies, such as thyroglossal duct cysts and thyroid hemiagenesis, are present in 8–10% of first-degree relatives of infants with thyroid dysgenesis. However, most thyroid dysgenesis is unlikely to be genetic given the high degree of discordance among monozygotic twins.

A small minority (2–5%) of thyroid dysgenesis is caused by genetic defects in one of several transcription factors essential for thyroid morphogenesis and differentiation, including NKX2.1 (formerly TTF1), FOXE1 (formerly TTF2), and PAX8. NKX2.1 is expressed in the thyroid, lung, and central nervous system, and recessive pathogenic variants in *NKX2-1* cause thyroid dysgenesis, respiratory distress, and neurologic problems (chorea and ataxia) **(brain-lung-thyroid syndrome)**. Recessive pathogenic variants in *FOXE1* cause thyroid dysgenesis, spiky or curly hair, cleft palate, and sometimes choanal atresia and bifid epiglottis **(Bamforth-Lazarus syndrome)**. PAX8 is expressed in the thyroid and kidney, and dominant *PAX8* variants are associated with thyroid dysgenesis and kidney and ureteral malformations.

Table 603.1 Etiologic Classification of Congenital Hypothyroidism

PRIMARY HYPOTHYROIDISM

Defect of thyroid development (dysgenesis)
- Agenesis
- Hypoplasia
- Ectopia

Defects in thyrotropin (TSH) responsiveness
- TSH receptor–blocking antibodies
- Pathogenic variants in TSH receptor *(TSHR)*
- Defects in Gsα *(GNAS)*—pseudohypoparathyroidism

Defect in thyroid hormone synthesis (dyshormonogenesis)
- Defective iodide uptake into follicular cell: sodium–iodide symporter *(NIS)*
- Defective iodide transport from follicular cell into colloid: Pendred syndrome *(SLC26A4)*
- Iodide organification defects: thyroperoxidase *(TPO)*, dual oxidase 2 (*DUOX2*), dual oxidase maturation factor 2 *(DUOXA2)*
- Thyroglobulin synthesis defect: thyroglobulin (TG)
- Deiodination defect: iodotyrosine deiodinase (IYD)
- Thyroid hormone transport defect: monocarboxylate transporter 8 *(SLC16A2)*—X-linked

Iodine deficiency (endemic goiter)

Iodine excess

Maternal medications
- Iodides, amiodarone
- Methimazole, propylthiouracil
- Radioactive iodine (^{131}I)

CENTRAL (SECONDARY) HYPOTHYROIDISM

Isolated TSH deficiency
- Pathogenic variant in TSH β-subunit (TSHβ)—depending on variant measured TSH level may be low, normal, or elevated
- Pathogenic variant in TRH receptor *(TRHR)*
- Pathogenic variant in *IGSF1*—X-linked central hypothyroidism and macroorchidism (prolactin deficiency and variable GH deficiency)
- Pathogenic variant in other genes: *TBL1X, IRS4*

Multiple pituitary hormone deficiencies
- Pathogenic variant in *POU1F1*—deficiency of TSH, GH, and prolactin
- Pathogenic variant in *PROP1*—deficiency of TSH, GH, LH, FSH, prolactin, and variably ACTH
- Pathogenic variant in *HESX1*—variable deficiencies of TSH, GH, LH, FSH, prolactin, and ACTH
- Pathogenic variants in other genes: *OTX2, LHX3, LHX4, SOX3, FGF8, FGFR1, GLI2, LEPR*

ACTH, Adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone.

Inactivating variants in the TSH receptor *(TSHR)* have been described in patients with congenital hypothyroidism, including thyroid dysgenesis or hypoplasia. *TSHR* variants may be homozygous or heterozygous with or without a concurrent change in another congenital hypothyroidism gene (such as *DUOX2* or *TG*). Infants with a severe TSHR defect have elevated TSH levels and are detected by newborn screening, whereas patients with a mild defect may remain euthyroid without treatment.

Congenital hypothyroidism can occur in infants with **pseudohypoparathyroidism** type 1a. These patients have somatic inactivating variants of the G-protein stimulatory α-subunit $G_s\alpha$ (GNAS), leading to impaired signaling of the TSH receptor (see Chapter 612).

Defects in Thyroid Hormone Synthesis (Dyshormonogenesis). A variety of defects in thyroid hormone biosynthesis account for 15% of cases of permanent congenital hypothyroidism detected by neonatal screening programs (1 in 30,000-50,000 live births). Because increased TSH stimulation has a trophic effect on thyroid follicular cells, a **goiter** is often present. When the synthetic defect is incomplete, the onset of hypothyroidism may be delayed for months or years.

Defective Iodide Transport. Rare defects in iodide uptake are caused by pathogenic variants in the sodium-iodide symporter (NIS) responsible for concentrating iodide in the thyroid gland. In contrast to other defects of thyroid hormone synthesis, uptake of radioiodine and pertechnetate is low, as in cases of thyroid dysgenesis. However, impaired iodide transport may be suggested by the absence of normal salivary gland iodine uptake on scintigraphy. A reduced saliva:serum ratio of ^{123}I supports the diagnosis, which can be confirmed by genetic testing of *NIS*. This condition may respond to large doses of potassium iodide, but treatment with levothyroxine is more reliable and preferable.

Pendred syndrome is a clinical syndrome consisting of sensorineural deafness and goiter. This syndrome is caused by a pathogenic variant in the chloride-iodide transport protein pendrin *(SLC26A4)* expressed in the thyroid gland and the cochlea. Pendrin allows the transport of iodide across the apical membrane of the thyroid follicular cell into the colloid, where it undergoes organification and incorporation into the tyrosine residues on thyroglobulin. Patients with a variant in *SLC26A4* have impaired iodide organification and a positive perchlorate discharge test. Pathogenic variants in pendrin are a relatively common genetic cause of sensorineural deafness, but some patients diagnosed based on their hearing disorder have no goiter or thyroid dysfunction. This finding has fueled speculation that pendrin is not the sole apical iodine transporter in the thyroid, but no other specific transporter has been confirmed to date.

Defects of Iodine Organification. Defects of iodine organification are the most common type of thyroid hormone synthetic defect. After the thyroid takes up iodide, it is rapidly oxidized and incorporated into tyrosine residues on thyroglobulin. These reactions are catalyzed by the key enzyme thyroperoxidase (TPO) and require H_2O_2 generated locally by the dual oxidase 2 system (DUOX2 and DUOXA2). Defects can occur in any of these components of organification, and there is considerable clinical and biochemical heterogeneity. In the Dutch neonatal screening program, a complete organification defect was present in 1 in 60,000 live births, but the prevalence in other areas is unknown. A characteristic finding of organification defects is a marked discharge of thyroid radioactivity when perchlorate or thiocyanate is administered 2 hours after a test dose of radioiodine (perchlorate discharge of 40–90% of radioiodine compared with <10% in normal individuals). Numerous pathogenic variants in *TPO* have been reported in children with congenital hypothyroidism.

Pathogenic variants in *DUOX2* can cause permanent or transient congenital hypothyroidism. Previously, it was thought that monoallelic *DUOX2* variants cause transient disease and biallelic variants cause permanent disease, but the reverse has been observed in some cases, and this relationship remains variable and unclear. *DUOX2* variants have been reported in 15–40% of patients with apparent dyshormonogenesis, with pathogenic variant rates as high as 50–60% in studies from China and South Korea. Dual oxidase maturation factor 2 (DUOXA2) is required to express DUOX2 enzymatic activity, and recessive variants in *DUOXA2* are a rare cause of congenital hypothyroidism.

Defects of Thyroglobulin Synthesis. Defects of thyroglobulin synthesis are characterized by congenital hypothyroidism with goiter and absent or low levels of circulating thyroglobulin. More than 40 different pathogenic variants in the thyroglobulin gene *(TG)* have been described.

Defects in Deiodination. Monoiodotyrosine and diiodotyrosine normally are released from thyroglobulin along with thyroxine (T_4) and triiodothyronine (T_3). The *IYD* gene (formerly *DEHAL1*) encodes the thyroidal enzyme iodotyrosine deiodinase, which deiodinates these intermediates so that the liberated iodide is recycled into thyroid hormone synthesis. In patients with rare variants in *IYD,* urinary excretion of monoiodotyrosine and diiodotyrosine rapidly causes severe iodine deficiency, leading to hypothyroidism and goiter that may present soon after birth or may be delayed.

Defects in Thyroid Hormone Transport. Passage of thyroid hormone into cells is facilitated by specific plasma membrane transporters. Pathogenic variants in the transporter MCT8 *(SLC16A2),* located on the X chromosome, impair the movement of T_4 and T_3 into cells. This leads to severe neurologic manifestations, including profound developmental delay, reduced muscle mass, dysarthria,

athetoid movements, and hypotonia that evolves to spastic paraplegia **(Allan-Herndon-Dudley syndrome)**. This syndrome is also characterized by low serum T_4 levels, normal or mildly elevated serum TSH levels, and elevated serum T_3 levels. Treatment with thyroid hormone analogs that do not require MCT8 for transmembrane transport can improve hypermetabolism in this disorder but has little effect on the neurologic phenotype.

Thyrotropin Receptor–Blocking Antibodies. Maternal TSHR–blocking antibodies (TRBAbs) cause about 2% of cases of congenital hypothyroidism detected by neonatal screening programs (1 in 50,000-100,000 infants). Transplacentally acquired maternal TRBAbs inhibit the binding of TSH to its receptor in the neonate. This condition should be suspected whenever there is a history of maternal autoimmune thyroid disease, including autoimmune thyroiditis or Graves disease, maternal hypothyroidism, or transient congenital hypothyroidism in previous siblings. However, TRBAbs can occur in the absence of any maternal history. When suspected, levels of TRBAb (measured as thyrotropin-binding inhibitory immunoglobulin [TBII]) should be measured in the mother during pregnancy or after birth in the neonate. Affected infants and their mothers also can have TSHR-stimulating antibodies and TPO antibodies. Ultrasonography typically demonstrates a normally positioned but small thyroid gland; however, thyroid tissue often will not be detected by scintigraphy because the blockade of TSHR function suppresses thyroidal iodine uptake. Serum thyroglobulin levels are low for the same reason. Treatment with levothyroxine is required initially, but remission of hypothyroidism occurs in approximately 3-6 months once the TRBAbs are cleared from the infant's circulation. Correct diagnosis of this cause of congenital hypothyroidism prevents unnecessarily protracted treatment and alerts the clinician to possible recurrences in future pregnancies. The prognosis is generally favorable, but developmental delay may occur in patients whose mothers had unsuspected (and untreated) hypothyroidism caused by TRBAbs during pregnancy.

Radioiodine Administration. Neonatal hypothyroidism can occur when radioiodine is administered to a mother during (a usually unrecognized) pregnancy as treatment for Graves disease or thyroid cancer. The fetal thyroid is capable of trapping iodide by 70-75 days of gestation. Therefore a pregnancy test must be performed in any individual capable of pregnancy before ^{131}I is given, regardless of menstrual history or reported history of contraception. Administration of radioactive iodine to lactating individuals is also contraindicated because it is excreted in breast milk.

Iodine Exposure. Congenital hypothyroidism can result from fetal exposure to excessive iodine. Perinatal exposure can occur from iodine-based antiseptic used to prepare the skin for cesarean section or to paint the cervix before delivery. In the neonate, especially in those of low birthweight (LBW), topical iodine-containing antiseptics used in nurseries or perioperatively can cause transient hypothyroidism, which newborn screening tests may detect. In older children, excess iodine may be present in proprietary preparations used to treat asthma or in amiodarone, an antiarrhythmic drug with high iodine content. In most of these instances, a goiter is present (see Chapter 605). Hypothyroidism has also been reported in breastfed infants born to mothers who consume large amounts of iodine daily (up to 12 mg) in nutritional supplements or large quantities of iodine-rich seaweed. Iodine-induced hypothyroidism is transient once the exposure is discontinued and therefore is important to distinguish from other forms of congenital hypothyroidism.

Iodine Deficiency (Endemic Goiter). See Chapter 605.3.

Iodine deficiency or endemic goiter is the most common cause of congenital hypothyroidism worldwide. The recommended iodine intake in adults is 150 μg daily, increasing to 220 μg daily during pregnancy to allow for fetal iodine requirements. Despite efforts at universal salt iodization, in many countries economic, political, and practical obstacles continue to prevent the realization of this goal. Although the U.S. population is generally iodine sufficient, approximately 15% of women of reproductive age are iodine deficient. Borderline iodine deficiency is more likely to cause problems in preterm infants, who depend on a maternal source of iodine for normal thyroid hormone production and often receive insufficient dietary iodine from standard preterm infant formulas or parenteral nutrition that is low in iodine.

Central (Secondary) Hypothyroidism

Thyrotropin (TSH) Deficiency. Central hypothyroidism caused by TSH deficiency can occur in any condition associated with developmental defects of the pituitary or hypothalamus (see Chapter 595). Central hypothyroidism occurs in 1 in 16,000-30,000 infants. However, neonatal screening does not detect many cases, mainly because many screening programs are designed to detect only primary hypothyroidism by measuring neonatal TSH. The majority (75%) of infants with central hypothyroidism have additional pituitary hormone deficiencies and may present with hypoglycemia, persistent jaundice, micropenis or cryptorchidism (in males), and midline defects such as midline cleft lip or palate or midface hypoplasia.

Congenital TSH deficiency may be caused by pathogenic variants in genes encoding transcription factors essential to pituitary development or thyrotroph cell differentiation. *POU1F1* variants cause deficiency of TSH, growth hormone, and prolactin. Patients with *PROP1* variants also have deficiency of TSH, growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and variable deficiency of adrenocorticotropic hormone. *HESX1* pathogenic variants are associated with TSH, growth hormone, prolactin, and adrenocorticotropic hormone deficiencies and are found in some patients with optic nerve hypoplasia (septo-optic dysplasia syndrome; see Chapter 631). Variants in multiple other genes involved in pituitary development can cause central hypothyroidism (Table 603.1).

Isolated congenital deficiency of TSH is rare. The most common genetic cause is a pathogenic variant in *IGSF1,* which results in an X-linked syndrome of congenital central hypothyroidism and macroorchidism. The mechanism remains unclear, but IGSF1 deficiency may impair TRH receptor signaling in pituitary thyrotrophs. Prolactin deficiency is usually present, and some patients also have growth hormone deficiency. Central hypothyroidism occurs in about 10% of female carriers of IGSF1 deficiency. Patients with pathogenic variants in the gene encoding the TSH β-subunit *(TSHB)* have central hypothyroidism with very low TSH levels, although in some cases, TSH levels are normal or even elevated. In other cases, levels of the TSH α-subunit are elevated. Variants in *TRHR,* which encodes the TRH receptor, are a rare cause of congenital central hypothyroidism. In this condition, both TSH and prolactin fail to respond to TRH stimulation.

Thyroid Function in Preterm and Low Birthweight Infants

Postnatal thyroid function in preterm and LBW infants is qualitatively similar but quantitatively reduced compared with term infants. The cord blood T_4 concentration is decreased in proportion to gestational age and birthweight. The postnatal TSH surge is reduced, and very premature or very LBW infants experience a decrease in serum T_4 in the first week of life, in contrast to term infants in whom T_4 increases during this time. Serum T_4 gradually increases to the range observed in term infants by about 6 weeks of life. However, serum free T_4 concentrations are less affected than total T_4, and free T_4 levels may be normal when measured by the gold standard technique of equilibrium dialysis. Preterm and LBW infants also have a higher incidence of delayed TSH elevation and apparent transient primary hypothyroidism. Mechanisms underlying these changes in thyroid function in preterm and LBW infants may include immaturity of the hypothalamic-pituitary-thyroid axis, loss of the maternal contribution of thyroid hormone normally present in the third trimester, severe illness and complications of prematurity, and exposure to medications that can affect thyroid function (e.g., dopamine and glucocorticoids).

Clinical Manifestations

Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn because most affected infants are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This is because of transplacental passage of maternal T_4, which provides fetal levels that are approximately one-third normal at

birth. Because symptoms are usually not present at birth, the clinician depends on neonatal screening tests to diagnose congenital hypothyroidism. However, some infants escape newborn screening, and laboratory errors occur, so pediatricians must be alert for symptoms and signs of hypothyroidism if they develop. Birth weight and length are normal, but head size may be slightly increased because of myxedema of the brain. The anterior and posterior fontanels are open widely, and the presence of this sign at birth may be a clue to early recognition of congenital hypothyroidism (only 3% of normal newborns have a posterior fontanel wider than 0.5 cm). Prolonged jaundice (indirect hyperbilirubinemia) may be present because of delayed maturation of hepatic glucuronide conjugation. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. Feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking spells during nursing, may be present during the first month of life. Respiratory difficulties, partly caused by macroglossia, include apneic episodes, noisy respirations, and nasal obstruction. There may be constipation that does not respond to treatment. The abdomen is large, and an umbilical hernia is often present. The temperature may be subnormal (often <35°C/95°F), and the skin may be cold and mottled, particularly on the extremities. Edema of the genitals and extremities may be present. The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common. Macrocytic anemia is often present. Because symptoms appear gradually and may be nonspecific, the clinical diagnosis of neonatal hypothyroidism is often delayed.

Approximately 10% of infants with congenital hypothyroidism have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported. Infants with congenital hypothyroidism may have associated hearing loss. Pathogenic variants in specific genes involved in thyroid gland development result in congenital hypothyroidism with other syndromic features (Table 603.2).

If congenital hypothyroidism goes undetected and untreated, the clinical manifestations progress. Delay of physical and mental development becomes more severe over time, and by 3-6 months of age, the clinical picture is fully developed (Fig. 603.1). When deficiency of thyroid hormone is only partial, the symptoms may be milder and their onset delayed. Although breast milk contains significant amounts of thyroid hormones, particularly T_3, this is inadequate to protect the breastfed infant from the effects of congenital hypothyroidism.

In the patient with untreated congenital hypothyroidism, growth is stunted, extremities are short, and head size is normal or increased. The anterior fontanel is large, and the posterior fontanel may remain open. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow, and the eyelids are swollen. The mouth is kept open, and the thick, broad tongue protrudes. Dentition is delayed. The neck is short and thick, and there may be fat deposits above the clavicles and between the neck and shoulders. The hands are broad, and the fingers are short. The skin is dry and scaly, and there is little perspiration. Myxedema occurs mainly in the skin of the eyelids, the back of the hands, and the external genitalia. The skin shows general pallor with a sallow complexion. Carotenemia can cause a yellow discoloration of the skin, but the sclerae remain white. The scalp is thickened, and the hair is coarse, brittle, and scanty. The hairline reaches far down on the forehead, which usually appears wrinkled, especially when the infant cries.

Development is usually delayed. Hypothyroid infants appear lethargic and are late in acquiring gross and fine motor skills. The voice is hoarse, and they do not learn to talk. The degree of physical and intellectual delay increases with age. Sexual maturation may be delayed or even absent. The muscles are usually hypotonic, but in rare instances, generalized muscular pseudohypertrophy occurs **(Kocher-Debré-Sémélaigne syndrome)**. Affected older children can have an athletic appearance because of pseudohypertrophy, particularly in the calf muscles. Its pathogenesis is unknown; nonspecific histochemical and ultrastructural changes seen on muscle biopsy return to normal with treatment.

Some infants with mild congenital hypothyroidism have normal thyroid function at birth and are not identified by newborn screening programs. In particular, some children with ectopic thyroid tissue produce adequate amounts of thyroid hormone for some time (even years) until the abnormal thyroid tissue fails. Affected children come to clinical attention because of a growing mass at the base of the tongue or in the midline of the neck, often at the level of the hyoid. Occasionally, thyroid ectopy is associated with **thyroglossal duct cysts**. Surgical removal of ectopic thyroid tissue from a euthyroid patient usually results in hypothyroidism because most such patients have no other thyroid tissue.

Laboratory Findings

In countries where newborn screening is performed, this is the most important method for identifying infants with congenital hypothyroidism. Blood obtained by heelprick between 1 and 5 days of life is placed on a filter paper card and sent to a central screening laboratory. Most

Table 603.2 Genes and Thyroid Development

GENE	THYROID PHENOTYPE	OTHER FEATURES
FOXE1	Athyreosis	Cleft palate, choanal atresia, kinky hair, bifid epiglottis
NKX2-1	Athyreosis to normal gland	Respiratory distress syndrome, developmental delays/hypotonia, ataxia/choreoathetosis
PAX8	Athyreosis to normal gland	Cysts within thyroid remnants, kidney and urinary tract malformations
GLIS3	Athyreosis to normal gland	Congenital glaucoma; deafness; liver/kidney and pancreatic abnormalities
TSHR	Athyreosis to normal gland	None
NKX2-5	Athyreosis, ectopy	Cardiac defects

From Kim G, Nandi-Munshi D, Diblasi CC. Disorders of the thyroid gland. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*, 10th ed. Philadelphia: Elsevier; 2018, Table 98.3, p. 1396.

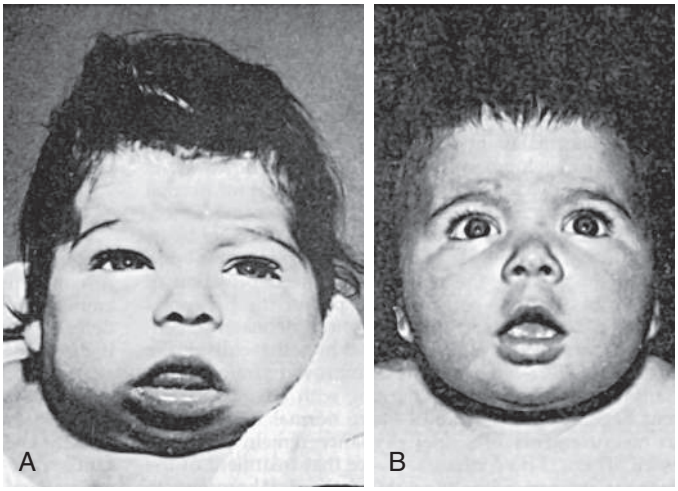

Fig. 603.1 Congenital hypothyroidism in an infant 6 mo of age. The infant ate poorly in the neonatal period and was constipated. She had persistent nasal discharge and a large tongue, was very lethargic, and had no social smile and no head control. **A,** Notice the puffy face, dull expression, and hirsute forehead. Tests revealed a negligible uptake of radioiodine. Osseous development was that of a newborn. **B,** Four months after treatment, note decreased face puffiness, decreased hirsutism of the forehead, and the alert appearance.

screening programs measure the level of TSH, which detects infants with primary hypothyroidism, including some with milder disease in whom TSH is elevated but T_4 is normal. However, this approach may not detect rarer disorders such as central hypothyroidism or primary congenital hypothyroidism with delayed TSH elevation. Some screening programs begin by measuring levels of T_4, followed by reflex measurement of TSH when the T_4 is low. This approach identifies infants with primary hypothyroidism, some with central hypothyroidism or delayed TSH elevation, and infants with thyroxine-binding globulin deficiency (a benign variant). All newborn screening results should be interpreted based on age-specific reference ranges, particularly in the first week of life (Table 603.3). Regardless of the approach used for screening, some infants escape detection because of technical or human errors, and clinicians must remain vigilant for clinical manifestations of hypothyroidism.

Several groups of patients deserve vigilance for congenital hypothyroidism. Infants with trisomy 21 or cardiac defects have an increased risk of congenital hypothyroidism. Monozygotic twins are usually *discordant* for congenital hypothyroidism. However, if twins are monochorionic, fetal hypothyroidism in the affected twin may be compensated by the normal twin through their shared fetal circulation. In such cases, the affected twin may go undetected on newborn screening in the first days of life and present later with untreated hypothyroidism. Preterm and LBW neonates have an increased incidence of congenital hypothyroidism and are more likely to have delayed TSH elevation that may be missed on initial screening. Therefore in all of these groups of infants, many newborn screening programs perform a routine second test 2-4 weeks after birth.

Patients with congenital hypothyroidism have low serum levels of T_4 and free T_4. Serum levels of T_3 are often normal and are not helpful for diagnosis. If primary hypothyroidism is present, levels of TSH are elevated, often to >100 mU/L in severe cases. Serum levels of thyroglobulin are usually low in infants with thyroid agenesis, defects of the TSH receptor (including *TSHR* pathogenic variants and TRBAb), or defects in the synthesis or secretion of thyroglobulin itself. In contrast, thyroglobulin levels are usually elevated in patients with thyroid ectopy and other defects of thyroid hormone synthesis, but there is a wide overlap of ranges.

Delay of osseous development can be shown radiographically at birth in approximately 60% of congenitally hypothyroid infants and indicates some deficiency of thyroid hormone during intrauterine life. The distal femoral and proximal tibial epiphyses, normally present at birth, are often absent (Fig. 603.2A). In untreated patients, the discrepancy between chronologic age and osseous development increases over time. The epiphyses often have multiple foci of ossification (epiphyseal dysgenesis; see Fig. 603.2B). Deformity (beaking) of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X-rays of the skull show large fontanels and wide sutures, and intersutural (wormian) bones are common. The sella turcica may be enlarged and round, and in rare instances, there may be bony erosion and thinning. Formation and eruption of teeth can be delayed. Cardiac enlargement or pericardial effusion may be present.

Scintigraphy can help define the underlying cause in infants with congenital hypothyroidism, but treatment should not be delayed to obtain such imaging. ^{123}I–sodium iodide is superior to ^{99m}Tc–sodium pertechnetate for this purpose. Scintigraphy will demonstrate an ectopic thyroid gland, but the absence of uptake in disorders of the TSH receptor (including TRBAb) or NIS may be mistaken for thyroid agenesis. Ultrasound of the thyroid can document the presence or absence of an anatomically normal gland, but it can miss some ectopic glands that are detectable by scintigraphy. Demonstration of ectopic thyroid tissue or the absence of thyroid tissue in its normal location is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment. A normally located thyroid gland with normal or increased uptake indicates a defect in thyroid hormone synthesis. Although extensive evaluation can be performed to elucidate the precise nature of the synthetic defect, this rarely affects clinical management and is unnecessary in most cases. Similarly, genetic testing may reveal potentially relevant variants in 60% or more of patients with defects of thyroid hormone synthesis. However, such testing may be costly, is not always conclusive, and usually does not alter management.

Treatment

Levothyroxine (L-T_4) given orally is the treatment for congenital hypothyroidism. Although T_3 is the biologically active form of thyroid hormone, 80% of circulating T_3 is derived from deiodination of circulating T_4, and therefore treatment with L-T_4 alone restores normal serum levels of T_4 and T_3. The recommended initial dose of L-T_4 is 10-15 μg/kg/day (37.5-50 μg/day for most term infants), and within this range the starting dose can be adjusted based on the severity of hypothyroidism. Newborns with more severe hypothyroidism, as judged by a serum T_4 <5 μg/dL and/or imaging studies confirming aplasia, should be started at the higher end of the dosage range. Rapid normalization of thyroid function (ideally within 2 weeks) is essential in achieving optimal neurodevelopmental outcomes. Lower doses of L-T_4 (8-10 mcg/kg/day) may be considered for infants with mild hypothyroidism (mildly elevated TSH and normal free T_4).

L-T_4 should be prescribed in tablet form. A liquid L-T_4 preparation has been approved, but optimal dosing may differ slightly from the tablet form. Tablets should be crushed and mixed with a small volume (1-2 mL) of liquid. L-T_4 tablets should not be mixed with soy protein formulas, concentrated iron, or calcium because these can inhibit L-T_4 absorption. Although it is often recommended to administer L-T_4 on an empty stomach and avoid food for 30-60 minutes, this is not practical in an infant. As long as the method of administration is consistent, dosing can be adjusted based on serum thyroid test results to achieve the desired treatment goals. One trial has suggested that brand-name L-T_4 may be superior to generic formulations in children with severe congenital hypothyroidism.

The goals of treatment are to maintain serum TSH in the reference range for age and the serum free T_4 or total T_4 in the upper half of the reference range for age (see Table 603.3). Levels of serum T_4 or free T_4 and TSH should be monitored at recommended intervals (every 1-2 months in the first 6 months of life, and then every 2-4 months between 6 months and 3 years of age). Care should be taken to avoid undertreatment, which has been related to adverse neurodevelopmental outcomes, including decreased intelligence quotient (IQ).

About 35% of infants with congenital hypothyroidism and a normally located thyroid gland have transient disease and do not require lifelong therapy. In patients who might have transient disease, a trial of L-T_4 may be undertaken after 3 years of age for 4 weeks to assess whether the TSH rises significantly, indicating the presence of permanent hypothyroidism. Such a trial is unnecessary in infants with proven thyroid dysgenesis or in those who have previously manifested elevated levels of TSH after 6-12 months of therapy because of poor medication adherence or an inadequate dose of T_4.

Prognosis

Thyroid hormone is critical for normal neurodevelopment, particularly in the early postnatal months. Prompt diagnosis and initiation of adequate treatment of congenital hypothyroidism in the first 2 weeks of life are essential to prevent irreversible brain damage and normal growth and development. In most infants detected by newborn screening, verbal development, psychomotor development, and global IQ scores are similar to unaffected siblings. However, the most severely affected newborns—those with the lowest T_4 levels and most delayed skeletal maturation—may have reduced IQ and other neuropsychologic sequelae such as incoordination, hypotonia or hypertonia, or problems with attention or speech despite early diagnosis and adequate treatment. Psychometric testing can show problems with vocabulary and reading comprehension, arithmetic, and memory. Approximately 10% of children with congenital hypothyroidism have a neurosensory hearing deficit. Outcome studies in adults diagnosed and treated as neonates reveal delayed social development, lower self-esteem, and a lower health-related quality of life. The latter appears to be related to those individuals with lower neurocognitive outcomes and associated congenital malformations.

Delay in diagnosis or treatment, failure to rapidly correct the initial hypothyroidism, inadequate treatment, or poor adherence to treatment

Table 603.3 Thyroid Function Tests

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 μg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 μg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 μg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 μg/L
THYROID-STIMULATING HORMONE, SERUM			
Premature Infants (28-36 wk)			
First wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
Term Infant			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
Full-Term Infants			
1-3 days	8.2-19.9 μg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 μg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 μg/dL	×12.9	79-192 nmol/L
Prepubertal Children			
1-3 yr	6.8-13.5 μg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 μg/dL	×12.9	71-165 nmol/L
Pubertal Children and Adults			
>10 yr	4.2-13.0 μg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 μg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L
1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT_3U), SERUM			
Newborn	26–36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26–35%	×0.01	0.26-0.35 fractional uptake

Continued

Table 603.3 Thyroid Function Tests—cont'd

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA. Reference ranges for laboratory tests and procedures. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*, 17th ed. Philadelphia: WB Saunders; 2004:2412–2413; TSH from Lem AJ, de Rijke YB, van toor H, et al. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *J Clin Endocrinol Metab*. 2012;97:3170–3178; Free T_3 from Elmlinger MW, Kuhnel W, Lambrecht H-G, et al. Reference intervals from birth to adulthood for serum thyroxine (T_4), triiodothyronine (T_3), free T_3, free T_4, thyroxine binding globulin (TBG), and thyrotropin (TSH). *Clin Chem Lab Med*. 2001;39:973–979.

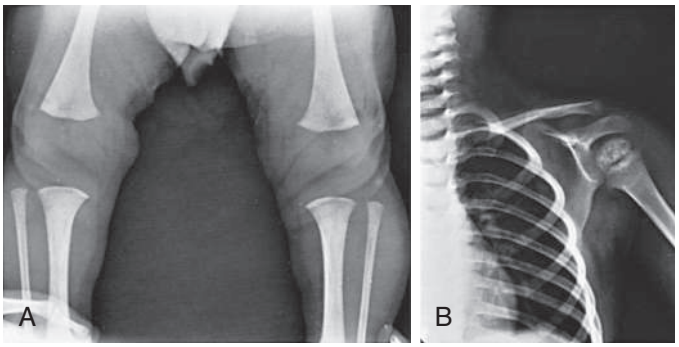

Fig. 603.2 Congenital hypothyroidism. **A,** Absence of distal femoral epiphyses in a 3-mo-old infant who was born at term. This is evidence for onset of the hypothyroid state during fetal life. **B,** Epiphyseal dysgenesis in the head of the humerus in a 9-yr-old girl who had been inadequately treated with thyroid hormone.

in the first 2-3 years of life may result in variable degrees of neurodevelopmental impairment. Without treatment, severely affected infants have profound intellectual disability and growth stunting. When hypothyroidism develops after 2 years of age, the outlook for neurodevelopment is much better even if diagnosis and treatment are delayed, which illustrates the critical dependence of brain development on thyroid hormone in the first year of life.

ACQUIRED HYPOTHYROIDISM

Epidemiology

Hypothyroidism occurs in approximately 0.3% (1 in 333) of school-age children. *Subclinical hypothyroidism* (defined as an elevated TSH with normal T_4 or free T_4) is more common, occurring in approximately 2% of adolescents. Autoimmune thyroiditis is the most common cause of acquired hypothyroidism: 6% of children age 12-19 years have evidence of autoimmune thyroiditis, and females are twice as likely to be affected as males. Although this condition typically arises in adolescence, it may present as early as the first year of life.

Etiology

The most common cause of acquired hypothyroidism (Table 603.4) is **autoimmune thyroiditis** (also called *Hashimoto* or *chronic lymphocytic thyroiditis*; see Chapter 604). Children with trisomy 21, Turner syndrome, Klinefelter syndrome, celiac disease, or type 1 diabetes mellitus are at higher risk for associated autoimmune thyroid disease (see Chapter 604), as are those with **autoimmune polyglandular syndromes** (**APSs**; see Chapter 608). APS type 1 (APS-1) is a rare autosomal recessive disorder caused by pathogenic variants in *AIRE*. It is classically characterized by the triad of mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency. Autoimmune thyroiditis is a less common feature (~10%), as are type 1 diabetes mellitus, primary hypogonadism, pernicious anemia, vitiligo, alopecia, nephritis, hepatitis, and gastrointestinal dysfunction. APS type 2 (APS-2) is far more common than APS-1, and its pathogenesis remains an obscure combination of genetic and environmental factors. APS-2 may consist of any combination of autoimmune thyroiditis (~70%), type 1 diabetes mellitus, celiac disease, or less common manifestations such as primary adrenal insufficiency, primary hypogonadism, pernicious anemia, and vitiligo. Patients with any of these other autoimmune conditions are at increased risk of developing hypothyroidism. For example, about 20% of children with **type 1 diabetes mellitus** develop thyroid autoantibodies and about 5% become hypothyroid.

In children with **trisomy 21**, thyroid autoantibodies develop in approximately 30%, and subclinical or overt hypothyroidism occurs in approximately 15–20%. In females with **Turner syndrome**, thyroid autoantibodies

Table 603.4 Etiologic Classification of Acquired Hypothyroidism

- Autoimmune
  - Autoimmune thyroiditis (Hashimoto thyroiditis)
  - Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)
  - IPEX
  - Celiac disease
- Drug-induced
  - Excess iodide: amiodarone, nutritional supplements, expectorants
  - Anticonvulsants: oxcarbazepine, phenytoin, phenobarbital, valproate
  - Antithyroid drugs: methimazole, propylthiouracil
  - Miscellaneous: lithium, rifampin, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, aminoglutethimide, dopamine, amiodarone, tetracycline, ipilimumab, nivolumab
- Iatrogenic
  - Irradiation (e.g., cancer therapy, bone marrow transplant)
  - Radioactive iodine (^{131}I)
  - Thyroidectomy
- Systemic infiltrative disease
  - Cystinosis
  - Langerhans cell histiocytosis
- Consumptive: inactivation of thyroid hormone by large liver hemangiomas (type 3 deiodinase)
- Decreased sensitivity to thyroid hormone (*MCT8, SEC16A2, THRA, THRB* pathogenic variants)
- Hypothalamic-pituitary disease (often with multiple pituitary hormone deficiencies)
  - Central nervous system tumors (e.g., craniopharyngioma)
  - Meningoencephalitis
  - Cranial irradiation
  - Head trauma
  - Langerhans cell histiocytosis

IPEX, Immunodysregulation polyendocrinopathy X-linked.

develop in approximately 40%, and subclinical or overt hypothyroidism occurs in approximately 15–30%, rising with increasing age. Additional autoimmune conditions with an increased risk of hypothyroidism include immune dysregulation–polyendocrinopathy–enteropathy–X-linked syndrome (IPEX) and IPEX-like disorders, immunoglobulin G_4–related diseases, Sjögren syndrome, and multiple sclerosis. **Williams syndrome** is associated with subclinical hypothyroidism, but this does not appear to be autoimmune, and thyroid autoantibodies are absent.

Medications can cause acquired hypothyroidism. Some medications containing iodine (e.g., expectorants or nutritional supplements) may cause hypothyroidism through the Wolff-Chaikoff effect (see Chapter 605). Amiodarone, a drug used for cardiac arrhythmias and consisting of 37% iodine by weight, causes hypothyroidism in approximately 20–30% of treated children. Children treated with amiodarone should have serial monitoring of thyroid function.

Anticonvulsants, including phenytoin, phenobarbital, and valproate, may cause thyroid dysfunction, usually in the form of subclinical hypothyroidism. In some cases, this is because of their effect of stimulating hepatic cytochrome P450 metabolism and excretion of T_4. The anticonvulsant oxcarbazepine can cause central (secondary) hypothyroidism. Hypothyroidism can be caused by overtreatment with antithyroid drugs (methimazole or propylthiouracil) for Graves disease. Additional drugs that can produce hypothyroidism include lithium, rifampin, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, and aminoglutethimide.

Children who receive **therapeutic irradiation**, such as for Hodgkin disease or other head and neck malignancies or before bone marrow transplantation, are at risk for thyroid damage and hypothyroidism. Approximately 30% of such children acquire elevated TSH levels within a year after therapy, and another 15–20% progress to hypothyroidism within 5-7 years. **Radioactive iodine** ablative treatment or **thyroidectomy** for Graves disease or thyroid cancer results in iatrogenic hypothyroidism. Thyroid tissue in a thyroglossal duct cyst may constitute the only source of thyroid hormone, and in this case, excision of the cyst results in hypothyroidism. Ultrasonographic examination or a radionuclide scan before surgery is indicated in these patients.

Children with **nephropathic cystinosis,** a disorder characterized by intralysosomal storage of cystine in body tissues, acquire impaired thyroid function. Hypothyroidism is usually subclinical but may be overt, and periodic assessment of TSH levels is indicated. By 13 years of age, two thirds of these patients require L-T_4 replacement.

Histiocytic infiltration of the thyroid in children with **Langerhans cell histiocytosis** (see Chapter 556.1) can result in hypothyroidism. Children with chronic **hepatitis C infection** are at risk for subclinical hypothyroidism that does not appear to be autoimmune.

Consumptive hypothyroidism can occur in children with large hemangiomas of the liver. These tumors may express massive amounts of the enzyme type 3 deiodinase, which inactivates T_4 and T_3, respectively, to the inert metabolites reverse T_3 and diiodothyronine (T_2). Hypothyroidism occurs when increased thyroidal secretion of thyroid hormones is insufficient to compensate for their rapid inactivation.

Some patients with mild forms of congenital hypothyroidism (thyroid dysgenesis or genetic defects in thyroid hormone synthesis) do not develop clinical manifestations until childhood. Although these conditions are often detected by newborn screening, very mild defects can escape detection and present later with apparently acquired hypothyroidism.

Any **hypothalamic** or **pituitary** disease can cause acquired central hypothyroidism (see Chapter 595). TSH deficiency may result from a hypothalamic-pituitary tumor (craniopharyngioma is most common in children) or from treatment for a tumor. Central hypothyroidism may develop in up to 10% of children receiving craniospinal irradiation. Other causes include head trauma or infiltrative diseases affecting the pituitary gland, such as Langerhans cell histiocytosis.

Clinical Manifestations

Slowing of growth is usually the first clinical manifestation of acquired hypothyroidism, but this sign often goes unrecognized (Figs. 603.3 and 603.4). Goiter is a common presenting feature of primary hypothyroidism. In autoimmune thyroiditis, the thyroid is typically nontender

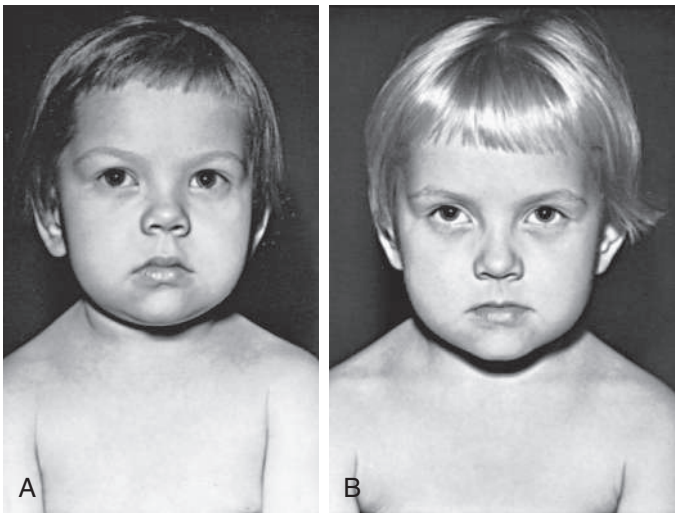

Fig. 603.3 **A,** Acquired hypothyroidism in a 6-yr-old female. She was treated with a wide variety of hematinics for refractory anemia for 3 years. She had almost complete cessation of growth, constipation, and sluggishness for 3 years. The height age was 3 years; the bone age was 4 years. She had a sallow complexion and immature facies with a poorly developed nasal bridge. Serum cholesterol, 501 mg/dL; radioiodine uptake, 7% at 24 hr; protein-bound iodine *(PBI),* 2.8 mg/dL. **B,** After therapy for 18 months, note the nasal development, increased luster and decreased pigmentation of hair, and maturation of the face. The height age was 5.5 years; the bone age was 7 years. There was a decided improvement in her general condition. Menarche occurred at 14 years. The ultimate height was 155 cm (61 in). She graduated from high school. The disorder was well controlled with daily L-thyroxine.



Fig. 603.4 **A,** This 12-yr-old male with hypothyroidism has short stature (108 cm, <3rd percentile), generalized myxedema, sleepy expression, protuberant abdomen, and coarse hair. Body proportions are immature for his age (1.25:1). **B,** Same boy 4 months after treatment. His height increased by 4 cm, and there is a marked change in body habitus owing to loss of myxedema, improved muscle tone, and bright facial expression. *(From LaFranchi SH. Hypothyroidism. Pediatr Clin North Am. 1979;26:33–51.)*

and firm, with a rubbery consistency and pebbly (bosselated) surface. Weight gain is mainly caused by fluid retention (myxedema), not true adiposity. Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. School performance usually does not suffer, even in severely hypothyroid children. Additional features may include bradycardia, muscle weakness or cramps, nerve entrapment, and ataxia. Skeletal maturation is delayed, and the degree of delay reflects the duration of the hypothyroidism. Adolescents typically have delayed puberty. Older adolescent females may have menometrorrhagia, and some may develop galactorrhea because of increased TRH, which stimulates prolactin secretion. In fact, long-standing primary hypothyroidism can result in enlargement of the pituitary gland, sometimes leading to headaches and vision problems. This is believed to result from thyrotroph hyperplasia but may be mistaken for a pituitary tumor, particularly a prolactinoma if prolactin is elevated (see Chapter 595). Rarely, young children with profound hypothyroidism may develop secondary sex characteristics (pseudoprecocious puberty), including breast development or vaginal bleeding in females and testicular enlargement in males. It is hypothesized that this phenomenon results from abnormally high concentrations of TSH binding and stimulating the follicle-stimulating hormone receptor.

Laboratory abnormalities in hypothyroidism may include hyponatremia, macrocytic anemia, hypercholesterolemia, and elevated creatine phosphokinase. Table 603.5 lists complications of severe hypothyroidism, all of which normalize with adequate replacement of T_4.

Diagnostic Studies

Children with suspected hypothyroidism should undergo measurement of serum TSH and free T_4. Because the normal range for thyroid tests varies by age and is different in children than in adults, it is important to interpret results using age-specific reference ranges (see Table 603.3). Detection of autoantibodies to thyroglobulin or TPO is diagnostic of autoimmune thyroiditis. Measurement of urine iodine can confirm excess iodine exposure, if suspected. In cases of goiter resulting from autoimmune thyroiditis, ultrasonography typically shows diffuse enlargement and heterogeneous echotexture, but ultrasonography generally is not indicated unless the physical exam raises suspicion for a thyroid nodule. A bone age x-ray at diagnosis may suggest the duration and severity of hypothyroidism based on the degree of bone age delay.

Treatment and Prognosis

L-T_4 is the treatment for children with hypothyroidism. The dose on a weight basis gradually decreases with age. For children ages 1-3 years, the average daily L-T_4 dose is 4-6 μg/kg; for ages 3-10 years, 3-5 μg/kg; and for ages 10-16 years, 2-4 μg/kg. Treatment should be monitored by measuring serum TSH every 4-6 months and 4-6 weeks after any change in dosage, and TSH should be maintained in the age-specific reference range. In young children (under age 3 years), serum free T_4 should also be measured and ideally maintained in the upper half of the age-specific reference range. In older children with primary hypothyroidism, serum free T_4 need not be measured routinely but may be helpful in certain situations, such as to assess for poor medication adherence. In children with central hypothyroidism, in which TSH levels by definition do not reflect systemic thyroid status, serum free T_4 alone should be monitored and maintained in the upper half of the age-specific reference range.

During the first year of treatment, deterioration of schoolwork, poor sleeping habits, restlessness, short attention span, and behavioral problems may develop. However, these issues are transient and more easily managed if families are forewarned about them. Some practitioners feel that these symptoms may be partially ameliorated by starting at a lower dose of L-T_4 and advancing slowly. The development of persistent headaches or vision changes should prompt an evaluation for pseudotumor cerebri, a rare complication after initiation of L-T_4 treatment in older children (age 8-13 years).

In older children, after catch-up growth is complete, the growth rate provides a good index of the adequacy of therapy. In children with long-standing hypothyroidism, catch-up growth may be incomplete, and final adult height may be irremediably compromised (see Fig. 603.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 603.5 Clinical Presentation and Implications of Hypothyroidism

	PRESENTATION	SIGNS AND IMPLICATIONS
General metabolism	Weight gain, cold intolerance, fatigue	Increase in body mass index, low metabolic rate, myxedema,* hypothermia*
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidemia, bradycardia, hypertension, endothelial dysfunction or increased intima–media thickness,* diastolic dysfunction,* pericardial effusion,* hyperhomocysteinemia,* electrocardiogram changes*
Neurosensory	Hoarseness of voice, decreased taste, vision, or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurologic and psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes, depression,* dementia,* ataxia,* carpal tunnel syndrome, and other nerve entrapment syndromes,* myxedema coma*
Gastrointestinal	Constipation	Reduced esophageal motility, nonalcoholic fatty liver disease,* ascites (very rare)
Endocrinologic	Infertility and subfertility, menstrual disturbance, galactorrhea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction, increased prolactin, pituitary hyperplasia*
Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation, Hoffman syndrome,* osteoporotic fracture* (most probably caused by overtreatment)
Hemostasis and hematologic	Bleeding, fatigue	Mild anemia, acquired von Willebrand disease,* decreased protein C and S,* increased red cell distribution width,* increased mean platelet volume*
Skin and hair	Dry skin, hair loss	Coarse skin, loss of lateral eyebrows,* yellow palms of the hand,* alopecia areata*
Electrolytes and kidney function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatremia*

*Uncommon presentation.
From Chaker L, Bianco AC, Jonklaas J, et al. Hypothyroidism. *Lancet.* 2017;390:1550–1560, Table 1.

Chapter 604

Thyroiditis

Jessica R. Smith and Ari J. Wassner

Thyroiditis refers to inflammation of the thyroid gland. Thyroiditis can be acute or chronic and can be categorized by etiology, pathology, and/or clinical features. Painful thyroiditis is typically due to infection or trauma, whereas painless thyroiditis is often autoimmune-mediated or due to drug exposure.

Depending on the etiology and phase of illness, patients with thyroiditis may be euthyroid, hypothyroid, or thyrotoxic. The classic pattern of thyroid function changes in transient forms of thyroiditis is thyrotoxicosis followed by hypothyroidism and then restoration of euthyroidism. In some cases, hypothyroidism can persist after transient thyroiditis. The thyrotoxicosis caused by thyroiditis is not due to increased thyroid hormone synthesis (in contrast to Graves disease), but rather release of preformed thyroid hormone from the damaged gland, which can last up to 60 days.

Treatment for patients with thyroiditis is directed at alleviating symptoms of pain and symptoms of thyrotoxicosis such as tachycardia, palpations, and tremors. Nonsteroidal antiinflammatory drugs (NSAIDs) usually alleviate thyroid pain effectively, but a short course of steroids (prednisone) can be considered if pain is severe. Because the thyrotoxicosis is caused by the release of preformed thyroid hormone, antithyroid drugs (which block thyroid hormone synthesis) are ineffective. Instead, treatment with β blockers (atenolol or propranolol) may be used to control cardiovascular symptoms until thyrotoxicosis resolves. Thyroid function tests should be monitored every 6-8 weeks until they normalize. If hypothyroidism is prolonged or symptomatic, replacement with levothyroxine may be initiated.

THYROIDITIS WITH PAIN

Acute infectious (suppurative) thyroiditis is uncommon in children and typically is preceded by a respiratory infection or pharyngitis. The most common pathogenic organisms are α-hemolytic streptococci and *Staphylococcus aureus,* followed by gram-negative organisms and anaerobic bacteria. Other pathogens, including mycobacteria, fungi, and pneumocystis, cause more indolent infection and occur in immunocompromised patients. Abscess formation can occur, and the left thyroid lobe is more commonly affected than the right. Recurrent episodes or detection of mixed bacterial flora suggest that the infection arises from a **piriform sinus fistula** or, less commonly, from a **thyroglossal duct** remnant. Acute infectious thyroiditis is characterized by acute onset of neck pain, thyroid tenderness, swelling, erythema, dysphagia, and decreased range of motion of the neck. Fever, chills, sore throat, and leukocytosis are common. Thyroid function is usually normal, but thyrotoxicosis can occur. A suspected abscess can be assessed by thyroid ultrasound, and fine needle aspiration can help identify the responsible microorganism. Treatment of a thyroid abscess includes incision and drainage and administration of parenteral antibiotics. After the infection subsides, a CT scan with contrast may be obtained to identify a fistulous tract that may require surgical resection.

Subacute thyroiditis (de Quervain disease, subacute granulomatous thyroiditis) is believed to have a viral or postviral etiology and is usually transient. It typically presents with low-grade fever, minimal thyroid tenderness, and laboratory evidence of thyrotoxicosis (suppressed TSH and elevated T_4 and T_3). Mild symptoms of thyrotoxicosis may be present, but radioiodine uptake is depressed in the thyrotoxic phase. The erythrocyte sedimentation rate (ESR) is increased. The course is variable but usually follows the classic pattern of thyrotoxicosis, hypothyroidism, and finally resolution to euthyroidism, usually occurring over several months. There is a strong association with HLA-B35.

Radiation thyroiditis can occur after treatment with radioactive iodine or external beam radiation. Thyroid pain and tenderness develop after 2-5 days because of radiation-induced destruction of the thyroid follicular cells and subsequent release of preformed thyroid hormone. The neck pain is responsive to antiinflammatory therapies.

Palpation- or trauma-induced thyroiditis can result from direct trauma to the thyroid gland, typically from surgery, accidental trauma, biopsy, or rarely, vigorous palpation.

THYROIDITIS WITHOUT PAIN

Autoimmune Thyroiditis (Hashimoto Thyroiditis, Chronic Lymphocytic Thyroiditis)

Autoimmune thyroiditis is the most common cause of thyroid disease in children and adolescents and accounts for many of the formerly designated *adolescent* or *simple* goiters. It is also the most common cause of acquired hypothyroidism, with or without goiter. Between 1 and 2% of school-age children and 6–8% of adolescents have positive thyroid autoantibodies as evidence of autoimmune thyroid disease.

Etiology

This typical organ-specific autoimmune disease results from a combination of inherited susceptibility in genes involved in immunoregulation and from environmental triggers, both poorly characterized. Early in the disease, there may be thyroid hyperplasia only. This is followed by infiltration of lymphocytes and plasma cells into thyroid follicles and formation of lymphoid follicles with germinal centers. Chronic inflammation eventually leads to follicular fibrosis and atrophy. Certain human leukocyte antigen (HLA) haplotypes (HLA-DR4, HLA-DR5) are associated with an increased risk of goiter and thyroiditis, and others (HLA-DR3) are associated with the atrophic variant of thyroiditis.

A variety of different autoantibodies to thyroid antigens are also present. Circulating antibodies to thyroperoxidase (TPO-Abs) or thyroglobulin (Tg-Abs) are detectable in most children with autoimmune thyroiditis and many patients with Graves disease. TPO-Abs are involved in activation of the complement cascade and antibody-dependent, cell-mediated cytotoxicity. Tg-Abs do not appear to play a role in the autoimmune destruction of the gland. TSH receptor-blocking antibodies (TRBAbs) may cause thyroid atrophy and have been demonstrated in 18% of patients with severe hypothyroidism (TSH >20 mU/L) caused by autoimmune thyroiditis.

Clinical Manifestations

Autoimmune thyroiditis is 4-6 times more common in females than in males. It can occur during the first 3 years of life but becomes more common after 6 years of age and reaches its peak incidence during adolescence. The most common clinical manifestations are goiter and growth deceleration. Goiter is primarily caused by thyroid inflammation and fibrosis, and it can appear insidiously and may be variable in size. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In some patients the gland may be asymmetric. Most affected children are euthyroid and asymptomatic. Children who develop hypothyroidism may be symptomatic, but others may have no symptoms despite laboratory evidence of overt hypothyroidism. In some cases, autoimmune thyroiditis can cause transient thyroiditis as a result of autoimmune thyroid destruction (so-called *Hashitoxicosis*). Such children may present with manifestations of thyrotoxicosis, such as tremulousness, irritability, increased sweating, and hyperactivity. Ophthalmopathy can occur in autoimmune thyroiditis even in the absence of Graves disease, although this is rare in childhood.

The clinical course of autoimmune thyroiditis is variable. Goiter may persist or regress spontaneously. Most children who are euthyroid at presentation remain euthyroid, but a subset of patients develop hypothyroidism within months or years. In children who have subclinical hypothyroidism at diagnosis (elevated TSH, normal free thyroxine [T_4]), approximately 35% revert to euthyroidism, 50% continue to have subclinical hypothyroidism, and approximately 15% develop overt hypothyroidism (elevated serum TSH, subnormal free T_4) within 5 years. There are few reliable predictors of progression to hypothyroidism, so periodic monitoring of TSH levels is indicated in children with autoimmune thyroiditis.

Familial clusters of autoimmune thyroiditis are common, and the incidence in siblings or parents of affected children may be as high as 25%. The concurrence within families of patients with autoimmune thyroiditis and Graves disease reflects a fundamental pathophysiologic relationship among these autoimmune thyroid disorders.

Autoimmune thyroiditis is associated with other autoimmune disorders. Autoimmune thyroiditis occurs in 10% of patients with **type 1 autoimmune polyglandular syndrome (APS-1),** characterized by autoimmune

polyendocrinopathy, candidiasis, and ectodermal dysplasia **(APECED)**, a rare autosomal recessive disorder caused by pathogenic variants in the autoimmune regulator *(AIRE)* gene (see Chapter 608). Autoimmune thyroiditis occurs in 70% of patients with **type 2 autoimmune polyglandular syndrome (APS-2)**, including type 1 diabetes mellitus, autoimmune primary adrenal insufficiency, pernicious anemia, vitiligo, and alopecia. TPO-Abs are found in approximately 20% of White and 4% of Black children with type 1 diabetes mellitus. The onset of APS-2 typically occurs in late childhood or early adulthood. Its cause is unknown but may be related to predisposing genetic factors shared among these autoimmune conditions (see Chapter 608). Autoimmune thyroiditis has also been described in children with **immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome**, including early-onset diabetes and colitis (see Chapter 608).

Autoimmune thyroiditis is common in patients with celiac disease or certain chromosomal disorders, particularly Turner syndrome (8–30%) and trisomy 21 (7–10%). Males with Klinefelter syndrome also appear to be at increased risk for autoimmune thyroid disease.

Table 604.1 compares the characteristics of autoimmune thyroiditis to other forms of thyroiditis.

Laboratory and Imaging Findings

Thyroid function tests are often normal. Elevation of serum TSH indicates hypothyroidism, which may be subclinical (normal free T_4) or overt (low free T_4). TPO-Abs are present in most children with autoimmune thyroiditis. Tg-Abs are present in many adolescents but are somewhat less sensitive in young children. Testing for both antibodies will detect about 95% of children with autoimmune thyroiditis. Antibody levels are lower in children than in adults, so repeated measurements of borderline levels may be indicated. Measurement of thyroid autoantibody levels is useful only for diagnosing autoimmune thyroiditis; antibody levels do not correlate with thyroid function and should not be monitored routinely after the initial diagnosis. In adolescent females with overt hypothyroidism, measurement of TSH receptor antibodies may identify patients at future risk of having babies with transient congenital hypothyroidism caused by transplacental passage of TRBAbs.

Thyroid scintigraphy and ultrasonography usually are not necessary for the diagnosis of autoimmune thyroiditis. If performed, thyroid scintigraphy reveals decreased radioisotope uptake that is patchy and irregular. Thyroid ultrasonography shows diffusely heterogeneous echogenicity and frequently an increased number of hyperplastic, benign-appearing cervical lymph nodes. Thyroid ultrasound is indicated for patients with a palpable thyroid nodule or significant thyroid asymmetry.

Treatment

If hypothyroidism is overt (elevated TSH with low free T_4) or symptomatic, treatment with levothyroxine is indicated at doses specific to size and age. Goiter may decrease in size but can persist for years. In a euthyroid patient, treatment with levothyroxine is unlikely to significantly decrease the goiter's size, and doses of levothyroxine sufficient to suppress TSH should be avoided because of potential adverse effects. Because autoimmune thyroiditis is self-limited in some instances, the need for continued therapy may be reevaluated periodically, particularly after growth and pubertal development are complete. Untreated euthyroid patients should have periodic monitoring for risk of progression to hypothyroidism. There is some controversy about the management of patients with subclinical hypothyroidism. Subclinical hypothyroidism has not been demonstrated to have clinically significant adverse effects, but studies are small and of limited quality. Therefore observation without treatment is acceptable, but some clinicians prefer to treat until growth and puberty are complete and then reevaluate their thyroid function.

OTHER CAUSES OF THYROIDITIS

Painless thyroiditis (silent thyroiditis) is characterized by transient thyrotoxicosis, followed sometimes by hypothyroidism, and then recovery. It accounts for 1–5% of cases of thyrotoxicosis. It can also occur in the postpartum period and in response to certain types of drugs.

Drug-induced thyroiditis can be caused by medications including lithium, amiodarone, interferon-α, interleukin-2, and tyrosine kinase inhibitors. Patients taking lithium are susceptible to both lithium-induced hypothyroidism and painless thyroiditis. The antiarrhythmic drug amiodarone contains a high concentration of iodine and can cause two types of thyrotoxicosis. Type 1 is caused by increased synthesis of thyroid hormone (hyperthyroidism), typically occurs in patients with underlying thyroid autoimmunity, and is amenable to treatment with antithyroid drugs (methimazole). Type 2 is a destructive thyroiditis causing excessive release of preformed thyroid hormone, which can be treated with glucocorticoids (prednisone).

Fibrous thyroiditis (invasive or Riedel thyroiditis) is quite rare in children and is characterized by extensive fibrosis and macrophage and eosinophil infiltration of the thyroid gland. The thyroid becomes enlarged, hard, and affixed to surrounding structures. Thyroid function tests are normal, and a biopsy is required to confirm the diagnosis. Glucocorticoids may alleviate symptoms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 604.1 Characteristics of Thyroiditis Syndromes

CHARACTERISTIC	AUTOIMMUNE THYROIDITIS	PAINLESS THYROIDITIS	SUBACUTE THYROIDITIS	ACUTE INFECTIOUS THYROIDITIS	FIBROUS THYROIDITIS
Sex ratio (F:M)	4-6:1	2:1	5:1	1:1	3-4:1
Cause	Autoimmune	Autoimmune	Unknown (probably viral)	Infectious (bacterial)	Unknown
Pathologic findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Usually euthyroidism; some hypothyroidism	Thyrotoxicosis, hypothyroidism, or both	Thyrotoxicosis, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	Present, persistent	Present, persistent	Low titer, absent, or transient	Absent	Usually present
ESR	Normal	Normal	High	High	Normal
^{123}I uptake	Usually low	Low	Low	Normal	Low or normal

ESR, Erythrocyte sedimentation rate; ^{123}I, iodine 123; TPO, thyroid peroxidase.
Data from Farwell AP, Braverman LE. Inflammatory thyroid disorders. *Otolaryngol Clin North Am.* 1996;4:541–556.

Chapter 605

Goiter

Jessica R. Smith and Ari J. Wassner

A goiter is an enlargement of the thyroid gland. Average thyroid volume is approximately 1 mL at birth and increases with age and body mass index. For clinical assessment of thyroid size, the "rule of thumb" states that in older children (>5 years) each lobe of the thyroid gland is approximately the size of the distal phalanx of the child's thumb. Children with an enlarged thyroid can have normal thyroid function **(euthyroidism)**, underproduction of thyroid hormone **(hypothyroidism)**, or overproduction of thyroid hormone **(hyperthyroidism)**. Most goiters are discovered by the patient or a caregiver or on physical examination. Detection of a goiter should prompt an investigation of its cause and assessment of thyroid function.

Goiter may be congenital or acquired, endemic or sporadic. Goiter often results from increased pituitary secretion of thyroid-stimulating hormone (TSH) in response to decreased circulating levels of thyroid hormone. The most common causes of pediatric goiter are inflammation (autoimmune thyroiditis) and, in endemic areas, iodine deficiency (endemic goiter). Other causes include inborn errors in thyroid hormone synthesis (dyshormonogenesis), maternal ingestion of antithyroid drugs, goitrogens, abnormal activation of the TSH receptor by circulating antibodies (TRSAb) in Graves disease or by genetic gain-of-function pathogenic variants, or disorders of inappropriate TSH secretion. Thyroid enlargement can also result from thyroid nodules or infiltrative processes.

605.1 Congenital Goiter

Ari J. Wassner and Jessica R. Smith

Congenital goiter usually results from a defect in fetal thyroxine (T_4) synthesis that leads to neonatal hypothyroidism. This defect may be intrinsic to the fetal thyroid or may be caused by transplacental transfer from the mother of substances that decrease fetal thyroid hormone synthesis. Antithyroid drugs (methimazole or propylthiouracil) administered during pregnancy to treat maternal thyrotoxicosis cross the placenta and can interfere with fetal synthesis of thyroid hormone. The neonatal consequences are most severe when overtreatment with antithyroid drugs causes concomitant hypothyroidism in the mother, which reduces the supply of maternal thyroid hormone to the fetus. Fetal effects can occur even with low doses of antithyroid drugs; therefore infants born to women treated with such drugs in the third trimester should undergo serum thyroid studies at birth, even if they appear clinically euthyroid. Levothyroxine treatment may be indicated for severe hypothyroidism or to reduce the size of goiter that causes airway obstruction. Hypothyroidism caused by maternal antithyroid drugs is transient and resolves once the antithyroid drug has been excreted by the neonate, usually after 1-2 weeks. Like antithyroid drugs, other medications containing large amounts of iodine can cause congenital goiter, including amiodarone and some cough preparations.

In cases of congenital goiter and hypothyroidism in which no cause is identifiable from the maternal or medication history, an intrinsic defect in synthesis of thyroid hormone **(dyshormonogenesis)** should be suspected. Such disorders are caused by genetic defects in one of the proteins critical to thyroid hormone synthesis and are usually inherited in autosomal recessive fashion. Neonatal screening programs detect congenital hypothyroidism caused by such a defect in about 1 in 25,000 infants. Treatment with levothyroxine should be initiated immediately. If a specific defect is suspected, genetic testing to identify a mutation may be considered (see Chapter 603). Monitoring subsequent pregnancies with ultrasonography can be useful to detect fetal goiter (see Chapter 117).

Iodine deficiency is an important cause of congenital goiter that is rare in countries that have adopted universal salt iodization, but iodine deficiency persists in endemic areas (see Chapter 605.3). Severe maternal iodine deficiency early in pregnancy can cause neurologic damage during fetal development because maternal hypothyroidism reduces the transfer of maternal thyroid hormones that typically protect neurodevelopment in a fetus unable to synthesize its own thyroid hormone.

Goiter is almost always present in the infant with **neonatal Graves disease**. Thyroid enlargement results from transplacental passage of maternal TSH receptor-stimulating antibodies that promote thyroid hyperplasia (see Chapter 606.2). These goiters usually are not large, and the infant manifests clinical symptoms of hyperthyroidism. The diagnosis of maternal Graves disease is usually known but occasionally may be discovered by evaluating unexpected neonatal hyperthyroidism. Activating pathogenic variants of the TSH receptor are a rare cause of congenital goiter with hyperthyroidism.

A very large congenital goiter of any cause can lead to tracheal compression and respiratory distress that interferes with feeding and can even be fatal. Therefore intervening to reduce the size of a large fetal goiter may be necessary before delivery. Treatment should be directed at the underlying cause. Iodine deficiency should be treated if present. In pregnant women treated with antithyroid drugs, reducing the dose of maternal medication is appropriate. In severe cases, fetal goiter caused by fetal hypothyroidism (including dyshormonogenesis) may be reduced by intraamniotic injections of levothyroxine. If the fetal goiter is caused by fetal hyperthyroidism (e.g., fetal Graves disease), treatment with antithyroid drugs administered to the mother is indicated. Large obstructing fetal goiters are often managed with the ex utero intrapartum treatment (EXIT) procedure during elective delivery (see Chapter 117). When postnatal respiratory obstruction is severe, endotracheal intubation, hormone therapy, and occasionally partial thyroidectomy is indicated (Fig. 605.1).

When a palpable congenital goiter is lobulated, asymmetric, firm, or unusually large, a teratoma in or near the thyroid must be considered (see Chapter 607).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

605.2 Intratracheal Goiter

Ari J. Wassner and Jessica R. Smith

One of the many potential ectopic locations of thyroid tissue is within the trachea. When present, intraluminal thyroid tissue lies beneath the tracheal mucosa and is often continuous with the normally located extratracheal thyroid gland. Both eutopic and ectopic thyroid tissue are susceptible to goitrous enlargement. Therefore when airway obstruction is associated with a goiter, it must be ascertained whether the obstruction is extratracheal or intratracheal. If obstructive manifestations are mild, administration of levothyroxine usually decreases the size of the goiter. When symptoms are severe, surgical removal of the intratracheal goiter is indicated.

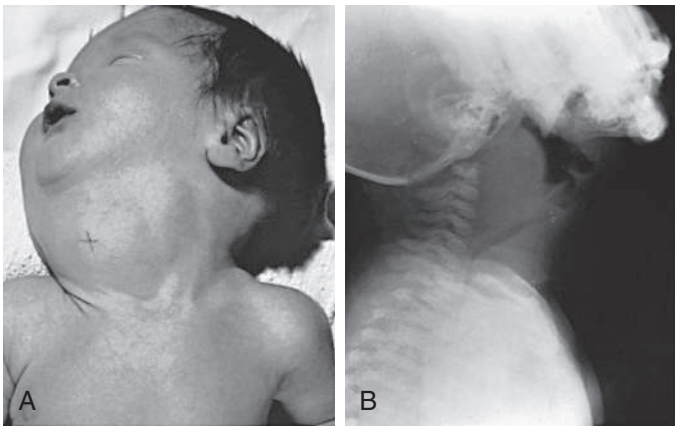

Fig. 605.1 Congenital goiter in infancy. **A,** Large congenital goiter in an infant born to a mother with thyrotoxicosis who had been treated with iodides and methimazole during pregnancy. **B,** A different infant, 6 wk old, with increasing respiratory distress and cervical mass since birth. Notice the anterior deviation and posterior compression of the trachea.

605.3 Endemic Goiter and Cretinism

Ari J. Wassner and Jessica R. Smith

ETIOLOGY

Goiter caused by iodine deficiency is termed *endemic goiter,* whereas *cretinism* refers to the clinical manifestations of severe hypothyroidism in early life. The association of dietary iodine deficiency with endemic goiter and cretinism is well established. The thyroid gland can overcome a moderate deficiency of iodine by increasing the efficiency of thyroid hormone synthesis. This increased activity is achieved by compensatory thyroid hypertrophy and hyperplasia (goiter). In cases of severe iodine deficiency, these compensatory mechanisms are insufficient, and hypothyroidism can result. The World Health Organization estimates that nearly 2 billion individuals have insufficient iodine intake, including one third of the world's school-age children. Thus despite significant progress in the global effort to reduce iodine deficiency, it remains a leading cause of preventable intellectual disability worldwide.

Because seawater is rich in iodine, endemic goiter is rare in coastal populations that consume much of their diet from the sea. In areas of iodine deficiency, iodized salt provides excellent prophylaxis, and endemic goiter has effectively disappeared in the United States and other countries that have introduced salt iodization programs. The U.S. recommended dietary allowance of iodine is:

- Infants under 6 months: 110 μg/day
- Infants 7-12 months: 130 μg/day
- Children 1-8 years: 90 μg/day
- Children 9-13 years: 120 μg/day
- Children 14 years and older: 150 μg/day
- Pregnant women: 220 μg/day
- Lactating women: 290 μg/day

Although the overall dietary iodine intake in the United States is considered adequate, recent data indicate that the median urinary iodine concentration among pregnant U.S. women has dropped to <150 μg/L (mild iodine deficiency). This highlights the re-emerging risk of iodine deficiency even in industrialized countries. These risks can be mitigated by the continued monitoring of iodine status, the adjustment of salt iodization levels, and the targeted supplementation of vulnerable subpopulations (e.g., promoting iodine-containing prenatal vitamins).

CLINICAL MANIFESTATIONS

In mild iodine deficiency, thyroid enlargement generally is not noticeable except when demand for thyroid hormone synthesis is increased, such as during rapid growth in adolescence and pregnancy. In regions of moderate iodine deficiency, goiter in school children can disappear with maturity and reappear during pregnancy or lactation. Iodine-deficient goiter is more common in girls than in boys. In areas of severe iodine deficiency, nearly half the population may have large goiters, and endemic cretinism is common (Fig. 605.2).

Serum T_4 levels are often low in individuals with endemic goiter, although clinical hypothyroidism is rare. Despite low serum T_4 levels, serum TSH concentrations are often normal or only mildly increased because of the elevated circulating levels of T_3 produced in response to iodine deficiency.

Endemic cretinism is the most severe consequence of iodine deficiency and occurs only in association with endemic goiter. The term *endemic cretinism* includes two distinct but overlapping syndromes (neurologic and myxedematous). The incidence of the two syndromes varies among different populations, but both syndromes are found in all endemic areas, and some individuals have intermediate or mixed features.

The **neurologic syndrome** is characterized by intellectual disability; deaf-mutism; disturbances in standing and gait; and pyramidal signs such as clonus of the foot, Babinski sign, and patellar hyperreflexia. Affected persons have a goiter but minimally impaired thyroid function and have normal pubertal development and adult stature. Persons with the **myxedematous syndrome** also have intellectual disability, deafness, and neurologic symptoms. In contrast to the neurologic type, they also have delayed growth and pubertal development and myxedema. Serum T_4 levels are low, TSH levels are markedly elevated, goiter is absent, and ultrasound demonstrates thyroid atrophy.

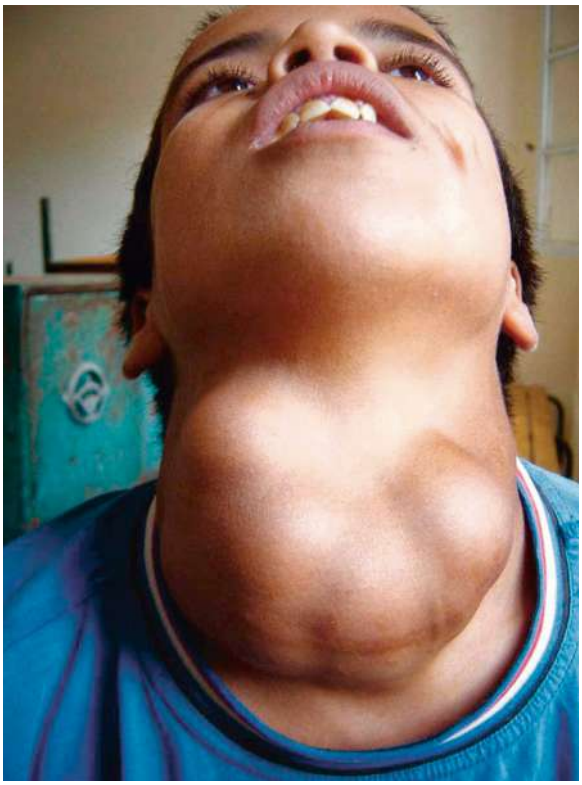

Fig. 605.2 A 14-yr-old male with a large nodular goiter was seen in 2004, in an area of severe iodine-deficiency disorders in northern Morocco. He had tracheal and esophageal compression and hoarseness, probably as a result of damage to the recurrent laryngeal nerves. *(From Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet. 2008;372:1251–1262, Fig. 2.)*

PATHOGENESIS

The pathogenesis of the **neurologic syndrome** is attributed to maternal iodine deficiency and hypothyroidism during pregnancy, leading to fetal and postnatal hypothyroidism. Maternal thyroid hormone is critical for early fetal neurodevelopment. Thyroid hormone receptors are expressed in the fetal brain as early as 7 weeks of gestation. Although the fetal thyroid gland does not produce significant amounts of thyroid hormone until midgestation, as early as 6 weeks there is measurable T_4 in the coelomic fluid that is of maternal origin. In addition, there is transplacental passage of maternal thyroid hormone into the fetus throughout gestation, which ameliorates the neurologic effects of fetal hypothyroidism in the second half of pregnancy. Thus maternal iodine deficiency affects fetal neurodevelopment throughout pregnancy. However, iodine intake after birth is often sufficient for the infant to maintain (near-)normal thyroid function.

The pathogenesis of the **myxedematous syndrome** and its persistent postnatal hypothyroidism is not well understood. Multiple environmental factors have been implicated (Table 605.1), as have thyroid autoimmunity and TSH receptor-blocking antibodies, but studies are conflicting, and the pathogenesis remains obscure.

TREATMENT

The optimal treatment of endemic goiter is prevention by ensuring iodine sufficiency in women before pregnancy. A single intramuscular injection of iodinated poppy seed oil administered to women prevents iodine deficiency during future pregnancies for approximately 5 years. This therapy is also effective in children younger than 4 years with myxedematous cretinism. However, older children and adults respond poorly, indicating a progressive inability of the thyroid gland to synthesize hormone, and these patients require treatment with levothyroxine. Large-scale prevention efforts include universal salt iodization in many countries, as well as

Table 605.1 Goitrogens and Their Mechanisms

GOITROGEN	MECHANISM
FOODS	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid
Cruciferous vegetables (cabbage, kale, cauliflower, broccoli, turnips)	Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid
Soy, millet	Flavonoids impair thyroid peroxidase activity
INDUSTRIAL POLLUTANTS	
Perchlorate	Competitive inhibitor of the sodium-iodide symporter, decreasing iodide transport into the thyroid
Others (e.g., disulfides from coal processes)	Reduce thyroidal iodine uptake
Smoking	Smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast
NUTRIENTS	
Selenium deficiency	Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and may blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A–mediated suppression of the pituitary TSH-β gene

TSH, Thyroid-stimulating hormone.
From Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet.* 2008;372:1251–1262, Table 1.

iodination of irrigation water in some areas. Nevertheless, political, economic, and practical obstacles have limited iodization efforts in many parts of the world.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

605.4 Acquired Goiter

Jessica R. Smith and Ari J. Wassner

Acquired goiter is usually sporadic and may develop from a variety of causes. The most common cause of acquired goiter is autoimmune thyroiditis (see Chapter 604). Other causes in children include painless sporadic thyroiditis and subacute thyroiditis (de Quervain disease; see Chapter 604). Ingestion of excess iodide or certain medications can cause goiter, as can congenital defects in thyroid hormone synthesis. The occurrence of goiter in siblings, onset in early life, and possible association with hypothyroidism are important clues to diagnosing congenital dyshormonogenesis.

IODIDE GOITER

Excessive iodine ingestion can result in a goiter. Large amounts of iodine are found in certain foods (such as seaweed) and some expectorants for chronic reactive airway disease or cystic fibrosis. Some children with iodine-induced goiter have underlying autoimmune thyroiditis or a subclinical congenital defect in thyroid hormone synthesis. In a normal thyroid gland, the acute intake of large doses of iodine inhibits thyroid hormone synthesis (Wolff-Chaikoff effect). However, this effect is short-lived and normally does not lead to hypothyroidism. If iodine administration continues, an autoregulatory mechanism limits iodide uptake by the thyroid, allowing thyroid hormone synthesis to resume. This "escape" from the Wolff-Chaikoff effect may not occur in individuals with underlying thyroid abnormalities (such as autoimmune thyroid disease or thyroid irradiation) or in neonates, potentially leading to hypothyroidism and iodine-induced goiter.

Iodine-Deficiency Goiter

Iodine deficiency is the most common cause of goiter worldwide, but salt iodization has nearly eradicated this entity in the United States and many other countries. A severely iodine-restricted diet can result in a goiter and hypothyroidism in children, adolescents, or neonates born to mothers with severe iodine deficiency (urine iodine concentration <50 mcg/L). Children with moderate or severe iodine deficiency and goiter have subclinical or mild hypothyroidism, but their serum T_3 concentrations may be normal or high because of preferential thyroidal T_3 secretion. Acquired iodine deficiency can be treated with either iodine or levothyroxine supplementation.

Goitrogens

Certain foods contain goitrogenic substances (see Table 605.1). When consumed alone, these substances are unlikely to cause goiter but can contribute to goiter formation when iodine intake is marginal.

Lithium carbonate can cause goiter and hypothyroidism in children. Lithium decreases T_4 and T_3 synthesis and release; the mechanism producing the goiter or hypothyroidism is similar to that described for iodide goiter. Lithium and iodide act synergistically to produce goiter, so their combined use should be avoided.

Amiodarone, a drug used to treat cardiac arrhythmias, can cause thyroid dysfunction with goiter because it is rich in iodine. Amiodarone can often cause hypothyroidism, particularly in patients with underlying autoimmune thyroid disease. In other patients, it can cause thyrotoxicosis through either transient thyroiditis or the Jod-Basedow effect.

SIMPLE GOITER (COLLOID GOITER)

Some children with euthyroid goiters have a simple goiter, a condition of unknown cause not associated with thyroid dysfunction and not caused by inflammation or neoplasia. Simple goiter is more common in girls, may be familial, and has its peak incidence during adolescence. Histologic examination of the thyroid either is normal or reveals variable follicular size, dense colloid, and flattened epithelium. The size of the goiter is variable. It can occasionally be firm, asymmetric, or nodular. Levels of TSH are normal, thyroid scintigraphy is normal, and thyroid antibodies are absent. Simple goiters usually decrease in size gradually over several years, without treatment. Patients should be reevaluated periodically because some have antibody-negative autoimmune thyroiditis and therefore are at risk for changes in thyroid function (see Chapter 604).

MULTINODULAR GOITER

Multinodular goiter is usually a firm goiter with a lobulated surface and one or more palpable nodules. Areas of cystic change, hemorrhage, and fibrosis may be present. The incidence of this condition has decreased markedly with the use of iodine-enriched salt. Ultrasonographic examination can reveal multiple nodules that are nonfunctioning on thyroid scintigraphy. Thyroid function is usually normal. Some children with autoimmune thyroiditis develop a multinodular goiter, and in such cases, thyroid antibodies may be present, and TSH may be elevated. If hypofunctioning nodules within a multinodular goiter grow to a significant size (≥1 cm) or have suspicious sonographic features, fine needle aspiration should be considered to rule out malignancy (see Chapter 607). Children with **McCune-Albright syndrome** or TSH receptor–activating mutations can develop a toxic multinodular goiter, characterized by suppressed TSH, hyperthyroidism, and multiple hyperfunctioning nodules.

TOXIC GOITER (HYPERTHYROIDISM)

See Chapter 606.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 606

Thyrotoxicosis

Jessica R. Smith and Ari J. Wassner

Although the terms *hyperthyroidism* and *thyrotoxicosis* are often interchanged in the literature, they are not synonymous. **Hyperthyroidism** specifically refers to the synthesis and secretion of excess thyroid hormone from the thyroid gland; in contrast, **thyrotoxicosis** refers to any state of excess circulating thyroid hormone (and its clinical manifestations) regardless of its source. This distinction is physiologically and clinically relevant because different therapies may be indicated depending on the mechanism of thyroid hormone excess.

Graves disease is the most common cause of hyperthyroidism in children (Table 606.1). It is an autoimmune disorder that results in the production of thyrotropin (TSH) receptor–stimulating antibodies (TRSAbs) that bind and activate the G protein–coupled TSH receptor (TSHR) to cause increased thyroid hormonogenesis and diffuse glandular growth. In infants born to mothers with Graves disease, hyperthyroidism can be caused by transplacental passage of TRSAbs, but this is transitory and resolves when TRSBAbs are cleared from the neonate's circulation. Etiologies of nonautoimmune hyperthyroidism include hyperfunctioning thyroid nodules and germline gain-of-function pathogenic variants in the TSHR (either autosomal dominant or sporadic). Hyperthyroidism can also occur in patients with **McCune-Albright syndrome** because of an activating pathogenic variant of the stimulatory α-subunit of the G protein. These patients can also develop a multinodular goiter. Other rare causes of hyperthyroidism include iodine-induced hyperthyroidism, TSH-secreting adenomas, toxic multinodular goiters, and hyperfunctioning thyroid carcinoma. Thyrotoxicosis not caused by hyperthyroidism (i.e., not the result of overproduction of thyroid hormone by the gland) can be caused by thyroiditis (see Chapter 604) or ingestion of exogenous thyroid hormone. Choriocarcinoma, hydatidiform mole, and struma ovarii can cause hyperthyroidism but are rarely diagnosed in children.

Laboratory evaluation of primary thyrotoxicosis reveals suppression of serum TSH and elevation of serum total thyroxine (T_4) and/or total triiodothyronine (T_3) levels. Elevated T_4 and T_3 with normal or elevated TSH suggests hyperthyroidism caused by inappropriate TSH secretion, which may be caused by a dominant-negative pathogenic variant in thyroid hormone receptor-β *(THRB)* resulting in **resistance to thyroid hormone (RTH)**. TSH-secreting pituitary tumors are extremely rare in the pediatric population. Elevated T_4 and/or T_3 levels with normal TSH may also be caused by abnormalities of thyroid hormone–binding proteins such as **thyroxine-binding globulin** excess or **familial dysalbuminemic hyperthyroxinemia**. In such cases, free T_4 levels are normal, and patients are euthyroid.

606.1 Graves Disease

Jessica R. Smith and Ari J. Wassner

EPIDEMIOLOGY

Graves disease occurs in approximately 0.02% of children (1:5,000) and is the most common cause of pediatric hyperthyroidism. It has a peak incidence in the 11- to 15-year-old age-group, and there is a 5:1 female:male ratio. Many children with Graves disease have a family history of autoimmune thyroid disease. Although rare in very young children, Graves disease has been reported between 6 weeks and 2 years of age in children born to mothers without a history of hyperthyroidism.

ETIOLOGY

Graves disease is a form of autoimmune thyroid disease characterized by infiltration of the thyroid gland by T-helper cells ($CD4^+$), cytotoxic T cells ($CD8^+$), and activated B lymphocytes. A postulated failure of T suppressor cells allows the expression of T helper cells sensitized to the TSH antigen to interact with B cells, which

Table 606.1 Pathogenic Mechanisms and Causes and Effects of Thyrotoxicosis

Thyrotoxicosis with hyperthyroidism (normal or high radioactive iodine uptake)	
EFFECT OF INCREASED THYROID STIMULATORS	
TSH-receptor antibody	Graves disease
Inappropriate TSH secretion	TSH-secreting pituitary adenoma; resistance to thyroid hormone β
Excess hCG secretion	Trophoblastic tumors (choriocarcinoma or hydatidiform mole); hyperemesis gravidarum
AUTONOMOUS THYROID FUNCTION	
Activating pathogenic variant in TSH receptor or $G_s\alpha$ protein	Solitary hyperfunctioning adenoma; multinodular goiter; familial nonautoimmune hyperthyroidism
Thyrotoxicosis without hyperthyroidism (low radioactive iodine uptake)	
INFLAMMATION AND RELEASE OF STORED HORMONE	
Autoimmune destruction of thyroid gland	Autoimmune thyroiditis; postpartum thyroiditis
Viral infection*	Subacute (painful) thyroiditis (de Quervain thyroiditis)
Toxic drug effects	Drug-induced thyroiditis (amiodarone, lithium, interferon-α)
Bacterial or fungal infection	Acute suppurative thyroiditis
Radiation	Radiation thyroiditis
EXTRATHYROIDAL SOURCE OF HORMONE	
Excess intake of thyroid hormone	Excess exogenous thyroid hormone (iatrogenic or factitious)
Ectopic hyperthyroidism (thyroid hormone produced outside the thyroid gland)	Struma ovarii; functional thyroid cancer
Ingestion of contaminated food	Hamburger thyrotoxicosis
EXPOSURE TO EXCESSIVE IODINE	
Jod-Basedow effect	Iodine-induced hyperthyroidism (radiocontrast agents or iodine in medications)

*Etiology is not definitive.
$G_s\alpha$, G protein alpha subunit; hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.
Modified from De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906–916, Table 1.

Table 606.2 Conditions Associated with Graves Disease

Type 1 diabetes mellitus
Celiac disease
Autoimmune adrenal insufficiency
Vitiligo
Psoriasis
Pernicious anemia
Alopecia areata
Myasthenia gravis
Rheumatoid arthritis
Trisomy 21
Turner syndrome

differentiate into plasma cells that produce TRSAbs. TRSAbs bind to and activate the TSHR, resulting in thyroid hyperplasia and unregulated thyroid hormone synthesis. Some patients with Graves disease also produce TSH receptor–blocking antibodies (TRBAbs) that bind to and block activation of the TSHR. In these cases, the clinical course of the disease correlates to the ratio between stimulating and blocking antibodies.

Ophthalmopathy may occur in Graves disease and appears to be caused primarily by autoimmunity to the TSHR, which is also expressed in orbital adipocytes and fibroblasts. TRSAb-mediated activation of these cells stimulates the synthesis of glycosaminoglycans and cytokines, resulting in retro-orbital inflammation and edema. Although 50–75% of children with Graves disease have some eye findings, the symptoms are much milder than in adults; significant ophthalmopathy is rare.

Graves disease is associated with specific human leukocyte antigen (HLA) haplotypes. It is also associated with other HLA-related disorders, such as autoimmune adrenal insufficiency, type 1 diabetes mellitus, myasthenia gravis, and celiac disease (Table 606.2). Systemic lupus erythematosus, rheumatoid arthritis, vitiligo, idiopathic thrombocytopenic purpura, and pernicious anemia have also been described in children with Graves disease. In family clusters, the condition associated most commonly with Graves disease is autoimmune thyroiditis. Polymorphisms in the *TSHR* gene and numerous immunomodulatory genes—including *FOXP3, IL2RA, CD40, CTLA4, PTPN22,* and *FCRL3*—have also been associated with increased susceptibility to Graves disease.

CLINICAL MANIFESTATIONS

The clinical course of Graves disease is variable, and children typically take longer to remit than adults. Because symptoms develop gradually, the interval between onset and diagnosis is typically 6-12 months and may be longer in prepubertal children than in adolescents.

Signs and symptoms of Graves disease in children are shown in Figure 606.1 and Table 606.3. Tremulousness, headaches, mood disturbances, behavioral swings, difficulties with sleep, decreased attention span, hyperactivity, and a decline in school performance are all common findings in childhood. Many hyperthyroid children are referred for evaluation of attention-deficit/hyperactivity disorder (ADHD). Children with hyperthyroidism may show acceleration in growth velocity and advanced skeletal maturation. The effect on growth may be more pronounced if hyperthyroidism presents earlier in childhood. The onset of puberty does not appear to be altered by hyperthyroidism, but postmenarchal females can develop secondary amenorrhea. There may also be an increase in appetite with either failure to gain weight or overt weight loss. Polyuria and more frequent defecation (although not usually frank diarrhea) contribute to changes in weight. Because of the increased risk



Fig. 606.1 A 15-yr-old female with classic Graves disease. Clinical features include a goiter and exophthalmos. She was treated with antithyroid drugs, to which she had a good response.

of comorbid autoimmune disorders, screening for type 1 diabetes, celiac disease, and inflammatory bowel disease should be considered in patients who present with these symptoms.

Most children with Graves disease have a diffuse goiter. The size of the thyroid is variable, but it is typically smooth and without nodules. A bruit can occasionally be auscultated over a markedly enlarged gland. Ocular manifestations can produce proptosis, pain, eyelid erythema, chemosis, decreased extraocular muscle function and decreased visual acuity (corneal or optic nerve involvement) (Table 606.4). In children with thyrotoxicosis and diffuse goiter, identifying these signs of ophthalmopathy on physical examination strongly suggests the diagnosis of Graves disease. However, stare and lid lag are eye findings caused by increased sympathetic activity and can be seen in thyrotoxicosis of any cause, not only Graves disease (Fig. 606.2). In general, ocular symptoms in children with Graves disease tend to be mild and improve with the restoration of euthyroidism.

Children with hyperthyroidism have an increase in cardiac output. Tachycardia, palpitations, increased systolic blood pressure, and a widened pulse pressure are common cardiac manifestations, whereas cardiac enlargement and insufficiency and atrial fibrillation are rare complications.

The skin is smooth and flushed, with excessive sweating. Occasionally, associated vitiligo or psoriasis can be present. Graves dermopathy, characterized by indurated, nonpitting edema often on the anterior shins (pretibial myxedema), is rare in children. Proximal muscular weakness may be present. Thyroid hormone stimulates bone resorption, leading to low bone density and increased fracture risk in patients with chronic hyperthyroidism. Bone density returns to normal with treatment.

Table 606.3 Clinical Manifestation of Thyrotoxicosis

	SYMPTOMS	SIGNS
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating, and polydipsia)	Weight loss
Neuromuscular	Tremor; nervousness; anxiety; fatigue; weakness; disturbed sleep; poor concentration	Tremor of the extremities; hyperactivity; hyperreflexia; pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia; systolic hypertension
Pulmonary	Dyspnea, shortness of breath	Tachypnea
Gastrointestinal	Hyperdefecation; nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin
Reproductive		Menstrual disturbances
Ocular (Graves disease)	Diplopia; sense of irritation in the eyes; eyelid swelling; retro-orbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital edema; conjunctival injection and chemosis; ophthalmoplegia

From De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906–916, Table 2.

Table 606.4 Clinical Assessment of the Patient with Graves Ophthalmopathy

ACTIVITY MEASURES*
- Spontaneous retrobulbar pain
- Pain on attempted up or down gaze
- Redness of the eyelids
- Redness of the conjunctivae
- Swelling of the eyelids
- Inflammation of the caruncle and/or plica
- Conjunctival edema

SEVERITY MEASURES
- Lid aperture (distance between the lid margins in millimeters with the patient looking in the primary position, sitting relaxed, and with distant fixation)
- Swelling of the eyelids (absent/equivocal, moderate, severe)
- Redness of the eyelids (absent/present)
- Redness of the conjunctivae (absent/present)
- Conjunctival edema (absent, present)
- Inflammation of the caruncle or plica (absent, present)
- Exophthalmos (measured in millimeters using the same Hertel exophthalmometer and the same intercanthal distance for an individual patient)
- Subjective diplopia score†
- Eye muscle involvement (ductions in degrees)
- Corneal involvement (absent/punctate keratopathy/ulcer)
- Optic nerve involvement (best corrected visual acuity, color vision, optic disc, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

*Based on the classic features of inflammation in Graves ophthalmopathy.
†Subjective diplopia score: 0, no diplopia; 1, intermittent (i.e., diplopia in primary position of gaze, when tired or when first awakening); 2, inconstant (i.e., diplopia at extremes of gaze); 3, constant (i.e., continuous diplopia in primary or reading position). The clinical activity score (CAS) is the sum (1 point each) of all items present; a CAS ≥3/7 indicates active ophthalmopathy.
From Davies TF, Laurberg P, Bahn RS. Hyperthyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology,* 13th ed. Philadelphia: Elsevier; 2016: Table 12.4.

Thyroid storm is an extreme form of hyperthyroidism characterized by severely elevated thyroid hormone levels, hyperthermia, tachycardia, heart failure, altered mental status, and GI symptoms (Table 606.5). If untreated, there may be rapid progression to delirium, coma, and death. Precipitating events include trauma, infection, radioactive iodine (RAI) treatment, or surgery.

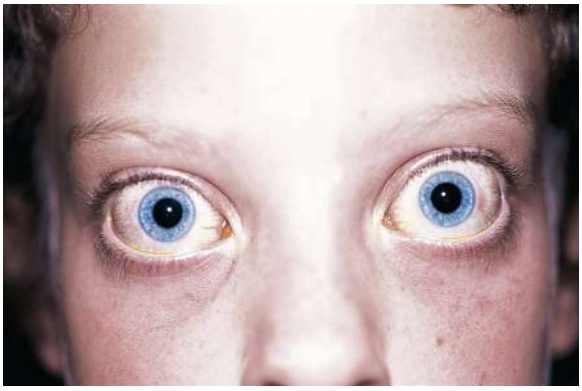

Fig. 606.2 Retraction of upper eyelids in the primary gaze (Dalrymple sign). *(From Kanski JJ. Systemic Diseases and the Eye: Signs and Differential Diagnosis. London: Mosby; 2001.)*

LABORATORY FINDINGS

In Graves disease, serum TSH is suppressed and free T_4 and T_3 are elevated. Most patients with Graves disease have measurable TRSAbs at diagnosis. TRSAbs can be measured either by a functional assay (thyroid-stimulating immunoglobulin [TSI]) that assesses the presence of antibodies capable of stimulating TSHR-mediated cyclic adenosine monophosphate (cAMP) generation, or by a competitive binding assay (thyrotropin-binding inhibitory immunoglobulin [TBII]) that assesses the presence of antibodies that bind to the TSHR, regardless of their effect on receptor activity. In a patient with thyrotoxicosis, both assays are highly sensitive and specific for Graves disease.

When the diagnosis cannot be established by history, physical examination, and laboratory evaluation, RAI uptake can be measured, preferably using ^{123}I. RAI uptake is elevated in Graves disease, whereas it is low in other causes of thyrotoxicosis like thyroiditis or exogenous thyroid hormone ingestion. If scintigraphy is also performed, the increased RAI uptake in Graves disease is present diffusely throughout the gland, whereas focally increased uptake is observed in hyperfunctioning thyroid nodules.

DIFFERENTIAL DIAGNOSIS

Elevated serum levels of T_4 or free T_4 and T_3 in association with suppressed levels of TSH are diagnostic of thyrotoxicosis (see Table 606.1).

Table 606.5 Diagnostic Criteria for Thyroid Storm

	POINTS
TEMPERATURE °F (°C)	
99-99.9 (37.2-37.7)	5
100-100.9 (37.8-38.2)	10
101-101.9 (38.3-38.8)	15
102-102.9 (38.9-39.4)	20
103-103.9 (39.4-39.9)	25
≥104.0 (>40.0)	30
CENTRAL NERVOUS SYSTEM EFFECTS	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
GASTROINTESTINAL-HEPATIC DYSFUNCTION	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
CARDIOVASCULAR DYSFUNCTION	
Tachycardia	
90-109	5
110-119	10
120-129	15
130-139	20
≥140	25
Congestive Heart Failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial Fibrillation	
Absent	0
Present	10
Precipitating History	
Absent	0
Present	10

In adults, a score ≥45 is highly suggestive of thyroid storm; a score of 25-44 is suggestive of impending thyroid storm; a score of <25 is unlikely to represent thyroid storm.
Data are from HB Burch, L Wartofsky. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am.* 1993;22:263–277. From De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906–916, Table 3.

The combination of diffuse goiter and prolonged thyrotoxicosis (>8 weeks) is most often caused by Graves disease; the presence of circulating TSHR antibodies or characteristic eye or skin changes is diagnostic.

If the etiology of thyrotoxicosis is unclear, ^{123}I radioiodine uptake can distinguish hyperthyroidism (increased uptake) from other causes of thyrotoxicosis, which will determine the appropriateness of antithyroid medication. If a discrete thyroid nodule is palpated, ^{123}I scintigraphy should be performed to assess for a hyperfunctioning nodule. Some children with toxic multinodular goiter may have a TSHR-activating pathogenic variant or McCune-Albright syndrome. If precocious puberty, polyostotic fibrous dysplasia, or café-au-lait macules are present, then McCune-Albright syndrome is likely.

Patients with thyroid hormone resistance have elevated levels of free T_4 and T_3, but levels of TSH are inappropriately elevated or normal. They must be differentiated from patients with TSH-secreting pituitary tumors who have elevated serum levels of the common α-subunit shared by TSH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG). Most other causes of elevated serum T_4 are uncommon but can result in an erroneous diagnosis. Patients with elevated thyroxine-binding globulin levels or familial dysalbuminemic hyperthyroxinemia have high serum T_4 but normal levels of free T_4 and TSH and are clinically euthyroid. Rare patients with pathogenic variants in *SLC16A2* (encoding the MCT8 thyroid hormone transporter) or *THRA* (encoding thyroid hormone receptor α) can present with high serum T_3, inappropriately normal or high TSH, and low or low-normal serum T_4 concentrations.

When thyrotoxicosis is caused by exogenous thyroid hormone, free T_4 and TSH levels are the same as those seen in Graves disease, but in contrast to Graves disease, thyroid size is small, serum thyroglobulin is very low, and ^{123}I radioiodine uptake is suppressed.

TREATMENT

Antithyroid Drugs

In most cases, antithyroid drugs (ATDs) are the preferred initial therapy for Graves disease in children. Alternative treatments include radioiodine ablation (in children older than 10 years of age) and thyroidectomy. Each therapeutic option has advantages and disadvantages (Table 606.6). Methimazole is the first-line ATD for children with Graves disease and functions by blocking the organification of iodide necessary to synthesize thyroid hormone. Methimazole has a long serum half-life (6-8 hours) that allows once- or twice-daily dosing. Propylthiouracil is similar to methimazole, but its use is not recommended in children because of its potential to cause liver failure. However, in rare instances of severe hyperthyroidism in which methimazole cannot be used, a short course of propylthiouracil may be offered to restore euthyroidism before definitive therapy.

Adverse reactions can occur with ATDs and range from mild to life-threatening. Minor adverse effects occur in approximately 10–20% of patients, and severe adverse effects occur in 2–5%. Reactions most commonly occur during the first 3 months of therapy but can occur at any time. Transient urticaria is common and may be managed with antihistamines or by a short period off therapy followed by restarting ATD. Agranulocytosis is a severe adverse reaction that occurs in 0.1–0.5% of patients and can lead to a fatal infection. Therefore during any episode of significant fever, pharyngitis, or oral ulcers, patients should stop taking methimazole and have an absolute neutrophil count checked. On the other hand, transient, asymptomatic granulocytopenia (<2,000/mm^3) is common in Graves disease; it is not a harbinger of agranulocytosis and is not a reason to discontinue treatment. Other severe reactions include hepatitis (0.2–1.0%), a lupus-like polyarthritis syndrome, glomerulonephritis, and antineutrophilic cytoplasmic antibody–positive vasculitis. Severe liver disease, including liver failure requiring transplantation, has been reported with propylthiouracil. The most common liver disease associated with methimazole is cholestatic jaundice, which is reversible when the drug is discontinued. Patients with severe adverse effects should be treated with radioiodine or thyroidectomy. Importantly, methimazole and propylthiouracil have been associated with congenital malformations in infants exposed to these drugs in utero. Methimazole exposure may be associated with aplasia cutis, omphalocele, choanal atresia,

Table 606.6 Treatments for Graves Disease

TREATMENT	ADVANTAGE	DISADVANTAGE	COMMENT
Antithyroid drugs	Noninvasive Less initial cost No risk of permanent hypothyroidism Possible remission	Remission rate 30–50% (with long-term treatment) Adverse drug reactions Drug compliance required	First-line treatment in children and adolescents
Radioactive iodine (^{131}I)	Cure of hyperthyroidism	Permanent hypothyroidism Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism	No evidence for infertility or birth defects with currently recommended doses
Surgery	Rapid, effective (especially in patients with large goiter)	Most invasive therapy Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Permanent hypothyroidism Pain, surgical scar	Useful when coexisting suspicious nodule is present or thyromegaly is massive Option for patients who do not desire radioiodine

Modified from Cooper DS. Hyperthyroidism. *Lancet.* 2003;362:459–468.

Table 606.7 Management of Thyroid Storm in Adolescents

GOAL	TREATMENT
Inhibition of thyroid hormone formation and secretion	Propylthiouracil 400 mg q8h PO/IV/NGT Saturated solution of potassium iodide, 3 drops every 8 hr
Sympathetic blockade	Propranolol 20-40 mg q4-6h or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related
Glucocorticoid therapy	Prednisone 20 mg bid
Supportive therapy	Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins) Temperature control (cooling blankets, acetaminophen; avoid salicylates) O_2 if required Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation Treatment of precipitating event (e.g., infection)

From Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine,* 22nd ed. Philadelphia: WB Saunders; 2004:1401.

and urinary system malformations, whereas propylthiouracil may be associated with malformations of the head, neck, and urinary system.

The initial dosage of methimazole is 0.5-1.0 mg/kg/24 hr (max 40 mg/day) administered once or twice daily. Smaller initial dosages should be used in early childhood or for mild disease. Careful surveillance is required after treatment is initiated. Low serum free T_4 or elevated serum TSH indicates overtreatment and warrants a dose reduction. The clinical response becomes apparent in 3-4 weeks, and adequate control is typically evident within 2-4 months. The dose is slowly decreased to the minimal level required to maintain a euthyroid state.

Most studies report a remission rate of approximately 25% after 2 years of ATD treatment in children. However, extended treatment appears to be associated with higher remission rates of 30–50% after 4-10 years of drug treatment. Among patients who remit, relapse may occur, often within 6-12 months after therapy has been discontinued. In cases of relapse, ATD therapy may be resumed, or definitive therapy with radioiodine or thyroidectomy can be pursued. Rituximab has been used as an adjuvant therapy for difficult-to-treat Graves disease.

Thyroid hormones potentiate the actions of catecholamines, leading to symptoms of tachycardia, tremor, excessive sweating, lid lag, and stare. *To ameliorate cardiovascular symptoms, a β-adrenergic blocking agent such as propranolol or atenolol is a useful initial supplement to ATDs.* However, these agents do not alter thyroid function or treat Graves ophthalmopathy. Table 606.7 lists additional therapies for **thyroid storm**.

Definitive Therapy

Radioiodine ablation or thyroidectomy is indicated when medical management is not possible because of patient nonadherence or severe side effects of ATDs, when an adequate trial of medical management has failed to result in remission, or if the patient prefers definitive therapy.

Radioiodine ablation with ^{131}I is an effective therapy for Graves disease in children. In patients with severe hyperthyroidism, euthyroidism should be restored with methimazole before radioiodine ablation to deplete the gland of preformed hormone and reduce the risk of a thyrotoxic flare from radiation thyroiditis. If a patient is taking methimazole, it should be stopped 3-5 days before radioiodine administration. The goal of radioiodine ablation is to administer a sufficient dose of radioiodine to ensure complete ablation of thyroid tissue. Some centers measure radioiodine uptake before treatment and use this to calculate an ^{131}I dose that delivers an absorbed thyroid dose of >150 μCi/g thyroid tissue (based on thyroid gland mass estimated by clinical examination or ultrasound). Alternatively, an empiric fixed dose of ^{131}I (usually 10-15 mCi) can be offered. The theoretical advantage of calculated doses is that they define the lowest administered dose for each patient who achieves the therapeutic target. This benefit is most important in small children because the absorbed radiation dose to the bone marrow and other normal tissues is inversely proportional to body size. Based on this concept and theoretical modeling of radiation exposure, ^{131}I therapy should be avoided in children younger than 5 years of age. It should be used in children between 5 and 10 years of age if the administered dose is <10 mCi. Radioiodine ablation has a low failure rate (5–20%), and

patients with persistent hyperthyroidism more than 6 months after their first ^{131}I therapy can be offered retreatment.

Thyroidectomy is a safe procedure when performed by an experienced surgeon. Thyroid surgery should be performed only after the patient has been rendered euthyroid with methimazole. A saturated solution of potassium iodide (SSKI; 1-3 drops, 2-3 times per day) may be added for 7-14 days before surgery to decrease the vascularity of the gland. Complications of surgical treatment include hypoparathyroidism (transient or permanent) and paralysis of the vocal cords. Total or near-total thyroidectomy should be performed rather than a less extensive subtotal resection. Patients become hypothyroid postoperatively, and recurrence of hyperthyroidism is rare. Referral to a surgeon with extensive experience in thyroidectomy and a low personal complication rate is paramount.

Graves **ophthalmopathy** usually remits gradually and independently of hyperthyroidism, but control of ophthalmopathy is facilitated by maintaining consistent euthyroidism. Severe ophthalmopathy can require treatment with high-dose glucocorticoids, orbital radiotherapy, or orbital decompression surgery. Teprotumumab, a human monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-1R) is effective in adults with ophthalmopathy. Cigarette smoking is a risk factor for thyroid eye disease and should be avoided or discontinued to avoid progression of eye involvement.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 606.3 Twins with neonatal hyperthyroidism confirmed by abnormal thyroid function tests. Clinical features include lack of subcutaneous tissue owing to a hypermetabolic state and a wide-eyed, anxious stare. They were given the diagnosis of neonatal Graves disease, but, in fact, their mother did not have Graves disease; they had persistent, not transient, hyperthyroidism. At age 8 years, they were treated with radioiodine. They are now believed to have had some other form of neonatal hyperthyroidism, such as a constitutive activation of the thyroid-stimulating hormone receptor.

606.2 Congenital Hyperthyroidism

Jessica R. Smith and Ari J. Wassner

Neonatal Graves disease is caused by transplacental passage of TRSAbs from mothers with a history of Graves disease. These mothers can have active Graves disease, Graves disease in remission, or a prior history of Graves disease treated with radioiodine ablation or thyroidectomy. Occasionally, there is a maternal history of autoimmune thyroiditis. High levels of TRSAb typically result in fetal and neonatal hyperthyroidism. However, if the mother has been treated with ATDs, the onset of hyperthyroidism may be delayed by 3-7 days postnatally until the ATD is metabolized by the neonate. If TRBAbs are also present, they may delay the onset of hyperthyroidism for several weeks or even cause neonatal hypothyroidism. Neonatal Graves disease typically remits spontaneously within 6-12 weeks but can persist longer, depending on the titer and rate of clearance of the TRSAbs (and TRBAbs, if present).

Neonatal hyperthyroidism occurs in approximately 2% of infants born to mothers with a history of Graves disease. Fetal tachycardia and goiter may suggest the diagnosis prenatally, and close ultrasound surveillance is recommended in mothers with uncontrolled hyperthyroidism, particularly in the third trimester. Elevated serum titers of TRSAb (more than 3 times the upper limit of normal) or a history of a prior child with neonatal thyroid dysfunction increases the likelihood of neonatal Graves disease.

CLINICAL MANIFESTATIONS

Many infants born with neonatal Graves disease are premature and have intrauterine growth restriction. Many infants also have a goiter, and tracheal compression can occur if the goiter is very large. Other signs and symptoms of neonatal Graves disease include stare, periorbital edema, retraction of the eyelids, hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, tachycardia, heart failure, hypertension, hepatomegaly, splenomegaly, cholestasis, jaundice, thrombocytopenia, and hyperviscosity (Fig. 606.3). Laboratory evaluation shows suppressed serum TSH and elevated serum levels of T_4, free T_4, and T_3. TRSAbs are elevated at birth and typically resolve within 3 months of life. If symptoms and signs are not recognized and treated promptly, cardiac failure and death can occur. Permanent sequelae of neonatal hyperthyroidism can include craniosynostosis and developmental delay.

TREATMENT

Treatment should be initiated at the onset of symptoms to avoid short-term and long-term complications. Therapy consists of methimazole (0.5-1.0 mg/kg/24 hr given every 12 hr) and oral or intravenous administration of a nonselective β-adrenergic blocker such as propranolol to decrease sympathetic hyperactivity. In refractory cases, Lugol solution or potassium iodide (1-2 drops per day) can be added. The first dose of iodide should be given at least 1 hour after the first dose of ATD to prevent the iodide from being used for further thyroid hormone synthesis. If severe hyperthyroidism induces heart failure, parenteral fluid therapy, corticosteroids, and digitalization may be indicated. Once serum thyroid hormone levels begin to decrease, ATDs should be gradually tapered to keep the infant euthyroid. Occasionally, a block-and-replace method with concurrent ATD and thyroid hormone replacement therapy may be required to ensure euthyroidism.

Most cases of neonatal Graves disease remit by 3 months of age, but occasionally neonatal hyperthyroidism persists into childhood. Typically, there is a family history of hyperthyroidism. **Neonatal hyperthyroidism** *without* evidence for autoimmune disease in mother or infant may be caused by a gain-of-function pathogenic variant in the *TSHR* gene that results in constitutive activation of the receptor. This can be transmitted in an autosomal dominant manner or can occur sporadically. Neonatal hyperthyroidism has also been reported in patients with McCune-Albright syndrome because of an activating pathogenic variant of the G protein stimulatory α-subunit. Under these circumstances, hyperthyroidism recurs when ATDs are discontinued, and these children eventually must be treated with radioiodine or surgery.

PROGNOSIS

Advanced osseous maturation, microcephaly, and cognitive impairment occur when treatment of neonatal hyperthyroidism is delayed. Intellectual development is normal in most treated infants with neonatal Graves disease, although some have neurocognitive problems likely caused by in utero hyperthyroidism. Therefore neurocognitive development should be monitored throughout childhood. After the resolution of neonatal hyperthyroidism, some infants develop transient or permanent central hypothyroidism that requires thyroid hormone replacement, likely resulting from poorly understood changes in hypothalamic-pituitary-thyroid feedback caused by in utero hyperthyroidism.

Resistance to Thyroid Hormone

The actions of thyroid hormones are mediated by two thyroid hormone receptors (α and β), each with a unique tissue distribution. Inactivating pathogenic variants in each of these receptors gives rise to a distinct syndrome of resistance to thyroid hormone. Resistance to thyroid hormone β (RTHβ) is an *autosomal dominant* disorder caused by pathogenic variants in the *THRB* gene. Because this receptor mediates the normal feedback of thyroid hormone on the hypothalamus and pituitary, patients have elevated serum levels of T_4 and T_3, but serum TSH levels are inappropriately normal or elevated. Goiter is almost always present, but symptoms of thyroid dysfunction are variable among individuals. There may be clinical features of hypothyroidism such as developmental delay, growth retardation, delayed skeletal maturation, and some features of hyperthyroidism like tachycardia and hyperreflexia. Affected children have an increased prevalence of learning disabilities and ADHD. The clinical symptoms, goiter, and elevated thyroid hormone levels may be mistaken for Graves disease, but RTHβ is confirmed by the presence of normal or elevated (not suppressed) TSH levels. This condition must also be differentiated from a pituitary TSH-secreting tumor, which is not familial and in which serum levels of the common α-subunit are elevated.

More than 100 distinct variants in *THRB* have been identified in patients with RTHβ, and genotype-phenotype correlation is poor even among affected members of the same family. Nearly all mutations have a dominant-negative effect in which the variant receptor interferes with normal receptor action, leading to disease even in heterozygotes. Individuals carrying two mutant alleles are severely affected. A very rare *autosomal recessive* form of this disorder has been reported in individuals homozygous for a deletion of the *THRB* gene.

Treatment usually is not required unless growth and skeletal stunting are present. Different therapies, including levothyroxine and triiodothyroacetic acid, have been successful in some patients. Intermittent administration of T_3 may be useful for reducing goiter size. Symptoms of hyperthyroidism can be treated with β blockers, but ATDs or radioiodine ablation are generally not used because they increase TSH levels and goiter size.

Pathogenic variants in the *THRA* gene, which encodes thyroid hormone receptor α, have also been reported. *THRA* variants are dominant negative and cause RTHα in heterozygous individuals. Clinical symptoms are those of untreated primary hypothyroidism, including skeletal dysplasia with short stature and macrocephaly, developmental delay, constipation, bradycardia, and macrocytic anemia. Serum thyroid function tests show subtle abnormalities of low or low-normal T_4, high or high-normal T_3 (with elevated T_3/T_4 ratio), and normal TSH, as well as the unique finding of markedly low reverse T_3. Treatment has not been clearly established for RTHα.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 607

Carcinoma of the Thyroid

Jessica R. Smith and Ari J. Wassner

Carcinoma of the thyroid is rare in childhood, with an annual incidence in children younger than 15 years of approximately 4-5 in 100,000 cases. The incidence of childhood thyroid cancer increases with age and peaks in adolescence. Females are more commonly affected than males. Compared to adults, childhood thyroid cancers are characterized by significantly higher rates of metastasis and recurrence. Despite often being metastatic at discovery, most pediatric thyroid cancers with adequate treatment have a favorable outcome.

PATHOGENESIS

The majority of differentiated thyroid cancers are of follicular cell origin; **papillary carcinoma** (85–90%) is the most common subtype. Although their histologic features are similar, papillary thyroid cancers of childhood are genetically distinct from their adult counterparts. About 70% of adults with papillary thyroid cancer exhibit pathogenic somatic variants in *BRAF* or *RAS*; pediatric papillary thyroid cancers are more commonly caused by somatic gene fusion events involving the oncogenic tyrosine kinases *RET* or *NTRK1/3*. **Follicular carcinoma** (8%) is the next most common type of childhood thyroid cancer and is also derived from thyroid follicular cells. **Medullary carcinoma** (4%), derived from thyroid C cells, and anaplastic thyroid cancers are relatively rare.

Up to 10% of cases of follicular cell–derived thyroid cancers may be familial. Genetic syndromes associated with an increased risk of thyroid neoplasia include ***PTEN* hamartoma tumor syndromes** (Cowden, Bannayan-Riley-Ruvalcaba, and Proteus syndromes) characterized by macrocephaly, mucocutaneous lesions (fibromas), and breast cancer and endometrial tumors; **familial adenomatous polyposis** (pathogenic variant in *APC*); and ***DICER1* syndrome**, which includes tumors of the lung, kidney, female reproductive tract, and other organs. The evaluation of a child with a thyroid nodule should include a medical and family history to assess for features of these syndromes. In addition, some families have a strong history of nonsyndromic nonmedullary thyroid cancer, but no specific genetic causes have been confirmed.

The thyroid gland of children is susceptible to radiation exposure, particularly in very young patients. Even a low dose (1 Gy) of radiation exposure results in a 7.7-fold increased relative risk of thyroid cancer. In past decades, irradiation of the cervical region for benign conditions (e.g., enlarged thymus or tonsils, adenitis) was a predominant cause of thyroid cancer in children. Currently, therapeutic irradiation for other regional neoplasms or bone marrow transplantation and the increased survival of these children have made this cause of thyroid cancer increasingly prevalent. Higher radiation dose, younger age at the time of treatment, and female sex are additional risk factors for the development of thyroid cancer. The relative risk of thyroid cancer is highest after radiation doses of 5-30 Gy, above which the excess risk declines but does not disappear. In studies of cancer survivors treated with radiation, ~10–30% develop benign thyroid nodules. There is an increased incidence of thyroid cancer beginning within 3-5 years after radiation treatment and peaking after 15-25 years.

Autoimmune thyroiditis and Graves disease may be associated with an increased risk of thyroid cancer, but data remain conflicting.

Therefore thyroid nodules detected in patients with these disorders should be evaluated for possible thyroid cancer. Thyroid cancer has been reported rarely in children with congenital goiter or ectopic thyroid tissue.

CLINICAL MANIFESTATIONS

Thyroid cancer usually presents as a *painless nodule* in the anterior neck. Rapid growth and large size, firmness, fixation to adjacent tissues, hoarseness, dysphagia, or neck lymphadenopathy should heighten the concern for thyroid cancer. Cervical lymph node metastasis is common, so any unexplained cervical lymphadenopathy warrants examination of the thyroid.

The lungs are the most common site of distant metastasis. Pulmonary metastases are usually asymptomatic, and pulmonary function testing may be normal even with widespread metastases. Radiologically, metastases may appear as diffuse miliary or nodular infiltrations, typically greatest in the posterior basal lung fields. Other sites of metastasis, including bones and brain, are rare in children. Almost all children with thyroid cancer are euthyroid, but rarely is the carcinoma functional and produces clinical and laboratory evidence of hyperthyroidism.

DIAGNOSIS

Patients usually present with a neck mass, and thyroid ultrasound demonstrates a thyroid nodule and/or diffuse infiltration of the thyroid. Although several imaging features (including calcifications, irregular margins, and the presence of abnormal lymph nodes) are significantly associated with thyroid cancer risk, the absence of these features does not exclude the possibility of thyroid cancer. The appropriate technique for evaluating sonographically suspicious nodules is fine needle aspiration (FNA), which can detect the characteristic nuclear abnormalities of papillary thyroid carcinoma, which is the most common form. In most cases, operative pathology is required to confirm the diagnosis of thyroid cancer and to determine the extent of disease.

TREATMENT

The primary therapy for thyroid cancer is surgical resection. Because intrathyroidal spread is common in papillary thyroid cancer, near-total thyroidectomy is recommended. Before surgery, neck ultrasonography should be performed to assess for abnormal lymph nodes, and suspicious lymph nodes may be biopsied preoperatively to determine the need for lymph node dissection. In patients with metastatic thyroid cancer, adjunctive therapy may be required with radioactive iodine (^{131}I) to ablate unresectable thyroid cancer and thyroid-stimulating hormone (TSH) suppression with supraphysiologic levothyroxine to reduce TSH-stimulated growth of residual cancer cells.

PROGNOSIS

Although regional and distant metastases are more common in the pediatric population than in adults, most children with thyroid cancer have an excellent prognosis. Long-term survival from pediatric thyroid cancer is >97%, although the disease may recur in up to 15–20%. Even in children with pulmonary metastasis at diagnosis, 30-year survival is 90%, and many patients who cannot achieve complete cure remain asymptomatic with stable or slowly progressive cancer burden over many years. For rare children with aggressive cancers that progress despite conventional therapy, targeted molecular therapies directed at the underlying genetic pathogenic variants are available and effective in many cases. Psychosocial supports, including access to social work and mental health professionals, are essential in caring for children with thyroid cancer.

Children with thyroid cancer require lifelong monitoring because of the risk of disease recurrence years or decades after initial treatment. For most patients, serum thyroglobulin is a sensitive and specific cancer marker. Circulating autoantibodies to thyroglobulin can confound the measurement of thyroglobulin levels and should be measured whenever serum thyroglobulin is assayed. Because most thyroid cancer recurrences occur in the thyroid bed or cervical lymph nodes, surveillance should include serial neck ultrasounds. Patients with a higher risk of recurrence or with distant metastases may require additional anatomic imaging (such as chest CT), whole-body radioactive iodine scanning (^{123}I), or combined anatomic and functional imaging (SPECT/CT).

MEDULLARY THYROID CARCINOMA

Medullary thyroid carcinoma (MTC) arises from the parafollicular cells (C cells) of the thyroid and accounts for approximately 4% of thyroid malignancies in children. In children, the majority of MTC cases are hereditary, as part of the syndrome of **multiple endocrine neoplasia type 2** (MEN2; see Chapter 609). Activating pathogenic variants in the *RET* proto-oncogene are responsible for most cases of MTC. These variants occur in the germline in patients with MEN2, but somatic *RET* changes are present in many sporadic cases of MTC.

The most common presentation of sporadic MTC is an asymptomatic thyroid nodule. When MTC occurs sporadically, it is usually unicentric, but in the familial form it may be multicentric. MTC begins as hyperplasia of the parafollicular cells (*C cell hyperplasia*), which is often present histologically in thyroid glands removed prophylactically from patients with MEN2. The diagnosis of MTC can also be made by cytology after FNA of a thyroid nodule. Because C cells produce calcitonin, a high calcitonin concentration in an FNA specimen or in a patient's serum can help confirm the diagnosis of MTC. The diagnosis warrants genetic testing for a germline *RET* variant, and in variant-positive patients, screening for pheochromocytoma and hyperparathyroidism should be obtained before anesthesia for thyroidectomy.

The most important treatment for MTC is surgical resection. Preoperative evaluation should include neck ultrasound to identify potential lymph node metastases. Baseline serum levels of calcitonin and carcinoembryonic antigen (CEA) should be measured preoperatively, and higher levels are correlated with a greater likelihood of metastatic disease. Surgical treatment includes total thyroidectomy and lymph node dissection of any involved lymph node compartments. Complete resection is often curative, but this can be difficult to achieve in patients with metastatic disease. Surveillance with neck ultrasound and serum levels of calcitonin and CEA can assess for the presence or progression of residual disease. Other treatment modalities for advanced or metastatic disease include specific *RET* inhibitors, external beam radiation, and radiofrequency ablation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

607.1 Thyroid Nodules

Jessica R. Smith and Ari J. Wassner

The frequency of thyroid nodules increases with age. Sonographically detectable thyroid nodules are present in 19–67% of adults but in only 1–2% of children. Although the risk of malignancy in a thyroid nodule is higher in children (20–25%) than in adults (5–15%), the majority of thyroid nodules in children are benign.

Benign disorders that can present as a thyroid mass include benign adenomatous or colloid nodules and various congenital cysts (Table 607.1). A thyroid mass that appears suddenly or enlarges rapidly can indicate hemorrhage into a cyst, a benign adenoma, or an infectious process.

Evaluation of a child with a thyroid nodule should begin by measuring serum TSH. A low serum TSH suggests a possible hyperfunctioning (autonomous) thyroid nodule, which should be evaluated by scintigraphy (^{123}I or ^{99m}Tc-pertechnetate). Autonomous nodules generally are not malignant and do not require biopsy. Patients with a normal or elevated TSH should undergo neck ultrasound, and any sonographically suspicious nodule(s) of significant size should be evaluated by ultrasound-guided FNA

Table 607.1 Etiologic Classification of Solitary Thyroid Nodules

Lymphoid follicle, as part of autoimmune thyroiditis
Thyroid developmental anomalies
Intrathyroidal thyroglossal duct cyst
Intrathyroidal ectopic thymus
Thyroid abscess (acute infectious thyroiditis)
Simple cyst
Neoplasms
Benign
Colloid (adenomatous) nodule
Follicular adenoma
Hyperfunctioning (toxic) adenoma
Lymphohemangioma
Malignant
Papillary carcinoma
Follicular carcinoma
Anaplastic carcinoma
Medullary carcinoma
Nonthyroidal
Lymphoma
Teratoma

(Fig. 607.1). Thyroid cytology is evaluated using a standardized system, most commonly the Bethesda System for Reporting Thyroid Cytopathology. Cytology may be interpreted as benign, positive for papillary thyroid cancer, indeterminate, or nondiagnostic. The predictive value of cytology for thyroid cancer varies by category and to some degree among institutions. In general, cytology positive for papillary thyroid cancer confers a >98% likelihood of cancer, and near-total thyroidectomy is appropriate. For a nodule of indeterminate cytology, lobectomy is commonly performed for definitive diagnosis; this may be followed by completion thyroidectomy if pathology shows a significant thyroid cancer. Molecular testing for oncogenic mutations may inform the management of certain indeterminate cytology. Patients with cytologically benign nodules have a low likelihood of malignancy and should be monitored with serial neck ultrasound. Surgical resection may be offered for benign nodules that cause symptoms, including dysphagia, globus sensation, or undesired appearance.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

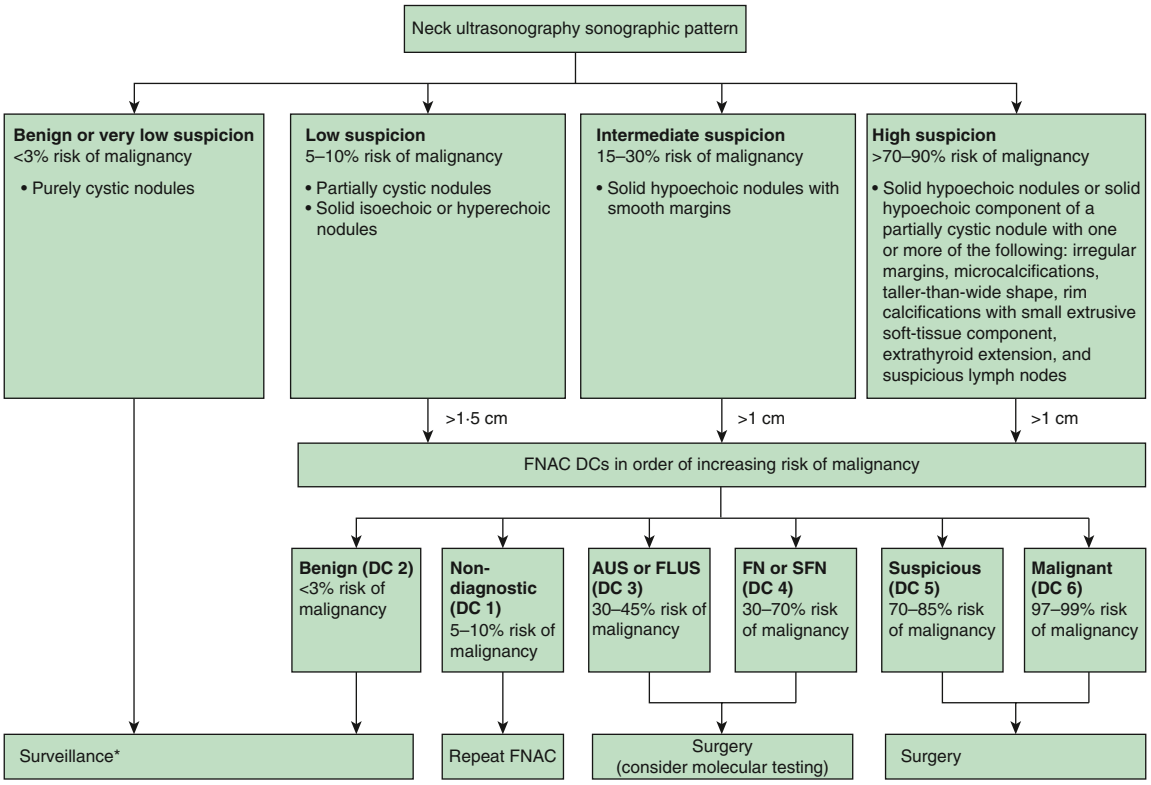

Fig. 607.1 Management algorithm for thyroid nodules based on sonographic patterns and cytology diagnostic categories of the Bethesda System. *Fine-needle aspiration can be considered (1) for nodules with a low-suspicion sonographic pattern and the largest diameter greater than 2 cm and (2) if there are suspicious clinical findings (e.g., firm mass, neck pain, cough, voice change, and a history of childhood neck irradiation or familial thyroid cancer), regardless of the sonographic appearances. AUS, Atypia of undetermined significance; DC, diagnostic category; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm; FNAC, fine needle aspiration cytology; SFN, suspicious for follicular neoplasm. *(From Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388:2783–2794, Fig. 2.)*

Chapter 608

Autoimmune Polyglandular Syndromes

Christina M. Astley, Jessica R. Smith, and Ari J. Wassner

An **autoimmune polyglandular syndrome (APS)** occurs when autoimmunity is directed at multiple glands and/or nonendocrine organs, sometimes associated with **immune dysregulation**. Endocrine glands and other organs commonly affected by APS have unique autoantigens that increase these tissues' susceptibility to damage by an untamed immune response. Most autoimmune endocrinopathies are caused by cell-mediated immunity from autoreactive T cells. Antibodies to one or more autoantigens are commonly associated with specific autoimmune manifestations and are markers of immune dysregulation. These autoantibodies are directly pathogenic in some nonendocrine tissues, but this is rarely the case in autoimmune endocrine disease. A notable exception is the autoantibodies in Graves disease that cause primary hyperthyroidism by activating the thyroid-stimulating hormone receptor (TSHR).

APS caused by monogenic disorders of immune dysregulation (including APS type 1 [**APS-1**]) have heritable lesions in key aspects of immune tolerance (Table 608.1). Polygenic disorders associated with APS (APS type 2 [**APS-2**]) and some chromosomal abnormalities (e.g., trisomy 21) also result in an aberrant immune response that causes multiorgan autoimmunity. Nongenetic factors (e.g., immune **checkpoint inhibitors** for cancer therapy) may lead to autoimmune polyglandular disease. Although APS is uncommon, patients can experience significant morbidity, particularly if the syndrome is not identified early and managed appropriately. There may be 1-2 decades between the presentations of the first and subsequent endocrinopathy. *The presence of hypoparathyroidism, primary adrenal insufficiency, neonatal type 1 diabetes mellitus, chronic mucocutaneous candidiasis, immune dysregulation, or a family history should raise particular suspicion for APS.*

MONOGENIC AUTOIMMUNE POLYGLANDULAR SYNDROMES

The number of recognized monogenic defects of immune regulation leading to APS continues to grow (see Table 608.1). The best-characterized monogenic APSs are caused by pathogenic genetic variants that primarily affect central immune tolerance **(APS-1)** or the development of regulatory T cells (immune dysregulation polyendocrinopathy enteropathy X-linked, or **IPEX**). Other monogenic APSs (the so-called IPEX-like disorders) are caused by defects in regulatory T-cell suppression or signaling.

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1

APS-1 is an archetypal monogenic polyendocrinopathy syndrome. It is a rare, autosomal recessive disorder caused by loss-of-function variants in the autoimmune regulator gene *(AIRE)* on chromosome 21q22.3. *AIRE* plays a critical role in the presentation of self-antigens to developing T cells in the thymus, which normally leads to central immune tolerance by inducing apoptosis of T cells specific for these autoantigens (negative selection). *AIRE* also plays a role in the development of regulatory T cells (see Chapter 174). Therefore patients with APS-1 develop autoreactive T cells and autoantibodies directed at multiple tissues.

APS-1 is defined by the presence of at least two of three classic clinical features **(Whitaker triad)** of **chronic mucocutaneous candidiasis**, **hypoparathyroidism**, and primary **adrenal insufficiency**. These three manifestations tend to emerge over time—candidiasis before around 5 years of age, hypoparathyroidism around 10 years, and adrenal insufficiency around 15 years—but the precise order and age of onset of each component are variable. Most patients develop additional autoimmune manifestations over time, with skin and gastrointestinal disorders typically emerging before age 20 and other endocrine disorders after the second decade (see Table 608.1).

Nearly every endocrine gland may be affected by APS-1. The commonly affected glands include parathyroids and adrenals. Other glands affected, in decreasing order of frequency, are the ovaries, testes, thyroid, pancreatic β cells, and pituitary. A wide range of nonendocrine tissues can be affected, sometimes before the first endocrinopathy is detected. The commonly affected nonendocrine tissues are teeth and nails, and ectodermal dystrophy is present in most patients. For this reason, APS-1 has also been called **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)**. Other manifestations include gastrointestinal malabsorption, autoimmune hepatitis, pernicious anemia, vitiligo, and alopecia. APS-1 patients are at increased risk of infection, possibly related to a combination of cytokine autoantibodies, splenic dysfunction, and compromised gastrointestinal mucosal integrity. Mucocutaneous candidiasis is quite common and can lead to oral or esophageal cancer if not diagnosed and treated. Esophageal cancer, autoimmune hepatitis, adrenal crisis, and severe hypocalcemia are important causes of mortality in APS-1 patients. Therefore APS-1 patients require close clinical follow-up with a multidisciplinary team to manage disease manifestations. (Treatment of individual endocrinopathies and other manifestations are reviewed separately in the relevant chapters, including Chapters 280, 611, and 615).

The initial diagnosis of APS-1 generally is made clinically. Pathogenic *AIRE* variants can be detected in the majority of patients with clinical APS-1, and confirmation of the diagnosis by *AIRE* sequencing is indicated for any patient with known or suspected APS-1. APS-1 caused by pathogenic *AIRE* variants is more common in certain founder populations (e.g., Iranian Jews, Sardinians, Finns, and Norwegians reported a prevalence ranging from 1 in 9,000 to 1 in 90,000). Knowledge of the specific pathogenic variant facilitates clinical and genetic counseling, including testing of family members. *AIRE* variants with autosomal dominant inheritance and an atypical APS-2–like clinical presentation (especially with pernicious anemia or vitiligo) have been reported. APS-1 patients without identifiable *AIRE* variants may benefit from further evaluation (e.g., immune dysregulation gene panel, whole exome sequencing, imaging for thymoma).

The clinical presentation of APS-1 is variable, even within families with the same *AIRE* variant, making it difficult to predict the disease course for affected individuals. Therefore patients with APS-1 should have regular screening for the development of new clinical manifestations. The importance of screening is illustrated by unexplained deaths in APS-1 patients or their siblings, presumably the result of undiagnosed manifestations such as adrenal insufficiency.

Multiple autoantibodies may be detectable in patients with APS-1 (Table 608.2). Many of these autoantibodies are also present in the corresponding single-organ autoimmune disease, but autoantibodies to some antigens (e.g., NALP5, interleukin-17 family cytokine, and type 1 interferons) are unique to APS-1. Measuring organ-specific autoantibodies has variable utility for predicting the onset of endocrine gland failure or other APS-1 manifestations. Therefore clinical suspicion, laboratory screening, and education about symptoms of evolving endocrinopathies and/or other APS-1 manifestations are paramount regardless of autoantibody status.

IMMUNE DYSREGULATION-POLYENDOCRINOPATHY-ENTEROPATHY X-LINKED

IPEX is caused by loss-of-function variants in *FOXP3,* which is located on the X chromosome (Xp11.23) (see Chapter 174). The inactivation of *FOXP3* results in impaired peripheral immune tolerance caused by impaired development of regulatory T cells, leading to the emergence of autoreactive T cells. The endocrinopathies commonly associated with IPEX are early-onset type 1 diabetes mellitus and autoimmune thyroiditis. *Any diagnosis of type 1 diabetes mellitus*

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation

	EPIDEMIOLOGY AND GENETICS				ENDOCRINOPATHIES				
APS	GENETIC ABNORMALITY	INHERITANCE	ONSET	CLASSIC PHENOTYPE	ADRENAL INSUFFICIENCY	THYROID	TD1	HPT	GONADAL INSUFFICIENCY
MONOGENIC APS									
APS-1	*AIRE*	AR (AD rare)	Infancy	Candidiasis, hypoparathyroidism, Addison disease, ectodermal dystrophy	●●●●	●●	●●	●●●●	●●
IPEX	*FOXP3*	XL	Infancy	Enteropathy, type 1 diabetes in infancy, eczematous dermatitis		●●●●	●●●●		
CTLA4	*CLTA4*	AD	Infancy	Enteropathy, cytopenia, lymphocytic aggregates, hypogammaglobulinemia		●●	●		
LRBA	*LRBA*	AR	Infancy	Enteropathy, respiratory tract disease, organomegaly, hypogammaglobulinemia		●	●		
STAT1	*STAT1*	AD	Infancy	Candidiasis, recurrent infections, multiple autoimmunity, cerebral aneurysm	●	●●	●		
STAT5b	*STAT5b*	AR	Infancy	Enteropathy, respiratory tract disease, recurrent infections, growth failure		●●			
CD25	*IL2RA*	AR	Infancy	Enteropathy, type 1 diabetes in infancy, recurrent infections		●●●●	●●●●		
OTHER APS AND APS-LIKE CONDITIONS									
APS-2	*HLA, MICA, PTPN22, CTLA4, NALP1*	Polygenic	Adulthood	Addison disease, autoimmune thyroid disease, type 1 diabetes	●●●●	●●●	●●		●
Turner syndrome	*46, X* (most)	N/A	Congenital	Short stature, ovarian insufficiency, webbed neck, coarctation of the aorta		●●	●		●●●●
Klinefelter syndrome	*47, XXY* (most)	N/A	Congenital	Tall stature, testicular insufficiency, gynecomastia	●	●	●		●●●●
Down syndrome	Trisomy 21	N/A (most)	Congenital	Hypotonia, epicanthal folds, Brushfield spots, single palmar crease, developmental delay		●●	●		

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation—cont'd

	NONENDOCRINE MANIFESTATIONS							
OTHER ENDOCRINE	**CANDIDA INFECTION**	**OTHER INFECTIONS**	**MALABSORPTION, ENTEROPATHY**	**GI AUTOIMMUNITY**	**AUTOIMMUNE HEPATITIS**	**VITILIGO**	**ECZEMA, ALLERGIC DISEASE**	**OTHER**
	●●●●	●●	●●	●●	●●	●●		Keratoconjunctivitis, periodic fever, asplenism
	●	●	●●●●		●		●●●●	Cytopenias, bacterial infections, nephritis
		●●●●	●●●●					Cytopenias, lung disease, psoriasis and skin disease
		●●●●	●●●	●		●	●	Respiratory infection, cytopenias, myasthenia gravis
	●●●●	●●●●	●●●●	●	●	●●	●●	Psoriasis, cytopenia, vascular, skin disease
GH resistance, hyperprolactinemia		●●●●	●●●●				●●●●	VZV infections, cytopenia
	●●●●	●●●●	●●●●				●●●●	EBV and CMV infections, cytopenia
			●	●●	●	●		
Short stature				●		●		Lymphedema, psoriasis, IBD
Tall stature, gynecomastia								Lupus, Sjogren syndrome, multiple sclerosis (rare)
Short stature				●				Congenital heart disease

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

Continued

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation—cont'd

	EPIDEMIOLOGY AND GENETICS				ENDOCRINOPATHIES				
APS	GENETIC ABNORMALITY	INHERITANCE	ONSET	CLASSIC PHENOTYPE	ADRENAL INSUFFICIENCY	THYROID	TD1	HPT	GONADAL INSUFFICIENCY
DiGeorge syndrome	*22q11.2 del*	AD	Congenital	Absent thymus, congenital heart disease, hypocalcemia, developmental delay		●	●	●●	
ROHHAD	None identified	N/A	Early childhood	Rapid-onset obesity, hypothalamic dysfunction, autonomic dysregulation, neuroblastic tumor					
Checkpoint inhibitor IRAE		N/A	Post-treatment	Oncology treatment, possible pre-existing autoimmunity	●	●	●		

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

before 6-9 months of age should prompt consideration of a monogenic APS or a genetic cause of β-cell dysfunction. Patients with IPEX often have autoimmune enteropathy and eczematous dermatitis. They may also have other autoimmunity (e.g., liver, kidney, cytopenias) and allergic dysregulation (e.g., food allergy, peripheral eosinophilia). Therapy for IPEX consists of immune modulation with immunosuppressants (e.g., glucocorticoids, tacrolimus), novel therapeutics (e.g., abatacept), or stem cell transplantation.

OTHER MONOGENIC IMMUNE DYSREGULATION DISORDERS

Several other disorders involve failure of peripheral tolerance and emergence of autoimmunity, often with some degree of immune dysregulation. These disorders include loss-of-function genetic variants in *IL2RA* (CD25), *LRBA, CTLA4, STAT5b,* and gain-of-function variants in *STAT1* and *STAT3* that are pathophysiologically similar to IPEX. Broadly, patients with these **IPEX-like disorders** are at high risk of type 1 diabetes mellitus and autoimmune thyroiditis (see Table 608.1). They also have multiple nonendocrine diseases, especially autoimmunity and immunodeficiency affecting the skin, lungs, and gastrointestinal tract. *STAT5b* participates in the IL2/STAT5 signal transduction axis necessary for growth hormone signaling and may also affect prolactin secretion. Therefore patients with **STAT5b** defects may have nonautoimmune growth hormone insensitivity and hyperprolactinemia in addition to immune dysregulation, hypergammaglobulinemia, and multiple autoimmunity. ***STAT1*** gain-of-function variants inhibit the normal production of Th17 cytokines, which leads to chronic mucocutaneous candidiasis. These patients also have increased risk of infection, squamous cell cancer, enteropathy, and arterial aneurysms. Patients with **CD25** defects are also at increased risk of infection because interleukin (IL)-2 signaling plays a role in Th17 responses. Many IPEX-like patients develop nonautoimmune endocrinopathies, including iatrogenic adrenal insufficiency, dysglycemia, hypocalcemia, poor bone health from high-dose glucocorticoid therapy, chronic inflammation/infection, and/or malabsorption/malnutrition.

POLYGENIC AUTOIMMUNE POLYGLANDULAR SYNDROME

APS-2 is a clinical syndrome defined by the presence of two or more syndrome-specific endocrinopathies: autoimmune primary adrenal insufficiency (Addison disease), autoimmune thyroid disease (Hashimoto thyroiditis or Graves disease), and/or type 1 diabetes mellitus. Some classification systems subdivide APS-2 according to the particular glands affected (e.g., subtype 2, 3, and 4 if adrenal, thyroid, or neither gland, respectively) or other autoimmune manifestations present (e.g., subtype 3A, 3B, and 3C if additional endocrine, gastrointestinal, or systemic autoimmunity are present, respectively). However, because there is no clear pathophysiologic distinction between these subtypes, they can be considered collectively as APS-2. When describing the characteristics of APS-2, it is important to recognize some degree of overlap between patients with clinical APS-2 and those with a single autoimmune endocrinopathy who may later develop another and be classified as APS-2.

Unlike monogenic APSs, which are rare diseases with early-childhood onset and a mendelian inheritance pattern, APS-2 is a common polygenic disease that usually manifests after the second decade in a patient with a personal or family history of autoimmune disease. APS-2 is most common in middle-age females (prevalence near 1 in 20,000). Primary gonadal insufficiency, vitiligo, alopecia, and chronic atrophic gastritis (with or without pernicious anemia) can occur. Autoimmune hypoparathyroidism and candidiasis are not typical of APS-2 and should prompt consideration of APS-1.

Addison disease is uncommon in the general population (prevalence near 1 in 10,000). However, patients with this condition are at high risk of developing additional endocrine autoimmunity constituting APS-2. Two thirds will have evidence of additional subclinical or clinical autoimmunity. Patients with Addison disease should have close follow-up, screening, and education about other autoimmune manifestations. About half of patients with Addison disease have autoimmune thyroid disease (**Schmidt syndrome**), and about 10% have type 1 diabetes mellitus **(Carpenter syndrome**). Less frequent comorbid autoimmune manifestations include Graves disease, ovarian insufficiency, alopecia, vitiligo, pernicious anemia, or celiac disease.

APS-2 develops less frequently in patients with type 1 diabetes mellitus than in those with Addison disease. Nevertheless, many patients with type 1 diabetes develop additional autoimmunity, and comorbid autoimmune thyroid and gastrointestinal disease are much more common (each about 20%) than comorbid adrenal disease (<1%). Because thyroxine and cortisol affect insulin sensitivity, metabolism, and appetite, unexplained hypoglycemia or deterioration in glycemic control may be the first clinical sign of APS-2 in a patient with preexisting type 1 diabetes mellitus. Unexplained hypoglycemia may also signal the onset of celiac disease. Indeed, **celiac disease** often precedes the onset of autoimmune endocrinopathies, including type 1 diabetes mellitus, hypothyroidism, and Addison disease.

The development of APS-2 in individuals with autoimmune thyroid disease is relatively infrequent. Nevertheless, the clinician should consider the possibility of adrenal insufficiency before treating

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation—cont'd

	NONENDOCRINE MANIFESTATIONS							
OTHER ENDOCRINE	**CANDIDA INFECTION**	**OTHER INFECTIONS**	**MALABSORPTION, ENTEROPATHY**	**GI AUTOIMMUNITY**	**AUTOIMMUNE HEPATITIS**	**VITILIGO**	**ECZEMA, ALLERGIC DISEASE**	**OTHER**
Short stature								Thymic dysplasia/aplasia, congenital heart disease, T-cell deficiency, cytopenias
Hypothalamic dysfunction, hyperprolactinemia								Autonomic dysregulation, central hypoventilation
								Multiple nonendocrine IRAE

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

Table 608.2 Autoantibodies Present in Autoimmune Polyglandular Syndromes and in Isolated Autoimmune Endocrinopathies

TISSUE OR GLAND	AUTOANTIGEN	DISEASE MANIFESTATION	NOTE
AUTOIMMUNE ENDOCRINOPATHIES			
Adrenal	CYP21A2, CYP11A1, CYP17A1	Primary adrenal insufficiency	Of the adrenal autoantibodies, CYP21A2 is most strongly associated with adrenal insufficiency. Higher risk of progression to adrenal insufficiency in children with positive adrenal autoantibodies (over 80%) compared with adults (near 20%). Adrenal autoantibodies detected in 50% of pediatric hypoparathyroidism and 1% of pediatric type 1 diabetes
Thyroid	TPO, Tg	Autoimmune thyroiditis (hypothyroidism)	Frequently positive without clinical thyroid disease
	TSHR	Graves disease (hyperthyroidism)	Only endocrine autoantibody that directly causes autoimmune endocrinopathy
Pancreatic β cell	IA-2, GAD65, insulin, ZnT8	Type 1 diabetes mellitus	Risk of type 1 diabetes increases with the number of positive autoantibodies; IA-2, but not GAD65, autoantibodies associated with time to type 1 diabetes diagnosis in APS-1
Parathyroid	NALP5, CaSR	Hypoparathyroidism	NALP5 antibodies are present only in hypoparathyroidism caused by APS-1
Gonad	CYP11A1, CYP17A1, NALP5 and TSGA10	Gonadal insufficiency	CYP11A1 antibodies associated with gonadal insufficiency in APS-1
Pituitary	TDRD6	Hypophysitis	Poorly predictive of clinical pituitary disease
NONENDOCRINE DISEASE			
Cytokines	IFN-ω, IFN-α, IL-22, IL-17F	APS-1	IFN-ω autoantibodies are 100% sensitive and 99% specific for APS-1; IL-22 autoantibodies associated with time to diagnosis and diagnosis of candidiasis in APS-1
Gastric	IF, H+/K+ ATPase	Pernicious anemia, autoimmune gastritis	IF autoantibodies associated with time to B_{12} deficiency in APS-1
Small intestine	TTG, gliadin	Celiac disease	
Gastrointestinal	TPH, GAD65	Intestinal dysfunction	TPH autoantibodies associated with time to intestinal dysfunction in APS-1. Both autoantibodies associated with diagnosis of intestinal dysfunction in APS-1

Continued

Table 608.2 Autoantibodies Present in Autoimmune Polyglandular Syndromes and in Isolated Autoimmune Endocrinopathies—cont'd

TISSUE OR GLAND	AUTOANTIGEN	DISEASE MANIFESTATION	NOTE
Liver	CYP1A2, TPH, AADC	Autoimmune hepatitis	TPH autoantibodies associated with diagnosis of autoimmune hepatitis in APS-1
Skin melanocytes	Tyrosinase, SOX9, SOX10, AADC	Vitiligo	
Hair follicle	Tyrosine hydroxylase	Alopecia	
Lung	KCNRG, BPIFB1	Interstitial lung disease	Both autoantibodies present in 90–100% of APS-1 patients with interstitial lung disease and are associated with time to diagnosis

AADC, Aromatic L-amino acid decarboxylase; BPIFB1, bactericidal/permeability-increasing fold-containing B1; CaSR, calcium sensing receptor; CYP11A1, side chain cleavage enzyme; CYP17A1, 17-α-hydroxylase; CYP1A2, cytochrome P450 1A2; CYP21A2, 21-hydroxylase; GAD65, glutamic acid decarboxylase; IA-2, islet antigen-2; IF, intrinsic factor; IFN, interferon; IL, interleukin; KCNRG, potassium channel-regulating protein; NALP5, NACHT leucine-rich-repeat protein 5; TDRD6, Tudor domain containing protein 6; Tg, thyroglobulin; TPH, tryptophan hydroxylase; TPO, thyroid peroxidase; TSGA10, testis-specific gene 10 protein; TSHR, thyroid-stimulating hormone receptor; TTG, tissue transglutaminase; ZnT8, zinc transporter 8.

hypothyroidism in a patient with features suggestive of APS-2 because thyroid hormone replacement may precipitate **adrenal crisis** in this setting. Autoantibodies to specific tissues may be detectable and may prompt functional screening before the onset of overt clinical disease (see Table 608.2); however, the predictive value of these autoantibodies for the development of clinical disease is variable.

Aberrant T-cell responses probably play a role in the pathogenesis of multiple gland destruction present in APS-2. The risk of autoimmunity directed against the adrenal glands, thyroid gland, and islet cells appears to be shared across certain human leukocyte antigen (HLA) haplotypes and other immune-related genetic loci. However, the magnitude of this risk varies substantially for each endocrinopathy. The prevalence of HLA-D3 and HLA-D4 alleles is increased in patients with APS-2, and they appear to confer an increased risk for the development of this disease. Particular alleles of the major histocompatibility complex class I chain-related genes A and B (*MICA* and *MICB*) also are associated with APS-2. Polymorphisms in other genes (e.g., *PTPN22*, *CTLA4*) have been associated with individual autoimmune endocrinopathies that constitute APS-2, but the contribution of these genes to the pathogenesis of APS-2 itself is uncertain. Although not well defined, there are likely environmental factors that promote the development of autoimmunity in genetically susceptible individuals, and many of the risk factors associated with endocrine and nonendocrine autoimmunity overlap (see individual chapters on these diseases for more detailed discussions of risk factors). Next-generation immune therapies combined with an understanding of autoimmunity pathways may lead to targeted treatments to prevent new endocrinopathies (e.g., type 1 diabetes mellitus) among those at high risk.

CHROMOSOMAL ABNORMALITIES ASSOCIATED WITH AUTOIMMUNE POLYGLANDULAR SYNDROME

Many genetic syndromes involving chromosomal deletions, duplications, and other copy number variations are associated with an increased risk of autoimmunity, particularly endocrine autoimmunity affecting the thyroid and pancreatic β cells (see Table 608.1). Clinical practice guidelines for many of these genetic syndromes recommend routine screening for autoimmune and endocrine manifestations. Males with **Klinefelter syndrome** and females with **Turner syndrome** have an increased risk of autoimmunity in multiple systems, including autoimmune endocrine disease. The mechanism of autoimmunity in **trisomy 21** remains unclear, although differences in *AIRE* gene expression, HLA susceptibility, and autoantibody profiles have been described. Thymic dysplasia is a typical feature of **DiGeorge syndrome** (22q11.2 deletion), and the resulting **immune dysregulation** may play a role in the increased risk of autoimmunity in this disorder. Patients with genetic syndromes and chromosomal abnormalities may have nonautoimmune endocrinopathies such as abnormal growth, primary gonadal failure, and hypoparathyroidism.

Mitochondrial diseases such as Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinal pigmentation, cardiac conduction defects) and MELAS (mitochondrial encephalomyopathy, lactic acidosis, strokelike episodes) have been associated with polyendocrinopathy syndromes, with some rare cases reported to be associated with autoimmunity. Endocrine manifestations of mitochondrial disease include diabetes mellitus, hypogonadism, adrenal insufficiency, hypoparathyroidism, and hypothyroidism. These manifestations may develop before neurologic and other organ injury and could be an early clue of mitochondrial dysfunction.

NONGENETIC AUTOIMMUNE CAUSES OF MULTIPLE ENDOCRINOPATHY

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation **(ROHHAD)** is a rare pediatric syndrome diagnosed by its cardinal clinical features (see Chapter 468.3). Children with ROHHAD abruptly develop rapid weight gain and associated autonomic deficits (e.g., ophthalmologic findings, gastrointestinal dysmotility, thermal dysregulation, bradycardia), central hypoventilation, and/or hypothalamic dysfunction. Patients have progressive dysfunction of hypothalamic-pituitary axes such as central hypothyroidism, growth hormone deficiency, hyperprolactinemia, and vasopressin dysregulation (see Chapter 468.3). It is hypothesized that ROHHAD is an autoimmune paraneoplastic neurologic syndrome based on the presence of cerebrospinal fluid inflammatory markers, response to immunosuppressive therapy in some patients, and identification of neuroblastic tumors in about half. Antineural autoantibody profiling and genetic testing have not yet identified the underlying cause of ROHHAD.

Novel immune-modulating biologic compounds are used increasingly in the treatment of malignancies and immune disorders. Monoclonal antitumor drugs that *inhibit immune checkpoints* such as CLTA4, PD1, and PD-L1 are associated with immune-related adverse effects (IRAEs). Clinically important IRAEs include acute onset of multiple autoimmune endocrinopathies, including hypophysitis with hypopituitarism (especially with CTLA4-directed therapies), thyroiditis with hyperthyroidism or hypothyroidism, type 1 diabetes mellitus, and primary adrenal insufficiency. Anti-CD52 antibodies used to treat multiple sclerosis have been linked to the development of Graves disease and other antibody-mediated autoimmune diseases (e.g., immune thrombocytopenic purpura). Preexisting autoimmunity may be a risk factor for developing autoimmune disease after exposure to a wide range of immunomodulatory therapies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 609

Multiple Endocrine Neoplasia Syndromes

Ari J. Wassner and Jessica R. Smith

Multiple endocrine neoplasia (MEN) syndromes are characterized by the development of tumors in two or more endocrine glands. These syndromes are divided clinically into two types based on the specific endocrine organs involved (Table 609.1). MEN type 1 is characterized by tumors of the parathyroid glands, anterior pituitary, and endocrine pancreas. In contrast, MEN type 2 is characterized by medullary thyroid cancer and pheochromocytoma. Both types of MEN are usually inherited in an autosomal dominant fashion, but sporadic cases can occur.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Multiple endocrine neoplasia type 1 (MEN1) most commonly presents in the fourth or fifth decade of life, but endocrine tumors can develop as early as 5 years of age. The endocrine tissues most frequently involved include the parathyroid glands, pituitary, and cells of the endocrine pancreas.

Primary hyperparathyroidism caused by a parathyroid adenoma or multigland hyperplasia is the most common manifestation of MEN1, with a lifetime cumulative incidence of 90–95%. In children with MEN1, hyperparathyroidism usually presents after 10 years of age and is often the first endocrine disorder to develop (in about 50% of cases). The diagnosis and management of hyperparathyroidism are discussed in Chapter 613. In patients with MEN1, bilateral surgical exploration is generally recommended over focused, minimally invasive approaches because of the tendency for multiple parathyroid glands to be hyperplastic. In such cases, subtotal (3- or 3.5-gland) parathyroidectomy may be required. MEN1 may be present in 15–70% of pediatric cases of primary hyperparathyroidism, and this syndrome should be considered in any child or adolescent with primary hyperparathyroidism, particularly if multigland hyperplasia is present.

Pituitary adenomas are the presenting feature of pediatric MEN1 in about 20% of cases and usually occur after age 10 years, although they have been reported in patients as young as 5 years. Although these adenomas most commonly secrete prolactin (60–70%), a few secrete growth hormone (5–10%) or adrenocorticotrophic hormone (5%), and the remainder are nonfunctioning (~25%). Diagnosis and management are similar to that of sporadic pituitary adenomas except that adenomas associated with MEN1 may be more locally aggressive and are more likely to cosecrete multiple pituitary hormones (see Chapter 598).

Patients with MEN1 can develop neoplasia of various **enteropancreatic endocrine** cells. Such tumors may occur in up to 70% of patients by adulthood but are found in only about 5–20% of affected children. Nonfunctioning pancreatic neuroendocrine tumors are the most common pancreatic lesions found in children with MEN1 and are usually detected by screening imaging. Insulinomas are the most common functional pancreatic tumor in children with MEN1, occurring in 3–10% of cases, and present with symptoms of hypoglycemia. These tumors may present before age 10 years but are more common in adolescence. Although gastrinomas represent over 50% of pancreatic tumors in adults with MEN1, they are rare in children (~2%) and occur after age 15 years. Rarer pancreatic tumors can secrete other hormones such as glucagon or vasoactive intestinal peptide (VIP).

MEN1 is also associated with several other rare tumors. Adrenocortical tumors in children with MEN1 may be benign or malignant, and they

Table 609.1 Clinical Manifestation of MEN Syndromes

SYNDROME	MEN 1	MEN 2		
		MEN 2A	MEN 2B	FAMILIAL MTC
Eponym	Wermer syndrome	Sipple syndrome	Gorlin syndrome	–
Gene	*MEN1* ~85%	*RET* ~100%	*RET* ~100%	*RET* ~100%
Prevalence	1/30,000	1/40,000	1/1,000,000	
Hyperparathyroidism	>90%	20–30%	–	–
Duodenopancreatic NETs: nonfunctioning 55%, gastrinoma 40%, insulinoma 10%, glucagonoma <1%, VIPoma <1%, somatostatinoma	30–80%	–	–	–
Pituitary adenoma	30–40%	–	–	–
Adrenal cortical tumor	20–40%	–	–	–
Pheochromocytoma	<1%	50%	50%	–
Medullary thyroid carcinoma (MTC)	–	100%	100%	100%
Thymic NET/bronchopulmonary NET/ gastric NET	2%/5%/30%		–	
Angiofibroma/collagenoma/lipoma	85%/70%/30%	–	–	–
Other tumors: meningioma 8%, ependymoma, melanoma, thyroid 25%	0–25%	–	–	–
Marfanoid habitus	–	–	75%	–
Mucosal neuroma	–	–	~100%	–
Cutaneous lichen amyloidosis	–	Up to 36%	–	–

MEN, Multiple endocrine neoplasia; NET, neuroendocrine tumor.
Modified from Al-Salameh, A, Baudry C, Cohen R. Update on multiple endocrine neoplasia type 1 and 2. *La Presse Médicale*. 2018;47(9):722–731, Table 1.

may be nonfunctional or hypersecrete cortisol, androgens, or aldosterone. Pheochromocytomas have been reported rarely. Meningiomas, carcinoid tumors, and neuroendocrine tumors of the thymus, bronchopulmonary tree, or stomach can also occur, usually in older adolescents. Older patients with MEN1 frequently manifest cutaneous angiofibromas or collagenomas, which are benign but may be a useful diagnostic clue.

The diagnosis of MEN1 can be made clinically based on the presence of at least two of the classical endocrine tumor types (parathyroid, pituitary, pancreas) or the presence of one of these tumors in a first-degree relative of a patient with known MEN1. Genetic testing should be used to confirm a clinical diagnosis of MEN1 or to diagnose the condition preclinically in a relative of an affected individual. The *MEN1* gene on chromosome 11q13 encodes the tumor suppressor menin. A single germline inactivating pathogenic variant in *MEN1* is inherited but is not sufficient to cause tumorigenesis; a second *somatic* variant that inactivates the remaining normal allele then leads to tumor formation in a specific tissue. MEN1 is generally inherited in an autosomal dominant fashion, although sporadic variants account for about 10% of cases. Over 1,000 *MEN1* variants have been described, including deletions and changes in noncoding regions; therefore genetic testing should include analysis for deletions in patients in whom MEN1 sequencing does not reveal a pathogenic variant. Children diagnosed with MEN1 should undergo routine age-based clinical, laboratory, and imaging surveillance for disease manifestations.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Multiple endocrine neoplasia type 2 (MEN2) is a rare genetic disorder that occurs in about 1 in 2 million individuals and is characterized by the development of **medullary thyroid carcinoma (MTC)** and **pheochromocytoma**. MEN2 is an autosomal dominant disorder caused by activating pathogenic variants in the *RET* proto-oncogene, a tyrosine kinase encoded on chromosome 10q11.2. The clinical features of the syndrome are related to the specific *RET* mutation present, although disease manifestations can vary even among family members carrying the same mutation.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A

Multiple endocrine neoplasia type 2A (MEN2A) is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism. At least 50 different *RET* pathogenic variants have been described in patients with MEN2A, the majority occurring in exons 10 or 11 (codons 609, 611, 618, 620, or 634) in the *RET* extracellular domain. Almost all patients with MEN2A develop MTC, but the occurrence of other manifestations is more variable. MTC, or its precursor C cell hyperplasia, is usually the first manifestation to occur, but the age at which it develops is variable. Pheochromocytomas are often bilateral and may be multiple, and they usually develop in the third decade or later but may occur in childhood. Hyperparathyroidism is caused by hyperplasia that may involve one or more parathyroid glands. Hyperparathyroidism occurs at an average age of about 30 years but can occur in childhood or adolescence. Variants in *RET* codon 634 confer a relatively high risk of pheochromocytoma and hyperparathyroidism compared to variants at other sites.

Additional clinical conditions associated with MEN2A include cutaneous lichen amyloidosis and Hirschsprung disease. **Cutaneous lichen amyloidosis** is a dermatologic lesion consisting of pruritic hyperpigmented papules that are usually distributed in the interscapular region and on extensor surfaces. These skin lesions may develop before MTC and may provide an early clue to the diagnosis of MEN2A. Some patients with **Hirschsprung** disease have variants in *RET,* particularly in exon 10. Although the *RET* variants that cause Hirschsprung disease are generally loss-of-function variants, some of these can nevertheless cause MEN2A. Therefore individuals with Hirschsprung disease who carry such *RET* pathogenic variants should be evaluated for MEN2A.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

Multiple endocrine neoplasia type 2B (MEN2B) is characterized by MTC and pheochromocytoma, but *not* hyperparathyroidism. Rather, the distinguishing features of MEN2B are the presence of **multiple neuromas** and a characteristic phenotype that includes **Marfan-like habitus**. Nearly all patients with MEN2B have a specific missense pathogenic variant (M918T) in the tyrosine kinase catalytic domain of *RET*. Although MEN2B can be inherited, about 75% of cases are caused by de novo variants.

MTC in MEN2B can develop early in childhood, including in infancy, and metastasis of MTC to local and distant sites is often present at diagnosis. Pheochromocytomas occur in about half of patients. The neuromas of MEN2B can occur throughout the digestive tract, most commonly on the tongue, buccal mucosa, lips, and conjunctivae. Diffuse proliferation of nerves and ganglion cells is found in mucosal, submucosal, myenteric, and subserosal plexuses throughout the digestive tract and may be associated with gastrointestinal symptoms. Peripheral neurofibromas and café-au-lait patches may be present. Affected individuals may be tall, with arachnodactyly and a Marfan-like appearance, including scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The eyelids may be thickened and everted, lips thickened, and jaw prognathic. Feeding difficulties, poor sucking, diarrhea, constipation, and failure to thrive can begin in infancy or early childhood, sometimes years before the appearance of neuromas or endocrine symptoms.

FAMILIAL MEDULLARY THYROID CARCINOMA

The familial occurrence of MTC without other clinical manifestations of MEN2 has been termed *familial medullary thyroid carcinoma* (FMTC). *RET* variants are commonly present in individuals with FMTC, and although some families appear to have truly isolated MTC, in other kindreds, the pattern of apparent FMTC may represent MEN2A in which other manifestations have not yet occurred or have not been diagnosed. FMTC is frequently regarded as a form of MEN2A, and evaluation for other manifestations of MEN2A is warranted in patients with FMTC.

MANAGEMENT OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Genetic testing of affected family members often leads to the diagnosis of MEN2 in a child before the development of any disease manifestations. MTC is highly likely to develop in these individuals. Although thyroidectomy is curative if performed before the development of MTC or while it is still localized to the thyroid gland, the prognosis is poor once MTC has metastasized beyond the thyroid. Therefore prophylactic thyroidectomy is required in most individuals with MEN2. However, the timing of prophylactic thyroidectomy must be determined for each patient based on balancing the likelihood of developing metastatic MTC against the need to minimize the risks of surgery, which are higher in younger children.

Factors influencing the risk of MTC include the specific *RET* variants present, the history of MTC in the family, and serum levels of calcitonin. The first two factors are not entirely predictive, as MTC behavior can vary significantly even in family members with the same variant. Some *RET* variants are associated with earlier-onset MTC, and consensus guidelines categorize *RET* variants as highest risk (M918T, usually associated with MEN2B), high risk (codon 634 and 883 mutations), or moderate risk (other variants) for MTC. Patients at highest risk should undergo thyroidectomy within the first year of life. Those with high-risk variants should undergo thyroidectomy at 5 years of age or earlier if calcitonin levels begin to rise. Patients at moderate risk should be monitored by neck ultrasound and serum calcitonin levels beginning at age 5 years, and thyroidectomy should be performed if calcitonin levels rise. However, the timing of surgery may be influenced by other factors, including family history or desire to avoid prolonged monitoring by proceeding with thyroidectomy. For patients who do not wish to undergo prophylactic thyroidectomy, regular careful surveillance is mandatory. Thyroidectomy should be performed by an experienced thyroid surgeon, especially in the youngest patients, to minimize the risk of surgical complications. Prophylactic thyroidectomy reduces morbidity and mortality from MTC in patients with MEN2, many of whom are found to have C cell hyperplasia, or even MTC, at the time of prophylactic thyroidectomy. The management of MTC is described in detail in Chapter 607.

Screening for pheochromocytoma and hyperparathyroidism should be performed in children with MEN2. The age at which screening should commence depends on the specific RET variant (11 years for high and highest risk; 16 years for moderate risk). Management of pheochromocytoma (see Chapters 555.4 and 613) and hyperparathyroidism (see Chapter 621) are discussed elsewhere.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

Disorders of the Parathyroid Gland

Chapter 610

Hormones and Peptides of Calcium Homeostasis and Bone Metabolism

Evan G. Graber and Daniel A. Doyle

Parathyroid hormone (PTH) and vitamin D are the principal regulators of calcium homeostasis (see Chapters 69 and 746). Calcitonin and PTH-related peptide (PTHrP) are important primarily in the fetus.

PARATHYROID HORMONE

PTH is an 84–amino acid chain (95 kDa), but its biologic activity resides in the first 34 residues. In the parathyroid gland, a pre–pro-PTH (115–amino acid chain) and a pro-PTH (90 amino acids) are synthesized. Pre–pro-PTH is converted to pro-PTH and pro-PTH to PTH. PTH (consisting of amino acids 1-84) is the major secretory product of the gland, but it is rapidly cleaved in the liver and kidney into smaller COOH-terminal, midregion, and NH_2-terminal fragments.

The occurrence of these fragments in serum has led to the development of a variety of assays. The 1-34 aminoterminal (N-terminus) fragments possess biologic activity but are present in low amounts in the circulation; assay of these fragments is most useful for detecting acute secretory changes. The carboxyterminal (C-terminus) and midregion fragments, although biologically inert, are cleared more slowly from the circulation and represent 80% of plasma immunoreactive PTH; concentrations of the C-terminal fragment are 50-500 times the level of the active hormone. The C-terminal assays are effective in detecting hyperparathyroidism, but because C-terminal fragments are removed from the circulation by glomerular filtration, these assays are less useful for evaluating the secondary hyperparathyroidism characteristic of renal disease. Only certain sensitive radioimmunoassays for PTH can differentiate the subnormal concentrations that occur in hypoparathyroidism from normal levels.

When serum levels of calcium fall, the signal is transduced through the calcium-sensing receptor, and secretion of PTH increases (Fig. 610.1). PTH stimulates activity of 1α-hydroxylase in the kidney, enhancing production of 1,25-dihydroxycholecalciferol, also written as $1,25(OH)_2D_3$. The increased level of $1,25(OH)_2D_3$ induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa, with resultant absorption of calcium. PTH also mobilizes calcium by directly enhancing bone resorption, an effect that requires $1,25(OH)_2D_3$. The effects of PTH on bone and kidney are mediated through binding to specific receptors on the membranes of target cells and through activation of a transduction pathway involving a G-protein coupled to the adenylate cyclase system (see Chapter 594).

The calcium-sensing receptor regulates the secretion of PTH and the reabsorption of calcium by the renal tubules in response to alterations in serum calcium concentrations. The gene for the receptor is located on chromosome 3q13.3-q21 and encodes a cell surface protein that is expressed in parathyroid glands and kidneys and belongs to the family of G-protein–coupled receptors. In the normally functioning calcium-sensing receptor, hypocalcemia induces increased secretion of PTH and hypercalcemia depresses PTH secretion. Loss-of-function pathogenic variants cause an increased set point with respect to serum calcium, resulting in hypercalcemia and in the conditions of familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. There is a close genotype/phenotype relationship that determines severity of illness. Acquired hypocalciuric hypercalcemia may be a result of autoantibodies to the calcium-sensing receptor and manifests with hypercalcemia and hyperparathyroidism. Gain-of-function variants result in depressed secretion of PTH in response to hypocalcemia, leading to the syndrome of familial hypocalcemia with hypercalciuria (see Fig. 610.1).

PARATHYROID HORMONE–RELATED PEPTIDE

PTHrP is homologous to PTH only in the first 13 amino acids of its amino terminus, 8 of which are identical to PTH. Its gene is on the short arm of chromosome 12 and that of PTH is on the short arm of chromosome 11.

PTHrP, like PTH, activates PTH receptors in kidney and bone cells and increases urinary cyclic adenosine monophosphate and renal production of $1,25(OH)_2D_3$. It is produced in almost every type of cell of the body, including every tissue of the embryo at some stage of development. PTHrP is critical for normal fetal development. Inactivating variants of the receptor for PTH/PTHrP results in a lethal bone disorder characterized by short limbs and markedly advanced bone maturation known as **Blomstrand chondrodysplasia** (see Fig. 610.1). PTHrP appears to have a paracrine or autocrine role because serum levels are low except in a few clinical situations. Cord blood contains levels of PTHrP that are threefold higher than in serum from adults; it is produced by the fetal parathyroid glands and appears to be the main agent stimulating maternal-fetal calcium transfer. PTHrP appears to be essential for normal skeletal maturation of the fetus, which requires 30 g of calcium during a normal gestation. During pregnancy, maternal absorption of calcium increases from about 150 mg daily to 400 mg during the second trimester.

PTHrP levels are increased during lactation and in patients with benign breast hypertrophy. Breast milk and pasteurized bovine milk have levels of PTHrP that are 10,000 times higher than those of normal plasma. Most instances of the hormonal **hypercalcemia syndrome of malignancy** are caused by elevated concentrations of PTHrP.

VITAMIN D

See Chapter 69.

CALCITONIN

Calcitonin is a 32–amino acid polypeptide. Its gene is on chromosome 11p and is tightly linked to that of PTH. The gene for calcitonin encodes three peptides: calcitonin, a 21–amino acid carboxyterminal flanking peptide (katacalcin), and a calcitonin gene–related peptide. Katacalcin and calcitonin are cosecreted in equimolar amounts by the parafollicular cells (C cells) of the thyroid gland. Calcitonin appears to be of little consequence in children and adults because very high levels in patients with medullary carcinoma of the thyroid (a tumor arising from the C cells) do not cause hypercalcemia. In the fetus, circulating levels are high and appear to augment bone metabolism and skeletal growth; these high levels are probably stimulated by the normally high fetal calcium levels. Unlike the high levels in cord blood and circulating concentrations in young children, levels in older children and adults are low. Infants and children with congenital hypothyroidism (and presumed deficiency of C cells) have lower levels of calcitonin than normal children.

Its action appears to be independent of PTH and vitamin D. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts. This action of calcitonin is the rationale for its use in treatment of Paget disease. Calcitonin is synthesized in other organs, such as the gastrointestinal tract, pancreas, brain, and pituitary. In these organs, calcitonin is thought to behave as a neurotransmitter to impose a local inhibitory effect on cell function.

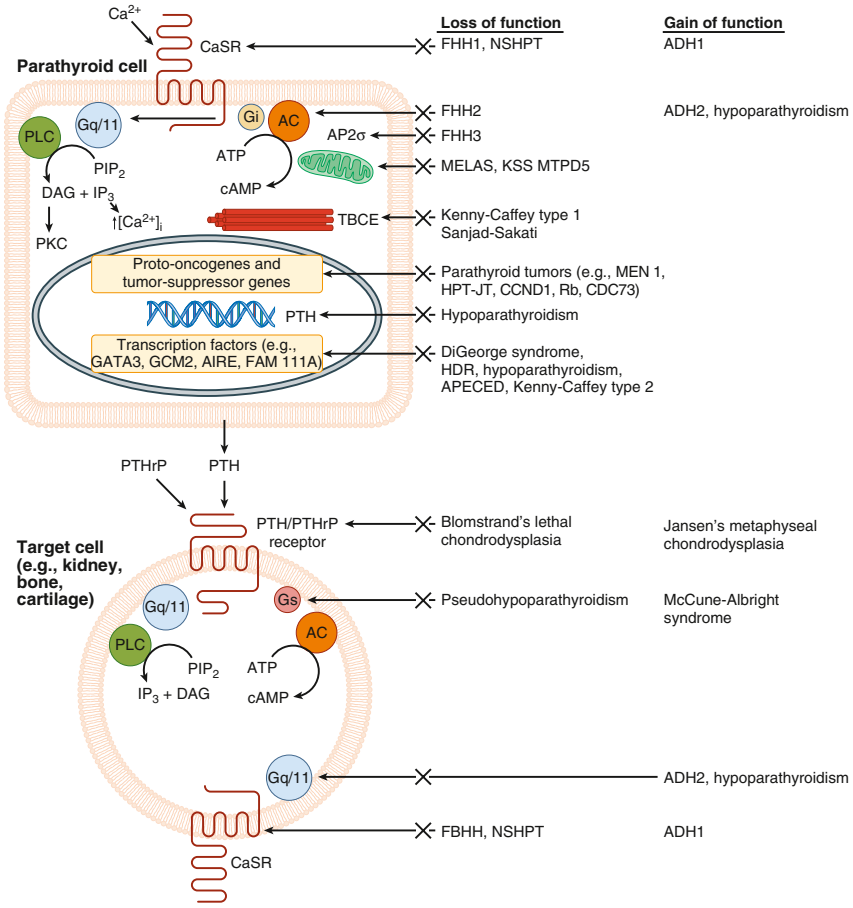

Fig. 610.1 Schematic representation of some of the components involved in calcium homeostasis. Alterations in extracellular calcium are detected by the calcium-sensing receptor *(CaSR)*, which is a 1078–amino acid, G protein–coupled receptor. The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor, which mediates the actions of and PTHrP, is also a G protein–coupled receptor. Thus Ca^{2+}, PTH, and PTHrP involve G protein–coupled signaling pathways, and interaction with their specific receptors can lead to activation of Gs, Gi, and Gq, respectively. Gs stimulates adenylcyclase *(AC)*, which catalyzes the formation of cyclic adenosine monophosphate *(cAMP)* from adenosine triphosphate *(ATP)*. Gi inhibits AC activity. cAMP stimulates protein kinase A *(PKA)*, which phosphorylates cell-specific substrates. Activation of Gq stimulates phospholipase C *(PLC)*, which catalyzes the hydrolysis of the phosphoinositide *(PIP_2)* to inositol triphosphate *(IP_3)*, which then increases intracellular calcium, and diacylglycerol *(DAG)*, activating protein kinase C *(PKC)*. These proximal signals modulate downstream pathways, which results in specific physiologic effects. Loss of function in several genes, shown with their respective sites of action on the right, has been identified in specific disorders of calcium homeostasis. ADH, autosomal dominant hypocalcemia; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; FBHH, familial benign hypocalciuric hypercalcemia; FHH, familial hypocalciuric hypercalcemia; HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HPT-JT, hyperparathyroidism-jaw tumor syndrome; KSS, Kearns-Sayre syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MEN, multiple endocrine neoplasia; MTPD, mitochondrial trifunctional protein deficiency; NSHPT, neonatal severe hyperparathyroidism. TBCE, tubulin-specific chaperone E. *(From Thakkerf RV. The parathyroid glands, hypercalcemia and hypocalcemia. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine, 25th ed. Philadelphia: Elsevier; 2016: Fig. 245.2, p. 1651.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 611

Hypoparathyroidism

Patrick C. Hanley and Daniel A. Doyle

Hypocalcemia is common in neonates between 12 and 72 hours of life, especially in premature infants, in infants with asphyxia, and in infants of diabetic mothers (**early neonatal hypocalcemia**; see Chapter 121.4; Table 611.1 and Fig. 611.1). After the second to third day and during the first week of life, the type of feeding also is a determinant of the level of serum calcium **(late neonatal hypocalcemia)**. The role played by the parathyroid glands in these hypocalcemic infants is unclear, although functional immaturity of the parathyroid glands is invoked as one pathogenetic factor. In a group of infants with **transient idiopathic hypocalcemia** (1-8 weeks of age), serum levels of parathyroid hormone (PTH) are significantly lower than those in unaffected infants. It is possible that the functional immaturity is a manifestation of a delay in development of the enzymes that convert glandular PTH to secreted PTH; other mechanisms are possible.

APLASIA OR HYPOPLASIA OF THE PARATHYROID GLANDS

Aplasia or hypoplasia of the parathyroid glands is often associated with **DiGeorge/velocardiofacial syndrome**. This syndrome occurs in 1 in 4,000 newborns. In 90% of patients, the condition is caused by a deletion of chromosome 22q11.2 with involvement of the *TBX1* gene. Approximately 25% of these patients inherit the chromosomal abnormality from a parent. Neonatal hypocalcemia occurs in 60% of affected patients, but it is transitory in the majority; hypocalcemia may recur or can have its onset later in life. Associated abnormalities of the third and fourth pharyngeal pouches are common; these include conotruncal defects of the heart in 25%, velopharyngeal insufficiency in 32%, cleft palate in 9%, renal anomalies in 35%, and aplasia of the thymus with severe immunodeficiency in 1%. This syndrome has also been reported in a small number of patients with a deletion of chromosome 10p13 thought to affect the *NEBL* gene, in infants of diabetic mothers, and in infants born to mothers treated with retinoic acid for acne early in pregnancy. Loss-of-function pathogenic variants in the *GCM2* gene, which is a key regulator of parathyroid gland development, leads to isolated parathyroid aplasia and hypoparathyroidism.

Table 611.1 Causes of Hypocalcemia

I. NEONATAL
A. Maternal Disorders
1. Diabetes mellitus
2. Toxemia of pregnancy
3. Vitamin D deficiency
4. High intake of alkali or magnesium sulfate
5. Use of anticonvulsants
6. Hyperparathyroidism
B. Neonatal Disorders
1. Low birthweight: prematurity, intrauterine growth restriction
2. Peripartum asphyxia, sepsis, critical illness
3. Hyperbilirubinemia, phototherapy, exchange transfusion
4. Hypomagnesemia, hypermagnesemia
5. Acute/chronic renal failure
6. Nutrients/medications: high phosphate intake, fatty acids, phytates, bicarbonate infusion, citrated blood, anticonvulsants, aminoglycosides
7. Hypoparathyroidism
8. Vitamin D deficiency or resistance
9. Osteopetrosis type II

II. HYPOPARATHYROIDISM
A. Congenital
1. Transient neonatal
2. Congenital hypoparathyroidism
   a. Familial isolated hypoparathyroidism
      (i) Autosomal recessive hypoparathyroidism *(GMC2, PTH)*
      (ii) Autosomal dominant hypoparathyroidism *(CASR, GNA11)*
      (iii) X-linked hypoparathyroidism *(SOX3)*
   b. DiGeorge syndrome types 1 and 2 *(TBX1, NEBL)*
   c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD) *(TBCE)*
   d. Kenny-Caffey syndrome type 1 (short stature, medullary stenosis, retardation) *(TBCE)*
   e. Kenny-Caffey syndrome type 2 (short stature, medullary stenosis) *(FAM111A)*
   f. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) *(GATA3)*
   g. Lymphedema-Hypoparathyroidism syndrome (nephropathy, mitral valve prolapse and brachytelephalangy).
   h. Mitochondrial disorders (Kearns-Sayre, Pearson, MELAS, trifunctional protein deficiency)
3. Insensitivity to PTH
   a. Blomstrand chondrodysplasia *(PTHR1)*
   b. Pseudohypoparathyroidism type IA *(GNAS)*
      (i) Pseudohypoparathyroidism type IB *(STX16, GNAS-A1)*
      (ii) Pseudohypoparathyroidism type IC *(GNAS)*
      (iii) Pseudohypoparathyroidism type II
      (iv) Pseudopseudohypoparathyroidism
   c. Acrodysostosis with hormone resistance *(PRKAR1A)*
   d. Hypomagnesemia
4. CaSR-activating mutation
   a. Sporadic
   b. Autosomal dominant (G protein subunit α11 mutation)

II. HYPOPARATHYROIDISM—cont'd
B. Acquired
1. Autoimmune polyglandular syndrome type I (*AIRE* gene mutation)
2. Activating antibodies to the CaSR
3. Postsurgical, radiation destruction
4. Infiltrative—excessive iron (hemochromatosis, thalassemia) or copper (Wilson disease) deposition; granulomatous inflammation, neoplastic invasion; amyloidosis, sarcoidosis
5. Hypomagnesemia/hypermagnesemia

III. VITAMIN D DEFICIENCY
IV. OTHER CAUSES OF HYPOCALCEMIA
A. Calcium Deficiency
1. Nutritional deprivation
2. Hypercalciuria
B. Disorders of Magnesium Homeostasis
1. Congenital hypomagnesemia
2. Acquired
   a. Acute renal failure
   b. Chronic inflammatory bowel disease, intestinal resection
   c. Diuretics
C. Hyperphosphatemia
1. Renal failure
2. Phosphate administration (intravenous, oral, rectal)
3. Tumor cell lysis
4. Muscle injuries (crush, rhabdomyolysis)
D. Miscellaneous
1. Hypoproteinemia
2. Hyperventilation
3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (plicamycin, asparaginase, cisplatinum, cytosine arabinoside, doxorubicin), citrated blood products
4. Hungry bone syndrome
5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock
   a. Organic acidemia: propionic, methylmalonic, isovaleric

CaSR, Ca^2-sensing receptor; HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and strokelike episode; PTH, parathyroid hormone.
Modified from Root AW, Diamond Jr FB. Disorders of mineral homeostasis in children and adolescents. In: Sperling MA. *Pediatric Endocrinology*, 4th ed. Philadelphia: Elsevier; 2014: Table 18.2A.

X-LINKED RECESSIVE HYPOPARATHYROIDISM

Familial clusters of hypoparathyroidism with various patterns of transmission have been described. In two large North American pedigrees, this disorder appears to be transmitted by an X-linked recessive gene located on Xq26-q27, which has a key role in the development of the parathyroid glands. In these families, the onset of afebrile hypocalcemic seizures characteristically occurs in infants from 2 weeks to 6 months of age. The absence of parathyroid tissue after detailed examination of a male with this condition suggests a defect in embryogenesis.

AUTOSOMAL RECESSIVE HYPOPARATHYROIDISM WITH DYSMORPHIC FEATURES

Autosomal recessive hypoparathyroidism with dysmorphic features has been described in Middle Eastern children. Parental consanguinity occurred for most of several dozen affected patients. Profound hypocalcemia occurs early in life, and dysmorphic features include microcephaly, deep-set eyes, beaked nose, micrognathia, and large floppy ears. Intrauterine and postnatal growth restriction are severe, and cognitive impairment is common. The putative gene *(TBCE)* is on chromosome 1q42-43. In a few patients with autosomal recessive inheritance of isolated hypoparathyroidism, pathologic variants of the *PTH* gene have been found.

HYPOPARATHYROIDISM, SENSORINEURAL DEAFNESS, AND RENAL ANOMALY SYNDROME

Hypoparathyroidism, sensorineural deafness, and renal anomaly (HDR) occur owing to pathologic variants of the *GATA3* gene. The protein encoded by this gene is essential in the development of the

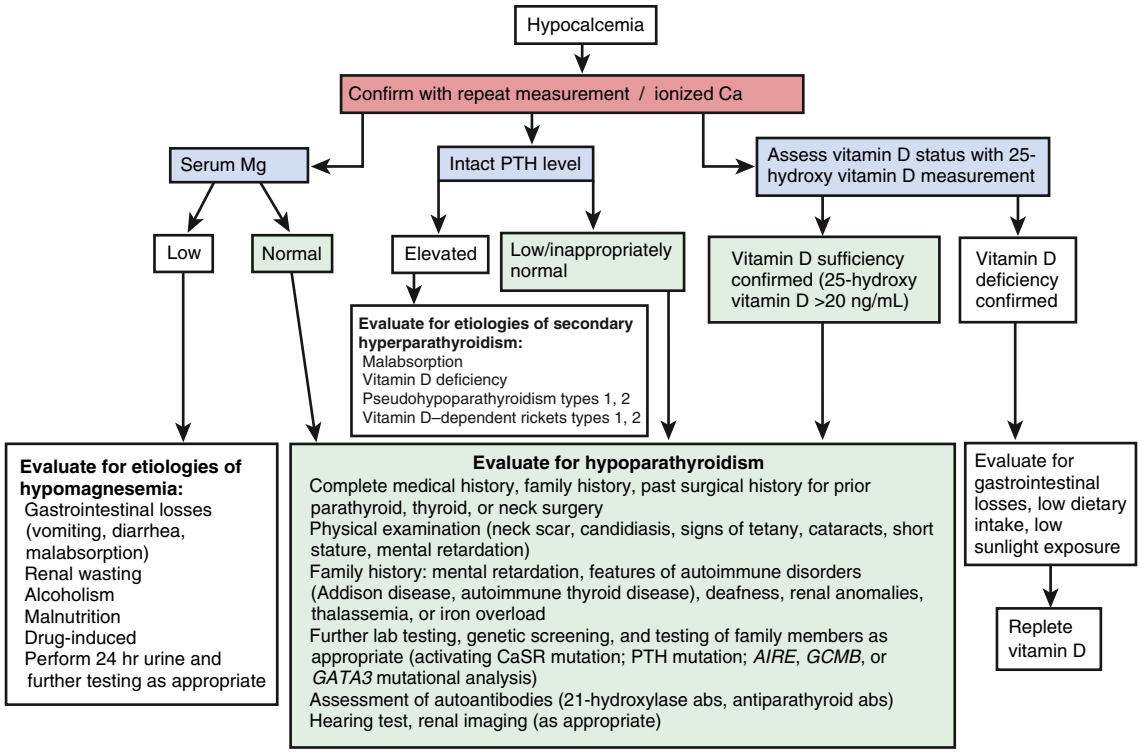

Fig. 611.1 Algorithm for the evaluation of hypocalcemia. Abs, autoantibodies; CaSR, Ca^2-sensing receptor; PTH, parathyroid hormone. *(From Bilezikian JP, Khan A, Potts Jr JT, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res. 2011;26:2317–2337, Fig. 1.)*

parathyroids, auditory system, and kidneys. The *GATA3* gene is located at chromosome 10p14 and is nonoverlapping with the DiGeorge critical region at 10p13 (see Fig. 610.1). Congenital ichthyosis and HDR have also been reported.

SUPPRESSION OF NEONATAL PARATHYROID HORMONE SECRETION BECAUSE OF MATERNAL HYPERPARATHYROIDISM OR MATERNAL FAMILIAL HYPOCALCIURIC HYPERCALCEMIA

Neonatal PTH secretion can be suppressed by maternal hyperparathyroidism, resulting in transient hypocalcemia in the newborn infant. It appears that neonatal hypocalcemia results from suppression of the fetal parathyroid glands by exposure to elevated levels of calcium in maternal and hence fetal serum. Tetany usually develops within 3 weeks but may be delayed by 1 month or more if the infant is breastfed. Seizures may occur within 1 week with familial hypocalciuric hypercalcemia (FHH1) because of maternal Ca^2-sensing receptor (CaSR) loss-of-function pathogenic variants. Hypocalcemia can persist for weeks or months. When the cause of hypocalcemia in an infant is unknown, measurements of calcium, phosphorus, and PTH should be obtained from the mother. Most affected mothers are asymptomatic, and the cause of their hyperparathyroidism is usually a parathyroid adenoma.

AUTOSOMAL DOMINANT HYPOPARATHYROIDISM

Patients with autosomal dominant hypoparathyroidism have an activating (gain-of-function) pathogenic variant of the Ca^{2+}-sensing receptor, forcing the receptor to an on state with subsequent depression of PTH secretion even during hypocalcemia. The patients have hypercalciuria. The hypocalcemia is usually mild and might not require treatment beyond childhood (see Fig. 610.1).

HYPOPARATHYROIDISM ASSOCIATED WITH MITOCHONDRIAL DISORDERS

Mitochondrial DNA pathogenic variants in Kearns-Sayre syndrome, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes) syndrome, and mitochondrial trifunctional protein–deficiency syndrome are associated with hypoparathyroidism. A diagnosis of mitochondrial cytopathy should be considered in patients with unexplained symptoms, such as ophthalmoplegia, sensorineural hearing loss, cardiac conduction disturbances, and tetany (see Fig. 610.1).

SURGICAL OR INFILTRATIVE HYPOPARATHYROIDISM

Removal or damage of the parathyroid glands can complicate thyroidectomy. Hypoparathyroidism has developed even when the parathyroid glands have been identified and left undisturbed at the time of operation. This may be the result of interference with the blood supply or of postoperative edema and fibrosis. Symptoms of tetany can occur abruptly postoperatively and may be temporary or permanent. In some instances, symptoms develop insidiously and go undetected until months after thyroidectomy. Occasionally, the first evidence of surgical hypoparathyroidism may be the development of cataract. The status of parathyroid function should be carefully monitored in all patients undergoing thyroidectomy.

Deposition of iron pigment or of copper in the parathyroid glands (thalassemia, Wilson disease) can also produce hypoparathyroidism.

AUTOIMMUNE HYPOPARATHYROIDISM

An autoimmune mechanism for hypoparathyroidism is strongly suggested by the finding of parathyroid antibodies and by its frequent association with other autoimmune disorders or organ-specific antibodies. Autoimmune hypoparathyroidism is often associated with Addison disease and chronic mucocutaneous candidiasis. The association of at least two of these three conditions has been classified as **autoimmune polyglandular disease type I** (see Chapter 608). It is also known as *autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy* (APECED). This syndrome is inherited in an autosomal recessive fashion and is not related to any single human leukocyte antigen–associated haplotype. Approximately one third of pediatric patients with this syndrome have all three components; 66% have only two of three conditions. The candidiasis almost always precedes the other disorders (70% of cases

occur in children *younger* than 5 years of age); the hypoparathyroidism (90% of cases occur *after* 3 years of age) usually occurs before Addison disease (90% of cases occur *after* 6 years of age). A variety of other disorders, including alopecia areata or totalis, malabsorption disorder, asplenia, pernicious anemia, gonadal failure, autoimmune hepatitis, vitiligo, dental enamel hypoplasia, nail dystrophy, keratoconjunctivitis, and insulin-dependent diabetes, occur at various times. Some of these associations might not appear until adult life. Autoimmune thyroid disease is a rare concomitant finding in pediatric patients.

Affected siblings can have the same or different constellations of disorders (hypoparathyroidism, Addison disease). The disorder is exceptionally prevalent among Finns and Iranian Jews. The gene for this disorder is designated *AIRE* (autoimmune regulator); it is located on chromosome 21q22. It appears to be a transcription factor that plays an essential role in the development of immunologic tolerance. Patients with Addison disease as part of polyendocrinopathy syndrome type I have demonstrated adrenal-specific autoantibody reactivity directed against the side-chain cleavage enzyme.

IDIOPATHIC HYPOPARATHYROIDISM

The term *idiopathic hypoparathyroidism* should be reserved for the small residuum of children with hypoparathyroidism for whom no causative mechanism can be defined. Most children in whom onset of hypoparathyroidism occurs after the first few years of life have an **autoimmune condition**. Autoantibodies to the extracellular domain of the Ca^2-sensing receptor have been identified in some patients with acquired hypoparathyroidism. One should always consider incomplete forms of DiGeorge syndrome or an activating Ca^2-sensing receptor pathogenic variant in the differential diagnosis.

Clinical Manifestations

There is a spectrum of parathyroid deficiencies with clinical manifestations varying from no symptoms to those of complete and long-standing deficiency. Mild deficiency may be revealed only by appropriate laboratory studies. Muscular pain and cramps are early manifestations; they progress to numbness, stiffness, and tingling of the hands and feet. There may be only a positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms. Seizures with or without loss of consciousness can occur at intervals of days, weeks, or months. These episodes can begin with abdominal pain, followed by tonic rigidity, retraction of the head, and cyanosis. Hypoparathyroidism is often mistaken for epilepsy. Headache, vomiting, increased intracranial pressure, and papilledema may be associated with seizures and might suggest a brain tumor.

In patients with long-standing hypocalcemia, the teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. The skin may be dry and scaly, and the nails might have horizontal lines. Mucocutaneous candidiasis, when present, antedates the development of hypoparathyroidism; the candidal infection most often involves the nails, the oral mucosa, the angles of the mouth, and less often, the skin; it is difficult to treat.

Cataracts in patients with long-standing untreated disease are a direct consequence of hypoparathyroidism; other autoimmune ocular disorders such as keratoconjunctivitis can also occur. Manifestations of Addison disease, lymphocytic thyroiditis, pernicious anemia, alopecia areata or totalis, hepatitis, and primary gonadal insufficiency may also be associated with those of hypoparathyroidism.

Permanent physical and mental deterioration occurs if initiation of treatment is long delayed.

Laboratory Findings

The serum calcium level is low (5-7 mg/dL), and the phosphorus level is elevated (7-12 mg/dL). Blood levels of ionized calcium (usually approximately 45% of the total) more nearly reflect physiologic adequacy but also are low. The serum level of alkaline phosphatase is normal or low, and the level of $1,25(OH)_2D_3$ is usually low, but high levels have been found in some children with severe hypocalcemia. The level of magnesium is normal but should always be checked in hypocalcemic patients. Levels of PTH are low relative to the calcium level when measured by immunometric assay. Radiographs of the bones occasionally reveal an increased density limited to the metaphyses, suggesting heavy metal poisoning, or an increased density of the lamina dura. Radiographs or CT scans of the skull can reveal calcifications in the basal ganglia. There is a prolongation of the QT interval on the electrocardiogram, which disappears when the hypocalcemia is corrected. The electroencephalogram usually reveals widespread slow activity; the tracing returns to normal after the serum calcium concentration has been within the normal range for a few weeks, unless irreversible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. When hypoparathyroidism occurs concurrently with Addison disease, the serum level of calcium may be normal, but hypocalcemia appears after effective treatment of the adrenal insufficiency.

Treatment

Emergency treatment of neonatal tetany consists of intravenous injections of 5-10 mL or 1-3 mg/kg of a 10% solution of calcium gluconate (elemental calcium 9.3 mg/mL) at the rate of 0.5-1.0 mL/min while the heart rate is monitored and a total dose not to exceed 20 mg of elemental calcium/kg. Additionally, 1,25-dihydroxycholecalciferol (calcitriol) should be given. The initial dosage is 0.25 μg/24 hr; the maintenance dosage ranges from 0.01-0.10 g/kg/24 hr to a maximum of 1-2 μg/24 hr. Calcitriol has a short half-life and should be given in two equally divided doses; it has the advantages of rapid onset of effect (1-4 days) and rapid reversal of hypercalcemia after discontinuation in the event of overdosage (calcium levels begin to fall in 3-4 days). Calcitriol is supplied as an oral solution.

An adequate intake of calcium should be ensured. Supplemental calcium can be given in the form of calcium gluconate or calcium glubionate to provide 800 mg of elemental calcium daily or 25-50 mg/kg day dosing of elemental calcium as needed. Foods with high phosphorus content such as milk, eggs, and cheese should be *reduced* in the diet. Other therapies used for some children with hypoparathyroidism in studies include hormone replacement with recombinant PTH 1-34 or recombinant PTH 1-84 given via a pump or subcutaneous injections in adult patients who do not respond to conventional therapy.

Clinical evaluation of the patient and frequent determinations of the serum calcium levels are indicated in the early stages of treatment to determine the requirement for calcitriol, calcium supplementation, or vitamin D_2. If hypercalcemia occurs, therapy should be discontinued and resumed at a lower dose after the serum calcium level has returned to normal. In long-standing cases of hypercalcemia, repair of cerebral and dental changes is not likely. Pigmentation, lowering of blood pressure, or weight loss can indicate adrenal insufficiency, which requires specific treatment. Patients with autosomal dominant hypocalcemic hypercalciuria can develop nephrocalcinosis and renal impairment if treated with vitamin D.

Differential Diagnosis

Magnesium deficiency must be considered in patients with unexplained hypocalcemia. Concentrations of serum magnesium <1.5 mg/dL (1.2 mEq/L) are usually abnormal (Table 611.2). Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. Oral supplements of magnesium are necessary to maintain levels of magnesium in the normal range.

Hypomagnesemia also occurs in malabsorption syndromes such as Crohn disease and cystic fibrosis. Patients with autoimmune polyglandular disease type I and hypoparathyroidism can also have concurrent

Table 611.2 Genetic Causes of Hypomagnesemia

CATEGORIES/NAMES OF DISORDERS*	GENE	INHERITANCE	DISTINCTIVE FINDINGS OTHER THAN HYPOMAGNESEMIA†
HYPERCALCIURIC HYPOMAGENESEMIAS			Hypercalciuria, nephrocalcinosis
FHHNC type 1	*CLDN16*	R	Polyuria/polydipsia, elevated serum iPTH, renal failure
FHHNC type 2	*CLDN19*	R	Same as FHHNC type 1, plus ocular abnormalities
ADHH Bartter syndrome type 5	*CASR*	D	Hypocalcemia with normal or low PTH
Bartter syndrome, type 3 (classical type)	*CLCNKB*	R	Gitelman-like phenotype possible, rarely nephrocalcinosis
GITELMAN-LIKE HYPOMAGNESEMIAS			Hypocalciuria, hypokalemia, metabolic alkalosis
Gitelman syndrome	*SLC12A3*	R	Chondrocalcinosis at older age
Bartter syndrome, type 4	*BSND*	R	Prenatal complications, renal failure early in life possible
EAST syndrome	*KCNJ10*	R	Sensorineural deafness, seizures, ataxia
IDH	*FXYD2*	D	
ADTKD/RCAD	*HNF1B*	D	Renal, genital, and pancreatic abnormalities and MODY5 in highly variable combination and presentation
HPABH4D/RCAD-like	*PCBD1*	R	MODY5-like
MITOCHONDRIAL HYPOMAGNESEMIAS			Variable
HHH	*MT-TI*	Mt	Hypertension and hypercholesterolemia
HUPRAS	*SARS2*	R	Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis
KSS	Mitochondrial deletion	Mt	External ophthalmoplegia, retinopathy and cardiac conduction defects
OTHER HYPOMAGNESEMIAS			Variable
HSH	*TRPM6*	R	Neonatal presentation with severe hypomagnesemia
IRH	*EGF*	R	Intellectual disability
NISBD2	*EGFR*	R	Severe inflammation of skin and bowel from birth
HSMR	*CNNM2*	D/R	Intellectual disability, seizures
ADH/EA1	*KCNA1*	D	Episodic myokymia
KCS2	*FAM111A*	D	Impaired skeletal development and hypocalcemic hypoparathyroidism

*ADH, Autosomal dominant hypomagnesemia; ADHH, autosomal dominant hypocalcemia with hypocalciuria; ADTKD, autosomal dominant tubulointerstitial kidney disease; EA1, episodic ataxia type 1; EAST, epilepsy, ataxia, sensorineural deafness and tubulopathy; FHHNC, familial hypomagnesemia with hypocalcemia and nephrocalcinosis; HHH, hypertension, hypercholesterolemia and hypomagnesemia; HPABH4D, hyperphenylalaninemia BH4-deficient; HSH, hypomagnesemia with secondary hypocalcemia; HSMR, hypomagnesemia with seizures and mental retardation; HUPRAS, hyperuricemia, pulmonary hypertension, renal failure and alkalotic syndrome; IDH, isolated dominant hypomagnesemia; IRH, isolated recessive hypomagnesemia; KCS2, Kenny-Chaffey syndrome type 2; KSS, Kearns-Sayre syndrome; NISBD2, neonatal inflammatory skin and bowel disease type 2; RCAD, renal cysts and diabetes.

†iPTH, Intact parathyroid hormone; MODY5, maturity onset diabetes of the young type 5.

Modified from Viering DHHM, de Baaij JHF, Walsh SB. et al. Genetic causes of hypomagnesemia, a clinical overview. *Pediatr Nephrol.* 2017;32:1123–1135.

steatorrhea and low magnesium levels. Therapy with aminoglycosides causes hypomagnesemia by increasing urinary losses.

It is not clear how low levels of magnesium lead to hypocalcemia. Evidence suggests that hypomagnesemia impairs release of PTH and induces resistance to the effects of the hormone, but other mechanisms also may be operative.

Poisoning with inorganic phosphate leads to hypocalcemia and tetany. Infants administered large doses of inorganic phosphates, either as laxatives or as sodium phosphate enemas, have had sudden onset of tetany, with serum calcium levels <5 mg/dL and markedly elevated levels of phosphate. Symptoms are quickly relieved by intravenous administration of calcium. The mechanism of the hypocalcemia is not clear (see Chapter 73.6).

Hypocalcemia can occur early in treatment of acute lymphoblastic leukemia. Hypocalcemia is usually associated with hyperphosphatemia resulting from destruction of lymphoblasts.

Episodic symptomatic hypocalcemia occurs in **Kenny-Caffey syndrome**, which is characterized by medullary stenosis of the long bones, short stature, delayed closure of the fontanel, delayed bone age, and eye abnormalities. Idiopathic hypoparathyroidism and abnormal PTH levels have been found. Autosomal dominant and autosomal recessive modes of inheritance have been reported. Pathogenic variants of the *TBCE* gene (1q43-44) perturb microtubule organization in diseased cells in Kenny-Caffey syndrome type 1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 612

Pseudohypoparathyroidism

Patrick C. Hanley and Daniel A. Doyle

In pseudohypoparathyroidism (PHP, also known as *Albright hereditary osteodystrophy*), the parathyroid glands are normal or hyperplastic, and they can synthesize and secrete parathyroid hormone (PTH). Serum levels of immunoreactive PTH are elevated even when the patient is hypocalcemic and may be elevated when the patient is normocalcemic. Neither endogenous nor administered PTH raises the serum levels of calcium or lowers the levels of phosphorus. The genetic defects in the **hormone receptor adenylate cyclase system** are classified into various types depending on the phenotypic and biochemical findings (Table 612.1).

TYPE Ia

Type Ia accounts for the majority of patients with PHP. Affected patients have a genetic defect of the α subunit of the stimulatory guanine nucleotide-binding protein ($G_s\alpha$). This coupling factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP). Heterogeneous pathogenic variants of the $G_s\alpha$ gene have been documented; the gene is located on chromosome 20q13.2. Deficiency of the $G_s\alpha$ subunit is a generalized cellular defect and accounts for the association of other endocrine disorders with type Ia PHP. The defect is inherited as an autosomal dominant trait, and the paucity of father-to-son transmissions is thought to be a result of decreased fertility in males.

Tetany is often the presenting sign. Affected children have a short, stocky build and a round face. Brachydactyly with dimpling of the dorsum of the hand is usually present. The second metacarpal is involved least often. As a result, the index finger occasionally is longer than the middle finger. Likewise, the second metatarsal is only rarely affected. There may be other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of the calvaria. These patients often have obesity, calcium deposits, and metaplastic bone formation subcutaneously. Moderate degrees of cognitive impairment, calcification of the basal ganglia, and lenticular cataracts are common in patients whose disease is diagnosed late.

Some members of affected kindreds may have the usual anatomic stigmata of PHP type Ia, but serum levels of calcium and phosphorus are normal despite reduced $G_s\alpha$ activity; however, PTH levels may be slightly elevated. Such patients have been labeled as having **pseudopseudohypoparathyroidism (PPHP)**. Affected patients with PPHP have pathologic variants in the *GNAS* gene inherited in an autosomal dominant pattern. PPHP patients have inactivating *GNAS* variants encoding the $G_s\alpha$ subunit that are paternally inherited. The signs and symptoms of PPHP are similar to those of patients with PHP type Ia, except patients with PPHP do not have the characteristic PTH resistance seen in PHP type Ia.

Patients with **PHP type Ic** also have the usual anatomic stigmata of PHP along with the laboratory abnormalities associated with PTH resistance, including elevated phosphorus and PTH in the setting of hypocalcemia. PHP type Ic is differentiated from PHP type Ia and PPHP in that patients do not have abnormal $G_s\alpha$ activity.

Transition from normocalcemia to hypocalcemia often occurs with increasing age of the patient. These phenotypically similar but metabolically dissimilar patients may be in the same family and have the same pathogenic variants of $G_s\alpha$ protein. It is not known what other factors cause clinically overt hypocalcemia in some

Table 612.1 Clinical, Biochemical, and Genetic Features of Hypoparathyroid and Pseudohypoparathyroid Disorders

		PSEUDOHYPOPARATHYROIDISM				
	HYPOPARATHYROIDISM	**PHP 1a**	**PPHP**	**PHP 1b**	**PHP 1c**	**PHP 2**
AHO manifestations	No	Yes	Yes	No	Yes	No
Serum calcium	↓	↓	N	↓	↓	↓
Serum PO_4	↑	↑	N	↑	↑	↑
Serum PTH	↓	↑	N	↑	↑	↑
Response to PTH:						
Urinary cAMP* (Chase-Auerbach test)	↑	↓	↑	↓	↓	↑
Urinary PO_4 (Ellsworth-Howard test)	↑	↓	↑	↓	↓	↓
$G_s\alpha$ activity	N	↓	↓	N	N	N
Inheritance	AD, AR, X	AD	AD	AD	AD	Sporadic
Molecular defect	PTH, CaSR, GATA3, Gcm2, others	GNAS1	GNAS1	GNAS1†	?Adenyl cyclase	?cAMP targets
Other hormonal resistance	No	Yes	No	No	Yes	No

*Plasma cyclic adenosine monophosphate (cAMP) responses are similar to those of urinary cAMP.
†Involves deletions that are located upstream of GNAS1.
↓, Decreased; ↑, increased; ?, presumed, but not proved; AD, autosomal dominant; AHO, Albright hereditary osteodystrophy; AR, autosomal recessive; N, normal; PHP, pseudoparathyroidism; PPHP, pseudopseudoparathyroidism; PTH, parathyroid hormone; X, X-linked.
From Thakker RV. The parathyroid glands, hypercalcemia and hypocalcemia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 25th ed. Philadelphia: Elsevier; 2016: Table 245-8.

affected patients and not in others. There is evidence that the $G_s\alpha$ variant is paternally transmitted in PPHP and maternally transmitted in patients with type Ia disease. The gene may be imprinted in a tissue-specific manner and have different methylation patterns.

In addition to resistance to PTH, resistance to other G protein–coupled receptors for thyroid-stimulating hormone (TSH), gonadotropins, growth hormone–releasing hormone (GHRH), calcitonin, and glucagon can result in various metabolic effects. Clinical hypothyroidism is uncommon, but basal levels of TSH are elevated and thyrotropin-releasing hormone–stimulated TSH responses are exaggerated. Moderately decreased levels of thyroxine and increased levels of TSH have been demonstrated by newborn thyroid-screening programs, leading to the detection of type Ia PHP in infancy. In adults, gonadal dysfunction is common, as manifested by sexual immaturity, amenorrhea, oligomenorrhea, and infertility. Each of these abnormalities can be related to deficient synthesis of cAMP secondary to a deficiency of $G_s\alpha$, but it is not clear why resistance to other G protein–dependent hormones (corticotropin, vasopressin) are much less affected.

Serum levels of calcium are low, and those of phosphorus and alkaline phosphatase are elevated. Clinical diagnosis can be confirmed by demonstration of a markedly attenuated response in urinary phosphate and cAMP after intravenous infusion of the synthetic 1-34 fragment of human PTH (teriparatide acetate). Definitive diagnosis is established by demonstration of the pathogenic variant in the G protein gene.

Type Ia with Precocious Puberty

Two males have been reported with both type Ia PHP and gonadotropin-independent precocious puberty (see Chapter 600.7). They were found to have a temperature-sensitive variant of the G_s protein. Thus at normal body temperature (37°C), the G_s is degraded, resulting in PHP, but in the cooler temperature of the testes (33°C) the G_s variant results in constitutive activation of the luteinizing hormone receptor and precocious puberty.

TYPE Ib

Affected patients have normal levels of G protein activity and a normal phenotypic appearance. These patients have tissue-specific resistance to PTH but not to other hormones. Serum levels of calcium, phosphorus, and immunoreactive PTH are the same as those in patients with type Ia PHP. These patients also show no rise in cAMP in response to exogenous administration of PTH. Bioactive PTH is not increased. The pathophysiology of the disorder in this group of patients is caused by paternal uniparental isodisomy of chromosome 20q and resulting *GNAS1* methylation. This, along with the loss of the maternal *GNAS1* gene, leads to PTH resistance in the proximal renal tubules, which leads to impaired mineral ion homeostasis. Pathologic genetic deletions in the *STX16* gene are also associated with PHP type Ib.

ACRODYSOSTOSIS WITH HORMONE RESISTANCE

Patients with acrodysostosis resemble those with PHP type Ia, but defects in the $G_s\alpha$ subunit are not present. Instead, in one subgroup of patients there is a defect in the gene encoding *PRKAR1A,* the cAMP-dependent regulatory subunit of protein kinase A that confers resistance to multiple hormones, including PTH. Another subgroup has a defect in a phosphodiesterase gene *Pde4d.* This subgroup also carries the phenotype of PHP type Ia but rarely exhibits the hormone resistance. **Acroscyphodysplasia** is a distinctive form of metaphyseal dysplasia characterized by the distal femoral and proximal tibial epiphyses embedded in cup-shaped, large metaphyses known as *metaphyseal scypho* or *cup deformity* and is a phenotypic variation of PHP and acrodysostosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 613

Hyperparathyroidism

Evan G. Graber and Daniel A. Doyle

Excessive production of parathyroid hormone (PTH) can result from a primary defect of the parathyroid glands such as an **adenoma** or hyperplasia **(primary hyperparathyroidism)**.

More often, the increased production of PTH is compensatory, usually aimed at correcting hypocalcemic states of diverse origins **(secondary hyperparathyroidism)**. In vitamin D–deficient rickets and the malabsorption syndromes, intestinal absorption of calcium is deficient, but hypocalcemia and tetany may be averted by increased activity of the parathyroid glands. In **pseudohypoparathyroidism**, PTH levels are elevated because a pathogenic variant in the $G_s\alpha$ protein interferes with response to PTH. Early in chronic renal disease, hyperphosphatemia results in a reciprocal fall in the calcium concentration with a consequent increase in PTH, but in advanced stages of renal failure, production of $1,25(OH)_2D_3$ is also decreased, leading to worsening hypocalcemia and further stimulation of PTH. In some instances, if stimulation of the parathyroid glands has been sufficiently intense and protracted, the glands continue to secrete increased levels of PTH for months or years after kidney transplantation, with resulting hypercalcemia.

ETIOLOGY

Childhood hyperparathyroidism is uncommon. Onset during childhood is usually the result of a single benign adenoma. It usually becomes manifested after 10 years of age. There have been some kindreds in which multiple members have hyperparathyroidism transmitted in an autosomal dominant fashion. Most of the affected family members are adults, but children have been involved in approximately 30% of the pedigrees. Some affected patients in these families are asymptomatic, and disease is detected only by careful study. In other kindreds, hyperparathyroidism occurs as part of the constellation known as the **multiple endocrine neoplasia** (MEN) syndromes (see Chapter 609) or of **hyperparathyroidism–jaw tumor syndrome**.

Neonatal severe hyperparathyroidism is rare. Symptoms develop shortly after birth and consist of anorexia, irritability, lethargy, constipation, and failure to thrive. Radiographs reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures. Symptoms may be mild, resolving without treatment, or can have a rapidly fatal course if diagnosis and treatment are delayed. Histologically, the parathyroid glands show diffuse hyperplasia. Affected siblings have been observed in some kindreds, and parental consanguinity has been reported in several kindreds. Most cases have occurred in kindreds with the clinical and biochemical features of **familial hypocalciuric hypercalcemia**. Infants with neonatal severe hyperparathyroidism may be homozygous or heterozygous for the pathogenic variant in the Ca^{2+}-sensing receptor gene, whereas most persons with one copy of this variant exhibit autosomal dominant familial hypocalciuric hypercalcemia.

MEN type 1 (see Chapter 609) is an autosomal dominant disorder characterized by hyperplasia or neoplasia of the endocrine pancreas (which secretes gastrin, insulin, pancreatic polypeptide, and occasionally glucagon), the anterior pituitary (which usually secretes prolactin), and the parathyroid glands. In most kindreds, hyperparathyroidism is usually the presenting manifestation, with a prevalence approaching 100% by 50 years of age and occurring only rarely in children younger than 18 years of age. With genetic testing, it is possible to detect carriers of the gene with 99% accuracy at birth, avoiding unnecessary biochemical screening programs.

The gene for MEN type 1 is on chromosome 11q13; it appears to function as a tumor-suppressor gene and follows the two-hit hypothesis of tumor development. The first variant *(germinal)* is inherited and is recessive to the dominant allele; this does not result in tumor formation. A second variant *(somatic)* is required to eliminate the normal allele, which then leads to tumor formation.

Hyperparathyroidism–jaw tumor syndrome is an autosomal dominant (*CDC73*) disorder characterized by parathyroid adenomas and fibro-osseous jaw tumors. Affected patients can also have polycystic kidney disease, renal hamartomas, and Wilms tumor. Although the condition affects adults primarily, it has been diagnosed as early as age 10 years. **MEN type 2** may also be associated with hyperparathyroidism (see Chapter 609).

Transient neonatal hyperparathyroidism has occurred in a few infants born to mothers with hypoparathyroidism (idiopathic or surgical) or with pseudohypoparathyroidism. In each case, the maternal disorder had been undiagnosed or inadequately treated during pregnancy. The cause of the condition is chronic intrauterine exposure to hypocalcemia with resultant hyperplasia of the fetal parathyroid glands. In the newborn, manifestations involve the bones primarily, and healing occurs between 4 and 7 months of age.

CLINICAL MANIFESTATIONS

At all ages, the clinical manifestations of hypercalcemia of any cause include muscle weakness, fatigue, headache, hyporeflexia, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia and polyuria **(nephrogenic diabetes insipidus)**, weight loss, and fever. When hypercalcemia is of long duration, calcium may be deposited in the renal parenchyma (nephrocalcinosis), with progressively diminished renal function. Renal calculi can develop and can cause renal colic and hematuria. Osseous changes can produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors. Height can decrease from compression of vertebrae; the patient can become bedridden. Detection of completely asymptomatic patients is increasing with the advent of automated panel assays that include serum calcium determinations.

Abdominal pain is occasionally prominent and may be associated with **acute pancreatitis**. Parathyroid crisis can occur, manifested by serum calcium levels >15 mg/dL and progressive oliguria, azotemia, stupor, and coma. In infants, failure to thrive, poor feeding, and hypotonia are common. Cognitive impairment, convulsions, and blindness can occur as sequelae of long-standing hypercalcemia. Psychiatric manifestations include depression, confusion, dementia, stupor, and psychosis.

LABORATORY FINDINGS

The serum calcium level is elevated; 39 of 45 children with adenomas had levels >12 mg/dL. The hypercalcemia is more severe in infants with parathyroid hyperplasia; concentrations ranging from 15 to 20 mg/dL are common, and values as high as 30 mg/dL have been reported. Even when the total serum calcium level is borderline or only slightly elevated, ionized calcium levels are often increased. The serum phosphorus level is reduced to approximately 3 mg/dL or less, and the level of serum magnesium is low. The urine can have a low and fixed specific gravity, and serum levels of nonprotein nitrogen and uric acid may be elevated. In patients with adenomas who have skeletal involvement, serum phosphatase levels are elevated, but in infants with hyperplasia, the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

The ECG may demonstrate a prolonged PR interval, short QT interval, widened QRS complex and bradycardia.

Serum levels of intact PTH are elevated, especially in relation to the level of calcium. Calcitonin levels are normal. Acute hypercalcemia can stimulate calcitonin release, but with prolonged hypercalcemia, hypercalcitoninemia does not occur.

The most consistent and characteristic radiographic finding is resorption of subperiosteal bone, best seen along the margins of the phalanges of the hands. In the skull, there may be gross trabeculation or a granular appearance resulting from focal rarefaction; the lamina dura may be absent. In more advanced disease, there may be generalized rarefaction, cysts, tumors, fractures, and deformities. Approximately 10% of patients have radiographic signs of rickets. Radiographs of the abdomen can reveal renal calculi or nephrocalcinosis.

DIFFERENTIAL DIAGNOSIS

Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism (Table 613.1 and Fig. 613.1). A low serum phosphorus level with hypercalcemia is characteristic of primary hyperparathyroidism; elevated levels of PTH are also diagnostic. With hypercalcemia of any cause except hyperparathyroidism and familial hypocalciuric hypercalcemia, PTH levels are suppressed. Pharmacologic doses of corticosteroids lower the serum calcium level to normal in patients with hypercalcemia from other causes but generally do not affect the calcium level in patients with hyperparathyroidism.

TREATMENT

When hyperparathyroidism is clearly established, imaging and possibly surgical exploration are indicated. All glands should be carefully inspected and if an adenoma is discovered, it should be removed. Very few instances of carcinoma are known in children. Most neonates with severe hypercalcemia require total parathyroidectomy; less severe hypercalcemia remits spontaneously in others. Still others have been treated successfully with bisphosphonates and calcimimetics. The patient should be carefully observed postoperatively for the development of hypocalcemia and tetany; intravenous administration of calcium gluconate may be required for a few days. The serum calcium level then gradually returns to normal, and, under ordinary circumstances, a diet high in calcium and phosphorus must be maintained for only several months after operation.

CT, real-time ultrasonography, and subtraction scintigraphy using sestamibi/technetium-pertechnetate alone and in combination have proved effective in localizing a single adenoma versus diffuse hyperplasia in 50–90% of adults. Parathyroid surgeons often rely on intraoperative selective venous sampling with intraoperative assay of PTH for localizing and removing the source of increased PTH secretion.

PROGNOSIS

The prognosis is good if the disease is recognized early and there is appropriate surgical treatment. When extensive osseous lesions are present, deformities may be permanent. A search for other affected family members is indicated.

613.1 Other Causes of Hypercalcemia

Evan G. Graber and Daniel A. Doyle

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FAMILIAL BENIGN HYPERCALCEMIA)

Patients with familial hypocalciuric hypercalcemia are usually asymptomatic, and the hypercalcemia is identified by chance during routine investigation for other conditions. Adults may have recurrent pancreatitis, chondrocalcinosis, or premature vascular calcification. The parathyroid glands are normal, PTH levels are inappropriately normal, and subtotal parathyroidectomy does not correct the hypercalcemia. Serum levels of magnesium are high-normal or mildly elevated. The ratio of calcium-to-creatinine clearance is usually decreased despite hypercalcemia.

The disorder is inherited in an autosomal dominant manner and is caused by a pathogenic variant *(CASR)* on chromosome 3q2 in ~65% of patients **(type 1)**. In **type 2**, there is a pathogenic variant in *GNA11,* and in **type 3**, the variant is on *AP2S1*. The disorder can be diagnosed early in childhood by serum and urinary calcium concentrations. Detection of other affected family members is important to avoid inappropriate parathyroid surgery. The defect in type 1 is an inactivating mutation in the Ca^{2+}-sensing receptor gene. This G-protein–coupled receptor senses the level of free Ca^{2+} in the blood and triggers the pathway to increase extracellular Ca^{2+} in the face of hypocalcemia. This receptor functions in the parathyroid and kidney to regulate calcium homeostasis; inactivating mutations lead to an increased set point with respect to serum Ca^{2+}, resulting in mild to moderate hypercalcemia in heterozygotes.

GRANULOMATOUS DISEASES

Hypercalcemia occurs in 30–50% of children with sarcoidosis and less often in patients with other granulomatous diseases such as tuberculosis. Levels of PTH are suppressed, and levels of $1,25(OH)_2D_3$ are elevated. The source of ectopic $1,25(OH)_2D_3$ is the activated macrophage, through stimulation by interferon-α from T lymphocytes, which are present in abundance in granulomatous lesions. Unlike renal tubular cells, the 1α-hydroxylase in macrophages is unresponsive to homeostatic regulation. Oral administration of prednisone lowers serum levels of $1,25(OH)_2D_3$ to normal and corrects the hypercalcemia.

Table 613.1 Causes of Hypercalcemia

I. NEONATE/INFANT
A. Maternal Disorders
1. Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
B. Neonate/Infant
1. Iatrogenic: excessive intake of calcium, vitamin D, vitamin A
2. Phosphate depletion
3. Subcutaneous fat necrosis
4. Williams syndrome (del7q11.23/WBSCR1)
5. Neonatal severe hyperparathyroidism *(CaSR)*
6. Metaphyseal chondrodysplasia, Murk-Jansen type *(PTH1R)*
7. Idiopathic infantile hypercalcemia *(CYP24A1)* (25-hydroxyvitamin D 24-hydroxylase)
8. Persistent parathyroid hormone–related protein
9. Lactase/disaccharidase deficiency *(LCT)*
10. Infantile hypophosphatasia *(TNSALP)*
11. Mucolipidosis type II *(GNPTAB)*
12. Blue diaper syndrome
13. Antenatal Bartter syndrome types 1 and 2 *(SLC12A1, KCNJ1)*
14. Distal renal tubular acidosis
15. IMAGe syndrome *(CDKN1C)*
16. Post bone marrow transplantation for osteopetrosis
17. Endocrinopathies: primary adrenal insufficiency, severe congenital hypothyroidism, hyperthyroidism

II. HYPERPARATHYROIDISM
A. Sporadic
1. Parathyroid hyperplasia, adenoma, carcinoma
B. Familial
1. Neonatal severe hyperparathyroidism *(CaSR)*
2. Multiple endocrine neoplasia, type 1 *(MEN1)*
3. Multiple endocrine neoplasia, type 2A *(RET)*
4. Multiple endocrine neoplasia, type 2B *(RET)*
5. Multiple endocrine neoplasia, type 4 *(CDKN1B)*
6. McCune-Albright syndrome *(GNAS)*
7. Familial isolated hyperparathyroidism 1 *(CDC73)*
8. Familial isolated hyperparathyroidism 2 (jaw tumor syndrome) *(CDC73)*
9. Familial isolated hyperparathyroidism 3
10. Jansen metaphyseal dysplasia *(PTH1R)*
C. Secondary/tertiary
1. Postrenal transplantation
2. Chronic hyperphosphatemia
D. Hypercalcemia of malignancy
1. Ectopic production of parathyroid hormone–related peptide
2. Metastatic dissolution of bone

III. FAMILIAL HYPOCALCIURIC HYPERCALCEMIA
A. Familial hypocalciuric hypercalcemia I (CaSR)
1. Loss-of-function mutations in *CaSR*
- Monoallelic: familial benign hypercalcemia
- Biallelic: neonatal severe hyperparathyroidism
B. Familial hypocalciuric hypercalcemia II (GNA11)
C. Familial hypocalciuric hypercalcemia III, Oklahoma variant (AP2S1)
D. CaSR-blocking autoantibodies

IV. EXCESSIVE CALCIUM OR VITAMIN D
A. Milk-alkali syndrome
B. Exogenous ingestion of calcium or vitamin D or topical application of vitamin D (calcitriol or analog)
C. Ectopic production of calcitriol associated with granulomatous diseases (sarcoidosis, cat scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, cryptococcosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease, Blau syndrome, granulomatosis with polyangiitis)
D. Neoplasia
1. Primary bone tumors
2. Metastatic tumors with osteolysis
3. Lymphoma, leukemia
4. Dysgerminoma
5. Pheochromocytoma
6. Langerhans cell histiocytosis
7. Tumors secreting parathyroid hormone–related peptide, growth factors, cytokines, prostaglandins, and osteoclast-activating factors
E. Williams-Beuren syndrome (del7q11.23)

V. IMMOBILIZATION
VI. OTHER CAUSES
A. Drugs: thiazides, lithium, vitamin A and analogs, calcium, alkali, antiestrogens, aminophylline, teriparatide, abaloparatide
B. Total parenteral nutrition
C. Endocrinopathies: hyperthyroidism, congenital hypothyroidism, Addison disease, pheochromocytoma
D. Vasoactive intestinal polypeptide–secreting tumor
E. Acute or chronic renal failure/administration of aluminum
F. Hypophosphatasia
G. Juvenile idiopathic arthritis: cytokine mediated
H. Late phase of rhabdomyolysis

IMAGe, intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, genital abnormalities; WBSCR1, Williams-Beuren syndrome chromosome region 1.
Adapted from Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. *Curr Opin Pediatr.* 2010;22:508–515; Benjamin RW, Moats-Staats BM, Calikoglu A, et al. Hypercalcemia in children. *Pediatr Endocrinol Rev.* 2008;5:778–784; Davies JH. A practical approach to the problems of hypercalcaemia. *Endocr Dev.* 2009;16:93–114.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia often occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloblastoma, leukemia, Burkitt lymphoma, dysgerminoma, and rhabdomyosarcoma. Serum levels of PTH are rarely elevated. In most patients, the hypercalcemia associated with malignancy is caused by elevated levels of parathyroid hormone–related peptide and not PTH. Rarely, tumors produce $1,25(OH)_2D_3$ or PTH ectopically.

MISCELLANEOUS CAUSES OF HYPERCALCEMIA

Hypercalcemia can occur in infants with **subcutaneous fat necrosis**. Levels of PTH are normal. In one infant, the level of $1,25(OH)_2D_3$ was elevated, and biopsy of the skin lesion revealed granulomatous infiltration, suggesting that the mechanism of the hypercalcemia was akin to that seen in patients with other granulomatous disease. In another infant, although the level of $1,25(OH)_2D_3$ was normal, PTH was suppressed, suggesting the hypercalcemia was not related to PTH. Treatment with prednisone is effective. Bisphosphonate therapy has also been effective in severe cases.

Hypophosphatasia, especially the severe infantile form, is usually associated with mild to moderate hypercalcemia (see Chapter 747). Serum levels of phosphorus are normal, and those of alkaline phosphatase are subnormal. The bones exhibit rachitic-like lesions on radiographs. Urinary levels of phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5′-phosphate are elevated; each is a natural substrate to a tissue-nonspecific (liver, bone, kidney) alkaline phosphatase enzyme. Missense variants of the tissue-nonspecific alkaline phosphatase enzyme gene result in an inactive enzyme in this autosomal recessive disorder.

Idiopathic hypercalcemia of infancy is manifested by failure to thrive and hypercalcemia during the first year of life, followed by spontaneous remission. Serum levels of phosphorus and PTH are normal. The condition has been defined as resulting from increased absorption of calcium from decreased degradation of $1,25(OH)_2D_3$. Pathogenic variants in the *CYP24A1* gene that encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme in $1,25(OH)_2D_3$ degradation, cause excessive levels of the active vitamin D metabolite, which, in turn, causes hypercalcemia in a subset of infants who receive supplemental vitamin D. An excessive rise in the level of $1,25(OH)_2D_3$ in response to PTH administration has been reported years after the hypercalcemic phase.

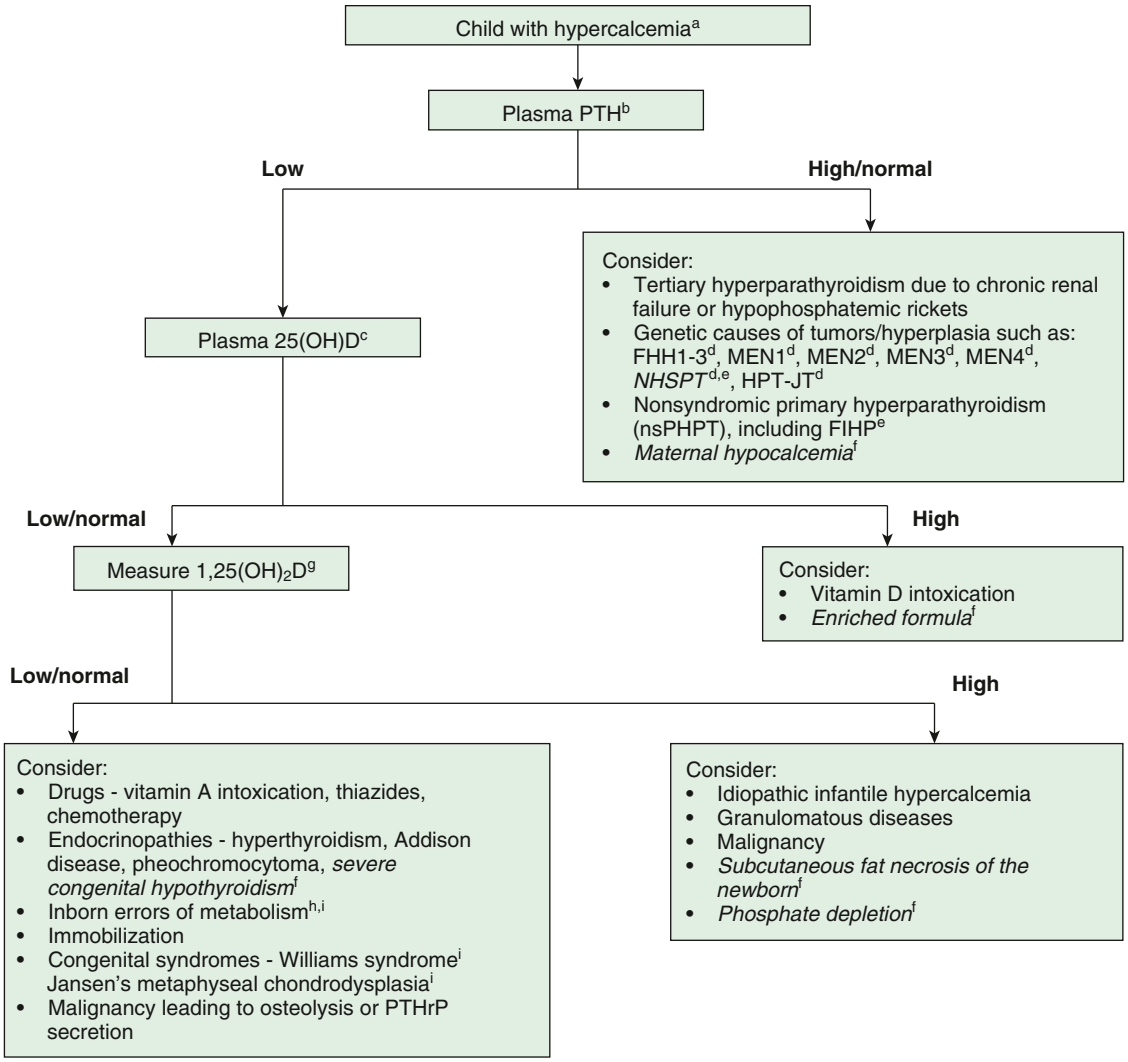

Fig. 613.1 Algorithm illustrating the clinical approach to investigation of causes of hypercalcemia in a child. [a]Confirm hypercalcemia, defined as plasma (or serum) adjusted calcium >10.5 mg/dL (2.60 mmol/L) or ionized calcium >5.25 mg/dL (1.32 mmol/L). [b]PTH, parathyroid hormone. [c]25(OH)D, 25-hydroxyvitamin D. [d]FHH1-3, familial hypocalciuric hypercalcemia types 1-3; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; MEN3, multiple endocrine neoplasia type 3; MEN4, multiple endocrine neoplasia type 4; NSHPT, neonatal severe primary hyperparathyroidism; HPT-JT, hyperparathyroid–jaw tumor syndrome. [e]FIHP, Familial isolated hyperparathyroidism. [f]Conditions affecting neonates (shown in italics). [g]1,25$(OH)_2$D, 1,25-dihydroxyvitamin D. [h]Inborn errors of metabolism, for example, hypophosphatasia, congenital lactase deficiency (CLD), and blue diaper syndrome. [i]These syndromes may be associated with dysmorphic features, for example, Williams syndrome, Jansen metaphyseal chondrodysplasia, and hypophosphatasia. PTHrP, parathyroid hormone-related peptide. *(From Stokes VJ, Nielsen MF, Hannan FM, Thaller RV. Hypercalcemic disorders in children. J Bone Miner Res. 2017;32:2157–2170, Fig. 2.)*

Approximately 15% of patients with **Williams syndrome** may exhibit hypercalcemia. Hypercalcemia is more common in patients <24 months of age. It is often transient and usually does not require treatment. The phenotype consists of feeding difficulties, slow growth, elfin facies (small mandible, prominent maxilla, upturned nose), renovascular disorders, and a gregarious "cocktail party" personality. Cardiac lesions include supravalvular aortic stenosis, peripheral pulmonic stenosis, aortic hypoplasia, coronary artery stenosis, and atrial or ventricular septal defects. **Nephrocalcinosis** can develop if hypercalcemia persists. The IQ score of 50-70 is curiously accompanied by enhanced quantity and quality of vocabulary, auditory memory, and social use of language. A contiguous gene deletion syndrome with a submicroscopic deletion at chromosome 7q11.23, which includes deletion of one elastin allele, occurs in 90% of patients and seems to account for the vascular problems. Definitive diagnosis can be established by specific fluorescence in situ hybridization. The hypercalcemia and central nervous system symptoms may be caused by deletion of adjacent genes. Hypercalcemia has been successfully controlled with either prednisone or calcitonin.

Hypervitaminosis D resulting in hypercalcemia from drinking milk that has been incorrectly fortified with excessive amounts of vitamin D has been reported. Not all patients with hypervitaminosis D develop hypercalcemia. Affected infants can manifest failure to thrive, nephrolithiasis, poor renal function, and osteosclerosis. Serum levels of 25(OH)D are a better indicator of hypervitaminosis D than levels of 1,25$(OH)_2D_3$ because 25(OH)D has a longer half-life.

Prolonged immobilization can lead to hypercalcemia and occasionally to decreased renal function, hypertension, and encephalopathy. Children who have hypophosphatemic rickets and undergo surgery with subsequent long-term immobilization are at risk for hypercalcemia and should therefore have their vitamin D supplementation decreased or discontinued.

Jansen-type metaphyseal chondrodysplasia is a rare genetic disorder characterized by short-limbed dwarfism and severe but asymptomatic hypercalcemia (see Chapter 735). Circulating levels of PTH and parathyroid hormone–related peptide are undetectable. These patients have an activating PTH–parathyroid hormone–related peptide receptor mutation that results in aberrant calcium homeostasis and abnormalities of the growth plate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Disorders of the Adrenal Gland

Chapter 614

Physiology of the Adrenal Gland

614.1 Histology and Embryology

Perrin C. White

The adrenal gland is composed of two endocrine tissues: the medulla and the cortex. The chromaffin cells of the adrenal medulla are derived from neuroectoderm, whereas the cells of the adrenal cortex are derived from mesoderm. Mesodermal cells also contribute to the development of the gonads. The adrenal glands and gonads have certain common enzymes involved in steroid synthesis; an inborn error in steroidogenesis in one tissue can also be present in the other.

The adrenal cortex of the older child or adult consists of three zones: the **zona glomerulosa**, the outermost zone located immediately beneath the capsule; the **zona fasciculata**, the middle zone; and the **zona reticularis**, the innermost zone, lying next to the adrenal medulla. The zona fasciculata is the largest zone, constituting approximately 75% of the cortex; the zona glomerulosa constitutes approximately 15%; and the zona reticularis approximately 10%. Glomerulosa cells are small, with a lower cytoplasmic:nuclear ratio, an intermediate number of lipid inclusions, and smaller nuclei containing more condensed chromatin than the cells of the other two zones. The cells of the zona fasciculata are large, with a high cytoplasmic:nuclear ratio and many lipid inclusions that give the cytoplasm a foamy, vacuolated appearance. The cells are arranged in radial cords. The cells of the zona reticularis are arranged in irregular anastomosing cords. The cytoplasmic:nuclear ratio is intermediate, and the compact cytoplasm has relatively little lipid content.

The zona glomerulosa synthesizes **aldosterone**, the most potent natural **mineralocorticoid** in humans. The zona fasciculata produces **cortisol**, the most potent natural **glucocorticoid** in humans, and the zona fasciculata and zona reticularis synthesize the adrenal androgens.

The adrenal medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. Neuroendocrine cells are polyhedral, with abundant cytoplasm and small, pale-staining nuclei. Under the electron microscope, the cytoplasm contains many large secretory granules that contain catecholamines. Glial cells have less cytoplasm and more basophilic nuclei.

The adrenogonadal primordium differentiates from the coelomic mesothelium at 4 weeks of gestation at the urogenital ridge, just cephalad to the developing mesonephros. At 5-6 weeks, it develops into the steroidogenic cells of the gonads and adrenal cortex; the adrenal and gonadal cells separate, the adrenal cells migrate retroperitoneally, and the gonadal cells migrate caudad. At 6-8 weeks of gestation, the gland rapidly enlarges, the cells of the inner cortex differentiate to form the fetal zone, and the outer subcapsular rim remains as the definitive zone. The primordium of the adrenal cortex is invaded at this time by sympathetic neural elements of ectodermal origin that differentiate into the chromaffin cells capable of synthesizing and storing catecholamines. Catechol *O*-methyltransferase, which converts norepinephrine to epinephrine, is expressed later in gestation. By the end of the eighth week of gestation, the encapsulated adrenal gland is associated with the upper pole of the kidney. By 8-10 weeks of gestation, the cells of the fetal zone are capable of active steroidogenesis.

In the full-term infant, the combined weight of both adrenal glands is 7-9 g. At birth, the inner fetal zone of the cortex makes up approximately 80% of the gland and the outer definitive zone 20%. Within a few days the fetal cortex begins to involute, undergoing a 50% reduction by 1 month of age. Conversely, the adrenal medulla is relatively small at birth and undergoes a proportionate increase in size over the first 6 months after birth. By 1 year, the adrenal glands each weigh <1 g. Adrenal growth thereafter results in adult adrenal glands reaching a combined weight of 8 g. The zonae fasciculata and glomerulosa are fully differentiated by about 3 years of age. The zona reticularis is not fully developed until puberty.

Adrenocorticotropic hormone (ACTH) is essential for fetal adrenal growth and maturation; feedback regulation of ACTH by cortisol is apparently established by 8-10 weeks of gestation. Additional factors important in fetal growth and steroidogenesis include placental chorionic gonadotropins and a number of peptide growth factors produced by the placenta and fetus.

Many transcription factors are critical for the development of the adrenal glands. At least four, EMX2, LHX1 (also termed LIM1), WT1, and WNT4, are required for development of the adrenogonadal primordium. WT1 upregulates expression of steroidogenic factor-1 (SF-1, encoded by the *NR5A1* gene). NR5A1 is one of at least three transcription factors associated with **adrenal hypoplasia** in humans; the others are *NR0B1* (dosage-sensitive sex reversal, adrenal hypoplasia congenita, X chromosome; *DAX1*), and the *GLI3* oncogene. Disruption of *NR5A1,* encoded on chromosome 9q33, results in gonadal and often adrenal agenesis, absence of pituitary gonadotropes, and an underdeveloped ventral medial hypothalamus. In-frame deletions and frameshift and missense pathogenic variants of this gene are associated with **46,XX ovarian insufficiency** and **46,XY gonadal dysgenesis**. Pathogenic variants in the *NR0B1* gene, encoded on Xp21, result in **adrenal hypoplasia congenita** and **hypogonadotropic hypogonadism** (see Chapter 615.1). Pathogenic variants in *GLI3* on chromosome 7p13 cause **Pallister-Hall syndrome**, other features of which include hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly.

The postnatal adrenal cortex is not static but is continually regenerated from a population of stem or progenitor cells under the adrenal capsule. These cells move radially inward (i.e., centripetally) and can differentiate into zona glomerulosa or fasciculata cells as needed in response to the appropriate trophic stimuli (see Chapter 614.3). Several signaling pathways, including sonic hedgehog (SHH) and WNT, regulate this process. SHH expression is restricted to the peripheral cortical cells that do not express high levels of steroidogenic genes but give rise to the underlying differentiated cells of the cortex. Wnt/β-catenin signaling maintains the undifferentiated state and adrenal fate of adrenocortical stem/progenitor cells, in part through induction of its target genes *DAX1* and inhibin-α, respectively. Adrenal tumors can result from constitutive activation of the WNT signaling pathway (see Chapter 617).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

614.2 Adrenal Steroid Biosynthesis

Perrin C. White

Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 614.1). Although adrenal cortex cells can synthesize cholesterol de novo from acetate, circulating plasma lipoproteins provide most of the cholesterol for adrenal cortex hormone formation. Receptors for both low-density lipoprotein and high-density lipoprotein cholesterol are expressed on the surface of adrenocortical cells; the receptor for high-density lipoprotein is termed *scavenger receptor class B, type I* (SR-BI). Patients with **homozygous familial hypercholesterolemia**

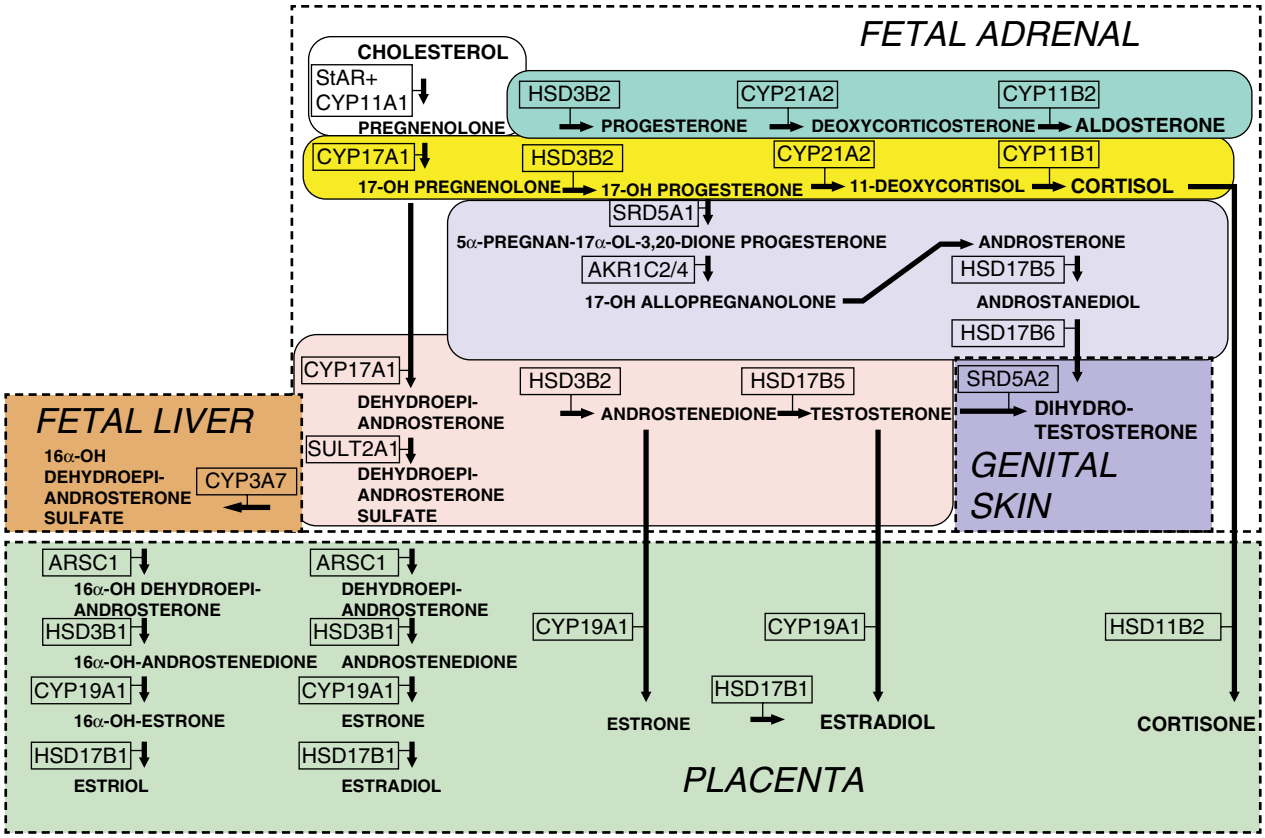

Fig. 614.1 Steroid biosynthesis and metabolism during gestation. Conversions within the fetal adrenal cortex, fetal liver *(brown rectangle),* male (i.e., testosterone-exposed) genital skin *(purple rectangle),* and placenta *(green rectangle)* are denoted by *arrows;* the enzyme mediating each conversion is also shown. Enzymatic conversions in the adrenal cortex are the same postnatally as prenatally, but cortisol and aldosterone biosynthesis (denoted by *yellow and turquoise boxes,* respectively) are more prominent, and normally little testosterone is synthesized *(pink rectangle).* A "backdoor pathway" *(lavender rectangle)* to convert 17-hydroxyprogesterone to dihydrotestosterone is active in the fetal adrenal and may assume particular importance in congenital adrenal hyperplasia (see Chapter 616). Many of the involved enzymes are cytochromes P450 (CYPs). The first step in all steroid biosynthesis is importation of cholesterol into mitochondria *(white rectangle)* mediated by the steroidogenic acute regulatory (StAR) protein. Adrenal enzymes include CYP11A1, cholesterol side-chain cleavage enzyme (P450scc in older terminology); HSD3B2, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 2; CYP17A1, 17β-hydroxylase/17,20-lyase (P450c17); CYP21A2, 21-hydroxylase (P450c21); CYP11B1, 11β-hydroxylase (P450c11); CYP11B2, aldosterone synthase (P450aldo; this enzyme mediates successive 11β-hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone); and AKR1C2/4, aldo-ketoreductases 1C2 and 1C4. Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP19, aromatase (P450arom); HSD3B1, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1, HSD17B5, and HSD17B6 are three different 17-hydroxysteroid dehydrogenase enzymes; SRD5A1 and SRD5A2, steroid 5α-reductase types 1 and 2, respectively; and SULT2A1, steroid sulfotransferase.

who lack low-density lipoprotein receptors have only mildly impaired adrenal steroidogenesis, suggesting that high-density lipoprotein is the more important source of cholesterol. Cholesterol is stored as cholesteryl esters in vesicles and subsequently hydrolyzed by cholesteryl ester hydrolases to liberate free cholesterol for steroid hormone synthesis.

The rate-limiting step of adrenal steroidogenesis is importation of cholesterol across the mitochondrial outer and inner membrane. This requires several proteins, particularly the steroidogenic acute regulatory (StAR) protein. The StAR protein has a very short half-life, and its synthesis is rapidly induced by trophic factors (corticotropin); it is the main short-term (minutes to hours) regulator of steroid hormone biosynthesis.

At the mitochondrial inner membrane, the side chain of cholesterol is cleaved to yield pregnenolone. This is catalyzed by the cholesterol side-chain cleavage enzyme (cholesterol desmolase, side-chain cleavage enzyme, P450scc, CYP11A1—the last term is the current systematic nomenclature), a cytochrome P450 (CYP) enzyme. Like other CYP enzymes, this is a membrane-bound hemoprotein with a molecular mass of approximately 50 kDa. It accepts electrons from a reduced nicotinamide adenine dinucleotide phosphate–dependent mitochondrial electron transport system consisting of two accessory proteins: adrenodoxin reductase (also called *ferredoxin reductase,* a flavoprotein) and adrenodoxin (or ferredoxin; a small protein containing nonheme iron). CYP enzymes use electrons and O_2 to hydroxylate the substrate and form H_2O. In the case of cholesterol side-chain cleavage, three successive oxidative reactions are performed to cleave the C20,22 carbon bond. Pregnenolone then diffuses out of mitochondria and enters the endoplasmic reticulum. The subsequent reactions that occur depend on the zone of the adrenal cortex.

ZONA GLOMERULOSA

In the zona glomerulosa, pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase type 2, an oxidized nicotinamide adenine dinucleotide–dependent enzyme of the short-chain dehydrogenase type. Progesterone is converted to 11-deoxycorticosterone by steroid 21-hydroxylase (CYP21A2, P450c21), which is another CYP enzyme. Like other such enzymes in the endoplasmic reticulum, it uses an electron transport system with only one accessory protein: P450 oxidoreductase.

Deoxycorticosterone then reenters mitochondria and is converted to aldosterone by aldosterone synthase (CYP11B2, P450aldo), a CYP enzyme structurally related to cholesterol side-chain cleavage enzyme. Aldosterone synthase also carries out three successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde.

ZONA FASCICULATA

In the endoplasmic reticulum of the zona fasciculata, pregnenolone and progesterone are converted by 17α-hydroxylase (CYP17A1, P450c17) to 17-hydroxypregenolone and 17-hydroxyprogesterone, respectively. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-Hydroxypregnenolone is converted to 17-hydroxyprogesterone and 11-deoxycortisol by the same 3β-hydroxysteroid and 21-hydroxylase enzymes, respectively, as are active in the zona glomerulosa. Thus inherited disorders in these enzymes affect both aldosterone and cortisol synthesis (see Chapter 616). Finally, 11-deoxycortisol reenters mitochondria and is converted to cortisol by steroid 11β-hydroxylase CYP11B1 (P450c11). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity. Thus under normal circumstances the zona fasciculata cannot synthesize aldosterone.

ZONA RETICULARIS

In the zona reticularis and to some extent in the zona fasciculata, the 17-hydroxylase (CYP17A1) enzyme has an additional activity: cleavage of the 17,20 carbon-carbon bond. This converts 17-hydroxypregnenolone to dehydroepiandrosterone (DHEA). DHEA is converted to androstenedione by HSD3B2. This may be further converted in other tissues to testosterone and estrogens.

The Alternative or "Backdoor" Pathway to Dihydrotestosterone

In addition to the classic pathway via DHEA, androstenedione, and testosterone, the most potent endogenous androgen, 5-dihydrotestosterone (DHT), can also be synthesized via an alternative or "backdoor" pathway, which is physiologically active during the major period of human sexual differentiation in the 6th to 10th week of human fetal development and into the second trimester. To enter the alternative pathway, progesterone or 17-hydroxyprogesterone is 5α-reduced by steroid 5α-reductase type 1 (SRD5A1) to yield 5α-dihydroprogesterone and 17α-hydroxydihydroprogesterone. These three ketosteroids are subsequently 3α-reduced to allopregnanolone and 17α-hydroxyallopregnanolone by isoforms of the AKR1C enzyme family. CYP17A1 converts allopregnanolone to 17α-hydroxyallopregnanolone and then to androsterone by its 17,20-lyase activity. Androsterone can then be activated to DHT by sequential 17β-reduction and 3α-oxidase reactions.

FETOPLACENTAL UNIT

Steroid synthesis in the fetal adrenal varies during gestation (see Figs. 614.1 and 614.2). Shortly after the fetal adrenal gland forms (weeks 8-10), it efficiently secretes cortisol, which is able to negatively feed back on the fetal pituitary and hypothalamus to suppress ACTH secretion. This is a critical time for differentiation of the external genitalia in both sexes (see Chapter 616.1); to prevent virilization, the female fetus must not be exposed to high levels of androgens of adrenal origin, and placental aromatase activity must remain low during this time to minimize conversion of testosterone to estradiol in male fetuses, which would interfere with masculinization. After week 12, HSD3B activity in the fetal adrenal gland decreases and steroid sulfokinase activity increases. Major steroid products of the midgestation fetal adrenal gland are DHEA and DHEA sulfate (DHEAS) and, by 16α-hydroxylation in the liver, 16α-hydroxy DHEAS. Aromatase activity increases in the placenta at the same time, and steroid sulfatase activity is high as well. The placenta uses DHEA and DHEAS as substrates for estrone and estradiol synthesis and 16α-OH DHEAS as a substrate for estriol synthesis. Cortisol activity is low during the second trimester, which might serve to prevent premature secretion of surfactant by the developing fetal lungs; surfactant levels can affect the timing of parturition. As term approaches, fetal cortisol concentration increases because of increased cortisol secretion and decreased conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2). Low levels of aldosterone are produced in midgestation, but aldosterone secretory capacity increases near term.

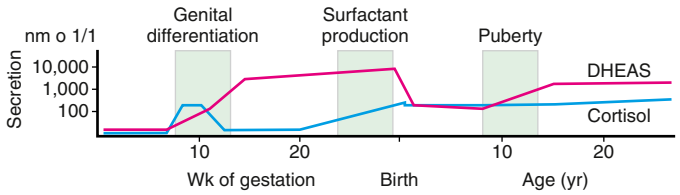

Fig. 614.2 Relative levels of cortisol and dehydroepiandrosterone sulfate (DHEAS) secretion by the fetal adrenal cortex during gestation and postnatally. Approximate times of several events are shown. Vertical axis is logarithmic, but values are approximate. Horizontal axis is not to scale.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

614.3 Regulation of the Adrenal Cortex

Perrin C. White

REGULATION OF CORTISOL SECRETION

Glucocorticoid secretion is regulated mainly by ACTH (corticotropin), a 39–amino acid peptide that is produced in the anterior pituitary (see Fig. 594.2). It is synthesized as part of a larger-molecular-weight precursor peptide known as *pro-opiomelanocortin*. This precursor peptide is also the source of β-lipotropin. ACTH and β-lipotropin are cleaved further to yield α- and β-melanocyte–stimulating hormone, corticotropin-like intermediate lobe peptide, γ-lipotropin, β- and γ-endorphin, and enkephalin (see Chapter 594).

ACTH is released in secretory bursts of varying amplitude throughout the day and night. The normal diurnal rhythm of cortisol secretion is caused by the varying amplitudes of ACTH pulses. Pulses of ACTH and cortisol occur every 30-120 minutes, are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 hours after sleep begins.

Corticotropin-releasing hormone (CRH), synthesized by neurons of the parvicellular division of the hypothalamic paraventricular nucleus, is the most important stimulator of ACTH secretion. Arginine vasopressin (AVP) augments CRH action. Neural stimuli from the brain cause the release of CRH and AVP (see Chapter 594). AVP and CRH are secreted in the hypophyseal-portal circulation in a pulsatile manner. This pulsatile secretion appears to be responsible for the pulsatile (ultradian) release of ACTH. The circadian rhythm of ACTH release is probably induced by the corresponding circadian rhythm of hypothalamic CRH secretion, regulated by the suprachiasmatic nucleus with input from other areas of the brain. Cortisol exerts a negative feedback effect on the synthesis and secretion of ACTH, CRH, and AVP. ACTH inhibits its own secretion, a feedback effect mediated at the level of the hypothalamus. Finally, the adrenal cortex has intrinsic rhythmicity in its responses to the ACTH. Thus the secretion of cortisol is a result of the interaction of the hypothalamus, pituitary, and adrenal glands and other neural stimuli.

ACTH acts through a specific G protein–coupled receptor (also termed *melanocortin receptor-2,* encoded by the *MCR2* gene) to activate adenylate cyclase and increase levels of cyclic adenosine monophosphate. Cyclic adenosine monophosphate has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of StAR protein. The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol. These transcriptional effects occur at least in part through increased activity of protein kinase A, which phosphorylates several transcriptional regulatory factors. MC2R trafficking and signaling are dependent on the MC2R accessory protein (MRAP). Pathogenic variants in either MC2R or MRAP can cause **familial glucocorticoid deficiency** (see Chapter 615).

REGULATION OF ALDOSTERONE SECRETION

The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by the renin-angiotensin system and by potassium levels, with ACTH having only a short-term effect. In response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. Renin is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an α_2-globulin produced by the liver, to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide angiotensin II. Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensins II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensins II and III occupy a G protein–coupled receptor activating phospholipase C. This protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol triphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated kinases. Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by calmodulin-activated kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis.

REGULATION OF ADRENAL ANDROGEN SECRETION

The mechanisms by which the adrenal androgens DHEA and androstenedione are regulated are not completely understood. **Adrenarche** is a maturational process in the adrenal gland that results in increased adrenal androgen secretion between the ages of 5 and 20 years. The process begins before the earliest signs of puberty and continues throughout the years when puberty is occurring. Histologically, it is associated with the appearance of the zona reticularis. Whereas ACTH stimulates adrenal androgen production acutely and clearly is the primary stimulus for cortisol release, additional factors have been implicated in the stimulation of the adrenal androgens. These include a relative decrease in expression of HSD3B2 in the zona reticularis and possibly increases in 17,20-lyase activity owing to phosphorylation of CYP17 or increased cytochrome b5 expression.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

614.4 Adrenal Steroid Hormone Actions

Perrin C. White

Steroid hormones act through several distinct receptors corresponding to the known biologic activities of the steroid hormones: glucocorticoid, mineralocorticoid, progestin, estrogen, and androgen. These receptors belong to a larger superfamily of nuclear transcription factors that include, among others, thyroid hormone and retinoic acid receptors. They have a common structure that includes a carboxyterminal ligand-binding domain and a midregion DNA-binding domain. The latter domain contains two zinc fingers, each of which consists of a loop of amino acids stabilized by four cysteine residues chelating a zinc ion.

Unliganded glucocorticoid and mineralocorticoid receptors are found mainly in the cytosol in complexes with other proteins. Hormone molecules diffuse through the cell membrane and bind receptors, changing their conformation and causing them to release their cytosolic binding proteins and translocate to the nucleus, where they bind DNA at specific hormone-response elements. Bound receptors can recruit other transcriptional coregulatory factors to DNA.

Whereas different steroids can share bioactivities because of their ability to bind to the same receptor, a given steroid can exert diverse biologic effects in different tissues. The diversity of hormonal responses is determined by the different genes that are regulated by each hormone in different tissues. Additionally, different combinations of coregulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes can increase or decrease the affinity of steroids for their receptors and thus modulate their activity. 11β-Hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid. This increases local glucocorticoid concentrations in several tissues, especially the liver, where glucocorticoids maintain hepatic glucose output (see Chapter 615.4). Overexpression of this enzyme in adipose tissue can predispose to the development of obesity. Conversely, HSD11B2 oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol (see Chapter 615.4).

Although corticosteroid receptors mainly act in the nucleus, some responses to both glucocorticoids and mineralocorticoids begin within minutes, an interval too short to be accounted for by increased gene transcription and protein synthesis. Such nongenomic effects can in some cases be mediated by cell membrane–associated isoforms of the classic glucocorticoid and mineralocorticoid receptors, which can couple to a variety of rapid intracellular signaling pathways such as G proteins. Direct interactions with other proteins, such as ion channels, have been documented as well, particularly in the nervous system.

ACTIONS OF GLUCOCORTICOIDS

Glucocorticoids are essential for survival. The term *glucocorticoid* refers to the glucose-regulating properties of these hormones. However, glucocorticoids have multiple effects on carbohydrate, lipid, and protein metabolism. They also regulate immune, circulatory, and renal function. They influence growth, development, bone metabolism, and central nervous system activity.

In stress situations, glucocorticoid secretion can increase up to 10-fold. This increase is believed to enhance survival through increased cardiac contractility, cardiac output, sensitivity to the pressor effects of catecholamines and other pressor hormones, work capacity of the skeletal muscles, and capacity to mobilize energy stores.

METABOLIC EFFECTS

The primary action of the glucocorticoids on carbohydrate metabolism is to increase glucose production by increasing hepatic gluconeogenesis. Glucocorticoids also increase cellular resistance to insulin, thereby decreasing entry of glucose into the cell. This inhibition of glucose uptake occurs in adipocytes, muscle cells, and fibroblasts. In addition to opposing insulin action, glucocorticoids can work in parallel with insulin to protect against long-term starvation by stimulating glycogen deposition and production in the liver. Both hormones stimulate glycogen synthetase activity and decrease glycogen breakdown. Glucocorticoid excess can cause hyperglycemia, and glucocorticoid deficiency can cause hypoglycemia.

Glucocorticoids increase free fatty acid levels by enhancing lipolysis, decreasing cellular glucose uptake, and decreasing glycerol production, which is necessary for reesterification of fatty acids. This increase in lipolysis is also stimulated through the permissive enhancement of lipolytic action of other factors such as epinephrine. This action affects adipocytes differently according to their anatomic locations. In the patient with glucocorticoid excess, fat is lost in the extremities, but it is increased in the trunk (centripetal obesity), neck, and face (moon facies). This may involve effects on adipocyte differentiation.

Glucocorticoids generally exert a catabolic or antianabolic effect on protein metabolism. Proteolysis in fat, skeletal muscle, bone, lymphoid, and connective tissue increases amino acid substrates that can be used in gluconeogenesis. Cardiac muscle and the diaphragm are almost entirely spared from this catabolic effect.

Circulatory and Renal Effects

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index. They have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood vessels. In the absence of glucocorticoids, decreased cardiac output and shock can develop; in states of glucocorticoid excess,

hypertension is often observed. This may be a result of activation of the mineralocorticoid receptor (see Chapter 615.4), which occurs when renal HSD11B2 is saturated by excessive levels of glucocorticoids.

Growth

In excess, glucocorticoids inhibit linear growth and skeletal maturation in children, apparently through direct effects on the epiphyses. However, glucocorticoids are also necessary for normal growth and development. In the fetus and neonate, they accelerate the differentiation and development of various tissues, including the hepatic and gastrointestinal systems, along with the production of surfactant in the fetal lung. Glucocorticoids are often given to pregnant women at risk for delivery of premature infants to accelerate these maturational processes.

Immunologic Effects

Glucocorticoids play a major role in immune regulation. They inhibit synthesis of glycolipids and prostaglandin precursors and the actions of bradykinin. They also block secretion and actions of histamine and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, and interleukin-6), thus diminishing inflammation. High doses of glucocorticoids deplete monocytes, eosinophils, and lymphocytes, especially T cells. They do so at least in part by inducing cell-cycle arrest in the G_1 phase and by activating apoptosis through glucocorticoid receptor–mediated effects. The effects on lymphocytes are primarily exerted on T-helper 1 cells and hence on cellular immunity, whereas the T-helper 2 cells are spared, leading to a predominantly humoral immune response. Pharmacologic doses of glucocorticoids can also decrease the size of immunologic tissues (spleen, thymus, and lymph nodes).

Glucocorticoids increase circulating polymorphonuclear cell counts, mostly by preventing their egress from the circulation. Glucocorticoids decrease diapedesis, chemotaxis, and phagocytosis of polymorphonuclear cells. Thus the mobility of these cells is altered such that they do not arrive at the site of inflammation to mount an appropriate immune response. High levels of glucocorticoids decrease inflammatory and cellular immune responses and increase susceptibility to certain bacterial, viral, fungal, and parasitic infections.

Effects on Skin, Bone, and Calcium

Glucocorticoids inhibit fibroblasts, leading to increased bruising and poor wound healing through cutaneous atrophy. This effect explains the thinning of the skin and striae that are seen in patients with Cushing syndrome.

Glucocorticoids have the overall effect of decreasing serum calcium and have been used in emergency therapy for certain types of hypercalcemia. This hypocalcemic effect probably results from a decrease in the intestinal absorption of calcium and a decrease in the renal reabsorption of calcium and phosphorus. Serum calcium levels, however, generally do not fall below normal because of a secondary increase in parathyroid hormone secretion.

The most significant effect of long-term glucocorticoid excess on calcium and bone metabolism is osteoporosis. Glucocorticoids inhibit osteoblastic activity by decreasing the number and activity of osteoblasts. Glucocorticoids also decrease osteoclastic activity but to a lesser extent, leading to low bone turnover with an overall negative balance. The tendency of glucocorticoids to lower serum calcium and phosphate levels causes secondary hyperparathyroidism. These actions decrease bone accretion and cause a net loss of bone mineral.

Central Nervous System Effects

Glucocorticoids readily penetrate the blood-brain barrier and have direct effects on brain metabolism. They decrease certain types of central nervous system edema and are often used to treat increased intracranial pressure. In large doses, they stimulate appetite and cause insomnia with a reduction in rapid eye movement sleep. There is an increase in irritability and emotional lability, with an impairment of memory and ability to concentrate. Mild to moderate glucocorticoid excess for a limited period often causes a feeling of euphoria or well-being, but glucocorticoid excess and deficiency can both be associated with clinical depression. *Glucocorticoid excess produces psychosis in some patients.*

Glucocorticoid effects in the brain are mediated largely through interactions with both the mineralocorticoid and glucocorticoid receptors (sometimes referred to in this context as *type I* and *type II corticosteroid receptors,* respectively). Activation of type II receptors increases sensitivity of hippocampal neurons to the neurotransmitter serotonin, which might help explain the euphoria associated with high doses of glucocorticoids. Glucocorticoids suppress release of CRH in the anterior hypothalamus, but they stimulate it in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, where it can mediate fear and anxiety states. Glucocorticoids and other steroids might have nongenomic effects by modulating activities of both γ-aminobutyric acid and *N*-methyl-D-aspartate receptors.

ACTIONS OF MINERALOCORTICOIDS

The most important mineralocorticoids are aldosterone and, to a lesser degree, 11-deoxycorticosterone; corticosterone and cortisol are normally not important as mineralocorticoids unless secreted in excess. Mineralocorticoids have more limited actions than glucocorticoids. Their major function is to maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions in the kidney, gut, and salivary and sweat glands. Aldosterone can have distinct effects in other tissues. Mineralocorticoid receptors are found in the heart and vascular endothelium, and aldosterone increases myocardial fibrosis in heart failure.

Mineralocorticoids have their most important actions in the distal convoluted tubules and cortical collecting ducts of the kidney, where they induce reabsorption of sodium and secretion of potassium. In the medullary collecting duct, they act in a permissive fashion to allow vasopressin to increase osmotic water flux. Thus patients with mineralocorticoid deficiency can develop weight loss, hypotension, hyponatremia, and hyperkalemia, whereas patients with mineralocorticoid excess can develop hypertension, hypokalemia, and metabolic alkalosis (see Chapters 615, 616, and 620).

The mechanisms by which aldosterone affects sodium excretion are incompletely understood. Most effects of aldosterone are presumably the result of changes in gene expression mediated by the mineralocorticoid receptor, and indeed levels of subunits of both the Na^+, K^+-adenosine triphosphatase and the epithelial sodium channel increase in response to aldosterone. Additionally, aldosterone increases expression of the serum- and glucocorticoid-regulated kinase, which indirectly reduces turnover of epithelial sodium channel subunits and thus increases the number of open sodium channels.

The mineralocorticoid receptor has similar affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy results from the action of HSD11B2, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic inhibition (as occurs with excessive consumption of licorice) or genetic deficiency of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension; the genetic condition is termed **apparent mineralocorticoid excess syndrome**.

ACTIONS OF THE ADRENAL ANDROGENS

Many actions of adrenal androgens are exerted through their conversion to active androgens or estrogens such as testosterone, dihydrotestosterone, estrone, and estradiol. In males, <2% of the biologically important androgens are derived from adrenal production, whereas in females approximately 50% of androgens are of adrenal origin. The adrenal contribution to circulating estrogen levels is mainly important in pathologic conditions such as feminizing adrenal tumors. Adrenal androgens contribute to the physiologic development of pubic and axillary hair during normal puberty. They also play an important role in the pathophysiology of **congenital adrenal hyperplasia**, **premature**

adrenarche, **adrenal tumors,** and **Cushing syndrome** (see Chapters 616-619).

In humans, circulating levels of DHEA and DHEAS, the chief adrenal androgen precursors, reach a peak in early adulthood and then decline. This has led to speculation that some age-related physiologic changes might be reversed by DHEA administration, and beneficial effects have been suggested (but not proved) on insulin sensitivity, bone mineral density, muscle mass, cardiovascular risk, obesity, cancer risk, autoimmunity, and the central nervous system.

Synthetic Corticosteroids

Many synthetic analogs of cortisone and hydrocortisone are available. Prednisone and prednisolone are derivatives with an additional double bond in ring A. Similar to cortisone, prednisone is not an active steroid, but it is converted to prednisolone by HSD11B1 in the liver. Prednisone and prednisolone are 4-5 times as potent in antiinflammatory and carbohydrate activity but have slightly less effect on retention of water and sodium than cortisol. Halogenated derivatives have different effects. Betamethasone and dexamethasone have 25-40 times the glucocorticoid potency of cortisol but have little mineralocorticoid effect. These analogs are usually used in pharmacologic doses for their antiinflammatory or immunosuppressive properties. The antiinflammatory activity of fludrocortisone is about 15 times that of hydrocortisone, but fludrocortisone is more than 125 times as active a mineralocorticoid; it is used to treat aldosterone deficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

614.5 Adrenal Medulla

Perrin C. White

The principal hormones of the adrenal medulla are the physiologically active catecholamines: dopamine, norepinephrine, and epinephrine (Fig. 614.3). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in chromaffin tissue outside the adrenal medulla. Metabolites of catecholamines are excreted in the urine, principally 3-methoxy-4-hydroxymandelic acid, metanephrine, and normetanephrine. Urinary metanephrines and catecholamines are measured to detect pheochromocytomas of the adrenal medulla and sympathetic nervous system (see Chapter 621).

The proportions of epinephrine and norepinephrine in the adrenal gland vary with age. In early fetal stages, there is practically no epinephrine; at birth, norepinephrine remains predominant. However, in adults, norepinephrine accounts for only 10–30% of the pressor amines in the medulla.

The effects of catecholamines are mediated through a series of G protein–coupled adrenergic receptors. Both epinephrine and norepinephrine raise the mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and calorigenic effects of norepinephrine are much less pronounced than are those of epinephrine.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

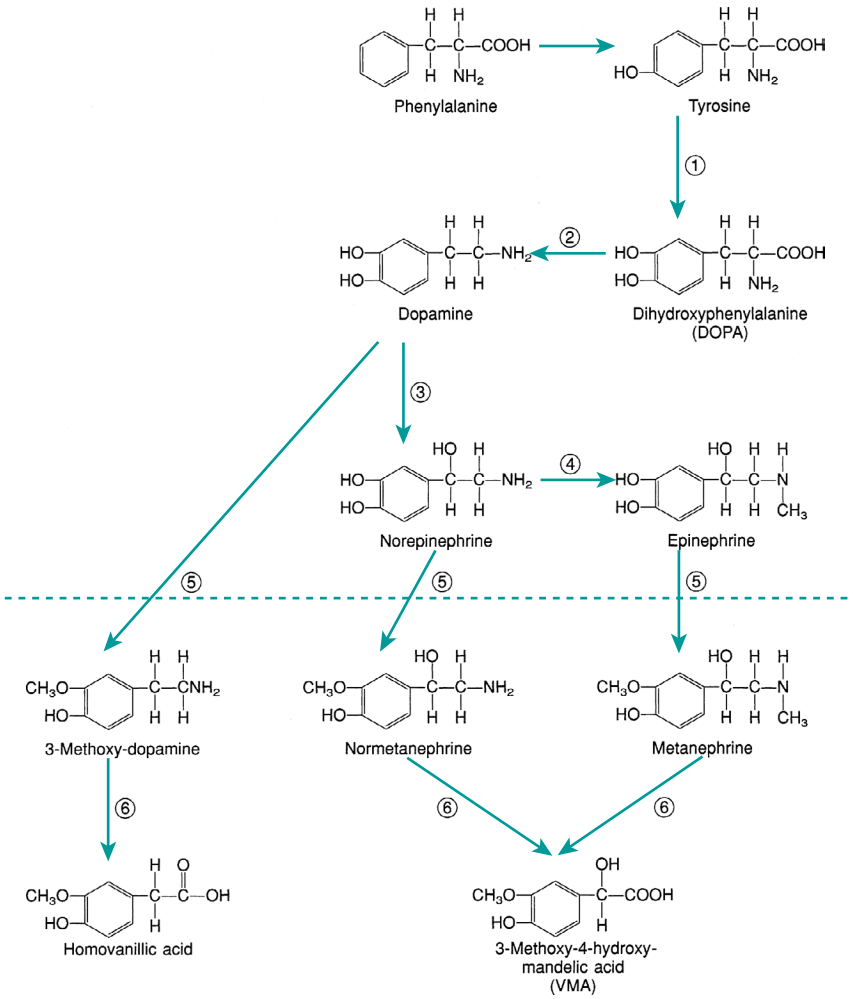

Fig. 614.3 Biosynthesis (above *dashed line*) and metabolism (below *dashed line*) of the catecholamines norepinephrine and epinephrine. Enzymes: *1*, tyrosine hydroxylase; *2*, dopa decarboxylase; *3*, dopamine β-oxidase; *4*, phenylethanolamine-*N*-methyltransferase; *5*, catechol *O*-methyltransferase; *6*, monoamine oxidase.

Chapter 615

Adrenocortical Insufficiency and Altered Sensitivity to Corticosteroids

Perrin C. White

In primary adrenal insufficiency, congenital or acquired lesions of the adrenal cortex prevent production of cortisol and often aldosterone (Table 615.1). Acquired primary adrenal insufficiency is termed **Addison disease**. Dysfunction of the anterior pituitary gland or hypothalamus can cause a deficiency of corticotropin (adrenocorticotropic hormone [ACTH]) and lead to hypofunction of the adrenal cortex, termed *secondary adrenal insufficiency;* the term *tertiary adrenal insufficiency* is sometimes used to denote cases arising from hypothalamic dysfunction (Tables 615.2 and 615.3).

615.1 Primary Adrenal Insufficiency

Perrin C. White

Primary adrenal insufficiency in children is most frequently caused by genetic conditions that are often, but not always, manifested in infancy and, less often, by acquired problems such as autoimmune conditions (Table 615.4) or syndromes (Table 615.5). Susceptibility to autoimmune conditions often has a genetic basis, and so these distinctions are not absolute.

INHERITED ETIOLOGIES

Inborn Defects of Steroidogenesis

The most common causes of adrenocortical insufficiency in *infancy* are the salt-losing forms of congenital adrenal hyperplasia (CAH, see Chapter 616). Approximately 75% of infants with 21-hydroxylase deficiency, almost all infants with lipoid adrenal hyperplasia, and most infants with a deficiency of 3β-hydroxysteroid dehydrogenase manifest salt-losing symptoms in the newborn period because they are unable to synthesize either cortisol or aldosterone. Relatively mild pathogenic variants in *STAR* (which controls cholesterol importation into mitochondria) or *CYP11A1* (which encodes the cholesterol side-chain cleavage enzyme) can cause adrenal insufficiency manifesting in childhood.

Aside from CAH and autoimmune adrenalitis, a genetic cause can be identified in >65% of patients with primary adrenal insufficiency presenting in *childhood*. These can be grouped into several categories: (1) ACTH unresponsiveness (familial glucocorticoid deficiency); (2) adrenal hypoplasia congenita caused by pathogenic variants in orphan nuclear hormone receptors that affect expression of other genes; (3) defects in lipid metabolism, particularly adrenoleukodystrophy; (4) syndromes associated with intrauterine growth restriction, adrenal hypoplasia, and disorders of sexual development, such as IMAGe and MIRAGE syndromes (activating variants of *CDKN1C* and *SAMD9,* respectively), and type 2 IMAGe syndrome (*POLE1* gene); and (5) deficiency of mitochondrial reactive oxygen species detoxification (*NNT* and *TXNRD2* genes).

Familial Glucocorticoid Deficiency

Familial glucocorticoid deficiency is a form of chronic adrenal insufficiency characterized by isolated deficiency of glucocorticoids, elevated levels of ACTH, and generally normal aldosterone production, although salt-losing manifestations present in most other forms of adrenal insufficiency occasionally occur. Patients may have hypoglycemia, seizures, and increased pigmentation during the first decade of life. The disorder affects both sexes equally and is inherited in an autosomal recessive manner. There is marked adrenocortical atrophy with relative sparing of the zona glomerulosa. Pathogenic variants in the gene for the ACTH receptor *(MCR2)* have been described in approximately 25% of these patients, most of which affect trafficking of receptor molecules from the endoplasmic reticulum to the cell surface. Another 10–20% of cases are caused by variants in *MRAP,* which encodes a melanocyte receptor accessory protein required for this trafficking.

Another syndrome of ACTH resistance occurs in association with achalasia and alacrima (**triple A** or **Allgrove syndrome**). These patients often have a progressive neurologic disorder that includes autonomic dysfunction, intellectual disability, motor neuropathy, and occasional deafness. This syndrome is autosomal recessive; the *AAAS* gene has been mapped to chromosome 12q13. The encoded protein, aladin, might help to regulate nucleocytoplasmic transport of other proteins.

Adrenal Hypoplasia Congenita

Adrenal hypoplasia congenita (AHC) is a relatively frequent cause of adrenal insufficiency in males, along with CAH, autoimmune disease, and adrenoleukodystrophy (ALD). AHC is predominantly a failure of development of the definitive zone of the adrenal cortex; the fetal zone may be relatively normal. Consequently, adrenal insufficiency generally becomes evident as the fetal zone involutes postnatally (see Chapter 614), with onset in infancy or in the first 2 years of life but occasionally in later childhood or even adulthood. In some cases, aldosterone deficiency becomes evident before cortisol deficiency.

The disorder is caused by pathogenic variants of *NR0B1 (DAX1)*, a member of the nuclear hormone receptor family, located on Xp21. Males with AHC often do not undergo puberty as a result of hypogonadotropic hypogonadism caused by the same variant of *NR0B1*. **Cryptorchidism**, sometimes noted in these males, is probably an early manifestation of hypogonadotropic hypogonadism, but often testicular function in infants is normal, with a typical or even an unusually prolonged testosterone surge in the first month of life.

AHC occasionally occurs as part of a *contiguous gene deletion* syndrome together with Duchenne muscular dystrophy, glycerol kinase deficiency, cognitive impairment, or a combination of these conditions.

The transcription factor NR5A1 (steroidogenic factor-1, SF-1) is required for adrenal and gonadal development (see Chapter 614). Males with heterozygous variants in *NR5A1* have impaired development of the testes despite the presence of a normal copy of the gene on the other chromosome and can appear to be female, similar to patients with lipoid adrenal hyperplasia (see Chapter 616). Rarely, such patients also have adrenal insufficiency.

Adrenal hypoplasia is also occasionally seen in patients with **Pallister-Hall syndrome** caused by pathogenic variants in *GLI3*.

Disorders of Lipid Metabolism

In **adrenal leukodystrophy (ALD)**, adrenocortical deficiency is associated with demyelination in the central nervous system (see Chapters 106.2 and 639.3). High levels of **very long-chain fatty acids** are found in tissues and body fluids, resulting from their impaired β-oxidation in the peroxisomes.

The most common form of ALD is an X-linked disorder with various presentations. The most common clinical picture is of a degenerative neurologic disorder appearing in childhood or adolescence and progressing to severe dementia and deterioration of vision, hearing, speech, and gait, with death occurring within a few years. Neurologic symptoms may be subtle at onset, sometimes consisting only of behavioral changes or deteriorating academic performance. Generalized but incomplete alopecia, resembling that of chemotherapy, is a characteristic but inconsistent finding. A milder form of X-linked ALD is **adrenomyeloneuropathy**, which begins in later adolescence or early adulthood. Patients may have evidence of adrenal insufficiency before, at the time of, or after neurologic symptoms develop, often with years

Table 615.1 Causes of Primary Adrenal Insufficiency

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
ADRENAL DESTRUCTION		
Autoimmunity		
Autoimmune primary adrenal insufficiency and autoimmune polyendocrine syndrome type 2	*HLA-DR3, DR4, CTLA4, BACH2, PTPN22, GATA3, CLEC16, MIC-A, MIC-B, NALP1,* and *AIRE*	Hypothyroidism, hyperthyroidism, premature ovarian insufficiency, vitiligo, type 1 diabetes, pernicious anemia, other organ-specific autoimmune features
Autoimmune polyendocrine syndrome type 1	*AIRE* (240300)	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, lymphomas (rarely)
Immunodeficiency 31C	*STAT1* (614162)	Chronic mucocutaneous candidiasis, susceptibility to *Staphylococcus aureus* and other bacterial, viral, and fungal infections, polyendocrinopathy (including hypothyroidism and type 1 diabetes), cerebral aneurysms
Peroxisomal Defects		
X-linked adrenoleukodystrophy	*ABCD1* (300100)	Progressive neurodegeneration, behavioral changes, cognitive decline, loss of speech, hearing, and vision, dementia, spasticity, seizures
Refsum disease	*PEX7* (266500)	Least severe form of peroxisome biosynthesis defects
Neonatal adrenoleukodystrophy (autosomal recessive)	*PEX1* (601539)	Craniofacial abnormalities, liver dysfunction, absence of peroxisomes
Zellweger syndrome	*PEX1* (214100)	Craniofacial abnormalities, hepatomegaly, severe intellectual disability and growth failure, hypotonia, deafness, blindness, genitourinary abnormalities, stippled epiphyses
Mitochondrial Defects		
Kearns-Sayre syndrome	Mitochondrial DNA deletions (530000)	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrinopathies
Hemorrhage	—	Bilateral adrenal hemorrhage of the newborn baby, primary antiphospholipid syndrome, anticoagulation
Trauma or Surgery	—	Bilateral adrenalectomy
Infection	—	Septic shock, meningococcal sepsis (Waterhouse-Friderichsen syndrome), tuberculosis, fungal infections (e.g., histoplasmosis, cryptococcosis, coccidioidomycosis, and blastomycosis), African trypanosomiasis, cytomegalovirus, HIV-1, syphilis
Infiltration	—	Metastatic cancers, primary adrenal lymphoma, amyloidosis, sarcoidosis (rare), hemochromatosis
DRUGS	—	Ketoconazole, rifampicin, phenytoin, phenobarbital, aminoglutethimide, mitotane, abiraterone acetate, etomidate, suramin, mifepristone, nivolumab, pembrolizumab
IMPAIRED STEROIDOGENESIS		
Impaired Cholesterol Transport		
Steroidogenic acute regulatory protein (congenital lipoid adrenal hyperplasia)	*StAR* (201710)	46,XY DSD, gonadal insufficiency
Steroidogenic Enzyme or Cofactor Deficiency Causing Congenital Adrenal Hyperplasia		
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2* (201810)	46,XX and 46,XY DSD, gonadal insufficiency
21-hydroxylase	*CYP21A2* (201 910)	46,XX DSD, hyperandrogenism
11β-hydroxylase	*CYP11B1* (202 010)	46,XX DSD, arterial hypertension
CYP17A1 deficiency	*CYP17A1* (202 110)	46,XY DSD, arterial hypertension, gonadal insufficiency
P450 oxidoreductase	*POR* (201 750)	46,XX and 46,XY DSD, gonadal insufficiency, bone malformation, dysfunction of all endoplasmic CYP450 enzymes
Steroidogenic Enzyme Deficiency (Noncongenital Adrenal Hyperplasia)		
P450 side-chain cleavage enzyme	*CYP11A1* (118 485)	46,XY DSD, gonadal insufficiency
Aldosterone synthase	*CYP11B2* (124 080)	Isolated mineralocorticoid deficiency
Defects of Cholesterol Synthesis or Metabolism		
Wolman disease (lysosomal acid lipase deficiency, and cholesterol ester storage disease)	*LIPA* (278 000)	Diffuse punctate adrenal calcification, xanthomatous changes in multiple organs, hypercholesterolemia, steatorrhea, poor prognosis

Continued

Table 615.1 Causes of Primary Adrenal Insufficiency—cont'd

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
Smith-Lemli-Opitz disease	*DHCR7* (270 400)	Intellectual disability, craniofacial malformations, limb abnormalities, growth failure
Abetalipoproteinemia	*MTP* (200 100)	Ataxia, retinopathy, acanthocytosis, fat malabsorption
ADRENAL DYSGENESIS		
X-linked adrenal hypoplasia congenital	*NROB1* (300 200)	Combined primary and secondary hypogonadism, Duchenne muscular dystrophy in contiguous gene syndrome
Adrenal hypoplasia steroidogenic factor-1 deficiency	*NR5A1* (184757)	46,XY DSD, gonadal insufficiency
IMAGe syndrome	*CDKN1C* (300 290)	Intrauterine growth restriction, metaphyseal dysplasia, adrenal insufficiency, genital anomalies
MIRAGE syndrome	*SMAD9* (617 053)	Myelodysplasia, infection, adrenal hypoplasia, growth restriction, genital anomalies, enteropathy
Pallister-Hall syndrome	*GLI3* (165 240)	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, postaxial polydactyly
Meckel syndrome	*MKS1* (249 000)	CNS malformation, polycystic kidneys with fibrotic liver changes, polydactyly
Pseudotrisomy 13	(264 480)	Holoprosencephaly, severe facial anomalies, postaxial polydactyly, various other congenital defects, and normal chromosomes
Hydrolethalus syndrome	*HYLS1* (236 680)	Severe prenatal-onset hydrocephalus, polydactyly
Galloway-Mowat syndrome	*WDR73* (251 300)	Early-onset severe encephalopathy, intractable epilepsy, nephrotic syndrome, microcephaly, hiatal hernia
ACTH RESISTANCE		
Familial glucocorticoid deficiency type 1	*MC2R* (202 200)	Tall stature, isolated deficiency of glucocorticoids, generally normal aldosterone production
Familial glucocorticoid deficiency type 2	*MRAP* (607398)	Isolated deficiency of glucocorticoids, generally normal aldosterone production
IMPAIRED REDOX HOMEOSTASIS		
Triple A syndrome (Allgrove syndrome)	*AAAS* (231550)	Alacrimia, achalasia, neurologic impairment, deafness, intellectual disability, hyperkeratosis
Mitochondrial deficiency of free radical detoxification	*NNT* (614736) and *TRXR2* (606448)	*NNT*: hypoglycemia, hyperpigmentation, low cortisol concentration, increased ACTH concentration, isolated deficiency of glucocorticoids; *TRXR2*: isolated deficiency of glucocorticoids
MISCELLANEOUS		
Defects in DNA repair	*MCM4* (609981)	Natural killer cell deficiency, growth failure, increased chromosomal breakage
Bioinactive ACTH	*POMC* (201400)	—
Sphingosine-1-phosphate lyase 1	*SGPL1* (617575)	Steroid-resistant nephrotic syndrome, ichthyosis, primary hypothyroidism, cryptorchidism, immunodeficiency, neurologic defects

*www.omim.org
ACTH, Adrenocorticotropic hormone; DSD, disorder of sex development; OMIM, Online Mendelian Inheritance in Man.
Modified from Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613–629, Table 1.

separating their presentation. X-linked ALD is caused by pathogenic variants in *ABCD1* located on Xq28. The gene encodes a transmembrane transporter involved in the importation of very long-chain fatty acids into peroxisomes. Clinical phenotypes can vary even within families, perhaps owing to modifier genes or other unknown factors. There is no correlation between the degree of neurologic impairment and severity of adrenal insufficiency. Prenatal diagnosis by DNA analysis and family screening by very long-chain fatty acid assays and gene analysis are available. Females who are heterozygous carriers of the X-linked ALD gene can develop neurologic symptoms in midlife or later; adrenal insufficiency is rare. This condition is part of the newborn screening panel.

Neonatal ALD is a rare *autosomal recessive* disorder. Infants have neurologic deterioration and have or acquire evidence of adrenocortical dysfunction. Most patients have severe, progressive cognitive impairment and die before 5 years of age. This disorder is a subset of **Zellweger (cerebrohepatorenal) syndrome**, in which peroxisomes do not develop at all owing to pathogenic variants in any of several genes (*PEX5*, *PEX1*, *PEX10*, *PEX13*, and *PEX26*) controlling the development of peroxisomes.

Patients with disorders of cholesterol synthesis or metabolism, including abetalipoproteinemia with deficient lipoprotein B–containing lipoproteins (such as low-density lipoprotein), and homozygous **familial hypercholesterolemia**, with impaired or absent low-density lipoprotein receptors, have mildly impaired adrenocortical function. Heterozygous familial hypercholesterolemia patients have normal adrenocortical function, which is unaffected by treatment with statin (HMG-CoA reductase inhibitor) drugs. Adrenal insufficiency has been reported in patients with **Smith-Lemli-Opitz syndrome**, an autosomal recessive disorder manifesting with facial anomalies, microcephaly, limb anomalies, and developmental delay (see Chapter 106.3), caused by pathogenic variants in the gene coding for sterol Δ^7-reductase on chromosome 11q12-q13.

Table 615.2 Causes of Secondary Adrenal Insufficiency in the Form of Pituitary Disorders

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
ACQUIRED CAUSES		
Steroid withdrawal syndrome	*PDGFD*	Endogenous glucocorticoid hypersecretion caused by Cushing syndrome and exogenous glucocorticoid administration for more than 2 wk
Opioids	—	Hypogonadotropic hypogonadism
Tumor	—	Craniopharyngioma, glioma, meningioma, ependymoma, germinoma, intrasellar or suprasellar metastases, adenoma, carcinoma
Trauma	—	Pituitary stalk lesions, battered child syndrome, vehicular trauma
Pituitary apoplexy (Sheehan syndrome)	—	High blood loss or hypotension
CONGENITAL CAUSES		
Aplasia or Hypoplasia		
PROP1 deficiency	*PROP1* (262600)	Additional deficiency of growth hormone, prolactin, thyroid-stimulating hormone, and luteinizing hormone or follicle-stimulating hormone, or both
LHX4 deficiency	*LHX4* (262700)	Additional deficiency of growth hormone and thyroid-stimulating hormone
SOX3 deficiency	*SOX3* (312000)	Additional deficiencies of pituitary hormones
Isolated ACTH Deficiency		
TBX19 deficiency	*TBX19* (201400)	Severe neonatal-onset adrenal insufficiency
Proopiomelanocortin	*POMC* (609734)	Adrenal insufficiency, early-onset obesity, red hair pigmentation
Proprotein convertase 1	*PCSK1* (600955)	Hypoglycemia, malabsorption, hypogonadotropic hypogonadism

*www.omim.org.
ACTH, Adrenocorticotropic hormone; OMIM, Online Mendelian Inheritance in Man.
From Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613–629, Table 2.

Table 615.3 Causes of Tertiary Adrenal Insufficiency

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
ACQUIRED CAUSES		
Steroid withdrawal syndrome	*PDGFD*	Endogenous glucocorticoid hypersecretion caused by Cushing syndrome and exogenous glucocorticoid administration for more than 2 wk
Opioids	—	Hypogonadotropic hypogonadism
Inflammatory disorders	—	Abscess, meningitis, encephalitis
Trauma	—	—
Radiation therapy	—	Craniospinal irradiation in leukemia and irradiation for tumors outside the hypothalamic-pituitary area
Surgery	—	—
Tumor	—	Craniopharyngioma, glioma, meningioma, ependymoma, germinoma, intrasellar or suprasellar metastases
Infiltrative diseases	—	Sarcoidosis, histiocytosis X, hemochromatosis
CONGENTIAL CAUSES		
Septo-optic dysplasia (de Morsier syndrome)	*HESX1* (182230)	Combined pituitary hormone deficiency, optic nerve hypoplasia, midline brain defects
Corticotropin-releasing hormone deficiency	—	—

*www.omim.org.
OMIM, Online Mendelian Inheritance in Man.
From Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613–629, Table 3.

This impairs the final step in cholesterol synthesis with marked elevation of 7-dehydrocholesterol and abnormally low cholesterol. **Wolman disease** is a rare autosomal recessive disorder caused by pathogenic variants in the gene encoding human lysosomal acid lipase on chromosome 10q23.2-23.3. Cholesteryl esters accumulate in lysosomes in most organ systems, leading to organ failure. Infants during the first or second month of life have hepatosplenomegaly, steatorrhea, abdominal distention, and failure to thrive. Adrenal insufficiency and bilateral adrenal calcification are present, and death usually occurs in the first year of life.

Multisystem Syndromes Associated with Growth Restriction

Pathogenic variants in genes that affect DNA replication may be associated with primordial dwarfism, immune deficiency, and adrenal insufficiency. Minichromosome maintenance-deficient 4 homolog *(MCM4)* functions to integrate several protein kinase signals that regulate progression of DNA replication through the S phase. Homozygous deficiency of MCM4 causes a primary **immunodeficiency syndrome** characterized by severe intrauterine and extrauterine growth

Table 615.4 Frequencies of Etiologies of Primary Adrenal Insufficiency

ETIOLOGY	%	AGE AT DIAGNOSIS
Congenital adrenal hyperplasia	59	Infancy
Autoimmune	16	Childhood to adolescence
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	6	Childhood to adolescence
Adrenoleukodystrophy	4	Childhood to adolescence
Other genetic causes	14*	
Hemorrhage	1	Infancy

*See Table 615.5.
Data from Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: twenty years' experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab.* 2005;90:3243–3250; Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. J Clin Endocrinol Metab. 2011;96:E925–E928.

Table 615.5 Other Genetic Etiologies for Primary Adrenal Insufficiency

GENE	FUNCTION	SYNDROME	FREQUENCY* %
MC2R	Melanocortin (ACTH) receptor	Familial glucocorticoid deficiency type 1	22
MRAP	Melanocortin receptor accessory protein	Familial glucocorticoid deficiency type 2	4
NROB1	DAX1 orphan nuclear receptor	X-linked adrenal hypoplasia congenita	6†
NR5A1	SF-1 orphan nuclear receptor	Gonadal dysgenesis	<1
STAR	Steroidogenic acute regulatory protein	Nonclassic lipoid adrenal hyperplasia	8
CYP11A1	Cholesterol side-chain cleavage enzyme	Nonclassic lipoid adrenal hyperplasia	8
NNT	Nicotinamide nucleotide transhydrogenase	Familial glucocorticoid deficiency type 4	8
AAAS	Aladin (nuclear transport protein)	Triple A syndrome	5
SAMD9	Factor inhibiting cell proliferation	MIRAGE syndrome	3
CDKN1C	Cyclin-dependent kinase inhibitor	IMAGE syndrome	1
POLE	Subunit of DNA polymerase	IMAGE syndrome type 2	rare

*Frequencies are from 95 Turkish and 155 United Kingdom patients in whom congenital adrenal hyperplasia, autoimmune etiologies, and metabolic disorders (e.g., adrenoleukodystrophy) had been excluded.
†Many cases of X-linked adrenal hypoplasia congenita had already been identified, so this frequency is an underestimate.

restriction, microcephaly, decreased numbers of natural killer (NK) cells, recurrent viral infections, and adrenal insufficiency. It is relatively frequent (1 in 2,506) in the Irish Traveller population.

MIRAGE syndrome is a form of syndromic adrenal hypoplasia, characterized by myelodysplasia, infections, restriction of growth, adrenal hypoplasia, genital abnormalities, and enteropathy. It is often fatal within the first decade of life, usually because of invasive infection. It is caused by pathogenic variants in *SAMD9* on chromosome 7q21, which encodes a protein that inhibits cell proliferation. Disease-causing variants are heterozygous and usually arise de novo. When expressed in cultured cells, the abnormal proteins strongly inhibit cell proliferation. There is a risk that affected cells will attempt to escape growth inhibition by selectively losing chromosome 7 carrying the variant causing haploinsufficiency of *SAMD9*. This can cause myelodysplastic syndrome.

IMAGE syndrome consists of intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies. Two forms have been identified: an autosomal dominant form caused by pathogenic variants in *CDKN1C* and an autosomal recessive form caused by variants in *POLE*. Adrenal insufficiency in cases associated with *CDKN1C* variants tends to present in early infancy, whereas in cases caused by *POLE* variants, it is manifested during early childhood. The recessive form is also associated with immunodeficiency and is therefore sometimes termed *IMAGEI syndrome.*

The *CDKN1C* gene product, also called *p57(KIP2),* binds G1 cyclin/CDK complexes and thus inhibits cell proliferation. It is located in the imprinted region of chromosome 11p15 and is preferentially expressed from the maternal allele. Inactivating variants in this gene cause some cases of Beckwith-Wiedemann syndrome (see Chapter 113), which is associated with macrosomia and tumor risk. Variants that interfere with binding of CDKN1C to DNA polymerase delta auxiliary protein enhance the growth inhibitory effect of CDKN1C (gain of function) and cause IMAGE syndrome when maternally inherited. Thus both genes involved in IMAGE syndrome have roles in DNA replication and repair.

Deficiency of Mitochondrial Reactive Oxygen Species Detoxification

Nicotinamide nucleotide transhydrogenase *(NNT)* is a mitochondrial protein that catalyzes transfer of a hydride ion between nicotinamide adenine dinucleotide, NAD(H), and oxidized nicotinamide dinucleotide phosphate, NADP(H). Its deficiency manifests generally in infancy or early childhood, and most patients have both mineralocorticoid and glucocorticoid deficiencies. A pathogenic variant in *TXNRD2* has been identified in a single kindred with glucocorticoid deficiency.

Type 1 Autoimmune Polyendocrinopathy Syndrome

Although autoimmune Addison disease most often occurs sporadically, it can occur as a component of two syndromes, each consisting of a constellation of autoimmune disorders (see Chapter 608). **Type 1 autoimmune polyendocrinopathy syndrome (APS-1)**, also known as *autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy* (APECED) syndrome, is inherited in a mendelian autosomal recessive manner, whereas APS-2 has complex inheritance. Patients with APS-1

may have autoantibodies to the adrenal cytochrome P450 enzymes CYP21A2, CYP17A1, and CYP11A1. The presence of such antibodies indicates a high likelihood of the development of Addison disease or, in female patients, ovarian failure. Adrenal failure can evolve rapidly in APS-1; death in patients with a previous diagnosis and unexplained deaths in siblings of patients with APS-1 have been reported, indicating the need to closely monitor patients with APS-1 (or any child with unexplained hypoparathyroidism) and to thoroughly evaluate apparently unaffected siblings of patients with this disorder.

Corticosteroid-Binding Globulin Deficiency and Decreased Cortisol-Binding Affinity

Corticosteroid-binding globulin deficiency (*SERPINA6* pathogenic variant) and decreased cortisol-binding affinity result in low levels of plasma cortisol but normal urinary free cortisol and normal plasma ACTH levels. A high prevalence of hypotension and fatigue has been reported in some adults with abnormalities of corticosteroid-binding globulin deficiency.

ACQUIRED ETIOLOGIES

Autoimmune Addison Disease

The most common cause of Addison disease is autoimmune destruction of the glands. The glands may be so small that they are not visible at autopsy, and only remnants of tissue are found in microscopic sections. Usually, the medulla is not destroyed, and there is marked lymphocytic infiltration in the area of the former cortex. In advanced disease, all adrenocortical function is lost, but early in the clinical course, isolated cortisol deficiency can occur. Most patients have **antiadrenal cytoplasmic antibodies** in their plasma; 21-hydroxylase (CYP21A2) is the most commonly occurring biochemically defined autoantigen.

Addison disease can occur as a component of two autoimmune polyendocrinopathy syndromes. Type 1 (APS-1) was discussed previously. **Type 2 autoimmune polyendocrinopathy (APS-2)** consists of Addison disease associated with autoimmune thyroid disease **(Schmidt syndrome)** or type 1 diabetes **(Carpenter syndrome)** (see Chapter 608). Frequencies of the human leukocyte antigen (HLA)-D3 and HLA-D4 alleles are increased in these patients and appear to confer an increased risk for development of this disease; particular alleles at the major histocompatibility complex class I chain–related genes A and B (*MICA* and *MICB*) also are associated with this disorder. Polymorphisms in genes involved in other autoimmune disorders have been inconsistently associated with primary adrenal insufficiency, and their contribution to its pathogenesis must be regarded as uncertain. These include the class II, major histocompatibility complex, transactivator *(CIITA),* C-type lectin domain family 16, member A (*CLEC16A*), and protein tyrosine phosphatase, nonreceptor type 22 *(PTPN22).* The disorder is most common in middle-age females and can occur in many generations of the same family. Antiadrenal antibodies, specifically antibodies to the CYP21A2, CYP17A1, and CYP11A1 enzymes, are also found in these patients. Autoimmune adrenal insufficiency may also be seen in patients with celiac disease and mitochondrial gene mutations.

Adrenal insufficiency remains a risk among patients previously treated with a prolonged course of steroids when stressed with an infection or trauma. Despite being "tapered or weaned" from the steroids, subclinical adrenal insufficiency may develop weeks to months later if stressed (see Chapter 615.2).

Infection

Tuberculosis was a common cause of adrenal destruction in the past but is currently much less prevalent. The most common infectious etiology for adrenal insufficiency is meningococcemia (see Chapter 237); adrenal crisis from this cause is referred to as **Waterhouse-Friderichsen syndrome**. Patients with AIDS can have a variety of subclinical abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, but frank adrenal insufficiency is rare. However, drugs used in the treatment of AIDS can affect adrenal hormone homeostasis.

Drugs

Ketoconazole, an antifungal drug, can cause adrenal insufficiency by inhibiting adrenal enzymes. Mitotane (o,p′-DDD), used in the treatment of adrenocortical carcinoma and refractory Cushing syndrome (see Chapters 617 and 619), is cytotoxic to the adrenal cortex and can also alter extraadrenal cortisol metabolism. Signs of adrenal insufficiency occur in a substantial percentage of patients treated with mitotane. **Etomidate**, used in the induction and maintenance of general anesthesia, inhibits 11β-hydroxylase (CYP11B1), and a single induction dose can block cortisol synthesis for 4-8 hours or longer. This may be problematic in severely stressed patients, particularly if repeated doses are used in a critical care setting. Abiraterone acetate, an androgen biosynthesis inhibitor that is used to treat metastatic prostate carcinoma, inhibits cortisol biosynthesis but leaves corticosterone biosynthesis unimpaired. This drug is not currently encountered in pediatric practice. **Immune checkpoint inhibitors** may rarely cause primary adrenal insufficiency. Although not themselves a cause of adrenal insufficiency, rifampicin and anticonvulsive drugs such as phenytoin and phenobarbital reduce the effectiveness and bioavailability of corticosteroid replacement therapy by inducing steroid-metabolizing enzymes in the liver.

Hemorrhage into Adrenal Glands

Hemorrhage into adrenal glands can occur in the neonatal period as a result of a difficult labor (especially breech presentation), or its etiology might not be apparent (Fig. 615.1). An incidence rate of 3 in 100,000 live births has been suggested. The hemorrhage may be sufficiently extensive to result in death from exsanguination or hypoadrenalism. An abdominal mass, anemia, unexplained jaundice, or scrotal hematoma may be the presenting sign. Often, the hemorrhage is asymptomatic initially and is identified later by calcification of the adrenal gland. Fetal adrenal hemorrhage has also been reported. Postnatally, adrenal hemorrhage most often occurs in patients being treated with anticoagulants. It can also occur as a result of child abuse.

CLINICAL MANIFESTATIONS

Primary adrenal insufficiency leads to cortisol and often aldosterone deficiencies. The signs and symptoms of adrenal insufficiency are most easily understood in the context of the normal actions of these hormones (see Chapter 614; Table 615.6).

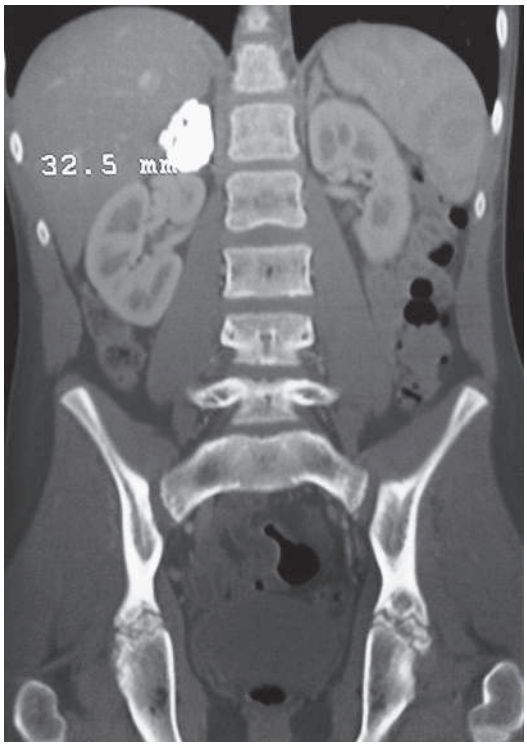

Fig. 615.1 Contrast-enhanced coronal CT confirming intraadrenal localization of a round hyperdense lesion compatible with a large calcification. *(From Llano JP, Beaufils E, Nicolino M. Uncommon cause of large paravertebral calcification in a child. J Pediatr. 2013;162:881, Fig. 2.)*

Table 615.6 Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

	PATHOPHYSIOLOGIC MECHANISM	PREVALENCE (%)*
SYMPTOMS		
Fatigue	Glucocorticoid deficiency	90
Anorexia, weight loss	Glucocorticoid deficiency	90
Nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency	90
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	20
Myalgia or joint pain	Glucocorticoid deficiency	
SIGNS		
Low blood pressure, orthostatic hypotension	Mineralocorticoid deficiency, glucocorticoid deficiency	70-100
Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)	Excess of proopiomelanocortin-derived peptides	70
LABORATORY FINDINGS		
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)	90
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	50
Hypoglycemia	Glucocorticoid deficiency	30
Ketosis	Glucocorticoid deficiency	30
Low random cortisol level	Glucocorticoid deficiency	80
Eosinophilia, lymphocytosis	Glucocorticoid deficiency	
High ACTH level (primary adrenal insufficiency only)	Glucocorticoid deficiency	100
High plasma renin activity (primary adrenal insufficiency only)	Mineralocorticoid deficiency	100

*Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.
Data from Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood J Clin Endocrinol Metab. 2011;96:E925–E928.

Cortisol deficiency decreases cardiac output and vascular tone; moreover, catecholamines such as epinephrine have decreased inotropic and pressor effects in the absence of cortisol. These problems are initially manifested as orthostatic hypotension in older children and can progress to frank shock in patients of any age. They are exacerbated by aldosterone deficiency, which causes hypovolemia owing to decreased resorption of sodium in the distal nephron.

Hypotension and decreased cardiac output decrease glomerular filtration and thus decrease the ability of the kidney to excrete free water. Vasopressin (AVP) is secreted by the posterior pituitary in response to hypotension and as a direct consequence of lack of inhibition by cortisol. These factors decrease plasma osmolality and lead to hyponatremia. Hyponatremia is also caused by aldosterone deficiency and may be much worse when both cortisol and aldosterone are deficient.

In addition to hypovolemia and hyponatremia, aldosterone deficiency causes hyperkalemia by decreasing potassium excretion in the distal nephron. Cortisol deficiency alone does not cause hyperkalemia.

Cortisol deficiency decreases negative feedback on the hypothalamus and pituitary, leading to increased secretion of ACTH. Hyperpigmentation is caused by ACTH and other peptide hormones (γ-melanocyte–stimulating hormone) arising from the ACTH precursor, proopiomelanocortin. In patients with a fair complexion, the skin can have a bronze cast. Pigmentation may be more prominent in skin creases, mucosa, and scars. In dark-skinned patients, it may be most readily appreciated in the gingival and buccal mucosa.

Hypoglycemia is a feature of adrenal insufficiency. It is often accompanied by ketosis as the body attempts to use fatty acids as an alternative energy source. Ketosis may cause or be aggravated by anorexia, nausea, and vomiting, all of which occur frequently.

The clinical presentation of adrenal insufficiency depends on the age of the patient, whether both cortisol and aldosterone secretion are affected, and to some extent on the underlying etiology. The most common causes in early infancy are inborn errors of steroid biosynthesis, sepsis, AHC, and adrenal hemorrhage. Infants have a relatively greater requirement for aldosterone than do older children, possibly owing to immaturity of the kidney and to the low sodium content of human breast milk and infant formula. Hyperkalemia, hyponatremia, and hypoglycemia are prominent presenting signs of adrenal insufficiency in infants. Ketosis is not consistently present because infants generate ketones less well than do older children. Hyperpigmentation is not usually seen because this takes weeks or months to develop, and orthostatic hypotension is obviously difficult to demonstrate in infants.

Infants can become ill very quickly. There may be only a few days of decreased activity, anorexia, and vomiting before critical electrolyte abnormalities develop.

In older children with Addison disease, symptoms include muscle weakness, malaise, anorexia, vomiting, weight loss, and orthostatic hypotension. These may be of insidious onset. It is not unusual to elicit, in retrospect, an episodic history spanning years with symptoms being noticeable only during intercurrent illnesses. Such patients can present with acute decompensation **(adrenal crisis)** during relatively minor infectious illnesses. *Some of these patients have been initially misdiagnosed with chronic fatigue syndrome, postmononucleosis syndrome, chronic Lyme disease, or psychiatric disorders (depression or anorexia nervosa).*

Hyperpigmentation is often, but not necessarily, present. **Hyponatremia** is present at diagnosis in almost 90% of patients. **Hyperkalemia** tends to occur later in the course of the disease in older children than in infants and is present in only half of patients at diagnosis. *Normal potassium levels must never be presumed to rule out primary adrenal insufficiency.*

Hypoglycemia and ketosis are common. The clinical presentation can be easily confused with gastroenteritis or other acute infections. Chronicity of symptoms can alert the clinician to the possibility of Addison disease, but this diagnosis should be considered in any child with

orthostatic hypotension, hyponatremia, hypoglycemia, and ketosis. Salt craving is seen in primary adrenal insufficiency with mineralocorticoid deficiency. Fatigue, myalgias, fever, eosinophilia, lymphocytosis, hypercalcemia, and anemia may be noted with glucocorticoid deficiency.

LABORATORY FINDINGS

Hypoglycemia, ketosis, hyponatremia, and hyperkalemia have been discussed. An electrocardiogram is useful for quickly detecting hyperkalemia in a critically ill child. Acidosis is often present, and the blood urea nitrogen level is elevated if the patient is dehydrated.

Cortisol levels are sometimes at the low end of the normal range but are invariably low when the patient's degree of illness is considered. ACTH levels are high in primary adrenal insufficiency but can take time to be reported by the laboratory. Similarly, aldosterone levels may be within the normal range but inappropriately low considering the patient's hyponatremia, hyperkalemia, and hypovolemia. Plasma renin activity is elevated. Blood eosinophils may be increased in number, but this is rarely useful diagnostically.

Urinary excretion of sodium and chloride is increased and urinary potassium is decreased, but these are difficult to assess in random urine samples. Accurate interpretation of urinary electrolytes requires more prolonged (24 hours) urine collections and knowledge of the patient's sodium and potassium intake.

The most definitive test for adrenal insufficiency is measurement of serum levels of cortisol before and after administration of ACTH; resting levels are low and do not increase normally after administration of ACTH. Occasionally, normal resting levels that do not increase after administration of ACTH indicate an absence of adrenocortical reserve. A low initial level followed by a significant response to ACTH can indicate secondary adrenal insufficiency. Traditionally, this test has been performed by measuring cortisol levels before and 30 or 60 minutes after giving 0.250 mg of cosyntropin (ACTH 1-24) by rapid intravenous infusion. Aldosterone will transiently increase in response to this dose of ACTH and may also be measured. A low-dose test (1 μg ACTH 1-24/1.73 m^2) is a more sensitive test of pituitary-adrenal reserve but has somewhat lower specificity (more false-positive tests).

DIFFERENTIAL DIAGNOSIS

Upon presentation, Addison disease often needs to be distinguished from more acute illnesses such as gastroenteritis with dehydration or sepsis. Additional testing is directed at identifying the specific cause for adrenal insufficiency. When CAH is suspected, serum levels of cortisol precursors (17-hydroxyprogesterone) should be measured along with cortisol in an ACTH stimulation test (see Chapter 616) (Fig. 615.2). Elevated levels of very long-chain fatty acids are diagnostic of ALD (see Chapter 639.3). Many genetic etiologies for primary adrenal insufficiency may be identified by direct genetic testing, but it can take weeks for results to become available. The presence of antiadrenal antibodies suggests an autoimmune pathogenesis. Patients with autoimmune Addison disease must be closely observed for the development of other autoimmune disorders. In children, hypoparathyroidism is a commonly associated disorder, and it is suspected if hypocalcemia and elevated phosphate levels are present.

Ultrasonography, CT, or MRI can help to define the size of the adrenal glands, but this is not usually necessary.

TREATMENT

Treatment of acute adrenal insufficiency must be immediate and vigorous. If the diagnosis of adrenal insufficiency has not been established, a blood sample should be obtained before therapy to determine electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma renin activity. If the patient's condition permits, an ACTH stimulation test can be performed while initial fluid resuscitation is underway. An intravenous solution of 5% glucose in 0.9% saline should be administered to correct hypoglycemia, hypovolemia, and hyponatremia. Hypotonic fluids (e.g., 5% glucose in water or 0.2% saline) must be avoided because they can precipitate or exacerbate hyponatremia. If hyperkalemia is severe, it can require treatment with intravenous calcium and/or bicarbonate, intrarectal potassium-binding resin (sodium polystyrene sulfonate, Kayexalate), or intravenous infusion of glucose and insulin. A water-soluble form of hydrocortisone, such as hydrocortisone sodium succinate, should be given intravenously. As much as 10 mg for infants, 25 mg for toddlers, 50 mg for older children, and 100 mg for adolescents should be administered as a bolus and a similar total amount then given in divided doses at 6-hour intervals for the first 24 hours. These doses may be reduced during the next 24 hours if progress is satisfactory. Adequate fluid and sodium repletion is achieved by intravenous saline administration, aided by the mineralocorticoid effect of high doses of hydrocortisone.

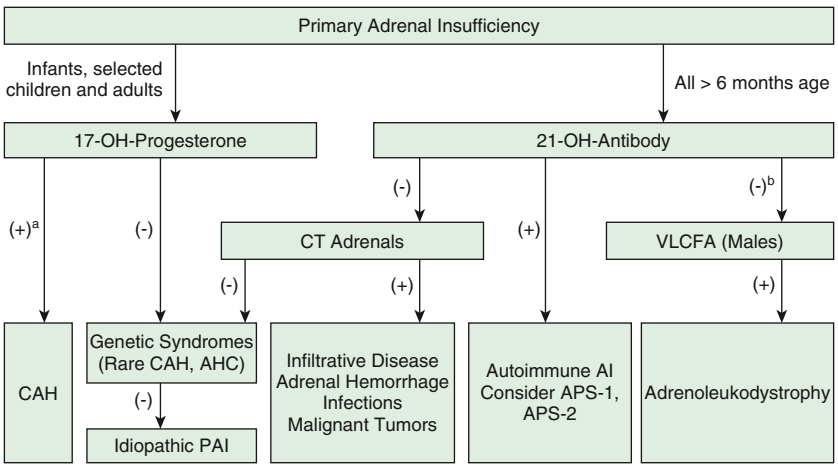

Fig. 615.2 Algorithm for the diagnostic approach to the patient with primary adrenal insufficiency (PAI). The most common causes of PAI are autoimmune destruction of the adrenal cortex in adults and congenital adrenal hyperplasia (CAH) in children. These etiologies can be screened for using 21-hydroxylase antibodies and a baseline serum 17-hydroxyprogesterone level, respectively. Males with negative 21-hydroxylase antibodies should be tested for adrenoleukodystrophy with plasma VLCFAs. If these diagnoses are excluded, a CT scan of the adrenals may reveal evidence of adrenal infiltrative processes or metastases, but this is of low yield in children and adolescents. The individual's clinical picture and family history may render some steps in the algorithm redundant or suggest specific genetic syndromes. The latter includes subtypes of autoimmune polyglandular syndromes or specific rare genetic disorders where adrenal failure is part of a broader phenotype. AHC, Adrenal hypoplasia congenita; AI, adrenal insufficiency; APS-1, type 1 autoimmune polyendocrinopathy syndrome; VLCFA, very long-chain fatty acid. [a]17-OH-progesterone >1,000 ng/dL is diagnostic for 21-OH deficiency. [b]VLCFA should be measured in the initial evaluation of preadolescent boys. *(Adapted from Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment, and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275:104–115.)*

Caution should be exercised in the rare patient with concomitant adrenal insufficiency and hypothyroidism, because thyroxine can increase cortisol clearance. Thus an adrenal crisis may be precipitated if hypothyroidism is treated without first ensuring adequate glucocorticoid replacement.

After the acute manifestations are under control, most patients require chronic replacement therapy for their cortisol and aldosterone deficiencies. Hydrocortisone (cortisol) may be given orally in daily doses of 10 mg/m^2/24 hr in three divided doses; some patients require 15 mg/m^2/24 hr to minimize fatigue, especially in the morning. Dividing the hydrocortisone into four doses daily may yield more physiologic drug profiles, but adherence to such frequent dosing may be problematic. Timed-release preparations of hydrocortisone are available in Europe and are undergoing clinical trials in the United States as of 2021. Subcutaneous infusion of hydrocortisone with a pump has also been examined in clinical trials; although this has the advantage that it can very closely mimic normal diurnal variation in cortisol secretion, it is expensive and has not yet entered routine clinical practice. Equivalent doses (20–25% of the hydrocortisone dose) of prednisone or prednisolone may be divided and given twice daily. ACTH levels may be used to monitor adequacy of glucocorticoid replacement in primary adrenal insufficiency; in CAH, levels of precursor hormones are used instead. Blood samples for monitoring should be obtained at a consistent time of day and in a consistent relation to (i.e., before or after) the hydrocortisone dose. Normalizing ACTH levels is unnecessary and can require excessive doses of hydrocortisone; in general, morning ACTH levels high in the normal range to 3-4 times normal are satisfactory. Because untreated or severely undertreated patients can acutely decompensate during relatively minor illnesses, assessment of symptoms (or lack thereof) should not be used as a substitute for biochemical monitoring. During situations of stress, such as periods of infection or minor operative procedures, the dose of hydrocortisone should be increased twofold to threefold. Major surgery under general inhalation anesthesia requires high intravenous doses of hydrocortisone similar to those used for acute adrenal insufficiency.

If aldosterone deficiency is present, fludrocortisone, a synthetic mineralocorticoid, is given orally in doses of 0.05-0.2 mg daily. Measurements of plasma renin activity are useful in monitoring the adequacy of mineralocorticoid replacement. Chronic overdosage with glucocorticoids leads to obesity, short stature, and osteoporosis, whereas overdosage with fludrocortisone results in hypertension and occasionally hypokalemia.

Replacement of dehydroepiandrosterone (DHEA) in adults remains controversial; prepubertal children do not normally secrete large amounts of DHEA. Many adults with Addison disease complain of having decreased energy, and replacing DHEA can improve this problem, particularly in women in whom adrenal androgens represent approximately 50% of total androgen secretion.

Additional therapy might need to be directed at the underlying cause of the adrenal insufficiency regarding infections and certain metabolic defects. Previous therapeutic approaches to ALD included administration of glycerol trioleate and glycerol trierucate (Lorenzo's oil), bone marrow transplantation, and lovastatin (see Chapter 639.3). Introducing a normal *ABCD1* gene into autologous stem cells with a lentiviral vector (officially termed *elivaldogene autotemcel*) has shown excellent results in preventing neurologic progression, but it remains investigational as of 2021.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

615.2 Secondary and Tertiary Adrenal Insufficiency

Perrin C. White

ABRUPT CESSATION OF ADMINISTRATION OF CORTICOSTEROIDS

Secondary adrenal insufficiency most commonly occurs when the HPA axis is suppressed by prolonged administration of high doses of a potent glucocorticoid and that agent is suddenly withdrawn or the dose is tapered too quickly. Patients at risk for this problem include those with leukemia, asthma (particularly when patients are transitioned from oral to inhaled corticosteroids), and collagen vascular disease or other autoimmune conditions and those who have undergone tissue transplants or neurosurgical procedures. The maximal duration and dosage of glucocorticoid that can be administered before encountering this problem is not known, but it is assumed that high-dose glucocorticoids (the equivalent of >10 times physiologic cortisol secretion) can be administered for less than 1 week without requiring a subsequent taper of dose. On the other hand, when high doses of dexamethasone are given to children with leukemia, it can take 6 months or longer after therapy is stopped before tests of adrenal function return to normal. Signs and symptoms of adrenal insufficiency are most likely in patients who are subsequently subjected to stresses such as severe infections or additional surgical procedures.

Corticotropin (Adrenocorticotropic Hormone) Deficiency

Pituitary or hypothalamic dysfunction can cause corticotropin deficiency (see Chapter 595), usually associated with deficiencies of other pituitary hormones such as growth hormone and thyrotropin. Destructive lesions in the area of the pituitary, such as craniopharyngioma and germinoma, are the most common causes of corticotropin deficiency. In many cases the pituitary or hypothalamus is further damaged during surgical removal or radiotherapy of tumors in the midline of the brain. Traumatic brain injury (see Chapter 750) frequently causes pituitary dysfunction, especially in the first days after the injury. However, corticotropin deficiency is difficult to detect in that period owing to frequent use of high doses of dexamethasone to minimize brain swelling, and permanent corticotropin deficiency is unusual after traumatic brain injury. In rare instances, autoimmune hypophysitis is the cause of corticotropin deficiency.

Congenital lesions of the pituitary also occur. The pituitary alone may be affected, or additional midline structures may be involved, such as the optic nerves or septum pellucidum. The latter type of abnormality is termed **septo-optic dysplasia**, or de Morsier syndrome (see Chapter 631.9). More severe developmental anomalies of the brain, such as anencephaly and holoprosencephaly, can also affect the pituitary. These disorders are usually sporadic, although a few cases of autosomal recessive inheritance have occurred. Isolated deficiency of corticotropin has been reported, including in several sets of siblings. Patients with multiple pituitary hormone deficiencies caused by pathogenic variants in the *PROP1* gene may develop progressive ACTH/cortisol deficiency. Isolated deficiency of corticotropin-releasing hormone has been documented in an Arab kindred as an autosomal recessive trait.

Up to 60% of children with **Prader-Willi syndrome** (see Chapter 99.8) have some degree of secondary adrenal insufficiency as assessed by provocative testing with metyrapone, although diurnal cortisol levels are normal. The clinical significance of this finding is uncertain, but it might contribute to the relatively high incidence of sudden death with infectious illness that occurs in this population. Although it is not yet a standard of care, some endocrinologists advocate treating patients who have Prader-Willi syndrome with hydrocortisone during febrile illness.

CLINICAL PRESENTATION

Aldosterone secretion is unaffected in secondary adrenal insufficiency because the adrenal gland is, by definition, intact and the renin-angiotensin system is not involved. Thus signs and symptoms are those of cortisol deficiency. Newborns often have hypoglycemia. Older children can have orthostatic hypotension or weakness. Hyponatremia may be present.

When secondary adrenal insufficiency is the consequence of an inborn or acquired anatomic defect involving the pituitary, there may be signs of associated deficiencies of other pituitary hormones. The penis may be small in male infants if gonadotropins are also deficient. Infants with secondary hypothyroidism are often jaundiced. Children with associated growth hormone deficiency grow poorly after the first year of life.

Some children with pituitary abnormalities have hypoplasia of the midface. Children with optic nerve hypoplasia can have obvious visual impairment. They usually have a characteristic wandering nystagmus, but this is often not apparent until several months of age.

LABORATORY FINDINGS

Because the adrenal glands themselves are not directly affected, the diagnosis of secondary adrenal insufficiency is sometimes challenging. The most commonly used test to diagnose secondary adrenal insufficiency is **low-dose ACTH stimulation testing** (1 μg/1.73 m^2 of cosyntropin given intravenously), the rationale being that there will be some degree of atrophy of the adrenal cortex if normal physiologic ACTH stimulation is lacking. Thus this test may be falsely negative in cases of acute compromise of the pituitary (e.g., injury or surgery). Such circumstances rarely pose a diagnostic dilemma; in general, this test provides excellent sensitivity and specificity. Although assays vary somewhat, a threshold cortisol level of 18-20 μg/dL 30 minutes after cosyntropin administration may be used to dichotomize normal and abnormal responses.

There seems to be little reason to use stimulation with corticotropin-releasing hormone instead of ACTH; although the corticotropin-releasing hormone test has the theoretical advantage of testing the ability of the anterior pituitary to respond to this stimulus by secreting ACTH (thus distinguishing secondary and tertiary adrenal insufficiency), in practice it does not provide improved sensitivity and specificity, and the agent is not as widely available.

TREATMENT

Iatrogenic secondary adrenal insufficiency (caused by chronic glucocorticoid administration) is best avoided by use of the smallest effective doses of systemic glucocorticoids for the shortest period. When a patient is thought to be at risk, tapering the dose rapidly to a level equivalent to or slightly less than the physiologic replacement (~10 mg/m^2/24 hr of hydrocortisone) and further tapering over several weeks can allow the adrenal cortex to recover without the patient developing signs of adrenal insufficiency. Patients with anatomic lesions of the pituitary should be treated indefinitely with glucocorticoids. Mineralocorticoid replacement is not required. In patients with panhypopituitarism, treating cortisol deficiency can increase free water excretion, thus unmasking central diabetes insipidus. Electrolytes must be monitored carefully when initiating cortisol therapy in panhypopituitary patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

615.3 Adrenal Insufficiency in the Critical Care Setting

Perrin C. White

Critical illness–related corticosteroid insufficiency (CIRCI) is encountered in up to 20–50% of critically ill pediatric patients, often as a transient condition. In many cases, it is considered functional or relative in nature, meaning that cortisol levels are within normal limits but cannot increase sufficiently to meet the demands of critical illness. The causes are heterogeneous (see Chapter 615.1). They include adrenal hypoperfusion from shock, particularly septic shock, as is often seen in meningococcemia. Inflammatory mediators during septic shock, particularly interleukin-6, can suppress ACTH secretion, directly suppress cortisol secretion, or both. Etomidate, used as sedation for intubation, inhibits steroid 11β-hydroxylase and thus blocks cortisol biosynthesis. Neurosurgical patients with closed head trauma or with tumors that involve the hypothalamus or pituitary might have ACTH deficiency in the context of panhypopituitarism. Some children have been previously treated with systemic corticosteroids (e.g., children with leukemia) and have suppression of the HPA axis for that reason. In the intensive care nursery, premature infants have not yet developed normal cortisol biosynthetic capacity and thus may not be able to secrete adequate amounts of this hormone when ill.

Additionally, plasma clearance of cortisol is markedly reduced during critical illness, owing to decreased activity of cortisol-metabolizing enzymes in the liver and kidney. Although this may help defend plasma levels of cortisol in the context of decreased cortisol secretion, the inflammation associated with sepsis may increase glucocorticoid resistance through activation of mitogen-activated protein kinases (MAPKs) and decreased activity of their regulators, dual-specific phosphatases (DUSPs).

CLINICAL MANIFESTATIONS

Cortisol is required for catecholamines to have their normal pressor effects on the cardiovascular system (see Chapters 614.4 and 614.5). Accordingly, adrenal insufficiency is often suspected in hypotensive patients who do not respond to intravenous pressor agents. Patients may be at increased risk for hypoglycemia or a presentation resembling the syndrome of inappropriate antidiuretic hormone secretion, but these conditions commonly occur in the context of sepsis, and the contribution of adrenal insufficiency may be difficult to distinguish.

LABORATORY FINDINGS

Although low random cortisol levels in severely stressed patients are certainly abnormal, very high levels are also associated with a poor outcome in such patients; the latter situation presumably reflects a maximally stimulated adrenal cortex with diminished reserve. ACTH (cosyntropin) stimulation testing is generally considered the best way to diagnose adrenal insufficiency in this setting (see Chapter 615.1); evidence suggests that the low-dose (1 μg/1.73 m^2) test may be superior to the 250-μg standard dose test, although this remains controversial. In general, a peak cortisol level <18 μg/dL or an increment of <9 μg/dL from baseline is considered suggestive for adrenal insufficiency in this context. In evaluating cortisol levels, cortisol in the circulation is mostly bound to cortisol-binding globulin; in hypoproteinemic states, total cortisol levels may be decreased, whereas free cortisol levels might be normal. It may be prudent to measure free cortisol before initiating treatment when total cortisol is low and albumin is <2.5 g/dL, but such measurements are not readily available in all institutions.

TREATMENT

It is likely that stress doses of hydrocortisone (e.g., 100 mg/m^2/day) improve responses to pressor agents in patients with shock *and* documented adrenal insufficiency (Waterhouse-Friderichsen syndrome). In adults with sepsis, corticosteroids probably reduce intensive care unit (ICU) and hospital length of stay and 28-day and hospital mortality, but there are limited data regarding treatment efficacy in critically ill children. The Surviving Sepsis Guidelines suggest using IV hydrocortisone (or not using it) to treat pediatric septic shock only if fluids and vasopressor therapy are unable to restore hemodynamic stability. This is a weak recommendation with low-quality evidence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

615.4 Altered End-Organ Sensitivity to Corticosteroids

Perrin C. White

Diseases can result from altered actions of hormones at their physiologic targets. These may be caused by abnormal metabolism of hormones, mutations in hormone receptors, or defects in cellular effectors (such as ion channels) that are targets of hormone action.

GENERALIZED GLUCOCORTICOID RESISTANCE

Patients with generalized glucocorticoid resistance have target-tissue insensitivity to glucocorticoids. The condition is usually inherited in an autosomal dominant manner, but sporadic cases occur. Impairment of normal negative feedback of cortisol at the levels of the hypothalamus and pituitary activates the HPA axis, with consequent increases in ACTH and cortisol concentrations. Generalized glucocorticoid resistance is caused by pathogenic variants in the glucocorticoid receptor *(NR3C1)*. Most variants are heterozygous; glucocorticoid receptors usually bind DNA as dimers, and three out of four dimers will contain at least one abnormal receptor molecule when a heterozygous variant is present.

Clinical Manifestations

The excess ACTH secretion causes adrenal hyperplasia with increased production of adrenal steroids with mineralocorticoid activity, including cortisol, deoxycorticosterone, and corticosterone, and also androgens and precursors, including androstenedione, DHEA, and DHEA sulfate. The high cortisol concentrations do not cause Cushing syndrome (see Chapter 619) because of the insensitivity to glucocorticoids; conversely, most signs and symptoms of adrenal insufficiency are absent except for the frequent occurrence of chronic fatigue and occasional anxiety (neonatal hypoglycemia was reported in one very unusual patient with a homozygous null variant). The mineralocorticoid and androgen receptors are normally sensitive to their ligands. Signs of **mineralocorticoid excess**, such as hypertension and hypokalemic alkalosis, are frequently noted. The increased concentrations of adrenal androgens may cause ambiguous genitalia in females and gonadotropin-independent precocious puberty in children of either gender; acne, hirsutism, and infertility in both sexes; menstrual irregularities in females; and oligospermia in males. Testicular adrenal rest tumors and ACTH-secreting pituitary adenomas occasionally occur.

Laboratory Findings

The diagnosis of generalized glucocorticoid resistance is suggested by elevated serum cortisol concentrations and increased 24-hour urinary free cortisol excretion in the absence of Cushing syndrome. Levels of other adrenal steroids are also increased. Plasma concentrations of ACTH may be normal or high. The circadian pattern of ACTH and cortisol secretion is preserved, although at higher-than-normal concentrations, and there is resistance of the HPA axis to dexamethasone suppression. Sequencing of the *NR3C1* gene can confirm the diagnosis.

Differential Diagnosis

Generalized glucocorticoid resistance should be distinguished from relatively mild cases of Cushing syndrome (whether caused by a pituitary adenoma or adrenal tumor, see Chapter 619); the latter is more likely to be associated with excessive weight gain or poor linear growth. Adrenocortical tumors may secrete mineralocorticoids such as deoxycorticosterone and also androgens, but ACTH levels are often suppressed and, of course, the tumor can usually be visualized with appropriate imaging techniques. CAH (see Chapter 616), particularly 11β-hydroxylase deficiency, may present with hypertension and signs of androgen excess, but in that condition cortisol levels are low and levels of cortisol precursors (17-hydroxyprogesterone, 11-deoxycortisol) are elevated. Obese patients may be hypertensive and have hyperandrogenism, but cortisol secretion should be readily suppressed by dexamethasone.

Treatment

The goal of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic activity. This requires administration of high doses of a pure glucocorticoid agonist such as dexamethasone (typically ~20-40 μg/kg/day) with careful titration to suppress endogenous corticosteroid secretion without causing signs of glucocorticoid excess such as excessive weight gain or suppression of linear growth.

CORTISONE REDUCTASE DEFICIENCY

Levels of active glucocorticoids in target tissues are modulated by two isozymes of 11β-hydroxysteroid dehydrogenase. The HSD11B2 isozyme converts cortisol to an inactive metabolite, cortisone; the two steroids differ in the presence of an 11β-hydroxyl versus an 11-oxo group, respectively. Pathogenic variants in this enzyme cause the syndrome of **apparent mineralocorticoid excess**. Conversely, the HSD11B1 isozyme converts cortisone to cortisol, and so it is sometimes referred to as *cortisone reductase*. This isozyme is expressed at high levels in glucocorticoid target tissues, particularly the liver, where it ensures adequate levels of active glucocorticoids (cortisol and corticosterone) to meet metabolic demands without requiring excessive adrenal cortisol secretion.

The HSD11B1 isozyme is located in the endoplasmic reticulum (i.e., it is a microsomal enzyme) and functions as a dimer. It accepts electrons from reduced nicotine–adenine dinucleotide phosphate, which is generated within the endoplasmic reticulum by hexose-6-phosphate dehydrogenase, an enzyme distinct from cytoplasmic glucose-6-phosphate dehydrogenase.

Apparent cortisone reductase deficiency is caused by homozygous pathogenic variants in hexose-6-phosphate dehydrogenase that prevent generation of reduced nicotine–adenine dinucleotide phosphate within the endoplasmic reticulum and thus starve HSD11B1 of its essential cofactor for the reductase reaction. Very rare patients have been reported to have heterozygous variants in *HSD11B1* itself and thus have "true" cortisone reductase deficiency; because the enzyme functions as a homodimer, heterozygous variants are able to impair three fourths of all dimers.

Clinical Manifestations

Because circulating cortisone is not converted to cortisol, the circulating half-life of cortisol is decreased, and the adrenal cortex must secrete additional cortisol to compensate. This leads to adrenocortical overactivity analogous to, but generally much milder than, that seen in generalized glucocorticoid resistance. This is usually not severe enough to cause hypertension, presenting instead with mild to moderate signs of androgen excess such as hirsutism, oligomenorrhea or amenorrhea, and infertility in females and precocious pseudopuberty (axillary and pubic hair and penile enlargement, but not testicular enlargement) in males.

Laboratory Findings

The ratio of cortisol to cortisone in blood is lower than usual. The same is true of urinary metabolites, typically measured as a ratio of the sum of the tetrahydrocortisol and allotetrahydrocortisol excretion to that of tetrahydrocortisone. These determinations are best accomplished by gas chromatography followed by mass spectrometry and are available in specialized reference laboratories. Absolute levels of cortisol and ACTH are within normal limits.

Differential Diagnosis

Cortisone reductase deficiency should be distinguished from and is much less common than other causes of androgen excess such as polycystic ovarian syndrome and nonclassical CAH as a result of 21-hydroxylase deficiency.

Treatment

Treatment is aimed at decreasing adrenal overactivity and thus reducing secretion of androgens. This can be accomplished by administration of hydrocortisone.

ALTERED END-ORGAN SENSITIVITY TO MINERALOCORTICOIDS

Pseudohypoaldosteronism

Pseudohypoaldosteronism type 1 (PHA1) is a monogenic disease in which aldosterone action is deficient and patients are thus unable

to resorb urinary sodium or excrete potassium properly. There are two forms. A relatively mild autosomal dominant form is caused by pathogenic variants in *NR3C2* encoding the human mineralocorticoid receptor. A heterozygous variant is sufficient to cause disease because the mineralocorticoid receptor interacts with DNA as a dimer, and three fourths of the dimers are defective in individuals carrying heterozygous variants (assuming mutant protein is synthesized). A more severe autosomal recessive form is usually the result of homozygous pathogenic variants in the α *(SCNN1A),* β *(SCNN1B),* or γ *(SCNN1G)* subunits of the epithelial Na^+ channel; one reported case of severe autosomal recessive disease was caused by homozygous variants in *NR3C2*.

PHA1 should not be confused with **pseudohypoaldosteronism type 2**, a rare mendelian syndrome characterized by hyperkalemia and, in contrast to PHA1, by hypertension from excessive renal sodium reabsorption. This disorder is caused by variants in the renal regulatory kinases WNK1 and WNK4 or components of an E3 ubiquitin ligase complex, Kelch-like 3 (KLHL3) and Cullin 3 (CUL3).

Transient or "secondary" (nongenetic) pseudohypoaldosteronism can occur in infants, mainly male, with urinary tract malformations and/or urinary tract infections.

Clinical Manifestations

Infants with PHA1 present with hyperkalemia, hyponatremia, hypovolemia, hypotension, and failure to thrive. In more severe (usually autosomal recessive) cases, salt loss is not confined to the kidney, but instead occurs from most epithelia. Mothers may report that the skin of their affected infants tastes salty. Some infants suffer from *cystic fibrosis–like pulmonary symptoms*. It is often difficult to control electrolyte abnormalities in patients with the autosomal recessive form, leading to frequent hospitalizations and a need for close clinical monitoring.

It is noteworthy that signs and symptoms of aldosterone deficiency tend to remit as the patients get older, particularly in the autosomal dominant form. This is similar to what is seen in actual aldosterone deficiency, as occurs in the salt-losing forms of CAH or aldosterone synthase deficiency. The kidney matures after early infancy to become more efficient at excreting potassium, and although breast milk and infant formula are low in sodium, the normal adult Western diet is relatively high in sodium, thus compensating for the renal salt wasting.

Laboratory Findings

Infants have marked hyperkalemia and hyponatremia. Both plasma renin and aldosterone are markedly elevated. Levels of cortisol and ACTH are normal. If hypovolemia is severe, patients may develop prerenal azotemia. With severe hyperkalemia, the electrocardiogram may include tall-peaked T waves or ventricular tachycardia.

Differential Diagnosis

PHA in infants should be distinguished from other causes of hyperkalemia and hyponatremia. These include renal failure of any cause, CAH, aldosterone synthase deficiency, and other causes of adrenocortical insufficiency such as AHC. Patients with renal failure will have elevated blood urea nitrogen and creatinine, but these may also be seen in severely dehydrated patients with PHA or adrenal insufficiency. Patients with any form of adrenal insufficiency in this clinical context will have low or low-normal aldosterone levels (with elevated plasma renin), in contrast to the elevated aldosterone levels seen in PHA. Patients with CAH have elevated levels of steroid precursors such as 17-hydroxyprogesterone (in patients with 21-hydroxylase deficiency), and patients with most forms of adrenal insufficiency have elevated ACTH levels.

Treatment

Infants must be given sodium supplementation (initially IV and then oral or enteral), typically approximately 8 mEq/kg/day. Potassium levels in the infant formula often need to be reduced, which may be accomplished by mixing the formula with polystyrene resin (Kayexalate) and then decanting the formula before feeding. Fludrocortisone, a synthetic mineralocorticoid, may be efficacious in milder autosomal dominant cases if administered in high doses (titrating up to ~0.5 mg daily). Significant electrolyte abnormalities require treatment with IV normal saline and rectal polystyrene resin. Severe hyperkalemia may require glucose and insulin infusions to keep it under control.

Secondary PHA owing to urinary tract infections or malformations generally resolves when the underlying condition is treated.

ACTIVATING PATHOGENIC VARIANTS IN THE MINERALOCORTICOID RECEPTOR

In contrast to PHA1, the S810L (serine-810 to leucine) variant of *NR3C2* causes autosomal dominant, severe, early-onset hypertension. This variant alters the ligand specificity of the mineralocorticoid receptor so that it is activated by cortisone and so HSD11B2 cannot protect it. It is also activated by progesterone, and consequently the hypertension is *exacerbated by pregnancy*. Conversely, the glucocorticoid and progesterone receptor antagonist mifepristone (RU-486) antagonizes the mutant receptor and might be useful therapeutically in nonpregnant individuals.

APPARENT MINERALOCORTICOID EXCESS

The syndrome of apparent mineralocorticoid excess is an autosomal recessive disorder caused by pathogenic variants in *HSD11B2* encoding the type 2 isozyme of 11β-hydroxysteroid dehydrogenase. The mineralocorticoid receptor has nearly identical affinities for aldosterone (the main mineralocorticoid hormone) and cortisol, yet cortisol is normally only a weak mineralocorticoid in vivo. This is because HSD11B2 is expressed along with the mineralocorticoid receptor in most target tissues such as the renal cortical collecting duct epithelium. It converts cortisol to cortisone, which is not an active steroid, thus preventing it from occupying the mineralocorticoid receptor. In contrast, aldosterone is not a substrate for the enzyme because its 11β-hydroxyl group forms a hemiketal with the 18-aldehyde group of the steroid and is thus not accessible to the enzyme. Thus in the absence of HSD11B2, cortisol efficiently occupies the mineralocorticoid receptor, and because cortisol concentrations are normally far higher than those of aldosterone, this results in signs and symptoms of mineralocorticoid excess.

A similar clinical picture occurs with excessive consumption of licorice or licorice-flavored chewing tobacco; licorice contains compounds, including glycyrrhetinic and glycyrrhizic acids, that inhibit HSD11B2. Carbenoxolone, an antihypertensive drug that is not marketed in the United States, has similar effects.

Clinical Manifestations

Affected infants often have some degree of intrauterine growth restriction, with birthweights of 2 kg typical for term infants. Infants and children often fail to thrive. Severe hypertension (to ~200/120 mm Hg) is almost always present. In some patients, the hypertension tends to be labile or paroxysmal with severe emotional stress as a precipitating factor. Complications of hypertension have included cerebrovascular accidents. Several patients have died during infancy or adolescence, either from electrolyte imbalances leading to cardiac arrhythmias or from vascular sequelae of hypertension. Hypokalemic alkalosis can eventually cause nephrocalcinosis (often visible on renal ultrasound) and nephrogenic diabetes insipidus leading to polyuria and polydipsia. Deleterious effects on muscle range from elevations in serum creatine phosphokinase to rhabdomyolysis. Electrocardiograms show left ventricular hypertrophy.

Laboratory Findings

Hypokalemia and alkalosis are common but not consistently present. Sodium levels are generally in the upper part of the reference range. Aldosterone and renin levels are very low because the

hypertension and hypervolemia are independent of aldosterone concentrations. Serum cortisol and ACTH levels are generally within normal limits. The serum half-life of cortisol is increased, but the test for this requires a radioactive tracer and is not clinically available. Total urinary excretion of cortisol metabolites is markedly decreased. The urinary ratio of free cortisol to free cortisone is elevated, as is the ratio of urinary tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone.

Differential Diagnosis

The differential diagnosis includes other forms of severe childhood hypertension such as renal artery anomalies, but relatively few conditions present with suppressed renin and aldosterone levels. **Liddle syndrome** has a similar presentation but no abnormalities in the steroid profile, typically has an autosomal dominant mode of inheritance, and does not respond to treatment with mineralocorticoid receptor antagonists. Hypertensive forms of CAH (see Chapter 616) also have suppressed renin and aldosterone levels, but they present with signs of androgen excess (11β-hydroxylase deficiency) or androgen deficiency (17α-hydroxylase deficiency); the latter can be difficult to appreciate in young children. The steroid profiles in CAH differ from those seen in apparent mineralocorticoid excess syndrome.

Patients with severe Cushing syndrome may have high enough cortisol levels to overwhelm renal HSD11B2, leading to severe hypertension with alterations in urinary cortisol-to-cortisone ratios. This occurs most often in patients with ectopic ACTH syndrome. This generally does not present a diagnostic dilemma because other signs of Cushing syndrome are present, including high cortisol levels.

Treatment

Treatment includes a low-salt diet, potassium supplementation, and mineralocorticoid receptor blockade with spironolactone or eplerenone; a sodium channel blocker, such as amiloride or triamterene, may work at least as well. In principle, suppression of cortisol secretion with dexamethasone (which does not bind the mineralocorticoid receptor) should work, but in practice it is much less effective than mineralocorticoid receptor blockade.

LIDDLE SYNDROME

Liddle syndrome is a form of hypertension and hypokalemia that is clinically similar to the syndrome of apparent mineralocorticoid excess, but it is inherited in an autosomal dominant manner. It is caused by an activating pathogenic variant in the β *(SCNN1B)* or γ *(SCNN1G)* subunits of the epithelial sodium channel. Most of these mutations prevent the channel subunits from being ligated to ubiquitin and targeted to the proteasome for degradation, a process that is normally regulated indirectly by aldosterone. The net effect is to increase the number of open channels at the apical surface of epithelial cells of the renal collecting duct, thus facilitating sodium resorption and potassium excretion.

Clinical Manifestations, Laboratory Findings, and Differential Diagnosis

Liddle syndrome is characterized by severe early-onset hypertension and by hypokalemia, which may not be persistent. Aldosterone and renin levels are suppressed, but all steroid hormone levels are normal.

The differential diagnosis is the same as that for apparent mineralocorticoid excess.

Treatment

The mainstays of treatment are a low-salt diet, potassium supplementation, and a sodium channel blocker such as amiloride or triamterene. Mineralocorticoid receptor antagonists such as spironolactone are ineffective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 616

Congenital Adrenal Hyperplasia and Related Disorders

Perrin C. White and Ming Yang

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis (normal adrenal steroidogenesis is discussed in Chapter 614). Cortisol deficiency increases secretion of corticotropin (adrenocorticotropic hormone [ACTH]), which, in turn, leads to adrenocortical hyperplasia and overproduction of intermediate metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or precocious puberty in affected males; and virilization or sexual infantilism in affected females (Figs. 616.1 and 616.2, Table 616.1).

616.1 Congenital Adrenal Hyperplasia Caused by 21-Hydroxylase Deficiency

Perrin C. White and Ming Yang

More than 90% of CAH cases are caused by 21-hydroxylase deficiency. This P450 enzyme (CYP21A2, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively (see Fig. 614.1 in Chapter 614). These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most severe,

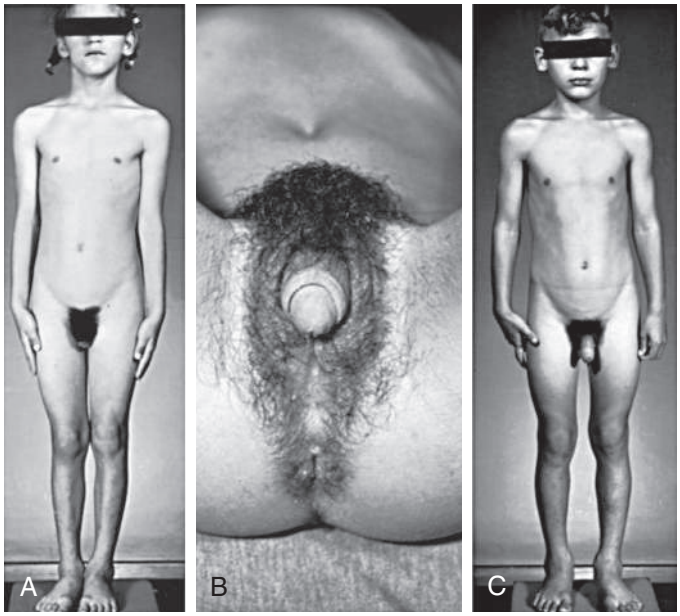

Fig. 616.1 **A,** A 6-yr-old female with congenital virilizing adrenal hyperplasia. The height age was 8.5 yr, and the bone age was 13 yr. **B,** Notice the clitoral enlargement and labial fusion. **C,** Her 5-yr-old brother was not considered to be abnormal by the parents. The height age was 8 yr, and the bone age was 12.5 yr.

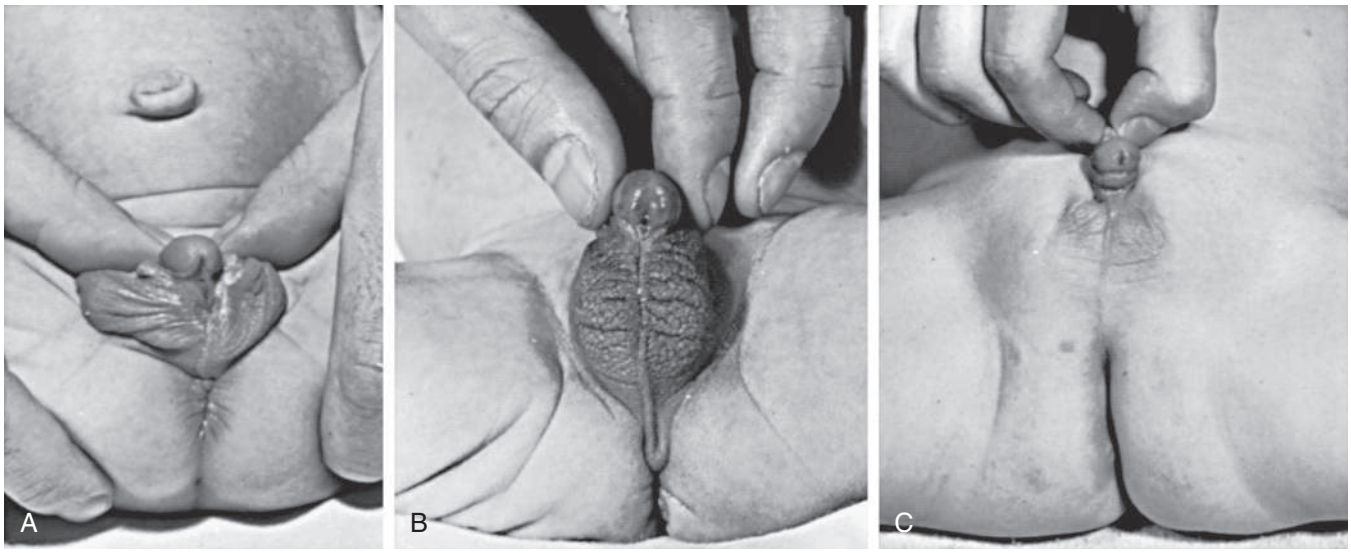

Fig. 616.2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants A and B had the salt-wasting form and received the diagnosis early in infancy. Infant C was referred at 1 yr of age because of bilateral cryptorchidism. Notice the completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.

salt-wasting form of the disease. Slightly less severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed **simple virilizing disease**. These two forms are collectively termed **classic 21-hydroxylase deficiency**. Patients with **nonclassic** disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth. Clinical presentation is dependent, in part, on the genotype (Table 616.2).

EPIDEMIOLOGY

Classic 21-hydroxylase deficiency occurs in approximately 1 in 14,000-18,000 births in most populations. Approximately 70% of affected infants have the salt-losing form, whereas 30% have the simple virilizing form of the disorder. In the United States, CAH is less common in African Americans compared with White children (1:42,000 vs 1:15,500). Nonclassic disease has a prevalence of approximately 1 in 1,000 in the general population but occurs more frequently in specific ethnic groups such as Ashkenazi Jews and Hispanics.

GENETICS

There are two steroid 21-hydroxylase genes—*CYP21P (CYP21A1P, CYP21A)* and *CYP21 (CYP21A2, CYP21B)*—which alternate in tandem with two genes for the fourth component of complement (C4A and C4B) in the human leukocyte antigen (HLA) major histocompatibility complex on chromosome 6p21.3 between the HLA-B and HLA-DR loci. Many other genes are in this cluster. *CYP21* is the active gene; *CYP21P* is 98% identical in DNA sequence to *CYP21* but is a pseudogene because of at least 10 different pathogenic variants. Although almost 300 variants have been reported, more than 90% of abnormal alleles causing 21-hydroxylase deficiency are the result of recombinations between *CYP21* and *CYP21P.* Approximately 20% are deletions generated by unequal meiotic crossing-over between *CYP21* and *CYP21P,* whereas the remainder are nonreciprocal transfers of deleterious variants from *CYP21P* to *CYP21,* a phenomenon termed *gene conversion.*

The deleterious variants in *CYP21P* have different effects on enzymatic activity when transferred to *CYP21.* Several variants completely prevent synthesis of a functional protein, whereas others are missense variants that yield enzymes with 1–50% of normal activity. Disease severity correlates well with the variants carried by an affected individual; patients with salt-wasting disease usually carry variants on both alleles that result in no enzymatic activity. Patients are frequently compound heterozygotes for different types of variants (i.e., one allele is less severely affected than the other), in which case the severity of disease expression is largely determined by the activity of the less severely affected of the two alleles.

Closely adjacent to, but on the opposite DNA strand from, *CYP21* is the tenascin-X *(TNX)* gene, which encodes a connective tissue protein. Rarely, deletions of *CYP21* extend into *TNX*. Such patients may have a contiguous gene syndrome (see Chapter 99.1) consisting of CAH and **Ehlers-Danlos syndrome** (see Chapter 744).

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Aldosterone and Cortisol Deficiency

Because both cortisol and aldosterone require 21-hydroxylation for their synthesis, both hormones are deficient in the most severe, salt-wasting form of the disease. This form constitutes approximately 70% of cases of classic 21-hydroxylase deficiency. The signs and symptoms of cortisol and aldosterone deficiency, and the pathophysiology underlying them, are essentially those described in adrenal insufficiency (see Chapter 615). These include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, and hyperkalemia. These problems typically first develop in affected infants at approximately 10-14 days of age. Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks.

CAH differs from other causes of primary adrenal insufficiency in that precursor steroids accumulate proximal to the blocked enzymatic conversion. Because cortisol is not synthesized efficiently, ACTH levels are high, leading to hyperplasia of the adrenal cortex and levels of precursor steroids that may be hundreds of times normal. In the case of 21-hydroxylase deficiency, these precursors include 17-hydroxyprogesterone and progesterone. Progesterone and perhaps other metabolites act as antagonists of the mineralocorticoid receptor and thus may exacerbate the effects of aldosterone deficiency in untreated patients.

It is not unusual for children with classic CAH to require hospitalization for intercurrent illnesses during childhood. This is most likely to occur in the first 2 years of life and to be precipitated by gastroenteritis, because such illnesses may cause fluid and electrolyte losses, and vomiting may interfere with medication dosing. Children requiring high fludrocortisone doses are most likely to be hospitalized, presumably because those patients have the greatest propensity to salt wasting.

Prenatal Androgen Excess

The most important problem caused by accumulation of steroid precursors is that 17-hydroxyprogesterone is shunted into the pathway for androgen biosynthesis, leading to high levels of androstenedione that

Table 616.1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids

Table 616.1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont'd

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in males and females	↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Maternal virilization Antley-Bixler syndrome	Decreased ratio of estrogens to androgens	

↓, Decreased; ↑, increased; ↑↑, markedly increased; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table 616.2 Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

VARIANT GROUP	A	B	C
Enzymatic activity, % normal	Nil	1–2%	20–50%
CYP21 variants (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6 cluster Q318X R356W Intron 2 splice*	I172N	P30L V281L P453S
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to mild
Incidence	1/20,000	1/50,000	1/500

*This variant is associated with both salt-wasting and simple virilizing disease.

are converted outside the adrenal gland to testosterone. This problem begins in affected fetuses by 8-10 weeks of gestation and leads to abnormal genital development in females (see Figs. 616.1 and 616.2).

The external genitalia of males and females normally appear identical early in gestation (see Chapter 622). Affected females who are exposed in utero to high levels of androgens of adrenal origin have masculinized external genitalia (see Figs. 616.1 and 616.2). This is manifested by enlargement of the clitoris and by partial or complete labial fusion. The vagina usually has a common opening with the urethra (urogenital sinus). The clitoris may be so enlarged that it resembles a penis; because the urethra opens below this organ, some affected females may be mistakenly presumed to be males with hypospadias and cryptorchidism. The severity of virilization is usually greatest in females with the salt-losing form of 21-hydroxylase deficiency (see Table 616.2). The internal genital organs are normal because affected females have normal ovaries and not testes and thus do not secrete antimüllerian hormone.

Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females. Females may demonstrate aggressive play behavior, tend to be interested in masculine toys such as cars and trucks, and often show decreased interest in playing with dolls. Women may have decreased interest in maternal roles. There is an increased frequency of homosexuality in affected females. Nonetheless, most function heterosexually and do not have gender identity confusion or dysphoria. It is unusual

for affected females to assign themselves a male role except in some with the severest degree of virilization.

Male infants appear normal at birth. The diagnosis may not be made in males until signs of adrenal insufficiency develop. Because patients with this condition can deteriorate quickly, infant males are more likely to die than infant females. For this reason, all 50 American states and many countries have instituted newborn screening for this condition (see Chapter 616.2).

Postnatal Androgen Excess

Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth. Males with the simple virilizing form of 21-hydroxylase deficiency often have a delayed diagnosis because they appear normal and rarely develop adrenal insufficiency.

Signs of androgen excess include **rapid somatic growth** and **accelerated skeletal maturation**. Affected patients are tall in childhood, but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted (see Fig. 616.1). Muscular development may be excessive. Pubic and axillary hair may appear, and acne and a deep voice may develop. The penis, scrotum, and prostate may become enlarged in affected males; however, the testes are usually prepubertal in size so that they appear small relative to the enlarged penis. Occasionally, ectopic adrenocortical cells in the testes of patients become hyperplastic similarly to the adrenal glands, producing **testicular adrenal rest tumors** (see Chapter 624). The clitoris may become further enlarged in affected females (see Fig. 616.1). Although the internal genital structures are female, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.

Similar but usually milder signs of androgen excess may occur in **nonclassic 21-hydroxylase deficiency** (see Table 616.2). In this attenuated form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth. Males and females may present with precocious pubarche and early development of pubic and axillary hair. Hirsutism, acne, menstrual disorders, and infertility may develop later in life, but many females and males are completely asymptomatic.

Adrenomedullary Dysfunction

Development of the adrenal medulla requires exposure to the extremely high cortisol levels normally present within the adrenal gland. Thus patients with classic CAH have abnormal adrenomedullary function, as evidenced by blunted epinephrine responses, decreased blood glucose, and lower heart rates with exercise. Ability to exercise is unimpaired, and the clinical significance of these findings is uncertain. Adrenomedullary dysfunction may exacerbate the cardiovascular effects of cortisol deficiency in untreated or undertreated patients.

LABORATORY FINDINGS

See Table 616.1.

Patients with salt-losing disease have typical laboratory findings associated with cortisol and aldosterone deficiency, including hyponatremia, hyperkalemia, metabolic acidosis, and, often, hypoglycemia, but these abnormalities can take 10-14 days or longer to develop after birth. Blood levels of 17-hydroxyprogesterone are markedly elevated. However, levels of this hormone are high during the first 2-3 days of life even in unaffected infants and especially if they are ill or premature. After infancy, once the circadian rhythm of cortisol is established, 17-hydroxyprogesterone levels vary in the same circadian pattern, being highest in the morning and lowest at night. Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels. In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females; testosterone is not elevated in affected males because normal infant males have high testosterone levels compared with those seen later in childhood. Levels of urinary 17-ketosteroids and pregnanetriol are elevated but are now rarely used clinically because blood samples are easier to obtain than 24-hour urine collections. ACTH levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level. However, renin levels are high in normal infants in the first few weeks of life.

Diagnosis of 21-hydroxylase deficiency is most reliably established by measuring 17-hydroxyprogesterone before and 30 or 60 minutes after an intravenous bolus of 0.125-0.25 mg of cosyntropin (ACTH 1-24). Nomograms exist that readily distinguish between unaffected individuals and patients with nonclassic and classic 21-hydroxylase deficiency. Heterozygous carriers of this autosomal recessive disorder tend to have higher ACTH-stimulated 17-hydroxyprogesterone levels than genetically unaffected individuals, but there is significant overlap between subjects in these two categories. However, in infants with frank electrolyte abnormalities or circulatory instability, it may not be possible or necessary to delay treatment to perform this test, as levels of precursors will be sufficiently elevated on a random blood sample to make the diagnosis.

Genotyping is clinically available and may help to confirm the diagnosis. Because the gene conversions that generate most pathogenic alleles may transfer more than one variant, at least one parent should also be genotyped to determine which variants are on each allele.

DIFFERENTIAL DIAGNOSIS

Disorders of sexual development are discussed more generally in Chapter 628. The initial step in evaluating an infant with ambiguous genitalia is a thorough physical examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads usually indicate the presence of testicular tissue and that the infant is a genetic male), and look for any other anatomic abnormalities. Ultrasonography is helpful in demonstrating the presence or absence of a uterus and can often locate the gonads. A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant. These results are all likely to be available before the results of hormonal testing and together allow the clinical team to advise the parents as to the genetic sex of the infant and the anatomy of internal reproductive structures. Injection of contrast medium into the urogenital sinus of a virilized female demonstrates a vagina and uterus; surgeons use this information to formulate a plan for surgical management.

PRENATAL DIAGNOSIS

Prenatal diagnosis of 21-hydroxylase is possible late in the first trimester by analysis of DNA obtained by chorionic villus sampling or during the second trimester by amniocentesis. This is usually done because the parents already have an affected child. Most often, the *CYP21A2* gene is analyzed for frequently occurring pathogenic variants; less common variants may be detected by DNA sequencing. Cell-free fetal DNA may be an adjunctive noninvasive testing method to help guide decision-making for possible prenatal treatment with dexamethasone, given that prenatal sex typing can be performed as early as 6-9 weeks. As of 2021, cell-free fetal DNA testing for this disorder is not yet available as part of routine clinical care.

NEWBORN SCREENING

Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency, all states in the United States and many other countries have instituted newborn screening programs. These programs analyze 17-hydroxyprogesterone levels in dried blood obtained by heelstick and absorbed on filter paper cards; the same cards are screened in parallel for other congenital conditions, such as hypothyroidism and phenylketonuria. Potentially affected infants are typically quickly recalled for additional testing (electrolytes and repeat 17-hydroxyprogesterone determination) at approximately 2 weeks of age. Infants with salt-wasting disease often have abnormal electrolytes by this age but are usually not severely ill. Screening programs are effective in preventing many cases of adrenal crisis in affected males. The nonclassic form of the disease is not

reliably detected by newborn screening, but this is of little clinical significance because adrenal insufficiency does not occur in this type of 21-hydroxylase deficiency.

The main difficulty with current newborn screening programs is that to reliably detect all affected infants, the cutoff 17-hydroxyprogesterone levels for first-tier screening are set so low that there is a very high frequency of false-positive results (i.e., the test has a low positive predictive value of as little as 1%). This problem is worst in premature infants. Positive predictive value can be improved by using cutoff levels based on gestational age and by using more specific second-tier screening methods such as liquid chromatography followed by tandem mass spectrometry.

TREATMENT

Glucocorticoid Replacement

Cortisol deficiency is treated with glucocorticoids. Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization. This often requires larger glucocorticoid doses than are needed in other forms of adrenal insufficiency, typically 12-15 mg/m^2/24 hr of hydrocortisone daily administered orally in 3 divided doses. Affected infants usually require dosing at the high end of this range. Double or triple doses are indicated during periods of stress, such as infection or surgery. Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present. Therapy must be individualized. It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles often indicates overtreatment with glucocorticoids. Overtreatment is also suggested by excessive weight gain. Pubertal development should be monitored by periodic examination, and skeletal maturation is evaluated by serial radiographs of the hand and wrist for bone age. Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning, before taking the morning medications, or at a consistent time in relation to medication dosing. Desirable 17-hydroxyprogesterone levels are in the high-normal range or several times normal; low-normal levels can usually be achieved only with excessive glucocorticoid doses. Hydrocortisone is the preferred glucocorticoid in growing children because its shorter half-life minimizes adverse side effects such as growth suppression, which is seen with longer half-life glucocorticoids. It is available as tablets, immediate-release granules, and a custom-compounded suspension. Use of continuous subcutaneous pump infusion devices to deliver hydrocortisone in a pattern more closely approximating the normal diurnal rhythm variation in cortisol secretion has been studied but has not entered clinical practice. Clinical trials for delayed-release hydrocortisone tablets are currently underway in the pediatric population.

Menarche occurs at the appropriate age in most females in whom good control has been achieved; it may be delayed in females with suboptimal control. Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3-7 years of age, at which time skeletal maturation may be 5 years or more in advance of chronological age. In some children, especially if the bone age is 12 years or more, spontaneous central (i.e., gonadotropin-dependent) puberty may occur when treatment is instituted, because therapy with hydrocortisone suppresses production of adrenal androgens and thus stimulates release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. This form of superimposed true precocious puberty may be treated with a gonadotropin hormone–releasing hormone analog such as leuprolide (see Chapter 600.1).

Males with 21-hydroxylase deficiency who have had inadequate corticosteroid therapy may develop **testicular adrenal rest tumors**, which may regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow Doppler examination help to define the character and extent of disease. Testis-sparing surgery to resect steroid-unresponsive tumors may be required in adult men to preserve fertility.

Mineralocorticoid Replacement

Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone. Infants may have very high mineralocorticoid requirements in the first few months of life, usually 0.1-0.3 mg daily in 2 divided doses, but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride 8 mmol/kg) in addition to the mineralocorticoid. Older infants and children are usually maintained with 0.05-0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even when these patients have normal aldosterone levels in the absence of mineralocorticoid replacement. Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids. Serum electrolytes should be measured frequently in early infancy as therapy is adjusted. Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.

Additional approaches to improve outcome have been proposed but have not yet become the standard of care. These include an antiandrogen such as flutamide to block the effects of excessive androgen levels and/or an aromatase inhibitor such as anastrozole or letrozole, which blocks conversion of androgens to estrogen and thus retards skeletal maturation, a process that is sensitive to estrogens in both males and females. Aromatase inhibitors generally should not be used in pubertal females, except in combination with a gonadotropin-releasing hormone agonist because this will expose the ovaries to excessive levels of gonadotropins. Growth hormone, with or without gonadotropin–releasing hormone agonists, has been suggested to improve adult height. Corticotropin-releasing hormone receptor antagonists such as crinecerfont and tildacerfont are in phase 2-3 studies as of 2021; they may reduce ACTH secretion, thus suppressing secretion of abnormal steroids at lower glucocorticoid doses than otherwise necessary. This strategy may reduce the adverse effects of high glucocorticoid doses. Abiraterone acetate, a CYP17A1 inhibitor that suppresses secretion of androgens and estrogens and is used for treatment of prostate cancer, may also permit reductions in glucocorticoid dosing and is in early-phase trials for CAH as of 2021.

Surgical Management of Ambiguous Genitals

Significantly virilized females usually undergo surgery between 2 and 6 months of age. If there is severe clitoromegaly, the clitoris is reduced in size, with partial excision of the corporal bodies and preservation of the neurovascular bundle; however, moderate clitoromegaly may become much less noticeable without surgery as the patient grows. Vaginoplasty and correction of the urogenital sinus usually are performed at the time of clitoral surgery; revision in adolescence is often necessary.

Risks and benefits of surgery should be fully discussed with parents of affected females. There is limited long-term follow-up of functional outcomes in patients who have undergone modern surgical procedures. It appears that female sexual dysfunction increases in frequency and severity in those with the most significant degrees of genital virilization and with the degree of enzymatic impairment (prenatal androgen exposure) caused by each patient's pathogenic variant (see Table 616.2). Sex assignment of infants with disorders of sexual differentiation (including CAH) is usually based on expected sexual functioning and fertility in adulthood, with early surgical correction of the external genitalia to conform with the sex assignment. The majority of females with CAH identify as female gender and are heterosexual. Gender dysphoria is not common with CAH; it occurs mostly in females with the salt-wasting form of the disease and the greatest degree of virilization.

Lay and medical opponents of genital surgery for other disorders of sexual differentiation raise the concern that it ignores any prenatally influenced gender role effects from androgen exposure and precludes the patient from having any decision as to the patient's own preferred sexual identity and what surgical correction of the genitals should be performed. They advocate that treatment should be aimed primarily at educating the patient, family, and others about the medical condition

and its treatment. They propose that surgery should be delayed until the patient decides on what, if any, surgery should be performed. There have not been any studies comparing early with late surgery. Not all lay groups support delaying surgery, and many agree with appropriate surgery during infancy. Severely virilized genotypic (XX) females raised as males have generally functioned well in the male gender as adults.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency (hirsutism, obesity, amenorrhea), bilateral laparoscopic adrenalectomy (with hormone replacement) may be an alternative to standard medical hormone replacement therapy, but because the adrenal glands have been removed, patients treated in this way may be more susceptible to acute adrenal insufficiency if treatment is interrupted. Moreover, they may exhibit signs of elevated ACTH levels such as abnormal pigmentation. There have also been reports of development of adrenal rest tumors in women after adrenalectomy, which defeats the purpose of adrenalectomy and allows the recurrence of androgen excess.

Prenatal Treatment

Besides genetic counseling, the main goal of prenatal diagnosis is to facilitate prenatal treatment of affected females. Mothers with pregnancies at risk may be given dexamethasone, a steroid that readily crosses the placenta, in an amount of 20 μg/kg pre-pregnancy maternal weight daily in 2 or 3 divided doses. This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. If started by 6 weeks of gestation, it ameliorates virilization of the external genitals in affected females. Chorionic villus biopsy is then performed to determine the sex and genotype of the fetus; therapy is continued only if the fetus is an affected female. DNA analysis of fetal cells isolated from maternal plasma for sex determination and *CYP21* gene analysis may permit earlier identification of the affected female fetus. Treatment should be considered only in affected female fetuses. Children exposed to this therapy have slightly lower birthweights. Reports of failure to thrive, stroke-like events, and midline defects have been observed in treated cases. Effects on personality or cognition, such as increased shyness, have been suggested but not consistently observed. At present there is insufficient information to determine whether the long-term risks are acceptable, particularly in the males and unaffected females who derive no direct benefit from the treatment. Maternal side effects of prenatal treatment have included edema, excessive weight gain, hypertension, glucose intolerance, cushingoid facial features, and severe striae. Consensus statements from professional societies recommend that prenatal treatment be carried out only under institutional protocols, but it is sometimes offered as an option outside the research setting by some high-risk obstetricians.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.2 Congenital Adrenal Hyperplasia Caused by 11β-Hydroxylase Deficiency

Perrin C. White and Ming Yang

Deficiency of 11β-hydroxylase is caused by a pathologic variant in the *CYP11B1* gene located on chromosome 8q21-q22. *CYP11B1* mediates 11-hydroxylation of 11-deoxycortisol to cortisol. Because 11-deoxycortisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors—particularly 11-deoxycortisol and deoxycorticosterone—accumulate and are shunted into androgen biosynthesis in the same manner as occurs in 21-hydroxylase deficiency. The adjacent *CYP11B2* gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally.

EPIDEMIOLOGY

11β-Hydroxylase deficiency accounts for approximately 5% of cases of adrenal hyperplasia; its incidence in the general population has been estimated as 1 in 250,000 to 1 in 100,000. The disorder occurs relatively frequently in Israeli Jews of North African origin (1 in 5,000-7,000 live births). In this ethnic group, almost all alleles carry an Arg448 to His (R448H) variant in *CYP11B1,* but many other variants have been identified. This disorder presents in a classic, severe form and very rarely in a nonclassic, milder form.

CLINICAL MANIFESTATIONS

Although cortisol is not synthesized efficiently, aldosterone synthetic capacity is normal, and some corticosterone is synthesized from progesterone by the intact aldosterone synthase enzyme. Thus it is unusual for patients to manifest signs of adrenal insufficiency such as hypotension or hypoglycemia. On the contrary, approximately 65% of patients become *hypertensive,* although this can take several years to develop. Hypertension is probably a consequence of elevated levels of deoxycorticosterone, which has mineralocorticoid activity. Infants may transiently develop signs of mineralocorticoid deficiency after treatment with hydrocortisone is instituted. This is presumably from sudden suppression of deoxycorticosterone secretion in a patient with atrophy of the zona glomerulosa caused by chronic suppression of renin activity.

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency may also occur in 11β-hydroxylase deficiency.

LABORATORY FINDINGS

Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated. Because deoxycorticosterone and some metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low even though the ability to synthesize aldosterone is intact. *Hypokalemic alkalosis occasionally occurs.*

TREATMENT

Patients are treated with hydrocortisone in doses similar to those used for 21-hydroxylase deficiency. Mineralocorticoid replacement is sometimes transiently required in infancy but is rarely necessary otherwise. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it is of long standing. Calcium channel blockers may be beneficial under these circumstances.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.3 Congenital Adrenal Hyperplasia Caused by 3β-Hydroxysteroid Dehydrogenase Deficiency

Perrin C. White and Ming Yang

Deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) occurs in less than 2% of patients with adrenal hyperplasia. This enzyme is required for conversion of Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, dehydroepiandrosterone [DHEA]) to Δ4 steroids (progesterone, 17-hydroxyprogesterone, and androstenedione). Thus deficiency of the enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA (see Fig. 614.1 in Chapter 614). The 3β-HSD isozyme expressed in the adrenal cortex and gonad is encoded by the *HSD3B2* gene located on chromosome 1p13.1. More than 30 pathogenic variants in *HSD3B2* have been described in patients with 3β-HSD deficiency.

CLINICAL MANIFESTATIONS

Because cortisol and aldosterone are not synthesized in patients with the classic form of the disease, infants are prone to **salt-wasting crises**. Because androstenedione and testosterone are not synthesized, *males*

are incompletely virilized; varying degrees of hypospadias may occur, with or without bifid scrotum or cryptorchidism. Because DHEA levels are elevated and this hormone is a weak androgen, females are mildly virilized, with slight to moderate clitoral enlargement. Postnatally, continued excessive DHEA secretion can cause precocious adrenarche. During adolescence and adulthood, hirsutism, irregular menses, and polycystic ovarian disease occur in females. Males manifest variable degrees of hypogonadism, although appropriate male secondary sexual development may occur. However, a persistent defect of testicular 3β-HSD is demonstrated by the high Δ5:Δ4 steroid ratio in testicular effluent.

LABORATORY FINDINGS

The hallmark of this disorder is the marked elevation of the Δ5 steroids (such as 17-hydroxypregnenolone and DHEA) preceding the enzymatic block. Patients may also have elevated levels of 17-hydroxyprogesterone because of the extraadrenal 3β-HSD activity that occurs in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency. The ratio of 17-hydrox ypregnenolone:17-hydroxyprogesterone is markedly elevated in 3β-HSD deficiency, in contrast to the decreased ratio in 21-hydroxylase deficiency. Plasma renin activity is elevated in the salt-wasting form.

DIFFERENTIAL DIAGNOSIS

It is not unusual for children with premature adrenarche, or females with signs of androgen excess, to have mild to moderate elevations in DHEA levels. It has been suggested that such individuals have *nonclassic 3β-HSD deficiency*. Variants in *HSD3B2* are usually not found in such individuals, and a nonclassic form of this deficiency may be quite rare. The activity of 3β-HSD in the adrenal zonae fasciculata and reticularis, relative to CYP17A1 (17-hydroxylase/17,20-lyase) activity, normally decreases during adrenarche to facilitate DHEA synthesis, and so modest elevations in DHEA in preteenage children or women usually represent a normal variant.

TREATMENT

Patients require glucocorticoid and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency. Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of 25 mg of a depot form of testosterone every 4 weeks early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.4 Congenital Adrenal Hyperplasia Caused by 17-Hydroxylase Deficiency

Perrin C. White and Ming Yang

Less than 1% of CAH cases are caused by 17-hydroxylase deficiency, but the condition is apparently more common in Brazil and China. A single polypeptide, CYP17A1, catalyzes two distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and the 17,20-lyase reaction–mediating conversion of 17-hydroxypregnenolone to DHEA and, to a lesser extent, 17-hydroxyprogesterone to Δ4-androstenedione. DHEA and androstenedione are steroid precursors of testosterone and estrogen (see Fig. 614.1 in Chapter 614). The enzyme is expressed in both the adrenal cortex and the gonads and is encoded by a gene on chromosome 10q24.3. Most pathogenic variants affect both the hydroxylase and lyase activities, but rare variants can affect either activity alone.

Pathogenic variants in genes other than *CYP17A1* can have the same phenotype as 17,20-lyase deficiency (i.e., deficient androgen synthesis with normal cortisol synthesis). These include an accessory electron transfer protein, cytochrome-b_5, (CYB5) and variants in two aldo-keto reductases AKR1C2 and AKR1C4. These AKR1C isozymes normally catalyze 3α-HSD activity, which allows synthesis of the potent androgen dihydrotestosterone through an alternative backdoor biosynthetic pathway that does not include testosterone as an intermediate (see Chapter 614).

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause **hypertension**, **hypokalemia**, and suppression of renin and aldosterone secretion, as occurs in 11β-hydroxylase deficiency. However, in contrast to 11β-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. *Affected males are incompletely virilized* and present as phenotypic females (but the gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with *failure of sexual development* at the expected time of puberty. 17-Hydroxylase deficiency in females must be considered in the differential diagnosis of primary hypogonadism (see Chapter 626). Levels of deoxycorticosterone are elevated, and renin and aldosterone are consequently suppressed. Cortisol and sex steroids are unresponsive to stimulation with ACTH and human chorionic gonadotropin, respectively.

Patients with isolated 17,20-lyase deficiency have deficient androgen synthesis with normal cortisol synthesis and therefore do not become hypertensive.

TREATMENT

Patients with 17-hydroxylase deficiency require glucocorticoid replacement with hydrocortisone to suppress secretion of deoxycorticosterone and thus control hypertension. Additional antihypertensive medication may be required. Females require estrogen replacement at puberty. Genetic males may require either estrogen or androgen supplementation depending on the sex of rearing. Because of the possibility of malignant transformation of abdominal testes, genetic males with severe 17-hydroxylase deficiency being reared as females require gonadectomy at or before adolescence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.5 Lipoid Adrenal Hyperplasia

Perrin C. White and Ming Yang

Lipoid adrenal hyperplasia is a rare disorder, most frequently found in Japanese persons. Patients with this disorder exhibit marked accumulation of cholesterol and lipids in the adrenal cortex and gonads associated with severe impairment of all steroidogenesis. Lipoid adrenal hyperplasia is usually caused by pathogenic variants in the gene for steroidogenic acute regulatory protein (StAR), a mitochondrial protein that promotes the movement of cholesterol from the outer to the inner mitochondrial membrane. However, pathogenic variants in *CYP11A1* (which encodes the cholesterol side-chain cleavage enzyme) have been reported in more than 30 patients. A milder, nonclassic form of StAR deficiency has been reported.

Some cholesterol is able to enter mitochondria even in the absence of StAR, so it might be supposed that this disorder would not completely impair steroid biosynthesis. However, the accumulation of cholesterol in the cytoplasm is cytotoxic, eventually leading to death of all steroidogenic cells in which StAR is normally expressed. This occurs prenatally in the adrenals and testes. The ovaries do not

normally synthesize steroids until puberty, so cholesterol does not accumulate, and the ovaries can retain the capacity to synthesize estrogens until adolescence.

Although estrogens synthesized by the placenta are required to maintain pregnancy, the placenta does not require StAR for steroid biosynthesis. Variants of StAR are not prenatally lethal.

CLINICAL MANIFESTATIONS

Patients with lipoid adrenal hyperplasia are usually unable to synthesize any adrenal steroids. Thus affected infants are likely to be confused with those with adrenal hypoplasia congenita. Salt-losing manifestations are typical, and many infants die in early infancy. Genetic males are unable to synthesize androgens and thus are **phenotypically female** but with gonads palpable in the labia majora or inguinal areas. Genetic females appear normal at birth and may undergo feminization at puberty with menstrual bleeding. They, too, progress to hypergonadotropic hypogonadism when accumulated cholesterol damages granulosa (i.e., steroid synthesizing) cells in the ovary.

LABORATORY FINDINGS

Adrenal and gonadal steroid hormone levels are low in lipoid adrenal hyperplasia, with a decreased or absent response to stimulation (ACTH, human chorionic gonadotropin). Plasma renin levels are increased.

Imaging studies of the adrenal gland demonstrating massive adrenal enlargement in the newborn help to establish the diagnosis of lipoid adrenal hyperplasia.

TREATMENT

Patients require glucocorticoid and mineralocorticoid replacement. Genetic males are usually assigned a female sex of rearing; thus both genetic males and females require estrogen replacement at the expected age of puberty.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.6 Deficiency of P450 Oxidoreductase (Antley-Bixler Syndrome)

Perrin C. White and Ming Yang

P450 oxidoreductase (*POR*; gene located on chromosome 7q11.3) is required for the activity of all microsomal cytochrome P450 enzymes (see Chapter 614), including the adrenal enzymes CYP17 and CYP21. Complete *POR* deficiency abolishes all microsomal P450 activity. This is embryonically lethal in mice and presumably also in humans. Patients with pathogenic variants that decrease but do not abolish *POR* activity have partial deficiencies of 17-hydroxylase and 21-hydroxylase activities in the adrenals. A single recurrent variant A287P (alanine-287 to proline) is found on approximately 40% of alleles.

Deficiency of 17-hydroxylase leads to incomplete masculinization in males; 21-hydroxylase deficiency may lead to virilization in females. In addition, aromatase *(CYP19)* activity in the placenta is decreased, leading to unopposed action of androgens produced by the fetal adrenal. This exacerbates virilization of female fetuses and may **virilize the mother** of an affected fetus as well. Although it is puzzling that affected females could be virilized despite a partial deficiency in *CYP17* (which is required for androgen biosynthesis), an alternative (backdoor) biosynthetic pathway is used in which 17-hydroxyprogesterone is converted to 5α-pregnane-3α,17α-diol-20-one, a metabolite that is a much better substrate for the 17,20-lyase activity of *CYP17* than the usual substrate, 17-hydroxypregnenolone (see Chapter 614). The metabolite is then converted in several enzymatic steps to dihydrotestosterone, a potent androgen.

Because many other P450 enzymes are affected, patients may have other congenital anomalies collectively referred to as **Antley-Bixler syndrome**. These include craniosynostosis; brachycephaly; frontal bossing; severe midface hypoplasia with proptosis and choanal stenosis or atresia; humeroradial synostosis; medial bowing of ulnas; long, slender fingers with camptodactyly; narrow iliac wings; anterior bowing of femurs; and malformations of the heart and kidneys.

EPIDEMIOLOGY

More than 130 cases of *POR* deficiency have been reported. Although the prevalence is not known with certainty, it might be the second most common cause of CAH in some populations such as Korea and Japan.

LABORATORY FINDINGS

Serum steroids that are not 17- or 21-hydroxylated are most increased, including pregnenolone and progesterone. 17-Hydroxy and 21-deoxysteroids are also increased, including 17-hydroxypregnenolone, 17-hydroxyprogesterone, and 21-deoxycortisol. Urinary steroid metabolites may be determined by quantitative mass spectrometry. Metabolites excreted at increased levels include pregnanediol, pregnanetriol, pregnanetriolone, and corticosterone metabolites. Urinary cortisol metabolites are decreased. Genetic analysis demonstrates pathogenic variants in *POR*.

DIFFERENTIAL DIAGNOSIS

This disorder must be distinguished from other forms of CAH, particularly 21-hydroxylase deficiency in females, which is far more common and has similar laboratory findings. Suspicion for *POR* deficiency may be raised if the mother is virilized or if the associated abnormalities of Antley-Bixler syndrome are present. Conversely, virilization of both the mother and her daughter can result from a luteoma of pregnancy, but in this case postnatal abnormalities of corticosteroid biosynthesis should not be observed. Antley-Bixler syndrome may also occur without abnormalities of steroid hormone biosynthesis, resulting from pathogenic variants in the fibroblast growth factor receptor FGFR2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.7 Aldosterone Synthase Deficiency

Perrin C. White and Ming Yang

This is an autosomal recessive disorder in which conversion of corticosterone to aldosterone is impaired; a group of Iranian Jewish patients has been the most thoroughly studied. Most cases result from pathogenic variants in *CYP11B2* coding for aldosterone synthase; however, linkage to *CYP11B2* has been excluded in other kindreds. When not caused by *CYP11B2* variants, the disorder has been termed **familial hyperreninemic hypoaldosteronism type 2**; the causative gene or genes have not yet been identified.

Aldosterone synthase mediates the three final steps in the synthesis of aldosterone from deoxycorticosterone (11β-hydroxylation, 18-hydroxylation, and 18-oxidation). Although 11β-hydroxylation is required to convert deoxycorticosterone to corticosterone, this conversion can also be catalyzed by the related enzyme, CYP11B1, located in the fasciculata, which is unaffected in this disorder. For the same reason, these patients have normal cortisol biosynthesis.

The disease has been classified into two types, termed **corticosterone methyloxidase deficiency types I and II**. They differ only in levels of the immediate precursor of aldosterone, 18-hydroxycorticosterone; levels are low in type I deficiency and elevated in type II deficiency.

CLINICAL MANIFESTATIONS

Infants with aldosterone synthase deficiency may have severe electrolyte abnormalities with **hyponatremia**, **hyperkalemia**, and

metabolic acidosis. Because cortisol synthesis is unaffected, infants rarely become as ill as untreated infants with salt-losing forms of CAH such as 21-hydroxylase deficiency. Thus some infants escape diagnosis. Later in infancy or in early childhood they may exhibit failure to thrive and poor growth. Adults often are asymptomatic, although they may develop electrolyte abnormalities when depleted of sodium through procedures such as bowel preparation for a barium enema.

LABORATORY FINDINGS

Infants have elevated plasma renin activity. Aldosterone levels are decreased; they may be at the lower end of the normal range but are always inappropriately low for the degree of hyperkalemia or hyperreninemia. Corticosterone levels are often elevated.

Some, but not all, patients have marked elevation of 18-hydroxycorticosterone; however, low levels of this steroid do not exclude the diagnosis. In those kindreds in which 18-hydroxycorticosterone levels are elevated in affected individuals, this biochemical abnormality persists in adults even when they have no electrolyte abnormalities.

DIFFERENTIAL DIAGNOSIS

It is important to distinguish aldosterone synthase deficiency from primary adrenal insufficiency in which both cortisol and aldosterone are affected (including salt-wasting forms of CAH), because the latter condition is usually associated with a much greater risk of shock and hyponatremia. This becomes apparent after the appropriate laboratory studies. **Adrenal hypoplasia congenita** may initially present with aldosterone deficiency; all male infants with apparently isolated aldosterone deficiency should be carefully monitored for subsequent development of cortisol deficiency. **Pseudohypoaldosteronism** (see Chapter 615.4) may have similar electrolyte abnormalities and hyperreninemia, but aldosterone levels are high, and this condition usually does not respond to fludrocortisone treatment.

TREATMENT

Treatment consists of giving enough fludrocortisone (0.05-0.2 mg daily) or sodium chloride, or both, to return plasma renin levels to normal. With increasing age, salt-losing signs usually improve, and drug therapy can often be discontinued.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

616.8 Glucocorticoid-Remediable Aldosteronism

Perrin C. White

Glucocorticoid-remediable aldosteronism (glucocorticoid-suppressible hyperaldosteronism, familial hyperaldosteronism type I) is an autosomal dominant form of *low-renin hypertension* in which hyperaldosteronism is rapidly suppressed by glucocorticoid administration. This unusual effect of glucocorticoids suggests that aldosterone secretion in this disorder is regulated by ACTH instead of by the renin-angiotensin system. In addition to abnormally regulated secretion of aldosterone, there is marked overproduction of 18-hydroxycortisol and 18-oxocortisol. The synthesis of these steroids requires both 17-hydroxylase (CYP17A1) activity, which is expressed only in the zona fasciculata, and aldosterone synthase (CYP11B2) activity, which is normally expressed only in the zona glomerulosa. These features imply that aldosterone synthase is being expressed in a manner similar to the closely related enzyme steroid 11-hydroxylase *(CYP11B1)*. The disorder is caused by unequal meiotic crossing-over events between the *CYP11B1* and *CYP11B2* genes, which are closely linked on chromosome 8q24. An additional "chimeric" gene is produced, having regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2*. This results in the inappropriate expression of a *CYP11B2*-like enzyme with aldosterone synthase activity in the adrenal fasciculata.

CLINICAL MANIFESTATIONS

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension, typically approximately 30 mm Hg higher than unaffected family members of the same age. Others have more symptomatic hypertension with headache, dizziness, and visual disturbances. A strong family history of early-onset hypertension or early strokes may alert the clinician to the diagnosis. Some patients have chronic hypokalemia, but this is not a consistent finding and is usually mild.

LABORATORY FINDINGS

Patients have elevated plasma and urine levels of aldosterone and suppressed plasma renin activity. *Hypokalemia is not consistently present.* Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol are markedly increased. The hybrid *CYP11B1/CYP11B2* gene can be readily detected by molecular genetic methods.

DIFFERENTIAL DIAGNOSIS

This condition should be distinguished from primary aldosteronism based on bilateral hyperplasia or an aldosterone-producing adenoma (see Chapter 620). Most cases of primary aldosteronism are sporadic, although several affected kindreds have been reported. Patients with primary aldosteronism may also have elevated levels of 18-hydroxycortisol and 18-oxocortisol, and these biochemical tests should be used cautiously when attempting to distinguish primary and glucocorticoid-suppressible aldosteronism. By definition, a therapeutic trial of dexamethasone should suppress aldosterone secretion only in glucocorticoid-remediable aldosteronism, and genetic testing should identify the hybrid gene if it is present.

TREATMENT

Glucocorticoid-remediable aldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone 25 μg/kg/day in divided doses. If necessary, effects of aldosterone can be blocked with a potassium-sparing diuretic such as spironolactone, eplerenone, or amiloride. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If hypertension is long standing, additional antihypertensive medication may be required, such as a calcium channel blocker.

GENETIC COUNSELING

Because of the autosomal dominant mode of inheritance, at-risk family members should be investigated for this easily treated cause of hypertension.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 617

Adrenocortical Tumors and Masses

Perrin C. White

Adrenocortical tumors are rare in childhood, with an incidence of 0.3-0.5 cases per 1 million child-years. They occur in all age-groups but most commonly in children younger than 6 years of age and are slightly more frequent (1.6-fold) in females. In 2–10% of cases, the tumors are bilateral. Almost half of childhood adrenocortical tumors are carcinomas. Pathogenic variants in many genes can influence the risk of developing adrenal tumors (Table 617.1).

Tumors may be associated with hemihypertrophy, usually occurring during the first few years of life. They are also associated with other congenital defects, particularly genitourinary tract and central nervous system abnormalities and hamartomatous defects.

Many adrenocortical tumors secrete sex hormones, cortisol, or aldosterone; these are discussed in Chapters 618, 619, and 620, respectively.

617.1 Adrenocortical Carcinoma

Perrin C. White

ETIOLOGY

The incidence of adrenocortical carcinoma is increased in several familial cancer syndromes resulting from abnormalities in genes that encode transcription factors implicated in cell proliferation, differentiation, senescence, apoptosis, and genomic instability. These include tumor protein 53 *(TP53)*, menin (the *MEN1* gene involved in multiple endocrine neoplasia type 1; 1–2% of MEN1 patients develop adrenocortical carcinoma), the *APC* gene involved in familial adenomatous polyposis coli, and the *PRKAR1A* gene encoding a cyclic adenosine monophosphate–dependent protein kinase regulatory subunit (also see Chapter 619).

Germline pathogenic variants in *TP53* (on chromosome 17p13.1) occur in 50–80% of children with adrenocortical carcinoma. They have been found in patients with isolated adrenal carcinoma and in patients with familial clustering of unusual malignancies (choroid plexus tumors, sarcomas, early-onset breast cancers, brain cancers, and leukemias); this latter condition is termed **Li-Fraumeni syndrome**. A 15-fold increased incidence of childhood adrenocortical tumors is found in southern Brazil, associated with an R337H variant in *TP53*.

Overexpression of insulin-like growth factor (IGF) 2 (encoded by *IGF2,* on chromosome 11p15.5) occurs in 80% of sporadic childhood adrenocortical tumors and in those associated with **Beckwith-Wiedemann syndrome**, in which there is loss of the normal imprinting of genes in this chromosomal region, including *H19, CDKN1C, KCNQ1,* and *KCNQ1OT1*. However, whereas 5–10% of patients with Beckwith-Wiedemann syndrome develop tumors, <1% develop an adrenocortical carcinoma. Further implicating IGFs in pathogenesis, many pediatric adrenocortical tumors overexpress the IGF receptor, IGF1R.

Pathogenic variants in the *MENIN* gene on chromosome 11q13 cause **multiple endocrine neoplasia type 1**. Approximately 10% of MEN1 patients have adrenocortical tumors, of which ~14% are malignant. Adrenocortical carcinomas also occur in patients with **Lynch syndrome**, a hereditary cancer syndrome (mainly colorectal and endometrial cancer) caused by pathogenic variants in genes involved in DNA mismatch repair, including *MLH1, MSH2, MSH6,* and *PMS2,* or loss of expression of *MSH2* caused by deletion in the *EPCAM* gene. Occasional adrenocortical carcinomas occur in patients with familial adenomatous polyposis, neurofibromatosis type 1, Werner syndrome, and Carney complex.

In adult adrenocortical carcinoma samples, *somatic* pathogenic variants are detected in nine genes (*ZNRF3, CTNNB1, TP53, CDKN2A, RB1, MEN1, DAXX, MED12,* and *TERT*), most frequently (21%) in *ZNRF3*. This gene encodes a cell surface transmembrane E3 ubiquitin ligase that acts as a negative feedback regulator of Wnt/β-catenin signaling. There are also tumor-specific differences in DNA methylation and in micro-RNA (miRNA) expression that have prognostic significance in adults, but there are no corresponding data in children.

CLINICAL MANIFESTATIONS

Symptoms of endocrine hyperfunction are present in 80–90% of children with adrenal tumors. Tumors that secrete cortisol and aldosterone are discussed in Chapters 619 and 621. Other tumors are detected because of symptoms related to local tumor growth, such as abdominal pain, or as incidental findings on abdominal imaging.

Tumors can usually be detected by ultrasonography, CT, or MRI. Preoperatively, the presence of metastatic disease should be determined by MRI or CT of the chest, abdomen, and pelvis. Because these tumors are metabolically active, ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT has very good sensitivity and specificity in distinguishing benign from malignant lesions, but it cannot distinguish adrenocortical carcinomas from other metabolically active tumors such as metastases, lymphoma, or pheochromocytoma. Radiochemical imaging of these tumors by PET may be improved with ^{11}C-metomidate or single photon emission CT or MRI with ^{123}I-iodometomidate.

PATHOLOGIC FINDINGS

Most pediatric adrenocortical tumors would be classified as malignant by the criteria used to classify adult tumors. Size is a useful prognostic factor, with tumors weighing less than 200 g, 200-400 g, and >400 g being classified, respectively, as low, intermediate, and high risk (>10 cm diameter has also been suggested as a high-risk category). Incomplete resection and gross local invasion or metastasis are also associated with a poor prognosis. However, most tumors occurring in children younger than 4 years of age have a favorable prognosis. Tumors associated with Cushing syndrome may have a poor prognosis, whereas the presence of germline *TP53* variants may be more favorable.

DIFFERENTIAL DIAGNOSIS

For functioning tumors, the differential diagnoses are those of the main presenting signs and symptoms. The differential diagnosis for Cushing syndrome is discussed in Chapter 619. For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 616) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for hormonally

Table 617.1 Genes Involved in Adrenal Neoplasia

SYNDROME	ADRENAL NEOPLASIA TYPE	GENE	OTHER PHENOTYPE
Li-Fraumeni syndrome	Adrenocortical carcinoma	*TP53*	Sarcoma, choroid plexus tumor, brain cancer, early breast cancer, leukemia, lymphoma
Multiple endocrine neoplasia type 1	Diffuse hyperplasia, nodular hyperplasia, adrenal adenoma, adrenocortical carcinoma	*MENIN*	Foregut neuroendocrine tumors, pituitary tumors, parathyroid hyperplasia or tumors, collagenoma, angiofibroma
Lynch syndrome	Adrenocortical carcinoma	*MSH2, MSH6, MLH1, PMS2*	Colorectal cancer, endometrial cancer, sebaceous neoplasms, ovarian cancer, pancreatic cancer, brain cancer
Beckwith-Wiedemann syndrome	Adrenal adenoma, adrenocortical carcinoma	*IGF2, CDKN1C, H19* methylation changes on 11p15	Macrosomia, hemihypertrophy, macroglossia, omphalocele, ear pits; Wilms tumor, hepatoblastoma
Familial adenomatous polyposis coli	Bilateral macronodular adrenal hyperplasia, aldosterone-producing adenoma, adrenocortical carcinoma	*APC*	Intestinal polyps, colon cancer, duodenal carcinoma, thyroid cancer, desmoid tumor, supernumerary teeth, congenital hypertrophy of the retina, osteoma, epidermoid cysts
Neurofibromatosis type 1	Adrenocortical carcinoma, pheochromocytoma	*NF1*	Malignant peripheral nerve sheet tumor, café-au-lait spots, neurofibroma, optic glioma, Lisch nodule, skeletal abnormalities
ADRENAL ADENOMA AND CARCINOMA			
Carney complex	Primary pigmented nodular adrenal disease, adrenocortical carcinoma	*PRKAR1A*	Large-cell calcifying Sertoli cell tumors, thyroid adenoma, myxoma, somatotroph pituitary adenoma, lentigines
	Primary pigmented nodular adrenal disease	*PDE8B* or *PDE11A*	
Overexpression of steroidogenic factor-1	Adrenal adenoma, adrenocortical carcinoma	Somatic amplification of *NR5A1*	
McCune-Albright syndrome	Nodular hyperplasia, cortisol-secreting adenoma	Activating somatic mosaic variant of *GNAS*	Hyperfunction of bone (producing fibrous dysplasia), gonads, thyroid, and pituitary
	Cortisol-secreting adenomas	Activating somatic variant in *PRKACA*	
Somatic pathogenic variants	Adrenocortical carcinoma	*CDKN2A, CTNNB1, DAXX, MED12, MEN1, RB1,TERT, or TP53*	
PRIMARY ALDOSTERONISM			
Genetic causes of excess cortisol and aldosterone secretion	Hypertrophy of zona glomerulosa, aldosterone-producing adenoma	Germline or somatic activating variant in *KCNJ5*	
	Aldosterone-producing adenoma	Germline variants in *CYP11B2, CLCN2, or CACNA1H*	
	Aldosterone-producing adenoma	Germline and somatic activating variants in *CACNA1D*	
	Aldosterone-producing adenoma	Somatic variants in *ATP1A1, ATP2B3, CTNNB1, or APC*	
Pheochromocytoma			
von Hippel-Landau syndrome	Pheochromocytoma	*VHL*	Retinal and central nervous system hemangioblastomas, renal clear cell carcinomas
Multiple endocrine neoplasia syndromes *MEN2A* and *MEN2B*	Pheochromocytoma	*RET*	Medullary thyroid carcinoma and parathyroid tumors; type 2B also may include multiple mucosal neuromas and intestinal ganglioneuromas, a marfanoid habitus, and other skeletal abnormalities
	Pheochromocytoma, often malignant	*SDHB, SDHD, SDHC, SDHA, SDHAF2, MAX, TMEM127*	Paragangliomas, sometimes associated with gastrointestinal stromal tumors and/or pulmonary chondromas (Carney-Stratakis dyad or triad)

inactive adrenocortical adenomas includes pheochromocytomas (see Chapter 621), adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma (very rare in children). Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Not infrequently, a low level of autonomous cortisol secretion is detected that does not cause clinically apparent symptoms; this condition is sometimes referred to as *subclinical Cushing syndrome.*

TREATMENT

Functioning adrenocortical tumors should be removed surgically. There are no data on which to base a recommendation regarding nonfunctioning childhood incidentalomas; in adults, such tumors may be closely observed with imaging and repeat biochemical studies if smaller than 4 cm in diameter, but it is not certain that this is prudent in children. Adrenalectomy should be performed transperitoneally to minimize the risk of surgical rupture of the capsule and consequent dissemination of malignant cells. Some adrenocortical neoplasms are highly malignant and metastasize widely, but less malignant, encapsulated tumors (stage I-II) are often curable if they can be resected without tumor spillage. Postoperatively, patients should be closely monitored biochemically, with frequent determinations of adrenal androgen levels and imaging studies. Recurrent symptoms or biochemical abnormalities should prompt a careful search for metastatic disease. Metastases primarily involve liver, lung, and regional lymph nodes. Most metastatic recurrences appear within 1 year of tumor resection. Repeat surgical resection of metastatic lesions should be performed if possible and adjuvant therapy instituted. Radiation therapy has not been generally helpful. Antineoplastic agents such as cisplatin, doxorubicin and etoposide, ifosfamide and carboplatin, and 5-fluorouracil and leucovorin have had limited use in children, toxicity is high, and in adults with metastatic disease, progression-free survival is only a few months. Therapy with o,p′-DDD (mitotane), an adrenolytic agent, may relieve the symptoms of hypercortisolism or virilization in recurrent disease. In adults, treatment with mitotane plus local or regional treatment (surgery or radiotherapy) is associated with improved survival. Other agents that interfere with adrenal steroid synthesis, such as ketoconazole, aminoglutethimide, and metyrapone, may also relieve symptoms of steroid excess but do not improve survival.

A neoplasm of one adrenal gland may produce atrophy of the other because excessive production of cortisol by the tumor suppresses adrenocorticotropic hormone stimulation of the normal gland. Consequently, **adrenal insufficiency** may follow surgical removal of the tumor. This situation can be avoided by giving 10-25 mg of hydrocortisone every 6 hours, starting on the day of operation and gradually decreased postoperatively. Adequate quantities of water, sodium chloride, and glucose also must be provided.

617.2 Adrenal Incidentaloma

Perrin C. White

Adrenal masses are discovered with increasing frequency in patients undergoing abdominal imaging for reasons unrelated to the adrenal gland. There are no published data on the frequency of the occurrence of such tumors in childhood. They are likely to be infrequent, being found in approximately 7% of autopsies of persons older than age 70 years but in <1% of those younger than age 30 years. They are detected in 1–4% of abdominal CT examinations in adults.

The unexpected discovery of such a mass presents the clinician with a dilemma in terms of diagnostic steps to undertake and treatment interventions to recommend. The differential diagnosis of adrenal incidentaloma includes benign lesions such as cysts, hemorrhagic cysts, hematomas, and myelolipomas. These lesions can usually be identified on CT or MRI. If the nature of the lesion is not readily apparent, additional evaluation is required. Included in the differential diagnosis of lesions requiring additional evaluation are benign adenomas, pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma. Benign, hormonally inactive adrenocortical adenomas make up the majority of incidentalomas. Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Functional tumors require removal. If the adrenal mass is nonfunctional but is larger than 4-6 cm, recommendations are to proceed with surgical resection of the mass. Lesions of 3 cm or less should be followed clinically with periodic reimaging. Treatment must be individualized; nonsecreting adrenal incidentalomas may enlarge and become hyperfunctioning. Nuclear scan, and occasionally fine-needle aspiration, may be helpful in defining the mass.

617.3 Adrenal Calcification

Perrin C. White

Calcification within the adrenal glands may occur in a wide variety of situations, some serious and others of no obvious consequence. Adrenal calcifications are often detected as incidental findings in radiographic studies of the abdomen in infants and children. The physician may elicit a history of anoxia or trauma at birth. Hemorrhage into the adrenal gland at or immediately after birth is probably the most common factor that leads to subsequent calcification (see Fig. 615.1). Although it is advisable to assess the adrenocortical reserve of such patients, there is rarely any functional disorder.

Neuroblastomas, ganglioneuromas, adrenocortical carcinomas, pheochromocytomas, and cysts of the adrenal gland may be responsible for calcifications, particularly if hemorrhage has occurred within the tumor. Calcification in such lesions is almost always unilateral.

In the past, tuberculosis was a common cause of both calcification within the adrenals and Addison disease. Calcifications may also develop in the adrenal glands of children who recover from Waterhouse-Friderichsen syndrome; such patients are usually asymptomatic. Infants with Wolman disease, a rare lipid disorder caused by a deficiency of lysosomal acid lipase, have extensive bilateral calcifications of the adrenal glands (see Chapter 106.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 618

Virilizing and Feminizing Adrenal Tumors

Perrin C. White

Virilization is the most common presenting symptom in children with adrenocortical tumors (see Chapter 617), occurring in 50–80%. In males, the clinical picture is similar to that of simple virilizing congenital adrenal hyperplasia: accelerated growth velocity and muscle development, acne, penile enlargement, and the precocious development of pubic and axillary hair. In females, virilizing tumors of the adrenal gland cause masculinization of a previously normal female with clitoral enlargement, growth acceleration, acne, deepening of the voice, and premature pubic and axillary hair development.

Conversely, adrenal tumors can occasionally (<10%) secrete high levels of estrogens because of overexpression of CYP19 (aromatase). Gynecomastia in males or premature thelarche in females is often the initial manifestation. Growth and development may be otherwise normal, or concomitant virilization may occur.

In addition to virilization, 15–40% of children with adrenocortical tumors also have Cushing syndrome (see Chapter 619). Whereas isolated virilization occurs relatively frequently, children with adrenal tumors usually do not have Cushing syndrome alone.

LABORATORY FINDINGS

Serum levels of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione are usually elevated, often markedly. Serum levels of testosterone are often increased, usually because of peripheral conversion of androstenedione, but infants with predominantly testosterone-secreting adenomas have been reported. Levels of estrone and estradiol are elevated in tumors from patients with feminizing signs. Urinary 17-ketosteroids (sex steroid metabolites) are also increased but are no longer routinely measured. Many adrenocortical tumors have a relative deficiency of 11β-hydroxylase activity and secrete increased amounts of deoxycorticosterone; these patients are hypertensive, and their tumors are often malignant.

DIFFERENTIAL DIAGNOSIS

For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 616) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for adrenal tumors is discussed in Chapter 617.

TREATMENT

Functioning adrenocortical tumors should be removed surgically (see Chapter 617).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 619

Cushing Syndrome

Perrin C. White

Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, a result of either an adrenal tumor or of hypersecretion of corticotropin (adrenocorticotropic hormone [ACTH]) by the pituitary (Cushing disease), or by a tumor (Table 619.1).

Table 619.1 Etiologic Classification of Adrenocortical Hyperfunction

EXCESS ANDROGEN
Congenital adrenal hyperplasia
21-Hydroxylase (CYP21A2) deficiency
11β-Hydroxylase (CYP11B1) deficiency
3β-Hydroxysteroid dehydrogenase (HSD3B2) defect (deficiency or dysregulation)
Tumor
EXCESS CORTISOL (CUSHING SYNDROME)
Bilateral adrenal hyperplasia
Adenoma
Hypersecretion of corticotropin (Cushing disease)
Ectopic secretion of corticotropin
Exogenous corticotropin
Adrenocortical nodular dysplasia
Pigmented nodular adrenocortical disease (Carney complex)
Tumor
McCune-Albright syndrome
EXCESS MINERALOCORTICOID
Primary hyperaldosteronism
Aldosterone-secreting adenoma
Bilateral micronodular adrenocortical hyperplasia
Glucocorticoid-suppressible aldosteronism
Tumor
Deoxycorticosterone excess
Congenital adrenal hyperplasia
• 11β-Hydroxylase (CYP11B1)
• 17α-Hydroxylase (CYP17A1)
Tumor
Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase type 2 [HSD11B2])
EXCESS ESTROGEN
Tumor

ETIOLOGY

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. This rarely represents a diagnostic challenge, but management of hyperglycemia, hypertension, weight gain, linear growth retardation, and osteoporosis often complicates therapy with corticosteroids.

Endogenous Cushing syndrome is most often caused in infants by a functioning adrenocortical tumor (see Chapter 617). Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing syndrome in children older than 7 years of age is **Cushing disease**, in which excessive ACTH secreted by a **pituitary adenoma** causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed **microadenomas**. They consist principally of chromophobe cells and frequently show positive immunostaining for ACTH and its precursor, proopiomelanocortin. Although most such tumors are sporadic, a small number occur in kindreds with **familial isolated pituitary adenoma syndrome**. This syndrome, which is caused by pathogenic variants in the *AIP* gene, accounts for perhaps 2% of pituitary adenomas; more commonly tumors with *AIP* variants secrete growth hormone or prolactin, and only rarely do they secrete ACTH. Similarly, multiple endocrine neoplasia type 1 (MEN1) patients who have pathogenic variants in the *MEN1* gene may develop pituitary tumors, but these are typically prolactinomas. Other genes have also been implicated (Fig. 619.1).

ACTH-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic ACTH secretion in children is associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more

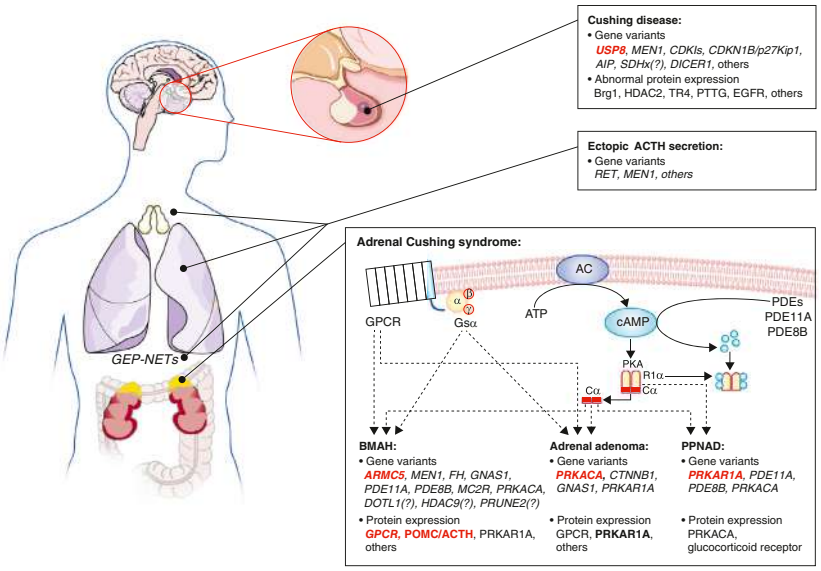

Fig. 619.1 Summary of genetic and molecular mechanisms implicated in Cushing syndrome. For each cause, the various pathogenic variants or abnormal protein expression believed to play a part in the pathophysiology is shown. The most frequent mechanisms are highlighted in red; the well-characterized mechanisms are highlighted in bold characters, and other potential mechanisms are in normal characters; a question mark shows an unconfirmed association or genetic predisposition. Please refer to the text for explanation of the various genetic defects under each diagnostic category. AC, Adenylate cyclase; ACTH, adrenocorticotropic hormone; BMAH, bilateral macronodular adrenal hyperplasia; Cα, catalytic subunit of PKA; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; GPCR, G protein–coupled receptor; PDEs, phosphodiesterases; PKA, protein kinase A; PPNAD, primary pigmented nodular adrenocortical disease; R1α, type 1α regulatory subunit of PKA. *(From Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. Lancet. 2015;386:913–927. Fig. 1.)*

common in ectopic ACTH syndrome than in other forms of Cushing syndrome, because very high cortisol levels may overwhelm type 2 11β-hydroxysteroid dehydrogenase in the kidney (see Chapter 615) and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas (see Chapter 617). In many cases they are caused by pathogenic variants in genes in the cyclic adenosine monophosphate (cAMP)–mediated signaling pathway by which ACTH normally regulates cortisol secretion. **Primary pigmented nodular adrenocortical disease (PPNAD)** is a distinctive form of ACTH-independent Cushing syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands are small and have characteristic multiple small (<4 mm in diameter), pigmented (black) nodules containing large cells with cytoplasm and lipofuscin; there is cortical atrophy between the nodules. This adrenal disorder occurs as a component of **Carney complex**, an autosomal dominant disorder also consisting of centrofacial lentigines and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A *(PRKAR1A)* on chromosome 17q22-24 and less frequently to chromosome 2p16. Patients with Carney complex and *PRKAR1A* variants generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. Conversely, children presenting with PPNAD as an isolated finding rarely have pathogenic variants in *PRKAR1A,* or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have pathogenic variants in *PDE8B* or *PDE11A* encoding different phosphodiesterase isozymes. In contrast, activating *somatic* variants have been documented in the PRKACA catalytic subunit of protein kinase A in cortisol-secreting adenomas.

ACTH-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of **McCune-Albright syndrome**, with symptoms beginning in infancy or childhood. McCune-Albright syndrome is caused by *somatic* variants of *GNAS* encoding the G protein, $G_s\alpha$, through which the ACTH receptor (MCR2) normally signals. When the variant is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

The genes causing nodular adrenocortical hyperplasia that have been identified mainly produce overactivity of the ACTH signaling pathway either by constitutively activating $G_s\alpha$ (McCune-Albright syndrome), by reducing the breakdown of cAMP and thus increasing its intracellular levels (variants of *PDE8B* or *PDE11A*), by disrupting the regulation of the cAMP-dependent enzyme protein kinase A (PRKAR1A mutations), or via microduplications encompassing *PRKACA*. Additionally, *ARMC5,* a tumor-suppressor gene, is abnormal in approximately 40% of cases of primary bilateral macronodular adrenocortical hyperplasia. Adrenocortical lesions, including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma, may occur as part of MEN1 syndrome (see Chapter 617), an autosomal dominant disorder in which there is homozygous inactivation of the menin (MEN1) tumor-suppressor gene on chromosome 11q13.

CLINICAL MANIFESTATIONS

Signs of Cushing syndrome have been recognized in infants younger than 1 year of age. The disorder appears to be more severe and the clinical findings more dramatic in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in females. Growth is impaired, with length falling below the third percentile, except when significant virilization produces normal or even accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

In older children, in addition to obesity, short stature is a common presenting feature (Table 619.2). Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. However, obesity of the neck and upper back ("buffalo hump") is a nonspecific finding to which excessive importance should not be attached. Purplish striae on the hips, abdomen, and thighs are common. Pubertal development may be delayed, or amenorrhea may occur in females past menarche. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis is common and may cause pathologic fractures.

Table 619.2	Presenting Signs and Symptoms of Cushing Syndrome in Children
Dermatologic	Facial plethora, acne, acanthosis nigricans, easy bruising, supratemporal and supraclavicular fat pads, moon facies, fungal infection, hirsutism, fine downy hair, violaceous striae (unusual in children <7 yr age)
Neurologic	Headaches
Cardiovascular	Hypertension, coagulopathy
Growth	Growth deceleration with concomitant weight gain, central obesity
Gonadal	Amenorrhea, virilization, gynecomastia
Other	Nephrolithiasis, bone fractures, impaired glucose tolerance, type 2 diabetes
Psychologic	Depression, anxiety, mood swings, irritability, fatigue

From Lodish MB, Keil MF, Stratakis CA. Cushing's syndrome in pediatrics: an update. *Endocrinol Metab Clin N Am.* 2018;47:451–462. Table 1.

LABORATORY FINDINGS

Cortisol levels in blood are normally highest at 8 AM and decrease to less than 50% of peak levels by midnight, except in infants and young children, in whom a diurnal rhythm is not always established. In patients with Cushing syndrome, this circadian rhythm is lost; *midnight cortisol levels >4.4 μg/dL strongly suggest the diagnosis*. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in *saliva samples*, which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing syndrome.

Urinary excretion of free cortisol is increased. This is best measured in a 24-hour urine sample and is expressed as a ratio of micrograms of cortisol excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.

A single-dose dexamethasone suppression test is often helpful; a dose of 25-30 μg/kg (maximum: 2 mg) given at 11 PM results in a plasma cortisol level of less than 5 μg/dL at 8 AM the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure the adequacy of dosing.

A glucose tolerance test is often abnormal but is of no diagnostic utility. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor (Fig. 619.2). ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors and are very high in patients with ectopic ACTH-secreting tumors, but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone, patients with ACTH-dependent Cushing syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The two-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120 μg/kg/24 hr in four divided doses, on consecutive days. In children with pituitary Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing syndrome do not show suppressed cortisol levels with dexamethasone.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after corticotropin-releasing hormone administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers, and moreover may be of decreased specificity in children.

DIFFERENTIAL DIAGNOSIS

Cushing syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are usually normal, and cortisol secretion is normally suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing syndrome occur in patients with generalized glucocorticoid resistance (see Chapter 615.4). Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

TREATMENT

Transsphenoidal pituitary microsurgery is the treatment of choice in *pituitary* Cushing disease in children. The overall success rate with follow-up of less than 10 years is 60–80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in most cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing disease in adults; remissions are usually not sustained after discontinuation of therapy. This agent is rarely used in children. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. Mifepristone, a glucocorticoid receptor antagonist, has been used in a limited number of cases. Pasireotide, a somatostatin analog, can inhibit ACTH secretion and is approved for use in adults with persistent disease after surgery or in whom surgery is contraindicated.

If a pituitary adenoma does not respond to treatment or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed **Nelson syndrome**, which occurs in ~25% of adults who have undergone adrenalectomy for Cushing syndrome.

Several drugs that inhibit adrenocortical function may be an alternative to adrenalectomy. FDA-approved agents include mitotane (which is toxic to adrenocortical cells) and osilodrostat (a cortisol synthesis inhibitor); levoketoconazole, a stereoisomer of ketoconazole, inhibits several steroidogenic enzymes and is in an advanced stage of development.

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/m^2/24 hr in three divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic-pituitary-adrenal axis. Postoperative complications may include sepsis, pancreatitis, thrombosis, poor wound healing, and sudden collapse, particularly in infants with Cushing syndrome. Substantial catch-up growth, pubertal progress, and increased bone density occur, but bone density remains abnormal and adult height is often compromised. The management of adrenocortical tumors is discussed in Chapter 617.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

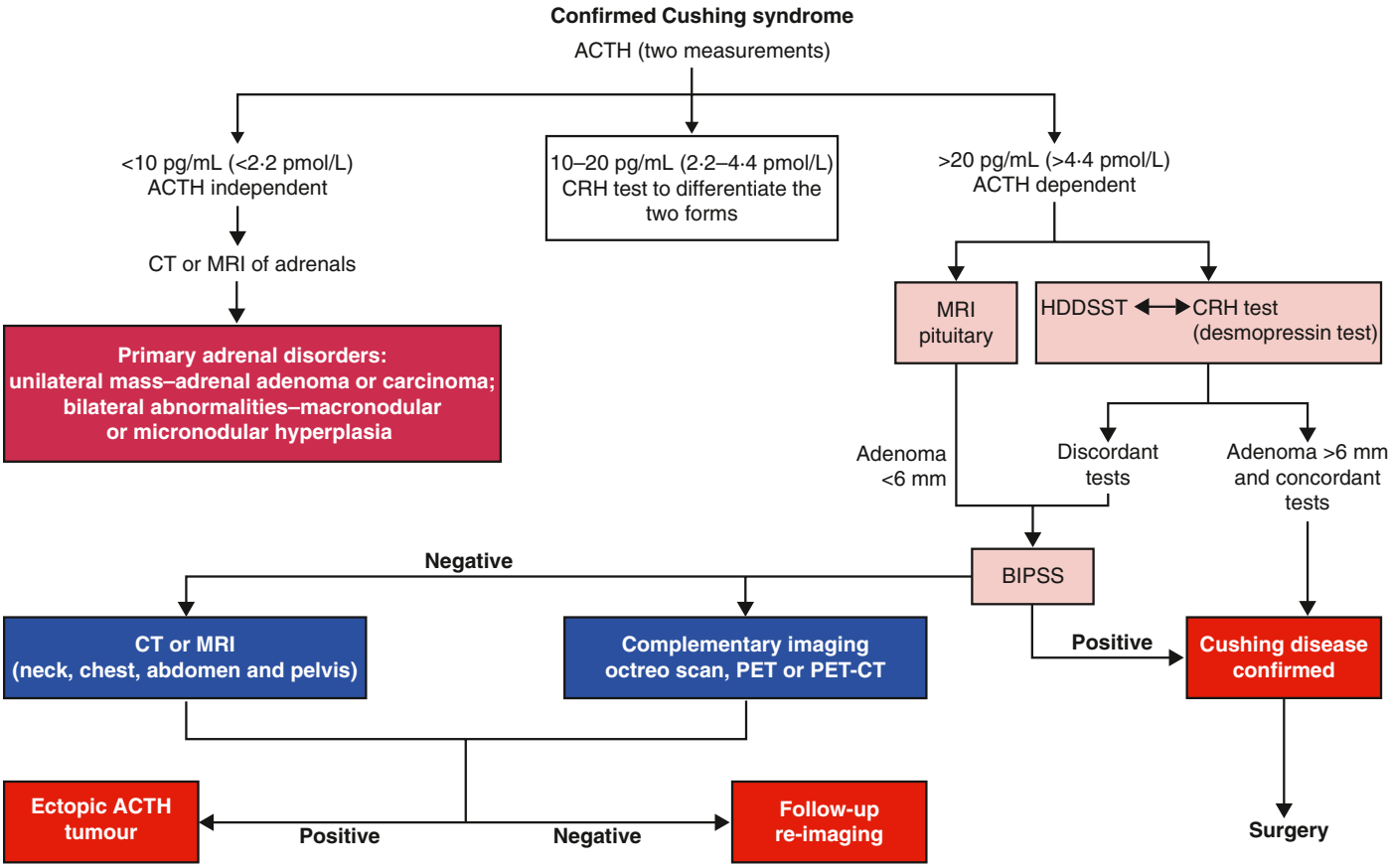

Fig. 619.2 Clinical decision-making algorithm for the differential diagnosis of confirmed Cushing syndrome of different causes. ACTH, Adrenocorticotropic hormone; BIPSS, bilateral inferior petrosal sinus sampling; CRH, corticotropin-releasing hormone; HDDSST, high-dose dexamethasone suppression test. *(From Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. Lancet. 2015;386:913–927. Fig. 3.)*

Chapter 620

Primary Aldosteronism

Perrin C. White

Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the renin-angiotensin system. These disorders are characterized by hypertension, hypokalemia, and suppression of the renin-angiotensin system.

Aldosterone-secreting adenomas are unilateral and have been reported in children as young as 3.5 years of age. They are rarely malignant. Bilateral micronodular adrenocortical hyperplasia tends to occur in older ages. Primary aldosteronism caused by unilateral adrenal hyperplasia may also occur. Glucocorticoid-suppressible hyperaldosteronism is discussed in Chapter 616.8.

EPIDEMIOLOGY

These conditions are thought to be rare in children, but they may account for 5–10% of cases of hypertension in adults. Although usually sporadic, kindreds with several affected members have been reported. Genetic linkage to chromosome 7p22 was reported in some kindreds, but the involved gene has not yet been identified. Pathogenic variants in *KCNJ5* on chromosome 11q24 (encoding G protein–gated inward rectifier potassium channel 4) have been identified in several kindreds; these variants (*G151R* and *G151E*) altered channel selectivity, producing increased Na^+ conductance and membrane depolarization, which increase aldosterone production and proliferation of adrenal glomerulosa cells. Such variants have been identified in a subset of sporadic aldosterone-producing adenomas. Germline variants have also been reported in *CYP11B2* (encoding aldosterone synthase), *CLCN2* (encoding voltage-gated chloride channel ClC-2), and *CACNA1H* (encoding a subunit of the T-type voltage-gated calcium channel CaV3.2). Germline and somatic variants have also been reported in *CACNA1D* encoding a voltage-sensitive calcium channel and *somatic* variants in *ATP1A1* and *ATP2B3,* respectively, encoding sodium-potassium and calcium ATPases. Most aldosterone-producing adenomas have pathogenic variants that activate the Wnt/β-catenin signaling pathway, either in β-catenin *(CTNNB1)* itself, or in *APC,* which regulates this pathway.

CLINICAL MANIFESTATIONS

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others have severe hypertension (up to 240/150 mm Hg), with headache, dizziness, and visual disturbances. If present, chronic hypokalemia may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, tetany, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

LABORATORY FINDINGS

Hypokalemia occurs frequently. Serum pH and carbon dioxide and sodium concentrations may be elevated and serum chloride and magnesium levels decreased. Serum levels of calcium are normal, even in children who manifest tetany. The urine is neutral or alkaline, and urinary potassium excretion is high. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24-hour urine collections are always increased. Plasma levels of renin are persistently low.

The diagnostic test of choice for primary aldosteronism is controversial. Both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. It is desirable to establish a consistent sampling protocol, for example, at midmorning after the patient has been sitting for 15 minutes. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks before testing, including diuretics, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal anti-inflammatory agents. Patients taking these agents may need to be changed to α-adrenergic blockers or calcium channel blockers that have smaller effects on the biochemical measurements. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism. Aldosterone does not decrease with administration of saline solution or fludrocortisone, and renin does not respond to salt and fluid restriction. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol may be increased but not to the extent seen in glucocorticoid-suppressible hyperaldosteronism.

DIFFERENTIAL DIAGNOSIS

Primary aldosteronism should be distinguished from glucocorticoid-remediable aldosteronism (also termed **glucocorticoid-suppressible hyperaldosteronism**, see Chapter 616.8), which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. **Glucocorticoid-remediable aldosteronism** is diagnosed by dexamethasone suppression tests or by specific genetic testing.

Patients with primary aldosteronism should be evaluated by computed tomography (CT). It does not reliably distinguish aldosterone-producing adenomas, which tend to be small, from bilateral hyperplasia, but it can exclude the presence of large tumors that might otherwise raise concern for adrenocortical carcinomas. Adrenal venous sampling can accurately determine if excess aldosterone secretion is originating in one gland or both, but it is invasive and may not be available in all centers. Positron emission tomography with ^{11}C-metomidate is a non-invasive alternative.

TREATMENT

The treatment of an aldosterone-producing adenoma is laparoscopic adrenalectomy; successful enucleation of aldosterone-producing adenomas has also been reported. Hyperaldosteronism caused by bilateral adrenal hyperplasia is treated with the mineralocorticoid antagonist spironolactone (1-3 mg/kg/day to a maximum of 100 mg/day) or eplerenone (25-100 mg/day in 2 divided doses), often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandrogenic properties that may be unacceptable in pubertal males. Eplerenone is a more specific antimineralocorticoid that is safe in children, but there is little specific experience with primary aldosteronism in the pediatric age-group. As an alternative, an epithelial sodium channel blocker, such as amiloride, may be used, with other antihypertensive agents added as necessary. In patients whose condition cannot be controlled medically, unilateral adrenalectomy may be considered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 621

Pheochromocytoma

Perrin C. White

See also Chapter 555.4.

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90%) is the adrenal medulla; however, tumors may develop anywhere along the abdominal sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation. They also appear in the periadrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. Ten percent occur in children, presenting most frequently between 6 and 14 years of age. Tumors vary from 1 to 10 cm in diameter; they are found more often on the right side than on the left. In more than 20% of affected children, the adrenal tumors are bilateral; in 30–40% of children, tumors are found in both adrenal and extraadrenal areas or only in an extraadrenal area.

Most pheochromocytomas are associated with germline pathogenic variants (see Table 555.2 in Chapter 555.4). They may be associated with genetic syndromes such as **von Hippel-Lindau disease, multiple endocrine neoplasia** (MEN) syndromes MEN2A and MEN2B, and less often, in association with **neurofibromatosis (type 1)** or **tuberous sclerosis**. The classic features of von Hippel-Landau syndrome, which occurs in 1 in 36,000 individuals, include retinal and central nervous system hemangioblastomas, renal clear cell carcinomas, and pheochromocytomas, but kindreds differ in their propensity to develop pheochromocytoma; in some kindreds, pheochromocytoma is the only tumor to develop. Germline variants in the *VHL* tumor-suppressor gene on chromosome 3p25-26 have been identified in patients with this syndrome. Variants of the *RET* protooncogene on chromosome 10q11.2 have been found in families with MEN2A and MEN2B. Patients with MEN2 are at risk of developing medullary thyroid carcinoma and parathyroid tumors; approximately 50% develop pheochromocytoma, with patients carrying variants at codon 634 of the *RET* gene being at particularly high risk. Variants are present in the *NF1* gene on chromosome 17q11.2 in neurofibromatosis type 1 patients (see Table 555.2 in Chapter 555.4).

Pheochromocytomas may occur in kindreds along with paragangliomas, particularly at sites in the head and neck. Such families typically carry pathogenic variants in *SDHB, SDHD,* and rarely the *SDHC* encoding subunits of the mitochondrial enzyme succinate dehydrogenase. Approximately 50% of tumors with *SDHB* variants are malignant. The *VHL* and the various *SDH* gene products participate in the *pseudohypoxia* signaling pathway (pseudohypoxia is a decrease in the ratio of the cytosolic oxidized to reduced forms of nicotinamide adenine dinucleotide [NAD (+)/NADH]) and thus represent a common pathogenetic pathway. In rare cases, individuals with germline variants in SDH genes develop pheochromocytomas and/or paragangliomas along with pituitary adenomas, which is termed the **3P association (3Pas)**.

Pheochromocytomas and paragangliomas can occur in association with **gastrointestinal stromal tumors** (GISTs; the association is termed the *Carney-Stratakis dyad*) and/or pulmonary chondromas (Carney-Stratakis triad) and adrenocortical tumors. These associations have heterogenous genetic etiologies but often involve variants in SDH genes.

CLINICAL MANIFESTATIONS

Pheochromocytomas detected by surveillance of patients who are known carriers of variants in tumor-suppressor genes may be asymptomatic. Particularly in adults, some are diagnosed on abdominal CT or MRI performed for another purpose (see Chapter 617). Otherwise, patients are detected owing to hypertension, which results from excessive secretion of metanephrines, epinephrine and norepinephrine. All

patients have hypertension at some point. Paroxysmal hypertension should particularly suggest pheochromocytoma as a diagnostic possibility, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When there are paroxysms of hypertension, the attacks are usually infrequent at first, but become more frequent and eventually give way to a continuous hypertensive state. Between attacks of hypertension, the patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Seizures and other manifestations of hypertensive encephalopathy may occur. In severe cases, precordial pains radiate into the arms; pulmonary edema and cardiac and hepatic enlargement may develop. Symptoms may be exacerbated by exercise or with the use of nonprescription medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Growth failure may be striking. The blood pressure may range from 180 to 260 mm Hg systolic and from 120 to 210 mm Hg diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction. The differential diagnosis is noted in Table 555.3.

LABORATORY FINDINGS

The urine may contain protein, a few casts, and occasionally glucose. Gross hematuria suggests that the tumor is in the bladder wall. Polycythemia is occasionally observed.

Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland. In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine (see Fig. 614.3 in Chapter 614). Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured.

Elevated levels of free catecholamines and metanephrines can also be detected in plasma. The consensus is to measure plasma free metanephrines and urinary fractionated metanephrines. The patient should be instructed to abstain from caffeinated drinks and to avoid acetaminophen, which can interfere with plasma normetanephrine immunoassays. If possible, the blood sample should be obtained from an indwelling intravenous catheter to avoid acute stress associated with venipuncture.

Most tumors in the area of the adrenal gland are readily localized by CT or MRI (Fig. 621.1), but extraadrenal tumors may be difficult to detect. ^{123}I or ^{131}I-metaiodobenzylguanidine (MIBG) is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors. PET-CT with ^{18}F-fluorodeoxyglucose or ^{68}Ga-DOTA(0)-Tyr(3)-octreotate (a somatostatin receptor ligand) is highly sensitive and a more favored imaging approach (Fig. 621.2 and Fig. 555.2) for difficult-to-localize tumors. Venous catheterization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

DIFFERENTIAL DIAGNOSIS

Various causes of hypertension in children must be considered, such as renal or renovascular disease; coarctation of the aorta; hyperthyroidism; Cushing syndrome; deficiencies of 11β-hydroxylase, 17α-hydroxylase, or 11β-hydroxysteroid dehydrogenase (type 2 isozyme); primary aldosteronism; adrenocortical tumors; and, rarely, essential hypertension (see Chapter 494). A nonfunctioning kidney may result from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma.

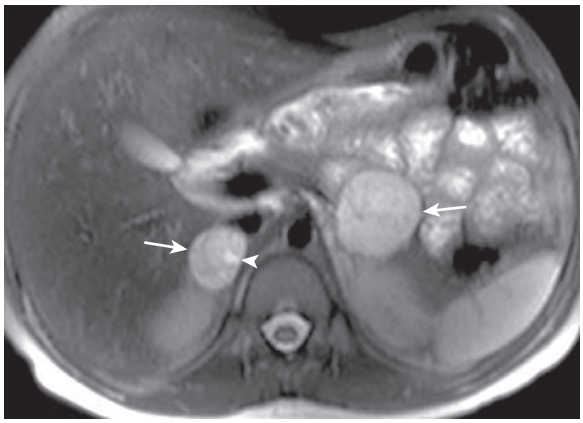

Fig. 621.1 Bilateral pheochromocytoma in an 11-yr-old child with von Hippel-Lindau disease and arterial hypertension. An axial fat-suppressed T2 weighted magnetic resonance image shows bilateral adrenal masses *(arrows)*, larger on the left. The masses are hyperintense with small cystic change on the right medially. *(From Navarro OM, Daneman A. Acquired conditions. In: Coley B, ed. Caffey's Pediatric Diagnostic Imaging, 12th ed. Philadelphia: Elsevier; 2013: Fig. 123.9.)*

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neuroendocrine tumors often produce hypertension, excessive sweating, flushing, pallor, rash, polyuria, and polydipsia. Chronic secretory diarrhea may be associated with these tumors, particularly with ganglioneuroma.

TREATMENT

These tumors must be removed surgically, but careful preoperative, intraoperative, and postoperative management is essential. Manipulation and excision of these tumors result in marked increases in catecholamine secretion that increase blood pressure and heart rate. Therefore preoperative α- *and β-adrenergic blockade* are required. Whereas phenoxybenzamine has been most often used, it may not be covered by insurance, and selective α_1-blockers, such as doxazosin, as well as calcium channel blockers like amlodipine, have also been used. Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Appropriate choice of anesthesia and *expansion of blood volume with appropriate fluids before and during surgery* are critical to avoid a precipitous drop in blood pressure during operation or within 48 hours postoperatively. Surveillance must continue postoperatively.

Because bilateral and recurrent pheochromocytomas occur frequently, some have advocated for adrenal cortex–sparing surgery to reduce the probability of causing Addison disease. However, this approach increases the risk of tumor recurrence.

Although these tumors often appear malignant histologically, the only accurate indicators of malignancy are the presence of metastatic disease or local invasiveness that precludes complete resection, or both. Approximately 10% of all adrenal pheochromocytomas are malignant. Such tumors are rare in childhood; pediatric malignant pheochromocytomas occur more frequently in extraadrenal sites and are often associated with pathogenic variants in *SDHB* encoding a subunit of succinate dehydrogenase. Prolonged follow-up is indicated, particularly in patients with germline mutations in risk loci, because functioning tumors at other sites may be manifested many years after the initial operation. Examination of relatives of affected patients may reveal other individuals harboring unsuspected tumors that may be asymptomatic.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 621.2 Paraganglioma in a 30-yr-old woman who presented with refractory hypertension. **A,** Axial T2-weighted MRI shows homogeneously T2-hyperintense left periaortic mass just above the level of the aortic bifurcation (Zuckerkandl organ), illustrating the "light bulb" T2-bright appearance of pheochromocytomas and paragangliomas. **B,** Axial contrast-enhanced T1-weighted MRI demonstrates heterogeneous enhancement within the mass. **C,** ^{123}I-MIBG fused SPECT/CT axial image shows diffuse uptake within the tumor, compatible with paraganglioma. *(From Ho LM. Adrenal glands. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig. 53-18.)*

Section 5

Disorders of the Gonads

Chapter 622

Development and Function of the Gonads

Patricia A. Donohoue

GENETIC CONTROL OF EMBRYONIC GONADAL DIFFERENTIATION

Gonadal differentiation is a complex, multistep process that requires the sequential action and interaction of multiple gene products. Early in the first trimester, the undifferentiated, bipotential fetal gonad begins as a thickening of the urogenital ridge, near the developing kidney and adrenal cortex. At 6 weeks of gestation, the gonad contains germ cells, stromal cells that will become Leydig cells in the testes or theca, interstitial, or hilar cells in the ovaries, and supporting cells that will develop into Sertoli cells in the testes or granulosa cells in the ovaries. In males, the *SRY* gene (**s**ex-determining **r**egion on the **Y** chromosome) is transiently expressed, followed by a sequential upregulation of a number of testis-specific genes. In the absence of *SRY,* the bipotential gonad will be able to develop into an ovary. Ovarian development is also characterized by expression of ovary-specific genes during the same period. One such gene is *R-spondin1*. During the gestation period of 6-9 weeks, a number of genes are upregulated to the same degree in both the testis and the ovary, including *WNT4* and *CTNNB1*.

A chromosome complement of 46,XX is necessary for the development of normal ovaries. Both the long and short arms of the X chromosome contain genes for normal ovarian development. The DSS (**d**osage **s**ensitive/**s**ex reversal) locus associated with the *DAX1* (**D**SS **a**drenal hypoplasia on the **X** chromosome) gene, which is defective in 46,XY patients with X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism, is a member of the nuclear receptor superfamily and acts as a repressor of male gene expression. The *DAX1* gene product acts by binding to a related nuclear receptor SF-1 (**s**teroidogenic **f**actor-1, also known as *NR5A1*). In vitro, the signaling gene *WNT4* stimulates expression of *DAX1,* resulting in the suppression of androgen synthesis in XX females. The WNTs are ligands that activate receptor-mediated signal transduction pathways and are involved in modulating gene expression as well as cell behavior, adhesion, and polarity. Once developed, the ovary requires FAX12 to preserve its differentiation and stability. A key to its role in humans was elucidated by a loss-of-function pathogenic variant of *WNT4* that was found in an 18-year-old 46,XX woman. She had an absence of müllerian-derived structures (uterus and fallopian tubes), unilateral renal agenesis, and clinical signs of androgen excess.

Pathogenic variants of the Wilms tumor 1 *(WT1)* gene may also affect sex differentiation. *WT1* pathogenic variants are associated with **Denys-Drash syndrome** (early-onset renal failure, abnormal external genitalia in genetic males, and Wilms tumor). Haploinsufficiency of a three–amino acid (KTS) form of *WT1* has been implicated in the gonadal dysgenesis of patients with **Fraser syndrome** (late-onset progressive glomerulopathy and 46,XY gonadal dysgenesis). Variants in the *FOXL2* and *SF-1* genes are associated with ovarian failure. Pathogenic variants of the *R-spondin1* gene has been described in individuals with 46,XX disorder of sex development (DSD). Other autosomal genes also play a role in normal ovarian organogenesis and testicular development. Several conditions of gonadal dysgenesis are associated with gross abnormalities of both autosomes and sex chromosomes. A deletion affecting the short arm of the X chromosome produces the typical somatic anomalies of Turner syndrome.

Development of the testis requires the short arm of the Y chromosome; this contains the *SRY* gene, which is required for testicular differentiation. During male meiosis, the Y chromosome must segregate from the X chromosome so that both X and Y chromosomes do not occur in the same spermatozoa. The major portion of the Y chromosome is composed of Y-specific sequences that do not pair with the X chromosome. However, a minor portion of the Y chromosome shares sequences with the X chromosome, and pairing does occur in this region. The genes and sequences in this area recombine between the sex chromosomes, behaving like autosomal genes. Therefore the term *pseudoautosomal region* is used to describe this portion of the chromosome, and the term indicates genetic behavior of these genes relative to pairing and recombinational events. The *SRY* gene is localized to the 35-kb portion proximal to the pseudoautosomal region of the Y chromosome. It contains a high-mobility group (HMG) nonhistone protein (HMG box), supporting SRY's role as a transcriptional regulator of other genes involved in sex differentiation. The gonadal ridge forms at around 33 days of gestation. SRY is detected at 41 days, peaks at 44 days when testis cords are first visible, and persists into adulthood.

Other genes that are found on autosomes are important in this process. *SOX9,* an *SRY*-related gene containing a region homologous with the HMG box 9 of *SRY,* is located on chromosome 17. Pathogenic variants of this gene result in **XY sex reversal** and **campomelic dysplasia**. *SF-1 (NR5A1)* on chromosome 9q33 is important

in adrenal and gonadal development, as well as the development of gonadotropin-releasing hormone–secreting neurons in the hypothalamus. *WTI,* especially the KST isoform on chromosome 11p13, is needed for early gonadal, adrenal, and renal development. Fibroblast growth factor-9, GATA-4, XH-2, and SOY9 are also important.

When genetic recombination events on sex chromosomes extend beyond the pseudoautosomal region, X- and Y-specific DNA may be transferred between the chromosomes. Such aberrant recombinations result in X chromosomes carrying *SRY,* resulting in **XX males**, or Y chromosomes that have lost *SRY,* resulting in **XY females**. SRY acts as a transcriptional regulator to increase cellular proliferation, attract interstitial cells from adjacent mesonephros into the genital ridge, and stimulate testicular Sertoli cell differentiation. Sertoli cells act as an organizer of steroidogenic and germ cell lines and produce **antimüllerian hormone** (AMH) that causes the female duct system to regress. Table 622.1 lists additional genes involved in sex development that, if abnormal, result in DSD.

Table 622.1 Pathogenic Genes in Disorders of Sex Development

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALIA	ASSOCIATED FEATURES/VARIANT PHENOTYPES
46,XY DSD								
DISORDERS OF GONADAL (TESTICULAR) DEVELOPMENT: SINGLE-GENE DISORDERS								
WT1	TF	607102	11p13	AD	Dysgenetic testis	±	Female or ambiguous	Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash, and Frasier syndromes)
SF1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis; ovotestis	±	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis; mothers who carry SF-1 mutation have premature ovarian insufficiency
SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	±	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	±	Female or ambiguous	Camptomelic dysplasia (17q24 rearrangements milder phenotype than point mutations)
DHH	Signaling molecule	605423	12q13.1	AR	Dysgenetic testis	±	Female	The severe phenotype of one patient included minifascicular neuropathy; other patients have isolated gonadal dysgenesis
ATRX	Helicase (?chromatin remodeling)	300032	Xq13.3	X	Dysgenetic testis	–	Female, ambiguous or male	α-Thalassemia, intellectual disability
ARX	TF	3003382	Xp22.13	X	Dysgenetic testis	–	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Gata4	TF	615542	8p23.1	AD in XY subjects	Dysgenetic testes	_	Ambiguous	Congenital heart disease
DISORDERS OF GONADAL (TESTICULAR) DEVELOPMENT: CHROMOSOMAL CHANGES INVOLVING KEY CANDIDATE GENES								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	±	Female or ambiguous	Intellectual disability
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	±	Female or ambiguous	
WNT4	Signaling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguous	Intellectual disability

Table 622.1 Pathogenic Genes in Disorders of Sex Development—cont'd

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALIA	ASSOCIATED FEATURES/VARIANT PHENOTYPES
DISORDERS IN HORMONE SYNTHESIS OR ACTION								
LHGCR	G-protein receptor	152790	2p21	AR	Testis	–	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	–	Variable	Smith-Lemli-Opitz syndrome: coarse facies, 2nd-3rd toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities
StAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	–	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	–	Female or ambiguous	Congenital adrenal hyperplasia (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	–	Ambiguous	CAH, primary adrenal failure, partial androgenization caused by ↑ DHEA
CYP17	Enzyme	202110	10q24.3	AR	Testis	–	Female ambiguous or micropenis	CAH, hypertension caused by ↑ corticosterone and 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxido-reductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	–	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley-Bixler skeletal dysplasia
HSD17B3	Enzyme	605573	9q22	AR	Testis	–	Female or ambiguous	Partial androgenization at puberty, ↑ androstenedione: testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	–	Ambiguous or micropenis	Partial androgenization at puberty, ↑ testosterone:DHT ratio
AKR1C4	Enzyme	600451	10p15.1	Unclear	Testis	–	Ambiguous or micropenis	DHT deficiency in patients once thought to have 17,20 lyase deficiency; dose effect with *AKR1C2* variant is possible
AKR1C2	Enzyme	600450	10p15.1	Unclear	Testis	–	Ambiguous or micropenis	DHT deficiency in patients once thought to have 17,20 lyase deficiency; dose effect with *AKR1C2* variant is possible
AMH	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	Persistent müllerian duct syndrome (PMDS); male
AHM receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	–	Normal male	External genitalia, bilateral cryptorchidism

Continued

Table 622.1 Pathogenic Genes in Disorders of Sex Development—cont'd

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALIA	ASSOCIATED FEATURES/VARIANT PHENOTYPES
Androgen receptor	Nuclear receptor TF	3130700	Xq11-12	X	Testis	–	Female, ambiguous, micropenis, or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility
46,XX DSD								
DISORDERS OF GONADAL (OVARIAN) DEVELOPMENT								
SRY	TF	480000	Yp11.3	Translocation	Testis or ovotestis	–	Male or ambiguous	
SOX9	TF	608160	17q24	dup17q24	ND	–	Male or ambiguous	
R-spondin1	TF	610644	1p34.3	AR	Ovotestis	±	Male or ambiguous	Palmoplantar hyperkeratosis and certain malignancies
ANDROGEN EXCESS								
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, partial androgenization caused by ↑ DHEA
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, ↑ 17-hydroxyprogesterone
CYP11B1	Enzyme	20210	8q21-22	AR	Ovary	+	Ambiguous	CAH, hypertension caused by ↑ 11-deoxycortisol and 11-deoxycorticosterone
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; associated with Antley-Bixler skeletal dysplasia
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguous	Maternal virilization during pregnancy, absent breast development at puberty, except in partial cases
Glucocorticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguous	↑ ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (patient heterozygous for a variant in *CYP21*)

ACTH, Adrenocorticotropin; AD, autosomal dominant (often de novo mutation); AR, autosomal recessive; CAH, congenital adrenal hyperplasia; ND, not determined; *OMIM #*, Online Mendelian Inheritance in Man number; TF, transcription factor; WAGR, Wilms, aniridia, genital anomalies, and retardation; X, X-chromosomal; Y, Y-chromosomal. Chromosomal rearrangements likely to include key genes are included.

From Lee PA, Houk CP, Ahmed SF, et al. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006;118:e488–e500; with additional data from Baxter RM, Arboleda VA, Lee H, et al. Exome sequencing for the diagnosis of 46,XY disorders of sex development. J Clin Endocrinol Metab. 2015;100:e333–e344; and Lourenco D, Brauner R, Rybczynska M, et al. Loss-of-function mutation in *GATA4* causes anomalies of human testicular development. PNAS. 2011;108:1597–1602.

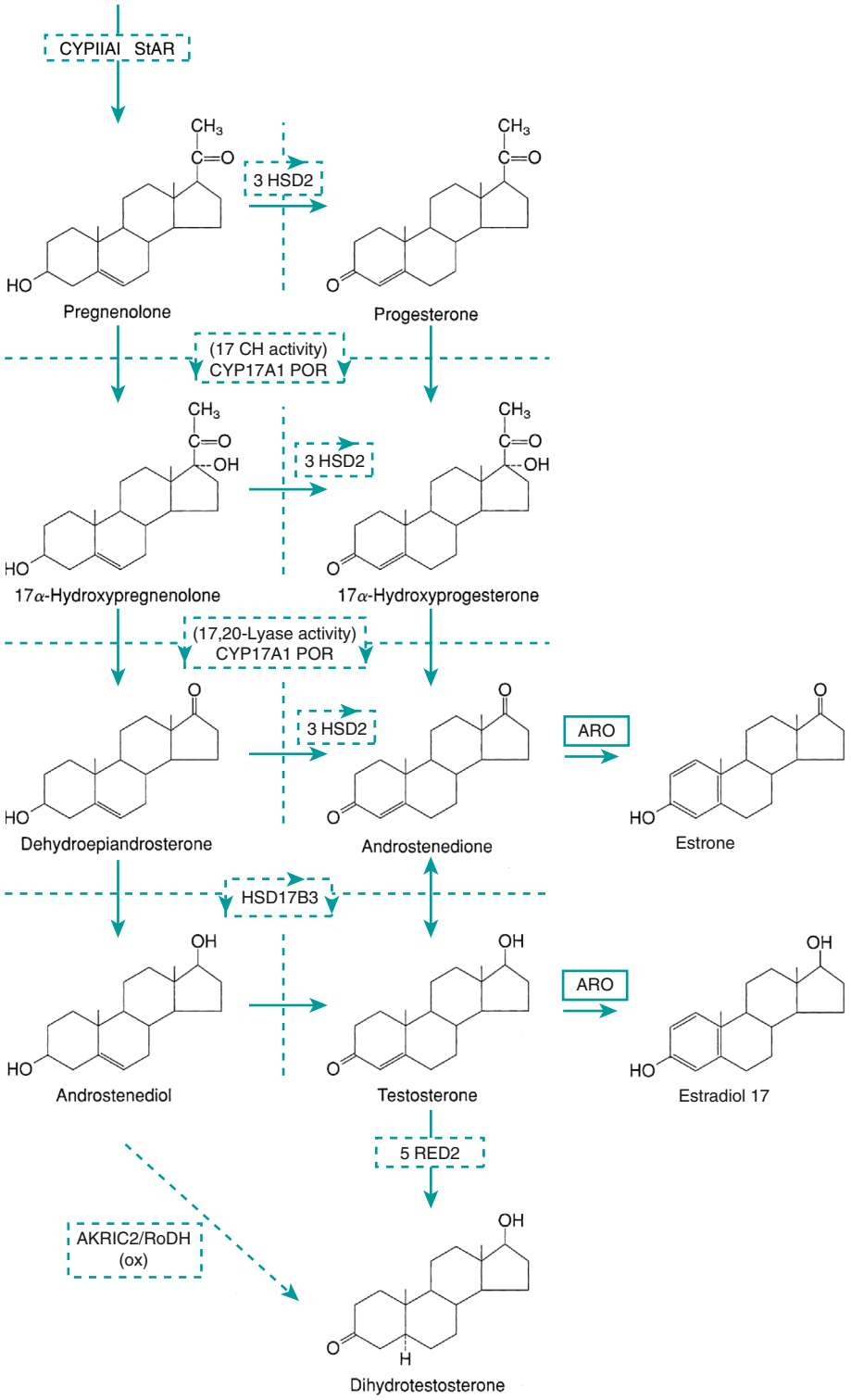

Fig. 622.1 Biosynthesis of sex steroids. *Dashed lines* indicate enzymatic defects associated with 46,XY disorders of sex development. 3β-HSD2, 3β-hydroxysteroid dehydrogenase type 2; 5RED2, 5α-reductase type 2; AKR1C2/RoDH (Ox), one of the enzymes in the alternative androgen biosynthetic pathway; ARO, aromatase; CYP17A1, the enzyme that catalyzes both 17α-hydroxylase (17-OH) and 17,20-lyase activities; HSD17B3, the enzyme that catalyzes the 17-ketoreductase reaction; POR, P450 oxidoreductase; StAR, steroidogenic acute regulatory protein.

Development of the ovary was once thought to be a passive process in the absence of SRY. Although the morphologic changes in the developing ovary are less marked than in the testis, sequentially expressed genes and pathways are required for complete ovarian development along with maintenance of ovarian integrity postnatally. One of these genes is *R-spondin1,* which if abnormal can result in testicular or ovotesticular development in 46,XX individuals. Some peptides in the Wnt-signaling pathway may antagonize testicular development, thus allowing for ovarian differentiation. This effect may be mediated by β-catenin signaling, which is required for suppressing testicular features. Once developed, the ovary requires FAX12 to preserve its differentiation and stability.

FUNCTION OF THE TESTES

Levels of placental chorionic gonadotropin peak at 8-12 weeks of gestation and stimulate the fetal Leydig cells to secrete testosterone, the main hormonal product of the testis (Fig. 622.1). By way of two different biosynthetic pathways, the more potent metabolite of testosterone, dihydrotestosterone (DHT), is produced. In the originally described

pathway, testosterone is converted by the enzyme 5α-reductase to DHT. In another pathway, DHT is produced from androstanediol. The early fetal period of DHT production and action is critical for normal and complete virilization of the XY fetus. Defects in this process lead to different forms of atypical male development (see Chapter 628.2). After virilization occurs, fetal levels of testosterone decrease but are maintained at lower levels in the latter half of pregnancy by luteinizing hormone (LH) secreted by the fetal pituitary; this LH-mediated testosterone secretion is required for continued penile growth and to some degree also for testicular descent.

As part of the normal transition from intrauterine to extrauterine life, perhaps related to the sudden withdrawal of maternal and placental hormones, newborns and young infants experience a transient surge of gonadotropins and sex steroids. This is the so-called **minipuberty**.

In males, LH and testosterone peak at 1-2 months of age and then decline to reach prepubertal levels by 4-6 months of age. Follicle-stimulating hormone (FSH), along with inhibin B, peak at 3 months and decline to prepubertal levels by 9 and 15 months, respectively. The LH rise is more dominant than that of FSH.

The neonatal surge may be important for postnatal maturation of the gonads, stabilization of male external genitalia, and perhaps also for gender identity and sexual behaviors. The postnatal surge in LH and testosterone is absent or blunted in infants with hypopituitarism, cryptorchidism, and complete androgen insensitivity syndrome. The development of nocturnal pulsatile secretion of LH marks the beginning of puberty.

Within specific target cells, 6–8% of testosterone is converted by 5α-reductase to DHT, the more potent androgen (see Fig. 622.1), and approximately 0.3% is acted on by aromatase to produce estradiol. Approximately half of circulating testosterone is bound to sex hormone–binding globulin and half to albumin; only 2% circulates in the free form. Plasma levels of sex hormone–binding globulin are low at birth, rise rapidly during the first 10 days of life, and then remain stable until the onset of puberty. Thyroid hormone may play a role in this physiologic increase because neonates with athyreosis (absence of the thyroid gland) have very low levels of sex hormone–binding globulin.

AMH (previously referred to as *müllerian inhibitory substance*), **inhibin**, and **activin** are members of the transforming growth factor-β (TGF-β) superfamily of growth factors. This group, which has more than 45 members, also includes bone morphogenetic proteins. Members of the TGF-β superfamily are involved in the regulation of developmental processes and multiple diverse human disease states, including chondrodysplasias and cancer.

AMH, a homodimeric glycoprotein hormone encoded by a gene on chromosome 19, is the earliest secreted product of the Sertoli cells of the fetal testis. Produced as a prohormone, its carboxyterminal fragment is cleaved to make it active. *AMH* transcription is initiated by *SOX9* acting through the HMG box, and its expression is upregulated by SF-1 binding to its promoter and further interacting with *SOX9, WT1,* and *GATA4.* AMH binds to two distinct serine/threonine receptors, each having a single transmembrane domain. The activated type 1 receptor signals to the SMAD family of intracellular mediators.

The gene for the AMH receptor (on chromosome 12) is expressed in Sertoli cells. In the female, it is expressed in fetal müllerian duct cells and in fetal and postnatal granulosa cells. During sex differentiation in males, AMH causes involution of the müllerian (paramesonephric) ducts, which are embryologic precursors of the cervix and uterus. It works in concert with SF-1 to cause involution of the fallopian tubes.

AMH is secreted in males by Sertoli cells during both fetal and postnatal life. In females, it is secreted by granulosa cells from 36 weeks of gestation to menopause but at lower levels. The serum concentration of AMH in males is highest at birth, whereas in females it is highest at puberty. After puberty, both sexes have similar serum concentrations of AMH. Its role in postnatal life is not yet fully characterized.

Inhibin is another glycoprotein hormone secreted by the Sertoli cells of the testes and granulosa and theca cells of the ovary. Inhibin A consists of an α-subunit disulfide linked to the β-A subunit, whereas inhibin B consists of the same α subunit linked to the β-B subunit. Activins are dimers of the B subunits, either homodimers (BA/BA, BB/BB) or heterodimers (BA/BB). Inhibins selectively inhibit, whereas activins stimulate pituitary FSH secretion. By means of immunoassays specific for inhibin A or B, it has been shown that inhibin A is absent in males and is present mostly in the luteal phase in women. Inhibin B is the principal form of inhibin in males and in females during the follicular phase. Inhibin B may be used as a marker of Sertoli cell function in males. FSH stimulates inhibin B secretion in females and males, but only in males is there also evidence for gonadotropin-independent regulation. Levels of inhibin B are potentially informative in children with various forms of gonadal and pubertal disorders. In males with delayed puberty, inhibin B may be a useful screening test to differentiate between constitutional delay of puberty and hypogonadotropic hypogonadism. In hypogonadotropic hypogonadism, the serum inhibin B level is very low to undetectable.

Like inhibin and activin, follistatin (a single-chain glycosylated protein) is produced by gonads and other tissues such as the hypothalamus, kidney, adrenal gland, and placenta. Follistatin inhibits FSH secretion principally by binding activins, thereby blocking the effects of activins at the level of both ovary and pituitary.

Many additional peptides act as mediators of the development and function of the testis. They include neurohormones such as growth hormone–releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, somatostatin, substance P, and neuropeptide Y; growth factors such as insulin-like growth factors (IGFs) and IGF-binding proteins, TGF-β, and fibroblast, platelet-derived, and nerve growth factors; vasoactive peptides; and immune-derived cytokines such as tumor necrosis factor and interleukins 1, 2, 4, and 6.

Clinical patterns of pubertal changes vary widely (see Chapter 599). In 95% of males, enlargement of the genitals begins between 9.5 and 13.5 years of age, reaching maturity at 13-17 years of age. In a minority of normal males, puberty begins after 15 years of age. In some males, pubertal development is completed in less than 2 years, but in others it may take longer than 4.5 years. Pubertal development and the adolescent growth spurt occur at an older age in males than in females by approximately 2 years.

The median age of sperm production (spermarche) is 14 years. This event occurs in midpuberty as judged by pubic hair, testis size, evidence of growth spurt, and testosterone levels. Nighttime levels of FSH are in the adult male range at the time of spermarche; the first conscious ejaculation occurs at about the same time.

FUNCTION OF THE OVARIES

In the normal female, the undifferentiated gonad can be identified histologically as an ovary by 10-11 weeks of gestation, after the upregulation of *R-spondin1*. Oocytes are present from the fourth month of gestation and reach a peak of 7 million by 5 months of gestation. For normal maintenance, oocytes need granulosa cells to form primordial follicles. Functional FSH (but not LH) receptors are present in oocytes of primary follicles during follicular development. Two normal X chromosomes are needed for maintenance of oocytes. In contrast to somatic cells, in which only one X chromosome is active, both X chromosomes are active in germ cells. At birth, the ovaries contain approximately 1 million active follicles, which decrease to 0.5 million by menarche. Thereafter, they decrease at a rate of 1,000/month and at an even higher rate after the age of 35 years.

The hormones of the fetal ovary are provided for the most part by the fetoplacental unit. As in males, peak gonadotropin secretion occurs in fetal life and then again at 2-3 months of life, with the lowest levels at about 6 years of age. In contrast to males, the FSH surge predominates over LH in females. FSH peaks around 3-6 months of age and declines by 12 months, but remains detectable for 24 months. Under LH influence, estradiol peaks at 2-6 months of age. The inhibin B response is variable, peaking between 2 and 12 months and remaining above prepubertal levels until 24 months.

In both infancy and childhood, gonadotropin levels are higher in females than in males.

The most important estrogens produced by the ovary are estradiol-17β (E_2) and estrone (E_1); estriol is a metabolic product of these two, and all three estrogens may be found in the urine of mature females. Estrogens also arise from androgens produced by the adrenal gland and both the female and male gonads (see Fig. 622.1). This conversion explains why in certain types of DSD in males, feminization occurs at puberty. In 17-ketosteroid reductase deficiency, for example, the enzymatic block results in markedly increased secretion of androstenedione, which is converted in the peripheral tissues to estradiol and estrone. These estrogens, in addition to those directly secreted by the testis, result in gynecomastia. Estradiol produced from testosterone in complete androgen insensitivity syndrome causes complete feminization in these XY individuals.

Estrogen regulates a host of functionally different activities in multiple tissues. There are at least two distinct estrogen receptors with different expression patterns. The ovary also synthesizes progesterone, the main progestational steroid; the adrenal cortex and testis also synthesize progesterone, where it is a precursor for other adrenal and testicular hormones.

A host of other hormones with autocrine, paracrine, and intracrine effects have been identified in the ovary. They include inhibins, activins, relaxin, and the growth factors IGF-1, TGF-α and TGF-β, and cytokines.

Plasma levels of estradiol increase slowly but steadily with advancing sexual maturation and correlate well with clinical evaluation of pubertal development, skeletal age, and rising levels of FSH. Levels of LH do not rise until secondary sexual characteristics are well developed. Estrogens, like androgens, inhibit secretion of both LH and FSH (negative feedback). In females, estrogens also provoke the surge of LH secretion that occurs in the midmenstrual cycle and stimulates ovulation. The capacity for this positive feedback is another maturational milestone of puberty.

The average age at menarche in American females is approximately 12.5-13 years, but the range of normal is wide, and 1–2% of normal females have not menstruated by 16 years of age. The age at onset of pubertal signs varies, with studies suggesting earlier ages than previously thought, especially in the US Black population (see Chapter 599). Menarche generally correlates closely with skeletal age. Maturation and closure of the epiphyses is estrogen-dependent, as demonstrated by a very tall 28-year-old, normally masculinized male with continued growth as a result of incomplete closure of the epiphyses, who had complete estrogen insensitivity caused by an estrogen receptor defect.

DIAGNOSTIC TESTING

In male infants, measurements of LH, FSH, and testosterone can detect pituitary and testicular defects. Leydig cell integrity in childhood can be determined by the testosterone response after human chorionic gonadotropin administration. One protocol is to inject 5,000 IU IM daily for 3 days; other protocols are available. The integrity and maturity of the hypothalamic-pituitary-gonadal axis in males and females can be assessed by measuring serial sex steroid, LH, and FSH levels after the subcutaneous administration of the gonadotropin-releasing hormone analog leuprolide. An ultrasensitive LH assay has been shown to differentiate between males with delayed puberty and those with complete, but not partial, hypogonadotropic hypogonadism.

The normal range for inhibin B levels has been established in infant males. Inhibin B may be a marker of spermatogenesis and also of tumors such as granulosa cell tumors. Inhibins may be involved in tumor suppression. Estrogen receptor assays may be clinically useful in the management of various ovarian cancers. AMH measurements are useful in the evaluation of children with nonpalpable gonads and DSD.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 623

Hypofunction of the Testes

Omar Ali and Patricia A. Donohoue

Testicular hypofunction during fetal life can be a component of some types of **disorders of sex development** (see Chapter 628.2) and may lead to varying degrees of ambiguous genitalia. After birth, neonates undergo *minipuberty* with relatively high levels of gonadotropins and sex steroids, but this phenomenon is transient, and its absence does not appear to lead to any obvious clinical findings. Because prepubertal children normally do not produce significant amounts of testosterone and are not yet producing sperm, there are no discernible effects of testicular hypofunction in this age-group. Testicular hypofunction from the age of puberty onward may lead to testosterone deficiency, infertility, or both. Such hypofunction may be primary in the testes **(primary hypogonadism)** or secondary to deficiency of pituitary gonadotropic hormones **(secondary hypogonadism)**. Insults to the testes (primary hypogonadism) tend to affect sperm counts more than testosterone secretion, as the seminiferous tubules take up much more of the testicular volume than Leydig cells do, so sperm production is usually affected more than testosterone production. On the other hand, hypogonadotropic hypogonadism tends to affect both testosterone and sperm production.

Both types of hypogonadism may be caused by inherited genetic defects or acquired causes, and in some cases the etiology may be unclear, but the level of the lesion (primary or secondary) is usually well defined; patients with primary hypogonadism have elevated levels of gonadotropins (hypergonadotropic); those with secondary hypogonadism have inappropriately low or absent levels (hypogonadotropic). Table 623.1 details the etiologic classification of male hypogonadism (see also Fig. 600.6).

623.1 Hypergonadotropic Hypogonadism in the Male (Primary Hypogonadism)

Omar Ali and Patricia A. Donohoue

Complete absence or severe dysfunction of the testes in the first trimester will lead to a lack of male sex differentiation and the fetus will have a female phenotype or pronounced ambiguous genitalia (see Chapter 628). If testicular function is present, sex differentiation is normally complete by the 14th week of intrauterine life. *Testicular dysfunction after this stage will lead to hypergonadotropic hypogonadism, and this can occur for a variety of reasons;* genetic or chromosomal anomalies may lead to testicular hypofunction that does not become apparent until the time of puberty, when these males may have delayed or incomplete pubertal development. In other cases, normally developed testes may be damaged by infarction, trauma, radiation, chemotherapy, infections, infiltration, or other causes after sexual differentiation has occurred. In some cases, genetic defects may predispose to atrophy or maldescent; torsion or infarction may lead to progressive testicular damage and atrophy after a period of normal development. If testicular compromise is global, both testosterone secretion and fertility (sperm production) are likely to be affected. Even when the primary defect is in testosterone production, low levels of intratesticular testosterone will frequently lead to infertility. The reverse is not necessarily true. Defects in sperm production and in the storage and transit of sperm may not be associated with low testosterone levels; infertility may thus be seen in patients with normal testosterone levels, normal libido, and normal secondary sexual characteristics.

Table 623.1 Etiologic Classification of Male Hypogonadism

HYPERGONADOTROPIC HYPOGONADISM (PRIMARY HYPOGONADISM; TESTES)
Congenital
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resistance
Pathogenic variants in steroid synthetic pathways
Gonadal dysgenesis
Klinefelter syndrome (47,XXY)
Noonan syndrome (RASopathy genes)
Cystic fibrosis (infertility)
Acquired
Cryptorchidism (some cases)
Vanishing testes
Chemotherapy
Testicular radiation
Infection (e.g., mumps)
Infarction (testicular torsion)
Trauma
HYPOGONADOTROPIC HYPOGONADISM (SECONDARY HYPOGONADISM; HYPOTHALAMIC-PITUITARY)
Congenital
Genetic defects causing Kallmann syndrome and/or normosmic hypogonadotropic hypogonadism (HH)
Other genetic disorders associated with HH: leptin gene, leptin receptor, DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), SF-1 (steroidogenic factor-1)
Inherited syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon-Biedl, Alström
Isolated HH at pituitary level (gonadotropin-releasing hormone receptor, FSH and LH β-subunit)
Multiple pituitary hormone deficiencies: septo-optic dysplasia (*HESX-1* in some cases) and other disorders of pituitary organogenesis (e.g., *PROP1, LHX3, LHX4, SOX-3*)
Idiopathic
Acquired
Anorexia nervosa
Drug use
Malnutrition
Chronic illness, especially Crohn disease
Hyperprolactinemia
Pituitary tumors
Pituitary infarction
Infiltrative disorders (e.g., histiocytosis, sarcoidosis)
Hemosiderosis and hemochromatosis
Cranial radiation

Various degrees of primary hypogonadism occur in a significant percentage of patients with chromosomal aberrations, as in **Klinefelter syndrome**, **males with more than one X chromosome**, and **XX males**. These chromosomal anomalies are also associated with other characteristic findings. Noonan syndrome is also associated with cryptorchidism and infertility, but other (nongonadal) features dominate its clinical picture (see Chapters 100 and 101).

CONGENITAL ANORCHIA OR TESTICULAR REGRESSION SYNDROME

Males in whom the external genitalia have developed normally (or nearly normally) and paramesonephric (müllerian) duct derivatives (uterus, fallopian tubes) are absent have had testicular function for at least some part of gestation. If their testes cannot be palpated at birth, they are said to have **cryptorchidism**. In most such cases, the testes are undescended or retractile, but in some cases no testes are found in any location, even after extensive investigation. This syndrome of absence of testes in a phenotypic male with a normal 46,XY karyotype (indicating that there was some period of testicular function in intrauterine life) is known as *vanishing testes, congenital anorchia,* or testicular regression syndrome.

Testicular regression syndrome is not uncommon. Cryptorchidism occurs in 1.5–9% of male births; in 10–20% of these cases, the testes are impalpable. Of children with impalpable testes, up to 50% may have no detectable testes after extensive investigation. Most cases appear to be sporadic and are thought to be the result of torsion or vascular accidents. The incompletely descended testis may be more prone to torsion, and this may be one of the causes of vanishing testes. Most cases are sporadic, but in a subset of patients, testicular regression syndrome occurs in monozygotic twins or in families with other affected individuals, suggesting a genetic etiology. Some cases are associated with micropenis, and in these cases the testicular loss probably occurred after the 14th week but well before the time of birth, or this may indicate a preexisting dysfunction of male hormonal development. Low levels of testosterone (<10 ng/dL) and markedly elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are found in the early postnatal months; thereafter levels of gonadotropins tend to decrease even in agonadal children, rising to very high levels again as the pubertal years approach. Stimulation with human chorionic gonadotropin (hCG) fails to evoke an increase in the level of testosterone. *Serum levels of antimüllerian hormone (AMH) are undetectable or low.* All patients with undetectable testes should be tested for AMH and should undergo an hCG stimulation test. If the results indicate that no testicular tissue is present (absent AMH and no rise in testosterone after hCG stimulation), then the diagnosis of testicular regression syndrome is confirmed. If testosterone secretion is demonstrated, then imaging with abdominal magnetic resonance imaging (MRI) and/or surgical exploration is indicated. A small fibrotic nodule may be found at the end of the spermatic cord in many cases of testicular regression syndrome. There is no possibility of normal fertility in these patients.

Treatment of male hypogonadism (primary or secondary) is discussed in Chapter 623.2.

Chemotherapy and Radiation-Induced Hypogonadism

Testicular damage is a frequent consequence of chemotherapy and radiotherapy for cancer. The frequency and extent of damage depend on the agent used, total dose, duration of therapy, and posttherapy interval of observation. Another important variable is age at therapy; it has been suggested that prepubertal testes are less prone to damage than pubertal testes, though the evidence is not conclusive. Chemotherapy is most damaging if more than one agent is used, and alkylating agents and platinum-containing agents are the ones most likely to lead to testicular damage. Although many chemotherapeutic agents produce azoospermia and infertility, Leydig cell damage (leading to low testosterone levels) is less common. In many cases the damage is transient and sperm counts recover after 12-24 months. The use of alkylating agents such as cyclophosphamide in prepubertal children may not impair pubertal development, even though there may be biopsy evidence of germ cell damage. Cisplatin causes transient azoospermia or oligospermia at lower doses, whereas higher doses (400-600 mg/m^2) can cause permanent infertility. Interleukin 2 can depress Leydig cell function, whereas interferon-α does not seem to affect gonadal function. Both chemotherapy and radiotherapy are associated with an increase in the percentage of abnormal gametes, but data concerning the outcomes of pregnancies after such therapy have *not* shown any increase in genetically mediated birth defects, possibly because of selection bias against abnormal sperm.

Radiation damage is dose dependent. Temporary oligospermia can be seen with doses as low as 0.1 Gy, with permanent azoospermia seen with doses greater than 2 Gy. Recovery of spermatogenesis can be seen 5 years (or more) after irradiation, with higher doses leading to slower recovery. Leydig cells are more resistant to irradiation. Mild damage as determined by elevated LH levels can be seen with up to 6 Gy; doses greater than 30 Gy cause hypogonadism in most patients. Whenever possible, testes should be shielded from irradiation. Testicular function should be carefully evaluated in adolescents after multimodal treatment for cancer in childhood. Replacement therapy with testosterone and counseling concerning fertility may be indicated. The storage of sperm before chemotherapy or radiation treatment in pubertal

and postpubertal males is an option. Even in those cases where sperm counts are abnormal, recovery is possible, though the chances of recovery decline with increasing dose of radiation. If sperm counts remain low, fertility is still possible in some cases with testicular sperm extraction and intracytoplasmic sperm injection.

Sertoli Cell–Only Syndrome

Small testes and azoospermia are seen in patients with the extremely rare Sertoli cell–only syndrome (**SCO**, **germ cell aplasia**, or **Del Castillo syndrome**). These patients have no germ cells in the testes but usually have normal testosterone production and present as adults with infertility. Typically, patients have small testes and elevated FSH levels with normal LH and testosterone. They may have gynecomastia because of FSH stimulation of aromatase activity. Inhibin B levels may be decreased when compared with individuals with normal spermatogenesis. Most cases are sporadic and idiopathic, but large deletions involving the azoospermia factor (AZF) region of the Y chromosome (Yq11) may be found in some cases. Y chromosome microdeletions are also occasionally identified as a cause of SCO syndrome.

Other Causes of Testicular Hypofunction

Atrophy of the testes may follow damage to the vascular supply because of manipulation of the testes during surgical procedures for correction of cryptorchidism or because of bilateral torsion of the testes. **Cryptorchidism** is a common condition (found in 3% of male children at birth, decreasing to 1% by age 6 months), and guidelines stress the importance of treatment before age 12 months (or even earlier) to maximize future fertility. But a small percentage of cases will develop fertility issues even when surgical treatment is successful and is completed within the first year of life. These cases may represent intrauterine damage, surgical damage, or genetic defects in testicular development and are therefore included among the causes of testicular hypofunction.

Acute orchitis is common in pubertal or adult males with mumps and may lead to subfertility in ~10% of cases, though infertility is rare. Testosterone secretion usually remains normal. The incidence of mumps orchitis in postpubertal males has increased in some areas because of a decrease in measles, mumps, and rubella vaccination uptake. **Autoimmune polyendocrinopathy** may be associated with primary hypogonadism (associated with anti-P450scc antibodies), but this appears to be more common in females.

Testicular Dysgenesis Syndrome

The incidence of testicular cancer has increased in many developed societies, and the incidence of cryptorchidism, hypospadias, low sperm counts, and sperm abnormalities also appears to have increased in some, but not all, studies. It has been proposed that all these trends are linked by prenatal testicular dysgenesis. The hypothesis is that some degree of testicular dysgenesis develops in intrauterine life from genetic and environmental factors and is associated with an increased risk of cryptorchidism, hypospadias, hypofertility, and testicular cancer. The environmental influences that have been implicated in this syndrome include environmental chemicals that act as endocrine disruptors, such as bisphenol A and phthalates (components of many types of plastics), several pesticides, phytoestrogens or mycoestrogens, and other chemicals. The fact that these lesions can be reproduced in some animal models by environmental chemicals has led to efforts to remove these chemicals from products used by infants and pregnant mothers and from the environment in general. Nonetheless the evidence is only suggestive and not conclusive.

CLINICAL MANIFESTATIONS

Primary hypogonadism may be suspected at birth if the testes and penis are abnormally small. Normative data are available for different populations. The condition is often not noticed until puberty, when secondary sex characteristics fail to develop. Facial, pubic, and axillary hair are scant or absent; there is neither acne nor regression of scalp hair; and the voice remains high pitched. The penis and scrotum remain infantile and may be almost obscured by pubic fat; the testes are small or not palpable. Fat accumulates in the region of the hips and buttocks and sometimes in the breasts and on the abdomen. The epiphyses close later than normal; therefore the extremities are long. The span may be several inches longer than the height, and the distance from the symphysis pubis to the soles of the feet (lower segment) is much greater than that from the symphysis to the vertex (upper segment). The proportions of the body are described as **eunuchoid**. The ratio of the upper to lower segment is considerably less than 0.9. Many individuals with milder degrees of hypogonadism may be detected only by appropriate studies of the pituitary-gonadal axis. Examination of the testes should be performed routinely by the pediatrician; testicular volumes as determined by comparison with standard orchidometers or by measurement of linear dimensions should be recorded.

DIAGNOSIS

Levels of serum FSH and, to a lesser extent, of LH are elevated to greater than age-specific normal values in early infancy (when minipuberty normally occurs and the gonadotropins are normally disinhibited). This is followed by a time when even agonadal children may not exhibit significant elevation in gonadotropins, indicating that the gonadotropins are also suppressed at this stage by some mechanism independent of feedback inhibition by gonadal hormones. In the latter half of childhood and several years before the onset of puberty, this inhibition is released and gonadotropin levels again rise above age-based normal levels in subjects with primary hypogonadism. These elevated levels indicate that even in the prepubertal child there is an active hypothalamic-gonadal feedback relationship. After the age of 11 years, FSH and LH levels rise significantly, reaching the agonadal range. Measurements of random plasma testosterone levels in prepubertal males are not helpful because they are low in normal prepubertal children, rising during puberty to attain adult levels. During puberty, these levels, when measured in an early morning blood sample, correlate better with testicular size, stage of sexual maturity, and bone age than with chronological age. In patients with primary hypogonadism, testosterone levels remain low at all ages. There is an attenuated rise or no rise at all after administration of hCG, in contrast to normal males in whom hCG produces a significant rise in plasma testosterone at any stage of development.

AMH is secreted by the Sertoli cells, and this secretion is suppressed by testosterone. AMH levels are elevated in prepubertal males and suppressed at the onset of puberty. Males with primary hypogonadism continue to have elevated AMH levels in puberty. Detection of AMH may be used in the prepubertal years as an indicator of the presence of testicular tissue (e.g., in patients with bilateral cryptorchidism). Inhibin B is also secreted by the Sertoli cells, is present throughout childhood, and rises at the onset of puberty (more in males than in females). It may be used as another marker of the presence of testicular tissue in bilateral cryptorchidism and as a marker of spermatogenesis (e.g., in delayed puberty, cancer survivors, and patients with Noonan syndrome). Bone age x-rays are useful to document delayed bone age in patients with constitutional growth delay as well as primary hypogonadism.

NOONAN SYNDROME

The term *Noonan syndrome* has been applied to males and females with normal karyotypes who have certain phenotypic features that occur also in females with Turner syndrome (although the genetic causes are completely distinct) (see Chapter 101). Males with this syndrome frequently have cryptorchidism and small testes. Testosterone secretion may be low or normal, but spermatogenesis may be affected even in those with normal testosterone (and normal secondary sexual characteristics). Serum inhibin-B is a useful marker of Sertoli cell function in these patients. Puberty is delayed, and adult height is achieved by the end of the second decade; the syndrome is discussed in detail in Chapter 101. Patients with significant hypogonadism will need treatment as discussed in Chapter 623.2.

KLINEFELTER SYNDROME

See also Chapter 99.4.

Klinefelter syndrome is the most common sex chromosomal aneuploidy in males, with an incidence of 0.1–0.2% in the general population

(1 in 500-1,000) and rising to 4% among infertile males and 10–11% in those with oligospermia or azoospermia. Approximately 80% of them have a 47,XXY chromosome complement, whereas mosaics and higher degrees of poly-X are seen in the remaining 20%. Even with as many as four X chromosomes, the Y chromosome determines a male phenotype. The chromosomal aberration most often results from meiotic nondisjunction of an X chromosome during parental gametogenesis; the extra X chromosome is maternal in origin in 54% and paternal in origin in 46% of patients. A national study in Denmark revealed a prenatal prevalence of 213 per 100,000 male fetuses, but in adult men the prevalence was only 40 per 100,000, suggesting that 25% of adult males with Klinefelter syndrome were diagnosed. The incidence of Klinefelter syndrome increases with maternal age and possibly also with paternal age.

Clinical Manifestations

In patients who do not have a prenatal diagnosis, the diagnosis is rarely made before puberty because of the paucity or subtlety of clinical manifestations in childhood. Behavioral or psychiatric disorders may be apparent long before defects in sexual development. These children tend to have learning disabilities and deficits in executive function (concept formation, problem solving, task switching, and planning), and the condition should be considered in males with psychosocial, learning, or school adjustment problems. Affected children may be anxious, immature, or excessively shy and tend to have difficulty in social interactions throughout life. In a prospective study, a group of children with 47,XXY karyotypes identified at birth exhibited relatively mild deviations from normal during the first 5 years of life. None had major physical, intellectual, or emotional disabilities; some were inactive, with poorly organized motor function and mild delay in language acquisition. Problems often first become apparent after the child begins school. Full-scale IQ scores may be normal, with verbal IQ being somewhat decreased. Verbal cognitive defects and underachievement in reading, spelling, and mathematics are common. By late adolescence, many males with Klinefelter syndrome have generalized learning disabilities, most of which are language based. Despite these difficulties, most complete high school.

The patients tend to be tall and slim and have a specific tendency to have long legs (disproportionate to the arms and longer than those seen with other causes of hypogonadism), but body habitus can vary markedly. The testes tend to be small for age, but this sign may become apparent only after puberty, when normal testicular growth fails to occur. The phallus tends to be smaller than average, and cryptorchidism is more common than in the general population. Bone mineral density may be low in adults with Klinefelter syndrome, and this correlates with lower testosterone levels.

Pubertal development may be delayed, although some children undergo apparently normal or nearly normal virilization. Despite normal testosterone levels, serum LH and FSH concentrations and their responses to gonadotropin-releasing hormone (GnRH) stimulation are elevated starting at around 13 years of age. Approximately 50–80% of adults have **gynecomastia**; they have sparser facial hair. The most common testicular lesions are spermatogenic arrest and Sertoli cell predominance. The sperm have a high incidence of sex chromosomal aneuploidy. Azoospermia and infertility are usual, although rare instances of fertility are known. It is now clear that germ cell numbers and sperm counts are higher in early puberty and decline with age. Testicular sperm extraction followed by intracytoplasmic sperm injection can result in the birth of healthy infants, with success rates declining with increasing age. In nonmosaic Klinefelter patients, most testicular sperm (94%) have a normal pattern of sex chromosome segregation, indicating that meiotic checkpoints can remove most aneuploid cells. Antisperm antibodies have been detected in 25% of tested specimens.

There is an increased incidence in adulthood of central adiposity, metabolic syndrome, pulmonary disease, varicose veins, and cancer of the breast. Among 93 unselected **male breast cancer** patients, 7.5% were found to have Klinefelter syndrome. Mediastinal germ cell tumors have been reported; some of these tumors produce hCG and cause precocious puberty in young males. They may also be associated with leukemia, lymphoma, and other types of hematologic neoplasia. The highest cancer risk (relative risk: 2.7) occurs in the 15- to 30-year age-group. A large cohort study in Britain demonstrated an overall significantly increased standardized mortality ratio, with increases in deaths from diabetes, epilepsy, peripheral and intestinal vascular sufficiency, pulmonary embolism, and renal disease. Mortality from ischemic heart disease was decreased. In adults, structural brain abnormalities correlate with cognitive deficits.

Patients with Klinefelter syndrome also have an increased risk of *autoimmune disorders*. It seems that the presence of one or more X chromosomes changes the risk of autoimmune disorders, which are similar to those seen in XX females. These patients have an increased incidence of rheumatoid arthritis, Sjogren syndrome, systemic lupus erythematosus (SLE), and other autoimmune disorders.

In adults with XY/XXY mosaicism, the features of Klinefelter syndrome are decreased in severity and frequency. Children with mosaicism have a better prognosis for virilization, fertility, and psychosocial adjustment.

Klinefelter Variants and Other Poly-X Syndromes

When the number of X chromosomes exceeds two, the clinical manifestations, including intellectual disability and impairment of virilization, are more severe. Height decreases with increasing number of X chromosomes. The **XXYY** variant is the most common variant (1 in 18,000-40,000 male births). In most, intellectual disability occurs with IQ scores between 60 and 80, but 10% have IQs greater than 110. The XXYY male phenotype is not distinctively different from that of the XXY patient except that XXYY adults tend to be taller than the average XXY patient. The **49,XXXXY** variant is sufficiently distinctive to be detected in childhood. Its incidence is estimated to be 1 in 80,000-100,000 male births. The disorder arises from sequential nondisjunction in meiosis. Affected patients are severely cognitively impaired and have short necks and typical coarse facies. The eyes are wide set, with a mild upward slant of the fissures as well as epicanthus and strabismus; the nose is upturned, wide, and flat; also noted is a large open mouth and large malformed ears. The testes are small and may be undescended, the scrotum is hypoplastic, and the penis is very small. Defects suggestive of Down syndrome (short, incurved terminal fifth phalanges, single palmar creases, and hypotonia) and other skeletal abnormalities (including defects in the carrying angle of the elbows and restricted supination) are common. The most frequent radiographic abnormalities are radioulnar synostosis or dislocation, elongated radius, pseudoepiphyses, scoliosis or kyphosis, coxa valga, and retarded bone age. Most patients with such extensive changes have a 49,XXXXY chromosome karyotype; several mosaic patterns have also been observed: 48,XXXY/49,XXXXY; 48,XXXY/49,XXXXY/50,XXXXXY; and 48,XXXY/49,XXXXY/50,XXXXYY. Prenatal diagnosis of a 49,XXXXY infant has been reported. The fetus had intrauterine growth restriction, edema, and cystic hygroma colli.

The **48,XXXY** variant is relatively rare. The characteristic features are generally less severe than those of patients with 49,XXXXY and more severe than those of 47,XXY patients. Mild intellectual disability, delayed speech and motor development, and immature but passive and pleasant behavior are associated with this condition.

Very few patients have been described with 48,XYYY and 49,XXYYY karyotypes. Dysmorphic features and cognitive impairment are common to both.

Laboratory Findings

Most males with Klinefelter syndrome go through life undiagnosed. The chromosomes should be examined in all patients suspected of having Klinefelter syndrome, particularly those attending child guidance, psychiatric, and cognitive disability clinics. In infancy, inhibin B and AMH levels are normal but testosterone levels are lower than in controls. Before 10 years of age, males with 47,XXY Klinefelter syndrome have normal basal plasma levels of FSH and LH. Responses to gonadotropin-stimulating hormone and to hCG are normal. The testes show normal growth early in puberty, but by midpuberty the testicular growth stops, gonadotropins become elevated, and testosterone levels

are slightly low. Inhibin B levels are normal in early puberty, decrease in late puberty, and are low in adults with the syndrome. Elevated levels of estradiol, resulting in a high ratio of estradiol to testosterone, account for the development of gynecomastia during puberty. Sex hormone–binding globulin levels are elevated, further decreasing free testosterone levels. A long androgen receptor polyglutamine (CAG) repeat length is associated with the more severe phenotype, including gynecomastia, small testes, and short penile length.

Testicular biopsy before puberty may reveal only deficiency or absence of germinal cells. After puberty, the seminiferous tubular membranes are hyalinized and there is adenomatous clumping of Leydig cells. Sertoli cells predominate. Azoospermia is characteristic, and infertility is the rule.

Management

Males known to have Klinefelter syndrome should be monitored closely for speech, learning, and behavioral problems; they should be referred for early evaluation and treatment as needed. Testosterone, LH, and FSH levels should be checked at 11-12 years of age; replacement therapy with testosterone is recommended once FSH and LH begin to rise above normal. Fasting glucose, lipids, and hemoglobin A_{1C} should also be obtained, as these children are at risk for central adiposity and metabolic syndrome. A baseline dual-energy x-ray absorptiometry scan to assess bone density is also recommended by some authorities. Although testosterone treatment will normalize testosterone levels, stimulate the development of secondary sexual characteristics, increase bone and muscle mass, and improve body composition, it will *not* improve fertility (and will, in fact, suppress spermatogenesis). There is some evidence that it also improves mood and may have a positive effect on cognition and social functioning, but the findings are not conclusive at this time. Either long-acting testosterone injections or a daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are not frequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly or subcutaneously every 3-4 weeks, with 50-mg increments every 6-12 months until a maintenance dose for adults (200-250 mg every 3-4 weeks) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older males, larger initial doses and increments can achieve more rapid virilization. The various transdermal preparations differ somewhat, and standard references should be consulted for recommendations regarding dosage and mode of application.

Gynecomastia may be treated with aromatase inhibitors (which will also increase endogenous testosterone levels), but medical treatment is not always successful and plastic surgery may be needed. Fertility is usually not an issue in the pediatric age-group, but adults can father children using testicular sperm extraction followed by intracytoplasmic sperm injection. Because sperm counts decrease rapidly after the onset of puberty in children with Klinefelter syndrome, sperm banking during early puberty is an option that can be discussed with a fertility specialist. Sperm counts can be stimulated using hCG treatment before testicular sperm extraction. Therapy, counseling, and psychiatric services should be provided as needed for learning difficulties and psychosocial disabilities.

XX MALES

This disorder is thought to occur in 1 in 20,000 newborn males. Affected individuals have a male phenotype, small testes, a small phallus, and no evidence of ovarian or müllerian duct tissue. They therefore appear to be *distinct from* those with the **ovotesticular disorder of sexual development**. Undescended testes and hypospadias occur in a minority of patients. Infertility occurs in practically all cases, and the histologic features of the testes are essentially the same as in Klinefelter syndrome. Patients with the condition usually come to medical attention in adult life because of hypogonadism, gynecomastia, or infertility. Hypergonadotropic hypogonadism occurs secondary to testicular failure. A few cases have been diagnosed perinatally as a result of discrepancies between prenatal ultrasonography and karyotype findings.

In 90% of XX males with normal male external genitalia, one of the X chromosomes carries the *SRY* (sex-determining region on the Y chromosome) gene. The exchange from the Y to the X chromosome occurs during paternal meiosis, when the short arms of the Y and X chromosomes pair. XX males inherit one maternal X chromosome and one paternal X chromosome containing the translocated male-determining gene. A few cases of 46,XX males with 9P translocations have also been identified. Most XX males who are identified before puberty have hypospadias or a micropenis; this group of patients may lack Y-specific sequences, suggesting other mechanisms for virilization. Fluorescent in situ hybridization and primed in situ labeling have been used to identify small *SRY* DNA segments. Yp fragment abnormalities may result in sexually ambiguous phenotypes.

45,X MALES

In a few male patients recognized with a 45,X karyotype, Yp sequences are translocated to an autosomal chromosome. In one instance, the terminal short arm of the Y chromosome was translocated onto an X chromosome. In another, *SRY/autosomal* translocation was postulated. A male with the 45,X karyotype and Leri-Weill dyschondrosteosis, *SHOX* gene loss, and an SRY to Xp translocation has also been described.

47,XXX MALES

A Japanese male with poor pubic hair development, hypoplastic scrotal testes (4 mL), normal penis and normal height, gynecomastia, and severe cognitive impairment had 47,XXX karyotype caused by an abnormal X-Y interchange during paternal meiosis and X-X nondisjunction during maternal meiosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

623.2 Hypogonadotropic Hypogonadism in the Male (Secondary Hypogonadism)

Omar Ali and Patricia A. Donohoue

In hypogonadotropic hypogonadism (HH), lack of gonadal function is secondary to deficiency of one or both gonadotropins: FSH or LH. The primary defect may lie either in the anterior pituitary or in the hypothalamus. Hypothalamic etiologies result in deficiency of GnRH. The testes are normal but remain in the prepubertal state because stimulation by gonadotropins is lacking. The disorder may be recognized in infancy but is much more commonly recognized because of marked pubertal delay. Rarely, patients with a milder inherited form of HH may go through puberty and may present with hypogonadism as adults.

HH may be genetic or acquired (Table 623.2). Several different genes can cause inherited forms of HH; the affected genes may be upstream of GnRH, at the level of GnRH receptors, or at the level of gonadotropin production. In addition, various genetic defects in transcription factors—such as POUF-1, LHX-3, LHX-4, and HESX-1—lead to defects in pituitary development and multiple pituitary hormone deficiencies, including deficiency of gonadotropins. Acquired pituitary gonadotropin deficiency may develop from various lesions in the hypothalamic-pituitary region (e.g., tumors, infiltrative disease, autoimmune disease, trauma, stroke).

ISOLATED GONADOTROPIN DEFICIENCY

Isolated gonadotropin deficiency in which other pituitary hormone levels are normal is more likely to be from defects in the secretion of GnRH from the hypothalamus rather than defects in gonadotropin synthesis in the pituitary. It affects approximately 1 in 10,000 males and 1 in 50,000 females and encompasses a heterogeneous group of entities. Many cases are associated with anosmia, and this combination of anosmia and HH defines **Kallmann syndrome**.

Table 623.2 Forms of Congenital Hypogonadotropic Hypogonadism and Differential Diagnosis

FORMS OF CHH
GnRH Deficiency and Defective Sense of Smell
Kallmann syndrome
Isolated GnRH Deficiency (Normal Sense of Smell)
Normosmic CHH
Complex Syndromes Including CHH or KS
Combined pituitary hormone deficiency
Septo-optic dysplasia
CHARGE syndrome
Adrenal hypoplasia congenita with HH
Waardenburg syndrome
Bardet-Biedl syndrome
Gordon Holmes syndrome
Others
DIFFERENTIAL DIAGNOSIS
Functional Causes
Malnutrition and/or malabsorption
Any chronic disease (e.g., IBD or asthma)
Celiac disease
Eating disorders
Excessive exercise
Systemic Causes
Hemochromatosis
Sarcoidosis
Histiocytosis
Thalassemia
Acquired Causes
Hyperprolactinemia
Pituitary adenomas and/or brain tumors
Rathke cleft cyst
Pituitary apoplexy
Radiation (brain or pituitary)
Medication induced (such as by steroids, opiates, or chemotherapy)

CHARGE, Coloboma, heart defects, atresia of choanae, retardation of growth and/or development, genital and/or urinary defects, ear anomalies or deafness; CHH, congenital hypogonadotropic hypogonadism; GnRH, gonadotropin-releasing hormone; HH, hypogonadotropic hypogonadism; IBD, inflammatory bowel disease; KS, Kallmann syndrome.

From Boehm U, Bouloux PM, Dattani MT, et al. European consensus statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. Nat Rev. 2015;11:547–564. Box 2.

Kallmann syndrome is the most common form of HH and is genetically heterogeneous, with autosomal recessive, X-linked, and autosomal dominant forms of inheritance. Clinically it is characterized by its association with anosmia or hyposmia; 85% of cases appear to be autosomal and 15% are X-linked, but a specific genetic defect may not be identified in more than half of the cases of HH. There is a wide spectrum of severity and associated features in patients with Kallmann syndrome, and the same genetic pathogenic variants may be associated with different phenotypes, even within the same family. Some kindreds contain anosmic individuals *with or without* hypogonadism; others contain hypogonadal individuals who are anosmic. Cleft lip and palate, hypotelorism, median facial clefts, sensorineural hearing loss, unilateral renal aplasia, neurologic deficits, and other findings occur in some affected patients.

The **X-linked** form (*ANOS1*, formerly known as *KAL1*) is caused by variants of *ANOS1* at Xp22.3. This leads to failure of olfactory axons and GnRH-expressing neurons to migrate from their common origin in the olfactory placode to the brain. The *ANOS1* gene product anosmin-1, an extracellular 95-kDa matrix glycoprotein, facilitates neuronal growth and migration. The *ANOS1* gene is also expressed in various parts of the brain, facial mesenchyme, and mesonephros and metanephros, thus explaining some of the associated findings in patients with Kallmann syndrome, such as synkinesia (mirror movements), hearing loss, midfacial defects, and renal agenesis.

When Kallmann syndrome is caused by terminal or interstitial deletions of the Xp22.3 region, it may be associated with other contiguous gene syndromes, such as steroid sulfatase deficiency, chondrodysplasia punctata, X-linked ichthyosis, or ocular albinism.

The **autosomal dominant** form of Kallmann syndrome (sometimes referred to as *KAL2*) occurs in up to 10% of patients and is caused by a loss-of-function pathogenic variant in the fibroblast growth factor receptor 1 *(FGFR1)* gene. Cleft lip and palate are associated with this form, but not with the X-linked form. Oligodontia and hearing loss may occur with both KAL1 and KAL2.

A variety of other genes—including *SOX10, FGF8, PROK2/PROKR2, NELF, CHD7* (responsible for CHARGE [coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies] syndrome, which includes hypogonadism in its phenotype), *HS6ST1, WDR11,* and *SEMA3A*—are associated with defects in neuronal migration that can result in Kallmann syndrome.

Hypogonadotropic Hypogonadism Without Anosmia

A specific genetic defect is not found in most cases of *normosmic idiopathic hypogonadotropic hypogonadism (IHH)*, but the list of genes associated with this disorder is growing; pathogenic variants in *KISS1/KISS1R, TAC3/TACR3,* and *GNRH1/GNRHR* lead to abnormalities in the secretion and action of GnRH and are seen exclusively in patients with normosmic IHH. Variants in *FGFR1, FGF8, PROKR2, CHD7,* and *WDR11* more commonly present with anosmia/hyposmia (Kallmann syndrome) but are also associated with normosmic IHH in some cases. It appears that kisspeptin (the gene product of the *KISS1* gene) and its G protein–coupled receptor (GPCR54) play an important role in triggering puberty in humans and act downstream of the leptin receptor in this pathway. Rare cases of leptin deficiency and leptin receptor defects are also associated with HH. In addition, starvation and anorexia are associated with hypogonadism, most likely acting via the leptin pathway.

There are no known human variants of the *GnRH* gene, but several families with variants in the GnRH *receptor* have been described. These variants account for 2–14% of IHH without anosmia. The severity of the defect is variable, and many patients will respond to high-dose GnRH with increased gonadotropin secretion, indicating that the receptor defect is partial.

Variants in gonadotropin genes are extremely rare. Variants in the common α-subunit are not known in humans. Variants in the LH-β subunit have been described in a few individuals and may lead to low, absent, or elevated LH levels, depending on the variant. This leads to testosterone deficiency (diminished Leydig cell function), but because intratesticular testosterone is critical for spermatogenesis, this also leads to diminished sperm counts. Defects in the FSH-β subunit may be the cause of azoospermia in a few rare cases. Interestingly these patients may also have testosterone deficiency, indicating that Sertoli cells also play a role in supporting normal Leydig cell function.

Children with **X-linked adrenal hypoplasia congenita (AHC)** have associated HH because of impaired GnRH secretion. In these patients, there is a pathogenic variant of *DAX1* at Xp21.2-21.3. This region of the X chromosome includes genes for glycerol kinase, Duchenne muscular dystrophy, and ornithine transcarbamoyltransferase (OTC); these genes may be affected as part of a contiguous gene deletion syndrome that includes AHC, glycerol kinase deficiency, Duchenne muscular dystrophy, and OTC deficiency. Most males with *DAX1* variants develop HH in adolescence, although a patient with adult-onset adrenal insufficiency and partial HH and two females with HH and delayed puberty have also been described, the latter as part of extended families including males with classic HH. The *DAX1* gene defect is, however, rare in patients with delayed puberty or HH without at least a family history of adrenal failure (see Chapter 616).

It should be noted that genotype-phenotype correlations in IHH appear to be complex, and pedigrees with digenic or oligogenic inheritance have been described. The same genetic defect may be associated with Kallmann syndrome, normosmic IHH, additional birth defects,

delayed normal puberty, or an apparently normal phenotype. This variability has been observed more frequently in kindreds with pathogenic variants in *FGF8/FGFR1* and in *PROK2/PROKR2* ligand-receptor pairs and may result from other interacting genes, epigenetic effects, or environmental factors.

OTHER DISORDERS WITH HYPOGONADOTROPIC HYPOGONADISM

HH has been observed in a few patients with **polyglandular autoimmune syndrome**, in some with elevated melatonin levels, and in those with a variety of other syndromes, such as **Bardet-Biedl, Prader-Willi, multiple lentigines, and several ataxia syndromes**. In rare cases, HH is associated with complex chromosomal abnormalities.

HYPOGONADOTROPIC HYPOGONADISM ASSOCIATED WITH OTHER PITUITARY HORMONE DEFICIENCIES

Defects in pituitary transcription factors such as PROP-1, HESX-1, LHX-4, SOX-3, and LHX-3 lead to multiple pituitary deficiencies including HH. Most of these present with multiple pituitary hormone deficiency in infancy, but some cases (especially with *PROP-1* pathogenic variants) may present with hypogonadism or hypoadrenalism in adult life. Growth hormone is almost always affected in multiple pituitary hormone deficiency, but thyroid-stimulating hormone and adrenocorticotropic hormone may be spared in some cases. In patients with organic lesions in or near the pituitary, the gonadotropin deficiency is usually pituitary in origin.

DIAGNOSIS

Levels of gonadotropins and gonadal steroids are normally elevated for up to 6 months after birth (minipuberty); if the diagnosis of HH is suspected in early infancy, these levels will be found to be inappropriately low. By the second half of the first year of life, these normally decline to nearly undetectable levels and remain suppressed until late childhood. Routine laboratory tests cannot distinguish HH from normal suppression of gonadotropins in this age-group. At the normal age of puberty, these patients fail to show clinical signs of puberty or a normal increase in LH and FSH levels. *Children with constitutional delay of growth and puberty will have the same clinical picture and similar laboratory findings (these cases are far more common than true HH, especially in males), and their differentiation from patients with HH is extremely difficult.* Dynamic testing with GnRH or hCG may *not* be able to distinguish these groups in a reliable manner. A testosterone level greater than 50 ng/dL (1.7 nmol/L) generally indicates that normal puberty is likely, but a lower level does not reliably distinguish these groups. At least one study showed that an inhibin B level of <35 pg/mL in Tanner stage 1 and <65 pg/mL in Tanner stage 2 may be able to distinguish IHH from constitutional delay in males, but no single test will reliably distinguish these conditions in all patients.

Insulin-like growth factor-1, thyroid-stimulating hormone, free thyroxine, and morning cortisol levels should be checked to assess the status of other anterior pituitary hormones; dynamic testing for growth hormone deficiency and adrenal insufficiency may be necessary if these are abnormal or equivocal. HH is very likely if the patient has evidence of another pituitary deficiency, such as a deficiency of growth hormone, particularly if it is associated with adrenocorticotropic hormone deficiency. **Hyperprolactinemia** is a known cause of delayed puberty and should be excluded by determination of serum prolactin levels in all patients. The presence of *anosmia* usually indicates permanent gonadotropin deficiency, but occasional instances of markedly delayed puberty (18-20 years of age) have been observed in anosmic individuals. Although anosmia may be present in the family or in the patient from early childhood, its existence is rarely volunteered, and direct questioning is necessary in all patients with delayed puberty. Formal olfactometry, such as the University of Pennsylvania Smell Identification Test, is advisable to determine if partial degrees of hyposmia are present, because IHH patients display a broad spectrum of olfactory function.

In the absence of family history, it may not be possible to make the diagnosis of HH with certainty, but the diagnosis will become more and more likely as puberty is delayed further beyond the normal age. If pubertal delay persists beyond age 18 years with low 8 AM testosterone levels and inappropriately low gonadotropins (normal values are inappropriately low in this setting), then the patient can be presumptively diagnosed with HH. *An MRI of the brain is indicated* to look for tumors and other anomalies in the hypothalamic-pituitary region. Genetic testing for pituitary transcription factors and several of the genes involved in isolated HH is also available and should be performed when possible. A renal ultrasound is recommended in patients with Kallmann syndrome because of its association with unilateral renal agenesis. Some authorities also recommend obtaining a baseline bone-density evaluation.

TREATMENT

Constitutional delay of puberty should be ruled out before a diagnosis of HH is established and treatment is initiated. Testicular volume of less than 4 mL by 14 years of age occurs in approximately 3% of males, but most of these are cases of constitutional delay of puberty, and true HH is a rare condition. Although constitutional delay is a benign condition that will (by definition) resolve spontaneously, even relatively moderate delays in sexual development and growth may result in significant psychologic distress and require attention. Initially an explanation of the variations characteristics of puberty and reassurance suffice for the majority of males. If by 15 years of age no clinical evidence of puberty is apparent and the testosterone level is <50 ng/dL, a brief course of testosterone may be recommended. Various regimens are used, including testosterone enanthate or cypionate 100 mg intramuscularly once monthly for 4-6 months or 150 mg once monthly for 3 months. Some practitioners use oral oxandrolone in a dose of 1.25-2.5 mg daily for 6-12 months, which has the theoretical advantage that it is not aromatized and may have less effect on bone age advancement (though definitive evidence of advantage is lacking). Oral oxandrolone may cause hepatic dysfunction, and liver function tests should be monitored if it is used. Treatment is not necessary in all cases of constitutional delay, but if used it is usually followed by normal progression through puberty, and this may differentiate constitutional delay in puberty from isolated gonadotropin deficiency. The age of initiation of this treatment must be individualized.

If puberty fails to progress spontaneously after a short course of testosterone has been attempted, then HH becomes the likely diagnosis and necessitates continuous use of testosterone for normal pubertal development. At this point the patient should undergo an MRI scan and genetic testing to try to make a specific diagnosis. Once a diagnosis of HH has been made, treatment with testosterone will induce secondary sexual characteristics but will *not* stimulate testicular growth or spermatogenesis. Treatment with gonadotropins (either as a combination of hCG and human menopausal gonadotropins or as GnRH pulse therapy) will lead to testicular development, including spermatogenesis, but it is much more complex to manage, so in most cases testosterone treatment is still the best option. Either long-acting testosterone injections or a daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are infrequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly or subcutaneously every 3-4 weeks, with 50-mg increments every 6-9 months until a maintenance dose for adults (200-250 mg every 3-4 weeks) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older males, larger initial doses and increments can achieve more rapid virilization.

Treatment with gonadotropins is more physiologic but is expensive and complex, so it is less commonly used in adolescence. This treatment may be attempted in adult life when fertility is desired. The treatment schedule varies from 1,250 to 5,000 IU hCG in combination with 12.5-150 IU human menopausal gonadotropins 3 times per week intramuscularly. It may require up to 2 years of treatment to achieve

adequate spermatogenesis in adults. Recombinantly produced gonadotropins (LH and FSH) are also able to stimulate gonadal growth and function but are much more expensive. Treatment with GnRH (when available) is the most physiologically appropriate, but it requires the use of a subcutaneous infusion pump to deliver appropriately pulsed therapy because continuous exposure to GnRH will suppress gonadotropins rather than stimulate them. In some cases, patients with GnRH defects also have pituitary or testicular dysfunction (a dual defect) and may fail to respond adequately to GnRH or gonadotropin treatment. The rare patient with isolated LH deficiency can be treated effectively using hCG injections.

It has been found that up to 10% of patients diagnosed with HH (with or without anosmia) may exhibit spontaneous reversal of hypogonadism with sustained normal gonadal function after treatment has been discontinued; this may even occur in patients with known genetic variants in various genes, including *FGFR1, PROK2, GNRH, CHD7,* and *TAC/TACR3*. Such recovery is more likely in patients who show an increase in testicular volume during treatment or when treatment has been discontinued. A brief trial of interruption of treatment is justified in patients with idiopathic HH. However, the recovery of gonadal function may not be lifelong.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 624

Pseudoprecocity Resulting from Tumors of the Testes

Omar Ali and Patricia A. Donohoue

Testicular tumors are relatively rare tumors in childhood, accounting for only 2–4% of all childhood cancers. 35% of prepubertal tumors are malignant, but in pubertal children most tumors are malignant (98% of painless testicular masses in pubertal males are malignant). Testicular tumors are discussed further in Chapter 552. Tumors that cause masculinization or feminization are rare and are derived from Leydig cells (producing androgens) or Sertoli cells (producing feminization). In addition, *enlargement* of the testes can be seen in congenital adrenal hyperplasia (CAH, caused by adrenal rests), in fragile X syndrome, and in cases where one testis is lost and the other hypertrophies to compensate.

Leydig cell tumors of the testes are rare causes of precocious pseudopuberty (gonadotropin-independent puberty) and cause asymmetric enlargement of the testes. Leydig cells are sparse before puberty, and tumors derived from them are more common in the adult. However, rare cases do occur in children; the youngest reported case was in a 1-year-old male. Although up to 10% of adult tumors may be malignant, metastasizing malignant tumors have not been reported in children, and pediatric Leydig cell tumors are usually unilateral and benign. Some tumors may be the result of somatic activating pathogenic variants of the luteinizing hormone receptor.

The clinical manifestations are those of puberty in the male; onset usually occurs at 5-9 years of age. Unilateral pubarche caused by local hormone action has been described. Gynecomastia may occur. The tumor of the testis can usually be readily felt; the contralateral unaffected testis is normal in size for the age of the patient.

Plasma levels of testosterone are markedly elevated, and follicle-stimulating hormone and luteinizing hormone levels are suppressed. Ultrasonography may aid in the detection of small nonpalpable tumors. Fine-needle aspiration biopsy may help define the diagnosis.

Treatment consists of surgical removal of the affected testis. These tumors are generally resistant to chemotherapy. Progression of virilization ceases after removal of the tumor, and partial reversal of the signs of precocity may occur.

Testicular adrenal rests may develop into tumors that mimic Leydig cell tumors. **Testicular adrenal rest tumors (TARTs)** are usually bilateral and occur in children with inadequately controlled CAH, usually of the salt-losing variety, during adolescence or young adult life. The stimulus for the growth of the adrenal rests is inadequate corticosteroid suppressive therapy causing excess adrenocorticotropic hormone secretion; treatment with adequate doses may result in their regression if they have not become quite large. These tumors are histologically similar to primary Leydig cell tumors, but definite evidence of their origin may be achieved by demonstrating their 21-hydroxylase activity. Misdiagnosis of these tumors as primary Leydig cell tumors may lead to unnecessary orchiectomy and should be avoided. Treatment is frequently unsatisfactory; improving the control of CAH will lower adrenocorticotropic hormone (ACTH) levels and prevent further growth of TARTs but may not shrink existing masses. Surgical removal can relieve pain (and is indicated if severe pain is present) but will not necessarily restore fertility. Sperm banking is recommended in adults with TARTs because these treatment modalities may not reverse their effect on fertility.

Fragile X syndrome (see Chapter 59) is caused by the amplification of a polymorphic CGG repeat in the 5′ untranslated region of *FMRI* at Xp17.3. The gene encodes an RNA-binding protein that is highly expressed in the brain and the testis. In otherwise normal individuals, 6-50 CGG repeats are present in the gene; the presence of 50-200 repeats is associated with mild intellectual disability and other abnormalities, and the presence of more than 200 repeats (fragile X pathogenic variant) is associated with the classic fragile X syndrome. 50 to 200 repeats are present in 1 in 1,000 White males, and pathogenic variants are found in 1 in 4,000-8,000. A cardinal characteristic of the condition is testicular enlargement *(macroorchidism)*, reaching 40-50 mL after puberty. Although the condition has been recognized in a child as young as 5 months of age, affected males younger than 6 years of age rarely have testicular enlargement; by 8-10 years of age, most have testicular volumes greater than 3 mL. The testes are enlarged bilaterally, are not nodular, and are histologically normal. Results of hormonal studies are normal. Direct DNA analysis searching for CGG repeat sequences permits definitive diagnosis.

Large-cell calcifying Sertoli cell tumors of the testes (usually associated with **Carney complex**) and **sex cord tumors with annular tubules** (frequently associated with **Peutz-Jeghers syndrome**) are extremely rare Sertoli cell tumors that may be a cause of breast development in young males. These tumors often occur bilaterally, are multifocal, and are detectible by ultrasonography. Excessive production of aromatase (P450arom), the enzyme that converts testosterone to estradiol, causes feminization of these males. Because these tumors are usually benign, they may be left in place if they are not causing pain; the gynecomastia can be treated with aromatase inhibitors.

Other causes of testicular enlargement are also present. In males with unilateral cryptorchidism, the contralateral testis is approximately 25% larger than normal for age. Testicular enlargement has also been noted in males with Henoch-Schönlein purpura and lymphangiectasia. Epidermoid and dermoid cysts of the testes have been reported but are rare.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 625

Gynecomastia

Omar Ali and Patricia A. Donohoue

Gynecomastia, the proliferation of mammary glandular tissue in the male, is a common condition. True gynecomastia (the presence of glandular breast tissue) must be distinguished from pseudogynecomastia, which is the result of accumulation of adipose tissue in the area of the breast that is commonly seen in overweight males. True gynecomastia is characterized by the presence of a palpable fibroglandular mass at least 0.5 cm in diameter that is located concentrically beneath the nipple and areolar region.

PHYSIOLOGIC FORMS OF GYNECOMASTIA

Gynecomastia occurs in many newborn males as a result of normal stimulation by maternal estrogen; the effect usually disappears in a few weeks. It is then extremely rare in prepubertal males, in whom it should always be investigated to identify the cause, but it again becomes common during normal puberty.

Neonatal Gynecomastia

Transient gynecomastia occurs in 60–90% of male newborns secondary to exposure to estrogens during pregnancy. Breast development may be asymmetric, and galactorrhea is seen in approximately 5%. Most cases resolve within 4-8 weeks of birth, but a few can last as long as 12 months. No treatment is necessary.

Pubertal Gynecomastia

During early to mid-puberty, up to 70% of males develop various degrees of subareolar hyperplasia of the breasts. Incidence peaks at the same time as peak height velocity, which is around 14 years of age, at Tanner stage 3-4 and at a testicular volume of 5-10 mL. Physiologic pubertal gynecomastia may involve only one breast, and it is not unusual for both breasts to enlarge at disproportionate rates or at different times. Tenderness of the breast is common but transient. Spontaneous regression may occur within a few months; it rarely persists longer than 2 years. Significant psychosocial distress may be present, especially in obese males with relatively large breasts.

The cause is thought to be an imbalance between estrogen and androgen action at the level of breast tissue. Testing usually fails to reveal any significant difference in circulating estrogen and androgen levels between affected and unaffected males, but minor degrees of imbalance in free hormone levels may still be present. Other hormones, including leptin, insulin-like growth factor 1 (IGF-1), and luteinizing hormone, may directly stimulate breast development and may play a role in pubertal gynecomastia. Some cases may be caused by an increased sensitivity to estrogens and/or relative androgen resistance in the affected tissue. As androgen levels continue to rise in later puberty, *most cases resolve and no specific treatment is needed.*

Pathologic Gynecomastia

Monogenic forms of gynecomastia are extremely rare. Familial gynecomastia has occurred in several kindreds as an X-linked or autosomal dominant sex-limited trait. Some of these cases were found to be caused by constitutive activation of the P450 aromatase enzyme *(CYP19A1),* leading to increased peripheral conversion of C-19 steroids to estrogens (increased aromatization). A report of this syndrome in a father and his son and daughter suggests autosomal dominant inheritance.

Exogenous sources of estrogens are an important cause of gynecomastia in prepubertal children. Very small amounts of estrogens can cause gynecomastia in male children, and accidental exposure may occur by inhalation, percutaneous absorption, or ingestion. Common sources of estrogens include oral contraceptive pills and oral and transdermal estrogen preparations. Gynecomastia has been reported in workers involved in the manufacture of estrogens and even in the children of such workers. Gynecomastia can also occur secondary to exposure to medications that decrease the level of androgens (especially free androgens), increase estradiol, or displace androgens from breast androgen receptors. Spironolactone, alkylating agents, anabolic steroids, human chorionic gonadotropin, ketoconazole, cimetidine, and androgen inhibitors such as flutamide are all associated with the occurrence of gynecomastia. Antipsychotic medications may also cause gynecomastia by inducing hyperprolactinemia and hypogonadism. Weaker associations are seen with a large number of other medications and drugs, including opiates, alcohol, and marijuana, although the association with marijuana may not be as strong as previously thought. Lavender, tea tree oils, and excessive consumption of soy are also implicated as possible causes of prepubertal gynecomastia. An increased incidence of gynecomastia has also been reported in cancer survivors, in whom the mechanisms include the antiandrogenic or hypogonadotropic effects of cytotoxic drugs and radiotherapy.

Klinefelter syndrome and other causes of *male hypogonadism* are strongly associated with gynecomastia. Significant gynecomastia is seen in 50% of adolescents with Klinefelter syndrome; it is also seen in other conditions characterized by male undervirilization, including partial androgen insensitivity syndrome and 17-ketosteroid reductase deficiency. Gynecomastia has also been observed in children with congenital virilizing adrenal hyperplasia caused by 11β-hydroxylase deficiency and with Leydig and Sertoli cell tumors of the testis or with feminizing tumors of the adrenal gland. Patients with Klinefelter syndrome may also develop gynecomastia because of estrogen-secreting germ cell tumors of the mediastinum. The finding of such a tumor should prompt a karyotype; conversely, the finding of elevated β-human chorionic gonadotropin (HCG) in a patient with Klinefelter syndrome should lead to imaging of the mediastinum to look for a possible germ cell tumor there. The testes may not be enlarged in patients with Sertoli or Leydig cell tumors, and the tumor is frequently multifocal and bilateral. Excessive aromatase production and/or excessive estrogen production accounts for the gynecomastia. Feminizing Sertoli cell tumors are also a feature of Peutz-Jeghers syndrome and Carney complex. When gynecomastia is associated with galactorrhea, a prolactinoma should be considered. Hyperprolactinemia can also cause gynecomastia indirectly by inducing hypogonadism. Hyperthyroidism alters the ratio of androgen to estrogen by increasing bound androgen and decreasing the free testosterone; this may result in gynecomastia in up to 40% of cases. Gynecomastia is also seen in malnourished patients after restoration of normal nutrition (refeeding syndrome), in whom it may result from hepatic dysfunction or abnormal activation of the gonadotropin axis.

EVALUATION OF GYNECOMASTIA

In pubertal cases a detailed history and physical examination may be all that is needed to exclude rare pathologic causes. Historical evaluation should include family history of male relatives with gynecomastia, history of liver or renal disease, use of medications or drugs of abuse, and exposure to herbal and cosmetic products that may contain phytoestrogens. Physical examination should include special attention to the breasts (looking for overlying skin changes, fixation, local lymphadenopathy, and nipple discharge) as well as a testicular exam. No laboratory evaluation is indicated in routine cases with no other associated abnormality; however, all prepubertal cases and pubertal cases with suspicious features should be investigated. *Suspicious features include diameter >4 cm, rapid progression, persistence for more than 2 years, and persistence after age 17.*

Initial laboratory evaluation should include thyroid function tests (to rule out hyperthyroidism), testosterone, estradiol, HCG, luteinizing hormone, follicle-stimulating hormone, and prolactin levels. Because of circadian variation, these hormone levels should ideally be obtained in the morning. Liver and kidney function should also be evaluated. Most cases of hyperprolactinemia are associated with galactorrhea, but hyperprolactinemia can also cause gynecomastia without associated galactorrhea by suppressing gonadotropins and

inducing some degree of hypogonadism. A karyotype should be checked in all cases where history, examination, or laboratory tests suggest the possibility of Klinefelter syndrome. Gonadotropin levels can be a useful screen for Klinefelter syndrome and will be elevated in pubertal males with this condition. If they are elevated, a karyotype should be performed.

TREATMENT

Treatment in cases of benign pubertal gynecomastia usually consists of reassuring the boy and his family of the physiologic and transient nature of the phenomenon. When the enlargement is striking and persistent and causes serious emotional disturbance to the patient, specific treatment may be justified. Unfortunately, medical treatment is generally ineffective in long-standing cases. Early cases respond better to medical treatment, but it is then harder to justify, as most cases will resolve spontaneously. Agents that have been used for medical treatment include androgens, aromatase inhibitors, and estrogen antagonists. The effectiveness of synthetic androgens is variable and side effects are a concern, so these are rarely used in pediatrics. Aromatase inhibitors have a physiologic rationale, but placebo-controlled trials have been disappointing. Estrogen antagonists like tamoxifen and raloxifene are more effective, with raloxifene being the superior agent in at least one well-designed trial. If medical treatment is attempted, it should be in early cases (<12 months standing) using raloxifene (in a dose of 60 mg/day) or tamoxifen (10-20 mg/day) for 3-9 months, with the understanding that success rates are generally low in severe cases and that mild cases will likely resolve on their own without treatment.

In those cases where breast development is excessive (Tanner stages 3-5), causes significant psychologic distress, or fails to regress in 18-24 months, surgical removal of the enlarged breast tissue may be indicated, particularly in males who have completed or nearly completed pubertal development. Careful examination and laboratory testing to exclude nonphysiologic causes are advisable before proceeding to surgery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 626

Hypofunction of the Ovaries

Alvina R. Kansra and Patricia A. Donohoue

Hypofunction of the ovaries can be either primary or central in etiology. It may be caused by congenital failure of development, postnatal injury (primary or hypergonadotropic hypogonadism), or lack of central stimulation by the pituitary and/or hypothalamus (secondary or tertiary hypogonadotropic hypogonadism). **Primary ovarian insufficiency** (hypergonadotropic hypogonadism), also termed *premature ovarian failure* (POF), is characterized by the arrest of normal ovarian function before 40 years of age. Certain genetic pathogenic variants have been identified that can result in primary ovarian insufficiency. Hypofunction of the ovaries because of a lack of central stimulation (hypogonadotropic hypogonadism) can be associated with other processes, such as multiple pituitary hormone deficiencies and some chronic diseases. Table 626.1 details the etiologic classification of ovarian hypofunction (see also Fig. 600.7).

626.1 Hypergonadotropic Hypogonadism in the Female (Primary Hypogonadism)

Alvina R. Kansra and Patricia A. Donohoue

A diagnosis of hypergonadotropic hypogonadism before puberty is difficult. Except in the case of Turner syndrome, most affected patients have no prepubertal clinical manifestations.

TURNER SYNDROME

The term *Ullrich-Turner syndrome* is frequently used in Europe but is infrequently used in the United States, where the condition is called just *Turner syndrome* (see Chapter 99.4). The syndrome is defined as the combination of the characteristic phenotypic features accompanied by a complete or partial absence of the second X chromosome with or without mosaicism.

Pathogenesis

Half the patients with Turner syndrome have a 45,X chromosomal complement. Approximately 15% of patients are mosaics for 45,X and a normal cell line (45,X/46,XX). Other mosaics with isochromosomes, 45,X/46,X,i(Xq); with rings, 45,X/46,X,r(X); or with fragments, 45,X/46fra, occur less often. Mosaicism is commonly detected when more than one tissue is examined. The single X chromosome is of maternal origin in nearly 80% of 45,X patients. The mechanism of chromosome loss is unknown, and the risk for the syndrome does not increase with maternal age. The genes involved in the Turner phenotype are X-linked genes that escape inactivation. A major locus involved in the control of linear growth has been mapped within the pseudoautosomal region of the X chromosome (PAR1). *SHOX,* a homeobox-containing gene of 170 kb of DNA within the PAR1, is thought to be important for controlling growth in children with Turner syndrome, with Leri-Weill syndrome, and, rarely, patients with idiopathic short stature. Genes for the control of normal ovarian function are postulated to be on Xp and perhaps two supergenes on Xq.

Turner syndrome occurs in approximately 1 in 1,500-2,500 liveborn females. The frequency of the 45,X karyotype at *conception* is approximately 3%. However, 99% of these are spontaneously aborted, accounting for 5–10% of all abortuses. Mosaicism (45,X/46,XX) occurs in a proportion higher than that seen with any other aneuploid state, but the mosaic Turner constitution is rare among the abortuses; these findings indicate preferential survival for mosaic forms.

The normal fetal ovary contains approximately 7 million oocytes, but these begin to disappear rapidly after the fifth month of gestation. At birth, there are only 2 million (1 million active follicles); by menarche, there are 400,000-500,000; and at menopause, 10,000 remain. In the absence of one X chromosome, this process is accelerated, and nearly all oocytes are gone by 2 years of age. In aborted 45,X fetuses, the number of primordial germ cells in the gonadal ridge appears to be normal, suggesting that the normal process of oocyte loss is accelerated in patients with Turner syndrome. Eventually, the ovaries are described as streaks and consist only of connective tissue, with very few germ cells present.

Clinical Manifestations

Many patients with Turner syndrome are recognizable at birth because of a characteristic edema of the dorsa of the hands and feet and loose skinfolds at the nape of the neck. Low birthweight and decreased birth length are common (see Chapter 99.4). Clinical manifestations in childhood include webbing of the neck, a low posterior hairline, small mandible, prominent ears, epicanthal folds, high arched palate, a broad chest presenting the illusion of widely spaced nipples, cubitus valgus, and hyperconvex fingernails. The diagnosis is often first suspected at puberty when breast development fails to occur.

Short stature, the cardinal finding in virtually all females with Turner syndrome, may be present with few other clinical manifestations. The linear growth deceleration begins in infancy and early childhood, gets progressively more pronounced in later childhood and adolescence,

Table 626.1 Etiologic Classification of Ovarian Hypofunction

HYPOGONADOTROPIC HYPOGONADISM

Hypothalamic

Genetic defects
- Kallmann syndrome: *KAL1, FGFR1, FGF8, PROK2, PROKR2, CHD7, WDR11, NELF, SEMA3A*
- Other gene defects: leptin, leptin receptor, KISS-1 (deficiency of kisspeptin), *DAX-1, TAC3* (deficiency of neurokinin B), *TACR3, SEMA7A*
- Inherited syndromes: Prader-Willi, Bardet-Biedl, and others
- Marked constitutional growth delay

Acquired defects (reversible)
- Anorexia nervosa
- Drug use
- Malnutrition
- Chronic illness, especially Crohn disease
- Hyperprolactinemia

Pituitary

Genetic defects
- Isolated gonadotropin deficiency (GnRH receptor, FSH, and LH β-subunit)
- Septo-optic dysplasia (*HESX-1* defect in some cases)
- Disorders of pituitary organogenesis (*PROP1, LHX3, LHX4, SOX-3*)

Acquired defects
- Hyperprolactinemia
- Pituitary tumors
- Pituitary infarction
- Infiltrative disorders (histiocytosis, sarcoidosis)
- Hemosiderosis and hemochromatosis
- Radiation

HYPERGONADOTROPIC HYPOGONADISM

Genetic
- Follicle-stimulating hormone and luteinizing hormone resistance
- Pathogenic variants in steroidogenic pathways
- 46,XX gonadal dysgenesis
- Turner syndrome and its variants
- Noonan syndrome (RASopathy genes)
- *SF-1* pathogenic variants
- Galactosemia
- Fragile X–associated disorders
- Bloom syndrome
- Werner syndrome
- Ataxia-telangiectasia
- Fanconi anemia

Acquired
- Chemotherapy
- Radiation
- Autoimmune ovarian failure from autoimmune polyendocrine syndromes 1 and 2

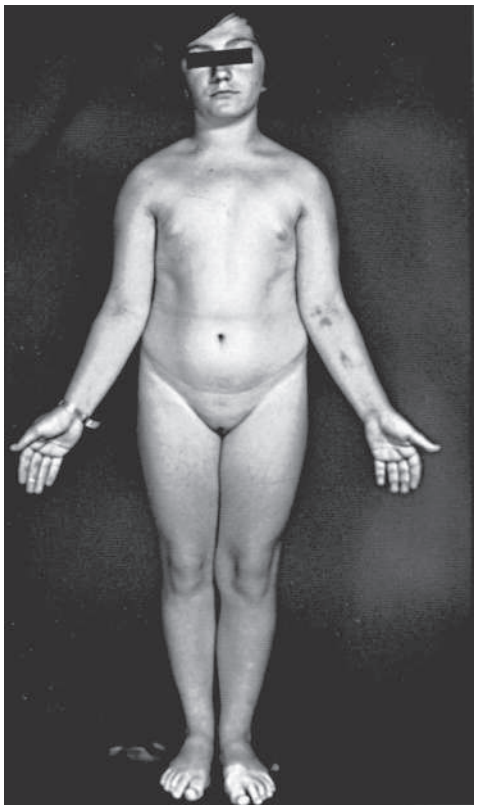

Fig. 626.1 Turner syndrome in a 15-yr-old female exhibiting failure of sexual maturation, short stature, cubitus valgus, and a goiter. There is no webbing of the neck. Karyotyping revealed 45,X/46,XX chromosome complement.

and results in significant adult short stature. Sexual maturation (breast development) fails to occur at the expected age; however, signs of adrenarche (pubic hair) are normally present. Among untreated patients with Turner syndrome, the mean adult height is 143-144 cm in the United States and most of Northern Europe, but 140 cm in Argentina and 147 cm in Scandinavia (Fig. 626.1). The height is well correlated with the midparental height (average of the parents' heights adjusted for child's sex). Specific growth curves for height have been developed for females with Turner syndrome.

Associated **cardiac defects** are common. In females with Turner syndrome, life-threatening consequences of X chromosome haploinsufficiency involve the cardiovascular system. There is a four- to fivefold increase in the rate of premature mortality secondary to congenital heart disease and premature coronary heart disease in adults with Turner syndrome. Clinically silent cardiac defects, mainly bicuspid aortic valve, are present in patients with Turner syndrome. Regardless of age, all patients with Turner syndrome need comprehensive cardiovascular evaluation by a cardiologist specializing in congenital heart disease at the time of diagnosis. Complete cardiologic evaluation, including echocardiography, reveals isolated nonstenotic bicuspid aortic valves in one third to half of the patients. In later life, bicuspid aortic valve disease can progress to dilation of the aortic root or aortic dissection. Less frequent defects include aortic coarctation (20%), aortic stenosis, mitral valve prolapse, and anomalous pulmonary venous drainage. In one study, 38% of patients with 45,X chromosomes had cardiovascular malformations compared with 11% of those with mosaic monosomy X; the most common were aortic valve abnormalities and aortic coarctation. Webbed neck in patients with or without recognized chromosome syndromes is associated with both flow-related and non–flow-related heart defects. Among patients with Turner syndrome, those with webbed necks have a much greater chance of having coarctation of the aorta than do those without webbed necks. Transthoracic echocardiogram in young females is adequate if cardiac anatomy is clearly seen; otherwise, magnetic resonance angiographic screening studies should be considered in asymptomatic individuals with Turner syndrome. During adolescence, and certainly before pregnancy (when possible) is contemplated, repeat cardiac evaluation should be considered even in those without prior findings of cardiac abnormalities. Blood pressure should be routinely monitored even in the absence of cardiac or renal lesions, especially in those with suggestions of aortic root dilation. Cardiac MRI is a valuable tool to detect and monitor aortic root dilation.

Renal ultrasound should be performed in all females with Turner syndrome at diagnosis. One fourth to one third of patients have **renal malformations** on ultrasonographic examination (50% of those with 45,X karyotypes). The more serious defects include pelvic kidney, horseshoe kidney, double collecting system, the complete absence of one kidney, and ureteropelvic junction obstruction. Some of the malformations may increase the risk of hypertension and urinary tract

infection. Idiopathic hypertension is also common. Females with Turner syndrome who had normal baseline renal ultrasound findings did not develop the renal disease during a follow-up period averaging 6 years.

When the ovaries are examined by ultrasonography, there are no age-related differences in detecting ovarian tissue; 27–46% of patients have detectable ovaries at various ages; 76% of those with X mosaicism and 26% of those with 45,X karyotypes have detectable ovaries.

Sexual maturation usually fails to occur, but 10–20% of females have spontaneous breast development, and a small percentage may have menstrual periods. Primary gonadal failure is associated with early onset of adrenarche (elevation in dehydroepiandrosterone sulfate) but delayed pubarche (pubic hair development). Spontaneous pregnancies have been reported in menstruating patients with Turner syndrome. Premature menopause, increased risk of miscarriage, and offspring with increased risk of trisomy 21 have been reported. A woman with a 45,X/46,X,r(X) karyotype treated with hormone replacement therapy had three pregnancies, resulting in a normal 46,XY male infant, a spontaneous abortion, and a healthy term female with Turner syndrome 45,X/46,Xr(X).

Antithyroid antibodies (thyroid peroxidase and/or thyroglobulin antibodies) occur in 30–50% of patients. The prevalence increases with advancing age. **Autoimmune thyroid disease**, with or without a goiter, occurs in 10–30% of patients. Age-dependent abnormalities in carbohydrate metabolism characterized by abnormal glucose tolerance and insulin resistance and, only rarely, frank type 2 diabetes occur in older patients with Turner syndrome. Impaired insulin secretion has been described in 45,X women. Cholesterol levels are elevated in adolescence, regardless of body mass index or karyotype.

Inflammatory bowel disease (both Crohn disease and ulcerative colitis), gastrointestinal bleeding because of abnormal mesenteric vasculature, and delayed gastric emptying time have all been reported. Screening for celiac disease is recommended because the risk of celiac disease is increased in Turner syndrome, with 4–6% of individuals affected. Although autoimmune diseases have been associated with Turner syndrome, the prevalence of type 1 diabetes with Turner syndrome is not very high.

Chronic liver disease may develop in adults with Turner syndrome. Its pathogenesis is poorly defined.

Sternal malformations can be detected by lateral chest radiography. An increased carrying angle at the elbow is usually not clinically significant. Scoliosis occurs in approximately 10% of adolescent females. Congenital hip dysplasia occurs more commonly than in the general population. Reported eye findings include anterior segment dysgenesis and keratoconus. Pigmented nevi become more prominent with age; melanocytic nevi are common. Essential hyperhidrosis, torus mandibularis, and alopecia areata occur rarely.

Recurrent bilateral otitis media develops in approximately 75% of patients. Sensorineural hearing deficits are common, and the frequency increases with age. Problems with gross and fine motor sensory integration, failure to walk before 15 months of age, and early language dysfunction often raise questions about developmental delay, but intelligence is normal in most patients. However, cognitive impairment does occur in patients with 45,X/46,X,r(X); the ring chromosome is unable to undergo inactivation and leads to two functional X chromosomes.

Special attention should be given to psychosocial development in females with Turner syndrome. In general, behavior is normal in females with Turner syndrome, but they are at an increased risk for social isolation, immaturity, and anxiety. Other conditions, such as dyslexia, nonverbal learning disability, and attention-deficit disorder, have been reported in females with Turner syndrome. In adults, deficits in perceptual spatial skills are more common than they are in the general population. Some unconfirmed data suggest the existence of an imprinted X-linked locus that affects cognitive function such as verbal and higher-order executive function skills. These functions are apparently better when the X is paternal in origin.

The prevalence of mosaicism depends in large part on the techniques used for studying chromosomal patterns. The use of fluorescent in situ hybridization and reverse transcription–polymerase chain reaction (PCR) has increased the reported prevalence of mosaic patterns to as high as 60–74%.

Mosaicism involving the Y chromosome occurs in 5%. A population study using PCR with five different primer sets found Y chromosome material in 12.2%. **Gonadoblastoma** among Y-positive patients occurred in 7–10%. Therefore the recommendation is that prophylactic gonadectomy be performed even in the absence of MRI or CT evidence of tumors. The recommended timing of this procedure is at the time of diagnosis, but this may need to be reevaluated in the future. The gonadoblastoma locus on the Y chromosome (GBY) maps close to the Y centromere. The presence of only the SRY (sex-determining region on the Y chromosome) locus is not sufficient to confer increased susceptibility for the development of gonadoblastoma. Routine PCR for Y chromosome detection for the purpose of assigning gonadoblastoma risk is not indicated. High-throughput quantitative genotyping may provide an effective and inexpensive method for the identification of X chromosome abnormalities and Y chromosome material identification.

In patients with 45,X/46,XX mosaicism, the clinical abnormalities are attenuated and fewer; short stature is as frequent as it is in the 45,X patient and may be the only manifestation of the condition other than ovarian failure (see Fig. 626.1).

Laboratory Findings

Chromosomal analysis must be considered routinely in females who have unexpected short stature based on parental heights. Turner syndrome is detected in ~5% of females referred to an endocrinology service because of short stature. Patients with a marker chromosome in some or all cells should be tested for DNA sequences at or near the centromere of the Y chromosome for GBY.

Ultrasonography of the heart, kidneys, and ovaries is indicated after the diagnosis is established. The most common skeletal abnormalities are shortening of the fourth metatarsal and metacarpal bones, epiphyseal dysgenesis in the joints of the knees and elbows, Madelung deformity, scoliosis, and, in older patients, inadequate osseous mineralization.

Plasma levels of gonadotropins, particularly follicle-stimulating hormone (FSH), are markedly elevated to greater than those of age-matched controls during infancy; at 2-3 years of age, a progressive decrease in levels occurs until they reach a nadir at 6-8 years of age, and by 10-11 years of age, they rise to adult agonadal levels.

Thyroid peroxidase antibodies should be checked to detect autoimmune thyroiditis if the thyroid-stimulating hormone (TSH) level is abnormal. Annual or biannual TSH levels are recommended. Females with Turner syndrome should be screened for celiac disease by measuring tissue transglutaminase immunoglobulin A antibodies. Initial testing should be done around age 4 years and repeated every 2-5 years. Extensive studies have failed to establish that growth hormone deficiency plays a primary role in the pathogenesis of the growth disorder. Defects in normal secretory patterns of growth hormone are seen in adolescents because of a lack of gonadal steroids, but not in younger females with Turner syndrome.

Treatment

Treatment with recombinant human growth hormone increases height velocity and ultimate stature in most, but not all, children with Turner syndrome. Many females achieve heights of greater than 150 cm with early initiation of treatment. In one clinical trial, 99 patients with Turner syndrome who started receiving growth hormone at a mean age of 10.9 years at doses between 0.27 and 0.36 mg/kg/wk achieved a mean height of 149 cm, with nearly one third reaching heights greater than 152.4 cm (60 in). In the Netherlands, higher doses of growth hormone (up to 0.63 mg/kg/wk in the third year of treatment) resulted in 85% of the subjects reaching adult heights in the normal range for the Dutch reference population. Growth hormone treatment should be initiated in early childhood and/or when there is evidence of height velocity attenuation on specific Turner syndrome growth curves. Growth hormone therapy does not significantly aggravate carbohydrate tolerance and does not result in marked adverse events in patients with Turner syndrome. Serum levels of insulin-like growth factor 1 should be monitored if the patient is receiving high doses of growth hormone. If the insulin-like growth

factor 1 levels are significantly elevated, the dose of growth hormone may need to be reduced. Treatment with growth hormone can cause excessive growth of the hands and feet in some females with Turner syndrome.

Oxandrolone has also been used to treat the short stature associated with Turner syndrome, either alone or in combination with growth hormone. This nonaromatizable synthetic anabolic steroid has weak androgenic effects, and patients should be monitored for signs of pubarche and hepatotoxicity. The latter is rare.

Replacement therapy with estrogens is indicated, but there is variation among pediatric endocrinologists about the optimal age at which to initiate treatment. The psychologic preparedness of the patient to accept therapy must be considered. The improved growth achieved by females treated with growth hormone in childhood permits initiation of estrogen replacement at 12-13 years. Delaying estrogen therapy to optimize height potential until 15 years of age, as previously recommended, seems unwarranted. This change to starting earlier estrogen therapy was considered because of the psychologic importance of age-appropriate pubertal maturation. In addition, delaying estrogen therapy could be deleterious for bone health and potentially other aspects of the child's health. Low-dose estrogen replacement at 12 years of age permits a normal pace of puberty without interfering with the positive effect of growth hormone on the final adult height. Estrogen therapy improves verbal and nonverbal memory in females with Turner syndrome. In young women with age-appropriate pubertal development who achieve normal height, health-related quality-of-life questionnaires have yielded normal results.

Many forms of estrogen are available. Oral estrogens had been mostly used in the past. Transdermal patches are increasing in popularity. This is because transdermal patches bypass the first-pass hepatic metabolism, requiring only a small amount of estrogen to attain adequate function. Many treatment protocols have been developed, and several are as follows. For oral preparations, a conjugated estrogen (Premarin), 0.15-0.625 mg daily, or micronized estradiol (Estrace), 0.5 mg given daily for 3-6 months, is usually effective in inducing puberty. The recommendations for transdermal patch therapy are 6.25 μg daily, gradually increased over 2 years to the adult dose of 100-200 μg daily. The estrogen may be cycled (taken on days 1-23) or not. A progestin (Provera) is added (taken on days 10-23) in a dose of 5-10 mg daily. In the week after the progestin, withdrawal bleeding usually occurs. Combination oral contraceptive pills may also be used for hormone replacement therapy.

Prenatal chromosome analysis for advanced maternal age has revealed a frequency of 45,X/46,XX that is 10 times higher than when diagnosed postnatally. Most of these patients have no clinical manifestations of Turner syndrome, and levels of gonadotropins are normal. Awareness of this mild phenotype is important in counseling patients.

Psychosocial support for these females is an integral component of treatment. A comprehensive psychologic education evaluation is recommended either at the time of Turner syndrome diagnosis, depending on the patient's age, when any of the components of behavior or cognition become obvious, or immediately preceding school entry. In addition to the healthcare team, the Turner Syndrome Society, which has local chapters in the United States and similar groups in Canada and other countries, provides a valuable support system for these patients and their families.

Successful pregnancies have been carried to term using ovum donation and in vitro fertilization. Adolescents with few signs of spontaneous puberty may have ovaries with follicles. There remains a future possibility of using cryopreserved ovarian tissue with immature oocytes before the regression of the ovaries for future pregnancies. In adult women with Turner syndrome, there seems to be a high prevalence of undiagnosed bone mineral density, lipid, and thyroid abnormalities. Glucose intolerance diminished first-phase insulin response, elevated blood pressure, and lowered fat-free mass are common. Glucose tolerance worsens, but fat-free mass and blood pressure and general physical fitness improve with sex hormone replacement. The neurocognitive profile of adult women is unaffected by estrogen status.

XX GONADAL DYSGENESIS

Some phenotypically and genetically normal females have gonadal lesions identical to those in 45,X patients but without somatic features of Turner syndrome; their condition is termed **pure gonadal dysgenesis** or pure **ovarian dysgenesis**.

The disorder is rarely recognized in prepubertal children because the external genitals are normal, no other abnormalities are visible, and growth is normal. At pubertal age, sexual maturation fails to take place. Plasma gonadotropin levels are elevated. Delay of epiphyseal fusion may result in a *eunuchoid* habitus. Pelvic ultrasonography reveals streak ovaries.

Affected siblings, parental consanguinity, and failure to uncover mosaicism suggest female-limited autosomal recessive inheritance. The disorder appears to be especially frequent in Finland (1 in 8,300 liveborn females). In this population, several pathogenic variants in the FSH receptor gene (on chromosome 2p) are demonstrated as the cause of the condition. In contrast, FSH receptor gene variants are not detected in Mexican women with 46,XX gonadal dysgenesis. In some patients, XX gonadal dysgenesis has been associated with sensorineural deafness (**Perrault syndrome**). A patient with this condition and concomitant growth hormone deficiency and virilization has also been reported. There may be distinct genetic forms of this disorder. **Müllerian agenesis**, or **Mayer-Rokitansky-Küster-Hauser** syndrome, which is second to gonadal dysgenesis as the most common cause of primary amenorrhea, occurring in 1 in 4,000-5,000 females, has been reported in association with 46,XX gonadal dysgenesis in a 17-year-old adolescent with primary amenorrhea and lack of breast development. One case of dysgerminoma with syncytiotrophoblastic giant cells was reported. An 18-year-old woman with primary amenorrhea and an absence of müllerian-derived structures, unilateral renal agenesis, and clinical signs of androgen excess—a phenotype resembling Mayer-Rokitansky-Küster-Hauser syndrome—was found to have a loss-of-function variant in *WNT4*. Treatment consists of estrogen replacement therapy.

45,X/46,XY GONADAL DYSGENESIS

45,X/46,XY gonadal dysgenesis, also called **mixed gonadal dysgenesis**, has extreme postnatal phenotypic variability that may extend from a Turner-like syndrome to a male phenotype with a penile urethra; it is possible to delineate three major clinical phenotypes. Short stature is a major finding in all affected children. Ninety percent of prenatally diagnosed cases have a normal male phenotype.

Some patients have no evidence of virilization; they have a female phenotype and often have the somatic signs of Turner syndrome. The condition is discovered prepubertally when chromosomal studies are made in short females or later when chromosomal studies are made because of failure of sexual maturation. Fallopian tubes and uterus are present. The gonads consist of intraabdominal undifferentiated streaks; chromosomal study of the streak often reveals an XY cell line. The streak gonad differs somewhat from that in females with Turner syndrome; in addition to wavy connective tissue, there are often tubular or cordlike structures, occasional clumps of granulosa cells, and, frequently, mesonephric or hilar cells.

Some children have mild virilization manifested only by prepubertal clitoromegaly. Normal müllerian structures are present, but at puberty virilization occurs. These patients usually have an intraabdominal testis, a contralateral streak gonad, and bilateral fallopian tubes.

Many 45,X/46,XY children present with frank ambiguity of the genitals in infancy (Fig. 626.2). A testis and vas deferens are found on one side in the labioscrotal fold, and a streak gonad is identified on the contralateral side. Despite the presence of a testis, fallopian tubes are often present bilaterally. An infantile or rudimentary uterus is often present.

Other genotypes and phenotypes have been described in mixed gonadal dysgenesis. Approximately 25% of 200 analyzed patients have a dicentric Y chromosome (45,X/46,X,dic Y). In some patients the Y chromosome may be represented by only a fragment (45,X/45,X +fra); application of Y-specific probes can establish the origin of the fragment. It is unclear why the same genotype (45,X/46,XY) can result in



Fig. 626.2 A 45,X/46XY neonate with sex chromosome disorder of sex development was noted at birth to have male-appearing external genitalia with a phallus measured at 2.5 × 1.2 cm and penoscrotal hypospadias. The left gonad was palpable in an incompletely fused scrotum, whereas the right gonad was not palpable. Gonadal biopsy revealed a testis on the left side and streak gonad on the right. The diagnosis was mixed gonadal dysgenesis. *(From Remeithi SA, Wherret DK. Disorders of sexual development. In: Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff and Martin's Neonatal-Perinatal Medicine, 10th ed. Philadelphia: Elsevier; 2015: Fig. 98–13)*

diverse phenotypes. Pathogenic variants in *SRY* have been described in some patients.

Children with a female phenotype present no problem in gender of rearing. Patients who are only slightly virilized are usually assigned a female gender of rearing before a diagnosis is established. Patients with ambiguity of the genitals are often clinically indistinguishable from patients with various types of 46,XY disorders of sex development (46,XY DSD). In some instances, there may need to be careful consideration regarding gender of rearing. Factors that may influence this decision include short stature, the need for surgical genital reconstruction, the presence of müllerian structures, and the need for gonadectomy because of predisposition of the gonad to the development of malignancy. In some patients followed to adulthood, the putative normal testis proves to be dysgenetic with eventual loss of Leydig and Sertoli cell function (see Chapter 623). In an analysis of 22 patients with mixed gonadal dysgenesis, no significant associations or correlations were found between internal and external phenotypes or endocrine function and gonadal morphologic features. The appearance of the external genitalia determined the gender of rearing. In 11 patients, basal and human chorionic gonadotropin–stimulated testosterone levels were lower than in control subjects.

Gonadal tumors, usually **gonadoblastomas**, occur in approximately 25% of these children. A gonadoblastoma locus has been localized to a region near the centromere of the Y chromosome (GBY). These germ cell tumors are preceded by the changes of carcinoma in situ. Accordingly, both gonads should be removed in all patients reared as females, and the undifferentiated gonad should be removed in the patients reared as males.

There is no correlation among the proportion of 45,X/46,XY cell lines in either blood or fibroblasts with the phenotype. In the past, all patients came to clinical attention because of their abnormal phenotypes. However, 45,X/46,XY mosaicism is found in approximately 7% of fetuses, with true chromosome mosaicism encountered prenatally. Of 76 infants with 45,X/46,XY mosaicism diagnosed prenatally, 72 had a normal male phenotype, 1 had a female phenotype, and only 3 males had hypospadias. Of 12 males whose gonads were examined, only 3 were abnormal. These data must be considered when counseling a family in which a 45,X/46,XY infant is discovered prenatally.

XXX, XXXX, AND XXXXX FEMALES

XXX Females

The 47,XXX (trisomy) chromosomal constitution is the most frequent extra X chromosome abnormality in females, occurring in almost 1 in 1,000 liveborn females. In 68%, this condition is caused by maternal meiotic nondisjunction, but paternal sex chromosome errors cause most 45,X and half of 47,XXY constitutions. The phenotype is that of a normal female; affected infants and children are not recognized based on the genital appearance.

Sexual development and menarche are normal. Most pregnancies have resulted in normal infants. By 2 years of age, delays in speech and language become evident, and some see a lack of coordination, poor academic performance, and immature behavior. These females tend to be tall, manifest behavior disorders, and often require special education classes. Using high-resolution MRI, 47,XXX subjects have lower amygdala volumes than euploid controls; 47,XXY subjects had even lower amygdala volumes. In a review of 155 females, 62% were physically normal. There is marked variability within the syndrome, and a small proportion of affected females are well coordinated, socially outgoing, and academically superior.

XXXX and XXXXX Females

The great majority of females with these rare karyotypes have intellectual disabilities. Commonly associated defects are epicanthal folds, hypertelorism, clinodactyly, transverse palmar creases, radioulnar synostosis, and congenital heart disease. Sexual maturation is often incomplete and may not occur at all. Nevertheless, three women with tetra-X syndrome gave birth, but no pregnancies were reported in 49,XXXXX women. Most 48,XXXX women tend to be tall, with an average height of 169 cm, whereas short stature is a common feature of the 49,XXXXX phenotype.

NOONAN SYNDROME

Females with Noonan syndrome show certain anomalies also seen in females with 45,X Turner syndrome, but they have normal 46,XX chromosomes (see Chapter 101.1). The most common abnormalities are the same as those described for males with Noonan syndrome (see Chapter 623). Short stature is one of the cardinal signs of this syndrome. The phenotype differs from Turner syndrome in several respects. Cognitive impairment is often present, the cardiac defect is most often pulmonary valvular stenosis or an atrial septal defect rather than an aortic defect, normal sexual maturation usually occurs but is delayed by 2 years on average, and POF has been reported. The FDA approves growth hormone therapy for use in Noonan syndrome patients with short stature.

OTHER OVARIAN DEFECTS

Some young women with no chromosomal abnormalities are found to have streak gonads that may contain only occasional or no germ cells. Gonadotropins are increased. Cytotoxic drugs, especially alkylating agents such as cyclophosphamide and busulfan, procarbazine, etoposide, and exposure of the ovaries to irradiation for the treatment of malignancy are frequent causes of ovarian failure. Young women with Hodgkin disease demonstrate that combination chemotherapy and pelvic irradiation may be more deleterious than either therapy alone. Teenagers are more likely than older women to retain or recover ovarian function after irradiation or combined chemotherapy; normal pregnancies have occurred after such treatment. Treatment regimens may result in some ovarian damage in most females treated for cancer. The median lethal dose for the human oocyte is estimated to be approximately 4 Gy; doses as low as 6 Gy have produced primary amenorrhea. Ovarian transposition before abdominal and pelvic irradiation

in childhood can preserve ovarian function by decreasing the ovarian exposure to less than 4-7 Gy.

Autoimmune ovarian failure occurs in 60% of children older than 13 years of age with type I autoimmune polyendocrinopathy (Addison disease, hypoparathyroidism, mucocutaneous candidiasis). This condition, also known as *polyglandular autoimmune disease type 1,* is rare worldwide but not in Finland, where, as a result of a founder gene effect, it occurs in 1 in 25,000 people. Affected females may not develop sexually; secondary amenorrhea may occur in young women. The ovaries may have lymphocytic infiltration or appear simply as streaks. Most affected patients have circulating steroid cell antibodies and autoantibodies to 21-hydroxylase. Among patients with polyglandular autoimmune syndromes, 5% have hypogonadism.

The condition also occurs in young women as an isolated event or in association with other autoimmune disorders, leading to secondary amenorrhea (POF). It occurs in 0.2–0.9% of women younger than 40 years of age. POF is a heterogeneous disorder with many causes: chromosomal, genetic, enzymatic, infectious, and iatrogenic. When associated with autoimmune adrenal disease, steroid cell autoantibodies are usually present. These antibodies react with P450scc, 17α-OH, or 21-OH enzymes. Steroid cell autoantibodies are rarely found when associated with an entire host of endocrine and nonendocrine autoimmune diseases and not adrenal autoimmunity. A second autoimmune disorder, often subclinical, is found in 10–39% of adult patients with POF, including autoimmune thyroid disease, type 1 diabetes, systemic lupus erythematosus (SLE), inflammatory bowel disease, immune thrombocytopenia or hemolytic anemia, celiac disease, myasthenia gravis, and rheumatoid arthritis. One 17-year-old with idiopathic thrombocytopenic purpura and 47,XXX chromosomes had autoimmune POF. Patients with POF do not have the neurocognitive defects found in Turner syndrome patients.

Galactosemia, particularly the classical form of the disease, usually results in ovarian damage, beginning during intrauterine life. Levels of FSH and luteinizing hormone (LH) are elevated early in life. Ovarian damage may be caused by deficient uridine diphosphate-galactose (see Chapter 107.2). **Denys-Drash syndrome** caused by a *WT1* pathogenic variant can result in ovarian dysgenesis.

Ataxia-telangiectasia may be associated with ovarian hypoplasia and elevated gonadotropins; the cause is unknown. Gonadoblastomas and dysgerminomas have occurred in a few females.

Hypergonadotropic hypogonadism occurs as a result of resistance of the ovary to both endogenous and exogenous gonadotropins **(Savage syndrome)**. This condition also occurs in women with POF. Antiovarian antibodies or FSH receptor abnormalities may cause this condition. The FSH receptor gene variants have been reported as an autosomal recessive condition (see Chapter 622). A few females with 46,XX chromosomes presenting in primary amenorrhea with elevated gonadotropin levels were found to have inactivating variants of the LH receptor gene. This suggests that LH action is needed for normal follicular development and ovulation. Other genetic defects associated with ovarian failure include pathogenic variants in *SF-1, FOXL2, GNAS, CYP17,* and *CYP19.*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

626.2 Hypogonadotropic Hypogonadism in the Female (Secondary Hypogonadism)

Alvina R. Kansra and Patricia A. Donohoue

Hypofunction of the ovaries can result from failure to secrete normal pulses of the gonadotropins LH and FSH. Hypogonadotropic hypogonadism (HH) may occur if the hypothalamic-pituitary-gonadal axis is interrupted either at the hypothalamic or pituitary level. The mechanisms that result in HH include failure of the hypothalamic LH–releasing hormone (also known as *gonadotropin-releasing hormone*) pulse generator or inability of the pituitary to respond with secretion of LH and FSH. It is often difficult to distinguish between marked constitutional delay and HH.

HYPOPITUITARISM

Hypogonadotropic hypogonadism is most commonly seen with multiple pituitary hormone deficiencies resulting from malformations (e.g., septo-optic dysplasia, other midline defects), pituitary transcription factor defects such as in PROP-1, or lesions of the pituitary that are acquired postnatally. Familial isolated gonadotropin deficiency associated with anosmia (Kallmann syndrome) may occur in females. Many other genetic causes for HH have been identified. A gene important in LH-releasing hormone secretion is named *KISS* (encoding the protein kisspeptin), which is suggested to play a significant role in the development of the LH-releasing hormone–secreting cells. Another set of genes implicated in HH are the genes for neurokinin B *(TAC3)* and its receptor *(TAC3R).*

In children with idiopathic hypopituitarism, the defect is usually found in the hypothalamus. In these patients, administration of gonadotropin-releasing hormone results in increased plasma levels of FSH and LH, establishing the integrity of the pituitary gland.

Hypogonadotropic hypogonadism is less common than hypergonadotropic hypogonadism. Ovarian function may be abnormal when associated with LH excess, a condition known as *polycystic ovarian syndrome* (polycystic ovary syndrome; see Chapter 589).

Isolated Deficiency of Gonadotropins

This heterogeneous group of disorders is evaluated more fully with the use of the gonadotropin-releasing hormone analog stimulation test rather than a single measurement of gonadotropin levels. In most children the pituitary gland is normal, and the defect causing gonadotropin deficiency resides in the hypothalamus. Patients with **hyperprolactinemia**, most often caused by a pituitary prolactin-secreting adenoma, often have suppression of gonadotropin secretion. If breast development has occurred, then galactorrhea and amenorrhea are frequently seen.

Several sporadic instances of anosmia with hypogonadotropic hypogonadism have been reported. **Anosmic** hypogonadal females have also been reported in kindreds with Kallmann syndrome, but hypogonadism more frequently affects the males in these families. Pathogenic variants in the gene for the β-subunit of FSH and LH have been reported.

Some autosomal recessive disorders, such as Laurence-Moon-Biedl, multiple lentigines, and Carpenter syndromes, appear in some instances to include gonadotropic hormone deficiency. Patients with Prader-Willi syndrome usually have some degree of HH. Females with severe thalassemia may have gonadotropin deficiency from pituitary damage caused by chronic iron overload secondary to multiple transfusions. Anorexia nervosa frequently results in HH. The rare patients described with leptin deficiency or leptin receptor defects have failure of pubertal maturation because of gonadotropin deficiency.

DIAGNOSIS

The diagnosis may be apparent in patients with other deficiencies of pituitary tropic hormones, but, as in males, it is difficult to differentiate isolated hypogonadotropic hypogonadism from physiologic delay of puberty. Repeated measurements of FSH and LH, particularly during sleep, may reveal the rising levels that herald the onset of puberty. Stimulation testing with gonadotropin-releasing hormone analog may help to establish the diagnosis. Morbidity for both men and women with hypogonadism includes infertility and an increased risk of osteoporosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 627

Pseudoprecocity Resulting from Lesions of the Ovary

Alvina R. Kansra and Patricia A. Donohoue

Females with signs of early puberty may, in rare circumstances, have ovarian tumors or cysts that secrete estrogenic, androgenic, or both types of hormones. In these patients, the sex steroid production is not mediated by pituitary gonadotropin secretion; they produce pseudoprecocity.

Ovarian tumors are rare in the pediatric population, occurring at a rate of fewer than 3 in 100,000. Most ovarian masses are benign, but 10–30% may be malignant. If they occur before 8 years of age, they may cause signs of puberty. Ovarian malignancies, the most common genital neoplasms in adolescence, account for only 1% of childhood cancers. More than 60% are germ cell tumors, which are dysgerminomas that can secrete tumor markers and sex hormones (see Chapter 552). Five to 10% of germ cell tumors occur in phenotypic females, with abnormal gonads associated with the presence of a Y chromosome. The next most common are epithelial cell tumors (20%), and nearly 10% are sex cord/stromal tumors (granulosa, Sertoli cell, and mesenchymal tumors). Multiple tumor markers can be seen in ovarian tumors, including α-fetoprotein, human chorionic gonadotropin, carcinoembryonic antigen, oncoproteins, p105, p53, *KRAS* pathogenic variants, cyclin D_1, epidermal growth factor–related proteins and receptors, cathepsin B, and others. Variable levels of inhibin-activin subunit gene expression have been detected in ovarian tumors.

Functioning lesions of the ovary consist of benign cysts or malignant tumors. The majority synthesize estrogens; a few synthesize androgens. The most common estrogen-producing ovarian tumor causing precocious puberty is the granulosa cell tumor. Other tumors that can cause precocious puberty are thecomas, luteomas, mixed types, theca-lutein, follicular cysts, and other ovarian tumors (i.e., teratoma, choriocarcinoma, and dysgerminoma).

ESTROGENIC LESIONS OF THE OVARY

These lesions cause **isosexual** precocious sexual development but account for only a small percentage of all cases of precocity. Benign ovarian follicular cysts are the most common tumors associated with isosexual precocious puberty in females; they may rarely be gonadotropin dependent. Gonadotropin-independent follicular cysts that produce estrogen are often associated with **McCune-Albright syndrome**.

Juvenile Granulosa Cell Tumor

In childhood, the most common neoplasm of the ovary with estrogenic manifestations is the granulosa cell tumor, although it makes up only 1–10% of all ovarian tumors. These tumors have distinctive histologic features that differ from those encountered in older females (adult granulosa cell tumor). The cells have high mitotic activity, follicles are often irregular, Call-Exner bodies are rare, and luteinization is frequent. The tumor may be solid or cystic or both. It usually is benign. This tumor has been associated with multiple enchondromas **(Ollier disease)** and with multiple subcutaneous hemangiomas **(Maffucci syndrome)**.

Clinical Manifestations and Diagnosis

The juvenile granulosa cell tumor has been observed in newborns and may manifest with sexual precocity at 2 years of age or younger; about half these tumors occurred before 10 years of age. The mean age at diagnosis is 7.5 years. The tumors are almost always unilateral. The breasts become enlarged, rounded, and firm, and the nipples prominent. The external genitals resemble those of a normal girl at puberty, and the uterus is enlarged. A white vaginal discharge is followed by irregular or cyclic menstruation. However, ovulation does not occur. The presenting manifestation may be abdominal pain or swelling. Pubic hair is usually absent unless there is mild virilization.

A mass is readily palpable in the lower portion of the abdomen in most children by the time sexual precocity is evident. However, the tumor may be small and escape detection even on careful rectal and abdominal examination; ultrasonography may detect the tumors, but CT or MRI scans are most sensitive. Most tumors are diagnosed at very early stages of malignancy.

Plasma estradiol levels are markedly elevated. Plasma levels of gonadotropins are suppressed and do not respond to gonadotropin-releasing hormone analog stimulation. Levels of antimüllerian hormone, inhibin B, and α-fetoprotein may be elevated. Activating pathogenic variants of $G_S\alpha$ are seen in 30%, and GATA-4 expression is retained in the more aggressive tumors, whereas antimüllerian hormone levels are inversely proportional to tumor size. Bone age is moderately advanced. Several case reports showing the association of 45,X/46,XY karyotype and ambiguous genitalia with ovarian granulosa tumor have been published.

Treatment and Prognosis

The tumor should be removed as soon as the diagnosis is established. Prognosis is excellent because less than 5% of these tumors in children are malignant. However, advanced-stage tumors behave aggressively and require difficult decisions regarding surgical approaches and the use of irradiation and chemotherapy. In adults with granulosa cell tumors, p53 expression is associated with unfavorable prognosis. Vaginal bleeding immediately after removal of the tumor is common. Signs of precocious puberty abate and may disappear within a few months after the operation. The secretion of estrogens returns to normal.

Sex cord tumor with annular tubules is a distinctive tumor, thought to arise from granulosa cells, that occurs primarily in patients with **Peutz-Jeghers syndrome**. These tumors are multifocal, bilateral, and usually benign. The presence of calcifications aids ultrasonographic detection. Increased aromatase production by these tumors results in gonadotropin-independent precocious puberty. Inhibin A and B levels are elevated and decrease after tumor removal. In one study, 9 of 13 sex cord/stromal tumors exhibited follicle-stimulating hormone receptor pathogenic variants, suggesting a role for such mutation in the development of these tumors.

Chorioepithelioma has been reported only rarely. This highly malignant tumor is thought to arise from a preexisting teratoma. The usually unilateral tumor produces large amounts of human chorionic gonadotropin, which stimulates the contralateral ovary to secrete estrogen. Elevated levels of human chorionic gonadotropin are diagnostic.

Follicular Cyst

Small ovarian cysts (<0.7 cm in diameter) are common in prepubertal children. At puberty and in females with true isosexual precocious puberty, larger cysts (1-6 cm) are often seen; these are secondary to stimulation by gonadotropins. Similar larger cysts occur occasionally in young females with precocious puberty in the absence of luteinizing hormone and follicle-stimulating hormone. Surgical removal or spontaneous involution of these cysts results in regression of pubertal changes. The mechanism of production of these autonomously functioning cysts is unknown. Such cysts may form only once, or they may disappear and recur, resulting in waxing and waning of the signs of precocious puberty. They may be unilateral or bilateral. The sexual precocity that occurs in young females

with **McCune-Albright syndrome** is usually associated with autonomous follicular cysts caused by somatic-activating pathogenic variants of the $G_S\alpha$-protein occurring early in development (see Chapter 600.6). Gonadotropins are suppressed, and estradiol levels are often markedly elevated, but they may fluctuate widely and even temporarily may return to normal. Gonadotropin-releasing hormone analog stimulation fails to evoke an increase in gonadotropins. Ultrasonography is the method of choice for the detection and monitoring of such cysts. Aromatase inhibitors are shown to be the mainstay of therapy in females with McCune-Albright syndrome and persistent estradiol elevation. Estrogen receptor blockers have also been used. A short period of observation to ascertain the lack of spontaneous resolution is advisable before cyst aspiration or cystectomy is considered. Cystic neoplasms must be considered in the differential diagnosis.

ANDROGENIC LESIONS OF THE OVARY

Virilizing ovarian tumors are rare at all ages but particularly so in prepubertal females. **Arrhenoblastoma** has been reported as early as 14 days of age, but few cases have been reported in females younger than 16 years of age.

The **gonadoblastoma** occurs exclusively in dysgenetic gonads, particularly in phenotypic females who have a Y chromosome or a Y fragment in their genotype (46,XY; 45,X/46,XY; 45,X/46,X-fra). There is a gonadoblastoma locus on the Y chromosome (GBY). The tumors may be bilateral. Virilization occurs with some, but not all, tumors. The clinical features are the same as those seen in patients with virilizing adrenal tumors and include accelerated growth, acne, clitoral enlargement, and growth of sexual hair. A palpable, abdominal mass is found in about 50% of patients. Plasma levels of testosterone and androstenedione are elevated, and gonadotropins are suppressed. Ultrasonography, CT, and MRI usually localize the lesion. The dysgenetic gonad of phenotypic females with a Y chromosome or fragment of Y chromosome containing GBY should be removed prophylactically. *When a unilateral tumor is removed, the contralateral dysgenetic gonad should also be removed.* Association of gonadoblastoma and WAGR (Wilms tumor, aniridia, genitourinary anomalies, mental retardation) syndrome is also reported. In an immunohistochemical study of two gonadoblastomas, expressions of *WT1, p53,* and *MIS*, as well as inhibin, were all demonstrated.

Virilizing manifestations occur occasionally in females with **juvenile granulosa cell tumors**. Adrenal rests and hilum cell tumors rarely lead to virilization. Activating pathogenic variants of G protein genes have been described in ovarian (and testicular) tumors. $G_S\alpha$ variants, usually seen in gonadal tumors associated with **McCune-Albright syndrome**, were also noted in four of six Leydig cell tumors (three ovarian, one testicular). Two granulosa cell tumors and 1 thecoma of 10 ovarian tumors studied were found to have *GIP-2* variants.

Sertoli-Leydig cell tumors, rare sex cord/stromal neoplasms, constitute less than 1% of ovarian tumors. The average age at diagnosis is 25 years; less than 5% of these tumors occur before puberty. α-Fetoprotein levels may be mildly elevated. In one 12-month-old with Sertoli-Leydig cell tumor presenting with isosexual precocity, the only detectable tumor marker was the serum inhibin level, with elevations in both A and B subunits. Five-year survival rates are 70–90%.

Of 102 consecutive patients who underwent surgery because of ovarian masses over a 15-year period, the presenting symptoms were acute abdominal pain in 56% and abdominal or pelvic mass in 22%. Of nine children whose cause for surgery was presumed malignancy, three had dysgerminomas, two had teratomas, two had juvenile granulosa cell tumors, one had a Sertoli-Leydig cell tumor, and one had a yolk sac tumor.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 628

Disorders of Sex Development

Patricia A. Donohoue

SEX DIFFERENTIATION

See also Chapter 622.

Differentiation and development of the gonads and genitalia are largely complete in the first half of gestation. In normal differentiation, the final form of all sexual structures is consistent with normal sex chromosomes (either XX or XY). A 46,XX complement of chromosomes, as well a genetic factors such as DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), the signaling molecule WNT-4, and R-Spondin1, are among the many needed for the development of normal ovaries. Development of the male phenotype is potentially more complex. It requires a Y chromosome and, specifically, an intact *SRY* (sex-determining region on the Y chromosome) gene, which, in association with genes such as *SOX9, SF-1* (steroidogenic factor-1), *WT1* (Wilms tumor 1), and others (see Chapter 622), directs the undifferentiated gonad to become a testis. Aberrant recombinations may result in X chromosomes carrying *SRY,* resulting in XX males, or Y chromosomes that have lost *SRY,* resulting in XY females.

Antimüllerian hormone (AMH) causes the müllerian (paramesonephric) ducts to regress; in its absence, they persist as the uterus, fallopian tubes, cervix, and upper vagina. AMH activation in the testes probably requires the *SF-1* gene. By about 8 weeks of gestation, the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG), which peaks at 8-12 weeks. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. Testosterone produced locally initiates development of the ipsilateral wolffian (mesonephric) duct into the epididymis, vas deferens, and seminal vesicle. Complete development of the external genitalia also requires dihydrotestosterone (DHT), the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary to fuse the genital folds to form the penis and scrotum. DHT is produced from testosterone via the action of the enzyme 5α-reductase. DHT is also produced through an alternative biosynthetic pathway from androstanediol, and this pathway must be intact for normal and complete prenatal virilization to occur. Figure 628.1 illustrates the production of steroid hormones in various glands and the integrated pathways to the synthesis of DHT. A functional androgen receptor, produced by an X-linked gene, is required for testosterone and DHT to induce these androgen effects.

In the XX fetus with normal long and short arms of the X chromosome, the bipotential gonad develops into an ovary by about the 10th to 11th week. This occurs only in the absence of SRY, testosterone, and AMH and requires a normal gene in the dosage-sensitive/sex-reversal locus *DAX1,* the WNT-4 molecule, and R-Spondin1. A female external phenotype develops in the absence of fetal gonads. However, the male phenotype development requires androgen production and action. Estrogen is unnecessary for normal prenatal sexual differentiation, as demonstrated by 46,XX patients with aromatase deficiency.

Chromosomal aberrations may result in ambiguity of the external genitalia. Conditions of aberrant sex differentiation may also occur with the XX or XY genotype. The appropriate term for what was previously called *intersex* is **disorders of sex development (DSD)**. This term defines a condition "in which development of chromosomal, gonadal, or anatomic sex is atypical." It is increasingly preferable to use the term *atypical genitalia* rather than *ambiguous genitalia.* Tables 628.1 and 628.2 compare previous

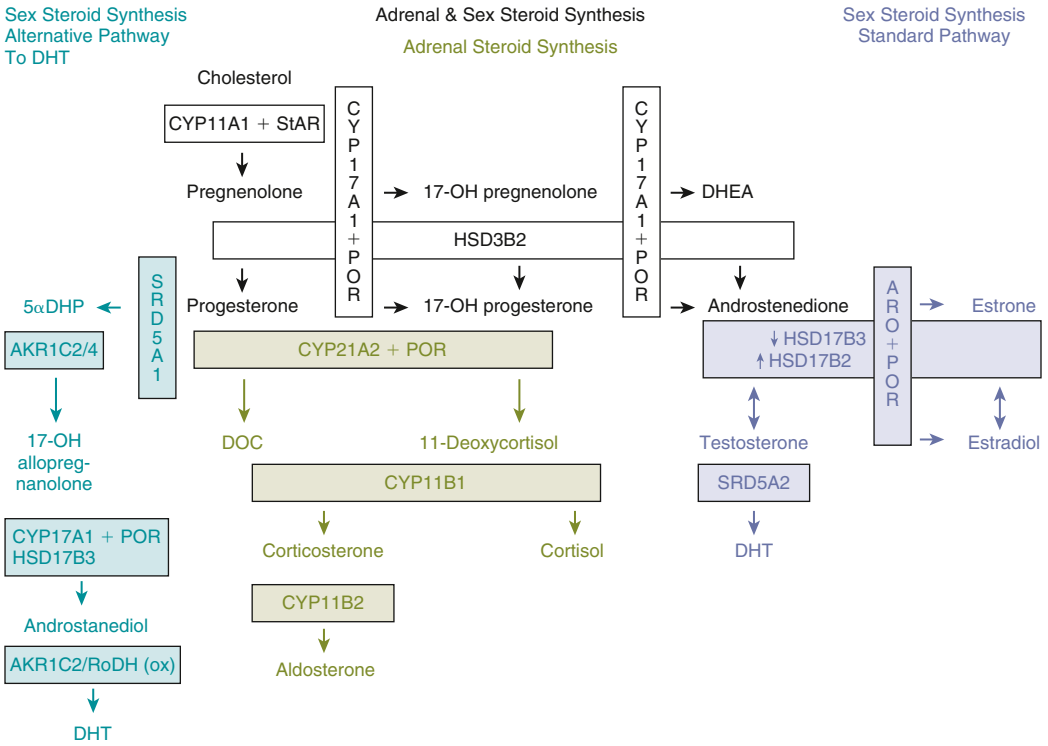

Fig. 628.1 Steroidogenic pathways enzyme names and activities. CYP11A1: cholesterol side-chain cleavage. Enzyme activities include 20-hydroxylase, 22-hydroxylase, and 20,22-lyase. CYP17A1: activities include 17α-hydroxylase and 17,20-lyase. 3βHSD2 (HSD3B2): activities include 3β-hydroxysteroid dehydrogenase (type 2) and D5D4-isomerase. CYP21A2: activity is 21-hydroxylase. CYP11B1: activity is 11β-hydroxylase. CYP11B2: activities include 18-hydroxylase (CMOI) and 18-dehydrogenase (CMOII). SRD5A1: activity is 5α-reductase type 1. SRD5A2: activity is 5α-reductase type 2. HSD17B2: activity is 17β-hydroxysteroid dehydrogenase type 2. HSD17B3: activity is 17β-hydroxysteroid dehydrogenase type 3. AKR1C2/4: activities are 3α-reductase types 1 and 3. AKR1C2/RoDH (ox): activities are 3α-reductase and 3-hydroxyepimerase. ARO, aromatase; CMOI, corticosterone methyl oxidase type 1; CMOII, corticosterone methyl oxidase type 2; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; 5αDH*P*, 5α dihydroprogesterone. *(Adapted from Kim MS, Donohoue PA. Adrenal disorders. In Kappy MS, Allen DB, Geffner ME, eds. Pediatric Practice Endocrinology, 2nd ed. New York: McGraw Hill, 2014; and Flück CE, Meyer-Böni M, Pandey AV, et al. Why boys will be boys: two pathways of fetal testicular androgen biosynthesis are needed for male sexual differentiation. Am J Hum Genet. 2011;89:201–218.)*

Table 628.1 Revised Nomenclature

PREVIOUS	CURRENTLY ACCEPTED
Intersex	Disorders of sex development (DSDs)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

From Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics*. 2006;118:e488–e500. Table 1.

terms with their revised etiologic classification nomenclature. Table 622.1 in Chapter 622 lists some of the many genes that may be abnormal in various forms of DSD. Gender fluidity (nonconformity) has become a socially and, in New York State, legally accepted concept and is often expressed by self-identified people as intersex. New York State has an intersex category on its birth certificate. Partial androgen insensitivity, 5α-reductase deficiency, and mixed gonadal dysgenesis are often associated with gender dissatisfaction, and an intersex designation may help with future self-identification once the child is mature.

The definition of atypical or ambiguous genitalia, in a broad sense, is any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations in size of these structures do not always constitute ambiguity.

Development of the external genitalia begins with the potential to be either male or female (Fig. 628.2). Virilization of a female, the most common form of DSD, results in varying phenotypes (Fig. 628.3) that develop from the basic bipotential genital appearances of the embryo (see Fig. 628.2).

DIAGNOSTIC APPROACH TO THE PATIENT WITH ATYPICAL OR AMBIGUOUS GENITALIA

The appearance of the external genitalia is rarely diagnostic of a particular disorder and thus does not often allow distinction among the various forms of DSD. The most common forms of 46,XX DSD are *virilizing forms of congenital adrenal hyperplasia*. It is important to note that in 46,XY DSD, the specific diagnosis is not found in up to 50% of cases; partial androgen insensitivity syndrome (PAIS) and

Table 628.2 Etiologic Classification of Disorders of Sex Development

46,XX DSD
Androgen Exposure
Fetal/fetoplacental source
21-Hydroxylase (P450c21 or CYP21) deficiency
11β-Hydroxylase (P450c11 or CYP11B1) deficiency
3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency
Cytochrome P450 oxidoreductase (POR deficiency)
Aromatase (P450arom or CYP19) deficiency
Glucocorticoid receptor gene pathogenic variant
Maternal source
Virilizing ovarian tumor
Virilizing adrenal tumor
Androgenic drugs
Disorder of Ovarian Development
XX gonadal dysgenesis
Testicular DSD (SRY+, SOX9 duplication)
Undetermined Origin
Associated with genitourinary and gastrointestinal tract defects
46,XY DSD
Defects in Testicular Development
Denys-Drash syndrome (pathogenic variant in *WT1*)
WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation)
Deletion of 11p13
Campomelic syndrome (autosomal gene at 17q24.3-q25.1) and SOX9 pathogenic variant
XY pure gonadal dysgenesis (Swyer syndrome)
Pathogenic variant in SRY
XY gonadal agenesis
Unknown cause
Deficiency of Testicular Hormones
Leydig cell aplasia
Pathogenic variant in LH receptor
Lipoid adrenal hyperplasia (P450scc or CYP11A1) deficiency; pathogenic variant in StAR (steroidogenic acute regulatory protein)
3β-HSD II deficiency
17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency
Persistent müllerian duct syndrome because of antimüllerian hormone gene variants or receptor defects for antimüllerian hormone
Defect in Androgen Action
Dihydrotestosterone deficiency because of 5α-reductase II pathogenic variants or AKR1C2/AKR1C4 variants
Androgen receptor defects:
Complete androgen insensitivity syndrome
Partial androgen insensitivity syndrome (Reifenstein and other syndromes)
Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHCR7)
OVOTESTICULAR DSD
XX
XY
XX/XY chimeras
SEX CHROMOSOME DSD
45,X (Turner syndrome and variants)
47,XXY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

DSD, Disorders of sex development.
Data from Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics.* 2006;118:e488–e500.

pure gonadal dysgenesis are common identifiable etiologies in XY DSD. At one center with a large experience, the etiologies of DSD in 250 patients older than 25 years were compiled. The six most common diagnoses accounted for 50% of the cases. These included virilizing congenital adrenal hyperplasia (14%), androgen insensitivity syndrome (AIS; 10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46,XY small-for-gestational-age males with hypospadias (6%). Potential diagnostic clues are noted in Tables 628.3 and 628.4.

The potential of not finding a diagnosis in patients with DSD and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects in each patient with genital ambiguity. The parents need counseling about the potentially complex nature of the baby's condition and guidance as to how to deal with their well-meaning but curious friends and family members. The evaluation and management should be carried out by a multidisciplinary team of experts that includes pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine, genetics, and psychology. Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical exam, the common diagnostic approach includes multiple steps, described in the following outline. These steps are usually performed simultaneously rather than waiting for results of one test before performing another, because of the sensitive and sometimes urgent nature of the condition. Careful attention to the presence of physical features other than the genitalia is crucial to determine if a diagnosis of a particular multisystem syndrome is possible (see Chapters 628.1, 628.2, and 628.3). Table 628.5 summarizes many of the features of commonly encountered causes of DSD. Exome sequencing or molecular testing using specific DSD DNA panels are quite useful in the diagnostic evaluation, especially in 46,XY DSD, and may become first-line diagnostic tests.

Diagnostic tests include the following:

1. Blood karyotype, with rapid determination of sex chromosomes (in many centers this is available within 24-48 hours)
2. Other blood tests
   a. Screen for congenital adrenal hyperplasia: cortisol biosynthetic precursors and adrenal androgens (particularly 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form). In the United States, all 50 states have a newborn screen for 21-hydroxylase deficiency.
   b. Screen for androgen biosynthetic defects with serum levels of androgens and their precursors.
   c. Assess for gonadal response to gonadotropin stimulation to screen for the presence and function of testicular gonadal tissue: obtain serum levels of testosterone and DHT before and after IM injections of hCG.
   d. Molecular genetic analyses for SRY, other Y-specific loci, and when needed, other single-gene defects associated with DSD.
   e. Gonadotropin (LH and follicle-stimulating hormone [FSH]) levels.
3. The internal anatomy of patients with ambiguous genitalia can be defined with one or more of the following studies:
   a. Voiding cystourethrogram
   b. Endoscopic examination of the genitourinary tract
   c. Pelvic ultrasound; renal and adrenal ultrasound
   d. Pelvic MRI
   e. Exploratory laparoscopy to locate and characterize/biopsy the gonads

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

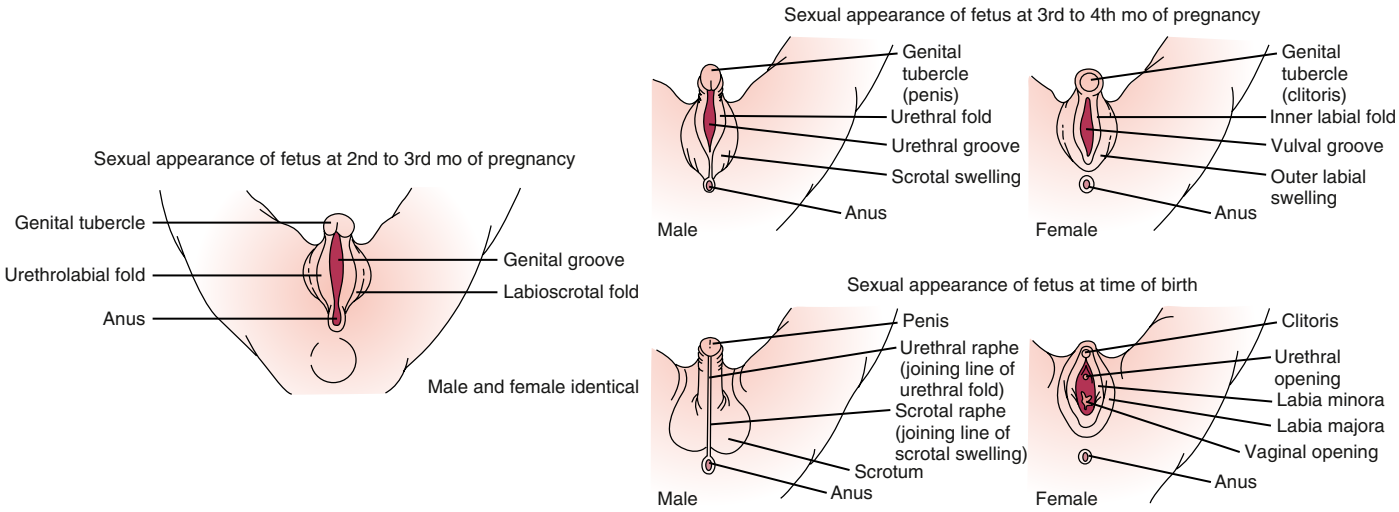

Fig. 628.2 Schematic demonstration of differentiation of normal male and female genitalia during embryogenesis. *(From Zitelli BJ, Davis HW. Atlas of Pediatric Physical Diagnosis, 4th ed. St. Louis: Mosby, 2002: p. 328.)*

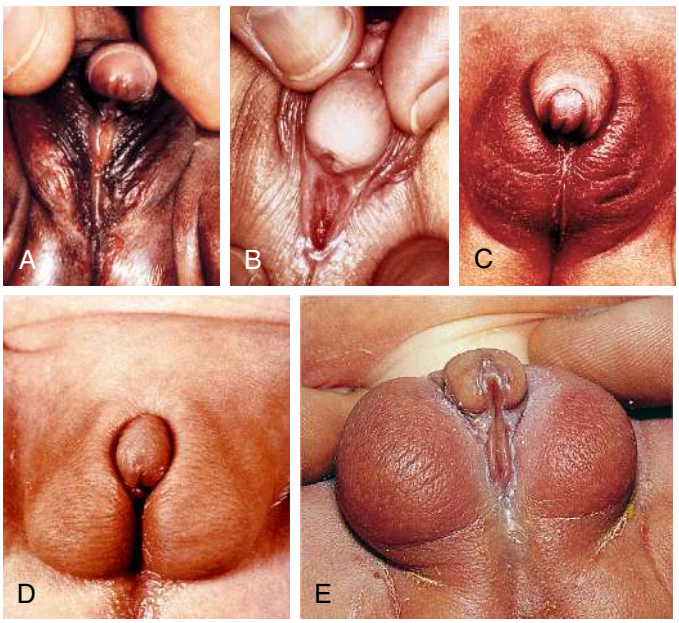

Fig. 628.3 Examples of atypical genitalia. These cases include ovotesticular disorder of sexual development **(A)** and congenital virilizing adrenal hyperplasia **(B-E)**. **(B-D,** *Courtesy D. Becker, MD, Pittsburgh. From Zitelli BJ, Davis HW. Atlas of Pediatric Physical Diagnosis, 4th ed. St. Louis: Mosby, 2002: p. 329.)*

628.1 46,XX DSD

Patricia A. Donohoue

The genotype is XX and the gonads are ovaries, but the external genitalia are virilized. There is no significant prenatal AMH production because the gonads are ovaries. Thus the uterus, fallopian tubes, and cervix develop. The varieties and causes of this condition are relatively few. Most instances result from exposure of the female fetus to excessive *exogenous* or *endogenous* androgens during intrauterine life. The changes consist principally of virilization of the external genitalia (clitoral hypertrophy and labioscrotal fusion).

CONGENITAL ADRENAL HYPERPLASIA

See Chapter 616.1.

Table 628.3 Associations of Genital Abnormalities

ABNORMAL CHARACTERISTICS	EXAMPLES OF ASSOCIATED DISORDERS
MALE-APPEARING GENITALIA	
Micropenis	Growth hormone or luteinizing hormone deficiency Testosterone deficiency (in second and third trimesters) Partial androgen insensitivity Syndrome: idiopathic
Hypospadias (more severe)	Disorders of gonadal development 46,XX DSD Ovotesticular DSD 46,XX or 46,XY DSD Syndrome: idiopathic
Impalpable gonads	Anorchia Persistent müllerian duct syndrome 46,XX DSD with 21- or 11β-hydroxylase deficiency Cryptorchidism
Small gonads	47,XXY, 46,XX DSD Dysgenetic or rudimentary testes
Inguinal mass (uterus or tube)	Persistent müllerian duct syndrome, dysgenetic testes
FEMALE-APPEARING GENITALIA	
Clitoromegaly	XX with 21- or 11β-hydroxylase or 3β-hydroxy dehydrogenase deficiency Other 46,XX DSD Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD 46,XY DSD Tumor infiltration of clitoris Syndrome: idiopathic
Posterior labial fusion	As for clitoromegaly
Palpable gonad(s)	Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD 46,XY DSD
Inguinal hernia or mass	As for palpable gonad(s)

DSD, Disorders of sex development.
From Al Remeithi S, Wherrett DK. Disorders of sex development. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine*, 10th ed. Philadelphia: Elsevier; 2015: Table 98.3.

Table 628.4 Key Points in Evaluation of Infants with Disorders of Sexual Development

Identification of syndromic features in physical exam	• Craniosynostosis and other synostosis in POR deficiency • Cleft palate and second to third toe syndactyly in Smith-Lemli-Opitz (SLO) syndrome • Pierre Robin sequence or campomelia for *SOX9* pathogenic variants • Kidney abnormalities or dysfunction in *WTI* or *WNT4* pathogenic variants • Cardiac abnormalities in Turner syndrome, mixed gonadal dysgenesis or *GATA4* pathogenic variants • Adrenal insufficiency in cases of *SLO*, *NR5A1 (SF-1)* pathogenic variants • POR deficiency or congenital adrenal hyperplasia or hypoplasia forms • Polyneuropathy in *DHH* pathogenic variants • Chondrodysplasia in *HHAT* pathogenic variants • Blepharophimosis/ptosis in *FOXL2* pathogenic variants
Evaluation of internal genitalia to conclude about exposure to AMH using pelvic ultrasound or MRI	*Normal Uterus In:* 46,XY complete gonadal dysgenesis (CGD) 46,XX CGD 46,XX with androgen exposure (i.e., virilizing forms of CAH) Turner syndrome *Abnormal Uterus In:* 46,XY PGD (partial gonadal dysgenesis) Mixed gonadal dysgenesis *Absent Uterus In:* 46,XY DSD with androgen synthesis defects and androgen action defects 46,XX testicular DSD

POR, P450 oxidoreductase; AMH, anti-Mullerian hormone; CAH, congenital adrenal hyperplasia.
Modified from Rodriguez-Buritica D. Overview of genetics of disorders of sexual development. Curr Opin Pediatr. 2015;27:675–684. Table 1.

This is the most common cause of atypical genitalia and of 46,XX DSD. Females with the 21-hydroxylase and 11-hydroxylase defects are the most highly virilized, although minimal virilization also occurs with the type II 3β-hydroxysteroid dehydrogenase defect (see Fig. 628.3). Female patients with salt-losing congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency tend to have more virilization than do patients with the non–salt-losing form. Masculinization may be so complete that a penile urethra results, and the patient may appear to be a male with bilateral cryptorchidism.

AROMATASE DEFICIENCY

In 46,XX females, the rare condition of aromatase deficiency during fetal life leads to 46,XX DSD and results in hypergonadotropic hypogonadism at puberty because of ovarian failure to synthesize estrogen.

Examples of this condition include two 46,XX infants who had enlargement of the clitoris and posterior labial fusion at birth. In one instance, maternal serum and urinary levels of estrogen were very low and serum levels of androgens were high. Cord serum levels of estrogen were also extremely low, and levels of androgen were elevated. The second patient also had virilization of unknown cause since birth, but the aromatase deficiency was not diagnosed until 14 years of age, when she had further virilization and failed to go into puberty. At that time, she had elevated levels of gonadotropins and androgens but low estrogen levels, and ultrasonography revealed large ovarian cysts bilaterally. These patients demonstrate the important role of aromatase in the conversion of androgens to estrogens. Additional female and male patients with aromatase deficiency as a consequence of pathogenic variants in the *aromatase gene (CYP19)* are known. Two siblings with this gene defect were described, both of whom had tall stature because of a lack of estrogen-mediated epiphyseal fusion. The 28-year-old XX proband was 177.6 cm tall (+2.5 SD) after having received hormonal replacement therapy. Her 24-year-old brother was 204 cm tall (+3.7 SD) and had a bone age of 14 years. Low-dose estradiol replacement, carefully adjusted to maintain normal age-appropriate levels, may be indicated for affected females, even prepubertally.

CORTISOL RESISTANCE CAUSED BY A GLUCOCORTICOID RECEPTOR GENE PATHOGENIC VARIANT

A 9-year-old female with 46,XX DSD, thought to be caused by 21-hydroxylase deficiency (CAH) since the age of 5 years, had elevated cortisol levels both at baseline and after dexamethasone, hypertension, and hypokalemia, suggestive of the diagnosis of generalized glucocorticoid resistance. A novel homozygous variant in exon 5 of the glucocorticoid receptor was demonstrated. In this Brazilian family, the condition was autosomal recessive. Virilization occurs because of excess adrenocorticotropic hormone (ACTH) stimulation of adrenal steroid production because the glucocorticoid receptor defect is also present in the pituitary gland, which senses inadequate cortisol effect to provide negative feedback.

P450 Oxidoreductase Deficiency

Cytochrome P450 oxidoreductase (POR), encoded by a gene on 7q11.2, is a cofactor required for normal enzymatic activity of the microsomal 21- and 17-hydroxylases. POR deficiency thus causes partial combined P450C17 and P450C21 steroidogenic defects. Females are born with ambiguous genitalia, but as opposed to classic CAH, the virilization does not progress postnatally and androgen levels are normal or low. Males may be born undervirilized. Both may exhibit bony abnormalities seen in **Antley-Bixler syndrome**. Conversely, in a series of Antley-Bixler syndrome patients, those with ambiguous genitalia and disordered steroidogenesis had cytochrome POR deficiency. Those without genital ambiguity with normal steroidogenesis had *FGFR2* pathogenic variants. The cardinal features of Antley-Bixler syndrome include craniosynostosis, severe midface hypoplasia, proptosis, choanal atresia/stenosis, frontal bossing, dysplastic ears, depressed nasal bridge, radiohumeral synostosis, long bone fractures and femoral bowing, and urogenital abnormalities.

VIRILIZING MATERNAL TUMORS

Rarely, the female fetus has been virilized by a *maternal* androgen-producing tumor. In a few cases, the lesion was a benign adrenal adenoma, but all others were ovarian tumors, particularly androblastomas, luteomas, and Krukenberg tumors (Table 628.6). **Maternal virilization** may be manifested by enlargement of her clitoris, acne, deepening of the voice, decreased lactation, hirsutism, and elevated levels of androgens. In the infant, there is enlargement of the clitoris of varying degrees, often with labial fusion. Mothers of children with unexplained 46,XX DSDs should undergo physical examination and measurements of their own levels of plasma testosterone, dehydroepiandrosterone (DHEA) sulfate, and androstenedione.

EXPOSURE TO ANDROGENIC DRUGS BY WOMEN DURING PREGNANCY

Testosterone and 17-methyltestosterone have been reported to cause 46,XX DSDs in some instances (see Table 628.6). The greatest number of cases has resulted from the use of certain progestational compounds

Table 628.5 Atypical Genitalia: Steps in Establishing the Diagnosis

	21-OH DEFICIENCY	GONADAL DYSGENESIS WITH Y CHROMOSOME	OVOTESTICULAR DSD	PARTIAL ANDROGEN INSENSITIVITY	BLOCK IN TESTOSTERONE SYNTHESIS
CLINICAL FEATURE					
Palpable gonad(s)	–	±	±	+	+
Uterus present*	+	+	Usually	–	–
Increased skin pigmentation	±	–	–	–	–
Sick baby	±	–	–	–	±
Dysmorphic features	–	±	–	–	–
DIAGNOSTIC CONSIDERATIONS					
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX most common	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive response	Reduced or absent
Gonadal biopsy	NA	Dysgenetic gonad	Ovotestis	Normal testis with ± Leydig cell hyperplasia	Normal testis
Other testing				Genital skin fibroblast culture AR assay, OR blood DNA screening for AR gene variants	Measure testosterone precursors

*As determined by ultrasound, MRI, or rectal examination.
AR, Androgen receptor; DSD, disorder of sex development; hCG, human chorionic gonadotropin; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NA, not applicable.
Adapted from Donohoue PA, Saenger PH. Ambiguous genitalia. In Finberg L, Kleinman RE, eds. Saunders Manual of Pediatric Practice, Philadelphia: WB Saunders, 2002: p. 874.

Table 628.6 Sources of Maternal-Derived Androgens

ENDOGENOUS
Benign
Luteoma of pregnancy
Adrenal adenoma
Hyperreactio luteinalis
Thecoma/fibroma
Stromal hyperthecosis
Brenner tumor
Serous cystadenoma
Mature cystic teratoma (dermoid cyst)
Malignant
Metastatic carcinomas (Krukenberg tumor)
Sex-cord stromal tumors—granulosa cell and Sertoli-Leydig tumors
Adrenal cortical carcinoma
Cystadenocarcinoma
Hilar cell tumor
EXOGENOUS
Synthetic Androgens
Danazol
Progestins (medroxyprogesterone acetate)
Potassium-sparing diuretics

From Auchus RJ, Chang AY. 46,XX DSD: the masculinised female. *Best Pract Res Clin Endocrinol Metab*. 2010;24:219–242. Table 2.

for the treatment of threatened abortion. These progestins have since been replaced by nonvirilizing ones.

Infants with virilization and 46,XX chromosomes and caudal anomalies have been reported for whom no virilizing agent could be identified. In such instances, the disorder is usually associated with other congenital defects, particularly of the urinary and gastrointestinal tracts. Y-specific DNA sequences, including *SRY*, are absent. In one case, a scrotal raphe and elevated testosterone levels were found, but the cause remains unknown.

SF-1 Pathogenic Variants

In a worldwide study of patients with **46,XX ovotesticular DSD**, a specific variant in *SF-1* was identified: p.Arg92Trp. Functional studies showed that the variant probably interfered with inhibition of testicular development. In one family with a maternally transmitted variant, the mother had early menopause. Multiple other *SF-1* variants have been reported to cause isolated ovarian insufficiency, some associated with 46,XY DSDs in their offspring.

46,XX Testicular DSD

In this condition, also known as **XX male**, the gonads are testicular and virilization is typically incomplete. Infertility and/or gonadal failure may develop after childhood. Many cases are caused by translocation of *SRY* sequences onto one of the X chromosomes, often paired with duplication of *SOX-9*. The appropriate sex of rearing may be difficult to determine.

46,XX Gonadal Dysgenesis

These females typically present at puberty with normal female genitalia and lack of breast development and hypergonadotropic hypogonadism. Normal müllerian structures are present, but ovaries are absent or streaked.

Undetermined/Unknown

Rarely, 46,XX DSDs can be associated with other congenital anomalies, especially those of the GU or GI tract, and are thus multifactorial in

origin. These include cloacal exstrophy and **MURCS association** (müllerian hypoplasia, renal agenesis, and cervicothoracic somite abnormalities). Isolated deficiency of müllerian development is known as **Meyer-Rokitansky-Küster-Hauser syndrome**.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

628.2 46,XY DSD

Patricia A. Donohoue

In this condition the genotype is XY but the external genitalia are either not completely virilized, are ambiguous (atypical), or are completely female. When gonads can be found, they typically contain *testicular* elements; their development ranges from rudimentary to normal. Because the process of normal virilization in the fetus is so complex, it is not surprising that there are many varieties and causes of 46,XY DSD. The etiology is not identified in up to 50% of cases.

DEFECTS IN TESTICULAR DIFFERENTIATION

The first step in male differentiation is conversion of the bipotential gonad into a testis. In the XY fetus, if there is a deletion of the short arm of the Y chromosome or of the *SRY* gene, male differentiation does not occur. The phenotype is female; müllerian (paramesonephric) ducts are well developed because of the absence of AMH, and gonads consist of undifferentiated streaks. By contrast, even extreme deletions of the long arm of the Y chromosome (Yq−) have been found in normally developed males, most of whom are azoospermic and have short stature. This indicates that the long arm of the Y chromosome normally has genes that prevent these manifestations. In many syndromes in which the testes fail to differentiate, Y chromosomes are morphologically normal on karyotyping.

Wilms Tumor-Suppressor Gene Pathogenic Variants: Denys-Drash, Frasier, and WAGR Syndromes

Denys-Drash syndrome: The constellation of nephropathy with atypical (ambiguous) genitalia and bilateral Wilms tumor is the major phenotype of this syndrome. Most reported cases have been 46,XY. Müllerian ducts are often present, indicating a global deficiency of fetal testicular function. Patients with a 46,XX karyotype have normal external genitalia. The onset of proteinuria in infancy progresses to nephrotic syndrome and end-stage renal failure by 3 years of age, with focal or diffuse mesangial sclerosis being the most consistent histopathologic finding. Wilms tumor usually develops in children younger than 2 years of age and is frequently bilateral. Gonadoblastomas have also been reported.

Several pathogenic variants in *WT1,* located on chromosome 11p13, have been found. *WT1* functions as a tumor suppressor gene and a transcription factor and is expressed in the genital ridge and fetal gonads. Nearly all reported variants are near or within the zinc finger–coding region. One report found a zinc finger domain variant in the *WT1* alleles of a patient with no GU abnormalities, suggesting that some cases of sporadic Wilms tumor may carry the *WT1* pathogenic variant.

Frasier syndrome: Different pathogenic variants in *WT1,* constitutional heterozygote variants at intron 9, have been described in Frasier syndrome, a condition of nonspecific focal and segmental glomerulosclerosis, 46,XY gonadal dysgenesis, and frequent gonadoblastoma, but *without* Wilms tumor.

WAGR syndrome: This acronym refers to a contiguous gene syndrome consisting of Wilms tumor, aniridia, GU malformations, and retardation (WAGR). These children have a deletion of one copy of chromosome 11p13, which may be visible on karyotype analysis. The deleted region encompasses the aniridia gene *(PAX6)* and the Wilms tumor suppressor gene *(WT1).* Only the 46,XY patients have genital abnormalities, ranging from cryptorchidism to severe deficiency of virilization. Gonadoblastomas have developed in the dysgenetic gonads. Wilms tumor usually occurs by 2 years of age. Some cases also had unexplained obesity, raising the question of an obesity-associated gene in this region of chromosome 11 and naming the syndrome *WAGRO.*

Campomelic Syndrome

See Chapter 735.

This form of **short-limbed skeletal dysplasia** is characterized by anterior bowing of the femur and tibia, small, bladeless scapulae, small thoracic cavities, and 11 pairs of ribs, along with malformations of other organs. It is usually lethal in early infancy. Approximately 75% of reported 46,XY patients exhibit a completely **female phenotype**; the external and internal genitalia are female. Some 46,XY patients have ambiguous genitalia. The gonads appear to be ovaries but histologically may contain elements of both ovaries and testes.

The gene responsible for the condition is *SOX9* and is on 17q24-q25. This gene is structurally related to *SRY* and directly regulates development of the type II collagen gene *(COL2A1)*. The same variants may result in different gonadal phenotypes. Gonadoblastoma was reported in a patient with this condition. The inheritance is autosomal dominant.

SF-1 (Also Known as *Ad4BP* and *NR5A1*) Defects and 46,XY DSD

Adrenal insufficiency and 46,XY gonadal dysgenesis have been described in patients with pathogenic variants in *SF-1*. In some of these patients, if the mother shares the *SF-1* variant, she has premature ovarian insufficiency. *SF-1*–related 46,XY DSD may also occur in the absence of adrenal insufficiency and may resemble PAIS.

46,XY sex reversal has also been described in patients with deletions of parts of autosomal loci on chromosomes 2q, 9p, and 10q.

XY Pure Gonadal Dysgenesis (Swyer Syndrome)

The designation *pure* distinguishes this condition from forms of gonadal dysgenesis that are of chromosomal origin and associated with somatic anomalies. Affected patients have normal stature and a female phenotype, including vagina, uterus, and fallopian tubes, but at pubertal age, breast development and menarche fail to occur. None of the other phenotypic features associated with 45,X (Turner syndrome) are present. Patients present at puberty with hypergonadotropic primary amenorrhea. Familial cases suggest an X-linked or a sex-limited dominant autosomal transmission. Most of the patients examined have had pathogenic variants in *SRY*. The gonads consist of almost totally undifferentiated streaks despite the presence of a cytogenetically normal Y chromosome. The primitive gonad cannot accomplish any testicular function, including suppression of müllerian (paramesonephric) ducts. There may be hilar cells in the gonad capable of producing some androgens; accordingly, some virilization, such as clitoral enlargement, may occur at the age of puberty. The streak gonads may undergo neoplastic changes, such as gonadoblastomas and dysgerminomas, and should be removed as soon as the diagnosis is established, regardless of the age of the patient.

Pure gonadal dysgenesis also occurs in XX individuals.

XY Gonadal Agenesis Syndrome (Embryonic Testicular Regression Syndrome)

In this rare syndrome, the external genitalia are slightly ambiguous but more nearly female. Hypoplasia of the labia; some degree of labioscrotal fusion; a small, clitoris-like phallus; and a perineal urethral opening are present. No uterus, no gonadal tissue, and usually no vagina can be found. At the age of puberty, no sexual development occurs and gonadotropin levels are elevated. Most children have been reared as females. In several patients with XY gonadal agenesis in whom no gonads could be found on exploration, significant rises in testosterone followed stimulation with hCG, indicating

Leydig cell function somewhere. Siblings with the disorder are known.

It is presumed that testicular tissue was active long enough during fetal life for AMH to inhibit development of müllerian ducts but not long enough for testosterone production to result in virilization. In one patient, no deletion of the Y chromosome was found by means of Y-specific DNA probes. Testicular degeneration seems to occur between the 8th and 12th fetal week. Regression of the testis before the 8th week of gestation results in Swyer syndrome; between the 14th and 20th weeks of gestation, it results in the rudimentary testis syndrome; and after the 20th week, it results in anorchia.

In **bilateral anorchia**, sometimes referred to as *vanishing testes syndrome,* testes are absent, but the male phenotype is complete; it is presumed that tissue with fetal testicular function was active during the critical period of genital differentiation but that sometime later it was damaged. Bilateral anorchia in identical twins and unilateral anorchia in identical twins and in siblings suggest a genetic predisposition. Coexistence of anorchia and gonadal agenesis syndrome in a sibship is evidence for a relationship between the disorders. A retrospective review of urologic explorations revealed absent testes in 21% of 691 testes. Of those, 73% had blind-ending cord structures with the suggested site of the vanishing testes being the inguinal canal (59%), abdomen (21%), superficial inguinal ring (18%), and scrotum (2%). It was suggested that the presence of cord structures on laparoscopy should prompt inguinal exploration because viable testicular tissue was found in four of these children.

DEFICIENCY OF TESTICULAR HORMONE PRODUCTION

Several genetic defects have been delineated in the enzymatic synthesis of testosterone by the fetal testis, and a defect in Leydig cell differentiation has been described. These defects produce 46,XY males with inadequate masculinization. Because levels of testosterone are normally low before puberty, an hCG stimulation test may be needed in children to assess the ability of the testes to synthesize testosterone.

Leydig Cell Aplasia

Patients with aplasia or hypoplasia of the Leydig cells usually have female phenotypes, but there may be mild virilization. Testes, epididymis, and vas deferens are present; the uterus and fallopian tubes are absent because of normal production of AMH. There is no breast development at puberty, but pubic hair development may be normal because of the production of adrenal androgens. Plasma levels of testosterone are low and do not respond to hCG; LH levels are elevated. The Leydig cells of the testes are absent or markedly deficient. The defect may involve a lack of functional receptors for LH. In children, hCG stimulation is necessary to differentiate the condition from the AISs. There is male-limited autosomal recessive inheritance. The human LH/chorionic gonadotropin (CG) receptor is a member of the G-protein–coupled superfamily of receptors that contains seven transmembrane domains. Several inactivating pathogenic variants of the LH/CG receptor have been described in males with hypogonadism suspected of having Leydig cell hypoplasia or aplasia.

High serum LH and low FSH were noted in one male with hypogonadism owing to a pathogenic variant in the gene for the β-subunit of FSH (see Table 622.1).

Lipoid Adrenal Hyperplasia

See Chapter 616.

This is the most severe form of CAH; enlarged adrenal glands result from accumulation of cholesterol and cholesterol esters. The rate-limiting process in steroidogenesis is the transport of free cholesterol through the cytosol to the inner mitochondrial membrane, where the P450 side-chain cleavage enzyme (P450scc; CYP11A1) acts. Cholesterol transport into mitochondria is mediated by the steroidogenic acute regulatory protein (StAR). StAR is a 30-kDa protein essential for steroidogenesis and is encoded by a gene on chromosome 8p11.2. The mitochondrial content of StAR increases between 1 and 5 hours after ACTH stimulation, long after the acute ACTH-induced increase in steroidogenesis. This has led some to suggest that extramitochondrial StAR might also be involved in the acute response to ACTH. Most patients with lipoid CAH have pathogenic variants in the gene encoding *StAR,* and a few have variants in *CYP11A1*.

All serum steroid levels are low or undetectable, whereas ACTH and plasma renin levels are quite elevated. The phenotype is female in both genetic females and males. Genetic males have no müllerian structures because the testes can produce normal AMH but no steroid hormones. These children present with acute adrenal crisis and salt wasting in infancy. Most patients are 46,XY. In a few patients, ovarian steroidogenesis is present at puberty.

The regulatory role of StAR-independent steroidogenesis is illustrated by 46,XX 4-month-old twins with lipoid adrenal hyperplasia. One died at 15 months because of cardiac complications related to coarctation of the aorta. The adrenal glands had characteristic lipid deposits. The surviving twin had spontaneous puberty with feminization at 11.5 years and menarche at 13.8 years. When restudied at the age of 15 years, a homozygous frameshift-inactivating variant in *StAR* was discovered. This supports the hypothesis that StAR-independent steroidogenesis was able to proceed until enough intracellular lipid accumulated to damage steroidogenic activity. Partial defects in only partially virilized males and delayed onset of salt wasting have been described. Complete *CYP11A1* defects may be incompatible with life because only this enzyme can convert cholesterol to pregnenolone, which then becomes progesterone, a hormone essential for the maintenance of normal mammalian pregnancy. Heterozygous variants in *CYP11A1* were described in a 4-year-old with 46,XY sex reversal and late-onset form of lipoid adrenal hyperplasia. At 6-7 weeks of gestation, when maternal corpus luteum progesterone synthesis stops, the placenta, which does not express StAR, produces progesterone by StAR-independent steroidogenesis using the CYP11A1 enzyme system.

3β-Hydroxysteroid Dehydrogenase Deficiency

Males with this form of CAH (see Chapter 616) have various degrees of hypospadias, with or without bifid scrotum and cryptorchidism, and, rarely, a complete female phenotype. Affected infants usually develop salt-losing manifestations shortly after birth. Incomplete defects, occasionally seen in males with premature pubarche, as well as late-onset nonclassic forms, have been reported. These children have pathogenic variants of the gene for type II 3β-hydroxysteroid enzyme, resulting in impairment of steroidogenesis in the adrenals and gonads; the impairment may be unequal between adrenals and gonads. Normal pubertal changes in some males could be explained by the normally present type I 3β-hydroxysteroid dehydrogenase present in many peripheral tissues. Infertility is frequent. There is no correlation between degree of salt wasting and degree of phenotypic abnormality.

Deficiency of 17-Hydroxylase/17,20-Lyase

A single enzyme (CYP17A1) encoded by a single gene on chromosome 10q24.3 has both 17-hydroxylase and 17,20-lyase activities in adrenal and gonadal tissues (see Chapter 616). Many different pathogenic gene variants have been reported. Genetic males usually have a complete female phenotype or, less often, various degrees of undervirilization, from labioscrotal fusion to perineal hypospadias and cryptorchidism. Pubertal development fails to occur in both genetic sexes.

In the classical disorder, there is decreased synthesis of cortisol by the adrenals and of sex steroids by the adrenals and gonads. Levels of the steroid precursor with mineralocorticoid activity, deoxycorticosterone and corticosterone, are markedly increased and lead to the hypertension and hypokalemia characteristic of this form of 46,XY

DSD. Although levels of cortisol are low, the elevated ACTH and corticosterone levels prevent symptomatic cortisol deficiency. The renin-aldosterone axis is suppressed because of the strong mineralocorticoid effect of elevated deoxycorticosterone. Virilization does not occur at puberty; levels of testosterone are low and those of gonadotropins are increased. Because fetal production of AMH is normal, no müllerian duct remnants are present. In XY phenotypic females, gonadectomy and replacement therapy with hydrocortisone and sex steroids are indicated.

The defect follows autosomal recessive inheritance. Affected XX females are usually not detected until young adult life, when they fail to experience normal pubertal changes and are found to have hypertension and hypokalemia. This condition should be suspected in patients presenting with primary amenorrhea and hypertension whose chromosomal complement is either 46,XX or 46,XY.

Some patients originally described as having isolated 17,20 lyase deficiency were subsequently shown to have a defect in the production of DHT because of deficiency of enzymes in the alternative pathway of DHT synthesis.

Deficiency of 17-Ketosteroid Reductase

This enzyme, also called *17β-hydroxysteroid dehydrogenase,* catalyzes the final step in testosterone biosynthesis. It is necessary to convert androstenedione to testosterone, DHEA to androstenediol, and estrone to estradiol. Deficiency of 17-ketosteroid reductase in the fetal testis causes the male fetus to have complete or near-complete female phenotype. Müllerian ducts are absent, and a shallow vagina is present. The diagnosis is based on the ratio of androstenedione to testosterone. In prepubertal children, stimulation with hCG may be necessary to make the diagnosis.

The defect is inherited in an autosomal recessive fashion. At least four different types of 17β-hydroxysteroid dehydrogenase are recognized, each coded by genes on different chromosomes. Type III is the enzyme responsible for testicular production of testosterone. This defect is more common in a highly inbred Arab population in Gaza than it is in other populations. The gene for the disorder is at 9q22 and is expressed only in the testes, where it converts androstenedione to testosterone. Most patients are diagnosed at puberty because of virilization and the failure to menstruate. Testosterone levels at puberty may approach normal, presumably as a result of peripheral conversion of androstenedione to testosterone; at this time, some patients may spontaneously adopt a male gender role.

Type I 17β-hydroxysteroid dehydrogenase, encoded by a gene on chromosome 17q21, converts estrone to estradiol and is found in the placenta, ovary, testis, liver, prostate, adipose tissue, and endometrium. Type II, whose gene is on chromosome 16q24, reverses the reactions of types I and III (converting testosterone to androstenedione and estrone to estradiol, respectively). Type IV is similar in action to type II. A late-onset form of 17-ketosteroid reductase deficiency presents as gynecomastia in young adult males.

Persistent Müllerian Duct Syndrome

In this disorder, there is persistence of müllerian (paramesonephric) duct derivatives in otherwise completely virilized males. Cases have been reported in siblings and identical twins. Cryptorchidism is present in 80% of affected males, and during surgery for this or inguinal hernia, the condition is discovered when a fallopian tube and uterus are found. The degree of müllerian development is variable and may be asymmetric. Testicular function is normal in most, but testicular degeneration has been reported. Some affected males acquire testicular tumors after puberty. In a study of 38 families, 16 families had defects in the AMH gene, located on the short arm of chromosome 19. Affected patients had low AMH levels. In 16 families with high AMH levels, the defect was in the AMH type II receptor gene, with 10 of 16 having identical 27-bp deletions on exon 10 in at least one allele.



Fig. 628.4 5α-Reductase deficiency. *(From Wales JKH, Wit JM, Rogol AD. Pediatric Endocrinology and Growth, 2nd ed. Philadelphia: Saunders, 2003: p. 165.)*

Treatment consists of removal of as many of the müllerian structures as possible without causing damage to the testis, epididymis, or vas deferens.

DEFECTS IN ANDROGEN ACTION

Dihydrotestosterone Deficiency

Decreased production of DHT in utero results in marked ambiguity of external genitalia of affected males. Biosynthesis and peripheral action of testosterone are normal.

The phenotype commonly associated with this condition results in males who have a small phallus, bifid scrotum, urogenital sinus with perineal hypospadias, and a blind vaginal pouch (Fig. 628.4). Testes are in the inguinal canals or labioscrotal folds and are normal histologically. There are no müllerian structures. Wolffian (mesonephric) structures—the vas deferens, epididymis, and seminal vesicles—are present. Most affected patients have been identified initially as females but at puberty, *virilization occurs;* the phallus enlarges, the testes descend and grow normally, and spermatogenesis occurs. There is no gynecomastia. Beard growth is scanty, acne is absent, the prostate is small, and recession of the temporal hairline fails to occur. Virilization of the wolffian duct is caused by the action of testosterone itself, although masculinization of the urogenital sinus and external genitals depends on the action of DHT during the critical period of fetal masculinization. Growth of facial hair and of the prostate also appears to be DHT dependent.

The adult height reached is close to that of the father and other male siblings. There is significant phenotypic heterogeneity. This has led to a classification of such patients into five types of **steroid 5α-reductase deficiency (SRD)**.

Several different gene defects of *SRD5A2* (the 5α-reductase type 2 gene leading to SRD) have been identified, located on the short arm of chromosome 2, in patients from throughout the world. Familial clusters have been reported from the Dominican Republic, Turkey, Papua New Guinea, Brazil, Mexico, and the Middle East. There is no reliable correlation between genotype and phenotype.

The disorder is inherited as an autosomal recessive trait but is limited to males; normal homozygous females with normal fertility indicate that in females DHT has no clinically significant role in sexual differentiation or in ovarian function later in life. The clinical diagnosis

should be made as early as possible in infancy. It is important to distinguish this from PAIS because patients with PAIS are far less sensitive to androgen than are patients with SRD. The biochemical diagnosis of SRD is based on finding normal serum testosterone levels, normal or low DHT levels with markedly increased basal and especially hCG-stimulated testosterone:DHT ratios (>17), and high ratios of urinary etiocholanolone to androsterone. Children with androgen insensitivity have normal hepatic 5α reduction and thus a normal ratio of tetrahydrocortisol to 5α-tetrahydrocortisol, as opposed to those with SRD.

It is important to note that many, but not all, children with SRD reared as females in childhood have changed to a male role around the time of puberty. It appears that exposures to testosterone in utero, neonatally, and at puberty have variable contributions to the formation of male gender identity. Infants with this condition should be reared as males whenever practical. Treatment of male infants with DHT results in phallic enlargement.

Another cause of DHT deficiency is a block in an alternative pathway of DHT synthesis. Patients previously thought to have 46,XY DSD because of isolated 17,20-lyase deficiency have subsequently been characterized as having pathogenic variants in *AKR1C2* (3α-reductase type 3) or both *AKR1C2* and *AKR1C4* (3α-reductase type 4) (see Fig. 628.1). These findings showed that both the classical and alternative pathways to DHT must be intact for normal prenatal virilization.

Androgen Insensitivity Syndromes

The AISs are the most common forms of male DSDs, occurring with an estimated frequency of 1/20,000 genetic males. This group of heterogeneous X-linked recessive disorders is caused by more than 150 different pathogenic variants in the androgen receptor gene, located on Xq11-12: single point variants result in amino acid substitutions or premature stop codons, frameshift and premature terminations, gene deletions, and splice-site variants.

Clinical Manifestations

The clinical spectrum of patients with AISs, all of whom have a 46,XY chromosomal complement, range from phenotypic females (in *complete* AIS), to males with various forms of ambiguous genitalia and undervirilization (*partial* AIS, or clinical syndromes such as **Reifenstein syndrome**), to phenotypically normal-appearing males with infertility. In addition to normal 46,XY chromosomes, the presence of testes and normal or elevated testosterone and LH levels are common to all such children (Figs. 628.5 and 628.6).

In **complete androgen insensitivity syndrome (CAIS)**, an extreme form of failure of virilization, genetic males appear female at birth and are invariably reared accordingly. The external genitalia are female. The vagina ends blindly in a pouch, and the uterus is absent because of the normal production and effect of AMH by the testes. In ~30% of patients, unilateral or bilateral fallopian tube remnants are found. The testes are usually intraabdominal but may descend into the inguinal canal; they consist largely of seminiferous tubules. At puberty, there is normal development of breasts and the habitus is female, but menstruation does not occur and sexual hair is absent. Adult heights are commensurate with those of normal males despite profound congenital deficiency of androgenic effects.

The testes of affected adult patients produce normal male levels of testosterone, which are converted to normal levels of DHT. Failure of normal male differentiation during fetal life reflects a defective response to androgens at that time. The absence of androgenic effects is caused by a striking resistance to the action of endogenous or exogenous testosterone at the cellular level.

Prepubertal phenotypic females with this disorder are often detected when inguinal masses prove to be testes or when a testis is unexpectedly found during herniorrhaphy. Approximately 1–2% of females with an inguinal hernia prove to have this disorder. In infants, elevated LH levels should suggest the diagnosis. In older children and adults, amenorrhea is the usual presenting symptom. In prepubertal children, the condition must be differentiated from other types of XY undervirilized males in which there is complete feminization. These include XY gonadal dysgenesis **(Swyer syndrome)**, true agonadism, Leydig cell aplasia including LH receptor defects, and 17-ketosteroid reductase deficiency. All these conditions, unlike CAIS, are characterized by low

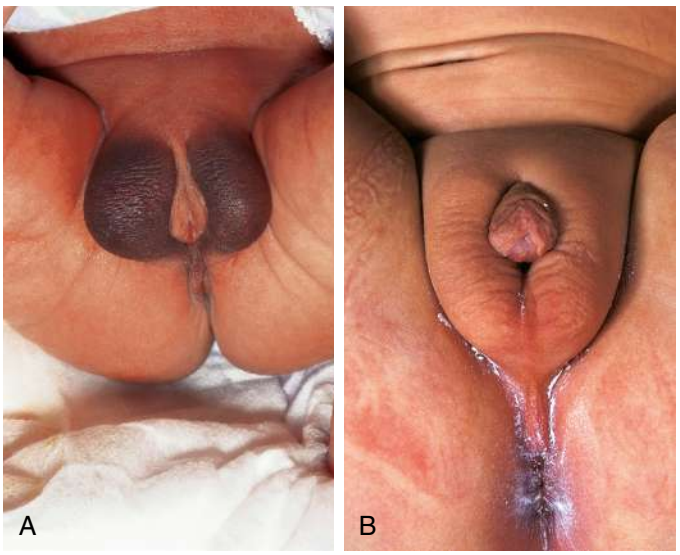

Fig. 628.5 A, Partial androgen insensitivity with descended testes in bifid labioscrotal folds. B, Less severe partial androgen insensitivity with severe hypospadias and maldescent of testes. *(From Wales JKH, Wit JM, Rogol AD. Pediatric Endocrinology and Growth, 2nd ed. Philadelphia: Saunders, 2003: p. 165.)*



Fig. 628.6 Partial androgen insensitivity syndrome at adolescence, male sex of rearing. Note gynecomastia from peripheral aromatase conversion of testosterone to estrogen. Abundant pubic hair implies only partial resistance. *(From Wales JKH, Wit JM, Rogol AD. Pediatric Endocrinology and Growth, 2nd ed. Philadelphia: Saunders, 2003: p. 165.)*

Table 628.7 Causes of a Partial Androgen Insensitivity Syndrome–Like Phenotype

DEFECTS IN ANDROGEN PRODUCTION
Partial gonadal dysgenesis
Pathogenic variants in *SRY, NR5A1, WT1*
Pathogenic variants of the luteinizing hormone receptor
Biosynthetic enzyme deficiencies
17,20-Lyase deficiency
P450 oxidoreductase deficiency
17β-hydroxysteroid dehydrogenase deficiency type 3
5α-Reductase deficiency type 2
GENETIC
Klinefelter syndrome
Smith-Lemli-Opitz syndrome
Denys-Drash syndrome
Frasier syndrome
PAIS
Pathogenic variants of the androgen receptor gene
Normal androgen receptor gene with fetal growth restriction

NR5A1, Nuclear receptor subfamily 5 A1; PAIS, partial androgen insensitivity syndrome; SRY, sex-determining region Y; WT1, Wilms tumor 1.

From Hughes IA, Davies JD, Bunch TI, et al. Androgen insensitivity syndrome. *Lancet.* 2012;380:1419–1428. Panel 1.

levels of testosterone as neonates and during adult life and by failure to respond to hCG during the prepubertal years.

Although patients with CAIS have unambiguously female external genitals at birth, those with **PAIS** have a wide variety of phenotypic presentations, ranging from **perineoscrotal hypospadias**, bifid scrotum, and cryptorchidism to extreme undervirilization appearing as clitoromegaly and labial fusion. Some forms of PAIS are known as specific syndromes. Patients with **Reifenstein syndrome** have incomplete virilization characterized by hypogonadism, severe hypospadias, and gynecomastia (see Fig. 628.6). **Gilbert-Dreyfus** and **Lubs syndromes** are also classified as PAISs. In all cases, abnormalities in the androgen receptor gene have been identified. Table 628.7 lists other causes of a PAIS-like syndrome.

Diagnosis

The diagnosis of patients with PAIS may be particularly difficult in infancy. The postnatal surge in testosterone and LH is diminished in those with CAIS but not in those with PAIS. In some, especially those sufficiently virilized in infancy, the diagnosis is not suspected until puberty, when there is inadequate virilization with lack of facial hair or voice change and the appearance of gynecomastia. Azoospermia and infertility are common. Androgen receptor defects are recognized in adults who have a small phallus and testes and infertility. A single–amino acid substitution in the androgen receptor was reported in a large Chinese family in whom some affected members were fertile whereas others had gynecomastia and/or hypospadias.

Treatment and Prognosis

In patients with CAIS whose sexual orientation is unambiguously female, the testes should be removed because they have malignant potential. Historically, they were removed as soon as they were discovered. However, there is a trend to allow the testes to remain because they are the source of estradiol (through conversion from testosterone), and this results in normally timed puberty with the individual's endogenous hormones. Careful monitoring for testicular masses should be performed, and removal of the testes is advised in early adulthood. Laparoscopic removal of Y chromosome–bearing gonads has been performed in patients with AIS and in those with gonadal dysgenesis. In ~30% of patients, malignant tumors, usually seminomas, develop by 50 years of age. Several teenage females developed seminomas. Replacement therapy with estrogens is indicated at the age of puberty in those whose testes were removed in childhood.

Normal breasts develop in affected females who have not had their testes removed by the age of puberty. The absence of androgenic activity in addition to the production of estradiol contributes to the feminization of these women.

The psychosexual and surgical management of patients with PAIS is extremely complex and depends in large part on the presenting phenotype. Osteopenia is recognized as a late feature of AIS.

Molecular analyses have suggested that phenotype may depend in part on somatic mosaicism of the androgen receptor gene. The presence of mosaicism shifts the phenotype to a higher degree of virilization than expected from the genotype of the mutant allele alone.

Genetic counseling is difficult in families with androgen receptor gene variants. In addition to lack of genotype-phenotype correlations, there is a high rate (27%) of de novo pathogenic variants in families.

Sex hormone–binding globulin reduction after exogenous androgen administration (stanozolol) correlates with the severity of the receptor defect and may become a useful clinical tool. Successful therapy with supplemental androgens has been reported in patients with PAIS and various variants of the androgen receptor in the DNA-binding domain and the ligand-binding domain.

Pathogenic variants in androgen receptors are also reported in patients with **spinal and bulbar muscular atrophy** in whom clinical manifestations including testicular atrophy, infertility, gynecomastia, and elevated LH, FSH, and estradiol levels usually manifest between the third and fifth decades of life.

UNDETERMINED CAUSES

Other XY undervirilized males display great variability of the external and internal genitalia and various degrees of phallic and müllerian development. The testes may be histologically normal or rudimentary, or there may only be one. No recognized cause is identified in up to 50% of children with 46,XY DSDs. Some ambiguity of the genitalia is associated with a wide variety of chromosomal aberrations, which must always be considered in the differential diagnosis, the most common being 45,X/46,XY syndrome (see Chapter 626.1). It may be necessary to karyotype several tissues to establish mosaicism. Other complex genetic syndromes, many resulting from single-gene variants, are associated with varying degrees of ambiguity of the genitalia, particularly in the male. These entities must be identified by the associated extragenital malformations.

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by pathogenic variants in the sterol Δ7-reductase gene located on chromosome 11q12-q13. It is characterized by prenatal and postnatal growth restriction, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the second to third toes, and severe cognitive impairment (see Chapter 106.3). Its incidence is 1 in 20,000-30,000 live births in populations of Northern and Central European origin; 70% are male. Genotypic males usually have genital ambiguity and, occasionally, partial sex reversal with female genital ambiguity or complete sex reversal with female external genitalia. Müllerian duct derivatives are usually absent. Affected 46,XX patients have normal genitalia. Two types of Smith-Lemli-Opitz syndrome have been recognized: the **classical form (type I)** described earlier and the acrodysgenital syndrome, which is usually lethal within 1 year and is associated with severe malformations, postaxial polydactyly, and extremely abnormal external genitalia **(type II)**. Pyloric stenosis is associated with Smith-Lemli-Opitz syndrome type I and Hirschsprung disease with type II. Cleft palate, skeletal abnormalities, and one case of a lipoma of the pituitary gland have been seen in **type II** cases. Some authors believe in a spectrum of disease severity rather than in the previous classification. Low plasma cholesterol with elevated 7-dehydrocholesterol, its precursor, are found in types I and II, and the levels do not correlate with severity. Maternal apolipoprotein E values do seem to correlate with severity. The most common prenatal expression of Smith-Lemli-Opitz syndrome is intrauterine growth retardation (see Chapter 106.3 for treatment).

46,XY DSD subjects also have been described in siblings with α-thalassemia/mental retardation syndrome.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

628.3 Ovotesticular DSD

Patricia A. Donohoue

In ovotesticular DSD, both ovarian and testicular tissues are present, either in the same or in opposite gonads. Affected patients have ambiguous genitalia, varying from normal female genitalia with only slight enlargement of the clitoris to almost normal male external genitalia (see Fig. 628.3A).

Approximately 70% of all patients have a 46,XX karyotype. Ninety-seven percent of affected patients of African descent are 46,XX. Less than 10% of persons with ovotesticular DSD are 46,XY. Approximately 20% have 46,XX/46,XY mosaicism. Half of these are derived from more than one zygote and are chimeras (chi 46,XX/46,XY). The presence of paternal and both maternal alleles for some blood groups is demonstrated. An ovotesticular DSD chimera, 46,XX/46,XY, was reported as resulting from embryo amalgamation after in vitro fertilization. Each embryo was derived from an independent, separately fertilized ovum.

Examination of 46,XX ovotesticular DSD patients with Y-specific probes has detected less than 10% with a portion of the Y chromosome, including the *SRY* gene. Ovotesticular DSD is usually sporadic, but several siblings have been reported. The cause of many cases of ovotesticular DSD is unknown.

The most frequently encountered gonad in ovotesticular DSD is an ovotestis, which may be bilateral. If unilateral, the contralateral gonad is usually an ovary but may be a testis. The ovarian tissue is normal, but the testicular tissue is dysgenetic. The presence and function of testicular tissue can be determined by measuring basal and hCG-stimulated testosterone levels along with AMH levels. Patients who are highly virilized and have had adequate testicular function with no uterus are usually reared as males. If a uterus exists, virilization is often mild and testicular function minimal; assignment of female sex may be indicated. Selective removal of gonadal tissue inconsistent with sex of rearing may be indicated. In a few families, 46,XY ovotesticular DSD subjects and 46,XX males have been described in the same sibship.

Defects in R-Spondin1, encoded by the *RSPO1* gene, have been described in 46,XX ovotesticular DSD. Defects in SF-1 have been described in both XX and XY ovotesticular DSD.

Pregnancies with living offspring have been reported in 46,XX ovotesticular DSD individuals reared as females, but very few males with ovotesticular DSD have fathered children. Approximately 5% of patients will develop gonadoblastomas, dysgerminomas, or seminomas.

DIAGNOSIS AND MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT

In the neonate, ambiguity of the genitals requires immediate attention to decide on the sex of rearing as early in life as possible. The family of the infant needs to be informed of the child's condition as early, completely, compassionately, and honestly as possible. Caution must be used to avoid feelings of guilt, shame, and discomfort. Guidance needs to be provided to alleviate both short-term and long-term concerns and to allow the child to grow up in a completely supportive environment. The initial care is best provided by a team of professionals that includes neonatologists and pediatric specialists, endocrinologists, radiologists, surgeons/urologists, psychologists, and geneticists, all of whom remain focused foremost on the needs of the child. Management of the potential psychologic upheaval that these disorders can generate in the child or the family is of paramount importance and requires physicians and other healthcare professionals with sensitivity, training, and experience in this field.

While awaiting the results of chromosomal analysis, pelvic ultrasonography is indicated to determine the presence of a uterus and ovaries. Presence of a uterus and absence of palpable gonads usually suggest a virilized XX female; however, as described previously, these structures may also be found in 46,XY DSD. A search for the source of virilization should be undertaken; this includes studies of adrenal hormones to rule out varieties of congenital adrenal hyperplasia, and studies of androgens and estrogens occasionally may be necessary to rule out aromatase deficiency. Virilized XX females are generally (but not always) reared as females even when highly virilized.

The absence of a uterus, with or without palpable gonads, often indicates an undervirilized male and an XY karyotype. Measurements of levels of gonadotropins, testosterone, AMH, and DHT are necessary to determine whether testicular production of androgen is present and is normal. Undervirilized males who are totally feminized may be reared as females. Certain significantly feminized infants, such as those with 5α-reductase deficiency, may be reared as males because these children virilize normally at puberty. Sixty percent of individuals with 5α-reductase deficiency assigned as female in infancy live as males as adults. An infant with a comparable degree of feminization resulting from an androgen receptor defect, such as CAIS, may be successfully reared as a female.

When receptor disorders are suspected in the XY male with a small phallus (micropenis), a course of three monthly IM injections of testosterone enanthate (25-50 mg) may assist in the differential diagnosis of androgen insensitivity and in the treatment of the small phallus.

In some mammals, the female exposed to androgens prenatally or in early postnatal life exhibits nontraditional sexual behavior in adult life. Most, but not all, females who have undergone fetal masculinization from CAH or from maternal progestin therapy have female sexual identity, although during childhood they may appear to prefer male playmates and activities over female playmates and feminine play with dolls in mothering roles.

In the past it was thought that surgical treatment of ambiguous genitalia to create a female appearance, particularly when a vagina is present, was more successful than construction of male genitalia. Considerable controversy exists regarding these decisions. Sexual functioning is to a large extent more dependent on neurohormonal and behavioral factors than the physical appearance and functionality of the genitalia. Similarly, controversy exists regarding the timing of the performance of invasive and definitive procedures, such as surgery. Whenever possible without endangering the physical or psychologic health of the child, an expert multidisciplinary team should consider deferring elective surgical repairs and gonadectomies until the child can participate in the informed consent for the procedure. One study of children (59 males and 18 females) with gender dysphoria but without documentation of genomic or enzymologic abnormalities indicated that most of these children no longer have gender dysphoria after completion of puberty. Among those who do, homosexuality and bisexuality are the most frequent diagnoses.

For patients with DSD who have Y-chromosome material and intraabdominal gonads, gonadectomy is generally recommended because of the risk of gonadal tumors, many of which are malignant.

The pediatrician, pediatric endocrinologist, and psychologist, along with the appropriate additional specialists, should provide ongoing compassionate, supportive care to the patient and the patient's family throughout childhood, adolescence, and adulthood. Support groups are available for families and patients with many of the conditions discussed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 6

Diabetes Mellitus in Children

Chapter 629

Diabetes Mellitus

629.1 Classification of Diabetes Mellitus

David R. Weber

Diabetes mellitus (DM) is a common chronic metabolic disease characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are differentiated by insulin deficiency versus insulin resistance: **type 1 diabetes mellitus (T1DM)** results from deficiency of insulin secretion because of pancreatic β-cell damage; **type 2 diabetes mellitus (T2DM)** is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment. T1DM is the most common endocrine metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Individuals with T1DM confront serious lifestyle alterations, including an absolute daily requirement for exogenous insulin, the need to monitor their own glucose level, and the need to pay attention to dietary intake. Morbidity and mortality stem from a constant potential for acute metabolic derangements and from long-term complications. Potential acute complications include the development of hypoglycemia related to insulin excess or hyperglycemic ketoacidosis from insulin deficiency. Long-term complications typically manifest in adulthood and are related to the adverse effects of chronic hyperglycemia and associated metabolic abnormalities on tissues and organ systems. This can result in microvascular diseases such as retinopathy, nephropathy, and neuropathy and macrovascular complications such as ischemic heart disease and arterial obstruction with gangrene of the extremities.

DM is not a single entity, but rather a heterogeneous group of disorders in which there are distinct genetic patterns and other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance through deficient insulin production or action. The American Diabetes Association (ADA) has proposed a diabetes classification system that includes four categories: type 1 diabetes, type 2 diabetes, other specific types, and gestational diabetes. An expanded list of diabetes etiologies is provided in Table 629.1. The current criteria for the diagnosis of diabetes are provided in Table 629.2. A thorough clinical history and physical exam are often sufficient to determine the etiology; however, in some cases additional testing may be required.

TYPE 1 DIABETES MELLITUS

Formerly called *insulin-dependent diabetes mellitus* (IDDM) or *juvenile diabetes,* T1DM is characterized by low or absent levels of endogenously produced insulin and by dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of T1DM. The natural history includes four distinct stages: (1) preclinical β-cell autoimmunity with progressive defect of insulin secretion, (2) onset of clinical diabetes, (3) transient remission honeymoon period, and (4) established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy. The onset occurs predominantly in childhood, with a median age of 7-15 years, but it may present at any age. The incidence of T1DM varies markedly across the world but has increased in nearly all parts of the world over recent decades (Fig. 629.1). Both genetic susceptibility and environmental factors contribute to the pathogenesis. Susceptibility to T1DM is genetically controlled by alleles of the major histocompatibility complex (MHC) class II genes expressing human leukocyte antigens (HLAs). Autoantibodies to β-cell antigens, including islet cell cytoplasm (ICA), insulin autoantibody (IAA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2A, formerly ICA512), and zinc transporter 8 (ZnT8A), are detected in serum from affected subjects. These can be detected months to years before the clinical onset of T1DM. In some children and adolescents with apparent T1DM, the β-cell destruction is not immune mediated. This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β-cell destruction such as drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and ionizing radiation. These individuals may have ketoacidosis, but they have extensive periods of remission with variable insulin deficiency, similar to patients with T2DM. Patients with T1DM require lifelong treatment with insulin.

TYPE 2 DIABETES MELLITUS

Formerly known as *adult-onset diabetes mellitus* or *non–insulin-dependent diabetes mellitus,* T2DM develops because of insulin resistance and progressive non-autoimmune β-cell failure. There is a strong heritable component to T2DM, although the genetic basis remains poorly understood. Population-based studies have linked T2DM risk with polymorphisms in a large number of genes related to insulin secretion, insulin action, energy expenditure, and birthweight; however, the collective contribution of these variants to overall T2DM risk remains low at <20%. Although T2DM has long been the most prevalent form of diabetes in adults, the rise in childhood obesity over the past few decades has led to a markedly increased incidence of this disease in children and adolescents. Pediatric T2DM accounts for most of the new cases of diabetes in high-risk populations such as obese adolescents of Black or Hispanic population ancestry (see Chapter 65). *Childhood-onset T2DM differs from adult disease in that it is associated with a more rapid decline in β-cell function and the earlier development of T2DM-related complications.*

The presentation of T2DM is typically more insidious than that with T1DM. In contrast to patients with T1DM, who are usually ill at the time of diagnosis and whose presentation rarely spans more than a few weeks, children with T2DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or the incidental finding of glycosuria during routine physical examination. A history of polyuria and polydipsia is not always a cardinal clinical feature in these patients. **Acanthosis nigricans** (dark pigmentation of skin creases in the nape of the neck especially), a sign of insulin resistance, is present in the majority of patients with T2DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis. However, as the disease progresses, β-cell function becomes increasingly impaired such that children with advanced T2DM often present in diabetic ketoacidosis (DKA).

Healthy lifestyle interventions and treatment with metformin remain the cornerstones of T2DM treatment in children and adolescents. Liraglutide (a glucagon-like peptide-1 receptor agonist) is approved in children ≥10 years and may have an additional benefit of slowing weight gain. Insulin therapy is required for patients who present with severe hyperglycemia and for those patients in whom hyperglycemia worsens in spite of lifestyle modification and noninsulin pharmacologic management.

OTHER SPECIFIC TYPES OF DIABETES

Monogenic Diabetes

The term *monogenic diabetes* is used to refer to a heterogeneous group of single-gene disorders resulting in impaired insulin secretion. This category encompasses **maturity-onset diabetes of the young (MODY)** and **transient and permanent neonatal diabetes (TND or PND)**. Characteristics of monogenic diabetes can include age of onset before 6 months (for TND or PND), development of hyperglycemia before 25 years of age, and strong family history of diabetes. Monogenic etiologies are estimated to comprise anywhere from 1% to 10% of all diabetes cases, with the uncertainty related to the clinical difficulty in differentiating these cases from T1DM and T2DM. Monogenic forms of diabetes may present with hyperglycemia, and consequent polyuria and polydipsia, or may be diagnosed simply by routine screening. Extrapancreatic manifestations vary by genetic defect (see Table 629.1 and Chapter 629.4) and can include hepatic, renal, and central nervous system (CNS) manifestations. Treatment is guided by genetic diagnosis and clinical course, with

Table 629.1 Etiologic Classifications of Diabetes Mellitus

I. TYPE 1 DIABETES (B-CELL DESTRUCTION ULTIMATELY LEADING TO COMPLETE INSULIN DEFICIENCY)
- *A. Immune Mediated*
- *B. Idiopathic*

II. TYPE 2 DIABETES (VARIABLE COMBINATIONS OF INSULIN RESISTANCE AND INSULIN DEFICIENCY)
- *A. Typical*
- *B. Atypical*

III. OTHER SPECIFIC TYPES
- *A. Genetic Defects Of β-Cell Function (Monogenic Diabetes)*
  1. Neonatal diabetes
     a. Pathogenic variants leading to transient neonatal diabetes (*KCNJ11, ABCC8, 6q24 overexpression, INS, ZFP57, SLC2A2 HNF1β*)
     b. Pathogenic variants leading to permanent neonatal diabetes (*KCNJ11, ABCC8, INS, GATA6, EIF2AK3, GCK, PTF1A, FOXP3, GLIS3, PDX1, SLC2A2, SLC19A2, GATA4, NEUROD1, NEUROG3, NKX2-2, RFX5, IER3IP1, MNX1*)
  2. MODY (maturity-onset diabetes of the young) syndromes
     a. MODY 1 chromosome 20, *HNF4α*
     b. MODY 2 chromosome 7, *GCK*
     c. MODY 3 chromosome 12q24.2, *HNF1α, TCF-1*
     d. MODY 4 chromosome 13q12.1, *IPF-1 (PDX1)*
     e. MODY 5 chromosome 17, *HNF1β, TCF-2*
     f. MODY 6 chromosome 2q32, *NEUROD1*
     g. MODY 7 chromosome 2p25, *KLF11*
     h. MODY 8 chromosome 9q34, *CEL*
     i. MODY 9 chromosome 7q32, *PAX4*
     j. MODY 10 chromosome 11p15.5, *INS*
     k. MODY 11 chromosome 8p23, *BLK*
     l. MODY 12 chromosome 11p15, *ABCC8*
     m. MODY 13 chromosome 11p15, *KCNJ11*
     n. MODY 14 chromosome 3p14, *APPL1*
  3. Mitochondrial DNA pathogenic variants (includes one form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, and maternally inherited diabetes and deafness)
  4. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness):
     a. WFS1-Wolframin—chromosome 4p
     b. Wolfram locus 2—chromosome 4q22-24
     c. Wolfram mitochondrial
  5. Thiamine-responsive megaloblastic anemia and diabetes
- *B. Genetic Defects of Insulin Action*
  1. Type A insulin resistance
  2. Donohue syndrome
  3. Rabson-Mendenhall syndrome
  4. Lipoatrophic diabetes syndromes
- *C. Other Genetic Syndromes Associated With Diabetes (Insulin Resistance Or Deficiency)*
  1. Down syndrome
  2. Turner syndrome
  3. Klinefelter syndrome
  4. Prader-Willi syndrome
  5. Bardet-Biedl syndrome
  6. Alström syndrome
  7. Werner syndrome
  8. Friedreich ataxia
- *D. Other Autoimmune Syndromes Associated With Diabetes*
  1. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
  2. Autoimmune polyendocrinopathy syndromes (APS)
     a. APS-1 (APCED)
     b. APS-2
  3. Stiff person syndrome
  4. Anti-insulin receptor antibodies
- *E. Drug Or Chemical Induced*
  1. Antirejection—cyclosporine, sirolimus
  2. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
  3. l-Asparaginase
  4. β-Adrenergic blockers
  5. Vacor (rodenticide)
  6. Phenytoin (Dilantin)
  7. α-Interferon
  8. Diazoxide
  9. Nicotinic acid
  10. Pentamidine
  11. Immune checkpoint inhibitors (immune mediated)
- *F. Diseases of Exocrine Pancreas*
  1. Cystic fibrosis
  2. Trauma/pancreatectomy
  3. Pancreatitis/ionizing radiation
  4. Hemochromatosis
  5. Fibrocalculous pancreatopathy
- *G. Infections*
  1. Congenital rubella
  2. Cytomegalovirus
  3. Hemolytic-uremic syndrome
- *H. Endocrinopathies Associated With Diabetes*
  1. Cushing (hypercortisolism)
  2. Acromegaly (growth hormone excess)
  3. Pheochromocytoma
  4. Glucagonoma
  5. Somatostatinoma
  6. Aldosteronoma

IV. GESTATIONAL DIABETES

Modified from Sperling MA, Tamborlane WV, Battelino T, et al. Diabetes mellitus. In: Sperling MA. *Pediatric Endocrinology*, 4th ed. Philadelphia: Elsevier; 2014: Box 19-1.

some forms being responsive to oral sulfonylureas and others requiring insulin replacement. *Children diagnosed with diabetes before 6 months of age should have genetic testing for TND/PND, and older individuals with diabetes not characteristic of T1DM or T2DM in the setting of a family history of diabetes should have genetic testing for monogenic forms of diabetes.* A comparison of the four types of diabetes is noted in Table 629.3.

OTHER ETIOLOGIES OF DIABETES

Examples include diabetes secondary to exocrine pancreatic diseases (cystic fibrosis), other endocrine diseases (Cushing syndrome), infection, and ingestion of certain drugs or poisons (the rodenticide Vacor). In organ transplantation survivors, there is a linkage between cyclosporine and tacrolimus and post-transplantation DM, ascribed to a number of mechanisms. Certain genetic syndromes, including those with abnormalities of the insulin receptor or the immune system, are also included in this category.

PREDIABETES

The term *prediabetes* is used to identify individuals with abnormalities in blood glucose homeostasis who are at increased risk for the development of diabetes (see Table 629.2). Prediabetes is defined by **impaired fasting glucose** (IFG, fasting glucose 100-125 mg/dL

Table 629.2 Diagnostic Criteria for Dysglycemia and Diabetes Mellitus

DYSGLYCEMIA	DIABETES MELLITUS
IMPAIRED FASTING GLUCOSE	
Fasting (at least 8 hr) plasma glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) *Or*
IMPAIRED GLUCOSE TOLERANCE	
2-hr plasma glucose during OGTT ≥140 mg/dL (7.8 mmol/L), but <200 mg/dL (11.1 mmol/L)	2-hr plasma glucose during OGTT ≥200 mg/dL (11.1 mmol/L) *Or*
PREDIABETES	
Hemoglobin A_{1c} 5.7–6.4% (39-47 mmol/mol)	Hemoglobin A_{1c} ≥6.5% (48 mmol/mol) *Or* Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L)†

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.
†Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.
OGTT, Oral glucose tolerance test.
Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1999;20(Suppl 1):S5; with data from American Diabetes Association. Standards in Medical Care of Diabetes – 2017. *Diabetes Care.* 2017;40(Suppl 1):S11–S24.

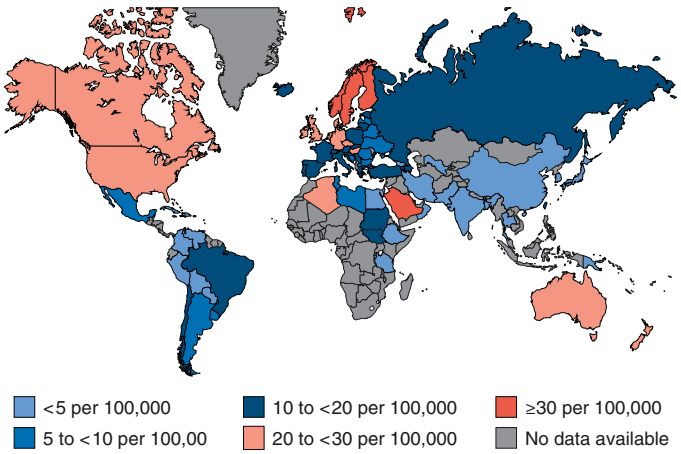

Fig. 629.1 Map of age-sex standardized incidence rates (per 100,000) from publications of type 1 diabetes in children age under 15 yr. *(From Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107842. Fig 1.)*

[5.6-6.9 mmol/L]), **impaired glucose tolerance** (IGT, 2 hours postprandial glucose 140-199 mg/dL [7.8-11 mmol/L]), or hemoglobin A_{1c} (HbA_{1c}) values of 5.7–6.4% (39-47 mmol/mol). A fasting glucose concentration of 99 mg/dL (5.5 mmol/L) is the upper limit of normal. This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications. Many individuals with IFG are euglycemic in their daily lives and may have normal or nearly normal HbA_{1c} levels. Individuals with IFG often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test (OGTT).

Prediabetes is not a clinical entity, but rather a risk factor for future diabetes and cardiovascular disease. This may be observed as an intermediate stage in any of the disease processes listed in Table 629.1. Prediabetes is often associated with **insulin resistance syndrome** (also known as **metabolic syndrome**), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both in addition to hypertension. Insulin resistance is directly involved in the pathogenesis of T2DM.

629.2 Type 1 Diabetes Mellitus (Immune Mediated)

David R. Weber

EPIDEMIOLOGY

T1DM accounts for approximately 10% of all cases of diabetes in all ages, affecting up to 2 million people in the United States and more than 15 million people in the world; approximately 15,000 youths are diagnosed with T1DM each year. Although T1DM accounts for most cases of diabetes in childhood, it is not limited to this age-group; new cases continue to present in adult life, and up to 50% of individuals with T1DM present as adults. The incidence of T1DM is highly variable among different racial and ethnic groups (see Fig. 629.1). The overall age-adjusted incidence of T1DM varies from <5 in 100,000 per year in parts of Asia, Africa, and South America to more than 30 in 100,000 per year in Northern Europe. The incidence of T1DM is increasing in most (but not all) populations, and this increase appears to be most marked in populations where the incidence of autoimmune diseases was historically low. Data from Western European diabetes centers suggest that the annual rate of increase in T1DM incidence is 2–5%, whereas some Central and Eastern European countries demonstrate an even more rapid increase—up to 9%. Data from the United States have shown that the incidence of T1DM in children increased by 1.9% per year from 2002 to 2015 from 19.5/100,000 to 22.3/100,000. Steeper increases in annual incidence were seen in people of Asian/Pacific Islander (4.4%), Hispanic (4%), and Black (2.7%) versus those of White (0.7%) racial/ethnic background.

Females and males are almost equally affected, with a modest male preponderance in some populations (Western European/United States and a female preponderance in others (Japanese); there is no apparent correlation with socioeconomic status. Peaks of presentation occur in two age-groups: at 5-7 years of age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the second peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin). The understanding of the cause of diabetes or of its increased incidence remains elusive. A growing number of cases are presenting between 1 and 2 years of age, especially in high-risk groups; the average age of presentation is older in low-risk populations. Low-risk groups that migrate to a high-risk country seem to acquire the increased risk of that country. There can be marked differences in incidence rates in various ethnic groups within the same country; incidence rates (per 100,000) in the 10- to 14-year-old age-group in the United States range from a low of 7.1 in Native Americans to 17.6 in Hispanics, 19.2 in Black Americans, and 32.9 in Whites.

GENETICS

There is a clear familial clustering of T1DM, with prevalence in siblings approaching 8%, whereas the prevalence in the general population in the United States is only 0.4%. Risk of T1DM is also increased when a parent has T1DM, and this risk differs between the two parents; the risk is 3–4% if the mother is affected but 5–6% when the father is affected. In monozygotic twins, the concordance rate ranges from 30% to 65%, whereas dizygotic twins have a concordance rate of 6–10%.

Table 629.3 Key Features of Diabetes in Pediatric Patients

	TYPE 1 DIABETES	TYPE 2 DIABETES	MONOGENIC DIABETES (MATURITY-ONSET DIABETES IN THE YOUNG)	NEONATAL DIABETES
Age at diagnosis	6 mo-18 yr	Puberty; rarely younger than 10 yr	Younger than 25 yr	Younger than 6 mo
Causes and genetic factors	Autoimmune; genetic predisposition (HLA and other genes)	Obesity; genetic and ethnic predisposition	Autosomal dominant; *HNF1A, HNF4A, GCK, HNF1B* (see Table 629.1)	*KCNJ11, ABCC8, INS* (see Table 629.1)
Associated features	Lean or mildly overweight at diagnosis, often with weight loss; thyroid autoimmunity; celiac disease	Obesity; acanthosis nigricans; polycystic ovarian syndrome; hypertension; hyperlipidemia; fatty liver disease; family history	Lean or weight loss at diagnosis; *GCK* variants are asymptomatic	Failure to thrive
Diabetic ketoacidosis at presentation	Yes; about 25%	Yes; 5–20%	No	Yes; frequency not described
Treatment	Insulin	Lifestyle modification; metformin; liraglutide; insulin; bariatric surgery	Sulfonylurea; no treatment for *GCK* variants	Sulfonylurea for *KCJN11* and *ABCC8* variants; insulin for other variants

Adapted from Cameron FJ, Wherrett DK. Care of diabetes in children and adolescents: controversies, changes, and consensus. Lancet. 2015;385:2096–2104. Table 1.

Because the concordance rate of dizygotic twins is higher than the sibling risk, factors other than the shared genotypes (e.g., the shared intrauterine environment) may play a role in increasing the risk in dizygotic twins. Furthermore, the genetic susceptibility for T1DM in the parents of an affected child is estimated at 3%. It should be kept in mind that although there is a large genetic component in T1DM, 85% of newly diagnosed patients with T1DM do not have an affected family member.

Monogenic Type 1 Diabetes Mellitus

Classic single-gene defects are an extremely rare cause of autoimmune-mediated T1DM. **IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome** is caused by pathogenic variants in *FOXP3* and other genes. The *FOXP3* is a gene involved in immune system responses. A member of the FOX protein family, *FOXP3* appears to function as the master regulator in the development and function of regulatory T cells. These variants lead to the lack of a major population of regulatory T lymphocytes, with resulting overwhelming autoimmunity and development of diabetes (as early as 2 days of age) in approximately 80% of the children with this disorder.

Wolfram syndrome (DIDMOD: diabetes insipidus, diabetes mellitus, optic atrophy, deafness) is an autosomal recessive disease caused predominantly by pathogenic variants in *WFS1* and is a progressive neurodegenerative disease. Case definition requires the presence of T1DM and optic atrophy. This syndrome may be present in ~5% of patients with T1DM.

Autoimmune polyendocrinopathy syndrome type 1 (APS-1) is caused by pathogenic variants in *AIRE* leading to abnormalities in expression of peripheral antigens within the thymus and/or abnormalities of negative selection in the thymus. This results in widespread autoimmunity. Approximately 18% of children with this syndrome develop T1DM.

Genes Altering the Risk of Autoimmune Type 1 Diabetes Mellitus

The risk of developing T1DM is modified by the influence of several risk loci. The genomic region with by far the greatest contribution to the risk of T1DM is the MHC on chromosome 6p21. Outside of the MHC, genome-wide association studies have identified T1DM to be associated with at least 100 different single-nucleotide polymorphisms, from which about 50 genes have emerged as potentially causal. Notable high-risk loci include *INS*, *PTPN22*, *IL2RA*, *CTLA4*, *IFIH1*, *ERBB3*, and *BAD*. The contribution of each non-MHC locus to T1DM risk is small, making individual variants less useful for predicting the genetic risk of T1DM in a patient. The known functions of these genes suggest the primary etiologic pathways of diabetes, namely, HLA class II and class I molecules binding, T- and β-cell activation, innate pathogen viral responses, chemokine and cytokine signaling, and T-regulatory and antigen-presenting cell functions.

Major Histocompatibility Complex/Human Leukocyte Antigen–Encoded Susceptibility to Type 1 Diabetes Mellitus

The MHC is a large genomic region that contains a number of genes related to immune system function in humans. These genes are further divided into HLA classes I, II, III, and IV. Class II genes are the ones most strongly associated with risk of T1DM, but some of the risk associated with various HLA types is a result of variation in genes in HLA classes other than class II. Overall, genetic variation in the HLA region can explain 40–50% of the genetic risk of T1DM.

Some of the known associations include the HLA DR3/4-DQ2/8 genotype; compared to a population prevalence of T1DM of approximately 1 in 300, DR3/4-DQ2/8 newborns from the general population have a 1 in 20 genetic risk. This risk of development of T1DM is even higher when the high-risk HLA haplotypes are shared with a sibling or parent with T1DM. If one sibling has T1DM and shares the same high-risk DR3/4-DQ2/8 haplotype with another sibling, the risk of autoimmunity in the other sibling is 50%. Moreover, this risk approaches 80% when siblings share both HLA haplotypes identical by descent. This is known as the *relative paradox* and points to the existence of other shared genetic risk factors (most likely in the extended HLA haplotype).

With advances in genotyping, further discrimination is possible and we can identify more specific risk ratios for specific haplotypes. For example, the DRB1*0401-DQA1*0301g-DQB1*0302 haplotype has an odds ratio (OR) of 8.39, whereas the DRB1*0401-DQA1*0301g-DQB1*0301 haplotype has an OR of 0.35, implicating the DQB1*0302 allele as a critical susceptibility allele. There are some dramatically protective DR-DQ haplotypes (e.g., DRB1*1501-DQA1*0102-DQB1*0602 [OR = 0.03], DRB1*1401-DQA1*0101-DQB1*0503 [OR = 0.02], and DRB1*0701-DQA1*0201-DQB1*0303 [OR = 0.02]). The DR2 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) is dominantly protective and is present in 20% of the general population but is seen in only 1% of patients with T1DM.

Role of Aspartate at Position 57 in DQB1

DQB1*0302 (high risk for diabetes) differs from DQB1*0301 (protective against diabetes) only at position 57, where it lacks an aspartic acid

residue. The DQB1*0201 allele (increased risk for diabetes) also lacks aspartic acid at position 57, and it has been proposed that the presence of aspartate at this position alters the protein-recognition and protein-binding characteristics of this molecule. Although the absence of aspartate at this position appears to be important in most studies on White individuals, it does not have the same role in Korean and Japanese populations. Moreover, certain low-risk DQB1 genotypes also lack aspartic acid at position 57, including DQB1*0302/DQB1*0201 (DR7) and DQB1*0201 (DR3)/DQB1*0201 (DR7). Thus the presence of aspartate at this position is usually, but not always, protective in White populations but not necessarily in other populations.

Role of Human Leukocyte Antigen Class I

Although the alleles of class II HLA genes appear to have the strongest associations with diabetes, recent genotyping studies and analyses of pooled data have identified associations with other elements in the HLA complex, especially HLA-A and HLA-B. The most significant association is with HLA-B39, which confers high risk for T1DM in three different populations, makes up the majority of the signal from HLA-B, and is associated with a lower age of onset of the disease.

Non-MHC/HLA Genes Associated with T1DM Risk

The second locus found to be associated with risk of T1DM was localized to a region upstream of the *INS*. Susceptibility in this region has been primarily mapped to a variable number of tandem repeats approximately 500 base pairs (bp) upstream of the insulin gene. This highly polymorphic region consists of anywhere from 30 to several hundred repeats of a 14- to 15-bp unit sequence (ACAGGGGTCTGGGG). The high-risk allele has been found to be associated with lower insulin and messenger RNA (mRNA) production in the thymus, suggesting a possible mechanism for decreased immune tolerance to insulin. A number of candidate genes linked to T1DM susceptibility have also been associated with increased risk of *other* autoimmune disease. These include the genes *PTPN22, IL2RA, CTLA4,* and *IFIH1,* which are involved in immune system regulation. Others, such as *ERBB3* and *BAD,* are thought to be associated with cell apoptosis.

ENVIRONMENTAL FACTORS

That ~45–70% of monozygotic twins are discordant for T1DM, the variation seen in urban and rural areas populated by the same ethnic group, the change in incidence that occurs with migration, the increase in incidence that has been seen in almost all populations in the last few decades, and the occurrence of seasonality all provide evidence that environmental factors also play a significant role in the causation of T1DM.

Viral Infections

It is possible that various viruses play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism, stands out in the environmental etiology of T1DM. Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts. Invoked mechanisms involve direct infection of β cells by viruses resulting in lysis and release of self-antigens, direct viral infection of antigen-presenting cells causing increased expression of cytokines, and molecular mimicry, which is the notion that viral antigens exhibit homology to self-epitopes.

The clearest evidence of a role for viral infection in human T1DM is seen in congenital rubella syndrome. Prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children. The time lag between infection and development of diabetes may be as large as 20 years. T1DM after congenital rubella is more likely in patients who carry the higher-risk genotypes. Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth or when live-virus rubella immunization is used.

Studies have shown an increase in evidence of enteroviral infection in patients with T1DM and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently develop T1DM. It has been reported that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM in some cases. Although mumps may play a role in some cases, the fact that T1DM incidence has increased steadily in several countries after universal mumps vaccination was introduced and that the incidence is extremely low in several populations where mumps is still prevalent indicates that mumps alone is not a major causal factor in diabetes.

The Hygiene Hypothesis: Possible Protective Role of Infections

Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes. The hygiene hypothesis states that T1DM risk is increased in industrialized countries, where the observation that there are fewer infections implies that the immune system is less well trained for its main task, namely host defense. Some call this theory the *microbial deprivation hypothesis*. The hygiene hypothesis states that lack of exposure to childhood infections may increase an individual's chances of developing autoimmune diseases, including T1DM. Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed. The incidence of T1DM differs almost sixfold between Russian Karelia and Finland, even though both are populated by genetically related populations and are adjacent to each other and at the same latitude. The incidence of autoimmunity in the two populations varies inversely with immunoglobulin (Ig) E antibody levels, and IgE is involved in the response to parasitic infestation. All these observations suggest that decreased exposure to certain parasites and other microbes in early childhood may lead to an increased risk of autoimmunity in later life, including autoimmune diabetes. Nonetheless, retrospective case-control studies have been equivocal at best, and direct evidence of protection by childhood infections is still lacking.

Gastrointestinal Microbiome

There is emerging evidence that the intestinal microbiome is altered in T1DM; however, a cause-and-effect relationship has yet to be established. Human studies have found that the intestinal microbiome in T1DM has decreased diversity of microbial species and contains fewer butyrate-producing organisms compared to healthy controls. Butyrate is a short-chain fatty acid that is thought to be antiinflammatory and may have a role in protecting the intestinal epithelium, either directly or indirectly, through an effect to increase mucin production. Theoretically, a disruption in epithelial integrity (the so-called *leaky gut*) could trigger inflammation and an enhanced autoimmune response because of increased entry of pathogenic or dietary antigens into the bloodstream. Early, small-scale prospective studies in infants and children at high risk for T1DM have shown an imbalance favoring species including *Bacteroides dorei* and *Bacteroides vulgatus* among individuals who went on to develop T1DM autoantibodies or disease compared with those who did not. A larger study across six different study sites in The Environmental Determinants of Diabetes in the Young (TEDDY) study identified significant geographic differences in fecal microbiome composition, highlighting the challenges in this field of study.

Diet

Dietary exposure may modify T1DM risk; a definitive link between any single dietary exposure and T1DM development has not been found. The majority of interventional studies have not shown an effect of delayed gluten exposure or the use of hydrolyzed formula to reduce the risk for development of T1DM autoantibodies of disease. A meta-analysis of both interventional and observational studies concluded that there was no association between early exposure of gluten or milk protein and risk of T1DM. Some, but not all, studies have suggested that breastfeeding lowers the risk of T1DM. The potential mechanism for a protective effect of breast milk is not well understood but could be related to a beneficial effect of breast milk on the infant immune system or an indirect effect such as reduced exposure to other dietary antigens early in life. Timing of solid food introduction may modify T1DM risk, as seen in a report from the Diabetes Autoimmunity Study in the

Young (DAISY), which found that both early (before 4 months of age) and late (after 6 months of age) introduction of solid foods predicted development of T1DM.

Other dietary factors that have been suggested at various times as playing a role in T1DM risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), and deficiency is more common in northern countries like Finland where T1DM incidence is highest; however, most observational studies have failed to find associations between vitamin D level or supplementation and T1DM risk. Interventional studies to assess the effect of vitamin D supplementation on T1DM risk are lacking.

PATHOGENESIS AND NATURAL HISTORY OF TYPE 1 DIABETES MELLITUS

In T1DM, a genetically susceptible host develops autoimmunity against the host's own β cells. What triggers this autoimmune response is complex and multifactorial. In some (but not all) patients, this immune-mediated process results in progressive destruction of β cells until a critical mass of β cells is lost and insulin deficiency develops. Insulin deficiency, in turn, leads to the onset of clinical signs and symptoms of T1DM. At the time of diagnosis, if viable β cells are still present and produce some insulin, there may be a partial remission of the disease (**honeymoon period**), but over time, more β-cell mass is destroyed, despite any regeneration and/or persistence of β cells, and the patient becomes totally dependent on exogenous insulin for survival (Fig. 629.2). Over time, some of these patients develop secondary complications of diabetes that appear, in part, to be related to how well-controlled the diabetes has been. The natural history of T1DM involves some or all of the following stages, with two distinct identifiable stages before onset of symptoms:

1. Persistence of one or more islet autoantibodies with normoglycemia and presymptomatic; can last years to decades (onset of autoimmune islet disease AID])
2. β-cell autoimmunity with dysglycemia and presymptomatic; shorter
3. Onset of symptomatic disease; usually quite brief, weeks, rarely months
4. Transient remission, usually within weeks of onset, may last 6-12 months ("honeymoon")
5. Established disease, lifelong
6. Development of complications, quite variable

Initiation of Autoimmunity

Genetic susceptibility to T1DM is determined by several genes, with the largest contribution coming from variants in the HLA system. Nonetheless even with the highest-risk haplotypes, most carriers will not develop T1DM. In monozygotic twins, the concordance of the development of T1DM is reported to be 30–65%. The observed rise in incidence of T1DM, and particularly so in younger children with an essentially genetically stable patient population, implies that something has accordingly changed in the environment. A number of factors, including maternal and intrauterine environmental influences, route of neonatal delivery, foods and diet in infancy, viral infections, lack of exposure to certain infections and antibiotic use, host microbiome, and even psychologic stress, are implicated in the pathogenesis of T1DM, but their exact role and the mechanism by which they trigger or aggravate autoimmunity remain uncertain. What is clear is that markers of autoimmunity are much more prevalent than clinical T1DM, indicating that initiation of autoimmunity is a necessary, but not a sufficient, condition for T1DM. Although no conclusive triggering factor has been identified, it seems that in most cases of T1DM that are diagnosed in childhood, the onset of autoimmunity occurs very early in life. In most children diagnosed before age 10 years, the first signs of autoimmunity appear before age 2 years. Development of autoimmunity is associated with the appearance of several autoantibodies. IAAs are usually the first to appear in young children, followed by GAD, and later by IA-2 and ZnT8 antibodies. The earliest antibodies are predominantly of the IgG_1 subclass. Not only is there spreading of autoimmunity to more antigens (IAA, GAD, IA-2A, ZnT8) but there is also epitope spreading within one antigen. Initial GAD antibodies tend to be against the middle region or the carboxyl-terminal region, whereas amino terminal antibodies usually appear later and are less common in children.

Preclinical Autoimmunity with Progressive Loss of β-Cell Function

In nearly all patients, the appearance of autoimmunity is followed by progressive or eventual destruction of β cells (Figs. 629.3 and 629.4).

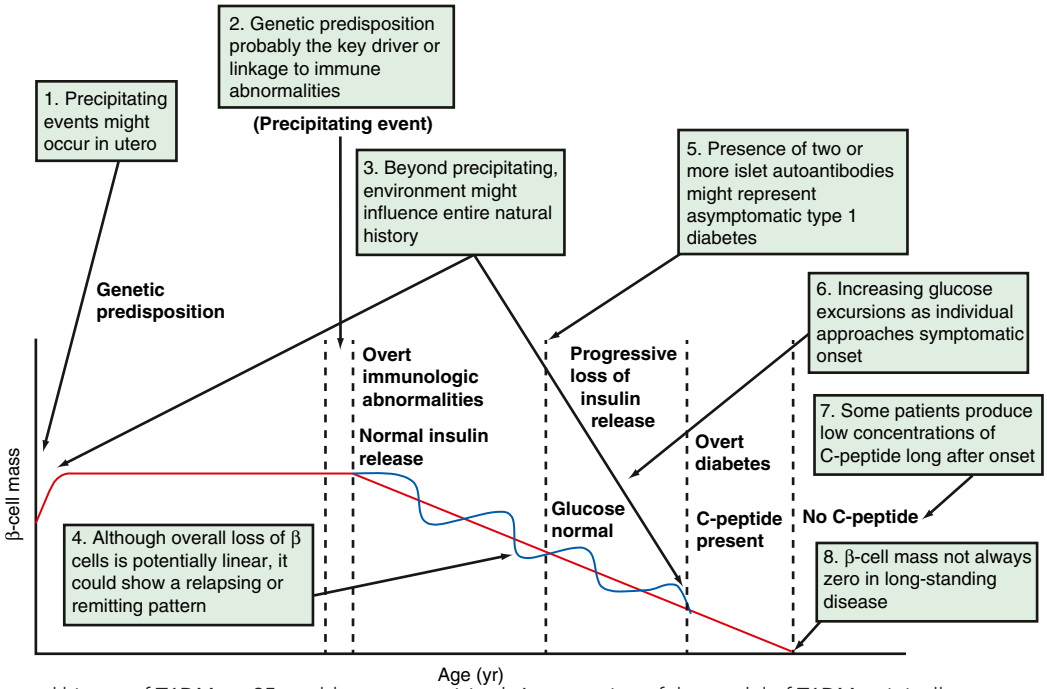

Fig. 629.2 The natural history of T1DM—a 25-yr-old concept revisited. A re-creation of the model of T1DM, originally proposed in 1986, is shown in *black*. Additions and conjectures based on recent knowledge gains are shown in *green boxes*. *(From Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383:69–78. Fig. 4.)*

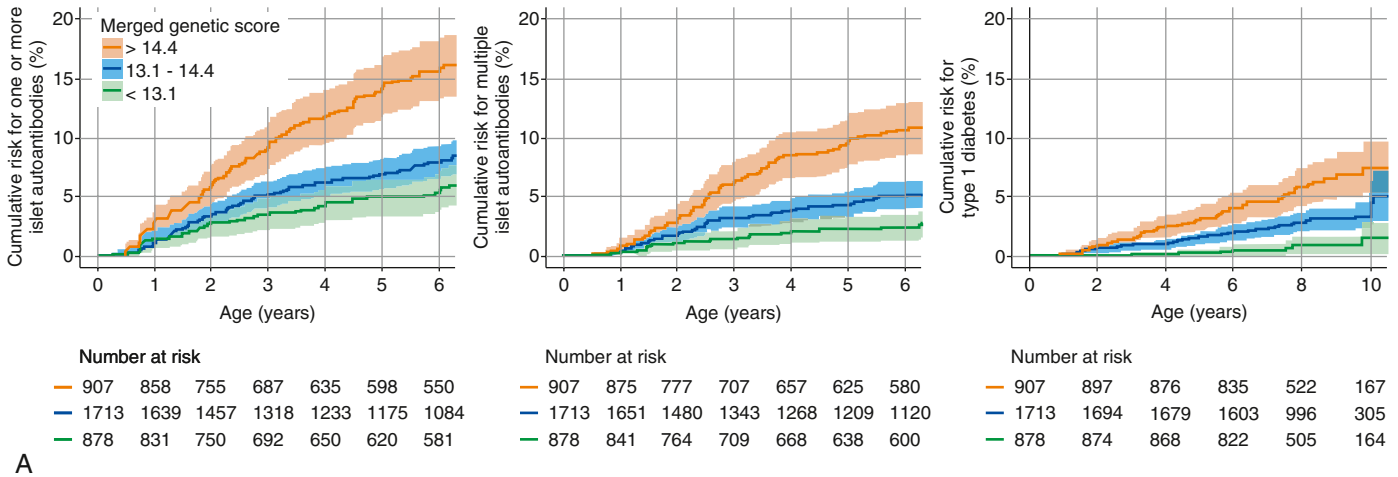

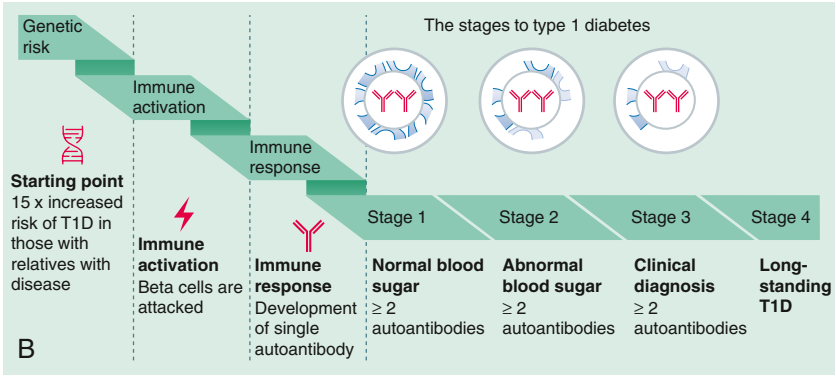

Fig. 629.3 Contributing factors and disease progression in type 1 diabetes. **A,** Cumulative risks of one or more islet autoantibodies, multiple islet autoantibodies, and type 1 diabetes development in TEDDY children with the HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8 genotype stratified by their merged score. The cumulative risk of developing one or more islet autoantibodies *(left graph)*, multiple islet autoantibodies *(middle graph)*, and type 1 diabetes (*right graph, y* axis) is shown relative to age in yr (*x* axis) and was calculated using the Kaplan ± Meier method. Curves are shown for children with genetic scores in the upper *(orange line)*, lower *(green line)*, and two middle *(blue line)* quartiles. The shaded areas represent the 95% confidence interval of the cumulative risk. The numbers at risk indicate the number of children included in the analysis at each age. **B,** Type 1 diabetes progression and stages of type 1 diabetes. Stage 1 is the start of type 1 diabetes, marked by individuals having two or more diabetes-related autoantibodies and normal blood sugar concentrations. In stage 2, individuals have dysglycemia without symptoms. Stage 3 is the time of clinical diagnosis. T1D, type 1 diabetes. *(**A** from Bonifacio E, Beyerlein A, Hippich M, et al. Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: A prospective study in children. PLoS Med. 2018;15:e1002548. Fig. 4; **B** from Greenbaum CJ, Speake C, Krischer J, et al. Strength in numbers: opportunities for enhancing the development of effective treatments for type 1 diabetes—the TrialNet experience. Diabetes. 2018;67:1216–1225.)*

Antibodies are a marker for the presence of autoimmunity, but the actual damage to the β cells is primarily T-cell mediated (see Fig. 629.4). Histologic analysis of the pancreas from patients with recent-onset T1DM reveals insulitis, with an infiltration of the islets of Langerhans by mononuclear cells, including T and B lymphocytes, monocytes/macrophages, and natural killer cells. The process in human T1DM is not necessarily linear, and there may be an undulating downhill course, with remissions and relapses, in the development of T1DM.

Role of Autoantibodies

Even though T1DM does not occur as a direct consequence of autoantibody formation, the risk of developing clinical disease increases dramatically with an increase in the number of antibodies; only 15% of children with one antibody will progress to diabetes in 10 years, but this risk increases to 70% when two antibodies are present and 90% when three are present. The risk of progression also varies with the intensity of the antibody response, and those with higher antibody titers are more likely to progress to clinical disease. Another factor that appears to influence progression of β-cell damage is the age at which autoimmunity develops; children in whom IAAs appeared within the first 2 years of life rapidly developed anti–islet cell antibodies and progressed to diabetes more frequently than children in whom the first antibodies appeared between ages 5 and 8 years.

Role of Genetics in Disease Progression

In a large study of *healthy* children, the appearance of single antibodies is relatively common and usually transient and does not correlate with the presence of high-risk HLA alleles; those carrying high-risk HLA alleles are more likely to develop multiple antibodies and progress to disease. Similarly, the appearance of antibodies is more likely to predict diabetes in those with a family history of diabetes versus those with no family history of T1DM. Environmental factors may induce transient autoimmunity in many children, but those with genetic susceptibility are more likely to see progression of autoimmunity and eventual development of diabetes.

Role of Environmental Factors

Environmental factors may also act as accelerators of T1DM after the initial appearance of autoimmunity. This is evident from the fact that the incidence of T1DM can vary several-fold between populations that have the same prevalence of autoimmunity. The incidence of T1DM in Finland is almost fourfold higher than in Lithuania, but the incidence of autoimmunity is similar in both countries.

The fact that all children with evidence of autoimmunity and of autoreactive T cells do not progress to diabetes indicates that there are checkpoints at which the autoimmune process can be halted or reversed before it progresses to full-blown diabetes.

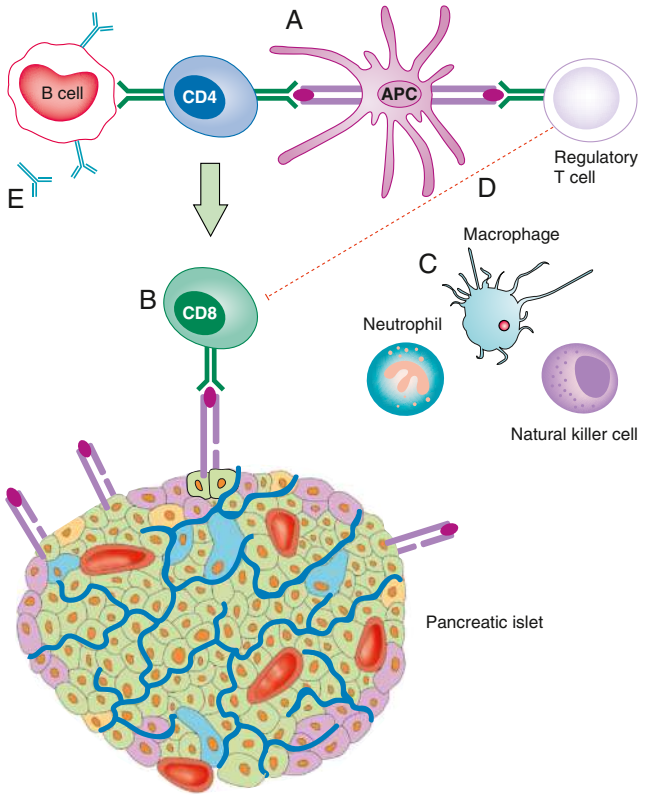

Fig. 629.4 The immunopathogenesis of type 1 diabetes. The development of type 1 diabetes is thought to be initiated by the presentation of β-cell peptides by antigen-presenting cells *(APCs)*. APCs bearing these autoantigens migrate to the pancreatic lymph nodes, where they interact with autoreactive $CD4^+$ T lymphocytes, which in turn mediate the activation of autoreactive $CD8^+$ T cells *(A)*. These activated $CD8^+$ T cells return to the islet and lyse β cells expressing immunogenic self-antigens on major histocompatibility complex class I surface molecules *(B)*. β-Cell destruction is further exacerbated by the release of proinflammatory cytokines and reactive oxygen species from innate immune cells (macrophages, natural killer cells, and neutrophils) *(C)*. This entire process is amplified by defects in regulatory T lymphocytes, which do not effectively suppress autoimmunity *(D)*. Activated T cells within the pancreatic lymph node also stimulate B lymphocytes to produce autoantibodies against β-cell proteins. These autoantibodies can be measured in circulation and are considered a defining biomarker of type 1 diabetes *(E)*. *(From DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391:2449–2458. Fig. 3.)*

Onset of Clinical Disease

Patients with progressive β-cell destruction will eventually present with clinical T1DM. It was thought that 90% of the total β-cell mass is destroyed by the time clinical disease develops, but other studies have revealed that this is not always the case. It appears that β-cell destruction is more rapid and more complete in younger children, whereas in older children and adults, the proportion of surviving β cells is greater (10–20% in autopsy specimens), and some β cells (about 1% of the normal mass) survive up to 30 years after the onset of diabetes. Because autopsies are usually done only on patients who died of DKA, these figures may underestimate the actual β-cell mass present at diagnosis. Functional studies indicate that up to 40% of the insulin secretory capacity may be preserved in adults at the time of presentation of T1DM. Ultrasensitive assays indicate that C-peptide production is measurable decades after the onset of T1DM. The fact that newly diagnosed diabetic individuals may still have a significant surviving β-cell mass is important because it raises the possibility of *secondary* prevention of T1DM. Similarly, the existence of viable β cells years or decades after initial presentation indicates that even patients with long-standing diabetes may be able to exhibit some recovery of β-cell function if the autoimmune destructive process could be halted and if islet cell regeneration could occur.

PREDICTION

Autoimmunity precedes clinical T1DM, and indicators of autoimmune responses may be useful markers for disease prediction. Individuals at risk for T1DM can be identified by a combination of genetic, immunologic, and metabolic markers. The most informative genetic locus, HLA class II, confers about half of the total genetic risk but has a low positive predictive value (PPV) when used in the general population. Autoantibodies provide a practical readout of β-cell autoimmunity, are easily sampled in venous blood, and have become the mainstay of T1DM prediction efforts. By comparison, and even though T lymphocytes mediate β-cell destruction, T cells are rare in blood, and assays of their function have been difficult to standardize and validate. In the first-degree relatives of patients with T1DM, the number of positive autoantibodies can help estimate the risk of developing T1DM: low risk (single autoantibodies: PPV of 2–6%), moderate risk (2 autoantibodies: PPV of 21–40%), and high risk (>2 autoantibodies: PPV of 59–80%) over a 5-year period. In children carrying the T1DM highest-risk genotype (HLA-DQB1*0201-DQA1*05/DQB1*0302-DQA1*03), insulitis is almost 10 times more frequent (PPV 21%) than in children with other genotypes (PPV 2.2%). But although autoantibodies are useful for the prediction of T1DM in the relatives of patients with T1DM, outside of that obvious population, the screening of the general population would be required to identify healthy subjects at risk of T1DM. Indeed, ~90% of individuals with new-onset T1DM have no family background of T1DM. Screening the general population is difficult to justify, in part, because the observed autoantibody prevalence greatly exceeds the low disease prevalence in nonrelatives, leading to high false-positive rates.

PREVENTION

Strategies for the prevention of T1DM are focused primarily on slowing progression of β-cell loss after the onset of autoimmune islet disease through targeted immunosuppression of autoreactive regulatory T cells. Numerous compounds are under investigation for this purpose, including agents that could modulate regulatory T cells via stimulating interleukin (IL)-2, tumor necrosis factor (TNF)-α signaling, or CTLA signaling and by inhibiting IL-17 or T-cell receptor (TCR) signaling. Teplizumab, a humanized anti-CD3 monoclonal antibody that inhibits TCR signaling, has been shown to delay the onset of clinical diabetes in high-risk children and young adults. It is approved for use in the United States for patients 8 years and older with stage 2 T1DM, defined by at least two positive pancreatic islet cell autoantibodies and dysglycemia without hyperglycemia.

PATHOPHYSIOLOGY OF T1DM

Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use. Insulin levels must be lowered to then mobilize stored energy during the fasted state. Thus in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue (Table 629.4). T1DM is a progressive low-insulin catabolic state in which feeding does not reverse, but rather exaggerates, these catabolic processes. With moderate insulinopenia, glucose use by muscle and fat decreases and postprandial hyperglycemia appears. At even lower insulin levels, the liver produces excessive glucose via glycogenolysis and gluconeogenesis, and fasting hyperglycemia begins. Hyperglycemia produces an osmotic diuresis (glycosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L). The resulting loss of calories and electrolytes, as well as the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon). These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting

Table 629.4 Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue*

	HIGH PLASMA INSULIN (POSTPRANDIAL STATE)	LOW PLASMA INSULIN (FASTED STATE)
Liver	Glucose uptake	Glucose production
	Glycogen synthesis	Glycogenolysis
	Absence of gluconeogenesis	Gluconeogenesis
	Lipogenesis	Absence of lipogenesis
	Absence of ketogenesis	Ketogenesis
Muscle	Glucose uptake	Absence of glucose uptake
	Glucose oxidation	Fatty acid and ketone oxidation
	Glycogen synthesis	Glycogenolysis
	Protein synthesis	Proteolysis and amino acid release
Adipose tissue	Glucose uptake	Absence of glucose uptake
	Lipid synthesis	Lipolysis and fatty acid release
	Triglyceride uptake	Absence of triglyceride uptake

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, if untreated, results in exaggerated fasting.

glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose use and glucose clearance (epinephrine, growth hormone, cortisol).

The combination of insulin deficiency and elevated plasma values of the counterregulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids. The hormonal interplay of insulin deficiency and glucagon excess shunts the free fatty acids into ketone body formation; the supranormal rate of formation of these ketone bodies, principally β-hydroxybutyrate and acetoacetate, exceeds the capacity for peripheral use and renal excretion. Accumulation of these keto acids results in metabolic acidosis (DKA) and compensatory rapid, deep, nondyspneic breathing to excrete excess CO_2 (Kussmaul respiration). Acetone, formed by nonenzymatic conversion of acetoacetate, is responsible for the characteristic fruity odor of the breath. Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte and bicarbonate regenerating ability. With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen use, consciousness becomes impaired, and the patient ultimately becomes comatose.

CLINICAL MANIFESTATIONS

The classic clinical manifestations of new-onset diabetes in children reflect the hyperglycemic and catabolic physiologic state and include polyuria, polydipsia, polyphagia, and weight loss. Other common symptoms include fatigue, weakness, and a general feeling of malaise. Patients presenting with more advanced disease will exhibit signs of **DKA**, including dehydration, nausea, vomiting, lethargy, altered mental status, and in extreme cases, coma. If the diagnosis is not recognized, the progression of symptoms follows a predictable course from early intermittent polyuria, to sustained polyuria and weight loss, followed by development of DKA. In most cases, this initial progression occurs over a period of weeks rather than months.

Initially, when only insulin reserve is limited, occasional asymptomatic postprandial hyperglycemia occurs. When insulin secretory capacity declines, blood glucose levels begin to rise. When the blood glucose increases above the renal threshold, intermittent polyuria and/or nocturia begins. With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, which often includes nocturnal enuresis in younger children. Female patients may develop vulvovaginal candidiasis from the chronic glycosuria. Eventually, daily losses of water and glucose may be as high as 5 L and 250 g, respectively, representing 1,000 calories, or 50%, of the average daily caloric intake. These losses trigger compensatory polydipsia and polyphagia; however, progressive dehydration and weight loss will inevitably ensue unless treatment is initiated.

When the disease continues to progress, ketoacids begin to accumulate. At this stage in the disease, rapid clinical deterioration is possible. Ketoacids produce abdominal pain, anorexia, nausea, and emesis and thereby impede the patient's ability to maintain sufficient oral replacement of urinary water losses. Dehydration accelerates, as manifested by weakness, orthostasis, and further weight loss. As in any hyperosmotic state, the degree of dehydration may be clinically underestimated because intravascular volume is conserved at the expense of intracellular volume. Signs and symptoms of advanced ketoacidosis include Kussmaul respirations (deep, heavy, nonlabored, rapid breathing), fruity breath odor (acetone), prolonged corrected Q-T interval, diminished neurocognitive function, and coma. Approximately 20–40% of children with new-onset diabetes progress to DKA before diagnosis; data from the United States suggest that the prevalence of DKA at onset of T1DM is increasing.

Clinical progression typically happens more quickly in younger children, owing to either more aggressive autoimmune destruction of β-cells and/or to lower β-cell mass. Disease onset in infancy is associated with a greater likelihood of DKA at presentation. Weight loss in younger children and individuals with more rapidly progressive disease will be composed mostly of acute fluid loss, whereas weight loss in adolescents and individuals with slowly progressive disease will also include significant fat and lean mass deficits as a result of prolonged starvation. In any child, the progression of symptoms may be accelerated by the stress of an intercurrent illness or trauma, when counterregulatory (stress) hormones counter the limited insulin secretory capacity.

DIAGNOSIS

The diagnosis of T1DM is usually straightforward (see Table 629.2). Although most symptoms are nonspecific, the most important clue is an inappropriate polyuria in any child with signs of dehydration and poor weight gain. Hyperglycemia can be identified quickly from capillary blood by use of a glucometer; glycosuria and ketonuria can readily be determined by urine dipstick. Nonfasting blood glucose greater than 200 mg/dL (11.1 mmol/L) with typical symptoms is diagnostic with or without ketonuria. In the obese child, T2DM must be considered (see Chapter 629.3). Once hyperglycemia is confirmed, it is prudent to determine whether DKA is present (especially if ketonuria is found) by checking a venous blood sample for bicarbonate and pH and also to evaluate for electrolyte abnormalities—even if signs of dehydration are minimal. A baseline HbA_{1c} will be confirmatory and allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy. Falsely low HbA_{1c} levels are noted in hemolytic anemias (sickle cell anemia, others), pure red cell aplasia, blood transfusions, and anemias associated with hemorrhage, cirrhosis, myelodysplasias, or renal disease treated with erythropoietin.

Testing for autoimmunity (T1DM autoantibodies) (see Chapter 629.1) should be considered in cases where the differentiation between T1DM and T2DM is not apparent and in cases where there is a strong family history suggestive of monogenic and syndromic diabetes. The presence of other autoimmune diseases associated with T1DM should be sought at or shortly after diagnosis, including celiac disease (by tissue transglutaminase immunoglobulin A [IgA] and total IgA) and autoimmune hypothyroidism (by thyroid-stimulating hormone [TSH] and free or total thyroxine). Because significant physiologic perturbations can affect thyroid and celiac screening tests, individuals with

only mild abnormalities should have tests repeated *after* several weeks before instituting therapy. In addition, because there is an increased risk of cardiovascular disease associated with diabetes, it is also recommended to obtain a fasting lipid profile in children ≥10 years of age once glucose control has been established.

Rarely, a child has transient hyperglycemia with glycosuria while under substantial physical stress or illness. This usually resolves permanently during recovery from the stressors. **Stress-produced hyperglycemia** can reflect a limited insulin reserve temporarily revealed by elevated counterregulatory hormones. A child with temporary hyperglycemia should therefore be monitored for the development of symptoms of persistent hyperglycemia and be tested with an HbA_{1c} if such symptoms occur. Formal testing in a child who remains clinically asymptomatic is not necessary.

Routine screening procedures, such as postprandial determinations of blood glucose or screening OGTTs, have yielded low detection rates in healthy, asymptomatic children, even among those considered at risk, such as siblings of diabetic children. Accordingly, such screening procedures are not recommended in children.

TREATMENT

Therapy is tailored to the degree of insulinopenia at presentation. Most children with new-onset T1DM have mild to moderate symptoms, have minimal dehydration with no history of emesis, and have not progressed to ketoacidosis. They can be started on subcutaneous insulin therapy directly. About 20–40% of children with new-onset diabetes present in DKA, which can be arbitrarily classified as mild, moderate, or severe (Table 629.5), and the range of symptoms depends on the degree of ketoacidosis. Cardinal biochemical abnormalities include elevations in blood and urine ketones, an increased anion gap, a decreased serum bicarbonate (or total CO_2) and pH, and an elevated effective serum osmolality. Hyponatremia is commonly present with hyperglycemia and is the result of an osmotic dilution as water shifts into the extracellular fluid. Potassium and phosphate depletion is common after prolonged polyuria but may be masked by acidosis, which leads to extracellular shifting of these ions.

Treatment of Diabetic Ketoacidosis

Severe insulinopenia (or lack of effective insulin action) results in a physiologic cascade of events in three general pathways:

1. Excessive glucose production coupled with reduced glucose use raises serum glucose. This triggers an osmotic diuresis, with urinary loss of fluid and electrolytes, dehydration, and activation of the renin-angiotensin-aldosterone axis with accelerated potassium loss. When glucose elevation and dehydration are severe and persist for several hours, the risk of cerebral edema increases.
2. Increased catabolic processes result in cellular losses of sodium, potassium, and phosphate.
3. Increased release of free fatty acids from peripheral fat stores supplies substrate for hepatic ketoacid production. When ketoacids accumulate, buffer systems are depleted, and a metabolic acidosis ensues.

Therapy must address both the initiating event in this cascade (insulinopenia) and the subsequent physiologic disruptions.

Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema. Any protocol must be used with caution and close monitoring of the patient. Adjustments based on sound medical judgment may be necessary for any given level of DKA (Figs. 629.5 and 629.6).

Dehydration and Hyperglycemia

Judicious fluid resuscitation is the first step in the medical management of DKA. Correction of fluid deficits must be tempered by the potential risk of cerebral edema. It is prudent to approach any child in any hyperosmotic state with cautious rehydration. The effective serum osmolality ($E_{osm} = 2 \times [Na_{uncorrected}] + [glucose]$) is an accurate index of tonicity of the body fluids, reflecting intracellular and extracellular hydration better than measured plasma osmolality. It is calculated with sodium and glucose in mmol/L. This value is usually elevated at the beginning of therapy and should steadily normalize. A rapid decline, or a slow decline to a subnormal range, may indicate an excess of free water entering the vascular space and an increasing risk of cerebral edema. Therefore patients should not be allowed oral fluids until rehydration is well underway and significant electrolyte shifts are no longer likely. Limited ice chips may be given as a minimal oral intake. All fluid intake and output should be closely monitored.

Calculation of fluid deficits using clinical signs is difficult in children with DKA because intravascular volume is better maintained in the hypertonic state. For any degree of tachycardia, delayed capillary refill, decreased skin temperature, or orthostatic blood pressure change, the child with DKA will be more dehydrated than the child with a normotonic fluid deficit. Typically, an initial intravenous bolus of 10-20 mL/kg of glucose-free isotonic sodium salt solution such as Ringer lactate or 0.9% sodium chloride is given over 1 to 2 hours. Further fluid boluses should be given only for hemodynamically unstable patients. This bolus is given as isotonic saline because the patient is inevitably hypertonic, keeping most of the initial infusion in the intravascular space. Subsequent fluid replacement then consists of 0.45% or 0.9% sodium chloride infused at a rate calculated to replace the fluid deficit (after subtracting initial fluid bolus) over 24-48 hours plus maintenance. The fluid deficit can be calculated empirically if a recent weight is available, estimated at 5–10% of body weight based upon clinical severity, or by assuming a standard water deficit (85 mL/kg). Practically, this is generally equivalent to a rate of ~1.5 times maintenance, which can be substituted for simplicity in most situations.

The optimal fluid protocol to prevent CNS complications (cerebral edema) of DKA remains uncertain. When children with DKA were randomly assigned to one of four treatment arms consisting of fast or slow fluid deficit repletion of 0.9% or 0.45% sodium chloride, there were no differences in short- or long-term neurocognitive outcomes among any of the treatment arms. In general, after reestablishing the intravascular volume and avoiding rapid declines of blood glucose levels and hyponatremia, fluid replacement rates or fluid composition may subsequently be administered per protocol (see Fig. 629.5). *It is possible that cerebral injury preceded therapy and is the result of DKA and not rates or composition of IV fluids.*

Insulin must be given to promote movement of glucose into cells, to subdue hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver. An initial IV insulin bolus does not speed recovery and may increase the risk of hypokalemia and hypoglycemia. *Therefore insulin infusion is typically begun without an insulin bolus at*

Table 629.5 Classification of Diabetic Ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE*
HCO_2 (mEq/L, venous)†	20-28	16-20	10-15	<10
pH (venous)†	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.
†HCO_2 and pH measurement are method dependent; normal ranges may vary.

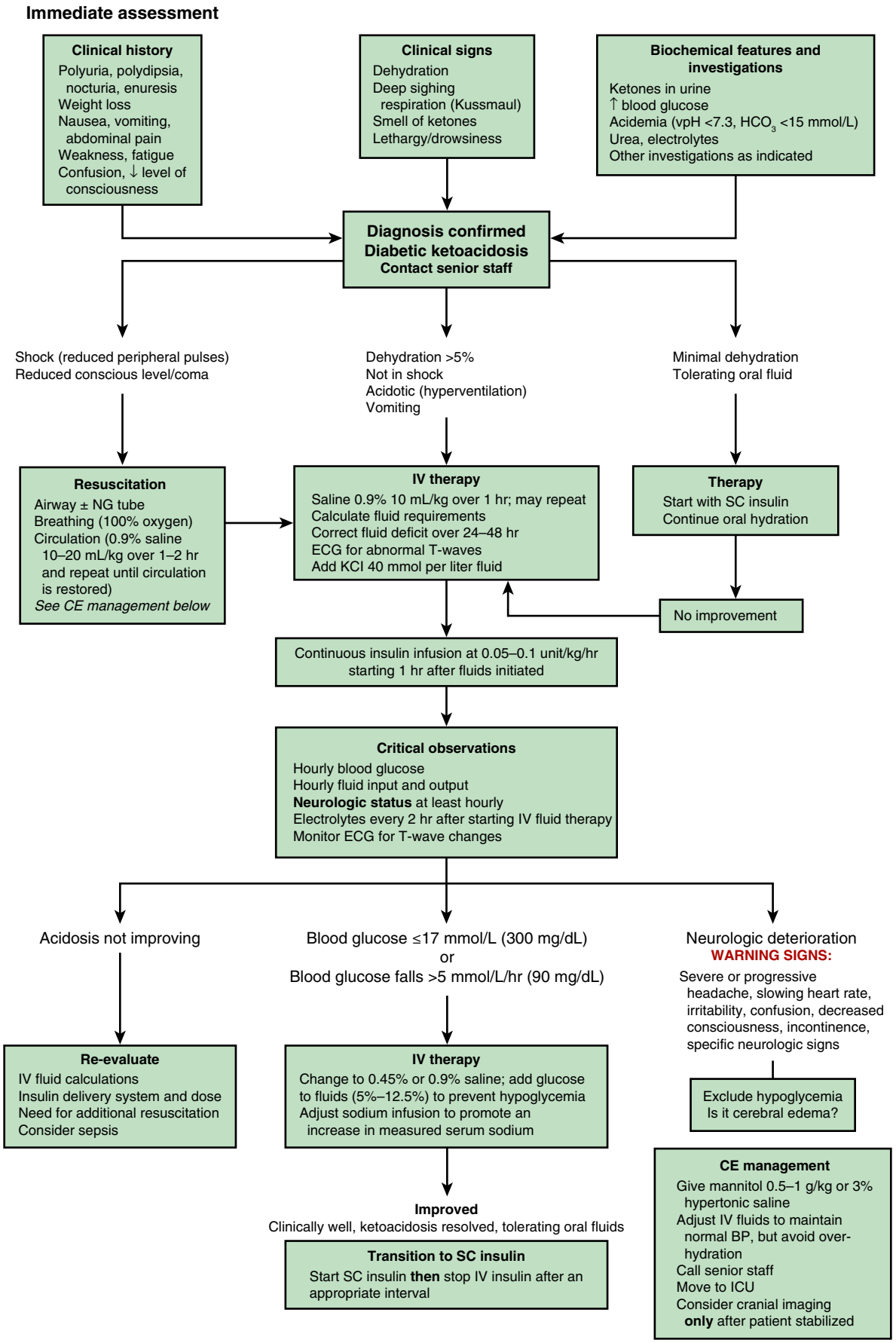

Fig. 629.5 Algorithm for the management of diabetic ketoacidosis. CE, cerebral edema; ECG, electrocardiogram; KCl, potassium chloride; SC, subcutaneous. *(Adapted from Pinhas-Hamiel O, Sperling M. Diabetic ketoacidosis. In: Hochberg Z, ed. Practical Algorithms in Pediatric Endocrinology. 3rd ed. Basel, Switzerland: Karger; 2017:112–113.)*

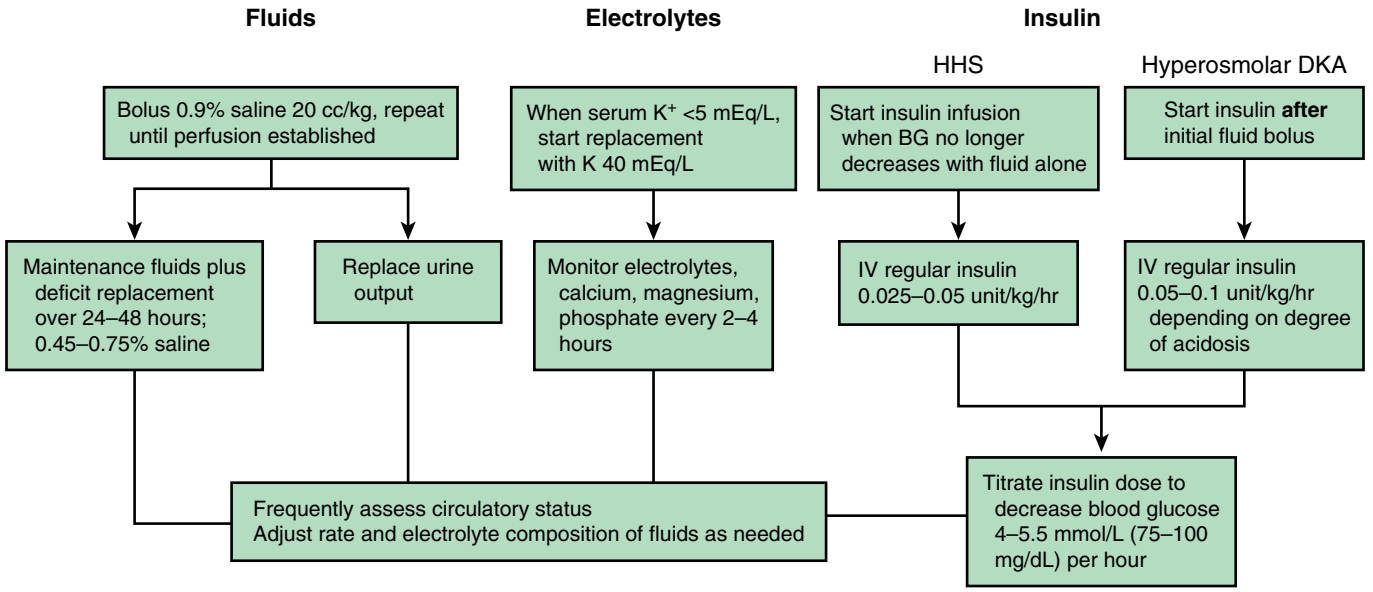

Fig. 629.6 Algorithm for the treatment of hyperglycemic hyperosmolar syndromes (HHS). BG, blood glucose. *(From Zeitler P, Haqq A, Rosenbloom A, Glaser N. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr. 2011;158(1):9–14, 14.e1–2.)*

a rate of 0.05 to 0.1 units/kg/hr after initial fluid resuscitation is complete. This approximates maximal insulin output in normal subjects during an OGTT. Rehydration alone also lowers glucose levels by improving renal perfusion and enhancing renal excretion. The combination of these therapies usually causes a rapid initial decline in serum glucose levels. Persistent decreases in serum glucose of >100 mg/dL/hr may increase the risk of cerebral edema; therefore careful monitoring of serum glucose and adjustment of the dextrose concentration of the IV fluids is essential. The dextrose concentration of the IV fluids should be 5% (D5) once serum glucose falls below ~300 mg/dL and 10% once glucose is below 200 mg/dL. The use of a two-bag system is the preferred approach for managing the dextrose concentrations of the infused IV fluid during DKA. A two-bag system consists of two IV bags of identical electrolyte concentrations, where one bag contains 0% dextrose and the other contains 10% dextrose. The fluids are administered via a Y-site and can be easily titrated to infuse fluids ranging from 0% to 10% dextrose.

Once the blood glucose level decreases below ~180 mg/dL (10 mmol/L), the osmotic diuresis stops and rehydration accelerates without further increase in the infusion rate. Repair of hyperglycemia occurs well before correction of acidosis. Therefore insulin is still needed to control fatty acid release and ketosis after normal glucose levels are reached. If serum glucose levels fall below 100 mg/dL despite an infusion of D10-containing IV fluids, the glucose infusion rate can be increased by increasing dextrose to 12.5% or by increasing the infusion rate. Alternatively, the IV insulin rate can be decreased if ketosis continues to improve.

The initial serum sodium is usually normal or low because of the osmolar dilution caused by hyperglycemia and the effect of an elevated sodium-free lipid fraction. An estimate of the reconstituted, or "true," serum sodium for any given glucose level above 100 mg/dL (5.6 mmol/L) is calculated as follows:

$$\left[Na^+\right] + \left(\begin{array}{l}1.6\,\text{mEq/L}\,Na^+ \text{ for every } 100\,\text{mg/dL glucose in}\\ \text{excess of } 100\end{array}\right)$$

or

$$\left[Na^+\right] + \left(\frac{1.6\,\text{mEq}}{\begin{array}{l}\text{L}Na^+ \text{ for every } 5.6\,\text{mmol}\\ \text{L glucose}\end{array}} \text{ in excess of } 5.6\right)$$

The sodium should *increase* by approximately 1.6 mmol/L for each 100 mg/dL *decline* in the glucose. The corrected sodium is usually normal or slightly elevated and indicates moderate hypernatremic dehydration. If the corrected value is greater than 150 mmol/L, severe hypernatremic dehydration may be present and may require *slower* fluid replacement. The sodium should steadily increase with therapy. *Declining sodium may indicate excessive free water accumulation and increased risk of cerebral edema.*

Both the metabolic shift to a catabolic predominance and the acidosis move potassium and phosphate from the cell to the serum. The osmotic diuresis, the kaliuretic effect of the hyperaldosteronism, and the ketonuria then accelerate renal losses of potassium and phosphate. Sodium is also lost with the diuresis, but free water losses are greater than isotonic losses. With prolonged illness and severe DKA, total body losses can approach 10-13 mEq/kg of sodium, 5-6 mEq/kg of potassium, and 4-5 mEq/kg of phosphate. These losses continue for several hours during therapy until the catabolic state is reversed and the diuresis is controlled. For example, 50% of infused sodium may be lost in the urine during IV therapy. Even though the sodium deficit may be repaired within 24 hours, intracellular potassium and phosphate may not be completely restored for several days.

Although patients with DKA have a total body potassium deficit, the initial serum level is often normal or elevated. This is caused by the movement of potassium from the intracellular space to the serum, both as part of the ketoacid buffering process and as part of the catabolic shift. These effects are reversed with therapy, and potassium returns to the cell. Improved hydration increases renal blood flow, allowing for increased excretion of potassium in the elevated aldosterone state. The net effect is often a dramatic decline in serum potassium levels, especially in severe DKA. This can precipitate changes in cardiac conductivity, flattening of T waves, and prolongation of the QRS complex and can cause skeletal muscle weakness or ileus. The risk of myocardial dysfunction is increased with shock and acidosis. Potassium levels must be closely followed and electrocardiographic monitoring continued until DKA is substantially resolved. Potassium should be added to the IV fluids once serum potassium declines below 5.5 mEq/L and titrated. A 1:1 mixture of potassium chloride (or acetate) and potassium phosphate is typically used. Rarely, the IV insulin must be temporarily held if serum potassium levels drop below 3 mEq/L. It is unclear whether phosphate deficits contribute to symptoms of DKA such as generalized muscle weakness. In pediatric patients, a deficit has not been shown to compromise oxygen delivery via a deficiency of 2,3-diphosphoglycerate. In most cases, the inclusion of potassium phosphate as outlined earlier will be sufficient; however, additional IV supplementation with potassium phosphate can be used if needed.

Pancreatitis (usually mild) is occasionally seen with DKA, especially if prolonged abdominal distress is present; serum amylase and lipase may be elevated. If the serum lipase is not elevated, the amylase is likely nonspecific or salivary in origin. Serum creatinine adjusted for age may be falsely elevated owing to interference by ketones in the autoanalyzer methodology. An initial elevated value rarely indicates renal failure and should be rechecked when the child is less ketonemic. Blood urea nitrogen may be elevated with prerenal azotemia and should be rechecked as the child is rehydrated. Mildly elevated creatinine or blood urea nitrogen is not a reason to withhold potassium therapy if good urinary output is present.

Ketoacid Accumulation

Low insulin infusion rates (0.02-0.05 units/kg/hr) are usually sufficient to stop peripheral release of fatty acids, thereby eliminating the flow of substrate for ketogenesis. Ketogenesis continues until fatty acid substrates already in the liver are depleted, but this production declines much more quickly without new substrate inflow. Bicarbonate buffers, regenerated by the distal renal tubule and by metabolism of ketone bodies, steadily repair the acidosis once ketoacid production is controlled. *Bicarbonate therapy may increase the risk of hypokalemia and cerebral edema; it should be considered only in rare situations with severe acidosis unresponsive to standard DKA management.*

There should be a steady increase in pH and serum bicarbonate as therapy progresses. Kussmaul respirations should abate and abdominal pain resolve. Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or rarely lactic acidosis. Urine ketones may be positive after ketoacidosis has resolved because the nitroprusside reaction routinely used to measure urine ketones by dipstick measures only acetoacetate. During DKA, most excess ketones are β-hydroxybutyrate, which increases the normal ratio to acetoacetate from 3:1 to as high as 8:1. With resolution of the acidosis, β-hydroxybutyrate converts to acetoacetate, which is excreted into the urine and detected by the dipstick test. Therefore persistent ketonuria may not accurately reflect the degree of clinical improvement and should not be relied on as an indicator of therapeutic failure. β-Hydroxybutyrate can be measured from serum and even by bedside capillary ketometer and is used in some protocols to monitor the resolution of DKA and help determine when to transition from IV to subcutaneous insulin administration.

All patients with known diabetes presenting in DKA should be checked for precipitating events (infection, poor compliance, trauma) that may have triggered the metabolic decompensation.

Diabetic Ketoacidosis Protocol

See Figure 629.5.

Even though DKA can be of variable severity, a common approach to all cases simplifies the therapeutic regimen and can be safely used for most children. Fluids are best calculated based on weight, not body surface area (m^2), because heights are rarely available for the acutely critically ill child. Children with milder DKA recover in 10-20 hours (and need less total IV fluid before switching to oral intake), whereas those with more severe DKA may require up to 36 hours with this protocol. Any child can be transitioned to oral intake and subcutaneous insulin when DKA has resolved (total CO_2 >15 mEq/L; pH >7.30; sodium is stable between 135 and 145 mEq/L; anion gap closed; no emesis). A dose of long-acting insulin is given (or continuous subcutaneous infusion is started via pump) and the insulin drip is discontinued approximately 30 minutes later. Typically, transition is timed to occur around mealtime so that short-acting insulin can be given as well. Frequent (every 2-3 hours) short-acting insulin bolusing may need to be given until ketosis resolves.

A flow sheet is mandatory for accurate monitoring of changes in acidosis, electrolytes, fluid balance, and clinical status, especially if the patient is transferred from the emergency department to an inpatient setting with new caretakers. This flow sheet is best implemented by a central computer system, which allows for rapid update and wide availability of results, as well as rule-driven highlighting of critical values. A paper flow sheet suffices if it stays with the patient, is kept current, and is reviewed frequently by the physician. Any flow sheet should include columns for serial electrolytes, pH, glucose, and fluid balance. Blood glucose should be tested every hour and electrolytes should be tested every 1-2 hours for children with severe DKA and every 3-4 hours for those with mild to moderate DKA.

Cerebral Edema

Cerebral edema is an important cause of morbidity and mortality in children and adolescents with T1DM. Despite the clinical significance of this complication, its etiology remains incompletely understood. A case control study of DKA suggested that baseline acidosis and abnormalities of sodium, potassium, and blood urea nitrogen concentrations were important predictors of risk of cerebral edema. Early bolus administration of insulin and high volumes of fluid were also identified as risk factors. The incidence of cerebral edema in children with DKA has not changed over the past 15-20 years, despite the widespread introduction of gradual rehydration protocols during this interval. Radiographic imaging is frequently unhelpful in making the diagnosis of cerebral edema. Consequently, each patient must be closely monitored (see Fig. 629.5). For all but the mildest cases, this includes frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, ptosis, posturing, and seizures. In the event of the development of cerebral edema, immediate interventions should include elevation of the head of the bed, reduction in IV fluid rate, and administration of mannitol (typically 1 g/kg infused intravenously over 20 minutes). Children with moderate to severe DKA have a higher overall risk of cerebral edema and should be treated in a hospital environment where appropriate monitoring can occur.

Nonketotic Hyperosmolar Coma

This syndrome is characterized by severe hyperglycemia (blood glucose >800 mg/dL; 44 mmol/L), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Respirations are usually shallow, but coexistent metabolic (lactic) acidosis may be manifested by Kussmaul breathing. Serum osmolarity is commonly 350 mOsm/kg or greater. This condition is uncommon in children, although it may be increasing in frequency with the rise in the incidence of T2DM. Among adults, mortality rates are high, possibly in part because of delays in recognition and institution of appropriate therapy. In children, there has been a high incidence of preexisting neurologic injury. Profound hyperglycemia may develop over a period of days, and initially, the obligatory osmotic polyuria and dehydration may be partially compensated for by increasing fluid intake. In some cases, consumption of excessive sugar-sweetened beverages may further exacerbate hyperglycemia. With progression of disease, thirst becomes impaired, possibly because of alteration of the hypothalamic thirst center by hyperosmolarity and, in some instances, because of a preexisting defect in the hypothalamic osmoregulating mechanism.

The low production of ketones is attributed mainly to the hyperosmolarity, which in vitro blunts the lipolytic effect of epinephrine and the antilipolytic effect of residual insulin; blunting of lipolysis by the therapeutic use of β-adrenergic blockers may contribute to the syndrome. Depression of consciousness is closely correlated with the degree of hyperosmolarity in this condition and in DKA. Hemoconcentration may also predispose to cerebral arterial and venous thromboses before therapy is initiated.

Treatment of nonketotic hyperosmolar coma is directed at rapid repletion of the vascular volume deficit with normal saline and very slow correction of the hyperosmolar state (see Fig. 629.6). The fluid deficit should be estimated at 12–15% of body weight. Additional normal saline boluses may be required to reduce tachycardia and poor perfusion. One-half isotonic saline (0.45% NaCl; may use normal saline) is administered at a rate estimated to replace 50% of the volume deficit in the first 12 hours, and the remainder is administered during the ensuing 24 hours. The rate of infusion and the saline concentration are titrated to result in a slow decline of serum osmolality. When

the blood glucose concentration approaches 300 mg/dL, the hydrating fluid should be changed to 5% dextrose in 0.45% NaCl. Approximately 20 mEq/L of potassium chloride should be added to each of these fluids to prevent hypokalemia. Serum potassium and plasma glucose concentrations should be monitored at 2-hour intervals for the first 12 hours and at 4-hour intervals for the next 24 hours to permit appropriate adjustments of administered potassium and insulin.

Insulin can be given by continuous intravenous infusion only after serum glucose levels no longer decline with fluid administration. The IV insulin should be initiated at a low dose of 0.025-0.05 units/kg/hr and titrated to achieve a slow decline in serum glucose of 50-75 mg/dL/hr (2.8-4.2 mmol/L/hr). The presence of ketosis or more severe acidosis may necessitate earlier insulin initiation.

INITIATION OF SUBCUTANEOUS INSULIN THERAPY

Excellent diabetes control involves many goals: to maintain blood glucose and HbA_{1c} levels as close to normal without causing hypoglycemia, to eliminate polyuria and nocturia, to prevent ketoacidosis, to permit normal growth and development, and to avoid development of diabetes-related complications—all while minimizing the impact on lifestyle. The specific components of therapy include initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishment of the life routines. Each aspect should be addressed early in the overall care.

Insulin Therapy

Insulin therapy is initiated at the time of diagnosis for all patients with T1DM. The starting dose may range from 0.4 to 1.2 units/kg/day and is calculated based on a number of factors, including age, pubertal stage, and presence or absence of DKA. Typically, prepubertal children presenting without DKA can be started on a dose of 0.4-0.6 units/kg/day. Overweight pubertal adolescents presenting with DKA may need up to 1-1.2 units/kg/day. Insulin requirements in infancy vary tremendously, from <0.2 units/kg/day to >1 unit/kg day. Table 629.6 shows typical starting ranges for total daily insulin dose (units/kg/day) in children.

The precise optimal insulin dose can only be determined empirically, after beginning with the previously mentioned starting doses, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team. Many children with new-onset diabetes have some residual β-cell function (the honeymoon period), which is associated with reduced exogenous insulin needs shortly after starting treatment. Residual β-cell function usually fades within a few months and is reflected as a steady increase in insulin requirements and wider glucose excursions.

The initial insulin schedule should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β cell. There are inherent limits to our ability to mimic the β cell. Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose. Absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin secretion ceases and serum levels quickly lower with a normally rapid clearance. The absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation. Despite these fundamental physiologic differences, acceptable glucose control can be obtained with insulin analogs used in a **basal-bolus regimen**. Basal-bolus regimens can be accomplished with multiple daily injections (MDIs), where a slow-onset, long-duration background insulin is given once or twice daily for between-meal glucose control (basal) and a rapid-onset insulin is given with meals to provide carbohydrate coverage and correct hyperglycemia. Alternatively, an **insulin pump** can be used, where a rapid-onset insulin is used to provide both basal (via continuous infusion) and bolus (at mealtimes and as needed for hyperglycemia) coverage. The doses of short-acting insulin include two components: **carbohydrate ratio** (typically expressed as 1 unit of insulin for a set number of grams of carbohydrates) and **insulin sensitivity factor** (ISF), also referred to as the *correction factor,* and typically expressed as 1 unit of insulin will decrease blood sugar by a set number of mg/dL to achieve a target blood glucose level). Target blood glucose levels should be individualized according to factors including age, duration of diabetes, history of hypoglycemia, time of day, and physical activity, but will generally range between 90 and 180 mg/dL. Formulas for calculating the basal dose, carbohydrate ratio, and ISF from the total daily insulin dose are provided in Table 629.6

Table 629.6 Approach to Calculating Initial Subcutaneous Insulin Doses at Diagnosis of Type 1 Diabetes (or Type 2 Diabetes Requiring Intensive Insulin Therapy) for Patients Starting on a Basal-Bolus Regimen

CALCULATE *TOTAL DAILY DOSE* (TDD) OF INSULIN*	
Minimum starting dose:	0.2 units/kg/day
Add to the minimum dose as follows:	
- Initial blood glucose >200 mg/dL	+ 0.2 units/kg/day
- Ketosis at presentation	+ 0.2 units/kg/day
- Acidosis (by pH or serum bicarbonate)	+ 0.2 units/kg/day
- Puberty (Tanner stage 2 or greater)†	+ 0.2 units/kg/day
CALCULATE DOSES OF *BASAL* AND *BOLUS* INSULIN‡	
Basal dose (long-acting insulin)	x = 50% of TDD (x = daily dose of basal insulin, typically given as one dose before bedtime)
Carbohydrate coverage (short-acting insulin)	y = 450 / TDD (1 unit of insulin for every "y" grams of carbohydrates consumed at snacks/meals)
Insulin sensitivity factor (short-acting insulin)	z = 1800 / TDD (1 unit of insulin will lower blood glucose by "z" mg/dL)

*Patients with obesity or severe insulin resistance may require an additional 0.2 units/kg/day (or more) of insulin.

†For example, a prepubertal child presenting with hyperglycemia only with a blood glucose of 325 mg/dL would be started on a TDD of insulin of 0.4 units/kg/day, whereas a pubertal adolescent presenting in DKA would be started on 1 units/kg/day.

‡Other equations for calculating basal and bolus insulin doses have been proposed and can be found in the literature. All equations provide only an estimate of insulin requirements. All patients need frequent monitoring of blood glucose after initiation of insulin, and most will require dose adjustments.

All preanalog insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation. Thus a detectable effect for **regular insulin** is delayed by 30-60 minutes after injection. This, in turn, requires delaying the meal 30-60 minutes after the injection for optimal effect—a delay rarely attained in a busy child's life. Regular insulin has a wide peak and a long tail for bolus insulin. This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia. **Neutral protamine Hagedorn** (**NPH**, also known as *insulin isophane*) is an intermediate-acting insulin with inherent limitations as a basal insulin because it does not achieve a peakless background insulin level. This produces a significant hypoglycemic effect during the midrange of the duration. Thus it is often difficult to predict its interaction with fast-acting insulins. When regular insulin is combined with NPH, the composite insulin profile poorly mimics normal endogenous insulin secretion. Lente and ultralente insulins were other intermediate-acting insulins that have since been discontinued.

Lispro, **aspart**, and **glulisine insulin** are rapid-onset analogs that are absorbed much more quickly because they do not form hexamers. They provide discrete pulses, with onset of action in as little as 10 minutes, with little, if any, overlap and short tail effect. This allows better control of postmeal glucose increase and reduces between-meal or nighttime hypoglycemia. Other ultra-fast-acting insulin analogs are being developed that promise even faster onset of action, a feature that

may make these insulins especially useful in insulin pumps and closed-loop systems.

The **long-acting analogs glargine**, **detemir**, and **degludec** are designed to provide longer duration of action, ranging from ~20 hours (glargine) to ~40 hours (degludec). Glargine forms a precipitate after subcutaneous injection, detemir binds to circulating albumin, and degludec forms dihexamers—all of which lead to stabilization of the hexameric structure, slower disassociation into insulin monomers, and prolonged duration of action. The result is a flatter 24-hour profile, making it easier to predict the combined effect of a rapid bolus (lispro, aspart, or glulisine) on top of the basal insulin and thereby create a more physiologic pattern of insulin effect. Postprandial glucose elevations are better controlled, and between-meal and nighttime hypoglycemia are reduced. An illustration of the insulin effect profiles of the currently available short- and long-acting insulins is provided in Figures 629.7 and 629.8.

At diagnosis, the basal dose of long-acting insulin is typically calculated to provide around 50% of the total daily dose, with the remainder provided with bolus doses of short-acting insulin at mealtimes (calculations used to determine insulin doses are provided in Table 629.6). Over time the ratio of basal to bolus will typically shift downward and will be affected by the magnitude of carbohydrate intake (especially during adolescence). Some infants and toddlers may do well with a higher percentage of their daily insulin provided as basal. There is considerable individual variability in the duration of action of long-acting insulins, and some younger children and obese adolescents will require twice-daily dosing of glargine. Both long- and short-acting insulins are available for administration via multidose insulin pens, which are generally easier to use compared with a traditional syringe and vial approach.

Some families may be unable to administer four daily injections. In these cases, a compromise may be needed. A three-injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid-acting analog bolus at supper, and glargine at bedtime may provide fair glucose control and eliminate the need for an injection at school. Further compromise to a two-injection regimen may occasionally be needed and frequently involves use of premixed insulin preparations that include both rapid- and intermediate-acting insulins (e.g., 70/30). For this regimen, 70% of the total daily dose (TDD) is typically provided with breakfast and 30% of TDD with dinner. An illustration of commonly used insulin regimens is shown in Figure 629.8.

Insulin Pump Therapy

Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens. Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the ISF and carbohydrate ratios for premeal glucose levels. At mealtimes, the patient enters the blood glucose level (or it is automatically transmitted from a linked glucometer) and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin bolus dose. Although CSII frequently improves metabolic control, this may not always be the case. The degree of glycemic control is mainly dependent on how closely patients adhere to the principles of diabetes self-care, regardless of the type of intensive insulin regimen. One benefit of pump therapy may be a reduction in severe hypoglycemia and associated seizures. Randomized trials comparing multiple daily insulin regimens using glargine insulin and CSII in children with T1DM demonstrate similar metabolic control and frequency of hypoglycemic events. Most patients will initiate therapy with insulin pens; timing of transition to an insulin pump can be individualized per patient preference as soon as 6-12 months after diagnosis.

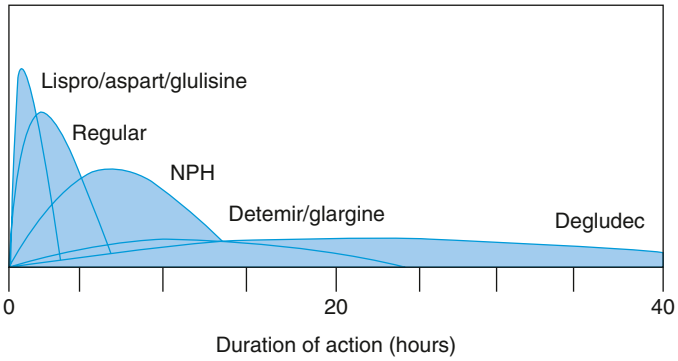

Fig. 629.7 Approximate insulin effect profiles. The following relative peak effect and duration units are used: lispro/aspart/glulisine, peak 20 for 4 hr; regular, peak 15 for 7 hr; neutral protamine Hagedorn *(NPH)* peak 12 for 12 hr; detemir/glargine, peak 5 for 20-24 hr; degludec peak 5 for 42 hr.

Continuous Glucose Monitoring Systems

Continuous glucose monitoring systems (CGMs) consist of a subcutaneous glucose sensor that continuously measures interstitial fluid glucose levels and a receiver to collect and display glucose data. CGMs reduce, but do not eliminate, the need for finger stick blood glucose checking, as calibrations with capillary blood glucose readings are required at least every 12 hours. CGMs report blood glucose levels to the patient/caregiver in real time and can be integrated with smartphones/watches for remote monitoring. To avoid hypoglycemia, the CGM system sounds an alarm once a critical low blood sugar threshold is reached. Additional alerts can be set to notify users of hyperglycemia or rapid rates of change in glucose levels. Short-term studies indicate clinical benefits of these devices as compared to conventional methods of blood glucose monitoring when used by motivated and well-informed patients. CGMs also allow for the determination of **time in range**, where the amount of time in and out of the target glycemic range *(defined by international consensus as glucose between 70 and 180 mg/dL)* can be determined and tracked. Glycemic control has been traditionally monitored by HbA_{1c}, which provides an estimate of average blood glucose over the prior 2 to 3 months. Time in range allows for a more granular assessment of glucose excursions within and between days and may prove to be a more clinically significant metric of diabetes control. A limitation of CGM-only systems is that they require the user to respond to the alert, interpret the data, and intervene to prevent hypoglycemic or hyperglycemic episodes. This limitation is mitigated when the CGM is combined with an insulin pump in a closed-loop system.

Closed-Loop Systems

A closed-loop system allows for direct communication between the continuous glucose sensor and insulin pump for automatic adjustment of insulin infusion rates in response to glucose levels (Fig. 629.9). A fully closed-loop system would be completely independent of the user and theoretically could improve glycemic control through the early identification and response to glucose perturbation and by minimizing the opportunity for human error in insulin dosing. Both single-hormone (insulin only) and bihormone (insulin and glucagon) systems are undergoing clinical investigation.

Several hybrid closed-loop systems with integrated insulin pumps and continuous glucose sensors have gained regulatory approval and entered clinical practice. There is emerging evidence from short-term clinical trials that the use of hybrid closed-loop systems can improve time in range and reduce hyperglycemia and hypoglycemia compared to sensor-augmented systems. Current issues hampering full implementation of this technology include limitations in the accuracy and precision of interstitial fluid glucose sensing, the need for short-acting insulins with more rapid onset of action, and complexity of day-to-day use.

Adjunct Pharmacotherapy

Pramlintide acetate, a synthetic injectable analog of amylin, may be of therapeutic value combined with insulin therapy. However, it has not

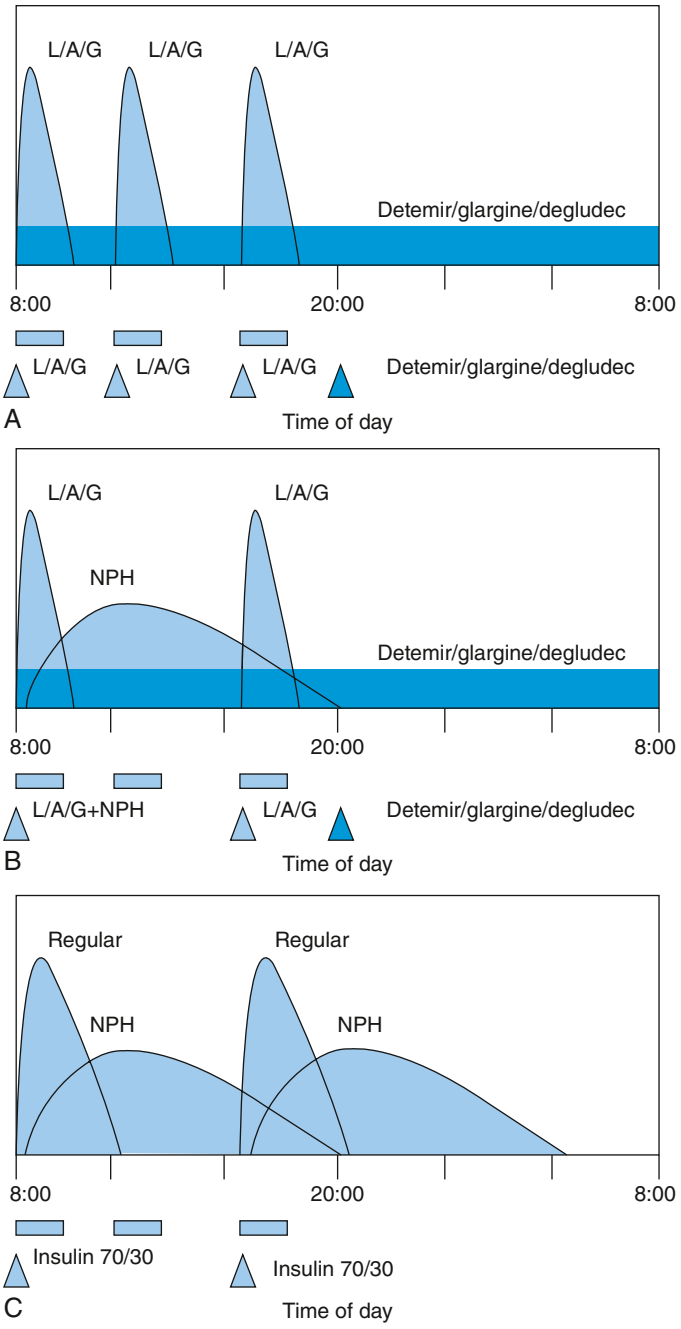

Fig. 629.8 Approximate composite insulin effect profiles of various insulin dosing strategies. Meals are shown as *rectangles* below the time axis. Injections are shown as labeled *triangles;* L/A/G, lispro, aspart, glulisine. All profiles are idealized using average absorption and clearance rates. In typical clinical situations, these profiles vary among patients. A given patient has varying rates of absorption depending on the injection site, physical activity, and other variables. **A,** Basal-bolus regimen: A short-acting insulin (Lantus/aspart/glulisine) is injected before meals, and a long-acting basal insulin (glargine/detemir/degludec) is injected at bedtime. Additional short-acting insulin is given to cover between-meal snacks as needed (not shown). For patients on insulin pumps, the composite insulin profile is similar; however, the basal insulin coverage is provided by a continuous infusion of short-acting insulin. **B,** Thrice-daily injection regimen: A short-acting insulin (Lantus/aspart/glulisine) and neutral protamine Hagedorn *(NPH)* are injected with breakfast (the two types of insulin can be drawn up into one syringe for administration with a single injection), a short-acting insulin is injected with dinner, and a long-acting basal insulin (glargine/detemir/degludec) is injected at bedtime. Because NPH is not a peakless insulin, this regimen is associated with greater risk of hypoglycemia compared with the basal-bolus regimen show in Figure 629.6A but does offer the advantage of eliminating the need for an injection at lunchtime. **C,** Twice-daily injection regimen: The use of a premixed insulin containing a short- and an intermediate-acting insulin that is given twice daily is sometimes necessary for families who are unable to manage more complex dosing regimens. Insulin 70/30 is one such product that combines regular and NPH insulins. This produces the least physiologic profile, with large excesses before lunch and during the early night, combined with poor coverage before supper and breakfast.

gained widespread use. Metformin, an oral antihyperglycemic commonly used to treat T2DM, is sometimes used clinically as an adjunct therapy in T1DM patients with evidence of significant insulin resistance (i.e., obesity, insulin requirements >1.2 units/kg/day, acanthosis nigricans on exam). A clinical trial investigating the addition of metformin in overweight adolescents with T1DM did not find a sustained effect of metformin to lower HbA_{1c} but did show a reduction in daily insulin dose and body mass index (BMI). Reports from observational studies are likewise mixed. These agents would typically not be started at diagnosis of T1DM.

Basic and Advanced Diabetes Education

Therapy consists not only of initiation and adjustment of insulin dose but also of education of the patient and family. Teaching is most efficiently provided by experienced diabetes educators and dietitians. In the acute phase, the family must learn the basics, which includes monitoring the child's blood glucose and urine and/or blood ketones, preparing and injecting the correct insulin dose subcutaneously at the proper time, recognizing and treating low blood glucose reactions, and having a basic meal plan. Most families are trying to adjust psychologically to the new diagnosis of diabetes in their child and thus have a limited ability to retain new information. Written materials covering these basic topics help the family during the first few days.

Children and their families are also required to complete advanced self-management classes to facilitate implementation of flexible insulin management. These educational classes will help patients and their families acquire skills for managing diabetes during athletic activities and sick days. Likewise, further patient and caregiver education with a diabetes educator familiar with diabetes technology is imperative when adding a CGM or transitioning to an insulin pump.

Nutritional Management

Nutrition plays an essential role in the management of patients with T1DM. This is of critical importance during childhood and adolescence, when appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development. There are no special nutritional requirements for the diabetic child other than those for optimal growth and development. Nutritional requirements for the child are outlined on the basis of age, sex, weight, activity, and food preferences. Cultural ethnic considerations must also be integrated into the nutrition plan.

Total recommended caloric intake is based on size or surface area and can be obtained from standard tables (Tables 629.7 and 629.8). The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein, but must be individualized to meet specific patient needs. Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited. Complex carbohydrates require prolonged digestion and absorption and thereby raise plasma glucose levels slowly, whereas glucose from refined sugars, including carbonated beverages, is rapidly absorbed and may cause wide swings in the metabolic pattern. The consumption of sugar-sweetened beverages, including soda and juice, should be discouraged. Priority should be given to total calories and total carbohydrates consumed rather than the source. Carbohydrate counting has become a mainstay in the nutrition education and management of patients with T1DM. Patients and their families are provided with information regarding the carbohydrate contents of different foods and food label reading. This allows patients to adjust their insulin dosage to their mealtime carbohydrate

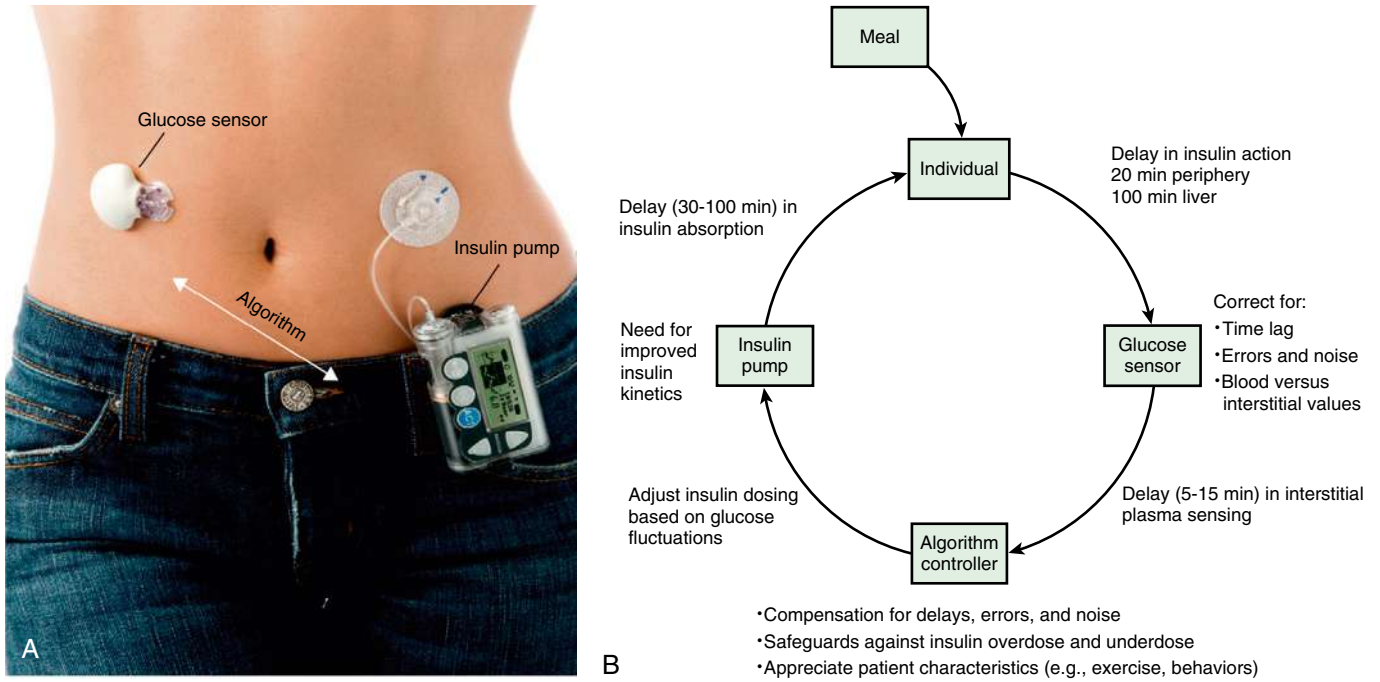

Fig. 629.9 Closed-loop system for T1DM (artificial pancreas). **A,** Prototype of a closed-loop system. **B,** Components of a closed-loop system. Three potential delays in the system include glucose sensing in interstitial fluid, insulin absorption (depends on use of rapid vs regular insulin), and insulin action in peripheral tissues and liver. *(From Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383:69–78. Fig. 5.)*

Table 629.7 Calorie Needs for Children and Young Adults

AGE	KCAL REQUIRED/KG BODY WEIGHT*
CHILDREN	
0-12 mo	120
1-10 yr	100-75
YOUNG WOMEN	
11-15 yr	35
≥16 yr	30
YOUNG MEN	
11-15 yr	80-55 (65)
16-20 yr	
Average activity	40
Very physically active	50
Sedentary	30

*Gradual decline in calories per unit weight as age increases.
Numbers in parentheses are means.
From *Nutrition Guide for Professionals. Diabetes education and meal planning.* Alexandria, VA, and Chicago, IL: The American Diabetes Association and The American Dietetic Association, 1988.

intake. The use of carbohydrate counting and insulin-to-carbohydrate ratios as a part of an MDI regimen allows for less rigid meal planning. Flexibility in the use of insulin in relation to carbohydrate content of food improves the quality of life.

Diets with high fiber content are useful in improving control of blood glucose. Daily recommended fiber intake can be determined using the equation:

$$\text{Age in years} + 5 = \text{grams of fiber per day}$$

Moderate amounts of sucrose consumed with fiber-rich foods such as whole-grain bread may have no more glycemic effect than their low-fiber, sugar-free equivalents. Saturated fat intake may increase in patients with T1DM who reduce carbohydrate consumption to avoid taking insulin doses by ingesting carbohydrate-free foods. Total energy from fat should not exceed 35%, and education should be provided such that <10% of total energy should come from saturated and trans fats. Dietary fats derived from animal sources should be reduced and replaced by polyunsaturated fats from vegetable sources. Substituting vegetable oil for animal oils or butter in cooking and lean cuts of meat, poultry, and fish for fatty meats can help to achieve these goals. The intake of cholesterol is also reduced by these measures. These simple measures may reduce serum low-density lipoprotein cholesterol, a predisposing factor to atherosclerotic disease. Table 629.8 summarizes typical nutritional guidelines for T1DM.

Each child and family can and should select a diet based on personal taste with the help of the physician or dietitian (or both). Emphasis should be placed on lifestyle changes to promote adherence to a healthy, balanced diet on a daily basis. Occasional excesses (treats) are permissible but should be limited just as for any child without diabetes. Adjustments in meal planning must constantly be made to meet the needs and the desires of each child. A consistent eating pattern with appropriate supplements for exercise, the pubertal growth spurt, and pregnancy in an adolescent with diabetes is important for metabolic control.

Monitoring

Success in the daily management of the child with diabetes can be measured by the competence acquired by the family, and subsequently by the child, in assuming responsibility for daily self-care. Their initial and ongoing instruction in conjunction with their supervised experience can lead to a sense of confidence in adjusting an insulin dosage for dietary deviations, for unusual physical activity, and for some intercurrent illnesses. Such acceptance of responsibility should make them relatively independent of the physician for their ordinary care. The physician must maintain ongoing interested supervision and shared responsibility with the family and the child.

Self-monitoring of blood glucose is an essential component of managing diabetes. Effective monitoring often also includes other factors that influence blood glucose such as insulin dose, physical activity,

Table 629.8 Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus

NUTRITION CARE PLAN		
Promotes optimal compliance.		
Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach.		
NUTRITION RECOMMENDATIONS AND DISTRIBUTION		
NUTRIENT	% OF CALORIES	RECOMMENDED DAILY INTAKE
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber		>20 g/day
Protein	12–20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6–8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000-4,000 mg if hypertensive
ADDITIONAL RECOMMENDATIONS		
Energy: If using measured diet, reevaluate prescribed energy level at least every 3 mo.		
Protein: High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore 12–20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.		
Alcohol: Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.		
Snacks: Snacks vary according to individual needs (generally three snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).		
Alternative sweeteners: Use of a variety of sweeteners is suggested.		
Educational techniques: No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.		
Eating disorders: Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.		
Exercise: Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.		

From Connell JE, Thomas-Doberson D. Nutritional management of children and adolescents with insulin-dependent diabetes mellitus: a review by the Diabetes Care and Education Dietetic Practice Group. J Am Diet Assoc. 1991;91:1556.

dietary changes, hypoglycemia, and illness. A record of these items may be valuable in interpreting the self-monitoring of blood glucose, prescribing appropriate adjustments in insulin doses, and teaching the family. If there are discrepancies in the self-monitoring of blood glucose and other measures of glycemic control (such as the HbA_{1c}), the clinician should attempt to clarify the situation in a manner that does not undermine their mutual confidence.

Daily blood glucose monitoring is accomplished using blood test strips or a CGM. Test strips are impregnated with glucose oxidase that permit blood glucose measurement from a drop of blood. A portable calibrated reflectance meter can approximate the blood glucose concentration accurately. Glucometers contain a memory chip enabling recall of each measurement and the ability to calculate measurement average over a given interval and display the pattern on a computer screen. Such information is a useful educational tool for verifying degree of control and modifying recommended regimens. A small, spring-loaded device that automates capillary bloodletting (lancing device) in a relatively painless fashion is commercially available. Parents and patients should be taught to use these devices and measure blood glucose at least 4 times daily—before breakfast, lunch, and supper and at bedtime. When insulin therapy is initiated and when adjustments are made that may affect the overnight glucose levels, self-monitoring of blood glucose should also be performed at midnight and 3 AM to detect nocturnal hypoglycemia. Standard blood glucose targets are 90-130 mg/dL before meals and 90-150 mg/dL before bedtime; however, glycemic goals must be individualized to the patient based on age, hypoglycemia risk, and other factors.

Glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose. If the fasting blood glucose is high, the evening dose of long-acting insulin (or the early morning/overnight basal rate for insulin pump users) is increased by 10–20% and/or additional fast-acting insulin coverage for a bedtime snack may be considered. If the noon glucose level exceeds set limits, the morning fast-acting insulin-to-carbohydrate ratio is increased by 10–20%. If the presupper glucose is high, the noon fast-acting insulin-to-carbohydrate ratio is increased by 10–20%. If the prebedtime glucose is high, the presupper fast-acting insulin-to-carbohydrate ratio is increased by 10–15%. The ISF can be increased by 10–20% if it is found that insulin corrections given for hyperglycemia do not normalize glucose levels as expected. Similarly, reductions in the insulin type and dose should be made if the corresponding blood glucose measurements are consistently below desirable limits.

A minimum of four daily blood glucose measurements (or CGM use) should be performed. However, some children and adolescents may need to have more frequent blood glucose monitoring based on their level of physical activity and history of frequent hypoglycemic reactions. Families should be encouraged to become sufficiently knowledgeable about managing diabetes.

The FDA has approved the use of CGMs to replace finger stick blood glucose checking for the monitoring and treatment of diabetes in children 2 years of age and older. CGMs are minimally invasive and entail the placement of a small, subcutaneous catheter that can be easily worn by adults and children. The system provides information that allows the patient and healthcare team to adjust the insulin regimen and the nutrition plan to improve glycemic control. CGMs can be helpful in detecting asymptomatic nocturnal hypoglycemia and in lowering HbA_{1c} values without increasing the risk for severe hypoglycemia. Although there are potential pitfalls in CGM use, including suboptimal compliance, human error, incorrect technique, and sensor

failure, the implementation of CGMs in ambulatory diabetes practice allows the clinician to diagnose abnormal glycemic patterns in a more precise manner. In many cases, CGMs are now factory calibrated and nearly eliminate the need for finger sticks. For these reasons, CGMs are increasingly replacing finger stick blood testing as the primary means of glucose monitoring in many patients with T1DM.

Glycosylated Hemoglobin (HbA_{1c})

A reliable index of long-term glycemic control is provided by measurement of glycosylated hemoglobin. HbA_{1c} represents the fraction of hemoglobin to which glucose has been nonenzymatically attached in the bloodstream. The formation of glycosylated hemoglobin is a slow reaction that is dependent on the prevailing concentration of blood glucose; it continues irreversibly throughout the red blood cell's life span of approximately 120 days. The higher the blood glucose concentration and the longer the red blood cell's exposure to it, the higher the fraction of glycosylated hemoglobin, which is expressed as a percentage of total hemoglobin. Because a blood sample at any given time contains a mixture of red blood cells of varying ages, exposed for varying times to varying blood glucose concentrations, an HbA_{1c} measurement reflects the average blood glucose concentration from the preceding 2-3 months. For some patients, it may be helpful to translate HbA_{1c} into estimated average glucose (eAG) using the following equation:

$$eAG = 28.7 * HbA_{1c} - 46.7$$

When measured by standardized methods to remove labile forms, HbA_{1c} is not influenced by an isolated episode of hyperglycemia.

HbA_{1c} measurements should be obtained three to four times a year to obtain a profile of long-term glycemic control. The lower the HbA_{1c} level, the more likely it is that microvascular complications such as retinopathy and nephropathy will be less severe, delayed in appearance, or even avoided altogether. Depending on the method used for determination, HbA_{1c} values may be spuriously elevated in thalassemia (or other conditions with elevated hemoglobin F) and spuriously lower in sickle cell disease (or other conditions with high red blood cell turnover). Fructosamine can be used instead of HbA_{1c} in these patients. Although values of HbA_{1c} may vary according to the method used for measurement, in individuals without diabetes, the HbA_{1c} is usually less than 6%. The HbA_{1c} target should be individualized, but the general recommendation of the ADA and the International Society for Pediatric and Adolescent Diabetes is that children, adolescents, and young adults with T1DM should aim to achieve an HbA_{1c} of <7%.

Exercise

Regular, daily exercise with the goal of 60 minutes of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week is recommended for all children with T1D. A potential complication of exercise in patients with diabetes is the development of hypoglycemia during or within the hours after exercise. Patients and families should be educated on the risk of hypoglycemia and taught strategies to ameliorate this risk, including frequent glucose monitoring before, during, and after exercise; modifying diet and insulin doses around times of exercise; and ensuring access to fast-acting carbohydrates during exercise to treat hypoglycemia should it develop. Regular exercise also improves glucoregulation by increasing glucose use by muscles and increasing the insulin receptor number. In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counterregulatory hormones.

Benefits of Improved Glycemic Control

The Diabetes Control and Complications Trial (DCCT) established conclusively the association between higher glucose levels and long-term microvascular complications. Intensive management produced dramatic reductions of retinopathy, nephropathy, and neuropathy by 47–76%. The data from the adolescent cohort demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications.

The beneficial effect of intensified treatment was determined by the degree of blood glucose normalization independently of the type of intensified treatment used. Frequent blood glucose monitoring was considered an important factor in achieving better glycemic control for the intensively treated adolescents and adults. Patients who were intensively treated had individualized glucose targets, frequent adjustments based on ongoing capillary blood glucose monitoring, and a team approach that focused on the person with diabetes as the prime initiator of ambulatory care. Care was constantly adjusted toward reaching normal or near-normal glycemic goals while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a preventive approach to blood glucose fluctuations with constant readjustment to counterbalance any high or low blood glucose readings. Target blood glucose goals were adjusted upward if hypoglycemia could not be prevented.

Total duration of diabetes contributes to development and severity of complications. Nonetheless, many professionals have concerns about applying the results of the DCCT to preschool-age children, who often have hypoglycemia unawareness with unique safety issues, and to prepubertal school-age children, who were not included in the DCCT. The follow-up study to the DCCT, called Epidemiology of Diabetes Interventions and Complications (EDIC), assessed the incidence and predictors of cardiovascular disease events such as heart attack, stroke, or needed heart surgery, as well as diabetic complications related to the eye, kidney, and nerves. The EDIC demonstrated that intensive blood glucose control reduced the risk of any cardiovascular disease event by 42%. In addition, intensive therapy reduced the risk of nonfatal heart attack, stroke, or death from cardiovascular causes by 57%.

Hypoglycemic Reactions

Hypoglycemia is the major limitation to tight control of glucose levels. Once injected, insulin absorption and action are independent of the glucose level, thus creating a unique risk of hypoglycemia from an unbalanced insulin effect. Insulin analogs may help reduce, but cannot eliminate, this risk. Most children with T1DM can expect mild hypoglycemia each week, moderate hypoglycemia a few times each year, and severe hypoglycemia every few years. These episodes are usually not predictable, although exercise, delayed meals or snacks, and wide swings in glucose levels increase the risk. Infants and toddlers are at higher risk for hypoglycemia because they have more variable meals and activity levels, are unable to recognize early signs of hypoglycemia, and are limited in their ability to seek a source of oral glucose to reverse the hypoglycemia. The very young have an increased risk of permanently reduced cognitive function as a long-term sequela of severe hypoglycemia. For these reasons, a more relaxed degree of glucose control may be tolerated in infants and young children.

Hypoglycemia can occur at any time of the day or night. Early symptoms and signs (mild hypoglycemia) may occur with a sudden decrease in blood glucose to levels that do not meet standard criteria for hypoglycemia in children without diabetes. The child may show pallor, sweating, apprehension or fussiness, hunger, tremor, and tachycardia, all as a result of the surge in catecholamines as the body attempts to counter the excessive insulin effect. Behavioral changes such as tearfulness, irritability, and aggression are more prevalent in children. As glucose levels decline further, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia), progressing to inability to seek help and seizures or coma (severe hypoglycemia). Prolonged severe hypoglycemia can result in a depressed sensorium or strokelike focal motor deficits that persist after the hypoglycemia has resolved. Although permanent sequelae are rare, severe hypoglycemia is frightening for the child and family and can result in significant reluctance to attempt even moderate glycemic control afterward.

Important counterregulatory hormones in children include growth hormone, cortisol, epinephrine, and glucagon. The latter two seem more critical in the older child. Many older patients with long-standing T1DM lose their ability to secrete glucagon in response to hypoglycemia. In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy. This substantially increases the

risk of hypoglycemia because the early warning signals of a declining glucose level are as a result of catecholamine release. Recurrent hypoglycemic episodes associated with tight metabolic control may aggravate partial counterregulatory deficiencies, producing a syndrome of hypoglycemia unawareness and reduced ability to restore euglycemia (hypoglycemia-associated autonomic failure). Avoidance of hypoglycemia allows some recovery from this unawareness syndrome.

The most important factors in the management of hypoglycemia are an understanding by the patient and family of the symptoms and signs of the reaction and an anticipation of known precipitating factors such as gym or sports activities. Tighter glucose control increases the risk. Families should be taught to look for typical hypoglycemic scenarios or patterns in the home blood glucose log, so that they may adjust the insulin dose and avert predictable episodes. A source of emergency glucose should be available at all times and places, including at school and during visits to friends. If possible, it is important to document the hypoglycemia before treating, because some symptoms may not always be from hypoglycemia. Any child suspected of having a moderate to severe hypoglycemic episode should be treated before testing. It is important not to give too much glucose in response to hypoglycemia; 15 g should be given as juice or a sugar-containing beverage or candy, and the blood glucose checked 15-20 minutes later.

Patients, parents, and teachers should also be instructed in the administration of **glucagon** when the child cannot take glucose orally. Glucagon is available for intramuscular or subcutaneous injection and as a nasal powder. A glucagon kit should be kept at home and school. The intramuscular dose of glucagon is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg; the subcutaneous dose (via prefilled device) is 0.5 mg if less than 45 kg and 1.0 mg if more than 45 kg; the intranasal dose is 3 mg. Glucagon produces a brief release of glucose from the liver. Glucagon often causes emesis, which precludes giving oral supplementation if the blood glucose declines after the glucagon effects have waned. Caretakers must then be prepared to take the child to the hospital for IV glucose administration, if necessary. Mini-dose glucagon (10 μg/yr of age up to a maximum of 150 μg subcutaneously) is effective in treating hypoglycemia in children with blood glucose less than 60 mg/dL who fail to respond to oral glucose and remain symptomatic. Glucagon is reconstituted as per standard instructions, then drawn up for subcutaneous injection using a standard insulin syringe, whereby 1 unit is the equivalent of 10 mcg of glucagon.

Dawn Phenomenon and Somogyi Phenomenon

There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common is a simple decline in insulin levels. This usually results in routinely elevated morning glucose. The **dawn phenomenon** is thought to be mainly caused by overnight growth hormone secretion and increased insulin clearance. It is a normal physiologic process seen in most adolescents without diabetes, who compensate with more insulin output. A child with T1DM cannot compensate. The dawn phenomenon is usually recurrent and modestly elevates most morning glucose levels. Rarely, high morning glucose is caused by the **Somogyi phenomenon**, a theoretical rebound from late-night or early-morning hypoglycemia thought to be from an exaggerated counterregulatory response. It is unlikely to be a common cause, in that most children remain hypoglycemic (do not rebound) once nighttime glucose levels decline. CGMs may help clarify a child's ambiguously elevated morning glucose levels.

Behavioral/Psychologic Aspects and Eating Disorders

Diabetes in a child affects the lifestyle and interpersonal relationships of the entire family. Feelings of anxiety and guilt are common in parents. Similar feelings, coupled with denial and rejection, are equally common in children, particularly during the rebellious teenage years. Family conflict has been associated with poor treatment adherence and poor metabolic control among youths with T1DM. On the other hand, it has been shown that shared responsibility is consistently associated with better psychologic health, good self-care behavior, and good metabolic control, whereas responsibility assumed by either the child or parent alone does not have outcomes that are equally successful. In some cases, links of shared responsibility to health outcomes were stronger among older adolescents. However, no specific personality disorder or psychopathology is characteristic of diabetes; similar feelings are observed in families with children who have other chronic diseases.

COGNITIVE FUNCTION

There is evidence that children with T1DM are at higher risk of developing small differences in cognitive abilities compared to healthy age-matched peers. Evidence suggests that early-onset diabetes (younger than 7 years) is associated with cognitive difficulties compared to late-onset diabetes and healthy controls. The cognitive difficulties observed were primarily learning and memory skills (both verbal and visual) and attention/executive function skills. It is likely that the impact of diabetes on pediatric cognition appears shortly after diagnosis. Indeed, it has been observed that early-onset diabetes and longer duration of diabetes in some children with diabetes adversely affect their school performance and educational achievements.

COPING STYLES

Children and adolescents with T1DM are faced with a complex set of developmental changes and shifting burdens of the disease. Adjustment problems might affect psychologic well-being and the course of the disease by affecting self-management and leading to poor metabolic control. Coping styles refer to typical habitual preferences for ways of approaching problems and might be regarded as strategies that people generally use to cope across a wide range of stressors. Problem-focused coping refers to efforts directed toward rational management of a problem, and it is aimed at changing the situation causing distress. On the other hand, emotion-focused coping implies efforts to reduce emotional distress caused by the stressful event and to manage or regulate emotions that might accompany or result from the stressor. In adolescents with diabetes, avoidance coping and venting emotions have been found to predict poor illness-specific self-care behavior and poor metabolic control. Patients who use more mature defenses and exhibit greater adaptive capacity are more likely to adhere to their regimen. Coping strategies seem to be age dependent, with adolescents using more avoidance coping than younger children with diabetes.

NONADHERENCE

Family conflict, anger, sadness, or denial and feelings of anxiety or loss of control find expression in nonadherence to instructions regarding nutritional and insulin therapy and in noncompliance with self-monitoring. When adolescents externalize behavior problems, such behaviors interfere with adherence and may result in deterioration of glycemic control. Such externalizing behaviors are common, whereas repeated omission of insulin resulting in ketoacidosis in the same individual is less common, and episodes of deliberate overdosage with insulin resulting in hypoglycemia are even less prevalent. They may, however, be pleas for psychologic help or be manipulative attempts to escape an environment perceived as undesirable or intolerable; occasionally, they may be manifestations of suicidal intent. Frequent admissions to the hospital for ketoacidosis or hypoglycemia should arouse suspicion of an underlying emotional conflict. Overprotectiveness on the part of parents is common and often is not in the best interest of the adolescent patient. Feelings of being different or of being alone, or both, are common and must be acknowledged. Tailoring the insulin administration and the timing of meals and blood sugar tests may support individual lifestyle choices. Aggregating what they know about diabetes, families and patients worry about the risk of complications from diabetes and about the decreased life span. Unfortunately, misinformation abounds about the risks of the development of diabetes in siblings or offspring and of pregnancy in young diabetic women. Even appropriate information may cause further anxiety.

All of these issues must be spoken about at the outset, and many of these problems can be averted through continued empathic counseling based on correct information, focusing on normality and on planning to be a productive member of society. Recognizing the potential

impact of these problems and that feelings of isolation and frustration tend to be lessened by the sharing of common problems, peer discussion groups have been organized in many locales. Summer camps for diabetic children afford an excellent opportunity for learning and sharing under expert supervision. Education about the pathophysiology of diabetes, insulin dose, technique of administration, nutrition, exercise, and hypoglycemic reactions can be reinforced by medical and paramedical personnel. The presence of numerous peers with similar problems offers new insights to the diabetic child. Residential treatment for children and adolescents with difficult-to-manage T1DM is rarely available.

ANXIETY AND DEPRESSION

It has been shown that there are significant correlations between poor metabolic control and depressive symptoms, a high level of anxiety, or a previous psychiatric diagnosis. In a similar way, poor metabolic control is related to higher levels of personal, social, school maladjustment, or family environment dissatisfaction. It is estimated that 20–26% of adolescent patients may develop major depressive disorder. The prevalence of depression is twofold greater than controls in children with diabetes and threefold greater in adolescents. Additionally, the prevalence of psychopathology is greater in people with diabetes. The course characteristics of depression in young diabetic subjects and psychiatric control subjects appear to be similar. However, eventual propensity of diabetic youths for more protracted depressions is greater. There is also a higher risk of recurrence among young diabetic females. On balance, anxiety and depression play an important and complex role in T1DM; their relationship to metabolic control does not yet appear clear. Therefore the healthcare providers managing a child or adolescent with diabetes should be aware of their pivotal role as counselor and advisor and should closely monitor the mental health of patients with diabetes. Accordingly, the recommendation is screening for anxiety and/or depression in subjects exhibiting symptoms, using a validated screening tool, followed by the appropriate referral to mental health providers when warranted.

FEAR OF SELF-INJECTING AND SELF-TESTING

Extreme fear of self-injecting insulin *(injection phobia)* is likely to compromise glycemic control and emotional well-being. Likewise, fear of finger pricks of CGM and pump site insertions can be a source of distress and may seriously hamper self-management. Children and adolescents may either omit insulin dosing or refuse to rotate their injection sites because repeated injection in the same site is associated with less pain sensation. Failure to rotate injection sites results in subcutaneous scar formation **(lipohypertrophy)**. Insulin injection into the lipohypertrophic skin is usually associated with poor insulin absorption, consequent frustration with lack of expected glucose control, and/or insulin leakage with resultant suboptimal glycemic control. Children and adolescents with injection phobia and fear of self-testing can be counseled by a trained behavioral therapist and benefit from such techniques as desensitization and biofeedback to attenuate pain sensation and psychologic distress associated with these procedures.

EATING DISORDERS

Treatment of T1DM involves constant monitoring of food intake. In addition, improved glycemic control is sometimes associated with increased weight gain. These factors, along with individual, familial, and socioeconomic factors, can lead to an increased incidence of both nonspecific and specific eating disorders, which can disrupt glycemic control and increase the risk of long-term complications. Eating disorders and subthreshold eating disorders are almost twice as common in adolescent females with T1DM as in their nondiabetic peers. There is less information regarding the prevalence of eating disorders among male adolescents with T1DM. The prevalence of eating disorders identified in females with T1DM has ranged from 9% to 32% in different studies. Other studies have found that approximately 11% of T1DM adolescent females take less insulin than prescribed to lose weight. Among adolescent females with T1DM and an eating disorder, the misuse of insulin to lose weight is not uncommon.

When behavioral/psychologic problems and/or eating disorders are assumed to be responsible for poor adherence with the medical regimen, referral for psychologic evaluation and management is indicated. Behavioral therapists and psychologists usually form part of the pediatric diabetes team in most centers and can help assess and manage emotional and behavioral disorders in diabetic children. Evaluation of nurse-delivered motivational enhancement with and without cognitive-behavioral therapy in adults revealed that combined therapy resulted in modest improvement in glycemic control. However, motivational enhancement therapy alone did not improve glycemic control. Whereas in some studies the effect of therapist-delivered motivational enhancement therapy on glycemic control in adolescents with T1DM lasted only as long as intensive individualized counseling continued, in other studies, motivational interviewing was shown to be an effective method of facilitating changes in a teenager's behavior with T1DM, with corresponding improvement in glycemic control.

Management During Infections

Although infections are no more common in diabetic children than in nondiabetic ones, they can disrupt glucose control and may precipitate DKA. In addition, the child with diabetes is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counterregulatory hormones associated with stress blunt insulin action and elevate glucose levels. If anorexia occurs from ketosis, lack of caloric intake increases the risk of hypoglycemia. Although children younger than 3 years of age tend to become hypoglycemic and older children tend toward hyperglycemia, the overall effect is unpredictable. Therefore frequent blood glucose monitoring, monitoring of urine and/or blood ketones, and adjustment of insulin doses are essential elements of **sick day guidelines** (Table 629.9).

The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis. This can usually be done at home if proper sick day guidelines are followed and with telephone contact with healthcare providers. The development of ketones in a patient on insulin pump therapy may be a sign of infusion failure and the infusion set should be changed. The family should seek advice if home treatment does not

Table 629.9 Guidelines for Sick Day Management

	GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN		
URINE KETONE STATUS	**INSULIN**	**CORRECTION DOSES***	**COMMENT**
Negative or small†	q2h	q2h for glucose >250 mg/dL	Check ketones every other void
Moderate to large‡	q1h	q1h for glucose >250 mg/dL	Check ketones each void; go to hospital if emesis occurs

*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.
†For home serum ketones <1.5 mmol/L per commercial kit.
‡For home serum ketones >1.5 mmol/L.
Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.
Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.
Call physician or nurse if blood glucose remains elevated after three extra doses, if blood glucose remains <70 mg/dL and child cannot take oral supplement, if dehydration occurs.

control ketosis, hyperglycemia, or hypoglycemia or if the child shows signs of dehydration or has persistent vomiting. A child with significant ketosis and emesis should be seen in the emergency department for a general examination, to evaluate hydration, and to determine whether ketoacidosis is present by checking serum electrolytes, glucose, pH, and total CO_2. A child whose blood glucose declines to less than 50-60 mg/dL (2.8-3.3 mmol/L) and who cannot maintain oral intake may need IV glucose, especially if further insulin is needed to control ketosis.

Management During Surgery

Surgery can disrupt glucose control in the same way as intercurrent infections can. Stress hormones associated with the underlying condition and with the surgery itself cause insulin resistance. This increases glucose levels, exacerbates fluid losses, and may initiate DKA. On the other hand, caloric intake is usually restricted, which decreases glucose levels. The net effect is as difficult to predict as during an infection. Vigilant monitoring and frequent insulin adjustments are required to maintain euglycemia and avoid ketosis.

For most elective and other smaller surgical procedures, patients can simply be continued on their typical home basal regimens. This includes injection of the usual dose of long-acting insulin at the usual time for patients on shots. Patients on pumps can simply wear the pump during the surgery, if approved by hospital policy. Blood sugar should be monitored hourly during the procedure and perioperatively; hyperglycemia can be corrected using the standard home ISF, and IV dextrose can be provided as needed for hypoglycemia. For major procedures, trauma, or situations where a prolonged period of decreased oral intake is expected postoperatively, it is advisable to manage insulin requirements with an IV insulin drip (Table 629.10). IV insulin is typically started at a dose of 0.03 units/kg/hr for patients who are euglycemic at the time of surgery. Serum glucose levels should be followed every hour operatively and perioperatively, and the insulin dose and/or the dextrose concentration of the IV fluids can be adjusted as needed. In patients who are found to be hyperglycemic preoperatively (serum glucose >250 mg/dL), it is advisable to check for ketones before starting surgery. If significant ketosis is identified, surgery should be delayed (if possible) until the ketosis can be treated and resolved. Postoperatively, the patient should not be discharged until blood glucose levels are stable and oral intake is tolerated.

LONG-TERM COMPLICATIONS: RELATION TO GLYCEMIC CONTROL

Complications of DM include microvascular complications, such as retinopathy and nephropathy; macrovascular complications, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease; peripheral and autonomic neuropathies; and diabetic osteopathy manifesting as increased risk for osteoporosis and fracture.

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of blindness in the United States in adults age 20-65 years. The risk of diabetic retinopathy after 15 years' duration of diabetes is 98% for individuals with T1DM and 78% for those with T2DM. Rates for diabetic retinopathy range from close to 15% to up to 30%. Lens opacities (caused by glycation of tissue proteins and activation of the polyol pathway) are present in at least 5% of those younger than age 19 years. Metabolic control has an impact on the development of this complication, as prevalence rates are substantially higher with increased duration of diabetes and higher HbA_{1c}, hypertension, and high cholesterol levels. Independent of duration, the prevalence of diabetic retinopathy is higher in T1DM. Genetic factors may have a role, because only 50% of patients develop proliferative retinopathy. The earliest clinically apparent manifestations of diabetic retinopathy are classified as nonproliferative or background diabetic retinopathy—microaneurysms, dot and blot hemorrhages, hard and soft exudates, venous dilation and beading, and intraretinal microvascular abnormalities. These changes do not impair vision. The more severe form is proliferative diabetic retinopathy, which manifests by neovascularization, fibrous proliferation, and preretinal and vitreous hemorrhages. Proliferative retinopathy, if not treated, is relentlessly progressive and impairs vision, leading to blindness. The mainstay of treatment is panretinal laser photocoagulation. In advanced diabetic eye disease—manifested by severe vitreous hemorrhage or fibrosis, often with retinal detachment—vitrectomy is an important therapeutic modality. Eventually, the eye disease becomes quiescent, a stage termed *involutional retinopathy.* A separate subtype of retinopathy is diabetic maculopathy, which is manifested by severe macular edema impairing central vision. Focal laser photocoagulation may be effective in treating diabetic maculopathy.

Diabetic patients should have an initial dilated and comprehensive examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with T2DM and within 3-5 years after the onset of T1DM (but not before age 10 years). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both T1DM and T2DM patients should be repeated every 1-2 years as recommended by an eye care professional experienced in the diagnosis and management of diabetic retinopathy (Table 629.11).

Diabetic Nephropathy

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States. Most ESRD from diabetic nephropathy is preventable. Diabetic nephropathy affects 20–30% of patients with T1DM and 15–20% of T2DM patients 20 years after onset. The mean 5-year life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term T1DM may be the result of nephropathy, which may account for approximately 50% of deaths. The risk of nephropathy increases with the duration of diabetes (up until 25-30 years' duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Only 30–40% of patients affected by T1DM eventually experience ESRD. The glycation of tissue proteins results in glomerular basement membrane thickening. The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate of 30-300 mg/24 hr (20-200 μg/min)—**microalbuminuria**—can be detected and constitutes an early stage of nephropathy from intermittent to persistent (incipient), which is commonly associated with glomerular hyperfiltration and blood pressure elevation. As nephropathy evolves to an early overt stage with proteinuria (albumin excretion rate >300 mg/24 hr or >200 μg/min), it is accompanied by hypertension. Advanced-stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and hypertension. Progression to ESRD is recognized by the appearance of uremia, nephrotic syndrome, and the need for renal replacement (transplantation or dialysis).

Screening for diabetic nephropathy is a routine aspect of diabetes care. The ADA recommends yearly screening for individuals with T2DM and yearly screening for those with T1DM after 5 years' duration of disease with a random spot urine sample for albumin-to-creatinine ratio. Abnormal results should be confirmed by two

Table 629.10 Guidelines for Intravenous Insulin Coverage During Surgery

BLOOD GLUCOSE LEVEL (mg/dL)	INSULIN INFUSION (units/kg/hr)	BLOOD GLUCOSE MONITORING
<120	0.00	1 hr
121-200	0.03	2 hr
200-300	0.06	2 hr
300-400	0.08	1 hr*
400	0.10	1 hr*

*Check urine ketones.
An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times the maintenance rate.

Table 629.11 Screening Guidelines

	INITIAL TESTING	FREQUENCY	TEST
Thyroid disease	At diagnosis	Every 1-2 yr or sooner if symptoms	TSH, thyroid antibodies
Celiac	At diagnosis	Within 2 yr and again at 5 yr or sooner if symptoms	IgA and TTG
Hypertension	At diagnosis	Each visit	Elevated BP based on ≥90th% for age, sex, height on three separate occasions
Dyslipidemia	≥10 yr of age at diagnosis once glucose control established	If abnormal annually; every 5 yr if initially normal	Goal LDL-C <100 mg/dL
Nephropathy	At puberty or age ≥10 yr whichever comes first, if T1DM ≥5 yr	Annually	Albuminuria; urine albumin-to-creatinine ratio
Retinopathy	T1DM ≥3-5 yr when ≥10 yr or puberty, whichever comes first	Annually	Dilated eye exam
Neuropathy	At puberty or ≥10 year, whichever earlier if T1DM >5 yr	Annually	Foot exam

BP, Blood pressure; IgA, immunoglobulin A; LDL, low density lipoprotein; TSH, thyroid-stimulating hormone; TTG, tissue transglutaminase.
Data from American Diabetes Association. Children and adolescents: standards of medical care in diabetes—2018. Diabetes Care. 2018;41(Suppl 1):S126–S136.

additional specimens on separate days because of the high variability of albumin excretion in patients with diabetes. Short-term hyperglycemia, strenuous exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevation in urinary albumin excretion. There is marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3- to 6-month period should show elevated levels before microalbuminuria is diagnosed and treatment is started. Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys: (1) meticulous control of hyperglycemia, (2) aggressive control of systemic blood pressure, (3) selective control of arteriolar dilation by use of angiotensin-converting enzyme inhibitors (thus decreasing transglomerular capillary pressure), and (4) dietary protein restriction (because high protein intake increases the renal perfusion rate). Tight glycemic control will delay the progression of microalbuminuria and slow the progression of diabetic nephropathy.

DIABETIC NEUROPATHY

Both the peripheral and autonomic nervous systems can be involved; diabetic neuropathy can develop in both children and adolescents. The etiology of diabetic neuropathy remains incompletely understood, and the impact of hyperglycemia on its development remains uncertain. Observational studies done in the years before the era of intensive insulin therapy for T1DM reported a higher incidence of neuropathy compared with more recent studies. However, several studies have found that the development of preclinical and symptomatic peripheral diabetic neuropathy in childhood is not strongly associated with either glycemic control or duration of disease. The polyol pathway, nonenzymatic glycation, and/or disturbances of myoinositol metabolism, affecting one or more cell types in the multicellular constituents of the peripheral nerve, have been hypothesized to have an inciting role. Other factors, such as possible direct neurotrophic effects of insulin, insulin-related growth factors, nitric oxide, and stress proteins, may also contribute to the development of neuropathy. Using quantitative sensory testing, abnormal cutaneous thermal perception is a common finding in both upper and lower limbs in neurologically asymptomatic young diabetic patients. Heat-induced pain threshold in the hand is correlated with the duration of the diabetes. There is no correlation between quantitative sensory testing scores and metabolic control. Subclinical motor nerve impairment as manifested by reduced sensory nerve conduction velocity and sensory nerve action potential amplitude have been detected in as many as 10–58% of children with diabetes. An early sign of autonomic neuropathy, such as decreased heart rate variability, may present in adolescents with a history of long-standing disease and poor metabolic control. A number of therapeutic strategies have been attempted with variable results. These treatment modalities include (1) improvement in metabolic control, (2) use of aldose reductase inhibitors to reduce by-products of the polyol pathway, (3) use of α-lipoic acid (an antioxidant) that enhances tissue nitric oxide and its metabolites, (4) use of anticonvulsants (e.g., lorazepam, valproate, gabapentin, carbamazepine, pregabalin, phenytoin, tiagabine, and topiramate) for treatment of neuropathic pain, and (5) use of antidepressants (amitriptyline, imipramine, and selective serotonin reuptake inhibitors). Additional medications include antiarrhythmics such as lidocaine, topical analgesics, and nonsteroidal antiinflammatory drugs.

Skeletal Effects of Type 1 Diabetes Mellitus

The skeleton is adversely affected by diabetes, with T1DM patients at greater risk for skeletal complications than those with T2DM. T1DM is associated with an increased risk of fracture that first becomes evident in childhood and persists across the entire life span. This includes a dramatically increased hip fracture risk in adults, ranging from two- to sevenfold higher than patients without diabetes, depending on the population studied. Most, but not all, studies have shown T1DM to be associated with low bone mineral density. This differs from T2DM, where bone density is normal or even above average because of increased mechanical loading in association with obesity. The deficits in bone density do not appear to be sufficient to explain the degree of increased fracture risk, leading to the hypothesis that bone quality may be impaired as well. The mechanism(s) underlying diabetic-related osteopathy is poorly understood and presumed to be multifactorial. Most, but not all, studies show an association between poor glycemic control and adverse skeletal outcomes, suggesting a role for hyperglycemia and/or insulin deficiency. Chronic exposure to hyperglycemia may weaken bone strength through the accumulation of advanced glycation end products (AGEs) in bone. Other factors hypothesized to impair bone health in diabetes include chronic inflammation, abnormalities in the growth hormone-insulin-like growth factor 1 (IGF-1) axis, and abnormalities in bone mineral metabolism including excess urinary calcium loss. There are no standard guidelines for bone health screening in children. Assessment of bone density by dual-energy x-ray absorptiometry (DXA) and markers of bone mineral metabolism is recommended in adults with fracture history and other risk factors for osteoporosis. Dietary education should reinforce the importance of meeting the recommended daily allowance (RDA) for calcium and vitamin D intake from diet and supplements.

Other Complications

Mauriac syndrome is a rare complication related to chronic underinsulinization that is characterized by growth failure and hepatomegaly

caused by excess glycogen accumulation in the liver. It has become much less common since longer-acting insulins have become available. Clinical features of Mauriac syndrome include moon face, protuberant abdomen, proximal muscle wasting, and enlarged liver from fat and glycogen infiltration.

The syndrome of **limited joint mobility** is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and nephropathy, which may appear before 18 years of age. The prevalence of limited joint mobility has significantly decreased, which is attributed to the improved overall metabolic control of children and adolescents with T1DM.

PROGNOSIS

T1DM is a serious, chronic disease. It has been estimated that the average life span of individuals with diabetes is approximately 10 years shorter than that of people without diabetes, but with improved care, that figure is lessening consistently. Although most children with T1DM eventually attain a height within the normal adult range, puberty may be delayed, and the final height may be less than the genetic potential. From studies in identical twins, it is apparent that despite seemingly satisfactory control, the affected twin manifests delayed puberty and a substantial reduction in height when the onset of disease occurs before puberty. These observations indicate that, in the past, conventional criteria for judging control were inadequate and that adequate control of T1DM was almost never achieved by routine means.

The changing pattern of metabolic control is having a profound influence on reducing the incidence and the severity of certain complications. For example, after 20 years of diabetes, there was a decline in the incidence of nephropathy in T1DM in Sweden among children whose disease was diagnosed in 1971–1775 compared with in the preceding decade. In addition, in most patients with microalbuminuria in whom it was possible to obtain good glycemic control, microalbuminuria disappeared. This improved prognosis is directly related to metabolic control.

PANCREAS AND ISLET TRANSPLANTATION AND REGENERATION

In an attempt to cure T1DM, transplantation of a segment of the pancreas or of isolated islets has been performed in adults. These procedures are both technically demanding and associated with the risks of disease recurrence and complications of rejection or its treatment by immunosuppression. Long-term complications of immunosuppression include the development of malignancy. Some antirejection drugs, notably cyclosporine and tacrolimus, are toxic to the islets of Langerhans, impairing insulin secretion and even causing diabetes. Hence, segmental pancreas transplantation is generally only performed in association with transplantation of a kidney for a patient with ESRD caused by diabetic nephropathy in which the immunosuppressive regimen is indicated for the renal transplantation. Several thousand such transplants have been performed in adults. With experience and better immunosuppressive agents, functional survival of the pancreatic graft may be achieved for up to several years, during which time patients may be in metabolic control with no or minimal exogenous insulin and reversal of some of the microvascular complications. However, because children and adolescents with DM are not likely to have ESRD from their diabetes, pancreas transplantation as a primary treatment in children cannot be recommended.

Islet cell transplantation is challenging because of limited survival of the transplanted cells and because of rejection. An islet transplantation strategy (Edmonton protocol) infused isolated pancreatic islets into the portal vein of adults with T1DM, along with immunosuppressive medications that had lower side effect profiles than other drugs. Although lasting insulin independence was initially low, engraftment and insulin independence have improved over the last decade, and over a thousand patients have undergone the procedure. There has been improved islet engraftment using improved induction and maintenance immunosuppression. Still, in 5-year follow-up studies, only ~10% maintain insulin independence, with an average duration of insulin independence of ~15 months. Long-term challenges remain the toxicity of immunosuppression, the limited procurement of viable tissue, and funding and limitations of engraftment itself.

629.3 Type 2 Diabetes Mellitus

David R. Weber

Formerly known as *non–insulin-dependent diabetes* or *adult-onset diabetes,* T2DM is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of the β cell to keep up with increasing insulin demand. Patients with T2DM have relative rather than absolute insulin deficiency. Generally, they are not ketosis prone, but ketoacidosis is the initial presentation in 5–10% of affected subjects (Table 629.12).

NATURAL HISTORY

T2DM is a heterogenous, polygenic disease aggravated by environmental factors, including low physical activity and excessive caloric intake. Most patients are obese, although the disease can occasionally be seen in normal-weight individuals. People of Asian ancestry appear to be at risk for T2DM at lower degrees of total adiposity. Obesity, in particular central obesity, is associated with the development of insulin resistance (Fig. 629.10). In addition, patients who are at risk for developing T2DM exhibit decreased glucose-induced insulin secretion. Obesity does not lead to the same degree of insulin resistance in all individuals, and even those who develop insulin resistance do not necessarily exhibit impaired β-cell function. Thus many obese individuals have some degree of insulin resistance but compensate for it by increasing insulin secretion.

Those individuals who are unable to adequately compensate for insulin resistance by increasing insulin secretion develop IGT and IFG, usually, although not always, in that order. Hepatic insulin resistance leads to excessive hepatic glucose output (failure of insulin to suppress hepatic glucose output), and skeletal muscle insulin resistance leads to decreased glucose uptake in a major site of glucose disposal. Over time hyperglycemia worsens, a phenomenon that has been attributed to the deleterious effect of chronic hyperglycemia (glucotoxicity) or chronic hyperlipidemia (lipotoxicity) on β-cell function and is often accompanied by increased triglyceride content and decreased insulin gene expression.

At some point, blood glucose elevation meets the criteria for a diagnosis of T2DM (see Table 629.2), but most patients with T2DM remain asymptomatic for months to years after this point because hyperglycemia is moderate and symptoms are not as dramatic as the polyuria and weight loss at presentation of T1DM. Weight gain may even continue. The prolonged hyperglycemia may be accompanied by the development of microvascular and macrovascular complications. Among the differences between T2DM in children and adults is a faster decline in β-cell function and insulin secretion, as well as faster development of diabetes complications in children.

In T2DM, insulin deficiency is rarely absolute, so patients usually do not need insulin to survive, at least early in the disease course. However, in some cases, the degree of hyperglycemia is such that exogenous insulin therapy is needed. DKA is uncommon in patients with T2DM but does occur and appears to be more common in children than in adults. Although it is generally believed that autoimmune destruction of pancreatic β-cells does not occur in T2DM, autoimmune markers of T1DM—namely, GAD, ICA512, and IAA—may be positive in ~30% of the cases of adolescent T2DM. The presence of these autoimmune markers does not rule out T2DM in children and adolescents. At the same time, because of the general increase in obesity, the presence of obesity does not preclude the diagnosis of T1DM. Although most newly diagnosed children and adolescents can be confidently assigned a diagnosis of T1DM or T2DM, a few exhibit features of both types and are difficult to classify.

EPIDEMIOLOGY

The prevalence of T2DM in children (10-19 years) has risen dramatically from 34 cases per 100,000 youth in 2001 to 67 cases per 100,000

Table 629.12 Characteristics at Presentation for Type 1, Type 2, and Monogenic Diabetes

	TYPE 1 DIABETES	TYPE 2 DIABETES	MATURITY-ONSET DIABETES OF THE YOUNG
Age of onset during childhood and adolescence	Any	Rarely before puberty	Any
Weight status	Any	Rarely with normal weight	Any
Symptomatic (polyuria, polydipsia, weight loss)	Nearly universal	Two thirds	Common
Duration of symptoms before presentation	<1 mo	Frequently >1 mo	Any
Diabetic ketoacidosis at presentation	Common	Rare (6–11%)	—
Family history of diabetes before age 40	Uncommon	Strong family history for type 2 diabetes	Very strong family history, classically in three generations
Acanthosis nigricans	Rare	Common (86%)	—
Ethnicity	Any	Predominantly Black or minority ethnicity	Any
Diabetes-associated antibodies (IA2, glutamate decarboxylase, insulin)	Positive in majority	Negative (<10%)	Negative (<1%)
Pathogenic variants in *HNF1A, GCK,* or *HNF4A*	Negative	Negative	Nearly universal
Complications at presentation	Very rare	Common	Rare

IA2, Tyrosine phosphatase-related islet antigen 2.
From Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet. 2017;389:2252–2260.

in 2017. Certain ethnic groups appear to be at higher risk; for example, Native Americans, Hispanic Americans, and Black Americans (in that order) have higher incidence rates than White Americans (Fig. 629.11). Although most children presenting with diabetes have T1DM, the percentage of children presenting with T2DM is increasing and represents up to 50% of the newly diagnosed children in some centers.

GENETICS

T2DM has a strong genetic component; concordance rates among identical twins are in the 40–80% range, but there is not a simple mendelian pattern. Twinning itself increases the risk of T2DM (because of intrauterine growth restriction), and this may distort estimates of genetic risk. Monozygotic twins have a lifetime concordance of T2DM of around 70%, indicating that shared environmental factors (including the prenatal environment) may have a role in the development of T2DM; dizygotic twins have a lifetime concordance of around 20–30%. The genetic basis for T2DM is complex and incompletely defined; no single identified defect predominates. Genome-wide association studies have identified certain genetic polymorphisms that are associated with increased T2DM risk in most populations studied; the most consistently identified are variants of *TCF7L2,* which may have a role in β-cell function. Other identified risk alleles include variants in *PPARG* and *KCNJ11-ABCC8.* These variants only explain a small portion (probably less than 20%) of the population risk of diabetes, and in many cases the mechanism by which these polymorphisms confer risk of T2DM is not clear.

EPIGENETICS AND FETAL PROGRAMMING

Low birthweight and intrauterine growth restriction are associated with increased risk of T2DM. This risk appears to be higher in low-birthweight infants who gain weight more rapidly in the first few years of life. These findings have led to the formulation of the *thrifty phenotype hypothesis,* which postulates that poor fetal nutrition programs these children to maximize storage of nutrients and makes them more prone to future weight gain and development of diabetes. Epigenetic modifications may play a role in this phenomenon, given that so few of the known T2DM genes are associated with low birthweight.

ENVIRONMENTAL AND LIFESTYLE-RELATED RISK FACTORS

Obesity is the most important lifestyle factor associated with development of T2DM. This, in turn, is associated with the intake of high-energy foods, physical inactivity, excess screen time, and low socioeconomic status. Maternal smoking also increases the risk of diabetes and obesity in the offspring. Increasingly, exposure to land pollutants and air pollutants is demonstrated to contribute to insulin resistance. The lipophilic nature of these organic pollutants and their consequent storage in adipose tissue may promote obesity and insulin resistance. In addition, sleep deprivation and psychosocial stress are associated with increased risk of obesity in childhood and with IGT in adults, possibly via overactivation of the hypothalamic-pituitary-adrenal axis. Many antipsychotics (especially the atypical antipsychotics like olanzapine and quetiapine) and antidepressants (both tricyclic antidepressants and newer antidepressants like fluoxetine and paroxetine) induce weight gain. In addition to the risk conferred by increased obesity, some of these medications may also have a direct role in causing insulin resistance, β-cell dysfunction, leptin resistance, and activation of inflammatory pathways.

CLINICAL FEATURES

In the United States, T2DM in children is more likely to be diagnosed in Native American, Hispanic American, and Black American youth, with the highest incidence being reported in Pima Indian youth. Although cases may be seen as young as 4 years of age, most are diagnosed in adolescence; the incidence increases with increasing age. Family history of T2DM is present in most cases. Patients are obese and present with mild symptoms of polyuria and polydipsia or are asymptomatic and T2DM is detected on screening tests. Presentation with DKA occurs in ~10% of cases. Physical examination frequently reveals the presence of acanthosis nigricans, most commonly on the neck and in other flexural areas. Other findings may include striae and an increased waist-to-hip ratio. Laboratory testing reveals elevated HbA_{1c} levels. Hyperlipidemia characterized by elevated triglycerides and low-density lipoprotein cholesterol levels is commonly seen in patients with T2DM at diagnosis. Lipid screening is indicated in all new cases of T2DM. The current recommendation is that blood pressure measurement, random urine

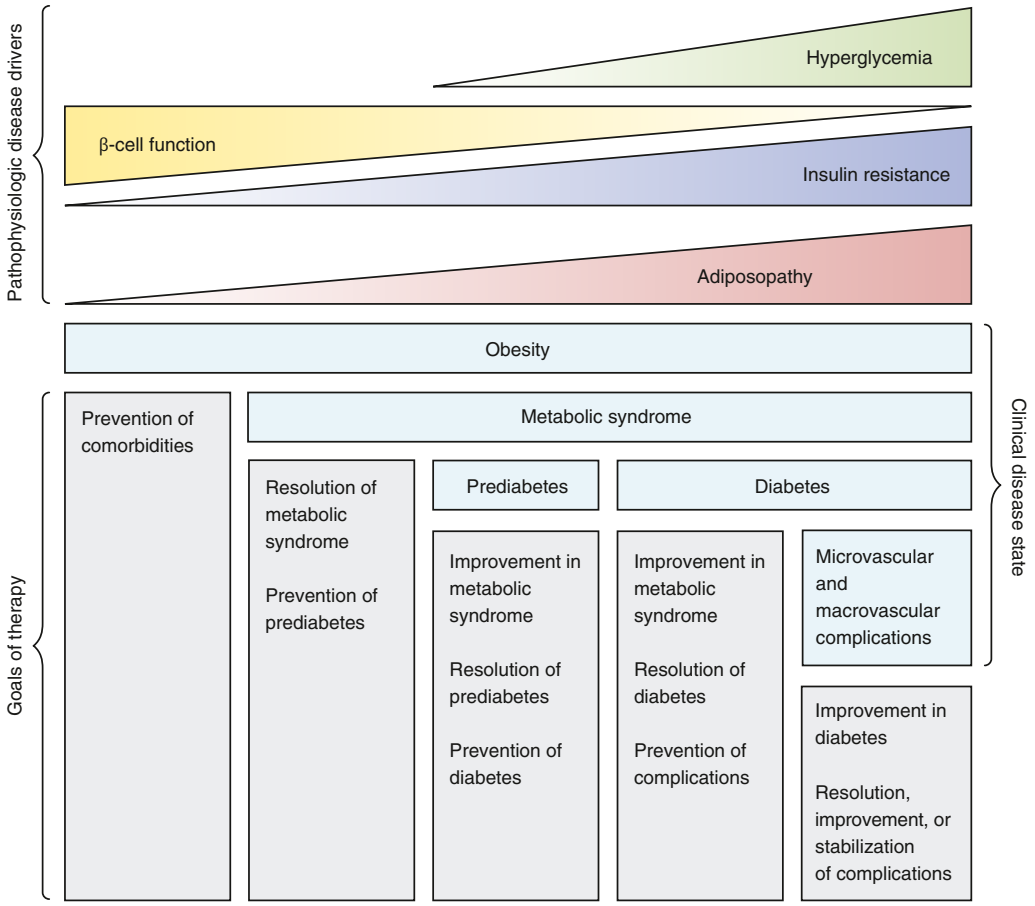

Fig. 629.10 The disease continuum for weight-related type 2 diabetes. *(From Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet. 2022;399:394–404.)*

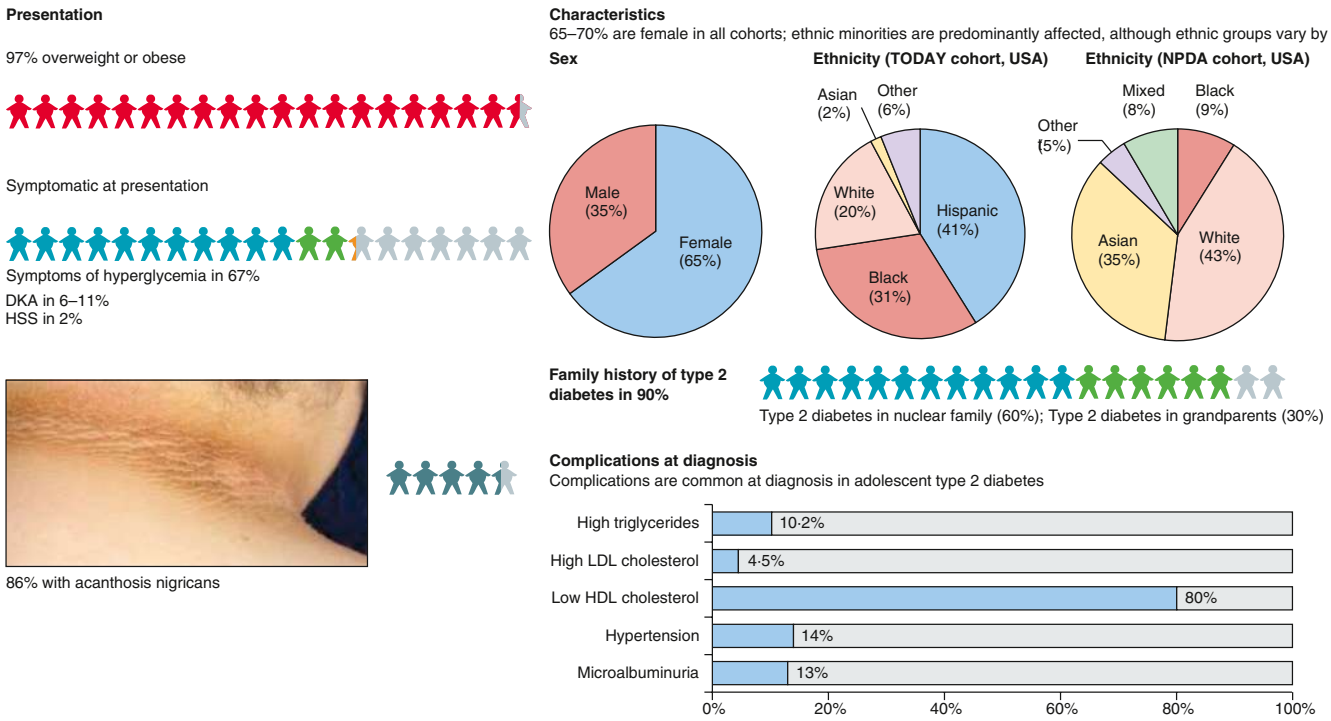

Fig. 629.11 Features of adolescent type 2 diabetes at diagnosis. DKA, diabetic ketoacidosis. HHS, hyperglycemic hyperosmolar syndrome; NPDA, National Diabetes Pediatric Audit; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth. *(From Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet. 2017;389:2252–2260.)*

albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis.

Because hyperglycemia develops slowly and patients may be asymptomatic for months or years after they develop T2DM, screening is recommended in high-risk children (Table 629.13). All youth who are overweight and have at least one other risk factor should be tested for T2DM beginning at age 10 years or at the onset of puberty. Risk factors include family history of T2DM in first- or second-degree relatives, history of gestational diabetes in the mother, belonging to a high-risk racial or ethnic group (i.e., Native American, Black American, Hispanic, or Asian/Pacific Islander groups), and having signs of insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome). The current recommendation is to use the HbA_{1c} the screening tool; fasting plasma glucose is also acceptable. In borderline or asymptomatic cases, the diagnosis may be confirmed using a standard OGTT, but this test is not required if typical symptoms are present or fasting plasma glucose or HbA_{1c} is clearly elevated.

TREATMENT

T2DM is a progressive syndrome that gradually leads to complete insulin deficiency during the patient's life. A systematic approach for the treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when hyperglycemia cannot be controlled by lifestyle and noninsulin pharmacotherapy. Lifestyle modification (diet and exercise) is an essential part of the treatment regimen, and consultation with a dietitian is usually necessary (see Fig. 629.10). An oral agent monotherapy may not maintain lasting glucose control in close to half of those with T2DM.

Recommendations are to implement a comprehensive lifestyle modification plan designed to induce weight loss of 7–10%. There is no specific dietary or exercise regimen that has been conclusively shown to be superior, and practitioners recommend a low-calorie, low-fat diet and 30-60 minutes of physical activity at least 5 times a week. Screen time should be limited to 1-2 hours a day. Education is provided to diminish unhealthy habits such as skipping meals, heavy snacking, and excessive screen time. Adolescents may engage in non–appetite-based eating (i.e., emotional eating, television-cued eating, boredom) and cyclic dieting ("yo-yo" dieting). Treatment in these cases is frequently challenging and may not be successful unless the entire family buys into the need to change their unhealthy lifestyle.

Pharmacologic therapy should be initiated at diagnosis of T2DM. Noninsulin pharmacotherapies used in the treatment of T2DM are shown in Table 629.14; most of these are not approved for use in patients under the age of 18 years. Metformin is the first line of pharmacotherapy and should be started in all patients. Renal insufficiency and liver disease are contraindications to metformin use and may increase the risk of lactic acidosis. Patients with markedly elevated liver transaminases should undergo evaluation by a gastroenterologist/hepatologist before initiating therapy. The starting dose is 500-1000 mg/day, which should be increased over a few weeks to the full therapeutic dose of 2,000 mg daily. Patients who present with significant (HbA_{1c} >8.5%) or symptomatic (e.g., polyuria, polydipsia) hyperglycemia should be started on basal insulin with a long-acting insulin analog, typically at a dose of 0.5 units/kg/day. Those presenting in DKA will require initial treatment with insulin using protocols similar to those used for treating T1DM. Once blood glucose levels are under control, many cases can be managed with hypoglycemic agents and lifestyle interventions, but some patients will continue to require insulin therapy.

Ongoing care should include periodic review of weight and BMI, diet, and physical activity; blood glucose monitoring; and monitoring of HbA_{1c} at 3-month intervals. Frequency of home glucose monitoring can range from 3-4 times daily for those on multiple daily insulin injections to twice daily for those on a stable long-acting insulin regimen or metformin. Alternatively, blood glucose monitoring can be done by CGM. Patients who fail to achieve glycemic targets (typically HbA_{1c} <7%) with lifestyle modification and metformin alone will require escalation of therapy with the addition of basal insulin or liraglutide. Liraglutide is an injectable glucagon-like peptide-1 (GLP-1) analog approved by the FDA for use in children ≥10 years. A potential benefit of liraglutide over basal insulin is that it may promote weight loss. The typical starting dose is 0.6 mg/daily, increased as tolerated by 0.6 mg/day per week until a maximum dose of 1.8 mg is achieved. Gastrointestinal symptoms are the most common side effect. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN 2), based on animal data showing a dose- and duration-dependent effect to promote thyroid C-cell tumors in rodents.

Other agents such as thiazolidinediones, sulfonylureas, other GLP-1 analogs, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), pramlintide, and sodium-glucose transport protein inhibitors (SGLT2 inhibitors) are used with variable frequency in adults but are infrequently used in children. Sulfonylureas cause insulin release by closing the potassium channel (K_{ATP}) on β cells. They are occasionally used when metformin monotherapy is unsuccessful or contraindicated for some reason (use in certain forms of neonatal diabetes is discussed in the relevant section). Thiazolidinediones increase insulin sensitivity via activation of the peroxisome proliferator-activated receptor pathway, but use is limited because of concerns about adverse cardiac effects. Pramlintide is an analog of islet amyloid polypeptide (IAPP), which delays gastric emptying, suppresses glucagon, and possibly suppresses food intake. It is not approved for pediatric use and increases the risk of hypoglycemia when used with insulin or other hypoglycemic agents.

Incretins are gut-derived peptides like GLP-1, GLP-2, and GIP (glucose-dependent insulinotropic peptide, previously known as *gastric inhibitory protein*) that are secreted in response to meals and act to enhance insulin secretion and action, suppress glucagon production, and delay gastric emptying (among other actions). Other daily and weekly forms of GLP-1 agonists beyond liraglutide are commonly used in adults. DPP-4 inhibitors are oral agents that prolong the action of GLP-1 and are currently being studied for use in children. The SGLT-2 inhibitors act by blocking glucose reabsorption in the proximal renal tubule and are commonly used as second- or third-line agents in adults, with specific benefits in improving cardiorenal outcomes in patients with heart failure or declining renal function. SGLT-2 inhibitors are currently under evaluation for potential use in children. Adults with T2DM have been treated with *double incretion* therapy (tirzepatide) with the combination of a GLP-1 agonist and GIP.

Further rises in HbA_{1c} despite the addition of basal insulin and/or liraglutide will necessitate addition of short-acting insulin at mealtimes. Bariatric surgery is also used in adolescents with moderate to severe obesity and frequently leads to complete remission of T2DM. Guidelines for the routine use of bariatric surgery in adolescents continue to emerge, but expert opinion suggests that adolescents with BMI ≥35 or 120% of the 95th percentile for age and gender with a clinically significant complication (including T2DM) are potential candidates, provided there is access to a quality multidisciplinary center with pediatric experience.

Table 629.13 Testing for Type 2 Diabetes in Children

- **Criteria***

Overweight (body mass index >85th percentile for age and sex
Plus
One or more of the following risk factors:
- Family history of type 2 diabetes in first- or second-degree relative or gestational diabetes in the mother
- High risk racial/ethnic background (Native American, Black American, Hispanic, Asian/Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)

- **Age of initiation**: age 10 yr or at onset of puberty if puberty occurs at a younger age
- **Frequency:** every 1-2 yr, based upon clinical suspicion
- **Test:** fasting glucose, HbA_{1c}, or oral glucose tolerance teat

*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

Table 629.14 Noninsulin Pharmacotherapies Used to Treat T2DM

MEDICATIONS	CLASS	MECHANISM OF ACTION	ROUTE	FDA-APPROVED AGE
Pramlintide	Amylin analogue	Increases satiety, slows gastric emptying, and suppresses postprandial glucagon secretion, resulting in decreased postmeal glucose excursions	Subcutaneous injection	>18 yr
Metformin	Biguanide	Improves hepatic insulin sensitivity. Increases GLP-1 and PYY	Oral	>10 yr
Alogliptin Linagliptin Saxagliptin Sitagliptin	DPP-4 inhibitors	Inhibits DPP-4 from degrading GLP-1 and GIP	Oral	>18 yr
Albiglutide Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Glucagon-like peptide agonists	Increase release of GLP-1, which stimulates release of insulin	Subcutaneous injection	>8 yr, with exception of liraglutide, which is >10 yr
Nateglinide Repaglinide	Meglitinides	Causes rapid secretion of insulin by acting on the ATP sensitive potassium channel of pancreatic beta cells	Oral	>18 yr
Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Sodium-glucose co-transporter 2 inhibitors	Promotes renal excretion of glucose at the level of the proximal tubule causing an osmotic diuresis	Oral	>18 yr
Gliclazide Glimepiride Glipizide Glyburide	Sulfonylureas	Increase insulin section via interaction with the K-ATP channel in β cells	Oral	>18 yr
Pioglitazone Rosiglitazone	Thiazolidinediones	Increase insulin sensitivity at adipose and muscle tissue	Oral	>18 yr

DPP-4, Dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1 agonist; PYY, peptide YY.

COMPLICATIONS

In one study of diabetes in youth, 92% of the patients with T2DM had two or more elements of **metabolic syndrome** (hypertension, hypertriglyceridemia, decreased high-density lipoprotein, increased waist circumference), including 70% with hypertension. In addition, the incidence of microalbuminuria and diabetic retinopathy appears to be higher in T2DM than it is in T1DM. In long-term follow-up from another study, the participants at a mean of age 26 years reported a cumulative incidence of hypertension of 68%, dyslipidemia 52%, diabetic kidney disease 55%, and nerve disease 32%.

Given the extremely high risk of diabetes-related comorbidities, routine screening for microalbuminuria, dyslipidemia, hypertension, and retinopathy should commence shortly after diagnosis. Sleep apnea and fatty liver disease are being diagnosed with increasing frequency and may necessitate referral to the appropriate specialists. Complications associated with all forms of diabetes and recommendations for screening are noted in Table 629.12; Table 629.15 lists conditions particularly associated with T2DM.

PREVENTION

The difficulties in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for T2DM, which is linked to modifiable risk factors (obesity, a sedentary lifestyle). The Diabetes Prevention Program demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of T2DM. Lifestyle intervention reduced the diabetes incidence by 58%; metformin reduced the incidence by 31% compared with placebo. Lifestyle interventions are believed to have similar beneficial effects in obese adolescents with IGT.

629.4 Other Specific Types of Diabetes

David R. Weber

Most cases of diabetes in children and adults fall into the two broad categories of T1DM and T2DM, but between 1% and 10% of cases are caused by single-gene disorders. These disorders include hereditary defects of β-cell function and insulin action, as well as rare forms of mitochondrial diabetes.

GENETIC DEFECTS OF β-CELL FUNCTION

Transient Neonatal Diabetes Mellitus

Neonatal diabetes is transient in approximately 50% of cases, but after an interim period of normal glucose tolerance, 50–60% of these patients develop permanent diabetes (at an average age of 14 years). It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classic T1DM is a chance occurrence or causally related (Fig. 629.12).

The syndrome of **transient DM** in the newborn infant has its onset in the first week of life and persists several weeks to months before spontaneous resolution. Median duration is 12 weeks. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and, at times, metabolic acidosis, but with only minimal or no ketonemia or ketonuria. There may also be findings such as umbilical hernia or large tongue. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations are normal. After spontaneous recovery, the insulin responses to these same stimuli are brisk and normal, implying a possible functional delay in β-cell maturation with spontaneous resolution. Occurrence of the syndrome in

Table 629.15 Monitoring for Complications and Comorbidities in T2DM

CONDITION	SCREENING TEST	COMMENT
Hypertension	Blood pressure	
Fatty liver	Aspartate aminotransferase, alanine aminotransferase, possibly liver ultrasound	
Polycystic ovary syndrome	Menstrual history, assessment for androgen excess with free/total testosterone, dehydroepiandrosterone sulfate	
Microalbuminuria	Urine albumin concentration and albumin-to-creatinine ratios	
Dyslipidemia	Fasting lipid profile (total, low-density lipoprotein, high-density lipoprotein cholesterol, triglycerides)	Obtain at diagnosis and every 2 yr
Sleep apnea	Polysomnography: Sleep study to assess overnight oxygen saturation, airflow, heart rate, electromyography, and eye movements	

consecutive siblings has been reported. About 70% of cases are the result of abnormalities of an imprinted locus on chromosome 6q24, resulting in overexpression of paternally expressed genes such as *PLAGL1/ZAC* and *HYMAI*. Most of the remaining cases are caused by pathogenic variants in K_{ATP} channels. Variants in K_{ATP} channels also cause many cases of permanent neonatal diabetes, but there is practically no overlap between the variants that lead to transient neonatal DM and those causing permanent neonatal DM. This syndrome of transient neonatal DM should be distinguished from the severe hyperglycemia that may occur in hypertonic dehydration that usually occurs in infants beyond the newborn period and responds promptly to rehydration with minimal or no requirement for insulin.

Administration of insulin is mandatory during the active phase of DM in the newborn. Rehydration and IV insulin are usually required initially; transition to subcutaneous insulin can occur once clinically stable. A variety of regimens, including intermediate- or long-acting insulin given in one to two daily doses or continuous insulin therapy with an insulin pump, have been used successfully. The starting dose is typically 1-2 units/kg/day but will need to be adjusted based upon blood glucose levels. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifested or after 2 months of age.

Permanent Neonatal Diabetes Mellitus

Permanent DM in the newborn period is caused, in approximately 50% of the cases, by pathogenic variants in the *KCNJ11* and *ABCC8* genes (see Figs. 629.12 and 629.13). These genes code for the Kir6.2 and SUR1 subunits of the adenosine triphosphate–sensitive potassium channel, which is involved in an essential step in insulin secretion by the β cell. Some cases are caused by pancreatic agenesis because of homozygous pathogenic variants in *IPF-1* (where heterozygous variants cause MODY4); homozygous variants in the glucokinase gene (where heterozygous variants cause MODY2); and variants in the insulin gene (see Tables 629.1 and 629.12). Almost all these infants are small at birth because of the role of insulin as an intrauterine growth factor. Instances of affected twins and families with more than one affected infant have been reported. Infants with permanent neonatal DM may be initially euglycemic and typically present between birth and 6 months of life (mean age of presentation is 5 weeks), but rarely can present up to 1 year of age. There is a spectrum of severity, and up to 20% have neurologic features. The most severely affected patients have the syndrome of *d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes (**DEND syndrome**).

Activating pathogenic variants in the *KCNJ11* gene (encoding the adenosine triphosphate–sensitive potassium channel subunit Kir6.2) are associated with both TND and PND, with variants associated with each phenotype. More than 90% of these patients respond to sulfonylureas (at higher doses than those used in T2DM), but patients with severe neurologic disease may be less responsive. Pathogenic variants in *ABCC8* (encoding the SUR1 subunit of this potassium channel) were thought to be less likely to respond to sulfonylureas (because this is the subunit that binds sulfonylurea drugs), but some of these variants are reported to respond; patients have been successfully switched from insulin to oral therapy. Several protocols for switching the patient from insulin to glyburide are available, and patients are usually stabilized on doses ranging from 1 to 2.5 mg/kg/day. Because approximately 50% of neonatal diabetics have potassium-channel variants that can be switched to sulfonylurea therapy, with dramatic improvement in glycemic control, neurologic outcomes, and quality of life, all patients with diabetes diagnosed before 6 months of age (and perhaps even those diagnosed before 12 months of age) in whom insulin dependence persists beyond 7-10 days should have genetic testing (Fig. 629.14).

Maturity-Onset Diabetes of Youth

Several forms of diabetes are associated with **monogenic defects in β-cell function**. Before these genetic defects were identified, this subset was diagnosed on clinical grounds and described by the term *MODY*. This subtype of DM consists of a group of heterogeneous clinical entities that are characterized by onset before 25 years, autosomal dominant inheritance, and a primary defect in insulin secretion. Strict criteria for the diagnosis of MODY include diabetes in at least three generations with autosomal dominant transmission and diagnosis before age 25 years in at least one affected subject. Pathogenic variants have been found in at least 14 different genes, accounting for the dominantly inherited monogenic defects of insulin secretion, for which the term MODY is used (Table 629.16). The ADA groups these disorders together under the broader category of *genetic defects of β-cell function*. Just three of them (MODY2, MODY3, and MODY5) account for 90% of the cases in this category in European populations, but the distribution may be different in other ethnic groups. Except for MODY2 (which is caused by variants in the enzyme glucokinase), all other forms are caused by genetic defects in various transcription factors (see Table 629.16).

MODY2

This is the second most common form of MODY and accounts for approximately 15–30% of all patients diagnosed. Glucokinase plays an essential role in β-cell glucose sensing, and heterozygous pathogenic variants in this gene lead to mild reductions in pancreatic β-cell response to glucose. Homozygotes with the same variants are completely unable to secrete insulin in response to glucose and develop a form of PND. Patients with heterozygous variants have a higher threshold for insulin release but are able to secrete insulin adequately at higher blood glucose levels (typically 125 mg/dL [7 mmol/L] or higher). This results in a relatively mild form of diabetes (HbA_{1c} is usually less than 7%), with mild fasting hyperglycemia and IGT in most patients. MODY2 may be misdiagnosed as T1DM in children, gestational diabetes in pregnant women, or well-controlled T2DM in adults (see Table 629.12). An accurate diagnosis is important because most cases are not progressive, and except for gestational diabetes, may not require treatment. When needed, they can usually be treated with small doses of exogenously administered insulin. Treatment with oral agents (sulfonylureas and related drugs) can be successful and may be more acceptable to many patients.

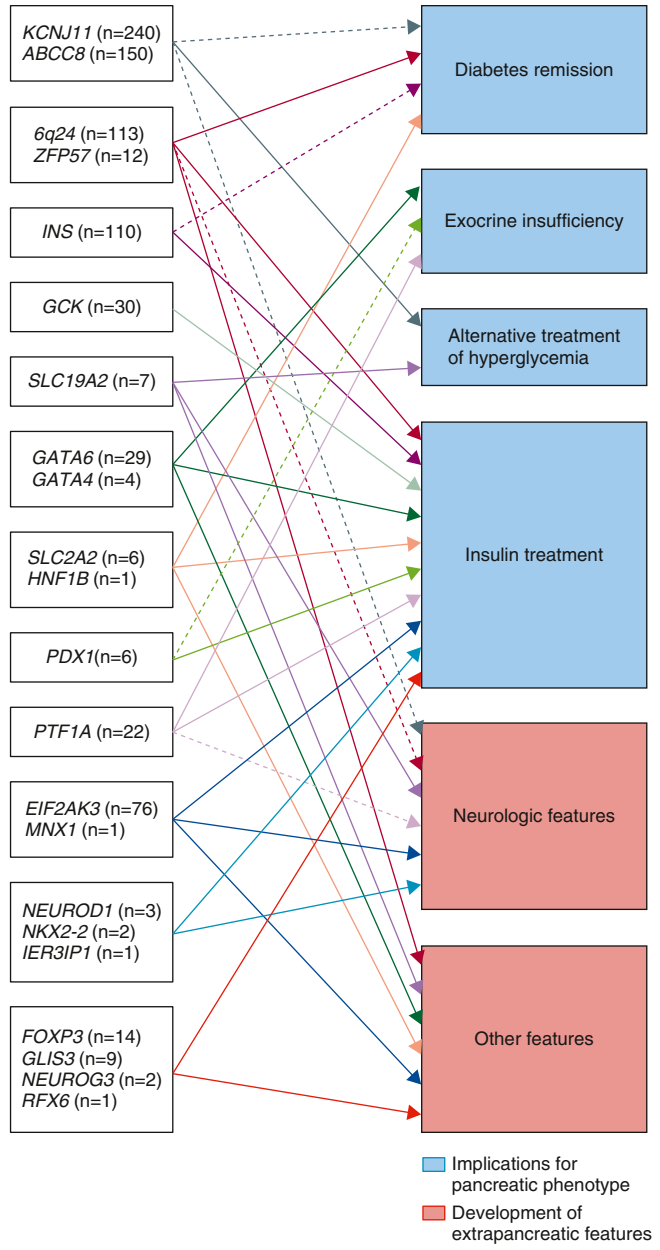

Fig. 629.12 A genetic diagnosis guides clinical management. Schematic representation of genetic causes of neonatal diabetes and the implications of this genetic diagnosis. *n* indicates the number of patients identified with pathogenic variants in each of the genes in the 1,020 neonatal diabetes patient cohort. *Solid arrows* indicate implications for most pathogenic variants in the genes. *Dashed arrows* indicate the implications for specific variants. *(From De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet. 2015;386:957–963. Fig. 3.)*

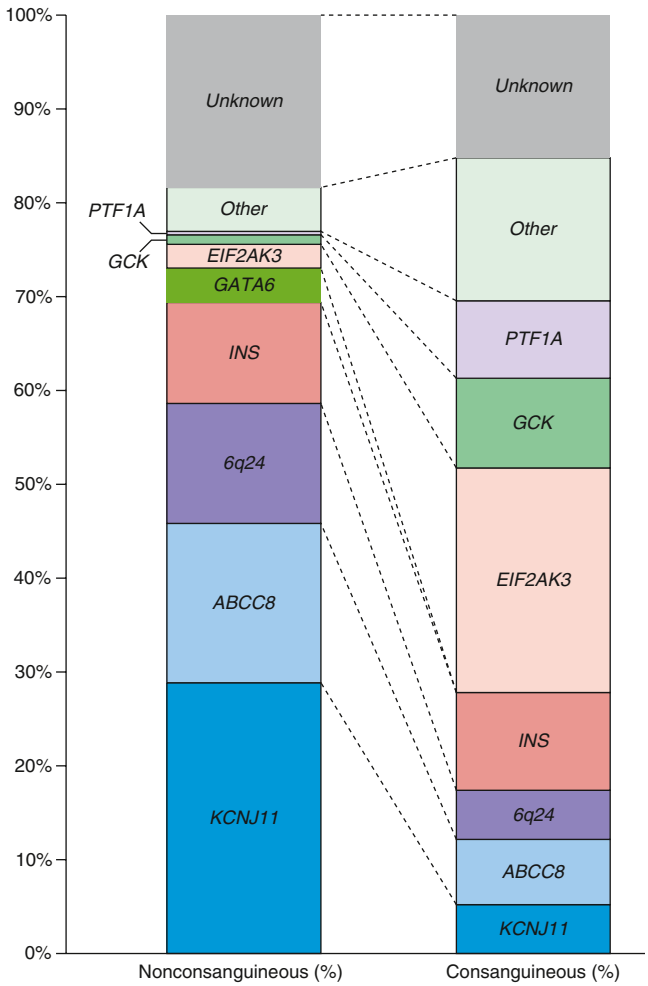

Fig. 629.13 Different genetic causes of neonatal diabetes in patients born to nonconsanguineous and consanguineous parents. Comparison of genetic causes of neonatal diabetes in nonconsanguineous (*n* = 790) and consanguineous groups (*n* = 230). Consanguinity is defined by parents being second cousins or more closely related or by the presence of 1.56% or higher total homozygosity. Genes involved in less than 2.5% of patients in both cohorts were grouped in the other category. *(From De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet. 2015;386:957–963. Fig. 2.)*

MODY3

Patients affected with pathogenic variants in the transcription factor hepatocyte nuclear factor-1α show abnormalities of carbohydrate metabolism varying from IGT to severe diabetes and often progressing from a mild to a severe form over time. They are also prone to the development of vascular complications. This is the most common MODY subtype and accounts for 30–60% of all cases of MODY. These patients are very sensitive to the action of sulfonylureas and can usually be treated with relatively low doses of these oral agents, at least in the early stages of the disease. In children, this form of MODY is sometimes misclassified as T1DM and treated with insulin. Evaluation of autoimmune markers helps to rule out T1DM; genetic testing for MODY is available and is indicated in patients with relatively mild diabetes and a family history suggestive of autosomal dominant inheritance. Accurate diagnosis can lead to avoidance of unnecessary insulin treatment and specific genetic counseling (see Fig. 629.14).

Less Common Forms of Monogenic Diabetes

Hepatocyte nuclear factor-4α (MODY1), insulin promoter factor (IPF)-1, also known as (PDX-1) (MODY4), hepatocyte nuclear factor 1β/TCF2 (MODY5), and NeuroD1 (MODY6) are all transcription factors that are involved in β-cell development and function, and mutations in these lead to various rare forms of MODY. In addition to diabetes, they can also have specific findings unrelated to hyperglycemia; for example, MODY1 is associated with low triglyceride and lipoprotein levels, and MODY5 is associated with renal cysts and renal dysfunction. In terms of treatment, MODY1 and MODY4 may respond to oral sulfonylureas, but MODY5 does not respond to oral agents and requires treatment with insulin. NeuroD1 defects are extremely rare and not much is known about their natural history.

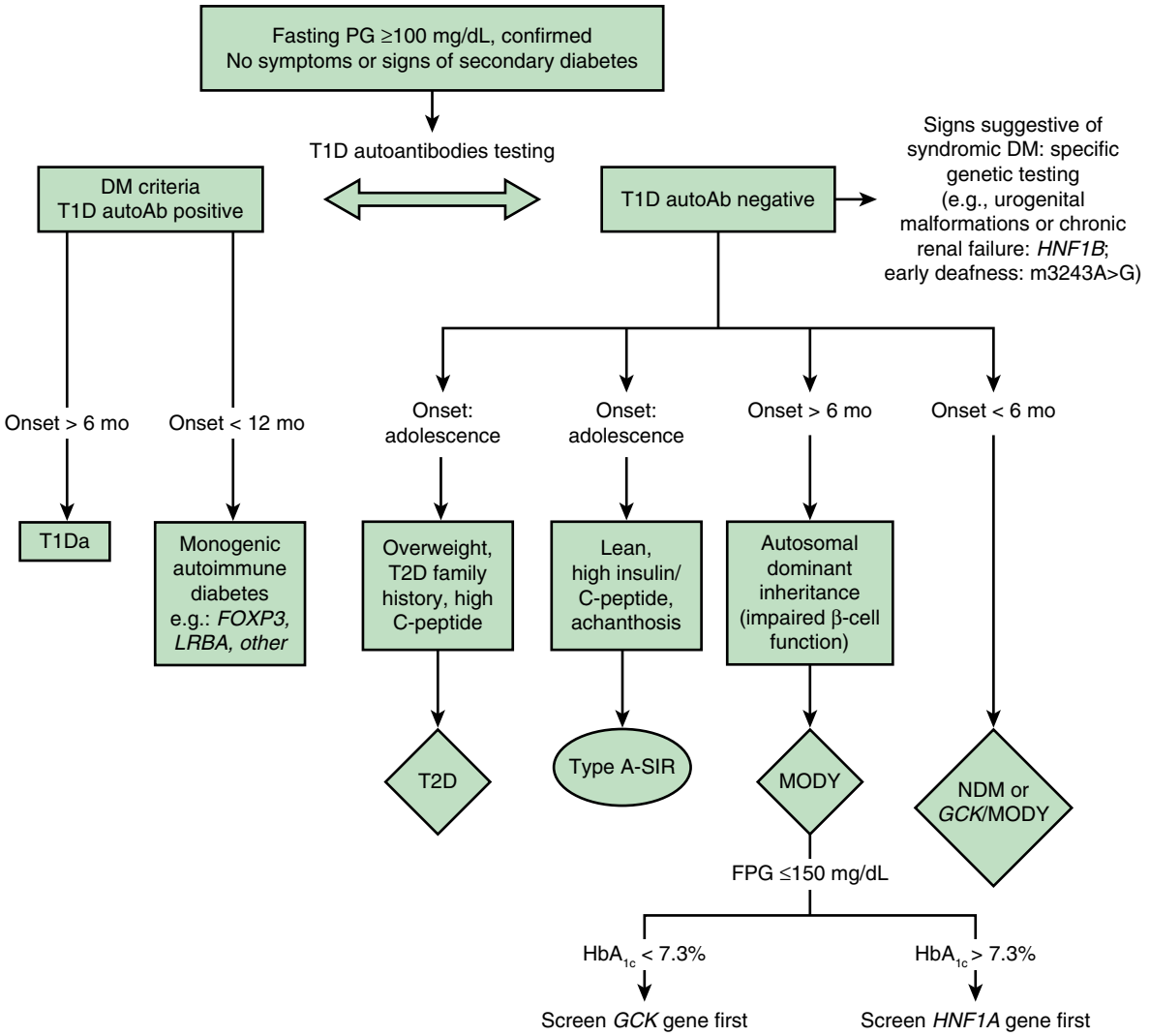

Fig. 629.14 Diagnostic algorithm of monogenic forms of diabetes. Negativity of genetic testing of two common subtypes of MODY in children and adolescents implies that further testing is mandatory if the clinical diagnosis is robust. FPG, fasting plasma glucose; MODY, maturity onset diabetes of the young; NDM, neonatal diabetes mellius; SIR, severe insulin resistance. *(From Barbetti F, D'Annunzio G. Genetic causes and treatment of neonatal diabetes and early childhood diabetes. Best Pract Res Clin Endocrinol Metab. 2018;32[4]:575-591. Fig. 1.)*

Primary or secondary defects in the glucose transporter-2, which is an insulin-independent glucose transporter, may also be associated with diabetes. Diabetes may also be a manifestation of a polymorphism in the glycogen synthase gene. This enzyme is crucially important for storage of glucose as glycogen in muscle. Patients with this defect are notable for marked insulin resistance and hypertension, as well as a strong family history of diabetes.

Another form of IDDM is **Wolfram syndrome** (Table 629.17). Wolfram syndrome 1 is characterized by diabetes insipidus, DM, optic atrophy, and deafness—thus the acronym **DIDMOAD**. Some patients with diabetes appear to have severe insulinopenia, whereas others have significant insulin secretion as judged by C-peptide. The overall prevalence is estimated at 1 in 770,000 live births. The sequence of appearance of the stigmata is as follows: non-autoimmune IDDM in the first decade, central diabetes insipidus and sensorineural deafness in ~65–75% of the patients in the second decade, renal tract anomalies in ~50% of the patients in the third decade, and neurologic complications such as cerebellar ataxia and myoclonus in half to two thirds of the patients in the fourth decade. Other features include primary gonadal atrophy in most males and a progressive neurodegenerative course with neurorespiratory death at a median age of 30 years. Some cases are caused by pathogenic variants in *WFS-1*. Wolfram syndrome 2 has early-onset optic atrophy, DM, deafness, and a shortened life span but no diabetes insipidus; the associated gene is *CISD2*. Other forms of Wolfram syndrome may be caused by variants in mitochondrial DNA. Other syndromes associated with diabetes are noted in Table 629.17.

Mitochondrial Gene Defects

Pathogenic variants in mitochondrial DNA are associated with **maternally inherited DM and deafness**. The most common mitochondrial DNA variant in these cases is the variant m.3243A>G in the transfer RNA leucine gene. This variant is identical to the variant in MELAS (myopathy, encephalopathy, lactic acidosis, and strokelike syndrome), but MELAS syndrome is not associated with diabetes; the phenotypic expression of the same defect varies. Diabetes in most of these cases presents insidiously, but approximately 20% of patients have an acute presentation resembling T1DM. The mean age of diagnosis of diabetes is 37 years, but cases have been reported as young as 11 years; not all patients have deafness. This variant has been estimated to be present in 1.5% of Japanese people with diabetes, which may be higher than the prevalence in other ethnic groups. Metformin should be avoided in these patients because of the theoretical risk of severe lactic acidosis in the presence of mitochondrial dysfunction. Some children with mitochondrial DNA mutations affecting complex I and/or complex IV may also develop diabetes.

Table 629.16 Clinical Characteristics of Maturity-Onset Diabetes of the Young (MODY) Genetic Subtypes

MODY TYPE	GENE NAME (LOCUS)	PREVALENCE (%)	OTHER FEATURES	TREATMENT
MODY 1	*HNF4A* (20ql2)	5–10	Neonatal hyperinsulinemia and hypoglycemia with associated macrosomia, low serum levels of cholesterol	Sensitive to sulfonylureas
MODY 2	*GCK* (7pl3)	30–60	Mild fasting hyperglycemia throughout life, often asymptomatic, gestational diabetes, low birthweight (with unaffected mother)	No treatment outside of pregnancy
MODY 3	*HNF1A* (12q24.2)	30–60	Glycosuria	Sensitive to sulfonylureas
MODY 4	*PDX1* (13ql2.1)	<1	Homozygote: pancreatic agenesis	Diet, OAD, or insulin
MODY 5	*HNFIB* (17q21)	5–10	Diabetes in association with renal and genitourinary abnormalities	Insulin
MODY 6	*NEUROD I* (2q31.3)	<1	Obesity and insulin resistance	OAD or insulin
MODY 7	*KLF11* (2p25)	<1	Impaired glucose tolerance to overt diabetes	OAD or insulin
MODY 8	*CEL* (9p34)	<1	Diabetes and pancreatic exocrine deficiency	OAD or insulin
MODY 9	*PAX4* (7q32)	<1	Ketosis-prone diabetes	Diet, OAD, or insulin
MODY 10	*INS* (llpl5.5)	<1	May result in neonatal diabetes, antibody-negative diabetes, and MODY	OAD or insulin
MODY 11	*BLK* (8p23)	<1	Obesity common	Diet, OAD, or insulin
MODY 12	*ABCC8* (11pl5.1)	<1	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas
MODY 13	*KCNJ11* (11p 15.13)	<1	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas
MODY 14	*APPL1* (3pl4.3)	<1	Adult-onset diabetes	Diet, OAD, or insulin

ABCC8, ATP-binding cassette, subfamily C (CFTR/MRP), member 8; APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; BLK, B-lymphocyte kinase; CEL, carboxyl ester lipase enzyme; GCK, glucokinase; HNF1A, hepatocyte nuclear factor-lα; HNF1B, hepatocyte nuclear factor-lβ; INS, preproinsulin; KCNJ11, potassium channel, inwardly rectifying subfamily J, member 11; KLF11, Kruppel-like factor 11; NEUROD 1, neurogenic differentiation factor 1; OAD, oral antidiabetic; PAX4, paired box gene 4; PDX1, pancreas/duodenum homeobox protein 1.
Modified from Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. Curr Diab Rep. 2018;18:58. Table 1.

Abnormalities of the Insulin Gene

Diabetes of variable degrees may also result from pathogenic variants in the insulin gene that impair the effectiveness of insulin at the receptor level. Insulin gene defects are exceedingly rare and may be associated with relatively mild diabetes or even normal glucose tolerance. Diabetes may also develop in patients with faulty processing of proinsulin to insulin (an autosomal dominant defect). These defects are notable for the high concentration of insulin as measured by radioimmunoassay, whereas MODY and glucose transporter-2 defects are characterized by relative or absolute deficiency of insulin secretion for the prevailing glucose concentrations.

GENETIC DEFECTS OF INSULIN ACTION

Various genetic variants in the insulin receptor can impair the action of insulin at the insulin receptor or impair postreceptor signaling, leading to insulin resistance. The mildest form of the syndrome with variants in the insulin receptor was previously known as **type A insulin resistance**. This condition is associated with hirsutism, hyperandrogenism, and cystic ovaries in females, without obesity. Acanthosis nigricans may be present, and life expectancy is not significantly impaired. More severe forms of insulin resistance are seen in two variants in the insulin receptor gene that cause the pediatric syndromes of **Donohue syndrome** (formerly called *leprechaunism*) and **Rabson-Mendenhall syndrome**.

Donohue Syndrome

This is a syndrome characterized by intrauterine growth restriction, fasting hypoglycemia, and postprandial hyperglycemia in association with profound resistance to insulin; severe hyperinsulinemia is seen during an OGTT. Various defects of the insulin receptor have been described, thereby attesting to the important role of insulin and its receptor in fetal growth and possibly in morphogenesis. Many of these patients die in the first year of life. Potential treatments include high-dose insulin, metformin, and continuous IGF-1 via insulin pump.

Rabson-Mendenhall Syndrome

This entity is defined by clinical manifestations that appear to be intermediate between those of acanthosis nigricans with insulin resistance type A and Donohue syndrome. The features include extreme insulin resistance, acanthosis nigricans, abnormalities of the teeth and nails, and pineal hyperplasia. It is not clear whether this syndrome is entirely distinct from Donohue syndrome; however, by comparison, patients with Rabson-Mendenhall tend to live significantly longer. Therapies with modest benefit have included IGF-1 and leptin.

Lipoatrophic Diabetes

Various forms of lipodystrophy are associated with insulin resistance and diabetes (Table 629.18). **Familial partial lipoatrophy**, or **lipodystrophy**, is associated with pathogenic variants in *LMNA*, encoding nuclear envelope proteins lamin A and C. **Severe congenital generalized lipoatrophy** is associated with variants in the seipin and *AGPAT2* genes, but the mechanism by which these variants lead to insulin resistance and diabetes is not known.

Stiff-Person Syndrome

This is an extremely rare autoimmune CNS disorder that is characterized by progressive stiffness and painful spasms of the axial muscles

Table 629.17 Syndromic Forms of Diabetes that May Present in Childhood or Early Childhood

SYNDROME	GENE (LOCUS)	INHERITANCE	TYPE OF DIABETES	CLINICAL FEATURES
Diabetes and deafness	Mitochondria tRNA	Maternal	Insulin deficient	Adult-onset diabetes, sensorineural deafness
Wolfram syndrome 1	*WFS1*(4p16)	AR/AD	Insulin deficient	Childhood-onset diabetes, optic atrophy, deafness, diabetes insipidus
Wolfram syndrome 2	*CISD2*(4q24)	AR	Insulin deficient	Childhood-onset, diabetes, optic atrophy, deafness, and defective platelet aggregation
Thiamine-responsive megaloblastic anemia syndrome	*SLC19A2*(1q23)	AR	Vitamin dependent	Childhood-onset diabetes, megaloblastic or sideroblastic anemia, sensorineural deafness
Mitchell-Riley syndrome	*RFX6*(6q22)	AR	Insulin deficient	Rare cases with childhood-onset, pancreatic hypoplasia, intestinal atresia, and gallbladder aplasia or hypoplasia
Alström syndrome	*ALMS1*(2p13)	AR	Insulin resistant	Childhood to early adulthood, pigmentary retinopathy, deafness, obesity, dilated cardiomyopathy
Bardet-Biedl syndrome	*BBS1–BBS21*	AR/DR	Insulin resistant	Childhood to early adulthood, developmental delay, pigmentary retinopathy, polydactyly, obesity, hypogonadism
Insulin resistance syndrome type A	*INSR*(19p13)	AD/AR	Insulin resistant	Childhood to early adulthood, obesity, diabetes, and acanthosis nigricans

ALMS1, Alström syndrome 1; AD, autosomal dominant; AR, autosomal recessive; BBS, Bardet-Biedl; CISD2, CDGSH iron sulfur domain 2; DR, digenic recessive; INSR, insulin receptor; RFX6, regulatory factor X6; SLC19A2, solute carrier family 19 member 2; tRNA, transfer RNA; WFS1, wolframin.
Modified from Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. Curr Diab Rep. 18:58, 2018. Table 2.

Table 629.18 Clinical and Biochemical Features of Inherited Lipodystrophies

	CONGENITAL GENERALIZED LIPODYSTROPHY		FAMILIAL PARTIAL LIPODYSTROPHY	
SUBTYPE	***BSCL1***	***BSCL2***	***FPLD2***	***FPLD3***
DEFECTIVE GENE	***AGPAT2***	***BSCL2***	***LMNA***	***PPARG***
Clinical onset	Soon after birth	Soon after birth	Puberty	Usually puberty, but may present in younger children
Fat distribution	Generalized absence	Generalized absence	Loss of limb and gluteal fat; typically excess facial and nuchal fat; trunk fat often lost	Loss of limb and gluteal fat; preserved facial and trunk fat
Cutaneous features	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women
Musculoskeletal	Acromegaloid features common	Acromegaloid features common	Frequent muscle hypertrophy; some have overlap features of muscular dystrophy	Muscle hypertrophy
Nonalcoholic fatty liver disease	Severe	Severe	Yes	Yes
Dyslipidemia	Severe; associated with pancreatitis	Severe; associated with pancreatitis	Yes, may be severe	Yes, may be severe
Insulin resistance	Severe; early onset	Severe; early onset	Severe	Severe; early onset in some
Diabetes onset	<20 yr	<20 yr	Variable; generally later in men than women	Variable; generally later in men than women
Hypertension	Common	Common	Common	Very common
Other		Mild mental retardation possible		

From Semple RK, Savage DB, Halsall DJ, O'Rahilly S. Syndromes of severe insulin resistance and/or lipodystrophy. In Weiss RE, Refetoff S, eds. *Genetic Diagnosis of Endocrine Disorders*. Philadelphia: Elsevier; 2010: Table 4.2.

and very high titers of glutamic acid decarboxylase antibodies. About one third of patients also develop T1DM.

Systemic Lupus Erythematosus

In rare cases, patients with systemic lupus erythematosus may develop autoantibodies to the insulin receptor, leading to insulin resistance and diabetes.

CYSTIC FIBROSIS–RELATED DIABETES

See Chapter 454.

As patients with cystic fibrosis (CF) live longer, an increasing number are being diagnosed with **cystic fibrosis–related diabetes (CFRD)**; up to 20% of children and 50% of adults are affected with CFRD. There is an association with pancreatic insufficiency, and there may be a higher risk in patients with class I and class II CF transmembrane conductance regulator variants. Cross-sectional studies indicate that the prevalence of IGT may be significantly higher than this, and up to 65% of children with CF have diminished first-phase insulin secretion, even when they have normal glucose tolerance. In Denmark, oral glucose tolerance screening of the entire CF population demonstrated no diabetes in patients younger than 10 years, diabetes in 12% of patients age 10-19 years, and diabetes in 48% of adults age 20 years and older.

Patients with CFRD have features of both T1DM and T2DM. In the pancreas, exocrine tissue is replaced by fibrosis and fat; many of the pancreatic islets are destroyed. The remaining islets demonstrate diminished numbers of β-, α-, and pancreatic polypeptide-secreting cells. Secretion of the islet hormones insulin, glucagon, and pancreatic polypeptide is impaired in patients with CF in response to a variety of secretagogues. This pancreatic damage leads to slowly progressive insulin deficiency, of which the earliest manifestation is an impaired first-phase insulin response. When patients age, this response becomes progressively delayed and less robust than normal. At the same time, these patients develop insulin resistance because of chronic inflammation and the intermittent use of corticosteroids. Insulin deficiency and insulin resistance lead to a gradual onset of IGT that eventually evolves into diabetes. In some cases, diabetes may wax and wane with disease exacerbations and the use of corticosteroids. The clinical presentation is similar to that of T2DM in that the onset of the disease is insidious and the occurrence of ketoacidosis is rare. Islet antibody titers are negative. Microvascular complications do develop but may do so at a slower rate than in typical T1DM or T2DM. Macrovascular complications do not appear to be of concern in CFRD. Several factors unique to CF influence the onset and the course of diabetes: (1) frequent infections are associated with waxing and waning of insulin resistance; (2) energy needs are increased because of infection and pulmonary disease; (3) malabsorption is common, despite enzyme supplementation; (4) nutrient absorption is altered by abnormal intestinal transit time; (5) liver disease is frequently present; (6) anorexia and nausea are common; (7) there is a wide variation in daily food intake based on the patient's acute health status; and (8) both insulin and glucagon secretion are impaired (in contrast to autoimmune diabetes, in which only insulin secretion is affected).

IGT and CFRD are associated with poor weight gain, and there is evidence that treatment with insulin improves weight gain and slows the rate of pulmonary deterioration. Because of these observations, guidelines recommend that routine diabetes screening of all children with CF begin at age 10 years. Despite debate over the ideal screening modality, the recommendation is the 2-hour OGTT, although growing evidence suggests a role for mid-OGTT hyperglycemia at the 1-hour mark as a clinically relevant finding. When hyperglycemia develops, the accompanying metabolic derangements are usually mild, and relatively low doses of insulin usually suffice for adequate management. Basal insulin may be started initially, but basal-bolus therapy similar to that used in T1DM will eventually be needed. Dietary restrictions are minimal, as increased energy needs are present and weight gain is usually desired. Ketoacidosis is uncommon but may occur with progressive deterioration of islet cell function. IGT is not necessarily an indication for treatment, but patients who have poor growth and inadequate weight gain may benefit from the addition of basal insulin even if they do not meet the criteria for a diagnosis of diabetes.

Friedreich Ataxia

Friedreich ataxia (FRDA) is a multisystem neurodegenerative disorder resulting from alterations in *FXN*. Approximately 20% of patients with FRDA will develop diabetes. Individuals with early-onset diabetes during childhood display a phenotype similar to T1DM characterized by insufficient pancreatic insulin secretion, hyperglycemia, and ketosis. Insulin therapy is typically required from diagnosis. By contrast, adults with FRDA who develop diabetes have a phenotype more similar to T2DM, where insulin resistance appears to play a role in the pathogenesis.

DRUGS

High-dose oral or parenteral steroid therapy usually results in significant insulin resistance leading to glucose intolerance and overt diabetes. The immunosuppressive agents cyclosporine and tacrolimus are toxic to β cells, causing IDDM in a significant proportion of patients treated with these agents. Their toxicity to pancreatic β cells was one of the factors that limited their usefulness in arresting ongoing autoimmune destruction of β cells. Streptozotocin and the rodenticide Vacor are also toxic to β cells, causing diabetes.

There are no consensus guidelines regarding treatment of *steroid-induced hyperglycemia* in children. Many patients on high-dose steroids have elevated blood glucose during the day and evening but become normoglycemic late at night and early in the morning. In general, significant hyperglycemia in an inpatient setting is treated with short-acting insulin on an as-needed basis. Basal insulin may be added when fasting hyperglycemia is significant. Outpatient treatment can be more difficult, but when treatment is needed, protocols similar to the basal-bolus regimens used in T1DM are used.

Immune checkpoint inhibitors used to treat malignancies by blocking inhibitory immune receptors have been associated with the rare development of DM and other autoimmune diseases. DM may develop after one to two cycles of therapy and present with DKA. Some are GAD antibody positive; all require insulin therapy.

GENETIC SYNDROMES ASSOCIATED WITH DIABETES MELLITUS

A number of rare genetic syndromes associated with IDDM or carbohydrate intolerance have been described (see Tables 629.1 and 629.17). These syndromes represent a broad spectrum of diseases, ranging from premature cellular aging, as in **Werner** and **Cockayne** syndromes (see Chapter 109), to excessive obesity associated with hyperinsulinism, resistance to insulin action, and carbohydrate intolerance, as in **Prader-Willi syndrome** (see Chapters 97 and 98). Some of these syndromes are characterized by primary disturbances in the insulin receptor or in antibodies to the insulin receptor without any impairment in insulin secretion. Although rare, these syndromes provide unique models to understand the multiple causes of disturbed carbohydrate metabolism from defective insulin secretion or from defective insulin action at the cell receptor or postreceptor level.

AUTOIMMUNE DISEASES ASSOCIATED WITH T1DM

IPEX Syndrome

IPEX (immunodysregulation, polyendocrinopathy, and enteropathy, X-linked) is a genetic syndrome leading to autoimmune disease. In most patients with IPEX, pathogenic variants in *FOXP3,* a specific marker of natural and adaptive regulatory T cells, leads to severe immune dysregulation and rampant autoimmunity. Autoimmune diabetes develops in >90% of cases, usually within the first year of life, and is accompanied by enteropathy, failure to thrive, and other autoimmune disorders.

Autoimmune Polyendocrine Syndromes

Autoimmune polyendocrine syndrome type 1 (APS-1, also known as *APCED*) is a syndrome of multiple endocrinopathy related to pathogenic variants in *AIRE*. It typically first manifests in infancy with

recurrent mucocutaneous candidiasis, followed variably by hypocalcemia (autoimmune hypoparathyroidism), adrenal insufficiency (Addison disease), T1DM, hypothyroidism (Hashimoto disease), celiac disease, and other autoimmune conditions. It is clear that any patient with an autoimmune disease is at increased risk for the development of T1DM (and any patient with T1DM is at increased risk of other autoimmune diseases) and should be counseled regarding the signs and symptoms of new-onset diabetes. See Table 629.11 for recommendations regarding screening tests to look for other autoimmune diseases in patients with T1DM.

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is frequently associated with T1DM in children (see Chapter 604). About 20% of patients with insulin-dependent diabetes have thyroid antibodies in their serum; the prevalence is 2-20 times greater than in control populations. Only a small proportion of these patients acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 years.

Celiac disease, which is caused by hypersensitivity to dietary gluten, is another autoimmune disorder that occurs with significant frequency in children with T1DM (see Chapter 384). It is estimated that approximately 7–15% of children with T1DM develop celiac disease within the first 6 years of diagnosis, and the incidence of celiac disease is significantly higher in children younger than 4 years of age and in females. Young children with T1DM and celiac disease can present with gastrointestinal symptoms (abdominal cramping, diarrhea, constipation, gastroesophageal reflux), growth failure as a consequence of suboptimal weight gain, unexplained hypoglycemic reactions because of nutrient malabsorption, and less commonly hypocalcemia caused by severe vitamin D malabsorption; in some cases the disease can be asymptomatic.

When diabetes and thyroid disease coexist, the possibility of autoimmune adrenal insufficiency should be considered. It may be heralded by decreasing insulin requirements, increasing pigmentation of the skin and buccal mucosa, salt craving, weakness, asthenia and postural hypotension, or even frank adrenal crisis. This syndrome is unusual in the first decade of life, but it may become apparent in the second decade or later.

Circulating antibodies to gastric parietal cells and to intrinsic factor are 2-3 times more common in patients with T1DM than in control subjects. The presence of antibodies to gastric parietal cells is correlated with atrophic gastritis, and antibodies to intrinsic factor are associated with malabsorption of vitamin B_{12}. However, megaloblastic anemia is rare in children with T1DM.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

The Nervous System

PART XXV

Chapter 630

Neurologic Evaluation

Yolanda F. Holler-Managan

HISTORY

A detailed history is the cornerstone of neurologic assessment. Although parents may be the primary informants, most children older than 3-4 years can contribute to their history and should be questioned. The history should begin with the chief complaint and its significance in the context of normal development (see Chapters 21-28). The latter step is critical because a 13-month-old who cannot walk may be normal, whereas a 4-year-old who cannot walk might have a serious neurologic condition.

Next, the history of the present illness should provide a chronological outline of the patient's symptoms, with attention paid to location, quality, intensity, duration, associated features, and alleviating or exacerbating factors. It is essential to perform a review of systems because abnormalities of the central nervous system (CNS) often manifest with vague, nonfocal symptoms that may be misattributed to other organ systems (e.g., vomiting, constipation, urinary incontinence). A detailed history might suggest that vomiting is a result of increased intracranial pressure (ICP) rather than gastritis or that constipation and urinary incontinence are caused by a spinal cord tumor rather than behavioral stool withholding. In addition, a systemic illness may produce CNS manifestations, as do lupus erythematosus (seizures, psychosis, demyelination), mitochondrial disorders (developmental delay, strokes, hypotonia), or celiac disease (headaches, seizures, peripheral neuropathy).

After obtaining the chief complaint and history of the present illness, the physician should obtain a complete birth history, particularly if a congenital or perinatal disorder is suspected. The birth history should begin with a review of the pregnancy, including specific questions about common complications, such as pregnancy-induced hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and falls. It is important to quantify any cigarette, alcohol, or drug (prescription, herbal, illicit) use. Inquiring about fetal movement might provide clues to an underlying diagnosis, because decreased or absent fetal activity can be associated with chromosomal anomalies and CNS or neuromuscular disorders. Finally, any abnormal ultrasound or amniocentesis results should be noted.

The mother's labor history should address the gestational age at birth and mode of delivery (spontaneous vaginal, vacuum- or forceps-assisted, cesarean section) and should comment on the presence or absence of fetal distress. If delivery was by cesarean section, it is essential to record the indication for surgery.

The birthweight, length, and head circumference provide useful information about the duration of a given problem, as well as insights into the uterine environment. Parents can usually provide a reliable history of their child's postnatal course; however, if the patient was resuscitated or had a complicated hospital stay, it is often helpful to obtain the hospital records. The physician should inquire about the infant's general well-being, feeding and sleeping patterns, activity level, and the nature of the infant's cry. If the infant had jaundice, it is important to determine both the degree of jaundice and how it was managed. Features of neurologic dysfunction at full term include inability to breathe spontaneously; poor, uncoordinated suck; or the need for an inordinate amount of time to feed or a requirement for gavage feeding. Again, it is important to consider the developmental context because all of these issues would be expected in premature infants, particularly those with a very low birthweight. Double-checking the newborn screening results may provide a clue to abnormal neurologic manifestations in an infant.

A major component of the neurologic history is the **developmental assessment** (see Chapters 21-28). Careful evaluation of a child's social, cognitive, language, fine motor skills, and gross motor skills is required to distinguish normal development from either an isolated or a global (i.e., in two or more domains) developmental delay. A static abnormality in development from birth suggests a congenital, intrauterine, or perinatal cause, but a loss of skills **(regression)** over time strongly suggests an underlying degenerative disease of the CNS, such as an inborn error of metabolism or genetic disorder. The ability of parents to recall the precise timing of their child's developmental milestones is extremely variable. It is often helpful to request old photographs of the child or to review the baby book, where the milestones may have been dutifully recorded. In general, parents are aware when their child has a developmental problem, and the physician should show appropriate concern. Table 630.1 outlines the upper limits of normal for attaining specific developmental milestones. Chapter 28 includes a comprehensive review of developmental screening tests and their interpretation.

Next, the family history must be reviewed. Most parents are cooperative in securing medical information about family members, particularly if it might have relevance for their child. The history should document the age and history of neurologic disease, including developmental delay, epilepsy, migraine, stroke, and inherited disorders, for all first- and second-degree relatives. It is important to inquire directly about miscarriages or fetal deaths and to document the sex of the relevant embryo or fetus, as well as the gestational age at the time of demise. When available, the results of postmortem examinations should be obtained, because they can have a direct bearing on the patient's condition. The parents should be questioned about their ethnic backgrounds because some genetic disorders occur more commonly within specific populations (e.g., Tay-Sachs disease in the Ashkenazi Jewish population). They should also be asked if there is any chance that they could be related to each other, because the incidence of metabolic and degenerative disorders of the CNS is increased significantly in children of *consanguineous* marriages.

The social history should detail the child's current living environment and the child's relationship with other family members. It is important to inquire about recent stressors, such as divorce, remarriage, birth of a sibling, or death of a loved one, because they can affect the child's behavior. If the child is in daycare or school, one should document the child's academic and social performance, paying particular attention to any abrupt changes. Academic performance can be assessed by asking about the child's latest report card, and peer relationships can be evaluated by having the child name his or her best friends. Any child who is unable to name at least two or three playmates might have abnormal social development. In some cases, discussions with the daycare worker or teacher provide useful ancillary data.

NEUROLOGIC EXAMINATION

The neurologic examination begins during the interview. Indirect observation of the child's appearance and movements can yield valuable information about the presence of an underlying disorder. For instance, it may be obvious that the child has dysmorphic facies, an unusual posture, or an abnormality of motor function manifested by a hemiparesis or gait disturbance. The child's behavior while playing and interacting with his or her parents may also be telling. A normal child usually plays independently early in the visit but then engages in the interview process. A child with attention-deficit/hyperactivity disorder

Table 630.1 Screening Scheme for Developmental Delay: Upper Range

AGE (MO)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with one hand held	Releases an object on command	Comes when called	One to two meaningful words
18	Walks upstairs with assistance	Feeds self from a spoon	Mimics actions of others	At least six words
24	Runs	Builds a tower of six blocks	Plays with others	Two- to three-word sentences

might display impulsive behavior in the examining room, and a child with neurologic impairment might exhibit complete lack of awareness of the environment. Finally, note should be made of any unusual odors about the patient, because some metabolic disorders produce characteristic scents (e.g., the musty smell of phenylketonuria or the sweaty feet smell of isovaleric acidemia; see Chapter 104). If such an odor is present, it is important to determine whether it is persistent or transient, occurring only with illnesses.

The examination should be conducted in a nonthreatening, child-friendly setting. The child should be allowed to sit where the child is most comfortable, whether it be on a parent's lap or on the floor of the examination room. The physician should approach the child slowly, reserving any invasive, painful, or discomforting tests for the end of the examination (e.g., measurement of head circumference, gag reflex). In the end, the more that the examination seems like a game, the more the child will cooperate. Because the neurologic examination of an infant requires a somewhat modified approach from that of an older child, these two groups are considered separately (see Chapters 21-23 and 115 vs Chapters 24-27).

Mental State

Age aside, the neurologic examination should include an assessment of the patient's mental state in terms of both the level of arousal and the interaction with the environment. Premature infants born at <28 weeks of gestation do not have consistent periods of alertness, whereas slightly older infants arouse from sleep with gentle physical stimulation. Sleep–wake patterns are well developed at term. Because the level of alertness of a neonate depends on many factors, including the time of the last feeding, room temperature, and gestational age, serial examinations are critical when evaluating for changes in neurologic function. An older child's mental state can be assessed by watching the child play. Having the child tell a story, draw a picture, or complete a puzzle can also be helpful in assessing cognitive function. Memory can be evaluated informally as patients recount their personal information, as well as more formally by asking them to register and recall three objects or perform a digit span.

Head

Correct measurement of the **head circumference** is important. It should be performed at every visit for patients younger than 3 years and should be recorded on a suitable head growth chart. To measure, a nondistensible plastic measuring tape is placed over the mid-forehead and extended circumferentially to include the most prominent portion of the occiput. If the patient's head circumference is abnormal, it is important to document the head circumferences of the parents and siblings. Errors in the measurement of a newborn skull are common because of scalp edema, overriding sutures, and the presence of cephalohematomas. The average rate of head growth in a healthy premature infant is 0.5 cm in the first 2 weeks, 0.75 cm in the third week, and 1.0 cm in the fourth week and every week thereafter until the fortieth week of development. The head circumference of an average term infant measures 34-35 cm at birth, 44 cm at 6 months, and 47 cm at 1 year of age (see Chapters 21 and 22).

If the brain is not growing, the skull will not grow; therefore a small head frequently reflects a small brain, or **microcephaly**. Microcephaly may develop in utero or postnatally and may, for example, be related to intrauterine infection or drug exposure or to perinatal or postnatal injury. Conversely, a large head may be associated with a large brain, or **macrocephaly**, which is most commonly familial but may be from a disturbance of growth (Sotos syndrome), neurocutaneous disorder (e.g., neurofibromatosis), chromosomal defect (e.g., Klinefelter syndrome), or lysosomal storage disorder. Alternatively, the head size may be increased secondary to hydrocephalus (Fig. 630.1) or chronic subdural hemorrhages. In the latter case, the skull tends to assume a square or boxlike shape, because the long-standing presence of fluid in the subdural space causes enlargement of the middle fossa.



Fig. 630.1 Congenital hydrocephalus. Note the enlarged cranium and prominent scalp veins.

The shape of the head should be documented carefully. Plagiocephaly, or flattening of the skull, can be seen in normal infants but may be particularly prominent in hypotonic or weak infants, who are less mobile. A variety of abnormal head shapes can be seen when cranial sutures fuse prematurely, as in the various forms of inherited **craniosynostosis** (see Chapter 631.10).

An infant has two **fontanels** at birth: a diamond-shaped anterior fontanel at the junction of the frontal and parietal bones that is open at birth, and a triangular posterior fontanel at the junction of the parietal and occipital bones that can admit the tip of a finger or may be closed at birth. If the posterior fontanel is open at birth, it should close over the ensuing 6-8 weeks; its persistence suggests underlying hydrocephalus or congenital hypothyroidism. The anterior fontanel varies greatly in size, but it usually measures approximately 2 × 2 cm. The average time of closure is 18 months, but the fontanel can close normally as early as 9 months. A very small or absent anterior fontanel at birth might indicate craniosynostosis or microcephaly, whereas a very large fontanel can signify a variety of problems. The fontanel is normally slightly depressed and pulsatile and is best evaluated by holding the infant upright while the infant is asleep or feeding. A bulging fontanel is a potential indicator of increased ICP, but vigorous crying can cause a protuberant fontanel in a normal infant.

Inspection of the head should include observation of the venous pattern, because increased ICP and thrombosis of the superior sagittal sinus can produce marked venous distention. Dysmorphic facial features can indicate a neurodevelopmental aberration. Likewise, cutaneous abnormalities, such as cutis aplasia or abnormal hair whorls, can suggest an underlying brain malformation or genetic disorder.

Palpation of a newborn's skull characteristically reveals **molding** of the skull accompanied by **overriding sutures**—a result of the pressures exerted on the skull during its descent through the pelvis. Marked overriding of the sutures beyond the early neonatal period is cause for alarm, because it suggests an underlying brain abnormality. Palpation additionally might reveal bony bridges between sutures **(craniosynostosis)**, cranial defects, or, in premature infants, softening of the parietal bones **(craniotabes)**.

Auscultation of the skull is an important adjunct to the neurologic examination. **Cranial bruits** may be noted over the anterior fontanel, temporal region, or orbits and are best heard using the diaphragm of the stethoscope. Soft symmetric bruits may be discovered in normal children younger than 4 years of age or in association with a febrile illness. Demonstration of a loud or localized bruit is usually significant and warrants further investigation because it may be associated with severe anemia, increased ICP, or arteriovenous malformations of the middle cerebral artery or vein of Galen. It is important to exclude murmurs arising from the heart or great vessels, because they may be transmitted to the cranium.

Cranial Nerves

Olfactory Nerve (Cranial Nerve I)

Anosmia, or loss of smell, most commonly occurs as a transient abnormality in association with an upper respiratory tract infection or allergies. Permanent causes of anosmia include head trauma with damage to the ethmoid bone or shearing of the olfactory nerve fibers as they cross the cribriform plate, tumors of the frontal lobe, intranasal drug use, and exposure to toxins (acrylates, methacrylates, cadmium). Occasionally, a child who recovers from purulent meningitis or develops hydrocephalus has a diminished sense of smell. Rarely, anosmia is congenital, in which case it can occur as an isolated deficit or as part of **Kallmann syndrome**, a familial disorder characterized by hypogonadotropic hypogonadism and congenital anosmia. Although not a routine component of the examination, smell can be tested reliably as early as the 32nd week of gestation by presenting a stimulus and observing for an alerting response or withdrawal, or both. Care should be taken to use appropriate stimuli, such as coffee or peppermint, as opposed to strongly aromatic substances (e.g., ammonia inhalants) that stimulate the trigeminal nerve. Each nostril should be tested individually by pinching shut the opposite side.

Optic Nerve (Cranial Nerve II; see also Part XXVII)

Assessment of the optic disc and retina (see Chapters 659, 670, and 671) is a critical component of the neurologic examination. Although the retina is best visualized by dilating the pupil, most physicians do not have ready access to mydriatic agents at the bedside; therefore it may be necessary to consult an ophthalmologist in some cases. Mydriatics should not be administered to patients whose pupillary responses are being followed as a marker for impending cerebral herniation or to patients with glaucoma or cataracts. When mydriatics are used, both eyes should be dilated, because unilateral papillary fixation and dilation can cause confusion and worry in later examiners unaware of the pharmacologic intervention. Examination of an infant's retina may be facilitated by providing a nipple or soother and by turning the head to one side. The physician gently strokes the patient to maintain arousal while examining the closer eye. An older child should be placed in the parent's lap and should be distracted by bright objects or toys. The color of the optic nerve is salmon-pink in a child but may be gray-white in a newborn, particularly if the newborn has fair coloring. This normal finding can cause confusion and can lead to the improper diagnosis of optic atrophy.

Disc edema refers to swelling of the optic disc, and **papilledema** specifically refers to swelling that is secondary to increased ICP. Papilledema rarely occurs in infancy because the skull sutures can separate to accommodate the expanding brain. In older children, papilledema may be graded according to the Frisen scale (Fig. 630.2). Disc edema must be differentiated from **papillitis**, or inflammation of the optic nerve.

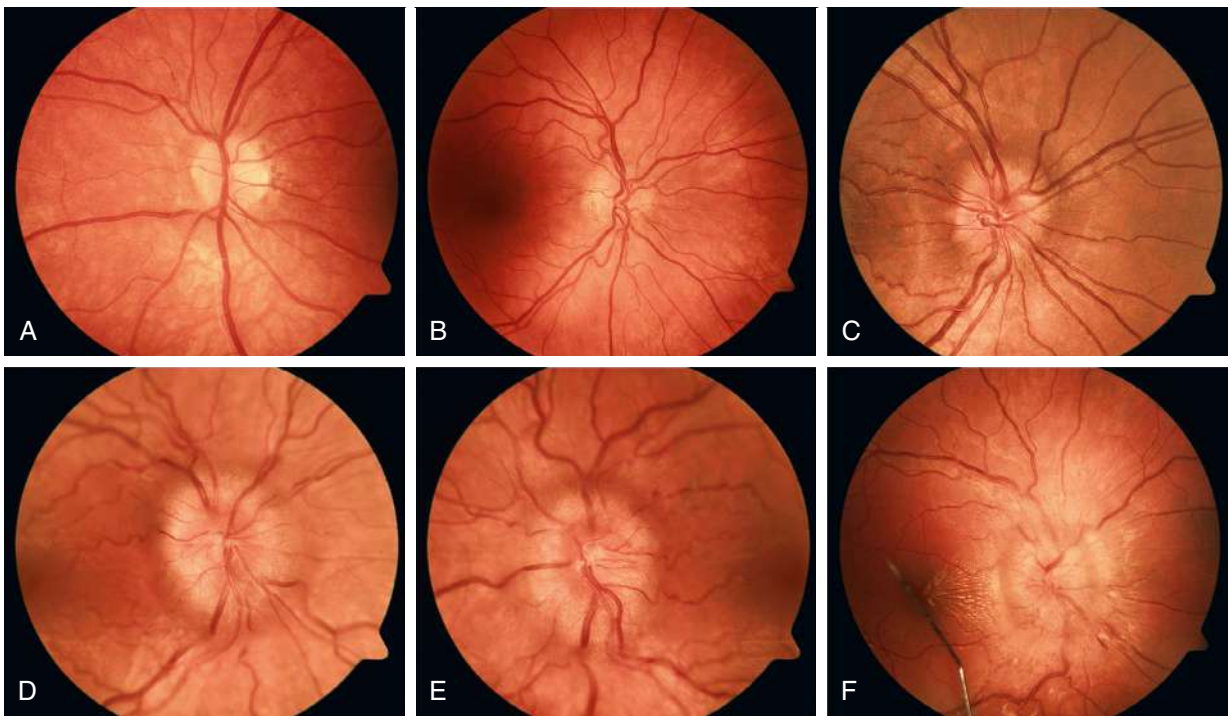

Fig. 630.2 Stages of papilledema (Frisen scale). **A**, Stage 0: Normal optic disc. **B**, Stage 1: Very early papilledema with obscuration of the nasal border of the disc only, without elevation of the disc borders. **C**, Stage 2: Early papilledema showing obscuration of all borders, elevation of the nasal border, and a complete peripapillary halo. **D**, Stage 3: Moderate papilledema with elevation of all borders, increased diameter of the optic nerve head, obscuration of vessels at the disc margin, and a peripapillary halo with finger-like extensions. **E**, Stage 4: Marked papilledema characterized by elevation of the entire nerve head and total obscuration of a segment of a major blood vessel on the disc. **F**, Stage 5: Severe papilledema with obscuration of all vessels and obliteration of the optic cup. Note also the nerve fiber layer hemorrhages and macular exudate. *(**A-C** courtesy Dr. Deborah Friedman; **D-F** courtesy Flaum Eye Institute, University of Rochester.)*

Both conditions manifest with enlargement of the blind spot, but visual acuity and color vision tend to be spared in early papilledema in contrast to what occurs in optic neuritis.

Retinal hemorrhages occur in 30–40% of all full-term newborn infants. The hemorrhages are more common after vaginal delivery than after cesarean section and are not associated with birth injury or with neurologic complications. They disappear spontaneously by 1-2 weeks of age. The presence of retinal hemorrhages beyond the early neonatal period should raise a concern for nonaccidental trauma.

Vision

A full description of the age-appropriate evaluation of vision can be found in Chapter 659. Evaluation of vision in the premature infant presents unique challenges. At 28 weeks of corrected gestational age, a premature infant blinks in response to a bright light, and at 32 weeks, the infant maintains eye closure until the light source is removed. The pupil reacts to light by 29-32 weeks of corrected gestational age; however, the pupillary response is often difficult to evaluate, because premature infants resist eye opening and have poorly pigmented irises. A normal 37-week infant turns the head and eyes toward a soft light, and a term infant is able to fix on and follow a target, such as the examiner's face.

Oculomotor (Cranial Nerve III), Trochlear (Cranial Nerve IV), and Abducens (Cranial Nerve VI) Nerves

The globe is moved by six extraocular muscles, which are innervated by the oculomotor, trochlear, and abducens nerves. These muscles and nerves can be assessed by having the patient follow an interesting toy or the examiner's finger in the six cardinal directions of gaze. The physician observes the range and nature (conjugate vs dysconjugate, smooth vs choppy or saccadic) of the eye movements, particularly noting the presence and direction of any abnormal eye movements. Premature infants older than 25 weeks of gestational age and comatose patients can be evaluated using the oculocephalic (doll's eye) maneuver, in which the patient's head is quickly rotated to evoke reflex eye movements. If the brainstem is intact, rotating the patient's head to the right causes the eyes to move to the left and vice versa. Similarly, rapid flexion and extension of the head elicits vertical eye movement.

Dysconjugate gaze can result from extraocular muscle weakness; cranial nerve (CN) III, IV, or VI palsies; or brainstem lesions that disrupt the medial longitudinal fasciculus. Infants who are younger than 2 months can have a slightly dysconjugate gaze at rest, with one eye horizontally displaced from the other by 1 or 2 mm **(strabismus)**. Vertical displacement of the eyes requires investigation because it can indicate trochlear nerve (CN IV) palsy or **skew deviation** (supranuclear ocular malalignment that is often associated with lesions of the posterior fossa). Strabismus is discussed further in Chapter 663.

The oculomotor nerve innervates the superior, inferior, and medial recti, as well as the inferior oblique and levator palpebrae superioris muscles. Complete paralysis of the oculomotor nerve causes ptosis, dilation of the pupil, displacement of the eye outward and downward, and impairment of adduction and elevation. The trochlear nerve supplies the superior oblique muscle, which depresses and internally rotates the globe during activities such as reading and walking down stairs. Patients with an isolated paralysis of the trochlear nerve often have a compensatory head tilt away from the affected side, which helps to alleviate their diplopia. The abducens nerve innervates the lateral rectus muscle; its paralysis causes medial deviation of the eye with an inability to abduct beyond the midline. Patients with increased ICP often respond positively when questioned about double vision **(diplopia)** and exhibit incomplete abduction of the eyes on lateral gaze as a result of partial palsies of nerve VI. This false-localizing sign occurs because CN VI has a long intracranial course, making it particularly susceptible to being stretched. **Internuclear ophthalmoplegia**, caused by a lesion in the medial longitudinal fasciculus of the brainstem which functionally serves the conjugate gaze by connecting CN VI on one side to CN III on the other, results in paralysis of the medial rectus function in the adducting eye and nystagmus in the abducting eye.

When there is a subtle eye movement abnormality, the **red glass test** may be helpful in localizing the lesion. To perform this test, a red glass is placed over one of the patient's eyes and the patient is instructed to follow a white light in all directions of gaze. The child sees one red/white light in the direction of normal muscle function but notes a separation of the red and white images that is greatest in the plane of action of the affected muscle.

In addition to gaze palsies, the examiner might encounter a variety of adventitious movements. **Nystagmus** is an involuntary, rapid movement of the eye that may be subclassified as being **pendular**, in which the two phases have equal amplitude and velocity, or **jerk**, in which there is a fast and a slow phase. Jerk nystagmus can be further characterized by the direction of its fast phase, which may be left-, right-, up-, or downbeating; rotatory; or mixed. Many patients have a few beats of nystagmus with extreme lateral gaze **(end-gaze nystagmus)**, which is of no consequence. Pathologic horizontal nystagmus is most often congenital, drug-induced (e.g., alcohol, anticonvulsants), or a result of vestibular system dysfunction. By contrast, vertical nystagmus is often associated with structural abnormalities of the brainstem and cerebellum. **Ocular bobbing** is characterized by a downward jerk followed by a slow drift back to primary position and is associated with pontine lesions. **Opsoclonus** describes involuntary, chaotic, conjugate oscillations of the eyes, which are often seen in the setting of neuroblastoma or viral infection.

Trigeminal Nerve (Cranial Nerve V)

The three divisions of the trigeminal nerve—ophthalmic, maxillary, and mandibular—convey information about facial protopathic (pain, temperature) and epicritic (vibration, proprioception) sensation. Each modality should be tested and compared with the contralateral side. In patients who are uncooperative or comatose, the integrity of the trigeminal nerve can be assessed by the corneal reflex, elicited by touching the cornea with a small pledget of cotton and observing for symmetric eye closure, and nasal tickle, obtained by stimulating the nasal passage with a cotton swab and observing for symmetric grimace. An absent reflex may be because of a sensory defect (trigeminal nerve) or a motor deficit (facial nerve). The motor division of the trigeminal nerve can be tested by examining the masseter, pterygoid, and temporalis muscles during mastication and by evaluation of the jaw jerk.

Facial Nerve (Cranial Nerve VII)

The facial nerve is a predominantly motor nerve that innervates the muscles of facial expression—the buccinator, platysma, stapedius, and stylohyoid muscles—and the posterior belly of the digastric muscle. It also has a separate division, called the *chorda tympani,* that contains sensory, special sensory (taste), and parasympathetic fibers. Because the portion of the facial nucleus that innervates the upper face receives bilateral cortical input, lesions of the motor cortex or corticobulbar tract have little effect on upper face strength. Rather, such lesions manifest with flattening of the contralateral nasolabial fold or drooping of the corner of the mouth. Conversely, lower motor neuron or facial nerve lesions tend to involve upper and lower facial muscles equally. Facial strength can be evaluated by observing the patient's spontaneous movements and by asking the patient to mimic a series of facial movements (e.g., smiling, raising the eyebrows, inflating the cheeks). A facial nerve palsy may be congenital; idiopathic **(Bell palsy)**; or secondary to trauma, demyelination (Guillain-Barré syndrome), infection (Lyme disease, herpes simplex virus, HIV), granulomatous disease, neoplasm, or meningeal inflammation or infiltration. Facial nerve lesions that are proximal to the junction with the chorda tympani will result in an inability to taste substances with the anterior two thirds of the tongue. If necessary, taste can be tested by placing a solution of saline or glucose on one side of the extended tongue. Normal children can identify the test substance in <10 seconds. Other findings that may be associated with facial nerve palsy include hyperacusis, resulting from stapedius muscle involvement, and impaired tearing.

Vestibulocochlear Nerve (Cranial Nerve VIII)

The vestibulocochlear nerve has two components within a single trunk: the vestibular nerve, which innervates the semicircular canals of the inner ear and is involved with equilibrium, coordination, and

orientation in space, and the cochlear nerve, which innervates the cochlea and carries auditory sensory information.

Dysfunction of the vestibular system results in **vertigo**, the sensation of environmental motion. On examination, patients with vestibular nerve dysfunction typically have nystagmus, in which the fast component is directed away from the affected nerve. With their arms outstretched and eyes closed, their limbs tend to drift toward the injured side. Likewise, if they march in place, they slowly pivot toward the lesion **(Fukuda stepping test)**. On Romberg and tandem gait testing, they tend to fall toward the abnormal ear. Vestibular function can be further evaluated with **caloric testing**. Before testing, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. In an obtunded or comatose patient, 30-50 mL of ice water is then delivered by syringe into the external auditory canal with the patient's head elevated 30 degrees. If the brainstem is intact, the eyes deviate toward the irrigated side. A much smaller quantity of ice water (2 mL) is used in awake, alert patients to avoid inducing nausea. In normal subjects, introduction of ice water produces eye deviation toward the stimulated labyrinth followed by nystagmus, with the fast component away from the stimulated labyrinth.

Because hearing is integral to normal language development, the physician should inquire directly about hearing problems. The parents' concern is often a reliable indicator of hearing impairment and warrants a formal audiologic assessment with either audiometry or brainstem auditory evoked potential testing (see Chapter 677). Even in the absence of parents' concern, formal testing is recommended in all newborns with the goal for all infants to be tested within the first month of life. Children at risk for hearing problems include those with a family history of early-life or syndromic deafness or a personal history of prematurity, severe asphyxia, exposure to ototoxic drugs, hyperbilirubinemia, congenital anomalies of the head or neck, bacterial meningitis, and congenital TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections. For all other infants and children, a simple bedside assessment of hearing is usually sufficient. Newborns might have subtle responses to auditory stimuli, such as changes in breathing, cessation of movement, or opening of the eyes and/or mouth. If the same stimulus is presented repeatedly, normal neonates cease to respond, a phenomenon known as *habituation*. By 3-4 months of age, infants begin to orient to the source of sound. Hearing-impaired toddlers are visually alert and appropriately responsive to physical stimuli but might have more frequent temper tantrums and abnormal speech and language development.

Glossopharyngeal Nerve (Cranial Nerve IX)

The glossopharyngeal nerve conveys motor fibers to the stylopharyngeus muscle; general sensory fibers from the posterior third of the tongue, pharynx, tonsil, internal surface of the tympanic membrane, and skin of the external ear; special sensory (taste) fibers from the posterior third of the tongue; parasympathetic fibers to the parotid gland; and general visceral sensory fibers from the carotid bodies. The nerve is tested by stimulating one side of the lateral oropharynx or soft palate with a tongue blade and observing for symmetric elevation of the palate **(gag reflex)**. An isolated lesion of CN IX is rare because it runs in close proximity to CN X. Potential causes of injury and/or dysfunction include birth trauma, ischemia, mass lesions, motor neuron disease, retropharyngeal abscess, and Guillain-Barré syndrome.

Vagus Nerve (Cranial Nerve X)

The vagus nerve has 10 terminal branches: meningeal, auricular, pharyngeal, carotid body, superior laryngeal, recurrent laryngeal, cardiac, pulmonary, esophageal, and gastrointestinal. The pharyngeal, superior laryngeal, and recurrent laryngeal branches contain motor fibers that innervate all of the muscles of the pharynx and larynx, with the exception of the stylopharyngeus (CN IX) and tensor veli palatini (CN V) muscles. Thus unilateral injury of the vagus nerve results in weakness of the ipsilateral soft palate and a hoarse voice; bilateral lesions can produce respiratory distress as a result of vocal cord paralysis, as well as nasal regurgitation of fluids, pooling of secretions, and an immobile, low-lying soft palate. Isolated lesions to the vagus nerve may be a complication of thoracotomies or may be seen in neonates with type II Chiari malformations. If such a lesion is suspected, it is important to visualize the vocal cords. In addition to motor information, the vagus nerve carries somatic afferents from the pharynx, larynx, ear canal, external surface of the tympanic membrane, and meninges of the posterior fossa; visceral afferents; taste fibers from the posterior pharynx; and preganglionic parasympathetics.

Accessory Nerve (Cranial Nerve XI)

The accessory nerve innervates the sternocleidomastoid (SCM) and trapezius muscles. The left SCM acts to turn the head to the right side and vice versa; acting together, the SCMs flex the neck. The trapezius acts to elevate the shoulder. Lesions to the accessory nerve result in atrophy and paralysis of the ipsilateral SCM and trapezius muscles, with resultant depression of the shoulder. Because several cervical muscles are involved in head rotation, unilateral SCM paresis might not be evident unless the patient is asked to rotate the head against resistance. Skull base fractures or lesions, motor neuron disease, myotonic dystrophy, and myasthenia gravis commonly produce atrophy and weakness of these muscles; congenital torticollis is associated with SCM hypertrophy.

Hypoglossal Nerve (Cranial Nerve XII)

The hypoglossal nerve innervates the tongue. Examination of the tongue includes assessment of its bulk and strength, as well as observation for adventitious movements. Malfunction of the hypoglossal nucleus or nerve produces atrophy, weakness, and fasciculations of the tongue. If the injury is unilateral, the tongue deviates toward the side of the injury; if it is bilateral, tongue protrusion is not possible, and the patient can have difficulty swallowing **(dysphagia)**. Werdnig-Hoffmann disease (infantile spinal muscular atrophy, or spinal muscular atrophy type 1) and congenital anomalies in the region of the foramen magnum are the principal causes of hypoglossal nerve dysfunction.

Motor Examination

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for involuntary movements that might indicate central or peripheral nervous system pathology.

Bulk

Decreased muscle bulk **(atrophy)** may be secondary to disuse or to diseases of the lower motor neuron, nerve root, peripheral nerve, or muscle. In most cases, neurogenic atrophy is more severe than myogenic atrophy. Increased muscle bulk **(hypertrophy)** is usually physiologic (e.g., body builders). **Pseudohypertrophy** refers to muscle tissue that has been replaced by fat and connective tissue, giving it a bulky appearance with a paradoxical reduction in strength, as in Duchenne muscular dystrophy.

Tone

Muscle tone, which is generated by an unconscious, continuous, partial contraction of muscle, creates resistance to passive movement of a joint. Tone varies greatly based on a patient's age and state. At 28 weeks of gestation, all four extremities are extended and there is little resistance to passive movement. Flexor tone is visible in the lower extremities at 32 weeks and is palpable in the upper extremities at 36 weeks. A normal term infant's posture is characterized by flexion of all four extremities.

There are three key tests for assessing postural tone in neonates: the traction response, vertical suspension, and horizontal suspension (Fig. 630.3; see Chapters 115 and 122). To evaluate the **traction response**, the physician grasps the infant's hands and gently pulls the infant to a sitting position. Normally, the infant's head lags slightly behind the infant's body and then falls forward upon reaching the sitting position. To test **vertical suspension**, the physician holds the infant by the axillae without gripping the thorax. The infant should remain suspended with the infant's lower extremities held in flexion; a hypotonic infant will slip through the physician's hands. With **horizontal suspension**, the physician holds the infant prone by placing a hand under the

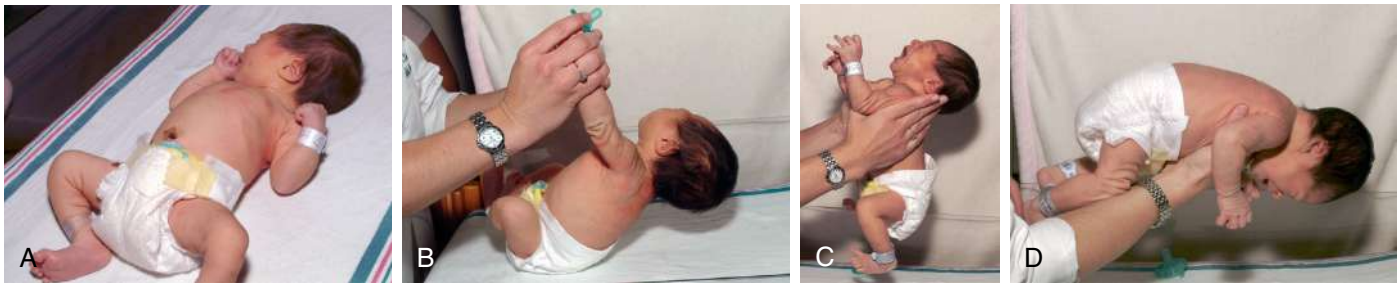

Fig. 630.3 Normal tone in a full-term neonate. A, Flexed resting posture. B, Traction response. C, Vertical suspension. D, Horizontal suspension.

infant's abdomen. The head should rise and the limbs should flex, but a hypotonic infant will drape over the physician's hand, forming a U shape. Assessing tone in the extremities is accomplished by observing the infant's resting position and passively manipulating the infant's limbs. When the upper extremity of a normal term infant is pulled gently across the chest, the elbow does not quite reach the mid-sternum **(scarf sign)**, whereas the elbow of a hypotonic infant extends beyond the midline with ease. Measurement of the **popliteal angle** is a useful method for documenting tone in the lower extremities. The examiner flexes the hip and extends the knee. Normal term infants allow extension of the knee to approximately 80 degrees. Similarly, tone can be evaluated by flexing the hip and knee to 90 degrees and then internally rotating the leg, in which case the heel should not pass the umbilicus.

Abnormalities of tone include spasticity, rigidity, and hypotonia. **Spasticity** is characterized by an initial resistance to passive movement, followed by a sudden release, referred to as the **clasp-knife** phenomenon. Because spasticity results from upper motor neuron dysfunction, it disproportionately affects the upper-extremity flexors and lower-extremity extensors and tends to occur in conjunction with disuse atrophy, hyperactive deep tendon reflexes, and extensor plantar reflexes **(Babinski sign)**. In infants, spasticity of the lower extremities results in scissoring of the legs upon vertical suspension. Older children can present with prolonged commando crawling or toe-walking. **Rigidity**, seen with lesions of the basal ganglia, is characterized by resistance to passive movement that is equal in the flexors and extensors regardless of the velocity of movement **(lead pipe)**. Patients with either spasticity or rigidity might exhibit **opisthotonos**, defined as severe hyperextension of the spine caused by hypertonia of the paraspinal muscles (Fig. 630.4), although similar posturing can be seen in patients with Sandifer syndrome (gastroesophageal reflux or hiatal hernia associated with torsional dystonia). **Hypotonia** refers to abnormally diminished tone and is the most common abnormality of tone in neurologically compromised neonates. A hypotonic infant is floppy and often assumes a frog-leg posture at rest. Hypotonia can reflect pathology of the cerebral hemispheres, cerebellum, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.

Strength

Older children are usually able to cooperate with formal strength testing, in which case muscle power is graded on a scale of 0-5 as follows: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; and 5 = normal power. An examination of muscle power should include all muscle groups, including the neck flexors and extensors and the muscles of respiration. It is important not only to assess individual muscle groups but also to determine the pattern of weakness (i.e., proximal vs distal; segmental vs regional). Testing for **pronator drift** can be helpful in localizing the lesion in a patient with weakness. This test is accomplished by having the patient extend his or her arms away from the body with the palms facing upward and the eyes closed. *Together, pronation and downward drift of an arm indicate a lesion of the contralateral corticospinal tract.*

Because infants and young children are not able to participate in formal strength testing, they are best assessed with functional measures. Proximal and distal strength of the upper extremities can be tested by having the child reach overhead for a toy and by watching the child manipulate small objects. In infants younger than 2 months, the physician can also take advantage of the palmar grasp reflex in assessing distal power and the Moro reflex in assessing proximal power. Infants with decreased strength in the lower extremities tend to have diminished spontaneous activity in their legs and are unable to support their body weight when held upright. Older children may have difficulty climbing or descending steps, jumping, or hopping. They might also use their hands to climb up their legs when asked to rise from a prone position, a maneuver called **Gowers sign** (Fig. 630.5).

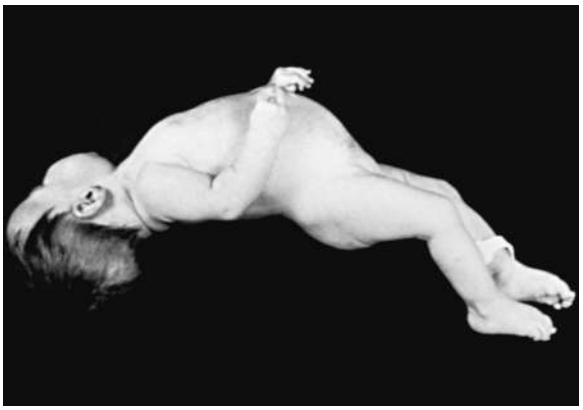

Fig. 630.4 Opisthotonos in a brain-injured infant.

Involuntary Movements

Patients with lower motor neuron or peripheral nervous system lesions might have **fasciculations**, which are small, involuntary muscle contractions that result from the spontaneous discharge of a single motor unit and create the illusion of a bag of worms under the skin. Because most infants have abundant body fat, muscle fasciculations are best observed in the tongue in this age-group.

Most other involuntary movements, including tics, dystonia, chorea, and athetosis, stem from disorders of the basal ganglia. Tremor seems to be an exception, as it is thought to be mediated by cerebellothalamocortical pathways. Further detail on the individual movement disorders is provided in Chapter 637.

Sensory Examination

The sensory examination is difficult to perform on an infant or uncooperative child and has a relatively low yield in terms of the information that it provides. A gross assessment of sensory function can be achieved by distracting the patient with an interesting toy and then touching the patient with a cotton swab in different locations. Normal infants and children indicate an awareness of the stimulus by crying, withdrawing the extremity, or pausing briefly; however, with repeated testing, they lose interest in the stimulus and begin to ignore the examiner. It is therefore critical that any areas of concern are tested efficiently and, if necessary, reexamined at an appropriate time.

Fortunately, isolated disorders of the sensory system are less common in the very young pediatric population than in the adult population, so



Fig. 630.5 A-D, Gowers sign in a child with hip girdle weakness because of Duchenne muscular dystrophy. When asked to rise from a prone position, the patient uses his hands to walk up his legs to compensate for proximal lower extremity weakness.

Table 630.2 Timing of Selected Primitive Reflexes

REFLEX	ONSET	FULLY DEVELOPED	DURATION
Palmar grasp	28 wk gestation	32 wk gestation	2-3 mo postnatal
Rooting	32 wk gestation	36 wk gestation	4-6 mo postnatal
Moro	28-32 wk gestation	37 wk gestation	5-6 mo postnatal
Tonic neck	35 wk gestation	1 mo postnatal	6-7 mo postnatal
Parachute	7-8 mo postnatal	10-11 mo postnatal	Remains throughout life

detailed sensory testing is rarely warranted. Furthermore, most patients who are old enough to voice a sensory complaint are also old enough to cooperate with formal testing of light touch, pain, temperature, vibration, proprioception, and cortical sensation (e.g., stereognosis, two-point discrimination, extinction to double simultaneous stimulation). A notable exception is when the physician suspects a spinal cord lesion in an infant or young child and needs to identify a sensory level. In such situations, observation might suggest a difference in color, temperature, or perspiration, with the skin cool and dry below the level of injury. Lightly touching the skin above the level can evoke a squirming movement or physical withdrawal. Other signs of spinal cord injury include decreased anal sphincter tone and strength and absence of the superficial abdominal, anal wink, and cremasteric reflexes.

Reflexes

Deep Tendon Reflexes and the Plantar Response

Deep tendon reflexes are readily elicited in most infants and children. In infants, it is important to position the head in the midline when assessing reflexes, because turning the head to one side can alter reflex tone. Reflexes are graded from 0 (absent) to 4+ (markedly hyperactive), with 2+ being normal. Reflexes that are 1+ or 3+ can be normal as long as they are symmetric. Sustained clonus is always pathologic, but infants younger than 3 months old can have 5-10 beats of clonus, and older children can have 1-2 beats of clonus, provided that it is symmetric.

The ankle jerk is hardest to elicit, but it can usually be obtained by passively dorsiflexing the foot and then tapping on either the Achilles tendon or the ball of the foot. The knee jerk is evoked by tapping the patellar tendon. If this reflex is exaggerated, extension of the knee may be accompanied by contraction of the contralateral adductors **(crossed adductor response)**. Hypoactive reflexes generally reflect lower motor neuron or cerebellar dysfunction, whereas hyperactive reflexes are consistent with upper motor neuron disease, although acute upper motor neuron injury can result in hypoactive or absent deep tendon reflexes. The plantar response is obtained by stimulation of the lateral aspect of the sole of the foot, beginning at the heel and extending to the base of the toes. The **Babinski sign**, indicating an upper motor neuron lesion, is characterized by extension of the great toe and fanning of the remaining toes. Too vigorous stimulation may produce withdrawal, which may be misinterpreted as a Babinski sign. Plantar responses have limited diagnostic utility in neonates because they are mediated by several competing reflexes and can be either flexor or extensor, depending on how the foot is positioned. Asymmetry of the reflexes or plantar response is a useful lateralizing sign in infants and children.

Primitive Reflexes

Primitive reflexes appear and disappear at specific times during development (Table 630.2), and their absence or persistence beyond those times signifies CNS dysfunction. Although many primitive reflexes have been described, the Moro, grasp, tonic neck, and parachute reflexes are the most clinically relevant. The **Moro reflex** is elicited by supporting the infant in a semierect position and then allowing the infant's head to fall backward onto the examiner's hand. A normal response consists of symmetric extension and abduction of the fingers and upper extremities, followed by flexion of the upper extremities and an audible cry. An asymmetric response can signify a fractured clavicle, brachial plexus injury, or hemiparesis. Absence of the Moro reflex in a term newborn is ominous, suggesting significant dysfunction of the CNS. The **grasp response** is elicited by placing a finger in the open palm of each hand; by 37 weeks of gestation, the reflex is strong enough that the examiner

can lift the infant from the bed with gentle traction. The **tonic neck reflex** is produced by manually rotating the infant's head to one side and observing for the characteristic fencing posture (extension of the arm on the side to which the face is rotated and flexion of the contralateral arm). An obligatory tonic neck response, in which the infant becomes stuck in the fencing posture, is always abnormal and implies a CNS disorder. The **parachute reflex**, which occurs in slightly older infants, can be evoked by holding the infant's trunk and then suddenly lowering the infant as if he or she were falling. The arms will spontaneously extend to break the infant's fall, making this reflex a prerequisite to walking (Fig. 630.6).

Coordination

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts and is usually the result of cerebellar dysfunction. Lesions to the cerebellar vermis result in unsteadiness while sitting or standing **(truncal ataxia)**. Affected patients might have a wide-based gait or may be unable to perform tandem gait testing. Lesions of the cerebellar hemispheres cause appendicular ataxia, which may be apparent as the patient reaches for objects and performs finger-to-nose and heel-to-shin movements. Other features of cerebellar dysfunction include errors in judging distance **(dysmetria)**, inability to inhibit a muscular action **(rebound)**, impaired performance of rapid alternating movements **(dysdiadochokinesia)**, intention tremor, nystagmus, scanning dysarthria, hypotonia, and decreased deep tendon reflexes. Acute ataxia suggests an infectious or postinfectious, endocrinologic, toxic, traumatic, vascular, or psychogenic process, and chronic symptoms suggest a metabolic, neoplastic, or degenerative process.

Station and Gait

Observation of a child's station and gait is an important aspect of the neurologic examination. Normal children can stand with their feet close together without swaying; however, children who are unsteady may sway or even fall. On gait testing, the heels should strike either side of an imaginary line, but children with poor balance tend to walk with their legs farther apart to create a more stable base. Tandem gait testing forces patients to have a narrow base, which highlights subtle balance difficulties.

There are a variety of abnormal gaits, many of which are associated with a specific underlying etiology. Patients with a **spastic gait** appear stiff-legged like a soldier. They may walk on tiptoe as a result of tightness or contractures of the Achilles tendons, and their legs may scissor as they walk. A **hemiparetic gait** is associated with spasticity and circumduction of the leg, as well as decreased arm swing on the affected side. **Cerebellar ataxia** results in a wide-based, reeling gait like that of a drunk person, whereas **sensory ataxia** results in a wide-based **steppage gait**, in which the patient lifts the legs up higher than usual in the swing phase and then slaps the foot down. A **myopathic**, or waddling, **gait** is associated with hip girdle weakness. Affected children often develop a compensatory lordosis and have other signs of proximal muscle weakness, such as difficulty climbing stairs. During gait testing, the examiner might also note hypotonia or weakness of the lower extremities; extrapyramidal movements, such as dystonia or chorea; or orthopedic deformities, such as pelvic tilt, genu recurvatum, varus or valgus deformities of the knee, pes cavus (high arches) or pes planus (flat feet), and scoliosis.

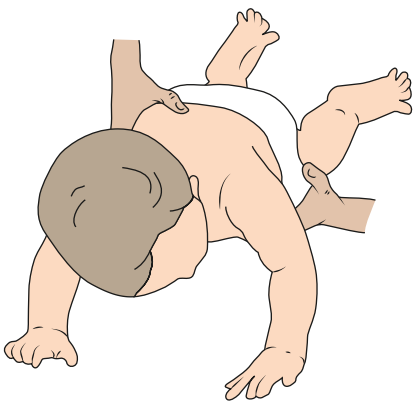

Fig. 630.6 Infant in the parachute reflex position. This primitive reflex develops later in infancy (around 6 mo), and its absence can signal delayed walking. It is elicited by holding the infant face down and rapidly lowering the infant, causing the infant to extend out the arms.

GENERAL EXAMINATION

Examination of other organ systems is essential because myriad systemic diseases affect the nervous system. Dysmorphic features can indicate a genetic syndrome (see Chapter 95). Heart murmurs may be associated with rheumatic fever (Sydenham chorea), cardiac rhabdomyoma (tuberous sclerosis), cyanotic heart disease (cerebral abscess or thrombosis), and endocarditis (cerebral vascular occlusion). Hepatosplenomegaly can suggest an inborn error of metabolism, storage disease, HIV infection, or malignancy. Cutaneous lesions may be a feature of a neurocutaneous syndrome (see Chapter 636).

SPECIAL DIAGNOSTIC PROCEDURES

Lumbar Puncture and Cerebrospinal Fluid Examination

Examination of the cerebrospinal fluid (CSF) and measurement of the pressure it creates in the subarachnoid space is essential in confirming the diagnosis of meningitis, encephalitis (autoimmune, infectious), and idiopathic intracranial hypertension (previously referred to as *pseudotumor cerebri*), and it is often helpful in assessing subarachnoid hemorrhage; demyelinating, degenerative, and collagen vascular diseases; and intracranial neoplasms. Having an experienced assistant who can position, restrain, and comfort the patient is critical to the success of the procedure.

The patient should be situated in a lateral decubitus or seated position with the neck and legs flexed to enlarge the intervertebral spaces. As a rule, sick neonates should be maintained in a seated position to prevent problems with ventilation and perfusion. Regardless of the position chosen, it is important to make sure that the patient's shoulders and hips are straight to prevent rotating the spine.

Once the patient is situated, the physician identifies the appropriate interspace by drawing an imaginary line from the iliac crest downward perpendicular to the vertebral column. In adults, lumbar punctures are usually performed in the L3-L4 or L4-L5 interspaces. Next, the physician dons a mask, gown, and sterile gloves. The skin is thoroughly prepared with a cleansing agent, and sterile drapes are applied. The skin and underlying tissues are anesthetized by injecting a local anesthetic (e.g., 1% lidocaine) at the time of the procedure or by applying a eutectic mixture of lidocaine and prilocaine (EMLA) to the skin 30 minutes before the procedure. A 22-gauge, 1.5- to 3.0-inch, sharp, beveled spinal needle with a properly fitting stylet is introduced in the midsagittal plane and directed slightly cephalad. The physician should pause frequently, remove the stylet, and assess for CSF flow. Although a pop can occur as the needle penetrates the dura, it is more common to experience a subtle change in resistance.

Once CSF has been detected, a manometer and three-way stopcock can be attached to the spinal needle to obtain an opening pressure. If the patient was seated as the spinal needle was introduced, the patient should be moved carefully to a **lateral decubitus position** with the head and legs extended before the manometer is attached. In children between 1 and 18 years of age, the reference range parameter for abnormally elevated opening pressure, determined as the 90th percentile for all patients in the reference population, is 28 cm of water. The threshold for an abnormally reduced pressure in the 10th percentile is 11.5 cm of water. The most common cause of an elevated opening pressure is an agitated patient. Sedation and a high body mass index can also increase the opening pressure (see Chapter 645).

Contraindications to performing a lumbar puncture include suspected mass lesion of the brain, especially in the posterior fossa or

above the tentorium and causing shift of the midline; suspected mass lesion of the spinal cord; symptoms and signs of impending cerebral herniation in a child with probable meningitis; critical illness (on rare occasions); skin infection at the site of the lumbar puncture; and thrombocytopenia with a platelet count of $<20 \times 10^9$/L. If optic disc edema or focal findings suggest a mass lesion, a rapid CT scan of the head should be obtained before proceeding with lumbar puncture to prevent uncal or cerebellar herniation as the CSF is removed. In the absence of these findings, routine head imaging is not warranted. The physician should also be alert to clinical signs of impending herniation, including alterations in the respiratory pattern (e.g., hyperventilation, Cheyne-Stokes respirations, ataxic respirations, respiratory arrest), abnormalities of pupil size and reactivity, loss of brainstem reflexes, and decorticate or decerebrate posturing. If any of these signs are present or the child is so ill that the lumbar puncture might induce cardiorespiratory arrest, blood cultures should be drawn and supportive care, including antibiotics, should be initiated. Once the patient has stabilized, it may be possible to perform a lumbar puncture safely.

Normal CSF contains up to 5/mm^3 white blood cells, and a newborn can have as many as 15/mm^3. Polymorphonuclear cells are always abnormal in a child, but 1-2/mm^3 may be present in a normal neonate. An elevated polymorphonuclear count suggests bacterial meningitis or the early phase of aseptic meningitis (see Chapter 643). CSF lymphocytosis can be seen in aseptic, tuberculous, or fungal meningitis; demyelinating diseases; brain or spinal cord tumor; immunologic disorders, including collagen vascular diseases; and chemical irritation (after myelogram, intrathecal methotrexate).

Normal CSF contains no red blood cells; thus their presence indicates a traumatic tap or a subarachnoid hemorrhage. Progressive clearing of the blood between the first and last samples indicates a traumatic tap. Bloody CSF should be centrifuged immediately. A clear supernatant is consistent with a bloody tap, whereas **xanthochromia** (yellow color that results from the degradation of hemoglobin) suggests a subarachnoid hemorrhage. Xanthochromia may be absent in bleeds <12 hours old, particularly when laboratories rely on visual inspection rather than spectroscopy. Xanthochromia can also occur in the setting of hyperbilirubinemia, carotenemia, and markedly elevated CSF protein.

The normal CSF protein is 10-40 mg/dL in a child and as high as 120 mg/dL in a neonate. The CSF protein falls to the normal childhood range by 3 months of age. The CSF protein may be elevated in many processes, including infectious, immunologic, vascular, and degenerative diseases; blockage of CSF flow; as well as tumors of the brain (primary CNS tumors, systemic tumors metastatic to the CNS, infiltrative acute lymphoblastic leukemia) and spinal cord. With a traumatic tap, the CSF protein is increased by approximately 1 mg/dL for every 1,000 red blood cells/mm^3. Elevation of CSF immunoglobulin G, which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis, in postinfectious encephalomyelitis, and in some cases of multiple sclerosis. If the diagnosis of multiple sclerosis is suspected, the CSF should be tested for the presence of oligoclonal bands.

The CSF glucose content is approximately 60% of the blood glucose in a healthy child. To prevent a spuriously elevated blood:CSF glucose ratio in a case of suspected meningitis, it is advisable to collect the blood glucose before the lumbar puncture when the child is relatively calm. Hypoglycorrhachia is found in association with diffuse meningeal disease, particularly bacterial and tubercular meningitis. Widespread neoplastic involvement of the meninges, subarachnoid hemorrhage, disorders involving the glucose transporter protein type 1 (e.g., GLUT1 deficiency), fungal meningitis, and, occasionally, aseptic meningitis can produce low CSF glucose as well.

A Gram stain of the CSF is essential if there is a suspicion for bacterial meningitis; an acid-fast stain and India ink preparation can be used to assess for tuberculous and fungal meningitis, respectively. CSF is then plated on different culture media depending on the suspected pathogen. When indicated by the clinical presentation, it can also be helpful to assess for the presence of specific antigens or polymerase chain reaction studies (e.g., *Neisseria meningitidis, Haemophilus influenzae* type b, or *Streptococcus pneumoniae*) or to obtain antibody or polymerase chain reaction studies (e.g., herpes simplex virus 1 and 2, West Nile virus, Zika, enteroviruses). In noninfectious cases, levels of CSF metabolites, such as lactate, amino acids, and autoimmune encephalitis panel, can provide clues to the underlying metabolic disease.

Neuroradiologic Procedures

Skull x-rays have limited diagnostic utility. They can demonstrate fractures, bony defects, intracranial calcifications, or indirect evidence of increased ICP. Acutely increased ICP causes separation of the sutures, whereas chronically increased ICP is associated with erosion of the posterior clinoid processes, enlargement of the sella turcica, and increased convolutional markings.

Cranial ultrasonography is the imaging method of choice for detecting intracranial hemorrhage, periventricular leukomalacia, and hydrocephalus in infants younger than 6 months with patent anterior fontanels. Ultrasound is less sensitive than either cranial CT scanning or MRI for detecting hypoxic-ischemic injury, but the use of color Doppler or power Doppler sonography, both of which show changes in regional cerebral blood flow velocity, improve its sensitivity. In general, ultrasound is not a useful technique in older children, although it can be helpful intraoperatively when placing shunts, locating small tumors, and performing needle biopsies.

Cranial CT is a valuable diagnostic tool in the evaluation of many neurologic emergencies and in some nonemergent conditions. It is a noninvasive, rapid procedure that can usually be performed without sedation. CT scans use conventional x-ray techniques, meaning that they produce ionizing radiation. Because children younger than 10 years of age are several times more sensitive to radiation than adults, it is important to consider whether imaging is actually indicated and, if it is, whether an ultrasound or MRI might be the more appropriate study. In the emergency setting, a noncontrast CT scan can demonstrate skull fractures, pneumocephalus, intracranial hemorrhages, hydrocephalus, and impending herniation. If the noncontrast scan reveals an abnormality and an MRI cannot be performed in a timely fashion, nonionic contrast should be used to highlight areas of breakdown in the blood-brain barrier (e.g., abscesses, tumors) and/or collections of abnormal blood vessels (e.g., arteriovenous malformations). CT is less useful for diagnosing acute infarcts in children because radiographic changes might not be apparent for up to 24 hours. Some subtle signs of early (<24 hours) infarction include sulcal effacement, blurring of the gray-white junction, and the hyperdense middle cerebral artery sign (increased attenuation in the middle cerebral artery that is often associated with thrombosis). In the routine setting, CT imaging can be used to demonstrate intracranial calcifications or, with the addition of three-dimensional reformatting, to evaluate patients with craniofacial abnormalities or craniosynostosis. Although other pathologic processes may be visible on CT scan, *MR is generally preferred because it provides a more detailed view of the anatomy without exposing the patient to ionizing radiation* (Table 630.3).

Cranial CT angiography is a useful tool for visualizing vascular structures and is accomplished by administering a tight bolus of iodinated contrast through a large-bore intravenous catheter and then acquiring CT images as the contrast passes through the arteries.

Brain MRI is a noninvasive procedure that is well suited for detecting a variety of abnormalities, including those of the posterior fossa and spinal cord. MR scans are highly susceptible to patient motion artifact; consequently, many children younger than age 8 years require sedation to ensure an adequate study. The need for sedation has decreased in some centers as MRI technology improves and allows for faster performance of studies and as visual distraction techniques are better designed to be used by a child while in the MRI scanner. Because the American Academy of Pediatrics recommends that infants be kept nothing by mouth (NPO) for 4 hours or longer and older children for 6 hours or longer before deep sedation, it is often difficult to obtain an MRI on an infant or young child in the acute

Table 630.3 Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK
- CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions
- Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images
- If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA
- Obtain an MRV if the infarct does not follow an arterial distribution
- CT or MRI can detect infarcts more than 24 hours old, although MRI is generally preferred to avoid exposure to ionizing radiation

INTRAPARENCHYMAL HEMORRHAGE
- CT if <24 hr; MRI if >24 hr
- MRI and MRA to assess for underlying vascular malformation, tumor, and so on
- Catheter angiography if MRA is nondiagnostic

ARTERIOVENOUS MALFORMATION
- CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible
- Catheter angiography if noninvasive imaging is nondiagnostic

CEREBRAL ANEURYSM
- CT without contrast for acute subarachnoid hemorrhage
- MRA or CTA to identify the aneurysm
- Catheter angiography may be necessary in some cases
- TCD to detect vasospasm

HYPOXIC-ISCHEMIC BRAIN INJURY
- Ultrasound in infants
- If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI
- In older children, CT if unstable; otherwise, MRI
- MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes

METABOLIC DISORDERS
- MRI, particularly T2-weighted and FLAIR images
- Diffusion-weighted images may be useful in distinguishing acute and chronic changes
- MRS, SPECT, and PET may be useful in certain disorders

HYDROCEPHALUS
- Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus
- MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus
- Ultrasound (in infants) or CT to follow ventricular size in response to treatment

HEADACHE
- CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations because it does not involve ionizing radiation and provides a better view of the parenchyma)

HEAD TRAUMA
- CT without contrast initially
- MRI after initial assessment and treatment if clinically indicated; diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities

EPILEPSY
- MRI with and without gadolinium; thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected
- PET
- Interictal SPECT

BRAIN TUMOR
- MRI with and without gadolinium
- MRS
- PET

MULTIPLE SCLEROSIS
- MRI with and without gadolinium
- Obtain sagittal FLAIR images

MENINGITIS OR ENCEPHALITIS
- CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination
- MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis

BRAIN ABSCESS
- MRI with and without gadolinium
- Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor
- If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible

MOVEMENT DISORDERS
- MRI with and without gadolinium
- PET
- DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes)

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

setting. MRI can be used to evaluate for congenital or acquired brain lesions, migrational defects, dysmyelination or demyelination, posttraumatic gliosis, neoplasms, cerebral edema, and acute stroke (see Table 630.3). Paramagnetic MR contrast agents (e.g., gadolinium-diethylenetriaminepentaacetic acid [DTPA]) are efficacious in identifying areas of disruption in the blood-brain barrier, such as those occurring in primary and metastatic brain tumors, meningitis, cerebritis, abscesses, and active demyelination. **MR angiography** and **MR venography** provide detailed images of major intracranial vasculature structures and assist in the diagnosis of conditions such as stroke, vascular malformations, and cerebral venous sinus thrombosis. MR angiography is the procedure of choice for infants and young children because of the lack of ionizing radiation and contrast; however, CT angiography may be preferable in older children because it is faster and can eliminate the need for sedation; it is particularly useful for looking at blood vessels in the neck, where there is less interference from bone artifact than in the skull-encased brain.

Functional MRI is a noninvasive technique used to map neuronal activity during specific cognitive states and/or sensorimotor functions. Data are usually based on blood oxygenation, although they can also be based on local cerebral blood volume or flow. Functional MRI is useful for presurgical localization of critical brain functions and has several advantages over other functional imaging techniques. Specifically, functional MRI produces high-resolution images without exposure to ionizing radiation or contrast, and it allows coregistration of functional and structural images.

Proton MR spectroscopy (MRS) is a molecular imaging technique in which the unique neurochemical profile of a preselected brain region is displayed in the form of a spectrum. Many metabolites can be detected, the most common of which are *N*-acetylaspartate, creatine and phosphocreatine, choline, myoinositol, and lactate. Changes in the spectral pattern of a given area can yield clues to the underlying pathology, making MRS useful in the diagnosis of inborn errors of metabolism, as well as the preoperative and posttherapeutic

assessment of intracranial tumors. MRS can also detect areas of cortical dysplasia in patients with epilepsy because these patients have low *N*-acetylaspartate:creatine ratios. Finally, MRS may be useful in detecting hypoxic-ischemic injury in newborns in the first day of life because the lactate peak enlarges and the *N*-acetylaspartate peak diminishes before MRI sequences become abnormal.

Catheter angiography is the gold standard for diagnosing vascular disorders of the CNS, such as arteriovenous malformations, aneurysms, arterial occlusions, and vasculitis. A four-vessel study is accomplished by introducing a catheter into the femoral artery and then injecting contrast media into each of the internal carotid and vertebral arteries. Because catheter angiography is invasive and requires general anesthesia, it is typically reserved for treatment planning of endovascular or open procedures and for cases in which noninvasive imaging results are not diagnostic.

Positron emission tomography (PET) provides unique information on brain metabolism and perfusion by measuring blood flow, oxygen uptake, and/or glucose consumption. PET is an expensive technique that is most often used in the context of epilepsy surgery programs. **Single-photon emission CT** using ^{99m}Tc hexamethylpropyleneamine oxime is a sensitive and inexpensive technique to study regional cerebral blood flow. Single-photon emission CT is particularly useful in assessing for vasculitis, herpes encephalitis, dysplastic cortex, and recurrent brain tumors. PET-MRI is only available in a few pediatric centers in the United States; it provides better resolution and tissue definition than single-photon emission CT. This emerging clinical modality is of particular use in epilepsy surgery evaluation and neuro-oncology.

Electroencephalography

An electroencephalogram (EEG) provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it likely originates from postsynaptic potentials in the dendrites of cortical neurons. Even with amplification of the electrical activity, not all potentials are recorded because there is a buffering effect of the scalp, muscles, bone, vessels, and subarachnoid fluid. EEG waves are classified according to their frequency as delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-20 Hz). These waves are altered by many factors, including age, level of alertness, eye closure, drugs, and disease states.

The normal waking EEG is characterized by the posterior dominant rhythm—a sinusoidal, 8- to 12-Hz rhythm that is most prominent over the occipital region in a state of relaxed wakefulness with the eyes closed. This rhythm first becomes apparent at 3-4 months of age, and most children have achieved the adult frequency of 8-12 Hz by age 8 years.

Normal sleep is divided into three stages of non–rapid eye movement sleep—designated N1, N2, and N3—and rapid eye movement sleep. N1 corresponds to drowsiness, and N3 represents deep, restorative, slow-wave sleep. Rapid eye movement sleep is rarely captured during a routine EEG but may be seen on an overnight recording. The American Electroencephalography Society Guideline and Technical Standards states that "sleep recordings should be obtained whenever possible"; however, it appears that sleep deprivation—not sleep during the EEG—is what increases the yield of the study, particularly in children with one or more clinically diagnosed seizures and in children older than 3 years of age.

EEG abnormalities can be divided into two general categories: epileptiform discharges and slowing. Epileptiform discharges are paroxysmal spikes or sharp waves, often followed by slow waves, which interrupt the background activity. They may be focal, multifocal, or generalized. Focal discharges are often associated with cerebral dysgenesis or irritative lesions, such as cysts, slow-growing tumors, or glial scar tissue; generalized discharges typically occur in children with structurally normal brains. Generalized discharges can occur as an epilepsy trait in children who have never had a seizure and, by themselves, are not an indication for treatment. Epileptiform activity may be enhanced by activation procedures, including hyperventilation and photic stimulation.

As with epileptiform discharges, slowing can be either focal or diffuse. Focal slowing should raise a concern for an underlying functional or structural abnormality, such as an infarct, hematoma, or tumor. Diffuse slowing is the hallmark of encephalopathy and is usually secondary to a widespread disease process or toxic-metabolic insult.

Long-term video EEG monitoring provides a precise characterization of seizure types, which allows specific medical or surgical management. It facilitates more accurate differentiation of epileptic seizures from paroxysmal events that mimic epilepsy, including recurrent psychogenic seizure-like attacks. Long-term EEG monitoring can also be useful during medication adjustments.

Evoked Potentials

An evoked potential is an electrical signal recorded from the CNS after the presentation of a specific visual, auditory, or sensory stimulus. Stimulation of the visual system by a flash or patterned stimulus, such as a black-and-white checkerboard, produces **visual evoked potentials** (VEPs), which are recorded over the occiput and averaged in a computer. Abnormal VEPs can result from lesions to the visual pathway anywhere from the retina to the visual cortex. Many demyelinating disorders and neurodegenerative diseases, such as Tay-Sachs, Krabbe, or Pelizaeus-Merzbacher disease, or neuronal ceroid lipofuscinoses show characteristic VEP abnormalities. Flash VEPs can also be helpful in evaluating infants who have sustained an anoxic injury; however, detection of an evoked potential does not necessarily mean that the infant will have functional vision.

Brainstem auditory evoked responses (BAERs) provide an objective measure of hearing and are particularly useful in neonates and in children who have failed, or are uncooperative with, audiometric testing. BAERs are abnormal in many neurodegenerative diseases of childhood and are an important tool in evaluating patients with suspected tumors of the cerebellopontine angle. BAERs can be helpful in assessing brainstem function in comatose patients because the waveforms are unaffected by drugs or by the level of consciousness; however, they are not accurate in predicting neurologic recovery and outcome.

Somatosensory evoked potentials (SSEPs) are obtained by stimulating a peripheral nerve (peroneal, median) and then recording the electrical response over the cervical region and contralateral parietal somatosensory cortex. SSEPs determine the functional integrity of the dorsal column-medial lemniscal system and are useful in monitoring spinal cord function during operative procedures for scoliosis, aortic coarctation, and myelomeningocele repair. SSEPs are abnormal in many neurodegenerative disorders and are the most accurate evoked potential in the assessment of neurologic outcome after a severe CNS insult.

Specific and General Genetic and Metabolic Testing

Children with intellectual disability or developmental delay are often evaluated with metabolic and/or genetic testing. Newborn screening study results should be rechecked before new studies are done. Specific accompanying features of the child's history and physical examination may point to a particular disorder or group of disorders, allowing for specific genetic or metabolic testing or for chromosomal studies to be fruitful. Whole exome sequencing is often used in situations in which these studies are negative or there are no distinguishing features of the child's history or physical examination that point to a particular subgroup of diagnoses.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 631

Congenital Anomalies of the Central Nervous System

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

631.1 Neural Tube Defects

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close properly during development. The etiology of NTDs appears to be multifactorial and remains incompletely understood. There is evidence for various environmental risk factors, including hyperthermia, teratogens (e.g., valproic acid, dolutegravir), maternal malnutrition, suboptimal folate levels, and maternal obesity or diabetes. Genetic determinants also play a role; studies have revealed relatively few monogenic causes and suggest a polygenic mode of inheritance. Genes associated with NTDs are also linked to known environmental risk factors (maternal obesity/diabetes and folate metabolism). NTDs vary widely in type and severity, depending on when and how the developmental process is disrupted.

The human nervous system originates from the primitive ectoderm, which, along with the endoderm and mesoderm, form the three primary germ layers (Fig. 631.1). During primary neurulation (3-4 weeks postgestation), the dorsal neural ectoderm differentiates into the neural plate. The neural plate then begins to invaginate as the edges fold upward, forming the neural tube, the structure that will ultimately give rise to the brain and spinal cord. Initial closure of the neural tube is accomplished in the area corresponding to the future junction of the spinal cord and medulla and moves rapidly both caudally and rostrally. As the neural tube is closing, a conglomerate of cells from the dorsal tube differentiates into the neural crest, which forms the peripheral nervous system, leptomeninges, and Schwann cells. The surrounding mesoderm gives rise to the dura and vertebrae. Defects in primary neurulation lead to open NTDs, in which neural tissue is exposed. Failure of the neural tube to close allows excretion of fetal substances (e.g., α-fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid. *Fetal ultrasonography has a higher sensitivity to detect NTDs and has largely replaced prenatal screening of maternal serum for AFP in the 16th to 18th wk of gestation; both can be used to identify pregnancies at risk for fetuses with NTDs in utero.* The type of open NTD depends on the location of the defect. Anterior NTDs affect the brain (anencephaly, encephalocele), whereas posterior lesions affect the spinal cord (myelomeningocele).

Secondary neurulation occurs after completion of primary neurulation during weeks 5-6 of gestation and refers to the formation of the caudal neural tube. Defects in secondary neurulation are thought to underlie closed NTDs (occult spinal dysraphism), in which the neural tissue is covered by skin and not exposed. Relative to the severity of open NTDs, closed NTDs usually present with relatively mild, if any, neurologic deficits.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.2 Myelomeningocele

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Myelomeningocele is the most common NTD and results from incomplete closure of the posterior neural tube, leading to protrusion of neural tissue through a defect in the vertebra. This is also known as an *open* NTD because the neural tissue is exposed to the environment.

ETIOLOGY

The etiology of myelomeningocele remains incompletely understood, but as with all neural tube closure defects, a genetic predisposition exists. The risk of recurrence after one affected child is 3–4% and increases to 10% with two prior affected children. Both epidemiologic evidence and the familial aggregation studies indicate polygenic risk factors contribute to the etiology of NTDs.

Nutritional and environmental factors have a role in the etiology of myelomeningocele as well. In particular, folate is intricately involved in the prevention and etiology of NTDs. Folate coenzymes are involved in DNA synthesis, purine synthesis, and amino acid interconversion—specifically, the conversion of homocysteine to methionine. Pathogenic variants in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningomyelocele. These enzymes include 5,10-methylenetetrahydrofolate reductase (encoded by *MTHFR*), cystathionine β-synthase, and methionine synthase. An association between a thermolabile variant of *MTHFR* and mothers of children with NTDs might account for up to 15% of preventable NTDs.

PREVENTION

See also Chapter 67.6.

Maternal periconceptional use of folic acid supplementation reduces the incidence of NTDs in pregnancies at risk by at least 50%. The US Public Health Service recommends that all women of childbearing age who can become pregnant take 0.4-0.8 mg of folic acid daily. To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th week of gestation, when neurulation is complete. If a pregnancy is planned in high-risk women (previously affected child), supplementation should be started with 4 mg of folic acid daily, beginning 1 month before the time of the planned conception.

The modern diet provides about half the daily requirement of folic acid. To increase folic acid intake, fortification of flour, pasta, rice, and cornmeal with 0.15 mg folic acid per 100 g was mandated in the United States and Canada in 1998. Although this decreased the incidence of NTDs, the added folic acid is insufficient to maximize the prevention of preventable NTDs, and it is believed that many women may still have suboptimal folate levels, estimated as a red blood cell folate level less than 900-1,000 nmol/L. Therefore informative educational programs and folic acid vitamin supplementation remain essential for women planning a pregnancy and possibly for all women of childbearing age. In addition, certain drugs, including drugs that antagonize folic acid, such as trimethoprim and some anticonvulsants (valproic acid, carbamazepine, phenytoin, phenobarbital, and primidone), increase the risk of myelomeningocele. The anticonvulsant valproic acid causes NTDs in approximately 1–2% of pregnancies when administered during pregnancy, prompting some epilepsy clinicians to recommend that all female patients of childbearing potential who take anticonvulsant medications also receive folic acid supplements.

Diagnosis is usually made prenatally by fetal ultrasonography (see Chapter 117.7). Measurement of maternal serum AFP is an alternative screening test, although it has been shown to have a lower sensitivity than second-trimester ultrasonography. Early diagnosis allows time for prenatal counseling, further testing, and early treatment options, including fetal surgery. When a prenatal diagnosis is made, it is helpful to look for other associated anomalies. Genetic testing, particularly

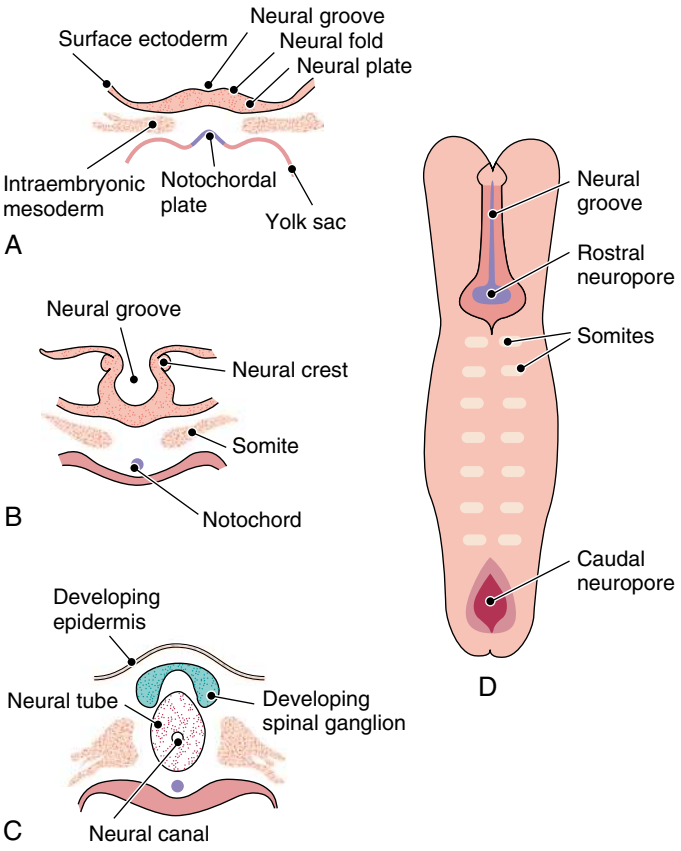

Fig. 631.1 Diagrammatic illustration of the developing nervous system. **A**, Transverse sections of the neural plate during the third wk. **B**, Formation of the neural groove and the neural crest. **C**, The neural tube is developed. **D**, Longitudinal drawing showing the initial closure of the neural tube in the central region. **E**, Cross-sectional drawing of the embryonic neural tube (primitive spinal cord).

chromosomal microarray, can be considered because chromosomal abnormalities are found at higher rates in fetuses with NTDs, particularly in the setting of other associated anomalies. Current cell-free fetal DNA prenatal tests only detect trisomies and sex aneuploidies as screening tests and are not diagnostic and do not detect NTDs.

CLINICAL MANIFESTATIONS

Neurologic deficits are hypothesized to be caused in part by neurodegeneration of the exposed area of the spinal cord secondary to contact with amniotic fluid in utero. The extent and degree of the neurologic deficit depend largely on the location of the myelomeningocele and any associated intracranial abnormalities.

Although a myelomeningocele may be located anywhere along the neuraxis, the lumbosacral region accounts for ~75% of the cases. The majority of patients with myelomeningocele have bowel and bladder incontinence. Ambulation and motor control over the lower extremities depend greatly on the level of the lesion. Generally, patients with a lesion in the low sacral region are ambulatory, in contrast to patients with lesions above L2, who are usually nonambulatory; those with intermediate lesions may walk with assistive devices (crutches, braces). Cervical myelomeningoceles are rare and differ in their anatomy from other myelomeningoceles because the spinal cord structure is usually close to normal and the neural tissue itself is covered by skin (i.e., a closed NTD). Therefore patients with these lesions generally have a more favorable prognosis, although they can have bowel/bladder dysfunction.

On exam, the myelomeningocele is generally readily apparent as a saclike cystic structure covered by a thin layer of partially epithelialized tissue or an exposed flat neural placode without overlying tissues (Fig. 631.2C). When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

Examination of the infant generally shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy. Myelomeningocele above the midlumbar region tends to produce lower motor neuron signs because of abnormalities and disruption of the conus medullaris and higher spinal cord structures.

Most children with a myelomeningocele also have displacement of the cerebellum and brainstem down through the foramen magnum, which is termed a **Chiari II malformation** (see Fig. 631.2A). Because this malformation can lead to obstruction of CSF outflow, hydrocephalus is a common complication, particularly if surgical repair is not pursued early. Therefore there should be a low threshold for consideration of hydrocephalus, which can present with classic signs of increased intracranial pressure (ICP), including a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting in association with an increased head circumference. Older children may also have headache, emesis, and lethargy. Additionally, approximately 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain (brainstem) dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This **Chiari crisis** is caused by downward herniation of the medulla and cerebellar tonsils through the foramen magnum, as well as endogenous malformations in the cerebellum and brainstem.

Other CNS anomalies are associated with myelomeningocele, including cortical dysplasias, polymicrogyria, callosal abnormalities, and cerebellar abnormalities. Long-term complications include tethered cord, usually secondary to scar tissue at the surgical repair site, and hydromyelia, which is CSF buildup in the central canal of the spinal cord caused by worsening hydrocephalus.

TREATMENT (SEE ALSO CHAPTER 754)

Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with one individual (often a pediatrician) acting as the advocate and coordinator of the treatment program.

Surgery to close the lesion is usually performed prenatally or within the first 72 hours of life (see Chapters 117 and 118). After repair of a myelomeningocele (especially postnatal repair), most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting. The

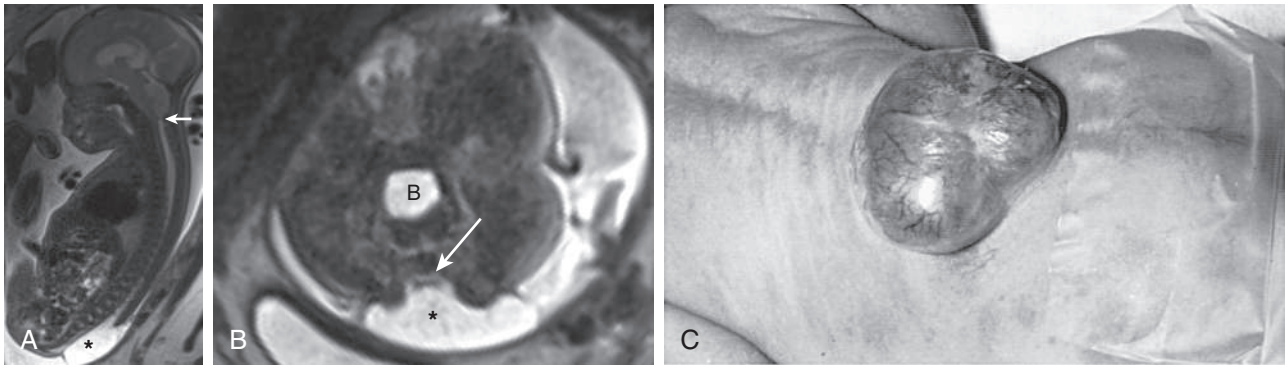

Fig. 631.2 Typical MRI imaging and physical exam findings of a lumbosacral myelomeningocele. **A,** Single-shot sagittal T2-weighted image of a fetus at 28 wk gestation demonstrates a lumbosacral spinal defect with protruding myelomeningocele sac *(asterisk)* and herniation of the brainstem/cerebellum into the upper spinal canal, a Chiari II malformation *(arrow)*. **B,** Single-shot axial T2-weighted images of the same fetus at the level of the myelomeningocele demonstrates a neural placode *(arrow)* at the base of the myelomeningocele sac *(asterisk)*. Urinary bladder marked with B. **C,** A lumbar myelomeningocele is covered by a thin layer of skin.

Management of Myelomeningocele Study (MoMS) has demonstrated the success of in utero surgical closure (see Chapters 117.7 and 118) with a lower incidence of hindbrain abnormalities and hydrocephalus (fewer shunts). Long-term follow-up of prenatal treatment into the school-age years demonstrates improved motor outcomes, although there are no differences in cognitive functioning. This suggests that some deficits may be progressive in utero and that prenatal closure might prevent the development of further loss of function.

Careful evaluation and reassessment of the genitourinary system is an important component of management. Teaching the parents and, ultimately, the patient, to regularly catheterize a neurogenic bladder is a crucial step in maintaining a low residual volume and bladder pressure that prevents urinary tract infections and reflux, which can lead to pyelonephritis, hydronephrosis, and bladder damage. *Latex-free catheters and gloves must be used to prevent development of latex allergy*. Periodic urine cultures and assessment of renal function, including serum electrolytes and creatinine as well as renal scans, vesiculourethrograms, renal ultrasonograms, and cystometrograms, are obtained according to the risk status and progress of the patient and the results of the physical examination. This approach to urinary tract management has greatly reduced the need for urologic diversionary procedures and has decreased the morbidity and mortality associated with progressive renal disease in these patients. Some children can become continent with bladder augmentation at a later age.

Incontinence of fecal matter is common and distressing to patients and families; occasionally, fecal impaction and/or megacolon may develop. Many children can be bowel-trained with a regimen of timed enemas or suppositories that allows evacuation at a predetermined time once or twice a day. Special attention to low anorectal tone and enema administration and retention is often required. Appendicostomy for antegrade enemas may also be helpful.

Functional ambulation may be possible, depending on the level of the lesion and on intact function of the iliopsoas muscles (see Chapter 754). Most children with a sacral or lumbosacral lesion obtain functional ambulation; approximately half the children with higher defects ambulate with the use of braces, other orthotic devices, and canes. Ambulation is often more difficult as adolescence approaches and when body mass increases. *Deterioration of ambulatory function, particularly during earlier years, should prompt referral for evaluation of tethered spinal cord, shunt malfunction, hydromyelia, and other neurosurgical issues.*

PROGNOSIS

For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10–15%, and most deaths occur before age 4 years, often the result of hydrocephalus, infections, and cardiac/respiratory complications. However, life-threatening complications occur at all ages, and renal dysfunction is one of the most important determinants of mortality. At least 70% of individuals (nonsyndromic, no associated anomalies) have no intellectual disability, but learning problems and seizure disorders are more common than in the general population. Previous episodes of meningitis (shunt infections) or ventriculitis may adversely affect intellectual and cognitive function. Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.3 Occult Spinal Dysraphism

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Occult spinal dysraphisms, often called *spina bifida occulta,* are a closed NTD that consist of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges. The most common type only affects the vertebra, which are often asymptomatic and lack neurologic signs. Other clinically more significant forms of closed spinal cord malformations can be associated with developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, lipoma, fatty filum, dermal sinus, and/or a tethered cord. In most of these cases, there are overlying cutaneous manifestations such as a hemangioma, discoloration of the skin, pit, lump, dermal sinus, or hairy patch (Figs. 631.3 and 631.4). A spine x-ray in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1; there is no abnormality of the meninges, spinal cord, or nerve roots. However, a spine x-ray in cases with spinal cord involvement might show bone defects or may be normal. *All cases of occult spinal dysraphism are best investigated with MRI* (Fig. 631.5 and see Fig. 631.4). Initial *screening* in the neonate may include ultrasonography, but MRI is more accurate at any age.

A **meningocele** is formed when the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum. The spinal cord is usually normal and assumes a normal position in the spinal canal; therefore neurologic outcome is often normal. However, there may be tethering of the cord, syringomyelia, or diastematomyelia, so careful neurologic examination and follow-up are necessary. Orthopedic and urologic examination should also be considered. In asymptomatic children with normal neurologic findings and full-thickness skin covering the meningocele, surgery may be delayed. Given the high rate of association between meningocele and tethered cord syndrome, exploration of the spinal canal is necessary to potentially release the associated tethered cord.

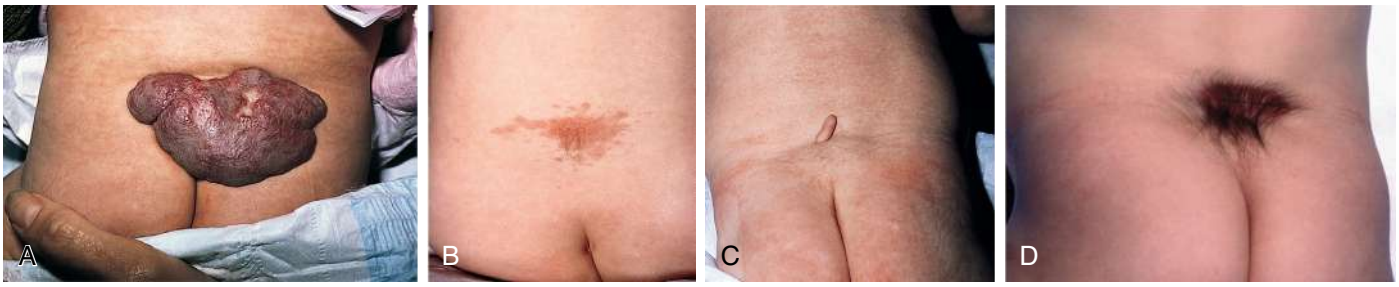

Fig. 631.3 Clinical aspects of congenital median lumbosacral cutaneous lesions. **A,** Midline sacral hemangioma in a patient with an occult lipomyelomeningocele. **B,** Capillary malformation with a subtle patch of hypertrichosis in a patient with a dermal sinus. **C,** Human tail with underlying lipoma in an infant with lipomyelomeningocele. **D,** Midline area of hypertrichosis (faun tail) overlying a patch of hyperpigmentation. *(A-C from Kos L, Drolet BA. Developmental abnormalities. In: Eichenfield LF, Frieden IJ, Esterly NB, eds. Neonatal Dermatology, 2nd ed. Philadelphia: WB Saunders; 2008; D from Tay VS, Kornberg A, Cook M. Spine and spinal cord: developmental disorders. In: Schapira AH, ed. Neurology and Clinical Neuroscience. Philadelphia: Mosby; 2007, Fig. 38-11C.)*

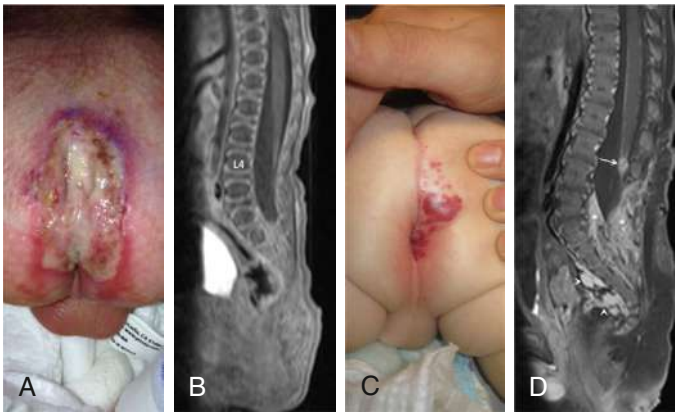

Fig. 631.4 **A,** Lumbosacral ulcerative plaque with surrounding red vascular rim was noted on initial examination. **B,** Midline sagittal contrast-enhanced, T1-weighted, fat-saturated image of the lumbosacral spine at presentation reveals low-lying conus at the L4 vertebral level suggestive of tethered cord. **C,** Recurrence of lumbosacral hemangioma after discontinuation of oral propranolol. **D,** Midline sagittal contrast-enhanced, T1-weighted, fat-saturated image of the lumbosacral spine at 6 mo of age shows new nodular enhancing lesion at the lower end of the conus *(arrow)* compatible with intrathecal hemangioma. In addition, there is a large hemangioma in the epidural space in the sacral spinal canal *(asterisks)* with presacral extension *(arrowheads). (From Yu J, Maheshwari M, Foy AB, et al. Neonatal lumbosacral ulceration masking lumbosacral and intraspinal hemangiomas associated with occult spinal dysraphism. J Pediat. 2016;175:211–215.)*

A **congenital dermal sinus** is a tract between the skin and the spinal cord, sometimes indicated at the skin surface by protruding hairs, a hairy patch, or a vascular nevus. Dermal sinuses occur in the midline at the sites where meningoceles or encephaloceles can occur: the lumbosacral region or occiput, respectively, and occasionally in the cervical or thoracic area. Dermal sinus tracts can pass through the dura, acting as a conduit for the spread of infection. Recurrent meningitis of occult origin should prompt careful examination for a small sinus tract in the posterior midline region, including the back of the head. Lumbosacral sinuses are usually *above* the gluteal fold and are *directed* cephalad. Tethered spinal cord syndrome may also be an associated problem.

Diastematomyelia is when the spinal cord is split, or bifid, and commonly has bony abnormalities that require surgical intervention along with untethering of the spinal cord.

An approach to imaging of the spine in patients with cutaneous lesions is noted in Table 631.1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.4 Encephalocele

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect, called **cranium bifidum**. A cranial *meningocele* consists of a CSF-filled meningeal sac only. Cranial *encephalocele* contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem (Fig. 631.6). These abnormalities are one tenth as common as neural tube closure defects involving the spine. Microscopic examination of the neural tissue within an encephalocele often reveals abnormalities, but not always, which has led to speculation that the primary problem is not abnormal neurulation, but rather abnormal mesodermal development leading to skull anomalies. The cranial defect occurs most commonly in the occipital region at or below the inion. However, in certain parts of the world, frontal or nasofrontal encephaloceles (transethmoidal, sphenoethmoidal, sphenomaxillary, sphenoorbital, transsphenoidal) are more common. Some frontal lesions are associated with a cleft lip and palate.

Cranial encephalocele is often part of a larger syndrome. One of the more commonly associated genetic syndromes is **Meckel-Gruber syndrome**, a rare autosomal recessive condition caused by pathogenic variants in multiple genes involved in cilia function. This syndrome is characterized by an occipital encephalocele, cleft lip or palate, microcephaly, microphthalmia, abnormal genitalia, polycystic kidneys, and polydactyly. Other associated syndromes include muscular dystrophy–dystroglycanopathy type A1 (Walker-Warburg syndrome, due to pathogenic variants in *POMT*) and Knobloch syndrome (due to pathogenic variants in *COL18A*).

Determination of maternal serum AFP levels and ultrasound measurement of the biparietal diameter, as well as identification of the encephalocele itself, can diagnose encephaloceles in utero. Fetal MRI can help define the extent of associated CNS anomalies and the degree of brain herniated into the encephalocele.

Infants with a cranial encephalocele are at increased risk for developing hydrocephalus because of **aqueductal stenosis**, **Chiari malformation**, or **Dandy-Walker syndrome**. Examination might show a small sac with a pedunculated stalk or a large cystlike structure that can exceed the size of the cranium. The lesion may be completely covered with skin, but areas of denuded lesion can occur and require urgent surgical management. Transillumination of the sac can indicate the presence of neural tissue. A plain x-ray of the skull and cervical spine is indicated to define the anatomy of the cranium and vertebrae. Ultrasonography is most helpful in determining the contents of the sac. MRI or CT further helps define the spectrum of the lesion. Children with a cranial meningocele generally have a good prognosis, whereas patients with an encephalocele are at risk for vision problems, microcephaly, intellectual disability, and seizures. Generally, children with neural

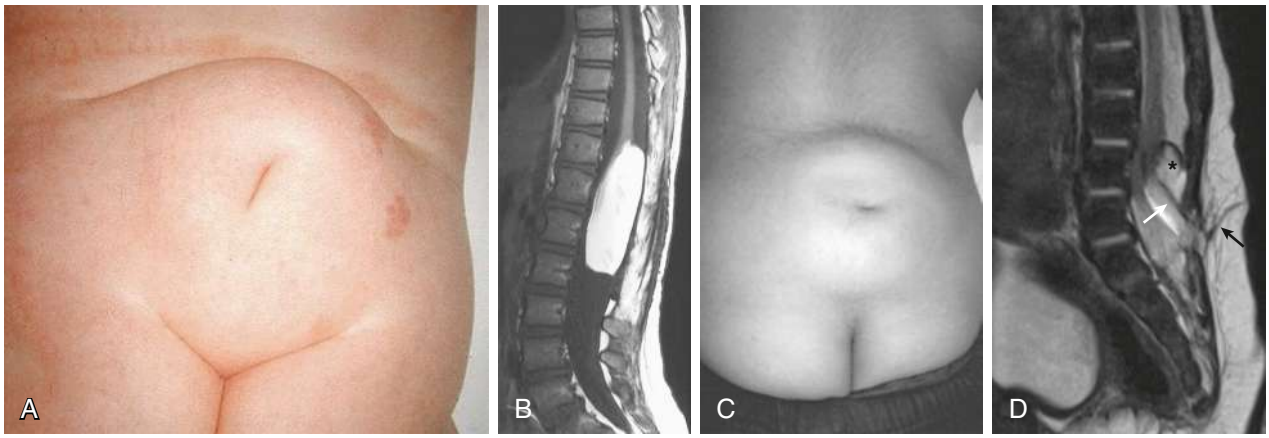

Fig. 631.5 Clinical features and imaging findings associated with occult spinal dysraphism. **A,** Lumbosacral lipoma. The subcutaneous lipoma is in continuity with the spinal cord via a defect in the underlying muscles, bone, and dura. **B,** Sagittal T1-weighted image shows a huge intradural lipoma merging with the conus medullaris superiorly. **C,** Lipoma and central dermal sinus. **D,** A sagittal T2-weighted MRI of the lumbar spine demonstrates a dermal sinus *(black arrow)* looping underneath the lowest lamina before ascending to the low-lying conus medullaris, which it tethers. The intradural portion of the sinus tract *(white arrow)* is encircled by intradural lipoma *(asterisk). (**A** from Thompson DNP. Spinal dysraphic anomalies: classification, presentation and management. Paed Child Health. 2014;24:431–438. Fig. 4; **B** from Rossi A, Biancheri R, Cama A, et al. Imaging in spine and spinal cord malformations. Eur J Radiol. 2004;50[2]:177–200, Fig. 9a; **C,** From Jaiswal AK, Garg A, Mahapatra AK. Spinal ossifying lipoma. J Clin Neurosci. 2005;12:714–717, Fig. 1.)*

Table 631.1 Cutaneous Lesions Associated with Occult Spinal Dysraphism

IMAGING INDICATED
Subcutaneous mass or lipoma
Hairy patch
Dermal sinus or cyst
Atypical dimples (deep, >5 mm, >25 mm from anal verge)
Vascular lesion (e.g., hemangioma or telangiectasia)
Skin appendages or polypoid lesions (e.g., skin tags, tail-like appendages)
Scarlike lesions (aplasia cutis)
IMAGING UNCERTAIN
Hyperpigmented patches
Deviation of the gluteal fold
IMAGING NOT REQUIRED
Simple dimples (<5 mm, <25 mm from anal verge)
Coccygeal pits

From Williams H. Spinal sinuses, dimples, pits and patches: what lies beneath? *Arch Dis Child Educ Pract Ed.* 2006;91:ep75–80.

tissue within the sac and associated hydrocephalus have the least favorable prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

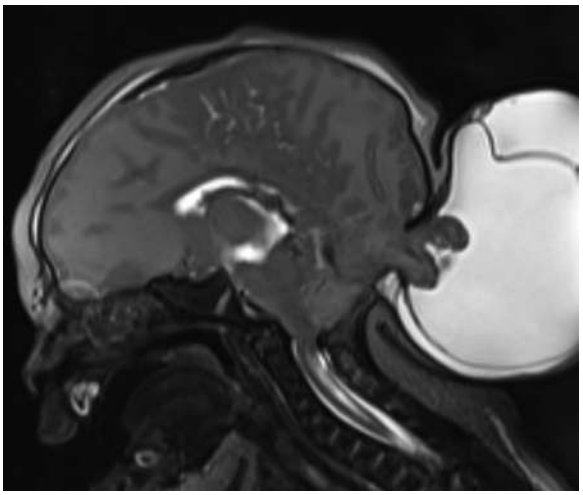

Fig. 631.6 Occipital encephalocele. Sagittal T2-weighted MRI of a newborn with prenatally diagnosed cephalocele demonstrates encephalomalacic brain protruding through an occipital skull defect with entrapped CSF in the cephalocele sac representing a mixture of subarachnoid (deep) and subdural (superficial) fluid. Note that the intracranial subarachnoid spaces (e.g., basal cistern) are contracted because of the large extracranial CSF reservoir.

631.5 Anencephaly

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

An anencephalic infant presents with a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain. Anencephaly is a result of failure of closure of the rostral neuropore, the opening of the anterior neural tube. The opened neural tube leads to failure of the development of the skull vault. The embryologic precursor stages of anencephaly start with acrania (absence of the skull), followed by exencephaly (cerebral tissue protruding without an overlying skull), and ultimately the cerebral tissue degenerates because of prolonged exposure to the amniotic fluid.

In anencephaly, the cerebral hemispheres and cerebellum are usually absent, and only a residue of the brainstem can be identified (Fig. 631.7). The pituitary gland is hypoplastic, and the spinal cord pyramidal tracts are missing because of the absence of the cerebral cortex. Additional anomalies, including folding of the ears, cleft palate, and congenital heart defects, occur in 10–20% of cases. Most anencephalic infants are stillborn or die within several days of birth.

The incidence of anencephaly in the United States has been decreasing since the 1990s and approximates 0.2-0.3 in 1,000 live births; this varies across the world. As with myelomeningoceles, the recurrence risk is approximately 4% and increases to 10% if a couple has had two previously affected pregnancies. Environmental factors in addition to genetics are implicated as a cause of anencephaly, including low socioeconomic status, nutritional and vitamin deficiencies, as well as certain exposures. It is very likely that several noxious stimuli interact on a genetically susceptible host to produce anencephaly. Approximately 50% of cases of anencephaly have associated polyhydramnios. Couples who have had an anencephalic infant should have successive

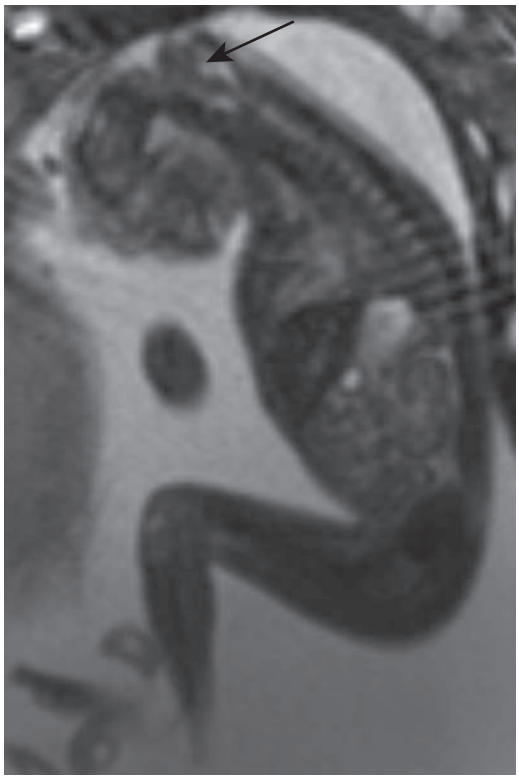

Fig. 631.7 Anencephaly. On this sagittal MR image of an 18-wk-gestational-age fetus, there is abrupt truncation of the neuraxis above the brainstem *(arrow),* no cerebral tissue, and an open skull defect exposed to amniotic fluid consistent with anencephaly.

pregnancies monitored, including with amniocentesis, determination of AFP levels, and ultrasound examination, between the 14th and 16th weeks of gestation. Prenatal folic acid supplementation decreases the risk of this condition.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.6 Malformations of Cortical Development

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Disorders of neuronal proliferation, migration, and organization can cause a spectrum of abnormalities of CNS structure and/or function. Often these present with developmental delays/intellectual disability and/or epilepsy; less severe cases may be detected as incidental findings on a brain MRI.

The major period for neuronal proliferation in the developing human brain occurs between 8 and 15 weeks of gestation. Neural progenitor cells and radial glial cells (which generate both neurons and glial cells) proliferate in the ventricular and subventricular zones. The radial glial cells then play a critical role in the control of neuronal migration, as they form the radial glial fiber system that guides cortical projection neurons to their proper sites. Migrating neurons attach to the radial glial fiber and disembark at predetermined sites to form the precisely designed six-layered cerebral cortex by 28 weeks of gestation. Another important mechanism is the tangential migration of progenitor neurons destined to become cortical interneurons. The severity and the extent of a disorder of neuronal proliferation, migration, and/or organization depend on numerous factors, including the timing of a particular insult and a host of environmental and genetic contributors.

Disorders of neuronal *proliferation* generally present with abnormal brain size (microcephaly, megalencephaly). Disorders of neuronal *migration* and *organization* may also present with associated abnormalities in brain size, but this is not always present. *These disorders often present clinically with either seizures and/or developmental delays and are best diagnosed by identification of the specific cortical malformation by brain MRI.* Although many brain malformations can be apparent from early in life (even on fetal MRI), some more subtle malformations (e.g., focal cortical dysplasias) may not be clearly visible until myelination is largely completed (around 2 years of age). *Genetic testing is indicated given the increasing number of identifiable genetic causes of brain malformations* (Table 631.2). *Somatic variants* have been found to cause some disorders of migration/organization. Somatic variants are genetic changes that *occur after* conception and do not affect the germ cells. Mosaicism from somatic variants is often not detected by standard clinical genetic testing.

MICROCEPHALY

Microcephaly is defined as a head circumference that measures more than 2-3 standard deviations (SD) below the mean for age and sex. Microcephaly may be subdivided into two main groups: primary (genetic) microcephaly, thought to be caused by defects in neuronal proliferation, and secondary (nongenetic) microcephaly, generally associated with destructive events after initial neuronal proliferation (e.g., hypoxic-ischemic injury, infection). A precise diagnosis is important for genetic counseling and for prediction of future pregnancies.

ETIOLOGY

Primary microcephaly refers to a group of conditions that follow a mendelian pattern of inheritance or are associated with a specific genetic syndrome and is generally thought to be secondary to a disruption in neuronal proliferation. Affected infants are usually identified prenatally or at birth because of a small head circumference. **Microcephaly vera** refers to a group of autosomal recessive disorders characterized by isolated microcephaly, with 16 genetic loci implicated to date. Many of the causative genes at those loci have been identified, including several involved in normal mitosis (e.g., *CDK5RAP2*, *ASPM*, *CENPJ*). The genetic causes of microcephaly also include autosomal dominant and X-linked recessive disorders, as well as a series of chromosomal syndromes (Table 631.3); some of these are associated with other malformations of cortical development. **Secondary microcephaly** can result from a number of noxious agents that affect early neurodevelopment; these include irradiation, maternal alcohol or cocaine use, maternal hyperphenylalaninemia, and infections (rubella, cytomegalovirus, HIV, Zika virus).

Acquired microcephaly, which develops postnatally, can be seen as a result of parenchymal injury (e.g., hypoxic ischemic injury), as well as various genetic conditions, including Rett, Seckel, and Angelman syndromes and developmental epileptic encephalopathy syndromes.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A thorough family history should be taken, seeking additional cases of microcephaly or disorders affecting the nervous system. It is important to measure a patient's head circumference at birth to diagnose microcephaly as early as possible. A very small head circumference implies a process that began early in embryonic or fetal development. An insult to the brain that occurs later in life, particularly beyond the age of 2 years, is less likely to produce severe microcephaly. Serial head circumference measurements are more meaningful than a single measurement, particularly when the measurement is borderline or if the microcephaly is progressive. The head circumference of each parent and any siblings should be recorded. The timing and progression of microcephaly, along with familial measurements, may help narrow the differential diagnosis.

Laboratory investigation of a microcephalic child is determined by the history and physical examination. If the cause of the microcephaly is unknown, the mother's serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant. Newborn screening in the United States will detect most of these cases. *Array comparative genomic hybridization*

Table 631.2 Malformations of Cortical Development

CLASSIFICATION	CLINICAL FINDING	GENETIC/METABOLIC ETIOLOGY
Disorders primarily of neuronal proliferation	Microcephaly	Primary microcephaly (MCPH 1-18)*: *MCPH1, WDR62, CDK5RAP2, CASC5, ASPM, CENPJ, STIL, CEP135, CEP152, ZNF335, PHC1, CDK6, CENPE, SASS6, MFSD2A, ANKLE2, CIT, WDFY3*
		Syndromic microcephaly
		Acquired microcephaly
	Macrocephaly†	Metabolic: • Organic acid disorders (e.g., glutaric aciduria – *GCDH*) • Lysosomal storage disorders (e.g., Tay-Sachs disease – *HEXA*) • Leukoencephalopathies (e.g., Alexander disease – *GFAP*)
		Somatic overgrowth: *NSD1, GPC3, GPC4, FMR1, EZH2, PTEN*
		Neurocutaneous: *NF1, NF2, TSC1, TSC2*
		More than 300 listed conditions in OMIM
Disorders primarily of neuronal migration	Lissencephaly-pachygyria spectrum	Isolated: *PAFAH1B1 (LIS1)* Miller-Dieker syndrome: 17p13.3 deletion *(PAFAH1B1, YWHAE)*
		Subcortical band heterotopia: *DCX* (female)
		X-linked: *DCX* (male), *ARX*
		Tubulinopathies: *TUBA1A, TUBB2A, TUBB2B*
		Cobblestone: *POMT1, POMT2, POMGNT1, FKTN, FKRP, LARGE*
		More than 50 listed conditions in OMIM (e.g., *RELN, VDLR*)
	Neuronal heterotopias	Isolated periventricular nodular heterotopias: *FLNA* (female)
		Also seen in association with other malformations, more than 10 listed conditions in OMIM
Disorders primarily of neuronal organization	Polymicrogyria	Over 200 listed conditions in OMIM (also see Table 631.4)
	Schizencephaly	In utero injury/infection
		For most cases, unclear genetic etiology; few cases associated with *COL4A1, SHH, SIX3*
Mixed disorders	Hemimegalencephaly	*AKT1, AKT3, DEPDC5, MTOR, PIK3CA, PIK3R2, PTEN, TSC1, TSC2*
	Focal cortical dysplasia	*DEPDC5, MTOR, NPRL2, NPRL3, PIK3CA, TSC1, TSC2*

*See Jayaraman D, Bae BI, Walsh CA. The genetics of primary microcephaly. *Annu Rev Genomics Hum Genet*. 2018;19:177–200 for comprehensive review.
†See Winden KD, Yuskaitis CJ, Poduri A. Megalencephaly and macrocephaly. *Semin Neurol*. 2015;35(3):277–287 for comprehensive review.

(chromosome microarray) study and/or karyotype is obtained if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, or any additional congenital anomalies. Whole exome sequencing or gene panel testing should also be considered, as pathogenic genetic variants can also cause primary microcephaly and syndromic microcephaly. MRI is useful in identifying any associated structural abnormalities of the brain, such as lissencephaly, pachygyria, and polymicrogyria. CT scanning is useful to detect intracerebral calcification. Additional studies include a fasting plasma and urine amino acid and organic acid analysis; serum ammonia determination; *t*oxoplasmosis, *r*ubella, *c*ytomegalovirus, and *h*erpes simplex (TORCH) titers; HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus. Zika virus–specific testing is also indicated when the infant is born in a high-risk environment or if a parent has a history of travel to endemic areas.

MACROCEPHALY AND MEGALENCEPHALY

Megalencephaly is an anatomic disorder of brain growth defined as a brain weight:volume ratio of more than the 98th percentile for age (or ≥2 SD above the mean) that is usually accompanied by macrocephaly (an occipitofrontal circumference >98th percentile). Macrocephaly can also be secondary to enlarged skull bones, hydrocephalus/ventriculomegaly, and enlarged extraaxial spaces.

Megalencephaly can be categorized as anatomic or metabolic. Although metabolic diseases can present with microcephaly as well, there are certain syndromes (e.g., Alexander disease, Canavan disease, megalencephalic leukoencephalopathy with subcortical cysts) that classically present with macrocephaly and should be considered in the differential diagnosis.

The most common cause of anatomic megalencephaly is **benign familial macrocephaly**. This condition is easily diagnosed by a careful family history and measurement of the parents' head circumferences (occipitofrontal circumferences). Other common megalencephaly-associated macrocephaly syndromes include syndromes with prenatal and/or postnatal somatic overgrowth, such as Sotos *(NSD1)*, Simpson-Golabi-Behmel (*GPC3* and *GPC4*), fragile X *(FMR1)*, Weaver *(EZH2)*, and macrocephaly–cutis marmorata telangiectatica congenita syndromes. Multiple somatic overgrowth syndromes are associated with macrocephaly and pathogenic variants in *PTEN*, including Bannayan-Ruvalcaba-Riley, Cowden, and Proteus-like syndromes. *PTEN* has also been commonly implicated in patients with autism spectrum disorder and macrocephaly.

Additionally, many of the neurocutaneous syndromes, including neurofibromatosis (*NF1* and *NF2*), Sturge-Weber syndrome, and tuberous sclerosis, can present with macrocephaly. Tuberous sclerosis results from pathogenic variants in *TSC1* or *TSC2*, encoding the proteins hamartin and tuberin, which act in the mammalian target of rapamycin (mTOR) signaling pathway, a pathway known to be critical to regulating cell growth and proliferation. Indeed, variants in many genes in the mTOR signaling pathway have emerged as important causes of cortical malformations (Fig. 631.8) (see Hemimegalencephaly and Focal Cortical Dysplasia).

Table 631.3 Causes of Microcephaly

PRIMARY MICROCEPHALY	
Isolated microcephaly	Microcephaly vera (autosomal recessive microcephaly) Autosomal dominant microcephaly X-linked microcephaly
Syndromic microcephaly	Chromosomal abnormalities • Trisomy 13 • Trisomy 18 • Trisomy 21
	Chromosomal deletions • 4p deletion (Wolf-Hirschhorn syndrome) • 5p deletion (Cri-du-chat syndrome) • 7q11.23 deletion (Williams syndrome) • 17p13.3 deletion (Miller-Dieker syndrome)
	Over 1000 other syndromes listed in OMIM, including: • Feingold syndrome *(MYCN, MIR17HG)* • Cornelia de Lange syndrome *(NIPBL, SMC1A, SMC3, RAD21, HDAC8)* • Smith-Lemli-Opitz syndrome *(DHCR7)* • Rubinstein-Taybi syndrome *(CREBBP, EP300)*
ACQUIRED MICROCEPHALY	
Genetic acquired microcephaly	Rett syndrome *(MECP2)* Angelman syndrome *(UBE3A)* Developmental epileptic encephalopathies
Intrauterine infection	Toxoplasmosis Cytomegalovirus Rubella Zika virus
Teratogens	Alcohol Hydantoin Radiation
Other exposures/ injury	Maternal hyperphenylalaninemia Maternal diabetes mellitus Hypoxic-ischemic injury

Adapted from Abuelo D. Microcephaly syndromes. *Semin Pediatr Neurol.* 2007;14(3):118–127.

HEMIMEGALENCEPAHLY

Hemimegalencephaly, or unilateral macrocephaly, appears to result from a more focal aberrancy in neuronal proliferation during development, which also results in abnormal neuronal migration and organization (see Fig. 631.8). These patients generally present with early-onset refractory epilepsy and developmental delays. Various syndromes are associated with hemimegalencephaly, including epidermal nevus syndrome, Proteus syndrome, and hypomelanosis of Ito. As with other malformations of cortical development (see Macrocephaly and Megalencephaly and Focal Cortical Dysplasias), the mTOR signaling pathway appears to play a critical role in the pathogenesis of hemimegalencephaly, with many cases resulting from variants in genes involved in this pathway, including *AKT1* in Proteus syndrome.

FOCAL CORTICAL DYSPLASIAS

Focal cortical dysplasias consist of abnormal cortical lamination in a discrete area of cortex and are thought to be disorders of neuronal proliferation, migration, and organization. These can be difficult to detect, particularly in younger children with immature myelination. Therefore high-resolution, thin-section MRI can be useful, particularly in patients with refractory epilepsy undergoing consideration for surgery (see Fig. 631.8). Increasingly, germline and somatic pathogenic variants in genes involved in the mTOR pathway (*DEPDC5, NPRL2, NPRL3, AKT3,* others) have been implicated in the pathogenesis of focal cortical dysplasias.

LISSENCEPHALY-PACHYGYRIA

Lissencephaly, or agyria, is a rare disorder that is characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure, giving the appearance of a 3- to 4-month-old fetal brain. The condition is probably a result of faulty neuronal migration during early embryonic life. The cortical layering of a lissencephalic brain is disrupted and results in a two- to four-layered cortex, rather than the usual six-layered one. A unique form of lissencephaly is subcortical band heterotopia, or double-cortex syndrome, in which a thick band of gray matter is located deep to the cortex, which may appear normal. **Pachygyria** is on the milder end of the lissencephaly spectrum, with some gyri present, although these are abnormal and markedly reduced in number.

Infants with lissencephaly-pachygyria present with failure to thrive, progressive microcephaly, marked developmental delay, and

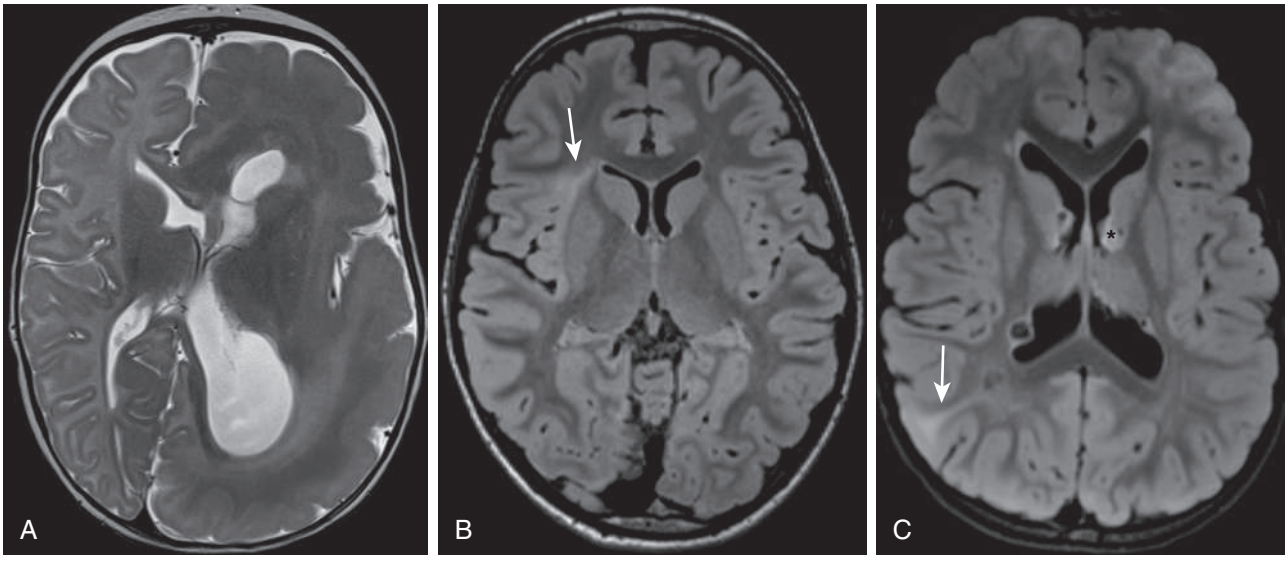

Fig. 631.8 Spectrum of *mTOR*-related cortical malformations on brain MRI. **A,** An axial T2-weighted image of a 4-mo-old female with hemimegalencephaly caused by a somatic *mTOR* variant demonstrates diffuse enlargement of the left hemisphere, cortical thickening, and white matter T2 hypointensity consistent with some combination of accelerated myelination and heterotopic neurons. **B,** Axial FLAIR imaging of a 6-yr-old female with intractable epilepsy demonstrates a transmantle region of signal abnormality *(arrow)*, which fans out as it extends centrifugally from the periventricular white matter to the cortex, a typical appearance of focal cortical dysplasia type IIB. **C,** By comparison, an axial FLAIR image of a 4-yr-old male with tuberous sclerosis demonstrates a multiplicity of transmantle signs consistent with tubers (largest right occipital focus denoted by an *arrow*) as well as subependymal nodules lining the lateral ventricles and a subependymal giant cell tumor at the left caudothalamic groove *(asterisk)*.

often refractory epilepsy. Various genetic causes of lissencephaly have been identified, including pathogenic variants in *PAFAH1B1 (LIS1)* on chromosome 17p13.3 (Fig. 631.9); larger deletions at this locus (encompassing the *YWHAE* gene in addition to the *PAFAH1B1* gene) are linked to **Miller-Dieker syndrome**, characterized by lissencephaly and other features, including distinctive facies (a prominent forehead, bitemporal hollowing, anteverted nostrils, a prominent upper lip, and micrognathia), and cardiac and genital anomalies. *DCX* is on the X chromosome, with genetic disruption leading to lissencephaly in males and subcortical band heterotopia in females (see Fig. 631.9). Pathogenic variants in *ARX* are a rarer cause of X-linked lissencephaly in males. The tubulinopathies (related to variants in *TUBA1A, TUBB2A, TUBB2B,* and others) are another important cause of lissencephaly. Certain disorders (e.g., Walker-Warburg syndrome, Fukuyama congenial muscular dystrophy, and muscle-eye-brain disease) present with a cobblestone lissencephaly, an overmigration disorder, with a bumpy cortical surface composed of groups of heterotopic neurons and altered myelination (see Fig. 631.9).

NEURONAL HETEROTOPIAS

Subtypes of neuronal heterotopias include **periventricular nodular heterotopias**, **subcortical heterotopia** (including band type), and marginal glioneuronal heterotopias. Intractable seizures are a common feature. Several genes have been identified that are a cause of these conditions, including most commonly the X-linked *FLNA* gene, which causes bilateral periventricular nodular heterotopia in affected females (Fig. 631.10).

POLYMICROGYRIA AND SCHIZENCEPHALY

Polymicrogyria is characterized by an augmentation of small convolutions separated by shallow enlarged sulci (Fig. 631.11). Polymicrogyria is commonly seen in the temporal lobes in the perisylvian region. Pathogenic variants in numerous genes have been associated with polymicrogyria, as noted in Table 631.4. Epilepsy, including drug-resistant forms, and oromotor discoordination are common features.

Schizencephaly is the presence of unilateral or bilateral *clefts* within the cerebral hemispheres caused by an abnormality of morphogenesis (see Fig. 631.11). The cleft may be fused or unfused and, if unilateral and large, may be confused with a porencephalic cyst. Not infrequently, the borders of the cleft are surrounded by abnormal brain, particularly polymicrogyria.

When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control and microcephaly with spastic quadriparesis. Some cases of bilateral schizencephaly are associated with **septo-optic dysplasia** and endocrinologic disorders. Unilateral schizencephaly is a common cause of *congenital hemiparesis*. Schizencephaly is associated with fetal cytomegalovirus infection. It can also be secondary to in utero vascular injury, sometimes in the setting of pathogenic variants in *COL4A1,* a gene associated with increased risk of intracranial hemorrhage. Some reports have suggested the involvement of the sonic hedgehog signaling pathway, but most cases remain without a clearly defined genetic etiology.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.7 Disorders with Midline Defects

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

HOLOPROSENCEPHALY

Holoprosencephaly encompasses a group of developmental disorders that result from defective prosencephalic cleavage. These disorders span a spectrum of severity and are classified into three groups, alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality (Fig. 631.12). **Alobar holoprosencephaly** is the most severe form, with complete fusion of the cerebral hemispheres and deep nuclei and complete absence of the corpus callosum and olfactory bulbs and tracts. **Semilobar holoprosencephaly** presents with fusion of the anterior cerebral hemispheres and absence of the anterior corpus callosum. **Lobar holoprosencephaly**, the least severe form, generally presents with full separation between the cerebral hemispheres, partial or full separation between the deeper nuclei, and full development of the posterior corpus callosum, with some underdevelopment of the anterior corpus callosum. A fourth type, the middle interhemispheric variant, or **syntelencephaly**, involves a segmental area of nonseparation of the posterior frontal and parietal lobes. Facial abnormalities, including cyclopia, synophthalmia, cebocephaly, single nostril, choanal atresia, solitary

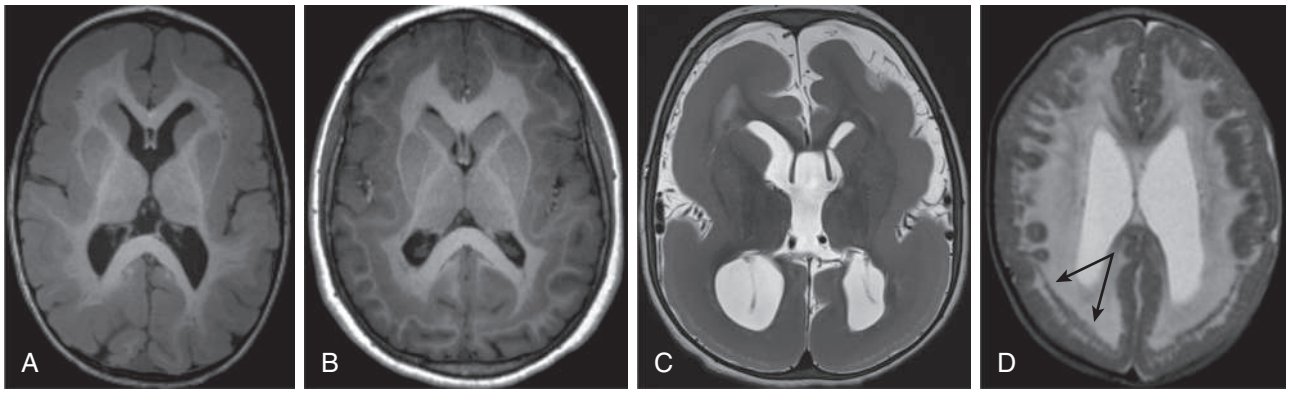

Fig. 631.9 Pachygyria and subcortical band heterotopia spectrum on brain MRI. **A,** An axial T1-weighted image of an 18-mo-old male demonstrates thickening of the cortex and attenuation of gyration, hallmarks of pachygyria. In this patient with a pathogenic *DCX* variant, there is greater severity of the pachygyria anteriorly, which is typically the case for pachygyria caused by mutations in this gene. **B,** By contrast, an axial T1-weighted sequence of a 10-yr-old female demonstrates a normal-thickness cortical ribbon with a subjacent layer of gray matter signal, consistent with subcortical band heterotopia. This patient also has a pathogenic *DCX* variant but has an attenuated phenotype because of X-linked inactivation and mosaic expression of the disease-causing variant. **C,** An axial T2-weighted image of a 4-yr-old female demonstrates marked cortical thickening and severe posterior predominant agyria (lissencephaly), the latter being a classic manifestation of the patient's *LIS1* variant. **D,** An axial T2-weighted image of cobblestone malformation (previously called *type II lissencephaly*) from a 3-mo-old female with infantile spasms, occipital cephalocele, developmental delay, and elevated creatine kinase levels. Note the centrifugal streaks of gray matter extending to a smooth thickened cortex. Although superficially reminiscent of lissencephaly like that in the prior case, a key distinguishing feature is the nodularity of the gray-white matter interface and the centrifugal islands of gray matter (e.g., *arrowed* right occipital foci). The islands of gray matter represent migration of neurons through the pial limiting membrane into the subarachnoid space, a typical feature of cobblestone malformation.



Fig. 631.10 Periventricular nodular heterotopia. An axial T1-weighted brain MR image of a 16-yr-old female with valvular heart disease and joint laxity demonstrates confluent subependymal nodules of gray matter signal consistent with periventricular nodular heterotopia (marked with *dashed oval*). The patient was ultimately found to have a pathogenic *FLNA* variant.

central incisor tooth, and premaxillary agenesis, are common in severe cases, because the prechordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. Milder facial abnormalities, such as ocular hypotelorism, can be seen in milder forms.

Affected children with the severe alobar type have a high mortality rate within the first year of life, but some can live for years. Mortality and morbidity with milder types are more variable, with neurologic symptoms generally correlating with the severity of the underlying abnormality. In addition to neurologic symptoms, patients with impaired hypothalamic cleavage can also have various endocrinopathies. The incidence of holoprosencephaly is 1 in 10,000 live births. A prenatal diagnosis can be confirmed by ultrasonography after the 10th week of gestation for more severe types, but fetal MRI at later gestational ages gives far greater anatomic, and therefore diagnostic, precision.

Genetic and environmental factors both play a role in the development of holoprosencephaly. Chromosomal abnormalities account for approximately 60% of all cases, of which trisomy 13 is the most common. Other associated chromosomal abnormalities include trisomy 18 and deletions or trisomies of chromosomes 2, 3, 7, and 21. Diagnosis with a chromosomal abnormality in the setting of holoprosencephaly is a negative prognostic factor, with most patients not surviving past the first year of life. Monogenic syndromic causes include CHARGE syndrome *(CHD),* Pallister-Hall *(GLI3),* Rubenstein-Taybi *(CREB-BP),* and Smith-Lemli-Opitz *(DHCR7)* syndromes. Genetic variants, particularly in the sonic hedgehog signaling pathway *(SHH, SIX3),* have also been implicated in nonsyndromic holoprosencephaly. Environmental factors, particularly maternal diabetes, are risk factors for holoprosencephaly.

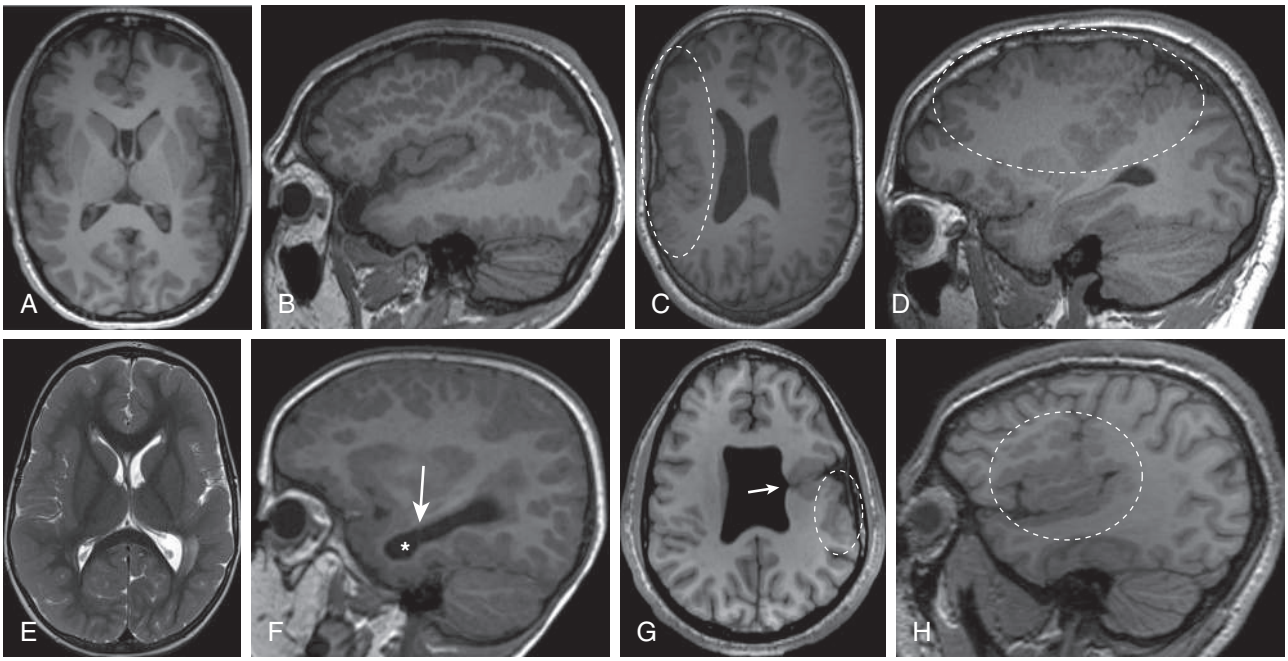

Fig. 631.11 Polymicrogyria spectrum by brain MRI. Axial (**A**) and sagittal (**B**) T1-weighted images of a 17-yr-old male with 22q11 deletion syndrome demonstrate diffusely increased gyral frequency and a bumpy surface contour of the cerebral cortex consistent with polymicrogyria, with some sparing of the frontal poles and occipital lobes. Axial (**C**) and sagittal (**D**) T1-weighted images of a 23-yr-old male demonstrate a unilateral area of right perisylvian polymicrogyria *(dashed ovals)* with reduced underlying white matter volume. Axial T2-weighted (**E**) and sagittal T1-weighted (**F**) sequences demonstrate diffuse polymicrogyria in a 28-mo-old with hearing loss, developmental delay, and congenital cytomegalovirus (CMV) exposure. Although the calcifications associated with TORCH infections are frequently not evident on MRI, clues to CMV as the etiology for polymicrogyria include microcephaly on clinical evaluation and subependymal cysts, the latter evident in this patient at the classic temporal horn location *(asterisk)* where it is separated from the remaining ventricular system by a thin membrane (*arrow*, **F**). Axial (**G**) and sagittal (**H**) T1-weighted images of a 17-yr-old male demonstrate an absent septum pellucidum and an apposed gray matter lined cleft through the left frontal lobe consistent with closed-lip schizencephaly (*arrow*, **G**). As is invariably the case in schizencephaly, the schizencephalic cleft is marginated by polymicrogyria (*ovals*, **G** and **H**).

Table 631.4 Genes Associated with Polymicrogyria

PATHWAY/ PATHOLOGY	GENE[1]	HEAD SIZE[2]			BRAIN FINDINGS	DISORDER NAME	MOI
		MAC	MIC	N/MS			
mTORopathies	*AKT3*	x			Bilateral perisylvian PMG	MPPH syndrome	AD
	CCND2	x					
	MTOR	x				Smith-Kingsmore syndrome	AD
	DEPDC5	x			Diffuse, focal, or multifocal PMG (less common than FCD)		AD
	PI4KA			x	Perisylvian PMG		AR
	PIK3CA	x			Bilateral perisylvian PMG	MCAP syndrome	See footnote 4
	PIK3R2	x				MPPH syndrome	AD
	PTEN	x			Diffuse, focal, or multifocal PMG		AD
Tubulinopathies	*DYNC1H1*		x	x	Frontal or diffuse PMG		AD
	KIF5C			x	Perisylvian PMG		AD
	TUBA1A		x	x	Diffuse, focal, or multifocal PMG; bilateral, asymmetric, perisylvian PMG	Lissencephaly 3	AD
	TUBB		x		PMG		AD
	TUBB2A		x		Bilateral, asymmetric, anterior predominant PMG		AD
	TUBB2B		x	x			
	TUBB3		x	x	Frontoparietal PMG		AD
Cobblestone dysplasia – alpha dystroglycan-opathies	*FKTN*			x	Diffuse (cerebral and cerebellar) PMG		AR
	POMGNT1			x	PMG		AR
	POMT2			x	PMG		AR
Cobblestone dysplasia – other (laminopathies and congenital disorders of glycosylation)	*ADGRG1 (GPR56)*			x	Bilateral frontoparietal PMG		AR
	COL3A1	x		x	Diffuse cobblestone cortex; PMG A > P		AR
	ATP6V0A2		x	x	Frontoparietal PMG	Autosomal recessive cutis laxa type 2A	AR
	LAMA2			x	Occipital PMG; white-matter signal abnormalities	Muscular dystrophy, congenital merosin-deficient, 1A	AR
	LAMB1	x		x	Porencephaly; cobblestone lissencephaly P > A	Lissencephaly 5	AR
	LAMC3			x	Occipital PMG		AR
	SNAP29		x		Perisylvian or diffuse PMG		AR
	SRD5A3			x	Frontal PMG	SRD5A3-CDG *(CDG-Iq)*	AR

Continued

Table 631.4 Genes Associated with Polymicrogyria—cont'd

PATHWAY/ PATHOLOGY	GENE[1]	HEAD SIZE[2]			BRAIN FINDINGS	DISORDER NAME	MOI
		MAC	MIC	N/MS			
Other	*BICD2*			x	Perisylvian PMG		AD
	COL18A1			x	Frontal PMG	Knobloch syndrome 1	AR
	DDX3X		x	x	Frontoparietal or diffuse PMG	*DDX3X*-related neurodevelopmental disorder	XL
	EML1	x			Ribbon-like heterotopia with overlying PMG; ACC		AR
	EOMES (TBR2)		x		Bilateral perisylvian or diffuse PMG		AR
	EZH2	x			Bilateral perisylvian PMG	Weaver syndrome	AD
	FIG4		x	x	Bilateral or temporo-occipital PMG		AR
	GPSM2	x			Parasagittal PMG; ACC	Chudley-McCollough syndrome	AR
	GRIN1		x		Extensive bilateral PMG		AD
	GRIN2B		x	x	Diffuse PMG		AD
	KIFBP (KIAA1279)		x		Diffuse PMG	Goldberg-Shprintzen syndrome	AR
	MAP1B				Perisylvian PMG; PNH		AD
	NDE1		x		Diffuse PMG		AR
	NEDD4L			x	Bilateral perisylvian PMG; PNH		AD
	OCLN		x		Bandlike calcifications with diffuse PMG	Pseudo-TORCH syndrome 1	AR
	OFD1	x			Frontal and parietal PMG	Joubert syndrome (XLR); orofaciodigital syndrome 1 (XLD)	XL
	PAX6		x		Variable temporal PMG		AR
	RAB18		x	x	Diffuse or frontal PMG	RAB18 deficiency[3]	AR
	RAB3GAP1		x	x			
	RAB3GAP2		x	x			
	RTTN		x		Variable diffuse, asymmetric PMG		AR
	TBC1D20			x	Diffuse or bilateral frontal PMG	RAB18 deficiency[3]	AR
	TCTN1			x	Frontal PMG	Joubert syndrome	AR
	TMEM216			x	Variable PMG	Meckel-Gruber syndrome, Joubert syndrome	AR
	WDR62		x		± Diffuse or asymmetric PMG		AR
Metabolic disorders	*FH*		x		Variable PMG	Fumeric aciduria	AR
	PEX genes		x	x	Perisylvian PMG	Zellweger spectrum disorders	AR

[1]Genes are in alphabetic order.
[2]Head size:
N/MS = normal/mildly small (i.e., head circumference >3 SD and <97%)
MIC = severe microcephaly (i.e., birth head circumference <3 SD or earliest HC <4 SD)
MAC = macrocephaly (i.e., head circumference >97%)
[3]RAB18 deficiency is a spectrum that includes Warburg microsyndrome (at the severe end) and Martsolf syndrome (at the mild end). Additional findings are eye involvement (bilateral congenital cataracts, microphthalmia, and microcornea); severe-to-profound intellectual disability; and hypogonadism.
[4]De novo germline pathogenic variants in PIK3CA are reported; however, most affected individuals with MCAP reported had somatic mosaicism for pathogenic variants in PIK3CA, suggesting that the mutation occurred post fertilization in one cell of the multicellular embryo.https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/
A, Anterior; ACC, absence of the corpus callosum; AD, autosomal dominant; AR, autosomal recessive; CDG, congenital disorder of glycosylation; FCD, focal cortical dysplasia; MCAP, megalencephaly-capillary malformation-PMG; MOI, mode of inheritance; MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus; P, posterior; PNH, periventricular nodular heterotopia; XL, X-linked; XLD, X-linked dominant; XLR, X-linked recessive
Adapted from Stutterd CA, Dobyns WB, Jansen A, et al. Polymicrogyria overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2005.

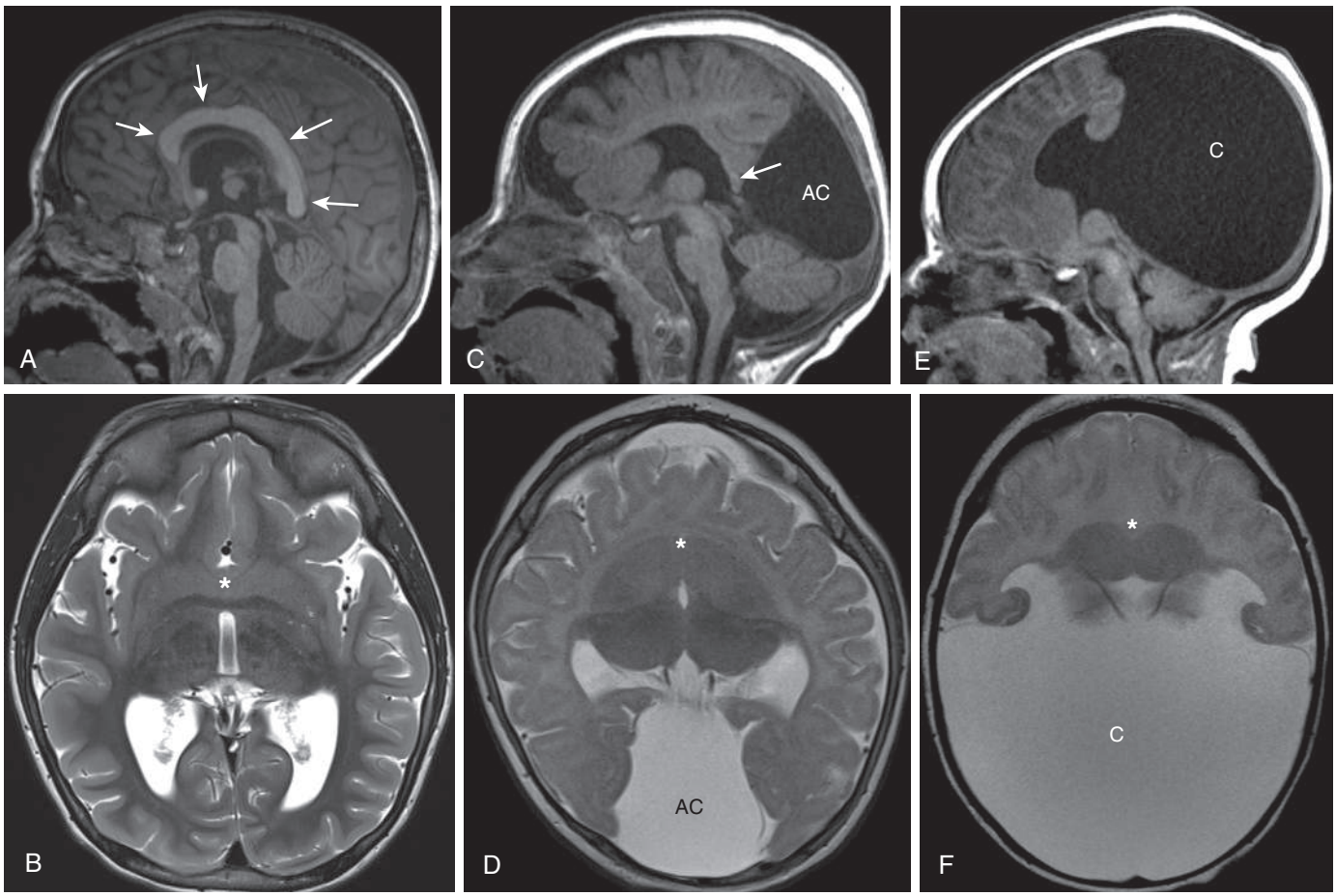

Fig. 631.12 Gradations of severity in holoprosencephaly. Holoprosencephaly results from incomplete cleavage of the cerebral hemispheres early in embryogenesis. As illustrated in these pairs of brain MRI sagittal T1-weighted (**A, C, and E**) and axial T2-weighted images (**B, D, and F**), severity ranges from mildly affected patients with lobar holoprosencephaly (**A, B**), to more severely affected patients with semilobar holoprosencephaly (**C, D**), to the most severely affected patients with alobar holoprosencephaly (**E, F**). More mildly affected holoprosencephaly patients have greater separation of the cerebral hemispheres, particularly anteriorly and ventrally (e.g., less deep gray matter structure fusion marked with *asterisks* in **B, D,** and **F**). Milder holoprosencephaly also demonstrates greater formation of the corpus callosum (*arrows* in **A, C**) which is absent in alobar holoprosencephaly (**E**). Unlike alobar holoprosencephaly, which typically demonstrates a monoventricle with or without a dorsal cyst (C in **E, F**), semilobar and lobar holoprosencephaly demonstrate partial to complete formation of the lateral ventricles (e.g., frontal/temporal horns). The shown case of semilobar holoprosencephaly (**C, D**) has an arachnoid cyst (AC), but it is not in communication with the ventricular system.

AGENESIS OF THE CORPUS CALLOSUM

Agenesis of the corpus callosum consists of a heterogeneous group of disorders that result from defective midline prosencephalic development. These disorders vary in clinical presentation from patients with severe intellectual deficits and neurologic abnormalities to the asymptomatic and normally intelligent patient (Fig. 631.13). In addition, patients may experience hypethermia or hypothermia and hyperhidrosis (Shapiro syndrome).

When agenesis of the corpus callosum is an *isolated* phenomenon, the patient may be asymptomatic. When it is accompanied by associated brain anomalies, such as heterotopias, polymicrogyria, and pachygyria (broad, wide gyri), and/or other syndromic or genetic disorders, patients often have significant neurologic abnormalities, including intellectual disability, microcephaly, hemiparesis or diplegia, and seizures.

The anatomic features of agenesis of the corpus callosum are best depicted on MRI and include widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect. **Colpocephaly** refers to an abnormal enlargement of the occipital horns of the ventricular system and can be identified as early as the fetal period. It is often associated with agenesis of the corpus callosum, but it can occur in isolation. There are numerous genetic causes of agenesis of the corpus callosum, including chromosomal abnormalities, syndromic genetic disorders, and nonsyndromic monogenetic disorders (Table 631.5).

Aicardi syndrome is one syndrome that presents with partial or complete agenesis of the corpus callosum, as well as other brain abnormalities (e.g., cortical dysplasias, periventricular nodular heterotopias, intracranial cysts) and distinctive chorioretinal lacunae. Patients are almost all female, suggesting that the genetic abnormality is X-linked dominant. Seizures, including infantile spasms, are common and are typically resistant to anticonvulsants. An electroencephalogram shows independent activity recorded from both hemispheres as a result of the absent corpus callosum and often shows hemihypsarrhythmia. All patients have severe intellectual disability and can have abnormal vertebrae that may be fused or only partially developed (hemivertebra).

ABSENCE OF THE SEPTUM PELLUCIDUM

Absence of the septum pellucidum is another developmental midline defect that is almost always associated with other brain anomalies, particularly schizencephaly, although it can also be seen with holoprosencephaly, agenesis of the corpus callosum, and septo-optic dysplasia. It can also result through destruction of the septum pellucidum, secondary to hydrocephalus or ischemic injury. Therefore the clinical presentation of patients with absence of the septum pellucidum largely depends on the etiology, associated brain anomalies, and any underlying chromosomal and/or genetic diagnosis. Cavum septum pellucidum refers to the cavity between the two septal leaflets; although this is normal in the fetal brain, the septal leaflets generally fuse during development. A persistent cavum septum pellucidum is generally considered to be a normal variant (Fig. 631.14).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

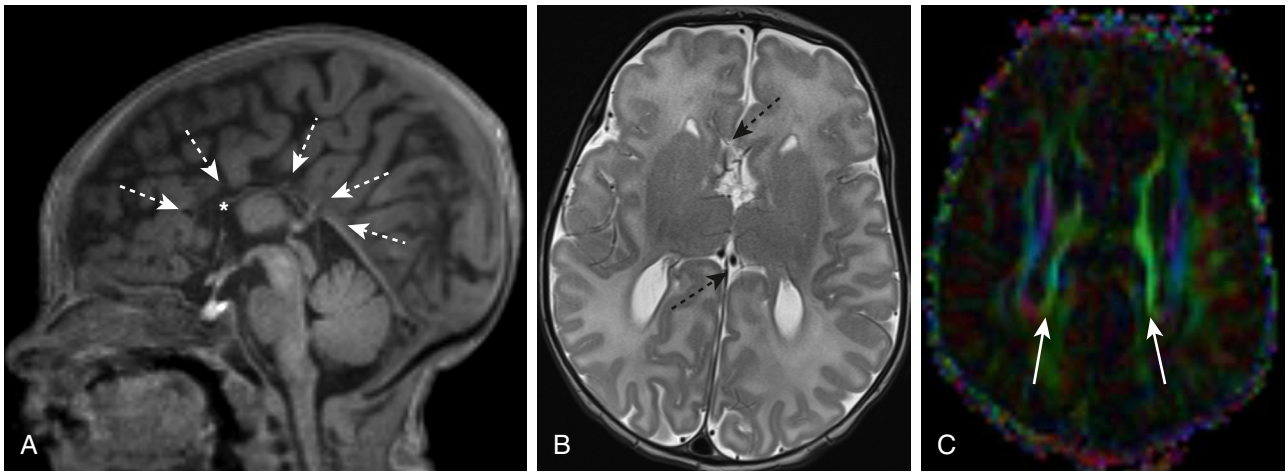

Fig. 631.13 Complete corpus callosum (callosal) agenesis by brain MRI. **A,** Sagittal T1-weighted sequence of a newborn with callosal agenesis demonstrates lack of a normal corpus callosum (*dashed arrows* along expected course) with multiple sulci radiating without interruption from the third ventricle *(asterisk)*. **B,** An axial T2-weighted image of this patient demonstrates a parallel rather than curved course of the lateral ventricles (missing callosal genu and rostrum denoted by *dashed arrows*). **C,** Redirection of white matter tracts (Probst bundles) can be directly visualized in callosal agenesis using colored fractional anisotropy maps, where green denotes anteroposterior fiber tracts running parallel to the lateral ventricles rather than crossing the midline.

Table 631.5 Disorders Associated with Agenesis of the Corpus Callosum*

DISORDER	SALIENT FEATURES
WITH IDENTIFIED GENES†	
Andermann syndrome *(KCC3)*	ACC, progressive neuropathy, and dementia
Donnai-Barrow syndrome *(LRP2)*	Diaphragmatic hernia, exomphalos, ACC, deafness
Frontonasal dysplasia *(ALX1)*	ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft
XLAG *(ARX)*	Lissencephaly, ACC, intractable epilepsy
Microcephaly *(TBR2)*	ACC, polymicrogyria
Microcephaly with simplified gyral pattern and ACC *(WDR62)*	ACC, other brain malformations
Mowat-Wilson syndrome *(ZFHX1B)*	Hirschsprung disease, ACC
Pyridoxine-dependent epilepsy *(ALDH7A1)*	ACC, seizures, other brain malformations
Pyruvate dehydrogenase deficiency *(PDHA1, PDHB, PDHX)*	ACC with other brain changes
ACC with fatal lactic acidosis *(MRPS16)*	Complexes I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes *(L1CAM)*	Hydrocephalus, adducted thumbs, ACC, MR
ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED)	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasms, MR
Chudley-McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniofacial changes, MR
Toriello-Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC SEEN OCCASIONALLY (PARTIAL LIST)‡	
ACC with spastic paraparesis *(SPG11, SPG15)*	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes
Marden-Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel-Gruber syndrome	Encephalocele, polydactyly, polycystic kidneys

Table 631.5 Disorders Associated with Agenesis of the Corpus Callosum —cont'd

DISORDER	SALIENT FEATURES
Nonketotic hyperglycinemia *(GLDC, GCST, GCSH)*	ACC, cerebral and cerebellar atrophy, myoclonus, progressive encephalopathy
Microphthalmia with linear skin defects	Microphthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein-Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septooptic dysplasia (de Morsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microphthalmia, microgenitalia, MR
Wolf-Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p−

*Reliable incidence data are unavailable for these very rare syndromes.
†Gene symbols in parentheses.
‡Many of these also may consistently have a thin dysplastic corpus callosum, such as Sotos syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.
4p−, Deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl co-transporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.
From Sherr EH, Hahn JS. Disorders of forebrain development. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Table 23-2.

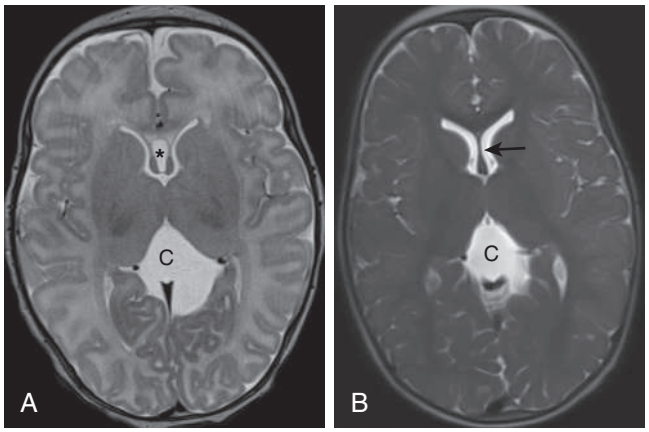

Fig. 631.14 Age-expected evolution of the septum pellucidum. Throughout fetal life, the septum pellucidum exists as paired leaflets enclosing a midline CSF space. This configuration is known as a *cavum septum pellucidum* and undergoes fusion into a single membrane during the first months of postnatal life. **A,** A brain MRI axial T2-weighted image of a 42-day-old female followed for a cistern of the velum interpositum cyst (C) demonstrates normal separation of the septal leaflets with an intervening CSF pocket, the cavum septum pellucidum *(asterisk)*. **B,** An axial single-shot T2-weighted brain MR image at 13 mo in the same patient demonstrates expected fusion of the leaflets into a single membrane *(arrow)*.

631.8 Dysgenesis of the Cranial Nerves and the Posterior Fossa

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

The classification of disorders of development of the cranial nerve, brainstem, and cerebellum remains anatomic, but future classification systems will likely be based on the molecular biology of brain development based on the genes involved and the roles they play in orchestrating brain architecture.

CONGENITAL CRANIAL DYSINNERVATION DISORDERS

Congenital cranial dysinnervation disorders (CCDDs) are congenital nonprogressive disorders that affect the cranial nerves, primarily presenting with abnormal eye and/or facial movements. These disorders include Möbius syndrome, Duane syndrome, and congenital fibrosis of the external ocular muscles (CFEOM). Increasingly, genetic causes for these disorders have been identified.

Möbius syndrome is generally characterized by bilateral facial weakness (seventh cranial nerve) and sixth nerve palsies (limited eye abduction). Injury or abnormal development at any level (i.e., cranial nerve nuclei, roots, nerves, or muscles) can lead to Möbius syndrome, but most patients have pathology at the level of the cranial nerve nuclei. The genetics of Möbius syndrome remain incompletely understood. Genetic linkage mapped inheritance to chromosome 13q12.2-q13, with identification of de novo pathogenic variants in *PLXND1* and *REV3L* in some patients. Environmental factors may also play a role. Affected infants present in the newborn period with facial weakness, causing feeding difficulties owing to a poor suck. Möbius syndrome can also be associated with other congenital anomalies, including talipes equinovarus (clubfoot), arthrogryposis, and syndactyly. Over 30% of patients with Möbius syndrome are reported to have autism spectrum disorder and/or intellectual disability.

Duane retraction syndrome is characterized by congenital limitation of horizontal globe movement and globe retraction and palpebral fissure narrowing on attempted adduction. This is caused by underdevelopment or absence of the abducens nuclei and nerves, as well as aberrant innervation of the lateral rectus muscle by the oculomotor nerve. Duane syndrome often occurs in families with an autosomal dominant pattern of inheritance, with three genes (*CHN1, MAFB,* and *SALL4*) identified thus far as well as associations with chromosome 8q13, 20q12, and 2q21.1.

Congenital fibrosis of the extraocular muscles (CFEOM) is characterized by severe restriction of eye movements and ptosis from abnormal oculomotor and trochlear nerve development and/or from abnormalities of extraocular muscle innervation. The most common form is caused by pathogenic autosomal dominant variants in *KIF21A,* which encodes a kinesin motor protein. Variants in *KIF21A* therefore lead to abnormal axonal transport. Other autosomal dominant causes

of CFEOM include pathogenic variants in the tubulin genes *TUBA1A, TUBB2B,* and *TUBB3*. Malformations of cortical development can also be associated with these and other tubulinopathy genes. Autosomal recessive forms of CFEOM are associated with variants in *PHOX2A* and *COL25A1*.

BRAINSTEM AND CEREBELLAR DISORDERS

Disorders of the posterior fossa structures include abnormalities not only of the brainstem and cerebellum but also of the CSF spaces.

Chiari malformation, the most common malformation of the posterior fossa and hindbrain, consists of downward displacement of the cerebellum and sometimes the brainstem through the foramen magnum. Often, there is an associated developmental abnormality of the bones of the skull base leading to a small posterior fossa. Chiari malformations are divided into three groups (type I, II, and III). In **Chiari type I**, the cerebellar tonsils are downwardly displaced (Fig. 631.15). Chiari type I malformations can be asymptomatic. When symptoms develop, they often do not do so until late childhood. Symptoms include headaches that are worse with straining and other Valsalva maneuvers that increase ICP. Symptoms of brainstem compression such as diplopia, oropharyngeal dysfunction, spasticity, tinnitus, sleep apnea, and vertigo can also occur. Type I malformations are not associated with hydrocephalus. Syrinx of the spinal cord, especially in the cervical region, should be looked for on MRI imaging. This can result in neck pain, urinary frequency, and progressive lower extremity spasticity. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the fourth ventricle during fetal development is responsible. Chiari type I malformations may be associated with Ehlers-Danlos syndrome.

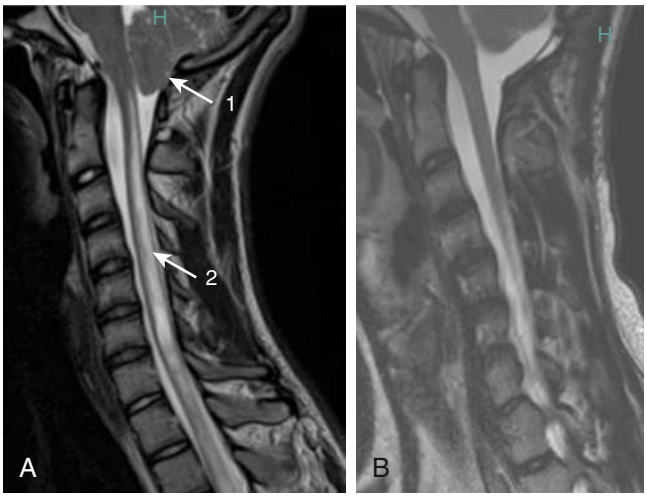

Fig. 631.15 A, A 16-yr-old male with Chiari malformation type 1 *(arrow 1)* and syringomyelia *(arrow 2)*. B, Postoperative MRI reveals decompression of the Chiari malformation and resolution of the syrinx. *(From Albert GW. Chiari malformation in children. Pediatr Clin N Am. 2021;68:783–792, Fig. 1, p. 786.)*

With **Chiari type II**, the inferior cerebellar vermis, cerebellar tonsils, and medulla are displaced through the foramen magnum. Most patients with myelomeningocele have a Chiari type II malformation (also see Neural Tube Defects). **Chiari type III**, the rarest form, also consists of downward displacement of the medulla, as well as a high cervical or occipital encephalocele. Chiari type II is usually identified early in life because of the association with myelomeningocele and, as with Chiari type I, can cause symptoms from brainstem compression. Complications for all the Chiari malformations include obstructive hydrocephalus and/or syringomyelia. Patients with Chiari type III are more severely affected, with high mortality and neurologic morbidity.

Dandy-Walker malformation consists of cystic dilation of the fourth ventricle, hypoplasia or agenesis of the cerebellar vermis, and an enlarged posterior fossa with elevation of the lateral venous sinuses and the tentorium (Fig. 631.16). Various associated brain malformations can also be seen, including agenesis of the corpus callosum and malformations secondary to abnormal neuronal migration. Most patients will develop hydrocephalus in infancy, and variable degrees of neurologic impairment are usually present. The etiology of Dandy-Walker malformation is heterogeneous and includes chromosomal abnormalities, single gene disorders, and exposure to teratogens. It is important to distinguish Dandy-Walker malformation from other causes of posterior fossa CSF collections (see Fig. 631.16). These include the **Blake pouch cyst**, a benign variant that consists of enlargement of the fourth ventricle, caused by persistence of the developmental Blake pouch structure. Isolated **mega cisterna magna**, another benign normal variant, refers to an enlarged cisterna magna with otherwise normal cerebellar architecture and size. Finally, posterior fossa **arachnoid cysts** can lead to hydrocephalus caused by obstruction of CSF flow but often remain asymptomatic.

Joubert syndrome and related disorders are a group of autosomal recessive disorders in which there is cerebellar vermis hypoplasia and the pontomesencephalic **molar tooth sign** (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles) (Fig. 631.17). It is associated with hypotonia, ataxia, characteristic breathing abnormalities including episodic apnea and hyperpnea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis, and oculomotor apraxia. Joubert syndrome is

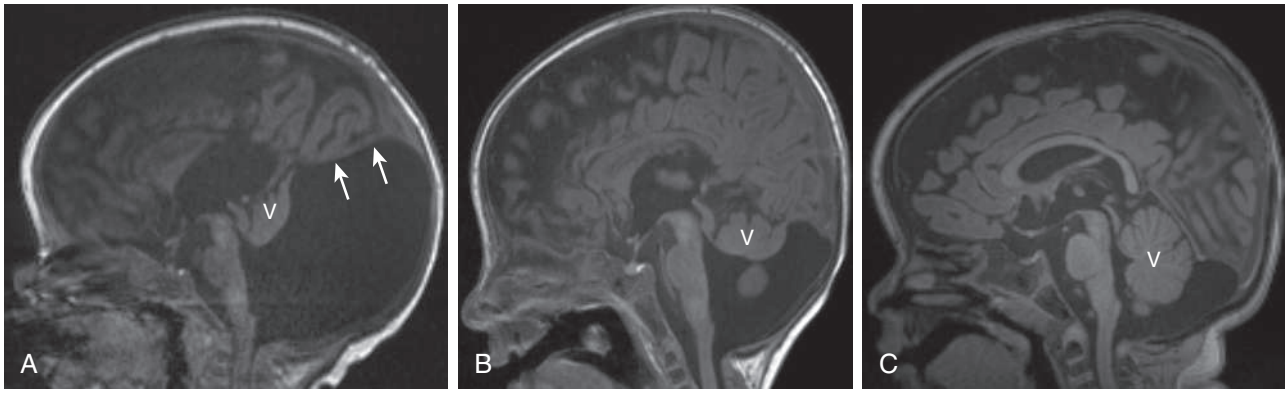

Fig. 631.16 Dandy-Walker spectrum posterior fossa abnormalities. Abnormal fenestration of embryologic outlets of the fourth ventricle and associated hypoplasia of the vermis (V in A-C) result in so-called Dandy-Walker spectrum. As illustrated by these sagittal T1-weighted brain MRI sequences, the most severe end of the spectrum consists of the classic Dandy-Walker malformation (A) where there is severe vermian hypoplasia and a remodeling of an enlarged posterior fossa CSF space (e.g., elevation of the tentorium and torcula above the confluence of the lambdoid sutures, *arrows*). At the least severe end of the spectrum, the vermis is fully formed but there is a prominent retrocerebellar and cisterna magna CSF space without expansion of the posterior fossa: a mega cisterna magna (C). In between these extremes, one may encounter vermian hypoplasia and posterior fossa CSF space prominence without overt expansion of the posterior fossa (e.g., vermian hypoplasia with rotation in B).

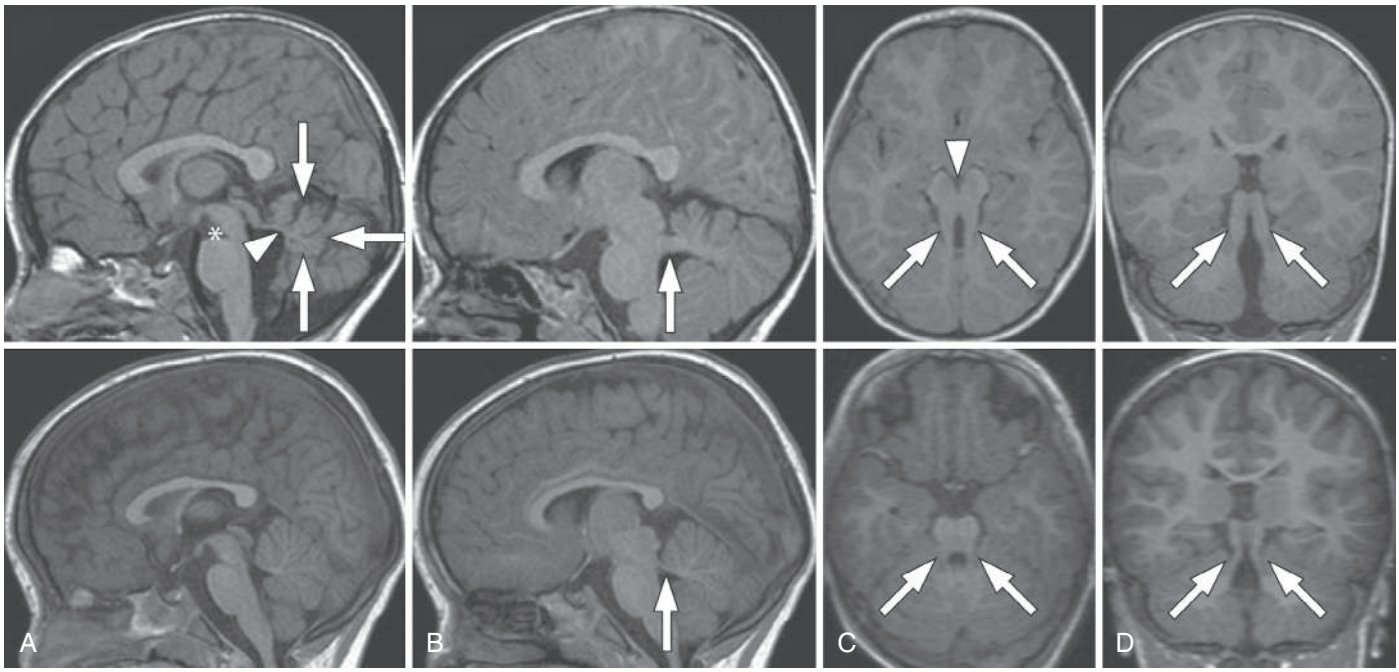

Fig. 631.17 Neuroimaging findings in a 2-yr-old child with pure Joubert syndrome *(upper panels)* compared with a healthy control *(lower panels)*. **A,** Parasagittal T1-weighted image shows the thickened, elongated, and horizontally oriented superior cerebellar peduncles *(white arrow)*. **B,** Midsagittal T1-weighted image demonstrates a moderate hypoplasia and dysplasia of the cerebellar vermis *(white arrows)* with secondary distortion and enlargement of the fourth ventricle, with rostral shifting of the fastigium *(white arrowhead)*. A deepened interpeduncular fossa is also noted. **C,** Axial T1-weighted image at the level of the pontomesencephalic junction shows the molar tooth sign with a deepened interpeduncular fossa *(white arrowhead)* and elongated, thickened, and horizontally oriented superior cerebellar peduncles *(white arrows)*. Additionally, the cerebellar vermis appears to be hypoplastic and its remnants dysplastic. **D,** Coronal T1-weighted image reveals the thickened superior cerebellar peduncles *(white arrows)*. *(From Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol. 2013;12:894–905, Fig. 1.)*

considered a ciliopathy, as many of the 35 genes implicated encode for proteins important in cilia function (e.g., *AHI1, CC2D2A, CEP290*). There can also be associated systemic features, including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue (Fig. 631.18).

Rhombencephalosynapsis consists of an absent or small vermis associated with a nonseparation or fusion of the deep midline cerebellar structures. Ventriculomegaly or hydrocephalus is often seen. There is a variable clinical presentation from normal function to cognitive and language impairments, epilepsy, and spasticity.

The **pontocerebellar hypoplasias** (PCHs) are a group of autosomal recessive disorders characterized by impairment of cerebellar and pontine development. Ten types have been defined to date, with increasing identification of underlying genetic causes (e.g., *TSEN2, TSEN34, RARS2*). Patients tend to be severely affected, with hypotonia, feeding difficulties, developmental delay, breathing difficulties, and seizures. Other disorders can also present with some PCH, most commonly including Walker-Warburg syndrome, muscle-eye-brain disease, congenital disorders of glycosylation type 1A, and mitochondrial cytopathies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.9 Hydrocephalus

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma (Tables 631.6 and 631.7).

PHYSIOLOGY

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originate from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child, approximately 20 mL/hr of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages; through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion, the CSF.

CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mmH_2O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mmH_2O. Normally, CSF flows from the lateral ventricles through the foramina of Monro into the third ventricle. It then traverses the narrow aqueduct of Sylvius, which is approximately 3 mm long and 2 mm in diameter in a child, to enter the fourth ventricle. The CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain. Hydrocephalus resulting from obstruction within the ventricular system is called *obstructive* or *noncommunicating hydrocephalus*. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser

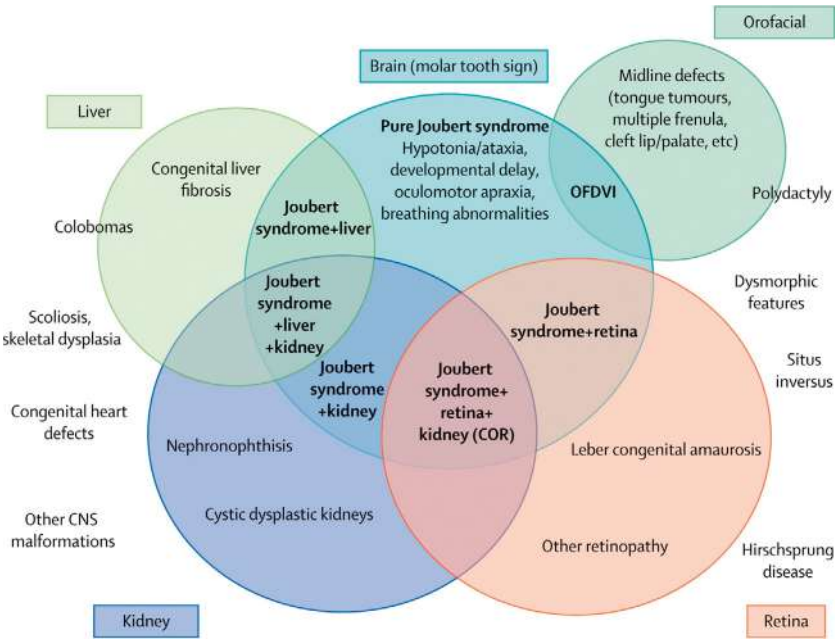

Fig. 631.18 Spectrum of organ involvement in Joubert syndrome and classification in clinical subgroups *(in bold)*. Chorioretinal colobomas are more frequently found in the subgroup of Joubert syndrome with liver involvement but can be present also in other subgroups. Similarly, polydactyly (especially if preaxial or mesoaxial) is invariably present in the orofaciodigital type VI subgroup, but postaxial polydactyly is frequently observed also in association with other Joubert syndrome phenotypes. Other clinical features outside the circles occur more rarely, without a specific association to a clinical subgroup. CNS, Central nervous system; COR, cerebellooculorenal; OFDVI, orofaciodigital type VI syndrome. *(From Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol. 2013;12:894–905, Fig. 3.)*

Table 631.6 Causes of Pediatric Hydrocephalus

	CAUSE	PROPOSED MECHANISM
ACQUIRED HYDROCEPHALUS		
Inflammatory		
Subarachnoid hemorrhage or infection	Arachnoid scar	Dysfunctional subarachnoid space
Intraventricular hemorrhage or infection	Ependymal scar	Ventricular obstruction
Neoplasm		
Parenchymal brain tumor	Mass effect	Ventricular obstruction
Spinal cord tumor	Altered CSF composition	Dysfunctional subarachnoid space
Disseminated tumor	Tumors with meningeal infiltration (e.g., primitive neuroectodermal tumor)	Dysfunctional subarachnoid space
Choroid plexus tumor	Altered CSF composition	Dysfunctional subarachnoid space
Choroid plexus tumor	Mass effect	Ventricular obstruction
Choroid plexus tumor or hyperplasia	Altered choroid plexus function	CSF overproduction or hyperdynamic intraventricular pulsations
Vascular		
Vascular malformation	Ventricular obstruction (e.g., vein of Galen malformation); venous hypertension (e.g., arteriovenous malformation)	Ventricular obstruction; decreased venous compliance or decreased CSF absorption
Disordered cerebral venous function	Extrinsic venous obstruction (e.g., skeletal dysplasias); intrinsic venous obstruction (e.g., venous sinus thrombosis); idiopathic venous dysfunction (e.g., congenital idiopathic hydrocephalus)	Decreased venous compliance or decreased CSF absorption
CONGENITAL OR DEVELOPMENTAL HYDROCEPHALUS		
Congenital aqueduct stenosis	Third ventricle outlet obstruction	Ventricular obstruction
Neural tube defects (e.g., myelomeningocele and Chiari II malformation)	Third or fourth ventricle outlet obstruction; altered venous compliance; arachnoid or ependymal scar	Variable
Posterior fossa malformations	Fourth ventricle outlet obstruction (e.g., Dandy-Walker complex); Chiari I malformation	Ventricular obstruction
Developmental cysts	Mass effect	Ventricular obstruction
Congenital foramen of Monro atresia	Lateral ventricle outlet obstruction	Ventricular obstruction

From Kahle KT, Kulkarni AV, Limbick DD Jr, et al. Hydrocephalus in children. *Lancet*. 2016;387:788–798, Table 1.

extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called *nonobstructive* or *communicating hydrocephalus*.

Table 631.7 Genetic Abnormalities Associated with Pediatric Hydrocephalus

	PUTATIVE GENETIC LINK
X-linked hydrocephalus with aqueduct stenosis (307000)	*L1CAM*
Nonsyndromic autosomal recessive hydrocephalus (HYC; 236600 [HYC1]; 615219 [HYC2])	*CCDC88C; MPDZ*
Fried-type syndromic mental retardation (304340)	*AP1S2*
Walker-Warburg syndrome (multiple subtypes)	*POMT1, POMT2, POMGNT1,* and others
Neural tube defects (folate-sensitive [601634] and insensitive [182940] forms)	Multiple susceptibility genes involved in planar-cell polarity (e.g., *FUZ, VANGL1/2, CCL2,* and others); folate-sensitive neural tube defects associated with genes in folate synthesis pathway (*MTR, MTRR, MTHFR, MTHFD*)
Primary ciliary dyskinesias and other ciliopathies (including the many heterogeneous subtypes of Meckel-Gruber syndrome and Joubert syndrome)	Multiple genes involved in cilia structure, function, and regulation (e.g., *CC2D2A, TMEM67, MKS1,* and others)
RAS-opathies (e.g., neurofibromatosis type 1, Noonan syndrome, Costello syndrome, cardiofaciocutaneous syndrome)	*NF1*; Ras-Raf-MEK-ERK pathway genes) e.g., *KRAS, BRAF, PTPN11,* and others)
VACTERL-H (association of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies plus hydrocephalus; 276950)	*PTEN*
X-linked VACTERL-H (300515)	*FANCB*

Numbers given are Online Mendelian Inheritance in Man (OMIM) identifiers.
From Kahle KT, Kulkarni AV, Limbick DD Jr, et al. Hydrocephalus in children. *Lancet.* 2016;387:788–798, Table 2.

PATHOPHYSIOLOGY AND ETIOLOGY

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct of Sylvius or a lesion in the fourth ventricle. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with branching or forking (Fig. 631.19). In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Rarely, aqueductal stenosis is associated with neurofibromatosis. Aqueductal gliosis can also give rise to hydrocephalus. As a result of neonatal meningitis or a subarachnoid hemorrhage in a premature infant, the ependymal lining of the aqueduct is interrupted, and a brisk glial response results in complete obstruction. Intrauterine viral infections can also produce aqueductal stenosis followed by hydrocephalus. A vein of Galen malformation can expand and, because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and Dandy-Walker syndrome, as previously discussed.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can disrupt CSF flow through the cisterns or damage the arachnoid villi resulting in obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus. Tumors or arteriovenous malformations in the spinal cord or cauda equina are uncommon etiologies of communicating hydrocephalus.

CLINICAL MANIFESTATIONS

The clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing the obstruction, and the duration and rate of increase of the ICP. In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and scalp veins can be dilated. The forehead is broad, and the eyes might deviate downward (i.e., setting-sun eye sign) because of impingement of the dilated suprapineal recess on the brainstem tectum. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common because of stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. In an older child, the cranial sutures are less accommodating, so that the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age-groups, and headache is a prominent symptom in older patients. A gradual

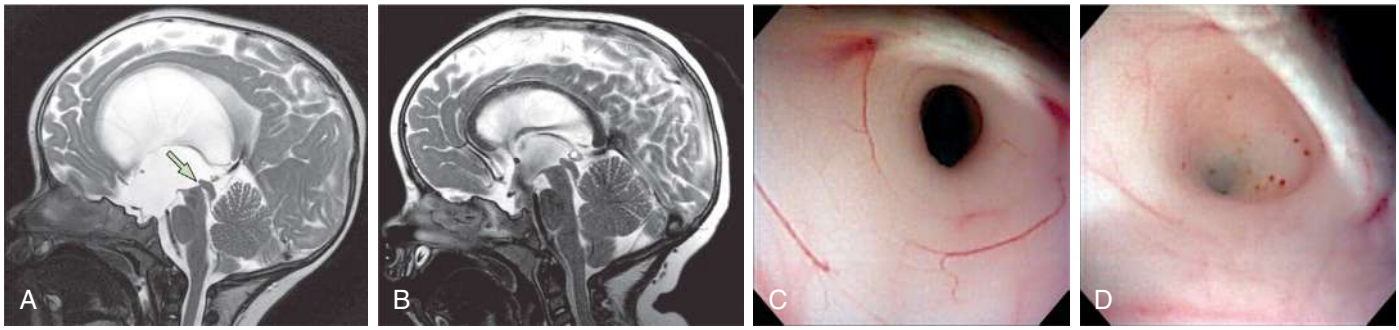

Fig. 631.19 Aqueduct stenosis. **A,** Sagittal brain T2-weighted MRI of infant with hydrocephalus secondary to congenital aqueduct stenosis. *Arrow* indicates point of obstruction. **B,** Same patient after endoscopic third ventriculostomy; note dark flow void indicating flow across endoscopic third ventriculostomy. **C,** Endoscopic view of healthy patent aqueduct. **D,** Endoscopic view of obstructed aqueduct in aqueduct stenosis; note posterior commissure at dorsal margin of the aqueduct ostium in both **A** and **B**. *(From Kahle KT, Kulkarni AV, Limbick Jr DD, et al. Hydrocephalus in children. Lancet. 2016;387:788–798, Fig. 1.)*

change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. Percussion of the skull might produce a cracked pot sound or Macewen sign, indicating separation of the sutures. Serial head circumference measurements, with special attention to the velocity of growth, are important measurements when identifying hydrocephalus and tracking resolution. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.

Type II Chiari malformations can manifest with progressive hydrocephalus. Approximately 10% of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by decompression of the posterior fossa. A more indolent form consists of abnormalities of gait, spasticity, and increasing incoordination (including the arms and hands) during childhood. Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression, but asymptomatic or mildly symptomatic patients may be managed conservatively.

Approximately 90% of patients with Dandy-Walker malformation have hydrocephalus, and a significant number of children have associated anomalies, including agenesis of the posterior cerebellar vermis and corpus callosum. Infants present with a rapid increase in head size and a prominent occiput. Most children have evidence of long-tract signs, cerebellar ataxia, and delayed motor and cognitive milestones, probably because of the associated structural anomalies. Dandy-Walker malformation is managed by shunting the cystic cavity (and on occasion the ventricles as well) in the presence of hydrocephalus.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueduct stenosis. A history of prematurity with intracranial hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of hair, lipoma, or angioma, that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation (Fig. 631.20). Transillumination of the skull is positive with massive dilation of the ventricular system or in Dandy-Walker syndrome. A fundoscopic exam is mandatory because the finding of chorioretinitis suggests an intrauterine infection, such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate in the setting of the increased pressure.

An ultrasound is a quick and easy study to perform on infants with an open fontanelle to identify and monitor the trajectory of hydrocephalus. Brain MRI has the capability to perform specific sequences to evaluate CSF flow dynamics as well as evaluating for etiology and additional abnormalities that may be present. In many centers, CT scans are often limited to evaluating for acute symptomatic hydrocephalus and skull abnormalities to avoid radiation exposure. Although rarely used, plain skull films can show separation of the sutures, erosion of the posterior clinoids in an older child, and an increase in convolutional markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP.

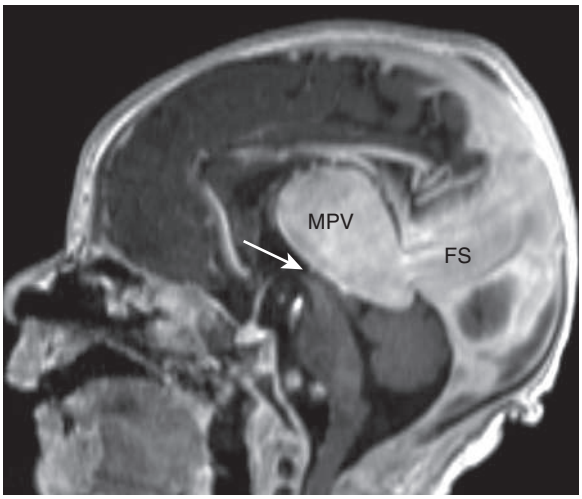

Fig. 631.20 Vein of Galen malformation. A vein of Galen malformation is an arteriovenous fistula between intracranial arteries and the embryologic median prosencephalic vein. As seen in this postcontrast sagittal T1-weighted brain MR image of a newborn with a prenatally diagnosed vein of Galen malformation, this vascular malformation is characterized by marked distension of the median prosencephalic vein (MPV) and distension of downstream dural sinuses, commonly through a persistent embryologic falcine sinus (FS). The ensuing high-velocity arteriovenous shunting can cause venous hypertension, communicating hydrocephalus, and high-output cardiac failure. Although large median prosencephalic veins can compress the cerebral aqueduct *(arrow)*, the primary treatment modality is still endovascular intervention (embolization) rather than CSF diversion.

Rapid head growth raises suspicion of hydrocephalus; however, other etiologies must be considered. Accelerated skull growth from a thickened cranium can result from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. Benign external hydrocephalus is often associated with macrocephaly with notable increase in volume of the subarachnoid spaces on brain imaging. No intervention is required for this self-limited hydrocephalus, which is hypothesized to be the result of a delayed maturation of the arachnoid villi. Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease). In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes, and neurofibromatosis are characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of the parents' head circumferences is necessary to establish the diagnosis.

Ventriculomegaly can exist without increased ICP (normal-pressure hydrocephaly) or in patients with loss of white or gray matter secondary to prior injury (cerebral atrophy with ventricular dilation ex vacuo). It can be difficult to distinguish between ventriculomegaly and true hydrocephalus by static neuroimaging alone unless CSF flow assessment is included in the MRI. Additional clinical information (e.g., clinical context, fundoscopic exam, lumbar puncture with pressure measurements) may also be required. This is an important clinical distinction to make, as the management of ventriculomegaly secondary to hydrocephalus is quite different from the management of ventriculomegaly secondary to brain volume loss.

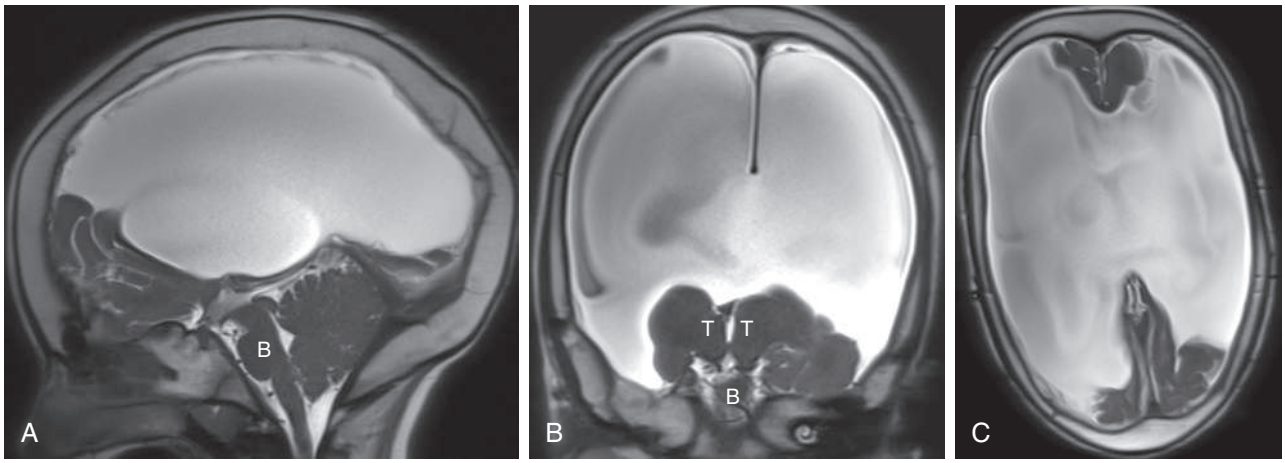

Fig. 631.21 Hydranencephaly. Brain MRI sagittal (**A**), coronal (**B**), and axial (**C**) single-shot T2-weighted images of a 13-yr-old female with severe neurologic impairment demonstrates lysis of the cerebral hemispheres apart from small remnants of the frontal/occipital poles and left temporal pole. There is preservation of the thalami (T) and brainstem (B). This congenital lysis of the cerebrum is dubbed *hydranencephaly* and believed to reflect anterior circulation vascular insufficiency in utero.

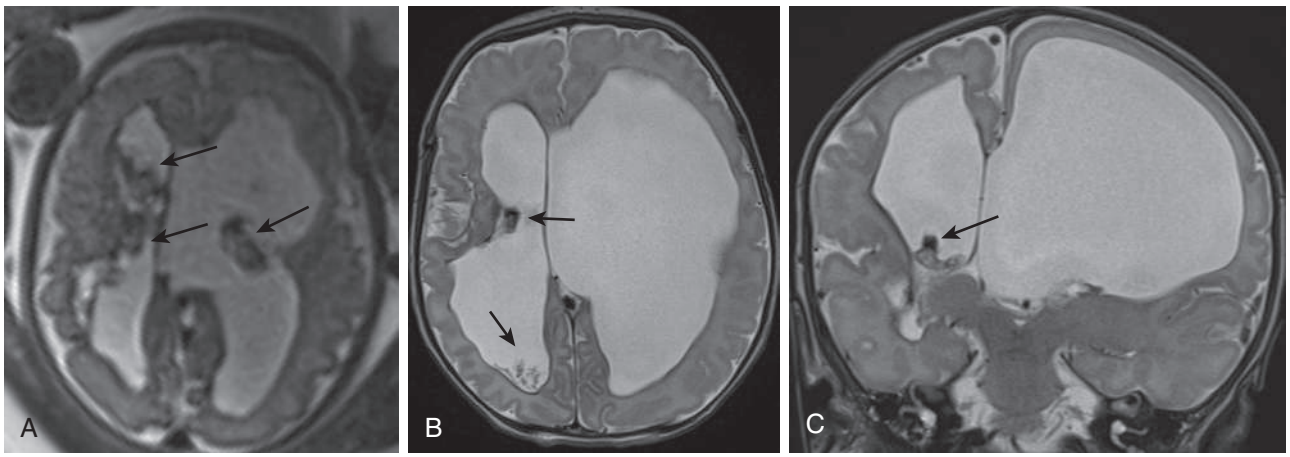

Fig. 631.22 Porencephaly from in utero encephaloclastic/hemorrhagic injury. High-grade in utero germinal matrix hemorrhage results in venous infarction and hemorrhagic injury to the brain parenchyma. As a result, there is focal lysis and thinning of the brain parenchyma, resulting in a hemispheric cavity in communication with the ventricular system called *porencephaly*. **A**, Axial single-shot brain MR T2-weighted imaging of a fetus at 32 wk demonstrates severe ventriculomegaly with a clot in the ventricular system *(arrows)* and hemosiderin-stained (hypointense) tissue lysis in the surrounding cerebral hemispheres. Axial (**B**) and coronal (**C**) T2-weighted imaging of the same patient during the first day of life better depicts the areas of hemosiderin staining and parenchymal thinning/lysis as well as residual clot in the ventricular system *(arrows)*.

HYDRANENCEPHALY

Hydranencephaly may be confused with hydrocephalus. The cerebral hemispheres are absent or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over the membrane. The midbrain and brainstem are relatively intact (Fig. 631.21). The cause of hydranencephaly is unknown, but bilateral occlusion of the internal carotid arteries during early fetal development would explain most of the pathologic abnormalities. Affected infants can have a normal circumference at birth that grows at an excessive rate postnatally because of excessive CSF production and absorption. Transillumination shows an absence of the cerebral hemispheres. The child is irritable, feeds poorly, develops seizures and spastic quadriparesis, and has little or no cognitive development. A ventriculoperitoneal shunt prevents massive enlargement of the cranium.

PORENCEPHALY

Porencephaly is the presence of cysts or cavities within the brain that result from developmental defects or acquired lesions, including infarction of tissue. True porencephalic cysts are most commonly located in the region of the sylvian fissure and typically communicate with the subarachnoid space or the ventricular system, or both. They represent developmental abnormalities of cell migration and are often associated with other malformations of the brain, including microcephaly, abnormal patterns of adjacent gyri, and encephalocele. Affected infants tend to have many problems, including intellectual disability, spastic hemiparesis or quadriparesis, optic atrophy, and seizures.

Several risk factors for porencephalic cyst formation have been identified, including hemorrhagic venous infarctions, various thrombophilias such as protein C deficiency and factor V Leiden variants, perinatal alloimmune thrombocytopenia, von Willebrand disease, maternal warfarin use, maternal cocaine use, congenital infections, trauma such as amniocentesis, and maternal abdominal trauma. Pathogenic variants in the *COL4A1* and *COL4A2* genes have been described in cases of familial porencephaly (Fig. 631.22).

TREATMENT

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt. Endoscopic third ventriculostomy is a viable approach, and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Endoscopic fenestration of the floor of the third ventricle with drainage into the subarachnoid space (prepontine cistern) is attempted in patients over 6 months of age with noncommunicating hydrocephalus. It often requires cauterization of the choroid plexus as an additional procedure (see Fig. 631.19). Ventricular shunting may be avoided with this approach. The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, and mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by *Staphylococcus epidermidis*. With meticulous preparation, the shunt infection rate can be reduced to <5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyelocele.

PROGNOSIS

The prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Children with hydrocephalus are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP. The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus. Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele is relatively common, possibly because of increased gonadotropin secretion in response to increased ICP. It is imperative that children with hydrocephalus receive long-term follow-up in a multidisciplinary setting.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

631.10 Craniosynostosis

Irene M.J. Mathijssen

See also Chapter 101.4.

Craniosynostosis is defined as premature closure of the cranial sutures and is classified as primary or secondary. It is associated with varying types of abnormal skull shape (see Fig. 101.5). Primary craniosynostosis refers to closure of one or more sutures owing to abnormalities of skull development, whereas secondary craniosynostosis results from failure of brain growth and expansion (e.g., microcephaly or after insertion of a ventriculoperitoneal shunt), specific medication during pregnancy (e.g., valproate), or metabolic disorders. The incidence of primary craniosynostosis approximates 1 in 2,000 live births. The cause is unknown in the majority of children; however, genetic syndromes account for 10–20% of cases (see Table 101.5). The distinction between craniosynostosis and deformational forces is important in occipital and frontal plagiocephaly to allow successful intervention to be offered in the form of physical therapy for torticollis and other positional asymmetries that lead to plagiocephaly.

Table 631.8 Commonly Used Clinical Genetic Classifications of Craniosynostoses

DISORDER	CAUSE
ISOLATED CRANIOSYNOSTOSIS	
Unicoronal synostosis	Unknown, consider *TWIST1, FGFR1, FGFR2, FGFR3, TCF12, IL11RA*, ERF pathogenic variants
Metopic and sagittal synostosis	SMAD6
SYNDROMIC CRANIOSYNOSTOSIS	
Antley-Bixler syndrome	*FGFR2, POR*
Apert syndrome	Usually one of two pathogenic variants in *FGFR2*
Beare-Stevenson syndrome	*FGFR2*
Baller-Gerold syndrome	*RECQL4*
Carpenter syndrome	*RAB23* in most; *MEGF8* in some
Craniofrontonasal syndrome	*EFNB1*
Crouzon syndrome (and Pfeiffer syndrome)	Numerous different pathogenic variants at *FGFR2; rarely FGFR1*
Crouzon acanthosis nigricans syndrome	Ala391Glu pathogenic variants in *FGFR3*
Muenke syndrome	Pro250Arg pathogenic variants in *FGFR3*
Saethre-Chotzen syndrome	Pathogenic variants or deletion in *TWIST1*
TCF-12 related craniosynostosis	Pathogenic variants or deletion of *TCF12*
IL11RA-related craniosynostosis	*IL11RA*
ERF-related craniosynostosis	*ERF*
Shprintzen-Goldberg syndrome	Pathogenic variants in *FBN1 or SKI*

DEVELOPMENT AND ETIOLOGY

The bones of the cranium are well developed by the fifth month of gestation (frontal, parietal, temporal, and occipital) and are separated by sutures and fontanels. The brain grows rapidly in the first several years of life and is normally not impeded because of equivalent growth along the suture lines. The cause of craniosynostosis is largely unknown. Genetic factors have been identified for some isolated and for many syndromic causes of craniosynostosis (Table 631.8; see Table 101.5).

CLINICAL MANIFESTATIONS AND TREATMENT

Most cases of craniosynostosis are evident at birth and are characterized by a progressive skull deformity that is a direct result of premature suture fusion. Fusion of metopic and sagittal suture reveals a palpable prominent bony ridge, and fusion of the suture may be confirmed by plain skull roentgenograms, ultrasound, 3D-CT scan, or black bone MRI (Table 631.9).

Scaphocephaly is the result of premature closure of the sagittal suture and produces a long and narrow skull, the most common form of craniosynostosis. Scaphocephaly is associated with a prominent occiput, a broad forehead, and a triangular-shaped anterior fontanel. The condition is sporadic, is more common in males, and can cause difficulties during labor because of cephalopelvic disproportion resulting from a head circumference of ≥2 SD. Scaphocephaly is associated with increased ICP in about 10% of patients

Table 631.9 Epidemiology and Clinical Characteristics of the Common Craniosynostoses

TYPE	EPIDEMIOLOGY	SKULL DEFORMITY	CLINICAL PRESENTATION
Sagittal	Most common CSO affecting a single suture, 80% male	Dolichocephaly or scaphocephaly (boat-shaped)	Frontal bossing, prominent occiput, palpable keel ridge; OFC increased and reduced biparietal diameter
Coronal	More common in girls Associated with various syndromes	Unilateral: plagiocephaly Bilateral: brachycephaly	Unilateral: flattened forehead and elevated orbit on affected side, nose deviation; higher supraorbital margin Bilateral: broad, flattened forehead.
Lambdoid	Rare	Unilateral: Lambdoid/occipital plagiocephaly Bilateral: pachycephaly	Unilateral: flattening of ipsilateral occiput, bulging of ipsilateral forehead, ipsilateral ear and mastoid is inferiorly displaced, curvature in face Bilateral: brachycephaly with bilateral inferiorly displaced ears and mastoids
Metopic	SMAD 6 mutation; genetic overlap with developmental delay disorders	Trigonocephaly	Pointed forehead and midline ridge, hypotelorism
Multiple	Often syndromic	Depending on which sutures are involved	

CSO, Craniosynostosis; OFC, occipital–frontal circumference.

at the age of 12 months if left untreated and thus requires surgical treatment.

Trigonocephaly is the next most common form of craniosynostosis, caused by premature fusion of the metopic suture. These children have a keel-shaped forehead and hypotelorism and are at risk for associated cognitive impairment, behavioral problems and visual disturbances. The phenotype also includes milder presentations, which are usually self-limiting over time. Metopic ridging occurs with closure of the suture around the time of birth and is a physiologic process. The risk on increased ICP is limited, even in the more severe presentation.

Frontal plagiocephaly is characterized by unilateral flattening of the forehead, elevation of the orbit and eyebrow, and a caudal displacement of the ear on the corresponding side, with contralateral bossing of the forehead. The condition is more common in females and is the result of premature fusion of one of the coronal sutures. These children can present with raised ICP in up to 16% at 1 year of age and have a high risk of visual disturbances. Therefore skull surgery is indicated in addition to close monitoring by the optometrist. Unicoronal synostosis can be a presentation of a syndrome, and genetic analysis is always indicated (see Table 101.5).

Occipital plagiocephaly is most often a result of positioning during infancy and is more common in an immobile child or a child with a disability, but fusion of the lambdoid suture can cause unilateral occipital flattening and caudal displacement of the ipsilateral ear and mastoid and of the contralateral parietal bone. Surgery is indicated to prevent the development of distinct asymmetry of the face.

GENETIC DISORDERS

The most prevalent genetic disorders associated with craniosynostosis include Crouzon, Apert, Saethre-Chotzen, and Muenke syndromes.

Crouzon syndrome (including Pfeiffer syndrome) is characterized by premature craniosynostosis and is inherited as an autosomal dominant trait. The shape of the head depends on the timing and order of suture fusion but often is a compressed back-to-front diameter or **brachycephaly** resulting from bilateral closure of the coronal sutures. Pansynostosis is also common, in which all sutures close and the skull shape appears to be normal initially. The orbits are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features. Crouzon syndrome can be associated with the skin condition acanthosis nigricans.

Apert syndrome has many features in common with Crouzon syndrome. Apert syndrome is usually a sporadic condition and linked to increased paternal age, although autosomal dominant inheritance can occur. It is associated with premature fusion of multiple sutures, especially the two coronal sutures. Apert syndrome is characterized by symmetric complex syndactyly of the hands and feet. Severe acne often develops during puberty, and most patients have a developmental delay.

Saethre-Chotzen syndrome is characterized by unicoronal or bicoronal synostosis. The condition is inherited as an autosomal dominant trait. It is associated with ptosis of one or both eyelids, short fingers, and soft tissue syndactyly of the second and third fingers and/or toes.

Muenke syndrome is the most prevalent of the genetic syndromes and usually presents with bicoronal synostosis. It is associated with sensorineural hearing loss and behavioral issues.

Pathogenic variants of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with specific types of craniosynostosis. Crouzon syndrome is mainly caused by variants in *FGFR2* and incidentally of *FGFR1* and *FGFR3*. Apert syndrome is mainly caused by two specific types of *FGFR2* variants. Saethre-Chotzen syndrome results from variants or deletions in *TWIST1*, and Muenke syndrome is solely caused by the Pro250Arg variant in *FGFR3*.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased ICP, optic atrophy, respiratory problems secondary to upper airway anomalies, and disorders of speech and hearing. Vault expansion is mandatory for management of increased ICP, treatment to reduce the respiratory difficulties such as midface advancement, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children until adulthood. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 632

Deformational Plagiocephaly

Megan L. Dietze-Fiedler and John A. Girotto

Deformational plagiocephaly (DP), also known as positional plagiocephaly, is the development of cranial flattening and asymmetry in the infant as a result of extrinsic molding forces placed on the skull, such as consistently sleeping on the same area of the head. Since the suggestion was made to place sleeping infants on their backs for the prevention of sudden infant death syndrome, the incidence of DP has risen dramatically, up to 46.6% and peaking between 7 weeks and 4 months of age.

EPIDEMIOLOGY AND ETIOLOGY

Risk Factors

Infants cannot reposition their heads in the first few postnatal weeks and are unable to hold their heads up until about 4 months of age. It is for this reason that DP is most severe around 4 months of age. It is also during this time that an infant's head circumference increases rapidly: about 2 cm/month in the first 3 months, 1 cm/month from 4 to 6 months of age, and 0.5 cm/month after 6 months of age. By ~6 months of age, infants have developed head control, and this ability to actively reposition their head allows for the gradual improvement of the cranial shape because of pressure offloading and continued brain growth.

Congenital torticollis, positional preference when sleeping, and lower levels of activity are especially prominent in patients with DP. Table 632.1 lists other risk factors. Many of these risk factors cannot be prevented, but sleeping supine with the head always turned to the same side is associated with DP independent of the other factors, and this factor *can* be prevented. There may be an association between developmental delay and DP. Although not causal, studies have identified significant differences in gross motor development (e.g., sitting up, crawling, and rolling back to side) between babies with and without DP. Family demographics, such as lower maternal education, primiparity, more prenatal education, and siblings with cranial asymmetries, may also be associated with the development of DP. The increased prevalence of DP in infants of mothers receiving more prenatal education is considered related to the emphasis placed on sudden infant death syndrome and the Back to Sleep campaign.

Causes

Prenatal causes of DP include uterine compression and intrauterine constraint, such as occurs with oligohydramnios or multifetus pregnancy. Postnatal causes of DP include infant sleeping position and congenital muscular torticollis.

Table 632.1 Factors that Increase the Risk for Deformational Plagiocephaly

- Male
- First-born child
- Prematurity
- Multiple pregnancy (twins, triplets)
- Limited passive neck rotation at birth (e.g., congenital torticollis)
- Developmental delay
- Sleep position is supine at birth and at 6 wk
- Bottle feeding only
- Tummy time <3 times/day
- Lower activity level, slower milestone achievement
- Sleeping with head to same side, positional preference

Muscular torticollis is a condition that is present in as many as one in six newborns and causes continuous tightening of muscles in the neck, preventing passive rotation (see Chapter 721.1). It is thought that this condition precedes the development of cranial deformity. However, head position preference may result from cervical asymmetry that leads to torticollis and later flattening of a side of the skull from acquired positional preference. Muscular and positional issues lead to nonsynostotic plagiocephaly rather than the opposite. Given that DP results from more time spent on one side of the head and that torticollis (and other neck muscle imbalances) are likely to lead to this disproportional partitioning of time, they are most likely causes, not effects, of DP.

Sleeping position plays a major role in the incidence of DP. When an infant continuously sleeps with the same part of the skull resting on a flat surface, a continuous force is placed in this area. During this time of rapid skull development, the growth is inhibited at the area where it rests on a hard surface, causing a flat spot. Because of this inhibition, growth is increased in opposite directions, causing a deformation that can be distinguished from other types of plagiocephaly.

EXAMINATION AND DIFFERENTIATING BETWEEN DEFORMATIONAL PLAGIOCEPHALY AND CRANIOSYNOSTOSIS

An abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out **craniosynostosis** as a primary cause for cranial asymmetry in infants because management of this condition is quite different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 631.10). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents similarly to posterior DP.

History and Physical Examination

Tables 632.2 and 632.3 outline the key components of the history and physical examination.

Observation of cranial shape and ear displacement are the first steps. It is critical to observe the child anteriorly, laterally, and from a vertex view. When cranial shape is viewed from above, DP typically looks like a **parallelogram**, and the ear on the same side of the flat or bald spot is **displaced anteriorly**. In lambdoidal craniosynostosis, the head has a trapezoid shape and the ear on the same side as the flat spot is posteriorly displaced (Fig. 632.1). It is important to note that the ear position, though more likely to be anterior in DP and posterior in lambdoidal craniosynostosis, may present anteriorly in both conditions.

Palpation will help to differentiate these two conditions. Craniosynostosis presents with palpable ridges along the suture, whereas DP does not. Additionally, patients with craniosynostosis will not have mobile calvarial bones. This can be tested by applying gentle pressure on two adjacent skull bones separated by a suspected synostotic suture. If the plates do not move relative to each other, then the suspicion for craniosynostosis is raised.

Verifying neck muscle tone and range of motion is a key part of the examination because it helps in evaluating motor development and in diagnosing congenital torticollis. Resistance to passive motion raises the concern for torticollis. Decreased tone should prompt further evaluation of motor development. Infants do not gain the muscle control to turn or lift their heads until approximately 4 months of age, and delays in motor development could increase the infant's risk of DP at later

Table 632.2 Important Factors to Evaluate in the History and Physical Examination of the Patient with Plagiocephaly

	DEFORMATIONAL	SYNOSTOTIC
Birth history	Intrauterine compression First-born child	Typically no complications
Head shape at birth	Typically normal	Can be irregular
Age at which shape irregularity first noticed	Usually in first few months of life	Can be at birth
How patient prefers to sleep	Same side, same position Same even during naps	Variable
Bald spot	Yes	No
Motor development for age	If age is atypical for deformational plagiocephaly, motor development is typically slow for age Torticollis present History of limited activity or mobility	Varies depending on presence of concomitant syndrome
Tummy time	Decreased	Suggested time
Signs or symptoms of increasing intracranial pressure	No	Possible

Table 632.3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	External forces applied to the skull Prenatal: uterine compression, intrauterine constrained Postnatal: congenital torticollis, sleeping position	Premature fusion of one or more cranial sutures
Common types	Lateral Posterior	Bilateral coronal Sagittal Metopic
Common distinguishing features	Normal round head shape at birth Parallelogram shape to head Ipsilateral ear anteriorly displaced No palpable bony ridges or open fontanels	Can have abnormal head shape at birth Trapezoid shape to head Ipsilateral ear posteriorly displaced Palpable bony ridges
Management	Repositioning Physical therapy Helmet in some cases	Surgery Helmet in some cases

Adapted from Nield LS, Brunner MD, Kamat D. The infant with a misshapen head. *Clin Pediatr (Phila).* 2007;46:292–298, Tables 1 and 2.

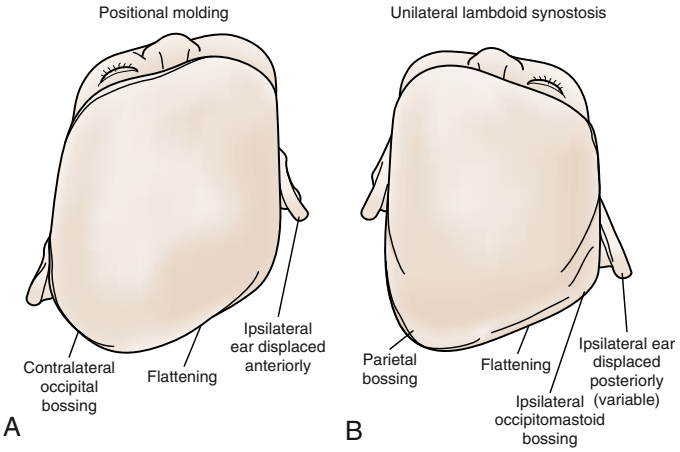

Fig. 632.1 Differentiating physical findings between deformational plagiocephaly and craniosynostosis. Vertex views. **A,** Right-sided deformational plagiocephaly exhibiting a parallelogram head shape. **B,** Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape. *(From Lin AY, Losee JE. Pediatric plastic surgery. In: Zitelli BJ, McIntire SC, Norwalk AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th ed. Philadelphia: Elsevier; 2012: Fig. 22-5.)*

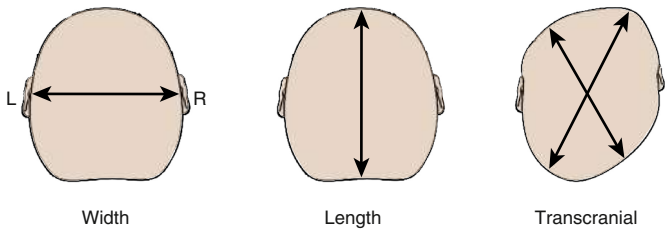

Fig. 632.2 Cranial measurements. *(Modified from Looman WS, Flannery AB. Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis. J Pediatr Health Care. 2012;26:242–250, Table 1.)*

ages than those at which it usually occurs. Decreased range of motion can also be seen in cervical spine abnormalities, although this is rare. Early recognition of these conditions is critical in treatment, management, and outcome.

Accurate and consistent measurements will help to distinguish etiologies and manage infants presenting with an abnormally shaped skull. Along with the usual head circumference measurements, the clinician should also measure cranial width, length, and transcranial diagonal diameter (Fig. 632.2), which is best performed with calipers. These

Table 632.4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

	LATERAL DEFORMATIONAL PLAGIOCEPHALY	POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)			
DETERMINING TYPE BASED ON CLINICAL FINDINGS					
Occiput (vertex view)	Ipsilateral occipital flattening; contralateral occipital bossing	Uniform occipital flattening			
Ear position (vertex view)	Ipsilateral ear may be anteriorly displaced	Normal			
Face, forehead (anterior, lateral, and vertex views)	May be normal; more severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced	Temporal bossing, increase in vertical height in severe cases			
Other	Torticollis, head position preference	Large size, history of limited activity or limited mobility			
DETERMINING SEVERITY					
Mild	TDD 3-10 mm	Type I	Flattening restricted to back of the skull	CI: 0.82-0.9	Central posterior deformity (ping-pong ball depression)
Moderate	TDD 10-12 mm	Type II Type III	Malposition of ear Forehead deformity	CI: 0.9-1.0	Central posterior deformity and widening of posterior skull
Severe	TDD > 12 mm	Type IV Type V	Malar deformity Vertical or temporal skull growth	CI: >1.0	Vertical head, head growth, or temporal bossing

CI, Cephalic index (cranial index); TDD, transcranial diagonal diameter difference.

measurements allow the clinician to diagnose, determine severity, and monitor the plagiocephaly:

- *Cranial length:* Distance from the most prominent point between the eyebrows to the most prominent point of the occiput.
- *Width:* Maximum transverse diameter, horizontal.
- *Cephalic index* (cranial index): Ratio of the cranial width to the cranial length.
- *Occipital-frontal transcranial diameter:* Find the points on either side of the head where the deformation is the worst (two on the right, two on the left), then measure the diagonal distances between these points.
- *Transdiagonal difference* (transcranial diagonal difference): The difference between two transcranial diagonal diameters.
- *Cranial vault asymmetry:* Ratio of oblique measurements. This is difficult to implement because different physicians and authors propose varying points to use for these measurements.

One technology for the evaluation of the severity and improvement over time of DP is the three-dimensional photographic system. Advantages of this system include an easy and comfortable ability to image in an unbiased manner. Similarly, the use of laser scanners for the prefabrication scans for helmets is frequently employed by orthotists.

After observations and measurements, the clinician can determine the type and severity of the DP (Table 632.4 and Fig. 632.3). For *lateral DP,* bossing of the occiput occurs opposite the flattened deformity and the ear on the same side as the flat area can be anteriorly displaced. This type of DP is typically associated with infants who have torticollis or a head position preference to one side. Transdiagonal diameter is typically abnormal in this type of plagiocephaly, and this measurement is the gold standard for determining severity.

In *posterior DP,* the occiput is uniformly flattened, temporal bossing can occur, and the ears are normal. It is usually associated with large head size and a history of limited activity or mobility. The cephalic index is increased with posterior DP.

Time and accurate exam records can help in management. If deformation is worsening when DP typically begins to demonstrate improving head shape, craniosynostosis should be suspected.

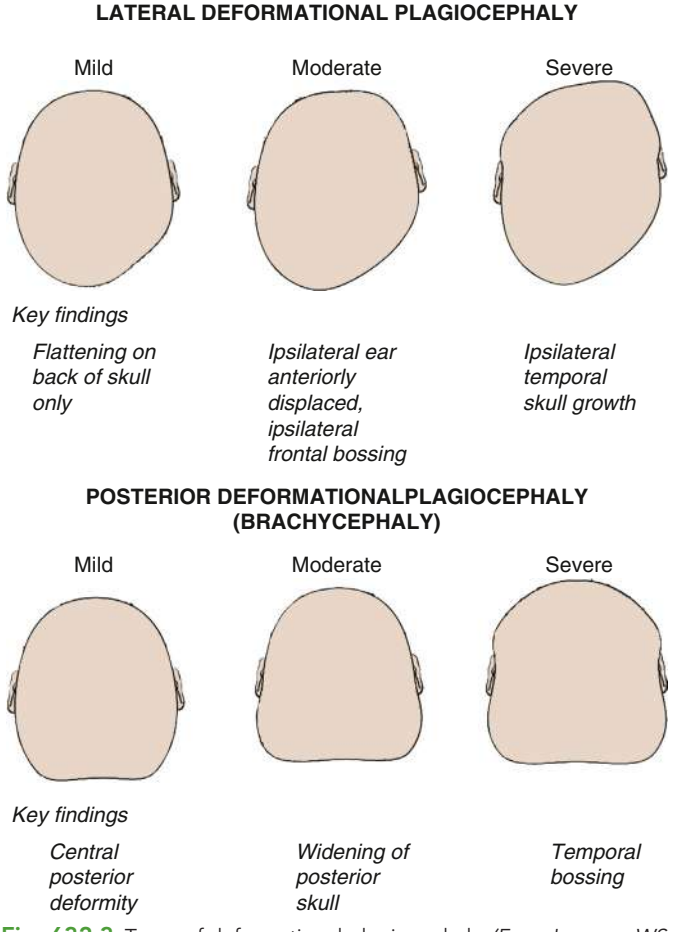

Fig. 632.3 Types of deformational plagiocephaly. *(From Looman WS, Flannery AB. Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis. J Pediatr Health Care. 2012;26:242–250, Fig. 1.)*

TREATMENT

Prevention

The sleep position should be monitored and varied. Alternating the infant's head to face the head and foot of the crib on alternate nights will allow the infant to sleep facing into the room without always lying on the same side of the head. Consistently alternating the sleeping position early on allows the infant to have equal time on both sides of the occiput, and the infant will become used to this pattern. Infants who have an obvious positional preference for a particular side will take more time and make more effort to purposefully reposition themselves counter to their preference. Parents must be counseled in the benefit of this strategy in preventing bald spots or flat spots that can progress to cranial deformity.

Tummy time is the term used to describe the infant's awake time spent lying on the stomach. The suggested amount of tummy time is 10-15 minutes at least 3 times a day. Reassure parents that sleep is the only time during which the prone position should be avoided, and educate the parents as to the benefits for the infant of awake prone positioning to help progression of motor development.

Treatment Options

Cranial asymmetry from DP does not usually spontaneously improve, nor do the more severe manifestations of facial and ear asymmetry disappear. Once a flat spot develops, it is unlikely that the infant will be able to overcome the pull to lie on the same spot in time to allow for reversal of the asymmetry.

Watch-and-wait management is not recommended in infants with DP. Evidence suggests that, at a minimum, repositioning and physiotherapy (RPPT) should be initiated as soon as asymmetry is observed.

RPPT includes the counseling and teaching of parents about positional changes and tummy time for their child, as well as the referral to physical therapy in the case of congenital torticollis. RPPT is the optimal treatment choice for patients younger than 4 months of age who have mild or moderately severe DP. The earliest types of behavioral modifications can be as simple as increasing tummy time or repositioning the infant's crib such that everything interesting in the room is on the side opposite the DP.

Molding therapy (helmet therapy) is the use of an orthotic helmet to promote the resolution of cranial asymmetry while the infant's head is still rapidly growing. Orthotic helmets do not actively mold the skull; rather, they protect the areas that are flat and allow the child to grow into the flat spot. Helmet therapy achieves correction 3 times faster and better than repositioning alone. This therapy is still debated because of its expense, time requirements, coverage, and side effects (irritation, rashes, and pressure sores). Combined treatment with helmet therapy and RPPT is the most beneficial management of infants older than 4 months with severe DP or with worsening of mild or moderate DP trialed on RPPT. Infants with severe DP should be considered for helmet therapy at any age.

Studies suggest helmet therapy should be started for significant DP between 4 and 8 months and continued for 7-8 months. Parents should be counseled on the commitment involved in this treatment because helmets need to be worn up to 23 hours per day. Noncompliance has been documented in 80% of study patient populations in as little as 4 months.

Risk factors are associated with failure of RRPT and helmet therapy. Table 632.5 provides a list of these risk factors by treatment modality. These are important to consider when prescribing treatment regimens to families in order to give the patient the best chance at a successful outcome.

Table 632.5 Risk Factors for Failure of Conservative and Helmet Therapy in the Treatment of Deformational Plagiocephaly

CONSERVATIVE THERAPY	HELMET THERAPY
Poor compliance	Advanced age*
Advanced age*	Poor compliance
Presence of torticollis	
Presence of developmental delay	
Increases severity of cranial deformity at time of therapy (via cranial ratio and diagonal difference)	

*Advanced age is defined as older than 6 mo.

Patients with **craniosynostosis** require surgery. Sometimes, a molding helmet can be used as an adjunctive therapy after surgery but never as monotherapy.

OUTCOMES

Outcomes may be better when helmet therapy is started before 6 months of age; infants starting therapy later than that do not achieve the same degree of normal head measurements as those whose helmet therapy is started before 6 months of age. Significant improvements in asymmetry are usually obvious at 4-11 weeks after starting helmet therapy. An 8-year single-center review analyzing 4,378 patients found complete correction in 77.1% of patients undergoing conservative (RRPT) therapy and 94.4% of patients treated with helmet therapy.

Studies in patients with a median follow-up age of 9 years found that 75% of cases had what both parents and patients considered to be a normal head appearance. Nine percent of patients and 4% of parents noted residual asymmetry that they considered significant. Though some literature hints at more satisfaction and less anxiety in parents of helmeted children, there is evidence to suggest that the treatment modality and outcome make no difference regarding parents' long-term satisfaction.

There is a small but growing body of literature that suggests conservative therapy (RRPT) may be as effective as helmet therapy for correcting certain cases of DP. Generalization of these findings to larger populations is not currently possible.

Cognitive and academic outcomes may be different depending on the side of deformity. Poorer academic performance and greater speech abnormalities were found in patients with left-sided deformities than in those with right-sided deformities. This manifested as double the number of patients with expressive speech abnormalities and triple the number of special education needs. It is unclear what the underlying mechanism is; treatment differences were apparently not a factor. In general, children with DP and without comorbid conditions are usually developmentally normal, healthy children. This development contrasts with craniosynostosis, in which increases in intracranial pressure may have deleterious effects on central nervous system function.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 633

Seizures in Childhood

Mohamad A. Mikati, Dmitry Tchapyjnikov, and Kevin M. Rathke

An epileptic seizure is a sudden transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International League Against Epilepsy (ILAE) operational classification of seizure types divides epileptic seizures into four categories based on the presumed mode of seizure onset: focal, generalized, unknown onset, and unclassified (Figs. 633.1 and 633.2). In **focal** (formerly known as *partial*) **seizures**, the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of one cerebral hemisphere. Focal seizures can be described as motor or nonmotor and are further characterized by preserved or impaired consciousness, which is used synonymously with the term **awareness**. Simple partial seizure is an outdated term that refers to a focal seizure with no alteration in consciousness or awareness; the current term is **focal aware seizure**. Complex partial seizure is also an outdated term that denotes focal seizures with altered consciousness or awareness of the surroundings; they are currently referred to as **focal seizures with impaired awareness**. In **generalized seizures**, the first clinical and EEG changes indicate synchronous involvement of both hemispheres. A seizure may be labeled as being of **unknown onset** if there is not enough clinical information available to determine if the seizure is focal or generalized. If the clinical characteristics of a seizure are unusual and a determination of onset cannot be made despite an adequate evaluation, the seizure may be labeled as **unclassified**. Approximately 30% of patients who have a first afebrile seizure later develop epilepsy; the risk is approximately 20% if the neurologic exam, EEG, and neuroimaging are normal.

Febrile seizures are a separate category (see Chapter 633.1). **Acute symptomatic** or **provoked seizures** occur secondary to an acute problem affecting brain excitability, such as an electrolyte imbalance; most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of developing epilepsy from it. An **unprovoked seizure** is one that is not an acute symptomatic seizure. A **remote symptomatic seizure** is one secondary to a distant brain injury, such as an old stroke.

Reflex seizures are a type of seizure precipitated by a sensory stimulus. These types of seizures can be caused by a variety of stimuli, including visual (flickering lights, patterns, reading), auditory (music), somatosensory, or proprioceptive stimuli; praxis; eating; bathing in hot water; or being startled (see Chapter 631.9).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition (see Fig. 633.2). The clinical diagnosis of epilepsy usually requires the occurrence of at least one unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly establish an enduring predisposition to develop recurrences. For epidemiologic and, commonly, for clinical purposes, epilepsy is considered present when two or more unprovoked seizures occur in a time frame of longer than 24 hours in between them. Approximately 4–10% of children experience at least one seizure (febrile or afebrile) in the first 16 years of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the disorders start in childhood. The annual prevalence is 0.5–1.0%. Thus the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. **Seizure disorder** is a general term that is usually used to include any one of several disorders, including epilepsy, febrile seizures, and, possibly, single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An **epileptic syndrome** is a disorder that manifests as one or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished (Tables 633.1-633.6; Fig. 633.3). This category must be distinguished from the category of epileptic seizures that refers to single events rather than to clinical syndromes. In general, the seizure type is the primary determinant of the medications to which the patient is likely to respond, and the epilepsy syndrome determines the prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality that is thought to result in cognitive and other impairments. **Developmental encephalopathy** denotes a disorder in which the underlying etiology (e.g., a specific gene variant) contributes to a developmental delay independently of the patient's seizure burden and/or EEG abnormalities. The terms *epileptic* and *developmental encephalopathy* can be combined (i.e., **developmental epileptic encephalopathy**) in specific situations where both the EEG abnormalities and the underlying etiology contribute to the patient's developmental delay.

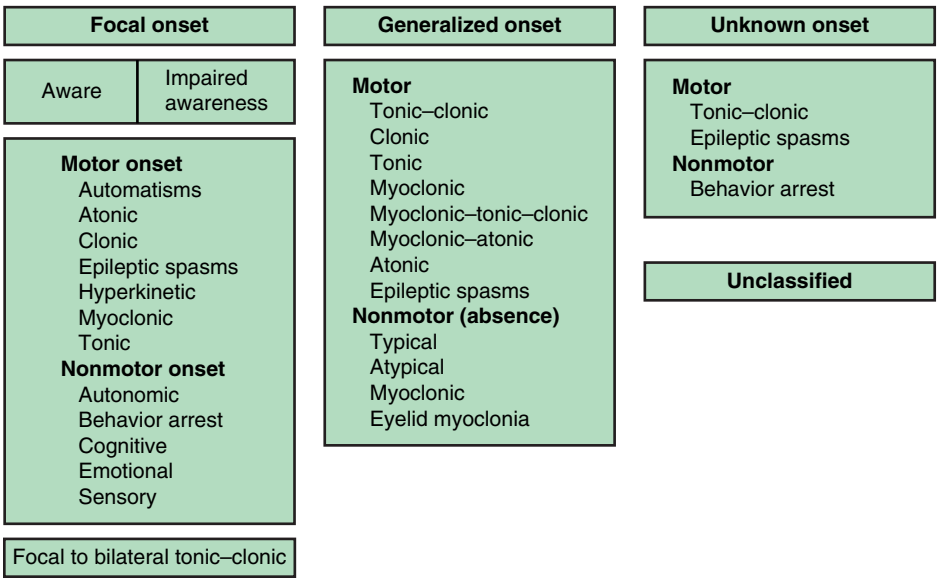

Fig. 633.1 International League Against Epilepsy classification of seizures. *(Modified from Katyayan A, Diaz-Medina G. Epilepsy: epileptic syndromes and treatment. Neurol Clon. 2021;39:779–794, Fig. 1, p. 780.)*

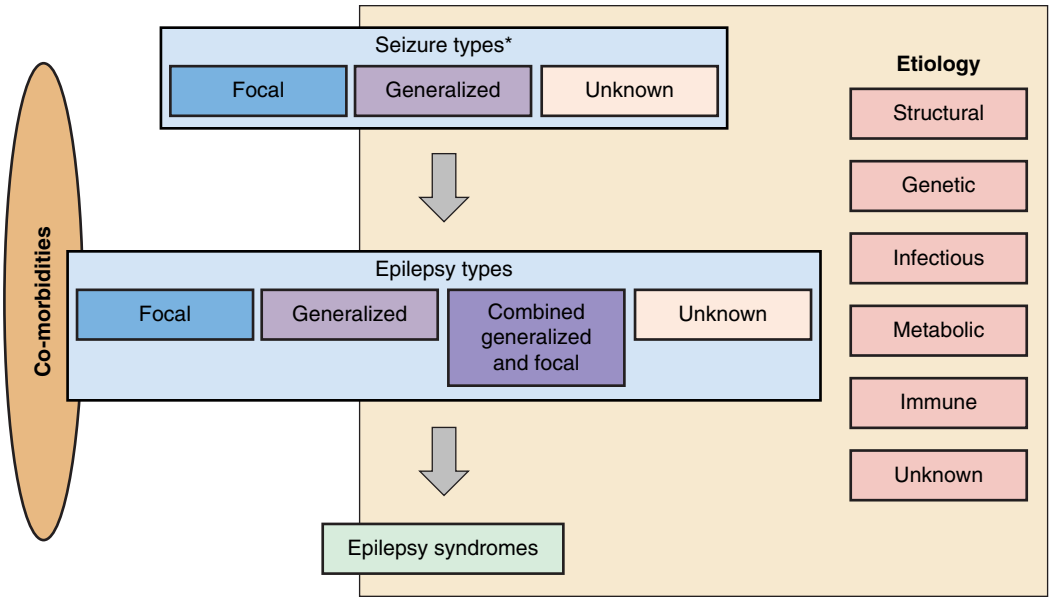

Fig. 633.2 ILAE classification of epilepsies. *Denotes onset of seizure. *(From Katyayan A, Diaz-Medina G. Epilepsy: epileptic syndromes and treatment. Neurol Clon. 2021;39:779–794, Fig. 2, p. 781.)*

The ILAE Task Force on Classification has proposed a multilevel framework for categorizing epilepsies (Table 633.7). This framework should help guide therapeutic decisions and assist with prognostication. At the most basic level **(level 1)**, a patient's epilepsy can be classified by seizure type (focal, generalized, focal and generalized, or unknown). At the next level **(level 2)**, based on available clinical data and known seizure types, an epilepsy type can be assigned (focal, generalized, focal and generalized, or unknown). At the next level **(level 3)**, if further clinical data are available and based on supporting studies (e.g., EEG and/or MRI), the diagnosis of a specific epilepsy syndrome can be made (e.g., juvenile myoclonic epilepsy). Concurrent to this classification paradigm, the associated comorbidities and the underlying cause for the epilepsy must also be considered. If categorized by etiology, epilepsies are grouped into genetic, structural, metabolic, immune, infectious, or unknown categories. It is important to note that these categories are not mutually exclusive, and a patient's epilepsy may have multiple concurrent etiologies (e.g., genetic and structural). At the final level **(level 4)** of categorizing and diagnosing the epilepsy, the epilepsy syndrome, the underlying etiology, and associated comorbidities are considered.

Genetic epilepsy (previously also referred to as *idiopathic epilepsy*) implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) that is not causative of a brain structural or metabolic disorder other than the epilepsy. This category encompasses *genetic generalized epilepsies* (previously called *idiopathic generalized epilepsies*), such as childhood absence epilepsy, as well as epilepsies caused by a known gene defect (see Tables 633.1-633.6).

Structural epilepsy (previously called *symptomatic epilepsy*) refers to an epilepsy syndrome caused by an underlying structural brain disorder that may or may not be genetic. This includes etiologies such as old stroke or hypoxic-ischemic injury, as well as epilepsy secondary to tuberous sclerosis (which is also genetic). **Immune-mediated epilepsy** is an important category that describes epilepsies occurring secondary to immune-mediated central nervous system (CNS) inflammation. This group of disorders warrants special attention because immunotherapies such as steroids and intravenous immunoglobulin (IVIG) may be the first-line treatments. **Autoimmune encephalitides** such as anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis and anti-LG1 limbic encephalitis are examples of immune-mediated epilepsies. **Infectious epilepsy** describes epilepsies secondary to chronic infectious conditions such as tuberculosis and HIV rather than acute infections such as bacterial meningitis or herpes simplex virus (HSV) encephalitis.

The older terms *cryptogenic epilepsy* and *presumed symptomatic epilepsy* refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function, but the underlying disorder is not known; the disorder is now referred to as **unknown epilepsy**, designating that the underlying cause of the epilepsy is still unknown.

EVALUATION OF THE FIRST SEIZURE

The initial evaluation of an infant or a child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration. For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures, such as meningitis, systemic sepsis, unintentional or intentional head trauma, and ingestion of drugs or medications or other toxins. The history should aim to determine if the event was a seizure or not and to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child's postictal state.

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** could include forceful turning of the head and eyes to one side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesia or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often either secondary to a lesion or the result of a genetic, formerly known as *idiopathic,* epilepsy. Focal seizures in a neonate may be seen because of focal lesions such as perinatal stroke or because of a metabolic abnormality such as hypocalcemia that results in focal seizures that may not generalize because of immaturity of the brain connections. Focal and generalized motor seizures may be tonic-clonic, tonic, clonic, myoclonic, or atonic. **Tonic seizures** are characterized by increased tone or rigidity (usually lasting 2 seconds up to several minutes), and **atonic seizures** are characterized by flaccidity and lack of movement. **Clonic seizures** consist of rhythmic, fast muscle contractions and slightly longer relaxations; **myoclonus** is a shocklike contraction of a muscle of <50 milliseconds that is often repeated. The duration of

Table 633.1 Classification of Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE RANGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
NEONATAL						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, TPM, PB	—	No
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BZD, ZON, TPM, LEV, ketogenic diet	No
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	LEV, TPM, PB	—	No
INFANCY						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	LEV, TPM, PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	LEV, TPM, OXC, CBZ, PB	—	No
Epilepsy of infancy with migrating focal seizures	Infant	No remission	Ominous	LEV, PB, OXC, CBZ, PHT, TPM, QND	BZD, bromides, LAC, VPA, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BZD, FBM, IVIG, TPM, ZON, ketogenic diet	Lesionectomy ± cortical resection
Dravet syndrome (severe myoclonic epilepsy in infancy)	Infant	No remission	Severe	CLB, stiripentol, VPA (only after age 2 yr)	BZD, TPM, LEV, ZON, ketogenic diet	No
Benign myoclonic epilepsy in infancy	3 mo-3 yr	3-5 yr	Variable	LEV, TPM, BZD	VPA, ZON	No
CHILDHOOD						
Benign childhood epilepsy with centrotemporal spikes	3-13 yr	16 yr	Good	OXC, CBZ, LEV, VPA	LAC, PER	No
Early and late-onset idiopathic occipital epilepsy	2-8 yr; 6-17 yr	12 yr or younger; 18 yr	Good	OXC, CBZ, LEV, VPA	LAC, PER	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	OXC, CBZ, LEV	CLB, PB, PHT, LAC, PER, GBP, TPM	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	OXC, CBZ, LEV	CLB, PB, PHT, GBP, TPM, VPA, LAC, PER	No, except in rare cases
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, LEV, VPA (depending on seizure type)	CLB, TPM, PER	No
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long- lasting	Variable	OXC, CBZ, LEV	CLB, GBP, LAC, PB, PER, PHT, ZON, TPM, VPA	Temporal resection
Rasmussen syndrome	6-12 yr	Progressive	Ominous	LEV, OXC, CBZ, plasmapheresis, immunoglobulins	LAC, PB, PER, PHT, TPM	Functional hemispherectomy
Hemiconvulsion-hemiplegia syndrome	1-5 yr	Chronic	Severe	OXC, CBZ, LEV	CLB, GBP, LAC, PB, PER, PHT, ZON, TPM, VPA	Functional hemispherectomy
Epilepsy with myoclonic astatic seizures	3-5 yr	Variable	Variable	ESM, TPM, VPA, LEV, ZON	BZD, ketogenic diet, LTG, PER, steroids	No
Childhood absence epilepsy	5-6 yr	10-12 yr	Good	ESM, LTG, VPA	Acetazolamide, CZP, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12 yr	Variable	Guarded	ESM, VPA, CZP	ZON, LTG	No

Table 633.1 Classification of Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

SPECIFIC SYNDROMES	AGE RANGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
Lennox-Gastaut syndrome	3-10 yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BZD, FBM, IVIG, PER, steroids, ZON, ketogenic diet	Callosotomy
Landau-Kleffner syndrome	3-6 yr	8-12 yr	Guarded	Nocturnal DZP, steroids, VPA, LEV	CLB, ESM, IVIG, LTG, ketogenic diet	Multiple subpial transections, rarely lesionectomy
Epilepsy with continuous spike waves during slow-wave sleep	4-7 yr	8-12 yr	Guarded	Nocturnal DZP, steroids, VPA, LEV	CLB, ESM, IVIG, LTG, ketogenic diet	No
Other visual-sensitive epilepsies	2-5 yr	Unclear	Variable	VPA	BZD, LEV, LTG, ZON	No
Febrile seizures	3-5 yr	3-6 yr	Good	BZD (only as needed for febrile periods if frequent febrile seizures)	—	No
JUVENILE ONSET						
Juvenile absence epilepsy	10-12 yr	Usually lifelong	Good	ESM, LTG, VPA	Same as in childhood absence epilepsy	No
Juvenile myoclonic epilepsy	12-18 yr	Usually lifelong	Good	LEV, TPM, VPA	BZD, LTG, PB, PER, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18 yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BZD, CBZ, PER, ZON	No
Idiopathic photosensitive occipital lobe epilepsy	10-12 yr	Unclear	Variable	VPA, LEV	BZD, LTG, ZON	No
Progressive myoclonic epilepsies (e.g., Unverricht-Lundborg, Lafora, ceroid lipofuscinoses)	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON, LEV	BZD, PB, CLB, PER, ketogenic diet	No
VARIABLE AGE OF ONSET						
Mesial temporal lobe epilepsy defined by location and cause	Variable	Long-lasting	Variable	LEV, OXC, CBZ, TPM, VPA	PHT, PB, CLB, GBP, LAC, PER, ZON	Lesionectomy ± cortical resection
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long-lasting	Variable	LEV, OXC, CBZ, TPM, VPA	CLB, GBP, LAC, PB, PER, PHT, ZON	Temporal resection
Startle epilepsy	Variable	Long-lasting	Guarded	OXC, CBZ, LEV, TPM, VPA	CLB, LEV, PB, PHT, ZON, GBP	Lesionectomy ± cortical resection in some
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and early posttraumatic seizures	Variable	n/a		LEV, PHT	—	No

*Reflects current trends in practice, which may be off-label and may not be FDA-approved for that indication. Order of listing does not necessarily imply preference of use in that order. See Table 633.13 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types but has been FDA-approved as an adjunct therapy in patients 4 yr or older with medically refractory partial-onset seizures.

ACTH, Adrenocorticotropic hormone; BZD, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP, diazepam; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; PRM, primidone; QND, quinidine; RFD, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZON, zonisamide.

Modified from Guerrini R. Epilepsy in children. *Lancet*. 2006;367:499–524; and Parisi P, Verrotti A, Paolino MC, et al. "Electro-clinical syndromes" with onset in the pediatric age group: the highlights of the clinical-EEG, genetic, and therapeutic advances. *Ital J Pediatr*. 2011;37:58.

Table 633.2 Ion Channel Pathogenic Gene Variants and Associated Epilepsy Syndromes/Seizure Types

ION CHANNEL	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
SODIUM			
α Subunit	*SCN1A*	DS, GEFS+, GTCs	Infancy, childhood
	SCN2A	Benign familial neonatal-infantile epilepsy, sporadic infantile spasm, sporadic neonatal epileptic encephalopathy	Neonatal, infancy
	SCN3A	Cryptogenic focal epilepsy, focal unaware to bilateral GTC, GTC, myoclonic	Neonatal, infancy, childhood
	SCN8A	GTC, tonic, myoclonic	Neonatal, infancy
β Subunit	*SCN9A*	Febrile seizures, focal unaware, GTC	Childhood
	SCN1B	GEFS+	Childhood, adolescence, adulthood
POTASSIUM			
Voltage dependent	*KCNA2*	GTC, focal unaware, alternating hemiclonic seizures, absence, juvenile myoclonic epilepsy	Infancy, childhood
	KCNB1	GTC, focal unaware, infantile spasm, West syndrome, Lennox-Gastaut	Infancy, childhood
	KCND2	GTC, focal unaware	Infancy, adolescence
	KCNQ2	Benign familial neonatal seizures, tonic	Neonatal, infancy
	KCNQ5	Focal unaware, infantile spasm	Infancy, childhood
	KCNH1	Temple-Baraitser syndrome, GTC, focal unaware, myoclonic, tonic, clonic	Neonatal, infancy
	KCNH5	GTC, hemiclonic	Infancy
	KCNMA1	GTC	Childhood
Non–voltage dependent	*KCNT1*	MMFSI, ADNFLE	Infancy, childhood
	KCNJ10	EAST syndrome, idiopathic generalized epilepsies, childhood absence epilepsy	Infancy, childhood
CHLORIDE			
K^+/Cl^- co-transporter	*CLCN1*	Idiopathic generalized epilepsies	Infancy
	CLCN2	Idiopathic generalized epilepsies, childhood absence, juvenile absence, GTC, tonic	Infancy, childhood
	SLC12A5	Epileptic encephalopathy with focal migrating seizures, idiopathic generalized epilepsy, GTC, myoclonic, absence	Infancy
CALCIUM			
α Subunit	*CACNA1H*	Idiopathic generalized epilepsies	Infancy, childhood
	CACNA1A	Epileptic encephalopathy, absence	Infancy
β Subunit	*CNCNB4*	Myoclonic epilepsy, tonic, idiopathic generalized epilepsies	Infancy, childhood

ADNFLE, Autosomal dominant nocturnal frontal lobe epilepsy; EAST, epilepsy, ataxia, sensorineural deafness, and tubulopathy; GEFS+, genetic epilepsy with febrile seizures plus; GTCs, generalized tonic-clonic seizures; MMFSI, malignant migrating focal seizures of infancy.
Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin*. 2021;39:743–777, Table 1, p. 745–747.

Table 633.3 Defects in Neurotransmitter Receptors and Associated Epilepsy Syndromes/Seizure Types

RECEPTOR	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
GABA	*GABRA1*	Absence, idiopathic generalized epilepsy, epileptic encephalopathy, juvenile myoclonic epilepsy	Infancy, childhood, adolescence
	GABRB3	Childhood absence, epileptic encephalopathy	Neonatal, infancy, childhood
	GABRG2	Childhood absence, GEFS+, idiopathic generalized epilepsy, epileptic encephalopathies	Neonatal, infancy
	GABRE	Infantile spasm, focal unaware, focal unaware to bilateral GTC, GTC	Infancy
Nicotinic acetylcholine	*CHRNA4*	ADSHE	Childhood, adolescence
	CHRNB2	ADSHE	Childhood, adolescence
	CHRNA2	Benign infantile familial seizures	Infancy
Glutamate	*GRIN1*	Infantile spasm, tonic, atonic, hypermotor, focal dyscognitive, GTC	Neonatal, infancy, childhood
	GRIN2A	Childhood focal epilepsy, rolandic epilepsy, epileptic encephalopathy, absence, tonic, myoclonic	Infancy, childhood
	GRIN2B	West syndrome, childhood-onset focal epilepsy, epileptic encephalopathy	Infancy, childhood
	GRIN2D	Infantile spasm, focal unaware to bilateral GTC, GTC, myoclonic, atypical absence	Neonatal, infancy, childhood

ADSHE, Autosomal dominant sleep-related hypermotor epilepsy; GEFS+, genetic epilepsy with febrile seizures plus; GTC, generalized tonic-clonic seizure.
Modified from Martinez LA, Lai YV, Holder Jr. JL, Anderson AE. Genetics in epilepsy. *Neurol Clin*. 2021;39:743–777. Table 2, p. 748.

Table 633.4 Pathogenic Gene Variants of Synaptic Complexes and Associated Epilepsy Syndromes/Seizure Types

LOCATION	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
Presynaptic	*DNM-1*	Infantile spasms, absence with eyelid myoclonia, atonic, myoclonic, tonic, focal, GTCs	Neonatal, infancy
	NRXN1	Absence, GTCs, myoclonic	Childhood
	SNAP25	Infantile spasms, GTCs, focal, absence, myoclonic, tonic	Neonatal, infancy, childhood
	STX1B	GTC, partial, absence, tonic, atonic, Ohtahara syndrome, West syndrome	Infancy, childhood, adolescence
	SV2A	Myoclonic, tonic	Infancy
	TBC1D24	Myoclonic, GTC, partial, absence, infantile spasms	Neonatal, infancy, childhood
Postsynaptic	*CNTNAP2*	Focal, tonic	Infancy, childhood
	IQSEC2	Atypical absence, GTCs	Infancy, childhood
	PCDH19	GTC, tonic, absence, atonic, partial, myoclonic	Infancy
	SHANK3	GTC, partial, absence, tonic, myoclonic, atonic	Infancy, childhood
	SYNGAP1	GTC, atonic, absence with eyelid myoclonia, myoclonic	Childhood
	STXBP1	Infantile spasms, myoclonic, GTC, atonic, absence, partial	Neonatal, infancy

GTCs, Generalized tonic-clonic seizures.
Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin*. 2021;39:743–777, Table 3, p. 749.

Table 633.5 Defects in Intracellular Pathways/Organelles and Associated Epilepsy Syndromes/Seizure Types

	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
mTOR pathway	*TSC1, TSC2*	Tuberous sclerosis	Infancy, childhood, adolescence, adulthood
	MTOR	Focal cortical dysplasia	Variable age of onset
	RHEB	Focal cortical dysplasia	Variable age of onset
	DEPDC5	Focal cortical dysplasia	Neonatal, infancy, childhood
	NPRL2, NPRL3	Nocturnal frontal lobe epilepsy, frontal lobe epilepsy, temporal lobe epilepsy	Infancy, childhood
	AKT3	Infantile spasm	Infancy
Mitochondria	*POLG*	Alpers-Huttenlocher syndrome	Childhood
	MT-TK	Myoclonic epilepsy with red, ragged fibers	Childhood, adolescence, adulthood
	PDHA1	Infantile spasm, myoclonic absence, atypical absence, West syndrome, Lennox-Gastaut	Neonatal, infancy
	PDHB	Infantile spasm, myoclonic absence, atypical absence, West syndrome, Lennox-Gastaut	Neonatal, infancy
Lysosome	*SCARB2*	AMRF	Adolescence, adulthood
	CLN1–CLN8, CLN10–CLN14	Myoclonic epilepsy, atypical absence	Variable age of onset depending on specific *CLN* gene defect
	NEU1	Progressive myoclonic epilepsy, GTC	Adolescence, adulthood

AMRF, Action myoclonus–renal failure, progressive myoclonic epilepsy; mTOR, mechanistic target of rapamycin; PDHB, pyruvate dehydrogenase complex E1-beta.
Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin*. 2021;39:743–777, Table 4, p. 750.

Table 633.6 Metabolic Defects and Associated Epilepsy Syndromes/Seizure Types

	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
Pyridoxine	*ALDH7A1*	Focal, GTC, infantile spasm, myoclonic	Neonatal, infancy, childhood
	PNPO	GTC, tonic, clonic, myoclonic, focal	Neonatal
Biotin	*BTD*	GTC, myoclonic, infantile spasm, Ohtahara syndrome	Neonatal, infancy
Folic acid	*FOLR1*	Myoclonic-astatic, myoclonic, GTC	Childhood
Glycine	*GLDC*	Nonketotic hyperglycinemia	Neonatal
	AMT	Nonketotic hyperglycinemia	Neonatal
Glutamate	*SLC2A1*	Focal, absence, myoclonic-astatic	Infancy
Uridine	*CAD*	GTC, focal	Infancy

GTC, Generalized tonic-clonic seizures.
Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin*. 2021;39:743–777, Table 5, p. 751.

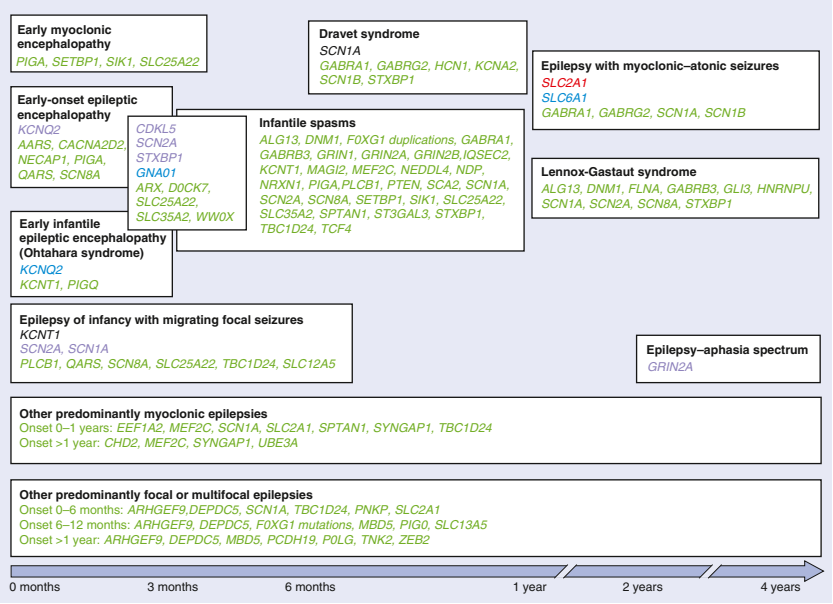

Fig. 633.3 Genetic causes, and proportion of cases caused by each gene, including only nonchromosomal, nonmalformative, and nonmetabolic disorders. Only genes with more than one case reported are included. *Black font* denotes genes that account for at least 50% of cases, *purple font* 10–50% of cases, and *red font* 5–10% of cases. *Blue font* denotes genes that account for less than 5% of cases, and *green font* denotes genes that account for an unknown percentage of cases. *(From McTague A, Howell KB, Cross JH, et al. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet. 2016;15:304–316.)*

Table 633.7 Diagnostic and Classification Scheme of Epilepsies

Level 1: Determine if the event was an epileptic seizure and, if so, characterize the seizure type or types based on available clinical information as focal, generalized, or unknown. (Refer to Fig. 633.1 for more detailed characterizations.)
Level 2: Determine the type of epilepsy the patient has (focal, generalized, focal and generalized, or unknown).
Level 3: Determine if the epilepsy fits into a particular epilepsy syndrome (refer to Table 633.2).
Level 4: Establish a unifying diagnosis that takes into account the epilepsy syndrome, underlying etiologies, and associated comorbidities.
The etiology for the epileptic seizures should be considered at **all** levels of an epilepsy diagnosis as listed earlier; etiologic categories include:
Genetic
Structural
Metabolic
Immune
Infectious
Unknown
Comorbidities should be considered at **all** levels of an epilepsy diagnosis. These can include developmental delay, psychiatric symptoms, behavioral issues, academic difficulties, movement abnormalities, and many others.

Modified from Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521.

the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an **aura** preceded the convulsion and the behavior the child was exhibiting immediately preceding the seizure. Auras can take the form of a number of sensations, including visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending on the precise localization of the origin of the seizures. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (more commonly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted. The provider taking the history should ask specifically about each of these symptoms as appropriate because caretakers may not spontaneously report them. Determination of focal versus generalized onset is sometimes difficult historically. A seizure may start focally and secondarily generalize too quickly to manifest observable early focal symptoms. In addition, a caregiver witnessing the seizure later in its evolution may describe only the more generalized-appearing signs.

In addition to clarifying the seizure semiology, a detailed history is crucial in identifying an underlying cause for the seizure. Reported personality changes or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Acute to subacute personality changes, psychiatric symptoms, and/or associated movement abnormalities may suggest an autoimmune etiology.

The examination of a child with a seizure disorder should also be geared toward the search for an organic cause. The child's head circumference, length, and weight are plotted on a growth chart and compared with previous measurements. A careful general and neurologic examination should be performed. A funduscopic exam should be performed to evaluate for the presence of papilledema, optic neuritis, retinal hemorrhages, uveitis, chorioretinitis, coloboma, or macular changes, as well as retinal phakoma. The finding of unusual facial features or of associated physical findings such as hepatosplenomegaly may point to storage disease or inborn error of metabolism as the cause of the neurologic disorder. The presence of a **neurocutaneous disorder** may be indicated by the presence of vitiliginous ash leaf–type lesions usually better seen using an ultraviolet light (Wood lamp); of adenoma sebaceum, shagreen patches, or retinal phakomas (tuberous sclerosis); of multiple café-au-lait spots (neurofibromatosis); or of V1- or V2-distribution nevus flammeus (Sturge-Weber syndrome) (see Chapter 636).

Localizing neurologic signs, such as a subtle **hemiparesis** with hyperreflexia, an equivocal or positive Babinski sign, and pronator drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thumbnail, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

In an acute setting such as the emergency department, the decision to pursue further laboratory testing, including serum electrolytes, a

complete blood count, and/or urine toxicology tests, should be made on a case-by-case basis that considers the patient's clinical history and examination. ECG to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see Chapter 634). A lumbar puncture is usually of limited value in an acute workup of a *nonfebrile* seizure unless the history or examination is concerning for an infectious or inflammatory process or if there is clinical concern for intracranial bleeding despite normal brain imaging. *A routine EEG should be performed in all cases of a first unprovoked nonfebrile seizure to help predict the risk of seizure recurrence.* If the patient's neurologic status has returned to baseline, the EEG can often be done on an outpatient basis even though the yield may be slightly lower because the EEG has been delayed beyond the first 12 hours. Emergent brain imaging with a head CT or brain MRI is usually performed if the seizure was focal, if there are postictal focal deficits on neurologic exam, or if the patient's status is not returning to baseline; in patients with trauma preceding the seizure; and in patients with a high-risk medical history. In other situations, the yield of emergent imaging identifying an abnormality that warrants emergent intervention is less than 1%. *Brain MRI is preferred over a CT scan, and performing it on a nonemergent basis should be considered in most patients.* CT is useful if a rapid study is needed to look for trauma, a mass, or signs of increased intracranial pressure. In select situations, such as when the clinical and EEG manifestations are consistent with a genetic generalized epilepsy such as childhood absence epilepsy, a brain MRI may not be necessary. Gadolinium (contrast) does not need to be routinely used when performing the brain MRI unless there is clinical suspicion of a neoplasm, vascular malformation, abscess, or another infectious or inflammatory process. Further details regarding the approach to a first seizure are included in Chapter 633.2. The 2021 guidelines from the American College of Radiology provide recommendations in different clinical scenarios (variants) for pediatric patients presenting with seizures while taking into consideration the patient's age, precipitating events, clinical findings, EEG, and neurodevelopmental status. These address neonatal seizures, simple and complex febrile seizures, posttraumatic seizures, focal seizures, and primary generalized seizures (Table 633.8).

Table 633. 8 American College of Radiology Panel Summary of Recommendations for Imaging After a Seizure

Variant 1: MRI head without IV contrast is usually appropriate for the initial imaging of neonatal seizures.
Variant 2: Imaging is usually not appropriate for the assessment of simple febrile seizures in children 6 months to 5 years of age.
Variant 3: MRI head without IV contrast may be appropriate for the initial imaging of children 6 months to 5 years of age with complex febrile seizures.
Variant 4: CT head without IV contrast or MRI head without IV contrast is usually appropriate for the initial imaging of children with posttraumatic seizures (not including abusive head trauma). These procedures are equivalent alternatives (i.e., only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
Variant 5: MRI head without IV contrast is usually appropriate for the initial imaging of a child with focal seizures (not including abusive head trauma). The panel did not agree on recommending MRI head without and with IV contrast for this clinical scenario. There is insufficient medical literature to conclude whether or not these patients would benefit from this procedure in this clinical setting. Imaging in this patient population is controversial but may be appropriate.
Variant 6: MRI head without IV contrast may be appropriate for the initial imaging of children with primary generalized seizure (neurologically normal).
Variant 7: MRI head without IV contrast is usually appropriate for the initial imaging of children with generalized seizure (neurologically abnormal).
Variant 8: MRI head without IV contrast is usually appropriate for children with intractable seizures or refractory epilepsy. The panel did not agree on recommending MRI head without and with IV contrast for children with intractable seizures or refractory epilepsy. There is insufficient medical literature to conclude whether or not these patients would benefit from administration of IV gadolinium contrast in this clinical setting.

Modified from Expert Panel on Pediatric Imaging, Trofimova A, Milla SS, Ryan ME, et al. ACR appropriateness criteria seizures-child. *J Am Coll Radiol.* 2021;18(55):S199–S210 (Summary of Expectations, p. S208-S209).

633.1 Febrile Seizures

Mohamad A. Mikati, Dmitry Tchapyjnikov, and Kevin M. Rathke

Febrile seizures are seizures that occur between the ages of 6 and 60 months of life (peak 12-18 months old) with a temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A **simple febrile seizure** is a primary generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum of 15 minutes, and not recurrent within a 24-hour period. A **complex febrile seizure** is more prolonged (>15 minutes), and/or is focal, and/or recurs within 24 hours. **Febrile status epilepticus** is a febrile seizure lasting longer than 30 minutes. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure. **Febrile infection–related** (or **refractory**) **epilepsy syndrome (FIRES)** is a very different disorder seen predominantly in older (>5 years of age) usually male children and associated with an encephalitis-like illness but without an identifiable infectious agent. Children with FIRES were previously normal but subsequently develop difficult-to-treat epilepsy.

Between 2% and 5% of neurologically healthy infants and children experience at least one, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are concerning to the parents. Complex febrile seizures may have an approximately twofold long-term increase in mortality rates as compared with the general population over the subsequent 2 years, probably secondary to a coexisting pathology. There are no long-term adverse effects of having one or more *simple* febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after two or more episodes, and in 50% of infants younger than 1 year of age at febrile seizure onset. Several factors affect the recurrence risk (Table 633.9). Although approximately 15% of children with epilepsy have had febrile seizures, only 5% (range 1–33%, dependent on risk factors) of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures (Table 633.10).

GENETIC AND OTHER FACTORS LEADING TO FEBRILE SEIZURES

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and many genes predisposing to it remain to be identified. Genes associated with febrile seizures include *SCN1A, SCN1B, SCN9A,* and *CPA6.* In terms of other etiologies, a dysregulation between the proinflammatory interleukin (IL)-1β, IL-6, and IL-8 cytokines and antiinflammatory ILR-1A cytokines has been associated with **febrile status epilepticus**. A decreased ILR-1A/IL-8 ratio (suggestive of an overall proinflammatory state) is predictive of hippocampal abnormalities on MRI done after febrile status epilepticus. The ILR-1A/IL-8 ratio may thus prove to be a potential biomarker for identifying febrile seizure patients who may be at higher risk for developing mesial temporal lobe epilepsy later in life.

Table 633.9 Risk Factors for Recurrence of Febrile Seizures*

MAJOR
Age <1 yr
Duration of fever <24 hr
Fever 38–39°C (100.4–102.2°F)
MINOR
Family history of febrile seizures
Family history of epilepsy
Complex febrile seizure
Daycare
Male gender
Lower serum sodium at time of presentation

*Having no risk factors carries a recurrence risk of approximately 12%; one risk factor, 25–50%; two risk factors, 50–59%; three or more risk factors, 73–100%.

Table 633.10 Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure*

RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (>15 min in duration or recurrent within 24 hr)	6%
Fever <1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

*Having more than one risk factor is at least in part additive.

Almost any type of epilepsy can be preceded by febrile seizures. A few epilepsy syndromes typically start with febrile seizures; these are **generalized epilepsy with febrile seizures plus** (GEFS+), **severe myoclonic epilepsy of infancy** (SMEI or **Dravet syndrome**), and, in many patients, temporal lobe epilepsy secondary to mesial temporal sclerosis. **GEFS+** is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood, and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic-clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity. A focal febrile seizure plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

Dravet syndrome is the most severe of the phenotypic spectrum of *febrile seizure–associated epilepsies*. It constitutes a distinct entity, the onset of which is in infancy. It is initially characterized by febrile and afebrile unilateral clonic seizures that recur every 1 or 2 months. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, more frequent, and focal and recur in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the second year of life, myoclonus, atypical absences, and focal seizures occur frequently, and developmental delay usually follows (Fig. 633.4). This syndrome is usually caused by a de novo pathogenic variant, although rarely it is inherited in an autosomal dominant manner or may be inherited from a nonaffected carrier parent. Variants in the *SCN1A* gene are the most common cause of Dravet syndrome (causing ~80% of all cases). The same gene is affected in the GEFS+ spectrum; however, in Dravet syndrome the variant leads to loss of function and thus to a more severe phenotype. There are several *milder variants* of Dravet syndrome that manifest some, but not all, of the previous features and that are referred to as **Dravet syndrome spectrum** or SMEI-Borderland. Rarely the *GABRG2, SCN1B,* and *SCN2A* genes may cause Dravet syndrome; however, in 10–20% of the cases a specific gene variant is not identified.

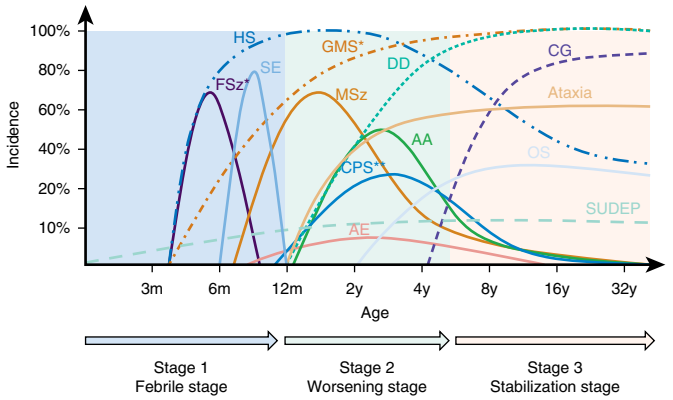

Fig. 633.4 Schematic representation of the varied clinical manifestations of Dravet syndrome and their relative incidence according to age. AA, Atypical absences; AE, acute encephalopathy; CG, crouching gait; CPS, complex partial seizures; DD, developmental delay; FSz, complex febrile seizures; GMS, generalized motor seizures; HS, hyperthermia sensitivity; MSz, myoclonic seizures; OS, obtundation status; SE, convulsive status epilepticus; Ataxia; SUDEP, sudden unexpected death in epilepsy. *Moderate fever for 60%; mostly clonic generalized and unilateral motor seizures. **Difficult distinction between atypical absences and complex partial seizures without ictal EEG recording, so their precise incidence is unknown; including generalized tonic-clonic and unilateral seizures. However, unilateral seizures are less frequent after the age of 7 yr, whereas sleep seizures increase after 6-7 yr and become predominant after age of 9-10 yr. *(From Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. Seizure. 2017;44:58–64, Fig. 1, p. 59.)*

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from vaccine encephalopathy (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome pathogenic gene variants, indicating that their disease is caused by the variant and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed *vaccine encephalopathy.*

EVALUATION

Figure 633.5 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media; roseola and human herpesvirus (HHV) 6 infections; and infections with norovirus, parechovirus, enteroviruses, *Shigella,* or similar agents, making the evaluation more demanding. In patients with febrile status epilepticus, HHV-6B (more frequently) and HHV-7 infections may account for 30% of the cases.

Lumbar Puncture

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 months of age who present with fever and seizure, if the child is ill-appearing, or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6-12 months of age who is deficient in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* immunizations or for whom the immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. In uninfected patients presenting with febrile status epilepticus, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in

the CSF) with a concurrently normal CSF protein and glucose. Pleocytosis suggests bacterial or viral infection.

Electroencephalogram

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 years, and these do not predict later epilepsy. EEGs performed within 2 weeks of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 weeks have passed. An EEG should therefore generally be restricted to special cases in which epilepsy is highly suspected (see Table 633.10), and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 minutes in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, an EEG can help distinguish between ongoing seizure activity and a prolonged postictal state. After febrile status epilepticus, focal EEG slowing over the temporal lobe increases the chance that the patient may have medial temporal sclerosis on follow-up.

Blood Studies

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and a complete blood count) are not routinely recommended in the workup of a child with a first simple febrile seizure. Blood glucose should be measured initially and with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in the physical examination. If clinically indicated (e.g., dehydration), these tests should be performed. A low sodium level is associated with a higher risk of recurrence of the febrile seizure within the following 24 hours.

Neuroimaging

A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The workup of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 10% of children with febrile status epilepticus are reported to have unilateral or, less frequently, bilateral swelling of their hippocampus acutely; subsequent long-term hippocampal atrophy is evident in about 71% of those who had the acute findings. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

TREATMENT

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with one or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 minutes, acute treatment with lorazepam, midazolam, or diazepam is needed (see Chapter 633.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to families to be used at home as a rescue medication if a febrile seizure lasts longer than 5 minutes (see Table 633.14 for dosing). Alternatively, buccal or intranasal midazolam or diazepam may be used. In cases of frequently recurring febrile seizures, intermittent oral clonazepam (0.01 mg/kg every 8-12 hours up to a maximum dose of 1.5 mg/day) or oral diazepam (0.33 mg/kg every 8 hours) can be given during febrile illnesses. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Historically, continuous therapy with the antiepileptic drugs (AEDs) phenobarbital or valproic acid was occasionally used to prevent febrile seizures. However, in the vast majority of cases, use of continuous therapy is not justified because of the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.

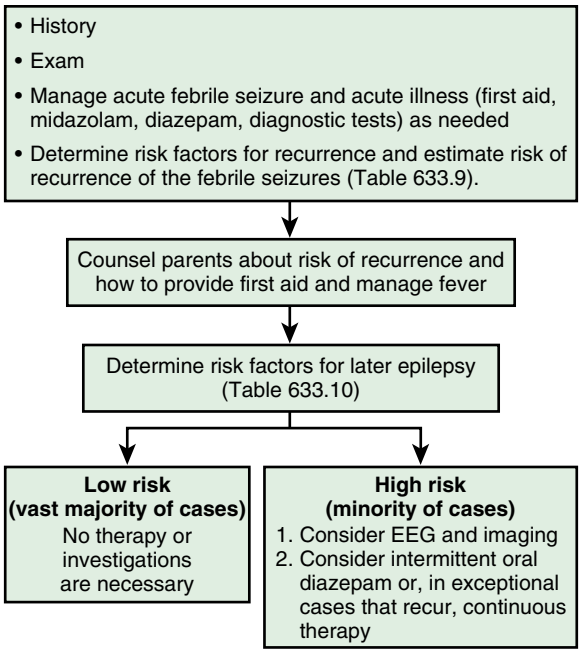

Fig. 633.5 Treatment algorithm for the management of febrile seizures. *(Modified from Mikati MA, Rahi A. Febrile seizures: from molecular biology to clinical practice. Neurosciences [Riyadh]. 2004;10:14–22.)*

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. The possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appear appropriate. A recent Delphi-type European study generated specific recommendations for providers to deliver to caretakers after a febrile seizure (reference provided later). These included the definition of febrile seizures, basis of this clinical diagnosis, acknowledging parental stress, risk of recurrence, and long-term care of the child, which also should include that the parents should avoid cosleeping, which is dangerous for their child and does not prevent febrile seizures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.2 Unprovoked Seizures

Mohamad A. Mikati, Dmitry Tchapyjnikov, and Kevin M. Rathke

HISTORY AND EXAMINATION

Evaluation of a first-time seizure was discussed earlier in this chapter. It entails stabilization of the patient if the child presents during or shortly after the seizure. A careful history and examination are done to accurately characterize the seizure, exclude acute intervenable causes, and attempt to determine the underlying etiology of the seizure.

DIFFERENTIAL DIAGNOSIS

This involves consideration of nonepileptic paroxysmal events (see Chapter 634), determination of the seizure type as classified by the ILAE system (see Fig. 633.1), and consideration of potential underlying etiologies. Some seizures might begin with **auras**, which are sensory experiences reported by the patient and are not observed externally.

Motor seizures can be **tonic**, **clonic**, **myoclonic**, **atonic**, or **astatic**. **Astatic** seizures often follow myoclonic seizures and cause a momentary loss of tone with a sudden fall. **Atonic** seizures, on the other hand, are usually longer, and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atonic, or astatic seizures based on the history alone when the family reports only that the patient falls; in such cases, the seizure may be described as a **drop attack**. Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a **head drop**. Tonic, clonic, tonic-clonic, myoclonic, and atonic seizures can be focal (including one limb or one side only), focal with secondary generalization, or primary generalized. Epileptic spasms, or **axial spasms** (these terms being preferred over infantile spasms because the spasms can occur beyond infancy), consist of flexion or extension of the truncal and extremity musculature that is sustained for 1-2 seconds, shorter than the duration seen in tonic seizures, which last longer than 2 seconds. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed **epilepsia partialis continua**.

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for a few seconds. **Typical absences** are associated with 3-Hz spike–and–slow-wave discharges and with childhood absence epilepsy, which has a good prognosis. **Atypical absences** are associated with 1- to 2-Hz spike–and–slow-wave discharges and with head atonia and myoclonus during the seizures. They occur in **Lennox-Gastaut syndrome** and similar syndromes, which have a poor prognosis. **Juvenile absences** are similar to typical absences but are associated with 4- to 5-Hz spike–and–slow-wave discharges and often occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of **epilepsy syndrome** with which a particular patient is afflicted (see Tables 633.1-633.6; see also Chapters 633.3 and 633.4).

A family history of certain forms of epilepsy, such as benign familial neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Specific findings on physical exam may point to an underlying disorder causing the seizure, such as tuberous sclerosis, Sturge-Weber syndrome, neurofibromatosis, or other brain malformations.

LONG-TERM APPROACH TO THE PATIENT AND ADDITIONAL TESTING

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in Table 633.7. Most epilepsy syndromes are potentially caused by any one of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see Tables 633.1-633.6 and Fig. 633.3). Different pathogenic variants of the same gene can result in different epilepsy syndromes, whereas variants of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy is indicated in patients manifesting specific underlying malformational, metabolic, or degenerative disorders; patients with severe epilepsy syndromes (such as West and Dravet syndromes and progressive myoclonic epilepsies); and patients with syndromes of mendelian inheritance (see Tables 633.1 and 633.6). Gene testing is indicated in epilepsy encephalopathy syndromes and in patients with other organ involvement (hepatic, muscle, cardiac, intestinal) and in atypical phenotypes.

In patients with drug-resistant epilepsy or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic workup, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very long-chain fatty acids, ammonia, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).
3. Serum immune isoelectric focusing (or gene panels) is performed for carbohydrate-deficient transferrin in disorders of glycosylation.

CSF glucose testing looks for glucose transporter deficiency, and the CSF can be examined for cells and proteins (for parainfectious and postinfectious syndromes and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).

4. Other laboratory studies include CSF immunoglobulin (Ig) G index, NMDA receptor, and other autoimmune encephalitis–associated antibodies, as well as measles titers in serum and CSF.
5. CSF tests can also confirm, with the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal-5-phosphate dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies.

In infants who do not respond immediately to antiepileptic therapy, vitamin B_6 (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a preadministration baseline recording period. Before the vitamin B_6 trial, a pipecolic acid level and serum, urine, or CSF α-aminoadipic acid semialdehyde levels should be drawn because they are often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Patients with cerebral folate deficiency can also have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg/day given every 6 hours) and folinic acid (2.5-5 mg twice a day, if needed; can titrate up to a maximum dose of 8 mg/kg/day) over several weeks can help diagnose these rare disorders while one is waiting for the definitive diagnosis from CSF or genetic testing. Certain EEG changes such as continuous spike–and–slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.

6. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy can be performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.
7. Gene testing looks for specific disorders that can manifest with seizures, including *SCN1A* pathogenic variants in Dravet syndrome; *ARX* gene for West syndrome in males; *MECP2, CDKL5,* and protocadherin 19 for Rett syndrome and similar presentations; syntaxin-binding protein for Ohtahara syndrome; and polymerase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.
8. Muscle biopsy can be performed for mitochondrial DNA and oxidative enzymes as well as coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease.
9. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole exome or genome sequencing is also available. The availability of gene panels, particularly ones that can test for amenably treatable conditions such as vitamin B_6–dependent epilepsy, and the rapid turnaround time have replaced the need for many of the tests listed in points 1-9.
10. MRI should also be performed to identify congenital disorders (cortical dysplasias, lissencephaly, schizencephaly), calcifications, focal lesions (basal ganglia), and myelinization disorders (acute disseminated encephalomyelitis [ADEM], leukodystrophies). MRI may identify specific disorders such as posterior reversible encephalopathy syndrome (PRES), stroke (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes [MELAS]), Rasmussen encephalitis, tumors, cerebral edema, hemorrhage, or venous thrombosis (see Table 633.8). It should also be noted that seizures alone may cause nonspecific-nondiagnostic transient MRI abnormalities; these may include transient gray matter and subcortical white matter signals or transient hippocampal and temporal lobe abnormalities.

Most patients do not require an extensive evaluation. The pace and extent of the workup must depend on the clinical epileptic and nonepileptic features, the family and antecedent personal history of the patient, the medication responsiveness of the seizures, the likelihood of identifying a treatable condition, and the wishes and need of the family to assign a specific diagnosis to the child's illness.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.3 Focal Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Dmitry Tchapyjnikov

Focal seizures account for approximately 40% of seizures in children and can be divided into **focal seizures with preserved awareness**, in which consciousness is not impaired, and **focal seizures with impaired awareness**, in which consciousness is affected.

Focal seizures with preserved or impaired awareness can each occur in isolation, one can temporally lead to the other (usually from preserved to impaired awareness), and/or each can progress into secondary generalized seizures, called **focal to bilateral tonic-clonic seizures**, although less commonly, the secondary generalized seizure may also be tonic, clonic, or atonic.

FOCAL SEIZURES WITH PRESERVED AWARENESS

These can take the form of sensory seizures (auras, called *focal aware seizures*) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (Jacksonian) march from face to arm to leg, adversive head and eye movements to the contralateral side, or postictal **(Todd) paralysis** that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and are less likely than tics to manifest different types in a given patient.

FOCAL SEIZURES WITH IMPAIRED AWARENESS

These seizures usually last 1-2 minutes and are often preceded by an **aura**, such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 years old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. **Automatisms** are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking, or bicycling movements). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.

FOCAL TO BILATERAL TONIC-CLONIC SEIZURES

These can either start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus) or as focal seizures with subsequent clinical generalization. There is often adversive eye and head deviation to the side contralateral to the side of the seizure focus, followed by generalized tonic, clonic, or tonic-clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 minutes. Focal tonic or focal to bilateral tonic-clonic seizures often manifest as adversive head deviation to the contralateral side, fencing, hemi- or full figure-of-four arm, and/or Statue of Liberty postures. These postures usually suggest a frontal origin and, when awareness is preserved during them, favor that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A *sleep-deprived* EEG with recording during sleep increases the diagnostic yield and is advisable in all patients (Fig. 633.6). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hour video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough because it then can allow visualization of the clinical events and the corresponding EEG tracing.

Brain imaging is critical in patients with focal seizures. MRI is preferable to CT, which misses subtle but, occasionally, potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 633.7). Of note is that patients with focal seizures and epilepsies can have focal corresponding neuropsychologic deficits but also have patterns of network-related deficits such as impaired social cognition, deficits that are shared with generalized epilepsies.

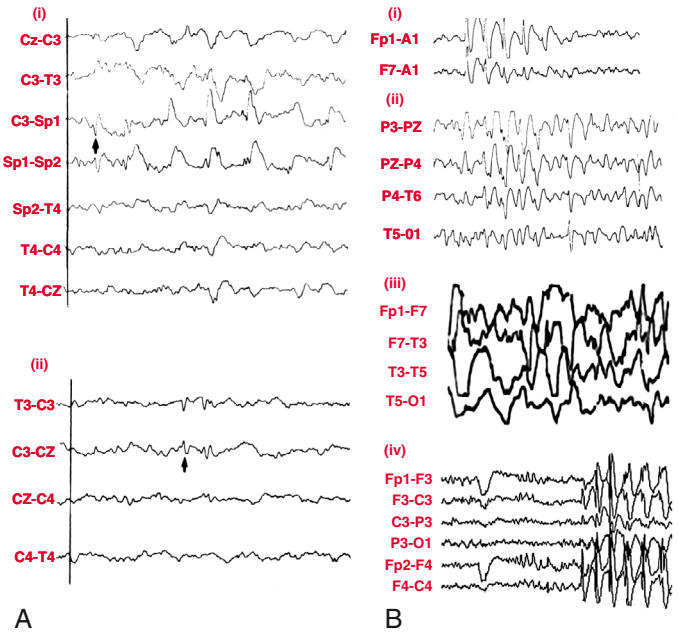

Fig. 633.6 A, Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe *(arrow)* in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes *(arrow)* characteristic of benign partial epilepsy with centrotemporal spikes. B, Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypsarrhythmia with irregular multifocal high-voltage spike-and-wave activity with a chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.

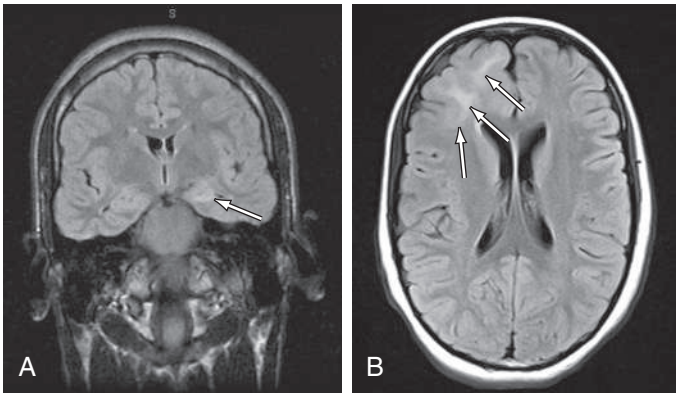

Fig. 633.7 A, Coronal fluid-attenuated inversion-recovery (FLAIR) MRI scan of a 13-yr-old with intractable seizures and mesial temporal sclerosis (MTS). The *arrow* points at the hippocampus with the high-intensity signal characteristic of MTS. B, Axial FLAIR MRI of a 7-yr-old with intractable seizures and right frontal cortical dysplasia. The *arrows* point at the high-intensity signal corresponding to the dysplasia. (*A from Lee JYK, Adelson PD. Neurosurgical management of pediatric epilepsy. Pediatr Clin North Am. 2004;51:441–456.*)

These observations support current thinking that not only generalized but also focal epilepsy involves network-related pathophysiology.

BENIGN EPILEPSY SYNDROMES WITH FOCAL SEIZURES

The most common such syndrome is **benign childhood epilepsy with centrotemporal spikes (BECTS)**, which typically starts during childhood (ages 3-10 years) and is outgrown by adolescence. The child typically wakes up at night because of a focal seizure with preserved awareness causing buccal and throat tingling and tonic or clonic contractions of one side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Focal seizures with impaired awareness and secondary generalized seizures can also occur. EEG shows typical wide-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to AEDs such as oxcarbazepine and carbamazepine. In some patients who only have rare and mild seizures, treatment might not be needed. Traditionally patients with BECTS are considered to have normal neurocognitive development, but some studies have documented problems in memory and in other neuropsychologic functions and in attention. **Atypical BECTS** is a less common variant of the disorder characterized by often a younger age of onset, multiple seizure types including drop attacks, atypical EEG patterns including secondary bilateral synchrony, and/or other comorbidities such as developmental delay.

Benign epilepsy with occipital spikes can occur in early childhood **(Panayiotopoulos type)** and manifests with focal seizures with impaired awareness and with ictal vomiting; they may also first appear in later childhood **(Gastaut type)** as focal seizures with impaired awareness, visual auras, and migraine headaches that occur independently or postictally (epilepsy-migraine sequence). Both are typically outgrown in a few years.

In infants, several less common **benign infantile familial convulsion syndromes** have been reported. For some of these, the corresponding gene variant and its function are known (see Table 633.1), including **benign familial neonatal seizures** *(KCNQ2, KCNQ3)*, **benign familial neonatal infantile seizures** *(SCN2A)*, and **early familial neonatal infantile seizures** (*SCN2A*).

A number of **benign infantile nonfamilial syndromes** have been reported, including focal seizures with impaired awareness with temporal foci, focal to bilateral tonic-clonic seizures with variable foci, tonic seizures with midline foci, and focal seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly; often, only short-term therapy (e.g., 6 months), if any therapy, is needed. **Nocturnal autosomal dominant frontal lobe epilepsy** has been linked to acetylcholine-receptor and to *KCNT1* pathogenic variants. It manifests with nocturnal seizures with dystonic posturing, agitation, screaming, and kicking that respond promptly to carbamazepine. Several other less frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults.

SEVERE EPILEPSY SYNDROMES WITH FOCAL SEIZURES

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than genetic (idiopathic) epilepsy. Many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, *drug-resistant epilepsy* with focal seizures is often caused by severe metabolic problems, hypoxic-ischemic injury, or congenital malformations. In addition, in this age-group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called **epilepsy of infancy with migrating focal seizures** (EIMFS; previously called *malignant migrating partial seizures of infancy*) has been described. Some cases of EIMFS are secondary to pathogenic variants in the calcium-sensitive potassium channel *KCNT1*. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber cutaneous lesion, tuberous sclerosis, and congenital tumors such as ganglioglioma and dysembryoplastic neuroepithelial tumors and others. The intractable seizures can be focal seizures with or without impaired awareness, focal to bilateral tonic-clonic seizures, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut syndrome and has been termed by some as **pseudo–Lennox-Gastaut syndrome**.

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is **mesial** (also termed **medial**) **temporal sclerosis**, a condition often preceded by febrile seizures. They are rarely genetic in origin. Pathologically, these patients have atrophy, gliosis, or cortical dysplasia of the hippocampus and, in some these conditions, of the amygdala. Some patients with mesial temporal sclerosis have pathogenic variants in *SUCO*. Medial temporal lobe epilepsy is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other structural or genetic focal or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia **(Landau-Kleffner epileptic aphasia syndrome)**. Activation of secondary generalized and at times focal discharges in sleep leads to more global delay secondary to the **syndrome of continuous spike waves in slow-wave sleep** (>85% of the slow-wave sleep recording is dominated by discharges).

The syndrome of **Rasmussen encephalitis** is a form of chronic encephalitis that manifests with *unilateral* intractable partial seizures, epilepsia partialis continua, and progressive hemiparesis of the affected side, with progressive atrophy of the involved hemisphere. The etiology is usually unknown, although autoimmune etiologies have been hypothesized.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.4 Generalized Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Dmitry Tchapyjnikov

ABSENCE SEIZURES

Typical absence seizures usually start at 5-8 years of age and are often, because of their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike focal seizures with impaired awareness, they *do not* have an aura, usually last

for only a few seconds, and are sometimes accompanied by eyelid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms seen in focal seizures with impaired awareness (absence seizures can have simple automatisms such as lip smacking or picking at clothing, and the head can very minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3-5 minutes can precipitate the seizures and the accompanying 3-Hz spike–and–slow-wave discharges. The presence of eye closure eyelid myoclonia **(Jeavons syndrome)** and periorbital, perioral, or limb myoclonic jerks (the latter called **myoclonic absences**) with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early-onset absence seizures (<4 years of age) or drug resistance should trigger evaluation for a glucose transporter defect, which is often associated with low CSF glucose levels and an abnormal sequencing test of the *SLC2A1* transporter gene.

Atypical absence seizures have associated myoclonic components and tone changes of the head (head drop) and body, usually last longer than typical absence seizures, and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1- to 2-Hz spike–and–slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4- to 6-Hz spike–and–slow-wave and polyspike–and–slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see "Benign Generalized Epilepsies").

GENERALIZED MOTOR SEIZURES

The most common generalized motor seizures are generalized tonic-clonic seizures that can be either primarily generalized (bilateral) or focal to bilateral tonic-clonic (as described in Chapter 633.3) from a unilateral focus. If there is no partial component, the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops, usually 1-2 minutes later. Incontinence and a postictal period often follow. The latter usually lasts for a few minutes up to several hours with semicoma or obtundation and postictal sleepiness, weakness, ataxia, hyperreflexia or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if necessary, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner's finger). Many patients have single **genetic generalized tonic-clonic seizures** that may be associated with a concurrent illness or with a cause that cannot be ascertained (see Chapter 633.2). Generalized tonic, atonic, and astatic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see "Benign Generalized Epilepsies" and "Severe Generalized Epilepsies").

BENIGN GENERALIZED EPILEPSIES

Childhood absence epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic-clonic seizures, half before and half after the onset of absences. **Benign myoclonic epilepsy of infancy** consists of the onset of myoclonic and other seizures during the first year of life, with generalized 3-Hz spike–and–slow-wave discharges. Often, it is initially difficult to distinguish this type from more severe syndromes, but follow-up clarifies the diagnosis. **GEFS+** manifests as febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see Chapter 633.1).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to pathogenic variants in many genes, including *CACNB4; CLNC2; EJM2, 3, 4, 5, 6, 7, 9; GABRA1; GABRD;* and *myoclonin1/EFHC1*. Typically, it starts in early adolescence with one or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic-clonic or clonic-tonic-clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4- to 5-Hz polyspike–and–slow-wave discharges.

There are other forms of generalized epilepsies such as **photoparoxysmal epilepsy**, in which generalized tonic-clonic, absence, or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels, and viewing video games. Other forms of **reflex** (i.e., **stimulus-provoked**) **epilepsy** can occur; associated seizures are usually generalized, although some may be focal (see Chapter 633.9).

SEVERE GENERALIZED EPILEPSIES

Severe generalized epilepsies are associated with intractable seizures *and* developmental delay. **Early myoclonic encephalopathy (EME)** starts during the first 2 months of life with severe myoclonic seizures and a burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as nonketotic hyperglycinemia. **Early infantile epileptic encephalopathy (Ohtahara syndrome)** has a similar age of onset and EEG but manifests as tonic seizures and is usually caused by brain malformations or various epileptogenic gene mutations. The term *early infantile epileptic encephalopathy* (EIEE) has also been applied to the increasing number (~36) of other genetic epileptic encephalopathies and developmental epileptic encephalopathies that are associated with an increasing number of specific genes with pathogenic variants (Table 633.11); these may or may not manifest as Ohtahara syndrome, but all share the characteristic of early-onset epileptic encephalopathy. For example, EIEE type 4 is Ohtahara syndrome caused by syntaxin-binding protein 1 pathogenic variants. **Severe myoclonic epilepsy of infancy (Dravet syndrome)**, most often caused by pathogenic variants in *SCN1A,* starts as focal febrile status epilepticus or focal febrile seizures and later manifests as myoclonic and other seizure types (see Chapter 633.1).

West syndrome starts between the ages of 2 and 12 months and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called **hypsarrhythmia** (see Fig. 633.6). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with *cryptogenic/idiopathic* (referred to as *unknown etiology*) West syndrome have normal development before onset, whereas patients with *symptomatic* West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, infections like with congenital Zika virus, or other etiologies (see Chapter 633.2). In males, West syndrome can also be caused by *ARX* gene variants (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases where the etiology is unknown (i.e., cases that are not explained by the presence of a gene variant or a structural brain anomaly), is a medical emergency because a delay in diagnosis of 3 weeks or longer can affect the long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or other benign paroxysmal syndromes (see Chapter 634).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 years and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, and myoclonic, astatic, and tonic seizures, as well as specific EEG abnormalities. The tonic and/or atonic seizures occur either in wakefulness (causing falls and injuries, broadly termed **drop attacks**) or also, typically, in sleep. The third component is the EEG findings (see Fig. 633.6): 1- to 2-Hz spike and slow waves, polyspike bursts in sleep (also *called generalized*

Table 633.11 Early Infantile Epileptic Encephalopathy (EIEE)

GENE	PROTEIN
ARX (EIEE1)	Aristaless-related homeobox
CDKL5 (EIEE2)	Cyclin-dependent kinase-like 5
SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
STXBP1 (EIEE4)	Syntaxin-binding protein 1
SPTAN1 (EIEE5)	α_2-Spectrin
SCN1A (EIEE6)	Sodium-channel protein type 1α
KCNQ2 (EIEE7)	Potassium voltage-gated channel
ARHGEF9 (EIEE8)	Rho guanine nucleotide exchange factor 9
PDCH19 (EIEE9)	Protocadherin-19
PNKP (EIEE10)	Bifunctional polynucleotide phosphatase/kinase
SCN2A (EIEE11)	Sodium-channel protein type 2α
PLCβ1 (EIEE12)	Phospholipase C β1
SCN8A (EIEE13)	Sodium-channel, voltage-gated, type VIII, alpha subunit
KCNT1 (EIEE14)	Potassium-channel subfamily T, member 1
ST3GAL3 (EIEE15)	ST3 beta-galactoside alpha-2,3-sialyltransferase 3
TBC1D24 (EIEE16)	TBC1 domain family, member 24
GNAO1 (EIEE17)	Guanine nucleotide-binding protein G(o) subunit alpha
SZT2 (EIEE18)	Seizure threshold 2 homolog
GABRA1 (EIEE19)	Gamma-aminobutyric acid receptor subunit alpha-1
PIGA (EIEE20)	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
NECAP1 (EIEE21)	Adaptin ear-binding coat-associated protein 2
SLC35A2 (EIEE22)	UDP-galactose translocator
DOCK7 (EIEE23)	Dedicator of cytokinesis 7
HCN1 (EIEE24)	Potassium/sodium hyperpolarization–activated cyclic nucleotide-gated channel 1
SLC13A5 (EIEE25)	Solute carrier family 13 (sodium-dependent citrate transporter), member 5
KCNB1 (EIEE26)	Potassium voltage-gated channel, Shab-related subfamily, member 1
GRIN2B (EIEE27)	NMDA receptor subtype 2B
WWOX (EIEE28)	WW domain–containing oxidoreductase
AARS (EIEE29)	Alanyl-tRNA synthetase
SIK1 (EIEE30)	Salt inducible kinase 1
DNM1 (EIEE31)	Dynamin-1
KCNA2 (EIEE32)	Potassium voltage-gated channel subfamily A member 2
EEF1A2 (EIEE33)	Elongation factor 1-alpha 2
SLC12A5 (EIEE34)	Potassium–chloride transporter member 5
ITPA (EIEE35)	Inosine triphosphate pyrophosphatase
ALG13 (EIEE36)	Asparagine-linked glycosylation 13 homolog

paroxysmal fast activity or GPFA), and a slow background in wakefulness. Most patients are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. **Myoclonic astatic epilepsy (Doose syndrome)** is a syndrome similar to, but milder than, Lennox-Gastaut syndrome and is characterized by seizures consisting of myoclonic jerking rapidly followed by an atonic (astatic) drop attack. Patients with Doose syndrome usually do not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by atonic seizures causing head nodding as well as tonic, clonic, and stimulus-sensitive seizures is **nodding syndrome**, which is seen in some African countries and is often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is a likely autoimmune reaction to the parasitic worm *Onchocerca volvulus.* The head nodding is associated with generalized slow waves and electrodecrement, likely representing generalized ictal activity, but is commonly resistant to drug therapy.

Progressive myoclonic epilepsies (EPM) are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. **Type I**, or **Unverricht-Lundborg disease**, is caused by pathogenic variants in the *CSTB* gene, is more slowly progressive than the other types, and usually starts in adolescence. **Type II**, or **Lafora body disease**, can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the second or third decade of life. It can be associated with photosensitivity, manifests periodic acid–Schiff–positive Lafora inclusions on muscle or skin biopsy (in eccrine sweat gland cells), and has been shown to be caused by laforin *(EPM2A)* or malin *(EPM2B)* gene variants and possibly *PRDM8* in 90% of patients. Other causes of progressive myoclonic epilepsy include **myoclonic epilepsy with ragged red fibers** (**MERRF**, caused by various pathogenic variants in mitochondrial DNA), **sialidosis type I** (caused by variants in *NEU1*), **neuronal ceroid lipofuscinoses** (lysosomal storage disorders caused by variants in *CLN1-CLN14*), **type 3 neuronopathic Gaucher disease** (caused by lysosomal glucocerebrosidase deficiency), **dentatorubral-pallidoluysian atrophy** (caused by unstable expansion of trinucleotide repeats on the *ATN1* gene), **action myoclonus–renal failure syndrome** (aka *EPM4,* caused by variants in *SCARB2*), **progressive myoclonus epilepsy–ataxia syndrome** (aka *EPM5,* caused by variants in *PRICKLE1*), and **North Sea progressive myoclonic epilepsy** (aka *EPM6,* caused by variants in *GOSR2*).

Myoclonic encephalopathy in nonprogressive disorders is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

Landau-Kleffner syndrome is a rare condition of presumed autoimmune but sometimes also of genetic (*GRIN2A* variants) etiology. It is characterized by loss of language skills and by verbal auditory agnosia in a previously normal child; ~70% have associated clinical seizures. The seizures, when they occur, are of several types, including focal with preserved awareness, focal to bilateral tonic-clonic, atypical absence, focal with impaired awareness, and occasionally myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non–rapid eye movement sleep; a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome called **epileptic encephalopathy with continuous spike waves in slow-wave sleep (CSWS)**, the discharges occur in >85% of the slow-wave sleep, a finding termed **electrical status epilepticus in sleep (ESES)**. ESES can also occur in Landau-Kleffner syndrome, but in CSWS the discharges are usually frontal or generalized and the delays usually global. The approach to and therapy for the two syndromes are similar. Although valproic acid and benzodiazepines are often used first, the evidence favors that they address the seizures and that steroids and possibly nocturnal diazepam are the more effective agents for the aphasia. Some children respond to the combination of valproic acid and clobazam or to levetiracetam. Nocturnal diazepam (0.2-0.5 mg/kg orally at bedtime for several months) is often used as first- or second-line therapy, as are steroids used either

orally (more commonly studied) or intravenously. Oral prednisone is started at 2 mg/kg/day for 1-2 months, then weaned over a period of 1-3 months. Alternatively, monthly infusions of high-dose intravenous methylprednisolone have been used instead of oral steroids. Long-term therapy is often needed irrespective of which drug(s) elicit a patient response. If the seizures and aphasia persist after diazepam and steroid trials, then a course of IVIGs should be considered because many patients can respond to that. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

Amenably treatable metabolic epilepsies are well recognized (see Table 633.6). **Pyridoxine-dependent epilepsy** typically presents with a neonatal or infantile (and rarely childhood) onset of encephalopathy with, at times, reports of increased fetal movements (seizures) in utero. There are recurrent focal motor seizures, generalized tonic seizures, and myoclonus. Seizures progress to status epilepticus if no pyridoxine is used. Diagnosis is confirmed by the presence of elevated plasma, urine, and CSF α-aminoadipic semialdehyde and elevated plasma and CSF pipecolic acid levels. The presence of either homozygous or compound heterozygous pathogenic variants in *ALDH7A1* (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (higher doses, up to 500-600 mg/day, have been used) or intravenously helps stop the seizures. Variants of *PROSC* can also cause pyridoxine-dependent epilepsy. **Pyridoxal phosphate–responsive neonatal epileptic encephalopathy** (pyridox[am]ine 5′-phosphate oxidase [PNPO] deficiency) may present similarly in the absence of gastrointestinal symptoms sometimes seen with pyridoxine-dependent epilepsy. Diagnostically, there are reduced pyridoxal phosphate levels in the CSF with increased levels of CSF levodopa and 3-methoxytyrosine, along with decreased CSF homovanillic acid and 5-hydroxyindoleacetic acid. The EEG may show a burst suppression pattern. Treatment is by enteral administration of pyridoxal phosphate (up to 50 mg/kg/day every 6 hours). **Folinic acid–responsive seizures** may also present with neonatal or infantile epileptic encephalopathy and intractable seizures. Some of these patients have a diagnostic profile similar to that of pyridoxine-dependent epilepsy patients, and their disorder is caused by the same gene variants but responds to folinic acid supplementation in addition to pyridoxine. **Cerebral folate deficiency**, which also responds to high doses of folinic acid (1-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinesias, and autism. CSF 5-methyltetrahydrofolate levels are decreased, with normal plasma and red blood cell folate levels. There are usually pathogenic variants in the folate receptor *(FOLR1)* gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. **Tetrahydrobiopterin deficiencies** with or without hyperphenylalaninemia may present with epilepsies and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes), and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. **Creatine deficiency syndromes** present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by gene sequencing and abnormal levels of urine creatine and guanidinoacetic acid and/or, particularly in the case of creatine transporter deficiency, an absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions is helpful. **Biotinidase deficiency** presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and an organic acid profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine. **Developmental delay**, **epilepsy**, and **neonatal diabetes** are caused by activating pathogenic variants in the adenosine triphosphate–sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the CNS symptoms and affect seizures. **Hyperinsulinism-hyperammonemia syndrome** is caused by activating variants of the glutamate dehydrogenase encoded by *GLUD1*. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 μmol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). **GLUT-1 deficiency syndrome** (caused by pathogenic variants in *SLC2A1,* which encodes for a glucose transporter) classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain that is typically diagnosed by genetic testing or a finding of low CSF lactate and CSF glucose or low CSF–to–serum glucose ratios (<0.4). The manifestations of the disease are usually responsive to the ketogenic diet. **Thiamine transporter variants with acute basal ganglia disease** often presents with accompanying seizures and is responsive to biotin and thiamine supplementation. **Riboflavin transporter deficiency** can also manifest as a seizure in addition to the usual symptoms of neuromuscular (polyneuropathy) weakness; it is treated with high-dose riboflavin supplementation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.5 Mechanisms of Seizures

Mohamad A. Mikati, Muhammad S. Zafar, and Dmitry Tchapyjnikov

There are four distinct, often sequential, mechanistic processes in the pathophysiology of epilepsy. First is the **underlying etiology**, which is any pathology or pathologic process that can disrupt neuronal function and connectivity, leading to the second process **(epileptogenesis)**, which makes the brain epileptic. Sometimes the underlying etiology can directly increase excitability even without the contribution of the downstream effects of epileptogenesis.

In some **genetic epilepsies**, a disorder in ion channel function and/or structure is the underlying etiology that leads to aberrant signal transduction, which can cause seizures (see Tables 633.2-633.4). These variants can involve voltage-gated channels (Na^+, K^+, Ca^{2+}, Cl^-, and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ-aminobutyric acid A receptors [$GABA_A$]), or other proteins. For example, in Dravet syndrome, the loss-of-function pathogenic variant in *SCN1A* encodes a voltage-gated sodium channel and causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. Gene variants can also affect neurotransmitter function through other mechanisms (see Table 633.3). For example, *ARX* variants can lead to dysfunction in GABAergic neurons and can cause X-linked West syndrome, among other epilepsies. In fragile X syndrome, it is hypothesized that variants in *FMR* cause enhanced glutamatergic signaling via the mGluR5 receptor. In Rett syndrome, variants in *MECP2* lead to increased NMDA receptor expression, which can cause epilepsy and other symptoms associated with the disorder.

In infantile spasms, animal models suggest that increases in the stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms.

Autoimmune etiologies for epilepsy are also recognized. Autoantibodies, sometimes generated because of cross-reactivity from a recent infection or secondary to a malignancy, can bind to extracellular receptors or other proteins expressed in neurons. This, in turn, leads to an inflammatory response and, in some cases, seizures. NMDA-receptor antibody encephalitis is probably the best-characterized autoimmune cause of epilepsy. Other epilepsy syndromes have been associated with autoantibodies targeting the voltage-gated potassium channel complex (anti-LGI2 and anti-CASPR2), GABA receptors (GABA-A and GABA-B), glycine receptors, and glutamic acid decarboxylase (GAD).

Abnormalities in the **structure** of the brain can be the underlying etiology for epilepsy. The structural abnormalities can be scarring from

previous injuries (hypoxic ischemic encephalopathy [HIE], stroke, cerebral hemorrhage), brain tumors, vascular malformations (cavernomas or arteriovenous malformations), and Sturge-Weber syndrome. In some cases where no identifying underlying etiology is found, epilepsy may be from the self-resolving maturational process of developing brains like BECTS and childhood occipital epilepsy syndromes (Gastaut and Panayiotopoulos types).

Second, **epileptogenesis** is the mechanism through which the brain, or part of it, turns epileptic. The role of large-scale molecular cell signaling pathways in epileptogenesis has been implicated in the mechanisms leading to epilepsy, namely, the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)–silencing transcription factor (REST) pathways. The mTOR pathway is seen in tuberous sclerosis, hemimegalencephaly, and cortical dysplasia–related epilepsies; the Ras/ERK pathway in a number of syndromes; and the REST pathway in epileptogenesis after acute neuronal injury. Repeat seizures lead through the earlier and other mechanisms to rewiring of the brain and to long-term epilepsy.

The third process is the resultant **epileptic state of increased excitability** present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. A dysregulation of glutamatergic excitation versus GABAergic inhibition occurs in epileptogenic neurons, which creates a seizure focus or network.

The fourth process is **seizure-related neuronal injury**, as often is demonstrated by MRI in patients after prolonged status epilepticus or those with long-term drug-resistant epilepsy. Many patients show acute swelling in the hippocampus or other regions after status epilepticus and long-term hippocampal atrophy with sclerosis on MRI. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of drug-resistant epilepsy. There is evidence that the pathophysiology of epileptic seizures, whether focal or generalized, and of the coexisting comorbidities involves disruption of neural networks of the brain resulting not only in increased excitability but the often-associated abnormal neurologic dysfunction.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.6 Treatment of Seizures and Epilepsy

Mohamad A. Mikati, Muhammad S. Zafar, and Dmitry Tchapyjnikov

DECIDING ON LONG-TERM THERAPY

After a first seizure, if the risk of recurrence is low, such as when the patient has a normal neurodevelopmental status, EEG, and MRI (risk ~20%), treatment is usually not started. If the patient has an abnormal EEG, MRI, developmental status, and/or neurologic exam and/or has a positive family history of epilepsy, the risk is higher, and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents' ability to manage recurrences or AED therapy in children. The decision is individualized and should be discussed with the family. Figure 633.8 presents an overview of the approach to the treatment of seizures and epilepsy.

COUNSELING

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to live with them. Restrictions on driving (in adolescents), swimming, and certain sports are usually necessary (Table 633.12). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the patient's responsibility. The physician is then requested to complete a specific form for patients who are being cleared to drive. In addition, in most states, a seizure-free period of 6 months, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or the sea and underwater diving are prohibited, but swimming in pools may be allowable. When swimming, even patients with epilepsy under excellent control should be under the continuous supervision of an observer who is aware of the condition and capable of lifeguard-level rescue.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. The ILAE Task Force on Sports and Epilepsy recommendations group sports into categories based on the potential risk of injury or death to the patient and to bystanders. **Group 1 sports** are associated with no significant additional risk to patients with epilepsy and include most athletics (excluding pole vaulting), bowling, most collective contact sports such as judo and wrestling, most ground-based collective sports (e.g., baseball, basketball, cricket, field hockey, football, rugby), cross country skiing, curling, dancing, golf, and racquet sports, including tennis and table tennis. **Group 2 sports** are associated with moderate risk to patients with epilepsy but not to bystanders; they include alpine skiing, archery, pole vaulting, biathlon/triathlon/modern pentathlon, canoeing, collective sports that can potentially lead to serious injury (e.g., boxing, karate, kickboxing), cycling, fencing, gymnastics, horse riding, ice hockey, shooting, skateboarding, roller and ice skating, skiing and snowboarding, swimming, water skiing, and weightlifting. **Group 3 sports** are considered high risk for the patient and for bystanders; they include aviation, climbing, platform and springboard diving, horse racing, motorsports, parachuting and other forms of skydiving, rodeo, scuba diving, ski jumping, solitary sailing, and surfing and windsurfing (see Table 633.12). In general, there has been a shift toward encouraging safe sports participation in patients with epilepsy rather than indiscriminately restricting their participation; however, the decision has to be individualized to the patient and his or her family. Staying physically active has been shown to reduce the chance for neuropsychologic impairments that often are associated with epilepsy.

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, a psychologic evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with epilepsy. Epilepsy does carry a risk of increased mortality rates (2 or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus it is recommended that family members be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are advertised seizure-detection devices that use motion sensors placed under the mattress or worn on the wrist to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging. They are useful in detecting a majority of generalized tonic-clonic seizures during sleep; most have not been rigorously studied. Whether such measures can reduce the risk of **sudden unexpected death in epilepsy (SUDEP)** remains to be seen. The parents need to guard against being overprotective to avoid adversely affecting the child's psychology. Education about what to do in case of seizures, the choices of treatment or no treatment and medications and their side effects, and the potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

PRINCIPLE OF DRUG THERAPY

The clinical pharmacology of an AED consists of three important facets: pharmacokinetics, pharmacodynamics, and pharmacogenomics.

Pharmacokinetics describes how the body affects antiepileptics after administration through the mechanisms of absorption and distribution, as well as the metabolic changes of the substance in the body. The steps involved in pharmacokinetics are liberation (the process of release of a drug from the pharmaceutical formulation), absorption

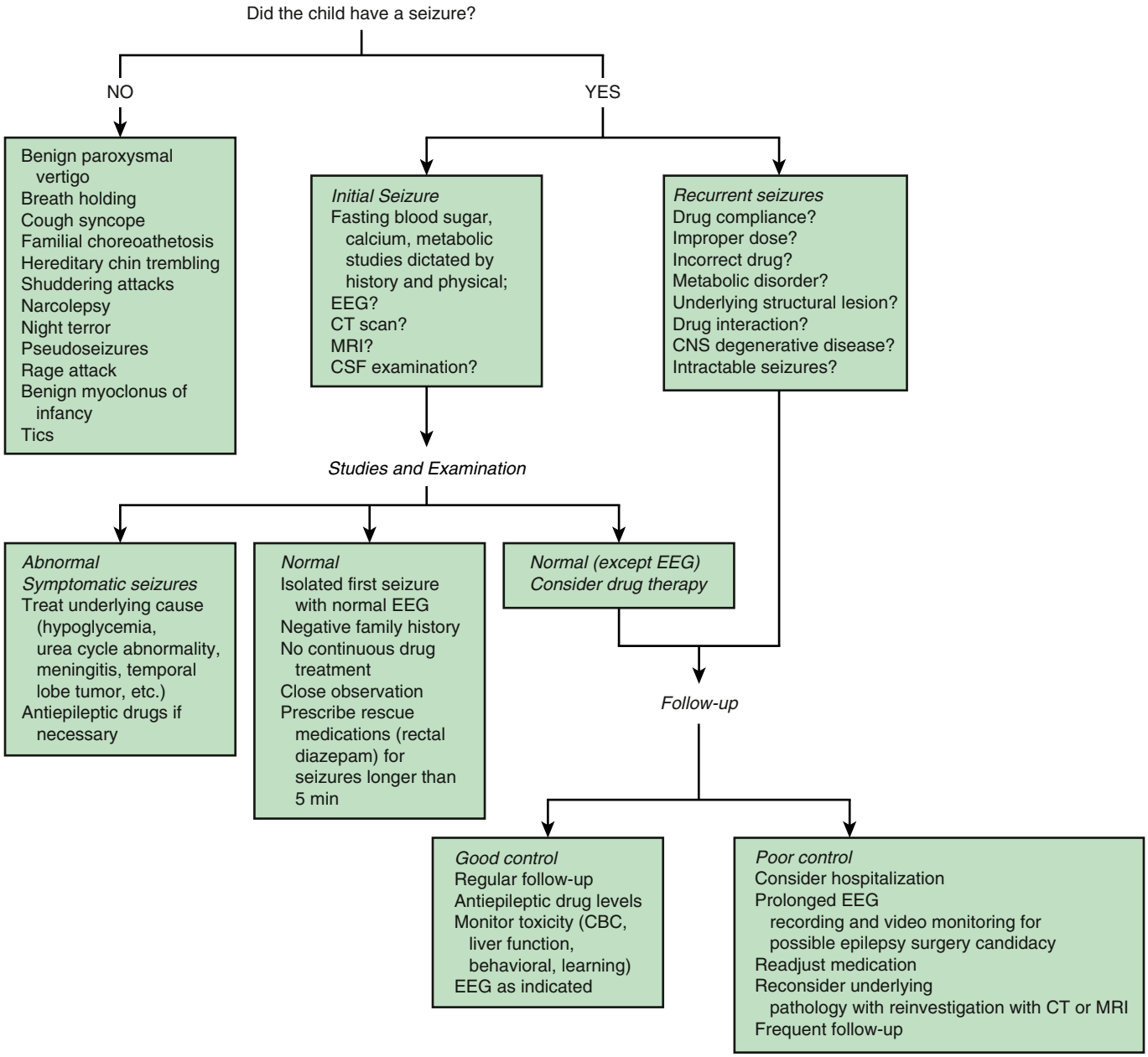

Fig. 633.8 Algorithm for the approach to the child with a suspected convulsive disorder.

Table 633.12 Sports and Special Considerations for the Child with Epilepsy*

CLINICAL SITUATION	GROUP 1	GROUP 2	GROUP 3
Acute symptomatic seizures (one or more)	Permitted	Neurologist's discretion	Neurologist's discretion
One unprovoked seizure	Permitted	Permitted if >12 mo of seizure freedom	Permitted if >12 mo of seizure freedom
Seizure freedom for >12 mo	Permitted	Permitted	Permitted
Sleep-related seizures	Permitted	Neurologist's discretion	Neurologist's discretion
Seizures without impaired awareness	Permitted	Neurologist's discretion	Not recommended
Seizures with impaired awareness	Neurologist's discretion	Neurologist's discretion	Not recommended
Resolved epilepsy with no seizures >10 yr and off AEDs >5 yr	Permitted	Permitted	Permitted
Medication withdrawal	Neurologist's discretion	Neurologist's discretion	Neurologist's discretion

*Specific advice should be individualized, depending on the patient's clinical condition. Group 1: low-risk sports; Group 2: moderate-risk sports; Group 3: high-risk sports. Refer to Chapter 633.6 for further details about the definition of each group.

Modified from Capovilla G, Kaufman KR, Perucca E, et al. Epilepsy, seizures, physical exercise, and sports: a report from the ILAE Task Force on Sports and Epilepsy. *Epilepsia*. 2016;57:6–12.

(the process of a substance entering the blood circulation), distribution (the dispersion or dissemination of substances throughout the fluids and tissues of the body), metabolism (the irreversible transformation of parent compounds into daughter metabolites), and excretion (the removal of the substances from the body).

Pharmacodynamics describes the biochemical and physiologic effect of AED dose or concentration. The response may be desirable *(effectiveness)* or untoward *(toxicity)*. **Pharmacogenomics** is the study of how variant forms of human genes contribute to interindividual variability in drug response.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

AEDs reduce excitability by interfering with sodium, potassium, or calcium ion channels by reducing excitatory neurotransmitter release or function or enhancing GABAergic inhibition (Fig. 633.9). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels found in the thalamus area are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam.

$GABA_A$ receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on $GABA_B$ presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutaminergic transmission is decreased by felbamate that blocks NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam and brivaracetam bind to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly result in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

The precise mechanisms by which cannabidiol (CBD) exerts its anticonvulsant effect in humans are unknown. CBD does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors. Fenfluramine increases extracellular levels of serotonin through interaction with serotonin transporter proteins and exhibits agonist activity at serotonin 5HT-2 receptors. Everolimus is

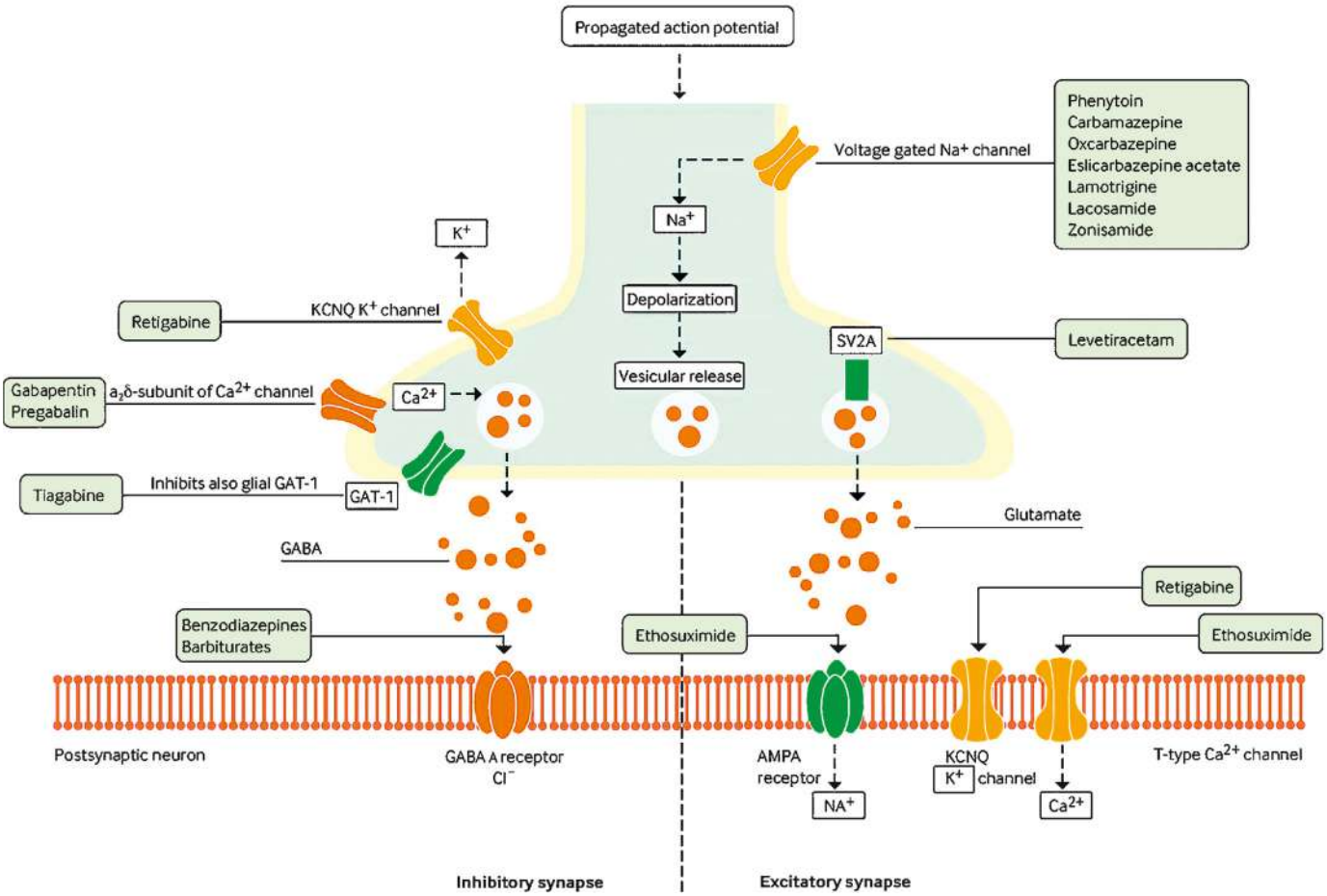

Fig. 633.9 Mechanisms of action of AEDs, which are diverse, mainly involving modulation of voltage-activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved AEDs have effects on inhibitory *(left-hand side)* and excitatory *(right-hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-ons does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism-driven drug discovery has played only a minor role. AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. *(From Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. BMJ. 2014;348:g254.)*

an inhibitor of mTOR, a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated (too active) in tuberous sclerosis. Ganaxolone is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors. It is being studied for long-term use in certain types of epilepsy and in acute treatment of status epilepticus.

There is also a role for immune modulation in treating epilepsy, as depicted by the use of adrenocorticotropic hormone (ACTH), IVIG, oral prednisone, and intravenous methylprednisolone.

CHOICE OF DRUG ACCORDING TO SEIZURE TYPE AND EPILEPSY SYNDROME

Drug therapy should be based on the type of seizure and the epilepsy syndrome and on other individual factors. In general, the **drugs of first choice** for focal seizures and epilepsies are oxcarbazepine and levetiracetam; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, valproate (less so in women because of its hormonal and fetal side effects); other choices include levetiracetam (which is often the first drug to use in other primary generalized seizures), lamotrigine, zonisamide, topiramate, and perampanel. There is significant controversy about these choices, and therapy should always be individualized (see "Choice of Drug: Other Considerations").

West syndrome is best treated with hormonal therapy in the form of either ACTH injections or, possibly, oral steroids. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m^2 (divided into twice-daily intramuscular injections of 75 units/m^2) administered over a 2-week period with a subsequent gradual taper over a 2-week period (30 units/m^2 in the morning for 3 days; 15 units/m^2 in the morning for 3 days; 10 units/m^2 in the morning for 3 days; and 10 units/m^2 every other morning for 6 days; then stop). Response is usually observed within the first 7 days. During the tapering period of any regimen, spasm relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 weeks and then beginning the taper again. Synthetic ACTH (tetracosactide/cosyntropin) can also be used as long as the long-acting (depot) preparation is chosen. Oral high-dose prednisolone is a lower-cost alternative to ACTH and does not necessitate families learning how to administer intramuscular injections; however, it may be inferior in efficacy to ACTH, particularly in those with cryptogenic (of unknown etiology) West syndrome.

Awake and asleep EEGs are often done 1, 2, and 4 weeks after the initiation of hormonal therapy to monitor the patient's response, with the aim of clearing the EEG from hypsarrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. Prophylactic therapy for ulcers with an H_2 blocker or protein pump inhibitor is desirable while the patient is receiving hormonal therapy. Also, live vaccines are contraindicated, and other vaccines are not effective during ACTH and steroid therapy because of the immune-suppressive effects of these hormonal agents. Thus all vaccines are not given during hormonal therapy and in the period after it (usually ≤3 months after the last dose).

Vigabatrin can be used as a first-line agent to treat **infantile spasms** in patients with tuberous sclerosis and is the second-line choice if hormonal therapy was unsuccessful in other cases of infantile spasms. Its principal side effect is retinal toxicity, seen in approximately 30% of patients, most often if the drug is used for longer than 6 months, with resultant visual field defects that persist despite the withdrawal of the drug. Because of this toxicity, vigabatrin is available only through a restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications. Emerging evidence suggests that dual treatment with vigabatrin and hormonal therapy at the onset of spasms may be superior to hormonal therapy alone but may predispose to the CNS neurotoxicity of vigabatrin associated with increased T2 signal in the basal ganglia. The ketogenic diet is probably the third-line therapy. Subsequent alternative treatment options for spasms include valproate, benzodiazepines such as nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide, pyridoxine, and IVIG. None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with idiopathic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in the syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic-astatic seizures), clobazam, valproate, lamotrigine, topiramate, felbamate, and rufinamide are considered effective. The FDA also approved CBD and fenfluramine to be used in Lennox-Gastaut syndrome. Fenfluramine is available only through a restricted distribution REMS program because of the risk of valvular heart disease and pulmonary arterial hypertension.

Felbamate is used as a last-resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic-clonic, atypical absence, other tonic, myoclonic). For patients who have a preponderance of atypical absence seizures, valproate, lamotrigine, or ethosuximide are often suitable drugs to try because they are relatively less toxic than many alternative drugs. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling and often tolerance to its antiepileptic effects develops in a few months. Consequently, in Lennox-Gastaut or other drug-resistant epilepsy syndromes, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation) or as a bridge over a few days until dose changes of background medications take effect. In resistant cases of Lennox-Gastaut syndrome and related epilepsies, ketogenic diet, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, or IVIG can be used.

Dravet syndrome is usually treated with benzodiazepines such as clobazam and with valproate. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam; doses need to be adjusted because stiripentol can increase clobazam levels, and valproate can increase stiripentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, oxcarbazepine, and phenytoin are reported to exacerbate seizures in Dravet syndrome. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

The FDA has approved CBD and fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥2 years. The starting dose is 2.5 mg/kg taken twice daily (5 mg/kg/day). After 1 week, the dose is usually increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). If it is tolerated and needed, the dose may be increased up to 10 mg/kg twice daily (20 mg/kg/day). It comes as an oral solution (100 mg/mL). Checking the package insert of all these medications before initiating their use is essential because of the frequent interactions with concurrent antiseizure and other medications.

Absence seizures are most often initially treated with ethosuximide, which is as effective as, but less toxic than, valproate; both are more effective than lamotrigine (which has fewer side effects than valproate). Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic-clonic seizures coexist with absence seizures. These two medications are effective against the latter seizures, whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents' observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic-clonic and absence seizures. Zonisamide, clonazepam, lamotrigine, and topiramate are alternatives.

Severe myoclonic epilepsies are treated with medications effective for Lennox-Gastaut syndromes, such as topiramate, clobazam, valproate, and zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Focal and focal to bilateral tonic-clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, phenobarbital, topiramate, lacosamide, zonisamide, valproic acid, lamotrigine, clobazam, perampanel, or clonazepam (see Table 633.1). Oxcarbazepine and levetiracetam are often used first.

Vigabatrin is the preferred treatment for infantile spasms due to **tuberous sclerosis**. The FDA also approved CBD and everolimus to treat a seizure in tuberous sclerosis in patients older than 2 years of age.

For children with ESES and SWS, nighttime benzodiazepine and daily or pulsed-dose steroids are preferentially used. Alternatively, other AEDs like valproate, clobazam, levetiracetam, and acetazolamide and ketogenic therapy have been used.

CHOICE OF DRUG: OTHER CONSIDERATIONS

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated next:

- **Comparative effectiveness** (Tables 633.13 and 633.14 list dosages) and the **potential for paradoxical seizure aggravation** by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered. Although many antiseizure medications have not been studied in the pediatric population, off-label use of these medications in children is common, and there are studies that have shown that, in general, their efficacy in adults is predictive of their efficacy in children with the same seizure types.
- **Comparative tolerability** (Table 633.15): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 years of age, taking polytherapy, and/or have metabolic disorders. Thus if metabolic disorders are suspected, other drugs should be considered first, and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate, pyruvate, liver function tests, and perhaps gene testing for mitochondrial disorders (see the paragraph on the presence of comorbid conditions later). The choice of an AED can also be influenced by the likelihood of occurrence of nuisance side effects, such as weight gain (valproate, carbamazepine), gingival hyperplasia (phenytoin), alopecia (valproate), hyperactivity (benzodiazepines, barbiturates, levetiracetam, valproate, gabapentin), or irritability/anger (levetiracetam and perampanel). Children with behavior problems and/or with attention-deficit disorder can become particularly hyperactive with the GABAergic drugs mentioned earlier. This often affects the choice of medications. In general, newer-generation antiepileptic medications provide a better side effect profile than older medications.
- **Cost and availability**: The cost of the newer AEDs often precludes their use, particularly in developing countries. Many drugs are not available in all countries (1) because they are too expensive; (2) because, paradoxically, they are too inexpensive (lower profit margin); or (3) because of regulatory restrictions. AEDs have a narrow therapeutic range, and thus switching from brand name to generic formulations or from one generic to another can result in changes in levels that could result in breakthrough seizures or side effects.
- **Ease of initiation** of the AED: Medications started very gradually, such as lamotrigine and topiramate, should not be chosen in situations when there is a need to quickly achieve a therapeutic level. In such situations, medications that have intravenous preparations or

Table 633.13 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED†	ILAE (2013)*†
Focal-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, PER, PHT, TPM, VGB	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS
BCECT	None	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM
Childhood absence epilepsy	ESM, VPA	A: ESM, VPA B: None C: LTG D: None
Juvenile myoclonic epilepsy	LEV, LTG, TPM	A, B, C: None D: TPM, VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	Not reviewed
Infantile spasms	ACTH, VGB	Not reviewed
Primary generalized tonic-clonic seizures	LEV, LTG, TPM, PER	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: one or more class I randomized controlled trials (RCTs) or two or more class II RCTs; Level B: one class II RCT or two or more class III RCTs; Level C: two or more class III RCTs; Level D: one class III double-blind or open-label study *or* one class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

†More recent data are available after FDA approval and ILAE review, and the implications of these data have been incorporated as much as possible into Table 633.13. Together, these two tables aim to provide as complete a picture as possible of the state of the art and the approved indications for the therapy of pediatric epilepsy.

ACTH, Adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League Against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Perucca E, Tomson T. ILAE Subcommission on AED Guidelines: updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551–563.

Table 633.14 Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Acetazolamide	Absence seizures (adults)	1-12 mo: 10 >1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Brivaracetam	Focal sz (age >16 yr)	50-200 mg/day	bid		10, 25, 50, 75, 100 mg tabs; 10 mg/mL oral and IV solns
Bromide		50-100	bid or qd	10-15 mEq/L, other references 75-352 mg/dL	Supplied as triple bromide soln (240 mg/mL or 500 mg/mL of bromide salt)
Carbamazepine*	Focal and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps; 100, 200, 400 mg ER tabs 100 mg chewable tabs; 200 mg tabs; 100 mg/5 mL susp
Cenobamate	Focal in adults ≥18 yr	200-400 mg/day final dose	Once per day	—	12.5, 25, 50, 100, 150, 200 and 400 mg tabs
Clobazam†	LGS (all ages above 2 yr)	10-40 mg/day	bid	60-200 µg/L	10 mg, 20 mg tabs; 2.5 mg/mL soln
Clonazepam†	Absence sz, LGS, myoclonic sz (all ages)	0.05	bid or tid	25-85 µg/L	0.5, 1, 2 mg tabs; 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Focal sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age)	bid or tid	100-700 µg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln; rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Eslicarbazepine	Focal sz (adult)	800-1600 mg/day	qd		200, 400, 600, 800 mg tabs
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps; 250 mg/5 mL soln
Felbamate	LGS (>2 yr) Focal sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs; 600 mg/5 mL susp
Gabapentin‡	Focal sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps; 300, 600, 800 mg tabs; 250 mg/5 mL soln; 25 mg/mL susp
Lacosamide	Focal sz (>17 yr)	4-12	bid	≤15 µg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln
Lamotrigine	LGS, focal and tonic-clonic sz (age >2 yr)	5-15§ 1-5¶	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam†	Focal-onset (age ≥1 mo), tonic-clonic sz (age ≥6 yr), myoclonic (age ≥12 yr)	20-60	bid or tid	6-40 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 µg/L	0.5, 1, 2 mg tabs 2 mg/mL soln

Continued

Table 633.14 Dosages of Selected Antiepileptic Drugs—cont'd

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Methsuximide	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	—	0.25-1	bid or tid	<200 µg/L	5 mg tabs
Oxcarbazepine*	Focal sz (>2 yr)	20-60	bid	13-35 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Focal sz (>12 yr)	2-12 mg per day (>12 yr)	qhs	20-800 ng/mL	2, 4, 6, 8, 10, 12 mg tabs; 0.5 mg/mL soln
Phenobarbital	Myoclonic, focal and tonic-clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Focal, tonic-clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30,100 mg caps 125 mg/5 mL susp
Pregabalin	Focal sz (adults)	2-14	bid	Up to 10 µg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Focal and tonic-clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide†	LGS (age >4 yr)	30-45	bid	<60 µg/mL	200, 400 mg tabs
Sulthiame**		5-15	bid or tid	1.5-20 µg/mL	50, 200 mg caps
Tiagabine	Focal sz (age >2 yr)	0.5-2	bid, tid, qid	80-450 µg/L	2, 4, 12, 16 mg tabs
Topiramate†	LGS, focal and tonic-clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, focal and tonic-clonic sz (age >2 yr)	15-40; higher doses are used if patient is on enzyme inducers (≤60 mg/kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and focal sz (age >1 mo)	50-150	bid	20-160 µg/mL (following levels is not useful for this drug)	500 mg tabs 500 mg powder for soln
Zonisamide	Focal sz (age >16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

*Usually start with one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.
†Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.
‡Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.
§Child receiving enzyme inducers.
**Available in some European countries.
¶Child receiving valproate.
Unless specified otherwise earlier, one would usually target the lower range of the therapeutic dose and then adjust it as needed, depending on the response, side effects, and/or levels. The dosing schedule (e.g., bid or tid) can depend on if a sustained-release preparation is available and if the patient is taking enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect the drug (as indicated in the dosing schedule in the table and in the text).
cap, Capsule; ER, extended release; GTC, generalized tonic-clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

Table 633.15 Some Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECTS
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome, renal calculi
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Brivaracetam	Dizziness, nausea/vomiting, fatigue, depressed mood
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride due to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Cenobamate	Drug reaction with eosinophilia and systemic symptoms (DRESS), short QT, sedation, H/A Contraindicated in familial short QT syndrome
Clobazam	Nuisance: drowsiness, sedation, drooling Serious: Stevens-Johnson syndrome, toxic epidermal necrolysis
Eslicarbazepine	Dizziness, ataxia, nausea/vomiting, diplopia, tremor, somnolence, headache, fatigue
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurologic disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, ECG abnormalities (both have FDA warning about them), rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: anger, irritability, other behavioral symptoms In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Aggression, homicidal ideation, suicidal thoughts/behavior
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other hydantoins	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, hypohidrosis, fever Serious: precipitation of glaucoma, renal calculi
Valproic acid	Nuisance: weight gain, hyperammonemia, tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow-up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever, renal calculi

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions. For a full list of side effects, please review the drug's FDA-approved packet insert.
AED, Antiepileptic drug; CNS, central nervous system.

that can be started and titrated more quickly, such as levetiracetam, phenytoin, lacosamide, or valproate, should be considered instead.

- **Drug interactions** and the presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications such as gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate; it also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction; and thus the free and not the total level needs to be checked when both medications are used together. Enzyme inducers such as phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate, zonisamide, and perampanel. Medications exclusively excreted by the kidney, such as levetiracetam and gabapentin, are not subject to such interactions.
- **The presence of comorbid conditions**: The presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions, such as valproate, topiramate, or zonisamide. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases the appetite, such as topiramate or zonisamide, might be used instead. In adolescent females of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations. Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ pathogenic variant *(POLG)* with mitochondrial DNA depletion (also known as **Alpers-Huttenlocher syndrome**), other mitochondrial disorders (Leigh syndrome; **MELAS**; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy–myopathy–sensory ataxia syndrome), and hyperammonemic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy. Attention-deficit/hyperactivity disorder (ADHD) is a common comorbid condition in children with epilepsy. The presence of epilepsy should not necessarily discourage treatment with stimulants if indicated.
- **Coexisting seizures**: In a patient with both absence and generalized tonic-clonic seizures, a drug that has a broad spectrum of antiseizure effects, such as lamotrigine or valproate, could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.
- **History of prior response** to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to levetiracetam, levetiracetam could be a desirable choice.
- **Mechanism of drug actions**: At present, in most patients the current understanding of the pathophysiology of epilepsy does not allow a specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.
- **Ease of use**: Medications given once or twice a day are easier to use than medications given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role. Some drugs are also available as sprinkles and biofilm formulation for use in children.
- **Ability to monitor the medication** and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications, such as valproate and phenobarbital, also require blood level monitoring for optimal titration. Monitoring can represent a practical or patient satisfaction disadvantage for the older drugs compared with the newer AEDs, which generally require less blood level monitoring most often to check for compliance.
- **Patient's and family's preferences**: The choice between two or more acceptable alternative AEDs might also depend on the patient's or family's preferences. For example, some patients might want to avoid gingival hyperplasia and hirsutism as side effects but might tolerate weight loss or vice versa.
- **Genetics** and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. There is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, oxcarbazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, Southeast Asian populations; hence, these AEDs should be avoided in genetically susceptible persons after testing for the allele. Pathogenic variants of the *SCN1A* sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, oxcarbazepine, and phenytoin and to the use of the more appropriate valproate, clobazam, or stiripentol.
- **Teratogenic profiles**: Based on available evidence, levetiracetam and lamotrigine are FDA pregnancy category C drugs and probably the safest AEDs to use during pregnancy. Valproate is a category X drug that is associated with neural tube defects, hypospadias, and cardiovascular malformations. *The use of valproate should thus be avoided during pregnancy if possible.* Topiramate, phenobarbital, and phenytoin are category D drugs with birth defects associated with their use reported in humans. The decision to transition to a less teratogenic AED rather than continuing with an existing regimen must be made on a case-by-case basis and consider the risk of seizures during pregnancy versus the risk of teratogenicity.
- **Underlying etiology**: The cause for the patient's epilepsy must be considered and can lead to more specific therapy choices, such as the use of immune-modulating therapy for autoimmune encephalopathy or personalized and precision therapies for specific epileptic channelopathies or vitamin-responsive epilepsies.

INITIATING AND MONITORING THERAPY

In nonemergency situations or when loading is not necessary, the **maintenance dose** of the chosen AED is started (see Table 633.14). With some medications (e.g., oxcarbazepine, carbamazepine, topiramate, and perampanel), even smaller doses are initially started and then **gradually increased** up to the maintenance dose to build a tolerance to adverse effects such as sedation. The starting dose of oxcarbazepine is usually 8-10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose is usually tolerated. With some, such as levetiracetam and gabapentin, either approach can be used. Patients should be counseled about potential adverse effects, and these should be monitored during follow-up visits (see Table 633.15).

Titration

Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs, such as phenytoin, carbamazepine, valproate, phenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2-7 days (half-life: 6-24 hours). For phenobarbital, it is 2-4 weeks (mean half-life: 69 hours). For zonisamide, it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hours in monotherapy and 27-38 hours during combination therapy with enzyme inducers). If a therapeutic level has to be achieved faster, a loading dose may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate, it is 20 mg/kg; for phenytoin, it is 20 mg/kg; and for phenobarbital, it is 10-20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hours) to avoid excessive sedation.

Only one drug should be used initially, and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and

the initial drug subsequently tapered. Control with one drug **(monotherapy)** should be the goal, although some patients eventually need to take multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess the response for absence seizures because the EEG mirrors the response in such patients.

Monitoring

For the older AEDs, before starting treatment, baseline laboratory studies, including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the first 3-6 months of therapy. These laboratory studies are usually initially checked once or twice during the first month, then every 3-4 months after that. Significant concerns have been raised about the usefulness of routine monitoring in the absence of clinical signs because the yield of significant adverse effects is low. There are currently many advocates of less frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients taking carbamazepine or phenytoin. This adverse effect responds to decreasing the dose or stopping the medication and is distinguished from the much less common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 years of age with complex neurologic disorders who are taking the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or a change of medication. An allergic rash can occur with any medication but is probably most common with lamotrigine, carbamazepine, and phenytoin.

Because of the risk of valvular heart disease and pulmonary arterial hypertension with fenfluramine and irreversible peripheral vision loss with vigabatrin, these drugs are available only through a restricted distribution REMS program. In addition, the FDA has circulated a warning about factoring in the possibility of cardiac arrhythmias when deciding on lamotrigine use, particularly in cardiac patients and the need to monitor ECG during its use.

SIDE EFFECTS

Occasionally, a Stevens-Johnson–like syndrome develops, probably most commonly with lamotrigine but also with other medications like clobazam; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking oxcarbazepine, carbamazepine, and/or lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce the 25-hyrdroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients taking chronic AED therapy because it is often associated with osteopenia independent of or secondary to vitamin D deficiency (low bone density, rickets, and hypocalcemia), particularly in patients taking enzyme-inducing medications. Thus counseling the patient about sun exposure and vitamin D intake, monitoring vitamin D levels, and, in most cases, giving vitamin D supplementation are recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 years old) who are receiving valproate in combination with other AEDs, particularly those who might have inborn errors of metabolism such as aminoacidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The FDA has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications.

When adding a new AED, the doses used are often affected by the background medications. If the patient is receiving enzyme inducers, the doses needed of valproate, lamotrigine, topiramate, zonisamide, and perampanel are often higher, sometimes 1.5-2 times, than the usual maintenance doses. On the other hand, if the patient is taking valproate (an enzyme-inhibiting AED), the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Changes in the dosing of the background medication are often done as the interacting medication is being started or stopped. Genetic variability in enzymes that metabolize AEDs and in the presence of inducible multidrug-resistance genes (pharmacogenomics) might account for some of the variation among individuals in responding to certain AEDs and for the variability in the drug dose necessary for seizure control.

ADDITIONAL TREATMENTS

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug and **dual (combination) therapy** are considered.

Patients with **drug-resistant** (previously referred to as *intractable* or *refractory*) **epilepsy** (those who have failed at least two trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see Chapter 633.2) and to investigate drug-resistant patients for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as drug-resistant epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; cerebral folate deficiency; other vitamin-responsive conditions (such as biotin/thiamine-responsive basal ganglia disease and riboflavin-responsive epilepsy); neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy, and neonatal diabetes; and hyperinsulinemia-hyperammonemia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

Steroids may be the first-line treatment in certain cases (e.g., ACTH use in West syndrome) but may also be used for other drug-resistant epilepsy syndromes such as Lennox-Gastaut, myoclonic-astatic, continuous spike waves in slow-wave sleep, and Landau-Kleffner syndromes. In these situations, steroid therapy is typically given as a monthly intravenous infusion (pulse steroids) or as daily oral prednisone 2 mg/kg/day (or equivalent). This dose is maintained for 1-2 months, then tapered off over 1-3 months. Pulse steroids are usually better tolerated than a daily steroid regimen, which can cause more weight gain, hyperglycemia, hypertension, immunosuppression, and other side effects. Because relapses occur commonly during tapering and in such syndromes as Landau-Kleffner and continuous spike waves in slow-wave sleep, therapy for longer than 1 year is often needed.

IVIG has also been reported to be similarly effective in nonimmunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion that can occur even in the absence of IgA deficiency. Low IgA, low IgG_2, and male sex are reported to predict a possibly favorable response. The usual regimen is 2 g/kg divided over 2-4 consecutive days followed by 1 g/kg once a month for 6 months.

The mechanisms of action of steroids and IVIG are not known but are presumed to be antiinflammatory because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The ketogenic diet is considered effective in glucose transporter protein 1 deficiency (GLUT-1), pyruvate dehydrogenase deficiency, myoclonic-astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also a suggestion of possible efficacy in selected mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary), carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, medium-chain acyl dehydrogenase deficiency, long-chain acyl dehydrogenase deficiency, short-chain acyl dehydrogenase deficiency, long-chain 3-hydroxyacyl-coenzyme A deficiency, medium-chain 3-hydroxyacyl–coenzyme A deficiency, pyruvate carboxylase deficiency, and porphyrias. Thus an appropriate metabolic workup, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile, total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3:1 or 4:1 fat:nonfat calorie ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it, owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic-index diet and the modified Atkins diet are easier to institute, do not require hospitalization, and may also be effective in treating epilepsy.

CBD is a nonpsychoactive extract of the cannabis plant that has gained prominence as a possible adjunct (add-on) therapy for drug-resistant epilepsies such as Dravet and Lennox-Gastaut syndromes.

Precision genetic-based therapy is defined as a patient-specific, or more accurately physiology-specific, selection of therapy as determined by the available information regarding the underlying pathophysiology based on the primary specific genetic, metabolic, and/or other cause of epilepsy in that patient. The use of precision therapies (Table 633.16) has expanded as more epileptogenic gene pathogenic variants are identified as part of routine genetic screening for drug-resistant epilepsies. This has allowed for targeted therapy based on the specific gene variant (see Table 633.16). Examples include the use of quinidine for gain-of-function *KCNT1* variants and retigabine for loss-of-function *KCNQ2* variants. Gain-of-function *KCNQ2* variants do not respond to retigabine, a fact that emphasizes the need for careful gene analysis that accounts for the functional outcome of each particular gene. The same applies to pathogenic variants of sodium channels; patients with epilepsy caused by **gain-of-function** variants show good response to sodium channel–blocking agents, a response not shared by patients with epilepsy caused by *loss-of-function* variants in the sodium channel gene.

Vitamin-responsive epilepsies also warrant special attention because if they are diagnosed early and precision therapy is given for them, the therapy can significantly affect seizure control and neurodevelopmental outcomes. Examples include the use of pyridoxine for antiquitin deficiency–associated epilepsies, biotin for biotinidase deficiency, folate for cerebral folate deficiency, and biotin/thiamine for **biotin thiamine–responsive basal ganglia disease**, which can have coexisting epilepsy and is caused by defects in a cerebral thiamine transporter.

Table 633.16 Precision Therapy: Treatment Considerations for Genetic Epilepsies and Other Syndromes with a High Prevalence of Epilepsy

GENE MUTATION	EPILEPTIC DISORDER	TREATMENT CONSIDERATIONS
ALDH7A1	Pyridoxine-dependent epilepsy	Pyridoxine
BTD	Biotinidase deficiency–associated epilepsy	Biotin
FOLR1	Cerebral folate deficiency	Folinic acid
GRIN2A	GRIN2A-related epilepsy	Memantine and dextromethorphan for gain-of-function variant
KCNQ2	Benign familial neonatal or infantile seizures; KCNQ2-related epileptic encephalopathy	Retigabine for loss-of-function variants*
KCNT1	Migrating focal seizures of infancy	Quinidine for gain-of-function variants
PNPO	Pyridoxal 5′-phosphate dependent epilepsy	Pyridoxal 5′-phosphate
PRRT2	Benign familial infantile epilepsy; paroxysmal dyskinesias; hemiplegic migraine; episodic ataxia	Oxcarbazepine and carbamazepine
SCN1A	Dravet syndrome; GEFS+; other SCN1A-related epilepsies	Avoid using sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine, lacosamide, phenytoin) and vigabatrin
SCN2A	Benign neonatal or infantile seizures; Dravet syndrome; GEFS+; infantile spasms; other early infantile epileptic encephalopathies	Phenytoin and carbamazepine
SCN8A	Early infantile epileptic encephalopathies; benign infantile seizures; movement disorders	High-dose phenytoin
SLC2A1	Glucose transporter–deficiency syndrome	Ketogenic diet
SLC19A3	Biotin thiamine–responsive basal ganglia disease	Biotin and thiamine
TSC1; TSC2	Tuberous sclerosis complex	Vigabatrin for infantile spasms; possibly everolimus for drug-resistant seizures

*Withdrawn from market.

Data from Hani A, Mikati MA. Current and emerging therapies of severe epileptic encephalopathies. *Semin Pediatr Neurol*. 2016;23(2):180–186; Mudigoudar B, Weatherspoon S, Wheeless JW. Emerging antiepileptic drugs for severe pediatric epilepsies. *Semin Pediatr Neurol*. 2016;23(2):167–179; and Smith LA, Ullman JFP, Olson HE, et al. A model program for translational medicine in epilepsy genetics. *J Child Neurol*. 2017;32(4):429–436.

APPROACH TO EPILEPSY SURGERY

If a patient has failed three drugs, the chance of achieving seizure freedom using AEDs is <10%. Therefore proper evaluation for surgery is necessary when a patient fails two or three AEDs, usually within 2 years of the onset of epilepsy and often sooner than 2 years. Performing epilepsy surgery in children at an earlier stage (e.g., <5 years of age) allows the transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably nontoxic doses; absence of expected unacceptable adverse consequences of surgery; and a properly defined **epileptogenic zone** (the area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis of the following parameters: seizure semiology, video-EEG long-term monitoring, neuropsychologic profile, and brain MRI. 7-Tesla MRI may, in some cases, have some advantage over 3-Tesla MRI. Other techniques, such as high-density EEG (HD-EEG), invasive EEG (depth electrodes, subdural grid or strips, intraoperative electrocorticography), single-photon emission CT (SPECT), magnetoencephalography (MEG), and positron emission tomography (PET), are also needed if the epileptogenic zone is difficult to localize or when it is close to the eloquent cortex. **Stereo-EEG** is a method of invasive EEG monitoring used to localize epileptic areas of the cortex. It involves the stereotactic implantation of depth electrodes through multiple burr holes in the skull using robot-assisted implantations and computer-based 3D localization. Several procedures can be used to avoid resection of eloquent cortex, including the **Wada test**, **functional MRI**, MEG, transcranial magnetic stimulation, and cortical stimulation with subdural and depth electrodes. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes video-EEG monitoring, brain imaging, and age-specific neuropsychologic assessment.

Epilepsy surgery is often used to treat drug-resistant epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, encephalomalacia from prior cerebrovascular insult, mesial temporal sclerosis, Landau-Kleffner syndrome, and hemispheric syndromes such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with drug-resistant epilepsy resulting from metabolic or degenerative problems *are not* candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. **Hemispherectomy** is used for diffuse hemispheric lesions in cases such as Rasmussen encephalitis, hemimegalencephaly, large perinatal stroke, Sturge-Weber syndrome; **multiple subpial transections**, a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in the eloquent cortex, as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used as a palliative procedure for drop attacks.

Laser interstitial thermal therapy (LITT) is a less invasive surgical technique that uses a laser to ablate relatively small (<3 × 3 cm) epileptic areas in the cortex; it has been used to treat mesial temporal sclerosis, tuberous sclerosis, and hypothalamic hamartomas and for corpus callosotomies. Other minimally invasive techniques include gamma knife stereotactic radiosurgery that uses gamma radiation. Focal resection and hemispherectomy result in a high rate (50–80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates of seizure freedom (5–10% for vagus nerve stimulation [VNS] and lower for callosotomy); however, these procedures do result in significant reductions in the frequency and severity of seizures, decreases in medication requirements, and meaningful improvements in the patient's quality of life in approximately half or more of eligible patients.

VNS is often used for drug-resistant epilepsies of various types (partial, generalized, Lennox-Gastaut) and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery (Fig. 633.10). VNS is approved for age 4 years and above but has also been used in even younger ages. This technique is considered palliative rather than curative because it most often leads to seizure

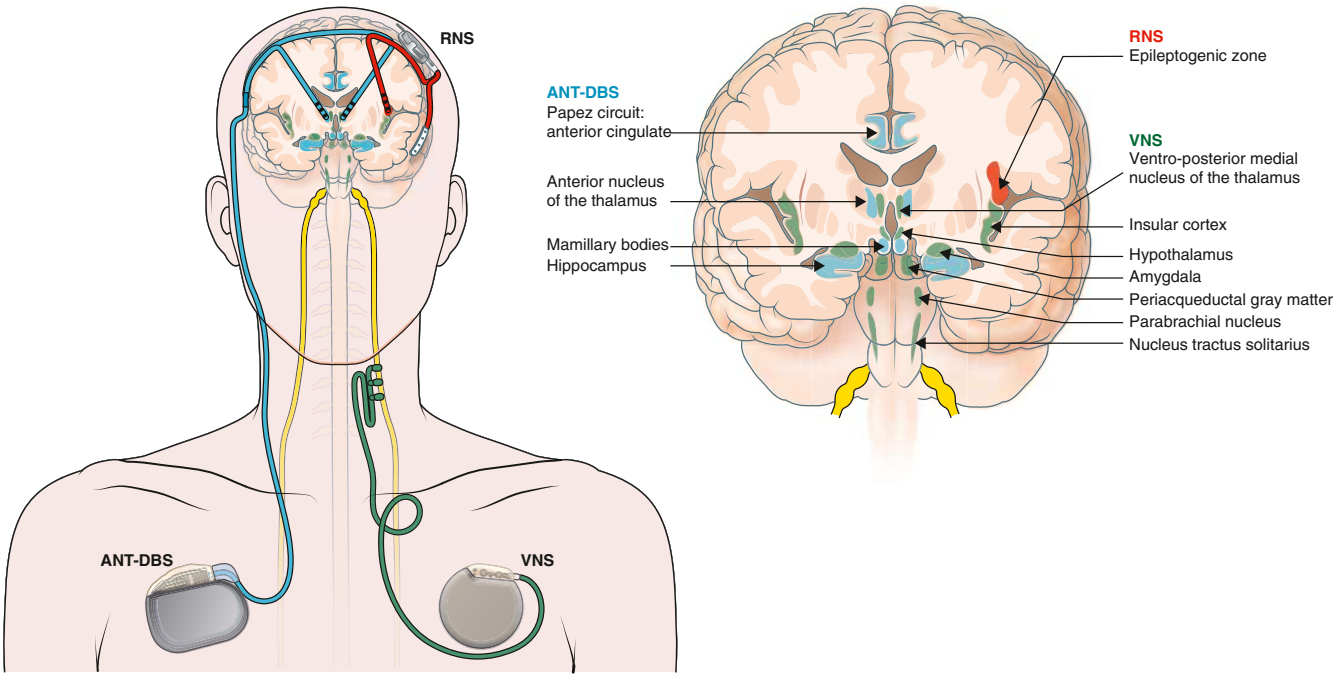

Fig. 633.10 Approved neuromodulation therapies in epilepsy. The brain targets for each neuromodulation approach according to sites of stimulation and known primary anatomic pathways. This illustration is not meant to be comprehensive. VNS is expected to activate the nucleus tractus solitarius, with downstream effects on its brainstem, subcortical, and cortical efferences; ANT-DBS stimulation is expected to modulate the activity of the anterior nucleus of the thalamus and the associated Papez circuit, and RNS stimulation is expected to inhibit the suspected cortical epileptogenic zone. ANT-DBS, Deep brain stimulation of the anterior nucleus of the thalamus; RNS, responsive neurostimulation; VNS, vagus nerve stimulation. *(From Ryvlin P, Rheims S, Hirsch LJ, et al. Neuromodulation in epilepsy: state-of-the art approved therapies. Lancet Neurol. 2021;20[12]:1038–1047, Fig. 1, p. 1039.)*

frequency *reduction* rather than seizure cessation. By producing low-amplitude current stimulations, usually once every 5 minutes, this device results in a reduction of seizures. Also, caretakers can activate the device by swiping a magnet over it at the time of the seizure, which can shorten seizure duration. Vagus nerve stimulators also have integrated heart rate monitoring that detects tachycardia patterns typically associated with seizures and then activates the stimulator during these times. **Responsive neurostimulation (RNS)** is a technique that has been used in adults with epilepsy; it requires the implantation of subdural or depth electrodes to directly monitor seizure activity on a long-term basis to detect and abort the seizures. Once a seizure is detected, electrical stimulation is delivered to that area of the brain to stop the seizure. **Deep brain stimulation (DBS)** is approved for refractory partial epilepsy in adults. In DBS, the electrical stimulation is provided by two stereotactically placed electrodes in bilateral thalamic nuclei (anterior nuclei for focal epilepsy and centromedian nuclei, as being studied, in generalized epilepsies).

DISCONTINUATION OF THERAPY

Discontinuation of AEDs is usually indicated when otherwise well children are free of seizures for at least 2 years. In more severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom with treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 months.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 years or longer and who have a normal EEG when AED withdrawal is initiated remain free of seizures after discontinuing medication, and most relapses occur within the first 6 months.

Certain risk factors can help clinicians predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign (idiopathic) epilepsy. In patients with absences or in patients treated with valproate or other medications for primary generalized epilepsy, the risk of relapse might be high despite a normal EEG because valproate (and less so other AEDs for primary generalized epilepsy) can normalize EEGs with generalized spike-wave abnormalities. Thus in these patients, repeating the EEG during drug tapering may help identify a recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than one AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually, often over a period of 3-6 months, but many advocate for shorter periods down to 6 weeks. Abrupt discontinuation can result in withdrawal seizures or in status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2-3 months after AEDs are completely discontinued indicate a relapse, and resumption of treatment is usually warranted. Seizures that occur before that, such as during or shortly after a medication taper, may be withdrawal seizures or may indicate a relapse.

The decision to attempt AED withdrawal must be assessed mutually by the clinician, the parents, and the child depending on the child's age. The American Academy of Neurology in collaboration with the American Epilepsy Society has developed guidelines regarding such withdrawals. In addition, there is an online risk calculator tool that has been generated based on clinical nomograms from an independent participant data meta-analysis. This tool can be used, with caution, as an aid to estimate risk of recurrence, but individualized decision based on each case's particulars and on the discussions with the caretakers should be the final guide in planning the course of care. The patient and family should be counseled fully on what to expect, what precautions to take (e.g., cessation of driving for a period), and what to do in case of relapse. A prescription for rectal diazepam or intranasal midazolam to be given at the time of seizures that might occur during and after tapering is usually warranted (see Table 633.23 for dosing).

Table 633.17 Measures in Clinical Practice to Reduce the Risk of SUDEP

Counseling: Explaining SUDEP and risk factors is imperative, even if the discussion may be uncomfortable. Emphasize modifiable risk factors, such as compliance with taking medication.
Reduction of tonic-clonic seizures: Optimum treatment, good drug compliance, lifestyle advice (e.g., alcohol intake, sleep deprivation).
Treatment changes: Change in a gradually staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patient should have access to immediate advice in the event of worsening seizures during periods of change.
Supervision at night for patients at high risk: Attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring).
Choice of drugs: Caution with AEDs with potential cardiorespiratory adverse effects.
Act on ictal warning signs: Tonic-clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnea, and postictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with preexisting cardiac or respiratory impairment.
Supervision after a tonic-clonic seizure: Continuous attendance until full consciousness is restored; call emergency services for high-risk seizures.

EEG, Electroencephalogram; SUDEP, sudden unexpected death in epilepsy.
From Shorvan S, Tomson T. Sudden unexpected death in epilepsy. *Lancet.* 2011;378:2028–2036.

SUDDEN UNEXPECTED DEATH IN EPILEPSY

SUDEP is the most common epilepsy-related cause of mortality and is responsible for up to 17% of deaths in patients with epilepsy. Risk factors include polytherapy with more than three AEDs, male gender, young age at epilepsy onset, developmental delay, poor AED compliance, nocturnal seizures, poorly controlled convulsive seizures (especially if >3 per year), high frequency of seizures (especially if >50 per year), and having epilepsy for >30 years in adults. Patients are usually found dead in their bed in a prone position, with evidence suggesting a recent seizure.

Respiratory, cardiogenic, and mixed respiratory/cardiogenic mechanisms have been hypothesized to cause SUDEP. Respiratory models include seizure-induced central hypoventilation, neurogenic pulmonary edema, and disturbances in the brainstem serotonergic system leading to respiratory arrest. Cardiogenic models include seizure-induced cardiac arrhythmia as well as **cardiocerebral channelopathies** in which ion channels are expressed in both the brain and heart, causing cardiac dysfunction concurrent with the seizures. *SCN1A, SNC8A, ATP1A3,* and *KCNQ1* are examples of genes that encode for cardiocerebral ion channels known to cause epilepsy and that have also been associated with SUDEP. Mixed respiratory/cardiogenic models include seizure-induced dysautonomia, high adenosine levels during seizure causing cardiorespiratory collapse, and spreading depression in the brainstem causing dysautonomia. More data are needed to determine if safety pillows, seizure detection devices, or selective serotonin reuptake inhibitors may be of benefit in preventing SUDEP. *It is currently recommended to counsel the patients and family regarding SUDEP, even if the topic is not comfortable to talk about.* In addition to providing them with important information, such counseling may also encourage families to address modifiable risk factors such as AED compliance. Table 633.17 lists other possible preventive measures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.7 Neonatal Seizures

Mohamad A. Mikati and Monica E. Lemmon

Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period of life: seizures occur in 57.5 per 1,000 in infants with birthweights <1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g. The etiology of neonatal seizures depends on postnatal age of onset (Fig. 633.11, Table 633.18) as well as EEG and clinical features (Fig. 633.12, Table 633.18 and Table 633.19).

PATHOPHYSIOLOGY

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these include a delay in Na^+, K^+-adenosine triphosphatase maturation and increased NMDA and AMPA receptor density. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GLUR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical scenario.

Another difference is delay in the development of inhibitory GABAergic transmission. In fact, GABA in the immature brain has an excitatory function because the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. How applicable this is to human neonates and, if so, at what conceptional ages, is not clear yet. This phenomenon, however, appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures.

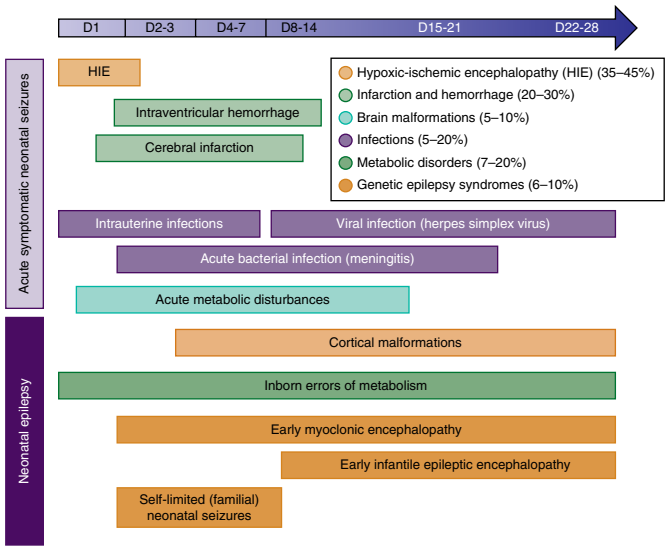

Fig. 633.11 Etiologies of neonatal seizures according to seizure onset timing. The most common causes of seizures occurring within the first 24 hr of life are hypoxic-ischemic encephalopathy or vascular etiologies, followed by acute metabolic disturbances such as hypoglycemia or inborn errors of metabolism such as pyridoxine dependency. Within the next 24-72 hr, the main etiologies include infection, cortical malformations, cerebral infarction, inborn errors of metabolism such as glycine encephalopathy, urea cycle disturbances, pyridoxine dependency, and benign familial neonatal seizures. Over the next 72 hr to a week, causes include cortical malformations, cerebral infarction or hemorrhage, or inborn errors of metabolism, such as urea cycle disturbances. In the next 1-4 wk, the differential includes cortical malformations, viral infections such as herpes simplex, or genetic epilepsy syndromes. *(From Kim EH, Shin J, Lee BK. Neonatal seizures: diagnostic updates based on new definition and classification. Clin Exp Pediatr. 2022;65[8]:387–397, Fig. 1, p. 389.)*

TYPES OF NEONATAL SEIZURES

There are two main neonatal seizure types: electroclinical and electrographic only. Electroclinical seizures can be categorized as motor, nonmotor, and sequential. Motor seizures include automatisms, clonic seizures, epileptic spasms, myoclonic seizures, and tonic seizures. Nonmotor seizures include autonomic seizures and behavioral arrest (see Fig. 633.12 and Table 633.19). Differentiating seizure types based on

Table 633.18 Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS

Hypoxic-ischemic encephalopathy
Drug withdrawal, maternal drug use of opiate or barbiturates
Drug toxicity: lidocaine, penicillin
Intraventricular hemorrhage
Sepsis
Acute metabolic disorders
- Hypocalcemia
- Maternal hyperthyroidism, or hypoparathyroidism
- Hypoglycemia
- Maternal diabetes
- Hyperinsulinemic hypoglycemia
- Hypomagnesemia
- Hyponatremia or hypernatremia
- Iatrogenic or inappropriate antidiuretic hormone secretion

Inborn errors of metabolism
- Galactosemia
- Hyperglycinemia
- Urea cycle disorders

Pyridoxine dependency and pyridoxal-5-phosphate dependency (must be considered at any age)

AGES 4-14 DAYS

Infection
- Meningitis (bacterial)
- Encephalitis (enteroviral, herpes simplex)

Metabolic disorders
- Hypocalcemia related to diet, milk formula
- Hypoglycemia, persistent
- Inherited disorders of metabolism
- Galactosemia
- Fructosemia
- Leucine sensitivity
- Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome
- Anterior pituitary hypoplasia, pancreatic islet cell tumor
- Beckwith syndrome

Drug withdrawal, maternal drug use of narcotics or barbiturates
Benign neonatal convulsions, familial and nonfamilial
Kernicterus, hyperbilirubinemia
Developmental delay, epilepsy, neonatal diabetes syndrome

AGES 2-8 WK

Infection
- Herpes simplex or enteroviral encephalitis
- Bacterial meningitis

Head injury
- Subdural hematoma
- Child abuse

Inherited disorders of metabolism
- Aminoacidurias
- Urea cycle defects
- Organic acidurias
- Neonatal adrenoleukodystrophy

Malformations of cortical development
- Lissencephaly
- Focal cortical dysplasia

Tuberous sclerosis
Sturge-Weber syndrome

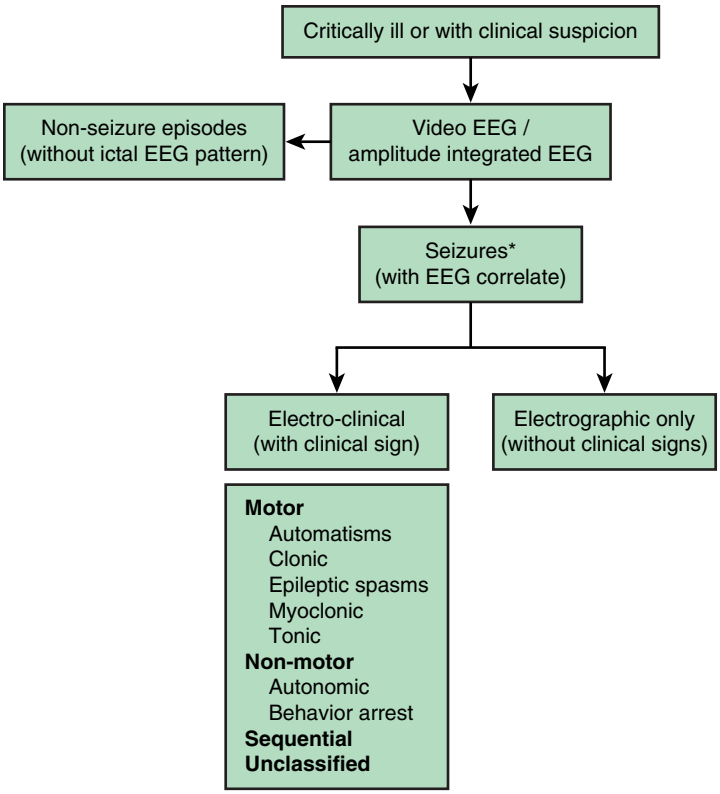

Fig. 633.12 Diagnostic framework of seizures in the neonatal period, including classification of seizures. Adapted from 2017 ILAE seizure classification. Neonates present with discrete events suspected to be epileptic seizures or are critically ill (often ventilated, sedated, and treated with muscle relaxants in intensive care). *If no EEG is available, refer to global alignment of immunization safety assessment in pregnancy levels of diagnostic certainty. *(From Pressler RM, Cilio MR, Mizrahi EM, et al, The ILAE classification of seizures and the epilepsies: modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. Epilepsia. 2021;62[3]:615–628, Fig. 2.)*

Table 633.19 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on one side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetric posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Generalized tonic	Sustained symmetric posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk: asymmetric or symmetric Typically not repetitive or may recur at a slow rate May be generalized, focal, multifocal, or fragmentary May be provoked by stimulation Presumed pathophysiology: may be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor/flexor Unilateral or bilateral May occur in clusters Asymmetric or symmetric Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
MOTOR AUTOMATISMS (UNILATERAL, BILATERAL, ASYMMETRIC OR SYMMETRIC)	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic

From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures.* Philadelphia: Lippincott-Raven, 1998: Table 4, p. 21.

clinical appearance alone is challenging. Thus in many cases, specifically in sick neonates with a history of suspected neurologic injury, continuous bedside EEG is necessary to make this distinction.

Motor Seizures

Automatisms

Automatisms include transient eye deviations, nystagmus, blinking, mouthing, and abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping). Automatisms occur more commonly in premature than in full-term infants.

Clonic Seizures

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a non-Jacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period, presumably because of decreased connectivity associated with incomplete myelination at this age.

Epileptic Spasms

Epileptic spasms are sudden generalized jerks lasting 1-2 seconds that are distinguished from generalized tonic spells by their shorter duration and by the fact that spasms are usually associated with a single, very brief, generalized discharge.

Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 milliseconds) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of the upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

Tonic Seizures

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of the trunk or neck in an asymmetric way, often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extensions or tonic flexions of the upper extremities often associated with tonic extension of the lower extremities and trunk.

Nonmotor Seizures

Autonomic

Autonomic seizures involve fluctuations in autonomic system function, including alterations in the cardiovascular, vasomotor, pupillary, and thermoregulatory function. These seizures may include heart rate changes, hypertension episodes, and apnea. Autonomic seizures typically accompany additional seizure types and are rarely seen in isolation.

Behavioral Arrest

Behavioral arrest seizures include cessation of activity or immobilization. This seizure type is rarely seen in isolation and can be seen as a component of sequential seizures.

Sequential

Sequential seizures have been defined by the ILAE as a seizure type for "events with a sequent of signs, symptoms, and EEG changes at different times." An example would be a sequence of tonic, then clonic, then automatisms, and autonomic manifestations with varying lateralization during one seizure. In these seizures, it can be challenging to define the predominant semiology, and features present in a sequence. These are most commonly associated with genetic epilepsies, including KCNQ2 encephalopathy.

Seizures Versus Jitteriness

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Unlike jitteriness, seizures often involve eye deviation and autonomic changes.

ETIOLOGY

Table 633.18 and Table 633.20 and Figure 633.11 list causes of neonatal seizures.

Hypoxic-Ischemic Encephalopathy

This is the most common cause of neonatal seizures, accounting for 50–60% of patients. Seizures secondary to this encephalopathy occur within 24 hours of birth. Abnormal EEG background, including excessive discontinuity, burst suppression, and extremely low voltage patterns, are strongly associated with the development of seizures.

Vascular Events

These include intracranial bleeds and ischemic strokes and account for 10–20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinal matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure, and these can be diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

Intracranial Infections

Bacterial and nonbacterial infections account for 5–10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus) infections, and, particularly, herpes simplex encephalitis.

Brain Malformations

Brain malformations account for 5–10% of neonatal seizure cases. An example is **Aicardi syndrome**, which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures, including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

Metabolic Disturbances

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency (Table 633.21).

Hypoglycemia can cause neurologic disturbances and is common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypocalcemia occurs with two peaks. The first peak corresponds to low birthweight infants and is evident in the first 2-3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hyponatremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion or water intoxication.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics that are inadvertently administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic workup (see Chapter 633.2), including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine

Table 633.20 Clinical Characteristics and Genetic Variants of Neonatal Epilepsy Syndromes

SYNDROME	SEIZURE ONSET	TYPES OF SEIZURE	ETIOLOGY	EEG FEATURES	PROGNOSIS
Self-limited familial neonatal seizures	Days 2-3	Focal tonic seizures, often with apnea, vocalization, or autonomic change, frequent brief seizures	Autosomal dominant variants in *KCNQ2, KCNQ3, SCN2A*	Background: usually normal Interictal: a theta pointu alternant pattern or focal or multifocal epileptiform abnormalities	Favorable outcome, typically resolved seizures by 6 mo of age
Self-limited neonatal seizures	Days 4-6	Unilateral or bilateral clonic seizures, frequent seizure clusters	Most unknown, rare *KCNQ2* variant	Ictal: focal rhythmic spike or slow waves	Favorable outcome, usually decreased seizure within 48 hr
Early-infantile epileptic encephalopathy	First 2 wk, up to 3 mo	Tonic seizures, epileptic spasms	Structural brain malformations, genetic variants in *ARX, CDKL5, SLC25A22, STXBP1, KCNQ2, SPTAN1, SCN2A*, metabolic disorders	Background/interictal: suppression-burst patten: same asleep and awake Ictal: diffuse attenuation with emergency of low-voltage, high-frequency activity, or focal ictal rhythms	Frequent early-life mortality, severe developmental disabilities
Early myoclonic encephalopathy	Hours to months	Multifocal erratic myoclonus	Metabolic disorders, genetic variants in *STXBP1, TBC1D24, GABRA1*	Background/interictal: suppression-burst patten, enhanced by sleep Ictal: no ictal pattern but followed by bursts, or focal ictal rhythms	
Epilepsy of infancy with migrating focal seizures	Days to months	Nearly continuous focal clonic and/or tonic, autonomic, migrating seizures	Pathogenic variants in *KCNT1, SCN2A, SCN1A, SLC25A22, PLCB1, QARS*	Background: normal or diffuse slowing Interictal: multifocal discharges Ictal: rhythmic alpha or theta activities that evolve simultaneously from different brain regions and migrate to contiguous or contralateral regions	Generally poor with refractory seizures and severe developmental disabilities

From Kim EH, Shin J, Lee BK. Neonatal seizures: diagnostic updates based on new definition and classification. *Clin Exp Pediatr*. 2022;65(8):387–397. Table 1, p. 390.

for organic acids, α-aminoadipic acid semialdehyde, and sulfocysteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α-aminoadipic acid semialdehyde, pyridoxal phosphate, 5-methyltetrahydrofolate (5-MTHF), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups, which these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia**, for example, requires measuring the ratio of CSF glycine to plasma glycine.

Pyridoxine- and **pyridoxal-dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the first few hours of life. Cognitive impairment is often associated if therapy is delayed (see Chapter 633.4).

Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal after birth. Such drugs include narcotic analgesics, sedative-hypnotics, and others. The associated seizures appear during the first 3 days of life.

Neonatal Seizure Genetic Syndromes

Seizure syndromes include **benign neonatal convulsions (fifth-day fits)**, which are usually apneic, and focal motor seizures that start around the fifth day of life (see Table 633.20). Interictal EEG shows a distinctive pattern called *theta pointu alternant* (runs of sharp 4- to 7-Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have an onset at 2-4 days of age and usually remit at 2-15 weeks of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by pathogenic variants in *KCNQ2* and *KCNQ3*. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy (Ohtahara syndrome)** are discussed in Chapter 633.4.

Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see Chapter 634).

DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history and performing an adequate physical examination; however, the *American Clinical Neurophysiology Society Guidelines for Neonatal EEG Monitoring recommend EEG monitoring in cases where there is a clinical concern for seizure and/or when*

Table 633.21 Overview of Diagnostic Findings in Inborn Errors of Metabolism Presenting with Isolated Neonatal Seizures

DISORDER	MRI AND MRS FINDINGS	CSF FINDINGS	FURTHER DIAGNOSTIC TESTING
Pyridoxine-dependent seizures	Normal or hypoplasia of corpus callosum and cerebellum	Increased levels of α-AASA, pipecolic acid, and neurotransmitter markers	Urinary and serum α-AASA or pipecolic acid, *ALDH7A1* gene testing
Pyridoxal-phosphate–dependent seizures	Generalized atrophy	May be normal or nonspecific changes	Pyridoxamine-5-phosphate oxidase gene testing
Defects of serine biogenesis	Initially normal, progressing to profound hypomyelination	Low levels of serine; may also have low levels of glycine or 5-MTHF	Skin biopsy for 3-phosphoglycerate dehydrogenase activity
GLUT-1 deficiency	Normal or generalized atrophy	CSF glucose <40 mg/dL or <half of serum glucose	FDG-PET; 3-OMG uptake in red blood cells; gene testing for *SLC2A1*
Nonketotic hyperglycinemia	Normal, or agenesis or thinning of the corpus callosum	Increased levels of glycine, and increased CSF/plasma glycine ratio	Liver glycine cleavage complex enzyme activity; gene testing for nonketotic hyperglycinemia
Sulfite oxidase/molybdenum cofactor deficiency	MRI findings can mimic those of hypoxic-ischemic injury; MRS reveals increased levels of lactate, myoinositol, and choline, with decreased levels of NAA	Normal or nonspecific changes in amino acid profile	Plasma homocysteine and uric acid; urine sulfites, sulfocysteine, and thiosulfates; sulfite oxidase enzyme activity in skin or liver biopsy
Congenital neuronal ceroid-lipofuscinosis	Generalized cerebral hypoplasia	Normal	Cathepsin D gene testing
γ-Aminobutyric acid transferase deficiency	MRI indicates leukodystrophy and agenesis of the corpus callosum; MRS indicates elevated levels of γ-aminobutyric acid in the basal ganglia	Increased levels of homocarnosine	Enzyme activity in lymphocytes
Dihydropyrimidine dehydrogenase deficiency	Diffuse atrophy	Increased levels of uracil and thymine	Dihydropyrimidine dehydrogenase gene testing
Creatine deficiency syndromes	MRI indicates delayed myelination MRS reveals absent creatine peak	Normal	Serum creatine and guanidinoacetate; urinary creatine, creatinine, and guanidinoacetate; fibroblast enzyme activity; specific genetic testing

For current information on the best locations to perform biochemical and genetic testing, see genereviews.org.
3-OMG, 3-O-methyl-D-glucose; 5-MTHF, 5-methyltetrahydrofolate; α-AASA, α-aminoadipic emialdehyde; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate.
From Ficicioglu C, Bearden D. Isolated neonatal seizures: when to suspect inborn errors of metabolism. *Pediatric Neurol.* 2011;45:283–291. Table 2.

an infant has a condition that predisposes the infant to seizures. EEG monitoring can show epileptiform activity (e.g., sharp waves) between the seizures (suggesting an increased risk for seizures) and confirm electrographic seizure activity if a clinical seizure is recorded. Additionally, EEG monitoring is often necessary because electrographic seizures can occur without observed clinical signs **(electroclinical dissociation)**. This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal clinical manifestations.

Continuous bedside EEG monitoring in the neonatal intensive care unit is the preferred clinical practice for neonates at risk for neonatal seizures and brain injury. Amplitude-integrated EEG (aEEG) monitoring is also used as an *adjunct* to conventional EEG monitoring and provides a bedside graphic representation of a neonate's electrocerebral activity, which may aid in earlier seizure identification. Appropriately trained nurses and providers can identify possible seizure activity using aEEG and can then contact the neurophysiologist to confirm the presence or absence of seizures. Examples of situations in which continuous EEG monitoring should be used include cases of **hypoxic-ischemic injury** (particularly if an infant is undergoing therapeutic hypothermia), intracranial infarct or hemorrhage, or CNS infection; for seizure screening in infants receiving paralytics; in infants with congenital cerebral malformations; and/or in infants in whom clinical events suspected to be seizures need to be characterized.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the retina might show the presence of chorioretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. **Aicardi syndrome** is associated with coloboma of the iris and retinal lacunae. Inspection of the skin might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on ultraviolet light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, bedside serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity,

DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium 0.2 mL/kg of a 50% solution of $MgSO_4$. Serum electrolyte measurement can indicate significant hyponatremia (serum sodium <115 mEq/L) or hypernatremia (serum sodium >160 mEq/L) as a cause of the seizure disorder.

A **lumbar puncture** may be indicated in neonates with seizures, unless the cause is obviously related to a metabolic disorder (such as hypoglycemia or hypocalcemia) or attributable to a structural etiology such as hypoxic-ischemic injury or intracranial hemorrhage. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the two disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many **inborn errors of metabolism** cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the first few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of an **organic acidemia** such as methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, a bulging fontanel, and muscle rigidity during the first week of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include **nonketotic hyperglycinemia**, an intractable condition characterized by markedly elevated plasma and CSF glycine levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease, suggested by elevated levels of serum and CSF lactate or an increased lactate:pyruvate ratio. **Biotinidase deficiency** should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part IX, Metabolic Disorders.

Unintentional **injection of a local anesthetic** into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the second to third day of life, with a seizure frequency of 10-20/day. Patients are normal between seizures, which stop in 1-6 months. These are caused by pathogenic variants in the voltage-sensitive potassium channel genes *Kv7.2* and *Kv7.3* (*KCNQ2* and *KCNQ3*). Other variants in *Kv7.2* cause severe neonatal epileptic encephalopathy. **Fifth-day fits** occur on day 5 of life (4-6 days) in normal-appearing neonates. The seizures are multifocal and are often present for <24 hours. The diagnosis requires exclusion of other causes of seizures and sequencing of the previously mentioned genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin even if there is an initial treatment response. The history may suggest that similar seizures occurred in utero. When pyridoxine-dependent seizures are suspected, 100 mg of pyridoxine should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of intravenous pyridoxine. Therefore a 6-week trial of oral pyridoxine (100-200 mg/day) or, preferably, pyridoxal phosphate (because pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to intravenous pyridoxine. Measurement of serum pipecolic acid and α-aminoadipic acid semialdehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folinic acid) or pyridoxal phosphate (up to 50 mg/kg/day given every 6 hours). **Cerebral folate deficiency** should also be ruled out by a medication trial (folinic acid 1-3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 633.4). The earlier the therapy is initiated in these vitamin-responsive disorders, the more favorable the outcome.

Drug withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. Drugs include barbiturates, benzodiazepines, heroin, buprenorphine, fentanyl, and methadone. The infant may be jittery, irritable, and lethargic and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe **cytoarchitectural abnormalities** of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders.

PROGNOSIS

The prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care but depends on the etiology and other organ system injury. Prematurity and high seizure burden have been shown to be associated with early death. The correlation between EEG findings and prognosis is clear. An abnormal EEG background is a powerful predictor of a less favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere are also correlated with a poorer outcome. Patients with seizures secondary to severe hypoxic-ischemic encephalopathy have a 50% chance of typical development, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

TREATMENT

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., HIE, hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma) whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of electroclinical and electrographic seizures. An important consideration before starting anticonvulsants is deciding, based on the severity, duration, and frequency of the seizures, if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply

be started on maintenance doses of a long-acting drug. Patients may require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

Lorazepam and Other Benzodiazepines

Lorazepam is often used in the acute treatment of neonatal seizures; it is distributed to the brain very quickly and exerts its anticonvulsant effect in less than 5 minutes. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hours. Usually, it does not cause hypotension or respiratory depression. The dose is 0.1 mg/kg when used for acute treatment of seizures, and 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hours when used as a scheduled medication. Diazepam has also been used, and midazolam is often started as a continuous infusion for refractory cases of neonatal seizures. Midazolam doses used have been in the range of 0.05-0.15 mg/kg as an initial intravenous bolus, with a continuous infusion of 0.5-1 μg/kg/min intravenously that can then be gradually titrated upward, if tolerated, every 5 minutes or longer, to a maximum of approximately 33 μg/kg/min (2 mg/kg/hr).

Phenobarbital

Consensus guidelines and existing data support the use of phenobarbital as the first-choice treatment of neonatal seizures. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 10-20 mg/kg can be given until a cumulative dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day, usually administered in two separate doses. Phenobarbital is metabolized in the liver and is excreted through the kidneys. Thus any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter the serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully. The use of phenobarbital can be associated with electroclinical dissociation, where electrographic seizures persist despite the resolution of clinical seizures, after the drug is given. Subsequent EEG monitoring is therefore imperative to rule out subclinical seizure activity.

Phenytoin and Fosphenytoin

Consensus guidelines support the use of fosphenytoin as a second line anti-seizure medication in neonatal seizures. The only randomized controlled trial to compare the efficacy of phenobarbital versus phenytoin did not find that one drug was superior to the other for the treatment of neonatal seizures. Because of its reduced solubility, potentially severe local cutaneous reactions, interactions with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used, and fosphenytoin is the preferred agent. Phenytoin is given at a loading dose of 20 mg/kg at a rate not to exceed 0.5-1.0 mg/kg/min, so as to prevent cardiac problems; the medication should be used with caution or avoided in patients with significant heart disease. The heart rate should be monitored while the drug is administered. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Additionally, phenytoin and fosphenytoin should not be used in conjunction with intravenous lidocaine owing to the concern that both drugs can increase the risk of cardiac arrhythmias and hypotension.

As stated earlier, fosphenytoin, which is a phosphate ester prodrug, is preferable to phenytoin. It is highly soluble in water and can be administered safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 minutes. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.

Other Medications

Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phenytoin, and an additional 15% respond to the second agent. **Levetiracetam** (which can be given intravenously with a later convenient conversion to oral solution) is commonly used as a second- or third-line agent. In a randomized controlled trial of levetiracetam (40-60 mg/kg) versus phenobarbital (20-40 mg/kg) for neonatal seizures, 28% of infants responded to levetiracetam as a first-line agent, as compared with 80% of infants who received phenobarbital. The maintenance dosages used are 40-60 mg/kg/day of levetiracetam, dosed 3 times daily. Topiramate, a possible third line agent, can be given at a dose of 5-10 mg/kg/day (sometimes higher). There is growing evidence that lidocaine is an effective second- or third-line agent, and some studies suggest it may be superior to benzodiazepines in treating neonatal seizures. A bolus dose of 2 mg/kg is given, followed by an infusion at a rate of 4-6 mg/kg/hr. Cardiac arrhythmias and hypotension were not reported at this dosing range but are potential side effects at higher doses. Lidocaine should not be used in conjunction with phenytoin or fosphenytoin owing to concern for cardiac side effects. A randomized controlled trial suggested that bumetanide provided added reduction in seizure burden when used as an adjunct agent without an increased risk of adverse events. Studies of the efficacy and safety of lacosamide for neonatal seizures are ongoing. Primidone, carbamazepine, lamotrigine, or valproate use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 years of age than in older children.

Duration of Therapy

The duration of therapy is related to the risk of epilepsy developing later in infants suffering from neonatal seizures, a risk that ranges from 10% to 30% and depends on the individual neurologic examination and the etiology of the seizures. Existing data and consensus guidelines support the discontinuation of anticonvulsant medications before hospital discharge in neonates with acute symptomatic seizures.

ADDRESSING FAMILY NEEDS

Over half of parents of newborns with seizures experience symptoms of anxiety, one third experience symptoms of depression. Existing data suggest that parents of newborns with seizures experience consistent challenges, including prognostic uncertainty, concern about adapting their family life, and the physical and emotional toll of caring for a critically ill infant. Clinicians can help address these needs by attending to parent psychosocial needs, connecting parents to peer support, and communicating effectively.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.8 Status Epilepticus

Mohamad A. Mikati and Dmitry Tchapyjnikov

Status epilepticus (SE) is a medical emergency that should be anticipated in any patient who presents with an acute seizure. The ILAE has refined the definition of SE to reflect the time at which treatment should be initiated (t_1) and time at which continuous seizure activity leads to long-term sequelae (t_2) such as neuronal injury, depending on the type of SE. For generalized tonic-clonic seizures, SE is defined as continuous convulsive activity or recurrent generalized convulsive seizure activity without regaining consciousness (t_1 = 5 minutes, t_2 ≥30 minutes). The definition differs for SE consisting of focal seizures with impaired awareness (t_1 = 10 minutes, t_2 = 30 minutes) and absence SE (t_1 = 10-15 minutes, t_2 = unknown). The most common type of SE is **convulsive status epilepticus** (generalized tonic, clonic, or tonic-clonic), but other types do occur, including **nonconvulsive status** (focal with impaired awareness, absence), myoclonic status, epilepsia partialis continua, and neonatal SE. The incidence of SE ranges between 10 and 60 per 100,000 population in various studies. SE is most common in children younger than 5 years of age, with an incidence in this age-group of ~100 per 100,000 children.

Approximately 30% of patients presenting with SE are having their first seizure, and approximately 40% of these later develop epilepsy.

Febrile status epilepticus is the most common type of SE in children. Currently, with the recognition of SE as a medical emergency, the mortality rate is 4–5%, most of it secondary to the underlying etiology rather than to the seizures. SE carries an approximately 14% risk of new neurologic deficits, most of them (12.5%) secondary to the underlying pathology.

Table 633.22 Clinical Features of Febrile Infection–Related Epilepsy Syndrome (FIRES)

Age of onset: 2-17 (median 8) yr
Medical history: febrile seizures in rare cases, no epilepsy or other chronic disease, normal psychomotor development
Family history: uninformative (e.g., no allergies and especially no other family member with FIRES)
Prodromal phase:
- Different types of febrile infections, often flulike
- Frequently followed by an afebrile and asymptomatic interval of 1-2 days resulting in a consistent neurologic syndrome

Neurologic syndrome:
- Peracute/explosive onset of multifocal or generalized seizures of different types directly evolving into superrefractory status epilepticus
- Without other neurologic features (pure seizure phenotype)

EEG: global slowing or multifocal discharges with bilateral frontotemporal predominance, or both
CSF: normal or pleocytosis, normal protein concentration, no oligoclonal bands
MRI (during the acute phase of status epilepticus):
- No or nonextensive bitemporal or diffuse abnormalities
- Sporadic involvement of the basal ganglia, diffuse cortical edema, and/or hydrocephalus

Cause: extensive infectiologic (e.g., brain biopsies), metabolic (e.g., muscle biopsy), and genetic investigations (e.g., *POLG, SCN1A, PCDH19* genes, CNVs, exome sequencing) without causative findings
Coexisting autoimmunities: some patients with autoantibodies (e.g., TPO or GluR antibodies)
Treatment: resistance to nearly all drugs and even anesthetics
Outcome:
- Almost always chronic epilepsy without silent period
- Often global brain atrophy after a few weeks with mild to severe neuropsychologic impairments

CNVs, Copy number variants; GluR, glutamate receptor; TPO, thyroid peroxidase.
From van Baalen A, Vezzani A, Hausker M, et al. Febrile infection-related epilepsy syndrome: clinical review and hypotheses of epileptogenesis. *Neuropediatrics.* 2017;48:5–18, Table 1, p.6.

Nonconvulsive status epilepticus (NCSE) can manifest as a confusional state, dementia, fluctuating mental status, hallucinations, paranoia, aggressiveness, catatonia, and/or psychotic symptoms. It should be considered in all children who present to the hospital in an encephalopathic state or in the intensive care unit when a child's mental status fails to improve. **Epilepsia partialis continua** has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (MELAS), and Rasmussen encephalitis.

Refractory status epilepticus is SE in which a child's seizures fail to resolve despite therapy with both a benzodiazepine and a nonbenzodiazepine medication. **Superrefractory status epilepticus** is SE that has failed to resolve, or recurs, within 24 hours or more despite therapy that includes a continuous infusion such as midazolam and/or pentobarbital.

New-onset refractory status epilepticus (NORSE) is defined as SE without a clear etiology after initial investigations (typically brain imaging as well as blood and CSF analysis) have ruled out common causes for SE, including stroke, infection, and toxic/metabolic derangements. Children presenting with NORSE may sometimes have a prodromal flulike illness before developing seizures but are otherwise often previously healthy with no history of seizures. A clear etiology is ultimately determined only 50% of the time and includes inflammatory and autoimmune causes (such as anti–NMDA receptor encephalitis), rare infectious disorders, or genetic causes that predispose the child to having prolonged seizures (such as pathogenic variants in *PCDH19*). Children with NORSE almost always develop superrefractory status epilepticus, and the prognosis is often poor with >10% mortality and up to two thirds developing long-term neurologic disability. **Febrile infection-related epilepsy syndrome (FIRES)** is a subtype of NORSE in which the child also has a febrile illness 1-14 days preceding seizure onset (Table 633.22 and Fig. 633.13). A fever does not have to be present at the time of seizure onset as long as a fever was present in the preceding period. FIRES was thought to be a condition mostly affecting children; however, it is recognized that NORSE and FIRES can occur in both adults and children. An international group of pediatric epileptologists, pediatric neurointensivists, rheumatologists, and basic scientists with interest and expertise in FIRES published recommendations regarding the approach to and management of FIRES (Figs. 633.14 and 633.15). FIRES should be considered in all previously healthy patients older than 2 years of age who present with sudden-onset refractory SE within 2 weeks of a prior febrile illness (see Table 633.22). They also recommended early use of the ketogenic diet and the IL-1 receptor

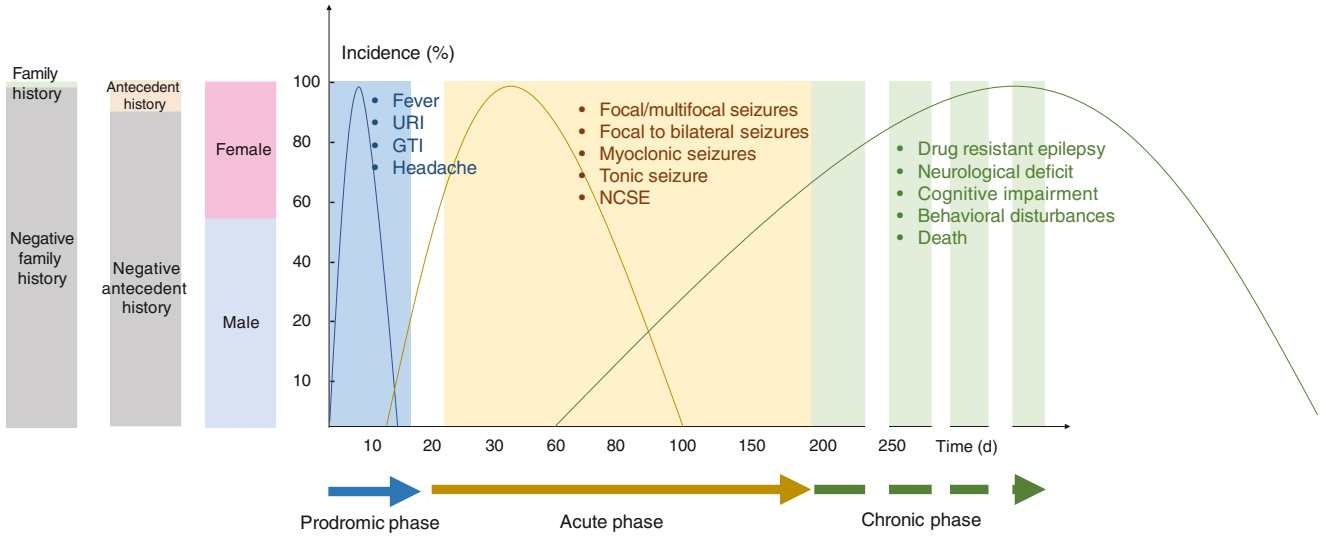

Fig. 633.13 Clinical findings in FIRES and NORSE, including family history, antecedents, and sex predominance. The graph shows the symptoms during the prodromic phase, type of seizures in the acute phase, and clinical findings during the chronic phase. GTI, Gastrointestinal tract infections; NCSE, nonconvulsive status epilepticus; URI, upper respiratory infection. *(From Specchio N, Pietrafusa N. New-onset refractory status epilepticus and febrile infection-related epilepsy syndrome. Dev Med Child Neurol. 2020;62:897–905, Fig. 1, p. 899.)*

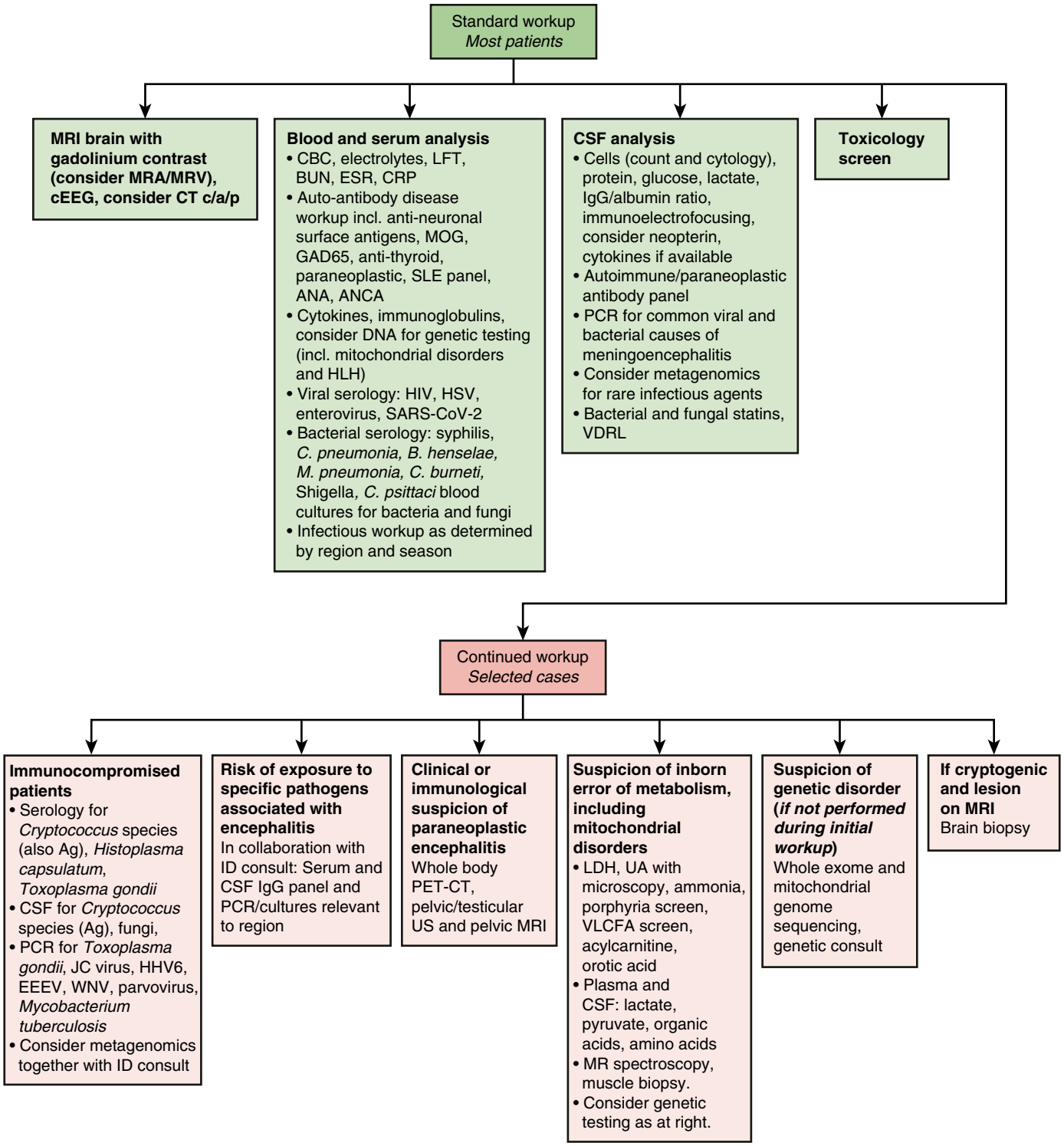

Fig. 633.14 Algorithm for diagnostic workup in NORSE, including FIRES. Ag, Antigen; ANA, anti-nuclear antibodies, ANCA, anti-neutrophil cytoplasmic antibodies; *B. henselae*, *Bartonella henselae*; BUN, blood urea nitrogen; *C. burnetii*, *Coxiella burnetii*; *C. pneumoniae*, *Chlamydia pneumoniae*; *C. psittaci*, *Chlamydia psittaci*; CBC, complete blood count; cEEG, continuous EEG; CRP, C-reactive protein; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; EEEV, eastern equine encephalitis virus; EEG, electroencephalography; ESR, erythrocyte sedimentation rate; GAD, glutamic acid decarboxylase; HHV, human herpesvirus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; ID, infectious disease; IgG, immunoglobulin G; JC, John Cunningham; LDH, lactate dehydrogenase; LFT, liver function test; *M. pneumoniae*, *Mycoplasma pneumoniae*; MOG, myelin oligodendrocyte glycoprotein; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PCR, polymerase chain reaction; PET-CT, positron emission tomography–computed tomography; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; UA, urine analysis; US; ultrasound; VLCFA, very long-chain fatty acid; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus; WNV, West Nile virus. *(Adapted from NORSE Institute website norseinstitute.org; and from Sculier C, Gaspard N. New onset refractory status epilepticus [NORSE]. Seizure. 2019;68:72–78, Fig. 1.)*

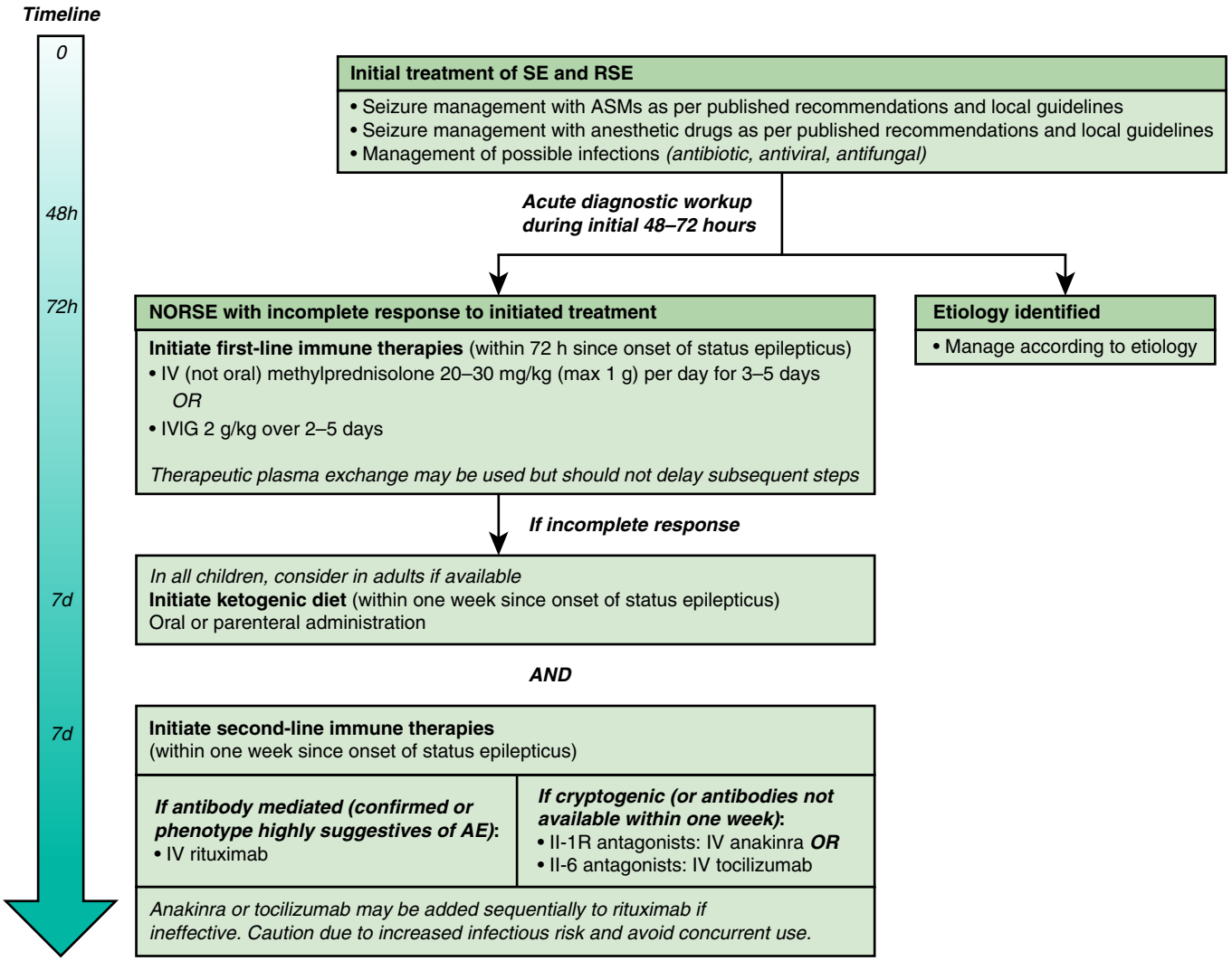

Try to minimize the exposure to anesthetic drugs, especially barbiturates, and monitor the patient closely for complications of prolonged sedation

Fig. 633.15 Suggested treatment algorithm for NORSE, including FIRES (expert opinion). AE, Autoimmune encephalitis; ASM, antiseizure medication; IV, intravenous; IVIG, intravenous immunoglobulins; RSE, refractory status epilepticus; SE, status epilepticus. *(From Wickström R, Taraschenko O, Dilena R, et al. International consensus recommendations for management of new onset refractory status epilepticus [NORSE] including febrile infection-related epilepsy syndrome [FIRES]: summary and clinical tools. Epilepsia. 2022;63:2827–2839, Fig. 2, p. 2836.)*

antagonist that blocks IL-1β activity, anakinra, in FIRES patients (see Fig. 633.15).

ETIOLOGY

Etiologies of SE include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol misuse in adolescents; drug withdrawal or overdose in patients taking AEDs; hypoglycemia; hypocalcemia; hyponatremia; hypomagnesemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (anti–NMDA receptor; steroid-responsive encephalopathy associated with autoimmune thyroiditis [SREAT], and anti–voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine- and pyridoxal-phosphate dependency (these usually present in infancy, but childhood onset is also possible); inborn errors of metabolism (see Chapter 633.2) such as nonketotic hyperglycinemia in neonates and MELAS in infants, children, and adolescents; ion channel–related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections earlier); hypoxic-ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain tumors; and any other disorder that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, and storage diseases).

A rare condition called **hemiconvulsion-hemiplegia-epilepsy syndrome** consists of prolonged febrile SE presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition FIRES are likely to have a parainfectious-autoimmune etiology. In addition, hemophagocytic lymphocytic histiocytosis has been reported to cause FIRES. **Rasmussen encephalitis** often causes epilepsia partialis continua (see Chapter 633.3) and sometimes convulsive SE. Several types of infections are more likely to cause encephalitis with SE, such as herpes simplex (complex partial and convulsive status), *Bartonella* (particularly nonconvulsive status), Epstein-Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of SE, including refractory SE. HHV-6 can cause a distinct epileptic syndrome with limbic SE in immunosuppressed patients.

MECHANISMS

The mechanisms leading to the establishment of sustained seizure activity seen in SE appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus causing the persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of $GABA_A$ receptors. This explains the clinical observation that SE is often less likely to stop in the next specific period the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During SE, there is an increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 minutes, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from SE.

THERAPY

SE is a medical emergency that requires initial and continuous attention to securing the airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies, including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic drug screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. EEG is helpful in ruling out **pseudo–status epilepticus** (psychologic functional neurologic disorder mimicking SE) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/decorticate posturing. The EEG can also be helpful in identifying the type of SE (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of SE in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation) and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology.

The initial emergent therapy should be started for convulsive seizures lasting longer than 5 minutes and involves the use of a benzodiazepine medication (Fig. 633.16). The American Epilepsy Society SE

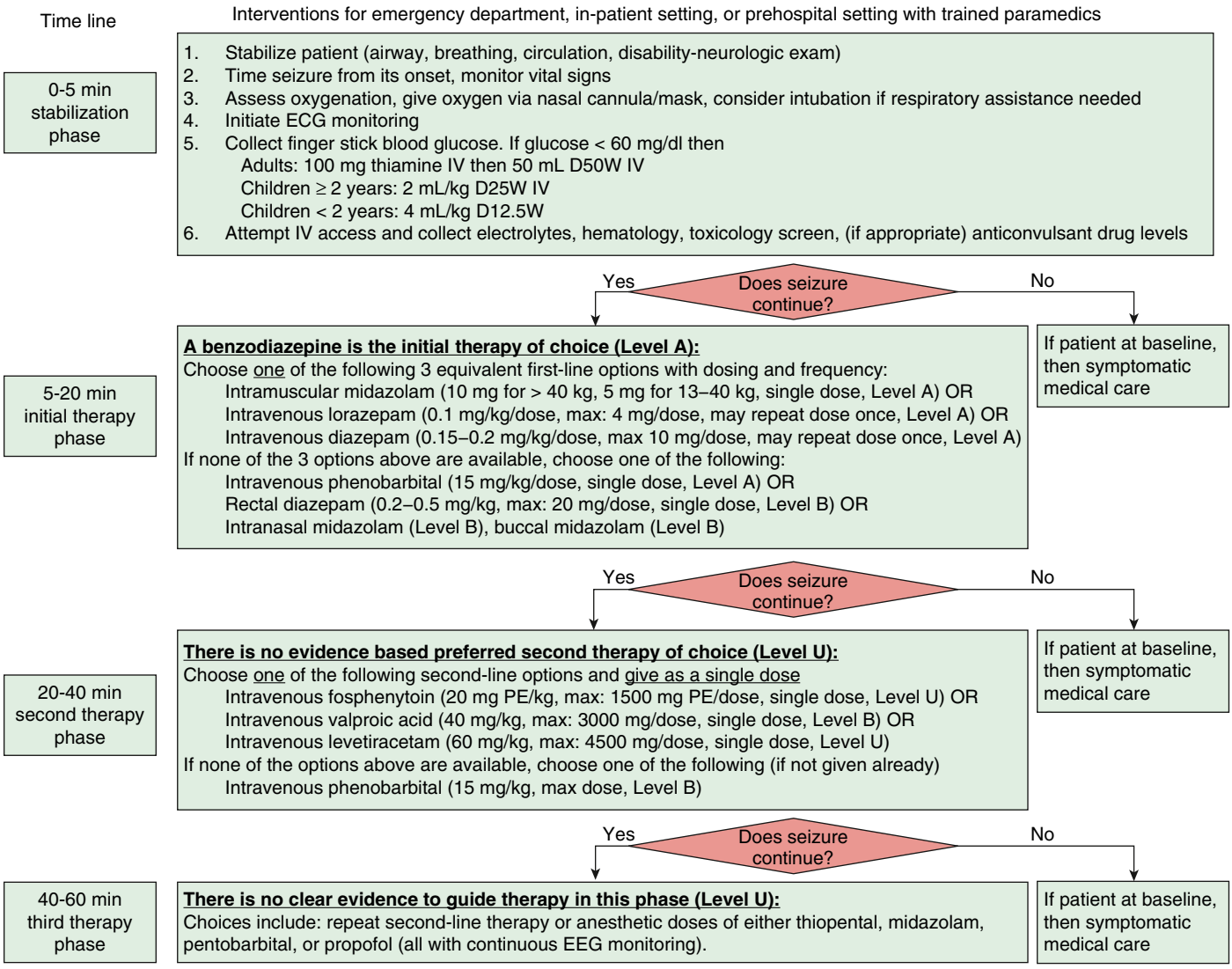

Fig. 633.16 Proposed treatment algorithm for status epilepticus. Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate. *(From Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr. 2016;16[1]:48–61, Fig.1.)*

Table 633.23 Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous Intranasal	0.1 mg/kg up to maximum of 4 mg, may repeat in 5-10 min 0.1 mg/kg up to maximum of 5 mg
Midazolam	Intravenous Intramuscular Intranasal Buccal	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min Continuous infusion maintenance: 0.05-2 mg/kg/hr 0.2 mg/kg 0.2 mg/kg 0.5 mg/kg
Diazepam	Intravenous	0.15 mg/kg up to a maximum total dose of 10 mg; may repeat in 5-10 min
	Rectal	2-5 yr: 0.5 mg/kg 6-11 yr: 0.3 mg/kg ≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	Loading: 20 mg/kg PE, infusion rate maximum 50 mg PE/min Maintenance: 4-8 mg/kg/24 hr divided tid
Ketamine	Intravenous	Loading: 1 mg/kg Maintenance: 0.5-2 mg/kg/hr
Phenobarbital	Intravenous	Loading: 15-20 mg/kg (maximum 1,000 mg) Maintenance: 3-5 mg/kg/24 hr divided bid
Pentobarbital coma	Intravenous	Loading: 5-15 mg/kg Maintenance: 1-5 mg/kg/hr
Propofol	Intravenous	Loading: 1-2 mg/kg Maintenance infusion: 1.2 -3.9 mg/kg/hr
Thiopental	Intravenous	Loading: 2-7 mg/kg, infusion rate maximum 50 mg/min Maintenance infusion: 0.5-5 mg/kg/hr
Valproate	Intravenous	Loading: 20-40 mg/kg Maintenance: 30-60 mg/kg/24 hr divided bid
Lacosamide†	Intravenous	Loading: 4-8 mg/kg (maximum 400 mg) Maintenance: 4-12 mg/kg/day divided bid (maximum 400 mg/day)
Levetiracetam	Intravenous	Loading: 30-60 mg/kg (maximum 4,500 mg) Maintenance: 30-60 mg/kg/24 hr divided bid (maximum 3,000 mg/day)
Topiramate	Enterally	Loading: 5-10 mg/kg Maintenance: 5-12 mg/kg/day divided bid (maximum 400 mg/day)

*Reflects current trends in use that may not be FDA approved. For FDA indications, see Table 633.13.
†May cause PR prolongation.
PE, Phenytoin sodium equivalents.

Guidelines recommend using either intravenous lorazepam, intravenous diazepam, or intramuscular midazolam as a first-line agent. The Neurocritical Care Society SE Guidelines recommend intravenous lorazepam as a first-line agent and, if the patient does not have intravenous access, using intramuscular midazolam. Table 633.23 outlines the drugs and dosages typically used in SE. If intravenous access is not available, other options besides intramuscular midazolam include buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. If seizures persist 5 minutes after the initial benzodiazepine dose, a second dose of the drug should be given. Less evidence supports the use of phenytoin/fosphenytoin, phenobarbital, valproate, or levetiracetam as alternative first-line agents. Additionally, in some infants, a trial of pyridoxine may be warranted.

If the emergency therapy with a benzodiazepine is unsuccessful (persistent seizures 5 minutes after the second benzodiazepine dose), fosphenytoin, valproate, or levetiracetam is the recommended option for urgent therapy. Fosphenytoin is given at a loading dose of 20 mg/kg, and a level is usually taken 2 hours later to ensure achievement of a therapeutic concentration. Depending on the level and response, a maintenance dose can be started right away or, more commonly, 6 hours after the initial bolus. Valproate is given at a loading dose of 40 mg/kg, but its use should be avoided in patients younger than 2 years of age and in those with hepatic dysfunction or mitochondrial disease. Levetiracetam is given at loading doses of 60 mg/kg and is well tolerated. Several prospective studies have compared the efficacy of these second-line agents in treating SE that failed to respond to benzodiazepines. One demonstrated the noninferiority of levetiracetam, fosphenytoin, and valproate. Others demonstrated the noninferiority of levetiracetam to phenytoin. In all of these studies, roughly half the patients have seizure resolution with a second-line agent.

Intravenous phenobarbital is an alternative option if valproate, fosphenytoin, or levetiracetam is not available but is not recommended as a first-line urgent therapy because of its side effects. The phenobarbital dose used in neonates is usually 20 mg/kg as a loading dose, but in infants and children the dose is often lower to avoid respiratory depression, with the dose repeated if there is not an adequate response. If seizures persist after administration of the urgent therapy medication, a decision must be made regarding redosing with another second-line agent or proceeding to a continuous infusion. This decision is case-dependent. The Neurocritical Care Society Guidelines on SE suggest that definitive seizure control should be achieved within 60 minutes of seizure onset, which may prompt opting for the more aggressive therapy (i.e., proceeding to continuous infusion and intubation) in a

patient who has already had convulsive seizures for more than 30-60 minutes.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with SE, even the ones who respond, need to be admitted to the intensive care unit for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 minutes so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For **refractory status epilepticus treatment**, an intravenous bolus followed by continuous infusion of midazolam, propofol, pentobarbital, or thiopental is used. Subsequent boluses and adjustment of the rate of the infusion are usually made, depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to monitor response to therapy. The goal is to stop electrographic seizure activity before reducing the therapy. Usually this implies achievement of complete flattening of the EEG, a pattern called **burst suppression**. Some consider that achieving a burst suppression pattern may be enough, and the periods of flattening in such a case need to be 8-20 seconds to ensure interruption of electrographic seizure activity. Evidence suggests that patients who receive higher doses of intravenous anesthetic therapy earlier and achieve EEG voltage suppression sooner are more likely to have fewer complications and shorter duration for need for mechanical ventilation.

Patients receiving these therapies require careful attention to blood pressure and to systemic complications, and some develop multiorgan failure. It is not unusual for patients put into pentobarbital coma to have to be given multiple vasopressors to maintain their blood pressure during therapy.

The choice among these options to treat refractory and superrefractory SE often depends on the experience of the specific center. Midazolam probably has fewer side effects but is less effective, and barbiturate coma is more effective but carries a higher risk of side effects. Some patients taking propofol develop propofol infusion syndrome with lactic acidosis, hemodynamic instability, and rhabdomyolysis with higher infusion rates (>67 μg/kg/min). This limits the use of propofol in the pediatric population. Electrolytes, creatine phosphokinase, and organ function studies need to be monitored if a patient is being given propofol infusion therapy. Often, barbiturate coma and similar therapies are maintained for one or more days before it is possible to gradually taper the therapy, usually over a few days. However, in some cases, including cases of NORSE, such therapies need to be maintained for several weeks or even months. Even though the prognosis in NORSE (and FIRES) cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible.

Patients with **superrefractory status epilepticus (SRSE)** have persistent seizure activity or seizure recurrence despite 24 hours of general anesthesia with medications such as midazolam, pentobarbital, and/or propofol. In addition to these continuous infusions, polytherapy with other AEDs is usually initiated, although data are lacking regarding the optimal treatment strategy. The most commonly used drugs are fosphenytoin, valproate, phenobarbital, levetiracetam, topiramate, and lacosamide.

Ketamine infusion is a recognized treatment option for SRSE. It is an NMDA receptor antagonist and may be of particular benefit because NMDA receptors are upregulated in SE. The **ketogenic diet** has also been found to be effective in children, although the response may take up to a week after diet initiation and ketosis may be more difficult to achieve if the patient is receiving pentobarbital, which has a carbohydrate-rich carrier fluid. Immunotherapy with intravenous steroids, immunoglobulins, and/or plasma exchange is often used in cases of SRSE of unclear etiology. In specific situations such as **anti–NMDA receptor encephalitis** or **CNS vasculitis**, immunotherapy may be the first-line therapy. Because it can take some time to definitively diagnose autoimmune encephalitides, immunotherapy is often initiated empirically if the clinical history is consistent with the diagnosis. **Inhaled anesthetics** such as isoflurane have been used for SRSE but are associated with a number of adverse reactions and require the presence of an anesthesiologist at bedside, which limits their use. **Induced hypothermia** has also been used, but further studies are needed to assess its safety and efficacy. In select cases of lesional SRSE, emergent neurosurgery may be an option. Such cases include performing hemispherectomy for **Rasmussen encephalitis** or focal resection if the seizures are secondary to an area of cortical dysplasia. The use of VNS, electroconvulsive therapy, and transcranial magnetic stimulation (for epilepsia partialis continua) has also been reported. Allopregnanolone, a neurosteroid, has shown promise in the treatment of pediatric and adult SRSE, and clinical trials are currently underway to better determine its efficacy.

For **nonconvulsive status epilepticus** and **epilepsia partialis continua**, therapy needs to be tailored according to the clinical manifestations and often consists of trials of sequential oral or sometimes parenteral AEDs without resorting to barbiturate coma or overmedication that could result in respiratory compromise. The approach to focal SE with impaired awareness is sometimes similar to the approach to generalized convulsive SE and sometimes intermediate between the approach for epilepsia partialis and that for convulsive status, depending on severity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.9 Reflex Seizures (Stimulus-Precipitated Seizures)

Mohamad A. Mikati, Dmitry Tchapyjnikov, and Kevin M. Rathke

Many patients with epilepsy can identify precipitating or provoking events that predispose them to having a seizure. Common precipitants in these patients include stress, lack of sleep, fever, or fatigue.

However, there is another group of patients who have seizures in response to a specifically identifiable sensory stimulus or activity and are considered to have reflex seizures. Because no known reflex may be involved, more appropriate terms may be *sensory-precipitated* or *stimulus-sensitive seizures.* Stimuli may be external (light, patterns, music, brushing teeth) or internal (math, reading, thinking, self-induced). Reflex seizures may be generalized, focal, nonconvulsive, absence, or myoclonic. One pattern is photosensitive seizures in which repetitive **photic stimulation** induces photoparoxysmal epileptogenic discharges on EEG and sometimes seizures.

Photosensitive seizures are a well-recognized disorder stimulated by bright or flashing lights (TV, video games, discotheques, concert light shows) or by patterns (TV, video games, lines on the road while traveling). Visual sensitivity may occur in 0.3–3% of the population, whereas photosensitive or pattern-induced seizures may occur in 1 in 4,000 people in the at-risk age-group of 5-25 years. When Japanese children were exposed to a Pokémon cartoon that induced seizures in many, only 24% of those had a history of prior spontaneous seizures. Some children with photosensitive epilepsies stimulate seizures purposefully by rapidly blinking or waving a hand in front of their face (sunflower syndrome). Patients tend to outgrow photosensitive or pattern-induced seizures in their 30s. Photoparoxysmal responses, with an abnormal EEG response to photic stimulation, are more common than photic-induced seizures.

For patients with isolated photosensitive or pattern-induced seizures, avoidance or modification of stimuli is the initial approach. Such activities may include wearing blue or polarized sunglasses, avoiding high-contrast flashing-light video games, avoiding discotheques, watching television in a well-lit room at a distance of >8 feet, and covering one eye when in a provocative situation. A number of genes have been associated with certain patients with reflex epilepsy such as *CHD2* with photosensitive or self-induced seizures caused by fixation-off sensitivity, *LGI1* or *SCN1A* with musicogenic seizures, *MECP2* with eating seizures in Rett syndrome, and *SYN1, GPR56,* or *SYNGAP1* with hot water or bathing epilepsy. Not all patients with these reflex seizures have these pathogenic variants, nor do all patients with variants in these genes have reflex seizures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

633.10 Nodding Syndrome

Michael J. Boivin and Itziar Familiar-Lopez

Nodding syndrome (NS) is form of epilepsy that mainly affects children between 3 and 18 years of age who live in distinct regions of Uganda, Liberia, Tanzania, the Democratic Republic of Congo, and southern Sudan. The prevalence is approximately 6.8 per 1,000 children. The first clinical symptom is usually an involuntary nodding of the head in a previously healthy child. These nodding episodes are characterized by at least daily rapid, paroxysmal, forward head-bobbing spells lasting several minutes; some patients are unresponsive, whereas others may respond to commands or continue what they were doing before the episode. Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperatures may also trigger a nodding episode. Head nodding has been determined to be a type of atonic seizure, although other types of seizures, including generalized tonic-clonic or *absence* seizures, may develop. Given the extent of the brain pathogenesis in NS, it is not surprising that it is accompanied by lifelong profound cognitive neurodisability, severe behavior and psychiatric difficulties, growth stunting, delayed puberty, and high mortality rates (Table 633.24 lists case definitions).

Although the diagnosis remains largely based on clinical presentation, the EEG demonstrates a disorganized slow background and interictal generalized 2.5- to 3.0-Hz spike–and–slow waves, with generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. NS is characterized by stunted brain growth, which includes significant brain atrophy near the hippocampal and glial matter of the brain and significant cerebellar involvement. Routine CSF analyses are usually negative, but brain MRI shows cerebral and cerebellar atrophy. An MRI study of Tanzanian nodding disease patients revealed that the most frequent abnormality was generalized atrophy, followed by intraparenchymal pathologies such as changes in the hippocampus, gliotic lesions, and subcortical signal abnormalities.

Treatment of seizures is indicated, and choice of AED should be based on the type of seizure presented. Sodium valproate is indicated for atonic seizures and may be a good option to simultaneously treat behavioral difficulties like aggression and impulsive behavior. The suggested starting dose is 10 mg/kg/day in two divided doses and increase the dose by 5 mg/kg/day until seizure control is achieved or the maximum dose is reached (40 mg/kg/day). Other antiepileptic medications used for NS include phenytoin and phenobarbitone, either individually or combined. Management of behavioral and psychiatric difficulties, nursing care, nutritional, and subsequently, physical and cognitive rehabilitation should also be considered.

Despite extensive investigations, the etiology of NS remains unknown. A systematic review using the Bradford Hill criteria for causality identified *Onchocerca volvulus* as the most likely trigger of NS and other forms of onchocerciasis-associated epilepsy. *O. volvulus* is a nematode carried by the blackfly, the bites of which can cause onchocerciasis, a highly prevalent type of blindness caused by infection. High prevalence of NS overlaps with onchocerciasis-endemic areas with high rates of *O. volvulus* transmission and low or no coverage of community-directed treatment with ivermectin. However, the pathophysiologic mechanism through which *O. volvulus* could directly cause the neurologic damage observed in NS patients remains unknown, as microfilariae are not known to invade the brain.

Studies in Uganda support the hypothesis that NS may be an autoimmune epileptic disorder caused by molecular mimicry with *O. volvulus* antigens. Histologic postmortem examination of brains has revealed polarizable material in the majority of specimens, but it has proved difficult to characterize or identify. There is evidence of autoantibodies to leiomodin-1 in both the sera and CSF of Ugandan patients with nodding syndrome. Because leiomodin-1 antibodies cross react with *O. volvulus* proteins, nodding syndrome may be an autoimmune epilepsy initiated by the infection caused by this parasite. Therefore it may be preventable by treatment with antiparasitic strategies, such as the drug ivermectin. It may also perhaps be treatable in its early stages with immunomodulatory therapies.

Onchocerciasis tends to have the highest prevalence in rural east and central African areas with poorly developed healthcare and social service infrastructures. Because of this, families with children affected by nodding disease, often existing on the margins of their resources in impoverished areas, have little in the way of caregiving resources needed to cope with the profound disability that results from this disease. This further diminishes the prognosis for these children because of further risk to their health from accidental injury (e.g., burns from cooking fires), malnutrition because of difficulty in feeding, and/or neglect.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 633.24 Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome, Uganda, 2012–2013*

TYPE OF CASE	CONSENSUS CASE DEFINITION	MODIFIED CONSENSUS CASE DEFINITION
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on two or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on two or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: Age of onset of nodding ranging from 3 to 18 yr Frequency of nodding 5-20 per min Plus at least one of the following minor criteria: Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) Clustering in space or time with similar cases Triggering by food or cold weather Stunting or wasting Delayed physical development/absence of development of secondary sexual characteristics Psychiatric symptoms	Suspected case of head nodding, with one major criterion: Age of onset of nodding ranging from 3 to 18 yr Plus at least one of the following minor criteria: Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) Clustering in space or time with similar cases Triggering by food or cold weather Stunting or wasting Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode Observed and recorded by a trained healthcare worker, *or* Videotaped nodding episode, *or* Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode Observed and recorded by a trained healthcare worker, *or* Videotaped nodding episode, *or* Video/EEG/EMG documenting head nodding as atonic seizures

*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30 to August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf. The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by the Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess the prevalence of nodding syndrome in Uganda.

EEG, Electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al. Prevalence of nodding syndrome–Uganda, 2012-2013. *MMWR Morb Mortal Wkly Rep*. 2014;63:603–606, Table 1.

Chapter 634

Conditions That Mimic Seizures

Mohamad A. Mikati and Makram M. Obeid

The misdiagnosis of epilepsy is estimated to be as high as 5–40%. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough clinical examination, but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age at presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other paroxysmal movements and postures, (3) oculomotor and visual abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 634.1 and Fig. 634.1).

SYNCOPE AND OTHER GENERALIZED PAROXYSMS

Apnea

Apneic episodes (cessation of breathing >20 seconds) in neonates and apnea caused by brainstem compression are usually associated with bradycardia. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Exceptions are seen because bradycardia can occur during some epileptic seizures, and severe apnea of any cause can be followed by anoxic seizures. The term **brief resolved unexplained event (BRUE)** is defined as an event in an infant reported as a sudden, brief, self-resolving episode consisting of one or more of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) a marked change in tone (hyper- or hypotonia); and (4) an altered level of responsiveness (see Chapter 424). A BRUE, which usually lasts less than 1 minute, is diagnosed only when no explanation is evident after an appropriate history and physical examination have been conducted. **Apnea** can either be obstructive or central, most commonly in premature neonates. Central apnea also occurs in the context of certain neurogenetic syndromes, the prototype of which is congenital central hypoventilation syndrome secondary to pathogenic variants in *PHOX2B*. **Ondine's curse** (idiopathic congenital central alveolar hypoventilation syndrome) consists of an inadequate respiratory drive in sleep with periods of prolonged apnea requiring tracheostomy and mechanical ventilation (see Chapter 468.2). Apnea can also be secondary to near cerebral herniation and intermittent brainstem compression in the context of increased intracranial pressure or Chiari malformations.

Breath-Holding Spells

The term *breath-holding spells* is actually a misnomer, because they are not necessarily self-induced but result from the immaturity of the autonomic system and occur in two different forms. The first type is the **pallid breath-holding spell**, which is caused by reflex vagal-cardiac bradycardia and asystole. The second type is the **cyanotic**, or **blue**, **breath-holding spell**, which does not occur during inspiration but results from prolonged expiratory

Table 634.1 Conditions that Mimic Seizures According to Age of Presentation

AGE	SYNCOPE AND OTHER GENERALIZED PAROXYSMS	MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS	OCULOMOTOR AND VISUAL ABNORMALITIES	SLEEP DISORDERS
Neonate	Apnea Paroxysmal extreme pain disorder	Jitteriness, tremor, increased startle reflex, hiccups Hyperekplexia, paroxysmal dystonic choreoathetosis	Paroxysmal tonic upgaze Alternating hemiplegia of childhood, staring, daydreaming, and time-out "unresponsiveness"	Benign neonatal sleep myoclonus Sleep transition disorders, REM
Infants	Reflex anoxic seizures Breath-holding spells Benign paroxysmal vertigo Paroxysmal extreme pain disorder	Jitteriness Sandifer syndrome Paroxysmal dystonic choreoathetosis Benign myoclonus of early infancy Pathologic startle Shuddering attacks, infantile head atonic attacks Benign paroxysmal torticollis Psychologic disorders Alternating hemiplegia of childhood Jactatio capitis (head banging) Drug reactions	Paroxysmal tonic upgaze Oculomotor apraxia Spasmus nutans Opsoclonus-myoclonus syndrome, staring, daydreaming, and time-out "unresponsiveness"	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy)
Children and adolescents	Benign paroxysmal vertigo Compulsive Valsalva-like maneuver Familial hemiplegic migraine Syncope (long QT, vasovagal, orthostatic, migraine-induced) Psychogenic seizures Transient global amnesia Hyperventilation spells, factitious disorder	Tics Tremor Pathologic startle Paroxysmal dyskinesias Alternating hemiplegia of childhood Benign paroxysmal torticollis Episodic ataxia Psychologic disorders, including factitious disorder imposed on another, malingering Masturbation Psychogenic seizures Cataplexy Jactatio capitis (head banging) Episodic rage, drug reactions, factitious disorder	Staring, daydreaming, and time-out "unresponsiveness" Drug reactions, hallucinations, visual snow Conversion reactions, factitious disorder	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy) Sleep myoclonus Restless legs syndrome, conversion reactions, factitious disorder

REM, Rapid eye movement.
From Obeid M, Mikati MA. Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy. *Pediatr Neurol*. 2007;37(5):309–316.

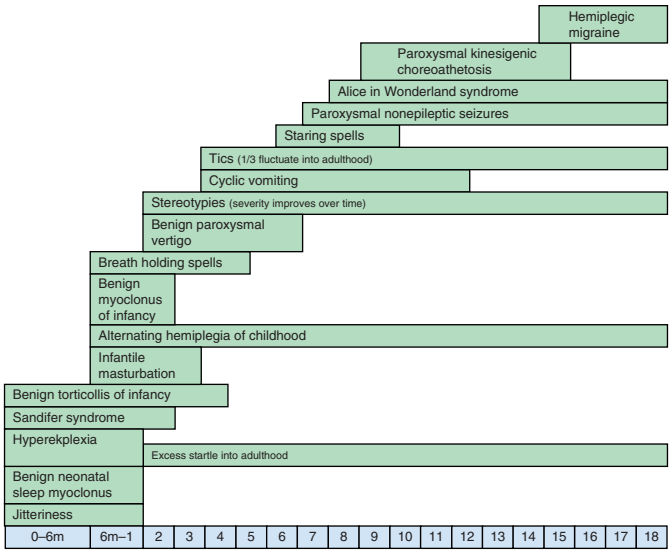

Fig. 634.1 Age ranges (months and years) of seizure mimics, typical onset, and resolution. *(From Stainman RS, Kossoff EH. Seizure mimics in children: an age-based approach. Curr Probl Pediatr Adolesc Health Care. 2020;50:100894, Fig. 1.)*

apnea and intrapulmonary shunting (see Chapter 43). Episodes usually start with a cry (often, in the case of the pallid type, a silent cry with marked pallor) and progress to apnea and cyanosis. Spells usually begin between 6 and 18 months of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more severe episodes, particularly in breath-holding spells of the pallid type. Injury (such as even a minor bump on the head), pain, and frustration, particularly with surprise, are common triggers. There usually is a family history of vasovagal syncope or breath-holding spells. Education and reassurance of the parents are usually all that is needed because these episodes are, as a rule, self-limited and are outgrown within a few years. However, screening for anemia and for electrical cardiac disturbances with an electrocardiogram is recommended because the spells are worsened by iron-deficiency anemia and can rarely be the presenting sign of long QT (LQT) syndromes. Anticholinergic drugs, for the selected cases of pallid breath-holding spells (e.g., atropine sulfate 0.03 mg/kg/day in two to three divided doses with a maximum daily dose of 1.2 mg) or antiseizure drug therapy for coexisting anoxic seizures that are recurrent, prolonged, and not responding to other measures may rarely be needed. If antiseizure medications are needed, it is ill-advised to use medications that may increase irritability, such as levetiracetam. It is important also to educate parents on how to handle more severe spells with first aid measures or even basic cardiopulmonary resuscitation when needed. Extremely severe episodes resulting in marked bradycardia and asystole have been reported to respond to a cardiac pacemaker. All parents should be taught not to provide secondary gain when the episodes occur, because this can reinforce them. Also, preparation for unpleasant experiences (such as receiving a shot) rather than surprising the child with them can help limit the number of spells.

Compulsive Valsalva-Like Maneuver

In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers such as the Valsalva maneuver. In this case, true breath holding occurs, and it usually lasts for approximately 10 seconds during inspiration. Some clinicians advocate the use of naloxone in such cases. In the authors' experience, a compulsive Valsalva-like maneuver can rarely be a feature of a panic attack or conversion disorder. When clinically stereotyped, a prolonged EEG and a careful workup by a pediatric epileptologist are needed in order to rule out epileptic seizures.

Neurally Mediated Syncope

Syncope can present with drop attacks and can also lead to generalized convulsions, termed *anoxic seizures*. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to, and can be misdiagnosed as, generalized epileptic seizures. **Vasovagal (neurocardiogenic) syncope** is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, sudden exposure to cold as with cold water immersion, and a sudden episode of stress (see Chapter 84). The history is usually the clue to distinguishing syncope from epileptic seizures: there is initially pallor and sweating followed by blurring of vision, dizziness, and nausea and then a gradual collapse with loss of consciousness. Of importance is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However, in epilepsy, when auras with similar features precede an epileptic seizure, such features are usually sudden, short in duration, and followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope and can be a trigger or a consequence of that process (intestinal vagal hyperactivity). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected first-degree relative; reports demonstrate autosomal dominant inheritance at least in some families. The EEG is normal, and the tilt test has been used for diagnostic purposes in selected cases. In most cases with a typical history, this test is not needed. In addition, **exercise-induced anaphylaxis** has rarely been reported. In **stretch syncope**, which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some other cases, this may be associated with an abnormally prolonged stylomastoid process compressing the carotids. If the latter condition is suspected, neuroimaging with cranial CT or MRI is required for proper diagnosis of the stylomastoid anomaly. **Migraine** can also induce vasovagal syncope. Other causes of syncope include primary autonomic failure, which is rare in children, and familial dysautonomia is the only relatively common form. **Familial dysautonomia**, a disease found in Ashkenazi Jews, is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction after intradermal histamine. **Dopamine β-hydroxylase deficiency** is a rare cause of primary autonomic failure and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, nocturia, and later impaired ejaculation.

Postural Tachycardia Syndrome

See Chapter 84.1.

Cardiac Syncope

See Chapters 84 and 485.

LQT syndromes can cause life-threatening pallid syncope. Accompanying this are ventricular arrhythmias and, usually, torsades de pointes or even ventricular fibrillation. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and **Lange-Nielsen syndrome** (type 1, LQT 1, associated with the *KvLQT1* potassium channel pathogenic variant). **Romano-Ward syndrome** is an autosomal dominant syndrome with incomplete penetrance (LQT 2 associated with an *HERG* potassium channel variant). LQT 3 is associated with an *SCN1A* sodium channel variant, LQT 4 with an ankyrin protein mutation, LQT 5 (milder form) with *KCNE1* variants, LQT 6 with *KCNE2* potassium channel gene variants, LQT 9 with caveolin sodium channel–related protein variants, and LQT 10 with *SCN4B* sodium channel variants. LQT 7 and LQT 8 have associated clinical and neurologic manifestations. LQT 7 **(Andersen-Tawil)** syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (variants in *KCNJ2*). LQT 8, or **Timothy syndrome** (variants in the calcium channel gene *CACNA1C*), manifests with congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected child should be investigated. Affected individuals

need insertion of cardiac defibrillators, and their families should be taught cardiopulmonary resuscitation. Children with a new-onset seizure disorder of unclear etiology should get an electrocardiogram to rule out LQT syndrome masquerading as a seizure disorder. Cardiac syncope is usually sudden, without the gradual onset and symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of exercise (usually hypertrophic) or directly at the end (usually valvular) and, if suspected, warrants an echocardiogram.

Migraine and Migraine Variants

Familial hemiplegic migraine (FHM) is a rare type of autosomal dominant migraine with the prominent feature of transient motor weakness. Attacks begin as early as 5-7 years of age. In a genetically susceptible child, attacks may be precipitated by head trauma, exertion, or emotional stress. The three genes commonly identified are *CACNA1*A in FHM1 (neuronal calcium channel subunit), *ATP1A2* in FHM2 (sodium potassium adenosine triphosphatase subunit), and *SCN1A* in FHM3 (neuronal sodium channel subunit). Pathogenic variants of other genes such as *PRRT2* may also cause FHM. However, at least a quarter of the affected families and most of the sporadic patients do not carry a pathogenic variant in these genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights) and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks, and verapamil and ketamine have been used for the acute episode; ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patients with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and strokelike episodes, as well as alternating hemiplegia of childhood).

Benign paroxysmal vertigo of childhood is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that are often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubans) where children sometimes report that objects seem to be moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 years of age. MRIs and EEGs are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydramine 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may rarely be needed for frequent attacks.

Cyclic vomiting syndrome (CVS) is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. Recurrent vomiting can also be caused by neuromyelitis optica, juvenile Alexander disease, brainstem pathology, inborn errors of metabolism with intermittent presentations, and seizures, usually from the nondominant temporal lobe. With the latter, there is, as a rule, impaired consciousness. Prophylaxis for CVS has included medications such as amitriptyline, propranolol, cyproheptadine, sumatriptan, erythromycin, coenzyme Q, fluoxetine, or antiepileptics. Acute therapy usually consists of 10% dextrose intravenously with ondansetron and an antihistamine or benzodiazepine.

Alice in Wonderland syndrome (see "Visual Hallucinations," later), confusional migraine, and abdominal migraine are also migraine variants. One should note that many patients with migraine or migraine variants (including FHM) have coexisting epilepsy, and children with epilepsy have a higher incidence of migraine headaches compared with the general population, so providers should be aware that such patients may have symptoms attributable to either.

Nonepileptic Seizures (Formerly, Functional Disorders)

Nonepileptic seizures are a form of functional neurologic disorder that can be diagnosed clinically based on the characteristics of the spells (Tables 634.2 and 634.3). A video of the event is usually possible because most of the events are witnessed and tend to be more prolonged than epileptic seizures. If needed, a diagnosis can be confirmed by video-EEG with capture of an episode to eliminate any residual doubts about its nature because these functional paroxysms can often occur in patients who also have epileptic seizures. A social history is very important because psychogenic nonepileptic seizures (PNESs) are often a reaction to physical or sexual abuse or to the inability to cope with psychosocial tasks. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes; an early accurate diagnosis and timely management result in more favorable outcomes. The use of terms such as *nonepileptic stress seizures* facilitates communication with families, given the often-perceived negative connotation of the term *psychogenic*. Psychiatric evaluation and follow-up are needed to uncover an underlying psychopathology and to establish continued support because psychogenic seizures can persist over long periods. Malingering and factitious disorder imposed on another (formerly called *Munchausen syndrome by proxy*) are often difficult to diagnose, but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful. Sad cases of loss of consciousness related to suffocation by caregivers in infants and toddlers have also been reported.

Paroxysmal Extreme Pain Disorder

Paroxysmal extreme pain disorder, previously called *familial rectal pain syndrome,* is caused by an autosomal dominant gain-of-function variant in a sodium channel (Nav1.7) encoded by the *SCN9A* gene. Paroxysmal extreme pain disorder usually starts in infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole occurs. Later, the disorder is characterized by attacks of excruciating, deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defecation, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Neurologically impaired children can often have irritability without clear etiology even after investigations, and this has been reported to respond to gabapentin (for neurologic irritability).

Autonomic Storms

Autonomic storms are also referred to as diencephalic seizures, paroxysmal sympathetic hyperactivity, sympathetic storms, paroxysmal autonomic instability with dystonia, dysautonomia, and central autonomic dysfunction. Spells of hyperhidrosis and changes in blood pressure, temperature, and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term diencephalic seizures is discouraged because the episodes are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, propranolol, baclofen (oral or intrathecal), benzodiazepines (particularly clonazepam), bromocriptine, chlorpromazine, hydralazine, methadone, cyproheptadine, morphine, and sympathectomy.

Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs such as St. John's wort, and some other medications can produce similar symptoms, and if not recognized, can at times be fatal, as can the similar **neuroleptic malignant syndrome** caused by antipsychotic medications.

Table 634.2 Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic or, in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing	Blurring of vision, tinnitus, dizziness, nausea, sweating Crying in breath-holding spells	Loss of consciousness for seconds, pallor, and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Syncope with reflex anoxic seizures	Minor bump to head, upsetting surprises			
Syncope: trigeminal vagal	Cold water on face			
Syncope: orthostatic	Standing up, bathing, awakening			
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only for a few seconds, pallor	Rarely
Nonepileptic seizures (formerly, functional disorders)	Suggestion, stress	None; some have headache, nausea, palpitations, poor concentration, panic-like attack	Eyes closed, with active opposition to attempts to open them Asynchronous (nonrhythmic) flailing or tremulous limb movements that vary between attacks Motor activity stops and starts during a spell Weeping and crying No injury May respond to suggestion during "loss of consciousness" Usually longer than 5 min, decrease in intensity when provider places hand on patient's shoulder	No postictal depression

Adapted from Obeid M, Mikati MA. Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy. *Pediatr Neurol*. 2007;37(5):309–316.

Table 634. 3 Positive Diagnostic Features and Biomarkers of Nonepileptic Seizures and Functional Movement Disorder

	ESTABLISHED DIAGNOSTIC FEATURES	NEW DIAGNOSTIC FEATURES*
NONEPILEPTIC SEIZURES		
Seizures	Eyes closed; prolonged attacks; hyperventilation; awareness during generalized shaking; ictal or postictal weeping	Suggestive seizure induction; qualitative conversation analysis; use of smartphone video; wrist-worn accelerometers; postictal plasma proteins
FUNCTIONAL MOVEMENT DISORDER		
Tremor	Tremor entrainment or cessation to externally cued rhythm; variability of frequency and amplitude of tremors	"Whack-a-mole" sign: holding down a tremulous body part induces tremor in another body part; coherence between antagonist muscles measured with standard coherence or wavelets
Dystonia	Fixed inverted or plantar flexed ankle; fixed clenched fist	Dystonia of the face: downward lip pulling, orbicularis oculi spasm, platysma spasm; sustained facial movement to evoke a spasm; functional hemifacial spasm lacks the "other Babinski sign" (i.e., raising of eyebrow on affected side)
Gait and balance	Variability of gait performance; gait performance shows excellent balance; "walking-on-ice" gait, dragging monoplegic gait, or knee-buckling gait	Classification of gait types into seven types: ataxic, spastic, weak gait, antalgic, parkinsonian, hemiparetic, and dystonic; "huffing and puffing" sign: huffing, grunting, grimacing, and breath holding after small amounts of exercise; posturographic improvement with distraction (guessing numbers written on back or cognitive task)
Jerks or myoclonus	Truncal jerking, especially with facial movement†; positive bereitschaftspotential before movement using back averaging	Increased startle; event-related desynchronization using back averaging
Limb weakness and generic motor dysfunction	Hoover sign; hip abductor sign; drift without pronation	Absence of amplitude suppression of median nerve somatosensory evoked potential; decreased prepulse inhibition of the blink reflex by stimulation of the index finger; absence of contingent negative variation in reaction time task

*Described in the past 10 years.
†The diagnosis of functional jerks can be difficult, but 104 (58%) of 179 patients with truncal myoclonus had functional neurologic disorder in one series.
From Hallett M, Aybek S, Dworetzky BA, et al. Functional neurological disorder: new subtypes and shared mechanisms. *Lancet Neurol*. 2022;21:537–550, p. 539.

MOVEMENT DISORDERS AND OTHER PAROXYSMAL MOVEMENTS AND POSTURES

Neonatal Jitteriness and Clonus

Jitteriness consists of recurrent tremors. These movements manifest as equal backward-and-forward movements of the limbs, either occurring spontaneously or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the two-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks point to a nonepileptic event. Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic-ischemic encephalopathy are possible etiologies, but jitteriness is also often seen in normal neonates. Clonus as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by a change in position. Two to three beats of clonus can be within normal in some neonates.

Hyperekplexia (Stiff Baby Syndrome) and Pathologic Startles

Hyperekplexia is a rare, sporadic, or dominantly inherited (less often recessive or X-linked) disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 year of age and may disappear during sleep. The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. However, other less common pathogenic variants that disrupt the glycine receptor signaling complex have also been described. Pathogenic variants in *GLRA1* or *SLC6A5* are the most common genes followed by *GLRB, GPHM,* and *ARHGEF9* (X-linked). A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important so that treatment with clonazepam can be initiated, because hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes. Rare challenging cases of children with hyperekplexia and concomitant epileptic seizures (including myoclonic seizures) have been reported. In other children after brain injury, and in many patients with cerebral palsy, an **exaggerated startle reflex** can occur; this is more common than hyperekplexia. In Tay-Sachs disease and similar gangliosidoses, an exaggerated startle to sound occurs and has been inappropriately interpreted as hyperacusis. **Hiccups** can occur normally in newborns but can be a feature of nonketotic hyperglycinemia, citrullinemia, and neuromyelitis optica syndromes, with the latter presenting during later childhood and adolescence rather than in neonates. In addition, in children with neurologic diseases, a related limited repertoire of movements and behaviors, startle, arousal, or signs of distress may be clinically expressed with stereotyped movements that can mimic epileptic seizures.

Benign Paroxysmal Torticollis of Infancy

This condition typically presents as morning episodes of painless retrocollis and, later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements and progress to stillness in an abnormal posture. Vomiting, malaise, irritability, and ataxia may be present during the spells that usually last minutes (paroxysmal) or, more commonly, hours and, at times, days (periodic). Neurologic exam between attacks, EEG, and neuroimaging studies are normal. The condition affects girls more than boys (3:1), often begins in infancy, and spontaneously remits before the age of 5 years. However, some children, particularly those with migrainous features during attacks, develop migraine later in life. Indeed, this condition is considered to be a migraine equivalent and cosegregates with migraine in families. Medical therapy is supportive during the attacks, especially when vomiting is a prominent feature.

Sandifer Syndrome and Rumination

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodes often occur 30 minutes after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of laterocollis, retrocollis, or torticollis, the exact pathophysiology of which remains elusive. Reflux can also present with rumination consisting of contraction of abdominal muscles followed by mouthing and swallowing movements and at times vomiting.

Alternating Hemiplegia of Childhood

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting one or both sides lasting minutes to days, starting in the first 18 months of life. Earlier manifestations include paroxysmal nystagmus, which is often monocular and ipsilateral to the hemiplegia or dystonia. Dystonic spells are the rule also. Patients can have episodes of reduced consciousness and confusion that are not epileptic. Most affected children also have ataxia and developmental delay, and many have choreoathetosis and behavioral problems. Most of the patients are initially misdiagnosed as having refractory focal epilepsy with Todd paralysis. About half of them also have epileptic seizures, which makes the differential diagnosis even more difficult. Flunarizine 2.5-20 mg/day reduces the frequency and severity of the attacks. This condition is most commonly caused by variants in *ATP1A3,* but it can also result from variants in *ATP1A2* or the glucose transporter 1 *(GLUT-1/SLC2AI)*, variants that are notoriously associated with diagnostically challenging protean manifestations ranging from epilepsy, usually in early life, to movement disorders thereafter. The *ATP1A3* gene has also been reported in a syndrome of **relapsing encephalopathy with cerebellar ataxia (RECA)** during febrile illnesses. Another syndrome is benign nocturnal alternating hemiplegia, which manifests during sleep and is generally outgrown and has been linked to *PRRT2* variants.

Paroxysmal Dyskinesias and Other Movement Disorders

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 633.4 and see Table 634.3). Despite their historical classification into distinct entities, emerging insight into their clinical features and their underlying genetic causes is revealing a significant overlap with phenotypic pleiotropy whereby a pathogenic variant in a single gene may be associated with multiple types of dyskinesias and paroxysms, including epileptic seizures even in the same child. A sensation of fatigue or weakness confined to one side may herald an attack. Consciousness is preserved and patients may be able to perform a motor activity, such as walking, despite the attack. The variability in the pattern of severity and localization between different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence and steadily decreases in the third decade. Neurologic examination between attacks, laboratory investigations, and imaging studies are usually normal. Because the co-occurrence of movement disorders and epileptic seizures is not uncommon, the nature of each type of paroxysmal event has to be characterized as epileptic or not, often with a cautiously analyzed video-EEG, as movement-related artifact may be misread as epileptiform. **Chorea** consists of involuntary rapid fast movements that are slower than myoclonus and not rhythmic. Common causes are poststreptococcal Sydenham chorea, antiphospholipid antibody syndrome, and systemic lupus erythematosus. Action

Table 634.4 Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

FEATURES	PKD	PNKD		PED	PHD (EPILEPSY WITH DYSTONIC EPILEPTIC SEIZURES)
		PNKD1 (MR1+ VE)	PNKD2 (MR1- VE)		
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD–16q	AD–2q35	AD–2q13	AD/AR	AD–20q13, 15q24, 1q21, 8p21
Gene	*PRRT2* (most common), *SCN8A*, *DEPDC5*	*MR1* (now called *PNKD*)	Not well characterized *KCNMA1*, *ATP1A3*	*SLC2A1*	*CHRNA4*, *CHRNB2*, *KCNT1*
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually childhood
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 min of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up with dystonic posture
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/wk	1/wk	Daily, weekly, or monthly	Several/night
Associations	Infantile seizures (ICCA), migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin Oxcarbazepine	Benzodiazepines, mainly clonazepam	Benzodiazepines, mainly clonazepam	Acetazolamide L-DOPA Antiepileptics Trihexyphenidyl Ketogenic diet in *SLC2A1* mutation cases	Carbamazepine Oxcarbazepine
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, Autosomal dominant; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AR, autosomal recessive; FPC, familial paroxysmal choreoathetosis; ICCA, infantile convulsions choreoathetosis syndrome; MR1+, myofibrillogenesis regulator 1–positive; MR1−, myofibrillogenesis regulator 1–negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer's cramp.
From Friedman NR, Ghosh D, Moodley M. Syncope and paroxysmal disorders other than epilepsy. In: Swaiman KF, Ashwal S, Ferriero DM, et al, eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Table 65-1.

myoclonus and paroxysmal lower body action dystonia occur in children with myoclonus dystonia—a syndrome caused by pathogenic variants in *SGCE* or *RELN*. **Drug reactions** can result in abnormal movements; they include **oculogyric crisis** with many antiemetics and lamotrigine toxicity, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Indeed, paroxysmal dyskinesia may be secondary to basal ganglia lesions, and various forms of nonepileptic paroxysms, including dystonic posturing, bicycling, and rhythmic boxing, may occur in children with decompensated maple syrup urine disease.

Episodic Ataxias

Episodic ataxias form a clinically and genetically heterogeneous group of diseases that manifest with recurrent truncal ataxia and incoordination. Of the nine syndromes described so far, only two (types 1 and 2) have been reported in a large number of families from different ethnic groups. **Type 1** is caused by pathogenic variants in *KCNA1* that encodes the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia and occasional seizures with interictal myokymia as a main diagnostic feature. **Type 2** is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by variants in the voltage-gated calcium channel gene *CACNA1A*. This type is more responsive than type 1 to acetazolamide; the drug can reduce the frequency and severity of attacks but not the interictal signs and symptoms. The other types of episodic ataxia are not well-characterized, but types 5, 6, and 9 have been associated with variants in *CACNB4*, *SLC1A3*, and *FGF14*, respectively. Spells of episodic ataxia may also occur in children with paroxysmal dyskinesia secondary to variants in *CACNA1A* or *PRRT2*, in line with the previously discussed phenotypic pleiotropy of these conditions. Although epileptic seizures have been primarily described in episodic ataxia type 1, they have also been reported with the other types, specifically types 2 and 6. Glucose transporter deficiency can at times present as episodic ataxia.

Motor Tics

These are movements that are under partial control and are associated with an urge to do them and with subsequent relief. They are usually exacerbated by emotions and often change in character over time. **Simple tics**, which occur at some time in about one in five children, involve one or two muscle groups; **complex tics** involve multiple tics or muscle groups; and **Tourette syndrome** consists of multiple motor tics and vocal tics for more than a year. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive-compulsive disorder or personality traits. Some rare cases appear to occur after preceding streptococcal infections and have been termed **PANDAS** (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections). **PANS**, on the other hand, refers to an acute onset of obsessive-compulsive symptoms

with other behavioral problems and often with tics but without the association of streptococcal infections (acute-onset neuropsychiatric syndrome).

Benign Motoric Paroxysms in Infancy

Benign myoclonus of infancy consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep with no concurrent epileptic EEG changes in a neurologically normal child. **Shuddering attacks** are characterized by rapid tremors of the head, shoulder, and trunk lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor because a family history of essential tremor is often present. **Infantile head atonic attacks** consist of repeated head drops, hundreds to thousands per day, usually appearing at 3-6 months of life and spontaneously subsiding by the first year of life, without concurrent EEG epileptic activity. Spontaneous remission occurs in all three syndromes, usually within a few months. Video-EEG is normal ictally and interictally in these syndromes but should be performed to differentiate them from infantile spasms and epileptic myoclonus. **Hereditary chin trembling** at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

Brainstem Dysfunction

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus, intracranial hemorrhage, brainstem tumors, Chiari malformation, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. The term *cerebellar fits* has been used to describe drop attacks, extensor posturing with varying degrees of altered consciousness and respiratory compromise secondary to crowding of the posterior fossa, and near herniation in decompensated cerebellar tumors and certain cases of Chiari malformation.

Behavioral Conditions

Many behavioral disorders can be mistaken for epileptic seizures. Pleasurable behaviors similar to masturbation may occur from infancy onward and may consist of rhythmic rocking movements in the sitting or lying position or rhythmic hip flexion and adduction. **Infantile gratification** (masturbation), which is more common in females, usually occurs at 2-3 years of age and is often associated with perspiration, irregular breathing, and grunting but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. **Stereotypies**, or repetitive movements that are more complex than tics and do not change and wax and wane as do tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. A **mannerism** is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies, which are generally pervasive over almost every other activity, such as head shaking or hand flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 years, involve more body parts, are more rhythmic, and most importantly occur when a child is engrossed with an object or activity of interest; children rarely try to suppress stereotypies. **Panic and anxiety attacks** have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures and therefore may necessitate video-EEG monitoring. **Rage attacks** usually occur in patients with a personality disorder and are usually not seizures, although rare cases of partial seizures can manifest as rage attacks. **Hyperventilation spells** can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. **Transient global amnesia** consists of isolated short-term memory loss for minutes to hours that occurs mostly in adults but has been reported in children. The etiology can be emotional stress, an epileptic disorder, migraine, a vascular disorder, or a drug-related reaction.

OCULOMOTOR AND VISUAL ABNORMALITIES

Paroxysmal Tonic Upgaze of Childhood

This usually starts before 3 months of age and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Although imaging and laboratory tests were nonrevealing in the seminal cases, white matter lesions have been later reported in some patients. An association with *CACNA1A* gene variants in a few patients who also suffered from ataxia has been reported, pointing to etiologic and clinical heterogeneity. The differential diagnosis includes drug reactions, tics, Chediak-Higashi disease, Rett syndrome, and Wilson disease. Most of those, however, occur at a later age. Therapy with carbonic anhydrase inhibitors or low-dose levodopa/carbidopa may be helpful in severe cases. Concomitant absence epilepsy has been reported in few cases.

Oculomotor Apraxia and Saccadic Intrusions

In oculomotor apraxia, saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan congenital oculomotor apraxia) or may occur in the context of Joubert syndrome, ataxia telangiectasia, spinocerebellar ataxias, or lysosomal storage diseases. A selective loss of Purkinje cells required to suppress omnipause neurons and initiate saccadic eye movement is believed to occur in some of the disorders. Saccadic intrusions are involuntary, sudden, conjugate eye movements away from the desired eye position. These are not necessarily pathologic.

Spasmus Nutans

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like those of epileptic seizures. A brain MRI should be performed because the triad has been associated with masses in the optic chiasm and third ventricle. Retinal disease should also be ruled out. In the absence of these associations, remission occurs before 5 years of age.

Opsoclonus-Myoclonus Syndrome

In opsoclonus-myoclonus syndrome, the term *dancing eyes* refers to continuous, random, irregular, and conjugate eye movements that may fluctuate in intensity. The finding usually accompanies myoclonus and ataxia (dancing feet). Neuroblastoma (more commonly), encephalitis, and a presumed postinfectious etiology are possible causes. In addition to treating the underlying etiology, adrenocorticotropic hormone (ACTH), corticosteroids, rituximab, and clonazepam are often needed. Recurrences are not infrequent, and developmental delay is common. The opsoclonus and myoclonus may recur after treatment. The long-term neurologic prognosis remains poor, yet the presence of this syndrome is associated with a favorable treatment response of a coexisting neuroblastoma. Opsoclonus with epileptic myoclonus has also been described in a child with GLUT-1 deficiency.

Daydreaming and Behavioral Staring

Staring may be a manifestation of absence seizures, which should be differentiated from daydreaming and from behavioral staring because of fatigue and inattention. This is common in children with **attention-deficit disorder** because these patients are often referred to rule out absence seizures. Hyperventilation in the office precipitates absences and is a useful clinical test. Episodes of staring only in certain settings

(e.g., school) are unlikely to be seizures. In addition, responsiveness to stimulation such as touch and lack of interruption of playing activity characterize nonepileptic staring. **Daydreaming** occurs often in children, and **time-out staring** occurs in children when they are overwhelmed with external stimuli or with demands and shut down, ignoring their surroundings and staring.

Visual Hallucinations

Temporal lobe seizures can be associated with complex visual auras, such as seeing people and places, often with subsequent focal seizure manifestations. **Occipital lobe seizures** usually cause simple visual hallucinations and may occur as isolated auras or may be accompanied by headache and nausea (**Gastaut type** of benign occipital epilepsy), making them difficult to differentiate from **migraine**. Hallucinations in occipital seizures are characterized by colorful shapes, circles, and spots seen for seconds and confined to one hemifield, whereas migrainous auras usually last minutes and consist of black-and-white lines, scotomas, and/or fortification spectra that start in the center of the vision. **Visual snow** is a phenomenon that can be confused with occipital seizures and a migraine aura. It consists of dynamic continuous tiny dots in all of the visual field lasting >3 months with at least two to four additional specific visual symptoms (afterimages [i.e., palinopsia], enhanced visual phenomena [i.e., entotopic phenomena such as excessive floaters and photopsias], photophobia, and impaired night vision [i.e., nyctalopia]). Although it can occur in patients with migraine or with psychologic stress, the underlying pathology is not clear. Unlike migraine, it is associated with increased, rather than decreased, metabolism on PET scans of the lingual gyrus, which is the visual memory area, and patients usually do not respond to antimigraine therapies. **Alice in Wonderland syndrome** consists of the visual distortion of one's body or surroundings (bigger, smaller, closer, or more distant) and has been associated with migraine, epilepsy, acute infection such as Epstein-Barr virus, or fever. Hallucinations can also be **secondary to other causes**: drug exposure, midbrain lesions, and psychiatric illnesses. In addition, retinal-associated hallucinations can occur in the form of flashes of light in the context of inflammatory etiologies, trauma, or optic nerve edema. **Charles Bonnet syndrome** is the occurrence of visual hallucinations caused by ocular-origin visual loss or, at times, intracranial pathology.

SLEEP-RELATED DISORDERS (SEE ALSO CHAPTER 31)

Paroxysmal nonepileptic sleep events are more common in epileptic patients than in the general population, which makes their diagnosis difficult. The EEG pattern of frontal lobe epileptic seizures may be similar to the one seen in normal arousals, making their diagnosis challenging, especially because they have nonspecific hypermotor manifestations such as thrashing, body rocking, kicking, boxing, pedaling, bending, running, and various vocalizations. The diagnosis of such epileptic seizures is made on the basis of highly stereotyped, usually brief (<1 minute) events arising several times a night from non–rapid eye movement sleep.

Benign Sleep Myoclonus and Neonatal Sleep Myoclonus

Physiologic sleep myoclonus consists of repetitive, usually bilateral, rhythmic jerks involving the upper and lower limbs during non–rapid eye movement (REM) sleep, sometimes mimicking clonic seizures. Although the rule is that it is not stimulus sensitive, a slow (1-Hz) rocking of the infant in a head-to-toe direction is a specific diagnostic test that may sometimes reproduce the neonatal sleep myoclonus. The lack of autonomic changes, occurrence only in sleep, and suppression by awakenings may help in differentiating these events from epileptic seizures. Remission is spontaneous, usually at 2-3 months of age. In older children and adults, sleep myoclonus consists of random myoclonic jerks of the limbs.

Non–Rapid Eye Movement Partial Arousal Disorders

Brief **nocturnal confusional arousals** occur during slow-wave sleep and are normal in children. Such episodes can vary from chewing, sitting up, and mumbling to agitated sleepwalking and usually last for 10-15 minutes. With **somnambulism**, there is often a positive family history, and it usually occurs 1-3 hours after sleep onset. **Night terrors** similarly occur in deep sleep, most often at 2-7 years of age and more so in males. Stress increases the risk of both. In night terrors, the child screams; appears terrified; has dilated pupils, tachycardia, tachypnea, unresponsiveness, agitation, and thrashing that increase with attempts to be consoled; is difficult to arouse; and may have little or no vocalization. In older children with persistent night terrors, an underlying psychologic etiology may be present. The diagnosis is based on the history. However, rarely, video-EEG monitoring may be needed, especially if stereotyped motoric features are suggested by the history. At times, the use of bedtime diazepam (0.2-0.3 mg/kg) or clonazepam (0.125-0.5 mg) may help control the problem while psychologic factors are being investigated. **Restless legs syndrome** can cause painful leg dysesthesias that cause nocturnal arousals and insomnia. It can be either genetic or associated with iron deficiency, systemic illness, or some drugs such as antidepressants. Therapy depends on treating the underlying cause and, if needed, on dopaminergic drugs, such as levodopa/carbidopa, or antiepileptics, such as gabapentin.

Rapid Eye Movement Sleep Disorders

Unlike night terrors, **nightmares** tend to occur later during the night and the child has a memory of the event. **REM sleep behavior disorder** consists of loss of atonia during REM sleep, enabling patients to act out their dreams and thus mimicking nocturnal frontal or temporal lobe seizures. It is more common in adults. Children with autism and developmental delay are more likely to have it than other children.

Sleep Transition Disorders

Nocturnal head banging **(jactatio capitis nocturna)**, rolling, repetitive limb movements, or body rocking often occur in infants and toddlers as they are trying to fall asleep and can be mistaken for seizures or spasms. They usually remit spontaneously by 5 years of age. No specific therapy is needed, but in exceptional cases, clonazepam at bedtime may be used.

Narcolepsy-Cataplexy Syndrome

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnogogic hallucinations, and disturbed nighttime sleep (see Chapter 31). The persistence of REM sleep atonia upon awakening or its intrusion during wakefulness leads to sleep paralysis or cataplexy, respectively. Loss of tone in cataplexy occurs in response to strong emotions and spreads from the face downward, leading to a fall in a series of stages rather than a sudden one. Consciousness is maintained in cataplexy. A selective loss of hypocretin-secreting neurons in the hypothalamus is at the origin of this disorder. The fact that DQB1*0602 is a predisposing human leukocyte antigen (HLA) allele identified in 85–95% of patients with narcolepsy-cataplexy suggests an autoimmune-mediated neuronal loss. Secondary narcolepsy has also been described in children with brain lesions affecting the brainstem or hypothalamic regions subserving wakefulness. The diagnosis is based on the multiple sleep latency test. Therapy relies on scheduled naps; medications such as amphetamines, methylphenidate, tricyclic antidepressants, modafinil, or sodium oxybate; and counseling about precautions in work and driving.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 635

Headaches

Andrew D. Hershey, Marielle Kabbouche, and Joanne Kacperski

Headache is a common complaint in children and adolescents. Headaches can be a *primary* problem or occur as a symptom of another disorder (a *secondary* headache). Recognizing this difference is essential for choosing the appropriate evaluation and treatment to ensure successful management of the headache. Primary headaches should be thought of as a disease themselves and are most often present as recurrent, episodic headaches, and for most children are sporadic in their presentation. This oftentimes creates confusion when patients and providers focus on the events (i.e., the headache, calling it a "migraine") rather than the disease itself.

The most common forms of *primary headache* in childhood are migraine and tension-type headache (Table 635.1). Other forms of primary headache, including the trigeminal autonomic cephalalgias and cluster headaches, occur much less commonly. Primary headache disorders can progress to very frequent or even daily headaches, with chronic migraine and chronic tension-type headache being recognized as a problem for children and adolescents. These more frequent headaches can have an enormous impact on the life of the child and adolescent, as reflected in school absences and decreased school performance, social withdrawal, and changes in family interactions. To reduce this impact, a treatment strategy that incorporates acute treatments, preventive treatments, and biobehavioral therapies must be implemented.

Secondary headache is a headache that is a symptom of an underlying illness (see Table 635.1). The underlying illness should be clearly present as a direct cause of the headaches with close association of timing and symptomatology. This is often difficult when two or more common conditions occur in close temporal association. This frequently leads to the misdiagnosis of a primary headache as a secondary headache. This is the case when the headaches caused by migraine are misdiagnosed as sinus headaches. The key components of a secondary headache are the likely direct cause-and-effect relationship between the headache and the precipitating condition. In this regard, when the presumed cause of the secondary headache has been treated (antibiotics) or given adequate time to recover (posttraumatic headache), the headache symptoms should resolve. If this does not occur, either the diagnosis must be reevaluated or the effectiveness of the treatment reassessed.

In all instances of primary headaches, the neurologic examination should be normal. If it is not normal or a secondary headache is suspected, this raises a red flag. *The presence of an abnormal neurologic examination (including fundoscopic) or unusual neurologic symptoms is a key clue that additional investigation is warranted.*

635.1 Migraine

Andrew D. Hershey, Marielle Kabbouche, and Joanne Kacperski

Migraine is a disease that has a genetic basis (Table 635.2) and represents the most frequent reason recurrent headaches are brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children and adolescents. Migraine is characterized by episodic attacks. These attacks are typically thought of as headaches, but in children there are also periodic syndromes that may represent attacks of migraine. The headaches may be moderate to severe in intensity, be focal in location, have a throbbing quality, and be associated with nausea, vomiting, light sensitivity, and/or sound sensitivity. Compared with migraine in adults, migraine in children and adolescents may be shorter in duration and has a bilateral, often bifrontal, location. The headaches can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (hemiplegic, Alice in Wonderland syndrome) (Tables 635.3-635.7). Migraine may present with a number of variants in children, including abdominally related symptoms without headache and components of the periodic syndromes of childhood—also called *episodic disorders associated with migraine* (see Table 635.1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling or long lasting, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

EPIDEMIOLOGY

Up to 75% of children report having a significant headache by the time they are 15 years of age. Recurrent headaches are less common but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 years and up to 28% of older adolescents. When headaches are occurring more than 15 days per month, they are termed *chronic migraine* and may occur in up to 1% of children and adolescents. The risk of conversion to a daily headache becomes more likely as the frequency increases or ineffective acute treatments are used. This explains the necessity to treat the headaches aggressively or prevent the headaches altogether, trying to block transformation to chronic migraine.

Migraine can affect a patient's life through school absences, limitation of home activities, and restriction of social activities. This can be assessed through simple tools such as PedMIDAS (pediatric migraine disability assessment tool). When headaches become more frequent, their negative impact increases in magnitude. This can lead to further complications, including anxiety and school avoidance, requiring a more extensive treatment plan.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Criteria have been established to guide the clinical and scientific study of headaches; these are summarized in *The International Classification of Headache Disorders*, 3rd edition (ICHD-3). Table 635.1 contrasts the different clinical types of migraine; Tables 635.3-635.7 list the specific criteria for migraine types.

Migraine Without Aura

Migraine without aura is the most common form of migraine in both children and adults. The ICHD-3 (see Table 635.3) requires this to be recurrent (at least five headaches that meet the criteria, typically over the past year, but no firm period is required). The recurrent episodic nature helps differentiate this from a secondary headache and separates migraine from tension-type headache. Because headaches may first start in young childhood, this may limit the diagnosis in children as they are just beginning to develop headaches.

The duration of the headache is defined as 4-72 hours for adults. It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce this duration to 2-72 hours in children and adolescents under the age of 18 years. Note that this duration is for the untreated or unsuccessfully treated headache. Furthermore, if the child falls asleep with the headache, the entire sleep period is considered part of the duration. These duration limits help differentiate migraine from both short-duration headaches, including the trigeminal autonomic cephalalgias, and prolonged headaches, such as those caused by idiopathic intracranial hypertension (pseudotumor cerebri). Some prolonged headaches may still be migraine, but a migraine that persists beyond 72 hours is classified as a variant termed **status migrainosus**.

The quality of migraine pain is often, but not always, throbbing or pounding. This may be difficult to elicit in young children, and drawings or demonstrations may help confirm the throbbing quality.

The location of the pain has classically been described as **unilateral (hemicrania)**; in young children it is more commonly bilateral. A more appropriate way to think of the location would therefore be focal to differentiate it from the diffuse pain of tension-type headaches.

Table 635.1 Classification of Headaches (ICHD-3 Code Diagnosis)

MIGRAINE
Migraine with or without aura
Migraine with typical aura (with or without headache)
Migraine with brainstem aura
Hemiplegic migraine (sporadic or familial types 1, 2, 3 or other genetic loci)
Retinal migraine
Chronic migraine

Complications of Migraine
Status migrainosus
Persistent aura without infarction
Migrainous infarction
Migraine aura–triggered seizure

Episodic Syndromes that May Be Associated with Migraine
Recurrent gastrointestinal disturbance
Cyclical vomiting syndrome
Abdominal migraine
Benign paroxysmal vertigo
Benign paroxysmal torticollis
Episodic colic

TENSION-TYPE HEADACHE (TTH)
Infrequent episodic TTH associated with or without pericranial tenderness
Frequent episodic TTH associated with or without pericranial tenderness
Chronic TTH associated with or without pericranial tenderness
Probable TTHs

TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)
Cluster headache (episodic or cluster)
Paroxysmal hemicrania (episodic or cluster)
Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)
Episodic SUNCT
Chronic SUNCT
Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)
Episodic SUNA
Chronic SUNA
Hemicrania continua
Probable trigeminal autonomic cephalalgias

OTHER PRIMARY HEADACHE DISORDERS
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache (external application, ingestion, or inhalation)
External-pressure headache
External-compression headache
External-traction headache
Primary stabbing headache
Nummular headache
Hypnic headache
New daily persistent headache (NDPH)

HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK
Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head
Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head
Acute or persistent headache attributed to whiplash
Acute or persistent headache attributed to craniotomy

HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER
Headache attributed to ischemic stroke or transient ischemic attack
Headache attributed to nontraumatic intracerebral hemorrhage
Headache attributed to nontraumatic subarachnoid hemorrhage
Headache attributed to nontraumatic acute subdural hemorrhage
Headache attributed to unruptured vascular malformation
Headache attributed to unruptured saccular aneurysm
Headache attributed to arteriovenous malformation
Headache attributed to dural arteriovenous fistula
Headache attributed to cavernous angioma
Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome)
Headache attributed to arteritis
Headache attributed to giant cell arteritis
Headache attributed to primary angiitis of the central nervous system
Headache attributed to secondary angiitis of the central nervous system
Headache attributed to cervical carotid or vertebral artery disorder
Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection
Postendarterectomy headache
Headache attributed to carotid or vertebral angioplasty
Headache attributed to cerebral venous thrombosis
Headache attributed to other acute intracranial arterial disorder
Headache attributed to an intracranial endovascular procedure
Angiography headache
Headache attributed to reversible cerebral vasoconstriction syndrome
Headache attributed to intracranial arterial dissection
Headache attributed to genetic vasculopathy
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)
Headache attributed to another genetic vasculopathy
Headache attributed to pituitary apoplexy

HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER
Headache attributed to increased cerebrospinal fluid pressure
Headache attributed to idiopathic intracranial hypertension
Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes
Headache attributed to intracranial hypertension secondary to hydrocephalus
Headache attributed to low cerebrospinal fluid pressure
Post–dural puncture headache
Cerebrospinal fluid fistula headache
Headache attributed to spontaneous intracranial hypotension
Headache attributed to noninfectious inflammatory disease
Headache attributed to neurosarcoidosis
Headache attributed to aseptic (noninfectious) meningitis
Headache attributed to other noninfectious inflammatory disease
Headache attributed to lymphocytic hypophysitis
Syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL)
Headache attributed to intracranial neoplasm
Headache attributed to colloid cyst of the third ventricle
Headache attributed to carcinomatous meningitis
Headache attributed to hypothalamic or pituitary hypersecretion or hyposecretion
Headache attributed to intrathecal injection
Headache attributed to epileptic seizure
Hemicrania epileptica
Postictal headache
Headache attributed to Chiari malformation type I
Headache attributed to other nonvascular intracranial disorder

Table 635.1 Classification of Headaches (ICHD-3 Code Diagnosis)—cont'd

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL
- Headache attributed to use of or exposure to a substance
- Nitric oxide donor–induced headache
- Phosphodiesterase inhibitor–induced headache
- Carbon monoxide–induced headache
- Alcohol-induced headache
- Monosodium glutamate–induced headache
- Cocaine-induced headache
- Histamine-induced headache
- Calcitonin gene-related peptide–induced headache
- Headache attributed to exogenous acute pressor agent
- Headache attributed to occasional or long-term use of non–headache medication
- Headache attributed to exogenous hormone

Medication-Overuse Headache (MOH)
- Ergotamine-overuse headache
- Triptan-overuse headache
- Simple analgesic–overuse headache
- Paracetamol (acetaminophen)-overuse headache
- Acetylsalicylic acid–overuse headache
- Other nonsteroidal antiinflammatory drug–overuse headache
- Opioid-overuse headache
- Combination analgesic–overuse headache

Headache Attributed to Substance Withdrawal
- Caffeine-withdrawal headache
- Opioid-withdrawal headache
- Estrogen-withdrawal headache

HEADACHE ATTRIBUTED TO INFECTION
- Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis
- Persistent headache attributed to past bacterial meningitis or meningoencephalitis
- Acute or chronic headache attributed to intracranial fungal or other parasitic infection
- Headache attributed to brain abscess
- Headache attributed to subdural empyema
- Headache attributed to systemic infection (acute or chronic)

HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS
- Headache attributed to hypoxia and/or hypercapnia
- High-altitude headache
- Headache attributed to airplane travel
- Diving headache
- Sleep apnea headache
- Dialysis headache
- Headache attributed to arterial hypertension
- Headache attributed to pheochromocytoma
- Headache attributed to hypertensive crisis with or without hypertensive encephalopathy
- Headache attributed to preeclampsia or eclampsia
- Headache attributed to autonomic dysreflexia
- Headache attributed to hypothyroidism
- Headache attributed to fasting
- Cardiac cephalalgia
- Headache attributed to other disorder of homoeostasis

HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE
- Headache attributed to disorder of cranial bone
- Headache attributed to retropharyngeal tendonitis
- Headache attributed to craniocervical dystonia
- Headache attributed to acute glaucoma
- Headache attributed to refractive error
- Headache attributed to heterophoria or heterotropia (latent or persistent squint)
- Headache attributed to ocular inflammatory disorder
- Headache attributed to tracheitis
- Headache attributed to disorder of the ears
- Headache attributed to acute or chronic or recurring rhinosinusitis
- Headache attributed to temporomandibular disorder
- Head or facial pain attributed to inflammation of the stylohyoid ligament
- Headache or facial pain attributed to other disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure

HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER
- Headache attributed to somatization disorder
- Headache attributed to psychotic disorder

PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS
- Classical trigeminal neuralgia
- Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain
- Painful trigeminal neuropathy
- Painful trigeminal neuropathy attributed to acute herpes zoster
- Postherpetic trigeminal neuropathy
- Painful posttraumatic trigeminal neuropathy
- Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
- Painful trigeminal neuropathy attributed to space-occupying lesion
- Painful trigeminal neuropathy attributed to other disorder
- Glossopharyngeal neuralgia
- Classical nervus intermedius (facial nerve) neuralgia
- Nervus intermedius neuropathy attributed to herpes zoster
- Occipital neuralgia
- Optic neuritis
- Headache attributed to ischemic ocular motor nerve palsy
- Tolosa-Hunt syndrome
- Paratrigeminal oculosympathetic (Raeder) syndrome
- Recurrent painful ophthalmoplegic neuropathy
- Burning mouth syndrome (BMS)
- Persistent idiopathic facial pain (PIFP)
- Central neuropathic pain
- Central neuropathic pain attributed to multiple sclerosis
- Central post-stroke pain (CPSP)

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders,* 3rd ed. Cephalalgia. 2018;38(1):1–211.

Of particular concern is the exclusively occipital headache because although these can be migraines, they are more frequently secondary to another more proximate etiology such as posterior fossa abnormalities.

The headaches of migraine, when allowed to fully develop, often worsen with activity. Worsening of the pain occurs classically in adults when going up or down stairs. This history is often not elicited in children. A change in the child's activity pattern can be easily observed as a reduction in play or physical activity. Older children may limit or restrict their sports activity or exercise during a headache attack.

The attacks may have a variety of associated symptoms. In younger children, nausea and vomiting may be the most obvious symptoms and often outweigh the headache itself. This often leads to the overlap with several of the gastrointestinal periodic diseases, including recurrent abdominal pain, recurrent vomiting, cyclic vomiting, and abdominal migraine. The common feature among all of these related conditions is an increased propensity among children with them for the later development of a typical description of a headache caused by migraine. Early childhood recurrent vomiting may in fact be migraine, but the child is not asked about or is unable to describe headache pain. This may occur as early as infancy because babies with colic have a higher incidence of migraine once they are able to express their symptoms. Once a clear head pain becomes evident, the earlier diagnosis of a gastrointestinal disorder is no longer appropriate.

Table 635.2 Genetics in Migraine

KEY FACTS

- Based on studies with twins, the heritability of migraine has been estimated as 42%
- A genome-wide association meta-analysis identified 38 genomic loci that affect migraine risk
- The relative risk of migraine without aura is 1.9 in first-degree relatives of probands with migraine without aura
- The relative risk of migraine with aura is 3.8 in first-degree relatives of probands with migraine with aura

GENETIC BIOMARKERS FOR MONOGENIC SUBTYPES OF MIGRAINE OR MIGRAINE-RELATED SYNDROMES

- Familial hemiplegic migraine
  - Type 1 (*CACNA1A* gene)
  - Type 2 (*ATP1A2* gene)
  - Type 3 (*SCN1A* gene)
  - Possible association with *PRRT2* gene
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (*NOTCH3* gene)
- Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (*TREX1* gene)
- Familial advanced sleep phase syndrome (*CSNK1D* gene)

Modified from Ashina M, Terwindt GM, Al-Mahdi Al-Karagholi M, et al. Migraine: disease characterization, biomarkers, and precision medicine. *Lancet.* 2021;397:1496–1504, Panel 2, p. 1498.

Table 635.3 Migraine Without Aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 4.

Table 635.4 Migraine with Typical Aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. Visual
   2. Sensory
   3. Speech/language symptoms
   4. Motor
   5. Brainstem
   6. Retinal
C. At least three of the following six characteristics:
   1. At least one aura symptom spreads gradually over 5 or more minutes
   2. Two or more symptoms occur in succession
   3. Each individual aura symptom lasts 5-60 min
   4. At least one aura symptom is unilateral
   5. At least one aura symptom is positive
   6. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 6.

Table 635.5 Migraine with Brainstem Aura

A. At least two attacks fulfilling criteria for migraine with aura and criterion B
B. Aura with both of the following
   1. At least two of the following brainstem symptoms:
      a. Dysarthria
      b. Vertigo
      c. Tinnitus
      d. Hyperacusis
      e. Diplopia
      f. Ataxia
      g. Decreased level of consciousness
   2. No motor or retinal symptoms

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 7.

Table 635.6 Vestibular Migraine with Vertigo

A. At least five episodes fulfilling criteria C and D
B. A current or past history of *migraine without aura* or *migraine with aura*
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
D. At least 50% of episodes are associated with at least one of the following three migrainous features:
   1. Headache with at least two of the following four characteristics:
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe intensity
      d. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

From Headache Classification Committee of the International Headache Society (HIS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 8.

Table 635.7 Chronic Migraine

A. Headache (tension-type–like and/or migraine-like) on 15 or more days/mo for more than 3 mo and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for *migraine without aura* and/or criteria B and C for *migraine with aura*
C. On 8 or more days/mo for more than 3 mo, fulfilling any of the following:
   1. Criteria C and D for *migraine without aura*
   2. Criteria B and C for *migraine with aura*
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 9.

When headache is present, vomiting raises the concern of a secondary headache, particularly related to increased intracranial pressure. *One of the red flags for this is the daily or near-daily early morning vomiting or headaches waking the child up from sleep or with the Valsalva maneuver.* When the headaches associated with vomiting episodes are sporadic and not worsening, it is more likely that the diagnosis is migraine. Vomiting and headache caused by increased intracranial pressure are frequently present on first awakening and remit with maintenance of upright posture. In contrast, if a migraine is present on

first awakening *(a relatively infrequent occurrence in children)*, getting up and going about normal, upright activities usually makes the headache and vomiting worse.

When the child matures, light and sound sensitivity (**photophobia** and **phonophobia**) may become more apparent. This is either by direct report of the patient or the interpretation by the parents of the child's activity because the parent may become aware of this symptom before the child. These symptoms are likely a component of the hypersensitivity that develops during an acute migraine attack and may also include smell sensitivity **(osmophobia)** and touch sensitivity **(cutaneous allodynia)**. Although only the photophobia and phonophobia are components of the ICHD-3 criteria, these other symptoms are helpful in confirming the diagnosis and may be helpful in understanding the underlying pathophysiology and determining the response to treatment. The final ICHD-3 requirement is the exclusion of causes of secondary headaches, and this should be an integral component of the headache history.

Migraine typically runs in families, with reports of up to 90% of children having a first- or second-degree relative with recurrent headaches. Given the underdiagnoses and misdiagnosis in adults, this is often not recognized by the family, and a headache family history is required. When a family history is not identified, this may be the result of either a lack of awareness of migraine within the family or an underlying secondary headache in the child. *Any child whose family, upon close and both direct and indirect questioning, does not include individuals with migraine or related syndromes (e.g., motion sickness, cyclic vomiting, menstrual headache) should have an imaging procedure performed to look for anatomic etiologies for headache.*

In addition to the classifying features, there may be additional markers of a migraine disorder. These include such things as **triggers** (skipping meals, inadequate or irregular sleep, dehydration, and weather changes are the most common), **pattern recognition** (associated with menstrual periods in adolescents or Monday-morning headaches resulting from changes in sleep patterns over the weekend and nonphysiologic early waking on Monday mornings for school), and **prodromal symptoms** (a feeling of irritability, tiredness, and food cravings before the start of the headache) (Fig. 635.1). Although these additional features may not be consistent, they do raise the index of suspicion for migraine and provide a potential mechanism of intervention. In the past, food triggers were considered widely common, but the majority have either been discredited with scientific study or represent such a small number of patients that they only need to be addressed when consistently triggering the headache.

Migraine with Aura

The aura associated with migraine is a neurologic warning that a migraine is going to occur. In the common forms, this can be the start of a typical headache without migraine, or it may even occur in isolation. For a typical aura, the aura needs to be visual, sensory, or dysphasic, lasting longer than 5 minutes and less than 60 minutes, with the headache starting within 60 minutes (see Table 635.4). The importance of the aura lasting longer than 5 minutes is to differentiate the migraine aura from a seizure with a postictal headache, whereas the 60-minute maximal duration is to separate migraine aura from the possibility of a more prolonged neurologic event such as a transient ischemic attack. The ICHD-3 criteria have also added the requirements that for a diagnosis of aura, there needs to be a positive symptom and not just a loss of function (i.e., flashing lights, tingling, not just blurring of vision).

The most common type of visual aura in children and adolescents is **photopsia** (flashes of light or light bulbs going off everywhere). These photopsias are often multicolored, and when gone, the child may report not being able to see where the flash occurred. Less likely in children are the typical adult auras, including *fortification spectra* (brilliant white zigzag lines resembling a starred pattern castle) or *shimmering scotoma* (sometimes described as a shining spot that grows or a sequined curtain closing). In adults, the auras typically involve only half the visual field, whereas in children they may be randomly dispersed. Blurred vision is often confused as an aura but is difficult to separate from photophobia or difficulty concentrating during the pain of the headache.

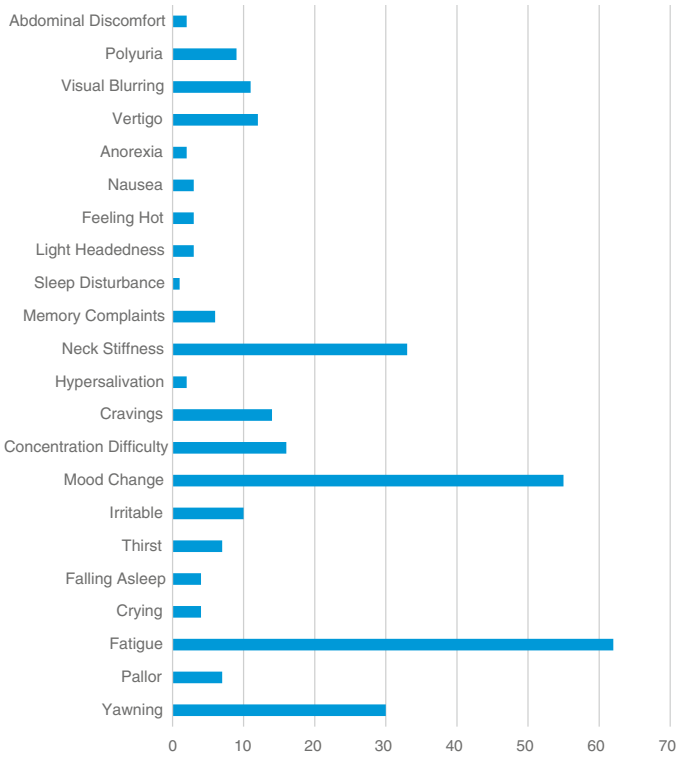

Fig. 635.1 Frequency of different premonitory symptoms reported. *(From Karsan N, Prabhakar P, Goadsby PJ. Characterizing the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. J Head Pain. 2016;17:94, Fig. 1.)*

Sensory auras are less common. They typically occur unilaterally. Many children describe this sensation as insects or worms crawling from their hand, up their arm, to their face with a numbness following this sensation. Once the numbness occurs, the child may have difficulty using the arm because they have lost sensory input, and a misdiagnosis of hemiplegic migraine may be made.

Dysphasic auras are the least common type of typical aura and have been described as an inability or difficulty to respond verbally. The patient afterward will describe an ability to understand what is being asked but cannot answer back. This may be the basis of what in the past has been referred to as *confusional migraine,* and special attention needs to be paid to asking the child about this possibility and their degree of understanding during the initial phases of the attack. Most of the time, these episodes are described as a motor aphasia, and they are often associated with sensory or motor symptoms.

Much less commonly, *rarer forms of aura can occur,* including hemiplegia (true weakness, not numbness, and may be familial), vertigo or lower cranial nerve symptoms–brainstem aura (formerly called *basilar-type* and once thought to be caused by basilar artery dysfunction, now thought to be a more brainstem-based migraine with brainstem aura) (see Table 635.4), and distortion (Alice in Wonderland syndrome). Whenever these rarer forms of aura are present, further investigation is warranted. Not all motor auras can be classified as hemiplegic migraine spectrum, and they should be differentiated from those specific migrainous events, because the diagnosis of hemiplegic migraine has genetic, pathophysiologic, and therapeutic implications.

Hemiplegic migraine is one of the better-known forms of rare auras. This transient unilateral weakness usually lasts only a few hours but may persist for days. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with pathogenic variants in three separate genes: *CACNA1A, ATP1A2,* and *SCN1A* (see Table 635.2). Some patients with familial hemiplegic migraine have other yet-to-be-identified genetic variants. Multiple polymorphisms have been described for these genes. Hemiplegic migraines may be triggered by minor head

trauma, exertion, or emotional stress. The motor weakness is usually associated with another aura symptom and may progress slowly over 20-30 minutes, first with a visual aura and then, in sequence, with sensory, motor, aphasic, and basilar auras. Headache is present in more than 95% of patients and usually begins during the aura; headache may be unilateral or bilateral and may have no relationship to the motor weakness. Some patients may develop attacks of coma with encephalopathy, cerebrospinal fluid (CSF) pleocytosis, and cerebral edema. Long-term complications may include seizures, repetitive daily episodes of blindness, cerebellar signs with the development of cerebellar atrophy, and mental disabilities.

Migraine with brainstem aura (basilar-type migraine) was formerly considered a disease of the basilar artery because many of the unique symptoms were attributed to dysfunction in this area of the brainstem. Some of the symptoms described include vertigo, tinnitus, diplopia, blurred vision, scotoma, ataxia, and an occipital headache. The pupils may be dilated, and ptosis may be evident.

Syndrome of transient headache and neurologic deficits with CSF lymphocytosis (HaNDL) describes transient migraine-like headaches associated with neurologic deficits (motor, sensory, language impairments) and CSF showing pleocytosis. It is considered a self-limited migraine-like syndrome of unknown etiology and is rarely reported in the pediatric population.

Childhood periodic syndromes are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (colic, motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleep talking, and night terrors), unexplained recurrent fevers, and even seizures.

The **gastrointestinal symptoms** span the spectrum from the relatively mild (motion sickness on occasional long car rides) to severe episodes of uncontrollable vomiting that may lead to dehydration and the need for hospital admission to receive fluids. These latter episodes may occur on a predictable time schedule and are called **cyclic vomiting**. During these attacks, the child may appear pale and frightened but does not lose consciousness. After a period of deep sleep, the child awakens and resumes normal play and eating habits as if the vomiting had not occurred. Many children with cyclic vomiting have a positive family history of migraine and as they grow older have a higher-than-average likelihood of developing migraine. Cyclic vomiting may be responsive to migraine-specific therapies; careful attention is needed for fluid replacement if the vomiting is excessive. **Cyclic vomiting of migraine** must be differentiated from gastrointestinal disorders, including intestinal obstruction (malrotation, intermittent volvulus, duodenal web, duplication cysts, superior mesenteric artery compression, and internal hernias), peptic ulcer, gastritis, giardiasis, chronic pancreatitis, and Crohn disease. Abnormal gastrointestinal motility and pelviureteric junction obstruction can also cause cyclic vomiting. Metabolic causes include disorders of amino acid metabolism (heterozygote ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia, methylmalonic acidemia), fatty acid oxidation defects (medium-chain acyl-coenzyme A dehydrogenase deficiency), disorders of carbohydrate metabolism (hereditary fructose intolerance), acute intermittent porphyria, and structural central nervous system lesions (posterior fossa brain tumors, subdural hematomas, or effusions). The diagnosis is a diagnosis of exclusion, and children will need a full workup to be labeled as having cyclic vomiting syndrome. Cyclic vomiting syndrome is more frequent in younger children and will gradually transform into a typical migraine attack by puberty (see Chapter 390).

The diagnosis of **abdominal migraine** can be confusing but can be thought of as a migraine without the headache. Like a migraine, it is an episodic disorder characterized by midabdominal pain with pain-free periods between attacks. At times this pain is associated with nausea and vomiting (thus crossing into the recurrent abdominal pain or cyclic vomiting spectrum). The pain is usually described as dull and may be moderate to severe. The pain may persist from 1 to 72 hours, and although it is usually in the midline, it may be periumbilical or poorly localized by the child. To meet the criteria of abdominal migraine, the child must complain at the time of the abdominal pain of at least two of the following: anorexia, nausea, vomiting, or pallor. Similar to cyclic vomiting, a thorough history and physical examination with appropriate laboratory studies must be completed to rule out an underlying gastrointestinal disorder as a cause of the abdominal pain. Careful questioning about the presence of headache or head pain needs to be addressed directly to the child because many times, this is truly a migraine but in the child's mind (and the parents' observation), the abdominal symptoms are paramount.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A thorough history and physical examination, including a neurologic examination with special focus on headache, has been shown to be the most sensitive indicator of an underlying etiology. The history needs to include a thorough evaluation of the prodromal symptoms, any potential triggering events or timing of the headaches, associated neurologic symptoms, and a detailed characterization of the headache attacks, including frequency, severity, duration, associated symptoms, use of medication, and disability. The disability assessment should include the impact on school, home, and social activities and can easily be assessed with tools such as PedMIDAS. A family history of headaches and any other neurologic, psychiatric, and general health conditions is also important both for identification of migraine within the family and the identification of possible secondary headache disorders. The familial penetrance of migraine is so robust that the absence of a family history of migraine or its equivalent phenomena should raise the concern that the diagnosis may not be migraine and warrants further history taking, referral to a headache specialist, or investigation. The lack of a family history may be the result of a lack of awareness of the family of the migraine ("doesn't everybody get headaches?"). When headaches are refractory, a history of potential comorbid conditions, which includes mood disorders and illicit substance use, especially in teenagers, that may influence adherence and acceptability of the treatment plan, may also need to be addressed. Patients with difficult-to-treat chronic migraines may have raised intracranial pressure; a lumbar puncture with lowering of the pressure may resolve the migraine. These patients may not have papilledema. In addition, disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Moyamoya disease, reversible cerebral vasoconstriction syndrome, and strokelike migraine attacks after radiation therapy (SMART) may initially present with migraines (Table 635.8).

Neuroimaging is warranted when the neurologic examination is abnormal or unusual neurologic features occur during the migraine; when the child has headaches that awaken the child from sleep or that are present on first awakening and remit with upright posture; when the child has brief headaches that only occur with cough or bending over; when the headache is mostly in the occipital area; and when the child has migrainous headache with an absolutely negative family history of migraine or its equivalent (e.g., motion sickness, cyclic vomiting; Table 635.9). In this case, an MRI is the imaging method of choice because it provides the highest sensitivity for detecting posterior fossa lesions and does not expose the child to radiation.

In the child with a headache that is instantaneously at its worst at onset, a CT scan looking for blood is the best initial test; if it is negative, a lumbar puncture should be done looking especially for xanthochromia of the CSF. There is no evidence that laboratory studies or an electroencephalogram is beneficial in a typical migraine without aura or migraine with aura.

TREATMENT

Table 635.10 outlines the drugs used to manage migraine headaches in children. The American Academy of Neurology established useful practice guidelines for the management of migraine as follows:

- Reduction of headache frequency, severity, duration, and disability
- Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improvement in quality of life
- Avoidance of acute headache medication escalation

Table 635.8 Migraine Mimics and Secondary Migraine

Trigeminal autonomic cephalgias (TACs)
Cluster headache
Hemicrania continua
Short-lasting unilateral neuralgiform headache attacks with or without conjunctival tearing (injection) (SUNCT/SUNA)
Ophthalmoplegic (CN III, IV, VI) migraine
Arterial dissection
Vasculitis/vasculopathies
Giant cell arteritis
Moyamoya
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) *(NOTCH 3)*
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) *(HTRA1)*
SLE
Granulomatosis with polyangiitis
Primary CNS vasculitis
Reversible cerebral vasoconstriction syndrome (RCVS)
Antiphospholipid antibody syndrome
MELAS
Idiopathic intracranial hypertension (pseudotumor cerebri)
Occipital epilepsy
Sudden vision loss
Transient ischemic attack
Acute glaucoma
Sinusitis with intracranial extension
Epilepsy with aura
Transient headache and neurologic deficits with CSF lymphocytosis (HaNDL)
Alternating hemiplegia of childhood *(ATP1A3)*
Fabry disease
SMART syndrome

CN, Cranial nerve; CNS, central nervous system; CSF, cerebrospinal fluid; MELAS, mitochondrial encephalopathy, lactic acidosis, and strokelike episodes; SMART, strokelike migraine attack after radiation therapy.
Modified from Lauck SM, Gage S. Headaches. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.17, p. 560.

Table 635.9 Indications for Neuroimaging in a Child with Headaches

Abnormal neurologic examination
Abnormal or focal neurologic signs or symptoms
• Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)
• Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase
Seizures or very brief auras (<5 min)
Unusual headaches in children
• Atypical auras, including basilar-type, hemiplegic
• Trigeminal autonomic cephalalgia, including cluster headaches in child or adolescent
• An acute secondary headache (i.e., headache with known underlying illness or insult)
Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache
Brief cough headache in a child or adolescent
Headache worst on first awakening or that awakens the child from sleep
Migrainous headache in the child with no family history of migraine or its equivalent

- Education and enabling of patients to manage their disease to enhance personal control of their migraine
- Reduction of headache-related distress and psychologic symptoms

To accomplish these goals, three components need to be incorporated into the treatment plan: (1) an acute treatment strategy should be developed for stopping a headache attack on a consistent basis with return to function as soon as possible, with the goal being 2 hours maximum; (2) a preventive treatment strategy should be considered when the headaches are frequent (one or more per week) and disabling; and (3) biobehavioral therapy should be started, including a discussion of adherence, elimination of barriers to treatment, and healthy habit management.

Acute Treatment

Management of an acute attack is designed to provide headache freedom as quickly as possible with return to normal function. This mainly includes two groups of medicines: nonsteroidal antiinflammatory drugs (NSAIDs) and triptans. Small-molecule calcitonin gene–related peptide modulator (CGRP receptor antagonists) therapies are approved for patients 18 and older for acute headache treatment, but they are still under investigation for efficacy and tolerability in children and adolescents. Most headaches caused by migraine in children will respond to appropriate doses of NSAIDs when they are administered at the *onset* of the headache attack. Ibuprofen has been well documented to be effective at a dose of 7.5-10.0 mg/kg and is often preferred; however, acetaminophen (15 mg/kg) can be effective in those with a contraindication to NSAIDs. Special concern for the use of ibuprofen or other NSAIDs includes ensuring that the children can recognize and respond to onset of the headache. This means discussing with the child the importance of telling the teacher when the headache starts at school and ensuring that proper dosing guidelines and permission have been provided to the school. In addition, medication overuse needs to be avoided, limiting NSAIDs and other pain medications for headache (or any combination of nonprescription analgesics) to not more than 2-3 times per week. The limitation of any analgesic to not more than three headaches per week is necessary to prevent the transformation of the migraines into **medication-overuse headaches (MOHs)**. If a patient has maximized the weekly allowance of analgesics, the patient's next step is to only use hydrating fluids for the rest of the week as an abortive approach. If ibuprofen is not effective, naproxen sodium also may be tried in similar doses. Aspirin is also a reasonable option but is usually reserved for older children (>16 years). Use of other NSAIDs has yet to be studied in pediatric migraine. The goal of the acute medication should be relief of headache and associated symptoms within 1 hour, with return to function in 10 of 10 headaches.

When an attack of migraine is especially severe, NSAIDs alone may not be sufficient. In this case, a triptan may be considered. Multiple studies have demonstrated their effectiveness and tolerability. There are currently three triptans that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of episodic migraine in the pediatric population. Almotriptan is approved for the treatment of acute migraine in adolescents (ages 12-17 years). Rizatriptan is approved for the treatment of migraine in children as young as age 6 years. The intranasal formulation of zolmitriptan is also approved by the FDA in the United States for use in children ages 12 and over. Several studies have shown it to provide rapid and effective relief, and it has been demonstrated to be well tolerated for treatment of acute migraine in patients 12 years and older. Zolmitriptan nasal spray may be of particular benefit to those with nausea and in patients who have difficulty swallowing tablets.

The combination of naproxen sodium and sumatriptan has been studied and may be effective in children. Controlled clinical trials demonstrate that intranasal sumatriptan is safe and effective in children older than age 8 years with moderate to severe migraine. At present, pediatric studies showing the effectiveness of oral sumatriptan are lacking, and there is insufficient evidence to support the use of subcutaneous sumatriptan in children. For most adolescents, dosing is the same as for adults; a reduction in dose is made for children weighing less than 40 kg. The triptans vary by rapidity of onset and biologic half-life. This is related to both their variable lipophilicity and dose. Clinically, 60–70% of patients respond to the first triptan tried, with 60–70% of

Table 635.10 Drugs Used in the Management of Migraine Headaches in Children

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
ACUTE MIGRAINE				
Analgesics				
Acetaminophen	15 mg/kg/dose	Analgesic effects	Overdose, fatal hepatic necrosis	Effectiveness limited in migraine
Ibuprofen	7.5-10 mg/kg/dose	Antiinflammatory and analgesic	GI bleeding, stomach upset, kidney injury	Avoid overuse (2-3 times per wk)
Triptans				
Almotriptan* (ages 12-17 yr)	12.5 mg	5-$HT_{1b/1d}$ agonist	Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort	Avoid overuse (>4-6 times per mo)
Eletriptan	40 mg	Same	Same	Avoid overuse (>4-6 times per mo)
Frovatriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (>4-6 times per mo)
Naratriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (>4-6 times per mo)
Rizatriptan* (ages 6-17 yr)	5 mg for child weighing <40 kg, 10 mg	Same	Same	Available in tablets and melts Avoid overuse (>4-6 times per mo)
Sumatriptan	Oral: 25, 50, 100 mg Nasal: 10 mg SC: 6 mg	Same	Same	Avoid overuse (>4-6 times per mo)
Zolmitriptan (NS ages 12+)	Oral: 2.5, 5 mg Nasal: 5 mg*	Same	Same	Available in tablets and melts Avoid overuse (>4-6 times per mo)
PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)				
Calcium Channel Blockers				
Flunarizine†	5 mg hs	Calcium channel blocking agent	Headache, lethargy, dizziness	May ↑ to 10 mg hs
Anticonvulsants				
Valproic acid	20 mg/kg/24 hr (begin 5 mg/kg/24 hr)	↑ Brain GABA	Nausea, pancreatitis, fatal hepatotoxicity	↑ 5 mg/kg every 2 wk
Topiramate* (12-17 yr)	100-200 mg divided bid	↑ Activity of GABA	Fatigue, nervousness	Increase slowly over 12-16 wk
Levetiracetam	20-60 mg/kg divided bid	Unknown	Irritability, fatigue	Increase every 2 wk starting at 20 mg/kg divided bid
Gabapentin	900-1800 mg divided bid	Unknown	Somnolence, fatigue, aggression, weight gain	Begin 300 mg, ↑ 300 mg/wk
Antidepressants				
Amitriptyline	1 mg/kg/day	↑ CNS serotonin and norepinephrine	Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion	Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime
Antihistamines				
Cyproheptadine	0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr	H_1-receptor and serotonin agonist	Drowsiness, thick bronchial secretions	Preferred in children who cannot swallow pills; not well tolerated in adolescents
Antihypertensive				
Propranolol	10-20 mg tid	Nonselective β-adrenergic blocking agent	Dizziness, lethargy	Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)
Others				
Coenzyme Q10	1-3 mg/kg/day	Increases fatty acid oxidation in mitochondria	No adverse effects reported	Fat soluble; ensure brand contains small amount of vitamin E to help absorption
Riboflavin	50-400 mg daily	Cofactor in energy metabolism	Bright yellow urine, polyuria and diarrhea	

Table 635.10 Drugs Used in the Management of Migraine Headaches in Children—cont'd

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
Magnesium	9 mg/kg divided tid	Cofactor in energy metabolism	Diarrhea or soft stool	
Butterbur	50-150 mg daily	May act similar to a calcium channel blocker	Burping	
OnabotulinumtoxinA	100 units (age 11-17 yr)	Inhibits acetylcholine release from nerve endings	Ptosis, blurred vision, hematoma at injection site	Used off-label in children
SEVERE INTRACTABLE				
Prochlorperazine	0.15 mg/kg/IV; max dose 10 mg	Dopamine antagonist	Agitation, drowsiness, muscle stiffness, akinesia and akathisia	May have increased effectiveness when combined with ketorolac and fluid hydration
Metoclopramide	0.2 mg/kg IV; 10 mg max dose	Dopamine antagonist	Drowsiness, urticaria, agitation, akinesia and akathisia	Caution in asthma patients
Ketorolac	0.5 mg/kg IV; 15 mg max dose	Antiinflammatory and analgesic	GI upset, bleeding	
Valproate sodium injection	15 mg/kg IV: 1,000 mg max dose	↑ Brain GABA	Nausea, vomiting, somnolence, thrombocytopenia	Would avoid in hepatic disease
Dihydroergotamine IV	0.5 mg/dose every 8 hr (<40 kg) 1.0 mg/dose every 8 hr (>40 kg)		Nausea, vomiting, vascular constriction, phlebitis	Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase)
Nasal spray	0.5-1.0 mg/dose 0.5 mg/spray			

*FDA approved in the pediatric population.
†Available in Europe.
↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

the patients who did not respond to the first triptan responding to the next triptan. Therefore in the patient who does not respond to the first triptan in the desired way (rapid reproducible response without relapse or side effects), it is worthwhile to try a different triptan. The most common side effects of the triptans are caused by their mechanism of action—tightness in the jaw, chest, and fingers as a result of vascular constriction and a subsequent feeling of grogginess and fatigue from the central serotonin effect. The vascular constriction symptoms can be alleviated through adequate fluid hydration during an attack.

The most effective way to administer acute treatment is with the recognition that NSAIDs and triptans have different mechanisms of action. NSAIDs are used for all headaches, mild to severe, with their use being restricted to fewer than two to three attacks per week; the triptans are added for moderate to severe headaches, with their use being restricted to not more than six to eight attacks per month. For an acute attack, the NSAIDs can be repeated once in 3-4 hours, if needed for that specific attack, and the triptans can be repeated once in 2 hours if needed. It is important to consider the various formulations available, and these options should be discussed with pediatric patients and their parents, especially if a child is unable to swallow pills or take an oral dose because of nausea and/or vomiting.

Because vascular dilation is a common feature of migraine that may be responsible for some of the facial flushing, followed by paleness and the lightheaded feeling accompanying the attacks, fluid hydration should be integrated into the acute treatment plan. For oral hydration, this can include the sports drinks that combine electrolytes and sugar to provide the intravascular rehydration.

Antiemetics are used for acute treatment of the nausea and vomiting. Further study has identified that their unique mechanism of effectiveness in headache treatment is related to their antagonism of dopaminergic neurotransmission. Therefore the antiemetics with the most robust dopamine antagonism (i.e., prochlorperazine and metoclopramide) have the best efficacy. These can be very effective for status migrainosus or a migraine that is unresponsive to NSAIDs and triptans. They require intravenous administration because other forms of administration of these drugs are less effective than the NSAIDs or triptans. When combined with ketorolac and intravenous fluids in the emergency department or an acute infusion center, intravenous antiemetics can be highly effective. When they are not effective, further inpatient treatment may be required using dihydroergotamine (DHE), which will mean an admission to an inpatient unit for more aggressive therapy of an intractable attack.

There are also a growing number of devices that appear to be effective for the acute treatment of headache attacks caused by migraine. Currently both a remote electrical neuromodulation (REN) device and a vagal nerve stimulator are approved for the acute treatment of attacks down to age 12. These devices have the benefit of improving the adolescent's locus of control, as they can modulate the degree and duration of treatment, without the need to swallow a pill.

Emergency Department Treatments for Intractable Headaches

When an acute migraine attack does not respond to the recommended outpatient regimen and the headache is disabling, more aggressive therapeutic approaches are available and may be necessary to prevent further increase in the duration and frequency of headaches. These migraines fall into the classification of status migrainosus (migraine attack lasting more than 72 hours), and patients may need to be referred to an infusion center, the emergency room, or an inpatient unit.

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medications such as prochlorperazine and metoclopramide, NSAIDs such as ketorolac, vasoconstrictor medications such as DHE, and antiepileptic drugs such as sodium valproate.

Antidopaminergic Drugs: Prochlorperazine and Metoclopramide

The use of antidopaminergic medications is not limited to controlling the nausea and vomiting often present during a migraine headache. Their potential pharmacologic effect may be a result of their antidopamine property and the underlying pathologic process involving the dopaminergic system during a migraine attack. Prochlorperazine is highly effective in aborting an attack in the emergency room when given intravenously with a bolus of intravenous fluid. Results show a 75% improvement with 50% headache freedom at 1 hour and 95% improvement with 60% headache freedom at 3 hours. Prochlorperazine may be more effective than metoclopramide. The average dose of metoclopramide is 0.13-0.15 mg/kg, with a maximum dose of 10 mg given intravenously over 15 minutes. The average dose of prochlorperazine is 0.15 mg/kg, with a maximum dose of 10 mg. These medications are usually well-tolerated, but *extrapyramidal reactions* are more frequent in children than in older persons. An acute extrapyramidal reaction can be controlled in the emergency room with 25-50 mg of diphenhydramine given intravenously. There is no need for premedication with diphenhydramine to prevent side effects. Diphenhydramine should only be used if needed when side effects are present.

Nonsteroidal Antiinflammatory Drugs: Ketorolac

It is known that an aseptic inflammation occurs in the central nervous system as a result of the effect of multiple reactive peptides in patients with migraines, including the CGRP molecules. Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement. When ketorolac is combined with prochlorperazine, the response rate jumps to 93%.

Antiepileptic Drugs: Sodium Valproate

Antiepileptic drugs have been used as prophylactic treatment for migraine headache for years with adequate double-blinded, controlled studies on their efficacy in adults. The mechanism by which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15-20 mg/kg push (over 10 minutes). This intravenous load is followed by an oral dose (15-20 mg/day) in the 4 hours after the injection. Patients may benefit from a short-term preventive treatment with an extended-release form after discharge from the emergency room for 2 weeks to keep the level in the therapeutic range. Sodium valproate is usually well tolerated. Patients should receive a fluid load during the procedure to prevent a possible hypotensive episode.

Triptans

Subcutaneous sumatriptan (0.06 mg/kg) has an overall efficacy of 72% at 30 minutes and 78% at 2 hours, with a recurrence rate of 6%. Because children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population. DHE, if recommended for the recurrences, should not be given in the 8 hours after triptan use. Triptans are contraindicated in patients treated with ergotamine within 24 hours and within 2 weeks of treatment with monoamine oxidase inhibitors. Triptans may rarely produce serotonin syndrome in patients taking a serotonin receptor reuptake inhibitor. *Both triptans and ergotamine are contraindicated in hemiplegic migraines.*

Dihydroergotamine

DHE is a medication used as a vasoconstrictor to abort the vascular phase of migraine headache. The effectiveness is discussed in detail in the section "Inpatient Management of Intractable Migraine and Status Migrainosus," next. One dose of DHE can be effective for abortive treatment in the emergency department. Emergency room treatment of migraine shows a recurrence rate of 29% at 48-72 hours, with 6% of patients needing even more aggressive therapy in an inpatient unit.

Inpatient Management of Intractable Migraine and Status Migrainosus

About 6–7% of patients fail acute treatment in the emergency department. These patients are usually admitted for 3-5 days to an inpatient unit and receive extensive parenteral treatment. Admission is reserved for patients who are disabled by their acute migraine attack and those who did not experience relief from all other abortive approaches as discussed earlier: (1) for acute status migrainosus, (2) for exacerbation of an underlying chronic migraine when the episode fits the criteria for a status migrainosus occurring on top of their continuous baseline headache, and (3) for severe analgesic overuse headache that did not respond to any other recommended abortive therapy. The goal of inpatient treatment is to control a headache that has been unresponsive to other outpatient abortive therapies and is disabling to the child. Treatment protocols include the use of DHE, antiemetics, sodium valproate, and other drugs.

Dihydroergotamine

Ergots are one of the oldest treatments for migraine headache. DHE is a parenteral form used for acute exacerbations. Its effect stems from the $5HT_{1A\text{-}1B\text{-}1D\text{-}1F}$ receptor agonist affinity and central vasoconstriction. DHE has greater α-adrenergic antagonist activity and is less vasoconstrictive peripherally. Before initiation of an intravenous ergot protocol, a full history should be obtained and a neurologic examination performed to rule out any possibility of secondary headache before the initiation of the treatment, keeping in mind that patients with migraine can still develop a secondary headache. Females of childbearing age should be evaluated for pregnancy before ergots are administered.

The DHE protocol consists of the following: Patients are premedicated with 0.13-0.15 mg/kg of prochlorperazine 30 minutes before the DHE dose (maximum of three prochlorperazine doses to prevent extrapyramidal syndrome; after three doses of prochlorperazine, a non–dopamine antagonist antiemetic should be used, such as ondansetron). A dose of 0.5-1.0 mg of DHE is used (depending on age and tolerability) every 8 hours until headache freedom is achieved or headache returns back to baseline for those with a continuous headache. The first dose should be divided into two half-doses separated by 30 minutes if the patient is naïve to treatment with DHE. When the headache ceases, an extra dose of DHE is given in an attempt to prevent recurrence after discharge. The response to this protocol is a 97% improvement and 77% headache freedom. The response is noticeable by the fifth dose; the drug can reach its maximum effects after the tenth dose. Common side effects of DHE include nausea, vomiting, abdominal discomfort, a flushed face, muscle cramping, and increased blood pressure. The maximum dose used in this protocol is 15 mg total of DHE.

Sodium Valproate

Sodium valproate is used when DHE is contraindicated or has been ineffective. One adult study recommends the use of valproate sodium as follows: bolus with 15 mg/kg (maximum of 1,000 mg), followed by 5 mg/kg every 8 hours until headache freedom or up to a maximum of 10 doses. An extra dose is recommended after the headache ceases to prevent recurrence. This protocol was studied in adults with chronic daily headaches and showed an 80% improvement. It is well tolerated and is useful in children when DHE is ineffective, contraindicated, or not tolerated.

Other Inpatient Therapies

During an inpatient admission for status migrainosus, other services such as behavioral medicine and holistic medicine should be involved if they are available. The behavioral medicine staff can play a major role in talking to patients about their specific triggers and can also evaluate school, as well as home and social stressors. The staff would also initiate some coping skills training during the admission and evaluate the necessity for further outpatient follow-up for cognitive-behavioral therapy, biofeedback, or treatment for other comorbidities. The holistic medicine staff, when consulted, can offer holistic approaches to pain control, including relaxation techniques, medical massage, and craniosacral therapy.

Preventive Therapy

When the headaches are frequent (more than one headache per week) or disabling (causing the patient to miss school, home, or social activities or with a PedMIDAS score >20), preventive or **prophylactic**

therapy may be warranted. The goal of this therapy should be to reduce the frequency to one headache or fewer per week and level of disability (PedMIDAS score <10). Prophylactic agents should be given for at least 4-6 months at an adequate dose and then weaned over several weeks. Evidence in adult studies has begun to demonstrate that persistent frequent headaches foreshadow an increased risk of progression with decreased responsiveness and increased risk of refractoriness in the future. It is unclear whether this also occurs in children and/or adolescents and whether early treatment of headache in childhood prevents development of refractory headache in adulthood.

Multiple preventive medications have been used for migraine prophylaxis in children. When analyzed as part of a practice parameter, one medication, **flunarizine** (a calcium channel blocking agent), demonstrated a level of effectiveness viewed as substantial; it is not available in the United States. Flunarizine is typically given at 5 mg orally daily and increased after 1 month to 10 mg orally daily, with a month off the drug every 4-6 months.

A commonly used preventive therapy for headache and migraine is amitriptyline. Typically, a dose of 1 mg/kg daily at dinner or in the evening is effective. However, this dose needs to be reached slowly (i.e., over weeks, with an increase every 2 weeks until the goal is reached) to minimize side effects and improve tolerability. Side effects include sleepiness and those related to amitriptyline's anticholinergic activity. Weight gain has been observed in adults using amitriptyline but is a less frequent occurrence in children. Amitriptyline does have the potential to exacerbate prolonged QT syndrome, so it should be avoided in patients with this diagnosis and looked for in patients taking the drug who complain of a rapid or irregular heart rate.

Antiepileptic medications are also used for migraine prophylaxis, with topiramate, valproic acid, and levetiracetam having been demonstrated to be effective in adults. There are limited studies in children for migraine prevention, but all of these medications have been assessed for safety and tolerability in children with epilepsy.

Topiramate has become widely used for migraine prophylaxis in adults. Topiramate was also demonstrated to be effective in an adolescent study. This study demonstrated that a 25-mg dose twice a day was equivalent to placebo, whereas a 50-mg dose twice a day was superior. Thus it appears that the adult dosing schedule is also effective in adolescents with an effective dosage range of 50 mg twice a day to 100 mg twice a day. This dose needs to be reached slowly to minimize the cognitive slowing associated with topiramate use. Side effects include weight loss, paresthesias, kidney stones, lowered bicarbonate levels, decreased sweating, and rarely glaucoma and changes in serum transaminases. In addition, in adolescent females taking birth control pills, the lowering of the effectiveness of the birth control by topiramate needs to be discussed.

A comparative effectiveness study in children (8-17 years) of the two most common treatments (amitriptyline and topiramate) compared with placebo (the CHAMP study) demonstrated that all three treatments were effective, but there was not statistical superiority for amitriptyline or topiramate over placebo.

Valproic acid has long been used for epilepsy in children and has been demonstrated to be effective in migraine prophylaxis in adults. The effective dose in children appears to be 10 mg/kg orally twice a day. Side effects of weight gain, ovarian cysts, and changes in serum transaminases and platelet counts need to be monitored. Other antiepileptics, including lamotrigine, levetiracetam, zonisamide, gabapentin, and pregabalin, are also used for migraine prevention.

β Blockers have long been used for migraine prevention. The studies on β blockers have a mixed response pattern with variability both between β blockers and between patients with a given β blocker. Propranolol is the best studied for pediatric migraine prevention with unequivocally positive results. The contraindication for the use of propranolol in children with asthma or allergic disorders or diabetes and the increased incidence of depression in adolescents using propranolol limit its use somewhat. It may be effective for a mixed subtype of migraine (basilar-type migraine with postural orthostatic tachycardia syndrome). This syndrome has been reported to be responsive to propranolol. α-Blockers and calcium channel blockers, aside from flunarizine, also have been used in pediatric migraine; their effectiveness, however, remains unclear.

In very young children, cyproheptadine may be effective in the prevention of migraine or the periodic syndromes of childhood. Young children tend to tolerate the increased appetite induced by the cyproheptadine and tend not to be subject to the lethargy seen in older children and adults; the weight gain is limiting once children start to enter puberty. Typical dosing is 0.1-0.2 mg/kg orally twice a day.

Nutraceuticals are popular choices, especially among families who prefer a more natural approach to headache treatment. Despite studies showing success of these therapies in adults, few studies have shown effectiveness in pediatric headaches. Riboflavin (vitamin B_2), at doses ranging from 25 to 400 mg, is the most widely studied with good results. Side effects are minimal and include bright yellow urine, diarrhea, and polyuria. Coenzyme Q10 supplementation may be effective in reducing migraine frequency at doses of 1-2 mg/kg/day. Butterbur is also effective in reducing headaches, with minimal side effects, including burping. Use in children has been limited to avoid the potential toxicity of butterbur-containing pyrrolizidine alkaloids, which are naturally contained and are a known carcinogen and toxic to the liver.

OnabotulinumtoxinA is the first medication FDA-approved for chronic migraine in adults. There are studies in children indicating its effectiveness; use in children is considered off-label. The limited available studies revealed the following: The average dose used was 188.5 units ± 32 units with a minimum dose of 75 units and maximum of 200 units. The average age of patients receiving the treatment was 16.8 ± 2.0 years (minimum 11 years; maximum 21 years). OnabotulinumtoxinA injections improved disability scores (PedMIDAS) and headache frequency in pediatric chronic daily headache patients and chronic migraine in this age-group. OnabotulinumtoxinA not only had a positive effect on the disability scoring for these young patients with headache but was also able to transform the headaches from chronic daily to intermittent headaches in more than 50% of the patients.

Eptinezumab, erenumab, galcanezumab, and fremanezumab—humanized monoclonal antibodies against the CGRP or its receptor—have demonstrated safety and efficacy in adult patients with migraine. The FDA has approved these agents for use in adults with migraine, including chronic migraine. There are no completed studies in children and adolescents.

Biobehavioral Therapy

Biobehavioral evaluation and therapy are essential for effective migraine management. This includes identification of behavioral barriers to treatment, such as a child's shyness or limitation in notifying a teacher of the start of a migraine or a teacher's unwillingness to accept the need for treatment. Additional barriers include a lack of recognition of the significance of the headache problem and reverting to bad habits once the headaches have responded to treatment. Adherence is equally important for acute and preventive treatment. The need to have a sustained response long enough to prevent relapse (to stay on preventive medication) is often difficult when the child starts to feel better. Establishing a defined treatment goal (one or two or fewer headaches per month for 4-6 months) helps with acceptance.

Because many of the potential triggers for attacks of migraine (skipping meals, dehydration, decreased or altered sleep) are related to a child's daily routine, a discussion of healthy habits is a component of biobehavioral therapy. This should include adequate fluid intake without caffeine, regular exercise, not skipping meals and making healthy food choices, and adequate (8-9 hours) sleep on a regular basis. Sleep is often difficult in adolescents because middle and high schools often have very early start times, and the adolescent's sleep architecture features a shift to later sleep onset and waking. This has been one of the explanations for worsening headaches during the school year in general and at the beginning of the school year and week.

Biofeedback-assisted relaxation and cognitive-behavioral therapy (usually in combination with amitriptyline) are effective for both acute and preventive therapy and may be incorporated into this multiple treatment strategy. This provides the child with a degree of self-control over the headaches and may further help the child cope with frequent headaches.

Young Adults and the Transition of Headache Care from a Pediatric to an Adult Provider

Migraine is a chronic condition that may first present in childhood. Males are diagnosed at a younger age than females; however, during development, the prevalence becomes highest among women, starting at puberty. Some adolescents and women report migraine associated with menses; the pain symptoms are described as lasting longer and having a higher intensity. The role of oral contraceptive pills (OCPs) is often a topic of discussion among female adolescents and young women. Studies have shown improvement of menstrual migraine in adult patients taking oral estrogens and progesterone; similar studies have not been done in adolescents. OCPs are not approved by the FDA for treatment of menstrual migraine; they have been associated with an increased risk of stroke among women with migraine aura. Therefore their use in adolescents as a prophylactic agent is not advised.

Comorbid conditions such as anxiety and depression are seen with a high prevalence among adults with migraine; however, the prevalence among adolescent patients remains unclear. Diagnostic tools capable of differentiating mood disorders from pain symptoms in the pediatric population are limited, which makes identifying those at risk challenging. However, it is important to keep in mind the potential of mood disorders, especially in young adults.

Remission of migraine is seen in up to 34% of adolescents, and almost 50% continue to have migraine persisting into adulthood. Successful transition of care from a pediatric to an adult provider has been shown to improve outcomes in patients with chronic disease.

Early diagnosis and treatment of migraine can help minimize the progression of the disease in adults. This, together with careful screening for comorbid conditions, may help identify those at risk for refractory migraine, minimize disability, and improve overall headache outcomes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

635.2 Secondary Headaches

Andrew D. Hershey, Marielle Kabbouche, and Joanne Kacperski

Headaches can be a common symptom of other underlying illnesses. In recognition of this, the ICHD-3 has classified potential secondary headaches (see Table 635.1). The key to the diagnosis of a secondary headache is to recognize the underlying cause and demonstrate a direct cause and effect. Until this has been done, the diagnosis is speculative. This is especially true when the suspected etiology is common.

Headache is a common occurrence after concussion or mild traumatic brain injury (mTBI), reported in as many as 86% of high school and college athletes who have suffered from head trauma (see Chapter 729). Although there are no strict criteria for determining who will develop persistent headache after concussion, it is important to gather information to rule out other secondary headaches and significant primary headache disorders and to identify those who may be at risk for persistent headache after concussion.

Chronic or persistent headaches are headaches that last for more than 3 months after head trauma. This definition is consistent with the classification of persistent posttraumatic headaches in the ICHD-3. Although concussion and posttraumatic headache are rapidly evolving areas of study, there is an unfortunate lack of definitive scientific evidence at this time on these topics in pediatrics. The ICHD-3 classifies posttraumatic headaches as acute if they last less than 3 months and persistent if they last more than 3 months after injury. This period is consistent with ICHD-II diagnostic criteria, although the term *persistent* has been adopted in place of *chronic*. Although the ICHD-3 criteria state that posttraumatic headaches begin within 7 days after injury to the head or after regaining consciousness, this 7-day cutoff is arbitrary, and some experts believe that headaches may develop after a longer interval. Some studies have shown that ~50% of children with posttraumatic headache 3 months after concussion had a history of preexisting headaches, and 31% had a history of migraine or probable migraine before the injury. Furthermore, 56% of patients with headaches at 3 months after injury had a family history of migraine. Based on clinical experiences of patients with prolonged postconcussion symptoms, those with *prior* concussion and *persistent* posttraumatic headaches, preexisting anxiety and/or depression, and maladaptive coping styles may also be at higher risk for persistent posttraumatic headache.

Despite being classified as a secondary headache, a posttraumatic headache generally presents with clinical features that are observed in primary headache disorders, including tension-type, migraine, and cervicogenic headaches. The few reports that have thus far assessed the characteristics of posttraumatic headache in the pediatric population have also reported various proportions of migraine or tension-type characteristics, with the reported prevalence of each varying among individual studies.

Although headache is reported to be the most common symptom after concussion, there is a paucity of studies regarding the safety and efficacy of headache treatments for persistent posttraumatic headaches. Posttraumatic headaches may be difficult to treat. There are currently no established guidelines for their treatment, especially when persistent, and practices can vary widely. Most treatment algorithms proposed have been extrapolated from the primary headache literature and small noncontrolled trials of posttraumatic headache regimens. When posttraumatic headaches become problematic or persistent, a multidimensional management approach, including pharmacologic intervention, physical rehabilitation, and cognitive-behavioral therapies, are often used. Management should therefore be relevant to the type of headache and focused on the clinical needs of the child.

Like primary headache disorders, these headaches can have a substantial effect on the child's life, leading to lost school days and withdrawal from social interactions. Referral for biobehavioral therapy and coping strategies may be necessary. Adherence should be promoted and can be optimized by educating both the patient and the family about the proper use of acute and prophylactic medications, establishing realistic expectations (including expectations for recovery), and emphasizing compliance at the initiation of treatment.

Children with persistent posttraumatic headaches may require frequent analgesics. Rebound headaches are common and can complicate treatment. The excessive use of symptomatic headache medicines, most commonly simple analgesics, can cause MOHs in susceptible patients and has been well-described in patients with primary headache disorders. Medication overuse can be a contributing factor in headache chronicity in 20–30% of children and adolescents, with chronic daily headache unrelated to concussion. Because analgesics are commonly recommended for the treatment of acute headaches after concussion, some susceptible patients with concussion are at risk for developing a medication-overuse pattern that causes a chronic headache syndrome.

There is no clear evidence to help guide the clinician on the timing of initiation of preventive therapy in children to decrease the likelihood of developing persistent posttraumatic headaches. Although many medications are being used to manage persistent posttraumatic headaches, most have supporting data for the management of migraine or chronic migraine, and few have been studied for the treatment of persistent posttraumatic headaches in a systematic manner.

Sinus headache is the most overdiagnosed form of recurrent headache. Although no studies have evaluated the frequency of misdiagnosis of an underlying migraine as a sinus headache in children, in adults, it has been found that up to 90% of adults diagnosed as having a sinus headache either by themselves or their physician appear to have migraine. When headaches are recurrent and respond within hours to analgesics, migraine should be considered first. In the absence of purulent nasal discharge, fever, or chronic cough, the diagnosis of sinus headache should not be made.

MOHs frequently complicate primary and secondary headaches. An MOH is defined as a headache present for more than 15 days/month for longer than 3 months and intake of a simple analgesic on

Table 635.11 History-Related Red Flags for Secondary Headache

QUALITY
"Thunderclap" rapid-onset headache or the "worst headache of my life"
Recent worsening in severity or frequency
Change in quality
New-onset symptoms consistent with cluster headache
LOCATION
Unilateral without alteration of sides
Chronic or recurrent occipital headache
TIMING
Awakens from sleep
Occurs in morning or causes morning vomiting
Acute or chronic progressive pattern
POSITIONAL OR ACTIVITY-RELATED VARIATIONS
Worsened in the recumbent position or when bending over
Headache experienced or worsened with cough or the Valsalva maneuver
ASSOCIATED NEUROLOGIC HISTORY
Neurologic dysfunction other than typical aura
Altered sensorium during headache
Sensory deficits or changes in vision, gait, or coordination
Other focal neurologic deficits
Seizures or syncope
Decreased visual acuity
Mental status changes (e.g., confusion or disorientation)
Regression in fine or gross motor developmental skills
Decline in cognition or school performance
Change in mood, behavior, or personality
ASSOCIATED GENERAL HISTORY
Vomiting without nausea and morning/fasting nausea or vomiting
Polyuria or polydipsia
Preschool or younger age
History of head trauma
Neck pain
Medical comorbidities
History of ventriculoperitoneal shunt
Certain medications
Signs of systemic or localized head/neck infection
Negative family history of primary headache disorders

From Lauck SM, Gage S. Headaches. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 34.5, p. 553.

Table 635.12 Physical Examination Red Flags for Secondary Headaches

ABNORMAL VITAL SIGNS
Hypertension
Growth failure
Increased head circumference or bulging fontanel
Fever
Meningeal signs with or without fever
Evidence of cranial trauma
Cranial bruit
Frontal bony tenderness
Macrocephaly
ABNORMAL OPHTHALMOLOGIC FINDINGS
Papilledema
Abnormal ocular movements
Squinting
Pathologic pupillary response
Visual field defects
ABNORMAL NEUROLOGIC FINDINGS
Impaired mental status
Cranial nerve palsy
Ataxia
Abnormal gait
Abnormal coordination
Abnormal reflexes
Asymmetric motor or sensory examination
Hemiparesis
Developmental regression
Precocious, delayed, or arrested puberty
SKIN FINDINGS
Café-au-lait or ash leaf macules
Petechiae or purpura
Facial hemangioma
Malar rash

From Lauck SM, Gage S. Headaches. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 34.6, p. 553.

more than 15 days/month and/or prescription medications, including triptans or combination medications, on more than 10 days/month. Some of the signs that should raise suspicion of medication overuse are the increasing use of analgesics (nonprescription or prescription) with either decreased effectiveness or frequent wearing off (i.e., analgesic rebound). An MOH can be worsened by ineffective medications or misdiagnosis of the headache. Patients should be cautioned against the frequent use of antimigraine medications, including combination analgesics or triptans.

Serious causes of secondary headaches are likely to be related to **increased intracranial pressure**. This can be caused by a mass (tumor, vascular malformation, cystic structure) or an intrinsic increase in pressure (idiopathic intracranial hypertension, also known as *pseudotumor cerebri*). In the former case, the headache is caused by the mass effect and local pressure on the dura; in the latter case, the headache is caused by diffuse pressure on the dura. The etiology of idiopathic intracranial hypertension may be the intake of excessive amounts of fat-soluble compounds (e.g., vitamin A, retinoic acid, and minocycline), hormonal changes (increased incidence in females), or blockage of venous drainage (as with inflammation of the transverse venous sinus from mastoiditis). When increased pressure is suspected, either by historical suspicion or the presence of papilledema, an MRI with magnetic resonance angiography and magnetic resonance venography should be performed, followed by a lumbar puncture if no mass or vascular anomaly is noted. The lumbar puncture can be diagnostic and therapeutic of idiopathic intracranial hypertension but must be performed with the patient in a relaxed recumbent position with legs extended, because abdominal pressure can artificially raise intracranial pressure. If headache persists or there are visual field changes, pharmaceutical treatment with a carbonic anhydrase inhibitor, optic nerve fenestration, or a shunt needs to be considered.

Additional causes of secondary headaches in children that may not be associated with increased intracranial pressure include arteriovenous malformations, berry aneurysm, collagen vascular diseases affecting the central nervous system, hypertensive encephalopathy, infectious or autoimmune etiologies, acute subarachnoid hemorrhage, and stroke. The management of secondary headache depends on the cause. Helpful laboratory tests and neuroradiologic procedures depend on the clues provided by the history (Table 635.11) and physical (Table 635.12) examination. By definition, a secondary headache has a specific cause and should resolve once this cause is treated. If the headache persists, the diagnosis and treatment should be questioned because either the diagnosis, which may include a primary headache, or the treatment, or both, may be incorrect.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

635.3 Tension-Type Headaches

Andrew D. Hershey, Marielle Kabbouche, and Joanne Kacperski

Tension-type headaches (TTHs) may be common in children and adolescents, with a prevalence in some studies as high as 48%, with those having a combination of migraine and TTH around 20%. Because of their mild to moderate nature, relative lack of associated symptoms, and lower degree of associated disability, they are often ignored or have minimal impact. The ICHD-3 subclassifies TTHs as infrequent (<12 headaches/year) (Table 635.13), frequent (1-15 headaches/month), and chronic (>15 headaches/month). They can further be separated into headaches with or without pericranial muscle tenderness. The classification of TTH can be likened to the opposite of migraine. Whereas migraines are typically moderate to severe, are focal in location, are worsened by physical activity or limit physical activity, and have a throbbing quality, TTHs are mild to moderate in severity, are diffuse in location, are not affected by activity (although the patient may not feel like being active), and are nonthrobbing (often described as a constant pressure). TTH is much less frequently associated with nausea, photophobia, or phonophobia and is never associated with more than one of these at a time or with vomiting. TTH must be recurrent, but at least 10 headaches are required, and the duration can be 30 minutes to 7 days. Secondary headaches with other underlying etiologies must be ruled out.

Evaluation of patients with suspected TTHs requires a detailed headache history and complete general and neurologic examination. This is to establish the diagnosis and ensure exclusion of secondary etiologies. When secondary headaches are suspected, further directed evaluation is indicated.

Treatment of TTHs can require acute therapy to stop attacks, preventive therapy when frequent or chronic, and behavioral therapy. It is often suspected that there may be underlying psychologic stressors (hence, the misnomer as a stress headache), but this is often difficult to identify in children, and although it may be suspected by the parents, it cannot be confirmed in the child. Studies of and conclusive evidence to guide the treatment of TTH in children are lacking, but the same general principles and medications used in migraine can be applied to children with TTHs (see Chapter 635.1). Oftentimes, simple analgesics (ibuprofen or acetaminophen) can be effective for acute treatment. Flupirtine is a nonopioid analgesic that has been approved in Europe for the treatment of TTH in children as young as age 6 years but is not available in the United States. Amitriptyline has the most evidence of effective prevention of TTH; biobehavioral intervention, including biofeedback-assisted relaxation training and coping skills, can be useful as well.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 635.13 Infrequent Episodic Tension-Type Headache

A. At least 10 episodes of headache occurring on <1 day/mo on average (<12 days/yr) and fulfilling criteria B-D
B. Lasting from 30 min to 7 days
C. At least two of the following four characteristics:
   1. Bilateral location
   2. Pressing or tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity, such as walking or climbing stairs
D. Both of the following:
   1. No nausea or vomiting
   2. No more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (HIS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 10.

Chapter 636 Neurocutaneous Syndromes

Mustafa Sahin, Nicole Ullrich, Siddharth Srivastava, and Anna L. Pinto

The neurocutaneous syndromes include a heterogeneous group of disorders characterized by abnormalities of both the integument and central nervous system (CNS) of variable severity (Table 636.1). Many of the disorders are hereditary and believed to arise from a defect in differentiation of the primitive ectoderm (nervous system, eyeball, retina, and skin). Disorders classified as neurocutaneous syndromes include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), Sturge-Weber syndrome (SWS), von Hippel-Lindau disease (VHL), PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, eye abnormalities) syndrome, ataxia-telangiectasia (AT), linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti.

636.1 Neurofibromatosis

Nicole Ullrich

NF refers to a group of autosomal dominant genetic conditions that cause tumors to grown on nerves throughout the body. The types of NF include neurofibromatosis type 1 (NF1) and all types of schwannomatosis (SWN), including NF2-related schwannomatosis (NF2-SWN, formerly called neurofibromatosis type 2, or NF2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

NF1 has an incidence of 1 in 2,500 live births and is caused by autosomal dominant loss-of-function pathogenic variants in the *NF1* gene. Approximately 50% are inherited from an affected parent, and the other 50% result from a sporadic gene variant. The diagnostic criteria for NF1 were updated in 2021 by an international expert panel. The disease is clinically diagnosed when any two of the following manifestations are present: **(1)** Six or more café-au-lait macules (CALMs) >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals (Fig. 636.1). CALMs are the hallmark of neurofibromatosis and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the first few years of life. The CALMs are scattered over the body surface, with predilection for the trunk and extremities. CALMs are not specific for NF1 and may be observed in other disorders (Table 636.2). **(2)** Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter; at least one of the two pigmentary findings (café-au-lait macules or freckling) must be bilateral (Fig. 636.2). Skinfold freckling usually appears between 3 and 5 years of age. The frequency of axillary and inguinal freckling is reported to be >80% by 6 years of age. **(3)** Two or more iris Lisch nodules, which are hamartomas located within the iris and are best identified by a slit-lamp examination, or two or more choroidal abnormalities (Fig. 636.3). They are present in more than 74% of patients with NF1. The prevalence of Lisch nodules increases with age, from only 5% of children younger than 3 years of age, to 42% among children 3-4 years of age, and virtually 100% of adults older than 21 years of age. **(4)** Two or more neurofibromas or one plexiform neurofibroma. Neurofibromas are most visible on the skin, but they may occur on any peripheral nerve in the body, including along peripheral nerves and blood vessels and within viscera, including the gastrointestinal

Table 636.1 Genetic and Clinical Features Associated with Neurocutaneous Syndromes

SYNDROME	GENE(S)	INHERITANCE	CLINICAL FEATURES
Tuberous sclerosis complex	*TSC1 (tuberous sclerosis 1; hamartin)* *TSC2 (tuberous sclerosis 2; tuberin)*	Autosomal dominant	Angiofibromas, hypomelanotic macules, shagreen patches, ungual fibromas, cortical dysplasias, subependymal giant cell astrocytomas, subependymal nodules, intellectual disability, epilepsy including infantile spasms, autism spectrum disorder, retinal hamartomas, cardiac rhabdomyomas, lymphangioleiomyomatosis, renal angiomyolipomas
Neurofibromatosis type 1	*NF1* (neurofibromin)	Autosomal dominant	
Schwannomatosis		Autosomal dominant	
NF2-related schwannomatosis	*NF2*		Vestibular schwannoma, meningioma, ependymoma, schwannoma, juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane, affected parent, *NF2* pathogenic variant in at least two distinct tumors (formerly called NF2)
Non-NF2-related schwannomatosis			Two or more schwannomas or hybrid nerve sheath tumors AND pathogenic variant identified; no vestibular schwannomas identified
SMARCB1-related schwannomatosis	*SMARCB1*		
LZTR1-related schwannomatosis	*LZTR1*		
22q-related schwannomatosis	LOH of chromosome 22		
Schwannomatosis NOS (not otherwise specified): For those who have not had genetic testing			
Schwannomatosis NEC (not elsewhere classified): For those in whom genetic testing of blood/saliva and tumors failed to detect a pathogenic variant			
Von Hippel-Lindau	*VHL (von Hippel-Lindau tumor suppressor)*	Autosomal dominant	Cerebellar hemangioblastomas, retinal angiomas, endolymphatic sac tumors, pancreatic neuroendocrine tumors, renal cysts, renal cell carcinomas, pheochromocytomas
Linear nevus sebaceous	*HRAS (HRas proto-oncogene, GTPase)* *KRAS (KRAS proto-oncogene, GTPase)* *NRAS (neuroblastoma RAS viral oncogene homolog)*	Somatic mosaicism	Linear sebaceous nevus, hemimegalencephaly, ventriculomegaly, intellectual disability, epilepsy, ocular defects (e.g., strabismus), cardiac defects (e.g., coarctation of the aorta), urogenital defects (e.g., horseshoe kidney), skeletal defects (e.g., fibrous dysplasia)
PHACE	Unknown		Posterior fossa malformations, hemangiomas, arterial lesions (e.g., dysplasia of cerebral arteries), cardiac defects (e.g., coarctation of the aorta), ocular defects (e.g., microphthalmia), ventral defects (e.g., sternal clefting)
Incontinentia pigmenti	*IKBKG (inhibitor of kappa B kinase gamma)*	X-linked dominant	Distinctive skin lesion appearing in four stages (bullous, verrucous, pigmentary, atretic), alopecia, dental anomalies (e.g., hypodontia), intellectual disability, epilepsy, ocular defects (e.g., retinal neovascularization), nail defects (e.g., dystrophic nails)

tract. These lesions appear characteristically during adolescence or pregnancy, suggesting a hormonal influence. They are usually small, rubbery lesions with a slight purplish discoloration of the overlying skin. Plexiform neurofibromas are typically congenital and result from diffuse thickening of nerve trunks and surrounding soft tissues. The skin overlying a plexiform neurofibroma may be coarse and associated with hyperpigmentation. Plexiform neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. **(5)** A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos), anterolateral bowing of tibia (tibial dysplasia), or pseudarthrosis of a long bone. **(6)** Optic pathway gliomas are present in approximately 15–20% of individuals with NF1;



Fig. 636.1 Neurofibromatosis type 1 (NF1). The presence of six or more café-au-lait (CAL) spots larger than 0.5 cm in diameter in children and 1.5 cm in adolescents suggests the possibility of NF1, although having CAL spots alone does not allow for definitive diagnosis. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2016, Fig. 11-44.)*

however, only ~30% of these are clinically symptomatic and require tumor-directed therapy. They are the most frequently observed CNS tumor in NF1. Because of visual acuity compromise, it is recommended that all children with NF1 undergo at least annual ophthalmologic examinations, or more frequent ones if there is a concern. The most common time to develop symptoms is between the ages of 2 and 6 years; they manifest as a change in visual acuity, a change in the visual fields, or pallor of the optic nerve. Extension into the hypothalamus can lead to precocious puberty. The brain MRI findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm (Fig. 636.4). **(7)** A parent with NF1 whose diagnosis was based on the aforementioned criteria. **(8)** A pathogenic *NF1* gene variant. It is important to note that genetic testing is not required to make a diagnosis of NF1, but it may allow for an earlier diagnosis. In addition, presence of a genetic variant *alone* is not sufficient to diagnose NF1; a second diagnostic feature is required.

Children with NF1 are susceptible to **neurologic complications**. MRI studies of selected children have shown abnormal hyperintense T2-weighted signals in the optic tracts, brainstem, globus pallidus, thalamus, internal capsule, and cerebellum (Fig. 636.5). These signals, **unidentified bright objects** or focal areas of signal abnormality (FASI), tend to disappear with age; most have disappeared by 30 years of age. It is unclear what the unidentified bright objects represent pathologically, and there is disagreement as to the relationship between the presence and number of unidentified bright objects and the occurrence of learning disabilities, attention-deficit disorders, behavioral and psychosocial problems, and abnormalities of speech among affected children. Therefore imaging studies such as brain MRIs should be reserved for patients with clinical symptoms only.

One of the most common complications is a learning disability affecting more than half of individuals with NF1. Seizures are observed in approximately 8% of NF1 patients. The cerebral vessels may develop aneurysms or stenosis consistent with moyamoya syndrome (see Chapter 641). Neurologic sequelae of these vascular abnormalities include transient cerebrovascular ischemic attacks, hemiparesis, and cognitive defects. Precocious puberty may become evident in the presence or absence of lesions of the optic pathway tumors. Malignant peripheral nerve sheath tumors are in the family of aggressive sarcomas and occur either de novo or as the result of malignant degeneration of an existing plexiform neurofibroma. The lifetime risk is 8–13%. Additionally, the incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. Scoliosis is a common complication found in approximately 10% of the patients. Patients with NF1 are at risk for hypertension, which may be present in isolation or result from renal vascular stenosis or a pheochromocytoma.

Table 636.2 Diseases Associated with Multiple Café-Au-Lait Macules

DISEASE	MAJOR FEATURES
Ataxia telangiectasia	Progressive ataxia, lymphoreticular malignancy
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, megalencephaly, lipomas, intestinal polyps
Basal cell nevus syndrome	Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies
Bloom syndrome	Short stature, photosensitivity, chromosome breaks, malignancy
Fanconi anemia	Limb anomalies, renal anomalies, pancytopenia
Gaucher disease	Jewish predilection, ataxia, mental retardation
Hunter syndrome	Thickened skin, coarse facies, skin papules, joint contractures
Jaffe-Campanacci syndrome	Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies
Legius syndrome	Axillary freckling, macrocephaly, a Noonan-like facial dysmorphism, lipomas
Maffucci syndrome	Venous malformations, enchondromas
McCune-Albright syndrome	Polyostotic fibrous dysplasia, precocious puberty
Multiple lentigines syndrome	Multiple lentigines, hypertelorism, pulmonic stenosis
Multiple mucosal neuroma syndrome	Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia
Neurofibromatosis type 1	Neurofibromas, optic pathway glioma, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies, learning disabilities
Neurofibromatosis type 2-related schwannomatosis	Vestibular schwannoma, meningioma, subcapsular cataracts, skin plexiform schwannomas, ependymoma
Schwannomatosis	Multiple schwannomas or hybrid nerve sheath tumors; subtypes distinguished by the molecular phenotype of the tumor. No vestibular schwannomas present.
Russell-Silver syndrome	Short stature, asymmetry, limb anomalies
Tuberous sclerosis	White macules, multiple hamartomas, central nervous system anomalies
Watson syndrome	Pulmonic stenosis, axillary freckles, low intelligence

From Marcoux DA, Duran-McKinster C, Baselga E, et al. Pigmentary abnormalities. In: Schachner LA, Hansen RC, eds. *Pediatric Dermatology,* 4th ed. Philadelphia: Mosby; 2011: Table 10-2.

Mosaic NF1 (also called *segmental NF1*) results from a pathogenic variant that occurs after conception, leading to a mixture of cells with and without the gene variant. The manifestations are therefore limited to one or more body segments secondary to somatic (or gonadal) variants expressed in those locations. Lesions may be unilateral or bilateral, asymmetric or symmetric, and confined to a narrow band or a single quadrant. Neurologic manifestations are rare but have been reported.



Fig. 636.2 Neurofibromatosis. Axillary freckling (Crowe's sign) is a pathognomonic sign. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004: Fig. 26-11.)*

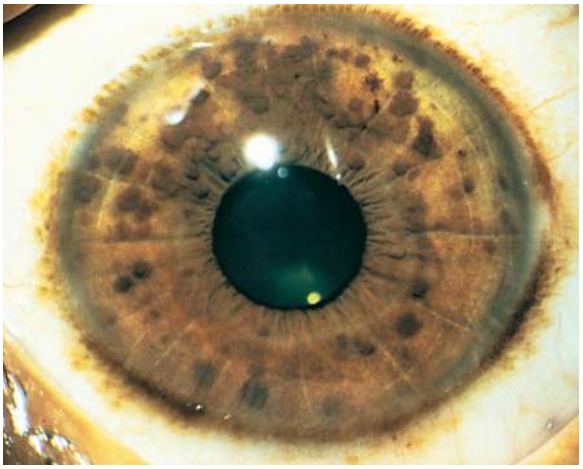

Fig. 636.3 Neurofibromatosis type 1 (NF1). Pigmented hamartomas of the iris (Lisch nodules). *(From Zitelli BJ, McIntire S, Nowalk AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th ed. Philadelphia: Mosby; 2012: Fig. 15-9.)*

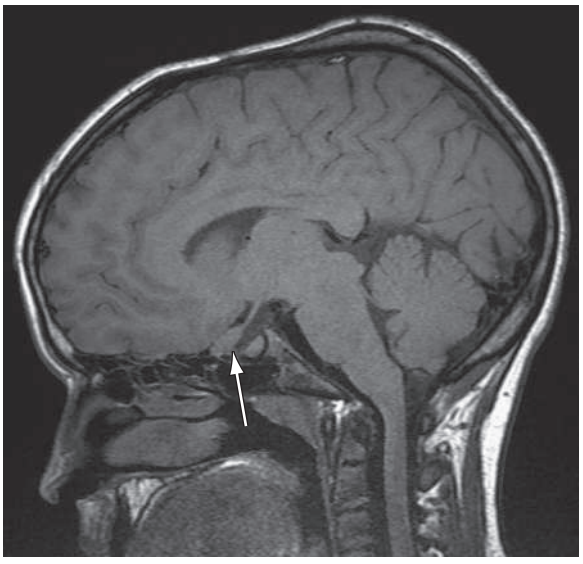

Fig. 636.4 Optic glioma. Sagittal T1-weighted MRI scan of a patient with NF1 shows thickening of the optic nerve *(arrow)*.

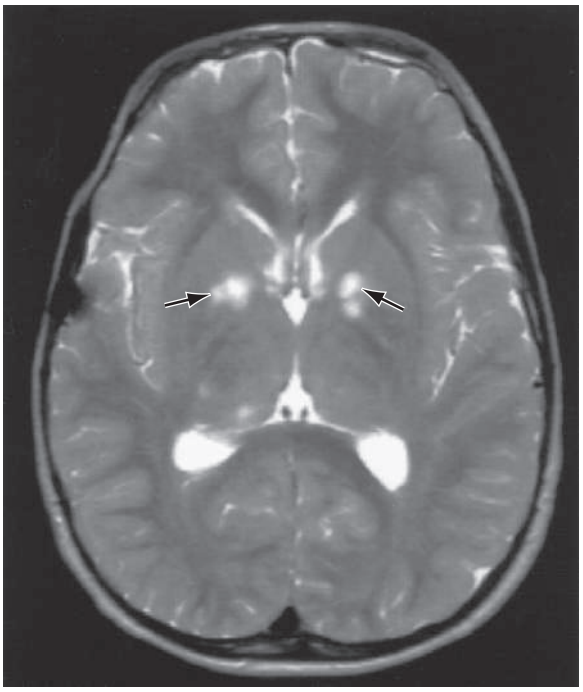

Fig. 636.5 T2-weighted MRI scan of a patient with NF1. Note the high-signal areas (unidentified bright objects or focal areas of signal abnormality [FASI]) in the basal ganglia *(arrows)*.

MANAGEMENT

Because of the diverse and unpredictable complications associated with NF1, close multidisciplinary follow-up is necessary. Patients with NF1 should have regular clinical assessments at least yearly, focusing the history and examination on the potential problems for which they are at increased risk. These assessments include yearly ophthalmologic examination, neurologic assessment, blood pressure monitoring, and scoliosis evaluation. Neuropsychologic and educational testing should be considered as needed. The National Institutes of Health (NIH) Consensus Development Conference has advised against routine imaging studies of the brain and optic tracts because treatment in these *asymptomatic* NF1 children is rarely required. However, all symptomatic cases (i.e., those with changes in visual acuity, optic pallor, proptosis, precocious puberty) should undergo MR imaging. Selumetinib, an oral inhibitor of mitogen-activated protein kinase kinase (MEK) 1 and 2, has been demonstrated in children (≥2 years of age) with NF1-related inoperable plexiform neurofibromas to be effective in inducing partial responses and reducing tumor progression.

GENETIC COUNSELING

Although NF1 is an autosomal dominant disorder, more than half the cases are sporadic, representing de novo pathogenic variants. The *NF1* gene on chromosome region 17q11.2 encodes for a protein also known as *neurofibromin*. Neurofibromin acts as an inhibitor of the oncogene Ras (Fig. 636.6). The diagnosis of NF1 is based on the clinical features; molecular testing for the *NF1* gene variants is available and now is included as one of the diagnostic criteria. Some scenarios in which genetic testing is particularly helpful include patients who meet only one of the criteria for clinical diagnosis, those with unusually severe disease, and those seeking prenatal/preimplantation diagnosis.

An international consensus group of NF experts updated the diagnostic criteria for neurofibromatosis type 2 and **schwannomatosis** (SWN). SWN is the umbrella term used to describe the group of overlapping conditions in which a patient has multiple schwannomas. The criteria also address the discovery of the genes involved, assists in distinguishing the types of neurofibromatosis and SWN using classification according to

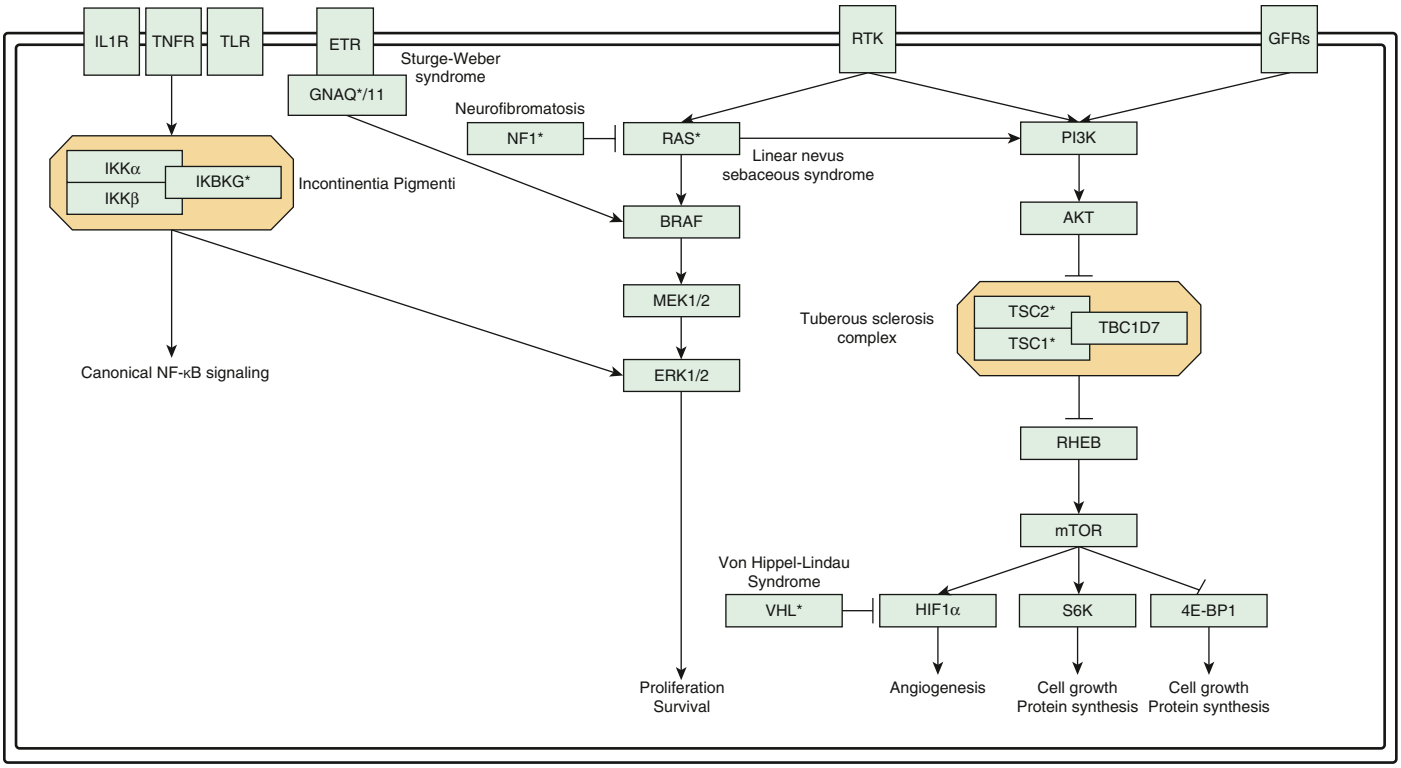

Fig. 636.6 Schematic representation of the cellular pathways affected by pathogenic variants in the genes associated with neurocutaneous disorders, such as NF1, TSC, and SWS. The *asterisks* denote genes with associated syndromes discussed in the chapter.

the pathogenic variant identified, and minimizes the misdiagnosis with NF1. Genetic testing for the variants involved in all subtypes of SWN is available and should be completed whenever possible for a patient suspected of having this diagnosis. This can be performed on a blood or saliva sample, but often requires tumor tissue. There are several key updates to the former NF2 diagnostic criteria: *NF2* pathologic variant added; clarification of first-degree relative with "other than sibling"; cataract clarified as juvenile cataract; retinal hamartoma added as a criterion; glioma and neurofibroma removed; and ependymoma added (Table 636.3).

Genetic testing identifies pathogenic variants in the *NF2* gene in 66-90% of individuals with *NF2*-schwannomatosis (*NF2*-SWN), which has an incidence of 1:25,000 worldwide. The *NF2* gene (which codes for a protein known as merlin or schwannomin) is located on chromosome 22q1.11. Table 636.4 notes the frequency of lesions in *NF2*. Testing is *not* required for the diagnosis and it remains possible to diagnose *NF2*-SWN based on clinical criteria. Genetic testing *is* required for the diagnosis of a specific type of schwannomatosis (except *NF2*-related or NOS). Excluding *NF2*-SWN, the other types of SWN affect 1:70,000 individuals. Genetic testing alone is not sufficient to make a diagnosis and there must also be a clinical feature. In most cases, tissue from schwannoma or hybrid nerve sheath tumor is required to diagnose the type of SWN and to distinguish between *LZTR1*-related SWN, *SMARCB1*-related SWN, *22q*-related SWN and SWN NOS/NEC.

Individuals with *NF2*-SWN may present with tinnitus, hearing loss, facial weakness, headache, and gait instability. Although this may present in childhood, VS are more likely to appear in the second and third decades of life. In the pediatric age group, café au lait macules and cutaneous plexiform schwannomas are the most common presentation and can be confused with the skin findings in NF1.

Workup should include ophthalmologic evaluation (assessing for subcapsular or cortical cataracts), MRI of the brain and spine, and audiology evaluation. These are all important components of ongoing surveillance and management of individuals with suspected or confirmed *NF2*-related SWN. The goal is to preserve hearing related to VS. Other forms of SWN should be suspected when an individual has two or more schwannomas in the absence

Table 636.3 Diagnostic Criteria for *NF2*-Related Schwannomatosis (Formerly Called Neurofibromatosis Type 2 [NF2])

A diagnosis of *NF2*-related schwannomatosis can be made when a patient has **one of the following:**

- Bilateral vestibular schwannomas (VS)
- An identical *NF2* pathogenic variant in at least two anatomically distinct *NF2*-related tumors (schwannoma, meningioma, and/or ependymoma)

Either **two major** OR **one major and two minor** criteria are present as follows:

MAJOR CRITERIA
- Unilateral vestibular schwannoma
- First-degree relative other than a sibling with *NF2*-related schwannomatosis
- Two or more meningiomas
- *NF2* pathogenic variant in an unaffected tissue, such as blood

MINOR CRITERIA

Can count more than one of a type (e.g. two schwannomas = two minor criteria)
- Ependymoma
- Schwannoma (note that if the major criterion is a unilateral VS, at least one schwannoma must be dermal in location)

Can count only once
- Juvenile subcapsular or cortical cataract
- Retinal hamartoma
- Epiretinal membrane in a person aged less than 40 years
- Single meningioma (meningioma cannot be used as both a major and a minor criteria)

Table 636.4 Frequency of Lesions Associated with Neurofibromatosis Type 2-Related Schwannomatosis*

	FREQUENCY OF ASSOCIATION WITH NF2-RELATED SCHWANNOMATOSIS
NEUROLOGIC LESIONS	
Bilateral vestibular schwannomas	90–95%
Other cranial nerve schwannomas	24–51%
Meningioma	45–58%
Spinal schwannomas	63–90%
Spinal ependymoma	20%
Peripheral neuropathy	Up to 66%
OPHTHALMOLOGIC LESIONS	
Juvenile subcapsular or cortical cataract	60–81%
Epiretinal membranes (age less than 40 years)	12–40%
Retinal hamartomas	6–22%
CUTANEOUS LESIONS	
Cutaneous schwannomas	59–68%
Subcutaneous tumors	43–48%
Intradermal tumors	Rare

*Formerly known as NF2.
Modified from Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet*. 2009;373:1974–1984, Table 1.

of bilateral vestibular schwannomas. Evaluation also includes imaging of the brain and spine to exclude VS and to distinguish from *NF2*-related SWN.

Legius syndrome (caused by *SPRED1* pathogenic variants) is an autosomal dominant disorder with skin findings that resemble and may be hard to distinguish from NF1 in younger individuals. Persons with Legius syndrome present with multiple CALMs and macrocephaly, with and without skinfold freckling. However, other typical features of NF1, such as Lisch nodules, neurofibromas, optic nerve gliomas, long bone dysplasia, plexiform neurofibromas, and malignant peripheral nerve sheath tumors, are not seen in individuals with *SPRED1* variants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

636.2 Tuberous Sclerosis

Siddharth Srivastava and Mustafa Sahin

Tuberous sclerosis complex (TSC) is a multisystem disease characterized by an autosomal dominant mode of inheritance, variable expressivity, and a prevalence of 1 in 6,000-10,000 newborns. Spontaneous pathogenic variants occur in 65% of the cases. Molecular genetic studies have identified two foci for TSC: the *TSC1* gene (located on chromosome 9q34) and the *TSC2* gene (located on chromosome 16p13). The *TSC1* gene encodes a protein called *hamartin,* and the *TSC2* gene encodes a protein called *tuberin*. Within a cell, these two molecules form a complex along with a third protein, TBC1D7 (Tre2-Bub2-Cdc16 1 domain family, member 7). Consequently, a pathogenic variant in either the *TSC1* gene or the *TSC2* gene results in a similar disease in patients, though individuals with *TSC2* variants tend to be more severely affected.

Tuberin and hamartin are involved in a key pathway in the cell that regulates protein synthesis and cell size (see Fig. 636.6). One of the ways cells regulate their growth is by controlling the rate of protein synthesis. A protein called *mechanistic target of rapamycin* (mTOR) is one of the master regulators of cell growth (mTOR has additional roles in the CNS, where it helps regulate neuronal development and synaptic plasticity). mTOR, in turn, is controlled by Ras homolog enriched in brain (RHEB), a small cytoplasmic guanosine triphosphatase. When RHEB is activated, the protein synthesis machinery is turned on, most likely via mTOR signaling, and the cell grows. Under normal conditions, the tuberin/hamartin complex keeps RHEB in an inactive state. However, in TSC, there is disinhibition of RHEB and subsequent overactivation of the mTOR pathway. Accordingly, the *TSC1* and *TSC2* genes can be considered tumor-suppressor genes. The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas).

TSC is an extremely heterogeneous disease with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and a lack of seizures. This variation is often seen within the same family, that is, with individuals within a family carrying the same variant. The disease affects many organ systems other than the skin and brain, including the heart, kidney, eyes, lungs, and bone (Fig. 636.7).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Definite TSC is diagnosed when at least two major or one major plus two minor features are present (Tables 636.5 and 636.6 list the major and minor features). In addition, carrying a pathogenic variant in *TSC1* or *TSC2* is sufficient for the diagnosis of TSC.

The hallmark of TSC is the involvement of the CNS. The characteristic brain lesion is a cortical tuber (Fig. 636.8). Brain MRI is the best way of identifying cortical tubers, which can form before birth.

Subependymal nodules are lesions found along the wall of the lateral ventricles, where they undergo calcification and project into the ventricular cavity, producing a candle-dripping appearance. These lesions do not cause any problems; however, in 5–10% of cases, these benign lesions can grow into **subependymal giant cell astrocytomas (SEGAs)**. These tumors can grow and block the circulation of cerebrospinal fluid around the brain and cause hydrocephalus, which requires immediate neurosurgical intervention. Thus it is recommended that all asymptomatic TSC patients undergo brain MRI every 1-3 years to monitor for new occurrences of SEGA. Patients with large or growing SEGAs, or with SEGAs causing ventricular enlargement without other manifestations, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential of new symptoms caused by increased intracranial pressure. Surgical resection should be performed for acutely symptomatic SEGA. For growing but otherwise asymptomatic SEGAs, either surgical resection or medical treatment with an mTOR inhibitor (sirolimus, everolimus) may be used. Treatment with everolimus can be effective in slowing the growth or even reducing the size of SEGAs. Everolimus is also effective in treating renal angiomyolipomas. Sirolimus is also effective in treating lymphangioleiomyomatosis, renal angiomyolipomas, and cardiac rhabdomyomas.

The most common neurologic manifestations of TSC are epilepsy, intellectual disability, and autism spectrum disorder. TSC may present during infancy with infantile spasms and a hypsarrhythmic electroencephalogram pattern. However, it is important to remember that TSC patients can have infantile spasms without hypsarrhythmia. The seizures may be difficult to control, and at a later age, they may develop into other seizure types such as focal-onset seizures or generalized myoclonic seizures (see Chapter 633). Vigabatrin is the first-line therapy for infantile spasms. Adrenocorticotropic hormone (ACTH) or prednisolone can be used if treatment with vigabatrin fails. Anticonvulsant therapy for other seizure types in TSC should generally follow that of other epilepsies, and epilepsy surgery can be considered for medically refractory TSC patients. Everolimus (adjunctive) has received U.S. Food and Drug Administration (FDA) approval for treatment-refractory focal seizures in TSC. Studies on prevention of epilepsy with preemptive treatment with vigabatrin have yielded mixed results so far. However, it is recommended that infants with TSC should undergo baseline EEG to enable early detection and treatment

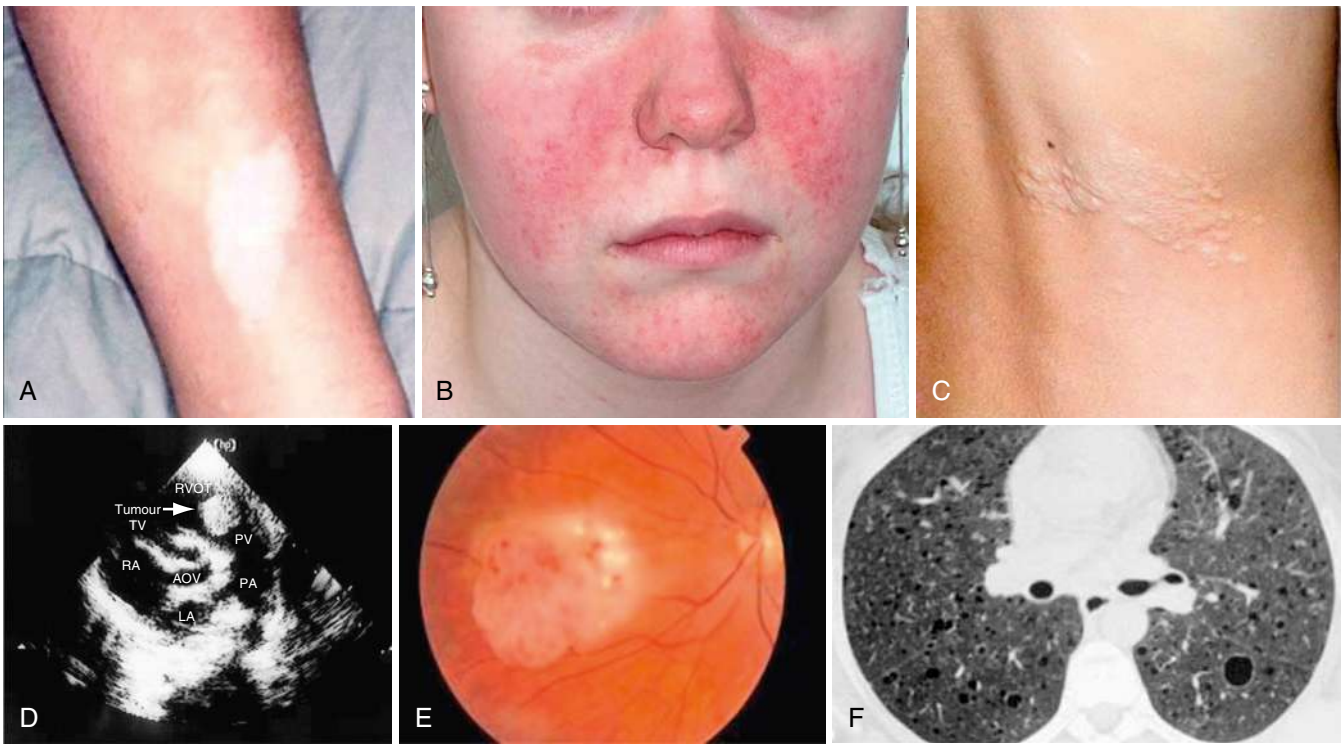

Fig. 636.7 Dermatologic, cardiac, and pulmonary manifestations of tuberous sclerosis. **A,** Hypomelanotic macules. **B,** Facial angiofibromas. **C,** Shagreen patch. **D,** Hyperechoic rhabdomyoma detected by echocardiography. **E,** Retinal hamartoma. **F,** Lymphangioleiomyomatosis. *(From Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372:657–668, Fig. 7.)*

Table 636.5	Major Features of Tuberous Sclerosis Complex
Cortical dysplasias (including tubers and cerebral white matter migration lines)	
Subependymal nodules	
Subependymal giant cell astrocytoma	
Facial angiofibromas (≥3) or forehead plaque	
Ungual fibromas (≥2)	
Hypomelanotic macules (≥3, ≥5 mm in diameter)	
Shagreen patch	
Multiple retinal nodular hamartomas	
Cardiac rhabdomyoma	
Renal angiomyolipoma	
Pulmonary lymphangioleiomyomatosis	

Table 636.6	Minor Features of Tuberous Sclerosis Complex
Dental enamel pits (>3)	
Intraoral fibromas (≥2)	
Retinal achromic patch	
Confetti skin lesions	
Nonrenal hamartomas	
Multiple renal cysts	

of seizures, and this should be repeated every 6 weeks until 12 months of age. In addition to epilepsy, about 90% of individuals with TSC have a spectrum of cognitive, behavioral, psychiatric, and academic impairments termed *tuberous sclerosis–associated neuropsychiatric disorders (TANDs),* which include intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, and depression. About 45% of individuals with TSC have intellectual disability, and up to 25-50% have autism spectrum disorder.

Skin Lesions

More than 90% of patients show the typical hypomelanotic macules that have been likened to an ash leaf on the trunk and extremities.

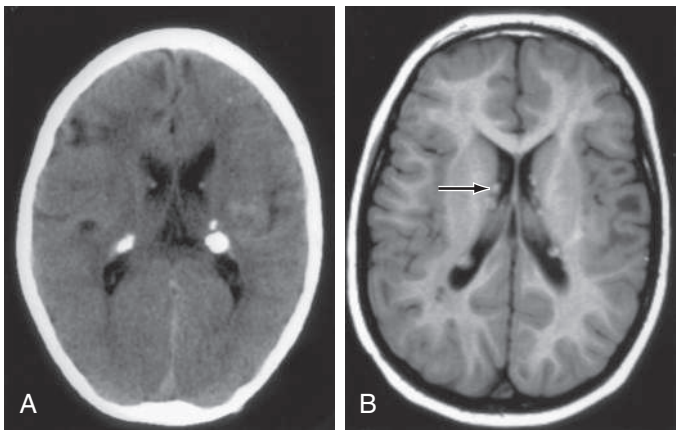

Fig. 636.8 Tuberous sclerosis. **A,** CT scan with subependymal calcifications characteristic of tuberous sclerosis. **B,** The MRI demonstrates multiple subependymal nodules in the same patient *(arrow).* Parenchymal tubers are also visible on both the CT and the MRI scan as low-density areas in the brain parenchyma.

Visualization of the hypomelanotic macule is enhanced by using a Wood ultraviolet lamp (see Chapter 694). To count as a major feature, at least three hypomelanotic macules must be present (see Fig. 636.7). Facial angiofibromas develop between 4 and 6 years of age; they appear as tiny red nodules over the nose and cheeks and are sometimes confused with acne (see Fig. 636.7). Later, they enlarge, coalesce, and assume a fleshy appearance. Topical rapamycin is approved for treatment of facial angiofibromas. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located primarily in the lumbosacral region (see Fig. 636.7). Forehead fibrous plaques usually occur on one side of the forehead. They are characteristically raised, yellow-brown or flesh-colored, and soft to hard in consistency. Forehead plaques are histologically similar to facial angiofibromas, though the former can appear at any point. During adolescence or later, small fibromas or nodules of skin may form around fingernails or toenails (ungual fibromas) in 15–20% of TSC patients (Fig. 636.9).



Fig. 636.9 Periungual fibroma in a patient with tuberous sclerosis complex (TSC).

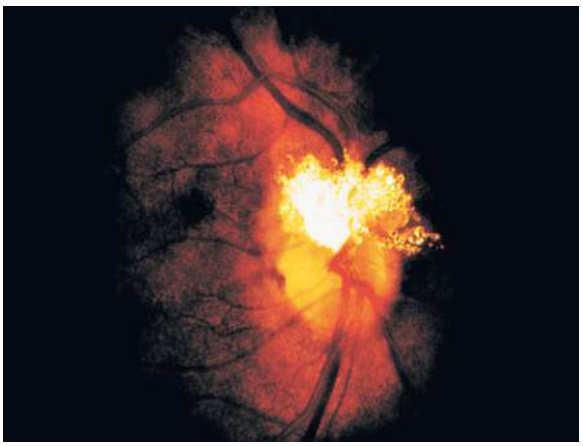

Fig. 636.10 A mulberry lesion involving the superior part of the optic nerve in a patient with tuberous sclerosis. *(From Yanoff M, Sassani JW. Ocular Pathology, 7th ed. Philadelphia: WB Saunders; 2015: Fig. 2-7.)*

Other Organ Involvement

Retinal lesions consist of two types: hamartomas (elevated mulberry lesions or plaquelike lesions (Fig. 636.10) and white depigmented patches (similar to the hypopigmented skin lesions). Approximately 50% of children with TSC have cardiac rhabdomyomas, which may be detected in the fetus by an echocardiogram, usually by 20-30 weeks of gestation. The rhabdomyomas may be numerous and located throughout the ventricular myocardium, and although they can cause congestive heart failure and arrhythmias in a minority of patients, they tend to slowly resolve spontaneously. In 75–80% of patients older than 10 years of age, the kidneys display angiomyolipomas that are usually benign tumors. Angiomyolipomas begin in childhood in many individuals with TSC, but they may not be problematic until young adulthood. By the third decade of life, they may cause lumbar pain and hematuria from slow bleeding, and rarely they may result in sudden retroperitoneal bleeding. Embolization followed by corticosteroids to alleviate postembolization syndrome is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy should be avoided as a way of maintaining renal function, because lesions can be numerous and bilateral. For asymptomatic, growing angiomyolipomas measuring larger than 3 cm in diameter, an mTOR inhibitor, everolimus, is approved for treatment by the FDA. Selective embolization or kidney-sparing resection is an alternative therapy for asymptomatic angiomyolipoma. Single or multiple renal cysts are also commonly present in TSC; renal cell carcinoma, on the other hand, is rare. Lymphangioleiomyomatosis is the classic pulmonary lesion in TSC and only affects women, beginning in late adolescence (≥15 years). Sirolimus is approved by the FDA for lymphangioleiomyomatosis. Topical rapamycin should be considered for treatment of facial angiofibromas.

Diagnosis of TSC relies on a high index of suspicion, especially when assessing a child with infantile spasms. A careful evaluation for the typical skin and retinal lesions should be completed in all patients with a seizure disorder or autism spectrum disorder. Brain MRI can confirm the clinical diagnosis in many cases. Genetic testing for pathogenic *TSC1* and *TSC2* variants is available and should be considered when the individual patient does not meet all the clinical criteria, or in order to provide molecular confirmation of a clinical diagnosis. Prenatal testing may be offered when a known pathogenic *TSC1/TSC2* variant exists in that family.

MANAGEMENT

The following are recommended for routine follow-up of individuals with TSC in addition to physical examination: brain MRI every 1-3 years, abdominal MRI to evaluate the kidneys every 1-3 years; echocardiogram every 1-3 years in patients with cardiac rhabdomyomas until there is regression of the rhabdomyomas; electrocardiogram every 3-5 years; high-resolution chest CT every 5-10 years in females older than 18 years; dental examination twice a year; skin examinations once a year; detailed ophthalmic examination once a year in patients with vision concerns or retinal lesions (sooner if they are receiving treatment with vigabatrin); neurodevelopmental testing at the beginning of first grade or sooner based on concerns; and screening for TAND at each clinic visit. Based on the complications of the disease, additional follow-up testing may be required for each individual. Symptoms and signs of increased intracranial pressure suggest obstruction of the foramen of Monro by a SEGA and warrant immediate investigation and surgical intervention.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

636.3 Sturge-Weber Syndrome

Anna L. Pinto

Sturge-Weber syndrome (SWS) is a segmental vascular neurocutaneous disorder with a constellation of symptoms and signs characterized by capillary malformation in the face (port-wine birthmark [PWB]) and brain (leptomeninges), as well as abnormal blood vessels of the eye leading to glaucoma. Low flow of the leptomeningeal capillary malformation appears to result in a chronic hypoxic state leading to cortical atrophy and calcifications. Patients present with seizures, hemiparesis, strokelike episodes, headaches, and developmental delay. Approximately 1 in 20,000-50,000 live births are affected with SWS.

ETIOLOGY

The nonsyndromic PWBs and SWS are caused by a pathologic somatic single-nucleotide variant (c.548G→A, p.Arg183Gln) in the *GNAQ* gene (see Fig. 636.6). Brain tissue from SWS patients also demonstrates the same change in the *GNAQ* gene. These results strongly suggest that SWS occurs as a result of a *mosaic pathologic genetic variant* in *GNAQ*.

The *GNAQ* p.R183Q variant is enriched in endothelial cells in SWS brain lesions, thereby revealing endothelial cells as a source of aberrant Gαq signaling. The timing of the somatic variant in *GNAQ* during development likely affects the clinical phenotype. Mosaic-activating *GNA11* and *GNB2* gene variants have been described in atypical SWS cases. The aberrant G-protein signaling provides a molecular basis to explain SWS lesions.

CLINICAL MANIFESTATIONS

Facial PWBs are present at birth, but not all are associated with SWS (Table 636.7). In fact, the overall incidence of SWS has been reported to be 20–40% in those with a PWB involving the forehead and upper eyelid. High-risk PWB for SWS includes hemifacial, median, and forehead phenotypes (Fig. 636.11), along with large segmental PWB. The PWB tends to be unilateral and ipsilateral to the brain involvement (Fig. 636.12). The capillary malformation may also be evident over the lower face and trunk and in the mucosa of the mouth and pharynx. Buphthalmos and glaucoma of the ipsilateral eye are common

Table 636.7 Port-Wine Birthmark–Associated Syndromes

Sturge-Weber syndrome
Klippel-Trénaunay syndrome
Parkes Weber syndrome
Phakomatosis pigmentovascularis
Proteus syndrome
CLOVES syndrome
Macrocephaly–capillary malformation (M-CM) syndrome
Capillary malformation–arteriovenous malformation (CM-AVM) syndrome
Cobb syndrome
Bannayan-Riley-Ruvalcaba syndrome
Beckwith-Wiedemann syndrome
Von Hippel-Lindau disease
Rubinstein-Taybi syndrome
Wyburn-Mason syndrome
Roberts syndrome
Coat disease
Nonsyndromic, idiopathic, neurologically asymptomatic

CLOVES, Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 5th ed. Philadelphia: Elsevier; 2016: Box 12-2.

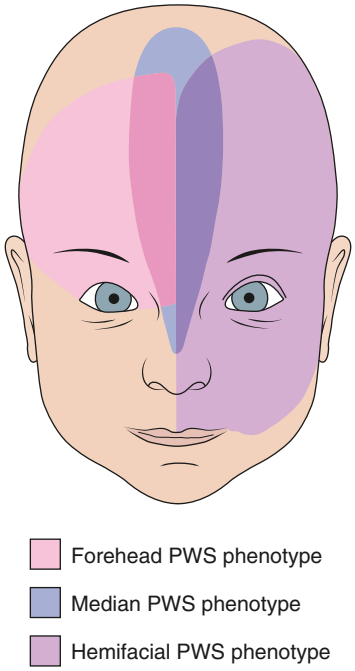

Fig. 636.11 Port-wine stain (birthmark) phenotypes associated with highest risk of Sturge-Weber syndrome. *(From Zallmann M, Mackay MT, Leventer RJ, et al. Retrospective review of screening for Sturge-Weber syndrome with brain magnetic resonance imaging and electroencephalography in infants with high-risk port-wine stains. Pediatr Dermatol. 2018;35:575–581, Fig.1, p. 576.)*

complications. Seizures occur in 75–80% of all SWS patients and in over 90% of those with bilateral brain involvement. Early onset of seizures will likely occur during the first year of life but rarely during the first month of life, and they are typically focal clonic and contralateral to the side of the facial PWB. They may become refractory to anticonvulsants, and status epilepticus is often associated. One third of children with intractable epilepsy associated with SWS experience episodes of *prolonged postictal deficits,* which would last from 1 day to a few years, until recovering back to baseline. Some patients also develop slowly progressive hemiparesis. Transient strokelike episodes or visual field defects persisting for several days and unrelated to seizure activity are common and probably result from thrombosis of cortical veins in the affected region. Although neurodevelopment appears to be normal in the first year of life, intellectual disability



Fig. 636.12 Port-wine birthmark involving both the V1 and V2 dermatomes. *(Courtesy Dr. Anne W. Lucky, Cincinnati Children's Hospital.)*

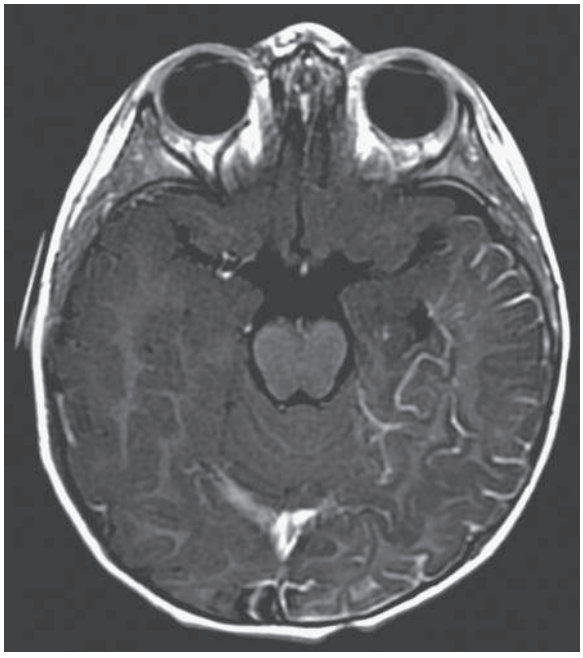

Fig. 636.13 Gadolinium-enhanced axial T1 fluid-attenuated inversion recovery (FLAIR) images of a 15-mo-old with Sturge-Weber syndrome show leptomeningeal enhancement in the left hemisphere.

or severe learning disabilities are present in at least 50% of patients in later childhood, probably the result of intractable epilepsy and increasing cerebral atrophy. The degree of visual field defect, hemiparesis, seizure frequency, and cognitive function (based on age-group: infant/preschooler, child, and adult) can be rated using a validated SWS neurologic rating system.

DIAGNOSIS

Brain MRI with contrast is the imaging modality of choice for demonstrating the extension of pial capillary malformation in SWS (Fig. 636.13). White matter abnormalities are common and are thought to be a result of chronic hypoxia. Often, atrophy is noted ipsilateral to the leptomeningeal capillary malformation. Calcifications can be seen best with a head CT (Fig. 636.14). The choroid plexus is frequently enlarged, and the degree of plexal enlargement shows a positive correlation with the extent of the leptomeningeal capillary malformation. Positron emission tomography using 18 F-deoxyglucose has been used to study cerebral metabolism in patients with SWS, and it has been useful for the surgical planning and prognosis. Ophthalmologic evaluation examining for glaucoma is also necessary and is a lifelong concern because ocular complications can occur at any moment during a lifetime. Based on the involvement of the brain and the face, there are three types of SWS in the Roach Scale:

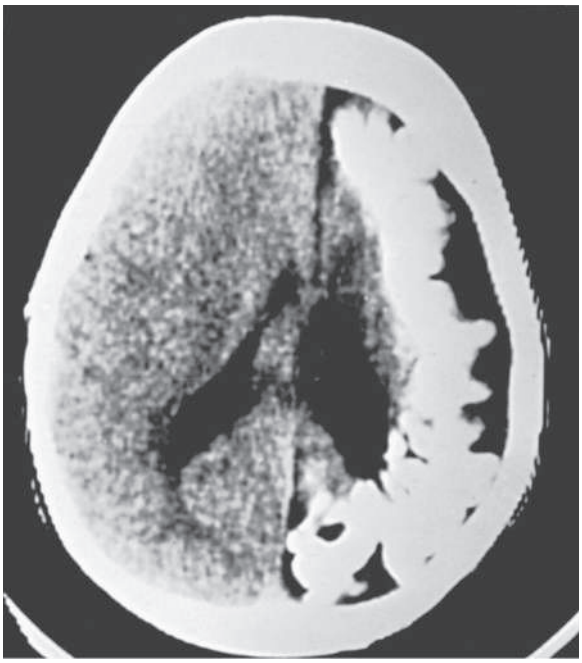

Fig. 636.14 CT scan of a patient with Sturge-Weber syndrome showing unilateral calcification and underlying atrophy of a cerebral hemisphere.

Type I: Classic facial and leptomeningeal capillary malformation present; often with glaucoma.
Type II: Facial capillary malformation alone (no CNS involvement); may have glaucoma.
Type III: Isolated leptomeningeal capillary malformation; usually no glaucoma.

In addition, there is an overlap syndrome between SWS and **Klippel-Trénaunay syndrome** (mixed capillary, venous, or lymphatic malformations involving bone and muscle in one limb).

MANAGEMENT

The management of SWS is primarily symptomatic and multidisciplinary but not well studied by prospective studies. Treatment is aimed at seizure control, relief of headaches, and prevention of strokelike episodes, as well as monitoring of glaucoma and laser therapy for the cutaneous capillary malformations. Most infants with SWS brain involvement have seizure onset by 2 years of age. Presymptomatic treatment in high-risk babies may prevent or delay seizure onset. For patients with well-controlled seizures and normal or near-normal development, management consists of anticonvulsants and surveillance for complications, including glaucoma and behavioral abnormalities. If the seizures are refractory to anticonvulsant therapy, especially in infancy and the first 1-2 years and arise from primarily one hemisphere, most medical centers advise a hemispherectomy or, if well indicated, focal disconnections. The use of low-dose aspirin is controversial. The medication is not used routinely, but patients with strokelike events and frequent refractory seizures may benefit from this form of treatment. Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated. The facial PWB is often a target of ridicule by classmates, leading to psychologic trauma. Pulsed-dye laser therapy often provides excellent clearing of the PWB, particularly if it is located on the forehead.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

636.4 Von Hippel-Lindau Disease

Siddharth Srivastava and Mustafa Sahin

von Hippel-Lindau disease affects many organs, including the cerebellum, spinal cord, retina, endolymphatic sac of the inner ear, kidney, pancreas, adrenal glands, epididymis, and broad ligament of the uterus. Its incidence is around 1 in 36,000 newborns. It results from an autosomal dominant pathogenic variant affecting a tumor suppressor gene, *VHL*. Approximately 80% of affected individuals have an inherited variant, and approximately 20% have a de novo variant. Molecular testing is available and detects pathogenic variants in most probands.

The major neurologic feature of the condition is CNS hemangioblastomas, including brain hemangioblastomas and spinal hemangioblastomas. In affected individuals, brain hemangioblastomas commonly affect the cerebellum. Patients with cerebellar hemangioblastoma can present in early adult life with symptoms and signs of increased intracranial pressure. A brain CT or MRI scan typically shows a cystic cerebellar lesion with a vascular mural nodule. A smaller number of patients have hemangioblastoma of the spinal cord, producing pain as well as sensory and motor changes. Syringomyelia often accompanies symptomatic spinal hemangioblastomas in von Hippel-Lindau disease. Surgical intervention for symptomatic CNS hemangioblastomas and syringomyelia is often warranted.

Approximately 70% of individuals with von Hippel-Lindau disease have retinal angiomas (also known as *retinal hemangioblastomas*), which have identical histology as CNS hemangioblastomas. Retinal angiomas, which can present in childhood, are characterized by small masses of thin-walled capillaries that are fed by large and tortuous arterioles and venules. They are usually located in the peripheral retina so that vision is unaffected. Exudation in the region of the angiomas may lead to retinal detachment and visual loss. Retinal angiomas are treated with photocoagulation and cryocoagulation, though outcomes can vary depending on the characteristics of the lesions, and complications such as retinal edema can occur.

Cysts (affecting the kidneys, pancreas, and liver), as well as tumors/malignancies (including endolymphatic sac tumors, pheochromocytoma, paragangliomas, neuroendocrine tumors of the pancreas, renal cell carcinomas, epididymis cystadenomas, and broad ligament cystadenomas) are associated with von Hippel-Lindau disease. Renal carcinoma and CNS hemangioblastomas can be causes of death in affected individuals. Regular follow-up and appropriate imaging studies are necessary to identify lesions that may be treated at an early stage. In affected individuals ≥1 year, there should be yearly ophthalmology evaluation for retinal angiomas. Beginning in the first decade of life, there should be yearly clinical assessment for neurological concerns, vision concerns, and hearing concerns, as well as measurement of blood pressure. At age 5 years, laboratory screening for pheochromocytoma should begin. Beginning at age 11 years, there should be brain and complete spine MRI every 2 years to evaluate for CNS lesions, with particular focus on the inner/petrous temporal bone and posterior fossa. Beginning at age 11 years, there should also be formal audiology assessment every 2-3 years to screen for endolymphatic sac tumors. Formal audiological assessment should occur sooner and more frequently if symptoms such as hearing loss, tinnitus, and vertigo are present. Beginning at age 15 years, there should be MRI of the abdomen (including kidney, pancreas, and adrenal glands) every 2 years to evaluate for visceral lesions. At age 15-20 years in asymptomatic individuals, there should be an MRI of internal auditory canals to screen for endolymphatic sac tumor.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

636.5 Linear Nevus Sebaceous Syndrome

Siddharth Srivastava and Mustafa Sahin

This sporadic condition is characterized by a large facial nevus, neurodevelopmental abnormalities, and systemic defects. The nevus is usually located on the forehead and nose and tends to be midline in its distribution, although it may affect other locations, such as the scalp and neck. It may be quite faint during infancy but later becomes hyperkeratotic, with a yellow-brown appearance.

The most common associated CNS finding is unilateral hemimegalencephaly (enlargement of one cerebral hemisphere), which affects

about half of patients. Other structural brain abnormalities include enlargement of the lateral ventricles, white matter hyperintensity on T2-weighted imaging, cortical dysplasia, pachygyria, agyria, agenesis of the corpus callosum, and Dandy-Walker malformation. The incidence of epilepsy and intellectual disability is as high as 75% and 60%, respectively. Focal neurologic signs, including hemiparesis and homonymous hemianopia, may occur.

Other organ systems may be involved, including the eyes (strabismus, retinal abnormalities, coloboma, cataracts, corneal revascularization, ocular hemangiomas, and lipodermoid scleral tumors); heart (aortic coarctation, ventricular septal defect); kidneys (horseshoe kidney); and skeleton (fibrous dysplasia, skeletal hypoplasia, scoliosis/kyphoscoliosis, and vitamin D-resistant hypophosphatemic rickets).

The syndrome is associated with somatic variants in members of the Ras family of oncogenes, including *HRAS* (HRas proto-oncogene, GTPase), *KRAS* (KRAS proto-oncogene, GTPase), and *NRAS* (neuroblastoma RAS viral oncogene homolog) (see Fig. 636.6).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

636.6 PHACE Syndrome

Siddharth Srivastava and Mustafa Sahin

See also Chapter 691.

The syndrome denotes *p*osterior fossa malformations, *h*emangiomas, *a*rterial anomalies, *c*oarctation of the aorta and other cardiac defects, and *e*ye abnormalities (see Chapter 691). It is also referred to as *PHACES syndrome* when ventral developmental defects, including *s*ternal clefting and/or a *s*upraumbilical raphe, are present. The hallmark of the disorder is infantile hemangiomas affecting the face, neck, and/or scalp. The underlying pathogenesis of PHACE syndrome remains unknown, though evidence that infantile hemangiomas may result from abnormal growth and differentiation of hemogenic endothelium highlights some avenues for further investigation. Overall, there is a female predominance, but the reasons for this association are unclear.

Other organ systems besides the skin are commonly affected in PHACE syndrome. Posterior fossa anomalies affect up to 80% of patients and encompass Dandy-Walker malformation and cerebellar hypoplasia/dysplasia. Less common structural brain anomalies include neuronal migration defects (polymicrogyria, heterotopia, cortical dysplasia), dysgenesis of the corpus callosum or septum pellucidum, and pituitary defects. Congenital heart disease affects up to two thirds of patients, and common defects are aortic anomalies (coarctation of aorta, dysplasia of aortic arch) and aberrant left subclavian artery. The facial hemangioma is typically ipsilateral to the aortic arch anomalies. Arterial anomalies include hypoplasia/dysplasia/altered anatomic course of cervical, cerebral, and brachiocephalic arteries. Cerebrovascular anomalies can result in progressive arterial stenosis and acute ischemic stroke. Ophthalmologic findings include persistent fetal vasculature (also known as *persistent hyperplastic primary vitreous*), retinal vascular anomalies, morning glory disc anomaly, optic nerve hypoplasia, peripapillary staphyloma, coloboma, cataracts, and microphthalmia. Endocrinopathies (such as hypopituitarism, hypogonadism, hypothyroidism, ectopic thyroid gland, growth hormone deficiency, and diabetes insipidus) can occur. Midline defects of the chest and abdomen encompass sternal defect, sternal pit, sternal cleft, and supraumbilical raphe. Dental abnormalities, specifically enamel hypoplasia, can be associated with PHACE syndrome.

There can be an assortment of neurologic symptoms, the most common of which is headaches, specifically migraines. Other reported neurologic symptoms are seizures, cyclical vomiting, developmental delay (language, gross motor, fine motor), hypotonia, tremor, dysphagia, opisthotonus, hearing loss (conductive, sensorineural, or mixed), and cranial nerve deficits. New onset of headaches in an individual with PHACE syndrome should prompt further evaluation for vessel disease and cerebral ischemia. Development can be affected: according to a case series of 29 children with PHACE syndrome, 69% had abnormal neurodevelopment, including 44% with language delay, 36% with gross motor delay, and 8% with fine motor delay. Certain medical comorbidities like posterior fossa malformations and oropharyngeal hemangiomas increase the risk for dysphagia. Sensorineural hearing loss may be caused by involvement of the cranial nerve VIII that is on the same side as the infantile hemangioma; similarly, conductive hearing loss may be caused by compression of the eustachian tube that is on the same side as the infantile hemangioma.

There are clinical diagnostic criteria for PHACE syndrome that delineate definite PHACE syndrome and possible PHACE syndrome. Definite PHACE syndrome is defined by either of the following: (1) infantile hemangioma (>5 cm in diameter) affecting the head/scalp in combination with one major or two minor criteria or (2) segmental infantile hemangioma of the neck, upper trunk, or trunk/proximal arm in combination with two major criteria. Possible PHACE syndrome is defined by one of the following: (1) infantile hemangioma (>5 cm in diameter) affecting the head/scalp in combination with one minor criteria; (2) segmental infantile hemangioma of the neck, upper trunk, or trunk/proximal arm in combination with one major or two minor criteria; and (3) absence of hemangioma but presence of two major criteria. Major and minor criteria pertain to arterial, structural brain, cardiovascular, ocular, and ventral/midline features of the syndrome.

Children newly diagnosed with PHACE syndrome should undergo a complete physical examination, screening echocardiogram, ophthalmologic examination, hearing screening, and MRI with and without gadolinium of the brain/neck as well as MRA of the brain/neck/aortic arch. Results of these baseline evaluations steer further management. The presence of a severe midline defect would prompt evaluation with pediatric surgery. Abnormalities on echocardiogram would require expertise from pediatric cardiology. Anomalies on ophthalmologic exam would likely require ongoing care. Hearing loss can be a risk factor for language delay, so affected children should have hearing screening if not already performed. If there are structural brain abnormalities identified on MRI, evaluation by pediatric neurology and neurosurgery (in the case of Dandy-Walker malformation or hydrocephalus) would be necessary. Pituitary defects would require endocrinologic evaluation. Results from MRA of cervical and cerebral arteries would classify patients into one of three risk tiers for cerebrovascular changes and stroke (low risk, intermediate risk, high risk), each with varying levels of need for follow-up neuroimaging and ongoing neurologic care.

Treatments in PHACE syndrome are symptom targeted. The β blocker propranolol can be used for infantile hemangiomas associated with PHACE syndrome, though there must be careful consideration in the presence of cerebrovascular abnormalities predisposing to stroke. Treatment of headaches is per standard clinical care, but certain vasoconstrictive medications, like triptans and ergotamine derivatives, should be avoided if there are arterial abnormalities. Dysphagia would require referral for feeding evaluation. Developmental delays should prompt neurodevelopmental assessment and developmental therapies such as physical therapy and speech-language therapy.

LUMBAR syndrome (*l*ower-segment hemangioma, *u*rogenital defects, *m*yelopathy of spinal cord, *b*ony deformities, *a*rterial and anorectal defects, *r*enal anomalies), also called **SACRAL syndrome** (*s*pinal dysraphism, *a*nogenital anomalies, *c*utaneous anomalies, *r*enal-urologic anomalies, *a*ngioma of *l*umbosacral localization), is a possible variant of PHACES syndrome in the lumbosacral region.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

636.7 Incontinentia Pigmenti

Siddharth Srivastava and Mustafa Sahin

Incontinentia pigmenti (IP) is a rare, heritable, multisystem ectodermal disorder that features dermatologic, dental, ocular, and CNS abnormalities. The phenotype is produced by defects in the X-linked

dominant gene *IKBKG (*previously *NEMO)*, which plays a role in activating the antiapoptotic signaling molecule NF-kappaB (NF-κB). In the majority of males, IP causes embryonic lethality, so affected males who survive have *somatic mosaicism* for a pathogenic *IKBKG* variant or a 47,XXY karyotype. With respect to a male with IP, some of his daughters may inherit a pathogenic *IKBKG* variant and hence be affected, but all of his sons would be unaffected. Among affected females, an abnormal gene product causes apoptosis in cells; therefore highly skewed X-inactivation can be a result. With respect to a female with IP, one third of her offspring are expected to be unaffected females, one third are expected to be affected females, and one third are expected to be unaffected males; this ratio accounts for the high rate of miscarriages in pregnancies with a male conceptus carrying a pathogenic variant in *IKBKG*.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

This disease has four stages, not all of which may occur in a given patient. The **first (bullous) stage** is evident at birth or in the first few weeks of life and consists of erythematous linear streaks and plaques of vesicles (Fig. 636.15) that are most pronounced on the limbs and circumferentially on the trunk. The lesions may be confused with those of herpes simplex, bullous impetigo, or mastocytosis, but the linear configuration is unique. Histopathologically, epidermal edema and eosinophil-filled intraepidermal vesicles are present. Eosinophils also infiltrate the adjacent epidermis and dermis. Blood eosinophilia as high as 65% of the white blood cell count is common. The **first stage** generally resolves by 4 months of age, but mild, short-lived recurrences of blisters may develop during febrile illnesses. In the **second (verrucous) stage**, as blisters on the distal limbs resolve, they become dry and hyperkeratotic, forming verrucous plaques. The verrucous plaques rarely affect the trunk or face and generally involute within 6 months. Epidermal hyperplasia, hyperkeratosis, dyskeratosis, and papillomatosis are characteristic. The **third (pigmentary) stage** is the hallmark of IP. It generally develops over weeks to months and may overlap the earlier phases or, more commonly, begin to appear in the first few months of life. Hyperpigmentation is more often apparent on the trunk than the limbs and is distributed in macular whorls, reticulated patches, flecks, and linear streaks that follow Blaschko lines. The axillae and groin are characteristically affected. The sites of involvement are not necessarily those of the preceding vesicular and warty lesions. The pigmented lesions, once present, persist throughout childhood. They generally begin to fade by early adolescence and often disappear by age 16 years. Occasionally, the pigmentation remains permanently, particularly in the groin. Histopathologically, the lesion shows vacuolar degeneration of the epidermal basal cells and melanin in melanophages of the upper dermis as a result of incontinence of pigment. In the **fourth (atretic) stage**, hairless, anhidrotic, hypopigmented patches or streaks occur as a late manifestation of IP; they may develop, however, before the hyperpigmentation of stage 3 has resolved. The lesions develop mainly on the flexor aspect of the lower legs and less often on the arms and trunk. On histology, there are decreased rete ridges (epidermal protrusions) and sweat gland secretory coils during this stage.



Fig. 636.15 Whorled vesicular phase of incontinentia pigmenti.

A large percentage of affected children have other dermal/dental defects. Alopecia, which may be scarring and patchy or diffuse, is most common on the vertex and occurs in up to 40% of patients. Hair may be coarse and wooly or sparse and brittle. Fingernails and toenails may demonstrate pigmentary or dystrophic changes (ridging, pitting), as well as painful subungual and periungual keratotic tumors. Dental anomalies consist of late dentition, hypodontia, conical teeth, malocclusion, and impaction.

CNS manifestations are found in up to 30% of affected children and include seizures, intellectual disability, learning disabilities, microcephaly, hemiplegia/hemiparesis (in the setting of stroke), spasticity, and cerebellar ataxia. Brain MRI in patients can be notable for periventricular and subcortical white matter changes, ischemic/hemorrhagic infarcts, hemorrhagic necrosis, dysgenesis of the corpus callosum, cerebral atrophy, cerebellar hypoplasia, cystic changes, and ventricular enlargement.

Ocular anomalies, such as retinal neovascularization, microphthalmos, strabismus, optic nerve atrophy, cataracts, and retrolenticular masses, occur in up to 77% of affected individuals. Nonetheless, >90% of patients have normal vision. Notably, retinal neovascularization could herald abnormalities in the CNS vasculature that predispose the patient to ischemic or hemorrhagic stroke.

Other medical issues have been reported in IP. Leukocytosis with eosinophilia can occur. Primary pulmonary hypertension is seen in some affected individuals.

Diagnosis of IP is made on clinical grounds, although major and minor criteria have been established to aid in the diagnosis. Satisfaction of the sole major criteria (pertaining to the characteristic skin lesions in the varying stages) is needed for a clinical diagnosis; lack of fulfillment of any of the minor criteria may direct the clinician toward the possibility of another diagnosis. Wood lamp examination may be useful in older children and adolescents to highlight pigmentary abnormalities. Clinical molecular testing is available, and around 65% of affected females and 16% of affected males have a recurrent pathogenic variant, an 11.7-kb deletion of exons 4-10 of *IKBKG*. Skin biopsy may be helpful if the patient has unclear clinical findings and negative genetic testing. For male patients with negative genetic testing from blood, a variant may be detectable in skin cells from an affected region, increasing the utility of a skin biopsy. The differential diagnosis includes hypomelanosis of Ito, which presents with similar skin manifestations and is often associated with chromosomal mosaicism.

MANAGEMENT

The choice of investigative studies and the plan of management depend on the occurrence of particular noncutaneous abnormalities. Medical genetics and genetic counseling can help establish a molecular diagnosis in addition to providing family counseling. Dermatology may be involved to characterize the nature of skin lesions and to manage skin manifestations that are extensive. Dentistry can provide teeth implants along with routine care. If dental issues affect speech or feeding, then input from speech pathologists and nutritionists may be necessary. Ophthalmology is important for delineating the presence and extent of retinal neovascularization (which can be treated with cryotherapy and laser photocoagulation) and other ocular abnormalities. Cardiology may be necessary if there is pulmonary hypertension. Neurology can help evaluate and treat relevant concerns such as microcephaly, seizures, and motor abnormalities. A brain MRI is useful if there are focal neurologic deficits or retinal neovascularization. Finally, developmental medicine can formulate recommendations regarding developmental and behavioral concerns. Surveillance includes regular ophthalmologic assessment (monthly until age 4 months, then every 3 months until age 1 year, then every 6 months until age 3 years, then annually thereafter). Regular evaluation with dentistry and neurologic/neurodevelopmental assessments are appropriate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 637

Movement Disorders

Jonathan W. Mink

INTRODUCTION

Movement disorders are characterized by impaired voluntary movements or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. Most movement disorders in children are characterized by involuntary movements. These involuntary movements can represent the sole disease manifestation, or they may be one of many signs and symptoms.

Evaluation of movement disorders begins with a comprehensive history and careful neurologic examination. It is often difficult for children and caregivers to describe abnormal movements, which makes observation of the movements by the clinician an essential component of the evaluation. If the movements are not apparent at the time of the examination, video examples from home or school can be invaluable.

There is no specific diagnostic test to differentiate among movement disorders. The category of movement assists in localizing the pathologic process, whereas the onset of the disorder, age of the patient, and degree of abnormal motor activity and associated neurologic findings help organize the investigation.

When considering the type of movement disorder, the following questions concerning the history and examination of the movement are helpful:

- What is the distribution of the movements across body parts?
- Are the movements symmetric?
- What is the speed of the involuntary movements? Are they rapid and fast or slow and sustained?
- When do the movements occur? Are they present at rest? Are they present with maintained posture or with voluntary actions?
- Are the movements seen in relation to certain postures or body positions?
- Do the abnormal movements occur only with specific tasks?
- Can the child voluntarily suppress the movements, even for a short time?
- Are the movements stereotyped?
- Are the movements rhythmic?
- What is the temporal pattern of the movements? Are they continuous or intermittent? Do they occur in discrete episodes?
- Are the involuntary movements preceded by an urge to make the movement?
- Do the movements persist during sleep?
- Are the movements associated with impairment of motor function?
- What factors aggravate or alleviate the movements?

The first decision to be made is whether the movement disorder is **hyperkinetic** (characterized by excessive and involuntary movements) or **hypokinetic** (characterized by slow voluntary movements and a general paucity of movement). Hyperkinetic movement disorders are much more common than hypokinetic disorders in children. Once the category of movement disorder is recognized, the etiology can be considered. The clinical history, including the birth history, medication/toxin exposure, trauma, infections, family history, progression of the involuntary movements, developmental progress, and behavior, should be explored as the underlying cause is established. Table 637.1 lists the types and clinical characteristics of selected hyperkinetic movement disorders. A diagnostic approach to paroxysmal movement disorders is noted in Figure 637.1; age-related presentations of paroxysmal movement disorders are noted in Figure 637.2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

637.1 Ataxias

Peter E. Morrison and Jonathan W. Mink

Ataxia is the inability to make smooth, accurate, and coordinated movements. It occurs because of a dysfunction of the cerebellum, its inputs or outputs, its sensory pathways in the posterior columns of the spinal cord, or a combination of these. Ataxias may be generalized but can also primarily affect the gait, the hands and arms, or the trunk; they may be acute or chronic, or acquired or genetic (Tables 637.2-637.8).

Signs and symptoms of ataxia include clumsiness, difficulty walking or sitting, falling to one side, slurred speech, low muscle tone, intention tremor, dizziness, delayed motor development, or a combination of these. Genetic or chronic causes of cerebellar ataxia are often characterized by a long duration of symptoms, a positive family history, muscle weakness and abnormal gait, abnormal tone and strength, abnormal deep tendon reflexes, pes cavus, and sensory defects. Distinguishing ataxia from vestibular dysfunction may be difficult; however, labyrinth disorders are often characterized by severe vertigo, nausea and vomiting, position-induced vertigo, and a severe sense of unsteadiness.

Congenital anomalies of the posterior fossa, including Dandy-Walker malformation, Chiari malformation, and encephalocele, are prominently associated with ataxia because of their destruction or abnormal development of the cerebellum (see Chapter 631.8). *MRI*

Table 637.1 Selected Types of Involuntary Movement in Childhood

TYPE	CHARACTERISTICS
Stereotypies (see Chapter 37)	Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition
Tics (see Chapter 37)	Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement.
Tremor (see Chapter 637.2)	Oscillating, rhythmic movements about a fixed point, axis, or plane
Dystonia (see Chapter 637.4)	Intermittent and sustained involuntary muscle contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality
Chorea (see Chapter 637.2)	Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly
Ballism	Involuntary, high-amplitude, flinging movements typically occurring proximally. Ballism is essentially a large-amplitude chorea
Athetosis (see Chapter 637.2)	Slow, writhing, continuous, involuntary movements
Myoclonus (see Chapter 637.3)	Sudden, quick, involuntary muscle jerks

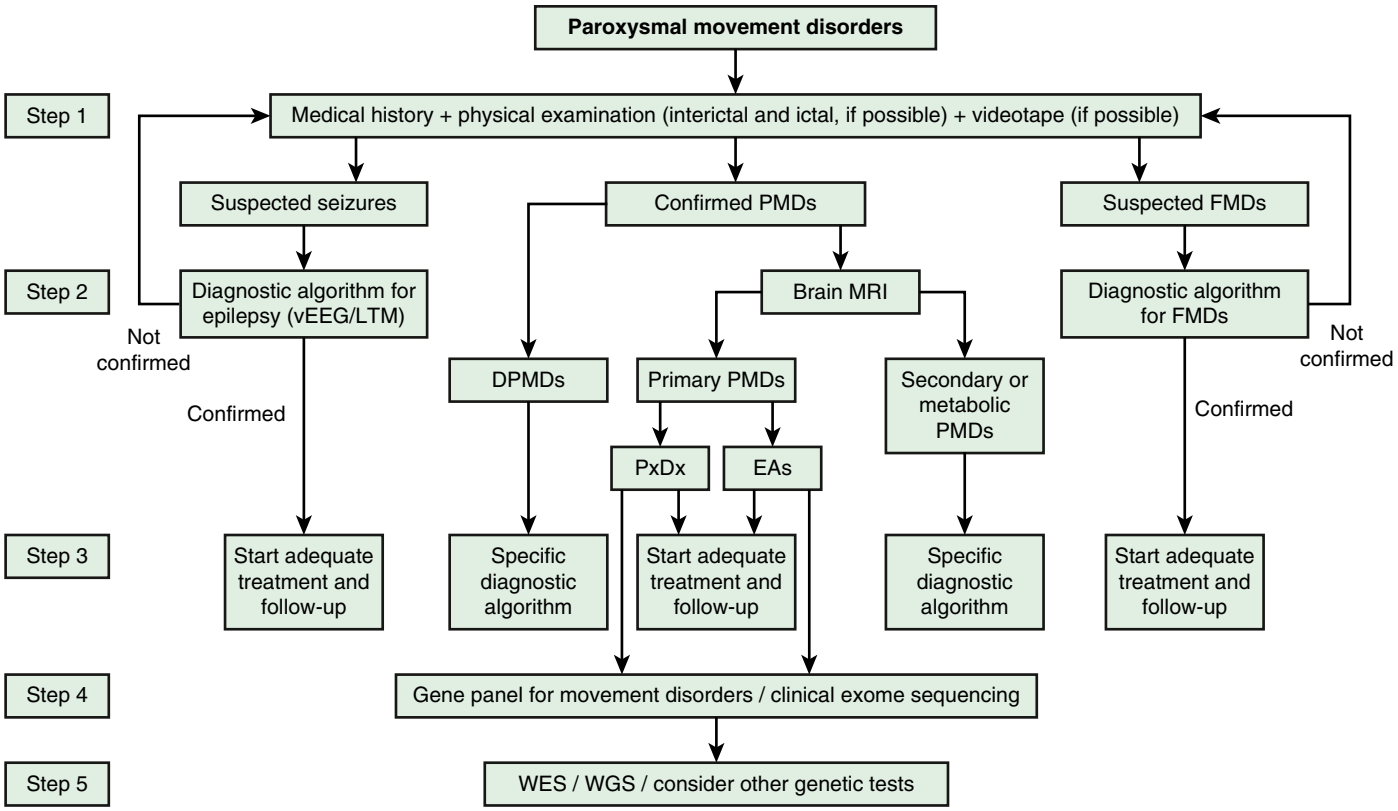

Fig. 637.1 Operative algorithm for pediatric-onset PMDs. DPMDs, developmental PMDs; EAs, episodic ataxias; FMDs, functional movement disorders; LTM, long-term EEG monitoring; PxDx, paroxysmal dyskinesias; vEEG, video electroencephalogram; WES, whole exome sequencing; WGS, whole genome sequencing. *(Modified from Garone G, Capuano A, Travaglini L, et al. Clinical and genetic overview of paroxysmal moment disorders and episodic ataxias. Inter J Mol Sci. 2020;21:3603, Fig. 5.)*

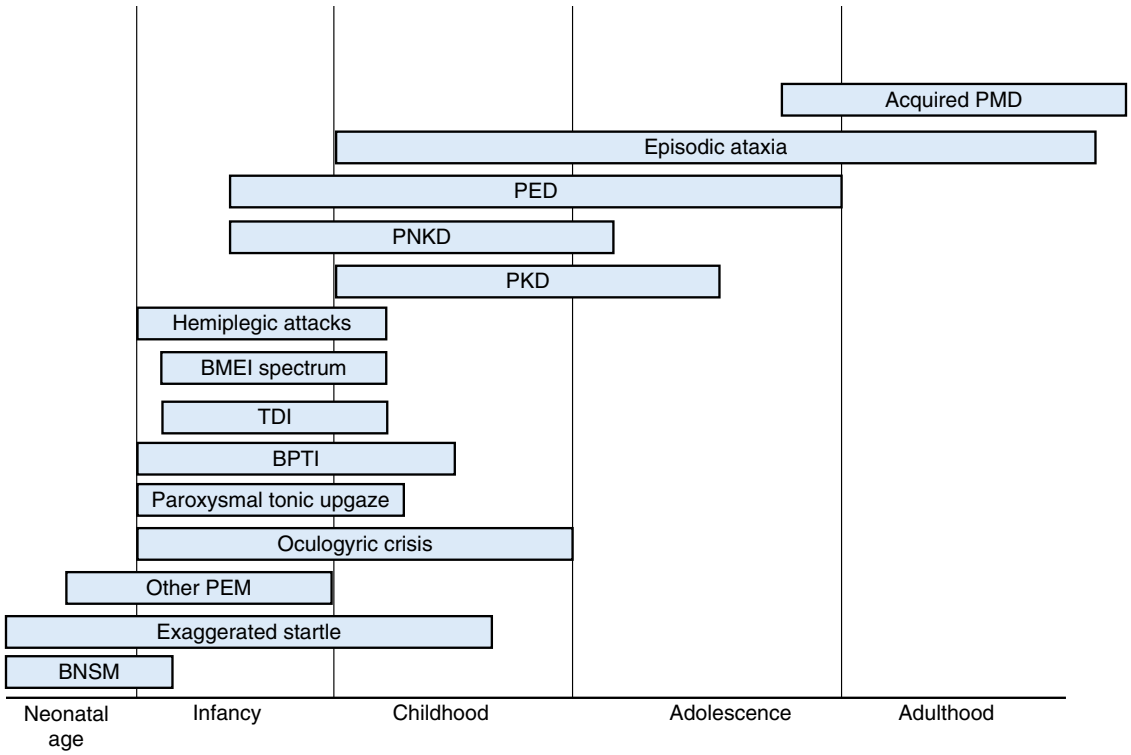

Fig. 637.2 Onset of different paroxysmal movement disorders (PMDs) according to age. BNSM, benign neonatal sleep myoclonus; BMEI, benign myoclonus of early infancy; BPTI, benign paroxysmal torticollis of infancy; PEM, paroxysmal eye movements; PED, paroxysmal exercise-induced dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia. *(From Garone G, Capuano A, Travaglini L, et al. Clinical and genetic overview of paroxysmal moment disorders and episodic ataxias. Inter J Mol Sci. 2020;21:3603, Fig. 1.)*

Table 637.2 Selected Causes of Ataxia in Childhood

CONGENITAL CAUSES
Agenesis of vermis of the cerebellum
Aplasia or dysplasia of the cerebellum
Basilar impression
Cerebellar dysplasia with microgyria, macrogyria, or agyria
Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
Chiari malformation
Dandy-Walker syndrome
Encephalocele
Hydrocephalus (progressive)
Hypoplasia of the cerebellum

DEGENERATIVE AND/OR GENETIC CAUSES
Acute intermittent cerebellar ataxia
Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
Ataxia-telangiectasia
Biemond posterior column ataxia
Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
Cockayne syndrome
Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
Familial ataxia with macular degeneration
Friedreich ataxia
Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
Hereditary cerebellar ataxia with myotonia and cataracts
Hypertrophic interstitial neuritis
Marie ataxia
Marinesco-Sjögren syndrome
Multiple system atrophy
Pelizaeus-Merzbacher disease
Periodic attacks of vertigo, diplopia, and ataxia: autosomal dominant inheritance
Posterior and lateral column difficulties, nystagmus, and muscle atrophy
Progressive cerebellar ataxia and epilepsy
Ramsay Hunt syndrome (myoclonic seizures and ataxia)
Roussy-Lévy disease
Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
Vanishing white matter syndrome

ENDOCRINOLOGIC CAUSES
Hypothyroidism (acquired or congenital)

INFECTIOUS, POSTINFECTIOUS, AND IMMUNE INFLAMMATORY CAUSES
Acute cerebellar ataxia
Acute disseminated encephalomyelitis
Autoimmune (anti–glutamic acid decarboxylase, anti–γ-aminobutyric acid-B receptor antibodies, idiopathic, gluten ataxia, Miller-Fisher syndrome, Hashimoto encephalopathy, lupus)
Cerebellar abscess
Cerebellitis
Coxsackievirus
Diphtheria
Echovirus
Fisher syndrome
Infectious mononucleosis (Epstein-Barr virus infection)
Infectious polyneuropathy
Japanese B encephalitis
Multiple sclerosis
Mumps encephalitis
Mycoplasma pneumonia
Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome)
Pertussis
Polio
Postbacterial meningitis
Rubeola
Tuberculosis
Typhoid
Varicella

METABOLIC CAUSES
Abetalipoproteinemia
Argininosuccinic aciduria
Ataxia with vitamin E deficiency (AVED)
Congenital disorders of glycosylation
GM_2 gangliosidosis (late)
Hartnup disease
Hyperalaninemia
Hyperammonemia I and II (urea cycle defects)
Hypoglycemia
Kearns-Sayre syndrome
Leigh disease
Maple syrup urine disease (intermittent)
Myoclonic epilepsy with ragged red fibers (MERRF)
Metachromatic leukodystrophy
Mitochondrial complex defects (I, III, IV)
Multiple carboxylase deficiency (biotinidase deficiency)
Neuronal ceroid-lipofuscinosis
Neuropathy, ataxia, retinitis pigmentosa (NARP)
Niemann-Pick disease (late infantile)
5-Oxoprolinuria
Pyruvate decarboxylase deficiency
Refsum disease
Sialidosis
Triose-phosphate isomerase deficiency
Tryptophanuria
Wernicke encephalopathy

NEOPLASTIC CAUSES
Frontal lobe tumors
Hemispheric cerebellar tumors
Midline cerebellar tumors
Neuroblastoma
Pontine tumors (primarily gliomas)
Spinal cord tumors

PRIMARY PSYCHOGENIC CAUSES
Functional disorder

TOXIC CAUSES
Alcohol
Benzodiazepines
Carbamazepine
Clonazepam
Dextromethorphan
Lead encephalopathy
Neuroblastoma
Phenobarbital
Phenytoin
Primidone
Tic paralysis poisoning

TRAUMATIC CAUSES
Acute cerebellar edema
Acute frontal lobe edema

VASCULAR CAUSES
Angioblastoma of the cerebellum
Basilar migraine
Cerebellar embolism
Cerebellar hemorrhage
Cerebellar thrombosis
Posterior cerebellar artery disease
Vasculitis
von Hippel-Lindau disease

Modified from Jafar-Nejad P, Maricich SM, Zoghbi HY. The cerebellum and the hereditary ataxias. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Box 67-1.

Table 637.3 Treatable Causes of Inherited Ataxia

DISORDER	METABOLIC ABNORMALITY	DISTINGUISHING CLINICAL FEATURES	TREATMENT
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab
Ataxia with vitamin E deficiency	Pathogenic variants in α-tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Pathogenic variants in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Primary CoQ10 deficiency (multiple types)	Mitochondrial dysfunction	Seizures, sensorineural hearing loss, lactic acidosis, cardiomyopathies	Possibly CoQ10
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α-hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α-ketoacids

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.
Modified from Stumpf DA. The inherited ataxias. *Pediatr Neurol*. 1985;1:129–133, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY. The cerebellum and the hereditary ataxias. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Table 67-1.

Table 637.4 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Clinical Findings

GENE*	DISORDER	MOI	DISTINGUISHING NONATAXIC CLINICAL FEATURES	COMMENT
MOST COMMONLY INVOLVED GENES				
ATN1	DRPLA	AD	Chorea, dementia, myoclonus, seizures; mimics Huntington disease	• Anticipation is prominent • More common in Japan
ATXN1	SCA1	AD	Peripheral neuropathy, pyramidal signs; early bulbar features; occasional cognitive decline	• Anticipation is more likely with paternal transmission.
ATXN2	SCA2	AD	↓ DTRs, dementia, peripheral neuropathy, slow saccadic eye movements	• Anticipation is more likely with paternal transmission • Large Cuban founder population
ATXN3	SCA3	AD	Amyotrophy, fasciculations, sensory loss; lid retraction, nystagmus, and ↓ saccade velocity; pyramidal and extrapyramidal signs; shortened life span	• Anticipation may be more likely with paternal transmission • Large Portuguese founder population • Also known as Machado-Joseph disease
ATXN7	SCA7	AD	Visual loss with retinopathy; often rapidly progressive; shortened life span	Anticipation is prominent with more marked repeat expansions with paternal transmission
ATXN8	SCA8	AD	Slowly progressive, sometimes brisk DTRs, ↓ vibration sense; rarely, cognitive impairment in persons with earlier onset	Anticipation is more likely with maternal transmission
ATXN8OS				

Continued

Table 637.4 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Clinical Findings—cont'd

GENE*	DISORDER	MOI	DISTINGUISHING NONATAXIC CLINICAL FEATURES	COMMENT
ATXN10	SCA10	AD	Seizures in certain families	• Anticipation can occur with paternal transmission • Large Mexican founder population
CACNA1A	SCA6	AD	May begin with episodic ataxia, very slow progression; onset often after age 50 yr; normal life span	• Anticipation is not seen • See Table 637.6 for ataxia caused by missense variants
FXN	Friedreich ataxia	AR	Generally childhood onset with slowly progressive ataxia, absent tendon reflexes, Babinski responses, posterior column sensory loss, cardiomyopathy, scoliosis, pes cavus, and diabetes; in some: onset ≥25 yr, slower progression, and retained reflexes	Anticipation is not seen
RFC1	RFC1 CANVAS/ spectrum disorder	AR	Spectrum ranges from typical cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS), to cerebellar, sensory, and vestibular impairment, to more limited phenotypes involving predominantly or exclusively one of the systems involved in balance control	Anticipation is not seen
TBP	SCA17	AD	Mental deterioration; occasional chorea, dystonia, myoclonus, epilepsy	Anticipation is infrequently observed
LESS COMMONLY INVOLVED GENES				
BEAN1	SCA31 (OMIM 117210)	AD	Normal sensation	Common in Japan
FMR1	Fragile X-associated tremor/ataxia syndrome (FXTAS)	XL		• Anticipation occurs almost exclusively with maternal transmission • Most common X-linked ataxia; occurs in male and female premutation carriers
NOP56	SCA36	AD	Hyperreflexia, muscle fasciculations, tongue atrophy	Insufficient evidence for anticipation
PPP2R2B	SCA12 (OMIM 604326)	AD	Action tremor in the fourth decade, cognitive/psychiatric disorders, including dementia, hyperreflexia, slowly progressive ataxia, subtle parkinsonism possible	Insufficient evidence for anticipation

*Genes are listed in alphabetic order within prevalence categories.
DRPLA, Dentatorubral-pallidoluysian atrophy; DTR, deep tendon reflex; SCA, spinocerebellar ataxia.
From Perlman S. Hereditary ataxia overview. 1998 Oct 28 [Updated 2022 Jun 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 1.

Table 637.5 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Molecular Genetics

GENE[1]	PATHOGENIC VARIANTS (%)	NUCLEOTIDE REPEAT (AMINO ACID)	REPEAT LOCATION	NORMAL REPEAT NUMBER	FULL-PENETRANCE PATHOGENIC REPEAT NUMBER	COMMENT
ATN1	100	CAG (Gln)	Exon 5	6-35	≥48	
ATXN1	100	CAG (Gln)	Exon 8	6-35	≥39	
ATXN2	100	CAG (Gln)	Exon 1	≤31	≥33	
ATXN3	100	CAG (Gln)	Exon 8	12-44	60-87	
ATXN7	100	CAG (Gln)	Exon 1	4-19	≥36	
ATXN8	100	CAG (Gln)	Exon 1	~80	Unknown	
ATXN8OS	100	CTG	3′ UTR	15-50 CTA/CTG	≥71-1300 CTA/CTG[2]	Penetrance is <100%[2]
ATXN10	100	ATTCT	Intron 9	10-32	≥800	Repeat interruptions are associated with presence of seizures

Table 637.5 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Molecular Genetics—cont'd

GENE[1]	PATHOGENIC VARIANTS (%)	NUCLEOTIDE REPEAT (AMINO ACID)	REPEAT LOCATION	NORMAL REPEAT NUMBER	FULL-PENETRANCE PATHOGENIC REPEAT NUMBER	COMMENT
BEAN1	100	TGGAA	Intron 6	0	2.5- to 3.8-kb insertion	
CACNA1A[3]	>99	CAG (Gln)	Exon 7	≤18	20-33	See Table 637.6 for phenotype associated with variants that are not nucleotide repeat disorders
FMR1	>99	CGG	5′ UTR	5-44	≥200	Premutation alleles: 55-200 CGG repeats
FXN	~98	GAA	Intron 1	5-33	≥66	In about 5% of affected persons one FXN allele is an expanded GAA repeat and one is a pathogenic missense variant
NOP56	100	GGCCTG	Intron 1	3-14	≥650	
PPP2R2B	100	CAG	Promoter	7-31	51-78	
RFC1	100	AAGGG[4]	Intron 2	Unknown	~400 to ~2000	ACAGG repeat expansion has been reported in three persons from Asian and Asian Pacific populations[4]
TBP	100	CAG or CAA (Gln)	Exon 3	25-40	≥49	

Based on Resources for Genetics Professionals — Genetic Disorders Caused by Nucleotide Repeat Expansions and Contractions
[1]Genes are listed in alphabetic order.
[2]Although penetrance less than 100% has been reported at all repeat sizes, higher penetrance is reported for CTA/CTG repeat sizes of 80-250.
[3]The majority of *CACNA1A* pathogenic variants are CAG repeat expansions associated with spinocerebellar ataxia type 6. Heterozygous *CACNA1A* missense, nonsense, splice site, frameshift, and exon/multiexon deletions have been reported in individuals with episodic ataxia type 2 and progressive cerebellar ataxia.
[4]*RFC1* intron 2 contains a microsatellite region with variable benign AAAAG repeats (range: 11-200 repeats) and/or benign AAAGG repeats (range: 40-1000 repeats). Interruption of the benign AAAAG/AAAGG repeated units with biallelic pathogenic AAGGG expansions has been identified in individuals with *RFC1* CANVAS/spectrum disorder.
From Perlman S. Hereditary Ataxia overview. 1998 Oct 28 [Updated 2022 Jun 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 2.

Table 637.6 Most Common Hereditary Ataxias (Excluding Nucleotide Repeat Disorders)

GENE[1]	MOI	PHENOTYPE		OTHER PHENOTYPIC FEATURES/COMMENTS	DESIGNATION/*GENEREVIEW*/OMIM
		ATAXIA	SPASTICITY		
AFG3L2	AD	+	+	Ophthalmoparesis, slow saccades, ptosis[3]	SCA28 (OMIM 610246)
	AR				SCAR5 (OMIM 614487)
ANO10	AR	+	+	Downbeat nystagmus, fasciculations	SCAR10 (OMIM 613728)
APTX	AR	+		Early-onset ataxia, oculomotor apraxia, extrapyramidal features, sensorimotor neuropathy, hypoalbuminemia; secondary coenzyme Q10 deficiency (see primary coenzyme Q10 deficiency)	Ataxia with oculomotor apraxia type 1
ATM	AR	+		Early-onset ataxia, oculomotor apraxia, extrapyramidal features, immunodeficiency, cancer risk, ↑ alpha-fetoprotein	Ataxia-telangiectasia
CACNA1A[2]	AD	+			Episodic ataxia type 2 (OMIM 108500)

Continued

Table 637.6 Most Common Hereditary Ataxias (Excluding Nucleotide Repeat Disorders)—cont'd

GENE[1]	MOI	PHENOTYPE		OTHER PHENOTYPIC FEATURES/COMMENTS	DESIGNATION/*GENEREVIEW*/OMIM
		ATAXIA	SPASTICITY		
ITPR1	AD	+		Adult onset, slowly progressive	SCA15/16 (OMIM 606658)
	AD[3]	+		Congenital, nonprogressive	SCA29 (OMIM 117360)
KCNC3	AD[3]	+		Adult onset, slowly progressive	SCA13
				Congenital, nonprogressive	
KCND3[4]	AD	+			SCA19/22 (OMIM 605411)
PRKCG	AD	+			SCA14
SACS	AR	+	+	Early-onset ataxia with spastic paraparesis and axonal-demyelinating sensorimotor neuropathy; hypointense pontine stripes on T2-weighted MRI[5]	ARSACS (SPAX6)
SETX[6]	AR	+	+	Early-onset ataxia, oculomotor apraxia with ↑ alpha-fetoprotein[5]	Ataxia with oculomotor apraxia type 2 (SCAR1)
SPG7	AR	+	+	Variable spasticity and cerebellar ataxia[5]	Spastic paraplegia 7
SPTBN2	AD	+			SCA5 (OMIM 600224)
	AR				SCAR14 (OMIM 615386)
SYNE1[7]	AR	+	+	Cerebellar ataxia, variable spasticity, and further multisystemic neurologic damage[5]	ARCA1 (SCAR8) (see SYNE1 deficiency)

Based on Synofzik & Schüle [2017] and Galatolo et al. [2018].
[1]Genes are listed in alphabetic order.
[2]Allelic disorders include familial hemiplegic migraine and spinocerebellar ataxia type 6.
[3]The disorder may occur as the result of a de novo pathogenic variant.
[4]Allelic disorder: Brugada syndrome.
[5]Synofzik and Schüle [2017].
[6]Allelic disorder: amyotrophic lateral sclerosis.
[7]Allelic phenotype: arthrogryposis multiplex congenita (see SYNE1 deficiency).
AD, Autosomal dominant; AR, autosomal recessive; ARCA, autosomal recessive cerebellar ataxia; MOI, mode of inheritance; OMIM, Online Mendelian Inheritance in Man; SCA, spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal recessive.
From Perlman S. Hereditary Ataxia overview. 1998 Oct 28 [Updated 2022 Jun 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 3.

Table 637.7 The Hereditary Spastic Ataxias

SPASTIC ATAXIA (MIM#)	GENE	MODE OF INHERITANCE	AGE OF ONSET (YR)	FEATURES
SPAX1 (108600)	*VAMP1*		10-20 yr	Progressive leg spasticity, dysarthria, ocular movement abnormalities
SPAX2 (611302)	*KIF1C*		1-16 yr	Frequent falls, ataxia, head tremor, hyperreflexia, fasciculations
SPAX3/ARSAL (611390)	*MARS2*	AR	2-59 yr; mean 15 yr	Ataxia and spasticity
SPAX4 (613672)	*MTPAP*	AR	Early childhood	Ataxia, spastic paraparesis, dysarthria, optic atrophy, upper limb hypertonia
SPAX5 (614487)	*AFG3L2*	AR	Childhood	Spasticity, ataxia, oculomotor apraxia, dystonia, myoclonic epilepsy
SPAX6/SACS/ARCSACS (270660)	*SACS*	AR	Childhood	Spasticity and ataxia, very slow course, stops progressing after age 20
SPAX7	Unknown	AD	Infancy to 20 yr	Symmetric ataxia, dysarthria, pyramidal signs, optic atrophy
SPAR (607565)	Unknown	—	15-35 yr	Later onset: spastic paraplegia Early onset + ataxia, mental retardation

From Jafar-Nejad P, Maricich SM, Zoghbi H. The cerebellum and the hereditary ataxias. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 6th ed. Philadelphia: WB Saunders; 2018: Table 91-5.

Table 637.8 Genetic and Metabolic Disorders that Can Cause a Spastic-Ataxic Syndrome

	AGE AT ONSET	TREATMENT AVAILABLE	DIAGNOSTIC TESTS, IN ADDITION TO METABOLIC TESTS	MODE OF INHERITANCE	GENES
Abetalipoproteinemia (MIM #200100)	C	Yes	Blood lipid profile, vitamin E	AR	*MTP*
Adrenomyeloneuropathy (MIM #300100)	A	Yes	MRI spinal cord, blood VLCFA	X-linked	*ABCD1*
Ataxia with (primary) vitamin E deficiency (MIM #277460)	C	Yes	Blood vitamin E	AR	*TTPA*
CAMOS (also SCAR5; MIM #606937)*	C	No	—	AR	*ZNF592*
CARASIL (MIM #600142)	A	No	MRI	AR	*HTRA1*
Cerebral amyloid angiopathy: presenile dementia with spastic ataxia (MIM #176500)*	A	No	MRI	AD	*ITM2B*
Cerebral folate deficiency (MIM #613068)	C	Yes	CSF folates	AR	*FOLR1*
Childhood-onset spastic ataxia with optic atrophy and mental retardation (MIM %270500)*	C	No	—	AR	Unknown
Coenzyme Q10 deficiency (MIM #607426)	C	Yes	—	AR	>3 different genes
Female carriers of EIEE1 (MIM #308350)*	A	No	—	X-linked	*ARX*
Gaucher disease type III (MIM #231000)	C-A	Yes	—	AR	*GBA*
Glutaric acidemia II (MIM #231680)	C	Yes	MRI	AR	*ETFA, ETFB, ETFDH*
GM2 gangliosidosis (MIM #272800)	A	No	MRI	AR	*HEXA, HEXB, GM2A*
Hereditary spastic ataxia with congenital miosis (MIM%108650) (SPAX7)*	C	No	—	AD	Unknown
Krabbe disease (MIM #245200)	C-A	No	MRI	AR	*GALC*
LBSL (MIM #611105)*	C-A	No	MRI	AR	*DARS2*
Megalencephalic leukoencephalopathy with subcortical cysts (MIM #604004)*	C	No	MRI	AR	*MLC1*
Metachromatic leukodystrophy (MIM #250100)	C-A	Yes	MRI	AR	*ARSA*
Nonketotic hyperglycinemia (MIM #605899)	C-A	Yes	CSF amino acids	AR	>3 different genes
Optic atrophy ± deafness, ophthalmoplegia, myopathy, ataxia, neuropathy (MIM #605290)*	C	No	—	AD	*OPA1*
PHARC (MIM #612674)*	C	No	—	AR	*ABHD12*
Triple H syndrome (MIM #238970)*	C-A	Yes	Blood ammonia, amino acids	AR	*SLC25A15*
Type III 3-methylglutaconic aciduria (MIM #258501)*	C	No	Urine organic acids	AR	*OPA3*
Vanishing white matter leukodystrophy (#603896)*	C	No	MRI	AR	>3 different genes

*OMIM (Online Mendelian Inheritance in Man).

A, Adult onset; C, childhood onset; C-A, all ages possible, predominantly onset in adolescence; CAMOS, cerebellar ataxia with mental retardation, optic atrophy, and skin abnormalities; CARASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy; EIEE1, early infantile epileptic encephalopathy 1; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MIM%, phenotype description or locus, molecular basis unknown; MIM#, phenotype description, molecular basis known; MRI, brain MRI unless otherwise stated; when MRI is indicated, a typical or pathognomonic pattern can be recognized; PHARC, polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract; triple H, hyperornithinemia-hyperammonemia-homocitrullinuria; VLCFA, very long-chain fatty acids.

Modified from deBot ST, Willemsen MAAP, Vermeer S, et al. Reviewing the genetic causes of spastic-ataxias. *Neurology*. 2012;79:1507–1514, Table 2.

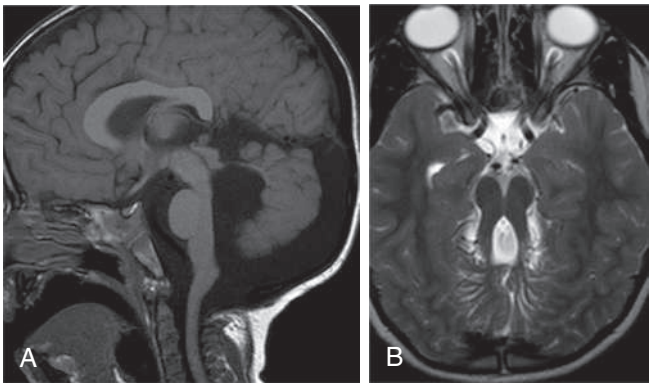

Fig. 637.3 Molar tooth syndrome. A, Sagittal T1-weighted MR image shows hypoplasia of the superior cerebellar vermis with upward bowing of the roof of the fourth ventricle. B, Axial T2-weighted image shows the molar tooth at the level of the midbrain, the hallmark of Joubert syndrome and related disorders (JSRD). *(From Rollins N. Congenital brain malformations. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019, Fig. 31.29AB, p. 286.)*



Fig. 637.4 Conjunctival telangiectasia in a patient with ataxia-telangiectasia. *(From Daroff RB, Jankovic J, Mazziotta JC, et al., eds. Bradley's Neurology in Clinical Practice, 7th ed. Philadelphia: Elsevier; 2016, Fig. 97.6, p. 1468.)*

is the method of choice for investigating congenital abnormalities of the cerebellum, vermis, and related structures. **Agenesis of the cerebellar vermis** presents in infancy with generalized hypotonia and decreased deep tendon reflexes. Delayed motor milestones and truncal ataxia are typical. **Joubert syndrome and related disorders** are autosomal recessive disorders marked by developmental delay, hypotonia, abnormal eye movements, abnormal respirations, and a distinctive malformation of the cerebellum and brainstem that manifests as the "molar tooth sign" on axial MRI (Fig. 637.3). Pathogenic variants in more than 21 different genes are associated with Joubert syndrome, but only approximately 50% of patients have demonstrated a pathogenic variant.

The major **infectious or postinfectious causes of ataxia** include acute cerebellar ataxia, infectious cerebellitis, immune-mediated cerebellitis, and acute labyrinthitis. **Acute cerebellar ataxia** occurs primarily in children 1-3 years of age and is a diagnosis of exclusion. The condition often follows a viral illness, such as varicella virus, coxsackievirus, or echovirus infection, by 2-3 weeks. It is thought to represent an autoimmune response to the viral agent affecting the cerebellum (see Chapter 643). The onset is typically sudden, and the truncal ataxia can be so severe that the child is unable to stand or sit. Vomiting may occur initially, but fever and nuchal rigidity are absent because of the lack of meningeal involvement. Horizontal nystagmus is evident in ~50% of cases; if the child is able to speak, dysarthria may be impressive. Examination of the cerebrospinal fluid is typically normal at the onset of ataxia, but a mild lymphocytic pleocytosis (10-30/mm^3) is not unusual. Later in the course, the cerebrospinal fluid protein undergoes a moderate elevation. The ataxia begins to improve in a few weeks but may persist for as long as 3 months, and rarely longer than that. The incidence of acute cerebellar ataxia appears to have declined with increased rates of vaccination against varicella. The prognosis for complete recovery is excellent. A small number of patients have long-term sequelae, including behavioral and speech disorders, as well as ataxia and incoordination. **Acute cerebellitis**, in contrast, is a more severe form of cerebellar ataxia characterized by abnormalities on MRI scans, more severe symptoms, and a worse long-term prognosis. Infectious agents include Epstein-Barr virus, mycoplasma, mumps, and influenza virus. An inflammatory process such as hemophagocytic lymphohistiocytosis may involve the cerebellum. Cerebellar abscesses can also occur with bacterial infections. In many, the etiology is unknown, but autoimmune cerebellitis may represent some of these unknown cases. Clinically, patients may present with ataxia, increased intracranial pressure from obstructive hydrocephalus, headache, and fever. **Acute labyrinthitis** may be difficult to differentiate from acute cerebellar ataxia in a toddler. The condition is associated with middle ear infections and presents with intense vertigo, vomiting, and abnormalities in labyrinthine function.

Toxic causes of ataxia include alcohol, thallium (which is used occasionally in homes as a pesticide), dextromethorphan, and anticonvulsants, particularly phenytoin and carbamazepine, when serum levels exceed the usual therapeutic range.

Brain tumors (see Chapter 546), including tumors of the cerebellum and frontal lobe, may present with ataxia. Cerebellar tumors cause ataxia because of direct disruption of cerebellar function or indirectly because of increased intracranial pressure from compression of the fourth ventricle. Frontal lobe tumors may cause ataxia as a consequence of destruction or interruption of the associated fibers connecting the frontal lobe with the cerebellum or because of increased intracranial pressure. Neuroblastoma (see Chapter 547) may be associated with a paraneoplastic encephalopathy characterized by progressive ataxia, myoclonic jerks, and opsoclonus (nonrhythmic, conjugate horizontal and vertical oscillations of the eyes).

Several **metabolic disorders** are characterized by ataxia, including abetalipoproteinemia, arginosuccinic aciduria, and Hartnup disease (see Table 637.2). **Abetalipoproteinemia** (Bassen-Kornzweig disease) is an autosomal recessive disorder caused by a pathogenic variant in the microsomal triglyceride transfer protein (MTP). This disorder begins in childhood with steatorrhea and failure to thrive. A blood smear shows acanthocytosis, which consists of spiculated red blood cells. Serum chemistries reveal decreased levels of cholesterol and triglycerides and absent serum β-lipoproteins. Neurologic signs become evident by late childhood and consist of ataxia, retinitis pigmentosa, peripheral neuritis, abnormalities of position and vibration sense, muscle weakness, and intellectual disability. Vitamin E is undetectable in the serum of patients with neurologic symptoms. In addition, ataxia may be one manifestation of a **mitochondrial disorder**; these include myoclonic epilepsy with ragged red fibers (MERFF), Kearns-Sayre syndrome, *POLG1* pathogenic variants, and Charlevoix-Saguenay syndrome.

Degenerative diseases of the central nervous system represent an important group of ataxic disorders of childhood because of the genetic consequences and poor prognosis. **Ataxia-telangiectasia**, an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded by ataxia beginning at approximately age 2 and progressing to loss of ambulation by adolescence. Ataxia-telangiectasia is caused by pathogenic variants in *ATM*. ATM is a phosphatidylinositol-3 kinase that phosphorylates proteins involved in DNA repair and cell-cycle control. Oculomotor apraxia of horizontal gaze, defined as difficulty shifting the gaze from one object to another and overshooting the target with lateral movement of the head, followed by refixating the eyes, is a frequent finding. In addition, strabismus, hypometric saccade pursuit abnormalities, and nystagmus are often seen. Ataxia-telangiectasia may also present with chorea (see Chapter 637.2) rather than ataxia. The telangiectasia becomes evident by mid-childhood and is found on the bulbar conjunctiva, over the bridge of the nose, and on the ears and exposed surfaces of the extremities (Fig. 637.4). Examination of the skin shows a loss of elasticity. Abnormalities of

immunologic function that lead to frequent sinopulmonary infections include decreased serum and secretory immunoglobulin (Ig) A, as well as diminished IgG2, IgG4, and IgE levels in more than 50% of patients. Children with ataxia-telangiectasia have a 50- to 100-fold increased risk of developing lymphoreticular tumors (lymphoma, leukemia, and Hodgkin disease) and brain tumors. Additional laboratory abnormalities include an increased incidence of chromosome breaks, particularly of chromosome 14, and elevated levels of α-fetoprotein. Death typically results from infection or tumor dissemination.

Friedreich ataxia is inherited as an autosomal recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, pyramidal tracts, and cerebellum and medulla. Most patients are homozygous for a GAA trinucleotide repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Pathogenic variants cause oxidative injury associated with excessive iron deposits in mitochondria. The onset of ataxia is somewhat later than in ataxia-telangiectasia but usually occurs before the age of 10. The ataxia is slowly progressive and involves the lower extremities to a greater degree than the upper extremities. Examination will demonstrate a positive Romberg test and absent deep tendon reflexes (particularly at the ankle); the plantar response is typically extensor (Babinski sign). Patients develop a characteristic explosive, dysarthric speech; nystagmus is present in most children. Although patients may appear apathetic, their intelligence is preserved. They may have significant weakness of the distal musculature of the hands and feet. Marked loss of vibration and joint position sense is common and is caused by degeneration of the posterior columns. Friedreich ataxia is also characterized by skeletal abnormalities, including high-arched feet (pes cavus) and hammer toes, as well as progressive kyphoscoliosis. Results of electrophysiologic studies, including visual, auditory brainstem, and somatosensory-evoked potentials, are often abnormal. Hypertrophic cardiomyopathy with progression to intractable congestive heart failure is the cause of death for most patients.

In addition to ataxia-telangiectasia and Friedreich ataxia, there are more than 40 other known inherited causes of either autosomal dominant or recessive forms of ataxia (Fig. 637.5; see Tables 637.4-637.8). More specifically, there are more than 20 dominantly inherited spinocerebellar ataxias (SCAs), some of which are also repeat expansion disorders and can present in childhood. These include those associated with CAG (polyglutamine) trinucleotide repeats and noncoding microsatellite expansions. There is also a separate group of dominantly inherited episodic ataxias (EAs) caused by potassium or calcium channel dysfunction. These disorders present as episodes of ataxia and muscle weakness and at times may respond to acetazolamide. The dominantly inherited **olivopontocerebellar atrophies** include ataxia, cranial nerve palsies, and abnormal sensory findings in the second or third decade, but can present in children with rapidly progressive ataxia, nystagmus, dysarthria, and seizures. **Roussy-Levy disease** has, in addition to ataxia, atrophy of the muscles of the lower extremity with a pattern of wasting similar to that observed in Charcot-Marie-Tooth disease. **Ramsay Hunt syndrome** has an associated myoclonic epilepsy.

Additional degenerative ataxias include **Pelizaeus-Merzbacher disease**, **neuronal ceroid lipofuscinoses**, and late-onset **GM_2 gangliosidosis** (see Chapter 639). Rare forms of progressive cerebellar ataxia have been described in association with **vitamin E deficiency**.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

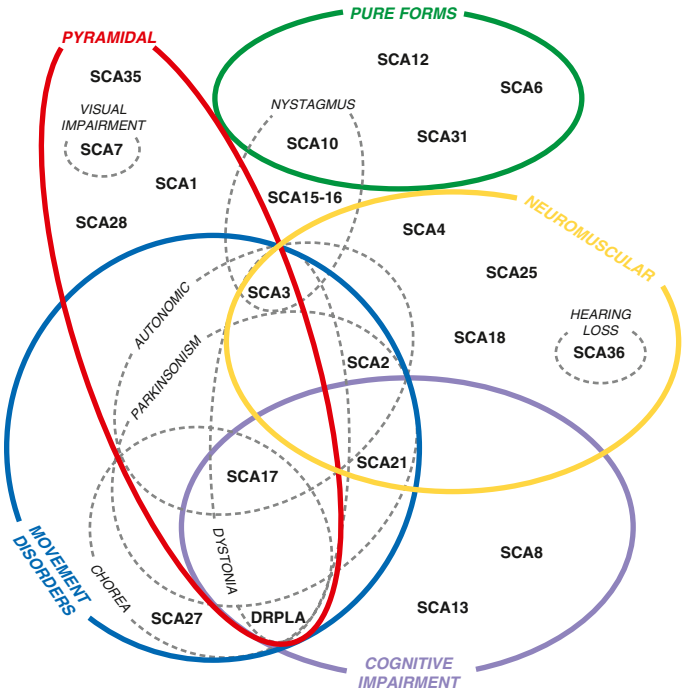

Fig. 637.5 Organization of spinocerebellar ataxias (SCA) according to main clinical features. *(From Rossi M, Perez-Lloret S, Doldan L, et al. Autosomal dominant cerebellar ataxias: a systematic review of clinical features. Eur J Neurol. 2014;21:607–615, Fig. 2.)*

637.2 Chorea, Athetosis, and Tremor

Jennifer A. Vermilion and Jonathan W. Mink

Chorea, meaning "dance-like" in Greek, refers to rapid, chaotic movements that seem to flow unpredictably from one body part to another. Affected individuals often appear restless, and movements exhibit randomness. They often demonstrate motor impersistence on neurologic examination, showing classic signs such as "darting tongue" (difficulty maintaining tongue protrusion) or "milkmaid grip" (difficulty maintaining grip). Chorea tends to occur both at rest and with action, although certain actions or postures can exacerbate chorea. Patients often attempt to incorporate the involuntary movements into more purposeful-seeming movements, making them appear fidgety. *Chorea increases with stress and disappears in sleep.* Chorea has traditionally been divided into primary and secondary forms; however, this classification scheme in movement disorders can cause confusion given the recent explosion of genetic discoveries in the field. Rather, it may be more helpful to classify chorea causes by etiology: acquired or inherited (Tables 637.9 and 637.10).

Sydenham chorea (St. Vitus dance; rheumatic chorea) is the most common acquired chorea of childhood, although the prevalence varies worldwide. It occurs in 10–20% of patients with **acute rheumatic fever**, typically weeks to months after a group A β-hemolytic streptococcal infection (see Chapter 194). Peak incidence is at age 8-9 years, with a female predominance of 2:1. There is evidence that group A β-hemolytic streptococci promote the generation of cross-reactive or polyreactive antibodies through molecular mimicry between streptococcal and host antigens. Specifically, antibodies against the *N*-acetyl-β-d-glucosamine epitope (GlcNAc) of streptococcal group A carbohydrate appear to target intracellular β-tubulin and extracellular lysoganglioside GM_1 in human caudate-putamen preparations. These antibodies are also capable of causing calcium/calmodulin–dependent protein kinase II activation, which may cause the neurologic manifestations of Sydenham chorea by increasing dopamine release into the synapse.

The clinical hallmarks of Sydenham chorea are chorea, hypotonia, and emotional lability. Onset of the chorea is typically over hours to days, but it may be more abrupt. Chorea is typically generalized, although often asymmetric; up to 20% have hemichorea. Parents may describe the child as seeming clumsy and dropping items while awake with cessation of adventitious movements during sleep. Hypotonia manifests with the *pronator sign* (arms and palms turn outward when held overhead) and the *choreic hand* (spooning of the extended hand by flexion of the wrist and extension of the fingers). When chorea and hypotonia are severe, the child may be incapable of feeding, dressing, or walking without assistance. Speech is often involved, sometimes to the point of being unintelligible. Periods of uncontrollable crying and extreme mood

Table 637.9 Acquired Causes of Chorea

STRUCTURAL-BASAL GANGLIA LESIONS	
Stroke	
Moyamoya disease	
Vascular malformations	
Hemorrhage	
Choreoathetoid cerebral palsy (dyskinetic cerebral palsy)	
Postcardiac transplant (postpump chorea)	
Mass lesions (CNS lymphoma, metastatic brain tumors)	
Multiple sclerosis plaque	
Extrapontine myelinolysis	
Trauma	
PARAINFECTIOUS AND AUTOIMMUNE DISORDERS	
Poststreptococcal Sydenham chorea	
Chorea secondary to systemic lupus erythematosus	
Chorea secondary to antiphospholipid antibody syndrome	
Acute disseminated encephalomyelitis	
Anti-NMDA receptor encephalitis	
Rasmussen encephalitis	
Chorea gravidarum	
Postinfectious or postvaccinal encephalitis	
Paraneoplastic choreas	
Celiac disease	
INFECTIOUS DISORDERS	
HIV encephalopathy	
Toxoplasmosis	
Cysticercosis	
Diphtheria	
Bacterial endocarditis	
Neurosyphilis	
Scarlet fever	
Viral encephalitis (mumps, measles, varicella)	
METABOLIC OR TOXIC DISORDERS	
Acute intermittent porphyria	
Hyponatremia/hypernatremia	
Hypocalcemia	
Hyperthyroidism	
Hypoparathyroidism	
Hepatic/renal failure	
Carbon monoxide poisoning	
Methyl alcohol	
Toluene	
Manganese poisoning	
Mercury poisoning	
Organophosphate poisoning	
Pheochromocytoma	
PSYCHOGENIC DISORDERS	
DRUG-INDUCED DISORDERS	
Dopamine-blocking agents (upon withdrawal or as a tardive syndrome)	Phenothiazines Butyrophenones Benzamides
Antiparkinsonian drugs	L-DOPA Dopamine agonists Anticholinergics
Antiepileptic drugs	Phenytoin Carbamazepine Valproic acid
Psychostimulants	Amphetamines Methylphenidate Cocaine
Calcium channel blockers	Cinnarizine Flunarizine Verapamil
Others	Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol

swings are characteristic and may precede the onset of the movement disorder. Patients may also demonstrate inattention, anxiety, obsessive-compulsive symptoms, paranoia, and a reluctance to speak. It is not clear if these psychiatric symptoms represent an increased susceptibility to developing Sydenham chorea or if they are part of the disorder.

Sydenham chorea is a clinical diagnosis; a combination of acute *and* convalescent serum antistreptolysin O titers may help to confirm an acute streptococcal infection. Negative titers do not exclude the diagnosis. All patients with Sydenham chorea should be evaluated for carditis and treated with long-term antibiotic prophylaxis to decrease the risk of rheumatic heart disease with recurrence (see Chapter 487). This prophylaxis should be continued until the patient is 21 years old. For patients with chorea that is impairing, treatment options include valproate, carbamazepine, and dopamine receptor antagonists. There have been conflicting data regarding the efficacy of prednisone, intravenous immunoglobulin (IVIG), and other immunomodulatory agents in Sydenham chorea, making it difficult to recommend their routine use. One study compared high-dose prednisone (2 mg/kg/day, max: 60 mg) for 4 weeks to placebo and found that steroids reduced the time to remission. Another trial of IVIG, plasma exchange, and low-dose prednisone demonstrated an overall decreased severity of chorea in the IVIG and plasma exchange groups at 1-month follow-up. There is no evidence that prednisone, IVIG, or plasma exchange *alters the recurrence rate or long-term outcome*. Given the lack of impact on long-term outcome and the potential for side effects, immunomodulatory treatments are optional.

Sydenham chorea usually resolves spontaneously within 1 year, but symptoms may recur in about 20% of patients despite penicillin prophylaxis. Remote recurrence of chorea is rare, but may be provoked by streptococcal infections, pregnancy **(chorea gravidarum)**, or oral contraceptive use.

Although less common than Sydenham chorea, **systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APS)** (see Chapter 199) are known causes of chorea in children. In some cases, chorea may be the presenting sign of these disorders and clinically may be indistinguishable from Sydenham chorea.

Anti *N*-methyl-D-aspartic acid (anti-NMDA) receptor encephalitis is an immune-mediated encephalitis with movement disorder as a prominent feature. Abnormal movements, including chorea, may be the presenting feature in some cases. Other commonly reported abnormal movements include dystonia, stereotypies (limb and oral), and motor perseveration. In addition to abnormal movements, psychiatric symptoms, seizures, and autonomic instability commonly occur. Treatment includes removal of the tumor, if present, and immune therapies such as steroids, IVIG, plasma exchange, and rituximab.

Additional causes of acquired chorea include metabolic (hyperthyroidism, hypoparathyroidism), infectious (Lyme disease), vascular (stroke, moyamoya disease, postpump chorea), heredodegenerative disorders (Wilson disease), and drugs (see Table 637.9). Although chorea is a hallmark of Huntington disease in adults, children who develop Huntington disease tend to present with rigidity and bradykinesia **(Westphal variant)** or dystonia rather than chorea.

Various genetic diseases may manifest with chorea; some present with predominantly chorea, but most have a combination of neurologic, psychiatric, and systemic manifestations that accompany the movement disorder (see Table 637.10). **Benign hereditary chorea** is a relatively rare cause of chorea in childhood. It typically presents before age 5 years; the chorea is either stable or slowly progressive. Chorea tends to improve in the late teen to young adult years and often remits by mid-adulthood. It is most commonly secondary to a pathogenic variant in *NKX2-1*, which encodes for the protein thyroid transcription factor-1 (TTF1). The majority of patients (80%) also have hypothyroidism or neonatal respiratory distress syndrome **(brain-lung-thyroid syndrome)**. Variants in *NKX2-1* confer increased risk of lung cancer or emphysema in adulthood. Although children are considered cognitively normal, there are reports of an increased incidence of learning disabilities and attention-deficit/hyperactivity disorder (ADHD) in this population.

In ***ADCY5*-related dyskinesia**, chorea is a core feature. There is a phenotypic variability to this disorder, but some patients present with a form of familial benign chorea with onset of paroxysmal movements starting

Table 637.10 Inherited Causes of Childhood-Onset Chorea

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTEMIC SYMPTOMS
CHOREA PROMINENT FEATURE					
Ataxia-telangiectasia	AR	*ATM*	18 mo to 3 yr	Chorea often initial symptom; also have oculomotor apraxia, ataxia, and dystonia	Telangiectasias, increased sinopulmonary infections, increased incidence of cancer
Ataxia with oculomotor apraxia 1 and 2 (especially type 1)	AR	*APTX*	Onset later than ataxia-telangiectasia	Chorea, dystonia, oculomotor apraxia, ataxia, distal sensory axonal neuropathy	
Friedreich ataxia	AR	GAAn in *FRDA*	Over 2 yr, usually teenagers	Gait ataxia, axonal neuropathy, areflexia, extensor plantar response. Can have various movements (tremor, dystonia, chorea, myoclonus). Cases of chorea without cerebellar signs described.	Cardiomyopathy, diabetes
GNAO1-related dyskinesias	AR	*GNAO1*	Infancy	Ballismus, chorea, orofacial dyskinesias; can alternatively cause Ohtahara syndrome	
FOXG1-related dyskinesias	AD	*FOXG1*	Infancy	Chorea, dystonia, athetosis, hand-mouthing stereotypies, postnatal microcephaly, epilepsy, severe developmental delay	
Benign hereditary chorea	AD	*NKX2-1*	Before age 5 yr	Chorea; can have myoclonus, learning disability	Thyroid disease, lung disease
ADCY5-associated dyskinesias	AD	ADCY5	Infancy to late adolescence	Chorea, choreic facial twitches (previously called myokymia); can have myoclonus or dystonia	Some reports of congestive heart failure
PDE10A-associated dyskinesias	AD or AR	*PDE10A*	AD: childhood AR: infancy	Chorea, MRI striatal changes in AD form	
Paroxysmal nonkinesigenic dyskinesias	AD	*PNKD*	Infancy to 10 yr	Dystonia, chorea, or a combination	
3-methylglutaconic aciduria type III (Costeff syndrome)	AR	*OPA3*	Infancy	Bilateral optic atrophy and chorea early; spasticity, ataxia, and dementia later	
Congenital cataracts, facial dysmorphism, and neuropathy	AR	*CTDP1*	Infancy or childhood	Progressive neuropathy, delayed psychomotor development, mild chorea, hypomyelination, hearing loss	Skeletal abnormalities, dysmorphic face, congenital cataracts, microcornea, hypogonadism
Dentatorubral-pallidoluysian atrophy	AD	CAGn in *atrophin-1*	Mostly adults but seen in a few children	Neurodegeneration, chorea, tics, dementia, seizures, ataxia, psychiatric symptoms	
Huntington chorea/ disease	AD	CAGn in *HTT*	Adolescence to 40s	Younger onset *without* chorea and with parkinsonism, but later, teenagers can manifest chorea, emotional disturbances similar to adult form	
Huntington disease-like-3 (HDL3)	AR	Linked to chromosome 4p15.3	Childhood	Neurodegeneration, chorea, dystonia, ataxia, dementia, seizures	
Idiopathic basal ganglia calcification (IBGC), childhood onset (bilateral striopallidodentate calcinosis)	AR or AD	*SLC20A2* or *PDGFRB*	Infancy to second decade of life	Tetraplegia, chorea, severe cognitive impairment, microcephaly, basal ganglia calcifications	Early death

Continued

Table 637.10 Inherited Causes of Childhood-Onset Chorea—cont'd

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTEMIC SYMPTOMS
Choreoacanthocytosis	AR	*VPS13A*	Mean age 20 yr but described in childhood	Psychiatric symptoms (e.g., obsessive-compulsive disorder) can precede neurologic symptoms. Neurodegeneration, progressive hyperkinetic movements (limb chorea, orofacial dyskinesias, tics, dystonia), dementia, seizures, cognitive decline, sensorimotor polyneuropathy.	Acanthocytosis, increased CK and/or liver transaminases
Spinocerebellar ataxia 1	AD	CAGn in *ATXN1*	Childhood	Neurodegeneration, progressive ataxia, mild cognitive impairment, dysarthria, ophthalmoplegia, optic atrophy, spasticity, dystonia or chorea	
Spinocerebellar ataxia 17	AD	CAGn or CAAn in *TBP*	Mostly early adulthood but some teenagers reported	Neurodegeneration, psychiatric symptoms (depression, hallucinations), frontal release signs, chorea, dystonia, and parkinsonism; may have ocular movement abnormalities	
Leigh syndrome	X-linked	*PDHA1*	Infancy or childhood	Neurodegeneration, psychomotor delay, hypotonia and chorea and other hyperkinetic movements can be prominent, progresses to feeding and swallowing defects, nystagmus, ophthalmoplegia, optic atrophy, seizures Lesions in basal ganglia, cerebrum, cerebellum, spinal cord	Lactic acidemia, respiratory failure
Nonketotic hyperglycemia (glycine encephalopathy)	AR	*GLDC, GCST,* or *GCSH*	Neonates/ infancy	Hypotonia, severe myoclonic epilepsy, profound cognitive impairment, restlessness	Hyperglycemia
Infantile bilateral striatal necrosis	AR	*NUP62*	Infancy	Developmental regression, intellectual disability, pendular nystagmus, optic atrophy, dysphagia, dystonia, choreoathetosis, spasticity, and severe bilateral striatal atrophy	
CHOREA SOMETIMES PRESENT					
Spinocerebellar ataxia 7	AD	CAGn in *ATXN7*	Childhood	Neurodegenerative mitochondrial disorder, progressive ataxia, dysarthria, dysphagia, optic atrophy, ophthalmoplegia, spasticity, dystonia or chorea may occur	Retinal degeneration
Wilson disease	AR	*ATP7B*	12 yr to early 20s	Dysarthria, drooling, pharyngeal dysmotility, clumsiness, tremor ("wing-beating"), psychiatric symptoms (decline in school, anxiety, depression, psychosis); chorea and dystonia variable	Hepatic dysfunction (asymmetric hepatomegaly, acute transient or fulminant hepatitis), Kayser-Fleischer rings of cornea
Lesch-Nyhan disease	X-linked	*HPRT*	Early childhood	Self-injurious behaviors, intellectual disability, motor disability, pyramidal signs, dystonia superimposed on hypotonia, may have chorea or ballismus, abnormal ocular motility	Hyperuricemia, nephrolithiasis, gout
Pantothenate kinase–associated neurodegeneration (PKAN), classic form	AR	*PANK2*	Before 6 yr old (in classic onset)	Progressive motor difficulties, personality changes, cognitive decline, dysarthria, spasticity; later onset of movements (dystonia most common, chorea or tremor may also be present); "eye of the tiger" sign on MRI of brain	Pigmentary retinal degeneration, acanthocytosis

Table 637.10 Inherited Causes of Childhood-Onset Chorea—cont'd

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTEMIC SYMPTOMS
Paroxysmal kinesigenic dyskinesia (PKD)	AD	*PRRT2*	1-20 yr	Short episodes triggered by sudden movement; dystonia is most common movement but can have chorea	
Biopterin-dependent hyperphenylalaninemia (group of disorders)	Usually AR	Multiple genetic causes	Neonate	Initially hypotonic with poor suck, decreased movements, and microcephaly; months later, oculogyric crises, swallowing difficulties, variable hypokinetic and hyperkinetic movements, seizures, cognitive impairment	Elevated phenylalanine level at birth; autonomic symptoms start several months later
Glutaric aciduria	AR	*GCDH*	First 6 mo	Hypotonia and jitteriness at birth; at 6-18 mo, progressive hyperkinetic movements (dystonia, choreoathetosis); may have seizures	
Alternating hemiplegia of childhood	AR	*ATP1A-3*	Neonate to <18 mo	Transient episodes of alternating hemiplegia/hemiparesis, dystonic attacks, paroxysmal abnormal ocular movements, seizures, episodes of autonomic dysfunction; between attacks, may have ataxia, dystonia, and/or choreoathetosis; most have intellectual disability	
Succinate semialdehyde dehydrogenase deficiency	AR	*ALDH5A*	Infancy to early childhood	Intellectual disability, pronounced language dysfunction, autistic traits, hypotonia, aggression, ataxia, anxiety, hallucinations, can have choreoathetosis	

anywhere from infancy to late adolescence. Although chorea is the most commonly described movement, there are reports of myoclonic or dystonic movements as well. Movements are more common in the arms and face and less common in the legs. *ADCY5*-related dyskinesia has commonly been associated with choreic facial twitches that were previously considered facial myokymia (known as **familial dyskinesia with facial myokymia**). Interestingly, movements in this form can persist in sleep. Symptoms can fluctuate such that chorea may be paroxysmal; they tend to be worsened by specific actions and anxiety. These patients also tend to have a stable or very slowly progressive course that tends to stabilize and even improve in middle age. *ADCY5*-related dyskinesia can have a more severe presentation with infantile onset of axial hypotonia and developmental delay. *ADCY5*-related dyskinesia has not been associated with thyroid or lung disease; however, heart failure has been reported in five patients. Although these conditions are called benign, these movements can be disabling and progressive in some patients. Therefore some patients may warrant symptomatic treatment. Although there is no proven symptomatic treatment for these conditions, there have been reports of benefit with dopamine receptor–blocking or –depleting agents. In a few cases, low-dose levodopa has provided benefit.

A pure, benign, and nonprogressive childhood-onset chorea has been described in a few patients with pathogenic variants in *PDE10A*, which encodes for a phosphodiesterase. Children with de novo dominant variants characteristically have symmetric T2 hyperintensities in the bilateral striatum on brain MRI. Children with recessive homozygous variants have been described with an earlier age of onset and a more severe clinical course.

Paroxysmal dyskinesias can present with chorea or dystonia, or both; chorea is most commonly associated with **paroxysmal nonkinesigenic dyskinesia (PNKD)**. This disorder presents in the first decade of life, with ~30% of patients manifesting symptoms in the first year of life. Patients often have both chorea and dystonia, although some patients manifest only dystonia. Episodes can last minutes to hours, and children are normal between episodes. The episodes are not triggered by sudden movement but can be precipitated by alcohol, caffeine, or emotional stress. About half of patients report a premonitory sensation or a sense of anxiety before an episode. Although various genes have been implicated in this disorder, *PNKD* (formerly known as *MR-1*) is most commonly associated with PNKD. Patients with a *PNKD* pathogenic variant often respond to benzodiazepines; avoidance of triggers is also important. Symptoms typically improve with age. Variants in *KCNMA1* can also cause a PNKD phenotype, although these children often have other neurologic abnormalities.

Some inherited disorders classified as ataxia syndromes also manifest with significant chorea. **Ataxia-telangiectasia** typically presents as a mixed movement disorder with ataxia, dystonia, and chorea in early childhood (18 months to 3 years). These symptoms present before the appearance of telangiectasias. Over time, children have progression of limb and gait involvement and typically become nonambulatory in childhood. Children also present with oculomotor apraxia (difficulty in initiating horizontal and vertical saccades). Ataxia-telangiectasia is an autosomal recessive disorder secondary to pathogenic variants in *ATM*. Because this gene encodes for a protein involved in DNA repair mechanisms, affected children are at increased risk of sinopulmonary infectious and lymphoreticular neoplasms. When this disease is suspected, the initial workup involves testing the alpha-fetoprotein (AFP) level, which is abnormally increased in this population. **Ataxia with oculomotor apraxia type 1 (AOA1)** is also associated with a mixed movement disorder and is caused by variants in *APTX*, which encodes for the aprataxin protein. Up to 80% of children have chorea and dystonia as their initial symptoms. Other neurologic symptoms include oculomotor apraxia, ataxia, and a distal sensory axonal neuropathy. The movement disorder tends to be most severe early in the disease and improves as the disease progresses. Unlike ataxia-telangiectasia, this disorder is not associated with skin findings or an increased incidence of cancer.

Chorea can also be a major manifestation in children with inherited conditions that have a progressive, severe course. **Pontocerebellar hypoplasia type 2A (PCH-2A)** is associated with chorea present from a young age. The majority of patients have chorea within the first 6 months of life. PCH-2A is associated with an acquired microcephaly, extrapyramidal dyskinesias, and spasticity. These children have significant psychomotor delay with early death. Although various genes have

been implicated in the different forms of pontocerebellar hypoplasia, PCH-2A is associated with pathogenic variants in *TSEN54,* which encodes for a protein involved in transfer RNA (tRNA) splicing. Variants in *GNAO1,* which encodes for the alpha subunit of G proteins, have been described as causing a particular movement disorder in affected children. This gene has previously been described as a cause of early infantile epileptic encephalopathy **(Ohtahara syndrome)**. However, affected children may instead manifest with hypotonia, developmental delay without epilepsy, and a movement disorder characterized by chorea and ballismus in the first decade of life. Chorea tends to start acutely during an illness. Some children with *GNAO1* variants have a severe movement disorder without seizures. Orofacial dyskinesias are common. Children often have periods of movement exacerbations that can be accompanied by autonomic changes. These movements can be refractory to treatment and led to death in two of the children in a study. Deep brain stimulation has been proposed as a potential treatment for these medically refractory children. *FOXG1* variants are associated with postnatal microcephaly, an early epileptic encephalopathy, and abnormal movements. Chorea is commonly reported and may involve the upper extremities and orolingual muscles. Dystonia, athetosis, and stereotypies are also reported.

Athetosis is characterized by slow, continuous, writhing movements that repeatedly involve the same body part(s), usually the distal extremities, face, neck, or trunk. Like chorea, athetosis may occur at rest and is often worsened by voluntary movement. Because athetosis tends to occur with other movement disorders, such as chorea **(choreoathetosis)** and dystonia, it is often difficult to distinguish as a discrete entity. Choreoathetosis is common in dyskinetic cerebral palsy, which can result from hypoxic ischemic encephalopathy, kernicterus, or other basal ganglia injuries. Cerebral palsy is a static disturbance in the developing brain that results in motor impairment. Dyskinetic cerebral palsy, the second most common form after spastic cerebral palsy, typically presents with dystonia and choreoathetosis. The choreoathetosis is typically more common in the upper body. Choreoathetosis is often seen in conjunction with **rigidity**—increased muscle tone that is equal in the flexors and extensors in all directions of passive movement regardless of the velocity of the movement. This is to be differentiated from **spasticity**, a velocity-dependent (clasp-knife) form of hypertonia that is seen with upper motor neuron dysfunction. Case reports in dyskinetic cerebral palsy report chorea improvement with levetiracetam. In addition, a small study of risperidone in children with dyskinetic cerebral palsy reported improvement in abnormal movements and behavior.

Tremor is a rhythmic, oscillatory movement around a central point or plane that results from the action of antagonist muscles. Tremor can affect the extremities, head, trunk, or voice and can be classified by both its frequency (slow [4 Hz], intermediate [4-7 Hz], and fast [>7 Hz]) and by the context in which it is most pronounced. **Rest tremor** is maximal when the affected body part is inactive and supported against gravity, whereas **postural tremor** is most notable when the patient sustains a position against gravity. **Action tremor** occurs with performance of a voluntary activity and can be subclassified into **simple kinetic tremor**, which occurs with limb movement, and **intention tremor**, which occurs as the patient's limb approaches a target and is a feature of cerebellar disease.

Essential tremor (ET) is the most common movement disorder in adults, and 50% of persons diagnosed with ET report an onset in childhood; thus ET may be the most common tremor disorder in children as well. Clinical experience in a pediatric movement disorders clinic suggests that ET is more common in the pediatric population than the literature would suggest. ET is an autosomal dominant condition with variable expressivity but complete penetrance by the age of 60 years. Although the genetics of ET are not fully understood, at least five genes (*EMT1, EMT2, EMT3, EMT4,* and *EMT5*) are linked to this condition. In addition, polymorphisms in the gene *LINGO1* (also known as *LRRN6A*) have been associated with ET.

ET is characterized by a slowly progressive, bilateral, 4- to 9-Hz postural tremor that involves the upper extremities and occurs in the absence of other known causes of tremor. Face, neck, and voice tremors are less common but can occur. Mild asymmetry in the upper extremities is common, but ET is rarely unilateral. ET may be worsened by actions, such as trying to pour water from cup to cup. Affected adults may report a history of ethanol responsiveness. In the adult literature, there is a consensus on diagnostic criteria; there are no specific criteria in children. Unlike adults, children do not require a 5-year duration of symptoms to make the diagnosis of ET. Most young children come to medical attention once a parent, teacher, or therapist notices the tremor, rather than because the tremor causes impairment. Most children with ET do not require pharmacologic intervention. If they are having difficulty with their handwriting or self-feeding, an occupational therapy evaluation and/or assistive devices, such as wrist weights and weighted silverware, may be helpful. Teenagers tend to report more impairment from ET. Teenagers who do warrant pharmacotherapy usually respond to the same medications that are used in adults—propranolol and primidone. Propranolol, which is generally considered the first-line treatment, can be started at 10-40 mg daily and titrated to effect, with most patients responding to doses of 60-80 mg/day. Propranolol should not be used in patients with reactive airway disease. Primidone can be started at 12.5-25 mg at bedtime and increased gradually in a twice-daily schedule. Most patients respond to doses of 50-200 mg/day. Other treatment options for ET reported in the adult literature include atenolol, gabapentin, pregabalin, topiramate, and alprazolam. Surgical treatments, which include deep brain stimulation of the thalamus and unilateral thalamotomy, are generally reserved for adults with medically refractory disabling tremor.

Enhanced physiologic tremor is one of the most common etiologies of tremor in adolescents. This tremor occurs in healthy people and is characterized by a symmetric hand tremor that is often of faster frequency and lower amplitude than an ET. Triggers include increased emotions, fatigue, fever, hunger, and waking from sleep. Substances such as caffeine may enhance a tremor. Weighted objects may decrease tremor frequency.

In children 3-7 years old, coordination difficulties due to developmental delay can present with nonprogressive tremor. Many children with motor delays will have a hand and possibly truncal tremor that is most apparent with fine motor tasks, such as drawing, using scissors, or playing with small toys. The history often shows that these children are behind typically developing children in terms of fine and/or gross motor skills and speech articulation. Examination shows that the movement tends to be a small-amplitude, regular or irregular postural or intention tremor. Walking and running may be clumsy. Evidence-based treatment has not been established for tremor related to developmental delay; however, referral to occupational therapy may help to identify strategies to improve coordination in these children.

Infantile tremor syndrome is a disorder of unknown etiology that presents at age 6-18 months with regression or plateaued development, coarse tremor, and anemia. Potential etiologies include deficiencies in vitamin B_{12}, iron, zinc, or magnesium.

There are numerous secondary etiologies of tremor in children (Table 637.11). **Holmes tremor**, previously referred to as *midbrain* or *"rubral" tremor,* is characterized by a slow-frequency, high-amplitude tremor that is present at rest and with intention. It is a symptomatic tremor, which usually results from lesions of the brainstem, cerebellum, or thalamus. **Functional (psychogenic) tremor** is distinguished by its variable appearance, abrupt onset and remission, nonprogressive course, and association with selective but not task-specific disabilities.

In some cases, tremor may even occur as a manifestation of another movement disorder, as is seen with position- or task-specific tremor (e.g., writing tremor), dystonic tremor, and myoclonic tremor.

When evaluating a child with tremor, it is important to screen for common metabolic disturbances, including electrolyte abnormalities and thyroid disease, assess the child's caffeine intake, and review the child's medication list for known tremor-inducing agents. It is also critical to exclude Wilson disease in teenagers with characteristic "wing-beating" tremor (low-frequency/high-amplitude posture initiated with horizontal position and abduction of arms, flexed elbows, and downward-facing palms with resultant shoulder and hand tremors) because this is a treatable condition.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 637.11 Selected Causes of Tremor in Children

BENIGN TREMORS
Enhanced physiologic tremor
Developmental delay
Shuddering attacks
Jitteriness
Spasmus nutans
STATIC INJURY/STRUCTURAL TREMORS
Cerebellar malformation
Stroke (particularly in the midbrain or cerebellum)
Multiple sclerosis
HEREDITARY/DEGENERATIVE TREMORS
Familial essential tremor
Fragile X premutation
Wilson disease
Huntington disease
Juvenile parkinsonism (tremor is rare)
Pallidonigral degeneration
METABOLIC TREMORS
Hyperthyroidism
Hyperadrenergic state (including pheochromocytoma and neuroblastoma)
Hypomagnesemia
Hypocalcemia
Hypoglycemia
Hepatic encephalopathy
Vitamin B12 deficiency
Inborn errors of metabolism
Mitochondrial disorders
DRUGS/TOXINS
Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, beta agonist, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors
PERIPHERAL NEUROPATHIES
FUNCTIONAL (PSYCHOGENIC) TREMORS

637.3 Myoclonus

Jonathan W. Mink

Myoclonus refers to brief, abrupt, involuntary, nonsuppressible, jerky contractions (or interruption of contractions) involving a single muscle or muscle group. The rapidity of these movements is often described as *shocklike*. In some cases, myoclonus can be elicited by a sensory stimulus (reflex myoclonus; the most common example is the acoustic startle response in infancy) or volitional movement (action myoclonus). It is present in normal and pathologic situations, both epileptic and nonepileptic. Epileptic myoclonus is discussed in Chapter 633. Etiologic classification of myoclonus is summarized in Table 637.12.

Physiologic myoclonus occurs in healthy individuals in specific settings. It includes such entities as hiccups, sleep starts, and sleep myoclonus. Sleep starts, also known as *hypnic or hypnagogic myoclonus,* occur with sleep initiation. They are often accompanied by a sense of falling. Sleep starts are normal physiologic phenomena, and no treatment is required. Sleep myoclonus (nocturnal myoclonus) is also a part of normal sleep physiology. It typically occurs during rapid eye movement (REM) sleep owing to transient failure of brainstem inhibition. Sleep myoclonus tends to persist throughout life. No treatment is required.

Benign myoclonus may occur in association with specific developmental stages. Benign neonatal sleep myoclonus is characterized by repetitive myoclonic jerks occurring during sleep. The myoclonus is typically more distal than proximal and is more prominent in the upper than the lower extremities. The myoclonus can be focal, multifocal, unilateral, or bilateral. Typically, the movements occur in clusters of jerks at 1-5 Hz over a period of several seconds. Benign neonatal sleep myoclonus begins during the first week of life, diminishes in the second month, and is usually gone before 6 months of age. The movements are most likely to occur during quiet (non-REM) sleep but have been described in all sleep stages. Waking the baby causes the movements to abruptly cease. Neurologic examination and outcome are normal.

Myoclonus also can occur with fever in otherwise normal children. The myoclonic jerks may be quite frequent, but they are self-limited, ceasing when the fever resolves. Febrile myoclonus may be more common in younger children. No treatment is required.

Opsoclonus myoclonus (ataxia) syndrome (OMS/OMAS) is characterized by a combination of rapid, chaotic involuntary eye movements (opsoclonus), multifocal myoclonus, and ataxia. Irritability is a common feature. It typically begins abruptly in early childhood, most often before age 5 years. A common misdiagnosis is acute cerebellar ataxia (ACA) because both ACA and OMAS have subacute, progressive disturbances in gait, truncal instability, and behavioral irritability. Irritable toddlers are difficult to examine thoroughly, adding to the challenge of discerning the presence of multifocal mini-myoclonus and action myoclonus plus ataxia in a toddler with OMAS versus titubation, gait, and limb ataxia in ACA. At its peak, OMAS can cause marked disability for the child.

OMAS is an autoimmune condition in which there is abnormal B-cell trafficking in the central nervous system. It may follow a viral infection in many cases. A large proportion of children (40% by one estimate) with OMAS have a neuroblastoma, a potentially fatal neural crest tumor (see Chapter 547). Conversely, only a small proportion of children with neuroblastoma (probably <5%) have OMAS. The subacute onset of OMAS and the association with neural crest tumors support an autoimmune paraneoplastic etiology. Intensive research into multiple circulating autoantibodies, including antibodies to Purkinje cell targets, has not, to date, identified any unique, consistently present, disease-associated antibody.

OMAS is a clinical diagnosis. In the presence of subacute irritability, tremor, and ataxia, a diagnosis of OMAS must be considered, and children diagnosed with ACA should continue to be monitored for the emergence of symptoms characteristic of OMAS. The presence of opsoclonus has a high positive predictive value for OMAS, but its absence does not have a high negative predictive value. That is because opsoclonus can be subtle, intermittent, or late, so clinicians and parents need to continue to watch for it. Brain MRI should be normal, and cerebrospinal fluid unremarkable. No immune studies are clinically established for this diagnosis. The search for a neuroblastoma should be thorough and persistent in this clinical setting. MRI with gadolinium or CT with contrast of the chest and abdomen has the highest yield. Nuclear medicine ^{131}I-MIBG (metaiodobenzylguanidine) or ^{111}In-penetreotide (somatostatin receptor ligand) PET scans and urine collection for elevated 24-hour urine catecholamines and serum neuron-specific enolase may be considered but have a lower yield.

Multimodal treatment is required for OMAS. If related to neuroblastoma, the child will likely need immune-modulating treatments even if a tumor is identified and resected. Adrenocorticotrophin (ACTH) protocols are recommended based on expert consensus and clinical experience. In addition to ACTH, combination treatment with IVIG, plasmapheresis, rituximab, or other immune-modulating therapies may be needed. Symptomatic pharmacologic and behavioral therapy for myoclonus, behavioral problems, aggression, and insomnia may also be beneficial. Physical therapy, occupational therapy, and speech therapy may be beneficial. Suboptimal cognitive outcomes occur in most cases.

Causes of other types of myoclonus are listed in Table 637.12. Differentiating myoclonus and other movement disorders from a functional neurologic disorder may be difficult. Clues to a functional disorder are noted in Table 637.13.

Treatment of myoclonus is symptomatic and may be ineffective in many cases. Cortical myoclonus may respond to benzodiazepines and is commonly treated with clonazepam (although sleep myoclonus may worsen). Valproic acid is sometimes helpful, but it must be used with caution because of its ability to cause tremor as a side effect, with consequent confusion of symptoms. Other epilepsy medications, including levetiracetam and zonisamide, may be effective in some forms of myoclonus. Carbamazepine can worsen myoclonus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 637.12 Etiologic Classification of Myoclonus

I. **Physiologic myoclonus (normal subjects)**
  A. Sleep jerks (hypnic jerks)
  B. Anxiety-induced
  C. Exercise-induced
  D. Hiccup (singultus)
  E. Benign infantile myoclonus with feeding
II. **Essential myoclonus (no known cause other than genetic and no other gross neurologic deficit)**
  A. Hereditary (autosomal dominant and most are likely myoclonus dystonia)
  B. Sporadic
III. **Epileptic myoclonus (seizures dominate and no encephalopathy, at least initially)**
  A. Fragments of epilepsy
    Isolated epileptic myoclonic jerks
    Photosensitive myoclonus
    Myoclonic absences in petit mal
    Epilepsia partialis continua
  B. Childhood myoclonic epilepsies
    Infantile spasms
    Myoclonic astatic epilepsy (Lennox-Gastaut)
    Cryptogenic myoclonus epilepsy (Aicardi)
    Juvenile myoclonus epilepsy of Janz
  C. Benign familial myoclonic epilepsy (Rabot)
  D. Progressive myoclonus epilepsy (Unverricht-Lundborg)
IV. **Symptomatic myoclonus (progressive or static encephalopathy dominates)**
  A. Storage disease
    Lafora body disease
    Lipidoses (e.g., GM1 and GM2 gangliosidosis, Krabbe)
    Ceroid-lipofuscinosis (Batten)
    Sialidosis ("cherry-red spot")
  B. Spinocerebellar degeneration
    Unverricht-Lundborg disease
    Ataxia telangiectasia
    Adult-onset cerebellar ataxias
    Some spinocerebellar ataxias (SCAs)
    Multiple system atrophy type C
  C. Basal ganglia degenerations
    Wilson disease
    Dystonia
    Pantothenate kinase–associated neurodegeneration
    Progressive supranuclear palsy
    Multiple system atrophy type P
    Huntington disease
    Corticobasal ganglionic degeneration
    Dentatorubro-pallidoluysian atrophy
    Parkinson disease
  D. Dementias
    Creutzfeldt-Jakob disease
    Alzheimer disease
  E. Viral encephalopathies
    Subacute sclerosing panencephalitis (SSPE)
    Encephalitis lethargica
    Arbor virus encephalitis
    Herpes simplex encephalitis
    Postinfectious encephalitis
    Whipple disease
    AIDS
    SARS-CoV-2
  F. Autoimmune
    Opsoclonus-myoclonus syndrome
    Celiac disease
  G. Metabolic
    Hepatic failure
    Renal failure
    Dialysis syndrome
    Hyponatremia
    Hypoglycemia
    Infantile myoclonic encephalopathy
    Nonketotic hyperglycemia
    Mitochondrial encephalomyopathy
    Multiple carboxylase deficiency
    Biotin deficiency
  H. Toxic encephalopathies
    Bismuth
    Heavy metal poisons
    Methyl bromide, DDT
    Drugs, including levodopa
    Serotonin syndrome (e.g., SSRIs)
  I. Physical encephalopathies
    Posthypoxic (Lance-Adams)
    Posttraumatic
    Heat stroke
    Electric shock
    Decompression injury
  J. Focal central nervous system damage
    Poststroke
    Postthalamotomy
    Tumor
    Trauma
    Dentato-olivary lesions (palatal myoclonus/tremor)
  K. Functional

From Jankovic J, Hallett M, Okun MS, et al., eds. *Principles and Practice of Movement Disorders,* 3rd ed. Philadelphia: Elsevier; 2022: Table 18.2, p. 498.

637.4 Dystonia

Shannon L. Dean and Erika F. Augustine

Dystonia is a disorder of movement characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures (Table 637.14). Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 637.15 and 637.16).

INHERITED PRIMARY DYSTONIAS

Primary generalized dystonia, also referred to as *primary torsion dystonia* or *dystonia musculorum deformans,* is caused by a group of genetic disorders with onset in childhood (Fig. 637.6). Many of these disorders are autosomal dominant with incomplete penetrance, but genetic dystonias may also appear sporadically or be inherited in an autosomal recessive, X-linked, or mitochondrial pattern. Children are more likely to manifest with or progress to generalized dystonia, whereas segmental or focal dystonia is more common in adolescents and adults.

One form, which occurs more commonly in the Ashkenazi Jewish population, is caused by a dominant change in *DYT1* coding for the adenosine triphosphate (ATP)–binding protein torsinA. The initial manifestation of ***DYT1* dystonia** is often intermittent unilateral posturing of a lower extremity, which assumes an extended and rotated position. Ultimately, all four extremities and the axial musculature can be affected, but the dystonia may also remain localized to one limb. Cranial involvement can occur in *DYT1* dystonia, but it is uncommon compared with non-*DYT1* dystonias. There is a wide clinical spectrum, varying even within families. If a family history of dystonia is absent, the diagnosis should still be considered, given the intrafamilial variability in clinical expression.

More than two dozen loci for genes for **torsion dystonia** have been identified *(DYT1-DYT31).* More sophisticated genetic testing and genotype-phenotype correlation have eliminated some of these designations, and others have been linked to specific chromosomal regions but not yet to a specific gene. In this text we review only those linked definitively to a specific gene.

One is the autosomal dominant disorder **dopa-responsive dystonia (DRD, *DYT5a*)**, also called *Segawa syndrome.* The gene for DRD codes

for guanosine triphosphate cyclohydrolase 1, the rate-limiting enzyme for tetrahydrobiopterin synthesis, which is a cofactor for synthesis of the neurotransmitters dopamine and serotonin. Thus the genetic alteration results in dopamine deficiency. The hallmark of the disorder, particularly in adolescents and adults, is diurnal variation: symptoms worsen as the day progresses and may transiently improve with sleep. Early-onset patients, who tend to present with delayed or abnormal gait from dystonia of a lower extremity, can easily be confused with patients with dystonic cerebral palsy. It should be noted that in the presence of a progressive dystonia, diurnal fluctuation, or loss of previously achieved motor skills, a prior diagnosis of cerebral palsy should be reexamined. **DRD responds dramatically to small daily doses of levodopa**. The responsiveness to levodopa is a sustained benefit, even if the diagnosis is delayed several years, as long as contractures have not developed. More rarely, an autosomal recessive form of this disorder is caused by alterations in the *TH* gene.

Myoclonus dystonia (DYT11), caused by alterations in the *SCGE* gene, is characterized by dystonia involving the upper extremities, head, and/or neck, as well as myoclonic movements in these regions. Although a combination of myoclonus and dystonia typically occurs, each manifestation can present in isolation. When repetitive, the myoclonus may take on a tremor-like appearance, termed *dystonic tremor*. Improvement in symptoms after alcohol ingestion, reported by affected adult family members, may be a helpful clue to this diagnosis.

Common to the inherited dystonias, there is considerable intrafamilial variability in clinical manifestations, distribution, and severity of dystonia. In primary dystonias, although the main clinical features are motor, there may be an increased risk for major depression. Anxiety, obsessive-compulsive disorder, and depression have all been reported in myoclonus-dystonia syndrome. Screening for psychiatric comorbidities should not be overlooked in this population.

Table 637.13 Clues Relating to the Signs and Symptoms That Suggest a Functional Movement Disorder

1. Abrupt onset
2. Inconsistent movements (changing characteristics over time; pattern, body distribution, rapidly varying severity)
3. Incongruous movements and postures (movements that do not fit with recognized patterns or with normal physiologic patterns)
4. Presence of certain types of abnormal movements that are fairly common among individuals with functional movement disorders, such as:
   - Rhythmical shaking
   - Bizarre gait
   - Deliberate slowness carrying out requested voluntary movement
   - Bursts of verbal gibberish
   - Excessive startle (bizarre movements in response to sudden, unexpected noise or threatening movement)
5. Presence of additional types of abnormal movements that are not known to be part of the primary or principal movement pattern that the patient manifests
6. Manifesting exhaustion, excessive fatigue
7. Delayed, often excessive, startle response to a stimulus
8. Spontaneous remissions
9. Decrease or disappearance of movements with distraction
10. Disappearance of tremors when handling treasured objects
11. Entrainment of the tremor to the rate of the requested rapid successive movement the patient is asked to perform
12. Response to placebo, suggestion, or psychotherapy
13. Dystonia beginning as a fixed posture
14. Twisting facial movements that move the mouth to one side or the other (note that organic dystonia of the facial muscles usually does not move the mouth sideways)

From Jankovic J, Hallett M, Okun MS, et al., eds. *Principles and Practice of Movement Disorders*, 3rd ed. Philadelphia: Elsevier; 2022: Table 27.2, p. 598.

DRUG-INDUCED DYSTONIAS

A number of medications are capable of inducing involuntary movements or drug-induced movement disorders in children and adults. Dopamine-blocking agents, including antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine), as well as atypical antipsychotics (e.g., risperidone, aripiprazole) can produce acute dystonic reactions or delayed (tardive) drug-induced movement disorders. **Acute dystonic reactions**, occurring in the first days of exposure, typically involve the face and neck and manifest as torticollis, retrocollis, oculogyric crisis, or tongue protrusion. Life-threatening presentations with laryngospasm and airway compromise can also occur, requiring prompt recognition and treatment of this entity. Intravenous diphenhydramine 1-2 mg/kg/dose (maximum dose 50 mg) may rapidly reverse the drug-related dystonia. The degree of potency of the dopamine blocker, young age, and prior dystonic reactions may be predisposing factors. Acute dystonic reactions have also been described with cetirizine.

Severe rigidity combined with high fever, autonomic symptoms (tachycardia, diaphoresis), delirium, and dystonia are signs of **neuroleptic malignant syndrome**, which typically occurs a few days after starting or increasing the dose of a neuroleptic drug or in the setting of withdrawal from a dopaminergic agent. In contrast to acute dystonic reactions, which take place within days, neuroleptic malignant syndrome typically occurs within a month of medication initiation or dose increase.

Delayed-onset involuntary movements, **tardive dyskinesias**, develop in the setting of chronic neuroleptic use, usually longer than 3 months. Involvement of the face, particularly the mouth, lips, and/or jaw with chewing or tongue thrusting, is characteristic. The risk of tardive dyskinesia, which is much less frequent in children compared with adults, increases as the medication dose, duration of treatment, and polypharmacy increase. There are data to suggest that children

Table 637.14 Classification of Dystonias by Affected Body Part

TYPE OF DYSTONIA	NO. OF BODY PARTS AFFECTED	DETAIL
Focal*	1	• Eyelids (blepharospasm) • Mouth (oromandibular dystonia, musician's cramp) • Larynx (dystonic adductor dysphonia, "whispering dysphonia") • Neck (cervical dystonia, previously known as spasmodic torticollis) • Hand and arm (writer's cramp)
Segmental	≥2 contiguous body parts	• Axial (neck and trunk) • Brachial (1 arm and trunk; both arms ± neck ± trunk) • Crural (1 leg and trunk; both legs ± trunk)
Multifocal	≥2 noncontiguous body parts	Faciobrachial (blepharospasm and writer's cramp)
Hemidystonia	≥2	Ipsilateral arm and leg
Generalized	≥3	Trunk and ≥2 other sites ± leg involvement

*Some localized dystonias may spread and eventually generalize.
From Klein C, Lohmann K, Marras C, et al. Hereditary dystonia overview. 2003 Oct 28 [Updated 2017 Jun 22]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 1.

Table 637.15 Causes of Dystonia in Childhood

STATIC INJURY/STRUCTURAL DISORDERS
Cerebral palsy
Hypoxic-ischemic injury
Kernicterus
Head trauma
Encephalitis
Tumors
Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)
Congenital malformations

HEREDITARY/DEGENERATIVE DISORDERS
DYT1 (early-onset primary torsion dystonia, *TOR1A*)
DYT2 (early-onset dystonia with craniocervical involvement, autosomal recessive)
DYT3 (adult-onset dystonia-parkinsonism, X-linked *TAF1*)
DYT4 (adult-onset spasmodic dysphonia, *TUBB4A*)
DYT5 (dopa-responsive dystonia, *GCH1*)
DYT6 (adult-onset torsion dystonia with craniocervical and laryngeal involvement, *THAP1*)
DYT7 (adult-onset cervical dystonia)
DYT8 (paroxysmal nonkinesigenic dyskinesia, *MR1*)
DYT10 (paroxysmal kinesigenic dyskinesia, *PRRT2*)
DYT11 (myoclonus dystonia, *SGCE*)
DYT12 (rapid-onset dystonia-parkinsonism, *ATP1A3*)
DYT16 (early-onset dystonia-parkinsonism, autosomal recessive, PRKRA)
DYT18 (paroxysmal exercise-induced dyskinesia, *SLC2A1*)
DYT23 (adult-onset cervical dystonia and myoclonus, CACNA1B/CIZ1)
DYT24 (craniocervical dystonia with limb tremor, *ANO3*)
DYT26 (early-onset myoclonic dystonia, KCTD17)
DYT27 (early-onset segmental dystonia, autosomal recessive, COL6A30
DYT 28 (early-onset generalized dystonia, KMT2B)
DYT29 (early-onset dystonia with optic atrophy and basal ganglia abnormalities, MECR)
DYT30 (progressive early-onset dystonia, VPS16)
DYT31 (early-onset multifocal or generalized dystonia, autosomal recessive, AOPEP)
Fahr disease (often caused by hypoparathyroid disease)
Neurodegeneration with brain iron accumulation
Huntington disease (particularly the Westphal variant, IT15-4p16.3)
Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)
Neuronal ceroid-lipofuscinoses (NCLs)
Rett syndrome
Striatal necrosis
Leigh disease
Leber hereditary ocular neuropathy (LHON)
Neuroacanthocytosis
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)
Ataxia-telangiectasia
POLG1 gene alterations
Tay-Sachs disease
Sandhoff disease
Niemann-Pick type C
GM_1 gangliosidosis
Mitochondrial membrane protein–associated neurodegeneration (MPAN)
Metachromatic leukodystrophy (MLD)
Lesch-Nyhan disease
Pantothenate kinase–associated neurodegeneration (PKAN)

METABOLIC DISEASE
Glutaric aciduria types 1 and 2
Acyl-coenzyme A (CoA) dehydrogenase deficiencies
Dopa-responsive dystonia
Aromatic l-amino acid decarboxylase deficiency
Aminolevulinic acid dehydrase
Biotin-responsive basal ganglia disease
Mitochondrial disorders
Wilson disease
Vitamin E deficiency
Homocystinuria
Methylmalonic aciduria
Tyrosinemia

DRUGS/TOXINS
Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)
Calcium channel blockers
Stimulants (amphetamine, cocaine, ergot alkaloids)
Anticonvulsants (carbamazepine, phenytoin)
Thallium
Manganese
Carbon monoxide
Ethylene glycol
Cyanide
Methanol
Wasp sting

PAROXYSMAL DISORDERS
Paroxysmal kinesigenic choreoathetosis (PKD)
Paroxysmal nonkinesigenic choreoathetosis (PNKD)
Paroxysmal exercise-induced dystonia (PED)
Complex migraine
Alternating hemiplegia of childhood (AHC)
Paroxysmal torticollis of infancy

DISORDERS THAT MIMIC DYSTONIA
Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)
Arnold-Chiari malformation type II
Atlantoaxial subluxation
Syringomyelia
Posterior fossa mass
Cervical spine malformation (including Klippel-Feil syndrome)
Skew deviation with vertical diplopia causing neck twisting
Juvenile rheumatoid arthritis
Sandifer syndrome (associated with hiatal hernia in infants)
Spasmus nutans
Tics
Infant masturbation
Spasticity
Myotonia
Rigidity
Stiff-person syndrome
Isaac syndrome (neuromyotonia)
Startle disease (hyperekplexia)
Neuroleptic malignant syndrome
Central herniation with posturing
Psychogenic dystonia

From Sanger TD, Mink JW. Movement disorders. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: Saunders; 2012: Box 68-2.

with autism spectrum disorders may also be at increased risk for this drug-induced movement disorder. Unlike acute dystonic reactions and neuroleptic malignant syndrome, discontinuation of the offending agent may not result in clinical improvement. In these patients, use of dopamine-depletors, such as reserpine, tetrabenazine, or valbenazine, may prove helpful.

Therapeutic doses of phenytoin, carbamazepine, or valproate rarely cause progressive dystonia in children with epilepsy, particularly in those who have an underlying structural abnormality of the brain.

During evaluation of new-onset dystonia, a careful history of prescriptions and potential medication exposures is critical

Table 637.16 Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene alteration (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis
GM_1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity
Huntington disease	Parkinsonism Epilepsy Family history of Huntington disease
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Rapid-onset dystonia parkinsonism (DYT12)	Acute onset Distribution face > arm > leg Prominent bulbar signs
Rett syndrome	Female Developmental regression after a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

CEREBRAL PALSY

See Chapter 638.1.

METABOLIC DISORDERS

Disorders of monoamine neurotransmitter metabolism, of which dopa-responsive dystonia is one, present in infancy and early childhood with dystonia, hypotonia, oculogyric crises, and/or autonomic symptoms. Common comorbidities such as epilepsy, developmental delay, and microcephaly, which are also found in cerebral palsy and other more common disorders, likely contribute to underdiagnosis of this group of rare diseases. The more common disorders in this group include DRD, tyrosine hydroxylase deficiency, and aromatic amino acid decarboxylase deficiency. With the exception of aromatic amino acid decarboxylase deficiency, most do respond at least partially to

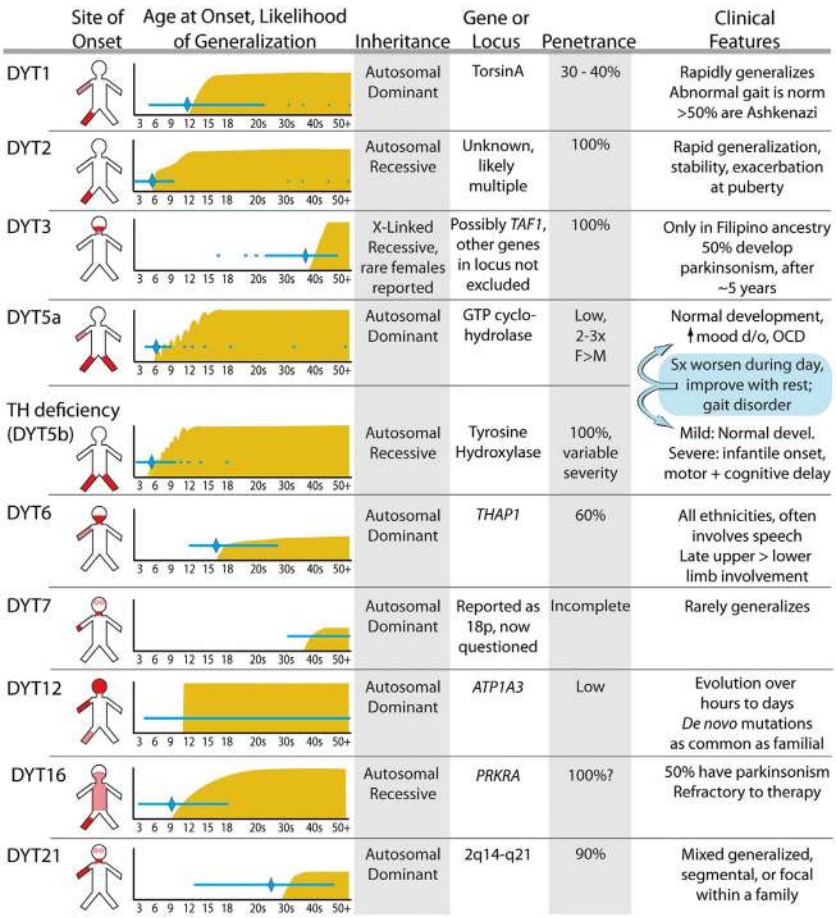

Fig. 637.6 Syndromes with dystonia as the presenting or a predominant feature; primary dystonias or dystonia-plus syndromes that commonly begin with dystonia are listed. The most common sites of dystonia onset are indicated on the homunculus in *red*, with less common sites of onset in *pink*. The distribution in age of onset is indicated by a *blue bar*, with the mean age indicated by a *blue diamond*, and rare but reported outliers indicated by *extralinear blue dashes*. Typical rates of progression and the likelihood of generalization are indicated by *yellow plots*. Note that homunculi and plots represent the most common clinical presentations, but variations on these axes are not uncommon. *(From Waugh JL, Sharma N. Clinical neurogenetics: dystonia from phenotype to genotype. Neurol Clin. 2013;31:969–986, Fig. 1.)*

levodopa. Abnormalities of the dopamine transporter (DAT) can also present in infancy with dystonia.

Wilson disease is an autosomal recessive inborn error of copper transport characterized by cirrhosis of the liver and degenerative changes in the central nervous system, particularly the basal ganglia (see Chapter 405.2). It has been determined that there are multiple alterations in the Wilson disease gene *(WND)*, accounting for the variability in presentation of the condition. The neurologic manifestations of Wilson disease rarely appear before age 10 years, and the initial sign is often progressive dystonia. Tremors of the extremities develop, unilaterally at first, but they eventually become coarse, generalized, and incapacitating. Other neurologic signs of Wilson disease relate to a progressive basal ganglia disease, such as parkinsonism, dysarthria, dysphonia, and choreoathetosis. Less frequent are ataxia and pyramidal signs. The MRI or CT scan shows ventricular dilation in advanced cases, with atrophy of the cerebrum, cerebellum, and/or brainstem, along with signal intensity change in the basal ganglia, thalamus, and/or brainstem, particularly the midbrain.

Pantothenate kinase–associated neurodegeneration is a rare autosomal recessive neurodegenerative disorder. Many patients have alterations in pantothenate kinase 2 *(PANK2)* localized to mitochondria in neurons. The condition usually begins before 6 years of age and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity (tissue necrosis and edema), or *eye-of-the-tiger* sign (Fig. 637.7). Neuropathologic examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. Similar disorders of high brain iron content without *PANK2* gene alterations, including phospholipase A2–associated neurodegeneration (PLAN), mitochondrial membrane protein–associated neurodegeneration (MPAN), beta-propeller protein–associated neurodegeneration (BPAN), neuroferritinopathy, aceruloplasminemia, and others, have been grouped as disorders of **neurodegeneration with brain iron accumulation** (Table 637.17). Patterns of iron deposition visualized by brain MRI have shown utility in differentiating these disorders.

Biotin-responsive basal ganglia disease manifests with episodes of acute dystonia, external ophthalmoplegia, and encephalopathy. *SLC19A3* is the responsible mutated gene. MRI demonstrates involvement of the basal ganglia, with vasogenic edema and the *bat-wing* sign (Fig. 637.8). **Treatment with biotin and thiamine results in improvement in 2-4 days** (Table 637.18).

Although dystonia may present in isolation as the first sign of a metabolic or neurodegenerative disorder, this group of diseases should be considered mainly in those who demonstrate signs of systemic disease (e.g., organomegaly, short stature, hearing loss, vision impairment, epilepsy) and those with episodes of severe illness, evidence of regression, or cognitive impairment. Table 637.16 outlines additional features suggestive of specific disorders.

OTHER DISORDERS

Although uncommon, movement disorders, including dystonia, may be part of the presenting symptoms of **complex regional pain syndrome**. Onset of involuntary movements within 1 year of the traumatic event, an affected lower limb, pain disproportionate to the inciting event, and changes in the overlying skin and blood flow to the affected area suggest complex regional pain syndrome. Although sustained dystonia can produce pain or discomfort, complex regional pain syndrome should be considered in those who have a prominent component of pain and a recent history of trauma to the affected limb.

Paroxysmal dyskinesias can cause a combination of dystonic posturing and choreoathetoid movements (Table 637.19). By far the most

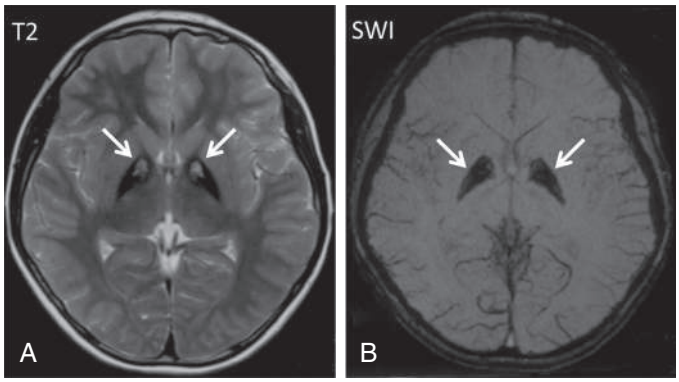

Fig. 637.7 Pantothenate kinase–associated neurodegeneration (PKAN). **A,** Axial T2-weighted image showing symmetric hypointensity in the bilateral globi pallidi with central hyperintensity (eye-of-the-tiger sign, *arrows*). **B,** Axial susceptibility-weighted image (SWI) image showing hypointensity in the globi pallidi representing increased iron accumulation *(arrows). (From Bosemani T, Meoded A, Poretti A. Susceptibility-weighted imaging in pantothenate kinase-associated neurodegeneration. J Pediatr. 2014;164:212.)*

common is **paroxysmal kinesigenic dyskinesia** (PKD), which most commonly presents around the age of 10 years with attacks of chorea or dystonic posturing lasting seconds to minutes. The movements are most commonly precipitated by voluntary movements and are often easily controlled by low doses of carbamazepine or other antiepileptic medications. Many patients have a gene alteration in *PRRT2,* a transmembrane protein that interacts with SNAP 25. **Paroxysmal nonkinesigenic dyskinesia** (PNKD) is characterized by prolonged attacks precipitated by emotional stress or alcohol rather than voluntary movement. The attacks are less frequent, perhaps a few times per year or less, but they may last hours. PNKD is less responsive to treatment than PKD. The rarest form of paroxysmal dyskinesia is **exercise-induced dystonia**. Dystonia in this disorder occurs after periods of prolonged exercise and tends to last between 10 and 30 minutes. Patients may also suffer from migraines and epilepsy. This disorder is caused by gene alteration in *SLC2A1,* which encodes the glucose transporter type 1 protein and is part of GLUT-1 deficiency syndrome. Dystonia may be present in classic GLUT-1 deficiency, although it is generally not the presenting sign. Case reports indicate some patients may have improvement in dystonia with the ketogenic diet.

There are disorders unique to childhood that warrant exploration in this section as well. **Benign paroxysmal torticollis of infancy** is

Table 637.17 Overview of NBIA Conditions and Genes (If Known)

CONDITION (ACRONYM)	SYNONYM	GENE	CHROMOSOMAL POSITION	AREAS OF HIGHEST IRON DENSITY	PATHOLOGIC MANIFESTATIONS
PKAN	NBIA1	*PANK2*	20p13	GP, eye of the tiger sign (central hyperintensity within a surrounding area of hypointensity).	GP with variable involvement of adjacent structures (putamen and internal capsule). Spheroid bodies. Only occasional peripheral manifestation.
PLAN	NBIA2, PARK14	*PLA2G6*	22q12	GP. Additional SN involvement in some.	Widespread cortical alpha-synuclein-positive Lewy body pathology. Presence of tau. Degeneration of the cerebellum, optic pathway and of brainstem and spinal cord long tracts.
FAHN	SPG35	*FA2H*	16q23	GP. Often white matter changes.	No human brain data. In animal models, cerebellar abnormalities, demyelination, and profound axonal loss in the CNS.
MPAN	—	C19orf12	19q12	GP and SN.	GP and SN iron-containing deposits, axonal spheroids, Lewy body-like inclusions, and tau-positive inclusions.
Kufor-Rakeb disease	PARK9	*ATP13A2*	1p36	Putamen and caudate.	No human brain data. On peripheral nerve biopsy cytoplasmic inclusion bodies resembling irregular primary lysosomes.
Aceruloplasminemia	—	*CP*	3q23	Basal ganglia, thalamus, dentate nuclei, and cerebral and cerebellar cortices. Liver, pancreas.	Basal ganglia and dentate nuclei, extending to the cerebral cortex.
Neuroferritinopathy	—	*FTL*	19q13	Caudate, GP, putamen, SN, and red nuclei.	Ferritin-positive spherical inclusions in iron-rich areas, mainly in the posterior putamen and cerebellum. Spheroids immunoreactive to ubiquitin and tau. Hepatic iron deposits may be present.
SENDA syndrome	—	n.k.	n.k.	GP and SN. White matter changes.	n.k.
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous.	n.k.

CP, Ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FTL, ferritin light chain; GP, globus pallidus; MPAN, mitochondrial-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, phospholipase A2–associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SN, substantia nigra; SPG, spastic paraplegia; n.k., not known.
From Schneider SA, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation. *Sem Pediatr Neurol*. 2012;19:57–66, Table 1, p. 58.

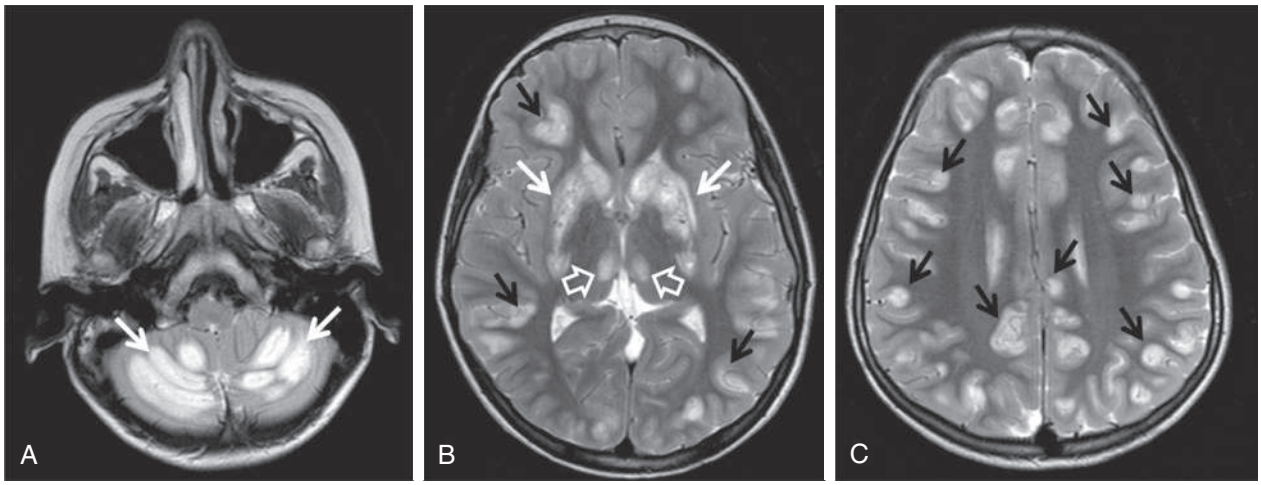

Fig. 637.8 Biotin-responsive basal ganglia disease. An initial brain MRI showed high signal intensity alterations on T2-weighted images bilaterally involving the (**A**) cerebellum *(arrows)*, (**B**) basal ganglia *(white arrows)*, and medial nucleus of the thalamus *(open arrows)* and (**B, C**) cerebral cortex *(black arrows)*. *(Modified from Tabarki B, Al-Sheikh F, Al-Shahwan S, Zuccoli G. Bilateral external ophthalmoplegia in biotin-responsive basal ganglia disease. J Pediatr. 2013;162:1291–1292.)*

Table 637.18 Dystonia Treatment

Nonspecific dystonia management	Trial of carbidopa/levodopa Botulinum toxin injection Also consider: neuroleptics, dopamine depletors Surgical options: baclofen pump, deep brain stimulation
Neurotransmitter disorders, including Segawa syndrome	Carbidopa/levodopa (except aromatic L-amino acid decarboxylase deficiency, which may worsen), dopamine agonists
Acute drug-induced dystonic reaction	Diphenhydramine, removal of offending agent
Tardive dyskinesia	Dopamine depletors, removal of offending agent
Paroxysmal dyskinesias	Carbamazepine, other AEDs (especially paroxysmal kinesogenic dyskinesia), acetazolamide (paroxysmal nonkinesogenic dyskinesia), ketogenic diet (exercise-induced dyskinesia)
Biotin-responsive basal ganglia disease	Biotin and thiamine
Complex regional pain syndrome and functional movement disorders	Physical therapy, occupational therapy, cognitive behavioral therapy

characterized by recurrent episodes of cervical dystonia beginning in the first few months of life. The torticollis may alternate sides from one episode to the next and may also persist during sleep. Associated signs and symptoms include irritability, pallor, vomiting, vertigo, ataxia, and occasionally limb dystonia. The family history is often notable for migraine and/or motion sickness in first-degree relatives. Despite the high frequency of spells, imaging studies are normal, and the outcome is uniformly benign with resolution by 3 years of age.

In **alternating hemiplegia of childhood (AHC)**, episodic hemiplegia affecting either side of the body is the hallmark of the disorder. However, patients are also affected by episodes of dystonia, ranging from minutes to days in duration. On average, both features of the disorder commence at approximately 6 months of age. Episodic abnormal eye movements are observed in a large proportion of patients (93%) with onset as early as the first week of life. AHC is associated with pathogenic variants in *ATP1A2* and *ATP1A3*. The disorder can be triggered by fluctuations in temperature, certain foods, or water exposure. Over time, epilepsy and cognitive impairment emerge, and the involuntary movements change from episodic to constant. Infantile onset and the paroxysmal nature of symptoms early in the disease course are key features to this diagnosis. Another disorder linked to variants in *ATP1A3*, **rapid-onset dystonia parkinsonism (RODP)**, often presents in adolescents with acute to subacute progressive dystonia and bradykinesia, often after a stressor such as recent illness. Although the classic forms of these two disorders, AHC and RODP, are generally caused by nonoverlapping gene alterations, molecular genetics has allowed the identification of patients with intermediate phenotypes.

Although it is a diagnosis of exclusion, the presence of odd movements or selective disability may indicate a functional dystonia in older children. There is considerable overlap in features of organic and **functional movement disorders**, making the diagnosis difficult to establish. Both organic and psychogenic movement disorders have the potential to worsen in the setting of stress and may dissipate with relaxation or sleep. The history should include a review of recent stressors, psychiatric symptoms, and exposure to others with similar disorders. On examination, a changing movement disorder, inconsistent motor or sensory exam, or response to suggestion is supportive of a possible psychogenic movement disorder. Early recognition of this disorder may lessen morbidity caused by unnecessary diagnostic and interventional procedures (see Table 637.13).

Practice guidance had once involved targeted, single-gene testing; currently the most appropriate approach to a child with dystonia not explained by a clear mechanism of injury will be a dystonia gene sequencing panel, followed by a microarray and then whole exome or genome sequencing if the panel was unrevealing. This includes children previously diagnosed with cerebral palsy but without severe perinatal distress and/or with injury solely confined to the basal ganglia on brain imaging. In families with a known history of a specific genetic dystonia, single-gene testing is the most appropriate initial approach. Because dystonia panels may vary in which genes they include, a knowledge of phenotypic features expected in various disorders can ensure that the dystonia panel selected is appropriate to a given patient. An approach to diagnostic testing is noted in Table 637.20 and Figure 637.9.

TREATMENT

Acute Treatment

Status dystonicus, or "dystonic storm," is a rare but potentially life-threatening emergency that often requires management in an intensive care setting. It is characterized by severe frequent dystonic posturing leading to vital sign instability, exhaustion, and/or muscle breakdown. It is likely underrecognized. About half of patients have

Table 637.19 Classification of Primary and Epilepsy Paroxysmal Dyskinesias

	PKD	PNKD	PED	PHD*
Inheritance	AD	AD	AD	Usually sporadic
Gender M:F	4:1	2:1	2:3	7:3
Age at onset, yr	<1-20	<1-20s	2-30	4-20s
Phenomenology of abnormal movements	Dystonia with or without chorea/ballism, unilateral or bilateral	Dystonia with or without choreoathetosis, unilateral or bilateral, rarely spasticity	Dystonia, sometimes in combination with choreoathetosis, unilateral or bilateral	Dystonia, chorea, ballism
Triggers	Sudden movement, change in direction, acceleration, startle	Alcohol, caffeine, emotions, fatigue	Prolonged exercise, muscle vibration	Sleep
Duration of paroxysms	Seconds up to 5 min	2 min to 4 hr	5 min to 2 hr	30 min up to 50 min
Frequency of paroxysms	1 per month to 100 per day	Few per week to few in a lifetime	Few per month	Few per year to few per night
Genetics	1. EKD1: 16p11.2-q12.1 (DYT10) with *PRRT2* gene within this region 2. EKD2: 16q13-q22.1 (DYT19) 3. EKD3: no variant on chromosome 16	1. *PNKD*: 2q35 (DYT8) 2. *SCL2A1*: chromosome 1 (DYT9) 3. *KCNMA1*: 10q22 4. Locus on 2q31 (DYT20)	1. *SCL2A1*: 1p35-p31.3 (DYT18)	1. *CHRNA4*: 20q13.2-q13.3 2. *CHRNB2*: chromosome 1q21 3. Locus on chromosome 15q24 4. Locus on chromosome 8p21
Treatment	Anticonvulsants (carbamazepine, phenytoin, others)	Avoiding triggers, benzodiazepines (clonazepam)	Avoiding triggers, ketogenic diet (in GLUT-1 deficiency)	Anticonvulsants

*Also known as autosomal dominant nocturnal frontal lobe epilepsy.
AD, Autosomal dominant; PED, paroxysmal exercise-induced dyskinesia; PHD, paroxysmal hypogenic dyskinesia (a seizure disorder); PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia.
From Joseph SA. Movement disorders in childhood. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 40.2, p. 719.

Table 637.20 Genetic Testing

All patients with early-onset dystonia without a clear family history or clear mechanism of injury, including those with "cerebral palsy" in the setting of only mild perinatal insults: comprehensive dystonia panel, consider microarray and whole exome sequencing if unrevealing
If the following features are present, ensure the appropriate gene is included in panel testing:
Limb-onset dystonia in early adolescence: torsinA (DYT1), especially with Ashkenazi ancestry
Cervical/cranial onset in mid-adolescence: THAP1 (DYT6), especially with strained speech (spasmodic dysphonia)
Normal gait in the morning, disabled by the evening: give levodopa; if symptoms improve, check guanosine triphosphate (GTP) cyclohydrolase 1 (DYT5a); tyrosine hydroxylase (DYT5b)
Mixed myoclonus and dystonia with onset throughout childhood: ε-sarcoglycan (DYT11), especially if symptoms are alcohol responsive in family members
Onset of dystonia ± parkinsonism over hours to days: ATP1A3 (DYT12), especially if symptoms progress in a rostral to caudal fashion
Paroxysmal dystonia ± chorea triggered by:
- Sudden movement: PRRT2 (DYT10), especially if there is a family history of complex migraines or benign seizures/chorea in infancy
- Caffeine or alcohol: PNKD (DYT8), especially if symptoms are rare but last many minutes to hours
- Exertion or if the ratio of cerebrospinal fluid/serum glucose is less than 0.5, SLC2A1 (DYT18), especially in families with unexplained cognitive delay or seizure disorder

Modified from Waugh JL, Sharma N. Clinical neurogenetics: dystonia from phenotype to genotype. *Neurol Clin*. 2013;31:969–986, Box, p. 975.

an underlying known cause of dystonia, such as cerebral palsy. Infections and changes in medications are frequently cited triggers. In addition, dystonic storm can also present in children with no prior history of movement disorders secondary to neurologic insults such as encephalitis or stroke. There are no consensus guidelines on treatment, but in general aggressive management with antidystonic agents such as anticholinergics, trihexyphenidyl, benzodiazepines, and baclofen is recommended. Midazolam infusion is generally chosen when sedation is needed because of its muscle relaxing properties. Intubation and other critical care supportive measures are commonly needed during treatment.

Chronic Treatment

Treatment strategy is summarized in Table 637.18. Children with Segawa syndrome and other neurotransmitter disorders generally have a robust response to low-dose carbidopa-levodopa. The evidence for efficacy in other causes of dystonia such as cerebral palsy is mixed. However, because neurotransmitter disorders are underdiagnosed and low-dose carbidopa-levodopa is generally well tolerated, a treatment trial is recommended unless there is a clear family history of a non–dopa-responsive dystonia.

Children with generalized dystonia, including those with involvement of the muscles of swallowing, may respond to the anticholinergic agent trihexyphenidyl. Titration occurs slowly over the course of months in an effort to limit untoward side effects, such as urinary retention, mental confusion, or blurred vision. Oral baclofen may also be used, although sedation may be a problem at higher doses. Dopamine depletors may be considered in treatment-refractory cases. Additional drugs that may be effective include benzodiazepines, neuroleptics, and antiepileptic drugs such as carbamazepine.

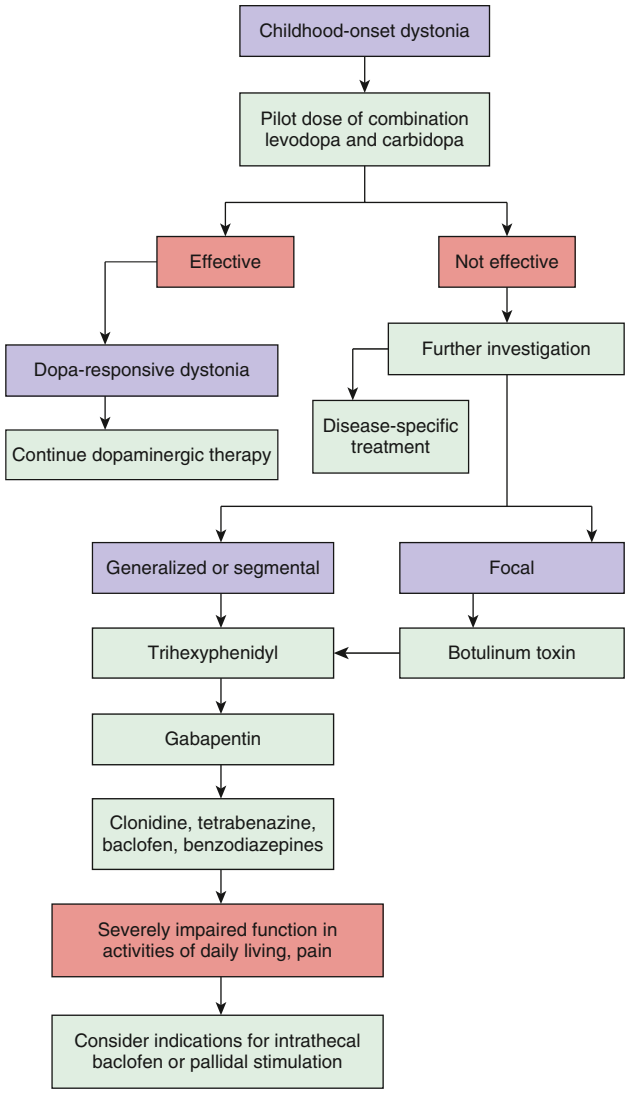

Fig. 637.9 Algorithm showing therapeutic approaches to the management of childhood-onset dystonia. Pharmacologic agents should be used sparingly where possible. High doses and polypharmacy inevitably arise when dystonia is severe enough to cause pain and interferes with daily cares, sitting comfort, and sleep. As with intractable epilepsy, consideration for functional neurosurgery should be considered when two or more drugs have failed to control dystonia. *(From Lin JP. Advances in pharmacotherapies for movement disorders in children: current limitations and future progress. Curr Opin Pediatr. 2017;29:652–664, Fig. 6.)*

Oral medications are not the only options for treatment. Segmental dystonia, such as torticollis, often responds well to botulinum toxin injections. Safe dosage restrictions limit the use of botulinum toxin in generalized dystonia, but it may be used as a supplemental treatment if symptoms in particular muscle groups are the most bothersome or functionally impairing.

Intrathecal baclofen delivered through an implantable constant-infusion pump may be helpful in some patients. It is often more effective in the lower extremities than the upper extremities.

Deep brain stimulation with leads implanted in the globus pallidus is most helpful for children with severe primary generalized dystonia. Deep brain stimulation may also be of benefit in children with secondary dystonias, such as cerebral palsy, although the effect is not as robust. A combination of factors are thought to reduce the efficacy in cerebral palsy, including a lack of normal neural substrate, reduced opportunity for motor learning during critical developmental windows, and the frequent presence of other neurologic impairments such as spasticity and weakness. It should only be considered if a trial of two to three oral agents has been unsuccessful.

DRUG-INDUCED DYSTONIAS

In the case of drug-induced dystonias, removal of the offending agent and treatment with intravenous diphenhydramine typically suffice. For neuroleptic malignant syndrome, dantrolene may be indicated. As tardive symptoms may not always respond to removal of the offending agent, dopamine depletors may be necessary

Visit Elsevier Ebooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 638

Encephalopathies

Elizabeth Barkoudah

Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive or static. The etiologies of the encephalopathies in children include infectious, toxic (carbon monoxide, drugs, lead), metabolic, genetic, and ischemic causes. Hypoxic-ischemic encephalopathy is discussed in Chapter 122.4.

638.1 Cerebral Palsy

Elizabeth Barkoudah

See also Chapters 56 and 637.4.

Cerebral palsy (CP) is a complex and heterogeneous disorder denoting a group of permanent motor conditions that cause physical disability in human development, chiefly in the various areas of body movement. It can be defined as a central motor dysfunction affecting muscle tone, posture, and movement that is attributed to *nonprogressive* disturbances in the developing fetal or infant brain. Despite being described as a nonprogressive disorder (historically referred to as *static encephalopathy* by some), the clinical expression of brain injury or insult changes over time. Therefore the condition should be viewed as a dynamic disorder that evolves because of factors such as growth, nervous system maturation, and aging.

Several classification systems are used to describe CP, which reflects the complexity underlying the heterogeneity of cause, distribution, type of motor involvement, and severity. Consideration of associated manifestations such as cognitive deficits, seizures, communication difficulties, visual impairment, and so on, as well as addressing the medical, surgical, and psychosocial needs requires a multidisciplinary approach.

EPIDEMIOLOGY AND ETIOLOGY

Cerebral palsy is the most common neuromotor disorder in childhood, with an overall incidence of 2.6-2.9 cases per 1,000 live births in the United States. Within developed countries, both cross-sectional and cohort-based studies estimate prevalence of CP as nearly 1-4 per 1,000 live births. In developing countries, available estimates of prevalence are similar. The estimated lifetime cost to care for someone with CP in 2003, according to the Centers for Disease Control and Prevention (CDC), was $1 million. Adjusting for inflation, this is now $1.2 million per individual and will continue to increase over time.

CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other etiologies that produce a common group of neurologic phenotypes. Thus CP should be based on phenotype rather than etiology. The prevalence of CP is higher for children born preterm or at a low birthweight, though this is influenced by sex, ethnicity, and socioeconomic status. There is a 30–40% greater prevalence in males. Prevalence is higher in low- and middle- versus

high-income communities. Rates of CP have only recently begun to decrease in developed countries, though direct interpretation of trends is complicated by changing patterns of neonatal care and survivorhood. Although overall prevalence has fluctuated, the specific etiologies and injury patterns have shifted over time given advances in perinatal and neonatal management.

In addition to prematurity and birthweight, numerous other prenatal and perinatal risk factors have been reported, though for many of these, a causal relationship has not been established. These risk factors include antenatal infection (chorioamnionitis, urinary tract infection), multiple pregnancy, and neonatal infection. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. CP is most often multifactorial, and multiple risk factors coexist.

The cerebral disruption associated with CP can occur prenatally, perinatally, or postnatally in the first 2 years of life given that brain development is ongoing during this critical period. Congenital CP (due to cerebral injury/maldevelopment before or during birth) accounts for 85–90% of total cases, whereas acquired CP (due to cerebral injury after 1 month of life) is responsible for the remaining cases.

One can also consider different etiologies based on premature versus term births. The major lesions that contribute to CP in preterm infants are **intracerebral hemorrhage** and **periventricular leukomalacia** (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. The incidence of cystic PVL caused by a more diffuse injury pattern is being replaced by focal necrosis. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 weeks of gestational age in former preterm infants are a predictor of later CP. MRI with diffusion tensor imaging is being used to map white matter tracts more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 638.1).

In term births, causes historically have primarily been thought to be by events during labor and delivery causing hypoxia. The mechanisms are predominately the result of cerebral ischemia and excitotoxicity. The cause can be obvious (i.e., placental abruption, meconium aspiration), though at other times the etiology can be difficult to pinpoint. Risk factors can include eclampsia, hypercoagulability, and placental pathology. For some, no predisposing clinical factors are identified. **Hypoxic-ischemic encephalopathy (HIE)** may be decreasing as an apparent cause of CP in developed countries. Therapeutic hypothermia may reduce the risk of CP in term patients with HIE.

There are several causes of acquired CP. The most common cause in this category is perinatal stroke, which can be ischemic, hemorrhagic, or thromboembolic in nature. The second most common cause is meningitis or encephalitis during infancy. Kernicterus is a rare cause of CP in developed countries, though cases (particularly in very preterm infants) persist.

Cryptogenic CP traditionally refers to an individual in which no clear perinatal etiology has been identified and accounts for ~30% of cases. Chromosomal copy number variants and single gene disorders have been identified in ~30% of patients with CP. Monogenic genetic variants have been identified in ~30% of cases who met diagnostic criteria for CP. A wide range of genes have been implicated in CP phenotypes, though a few are relatively more frequently seen including *TUBA1A, TUBB4A, COL4A1, SPAST, CTNNB1, GNAO1, STXBP1,* and *KIF1A*. Factors associated with exome sequencing–identified gene variants include patients without a perinatal risk factor, those with a positive family history, and patients with intellectual disability, epilepsy, or autism spectrum disorders.

CLINICAL MANIFESTATIONS

There are several classification systems to describe CP, a reflection of the complexity underlying the heterogeneity of cause, distribution, type of motor involvement, and severity (Table 638.1). Classification aids in understanding cause, coordinating care, monitoring comorbidities, treatment offerings and their prognosis, and long-term outcomes. One such classification system starts by determining the type of motor involvement: spastic or extrapyramidal. **Spastic** CP can then be

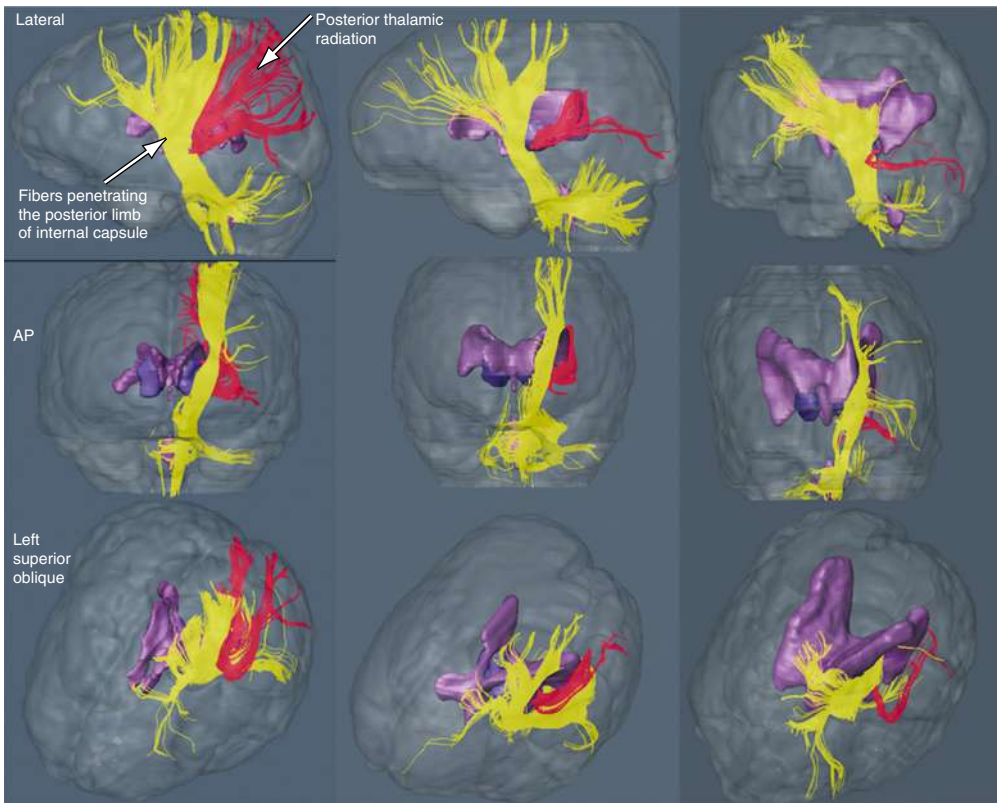

Fig. 638.1 Diffusion tensor image of white matter pathways in the brains of two patients with spastic diplegia on the right compared with a normal child on the far left. Yellow fibers are corticospinal pathways projected from the motor cerebral cortex at the top downward into the brainstem, whereas red fibers are thalamocortical sensory fibers projected from the thalamus upward to the cortex. In children with spastic diplegia, both the corticospinal and thalamocortical pathways are reduced in size but the ascending thalamocortical pathways are more affected. *(From Nagae LM, Hoon AH Jr, Stashinko E, et al. Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts. AJNR Am J Neuroradiol. 2007;28:1213–1222.)*

Table 638.1 Classification of Cerebral Palsy and Major Causes

MOTOR SYNDROME (APPROX % OF CP)	NEUROPATHOLOGY/MRI	MAJOR CAUSES
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared-off posterior ventricles	Prematurity Ischemia Infection Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia	Ischemia, infection
	Multicystic encephalomalacia Cortical malformations	Endocrine/metabolic, genetic/developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders Infection Genetic/developmental Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scarring of globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Hypoxia Kernicterus Mitochondrial Genetic/metabolic

further truncated topographically (Fig. 638.2), whereas extrapyramidal is further categorized based on the type of involuntary movement seen. In **extrapyramidal** CP, the brain injury or insult spares the pyramidal tracts that cause spasticity resulting in disorders of movement, coordination, and balance. Clinically, these patients exhibit dystonia and/or choreoathetosis (collectively referred to as *dyskinetic*) or ataxia associated with lesions in the cerebellum or its connections. Spastic CP accounts for 80% of cases, whereas extrapyramidal makes up 20% of cases (15% dyskinetic and 5% ataxic).

Historically, CP has been classified as mild, moderate, and severe without specified criteria for each group and primarily used for diagnostic purposes. The Gross Motor Function Classification System (GMFCS) was developed to categorize CP based on abilities and limitations in motor functioning. Goals included improved communication for treatment decisions, research into treatment outcomes, improved understanding and communication of the development of a child with CP, and anticipated future ambulatory needs. The emphasis is on *usual* rather than *best* motor performance in a variety of settings: home, school, and community.

Spastic hemiplegia has decreased spontaneous movements on the affected side and shows hand (handedness) preference at a very early age. The arm is often more involved than the leg, and difficulty in hand manipulation is evident by 1 year of age. Walking is usually delayed until 18-24 months, and a circumductive gait is apparent. Examination of the extremities may show growth arrest leading to shortened limbs and decreased muscle bulk on the affected side. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe (toe-walking) because of the increased tone in the antigravity gastrocnemius muscles and tight contracted Achilles tendon; the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. Difficulty in selective motor control is also present.

Spastic monoplegia is when only one limb is affected and may not be as obvious as other types of CP. Depending on which limb is affected, the child's motor disability ranges from challenges with either fine or gross motor skills. A monoplegia that affects the arm may result in challenges with bimanual tasks, whereas when the legs are involved, toe walking may be seen.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with injury to the immature white matter during the vulnerable period of immature oligodendroglia between 20 and 34 weeks of gestation, hence seen in those born prematurely. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal four-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. Examination of the child reveals symmetric spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, an extended scissoring posture of the lower extremities is maintained. Walking can be significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoes. Severe spastic diplegia is characterized by disuse atrophy, impaired growth of the lower extremities, and disproportionate growth with normal development of the upper torso.

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with other comorbidities, including intellectual disabilities, seizure disorders, communication and visual impairment, and feeding difficulties. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia and growth failure. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees, elbows, and wrists are often present by late childhood. Children with spastic quadriparesis can also have extrapyramidal findings given the diffuse involvement of the brain injury.

Extrapyramidal CP can be divided into the two main types of involuntary movement seen: ataxia and dyskinesias. In this type of CP, injury is typically to the subcortical areas, which are centers for coordination in movement and balance. Injury may not produce weakness, but rather the inability to voluntarily control movements. This type is less common than spastic CP and makes up approximately 15–20% of patients with CP.

Ataxic CP is the rarest form whose clinical picture is variable ranging from hypotonia to mild spasticity in addition to incoordination depending on the other systems involved. Walking gait is often very wide and sometimes irregular. Control of eye movements and depth perception can be impaired. Often, fine motor skills requiring coordination of the eyes and hands, such as writing, are difficult. Other causes of ataxia in infancy and childhood, including hydrocephalus, neoplasms, and degenerative disorders, should be ruled out before CP is diagnosed (see Chapter 637.1).

Dyskinetic CP is further divided into two groups: athetoid and dystonic. **Athetoid** CP includes cases with involuntary movement,

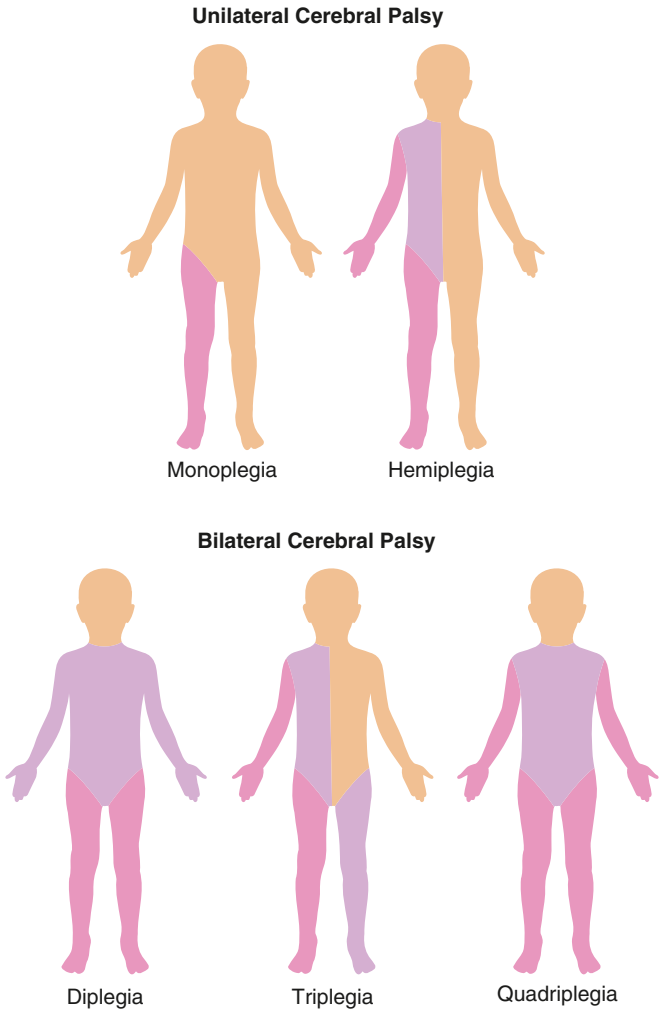

Fig 638.2 Topographical description in spastic cerebral palsy. Spastic cerebral palsy accounts for 70–80% of cases and is caused by an injury of the pyramidal tracts affecting voluntary movement. Monoplegia and hemiplegia affect one side of the body; in monoplegia one limb is affected, whereas in hemiplegia both the arm and leg on one side are affected. Hemiplegia can be asymmetric, affecting the arm or leg greater than the other extremity. Diplegia, triplegia, and quadriplegia affect both sides of the body. In diplegia, the predominant picture is involvement of the lower extremities. However, the arms can be affected though not to the same degree. In triplegia, both lower extremities and one arm are affected. A common picture is diplegia from periventricular leukomalacia and hemiplegia from an interventricular hemorrhage. This results in one lower extremity being more severely affected because of a dual mechanism of injury. In quadriplegia, all extremities are involved. *(From Graham HK, Rosenbaum P, Paneth N, et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2:15082, Fig. 2.)*

especially in the arms, legs, and hands. With the current management of Rh and ABO incompatibility, the incidence of CP characterized by athetosis has markedly decreased (see Chapter 637). Athetoid CP is often caused by **kernicterus** secondary to high levels of bilirubin, and in this case the MRI scan shows lesions in the globus pallidus bilaterally, or it may be normal. Cases are still seen as a result of HIE as well. The affected infant is initially hypotonic, but a tendency toward arching and opisthotonus (dystonia) is noted, and obligatory tonic neck reflexes are present. These primitive motor patterns preclude orderly motor development such as reaching, rolling, and sitting. **Dystonic CP** encompasses cases that affect the trunk muscles more than the limbs and results in a fixed, twisted posture. Toward the end of the first year, repetitive, involuntary movements become more consistent with the full-blown picture of dystonic CP. Dystonia in CP presents as hypertonia, involuntary postures and movements, or a combination.

Nearly all individuals with CP will have one or more medical, neurologic, or psychiatric comorbidities. Neuropsychiatric comorbidities that occur at higher rates with CP include intellectual disability, anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD) compared with the general population. Other associated comorbidities are common and include chronic pain, sleep difficulties, urinary dysfunction, decreased bone health, sialorrhea, respiratory disorders, feeding and growth challenges, gastrointestinal disorders including constipation and dysmotility, speech/communication difficulties, visual impairment, and hearing loss.

DIAGNOSIS

CP is a clinical diagnosis that considers elements from the history, physical examination, and ancillary testing including neuroimaging. The history should focus on whether there was perinatal or postnatal injury to the brain, what factors led to this injury, and contributory pregnancy factors. Another important factor is the developmental trajectory. It is important to quantify rates of development in the various domains and whether that trajectory has been one of continued acquisition of skills, plateauing, or regression. This—especially no loss of acquired milestones (regression)—helps preclude a **progressive disorder** of the central nervous system (CNS), including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy.

Multiple components to the physical examination are necessary to characterize abnormalities of tone, reflexes, movements, posture, and balance that may be consistent with the diagnosis of CP. The physical examination should focus on the following features: presence of any limb deformities, curvature of the spine, range of motion of joints, muscle tone, muscle strength, reflexes, presence of any movement disorders, and gait.

An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations; an MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. An MRI with abnormalities consistent with CP supports the diagnosis and increases the level of certainty, but the diagnosis remains a clinical one. An early diagnosis of CP is desirable to initiate appropriate services and therapies and to provide a definitive diagnosis for families.

Additional studies may include tests of hearing and visual function. Genetic evaluation should be considered in patients with congenital malformations, evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy), clinical features atypical of CP, or when there are no perinatal risk factors especially in term infants (Fig. 638.3, Tables 638.2 and 638.3).

The differential diagnosis must include disorders that may **mimic** the various types of CP (see Fig. 638.3). These may include the hereditary spastic diplegias (Table 638.4), monoamine transmitter disorders such as dihydroxyphenylalanine (DOPA)-responsive dystonia **(Segawa disease)** (Table 638.5 and Fig. 638.4), and many treatable inborn errors of metabolism, including disorders of amino acids, creatine, fatty acid oxidation, lysosomes, mitochondria, organic acids, and vitamin cofactors.

TREATMENT

The treatment strategy for CP is best developed in a multidisciplinary patient-centered setting, where medical interventions are embedded in a rehabilitation context considering the patient's individual goals (see Chapter 752). The overarching goal for patients with CP is to maximize functioning by improved biomechanics resulting from abnormal tone, musculoskeletal deformities, and muscle weakness. Other goals outside of those related to the neuromotor component can be equally important when they pertain to quality of life, comfort, and social stigmatization. Clear communication and coordination among the multidisciplinary team (physiatry, orthopedic, neurology/neurodevelopmentalists, neurosurgery) as well as physical and occupational therapy, speech pathology, social work, primary care physicians, developmental pediatricians, and educators maximize the chances of success.

Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that reduce the effects of abnormal muscle tone. Families and children also need to be instructed in the performance of a series of exercises designed to promote developmental progress, prevent long-term complications such as the development of contractures, preserve range of motion,

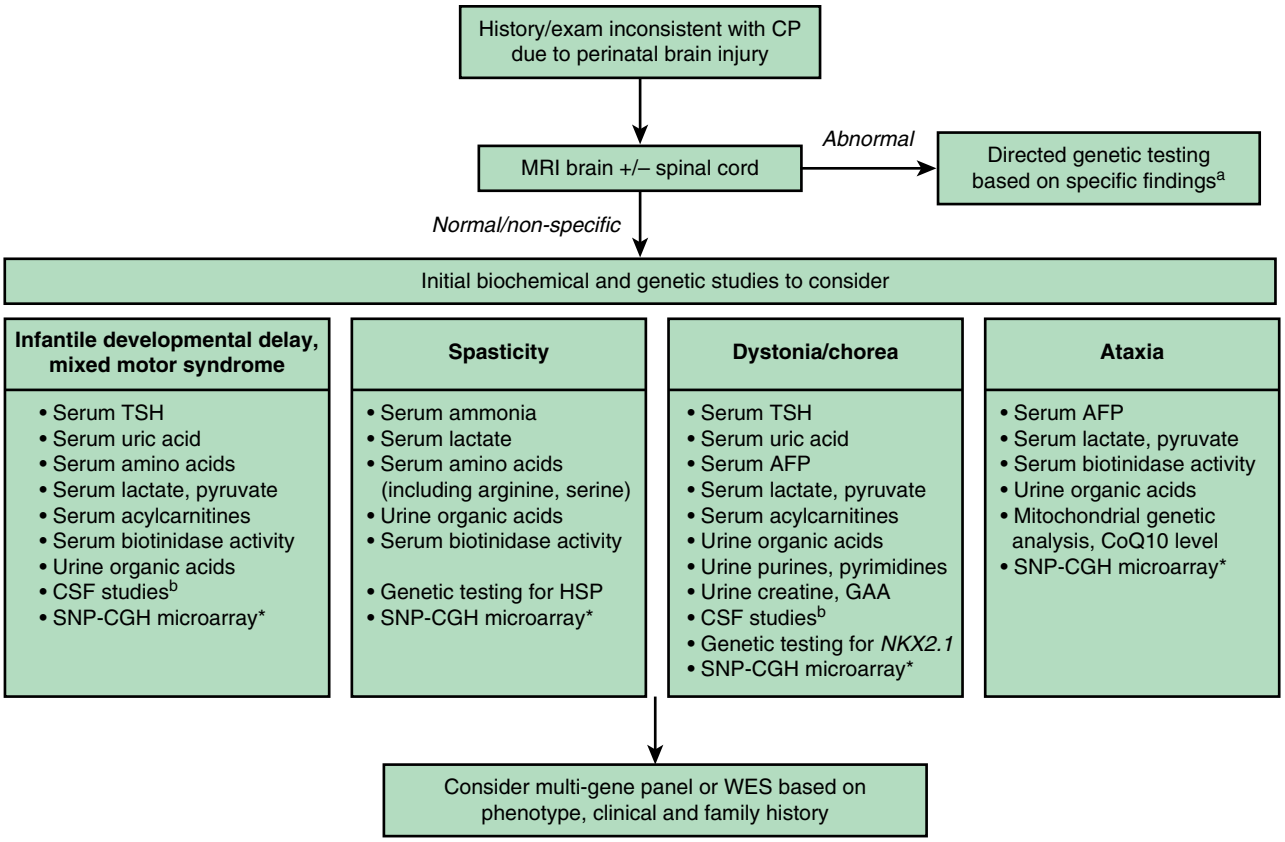

Fig. 638.3 Genetic mimics of cerebral palsy. Algorithm showing the general diagnostic approach to the patient with an infantile-onset, apparently nonprogressive motor disorder. Studies are grouped by predominant clinical presentation; it may be appropriate to consider investigations from more than one group depending on the specific clinical context. *In many situations WES has replaced microarray testing. [a]See examples in Tables 638.2 and 638.3 [b]CSF studies: glucose (+ serum glucose), lactate, pyruvate, neurotransmitter metabolites (biogenic amines + GABA), pterins, 5-methyltetrahydrofolate; HSP, hereditary spastic paraplegia. *(From Pearson TS, Pons R, Ghaoui R, Sue CM. Genetic mimics of cerebral palsy. Mov Disord. 2019;34:625–636, Fig. 1, p. 627.)*

Table 638.2 Clinical Features That Should Prompt Evaluation for Genetic and Metabolic Conditions in a Patient Presenting with Symptoms of CP

Absent history of any perinatal risk factor for brain injury
Family history of sibling with similar neurologic symptoms
Motor symptom onset after an initial period of normal development
Developmental regression
Progressive neurologic symptoms
Paroxysmal motor symptoms or marked fluctuation of motor symptoms
Clinical exacerbation in the setting of a catabolic state (e.g., febrile illness)
Isolated generalized hypotonia
Prominent ataxia
Signs of peripheral neuromuscular disease (reduced or absent reflexes, sensory loss)
Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements)

From Pearson TS, Pons R, Ghaoui R, et al. Genetic mimics of cerebral palsy. *Mov Disord.* 2019;34:625–636, Table. 1, p. 628.

Table 638.3 Brain MRI Findings Suggestive of Selected Genetic CP Mimics

FINDING	SELECTED CONDITIONS
Hypomyelination	*PLP1*-related dysmyelinating disorders H-ABC (*TUBB4A* variant) AGS (may also have basal ganglia and WM calcification) GM1 gangliosidosis
Demyelination	Krabbe disease Metachromatic leukodystrophy
Thin corpus callosum	HSP (i.e., SPG4, SPG11, SPG15, and others)
Globus pallidus lesions	T_2-hypointense: NBIA (SN also involved in BPAN, MPAN), fucosidosis T_2-hyperintense: MMA, PDH deficiency, creatine deficiency syndromes
Focal atrophy or hypoplasia	Glutaric aciduria type 1 (frontotemporal) H-ABC (cerebellum ± putamen) Joubert syndrome (cerebellum)

AGS, Aicardi-Goutières syndrome; BPAN, beta-propeller protein–associated neurodegeneration; H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum; HSP, hereditary spastic paraplegia; MMA, methylmalonic aciduria; MPAN, mitochondrial membrane protein-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PDH, pyruvate dehydrogenase; WM, white matter.

From Pearson TS, Pons R, Ghaoui R, et al. Genetic mimics of cerebral palsy. *Mov Disord.* 2019;34:625–636, Table 2, p. 628.

and strengthen weak muscles. Therapists help children to achieve their full potential and often recommend further evaluations and adaptive equipment.

Rehabilitative strategies include orthotics, casting, and physiotherapy (see Chapter 752). Adaptive equipment can help individuals with CP achieve a greater level of independence and autonomy. Equipment such as braces, wheelchairs, and walkers can significantly improve mobility and increase self-confidence. Orthotics are devices that are used to help prevent foot and ankle deformities, improve stability during walking, and

Table 638.4 Clinical and Neuroimaging Findings in Hereditary Spastic Paraplegias (HSP) with Pediatric Onset*

HSP FORM	HSP TYPE	INHERITANCE	GENE	CHILDHOOD ONSET	DISEASE CHARACTERISTICS†	NEUROIMAGING FINDINGS (BRAIN)
Pure	SPG3A	AD	*ATL1*	+++	None	Normal
Pure	SPG4	AD	*SPAST*	++	None	Leukoencephalopathy, thin corpus callosum
Pure	SPG6	AD	*NIPA1*	+	None	Normal
Pure	SPG10	AD	*KIF5A*	+++	Neuropathy	Normal
Pure	SPG12	AD	*RTN2*	+++	None	Normal
Pure	SPG31	AD	*REEP1*	++	None	Normal
Complicated	SPG1	X-linked	*L1CAM*	++	Intellectual disability, adducted thumb	Thin corpus callosum
Complicated	SPG2	X-linked	*PLP1*	+++	Intellectual disability, epilepsy	Normal
Complicated	SPG7	AR	*SPG7*	+	Optic atrophy, neuropathy, cerebellar ataxia	Cerebellar atrophy
Complicated	SPG11	AR	*KIAA1840*	+++	Intellectual disability, neuropathy	Leukoencephalopathy, thin corpus callosum
Complicated	SPG15	AR	*ZFYVE26*	+++	Intellectual disability, retinopathy, cerebellar ataxia	Leukoencephalopathy, thin corpus callosum
Complicated	SPG17	AR	*BSCL2*	+	Neuropathy	Normal

*Onset before 18yr of age.
†Other than the classic HSP symptoms, including spastic paraparesis, atrophy of the distal lower extremities, and neurogenic bladder dysfunction.
AD, autosomal dominant; AR., autosomal recessive; +, occasional; ++, common; +++, characteristic.
From Lee RW, Poretti A, Cohen JS, et al. A diagnostic approach for cerebral palsy in the genomic era. *Neurol Med*. 2014;16:821–844, Table 5, p. 832.

Table 638.5 Clinical Features of the Monoamine Neurotransmitter Disorders

ENZYME DEFICIENCY	AGE AT PRESENTATION	MOTOR AND COGNITIVE DELAY	EXTRAPYRAMIDAL HYPERKINETIC FEATURES	EXTRAPYRAMIDAL HYPOKINETIC FEATURES	PYRAMIDAL TRACT FEATURES	EPILEPSY	AUTONOMIC FEATURES	NEUROPSYCHIATRIC FEATURES
AD GTPCH-D	Childhood (but can occur at any age)	Not common	Yes	Yes	No	No	No	Yes
SR-D	Infancy	In most	Yes	Yes	Yes	Yes	Yes	Yes
AR GTPCH-D	Infancy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PTPS-D	Infancy to childhood	In most	Yes	Yes	Yes	Yes	Yes	Yes
DHPR-D	Infancy to childhood	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PCD-D	Infancy	No	No	No	No	No	No	No
TH-D	Infancy to early childhood	In most	Yes	Yes	Yes	Yes	Yes	No
AADC-D	Mainly infancy (but can occur at any age)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PLP-DE	Infancy to early childhood	In most	Yes	Yes	Yes	Yes	Yes	Yes
DTDS	Infancy	Yes	Yes	Yes	Yes, in older children	No	Yes	No

AD GTPCH-D, autosomal dominant GTP cyclohydrolase deficiency; SR-D, D-Serine; AR GTPCH-D, autosomal recessive GTP cyclohydrolase deficiency; PTPS-D, 6-pyruvoyl tetrahydropterin synthase deficiency; DHPR-D, dihydropteridine reductase deficiency; PCD-D, pterin-4α carbinolamine dehydrase deficiency; TH-D, tyrosine hydroxylase deficiency; AADC-D, aromatic l-amino acid decarboxylase deficiency; PLP-DE, pyridoxal 5 phosphate dependent enzymes; DTDS, dopamine transporter deficiency syndrome.
From Kurian MA, Gissen P, Smith M, et al. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. *Lancet Neurol*. 2011;10:721–731, Table, p. 722.

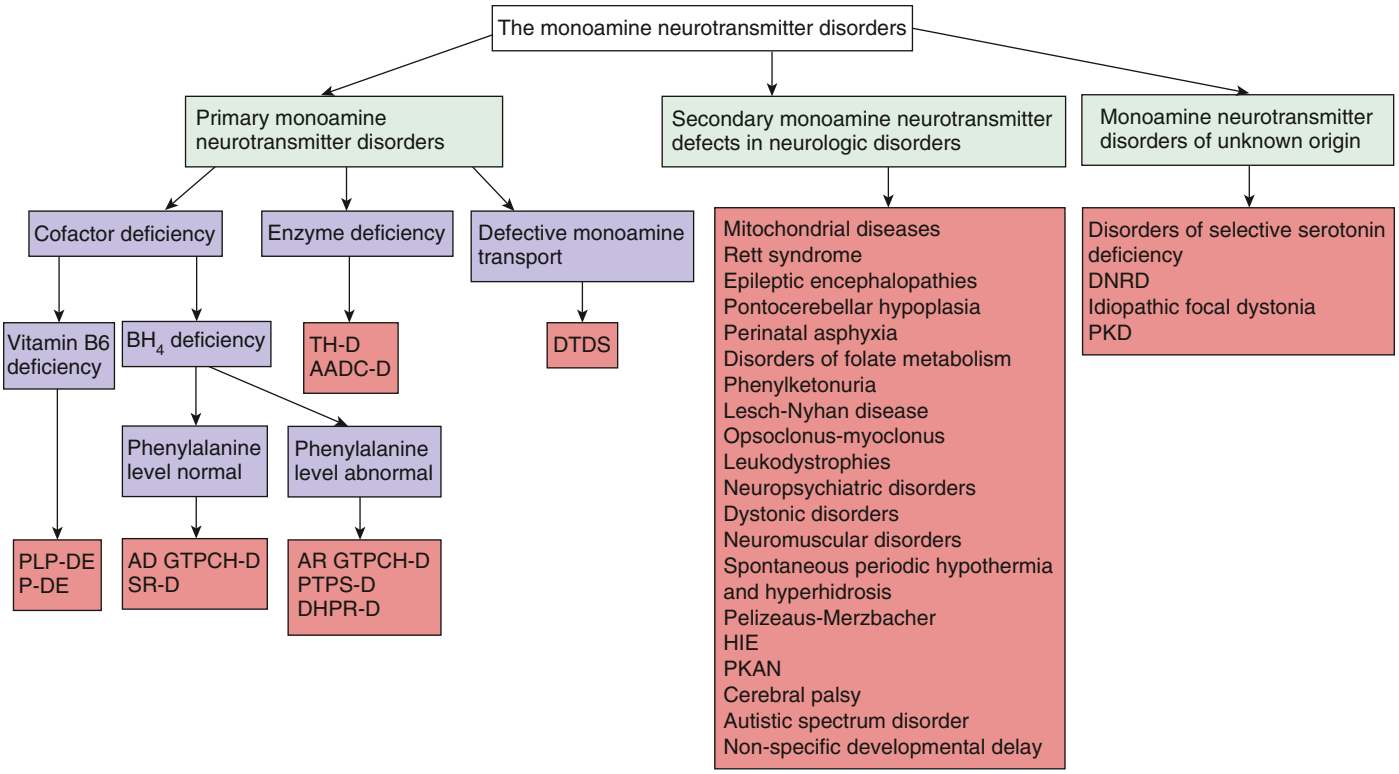

Fig. 638.4 Classification of the monoamine neurotransmitter disorders. BH_4, Tetrahydrobiopterin; TH-D, tyrosine hydroxylase deficiency; AADC-D, aromatic L-amino acid decarboxylase deficiency; DTDS, dopamine transporter deficiency syndrome; PLP-DE, pyridoxal-phosphate–dependent epilepsy; P-DE, pyridoxine-dependent epilepsy; AD GTPCH-D, autosomal dominant GTP cyclohydrolase 1 deficiency; SR-D, sepiapterin reductase deficiency; AR GTPCH-D, autosomal recessive GTP cyclohydrolase 1 deficiency; PTPS-D, 6-pyruvoyltetrahydropterin synthase deficiency; DHPR-D, dihydropteridine reductase deficiency; HIE, hypoxic-ischemic encephalopathy; PKAN, pantothenate kinase associated neurodegeneration; DNRD, dopa-nonresponsive dystonia; PKD, paroxysmal kinesigenic dyskinesia. *(From Kurian MA, Gissen P, Smith M, et al. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. Lancet Neurol. 2011;10:721–731, Fig. 1.)*

sometimes relieve pain. Additional equipment needs address activities of daily living such as bathing and hygiene, communication, and driving.

Pharmacotherapy is often the first-line approach used to manage the various tone abnormalities seen in CP and includes both enteral options and targeted injections. Systemic medications are often chosen for more widespread management of spasticity and dyskinesias. Although baclofen is routinely favored, other antispasticity medications such as tizanidine, dantrolene, and benzodiazepines are also available. Second-line medications such as clonidine or gabapentin may provide dual benefit for both tone management and other neurologic associations, including sleep disruption, dysautonomia, pain, and neuroirritability. Medications used to treat dystonia include enteral baclofen, benzodiazepines, trihexyphenidyl, clonidine, dantrolene, levodopamine, and gabapentin, but practice varies widely. Tetrabenazine can be useful for hyperkinetic movement disorders, including athetosis or chorea.

The management of focal/segmental spasticity or dystonia includes chemodenervation agents that target these specific locations. Targeted injections are often used in combination with systemic medications to augment tone management in specific areas that are more problematic. Examples include **botulinum toxin A** (BoNT-A), phenol, and ethyl alcohol. Targeted injections combined with rehabilitative therapies can allow for improved motor functioning and delay or avoid orthopedic surgery; these injections require repeat administration. Typically repeat injections are performed every 4-6 months, primarily to avoid the development of resistance; 3 months may be necessary. Injections into salivary glands may also help reduce the severity of drooling if it is not adequately treated with anticholinergic agents.

Neurosurgical options include intrathecal baclofen (ITB), selective dorsal rhizotomy (SDR), and deep brain stimulation (DBS). **ITB** can be considered in patients whose spasticity is not adequately treated with enteral baclofen or who are experiencing side effects such as sedation, weakness, or gastrointestinal (GI) symptoms. Baclofen is delivered with an implanted pump in children with severe spasticity; it is useful because it delivers the drug directly around the spinal cord, where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood-brain barrier. ITB may reduce dystonia with evidence for benefit with higher catheter placement.

The main goal of **SDR** is to improve the gait or functioning in those that function at GMFCS I-III with good selective motor control and minimal weakness. However, SDR is being looked at for management of tone, minimizing pain, and ease of caregiving in patients functioning on a GMFCS IV-V level. Because SDR is an irreversible treatment for spasticity, optimal selection of ideal candidates from a multidisciplinary approach is necessary to avoid short- and long-term complications. SDR's spasticity benefits are caused by a partial sensory deafferentation of the spinal cord. This is achieved by resection of dorsal nerve rootlets based on abnormal motor responses to electrical stimulation (Fig. 638.5). The total number of nerve rootlets resected ranges from 25% to 40%, though in some institutions it exceeds >40%. Combining both ventral and dorsal rhizotomies can help manage both spasticity and dystonia. SDR manages lower extremity tone equally as the ITB pump, may provide more upper-extremity tone control compared with the ITB pump, and improves bladder function.

DBS can be considered if there is severe hypertonia with combined spasticity and dystonia. DBS is a neurosurgical procedure that evolved from the recognition that pallidotomies and thalamotomies could help patients with medically refractory dystonia. It involves the introduction of stimulating electrodes in areas of the brain such as the globus pallidus and the subthalamic nucleus, which are connected to an extracranial pulse generator (see Chapter 637). After the surgical procedure, the beneficial effects are not immediately

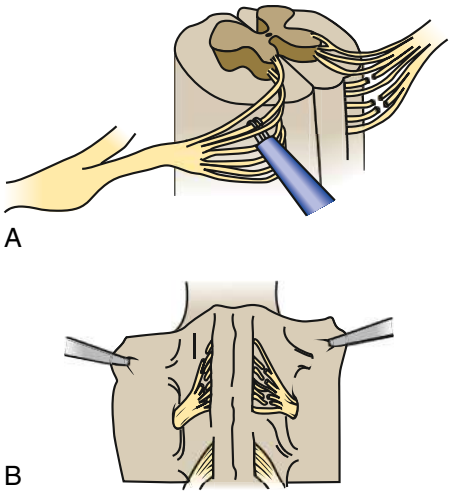

Fig. 638.5 Schematic of the technique of selective dorsal rhizotomy. A, After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. B, A proportion of rootlets is transected. *(From Koman LA, Smith BP, Shilt JS. Cerebral palsy. Lancet. 004;363:1619–1631. Reproduced with permission from Wake Forest University Orthopaedic Press.)*

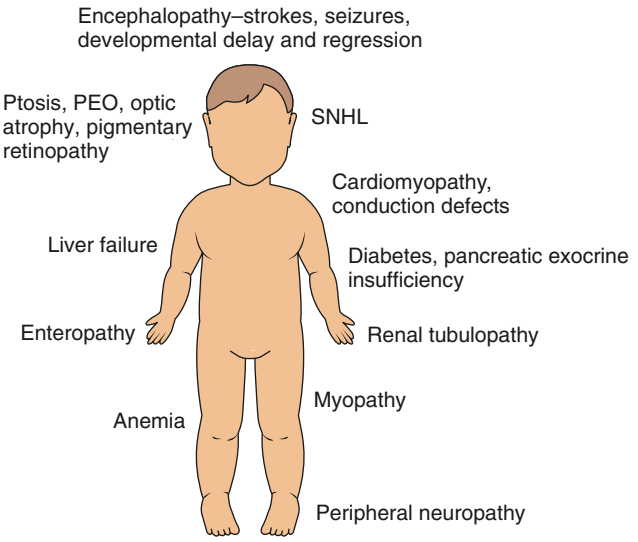

Fig. 638.6 Clinical features of mitochondrial encephalomyopathies. PEO, progressive external ophthalmoplegia; SNHL, sensorineural hearing loss. *(Adapted from Rahman S. Mitochondrial disease in children. J Intern Med. 2020;287[6]:609–633.)*

visible, often taking several months. The procedure is associated with perioperative risks as well as infection and hardware complications. Therefore patient selection and consideration of the appropriate target for stimulation for DBS are key. Most agree that the presence of spasticity, contractures/deformities, and myelopathy are poor predictors of response and that neurosurgical expertise, anatomic factors, and severity/time of dystonic symptoms may influence response.

Orthopedic interventions address musculoskeletal pathology, including fixed muscle contractures, torsion of long bones, hip displacement, and spine deformities. Several surgical methods exist for lengthening the muscle-tendon units for contraction management, though these are rarely necessary before 6 years of age. Before this, prevention of contracture development is key and often is a combination of tone management, bracing, and stretching exercises. Femoral and tibial torsion occur, respectively, because of failure of remodeling fetal anteversion and mostly as a response to abnormal biomechanical forces during walking. Derotational osteotomies are ideally performed between 6 and 12 years of age. With increasing GMFCS level comes increased risk of developing hip displacement and neuromuscular scoliosis. Monitoring and prevention strategies are paramount, as both hip displacement and scoliosis may progress with age. Conservative treatment and surgical approaches can be challenging when balancing the complexity of these surgical interventions and outcome goals defined presurgically.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

638.2 Mitochondrial Encephalomyopathies

Shamima Rahman

Mitochondrial encephalomyopathies are complex neurologic disorders caused by disturbed mitochondrial function. Mitochondria are dynamic cellular organelles with multitudinous roles, most notably energy generation via oxidative phosphorylation (OXPHOS), but other mitochondrial functions include intermediary metabolism (the Krebs cycle, fatty acid beta oxidation, and part of the urea cycle are housed in the mitochondrion), calcium homeostasis, intracellular signaling, apoptosis, and biosynthesis of coenzyme Q_{10}, heme, iron-sulfur clusters, and lipoic acid. Aberrant mitochondrial function most commonly involves disturbed energy generation via the OXPHOS system, but other mechanisms include oxidative stress mediated by increased production of reactive oxygen species (ROS), alterations of other metabolic processes within the mitochondria (such as pyruvate dehydrogenase, the Krebs cycle, vitamin metabolism and transport, and cofactor biosynthesis) and of the mitochondrial lipid membranes, protein quality control, import system, and organelle dynamics (disturbed fission and fusion).

Mitochondria are unique among cellular organelles in that they contain their own genome: the maternally inherited circular mitochondrial DNA (mtDNA) molecule comprising 16,569 base pairs in humans encoding 37 genes: 13 protein-coding genes, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs). The mitochondrial genome is present in multiple copies within each mitochondrion, and there are hundreds to thousands of mtDNA molecules per cell. mtDNA gene variants may be heteroplasmic (only a percentage of the mtDNA is mutated) or homoplasmic (100% of the mtDNA is mutated). Primary mitochondrial disease may be caused by maternally inherited or sporadic variants affecting the mtDNA or by recessive, dominant, X-linked, or de novo variants in nearly 400 nuclear genes involved in mitochondrial function and structure.

Mitochondrial disorders, especially those presenting in childhood, have a predilection for high-energy-consuming organs: the brain, skeletal muscle, eyes, ears, heart, kidneys, and liver. Neurologic features of primary mitochondrial disease in childhood include hypotonia, dystonia, spasticity, ptosis, progressive external ophthalmoplegia (PEO), seizures, and ataxia. Multisystem features that may be observed in children with mitochondrial disease are illustrated in Figure 638.6. Some mitochondrial syndromes with characteristic constellations of symptoms and signs were recognized many decades before their genetic basis was understood; several of these syndromes are summarized in Table 638.6.

Mitochondrial encephalomyopathies can be considered according to age at onset of symptoms. In early **infancy** the most frequent presentations include Leigh syndrome, the mtDNA depletion syndromes (MDDS), disorders of coenzyme Q_{10} (CoQ_{10}) biosynthesis, and reversible infantile respiratory chain disease (RIRCD). Clinical syndromes observed later in **childhood** include Kearns-Sayre syndrome (KSS), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), and neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP). However, many children presenting with mitochondrial disease have overlapping features not specific to an individual

Table 638.6 Clinical Manifestations of Syndromic Mitochondrial Encephalomyopathies

TISSUE	SYMPTOMS/SIGNS	LSS	KSS	MELAS	MERRF	NARP	LHON
CNS	Regression	+	+	+	+		
	Seizures	±		+	+		
	Ataxia	±	+	+	+	+	
	Cortical blindness	±		+			
	Deafness	±		+		+	
	Migraine			+			
	Hemiparesis			+			
	Myoclonus			+	+		
	Movement disorder	+		+	+		±
Nerve	Peripheral neuropathy	±	+	+	+	+	
Muscle	Ophthalmoplegia	±	+				
	Weakness	+	+	+	+	+	
	RRF on muscle biopsy	±	+	+	+		
	Ptosis	±	+				
Eye	Pigmentary retinopathy	±	+			+	
	Optic atrophy	+	+				+
Heart	Conduction block		+				±
	Cardiomyopathy	±	+				
	Lactic acidosis	+	+	+	+	+	
Endocrine	Diabetes mellitus		+	+			
	Short stature	+	+	+	+		
Kidney	Tubulopathy	±	+	+	+		

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia, and retinitis pigmentosa; RRF, ragged red fibers.
Courtesy Prof. Shamima Rahman, Great Ormond Street Institute of Child Health, London, United Kingdom.

syndrome, whereas others may present with a single clinical feature, such as an epileptic encephalopathy, leukoencephalopathy, myopathy, or isolated optic atrophy.

LEIGH SYNDROME

Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a clinical syndrome of neurodevelopmental delay and/or regression and variable other neurologic features, including dystonia, hypotonia, spasticity, ataxia, and seizures, with characteristic MRI brain appearances and biochemical evidence of mitochondrial dysfunction. Peak onset is usually in the first 2 years of life (mean 7 months), although longer surviving cases and adult onset are both recognized. Initial symptoms may be nonneurologic, including feeding difficulties, vomiting, and poor weight gain in infancy. Eye involvement is a frequent finding, including nystagmus, ptosis, PEO, optic atrophy, and retinitis pigmentosa. MRI reveals bilateral, usually symmetric T2-weighted hyperintense lesions variably affecting the basal ganglia, thalamus, midbrain, and brainstem structures (Fig. 638.7). These imaging lesions reflect the neuropathology, which consists of spongiform lesions with cavitation, neuronal loss, demyelination, and capillary proliferation.

Biochemical features are variable in Leigh syndrome and include elevated lactate in blood and/or cerebrospinal fluid (CSF) and isolated or combined deficiency of one or more OXPHOS enzymes. Normal biochemical findings do not exclude the diagnosis. Leigh syndrome is genetically heterogeneous, and more than 100 monogenic causes have been identified, including variants in both mtDNA-encoded genes (responsible for 25–30% of cases) and nuclear genes. Modes of inheritance include maternal (for mtDNA variants), autosomal recessive, X-linked, and de novo dominant. **MEGDEL** (3-**me**thyl**g**lutaconic aciduria with **d**eafness and **e**ncephalopathy, **L**eigh-like) syndrome is a subtype of Leigh syndrome caused by biallelic variants in *SERAC1* encoding a protein involved in remodeling mitochondrial membrane lipids. Affected infants typically fail the newborn hearing screen and have problems with hypoglycemia and hyperammonemia related to hepatic dysfunction. Some infants succumb to liver failure, but hepatic function improves in most affected individuals, who later progress to a neurodegenerative course with prominent dystonia and loss of skills.

A few causes of Leigh syndrome are potentially treatable. These include deficiencies of biotinidase (an enzyme required for biotin recycling within the cell), the thiamine transporter SLC19A3 (also associated with biotin-thiamine–responsive basal ganglia disease), and proteins required for biosynthesis of CoQ_{10}, a mobile electron carrier in the mitochondrial respiratory chain. All other forms of Leigh syndrome have no curative treatments and are associated with a progressive neurodegenerative course with early death, usually caused by respiratory failure secondary to brainstem lesions affecting the respiratory center. Median age at death was reported as 2.4 years in one cohort, but this is variable and related to the underlying genetic cause. Longer survival has been reported in some forms of Leigh syndrome, including MEGDEL and deficiencies of SURF1 (an assembly factor for OXPHOS complex IV) and SUCLA2 (a subunit of the Krebs cycle enzyme succinyl-CoA ligase).

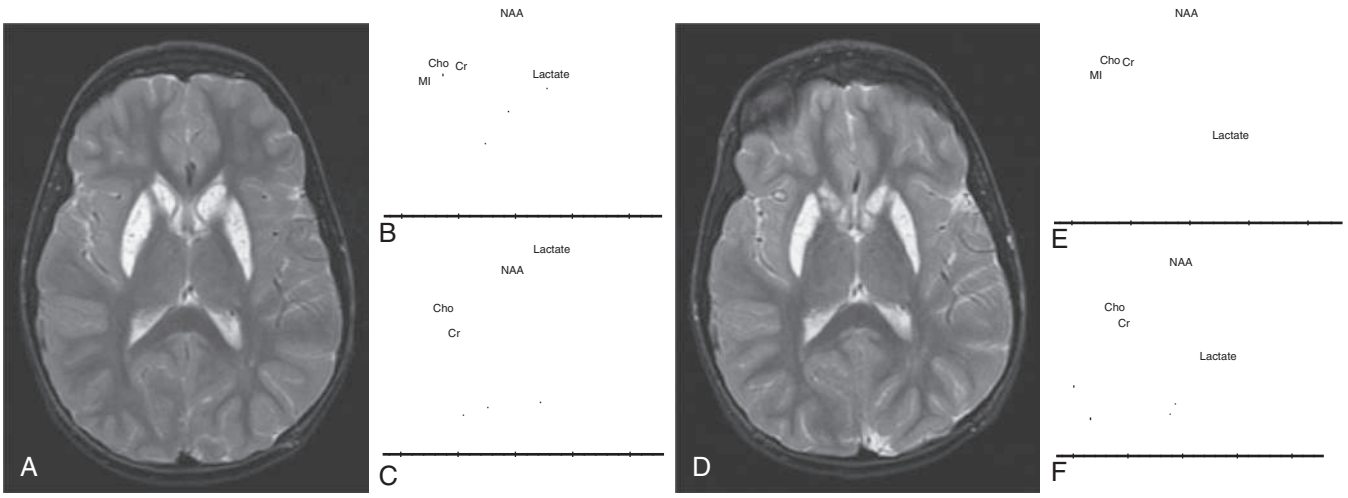

Fig. 638.7 Complex I deficiency in an 8-yr-old child with magnetic resonance examinations acquired approximately 3 mo apart. Axial T2-weighted (**A**), short echo magnetic resonance spectroscopy (MRS) (**B**), and long echo MRS (**C**) images were obtained. The imaging reveals a pattern characteristic of Leigh syndrome with an abnormal hyperintense signal bilaterally within the caudate and globus pallidus. The MRS image acquired in the left basal ganglia at a period of clinical exacerbation caused by febrile illness demonstrates a dramatic elevation of lactate compared with her routinely observed levels as shown in axial T2-weighted (**D**), short echo MRS (**E**), and long echo MRS (**F**) images. The spectra acquired 3 mo later demonstrate a significant reduction in lactate. A comparison of the imaging data is unremarkable between the examinations. The dramatic elevation of lactate revealed on MRS in (**B**) and (**C**) corresponds to worsening clinical symptoms (seizures and leg stiffening). The lactate levels observed in (**E**) and (**F**) are typical and consistent with this mitochondrial defect. *(From Cecil KM. MR spectroscopy of metabolic disorders. Neuroimaging Clin N Am. 2006;16:87–116.)*

Table 638.7 Mitochondrial DNA Depletion Syndromes

GENE*	FUNCTION	CLINICAL FEATURES	mtDNA DEPLETION	MULTIPLE DELETIONS
POLG	mtDNA replication	Alpers, juvenile epilepsy syndromes, ataxia, PEO	+	+
TWNK	mtDNA replication	Hepatocerebral disease, IOSCA, juvenile epilepsy syndromes, PEO	+	+
TFAM	mtDNA replication	Hepatocerebral disease	+	
MGME1	mtDNA replication	Encephalomyopathic	+	+
SLC25A4	Nucleoside metabolism	Encephalomyopathic, cardiac	+	+
DGUOK	Nucleoside metabolism	Hepatocerebral disease	+	+
TK2	Nucleoside metabolism	Progressive myopathy	+	+
MPV17	Nucleoside metabolism	Hepatocerebral disease	+	+
RRM2B	Nucleoside metabolism	Encephalomyopathic, SNHL, renal tubulopathy	+	+
SUCLA2	Nucleoside metabolism	Encephalomyopathic (LSS), SNHL	+	
SUCLG1	Nucleoside metabolism	Encephalomyopathic, hepatocerebral disease	+	
TYMP	Nucleoside metabolism	MNGIE	+	+

*All are recessive disorders, but, in addition, de novo dominant variants of *SLC25A4* may also present as MDDS.
IOSCA, Infantile-onset spinocerebellar ataxia; LSS, Leigh syndrome spectrum; MNGIE, mitochondrial neurogastrointestinal encephalopathy; PEO, progressive external ophthalmoplegia.
Courtesy Prof. Shamima Rahman, Great Ormond Street Institute of Child Health, London, United Kingdom.

MITOCHONDRIAL DNA DEPLETION SYNDROMES

The most prevalent MDDS is **Alpers-Huttenlocher syndrome** (progressive neuronal degeneration of childhood with epilepsy, PNDE) caused by recessively inherited gene variants in *POLG* encoding the catalytic subunit of DNA polymerase γ, the polymerase responsible for replicating the mtDNA. Affected individuals frequently present with intractable epilepsy, particularly epilepsia partialis continua, around 12 months of age. A characteristic EEG finding in the early stages of the disease is rhythmic high amplitude with delta spikes (RHADS). Repeated episodes of status epilepticus frequently lead to a median age of death of around 16 months (there is typically a median of 4 months between presentation with seizures and death). Sodium valproate is absolutely contraindicated in Alpers-Huttenlocher syndrome and other presentations of *POLG* disease because exposure to valproate may trigger fatal hepatic failure.

Recessive pathologic variants of at least 12 genes have been linked to infantile- and childhood-onset MDDS (Table 638.7). There is often a period of normal development lasting weeks to months before clinical

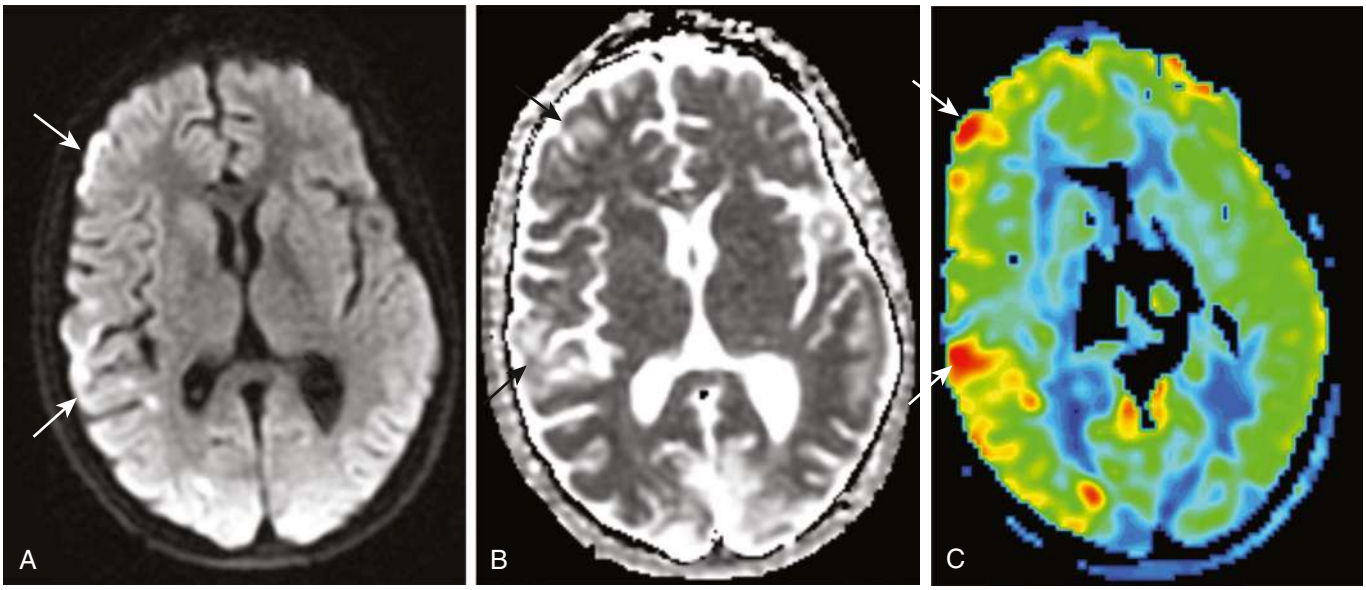

Fig. 638.8 Mitochondrial encephalomyopathy, lactic acidosis, and strokelike symptoms (MELAS) in a 13-yr-old male. Axial diffusion-weighted imaging (**A**), axial apparent diffusion coefficient (ADC) map (**B**), and an axial arterial spin labeling color map (**C**) are shown. Scattered foci of vasogenic edema denoted by *arrows* corresponding to increased perfusion are identified in the acute phase of the disease in the right cerebral hemisphere. *(From Zuccoli G, Cecil KM. Inherited metabolic and neurogenerative disorders. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 33.8, p. 312.)*

manifestations become apparent. Associated organ involvement may provide a clue to the underlying genetic diagnosis: sensorineural hearing loss (SNHL) and methylmalonic aciduria occur in *SUCLA2* defects, SNHL and renal tubular involvement in *RRM2B* defects, and hepatic involvement is associated with *DGUOK, MPV17, POLG, TWNK, TFAM,* and *SUCLG1* gene variants. **Thymidine kinase 2 (TK2) deficiency** appears to be a special case because this disorder leads to a pure myopathic presentation in most affected cases. Clinical response to nucleoside supplementation has been reported for TK2 deficiency but not for any other form of MDDS.

DISORDERS OF COENZYME Q_{10} BIOSYNTHESIS

CoQ_{10} functions as a mobile electron carrier and antioxidant in the mitochondrial inner membrane. CoQ_{10} is synthesized by a complex biosynthetic pathway, 10 defects of which have been linked to human disease. Clinical presentations of these recessive disorders include an infantile encephalomyopathy with prominent seizures and dystonia variably associated with multisystem features: SNHL, optic atrophy, pigmentary retinopathy, cardiomyopathy, and renal disease. Other presentations include ataxia, myopathy, and steroid-resistant nephrotic syndrome. Affected patients should be treated with high-dose CoQ_{10} supplementation, although clinical response is variable.

REVERSIBLE INFANTILE RESPIRATORY CHAIN DEFICIENCY

RIRCD, also known as *benign reversible mitochondrial myopathy,* typically presents after a period of normal development lasting 3-6 weeks with profound lactic acidosis and progressive muscle weakness, often leading to a need for enteral tube feeding and, in some cases where the respiratory muscles are severely affected, artificial ventilation. A ventilatory requirement may persist for up to 18 months. Muscle biopsy reveals ragged red and cytochrome *c* oxidase negative fibers with multiple OXPHOS enzyme deficiencies on spectrophotometric assay. This condition is linked to two homoplasmic variants at the same nucleotide in mtDNA: m.14674T>G and m.14674T>C. Although all maternally related individuals are homoplasmic for the variant, only a small proportion are clinically affected. Studies have also identified potential modifying variants in several nuclear-encoded genes involved in mitochondrial translation, particularly *EARS2*. Spontaneous recovery of muscle strength is associated with excellent neurodevelopmental outcomes. Because it is not possible to distinguish RIRCD from fatal infantile mitochondrial myopathies, rapid testing for the m.14674T>G/C variants is recommended in all infants presenting with severe muscle weakness and lactic acidosis, so that ventilatory support can be provided to affected infants if needed.

Another form of RIRCD is a reversible hepatopathy caused by recessive variants in the *TRMU* gene encoding a protein required to modify mitochondrial tRNAs. Affected infants present with acute liver failure, variably associated with encephalomyopathic features.

KEARNS-SAYRE SYNDROME

KSS is defined by a *clinical triad* of PEO, pigmentary retinopathy, and heart block, with age of onset <20 years. Other neurologic features include cerebellar ataxia, elevated CSF protein levels, progressive myopathy, and cognitive decline. A peculiar feature of KSS is white matter disease associated with cerebral folate deficiency. Low levels of CSF 5-methyltetrahydrofolate (5-MTHF) and clinical response to folinic acid supplementation have been documented in some patients. Variable associated multisystem disease features include SNHL, renal tubulopathy, endocrine dysfunction (diabetes mellitus, hypoparathyroidism, and short stature with growth hormone deficiency in some cases), and cardiomyopathy. KSS is usually a sporadic condition caused by single large-scale mtDNA deletions (SLSMDs); many individuals have a common 4.9kb mtDNA deletion. SLSMDs are associated with a continuous clinical spectrum ranging from infantile-onset Pearson syndrome to adult-onset isolated PEO without systemic features.

MITOCHONDRIAL ENCEPHALOMYOPATHY WITH LACTIC ACIDOSIS AND STROKELIKE EPISODES

MELAS is a maternally inherited disorder that typically presents toward the end of the first decade with migraine headache, vomiting, and seizures, which may lead to a strokelike episode. MRI of the brain reveals focal lesions with a parieto-occipital predilection not confined to a vascular territory (Fig. 638.8). Other clinical features include hemianopia during the strokelike episodes, ptosis, optic atrophy, pigmentary retinopathy, SNHL, exercise intolerance, cognitive decline, GI dysmotility, cardiomyopathy, renal impairment, and diabetes mellitus. Eighty percent of cases have a common maternally inherited mtDNA gene variant m.3243A>G in the *MT-TL1* gene encoding a tRNA for leucine. This gene variant is present in 1 in 400 of the general population, yet MELAS is a rare disorder. Most individuals harboring the

m.3243A>G variant are asymptomatic or oligosymptomatic or have non-MELAS presentations, including **maternally inherited diabetes and deafness (MIDD)**, cardiomyopathy, sudden unexpected death, or isolated renal involvement (focal segmental glomerulosclerosis). Other causes of MELAS include other mtDNA variants, particularly in the *MT-TL1* gene or in mtDNA-encoded subunits of complex I (especially ND5), and occasionally *POLG* disease can mimic MELAS.

MYOCLONIC EPILEPSY WITH RAGGED RED FIBERS

MERRF is a maternally inherited syndrome characterized by progressive myoclonic epilepsy and cerebellar ataxia with nystagmus and dysarthria. Onset may be in late childhood or adult life, and the disorder may be rapidly progressive or have a more indolent course. Other neurologic features include other seizure types, spasticity, peripheral neuropathy, SNHL, ptosis, PEO, optic atrophy, cognitive decline, and psychiatric manifestations. MERRF can also mimic MELAS, including strokelike episodes. MERRF is typically a multisystemic disorder; extraneurologic features include multiple symmetric lipomatosis, endocrine disturbance (growth hormone deficiency, hypothyroidism, adrenal insufficiency), and cardiomyopathy. A common mtDNA pathologic variant, m.8344A>G in the *MT-TK* gene encoding the tRNA for lysine, accounts for 80% of cases of MERRF. Patients with a very high percentage of this variant (typically >90%) present with **Leigh syndrome** in infancy. The remaining patients with MERRF have other mtDNA tRNA gene variants; occasionally *POLG* disease may mimic MERRF.

NEUROGENIC MUSCLE WEAKNESS, ATAXIA, AND RETINITIS PIGMENTOSA

NARP is a maternally inherited disorder caused by a relatively common mtDNA gene variant, m.8993T>G, in the *MT-ATP6* gene encoding the ATP6 subunit of ATP synthase (OXPHOS complex V). Patients usually have a gene variant load of ~70%, but those with a higher variant load (typically >90%) of the same variant present with maternally inherited Leigh syndrome. Clinical presentation of NARP is usually in late childhood or early adult life with numbness and paresthesias caused by the sensory neuropathy associated with muscle weakness and ataxia. Retinitis pigmentosa initially causes poor night vision and progresses slowly to severe visual loss. Other clinical features include developmental delay, learning disability, dementia, seizures, SNHL, diabetes mellitus, and cardiac conduction defects. *MT-ATP6* variants have also been reported to cause axonal **Charcot-Marie-Tooth disease** without CNS or other features.

MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a late-onset MDDS characterized by widespread demyelinating polyneuropathy leading to predominant GI symptoms and peripheral neuropathy with a relatively asymptomatic leukoencephalopathy. Onset of symptoms is usually toward the end of the second decade, but presentation in early childhood may occur. Major symptoms relate to GI dysmotility and pseudo-obstruction (nausea, vomiting, early satiety, abdominal pain, diarrhea) leading to severe weight loss and cachexia. Other clinical features include ptosis, PEO, SNHL, painful paresthesias, and foot drop. The disorder is caused by recessive variants in the *TYMP* gene encoding thymidine phosphorylase, a cytosolic enzyme whose function is essential to the maintenance of intramitochondrial nucleotide pools. Allogeneic hematopoietic stem cell or liver transplantation may be beneficial if performed early in the disease course.

JUVENILE *POLG* SYNDROMES

POLG variants may also present in later childhood or adult life with a range of clinical presentations, including PEO, proximal or distal myopathy, and juvenile and adult-onset epilepsy syndromes. Myoclonic epilepsy, myopathy, and sensory ataxia (MEMSA), incorporating an entity previously known as *spinocerebellar ataxia with epilepsy (SCAE),* typically presents with cerebellar ataxia in adolescence or young adult life, with later development of epilepsy. The seizures are focal initially, often affecting the right hand. Later they become generalized, including epilepsia partialis continua (EPC), and are refractory to therapy. The ataxia neuropathy spectrum (ANS) is characterized by ataxia and neuropathy and includes the previous acronyms MIRAS (mitochondrial recessive ataxia syndrome) and SANDO (sensory ataxia, neuropathy, dysarthria, ophthalmoplegia). ANS also frequently leads to an encephalopathy with seizures, so there is some overlap between MEMSA and ANS. *POLG* disease may also mimic MELAS, MERRF, and MNGIE. Variants in the *MT-ATP6* gene have also been linked to this condition.

MITOCHONDRIAL LEUKOENCEPHALOPATHIES

Several recessive mitochondrial disorders cause *cavitating* leukoencephalopathies (Table 638.8) that typically present in infancy or early childhood with acute- or subacute-onset of motor regression. Other clinical features include epileptic encephalopathy, hemiparesis, spastic paraparesis, bulbar problems, and visual loss (optic atrophy). Mitochondrial leukoencephalopathies may also present later in childhood or in adult life. Some of the mitochondrial tRNA aminoacyl synthetase deficiencies appear to cause specific white matter changes. Other genetic causes of mitochondrial leukoencephalopathy include variants in subunits of complexes I and II and defects of iron-sulfur cluster biosynthesis (see Table 638.8).

LEBER HEREDITARY OPTIC NEUROPATHY AND AUTOSOMAL DOMINANT OPTIC ATROPHY

Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) are two mitochondrial optic neuropathies that may occasionally present with additional encephalomyopathic features. **LHON** is maternally inherited and typically presents in the second or third decade of life (mean onset ~20 years, but childhood presentation is well-recognized) with subacute or acute visual loss sequentially affecting *both* eyes. Three common mtDNA variants in genes encoding complex I subunits (m.3460G>A in *MT-ND1*, m.11778G>A in *MT-ND4*, and m.14484T>C in *MT-ND6*) account for 90% of cases. Penetrance is incomplete, and there is an extreme male preponderance, which may be explained by a protective effect of estrogen in females with LHON variants. In most cases LHON presents as an isolated optic neuropathy, but other clinical manifestations in occasional cases include dystonia (with bilateral striatal necrosis), peripheral neuropathy, or cardiac conduction defects.

ADOA, also known as *Kjer disease,* is the most frequent genetic optic neuropathy and is caused by dominant variants of *OPA1,* encoding a protein needed for mitochondrial fusion. Usually this is an isolated optic neuropathy but may be associated with SNHL. In some patients there are biallelic variants of *OPA1* leading to multiple mtDNA deletions and additional manifestations, including PEO, RRF myopathy and white matter lesions, and cerebellar atrophy associated with ataxia, pyramidal signs, spasticity, and learning disability.

NONSYNDROMIC MITOCHONDRIAL DISORDERS

In childhood, many patients affected by mitochondrial disease present with complex multisystem features that do not align closely with any of the specific known mitochondrial syndromes or with nonsyndromic features, such as isolated epilepsy, leukoencephalopathy, or myopathy. These patients may lack biochemical features of mitochondrial disease such as lactic acidosis and are identified by exome and genome sequencing as a first-line diagnostic strategy in children with encephalomyopathies.

APPROACH TO DIAGNOSIS

When a mitochondrial disease is suspected, it is important to take a thorough personal and family history, including enquiring about early deaths within the extended family, and to screen for multisystemic involvement. This may include formal ophthalmologic, audiologic, and cardiac evaluation. There is no single diagnostic test that can detect all mitochondrial diseases. There are some characteristic MRI appearances, such as bilateral symmetric involvement of the basal ganglia and/or brainstem in Leigh syndrome, strokelike lesions

Table 638.8 Mitochondrial Leukoencephalopathies

GENE DEFECT(S)	CLASS OF MITOCHONDRIAL DISORDER	TYPE OF LEUKOENCEPHALOPATHY
NDUFV1	Complex I deficiency	Cystic leukoencephalopathy
NDUFA2	Complex I deficiency	Cystic leukoencephalopathy with tigroid-like changes
NUBPL	Complex I deficiency	Complex leukoencephalopathy involving deep cerebral white matter, basal ganglia, thalami and corpus callosum, with progressive cerebellar atrophy
SDHA, SDHB, SDHAF1	Complex II deficiency	Cystic leukoencephalopathy with succinate peak on MRS
LYRM7	Complex III deficiency	Cystic leukoencephalopathy
COA7	Complex IV deficiency	Cystic leukoencephalopathy with spinal cord hypotrophy
COA8	Complex IV deficiency	Cystic leukoencephalopathy with posterior predominance
TYMP	Disorder of mtDNA maintenance	Demyelinating leukoencephalopathy
mtDNA deletion	Disorder of mitochondrial translation	T2-hyperintense abnormalities of subcortical cerebral white matter, globus pallidus and substantia nigra (Kearns-Sayre syndrome)
DARS2	Disorder of mitochondrial translation	**L**eukoencephalopathy with **B**rainstem and **S**pinal cord involvement and **L**actate elevation on proton MRS (LBSL)
EARS2	Disorder of mitochondrial translation	**L**eukoencephalopathy (sparing periventricular rim) with **T**halamus and **B**rainstem involvement and **L**actate elevation on proton MRS (LTBL)
IBA57, ISCA2, NFU1	Iron-sulfur cluster biosynthesis defect	Cystic leukoencephalopathy

Courtesy Prof. Shamima Rahman, Great Ormond Street Institute of Child Health, London, United Kingdom.

in MELAS, and the specific leukoencephalopathies outlined in Tables 638.6 and 638.8. However, brain MRI rarely leads to a specific genetic diagnosis other than in these distinctive leukoencephalopathies. Metabolic investigations that may provide diagnostic clues include blood lactate, plasma amino acids and acylcarnitines, urine organic acids, and CSF lactate, amino acids, neurotransmitters, and 5-MTHF. The traditional approach to diagnose a mitochondrial disease included a muscle biopsy, which was subject to histologic, histochemical, and electron microscopic analysis, as well as spectrophotometric or polarographic assay of the individual OXPHOS enzyme complexes. However, in most centers muscle biopsy has been replaced by first-line genetic approaches that utilize next-generation sequencing to sequence the mtDNA, a large panel of nuclear genes, the exome or the whole genome. Muscle biopsy still retains a place in the investigation of critically unwell children with suspected mitochondrial disease and to provide functional validation of variants of unknown significance identified by genetic testing.

MANAGEMENT

There are no curative therapies for most mitochondrial encephalomyopathies, but there are a few notable exceptions. Leigh syndrome caused by deficiency of the SLC19A3 thiamine transporter may respond to a combination of biotin and thiamine, and some patients with disorders of CoQ_{10} biosynthesis may improve with high-dose CoQ_{10} supplementation. High-dose CoQ_{10} supplementation appears to be particularly effective in preventing (but not reversing) the renal manifestations of CoQ_{10} deficiency but has proved ineffective in treating the CNS manifestations of this disorder in prenatal/neonatal-onset CoQ_{10} biosynthesis disorders associated with *COQ4* and *COQ9* variants.

Symptomatic therapies are the mainstay of management for children with mitochondrial encephalomyopathies. Supportive measures may include antiepileptic drugs, hearing aids, cochlear implantation, ptosis surgery, enteral feeding, pancreatic enzyme supplements, hormone replacement (thyroxine, cortisol, growth hormone, insulin, estrogen), cardiac pacing (which can be lifesaving in heart block caused by KSS), and medical management of heart failure.

Emerging therapies under investigation for mitochondrial encephalomyopathies can be divided broadly into pharmacologic and genetic approaches. Pharmacologic therapies under development include redox modulation and strategies to replenish reduced nicotinamide adenine dinucleotide (NAD) boost mitochondrial biogenesis, and stabilize cardiolipin, the membrane lipid unique to mitochondria. A successful trial of adeno-associated virus (AAV) gene replacement has been published for LHON caused by *MT-ND4* variants, and gene therapy has been reported for mouse models of several nuclear-encoded mitochondrial diseases but has yet to be translated to the clinic.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

638.3 Other Encephalopathies

Michael Perry and Cheryl Hemingway

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical syndrome of acute neurologic dysfunction in the presence of vasogenic subcortical brain edema.

The pathophysiologic mechanisms underlying PRES are poorly understood. Endothelial injury, however, with subsequent blood-brain barrier breakdown and vasogenic edema, appears to be a critical factor. Sudden increases in blood pressure exceeding capacity for cerebral blood flow autoregulation, direct cytokine effects, and cytotoxic drugs are all plausible mediators of the endothelial dysfunction. The posterior circulation may be more vulnerable to increased blood pressure because of a relative lack of sympathetic innervation. Children taking immunosuppressant or cytotoxic drugs (e.g., calcineurin inhibitors,

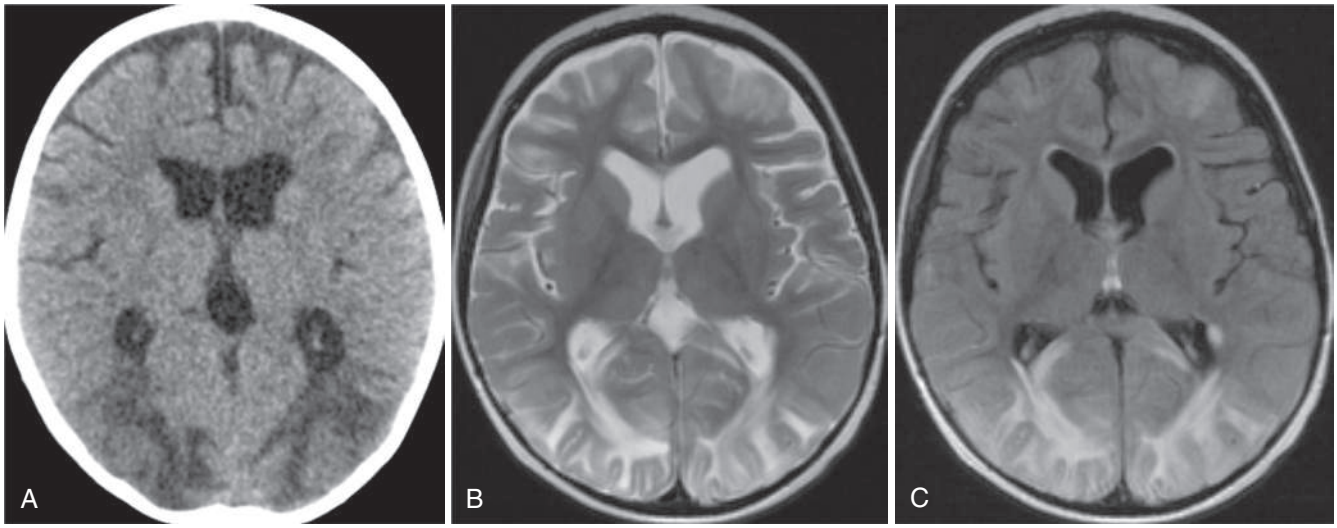

Fig. 638.9 Posterior reversible encephalopathy syndrome (PRES). **A,** Emergent head CT was performed for acute hypertension in this 2-yr-old female with a history of severe aplastic anemia undergoing bone marrow transplantation. A symmetric pattern of posterior-predominant vasogenic edema was evident. Also noteworthy is the moderate parenchymal volume loss, likely related to the patient's other underlying medical conditions. Subsequently obtained T2-weighted **(B)** and FLAIR **(C)** MRIs showed a symmetric abnormally high signal in the posterior cerebral white matter. *(From Nazarian JP, Wolansky L, Gupta A, Coffey M. Demyelinating disease and leukoencephalopathies. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig. 19.18, p. 580.)*

cyclosporine, tacrolimus) in the context of organ transplantation, cancer, and autoimmune disease are at highest risk of developing PRES; renal disease (e.g., glomerulonephritis, IgA vasculitis) is also a risk factor.

Neurologic symptoms in PRES (i.e., seizures, encephalopathy, headache, and visual disturbances) develop over hours to days. Seizures occur almost universally; a focal onset with subsequent generalization is common, and status epilepticus may occur. Encephalopathy can range from mild alteration of mental state to coma. Focal deficits (e.g., hemiparesis) are seen in a small minority of patients.

MRI characteristically shows asymmetric T2/FLAIR high-signal intensities corresponding to vasogenic edema predominantly in the parieto-occipital regions (Fig. 638.9). The basal ganglia, cerebellar hemispheres, and brainstem may also be involved. The changes are almost always seen bilaterally and invariably involve the subcortical white matter with or without hemorrhage (intraparenchymal, petechial, or subarachnoid), restricted diffusion, or contrast enhancement (leptomeningeal, cortical, or nodular). Radiologic resolution typically occurs in days to weeks.

There are no PRES-specific treatments. Care is therefore supportive and should be directed at restoration of a normotensive state, control of seizures with appropriate anticonvulsants, and discontinuation of any offending agent (e.g., cytotoxic drugs). Continuous infusions of antihypertensives may be useful to prevent dramatic fluctuations of blood pressure.

Contrary to what its name suggests, PRES is not always reversible (nor does it always occur posteriorly). Despite this, the prognosis is generally favorable with complete recovery seen in up to 85% of children. Clinical and radiologic improvement becomes evident days to weeks after symptom onset. Hemorrhage is most often responsible for permanent disability.

ACUTE NECROTIZING ENCEPHALOPATHY

Acute necrotizing encephalopathy (ANE) is a rare severe encephalopathy characterized by a rapid and fulminant course. It is seen most often in children under 2 years old in East Asian countries, particularly Japan and Taiwan. Most cases are monophasic and sporadic. However, a familial and recurrent form has been reported in White children in North America and Europe. Approximately half of these cases are associated with pathogenic variants in the mitochondria-related RAN-binding protein 2 *(RANBP2)* gene; this variant is termed *ANE1*. The pathogenesis is not well understood but may be driven by hyper-cytokinemia (e.g., interleukin [IL]-6) triggered by a preceding viral infection (e.g., influenza, rotavirus, respiratory syncytial virus [RSV], parainfluenza virus, enterovirus, human herpesvirus [HHV]-6, SARS-CoV-2) in a genetically susceptible host.

ANE presents with a dramatic encephalopathy after a febrile, "viral" prodrome. Neurologic deficits are profound with rapid progression to coma. Seizures are normally present, and progression of systemic inflammatory dysregulation such as shock, organ failure, and disseminated intravascular coagulation is common. Elevated hepatic enzymes without hyperammonemia are a unique feature. MRI is characterized by bilateral symmetric thalamic lesions with or without lesions in the tegmentum, cerebellar medulla, internal capsule, or periventricular white matter (Fig. 638.10). Table 638.9 lists the diagnostic criteria.

Table 638.9 Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

1. Acute encephalopathy after (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.
2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein.
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellar medulla. No involvement of other central nervous system regions.
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.
5. Exclusion of mimics.
   A. Differential diagnosis from clinical viewpoints. Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic-uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke
   B. Differential diagnosis from radiologic viewpoints. Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

Modified from Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev.* 2012;34:337–343, Table 1.

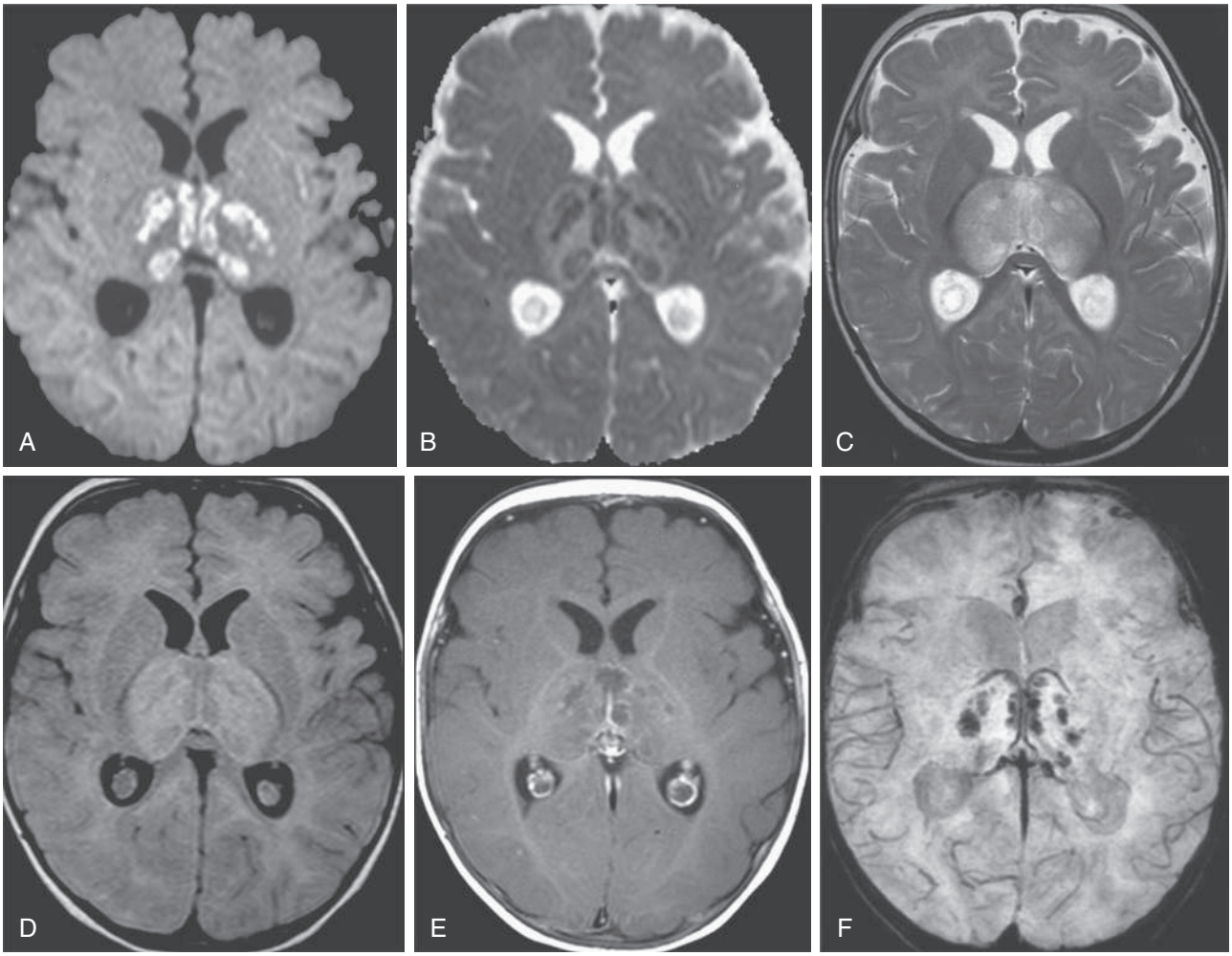

Fig. 638.10 Acute necrotizing encephalopathy. MRI at presentation. **A,** Axial diffusion-weighted image. **B,** Axial apparent diffusion coefficient (ADC) map. **C,** Axial T2-weighted image. **D,** Axial fluid-attenuated inversion recovery (FLAIR) image. **E,** Contrast-enhanced axial T1-weighted image. **F,** Axial susceptibility weighted image. Diffusion-weighted images (**A**) and corresponding ADC map (**B**) clearly show multiple areas of restricted diffusion against a background of increased diffusion involving both thalami, which are swollen. On T2-weighted (**C**) and FLAIR (**D**) images, the thalami are markedly swollen and hyperintense. On T1-weighted images obtained after intravenous gadolinium chelate injection (**E**), multiple necrotic portions are well delineated by peripheral faint, linear enhancement. Incidental choroid plexus cysts are detected. Susceptibility weighted image (**F**) shows multiple hypointense spots, consistent with petechial hemorrhage. *(From Bergamino L, Capra V, Biancheri R, et al. Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: is it useful? Brain Dev. 2012;34:384–391, Fig. 1.)*

There are no formal treatment guidelines. There is limited evidence from small case series demonstrating some response to early (<24 hours from symptom onset) and aggressive high-dose pulsed IV methylprednisolone. Intravenous immunoglobulin (IVIG) may also be of some benefit. Treatment is otherwise supportive, usually in an intensive care setting. Prognosis in ANE is poor, particularly in children with brainstem involvement. Mortality rates approach 40%, and severe neurologic sequelae are typical in surviving children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

638.4 Autoimmune Encephalitis

Thaís Armangué and Josep Dalmau

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 year to adult) but preferentially affect children and younger adults. Some of these disorders are associated with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity, or neuronal excitability. The syndromes vary according to the associated antibody, with phenotypes that resemble those in which the function of the target antigen is pharmacologically or genetically modified.

Most of these disorders are severe and potentially fatal, but patients frequently respond to immunotherapy with good outcomes. Moreover, because of the broad spectrum of symptoms—including alterations of behavior, psychosis, catatonia, insomnia, memory deficits, seizures, abnormal movements, and autonomic dysregulation—patients usually require a multidisciplinary treatment approach.

The identification of autoimmune mechanisms has provided a definitive diagnosis to many cases of encephalitis previously considered idiopathic, infectious, or postinfectious even though no causative agents were found. More than half of cases previously defined as encephalitis lethargica or choreoathetosis post–herpes simplex encephalitis are currently known to be anti–*N*-methyl-D-aspartate receptor **(NMDAR) encephalitis**.

The mechanisms that trigger the production of the antibodies are unknown. In a small subgroup of adolescent or young adult patients, the presence of a tumor that expresses the target neuronal antigen likely contributes to the triggering of the immune response. In addition, the high prevalence of prodromal viral-like symptoms has suggested that nonspecific viral infections may contribute to altering the

immune tolerance for neuronal proteins and increasing the permeability of the blood-brain barrier to antibodies. Nonetheless, in many of these diseases the blood-brain barrier appears intact, and there is evidence that the autoantibodies are synthesized within the CNS by plasma cells that form part of the local brain and meningeal inflammatory infiltrates.

GENERAL DIAGNOSTIC APPROACH TO AUTOIMMUNE ENCEPHALITIS

Most autoimmune encephalitides have a rapid presentation of multiple symptoms, usually in less than 3 months, including neurologic and/or psychiatric alterations frequently associated with seizures or abnormal EEG, and CSF or MRI evidence of inflammatory changes.

Depending on the combination of clinical features and presence of neuronal-specific antibodies, three diagnostic categories have been established: possible autoimmune encephalitis, probable antibody-negative autoimmune encephalitis, and definite antibody-positive autoimmune encephalitis (Table 638.10).

In the pediatric population, the number of autoimmune encephalitis cases associated with well-defined antibodies is substantially lower than that affecting the adult population (Table 638.11).

ANTI-*N*-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS

In this disease, the immunoglobulin G antibodies target the GluN1 subunit of the NMDA receptor. The estimated annual incidence of this disorder is 1.2-1.5 cases per million persons, and it is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM) in children and adolescents. Overall, the disease predominates in females (80%); in patients younger than 12 years, the frequency of males is >40%. The resulting syndrome is highly predictable and usually evolves in stages. In teenagers and young adults, the disorder usually presents with *prominent psychiatric manifestations* that may include rapidly progressive anxiety, agitation, delusional thoughts, bizarre behavior, labile affect, mood disturbances (mania), catatonic features, memory deficit, language disintegration, aggression, and insomnia or other sleep disturbances. In many cases, these symptoms had been preceded by a few days of prodromal headache, fever, or viral infection–like symptoms. Patients are often misdiagnosed with new-onset psychosis or a primary psychiatric disorder. However, in a few days or weeks, additional symptoms occur, including a decreased level of consciousness, seizures (including status epilepticus), limb or oral dyskinesias, choreoathetoid movements, and *autonomic instability* that usually includes tachycardia, bradycardia, fluctuation of blood pressure, hypoventilation, hyperthermia, and sialorrhea. In rare instances, bradycardia and cardiac pauses occur, at times requiring the transient use of a pacemaker. The disorder also occurs in toddlers and infants (the youngest patient identified to date was 2 months old), and although the evolution of the syndrome is similar to that of adults, young patients more frequently present with seizures and movement disorders. Because of the age of patients, the psychiatric-behavioral features may be missed. In this young age-group, behavior changes include irritability, new-onset temper tantrums, agitation, aggression, reduced speech, mutism, and autistic-like regression. Moreover, compared with adults, some children also develop cerebellar ataxia and hemiparesis; in contrast, autonomic dysfunction is usually milder and less severe in children.

Brain MRI studies are abnormal in approximately 35% of patients, usually showing nonspecific cortical and subcortical T2–fluid-attenuated inversion recovery (FLAIR) signal abnormalities, sometimes with transient cortical or meningeal enhancement; nonspecific white matter abnormalities can occur. However, if white matter changes are predominant, an overlapping syndrome with a demyelinating disease should be suspected (Fig. 638.11A). The CSF is initially abnormal in approximately 80% of patients, showing moderate lymphocytic pleocytosis and, less frequently, increased protein synthesis and oligoclonal bands. The EEG is abnormal in *virtually all* patients; it usually shows focal or diffuse slow activity in the delta and theta ranges, which does not correlate with abnormal movements. In addition, many patients develop epileptic activity, requiring video monitoring for adequate clinical management. A distinctive EEG pattern called *extreme delta brush,* characterized by beta-delta complexes, occurs in 30% of adults and less frequently in children (Fig. 638.12).

The diagnosis of the disorder is established by demonstrating NMDAR antibodies in CSF. The sensitivity is higher in CSF compared with serum (100% vs 85%), and the levels of antibodies in CSF appear to correlate better with the outcome. Antibodies may remain detectable, albeit at lower titers, after patients recover.

The presence of an underlying tumor, usually a teratoma, is age and sex dependent. Whereas 40% of females older than 12 years have an underlying teratoma of the ovary, the presence of a tumor is unusual in young males and females or young adult male patients. In children, an MRI of the abdomen and pelvis and abdominal and testicular ultrasound are the preferred tumor screening tests.

In a small number of patients, anti-NMDAR encephalitis occurs simultaneously with or after infections with a variety of pathogens, including *Mycoplasma pneumoniae,* herpes simplex virus (HSV), human herpesvirus 6, enterovirus, COVID-19, and influenza virus. With the exception of HSV1, a pathogenic link with most of these infections has not been established. There is evidence that about 50% of patients with HSV encephalitis develop antibodies against the GluN1 subunit of the NMDAR and other neuronal cell surface proteins and receptors, and of these about half the patients develop new or relapsing neurologic symptoms 2-12 weeks after completing treatment for HSV encephalitis. In children younger than 4 years, this type of autoimmune encephalitis usually manifests with choreoathetosis and dyskinesias (known as *choreoathetosis post-HSV encephalitis;* see **Videos 638.1, 638.2, and 638.3**). In contrast, older children and adults more often develop predominantly behavioral symptoms. A similar complication has been reported in patients with Japanese encephalitis, who develop autoimmune encephalitis (usually with NMDAR antibodies) after the viral encephalitis has subsided.

There is evidence that tumor removal, when appropriate, and prompt immunotherapy improve the outcome. Most children receive first-line immunotherapies, including corticosteroids, IVIG, or plasma exchange. However, because these treatments fail in ~50% of patients, and with multiple reports showing that rituximab is effective, this treatment is increasingly being used in combination with IVIG and steroids or after first-line immunotherapies fail. Cyclophosphamide can be effective when there has been no response to these treatments.

Approximately 80% of patients recover substantially or fully; mortality is estimated to be ~5%, usually as a result of infections or autonomic dysregulation during the acute phase of the disease. Recovery is usually slow and can take as long as 2 years after symptom onset. The last symptoms to improve are problems in social interactions and language and executive functions. **Relapses** occur in approximately 15% of patients; they can develop as partial syndromes, are usually milder than the initial episode, and respond equally well to immunotherapy. Initial comprehensive immunotherapy and rituximab appear to prevent or reduce the number of relapses. The efficacy of chronic immunosuppression with drugs such as azathioprine or mycophenolate mofetil in preventing relapses is unknown. Young children with autoimmune encephalitis, post-HSV encephalitis, and NMDAR antibodies have a poorer prognosis than patients with classical anti-NMDAR encephalitis (see Fig. 638.11B).

The differential diagnosis of anti-NMDAR encephalitis is extensive and varies according to the stage of the disease (Table 638.12). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug misuse.

OTHER TYPES OF ENCEPHALITIS ASSOCIATED WITH ANTIBODIES AGAINST NEURONAL CELL SURFACE ANTIGENS

Encephalitis with antibodies against the γ-aminobutyric acid A receptor ($GABA_AR$) is a rare autoimmune encephalitis that can affect

Table 638.10 Classification Criteria for Possible and Definite Antibody-Positive Autoimmune Encephalitis and Probable Antibody-Negative Pediatric Autoimmune Encephalitis

CATEGORICAL FEATURES OF AUTOIMMUNE ENCEPHALITIS	SPECIFIC DIAGNOSTIC FEATURES	DIAGNOSTIC CATEGORIES		
		POSSIBLE AE	PROBABLE ANTIBODY-NEGATIVE AE	DEFINITE ANTIBODY-POSITIVE AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include:	≥2 features present	≥2 features present	≥2 features present
	Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)			
	Focal neurologic deficits			
	Cognitive difficulties[a]			
	Acute developmental regression			
	Movement disorder (except tics)			
	Psychiatric symptoms			
	Seizures not explained by a previously known seizure disorder or other condition			
3. Paraclinical evidence of neuroinflammation	Features include:	Not available*	≥1 feature present	≥1[b] feature present
	CSF inflammatory changes (leukocytosis >5 cells/mm^3 and/or oligoclonal banding)			
	MRI features of encephalitis			
	Brain biopsy showing inflammatory infiltrates and excluding other disorders			
4. Autoimmune encephalitis serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with autoimmune encephalitis[b]	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

[a]Severe cognitive dysfunction that is not attributable to a primary psychiatric syndrome as documented by a qualified clinician (e.g., neurologist, psychiatrist, and neuropsychologist) or a significant drop in IQ (>20 points).

[b]When antibodies against *N*-methyl-D-aspartate receptor (NMDAR), gamma-aminobutyric acid A receptor ($GABA_AR$), or glutamic acid decarboxylase 65 (GAD65) are present in the CSF, further paraclinical biomarkers of neuroinflammation are not required to diagnose definite autoimmune encephalitis. When only serum antibodies are present, one or more paraclinical marker(s) of neuroinflammation is required.

*If clinical criteria of possible AE are met, the authors recommend proceeding with paraclinical and antibody testing and consider initiating immune therapy if the paraclinical tests are abnormal.

AE, Autoimmune encephalitis.

Adapted from Cellucci T, Van Matter H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e663.

Table 638.11 Autoimmune Encephalitis in Children

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
Anti-NMDAR encephalitis	Antibodies against the GluN1 subunit of the NMDAR. In children, most cases are idiopathic. In a subgroup of patients, the disease is triggered by the presence of a tumor. In another subgroup, the disease is triggered by HSV encephalitis.	Psychiatric symptoms, decreased verbal output, sleep disorder (mainly insomnia), seizures, dyskinesias (orofacial, limbs), dystonia, rigidity and other abnormal movements, autonomic dysfunction, hypoventilation	EEG: almost always abnormal (epileptic and/or slow activity). In some patients it shows the pattern of extreme delta brush. Brain MRI: nonspecific abnormal findings in ~35% CSF: pleocytosis and/or increased proteins in ~80%	80% substantial or complete recovery after immunotherapy and tumor removal (if appropriate). About 50% of patients need second-line immunotherapies.* Relapses in ~15% of patients. Worse outcome when post-HSV encephalitis
Encephalitis associated with $GABA_AR$ antibodies	Antibodies against α1, β3, or γ2 subunits of the $GABA_AR$. ~40% of adults have an underlying tumor (thymoma). Children usually do not have tumor association.	Refractory seizures, epilepsia partialis continua. Patients may develop limb or orofacial dyskinesias.	EEG: almost always abnormal; frequent epileptic activity MRI: multifocal corticosubcortical FLAIR/T2 hyperintensities in 77% of patients CSF: pleocytosis and/or increased proteins	80% show moderate or good recovery after immunotherapy.
Encephalitis with mGluR5 antibodies** (Ophelia syndrome)	Antibodies against mGluR5 Frequent association with Hodgkin lymphoma	Abnormal behavior, seizures, memory deficits	EEG: frequently abnormal with nonspecific findings MRI: normal or nonspecific findings CSF: frequent pleocytosis and/or increased proteins	Good recovery after tumor treatment and immunotherapy
Other autoimmune encephalitis** (very infrequent in children)	Antibodies against neuronal cell surface ($GABA_BR$, DPPX, GlyR, mGluR2, LGI1, Caspr2, GluK2) or intraneuronal antigens (Hu, Ma2, GAD65 amphiphysin) All these antibodies rarely associate with tumors in children.	The syndrome varies depending on the autoantibody, and the phenotypes are often different from those reported in adults. $GABA_BR$: encephalitis, seizures, cerebellar ataxia DPPX: CNS hyperexcitability, PERM GlyR: PERM, stiff person syndrome*** mGluR2: paraneoplastic cerebellar ataxia LGI1: similar syndrome as that of the adults but without FBDS and hyponatremia. Caspr2: similar syndrome as that of the adults and hypertensive encephalopathy, hormonal dysfunction, palmoplantar erythema Gluk2: cerebellitis and/or autoimmune encephalitis with prominent ataxia Hu: brainstem or limbic encephalitis GAD65****: encephalitis with epilepsy	MRI: variable changes depending on the syndrome. CSF: frequent pleocytosis and/or increased proteins	Disorders with antibodies against cell surface antigens are substantially more responsive to immunotherapy than those with antibodies against intracellular antigens.
Encephalitis associated with MOG antibodies	In children the most common clinical manifestation is ADEM	Seizures, motor deficits, ataxia, or visual dysfunction accompanied by encephalopathy	MRI with T2/FLAIR large, hazy abnormalities, with or without involvement of the deep gray matter Some patients develop encephalitis with predominant cortical involvement CSF: frequent pleocytosis and/or increased proteins	In ~70-80% of patients, the disease is monophasic and shows good response to steroids. Some patients develop relapsing disease (with prolonged detection of serum MOG antibodies).

Continued

Table 638.11 Autoimmune Encephalitis in Children—cont'd

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
NMOSD	Patients can have AQP4 or MOG antibodies; some patients are seronegative.	Typical involvement of optic nerves and spinal cord Encephalopathy in the context of diencephalic or area postrema syndromes	Characteristic involvement of brain areas rich in AQP4 (periaqueductal gray matter, hypothalamus, optic nerve and central involvement of the spinal cord)	High risk of relapses and long-term disability. Requires chronic immunotherapy. Patients with MOG antibodies have better long-term outcome than those with AQP4 antibodies or seronegative cases.
Acute cerebellar ataxia and acute cerebellitis	Frequently triggered by infections. Most patients do not have detectable autoantibodies (a few patients have GluK2 antibodies).	Ataxia and dysmetria. Some patients present with headache, vomiting, and decreased level of consciousness caused by intracranial hypertension	MRI: normal in acute cerebellar ataxia; several MRI patterns in acute cerebellitis: diffuse (more frequent) or focal bihemispheric acute cerebellitis with T2/FLAIR hyperintensities in the cerebellar parenchyma; hemicerebellitis (only one hemisphere involved).	Usually self-limiting and benign course in acute cerebellar ataxia; Immunotherapy is usually effective in acute cerebellitis, but some patients may need urgent decompressive craniectomy, and residual neurologic symptoms are frequent.
Opsoclonus-myoclonus and other cerebellar-brainstem encephalitis	Most patients do not have detectable autoantibodies (a few patients with neuroblastoma have Hu antibodies). Neuroblastoma occurs in 50% of children <2yr old; teratoma in teenagers and young adults.	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	MRI: usually normal; it may show cerebellar atrophy over time. EEG: Normal. CSF: may be normal or show abnormalities suggesting B-cell activation.	Neuroblastoma treatment (if it applies). Partial neurologic response to immunotherapy in many young children regardless of presence or absence of neuroblastoma. (Better outcomes if aggressive immunotherapy is used.) Good response to treatment in teenagers with teratoma-associated opsoclonus.
Bickerstaff encephalitis	GQ1b antibodies (~65%, nonspecific for this disorder)	Ophthalmoplegia, ataxia, and decreased level of consciousness. Frequent hyperreflexia. Patients may develop hyporeflexia and overlap with Miller-Fisher syndrome.	MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~45% (predominant axonal degeneration, and less often demyelination)	Good response to steroids, IVIG, or plasma exchange
Steroid responsive encephalopathy with autoimmune thyroiditis (SREAT) (Hashimoto encephalitis)	TPO antibodies† (nonspecific for this disorder)	Strokelike symptoms, tremor, myoclonus, aphasia, seizures, ataxia, sleep and behavioral problems	48% hypothyroidism (usually subclinical), MRI often normal EEG: slow activity CSF: elevated protein	Steroid-responsive. Partial responses are frequent.
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. The most effective treatment is functional hemispherectomy.
Basal ganglia encephalitis	Infrequent antibodies against D2R	Lethargy, abnormal movements, behavioral change, agitation, psychosis	MRI: Basal ganglia T2/FLAIR abnormalities, but may be normal in up to 50% CSF: frequently, elevated protein	Mostly monophasic, variable outcome; 40% complete recovery with immunotherapy.
CLIPPERS	No specific autoantibody association Probably represents different diseases. Important differential diagnosis with lymphoma	Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction	MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord	Steroid-responsive but patients may require chronic steroid or other immunosuppressive therapy.

Table 638.11 Autoimmune Encephalitis in Children—cont'd

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
ROHHAD	Postulated autoimmune or genetic; some patients have antibodies against ZSCAN1. Frequently associated with neural crest tumors	Rapid-onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic treatment. In some patients, limited response to immunotherapy.

*Includes rituximab and cyclophosphamide.
**Commercial testing panels do not include GluK2, D2R, or mGluR antibodies. Therefore when one of these conditions is suspected, the samples should be investigated in a research laboratory.
***Low titers of GlyR ab have been reported in the serum of multiple different disorders, and their clinical significance is unclear; demonstration of antibodies in CSF has higher disease-specificity and is found usually associated with PERM.
****Lower titers of GAD65 antibodies in serum are found in patients with diabetes mellitus (~100-fold lower titers than those associated with GAD-antibody–associated neurologic disorders), other non-neurologic autoimmune conditions, and healthy persons.
†Diagnosis of exclusion, after ruling out relevant autoantibodies (e.g., NMDAR, AMPAR, among others).
AQP4, Aquaporin 4; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; Caspr2, contactin-associated protein-like 2; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; DPPX, dipeptidyl-peptidase-like protein-6; EEG, electroencephalography; FBDS, faciobrachial dystonic seizures; FLAIR, fluid-attenuated inversion recovery; $GABA_AR$, γ-aminobutyric acid-A receptor; $GABA_BR$, γ-aminobutyric acid-B receptor; GAD65, glutamic acid decarboxylase 65; GluK2, glutamate kainate receptor 2; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; LGI1, leucine-rich glioma-inactivated 1; mGluR, metabotropic glutamate receptor; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; PERM, progressive encephalomyelitis with rigidity and myoclonus; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase; ZSCAN1, Zinc finger and SCAN domain-containing protein 1.

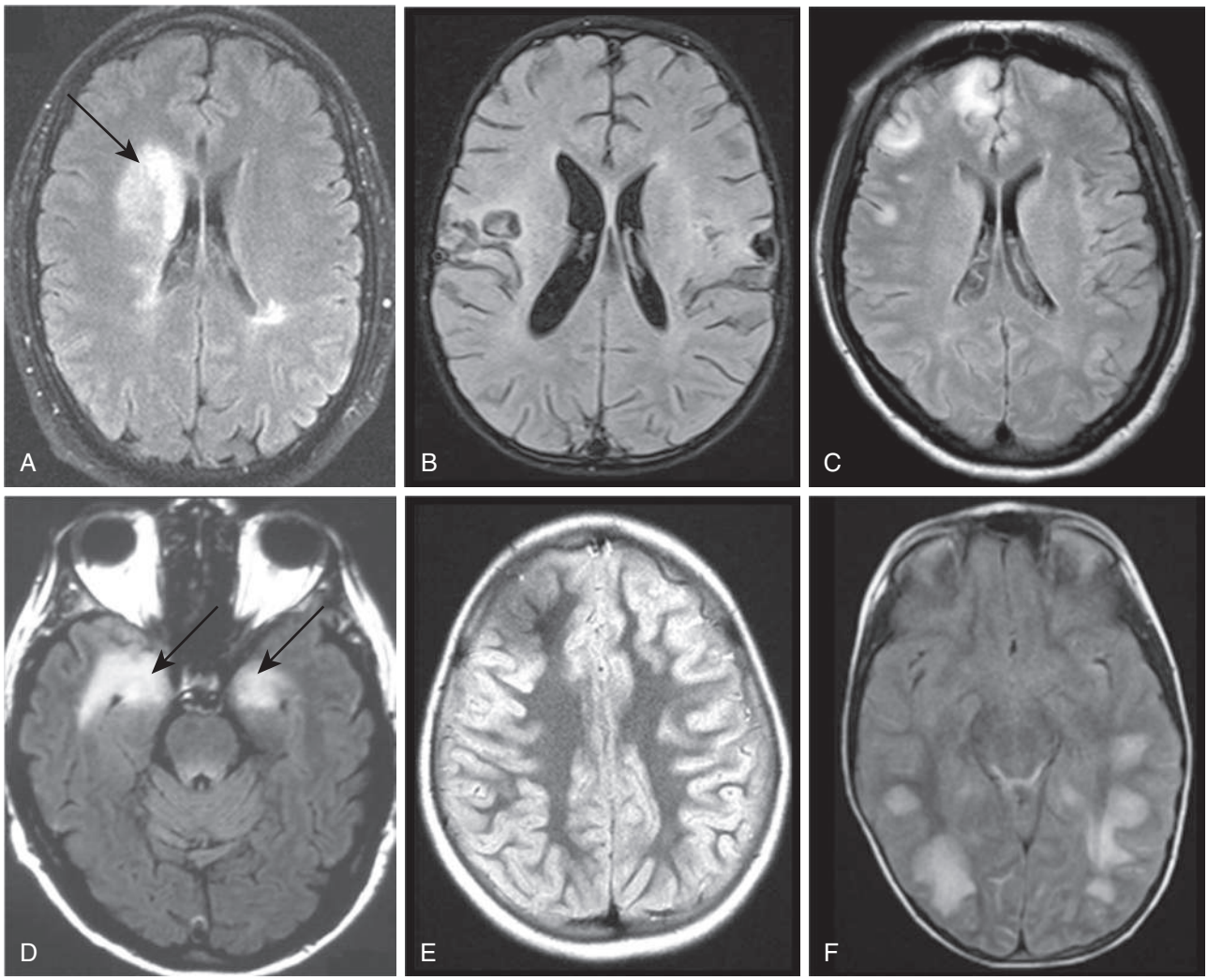

Fig 638.11 Brain MRI patterns in autoimmune encephalitis. **A,** FLAIR MRI image of a patient with anti-NMDAR encephalitis and concurrent MOG antibodies; it shows a prominent right frontal abnormality compatible with demyelination. **B,** T1-weighted MRI image of a 2-yr-old male with anti-NMDAR encephalitis after herpes simplex encephalitis. There are extensive necrotic areas in temporal regions that are residual from the viral encephalitis, without new MRI lesions produced by the autoimmune encephalitis. **C,** FLAIR MRI image from a patient with anti-$GABA_AR$ encephalitis; it shows multiple cortical-subcortical bilateral right frontal predominant hyperintensities. **D,** FLAIR MRI image showing typical features of limbic encephalitis with bilateral medial temporal lobe abnormalities; this adult patient with autopsy-proven limbic encephalitis did not have serum or CSF antineuronal antibodies. **E,** FLAIR MRI image showing extensive cortical involvement in a 9-yr-old with fatal encephalitis associated with MOG antibodies and severe intracranial hypertension. **F,** Typical FLAIR MRI findings in a 4-yr-old female with acute disseminated encephalomyelitis associated with MOG antibodies; it shows bilateral large abnormalities in the white matter. Left side of images = right side of brain. (***A*** *and* ***D*** *from Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15:391–404. Fig. 2.;* **C** *courtesy Dr. Mateus Mistieri Simabukuro;* ***B***, ***E***, *and* **F** *courtesy Drs. Thaís Armangué and Josep O. Dalmau.)*

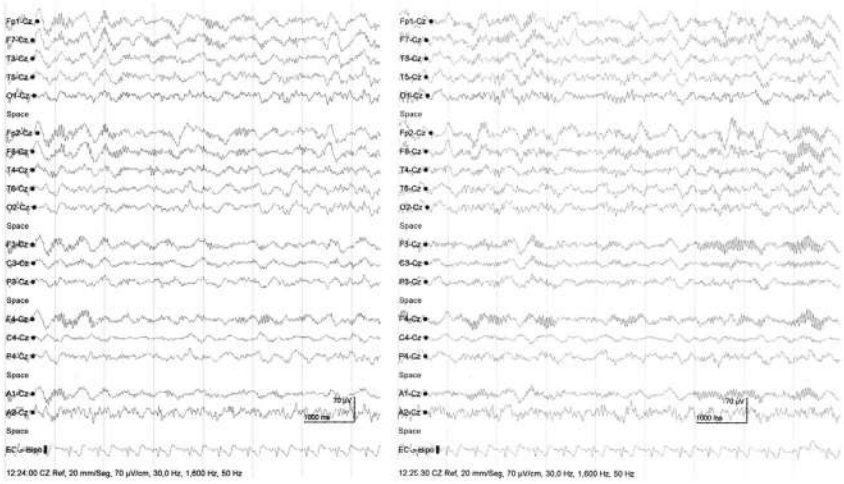

Fig. 638.12 Electroencephalogram showing a pattern called extreme delta brush in a 14-yr-old female with anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. This pattern has been found to be characteristic of anti-NMDAR encephalitis. It consists of a nearly continuous combination of delta activity with superimposed fast activity, usually in the beta range, symmetrically involving all regions, with a frontal preference in patients who are not under sedation or anesthesia. *(From Armangue T, Titulaer MJ, Málaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis: clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2012;162:850–856, Fig. 2.)*

children (40% of patients are <18 years) and develops with status epilepticus, refractory seizures, or epilepsia partialis continua in association with antibodies against the α1, β3, or γ2 subunits of the $GABA_AR$. Young children can develop abnormal movements suggestive of anti-NMDAR encephalitis but with studies negative for NMDAR antibodies. Unlike other types of autoimmune encephalitis in which the brain MRI is usually normal or shows nonspecific findings, pediatric and adult patients with this disorder frequently develop multifocal hyperintense cortical-subcortical FLAIR/T2 abnormalities (see Fig. 638.11C). In adults, this encephalitis may occur with thymoma, but children rarely have an underlying tumor.

Ophelia syndrome is a form of encephalitis that occurs in association with Hodgkin lymphoma and predominantly affects young adults, teenagers, or children. Some patients develop antibodies against mGluR5, a receptor involved in learning and memory. Neurologic symptoms are highly responsive to treatment of the tumor and immunotherapy.

Autoimmune limbic encephalitis refers to an inflammatory process of the limbic system, including the medial temporal lobes, amygdala, and cingulate gyri (see Fig. 638.11D). In adults, the most frequent immune-mediated limbic encephalitis occurs in association with antibodies against proteins that were once thought to be voltage-gated potassium channels (VGKCs) but which, in fact, target a secreted neuronal protein called *leucine-rich glioma-inactivated 1* (LGI1) and a protein called *Caspr2* expressed in the brain and the juxtaparanodal regions of myelinated nerves. Adult patients with LGI1 antibody–associated limbic encephalitis often develop *hyponatremia;* in some patients, the disorder is preceded by dystonic or myoclonic-like movements, described as *faciobrachial dystonic seizures.* Adult patients with Caspr2 antibodies can develop limbic encephalitis, neuromyotonia, or **Morvan syndrome**, which includes encephalopathy, seizures, a sleep disorder, autonomic dysfunction, and neuromyotonia. In children, encephalitis with LGI1 or Caspr2 antibodies is extremely rare. Children with LGI1 antibodies do not develop hyponatremia or faciobrachial dystonic seizures. Younger children with Caspr2 antibodies often have similar symptoms to those of the adults, which can also be accompanied by generalized weakness, flaccid paresis, hypertensive encephalopathy, hormonal dysfunction, and palmoplantar erythema or eczema that has been attributed to sweating and itching. Children with Caspr2 antibodies do not have associated tumors.

VGKC-complex antibodies have very limited clinical utility unless they are specifically characterized as antibodies against LGI1 or Caspr2 proteins. Thus a positive test for VGKC-complex antibodies without further information on LGI1 or Caspr2 specificity should be interpreted with caution because it does not necessarily indicate autoimmune encephalitis.

Excluding patients with anti-NMDAR– or GABAAR antibody–associated encephalitis, an exceptionally low number of children with limbic and other types of neuronal antibody-associated encephalitis have been reported in the English literature, some of them with antibodies against neuronal cell surface proteins ($GABA_BR$, DPPX, GlyR) or intracellular proteins (Hu, Ma2, GAD65, amphiphysin). In some patients, an underlying malignancy was identified, including leukemia, ganglioneuroblastoma, neuroblastoma, or small cell carcinoma of the ovary.

Determination of the type of autoantibodies and location of the target antigens is important because an encephalitis in which the antigens are on the cell surface (e.g., NMDAR or GABAAR) responds better to immunotherapy than one in which the antigens are intracellular (e.g., GAD65).

ACQUIRED DEMYELINATING SYNDROMES WITH ENCEPHALOPATHY

ADEM is the most frequent autoimmune encephalitis in children (see Chapter 640.1). Symptoms may include seizures, motor deficits, ataxia, and visual dysfunction, among others. The brain MRI typically shows multifocal demyelinating lesions that can also involve the basal ganglia, brainstem, or cerebellum, with variable contrast enhancement (see Fig. 638.11F). Antibodies against myelin oligodendrocyte glycoprotein (MOG) occur in 50–60% of patients with ADEM and have a negative predictive value for evolution to multiple sclerosis in children with a first demyelinating event (see Chapter 640.1). Some children with MOG antibodies develop a clinical picture resembling autoimmune encephalitis with MRI FLAIR/T2 increased signal involving cortical regions, with variable contrast enhancement, or presenting as nondemyelinating focal or diffuse lesions (see Fig. 638.11E). MOG antibodies may also coexist with NMDAR antibodies; these patients usually develop overlapping syndromes related to these autoimmunities.

Neuromyelitis optica spectrum disorder (NMOSD) can present as an encephalopathy with predominant involvement of diencephalic and area postrema regions. These patients often harbor aquaporin 4 (AQP4) antibodies or MOG antibodies. Determination of these antibodies should be considered in patients with encephalopathy and MRI findings showing involvement of AQP4-rich regions, such as the periaqueductal gray matter, hypothalamus, optic nerves, and central region of the spinal cord (see Chapter 640.2).

HASHIMOTO ENCEPHALOPATHY

Hashimoto encephalopathy, also known as **steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT)**, is a controversial disorder defined by the detection of thyroid peroxidase (TPO) antibodies in patients with acute or subacute encephalitis that responds to corticosteroids. Clinical features are not specific and may include strokelike episodes, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The CSF, MRI, and EEG findings are not specific. The diagnosis of this disorder should be based on the exclusion of other inflammatory and autoimmune diseases. Pretreatment criteria of Hashimoto encephalopathy do

Table 638.12 Differential Diagnosis of Anti-NMDAR and Other Types of Autoimmune Encephalitis in Children

DISORDER	COMMENTS
Viral encephalitis	Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.
New neurological symptoms post-HSV encephalitis	Occurs ~2-12 wk after successful treatment of HSV encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir) or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.
New-onset psychosis	Because most patients with anti-NMDAR encephalitis present with psychosis, a psychiatric disorder is frequently considered. When the disease evolves, the development of neurologic symptoms usually reveals the diagnosis.
Drugs/toxins	The acute development of personality and behavioral changes and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug use (e.g., ketamine, phencyclidine, synthetic cannabinoids, among others).
Neuroleptic malignant syndrome (NMS)	The occurrence of an altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.
Limbic encephalitis (LE)	Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include acute or subacute encephalitis with at least three of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Many patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.
Childhood disintegrative disorder/late-onset autism	Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. Although the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have a substantial clinical recovery.
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and childlike behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis or as permanent sequelae. However, different from the Kleine-Levin syndrome, the symptoms in anti-NMDAR encephalitis are not relapsing-remitting
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson syndrome, and Lesch-Nyhan syndrome. Pantothenate kinase–associated neurodegeneration, porphyria, and urea cycle defects should also be considered.
Genetic disorders that can manifest as autoimmune encephalitis	HLH (often initial presentation as primary CNS with later 1-2 yr onset of systemic features) RANBP2 variants, interferonopathies, autoinflammatory syndromes including cryopyrin-associated periodic syndromes, Aicardi-Goutières syndrome, and CTLA4 deficiency can present with clinical features mimicking ADEM or autoimmune or infectious encephalitis. MRI often shows hyperintense T2/FLAIR abnormalities involving white matter with contrast enhancement in HLH and CTLA4 deficiency; both thalami in *RANBP2* variants; and may show striatal necrosis with or without associated hypomyelination in ADAR1 interferonopathy. CSF is abnormal in most patients. Some patients develop systemic symptoms (e.g., fever, arthralgias or rash in autoinflammatory syndromes, or autoimmune cytopenias or hypogammaglobulinemia in CTLA4 deficiency) that can help to make the diagnosis, which is confirmed by genetic testing.
Monoamine neurotransmitter disorders	Deficiency of dopamine or serotonin, or both, can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.
Acquired demyelinating disorders	ADEM and NMOSD are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis, these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMOSD, the presence of AQP4 antibodies in serum or CSF is associated with relapses and poor prognosis. MOG antibodies occur in ~50% of children with ADEM and some patients with NMOSD.

Continued

Table 638.12 Differential Diagnosis of Anti-NMDAR and Other Types of Autoimmune Encephalitis in Children—cont'd

DISORDER	COMMENTS
CNS vasculitis	CNS vasculitis (including RVCLS: *TREX1*) results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large-vessel angiitis and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter suggesting ischemia and microhemorrhages, but are not restricted to vascular territories and frequent leptomeningeal and/or local enhancement.
Systemic rheumatic disorders	Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.

ADEM, Acute disseminated encephalomyelitis; CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; HSV, herpes simplex virus; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; HLH, hemophagocytic lymphohistiocytosis; LE, limbic encephalitis; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction; RANBP2, Ras-related nuclear protein-binding protein 2; RVCLS, retinovasculopathy and cerebral leukodystrophy with systemic features, CTLA4, cytotoxic T-lymphocyte–associated protein 4; ADAR1, adenosine deaminase acting on RNA 1.

not predict steroid responsiveness. Because TPO antibodies occur in approximately 10% of asymptomatic children (i.e., nonencephalopathic and, in most cases, euthyroid) and can also be found in some patients who have more relevant antibody-associated diseases, the detection of TPO antibodies should be viewed as a marker of autoimmunity rather than a disease-specific or pathogenic antibody. Therefore detection of TPO antibodies should not prevent testing for more relevant antibodies, such as NMDAR antibodies.

Acute cerebellar ataxia and acute cerebellitis are the most frequent causes of cerebellar dysfunction in children. Ataxia and dysmetria are usually the main presenting symptoms, but some patients present with headache, vomiting, and decreased level of consciousness caused by intracranial hypertension. Brain MRI is normal in patients with acute cerebellar ataxia, but in cases of cerebellitis it shows T2/FLAIR hyperintensities in the white and gray matter of the cerebellum along with edema that may cause obstruction of the fourth ventricle and hydrocephalus. Treatment with steroids is usually effective, but some patients may need decompressive craniectomy. Whereas acute cerebellar ataxia with normal MRI is often self-limiting and has a benign course, cerebellitis with MRI abnormalities associates with a less favorable prognosis and almost half of them have residual neurologic deficits. The most frequent cause of acute cerebellar ataxia and cerebellitis is a viral infection; much less frequently, they may occur after bacterial infections or vaccines. A few cases with antibodies against the glutamate kainate 2 (GluK2) receptor have been reported.

OPSOCLONUS-MYOCLONUS AND OTHER TYPES OF RARE BRAINSTEM-CEREBELLAR ENCEPHALITIS

Opsoclonus-myoclonus occurs in infants, teenagers, and adults, although it probably represents different diseases and pathogenic mechanisms. In infants, the syndrome usually develops in the first 2 years of life (mean: 20 months), and at least 50% of patients have an underlying neuroblastoma. The child often presents with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms may include a refusal to walk or sit, speech problems, hypotonia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients may initially be diagnosed with acute cerebellitis. Typically, CSF abnormalities suggest B-cell activation, and the presence of antibodies against neuronal proteins has been demonstrated in rare instances, but the identification of a specific autoantigen has been elusive.

Immunotherapy, including corticosteroids and IVIG, often improves the abnormal eye movements, but residual behavioral, language, and cognitive problems persist in the majority of patients. In addition, insomnia and an abnormal response to pain are common. Relapses occur in 50% of patients, usually as a result of an intercurrent infection or drug tapering. Patients treated with more aggressive immunosuppression (often including rituximab) have better outcomes compared with historic control series or patients who did not receive these treatments. Delay in treatment appears to be associated with a poorer neurologic outcome; therefore in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.

In teenagers and young adults, opsoclonus-myoclonus and brainstem-cerebellar encephalitis without opsoclonus are often considered idiopathic or postinfectious; however, there is evidence that some of these patients have an underlying **teratoma**, usually in the ovaries. These patients do not harbor NMDAR antibodies, and compared with those with anti-NMDAR encephalitis, they are less likely to present with psychiatric symptoms or dyskinesias. Although these patients do not appear to have neuronal antibodies, the CSF often shows pleocytosis and an elevated protein concentration. Treatment with immunotherapy (corticosteroids, IVIG, and/or plasma exchange) and removal of the ovarian teratoma frequently associate with full recovery. The prognosis of opsoclonus-myoclonus in teenagers and young adults seems better than that of young children (with or without neuroblastoma) or of the paraneoplastic opsoclonus of older patients, usually related to breast, ovarian, or lung cancer.

BICKERSTAFF ENCEPHALITIS

This term is used to describe patients with rapid progression (<4 weeks) of bilateral external ophthalmoplegia, ataxia, and decreased level of consciousness. Although this entity has been described more frequently in adults, children as young as 3 years old have been identified. Most patients are treated with steroids, IVIG, or plasma exchange; they often have a good outcome. Serum GQ1b immunoglobulin G antibodies are found in 66% of patients. Brain MRI abnormalities occur in 30% of patients and usually include increased T2-signal abnormalities in the brainstem, thalamus, and cerebellum and sometimes in the cerebral white matter. Some patients develop hyporeflexia and limb weakness, with predominant axonal involvement, overlapping with symptoms of Miller-Fisher syndrome and the axonal subtype of Guillain-Barré syndrome.

CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS

This is a clinically and radiologically distinct pontine-predominant encephalomyelitis. Patients usually present with episodic diplopia or facial paresthesias with subsequent development of symptoms of

brainstem, cerebellum, and, occasionally, spinal cord dysfunction. A brain MRI shows symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, and midbrain and occasionally into the spinal cord. The clinical and radiologic findings usually respond to high-dose steroids but may worsen after steroid tapering, requiring chronic steroid or other immunosuppressive therapy. The differential diagnosis is extensive and includes infections, acquired demyelinating syndromes, granulomatous disease, lymphoma, or vasculitis. Biopsy studies may be needed to exclude these and other conditions.

AUTOIMMUNE ENCEPHALOPATHIES ASSOCIATED WITH EPILEPSY AND STATUS EPILEPTICUS

Rasmussen encephalitis is an inflammatory encephalopathy characterized by progressive refractory focal seizures, cognitive deterioration, and focal neurologic deficits that occur with gradual atrophy of one brain hemisphere. The disorder frequently presents in children 6-8 years old, although adolescents and adults can be affected. The etiology is unknown, and therefore multiple theories are proposed, including the presence of neuronal antibodies and T-cell–mediated mechanisms triggered by a viral infection. None of these mechanisms satisfactorily explain the unilateral brain involvement characteristic of the disorder. Treatment with high-dose steroids, plasma exchange, or IVIG can ameliorate symptoms in early stages of the disease. Multiple different approaches with immunotherapy, including rituximab, tacrolimus, azathioprine, adalimumab, mycophenolate mofetil, natalizumab, or anakinra have not substantially changed the poor outcome of most patients. The most effective treatment for control of the seizures is functional hemispherectomy, which consists of surgical disconnection of the affected hemisphere.

OTHER SUSPECTED TYPES OF AUTOIMMUNE ENCEPHALITIS

Vasculitis of the CNS and rheumatic diseases associated with autoimmune mechanisms that can result in encephalitis are discussed in Chapter 642.

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is discussed in Chapter 468.3.

The term **basal ganglia encephalitis** is used to describe patients with predominant or isolated involvement of the basal ganglia. These patients typically have abnormal movements such as dystonia, chorea, or parkinsonism and neuropsychiatric disease. Although these clinical manifestations may have multiple etiologies, including metabolic, toxic, genetic, and infectious processes, an immune-mediated etiology has been postulated in some patients. There have been no clinical trials, but case reports and small noncontrolled case series describe the potential benefit of immunotherapy. Antibodies against the dopamine-2 receptor have been infrequently identified in these patients.

Pseudomigraine syndrome with CSF pleocytosis (PMP) or **headache with neurologic deficits and CSF lymphocytosis (HaNDL)** is an ill-defined entity that predominantly affects young male adults with a family history of migraine, although adolescents can be affected. This syndrome is characterized by repeat episodes of severe headache with transient neurologic deficits, accompanied by aseptic CSF lymphocytosis and a normal brain MRI. Patients frequently show a high CSF opening pressure, an elevated CSF protein concentration, and focal EEG slowing, which normalize after the episodes of headache. Because of the inflammatory characteristics of the CSF and the high prevalence of prodromal viral-like symptoms, an infectious–immune-mediated mechanism has been proposed. Other theories include spreading cortical depression and trigeminal-vascular activation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 639

Neurodegenerative Disorders of Childhood

Kristin A. Seaborg and Jennifer M. Kwon

Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases caused by specific genetic and biochemical defects. Although many children with neurodegenerative disorders first present with developmental delay or seizures, the hallmark of a neurodegenerative disease is **regression and progressive deterioration** of neurologic function with loss of speech, vision, hearing, locomotion, feeding difficulties, and cognitive decline. The age of onset, rate of progression, and principal neurologic findings determine whether the disease affects primarily the white or the gray matter. Upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders; convulsions and intellectual and visual impairments that occur early in the disease course are the hallmarks of gray matter disorders. A precise history confirms regression or delay of developmental milestones, and the neurologic examination localizes the process within the nervous system. At that point, modern neuroimaging techniques and specific biochemical and molecular diagnostic tests are used to arrive at a diagnosis. Although available therapies are often limited, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented. Bone marrow transplantation, enzyme replacement therapies, cell-based gene therapy, immune modulation, and dietary restrictions may prevent the progression of disease in certain individuals who are either presymptomatic or very early in their disease course. For all conditions in which the specific genetic defect is known, prevention by prenatal diagnosis through chorionic villus sampling or amniocentesis is possible, as is carrier detection. Table 639.1 summarizes selected inherited neurodegenerative and metabolic disorders by their usual age of onset.

639.1 Sphingolipidoses

Kristin A. Seaborg and Jennifer M. Kwon

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes (Fig. 639.1). Poorly degraded sphingolipids accumulate in neuronal lysosomes leading to cellular dysfunction and death. There are multiple sphingolipidoses, including Niemann-Pick disease, Gaucher disease, GM_1 gangliosidosis, GM_2 gangliosidosis, Krabbe disease (KD), and metachromatic leukodystrophy. Niemann-Pick disease and Gaucher disease are discussed in Chapter 106.4.

GANGLIOSIDOSES

See also Chapter 106.4.

Gangliosides are sphingolipids consisting of an oligosaccharide chain attached to a hydroxyl group of ceramide and sialic acid bound to galactose. The gangliosides are catabolized by sequential cleavage of the sugar molecules by specific exoglycosidases. Abnormalities in catabolism result in an accumulation of the ganglioside within the cell, resulting in disease. Defects in ganglioside degradation include GM_1 gangliosidosis and the GM_2 gangliosidoses.

GM_1 Gangliosidosis

GM_1 gangliosidosis is an autosomal recessive condition caused by deficiency of acid β-galactosidase from pathogenic variants in *GLB1*. It is further classified by age at presentation: infantile (type I), juvenile (type II), and adult (type III), where the age of onset and severity

Table 639.1 Selected Metabolic Conditions Associated with Developmental Regression

AGE AT ONSET (YR)	CONDITIONS	COMMENTS
<2, often with hepatomegaly or hepatic effects	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	GM_1 gangliosidosis	Coarse facies, macroglossia, cherry- red spot in macula
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Zellweger syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, microcephaly
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Tay-Sachs disease, GM_2 gangliosidoses	Seizures, cherry-red spot of macula, increased startle response
	Subacute necrotizing encephalopathy or Leigh disease	White matter disease, basal ganglia, brainstem lesions
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease (see Table 639.4)	Cerebellar atrophy, optic atrophy, iron accumulation in basal ganglia, movement disorder
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia-telangiectasia	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, vision loss
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2- to 5-yr-olds
	Neuronal ceroid lipofuscinosis, juvenile and adult forms	Gray matter disease
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies

Adapted from Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004:542.

depends on the degree of β-galactosidase deficiency. Diagnosis can be made by enzyme assay or by identification of biallelic pathogenic variants in *GLB1* by molecular genetic testing. Prenatal diagnosis is possible by enzyme or direct molecular testing of cultured amniotic cells.

Infantile GM_1 gangliosidosis presents during the neonatal period with poor sucking and inadequate weight gain. Development is delayed, and generalized seizures are prominent. The phenotype is characterized by coarse facial features, prominent forehead, depressed nasal bridge, large tongue (macroglossia), and gum hypertrophy. There is early hepatosplenomegaly from intracellular accumulation of foamy histiocytes and kyphoscoliosis from anterior beaking of the vertebral bodies. The neurologic examination is notable for progressive blindness, deafness,

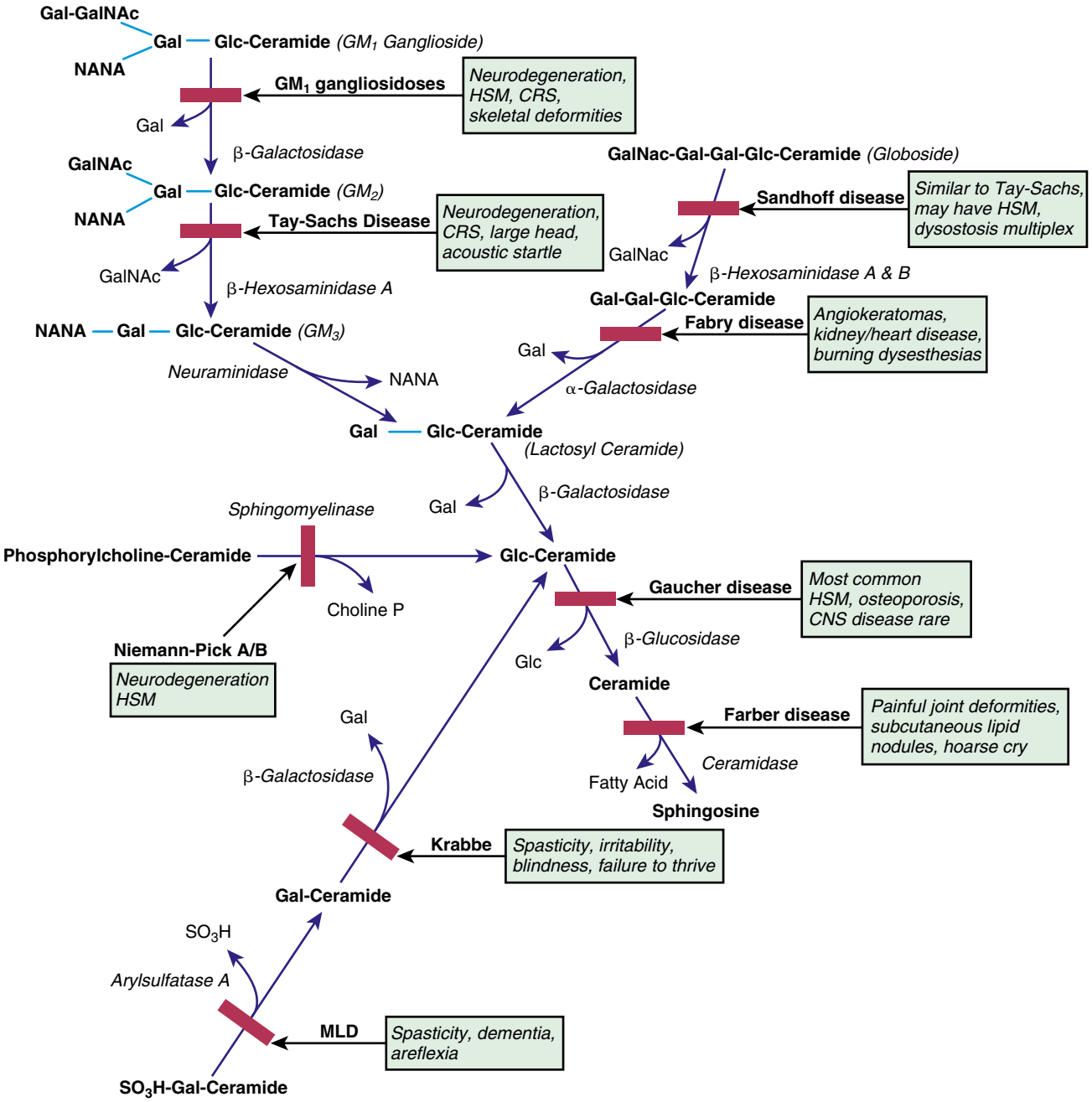

Fig. 639.1 Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macula is visualized in approximately 50% of cases (Fig. 639.2). Treatment is supportive, and children rarely survive beyond age 2-3 years. Death is often from aspiration pneumonia.

Type II GM_1 gangliosidosis presents later in infancy, before 3 years. Initial symptoms consist of weakness, ataxia, and regression of language. Thereafter, convulsions, spasticity, decerebrate rigidity, and blindness are the major findings. Unlike type I, coarse facial features and hepatosplenomegaly are not usually seen. Lumbar vertebrae may show minor beaking. Children rarely survive beyond 10 years of age. **Adult GM_1 gangliosidosis** is a slowly progressive disease with onset between ages 3 and 30 years consisting of spasticity, ataxia, dysarthria, cardiomyopathy, and a gradual loss of cognitive function.

GM_2 Gangliosidoses

The GM_2 gangliosidoses are a heterogeneous group of autosomal recessive disorders caused by abnormal catabolism of the GM_2 ganglioside, which accumulates in neuronal lysosomes. GM_2 catabolism requires functional isoenzymes β-hexosaminidase and GM_2 activator protein. Tay-Sachs disease (TSD), Sandhoff disease, juvenile GM_2 gangliosidosis, and adult GM_2 gangliosidosis are caused by genetic variants in the genes that encode the alpha and beta subunits of β-hexosaminidase and lead to decreased or absent β-hexosaminidase activity with subsequent accumulation of GM_2.

TSD is most prevalent in the Ashkenazi Jewish population, with an approximate carrier rate of 1 in 30 Jews in the United States. TSD is caused by pathogenic variants in *HEXA* on chromosome 15q23, which

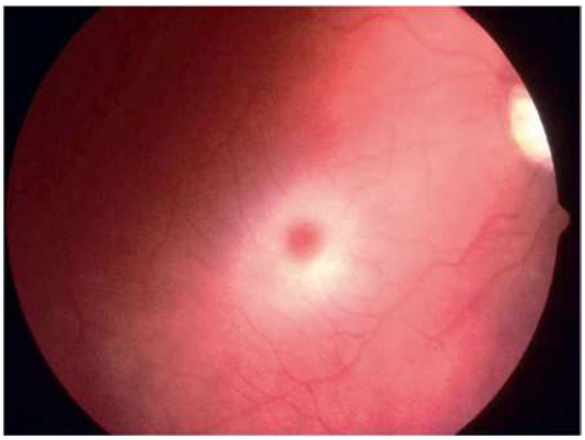

Fig. 639.2 A cherry-red spot in a patient with GM_1 gangliosidosis. Note the whitish ring of sphingolipid-laden ganglion cells surrounding the fovea. *(From Leavitt JA, Kotagal S. The "cherry red" spot. Pediatr Neurol. 2007;37:74–75, Fig. 1.)*

encodes the α subunit of β-hexosaminidase. Affected infants often have a *marked startle reaction* to noise that is evident soon after birth but otherwise have normal development until ~6 months of age. They then begin to lag in developmental milestones and gradually lose the ability to stand, sit, and vocalize by age 1. Children with TSD have earlier onset of dysphagia than children with other GM_2 gangliosidoses. Early hypotonia develops into progressive spasticity and relentless deterioration follows, with convulsions, blindness, deafness, and cherry-red spots in almost all patients (see Fig. 639.2). Macrocephaly becomes apparent by 1 year of age and results from the 200- to 300-fold normal content of GM_2 ganglioside deposited in the brain. Few children live beyond 3-4 years of age, and death is usually associated with aspiration or bronchopneumonia.

To diagnose TSD or any of the GM_2 gangliosidoses, a deficiency of the isoenzyme β-hexosaminidase is found in blood, serum, or fibroblasts. In addition, molecular genetic testing may be done to evaluate for variants in the *HEXA* or *HEXB* gene to confirm the diagnosis.

Sandhoff disease occurs secondary to a variant *HEXB* gene located on chromosome 5q13. Affected infants present very similar to TSD, including progressive loss of motor and language milestones beginning at 6 months of age. Unlike children with TSD, children with Sandhoff disease may also have visceromegaly. The visual evoked potentials (VEPs) are normal early in the course of Sandhoff disease and TSD but become abnormal or absent as the disease progresses. The auditory brainstem responses show prolonged latencies. The diagnosis of Sandhoff disease is established by finding deficient levels of hexosaminidases A and B in serum and leukocytes. Children usually die by 3 years of age.

Juvenile GM_2 gangliosidosis develops in mid-childhood, initially with clumsiness followed by ataxia. Signs of spasticity, athetosis, loss of language, and seizures gradually develop. Progressive visual loss is associated with optic atrophy, but cherry-red spots rarely occur in juvenile GM_2 gangliosidosis. A deficiency of hexosaminidase is variable (total deficiency to near normal) in these patients. Death occurs around 15 years of age.

Although the genetic etiologies of the gangliosidoses are well-established, there is currently no known treatment for these disorders other than supportive management and palliative care. An adeno-associated virus-HEXA/HEXB–directed gene therapy proof-of-concept trial has been performed in two children with TSD.

KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)

Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. The gene for KD *(GALC)* is located on chromosome 14q24.3-q32.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β-galactosidase (GALC). KD is a disorder of myelin destruction rather than abnormal myelin formation. Normally, myelination begins in the third trimester, corresponding with a rapid increase of GALC activity in the brain. In patients with KD, galactocerebroside cannot be metabolized during the normal turnover of myelin because of deficiency of GALC. Nonmetabolized galactocerebroside stimulates the formation of globoid cells, which can be cytotoxic to oligodendrocytes. Because oligodendroglial cells are responsible for the elaboration of myelin, their loss results in myelin breakdown, thus producing additional galactocerebroside and causing a vicious circle of myelin destruction.

Myelin exists in both the central and peripheral nervous system and allows for rapid conduction along axons. With GALC deficiency and associated rapid and severe demyelination, the symptoms of KD become evident in the first few months of life and include excessive irritability and crying, poor head control, episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or milk allergy with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos as well as visual inattentiveness caused by optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep tendon reflexes, autonomic instability, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 years of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in KD. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms. Recombinant GALC triggers an immune reaction, and the large protein does not efficiently cross the blood-brain barrier.

Late-onset KD has been described beginning in childhood or adolescence. Patients present with pes cavus, sensorimotor demyelinating neuropathy, optic atrophy, and cortical blindness; their condition may be confused with adrenoleukodystrophy. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent. Globoid cells are abundant in the white matter, and leukocytes are deficient in GALC. MRI may reveal white matter lesions. An examination of the cerebrospinal fluid shows an elevated protein content, and the nerve conduction velocities are markedly delayed as a result of segmental demyelination of the peripheral nerves.

METACHROMATIC LEUKODYSTROPHY

This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity. The *ARSA* gene is located on chromosome 22q13.33. The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate within the myelin in both the central and peripheral nervous systems, and the excessive cerebroside sulfate is thought to cause myelin breakdown. Prenatal diagnosis of metachromatic leukodystrophy (MLD) is made by assaying arylsulfatase A activity in chorionic villi or cultured amniotic fluid cells. Those affected with MLD are generally classified according to age of onset: late infantile, juvenile, and adult.

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 years of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required to walk. The extremities are hypotonic, and the deep tendon reflexes are absent or diminished. Within the next several months, the child can no longer stand, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 year from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired because of pseudobulbar palsies. Affected children develop seizures and painful muscle spasms and generalized irritability. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5-6 years. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities caused by

peripheral myelin damage and progressive changes in the VEPs, auditory brainstem responses, and somatosensory evoked potentials. CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebellar and cerebral white matter, and examination of the cerebrospinal fluid shows an elevated protein content.

Late infantile MLD is characterized by little to no functional arylsulfatase A, resulting in rapid accumulation of sulfatides and disease progression. Bone marrow transplant or lentiviral autologous hematopoietic stem cell gene (ARSA-cDNA) therapy is a promising experimental therapy for the management of late infantile MLD patients identified very early in the course of their disease.

Juvenile MLD has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5-10 years of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. Muscle tone becomes increased, and ataxia, dystonia, tremor, or diminished deep tendon reflexes may be present. In the terminal stages, generalized tonic-clonic convulsions are prominent and are difficult to control. Patients rarely live beyond mid-adolescence. Patients with juvenile MLD usually have one functional copy of *ARSA* with some residual enzyme activity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

639.2 Neuronal Ceroid Lipofuscinoses

Kristin A. Seaborg and Jennifer M. Kwon

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, **lysosomal storage disorders** characterized by visual loss, progressive dementia, seizures, motor deterioration, and early death. The NCLs are named because of the intracellular accumulation of fluorescent lipopigments ceroid and lipofuscin. They comprise a genetically and phenotypically heterogeneous group of disorders (currently there are at least 14 NCL types) that have traditionally been subclassified by age of onset, among other clinical features. With the exception of CLN4 (Parry disease), which is transmitted as an autosomal dominant trait, all other types of NCL are autosomal recessive. They differ from one another in the associated ultrastructural patterns of the inclusions as seen by electron microscopy. With the advent of enzymatic and molecular testing methods, clinicians can make specific NCL diagnoses using genetic and biochemical testing (Table 639.2).

Table 639.2 NCL of Childhood Onset: Clinical Classification and Major Diagnostic Procedure

CLINICAL FORM	AGE OF ONSET	DISEASE	GENE	DIAGNOSIS	MAJOR SYMPTOMS AT ONSET
Congenital	Birth	CLN10	*CLN10/CTSD*	NGS Enzymatic assay	Microcephaly, dysmorphic features, seizures, hyperkinetic movements
Infantile	6-18 mo	CLN1	*CLN1/PPT1*	NGS enzymatic assay	Decreased head growth, neurodevelopmental regression, seizures
		CLN10	*CLN10/CTSD*	NGS enzymatic assay	Decreased head growth, neurodevelopmental regression
		CLN14	*CLN14/KCDT7*	NGS	Decreased head growth, seizures (myoclonus)
LATE INFANTILE Classical	2-4 yr	CLN2	*TPP1*	NGS enzymatic assay	Seizures, ataxia, visual loss, delayed language development
Variant	2-5 yr	CLN1	*CLN1/PPT1*	NGS enzymatic assay	Seizures, neurodevelopmental regression, behavioral disturbances
		CLN5	*CLN5*	NGS	Impaired learning and cognition
		CLN6	*CLN6*	NGS	Seizures, ataxia, delayed language development
		CLN7	*CLN7/MFSD8*	NGS	Seizures, visual loss, motor and cognitive regression
		CLN8	*CLN8*	NGS	Seizures, visual loss, motor and cognitive regression
JUVENILE Classical	3-5 yr	CLN3	*CLN3*	NGS	Visual loss, behavioral problems, cognitive decline
	5-7 yr	CLN5	*CLN5*	NGS	Motor and cognitive regression, behavioral problems
	5-7 yr	CLN1	*CLN1/PPT1*	NGS enzymatic assay	Visual loss, cognitive decline
Late	8-12 yr	CLN6 CLN10	*CLN6* *CLN10/CTSD*	NGS NGS enzymatic assay	Myoclonic seizures, cognitive decline; ataxia, cognitive decline, visual loss
	13-16 yr	CLN12	*ATP13A2*	NGS	Rigidity, hypokinesia

NSG, Next-generation sequencing.
From Simonati A, Williams RE. Neuronal ceroid lipofuscinosis: the multifaceted approach to the clinical issues, an overview. *Frontiers Neurol*. 2022;13:Article 811686, Table 1.

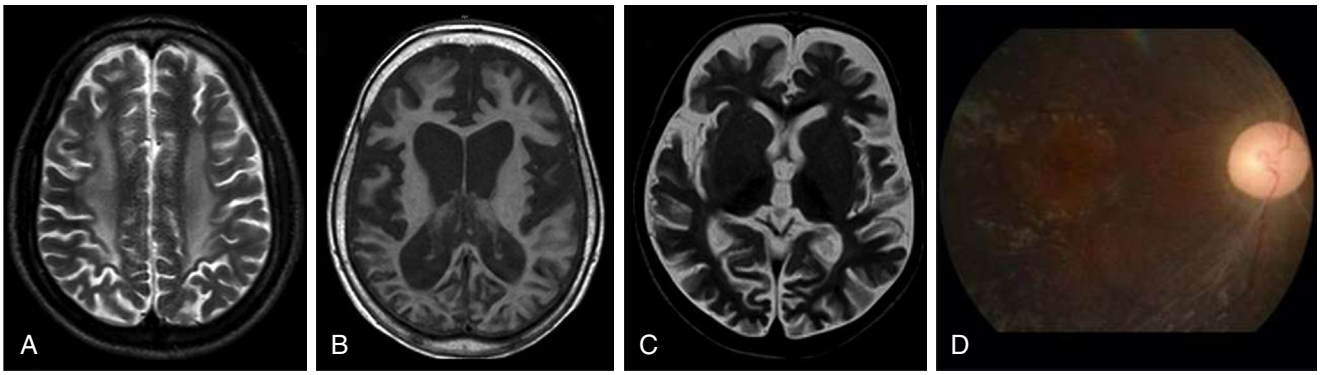

Fig. 639.3 A, T2-weighted (axial) image showing leukoencephalopathy in a child with late infantile neuronal ceroid lipofuscinoses (NCL). B, T1-weighted (axial) sequence revealing diffuse atrophy in a child with late infantile NCL. C, A child with late infantile NCL with cerebellar atrophy in T2-weighted axial section of the brain. D, Fundus photograph showing atypical retinitis pigmentosa with optic atrophy in a child with juvenile NCL. *(Modified from Jadav RH, Sinha S, Yasha TC, et al. Clinical, electrophysiological, imaging, and ultrastructural description in 68 patients with neuronal ceroid lipofuscinoses and its subtypes. Pediatr Neurol. 2014;50:85–95, Fig. 1, p. 88.)*

Infantile-type neuronal ceroid lipofuscinosis (ICLN, Santavuori disease) begins in the first year of life with developmental delay, myoclonic seizures, intellectual deterioration, and blindness. Optic atrophy and brownish discoloration of the macula are evident on examination of the retina, and cerebellar ataxia is prominent. The infantile form is caused by recessive pathogenic variants of the gene for the lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1) on chromosome 1p32. A number of cell types in INCL patients show characteristic intracellular fine granular osmiophilic deposits discernible by electron microscopy.

Although death typically occurs during early childhood, a subset of children with PPT1 enzyme deficiency has a much less severe course with clinical features resembling those of the juvenile-onset NCL patients. Clinically, these variant INCL patients have a course that is often quite distinct from the typical, classic, rapidly degenerating infantile form, yet they have PPT1 deficiency and granular osmiophilic deposits on pathology. There is no clear *CLN1* genotype that predicts severity of phenotype.

Late infantile-type neuronal ceroid lipofuscinosis (LINCL, Jansky-Bielschowsky) is the second most common type of NCL and generally presents with myoclonic seizures beginning between 2 and 4 years of age in a previously normal child. Dementia and ataxia are combined with a progressive loss of visual acuity and microcephaly. Examination of the retina shows marked attenuation of vessels, optic atrophy, and a subtle brown pigment in the macular region, with associated visual changes early in the course of disease (Fig. 639.3). The autofluorescent material is deposited in neurons, fibroblasts, and secretory cells.

LINCL can be caused by autosomal recessive variants of several different genes: *CLN2* gene, which codes for a tripeptidyl peptidase-1 (TPP1) that is essential for the degradation of cholecystokinin-8, as well as the *CLN5, CLN6,* CLN8, and *CLN14* genes, which code for membrane proteins that have not been completely characterized. *CLN8* is also known as *locus of northern epilepsy syndrome,* which is often called *progressive epilepsy with cognitive impairment.*

At this time, there is only one clinically approved treatment for all types of NCL. *CLN2* can be treated with *intraventricular* cerliponase alfa, a recombinant human proenzyme of TPP1. Treatment with cerliponase alfa can attenuate motor and language decline but does not alter visual symptoms. Stem cell therapy, gene therapy, and immunomodulatory therapy to repair genetic variants or alter adaptive immunoresponses are all in preclinical studies for adjunctive treatment of NCL.

Juvenile-type neuronal ceroid lipofuscinosis (JNCL, Spielmeyer-Vogt or Batten disease) is the most common form of NCL disease and is generally caused by autosomal recessive variants in *CLN3.* Children affected with JNCL tend to develop normally for the first 5 years of life. Their initial symptom is usually progressive visual loss, and their retinal pigmentary changes often result in an initial diagnosis of retinitis pigmentosa. The funduscopic changes are similar to those for LINCL. After disease onset, there may be a rapid decline with changes in cognition and personality, motor incoordination, and seizures. Myoclonic seizures are not as prominent as in LINCL, but parkinsonism can develop and impair ambulation. Patients die in their late 20s to early 30s. In JNCL caused by *CLN3,* the electron microscopy of tissues shows deposits called *fingerprint profiles,* and routine light microscopy of a peripheral blood smear may show lymphocyte vacuoles.

A possible mimic of JNCL is **Lafora disease (LD)** caused by pathogenic variants in *EPM2A* and *EPM2B.* LD also has skin (eccrine) inclusion bodies in addition to seizures, myoclonus, ataxia, dysarthria, progressive loss of milestones, and death within 10 years of onset. The diseases can be distinguished by specific gene sequencing.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

639.3 Adrenoleukodystrophy

See Chapter 106.2.

639.4 Sialidosis

Kristin A. Seaborg and Jennifer M. Kwon

Sialidosis is the result of lysosomal sialidase deficiency secondary to an autosomal recessive pathogenic variant in the sialidase (α-neuraminidase, *NEU1*) gene on chromosome 6p21.3. Up to 40 pathologic variants of *NEU1* have been identified. The accumulation of sialic acid–oligosaccharides with markedly increased urinary excretion of sialic acid–containing oligosaccharides is associated with clinical presentations that range from the milder sialidosis type I to the more severe sialidosis type II.

Sialidosis type I, **cherry-red spot myoclonus syndrome**, usually presents in the second decade of life, when a patient complains of visual deterioration. Inspection of the retina shows a cherry-red spot, but, unlike patients with TSD, visual acuity declines slowly in individuals with cherry-red spot myoclonus syndrome. Myoclonus of the extremities is gradually progressive and eventually renders patients nonambulatory. The myoclonus is triggered by voluntary movement, touch, and sound and is not controlled with anticonvulsants. Generalized convulsions responsive to antiseizure medications occur in most patients.

Sialidosis type II patients present at a younger age and have cherry-red spots and myoclonus, as well as somatic involvement, including coarse facial features, hepatosplenomegaly, corneal clouding (rarely), and dysostosis multiplex, producing anterior beaking of the lumbar vertebrae. Type II patients may be further subclassified into congenital and infantile (childhood) and juvenile forms, depending on the age of onset and severity. Examination of lymphocytes shows vacuoles in the cytoplasm, biopsy of the liver demonstrates cytoplasmic vacuoles in Kupffer cells, and membrane-bound vacuoles are found in Schwann cell cytoplasm, all attesting to the multiorgan nature of sialidosis type II. Identification of genetic variants in the *NEU1* gene can confirm the diagnosis.

Some cases of what appears to be sialidosis type II are the result of combined deficiencies of β-galactosidase and α-neuraminidase resulting from deficiency of protective protein/cathepsin A that prevents premature intracellular degradation of these two enzymes. These patients have galactosialidosis, and they are clinically indistinguishable from those with sialidosis type II. Consequently, patients who have features of sialidosis type II with marked urinary excretion of oligosaccharides should be tested for protective protein/cathepsin A deficiency as well as sialidase deficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

639.5 Miscellaneous Neurodegenerative Disorders

Kristin A. Seaborg and Jennifer M. Kwon

PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder characterized by nystagmus and abnormalities of myelin. PMD is caused by gene variants in the *PLP1* gene on chromosome Xq22, which is essential for CNS myelin formation and oligodendrocyte differentiation. Different variants in the same gene can cause a spectrum of disorders, ranging from the milder **familial spastic paraparesis** (progressive spastic paraparesis type 2, SPG2) to the more severe connatal form associated with rapid neurologic decline from an early age and death in the first decade of life. *PLP1* variants causing disease include point changes, deletions, gene duplications, and other gene dosage variants.

Classic PMD is the most common type, clinically recognized by nystagmus and roving eye movements along with head nodding during infancy. Developmental milestones are delayed; ataxia, choreoathetosis, and spasticity ultimately develop. Optic atrophy and dysarthria are associated findings, and death occurs in the second or third decade. The major pathologic finding is a loss of myelin with intact axons, suggesting a defect in the function of oligodendroglia. An MRI scan shows a symmetric pattern of delayed myelination. The final diagnosis can be made through genetic testing for variants in the *PLP1* gene.

Other PMD-like, hypomyelinating leukodystrophies continue to be identified and should be considered in the differential diagnosis of PMD. These include Allan-Herndon-Dudley syndrome, TUBB4A-related disorders, and hypomyelinating leukodystrophy 7 or 8.

ALEXANDER DISEASE

This is a rare disorder that causes progressive macrocephaly and leukodystrophy. Alexander disease is caused by dominant pathogenic variants in the *GFAP* gene on chromosome 17q21; cases are usually sporadic. Pathologic examination of the brain discloses deposition of eosinophilic hyaline bodies called *Rosenthal fibers* in astrocyte processes. In the classic infantile form of Alexander disease **(type I)**, degeneration of white matter is most prominent frontally. The diagnosis may be suggested by MRI (Fig. 639.4) and MR spectroscopy demonstrating abnormal metabolic substrates. Affected children develop progressive loss of intellect, spasticity, and treatment-resistant seizures causing death by 5 years of age. Patients with **type II** Alexander disease present later in life and may not have the characteristic frontal predominance or megalencephaly. Most patients with type II Alexander disease develop ataxia, and approximately 50% develop difficulty with speech or swallowing.

CANAVAN SPONGY DEGENERATION

See Chapter 105.15.

OTHER LEUKODYSTROPHIES

Metabolic and degenerative disorders can present with significant cerebral white matter changes, such as some mitochondrial disorders (see Chapters 106.1 and 108) and glutaric aciduria type 1. In addition, the broader use of brain MRI has brought to light new leukodystrophies.

One example is vanishing white matter disease or childhood ataxia with central nervous system (CNS) hypomyelination characterized by ataxia and spasticity (Fig. 639.5). Some patients also have optic

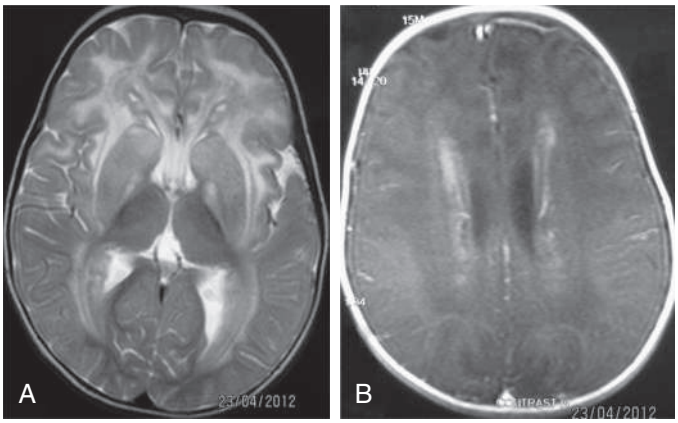

Fig. 639.4 Alexander disease. MRI of the index patient at the age of 15 mo. **A,** Axial T2-weighted sequences (TR/TE: 4000/99) at the basal ganglia and thalamus level demonstrating diffuse bilateral, symmetric increased signal predominantly of the frontal periventricular but also of the subcortical, white matter and the basal ganglia. **B,** Significant periventricular rim after intravenous gadolinium infusion (T1-weighted sequences; TR/TE: 400/88). *(From Zafeiriou DI, Dragoumi P, Vargiami E. Alexander disease. J Pediatr. 2013;162:648.)*

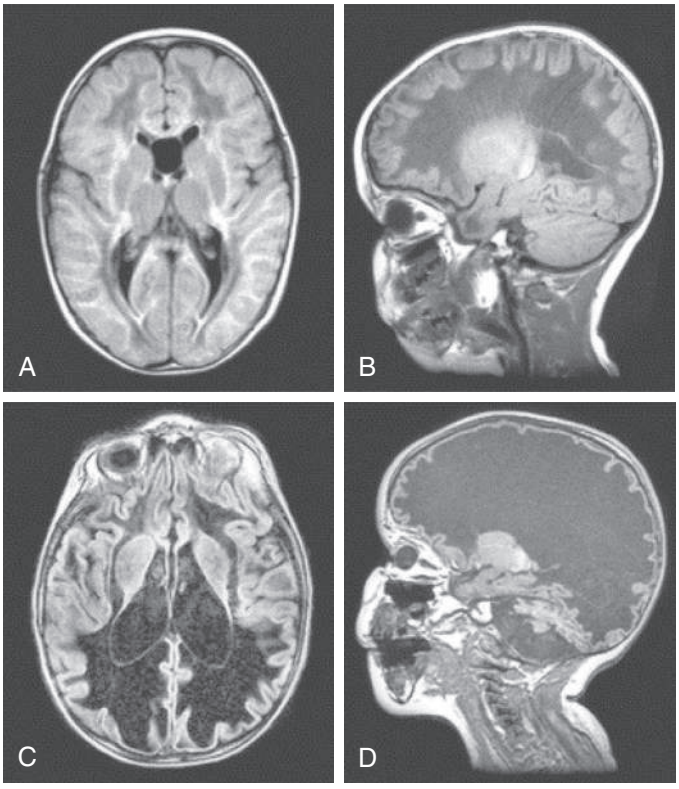

Fig. 639.5 T1-weighted and FLAIR images of a patient with vanishing white matter disease. Axial FLAIR (**A, C**) and sagittal T1-weighted (**B, D**) images of a patient at ages 1½ and 2½ yr. The first MRI (**A, B**) was obtained soon after the onset of symptoms. The initial FLAIR image (**A**) shows diffuse abnormality and partial cystic degeneration of the cerebral white matter, whereas the follow-up FLAIR image (**C**) shows that all of the cerebral white matter has been replaced by fluid. The initial T1-weighted sagittal image (**B**) shows the typical stripelike pattern within the abnormal white matter, whereas the follow-up image (**D**) shows that all of the cerebral white matter has disappeared and that only the cerebral cortex and ependymal lining are preserved. The cerebellum has become highly atrophic. *(A, C from Van der Knaap MS, Valk J. Magnetic Resonance of Myelination and Myelin Disorders, 3rd ed. Heidelberg: Springer; 2005, Fig 65.3; B, D from van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol. 2006;5:413-423. Fig. 3.)*

atrophy, seizures, and cognitive deterioration. Symptoms worsen rapidly after episodes of fever, head trauma, or external stressors. The age of presentation and the rapidity of decline in leukodystrophies can be quite variable. In the early-onset forms, decline is usually rapid and followed quickly by death; in the later-onset forms, mental decline is usually slower and milder. Interestingly, acute demyelination in these disorders can be triggered by fever or fright. The diagnosis of vanishing white matter disease or childhood ataxia with CNS hypomyelination is based on clinical findings, characteristic abnormalities on cranial MRI, and autosomal recessive gene variants in one of five causative genes (*EIF2B1, EIF2B2, EIF2B3, EIF2B4,* and *EIF2B5*) encoding the five subunits of the eukaryotic translation initiation factor, eIF2B, which regulates cellular protein synthesis. An approach to leukodystrophies based on MRI findings is noted in Figure 639.6 and associated clinical features in Figure 639.7, and the diagnostic evaluation is noted in Table 639.3.

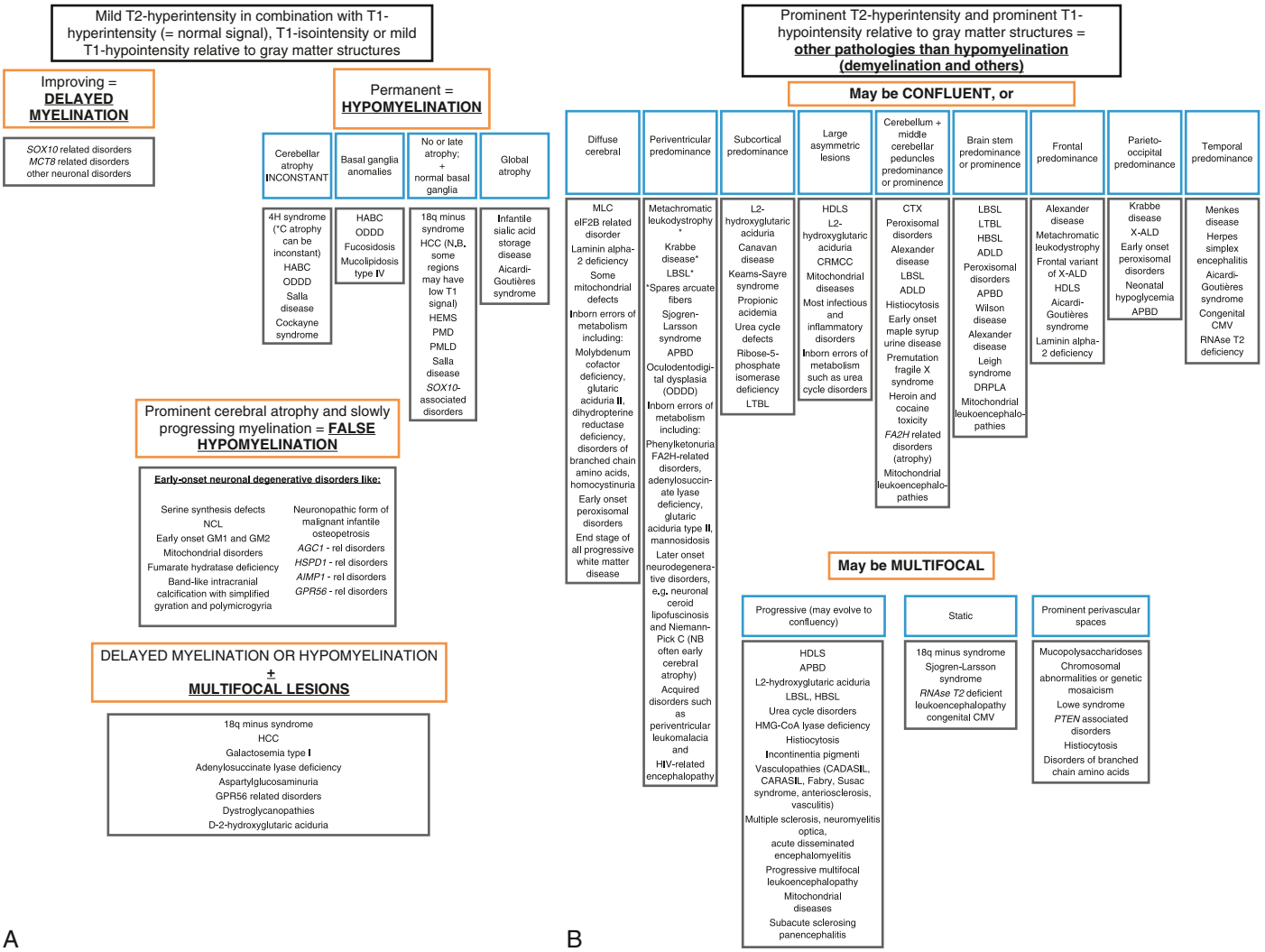

Fig. 639.6 MRI pattern recognition in the leukodystrophies and genetic leukoencephalopathies (gLEs). Three major MRI characteristics help to discriminate between the different types of leukodystrophy and gLE. The first discriminator is the presence or absence of *hypomyelination* (**A**). Within this subset, the presence of improvement of myelination or atrophy directs the clinician toward a series of gLEs. Within the true hypomyelinating leukodystrophies, the presence of basal ganglia and cerebellar involvement further helps refine the diagnosis. If the pattern is not one of hypomyelination, then the second discriminator is whether the white matter abnormalities are *confluent or isolated and multifocal* (**B**). If the white matter abnormalities are confluent, then the third discriminator is the *predominant localization of the abnormalities* (**B**). 4H, Hypomyelination, hypodontia, and hypogonadotropic hypogonadism; HACB, hypomyelination with atrophy of the basal ganglia and cerebellum; HEMS, hypomyelination of early myelinating structures; ODDD, oculodentodigital dysplasia; HCC, hypomyelination with congenital cataract; PMD, Pelizaeus-Merzbacher disease; PMLD, Pelizaeus-Merzbacher–like disease; NCL, neuronal ceroid lipofuscinosis; APBD, adult polyglucosan body disease; ADLD, autosomal dominant leukodystrophy with autonomic symptoms; CRMCC, cerebroretinal microangiopathy with calcifications and cysts; CTX, cerebrotendinous xanthomatosis; DRPLA, dentatorubral pallidoluysian atrophy); HDLS, hereditary diffuse leukoencephalopathy with spheroids/neuroaxonal leukodystrophy with spheroids; HBSL, hypomyelination with brainstem and spinal cord and leg involvement; LTBL, leukoencephalopathy with thalamic and brainstem involvement and high lactate; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MLC, megalencephalic leukodystrophy with subcortical cysts; X-ALD, X-linked adrenoleukodystrophy. *(Pattern recognition reprinted with permission from GeneReviews; from Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. Mol Gen Metab. 2018;114:501–515, Fig. 2, pp. 508–509.)*

Leukodystrophies: "special" clinical features

Peripheral neuropathy	Ophthalmologic	Hearing loss	Endocrine	Skin	Dental	Skeletal	Other
MLD Krabbe PMDL PMD (mutations leading to loss of both PLP1 and DM20) HCC LCC *SOX10*-related disorder APBD CTX ALD and variants MNGIE	Early-onset VWM (cataracts) HCC (cataracts) 4H leukodystrophy (severe myopia) Aicardi-Goutières (glaucoma) Cockayne (retinitis pigmentosa) HSMD (retinitis pigmentosa) CTX (cataracts) SLS (macular degeneration, retinitis pigmentosa, white glistening spots) Coats plus (retinal telangiectasia and exudates) *SOX10*-related disorder (iris heterochromia) AMACR deficiency (retinitis pigmentosa) Early-onset peroxisomal disorders (retinitis pigmentosa) Mitochondrial LDs (cataracts, retinitis pigmentosa) Late stage of many LDs (optic atrophy)	*SOX10*-related disorder Cockayne 18q minus Early-onset peroxisomal disorders Fabry Mitochondrial LDs	VWM (premature ovarian failure) *AARS2*-related LD (premature ovarian failure) ALD and variants (adrenal failure, testicular failure) 4H leukodystrophy (delayed puberty, growth hormone deficiency) Cockayne (hypothyreosis) 18q minus (growth hormone deficiency) KSS (growth hormone deficiency, diabetes, hypo-parathyroidism)	Generalized pigmentation (ALD and variants) Aicardi-Goutières (chilblains) Cockayne (photo-sensitivity) Trichothiodys-trophy (photosensitivity) CTX (tendon xanthomas) SLS (ichthyosis) Fabry (angiokeratoma) Fucosidosis (angiokeratoma) Hyperpigmentation (Addison in ALD and variants) Linear pigment alterations (chromosomal mosaicism)	4H leukodystrophy (delayed dentition, hypodontia, abnormal tooth shape, caries) ODDD (hypodontia, abnormal tooth shape, caries) Cockayne (caries) Early-onset peroxisomal disorders (enamel hypoplasia) Periodontal Ehlers Danlos (premature loss of teeth)	HSMD (spondylo-metaphyseal dysplasia) 4H leukodystrophy (osteosclerosis) Fucosidosis (dysostosis multiplex) ODDD (syndactyly of 4th and 5th fingers) Coats plus (osteopenia with poor bone healing) Early-onset peroxisomal disorders (skeletal dysplasia)	MLD (gallbladder) Early-onset VWM (liver, pancreas, kidneys) Salla (hepatospleno-megaly) Fucosidosis (hepatospleno-megaly) Early-onset peroxisomal disorders (liver, kidney) CTX (neonatal cholestasis, diarrhea) Congenital muscular dystrophies 18q minus (congenital heart defects) Coats plus (gastrointestinal bleeding and portal hypertension) *SOX10*-related disorder (Hirschsprung disease; white lock of hair) MNGIE (intestinal pseudo-obstruction) *NRF2*-related LD (immune deficiency) *PUS3*-related LD (nephropathy)

Fig. 639.7 Leukodystrophies: "Special" clinical features. MLD, Metachromatic leukodystrophy; PMDL, Pelizaeus-Merzbacher–like disease; PMD, Pelizaeus-Merzbacher disease; HCC, hypomyelination with congenital cataracts; LCC, leukodystrophy with calcifications and cysts; APBD, adult polyglucosan body disease; CTX, cerebrotendinous xanthomatosis; ALD, adrenoleukodystrophy; MNGIE, myoneurogastrointestinal encephalopathy; VWM, vanishing white matter; HSMD, X-linked hypomyelination with spondylometaphyseal dysplasia; SLS, Sjögren-Larsson syndrome; AMACR, alpha-methylacyl-CoA racemase; KSS, Kearns-Sayre syndrome; ODDD, oculodentodigital dysplasia; LD, leukodystrophy. *(From van der Knaap MS, Schiffmann R, Mochel F, Wolf NI. Diagnosis, prognosis, and treatment of leukodystrophies. Lancet Neurol. 2019;18:962–972, Appendix Fig. 2.)*

MENKES DISEASE

Menkes disease (kinky hair disease) is a progressive neurodegenerative condition inherited as an X-linked recessive trait. The Menkes gene, *ATP7A*, on Xq21.1, codes for a copper-transporting, P-type adenosine triphosphatase, and mutations in the protein are associated with low serum copper and ceruloplasmin levels, as well as a defect in intestinal copper absorption and transport. The clinical symptoms of Menkes disease depend on the activity of different enzymes that use copper as a cofactor, such as superoxide dismutase, cytochrome *c* oxidase, and dopamine β hydroxylase, among others. Symptoms begin in the first few months of life and include hypothermia, hypotonia, and generalized myoclonic seizures. The facies are distinctive, with chubby, sagging, rosy cheeks and kinky, colorless, friable hair. Microscopic examination of the hair shows several abnormalities, including **trichorrhexis nodosa** (fractures along the hair shaft) and **pili torti** (twisted hair). Feeding difficulties are prominent and lead to failure to thrive. Severe cognitive impairment, vascular tortuosity, and optic atrophy are constant features of the disease. Neuropathologic changes include tortuous degeneration of the gray matter and marked changes in the cerebellum with loss of the internal granule cell layer and necrosis of the Purkinje cells. Death can occur by 3 years of age in untreated patients. Very rarely does Menkes disease manifest in females, and when it does, symptoms are milder.

Copper histidine therapy may be effective in preventing neurologic deterioration in some patients with Menkes disease, particularly when treatment is begun in the neonatal period or, preferably, with the fetus. These presymptomatic children are identified because of a family history of an affected brother and confirmed by target analysis for variants in the *ATP7A* gene. Infants diagnosed presymptomatically in the first 10 days of life can be started on an experimental protocol of daily

Table 639.3 Clinical and Laboratory Tests that Aid in the Diagnosis of Leukodystrophies and Genetic Leukoencephalopathies

CLINICAL/LABORATORY TEST*	DIAGNOSTIC TARGET
Brain and spinal MRI (± gadolinium, ± MRS)	Establish white matter disease; ± evidence of leaky blood-brain barrier and metabolite accumulation (mitochondrial disorders, Canavan disease, Sjögren-Larson syndrome, peroxisomal biogenesis disorders)
Ophthalmologic exam	Document ophthalmologic signs in several leukodystrophies
Head CT	Assess for calcifications
Plasma very long-chain fatty acids	X-linked adrenoleukodystrophy and adrenomyeloneuropathy and peroxisomal biogenesis disorders
Lysosomal enzymes (leukocytes)	Metachromatic leukodystrophy, Krabbe disease, multiple sulfatase deficiency, galactosialidosis, sialidosis
Blood lactate, pyruvate, amino acids	Mitochondrial disorders
Lumbar puncture (cell count, protein, ± CSF neopterin, ± interferon-alpha)	Nonspecific marker of demyelination; ± pleocytosis and markers for Aicardi-Goutières syndrome
Urine sulfatides	Metachromatic leukodystrophy, multiple sulfatase deficiency
Urine organic acids	L-2-hydroxyglutarate; N-acetyl aspartic acid for Canavan disease; Krebs cycle intermediates (mitochondrial disorders)
Neurophysiologic studies (BAER EMG/NCV, VEP, SSEP)	Characterize involvement of cranial and peripheral nerves, optic tracts, and spinal tracts
Genetic analyses	As indicated for each leukodystrophy or genetic leukoencephalopathy

*Additional tests may be indicated for patients with certain distinctive clinical presentations or extraneurologic features suggestive of one or more specific leukodystrophies.

BAER, Brainstem auditory evoked response test; CSF, cerebrospinal fluid; CT, computed tomography; EMG, electromyogram; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NCV, nerve conduction velocity test; SSEP, somatosensory evoked potential test; VEP, visual evoked potential test.

From Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Mol Gen Metab.* 2018;114:501–515, Table 6.

copper-histidine subcutaneous injections. Optimal response to treatment appears to occur only in patients who are identified in the newborn period and whose mutations permit residual copper transport activity.

RETT SYNDROME

This syndrome is characterized as a disorder of early brain development marked by a period of developmental regression and deceleration of brain growth after a relatively normal neonatal course. It is an X-linked disease that occurs predominantly in females and is one of the most common causes of cognitive disability in females. The frequency is approximately 1 in 10,000-15,000 live births. Rett syndrome is caused by pathogenic variants in *MeCP2* on Xq28, which codes for a transcription factor that binds to methylated CpG islands and silences transcription.

Clinically, development may proceed normally until 1 year of age, when regression of language and motor milestones and acquired microcephaly become apparent. Some atypical forms of Rett syndrome are congenital and can be associated with early-onset seizures and developmental impairment within the first months of life. An ataxic gait or fine tremor of hand movements is an early neurologic finding. Most children develop peculiar sighing respirations with intermittent periods of apnea that may be associated with cyanosis. The hallmark of Rett syndrome is repetitive hand-wringing movements and a loss of purposeful and spontaneous use of the hands; these features may not appear until 2-3 years of age. Autistic behavior is a typical finding in all patients. Generalized tonic-clonic convulsions occur in the majority but may be well controlled by anticonvulsants. Feeding disorders and poor weight gain are common. After the initial period of neurologic regression, the disease process appears to plateau, with persistence of the autistic behavior. Cardiac arrhythmias may result in sudden, unexpected death at a rate that is higher than the general population. Females usually survive into adulthood.

Although very few males survive with the classic Rett syndrome phenotype, genotyping of males without the classic Rett syndrome phenotype but with intellectual disability and other atypical neurologic features has detected patients with variants in *MeCP2.* Gene variants in *MeCP2* have been demonstrated in normal female carriers, females with Angelman syndrome, and males with fatal encephalopathy, Klinefelter (47,XXY) syndrome, and familial X-linked cognitive impairment. Males may present with a Rett-like syndrome if they have an *MECP2* duplication.

Classic Rett syndrome has been treated with trofinetide, an analog of the amino-terminal tripeptide of insulin-like growth factor 1. Its potential antiinflammatory and trophic properties may be the mechanisms that produce a positive clinical effect. It is approved for patients ≥2 years of age.

Some females have an atypical Rett phenotype associated with severe myoclonic seizures in infancy, slowing of head growth, and developmental arrest and have variants in another X-linked gene encoding for cyclin-dependent kinase–like 5 (CDKL5), which may interact with MeCP2 and other proteins regulating gene expression.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation represents multiple age-of-onset–dependent disorders characterized by extrapyramidal symptoms and intellectual deterioration and regression, with iron deposition in the basal ganglia. There is significant phenotypic variability of these disorders; however, a characteristic finding on MRI demonstrates symmetric T2-signal homogeneous *hypointensity.* Common neurodegeneration with brain iron accumulation disorders are distinguished in Table 639.4, and an approach to their diagnosis is noted in Figure 639.8. Clinical features, which are highly variable, may include dystonia, parkinsonism, ataxia, spasticity, psychiatric symptoms, and intellectual impairment. Treatment should focus on the specific disorder and is usually symptomatic relief rather than curative. Iron chelation has been attempted without major long-term benefit.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 639.4 Overview of Neurodegeneration with Brain Iron Accumulation Conditions and Genes (If Known)

					CHILDHOOD-ONSET VARIANT		LATE-ONSET VARIANT	
CONDITION (ACRONYM)	**SYNONYM**	**GENE**	**CHROMOSOMAL POSITION**	**LB PATHOLOGY**	**AGE OF ONSET**	**CLINICAL PRESENTATION**	**AGE OF ONSET**	**CLINICAL PRESENTATION**
PKAN	NBIA1	*PANK2*	20p13	No	Early childhood, around age 3	Typical PKAN	Teens or early adulthood	Atypical PKAN
PLAN	NBIA2, PARK14	*PLA2G6*	22q12	√	Infancy	Infantile neuroaxonal dystrophy	Teens or early adulthood	Dystonia parkinsonism
FAHN	SPG35	*FA2H*	16q23	Not known	Childhood	Leukodystrophy, hereditary spastic paraplegia	Adulthood (age range up to 30 yr)	May resemble idiopathic Parkinson disease
MPAN	—	*C19orf12*	19q12	√	—	Pyramidal extrapyramidal syndrome		
Kufor-Rakeb disease	PARK9	*ATP13A2*	1p36	√	Childhood- teens	Parkinsonism, pyramidal tract signs, eye movement disorder		
BPAN	SENDA syndrome	*WDR45*	Xp11.23	Not known	Childhood	Encephalopathy with psychomotor regression, then static	Then: 20s to 30s	Sudden-onset progressive dystonia parkinsonism
Aceruloplasminemia	—	*CP*	3q23	No	—	—	50s (range: 16-70)	Extrapyramidal, diabetes, dementia
Neuroferritinopathy	—	*FTL*	19q13	No	—	—	40s	Chorea, dystonia, dementia
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous	—	—	Heterogeneous	Parkinsonism; it may resemble idiopathic Parkinson disease

√, Present; BPAN, beta-propeller–associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FAHN, fatty acid 2-hydroxylase–associated neurodegeneration; FTL, ferritin light chain; LB, Lewy body; MPAN, mitochondrial membrane–associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PKAN, pantothenate kinase–associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, PLA2G6-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia.

From Schneider SA, Zorzi G, Nardocci N. Pathophysiology and treatment of neurodegeneration with brain iron accumulation in the pediatric population. *Curr Treat Option Neurol.* 2013;15:652–667, Table 1.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 22, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

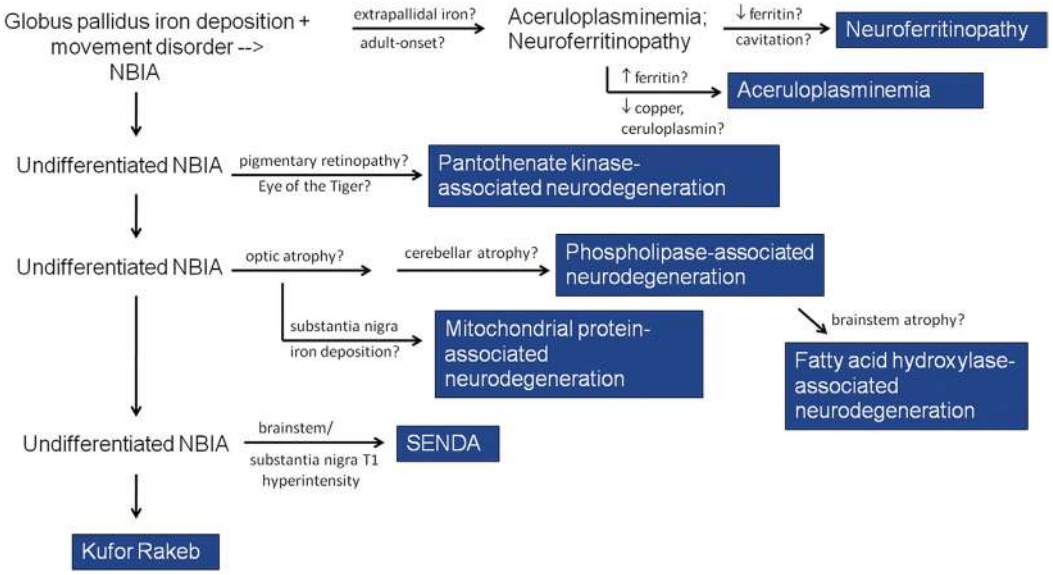

Fig. 639.8 Algorithm showing the clinical and radiographic approach to neurodegeneration with brain iron accumulation. NBIA, neurodegeneration with brain iron accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood. *(From Kruer MC, Boddaert N. Neurodegeneration with brain iron accumulation: a diagnostic algorithm. Semin Pediatr Neurol. 2012;19:67–74, Fig. 1.)*

Chapter 640

Demyelinating Disorders of the Central Nervous System

Michael Perry and Cheryl Hemingway

Acquired demyelinating syndromes (ADSs) of the central nervous system (CNS) are rare disorders, occurring with an approximate annual incidence of 9.8 per million children per year. They present with neurologic dysfunction caused by immune-mediated injury to the myelin sheath of the brain, optic nerves, and spinal cord. In contrast to genetically determined **leukodystrophies** (sometimes called *dysmyelinating disorders*) that *produce* disrupted white matter, acquired demyelinating disorders target normally formed white matter. They can be monophasic or relapsing.

The pathogenesis often involves demyelination together with B cells and CNS antibodies. Two immunoglobulin G (IgG) antibodies recognized as playing an important part in demyelination are aquaporin 4-antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab). The aquaporins are plasma membrane water-transporting proteins expressed in astrocytes and are primarily involved in water movement, cell migration, and neuroexcitation. Myelin oligodendrocyte glycoprotein (MOG) is exclusively expressed in the CNS. Although MOG comprises only a minor component of the myelin sheath, its location on the outermost lamellae and on the cell surface of oligodendrocytes makes it available for antibody binding. Increasing knowledge of the importance of these antibodies in disease, together with available disease-modifying treatments (DMTs) has made accurate diagnosis in demyelinating disorders crucial. Pediatric demyelinating syndromes may be clinically characterized by:

1. Localization of neurologic deficits: monofocal vs polyfocal
2. Presence or absence of encephalopathy
3. Disease course: monophasic vs polyphasic
4. Presence or absence of specific antibodies

MRI of the brain and spine is essential to characterize both symptomatic and *clinically silent* demyelinating lesions, aid in the diagnosis of the specific demyelinating syndrome, predict likelihood of recurrence, and rule out other etiologies. Serial MRIs may be needed to confirm the diagnosis and can also be used to monitor the treatment response and guide DMT use. The presence of **oligoclonal bands (OCBs)** in cerebrospinal fluid (CSF) analysis is useful to help confirm the diagnosis of multiple sclerosis (MS) (Table 640.1); their absence may suggest an alternative diagnosis. OCBs, matched or unmatched (to blood OCB), may also be seen in other CNS inflammatory diseases. Additional laboratory studies, including an autoimmune profile, antibody testing, metabolic testing, genetic testing, catheter angiography, and less often, brain biopsy, may be required to evaluate for mimics of demyelination. These mimics may include conditions such as migraine, systemic rheumatologic disorders, mitochondrial disorders, primary CNS angiitis, infection, neoplasm, and genetic conditions such as the inherited white matter disorders (e.g., leukodystrophies) and primary CNS hemophagocytic lymphohistiocytosis (HLH) (Tables 640.2 and 640.3).

Most children presenting with a first episode of demyelination will experience a monophasic course and do not relapse. Monophasic demyelinating disorders of childhood may include acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM); relapsing forms of demyelination include MS, MOG, multiphasic disseminated encephalomyelitis (MDEM), relapsing ON, and AQP4-Ab–associated demyelination and neuromyelitis optica spectrum disorder (NMOSD). Relapsing disease is often characterized by gradual accrual of physical disability and cognitive impairment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 640.1 Acute Demyelinating Disorders of the Central Nervous System

DISORDER	DEFINITION
Acute disseminated encephalomyelitis (ADEM)	A first polyfocal CNS event with presumed inflammatory cause Encephalopathy present that cannot be explained by fever MRI often showing bilateral diffuse, poorly demarcated T2 lesions No new symptoms, signs, or MRI findings after initial 3 mo
Multiphasic ADEM	New event of ADEM 3 mo or more after the initial event that can be associated with new or reemerging clinical and MRI findings Frequently associated with the presence of MOG-Ab
Clinically isolated syndrome (CIS)	A first monofocal or multifocal CNS demyelinating event Encephalopathy is absent, unless caused by fever
Multiple sclerosis (MS)	MS can be diagnosed in those for whom there is **no better explanation** if both dissemination in time (DIT) and dissemination in space (DIS) can be demonstrated. DIS Demonstrated by one or more T2 lesions affecting at least two of the following CNS sites: • Periventricular • Juxtacortical or cortical • Infratentorial • Spinal cord DIT Demonstrated by one of the following: • Simultaneous presence on MRI of one or more gadolinium-enhancing lesions AND one or more nonenhancing lesions • CSF oligoclonal bands • Follow-up MRI (>30 days from previous scan) with one or more new enhanced OR nonenhanced lesions • Two or more acute episodes typical of MS each lasting >24 hr and at least 30 days apart
Primary progressive MS (PPMS)	PPMS is exceedingly rare in childhood, and therefore in cases of suspected PPMS, or diagnostic uncertainty, specialist advice should be obtained. Biopsy and/or further genetic investigation may be appropriate to rule out mimics.
MOG-Ab–associated demyelination	MDEM: recurrent ADEM (see earlier) ADEM-ON: ADEM or MDEM followed by optic neuritis (ON) NMOSD: ON and acute transverse myelitis (ATM), either sequentially or simultaneously Relapsing inflammatory ON (RION) Brainstem demyelination: recurrent episodes of demyelination often involving the posterior fossa and brainstem
Neuromyelitis optica spectrum disorder (NMOSD)	If AQP4–positive, one of the following core criteria is required: • Optic neuritis • Acute myelitis • Area postrema syndrome (nausea, vomiting, hiccups) • Acute brainstem syndrome • Narcolepsy, acute diencephalic syndrome with MRI lesions • Symptomatic cerebral syndrome with MRI lesions If AQP4-negative or unavailable, two core criteria and all the following: 1. At least one core criteria must be optic neuritis, longitudinally extensive TM, or area postrema syndrome 2. Dissemination in space (≥2 different core criteria) 3. Exclusion of alternative diagnoses If Mog-Ab–positive with both ON and TM, then MOG + NMOSD may be diagnosed

640.1 Acute Disseminated Encephalomyelitis

Michael Perry and Cheryl Hemingway

Acute disseminated encephalomyelitis is an inflammatory, demyelinating event of early childhood presenting with acute-onset *polyfocal* neurologic deficits, accompanied by *encephalopathy* and MRI changes consistent with demyelination (see Table 640.1).

EPIDEMIOLOGY

Although ADEM can occur at any age, most studies report a mean age between 5 and 8 years with a slight male predominance and an incidence of 0.1-0.6 per 100,000 children per year. ADEM is usually *monophasic*, but recurrence can occur; this is termed **multiphasic disseminated encephalomyelitis (MDEM)** if the recurrence is 3 months or longer after the incident episode. Approximately 50% of ADEM cases are associated with serum MOG-Ab positivity (MOGAD) (see Chapter 640.5). MDEM patients are almost exclusively MOG-Ab positive. An episode of ADEM can also be followed by non-ADEM demyelination in a new location. If ADEM is followed by a relapse in a specific location, such as the optic nerve, then **ADEM-ON** is diagnosed. If the optic nerve and spinal cord are involved, then **NMOSD** (see Table 640.1) is diagnosed. Both ADEM-ON and NMOSD are associated with MOG-Ab positivity.

PATHOGENESIS

Molecular mimicry induced by infectious exposure has long been thought to trigger the production of CNS autoantigens, though causality has never been proven. Many patients experience a transient febrile

illness in the month before ADEM onset. Preceding infections associated with ADEM include influenza, Epstein-Barr virus (EBV), cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex, *Mycoplasma pneumoniae,* and COVID-19.

Table 640.2 Differential Diagnosis of Demyelinating Disorders

Multifocal white matter lesions	Demyelination (e.g., ADEM, MS, CIS, NMOSD, AHL) Autoantibody (e.g., NMDAR-Ab, Hashimoto encephalopathy) Migraine Prior insult and residual gliosis (e.g., congenital infections or hypoxic damage) Primary and secondary vasculitides (e.g., primary angiitis of the CNS, neurosarcoidosis, SLE, Behçet syndrome, scleroderma) Mitochondrial (e.g., Leber hereditary optic neuropathy [LHON], POLG) Leukoencephalopathy (e.g., DARS) X-linked Charcot-Marie-Tooth disease
Bilateral or diffuse white matter lesions	Leukodystrophy (e.g., X-linked adrenoleukodystrophy, Alexander disease, metachromatic LD, Krabbe disease) Leukoencephalopathy (e.g., Aicardi-Goutières syndrome) Mitochondrial (e.g., LHON, Leigh disease, MELAS, MERFF) Infection Tumor (e.g., gliomatosis cerebri, astrocytoma, lymphoma) Hemophagocytic lymphohistiocytosis (HLH)
Deep gray, thalamic, and striatal lesions	Infection (e.g., mycoplasma, Epstein-Barr virus, West Nile virus, Japanese B encephalitis, enterovirus) Biotin-responsive basal ganglia disease (e.g., *SLC19A3*) Acute necrotizing encephalopathy (ANE) and *RANBP2* pathogenic variant

CLINICAL MANIFESTATIONS

Initial symptoms of ADEM may include lethargy, fever, headache, vomiting, meningeal signs, and seizures, including status epilepticus. Encephalopathy is the hallmark of ADEM. It can range from behavioral change and persistent irritability to coma. Common neurologic signs include visual loss, ataxia, motor and sensory deficits, and cranial neuropathies. In cases with concurrent spinal cord involvement, bladder/bowel dysfunction may be seen. Focal neurologic deficits, however, can be difficult to ascertain in the obtunded or very young child. The clinical course is usually rapidly progressive over days, and intensive care may be required, particularly for patients with brainstem dysfunction or raised intracranial pressure.

NEUROIMAGING

Brain MRI typically shows large (sometimes confluent), bilateral, multifocal, edematous, masslike T2 lesions of the cerebral hemispheres, cerebellum, and brainstem. Deep gray matter structures (e.g., thalami, basal ganglia) are often involved (Figs. 640.1 and 640.2). Contrast enhancement is variable. The spinal cord may have an abnormal T2 signal or enhancement, with or without clinical signs of myelitis. ADEM lesions will typically appear to be of similar age on MRI, but their evolution often lags the clinical presentation. Serial MRI imaging 3-12 months after ADEM frequently demonstrates near-complete resolution of T2 abnormalities, though residual gliosis may remain.

Severe involvement may progress to an **acute hemorrhagic leukoencephalopathy** (Weston-Hurst disease). This leukodystrophy-like picture is characterized by large lesions, edema with mass affect, and a polymorphonucleated cell pleocytosis; this contrasts with the CSF lymphocytic pleocytosis typically noted in ADEM.

LABORATORY FINDINGS

There is no biologic marker for ADEM, and laboratory findings can vary widely. CSF studies are often normal or can exhibit pleocytosis with lymphocytic or monocytic predominance. CSF protein can be elevated, especially on repeat studies. Elevated CSF immunoglobulin production can be present, but true OCB positivity is rare. Electroencephalograms often show generalized slowing, consistent with encephalopathy. Polyregional demyelination of ADEM can also cause focal slowing or epileptiform discharges.

Table 640.3 MR Imaging Red Flags for the Diagnosis of Children with Acquired Demyelinating Syndromes

LEPTOMENINGEAL ENHANCEMENT	SVcPACNS Infection Tumor HLH	Leptomeningeal enhancement is not a feature of MS in adults; it has emerged as a red flag for vasculitic or malignant processes in the pediatric cohort.
LESION EXPANSION	Tumor Lymphoma PML Sarcoidosis	Increased size of T2 lesions on serial imaging is well recognized in MS, although this should always prompt consideration of malignancy. Increasing size of a white matter–predominant lesion without lesion enhancement in a patient treated with immunosuppressant therapy (or a patient with known HIV) should prompt consideration of PML. PML is a risk for MS patients exposed to more intense immunosuppressive therapies.
HEMORRHAGE	ANE Stroke Cerebellitis AHLE Large-vessel CNS vasculitis SVcPACNS	Although susceptibility-weighted imaging reveals tiny microfoci of hemosiderin in MS patients, hemorrhage large enough to be visible on conventional MRI sequences is not a feature of ADS or MS and should prompt consideration of disorders in which the cerebral vasculature is specifically involved.

ADS, Acquired demyelinating syndrome; AHLE, acute hemorrhagic leukoencephalitis; CNS, central nervous system; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; SVcPACNS, small-vessel childhood primary angiitis of the central nervous system.
From O'Mahony J, Shroff M, Banwell B. Mimics and rare presentations of pediatric demyelination. *Neuroimaging Clin North Am.* 2013;23:321–336, Table 2.

DIFFERENTIAL DIAGNOSIS

ADEM is a clinical diagnosis supported by MRI, CSF, and serum findings. The differential diagnoses for ADEM are broad; empirical antibiotic and antiviral treatment should be considered while infectious evaluations are pending. Follow-up MRI examinations 3-12 months after typical ADEM should show improvement; new or enlarging T2 lesions should prompt reevaluation for other etiologies such as MS, antibody-associated disorders, leukodystrophies, tumor, vasculitis, mitochondrial, metabolic, or rheumatologic disorders (Table 640.4 and see Tables 640.1-640.3).

TREATMENT

High-dose intravenous steroids are often prescribed (most commonly methylprednisolone 20-30 mg/kg/day for 5 days with a maximum dose of 1,000 mg/day) followed by an oral prednisolone taper of 1-2 mg/kg/day (maximum 40-60 mg/day) over 4-6 weeks. In *refractory* or *severe* cases, additional treatment options include intravenous immunoglobulin (2 g/kg administered over 2-5 days) or plasmapheresis (5-7 exchanges administered every other day). There is no consensus about the timing of these treatments for ADEM.

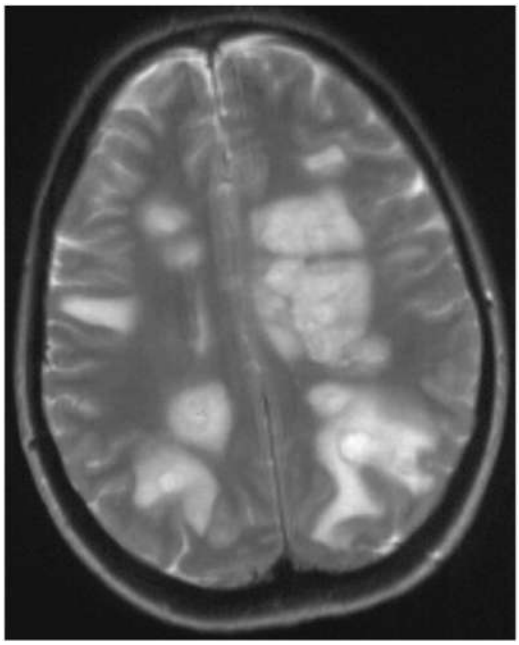

Fig. 640.1 6-year-old patient diagnosed with ADEM presenting with encephalopathy, ataxia, and motor deficits after mild viral infection. Axial T2-weighted MRI shows bilateral, diffuse, poorly demarcated lesions. Gray matter involvement, including the thalamus and basal ganglia, is commonly seen.

PROGNOSIS

Most children experience full motor recovery after ADEM, but residual deficits can be seen. Cognitive impairment or behavioral changes are not uncommon. Recovery starts within days to weeks, but symptoms can fluctuate throughout the course.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

640.2 Optic Neuritis

Michael Perry and Cheryl Hemingway

Optic neuritis (ON) is inflammation of one or both optic nerves. It presents with visual dysfunction. ON can occur in three phenotypes: (1) as a clinically isolated monophasic syndrome; (2) recurrently in isolation; or (3) as part of other multifocal systemic or CNS-specific inflammatory conditions such as ADEM, MS, or antibody-associated demyelination (e.g., AQP-4-Ab NMOSD or MOGAD).

EPIDEMIOLOGY AND CLINICAL PRESENTATION

ON is one of the most common of the acquired demyelinating syndromes, accounting for ~25% of all demyelinating presentations in childhood. The typical presentation is unilateral or bilateral visual loss over hours to days with abnormal color vision (typically red-green desaturation), visual field loss, and sometimes a relative afferent pupillary defect. The visual loss is often severe, with most children at 20/200 visual acuity (VA) or worse. Periocular pain and painful eye movements (often reported as headache in young children) are common. Bilateral ON is more common in younger children and frequently associated with MOG-Ab disease. Unilateral ON is more common in older children and more likely to be associated with MS. Funduscopic examination in over half of children reveals acute optic nerve head swelling (papillitis). However, when the inflammation occurs in the retrobulbar optic nerve portion, the appearance of the optic nerve may be normal. Optic nerve pallor is more often noted in the chronic stage after an initial episode or in those with relapsing ON. Bilateral ON, longitudinally extensive (>50% of the optic nerve), perineural optic sheath enhancement (perineuritis), and optic disc edema are features suggestive of ON caused by MOG-Ab disease. ON without papillitis and that involves the optic chiasm or tract is more typical of AQP4-Ab (NMOSD) disease.

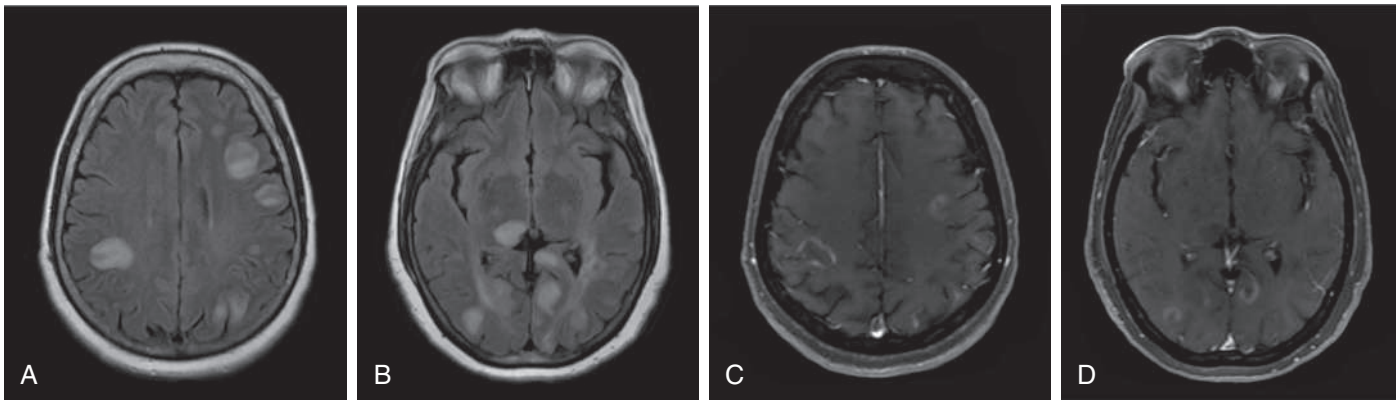

Fig. 640.2 Acute disseminated encephalomyelitis (ADEM). **A** and **B**, T2-weighted FLAIR images show numerous asymmetric, rounded, hyperintense, predominantly subcortical white matter lesions. Some lesions involve the cortex. A right pulvinar lesion is also seen. **C** and **D**, Postcontrast T1-weighted image demonstrates incomplete ring enhancement associated with these lesions. All the lesions show similar imaging features. Marked improvement was seen after steroid therapy. *(From Lerner A, Rajamohan A, Shiroishi MS, et al. Cerebral infections and inflammation. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig. 10-15, p. 280.)*

Table 640.4 Features that May Distinguish ADEM from a First Attack of MS

	ADEM WITH OR WITHOUT MOG-AB	MS
Age and sex	<10 yr Males and females equal	>10 yr Female preponderance
Seizures	+	–
Encephalopathy	+ /+/– for MOG-Ab	–
Fever/vomiting	+	–
Family history	No	20%
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
CSF	Pleocytosis (lymphocytosis) OCBs negative	Acellular OCBs positive
MRI	Large, fluffy, poorly demarcated T2 lesions involving white and gray matter	Ovoid T2 lesions involving juxtacortical, periventricular, or infratentorial areas or spinal lesions; T1 hypointense lesions
MRI follow-up after 30 days	No new lesions	New lesions seen

+, More likely to be present; –, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; OCBs, oligoclonal bands.

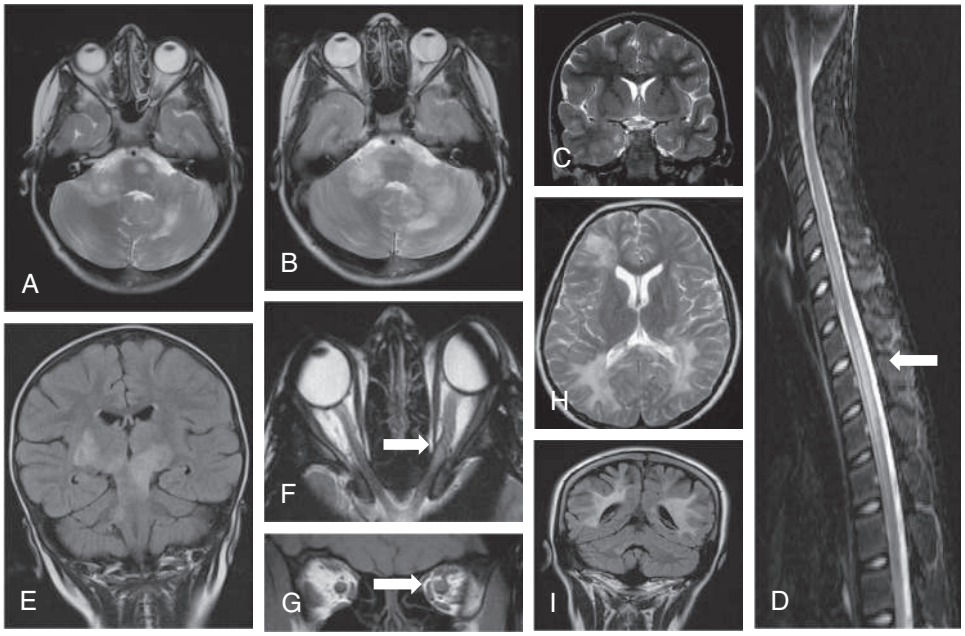

Fig. 640.3 MRI images highlighting the spectrum of possible phenotypes in relapsing myelin oligodendrocyte glycoprotein (MOG) antibody–associated disorders. **A,** Axial T2-weighted FLAIR MRI of brain from a 6-yr-old female with bilateral ON, ataxia, and lethargy, initially diagnosed with ADEM until her relapse (**B**) with further multiple brainstem lesions associated with MOG-Ab positivity. **C,** Coronal T2-weighted MRI with longitudinally extensive ON with both pre- and post-chiasm involvement and (**D**) sagittal MRI of spine with longitudinally extensive TM from a 9-yr-old female diagnosed with MOG-Ab–associated NMOSD after simultaneous presentation of bilateral visual impairment and paraparesis requiring ventilatory support. **E,** T2-weighted FLAIR MRI of brain demonstrating asymmetric, bilateral, poorly defined lesion involving the brainstem and extending into the middle cerebellar peduncle. **F** and **G,** Orbital MRI shows a thickened left optic nerve in a 13-yr-old female with recurrent left ON associated with positive MOG-Ab. **H,** Axial T2-weighted image shows diffuse, bilateral, asymmetric leukodystrophy-like phenotype associated with MOG-Ab. **I,** Coronal T2-weighted FLAIR MRI of brain similarly showing the leukodystrophy-like appearance seen over time in those with young-onset relapsing MOG-Ab–associated demyelination.

DIAGNOSTIC EVALUATION

MRI, optical coherence tomography (OCT), and visual evoked potentials (VEPs) are useful for evaluating and quantifying the functional and structural integrity of the optic nerve of a child with suspected ON.

Orbital MRI is useful but not required for a diagnosis of ON. Though sometimes normal, it will usually show optic nerve thickening on T1-weighted images with T2 hyperintensities and contrast enhancement. (Fig. 640.3F, G). Longitudinally extensive ON involving the chiasm is thought to be more commonly associated with antibody-mediated demyelination (see Fig. 640.3C). **Optical coherence tomography** can detect structural neuronal and retinal change, such as retinal nerve fiber layer (RNFL) thinning and may be helpful in monitoring the young child experiencing recurrent disease. In acute ON, VEPs may detect prolonged latency. VEPs in children may also detect clinically silent episodes of ON in the seemingly unaffected contralateral eye.

CSF OCB analysis is not always indicated; however, in the context of a normal MRI brain scan, negative OCBs predict a very low risk of subsequent MS development.

Many conditions can both mimic and be associated with ON. Therefore although a detailed ophthalmologic review is essential, other investigations must be carefully considered to exclude systemic rheumatologic disorders (e.g., systemic lupus erythematosus [SLE], sarcoidosis, celiac disease, Behçet disease), infectious diseases (viral disease, Lyme disease, syphilis, tuberculosis), mitochondrial disorders (e.g., Leber hereditary optic neuropathy), vascular events, toxic (methanol, ethylene, glycol, chloroquine, hydroxychloroquine), nutritional (folate, vitamin B12, copper deficiencies), or metabolic disorders, and optic nerve sheath meningioma or optic nerve glioma. Antibody testing in serum with live cell-based assays (CBAs) for both AQP4-Ab and MOG-Ab is recommended to ensure that prophylactic treatment can be provided if indicated (e.g., AQP4-Ab positive) or to provide counseling on the risk of recurrence (MOG-Ab positivity).

TREATMENT

The standard of care is based on expert clinical opinion and adult trials and typically includes high-dose intravenous steroids (e.g., methylprednisolone 20-30 mg/kg/day for 3-5 days, maximum 1000 mg/day). In adults, steroid administration leads to faster recovery, but with no difference in long-term visual outcome. As with other severe episodes of demyelination, further treatment options include intravenous immunoglobulin (usually 2 g/kg administered over 2-5 days) or plasmapheresis (typically 5-7 exchanges administered every other day); there is neither definitive trial evidence of their benefit nor consensus about when to use them in isolated ON. Trials in adults have concentrated on neuroprotection; phenytoin has a beneficial effect on RNFL thinning in acute ON.

The initiation of chronic immunotherapy is dependent on etiology, the presence or absence of glial antibodies (e.g., MOG-Ab), and risk of relapse (i.e., ON caused by AQP4 +NMOSD) and is best considered by a multidisciplinary team experienced in the treatment of pediatric neuroinflammatory disorders.

PROGNOSIS

Although it is reassuring that full recovery of high-contrast visual acuity (HCVA) does usually occur in children, irreversible damage is often detected in the structural integrity of affected optic nerves. This may be evidenced by RNFL thinning on OCT, defective color vision, and impairments in low-contrast visual acuity (LCVA). Pediatric patients with AQP4-antibody–associated optic nerve demyelination are more commonly left with long-term visual disability than patients with other causes of ON.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

640.3 Transverse Myelitis

Michael Perry and Cheryl Hemingway

Transverse myelitis (TM) is a condition characterized by the rapid development of both motor and sensory deficits of the spinal cord. It presents acutely as either partial or complete cord involvement at any level with bilateral neurologic signs; in adults and older children, there will usually be a clear sensory level. TM has multiple causes (Tables 640.5 and 640.6). It can be secondary to an immune-mediated condition (postinfectious or antibody-driven), a result of direct infection (e.g., infectious myelitis), or idiopathic. In TM, evidence of spinal cord inflammation can be demonstrated by an enhancing lesion on MRI, CSF pleocytosis (>10 cells), or an increased IgG index. The progression is rapid. Time to maximal disability typically occurs 5-6 days after symptom onset.

EPIDEMIOLOGY

TM is more common in adults but is estimated to affect ~2 children/million per year. A bimodal age distribution is observed in those younger than 5 years and older than 10 years. Children less than 5 years of age develop spinal cord dysfunction over hours to a few days. They often have a history of an infectious disease (e.g., viral or mycoplasma) in the weeks preceding development of neurologic symptoms. The motor dysfunction is often severe, approaching a complete loss of function. Recovery is slow (weeks to months) and usually incomplete, most commonly with residual bowel and bladder dysfunction (15–50%). Pathologic findings of perivascular infiltration with mononuclear cells suggest an infectious or inflammatory basis. Overt necrosis of the spinal cord may occur.

The syndrome may differ in older children, and outcomes vary by etiology. Although the onset is also rapid, recovery is faster and more

Table 640.5 Reported Cases of Transverse Myelitis

1. Acquired demyelinating disorders
   a. Multiple sclerosis
   b. NMO
   c. ADEM
   d. MOGAD
2. Systemic inflammatory autoimmune disorders
   a. SLE
   b. SS
   c. Antiphospholipid syndrome
   d. Behçet disease
   e. Vogt-Koyanagi-Harada disease
   f. Ankylosing spondylitis
   g. Mixed connective tissue disease
   h. Others: systemic sclerosis, anti-Jo-1 antibody, urticarial vasculitis, psoriatic arthritis, perinuclear ANCA systemic vasculitis, graft-versus-host disease, common variable immunodeficiency, celiac disease
3. Neurosarcoidosis
4. Parainfectious TM
   a. Viral: hepatitis A, hepatitis B, hepatitis C, hepatitis E, measles, mumps, rubella, varicella zoster, Epstein-Barr, cytomegalovirus, herpes simplex, influenza A/B, lymphocytic choriomeningitis virus, chikungunya, hantavirus, HIV, human T-cell lymphotropic virus, human herpes virus 6, Japanese encephalitis, Murray Valley encephalitis, St. Louis encephalitis, tickborne encephalitis, vaccinia, Rocky Mountain spotted fever, dengue virus, enterovirus 71, coxsackievirus A and B, West Nile virus, parvovirus B19, human corona virus, and echovirus
   b. Bacterial: *Mycoplasma pneumoniae, Campylobacter jejuni, Borrelia burgdorferi, Acinetobacter baumannii, Coxiella burnetii, Bartonella henselae, Chlamydia psittaci, Leptospira, Chlamydia pneumoniae*, Legionella pneumonia, *Orientia tsutsugamushi* (scrub typhus), *Salmonella* paratyphi B, *Mycobacterium tuberculosis, Treponema pallidum, Brucellosis melitensis,* and groups A and B streptococci
   c. Fungal: *Actinomyces, Blastomyces, Coccidioides, Aspergillus, Cryptococcus,* and *Cladophialophora bantiana*
   d. Parasitic: *Toxocara* species, *Schistosoma* species, *Gnathostoma spinigerum, Echinococcus granulosus, Taenia solium, Toxoplasma gondii, Acanthamoeba* species, *Paragonimus westermani,* and *Trypanosoma brucei*
5. Paraneoplastic syndromes
   a. Anti-Ri (ANNA-2) antibody
   b. CRMP-5-IgG antibody
   c. Anti-amphiphysin IgG antibody
   d. Anti-GAD65 antibody
   e. NMDAR antibody
6. Atopic myelitis
7. Drugs and toxins
   a. Tumor necrosis factor-alpha inhibitors
   b. Sulfasalazine
   c. Epidural anesthesia
   d. Chemotherapeutic agents: gemcitabine, cytarabine, cisplatin
   e. Heroin
   f. Benzene
   g. Brown recluse spider toxin
8. Idiopathic TM

MOGAD, MOG antibody disease.
From Beh SC, Greenberg BM, Frohman T, et al. Transverse myelitis. *Neurol Clin.* 2013;31:79–138, Box 5, p. 88–89.

Table 640.6 Mimics of Transverse Myelitis

ETIOLOGY	DESCRIPTION
Vitamin B_{12} deficiency	May present as an isolated myelopathy or in combination with neuropathy, encephalopathy, and/or behavioral changes. Dorsal column impairment is the most common manifestation, followed by pyramidal dysfunction (the classic subacute combined degeneration of the cord). Hematologic manifestations may be absent in up to 30% of patients with neurologic manifestations. MRI reveals T2-hyperintense signal in the posterior columns (the "inverted V" or "inverted rabbit ear" sign on axial views). In severe cases, MRI shows the "anchor" sign (because of involvement of the posterior, anterior, and pyramidal tracts).
Vitamin E deficiency	May cause a predominantly dorsal column syndrome associated with a peripheral neuropathy because of axonal degeneration. Preferentially affects the cervical cord. Clinically and radiologically similar to B_{12} deficiency.
Copper deficiency	May cause both myelopathy and optic neuropathy. Causes of acquired copper deficiency include malnutrition, zinc toxicity, Menke disease, bariatric surgery, gastrectomy, malabsorption syndromes, and use of copper chelating agents. Clinically and radiologically indistinguishable from B_{12} deficiency.
Nitrous oxide (N_2O) toxicity	Analgesic gas commonly abused because of euphoric effects. N_2O inactivates vitamin B_{12} by irreversible oxidation of the cobalt center of methylcobalamin, thereby inhibiting the methionine synthesis pathway. In healthy subjects, this does not cause clinical manifestations. In subclinically B_{12}-deficient individuals, N_2O exhausts residual stocks of vitamin B_{12}, leading to neurologic manifestations.
Neurolathyrism and neurocassivism	Neurolathyrism is caused by consumption of grass pea. Neurocassivism (konzo) is caused by bitter cassava root consumption. Both are found in malnourished populations and are characterized by subacute paraparesis with prominent UMN features.
Intramedullary primary spinal cord tumors	May be ependymomas, astrocytomas, or hemangioblastomas. Typically cause an insidious, progressive myelopathy. Hemorrhage or infarction of the tumor may result in an acute presentation and radiologic appearance mimicking TM.
Primary CNS lymphoma	May give rise to a clinical and radiologic picture mimicking TM compounded by its corticosteroid responsiveness. Congenital or acquired immunodeficiency is the only established risk factor. More common in middle-age and older men. Insidious onset of myelopathy with back pain and constitutional symptoms. Serum lactate dehydrogenase may be elevated. CSF: lymphocytic pleocytosis, markedly elevated protein, and hypoglycorrhachia. OCBs and IgG index are absent. Cytologic analysis may demonstrate malignant cells (large-volume CSF examination can increase the diagnostic yield). MRI: T2 hyperintensity, gadolinium enhancement, cord swelling, conus medullaris involvement, and concomitant brain lesions.
Intravascular lymphoma	Predominantly affects vessels in the skin and neurologic system. May mimic TM and even LETM. CSF: lymphocytic pleocytosis and increased protein, but no malignant cells. MRI: affects the conus medullaris (unlike TM).
Radiation myelitis	Early radiation myelopathy: begins 10-16 wk after starting radiotherapy with predominantly sensory phenomena (including Lhermitte sign) and typically resolves spontaneously. Delayed radiation myelopathy: begins months or years after radiation exposure and manifests as a subacute or insidious myelopathy. Concurrent use of chemotherapeutic agents may cause widespread white matter necrosis owing to synergistic toxicity. Preexisting myelopathy from any cause may be risk factors for radiation myelitis. MRI: cord swelling on T1-weighted images, intramedullary T2 hyperintensity, ringlike gadolinium enhancement.

CNS, Central nervous system; CSF, cerebrospinal fluid; Ig, immunoglobulin; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; OCB, oligoclonal bands; TM, transverse myelitis; UMN, upper motor neuron.
Modified from Beh SC, Greenberg BM, Frohman T, et al. Transverse myelitis. *Neurol Clin*. 2013;31:79–138, Table 10, p. 102–103.

likely to be complete. Necrosis and irreversible injury may occur in a small but important number of cases. Potentially associated underlying etiologies include systemic vasculitic entities (e.g., SLE), antibody-mediated CNS disorders (e.g., AQP4-Ab– or MOG-Ab–associated NMOSD), infectious etiologies (e.g., mycoplasma, enterovirus), or idiopathic disease. Pathology and imaging studies show acute inflammation with demyelination in some cases.

Acute Flaccid Myelitis

Acute flaccid myelitis (AFM) is an idiopathic neurologic disorder presenting with acute weakness and/or paralysis in previously healthy children. It is predominantly of infectious etiology. Although many viruses have been implicated, the recent biennial outbreaks since 2014 are likely to have been caused by enterovirus-D68. Abnormalities are often seen in the lower motor neurons of the anterior horn gray matter

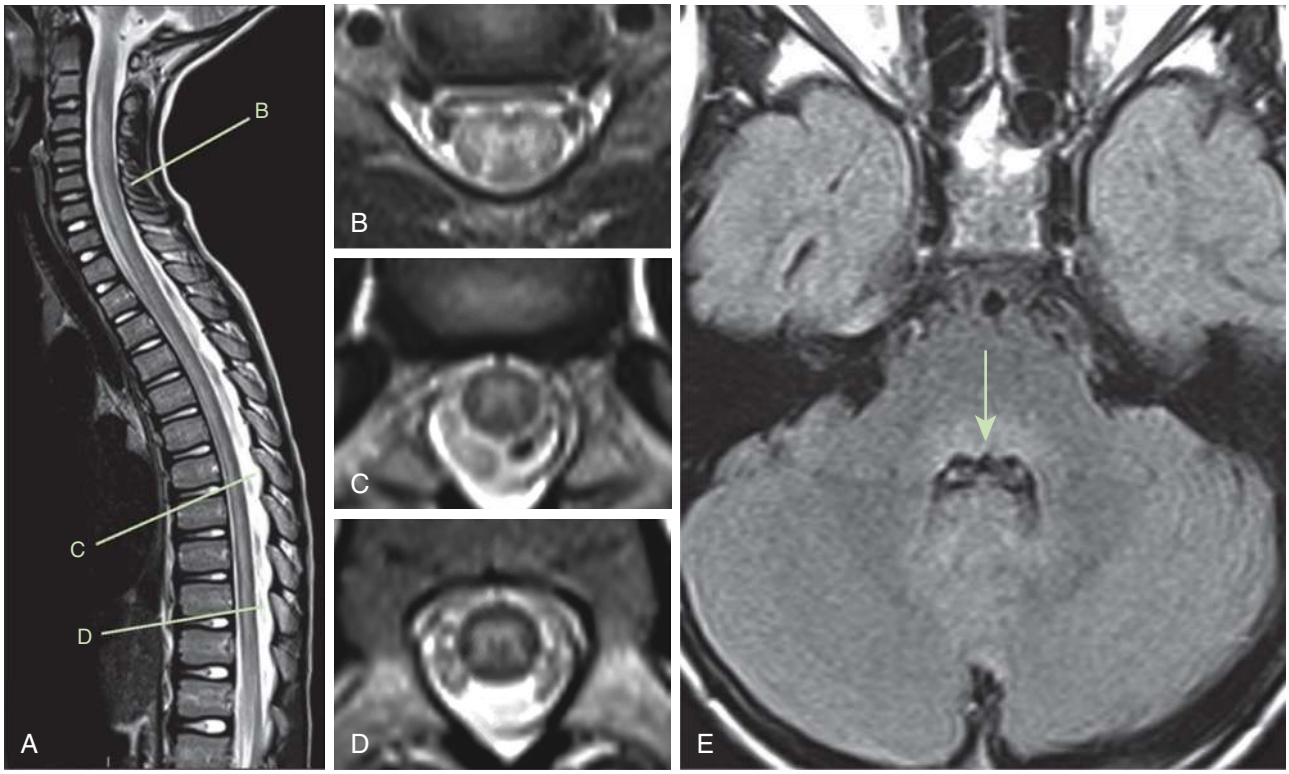

Fig. 640.4 Typical MRI findings in the acute phase of AFM. Spinal MRIs are shown of an 8-yr-old child with AFM, acquired 24 hr after onset of neurologic symptoms. **A,** Sagittal T2-weighted image showing an ill-defined, longitudinally extensive central/anterior spinal cord lesion. **B,** Axial T2-weighted image from C5–C6 shows hyperintensity of the entire gray matter of the spinal cord, with associated edema and some surrounding white matter hyperintensity. **C,** Axial T2-weighted image from T7 shows asymmetric hyperintensity of the gray matter (right more than left). **D,** Axial T2-weighted image from T10 shows hyperintensity of the entire gray matter. **E,** Axial FLAIR image at the level of the middle cerebellar peduncle demonstrates hyperintensity of the dorsal pons *(arrow)*. AFM, acute flaccid myelitis. *(From Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. Lancet. 2021;397:334–344, Fig. 1, p. 338.)*

(Fig. 640.4). Symptoms can progress rapidly; paralysis is often asymmetric and is not usually accompanied by a sensory deficit; cranial nerve involvement may include facial weakness, dysarthria, and dysphagia (Table 640.7).

In the United States, AFP is considered a generalized "umbrella" term for multiple clinical entities, including paralytic poliomyelitis, transverse myelitis, AFM, Guillain-Barré syndrome, toxic neuropathy, and muscle disorders. Essentially, this grouping helps with case ascertainment of AFM, but the individual diagnoses still remain important because each has its own differential diagnoses to consider.

A pragmatic case definition of AFP is "a clinical syndrome with rapid onset of weakness that frequently involves the respiratory and bulbar muscles." Whenever these criteria are met and poliomyelitis is a possibility, thorough investigation and reporting of potential poliomyelitis is required. Two diagnostic stool samples more than 24 hours apart should be collected within 14 days of onset of paralysis and then processed in a World Health Organization–approved laboratory. If poliomyelitis is confirmed, it may be caused by *wild poliovirus* (serotypes 1-3) or *vaccine-associated paralytic poliomyelitis*, and it will need full epidemiologic investigation. In the individual patient, disease progression with paralysis (with sensory preservation) is rapid, asymmetrical, and involves proximal more than distal muscles.

Other potential viral causes of AFP include coxsackie and echoviruses, Japanese B encephalitis, Murray Valley encephalitis, St. Louis encephalitis, and Russian spring encephalitis, tickborne viruses, and herpes virus. These causes vary by geography with, for example, EV-A71 being the cause in parts of Southeast Asia and West Nile virus being a cause in the United States. Therefore consider the following investigations for possible viral causes of AFP, as well as other conditions in the differential diagnosis:

- Imaging with MRI of the spine (and possibly brain)
- CSF sampling for differential cell counts, glucose, and protein; microbiology and diagnostic polymerase chain reaction (PCR) testing for enteroviruses and other infectious diseases; and for autoantibodies such as anti–myelin oligodendrocyte glycoprotein (anti-MOG, see later)
- Respiratory/nasopharyngeal secretion samples for viral PCR testing (e.g., enterovirus)
- Peripheral neurophysiology with nerve conduction studies (NCS) if differentiation from GBS is needed or botulism is suspected
- Studies for identification of possible metabolic disease (e.g., acute hypokalemic periodic paralysis, thyrotoxic periodic paralysis, acute intermittent porphyria) and/or toxin exposures (e.g., sporadic hypokalemic paralysis secondary to licorice, barium, or cottonseed oil exposure)
- Investigations to exclude paralytic syndromes that mimic or are misdiagnosed as AFP, such as vitamin B_{12} deficiency, which may be exacerbated by chronic cycad poisoning from evergreens, cyanide toxicity from cassava ingestion, and lathyrism.

CLINICAL MANIFESTATIONS OF TM

TM is often preceded within the previous 1-3 weeks by a mild nonspecific illness or minimal trauma. Discomfort or overt pain in the neck or back is common. Depending on its severity, the condition progresses to numbness, anesthesia, ataxia, areflexia, and motor weakness in the truncal and appendicular musculature at or distal to the lesion. Paralysis begins as flaccidity (paraparesis, tetraparesis). Spasticity then develops over weeks, accompanied by hyperreflexia and clonus. Weakness may rarely be unilateral, but usually such a finding suggests a hemicord lesion, which is most often associated with MS (particularly in adolescence). Urinary retention is a common early symptom; incontinence occurs later in the course. Early sensory findings may be isolated to the posterior column, necessitating evaluation of vibratory sensation. Progressive sensory loss may manifest as anesthesia, paresthesia, or

Table 640.7 Diagnostic Criteria for AFM

Diagnostic items	Definite	Probable	Possible	Uncertain
H1: Acute onset of limb(s) weakness (period from onset to nadir: hours to 10 days)	P	P	P*	P
H2: Prodromal fever or illness†	P/A	P/A	P/A	P
E1: Weakness involving one or more limbs, neck, face, or cranial nerves	P	P	P*	P
E2: Decreased muscle tone in at least one weak limb	P	P	P/A	P
E3: Decreased or absent deep tendon reflexes in at least one weak limb‡	P	P	P/A	P
MRI: Spinal cord lesion with predominant gray matter involvement, with or without nerve root enhancement§	P	P	P	ND
CSF: Pleocytosis (white cell count >5 cells/L)¶	P	A or ND	P/A or ND	P/A or ND

Factors that might suggest an alternative diagnosis

1. Encephalopathy that cannot be explained by fever, illness, respiratory distress, metabolic abnormalities, or medications
2. Presence of sensory deficits on examination‖
3. Presence of lesions in supratentorial white matter or cortex, which should prompt consideration of ADEM, MOG-antibody associated disease, neuromyelitis optica spectrum disorder, encephalomyelitis, and others
4. Absence of CSF pleocytosis, which should prompt consideration of Guillain-Barré syndrome, botulism, ischemic cord lesions, and others
5. Positive serum aquaporin-4 (AQP-4) antibody, which would exclude AFM
6. Positive serum MOG antibody, which would suggest MOG-antibody associated disease‖

From Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet.* 2021;397:334–344, Fig. 2, p. 339.

allodynia. Other potential findings include priapism, respiratory compromise, and spinal shock with subsequent autonomic dysreflexia. Rarely an overlap syndrome of TM with features of Guillain-Barré syndrome may occur.

DIAGNOSTIC EVALUATION

TM is a diagnosis of exclusion, and a thorough evaluation should be completed in all cases. The differential diagnoses include, among others, Guillain-Barré syndrome, demyelinating disorders, systemic rheumatologic conditions, meningitis, infectious myelitis, spinal cord infarction, arteriovenous malformations, trauma, mass lesions, bony and intervertebral disk distortion, abscess, and tumors of the spine and spinal cord (see Tables 640.5 and 640.6).

MRI with and without contrast enhancement is essential to rule out a mass lesion. T1-weighted images of the spine at the anatomic level of involvement may be normal or show spinal cord distension. In the infantile form, T2-weighted images show high signal intensity over multiple spinal segments. In the adolescent form, the high signal is often centrally located and involves both gray and white matter. It may be limited to one or two segments but is frequently more extensive. A limited degree of gadolinium contrast enhancement is expected (especially in the infantile form) and is indicative of an inflammatory condition. Cervical and cervicothoracic lesions represent most acute TM lesions. Axial cuts of the spinal cord are invaluable and can help to establish potential etiologies. Hemicord involvement may indicate MS. Holocord involvement with typical brain and optic nerve involvement suggests NMOSD. If gray matter involvement predominates, consider a vasculitic or infectious process (e.g., SLE or enterovirus). Nerve root enhancement is occasionally seen and should raise suspicion for a mixed picture (central and peripheral demyelination) or anterior horn cell involvement (Fig. 640.5). Up to 6% of cases do not show spinal cord lesions on MRI. Repeat imaging at 7 days may reveal atrophy in these cases. *MRI of the brain is also indicated.* Evidence of other foci of demyelination is seen in at least 40% of patients; lesion localization should guide further consideration for MS, ADEM, NMOSD, SLE, and enterovirus-associated acute flaccid myelitis. In any child with *encephalopathy,* ADEM must be considered.

Lumbar puncture is indicated after exclusion of a mass on MRI and should be analyzed for cells, protein, immunoglobulin index, OCBs, and infectious pathogens. Mononuclear cells are usually elevated in TM. Protein may be elevated or normal. The presence of CSF inflammatory cells is essential for the diagnosis of TM.

Because one of the most important possibilities for this condition is NMOSD, the serum and CSF of all patients should be analyzed for both AQP-4 and MOG antibodies. Older children should also have serum studies sent for other autoimmune disorders, particularly SLE.

TREATMENT

Treatment of childhood TM has not been standardized. Available evidence suggests immune response modulation may be effective in reducing the severity and duration of disease. High-dose steroids (i.e., methylprednisolone) are used acutely in TM. In cases of poor response to high-dose steroids, other acute therapeutic approaches include

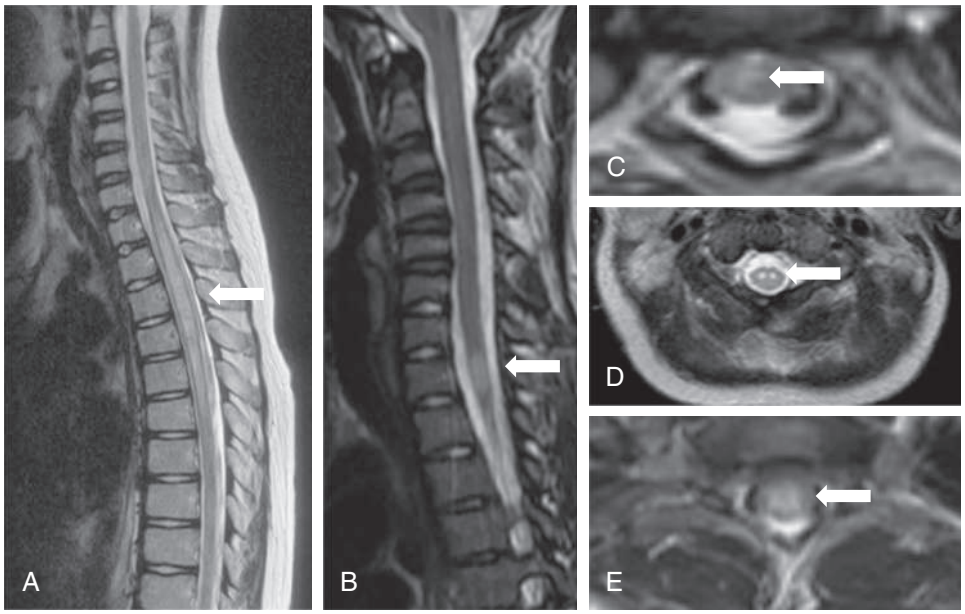

Fig. 640.5 Transverse myelitis. **A,** Sagittal T2-weighted image demonstrates a longitudinal hyperintense spinal cord lesion in a 12-yr-old female with first presentation of AQP4-Ab–positive NMOSD *(arrow)*. **B,** Sagittal T1-weighted image shows a short segment at T1-weighted *(arrow)* in a 14-yr-old female with ON and MS. Axial T2-weighted images of the spine with different etiologies showing typical hemicord appearance in MS (**C**), anterior horn cell involvement in polio (**D**), and holocord involvement in NMOSD (**E**). *(C- E courtesy Dr. Felice D'Arco, Great Ormond Street Hospital, London.)*

intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). Rituximab may be considered if an antibody-driven TM is suspected. Long-term prophylactic therapy is recommended for children with either relapsing disease or biomarkers indicating a risk for recurrence.

PROGNOSIS

Older children with acute TM have a better outcome than adults, with nearly 50% making a good recovery by 2 years. This may reflect the higher likelihood of MOG-Ab–associated disorders in the older child. The most common sequelae in the remaining 50% are sensory problems and bladder dysfunction. Outcomes in younger children with TM are comparatively poor. Recovery is slow and usually incomplete; the likelihood of independent ambulation is approximately 40%.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

640.4 Multiple Sclerosis

Michael Perry and Cheryl Hemingway

Multiple sclerosis (MS) is a chronic demyelinating autoimmune disorder of the brain, spinal cord, and optic nerves. It exhibits a relapsing-remitting course of neurologic events *without* encephalopathy separated in time (i.e., more than one episode of at least 24 hours at least 30 days apart) and space (i.e., in more than one CNS region). When occurring in those under 18 years, it is known as **pediatric-onset MS (POMS)**. Recurrent events lead to a characteristic accumulation of physical disability, cognitive impairment, and brain atrophy.

EPIDEMIOLOGY AND RISK FACTORS

MS is rare in childhood. In northern countries such as the United Kingdom and Canada, the annual incidence is estimated at 2 children per million. Interestingly, 5% of adult MS patients report in retrospect that they first experienced symptoms before age 18. POMS affects prepubescent males and females equally, but after puberty there is a 2:1 female predominance. Childhood MS is almost invariably relapsing-remitting in nature; features suggestive of primary progressive MS should prompt careful specialist evaluation for alternative conditions (Table 640.8).

In adults, a complex interplay of environmental (e.g., low sunlight exposure, low vitamin D, obesity, toxins), infectious (e.g., EBV exposure), and genetic/epigenetic factors (e.g., HLADRB1*15:01 homozygosity) are thought to synergistically influence MS susceptibility. Studies in pediatric MS have so far confirmed the role of some of the earlier factors; however, the rarity of MS, the modest effects of a multitude of candidate risk factors, and the near ubiquity of EBV in the general population have made identification of causality and quantification of risk challenging. A landmark study of U.S. military service members, however, has provided the best evidence yet that EBV infection, long postulated as a putative cause of MS, precedes the onset of disease and confers a 32-fold increase in the risk of disease development. B cells, then, a reservoir of latent EBV infection, may help to explain the effectiveness of anti-CD20 DMTs in MS and provide a target for future therapeutics or vaccines.

PATHOGENESIS

Dysregulation of both the innate and adaptive immune systems is at the heart of MS pathogenesis. The precise sequence of events leading to aberrant production of autoreactive immune cells is not well understood. Restriction of inflammation to the CNS suggests the presence of a CNS autoantigen. How and where an immune response (i.e., B- and T-cell activation) to a purported autoantigen is initiated is unclear; it is possible that CNS antigens migrate into the peripheral lymph nodes (via antigen-presenting cells) where autoreactive T and B cells become activated or that the triggering antigen is derived from the periphery itself (e.g., systemic infection). Clonal cells targeting the brain and spinal cord initiate a self-perpetuating deleterious cycle of inflammation, axonal demyelination, and astrocytic gliosis, and eventual axonal degeneration occurs in both white and gray matter. It is this axonal degeneration that directly contributes to permanent disability. DMTs target inflammatory infiltrates within actively demyelinating lesions of relapsing-remitting MS in an attempt to attenuate this cycle before axonal loss.

CLINICAL MANIFESTATIONS

Presenting symptoms are polyregional in more than half of patients. These include focal sensory loss or other paresthesia (39–63%); cerebellar symptoms such as ataxia or dysarthria (50%); unilateral (and sometimes bilateral) painful eye movement and reduced visual acuity (ON) (37%); brainstem symptoms in 30%; and motor deficits in up to 50%. Such motor dysfunction can manifest as focal deficits, hemiparesis, paraparesis, and bowel/bladder dysfunction (from TM or other spinal lesions). Except in cases of significant brainstem involvement, encephalopathy is not a feature.

Table 640.8 Differential Diagnosis of Multiple Sclerosis: Selected Disorders with a Progressive Course

	CLINICAL FEATURES	MRI FINDINGS	CSF FINDINGS	OTHER INVESTIGATIONS
HTLV1-associated myelopathy	Progressive myelopathy; residence or travel to an endemic area (especially West Indies or Japan)	Spinal cord atrophy (thoracic more than cervical); T2-hyperintense brain lesions in some patients	OCBs sometimes present	CSF HTLV1 antibody testing
Tumor	Progressive, variable features; headache, nonlocalizing symptoms of raised intracranial pressure; encephalopathy, vomiting, seizures, motor and/or sensory disturbances	Progressive enhancing and nonenhancing T2 lesions on serial imaging	OCBs absent	MRI; biopsy ± genetic investigations
Nutritional myelopathy (vitamin B_{12} or copper deficiency)	Subacute progressive myelopathy or myeloneuropathy; optic atrophy (severe vitamin B_{12} deficiency); anemia or pancytopenia	T2 hyperintensity of upper cervical cord classically affecting posterior columns; brain MRI normal	OCBs absent	Serum B_{12}, methylmalonic acid; serum copper levels, ceruloplasmin
Leukodystrophies: adrenomyeloneuropathy; Krabbe disease; Alexander disease; hereditary diffuse leukoencephalopathy with axonal spheroids	Progressive myelopathy (adrenomyeloneuropathy, Krabbe disease); bulbar symptoms, ataxia (Alexander disease); early cognitive impairment (hereditary diffuse leukoencephalopathy with axonal spheroids)	Highly variable; diffuse, symmetric T2 hyperintensity sparing subcortical U-fibers; with posterior hemispheric predominance (adrenomyeloneuropathy); spinal cord MRI normal or showing atrophy	OCBs absent	Very long-chain fatty acids (adrenomyeloneuropathy); genetic testing available for some leukodystrophies
Hereditary spastic paraplegia (especially *SPG5*)	Slowly progressive myelopathy (spasticity greater than weakness) with or without other neurologic symptoms and family history	Spinal cord atrophy; supratentorial and infratentorial white matter lesions *(SPG5)*; atrophy of corpus callosum	OCBs absent	Genetic testing
Spinocerebellar ataxias	Progressive cerebellar ataxia, with or without other neurologic symptoms and family history	Early, prominent cerebellar findings, with or without spinal cord atrophy	OCBs absent	Genetic testing

CSF, Cerebrospinal fluid; HTLV1, human T-lymphotropic virus type 1; OCB, oligoclonal band.
From Brownlee WJ, Hardy TA, Fazekas F, et al. Multiple sclerosis 1: diagnosis of multiple sclerosis: progress and challenges. *Lancet.* 2017;389:1336–1346, Table 2, p. 1341.

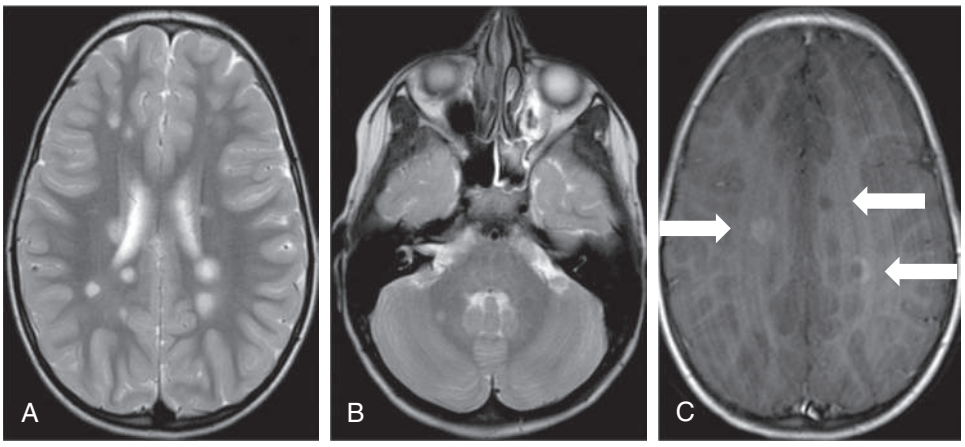

Fig. 640.6 5-year-old patient diagnosed on imaging with MS after presentation with left-sided weakness. **A,** Axial T2-weighted MRI of brain shows multiple discrete, ovoid white matter lesions in the periventricular region and cortical, juxtacortical, and infratentorial lesions **(B). C,** Axial T1-weighted area of hypointensity and two contrast-enhancing lesions *(arrows).*

IMAGING AND LABORATORY FINDINGS

Brain MRI exhibits typically discrete, ovoid, asymmetric T2 lesions in cerebral white matter, particularly periventricular, juxtacortical, cortical, brainstem and cerebellar. Less commonly, lesions are noted in the deep gray matter (Fig. 640.6). When involved, spine MRI typically reveals partial-width cord lesions restricted to one to two spinal segments. Longitudinally extensive lesions are more likely to occur in NMOSD (associated with MOG-Ab and AQP4-Ab) than in MS. CSF may be normal or exhibit mild lymphocytosis. OCBs are positive in CSF but not in serum (type 2 pattern) in more than 90% of pediatric

MS patients. In NMOSD, OCBs are usually either negative (type 1 pattern) or present in both CSF and serum (type 4 pattern). Evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Pediatric MS can usually be diagnosed after two demyelinating episodes *without* encephalopathy. Episodes must localize to one of four distinct CNS regions, last longer than 24 hours, and be separated by more than 30 days. Importantly in pediatric MS, there must exist no other plausible explanation for the symptoms. MRI may serve as a surrogate for recurrent demyelination, thereby enabling MS diagnosis after the first clinical event so long as it demonstrates dissemination in space (at least two T2 lesions involving juxtacortical, periventricular, infratentorial, or spine regions) and time (presence of gadolinium-enhancing lesion and nonenhancing T2 lesion in the same scan). A 10-year longitudinal study demonstrated that 96% of children diagnosed with POMS met 2017 McDonald criteria at presentation. Alternatively, MS can be diagnosed with a follow-up MRI at any time interval that exhibits accumulation of T2 or gadolinium-enhancing lesions in the brain or spine. The 2017 McDonald diagnostic criteria allow the presence of intrathecal OCBs to substitute for dissemination in time (see Table 640.1). Challenges may arise in distinguishing a first attack of pediatric MS from other acquired demyelinating syndromes, particularly those associated with antibodies (e.g., AQP4-Ab, MOG-Ab) or ADEM (Table 640.9 and see Table 640.4). Although irritability and lethargy may be present (particularly with brainstem lesions), encephalopathy is a highly atypical feature of MS, and one should be extremely cautious in making this diagnosis in a child with such symptoms. Indeed, the 2017 McDonald criteria's positive predictive value (PPV) was shown to be reduced because of the relative predominance of ADEM compared with MS in the under-12-years cohort. The absence of encephalopathy is therefore required to make a diagnosis of MS in this age-group.

TREATMENT

Relapses causing functional disability may be treated with intravenous methylprednisolone 20-30 mg/kg/day (maximum 1000 mg/day) for 3-5 days, with or without prednisolone taper. It should be noted that a study in adults demonstrated noninferiority of oral vs intravenous methylprednisolone in acute relapses in MS.

DMTs reduce both relapse frequency and T2 lesion load by targeting elements of the inflammatory response that predominates during the relapsing-remitting phase of MS. There is an increasing number of immunomodulatory and immunosuppressive treatment options available. They include injectables, oral medications, and infusions. The choice and sequencing of medications are becoming increasingly highly specialized (Table 640.10). Nearly all DMT use in pediatrics is currently off-label, though several randomized controlled trials are in progress. The only medication with FDA approval at the present time is fingolimod. One trial comparing oral fingolimod with intramuscular interferon-beta-1α demonstrated that fingolimod reduced the annualized relapse rate by 82% when compared with interferon-beta-1α in children between 10 and 18 years of age. This efficacy is greater than that seen in adults, possibly because of the greater inflammatory burden in POMS. This is but one of the reasons that prompt initiation of treatment is recommended for all those diagnosed with POMS.

An ongoing debate about DMT use concerns escalation vs induction—that is, whether to start with safer, less efficacious first-line agents and only escalate if treatment fails or whether remission should first be induced with the more aggressive and effective treatments before then maintaining on safer medications. Adult trials to answer this question are underway, and currently, the more efficacious treatments are generally reserved only for those with highly active MS. However, the increased inflammatory activity, higher relapse rate, and young age at which disability occurs in POMS have inspired research to investigate the theorized benefits of high-efficacy early treatment (HEET). One effectiveness study of DMTs in pediatric MS provided evidence in favor of HEET, having demonstrated marked superiority of high-efficacy medications in preventing both relapses and new brain lesions.

PROGNOSIS

Reliable prognostication in POMS remains a challenge for several reasons. The first is the long time over which the disease progresses. The second is the disconnect between inflammatory activity (e.g., lesion accumulation, relapse rate) and neuronal/axonal degeneration, which more directly corresponds to disability. Pediatric MS studies before widespread DMT use suggested a higher relapse rate but slower rate of disability accumulation compared with adults. Despite this longer interval to irreversible disability (20-30 years), pediatric MS patients acquire disability at a younger age than adults owing to the earlier age of onset of disease. Indeed, emerging evidence suggests the plasticity of the young brain likely accounts for the relative delays in disability accumulation and cognitive impairment. Nonetheless, like adults with MS, pediatric MS patients can acquire fixed neurologic deficits affecting the visual and other cranial nerves, motor and sensory function, balance, and bowel/bladder function. Children with MS have also been shown to have an overall smaller head size and brain volume that can be attributed to gray matter degeneration. Despite the marked reduction in annualized relapse rate (ARR), lesion load, and overall inflammatory burden compared with interferon-beta-1α, children treated with fingolimod still lost brain volume and failed to achieve age-expected brain volume increase. This underscores the difficulty in addressing cognitive impairment, which is increasingly recognized and present in up to 50% of young people with POMS, more than that seen in adult-onset MS.

Fatigue is also a major symptom in pediatric MS that can lead to a poor quality of life. It is important to address this in a multidisciplinary setting together with other factors, such as mood, sleep quality, and sleep hygiene. Pharmacologic management of fatigue is challenging, but psychology-based therapy with cognitive-behavioral therapy and pacing has been shown to be effective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

640.5 Myelin Oligodendrocyte Glycoprotein–Associated Disorders

Michael Perry and Cheryl Hemingway

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) encompasses a group of demyelinating disorders characterized by IgG autoantibodies to the MOG glycoprotein expressed in the outer layer of the myelin sheath. MOG antibodies are present in about 40% of all children with acquired demyelinating syndromes at first presentation. This increases to half of children with ADEM and nearly all those with relapsing ADEM (MDEM).

There is considerable *phenotypic* overlap between MOGAD, MS, and AQP4-Ab–positive NMOSD. Children with MOG-Ab seropositivity have often been classified as early MS or NMOSD; emerging evidence is drawing lines of demarcation between these entities. This paradigm is owed primarily to improved MOG-Ab assay techniques and specific clinical phenotypic description; differences in symptomatology, epidemiology, disease course, treatment response, prognosis, and histopathology between MOGAD, MS, and AQP4-Ab–positive NMOSD have been described. MOGAD may be either monophasic or relapsing; both MS and AQP4-NMOSD are characterized by a relapsing course. MOGAD has also demonstrated age-dependent variation of phenotype not seen in either MS or AQP4-NMOSD. Indeed, a minority of children with MOG antibodies may fit strict clinical and imaging criteria for a diagnosis of NMOSD with MOG (see Chapter 640.6). Most MOG-positive children (~60%) previously classified as NMOSD would no longer fit this criterion and thus represent a cohort distinct from NMOSD.

CLINICAL PRESENTATION

There are four main clinical phenotypes of MOGAD: (1) ADEM, (2) ON, (3) TM (NMOSD: ON and TM sequentially or simultaneously), and (4) cortical encephalitis. These may be monophasic or relapsing in nature, such as is seen with relapsing inflammatory optic neuritis (RION) or ADEM followed by

Table 640.9 Differential Diagnosis of Multiple Sclerosis: Clinical, MRI, and Serologic Findings of the Main Disorders that Can Resemble Relapsing-Remitting Disease

	NEUROLOGIC FEATURES	MRI FEATURES	BLOOD TEST AND CSF FINDINGS
Acute disseminated encephalomyelitis (most typically found in in pediatric cohorts)	Similar to MS symptoms but encephalopathy is typical; frequently multifocal symptoms	Large spectrum from small punctate lesions to tumefactive lesions with mass effect, in the supratentorial or infratentorial white matter, bilateral, and asymmetric; involvement of cerebral cortex, deep gray matter, brainstem, and spinal cord; enhancement	CSF pleocytosis; serum antibody to MOG
Antibody-associated disease (e.g., AQP-4 NMOSD, MOG-Ab ON)	ON or TM (often concomitant and/or severe in NMOSD); nausea and vomiting	Variable depending on etiology; longitudinally extensive spinal cord lesion (>3 vertebral segments) (NMOSD); longitudinally extensive optic nerve lesions (MOG); posterior optic nerve or chiasmal involvement (NMOSD); spinal lesions with prominent gray matter involvement (H-sign) (MOG); pencil-thin ependymal enhancement and cloudlike enhancement	Serum antibody to AQP4 or MOG; possible mild pleocytosis; CSF OCBs infrequent
Neurosarcoidosis	Cranial nerve involvement (primarily facial and optic nerve); headache; raised intracranial pressure; meningitis; seizures; myelopathy	Meningeal enhancement with pituitary, hypothalamic, and cranial nerve involvement; brain white matter lesions; simultaneous enhancement of all lesions	Raised serum and CSF ACE (not sensitive or specific for sarcoidosis); CSF OCBs sometimes present
CNS vasculitis	Confusion, headache, personality change; seizures; strokelike symptoms	Ischemic, multiple lesions; predominance of lesions at cortico-subcortical junction; intracranial hemorrhage; meningeal enhancement; simultaneous enhancement of all lesions; microbleeds	Serum antineutrophil cytoplasmic antibodies; CSF OCBs sometimes present
Susac syndrome	Visual loss; sensorineural hearing loss; encephalopathy; headache; memory loss; behavioral disturbances	Focal and small lesions in supratentorial and infratentorial regions (both white matter and gray matter); involvement of corpus callosum (snowball lesions); leptomeningeal enhancement	CSF OCBs usually absent
Hypoxic-ischemic vasculopathies (particularly small-vessel disorder)	Stroke events; cognitive decline; focal neurologic signs; gait disturbance	Punctate and peripheral white matter lesions, sparing U-fibers; symmetric and confluent periventricular lesions; lacunar infarcts; involvement of central transverse fibers in pons; microbleeds	Serum testing for vascular risk factors (diabetes, hypercholesterolemia); CSF OCBs absent
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Migraine; stroke events; psychiatric problems and dementia	Temporal pole lesions; external capsule and U-fiber lesions; microbleeds	CSF OCBs absent; testing for *NOTCH3* gene variant
Connective tissue disorders (SLE, Sjögren syndrome, antiphospholipid antibodies syndrome)	Optic nerve, brain, and spinal cord involvement; neuropsychiatric symptoms; seizures; ischemic episodes	Brain infarcts and hemorrhage; basal ganglia lesions; punctate (subcortical) lesions; spinal cord lesions; cerebral venous sinus thrombosis; parotid gland involvement in Sjögren syndrome	Serum antinuclear antibody; extractable nuclear antigens (in particular, anti SS-A(Ro) and SS-B(La) antibodies for Sjögren syndrome, and anti-Sm for SLE); CSF OCBs usually absent
Neuro-Behçet disease	Brainstem syndrome; myelopathy; meningoencephalitis	Large brainstem lesions; basal ganglia, subcortical white matter, and spinal cord lesions; gadolinium enhancement; cerebral venous sinus thrombosis	HLA-B5; CSF pleocytosis; CSF OCBs usually absent
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)	Cranial nerve dysfunction and long-tract signs; symptoms referable to brainstem or cerebellar dysfunction; spinal cord syndrome; cognitive dysfunction	Multiple punctate, patchy, and linear regions of gadolinium enhancement relatively confined to pons; lesions also involving cerebellum, basal ganglia, supratentorial white matter, brainstem, and spinal cord	CSF OCBs sometimes present; consider testing for primary CNS hemophagocytic lymphohistiocytosis even if meeting criteria for CLIPPERS (see later)

Table 640.9 Differential Diagnosis of Multiple Sclerosis: Clinical, MRI, and Serologic Findings of the Main Disorders that Can Resemble Relapsing-Remitting Disease—cont'd

	NEUROLOGIC FEATURES	MRI FEATURES	BLOOD TEST AND CSF FINDINGS
Primary CNS hemophagocytic lymphohistiocytosis (HLH)	Mimic of CLIPPERS, MDEM, and small vessel CNS vasculitis with a treatment-resistant and steroid-dependent disease pattern; symptoms include seizures, encephalopathy, weakness, ataxia, nystagmus, vomiting	Multifocal cerebral and cerebellar matter lesions with variable T2 hyperintensities; homogeneous enhancing nodules and curvilinear and punctate lesions of pons like that seen in CLIPPERS; diffuse cerebellar cortical edema	Genetic testing (e.g., *PRF1, UNC13D*); natural killer (NK)–cell function; CSF proteinosis or pleocytosis; neopterin may be a useful biomarker of disease activity
Fabry disease	Stroke events; vertigo	Posterior infarcts; multiple white matter lesions with pulvinar involvement (T1 hypointense lesions)	Reduced activity of GLA enzyme; analysis of *GLA* gene
Leber hereditary optic neuropathy	Bilateral sequential optic neuropathies with poor visual recovery; more common in men than women	Normal or might show white matter lesions (Harding disease)	OCBs absent; mitochondrial DNA (mtDNA) genetic testing for three most common (~90%) variants in first instance: MTND1m.3460G>A, MTND4m.11778G>A, MTND6m.14484T>C); full mtDNA sequencing indicated if targeted sequencing negative and clinical suspicion remains high

Infectious diseases are not included in this table but should be considered, especially in cases of atypical demyelinating lesions.
CSF, Cerebrospinal fluid; ACE, angiotensin-converting enzyme; GLA, α galactosidase A; OCB, oligoclonal band.
Modified from Thompson AJ, Baranzini SE, Geurts J, et al. Multiple sclerosis. *Lancet*. 2018;391:1622–1636, Table 3, pp. 1628–1629.

Table 640.10 Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
FIRST-LINE THERAPIES APPROVED FOR MS IN ADULTS				
Interferon-β-1a and β-1b (subcutaneous or intramuscular injection on alternate days, 3 times weekly, weekly or bimonthly depending on preparation)	Immunomodulator	Modulates T cells and cytokine production	Injection site reaction; flulike symptoms; headache, muscle aches, transaminitis; leukopenia; tissue necrosis at injection site (rare)	~33% decrease in ARR and slows progression of disability
Glatiramer acetate (daily or 3 times weekly, subcutaneous injection)	Immunomodulator	Stimulation of Th-2 regulatory T-cells	Injection site reactions; transient flushing, chest tightness and shortness of breath. Lipodystrophy at injection sites	~33% decrease in ARR and slows progression of disability
Dimethyl fumarate (DMF) (oral medication 12 hourly with food, i.e., twice a day)	Immunomodulator	Unclear mechanism; likely antiinflammatory promotion via modulation of nuclear factor κB; modulates cytokine production and reduces lymphocyte count. neuroprotectant; antioxidant	Flushing; viral URTI; dysmenorrhea; GI upset; headache; proteinuria, leukopenia. Rare reports of PML in those with severe prolonged lymphopenia	Reduces number of relapses by ~ 50% compared with placebo in adults; this has recently been shown to remain stable over 10 yr of treatment (ENDORSE). Small single-arm pediatric phase 2 + extension study (FOCUS + CONNECTED) demonstrates favorable safety and efficacy profile. Phase 3 pediatric RCT (CONNECT) ongoing
SECOND-LINE THERAPIES APPROVED FOR MS IN ADULTS				
Teriflunomide	Immunomodulator	Pyrimidine synthesis impairment via dihydroorotate dehydrogenase inhibition; reduction of T and B cells proliferation	Infections (respiratory tract); pancreatitis; headaches; diarrhea; liver inflammation or injury; alopecia; nail and skin disorders; teratogenicity	43% reduction in combined risk of clinical relapse or high MRI activity vs placebo; 55% reduction in new or enlarged T2 lesions vs placebo (TERIKIDS trial)

Continued

Table 640.10 Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders—cont'd

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
Natalizumab (infusion over 2-3 hr every 4 wk; alternatively subcutaneous injection every 4 wk)	Monoclonal antibody	Targets α_4-integrin on vascular endothelium, preventing T- and B-cell migration into CNS	Infusion reactions with headache, dizziness, rash; rare anaphylaxis. May affect liver function. Risk of PML able to be stratified by JC virus status, length of treatment, and previous treatments. Immune reconstitution syndrome after discontinuation; melanoma	Reduces number of relapses by ~70% in adults
Fingolimod (daily oral medication: first dose, cardiac monitoring required and need to ensure good compliance because of risks of first-dose bradycardia and heart block)*	Immunomodulator	Modulates sphingosine-1-phosphate receptors; causes T-cell sequestration in lymphoid compartments	First-dose bradycardia; cardiac arrhythmia; systemic viral infection; persistent lymphopenia with risk of severe herpetic and varicella infection; macular edema; transaminitis; basal cell carcinoma. Rare cases of PML	FDA approved for pediatrics May 2018 after first prospective RCT in children with POMS (PARADIGMS) showing 82% decrease in ARR compared with interferon β
Alemtuzumab (infusions 2 courses: first for 5 consecutive days; second 12 mo later for 3 consecutive days)†	Monoclonal antibody	Anti-CD52 antibody target; depletes mature B and T cells	Vascular disorders (see footnotes re: FDA black box warning: ischemic stroke, arterial dissection); Infusion reactions within first 2-3 hr; opportunistic infection, secondary autoimmune disorders, including thyroiditis (50% risk), hemophagocytic lymphohistiocytosis (HLH), autoimmune hepatitis, immune thrombocytopenia (1%); glomerular nephropathies including anti–glomerular basement membrane disease (Goodpasture syndrome). Monthly blood tests required for 4 yr after last course	Highly effective in adults; ~ 55% decrease in ARR compared with interferons. Pediatric single-arm, before and after switch study (LemKids) ongoing.
Cladribine (oral tablets two courses: first for 4-5 consecutive days during mo 1 and 2; second as before 12 mo later)	Immunomodulator	Selective activity against CD4 and CD8 T cells and CD19 B cells via adenosine deaminase activity	Neutropenia, lymphopenia, infection, oral herpes, GI disorders, and rash	Reduced relapses by ~58% vs placebo in adults and delay in disability progression. No pediatric trials conducted to date
Rituximab (infusions given 2 wk apart ~every 6 mo)	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Infusion-related side effects; hepatitis, PML (rate undefined)	Used off-label for adult MS; no efficacy assessments available in pediatric MS
Ocrelizumab (infusions given 2 wk apart ~every 6 mo)	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretic risk of PML (undefined) and, possibly, malignancy	In adult MS showed 50% reduction in ARR compared with interferons; a phase 3 pediatric trial (OPERETTA 2) is ongoing
OTHER MEDICATIONS USED FOR DEMYELINATING DISORDERS				
Azathioprine (intravenous infusion or oral tablets daily)	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	GI side effects, alopecia, bone marrow suppression, and blood dyscrasias, transaminitis, infections, secondary malignancy, alopecia. Increased side effects with low TPMT enzyme activity	No efficacy assessments available in pediatric MS; small retrospective studies for NMOSD

Table 640.10 Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders—cont'd

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
Intravenous immunoglobulin (IVIG)	Immunotherapy	Inhibits complement binding; promotes antiinflammatory interleukin secretion; promotes regulatory T cells	Generally better tolerated than PLEX; headache; rash; allergic reaction	Limited class C evidence (small pediatric case series) suggests improved outcomes in severe and/or relapsing cases of ADS
Mycophenolate mofetil (MMF) (intravenous infusion or oral tablets twice daily)	Immunosuppressant	Disrupts purine synthesis and impairs B- and T-lymphocyte proliferation	GI side effects, alopecia, bone marrow suppression and blood dyscrasias, transaminitis, infections, secondary malignancy, alopecia. Teratogenic.	
Plasma exchange (PLEX)	Extracorporeal immunotherapy	Removal of pathogenic autoantibodies and proinflammatory macromolecules	Electrolyte abnormalities (particularly hypocalcemia); infection; hypotension; allergic reaction; anemia	Limited pediatric case series and adult studies available support use as rescue and/or second-line therapy
Vitamin D	Vitamin/hormone	Modulates immune cell expression	Hypercalcemia and kidney stones at serum 25(OH) vitamin D level > 100 ng/mL	Prospective trials in pediatric and adult MS are currently underway

*Additional S1P inhibitors with more specific receptor selectivities (i.e., less cardiac cross reactivity) are coming to market; pediatric trials are currently ongoing.
†U.S. FDA black box warning regarding rare but serious vascular side effects including ischemic and hemorrhagic stroke and cervicocephalic dissection. To be used with caution only in specialist centers.
CNS, Central nervous system; ARR, annualized relapse rate; MS, multiple sclerosis; JC virus, John Cunningham virus; PML, progressive multifocal leukoencephalopathy; TPMT, thiopurine methyltransferase; GI, gastrointestinal.

optic neuritis (ADEM-ON) (see Table 640.1). Tumefactive lesions, cerebellar demyelination, cranial neuropathies, monofocal or polyfocal cerebral motor deficits, and occasionally a widespread progressive leukodystrophy-like pattern may also be seen. Children with cortical encephalitis may present with seizures, headache, fever, and cortical symptoms with cortical hyperintensities on T2-weighted MRI sequences. Symptoms may be preceded by a viral prodrome, but no pathogens have been causally linked.

The diagnostic guideline of the International MOGAD Panel requires fulfillment of three criteria (Table 640.11):

1. Presence of one of six core clinical demyelinating events: optic neuritis, myelitis, ADEM, cerebral monodical or polyfocal deficits, brainstem or cerebellar deficits, or cerebral cortical encephalitis
2. Serum MOG-Ab positivity
3. Exclusion of MS and other demyelinating syndromes

IMAGING AND LABORATORY FINDINGS

MRI findings are atypical for MS (Fig. 640.7 and see Fig. 640.3). Brain MRI may show widespread involvement of the supratentorial and infratentorial white matter that can over time develop into a leukodystrophy-like pattern. This may extend into the pons, middle cerebellar peduncle, medulla, or deep gray matter. Spinal imaging suspicious for MOG-Ab disease may show longitudinally extensive myelitis, a characteristic H-sign of the central cord, or a lesion of the conus medullaris. Accrual of MRI lesions in the absence of relapse (i.e., clinically silent), a hallmark of MS, is not a typical feature of MOGAD. MRI of the optic nerves can be particularly useful in discrimination of phenotype and may show specific findings that together may indicate MOG-Ab disease. These include perineural sheath enhancement, papilledema, bilateral ON, and longitudinal nerve involvement. Previously attributed to those with POMS, these findings are now recognized as hallmarks of MOG-Ab–associated disease.

Suspected cases should have serum tested for MOG antibodies via live CBA for the IgG Fc or IgG1 secondary antibodies; importantly, laboratories should ideally report both quantitative (i.e., titers) and qualitative results (i.e., low-positive or high-positive) (Fig. 640.8). Despite variation in assay protocols across laboratories globally, high positivity is reliably predictive of true MOG-Ab positivity. Low-positive or borderline results less reliably differentiate MOG-Ab disease from other entities and should prompt reconsideration of other diagnoses, particularly MS. Fixed CBAs may be used with some caution if live CBA is not available, but enzyme-linked immunosorbent assay (ELISA) should be avoided. Although useful for diagnostic purposes, MOG-Ab titer *levels* are unhelpful in predicting risk of relapse.

Intrathecal OCBs are not normally present. However, OCB positivity should not preclude a diagnosis of MOG in the presence of supportive clinical features (particularly TM) and high MOG-IgG antibodies. Elevated CSF white blood cells with pleocytosis is often present.

TREATMENT

Treatment of acute attacks is similar to other demyelinating disorders: high-dose methylprednisolone, PLEX, and IVIG. Most children with MOGAD will experience a monophasic course and thus should not be offered DMT after a first event.

There is currently no clarity about DMTs that may be helpful over the long term and in relapsing disease. A complicating factor is the potential for long intervals between relapses. This makes it exceedingly difficult to determine the true efficacy of DMTs and guide early decisions about initiating treatment. Some studies have even demonstrated an exacerbation of MOG-Ab disorders treated with traditional MS medications, highlighting again the importance of an accurate clinical diagnosis.

The decision to use long-term immunosuppressive agents after induction therapy can be difficult. Unlike MS and AQP4-NMOSD, MOGAD may be monophasic or relapsing. At present, reliable predictors for risk of relapse do not exist. Therefore children with MOGAD are assessed holistically to determine the appropriateness of chronic therapy based on the risk:benefit ratio of each individual patient. This may include the severity of initial presentation, response to acute treatment, recovery from index attack, and likelihood of relapse. In children assessed as likely to benefit from DMTs, medications such as mycophenolate mofetil and azathioprine are frequently

Table 640.11 Proposed Diagnostic Criteria for MOGAD*

(A) Core clinical demyelinating event	• Optic neuritis • Myelitis • ADEM • Cerebral monofocal or polyfocal deficits • Brainstem or cerebellar deficits • Cerebral cortical encephalitis often with seizures		
(B) Positive MOG-IgG test	Cell-based assay: serum	Clear positive	No additional supporting features required
		Low positive Positive without reported titer Negative but CSF positive	AQP4-IgG seronegative *AND* ≥1 supporting clinical or MRI feature
Supporting clinical or MRI features	Optic neuritis	• Bilateral simultaneous clinical involvement • Longitudinal optic nerve involvement (> 50% length of the optic nerve) • Perineural optic sheath enhancement • Optic disc edema	
	Myelitis	• Longitudinally extensive myelitis • Central cord lesion or H-sign • Conus lesion	
	Brain, brainstem, or cerebral syndrome	• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter • Deep gray matter involvement • Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla • Cortical lesion with or without lesional and overlying meningeal enhancement	
(C) Exclusion of better diagnoses including multiple sclerosis			

*Requires fulfillment of A, B, and C.
Modified from Banwell B, Bennett JL, Marignier R et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *Lancet Neurol.* 2023;22(3):268-282.

offered. This can be done with or without steroids. Rituximab has been used with some reports of benefit. However, there have also been concerning cases of severe exacerbations despite B-cell depletion, particularly in those with relapsing brainstem demyelination. It is important to remember that although both AQP4 and MOG disorders are antibody-driven, the former is an astrocytopathy, whereas the latter is an oligodendrocytopathy. Therefore extrapolation of treatment effects from one condition to the other is not necessarily possible. Monthly IVIG is the only treatment to date to consistently have shown benefit in high-risk individuals. However, there is great promise in new treatments such as satralizumab, an anti-IL-6 antibody, and anti-neonatal Fc receptor antibodies, which aim to reduce levels of pathogenic autoantibody by blocking IgG recycling.

PROGNOSIS

MOGAD is generally associated with a more benign course and favorable recovery compared with AQP4-Ab demyelination. Dramatic resolution is often seen in as little as 30 days on follow-up MRIs. MOGAD is particularly heterogenous, however, and certain phenotypes such as brainstem demyelination can have a very high relapse rate. Progression of disability is directly related with relapse rate, and therefore predictors of relapse rate is a focus of intense research. Approximately one third of MOG-positive children will relapse within 8 years of the first presentation. This risk is slightly higher in MOG-related ON and lower in isolated TM. Relapses can also occur many years after the first event, with intervals of more than 10 years having been reported. Cognitive deficits are seen frequently in those with young onset and frequent relapses.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

640.6 Neuromyelitis Optica Spectrum Disorders

Michael Perry and Cheryl Hemingway

The neuromyelitis optica spectrum disorders (NMOSDs) are severe autoimmune inflammatory diseases classically characterized by episodes of ON and/or longitudinally extensive TM. The discovery of pathogenic antibodies to the astrocyte water channel protein aquaporin-4 (AQP4) and the incorporation of these antibodies into the 2015 revised diagnostic criteria for NMOSDs have helped to distinguish AQP4-Ab–related disorders from other demyelinating conditions; it has also widened the spectrum of the group of disorders to include brainstem syndromes (e.g., area postrema syndrome) and recurrent forms of ON and TM (see Table 640.1). MOG-Ab has also been identified in many cases that were initially thought to have been AQP4-antibody–negative presentations. Reports of both antibodies being simultaneously present in a single individual are exceedingly rare; in these circumstances, a diagnosis of AQP4-Ab–positive NMOSD should take precedence and guide management.

EPIDEMIOLOGY

AQP4-Ab–positive NMOSD typically presents in older adults, whereas MOG-Ab NMOSD is much more common in children and young people. Both, however, can occur across a wide age spectrum. Population studies vary significantly but suggest a pediatric incidence for NMOSDs of 0.5–4.5% of all ADS presentations. AQP4-Ab–driven NMOSD is significantly more common in females than in males. NMOSD appears to have a higher mortality rate in Black people. Most cases of NMOSD are idiopathic; only occasionally have familial cases have been reported. Several genetic risk factors have been described, including the HLA-DRB1*0301 allele and a single-nucleotide polymorphism in CD58.

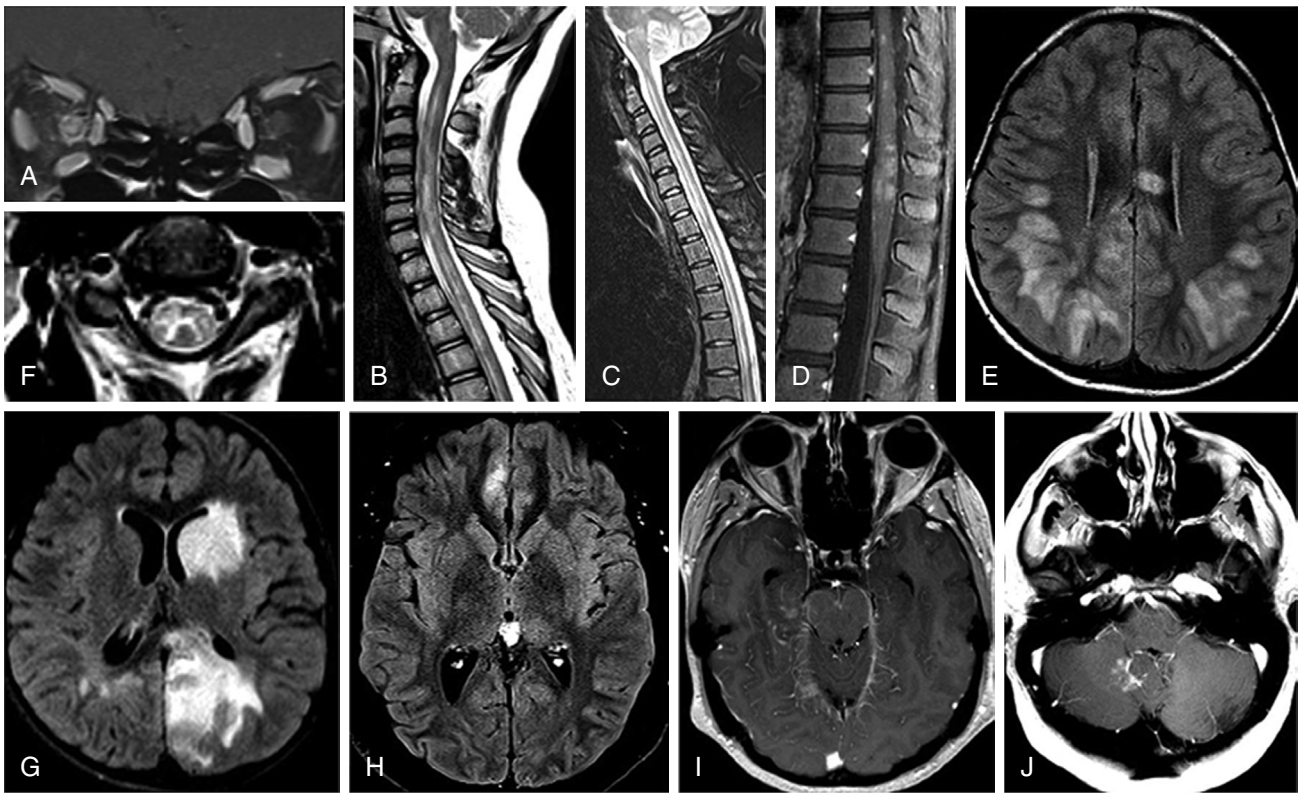

Fig. 640.7 Spectrum of anti-MOG–associated diseases. **A**, Coronal T1-weighted MRI of brain post-gadolinium contrast showing contrast enhancement of bilateral optic nerves and right optic nerve sheath consistent with perioptic neuritis. **B**, Sagittal STIR MRI of spine showing longitudinal extensive patchy lesion spanning from cervical to thoracic cord. **C**, Sagittal T2-weighted MRI of spine showing hyperintense, longitudinally extensive "pseudo-dilation" of central canal. **D**, Sagittal T1-weighted MRI of spine post-gadolinium contrast showing patchy enhancement of the conus medullaris. **E**, Axial FLAIR MRI of brain showing large subcortical and septal white matter lesions in a pediatric patient presenting with ADEM. **F**, Axial T2-weighted MRI of brain with hyperintense "H" sign outlining the central gray matter of the upper cervical cord in a teenager with myelitis. **G**, Axial T2-weighted MRI of brain with "fluffy" hyperintense lesion of gray and white matter of the left caudate and left occipital parietal regions in a pediatric patient who presented with ADEM. **H**, Axial T2-weighted MRI of brain showing unilateral FLAIR hyperintensity and edema of the right mesial frontal cortex in a patient with FLAMES syndrome. **I**, Axial T1-weighted MRI of brain post-gadolinium contrast showing leptomeningeal enhancement of the midbrain and right mesial temporal lobe. **J**, Axial T1-weighted MRI of brain post-gadolinium contrast showing a lesion adjacent to the cerebellar vermis and dorsal medulla in a patient with brainstem syndrome and no other lesions. *(From Parrotta E, Kister I. The expanding clinical spectrum of myelin oligodendrocyte glycoprotein [MOG] antibody associated diseases in children and adults. Front Neurol. 2020;11:Article 960, Fig. 1.)*

PATHOGENESIS

The water channels against which the AQP4-IgG antibody is directed are most abundant on the astrocyte foot processes within the periventricular regions, brainstem, optic nerves, and spinal cord; thus strictly speaking, NMOSD can be characterized as an autoimmune *astrocytopathy* with secondary demyelination. Antibody (primarily IgG1 subtype) binding occurs at the extracellular loops of the AQP4 protein. This activates the classical complement pathway with C5b-C9 component, stimulating leukocyte migration and degranulation, ultimately resulting in astrocytic death. Chemokine secretion from the dying astrocytes and activated leukocytes further attract additional macrophages, leading to oligodendrocyte and neuronal death. Subsequent necrosis or cavitation may occur.

CLINICAL MANIFESTATIONS

AQP4-positive NMOSD presents most commonly with ON, TM, or area postrema syndrome (i.e., hiccups, nausea, and/or intractable vomiting); vomiting is highly unusual in MOG-Ab NMOSD. The symptoms and signs of TM depend on the spinal level and completeness of the inflammatory changes. ON or TM may occur simultaneously or may be separated in time by weeks or even years. Some patients, particularly in MOG-Ab NMOSD, present with seizures and encephalopathy mimicking ADEM. Others exhibit endocrinopathies such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus (DI), hyperinsulinemia, disrupted puberty, or obesity. NMOSD may also be associated with other autoimmune conditions, such as SLE, Sjögren syndrome, diabetes mellitus (DM), and thyroiditis.

IMAGING AND LABORATORY FINDINGS

Neuroimaging studies must include the entire spine, optic nerves if visual symptoms are present, and brain. Although often manifesting with large, hazy, ill-defined white matter lesions and/or gray matter involvement, such as thalamic lesions, brain imaging may have only subtle white matter changes, or even be normal. Brain lesions most frequently localize to areas of high AQP4-Ab expression such as the periaqueductal gray matter, dorsal brainstem, and diencephalon (Fig. 640.9). Spinal imaging may reveal short or longitudinally extensive TM; longitudinally extensive ON involving the chiasm is more common in MOG-Ab disease. Imaging does not reliably differentiate AQP4-Ab and MOG-Ab. Both, however, are readily distinguished from MS by the absence of discrete, well-defined oval lesions in the periventricular white matter.

Although AQP4-Ab and MOG-Ab can be found in both the serum and CSF, their relative increased prevalence in the serum suggests extrathecal production of antibody. There are several different methods of varying sensitivity for antibody testing; the gold standard is the live CBA. Repeat testing is advised in cases of high clinical suspicion of an antibody-driven

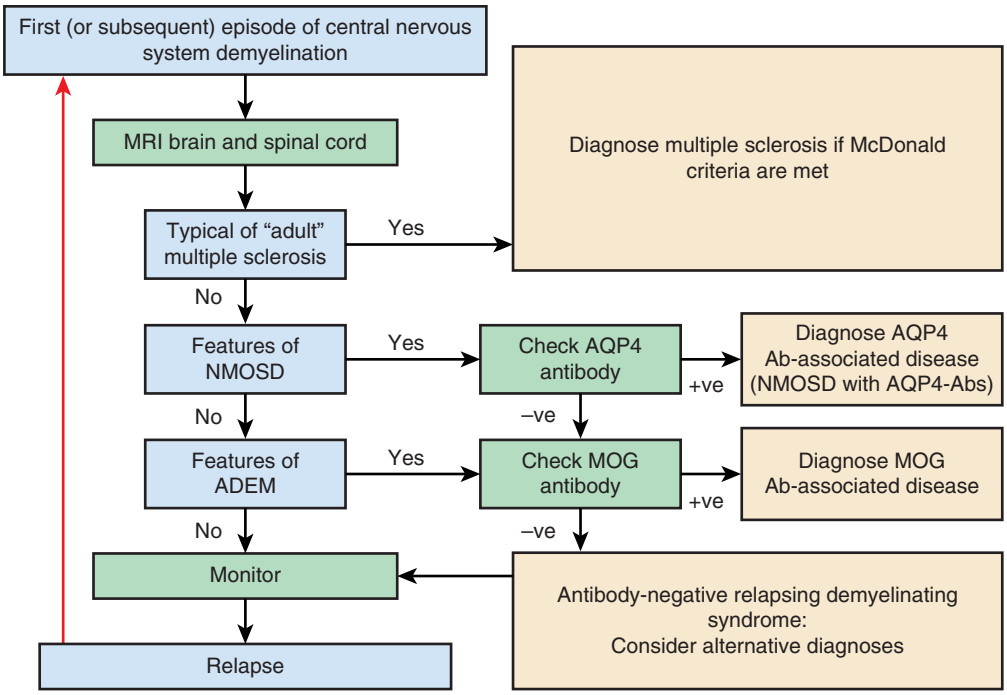

Fig. 640.8 Diagnostic algorithm that can be applied to any episode of CNS demyelination in children. The first recommended diagnostic test is brain and spinal cord MRI. If MRI findings are considered to be typical or suggestive of adult MS, then the McDonald diagnostic criteria should be applied. In children whose MRI is not typical or suggestive of MS but who have clinical and radiologic features suggestive of NMOSD, AQP4-Ab testing is recommended. In particular, this test is advised in children presenting with an area postrema syndrome, MRI abnormalities localized to the brainstem and hypothalamus, and destructive lesions. If AQP4-Ab is negative, then MOG-Ab should be tested. In children whose MRI is not typical of MS or NMOSD but the clinical and radiologic presentation has features of ADEM, MOG-Ab testing is recommended. Supporting features for MOG-Ab–associated disease include lesions in the cerebellar peduncle and leukodystrophy-like MRI pattern in the very young. Alternative diagnoses should be considered in the remaining Ab-negative patients. *(From Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology. 2017;89:269–287, Fig. 2.)*

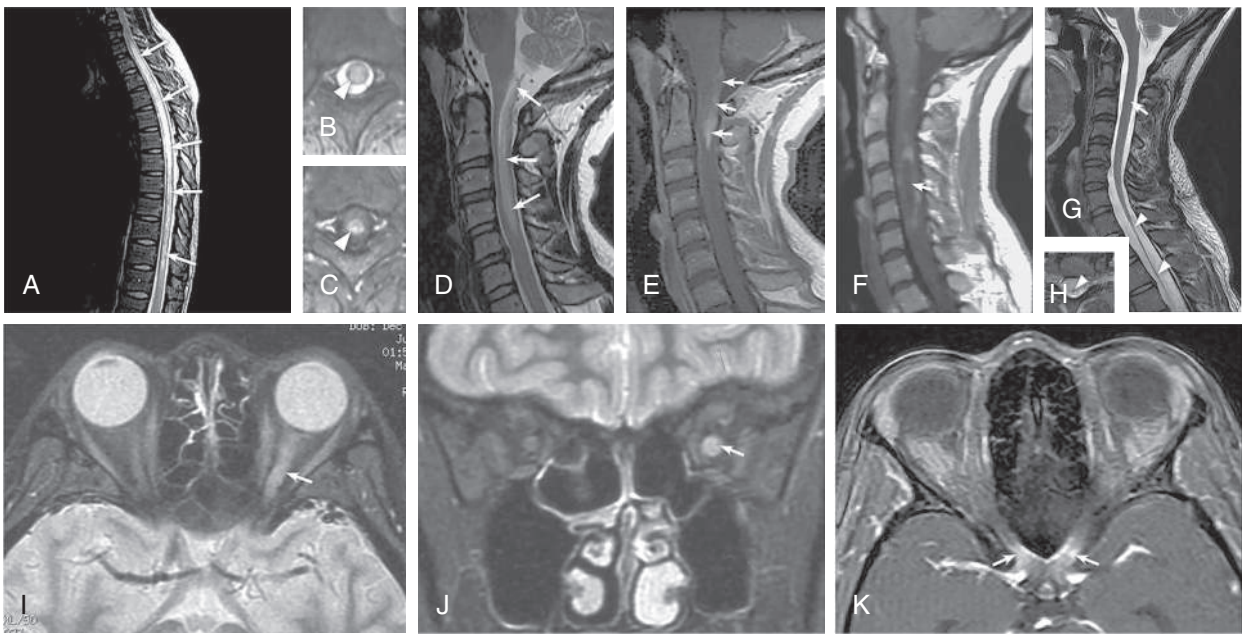

Fig. 640.9 Spinal cord and optic nerve MRI patterns in NMOSD. Spinal cord imaging in the context of acute myelitis in NMOSDs usually reveals a longitudinally extensive transverse myelitis (LETM) lesion extending over three or more vertebral segments. **A,** Sagittal T2-weighted MRI of the thoracic spinal cord demonstrates a typical LETM lesion involving most of the thoracic spinal cord *(arrows)*. LETM lesions have a predilection for the central cord, as shown by axial T2-weighted (**B**; *arrowhead*) and T1-weighted MRIs with gadolinium (**C**; *arrowhead*). Cervical LETM may extend into the medulla, a characteristic NMOSD pattern demonstrated in **D** (*arrows;* sagittal T2-weighted MRI) and **E** (*arrows;* sagittal T1-weighted MRI with gadolinium). Acute LETM lesions can be associated with intralesional hypointensity, as shown by sagittal T1-weighted MRI (**F**; *arrow*); in this example, a rim of gadolinium enhancement surrounds the hypointense region. Chronic sequelae of LETM may include longitudinally extensive segments of spinal cord atrophy, as shown by T2-weighted MRI using the sagittal plane (**G**; the two *arrowheads* indicate the atrophic segment, and the top *arrow* indicates the normal diameter of unaffected cervical spinal cord) and axial plane (**H**; *arrowhead* shows an atrophic spinal cord). Fast spin echo fat-suppressed T2-weighted MRI in the axial (**I**) and coronal (**J**) planes shows increased signal throughout most of the length of the left optic nerve, especially its posterior portion *(arrows)*. **K,** Axial T1-weighted MRI with gadolinium shows enhancement of the optic chiasm (*arrows*). These images are from two different patients experiencing acute ON in the setting of NMOSD. *(From Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177–189, Fig. 1.)*

disorder despite a negative test. CSF typically reveals elevated white blood cells (WBCs) and, unlike in MS, is usually negative for OCBs.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The International Panel for NMO Diagnosis (IPND) published new criteria for NMOSD in 2015. Emphasis is now placed on the presence or absence of AQP4 antibody (see Table 640.1). In seropositive patients (after exclusion of alternative diagnoses), only one core clinical criterion is required from the following six: (1) ON, (2) TM, (3) area postrema syndrome, (4) acute brainstem syndrome, (5) narcolepsy *or* diencephalic syndrome with compatible MRI lesions, and (6) symptomatic cerebral syndrome with typical brain lesions. If AQP4-Ab negative, the diagnosis is more stringent and two core clinical criteria are required, one of which must be ON, longitudinally extensive transverse myelitis (LETM), or area postrema syndrome. The heterogenous nature of this seronegative cohort suggests that further antibodies are yet to be discovered and likely represent multiple subgroups.

The differential diagnoses include other demyelinating disorders, such as MS or ADEM; vasculitis and rheumatologic disorders, including SLE, Behçet disease, and neurosarcoidosis (usually accompanied by other nonneurologic manifestations); idiopathic TM, tropical spastic paraparesis, and viral encephalomyelitis (none of which have NMO antibodies in the serum or CSF); genetic disorders such as familial HLH or pathogenic variants in *DARS*; metabolic causes such as biotinidase deficiency and riboflavin-responsive conditions; idiopathic causes of isolated ON; or other acute forms of monocular or binocular visual loss (Table 640.12; see also Chapter 671). Additional considerations include lymphoma, Langerhans cell histiocytosis, tuberculosis, and vitamins B_{12} and E deficiencies.

TREATMENT

In principle, treatment of NMOSD involves acute treatment with early aggressive antiinflammatory therapy (e.g., steroids) and removal of the antibody (PLEX or monoclonal) and longer-term relapse prevention with DMTs.

Initial episodes and relapses may be treated acutely with methylprednisolone 20-30 mg/kg/day (maximum 1,000 mg/day) usually for 5 days; this can be extended for severe attacks. An oral taper (though there is no consensus regarding length) is recommended, particularly if antibody results are not available at the time of discharge. In certain circumstances, treatment escalation in the acute phase may be indicated: for example, when minimal or no improvement is seen with steroids, or even initially in patients deemed to be high-risk (i.e., brainstem symptoms or ON in a child with preexisting deficit in the contralateral eye). In these cases, PLEX either before or after IVIG (2 g/kg over 2-5 days) with a repeat course of steroids may be considered. Rituximab can be used both acutely and to prevent further relapses.

In adults, AQP4-Ab–positive NMOSD has historically been treated with a range of DMTs, including azathioprine, mycophenolate mofetil (MMF), and rituximab. A study of satralizumab (interleukin [IL]-6 reuptake inhibitor of T- and B-cell activation, Th17 differentiation, and plasmablast survival) in NMOSD demonstrated clear benefit in pediatric patients, particularly those who were AQP4-Ab–positive, and it is licensed for use in children in the United States and Canada. Preliminary evidence in adults suggests that eculizumab, a monoclonal antibody against the C5 complement protein, reduces recurrence and may improve disability in patients with severe NMOSD. A pilot study of tocilizumab, an anti–IL-6 monoclonal antibody, demonstrated efficacy in AQP4-NMOSD in adults. Inebilizumab, an anti-CD19 antibody, has been shown to effectively ameliorate multiple NMOSD endpoints (time to relapse, disability scores, new MRI lesions) in adults and is now in pediatric clinical trials. Importantly, medications used for the treatment of MS are ineffective and can even exacerbate relapses, again highlighting the criticality of accurate diagnosis.

PROGNOSIS

The relapsing and aggressive nature of AQP4-positive NMOSD in pediatric patients very often results in poor recovery and a progressive accrual of disability. MOG-Ab–positive NMOSD is more likely to be monophasic. In relapsing phenotypes (either AQP4-Ab or MOG-Ab), the relapse rate is higher in those with AQP4-Ab, with emerging consensus for a better recovery and long-term prognosis for MOG-Ab–associated disorders. Like adults with NMOSD, pediatric patients are often (>50%) left with fixed neurologic deficits affecting VA, visual fields, color vision, motor and sensory function, balance, and bowel/bladder function, and the best outcomes are achieved with prompt treatment by a multidisciplinary team experienced in pediatric neuroinflammatory care.

Table 640.12 Red Flags: Findings Atypical for NMOSD and TM*

RED FLAGS (CLINICAL AND LABORATORY)
1. Clinical features and laboratory findings
Progressive overall clinical course (neurologic deterioration unrelated to attacks; consider MS)
Atypical time to attack nadir: less than 4 hr (consider cord ischemia/infarction); continual worsening for more than 4 wk from attack onset (consider sarcoidosis or neoplasm)
Partial TM, especially when not associated with LETM MRI lesion (consider MS)
Presence of CSF OCBs (OCBs occur in <20% of NMO cases vs >80% of MS cases)
2. Comorbidities associated with neurologic syndromes that mimic NMOSD
Sarcoidosis, established or suggestive clinical, radiologic, or laboratory findings thereof (e.g., mediastinal adenopathy, fever and night sweats, elevated serum angiotensin-converting enzyme or interleukin-2 receptor levels)
Cancer, established or with suggestive clinical, radiologic, or laboratory findings thereof; consider lymphoma or paraneoplastic disease (e.g., collapsin response mediator protein-5–associated optic neuropathy and myelopathy or anti-Ma–associated diencephalic syndrome)
Chronic infection, established or with suggestive clinical, radiologic, or laboratory findings thereof (e.g., HIV, syphilis)
RED FLAGS AND MIMICS (CONVENTIONAL NEUROIMAGING)
1. Brain
a. Imaging features (T2-weighted MRI) suggestive of MS (MS typical)
Lesions with orientation perpendicular to a lateral ventricular surface (Dawson fingers)
Lesions adjacent to lateral ventricle in the inferior temporal lobe
Juxtacortical lesions involving subcortical U-fibers
Cortical lesions
b. Imaging characteristics suggestive of diseases other than MS and NMOSD
Lesions with persistent (>3 mo) gadolinium enhancement
2. Spinal cord
a. Spinal nerve root inflammation (e.g., Guillain-Barré syndrome)
b. Tumor (e.g., neuroblastoma, Wilms tumor, Ewing sarcoma)
c. Destructive lesions (e.g., tuberculosis, lymphoma, Langerhans cell histiocytosis)
d. Vascular disorders (e.g., arteriovenous infarct, arteriovenous malformation, cavernomas, Cobb syndrome, spinal cord infarction)
e. Vasculitis (e.g., SLE, Behçet disease)
f. Characteristics more suggestive of MS than TM/NMOSD:
Lesions in <3 complete vertebral segments on sagittal T2-weighted sequences
Lesions located predominantly (>70%) in the peripheral cord on axial T2-weighted sequences
Diffuse, indistinct signal change on T2-weighted sequences (as sometimes seen with long-standing or progressive MS)

*These are some common or key findings that should prompt a thorough investigation for competing differential diagnoses before making a diagnosis of NMOSD or isolated TM.

LETM, Longitudinally extensive transverse myelitis lesions; TM, transverse myelitis; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders.

Modified from Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85:177–189, Table 2, p. 180 and 182; with data from Thomas T, Branson HM. Childhood transverse myelitis and its mimics. *Neuroimaging Clin North Am.* 2013;23:267–278, Box 1.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 641

Pediatric Stroke

Nomazulu Dlamini and Gabrielle A. deVeber

Stroke is an important cause of acquired brain injury in newborns, children, and adolescents. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are, together, more common than brain malignancy (incidence ~5 in 100,000 children per year). Perinatal ischemic stroke is especially common (1 in 2,500-4,000 live births) and is the leading cause of hemiparetic cerebral palsy. Beyond ischemic stroke, a similar number of children have hemorrhagic stroke (HS) and other forms of cerebrovascular disease. Acute stroke is a neurologic emergency; unfortunately, delays in recognition are common, and delayed treatment worsens outcomes. In comparison with stroke in adults, there is a more diverse group of disorders producing stroke in neonates and children.

641.1 Arterial Ischemic Stroke

Nomazulu Dlamini and Gabrielle A. deVeber

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of Willis. Strokes most often involve the middle cerebral artery territory but can occur in any cerebral artery of any size. AIS is the focal brain infarction that results from occlusion of these arteries.

The diagnosis of stroke in children is frequently delayed. This is a consequence of subtle and nonspecific clinical presentations, poor awareness by primary care physicians, a complicated differential diagnosis for hemiparesis (see Chapter 641.5), and a high frequency (>50%) of negative initial brain CT scans in true AIS. *The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise.* The most common focal presentation is hemiparesis, but acute visual, speech, sensory, or balance deficits also occur. Importantly, new-onset seizures, especially focal motor seizures, frequently herald stroke, especially in infants and younger children. Children with these presentations require urgent neuroimaging and consultation with a child neurologist because emergency interventions may be indicated. AIS is a clinical and radiographic diagnosis. Although CT imaging can demonstrate mature AIS and exclude hemorrhage, cerebral MRI is required to identify early and small infarcts and disorders of the cerebral arteries. **Diffusion-weighted MRI** demonstrates AIS from minutes to 7 days after the onset; MR angiography can confirm vascular occlusion and suggest possible arteriopathy (Fig. 641.1). Diffusion-weighted MRI can also demonstrate Wallerian degeneration in the descending corticospinal tract, which correlates with chronic hemiparesis.

Many possible risk factors for childhood AIS are recognized (Tables 641.1-641.3), although their specific pathophysiologic mechanisms remain poorly understood. Half of children with AIS are healthy before stroke onset. Three main categories of etiology should be considered: **arteriopathy**, **cardiac disease**, and **hematologic disease** (see Table 641.1). Hence, in addition to a careful history taking and physician examination, a full investigation (including vascular imaging,

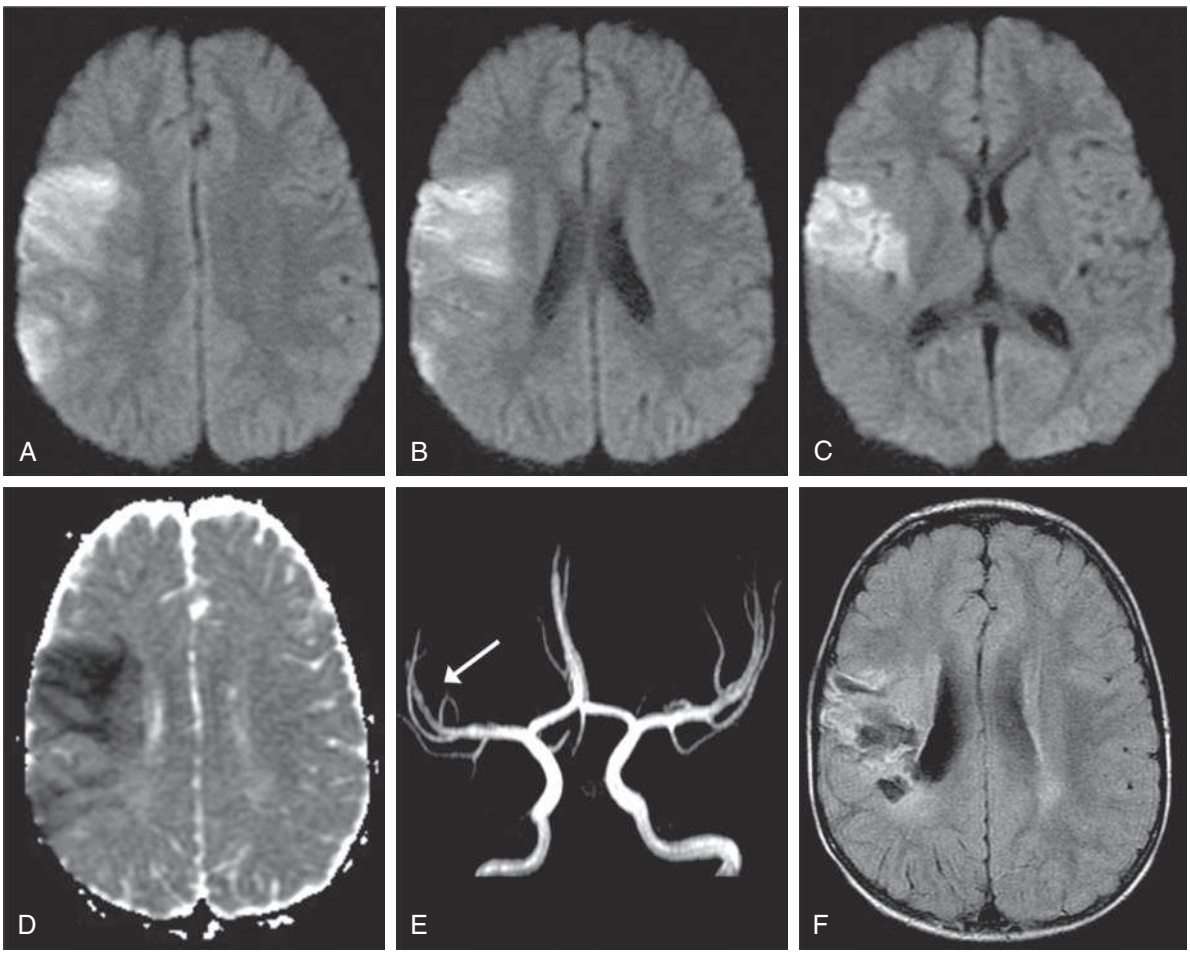

Fig. 641.1 Arterial ischemic stroke. A healthy 3-yr-old male had sudden onset of left-sided weakness. Examination also demonstrated left-sided hemisensory loss and neglect. **A-C,** Diffusion-weighted MRI shows focal increased signal in the right temporal-parietal region in the territory of the middle cerebral artery (MCA). **D,** Apparent diffusion coefficient map confirms restricted diffusion consistent with infarction (ischemic stroke). **E,** MR angiogram shows decreased flow in the corresponding branch of the MCA. **F,** Follow-up MRI at 3 mo shows atrophy and gliosis in the same region.

Table 641.1 Risk Factors and Causes of Stroke in Children

ARTERIOPATHIES
Focal or transient cerebral arteriopathy
Craniocervical arterial dissection
Fibromuscular dysplasia
Moyamoya disease or syndrome
Sickle cell arteriopathy
Primary CNS angiitis
HANAC syndrome
Genetic variants (see text and Table 641.2)

CARDIOVASCULAR DISEASE
Congenital
Aortic stenosis
Mitral stenosis
Ventricular septal defects
Patent ductus arteriosus
Patent foramen ovale
PHACE syndrome
Cyanotic congenital heart disease

Acquired
Endocarditis
Kawasaki disease
Cardiomyopathy
Atrial myxoma
Arrhythmia
Rheumatic heart disease
Prosthetic heart valve
Catheterization/surgery
ECMO

HEMATOLOGIC ABNORMALITIES
Hemoglobinopathies
Polycythemia
Leukemia/lymphoma
Thrombocytopenia including TTP
Disorders of coagulation
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Factor V (Leiden) resistance to activated protein C
- Lupus anticoagulant
- Oral hormonal contraception
- Pregnancy and the postpartum state
- Disseminated intravascular coagulation
- Paroxysmal nocturnal hemoglobinuria
- Inflammatory bowel disease
- Protein-losing enteropathy
- Nephrotic syndrome
- L-Asparaginase
- Prothrombin G20210A variant
- MTHFR deficiency
- Lipoprotein(a) elevation
- Antiphospholipid antibody syndrome
- PNH

SYSTEMIC DISORDERS
Meningitis
- Viral
- Bacterial
- Tuberculous

Systemic infection
- Viremia
- Bacteremia
- Local head and neck infections, including Lemierre syndrome
- Postinfectious (including varicella and other viruses)

Drug-induced inflammation and vasoconstriction
- Amphetamine
- Cocaine
- Ergot alkaloids

Autoimmune disease
- Systemic lupus erythematosus
- Juvenile idiopathic arthritis
- Takayasu arteritis
- Mixed connective tissue disease
- Polyarteritis nodosa
- Primary CNS vasculitis

Trisomy 21

METABOLIC DISEASES
Hyperhomocysteinemia/homocystinuria/elevated homocysteine levels
Fabry disease
Pseudoxanthoma elasticum
Sulfite oxidase deficiency (see Table 641.2)

MITOCHONDRIAL DISORDERS
MELAS
Leigh syndrome

INTRACEREBRAL VASCULAR PROCESSES
Ruptured aneurysm
Arteriovenous malformation
Migraine headache
Post–subarachnoid hemorrhage vasospasm
Hereditary hemorrhagic telangiectasia
Sturge-Weber syndrome
Carotid or vertebral artery dissection
Neurofibromatosis type 1
CADASIL
CARASIL

TRAUMA AND OTHER EXTERNAL CAUSES
Nonaccidental trauma
Head and neck trauma
Oral trauma
Placental embolism
Neck hyperextension (carotid dissection)
Lollipop stroke (pharyngeal trauma)

CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation; HANAC, hereditary angiopathy with nephropathy aneurysms, muscle cramps; MELAS, mitochondrial encephalomyopathy, lactic acidosis, strokelike episodes; MTHFR, methylenetetrahydrofolate reductase; PHACE, posterior fossa brain malformations, hemangiomas of the face, neck, and scalp, arterial anomalies, coarctation of the aorta and cardiac anomalies, and eye defects; PNH, paroxysmal nocturnal hemoglobinuria; TTP, thrombotic thrombocytopenic purpura.
Modified from Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 37.15, p. 652.

echocardiography, and blood tests for inflammatory, infectious, and prothrombotic disorders) are important because these tests often reveal multiple predispositions and triggering risk factors.

Arteriopathy, a disorder of the cerebral arteries, is a leading cause of childhood AIS, present in more than 50% of children. One common arteriopathy that affects healthy school-age children features unilateral irregular stenosis of the proximal middle cerebral artery and neighboring arteries with associated basal ganglia infarction. **Transient cerebral arteriopathy** is monophasic, nearly always self-limited, and may be the result of focal inflammation. This entity has been published under multiple names—**transient cerebral arteriopathy**, post–varicella angiopathy (Fig. 641.2), and nonprogressive childhood primary angiitis of the central nervous system (CNS). The term *focal cerebral arteriopathy (FCA)* is now used, reflecting uncertainty

Table 641.2 Genetic Associations with Thrombotic, Hemorrhagic, or Vascular Stroke

LIPID AND OTHER DISORDERS WITH ATHEROSCLEROSIS
Hereditary dyslipoproteinemias
Familial hypercholesterolemia
Familial hypertriglyceridemia
Hyperlipoproteinemia (types III and IV)
Familial hypoalphalipoproteinemia
Tangier disease
Progeria (de Lange, Seckel, Bloom, Cockayne syndromes)

ARTERIOPATHY, ANGIOPATHY, VASCULITIS
Ehlers-Danlos (type IV) syndrome
Pseudoxanthoma elasticum
Menkes syndrome
Marfan syndrome
Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia)
Sturge-Weber syndrome
Neurofibromatosis 1
Tuberous sclerosis complex
Polycystic kidney disease (autosomal dominant type 1, 2)
Fibromuscular dysplasia von Hippel-Lindau syndrome
Bannayan-Zonana syndrome
Moyamoya disease (*GUCY1A3*, *RNF213*, unknown)
Fabry disease
CARASIL *(HTRA1)*
CADASIL *(NOTCH3)*
RVCL *(TREX-1)*
DADA2 *(CECR1)*
COL4A1/A2 angiopathies, including:
- Hereditary angiopathy nephropathy and cramps (HANAC)
- Autosomal dominant porencephaly with infantile hemiplegia (POREN1)

FOXC1/PITX2: Digenetic inheritance
CARASAL (*CTSA*)
HCHWA – Dutch type
HCHWA – Icelandic type
FAP
ADA2 deficiency
ACTA2 gene variant

HEMATOLOGIC DISORDERS
Antithrombin deficiency
Protein C and S deficiency
Thrombomodulin deficiency
Activated protein C resistance
Factor V Leiden variant
Prothrombin G20210A variant
Sickle cell disease
Factor V, VII, VIII, IX, X, XI, XII, XIII deficiency
Hemoglobinopathies (hemoglobin C or S disorders)
Prekallikrein deficiency
C2 deficiency
β-thalassemia
Disorders of fibrinogen
- Afibrinogenemia
- Hypofibrinogenemia
- Dysfibrinogenemia

Elevated thrombin-activatable fibrinolysis inhibitor
Elevated factor VIII
Elevated factor IX
Elevated factor XI
Disorders of the fibrinolytic system
- Hypoplasminogenemia
- Tissue plasminogen activator defects

MTHFR gene variant
Heparin cofactor II deficiency
Hereditary platelet defects

CARDIAC DISORDERS
Familial atrial myxomas
Rhabdomyomas (tuberous sclerosis)
Mitral valve prolapse
Cardiac papillary fibroelastoma
Hereditary cardiac conduction disorders
Hereditary cardiomyopathies

INBORN ERRORS OF METABOLISM
Mitochondrial abnormalities
- MELAS
- Leigh disease
- MERRF

Organic acidemia
- Methylmalonic acidemia
- Propionic acidemia
- Isovaleric acidemia

Homocystinuria
Glutaric aciduria type II
Sulfite oxidase deficiency
11β-hydroxylase deficiency, 11β-ketoreductase deficiency, 17α-hydroxylase deficiency
3-Methylcrotonyl-CoA carboxylase 3-hydroxy-3-methylglutaryl-CoA lyase deficiency

OTHER DISORDERS
CCM1 *(KRIT1)*
CCM2 *(CCM2)*
CCM3 *(PDCD10)*

CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL, cathepsin A–related arteriopathy with strokes and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CCM, cerebral cavernous malformation; DADA2, deficiency of adenosine deaminase 2; FAP, familial amyloid polyneuropathy; HCHWA, hereditary cerebral hemorrhage with amyloidosis; MELAS, mitochondrial encephalopathy, lactic acidosis, and strokelike episodes; MERRF, mitochondrial encephalopathy with ragged red fibers; RVCL, retinal vasculopathy with deficiency of adenosine deaminase 2.
Modified from Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 37.17, p. 655.

regarding AIS pathogenesis at the time of presentation because it may be indistinguishable from intracranial dissection or early moyamoya disease. FCA can be subclassified as FCA inflammation type, FCA dissection type, and undetermined FCA.

Arterial dissection can be spontaneous or posttraumatic and involves extracranial (carotid, vertebral) arteries more frequently than intracranial arteries. **Moyamoya** demonstrates progressive occlusion of the distal internal carotid arteries. It may be idiopathic **(moyamoya disease)** or associated with other conditions **(moyamoya syndrome)** such as sickle cell anemia, neurofibromatosis type 1, trisomy 21, William syndrome, Alagille syndrome, chromosomal microdeletions/microduplications, and disorders after irradiation (Fig. 641.3). Diffuse, bilateral, progressive **vasculitis** is rare and can represent progressive childhood primary angiitis of the CNS or occur in association with systemic vasculitides (Table 641.4; see also Chapter 642). Cranial infections (e.g., bacterial or tuberculous meningitis) also produce **infectious arteritis** and thrombophlebitis of surface vessels. **Congenital/genetic disorders** of craniocervical arteries include PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, fibromuscular dysplasia, or CADASIL (cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy). *ACTA2, COL4A1,* and *ADA2* gene variants may be associated with AIS, and new genetic arteriopathic conditions are steadily being added to this list. Hence, targeted genetic testing and whole exome sequencing are recommended (see Table 641.2). Vasospasm, as occurs in migraine, subarachnoid hemorrhage, or reversible

Table 641.3 Risk Factors for Perinatal Arterial Ischemic Stroke (AIS)

TYPE OF RISK FACTOR	RISK FACTORS
TERM INFANTS WITH NEONATAL AIS	
Maternal	Thrombophilia Infertility Prolonged rupture of membranes Preeclampsia or gestational hypertension Smoking Intrauterine growth restriction Infection Maternal fever during delivery Smoking
Fetal	Thrombophilia (MTHFR variant, FVL, prothrombin gene variant, protein C/S deficiency) Congenital heart disease Arteriopathy Twin-twin transfusion syndrome Hypoglycemia Perinatal asphyxia Infection (sepsis/meningitis) Need for resuscitation Apgar score of <7 at 5 min
Placental	Chorioamnionitis Placental infarcts Distal villous immaturity Placenta weighing <10th percentile
PRETERM INFANTS WITH NEONATAL AIS	
Maternal	Infection Gestational bleeding
Fetal	Maternal smoking Maternal drug use Twin-twin transfusion syndrome Twin demise Abnormal fetal heart rate Hypoglycemia Thrombophilia (MTHFR variant, FVL)
PRESUMED PERINATAL AIS	
Maternal	Preeclampsia Infection
Fetal	Gestational bleeding Gestational diabetes Thrombophilia Congenital heart disease

MTHFR, Methylenetetrahydrofolate reductase deficiency; FVL, factor V Leiden deficiency.

Modified from Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol*. 2014;51:760–768.

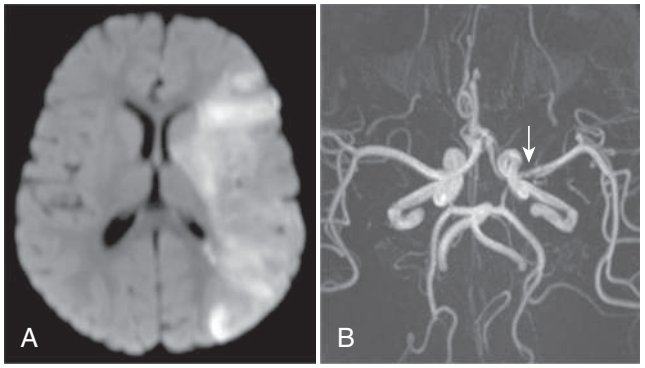

Fig. 641.2 A, Axial diffusion-weighted magnetic resonance imaging demonstrating hyperintense signal in the left middle cerebral artery distribution consistent with acute infarct. B, Magnetic resonance angiography axial maximum intensity projection images demonstrating narrowing of the left middle cerebral artery M1 segment *(arrow)*. *(From Vora SB, Amlie-Lefond C, Perez FA, et al. Varicella-associated stroke. J Pediatr. 2018;199:281, p. 281.)*

cerebral vasoconstriction syndrome (sometimes called *Call-Fleming syndrome*), can cause AIS. Metabolic strokes are seen in organic acidemia, methylmalonic acidemia, propionic acidemia, isovaleric acidemia, glutaric aciduria type II, mitochondrial encephalomyopathies, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (mitochondrial encephalopathy with ragged red fibers), MERRF/MELAS overlap syndrome, and Kearns-Sayre syndrome.

Cardioembolic stroke makes up approximately 25% of childhood AIS cases, with the maximal embolic risk concurrent with interventional catheterization, surgical repair, or ventricular assist device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries, and reoperation increases the risk. Although **complex congenital heart diseases** are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, should also be considered. A **patent foramen ovale** provides a possible conduit for paradoxical venous thromboembolism to the brain. All children with suspected AIS require a thorough cardiovascular examination, an electrocardiogram, and an echocardiogram. Prothrombotic coagulation disorders and infection identified at the time of the index cardiogenic stroke increase the stroke recurrence risk.

Hematologic disorders associated with AIS include **sickle cell anemia**, in which the stroke risk is increased 400-fold, although effective screening (using transcranial Doppler) and transfusion therapy have reduced the incidence. Iron-deficiency anemia also increases the risk and is easily treatable. **Coagulation disorders** are associated with childhood AIS. They include hereditary (e.g., factor V Leiden) and acquired (e.g., antiphospholipid antibodies, lipoprotein-a elevation) **prothrombotic states** and **prothrombotic medications**, including oral contraceptives and asparaginase chemotherapy. Additional AIS risk factors include migraine, acute childhood illnesses, chronic systemic illnesses, illicit drugs and toxins, and rare inborn errors of metabolism.

Treatment of childhood AIS is multifaceted, and multiple consensus-based guidelines are available. The safety and efficacy of thrombolysis and/or thrombectomy in children with AIS has only been reported anecdotally. Nonetheless, some pediatric stroke centers offer thrombolysis with or without thrombectomy for pediatric patients with AIS. Most candidates are preteen or adolescent patients with AIS; younger children may also be candidates for thrombolysis but often have mimics of stroke and must be evaluated carefully for other diagnoses. In adults, treatment with both thrombolysis (~4.5 hours) and endovascular thrombectomy (~16-24 hours) results in improved functional outcome. Pending additional data, for younger children (e.g., <5 years age who often have comorbidities, e,g., congential heart disease), thrombectomy treatment should probably be avoided.

Early initiation of antithrombotic strategies is paramount to prevent early reinfarction. Depending on the suspected cause, this includes anticoagulation with heparin or antiplatelet strategies, usually aspirin. Hyperacute neuroprotective strategies are essential to initiate within minutes in suspected stroke because they prevent progressive ischemic brain injury. These include control of blood glucose (avoid hypoglycemia and hyperglycemia) and temperature (avoid hyperthermia, maintain normal temperature) and maintenance of adequate cerebral perfusion (avoid hypotension and hypertension) and oxygenation. Urgent treatment of seizures is an important neuroprotective strategy, including possible monitoring with continuous electroencephalography (EEG). Early malignant infarct edema is life-threatening, more common in children, and predictable, and emergency surgical decompression can be lifesaving. Disease-specific treatments include transfusion therapy in sickle cell disease, immunosuppression in vasculitis, and revascularization surgery in moyamoya. Long-term

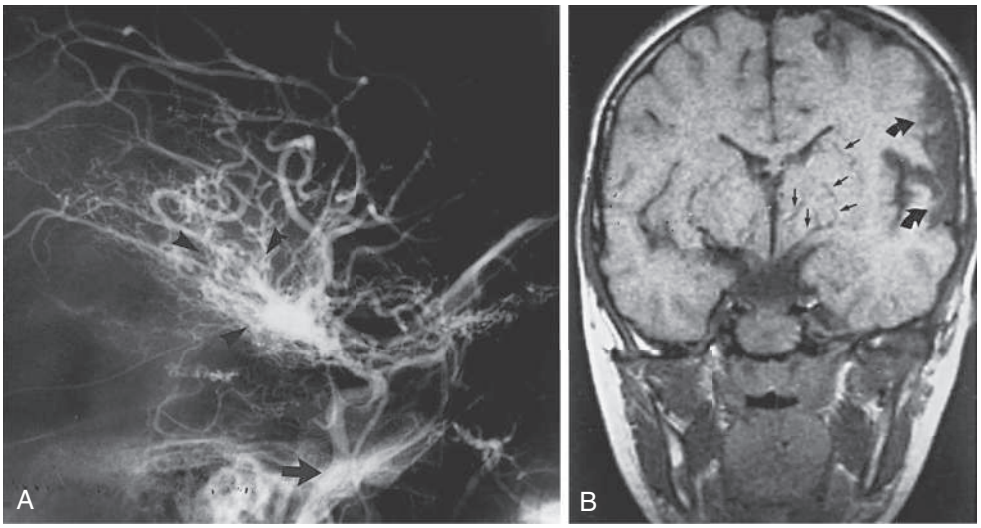

Fig. 641.3 Sudden onset of right hemiparesis in a 6-yr-old male. **A,** Cerebral angiogram shows the left internal carotid artery *(arrow)* leading to a highly arborized, telangiectatic network of vessels *(arrowheads)* characteristic for moyamoya disease. The typical middle cerebral artery vascular tree is absent. **B,** Cranial coronal MRI scan shows region of low signal in the middle cerebral artery territory and denotes infarction *(curved arrows)*. Flow voids in the basal ganglia *(straight arrows)* are radiographic manifestations of the basilar collateral circulation typical of this vascular anomaly. *(From Farias-Moeller R. Stroke. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023, Fig. 37.17, p. 653.)*

Table 641.4 Classification of Cerebral Vasculitis

INFECTIOUS VASCULITIS
BACTERIAL, FUNGAL, PARASITIC
Spirochetal (syphilis, Lyme disease, leptospirosis)
Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths
NECROTIZING VASCULITIDES
CLASSIC POLYARTERITIS NODOSA
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Necrotizing systemic vasculitis overlap syndrome
Lymphomatoid granulomatosis
VASCULITIS ASSOCIATED WITH COLLAGEN VASCULAR DISEASE
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Sjögren syndrome
VASCULITIS ASSOCIATED WITH OTHER SYSTEMIC DISEASES
Behçet disease
Ulcerative colitis
Sarcoidosis
Relapsing polychondritis
Kohlmeier-Degos disease
Takayasu arteritis
HYPERSENSITIVITY VASCULITIDES
IgA vasculitis
Drug-induced vasculitides
CHEMICAL VASCULITIDES
MISCELLANEOUS VASCULITIDES
VASCULITIS ASSOCIATED WITH NEOPLASIA
Vasculitis associated with radiation
Cogan syndrome
Dermatomyositis–polymyositis
X-linked lymphoproliferative syndrome
Kawasaki disease
Primary central nervous system vasculitis

From Biller J, Mathews KD, Love BB. *Stroke in Children and Young Adults.* Boston: Butterworth-Heinemann; 1994.

treatment goals include **secondary stroke prevention**, for example with antiplatelet therapy in arteriopathy and anticoagulation in cardiogenic causes. Multimodal, family-centered rehabilitation programs are required for most survivors, targeting motor deficits, language and intellectual impairments, behavioral and social disabilities, and epilepsy. Long-term attention to arterial health lifestyle factors is also important. Outcomes after childhood AIS include recurrent stroke in 10–50%, depending on the cause and preventive treatment, death in 2–6%; neurologic deficits in 60–70% (usually mild); and seizure disorders long-term in 30%.

Adolescents and young adults with idiopathic (cryptogenic) AIS and a patent foramen ovale (PFO) may benefit from percutaneous PFO closure to prevent a recurrent stroke.

PERINATAL ARTERIAL ISCHEMIC STROKE

Perinatal stroke is common. It differs from childhood stroke, and it has two distinct clinical presentations. Acute symptomatic neonatal AIS presents with focal seizures within 24-28 hours of birth (Fig. 641.4 and see Table 641.3). Cranial ultrasound frequently misses the diagnosis of AIS. MRI diffusion abnormalities in an arterial territory confirm recent infarction. Alternatively, some affected neonates are asymptomatic at birth and present in later infancy with signs of early hand preference and congenital hemiparesis. Hand dominance within the first year of life is abnormal and may be the result of perinatal stroke. Imaging reveals focal encephalomalacia in an arterial territory, typically porencephaly in the middle cerebral artery territory.

In acute neonatal AIS, seizure control is important, but antithrombotic agents are rarely required because recurrent stroke is rare; the exceptions are neonates with congenital heart disease and cardiac embolism, prothrombotic disorders, and, perhaps, those with congenital arterial anomalies (stenosis, hypoplasia). The pathophysiology is complex and poorly understood. Most are idiopathic, although established causes include congenital heart disease, thrombotic placentopathy, and meningitis. The role of prothrombotic conditions in noncardiac neonatal AIS is controversial, but they likely play an additive role alongside other risk factors. Many other maternal, prenatal, perinatal, obstetric, and neonatal factors have been investigated with several strong associations found (e.g., chorioamnionitis, infertility, primiparity, monozygotic twins). Outcomes include normal or mild deficit in ~50% of children; however, ~25% of children have significant long-term disabilities. Perinatal stroke accounts for most cases of hemiparetic cerebral palsy (congenital hemiplegia, see Chapter 638.1). Additional morbidity, seen in ~25%, includes disorders of language, learning, cognition, and behavior and longer-term epilepsy. Stroke recurrence rates in subsequent pregnancies are extremely low in the absence of a familial prothrombotic disorder.

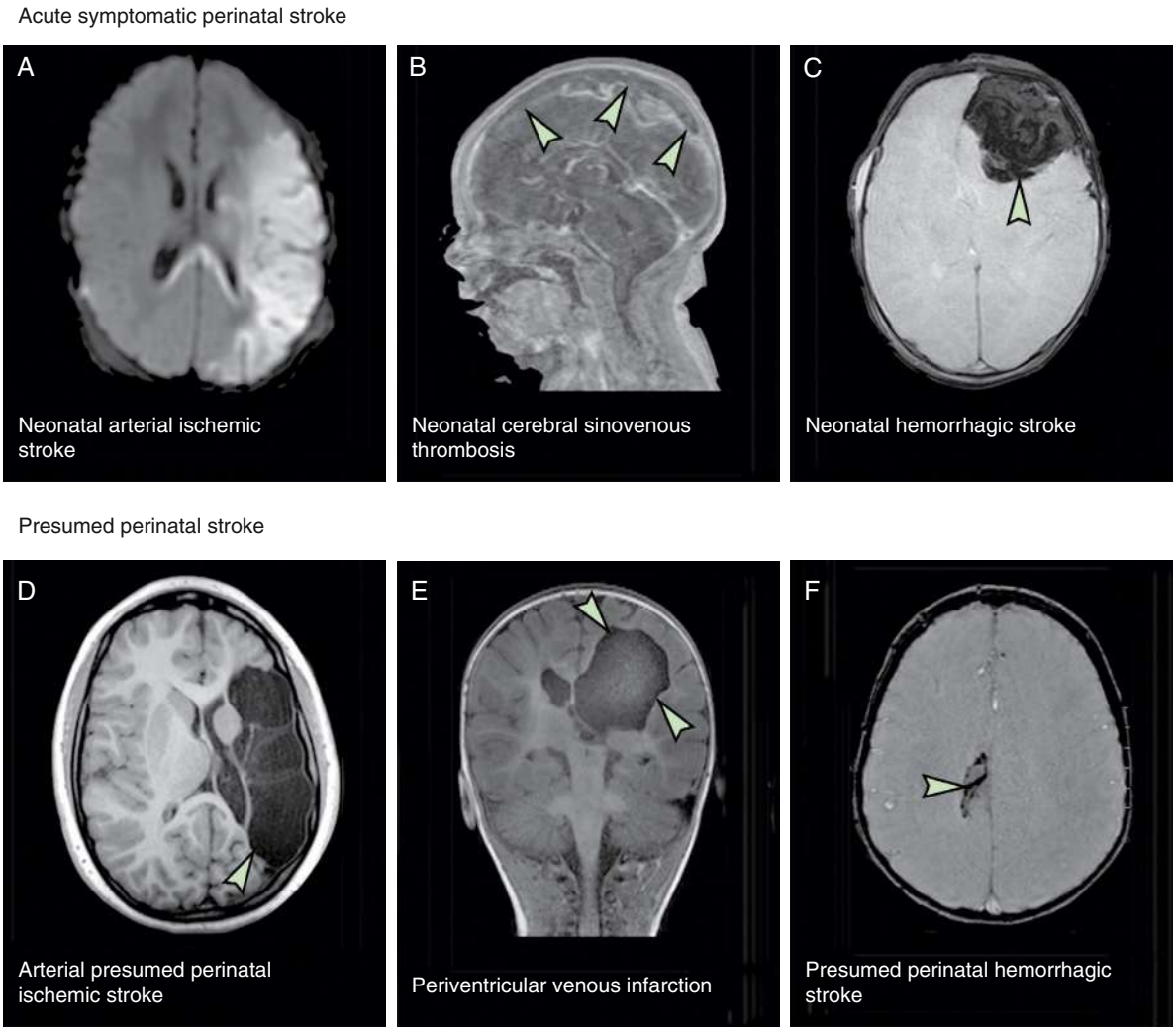

Fig. 641.4 Perinatal stroke diseases by MRI. **A,** Neonatal arterial ischemic stroke features acute restriction on axial diffusion-weighted MRI in an arterial territory; diaschisis of the splenium of the corpus callosum is also evident. **B,** Neonatal cerebral sinovenous thrombosis is evident as a filling defect on sagittal MR venogram (shown), in this case, in the superior sagittal sinus *(arrows)*. **C,** Neonatal hemorrhagic stroke detectable on gradient echo or susceptibility-weighted MRI *(arrow)*. **D,** Arterial presumed perinatal ischemic stroke in a child with hemiparesis is diagnosed by focal encephalomalacia on CT or MRI (axial T1-weighted MRI shown) in an arterial territory *(arrow)*. **E,** Periventricular venous infarction presents with congenital hemiparesis with a focal lesion affecting the periventricular white matter with sparing of the cortex and basal ganglia, shown on coronal T1-weighted MRI (porencephaly indicated with *arrows*). **F,** Presumed perinatal hemorrhagic stroke with a focal area of remote parenchymal injury showing hemorrhage (gradient echo, *arrow*). *(From Dunbar M, Kirton A. Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury. Lancet. 2018;2:666–676, Fig. 2, p. 668.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

641.2 Cerebral Sinovenous Thrombosis

Nomazulu Dlamini and Gabrielle A. deVeber

Cerebral venous drainage occurs via the cerebral sinovenous system. The superficial system (i.e., cortical veins, superior sagittal sinus) and deep system (i.e., internal cerebral veins, straight sinus) converge at the torcula to exit the cranial vault via the paired transverse and sigmoid sinuses and jugular veins. In cerebral sinovenous thrombosis (CSVT), thrombotic occlusion of these venous structures can create regional or diffuse increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction or hemorrhage (venous stroke). CSVT is more common in children than in adults, and risk is greatest in the neonatal period (Table 641.5).

Clinical presentations are typically gradual, variable, and nonspecific compared with AIS. Neonates often present with encephalopathy and seizures. Children may present with symptoms mimicking idiopathic intracranial hypertension, including progressive headache, papilledema, diplopia secondary to sixth cranial nerve palsy, or acute focal deficits. Seizures, lethargy, and confusion are common. Diagnosis requires a high clinical suspicion and specifically requested imaging of the cerebral venous system. Nonenhanced CT is insensitive in detecting CSVT, and so either contrast **CT venography** or MR venography is necessary to demonstrate filling defects in the cerebral venous system (Fig. 641.5). MRI offers superior parenchymal imaging compared with CT.

Table 641.5 lists the risk factors for CSVT. **Prothrombotic states** associated with childhood CSVT include inherited conditions (e.g., prothrombin gene mutation of 20210A) and acquired conditions (e.g., antiphospholipid antibodies), prothrombotic medications (e.g., asparaginase, oral contraceptives), and common childhood illnesses (e.g., otitis media, iron-deficiency anemia, and dehydration). **Systemic diseases** associated with increased risk of CSVT include leukemia, inflammatory bowel disease, and nephrotic syndrome.

Head and neck disorders can directly involve cerebral veins and sinuses thereby causing CSVT. Common infections, including

Table 641.5 Causes of Cerebral Venous Thrombosis

IDIOPATHIC	**INFECTIONS**
PROTHROMBOTIC STATE	Herpes zoster virus
Protein C or S deficiency	Myeloidosis
Antithrombin deficiency	Mucormycosis
Factor V Leiden variant	Aspergillosis
Activated protein C resistance	Pneumococcal meningitis
Prothrombin G20210A variant	Syphilis
Variants in thrombomodulin	HIV
Platelet glycoprotein IIIa (β_3) variant	Otitis media
Heparin cofactor II deficiency	Mastoiditis
Variants in plasminogen gene	Sinusitis
MTHFR C677 variant	Peritonsillar abscess
Dysfibrinogenemia	Endotoxemia
Elevated plasminogen activator inhibitor	Trichinosis
Tissue plasminogen activator deficiency	Sepsis
Increased factors VIII, IX, X; von Willebrand factor	**VASCULITIDES**
Variants in tissue factor pathway inhibitor	Behçet disease
Sickle cell disease and trait	Sarcoidosis
Reactive thrombocytosis and essential thrombocythemia	Polyangiitis with granulomatosis
Pregnancy and puerperium	Systemic lupus erythematosus
POSTOPERATIVE STATE	Polyarteritis nodosa
Antiphospholipid antibody syndrome	**TRAUMA**
Hyperhomocysteinemia	Head trauma
Homocystinuria	Neurosurgical procedures
Cancer	Strangulation
Inflammatory bowel diseases	Intravenous catheters
Dehydration	Cardiac pacemakers
Congestive heart failure	**OTHERS**
Paroxysmal nocturnal hemoglobinuria	Osteopetrosis
Marasmus	Malignant atrophic papulosis (Kohlmeier-Degos disease)
Iron-deficiency anemia	Chronic lung disease
Nephrotic syndrome	Diabetes mellitus
Thrombocytopenia	Budd-Chiari syndrome
Essential thrombocythemia	Arteriovenous malformation
Disseminated intravascular coagulation	Sturge-Weber syndrome
Thrombotic microangiopathies	Cerebral arterial occlusions
Polycythemia vera and secondary polycythemia	Neoplasm (meningioma, metastasis, glomus tumors)
Hyperlipidemia	
Familial histidine-rich glycoprotein deficiency	
DRUGS	
Asparaginase	
Estrogen and oral contraceptives	
Androgen	
ε-Aminocaproic acid	
Cisplatin and etoposide	
Medroxyprogesterone	
Heparin (heparin-induced thrombocytopenia)	
Immunoglobulin G (intravenous immunoglobulin)	

From Biller J. *Stroke in Children and Young Adults.* 2nd ed. Philadelphia: Saunders; 2009: Table 12-3, p. 237.

meningitis, otitis media, and mastoiditis, can cause **septic thrombophlebitis** of venous channels. CSVT can complicate head trauma especially in veins/venous sinuses adjacent to skull fractures. Neurosurgical procedures in proximity to cerebral venous structures may also lead to injury and CSVT. Finally, obstruction of the jugular veins and proximal stasis may result in CSVT. In neonates, because the cranial sutures are unfused, mechanical distortion of the underlying venous sinuses may occur and predispose to CSVT either during labor and delivery or with supine lying because of occipital bone compression of the posterior sagittal sinus.

Anticoagulation therapy plays an important role in childhood CSVT treatment. Substantial indirect evidence has led to a consensus recommendation for anticoagulation with unfractionated or low molecular weight heparins in most children. The presence of hemorrhagic venous infarcts is not an absolute contraindication. Treatment is usually planned for 6 months, although if reimaging at 3 months confirms recanalization, treatment is usually discontinued. However, anticoagulation of neonates is more controversial, and guidelines differ. Evidence suggests that 30% of untreated neonates and children will extend their thrombosis in the first week after diagnosis, and additional venous infarction can result. Therefore if anticoagulation is withheld, early (e.g., 5-7 days) repeat venous imaging is paramount. Protocols supporting initial anticoagulation recommend shorter treatment durations (i.e., 6 weeks to 3 months) in neonates. Children with persistent risk factors may require prophylactic long-term anticoagulation. At initial diagnosis, supportive interventions include management of infection, detection and treatment of seizures, and neuroprotective measures (e.g., normothermia, normotension, normovolemia, normoglycemia). **Compressive optic neuropathy** secondary to prolonged increased intracranial pressure after CSVT is an important complication that can lead to permanent visual loss. Regular funduscopic examination by an ophthalmologist and treatment directed at reducing intracranial pressure (e.g., acetazolamide, serial lumbar puncture) may be required. Most neurologic morbidity is suffered by those incurring venous infarction. Consistent with other forms of childhood stroke, a comprehensive neurorehabilitation program is required.

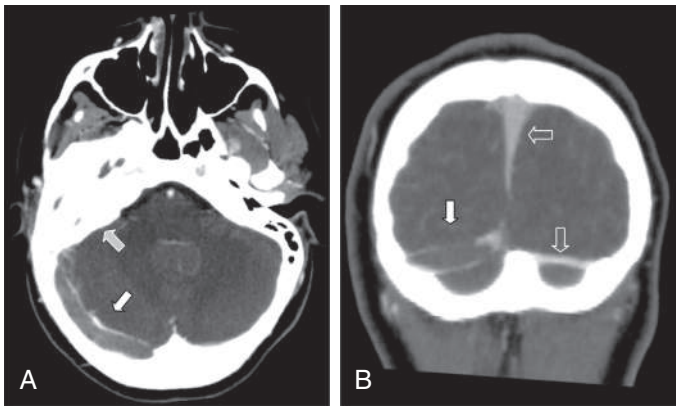

Fig. 641.5 Cerebral sinovenous thrombosis. A 9-yr-old female presented with fever and progressive right-sided headache. She complained of double vision and had papilledema on examination. Axial (A) and coronal (B) CT venography demonstrates a large thrombus in the right transverse sinus that fails to opacify with contrast *(solid arrows)*. Note normal filling in superior sagittal sinus and smaller left transverse sinuses *(open arrows, right)* and opacification of the mastoid air cells *(hatched arrow, left)*. The cause was otitis media/mastoiditis with septic thrombophlebitis of transverse sinus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

641.3 Spinal Cord Lesions Associated with Vascular Processes

Nomazulu Dlamini and Gabrielle A. deVeber

Most cases of **transverse myelitis** (TM) in childhood are postinfectious or, if recurrent, are associated with underlying demyelinating processes, such as multiple sclerosis (see Chapter 640.4) or neuromyelitis optica (see Chapter 640.2). However, in a small proportion of children presenting with acute spinal cord symptoms, infarction and necrosis may occur. This pathology may be associated with disease of the vessels, such as systemic lupus erythematosus (SLE)–associated **vasculitis** (see Chapter 199) or other vascular events such as **embolism** (including nucleus propulsus embolism–fibrocartilaginous embolism). Rarely, **arteriovenous malformations** of the spinal cord may exist and may cause myelopathy and infarction with hemorrhage in the spinal cord. An acute onset and a peak of symptoms over minutes to hours suggest a vascular process.

VASCULITIC PROCESSES: SYSTEMIC LUPUS ERYTHEMATOSUS

Most cases of SLE-associated *myelitis* are longitudinally extensive, and although reports in pediatric populations are rare, the disorder can occur. In 23–60% of cases, myelitis may be the first clinical manifestation of lupus and in many cases occurs at times of low systemic SLE disease activity. Poor recovery is frequent in these cases, with only 14% of patients experiencing complete recovery. In children, other vasculitic etiologies of cord disease, such as Bechet disease, exist.

SPINAL CORD EMBOLISM

Other rare etiologies of an acute increased T2 signal on a spinal cord MRI presenting clinically as TM include cord infarction caused by thromboembolism, either the result of fibrocartilaginous embolism or originating from a lower segment vertebral artery dissection or aortic dissection at the artery of Adamkiewicz. Ischemic myelopathy caused by a **vertebral artery dissection** occurs in the cervical spine; however, fibrocartilaginous embolism may occur anywhere in the spinal cord. A hyperacute onset and lesion appearance (wedge-shaped distribution) together with MRI diffusion-weighted imaging showing diffusion restriction may be helpful in distinguishing ischemic thromboembolic abnormalities from inflammatory TM.

Clinical Manifestations

Similar to *inflammatory* TM, patients present with acute onset of motor weakness accompanied by sensory abnormalities. The weakness progresses over minutes to hours. Pain or discomfort localized to the back or neck, depending on lesion localization, is frequent, with rapid progression of motor weakness and early areflexia reflecting **spinal shock**. Spasticity, hyperreflexia, and clonus occur in the ensuing weeks. A sensory level and motor weakness are present distal to the lesion, with urinary symptoms, including urinary retention, a frequent occurrence.

Investigations

MRI of the spinal cord, including T1- and T2-weighted axial as well as sagittal cuts with gadolinium, are necessary to evaluate for the presence of a focal spinal cord lesion. Given the frequency of longitudinally extensive lesions in myelopathy in pediatric populations, both cervical and thoracic spine imaging should be included in all patients presenting with acute TM. Inclusion of imaging sequences sensitive for hemorrhage (gradient echo sequences) may help, as will diffusion sequences. The inclusion of brain MRI scans, including associated vascular imaging of head and neck vessels, are useful to evaluate the possibility of large-vessel disease. In the event of a cervical spine lesion combined with ischemic brain lesions in the distribution of the posterior circulation, vertebral artery dissection should be investigated.

Lumbar puncture can be performed once MRI evaluation has ruled out a severe cord expansion or mass leading to complete spinal column block. Although inflammatory TM may be associated with elevations in the CSF white blood cells (WBCs) and protein, ischemic myelopathy caused by embolism does not show an acute pleocytosis. However, in a vasculitic event such as myelopathy associated with SLE, increased CSF protein and WBCs may be present.

Serum testing for the presence of underlying rheumatologic disorders should be performed in patients presenting with TM. A workup for hypercoagulable states should also be performed in cases with a high suspicion for ischemic myelopathy.

TREATMENT

In addition to supportive care, treatment is directed at the suspected underlying disease process. Given the low likelihood of complete recovery in ischemic lesions of the spinal cord and the significant disability associated with spinal cord injury, when underlying etiologies such as SLE are found, prophylactic treatment is recommended. Supportive care, including pain control for neuropathic pain, spasticity management, and management of urinary symptoms, is frequently required in this population. When vascular abnormalities are identified or if ischemic myelitis is the suspected cause, low-dose aspirin (2-4 mg/kg/day) for prevention of recurrence may be indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

641.4 Hemorrhagic Stroke

Nomazulu Dlamini and Gabrielle A. deVeber

HS includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location within the brain's substance. Intraventricular hemorrhage may be isolated within ventricles or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces.

Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or **thunderclap headache**, loss of consciousness, and nuchal rigidity in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus,

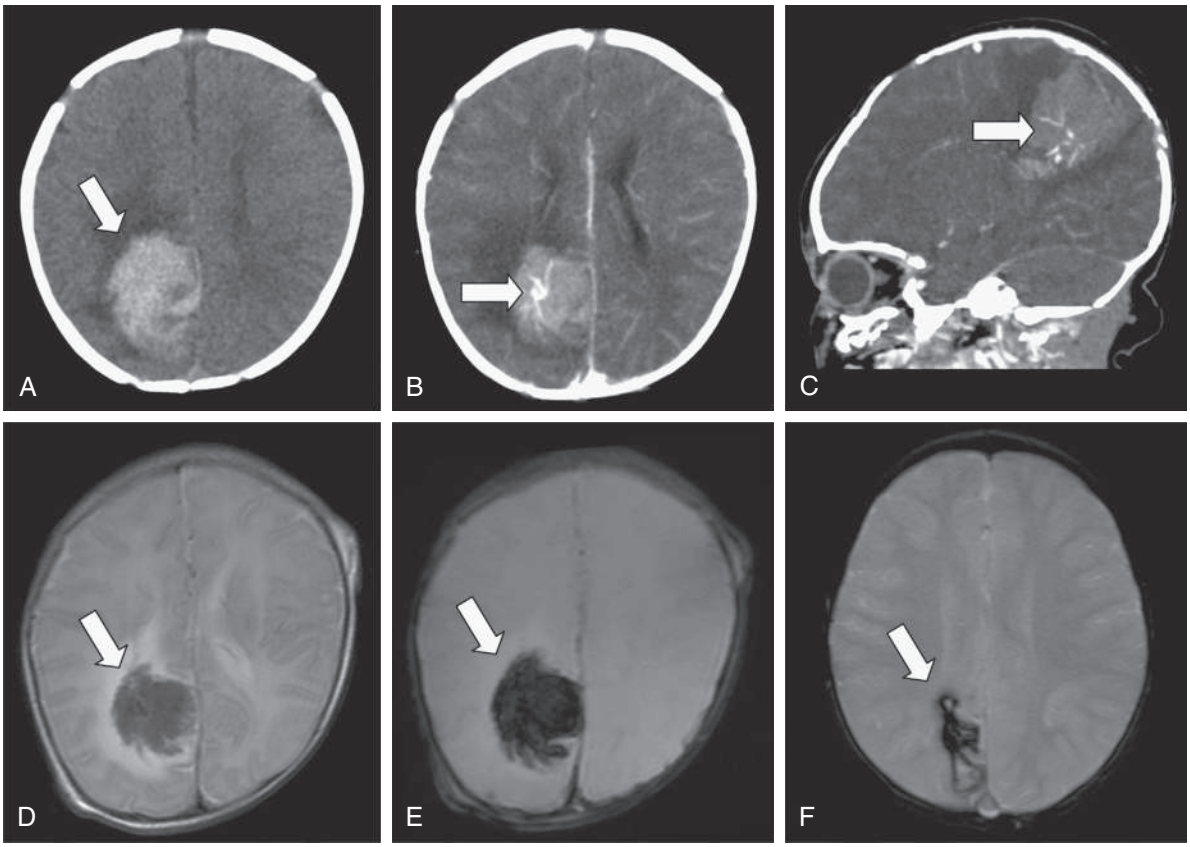

Fig. 641.6 Hemorrhagic stroke. A healthy 1-mo-old presented with sudden-onset irritability followed by focal left body seizures. Plain CT scan of head demonstrates a large hyperdense lesion in the right parietal region with surrounding edema, consistent with acute hemorrhage (**A**). Axial (**B**) and sagittal (**C**) contrast CT scans suggest an abnormal cluster of vessels in the center of the hemorrhage, consistent with an arteriovenous malformation. T2-weighted MRI differentiates the acute hemorrhage from surrounding edema (**D**). Gradient echo MRI, both acutely (**E**) and at 3 mo (**F**), demonstrates the presence of blood product.

cranial bruit, macrocephaly, and high-output heart failure may be present. The diagnosis relies on imaging, and CT scanning is highly sensitive to acute HS. However, lumbar puncture may be required to exclude subarachnoid hemorrhage. MRI is highly sensitive to even small amounts of both acute and chronic hemorrhage and offers improved diagnostic accuracy (Fig. 641.6). Angiography by CT, MR, or conventional catheterization means is often required to exclude underlying vascular abnormalities (e.g., vascular malformations, aneurysms).

Abusive head trauma with intracranial bleeding in children may present as primary subdural or parenchymal hemorrhage with no apparent history of trauma. Clinicians should search for the following: subtle scalp, suborbital, or ear bruising; retinal hemorrhages in multiple layers; and chronic failure to thrive. In infants with subdural bleeds, x-rays should be performed to rule out fractures. Epidural hematoma is nearly always caused by trauma, including middle meningeal artery injury typically associated with skull fracture. Subdural hematoma can occur spontaneously or with trivial trauma in children with brain atrophy because of stretching of bridging veins.

Causes of and risk factors for HS (Table 641.6) include vascular malformations and systemic disorders. **Arteriovenous malformations** are the most common cause of childhood subarachnoid and intraparenchymal HS and may occur anywhere. Neonates with vein of Galen malformations may present with heart failure, progressive macrocephaly, or, rarely, hemorrhage. In older children with arteriovenous malformations, the risk of bleeding is approximately 2–4% per year throughout life. Somatic gene variants in *KRAS* have been noted in some patients with arteriovenous malformations of the brain. Other vascular malformations leading to HS include cavernous angiomas **(cavernomas)**, dural arteriovenous fistulas, and vein of Galen malformations (Fig. 641.7). Cerebral cavernous malformations may be sporadic or familial (autosomal dominant) and associated with gene variants in the *CCM1, CCM2,* or *CCM3* genes. Cerebral aneurysms are a less common cause of subarachnoid hemorrhage in children and may suggest an underlying disorder (e.g., polycystic kidney disease, infective endocarditis) (Fig. 641.8 and Table 641.7). A common cause for HS is bleeding from a preexisting brain tumor. Arterial diseases that usually cause ischemic stroke, including fibromuscular dysplasia, vasculitis, intracranial dissection, and moyamoya, can also predispose to HS. Additional causes of parenchymal HS include hypertensive hemorrhage and hematologic disorders such as thrombocytopenic purpura, hemophilia, acquired coagulopathies (e.g., disseminated intravascular coagulopathy, liver failure), anticoagulant therapy (e.g., warfarin), or illicit drug use. Ischemic infarcts may undergo hemorrhagic transformation, particularly in CSVT, and may be difficult to differentiate from primary HS.

Management of acute childhood HS requires emergency neurosurgical intervention for a large or rapidly expanding hemorrhage. The same principles of neuroprotection for vulnerable brain suggested in the AIS sections also apply to HS. Reversal of anticoagulant therapy (with, for example, vitamin K, fresh-frozen plasma) may be required. The recurrence risk for those with structural lesions is significant, and serial imaging may be required. Definitive repair or removal of the vascular malformation may require a combined approach with interventional endovascular methods and neurosurgery. Outcomes from childhood HS are not well studied but likely depend on lesion size,

Table 641.6 Causes of Spontaneous Intracerebral Hemorrhage in Young Adults

VASCULAR MALFORMATIONS	**ICELANDIC FORM OF CAA**
AVMs	**ARTERITIS/ARTERIOPATHIES**
Capillary telangiectasias (HTT)	Infectious vasculitides
Cavernous malformations	Multisystem vasculitides
Developmental venous anomalies	Isolated CNS angiitis
ANEURYSMS	Moyamoya disease
Saccular	HANAC syndrome
Infective	**DRUG RELATED**
Traumatic	Amphetamines
Neoplastic	Cocaine
ARTERIAL HYPERTENSION	Phenylpropanolamine
Secondary	Pentazocine (Talwin)– tripelennamine (Pyribenzamine)
Primary	Phencyclidine
BLEEDING DIATHESES	Heroin
Leukemia	Monoamine oxidase inhibitor
Thrombocytopenia	Other drugs
Disseminated intravascular coagulation	**INTRACRANIAL TUMORS**
Polycythemia	Primary malignant or benign
Hyperviscosity syndromes	Metastatic
Hemophilia	**CEREBRAL VENOUS OCCLUSIVE DISEASE**
Hypoprothrombinemia	**MISCELLANEOUS**
Afibrinogenemia	Post–carotid endarterectomy
Selective factor deficiencies	Post–selective neurosurgical procedures
von Willebrand disease	Post–spinal anesthesia
Sickle cell anemia	Postmyelography
Antiplatelet therapy	Cold related
Anticoagulant therapy	Post–painful dental procedures
Thrombolytic therapy	Protracted migraine
Vitamin K deficiency	Methanol intoxication

AVM, Arteriovenous malformation; CAA, cerebral amyloid angiopathy; CNS, central nervous system; HANAC, hereditary angiopathy with nephropathy, aneurysms, muscle cramps; HHT, hereditary hemorrhagic telangiectasia.

From Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 37.2, p. 633.

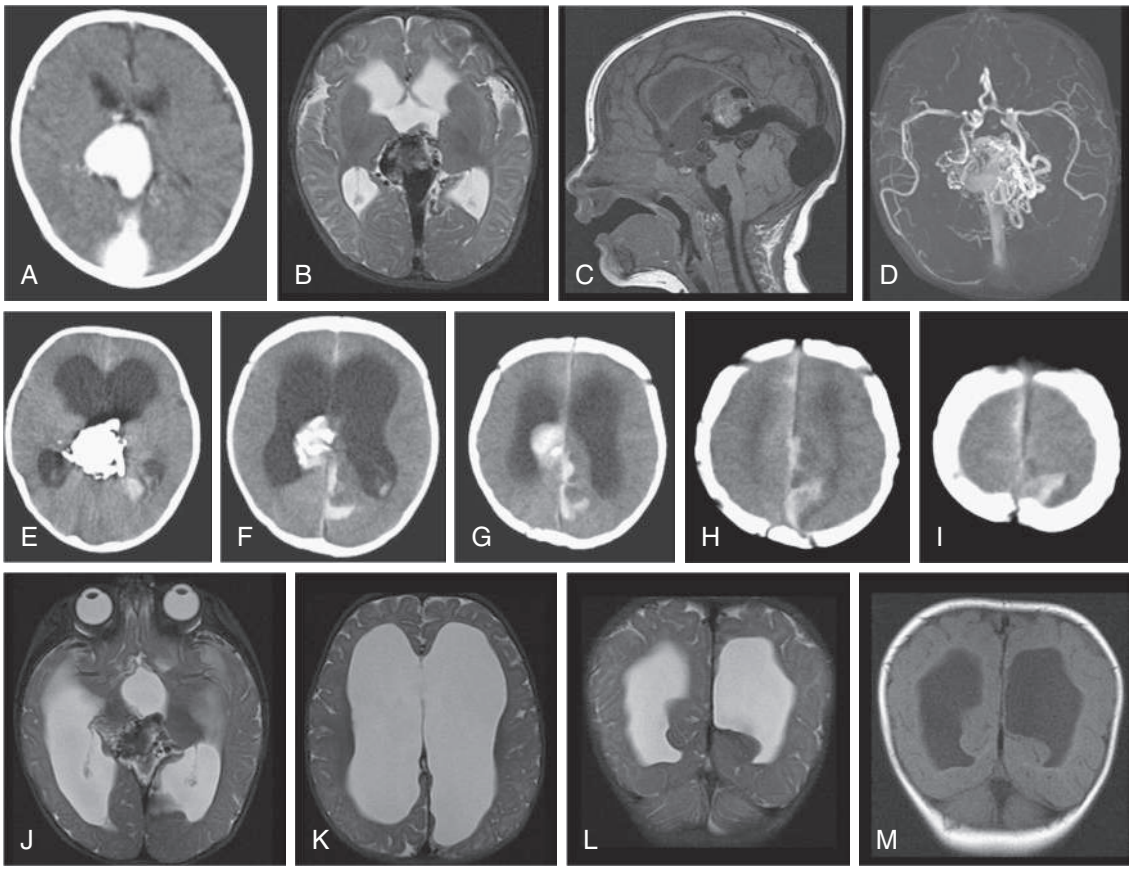

Fig. 641.7 Neonatal vein of Galen malformation and intraventricular hemorrhage. A 5-day-old female born at 38 weeks was noted to be drowsy with poor feeding. She had signs of cardiac failure. A CT scan (**A**) demonstrates vein of Galen aneurysmal malformation, which was partly treated by transarterial glue embolization without complication but with significant residual arteriovenous shunting (**B-D**). After a second embolization procedure, there was acute clinical deterioration with signs of raised intracranial pressure (**E-I**). CT shows acute intraventricular hemorrhage and hydrocephalus and a left parieto-occipital lobe low-density lesion (**E-G**) with adjacent subarachnoid and subdural hematoma (**H** and **I**). Some linear hyperdensity was believed to be the result of thrombus within the persistent falcine sinus (**H** and **I**). Follow-up imaging shows maturation of the focal left parieto-occipital lesion in keeping with an infarct (**J-M**), which is probably venous in origin. *(From Gunny RS, Lin D. Imaging of pediatric stroke. Magn Reson Imaging Clin North Am. 2012;20:1–33, Fig. 18.)*

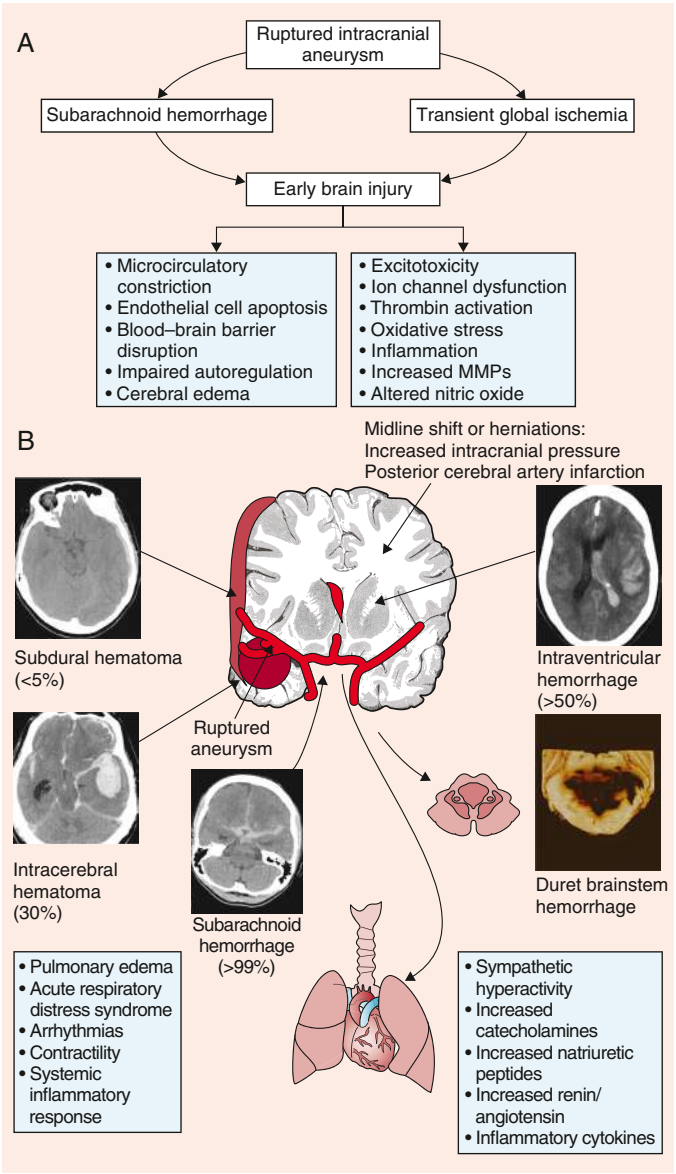

Fig. 641.8 Pathophysiology of subarachnoid hemorrhage. Hemorrhage into various compartments (subarachnoid, intraventricular, intracerebral, subdural) can cause brain shift, increased intracranial pressure, herniation, Duret brainstem hemorrhages, and death. Systemic effects of subarachnoid hemorrhage include cardiac and pulmonary complications. Brain injury from this condition initially is the result of transient global ischemia and effects of the hemorrhage. Delayed neurologic complications can ensue. MMPs, Matrix metalloproteinases. *(From Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. Lancet. 2017;389:655–666, Fig. 2.)*

location, and etiology. Compared with AIS, the HS mortality rate is higher, but long-term deficits are less common.

Neonatal HS has unique features. Cranial ultrasound can detect many neonatal parenchymal bleeds, especially in the preterm infant, where bleeds are located centrally within the cranium including germinal matrix bleeding and intraventricular hemorrhage, and in the cerebellum (see Chapter 122.3). Germinal matrix injury or bleeding may also occur in utero, resulting in periventricular venous infarction that presents in later infancy as chronic hemiparesis. Subarachnoid and subdural blood are common postpartum in normal-term newborns and may be detected by imaging in up to 25%. Term newborn HS is poorly studied and includes the etiologies listed earlier, although HS may be idiopathic in more than 50% of cases. Term intraventricular bleeding is often secondary to deep CSVT with specific management implications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 641.7 Causes of Spontaneous Subarachnoid Hemorrhage in Young Adults

Cerebral aneurysm rupture
Perimesencephalic hemorrhage
Vascular malformation rupture (arteriovenous malformation, arteriovenous fistula, cavernous malformations)
Other
Congenital disorders
Coarctation of the aorta
Pseudoxanthoma elasticum
Menkes kinky hair syndrome
Sturge-Weber syndrome
Tuberous sclerosis complex
Neurofibromatosis 1 (von Recklinghausen disease)
Hereditary hemorrhagic telangiectasia (Rendu-Osler disease)
Ehlers-Danlos syndrome
Klinefelter syndrome
Autosomal dominant polycystic kidney disease
Systemic vascular disease
Hypertension
Cerebral embolism
Moyamoya disease
Cerebral venous occlusive disease
Eclampsia
Hematologic disorders
Hemophilia
Aplastic anemia
Sickle cell anemia
Leukemias
Thrombocytopenic purpura
Anticoagulant therapy
Thrombolytic therapy
Infectious diseases
Infective endocarditis
Tuberculous meningitis
Luetic meningoencephalitis
Fungal central nervous system infections
Infectious mononucleosis
Tickborne relapsing fever
Autoimmune disorders
Systemic lupus erythematosus
Polyarteritis nodosa
Henoch-Schönlein purpura
Poststreptococcal glomerulonephritis
Kawasaki disease
Other systemic diseases
Heat stroke
Conn syndrome
Thyrotoxicosis
Wolman disease
Spinal endometriosis
Neoplasms
Gliomas
Meningiomas
Acoustic neuromas
Choroid plexus papillomas
Pituitary adenomas
Pineocytomas
Chordomas
Subependymomas
Metastatic carcinoma
Intraspinal neoplasms
Drugs
Amphetamines
Cocaine
Ephedrine
Monoamine oxidase inhibitors
Oral contraceptive pills
Phencyclidine
Alcohol
Miscellaneous
α-Galactosidase deficiency
α_1-Antitrypsin deficiency
Cystic fibrosis
Klippel-Trénaunay-Weber syndrome
Parry-Romberg syndrome
3-M syndrome

From Biller J. Stroke in Children and Young Adults. 2nd ed. Philadelphia: Saunders, 2009. Table 15-1, p. 290.

641.5 Differential Diagnosis of Strokelike Events

Nomazulu Dlamini and Gabrielle A. deVeber

The diagnosis of stroke in childhood requires a high index of suspicion balanced with awareness of the differential diagnosis for strokelike events (Table 641.8). An acute onset of a focal neurologic deficit should be considered a stroke until proven otherwise and assessed with urgent neuroimaging. However, pediatric stroke must also be differentiated from other strokelike disorders that may require their own urgent specific treatment.

MIGRAINE

A careful history and examination can often suggest migraine as the cause of acute focal deficits (see Chapter 635.1). Neurologic deficits associated with migraine typically evolve slowly compared with stroke, with sensory disturbance or weakness marching across body areas over minutes. Migraine auras should last between 5 and 60 minutes and resolve completely. Although evolution into a headache is expected in migraine, headache may also accompany true AIS. Furthermore, a group of uncommon "acephalic" migraine subtypes can occur without headache and can more closely mimic stroke in children. These entities include familial hemiplegic migraine, basilar migraine, and migraine aura without headache. Migraine can also (rarely) cause a stroke, referred to as *migrainous infarction*.

Reversible cerebral vasoconstriction syndrome (RCVS) presents in patients with a history of migraine, pregnancy, or exposure to drugs (sympathomimetic agents, SSRIs, migraine abortive agents). There is both multifocal arterial constriction and dilation producing intense (thunderclap) headache, migraine-like symptoms, seizures, or focal

Table 641.8 Distinguishing Clinical and Imaging Features of Stroke Mimics

DISORDER	CLINICAL DISTINCTION FROM STROKE	IMAGING DISTINCTION FROM STROKE
Migraine	Evolving or "marching" symptoms, short duration, complete resolution, headache, personal or family history of migraine	Typically normal Migrainous infarction is extremely rare
Seizure*	Positive symptoms, Todd paralysis is postseizure and time limited	Normal or may identify source of seizures (e.g., malformation, old injury)
Infection	Fever, encephalopathy, gradual onset, meningismus	Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis.
Demyelination	Gradual onset, multifocal symptoms, encephalopathy Accompanying optic neuritis or transverse myelitis	Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion
Hypoglycemia	Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms	Bilateral, symmetric May see restricted diffusion Posterior dominant pattern
Hypertensive encephalopathy (posterior reversible leukoencephalopathy syndrome)	Documented hypertension, bilateral visual symptoms, encephalopathy	Posterior dominant, bilateral, patchy lesions involving gray and white matter; usually no restricted diffusion
Inborn errors of metabolism	Preexisting delays/regression, multisystem disease, abnormal biochemical profiles	May have restricted diffusion lesions but bilateral, symmetric, not conforming to established vascular territories. Magnetic resonance spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes).
Vestibulopathy	Symptoms limited to vertigo, imbalance (i.e., no weakness); gradual onset	Normal
Acute cerebellar ataxia	Sudden-onset bilaterally symmetric ataxia; postviral	Normal
Channelopathy	Syndromic cluster of symptoms not localizing to single lesion; gradual onset, progressive evolution	Normal
Alternating hemiplegia	History of contralateral events Choreoathetosis/dystonia	Normal
Functional neurologic disorders	Recent psychosocial stressors Failure of signs and symptoms to localize to a specific lesion within the neural axis Presence of inconsistent examination findings Positive Hoover sign (when being evaluated for supposed lower extremity weakness, the patient with a functional disorder will exert downward pressure at the heel of the unaffected limb if the examiner holds the heel while asking the patient to raise the affected leg off the bed)	Normal

*Seizures, however, can also herald the onset of true stroke.
From Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 37.5, p. 636.

neurologic deficits (stroke). MRI is useful in differentiating RCVS from other disorders, especially primary angiitis of the central nervous system.

SEIZURE

Prolonged focal motor seizure activity is typified by stiffening or jerking movements, termed *positive* symptoms frequently followed by a period of focal neurologic deficit (so-called **Todd paresis**), which typically resolves rapidly over hours after the seizure (see Chapter 633). Very rarely, focal seizures can manifest with only "negative" symptoms producing only hemiparesis or other acute-onset focal neurologic deficits. A known history of seizures and epileptiform EEG findings may be helpful. Urgent brain imaging should be considered in new cases of prolonged or recurrent focal seizure with persisting Todd paresis because stroke in children is often associated with seizures at onset.

INFECTION

Life-threatening and treatable brain infections, including abscess, bacterial meningitis, and herpes encephalitis, can be mistaken for stroke (see Chapter 643). However, symptom onset in primary CNS infection is typically more gradual and less focal with fever as a consistent feature. Children with bacterial meningitis are at risk for both venous and arterial stroke.

DEMYELINATION

Acute disseminated encephalomyelitis, clinically isolated syndrome, multiple sclerosis, and other demyelinating conditions can present with acute focal neurologic deficits (see Chapter 640). The symptom onset and initial progression are, however, more gradual compared with stroke onset (i.e., typically hours or days versus minutes). Multifocal deficits, or concurrent encephalopathy in the case of acute disseminated encephalomyelitis, decreases the probability of stroke.

HYPOGLYCEMIA

Acute lowering of blood glucose levels can produce focal deficits mimicking stroke. New-onset hypoglycemia in otherwise healthy children is rare, but predisposing conditions include insulin-dependent diabetes, adrenal insufficiency, steroid withdrawal, and ketogenic diet.

GLOBAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Generalized reduction in cerebral perfusion can produce focal areas of watershed brain infarction, which, when asymmetric, can mimic vasoocclusive forms of stroke. Watershed ischemic injury should be accompanied by recognized hypotension or conditions predisposing to low cerebral perfusion, such as sepsis, dehydration, or cardiac dysfunction. Clinical presentations tend to be generalized and include bilateral cerebral dysfunction compared with stroke, and the anatomic location of the infarct on MRI or CT scanning is in typical bilateral watershed zones rather than conforming to an established arterial territory.

HYPERTENSIVE ENCEPHALOPATHY

Posterior reversible leukoencephalopathy syndrome is seen in children with hypertension, often in the context of an acute rise in blood pressure. The posterior regions are selectively involved, possibly resulting in symptoms of bilateral cortical visual dysfunction in addition to encephalopathy and seizures.

INBORN ERRORS OF METABOLISM

Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS; see Chapter 638.2) is the classic example of a metabolic strokelike condition, though other mitochondrial diseases can mimic stroke. Features favoring MELAS include a history of developmental regression, deafness, posterior (and often bilateral) lesions not respecting vascular territories on MRI, and elevated serum or CSF lactate on MR spectroscopy. In contrast to these types of metabolic infarctions, children with Fabry disease (see Chapter 653.6), hyperhomocysteinemia, and homocystinuria (see Chapter 105.4) are at risk of true ischemic stroke.

VESTIBULOPATHY AND ATAXIA

Acute-onset vertigo and/or ataxia can be confused with brainstem or cerebellar stroke. Simple bedside tests of vestibular function with otherwise intact brainstem functions are reassuring. This differential diagnosis includes acute vestibular neuronopathy, viral labyrinthitis, and the benign paroxysmal vertigos, as well as acute postviral cerebellar ataxia and episodic ataxias.

CHANNELOPATHIES

An increasing number of nervous system ion channel mutations are described that feature sudden focal neurologic deficits, thereby mimicking stroke. These include the migraine syndromes, as well as a growing list of episodic ataxias. A strong family history raises suspicion, but most require additional investigation.

ALTERNATING HEMIPLEGIA OF CHILDHOOD

Alternating hemiplegia of childhood typically presents in late infancy with acute intermittent episodes of hemiplegia that alternate from one side of the body to the other. The hemiplegia persists for minutes to weeks and then resolves spontaneously. Choreoathetosis and dystonic movements are commonly observed in the hemiparetic extremity. Signs spontaneously regress with sleep but recur with awakening. Affected children may also experience sudden attacks of redness and warmth (i.e., flushing) or unusual paleness (i.e., pallor) of the skin occurring during or separately from episodes of hemiplegia. Almost all affected individuals have some level of developmental delay and intellectual disability that typically progresses over time. Neuroimaging, including MRA, should be completed to exclude moyamoya disease. Alternating hemiplegia of childhood is linked to variants in the *ATP1A3* gene.

Chapter 642

Central Nervous System Vasculitis

Sona Narula

Autoimmune-mediated inflammatory brain diseases include primary central nervous system (CNS) vasculitis, secondary CNS vasculitis, and autoimmune encephalitis (Fig. 642.1; see Chapter 638.4).

Primary vasculitis or angiitis of the CNS (PACNS) is recognized as an underlying etiology of a broad spectrum of neurologic and psychiatric symptoms in children. Criteria characteristic of primary angiitis of the CNS in childhood (cPACNS) include (1) newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 years of age or younger, **plus** (2) angiographic and/or histologic evidence of vasculitis **in the absence of** (3) a systemic underlying condition known to cause or mimic the findings. Two broad categories of cPACNS are recognized based on the predominant vessel size affected: large/medium-vessel cPACNS and small-vessel cPACNS. Large/medium-vessel cPACNS is diagnosed by angiography demonstrating features of vessel wall inflammation, such as wall thickening and resulting luminal stenosis. Based on the clinical course and the corresponding distribution of vessel stenosis within the vascular tree of the CNS, children with large/medium-vessel cPACNS are classified as having a monophasic, nonprogressive subtype (NPcPACNS) or a progressive subtype (PcPACNS). The latter is characterized by chronic, progressive vessel wall inflammation affecting both proximal and distal vessel segments in one or both hemispheres. In contrast, NPcPACNS is a monophasic illness; vessel inflammation occurs in a characteristic distribution and is limited to

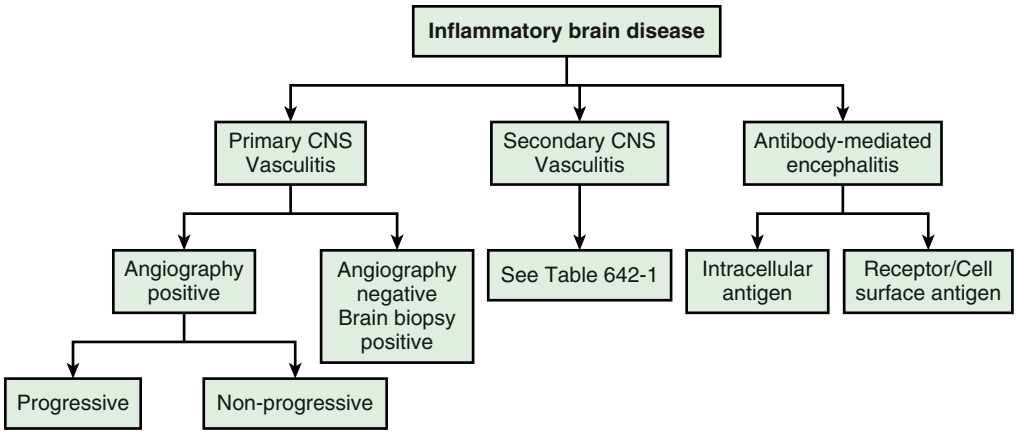

Fig. 642.1 Classification algorithm for CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

the proximal vessel segments of the anterior and/or middle cerebral artery and/or distal internal carotid artery of one hemisphere. Small-vessel cPACNS (SVcPACNS) is considered a progressive illness; the diagnosis is confirmed by brain biopsy, as angiography is typically normal.

Secondary childhood CNS vasculitis can affect all cerebral vessel segments and can occur in the context of infections, or rheumatic or other inflammatory conditions, or as a result of systemic or local vascular irritation (Table 642.1). The neuropsychiatric manifestations of secondary CNS vasculitis are the same as those of primary CNS vasculitis. Secondary CNS vasculitis is distinguished from primary CNS vasculitis largely by the non-CNS manifestations of the underlying systemic vasculitic disease.

EPIDEMIOLOGY

The incidence and prevalence of primary CNS vasculitis are undetermined. Increased physician awareness, improved diagnostic markers, sensitive neuroimaging techniques, and utilization of brain biopsies have led to dramatically increased recognition and decreased mortality rates. The disease has many names, including *isolated angiitis of the CNS, transient cerebral angiitis, postvaricella angiopathy,* and *focal cerebral arteriopathy*. Furthermore, children are frequently diagnosed with their presenting clinical phenotype, such as stroke, movement disorder, psychosis, or cognitive decline. Within clinical phenotypes such as arterial ischemic stroke or status epilepticus in children without preexisting epilepsy, cPACNS should be considered an important etiology.

CLINICAL MANIFESTATIONS

Recognition of childhood CNS vasculitis requires a very high level of suspicion because any neurologic or psychiatric presentation can be the result of an underlying CNS vasculitis. The clinical phenotype may provide clues to the size of the primarily affected vessel segments and resulting cPACNS subtype: the majority of children with large/medium cPACNS present with arterial ischemic stroke. Focal neurologic deficits, such as hemiparesis, facial droop, aphasia, or any other distinct gross or fine motor deficits, may be the result of large-vessel inflammation causing stenosis and a decreased blood supply to the specific functional areas of the brain. Initially, these focal deficits wax and wane; they may even briefly resolve without therapeutic intervention and can therefore be easily overlooked. Headaches can be a symptom of vascular disease and are commonly reported in cPACNS. New-onset headaches in children without any family history of migraine can serve as a diagnostic clue. Cognitive dysfunction in cPACNS often includes loss of higher executive function, concentration difficulties, learning and memory problems, atypical behavior or personality changes, and loss of social and emotional control. Seizures are a hallmark of SVcPACNS, as more than 80% of children with SVcPACNS present with seizures. In many centers, refractory status epilepticus is increasingly recognized as the presenting phenotype of SVcPACNS. Optic neuritis and spinal cord disease can also occur in the setting of SVcPACNS.

Constitutional features of fever or fatigue may point toward an underlying systemic illness causing a secondary CNS vasculitis. All children with suspected or confirmed CNS vasculitis require a careful assessment for a systemic illness.

Table 642.1 Causes of Secondary CNS Vasculitis

VIRAL INFECTIONS
Varicella-zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19
BACTERIAL INFECTIONS
Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Bartonella henselae, Rickettsia spp.
FUNGAL INFECTIONS
Aspergillosis, mucormycosis, coccidioidomycosis, candidiasis
PARASITIC INFECTIONS
Cysticercosis
SYSTEMIC VASCULITIDES
Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, Behçet disease, polyarteritis nodosa, IgA vasculitis, Kawasaki disease, giant-cell arteritis, Takayasu arteritis, Degos disease, *ADA2* deficiency, *TREX1*-associated diseases
CONNECTIVE TISSUE DISEASES
Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease
MISCELLANEOUS
Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, **drug-induced CNS vasculitis** (cocaine, amphetamine, ephedrine, phenylpropanolamine, immune checkpoint inhibitors), hemophagocytic lymphohistiocytosis, reversible vasoconstriction syndrome, Fabry disease, migrainous infarction, primary (*RNF213*) and secondary moyamoya disease, *NOTCH3* and *HTRA1* vasculopathies, genetic structural disorders (*COL4A1, ACTA2, MOPD2*).

From Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. *Lancet*. 2012;380:767–776.

DIAGNOSIS

The first step is considering vasculitis as a possible underlying etiology of newly acquired neurologic deficits and/or psychiatric symptoms (Table 642.2). The likelihood of CNS vasculitis in general and a specific

Table 642.2 Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
   - Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
   - Seizures or status epilepticus
   - Diffuse neurologic deficit, including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
   - Headaches
   - Meningitis symptoms, abnormal level of consciousness
   - Psychiatric symptoms, including hallucinations

   Differential diagnosis approach:
   - Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features
2. Laboratory tests
   - Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
   - Endothelial markers: von Willebrand factor (vWF) antigen
   - Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

   Differential diagnosis approach:
   - Infections/postinfectious inflammation: cultures, serologies, Gram stain
   - Autoimmune encephalitis: check neuronal antibodies in CSF and blood
   - Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
   - Thromboembolic conditions: procoagulatory profile
3. Neuroimaging
   - Parenchymal imaging on MRI
   - Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium
   - Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping
   - Vessel imaging
4. Brain biopsy

subtype of CNS vasculitis in particular depends on the demographic characteristics of the patient, the CNS and non-CNS features of the clinical presentation, the preceding symptoms, and the mode of onset of the disease. SVcPACNS is more commonly seen in females, whereas large/medium cPACNS has a clear male predominance. Seizures are a hallmark of SVcPACNS, whereas strokes often reflect large/medium-vessel inflammation. Laboratory markers of vasculitis typically include C-reactive protein, erythrocyte sedimentation rate, and complete blood counts. *However, inflammatory markers lack sensitivity and specificity in cPACNS, particularly when the CNS is involved in isolation.* More than 50% of children with large/medium-vessel cPACNS have normal inflammatory markers at diagnosis. In contrast, the majority of children with SVcPACNS present with mild to moderately raised markers. Von Willebrand factor antigen, an endothelial cell–derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating disorders. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS patients. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including elevated opening pressure, raised CSF cell count (typically with lymphocyte predominance), and raised CSF protein. Oligoclonal bands are positive in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see Chapter 638.4) and anti–myelin oligodendrocyte glycoprotein (MOG)–associated encephalitis are two of the key neuroinflammatory differential diagnoses of SVcPACNS.

Neuroimaging is a valuable diagnostic modality for cPACNS. Parenchymal lesions may be inflammatory or ischemic in nature and are best viewed on MRI, including T2/fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWIs) (Fig. 642.2). CNS lesions in children with large/medium-vessel cPACNS are predominantly ischemic in nature and restricted to large vascular territories. In contrast, MRI lesions in children with SVcPACNS are not restricted to major vascular territories; lesions are primarily inflammatory and may enhance with contrast. In this subtype, focal or generalized meningeal enhancement is commonly seen if children are imaged before initiation of immunosuppressive therapy.

Evidence of vessel stenosis confirms the diagnosis in large/medium-vessel cPACNS subtypes; brain biopsies are not required. Important information about the disease activity can be obtained from post–gadolinium contrast studies of the vascular wall. The vessel wall of an inflamed cerebral vessel in active large/medium-vessel cPACNS subtypes is thickened and enhances contrast. Vessel wall enhancement may also be useful for the assessment of ongoing disease activity. Conventional angiography, when compared with MR angiography, has a higher sensitivity in detecting vessel stenosis in the distal vessel segments, the posterior circulation, and in very young children. Vessel wall imaging is often normal in children with SVcPACNS, often mandating a brain biopsy to definitively confirm the diagnosis. Studies of regional blood flow or therapeutic trials of antiinflammatory or immunosuppressive agents are nonsurgical alternatives that do not afford specific diagnostic information.

If a biopsy is pursued, a targeted lesional biopsy is preferred if an accessible lesion is identified on imaging. Biopsies should target low-risk, nonfunctional areas identified on MRI. In the appropriate clinical context, nonlesional biopsies can also be done to confirm the diagnosis of SVcPACNS and are typically taken from the nondominant frontal lobe. Diagnostic yield is improved if the biopsy is full thickness and includes the meninges and gray and white matter and if it is done before initiation of immunosuppression. In adults, one study reported the diagnostic yield of biopsies for PACNS to be 11%, with an identified alternative diagnosis reported in about 30% of cases. In this study, smaller biopsies and closed procedures were less likely to be diagnostic, and biopsy-related complications occurred in 16% of patients.

Characteristic findings on biopsy in SVcPACNS include an intramural and/or perivascular lymphocytic infiltrate, evidence of endothelial activation, and reactive astrocyte activation. Gliosis and perivascular demyelination are hallmarks of long-standing disease. Hemorrhagic lesions have also been reported. Findings typically seen in adult PACNS, including granulomas or vessel wall necrosis, are less commonly seen in children with SVcPACNS. Disorders that may be seen in adolescents and young adults that produce the reversible vasoconstriction syndrome must also be considered. These include migraine, drug-induced vasospasm, and postpartum angiopathy. Differentiating vasculitis from these other etiologies is important for therapy and prognosis (Table 642.3).

TREATMENT

Corticosteroids are the mainstay of acute immunosuppressive management of cPACNS. Usually pulse therapy is initially given. Antithrombotic therapy is equally important, particularly in large/medium-vessel cPACNS subtypes, because children are at high risk for recurrent ischemic events. For the distinct cPACNS subtypes, different treatment regimens should be considered. Nonprogressive cPACNS is a monophasic inflammatory illness with the highest risk of poor neurologic outcome. Vessel wall inflammation causes severe proximal stenosis and a high risk of stroke recurrence. High-dose corticosteroid pulses are commonly given,

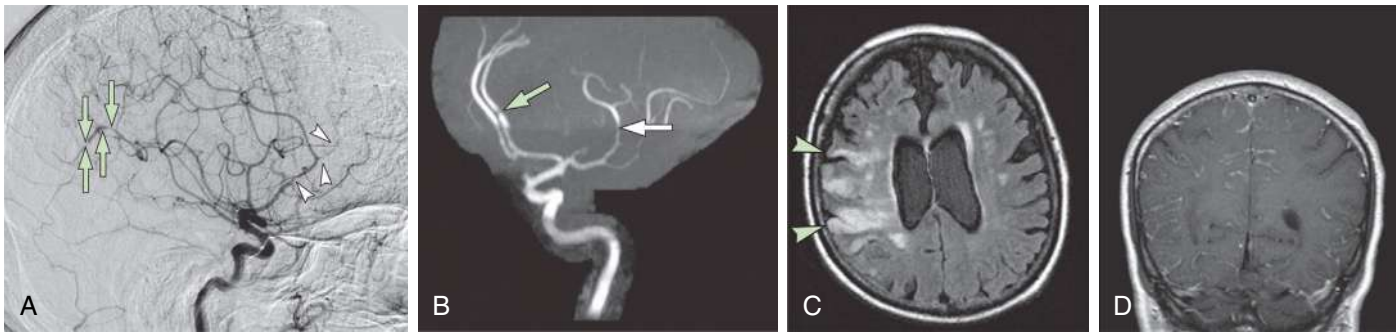

Fig. 642.2 Imaging of patients with primary CNS vasculitis. **A,** Cerebral angiogram shows alternating stenosis and dilation of the distal middle cerebral artery *(arrows)* and the anterior cerebral artery *(arrowheads).* **B,** MR angiography of the brain shows a short-segment stenosis of the anterior cerebral artery *(green arrow)* and stenosis of the distal middle cerebral artery *(white arrow).* **C,** Fluid attenuation inversion recovery–weighted MRI shows a large abnormality within the right cerebral hemisphere consistent with ischemia *(arrowheads).* **D,** MRI shows diffuse, asymmetric, nodular, and linear leptomeningeal enhancement, with the dura only slightly affected. *(From Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. Lancet. 2012;380:767–776, Fig. 2.)*

Table 642.3 Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome

	PCNSV	RCVS
Precipitating factor	None	Postpartum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leukocytosis and high total protein concentration)	Normal to near normal
MRI	Abnormal in almost all patients	Initially may be normal or demonstrate vasogenic edema, vasospasm, or sequelae of vasospasm
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetric arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings-of-beads appearance of cerebral arteries; abnormalities reversible within 6-12 wk
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

CSF, Cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.
From Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. *Lancet.* 2012;380:767–776, Table 2.

followed by a 6- to 12-week course of oral steroids at tapering doses. Second-line immunosuppressive agents are uncommonly used. All children require antithrombotic therapy, though no unifying regimen exists. Many centers initially use low molecular weight heparin followed by long-term antiplatelet therapy. When reimaged at 3 months, children should have stable or improved vessel disease, no newly affected vessel segments, and no evidence of vessel wall enhancement. At this point, the immunosuppressive therapy is commonly discontinued, and children are only kept on antiplatelet therapy.

Progressive cPACNS and SVcPACNS are considered chronic progressive vasculitis subtypes requiring a prolonged course of combination immunosuppression. High-dose corticosteroids are initially used, followed by long-term oral corticosteroids with a slow taper. Many centers use an induction-maintenance protocol, adding cyclophosphamide to corticosteroids (for 6 months), followed by mycophenolate mofetil or other oral second-line agents during maintenance therapy (usually 18 months). Symptomatic therapy is essential, including anticonvulsants or psychotropic medication if required. Supportive therapy includes bone protection with calcium and vitamin D, prophylaxis against *Pneumocystis* pneumonia, and gastric mucosal protection as required.

PROGNOSIS

The mortality rate of cPACNS has significantly improved. In large-vessel cPACNS, the risk of stroke recurrence is thought to be high in patients who are found to have progression on vascular imaging at 12 months (especially if there was simultaneous progression and improvement occurring across multiple vessels).

Some treatment protocols for SVcPACNS report a good outcome, defined as no functional neurologic deficits, in two thirds of children. Children presenting with status epilepticus and SVcPACNS have the poorest cognitive outcome. Multidisciplinary care involving neurology, rheumatology, hematology, and rehabilitation is ideal and may improve outcomes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 643

Central Nervous System Infections

Andrew B. Janowski and David A. Hunstad

Infection of the central nervous system (CNS) is a significant cause of morbidity and mortality in children. Identification of CNS infections can be problematic for clinicians because symptoms can be nonspecific in younger infants, and delayed or missed diagnosis can amplify the morbidity and mortality rates associated with these diseases. Implementation of multiple conjugate vaccines has greatly reduced the incidence of bacterial infections of the CNS. Nonetheless, bacterial and viral infections remain a significant cause of CNS disease, with atypical bacterial, fungal, and parasitic pathogens also causing a smaller number of cases.

Independent of etiology, many patients with CNS infection have similar clinical manifestations. **Common symptoms** include headache, nausea, vomiting, anorexia, photophobia, restlessness, altered state of consciousness, and irritability. **Common signs** of CNS infection include fever, neck pain, nuchal rigidity, focal neurologic deficits, seizures, obtundation, and coma. The severity and constellation of signs are determined by host-pathogen interactions and the affected region of the CNS. **Meningitis** describes primary involvement of the meninges, and **encephalitis** indicates brain parenchymal involvement. However, these anatomic boundaries may be indistinct during infection, and many patients have clinical or imaging evidence of both meningeal and parenchymal involvement. Terms such as *meningoencephalitis* may better describe diffuse infections of the CNS by pathogens such as viruses. Brain abscess is the most common example of a focal infection of the CNS (see Chapter 644).

The diagnosis of CNS infection depends on a combination of imaging of the brain, testing the cerebrospinal fluid (CSF) by culture, polymerase chain reaction (PCR), and serologic methods and, in rare situations, biopsy of brain tissue. Pending many of these tests, standard CSF studies provide initial data to help guide selection of empiric antimicrobials. Table 643.1 provides an overview of the typical CSF abnormalities with various CNS disorders.

643.1 Acute Bacterial Meningitis Beyond the Neonatal Period

Andrew B. Janowski and David A. Hunstad

Bacterial meningitis is one of the most serious pediatric infections because it is associated with a high rate of acute complications and a risk of long-term morbidity and mortality. However, the use of antibiotics and vaccines against the most common causes of bacterial meningitis has significantly altered the spectrum of disease. In the 1980s, the most common causes of bacterial meningitis in children older than 1 month of age in the United States were *Haemophilus influenzae* type b, *Streptococcus pneumoniae,* and *Neisseria meningitidis.* The incidence of meningitis caused by all three organisms has been significantly reduced in countries that have introduced universal immunization against these pathogens. *S. pneumoniae* is now the most common cause of bacterial meningitis in the United States. Demonstrating the impact of vaccination in the United States, invasive *H. influenzae* disease occurred in 67-129 cases per 100,000 children under 5 years of age in the 1980s. By 2019, *H. influenzae* type b–associated diseases were exceptionally rare; there were only 18 invasive cases in the United States, with a calculated national rate of 0.08 cases per 100,000 children under 5 in the year 2017. Nonetheless, other serotypes of *H. influenzae* (particularly type a and, rarely, other serotypes have emerged as a cause of meningitis).

EPIDEMIOLOGY

A major risk factor for bacterial meningitis is the lack of preexisting immunity to specific pathogens and serotypes, reflected in a higher incidence of meningitis in young infants. Additional risk factors include recent colonization with pathogenic bacteria, close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by *N. meningitidis* or *H. influenzae* type b, crowding, poverty, and male sex. The mode of transmission of these pathogens is through contact with respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and *H. influenzae* type b (12 times) relative to that for pneumococcus.

Indigenous Nation and Eskimo populations exhibit a higher incidence of bacterial meningitis because these populations have altered immunoglobulin production in response to encapsulated pathogens. Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease. Splenic dysfunction (e.g., in sickle cell anemia) or asplenia (caused by trauma or a congenital defect) is associated with an increased risk of pneumococcal, *H. influenzae* type b, and meningococcal sepsis and meningitis. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of *Listeria monocytogenes* infections of the CNS.

The risk of pneumococcal meningitis is increased in children with congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), fistulas of the middle ear (stapedial foot plate) or inner ear (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage as a result of basilar or other skull fracture. The risk of pneumococcal bacterial meningitis was historically increased by more than 30-fold in children with cochlear implants, though advances in implant design have reduced this risk. Lumbosacral dermal sinus and myelomeningocele are associated with staphylococcal, anaerobic, and gram-negative enteric bacterial meningitis. CSF shunt infections increase the risk of meningitis caused by *Pseudomonas aeruginosa, Staphylococcus* spp. (*S. aureus* and coagulase-negative species), *Cutibacterium* spp. (formerly *Propionibacterium* spp.), and other lower-virulence bacteria that typically colonize the skin.

Streptococcus pneumoniae

See also Chapter 228.

Although the incidence of pneumococcal meningitis has been reduced, *S. pneumoniae* remains the most frequently identified pathogen from cases of bacterial meningitis in the United States and in other countries that have adopted similar vaccination strategies. The seven-valent pneumococcal conjugate vaccine (PCV7) was included in the routine U.S. vaccination schedule in 2000 and contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, responsible for ~85% of invasive pneumococcal infections in the country. A dramatic decrease in the rate of pneumococcal meningitis followed, from 8.2 cases per 100,000 in 1998-1999 to 0.59 cases per 100,000 in 2004–2005. Similar reductions were also identified in other nations that introduced this vaccine. However, this was followed by an increased incidence of invasive disease caused by serotypes not contained in the original vaccine, known as *serotype replacement*. In response, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States in 2010, containing the serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A. Post-marketing surveillance data suggest the rate of invasive pneumococcal infections has decreased further, though there are conflicting data as to whether the rate of pneumococcal meningitis has decreased. Based on data from the Centers for Disease Control and Prevention (CDC) Active Bacterial Surveillance system, the incidence of invasive pneumococcal infections has fallen from 142.9 per 100,000 children under age 1 in 1977 to 13.3 per 100,000 children under age 1 in 2018. Children with anatomic or functional asplenia secondary to sickle cell disease and those infected with HIV have infection rates that are 20- to 100-fold higher than those of healthy children in the first 5 years of

Table 643.1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (cm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Normal	<28	<5, ≥75% Lymphocytes in neonates: <20	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% of serum glucose)	Organisms usually seen on Gram stain and isolated by culture or identified by PCR
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual, but mononuclear cells may predominate if pretreated for extended period	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain. Pretreatment may render CSF sterile. PCR-based assays may detect bacterial DNA.
Viral meningitis or meningoencephalitis	Normal or slightly elevated	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early, but mononuclear cells predominate through most of the course,	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15–20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on MRI or CT scans or EEG. Most arboviruses detected by PCR of CSF or urine and serology.
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of obstruction	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms rarely seen on smear. Large volumes of CSF required for recovery of organisms. *Mycobacterium tuberculosis* can be detected by PCR of CSF.
Fungal meningitis	Usually elevated	5-500; PMNs early, but mononuclear cells predominate for most of the course. Cryptococcal meningitis may lack pleocytosis. Coccidioidal meningitis may have eosinophilia	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered by culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection.
Syphilis (acute), Lyme disease, and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by smear or culture; dark-field examination may be positive. Positive Lyme serology.
Amebic *(Naegleria)* meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amoebas may be seen by wet-mount microscopy of CSF
BRAIN ABSCESSES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	CSF cultures are only positive in 24% of cases unless abscess ruptures into ventricular system

Continued

Table 643.1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

CONDITION	PRESSURE (cm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Subdural empyema	Usually elevated	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with ruptured dermoids
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal to elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF.
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR or other autoimmune antibody–positive (CSF is often more sensitive than serum)

CSF, Cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

life. Additional risk factors for contracting pneumococcal meningitis include endocarditis, otitis media, mastoiditis, sinusitis, pneumonia, CSF otorrhea or rhinorrhea, the presence of a cochlear implant, and immunosuppression.

Neisseria meningitidis

See also Chapter 237.

Six serogroups of meningococcus (A, B, C, X, Y, and W-135) are responsible for invasive disease in humans. Meningococcal meningitis may be sporadic or may occur in major epidemics, particularly in the African meningitis belt, where serogroup A accounts for 80–85% of outbreaks. In the United States, serogroup B is the most common cause of meningitis in infants and is also a cause of outbreaks on college campuses. Meningococcal cases are more common in the winter and spring, likely because of associations with viral infections, including influenza. Nasopharyngeal carriage of *N. meningitidis* occurs in up to 15% of adults. Most infections in children are acquired from a contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Colonization may last weeks to months; recent colonization places nonimmune younger children at greatest risk for meningitis. The incidence of disease occurring in association with an index case in the family is 1%, a 1,000-fold increase in risk in comparison to the general population. The risk of secondary cases occurring in contacts at daycare centers is approximately 1 in 1,000. Children under 5 years of age have the highest rates of meningococcal infection, and a second peak in incidence occurs in persons between 15 and 24 years of age. First-year college students living in dormitories have an increased incidence of infection compared with non–college-attending, age-matched controls.

Haemophilus influenzae Type b

See also Chapter 240.

Before universal *H. influenzae* type b vaccination in the United States, approximately 70% of cases of bacterial meningitis occurring in the first 5 years of life were caused by this pathogen. Invasive infections occurred primarily in infants 2 months to 2 years of age, the peak incidence was at 6-9 months of age, and 50% of cases occurred in the first year of life. The risk to children was markedly increased among household or daycare contacts of patients with *H. influenzae* type b disease. Global vaccination efforts have also led to remarkable declines in the incidence of this disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with immune-compromising conditions remain at risk for *H. influenzae* type b meningitis. Other serotypes of *H. influenzae* (a, f) have been associated with meningitis.

PATHOLOGY AND PATHOPHYSIOLOGY

A purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates) in addition to subdural effusions

and empyema. Perivascular inflammatory infiltrates may also be evident, and the ependymal membrane may be disrupted. Vascular and parenchymal cerebral changes have been described at autopsy, including polymorphonuclear infiltrates extending to the subintimal region of small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage, and cerebral cortical necrosis in the absence of identifiable thrombosis. Cerebral infarction is a frequent sequela that is caused by vascular occlusion from inflammation, vasospasm, or thrombosis. The extent of an infarct may range from microscopic to an entire hemisphere.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be an early nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. ICP may exceed 30 cm H_2O and cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus mean ICP) falls below 50 mm Hg as a result of systemic hypotension. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP (see Chapter 597). Hypotonicity of brain extracellular spaces may cause cytotoxic edema with cell swelling and lysis. Tentorial, falcine, or cerebellar herniation does not usually occur, because the increased ICP is transmitted to the entire subarachnoid space and there is little structural displacement. Furthermore, if the fontanels are still patent, increased ICP is not always dissipated.

Hydrocephalus can occur as an acute complication of bacterial meningitis because it is often caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus this thickening leads to interference with the normal resorption of CSF and development of hydrocephalus. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the cerebral aqueduct or the foramina of Magendie and Luschka.

Elevated CSF protein levels are partly a result of increased vascular permeability of the blood-brain barrier (BBB) and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually observed in the later phase of acute bacterial meningitis. **Hypoglycorrhachia** (reduced CSF glucose level) is attributable to altered glucose transport by the cerebral tissue.

Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and/or transudation (subdural effusions). These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later, psychomotor retardation.

PATHOGENESIS

Bacterial meningitis outside the neonatal period is typically the result of bacterial colonization of the nasopharynx with subsequent invasion into the bloodstream, causing bacteremia. Circulating bacteria then breach the BBB to cause CNS infection and inflammation.

Meningitic pathogens frequently colonize the nasopharynx of asymptomatic children, but rapid invasion after recent colonization may also occur. Bacterial proteins termed *adhesins* act to enhance colonization by enabling *N. meningitidis* and *H. influenzae* type b to attach to mucosal epithelial cell receptors. The microbiome of the nasopharynx is a complex community of bacteria that may enhance or inhibit colonization by other bacteria. *S. pneumoniae* can synthesize hydrogen peroxide, which can inhibit growth of *H. influenzae* type b; conversely, *H. influenzae* type b can invoke a specific immune response that targets clearance of *S. pneumoniae*. Other bacteria may alter the microbiome of the nasopharynx, and studies after implementation of PCVs have identified alterations to the composition of nasopharyngeal bacterial populations. Viruses can also enhance bacterial adherence by a combination of expression of viral factors that interact with host adhesion proteins.

After attachment to epithelial cells, bacteria may breach the mucosa and enter the bloodstream. Various models of invasion have been developed; *N. meningitidis* can be transported across the mucosal surface within a phagocytic vacuole after ingestion by the epithelial cell. Expression of the polysaccharide capsule in relevant bacteria also appears to be tightly regulated, as it can enhance or inhibit the efficiency of bacterial translocation across the mucosal barrier. Viral infection can disrupt the mucosal barrier, thereby facilitating bacterial invasion; specifically, there is a significant association between recent influenza infection and development of meningococcemia. Once bacteria reach the bloodstream, the capsule is a critical component for survival because it interferes with opsonic phagocytosis. Host-related immune defects in bacterial opsonic phagocytosis can also allow bacteremia. In nonimmune hosts, the defect may be from an absence of preformed IgM or IgG anticapsular antibodies (as in an unimmunized toddler), whereas deficiencies in components of the complement or properdin system may preclude effective opsonic phagocytosis. Asplenia may also hamper opsonic phagocytosis by the reticuloendothelial system.

There is a positive correlation between the bloodstream bacterial titer and the accompanying risk of developing meningitis, suggesting that a critical threshold may be necessary for breaching the BBB. Bacterial factors, including the capsule, play a role in crossing the BBB through transcellular, paracellular, or Trojan horse (within infected phagocytes) mechanisms. Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and subarachnoid space. Bacteria multiply rapidly because CSF concentrations of complement and antibodies are inadequate to contain bacterial proliferation. Chemotactic factors then incite a local inflammatory response characterized by polymorphonuclear cell (neutrophil) infiltration. The presence of lipopolysaccharide (endotoxin) from gram-negative bacteria (*H. influenzae* type b, *N. meningitidis*) or of pneumococcal cell wall components (teichoic acid, peptidoglycan) stimulates a marked inflammatory response, with local production of tumor necrosis factor, interleukin-1, prostaglandin E, and other inflammatory mediators. The subsequent inflammatory response is characterized by neutrophilic infiltration, increased vascular permeability, further compromise of the BBB, and vascular thrombosis. Meningitis-associated brain injury is not simply caused by bacterial-derived factors but also occurs as a consequence of the host inflammatory cascade triggered by bacterial components.

Uncommonly, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis; or it may occur after introduction of bacteria via penetrating cranial trauma, dermal sinus tracts, or myelomeningocele.

CLINICAL MANIFESTATIONS

The onset of acute meningitis has two predominant patterns. Most often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or, less often, gastrointestinal symptoms, followed by nonspecific signs of CNS infection, such as lethargy and irritability. Fortunately, the more dramatic presentation is less common and features sudden and progressive shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness, often resulting in progression to coma or death within 24 hours.

The signs and symptoms of meningitis reflect the nonspecific findings associated with any systemic infection and the manifestations of meningeal irritation. Nonspecific findings include fever, anorexia or poor feeding, headache, upper respiratory symptoms, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. The rash of meningococcemia is typified by an initial petechial rash that evolves into ecchymotic and purpuric lesions. Meningeal irritation is manifested as nuchal rigidity, back pain, **Kernig sign** (flexion of

the hip 90 degrees with subsequent pain upon extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12-18 months, Kernig and Brudzinski signs are not consistently present. In adults, fever, headache, and nuchal rigidity are present in only 40% of cases of bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanelle or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens nerve paralysis, hypertension with bradycardia, apnea, or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is more common in complicated meningitis and is suggestive of a chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion. Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also be the result of focal inflammation. Overall, 10–20% of children with bacterial meningitis have focal neurologic signs.

Seizures (focal or generalized) related to cerebritis, infarction, or electrolyte disturbances occur in 20–30% of patients with meningitis. Seizures that occur on presentation or within the first 4 days of onset usually are of little prognostic significance. Poorer prognosis is suggested when seizures persist after the fourth day of illness, as these can be refractory to treatment.

Alteration in mental status is common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis. Additional manifestations of meningitis include photophobia and tache cérébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 seconds.

DIAGNOSIS

Lumbar puncture (LP), to obtain CSF for Gram stain and culture, is the most important step in the diagnosis of meningitis. Testing of the CSF for neutrophilic pleocytosis, elevated protein, and/or reduced glucose concentrations can yield results within a few hours and can indicate bacterial meningitis (see Table 643.1). **Contraindications** to immediate LP include (1) evidence of increased ICP (other than a bulging fontanel), such as third or sixth cranial nerve palsy with a depressed level of consciousness, or the Cushing reflex (hypertension and bradycardia associated with respiratory abnormalities; see Chapter 630); (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; or (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP. **If LP is delayed, empiric antibiotic therapy should be initiated.**

Some clinicians obtain a head CT scan before LP to evaluate for evidence of increased ICP because an LP in the setting of elevated ICP may promote brain herniation. However, a head CT scan may delay diagnosis of meningitis and initiation of antimicrobials, and it does not always rule out increased ICP. Therefore **head CT scans before LP are not routinely recommended** unless the patient has clinical signs or is at risk for elevated ICP, including papilledema, focal neurologic findings, coma, history of hydrocephalus, or prior neurosurgical procedures including shunt placement. However, if a CT scan is to be obtained before LP, antimicrobial therapy should not be delayed. LP can safely be performed after increased ICP (if present) has been appropriately treated.

Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80–90% of cases of meningitis. Elevations of C-reactive protein, erythrocyte sedimentation rate, and procalcitonin can be seen in both bacterial and viral meningitis, but some clinical prediction tools include these tests to determine risk for bacterial meningitis.

Lumbar Puncture

See also Chapter 630.

The CSF leukocyte count in bacterial meningitis often is elevated to >1,000/mm^3 and, typically, there is a neutrophilic predominance (75–95%). Turbid CSF is observed when the leukocyte count exceeds 200-400/mm^3. Healthy neonates may have as many as 20 leukocytes/mm^3, but older children without viral or bacterial meningitis have <8 leukocytes/mm^3 in the CSF, and these should be nearly all lymphocytes or monocytes.

The CSF leukocyte count is <250/mm^3 in as many as 20% of patients with acute bacterial meningitis. Pleocytosis may be absent in patients with severe overwhelming sepsis associated with meningitis; this is a poor prognostic sign. Of note, neutrophilic pleocytosis may be present in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8-24 hours of an initial LP. In the absence of CNS infection or inflammatory disease, children with seizures (including febrile seizures) *do not* exhibit CSF pleocytosis.

A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children who have already received antibiotic therapy. This is a common clinical scenario, as 25–50% of children undergoing evaluation for bacterial meningitis have received antibiotics before a CSF sample is obtained. CSF from children with bacterial meningitis can be negative on Gram stain and culture as early as 2-4 hours after administration of antibiotics, especially in situations of *N. meningitidis* and sensitive *S. pneumoniae* meningitis. However, pleocytosis with a predominance of neutrophils, an elevated protein level, and a reduced concentration of CSF glucose will usually persist for several days after initiation of appropriate parenteral antibiotics. Therefore despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made on the basis of an abnormal CSF cell count, protein, and glucose. A multiplex PCR test for common CNS bacterial and viral pathogens is available for testing on CSF samples, with turnaround times of only a few hours. This test is often used as an adjunct (and rapid) diagnostic test, as its current sensitivity and specificity have not supplanted the use of routine bacterial cultures; in particular, its highest false-positive rate is for *S. pneumoniae*. PCR of bacterial 16S ribosomal RNA sequences may be useful in diagnosing the cause of culture-negative meningitis caused by prior antibiotic therapy or for the detection of nonculturable or fastidious pathogens.

A traumatic LP may also complicate the interpretation of CSF tests, as CSF leukocyte count and protein concentration are significantly affected by blood in the sample. However, the Gram stain, culture, and glucose level are unlikely to be influenced by blood in a CSF sample. Repeat LP at a higher interspace may produce fluid that is less hemorrhagic, but this fluid usually still contains red blood cells. Although methods for correcting for the presence of red blood cells have been proposed for red blood cell counts <10,000 cells/mm^3, these corrections can be imprecise and unreliable, so empiric treatment with antibiotics pending any bacterial culture result might be indicated.

DIFFERENTIAL DIAGNOSIS

Most bacterial meningitis is caused by *S. pneumoniae* and *N. meningitidis,* whereas *H. influenzae* type b is relatively rare in nations with high immunization rates. However, other pathogens less frequently identified in meningitis can cause similar clinical manifestations. These organisms include other bacteria, including non–type-b *H. influenzae, Mycobacterium tuberculosis, Nocardia* spp., *Treponema pallidum* (syphilis), and *Borrelia burgdorferi* (Lyme disease); fungi, such as those endemic to specific geographic areas (*Coccidioides, Histoplasma,* and *Blastomyces*) and those responsible for infections in compromised hosts (*Candida, Cryptococcus,* and *Aspergillus*); parasites, such as *Toxoplasma gondii* and *Taenia solium;* and most frequently, viruses (Tables 643.2 and 643.3 and see Chapter 643.2). Focal infections of the CNS, including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess), may also be confused with meningitis. In addition, noninfectious illnesses can cause generalized inflammation of the CNS; relative to infections, these disorders are very uncommon and include malignancy (lymphoma), immunologic diseases (CNS vasculitis, sarcoidosis, autoimmune encephalitis), and exposure to toxins (see Table 643.3).

Table 643.2 Causes of Aseptic Meningitis and Encephalitis Including Differential Diagnosis at Different Ages

AGE	INFECTIOUS	INFLAMMATION	AUTOIMMUNE	MIMICS
0-24 mo	Enteroviruses Parechovirus HSV Congenital infections Arboviruses HIV	Cryopyrin disorders Interferonopathies Complement disorders (HUS/TTP) Aicardi-Goutieres syndrome	Paraneoplastic rare under 12 mo	• Bacterial meningitis • Urea cycle disorders, maple syrup urine disease, MCAD deficiency, CPT2, mitochondrial disorders (Leigh) • Brain malformations • Intoxication • Epilepsy • Dravet (*SCNA1*) and other epilepsy encephalopathy syndromes • Acute adrenal crisis • Hydrocephalus • HLH • Glioma
2-5 yr	Enteroviruses HSV Influenza Arboviruses Adenovirus *Bartonella* *Ehrlichia* and *Borrelia* spp. Rabies	Complement disorders (HUS/TTP)	ADEM NMOSD VZV AFP TM	• Bacterial meningitis • Intoxication • MCAD deficiency • Epilepsy • Dravet (*SCNA1*) and other epilepsy encephalopathy syndromes • Infectious HUS • HLH • Mitochondrial disorders (MELAS) • Glioma; CNS lymphoma
5-18 yr	Enteroviruses HSV Influenza Arboviruses Adenovirus *Bartonella* *Ehrlichia* and *Borrelia* spp. Rabies		ADEM NMDAR NMOSD VZV AFP SLE TM	• Bacterial meningitis • Epilepsy • Intoxication • Psychosis • Wilson disease • Pseudotumor cerebri • Multiple sclerosis • Dravet (*SCNA1*) and other epilepsy encephalopathy syndromes • HLH • Mitochondrial disorders (MELAS) • Vasculitis (primary, rickettsia, VZV) • Tumors: Glioma; CNS lymphoma; Metastatic
Young adult	Enteroviruses HSV Influenza Arboviruses *Ehrlichia* and *Borrelia* spp. HIV Rabies		ADEM NMDAR NMOSD SLE Paraneoplastic AFP TM	• Bacterial meningitis • Intoxication • Psychosis • Wilson disease • HLH • Periarteritis nodosa, Takayasu, giant cell, ANCA + arteritis • Acute intermittent porphyria • Multiple sclerosis • Vasculitis (primary, rickettsia, VZV) • Tumors: Glioma; CNS lymphoma; metastatic
Older adult	Enteroviruses HSV Influenza Arboviruses *Ehrlichia* and *Borrelia* spp. HIV Rabies		Limbic encephalitis SLE AFP NMOSD NMDAR	• Bacterial meningitis • Intoxication • TTP • Neurodegeneration • Tumor metastases • HLH • Periarteritis nodosa, Takayasu, giant cell, ANCA + arteritis • Multiple sclerosis • Mitochondrial disorders (MELAS) • Vasculitis (primary, rickettsia, VZV) • Tumors: Glioma; CNS lymphoma; metastatic

ADEM, Acute disseminated encephalomyelitis; AFP, acute flaccid paralysis; ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; CPT2, carnitine palmitoyltransferase-2; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; HUS, hemolytic uremic syndrome; MCAD, medium-chain acylcarnitine deficiency; MELAS, mitochondrial encephalopathy lactic acidosis syndrome; NMDAR, N-methyl-D-aspartate receptor encephalitis; NMOSD, neuromyelitis optica spectrum disorder; SCNA1, sodium voltage-gated channel alpha subunit 1; SLE, systemic lupus erythematosus; SMA, spinal muscular atrophy; TM, transverse myelitis; TTP, thrombotic thrombocytopenic purpura; VZV, varicella-zoster virus

Modified from Kliegman RM. Encephalitis. In: Kliegman RM, Toth H, Bordini BJ, et al, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier, 2023: Table 42.2, p. 768.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
ARTHROPODS Mosquitoes		
	Togaviridae	
	Chikungunya virus	Humans and other vertebrates serve as reservoirs. Vertical transmission has been reported.
	Eastern equine encephalitis virus	Like Western equine encephalitis, birds are the primary reservoir, exposure to horses is not a risk factor. High frequency of symptomatic infections in children and elderly.
	Semliki Forest virus	Cases are rare; one reported death attributed as part of a possible laboratory accident
	Venezuelan equine encephalitis virus	Equids and small mammals are the primary reservoir. Children are at higher risk for development of long-term neurological sequelae.
	Western equine encephalitis (WEE) virus	Birds are the primary reservoir. Viremia is too low in humans or horses to infect mosquitoes, so horse exposure is not a true risk factor for disease.
	Flaviviridae	
	Dengue virus	The primary reservoir is humans and other primates. Vertical transmission has been reported, as well through organ transplant and blood transfusion
	Japanese encephalitis virus	Primary reservoir is birds and pigs. Bats may also contribute to circulation of the virus.
	Murray Valley encephalitis virus	Waterfowl are the primary reservoir
	St. Louis encephalitis virus	Birds are the primary reservoir
	West Nile virus	Birds are the primary reservoir. Transmission has also been reported through organ transplantation or blood transfusions.
	Zika virus	Humans and non-human primates are the like primary reservoir. Transmission has also been reported through sexual contact and vertical transmission.
	Reoviridae	
	Banna virus	Unknown reservoir
	Bunyavirales	
	Jamestown Canyon virus	The primary reservoir is deer and other ungulates (moose and bison)
	La Crosse encephalitis virus	Small mammals (chipmunks and squirrels) serve as the primary reservoir. Peak incidence in school-age children
	Rift Valley fever virus	Mosquitos are the vector and reservoir. Further viral amplification occurs in livestock and other domestic ruminants. Small mammals and bats may also contribute to persistence. Transmission may also occur from handling infected animal tissue or drinking unpasteurized milk.
Ticks		
	Anaplasma phagocytophilum	White-footed mouse is hypothesized the primary reservoir, with other sources including various mammals including deer. Rare reports of transmission through blood transfusion.
	Borrelia burgdorferi	White-footed mouse and other small mammals are the primary reservoir. Deer serve to support the tick population but not Borrelia.
	Ehrlichia chaffeensis	Primary reservoir is white-tailed deer. Transmission also reported through blood transfusion or solid organ transplantation.
	Ehrlichia ewingii	Dogs and deer are hypothesized to be the primary reservoirs.
	Powassan virus	Small mammals are the primary reservoir.
	Rickettsia rickettsii	Transmission may occur with very short tick attachment times. Ticks serve as both the vector and reservoir. Rare reports of transmission through blood transfusion.
	Kyasanur Forest disease virus	Transmission may also occur from contact with an infected animal. While it can infect livestock, there are no reports of transmission through unpasteurized milk
	Tickborne encephalitis virus	Reservoirs include ticks, birds, and small mammals. Transmission may also occur via direct contact, consuming unpasteurized dairy products, blood transfusion, organ transplantation, and breastfeeding.
Sandflies	*Bartonella bacilliformis*	Reservoir is unknown. Most infections occur at sunrise or sundown as the flies are most active during these time periods.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	Chandipura vesiculovirus	Mosquitos may also play a role in transmission. No other vertebrate has been identified as a potential reservoir. Cases described from India and West Africa.
	Toscana virus	Reservoir is presumed to be sandflies; very little data exist as to whether other mammals could serve as a source of the virus.
Tsetse flies	*Trypanosoma brucei gambiense*	Humans are the primary reservoir although it can also be identified in primates and ungulates. Vertical transmission has been reported.
	Trypanosoma brucei rhodesiense	Livestock such as cattle and other large mammals are considered to be the primary reservoir
WILD OR DOMESTIC ANIMALS		
Bats	Australian bat lyssavirus	It is assumed that any bat in Australia could carry this virus.
	Histoplasma capsulatum	Guano promotes fungal growth. Bats can develop chronic and disseminated infection with *Histoplasma*, but risk of transmission is likely highest through guano exposure.
	Nipah virus	Reports of transmission via direct contact with bats or coming into contact with bat bodily fluids on food. Human to human transmission has been reported.
	Rabies virus	Some bat bites are too small to be detected, often post-exposure prophylaxis is offered to anyone with direct contact with bats or if contact cannot be ruled out (e.g., an individual waking up to a bat flying in the same room). Transmission has been reported via solid organ transplant
Cattle	*Brucella abortus*	Many large mammals can be infected. Nearly eradicated from cattle in the US, Canada, Europe, Australia, New Zealand, and some Asian countries including Japan and Israel.
Dogs	Rabies virus	Many countries have been declared rabies-free in dogs, including Europe, Japan, the US, Australia, and New Zealand. Other countries remain at high risk for transmission from dogs.
	Toxocara canis	Dogs (especially puppies) shed eggs in feces, and organism survives in soil for prolonged period
Cats	*Bartonella henselae*	Typically follows scratch or bite from cat or kitten; highest incidence in children, in the fall, and around holidays (when cats are given as gifts)
	Rabies virus	In the US, more rabid cats are detected than dogs. In other countries, cats are second to dogs in prevalence.
	Toxoplasma gondii	Cats and other felines are reservoir hosts; they shed oocytes in feces, and the soil becomes contaminated. Sheep, goats, swine, cattle serve as intermediate hosts. Transmission may also occur vertically or through blood transfusion or solid organ transplantation. Worldwide distribution
	Toxocara cati	Cats, (specially kittens) shed eggs in feces, and organism survives in soil for prolonged period
Rodents	*Leptospira* spp.	Rodents (and many other animals) excrete organism in urine, and the organism remains viable in soil or water for weeks to months
	Lymphocytic choriomeningitis virus	Peak incidence in fall and winter; chronic infection in mice, hamsters, and guinea pigs; humans infected by inhalation or ingestion of dust or food contaminated by urine, feces, blood, nasopharyngeal secretions of infected rodents. Transmission has also occurred by vertical transmission and solid organ transplant,
Raccoons	*Baylisascaris procyonis*	Young children at risk due to pica, particularly near raccoon latrines. Other animal handlers, including hunters, at risk.
	Rabies virus	"Raccoon strain" extends along Eastern seaboard of the USA and has reached northward into Canada
Sheep, goats	*Brucella melitensis*	Direct contact with infected animals or their secretions. Present world-wide but has been eradicated in some countries including Northern and Central Europe, US, Canada, Australia, New Zealand, and Japan. Transmission has also occurred from sexual intercourse, vertical transmission, solid organ transplantation and transfusions.
	Coxiella burnetii	Inhalation; either direct exposure to animal or exposure to contaminated materials particularly dust or during birth. Rare reports of vertical transmission, through blood transfusions, or sexual intercourse
Birds	*Chlamydophila psittaci*	Birds can harbor and transmit organism to humans; usually acquired via inhalation of fecal dust/sections of birds. Rare cases have been reported in exposures to other non-avian livestock.

Continued

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	Cryptococcus neoformans	Primarily in immunocompromised individuals. Some association with exposure to soil contaminated with bird droppings, particularly pigeons
Old World monkeys	B virus	Bite of Old World macaques. Present in both wild and captive settings.
Horses	Hendra virus	Endemic in Australia; associated with excretions/tissues from horses
Swine	Nipah virus	Close contact with pigs was the primary cause of an outbreak in Malaysia
	Brucella suis	Prevalent in many locations in the world, some countries have achieved eradication including Europe, Canada, US, and Australia.
Skunks	Rabies virus	Skunk populations are the primary reservoir in the central US and California
Squirrels	Variegated squirrel bornavirus 1	Detected in Germany, particularly in captive squirrels originating from Latin America or Asia. Unclear if this virus originates in Europe or was imported.
INGESTION OR INHALATION		
Fresh water	*Leptospira* spp.	Organisms from animal urine or placental tissue can remain viable for weeks to months in soil or water; recreational exposure associated with wading or swimming in contaminated water (particularly after floods or hurricanes)
	Naegleria fowleri	Swimming in warm, natural bodies of water (rarely poorly chlorinated pools reported). Not found in salt water. Cases also linked to nasal rinses or neti pot usage.
Soil	Acanthamoeba spp.	Found in soil and water. Transmission through inhalation or inoculation; cases of keratitis associated with contact lens usage
	Balamuthia mandrillaris	Soil living organism, transmission presumably occurs through inhalation or inoculation into cuts or wounds. Transmission has also been reported via solid organ transplantation.
	Baylisascaris procyonis	Widespread in the US; export of raccoons has led to spread to Europe and Asia.
	Blastomyces dermatitidis	Present in the eastern half of the US (particularly along the Mississippi, Ohio, and St. Lawrence Rivers), Canada, Africa, and India.
	Coccidioides spp.	Also known as valley fever. Infection is seasonal and is acquired by inhalation of soil or dust. Transmission has occurred from solid organ transplantation.
	Histoplasma capsulatum	Inhalation of airborne spores from soil. Outbreaks have occurred in endemic areas with exposure to bird, chicken, or bat droppings or recently contaminated soil. Globally distributed, with as many as 80% of children have been infected.
	Toxocara canis/Toxocara cati	Eggs in sandboxes and playgrounds; organisms survive long periods in soil
Spelunking	*Histoplasma capsulatum*	Reports of infections due to indirect exposure near the entrance of bat caves
	Rabies virus	Aerosol transmission has been implicated in very rare cases after exploring caves with large bat populations
Undercooked pork, lamb, or beef	*Toxoplasma gondii*	Cook meats to a minimum of 145-160°F. Meat color is an insufficient marker to kill tissue cysts
Undercooked freshwater fish, birds, reptiles, or amphibians	*Gnathostoma* spp.	Marinating in lime juice (ceviche) does not kill the parasite.
Freshwater crayfish or crabs	*Paragonimus westermani*	Mostly in Asia. Related species present in Africa, North and South America.
Raw or undercooked meat	*Trichinella* spp.	Mostly associated with pigs but has been found in other wild game meat. Worldwide distribution
Raw or undercooked snails, slugs, freshwater prawns, crabs, or frogs,	*Angiostrongylus cantonensis*	Worldwide distribution. Snails and slugs can be accidentally chopped up with vegetables and consumed, leading to infection.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
Unpasteurized milk	Tickborne encephalitis virus	Unpasteurized milk or cheeses from cows, sheep, or goats have been implicated
	Coxiella burnetii	Highly prevalent in many types of raw milk, pasteurization reduces risk
	Listeria monocytogenes	Also found in various raw dairy, vegetable, and meat products
	Toxoplasma gondii	Consumption of raw goat, sheep, or camel milk
SEASONAL		
	Arthropod-borne pathogens	Prevalence mirrors insect populations, infections nadir during the winter in temperate regions.
	Common viral infections (influenza, coronaviruses, adenoviruses, astroviruses, and other respiratory or gastrointestinal viruses); mycoplasma	Many viral and atypical bacterial infections predominant in the winter in temperate regions. Unclear if SARS-CoV-2 will follow the same seasonality.
	Enteroviruses and parechoviruses	Peak incidence in late summer and early fall in temperate regions. In tropical regions, enteroviruses circulate year round. Hypothesized that humidity may stabilize viral particles in the environment.
	Enterovirus D68	Reemergence in 2014 in causing acute flaccid paralysis. Outbreaks occurred every two years until 2020.
	Naegleria fowleri	Thrives in warmer water temperatures, leading to increased incidence of disease during the summer and early fall.
SEXUAL ACTIVITY		
	Herpes simplex virus 1/2	Primary HSV-2 infection can cause meningitis particularly in young females.
	HIV	Highest risk with unprotected sex with viremic subjects. Undetectable viral load equals untransmittable.
	Treponema pallidum	Resurgence in cases over the past decade particularly in the US
	Zika virus	Reports of sexual transmission. Virus is present in saliva, semen, vaginal fluids, urine, and breast milk. Virus may persist longer in semen than other bodily fluids.
FOREIGN TRAVEL		
Global	Chikungunya virus	Spread to the Africa, Americas, Asia, and Europe. Large outbreak in Latin America in the mid 2010's.
	Dengue virus	Cases occur on most continents. In the US, occasional local transmission reported in Florida, Texas, Arizona, Hawaii, and US territories
	Rabies virus	Prevalent worldwide but most cases occur in Asia and Africa. Dog bites are the most common mode of acquisition in developing countries
	West Nile virus	Outbreaks have been reported on all continents except Antarctica. In the US, most cases now occur west of the Mississippi River. A few thousand cases are diagnosed each year in the US.
	Zika virus	Worldwide distribution including North/South America, Africa, Asia
	Measles	Most cases now occur in South America, Africa, and Asia, including the Malay Archipelago and the Philippines. Secondary spread has led to outbreaks in many other countries.
	Mumps	Remains prevalent worldwide and a frequent cause of viral meningitis
	Rubella	Endemic in the Eastern Hemisphere, particularly in Asia and Africa.
	Gnathostoma spp	Worldwide distribution of different species. Most cases have occurred in Asia and Latin America.
	Plasmodium spp.	Tropical and subtropical areas in most continents
	Taenia spp.	Endemic to most countries. Most cases are travel associated when they occur in the US, Canada, and Australia.
Africa	Poliovirus	Africa was declared polio free in 2020, but in 2023, transmission of poliovirus type 1 was detected in Mozambique
	Rift Valley fever virus	Most prevalent in southern and eastern Africa, most countries report cases or isolation of virus
	Toscana virus	Reported in Morocco, Tunisia, and Algeria

Continued

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	Blastomyces dermatitidis	Rare cases described throughout Africa. Other related *Blastomyces* spp. present in Africa.
	Trypanosoma brucei gambiense	West and central Sub-Saharan Africa
	Trypanosoma brucei rhodesiense	East Africa, predominantly Uganda, Kenya, Tanzania, Zambia, Malawi, Zimbabwe, and Mozambique
Asia	Banna virus	Detected in mosquitoes in China, Vietnam, Indonesia
	Japanese encephalitis virus	Mostly southern and eastern Asia, Malay archipelago, and Australia
	Kyasanur Forest disease virus	Detected so far only in India
	Nipah virus	Southeast Asia, particularly Malaysia
	Poliovirus	Wild type continues to circulate in Pakistan and Afghanistan.
	Tickborne encephalitis virus	Central Europe to eastern Asia, includes Japan
	Borrelia burgdorferi	Temperate forested regions throughout northern Asia
Australia	Australian bat lyssavirus	Exclusive to Australia, spread by bats. Closely related to rabies virus.
	Hendra virus	Exposure to body fluids and excretions of infected horses is the primary risk for transmission. Most cases reported in Queensland
	Japanese encephalitis virus	Cases reported in northern and eastern regions
	Murray Valley encephalitis virus	Cases throughout Australia, many have occurred in the Northern Territory. Also in New Guinea
Europe	Tickborne encephalitis virus	Central Europe to Japan
	Toscana virus	Endemic in most Mediterranean countries
	Anaplasma phagocytophilum	Temperate zones, particularly western and central Europe
	Borrelia burgdorferi	Temperate forested regions, particularly eastern and central Europe
North America	California/La Crosse virus	Most cases in Ohio, West Virginia, Tennessee, and North Carolina, but many other cases reported in the Midwest and South. From 2003-2022, a total of 1,431 cases have been reported to the CDC.
	Eastern equine encephalitis	A total of 189 cases reported to the CDC from 2003-2022. Most cases east of the Mississippi River, particularly Michigan, Florida, New Hampshire, and Massachusetts.
	Jamestown canyon virus	Majority of cases in Wisconsin and Minnesota, with other Midwest and Eastern states reporting cases. A total of 282 cases reported in the past decade to the CDC.
	Powassan virus	Wisconsin Minnesota, northeastern US, Canada. A total of 290 cases have been reported to the CDC between 2004-2002.
	St. Louis encephalitis virus	Most cases in Arizona, California and Texas, but many other states have sporadic cases. A total of 284 cases reported to the CDC in the past two decades
	Venezuelan equine encephalitis virus	Sporadic cases in Florida and along the Mexican border
	Western equine encephalitis virus	Most cases occurred west of the Mississippi River extending into Latin America. Cases are now rare; no infections reported to the CDC in over a decade.
	Anaplasma phagocytophilum	Majority of cases in Wisconsin, Minnesota and northeastern US. Cases also occur in mid-Atlantic, Midwest, West coast
	Borrelia burgdorferi	Eastern USA as far south as Ohio, West Virginia, Virginia, and North Carolina. Also includes Wisconsin and Minnesota, with cases occurring less commonly in California, Oregon, and Washington state. Nearly 500,000 Americans are diagnosed with Lyme disease each year.
	Ehrlichia chaffeensis	Southern and central USA and Mid-Atlantic and coastal states
	Rickettsia rickettsii	Majority of cases in a central band of the US including Kansas, Missouri, Arkansas, Kentucky, Tennessee, Mississippi, Alabama, Virginia and North Carolina. Other cases identified throughout the US.
	Blastomyces dermatitidis	Predominates along the Mississippi, Ohio, and St Lawrence Rivers, but many cases reported throughout the eastern US and Canada. Estimated ~2 cases per 100,000 each year in the US.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	Coccidioides spp.	Semiarid regions of southwestern US (California, Nevada, Utah, Arizona, New Mexico, Texas, and southern portions of Colorado and Oklahoma. Extends south into much of Mexico and central America. Around 20,000 cases diagnosed each year in the US.
South America	St. Louis encephalitis virus	Sporadic cases in Argentina, Brazil, and Peru, but far more prevalent in the US.
	Venezuelan equine encephalitis virus	Tropical latitudes, particularly Colombia, Venezuela, Peru, and Ecuador. Sporadic cases reported in Brazil, Bolivia, and Argentina.
	Western equine encephalitis virus	Rare cases in Brazil and Colombia.
	Rickettsia rickettsii	Cases reported in Colombia, Brazil, and Argentina.
	Coccidioides spp.	Many countries in Latin America, including Brazil, Argentina, Colombia, Venezuela, and Paraguay
	Bartonella bacilliformis	Predominantly occurs in the Andes at elevations of 3,000 to 10,000 feet above sea level. Most cases in Peru, but has been reported in Colombia and Ecuador.

Modified from Kliegman RM. Encephalitis. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier, 2023: Table 42.3, p. 770-775.

Determining the specific cause of CNS infection is facilitated by careful examination of the CSF with specific stains (e.g., Kinyoun carbol fuchsin for mycobacteria, India ink for fungi), cytology, antigen detection *(Cryptococcus),* CSF serology (syphilis, West Nile virus [WNV], arboviruses), and PCR (bacteria and viruses). Other potentially valuable diagnostic tests include blood cultures, CT or MRI of the brain, serum serologic tests, and, rarely, meningeal or brain biopsy.

Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis (see Table 643.2 and Table 643.3). Although children with viral meningoencephalitis typically appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity. Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial versus viral infection tend to be distinct (see Table 643.1), these cases can overlap in the number of CSF leukocytes and glucose and protein levels. Quite often, children are empirically treated with antibiotics for >48 hours to await CSF culture and PCR results to distinguish these two groups of pathogens.

TREATMENT

Essential to improving clinical outcomes in patients with bacterial meningitis is prompt recognition, diagnostic testing, and initiation of appropriate antimicrobial therapy. Several studies have demonstrated that delays in initiating antimicrobial therapy, even a few hours, are significantly associated with adverse clinical outcomes and death. If focal neurologic findings, papilledema, or increased ICP is present, antibiotics should be given before obtaining a head CT scan (and subsequent LP), and the increased ICP should be treated simultaneously (see Chapter 82). Some patients with meningitis will develop multisystem organ failure, shock (see Chapter 85), and acute respiratory distress syndrome (see Chapter 86), requiring further management in an intensive care unit.

Initial Antibiotic Therapy

The initial (empiric) choice of antibiotic therapy for meningitis in immunocompetent infants and children should achieve bactericidal levels in the CSF and have excellent activity against the typical bacterial causes of meningitis (Table 643.4). Although there is substantial geographic variation in the frequency of resistance of *S. pneumoniae* to β-lactam antibiotics, rates are increasing throughout the world. In the United States, 25–50% of meningitic strains of *S. pneumoniae* have some level of resistance to penicillin; relative resistance (minimal inhibitory concentration = 0.1-1.0 μg/mL) is more common than high-level resistance (minimal inhibitory concentration = 2.0 μg/mL). Resistance to ceftriaxone and cefepime is globally variable, but in some studies can be as high as 25%. Resistance to cephalosporins declined in the United States after the introduction of PCV13 because of the reduction in disease caused by serotype 19A, which is commonly associated with resistance. However, current surveillance suggests rising rates of cephalosporin resistance in non-PCV13 serotypes. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30–40% of isolates of *H. influenzae* type b and 10% of *H. influenzae* type a produce β-lactamases and therefore are resistant to ampicillin. These β-lactamase–producing strains remain sensitive to third- and fourth-generation cephalosporins.

The recommended empiric antibiotic regimen in suspected bacterial meningitis beyond the neonatal period is a third-generation cephalosporin (ceftriaxone) plus vancomycin. Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b, ceftriaxone (50 mg/kg/dose given every 12 hours) should be part of initial therapy. Based on the current incidence of cephalosporin-resistant strains of *S. pneumoniae,* vancomycin is also recommended as part of empiric therapy. Vancomycin dosing guidelines have shifted from trough-based dosing to area under the curve/minimum inhibitory concentration (AUC/MIC; see Chapter 225). Although current clinical data are limited, vancomycin dosing for meningitis should attain a target AUC/MIC of 400-600 mg*h/L (previous vancomycin trough goals were 15-20 mg/L). Patients allergic to penicillin and cephalosporin antibiotics can be treated with meropenem (40 mg/kg/dose every 8 hours); other alternatives include fluoroquinolones or chloramphenicol, if available. Alternatively, allergic patients can be desensitized to the preferred antibiotic (see Chapter 193).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (300 mg/kg/day, divided every 6 hours) also should be given because cephalosporins are inactive against *L. monocytogenes.* Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for *L. monocytogenes* and has documented clinical efficacy.

If a patient is immunocompromised and gram-negative bacterial meningitis is suspected, initial therapy might include cefepime or meropenem.

Duration of Antibiotic Therapy

The duration of antibiotic therapy for meningitis had been based on experience and expert opinion rather than randomized clinical trials.

Table 643.4 Antibiotics Used for the Treatment of Bacterial Meningitis*

	NEONATES (TERM)		
DRUGS	**0-7 DAYS**	**8-28 DAYS**	**INFANTS AND CHILDREN**
Amikacin†‡	15 divided q24h	18 divided q24h	15-22.5 divided q8h, q12h, or q24h
Ampicillin	300 divided q8h	300 divided q6h	300-400 divided q4h, max 12 g/day
Cefepime	100 divided q12h	100 divided q12h	150 divided q8h, max 6 g/day
Ceftriaxone§	—	—	100 divided q12h or q24h. max 4 g/day
Ceftazidime	100 divided q12h	150 divided q8h	150-200 divided q8h, max 6 g/day
Gentamicin†‡	4 divided q24h	5 divided q24h	7.5 divided q8h
Meropenem	60 divided q8h	90 divided q8h for days 14-28	120 divided q8h, max 6 g/day
Nafcillin	75 divided q8h	100 divided q6h	200 divided q4h-q6h, max 12 g/day
Penicillin G	450,000 divided q8h	500,000 divided q6h	300,000-400,000 divided q4h, max 24 million U/day
Rifampin	—	10 q24h	15-20 divided q12h or q24h, max 600 mg/day
Tobramycin†‡	4 divided q24h	5 divided q24h	7.5 divided q8h
Vancomycin†‡#	40 divided q12h	60 divided q8h	age 3 mo-12: 60-80 divided q6h age >12 yr: 60-70 divided q6h-q8h

*Dosages in mg/kg (units/kg for penicillin G) per day.
†Smaller doses and longer dosing intervals, especially of aminoglycosides and vancomycin for very low-birthweight neonates, may be advisable.
‡Monitoring of serum levels is recommended to ensure safe and therapeutic values.
§Use in neonates is not routinely recommended because of inadequate experience in neonatal meningitis and concerns of displacement of bilirubin from albumin, leading to worsening of hyperbilirubinemia. Some centers use ceftriaxone in term neonates older than 7 days of age who are not receiving calcium-containing solutions or total parenteral nutrition and have normal albumin level and total serum bilirubin <5 mg/dL.
#Goal vancomycin AUC/MIC of 400-600 mg*hr/L or trough of 15-20 mg/L.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267–1284. Table 6; with updated data from Kimberlin DW, Barnett ED, Lynfield R, et al. Red Book (2021): Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

In the past, the standard of care for the treatment of meningitis included repeating an LP before the end of antimicrobial therapy. The total length of therapy would be determined according to whether the CSF parameters (white blood cell count, protein, and glucose) had normalized or not. However, further studies showed that abnormal CSF parameters did not predict which patients would develop relapsed infection after stopping antibiotics. Therefore repeat LP before discontinuation of antibiotics for typical bacterial meningitis is not recommended.

Currently, the recommended treatment duration for uncomplicated *S. pneumoniae* meningitis is 10-14 days with a third-generation cephalosporin, or intravenous penicillin (300,000-400,000 units/kg/day, divided every 4 hours) for penicillin-sensitive isolates, or vancomycin if the isolate is resistant to penicillins and cephalosporins. For *N. meningitidis* meningitis, the recommended treatment duration is 5-7 days with intravenous penicillin for strains with an MIC of penicillin <0.1 μg/mL, or ceftriaxone for strains with an MIC of 0.1-1 μg/mL. Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days with ampicillin for β-lactamase–negative strains or with a third-generation cephalosporin for β-lactamase–positive isolates. Patients who receive intravenous or oral antibiotics before LP and do not have an identifiable pathogen from cultures but do have evidence of bacterial meningitis based on their CSF profile and PCR should receive therapy with ceftriaxone for 7-10 days. Shorter durations of antibiotics for meningitis might be effective; one double-blinded, randomized study of children with meningitis demonstrated equivalent outcomes when treating with ceftriaxone for 5 versus 10 days. In addition, during epidemics of meningococcal meningitis in Africa, single intramuscular dosages of ceftriaxone or chloramphenicol can be used.

Meningitis caused by *Escherichia coli* or *P. aeruginosa* may require therapy with a third- or fourth-generation cephalosporin or carbapenem active against the isolate in vitro. Many isolates of *E. coli* are sensitive to ceftriaxone, and isolates of *P. aeruginosa* are often sensitive to ceftazidime. Repeat examination of CSF should be considered in some neonates and in patients with meningitis from gram-negative bacilli or β-lactam–resistant *S. pneumoniae*. The CSF in most cases will be sterile within 24-48 hours of initiation of appropriate antibiotic therapy. Gram-negative bacillary meningitis should be treated for 3 weeks, or at least 2 weeks after CSF sterilization, if documented.

Side effects of antibiotic therapy for meningitis include phlebitis, drug fever, rashes, emesis, oral or vaginal candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis, detectable by abdominal ultrasonography. This is usually asymptomatic but may be associated with emesis and upper right quadrant pain.

Corticosteroids

Rapid killing of bacteria in the CSF by the host's immune response and antibiotics leads to release of inflammatory agents (e.g., endotoxin) that precipitate a cytokine-mediated inflammatory cascade. The resultant edema and neutrophilic infiltration may aggravate neurologic injury with worsening of CNS signs and symptoms. Therefore agents that restrain production of inflammatory mediators could be of benefit in bacterial meningitis.

In a Cochrane review of corticosteroid use in meningitis, steroids reduced hearing loss in children with meningitis caused by *H. influenzae* type b but not by other pathogens. The use of adjunctive steroids in children did not reduce mortality; however, steroids did improve survival rates in adults with pneumococcal meningitis. These data support

the use of intravenous dexamethasone 0.15 mg/kg/dose given every 6 hours for 2 days in the treatment of *H. influenzae* type b meningitis in children over 6 weeks of age. Corticosteroids appear to have maximum benefit if given 1-2 hours before antibiotics are initiated, which is difficult to operationalize; steroids may also be effective if given concurrently with or soon after the first dose of antibiotics. Pediatric data regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria remain inconclusive.

COMPLICATIONS

Treatment of meningitis can be accompanied by acute CNS complications, including seizures, increased ICP, cranial nerve palsies, stroke, cerebral or cerebellar herniation, SIADH, and thrombosis of dural venous sinuses.

Collections of fluid in the subdural space develop in 10–30% of patients with meningitis and are asymptomatic in 85–90% of patients. Subdural effusions are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, or abnormal results of cranial transillumination. CT or MRI scanning can confirm the presence of subdural effusion. In the presence of increased ICP or depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel (see Chapters 82 and 630). Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures (see Chapter 82).

Fever associated with bacterial meningitis usually resolves within 5-7 days of the onset of therapy. Prolonged fever (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually related to intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. In meningitis caused by *N. meningitidis,* pericarditis or arthritis may occur during treatment (sometimes accompanied by recrudescent fever) and is caused by either bacterial dissemination or immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than immune-mediated disease.

Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is observed most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.

PROGNOSIS

Appropriate antibiotic therapy and supportive care have reduced the mortality rate of bacterial meningitis beyond the neonatal period to under 10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10–20% of patients recovering from bacterial meningitis, and as many as 50% have some neurologic sequelae. The prognosis is poorer among infants under 6 months of age and in those with high CSF bacterial burden. Those with seizures occurring later than 4 days into therapy or with coma or focal neurologic signs on presentation also have increased risk of long-term sequelae. There does not appear to be a correlation between the duration of symptoms before a diagnosis of meningitis and the subsequent outcome.

The most common neurologic sequelae of meningitis include hearing loss, cognitive impairment, recurrent seizures, delay in acquisition of language, visual impairment, and behavioral problems. Sensorineural hearing loss is most frequently detected and is often already present at the time of initial presentation. It results from cochlear or auditory nerve inflammation and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal meningitis, and 5–20% of those with *H. influenzae* type b meningitis. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment in the outpatient setting is indicated for patients who develop a hearing deficit.

PREVENTION

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent two opportunities to reduce the transmission and development of secondary cases of bacterial meningitis.

Neisseria meningitidis

See also Chapter 237.

Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis, regardless of age or immunization status. Close contacts >1 month of age should be treated with rifampin 15-20 mg/kg/dose every 12 hours (maximum dose 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Alternative options include intramuscular ceftriaxone (125 mg once for children under age 15 years, or 250 mg once for persons older than 15 years) or ciprofloxacin 20 mg/kg as a single oral dose (maximum 500 mg). Close contacts include household, daycare, and nursery school contacts and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation). If there is a high suspicion of meningococcemia in the index patient, exposed contacts should be prophylaxed immediately. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Many countries have included quadrivalent conjugate meningococcal vaccine (types A, C, Y, and W-135) as part of routine immunization schedules. The Advisory Committee on Immunization Practices (ACIP) of the U.S. CDC recommends a two-dose vaccine series for all children, with the first dose administered at the age of 11-12 years and a second dose at age 16-18 years. Vaccination is also recommended for persons 2 months to 18 years of age who are at increased risk for meningococcal disease, including those with anatomic or functional asplenia or complement deficiencies or who are receiving a terminal complement inhibitor (e.g., eculizumab). Two meningococcal vaccines against serogroup B have been developed. In the United Kingdom, the vaccine is administered to all infants at 2, 4, and 12 months of age. This differs from the United States, where currently meningococcal B vaccine is recommended for children 10 years and older at increased risk for invasive disease and is optional for persons 16-23 years of age.

Haemophilus influenzae Type b

See also Chapter 240.

Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by *H. influenzae* type b *if* any close family member younger than 48 months has not been fully immunized or if an immunocompromised child of any age resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hours with the index case for at least 5 of the 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case, because over 50% of secondary cases occur in the first week after the index patient is hospitalized. The dose of rifampin is 20 mg/kg/day (maximum dose 600 mg) given once daily for 4 days.

Three conjugate monovalent vaccines for *H. influenzae* type b are licensed in the United States along with two other multivalent vaccines that include *H. influenzae* type b components. Although each vaccine elicits different profiles of antibody response in infants immunized at 2-6 months of age, all result in protective levels of antibody with a 93% efficacy rate against invasive infections after the primary series. Thus all children should be immunized with *H. influenzae* type b conjugate vaccine beginning at 2 months of age. Efficacy is not as consistent in Indigenous Nation populations, a group recognized as having a higher incidence of *H. influenzae* disease.

Streptococcus pneumoniae

See also Chapter 228.

Antibiotic prophylaxis should not be administered to contacts of children diagnosed with pneumococcal meningitis. Routine administration of pneumococcal conjugate vaccine is recommended for children under 5 years of age. The initial dose of the series is given at 2 months of age. Children who are at high risk for invasive pneumococcal infection, including those with functional or anatomic asplenia (including sickle cell disease), cochlear implants, CSF leaks, chronic illnesses (chronic heart disease, chronic lung disease, or diabetes mellitus), and underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should receive pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine (PPSV23).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

643.2 Viral Meningoencephalitis

Andrew B. Janowski and David A. Hunstad

Viral meningoencephalitis is an acute inflammatory process involving the meninges and/or brain parenchymal tissue. These infections are caused by a number of different pathogens, and quite often, no pathogen can be identified from the CSF or brain tissue specimens after routine clinical testing. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine bacterial culture. Outcomes are quite variable because cases of meningoencephalitis caused by some pathogens are self-limited, whereas others cause significant long-term neurologic sequelae.

ETIOLOGY

Among the most common causes of viral meningoencephalitis are viruses of the family Picornaviridae, including the **enteroviruses** (poliovirus, coxsackievirus, enterovirus, and echovirus) and **parechoviruses** (see Chapters 296 and 297) (see Tables 643.2 and 643.3). Meningoencephalitis caused by these viruses is often self-limited but can be severe in neonates or chronic in immunocompromised hosts (particularly X-linked agammaglobulinemia; see Chapter 166). Human coxsackievirus A7 and enteroviruses D68 and 71 have been associated with neurologic symptoms, including acute flaccid paralysis. Parechoviruses are an important cause of meningoencephalitis in infants and rarely cause disease in older children. Clinical manifestations in infants are generally similar to those of enteroviral infection, but infants with parechovirus infection may also exhibit abdominal signs or a sepsis-like syndrome. In addition, parechovirus infection is associated with more severe MRI lesions of the cerebral cortex, and CSF pleocytosis may be minimal or absent.

The term **arbovirus** refers to a broad range of viruses from multiple viral families that are transmitted by arthropod vectors, typically mosquitoes or ticks (see Chapters 314 and 315). Most of these viral infections are considered zoonotic, as their primary reservoir is in birds or small animals. Humans often represent dead-end hosts because sufficient viremia does not develop to enable transmission back to arthropod vectors. However, humans are the primary reservoir for viruses such as Zika, chikungunya, and dengue. The arboviruses that most often cause meningoencephalitis include WNV, Japanese encephalitis virus, and La Crosse virus; other arboviruses are described in Table 643.3. WNV made its appearance in the Western Hemisphere in 1999 and is now the most common arbovirus causing meningoencephalitis in the United States. WNV may also be transmitted by blood transfusion, organ transplantation, or vertically across the placenta. Most children with WNV are either asymptomatic or have nonspecific viral-like illness. Approximately 1% of infected humans develop CNS disease; adults are more severely affected than children.

Several members of the viral family Herpesviridae can cause meningoencephalitis (see Chapters 299-304). Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults, with progression to coma and death in 70% of cases without antiviral therapy. In neonates, severe encephalitis with diffuse brain involvement can be caused by HSV type 2, transmitted vertically at delivery. A mild transient (and sometimes recurrent) form of meningoencephalitis with HSV-2 may accompany genital herpes infection in sexually active adolescents and adults. Varicella-zoster virus (VZV) may cause CNS infection in a close temporal relationship with clinical manifestations of chickenpox. The most common manifestation of CNS involvement by VZV is cerebellar ataxia, whereas the most severe form is acute encephalitis. After primary infection, VZV establishes latency in spinal and cranial nerve roots and ganglia, and reactivation is evidenced by herpes zoster that can be accompanied by mild meningoencephalitis. Epstein-Barr virus is associated with various CNS syndromes (see Chapter 301). Cytomegalovirus (CMV) infection of the CNS can occur with congenital infection or disseminated disease in immunocompromised hosts, but it is an exceptionally rare cause of meningoencephalitis in immunocompetent infants and children (see Chapter 302). Human herpesvirus 6 is associated with encephalitis, but detection of the virus can also be reflective of latency in lymphocytes with reactivation caused by inflammation (see Chapter 303).

Mumps can cause meningoencephalitis and has a higher incidence in regions where the mumps vaccine is not implemented (see Chapter 295). Mumps meningoencephalitis is typically mild, but deafness from damage of the eighth cranial nerve can occur. Meningoencephalitis is also associated with acute infection with measles, rubella, respiratory viruses (adenovirus, coronaviruses, influenza virus, parainfluenza virus, respiratory syncytial virus), rotavirus, astroviruses, lymphocytic choriomeningitis virus, or rabies. HIV is associated with acute meningoencephalitis and can cause chronic encephalopathy leading to neurocognitive decline (see Chapter 322). In exceptionally rare situations, meningoencephalitis may follow live virus vaccination against polio, measles, mumps, rubella, or varicella.

EPIDEMIOLOGY

Meningoencephalitis has a seasonal pattern, with a peak incidence in the summer and late fall caused by a spike in circulation of enteroviruses and arboviruses. In 2018, the most common identifiable arbovirus responsible for meningoencephalitis in the United States was WNV, with a total of 2,647 cases; fewer than 200 combined cases were caused by the La Crosse, Jamestown Canyon, Powassan, St. Louis, and eastern equine encephalitis viruses (see Chapter 314). In 2019, an outbreak of 39 cases of eastern equine encephalitis occurred across the eastern United States, and 15 cases of St. Louis encephalitis were present in the western and central United States. In Asia, the most common cause is Japanese encephalitis virus, with an estimated >60,000 cases per year. Epidemiologic considerations in aseptic meningitis caused by agents other than enteroviruses also include the season, location of residence, recent travel, animal exposures, mosquito or tick bites, and additional factors related to specific pathogens.

Several studies have attempted to describe the causative pathogens associated with meningoencephalitis, including the California Encephalitis Project. Despite extensive testing, however, no pathogen can be identified in up to 63% of cases. Newer assays such as next-generation sequencing have the potential to identify novel or previously unrecognized pathogens in causing meningoencephalitis. Occult meningoencephalitis cases caused by pathogens such as *Leptospira,* astroviruses, and *Cutibacterium* (formerly *Propionibacterium*) *acnes* have been identified through this methodology. In addition to infectious agents, autoimmune encephalitis is a common cause of encephalitis-like illness (see Chapter 638.4).

PATHOGENESIS AND PATHOLOGY

Neurologic damage is caused by direct invasion and destruction of neural cells and tissues by actively multiplying viruses and by the host reaction to viral antigens. Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered to represent

predominantly "postinfectious" or autoimmune encephalitis. In HSV encephalitis, the cerebral cortex (classically the temporal lobes in HSV-1 infection) is often severely affected. Arboviruses tend to affect the entire brain, whereas rabies has a predilection for the basal structures. The involvement of the spinal cord, nerve roots, and peripheral nerves can be variable with these viruses.

CLINICAL MANIFESTATIONS

The progression and severity of disease are related to the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course of infection varies from case to case, even with the same causative pathogen. Some children may have mild symptoms at onset, only to lapse into a coma and rapidly die. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations, followed by complete recovery.

The onset of meningoencephalitis is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days' duration. The presenting manifestations in older children include headache and hyperesthesia and, in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. With high fevers, patients may develop altered mental status that progresses to encephalopathy in combination with uncontrolled body movements and seizures. Focal neurologic signs may be persistent, fluctuating, or migratory. WNV and nonpolio enteroviruses, including enterovirus D68, may cause anterior horn cell injury and acute flaccid paralysis. Encephalitis is more common than aseptic meningitis in WNV infection, whereas acute flaccid paralysis may be noted in approximately 5% of patients. Loss of bowel and bladder control and unprovoked emotional outbursts may also occur. Nonetheless, many patients have a nonspecific febrile illness caused by WNV infection and may never seek medical attention. Specific conditions associated with CNS viral infection include Guillain-Barré syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.

Exanthems can precede or accompany CNS signs, especially with enteroviruses, VZV, measles, rubella, and WNV.

During the pandemic caused by SARS-CoV-2, neurologic diseases were uncommonly associated with this infection in children, including encephalitis, Guillain-Barré syndrome, and stroke. In addition, in the multisystem inflammatory syndrome of children (MIS-C), encephalopathy is often observed, with some case series describing neurologic symptoms in over 50% of patients with MIS-C. Similar neurologic conditions have been observed in adults with SARS-CoV-2 infection, and persistent symptoms and impairments can be observed months after acute infection. It is unclear if the constellation of symptoms are the result of direct infection of the CNS by SARS-CoV-2 or if the inflammatory response to viral infection also contributes to the development of acute and chronic neurologic symptoms.

A syndrome of **mild encephalopathy with a reversible splenial lesion** (of the corpus callosum) has been associated with various pathogens, including rotavirus, respiratory syncytial virus (RSV), salmonella, CMV, adenovirus, and influenza virus.

DIAGNOSIS

CSF findings in viral meningoencephalitis are characterized by a pleocytosis of leukocytes with counts typically <1,000/mm^3 (see Table 643.1). In the initial hours of disease, the cells may be polymorphonuclear, whereas mononuclear cells predominate for the remainder of the illness. CSF protein concentration tends to be elevated, especially if brain destruction is extensive, as with HSV encephalitis. The glucose level is typically normal, although hypoglycorrhachia can occur with certain viruses (e.g., mumps). With parechoviruses, the CSF glucose, protein, and cell counts may be normal.

Identification of an infectious cause relies on analysis of the CSF for the presence of pathogens by PCR and serology and, in rare situations, identification of pathogens in brain biopsy material. CSF metagenomic sequencing is available in limited centers. A commercial multiplex PCR assay combines testing for common bacterial and viral pathogens in CNS infections. However, this assay does exhibit false-positive and false-negative results, so many clinicians still order individual PCR tests for common viral pathogens. In WNV meningoencephalitis, by the time patients present for medical care, viral nucleic acid may be absent in the CSF. Therefore the test of choice for detection of WNV and other arboviruses is serologic (on both blood and CSF). If initial CSF PCRs and serology are not diagnostic, serologic testing should be repeated 2-3 weeks later. A fourfold increase in titers for a specific virus or other pathogen would suggest the etiology of the patient's presentation.

Viruses detected in blood, nasopharyngeal, stool, and urine specimens can be used to suggest a potential viral etiology. However, caution must be practiced when viruses are detected in locations outside the CSF, because detection of these viruses may be incidental and not explain the patient's CNS symptoms. Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram (EEG) and MRI. EEG typically shows diffuse slow-wave activity, although focal changes in temporal regions can be observed in HSV meningoencephalitis. MRI of the brain may demonstrate focal brain lesions that correlate with clinical disease, including temporal lobe involvement to suggest HSV-1 disease. Hyperdense lesions may also be identified on T2 and FLAIR imaging (Fig. 643.1).

A diagnostic approach is noted in Table 643.5.

DIFFERENTIAL DIAGNOSIS

Meningoencephalitis is not exclusively caused by viruses, as other pathogens are also associated with this condition (see Table 643.3). The most important diagnosis to differentiate from meningoencephalitis is bacterial meningitis, given the consequences if that disease is untreated. Most children with acute bacterial meningitis are more critically ill than those with CNS viral infection (with HSV as an exception). Parameningeal bacterial infections, such as brain abscess or subdural or epidural empyema, may have features similar to viral CNS infections. Infections caused by *M. tuberculosis* (see Chapter 261), *T. pallidum* (syphilis, see Chapter 264), and *B. burgdorferi* (Lyme disease, see Chapter 268) may exhibit more indolent clinical courses. *Bartonella henselae* is associated with cat exposure, a papule at the site of inoculation, regional lymphadenopathy, and new-onset seizures (see Chapter 255). *Mycoplasma pneumoniae* has been suggested as a causative pathogen in meningoencephalitis, either as a direct pathogen or a trigger of postinfectious symptoms (see Chapter 269). However, serologic testing for *Mycoplasma* can be nonspecific, and IgM titers can be elevated for several months after infection, leading to incorrect interpretation of a positive result.

Infections caused by fungi, rickettsiae, protozoa, and other parasites may also need to be included in the differential diagnosis. Consideration of these agents usually arises as a result of exposure history, accompanying symptoms, local geographic epidemiology, and host immune factors.

Nonetheless, a significant proportion of patients will have a presentation and clinical testing that is consistent with a diagnosis of encephalitis, but despite exhaustive testing for pathogens, including metagenomic sequencing, no etiology will be identified. In this situation, many clinicians would agree that an infectious cause is less likely but still cannot be fully ruled out. Various noninfectious disorders may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include malignancy, autoimmune diseases, intracranial hemorrhage, and exposure to certain drugs or toxins. Attention to the history and other organ involvement usually allows elimination of these diagnostic possibilities. Autoimmune encephalitis caused by anti–*N*-methyl-D-aspartate (anti-NMDA) receptor antibodies is an important cause of noninfectious encephalitis in adolescents and young adults (see Chapter 638.4). Detection of these antibodies in the serum and CSF confirms this diagnosis. Anti-NMDA receptor encephalitis has also been associated with recent HSV encephalitis, but a mechanism explaining this posited association is unknown. Acute

disseminated encephalomyelitis (ADEM) may also initially be confused with encephalitis (see Chapter 640).

TREATMENT

For most causes of viral meningoencephalitis, no effective antiviral agents exist; therefore treatment is primarily supportive care. Intravenous fluids are typically administered because of poor oral intake. NSAIDs are often used for symptomatic relief of headache. It is important to monitor patients with severe encephalitis closely for seizures, cerebral edema, disturbed fluid and electrolyte balance, aspiration, respiratory failure, and cardiac arrest.

Members of the herpesvirus family can be treated with antivirals, with acyclovir, ganciclovir, cidofovir, and foscarnet having variable activities against these viruses (see Chapters 299-304). Parenteral acyclovir has been specifically shown to dramatically reduce morbidity and mortality rates in HSV-associated meningoencephalitis. When no pathogens are identified and a postinfectious or autoimmune etiology is suspected, patients are in some cases treated with a combination of steroids, intravenous immunoglobulin, and plasmapheresis (see Chapters 638 and 640).

PROGNOSIS

Supportive and rehabilitative efforts are very important after patients recover from the acute phase of illness. Motor incoordination, seizures, total or partial deafness, and behavioral disturbances may follow viral meningoencephalitis. Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur. Some sequelae of infection may be subtle; therefore neurologic, developmental, and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

Recovery from viral infections of the CNS depends on the severity of the clinical illness, the specific causative agent, and the age of

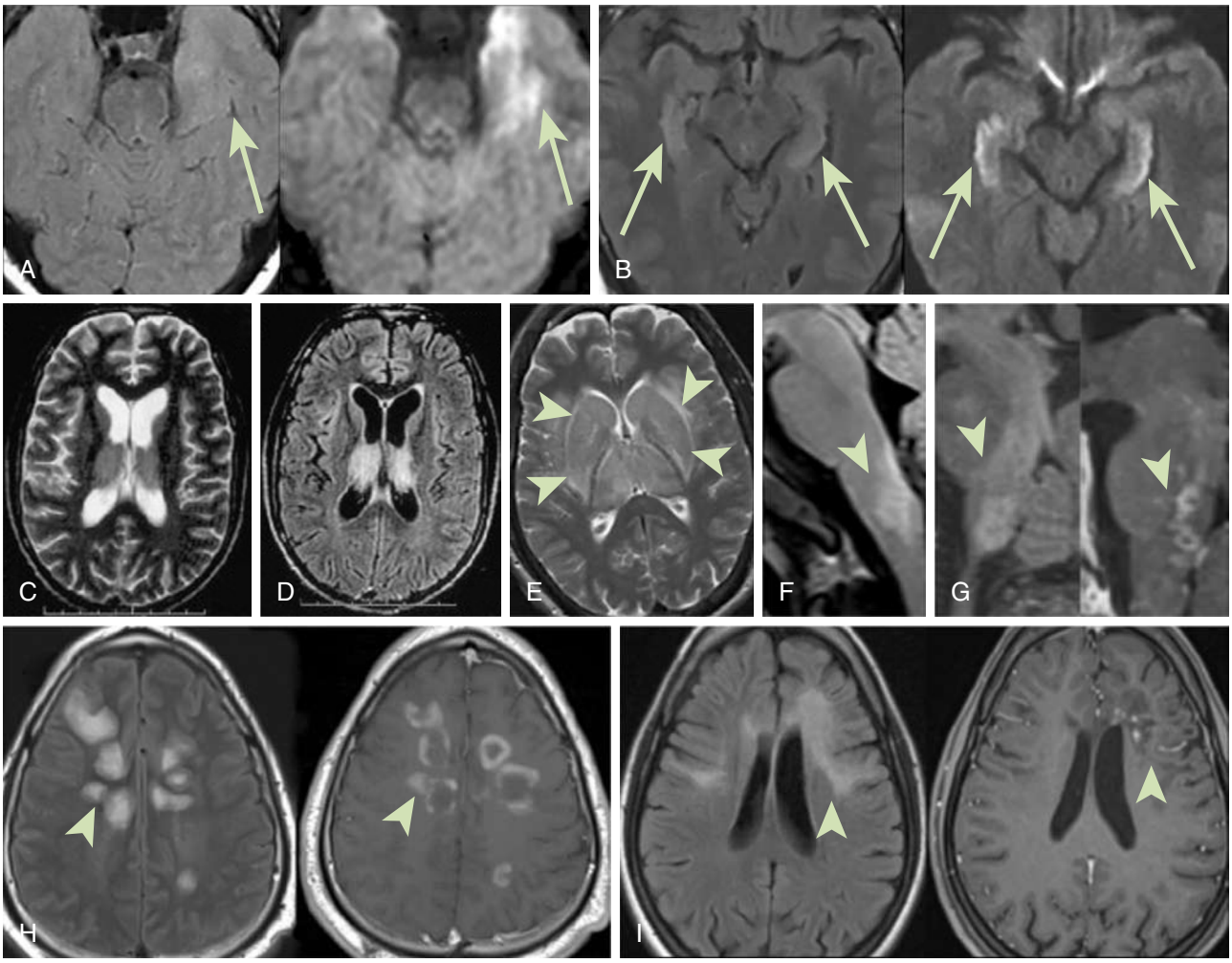

Fig. 643.1 MRI findings in acute encephalitis. Representative images from infectious and autoimmune encephalitides are shown. **A,** Early herpes simplex encephalitis; left temporal lobe abnormalities are more clearly seen on diffusion-weighted imaging (DWI) *(right)* than fluid-attenuated inversion recovery (FLAIR) *(left)*. **B,** Autoimmune limbic encephalitis; bilateral mesial temporal lobe abnormalities seen on both DWI *(right)* and FLAIR *(left)*—note the symmetric nature of the lesions. **C-E,** Arboviral encephalitis; T2-weighted image of a patient with Japanese encephalitis shows hyperintensities in bilateral thalamus **(C)**. The hyperintensities are better visualized in FLAIR image **(D)**. T2-weighted image of patient with **(E)** Eastern equine encephalitis shows increased signal intensity and swelling in the deep gray matter. **F,** Neuromyelitis optica; FLAIR image of a patient who presented with brainstem encephalitis and found to have antibodies to aquaporin-4. **G,** *Listeria* brainstem encephalitis; FLAIR *(left)* and post-gadolinium *(right)* images show T2 abnormalities similar to neuromyelitis optica (NMO) but also multiple rim-enhancing brainstem lesions typical of *Listeria*. **H,** In acute disseminated encephalomyelitis, multifocal areas of T2 hyperintensity are seen on FLAIR *(left)* with characteristic incomplete rims of enhancement after gadolinium administration *(right)*. **I,** In myelin oligodendrocyte glycoprotein encephalomyelitis, multifocal and confluent lesions can be seen on FLAIR imaging *(left)*, and post-gadolinium imaging *(right)* shows patchy areas of enhancement. *(**A, B,** and **F-H,** Modified from Venkatesan A, Michael BD, Probasco JC, et al. Acute encephalitis in immunocompromised adults. Lancet. 2019;393:702–716, Fig. 1, p. 709; **C** and **D,** Modified from Misra UK, Kalita J, Phadke RV, et al. Usefulness of various MRI sequences in the diagnosis of viral encephalitis. Acta Trop. 2010;116[3]:206–211, Fig 1ab; **E,** From Harvala H, Bremner J, Kealey S, et al. Case report: Eastern equine encephalitis virus imported to the UK. J Med Virol. 2009;81[2]:305–308; I, Courtesy Dr Michael Levy, Harvard Medical School.)*

Table 643.5 Laboratory Testing and Neuroimaging Characteristics of Selected Pathogens

	LABORATORY TESTING	CHARACTERISTIC BRAIN MRI FINDINGS
VIRUSES		
HSV	CSF PCR (false negative can occur in first 72 hours). PCR of skin lesions may also be helpful if they occur in conjunction with neurological disease. Blood PCR in neonates. In neonatal CNS disease, CSF PCR is completed near the end of therapy to guide final treatment duration.	For HSV-1: Asymmetric abnormalities in mesiotemporal lobes, orbitofrontal lobes, and insular cortex with edema, possible restricted diffusion or hemorrhage (late stage) HSV-2 in neonates can appear like HSV-1. In adults, HSV-2 meningitis has variable findings (including no abnormalities) or may mimic HSV-1 encephalitis.
Varicella-zoster virus	CSF PCR; skin lesion PCR, biopsy, or DFA for VZV	Could affect temporal lobes, similar to HSV-1; lesions can occur in cerebellum and brainstem; ischemic or hemorrhagic lesions in white matter or gray-white matter junction suggest vasculopathy
Enteroviruses	CSF PCR; Blood PCR; nasopharyngeal swabs can be difficult to interpret as asymptomatic rhino/enterovirus infections are frequently detected. Stool testing only recommended for epidemiological tracing, including for poliovirus or enterovirus D68.	Wide range of findings from normal to diffuse white matter changes. EV 71 causes lesions in the dorsal brainstem, dentate nuclei of cerebellum, and anterior horns of spinal cord. EV D68 often causes lesions of the brainstem, spinal cord with involvement of the central gray matter, and of anterior horn cells.
Parechoviruses	CSF PCR; blood PCR	Variable findings from normal to restricted diffusion of thalami, corpus callosum, subcortical, and periventricular white matter, predominating in the frontal and parietal regions.
Measles*	Serum IgG and IgM; PCR of nasopharyngeal, throat, or urine samples in early infection	Cerebral edema, multifocal lesions, can resemble ADEM in acute setting
Mumps*	CSF and serum IgM and IgG; PCR from throat swab	Lesions in brainstem, hippocampus, and splenium of corpus callosum
Influenza virus	PCR or antigen testing of respiratory secretions; CSF PCR is infrequently positive	Neuroimaging is often normal, although abnormalities can include reversible splenial lesions, deep gray T2 abnormalities, diffuse edema, and hemorrhagic and necrotizing lesions of thalami, brainstem, and cerebellum
Arboviruses (many including alphaviruses such as eastern equine encephalitis, and flaviviruses, such as Japanese encephalitis or West Nile)	CSF and serum IgM and IgG (some viruses will have serological cross-reactivity with related viruses and further confirmation is needed through plaque reduction neutralization testing); CSF PCR (low sensitivity because viral nucleic acid is often absent by the time the patient presents for medical care. Can be useful in immunocompromised individuals); serum PCR (Zika); urine PCR (Zika, West Nile virus)	Up to half will have normal brain MRI; abnormalities might involve deep gray matter (i.e., thalamus, basal ganglia) and brainstem
Rabies virus*	PCR from saliva; PCR and immunofluorescent staining from nuchal skin biopsy or brain tissue; serum and CSF rabies virus neutralizing antibodies	Multifocal abnormalities in temporal cortex, hippocampi, deep gray nuclei, substantia nigra, brainstem, cerebral white matter, gray matter >> white matter
BACTERIA		
Borrelia spp.	Serology (serial EIA and Western blot); VIsE C6 ELISA; CSF antibody index; and CSF PCR (low sensitivity and specificity)	Multifocal lesions in subcortical white matter, potentially mimicking multiple sclerosis
Brucella spp.	Serum and CSF IgG and IgM; CSF culture	Variably enhancing lesions with marked surrounding edema
Listeria monocytogenes	Blood and CSF culture	In rhombencephalitis, multiple small rim-enhancing lesions with variable restriction of diffusion
*Mycobacterium tuberculosis**	CSF AFB smear, culture, and PCR; sputum and blood AFB smear, culture, and PCR (in young children gastric aspirates are obtained instead of sputum). Often testing needs to be repeated (≥3) from the same site to enhance sensitivity; Tuberculin skin test or interferon-gamma release assay	Basilar meningeal enhancement, hydrocephalus, rim-enhancing lesions, and strokes in deep gray matter or internal capsule
Rickettsia and related diseases (*i.e.*, *Anaplasma* spp., *Coxiella burnetti*, *Ehrlichia* spp., and *Rickettsia* spp.)	Serum IgG and IgM; whole blood PCR (useful for *Ehrlichia* and *Anaplasma*); if rash, PCR or immunohistochemical staining of skin biopsy	Reversible splenial lesions; punctate areas of restricted diffusion
Treponema pallidum	Diagnosed via combination of serum and CSF treponemal (e.g., FTA-ABS) and non-treponemal (e.g., serum RPR, CSF VDRL) antibodies, CSF white count, protein	Variable mesial temporal lobe involvement has been described

Continued

Table 643.5 Laboratory Testing and Neuroimaging Characteristics of Selected Pathogens—cont'd

	LABORATORY TESTING	CHARACTERISTIC BRAIN MRI FINDINGS
FUNGI		
Cryptococcus spp.	CSF and serum cryptococcal antigen, CSF culture and PCR. Opening pressure from the lumbar puncture may also be significantly elevated.	Basilar meningeal enhancement and hydrocephalus; cryptococcomas are T1 hypointense and 12 hyperintense lesions in basal ganglia and midbrain
Others (*Coccidioides* spp., *Histoplasma* spp., and *Blastomyces* spp.)	CSF and serum serology; large volume CSF culture; serum and urine antigen	Basilar meningeal enhancement, hydrocephalus, and rim-enhancing lesions
PARASITES AND FREE-LIVING AMEBAE*		
Acanthoemeba spp.	Brain histopathology; CSF and brain tissue PCR and culture; serology	Hemorrhagic and necrotic rim-enhancing lesions
Balamuthia mandrillaris	Brain histopathology; CSF and brain tissue PCR; serology	Multifocal T2-weighted hyperintensities with rim enhancement, surrounding edema, and leptomeningeal extension
Baylisascaris procyonis	CSF and serum antibodies; peripheral or CSF eosinophilia	Multifocal or confluent white matter abnormalities and nodular enhancement
Naegleria fowleri	Wet mount preparation of warm CSF; brain histopathology; CSF and brain PCR and culture	Necrotic and hemorrhagic lesions often in CSF and brain PCR frontal lobes

*Coordinate testing with local, state, and national health departments.
When serum IgM/IgG testing is performed, acute and convalescent titers are typically obtained 1-4 weeks apart. Seroconversion and fourfold or greater rise in titer using paired sera are supportive of infection.
ADEM, Acute disseminated encephalomyelitis; AFB, acid-fast bacillus; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EIA, enzyme immunoassay, EV, enterovirus; FTA-ABS, fluorescent treponemal antibody absorption; HSV, herpes simplex virus; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory; VZV, varicella-zoster virus.
Adapted From Venkatesan A, Michael BD, Probasco JC, et al. Acute encephalitis in immunocompromised adults. *Lancet*. 2019-393-702-716, Table 3, p. 708.

the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor, with potential deficits being intellectual, motor, psychiatric, epileptic, visual, or auditory in nature. Severe sequelae should also be anticipated in those with infection caused by HSV if it was not diagnosed and treated early in the disease. Overall, several studies have found that most children will have persistent symptoms years after the diagnosis of meningoencephalitis. These poor outcomes are likely reflective of a combination of suboptimal diagnostics for identifying pathogens that cause meningoencephalitis and a lack of specific therapies for most viral pathogens.

PREVENTION

For some viruses that cause meningoencephalitis, vaccines are available for prevention. Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases in the United States. Vaccination against Japanese encephalitis virus is also available, but because of high costs, this vaccine has not been widely distributed in Asia. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis.

Control of encephalitis caused by arboviruses has been less successful because specific vaccines are only in various stages of development for clinical trials. The primary method for reducing arbovirus infections is vector control, through methods that include insecticides and eradicating insect breeding sites. Furthermore, minimizing mosquito and tick bites through the application of *N,N*-diethyl-3-methylbenzamide (DEET)–containing insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces risk for arboviral infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

643.3 Eosinophilic Meningitis

Andrew B. Janowski and David A. Hunstad

Eosinophilic meningitis is defined as >10 eosinophils/mm^3 of CSF or a finding that at least 10% of leukocytes in the CSF are eosinophils. The most common cause worldwide of eosinophilic CSF pleocytosis is CNS infection with helminthic parasites. Nonetheless, the differential diagnosis of CSF eosinophilic pleocytosis is broad, especially in countries where helminthic infestation is uncommon, such as the United States (Table 643.6).

ETIOLOGY

Although any tissue-migrating helminth may cause eosinophilic meningitis, the most common worldwide cause is human infection with the rat lungworm, *Angiostrongylus cantonensis* (see Chapter 343). Other parasites that can cause eosinophilic meningitis include *Gnathostoma spinigerum* (dog and cat roundworm; see Chapter 343), *Baylisascaris procyonis* (raccoon roundworm), *Ascaris lumbricoides* (human roundworm, see Chapter 337), *Toxocara canis* (see Chapter 344), *Trichinella spiralis* (see Chapter 345), *Toxoplasma gondii* (see Chapter 336), *Paragonimus westermani, Paragonimus kellicotti, Echinococcus granulosus* (see Chapter 350), *Schistosoma japonicum* (see Chapter 346), *Onchocerca volvulus,* and *Taenia solium* (see Chapter 349). Eosinophilic meningitis may also occur as an unusual manifestation of more common viral, bacterial, or fungal infections of the CNS; for example, coccidioidomycosis has been particularly associated with eosinophilic meningitis. Noninfectious causes of eosinophilic meningitis include multiple sclerosis, malignancy, hypereosinophilic syndrome, or a reaction to medications or ventriculoperitoneal shunt materials.

EPIDEMIOLOGY

A. cantonensis is found in Southeast Asia, the South Pacific, Japan, Taiwan, Egypt, the Ivory Coast, and Cuba. Infection is acquired by eating raw or undercooked freshwater snails, slugs, prawns, or crabs containing infectious third-stage larvae. *Gnathostoma* infections are found in Japan, China, India, Bangladesh, and Southeast Asia. Gnathostomiasis is acquired by eating undercooked or raw fish, frog, bird, or snake meat. *B. procyonis* is endemic in the United States and is acquired by children playing outdoors where raccoons may deposit the organisms (raccoon latrines).

CLINICAL MANIFESTATIONS

Patients with eosinophilic meningitis from helminthic infestation typically become ill 1-3 weeks after exposure, as this reflects the transit time for parasites to migrate from the gastrointestinal tract to the CNS. Concomitant findings include fever, vomiting, abdominal pain, creeping skin eruptions, pleurisy, or peripheral eosinophilia. Neurologic symptoms may include headache, meningismus, ataxia, cranial nerve

Table 643.6 Common Infectious Etiologies of Eosinophilic Meningitis

DISEASE	ETIOLOGIC AGENT	SOURCE	LOCATION	SYMPTOMS	DIAGNOSIS	TREATMENT	PROGNOSIS
Angiostrongyliasis (rat lung worm)	*Angiostrongylus cantonensis* *Angiostrongylus costaricensis*	Definitive host: rats Intermediate hosts: mollusks (snails, slugs) Paratenic hosts: crustaceans, frogs, vegetables	Thailand, China, South America, Caribbean Islands, United States (Hawaii, Louisiana), Australia, Egypt, Nigeria, Côte d'Ivoire	Severe headache Neck stiffness Nausea, vomiting Low-grade fever Hyperesthesia, paresthesia Rarely have focal neurologic deficits Children: more systemic symptoms (fever, abdominal pain)	CSF: eosinophilia, normal glucose, elevated protein, elevated opening pressure, symptomatic relief after lumbar puncture Peripheral blood eosinophilia ELISA (epitopes 29 kDa and 31 kDa) CT head: normal MRI brain: leptomeningeal enhancement, micronodular enhancement	Supportive interventions (repeat lumbar puncture, analgesics) Prednisolone 60 mg/day divided three times a day for 2 weeks Albendazole 15 mg/kg/day orally in two divided doses for 2 weeks	Self-limiting within 3–6 weeks Severe disease can cause coma, respiratory failure, and death (case fatality 5%) Children and elderly may have more severe disease
Gnathostomiasis (neurognathostomiasis)	*Gnathostoma spinigerum*	Definitive host: dogs, cats, pigs, fish-eating mammals Intermediate hosts: freshwater crustaceans Secondary intermediate hosts: freshwater fish, frogs Paratenic hosts: birds, reptiles, mammals	Southeast Asia (Thailand), China, India, Zambia, Botswana, Mexico, Central America, South America	Prodrome: abdominal pain, nausea, vomiting, diarrhea, cutaneous larvae migrans, fever Severe headache Neck stiffness Radicular pain Paresis Paralysis Cranial nerve deficits Seizures	CSF: eosinophilia, xanthochromia, elevated protein, normal glucose Peripheral blood eosinophilia ELISA (24 kDa epitope, immunoglobulin subclasses) CT head: nodular lesions, hemorrhage MRI brain: diffuse or segmental hyperintense micronodules, hemorrhagic tracts, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage	Supportive (repeat lumbar punctures, analgesics) Use of anthelmintics is controversial Steroids may help CNS inflammation Monitor closely for intracranial hemorrhage	Long-term neurologic disability 23–46% of survivors, including paraplegia, paresis, radicular pain, cranial nerve Case fatality rate 7-25%
	Baylisascaris procyonis	Definitive host: raccoons, domesticated dogs, kinkajou Paratenic hosts: small mammals (rabbits, rodents), birds	North America	Lethargy Seizures Sensory loss Ataxia Paralysis Spasticity Cranial nerve deficits Paresis Concurrent ocular involvement Rarely have fever More common in young children	CSF: eosinophilia, variable protein, normal glucose Variable peripheral blood eosinophilia ELISA (epitopes 33 kDa, 45 kDa, BpRAG1 protein) CT head and MRI brain: parenchyma inflammation, cerebral atrophy	Exposure: albendazole (2550 mg/kg per day orally for 1020 days) Treatment: albendazole (2550 mg/kg per day orally for 14 weeks) Corticosteroids	Fulminant eosinophilic meningoencephalitis Severe neurologic impairment Case fatality rate 38%

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 22, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 643.6 Common Infectious Etiologies of Eosinophilic Meningitis—cont'd

DISEASE	ETIOLOGIC AGENT	SOURCE	LOCATION	SYMPTOMS	DIAGNOSIS	TREATMENT	PROGNOSIS
CNS coccidioidomycosis (valley fever)	*Coccidioides immitis*, *Coccidioides posadasii*	Colonized soil in southwestern United States, Mexico, South America	Southwestern United States, Mexico, South America	Additional organ system involvement (lungs, skin, bone, soft tissue) Prodrome: febrile respiratory infection Gradual neurologic symptom onset Headache Vomiting Lethargy Fever	CSF: pleocytosis, elevated protein, decreased glucose, elevated opening pressure, culture CSF complement fixation antibodies	Lifelong fluconazole Ventriculoperitoneal shunt placement	Long-term neurologic sequelae (hydrocephalus, fatal without treatment)

CSF, Cerebrospinal fluid; *CT*, computed tomography; *ELISA*, enzyme-linked immunosorbent assay; *MRI*, magnetic resonance imaging.

From Weatherhead J, Mejia R. Eosinophilic meningitis. In Cherry J, Demmler-Harrison GJ, Kaplan SL, Steinbach W, Hotez PJ, eds. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 8th ed, vol 1, Philadelphia: Elsevier; 2019, Table 34.1. pp 350-351.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 22, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

palsies, and paresthesias. Paraparesis or incontinence can result from radiculitis or myelitis.

DIAGNOSIS

The presumptive diagnosis of helminth-induced eosinophilic meningitis is most often based on travel and exposure history in the presence of typical clinical and laboratory findings. Direct visualization of helminths in CSF is difficult because there typically is a low burden of organisms. Serologic assays for helminthic infections are also of limited utility because they are not readily available commercially and there is substantial cross-reactivity among different helminth species.

TREATMENT

Treatment is supportive, but anthelmintic drugs with or without steroids may be indicated (see Table 643.6). Anthelmintic drugs may provoke an inflammatory response because dying organisms can exacerbate symptoms. However, **treatment of *B. procyonis* should be initiated with albendazole and corticosteroids**. Steroids may decrease the duration of headaches in adults with eosinophilic meningitis. Analgesics should be given for headache and radiculitis, and CSF removal or shunting should be performed to relieve hydrocephalus, if present.

PROGNOSIS

Overall, up to 70% of patients improve significantly within 4 weeks after the onset of symptoms. The mortality rate associated with eosinophilic meningitis is <5%; untreated *Baylisascaris* infection may be fatal or associated with severe sequelae.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 644

Brain Abscess

Andrew B. Janowski and David A. Hunstad

Annually, approximately 0.3-1.3 cases of brain abscess per 100,000 people are diagnosed. Development of brain abscess is most often associated with an underlying etiology, including contiguous spread from an associated infection (meningitis, otitis media, mastoiditis, sinusitis, soft tissue infection of the face or scalp, orbital cellulitis, or dental infections); direct compromise of the blood-brain barrier due to penetrating head injuries or surgical procedures; embolic phenomena (endocarditis); right-to-left shunts (congenital heart disease or pulmonary arteriovenous malformation); immunodeficiency; or infection of foreign material inserted into the central nervous system (CNS), including ventriculoperitoneal shunts (Table 644.1).

PATHOLOGY

Cerebral abscesses occur in both hemispheres in children, but in adults, left-sided abscesses are more common, likely because of penetrating injuries from right-handed assailants. Nearly 80% of abscesses occur in the frontal, parietal, and temporal lobes, whereas abscesses in the occipital lobe, cerebellum, and brainstem account for the remainder of cases. In 18% of cases, multiple brain abscesses are present, and in nearly 20% of cases, no predisposing risk factor can be identified. Abscesses in the frontal lobe are often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with otitis media and mastoiditis.

Table 644.1 Predisposing Conditions and Microbiology of Brain Abscess

PREDISPOSING CONDITION	USUAL MICROBIAL ISOLATES
Otitis media or mastoiditis	Streptococci, *Bacteroides* spp., *Haemophilus* spp., Enterobacteriales, *Pseudomonas aeruginosa*
Sinusitis (frontoethmoid or sphenoid)	Streptococci, *Bacteroides* spp., Enterobacterales, *Staphylococcus aureus*, *Haemophilus* spp., *Fusobacterium* spp.
Dental infection	Streptococci, *Fusobacterium* spp., *Prevotella* spp., *Actinomyces* spp., *Bacteroides* spp., *Haemophilus* spp.
Penetrating trauma or postneurosurgical	*Staphylococcus* spp., streptococci, *Enterobacteriaceae*, *Clostridium* spp., *Cutibacterium* spp.
Lung abscess, empyema, bronchiectasis	Streptococci, *Fusobacterium* spp., *Actinomyces* spp., *Nocardia* spp.
Bacterial endocarditis	*Staphylococcus* spp., streptococci
Congenital heart disease	Streptococci, *Haemophilus* spp.
Neonates	*Streptococcus agalactiae* and other streptococci, Enterobacterales including *Citrobacter koserii*, *Cronobacter sakazakii*, *Serratia marcescens*, *Proteus mirabilis*, *Listeria monocytogenes*, *Candida* spp.
Neutropenia or after hematopoietic cell transplant	Streptococci, Enterobacterales, *Aspergillus* spp., Mucorales, *Candida* spp., *Nocardia* spp., *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, dematiaceous fungi and other mycoses, *Toxoplasma gondii*, *Mycobacterium tuberculosis*
Solid organ transplantation	Streptococci, Enterobacterales, *Aspergillus* spp., Mucorales, *Candida* spp., *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, dematiaceous fungi and other mycoses, *Nocardia* spp., *Toxoplasma gondii*, *Mycobacterium tuberculosis*, *Listeria monocytogenes*
HIV infection	*Toxoplasma gondii*, *Nocardia* spp., *Mycobacterium* spp., *Listeria monocytogenes*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*

Adapted from Gea-Banacloche JC, Tunkel AR. Brain abscess. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 90.1, p. 1249.

ETIOLOGY

The predominant organisms that cause brain abscesses are streptococci, which account for one third of all cases in children, with members of the *Streptococcus anginosus* group (*S. anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*) being the most common streptococci. Other important streptococci include *Streptococcus pneumoniae*, *Enterococcus* spp., and other viridans streptococci. *Staphylococcus aureus* is the second most common organism in pediatric brain abscesses, accounting for 11% of cases, and is most often associated with penetrating injuries. Other bacteria isolated from brain abscesses include gram-negative bacilli (*Haemophilus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp., and other Enterobacterales) and anaerobic bacteria (gram-positive organisms, *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., and *Actinomyces* spp.). In neonates with meningitis, abscess

formation is a complication in 13% of cases, with *Citrobacter koseri, Cronobacter sakazakii, Serratia marcescens,* and *Proteus mirabilis* being special considerations in this age group. In up to 27% of all cases, more than one organism is isolated on routine bacterial cultures. Metagenomics sequencing has revealed that this percentage is likely a significant underestimate, as DNA from additional uncultured species has been detected from purulent abscess fluid, including rare case reports of detection of archaea. Abscesses associated with mucosal infections (sinusitis or dental infections) are more frequently polymicrobial and include anaerobic pathogens. Atypical bacteria, including *Nocardia, Mycobacterium,* and *Listeria* spp., and fungi *(Aspergillus, Candida, Cryptococcus)* are more common in children with impaired host defenses.

CLINICAL MANIFESTATIONS

Often the early stages of cerebritis and abscess formation are asymptomatic or are associated with nonspecific symptoms, including low-grade fever, headache, and lethargy. As the inflammatory process proceeds, vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma may develop. The classic triad of headache, fever, and a focal deficit is noted in <50% of patients. A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache. If an abscess ruptures into the ventricular cavity, overwhelming shock and death may occur.

DIAGNOSIS

The key to diagnosis of brain abscesses is prompt imaging of the CNS. Brain MRI with contrast is the diagnostic test of choice because it can aid in differentiating abscesses from cysts and necrotic tumors (Fig. 644.1). As an alternative, cranial CT can provide more rapid imaging results but cannot provide the fine parenchymal detail offered by MRI (Fig. 644.2). Both MRI and CT scans with contrast can demonstrate a ring-enhancing abscess cavity. CT findings of cerebritis are characterized by a parenchymal low-density lesion, whereas T2-weighted MRI images feature increased signal intensity. Other abnormalities in common laboratory tests can be observed in children with brain abscesses. The peripheral white blood cell count is elevated in 60% of cases, and blood cultures are positive in 28% of cases. Lumbar puncture is not routinely recommended in cases of brain abscess, because the procedure could cause brain herniation from elevated intracranial pressure. When tested, the cerebrospinal fluid (CSF) is normal in 16% of cases, 71% of cases exhibit CSF pleocytosis, and 58% will have an elevated CSF protein level. CSF cultures are positive in only 24% of cases; therefore a culture obtained from the abscess fluid is essential for identifying bacterial pathogens. In some cases, culture of the abscess fluid can be sterile, and alternative testing, including 16S ribosomal RNA sequencing, may be used to identify organisms. An electroencephalogram (EEG) may identify corresponding focal slowing.

TREATMENT

The initial management of brain abscess includes prompt diagnosis and initiation of an antibiotic regimen that is based on the most likely pathogens (Table 644.2). Empiric therapy consists of a combination of a third-generation cephalosporin and metronidazole; often, vancomycin is added to provide coverage of methicillin-resistant *S. aureus* and resistant *S. pneumoniae.* Pharmacokinetics and penetration of the blood-brain barrier are essential considerations when using alternative agents. If resistant gram-negative organisms are suspected, as in cases of infected ventriculoperitoneal shunts, cefepime or meropenem may be used as the β-lactam in the initial regimen. *Listeria monocytogenes* may cause brain abscess in the neonate, and if this etiology is suspected, penicillin G or ampicillin with gentamicin is recommended. In immunocompromised patients, broad-spectrum antibiotic coverage is used, and amphotericin B or azole therapy should be considered for coverage of potential fungi.

Neurosurgical procedures for brain abscess have been greatly enhanced by stereotactic MRI or CT systems, allowing for optimized approaches to minimize morbidity. Aspiration of the abscess is recommended for diagnostic cultures and decompression unless contraindicated based on its location or the patient's condition. There are limited data regarding injection of antibiotics into the abscess cavity, and this technique is not routinely recommended. Small abscesses (under 2.5 cm in diameter) or multiple abscesses may be treated initially with antibiotics and without surgical drainage, with follow-up neuroimaging studies to ensure a decrease in abscess size. Surgical excision of an abscess is rarely required, because such a procedure may be

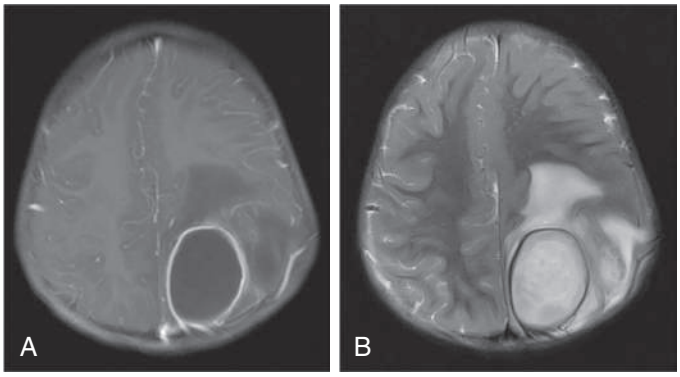

Fig. 644.1 Brain MRI in a 2-yr-old child with an atrial septal defect and brain abscess caused by MRSA. **A,** T1 fl2D postcontrast axial image demonstrating enhancement of the rim of the abscess. **B,** T2 TSE axial image showing a large fluid-filled lesion with surrounding edema.



Fig. 644.2 Brain abscess shown on CT with contrast. Note the large, wall-enhancing abscess in the left frontal lobe causing a rightward parenchymal shift. The patient had no neurologic signs until just before the CT scan, likely because the frontal lobe is a relatively "silent" area of the brain.

Table 644.2 Antimicrobial Therapy for Brain Abscess

ORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPIES
BACTERIA[1,2]		
Actinomyces spp.	Penicillin G	Ampicillin, ceftriaxone
Bacteroides fragilis	Metronidazole	Meropenem
Enterobacterales	Ceftriaxone or ceftazidime	Cefepime, meropenem, fluoroquinolones
Fusobacterium spp.	Metronidazole	Meropenem
Haemophilus spp.	Ampicillin or ceftriaxone/ceftazidime	Cefepime, meropenem
Listeria monocytogenes	Ampicillin or penicillin G + gentamicin	Trimethoprim-sulfamethoxazole, fluoroquinolones
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide + ethionamide or streptomycin	Consultation with an expert at TB Centers of Excellence is recommended for drug-resistant TB
Nocardia spp.	Trimethoprim-sulfamethoxazole + imipenem + amikacin (if involvement outside of the brain)	Minocycline, doxycycline, clarithromycin, ceftriaxone, linezolid
Prevotella melaninogenica	Metronidazole	Meropenem
Pseudomonas aeruginosa	Ceftazidime or cefepime	Meropenem, ciprofloxacin, aztreonam
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin, linezolid
Methicillin-resistant[3]	Vancomycin	Linezolid, trimethoprim-sulfamethoxazole
Streptococcus anginosus (milleri) group, other Penicillin G streptococci	Penicillin G or ceftriaxone	Vancomycin
SELECTED FUNGI		
Aspergillus spp.	Voriconazole	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate, or salvage therapy[4]
Candida spp.	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate (recommended in neonates) + flucytosine (in non-neonates)	Fluconazole, voriconazole
Cryptococcus neoformans	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate + flucytosine	Fluconazole
Mucorales	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate	Salvage therapy[4]
PROTOZOA		
Toxoplasma gondii	Pyrimethamine + sulfadiazine with folinic acid	Pyrimethamine + clindamycin;other options: trimethoprim- sulfamethoxazole; atovaquone

[1]Choice of specific antimicrobial agents for standard therapy, or consideration of alternative therapies, should be based on in vitro susceptibility testing for pathogens for which testing can be performed.
[2]Depending on the pathogenesis of bacterial brain abscess (see text), these bacteria may be isolated as part of a mixed infection.
[3]Other antibiotics with activity against methicillin-resistant *Staphylococcus* spp., daptomycin and ceftaroline, have limited data regarding penetration into the central nervous system. These drugs have been used in cases of salvage therapy.
[4]There is limited evidence for use of alternative anti-fungals for the central nervous system (CNS). Isavuconazole may have good CNS penetration but is understudied. Posaconazole and itraconazole have poor penetration, but successful usage has been reported. Echinocandins, in general, do not penetrate into the CNS.
Adapted from Gea-Banacloche JC, Tunkel AR. Brain abscess. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Philadelphia: Elsevier; 2020: Table 90.4, p. 1257

associated with greater morbidity compared with aspiration of a cavity. Administration of glucocorticoids can reduce edema, though evidence for improved outcomes with steroids is lacking.

The antibiotic regimen may be narrowed or made more specific once abscess culture data are available; importantly, most abscesses are polymicrobial, and not all organisms present may be isolated in culture. The duration of parenteral antibiotic therapy depends on the causative organism(s) and response to treatment (clinically and by imaging) but is typically 6 weeks. There has been interest in shorter regimens or use of oral antibiotics as an alternative to parenteral antibiotics, but clinical data are currently insufficient to support these alternative approaches.

PROGNOSIS

Mortality rates with contemporary use of CT and MRI, improved microbiologic techniques, and prompt antibiotic and surgical management are <10%. Factors associated with high mortality rate at the time of admission include delayed administration of antimicrobials, age <1 year, multiple abscesses, and coma. Long-term sequelae occur in about one third of patients and include hemiparesis, seizures, hydrocephalus, cranial nerve abnormalities, and behavioral and learning difficulties.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 645

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Alasdair P.J. Parker and Pooja D. Harijan

Idiopathic intracranial hypertension (IIH), or pseudotumor cerebri, is frequently considered a potential cause of headache *with* papilledema in children with normal findings on standard brain MRI. A false-positive diagnosis is common, and strategies are needed to avoid this. The pathophysiology remains poorly understood, particularly in children.

IIH is rare, affecting 1 in 100,000-150,000 children, but accurate diagnosis is essential because of the risk of loss of vision. Previously, normal levels of intracranial pressure (ICP) were unclear, leading to overdiagnosis of IIH. Studies in children with ICP monitoring show an upper limit of normal as 10 mm Hg (13.5 cm H_2O) between the ages of 2 and 5 years, with the adult level of cerebrospinal fluid (CSF) pressure being reached by 8 years of age. Currently, the 90th percentile of CSF pressure on lumbar puncture (LP) has been reported to be 28 cm CSF (22 mm Hg) in children age 5 to 18 years, without a significant age effect. Other normal parameters include CSF cell count, protein content, and ventricular size (although this could be slightly decreased on brain MRI). Papilledema may be overdiagnosed. With the advent of orbital coherence tomography (OCT), *B*-ultrasound, and MRI/venography, identification has improved (Figs. 645.1-645.3). Great care should be taken before the diagnosis of IIH, as there is a high rate of misdiagnosis (Fig. 645.4) and management is challenging.

ETIOLOGY

IIH, by definition, will not have an identifiable cause, despite typical findings. A large proportion of children referred to the pediatrician with possible/probable IIH after a thorough history, examination, and careful investigation will have *secondary IH* with an underlying cause identified. Table 645.1 lists some of the many disorders that cause IH with no obstructive lesion on MRI. Research in adults suggests abnormal CSF androgen profiles/endocrine dysfunction leading to abnormal CSF pressure; glucagon-like peptide-1 and 11β-hydroxysteroid dehydrogenase type 1 have been implicated.



Fig. 645.1 Optic nerve ultrasonography. *Left*, A sagittal schematic view of gel applied on top of the closed right eyelid with the orientation of the operator hand and ultrasonography probe to the orbit. *Right*, An ultrasonography machine screen showing a coronal section of the orbit and optic nerve sheath. The distance between the stars represents the diameter of the optic nerve sheath. *(From Koziarz A, Sne N, Kegel F, et al. Bedside optic verve ultrasonography for diagnosing increased intracranial pressure. Ann Intern Med. 2019;171[12]:896–905, Fig. 1, p. 897.)*

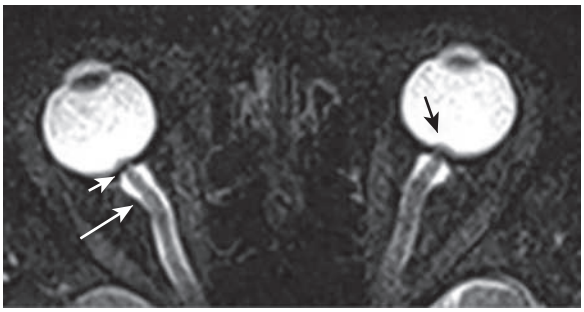

Fig. 645.2 Papilledema. Axial T2-weighted image with fat saturation of the orbits shows enlargement of the optic nerve sheaths *(long white arrow)*, flattening of the posterior sclera *(short white arrow)*, and protrusion of the optic disc head into the globe *(black arrow)*. *(Modified from Guarnizo A, Albreiki D, Cruz JP, et al. Papilledema: a review of the pathophysiology, imaging findings, and mimics. Can Assoc Radiol J. 2022;73[3]:557–567, Fig. 3a, p.561.)*

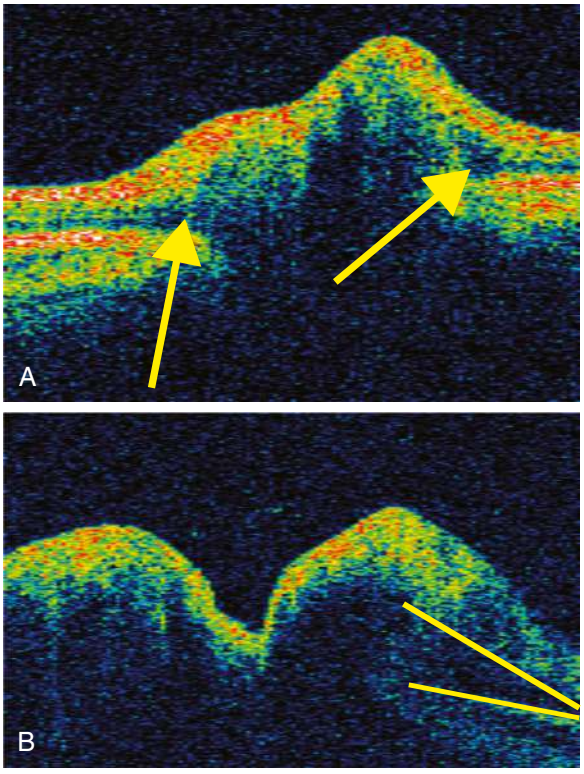

Fig. 645.3 A, Optical coherence tomogram (cross-sectional image) through an optic disc with drusen showing the typically irregular tissue underlying the elevated surface of the disc with no extension of the subretinal hyporeflective layer *(arrows)* beyond the optic nerve head. B, Optical coherence tomogram (cross-sectional image) of a papilledematous optic disc showing a smoothly elevated disc with underlying hyporeflective fluid extending beyond the disc into the subretinal space in a lazy-V pattern (illustrated by *yellow lines*). *(Courtesy Louise Allen, MD, FRCOphth, Cambridge, United Kingdom.)*

CLINICAL MANIFESTATIONS

IIH is rare under the age of 10 years. In postpubertal children, there is a female sex preponderance, and for reasons that are poorly understood, patients are much more likely to be obese. However, most obese children with headache do not have IH and are at risk of false-positive

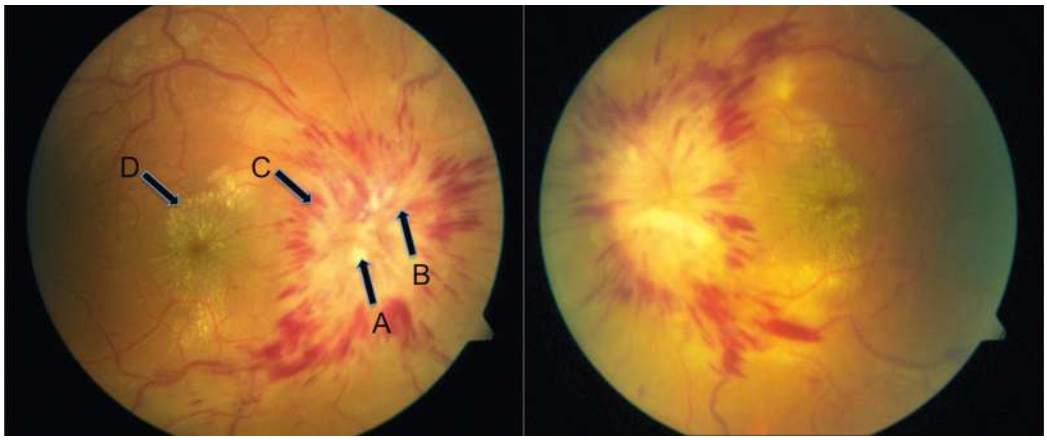

Fig. 645.4 Optic nerve photos of the right and left eyes, respectively, demonstrating grade 5 optic nerve head edema with characteristics, including *(A)* total obscuration of the optic cup, *(B)* total obscuration of a segment of a major blood vessel, *(C)* total obscuration of the disc margin, and *(D)* macular star. *(From Vickers AL, El-Dairi MA. Subacute vision loss in young, obese female. J Pediatr. 2013;163:1518–1519, Fig. 1.)*

Table 645.1 Secondary Intracranial Hypertension Without an Obstructive Lesion on MRI

HEMATOLOGIC DISORDERS	**NUTRITIONAL DISORDERS**
Wiskott-Aldrich syndrome	Hypovitaminosis A
Iron-deficiency anemia	Vitamin A intoxication
Aplastic anemia	Hyperalimentation in malnourished patient
Sickle cell disease	Refeeding syndrome
Polycythemia	Vitamin D–dependent rickets
Bone marrow transplantation and associated treatments	**CONNECTIVE TISSUE DISORDERS**
Prothrombotic states	Antiphospholipid antibody syndrome
Fanconi anemia	Systemic lupus erythematosus
Hemolytic anemia	Behçet disease
INFECTIONS	**ENDOCRINE DISORDERS**
Acute sinusitis	Polycystic ovarian syndrome
Otitis media (lateral sinus thrombosis)	Hypothyroidism
Mastoiditis	Hypoparathyroidism/hyperparathyroidism
Tonsillitis	Pseudohypoparathyroidism
Measles	Congenital adrenal hyperplasia
Roseola	Addison disease
Varicella, recurrent varicella-zoster virus infection	Recombinant growth hormone
Lyme disease	Menarche
HIV or associated treatment complications	**OTHER CONDITIONS**
DRUG-RELATED CONDITIONS	Dural sinus thrombosis
Tetracyclines	Transverse sinus stenosis
Sulfonamides	Obesity (in pubertal patients)
Nalidixic acid	Superior vena cava syndrome
Fluoroquinolones	Sleep apnea
Corticosteroid therapy and withdrawal	Guillain-Barré syndrome
Nitrofurantoin	Crohn disease
Cytarabine	Ulcerative colitis
Cyclosporine	Turner syndrome
Phenytoin	Galactosemia
Mesalamine	Atrial septal defect repair
Isotretinoin	Moebius syndrome
Amiodarone	Sarcoidosis
Oral contraceptive pills/implants	Hypophosphatasia
Valproic acid	Pregnancy
RENAL DISORDERS	
Nephrotic syndrome	
Chronic renal insufficiency	
Post–renal transplantation	
Peritoneal dialysis	

misdiagnosis. The most frequent symptom is chronic (weeks to months), progressive, frontal headache that may worsen with postural changes or a Valsalva maneuver. The headache phenotype attributed to IIH may mimic and/or coexist with chronic migraine and chronic tension-type headache. Calcitonin gene–related peptide has been implicated in the headache attributed to IIH (and in migraine). Although vomiting may occur, it is rarely as persistent and insidious as that associated with a posterior fossa tumor. **Transient visual obscuration (TVO)** lasting seconds and diplopia (secondary to dysfunction of the abducens nerve) may also occur, as may pulsatile tinnitus. TVO is a transient graying out or vision loss often associated with postural changes or Valsalva maneuvers. Children are alert and lack constitutional symptoms. **Papilledema** with an enlarged blind spot is the most consistent sign. It is frequently misdiagnosed. Optic nerve head drusen and/or optic neuritis may be mistaken for papilledema, and failure/delay on treating the latter can lead to irreversible visual

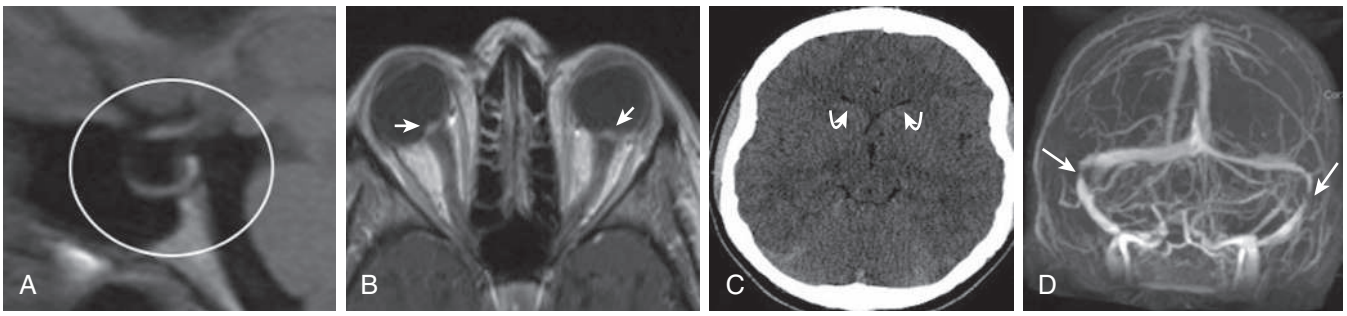

Fig. 645.5 Female with idiopathic intracranial hypertension. **A,** Sagittal T1-weighted image shows a partially empty sella. The pituitary gland is flattened against the floor of the sella, and the rest of the sella is filled with CSF *(circle)*. **B,** Axial T1-weighted postgadolinium image of the orbits demonstrates protrusion of the optic disc heads into the vitreous, with associated enhancement *(arrows)*. **C,** Axial head CT (shows slitlike appearance of the lateral ventricles *(arrows)*. **D,** Coronal CE-MRV MIP image shows focal stenosis at the junction of the transverse and sigmoid venous sinuses *(arrows)*. *(From Guarnizo A, Albreiki D, Cruz JP, et al. Papilledema: a review of the pathophysiology, imaging findings, and mimics. Can Assoc Radiol J. 2022;73:557–567, Fig. 2, p. 560.)*

impairment. OCT (see Fig. 645.3), *B*-ultrasound, and autofluorescence studies are strongly advised in all cases, as these will identify drusen and image the swelling. Inferior nasal or peripheral visual field defects may be detected. The presence of other focal neurologic signs prompts investigations to uncover a process other than IIH. All children should undergo cranial MRI, which may show any of the following: empty sella (in postpubertal children), posterior pituitary stalk displacement, meningoceles, posterior globe flattening, optic nerve head protrusion, optic nerve enhancement, optic nerve sheath distension, optic nerve tortuosity, slitlike ventricles, tight subarachnoid spaces, and inferior position of cerebellar tonsils (Fig. 645.5 and see Fig. 645.2). Absence of these findings does not rule out the diagnosis.

MR venography is essential, both to exclude venous thromboses/stenoses and to identify the tapering of the transverse sinuses that is commonly seen in intracranial hypertension (see Fig. 645.5). All children require measurement of their CSF pressure. Standard opening pressures in cm H_2O using a manometer can be falsely raised when the child is distressed or overflexed. More accurate recording will be achieved using an electronic transducer (similar equipment routinely attaches onto an arterial line), which will give a computer-aided recording with waveform analysis, both on opening and in steady state for 20 minutes (when the child is relaxed, happy, in the lateral decubitus position, and not held tightly or in an overflexed position). Cooperation of the child is required and is helped by the presence of a play specialist or use of nitrous oxide during needle insertion, thereby minimizing factors that may artificially alter ICP such as pain, crying, Valsalva maneuver, or abnormal respiration.

When LP opening pressure is measured under general anesthesia, it is important to record a normal end-tidal partial pressure of carbon dioxide (ET-PCo_2). Because secondary IH is more common, renal, liver, thyroid, hematologic, inflammatory, and autoimmune profiles should be obtained on venous blood testing. CSF infusion studies can also be helpful, particularly in borderline cases. Sterile fluid is infused via the spinal needle, and the resultant pressure-volume data can be analyzed to give the CSF dynamics and variables such as the pulse amplitude of ICP, the compensatory reserve, and the magnitude of slow waves of CSF pressure. Typically in IIH, the CSF pressure is elevated, the resistance to CSF outflow is low, and there is a depleted compensatory reserve. A summary of diagnostic criteria is noted in Table 645.2.

Table 645.2 Diagnostic Criteria for Idiopathic Intracranial Hypertension (IIH)

DIAGNOSIS OF IIH	DIAGNOSIS OF IIH WITHOUT PAPILLEDEMA
Diagnosis of IIH is definite if the patient fulfils A-E: A. Papilledema B. Normal neurologic examination except for sixth cranial nerve abnormalities C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, venous thrombosis excluded in all (best done on MRV) D. Normal CSF composition E. Elevated lumbar puncture opening pressure (≥250 mm CSF in adults; ≥280 in children or obese adults) in an appropriately performed lumbar puncture	In the absence of papilledema, a diagnosis of IIH can be made if B-E are satisfied and in addition the patient has unilateral or bilateral abducens nerve palsy In the absence of papilledema or sixth nerve palsy, a diagnosis of IIH can be suggested, but not made, if B-E are satisfied and in addition at least three of the following are present on neuroimaging: 1. Empty sella 2. Flattening of the posterior aspect of the globe 3. Distention of the perioptic subarachnoid space ± a tortuous optic nerve 4. Transverse venous sinus stenosis

From Mollan SP, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. *J Neurol Neurosurg Psychiatry.* 2018;89(10):1088–1100.

TREATMENT

Any causes of secondary IH should be treated (e.g., withdrawal of a drug). There are no randomized clinical trials (RCTs) to guide the treatment of IIH. The initial diagnostic LP may be therapeutic. The spinal needle produces a small hole in the dura that allows CSF to escape the subarachnoid space, thus reducing ICP. An additional LP and the removal of sufficient CSF to reduce the opening pressure by 50% occasionally lead to resolution of the process. Obese children with IIH need a weight-loss regimen, but the success rate is low. Medical management may include acetazolamide and topiramate. Acetazolamide (10-30 mg/kg/24 hours) has been found effective in adult RCT studies: some authors have recommended using topiramate, which has the added benefits of possible migraine prophylaxis and, in obese children, of being an appetite suppressant. Corticosteroids are not routinely administered because there is no benefit. When the symptoms such as headache and, in particular, visual deterioration, do not improve with an LP and acetazolamide or topiramate, then consideration of surgical management is necessary. In children first-line surgical management is currently CSF diversion (e.g., ventriculoperitoneal [VP] shunt, LP shunt); risks include obstruction and infection. There is a potential role for endovascular management of dural sinus stenosis (the technique of inserting a catheter to direct a self-expanding stent over a guide wire across a venous sinus stenosis)—this is increasingly first-line surgical treatment in adults; pediatric experience is limited. Repeated LP is likely to be traumatic for the child and unlikely to produce a longer-term solution. The value of optic nerve sheath fenestration (a decompressive procedure) is debated and is rarely performed; risks include ischemia and hemorrhage.

Any child whose ICP proves to be refractory to treatment warrants repeat full investigation. Serial monitoring of visual function (i.e., visual acuity, color vision, and visual fields) is required in children old enough to participate but remains a challenge in younger children. Serial optic nerve examination is also essential. OCT is useful to serially follow changes in papilledema. Serial visual-evoked potentials are useful if the visual acuity cannot be reliably documented.

Multidisciplinary management, including a pediatrician, pediatric neurologist, ophthalmologist, orthoptist, radiologist, specialist nurses, and, as needed, dietician, psychologist, interventional radiologist, and neurosurgeon, is helpful both in diagnosis and ongoing management.

The majority of adults with IIH continue to have headache after normalization of ICP and hence require continued headache management. Permanent visual function loss in IIH is rare; data from small studies suggest reduced visual acuity in up to 10% and permanent visual field defects in less than 17% of children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 646

Spinal Cord Disorders

Katie P. Fehnel and Mark R. Proctor

646.1 Tethered Cord

Katie P. Fehnel and Mark R. Proctor

Normally, as the spine flexes and extends, the spinal cord is free to move up and down within the spinal canal. If the spinal cord is fixed at any point, its movement is restricted, and the spinal cord and nerve roots can become stretched. This fixing of the spinal cord, regardless of the underlying cause, is called a *tethered cord*. When pain, neurologic deterioration, or bladder and bowel dysfunction occurs in response to the fixation, it is called **tethered cord syndrome**.

By full gestational age, the spinal cord ends, on average, at the lumbar L1-2 disk space, although there is a normal bell-shaped distribution from thoracic T12-L3. Spinal cord tethering cannot be determined by position of the conus medullaris alone, but a position below L3 is concerning for tethering, especially when associated with an abnormality that connects the cord to the bones or soft tissues around the spine. Similarly, the spinal cord can be tethered even if it terminates in a normal position if a tethering lesion is present. This can occur from a variety of causes.

In its simplest form, tethered cord syndrome results from a thickened filum terminale, which normally extends as a thin, very mobile structure from the tip of the conus to the sacrococcygeal region, where it attaches. When this structure is thickened and/or shortened, the cord can become tethered. This stretching between two points can cause symptoms later in life. Fatty infiltration is often seen in the thickened filum (Fig. 646.1).

Other conditions that are well-established as causes of symptomatic tethering include various forms of occult dysraphism, such as lipomyelomeningocele, myelocystocele, and diastematomyelia. These conditions can be associated with cutaneous manifestations such as midline lipomas, asymmetry of the gluteal fold (Fig. 646.2), dimples, and hairy patches called *hypertrichosis* (Fig. 646.3). Probably the most commonly known type of symptomatic tethered cord involves patients who had previously undergone closure of an open myelomeningocele and later become symptomatic with pain or neurologic deterioration. Tethered cord syndrome can also be iatrogenic and associated with scarring of the spinal cord in patients who have undergone surgical procedures that disrupt the pial surface of the spinal cord.

CLINICAL MANIFESTATIONS

Patients at risk for the subsequent development of tethered cord syndrome can often be identified at birth by the presence of an open myelomeningocele or by cutaneous manifestations of dysraphism (see Chapter 631). It is important to examine the back of the newborn for cutaneous midline lesions (lipoma, dermal sinus, tail, or hairy patch) that may signal an underlying form of occult dysraphism. Dermal sinuses are almost always located *above* the gluteal fold, and dimples in the gluteal cleft directly overlying the coccyx are generally benign fibrous tracts called *coccygeal pits* that are not associated with spinal tethering. However, cutaneous abnormalities may be absent in patients



Fig. 646.1 Sagittal T1-weighted MRI showing thickening and fatty infiltration of the filum terminale *(arrow)* in a patient with a symptomatic tethered spinal cord.



Fig. 646.2 Child with a lipomyelomeningocele demonstrating an extraspinal mass and an asymmetry of the gluteal fold indicative of underlying occult dysraphism. *(Used with permission from Barrow Neurological Institute.)*



Fig. 646.3 Hairy patch or hypertrichosis usually associated with diastematomyelia. *(Used with permission from Barrow Neurological Institute.)*

with tethered spinal cord, and these patients present later in life with clinical manifestations.

Patients who become symptomatic later in life generally present with one of four clinical manifestations, including neurologic, orthopedic, bowel/bladder, and/or pain symptoms. One orthopedic presentation is asymmetry of the feet, with a smaller, high-arched foot with clawing of the toes (Fig. 646.4), sometimes referred to as **neuroorthopedic syndrome**. Characteristically, there is no ankle jerk on the involved side and the calf is atrophied. Scoliosis can also be a presenting sign. Another clinical presentation is increasing urinary urgency, which may progress to incontinence. Constipation progressing to incontinence can affect the gastrointestinal system as well. Finally, severe generalized back pain, often radiating into the lower extremities, can occur, particularly in older adolescents and adults.

DIAGNOSTIC EVALUATION

When patients present with symptoms related to tethered cord syndrome, a thorough motor and sensory examination of the patient must be documented. Assessment of bladder function with an ultrasound of the bladder and urodynamic studies is useful in analyzing bladder innervation. Magnetic resonance imaging (MRI) is the diagnostic study of choice for the anatomy of the tethering lesion and to provide information about the risks of surgical intervention.

TREATMENT

There are no nonsurgical options for the management of tethered cord syndrome. Because the presence of asymptomatic tethering is most likely to be at least suspected in the newborn, prophylactic surgery to prevent late deterioration has been advocated by some neurosurgeons. This strategy remains controversial and depends to some extent on a careful assessment of the risks compared with the benefits. If surgical intervention is chosen, microsurgical dissection with release of the spinal cord attachment to the overlying dura and soft tissues is the goal of treatment.

OUTCOME

The outcome of surgery depends on the complexity of the underlying lesion and the presenting condition of the child because existing deficits are generally not reversed. Releasing a thickened filum terminale or detethering of patients with diastematomyelia generally yields a good outcome, and the chance of recurrent symptoms is quite low. Patients with symptomatic tethered cord who undergo repair of a myelomeningocele or a lipomyelomeningocele have a significant possibility of recurrent tethering and recurrent symptoms. In this cohort, the potential need for reoperation and sometimes even multiple reoperations is high. Given the technical challenges and increased neurologic risk in a patient multiply reoperated on for tethered cord, in adolescent patients for whom axial growth has completed, spinal column shortening procedures have been proposed as an alternative treatment modality. As opposed to surgery at the site of tethering, the tension is released by actual shortening of the vertebral column.



Fig. 646.4 Example of neuropathic changes to the right foot as a result of spinal cord tethering, with a smaller high-arched foot and absent ankle jerk on exam. *(Used with permission from Barrow Neurological Institute.)*

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

646.2 Diastematomyelia (Split-Cord Malformation)

Katie P. Fehnel and Mark R. Proctor

Diastematomyelia is a relatively rare form of occult dysraphism in which the spinal cord is divided into two halves and can present as tethered spinal cord. In **type 1** split-cord malformation, there are two spinal cords, each in its own dural tube and separated by a spicule of bone and cartilage (Fig. 646.5). In a **type 2** split-cord malformation, the two spinal cords are enclosed in a single dural sac with a fibrous septum between the two spinal segments (Fig. 646.6). In both cases, the anatomy of the outer half of the spinal cord is essentially normal but the medial half is extremely underdeveloped. Undeveloped nerve roots and dentate ligaments terminate medially into the medial dural tube in type 1 cases and terminate in the membranous septum in type 2 cases. Both types have an associated defect in the bony spinal segment. In the case of type 2 lesions, this defect can be quite subtle.

CLINICAL MANIFESTATIONS

Patients with both type 1 and type 2 split-cord malformations will have presentations similar to other types of spinal tethering lesions. This may include subtle signs of neurologic involvement, such as unilateral calf atrophy and a high arch in one or both feet early in life, but they are more likely to be neurologically normal. These patients are tethered by the adherence of the spinal cord, so they may develop progressive loss of bowel and bladder function and sensory and motor difficulties in the lower extremities. Back pain is a common symptom in adolescents and adults with split-cord malformation but is uncommon in small children.

Cutaneous manifestations of dysraphism are present in 90% of patients with split-cord malformations. Large, hairy, midline patches called *hypertrichosis,* the most common cutaneous manifestations, are present in approximately 60% of the cases.

DIAGNOSTIC EVALUATION

MRI, the study of choice, shows the two spinal cords. The frequent association of bony abnormalities in this condition may require further evaluation with computed tomography (CT).

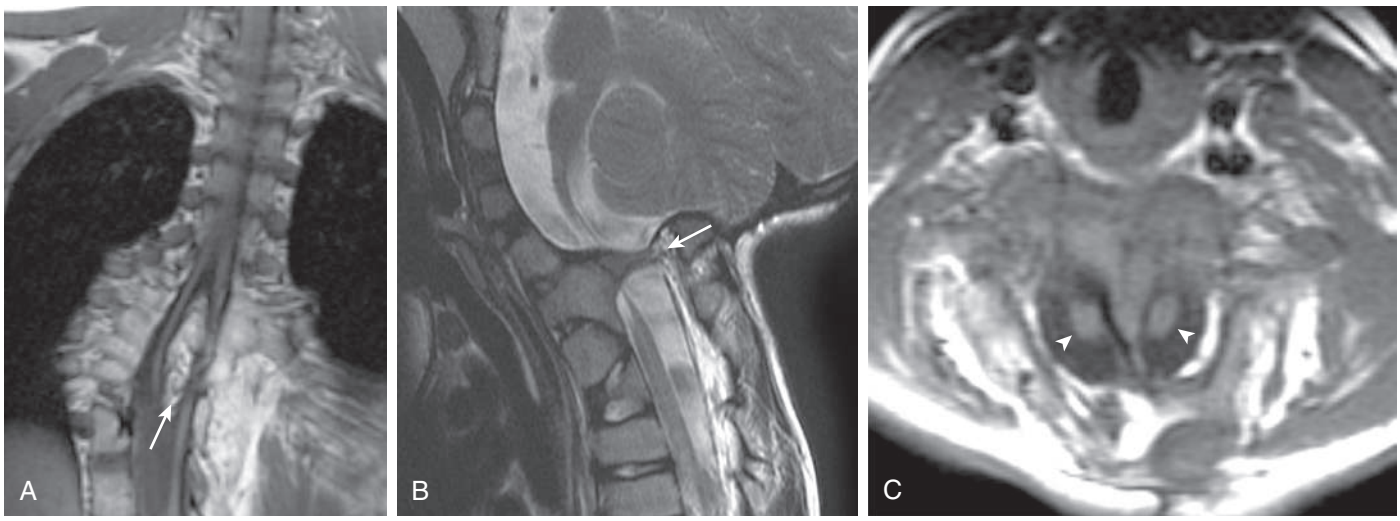

Fig. 646.5 Diastematomyelia type 1. **A**, Coronal T1-weighted MRI in a patient with type 1 DSM shows a large ossified spur *(arrow)* that splits the thoracic spinal cord. Numerous vertebral segmentation anomalies with posterior rib fusions are present. Sagittal T2-weighted (**B**) and axial T1-weighted (**C**) MRI of a different patient shows a type 1 cervical DSM with ossified spur (*arrow* in **B**) and two hemicords (*arrowheads* in **C**). *(From Moore KR. Congenital abnormalities of the spine. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 43-12.)*

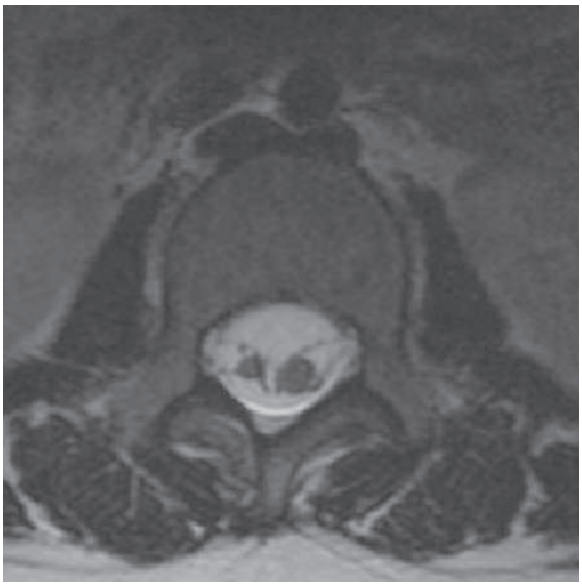

Fig. 646.6 Diastematomyelia type 2. Axial T2-weighted MRI in a patient with type 2 DSM shows the spinal cord split into two hemicords within a single dural tube. No fibrous or osseous septum was identified. *(From Moore KR. Congenital abnormalities of the spine. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 43-13.)*

TREATMENT

The treatment of split-cord malformation is surgical. This abnormality is a form of tethered cord syndrome, and its treatment is to release the spinal cord to move freely with movement of the spine. In type 1 split-cord malformations, the two half-cords are in separate dural sacs with medial attachment to the dura and bony septum. In this case, the dura needs to be opened, the bony septum removed, the medial attachments to the dura lysed, and a single dural tube created. For type 2 lesions, the membranous septum should be lysed. An attachment of this membrane to the anterior dura should be explored and lysed as well. Retethering of this type is rare, as there is no reason to disrupt the pial layer of the spinal cord.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

646.3 Syringomyelia

Katie P. Fehnel and Mark R. Proctor

Syringomyelia is a cystic distention of the spinal cord caused by obstruction of the flow of spinal fluid from within the spinal cord to its point of absorption. There are three recognized forms of syringomyelia, depending on the underlying cause. Communicating syringomyelia implies that cerebrospinal fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord and is assumed to be the source of the CSF that distends the spinal cord. Noncommunicating syringomyelia implies that ventricular CSF does not communicate with the fluid within the spinal cord. It primarily occurs in the context of intramedullary tumors and obstructive lesions. In the final form of syringomyelia, that is, posttraumatic syringomyelia, spinal cord injury results in damage and subsequent softening of the spinal cord. This softening, combined with the scarring of the surrounding spinal cord tissue, results in progressive distention of the cyst. Syringomyelia is highly associated with Chiari malformation and can also be seen after infection or trauma, but many cases seen on imaging are normal anatomic variants unassociated with syndromes or any symptoms. It is also associated with connective tissue disorders (Ehlers-Danlos syndrome).

CLINICAL MANIFESTATIONS

Signs and symptoms of syringomyelia develop insidiously over years or decades. The classic presentation is **central cord syndrome**. Syringomyelia affects the spinal cord beginning from the central region, where the cervical and thoracic nerve fibers are located, so it less commonly affects the lumbar and sacral fibers, which are more laterally located in the spinal cord. Therefore in syringomyelia the patient develops numbness beginning in the shoulder in a capelike distribution followed by the development of atrophy and weakness in the upper extremities. Trophic ulcers of the hands are characteristic of advanced cases.

Other forms of presentation include scoliosis that may be rapidly progressive and often can be presumed from the absence of superficial abdominal reflexes. Urgency and bladder dysfunction as well as lower extremity spasticity also may be part of the presentation.

In patients with syringomyelia related to significant prior spinal cord injury, the presentation is usually severe pain in the area of the spinal cord distention above the level of the initial injury. There is also an ascending level of motor and sensory dysfunction.

DIAGNOSTIC EVALUATION

MRI is the radiologic study of choice (Figs. 646.7 and 646.8). The study should include the entire spine, and gadolinium-enhanced sequences should be a part of it if there is a suspicion for tumor. Specific attention should be paid to the craniovertebral junction because of the frequent association of syringomyelia with Chiari malformations. Obstruction to the flow of CSF from the fourth ventricle can cause syringomyelia; therefore most patients also should undergo imaging of the brain if a Chiari malformation is seen on the cervical imaging.

TREATMENT

The treatment of syringomyelia should be tailored to the underlying cause, and rarely is the syringomyelia addressed directly. If that cause can be removed or ameliorated, the syrinx should improve. Direct surgery on the syrinx is associated with a much higher surgical risk profile.

Communicating syringomyelia is most frequently seen in the context of abnormalities at the craniovertebral junction, often associated with Chiari malformations (see Fig. 646.7). In such cases, decompression of the craniovertebral junction is usually effective in the management of the syringomyelia. In the context of Chiari II malformation associated with spina bifida, syringomyelia usually results from an insidious failure of the shunt used to treat the hydrocephalus. This distention of the spinal cord results in a rapid development of scoliosis and occasionally spasticity in the lower extremities. Repair of the shunt is often effective treatment, and only rarely is surgical decompression at the craniovertebral junction necessary. Other conditions that can cause obstruction at the craniocervical junction include inflammatory conditions such as chronic meningitis, as seen in tuberculosis or meningeal carcinomatosis.

Noncommunicating syringomyelia results from blocking the flow of spinal cord extracellular fluid or CSF within the central canal by an intramedullary spinal cord tumor or severe external compression of the spinal cord. In such cases, management should be directed to tumor resection or to decompression of constricting elements.

Traumatic syrinxes result from hematomyelia in the substance of the spinal cord coupled with severe arachnoidal scarring around the circumference of the spinal cord. When progressive, this form of syringomyelia is treated by exploration and lysis of the adhesions that fix the spinal cord to the overlying dura. Microscopic lysis of the scar surrounding the spinal cord at the point of injury allows the spinal cord to collapse and prevents it from being distorted by a hydrostatic column of spinal fluid pulsations.

In rare cases, direct drainage procedures must be employed and can result in symptomatic and radiographic improvement. Syrinx-to-subarachnoid or pleural shunting with a small piece of silicone tubing is the treatment option. These procedures often have short-lived success because the tubing tends to become obstructed, so they should be reserved for cases with obstructive symptoms.

In the current era, where many children are undergoing spinal MRI, some children who demonstrate no neurologic deficits are being referred to pediatric neurosurgeons with the diagnosis of syringomyelia. Many of these children were scanned because of back pain or as part of a screening for scoliosis. They are found on MRI to have a **persistent central canal**, and the diagnosis of syringomyelia is made. These syrinxes are 1-3 mm in diameter and may extend over several segments (see Fig. 646.8). There is no distortion of the spinal cord in the region and no change in signal of the surrounding spinal cord. These syrinxes have been called "idiopathic" syrinxes. Follow-up of significant numbers of such children has shown them to be benign in nature and probably represent a normal variant. There does not seem to be a need for routine follow-up imaging without new symptoms. They need no treatment and do not require limitations of activity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 646.7 Sagittal MRI of patient with a Chiari I malformation and a holocord syrinx. *(Used with permission from Barrow Neurological Institute.)*



Fig. 646.8 T2-weighted MRI scan of the cervical and thoracic spinal cord showing dilation of the central canal (C5-T1) in the absence of a Chiari malformation or other pathology.

646.4 Spinal Cord Tumors

Katie P. Fehnel and Mark R. Proctor

Tumors of the spine and spinal cord are rare in children. Different types of tumors have different relationships with the spinal cord, meninges, and bony elements of the spine (Fig. 646.9). Intramedullary spinal cord tumors arise within the substance of the spinal cord itself (Fig. 646.10). They represent between 5% and 15% of primary central nervous system tumors. This percentage may well reflect the relative volume of spinal cord compared with brain. Approximately 10% of intramedullary spinal cord tumors are malignant astrocytic tumors, but most are World Health Organization grade I or II tumors of glial or ependymal origin. In children, low-grade astrocytomas and gangliogliomas represent the most common tumor types, with ependymomas being less common than in adults.

Except in the context of neurofibromatosis (NF-1 and NF-2; see Chapter 636.1), intradural extramedullary tumors are extremely rare in children. Most are nerve sheath tumors, either schwannomas or neurofibromas. Intraspinal meningiomas in children are essentially found only in patients with NF-2 or those who have undergone prior irradiation for some reason. The intradural extramedullary compartment is also a site for metastatic tumors from primary cancers such as leukemia or primitive neuroectodermal tumors. Myxopapillary ependymoma, a benign subtype found in the filum terminale, is another extramedullary tumor seen in children.

Extradural spinal tumors characteristically begin in the bones of the spine. Primary tumors in this location include aneurysmal bone cysts, Langerhans cell histiocytosis (formerly called *eosinophilic granuloma*), osteoid osteoma, and giant cell tumors. In infants, the extradural space is often the site of neuroblastomas or ganglioneuroblastomas, which tend to extend from a paraspinal location into the epidural space through the intervertebral foramen. In older patients, the bones of the spine may be the site of multiple myeloma and metastases from common malignant tumors, such as chordoma and sarcomas.

CLINICAL MANIFESTATIONS

With the exception of the uncommon malignant glial tumors of the spinal cord, which tend to present precipitously, intramedullary spinal cord tumors present in a very insidious manner. Back pain related to the level of the tumor is a common presenting complaint. It is likely that this pain will awaken the child from sleep and improve as the day progresses. Before the use of MRI became routine, the time from the first onset of symptoms to diagnosis of the tumor could be very prolonged, extending years. Weakness, gait disturbance, and sensory deficits are usually subtle but detectable on formal neurologic examination. Scoliosis, limb asymmetry, and bowel or bladder disturbance may be the presenting complaints associated with intramedullary spinal cord tumors.

Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and present with symptoms and signs relative to the nerve root involved. Pain in a bandlike distribution around the chest or into an extremity is the most common presenting complaint. Tumor growth eventually leads to spinal cord compression and involvement of adjacent nerve roots, but pain is the more likely presenting symptom.

Extramedullary extradural tumors have a tendency to present more acutely owing to rapid growth within a confined space. Such children may present with acute paresis and urinary retention. They can also present abruptly with severe pain and neurologic deficit at the time of pathologic fracture of the vertebral body. Benign tumors such as giant cell tumors and aneurysmal bone cysts present more insidiously as the tumor slowly grows and begins to compress neural structures. Osteoid osteomas present with severe pain relieved by nonsteroidal antiinflammatory drugs.

DIAGNOSTIC EVALUATION

MRI with and without gadolinium enhancement of the spinal cord is the diagnostic study of choice and is essential in the diagnosis of spinal cord tumors, especially intramedullary spinal cord tumors. Most

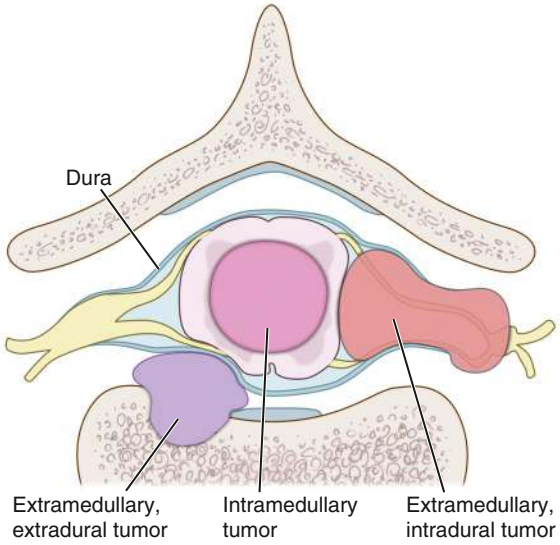

Fig. 646.9 Diagram of the relationship of various tumors to the spine, nerve roots, and spinal cord. *(Used with permission from Barrow Neurological Institute.)*



Fig. 646.10 T1 weighted MRI scan of a spinal cord tumor *(arrow)*. The fusiform expansion of the cervical cord enhances after intravenous gadolinium injection.

astrocytic tumors of the spinal cord and most ependymomas show diffuse enhancement and will distend the spinal cord focally. These tumors may involve the entire length of the spinal cord (holocord astrocytomas), although much of the change might be due to the associated syrinx. Nerve sheath tumors characteristically enhance and are focal. They may exit through the neural foramen and distend the canal, as can be seen on MRI. They also may be visualized on plain radiographs of the affected area of the spine because of their chronic effect on the bones.

Plain radiographs of the spine are helpful in defining the relationship of extradural tumors to the bony spine and in documenting evidence of instability in the case of pathologic compression fractures. When a pathologic fracture occurs, CT is essential to determine the effect of the tumor on the bone. Because many of these tumors occur as metastatic lesions, a general staging of the extent of disease is essential. In the

case of Langerhans cell histiocytosis, a thorough bone survey should be conducted to look for other lesions. Radionucleotide bone scanning, rapid STIR MRI, or PET MRI scans are useful in determining the extent of the disease.

TREATMENT

The primary treatment of both intramedullary and extramedullary intradural tumors is surgical removal. For both low-grade astrocytomas and ependymomas, microsurgical removal with the intent of total removal is the treatment of choice. This goal should be attainable in most patients with ependymomas and gangliogliomas and in many patients with low-grade astrocytomas. Though the majority of intramedullary spinal cord tumors are benign, the extent of resection may be limited in tumors that are diffusely infiltrating midline gliomas because of tumor invasion and infiltration of gray and white matter tracts. The invasive nature of these tumors is a leading cause of the poor prognosis for many of these patients, resulting in symptom progression and ultimately loss of neurologic function with profound implications on both quality and extent of life and is one of the most significant problems in spinal neurooncology. With the advent of routine molecular genetic testing, targetable pathogenic variants have been identified in some intramedullary spinal cord tumors, which will potentially expand nonsurgical and chemotherapeutic treatment options in as of now unresectable spinal cord tumors. Adjunctive treatment is often unnecessary in patients treated with adequate surgical resection. Likewise, schwannomas should be resectable. Occasionally, however, the nerve root must be resected. Doing so may be of no consequence in the thoracic spinal cord, but an attempt to remove the tumor while salvaging the motor root in the cervical and lumbosacral region is critical to preserve movement. Malignant astrocytic tumors cannot be resected without major morbidity and, in any case, carry an extremely poor prognosis. In the case of grades III and IV astrocytomas of the spinal cord, decompression and biopsy followed by radiation therapy and possibly chemotherapy are used.

The diagnosis and treatment of extramedullary spinal cord tumors must be individualized. Patients with bony involvement may be at risk of instability, and treatment will therefore involve both tumor resection and stabilization of the spine. For extramedullary tumors with soft tissue components such as neuroblastomas, treatment is determined by the nature of the tumor and degree of spinal cord compression and may require needle biopsy of the lesion to direct treatment. In the absence of significant neurologic compression, surgical intervention may not be indicated if adjuvant therapies might be effective.

OUTCOME

The prognosis for patients with benign intramedullary spinal cord tumors depends, to some extent, on the patient's condition at the time of surgical intervention. It is very unlikely that nonambulatory patients will improve after surgery, and most patients will have at least transient worsening with surgery. If, however, patients are ambulatory at the time of surgery, they are likely to recover at least to their preoperative level of function. The majority of intramedullary tumors in children are benign and behave like tumors with the same histologic findings in the brain. The evidence would point to the fact that intramedullary ependymomas act in a more benign fashion than they do in the fourth ventricle. Gross total removal without adjuvant treatment is the preferred method of treatment and carries not only a much longer progression-free survival time but an improved quality of life as well.

Malignant spinal cord tumors are usually lethal, with death resulting from diffuse metastases via the CSF pathways. Successful resection of nerve sheath tumors should be curative. In the context of neurofibromatosis, however, many more tumors can be found at other levels or can be expected to develop later in life. Surgical intervention in the context of neurofibromatoses should be performed only for clearly symptomatic lesions.

The outcome of treatment of extramedullary tumors depends on the cell type and, in most cases, on the efficacy of nonsurgical, adjunctive therapies. For aneurysmal bone cysts and giant cell tumors, resection of the tumor and fusion of the spine are the treatments of choice.



Fig. 646.11 T2 weighted MRI showing an extensive thoracic spinal arteriovenous malformation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

646.5 Spinal Arteriovenous Malformations

Katie P. Fehnel and Mark R. Proctor

Arteriovenous malformations of the spinal cord are rare lesions in children. Only about 60 patients younger than age 18 years are treated in the United States each year. These lesions are complex, and despite their rarity there are multiple subtypes, which require different treatment strategies. Patients commonly present with back or neck pain, depending on the segments of the spinal cord involved, and they may experience the insidious onset of motor and sensory disturbances. Sudden onset of paraplegia secondary to hemorrhage has been reported. Occasionally, patients present with subarachnoid hemorrhage without overt neurologic deficits, similar to the presentation associated with cerebral aneurysms. In some cases, bruits are audible upon auscultation over the bony spine.

DIAGNOSTIC EVALUATION

When a spinal arteriovenous malformation is suspected, MRI of the spinal cord is first needed to make the diagnosis and to obtain a general idea of the location of the lesion (Fig. 646.11). MR angiography or CT angiography may provide further information, but formal catheter angiography of the spinal cord is needed to obtain an adequate understanding of the complex anatomy of the lesion and to plan the intervention.

TREATMENT

Open microsurgery had been the mainstay of treatment for spinal cord arteriovenous fistulas and arteriovenous malformations. With the rapid development of interventional techniques, the percentage of patients undergoing microsurgery has decreased from 70% to approximately 30%. Stereotactic radiosurgery may be used adjunctively. Treatment of these complex lesions requires the commitment of an organized neurovascular treatment program.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Neuromuscular Disorders

PART XXVI

Chapter 647

Evaluation and Investigation of Neuromuscular Disorders

*Adnan Y. Manzur**

The term *neuromuscular disease* defines disorders of the motor unit and excludes influences on muscular function from the brain, such as spasticity. The motor unit has four components: a motor neuron in the brainstem or ventral horn of the spinal cord; its axon, which together with other axons forms the peripheral nerve; the neuromuscular junction; and all muscle fibers innervated by a single motor neuron. The size of the motor unit varies among different muscles and with the precision of muscular function required. In large muscles, such as the glutei and quadriceps femoris, hundreds of muscle fibers are innervated by a single motor neuron; in small, finely tuned muscles, such as the stapedius or the extraocular muscles, a 1:1 ratio can prevail. The motor unit is influenced by suprasegmental or upper motor neuron control that alters properties of muscle tone, precision of movement, reciprocal inhibition of antagonistic muscles during movement, and sequencing of muscle contractions to achieve smooth, coordinated movements. Suprasegmental impulses also augment or inhibit the monosynaptic stretch reflex; the corticospinal tract is inhibitory upon this reflex.

Diseases of the motor unit are common in children. These neuromuscular diseases may be genetically determined, congenital or acquired, acute or chronic, and progressive or static. Because specific therapy is available for many diseases and because of genetic and prognostic implications, a precise diagnosis is important; laboratory confirmation is required for most diseases because of overlapping clinical manifestations. Precise genetic diagnosis, to the point of characterization of the specific pathogenic gene variant, is crucial for the genetically based neuromuscular disorders because of increasing availability of specific genetic-based treatments; examples include nonsense variants and exon-specific treatments in Duchenne muscular dystrophy, and gene therapy chromosome 5q linked spinal muscular atrophy.

GENETIC TESTING

Many chromosomal loci are identified with specific neuromuscular diseases as a result of genetic linkage studies and the isolation and cloning of specific genes. In some cases, such as Duchenne muscular dystrophy, the genetic variant is a deletion, duplication, or point variant of nucleotide sequences and is associated with a defective protein product, dystrophin. In other cases, such as myotonic muscular dystrophy, the genetic variant is an expansion or repetition, rather than a deletion, in a codon (a set of three consecutive nucleotide repeats that encodes for a single amino acid), with many copies of a particular codon (in this example they are also associated with abnormal messenger RNA). Some diseases manifest as autosomal dominant and autosomal recessive traits in different pedigrees; these distinct mendelian genotypes can result from different genetic variants on different chromosomes (nemaline myopathy) or from small differences in the same gene at the same chromosomal locus (myotonia congenita), despite many common phenotypic features and shared histopathologic findings in a muscle biopsy specimen. Among the several clinically defined mitochondrial myopathies, specific mitochondrial DNA deletions and transfer RNA point variants are recognized. The inheritance patterns and chromosomal and mitochondrial loci of common neuromuscular diseases affecting infants and children are summarized in Table 648.2 in Chapter 648.

Genotype:phenotype correlations are not always as precise as one would like for diagnosis; many genetic variants, even on different chromosomes, cause the same phenotype, and the converse is also true in that the same pathogenic genetic variant may yield many clinical phenotypes in different patients. Even a disease as stereotyped and predictable as Duchenne muscular dystrophy is known to be associated with dozens of different genotype variations, in and out-of-frame deletions and point variants of the large dystrophin gene. This explains why specific therapies might be beneficial for some patients and not alter the natural course of the disease in others.

CLINICAL MANIFESTATIONS

Examination of the neuromuscular system includes an assessment of muscle bulk, tone, and strength. Tone and strength should not be confused: **passive tone** is range of motion around a joint, and a**ctive tone** is physiologic resistance to movement. Head lag when an infant is pulled to a sitting position from supine is a sign of weakness, not of low tone. Hypotonia may be associated with normal strength or with weakness; enlarged muscles may be weak or strong; and thin, wasted muscles may be weak or have unexpectedly normal strength. The distribution of these components is of diagnostic importance. In general, myopathies follow a proximal distribution of weakness and muscle wasting (with the notable exception of myotonic muscular dystrophy). Neuropathies are generally distal in distribution, with the notable exception of chromosome 5q spinal muscular atrophy (SMA 0,1,2,3; Table 647.1). Involvement of the face, tongue, palate, and extraocular muscles provides an important distinction in the differential diagnosis. **Tendon stretch reflexes** are generally lost in neuropathies and in motor neuron diseases and are diminished but preserved in myopathies (see Table 647.1). A few specific clinical features are important in the diagnosis of some neuromuscular diseases. **Fasciculations** of muscle, which are often best seen in the tongue, are a sign of denervation. Sensory abnormalities indicate neuropathy. Fatigable weakness is characteristic of neuromuscular junctional disorders. Myotonia is specific for myotonic dystrophy and non-dystrophic myotonias also described as skeletal muscle channelopathies.

Some features do not distinguish myopathy from neuropathy. Muscle pain or **myalgias** are associated with acute disease of either myopathic or neurogenic origin. Acute dermatomyositis and acute polyneuropathy (Guillain-Barré syndrome) are characterized by myalgias. Muscle pain is unusual in most muscular dystrophies and spinal muscular atrophies at presentation, but myalgia and cramps on exercise are a characteristic feature of Becker muscular dystrophy. Myalgias also occur in several metabolic diseases of muscle and in ischemic myopathy, including vascular diseases such as dermatomyositis. Myalgias denote the acuity, rather than the nature, of the process, so that progressive but chronic diseases, such as muscular dystrophy and spinal muscular atrophy, are not painful, but acute stages of inflammatory myopathies and acute denervation of muscle often do present with muscular pain and tenderness to palpation. **Contractures** of muscles, whether present at birth or developing later in the course of an illness, occur in both myopathic and neurogenic diseases.

* The editors are grateful to Dr. Harvey B. Sarnat, much of whose work on previous editions of this chapter is retained here.

Table 647.1 Localization of Symptoms on Neural Axis

	UPPER MOTOR UNIT		LOWER MOTOR UNIT			
	BRAIN	SPINAL CORD	ANTERIOR HORN CELL / ALPHA MOTOR NEURONS	PERIPHERAL NERVE	NEUROMUSCULAR JUNCTION	MUSCLE
Level of consciousness	↓	Normal	Normal	Normal	Normal	Normal
Strength	Mild to moderate ↓	Mild to moderate ↓	Marked ↓	Marked ↓	Marked ↓	Marked ↓
Tone	Spastic (hypotonia at onset possible)	↓ Acutely; ↑	↓, flaccid	↓	↓	↓
Deep tendon reflexes	Normal to ↑	↓ Acutely; ↑	↓ to absent	↓ to absent (lost early)	Normal	Normal to ↓ to absent
Babinski	Present	Present usually	Absent	Absent	Absent	Absent
Fasciculations	Absent	Absent	Present	Rarely	Absent	Absent
Atrophy	Mild to moderate	Mild to moderate	Present	Present	Absent	Present Pseudohypertrophy
Sensation	Normal	Absent below level of lesion	Normal	Abnormal in defined peripheral nerve distribution or glove/stocking	Normal	Normal
Creatine kinase level	Normal	Normal	Normal to moderately elevated (several 1,000s IU/L)	Normal or mildly elevated (100s IU/L)	Normal	Normal to severely elevated
Overall pattern	Hemibody deficits	Spinal level present	Proximal weakness in SMA; asymmetric weakness in other diseases	Distal, length-dependent usually, defined nerve territory	Symmetric, painless weakness of tonically active muscles	Proximal > distal weakness
Other	Seizures Developmental delay Regression Cortical signs (e.g., language)	Radicular back pain, bowel/bladder dysfunction			Fluctuating diurnal variation Fatigability	Myalgia, Gower sign

SMA, Spinal muscular atrophy.
From Konersman C. Hypotonia and weakness. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 35.3, p. 572.

Infant males who are weak in late fetal life and in the neonatal period often have **undescended testes.** The testes are actively pulled into the scrotum from the anterior abdominal wall by a pair of cords that consist of smooth and striated muscle called the gubernacula. The gubernacula are weakened in many congenital neuromuscular diseases, including spinal muscular atrophy, myotonic muscular dystrophy, and many congenital myopathies.

The thorax of infants with congenital neuromuscular disease often has a funnel shape, and the ribs are thin and radiolucent as a result of intercostal muscle weakness during intrauterine growth. This phenomenon is characteristically found in infantile spinal muscular atrophy but also occurs in myotubular myopathy, neonatal myotonic dystrophy, and other disorders (Fig. 647.1). Because of the small muscle mass, the birthweight may be low for gestational age.

Generalized hypotonia and motor developmental delay are the most common presenting manifestations of neuromuscular disease in infants and young children (Table 647.2 and Figs. 647.2-647.4). These features can also be expressions of neurologic disease, endocrine and systemic metabolic diseases, and Down syndrome, or they may be nonspecific neuromuscular expressions of malnutrition or chronic systemic illness (Table 647.3). A prenatal history of decreased fetal movements and intrauterine growth retardation is often found in patients who are symptomatic at birth. Developmental disorders tend to be of slow onset and are progressive. Acute flaccid paralysis in older infants

and children has a different differential diagnosis (Tables 647.4 and 647.5; see Fig. 647.3).

LABORATORY FINDINGS

Serum Enzymes

Several lysosomal enzymes are released by damaged or degenerating muscle fibers and may be measured in serum. The most useful of these enzymes is **creatine kinase (CK),** which is mainly found in three organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is not a universal screening test for neuromuscular disease because many diseases of the motor unit are not associated with elevated enzymes. The CK level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy, and the magnitude of increase is characteristic for particular diseases. CK may also be elevated in certain nonneuromuscular disorders (Table 647.6).

Rhabdomyolysis is often a dramatic event associated with high plasma CK levels, myoglobinuria, and muscle pain or tenderness. It may be acquired (Table 647.7; see Fig. 647.4), due to metabolic diseases (Table 647.8), or occur spontaneously or secondary to various triggers (Fig. 647.5).

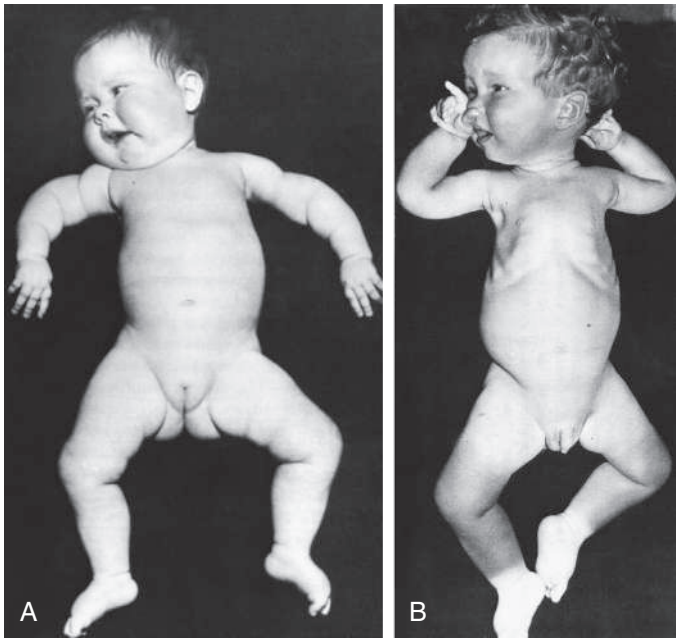

Fig. 647.1 Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Characteristic postures in 6-wk-old (A) and 1-yr-old (B) infants with severe weakness and hypotonia from birth. Note the frog-leg posture of the lower limbs and internal rotation ("jug handle") (A) or external rotation (B) at the shoulders. Note also intercostal recession, especially evident in B, and normal facial expressions. *(From Volpe J. Neurology of the Newborn, 4th ed. Philadelphia: Saunders; 2001: p 645.)*

Molecular Genetic Markers

Many DNA markers of hereditary neuromuscular diseases, including the common muscular dystrophies, and neuropathies are available from specific gene panels or whole exome or genome sequencing. If the clinical manifestations for a positive family history suggest a particular disease, these genetic tests can provide a definitive diagnosis and not subject the child to more invasive procedures, such as muscle biopsy. Other molecular markers are available only in muscle biopsy tissue.

Nerve Conduction Velocity

Motor and sensory nerve conduction velocity may be measured electrophysiologically by using surface electrodes. Neuropathies of various types are detected by decreased conduction. The site of a traumatic nerve injury may also be localized. The nerve conduction value at birth is about half of the mature value achieved by the age of 2 years. Tables are available for normal values at various ages in infancy, including for preterm infants. Because the nerve conduction velocity study measures only the fastest conducting fibers in a nerve, 80% of the total nerve fibers must be involved before slowing in conduction is detected.

Electromyography

Electromyography (EMG) requires insertion of a needle into the belly of a muscle and recording of the electrical potentials in various states of contraction. It is less useful in pediatrics than in adult medicine, in part because of technical difficulties in recording these potentials in young children and in part because the best results require the patient's cooperation for full relaxation and maximal voluntary contraction of a muscle. Many children are too frightened to provide such cooperation. Characteristic EMG patterns distinguish denervation from myopathic involvement. The specific type of myopathy is not usually definitively diagnosed, but certain specialized myopathic conditions, such as myotonia, may be demonstrated. An EMG can transiently raise the serum CK level.

EMG combined with repetitive electrical stimulation of a motor nerve supplying a muscle to produce tetany is useful in demonstrating myasthenic decremental responses. Small muscles, such as the

Table 647.2 Pattern of Weakness and Localization in the Hypotonic Infant

ANATOMIC REGION OF HYPOTONIA	CORRESPONDING DISORDERS	PATTERN OF WEAKNESS AND INVOLVEMENT
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	Spinal muscular atrophy	Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies Congenital muscular dystrophy Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

From Prasad AN, Prasad C. The floppy infant: contribution of genetic and metabolic disorders. *Brain Dev.* 2003;27:457–476.

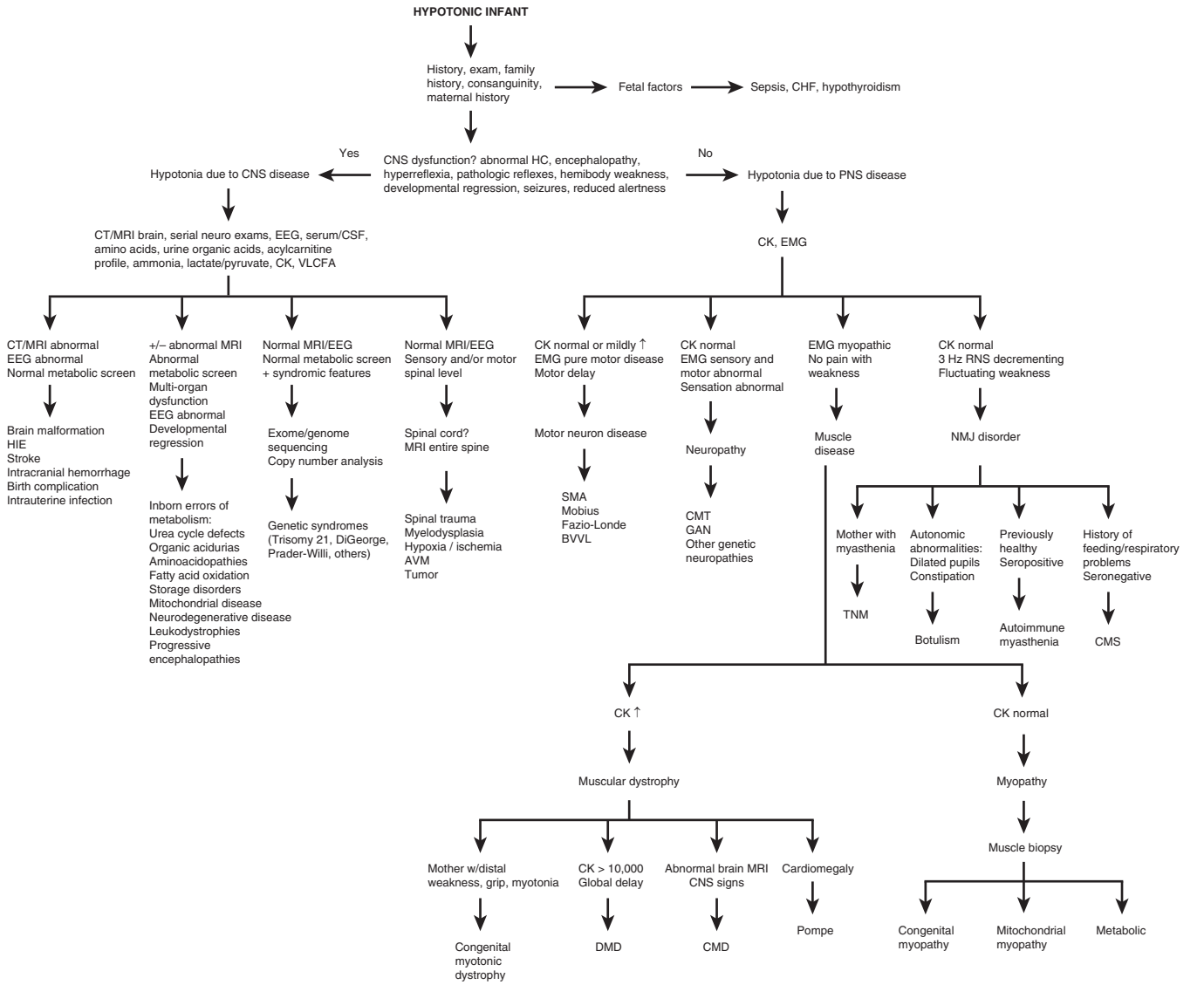

Fig. 647.2 Algorithm showing the diagnostic approach to the hypotonic infant. AVM, Arteriovenous malformation; BVVL, Brown-Vialetto-Van Laere syndrome; CHF, congestive heart failure; CK, creatine kinase; CMD, congenital muscular dystrophy; CMS, congenital myasthenic syndrome; CMT, Charcot-Marie-Tooth disease; CNS, central nervous system; CSF, cerebrospinal fluid; DMD, Duchenne muscular dystrophy; EMG, electromyography with nerve conduction; GAN, giant axonal neuropathy; HC, head circumference; HIE, hypoxic-ischemic encephalopathy; NMJ, neuromuscular junction; PNS, peripheral nervous system; RNS, repetitive nerve stimulation; SMA, spinal muscular atrophy; TNM, transient neonatal myasthenia; VLCFA, very long-chain fatty acids. *(From Konersman C. Hypotonia and weakness. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Fig. 35.1, p. 569.)*

abductor digiti quinti of the hypothenar eminence, are used for such studies. Additional specialized tests, such as single myofiber EMG, may provide supplementary evidence in selected cases, but are performed only in large neuromuscular centers.

IMAGING OF MUSCLES AND THE CENTRAL NERVOUS SYSTEM

Ultrasonography, computed tomography (CT) scans, and, more often and most helpful, magnetic resonance imaging (MRI) are used to image muscle in many neuromuscular diseases. Although these methods are not always definitively diagnostic, in experienced hands, they provide a supplementary means of following the progression of disease over time. MRI is quite useful in identifying inflammatory myopathies of immune (dermatomyositis) or infectious (viral, bacterial, parasitic) origin. MRI is the study of choice to image the spinal cord, if a tumor or other structural lesion of the spinal cord is suspected as the cause of muscular dysfunction, and the nerve roots and plexus (e.g., brachial plexus). Brain MRI is indicated in some myopathies, such as the congenital muscular dystrophies, in which cerebral malformations often accompany the myopathy because the mutated gene responsible is expressed in both muscle and the developing brain.

MUSCLE BIOPSY

The muscle biopsy is traditionally the most important and specific diagnostic study of most neuromuscular disorders. Molecular genetic diagnosis supersedes the muscle biopsy or renders it as secondary in diagnostic importance, to be used if a definitive diagnosis of a hereditary disease is not provided by molecular genetic testing in blood. Thus the muscle biopsy is no longer essential for spinal muscular atrophy, most muscular dystrophies, and most congenital myopathies. Muscle

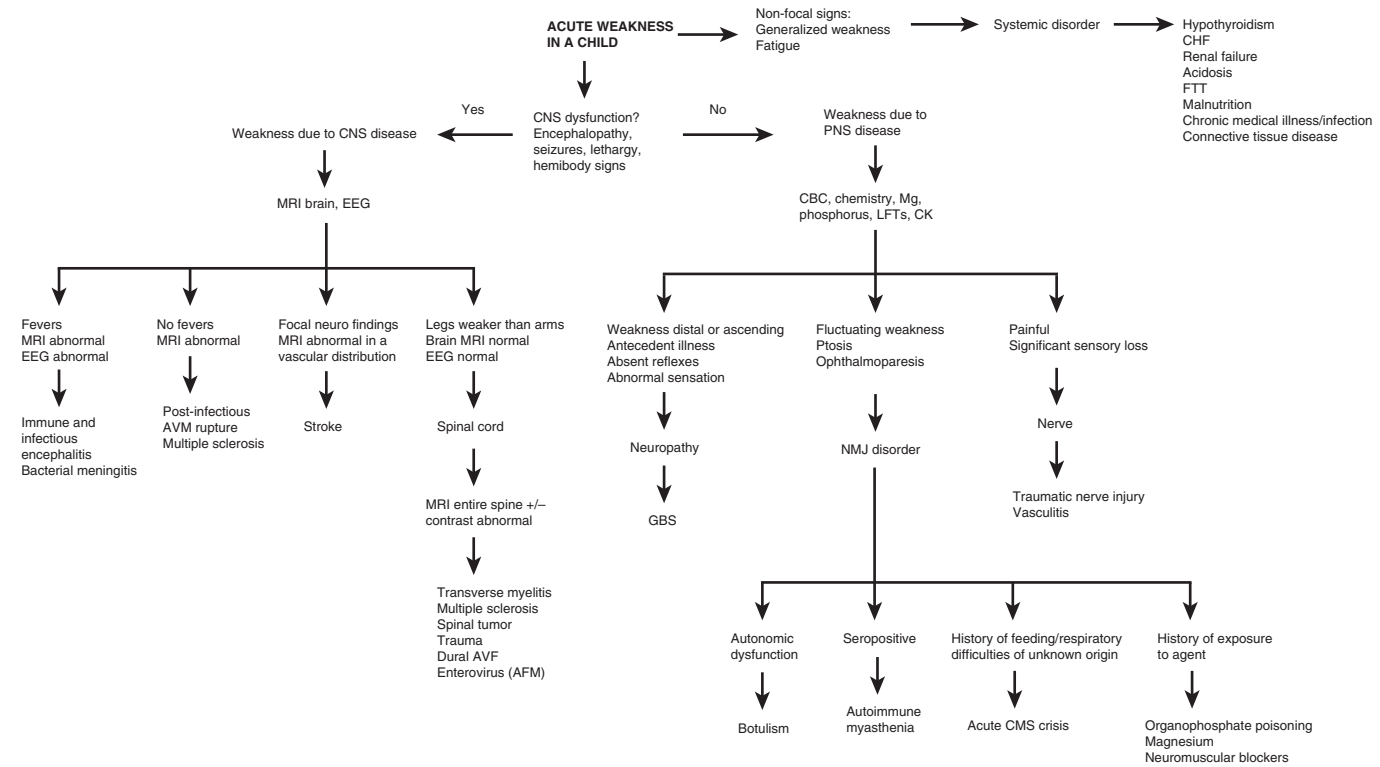

Fig. 647.3 Algorithm showing the diagnostic approach to the child with acute weakness. AFM, acute flaccid myelitis; AVF, arteriovenous fistula; AVM, arteriovenous malformation; CHF, congestive heart failure; CK, creatine kinase; CMS, congenital myasthenic syndrome; CNS, central nervous system; FTT, failure to thrive; GBS, Guillain-Barré syndrome; LFTs, liver function tests; NMJ, neuromuscular junction; PNS, peripheral nervous system. *(From Konersman C. Hypotonia and weakness. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Fig. 35.9, p. 579.)*

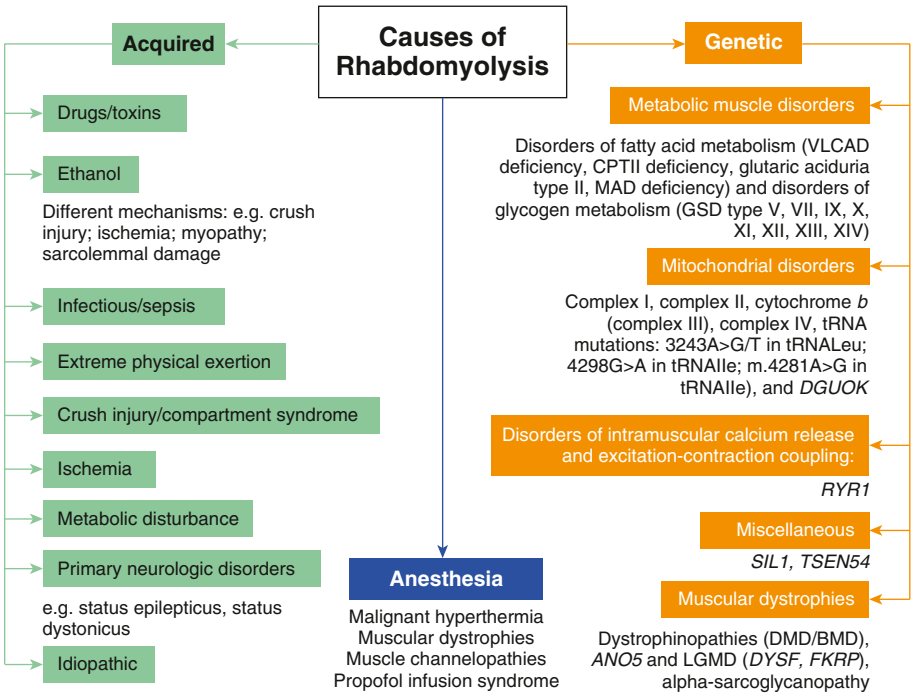

Fig. 647.4 Examples of conditions associated with rhabdomyolysis. In individual cases, both genetic and environmental factors may combine to trigger a rhabdomyolysis event; anesthesia-induced rhabdomyolysis is the best-characterized example. VLCAD, Very-long-chain acyl-CoA dehydrogenase; CPTII, carnitine palmitoyl-transferase-II; MAD, multiple acyl-CoA dehydrogenase; GSD, glycogen storage disease; tRNA, transfer ribonucleic acid; *DGUOK*, deoxyguanosine kinase gene; *RYR1*, ryanodine receptor 1 gene; *SIL1*, *Saccharomyces cerevisiae*, homolog of; *TSEN54*: tRNA splicing endonuclease 54 gene, *S. cerevisiae*, homolog of; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; *ANO5*, anoctamin 5 gene; LGMD, limb-girdle muscular dystrophy; *DYSF*, dysferlin gene; *FKRP*, fukutin-related protein gene. *(From Scalco RS, Gardiner AR, Pitceathly RDS, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015;10:51. Fig. 1.)*

Table 647.3 Differentiating the Causes of Infantile Hypotonia

LOCALIZATION	CAUSE	HISTORY AND EXAM FINDINGS	INVESTIGATION TO AID IN DIAGNOSIS
Brain	HIE Intracerebral hemorrhage	Prematurity, difficult delivery	Brain MRI
	Brain malformations	Cranial nerve abnormalities, Babinski sign, gradual development of hypertonia (especially axial), respiratory or feeding difficulties, global delay, micro-macrocephaly	Cerebral ultrasound, brain MRI
	Intrauterine infection	Fever, altered mental status	Microbial cultures/evaluations, CSF evaluation
	Postnatal birth injury	Seizures, focal neurologic deficits	Brain MRI, EEG
	Progressive encephalopathies (leukodystrophies, progressive myoclonic epilepsies, Lennox-Gastaut syndrome, infantile spasms)	Seizures, developmental regression, ataxia, focal neurologic deficits, visual loss	Brain MRI, EEG, EMG/NCS (useful in adrenoleukodystrophy, Krabbe disease, and metachromatic leukodystrophy), specific genetic testing
	Mitochondrial disease	Seizures, focal neurologic deficits, global delay, visual loss, hyper- or hyporeflexia	Brain MRI, lactate, pyruvate, creatine kinase, GDF-15, muscle biopsy, mitochondrial DNA sequencing and deletion/duplication analysis on muscle or affected tissue, EMG/NCS
Brainstem	Joubert syndrome Pontocerebellar hypoplasia Cobblestone malformations	Multiple cranial nerve abnormalities, breathing and feeding difficulties, possible intellectual delay, nystagmus, possible hyperreflexia, ataxia	Brain MRI (molar tooth sign in Joubert syndrome), genetic panels for specific disorders
Spinal cord	Myelodysplasia Spinal cord tumor Syringomyelia Hypoxia-ischemia Trauma AVM	Spinal level on exam, weakness below a defined spinal level, absent reflexes (acutely) or hyperreflexia (chronically) below the level, may have Babinski sign, history of trauma	Brain MRI, complete spinal MRI
Motor neuron	Spinal muscular atrophy	Absence of antigravity movements, tongue fasciculations, absent reflexes to hyporeflexia, normal cognition, breathing/feeding difficulties; weakness in legs more than arms in SMA types II-III	*SMN1* genetic analysis
	Poliomyelitis	Neck stiffness, muscle spasms, areflexia, asymmetric flaccid paralysis of a limb, respiratory distress, muscle atrophy, normal sensation	Isolation of poliovirus from stool, confirmation using RT-PCR, acute and convalescent serology showing fourfold increase in titer, EMG/NCS showing pure motor neuronopathy
	Incontinentia pigmenti	Skin blistering, verrucous skin lesions, hyperpigmented streaks, pale/hairless atrophic linear streaks that respect Blaschko lines, dental abnormalities, intellectual delay	DNA analysis, EMG/NCS showing pure motor neuronopathy
	Fazio-Londe disease Brown-Vialetto-Van Laere syndrome (BVVL)	Optic atrophy, nystagmus, bulbar palsy, facial weakness, hearing loss (BVVL only), tongue fasciculations, ptosis, respiratory compromise, muscle weakness	DNA analysis
Nerve	Guillain-Barré syndrome (GBS) Chronic inflammatory demyelinating polyneuropathy (CIDP)	Sensory ataxia with walking difficulties, rapidly (GBS) or slowly (CIDP) progressive weakness, absent reflexes or hyporeflexia, autonomic dysfunction, antecedent gastrointestinal or respiratory illness in GBS	EMG/NCS with absent or prolonged F waves, prolonged distal latencies, conduction block, demyelinating nerve conduction velocities, CSF showing cytoalbuminologic dissociation, MRI with edematous enhancing nerve roots
	Toxic neuropathies	History and temporal correlation with exposure to a neurotoxic drug, distal then proximal muscle weakness, absent reflexes or hyporeflexia, sensory ataxia with walking difficulties	EMG/NCS showing mixed axonal/demyelinating features, plasma drug levels
	Charcot-Marie-Tooth disease	Family history of similar disease, pes cavus and hammer toe foot deformities, ataxic gait, foot drop, absent reflexes or hyporeflexia	EMG/NCS to determine whether axonal or demyelinating subtypes, DNA analysis
	Hereditary sensory and autonomic neuropathies	Sensory loss in a stocking/glove distribution, chronic skin ulceration and poor wound healing, distal muscle weakness with foot deformity, absent reflexes or hyporeflexia, variable anhidrosis	EMG/NCS showing normal or mildly abnormal motor responses and abnormal sensory responses, nerve biopsy showing reduced myelinated and unmyelinated fibers, DNA analysis

Table 647.3 Differentiating the Causes of Infantile Hypotonia—cont'd

LOCALIZATION	CAUSE	HISTORY AND EXAM FINDINGS	INVESTIGATION TO AID IN DIAGNOSIS
	Refsum disease	Autosomal recessive inheritance, stocking/glove distribution of sensory and motor weakness, anosmia, hearing loss, ataxia, ichthyosis, short metacarpals and metatarsals, cardiac arrhythmia, and cardiomyopathy	Elevated plasma phytanic acid concentration, DNA analysis
	Giant axonal neuropathy	Stocking/glove distribution of sensory loss and motor weakness, cerebellar ataxia, absent reflexes or hyporeflexia, kinky hair (tightly curled), nystagmus, dysarthria, pyramidal tract signs, optic neuropathy, seizures	Brain MRI with white matter abnormalities, axonal sensorimotor polyneuropathy on EMG/NCS, nerve biopsy showing giant axons (axonal swelling) and disorganized neurofilaments, DNA analysis
	Metachromatic leukodystrophy Krabbe disease Adrenoleukodystrophy	Developmental regression, absent reflexes or hyporeflexia, Babinski signs	EMG/NCS showing demyelinating neuropathy, brain MRI showing white matter disease, DNA analysis
Neuromuscular junction	Botulism	Sudden poor feeding, constipation, weak cry, gradual muscle weakness, dilated poorly reactive pupils, exposure to soil/dust with bacterium or honey consumption	Presence of toxin in stool/serum, culture bacterium from stool, EMG/NCS showing low-amplitude motor responses or decrement on repetitive nerve stimulation in a weak muscle
	Transient acquired neonatal myasthenia	Ptosis, feeding and respiratory difficulties, aspiration, mother with signs or symptoms of autoimmune myasthenia	Maternal history of myasthenia, EMG/NCS showing decrement on repetitive nerve stimulation in a weak muscle, good response to acetylcholinesterase inhibitors
	Infantile (autoimmune) myasthenia	Ptosis, episodic weakness, recurrent feeding and respiratory difficulties, easy fatigability	EMG/NCS showing decrement on repetitive nerve stimulation in a weak muscle, good response to acetylcholinesterase inhibitors, anti-acetylcholine receptor antibody serology
	Congenital myasthenic syndrome	Ptosis, episodic weakness, recurrent feeding and respiratory difficulties, easy fatigability	EMG/NCS showing decrement on repetitive nerve stimulation in a weak muscle, DNA analysis, negative anti-acetylcholine receptor antibody serology
Muscle	Duchenne/Becker muscular dystrophy	X-linked pattern of inheritance, enlarged calves, proximal muscle weakness with a Gower maneuver	Markedly elevated CK, DNA analysis
	Congenital myotonic dystrophy	Autosomal dominant pattern of inheritance, frog-leg position, open down-turned mouth, minimal antigravity movements in infants, distal > proximal weakness in children, impaired relaxation of grip, dysarthria, myopathic facies with temporal wasting	Test mother (then father) for clinical myotonia or electrical myotonic discharges, EMG/NCS with myopathy in newborn period and myotonic discharges in older children, normal to mildly elevated CK, *DPMK* gene CTG repeat analysis
	Pompe disease	Absence of antigravity movements, severe cardiomegaly, feeding/respiratory difficulties, hepatomegaly	GAA enzyme activity in dried blood spot, lymphocytes or fibroblasts, *GAA* gene analysis
	Congenital muscular dystrophy	Family history, proximal > distal muscle weakness, feeding and respiratory difficulties, early-onset contractures in specific subtypes, keloids/hyperkeratosis pilaris in specific subtypes, CNS dysfunction in specific subtypes	Brain MRI, mild to markedly elevated CK, muscle biopsy showing dystrophic changes, muscle MRI, EMG/NCS to assess for demyelinating neuropathy component and myopathy, DNA analysis
	Congenital myopathies	Family history, proximal > distal muscle weakness, feeding and respiratory difficulties, ptosis and ophthalmoparesis in specific subtypes	Normal to mildly elevated CK, muscle biopsy showing specific changes (nemaline rods, cores, centrally placed nuclei), DNA analysis
	Metabolic myopathies	Family history, proximal muscle weakness, history of rhabdomyolysis or myoglobinuria, second-wind phenomenon in some subtypes	Normal to markedly elevated CK, EMG/NCS usually myopathic, metabolic evaluation (lactate, pyruvate, acylcarnitine profile, plasma amino acids, urine organic acids), muscle biopsy, DNA analysis
	Mitochondrial myopathies	Maternal inheritance pattern, proximal > distal weakness, ptosis, ophthalmoparesis, short stature, variable cardiac and CNS involvement, recurrent rhabdomyolysis	Normal to moderately elevated CK, abnormal GDF-15, EMG/NCS showing myopathy and variable neuropathy, muscle biopsy with ragged red fibers, mitochondrial DNA analysis

AVM, Arteriovenous malformation; CK, creatine kinase; CNS, central nervous system; CSF, cerebrospinal fluid; CTG, cytosine-thymine-guanine; EMG/NCS, electromyography/nerve conduction study; GAA, acid α-glucosidase; GDF-15, growth differentiation factor-15; HIE, hypoxic-ischemic encephalopathy; RT-PCR, reverse transcription-polymerase chain reaction; SMA, spinal motor atrophy.

Modified from Sparks SE. Neonatal hypotonia. *Clin Perinatol*. 2015;42:363–371.

biopsy remains useful in select cases, however, to provide morphologic details and metabolic profiles not revealed by genetic testing alone or as a primary diagnostic procedure if the genetics are equivocal or negative. Not only are neurogenic and myopathic processes distinguished by muscle biopsy, but the type of myopathy and specific enzymatic deficiencies also may be determined. *In addition, there are conditions that may have associated identifiable disease-causing genes in most but not all patients.*

The vastus lateralis (quadriceps femoris) is most frequently sampled. The deltoid should be avoided in most cases because it normally exhibits a 60–80% predominance of type I fibers, so that the distribution patterns of fiber types are difficult to recognize. Muscle biopsy is a simple outpatient procedure that may be performed under local anesthesia with or without femoral nerve block. Needle biopsies are preferred in some centers but are not percutaneous and require an incision in the skin similar to open biopsy; numerous samples must be taken to conduct an adequate examination of the tissue, and they provide inferior specimens. The volume of tissue from a needle biopsy is usually not adequate for all required studies, including supplementary biochemical studies, such as mitochondrial respiratory chain enzymes; a small, clean, open biopsy is therefore advantageous.

Histochemical studies of frozen sections of the muscle are obligatory in all pediatric muscle biopsies because many congenital and metabolic myopathies cannot be diagnosed from paraffin sections using conventional histologic stains. Immunohistochemistry is a useful supplement in some cases, such as for demonstrating dystrophin in suspected Duchenne muscular dystrophy or merosin in congenital muscular dystrophy. A portion of the biopsy specimen should be fixed for potential electron microscopy, but the ultrastructure has additional diagnostic value only in selected cases. Interpretation of muscle biopsy samples is complex and should be performed by an experienced pathologist. A portion of frozen muscle tissue should also be routinely saved for possible biochemical analysis (mitochondrial cytopathies, carnitine palmitoyltransferase, acid maltase).

Immunocytochemical reactivities can be applied to formalin-fixed, paraffin-embedded sections and do not require frozen sections. Some reactivities, such as slow and fast myosin, can distinguish fiber types and hence substitute for myofibrillar adenosine triphosphatase histochemical stains in frozen sections. An increasing number of sarcolemmal regional proteins can be demonstrated that are specific for each of the various muscular dystrophies and include the dystrophins, merosin, sarcoglycans, and dystroglycans. Ryanodine receptors, important in myasthenia gravis and in malignant hyperthermia, also can be demonstrated. In addition, immunocytochemical reactivities can distinguish the various types of inflammatory cells in autoimmune myopathies, including T and B lymphocytes and macrophages.

Table 647.4 Differential Diagnosis of Acute Flaccid Paralysis

Brainstem stroke
Brainstem encephalitis
Acute anterior poliomyelitis
- Caused by poliovirus
- Caused by other neurotropic viruses
- Unknown cause of acute flaccid myelitis

Acute myelopathy
- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy
- Guillain-Barré syndrome
- Post–rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biologic toxins, or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission
- Myasthenia gravis
- Biologic or industrial toxins
- Tic paralysis

Disorders of muscle
- Hypokalemia
- Hypophosphatemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis
- Familial periodic paralyses (normokalemic, hypokalemic, hyperkalemic)

From Hughes RAC, Camblath DR. Guillain-Barré syndrome. *Lancet*. 2005;366:1653–1666.

NERVE BIOPSY

Nerve biopsy is applied less frequently because of the precision diagnosis of many hereditary peripheral neuropathies by less invasive and more specific genetic diagnosis. In some cases not definitively diagnosed by genetic testing, the nerve biopsy still provides valuable diagnostic information. The most commonly sampled nerve is the sural nerve, a pure sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsy specimens of this nerve may be taken. When the sural nerve

Table 647.5 Differentiating Acute Flaccid Myelitis from Clinical Mimics

	ACUTE FLACCID MYELITIS	GUILLAIN-BARRÉ SYNDROME	ACUTE TRANSVERSE MYELITIS (DEMYELINATING OR IDIOPATHIC)	SPONTANEOUS SPINAL CORD INFARCTION
Prodromal illness	+++	+++	+/–	–
Temporal evolution	Hours to days	Days to weeks	Days to weeks	Minutes to hours
Pattern of weakness	Asymmetric, arms > legs	Symmetric, ascending	Variable	Symmetric, severe
Facial/bulbar weakness	++	++	+/–	+/–
Respiratory failure	++	++	+/–	+/–
Numbness/paresthesia	+/–	+++ (except AMAN)	+++	+
Sensory level	–	–	++	++
Optic neuritis	–	–	Variable	–
Encephalopathy	–	–	+/– (e.g., ADEM)	–
Bowel/bladder dysfunction	+/–	+/–	++	+++

From Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. Lancet. 2021;397:334-344. Table 2, p. 337.

Table 647.5 Differentiating Acute Flaccid Myelitis from Clinical Mimics—cont'd

	ACUTE FLACCID MYELITIS	GUILLAIN-BARRÉ SYNDROME	ACUTE TRANSVERSE MYELITIS (DEMYELINATING OR IDIOPATHIC)	SPONTANEOUS SPINAL CORD INFARCTION
Possible associated symptoms or syndromes	Headache, neck pain/stiffness, neuropathic pain	Neuropathic pain	Optic neuritis, encephalitis, seizures	Severe back/limb pain at onset
MRI spinal cord	Ill-defined gray matter–predominant lesion, +/− nerve root enhancement	Normal cord, +/− nerve root enhancement	Variable, but usually a well-defined enhancing white > gray matter lesion	No-enhancing anterior cord or gray matter lesion
CSF	Mild-moderate pleocytosis	Elevated protein	Mild-moderate pleocytosis	Sometimes elevated protein or mild pleocytosis
Microbiologic tests	Nasopharyngeal, rectal swabs and CSF for enteroviruses including polio and live polio vaccine virus if indicated. West Nile virus titers	Stool sample: bacterial culture, viral RT-PCR panel; respiratory sample: viral RT-PCR panel; serum: *Campylobacter jejuni* and *Mycoplasma pneumoniae* IgM/IgG; other organisms according to region and season	If indicated based on clinical presentation	Not usually indicated
Other useful tests	+/− EMG/NCS	EMG/NCS; serum: anti-ganglioside antibodies	Serum: MOG-IgG, aquaporin-4-IgG; CSF: oligoclonal bands	Angiography

AMAN, Acute motor axonal neuropathy subtype; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; EMG/NCS, electromyography and nerve conduction studies; MOG, myelin oligodendrocyte glycoprotein; RT-PCR, reverse transcription-polymerase chain reaction.
Modified from Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet*. 2021;397:334–344. Table 2, p. 337.

Table 647.6 Nonneuromuscular Disorders That Can Cause Elevated Creatine Kinase Levels

ENDOCRINE DISORDERS
Hyperthyroidism (rare)
Hypothyroidism
Hyperparathyroidism
Acromegaly
Cushing syndrome

METABOLIC DISTURBANCES
Hyponatremia
Hypokalemia
Hypophosphatemia

MUSCLE TRAUMA
Strenuous exercise
Intramuscular injections
Needle electromyography
Seizures

MEDICATIONS
Statins
Fibrates
Antiretrovirals
β Blockers
Clozapine
Angiotensin II receptor blockers
Hydroxychloroquine
Isotretinoin
Colchicine

OTHERS
Celiac disease
Malignancy
Macro creatine kinase
Surgery
Pregnancy
Cardiac disease
Acute kidney disease
Viral illness
Predisposition to malignant hyperthermia

From Moghadam-Kia S, Oddis CV, Aggarwal R. Approach to asymptomatic creatine kinase elevation. *Cleve Clin J Med*. 2016;83(1):37–42. Table 1.

is severed behind the lateral malleolus of the ankle, regeneration of the nerve occurs in more than 90% of cases, so that permanent sensory loss is not experienced. The sural nerve is often involved in many neuropathies in which the clinical manifestations are predominantly motor.

Electron microscopy is performed on most nerve biopsy specimens because many morphologic alterations cannot be appreciated at the resolution of a light microscope. Teased fiber preparations are sometimes useful in demonstrating segmental demyelination, axonal swellings, and other specific abnormalities, but these time-consuming procedures are not done routinely. Special stains may be applied to ordinary frozen or paraffin sections of nerve biopsy material to demonstrate myelin, axoplasm, and metabolic products.

CARDIAC ASSESSMENT

Cardiac evaluation is important if myopathy is suspected because of involvement of the heart in muscular dystrophies and in inflammatory and metabolic myopathies (Table 647.9). Electrocardiography often detects early cardiomyopathy or conduction defects that are clinically asymptomatic. At times, a more complete cardiac workup, including echocardiography and consultation with a pediatric cardiologist, is indicated. Serial pulmonary function tests also should be performed in muscular dystrophies and in other chronic or progressive diseases of the motor unit.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 647.7 Causes of Rhabdomyolysis

NONTRAUMATIC CAUSES *Nonexertional Causes* **Alcohol/drug use:** Ethanol, methanol, ethylene glycol, heroin, methadone, barbiturates, cocaine, caffeine, amphetamine, lysergic acid diethylamide, 3,4-methylene dioxymethamphetamine (MDMA, ecstasy), phencyclidine, benzodiazepines, toluene (from glue sniffing), gasoline/paint sniffing
Medication: Salicylates, fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil), neuroleptics, antipsychotics (haloperidol, fluphenazine, perphenazine, chlorpromazine), quinine, corticosteroids, statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin), theophylline, cyclic antidepressants, selective serotonin reuptake inhibitors, antibiotics (fluoroquinolones, pyrazinamide, trimethoprim/sulfonamide, amphotericin B, itraconazole, levofloxacin), zidovudine, benzodiazepines, antihistamines, aminocaproic acid, phenylpropanolamine
Toxic agents: Carbon monoxide (CO), hemlock herbs from quail, snake bites, spider venom, massive honey bee envenomations, *Tricholoma equestre* (mushroom), buffalo fish
Anesthetics and neuromuscular blocking agents: Barbiturates, benzodiazepines, propofol, succinylcholine in patients with Duchenne/Becker muscular dystrophy
Infections: *Viral:* influenza A and B, HIV, enterovirus, adenovirus, coxsackievirus, Epstein-Barr virus, echovirus, cytomegalovirus, herpes simplex virus, varicella-zoster virus, West Nile virus. *Bacterial: Legionella* species, *Salmonella* species, *Francisella* species, *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus, Pseudomonas aeruginosa, Neisseria meningitidis, Haemophilus influenzae, Coxiella burnetii, Leptospira* species, *Mycoplasma* species, *Escherichia coli,* fungal and malarial infections
Electrolyte disturbances: Hyponatremia, hypernatremia, hypokalemia, hypophosphatemia, hypocalcinemia, hyperosmotic conditions
Endocrine disorders: Hypothyroidism, hyperthyroidism, diabetic ketoacidosis, nonketotic hyperosmolar diabetic coma, hyperaldosteronism
Idiopathic inflammatory myopathies: Polymyositis, dermatomyositis, necrotizing myositis
Temperature extremes: Heatstroke, malignant hyperthermia, exposure to cold
Muscle ischemia: Thrombosis, embolism
NEUROLEPTIC MALIGNANT SYNDROME *Exertional Causes* Extreme physical exertion, sickle cell disease (crisis), status epilepticus, hyperkinetic syndrome, severe dystonia, status asthmaticus
TRAUMATIC CAUSES *Multiple Injury* **Crush injury:** Bombings, earthquakes, building collapse, mine accidents, train or motor vehicle accidents
High-voltage electrical injury
Extensive third-degree burns
Vascular/orthopedic surgery: Intraoperative use of tourniquets, tight dressings or casts, prolonged application of air splints or pneumatic antishock garments, and clamping of vessels during surgery
Prolonged immobility: Immobilization after trauma, anesthesia, coma, drug- or alcohol-induced unconsciousness

Modified from Zutt R, van der Kooi AJ, Linthorst GE, et al. Rhabdomyolysis: review of the literature. *Neuromuscul Disord.* 2014;24:651–659. Table 2.

Table 647.8 Inherited Neuromuscular Disorders Associated with Episodes of Rhabdomyolysis*

GENE	DISEASE NAME	BASELINE CREATINE KINASE LEVELS	PATTERN OF INHERITANCE	TRIGGER FOR RHABDOMYOLYSIS
DISORDERS OF GLYCOGEN METABOLISM				
PYGM	Glycogen storage disease type V, McArdle disease	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
PFKM	Glycogen storage disease type VII, Tarui disease	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
ALDOA	Glycogen storage disease type XII	Normal Mild elevation, high	AR	Febrile illness, infection
ENO3	Glycogen storage disease type XIII	Normal High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
PGAM2	Glycogen storage disease type X	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
PGK1	Phosphoglycerate kinase 1 deficiency	Normal High	X-linked	Aerobic and anaerobic exercise, symptom onset within minutes
PGM1	Glycogen storage disease type XIV	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes, general anesthesia
PHKA1 *PHKB*	Glycogen storage disease type IX	?	X-linked AR	Aerobic and anaerobic exercise, symptom onset within minutes
DISORDERS OF FATTY ACID METABOLISM:				
ACADVL	Deficiency of very-long-chain acyl-CoA dehydrogenase	Normal High	AR	Fasting, prolonged exercise, cold, infections, fever
CPT2	Carnitine palmitoyl-transferase deficiency	Normal	AR	Prolonged exercise, fasting, fever, infection, high fat intake, cold exposure, heat, emotional stress, drugs
ETFA *ETFB* *ETFDH*	Glutaric aciduria type II Multiple acyl-coenzyme A dehydrogenase deficiency	Normal Mildly to moderately elevated	AR	Physical exercise, fasting, irregular diet or infection
MITOCHONDRIAL DISORDERS				
COI (MTCO1)	Mitochondrial disorder	Normal	Maternal inheritance	Prolonged or repetitive exercise
COII (MTCO2)	Mitochondrial disorder	Normal	Maternal inheritance	Exercise
COIII (MTCO3)	Mitochondrial disorder	Normal	Maternal inheritance	Prolonged exercise, viral illness, unknown cause

Continued

Table 647.8 Inherited Neuromuscular Disorders Associated with Episodes of Rhabdomyolysis*—cont'd

GENE	DISEASE NAME	BASELINE CREATINE KINASE LEVELS	PATTERN OF INHERITANCE	TRIGGER FOR RHABDOMYOLYSIS
DGUOK	Mitochondrial disorder	?	AR	Viral illness
FDX1L	Mitochondrial disorder	Normal High	AR	?After exercise
HADHA *HADHB*	Mitochondrial trifunctional protein deficiency	Normal	AR	Strenuous physical activity
ISCU	Iron–sulfur cluster deficiency myopathy (mitochondrial disorder)	?	AR	Exercise
MTCYB	Mitochondrial disorder	Normal	Sporadic variants	Exercise
POLG1	One case report of rhabdomyolysis in association with propofol infusion syndrome		AD, AR	Propofol infusion syndrome
DISORDERS OF INTRAMUSCULAR CALCIUM RELEASE AND EXCITATION–CONTRACTION COUPLING				
RYR1	Malignant hyperthermia susceptibility, exertional rhabdomyolysis, congenital myopathy	Normal or mildly to moderately elevated (usually <1,000 IU/L)	AD, AR	Heat, infection, alcohol, drugs, anesthetic (malignant hyperthermia susceptibility), and exercise
MUSCULAR DYSTROPHIES				
ANO5	Anoctaminopathy-5	High	AR	Unprovoked; no trigger has been identified
DMD	Duchenne muscular dystrophy, Becker muscular dystrophy	High	X-linked	Exercise, anesthetic drugs
DYSF	Limb-girdle muscular dystrophy 2B, Miyoshi myopathy	High	AR	Exercise
FKTN	Fukuyama congenital muscular dystrophy	High	AR	One case following the use of halothane and succinylcholine
FKRP	Limb-girdle muscular dystrophy 2I	High	AR	Exercise
MISCELLANEOUS				
LPIN1	Phosphatidic acid phosphatase deficiency	Normal, high	AR	Febrile illness, anesthesia, and fasting
SIL1	Marinesco-Sjögren syndrome	Normal, high	AR	Febrile infection
TSEN54	Pontocerebellar hypoplasia type 2	Normal, high	AR	Hyperthermia
TANGO2	Encephalocardiomyopathy	High	AR	Encephalocardiomyopathy crisis

*The table summarizes genes, disease names, baseline serum CK levels (between acute episodes of rhabdomyolysis), patterns of inheritance, and triggers for rhabdomyolysis. Genes commonly associated with rhabdomyolysis episodes are in **bold**.

AD, Autosomal dominant; AR, autosomal recessive.

From Scalco RS, Gardiner AR, Pitceathly RDS, et al. Rhabdomyolysis: a genetic perspective. *Orphanet J Rare Dis*. 2015;10:51. Table 1.

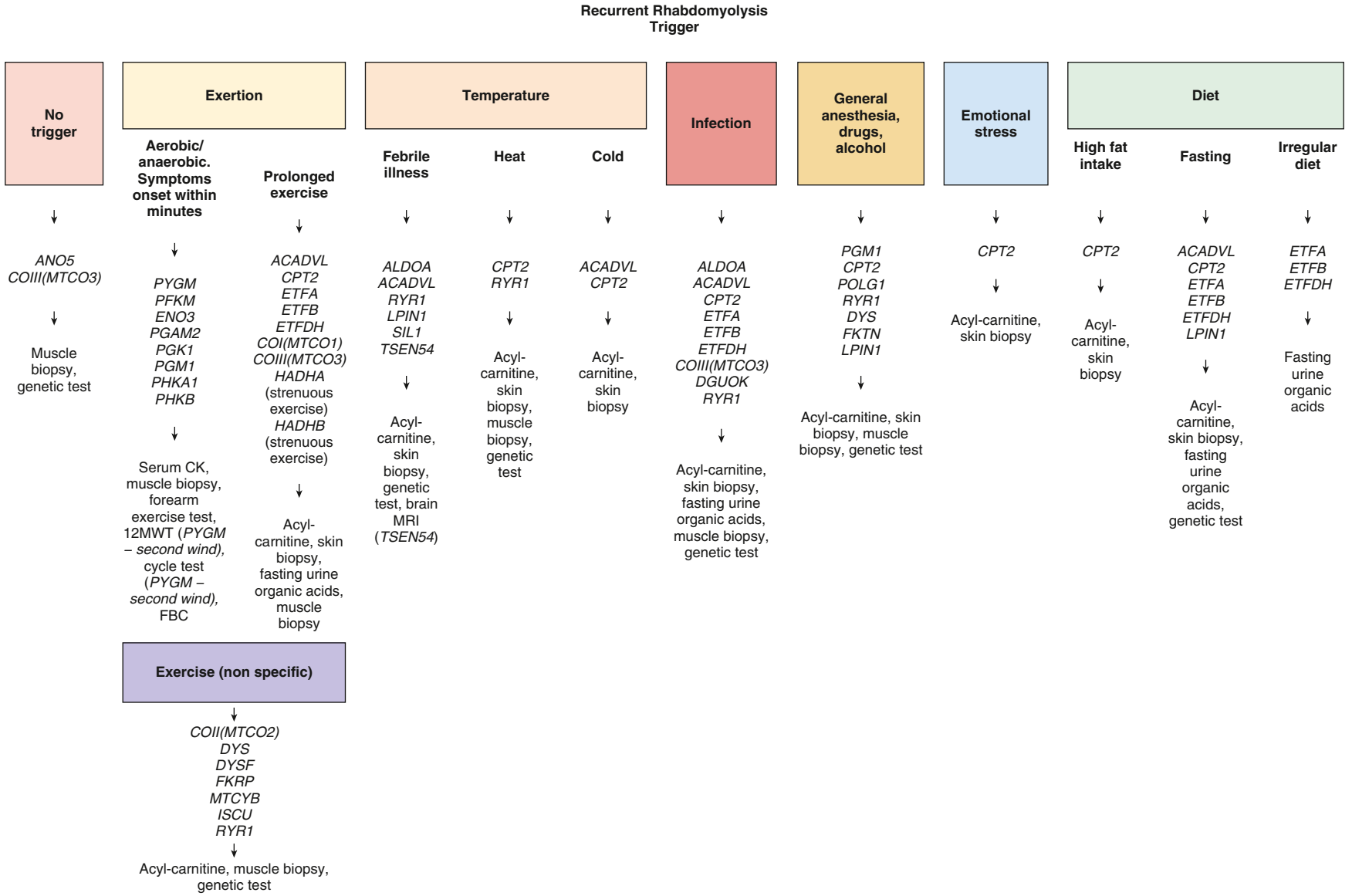

Fig. 647.5 Examples of different triggers of rhabdomyolysis. The identification of triggers may help in guiding genetic testing and may also aid in the interpretation of variants of uncertain significance identified on next-generation sequencing in patients presenting with rhabdomyolysis. CK, Creatine kinase; 12MWT, 12-minute walk test; FBC, full blood count. *(From Scalco RS, Gardiner AR, Pitceathly RDS, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015;10:51. Fig. 2.)*

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 22, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 647.9 Gene Variants and Cardiac Manifestations of the Neuromuscular Disorders

NEUROMUSCULAR DISORDER	GENE	CARDIOMYOPATHY	ECG	ARRHYTHMIA
Duchenne muscular dystrophy	Dystrophin	Dilated	Short PR interval, prolonged QT interval, increased QT:PT ratio, right ventricular hypertrophy, deep Q waves II, III, aVF, %, v6	Increased baseline HR, decreased rate variability, premature ventricular beats (58% of patients by 24 yr of age)
Duchenne muscular dystrophy, female carrier	Dystrophin	Dilated	None	Uncommon
Becker muscular dystrophy	Dystrophin	Dilated	Conduction system disease	Similar to DMD
Emery-Dreifuss autosomal dominant or proximal dominant limb-girdle muscular dystrophy IB	Lamin A/C	Dilated	Conduction abnormalities: prolonged PR interval and sinus bradycardia	Atrial fibrillation or flutter and atrial standstill. Ventricular dysrhythmias
Limb-girdle muscular dystrophy	α, β, γ, δ sarcoglycans	Dilated	Incomplete right bundle branch block, tall R waves in VI and V2 or left anterior hemiblock	Uncommon
Congenital muscular dystrophy	Laminin alpha 2	Dilated	None	None
Limb-girdle muscular dystrophy 21	Fukutin	Dilated	AV node and bundle branch block, age at onset late teens and early 20s	Atrial arrhythmias and/or ventricular arrhythmias
Emery-Dreifuss X-linked	Emerin	Rare	Conduction abnormalities: prolonged PR interval and sinus bradycardia	Atrial fibrillation or flutter and atrial standstill
Friedreich ataxia	Frataxin gene	Hypertrophic	T-wave inversion, left axis deviation and repolarization abnormalities	Ventricular arrhythmias
Myotonic dystrophy type 1, infantile	Myotonic dystrophy protein kinase gene	Hypertrophic	Conduction disease, prolonged PR interval, widening of the QRS complex	Atrial fibrillation and flutter, complete heart block
Myotonic dystrophy type 1	Myotonic dystrophy protein kinase gene	LV noncompaction	Conduction disease, prolonged PR interval, widening of the QRS complex	Atrial fibrillation and flutter, complete heart block

HR, Heart rate; DMD, Duchenne muscular dystrophy; AV, atrioventricular; LV, left ventricular.
From Hsu DT. Cardiac manifestations of neuromuscular disorders in children. *Paediatr Respir Rev*. 2010;11:35–38. Table 1.

Chapter 648

Developmental Disorders of Muscle

*Adnan Y. Manzur**

A heterogeneous group of congenital neuromuscular disorders is known as **congenital myopathies** (see Tables 649.1-649.7 in Chapter 649; Tables 648.1 and 648.2). Most of these disorders have subcellular abnormalities that can be demonstrated only by muscle biopsy, by means of histochemistry, immunocytochemistry, and electron microscopy. In others, the muscle biopsy abnormality is not a subcellular anatomic defect but an aberration in the ratio and sizes of specific myofiber types. A genetic etiology is demonstrated in most of the congenital myopathies, and molecular genetic testing from blood samples may confirm the diagnosis without muscle biopsy in several of the congenital myopathies, muscular dystrophies, and spinal muscular atrophy (SMA).

Most congenital myopathies are *nonprogressive conditions,* but some patients show slow clinical deterioration accompanied by additional changes in their muscle histology. In some congenital myopathies, such as severe neonatal nemaline myopathy, the clinical expression can be life-threatening because of dysphagia and respiratory and/or cardiac insufficiency. Cardiomyopathy develops in some patients with congenital myopathies (Table 648.3). Most of the diseases in the category of congenital myopathies are hereditary, some as classical mendelian traits and others as sporadic or novel point variants. Though clinical features (Table 648.4), including phenotype, can raise a strong suspicion of a congenital myopathy, the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen or by genetic testing in lymphocytes, most commonly by testing for panels of genes with next-generation sequencing (NGS). The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies, spinal muscular atrophies, and neuropathies, but there may be coexpression, exemplified by congenital muscle fiber–type disproportion (CMFTD) in infantile myotonic dystrophy. Many are reminiscent of the embryologic development of muscle, thus suggesting possible defects in the genetic regulation of muscle development.

Congenital myopathies often show closer genetic relationships than previously appreciated between entities that have quite distinct pathologic phenotypes in the muscle biopsy and distinctiveness in clinical expression with a degree of overlap. Pathogenic variants of the *TPM3* gene are one of the well-documented etiologies of nemaline myopathy, but identical genetic variants of this gene are also shown to be capable of causing isolated congenital fiber–type disproportion without nemaline rods, cap myopathy, centronuclear ("myotubular") myopathy, and central core/minicore disease.

MYOGENIC REGULATORY GENES AND GENETIC LOCI OF INHERITED DISEASES OF MUSCLE

A family of four myogenic regulatory genes shares encoding transcription factors of basic helix-loop-helix proteins associated with common DNA nucleotide sequences. These genes direct the differentiation of striated muscle from any undifferentiated mesodermal cell. The earliest basic helix-loop-helix gene to program the differentiation of myoblasts is myogenic factor 5 *(MYF5).* The second gene, *myogenin,* promotes fusion of myoblasts to form myotubes. *Herculin* (also known as *MYF6*) and *MYOD1* are the other two myogenic genes. *Myf5* cannot support myogenic differentiation without *myogenin, MyoD,* and *MYF6.* Each of these four genes can activate the expression of at least one other and, under certain circumstances, can autoactivate as well. Another gene known as myomaker also facilitates myoblast fusion. The expression of *MYF5* and of *herculin* is transient in early ontogenesis but returns later in fetal life and persists into adult life.

The human locus of the *MYOD1* gene is on chromosome 11, very near to the domain associated with embryonal rhabdomyosarcoma. The genes *Myf5* and *herculin* are on chromosome 12, and *myogenin* is on chromosome 1.

The myogenic genes are activated during muscle regeneration, recapitulating the developmental process; *MyoD* in particular is required for myogenic stem cell (progenitor satellite cell) activation in adult muscle. The *PAX3, PAX7,* and *WNT3a* genes also play important roles in myogenesis and interact with each of the four basic genes mentioned earlier. Another gene, *myostatin,* is a negative regulator of muscle development by preventing myocytes from differentiating.

The myogenic genes are important not only for fetal myogenesis but also for regeneration of muscle at any age, particularly in degenerative diseases such as muscular dystrophies and autoimmune inflammatory myopathies and in injuries of muscle secondary to trauma or to toxins. Satellite cells in mature muscle that mediate regeneration have the same somitic origin as embryonic muscle progenitor cells, but the genes that regulate them differ. *Pax3* and *Pax7* mediate the migration of primitive myoblast progenitors from the myotomes of the somites to their peripheral muscle sites in the embryo, but only one of two *Pax7* genes continues to act postnatally for satellite cell survival. Then it, too, no longer is required after the juvenile period for muscle satellite (i.e., stem) cells to become activated for muscle regeneration.

Table 648.1 Diagnosis of Myopathy Based on Age of Onset

MYOPATHIES PRESENTING AT BIRTH
Central core disease
Centronuclear (myotubular) myopathy
Congenital fiber-type disproportion
Congenital muscular dystrophy
Congenital myotonic dystrophy
Glycogen storage diseases (acid maltase and phosphorylase deficiencies)
Lipid storage diseases (carnitine deficiency)
Nemaline (rod) myopathy
MYOPATHIES PRESENTING IN CHILDHOOD
Congenital myopathies: nemaline myopathy, centronuclear myopathy, central core
Endocrine-metabolic disorders: hypokalemia, hypocalcemia, hypercalcemia
Glycogen storage disease (acid maltase deficiency)
Inflammatory myopathies: dermatomyositis, polymyositis (rarely)
Lipid storage disease (carnitine deficiency)
Mitochondrial myopathies
Muscular dystrophies: congenital, Duchenne, Becker, Emery-Dreifuss, facioscapulohumeral, limb-girdle
MYOPATHIES PRESENTING IN ADULTHOOD
Centronuclear myopathy
Distal myopathies
Endocrine myopathies: thyroid, parathyroid, adrenal, pituitary disorders
Inflammatory myopathies: polymyositis, dermatomyositis, inclusion body myositis, viral (human immunodeficiency virus)
Metabolic myopathies: acid maltase deficiency, lipid storage diseases, debrancher deficiency, phosphorylase b kinase deficiency
Mitochondrial myopathies
Muscular dystrophies: limb-girdle, facioscapulohumeral, Becker, Emery-Dreifuss
Myotonic dystrophy
Nemaline myopathy
Toxic myopathies: alcohol, corticosteroids, local injections of narcotics, colchicine, chloroquine

From Barohn RJ, Dimachkie MM, Jackson CR. A pattern recognition approach to the patient with a suspected myopathy. *Neurol Clin.* 2014;32(1):569–593. Box 7.

* The editors are grateful to Dr. Harvey B. Sarnat and Dr. Goknur Haliloglu, much of whose work on previous editions of this chapter is retained here.

Table 648.2 The Genetics of Congenital Myopathies

GENE	SUBTYPE	INHERITANCE PATTERN	PROTEIN	PRIMARY SUBCELLULAR INVOLVEMENT	POSSIBLE PATHOGENESIS
ACTA 1	Nemaline myopathy (NM)	AD, AR	Actin, alpha skeletal muscle	Thin filament involvement	Abnormal thin filament structure
	Cap disease (NM variant)	AD			
	Zebra body myopathy (NM variant)	AD			
	Congenital fiber type disproportion	AD			
TPM3	Nemaline myopathy (NM variant)	AD, AR	Tropomyosin-3		
	Cap disease (NM variant)	AD			
	Congenital fiber-type disproportion	AD			
TPM2	Nemalin myopathy (NM)	AD	Tropomyosin-2 (beta)		
	Cap disease (NM variant)	AD			
TNNTI	Nemalin myopathy (NM)	AR	Troponin T type 1 (skeletal, slow)		
NEB	Nemaline myopathy (NM) Core–rod myopathy	AR	Nebulin		Thin filament remodeling ± stability
LMOD3	Nemalin myopathy (NM)	AR	Leiomodin-3		
KBTBD13	Nemalin myopathy (NM)	AD	Kelch repeat and BTB (POZ) domain containing protein 13		
CFL2	Nemalin myopathy (NM)	AR	Cofilin 2 (muscle)		
KLHL40	Nemalin myopathy (NM)	AR	Kelchlike family member 40		
KLHL41	Nemalin myopathy (NM)	AR	Kelchlike family member 41		
MYO18B	Nemalin myopathy	AR	Myosin 18B	Unknown	Unknown
RYR1	Central core myopathy	AD, AR	Ryanodine receptor I	Triad involvement	Abnormal EC coupling
	Multiminicore myopathy	AR			
	Core–rod myopathy	AD, AR			
	Nemalin myopathy	AR			
	Congenital fiber type disproportion	AR			
	Centronuclear myopathy	AR			
	Congenital neuromuscular disease with uniform type 1 fiber	AD			
CACNASI	Congenital fiber type disproportion	AR	DHPR		
STAC3	Native American myopathy	AR	SH3 and cysteine-rich domain containing protein 3		
ORA11	Tubular aggregate myopathy	AD	Transmembrane protein 142A		Abnormal SOCE
ST1M1	Tubular aggregate myopathy	AD	Stromal interaction molecule 1		
SEPN1	Multiminicore myopathy	AR	Selenoprotein N1		Oxidative defects
	Congenital fiber type disproportion	AR			
CCDC78	Centronuclear myopathy	AD	Coiled coil domain containing protein 78		Abnormal EC coupling?
BIN 1	Centronuclear myopathy	AR, AD	Amphiphysin		Membrane remodeling ± stability
DNM2	Centronuclear myopathy	AD	Dynamin 2		
MTM1	Myotubular myopathy	XR	Myotubularin 1		

Table 648.2 The Genetics of Congenital Myopathies—cont'd

GENE	SUBTYPE	INHERITANCE PATTERN	PROTEIN	PRIMARY SUBCELLULAR INVOLVEMENT	POSSIBLE PATHOGENESIS
MTMR14[a]	Centronuclear myopathy		Myotubularin-related protein 14		
SPEG	Centronuclear myopathy with dilated cardiomyopathy	AR	SPEG complex locus		
PTPLA (=HCDA1)	Congenital myopathy related to PTPLA	AR	Protein tyrosine phosphatase-like (3-hydroxyacyl-CoA dehydratase)		
TTN	Centronuclear myopathy	AR	Titin		
	Congenital myopathy with fatal cardiomyopathy	AR			
MYH7	Myosin storage myopathy	AD	Myosin, heavy chain 7, cardiac muscleb		Abnormal ATPase and actin-binding properties
	Myosin storage myopathy with cardiomyopathy	AR			Structural abnormalities
	Congenital fiber type disproportion	AD			
MYH2	Myosin IIa myopathy	AD, AR	Myosin, heavy-chain 2, skeletal muscle	Heavy-chain neuromuscular junction (NJ)	Abnormal ATPase and actin-binding properties
CNTN1	Compton-North congenital myopathy	AR	Contactin-1		Structural abnormalities Aberrant NJ adhesion?
MEGF10	Early-onset myopathy, areflexia respiratory distress, and dysphagia	AR	Multiple EGF-like domains 10	Satellite cells	Abnormal regulation of satellite cells
	Minicores	AR			
ZAK	Congenital fiber type disproportion	AR	Sterile alpha motif and leucine zipper containing kinase AZK	Unknown	Mitogen-activated protein kinase (MAPK) signaling pathway

[a]Until now *MTMR14* has been proven to produce a myopathy only in animal models.

AD, Autosomal-dominant; AR, autosomal-recessive; AZK, sterile alpha motif and leucine zipper containing kinase; BTB, broad-complex, tramtrack and bric a brac; DHPR, dihydropyridine receptor; EC, excitation–contraction; EGF, epidermal growth factor; POZ, Pox virus and zinc finger; SOCE, store-operated calcium entry; XR, X-linked recessive.

From Castro D, Henriquez A. Treatment and management of spinal muscular atrophy and congenital myopathies. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management*, 2nd ed. Philadelphia: Elsevier; 2022: Table 13.2, p. 265.

Table 648.3 Myopathies Developing Ventricular Arrhythmias or Sudden Cardiac Death

MYOPATHIES	ARRHYTHMIAS	SUDDEN CARDIAC DEATH
DMD, XL-EDMD, MD1, MD2, mitochondrial MP, FAODs, VLCAD, Danon disease	VTs	r
BMD	Reentry VT	r
Laminopathy	VT, ventricular fibrillation	r
FSH, hypokalemic periodic paralysis	VTs	nr
MFM	Nonsustained VT	r
Desminopathy, MELAS	Sustained VT	r
NARP, PEO	Nonsustained VTs	nr
KSS	Torsade de pointes	r
CPT-II deficiency	Cardiac arrest	r
Barth syndrome	Ventricular arrhythmia	r

BMD, Becker muscular dystrophy; CPT, carnitine palmityl transferase; DMD, Duchenne muscular dystrophy; FAODs, fatty acid oxidation disorders; FSH, facioscapulohumeral muscular dystrophy; KSS, Kearns-Sayre syndrome; MD1 MD2, myotonic dystrophy; MELAS, mitochondrial encephalomyelopathy with lactic acidosis and stroke; MFM, myofibrillar myopathy; MP, myopathy; NARP, neuropathy, ataxia, and retinitis pigmentosa; nr, not reported; PEO, progressive external ophthalmoplegia; r, reported; VLCAD, very long chain acyl-CoA dehydrogenase deficiency; VT, ventricular tachycardia; XL-EDMD, Emery-Dreifuss muscular dystrophy.

Modified from Finsterer J, Stollberger C, Keller H. Arrhythmia-related workup in hereditary myopathies. *J Electrocardiol*. 2012;45:376–384. Table 5.

Table 648.4 Functional Assessment of Muscle Weakness

LOCATION	SIGNS OR SYMPTOMS OF WEAKNESS
Facial	Inability to bury eyelashes, horizontal smile, inability to whistle
Ocular	Double vision, ptosis, disconjugate eye movements
Bulbar	Nasal speech, weak cry, nasal regurgitation of liquids, poor suck, difficulty swallowing, recurrent aspiration pneumonia, cough during meals
Neck	Poor head control
Trunk	Scoliosis, lumbar lordosis, protuberant abdomen, difficulty sitting up
Shoulder girdle	Difficulty lifting objects overhead, scapular winging
Forearm/hand	Inability to make a tight fist, finger or wrist drop, inability to prevent escape from hand grip
Pelvic girdle	Difficulty climbing stairs, waddling gait, Gower sign
Leg/foot	Foot drop, inability to walk on heels or toes
Respiratory	Use of accessory muscles

From Barohn RJ, Dimachkie MM, Jackson CR. A pattern recognition approach to the patient with a suspected myopathy. *Neurol Clin.* 2014;32(1):569–593. Box 12, p. 578.

TREATMENT OF CONGENITAL MYOPATHIES

Treatment remains largely supportive care for respiratory insufficiency and feeding and swallowing difficulties in particular, but genetic approaches specific for identified mutations are being investigated and may eventually reverse some of the most disabling clinical deficits. Administration of steroids, as well as other antiinflammatory agents, which is useful in many patients with Duchenne muscular dystrophy, is not effective for the congenital myopathies. There is optimism for efficacy of adenoviral vector-based gene therapy for some of the congenital myopathies, and X-linked *MTM1* gene–related myotubular myopathy is a good example where efficacy and safety is being evaluated in human clinical trials. Long-term outcomes for some congenital myopathies are noted in Figures 648.1 and 648.2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.1 Myotubular Myopathy (Centronuclear Myopathy)

Adnan Y. Manzur

The term **myotubular myopathy** is a misnomer because it implies maturational arrest of fetal muscle during the myotubular stage of development at 8-15 weeks of gestation. It was based on the morphologic appearance of myofibers as a row of central nuclei and mitochondria within a core of cytoplasm, with contractile myofibrils forming a cylinder around this core. These morphologically abnormal myofibers are not true fetal myotubes; hence, the more neutral and descriptive term ***centronuclear myopathy*** (CNM) is preferred.

PATHOGENESIS

The common pathogenesis involves loss of myotubularin protein, leading to structural and functional abnormalities in the organization of T-tubules and sarcoplasmic reticulum and defective excitation-contraction coupling. In true fetal myotubes, the peripheral migration of central nuclei and the core of internuclear mitochondria is initiated

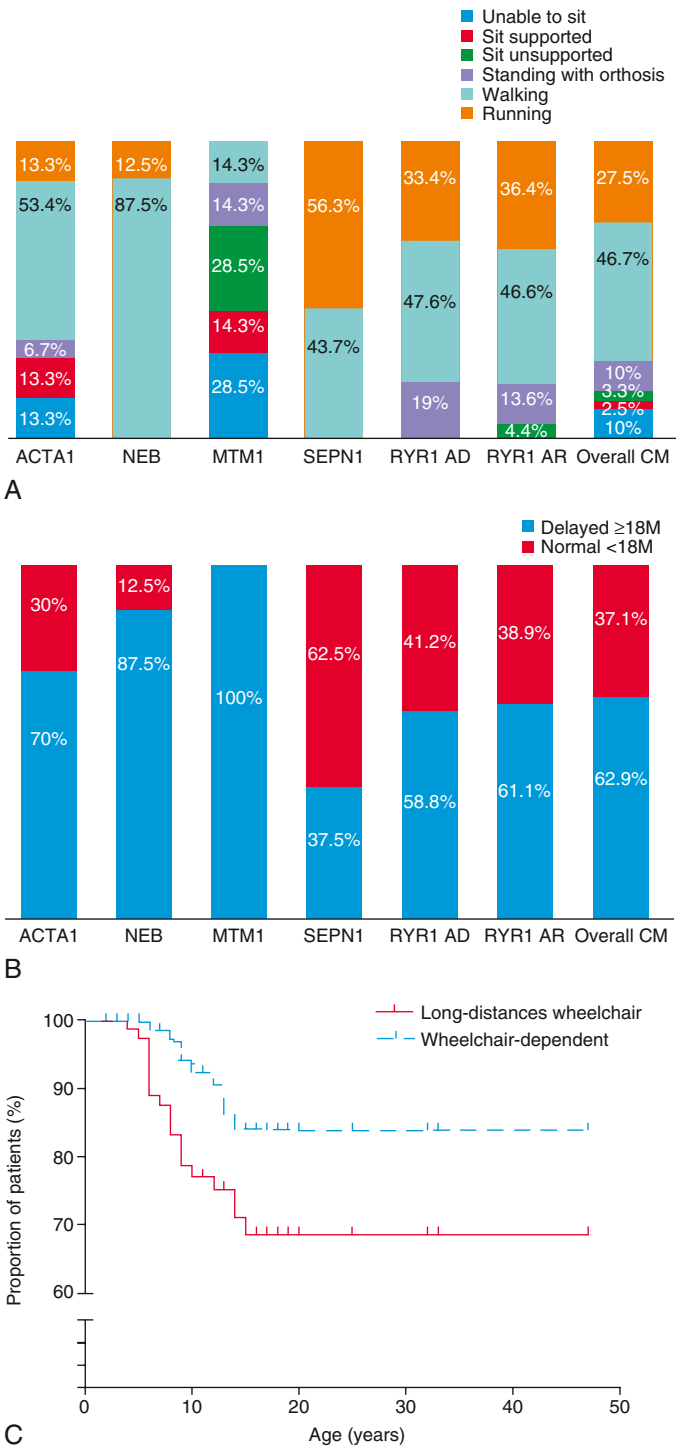

Fig. 648.1 Motor abilities. **A,** Maximal motor ability: all patients with *SEPN1* and *NEB* pathogenic variants walked independently, whereas motor ability was more variable with other genetic backgrounds. **B,** Walking age. The majority of ambulant patients walked late (39.3%) or at the upper limit of normal at 18 mo (23.6%). At last follow-up, 3.2% were younger than 18 mo. **C,** Kaplan-Meier curve showing wheelchair use in patients who achieved independent ambulation: 20 of 89 (22.5%) started with a manual wheelchair for long distances, whereas a further deterioration of motor performance was observed in 8 of 20, who became wheelchair-bound. *ACTA1*, Skeletal muscle α-actin; AD, autosomal dominant; AR, autosomal recessive; CM, congenital myopathy; *MTM1*, myotubularin; *NEB*, nebulin; *RYR1*, ryanodine receptor type 1; *SEPN1*, selenoprotein N. *(From Colombo I, Scoto M, Manzur AY, et al. Congenital myopathies. Neurology. 2015;84:28–35. Fig. 3.)*

by the regression of fetal vimentin intermediate filaments at 15-20 weeks of gestation that hold these structures in the center of the myotube, but this is not the mechanism of centronuclear myopathies, except perhaps in *neonatal myotonic dystrophy,* which does involve maturational arrest of some myofibers.

CLINICAL MANIFESTATIONS

Fetal movements can decrease in late gestation. Polyhydramnios is a common complication because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid.

At birth, affected infants have a thin muscle mass involving axial, limb girdle, and distal muscles; severe generalized hypotonia; and diffuse weakness. Respiratory efforts may be ineffective, requiring ventilatory support. Gavage feeding may be required because of weakness of the muscles of sucking and deglutition. The testes are often undescended. Facial muscles may be weak, but infants *do not* have the characteristic facies of myotonic dystrophy. Ptosis may be a prominent feature. Ophthalmoplegia is observed in a few cases. The palate may be high. The tongue is thin, but fasciculations *are not* seen. Tendon stretch reflexes are weak or absent.

Myotubular myopathy is not associated with cardiomyopathy (mature cardiac muscle fibers normally have central nuclei), but one report describes complete atrioventricular block without cardiomyopathy in a patient with confirmed X-linked myotubular myopathy. Congenital anomalies of the central nervous system (CNS) or of other systems are not associated. A single patient with progressive dementia was reported that had a variant removing the start signal of exon 2. Patients with much milder symptoms or a much later age of onset with variants in the same gene are also known. Some of these are *manifesting* carriers.

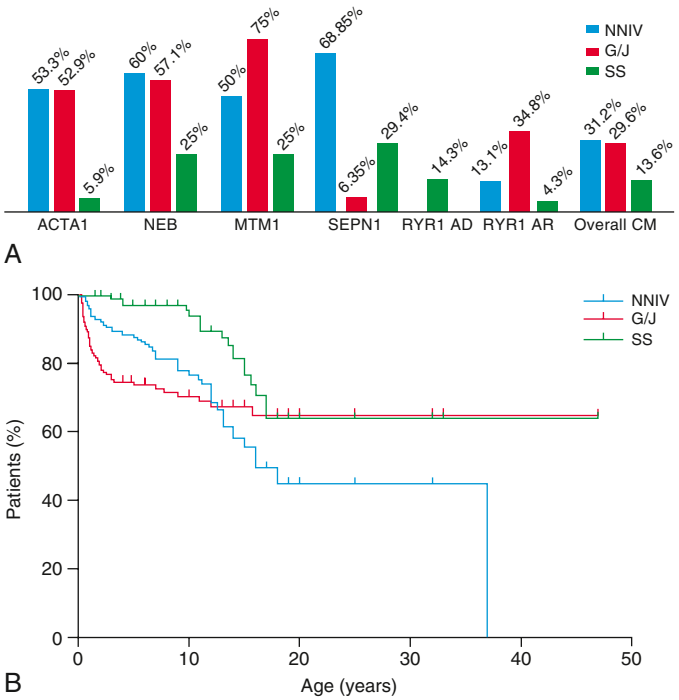

Fig. 648.2 Respiratory, feeding, and orthopedic procedures. **A,** Prevalence of NNIV, gastrostomy/jejunostomy (G/J), and scoliosis surgery (SS) according to genetic background: overall about one third of cases required NNIV and G/J insertion. Only a minority of cases required scoliosis surgery. **B,** Kaplan-Meier curves showing ventilation, G/J, and SS-free patients: NNIV was started at a mean age of 8.53 yr, whereas G/J was placed earlier, at a mean age of 2.74 yr, usually within the first year. SS was performed at a mean age of 12.0 yr. AD, Autosomal dominant; AR, autosomal recessive; CM, congenital myopathy. *(From Colombo I, Scoto M, Manzur AY, et al. Congenital myopathies. Neurology. 2015;84:28–35. Fig. 4.)*

LABORATORY FINDINGS

Serum levels of creatine kinase (CK) are normal. Electromyography does not show evidence of denervation; results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. The electrocardiogram appears normal. Chest radiographs show no cardiomegaly; the ribs may be thin.

DIAGNOSIS

If the diagnosis is strongly suspected from the clinical presentation, especially if this diagnosis was confirmed in a sibling, genetic tests can be performed in the neonatal period. In most cases the diagnosis is not so evident, but the muscle biopsy findings are diagnostic at birth, even in premature infants. More than 90% of muscle fibers are small and have centrally placed, large vesicular nuclei in a single row. Spaces between nuclei are filled with sarcoplasm containing mitochondria. Histochemical stains for oxidative enzymatic activity and glycogen reveal a central distribution as in fetal myotubes. The cylinder of myofibrils shows mature histochemical differentiation with adenosine triphosphatase stains. The connective tissue of muscle spindles, blood vessels, intramuscular nerves, and motor end plates is mature. Ultrastructural features other than those that define the disease are also mature. Electron microscopy shows disorganized triads and focal loss of myofilaments. Vimentin and desmin show strong immunoreactivity in muscle fibers in congenital CNM and no demonstrable activity in normal-term neonatal muscle. Several myotubularins are present in circulating platelets and may prove to be a simple noninvasive screening test in patients suspected of having this disease. The molecular genetic marker in blood is available also for early prenatal diagnosis if suspicion is strong because of a family history. Prenatal diagnosis by amniocentesis is feasible in strongly suspected involved fetuses. Table 648.5 distinguishes CNM from other congenital myopathies.

GENETICS

At least five genes are involved in this disorder and account for approximately 80% of patients. These include variants in myotubularin (*MTM1* gene) with X-linked severe manifestations; dynamin 2

Table 648.5 Specific Congenital Myopathies: Distinguishing Clinical Features

MYOPATHY	NEONATAL HYPOTONIA AND WEAKNESS	SEVERE FORM WITH NEONATAL DEATH	FACIAL WEAKNESS	PTOSIS	EXTRAOCULAR MUSCULAR WEAKNESS
Central core disease	+	0	±	0	0
Nemaline myopathy	+	+	+	0	0
Myotubular myopathy (centronuclear myopathy)	+	+	+	+	+
Congenital fiber-type disproportion	+	±	±	0	+

+, Often a prominent feature; ±, variably a prominent feature; 0, not a prominent feature.
From Volpe JJ. *Neurology of the Newborn,* 5th ed. Philadelphia: Saunders; 2008: p 820.

(DNM2) with autosomal dominant or sporadic occurrence; amphiphysin 2 *(BIN1)* and titin *(TTN)* variants with autosomal recessive inheritance and ryanodine receptor 1 *(RYR1),* with autosomal recessive or sporadic occurrence.

X-linked recessive inheritance is the most common trait in this disease affecting males. The mothers of affected infants are clinically asymptomatic, but their muscle biopsy specimens show minor alterations. Genetic linkage on the X chromosome has been localized to the Xq28 site, a locus different from the Xp21 gene of Duchenne and Becker muscular dystrophies. A deletion in the responsible *MTM1* gene has been identified. It encodes a protein called myotubularin. This gene belongs to a family of similar genes encoding enzymatically active and inactive forms of phosphatidylinositol-3-phosphatases that form dimers. *MTM1*, dynamin-2, and amphiphysin all are localized to the T-tubule wall in triads. This crucial region is where the action potential releases a signal to the ryanodine receptor to release calcium. The pathogenesis is in the regulation of enzymatic activity and binding to other proteins induced by dimer interactions. Although only a single *MTM1* gene is involved, five distinct point variants and many different alleles, as well as large duplications, can produce the same clinical disease. Variants in the dynamin-2 protein result in an autosomal dominant form of CNM and may account for up to half of all patients with CNM, but these cases usually are mild and might not manifest clinically until adult life as diffuse, slowly progressive weakness and generalized muscular pseudohypertrophy.

Other rarer centronuclear myopathies are also known; some are autosomal recessive and affect both sexes and others are sporadic and of unknown genetic origin. The recessive forms are sometimes divided into an early-onset form with or without ophthalmoplegia and a late-onset form without ophthalmoplegia.

TREATMENT

Only supportive and palliative treatment is presently available. Progressive scoliosis may be treated by long posterior fusion. Genetic and neuropathologic studies of X-linked centronuclear (myotubular) myopathy have led to effective gene therapy in mice and in dogs, so that the animals are more ambulatory and have improved weakness; the therapy results in long-term expression of the myotubularin transgene with normal muscular performance and neurologic function in the absence of muscle pathology. Human trials of gene therapy for X-linked CNM are in progress.

PROGNOSIS

Approximately 75% of severely affected neonates with the X-linked disease die within the first few weeks or months of life. Survivors experience a slowly progressive course and have major physical handicaps, rarely walk, remain severely hypotonic and weak, and mostly ventilator dependent. Late-onset and especially autosomal dominant forms have a much better prognosis, often with mild static weakness. Treatment by gene therapy may dramatically change this prognosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.2 Congenital Muscle Fiber–Type Disproportion

Adnan Y. Manzur

Congenital muscle fiber–type disproportion (CMFTD) occurs as an isolated congenital myopathy but also develops in association with various unrelated disorders, which include nemaline rod disease and Krabbe disease (globoid cell leukodystrophy), early in the course before the expression of the neuropathy; congenital muscular dystrophy (CMD) with merosin deficiency (occasionally); cerebellar hypoplasia and certain other brain malformations; fetal alcohol syndrome; some glycogenoses; multiple sulfatase deficiency; Lowe syndrome; rigid spine myopathy; and some infantile cases of myotonic muscular dystrophy. *CMFTD is, therefore, a syndrome.* Several specific genetic variants are confirmed causing the CMFTD histologic appearance and these include *TPM2, TPM3, MYH7, RYR1,* skeletal muscle α-actin gene *(ACTA1),* and *LMNA*.

PATHOGENESIS

The association of CMFTD with *cerebellar hypoplasia* suggests that the pathogenesis may be an abnormal suprasegmental influence on the developing motor unit during the stage of histochemical differentiation of muscle between 20 and 28 weeks of gestation. Muscle fiber types and growth are determined by innervation and are mutable even in adults. Although CMFTD does not actually correspond with any normal stage of development, it appears to be an embryologic disturbance of fiber-type differentiation and growth.

CLINICAL MANIFESTATIONS

As an isolated condition not associated with other diseases, CMFTD is usually a *nonprogressive* disorder present at birth. Patients have generalized hypotonia and weakness, but the weakness is usually not severe. *Contractures* are present at birth in 25% of patients. Poor head control and developmental delay for gross motor skills are common in infancy. Walking is usually delayed until 18-24 months but is eventually achieved. Because of the hypotonia, subluxation of the hips can occur. Muscle bulk is reduced. The muscle wasting and hypotonia are proportionately greater than the weakness, and the child may be stronger than expected during examination. Cardiomyopathy is a rare complication. Respiratory weakness usually is mild but can be demonstrated in 30% of neonates and young infants. Dysphagia is infrequent except if CMFTD is secondary to myotonic dystrophy, nemaline myopathy, or a systemic metabolic disease with additional encephalopathy.

The facies of children with CMFTD often raise suspicion, especially if the child is referred for assessment of developmental delay and hypotonia. The head is dolichocephalic, and facial weakness is present. The palate is usually high arched. Thin muscles of the trunk and extremities give a thin, wasted appearance. The phenotype is very similar to that of nemaline myopathy, which also includes CMFTD as part of the pathologic phenotype. Patients do not complain of myalgias. The clinical course generally is nonprogressive or only slowly progressive unless it is associated with other congenital myopathies.

LABORATORY FINDINGS

The serum CK, electrocardiogram, electromyography studies, and nerve conduction velocity results are normal in isolated CMFTD. If other diseases are associated, laboratory investigation of those conditions discloses the specific features. Specific genetic studies are indicated if there is a family history.

DIAGNOSIS

CMFTD is diagnosed by muscle biopsy that shows a disproportion in the size and relative ratios of the histochemical fiber types: type I fibers are uniformly small, and type II fibers are hypertrophic; type I fibers are more numerous than type II fibers. Degeneration of myofibers and other primary myopathic features are absent. The biopsy is diagnostic at birth. Table 648.5 lists the features that distinguish CMFTD from other congenital myopathies. Selective atrophy or even hypoplasia of type II myofibers is not CMFTD, though it has sometimes been labeled as *reverse CMFTD.*

GENETICS

Many cases of simple CMFTD are sporadic, although an autosomal recessive inheritance is well documented in some families and an autosomal dominant trait is suspected in others. The genetic basis is heterogeneous in hereditary forms; a pathogenic variant in the insulin receptor gene at 19p13.2 is reported. Translocation t(10;17) was seen in one family. X-linked transmission with linkage to Xp23.12-p11.4 and Xq13.1-q22.1 is also described. *LMNA* gene variants produce familial CMFTD, clearly a germline genetic variant with mendelian autosomal transmission. In three unrelated families with CMFTD, a heterozygous missense variant of the skeletal muscle α-actin gene *(ACTA1)* was demonstrated, but this genetic defect represents a minority; variants in

TPM3 or *TPM2* are the more common genetic findings. Large duplications in the *TPM3* gene can cause CMFTD. *MYH7* de novo gene variants lead to exon skipping. CMFTD may occur in RYR1 disease without obvious cores on muscle biopsy. In CMFTD associated with cerebellar hypoplasia, the epigenetic effect is on cerebellar development and the muscular expression is secondary.

TREATMENT

No drug therapy is available. Physiotherapy may be helpful for some patients in strengthening muscles that do not receive sufficient exercise in daily activities. Mild congenital contractures often respond well to gentle range-of-motion exercises and rarely require plaster casting or surgery. The relative rarity of early-onset congenital myopathies such as CMFTD and the diversity of the genotype make focused gene therapies difficult, but the identification of specific molecular mechanisms and novel gene editing strategies are a basis for future therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.3 Nemaline Rod Myopathy

Adnan Y. Manzur

Nemaline rods are rod-shaped, inclusion-like abnormal structures within muscle fibers. They are difficult to demonstrate histologically with conventional hematoxylin and eosin stain but are easily seen with special stains. They are not foreign inclusion bodies but rather consist of excessive Z-band material with a similar ultrastructure (Fig. 648.3). Chemically, the rods are composed of actin, α-actinin, tropomyosin-3, and the protein nebulin. Nemaline rod formation may be an unusual reaction of muscle fibers to injury because these rod structures have rarely been found in other diseases. They are most abundant in the congenital myopathy known as *nemaline rod disease.* Most rods are within the myofibrils, but intranuclear rods are occasionally demonstrated by electron microscopy. Intranuclear rods occur mainly in neonates with severe weakness. Fourteen causative genes have been identified, and *ACTA1* pathologic variants account for more than half of the severe cases. Nemaline myopathy caused by an *ACTA1* gene variant is one of a spectrum of *actinopathies.*

Pathologic variants in *TPM2* can cause a congenital myopathy *related* to nemaline rod myopathy, designated cap myopathy, in which accumulations of distorted myofilaments are focally present on the periphery of fibers. They may coexist with myofibrillar nemaline rods. Somatic mosaicism is demonstrated in *TPM2*-related nemaline myopathy with cap structures.

Gene variants in muscle-specific Kelch BTB genes *(KBTBD13, KLHL40, KLHL41)* cause nemaline myopathy with potential pathologic signatures on muscle biopsy. Autosomal dominant *KBTBD13* gene variants are identified in families with nemaline myopathy and cores. Autosomal recessive *KLHL40* and *KLHL41* variants are described in severe early onset nemaline myopathy with fetal akinesia phenotypes and congenital fractures (see Chapter 648.10).

CLINICAL MANIFESTATIONS

Prenatal, neonatal, infantile, juvenile, and adult-onset forms of the disease are known. There is a highly variable degree of muscle weakness, ranging from presentations within the *fetal akinesia* spectrum to only mildly affected adults. All defining features of congenital myopathies can occur in different contexts; although there is not a clear genotype-phenotype correlation, there may be clinical clues for specific gene variants. Prenatal and neonatal forms are severe and usually fatal because of respiratory failure since birth. In the infantile form, generalized hypotonia and weakness, which can include bulbar-innervated and respiratory muscles, and a very thin muscle mass are characteristic (Fig. 648.4). The head is dolichocephalic, and the palate high arched or even cleft. Muscles of the jaw may be too weak to hold it closed (Fig. 648.5). Decreased fetal movements are reported by the mother, and neonates suffer from hypoxia and dysphagia; arthrogryposis may be present (see Chapter 648.10). Infants with severe neonatal and infantile nemaline myopathy have facies and a phenotype that are nearly indistinguishable from those of *neonatal myotonic dystrophy,* but their mothers have normal facies.

In *NEB*-related nemaline myopathy, which is the most common form, patients usually present in infancy or childhood, and there is a disproportional axial and bulbar involvement compared with limb weakness. In spite of preserved ambulation, scoliosis and respiratory involvement are universal. Distal muscle involvement may be a presenting feature in some patients. *ACTA1*-related nemaline myopathy is typically severe, and additional phenotypes include (1) progressive scapuloperoneal and distal weakness in a large single family with autosomal dominant inheritance, demonstrating muscle atrophy without nemaline rods; (2) a severe congenital presentation with myofibrillar features on muscle biopsy; (3) limb-girdle muscular dystrophy (LGMD) phenotype; (4) autosomal recessive CMD with a rigid spine;

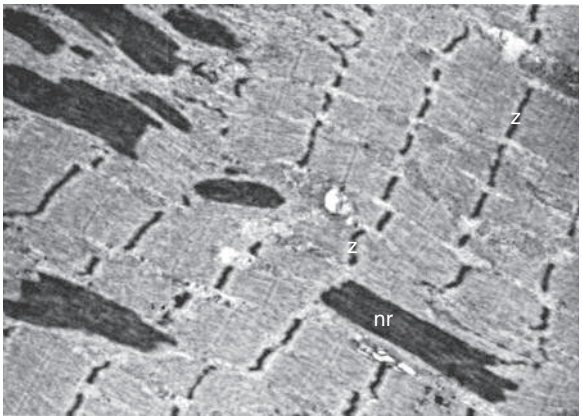

Fig. 648.3 Nemaline rods. Electron micrograph of the muscle from a patient shown in Figure 648.5. Nemaline rods (nr) are seen within many myofibrils. They are identical in composition to the normal Z bands (z) (×6,000).



Fig. 648.4 Back of a 13-yr-old female with the juvenile form of nemaline rod disease. The paraspinal muscles are very thin, and winging of the scapulae is evident. The muscle mass of the extremities is also greatly reduced proximally and distally.



Fig. 648.5 Infantile form of nemaline rod disease in a 6-yr-old male. Facial weakness and generalized muscle wasting are severe. The head is dolichocephalic. The mouth is usually open because the masseters are too weak to lift the mandible against gravity for more than a few seconds.

and (5) zebra body myopathy. Cardiomyopathy is not a feature of *NEB*-related nemaline myopathy; however, it has been rarely reported in patients with *ACTA1* gene variants.

The *juvenile form* is the mildest and is not associated with respiratory failure, but the phenotype, including facial involvement, is similar. *Adult-onset* presentations are in the form of slowly progressive proximal weakness with axial involvement, and although not symptomatic in childhood and adolescence, these patients retrospectively report difficulties with sportive activities in childhood.

LABORATORY FINDINGS

The serum CK level is normal or mildly elevated. The muscle biopsy is diagnostic. In addition to the characteristic nemaline rods, it also shows CMFTD or, at least, fiber-type I predominance. In some patients, uniform type I fibers are seen with few or no type II fibers. Focal myofibrillar degeneration and an increase in lysosomal enzymes have been found in a few severe cases associated with progressive symptoms. Intranuclear nemaline rods, demonstrated by electron microscopy, are correlated with the most severe neonatal manifestations. Potential pathologic hallmarks of *KLHL40* gene variants are miliary bodies and *LMOD3* gene variants; the latter are a fringe of thin filaments radiating from the nemaline bodies and paired nemaline bodies interconnected by thin filaments. Because nemaline bodies can occur in other myopathies, their presence in the muscle biopsy is **not** pathognomonic in the absence of the supportive clinical manifestations. **Sporadic late-onset nemaline myopathy (SLONM)** may be associated with monoclonal gammopathy, HIV infection, and various autoimmune disorders, and should be differentiated from genetic causes because it is a potentially treatable condition.

GENETICS

Autosomal dominant, autosomal recessive, and X-linked dominant forms in females can occur. Nemaline myopathy can be caused by gene variants in at least 10 genes, including *ACTA1* (skeletal muscle α-actin), *NEB* (nebulin), *TPM3* (slow muscle αα-tropomyosin), *TPM2* (ββ-tropomyosin), *CFL2* (skeletal muscle cofilin), *TNNT1* (slow muscle troponin-T), *LMOD3* (leiomodin 3), *KBTBD13* (Kelch-repeat and BTB domain containing 13), *KLHL40,* and *KLHL41* (Kelch-like 40 and 41). All of the genes implicated in nemaline myopathy encode proteins constituting the thin filaments of myofibrils or regulate thin-filament organization and stability. Overall, recessive gene variants in *NEB* and de novo dominant gene variants in *ACTA1* are most common, and represent approximately 50% and 25% of cases, respectively. *TNNT1* nemaline myopathy known to be specific for Old Order Amish populations is also identified in other populations. Gene variants in muscle specific Kelch proteins are increasingly recognized. *KBTBD13* nemaline myopathy is characterized by autosomal dominant inheritance and phenotypic variability. *KLHL40* and *KLHL41* nemaline myopathies represent the severest end of the spectrum, with in utero presentations, fetal akinesia, arthrogryposis, congenital fractures, and specific signatures on muscle biopsy samples (see Chapter 648.10). Kelch-BTB proteins act as E3-ubiquitin ligases and mediate protein turnover. In animal and cell culture studies, *KLHL40* was shown to stabilize leiomodin-3 (Lmod3) and the absence of KLHL40 was shown to reduce Lmod3 and Neb, which was further confirmed in muscle biopsy samples of some patients with *KLHL40*. This led to identification of pathologic variants in the gene encoding *leiomodin-3*, a protein especially present at the pointed end of muscle thin filaments. *LMOD3* nemaline myopathy is characterized by a severe phenotype with, again, potential hallmarks on muscle biopsy.

TREATMENT AND PROGNOSIS

There is no cure, and management is mainly supportive and symptomatic. Survivors are usually wheelchair dependent and unable to overcome gravity. Both proximal and distal muscles are involved. Congenital *arthrogryposis* and *fractures* can occur and predict a poor prognosis. Gastrostomy may be needed for chronic dysphagia. Special attention to respiratory function in patients presenting with scoliosis and axial involvement is important to recognize early signs and symptoms of **nocturnal hypoventilation syndrome.** In the juvenile form, patients are ambulatory and are able to perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. Cardiomyopathy is an uncommon complication. Death usually results from respiratory insufficiency, with or without superimposed pneumonia.

Based on preclinical data in experimental models of *ACTA1*-related nemaline myopathy, a variety of pharmacologic compounds and supplements, including L-tyrosine, have been tested in five patients with nemaline myopathy; a beneficial effect has been suggested, with reduced fatigue and improvement of drooling. Treatments targeting the neuromuscular junction are another option; a single patient with *KLHL40*-related nemaline myopathy had a sustained beneficial response to the acetylcholinesterase inhibitor pyridostigmine, a result that corresponds to experiences in other congenital myopathies, mainly centronuclear myopathies. Drugs targeting thin filaments and their interactions, myostatin inhibitors to promote muscle growth, and cardiac α-actin upregulation in *ACTA1*-related nemaline myopathy are being investigated in animal models.

Despite advances in our understanding of pathophysiologic concepts and efforts for therapy, genetic counseling and prenatal diagnosis should be considered in families with an index patient and a precise genetic diagnosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.4 Core Myopathies

Adnan Y. Manzur

The core myopathies are the most common form of congenital myopathy, consisting of *central core diseases* (CCDs), *multiminicore disease* (MmD), and *atypical cores.* Cores are regions within muscle fibers in which only amorphous, granular cytoplasm is found, with an absence of myofibrils and organelles. Cores are devoid of mitochondria that contain disordered sarcomeric proteins. Histochemical stains show a lack of enzymatic activities of all types within these cores, as well as an absence of contractile proteins (actin and myosin) that form the thin

and thick myofilaments. Longitudinally extensive areas in the central area of myofiber devoid of oxidative enzyme activity represent central cores, and multiple smaller areas of reduced activity affecting shorter segments of the myofiber are characteristic of multicores and minicores. On electron microscopy, cores are characterized by an abnormal sarcomeric structure, including Z-band streaming, complete myofibrillary disorganization, and accumulation of Z-band material. Although variants of central cores, called minicores and multicores, are described in some families, they are believed to represent the same basic disease process. Pathologic features may evolve, with changes and abnormalities becoming more evident over time.

CLINICAL MANIFESTATIONS

The phenotypical spectrum of core myopathies ranges from mild to severe. Hypotonia, joint laxity, motor developmental delay, hip girdle or axial muscle weakness, orthopedic complications such as recurrent shoulder or patellar dislocations, congenital hip dislocation or dysplasia, or foot deformities may be presenting features. In older children, CCD is an important differential diagnosis of progressive thoracolumbar scoliosis. There is also an intrafamilial variability, with some individuals presenting only with muscle stiffness, exertional myalgia, or rhabdomyolysis.

Genetic resolution of core myopathies has led to gene variant-specific clinical presentations and phenotype-genotype correlations.

Central Core Disease

Central core disease (CCD) is most commonly associated with *RYR1* gene variants, which are described as the predominant genetic causes of nondystrophic neuromuscular disorders. These disorders range from dominantly inherited CCD, subgroups of recessively inherited MmD, and CNM (see Chapter 648.1), and CFTD (see Chapter 648.2) to **malignant hyperthermia susceptibility (MHS)** trait. MHS is a dominantly inherited allelic trait, described as a pharmacogenetic predisposition to a severe and potentially life-threatening reaction in response to halogenated anesthetic agents and depolarizing muscle relaxants. MHS is suspected in an individual with congenital myopathy when (1) there is a positive family history of MHS, (2) there have been previous difficulties with anesthesia, and (3) the patient has a documented *RYR1* gene variant.

Dominantly inherited *RYR1*-related CCD is characterized by mild to moderate muscle weakness presenting from infancy to childhood (Fig. 648.6). The clinical spectrum ranges from fetal akinesia deformation sequence to milder adult forms. The distribution of weakness is typically proximal, with prominent hip girdle and axial muscle involvement. Congenital hip dislocation, scoliosis, and generalized joint laxity are common. In contrast to the recessive forms with a more severe clinical phenotype, there is no extraocular muscle involvement. Bulbar, respiratory, and cardiac involvement is uncommon. Myalgia may be prominent. Except for patients with a severe neonatal onset, most patients with CCD achieve independent ambulation. CCD tends to be stable over long periods, with a possible slowly progressive course in adulthood. *RYR1*-related MHS is allelic to CCD, and some patients with CCD may also be malignant hyperthermia susceptible. Figure 648.7 shows a family with a recessive *RYR1* gene variant in the index patient and his asymptomatic father who is carrying a dominant *RYR1*-MHS gene. Characteristics and phenotypes due to *RYR1* gene variants are summarized in Table 648.6.

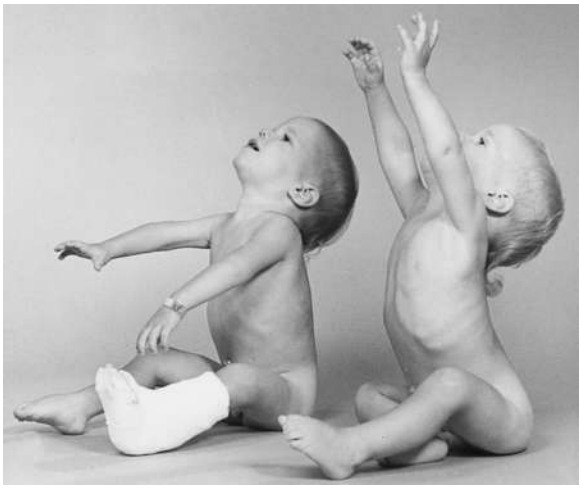

Fig. 648.6 Central core disease. Photograph of twins, one of whom has the disease. Note the weakness of the proximal upper extremities. *(From Cohen ME, Duffner PK, Heffner R. Central core disease in one of identical twins. J Neurol Neurosurg Psychiatry. 1978;41:659–663.)*

MHS-related *RYR1* gene variants have also been described as a common cause of induced and episodic phenotypes such as *exertional rhabdomyolysis,* which account for up to 30% of presentations in otherwise healthy individuals throughout life (see Chapter 647). Late-onset presentations in adulthood highlight the relevance of the congenital myopathies for adult neuromuscular practice. A predisposing genetic background should be considered if episodes are familial, recurrent, out of context to the exercise performed, or preceded by other symptoms, such as cramps, myalgia, and weakness. *RYR1*-related rhabdomyolysis may occur up to 72 hours after exercise and may mimic viral myositis; in contrast to other metabolic myopathies, fasting *does not* appear to be a triggering factor.

Due to expression of ryanodine receptors other than striated skeletal muscle, *nonskeletal muscle presentations of RYR1-related myopathies* are recognized. *Mild bleeding abnormalities* are described in patients with malignant hyperthermia carrying gain-of-function *RYR1* gene variants by altering vascular smooth muscle cell function. A bleeding defect in the animal model and one patient was reversed by treatment with the RyR1 antagonist dantrolene, suggesting a therapeutic role for *RYR1*-related bleeding disorders and, potentially, other bleeding disorders, as well. Another observed phenotype is severe CNS involvement in an adolescent suffering a malignant hyperthermia episode. Striking similarities in terms of cerebellar involvement seen in this patient and *heat stroke victims* indicated a potential link between *RYR1*-related exertional rhabdomyolysis and neuroleptic malignant syndrome. Some of the psychopharmacologic drugs, such as olanzapine, should be considered as triggering agents in patients with *RYR1* gene variants and exertional rhabdomyolysis. An emerging question is *cardiac involvement* in *RYR1*-related myopathies. Sudden unexplained death, dilated cardiomyopathy presumed to be due to a viral infection, bicuspid aortic valve, and sinus bradycardia are described; cardiologic assessment should be considered to define a cardiac phenotype associated with *RYR1*-related myopathies.

Multiminicore Disease

MmD is typically recessively inherited, and the clinical phenotype depends on the underlying genetic background. Presentations may vary and overlap between the most common and recognizable classic form, a severe neonatal form, a form with external ophthalmoplegia, and a moderate form with hand involvement. The *classic phenotype* due to recessive *SEPN1* gene variants can be summarized as axial weakness, early spinal rigidity, scoliosis, and respiratory impairment (Fig. 648.8). The onset is early, with predominant involvement of the neck muscles. Infants unable to hold up their heads, despite being able to walk independently, can present as having an *isolated neck myopathy* or *dropped-head syndrome.* A myopathic face, high-arched or cleft palate, high-pitched voice, feeding difficulties, and failure to thrive can be accompanying features. These patients may look very similar to each other, with an asthenic and atrophic muscle phenotype and growth retardation, and are mainly investigated and referred with a preliminary diagnosis of celiac disease. The proximal shoulder girdle muscles and inner thigh are affected more. Axial weakness is replaced with contractures of the spinal extensor muscles in time, leading to a *rigid spine deformity.* Usually by the second decade, there is a progressive scoliosis, lateral deviation of the trunk, and respiratory impairment that is overall in disproportion to the skeletal muscle weakness. MmD should be considered in the differential diagnosis of diseases presenting with

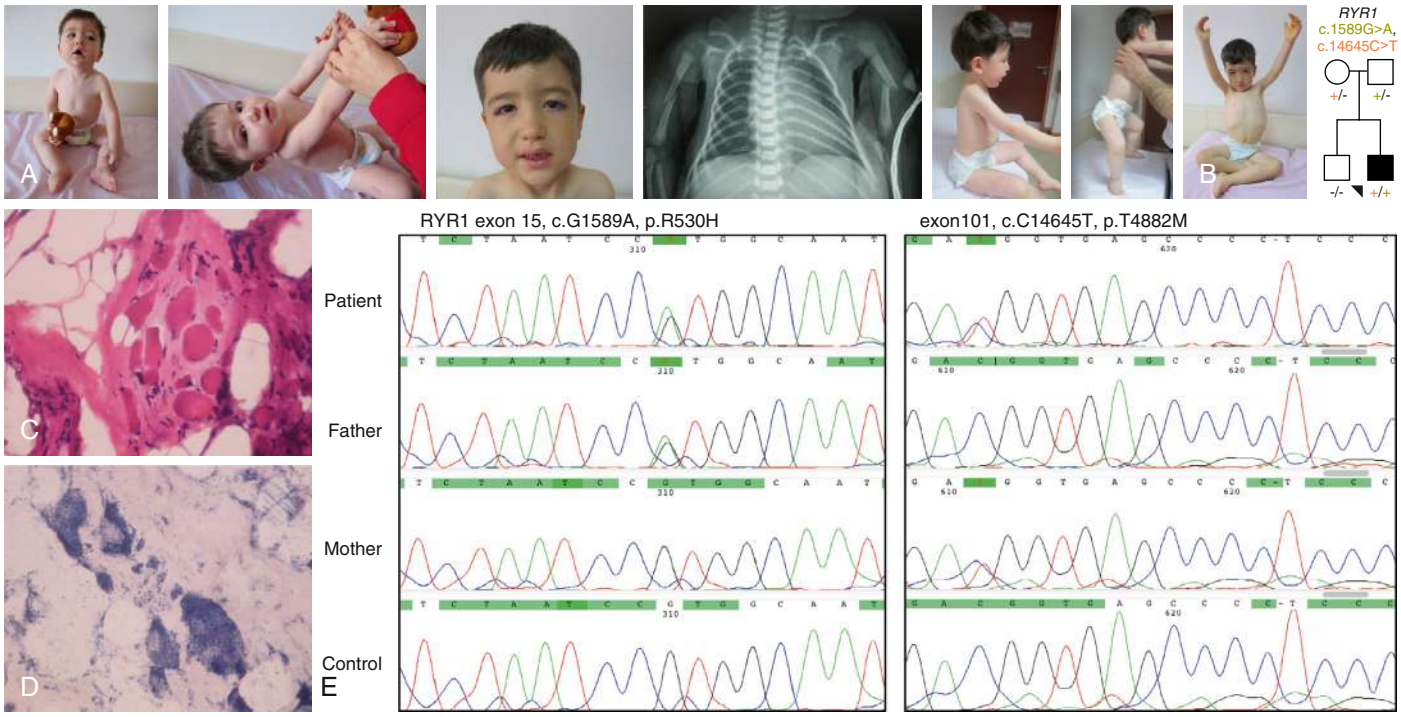

Fig. 648.7 Index patient presenting with developmental delay and hypotonia at the age of 19 mo. Note the bilateral humerus fractures at birth. He had a previous diagnosis of osteogenesis imperfecta. He has facial weakness, a myopathic face, and involvement of the neck flexor muscles with head-lag; his maximum motor capacity is to sit without support. **A,** He is unable to stand on his feet. **B,** At 4 yr of age, the patient is unable to walk. Muscle biopsy at the age of 19 mo demonstrating myopathic changes with increased fatty and fibrous tissue infiltration (HE) **(C)** and central cores (NADH) **(D).** The index patient is carrying a recessive *RYR1* gene variant, and his father is carrying a dominant *RYR1*-malignant hyperthermia susceptibility variant **(E).**

Table 648.6 Characteristics and Clinical Phenotypes Related to Ryanodine 1 *(RYR1)* Gene Variant–Related Central Core Disease

EARLY-ONSET *RYR1*-RELATED PHENOTYPES	LATE-ONSET *RYR1*-RELATED PHENOTYPES
Dominant gene variants typically present with congenital hypotonia, weakness, and hip dislocation at birth. Motor milestones are delayed; independent ambulation is eventually achieved. Weakness tends to involve hip girdle and quadriceps with sparing of facial and extraocular muscles.	Malignant hyperthermia susceptibility (MHS)
Recessive gene variants have a tendency of earlier and more severe presentation compared with most patients with dominant gene variants; however, they are also associated with a wide range of clinical phenotypes and pathologic features.	King-Denborough syndrome
Recessive phenotypes can be further grouped as clinical groups with and without ophthalmoparesis.	Exertional rhabdomyolysis
Dominant and recessive gene variants with a severe neonatal presentation leading to death are described.	Periodic paralysis
RYR1-related centronuclear myopathy (CNM) presents with a variable degree of external ophthalmoparesis, frequently associated with facial weakness.	Late-onset axial myopathy
Histopathologic features may resemble congenital fiber-type disproportion (CFTD) congenital muscular dystrophy (CMD).	

early neuromuscular chronic respiratory failure (i.e., chronic-onset respiratory muscle weakness while the patient is still ambulant). Respiratory involvement may lead to secondary cardiac failure. Ophthalmoplegia is not a feature of this classic form, but it has exceptionally been recognized in the last stages of disease in patients with a severe course.

MmD phenotypes due to *recessive RYR1 pathologic variants* are characterized by a milder respiratory but prominent bulbar impairment compared with those with the classic form. External ophthalmoplegia, recurrent episodes of periodic paralysis, distal weakness and wasting mainly affecting the hands, arthrogryposis, cryptorchidism, and dysmorphic features have also been described in the *RYR1*-related MmD spectrum. Hypertrophic cardiomyopathy associated with short-chain acyl-coenzyme A dehydrogenase deficiency, and primary cardiomyopathies due to gene variants in myosin heavy chain 7 *(MYH7)* or titin *(TTN)* genes, have been described in MmD. Although not reported in *SEPN1*-related MmD, there is a potential risk for MHS in *RYR1*-related MmD.

LABORATORY FINDINGS

The diagnosis of core myopathies may be challenging and requires a combination of a detailed clinical (phenotype recognition) and laboratory (histopathologic, muscle imaging, genetic) evaluation and interpretation. The serum CK value is normal, except during crises of malignant hyperthermia, which can result in rhabdomyolysis or



Fig. 648.8 Patients with a typical *SEPN1*-related multiminicore disease (MmD) phenotype at the ages of 10 yr (A), 12 yr (B), 7 yr (C), and 8 yr (D). Note asthenic, atrophic phenotype, with rigid spine syndrome, weakness in neck flexor muscles, and varying degrees of scoliosis.

extensive acute myofiber necrosis (see Chapter 651.2). Muscle imaging (ultrasonography and MRI) may serve as a noninvasive tool to describe characteristic selective muscle involvement. Recognition of these patterns may help to distinguish typical dominantly inherited CCD forms and *SEPN1*-related MmD from a variety of neuromuscular diseases. The diagnosis of a core myopathy based on pathologic findings may be straightforward; however, the typical picture may evolve over time, with early muscle biopsies showing almost no or minimal changes. Core formation is a nonspecific finding and may be observed in the denervation process, tenotomy, metabolic conditions, or even healthy probands after eccentric exercise. *Moth-eaten fibers* described in muscular dystrophies may resemble minicores in MmD. The presence of cores without associated weakness, as reported in some MHS individuals, is not sufficient to give a diagnosis of core myopathy. Cores and other structural abnormalities specific for other structural myopathies, such as nemaline rods or centralized nuclei, can coexist. Muscular dystrophies due to lamin A/C *(LMNA)* gene variants, collagen VI–related myopathies, metabolic myopathies (Pompe disease), myofibrillary myopathies in patients with cardiomyopathy, and congenital myasthenic syndromes may mimic core myopathies based on clinical and/or pathologic features and should be considered in the differential diagnosis.

Due to the extreme clinical and pathologic overlaps among the early-onset muscle diseases, there has been a shift in the traditional diagnostic pathways. Taking all of these issues into account, the diagnosis of core myopathies, like other congenital myopathies, requires a combined effort on the part of the clinician, pathologist, and molecular geneticist.

GENETICS

Central core myopathies are transmitted as either an autosomal dominant or autosomal recessive trait, or de novo dominant gene variants. They are caused by the same abnormal gene at the 19q13.1 locus. This gene programs the ryanodine receptor *(RYR1),* a tetrameric receptor that contains a non–voltage-gated calcium channel; it is prevalent in the sarcoplasmic reticulum and especially at the junction of the T-tubule with the cisternae of the sarcoplasmic reticulum. It contains the channel by which calcium is released among the myofilaments. Gene variants in the *RYR1* gene are also the cause of **malignant hyperthermia (MH).** In CNMs, autosomal recessive gene variants of *RYR1* are known to be a frequent cause, and a patient with a dominant de novo gene variant of *RYR1* was also described (see Chapter 651.2). Patients presenting with congenital myopathy, ptosis, external ophthalmoplegia, and prominent internal nuclei in addition to other structural findings are highly likely candidates for *RYR1* gene variants. Recessive core disease may be associated with tissue-specific silencing of the normal allele, an epigenetic phenomenon. Certain missense gene variants can be associated with autosomal dominant MH, and management of the asymptomatic carrier of the MHS allele should be treated accordingly.

Gene variants in the slow β-myosin gene *(MYH7),* autosomal recessive titin *(TTN)* gene variants, and recessive gene variants of the satellite cell gene *(MEGF10)* are other identified causes of core myopathy. The latter is characterized by *early-onset myopathy, areflexia, respiratory distress, and dysphagia* (**EMARRD**). A single patient has been described who presented with severe congenital myopathy and ophthalmoplegia and recessive variants in the gene encoding the alpha-1 subunit of the dihydropyridine receptor *(CACNA1S),* a gene in which dominant gene variants are known to be associated with **hypokalemic periodic paralysis** and **MH.** Functional studies are required to link *CACNA1S* gene variants to congenital myopathies.

MmD is caused mainly by recessive gene variants in *SEPN1* and *RYR1*. Selenoprotein N is an integral membrane protein localized in the endoplasmic reticulum, which is expressed in several tissues, including the skeletal muscle, heart, lung, and placenta. It is also highly expressed in the diaphragm; this could explain the finding of early restrictive respiratory insufficiency in patients. *SEPN1* gene variants also cause CFTD (see Chapter 648.2) and rigid spine muscular dystrophy (see Chapter 649).

TREATMENT AND PROGNOSIS

The treatment for core myopathies is symptomatic and should be, in general, parallel to consensus standard care guidelines in congenital myopathies. Orthopedic complications, rehabilitation, and feeding problems should be managed accordingly. Scoliosis and other skeletal deformities require special attention because they may develop quickly and progress in severity disproportionately to the limb weakness. Compared with other congenital myopathies, there are a higher number of treatment failures in congenital hip dislocation and dysplasia in CCD.

CCD is consistently associated with **MH,** which can precede the diagnosis of CCD. All patients and asymptomatic carriers should be counseled in terms of a potentially fatal adverse reaction to volatile anesthetics and muscle relaxants. Preoperative **anesthetic consultation** in patients known to be subject to general anesthesia should be considered. **Wearing a medical alert bracelet** should be advised in terms of any emergency. Treatment of MH requires dantrolene and additional supportive care measures. Prophylactic dantrolene is not recommended before anesthesia even in cases where MHS has been established.

There may be an insidious onset of respiratory muscle involvement, particularly in patients with MmD and *SEPN1* gene variants. Patients may be symptomatic after an intercurrent illness or anesthesia or even sedation at the time of a muscle biopsy procedure. Multidisciplinary care requires input from pulmonologists. Signs and symptoms of **sleep-disordered breathing, such as nocturnal hypoventilation syndrome,** should be questioned. Respiratory function tests in sitting and supine positions and polysomnography are necessary to introduce noninvasive positive-pressure ventilation in a timely manner. Patients with severe early-onset disease may require invasive mechanical ventilation. Cardiac complications are uncommon in CCD, but baseline electrocardiography and echocardiography studies are appropriate in most cases. Secondary right ventricular dysfunction and cardiac failure may complicate the situation in patients with respiratory impairment.

A subjective improvement in muscle strength and functional test results has been reported in patients with CCD who are taking β_2-agonists (salbutamol, albuterol). Current and future therapeutic approaches include (1) modification of *RYR1* function, (2) correction of associated oxidative abnormalities, (3) use of pharmacologic compounds enhancing muscle contractility and/or neuromuscular transmission, and (4) correction of a specific gene defect. N-acetylcysteine (NAC), as an antioxidant, may serve as a potential treatment option for *RYR1*- and *SEPN1*-related myopathies, and the first clinical trials in humans are currently under way.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.5 Myofibrillar Myopathies

Adnan Y. Manzur

Myofibrillar myopathies (MFMs) are rare, inherited or sporadic, *progressive* neuromuscular disorders, diagnosed based on distinct morphologic features. There is a wide range of clinical and genetic heterogeneity within MFMs, which are also subgrouped as **protein aggregate myopathies**. A variety of phenotypic presentations are described due to cardiac, skeletal, and smooth muscle involvement. Core histopathologic findings can be defined as focal disintegration of myofibrils predominantly at the Z-disc level, accumulation of myofibrillar degradation products, and ectopic expression of a large number of proteins. Myofibril dissolution begins at the Z-disc, and some sarcomeres of myofibers have disorganization or dissolution of myofibrils adjacent to other areas of normal sarcomeres within the same fiber. Abnormal protein aggregations, intense congophilia of many hyaline structures, internalized nuclei, fiber splitting, vacuoles, *corelike* lesions, a mild to severe increase in endomysial collagen, and increased fiber size variability ranging from very hypotrophic to hypertrophic fibers are among the common features. These zones are associated with streaming of the Z-discs, and there is an expression of a large number of proteins in the aggregates, including dystrophin, sarcoglycans, ubiquitin, desmin intermediate filaments, αB-crystallin, and several Z-disc proteins such as myotilin and filamin-C. *Mitochondrial dysfunction* in the form of abnormal mitochondrial distribution is a frequent finding. Although a detailed immunocytochemical and ultrastructural study of the muscle biopsy tissue is required for the diagnosis and can provide clues about the underlying causative gene, the final diagnosis of the MFM subtype depends on molecular genetic testing. Overexpression or upregulation of normal proteins, such as desmin or αB-crystallin in myofibers, may be an additional feature in many other neuromuscular conditions, so MFM should be used when these accumulations are due to a gene variant in the respective protein. The MFM subtypes are classified according to the affected protein, such as **desminopathy**, **αB-crystallinopathy**, or **Bag3opathy**.

CLINICAL MANIFESTATIONS AND MFM SUBTYPES ACCORDING TO GENETIC BACKGROUND

Most MFMs are not symptomatic in childhood, but occasionally older children and adolescents show early symptoms of nonspecific proximal and distal weakness. MFMs usually present in mid-adulthood, with a slowly progressive weakness involving proximal and distal muscles. The distal presentation is usually more pronounced than the proximal weakness. Sensory symptoms, muscle stiffness, aching, and cramps may be additional symptoms. Affected individuals may show signs of *peripheral neuropathy* and overt *cardiomyopathy.* Autosomal recessive forms present with an early and more severe course compared with autosomal dominant forms. There is also a large interfamilial and intrafamilial variability in the clinical expression of the disease. The degree of involvement and pattern of progression vary between affected individuals.

MFM subtypes with main clinical features are summarized in Table 648.7. Cardiac involvement can sometimes be the initial and only symptom, especially in desminopathies. Syncopal episodes, conduction defects (complete atrioventricular block, right bundle branch block, left anterior hemiblock), rhythm problems (ventricular arrhythmia), cardiomyopathy (dilated, restrictive, hypertrophic), persistent ductus arteriosus, and congestive heart failure are among the cardiac presentations. Facial, axial, and neck muscle involvement, bulbar signs, swallowing and feeding difficulties, rigid spine deformity, early respiratory insufficiency, and early-onset cataracts can be additional clues for the diagnosis. Smooth muscle involvement can present in the form of intestinal malabsorption and pseudoobstruction.

Some MFM subtypes may be associated with early-infantile onset. An example is a unique autosomal recessive myopathy in *Cree native infants* characterized by severe generalized muscular hypertonia that is not relieved by neuromuscular blockade; hence, it is myopathic in origin. Most die in infancy of respiratory insufficiency because of diaphragmatic involvement. The muscle biopsy shows similar findings to many other MFMs (Fig. 648.9); a novel αB-crystallin gene variant is the cause. An early disease onset may also be seen in desminopathy, Bag3opathy, autosomal recessive epidermolysis bullosa simplex with muscular dystrophy (EBS-MD) within the group of *plectinopathies,* hereditary myopathy with early respiratory failure (HMERF) within the group of *titinopathies,* actin-related MFM, and PYROXD1-myopathy.

MFM disease genes encode proteins that are structural and functional components of the sarcomere, extrasarcomeric cytoskeleton, or protein quality control systems. PYROXD1 is classified as a class I pyridine nucleotide-disulfide oxidoreductase, which belongs to an ancient family of enzymes that regulate the redox state of other proteins. An early-onset PYROXD1-myopathy is described, characterized histologically by multiple internalized nuclei, large zones of sarcomeric disorganization, accumulation of thin filaments, thickened Z bands, and desmin-positive inclusions. There is a distinctive histopathology that combines features of central and minicore disease and the centronuclear, myofibrillar, and nemaline myopathies in patients described so far, which clearly indicates the overlap between congenital myopathies and MFMs.

In about half of the affected individuals with MFMs, the genetic defect remains unknown.

LABORATORY FINDINGS

The diagnosis of MFMs rests on common morphologic features observed in muscle histologic studies. Immunocytochemical studies and electron microscopy of muscle can provide clues about the causative gene. Peripheral nerve and myocardial pathologic findings have been described briefly in a small number of patients with MFMs; testing is not routinely performed on clinical grounds. The serum CK level can be normal or mildly elevated. Electromyography reveals myopathic

Table 648.7 Subtypes of Myofibrillar Myopathies

GENE/PROTEIN	DISEASE	INHERITANCE PATTERN	AGE OF ONSET	MAIN CLINICAL FEATURES
DES/desmin	Desminopathy	Dominant, de novo	Early/middle adulthood	Distal > proximal weakness, cardiopathy, respiratory insufficiency
	Desminopathy	Recessive	Infancy/childhood	
CRYAB/αB-crystallin	αB-crystallinopathy	Dominant	Middle adulthood	Distal > proximal weakness, cardiopathy, respiratory insufficiency, cataracts
	αB-crystallinopathy	Recessive	Infancy	Limb and axial stiffness and weakness, respiratory failure
MYOT/myotilin	Myotilinopathy	Dominant	Middle/late adulthood	Distal and proximal weakness, cardiopathy, and respiratory insufficiency in a minority of patients
	Myotilinopathy	Recessive	Early/middle adulthood	Distal and proximal weakness, arrhythmia
ZASP/ZASP	ZASPopathy	Dominant	Middle/late adulthood	Distal > proximal weakness, cardiopathy, and neuropathy in a minority of patients
FLNC/filamin C	MFM-filaminopathy	Dominant	Middle adulthood	Proximal > distal weakness, respiratory failure, and cardiopathy in a subset of patients
BAG3/BAG3	BAG3 myopathy	De novo	Childhood	Proximal and distal weakness, respiratory insufficiency, hypertrophic cardiomyopathy, peripheral neuropathy
FHL1/FHL1	Reducing body myopathy, FHL1 myopathy	X-linked	Infancy/childhood, adulthood (rare)	Delayed motor milestones, proximal > distal weakness, scoliosis, contractures, rapid loss of ambulation, respiratory insufficiency; milder course in adult-onset patients
TTN/titin	Hereditary myopathy with early respiratory failure (HMERF)	Dominant	Early/late adulthood	Distal, proximal, and neck weakness, early respiratory insufficiency
PLEC/plectin	Epidermolysis bullosa simplex with muscular dystrophy (EBS-MD)	Recessive	Skin blistering since birth, myopathy in infancy/childhood, adulthood	Proximal and distal weakness, cardiomyopathy, cataracts, epidermolysis, nail and tooth abnormalities, brain abnormalities
ACTA1/α-actin	MFM-actinopathy	De novo	Infancy	Upper limb > lower limb weakness, respiratory insufficiency, contractures
HSPB8/HSPB8	HSPB8 myopathy	Dominant	Early/middle adulthood	Distal > proximal weakness, peripheral motor neuropathy
DNAJB6/DNAJB6	Limb-girdle muscular dystrophy 1D	Dominant	Middle adulthood	Distal and proximal weakness
PYROXD1/PYROXD1*	PYROXD1 myopathy	Recessive	Infancy/early childhood	Slowly progressive symmetric proximal and distal weakness, generalized reduction in muscle bulk, neck weakness, scapular winging, mild to moderate facial weakness, mild ptosis, high-arched palate, nasal speech, swallowing difficulties, mild restrictive lung disease, mild length-dependent axonal neuropathy and evidence of cardiac involvement in the third decade

*PYROXD1 is a nuclear-cytoplasmic oxidoreductase localized to the nucleus and to the striated sarcomeric components.
MFM, Myofibrillar myopathy.
Adapted from Kley RA, Olive M, Schroder R. New aspects of myofibrillar myopathies. *Curr Opin Neurol*. 2016;29:628–634.

or both myopathic and neuropathic features, abnormal nerve conduction studies, and electrical irritability (fibrillation potentials, positive sharp waves, complex repetitive discharges, and myotonic discharges). Muscle MRI can demonstrate different patterns of involvement according to MFM subtypes. The final diagnosis is based on the combination of clinical features, muscle biopsy features, and molecular genetic test results.

Proteomic analysis of protein aggregates yields to identification of diagnostic biomarkers in different MFM subtypes. The ratio of filamin C to myotilin in aggregates is described as a highly sensitive and specific diagnostic marker for myotilinopathy. The combination of immunofluorescence studies with proteomic findings will further facilitate identification of several proteins involved in protein quality control and degradation, which may also act as therapeutic targets.

The differential diagnosis includes congenital myopathies, myotonic dystrophy, mitochondrial diseases, and peripheral neuropathies in childhood.

TREATMENT

There is no curative treatment available for MFMs. Treatment is supportive and symptomatic. Cardiac screening (electrocardiography, echocardiography, and 24-hr Holter monitoring) should be performed

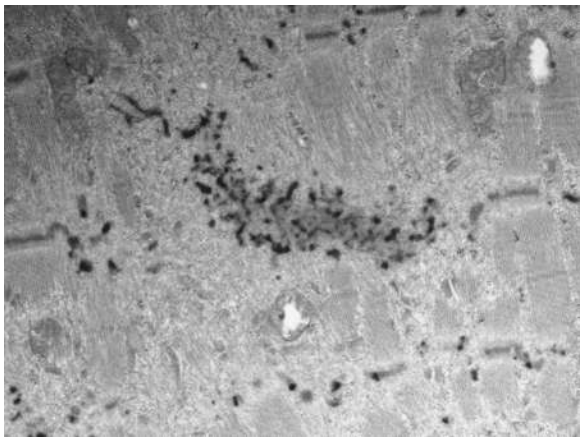

Fig. 648.9 Electron micrograph of quadriceps femoris muscle biopsy of a 1-mo-old Indigenous infant with Cree myofibrillar myopathy. Within the same myofiber, some sarcomeres are well formed and others exhibit disarray of the thick and thin myofilaments and fragmentation of Z bands. Mitochondria appear normal (×21,400).

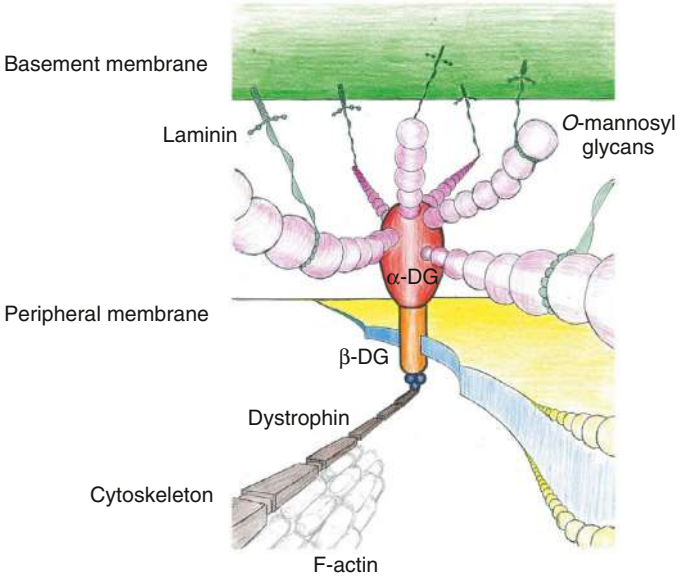

Fig. 648.10 Schematic drawing of dystrophin-glycoprotein complex (DGC) and glycosylated α-dystroglycan (DG). α-DG links extracellular components such as laminin, and links β-DG, a transmembrane glycoprotein. Via dystrophin it binds to actin cytoskeleton. α-DG is heavily glycosylated, and its glycans play a role in binding to laminin. *(From Taniguchi-Ikeda M, Morioka I, Iijima K, et al. Mechanistic aspects of the formation of α-dystroglycan and therapeutic research for the treatment of α-dystroglycanopathy: A review. Mol Aspects Med. 2016;51:115–124.)*

at least once a year. In the case of cardiac abnormalities or in patients with desminopathies, pediatric cardiology follow-up is recommended twice a year. A pacemaker and an implantable cardioverter defibrillator (ICD), cardiac transplantation, respiratory support, range-of-motion physical therapy, and assisted devices can be introduced accordingly. Slit-lamp examination for the detection of lens opacities should be considered. There is no known increased risk for MH; however, the possibility cannot yet be completely excluded. Genetic counseling and prenatal diagnosis should be offered according to the inheritance pattern and underlying gene defect.

The generation of patient-mimicking cell and animal models provides a basis for preclinical and clinical evaluation of novel therapeutic strategies. Initial animal studies are based on avoiding strenuous exercise, treatment with an antioxidant-N-acetyl-L-cysteine, modulation of autophagic activity, and use of antiaggregation drugs such as doxycycline and 4-phenylbutyrate (a chemical chaperone approved for urea cycle disorders).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.6 Brain Malformations and Muscle Development

Adnan Y. Manzur

Infants with cerebellar **hypoplasia** are hypotonic and developmentally delayed, especially in gross motor skills. Muscle biopsy is sometimes performed to exclude a congenital myopathy. A biopsy specimen can show delayed maturation of muscle, fiber-type predominance, or CMFTD. Other malformations of the brain may also be associated with abnormal histochemical patterns, but supratentorial lesions are less likely than brainstem or cerebellar lesions to alter muscle development. Abnormal descending impulses along bulbospinal pathways probably alter discharge patterns of lower motor neurons that determine the histochemical differentiation of muscle at 20-28 weeks of gestation. The corticospinal tract does not participate because it is not yet functional during this period of fetal life.

There are a variety of **muscular dystrophies** associated with cerebral and ocular phenotypes, suggesting common mechanisms affecting development of the muscle, the brain, and the eye. It is clear that in at least some of these cases, the abnormal protein implicated in pathogenesis is expressed in the muscle, brain, and eye, and is important for the stabilization of muscle, migration of central neurons, and normal tissue development in the eye.

Alpha dystroglycan–related dystrophies (αDG-RD) are a group of muscle diseases with a broad phenotypic and genetic spectrum, including several congenital muscular dystrophies (see Chapter 649.6), with severe brain involvement in the form of cobblestone lissencephaly (Walker-Warburg syndrome, Fukuyama disease, and muscle-eye-brain disease of Santavuori) to the LGMD spectrum (see Chapter 649.4).

The dystrophin-glycoprotein complex forms a critical link between the extracellular matrix and cytoskeleton, and in the muscle tissue, stabilizes the muscle membrane. Dystroglycans simply interact with proteins in the extracellular matrix and cytoskeleton via dystrophin (Fig. 648.10). αDG is a transmembrane glycoprotein, and extensive posttranslational glycosylation (*O*-linked mannosylation) is required for its proper function, to mediate binding to basement membrane proteins (laminin alpha-2 chain, perlecan, agrin), neurexin in the brain, pikachurin in the eye, and Slit (by interaction with laminin globular [G] domains).

Defects of *O*-glycosylation of αDG are considered to be central to the pathogenesis of αDG-RD. Deletion of dystroglycan or its glycosyltransferases results in migration defects in the form of type II cobblestone lissencephaly and a variety of eye malformations affecting both the retina and anterior chamber, such as glaucoma and cataracts.

Dystroglycan is required not only for the integrity of basement membranes along which developing axonal pathways extend, but also because it directly binds to the laminin G domain of Slit, organizing Slit distribution in vivo. It maintains a growth environment and functions as an extracellular scaffold that controls axon guidance events by organizing the availability of axonal growth and guidance cues at critical intermediate targets. Misregulation of Slit-Robo signaling involved in axonal guidance and neuronal connectivity is reflected to patients with αDG-RD.

Clinical classification is difficult because there are patients with milder abnormalities, such as microcephaly, cerebellar hypoplasia with or without cysts, learning disabilities with normal neuroimaging features and CMD or LGMD phenotype, and with normal cognitive function. Neuroimaging signatures on brain MRI can be summarized as cobblestone complex (type II cobblestone lissencephaly to focal pachygyria or polymicrogyria), midbrain hypoplasia, relatively thick tectum, fused colliculi, ventral pontine cleft, pontomesencephalic kink, abnormalities of cerebellar foliation, cerebellar cysts, hydrocephalus, occipital encephalocele, and patchy and confluent involvement of white matter

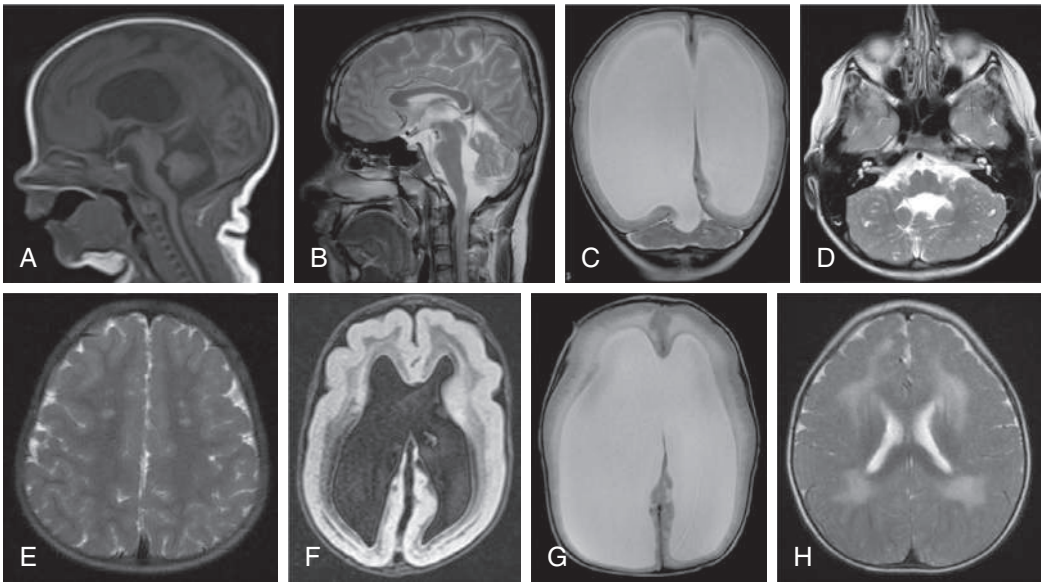

Fig. 648.11 A, Sagittal T1-weighted image shows hypoplastic and "kinked" brainstem, and cerebellar hypoplasia *(POMGnt1).* B, Sagittal T2-weighted image reveals dorsal pontine flattening *(POMK).* C, Coronal T2-weighted image demonstrates huge ventriculomegaly, cerebellar hypoplasia, and cortical cobblestone lissencephaly *(ISPD).* D, Axial T2-weighted image showing cerebellar microcysts *(FKRP).* E, Axial T2-weighted image reveals bilateral frontal polymicrogyria. F, Axial FLAIR image shows lissencephaly *(POMGnt1).* G, Axial T2-weighted image reveals cobblestone lissencephaly. H, Axial T2-weighted image shows cerebral periventricular white matter lesions.

with a high signal intensity on T2 weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 648.11). A **high serum CK level** in the presence of the previously mentioned imaging features simply differentiates a muscle disorder from other genetic causes of cortical malformations of development. A reduction or absence of immunolabeling with antibodies, which recognize glycosylated epitopes of αDG in muscle biopsy, is a pathologic signature for αDG-RD.

There is an ever-expanding list of genes involved in αDG-RD. Gene variants in up to 19 glycosyltransferases and accessory proteins have been found to be involved in the glycosylation of αDG *(DAG1, POMT1, POMT2, POMGnT1, POMGnT2, LARGE, FKRP, FKTN, ISPD, GTDC2, B3GNT1, B3GALNT2, GMPPB, TMEM5, SGK196, DPM1, DPM2, DPM3, DOLK);* the availability of targeted gene panels and NGS techniques increases the diagnostic yield in this spectrum.

Congenital disorders of glycosylation, involving both *N*- and *O*-glycosylation (gene variants in *DPM1, DPM2,* and *DPM3*), overlap with αDG-RD, and may present with high serum CK levels, cognitive impairment, microcephaly, feeding difficulties, myoclonic epilepsy, and cerebellar hypoplasia.

Another example is a **CMD form overlapping with Marinesco-Sjögren syndrome (MSS) and dystroglycanopathy** due to *INPP5K* gene variants, in patients with short stature, intellectual disability, and cataracts, described as a continuum of αDG-RD. *INPP5K* encodes inositol polyphosphate-5-phosphatase K, which has been shown to regulate myoblast differentiation and protein processing through its interaction with the endoplasmic reticulum chaperones.

Genes identified so far, functioning in the endoplasmic reticulum and/or Golgi apparatus, point to a common mechanism involving an interaction between the cells and the surrounding extracellular matrix in terms of brain malformations and muscle development.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for complete Bibliography.

648.7 Amyoplasia

Adnan Y. Manzur

Congenital absence of individual muscles is common and is often asymmetric. A common aplasia is the *palmaris longus muscle* of the ventral forearm, which is absent in 30% of normal subjects and is fully compensated for by other flexors of the wrist. Unilateral absence of a *sternocleidomastoid muscle* is one cause of congenital torticollis. Absence of one *pectoralis major muscle* is part of the **Poland anomalad.**

When innervation does not develop, as in the lower limbs in severe cases of *myelomeningocele,* muscles can fail to develop. In sacral *agenesis,* the abnormal somites that fail to form bony vertebrae can also fail to form muscles from the same defective mesodermal plate, a disorder of induction resulting in segmental amyoplasia. Skeletal muscles of the extremities fail to differentiate from embryonic myomeres if the long bones do not form. The absence of one long bone, such as the radius, is associated with variable aplasia or hypoplasia of associated muscles, such as the flexor carpi radialis. End-stage *neurogenic atrophy* of muscle is sometimes called **amyoplasia,** but this use is semantically incorrect.

Generalized amyoplasia usually results in fetal death, and live-born neonates rarely survive. A pathogenic variant in one of the myogenic genes is the suspected etiology because of genetic knockout studies in mice, but it has not been proven in humans. An estimated 400 discrete diagnoses can lead to congenital arthrogryposis. The two largest categories are amyoplasia and distal arthrogryposis, which combined make up 50–65% of all diagnoses within the arthrogryposis subset. Amyoplasia, the most common, is not clearly an inherited genetic syndrome of characteristic upper and lower limb contractures. Distal arthrogrypposes, by contrast, have an underlying genetic abnormality, which in many cases seems to target the fast-twitch muscles of the developing fetus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.8 Muscular Dysgenesis (Proteus Syndrome Myopathy)

Adnan Y. Manzur

Proteus syndrome is a disturbance of cellular growth involving ectodermal and mesodermal tissues, representing a cellular mosaicism. The genetic defect is a variant in the *AKT1* gene, of the same genetic family as *AKT3,* which causes hemimegalencephaly; indeed, many children with Proteus syndrome also have hemimegalencephaly as another tissue overgrowth, not a separate association. These genes participate in

the mammalian target of rapamycin (mTOR) pathway. Proteus syndrome also manifests as asymmetric overgrowth of the extremities, verrucous cutaneous lesions, angiomas of various types, thickening of bones, and excessive growth of muscles without weakness. Severe seizures, beginning in neonates, are uncommon. Histologically, the muscle demonstrates a unique *muscular dysgenesis.* Abnormal zones are adjacent to zones of normal muscle formation and do not follow anatomic boundaries.

Proteus syndrome is recognized as a phenotypical variety of the *epidermal nevus syndrome,* together with linear sebaceous nevus of Jadassohn, CLOVES syndrome, and others, as a postzygotic somatic mosaicism.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.9 Benign Congenital Hypotonia

Adnan Y. Manzur

Benign congenital hypotonia is not a disease, but it is a descriptive term for infants or children with nonprogressive hypotonia of unknown origin. The hypotonia is not usually associated with weakness or developmental delay, although some children acquire gross motor skills more slowly than normal. Tendon stretch reflexes are normal or hypoactive. There are no cranial nerve abnormalities, and intelligence is normal.

The **diagnosis** is one of exclusion (see Table 647.2 in Chapter 647) after results of laboratory studies, including muscle biopsy and imaging of the brain with special attention to the cerebellum, are normal. Muscle biopsy is deferred in some mild cases to follow the clinical evolution over time, but the diagnosis in these infants is more provisional. No known molecular genetic basis for this syndrome has been identified in the majority, but a rare form with an *RYR1* variant and MH is recognized. Table 647.3 in Chapter 647 lists the differential diagnoses.

The prognosis is generally good; no specific therapy is required. Contractures do not develop. Physical therapy might help achieve motor milestones (walking) sooner than expected. Hypotonia persists into adult life. The disorder is not always as *benign* as its name implies because a common complication is recurrent dislocation of joints, especially the shoulders. Excessive motility of the spine can result in stretch injury, compression, or vascular compromise of nerve roots or of the spinal cord. These are particular hazards for patients who perform gymnastics or who become circus performers because of agility of joints without weakness or pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

648.10 Arthrogryposis

Adnan Y. Manzur

See also Chapter 723.

Arthrogryposis (*arthro,* joint; *gryp,* curved), arthrogryposis multiplex congenita (*multiplex,* multiple; *congenita,* present at birth), and multiple congenital contractures are descriptive terms, used interchangeably to define contractures in two or more different body parts (Table 648.8). Arthrogryposis is a sign rather than a diagnosis; anything that interferes or limits normal fetal movement can lead to congenital contractures. The contractures usually (1) involve the limbs, but also may include the jaw, neck, and spine; (2) are nonprogressive in nature; and (3) improve over time with early physiotherapy and orthopedic interventions.

Although each specific type is rare, the incidence of arthrogryposis is described as 1 in 3,000-5,000 live births, according to population-based studies.

FETAL MOVEMENT AND THE LINK TO ARTHROGRYPOSIS

The main background factor in all forms of arthrogryposis is decreased or lack of fetal movement *(fetal akinesia/hypokinesia),* and the clinical severity is directly correlated with the onset. An early onset and long duration of decreased movements lead to a more severe phenotype at birth. The first trimester is a critical period in terms of progressive motor development. There is an evolution of the movement pattern; early fetal activity is believed to be generated by central pattern networks in the spinal cord and mediated by feedback from the immature muscle fibers of myotomes, shifting to a more specific pattern due to the development of the supraspinal parts of the brain. The development of joints, joint spaces, and movements start at 5½, 7, and 8 embryonic weeks, respectively. Therefore decreased fetal movement beyond 10 weeks is a sign of maldevelopment and/or dysfunction of the early fetal central or peripheral nervous system. General movements with relatively simple and stereotypical sideways bending of the head and trunk can be noticed as early as 7 weeks of gestation (embryonal, 5 weeks). They develop in a craniocaudal and proximal-to-distal direction, with a propagation from the shoulders and hips first, to the upper and, then, lower limbs (7-9 weeks). At this time point, jaw opening also begins. Isolated arm and leg movements can be visible from 8-9 weeks to 10 weeks, respectively. By 11 weeks of gestation, a full range of limb movements (extension, flexion, rotation, abduction, and adduction of each limb) develops. Developmentally, fetal sucking and swallowing are described in the early second trimester. Fetal breathing movements begin around 12-14 weeks, and by 20 weeks they become more regular. Facial movements are recognized in the late second trimester, and between 24 and 35 weeks show a developmental progression from unrelated facial movements toward fetal facial gestalts.

Table 648.8 Consensus-Based Definitions

TERM	DESCRIPTION/DEFINITION
Arthrogryposis multiplex congenita (AMC)	AMC is a term used to describe a group of congenital conditions characterized by joint contractures in two or more body areas.
Amyoplasia (classical arthrogryposis)	Amyoplasia is characterized by multiple congenital contractures presenting in a very specific pattern. It is typically symmetric, involving all four limbs, with internally rotated shoulders, fully extended and fixed elbows, the wrists fixed in flexion, partially flexed fingers, hips fixed in flexion or extension, adducted or abducted, and sometimes dislocated. The knees may be fixed in extension or flexion, and the feet are usually in severe equinovarus position. The jaw and trunk are relatively spared. Normal limb muscle tissue is replaced by fatty, fibrous tissue.
Distal arthrogryposis (DA)	DA is a group of rare arthrogryposis syndromes characterized by congenital contractures of two or more areas of the body, primarily involving the hands and feet, while the proximal joints are largely spared, in the absence of primary neurologic and/or muscle disease affecting limb function. Diagnostic features include camptodactyly or pseudocamptodactyly, hypoplastic or absent flexion creases, overriding fingers, ulnar deviation at the wrist, talipes equinovarus, calcaneovalgus deformities, vertical talus, and/or metatarsus varus.

From Hermansen MV, Wekre LL, Lidal IB. The range of publications on arthrogryposis multiplex congenita from 1995 to 2022—a scoping review. *Am J Med Genet.* 2023;1–11. Table 1.

Contracting musculature is the main role player in maintaining joint progenitor cells committed to their fate, and for correct joint cavitation and formation. A key modulator of joint formation, beta-catenin, is activated in a contraction-dependent manner. Further, a reduced muscle phenotype also has a differential effect on ossification centers, with significant decreases in bone formation. Muscle development, early spontaneous contraction, innervation, and joint and bone formation seem to be complex interdependent developmental processes that finally allow normal limb movement and maintenance. Although not investigated in detail, normal fetal breathing and/or swallowing and lung and gastrointestinal maturation may be affected through the same developmental processes.

Decreased movement is associated with a compensatory connective tissue response, *collagenosis* (an increase of connective tissue around the joints), which limits the joint movements and increases contractures. Any effort to mobilize the joints may lead to minor fractures of abnormal joint surfaces. Diaphragmatic and intercostal muscle dysfunction further results in loss of rhythmic thoracic movements and leads to a small thoracic cage and failure of maturation of the alveoli and surfactant, leading to pulmonary hypoplasia. By 15 weeks of gestation, development of the lung is arrested at the canalicular phase, which is also a critical point for joint development. Lack of muscle pull at sites of normal attachment may lead to craniofacial abnormalities, with facial weakness leading to a tented upper lip appearance.

Pathologic changes with an onset during intrauterine development are confined to primary alterations in anterior horn cells, roots, peripheral nerves, motor end plates, or muscles. Spinal cord involvement, with abnormal histology and unequal distribution of alpha motor neurons in anterior horn cells, is described in infants with the neurogenic forms of arthrogryposis.

BASIC CATEGORIES, ETIOLOGIES, AND CLASSIFICATIONS

Decreased or lack of in utero movements are all reflected in the clinical features of the **lethal forms of lower motor neuron diseases** and the **fetal akinesia/hypokinesia deformation sequence (FADS), Pena-Shokeir phenotype,** which represents the severe end of the arthrogryposis spectrum. This phenotype can be described as intrauterine growth restriction, multiple joint contractures, shortened limbs, craniofacial changes (micrognathia, cleft palate, high nasal root, ocular hypertelorism), pulmonary hypoplasia, polyhydramnios, decreased gut motility, a shortened gut, a short umbilical cord, skin changes, and short limbs. Iatrogenic fractures due to osteoporosis of long bones in the prenatal period can be an additional feature. They may be isolated or associated with additional organ system abnormalities.

Lower motor neuron diseases, characterized by degeneration of anterior horn cells of the spinal cord and descending tracts, may overlap with arthrogryposis and FADS. The prototype in childhood is **SMA** (see Chapters 652.2 and 652.3).

Lethal congenital contracture syndrome (LCCS) and **lethal arthrogryposis with anterior horn cell disease (LAAHD)** are two independent neurogenic arthrogryposis subtypes, with a remarkable phenotypic overlap and ever-expanding heterogeneity at the phenotypic and molecular genetic levels.

Amyoplasia and **distal arthrogryposis (DA)** are the two most common categories of conditions, accounting for up to 50–65% of the patients presenting with arthrogryposis.

The most common type is Amyoplasia (*A,* no; *myo,* muscle; and *plasia,* growth); it is also called classic arthrogryposis. Amyoplasia is a sporadic condition in which limb muscle tissue is replaced by fatty tissue. Despite extensive genetic studies, no chromosomal or single gene etiology has been identified to date. Amyoplasia (with a capital A), is a diagnosis of exclusion, so it should be distinguished from other genetic forms of arthrogryposis presenting with decreased or absent muscle mass. The natural course, management, and genetic counseling depend on a correct diagnosis. The incidence of Amyoplasia is 1/10,000 live births. Discordant monozygotic twinning is described, that is, at least 6.6% of the affected individuals are described to have an unaffected monozygotic twin.



Fig. 648.12 Typical appearance of a patient with amyoplasia with internal rotation of the shoulders, fixed extension of the elbows, clenched wrist (A), hip dysplasia, and equinovarus deformity (B).

The diagnosis should be considered in the presence of symmetric congenital, rigid contractures with a characteristic position of limbs in the newborn period (internal rotation of the shoulders, fixed extension of the elbows, pronation of the forearm, flexion of the wrist, camptodactyly, and severe equinovarus deformity of the feet; Fig. 648.12), accompanied by shortness of the affected limbs; a marked decrease in limb muscle mass; lack of flexion creases on limbs, fingers, and hands; mild intrauterine growth retardation; dimples overlying affected joints; spared trunk; nevus flammeus over the craniofacial midline; bone fractures; osteoporosis of the long bones; normal CNS function; and a negative family history. There may be spinal involvement. Muscle defects in the abdominal wall, inguinal hernias, bowel atresia, absence of trunk muscles, digit compromise, or constriction bands of the limbs or digits can accompany the clinical picture due to vascular compromise. There is a range of severity, from very mild to severe involvement, with almost 15% of patients presenting with a pure, isolated upper extremity or lower extremity involvement. The diagnosis of these forms requires experience and evaluation of a differential diagnostic list. Contractures usually improve over time with early physiotherapy and orthopedic care (see Chapter 723), with almost 85% of affected individuals being ambulatory by age 5 years and two thirds being able to live independent lives.

Distal arthrogryposis (DA) is a heterogeneous group with a wide phenotypic variability, primarily involving the hands and feet, with sparing of the proximal joints. The prevalence is not known. It is often associated with abnormal facies and autosomal dominant inheritance, but autosomal recessive and sporadic patients are also described. Patients usually present in an orthopedic environment. There is an expanded classification with 11 different syndromes (see Chapter 723, Table 723.2). Abnormalities of fast-twitch muscles are identified in a majority of patients with DA. Gene variants in sarcomeric muscle proteins (troponin, tropomyosin, and myosin) can cause DA or congenital myopathies. Other than this clinical overlap due to a particular gene variant, a particular phenotype may be associated with variants in different genes. Some of the DA forms prove that embryonic expression of some of the genes during fetal life, such as *MYH3,* affects sarcomeric proteins and the force generation in muscle cells. Dominant and recessive gene variants related to mechanotransduction are identified in the DA group.

Among over 400 conditions described within this complex category (including syndromes, gene variants, chromosomal abnormalities, deletions, and duplications), over 320 genes have been implicated, and a responsible gene has been identified in more than 150 of the conditions (Fig. 648.13). Considering this extreme clinical and genetic heterogeneity, it is suggested that classifications can be done at different levels, depending on the *area of involvement, overall cause of fetal*

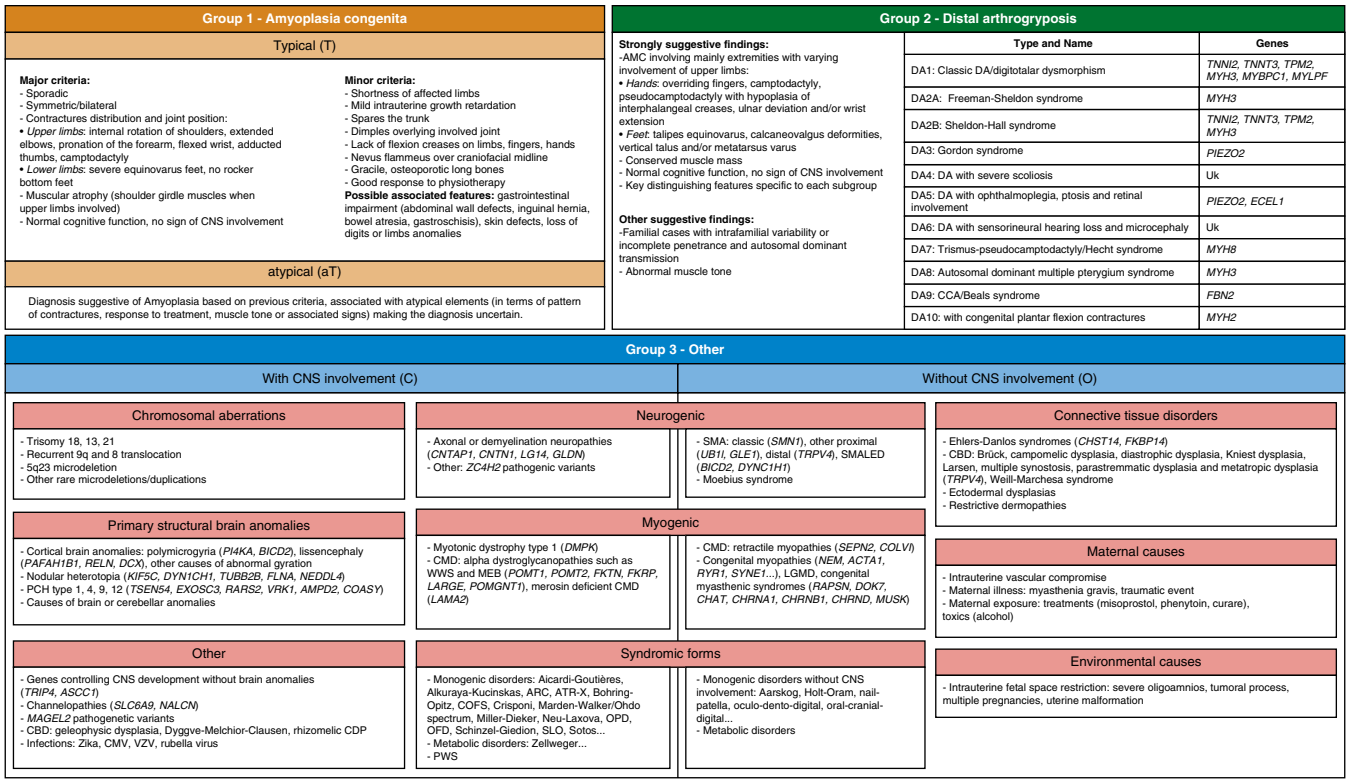

Fig. 648.13 Clinical classification of AMC. Clinical classification routinely used at the University Hospital Grenoble Alpes. It aims at distinguishing straight away the two main causes of AMC: Amyoplasia (Group 1) and DA (Group 2). Details on clinical criteria used to classify these patients into these groups are provided. Patients that cannot be classified into one of the previous groups are classified in Group 3 in which we distinguish cases with (C) or without (O) CNS involvement. Nine etiologic subgroups are defined in this Group 3. ARC, Arthrogryposis renal dysfunction and cholestasis; ATR-X, alpha-thalassemia/mental retardation syndrome; CBD, congenital bone disorder; CCA, congenital contractures arachnodactyly; CDP, chondrodysplasia; CMD, congenital muscular dystrophies; COFS, cerebro-facio-oculo-skeletal syndrome; LGMD, limb-girdle muscular dystrophies; MEB, muscle eye brain; OFD, oro-facio-digital syndrome; OPD, oto-palato-digital syndrome; PCH, pontocerebellar hypoplasia; PWS, Prader Willi syndrome; SLO, Smith-Lemli-Opitz syndrome; SMA, spinal muscular atrophy; SMALED, spinal muscular atrophy lower extremities predominant autosomal dominant; Uk, unknown; WWS, Walker Warburg syndrome. *(From Le Tanno P, Latypova X, Rendu J, et al. Diagnostic workup in children with arthrogryposis: description of practices from a single reference centre, comparison with literature and suggestion of recommendations. J Med Genet. 2023;60:13–24. Fig. 2.)*

akinesia/hypokinesia, and *etiologic process underlying the developmental dysfunction,* or taking into consideration the *cardinal features,* as in the case of amyoplasia and DA (Table 648.9). With the utility of NGS technologies, the field of arthrogryposis is moving to *gene-based classification* systems and grouping conditions according to affected or associated gene products and involved developmental pathways.

The etiology can be based on abnormalities of the CNS, nerve, muscle, and connective tissue; lack of space; maternal illness; environmental agents; or vascular compromise. They may result in decreased intrauterine movements. As an alternative approach, genetic, sporadic (amyoplasia), and environmental backgrounds or neurogenic, myopathic, syndromic, and metabolic categories can be used to review possible etiologies.

For practical purposes, the clinical classification is often based on the presence and absence of additional organ system abnormalities or malformations and the presence or absence of CNS involvement, including intellectual disability, and lethality. Of the children with arthrogryposis, ~30% will primarily have limb involvement, ~30% will have affected limbs plus other body areas but normal cognitive function, and ~30% will have CNS dysfunction.

DIAGNOSTIC APPROACH AND LABORATORY EVALUATION

In such a diverse group of disorders with extreme heterogeneity at the etiologic, phenotypic, and molecular genetic levels, establishing a specific diagnosis is important. The natural history, evolution, prognosis, therapeutic interventions, and genetic counseling/prenatal diagnosis depend on a precise diagnosis.

The first step in the diagnostic approach is detailed history taking, including information about the pregnancy, delivery, and family history, with at least a three-generation pedigree analysis (Table 648.10). The maternal perception of intrauterine movements, any difference compared with previous pregnancies, polyhydramnios, oligohydramnios, intrauterine infections, toxic exposures, maternal illness, maternal and paternal age, breech presentation, type of delivery, and any event complicating the delivery should be reviewed. Newborns with arthrogryposis are prone to hypoxic-ischemic insults.

There is not a standard set of laboratory investigations that can serve as a diagnostic tool (Table 648.11). Radiologic tests (brain and muscle MRIs), electrophysiologic tests (electromyography, nerve conduction velocities), muscle biopsy, chromosomal microarray analysis (array comparative genomic hybridization [CGH]), and molecular genetic tests must be individualized for each patient. Input from a clinical geneticist and experienced multidisciplinary team is invaluable. Documentation of the range of motion, distribution of contractures, muscle tone and strength, and facial involvement with serial photographs and/or videos should be a part of follow-up visits. There is no laboratory test that can substitute for experience in making the clinical judgment.

In the case of a recognized phenotype, molecular tests can be directed toward the working diagnosis. Depending on the availability of NGS technologies, the traditional diagnostic trend has shifted to a diagnosis by genetic sequencing. Disease-specific targeted gene panels can serve a diagnostic purpose, because other than a variety of early-onset muscle diseases, mitochondrial and metabolic diseases are covered, as well. In a large cohort of patients presenting with fetal akinesia/hypokinesia, arthrogryposis, or severe congenital myopathies,

Table 648.9 Major Causes of Arthrogryposis Multiplex Congenita

SITE OF MAJOR PATHOLOGIC FINDINGS	DISORDER
Cerebrum-brainstem	Microcephaly; migrational disorders: lissencephaly-pachygyria (e.g., Zellweger syndrome), schizencephaly, polymicrogyria, agenesis of corpus callosum; fetal alcohol syndrome; cytomegalovirus infection; pontocerebellar hypoplasia (type I); dentato-olivary dysplasia; leptomeningeal angiomatosis; encephaloclastic processes: neuronal destruction, porencephalies, hydranencephaly, multicystic encephalomalacia; hydrocephalus
Anterior horn cell	Developmental agenesis-hypoplasia-dysgenesis (amyoplasia congenita); destructive disorders (apparent intrauterine ischemic events); degenerative disorders (severe Werdnig-Hoffmann disease [SMA type 0 or IA], lethal congenital contracture syndrome, spinal muscular atrophy with pontocerebellar hypoplasia, spinal muscular atrophy with respiratory distress, X-linked infantile spinal muscular atrophy, early-onset non-5q spinal muscular atrophy); Möbius syndrome; cervical spinal atrophy; lumbar spinal atrophy; lumbosacral meningomyelocele; sacral agenesis; other
Peripheral nerve or root	Hypomyelinative polyneuropathy; axonal polyneuropathy; neurofibromatosis
Neuromuscular junction	Infant of myasthenic mother; congenital myasthenic syndromes; multiple pterygium syndrome (Escobar type); infant of mother with multiple sclerosis (?)
Muscle	Congenital muscular dystrophy (merosin-positive and merosin-negative); congenital myotonic dystrophy; myotubular myopathy; central core disease; nemaline myopathy; congenital myopathy due to sodium channel gene variant; congenital polymyositis; congenital fiber-type disproportion; glycogen storage myopathy (muscle phosphorylase deficiency, phosphofructokinase deficiency); mitochondrial myopathy; Freeman-Sheldon syndrome
Primary disorder of joint or connective tissue	Marfan syndrome; contractural arachnodactyly; other disorders of connective tissue; intrauterine periarticular inflammation
Intrauterine mechanical obstruction	Uterine abnormality; amniotic bands; oligohydramnios; twin pregnancy; extrauterine pregnancy

SMA, Spinal muscular atrophy.
From Ghosh PS, Volpe JJ. Arthrogryposis multiplex congenita. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn*, 6th ed. Philadelphia: Elsevier; 2018: Table 31-3.

Table 648.10 Clinical Evaluation of Arthrogryposis: Clues for a Detailed History

PREGNANCY
- Maternal illness, acute or chronic (diabetes, myasthenia gravis, myotonic dystrophy, etc.)
- Infections (rubella, rubeola, zika virus, coxsackievirus, enterovirus, Akabane virus, etc.)
- Fever (>39°C, determine timing in gestation)
- Nausea (viral encephalitis, position of baby, etc.)
- Drugs (curare, Robaxin, alcohol, phenytoin, addictive drugs, misoprostol, etc.)
- Fetal movement (polyhydramnios, fetal kicking in one place, rolling decreased)
- Oligohydramnios, chronic leakage of amniotic fluid
- Polyhydramnios, hydrops
- Trauma during pregnancy (blow to the abdomen, attempted termination, car accident, etc.)
- Other complications during pregnancy, such as bleeding, abnormal lie, threatened abortion
- Prenatal diagnosis (early amniocentesis, ultrasound studies, etc.)

DELIVERY HISTORY
- Presentation (breech, transverse, etc.)
- Length of gestation
- Traumatic delivery (limb, CNS, fracture, etc.)
- Intrauterine mass (twin, fibroid, etc.)
- Abnormal uterine structure or shape
- Abnormal placenta, membranes, or cord length or position
- Time of year, geographic location

FAMILY HISTORY
- Marked variability within family
- Change with time (degeneration vs improvement)
- Increased incidence of congenital contractures in second- and third-degree relatives
- Hyperextensibility or hypotonia present in family member
- Rule out myotonic dystrophy, myasthenia gravis in parents (particularly mother)
- Consanguinity
- Advanced parental (mother or father) age
- Increased stillbirths or miscarriages
- If more than one consecutively affected child, consider maternal antibodies to fetal neurotransmitter

Continued

Table 648.10 Clinical Evaluation of Arthrogryposis: Clues for a Detailed History—cont'd

NEWBORN EVALUATION

Description of contractures
- Which limbs and joints
- Proximal vs distal
- Flexion vs extension
- Amount of limitation (fixed vs passive vs active movement)
- Characteristic position at rest
- Severity
- Complete fusion or ankylosis vs soft tissue contracture

Other anomalies (contractures are most obvious, look for other anomalies)
Deformities
Genitalia (cryptorchid, lack of labia, microphallus, etc.)
Limbs (pterygium, shortening, webs, cord wrapping, absent patella, dislocated radial heads, dimples, etc.)
Jaw (micrognathia, trismus, etc.)
Facies (asymmetry, flat bridge of nose, hemangioma, movement, etc.)
Scoliosis and kyphosis (fixed or flexible)
Dimple (over specific joints or bones)
Skin (hemangioma, defects, hirsutism)
Dermatoglyphics
Hernias, inguinal and umbilical, abdominal wall defect
Other features of fetal akinesia sequence
- Intrauterine growth restriction
- Pulmonary hypoplasia
- Craniofacial anomalies (hypertelorism, cleft palate, depressed tip of nose, high-bridged nose)
- Functional short gut with feeding problem
- Short umbilical cord

MALFORMATIONS
- Eyes (small, corneal opacities, malformed, ptosis, strabismus, etc.)
- CNS (structural malformation, seizures, ID, etc.)
- Palate (high, cleft, submucous, etc.)
- Limb (deletion anomalies, radioulnar synostosis, etc.)
- GU (structural anomalies of kidneys, ureters, and bladder)
- Skull (craniosynostosis, asymmetry, microcephaly, etc.)
- Heart (congenital structural anomalies vs cardiomyopathy)
- Lungs (hypoplasia vs weak muscles or hypoplastic diaphragm)
- Tracheal and laryngeal clefts and stenosis
- Changes in vasculature (hemangiomas, cutis marmoratus, blue cold distal limbs, etc.)
- Other visceral anomalies

OTHER FEATURES

Neurologic examination (detailed)
- Vigorous vs lethargic
- Deep tendon reflexes (present vs absent, slow vs fast)
- Sensory intact or not

Muscle
- Mass (normal or decreased)
- Texture (soft vs firm)
- Fibrous bands
- Normal tendon attachments or not
- Changes with time

COURSE

Changes with time
Developmental landmarks (motor vs social and language)
Growth of affected limbs
Progression of contractures
Lethal vs CNS damage vs stable vs improvement
Asymmetry
Trunk vs limb changes
Intellectual abilities
Socialization
Feeding problems
Response to therapy
Spontaneous improvement
Response to physical therapy
Response to casting
Which surgery at which time
Development of motor strength proportionate to limb size
Abnormal reaction to drugs

CNS, Central nervous system; ID, intellectual disability; GU, genitourinary.
From Hall JG. Arthrogryposis (multiple congenital contractures): diagnostic approach to etiology, classification, genetics, and general principles. *Eur J Med Genet.* 2014;57:464–472.

Table 648.11 Laboratory Evaluation

Documentation of range of motion and position with photographs
Radiographs if • Bony anomalies (gracile, fusions, extra or missing carpals and tarsals, etc.) • Disproportionate • Scoliosis • Ankylosis • Dislocation (hips, radial head, patella, etc.)
MRI to evaluate CNS (brain and spinal cord) and muscle mass obscured by contractures
Ultrasonographic evaluation of CNS (brain and spinal cord) or other anomalies, and to establish potential muscle tissue
Chromosome studies/CGH array if • Multiple system involvement • CNS abnormality (eye, microcephaly, ID, lethargy, degenerative course) • Streaky or segmental involvement • Consider fibroblast studies if lymphocytes were normal and patient has ID with no diagnosis • DNA gene testing if condition fits a known disorder for which gene testing is available • Consider next-generation sequencing technologies (targeted gene panels, whole-exome sequencing, whole-genome sequencing) if family available
Video of movement, including facial, range of movement, strength-repeat at regular intervals
Viral culture as appropriate and specific antibodies or IgM levels in newborn
Muscle biopsy in normal and affected areas at time of surgery to distinguish myopathic forms from neuropathic forms (do special histopathology and electron microscopic studies). If elevated creatine kinase or unusual muscle response, consider muscle biopsy earlier, examine mitochondria
EMG in normal and affected area
Nerve conduction in normal and affected area
Creatine kinase if • Generalized weakness • Doughy or decreased muscle mass • Progressive course
Eye examination (opacities, retinal degeneration, etc.)
Maternal antibodies to neurotransmitters, if myasthenia gravis or recurrent affected pregnancies without diagnosis
Spinal muscular atrophy (SMA) DNA testing according to clinical features
Mitochondrial DNA analysis
Metabolic screening

CGH, Comparative genomic hybridization; CNS, central nervous system; EMG, electromyography; ID, intellectual disability; IgM, immunoglobulin M.
From Hall JG. Arthrogryposis (multiple congenital contractures): diagnostic approach to etiology, classification, genetics, and general principles. *Eur J Med Genet.* 2014;57:464–472.

the use of NGS provided a conclusive diagnosis in 18 of 38 families (47%). Diagnostic yields range between 20% and 60%, depending on the homogeneity of the patient population; however, despite all efforts, nearly 50% of patients with arthrogryposis of a genetic origin do not have a precise molecular diagnosis.

Autopsy evaluation is extremely valuable. It should include an extensive workup for visceral anomalies, malformations of cortical development, and the number of anterior horn cells and their size in the spinal cord, with special attention paid to patchy involvement and the presence or absence of tracts at various levels in the spinal cord. Evaluation of the peripheral nerve, eye, and muscle tissue from different muscle groups and the diaphragm is also needed. Tendon attachments, fibrous bands replacing muscle, and cartilaginous or bony fusions can be evaluated, in addition to the presence of other malformations, deformations, or disruptions. Microarray analysis from different tissues and DNA extraction and molecular testing are also possible.

DIFFERENTIAL DIAGNOSIS

There is an ever-expanding list of disorders presenting with arthrogryposis. Almost 50% of fetal akinesia/hypokinesia presentations are neuromuscular in origin, involving all points along the neuromuscular axis (motor neurons, peripheral nerves, neuromuscular junctions, and the skeletal muscle regulatory and contractile apparatus). Mechanosensitive ion channels are another area of interest.

On clinical grounds, from a neuromuscular standpoint, one can recognize severe spinal muscular atrophies (SMA type 0), atypical SMA forms with arthrogryposis and bone fractures (see Chapter 652.2), lower motor neuron diseases (see Chapter 652.3), CMDs with specific attempts to recognize early sclerotic forms of the Ullrich CMD phenotype (Fig. 648.14) (see Chapter 649.6), and CMD with CNS involvement-alpha dystroglycan–related CMD (Fig. 648.15) (see Chapter 648.6). In any infant with contractures and/or facial weakness with a tented upper lip, examination of the mother should be routinely performed for myotonic reactions as a first step for CMD (Fig. 648.16 and Video 648.1) (see also Chapter 649.3). With the same clinical presentation, if the myotonic reaction of the mother is negative, congenital myopathies (Fig. 648.17 and Video 648.2) (see also Chapter 648.3) should be included in the differential diagnosis. Fetal acetylcholine receptor inactivation syndrome is characterized by clinical features ranging from mild facial and bulbar myopathy to arthrogryposis, and *maternal treatment* can improve the outcome (see Chapter 652.1). Some pterygium syndromes may respond to *acetylcholine treatment.*

Prevention or treatment of metabolic disturbances (metabolic acidosis) or treating an inherited metabolic disease may also have a positive impact on the outcome. Carbohydrate-deficient glycoprotein

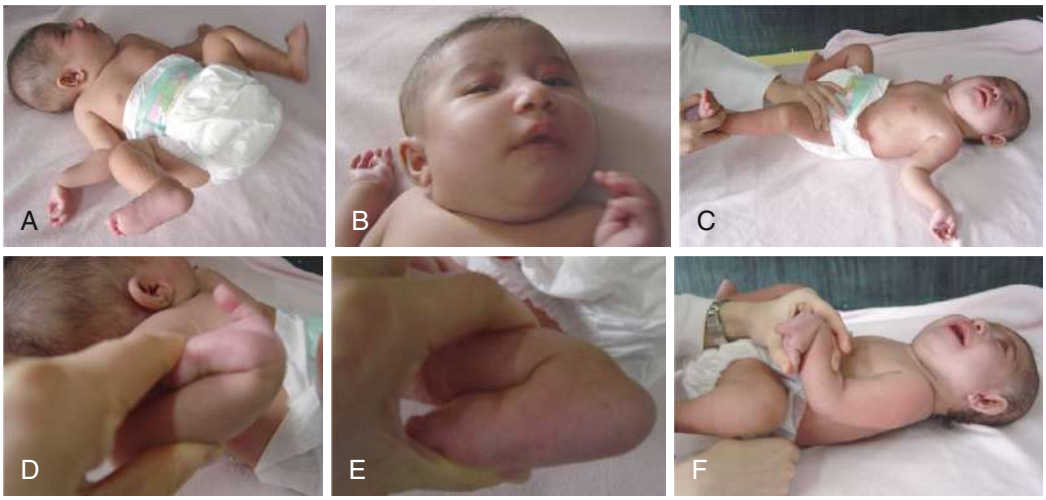

Fig. 648.14 A 3-mo-old male infant, born with arthrogryposis (A), congenital torticollis (B), proximal knee contractures (C), and distal laxity (D-F), a clinical phenotype consistent with Ullrich congenital muscular dystrophy.



Fig. 648.15 A 3-mo-old female infant with an intrauterine diagnosis of hydrocephalus and arthrogryposis. Ventriculoperitoneal shunt replacement at birth. Note dysmorphic facial features, megalocornea (A), failure to thrive, decrease in muscle mass, and generalized weakness (B). A high serum CK level with CNS malformation on brain MRI led to diagnosis of Walker-Warburg syndrome with *POMT1* gene variant.

syndrome (CDG), perinatal lethal forms of Gaucher disease, glycogen storage disease types IV and VII (phosphofructokinase deficiency), Zellweger syndrome spectrum, adenylosuccinate lyase deficiency, and ARC (arthrogryposis, renal dysfunction, cholestasis) syndrome are among the diseases in this group with an autosomal recessive inheritance.

GENETIC COUNSELING AND PRENATAL DIAGNOSIS

Establishing a molecular diagnosis in an index patient with a genetic form of arthrogryposis is required for appropriate genetic counseling and prenatal diagnosis. Despite maternal care and the availability of prenatal ultrasonography (US), which can confirm abnormal movements and postural findings as early as 11 weeks, 75% of affected individuals with arthrogryposis were reported to be not diagnosed before birth. Real-time US can visualize contractures, the quality of in utero movements, the joint positioning, lung hypoplasia, nuchal edema, the muscle mass, and the bone growth in the first or early second trimester. Prenatal or postnatal MR findings can be used as a complementary adjunct to US, especially for the evaluation of accompanying muscle and joint malformations. The maternal perception of decreased intrauterine movements and high-risk pregnancies should be carefully evaluated. In an effort to improve the detection rate and



Fig. 648.16 Arthrogryposis due to congenital myotonic dystrophy in the newborn period (A), at age 3 mo (B), and at 1 yr (C). Note severe hyperextension of the limbs at birth (A) and facial weakness characterized by tented upper lip (B and C), signs that should lead to physical examination of the mother. See also Video 648.1.

guide the diagnostic strategy, a fetal approach can be applied as early as the first prenatal ultrasound at 12 weeks, in the first trimester (Fig. 648.18).

Timely recognition leads to a further etiologic and diagnostic workup and pregnancy management and creates time for informed choices, in utero stimulation, or early delivery according to the degree of lung maturation. In a case of detection of contractures in a prenatal



Fig. 648.17 Arthrogryposis, respiratory insufficiency, and fractures at birth (**A-C**), with a family history of consanguinity and similarly affected infant at the age of 3 mo with dysmorphic features, severe facial involvement (tented upper lip), frontal bossing, epicanthus (**D**), pectus excavatum deformity, and severe generalized weakness (**E**). Muscle biopsy revealed intracytoplasmic nemaline rods (**F**), leading to a diagnosis of *KHL40*-nemaline myopathy. See also Video 648.2.

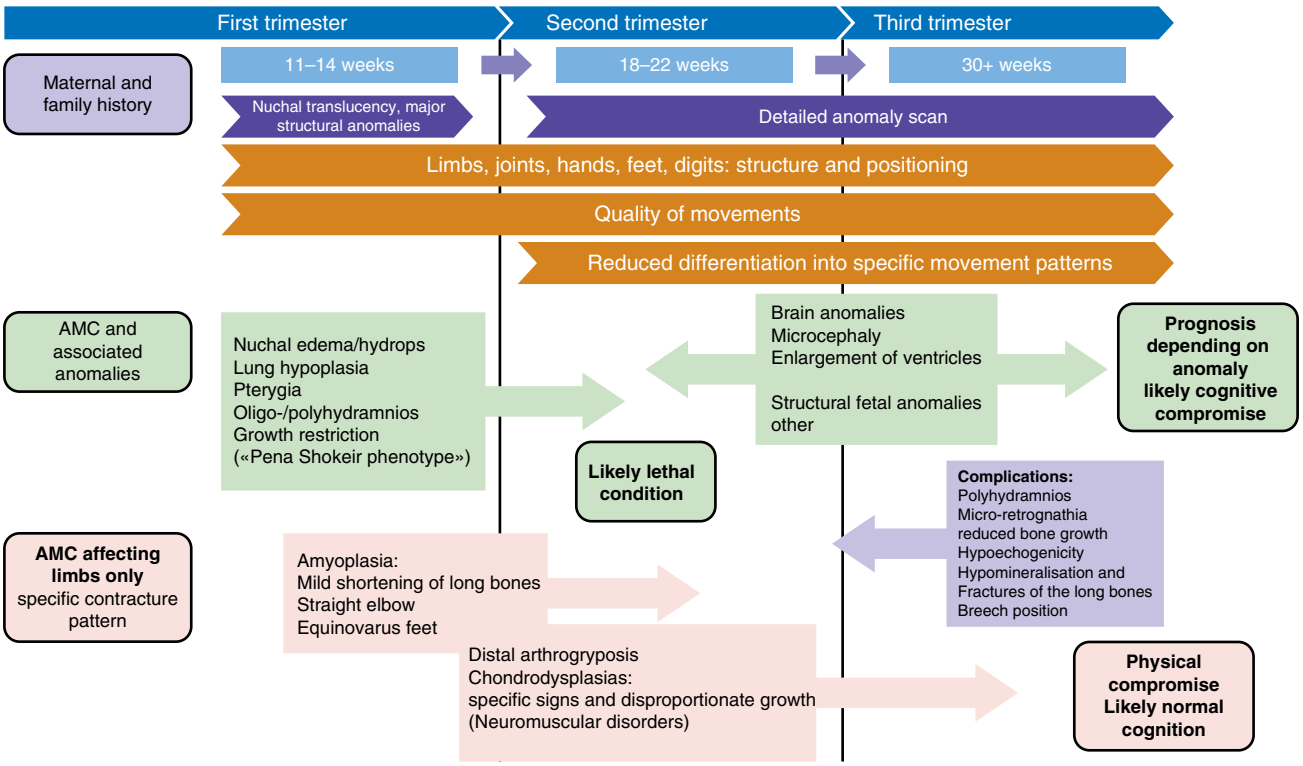

Fig. 648.18 Proposed ultrasound algorithm for improving the detection of AMC in prenatal care. Screening for limb, joints, hand, feet, digit anomalies, and positioning as the quality of movements should start as early as the first trimester and monitored throughout pregnancy. Reduced differentiation into specific movement patterns can likely be appreciated in the second trimester. Depending on the type of findings and the time of appearance during fetal development, a likely diagnosis and prognosis can be provided. Chromosomal microarray analysis is indicated in all fetuses with AMC, and further molecular testing including panel and genome-wide sequencing should be offered depending on the clinical presentation. *(From Filges I, Tercanli S, Hall JG. Fetal arthrogryposis: challenges and perspectives for prenatal detection and management. Am J Med Genet. 2019;181C:327–336. Fig. 2.)*

US study, physicians involved in the care of a pregnant woman should examine her to rule out myotonic dystrophy, in order to prevent serious complications. Due to high rates of infertility, before introducing artificial reproductive techniques, myotonic dystrophy should be considered. Because of genetic anticipation, the diagnosis of the mother may be delayed to the time of giving birth to a severely affected infant with arthrogryposis (see Chapter 649.3). Arthrogryposis with a history of myasthenia gravis in the mother should be evaluated accordingly, because miscarriage, stillbirth, or neonatal death can complicate the picture (see Chapter 652.1).

Chromosomal abnormalities and autosomal recessive, autosomal dominant, X-linked, and mitochondrial inheritance have been all described in the disorders related to arthrogryposis, and genetic counseling should be provided accordingly. If a specific diagnosis is not made, the empirical recurrence risk is defined as 3%, and it is slightly higher (7%) for arthrogryposis plus CNS involvement.

MANAGEMENT

Each affected individual with arthrogryposis is unique, and the natural course of the condition depends on the underlying etiology and management. A multidisciplinary team approach (pediatricians, pediatric orthopedic specialists, plastic or hand surgeons, rehabilitation physicians, occupational therapists, physical therapists, medical geneticists, neurologists) is essential in standard care (see Chapter 723). Management is shifting to a multidisciplinary clinic that provides patient-centered, comprehensive care in a coordinated manner.

In terms of amyoplasia, follow-up is required to identify treatment outcomes such as the development of degenerative arthritis, the need for orthotics for ambulation, or the possibility of becoming overweight in adulthood. Cytokines and other factors released in response to early therapeutic interventions are suggested to facilitate the elongation of pathologic periarticular soft tissues and increase joint motion. The core principle of management in DA is to preserve muscle function. Anesthesia-related complications due to limited jaw opening, restrictive pulmonary function, and the risk of MH should be considered in the setting of multiple surgeries.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 649

Muscular Dystrophies

*Adnan Y. Manzur**

A muscular dystrophy is distinguished from all other neuromuscular diseases by four obligatory criteria: it is a primary myopathy, it has a genetic basis, the course is progressive, and degeneration and death of muscle fibers occur at some stage in the disease. This definition excludes neurogenic diseases such as spinal muscular atrophy, nonhereditary myopathies such as dermatomyositis, nonprogressive and nonnecrotizing congenital myopathies such as congenital muscle fiber–type disproportion, and nonprogressive inherited metabolic myopathies. Some metabolic myopathies can fulfill the definition of a progressive muscular dystrophy but are not traditionally classified as dystrophies (muscle carnitine deficiency).

Many muscular dystrophies might eventually be reclassified as metabolic myopathies once the biochemical defects are better defined. Muscular dystrophies are a group of unrelated diseases, each transmitted by a different genetic trait and each differing in its clinical course and expression (Table 649.1). Identifiable pathogenic variants in some genes may lead to a spectrum of clinical phenotypes, ranging in age of onset, severity, and presence of comorbidities. Some muscular dystrophies are more severe and/or may be present at birth or soon after birth, typically defined as *congenital muscular dystrophies* (Table 649.2), whereas others may have an onset in childhood or even in adulthood. There is a range of severity from those that lead to death in the neonatal period to those that progress gradually over decades, generally with a normal lifespan. Some categories of dystrophies, such as limb-girdle muscular dystrophy (LGMD), are not homogeneous diseases but rather syndromes encompassing several distinct clinical entities and a number of putative genes.

* The editors are grateful to Dr. Diana X. Bharucha-Goebel, much of whose work on previous editions of this chapter is retained here.

649.1 Duchenne and Becker Muscular Dystrophies

Adnan Y. Manzur

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, and hypertrophy of the calves, with proliferation of connective tissue and progressive fibrosis in muscle. The incidence is 1 in 3,600 liveborn infant males. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. **Becker muscular dystrophy** (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

CLINICAL MANIFESTATIONS

Infant boys with DMD are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages, or may be mildly delayed. Distinctive facies are not an early feature because facial muscle weakness is a late event; in later childhood, a "transverse" or horizontal smile may be seen. Walking is often delayed past 18 months in approximately 50%, and hip girdle weakness may be seen in a subtle form as early as the second year. Toddlers might assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers sign may be seen by age 3 years, but nearly always is evident by age 5 or 6 years (see Fig. 630.5 in Chapter 630). A Trendelenburg (waddling) gait frequently appears at this time as well. Common presentations in toddlers include delayed walking, frequent falling, toe walking, and trouble running or walking upstairs, developmental delay, and, less often, malignant hyperthermia after anesthesia. A significant minority present with speech or global developmental delay and autistic spectrum traits. Some asymptomatic infants come to attention because of isolated transaminases aspartate transaminase (AST)/alanine transaminase (ALT) elevation, which originates from muscles secondary to sarcolemmal damage, and it is important to perform serum creatinine kinase (CK), which is found to be massively elevated. Non-recognition of this feature leads to hepatology workup and sometimes, an unnecessary muscle biopsy.

The length of time a patient with DMD remains ambulatory varies greatly. Patients may demonstrate increased difficulties with ambulation, due to the proximal lower extremity weakness, that is further confounded by progressive ankle contractures and toe walking. The age of complete loss of ambulation ranges typically from about 10-14 years. The age at which loss of independent ambulation occurs has increased over time with the advent of clinical care guidelines recommending the use of corticosteroids (e.g., prednisone or deflazacort) in boys with DMD (see the section "Treatment"). With orthotic bracing, physiotherapy, and sometimes minor surgery (Achilles tendon lengthening), most are able to walk until age 12 years. Maintenance of ambulation is not only important for preservation of autonomy in activities of daily living (which has psychosocial benefits for the patient and his family), but also provides additional benefits in slowing the progression of scoliosis (that typically worsens after loss of ambulation) and in maintenance of pulmonary health.

The relentless progression of weakness continues into the second decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard. As the disease progresses in the teenage years, the upper extremity strength declines further, and patients may have increased difficulties bringing hands to mouth independently, have fatigue with writing, and have worsening contractures, including in the hands and fingers. Respiratory muscle involvement frequently

Chromosomal abnormalities and autosomal recessive, autosomal dominant, X-linked, and mitochondrial inheritance have been all described in the disorders related to arthrogryposis, and genetic counseling should be provided accordingly. If a specific diagnosis is not made, the empirical recurrence risk is defined as 3%, and it is slightly higher (7%) for arthrogryposis plus CNS involvement.

MANAGEMENT

Each affected individual with arthrogryposis is unique, and the natural course of the condition depends on the underlying etiology and management. A multidisciplinary team approach (pediatricians, pediatric orthopedic specialists, plastic or hand surgeons, rehabilitation physicians, occupational therapists, physical therapists, medical geneticists, neurologists) is essential in standard care (see Chapter 723). Management is shifting to a multidisciplinary clinic that provides patient-centered, comprehensive care in a coordinated manner.

In terms of amyoplasia, follow-up is required to identify treatment outcomes such as the development of degenerative arthritis, the need for orthotics for ambulation, or the possibility of becoming overweight in adulthood. Cytokines and other factors released in response to early therapeutic interventions are suggested to facilitate the elongation of pathologic periarticular soft tissues and increase joint motion. The core principle of management in DA is to preserve muscle function. Anesthesia-related complications due to limited jaw opening, restrictive pulmonary function, and the risk of MH should be considered in the setting of multiple surgeries.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 649

Muscular Dystrophies

*Adnan Y. Manzur**

A muscular dystrophy is distinguished from all other neuromuscular diseases by four obligatory criteria: it is a primary myopathy, it has a genetic basis, the course is progressive, and degeneration and death of muscle fibers occur at some stage in the disease. This definition excludes neurogenic diseases such as spinal muscular atrophy, nonhereditary myopathies such as dermatomyositis, nonprogressive and nonnecrotizing congenital myopathies such as congenital muscle fiber–type disproportion, and nonprogressive inherited metabolic myopathies. Some metabolic myopathies can fulfill the definition of a progressive muscular dystrophy but are not traditionally classified as dystrophies (muscle carnitine deficiency).

Many muscular dystrophies might eventually be reclassified as metabolic myopathies once the biochemical defects are better defined. Muscular dystrophies are a group of unrelated diseases, each transmitted by a different genetic trait and each differing in its clinical course and expression (Table 649.1). Identifiable pathogenic variants in some genes may lead to a spectrum of clinical phenotypes, ranging in age of onset, severity, and presence of comorbidities. Some muscular dystrophies are more severe and/or may be present at birth or soon after birth, typically defined as *congenital muscular dystrophies* (Table 649.2), whereas others may have an onset in childhood or even in adulthood. There is a range of severity from those that lead to death in the neonatal period to those that progress gradually over decades, generally with a normal lifespan. Some categories of dystrophies, such as limb-girdle muscular dystrophy (LGMD), are not homogeneous diseases but rather syndromes encompassing several distinct clinical entities and a number of putative genes.

* The editors are grateful to Dr. Diana X. Bharucha-Goebel, much of whose work on previous editions of this chapter is retained here.

649.1 Duchenne and Becker Muscular Dystrophies

Adnan Y. Manzur

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, and hypertrophy of the calves, with proliferation of connective tissue and progressive fibrosis in muscle. The incidence is 1 in 3,600 liveborn infant males. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. **Becker muscular dystrophy** (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

CLINICAL MANIFESTATIONS

Infant boys with DMD are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages, or may be mildly delayed. Distinctive facies are not an early feature because facial muscle weakness is a late event; in later childhood, a "transverse" or horizontal smile may be seen. Walking is often delayed past 18 months in approximately 50%, and hip girdle weakness may be seen in a subtle form as early as the second year. Toddlers might assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers sign may be seen by age 3 years, but nearly always is evident by age 5 or 6 years (see Fig. 630.5 in Chapter 630). A Trendelenburg (waddling) gait frequently appears at this time as well. Common presentations in toddlers include delayed walking, frequent falling, toe walking, and trouble running or walking upstairs, developmental delay, and, less often, malignant hyperthermia after anesthesia. A significant minority present with speech or global developmental delay and autistic spectrum traits. Some asymptomatic infants come to attention because of isolated transaminases aspartate transaminase (AST)/alanine transaminase (ALT) elevation, which originates from muscles secondary to sarcolemmal damage, and it is important to perform serum creatinine kinase (CK), which is found to be massively elevated. Non-recognition of this feature leads to hepatology workup and sometimes, an unnecessary muscle biopsy.

The length of time a patient with DMD remains ambulatory varies greatly. Patients may demonstrate increased difficulties with ambulation, due to the proximal lower extremity weakness, that is further confounded by progressive ankle contractures and toe walking. The age of complete loss of ambulation ranges typically from about 10-14 years. The age at which loss of independent ambulation occurs has increased over time with the advent of clinical care guidelines recommending the use of corticosteroids (e.g., prednisone or deflazacort) in boys with DMD (see the section "Treatment"). With orthotic bracing, physiotherapy, and sometimes minor surgery (Achilles tendon lengthening), most are able to walk until age 12 years. Maintenance of ambulation is not only important for preservation of autonomy in activities of daily living (which has psychosocial benefits for the patient and his family), but also provides additional benefits in slowing the progression of scoliosis (that typically worsens after loss of ambulation) and in maintenance of pulmonary health.

The relentless progression of weakness continues into the second decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard. As the disease progresses in the teenage years, the upper extremity strength declines further, and patients may have increased difficulties bringing hands to mouth independently, have fatigue with writing, and have worsening contractures, including in the hands and fingers. Respiratory muscle involvement frequently

Table 649.1 Pathophysiologic Classification of Muscular Dystrophy

DISEASE	LOCUS	GENE	MODE OF INHERITANCE
LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD) CAUSED BY SARCOLEMMA OR CYTOSOLIC PROTEIN DEFECTS			
Duchenne/Becker MD	Xp21	Dystrophin	XR
LGMD 1A (myofibrillar myopathy)	5q31	Myotilin	AD
LGMD 1B (Emery-Dreifuss muscular dystrophy)	1q21	Lamin A/C	AD
LGMD 1C (rippling muscle disease)	3p25	Caveolin	AD
LGMD 1D (D1 DNAJB6-related LGMD)	7q36	DNAJB6	AD
LGMD 1E (myofibrillar myopathy)	6q23	Desmin	AD
LGMD 1F (D2 TNP03-related LGMD)	7q32	Transportin-3	AD
LGMD 1G (D3 HNRNPDL-related LGMD)	2q37	HNRDL	AD
LGMD 1H	3p23-25	Unknown—not confirmed	AD
LGMD 1L (D4 calpain-3–related LGMD)	15q15.1	Calpain-3	
LGMD 2A (R1 calpain-3–related LGMD)	15q15.1	Calpain-3	AR
LGMD 2B (R2 dysferlin–related LGMD)	2p13.1	Dysferlin	AR
LGMD 2C (R5 γ-sarcoglycan–related LGMD)	13q12	γ-Sarcoglycan	AR
LGMD 2D (R3 α-sarcoglycan–related LGMD)	17q21	α-Sarcoglycan	AR
LGMD 2E (R4 β-sarcoglycan–related LGMD)	4q12	β-Sarcoglycan	AR
LGMD 2F (R6 δ-sarcoglycan–related LGMD)	5q33	δ-Sarcoglycan	AR
LGMD 2G (R7-telethonin–related LGMD)	17q11.2	Telethonin (TCAP)	AR
LGMD 2H (R8 TRIM 32–related LGMD)	9q31-q33	Tripartite motif-containing 32 (TRIM32)	AR
LGMD 2I (R9-FKRP–related LGMD)	13q13.3	Fukutin-related protein (FKRP)	AR
LGMD 2J (R10-Titin–related LGMD)	2q31	Titin	AR/AD
LGMD 2K (R11-POMT1–related LGMD)	9q34.1	Protein-O-mannosyltransferase (POMT1)	AR
LGMD 2L (R12-anoctamin 5–related LGMD)	11p14.3	ANO5	AR
LGMD 2M (R13-fukutin–related LGMD)	9q31	Fukutin	AR
LGMD 2N (R14 POMT2–related LGMD)	14q24	POMT2	AR
LGMD 2O (R15 POMGNT1–related LGMD)	1p32	POMGnT1	AR
LGMD 2P (R16 α-dystroglycan–related LGMD)	3p21	DAG1	AR
LGMD 2Q (R17 plectin–related LGMD)	8q24	Plectin 1f	AR
LGMD 2R (myofibrillar myopathy)	2q35	Desmin	AR
LGMD 2S (R18 TRAPPC11–related LGMD)	4q35	TRAPPC11	AR
LGMD 2T (R19 GMPPB–related LGMD)	3p21	GMPPB	AR
LGMD 2U (R20 ISPD–related LGMD)	7p21	ISPD	AR
LGMD 2V (Pompe disease)	17q25	GAA	AR
LGMD 2W (PINCH-2–related myopathy)	2q14	LIMS2	AR
LGMD 2X (BVES-related myopathy)	6p21	BVES	AR
LGMD 2Y (TOR1AIP1-related myopathy)	3q13,33	POGLUT1	AR
LGMD 2Z	6q21	POPDC1	AR
CONGENITAL MUSCULAR DYSTROPHY (CMD) SECONDARY TO GLYCOSYLATION DISORDER			
Fukuyama MD (syndromic)	9q31	Fukutin	AR
Muscle-eye-brain disease (syndromic)	1p34.1	Protein O-linked mannose beta-1,2-N-acetylglucosaminyltransferase (POMGnT1)	AR
Walker-Warburg syndrome (syndromic)	9q34.1	Protein-O-mannosyltransferase (POMT1)	AR
MDC 1A (merosin-negative CMD)	6q22-23	Laminin-a2 (merosin)	
MDC 1B (merosin-positive CMD)	1q42	?	AR

Continued

Table 649.1 Pathophysiologic Classification of Muscular Dystrophy—cont'd

DISEASE	LOCUS	GENE	MODE OF INHERITANCE
MDC 1C	19q13.3	Fukutin-related protein (FKRP)	AR
MC 1D	22q12.3-q13.1	LARGE	AR
OTHER CONGENITAL MUSCULAR DYSTROPHIES			
CMD with early rigid spine (RSS)	1p36	Selenoprotein N-1	AR
CMD with ITGA7 mutations	12q	Integrin α7	AR
Ullrich syndrome/Bethlem myopathy	21q22.3 (A1, A2) 2q37 (A3)	Collagen VI α1, α2, and α3	AD
MUSCULAR DYSTROPHIES SECONDARY TO NUCLEAR ENVELOPE DEFECTS			
Emery-Dreifuss MD X1	Xq28	Emerin	XR
Emery-Dreifuss MD X2	q21.2	Lamin A/C	AD
Emery-Dreifuss MD X3	1q21.2	Lamin A/C	AR
Emery-Dreifuss MD X4	6q25	Synaptic nuclear envelope protein 1 (SYNE1; Nesprin-1)	AD
Emery-Dreifuss MD X5	14q23	SYNE2	AD
Emery-Dreifuss MD X6	Xq26	Four-and-a-half-LIM protein 1 (FHL1)	XR
Emery-Dreifuss MD X7?	3p25.1	LUMA (transmembrane protein 43)	AR
MUSCULAR DYSTROPHIES SECONDARY TO RNA METABOLISM DEFECTS			
Myotonic dystrophy 1 (DM1)	19q13.3	Myotonic dystrophy-associated protein kinase (DMPK)	AD
Myotonic dystrophy 2 (DM2)	3q21	Zinc finger, nucleic acid binding protein (ZNF9)	AD
OTHER MUSCULAR DYSTROPHIES OF UNKNOWN MECHANISM			
Facioscapulohumeral dystrophy (FSHD)	3q21	FRG-1 (FSH region gene 1)	AD
Oculopharyngeal MD	14q11.2-q13	PABPN1	AD

Note: LGMD table: Disease names in parentheses: New nomenclature proposed from 2018 European Neuromuscular Centre Workshop.
AD, Autosomal dominant; AR, autosomal recessive; MD, muscular dystrophy; MDC, muscular dystrophy congenita; XR, X-linked recessive.
From Rocha CT, Escolar DM. Treatment and management of muscular dystrophy. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management,* 2nd ed. Philadelphia: Elsevier; 2022: Table 20.1, p. 493–494.

Table 649.2 Specific Congenital Muscular Dystrophies: Distinguishing Clinical Features

SUBCATEGORY	DISTINGUISHING CLINICAL FEATURES	ASSOCIATED GENES
Collagen VI-related dystrophies	• Proximal muscle weakness in childhood • Severe hypotonia and diffuse weakness in infancy • Infantile onset typically never achieves ambulation • Early-onset proximal contractures diffusely • Distal joint hyperlaxity • Hyperkeratosis pilaris on skin (legs and arms) • Keloids • Atrophic, wide scars • Scoliosis (early) • Very thin body habitus • Severe restrictive lung disease early requiring bilevel ventilation • Normal intellect • CK usually elevated (100–several 1,000 U/L)	*COL6A1, COL6A2, COL6A3*
cLAMA2-related dystrophies	• Proximal muscle weakness in childhood • Severe hypotonia and diffuse weakness in infancy • Infantile onset typically never achieves ambulation • Early-onset proximal contractures diffusely • Brain MRI demonstrates white matter disease (clinically not significant) • Some develop seizures • Very thin body habitus • Severe restrictive lung disease early requiring bilevel ventilation • Nerve conductions demonstrate slowing • Normal intellect • CK usually in the 1,000s	*LAMA2*

Table 649.2 Specific Congenital Muscular Dystrophies: Distinguishing Clinical Features—cont'd

SUBCATEGORY	DISTINGUISHING CLINICAL FEATURES	ASSOCIATED GENES
Dystroglycan-related disorders (dystroglycanopathies, previously known as muscle-eye-brain disease)	• Mild to severe proximal muscle weakness and hypotonia in infancy • Varying degrees of CNS involvement • Brain MRI may be abnormal—lissencephaly, pachygyria, cerebellar hypoplasia, or dysplasia • *FKRP* and *FKTN* may cause a cardiomyopathy, if late onset • Varying degree of eye involvement—severe myopia, retinal hypoplasia • Intellectual delay ranging from normal to severe disability	*POMT1, POMT2, POMGnT1, POMGnT2, FKTN, FKRP, LARGE, ISPD, GTDC2, B3GALNT2, B3GNT1, B4GAT1, TMEM5, POMK, DPM1, DPM2, DPM3, DOLK, GMPPB, RXYLT1, DAG1*
Myofibrillar myopathy	• Distal and proximal muscle weakness developing in adolescence or early adulthood • Respiratory muscle weakness often necessitating noninvasive or invasive ventilatory support • Rigid spine • Possible sensory neuropathy	*BAG3, CRYAB, DES, FLNC, KY, LDB3, MYOT, PYROXD1*
Selenon-related myopathy	• Severe axial weakness • Early-onset scoliosis • Early-onset restrictive lung disease requiring bilevel noninvasive ventilation, before loss of ambulation (characteristic) • Normal intellect	*SEPN1*
LMNA-related dystrophy	• Severe hypotonia and diffuse weakness in infancy • Proximal muscle weakness in childhood • Prominent head drop in infancy (dropped-head syndrome); may achieve ambulation despite head drop • At risk of cardiac arrhythmia • Early diffuse contractures • Severe restrictive lung disease requiring bilevel ventilation	*LMNA*

CK, Creatine kinase; CNS, central nervous system.
From Konersman CG. Hypotonia and weakness. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 35.35, p. 616–617.

manifests as a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. Early pulmonary symptoms often include snoring and sleep apnea. Parents or patients may report an increased frequency of headaches, difficulty awakening in the mornings, and increased daytime fatigue as signs of sleep-disordered breathing. Pharyngeal weakness can lead to episodes of aspiration, nasal regurgitation of liquids, and an airy or nasal voice quality. The function of the extraocular muscles remains well preserved. Incontinence due to anal and urethral sphincter weakness is an uncommon and very late event.

Contractures most often involve the ankles, knees, hips, and elbows. As upper extremity weakness progresses, contractures are also seen in neck lateral rotation, shoulders, and fingers. **Scoliosis** is common in patients with DMD. The thoracic deformity further compromises the pulmonary capacity and compresses the heart. It may also lead to more discomfort, and if severe enough, risk for hip dislocation. Scoliosis usually progresses more rapidly after the child becomes nonambulatory. However, in the era of corticosteroid use, there may be a further protective effect on the development of and rate of progression of scoliosis. Enlargement of the calves (pseudohypertrophy) and wasting of thigh muscles are classic features. The enlargement is caused by hypertrophy of some muscle fibers, infiltration of muscle by fat, and proliferation of collagen. After the calves, the next most common site of muscular hypertrophy is the tongue, followed by muscles of the forearm. Abnormalities of the muscle are demonstrated using muscle MRI techniques to assess signal, water content, fat fractions, and even MR spectroscopy profiles (Fig. 649.1). Fasciculations of the tongue do not occur. The voluntary sphincter muscles rarely become involved.

Unless ankle contractures are severe, ankle deep tendon reflexes remain preserved until terminal stages. The knee deep tendon reflexes may be present until about 6 years of age but are less brisk than the ankle jerks and are eventually lost with the progression of weakness.

Cardiomyopathy, including persistent tachycardia and myocardial fibrosis, occurs in a majority of patients with DMD. The severity of cardiac involvement does not necessarily correlate with the degree of skeletal muscle weakness. In patients with DMD, the progression of cardiomyopathy typically occurs after loss of independent ambulation. However, in patients with BMD, patients may develop worsening of cardiomyopathy and even develop severe heart failure despite still being ambulant. Smooth muscle dysfunction, particularly of the gastrointestinal tract, is a minor, but often overlooked, feature.

Intellectual impairment occurs in a majority of patients, although only 20–30% have an IQ <70. There is a range in the extent of intellectual disability, with some patients requiring specialized education and having difficulty with reading and writing, to those less severely affected who may only require some additional tutoring or assistance. The extent of severity of the intellectual disability does not appear to correlate with the severity of the myopathy but may be related to the location of the mutations in the dystrophin gene. Epilepsy is slightly more common than in the general pediatric population, although it is not a salient feature of DMD. Autism-like behavior may develop in some patients. Dystrophin is expressed in brain and retina, as well as in striated and cardiac muscle, though the level is lower in brain than in muscle. This distribution might explain some of the central nervous system manifestations. Abnormalities in cortical architecture and of dendritic arborization may be detected neuropathologically; cerebral atrophy is demonstrated by MRI late in the clinical course. Patients with DMD and BMD may occasionally report myalgias that are often exercise or exertion induced. Calcinosis of muscle is rare.

Death in males with DMD occurs in the late teens to 20s.The causes of death are respiratory failure during sleep, intractable heart failure, pneumonia, or, occasionally, aspiration and airway obstruction. In the recent decade, and with the application of standards of care, survival is prolonged into the 30s in many patients.

In **BMD,** the onset is often after 5 years or 7 years of age, and most boys remain ambulatory into adulthood. Calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of CK are similar to those of patients with DMD. Cramps on exercise and myoglobinuria may be initial presenting features. Given the increased level of activity in BMD patients, the cardiac manifestations, including tachycardia, shortness of breath, or fatigue, may be evident earlier in patients with BMD and even in the setting of independent ambulation. Learning disabilities

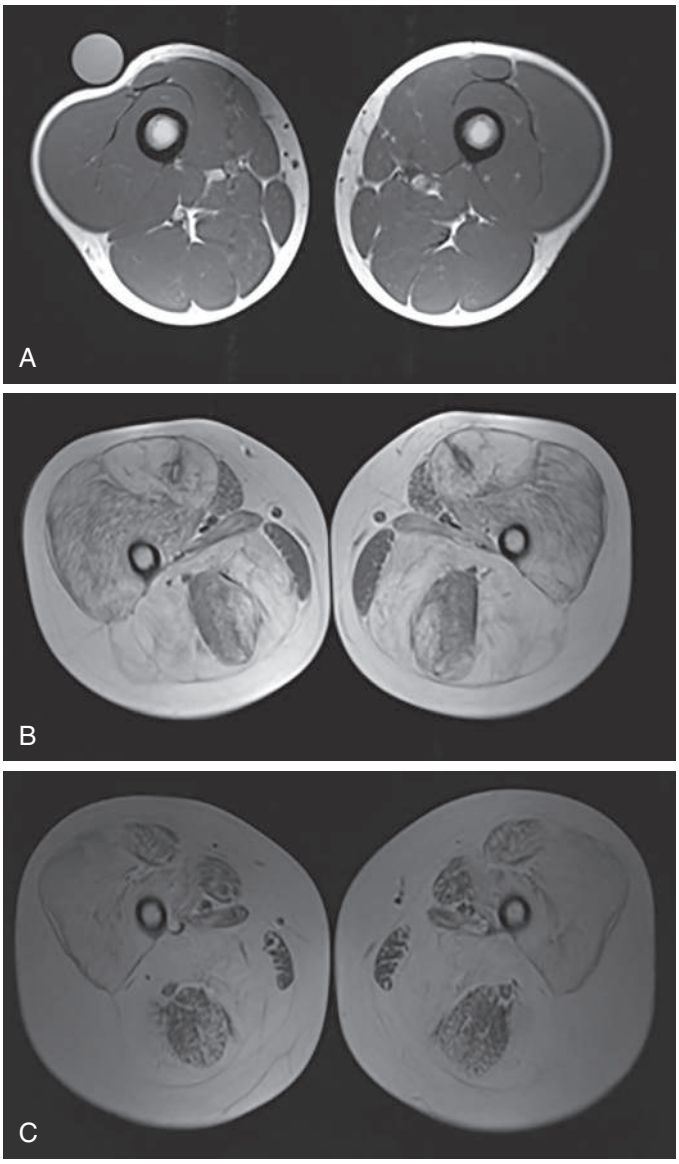

Fig. 649.1 Axial T1-weighted MRI images of the thigh in a healthy 14-yr-old male (**A**), 9-yr-old ambulant male with DMD (**B**), and 14-yr-old ambulant male with DMD (**C**), showing the increased fatty infiltration and muscle atrophy in males with DMD. *(Courtesy Dr. Ami Mankodi, Neurogenetics Branch, NINDS/NIH.)*

are less common. The onset of weakness is later in BMD than in DMD. The lifespan in patients with BMD is typically into the 40s and 50s, with cardiac complications as well as pulmonary complications frequently leading to morbidity.

LABORATORY FINDINGS

The serum CK level is consistently greatly elevated in DMD, even in presymptomatic stages, including at birth. The usual serum concentration is 15,000-35,000 IU/L (normal <160 IU/L). A normal serum CK level is incompatible with the diagnosis of DMD, although in terminal stages of the disease, the serum CK value may be considerably lower than it was a few years earlier because there is less muscle to degenerate. Other lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased but are less specific.

Cardiac assessment by echocardiography and ECG are essential and should be monitored. The recommendation is for cardiac surveillance every year starting at the time of diagnosis, and then yearly. After the diagnosis of DMD is established, patients should be referred to a pediatric cardiologist who is familiar with the care of DMD patients

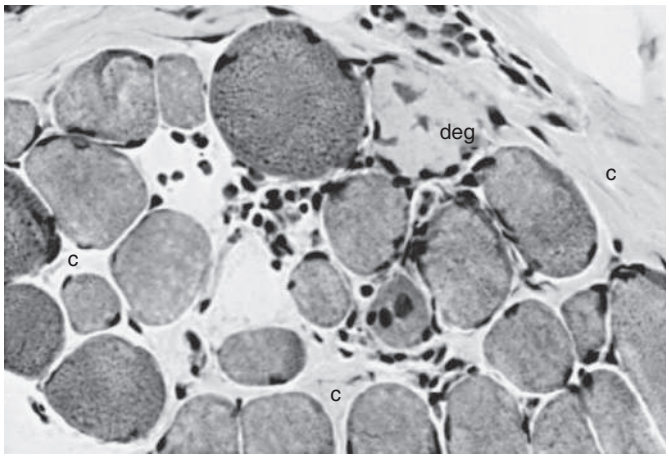

Fig. 649.2 Muscle biopsy of a 4-yr-old male with Duchenne muscular dystrophy. Both atrophic and hypertrophic muscle fibers are seen, and some fibers are degenerating *(deg)*. Connective tissue *(c)* between muscle fibers is increased (hematoxylin and eosin, ×400).

for long-term cardiac care. Cardiac MRI may detect changes such as muscle fibrosis in the heart evident even earlier than the changes seen by echocardiography.

Electromyography (EMG) shows characteristic myopathic features but is not specific for DMD. No evidence of denervation is found. Motor and sensory nerve conduction velocities are normal.

DIAGNOSIS

Genetic evaluation for DMD typically begins with deletion/duplication analysis of the dystrophin gene, using dosage analysis. If negative, then sequencing of the dystrophin gene by next-generation sequencing is performed. If genetic analysis is still negative for a pathogenic variant in the dystrophin gene, but if the suspicion is high based on clinical features and serum CK levels, then muscle biopsy with dystrophin immunohistochemistry may be useful. Immunohistochemical staining of frozen sections of muscle biopsy tissue detects differences in the rod domain, the carboxyl terminus (that attaches to the sarcolemma), and the N terminus or amino terminus (that attaches to the actin myofilaments) of the large dystrophin molecule and may be prognostic of the clinical course as Duchenne or Becker disease. More severe weakness occurs with truncation of the dystrophin molecule at the carboxyl terminus than at the amino terminus. Dystroglycans and other sarcolemmal regional proteins, such as merosin and sarcoglycans, also can be measured because they may be secondarily decreased. Further genetic testing could be done, which may include RNA sequencing from muscle to attempt to identify a variant altering splicing (e.g., one that may not be identified on next-generation sequencing). Accurate assignation of pathogenicity and anticipated severity of a particular dystrophin gene variant can be difficult, and free access to various international databases is most helpful for the clinician; the Leiden pathogenic variant database maintained by the Leiden University Medical Center and ClinVar hosted by the National Center for Biotechnology Information (Bethesda, MD), are good examples.

The **muscle biopsy** is diagnostic and shows characteristic changes (Figs. 649.2 and 649.3). Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still-functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level, allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary β-dystroglycan deficiency.

The decision about whether muscle biopsy should be performed to establish the diagnosis sometimes presents problems. If there is a

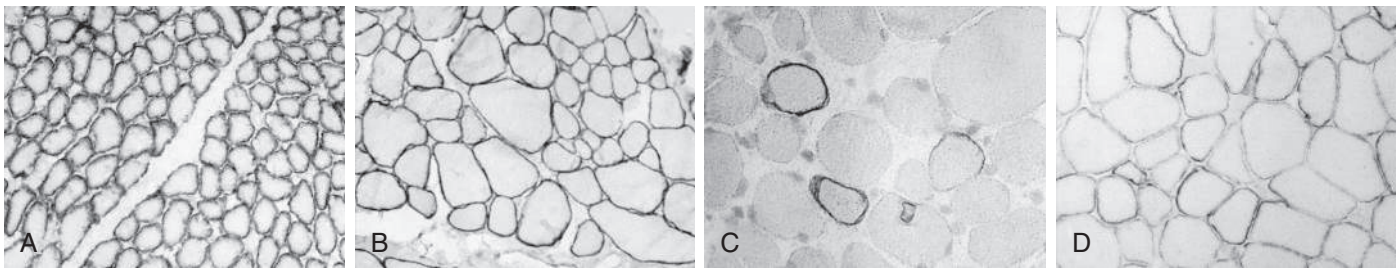

Fig. 649.3 Dystrophin is demonstrated by immunohistochemical reactivity in the muscle biopsies of a normal-term male neonate (A), a 10-yr-old male with limb-girdle muscular dystrophy (B), a 6-yr-old male with Duchenne muscular dystrophy (C), and a 10-yr-old male with Becker muscular dystrophy (D). In the normal condition, and also in non–X-linked muscular dystrophies in which dystrophin is not affected, the sarcolemmal membrane of every fiber is strongly stained, including atrophic and hypertrophic fibers. In Duchenne dystrophy, most myofibers express no detectable dystrophin, but a few scattered fibers known as revertant fibers show near-normal immunoreactivity. In Becker muscular dystrophy, the abnormal dystrophin molecule is thin, with pale staining of the sarcolemma, in which reactivity varies not only between myofibers but also along the circumference of individual fibers (×250).

family history of the disease, particularly in the case of an involved brother whose diagnosis has been confirmed, a patient with typical clinical features of DMD and high concentrations of serum CK probably does not need to undergo biopsy. The result of the genetic testing (dystrophin deletion/duplication analysis and sequencing) might also influence whether to perform a muscle biopsy. If there is a doubt about the pathogenicity of the dystrophin gene variant, muscle biopsy is useful in confirming or refuting the diagnosis. The most common muscles sampled are the vastus lateralis and the gastrocnemius.

GENETIC ETIOLOGY AND PATHOGENESIS

Despite the X-linked recessive inheritance in DMD, approximately 30% of cases are new or de novo pathogenic variant, and the mother is not a carrier. The female carrier state usually shows no muscle weakness, but due to skewed X-inactivation, about 8% of carrier females are *manifesting* carriers with some weakness, although typically milder than is seen in affected males. These symptomatic females are explained by the Lyon hypothesis, in which the normal X chromosome becomes inactivated and the one with the gene deletion is active (see Chapter 97). The full clinical picture of DMD has occurred in several females with Turner syndrome in whom the single X chromosome must have had the Xp21 gene deletion.

The asymptomatic carrier state of DMD is associated with elevated serum CK values in about 50% of cases. The level of increase is usually in the magnitude of hundreds or a few thousand but does not have the extreme values noted in affected males. Prepubertal females who are carriers of the dystrophy also have increased serum CK values, with highest levels at 8-12 years of age. If the mother of an affected male has normal CK levels, it is unlikely that her daughter can be identified as a carrier by measuring CK. Muscle biopsy of suspected female carriers can detect an additional 10% in whom serum CK is not elevated; a specific genetic diagnosis using polymerase chain reaction (PCR) on peripheral blood is definitive. Approximately 40% of female carriers may be at risk of developing cardiomyopathy or fibrosis (determined by cardiac imaging of carrier females), even in the absence of skeletal muscle weakness.

A 427-kDa cytoskeletal protein known as *dystrophin* is encoded by the gene at the Xp21.2 locus. This gene contains 79 exons of coding sequence and 2.5 Mb of DNA. This subsarcolemmal protein attaches to the sarcolemmal membrane overlying the A and M bands of the myofibrils and consists of four distinct regions or domains: the amino terminus contains 250 amino acids and is related to the *N*-actin binding site of α-actinin; the second domain is the largest, with 2,800 amino acids, and contains many repeats, giving it a characteristic rod shape; a third, cysteine-rich domain is related to the carboxyl terminus of α-actinin; and the final carboxyl-terminal domain of 400 amino acids is unique to dystrophin and to a dystrophin-related protein encoded by chromosome 6. The absence of dystrophin at the sarcolemma disrupts the membrane cytoskeleton and leads to loss secondarily of other components of the cytoskeleton.

The molecular defects in the dystrophinopathies vary and include intragenic deletions, duplications, or point variants of nucleotides. Approximately 65% of patients have deletions, approximately 10% exhibit duplications, and approximately 10% have point variants or smaller rearrangements. In less than 1% of cases, a deep intronic variant may lead to an alteration of splicing and thereby may impact the reading frame. The site or size of the intragenic abnormality does not always correlate well with the phenotypic severity; in both the Duchenne and Becker forms the variants are mainly near the middle of the gene, involving deletions in regions between exons 45 and 55. Phenotypic or clinical variations are explained by the alteration of the translational reading frame of messenger RNA (mRNA), which results in unstable, truncated dystrophin molecules and severe, classic DMD; variants that preserve the reading frame still permit translation of coding sequences further downstream on the gene and produce a semifunctional dystrophin, expressed clinically as BMD. An even milder form of adult-onset disease, formerly known as **quadriceps myopathy,** is also caused by an abnormal dystrophin molecule. The clinical spectrum of the dystrophinopathies, especially a presentation, not only includes the classic Duchenne and Becker forms but also global developmental delay with autistic spectrum features, failure to thrive, and symptomatic cardiomyopathy.

Analysis of the dystrophin protein requires a muscle biopsy and is demonstrated by Western blot analysis or in tissue sections by immunohistochemical methods using either fluorescence or light microscopy of antidystrophin antisera (see Fig. 649.3). In classic DMD, levels of <3% of normal are found; in BMD, the molecular weight of dystrophin is reduced to 20–90% of normal in 80% of patients, but in 15% of patients the dystrophin is of normal size but reduced in quantity, and 5% of patients have an abnormally large protein caused by excessive duplications or repeats of codons. Selective immunoreactivity of different parts of the dystrophin molecule in sections of muscle biopsy material distinguishes the Duchenne and Becker forms (Fig. 649.4). The demonstration of deletions and duplications also can be made from blood samples by the more rapid PCR, which identifies as many as 98% of deletions by amplifying 18 exons but cannot detect duplications. The diagnosis can thus be confirmed at the molecular genetic level from either the muscle biopsy material or from peripheral blood, although as many as 30% of males with DMD or BMD have a false-normal blood PCR; all cases of dystrophinopathy are detected by muscle biopsy.

The same methods of DNA analysis from blood samples may be applied for carrier detection in female relatives at risk, such as sisters and cousins, and to determine whether the mother is a carrier or whether a new variant occurred in the embryo. Prenatal diagnosis is possible as early as the 12th week of gestation by sampling chorionic villi for DNA analysis by Southern blot or PCR, and in cases of aborted fetuses with DMD, muscle demonstrates abnormal dystrophin staining by immunohistochemistry. Newborn screening for DMD is not currently part of the routine neonatal screening. Nonetheless, a CK-based test is available for families requesting screening.

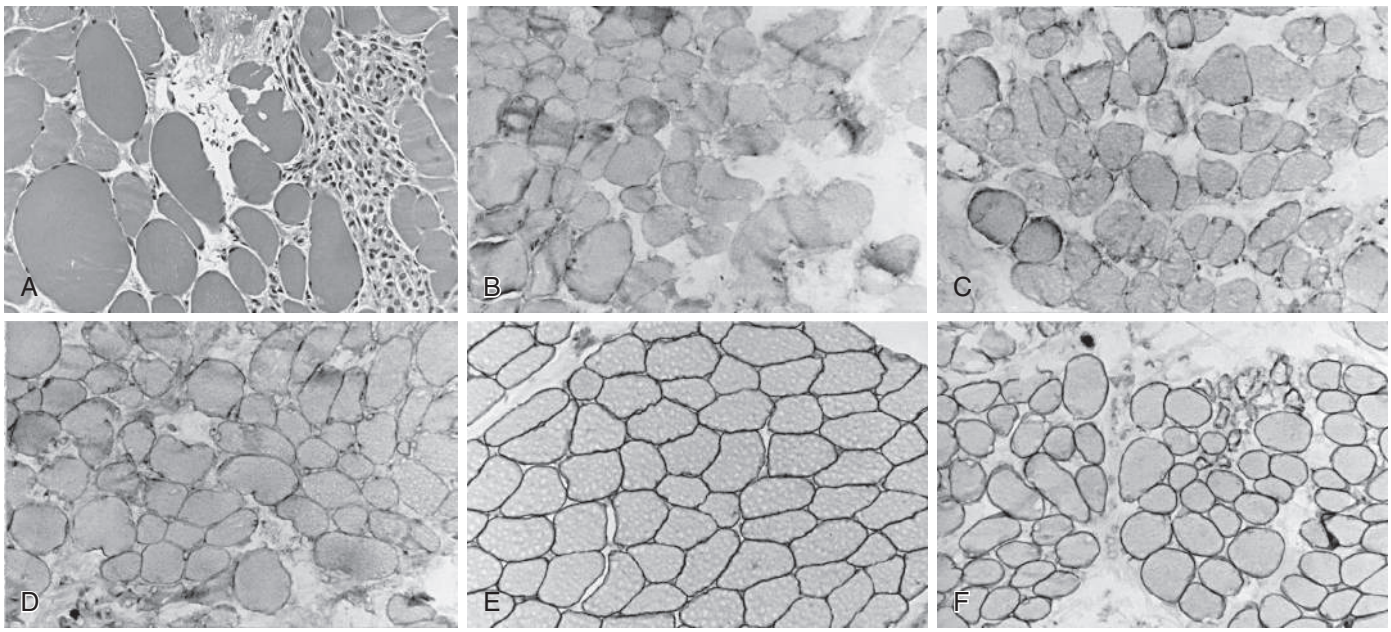

Fig. 649.4 Quadriceps femoris muscle biopsy specimens from a 4-yr-old male with Becker muscular dystrophy. **A**, Myofibers vary greatly in size, with both atrophic and hypertrophic forms; at the right is a zone of degeneration and necrosis infiltrated by macrophages, similar to Duchenne muscular dystrophy (hematoxylin and eosin, ×250). Immunoreactivity using antibodies against the dystrophin molecule in the rod domain (**B**), carboxyl terminus (**C**), and amino terminus (**D**) all show deficient but not totally absent dystrophin expression; most fibers of all sizes retain some dystrophin in parts of the sarcolemma but not around the entire circumference in cross section. Alternatively, the prominence of dystrophin is less, appearing weak, when compared with the simultaneously incubated normal control from another child of similar age (**E**). **F**, Merosin expression is normal in this patient with Becker dystrophy, in both large and small myofibers, and is lacking only in frankly necrotic fibers. Compare with classic Duchenne muscular dystrophy illustrated in Figures 649.3C and 649.8.

TREATMENT

There is no medical cure for this disease at this time. The mainstay of management for DMD has been supportive care and prevention of complications. Much can be done to treat complications and to improve the quality of life of affected children. Updated, international consensus care guidelines of DMD are available (pulmonary, cardiac, bone) and are a key driver for improvement and management.

Glucocorticoids (prednisone or deflazacort) have been shown to slow the decline in muscle strength and increase the time a patient maintains independent ambulation, and it may have additional benefits on scoliosis progression. Initiation of steroids is indicated when a child shows a plateau in development and/or a regression in motor development as compared with peers. This typically occurs by 4-6 years old. Recommended doses are prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day. Alternative protocols for steroid administration include weekend-only dosing, alternate-day regimens, or 10-day-on/10-day-off regimens; the daily regimen has been the preferred regimen based upon comparative studies. Long-term complications include weight gain, osteoporosis, delayed puberty, growth retardation, acne, glucose intolerance, and cataracts. Given the improvements with steroids in motor abilities, as well as potentially in pulmonary, orthopedic, and cardiac health, they are recommended for children with DMD. Vamorolone, a novel corticosteroid, may have greater efficacy and fewer adverse events (bone, growth, behavior) compared to conventional steroid therapy; it is approved for children ≥ 2 years old.

Exondys 51 (eteplirsen) is an exon 51 skipping antisense oligonucleotide approach that binds RNA and skips over the defective exon, restoring the reading frame, thereby producing a shorter but potentially functional dystrophin protein. This only applies to patients with pathogenic variants amenable to this repair (~13% of patients). It is given as a weekly IV infusion. Ataluren permits read through of premature stop codons (10–15% of patients) from a nonsense variant, resulting in production of a functional dystrophin. It may have benefits in patients at a certain level of disease progression. Golodirsen (Vyondys 53) and viltolarsen (Viltepso) are additional antisense oligonucleotides that are approved for the ~8% of patients with pathogenic variants in exon 53. Cardiosphere-derived cells, which have immune mediating, antifibrotic, and regenerative properties, are undergoing investigation for DMD.

Elevidys, an FDA approved recombinant gene therapy, delivers a shortened (138kDa vs 427kDa) dystrophin protein that is expressed in muscle in children 4-5 years old after a single intravenous dose.

Cardiac care initially includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or β blockers. Other agents used include aldosterone antagonists (e.g., Aldactone or eplerenone). Initiation of cardiac medications at the time of a drop in the left ventricular ejection fraction to <55% or for symptomatic cardiomyopathy is noncontroversial. The prophylactic use of ACE inhibitors and β blockers aiming to delay echocardiographic symptomatic cardiomyopathy is now recommended from age 10 years onward by most consensus care guidelines. This is based on recent data showing MRI changes in the heart preceding the echocardiogram abnormalities, and a potentially cardioprotective effect with agents such as ACE inhibitors. Due to potential risks for hyperkalemic or rhabdomyolytic reactions to anesthesia, it is recommended to avoid agents such as inhaled anesthetics or muscle relaxants.

Pulmonary infections should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated. When sleep-disordered breathing is suspected or the forced vital capacity drops below 60% predicted for age, children should undergo sleep studies and the use of bilevel positive airway pressure (BiPAP) should be considered. Additional devices such as lung volume recruitment bag or a cough assist device, proper suctioning, and nebulized therapies may assist with airway clearance as children develop weakness in coughing.

Preservation of a good **nutritional state** is important. DMD is not a vitamin-deficiency disease, and excessive doses of vitamins should be avoided. Adequate vitamin D and calcium intake is important to minimize osteoporosis in boys confined to a wheelchair. However, due to chronic corticosteroid use combined with the loss of ambulation, boys with DMD are at higher risk for osteopenia and osteoporosis, putting them at higher risk for fractures in the setting of even minor injuries or falls. Dual x-ray absorptiometry (DEXA) scans should be done in boys with DMD and vitamin D levels should be optimized. Some patients with low bone density may require additional therapies such as bisphosphonates, or testosterone in cases of pubertal delay. Because of the decreased caloric expenditure in nonambulant children and the

use of corticosteroids, these children tend to eat excessively and gain weight. Obesity makes a patient with myopathy even less functional because part of the limited reserve muscle strength is dissipated in lifting the weight of excess subcutaneous adipose tissue. Dietary restrictions with supervision may be needed.

Physiotherapy delays but does not always prevent contractures. At times, contractures are actually useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90 degrees and the muscles of the upper limb no longer are strong enough to overcome gravity, the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Stretching and bracing methods may be useful depending on the location of the contracture and level of severity of the contracture. Surgical interventions should be considered with caution and with input from the neurologist, physical therapist, and/or physical medicine and rehabilitation specialists involved in the child's care. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily functioning, and exercise cannot further strengthen involved muscles. Excessive exercise can actually accelerate the process of muscle fiber degeneration.

Special vigilance should be maintained in watching for scoliosis, which often progresses more rapidly once the patient loses independent ambulation, and coincident with pubertal growth spurt. Early referral to orthopedics is indicated as the definitive treatment for progressive scoliosis is with spinal fusion surgery, and multidisciplinary team management is required to ensure the safety of this major procedure, especially from the respiratory and cardiac perspective.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

649.2 Emery-Dreifuss Muscular Dystrophy/ Laminopathies

Adnan Y. Manzur

Emery-Dreifuss muscular dystrophy (EDMD) is a form of muscular dystrophy caused by pathogenic variants involving nuclear envelope proteins (see Table 649.1). It was first described as a rare X-linked recessive disorder caused by variant in *EMD* encoding emerin. The locus of its associated genetic abnormality is on the long arm within the large Xq28 region that includes other genes that cause myotubular myopathy, neonatal adrenoleukodystrophy, and the Bloch-Sulzberger type of incontinentia pigmenti. Subsequently, *dominant variants* in *LMNA* located on chromosome 1q21 that encodes for nuclear envelope protein lamin A/C, were found to be abnormal in male and female affected patients. This form can manifest both as a congenital muscular dystrophy (CMD) or one with an onset later in adolescence or adulthood, and it represents a broad phenotypic spectrum (see Table 649.2). In addition to the motor manifestations, which are variable, there is also a risk of sudden death from ventricular fibrillation, which can occur as early as in childhood in some cases.

Clinical manifestations range from a CMD with severe weakness, respiratory insufficiency, and contractures from infancy or children with weakness and a *dropped head syndrome* to the more classic EDMD forms. In the childhood-onset EDMD forms, symptoms may begin between 5 and 15 years of age, but many patients survive to late adult life because of the slow progression of the course of the disease. Muscles *do not* exhibit pseudohypertrophy. Contractures of the elbows, ankles, and neck extensor muscles develop early, and muscle becomes wasted in a scapulohumeroperoneal distribution. Facial weakness *does not* typically occur; this disease is thus distinguished clinically from autosomal dominant scapulohumeral and scapuloperoneal syndromes of *neurogenic* origin. Myotonia is absent. Intellectual function is normal. *Dilated cardiomyopathy* is severe and is often the cause of death, more commonly from conduction defects such as atrial fibrillation/flutter and sudden ventricular fibrillation than from intractable myocardial failure. Stroke is another complication, secondary to the cardiac arrhythmia. Respiratory insufficiency is more prominent in the early and severe forms and may require mechanical ventilation, especially in the severe congenital-onset patients. The serum CK value is only mildly to moderately elevated, further distinguishing this disease from other X-linked recessive muscular dystrophies.

Nonspecific myofiber necrosis and endomysial fibrosis are seen in the muscle biopsy. Many centronuclear fibers and a selective histochemical type I muscle fiber atrophy can cause confusion with myotonic dystrophy.

GENETICS

The defective gene in the X-linked form is called *EMD* or *EDMD* and encodes a protein, emerin. Unlike other dystrophies in which the defective gene is expressed at the sarcolemmal membrane, emerin is expressed at the inner nuclear membrane; this protein stabilizes the nuclear membrane against the mechanical stresses that occur during muscular contraction. It interacts with *Nesprin-1* and *Nesprin-2* genes, also critical for nuclear membrane integrity. Complete deletion of *EDMD* occurs in approximately 25% of cases and results from an inversion in the Xq28 region; total absence of emerin is demonstrated by both Western blotting and immunoreactivity in tissue sections. Another gene, *LMNA,* at the 1q21 locus, is linked to the nuclear envelope and encodes lamin A/C, sometimes termed *laminopathy.* This genetic variant causes a similar clinical phenotype to EMD defects, except that both sexes are affected, and it is transmitted as either an autosomal dominant or recessive trait. Most *EMD* deletions are null variants, whereas more than 80% of *LMNA* alterations are caused by missense variants, and with a minority being nonsense or out-of-frame variants. Desmin protein also may be abnormal and seen to be abnormally expressed in the muscle biopsy. Homozygous nonsense variants in these *lamin A/C* genes are lethal due to cardiomyopathy and conduction disturbances. *There remain many patients with an EDMD phenotype clinically, where the underlying genetic defect remains unknown.*

DIAGNOSTICS

In suspected cases, emerin deficiency may be demonstrated not only in the muscle biopsy by immunoreactivity and Western blotting techniques but also in a variety of other tissues, including circulating lymphocytes in peripheral blood, exfoliative buccal mucosal cells, and skin fibroblasts. Emerin is absent in varying proportions in female carriers. Muscle histology in *LMNA* patients is typically *nonspecific* with myopathic or mild dystrophic changes, with variability in fiber size, increase in connective tissue, and necrotic fibers. Genetic testing of the specific genes is available, and in a patient with typical phenotype may confirm the diagnosis without the need for muscle biopsy. Patients should have careful cardiac evaluation, including an electrocardiogram, echocardiogram, and at least 24-hour Holter monitoring. Serum CK levels may be moderately elevated. Muscle MRI of the glutei and lower extremities may be helpful, particularly in *LMNA* variants. EMG is not definitively diagnostic. Muscle biopsy is diagnostic from the onset of symptoms. In the differential diagnosis, an Emery-Dreifuss–like syndrome with joint contractures, mild weakness, and later-onset cardiac symptoms is caused by *FHL1* variants of *myofibrillar myopathy,* but reducing bodies are absent.

Treatment should be supportive, with special attention to cardiac conduction defects, and can require medications or a pacemaker. Implantable cardioverter-defibrillators are available and have prevented sudden death in some patients with EDMD. In patients with cardiac arrhythmias or a severe decrease in left ventricular function, there may be an increased risk of thromboembolic events, and antithrombotic drugs may be considered. Pulmonary care should include monitoring with pulmonary function tests as well as surveillance for sleep-disordered breathing if clinically indicated. Orthopedic management, use of orthotic devices, or physical therapy to try to minimize or slow down the rate of progression of contractures may be beneficial.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

649.3 Myotonic Muscular Dystrophy

Adnan Y. Manzur

Myotonic dystrophy is the second most common muscular dystrophy in North America, Europe, and Australia, having an incidence varying from 1 in 20,000 to 1 in 100,000 in the general population. It is inherited as an autosomal dominant trait (see Table 649.1). **Classic myotonic dystrophy (type 1)** (DM1, or Steinert disease) is caused by a CTG trinucleotide expansion on chromosome 19q13.3 in the 3′ untranslated region of *DMPK,* the gene that encodes a serine–threonine protein kinase. **Type 2 (DM2)** is associated with an unstable CCTG tetranucleotide repeat expansion on chromosome 3q21 of an intron of the zinc finger 9 protein gene. A third **late form (DM3)** is identified at locus 15q21-q24.

Myotonic dystrophy is an example of a genetic defect causing dysfunction in multiple organ systems. Not only is striated muscle severely affected, but smooth muscle of the alimentary tract and uterus is also involved, cardiac function is altered, and patients have multiple and variable endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, an increased risk for malignancies, intellectual impairment, and other neurologic abnormalities.

CLINICAL MANIFESTATIONS

DM1 becomes symptomatic at any age, but DM2 is rarely expressed in infancy or early childhood. In the usual clinical course, *excluding the severe neonatal form,* DM1 infants can appear almost normal at birth, or facial wasting and hypotonia can already be early expressions of the disease. The facial appearance is characteristic, consisting of an inverted-V–shaped upper lip, thin cheeks, and scalloped, concave temporalis muscles (Fig. 649.5). The head may be narrow, and the palate is high and arched because the weak temporal and pterygoid muscles in late fetal life do not exert sufficient lateral forces on the developing head and face.

In DM1, weakness is often mild in the first few years (childhood-onset form) or may not even become evident until adolescence or early adulthood (classic/adult-onset form). Progressive wasting of distal muscles becomes increasingly evident, particularly in the intrinsic muscles of the hands. The thenar and hypothenar eminences are flattened, and the atrophic dorsal interossei leave deep grooves between the fingers. The dorsal forearm muscles and anterior compartment muscles of the lower legs also become wasted. The tongue is thin and atrophic. Wasting of the sternocleidomastoids gives the neck a long, thin, cylindrical contour. Proximal muscles also eventually undergo atrophy, and scapular winging appears. Difficulty with climbing stairs and Gowers sign are progressive. Tendon stretch reflexes are usually preserved.

The distal distribution of muscle wasting in myotonic dystrophy is an *exception* to the general rule of myopathies having proximal and neuropathies with distal distribution patterns. The muscular atrophy and weakness in myotonic dystrophy are slowly progressive throughout childhood and adolescence and continue into adulthood. It is rare for patients with myotonic dystrophy to lose the ability to walk even in late adult life, although splints or bracing may be required to stabilize the ankles.

Myotonia, *a characteristic feature shared by few other myopathies*, does not occur in infancy and is usually not clinically or even electromyographically evident until about age 5 years. Exceptional patients develop it as early as age 3 years. Myotonia is a very slow relaxation of muscle after contraction, regardless of whether that contraction was voluntary or was induced by a stretch reflex or electrical stimulation. During physical examination, myotonia may be demonstrated by asking the patient to make tight fists and then to quickly open the hands (grip myotonia; Fig. 649.6). It may be induced by striking the thenar eminence with a rubber percussion hammer (percussion myotonia), and it may be detected by watching the involuntary drawing of the thumb across the palm. Myotonia can also be demonstrated in the tongue by pressing the edge of a wooden tongue blade against its dorsal surface and by observing a deep furrow that disappears slowly. The severity of myotonia does not necessarily parallel the degree of weakness, and the weakest muscles often have only minimal myotonia. *Myotonia is not a painful muscle spasm.* Musculoskeletal pain and fatigue are fairly commonly reported in patients with myotonic dystrophy.

The **speech** of patients with myotonic dystrophy is often articulated poorly and is slurred because of the involvement of the muscles of the face, tongue, and pharynx. Both myotonia and weakness can drive the difficulties in patients' speech and swallowing. Difficulties with swallowing sometimes occur, and more severely involved patients may be at risk for aspiration pneumonia. Incomplete external ophthalmoplegia sometimes results from extraocular muscle weakness.

Smooth muscle involvement of the **gastrointestinal tract** results in slow gastric emptying, poor peristalsis, and constipation. Some patients have encopresis associated with anal sphincter weakness. Women with myotonic dystrophy can have ineffective or abnormal uterine contractions during labor and delivery.

Cardiac involvement is usually manifested as heart block in the Purkinje conduction system and arrhythmias (and sudden death) rather than as cardiomyopathy, unlike most other muscular dystrophies. Atrial or ventricular tachyarrhythmias have also resulted in sudden death in adults and older children.

Endocrine abnormalities involve many glands and appear at any time during the course of the disease so that the endocrine status must be reevaluated annually. Hypothyroidism is common; hyperthyroidism occurs rarely. Adrenocortical insufficiency can lead to an addisonian crisis even in infancy. Diabetes mellitus is common in patients with myotonic dystrophy; some children have a disorder of insulin release rather than defective insulin production. The onset of puberty may be precocious or, more often, delayed. Testicular atrophy and testosterone deficiency are common in adults and are responsible for a high incidence of male infertility. Ovarian atrophy is rare. Frontal baldness is also characteristic in male patients and often begins in adolescence.

Immunologic deficiencies are common in myotonic dystrophy. The plasma immunoglobulin G level is often low.

Cataracts often occur in myotonic dystrophy. They may be congenital, or they can begin at any time during childhood or adult life. Early cataracts are detected only by slit-lamp examination; periodic examination by an ophthalmologist is recommended. Visual evoked potentials are often abnormal in children with myotonic dystrophy and are unrelated to cataracts. They are not usually accompanied by visual impairment.

About half of the patients with myotonic dystrophy are **intellectually impaired,** but severe intellectual impairment is unusual. The remainder are of average or occasionally above-average intelligence. Epilepsy is not common. Cognitive impairment might result from accumulations of variant *DMPK* mRNA and aberrant alternative splicing in cerebral cortical neurons. A higher than expected incidence of **autism** occurs in children with DM1.

A severe **congenital form** of myotonic dystrophy appears in a minority of involved infants born to mothers with myotonic dystrophy who may be symptomatic with known diagnosis, or pauci-symptomatic and undiagnosed (see Fig. 649.5). All patients with this severe congenital disease to date have had the DM1 form. Symptoms may present prenatally with polyhydramnios and decreased fetal movements. At birth, patients typically have marked hypotonia, respiratory difficulties or respiratory failure, and feeding difficulties; they may have additional orthopedic manifestations, such as clubfoot deformities or more extensive congenital contractures **(arthrogryposis multiplex congenita)**. Facial wasting is prominent. Infants can require gavage feeding or ventilator support for respiratory muscle weakness or apnea. Those requiring ventilation for <30 days often survive, and those with prolonged ventilation have an infant mortality rate of 25% and a lower likelihood of ventilator-free survival. Children ventilated for <30 days have better motor, language, and daily activity skills than those requiring prolonged ventilation. One or both leaves of the diaphragm may be nonfunctional. The abdomen becomes distended with gas in the stomach and intestine because of poor peristalsis from smooth muscle weakness. The distention further compromises respiration. Inability to empty the rectum can compound the problem. Myotonia is typically

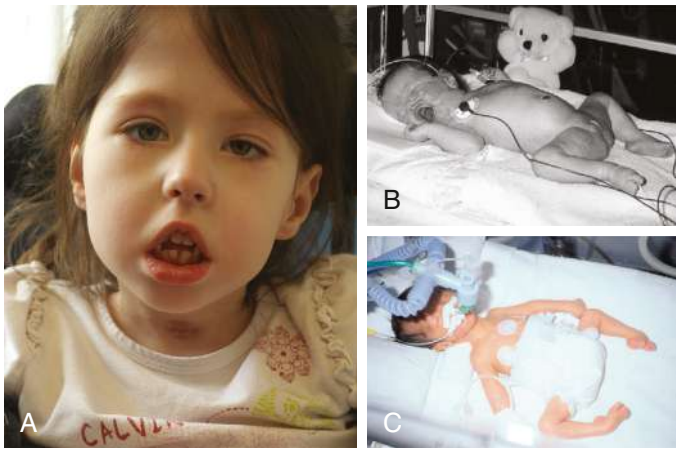

Fig. 649.5 A 6-yr-old with congenital myotonic dystrophy with 1975 cytosine-thymine-guanine (CTG) repeats in the *DMPK* gene showing the characteristic elongated facies, left ptosis, and an open, down-turned (tented) mouth with dental malocclusion. **A,** The tracheostomy scar is evidence of severe respiratory distress requiring intubation at the time of birth. Neonate with congenital myotonic dystrophy (**B**) also with an open, down-turned mouth and frog-leg position of lower extremities. **C,** A neonate with congenital myotonic dystrophy with severe respiratory distress and arthrogryposis. *(**A,** From Konersman C. Hypotonia, weakness, stroke. In: Kliegman RM, Lye PS, Bordini BJ, et al., eds. Nelson Symptom-Based Diagnosis. Philadelphia: Elsevier; 2018. Fig. 29.16; **B,** From Johnston H. The floppy weak infant revisited. Brain Dev. 2003;25:155–158; **C,** From Echenne B, Bassez G. Congenital and infantile myotonic dystrophy. Handbook Clin Neurol. 2013;113:1387–1393.)*

not present in the congenital form during the neonatal period but may be present in childhood (typically after 5 years old).

LABORATORY FINDINGS

The classic myotonic electromyogram is not found in infants but can appear in children in the early school years. The levels of serum CK and other serum enzymes from muscle may be normal or only mildly elevated in the hundreds (never the thousands).

ECG should be performed annually in early childhood. Ultrasound imaging of the abdomen may be indicated in affected infants to determine diaphragmatic function. Radiographs of the chest and abdomen and additional studies of gastrointestinal motility or swallowing studies may be needed.

Endocrine assessment should be undertaken to determine thyroid and adrenal cortical function and to verify carbohydrate metabolism (glucose tolerance test). Immunoglobulins should be examined, and, if needed, more extensive immunologic studies should be performed.

DIAGNOSIS

The primary diagnostic test is a DNA analysis of blood to demonstrate the abnormal expansion of the CTG or CCTG repeat. Prenatal diagnosis also is feasible. The muscle biopsy specimen in older children shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers, but degenerating fibers are usually few and widely scattered, and there is little or no fibrosis of muscle. Intrafusal fibers of muscle spindles are also abnormal. In young children with the common form of the disease, the biopsy specimen can even appear normal or at least not show myofiber necroses, which is a striking contrast with DMD. In the severe neonatal form of myotonic dystrophy, the muscle biopsy reveals maturational arrest in various stages of development in some and congenital muscle fiber–type disproportion in others. It is likely that the sarcolemmal membrane of muscle fibers not only has abnormal properties of electrical polarization but is also incapable of responding to trophic influences of the motor neuron. Muscle biopsy is not usually required for diagnosis, which in typical cases can be based on the clinical manifestations, including the family history, and molecular genetic diagnosis. **Neonatal myotonic dystrophy** causing arthrogryposis multiplex and/or severe neonatal hypotonia must be distinguished from amyoplasia, congenital muscular dystrophy with or without merosin expression, congenital myasthenia gravis, spinal muscular atrophy, and arthrogryposis secondary to oligohydramnios.



Fig. 649.6 The patient was asked to squeeze with both of his hands for several seconds and then suddenly release his grasp, and several seconds passed before full relaxation was achieved, an exam finding known as grip myotonia. *(From Hughes BN, Hogue JS, Hsieh DT. Grip and percussion myotonia in myotonic dystrophy type 1. J Pediatr. 2014;164:1234.)*

GENETICS

The genetic defect in myotonic muscular dystrophy is on chromosome 19 at the 19q13 locus. It consists of an expansion of the *DM* gene that encodes a serine–threonine kinase *(DMPK),* with numerous repeats of the CTG codon. Expansions range from 50 to >2,000, with the normal alleles of this gene ranging in size from 5-37; the larger the expansion, the more severe the clinical expression, with the largest expansions seen in the severe neonatal form. Rarely, the disease is associated with no detectable repeats, perhaps a spontaneous correction of a previous expansion but a phenomenon still incompletely understood. Another myotonic dystrophy **(proximal myotonic myopathy)** is a clinical entity linked to at least two different chromosomal loci than classic myotonic dystrophy but to one locus that shares a common unique pathogenesis in being mediated by a variant in mRNA. Defects in RNA splicing explain the insulin resistance in myotonic dystrophies as well as the myotonia.

Clinical and genetic expression can vary between siblings or between an affected parent and child. In the severe neonatal form of the disease, the mother is the transmitting parent in 94% of cases, a fact not explained by increased male infertility alone. Several cases of paternal transmission have been reported, but this is a very rare occurrence. Genetic analysis reveals that symptomatic neonates usually have many more repeats of the CTG codon than do patients with the more classic form of the disease, regardless of which parent is affected. Myotonic dystrophy often exhibits a pattern of **anticipation** in which each successive generation has a tendency to be more severely involved than the previous generation. Prenatal genetic diagnosis of myotonic dystrophy is available.

TREATMENT

There is no specific medical treatment, but the cardiac, endocrine, gastrointestinal, and ocular complications can often be treated. Physiotherapy and orthopedic treatment of contractures in the neonatal form of the disease may be beneficial. Myotonia may improve with exercise (warm-up phenomenon), and avoidance of extreme cold temperatures may be helpful. Cardiac surveillance with an annual ECG as well as Holter studies and an echocardiogram about every 2 years should be pursued. Cardiac pacemaker implantation might be considered for heart block, and antiarrhythmic drugs might be indicated but are needed only rarely in children. Respiratory issues should be addressed; management strategies may include BiPAP, cough assist, and incentive spirometry.

Myotonia may be diminished by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate. These drugs also have cardiotropic effects; thus cardiac evaluation is important before prescribing them. Phenytoin and carbamazepine are used in doses similar to those when used as antiepileptics (see Chapter 633.6); serum concentrations of 10-20 μg/mL for phenytoin and 5-12 μg/mL for carbamazepine should be maintained. If a patient's disability is caused mainly by weakness rather than by myotonia, these drugs will be of no value. Excess sleepiness is sometimes managed with methylphenidate or modafinil. Low-impact to moderate exercise may be beneficial for myalgias.

Anesthesia precautions should be considered given the higher rates of complications with anesthesia in patients with myotonia. Succinylcholine should be avoided due to the risk of myotonia, and, instead, short-acting nondepolarizing muscle relaxants should be used that are modified in terms of dosing for the extent of muscle wasting. For induction, a modified rapid-sequence induction for intubation should be used. During recovery, neostigmine should be used with caution, and extubation should occur when a patient is more fully awake. Following sedation, patients should be monitored closely because of the risk of aspiration.

OTHER MYOTONIC SYNDROMES

Most patients with myotonia have myotonic dystrophy. However, myotonia is not specific for this disease and occurs in several rarer conditions.

Myotonic chondrodystrophy (Schwartz-Jampel disease) is a rare congenital disease characterized by generalized muscle hypertrophy and weakness. Dysmorphic phenotypic features and the radiographic appearance of long bones are reminiscent of Morquio disease (see Chapter 107), but abnormal mucopolysaccharides are not found. Dwarfism, joint abnormalities, and blepharophimosis are present. Several patients have been the products of consanguinity, suggesting autosomal recessive inheritance. The muscle protein perlecan, encoded by the *SJS1* gene, a large heparan sulfate proteoglycan of basement membranes and cartilage, is defective in some cases of Schwartz-Jampel disease and explains both the muscular hyperexcitability and the chondrodysplasia.

EMG reveals continuous electrical activity in muscle fibers, closely resembling or identical to myotonia. Muscle biopsy reveals nonspecific myopathic features, which are minimal in some cases and pronounced in others. The sarcotubular system is dilated.

Myotonia congenita (Thomsen disease), a *channelopathy,* is the most common of the nondystrophic myotonia syndromes (Tables 649.3-649.6) and is characterized by weakness and generalized muscular hypertrophy so that affected children resemble bodybuilders (Herculean appearance). Myotonia is prominent and can develop at age 2-3 years, earlier than in myotonic dystrophy. The disease is clinically stable and is apparently not progressive for many years. EMG demonstrates myotonia. Muscle biopsy specimens show minimal pathologic changes and is not indicated for diagnosis. Various families are described as showing either autosomal dominant (Thomsen disease) or recessive (Becker disease, not to be confused with BMD or DMD) inheritance. Pathogenic variants may be nonsense, missense, or frameshift. However, specifically, missense variants that alter the activation of the CLC-1 dimer leads to the dominantly inherited forms of the disease. Patients with the recessive form (Becker disease) tend to have more severe disease. The autosomal dominant and autosomal recessive forms of myotonia congenita have been mapped to the same 7q35 locus. This gene is important for the integrity of chloride channels of the sarcolemmal and T-tubular membranes.

Paramyotonia is a *temperature-related* myotonia that is aggravated by cold and alleviated by warm external temperatures. Patients have difficulty when swimming in cold water or if they are dressed inadequately in cold weather. *Paramyotonia congenita* (Eulenburg disease) is a defect in a gene at the 17q13.1-13.3 locus, the identical locus identified in hyperkalemic periodic paralysis. By contrast with myotonia congenita, paramyotonia is a disorder of the voltage-gated sodium channel caused by a pathogenic variant in the α subunit. Myotonic dystrophy also is a sodium channelopathy (see Table 649.5).

In sodium channelopathies, exercise produces increasing myotonia, whereas in chloride channelopathies, exercise reduces the myotonia. This is easily tested during examination by asking patients to close the eyes forcefully and open them repeatedly; it becomes progressively more difficult in sodium channel disorders and progressively easier in chloride channel disorders.

Treatments for the nondystrophic myotonias include mexiletine as the first-line (both for sodium channel and chloride channel myotonias) treatment. Mexiletine has been shown to improve stiffness as well as decrease handgrip myotonia. Other treatment options include carbamazepine, phenytoin, and gabapentin.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 649.3 Chloride Channel Myopathies

CLINICAL FEATURES	AUTOSOMAL-DOMINANT MYOTONIA CONGENITA OF THOMSEN	AUTOSOMAL-RECESSIVE GENERALIZED MYOTONIA OF BECKER
Inheritance	Dominant	Recessive
Gene defect	Chromosome 7; variant in skeletal muscle chloride channel	Chromosome 7; variant in skeletal muscle chloride channel
Age of onset	Infancy to early childhood	Late childhood; occasionally starts earlier or begins in teens
Myopathy	Muscle hypertrophy frequent; no myopathy, although variants uncommonly develop weakness	Occasional muscle wasting and weakness can occur late; hypertrophy of muscles frequently occurs in legs
Myotonia	Generalized stiffness, especially after rest; improves with exercise; prominent myotonia of eye closure, but not paradoxical myotonia	Generalized stiffness, especially after rest; transient weakness is prominent after complete relaxation for several minutes; myotonia occurs in eyes; no paradoxical myotonia
Provocative stimuli	Prolonged rest or maintenance of the posture	Prolonged rest or maintenance of the same posture
Therapy for symptoms	Exercise; antimyotonia therapy (e.g., mexiletine); Achilles tendon stretching helps prevent need for heel cord–lengthening surgery	Exercise; especially avoiding prolonged rest; antimyotonia therapy (e.g., mexiletine); transient weakness does not improve after mexiletine

From Moxley III RT, Heatwole C. Channelopathies: myotonic disorders and periodic paralysis. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Table 151-3.

Table 649.4 Sodium Channel Myotonias Without Periodic Paralysis

CLINICAL FEATURES	ACETAZOLAMIDE-RESPONSIVE SODIUM CHANNEL MYOTONIA	MYOTONIA FLUCTUANS
Inheritance	Dominant	Dominant
Gene defect	Chromosome 17; variant in skeletal muscle sodium channel	Chromosome 17; variant in skeletal muscle sodium channel
Age of onset	First decade	First or second decade
Myopathy	Rare	Rare, muscle hypertrophy common
Myotonia	Face, paraspinal muscles, paradoxical myotonia of eyelids, grip limbs; varies in severity and often there is pain with myotonia	Face, limbs, eyelids; frequently fluctuates in severity; especially after exercise
Provocative stimuli	Fasting, cold, oral potassium, infection	Exercise-rest-exercise, oral potassium
Therapy for symptoms	Acetazolamide, mexiletine; avoid high-potassium diet; monitor during and after surgery for rigidity and rhabdomyolysis	Mexiletine; avoid high-potassium diet; monitor during and after surgery for rigidity and rhabdomyolysis

From Moxley III RT, Heatwole C. Channelopathies: myotonic disorders and periodic paralysis. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Table 151-4.

Table 649.5 Sodium Channel Myopathies with Periodic Paralysis

CLINICAL FEATURES	PARAMYOTONIA CONGENITA	PARAMYOTONIA CONGENITA WITH HYPERKALEMIC PERIODIC PARALYSIS	HYPERKALEMIC PERIODIC PARALYSIS WITH MYOTONIA
Inheritance	Dominant	Dominant	Dominant
Gene defect	Chromosome 17; variant in skeletal muscle sodium channel	Chromosome 17; variant in skeletal muscle sodium channel	Chromosome 17; variant in skeletal muscle sodium channel
Age of onset	First decade	First decade	First decade
Myopathy	Very rare	Rare	Infrequent
Myotonia	Especially paradoxical myotonia of the eyelids and grip	Especially paradoxical myotonia of the eyelids and grip	Especially paradoxical myotonia of the eyelids
Provocative stimuli	Cold exposure followed by exercise leads to focal paralysis; occasionally exercise provokes stiffness	Oral potassium load, rest after exercise mainly in morning (hyperkalemic weakness), cold exposure followed by exercise (focal paralysis)	Rest after exercise, cold, oral potassium
Therapy for symptoms	Mexiletine, mild exercise, keep patient warm	Mild exercise, thiazides, mexiletine	Thiazides, acetazolamide, sodium restriction

From Moxley III RT, Heatwole C. Channelopathies: myotonic disorders and periodic paralysis. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Table 151-5.

649.4 Limb-Girdle Muscular Dystrophies

Adnan Y. Manzur

LGMDs encompass a heterogeneous group of progressive hereditary muscular dystrophies that mainly affect muscles of the hip and shoulder girdles (Table 649.7). Distal muscles also eventually become atrophic and weak, and in a few subtypes, distal muscles such as calves may have weakness earlier in disease. Hypertrophy of the calves and ankle contractures develop in some forms, causing potential confusion with BMD. Over 30 genetic forms of LGMD are described, each at a different chromosomal locus and expressing different protein defects (see Table 649.1). Some include diseases classified with other traditional groups, such as the lamin A/C defects of the nuclear membrane (see EDMD), and some forms of CMD. **LGMD1** denotes autosomal dominant inheritance and **LGMD2** implies an autosomal recessive trait, but neither term defines the genetic etiology. LGMD2 is mainly a group of several *sarcoglycanopathies*, calpainopathy resulting from a mutation in the *calpain-3* gene (*CAPN3*), α-dystroglycanopathies, or dysferlinopathies that include Miyoshi myopathy (which usually does not become symptomatic until late adolescence into adult life).

The onset of disease is variable, with some patients manifesting by 4-5 years of age (e.g., sarcoglycanopathies), to others presenting in late adolescence to adulthood (e.g., dysferlinopathy or anoctaminopathy). For many LGMDs, the initial clinical manifestations rarely appear before middle or late childhood or may be delayed until early adult life. Low back pain may be a presenting complaint because of the lordotic posture resulting from gluteal muscle weakness. In many of these disorders, loss of independent ambulation may occur, ranging from within the first decade of life to loss of ambulation in early adulthood, highlighting the variability in rate of progression (even for the same disease). Although weakness of neck flexors and extensors is common, weakness of facial, lingual, and other bulbar-innervated muscles are rarely involved. As weakness and muscle wasting progress, tendon stretch reflexes become diminished. Cardiac involvement can occur in some of the subtypes. Intellectual function is generally normal in most, but can be involved to varying degrees, especially in some of the α-dystroglycanopathies (e.g., LGMDs due to gene variants in *POMT2, POMGnT1, GMPPB,* and *ISPD*). The clinical differential diagnosis of LGMD includes juvenile/type 3 spinal muscular atrophy (Kugelberg-Welander disease), myasthenia gravis, and metabolic myopathies.

The EMG and muscle biopsy frequently show confirmatory evidence of muscular dystrophy, but none of the findings are specific enough to make the definitive diagnosis without additional clinical or immunohistochemical criteria. In some cases, α-sarcoglycan

Table 649.6 Channelopathies with Hypokalemic Periodic Paralysis

CLINICAL FEATURES	ANDERSEN SYNDROME: PERIODIC PARALYSIS WITH CARDIAC DYSRHYTHMIA	CALCIUM CHANNEL PERIODIC PARALYSIS	SODIUM CHANNEL PERIODIC PARALYSIS	POTASSIUM CHANNEL PERIODIC PARALYSIS	PERIODIC PARALYSIS WITH THYROID DISEASE
Inheritance	Dominant	Dominant	Dominant	Dominant	Sporadic; occasionally dominant
Age of onset	First or second decade	First to third decade	First to third decade	Not yet determined	Third decade (males 20:1)
Myopathy	Typical; also short stature; dysmorphic features; prolonged QT interval on electrocardiogram; ventricular dysrhythmias	Moderately common late; vacuoles frequently seen on biopsy	Not yet determined	Not yet determined	Infrequent
Myotonia	No	No	No	No	No
Provocative stimuli	Rest after exercise, oral glucose	High-carbohydrate meals, rest after exercise, cold, emotional stress/ excitement	High-carbohydrate meals, rest after exercise, cold, emotional stress/ excitement	Usually by strenuous exercise followed by rest; less consistent provocation after high carbohydrate intake	High-carbohydrate meals, rest after exercise, acetazolamide
Therapy for symptoms	Mild exercise, glucose, high sodium intake, acetazolamide, dichlorphenamide	Acetazolamide, dichlorphenamide, potassium, spironolactone	Acetazolamide, dichlorphenamide, potassium, spironolactone	Acetazolamide	Propranolol, restoration of euthyroid state, oral potassium, spironolactone

From Moxley III RT, Heatwole C. Channelopathies: myotonic disorders and periodic paralysis. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Table 151-6.

Table 649.7 Limb-Girdle Muscular Dystrophies

TYPE	INHERITANCE	GENE	PROTEIN	CLINICAL FEATURES
LGMD1A	AD	*TTID*	Myotilin	Adult-onset myofibrillar myopathy; mildly elevated CK; muscle biopsy: rimmed vacuoles, rodlike inclusions, and Z-band streaming
LGMD1B	AD	*LMNA*	Lamin A/C	Onset first and fourth decade of life; contractures, +/− axial weakness, cardiac arrhythmia and/or cardiomyopathy (potentially life-threatening); CK normal or mildly elevated
LGMD1C	AD	*CAV3*	Caveolin	Onset variable: First decade to adulthood; presents with myalgias +/− rippling muscles and proximal weakness; CK 4-25× elevated
LGMD1D	AD	DNAJB6	HSP40	Onset classically adulthood; proximal weakness; CK normal to 5× elevated; gradually progressive
LGMD1E	AD	*DES*	Desmin	Myofibrillar myopathy; cardiomyopathy and cardiac arrhythmias; CK normal or mildly elevated; muscle biopsy: inclusions and desmin accumulation
LGMD1F	AD	*TNPO3*	Transportin	Onset variable: first decade to adulthood; proximal weakness +/− scapular winging; +/− respiratory involvement
LGMD2A	AR	*CAPN3*	Calpain 3	Onset at 8-15 yr, progression variable (variable loss of ambulation in second or third decade); scapular winging common; cardiac spared; CK very high
LGMD2B	AR	*DYSF*	Dysferlin	Onset in adolescence or early adulthood; mild weakness initially; limb-girdle pattern weakness or Miyoshi myopathy (calf weakness) at onset; gradually progressive; cardiac spared; gastric atrophy earlier in disease

Table 649.7 Limb-Girdle Muscular Dystrophies—cont'd

TYPE	INHERITANCE	GENE	PROTEIN	CLINICAL FEATURES
LGMD2C	AR	*SGCG*	γ-Sarcoglycan	Duchenne-like, onset 4-7 yr; CK very high; respiratory failure often in third decade; + cardiac involvement; loss of ambulation by teenage years
LGMD2D	AR	*SGCA*	α-Sarcoglycan (adhalin)	Duchenne-like, onset 2-15 yr; frequent loss of ambulation; quadriceps weakness; rare cardiomyopathy; CK very high
LGMD2E	AR	*SGCB*	β-Sarcoglycan	Phenotype between Duchenne and Becker muscular dystrophies; onset first decade; loss of ambulation 10-25 yr old; occasional cardiomyopathy
LGMD2F	AR	*SGCD*	δ-Sarcoglycan	Onset 2-10 yr old; loss of ambulation by first or second decade; dilated cardiomyopathy; also a milder phenotype described
LGMD2G	AR	*TCAP*	Telethonin	Rare disease; onset in adolescence; CK up to 10× normal
LGMD2H	AR	*TRIM32*	Tripartite motif containing 32	Seen in Hutterite population; onset childhood to young adulthood; proximal weakness; slowly progressive; ambulatory into adulthood
LGMD2I	AR	*FKRP*	Fukutin-related protein	Dystroglycanopathy; variable phenotype: early onset never ambulate to milder and later onset with muscle cramps; cardiomyopathy common; +/− respiratory failure
LGMD2J	AR	*TTN*	Titin	Onset 3-10 yr; variable severity; +/− respiratory insufficiency; progressive with loss of ambulation (some patients with the severe congenital myopathy phenotype may never ambulate); muscle biopsy: variable fiber size; rods; internal nuclei
LGMD2K	AR	*POMT1*	Protein O-mannosyltransferase 1	Onset first decade; mild weakness and fatigue; slow progression; intellectual disability
LGMD2L	AR	*ANO5*	Anoctamin	More common in Northern Europe and Canada; Onset second to third decade; no cardiomyopathy; report of patients with premature ventricular contractions. Limb-girdle or Miyoshi myopathy phenotypes
LGMD2M	AR	*FKTN*	Fukutin	Early onset, high CK, progression over time; variable intellectual disability; vermis hypoplasia and polymicrogyria; some patients develop dilated cardiomyopathy
LNGD2N	AR	*POMT2*	Protein O-mannosyltransferase 2	LGMD phenotype with or without intellectual disability
LGMD2O	AR	*POMGnT1*	*	More likely a congenital muscle disease/Walker-Warburg syndrome or muscle-eye-brain presentation (possible childhood LGMD phenotype)
LGMD2P	AR	*DAG1*	Dystroglycan	Childhood onset (first decade); very high CK; fatigue and proximal weakness; +/− CNS (intellectual disability), respiratory and eye (cataracts) involvement
LGMD2Q	AR	*PLEC1*	Plectin	Childhood onset, loss of ambulation in adulthood
LGMD2R	AR	*DES*	Desmin	Adult-onset weakness; proximal and distal weakness; cardiac: atrioventricular block (may require early pacemaker by 20s); cardiomyopathy (onset in childhood or 20s); with respiratory involvement
LGMD2S	AR	*TRAPPC11*	Transport protein particle complex 11	Onset infancy or childhood; high CK; proximal weakness; fatigue; +/− seizures, spasticity, hyperkinetic movements, intellectual disability
LGMD2T	AR	*GMPPB*	GDP-mannose pyrophosphorylase B	Can manifest as congenital onset or childhood onset LGMD with or without intellectual disability; seizures; cataracts
LGMD2U	AR	*ISPD*	Isoprenoid synthase domain	Can manifest as congenital muscular dystrophy or childhood-onset LGMD with or without intellectual disability; some patients lose independent ambulation; +/− cardiomyopathy; +/− respiratory insufficiency
LGMD2V	AR	*GAA*	α-1,4 glucosidase	Pompe disease (infantile, juvenile, or adult-onset forms): cardiomyopathy (more in infantile form), respiratory insufficiency, weakness. EMG: irritative myopathy (can see myotonia/cone–rod dystrophies and myopathic recruitment)

**POMGnT1* encodes for protein: Protein-O-linked mannose beta-1,2 N-acetylglucosaminyltransferase.
AD, Autosomal dominant; AR, autosomal recessive; CK, creatine kinase; CNS, central nervous system; EMG, electromyography; GDP, guanosine diphosphate; LGMD, limb-girdle muscular dystrophy.

(formerly known as *adhalin*), a dystrophin-related glycoprotein of the sarcolemma, is deficient; this specific defect may be demonstrated in the muscle biopsy by immunocytochemistry, as may deficiency of three other forms of sarcoglycan as well. Increased serum CK level is typical, but the magnitude of elevation varies among families. The ECG is usually unaltered.

A variant in dystrophin-associated protein in the sarcoglycan complex (**sarcoglycanopathy**; **LGMD types 2C, 2E, and 2F**) is responsible for some cases of autosomal recessive LGMD. Most sarcoglycanopathies result from a pathogenic variant in α-sarcoglycan; other LGMDs resulting from deficiencies in β-, γ-, and δ-sarcoglycan also occur. In normal smooth muscle, α-sarcoglycan is replaced by ε-sarcoglycan, and the others are the same. *Dystroglycanopathies* are caused by variants leading to the abnormal glycosylation of α-dystroglycan, and regardless of the gene, all variants seem to be implicated in a common pathway that impacts dystroglycan function. Histochemically, dystroglycanopathies often show defects (loss or reduction) of immunoreactivity to one of two antibodies, VIA41 or IIH6, which recognize carbohydrate moieties of α-dystroglycan. The extent of reduction can vary from subtle to severe.

Another group of LGMDs **(type 2B)** are caused by allelic variants of the dysferlin *(DYSF)* gene, another gene expressing a protein essential to structural integrity of the sarcolemma, though not associated with the dystrophin-glycoprotein complex. *DYSF* interacts with caveolin-3 or calpain-3, and *DYSF* deficiency may be secondary to defects in these other gene products. Dysferlinopathies can present with the classic LGMD pattern of proximal weakness or may present with early weakness in the lower legs, specifically calf weakness, known as Miyoshi myopathy. Primary calpain-3 defect (type 2A) has wide clinical variability, with age of onset ranging from 2-40 years old, and age at loss of independent ambulation ranging from 5 years old to the late 30s. Respiratory compromise can be seen later in the disease but is less severe than in some other LGMDs. Both are slowly progressive myopathies with onset in adolescence or young adult life and can affect distal as well as proximal muscles. Cardiomyopathy is rare. Chronically elevated serum CK in the thousands is found in dysferlinopathies. Ultrastructure shows a thickened basal lamina over defects in the sarcolemma and replacement of the sarcolemma by multiple layers of small vesicles. Regenerating myofibers outnumber degenerating myofibers. Pathogenic variants in *CAV3* can also have a variable neuromuscular phenotype ranging from: limb-girdle phenotype (LGMD1C) to distal myopathy to rippling muscle disease to hyperCKemia and exercise intolerance. There are also reports of patients with rhabdomyolysis with caveolinopathies. These disorders were formerly called *hyperCKemia* and *rippling muscle disease,* the latter sometimes confused with myotonia. An autosomal recessive variant in the calcium-activated chloride channel anoctamin-5 can causes one of the following phenotypes: a proximal LGMD2L, a distal Miyoshi myopathy phenotype, or hyperCKemia. It typically presents in adulthood and is more commonly seen in Northern Europe and Canada. There does not seem to be any associated cardiomyopathy, although there are reports of early premature ventricular contractions (PVCs).

There is genetic overlap of the group of LGMDs with the congenital muscular dystrophies, such as Walker-Warburg syndrome with *POMT*, Fukuyama muscular dystrophy with *FKRP* genetic defects, and *GMPPB*. Patients with pathologic variants in these genes can present with an early CMD-like phenotype to a childhood or later-onset LGMD phenotype, and in both motor phenotypes may or may not have varying degrees of intellectual disability.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

649.5 Facioscapulohumeral Muscular Dystrophy

Adnan Y. Manzur

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy (after Duchenne muscular dystrophy and myotonic dystrophy). Autosomal dominant inheritance is generally the mode of inheritance, and genetic anticipation is often found within several generations of a family, the succeeding more severely involved at an earlier age than the preceding. The genetic mechanism in autosomal dominant **FSHD1** involves integral deletions of a 3.3-kb tandem repeat (D4Z4) in the subtelomeric region at the 4q35 locus. D4Z4 acts as a lamin-dependent insulator, exhibiting both enhancer-blocking and barrier activities, and displaces the telomere toward the nuclear periphery. Normally, there are 11-100 tandem copies or D4Z4 repeats. When there are fewer repeats (<10 repeat units), this enables chromatin remodeling and leads to decreased methylation, thus turning on DUX4 expression (which is normally dormant). In addition, the disease will only manifest in chromosomes that carry a pLAM1 polyadenylate site distal to the last D4Z4 repeat. When these factors all exist, this creates a "permissive" haplotype or state that allows for the expression of DUX4, which is normally repressed. Approximately 5–10% of families with this phenotype do not map to the 4q35 locus. **FSHD2,** although clinically overlapping with FSHD1, is not caused by the contraction in D4Z4 repeats. However, instead, it is caused by pathogenic variants of *SMCHD1* (on chromosome 18p) that can lead to hypomethylation of D4Z4. When these variants exist in the setting of a permissive haplotype and the polyadenylation signal, DUX4 is expressed, again sharing a final common pathway in leading to the same clinical disease. The prevalence varies geographically but ranges from 1:8,000-20,000. Though the clinical onset is generally in later childhood or adult life, early molecular defects arising during myogenesis are demonstrated in the human fetus, and patients can present as early as in the infantile period.

CLINICAL MANIFESTATIONS

Facioscapulohumeral dystrophy (FSHD) shows the earliest and most severe weakness in facial and shoulder girdle muscles (Fig. 649.7). Asymmetric weakness or patchy weakness, when present, should raise suspicion for FSHD. The facial weakness in FSHD differs from that of myotonic dystrophy; rather than an inverted-V–shaped upper lip, the mouth in FSHD is rounded and appears puckered because the lips protrude. Inability to close the eyes completely in sleep is a common expression of upper facial weakness; some patients have extraocular muscle weakness, although ophthalmoplegia is rarely complete. FSHD has been associated with Möbius syndrome on rare occasions. Pharyngeal and tongue weakness may be absent and is never as severe as the facial involvement. Hearing loss, which may be subclinical, and retinal vasculopathy (indistinguishable from Coats disease) are associated features, particularly in severe cases of FSHD with early-childhood onset.

Scapular winging is prominent, often even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdle and thighs also eventually lose strength and undergo atrophy, and the Gowers sign and a Trendelenburg gait appear. Contractures of the extremities are rare. Finger and wrist weakness occasionally is the first symptom. Weakness of the anterior tibial and peroneal muscles can lead to foot drop; this complication usually occurs only in advanced cases with severe weakness. Lumbar hyperlordosis and kyphoscoliosis are common complications of axial muscle involvement. Calf pseudohypertrophy is not a usual feature but is described rarely.

There is a great deal of clinical variability, including within families. FSHD can be a mild disease, causing minimal disability. Clinical manifestations might not be expressed in childhood and are delayed into middle adult life. In more severe cases, patients may present early in life. About 20% of patients will lose independent ambulation, and about 10–15% of patients may require noninvasive or invasive respiratory support. Unlike most other muscular dystrophies, asymmetry of weakness is common. About 30% of affected patients are asymptomatic or show only mild scapular winging and decreased tendon stretch reflexes, of which they were unaware until formal neurologic examination was performed.

LABORATORY FINDINGS

Serum levels of CK and other enzymes vary greatly, ranging from normal or near normal to elevations of several thousand. An ECG should be performed, although the anticipated findings are usually normal. EMG reveals nonspecific myopathic muscle potentials. Diagnostic

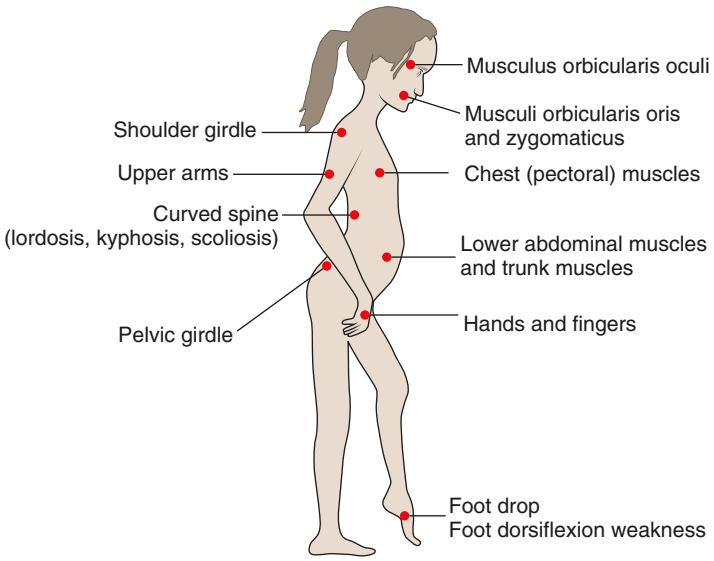

Fig. 649.7 Overview of affected muscles in FSHD. The symptoms tend to start at the upper half of the body and then spread to lower body parts involving the pelvic girdle and the leg muscles. There is a high degree of clinical variability in disease severity, and affected muscles are generally involved asymmetrically regarding the left-right body axis. In some cases, patients with foot drop can be supported by ankle-foot orthotics (AFOs) and knee-ankle-foot orthotics (KAFOs). Surgery to attach the scapula to the ribcage can enhance arm motion or alleviate pain. *(From Schätzl T, Kaiser L, Deigner HP. Facioscapulohumeral muscular dystrophy: genetics, gene activation and downstream signaling with regard to recent therapeutic approaches: an update. Orphanet J Rare Dis. 2021;16:129. Fig. 1.)*

molecular testing in individual cases and within families is indicated for prediction.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Molecular genetic diagnosis is the most specific confirmation if clinical suspicion is high, with or without a family history of the disease. Muscle biopsy distinguishes more than one form of FSHD, consistent with clinical evidence that several distinct diseases are embraced by the term *facioscapulohumeral dystrophy.* Muscle biopsy and EMG also distinguish the primary myopathy from a neurogenic disease with a similar distribution of muscular involvement. The general histopathologic findings in the muscle biopsy material are extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers. An *inflammatory* type of FSHD is also distinguished, characterized by extensive lymphocytic infiltrates within muscle fascicles. Despite the resemblance of this form to inflammatory myopathies such as polymyositis, there is no evidence of autoimmune disease, and steroids and immunosuppressive drugs do not alter the clinical course. A precise histopathologic diagnosis has important therapeutic implications. Mononuclear cell *inflammation* in a muscle biopsy sample of infants younger than 2 years old is usually FSHD or, less often, a CMD.

TREATMENT

Pulmonary function should be followed routinely, and if there are concerns for daytime headaches or increased fatigue, a sleep study should be performed to assess for any sleep-disordered breathing or sleep apnea. Light aerobic exercise and stretching regimens may help to prevent deconditioning or disuse atrophy over time. High-intensity training, strength training, or weightlifting are not recommended because they will not help in regaining strength or retarding the progression of weakness or muscle wasting. Foot drop and scoliosis may be treated by orthopedic measures. In selected cases, surgical wiring of the scapulae (scapular fixation surgery) to the thoracic wall provides improved shoulder stability and abduction of the arm, but brachial plexopathy, frozen shoulder, and scapular fractures are reported complications. Additional rehabilitation options for scapular support include kinesiotaping. Chronic pain can be seen commonly in patients with FSHD, and may require further management, including gabapentin, tricyclic antidepressants, or exercise and cognitive behavioral therapy. Cosmetic improvement of the facial muscles of expression may be achieved by reconstructive surgery, which grafts a fascia lata to the zygomatic muscle and to the zygomatic head of the quadratus labii superioris muscle. Exercise of facial muscles can help minimize secondary disuse atrophy. Routine eye exams should be performed (testing for Coats disease), and in young affected children, audiograms should be performed. No effective pharmacologic or genetic treatment is presently clinically available.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

649.6 Congenital Muscular Dystrophies

Adnan Y. Manzur

The term *congenital muscular dystrophies (CMDs)* refers to a group of hereditary disorders with early (prenatal, neonatal, or early-childhood) onset and histologic features suggestive of a dystrophic process. It is used to encompass several distinct diseases that have a common characteristic of severe involvement at birth or in early childhood but that, ironically, often follow a more benign clinical course than the early onset and histopathologic changes in the muscle biopsy would suggest. A distinguishing feature of the congenital dystrophies, by contrast with other muscular dystrophies, is a high association with **brain malformations**, particularly disorders of cortical development such as lissencephaly/pachygyria and polymicrogyria, often complicated by severe epilepsy (Fig. 649.8). Most of the CMDs are inherited in an autosomal recessive manner (see Table 649.2).

CLINICAL MANIFESTATIONS

In several distinct clinical and genetic diseases grouped under the umbrella term *congenital muscular dystrophies,* infants often have contractures or arthrogryposis at birth and are diffusely hypotonic. In some cases, weakness in infancy may be less significant and initial motor milestones may even be normal. The muscle mass is thin in the trunk and extremities. Head control is often poor due to neck weakness and marked axial hypotonia. Facial muscles may be mildly involved, but ophthalmoplegia, pharyngeal weakness, and weak sucking are not common. A minority has severe dysphagia and requires gavage or gastrostomy. Tendon stretch reflexes may be hypoactive or absent. Distal arthrogryposis is common in all forms of CMD (see Chapter 648.10). Congenital contractures involving axial or proximal joints (including, for example, of the elbows) are often suggestive of **Ullrich CMD** due to pathologic variant(s) in one of the three collagen VI genes *(COL6A1, COL6A2, COL6A3).*

The CMDs can be classified according to the type of protein altered by the specific genetic variants. Diseases of extracellular matrix proteins include LAMA2-related CMD (merosin deficiency, *LAMA2* pathogenic variant at locus 6q22-q23) and COL6-related CMD (Ullrich CMD in the more severe form, to Bethlem myopathy in the milder

form of the disease) (*COL6A1, -A2,* and *-A3* variants at 21q22 and 2q37 loci). A protein of the endoplasmic reticulum (*SEPN1* variant at 1p35) is the basis of rigid spine syndrome. Abnormal glycosylation of α-dystroglycan causes Walker-Warburg syndrome (*POMT1* variant at 9q34), muscle-eye-brain disease of Santavuori (*POMGnT1* variant at 1p32), Fukuyama muscular dystrophy (*FCMD* variant at 8q31-q33 and 9q31), and CMD with secondary merosin deficiency (*FKRP* variant at 19q13). Pathogenic variants in genes that affect the glycosylation of α-dystroglycan can also lead to milder or later-onset LGMD phenotypes (with or without intellectual involvement; see Chapter 649.4). Glycosylation defects (dystroglycanopathies) result in defective neuroblast migration in the fetal brain and also can cause dilated cardiomyopathy. The dystroglycan molecule interacts with both proteins of the plasma (sarcolemmal) membrane and those of the extracellular matrix and basal lamina not only in muscle but also in brain, where defective dystroglycan and poor glycosylation result in gaps in the pial limiting membrane, a discontinuous glia limitans, causing cobblestone lissencephaly and glioneuronal heterotopia of overmigrated neural cells during formation of the cerebral cortex.

The **Fukuyama type** of CMD is the second most common muscular dystrophy in Japan (after DMD); it has also been reported in children of Dutch, German, Scandinavian, and Turkish ethnic backgrounds. In the Fukuyama variety, severe cardiomyopathy and malformations of the brain usually accompany the skeletal muscle involvement. Signs and symptoms related to these organs are prominent: cardiomegaly and heart failure, intellectual disability, seizures, microcephaly, and failure to thrive.

Central neurologic disease can accompany forms of CMD other than Fukuyama disease. The mental and neurologic status is the most variable feature; an apparently normal brain and normal intelligence do not preclude the diagnosis if other manifestations indicate this myopathy. The cerebral malformations that occur are not consistently of one type and vary from severe dysplasias (holoprosencephaly, lissencephaly) to milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia). Seizures are a frequent complication, as early as the neonatal period, and may include infantile spasms and other severe infantile epilepsies.

CMD is a constant association with cerebral dysgenesis in the **Walker-Warburg syndrome** and in **muscle-eye-brain disease.** The neuropathologic findings are those of neuroblast migratory abnormalities in the cerebral cortex, cerebellum, and brainstem. Studies indicate considerably more genetic overlap between Walker-Warburg, Fukuyama, and muscle-eye-brain forms of CMD that explain mixed and transitional phenotypes, so that, for example, a *Fukutin*-related *(FKRP)* gene can cause a Walker-Warburg or muscle-eye-brain presentation, or *POMGnT1* also can produce phenotypes other than classic Walker-Warburg disease.

LABORATORY FINDINGS

The serum CK level is usually moderately elevated from several hundred to many thousand IU/L; only marginal increases are sometimes found. EMG shows nonspecific myopathic features. Investigation of all forms of CMD should include cardiac assessment and an imaging study of the brain. In the past, muscle biopsy was considered essential for the diagnosis, but currently a confirmed genetic mutation together with a typical phenotype or a confirmed genetic defect in a sibling, allows a confident diagnosis, avoiding a muscle biopsy.

DIAGNOSIS

Muscle biopsy is diagnostic in the neonatal period or thereafter. An extensive proliferation of endomysial collagen envelops individual muscle fibers even at birth, also causing them to be rounded in cross-sectional contour by acting as a rigid sleeve, especially during contraction. The perimysial connective tissue and fat are also increased, and the fascicular organization of the muscle may be disrupted by the fibrosis. Tissue cultures of intramuscular fibroblasts exhibit increased collagen synthesis, but the structure of the collagen is normal. Muscle fibers vary in diameter, and many show central nuclei, myofibrillar splitting, and other cytoarchitectural alterations. Scattered degenerating and regenerating fibers are seen. No inflammation or abnormal inclusions are found.

Immunocytochemical reactivity for merosin (α_2 chain of laminin) at the sarcolemmal region is absent in approximately 40% of cases and normally expressed in the others (Figs. 649.9 and 649.10). Merosin is a protein that binds the sarcolemmal membrane of the myofiber to the basal lamina or basement membrane. Merosin also is expressed in brain and in Schwann cells. The presence or absence of merosin does not always correlate with the severity of the myopathy or predict its course. Adhalin (α-dystroglycan) may be reduced to varying degrees

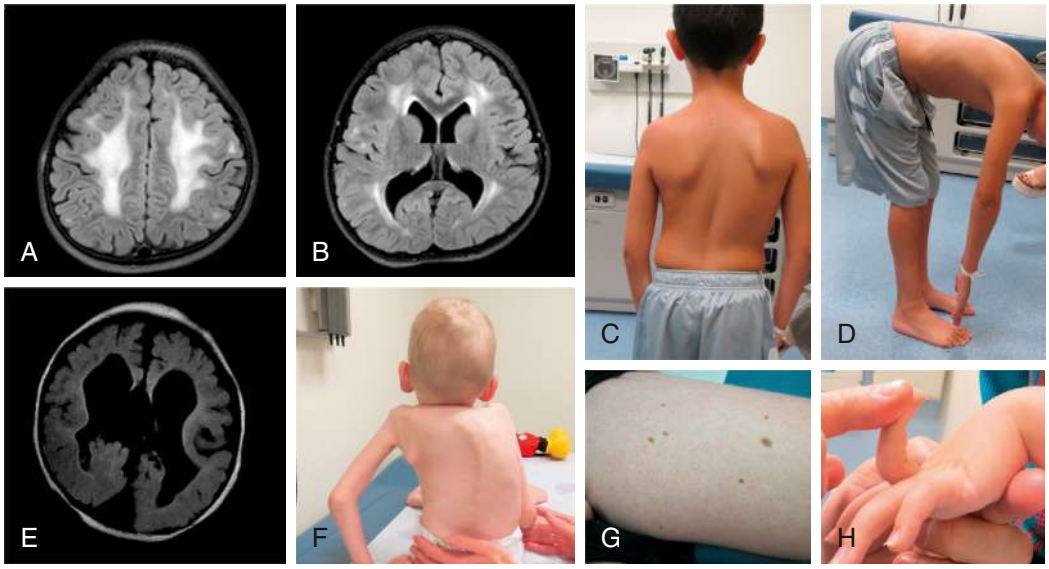

Fig. 649.8 Findings in congenital muscular dystrophies. **A** and **B,** Axial FLAIR brain MRI images showing the increased T2 hyperintensity seen within the white matter in patients with LAMA2 CMD. **C,** Scapular winging and scoliosis in patient with SEPN1 muscular dystrophy. **D,** Rigid spine noted in forward flexion in patient with SEPN1 muscular dystrophy. **E,** Brain MRI in patient with muscle-eye-brain disease with absent corpus callosum, Dandy-Walker malformation, subependymal cysts. **F,** Early and severe kyphoscoliosis in a child with Ullrich CMD. **G,** Keratosis pilaris, a common skin finding in patients with collagen VI–related CMDs. **H,** Distal hyperlaxity seen in patients with collagen VI–related CMDs. *(Courtesy Drs. Carsten Bönnemann and Reghan Foley, Neuromuscular and Neurogenetics Disorders of Childhood Section, NINDS/NIH.)*

in the α-dystroglycanopathies, and there can be secondary reduction of merosin (laminin 211). Collagen VI is selectively reduced, absent, or mislocalized in COL6-related CMDs. Mitochondrial dysfunction may be another secondary defect.

TREATMENT

Supportive care at this time is the mainstay of therapy. A consensus statement on the management of patients with congenital muscular dystrophies was published in 2010 by Wang, et al. Given the high prevalence of respiratory insufficiency in this population, it is important at every visit to screen for respiratory function with pulmonary function testing and eliciting information on the frequency and duration of respiratory illnesses, the frequency of lower respiratory infections, abnormal breathing in sleep, increased daytime fatigue, or headaches. Sleep studies should be performed early (especially in collagen VI CMD and SEPN1 muscular dystrophy), where the respiratory compromise can occur even in ambulant patients because of increased diaphragmatic weakness. Additional respiratory supports may include chest physical therapy, cough assist with suctioning, BiPAP, and, in more advanced stages, invasive ventilation or sip/puff ventilation options for continuous ventilator supports. Weight gain should be optimized to make sure the patient is not losing weight or gaining excess weight. Swallowing should be assessed to screen for dysphagia. Some children will require G-tube feeds due to insufficient oral intake to meet caloric needs, whereas others may require nearly full G-tube feeds due to swallowing difficulties. Speech therapy may be needed for assessment for dysphagia but also because some of these children will have some difficulty with articulation because of oromotor weakness that can affect communication early in life. Constipation occurs frequently and should be medically managed through diet or stool softeners. Physical therapists and physiatrists should be involved in working with the patients on assistive devices and stretching and bracing regimens to try to slow down the progression of or manage contractures. Children may develop scoliosis (or in collagen VI–related CMD, kyphoscoliosis deformities), and should be followed regularly by orthopedic specialists to determine when bracing or surgical interventions are needed. Children with α-dystroglycanopathies with central nervous system involvement may require additional supports, including speech therapies, individualized education plans for learning and intellectual disabilities, seizure management, and spasticity management.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for a Bibliography.

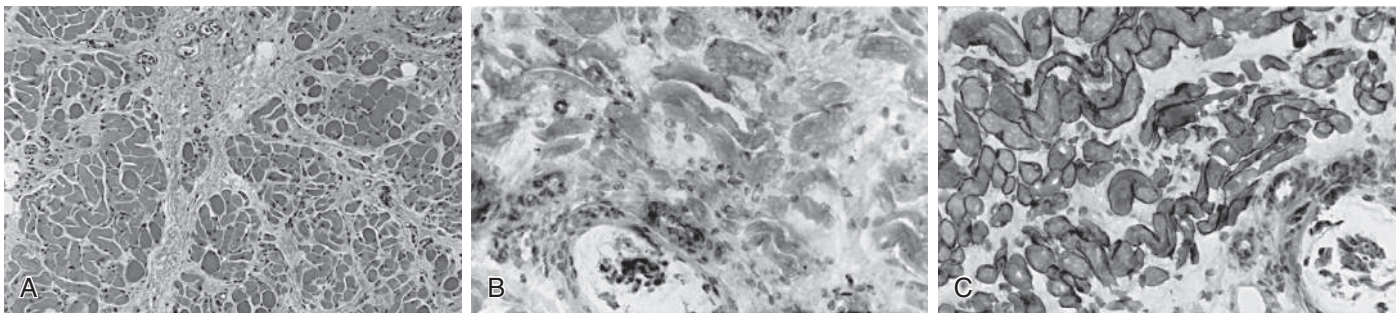

Fig. 649.9 Quadriceps femoris muscle biopsy of a 6-mo-old female with congenital muscular dystrophy associated with merosin (α_2-laminin) deficiency. **A,** Histologically, the muscle is infiltrated by a great proliferation of collagenous connective tissue; myofibers vary in diameter, but necrotic fibers are rare. **B,** Immunocytochemical reactivity for merosin (α_2-laminin) is absent in all fibers, including the intrafusal myofibers of a muscle spindle seen at bottom. **C,** Dystrophin expression (rod domain) is normal. Compare with Figures 649.3, 649.4, and 649.10.

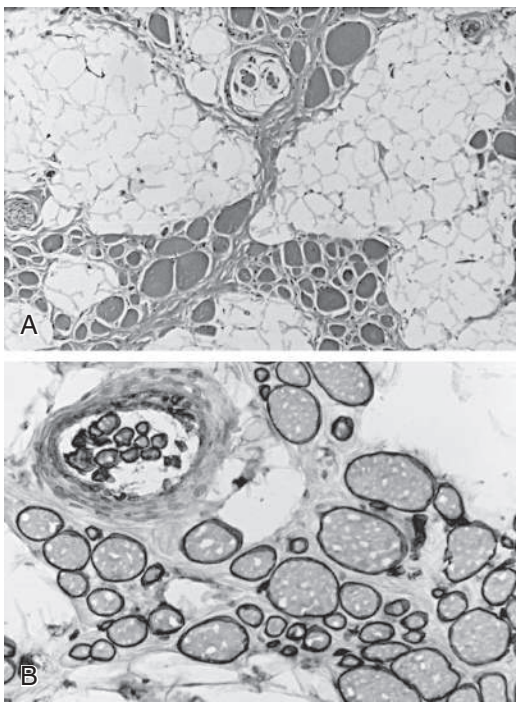

Fig. 649.10 Quadriceps femoris muscle biopsy specimen of a 2-yr-old female with congenital muscular dystrophy. **A,** The fascicular architecture of the muscle is severely disrupted, and muscle is replaced by fat and connective tissue; the remaining small groups of myofibers of variable size are seen, including a muscle spindle at top. **B,** Merosin expression is normal in both extrafusal fibers of all sizes and in intrafusal spindle fibers. The severity of the myopathy does not relate to the presence or absence of merosin in congenital muscular dystrophy. Compare with Figure 649.9.

Chapter 650

Endocrine and Toxic Myopathies

Adnan Y. Manzur*

THYROID MYOPATHIES

See also Chapters 601-606 and Table 650.1.

Thyrotoxicosis causes proximal weakness and wasting accompanied by myopathic electromyographic changes. Rarely the myopathy may be limited to painless external ophthalmoplegia and proptosis, at least initially. Thyroxine binds to myofibrils and, if in excess, impairs contractile function. Hyperthyroidism can also induce myasthenia gravis and hypokalemic periodic paralysis, the latter mainly affecting East Asian males who have a genetic predisposition. A pathologic variant in the gene *KCNJ18* may be responsible for altering the potassium channel Kir2.6 in up to one third of cases. Potassium supplementation and propranolol are useful in treating thyrotoxic periodic paralysis.

Hypothyroidism, whether congenital or acquired, consistently produces hypotonia and a proximal distribution of weakness. Although muscle wasting is most characteristic, one form of cretinism, Kocher-Debré-Sémélaigne syndrome, is characterized by generalized pseudohypertrophy of weak muscles. Infants can have a Herculean appearance reminiscent of myotonia congenita. The serum creatine kinase (CK) level is elevated in hypothyroid myopathy and returns to normal after thyroid replacement therapy.

Results of muscle biopsy in hypothyroidism reveal acute myopathic changes, including myofiber necrosis and sometimes central cores. In hyperthyroidism, the muscle biopsy specimen shows only mild, nonspecific myopathic changes without necrosis of myofibers. The clinical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolve after appropriate treatment of the thyroid disorder. Many of the systemic symptoms of hyperthyroidism, including myopathic weakness and ophthalmoparesis, improve with the administration of β blockers.

Most patients with primary **hyperparathyroidism** (see Chapter 613) develop weakness, fatigability, fasciculations, and muscle wasting that is reversible after removal of the parathyroid adenoma. The serum CK and muscle biopsy remain normal, but electromyography can show nonspecific myopathic features. A minority of patients develop myotonia that could be confused with myotonic dystrophy.

STEROID-HORMONE INDUCED MYOPATHY

Cushing disease and iatrogenic Cushing syndrome from exogenous corticosteroid administration can cause painless, symmetric, progressive proximal weakness, increased serum CK levels, and a myopathic electromyogram and muscle biopsy specimen (see Chapter 619). Myosin filaments may be selectively lost. The 9α-fluorinated steroids, such as dexamethasone, betamethasone, and triamcinolone, are the most likely to produce *steroid myopathy.* Dexamethasone alters the abundance of ceramides in myotubes in developing muscle. In patients with dermatomyositis or other myopathies treated with steroids, it is sometimes difficult to distinguish refractoriness of the disease from steroid-induced weakness, especially after long-term steroid administration. Vitamin D is another factor altering muscle metabolism and particularly its sensitivity to insulin; vitamin D deficiency may be accentuated and contribute to steroid myopathy, especially in type 2 diabetic patients and insulin resistance.

All patients who have been taking steroids for long periods develop reversible type II myofiber atrophy; this is a *steroid effect* but is not steroid myopathy unless it progresses to become a necrotizing myopathy. At greatest risk in the pediatric age-group are children requiring long-term steroid therapy for asthma, rheumatoid arthritis, dermatomyositis, lupus, and other autoimmune or inflammatory diseases or who are being treated for leukemia or other hematologic diseases. In addition to steroids, the drugs listed in Table 650.2 can cause acute or chronic toxic myopathies. An incompletely understood entity known as critical illness myopathy is a progressive weakness of patients with extended illnesses who remain in the intensive care unit; it is associated pathologically with selective loss of thick (myosin) myofilaments; immobility and excessive steroid treatment are believed to be important factors. Various steroids are sometimes used chronically in the treatment of Duchenne muscular dystrophy; they may actually exaggerate the weakness because of steroid myopathy superimposed on the dystrophic process (see Chapter 649).

Hyperaldosteronism is accompanied by episodic and reversible weakness similar to that of periodic paralysis. Another clinical presentation is muscle cramps at rest. The proximal myopathy can become irreversible in chronic cases. Elevated CK levels and even myoglobinuria sometimes occur during acute attacks. Arterial hypertension is a frequent manifestation, and in children, aldosterone-secreting adenomas up to 6 mm in diameter or multiple adrenocortical micronodules of 0.5 mm should be considered in the differential diagnosis of idiopathic hypertension and muscle weakness or cramps. Hereditary primary aldosteronism is due to a pathogenic variant in one of the potassium channel genes *KCNJ5* and *GIRK4*.

Chronic growth hormone excess (sometimes illicitly acquired by adolescent athletes or seen in acromegaly) produces atrophy of some myofibers and hypertrophy of others, and scattered myofiber degeneration. Despite the augmented protein synthesis induced by growth hormone, it impairs myofibrillar adenosine triphosphatase activity and reduces sarcolemmal excitability, with resultant diminished, rather than increased, strength corresponding to the larger muscle mass. It has been used therapeutically in muscular dystrophy with both a positive effect and complications. *Ghrelin* is an intestinal hormone that activates a growth hormone secretagogue receptor and stimulates growth hormone release. In addition to its effect as a "hunger hormone" that involves food intake and fat deposition, it also prevents muscular atrophy by inducing myodifferentiation and myoblast fusion.

STATIN-INDUCED RHABDOMYOLYSIS WITH MYOGLOBINURIA

Myalgias and a self-limited myopathy can be induced in 10–20% of patients taking statin drugs (HMG-CoA reductase inhibitors [HMGCR]). In addition, a less common but more severe statin-associated immune-mediated necrotizing myopathy may occur and is characterized by marked elevated CK levels, muscle edema and necrosis, and the presence of anti-HMGCR antibodies. These widely prescribed drugs are mainly used in adults to lower plasma cholesterol levels but also are sometimes administered to adolescents, particularly in familial cases of hypercholesterolemia. Statins lower the patient's levels of coenzyme-Q10, which is needed for mitochondrial electron transport. Myalgias are usually well tolerated, whereas myopathy requires stopping the statin. The immune-mediated muscle necrosis requires immune suppression with prednisone; steroid-sparing agents included intravenous immunoglobulin (IVIG) and rituximab.

* The editors are grateful to Dr. Harvey B. Sarnat, much of whose work on previous editions of this chapter is retained here.

Table 650.1 Neuromuscular Manifestations of Endocrine Disorders

DIABETES	SYMPTOMS	LABORATORY TEST RESULTS	EMG
Acromegaly	Proximal weakness, CTS, neuropathy, muscle atrophy	Normal CK (may be elevated), elevated growth hormone, IGF-1, TSH	Normal or myopathic
Hypopituitarism	Weakness (may be severe); muscle fatigue	Normal CK; multiple hormone deficiencies	Not defined
Adrenal insufficiency, Addison disease	Proximal weakness, cramps, fatigue	Elevated potassium, reduced cortisol levels, abnormally high corticotropin, normal CK	Normal
Thyrotoxic* periodic paralysis	Weakness with hypokalemia, usually after high-carbohydrate meals (occurs mainly in Asians, more common in men)	Elevated CK during attacks	Normal except for decreased CMAP during attacks, after exercise
Hypothyroidism (adult: Hoffmann syndrome; children: Kocher-Debré Sémélaigne)	Proximal weakness, muscle spasms, pain (adults); myoedema, delayed relaxation of reflexes; peripheral neuropathy, entrapment neuropathies, CTS	Elevated CK, elevated thyrotropin or low T_4	Nonspecific
Hyperthyroidism or thyrotoxic myopathy	Proximal weakness with little atrophy, more common in women; distal weakness in 20%, some bulbar involvement; Graves ophthalmopathy can occur, myasthenia gravis and periodic paralysis may occur; fasciculations and myokymia; peripheral neuropathy	Normal CK, high T_4 and T_3, reduced thyrotropin	Myopathy, with fibrillations and fasciculations
Diabetes	Peripheral polyneuropathy, focal neuropathy; myopathy unusual; muscle infarcts causing unilateral weakness, swelling; proximal muscle weakness (diabetic amyotrophy)	Elevated CK	Motor unit action potentials
Cushing disease (primary or drug induced)	Proximal weakness, myalgia, truncal adipose tissue accumulation, moon face	Normal CK, low potassium, elevated plasma cortisol	May show myopathic motor unit action potentials
Hyperparathyroidism, primary or secondary from renal disease	Proximal weakness and atrophy, muscle cramps, possible hypotonia	Elevated calcium levels, usually low phosphate and high alkaline phosphatase, normal or mildly elevated CK, elevated PTH and vitamin D levels	Small polyphasic motor units or potentials
Hypoparathyroidism	Hypocalcemia-induced tetany (Chvostek, Trousseau signs), cramps	Mildly elevated CK, hypocalcemia, hypomagnesemia	Multiplex discharges

CK, Creatine kinase; CMAP, compound muscle action potential; CTS, carpal tunnel syndrome; EMG, electromyography; IGF-1, insulin-like growth factor-1; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.
*Graves disease most common but also seen in toxic nodular goiter iodine or amiodarone-induced thyrotoxicosis or pituitary adenoma.
Modified from Bassam BA, Bertorini TE. Neuromuscular manifestations of acquired metabolic, endocrine, and nutritional disorders. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management,* 2nd ed. Philadelphia: Elsevier; 2022: Table 650.1, p 529.

MITOCHONDRIAL DYSFUNCTION IN TOXIC MYOPATHIES

Impaired mitochondrial function, enzymatic activity in the five respiratory chain complexes, and alterations in the mitochondrial ultrastructure are a common basis for the clinical effects of many toxic organic compounds and heavy metals that affect both muscle and peripheral nerves. Statin toxicity is mentioned previously. Another example is excessive zinc intake as a dietary supplement (see Chapter 654). These acquired, induced mitochondrial cytopathies can produce weakness and resemble the clinical progression of genetic mitochondrial myopathies plus neuropathy.

Table 650.2	Toxic Myopathies
INFLAMMATORY CAUSES	
Cimetidine	
D-Penicillamine	
Procainamide	
L-Tryptophan	
L-dopa	
NONINFLAMMATORY NECROTIZING OR VACUOLAR CAUSES	
Cholesterol-lowering agents (statins)	
Chloroquine	
Colchicine	
Emetine	
ε-Aminocaproic acid	
Labetalol	
Cyclosporine and tacrolimus	
Isotretinoic acid (vitamin A analog)	
Vincristine	
Statins	
Alcohol	
RHABDOMYOLYSIS AND MYOGLOBINURIA	
Cholesterol-lowering drugs (especially statins)	
Alcohol	
Heroin	
Amphetamine	
Toluene	
Cocaine	
ε-Aminocaproic acid	
Pentazocine	
Phencyclidine	
MALIGNANT HYPERTHERMIA	
Halothane	
Ethylene	
Diethyl ether	
Methoxyflurane	
Ethyl chloride	
Trichloroethylene	
Gallamine	
Succinylcholine	
MITOCHONDRIAL CAUSES	
Zidovudine	
MYOTONIA	
2,4-*d*-Chlorophenoxyacetic acid	
Anthracene-9-carboxylic acid	
Cholesterol-lowering drugs	
Chloroquine	
Cyclosporine	
MYOSIN LOSS	
Nondepolarizing neuromuscular blocking agents	
Intravenous glucocorticoids	

Modified from Goldman L, Ausiello D. *Cecil Textbook of Medicine,* 22nd ed. Philadelphia: WB Saunders; 2004: p 2399.

CRITICAL ILLNESS MYOPATHY

Patients who are in the intensive care unit for extended periods sometimes develop progressive weakness and myalgias that cannot be attributed simply to disuse atrophy. The pathogenesis remains uncertain, but some factors may include inhibition of protein synthesis, mitochondrial dysfunction, oxidative stress, and disruption of intramuscular calcium homeostasis. Patients with severe disease may even develop rhabdomyolysis, with elevated serum CK and myoglobinuria leading to renal damage.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 651

Metabolic Myopathies and Channelopathies*

651.1 Periodic Paralyses and Other Muscle Channelopathies

Adnan Y. Manzur

Episodic, reversible weakness or paralysis, known as **periodic paralysis,** is associated with transient alterations in serum potassium levels, usually hypokalemia but occasionally hyperkalemia. All familial forms of periodic paralysis are caused by pathogenic variants in genes encoding voltage-gated ion channels in muscle: sodium, calcium, and potassium (Table 651.1). Nonhereditary causes of periodic paralysis are caused by a diverse group of disorders that affect potassium balance (Table 651.2).

During attacks of **hypokalemic paralysis,** myofibers are electrically unexcitable, although the contractile apparatus can respond normally to calcium. The genetic disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, epinephrine including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice.

Episodes of hypokalemic paralysis often begin in infancy, particularly in the hyperkalemic form, and the disease is nearly always symptomatic by 10 years of age, affecting both sexes equally. Late childhood or adolescence is the more typical age of onset of the hypokalemic form, Andersen-Tawil syndrome, and paramyotonia congenita. Periodic paralysis is an episodic event; patients are unable to move after awakening and gradually recover muscle strength during the next few minutes or hours. All four extremities are involved. Muscles that remain active in sleep, such as the diaphragm, extraocular muscles (rapid eye movements), and cardiac muscle are not affected. Patients are normal between episodes, but in adult life episodes become more frequent, and the disorder causes progressive myopathy with permanent weakness even between episodes. The usual frequency of episodes in childhood is once a week. The differential diagnosis includes thyrotoxic periodic paralysis, myotonia congenita, and paramyotonia congenita. A triad of periodic paralysis, potentially fatal cardiac ventricular ectopy (caused by a defect in Kir2.1 channels for terminal repolarization), and characteristic physical features is known as **Andersen-Tawil syndrome.**

Alterations in serum potassium levels occur only during acute episodes and are accompanied by T-wave changes in the electrocardiogram. Hypokalemia may be caused by alterations in calcium gradients. The creatine kinase (CK) level may be mildly elevated at those times. Plasma phosphate levels often decrease during symptomatic periods. Muscle biopsy findings are often normal between episodes, but during an episode a vacuolar myopathy is demonstrated. Pathologic changes in the periodic paralyses are similar, whether the disease is the result of a sodium or a potassium channel defect, suggesting that the changes might result from the recurrent paralytic state rather than the specific channelopathy. The vacuoles are dilated sarcoplasmic reticulum and invaginations of the extracellular space into the cytoplasm, and they may be filled with glycogen. Muscle biopsy is

*The editors are grateful to Dr. Harvey B. Sarnat, much of whose work on previous editions of this chapter is retained here.

Table 651.1 Muscle Channelopathies

	MYOTONIA CONGENITA	PARAMYOTONIA CONGENITA	OTHER SODIUM CHANNEL MYOTONIAS	HYPERKALEMIC PERIODIC PARALYSIS	HYPOKALEMIC PERIODIC PARALYSIS	ANDERSEN-TAWIL SYNDROME	THYROTOXIC PERIODIC PARALYSIS	CENTRAL CORE/ MALIGNANT HYPERTHERMIA
Gene	*CLCN1*	*SCN4A*	*SCN4A*	*SCN4A*	*CACNA1S, SCN4A*	*KCNJ2*	*KCNJ18*	*RYR1*
Chromosome	7q35	17q23	17q23	17q23	1q32, 17q23*	17q24	17†	19q 13
Clinical features	Myotonia	Myotonia, episodic weakness	Myotonia	Episodic weakness, myotonia	Episodic weakness	Episodic weakness, premature ventricular contractions, ventricular tachyarrhythmia	Episodic weakness	Weakness, malignant hyperthermia, and rarely myotonia
Triggers	Cold (some patients)	Cold	Potassium (some patients)	Potassium, rest after exercise	Carbohydrates, rest after exercise	Rest after exercise, carbohydrates (some patients), potassium (some patients)	Thyrotoxicosis	Anesthesia
Acute treatment	n/a	n/a	n/a	Carbohydrate/ glucose	Potassium oral, rarely IV	Potassium (if attacks associated with hypokalemia)	Potassium, adrenergic blocking agents	IV fluids, support
Chronic treatment	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide, acetazolamide	Acetazolamide, dichlorphenamide	Potassium, acetazolamide, dichlorphenamide, potassium-sparing diuretic	Potassium (if attacks are associated with hypokalemia), acetazolamide, dichlorphenamide, potassium-sparing diuretic	Treatment of thyrotoxicosis	n/a
Exercise testing	Short exercise test (SET): Postexercise decrement, rapid return to baseline	SET: Postexercise decrement, facilitated by repetition or cold	SET: Often nondiagnostic	Long exercise test (LET): Postexercise decrement	LET: Postexercise decrement	LET: Postexercise decrement	LET: postexercise decrement (when symptomatic)	n/a
Laboratory features	n/a	n/a	n/a	Ictal high potassium‡	Ictal low potassium	Ictal high/low potassium	Ictal low potassium, elevated thyroid hormone	Elevated creatine kinase during malignant hyperthermia
Commercially available genetic testing	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

*Calcium channel gene chromosome 1, sodium channel gene chromosome 17.
†Exact location not determined.
‡Case reports of families with variants associated with hyperkalemic periodic paralysis and normal potassium.
IV, Intravenous; n/a, nonapplicable.
From Statland JM, Barohn RJ. Muscle channelopathies: the nondystrophic myotonias and periodic paralyses. *Continuum*. 2013;19(6):1598–1614. Table 4.1.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 25, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 651.2 Secondary Causes of Periodic Paralysis

HYPOKALEMIC
Thyrotoxic
Primary hyperaldosteronism (Conn syndrome)
Renal tubular acidosis (e.g., Fanconi syndrome)
Juxtaglomerular apparatus hyperplasia (Bartter syndrome)
Gastrointestinal potassium wastage
Villous adenoma
Laxative abuse
Pancreatic non–insulin-secreting tumors with diarrhea
Nontropical sprue
Barium intoxication
Potassium-depleting diuretics
Amphotericin B
Licorice
Corticosteroids
Toluene toxicity
p-Aminosalicylic acid
Carbenoxolone
HYPERKALEMIC
Addison disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

From Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Elsevier; 2012: Table 429-8, p. 2415.

not essential to diagnose periodic paralysis, however. Hypoglycemia does not occur. Loci for the majority of periodic paralyses have been demonstrated and the genes at least partially characterized, but many patients with the same clinical phenotype exhibit no variants in the identified genes.

TREATMENT

Paralytic episodes of hypokalemic periodic paralysis are best treated by the oral administration of potassium or even fruit juices that contain potassium. A low sodium intake and the administration of acetazolamide, 5 mg/kg/day bid or tid as a starting dose, often is effective in abolishing episodes or at least reducing their frequency and severity. Dichlorphenamide, a carbonic anhydrase inhibitor, is approved for the treatment of primary hypokalemic and hyperkalemic periodic paralysis syndromes in adults. The drug reduced the frequency, with few side effects (paresthesias, confusion, dysgeusia). Acetazolamide has also been used off label for these conditions.

OTHER MUSCLE CHANNELOPATHIES

Disorders of ion channels other than the well-documented potassium channelopathies also are recognized (see Table 651.1). A rare, severe **neonatal myotonia** is secondary to a pathologic variant of the voltage-gated sodium channel *SCN4A* gene; it is unrelated to neonatal myotonic dystrophy, myotonia congenita, or infantile myofibrillar myopathies. This same gene is also responsible for severe neonatal **episodic laryngospasm.** Mexiletine is effective treatment of the myotonia, but the long-term prognosis remains poor, with death by 2 years of age. Sodium channel blockers, such as carbamazepine, phenytoin, and procainamide, are alternatives.

Neuromyotonia, a continuous muscle activity of neurogenic origin, may be caused by pathogenic variants in genes encoding or antibodies against potassium channels, but is rare in childhood. **Schwartz-Jampel disease,** resulting from an autosomal recessive trait, involves severe muscle stiffness, myotonia, blepharospasm, and chondrodysplasia. It becomes symptomatic in the first year of life and is slowly progressive until midadolescence, after which it is stable. It is no longer considered a variant of myotonic dystrophy and is caused by a pathogenic variant in *HSPG2* which encodes perlecan, the major heparan sulfate proteoglycan of basement membranes. Sodium channel blockers may be useful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

651.2 Malignant Hyperthermia

Adnan Y. Manzur

See also Chapters 91 and 648.4.

Malignant hyperthermia susceptibility (MHS) is usually inherited as an autosomal dominant trait. It occurs in all patients with *RYR1*-related central core disease but is not limited to that particular myopathy. The *RYR1* is at the 19q13.1 locus and is responsible for both central core disease and MHS without this specific myopathy. At least 180 separate pathogenic variants in this gene are associated with malignant hyperthermia. The gene programs the ryanodine receptor, a tetrameric calcium-release channel in the sarcoplasmic reticulum, in apposition to the voltage-gated calcium channel of the transverse tubule (see Table 651.1). *RYR1* variants account for up to 75% of cases of malignant hyperthermia reactions. A similar rhabdomyolytic, but not true malignant hyperthermia, reaction occurs rarely in Duchenne and other muscular dystrophies. *CACNA1S* variants are a cause of periodic paralysis but rarely some variance in this gene is associated with MHS. Malignant hyperthermia is also a key risk in *STAC3*-related congenital myopathy, which was initially described in Native American Indians, but has been reported in multiple ethnicities. The key features of *STAC3* disease, also called **Bailey-Bloch congenital myopathy**, are myopathy with cleft palate, skeletal anomalies, delayed motor development, and MHS. MHS has also been observed in various other myopathies, in some children with scoliosis, and in an isolated syndrome not associated with other muscle disease. Affected children sometimes have peculiar facies, described in **King Denborough syndrome**. MHS is present in affected individuals at all ages, including premature infants whose mothers underwent general anesthesia for cesarean section. Overall, MHS affects 1:10,000 to 1:250,000, but prevalence of genetic abnormalities may be as high as 1:400.

Acute malignant hyperthermia episodes are precipitated by exposure to general anesthetics, and in particular the depolarizing muscle relaxant succinylcholine and halogenated inhaled anesthetic gases. Patients suddenly develop extreme fever, rigidity of muscles, masseter muscle spasm and metabolic and respiratory acidosis; the serum CK level rises massively and sometimes over 30,000 IU/L. Life-threatening hyperkalemia is a major risk. Myoglobinuria can result in tubular necrosis and acute renal failure.

The muscle biopsy specimen obtained during an episode of malignant hyperthermia or shortly afterward is not indicated but shows widely scattered necrosis of muscle fibers known as rhabdomyolysis. Between attacks, the muscle biopsy specimen is normal unless there is an underlying chronic myopathy.

It is important to recognize patients at risk of malignant hyperthermia because the attacks may be prevented by administering dantrolene sodium before an anesthetic is given. Patients at risk, such as siblings, are identified by genetic testing or by the caffeine contracture test: a portion of fresh muscle biopsy tissue in a saline bath is attached to a strain gauge and exposed to caffeine and other drugs; an abnormal spasm is diagnostic. The syndrome-associated receptor also may be demonstrated by immunochemistry in frozen sections of the muscle biopsy. The gene defect of the ryanodine receptor is present in 50% of patients; gene testing is available for this and for *STAC3*-related myopathy and MHS. Four other gene loci for MHS are known.

Apart from the genetic disorder of malignant hyperthermia, some drugs can induce acute rhabdomyolysis with myoglobinuria and potential renal failure, but this usually occurs in patients who are predisposed by some other metabolic disease (mitochondrial myopathies). Valproic acid can induce this process in children with mitochondrial cytopathies or with carnitine palmitoyltransferase (CPT) deficiency.

Dantrolene sodium is a specific treatment or preventive if administered to patients at risk before an anesthetic. The pediatrician has a crucial role in identifying the potential MHS, conveying the risk to the anesthetist, and a malignant hyperthermia safe protocol with total intravenous anesthetic is recommended for suspected or proven cases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

651.3 Glycogenoses

Adnan Y. Manzur

See Chapter 107.1 and Table 651.3.

Glycogenosis I (von Gierke disease) is not a true myopathy because the deficient liver enzyme glucose-6-phosphatase is not normally present in muscle. Nevertheless, children with this disease are hypotonic and mildly weak for unknown reasons.

Glycogenosis II (Pompe disease) is an autosomal recessively inherited deficiency of the glycolytic lysosomal enzyme α-glucosidase (formerly known as acid maltase) that cleaves the α-1,4 and α-1,6 glycosidic linkages. Of the 12 known glycogenoses, type II is the only one with a defective lysosomal enzyme. The defective gene is at locus 17q23, with more than 200 distinct variants. Two clinical forms are described. The **infantile** form is a severe generalized myopathy and cardiomyopathy. Patients have cardiomegaly and hepatomegaly and are diffusely hypotonic and weak. The serum CK level is greatly elevated. A muscle biopsy specimen reveals a vacuolar myopathy with abnormal lysosomal enzymatic activities such as acid and alkaline phosphatases. Evidence of secondary mitochondrial cytopathy is often demonstrated; it includes electron microscopic demonstration of paracrystalline structures within muscle mitochondria and low concentrations of respiratory chain enzymes. Death in infancy or early childhood is usual; however, enzyme replacement therapy has improved the outcome.

The **late childhood** or **adult** form is a much milder myopathy without cardiac or hepatic enlargement. It might not become clinically expressed until later childhood or early adult life but may be symptomatic as myopathic weakness and hypotonia even in early infancy. Even in late adult-onset acid maltase deficiency, >50% of the patients report difficulties with muscle strength dating from childhood. Ultrastructural evidence of secondary mitochondrial cytopathy also occurs, as with infantile Pompe disease. MRI of muscle may show distinctive changes that differ from other myopathies.

The serum CK level is greatly elevated, and the muscle biopsy findings are diagnostic even in the presymptomatic stage. The diagnosis of glycogenosis II is confirmed by quantitative assay of acid maltase activity in muscle or liver biopsy specimens.

A rare variant of the milder form of acid maltase deficiency can show muscle acid maltase activity in the low normal range with only intermittent decreases to subnormal values; the muscle biopsy findings are similar although milder. In another form, **Danon disease,** transmitted as an X-linked recessive trait at the Xq24 locus, the primary deficiency is lysosomal membrane protein-2 (LAMP2) and results in hypertrophic cardiomyopathy, proximal myopathy, and intellectual disability.

Glycogenosis III (Cori-Forbes disease), a deficiency of debrancher enzyme (amylo-1,6-glucosidase), is more common than is usually diagnosed, and it is generally the least severe. Hypotonia, weakness, hepatomegaly, and fasting hypoglycemia in infancy are common, but these features often resolve spontaneously, and patients become asymptomatic in childhood and adult life. Others experience slowly progressive distal muscle wasting, hepatic cirrhosis, recurrent hypoglycemia, and heart failure. This more serious chronic course is particularly seen in the Inuit population. Minor myopathic findings including vacuolation of muscle fibers are found in the muscle biopsy specimen.

Glycogenosis IV (Andersen disease) is a deficiency of brancher enzyme, resulting in the formation of an abnormal glycogen molecule, amylopectin, in the liver, reticuloendothelial cells, and skeletal and cardiac muscle. Hypotonia, generalized weakness, muscle wasting, and contractures are the usual signs of myopathic involvement. Most patients die before age 4 years because of hepatic or cardiac failure. A few children without neuromuscular manifestations have been described.

Glycogenosis V (McArdle disease) is caused by muscle glycogen phosphorylase deficiency inherited as an autosomal recessive trait at locus 11q13, encoded by *PMGM*. Exercise intolerance is the cardinal clinical feature. Physical exertion results in cramps, weakness, and myoglobinuria, but strength is normal between attacks. The serum CK level is elevated only during exercise. A characteristic clinical feature is lack of the normal rise in serum lactate levels during ischemic exercise because of inability to convert pyruvate to lactate under anaerobic conditions in vivo. Myophosphorylase deficiency may be demonstrated histochemically and biochemically in the muscle biopsy tissue. Some patients have a defect in adenosine monophosphate–dependent muscle phosphorylase β-kinase, a phosphorylase enzyme activator. Muscle phosphorylase deficiency can be diagnosed by MR spectroscopy, which shows that the intramuscular pH does not decrease with exercise and there is no depletion of adenosine triphosphatase but that the phosphocreatine concentration falls excessively. This noninvasive technique may be useful in some patients if the radiologist is experienced with the disease.

A rare **neonatal form of myophosphorylase deficiency** causes feeding difficulties in early infancy, may be severe enough to result in neonatal death, or can follow a course of slowly progressive weakness resembling a muscular dystrophy. The long-term prognosis is good. Patients must learn to moderate their physical activities, but they do not develop severe chronic myopathic handicaps or cardiac involvement.

Glycogenosis VII (Tarui disease) is muscle phosphofructokinase deficiency. Although this disease is rarer than glycogenosis V, the symptoms of exercise intolerance, clinical course, and inability to convert pyruvate to lactate are identical. The distinction is made by biochemical study of the muscle biopsy specimen. It is transmitted as an autosomal recessive trait at the 1cenq32 locus, and some gene variants are particularly prevalent in the Ashkenazi Jewish population.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

651.4 Mitochondrial Myopathies

Adnan Y. Manzur

See also Chapters 107.4 and 638.2 and Table 651.4.

Several diseases involving muscle, brain, and other organs are associated with structural and functional abnormalities of mitochondria, producing defects in aerobic cellular metabolism, the electron transport chain, and the Krebs cycle (see Table 651.4; Table 651.5). Because mitochondria are found in all cells except mature erythrocytes, the term **mitochondrial cytopathy** is used preferentially to emphasize the multisystemic nature of these diseases. The structural aberrations are best demonstrated by electron microscopy of the muscle biopsy sample, revealing a proliferation of abnormally shaped cristae, including stacked or whorled cristae and paracrystalline structures that occupy the space between cristae and are formed from CK. Muscle biopsies of neonates, infants, and toddlers show more severe involvement of endothelial cells of intramuscular capillaries than of myofibers, unlike the reverse in adults, but endothelial paracrystalline structures are globular rather than brick shaped as in myofibers. The endoplasmic reticulum becomes abnormally adherent to mitochondria. Similar endothelial mitochondrial alterations are seen in the brain in Leigh and other infantile mitochondrial encephalopathies. Histochemical study of the muscle biopsy specimen reveals abnormal clumping of oxidative enzymatic activity and scattered myofibers, with loss of cytochrome-*c* oxidase activity and with increased neutral lipids within myofibers. Ragged red muscle fibers occur in some mitochondrial myopathies, particularly those with a combination of respiratory chain complexes I and IV deficiencies. Accumulations of this membranous material

Table 651.3 Clinical Symptoms and Classification of Muscle Glycogen Storage Diseases

GSD	ENZYMATIC DEFECT	CHROMOSOME	CLINICAL SYNDROME(S)	CHARACTERISTIC FEATURES ON MUSCLE BIOPSY
DEFECTS IN GLYCOGEN METABOLISM				
0	Muscle glycogen synthase	19q13	Cardiomyopathy, exercise intolerance	Lack of glycogen
II (Pompe)	Lysosomal α-1,4-1, 6-glucosidase (acid maltase)	17q25	*Infantile "classic" form:* multiorgan involvement (heart, muscle, liver) *Late-onset form:* myopathy with atrophy and weakness, respiratory insufficiency	PAS-positive vacuoles; secondary changes: increased acid phosphatase reaction, mitochondrial alterations, autophagic vacuoles, neurogenic-like changes
III (Cori-Forbes)	Debranching enzyme (oligo-1,4-1,4-glucanotransferase, amylo-1,6-glucosidase)	1p21	*IIIa:* liver (hepatomegaly, growth retardation, fasting hypoglycemia), myopathy with atrophy and weakness or exercise intolerance *IIIb:* only liver involvement	PAS-positive vacuoles
IV (Andersen)	Branching enzyme (amylo-1,4-1,6-transglucosidase)	3p12	*Congenital form:* myopathy, cardiomyopathy, neuronal involvement *Childhood form:* myopathy, cardiomyopathy *Adult form:* myopathy or APBD	Diastase-resistant PAS-positive deposits; polyglucosan bodies
V (McArdle)	Myophosphorylase	11q13	Exercise intolerance, myopathy with atrophy and weakness (during late disease course), infantile form	PAS-positive deposits; negative phosphorylase staining
IX	Phosphorylase kinase α (muscle) subunit or β-subunit	Xq13 16q13	Exercise intolerance, muscle weakness Liver and muscle involvement	PAS-positive deposits
XIV	Phosphoglucomutase 1	1p31	Exercise intolerance	PAS-positive vacuoles
XV	Glycogenin	3q24	Muscle weakness; cardiac arrhythmia	PAS-positive deposits, polyglucosan bodies
DEFECTS OF GLYCOLYTIC METABOLISM				
VII (Tarui)	Phosphofructokinase (muscle isoform)	12q13.3	Exercise intolerance, chronic hemolysis, infantile form (rare)	PAS-positive deposits; negative PFK staining; polyglucosan bodies
	Phosphoglycerate kinase	Xq13	Exercise intolerance, chronic hemolysis; rare form with CNS involvement (oligophrenia, delayed motor development, epilepsy)	PAS-positive deposits
X	Phosphoglycerate mutase (muscle isoform)	7p12	Exercise intolerance	PAS-positive deposits
XI	Lactate dehydrogenase (muscle isoform)	11p15	Exercise intolerance, dermatologic symptoms	Normal
XII	Aldolase A	16q22-q24	Exercise intolerance, chronic hemolysis	Normal
XIII	β-Enolase	17pter-p12	Exercise intolerance	PAS-positive deposits
	Triosephosphate isomerase		Myopathy with atrophy and weakness, chronic hemolysis	PAS-positive deposits; secondary changes; mitochondrial alterations

APBD, Adult polyglucosan body disease (motor neuron involvement, polyneuropathy, dementia, urinary incontinence); CNS, central nervous system; GSD, glycogen storage disease; PAS, periodic acid–Schiff; PFK, phosphofructokinase.

From Vorgerd M, Deschauer M. Treatment and management of hereditary metabolic myopathies. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management,* 2nd ed. Philadelphia: Elsevier; 2022: Table 23.1, p. 575.

beneath the muscle fiber membrane are best demonstrated by special stains, such as modified Gomori trichrome.

These characteristic histochemical and ultrastructural changes are most consistently seen with point pathogenic variants in mitochondrial transfer RNA. The large mitochondrial DNA (mtDNA) deletions of 5 kb or 7.4 kb (the single mitochondrial chromosome has 16.5 kb) are associated with defects in mitochondrial respiratory oxidative enzyme complexes, if as few as 2% of the mitochondria are affected, but minimal or no morphologic or histochemical changes may be noted in the muscle biopsy specimen, even by electron microscopy. Hence, quantitative biochemical studies of the muscle tissue are needed to confirm the diagnosis. Because most of the subunits of the respiratory chain complexes are encoded by nuclear DNA (nDNA) rather than mtDNA, mendelian autosomal inheritance is possible, rather than maternal transmission as with pure mtDNA point variants. Complex II (succinate dehydrogenase) is the only enzyme complex in which all of its subunits are encoded by nDNA; it is histochemically reactive in all mitochondrial diseases with mtDNA

Table 651.4 Select Mitochondrial Disorders with Hypotonia Classified by Clinical Phenotypes

CLINICAL PHENOTYPE	ASSOCIATED VARIANTS	MODE OF INHERITANCE	COMMON CLINICAL FEATURES
MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes)	tRNA point variants: • m.3243A>G in $tRNA^{Leu}$ (~80% of cases) • m.3217T>C in $tRNA^{Leu}$ (~7.5% of cases) • m.13513G>A encoding NADH-ubiquinone (<15% of cases) • m.3252A>G in $tRNA^{Leu}$ (<5% of cases) • Multiple other mtDNA point variants	Maternal	• *Cardinal*: strokelike episodes, intermittent encephalopathy, T2/FLAIR abnormalities on brain MRI that do not respect vascular territory, lactic acidosis • *Other*: hearing loss, diabetes, short stature, gastrointestinal issues
MERRF syndrome (myoclonic epilepsy with ragged red fibers)	tRNA point variants: • m.8344A>G in $tRNA^{Lys}$ (>80% of cases) • m.8356T>C in $tRNA^{Lys}$ • m.8363G>A in $tRNA^{Lys}$ • m.8361G>A in $tRNA^{Lys}$ • Multiple other mtDNA point variants	Maternal	• *Cardinal:* myoclonus, proximal weakness, generalized epilepsy, ataxia • *Other*: multiple lipomatosis, hearing loss, cognitive impairment, neuropathy
KSS (Kearns-Sayre syndrome)	Single large mtDNA deletion (1.1-10-kb) • m.8470_13446del4977 (deletion of 4977 base pairs; most common) • Multiple other mtDNA deletions	Sporadic	• *Cardinal*: multisystemic disease with progressive external ophthalmoplegia, pigmentary retinopathy, cardiomyopathy before age 20 yr • *Other*: short stature, proximal muscle weakness, hearing loss, dementia, ataxia, multiple endocrinopathies (diabetes, hypothyroidism, hypoparathyroidism, hypogonadism)
CPEO (chronic progressive external ophthalmoplegia)	Single large mtDNA deletion (1.1-10kb)	Sporadic	• *Cardinal*: skeletal muscle disorder with ptosis, ophthalmoparesis, ±proximal muscle weakness
	• m.3243A>G in $tRNA^{Leu}$ (most common; same as MELAS) • Multiple other mtDNA point variants	Maternal	
	• Multiple mtDNA deletions caused by variants in the following nuclear genes: *SLC25A4* encoding ANT1, *C10orf2* encoding twinkle, *POLG1* encoding mtDNA polymerase, *POLG2, OPA1*	Autosomal dominant	
Leigh syndrome (subacute necrotizing encephalomyelopathy)	mtDNA variants: • m.8993T>G or m.8993T>C in *MT-ATP6* (~10% of cases) • Multiple other mtDNA point variants	Maternal	• Hypotonia, spasticity, movement disorders (chorea), cerebellar ataxia, neuropathy, bilateral basal ganglia lesions, seizures, lactic acidosis, psychomotor retardation/regression especially with illness between 3-12 mo of age • Hypertrophic cardiomyopathy
	• m.8470_13446del4977 (deletion of 4977 base pairs; also seen in KSS)	Sporadic	
	Nuclear gene variants resulting in respiratory chain complex deficiencies: • Complex I: *NDUFV1, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS7, NDUFS8, NDUFA1, NDUFA2, NDUFA10, NDUFA9, NDUFA12, NDUFAF2, NDUFAF5, NDUFAF6, FOXRED1* • Complex II: *SDHA, SDHAF1* • Complex III: *BCS1L, UQCRQ, TTC19* • Complex IV: *SURF1, COX10, COX15, SCO2, NDUFA4, PET100, LRPPRC*	Autosomal recessive	

Continued

Table 651.4 Select Mitochondrial Disorders with Hypotonia Classified by Clinical Phenotypes—cont'd

CLINICAL PHENOTYPE	ASSOCIATED VARIANTS	MODE OF INHERITANCE	COMMON CLINICAL FEATURES
NARP (neurogenic muscle weakness, ataxia, retinitis pigmentosa)	• m.8993T>G or m.8993T>C in *MT-ATP6* (50% of cases)	Maternal	• Proximal neurogenic muscle weakness, sensory neuropathy, seizures, ataxia, pigmentary retinopathy, learning difficulties, dementia with onset usually in childhood
Mitochondrial DNA depletion syndrome	• Homozygous or compound heterozygous variants in *TK2* (thymidine kinase 2), a mitochondrial deoxyribonuclease, resulting in mitochondrial depletion	Autosomal recessive	• Hypotonia, proximal muscle weakness, axial weakness, respiratory insufficiency, marked clinical variability with death in infancy to early adulthood due to respiratory insufficiency

FLAIR, Fluid-attenuated inversion recovery; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide, reduced form; tRNA, transfer RNA.
Data from DiMauro S, Hirano M. MERRF. *GeneReviews* [Internet], June 3, 2003. Seattle: University of Washington; DiMauro S, Hirano M. MELAS. *GeneReviews* [Internet]. February 27, 2001. Seattle: University of Washington; Thorburn DR, Rahman S. Mitochondrial DNA-associated Leigh syndrome and NARP. *GeneReviews* [Internet], October 30, 2003. Seattle: University of Washington; Liang C, Ahmad K, Sue CM. The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm. *Biochim Biophys Acta* 2014;1840:1360–1367; Konersman C. Hypotonia, weakness, and stroke. In: Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Symptom-Based Diagnosis*. Philadelphia: Elsevier; 2018: Table 29.11.

Table 651.5 Clinical Spectrum of Mitochondrial Disease

NERVOUS SYSTEM
Hypotonia
Failure to thrive
Motor regression
Stroke (nonvascular)
Dementia
Episodic encephalopathy (elevated cerebrospinal fluid lactate)
Intellectual disability
Neuropathy (axonal, demyelinating, or sensory ganglionopathy)
Ophthalmoparesis (slowly progressive)
Ptosis (slowly progressive; little diurnal variation; asymmetric at onset)
Optic atrophy
Retinitis pigmentosa (perimacular; vision usually spared)
Ataxia
Central apnea
Epilepsy (focal or multifocal myoclonus; status epilepticus; triggered by sodium valproate)
Migraines
Sensorineural hearing loss (asymmetric; young onset; partial recovery possible)
HEART
Cardiomyopathy
Conduction block or arrhythmia
SKELETAL MUSCLE
Myopathy (proximal, symmetric weakness; myalgia)
Exercise intolerance
Episodic rhabdomyolysis
OTHER
Lactic acidosis
Recurrent bowel obstruction (pseudoobstruction)
Short stature
Diabetes (young onset; nonobese)

Data from Amato A, Russell J. *Neuromuscular Disorders*. New York: McGraw-Hill, 2008; Liang C, Ahmad K, Sue CM. The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm. *Biochim Biophys Acta*. 2014;1840:1360–1367.

point variants. Serum lactate is elevated in some diseases, and cerebrospinal fluid lactate is more consistently elevated, even if serum concentrations are normal.

The term primary mitochondrial myopathies encompasses the group of genetic disorders where pathophysiology is impaired oxidative phosphorylation and the primary affected organ is the skeletal muscle. Several distinct or overlapping mitochondrial syndromes that primarily affect striated muscle or muscle and brain are identified. These can be divided clinically, or histopathologically, into the ragged red fiber diseases and non–ragged fiber diseases. The ragged red fiber diseases include Kearns-Sayre, MELAS (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes) syndrome, MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) syndrome, and progressive external ophthalmoplegia syndromes, which are associated with a combined defect in respiratory chain complexes I and IV. The non–ragged fiber diseases include Leigh encephalopathy and Leber hereditary optic atrophy; they involve complex I or IV alone or, in children, the common combination of defective complexes III and V. **Kearns-Sayre syndrome** is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and onset before age 20 years. Heart block, cerebellar deficits, and a high cerebrospinal fluid protein content are often associated. Visual evoked potentials are abnormal. Patients usually do not experience weakness of the trunk or extremities or dysphagia. Most cases are sporadic.

Chronic progressive external ophthalmoplegia may be isolated or accompanied by limb muscle weakness, dysphagia, and dysarthria. A few patients described as having *ophthalmoplegia plus* have additional central nervous system involvement. Autosomal dominant inheritance is found in some pedigrees, but most cases are sporadic.

MERRF and **MELAS syndromes** are other mitochondrial disorders affecting children. The latter is characterized by stunted growth, episodic vomiting, seizures, and recurring cerebral insults causing hemiparesis, hemianopia, or even cortical blindness, and dementia. The disease behaves as a degenerative disorder, and children die within a few years.

Other diseases of the central nervous system that also involve myopathy with mitochondrial abnormalities include **Leigh subacute necrotizing encephalopathy** (see Chapter 107.4) and **cerebrohepatorenal (Zellweger) disease, primarily a peroxisomal disease with secondary mitochondrial alterations** (see Chapter 106.2). Another recognized mitochondrial myopathy is **cytochrome-*c* oxidase deficiency. Oculopharyngeal muscular dystrophy** is also fundamentally a mitochondrial myopathy.

Mitochondrial depletion syndrome of early infancy is characterized by severely decreased oxidative enzymatic activities in most or all five of the complexes; in addition to diffuse muscle weakness, neonates and young infants can show multisystemic involvement, and the syndrome occurs in several forms: myopathic, encephalomyopathic, hepatoencephalopathic, and intestinal encephalopathic. Cardiomyopathy and sometimes bullous skin lesions or generalized edema also can occur.

One myopathic subgroup of mtDNA maintenance defect is related to the *TK2* gene, which encodes for thymidine kinase 2. The clinical presentation is with floppy infant and childhood-onset progressive limb and bulbar myopathy with restrictive lung disease and respiratory failure. The TK2 enzyme phosphorylates nucleosides in the pathway to generate deoxynucleoside triphosphates required for mtDNA replication and maintenance. Raised serum CK together with raised plasma

lactate is a good diagnostic clue, and the diagnosis can be confirmed by documenting autosomal recessive variants in the *TK2* gene. This group is of particular interest because of the potential for treatment with pyrimidine deoxynucleosides.

Alpers syndrome is genetically homogeneous and is caused by mtDNA depletion and variants in the *POLG1* gene. Several other genes are identified, mostly in later-onset forms; hence, mitochondrial depletion is a syndrome and not a single disease. **Barth syndrome** is an X-linked recessive mitochondrial disorder characterized by cardiomyopathy, myopathy of striated muscle, growth retardation, neutropenia, and high serum and urinary concentrations of 3-methyl-glutaconic acid.

Many rare diseases with only a few case reports are suspected of being mitochondrial disorders. It is also now recognized that secondary mitochondrial defects occur in a wide range of nonmitochondrial diseases, including inflammatory autoimmune myopathies, Pompe disease, and some cerebral malformations, and also may be induced by certain drugs and toxins, so that interpretation of mitochondrial abnormalities as primary defects must be approached with caution.

INVESTIGATIONS

Investigation for mitochondrial cytopathies begins with serum lactate. Lactic acid is not increased in all mitochondrial cytopathies, so that a normal result is not necessarily reassuring; cerebrospinal fluid lactate is increased in some cases in which serum lactate is normal, particularly if there are clinical signs of encephalopathy. Serum 3-methyl-glutaconic acid often is increased in mitochondrial cytopathies in general, demonstrated in more than 50 different genetic pathogenic variants, and is a good screening measurement; it rarely is increased in other metabolic diseases. This product may also be increased in urine. Hepatic enzymes (transaminases) should be measured in blood. Cardiac evaluation is often warranted. Molecular markers in blood for the common diseases with known mtDNA point variants identify many of the mitochondrial cytopathies presenting in adult life or adolescence, but less frequently in children and least in young infants. MRI of the brain may reveal hyperintense lesions of the basal ganglia and MR spectroscopy can demonstrate an increased lactate peak. The muscle biopsy provides the best evidence of all mitochondrial myopathies and should include histochemistry for oxidative enzymes, electron microscopy, and quantitative biochemical assay of respiratory chain enzyme complexes and coenzyme Q10; muscle tissue also can be analyzed for mtDNA. Many mitochondrial disorders also can affect the Schwann cells and axons of peripheral nerves and present clinically with neuropathy; hence, motor and sensory nerve conduction velocities can be measured in selected patients. Sural nerve biopsy is required only rarely if neuropathy is the predominant finding, and the diagnosis is not evident from other studies.

A diagnostic approach is noted in Figure 651.1.

TREATMENT

There is no effective treatment for majority of the mitochondrial cytopathies, but various *cocktails* are often used to try to overcome the metabolic deficits (see Chapter 638.2).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

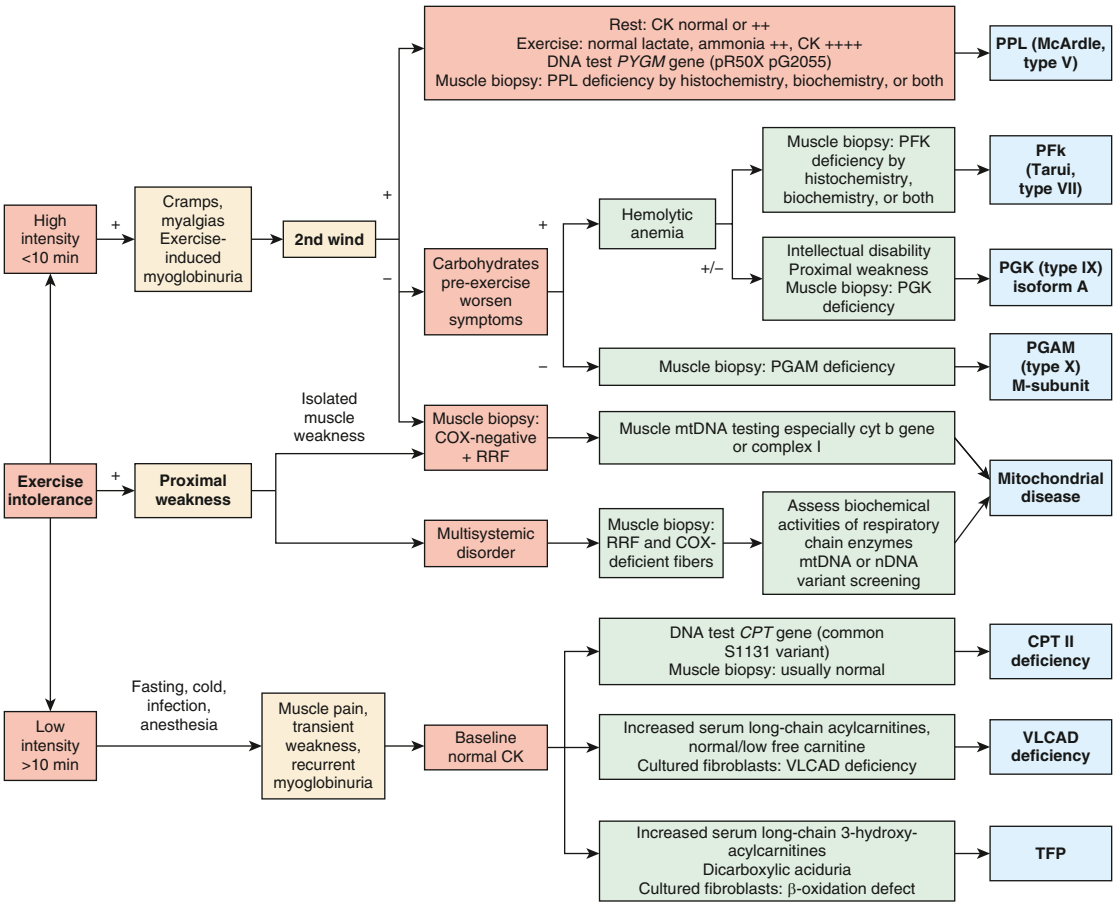

Fig. 651.1 Clinical diagnostic algorithm for patients with exercise intolerance in whom a metabolic myopathy is suspected. CK, Creatine kinase; COX, cytochrome-c oxidase; CPT, carnitine palmitoyltransferase; cyt *b*, cytochrome *b*; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; PFk, phosphofructokinase; PGAM, phosphoglycerate mutase; PGK, phosphoglycerate kinase; PPL, myophosphorylase; RRF, ragged red fibers; TFP, trifunctional protein deficiency; VLCAD, very long-chain acyl-coenzyme A dehydrogenase. *(From Berardo A, Di Mauro S, Hirano M. A diagnostic algorithm for metabolic myopathies. Curr Neurol Neurosci Rep. 2010;10:118–126. Fig. 1.)*

651.5 Lipid Myopathies

Adnan Y. Manzur

See Chapter 106.4.

Skeletal muscles are the most important sites in the body for long-chain fatty acid metabolism because of their large mass and their rich density of mitochondria where fatty acids are metabolized. Fatty acids are the major source of energy for skeletal muscle during sustained exercise or fasting. Hereditary disorders of lipid metabolism that cause progressive myopathy are an important, relatively common, and often treatable group of muscle diseases (Table 651.6). Increased lipid within myofibers is seen in the muscle biopsy of some mitochondrial myopathies and is a constant, rather than an unpredictable, feature of specific diseases. Among the ragged red fiber diseases, Kearns-Sayre syndrome always shows increased neutral lipid, whereas MERRF and MELAS syndromes do not, a useful diagnostic marker for the pathologist. Free fatty acids are converted to acyl-coenzyme A by fatty acyl-coenzyme A synthetases; the resulting long-chain fatty acids bind to carnitine and are transported into mitochondria where β-oxidation is carried out. Disorders of lipid fuel utilization and lipid storage disorders can be divided into defects of transport and oxidation of exogenous fatty acids within mitochondria and defects of endogenous triglyceride catabolism.

Muscle carnitine deficiency is an autosomal recessive disease caused by pathologic variants in the *SLC22A5* gene, involving deficient transport of dietary carnitine across the intestinal mucosa. Carnitine is acquired from dietary sources but is also synthesized in the liver and kidneys from lysine and methionine; it is the obligatory carrier of long- and medium-chain fatty acids into muscle mitochondria.

The clinical course may be one of sudden exacerbations of weakness or can resemble a progressive muscular dystrophy with generalized proximal myopathy and sometimes facial, pharyngeal, and cardiac involvement. Symptoms usually begin in late childhood or adolescence or may be delayed until adult life. Progression is slow but can end in death.

The serum CK level is mildly elevated. Muscle biopsy material shows vacuoles filled with lipid within muscle fibers in addition to nonspecific changes suggestive of a muscular dystrophy. Mitochondria can appear normal or abnormal. Carnitine measured in muscle biopsy tissue is reduced, but the serum carnitine level is normal.

Treatment stops the progression of the disease and can even restore lost strength if the disease is not too advanced. It consists of special diets low in long-chain fatty acids. Steroids can enhance fatty acid transport. Specific therapy with L-carnitine taken orally in large doses overcomes the intestinal barrier in some patients. Some patients also improve when given supplementary riboflavin, and other patients seem to improve with propranolol.

Systemic carnitine deficiency is a disease of impaired renal and hepatic synthesis of carnitine rather than a primary myopathy. Patients with this autosomal recessive disease experience progressive proximal myopathy and show muscle biopsy changes similar to those of muscle carnitine deficiency; the onset of weakness is earlier and may be evident at birth. Endocardial fibroelastosis can also occur. Episodes of acute hepatic encephalopathy resembling Reye syndrome can occur. Hypoglycemia and metabolic acidosis complicate acute episodes. Cardiomyopathy may be the predominating feature in some cases and result in death.

Cerebral infarctions and myopathy occur in children, particularly when accompanied by hypoglycemia. The mean age at presentation is approximately 9 years. A brain MRI shows distinctive changes related to multiple infarcts of various sizes.

The concentration of carnitine is reduced in serum as well as in muscle and liver. L-Carnitine deficiency can be corrected by oral administration of carnitine on a daily basis.

A similar clinical syndrome may be a complication of renal Fanconi syndrome because of excessive urinary loss of carnitine or loss during chronic hemodialysis.

Treatment with L-carnitine improves the maintenance of blood glucose and serum carnitine levels but does not reverse the ketosis or acidosis or improve the exercise capacity.

Muscle CPT deficiency manifests as episodes of cramps after exercise, rhabdomyolysis, coma, and elevated serum CK levels. It is the most commonly identified cause of recurrent myoglobinuria in adults, but myoglobinuria is not a constant feature. CPT transfers long-chain fatty acid acyl-coenzyme A residues to carnitine on the outer mitochondrial membrane for transport into the mitochondria. Exercise intolerance and myoglobinuria resemble glycogenoses V and VII. The degree of exercise that triggers an attack varies among individuals, ranging from casual walking to strenuous exercise. Fasting hypoglycemia can occur. Some patients present only in late adolescence or adult life with myalgias. Genetic transmission is autosomal recessive and is caused by a defect on chromosome 1 at the 1p32 locus. Administration of valproic acid can precipitate acute rhabdomyolysis with myoglobinuria in patients with CPT deficiency; it should be avoided in the treatment of seizures or migraine if they occur. Treatment includes a low fat, high carbohydrate diet. *Very long-chain acyl-coenzyme A dehydrogenase deficiency* has a similar clinical presentation but mainly with adult onset.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

651.6 Vitamin E Deficiency Myopathy

Adnan Y. Manzur

Deficiency of vitamin E (α-tocopherol, an antioxidant also important in mitochondrial superoxide generation) may produce a progressive myopathy closely resembling a muscular dystrophy. Myopathy and neuropathy are recognized in humans who lack adequate intake of this antioxidant. Patients with chronic malabsorption, those undergoing long-term dialysis, and premature infants who do not receive vitamin E supplements are particularly vulnerable. Treatment with high doses of vitamin E can reverse the deficiency. Myopathy caused by chronic hypervitaminosis E also occurs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 651.6 Defects of Lipid Metabolism Resulting in Myopathy

BIOCHEMICAL DEFECT	AFFECTED GENE(S)	TYPICAL MUSCLE PHENOTYPE	CHARACTERISTIC CHANGES OF ACYL-CARNITINE SPECTRUM IN BLOOD	MUSCLE HISTOLOGY
Carnitine palmitoyltransferase II deficiency	*CPT II*	Attacks with myoglobinuria	C16:0 and C18:1 carnitine elevated	Often normal interictally
Multiple acyl-coenzyme A (CoA) dehydrogenase deficiency (glutaric aciduria type 2)	*ETFDH*, *ETFA*, or *ETFB*	Permanent muscle weakness	Multiple acyl-carnitines (C4–C18:1) elevated	Lipid storage
Medium-chain acyl-CoA dehydrogenase deficiency	*MCAD*	Attacks with myoglobinuria; permanent muscle weakness	C8 carnitine elevated	Lipid storage
Very long-chain acyl-CoA dehydrogenase deficiency	*ACADVL*	Attacks with myoglobinuria	C14:1 carnitine elevated	Often normal interictally
Primary muscle carnitine deficiency	Unknown	Permanent muscle weakness	Carnitine rarely reduced	Lipid storage
Primary systemic carnitine deficiency (carnitine transporter defect)	*SLC22A5 (OCTN2)*	Hypotonia, cardiomyopathy	Carnitine reduced	Lipid storage
Trifunctional protein deficiency (deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase, long-chain 2-enoyl-CoA hydratase, and long-chain 3-ketoacyl-CoA thiolase)	*HADHA* and *HADHB*	Attacks with myoglobinuria	3-hydroxy C16 and C18 acylcarnitine elevated (can be normal interictally)	Often normal interictally
Short-chain acyl-CoA dehydrogenase deficiency	*ACADS*	Hypotonia	C4 carnitine elevated	Sometimes lipid storage
Neutral lipid storage disease with ichthyosis	*ABHD5 (GCI58)*	Permanent muscle weakness	Normal	Abundant lipid storage
Neutral lipid storage disease with myopathy	*PNPLA2*	Permanent muscle weakness	Normal C16:0, C18:0, C18:1	Abundant lipid storage
Carnitine-acylcarnitine-translocase deficiency (CACT deficiency)	*SLC25A20*	Hypotonia	C18:2 carnitine elevated	Not reported
Lipin deficiency	*LPIN1*	Attacks of myoglobinuria, permanent muscle weakness	C14:1 carnitine elevated	Normal interictally
Long-chain acyl-CoA deficiency (LCAD deficiency)	*ACADL*	Attacks of myoglobinuria, permanent muscle weakness	C4 carnitine elevated	Normal interictally
Short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (SCHAD deficiency)	*HADH*	Attacks of myoglobinuria, permanent muscle weakness	C4 carnitine elevated	Often normal interictally
Medium-chain 3-ketoacyl-CoA thiolase (MCKAT deficiency)	*MCKAT*	Attacks of myoglobinuria	C12–C16 carnitine elevated	Not reported

From Vorgerd M, Deschauer M. Treatment and management of hereditary metabolic myopathies. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management*, 2nd ed. Philadelphia: Elsevier; 2022: Table 23.2, p. 582.

Chapter 652

Disorders of Neuromuscular Transmission and of Motor Neurons*

652.1 Myasthenia Gravis

Adnan Y. Manzur

AUTOIMMUNE MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a chronic autoimmune disease of the postsynaptic end plate leading to abnormal neuromuscular transmission or blockade, characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing. It must be distinguished from congenital myasthenic syndrome, a genetic disorder of receptors on the presynaptic and postsynaptic membranes, as well as the synapse of the neuromuscular junction and toxin-induced disorders of neurotransmission, such as botulism (see later). In MG, the release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane (i.e., *sarcolemma*) or *motor end plate* is less responsive than normal. This is due to antibodies against the postsynaptic acetylcholine receptor (AChR), leading to an abnormal architecture/folding pattern of the postsynaptic membrane, as well as a decreased number of receptors to which ACh can bind.

Infants born to *myasthenic mothers* can have a **transient neonatal myasthenic syndrome** secondary to placentally transferred anti-AChR antibodies, distinct from congenital myasthenic syndromes (Tables 652.1-652.3).

Clinical Manifestations

The age of onset for *immune-mediated* MG ranges anywhere from 11 months to 17 years of age. In the prepubertal age-groups, the female:male ratio is about 1.5:1, and in the postpubertal age-groups, the female:male ratio is about 1:1 (Table 652.4). In juvenile autoimmune MG, unilateral or bilateral but usually *asymmetric ptosis* and some degree of extraocular muscle weakness are the earliest and most constant signs. Extraocular weakness is not confined to muscles innervated by just one or two of the three corresponding brainstem nuclei; it is progressive. Older children might complain of diplopia, and young children might hold open their eyes with their fingers or thumbs if the ptosis is severe enough to obstruct vision. Pupillary responses to light are preserved. Dysphagia and facial weakness also are common and, in early infancy, feeding difficulties are frequent as the cardinal sign of myasthenia; in severe cases, aspiration and airway obstruction may occur. Poor head control because of weakness of the neck flexors may be prominent. Involvement initially may appear to be limited to bulbar-innervated muscles, but the disease can be systemic and progressive weakness eventually involves limb-girdle muscles and distal muscles of the hands in many cases. Fasciculations of muscle, myalgias, and sensory symptoms do not occur. Tendon stretch reflexes may be diminished but rarely are lost. *Ocular MG may prove to be transitory over time, but in some patients, weakness never progresses to involve the axial or appendicular muscles.* This disorder accounts for approximately 25% of all juvenile MG patients and is most frequent in children of Chinese and southeastern Asian descent, suggesting an ethnic genetic predisposition. In addition, prepubertal patients are more likely to have *ocular only* myasthenia, whereas a majority of postpubertal patients with myasthenia will have generalized symptoms.

Rapid fatigue of muscles is a characteristic feature of MG that distinguishes it from most other neuromuscular diseases. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30-90 seconds. Holding the head up from the surface of the examining table while lying supine is very difficult (indicative of neck flexion weakness), and gravity cannot be overcome for more than a few seconds. Repetitive opening and closing of the fists produces rapid fatigue of hand muscles, and patients cannot elevate their arms for more than 1-2 minutes because of fatigue of the deltoids. Patients are more symptomatic late in the day or when tired. Dysphagia can interfere with eating, and the muscles of the jaw soon tire when an affected child chews. Reviewing activities of daily living helps determine the severity of symptoms (Table 652.5). Additional triggers for exacerbation of weakness may include heat and intercurrent illness. Application of cold packs over the eyes will reverse ptosis.

Left untreated, MG is usually progressive and can become life-threatening because of respiratory muscle involvement and the risk of aspiration, particularly at times when the child is otherwise unwell, as during an upper respiratory tract infection. Familial myasthenia (congenital myasthenic syndrome) usually is not progressive, but may vary in severity from milder forms, limb-girdle forms, to more severe forms, including those with respiratory failure.

Myasthenic crisis is an acute or subacute severe increase in weakness in patients with MG, usually precipitated by an intercurrent infection, surgery, or even emotional stress. It may require intravenous cholinesterase inhibitors, immunoglobulin, plasma exchange, gavage feeding, and even transient ventilator support. It must be distinguished from **cholinergic crisis** secondary to overdosing with anticholinesterase medications. The muscarinic effects include abdominal cramps, diarrhea, profuse sweating, salivation, bradycardia, increased weakness, and miosis. Cholinergic crisis requires only supportive care and withholding of further doses of cholinergic drugs, and it passes within a few hours; the dose of medication to be restarted should be reconsidered, unless the patient had taken an overdose that was not prescribed.

Approximately 70–80% of adolescents with immune-mediated MG will have elevated AChR antibodies, but anti-AChR antibodies are only occasionally demonstrated in the plasma of prepubertal children. Some with negative titers of anticholinesterase exhibit anti–muscle-specific tyrosine kinase (MuSK) circulating antibodies. MuSK is localized at the neuromuscular junction and appears essential to fetal development of this junction. Additional autoantibodies related to immune MG include LRP4, titin, and ryanodine receptor (RyR) antibodies. In some patients, no antibody is detected (unknown MG etiology).

Infants born to myasthenic mothers can have respiratory insufficiency, inability to suck or swallow, and generalized hypotonia and weakness, a syndrome typically referred to as transient neonatal myasthenia. They might show little spontaneous motor activity for several days to weeks. The onset of symptoms typically occurs within the first 1-3 days of life. Some require ventilatory support and feeding by gavage during this period. Some patients may also require pyridostigmine (acetylcholinesterase [AChE] inhibitor) management transiently. After the abnormal antibodies disappear from the blood and muscle tissue, these infants regain normal strength and are not at increased risk of developing MG in later childhood. Patients usually show full recovery by about 2 months of age. A small minority develops *fetal akinesia sequence* with multiple joint contractures *(arthrogryposis)* that develop in utero from lack of fetal movement. AChR antibodies can usually be demonstrated in maternal blood, but at times maternal antibodies may not be detected. Rates of transient neonatal myasthenia are estimated to be as high as 10–20% of infants born to mothers with MG.

CONGENITAL MYASTHENIC SYNDROMES

A heterogeneous group of genetic diseases of neuromuscular transmission is collectively called **congenital myasthenic syndromes (CMSs).** The etiology and pathogenesis of these syndromes are unrelated to either transitory neonatal myasthenia caused by placental transfer of

*The editors are grateful to Dr. Diana X. Bharucha-Goebel and Dr. Goknur Haliloglu, much of whose work on previous editions of this chapter is retained here.

Table 652.1 Congenital Myasthenic Syndromes: Subtypes and Distinguishing Clinical Features

CMS SUBTYPE[1]		% OF ALL CMS	GENE(S)[2]	DISTINGUISHING CLINICAL FEATURES	RESPONSE TO ACHE INHIBITORS
Postsynaptic CMS	Acetylcholine receptor (AChR) deficiency	50%[3]	*CHRNA1* *CHRNB1* *CHRND* *CHRNE*	*AChR deficiency (AR)* • Early onset • Mild to severe • Ptosis, EOP; bulbar, arm, leg weakness	Improvement
	Slow-channel CMS (SCCMS)			*SCCMS (AD)* • Selective severe neck, wrist, finger extensor weakness • Childhood to adult onset • Mild to severe • Progressive ventilatory insufficiency; may require assisted ventilation	Deterioration
	Fast-channel CMS (FCCMS)			FCCMS (AR): Mild to severe	Improvement
	Defect in AChR clustering pathway	15–20%	*RAPSN*	*Early onset* • Hypotonia, respiratory failure at birth • Episodic apnea • Arthrogryposis multiplex congenita • Mild to severe *Late onset:* • Limb weakness in adolescence or adulthood; as in seronegative myasthenia gravis	Improvement
		10–15%	*DOK7*	Limb-girdle pattern of predominantly proximal weakness, waddling gait, and ptosis but no EOP	Deterioration or ineffective
		<1%	*LRP4*	Respiratory failure at birth, delayed motor milestones, ptosis, ophthalmoparesis, limb weakness	See footnote 4
		<1%	*MUSK*	*Broad phenotype* • Prenatal onset with fetal akinesia deformation sequence • Early onset with ophthalmoplegia and respiratory failure • Isolated vocal cord paralysis • Late-onset limb-girdle weakness	Deterioration or ineffective
	Plectin deficiency	<1%	*PLEC*	*Childhood to adulthood onset:* • Fatigable proximal myopathy and ptosis • With or without skin blistering	Improvement
	Defect in skeletal muscle voltage-gated sodium channel	<1%	*SCN4A*	Phenotype overlapping with *SCN4A*-associated skeletal muscle sodium channelopathies: periodic paralysis, myotonia, myopathy	See footnote 4
Synaptic CMS	End plate AChE deficiency	10–15%	*COLQ*	• Often severe • In some with C-terminal missense pathogenic variants: later presentation, milder clinical course • EOP • General muscle weakness/severe involvement of axial muscles • Slow pupillary light response	Deterioration or ineffective
		1–2%; >14 independent kinships reported	*COL13A1*	• At birth, respiratory distress and dysphagia; may resolve • Recurrent apnea triggered by infections • In adulthood, bilateral nonfatigable ptosis and marked axial weakness • Sometimes improvement of muscle weakness by adulthood	Likely ineffective
	Defects in AChR clustering pathway	<1%	*AGRN*	• Early-onset or late-onset phenotype • Persons with late onset may present with distal muscle weakness and wasting in addition to myasthenia	Deterioration

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 23, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 652.1 Congenital Myasthenic Syndromes: Subtypes and Distinguishing Clinical Features—cont'd

CMS SUBTYPE[1]		% OF ALL CMS	GENE(S)[2]	DISTINGUISHING CLINICAL FEATURES	RESPONSE TO ACHE INHIBITORS
Presynaptic CMS	Defect in ACh synthesis	4–5%	*CHAT*	• Hypotonia, respiratory failure at birth • Episodic apnea • Improvement with age	Improvement
	Defects in ACh recycling	<1%	*SLC5A7*	• Early onset • More severe than *CHAT*-related CMS • Arthrogryposis/joint contractures, apneic crisis at birth, marked ptosis, ophthalmoplegia, and muscle fatigability • Some have limited survival, some have milder phenotypes. • Some with learning difficulties	Some improvement
		<1%	*SLC18A3*	Similar to *SLC5A7*	Some improvement
	Defects in synaptic vesicle docking, priming, fusing, and exocytosis	<1%	*SNAP25*	Myasthenia is element of a severe and complex phenotype: • Developmental and epileptic encephalopathy of infancy and childhood with diverse clinical manifestations • Severe ID, cerebellar ataxia, brain atrophy	See footnote 4
		<1%	*VAMP1*	• Early-onset phenotype with severe congenital hypotonia and muscle weakness, feeding difficulties, delayed motor development, ophthalmoparesis. • May have joint contractures or joint laxity • May have respiratory insufficiency	Likely improvement[4]
		<1%	*SYT2*	• AR: Severe congenital-onset hypotonia and weakness, with variable degrees of respiratory involvement; mimics severe congenital myopathy • AD: Mimics distal hereditary motor neuropathy, slowly progressive distal motor neuropathy, and myasthenic syndrome	See footnote 4
		<1%	*PREPL*	• Congenital hypotonia, feeding difficulties, ptosis, and proximal muscle weakness • Growth hormone deficiency • See footnote 5	ACh inhibitors possibly beneficial in infancy[4]
	Defects in axonal transport of proteins	<1%	*MYO9A*	• Early-onset, ptosis, ophthalmoplegia and moderate global weakness, bulbar involvement, respiratory crises • Additional CNS symptoms: ID or learning difficulties, nystagmus, oculomotor apraxia	Improvement[4]
	Defect in mitochondrial citrate carrier	<1%	*SLC25A1*	• Relatively mild CMS phenotype with ID • Subtle mitochondrial abnormalities	Improvement[4]
Pre- and postsynaptic CMS	Limb-girdle myasthenia with glycosylation deficiency	<1%	*ALG2* *ALG14*	Overlap with CDG syndromes	See footnote 4
		1–2%	*DPAGT1* *GFPT1* *GMPPB*	• "Limb-girdle" pattern of weakness with predominantly proximal weakness but usually no ptosis or EOP; tubular aggregates on muscle biopsy in some • ID may occur in *DPAGT1*-associated CMS • *GMPPB* associated with high CK and muscular dystrophy	Improvement

[1]CMS subtypes are grouped by site of defect and mechanism of neuromuscular junction defect.

[2]Additional genes are published as CMS genes or genes with an underlying pathology of the neuromuscular junction, but to date have been reported in only one or two studies. These genes include: postsynaptic proteins *RPH3A*, *MACF1*, and *CHD8*; synaptic proteins *LAMA5*, *LAMB2*, and *UNC13A*; as well as *TOR1AIP1* (encoding the inner nuclear membrane protein, lamin-associated protein 1), and *DES* (the muscle-specific member of the intermediate filament protein family linking the contractile apparatus to the sarcolemmal cytoskeleton, cytoplasmic organelles, and nucleus). *Note:* Neuromuscular end plate pathology has been associated with autosomal recessive loss-of-function variants in *DES* rather than autosomal dominant variants (associated with *DES*-related myopathies).

[3]*CHRNE* is by far the most common causative gene among the AChR-subunit genes *CHRNA1*, *CHRNB1*, *CHRND*, and *CHRNE*.

[4]No or limited data; small number of reported individuals.

[5] Additional non-myasthenic features (cystinuria, learning difficulties, endocrinologic defects, hyperphagia with tendency to obesity) may be associated with homozygous deletions of the two contiguous genes *PREPL* and *SLC3A1* on chromosome 2p21 (hypotonia-cystinuria syndrome; OMIM 606407).

ACh, Acetylcholine; AChE, acetylcholinesterase; AD, autosomal dominant; AR, autosomal recessive; CDG, congenital disorders of glycosylation; CMS, congenital myasthenic syndrome; CNS, central nervous system; EOP, external ophthalmoplegia; ID, intellectual disability.

Modified from Abicht A, Muller JS, Lochmuller H. Congenital myasthenic syndromes overview. In: *GeneReviews* [Internet]. Seattle (WA): University of Washington. 2003 May 9 [updated 2021 Dec 23]. Table 1.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 23, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 652.2 Differential Diagnosis of Myasthenia Gravis

DIAGNOSIS	SIMILARITIES	DIFFERENCES	DIAGNOSTIC TEST
Spinal muscular atrophy	Floppy infant or child with muscle weakness Respiratory and bulbar involvement Contractures (SMA1)	Absence of ptosis, and facial weakness Absent deep tendon reflexes Presence of tongue fasciculation, polyminimyoclonus	SMA genetics
Congenital myotonic dystrophy	Floppy infant or child with muscle weakness Respiratory and bulbar involvement Contractures Ptosis and facial weakness	Mother affected with myotonic dystrophy (may be undiagnosed) EMG shows no decrement on RNS or abnormal jitter/block	Myotonic dystrophy genetics
Congenital myopathy/ muscular dystrophy	Floppy infant or child with muscle weakness Respiratory and bulbar involvement Contractures Facial weakness May have ptosis	Characteristic muscle biopsy abnormalities EMG shows no decrement on RNS or abnormal jitter/block	Muscle biopsy Muscle MRI Genetics
Mitochondrial myopathy	Floppy infant or child with muscle weakness Respiratory and bulbar involvement Contractures Ptosis and facial weakness	May have other system involvement EMG shows decrement on RNS or abnormal jitter/block	Muscle biopsy Genetics
Myasthenia gravis	Fatigable muscle weakness Respiratory and bulbar involvement Ptosis and facial weakness EMG shows decrement on RNS or abnormal jitter/block	Age of onset (rare before 12 mo) Absence of family history Absence of ankle-dorsiflexion weakness Ptosis can be asymmetric	Antibody (RIA and cell-based assay if available) AChR, MuSK, and LRP4
Neonatal myasthenia gravis	Floppy neonate with muscle weakness Respiratory and bulbar involvement Ptosis and facial weakness EMG shows decrement on RNS or abnormal jitter/block	Mother with myasthenia gravis (may be undiagnosed)	Antibody testing of the mother
Limb-girdle muscular dystrophy	Proximal muscle weakness Respiratory involvement Positive family history	EMG shows no decrement on RNS or abnormal jitter/block	Muscle biopsy Muscle MRI Genetics
Chronic fatigue syndrome	History of fatigability with gross motor and fine motor activities	Clear period of prior normal motor function before onset of symptoms Absence of: muscle weakness of formal assessment; ptosis or facial weakness; EMG abnormalities	Clinical diagnosis
Hypermobility syndromes	History of "fatigability" with gross motor and fine motor activities	Absence of: muscle weakness on formal assessment; ptosis or facial weakness; EMG abnormalities	Clinical diagnosis

EMG, Electromyography; RNS, repetitive nerve stimulation; RIA, radioimmunoassay.
From Ramdas S, Beeson D. Congenital myasthenic syndromes: where do we go from here? *Neuromusc Dis.* 2021;31:943–1954. Table 1.

Table 652.3 Typical Distribution of Ocular Symptoms in Different Hereditary and Autoimmune Disorders Involving the Extraocular Muscles

	PTOSIS	OPHTHALMOPARESIS	DIPLOPIA	ASYMMETRY
CONGENITAL MYASTHENIC SYNDROME				
Presynaptic	Yes	No	Rare	No
Synaptic	Yes	Yes	No	No
Postsynaptic	Yes	Yes	Rare	No
Progressive external ophthalmoplegia (mitochondrial deletion syndrome)	Yes	Yes	No	Rare
Myotonic dystrophy	Yes	No	No	No
Autoimmune Lambert-Eaton myasthenic syndrome	Yes	Yes	Yes	Yes
Autoimmune acetylcholine receptor-positive myasthenia gravis	Yes	Yes	Yes	Yes
Autoimmune MuSK-positive myasthenia gravis	Yes	Yes	Yes	Yes
Orbital myositis	Rare	Yes	Yes	Yes
Thyroid orbitopathy	No	Yes	Yes	Yes

From Punga AR, Maddison P, Heckmann JM, et al. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. *Lancet Neurol.* 2022;23:176–185. Table 2.

Table 652.4 Pathophysiologic Characteristics of Myasthenia Gravis Subtypes

	ACETYLCHOLINE RECEPTOR MYASTHENIA GRAVIS SUBTYPES			MuSK MYASTHENIA GRAVIS	LRP4 MYASTHENIA GRAVIS	AGRIN MYASTHENIA GRAVIS	SERONEGATIVE MYASTHENIA GRAVIS	LAMBERT-EATON MYASTHENIC SYNDROME SUBTYPES		SERONEGATIVE LAMBERT-EATON MYASTHENIC SYNDROME
	EARLY-ONSET ACETYLCHOLINE RECEPTOR ANTIBODY-POSITIVE MYASTHENIA GRAVIS (ASSOCIATED WITH THYMIC FOLLICULAR HYPERPLASIA)	*THYMOMA-ASSOCIATED MYASTHENIA GRAVIS*	*LATE-ONSET, NON-THYMOMATOUS ACETYLCHOLINE RECEPTOR ANTIBODY-POSITIVE MYASTHENIA GRAVIS*					*NON-PARANEOPLASTIC (40–50%)*	*PARANEOPLASTIC SMALL-CELL LUNG CANCER (50–60%)*	
Antigenic target	Acetylcholine receptor	Acetylcholine receptor	Acetylcholine receptor	MuSK	LRP4	Agrin	Unknown	$Ca_V2{\cdot}1$ VGCCs (P/Q-type)	$Ca_V2{\cdot}1$ VGCCs (P/Q-type)	Unknown
Age at onset	<50 yr	Peak age 50 yr	>50 yr	<50 yr	Early onset	Unknown	Unknown	Bimodal (young females, older males)	>50 yr	Unknown
Gender bias	Yes (Female)	No	Yes (Male)	Yes (Female)	Yes (Female)	Unknown	Yes (Female)	No	Yes (Male)	Unknown
Dominant IgG isotype	IgG1-IgG3	IgG1-IgG3	IgG1-IgG3	IgG4	IgG1-IgG3	Unknown	Unknown	Potentially IgG1-IgG3	Potentially IgG1-IgG3	Unknown
Role of complement	Yes	Yes	Yes	No	Yes	Unknown	Unknown	Potentially yes	Potentially yes	Unknown
HLA association	DR3–B8	No	No consistent association	DR14–DQ5	Unknown	Unknown	Unknown	DR3–B8 and DQ2	No	Unknown
Tumor association	No	Thymoma	No	No	Unknown	Unknown	Unknown	No	Small cell lung cancer	Unknown

Most (about 85%) patients with myasthenia gravis have acetylcholine receptor autoantibodies. MuSK, LRP4, and agrin antibody-positive myasthenia gravis variants are much less prevalent (about 5%, 2%, and <1% of patients with myasthenia gravis, respectively). About 8% of patients with myasthenia gravis are seronegative for all these antibodies. About 15% of patients with Lambert-Eaton myasthenia gravis are seronegative (i.e., they have no detectable VGCC antibodies). Class I direct evidence: Patient antibodies are pathogenic upon passive transfer to animals or upon application in in vitro models. Class II indirect evidence: Active immunization with the antigen causes a myasthenia gravis phenotype in animals or transplacental transfer causes a temporary phenotype
in children. Class III circumstantial evidence: Pathogenicity is expected based on the biological role of the antigen or positive response to immunosuppressive treatments, although direct experimental evidence is lacking. Gender bias refers to overrepresentation of the syndrome in one of two sexes.

HLA, Human leukocyte antigen; LRP4, low-density lipoprotein receptor-related protein 4; MuSK, muscle-specific tyrosine kinase; NA, not applicable; VGCCs, voltage-gated calcium channels.

From Huijbers MG, Marx A, Plomp JJ, et al. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders. *Lancet Neurol*. 2022;21:163–174.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 23, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 652.5 Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

GRADE	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking, modifications in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant
TOTAL MG-ADL SCORE				

MG-ADL, Myasthenia Gravis Activities of Daily Living Scale.
From Wolfe GI, Herbelin L, Nations SP, et al. Myasthenia gravis activities of daily living profile. *Neurology*. 1999;52:1487–1489.

maternal antibodies or to autoimmune MG, despite overlap of clinical symptoms. CMSs are nearly always *permanent static* disorders without spontaneous remission (see Table 652.1). Several distinct genetic forms are recognized, nearly all with onset at birth or in early infancy with symptoms that may include hypotonia, external ophthalmoplegia, ptosis, dysphagia, weak cry, facial weakness, easy muscle fatigue generally, and sometimes respiratory insufficiency or failure, the last often precipitated by a minor respiratory infection. In the childhood-onset forms, findings such as fatigability, delayed motor milestones, and fluctuating ocular symptoms (ptosis and extraocular muscle weakness) are common. Cholinesterase inhibitors have a favorable effect in most, but in some forms the symptoms and signs are actually worsened. Children with most types of congenital MG do not experience myasthenic crises and rarely exhibit elevations of anti-ACh antibodies in plasma.

Pathologic gene variants responsible for CMS have been identified in over 30 different genes. The genetic variants are known in *less than half* of children with CMS. The most common genes associated with CMS include *CHAT, CHRNE, DOK7, COLQ, GFPT,* and *RAPSN*. CMS can be caused by pathogenic variants affecting proteins involved in ACh synthesis, vesicle fusion into the synaptic cleft, ACh breakdown in the synaptic cleft, and reuptake of choline, within subunits of the postsynaptic AChR, as well as in postsynaptic glycosylation pathways. Basal lamina-associated proteins can lead to synaptic cleft abnormalities due to variants in the *COLQ, COL13A1,* and *LAMB2* genes. These pathways emphasize the role of the integrity of the extracellular matrix proteins in the formation and maintenance of the synapse. Anti-AChR and anti-MuSK antibodies are usually, but not always, absent in serum, unlike in autoimmune forms of MG affecting older children and adults.

There may be clinical clues that aid in the diagnosis (see Tables 652.1 and 652.3). In patients with apneic episodes, consider *RAPSN, CHAT,* and *COLQ*. Apneic episodes in patients with choline acyltransferase (CHAT) variants can be episodic but can also be life-threatening. Although most CMS syndromes are inherited in a recessive fashion, there are several in which an autosomal dominant pattern of inheritance or de novo dominant pattern of inheritance can be seen, including *CHRNA1, CHRNB1, CHRND, CHRNE,* and *SYT2*. Variants in the *RAPSN* gene can lead to an early-onset hypotonia with respiratory failure and episodic apnea but can also present in milder limb-girdle patterns of weakness with an onset in childhood or adolescence. Genes associated with a more limb-girdle myasthenic syndrome phenotype include *GFPT1, DPAGT1, ALG2, ALG14, GMPPB,* and *PREPL*. Genes affecting the postsynaptic AChR subunits may be associated with a slow-channel CMS in which patients may have variable weakness, typically with worsening with AChE inhibitors, as well as a fast-channel CMS syndrome; they can show improvement in symptoms in response to AChE inhibitors.

RARE OTHER CAUSES OF MYASTHENIA

MG is occasionally associated with hypothyroidism, usually **Hashimoto thyroiditis.** Other collagen vascular diseases and also some centronuclear myopathies may be associated with defects in neuromuscular transmission. Thymomas, noted in some adults, rarely coexist with MG in children. Likewise, lung carcinomas that occur in adults associated with Lambert-Eaton myasthenic syndrome are not seen in children. Lambert-Eaton syndrome in children is rare but has been reported with lymphoproliferative disorders and with neuroblastoma. Postinfectious MG in children is transitory and usually follows a varicella-zoster infection by 2-5 weeks as an immune response.

Laboratory Findings and Diagnosis

MG is one of the few neuromuscular diseases in which electromyography (EMG) is more specifically diagnostic than a muscle or nerve biopsy. A *decremental response* is seen to repetitive nerve stimulation; the muscle potentials diminish rapidly in amplitude until the muscle becomes refractory to further stimulation. Electrophysiologically, this response is due to end plate potentials decreasing with subsequent repetitive stimulations, such that stimuli no longer result in end plate potentials that achieve a threshold resulting in a propagating motor action potential. This results in a cumulative lowering of the compound muscle action potential (CMAP) amplitude with the repeated stimuli. A decline of greater than 10% between waves 1 and 4 on repetitive stimulation is diagnostic for a decremental response, and suggestive of a disorder of neuromuscular transmission. The motor nerve conduction velocity remains normal. This unique EMG pattern is the electrophysiologic correlate of the fatigable weakness observed clinically and is reversed after a cholinesterase inhibitor is administered. A myasthenic decrement may be absent or difficult to demonstrate in muscles that are not involved clinically. This feature may be confusing in early cases or in patients showing only weakness of extraocular muscles. Stimulated single-fiber EMG methodology, when available, measures the variability in neuromuscular transmission as a value called jitter, and is highly sensitive and moderately specific for neuromuscular junction transmission abnormality. Special electrophysiologic studies are required in the classification of CMS and involve estimating the number of AChRs per end plate and in vitro study of end plate function. These special studies and patch-clamp recordings of kinetic properties of channels are performed on special biopsy samples of intercostal muscle strips that include both the origin and insertion of the muscle but are only

performed in specialized centers. If myasthenia is limited to the extraocular, levator palpebrae, and pharyngeal muscles, repetitive nerve stimulation of the distal and proximal muscles (e.g., abductor pollicis brevis muscle or trapezius muscle, respectively), although diagnostic in the generalized disease, is usually normal.

Anti-AChR antibodies should be assayed in the plasma but are inconsistently demonstrated. Antibodies against the MuSK receptor should be sought in children without circulating AChR antibodies, a diagnostic finding when elevated, which further delineates the etiology. Many cases of congenital MG result from failure to synthesize or release ACh at the presynaptic membrane. In some cases, the gene that mediates the enzyme choline acetyltransferase for the synthesis of ACh is identified. In others, there is a defect in the quantal release of vesicles containing ACh. The treatment of such patients with cholinesterase inhibitors is not effective. In some patients, such as those with *COLQ* and *DOK7* variants as well as slow-channel myasthenia, AChE inhibitors (e.g., pyridostigmine) can lead to no response or even worsening of symptoms. Clinical genetic testing for CMS can be done by panels that are commercially available and can test ~14-21 CMS-associated genes.

Other serologic tests of autoimmune disease, such as antinuclear antibodies and abnormal immune complexes, should also be sought. If these are positive, more extensive autoimmune disease involving vasculitis or tissues other than muscle is likely. A thyroid profile should always be examined. The serum creatine kinase (CK) level is normal in MG.

The heart is not involved, and electrocardiographic findings remain normal. Radiographs of the chest often reveal an enlarged thymus, but the hypertrophy is not a thymoma. It may be further defined by CT or MRI of the anterior mediastinum if the radiographic findings are uncertain, but caution should be used when selecting the optimal imaging modalities because of radiation exposure for CT and anesthetic risk in a myasthenic patient if sedated MRI is needed for a younger myasthenic child.

The role of conventional muscle biopsy in MG is limited. It is not required in most cases, but approximately 17% of patients show inflammatory changes, sometimes called *lymphorrhages,* that are interpreted by some physicians as a mixed myasthenia-polymyositis immune disorder. Muscle biopsy tissue in MG shows a nonspecific type II muscle fiber atrophy, similar to that seen with disuse atrophy, steroid effects on muscle, polymyalgia rheumatica, and many other conditions. The ultrastructure of motor end plates shows simplification of the membrane folds; the AChRs are located in these postsynaptic folds, as shown by bungarotoxin (snake venom), which binds specifically to the AChRs.

A clinical test for MG is administration of a short-acting cholinesterase inhibitor, usually edrophonium chloride. Ptosis and ophthalmoplegia improve within a few seconds, and the fatigability of other muscles decreases. The "edrophonium Tensilon test" should be undertaken with extreme caution because of risk of bradyarrhythmias and syncope, and it can cause paradoxical worsening of neuromuscular transmission in COLQ-related CMS. This test is now used rarely in centers where good neurophysiology, antibody, and molecular genetic testing are readily available.

Recommendations on the Use of Cholinesterase Inhibitors as a Diagnostic Test for Myasthenia Gravis in Infants and Children

Children 2 Years of Age and Older

- The child should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, or inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits is not a criterion.
- This test is recommended to be undertaken on an intensive care unit or high dependency unit setting where facilities for resuscitation are available, in case of adverse reactions to edrophonium.
- An intravenous infusion of normal saline should be started to enable the administration of medications in the event of an adverse reaction.
- Electrocardiographic monitoring is recommended during the test.
- A dose of atropine sulfate (0.01 mg/kg) should be *available* in a syringe, ready for intravenous administration at the bedside during the edrophonium test, to block acute muscarinic effects of the cholinesterase inhibitor, such as abdominal cramps and/or sudden diarrhea from increased peristalsis, profuse bronchotracheal secretions that can obstruct the airway, or, rarely, cardiac arrhythmias. Some physicians pretreat all patients with atropine before administering edrophonium, but this is not recommended unless there is a history of a reaction to tests. Atropine can cause the pupils to be dilated for as long as 14 days after a single dose, and the pupillary effects of homatropine can last 4-7 days.
- Edrophonium chloride (Tensilon) is administered intravenously. The initial test dose is 0.01 mg/kg (no more than 1 mg [for children <30 kg], and no more than 2 mg initial dose [for children >30 kg]). After the initial dose, repeat doses may be given intravenously. For children <30 kg, repeat at a rate of 1 mg every 30-45 seconds to a maximum cumulative dose of 5 mg. For children >30 kg, repeat doses of 1 mg every 30-45 seconds to a maximum cumulative dose of 10 mg. In adults, the average edrophonium dose to show positive responses is approximately 3.3 mg for ptosis and approximately 2.6 mg for oculomotor symptoms. Side effects include nausea and emesis; light-headedness from bradycardia (atropine is the antidote) and bronchospasm are less common side effects. The edrophonium test may be done by intramuscular or subcutaneous injection but may require modification of dosing.
- Effects should be seen within 10 seconds and disappear within 120 seconds. Weakness is measured as, for example, the distance between the upper and lower eyelids before and after administration, degree of external ophthalmoplegia, or ability to swallow a sip of water.
- Long-acting cholinesterase inhibitors, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness. The neostigmine (Prostigmin) test may be used (as outlined later) but might not be as definitively diagnostic as the edrophonium test.

Children Younger Than 2 Years of Age

- Infants ideally should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, and inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits makes it less easy to assess results but may be a criterion at times.
- An intravenous line should be started as a rapid route for medications in the event of an adverse effect of the test medication.
- Electrocardiographic monitoring is recommended during the test.
- Pretreatment with atropine sulfate to block the muscarinic effects of the test medication is not recommended, but atropine sulfate should be available at the bedside in a prepared syringe. If needed, it should be administered intravenously in a dose of 0.01 mg/kg.
- *Edrophonium is not recommended for use in infants*; its effect is too brief for objective assessment, and an increased incidence of acute cardiac arrhythmias is reported in infants, especially neonates, with this drug.
- Prostigmin methyl sulfate (neostigmine) is administered intramuscularly at a dose of 0.04 mg/kg. If the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hours after the first dose (a typical dose is 0.5-1.5 mg). The peak effect is seen in 20-40 minutes. Intravenous Prostigmin is **contraindicated** because of the risk of cardiac arrhythmias, including fatal ventricular fibrillation, especially in young infants.
- Long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness because the onset and duration are less predictable.

The test should be performed in the emergency department, hospital ward, or intensive care unit; the important issue is preparation for potential complications such as cardiac arrhythmia or cholinergic crisis, as outlined.

Treatment

Some patients with mild MG require no treatment. Cholinesterase-inhibiting drugs are the primary therapeutic agents. Pyridostigmine bromide (Mestinon) may be given orally starting at 0.5-1 mg/kg per

dose every 4-6 hours while the patient is awake to a maximum of 60 mg per dose. The maximum daily recommended dose is 7 mg/kg/day, with most adults achieving effect with total daily doses of <960 mg/day, divided in four to eight doses. Pyridostigmine is given in short-acting forms and can also be used in a long-acting form at bedtime for patients with more weakness upon awakening in the morning. Overdoses of cholinesterase inhibitors produce **cholinergic crises** with symptoms such as increased secretions, diarrhea, and cramping; atropine blocks the muscarinic effects but does not block the nicotinic effects that produce additional skeletal muscle weakness. In the rare familial MG caused by the absence of end plate AChE, cholinesterase inhibitors are not helpful and often cause increased weakness; these patients can be treated with ephedrine or diaminopyridine, both of which increase ACh release from terminal axons.

Because of the autoimmune basis of the disease, long-term steroid treatment with prednisone may be effective. Thymectomy should be considered and might provide a cure. Thymectomy is most effective in patients who have high titers of anti-AChR antibodies in the plasma and who have been symptomatic for <2 years. Thymectomy is ineffective in congenital and familial forms of MG. Treatment of hypothyroidism usually abolishes an associated myasthenia without the use of cholinesterase inhibitors or steroids.

If the specific genetic variant can be identified in a patient with one of the CMSs, specific therapeutic approaches are available for some that differ from the treatments listed earlier (see Tables 652.1 and 652.6).

Plasmapheresis is effective treatment in some children, particularly those who do not respond to steroids, but plasma exchange therapy provides only temporary remission. Intravenous immunoglobulin is beneficial and should be tried before plasmapheresis because it is less invasive. Plasmapheresis and intravenous immunoglobulin appear to be most effective in patients with high circulating levels of anti-AChR antibodies. Refractory patients, as well as patients with MuSK-related MG, might respond more effectively to rituximab, a monoclonal antibody to the B-cell CD20 antigen. Efgartigimod (Vyvgart) is an antibody fragment Fc receptor antagonist, inhibiting the Fc receptor from recycling IgG into the circulation, and is FDA approved for patients ≥18 years of age with severe, generalized AChR antibody–positive MG. Clinical trials have started in children 2-18 years of age.

Neonates with transient maternally transmitted MG require cholinesterase inhibitors for only a few days or occasionally for a few weeks, especially to allow feeding. No other treatment is usually necessary. In non–maternally transmitted congenital MG, identification of the specific molecular defect is important for treatment; Table 652.6 summarizes specific therapies for each type.

Complications

Children with MG do not tolerate neuromuscular-blocking drugs, such as succinylcholine and pancuronium, and may be paralyzed for weeks after a single dose. An anesthesiologist should carefully review myasthenic patients who require a surgical anesthetic, and such anesthetics should be administered only by an experienced physician/anesthesiologist. Also, certain antibiotics can potentiate myasthenia and should be avoided; these include the aminoglycosides, β-blocking agents, procainamide, chloroquine, and fluoroquinolones.

Prognosis

Some patients with autoimmune MG experience spontaneous remission after a period of months or years; others have a permanent disease extending into adult life. Immunosuppression, thymectomy, and treatment of associated hypothyroidism might provide a cure. Genetically determined CMSs may show initial worsening in infancy but then remain static throughout childhood and into adult life.

Table 652.6 Potential Therapies in Congenital Myasthenic Syndromes

SYNDROME	THERAPY
AChE deficiency, COLQ	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
AChR deficiency	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary, add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR fast channel	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary, add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR slow channel	Quinidine sulfate • *Adults*: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 μg/mL • *Children*: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults Avoid AChE inhibitors
ChAT	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary, add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
DOK7	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
Laminin β_2	Albuterol (Salbutamol): Start with 1 mg 3 times daily. Increase to 2 mg 3 times daily until 10 years age; maximum of 4 mg 3 times daily in older children, as tolerated. Albuterol has largely replaced the use of ephedrine, which is not obtainable in several countries. Reference dose of ephedrine as an alternative to albuterol: ephedrine 3 mg/kg/day in 3 divided doses, starting with 1 mg/kg. Second-line drug is 3,4 diaminopyridine mg/kg/day in 4 divided doses, up to 60 mg/day in adults. Avoid AChE inhibitors
MuSK	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses 3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Rapsyn	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary, add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults

AChE, Acetylcholinesterase; AChR, acetylcholine receptor.

Modified from Burke G, Hiscock A, Klein A, et al. Salbutamol benefits children with congenital myasthenic syndrome due to DOK7 mutations. *Neuromuscul Disord*. 2012;23:170–175; Chan HS, Wong VCN, Engel AG. Neuromuscular junction acetylcholinesterase deficiency responsive to albuterol. *Pediatr Neurol* 2012;47:137e140; Engel GA. The therapy of congenital myasthenic syndromes. *Neurotherapeutics*. 2007;4(2):252–257.

OTHER CAUSES OF NEUROMUSCULAR BLOCKADE

Organophosphate chemicals, commonly used as insecticides, can cause a myasthenia-like syndrome in children exposed to these toxins (see Chapter 94).

Botulism results from ingestion of food containing the toxin of *Clostridium botulinum,* a gram-positive, spore-bearing, anaerobic bacillus (see Chapter 256). The incubation period is short, only a few hours, and symptoms begin with nausea, vomiting, and diarrhea. Cranial nerve involvement soon follows, with diplopia, dysphagia, weak suck, facial weakness, and absent gag reflex. The mechanism is cleavage by the botulinum toxin of several of the structural glycoproteins of the wall (i.e., membrane) of synaptic vesicles within axonal terminals. These glycoproteins include synaptobrevin and synaptotagmin, but synaptophysin is resistant.

In **infantile botulism,** which classically presents between the ages of 4 and 7 months, honey as well as spores from dirt (e.g., near construction sites) are common sources of contamination. The earliest signs are usually constipation, poor feeding, and then a weak cry. On evaluation, patients appear hypotonic, with facial weakness, dysphagia, and a poor gag. Generalized weakness with a risk of respiratory failure can occur. Generalized hypotonia and weakness then develop and can progress to respiratory failure. Neuromuscular blockade is documented by EMG with repetitive nerve stimulation. Slow repetitive nerve stimulation may show a decremental response, and baseline CMAP amplitudes may be low. With rapid repetitive nerve stimulation, there is an incremental response. EMG/repetitive nerve stimulation studies may help in confirming a diagnosis if the clinical presentation is not straightforward. However, when suspected, botulinum toxin studies should be sent preferentially from stool samples from the patient, and then treatment should be initiated as soon as possible with Botulinum Immune Globulin IV (Baby-BIG or BIG-IV). BIG-IV, which is human-derived antibotulism toxin antibodies, is approved by the FDA for the treatment of infant botulism types A and B. Early use of BIG-IV has shortened the overall length of hospitalization and improved the time to recovery. Respiratory and feeding/gavage support may be required for days or weeks until the toxin is cleared from the body.

Tick paralysis is a disorder of ACh release from axonal terminals due to a neurotoxin that blocks depolarization. It also affects large, myelinated motor and sensory nerve fibers. This toxin is produced by the wood tick or dog tick, insects common in the Appalachian and Rocky Mountains of North America. The tick embeds its head into the skin, usually the scalp, and neurotoxin production is maximal about 5-6 days later. Motor symptoms include weakness, loss of coordination, and sometimes an ascending paralysis resembling Guillain-Barré syndrome. Tendon reflexes are lost. Sensory symptoms of tingling paresthesias can occur in the face and extremities. The diagnosis is confirmed by identification of the tick, and treatment involves the prompt removal of the entire tick. It is important to monitor patients closely, because some patients may show worsened respiratory symptoms for the first day after tick removal. Most patients will show rapid improvement within a few hours to a few days from the time of tick removal.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

652.2 Spinal Muscular Atrophies

Adnan Y. Manzur

Spinal muscular atrophy (SMA) is a degenerative disease of motor neurons that begins in fetal life and continues to be progressive in infancy and childhood. Among the autosomal recessive disorders in childhood, SMA is the most common cause of infant mortality, and is second in birth prevalence only to cystic fibrosis. The incidence of SMA is estimated to be 1 in 6,000-10,000 newborns, with a carrier frequency of approximately 1/40-1/60. It is a clinically heterogeneous, panethnic disorder. SMA is caused by a homozygous deletion in the survival motor neuron 1 *(SMN1)* gene on chromosome 5q13. Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form also occurs. There is also a separate group of clinically and genetically heterogeneous non-5q SMA forms (see Chapter 652.3).

The pathologic hallmark of SMA is the progressive denervation of muscle. This is compensated for in part by reinnervation from an adjacent motor unit, but giant motor units are thus created, with subsequent atrophy of muscle fibers when the reinnervating motor neuron eventually becomes involved. Motor neurons of cranial nerves III, IV, and VI to the extraocular muscles, as well as those of the sacral spinal cord innervating striated muscle of the urethral and anal sphincters, are selectively spared. The upper motor neurons (layer 5 pyramidal neurons in the cerebral cortex) also remain normal.

SMA is classified clinically into a severe infantile form, also known as **Werdnig-Hoffmann disease** or SMA type I; a late infantile and more slowly progressive form, SMA type II; a more chronic or juvenile form, **Kugelberg-Welander disease,** or SMA type III; and an **adult-onset form** (SMA type IV). A severe fetal form that is usually fatal in the perinatal period has been described as SMA type 0, with motor neuron degeneration demonstrated in the spinal cord as early as midgestation. These distinctions of types are based upon the age at onset, severity of weakness, maximum motor milestone achieved, and clinical course (Table 652.7). Some patients are transitional between types I and II or between types II and III in terms of clinical function. Of note, the *SMN* gene region comprises a centromeric copy containing the *SMN2* gene. There is a correlation between the severity of disease, age at onset, and *SMN2* copy number, and a higher *SMN2* copy number is associated with milder disease severity.

Muscle biopsy does not distinguish types I and II, though type III shows a more adult than perinatal pattern of denervation and reinnervation. Type 0 can show biopsy features more similar to those of myotubular myopathy because of maturational arrest; scattered myotubes and other immature fetal fibers also are demonstrated in the muscle biopsies of patients with types I and II, but they do not predominate. Autonomic motor neurons of both the sympathetic and parasympathetic systems are not spared, but usually do not show clinical manifestations until late stages. Autonomic deficits may involve the detrusor muscle of the urinary bladder or the smooth muscle urethral and anal sphincters, in all three forms of SMA. In some patients with type I SMA and respiratory distress, there may be severe autonomic dysregulation with dysautonomia and cardiovascular collapse leading to death or to severe ischemic brain damage. The differential diagnosis is noted in Table 652.8.

CLINICAL MANIFESTATIONS AND COURSE

The cardinal features of the classic, most common phenotype, **SMA type I,** can be summarized as a presentation before the age of 6 months with severe hypotonia (Fig. 652.1); symmetric generalized muscle weakness affecting the lower limbs more than the upper limbs, proximal more than distal; frog-leg posture; absence of deep tendon reflexes; tongue fasciculations; and selective involvement of the axial and intercostal muscles but sparing of diaphragm. SMA is in the differential diagnosis list of floppy infant syndrome (see Chapter 648). Due to the involvement of the intercostal respiratory muscles, there is a typical paradoxical abdominal breathing pattern, bell-shaped chest, and weak cough (Video 652.1). Infants lie flaccid with little movement, unable to overcome gravity, and lack head control. These infants rarely achieve improvements of motor function and acquire motor developmental milestones (see Fig. 648.1 in Chapter 648). In contrast to their severe weakness and floppiness, infants with SMA type I have an alert and bright expression with preserved cognitive functions. There is no involvement of the facial and extraocular muscles at presentation, although facial weakness does occur at later stages of the disease.

SMA type I is not homogeneous within itself. At least three clinical subgroups can be defined as (1) severe weakness from birth or the neonatal period and head control is never achieved; (2) presentation after the neonatal period, within the first 2 months, and head control is never achieved; and (3) onset after the neonatal period but head control is achieved, and rarely, some of the infants may gain the ability to sit with support. There may be a range of clinical presentations and courses of respiratory involvement and swallowing and sucking difficulties in this fragile group of SMA type I patients.

Infants with SMA type I develop respiratory failure within the first 2 years of life, and without respiratory and nutritional support, they

Table 652.7 Clinical Motor Neuron Entities with Established Genetic Linkage

CLINICAL ENTITY	GENE	CHROMOSOME	AGE AT ONSET	CLINICAL FEATURES
PROXIMAL SMA: AUTOSOMAL RECESSIVE				
SMA type 0	*SMN*	5q13	Prenatal	Severe Congenital heart defects Death around 30 days
SMA type 1	*SMN*	5q13	<6 mo	Severe Never sit, and fatal before age 2*
SMA type 2	*SMN*	5q13	6-18 mo	Sit independently, never walk* LE predominance
SMA type 3	*SMN*	5q13	>18 mo	Walk independently
Congenital with arthrogryposis	*SMN*	5q13	Congenital	Severe Facial weakness, respiratory failure at birth, contractures Death around 30 days
SMA + congenital fractures Type 1	*TRIP4*	15q22	Prenatal	Severe Pulmonary hypoplasia, congenital heart defects ± facial dysmorphisms Death at 2-16 mo
SMA + congenital fractures Type 2	*ASCC1*	10q22	Prenatal	Severe Pulmonary hypoplasia, congenital heart defects ± facial dysmorphisms Death at 2-16 mo
SMA + myoclonus epilepsy	*ASAH1*	8q22	3-30 yr	Seizures, proximal weakness, tongue fasciculations, respiratory insufficiency later in the disease
SMA + pontocerebellar hypoplasia Type 1A	*VRK1*	14q32	First decade Some prenatal	May walk but then lose ambulation Feeding difficulties Ataxia and nystagmus In severe cases, death before 6 mo
SMA + pontocerebellar hypoplasia Type 1B	*EXOSC3*	9p11	Congenital	Muscle wasting, distal contractures, microcephaly, and oculomotor apraxia
Spinal muscular atrophy with hypomyelination and cerebellar hypoplasia	*EXOSC8*	3q13	2-4 mo	Severe weakness, failure to thrive, hearing and vision impairment, death caused by respiratory failure before 20 mo
PROXIMAL SMA: AUTOSOMAL DOMINANT				
Adult	*VAPB*	20q13	30-60 yr	Proximal LE weakness and atrophy Fasciculations and reduced reflexes Slow progression
SMAJ adult onset	*CHCHD10*	22q11	30-70 yr	Proximal > distal and abdominal weakness Cramps and fasciculations
Bulbar SMA with gynecomastia	?	?	Second to third decade	Asymmetric, proximal weakness + tibialis anterior Nasal voice and tremors Limb and tongue fasciculations
HMN8	*TRPV4*	12q24	Congenital	LE weakness only; proximal > distal Arthrogryposis ± vocal cord paresis
HMSN-P (Okinawa type)	*TFG*	3q12	17-50 yr	Symmetric proximal > distal weakness Progression to severe disability and wheelchair
SMA with LE predominance (SMALED 1)	*DYNC1H1*	14q32	Early childhood	LE weakness and wasting Delayed walking Decreased patellar reflexes
RECESSIVE X-LINKED SMA				
Bulbospinal SMAX 1 (Kennedy disease)	Androgen receptor	Xq12	20-40 yr	Gynecomastia, bulbar involvement, hyperlipoproteinemia
SMAX 2 Infantile	*UBE1*	Xp11	Neonatal–early infantile	Severe Arthrogryposis and fractures
DISTAL SMA: AUTOSOMAL RECESSIVE				
SMA + diaphragm paralysis (SMARD1)	*GHMBP2*	11q13	Infantile	Severe Early respiratory failure
DHMNJ (Jerash type)	?	9p21	6-10 yr	LE weakness progressing to UE Brisk patellar reflexes and absent ankle + Babinski earlier on

Continued

Table 652.7 Clinical Motor Neuron Entities with Established Genetic Linkage—cont'd

CLINICAL ENTITY	GENE	CHROMOSOME	AGE AT ONSET	CLINICAL FEATURES
Type 3	?	11q13	Infancy to early adult	Distal weakness progressing to proximal and truncal weakness
Type 4	*PLEKHG5*	1p36		Generalized weakness, contractures, scapular winging, lordosis Progresses to severe disability over a decade
Type 5	*DNAJB2 (HSJ1)*	2q35	First to fourth decades	Severe, distal, LE weakness (foot drop; bulbar and respiratory weakness later in course)
Distal SMA + ataxia telangiectasia	*ATM*	11q22	Second decade	Distal weakness, LE > UE, resting tremor
Distal SMA + encephalopathy	*TBCE*	1q42	Neonatal to 14 mo	Global developmental delay, distal UE and LE weakness, spasticity, ± ataxia, ± optic atrophy Progressive
DISTAL SMA: AUTOSOMAL DOMINANT				
Calf predominant (HMN2D)	*FBXO38*	5p31	13-48 yr	Calves, hands, and feet weakness Slowly progressive
SMALED2A	*BICD2*	9q22	Congenital	Symmetric, proximal > distal, LE > UE weakness; ankle contractures; most patients are ambulant
Distal SMA + macular changes	*FBLN5*	14q32	First to ninth decades	Macular degeneration and weakness (70%)
Distal SMA + hearing loss	*MYH14*	19q13	4-23 yr	Symmetric distal weakness, hoarseness, and hearing loss
Scapuloperoneal neuropathy	*TRPV4*	12q24		Scapuloperoneal and distal weakness Laryngeal palsy
DISTAL SMA: X-LINKED				
SMAX 3	*ATP7A*	Xq21	1-61 yr	Distal (tibioperoneal) weakness Hand weakness later in disease Slow progression
DISTAL SMA: MITOCHONDRIAL INHERITANCE				
MTATP6 variant syndrome	*MTATP6*	N/A	First to second decade	Distal, LE > UE weakness; progressive Brisk reflexes

*Without treatment.
DHMNJ, Distal hereditary motor neuropathy, Jerash type; HMN8, distal hereditary motor neuronopathy type 8; HMSN-P, hereditary motor and sensory neuropathy with proximal predominance; LE, lower extremities; SMA, spinal muscular atrophy; SMAJ, spinal muscular atrophy, Jokela type; UE, upper extremities.
From Castro D, Henriquez A. Treatment and management of spinal muscular atrophy and congenital myopathies. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management,* 2nd ed. Philadelphia: Elsevier; 2022: Table 13.1, p. 262–263.

usually do not survive beyond their second birthday. A multidisciplinary approach (respiratory, gastrointestinal, and orthopedic interventions) combined with noninvasive ventilatory support (NIV) and enteral feeding have changed the natural course of the disease over the years. To date, the median time to either death or full-time NIV (NIV >16 hr/day) is 13.5 months with improved supportive respiratory and nutritional care. Infants who are symptomatic prenatally or at birth are classified as having a rare phenotype, **SMA type 0** (<1%); they can present with severe muscle weakness, respiratory distress, feeding problems, and cranial nerve involvement. Congenital contractures, ranging from simple clubfoot to generalized arthrogryposis, occur in approximately 10% of severely involved neonates (see Chapter 648.10). There is a perception of decreased intrauterine movements by the mother; these infants usually die within the first months of life. Although motor neurons are primarily affected tissue in SMA, other tissues, including those of the brain, cardiac system, vascular system, and even sensory nerves, may also contribute to the overall phenotype, especially in the most severe forms of the disease. Early-stage developmental congenital heart defects described in severe SMA patients, generally carrying one copy of *SMN2,* include atrial septal defects, a dilated right ventricle, ventricular septal defects, and hypoplastic left heart syndrome. These patients are also prone to possible involvement of the autonomic nervous system, which may result in arrhythmia and sudden death. Vasculopathy can be another rare presentation, and ulceration and necrosis of the fingers and toes have also been described in two severe type I SMA patients.

In **type II SMA,** affected infants are usually able to suck and swallow, and respiration is adequate in early infancy. Developmental delay in gross motor milestones or stagnation of motor development between the ages of 6 and 18 months is rather typical for this form. Proximal muscle weakness is again more prominent in the lower extremities compared with the upper extremities. Patients can sit without support but are unable to walk independently. These children show progressive weakness, but many survive into the school years or beyond, although they are confined to an electric wheelchair and severely handicapped. Nasal speech and problems with deglutition develop later. Respiratory complications are less severe and develop later during the course of the disease. Scoliosis becomes a major complication in many patients with long survival times. Gastroesophageal reflux may lead to malnutrition or to aspiration with acute airway obstruction or pneumonia.

Kugelberg-Welander disease is the mildest **SMA (type III),** and patients can appear normal in infancy. The progressive weakness is proximal in distribution, particularly involving the shoulder girdle muscles. Patients are ambulatory and develop a variable course of proximal muscle weakness after the age of 18 months. A significant proportion of children with SMAIII, especially the ones with onset of symptoms before 3 years of age, suffer loss of ambulation at some point during the course of the disease. Symptoms of bulbar muscle weakness are rare. Patients with SMA III may have muscular hypertrophy rather than atrophy, and it may easily be confused with a muscular dystrophy (Video 652.2). Longevity extends well into adult life. Fasciculations are a specific clinical sign of the denervation of muscle. In thin children, they may be seen in the deltoid and biceps brachii muscles and occasionally the quadriceps femoris muscles, but the continuous, involuntary, wormlike movements may be masked by a thick pad of subcutaneous fat. Fasciculations are best observed in the tongue, where almost no subcutaneous connective tissue

separates the muscular layer from the epithelium. If the intrinsic lingual muscles are contracted, as in crying or when the tongue protrudes, fasciculations are more difficult to see than when the tongue is relaxed. Cramps and myalgias of appendicular and axial muscles are common, especially in later stages, and problems of micturition may be present, though adolescent patients may be too embarrassed to state them unless the physician directly inquires.

Table 652.8 Differential Diagnosis of 5q Spinal Muscular Atrophy

SPINAL CORD DISORDERS
Neoplasms (SMA types I, II, III)
Other myelopathies (SMA types I, II, III)
OTHER MOTOR NEURON DISORDERS
SMARD1 (SMA type I)
Juvenile muscular atrophy of distal upper extremity (Hirayama disease)
Fazio-Londe disease, Brown-Vialetto-Van Laere syndrome
Other non-5q SMAs (SMA types I, II, III)
Juvenile ALS (SMA types I, II, III)
NEUROPATHIES
Congenital hypomyelinating or axonal neuropathies (SMA types I, II)
Hereditary motor and sensory neuropathies (SMA types I, II, III)
CIDP (SMA types II, III)
NEUROMUSCULAR JUNCTION DISORDERS
Botulism (SMA type I)
Congenital myasthenic syndromes (SMA types I, II, III)
Lambert-Eaton myasthenic syndrome (SMA type III)
Autoimmune myasthenia gravis (SMA types II, III)
MYOPATHIES
Congenital myopathies (SMA types I, II, III)
Congenital myotonic dystrophy (SMA type I)
Congenital muscular dystrophies (SMA types I, II)
Muscular dystrophies (DMD/BMD, LGMD) (SMA type III)
Mitochondrial myopathies (SMA types I, II, III)
Acid maltase/Pompe disease (SMA types I, II, III)
Other metabolic myopathies (SMA types I, II, III)
Inflammatory myopathies (SMA type III)
Channelopathies (SMA type III)
OTHER DISORDERS
Chromosomal abnormalities (SMA types I, II, III)
Prader-Willi syndrome (SMA type III)
Central nervous system abnormalities (SMA types I, II, III)
Hexosaminidase A deficiency (SMA types III, IV)

ALS, amyotrophic lateral sclerosis; BMD, Becker muscular dystrophy; CIDP, chronic inflammatory polyneuropathy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; SMARD1, spinal muscular atrophy with respiratory distress 1.
From Darras BT, Monani UR, De Vivo DC. Genetic disorders affecting the motor neuron: spinal muscular atrophy. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Box 139-1.

The outstretched fingers of children with SMA often show a characteristic tremor *(polyminimyoclonus)* due to fasciculations and weakness (Video 652.3). It should not be confused with a cerebellar tremor.

The adult phenotype of the disease is **SMA type IV,** which is characterized by a mild muscle weakness with an onset usually in the second or third decade of life. There may be an intrafamilial variability in the clinical expression of the disease.

The intelligence is normal, and children often appear brighter than their normal peers because the effort they cannot put into physical activities is redirected to intellectual development, and they are often exposed to adult speech more than to juvenile language because of the social repercussions of the disease. Progressive deterioration of ambulation and the high risk of falling and fracturing long bones or the pelvis eventually require use of a wheelchair; an electric wheelchair often is needed because weakness of the upper extremities does not allow the patient to manually push the wheels. Progressive scoliosis is another serious complication and may have a further adverse effect on respiration.

LABORATORY FINDINGS

The CK level may be normal, but more commonly is mildly elevated (up to twofold to fourfold), but usually not more than 10 times the normal upper limit. The chest x-ray in early-onset disease may demonstrate thin ribs. ECG may serve as a simple and practical tool in patients with SMA to demonstrate a baseline tremor as an artifact representing muscle fibrillations more prominent on lead II (Fig. 652.2). Although seen in mainly lower motor neuron diseases (MNDs), including poliomyelitis, recognition of this ECG pattern may prevent further electrophysiologic tests (EMG and nerve conduction studies [NCSs]) in SMA patients. Electrophysiologic studies (EMG-NCS) should be reserved for selected atypical patients. The results of motor NCSs are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy. EMG shows fibrillation potentials and other signs of the denervation of muscle. There is no need for a muscle biopsy, which demonstrates a neurogenic pattern with group atrophy in all forms of SMA.

DIAGNOSIS

The simplest, most definitive first-step diagnostic test in a patient with a clinical suspicion of SMA and normal and/or mildly elevated serum CK levels is a molecular genetic marker in the blood for the homozygous deletion in *SMN1* (Table 652.9). The current gold standard is *SMN1* deletion/variant and *SMN2* copy number testing, with a minimal standard of *SMN1* deletion testing. The homozygous absence of *SMN1* exon 7 (with or without deletion of exon 8) confirms the diagnosis of SMA. The genetic test for SMA has a 95% sensitivity and nearly 100% specificity (see Table 652.9). Real-time polymerase chain reaction (PCR) or multiplex ligation-dependent probe amplification (MLPA) tests give rapid and reliable *SMN1* gene copy numbers. Semiquantitative assays improve the diagnostic sensitivity up to 98%. According to different scenarios, if the patient has a single *SMN1* copy, the coding



Fig. 652.1 Type I spinal muscular atrophy (Werdnig-Hoffmann disease). Clinical manifestations of weakness of limb and axial musculature in a 4-mo-old infant with severe weakness and hypotonia. With vertical suspension **(A),** note the dangling lower limbs with lack of hip flexion, tendency of the upper limbs to slip through the examiner's hands, and lack of neck flexion with resulting head lag. When subject is supine, note the *frog-leg* positioning of the legs and the lack of traction response **(B)** and the lag of head **(C),** with attempts by the examiner to pull the infant to a sitting position. *(From Oskoui M, Darras BT, De Vivo DC. Spinal muscular atrophy: 125 years later and on the verge of a cure. In: Sumner CJ, Paushkin S, Ko C-P, eds. Spinal Muscular Atrophy: Disease Mechanisms and Therapy. San Diego: Academic Press; 2017. Chapters 1 and 3–19.)*

region of the second undeleted allele should be sequenced to identify the second causative variant, including point variations, insertions, and deletions. Direct sequencing of the gene is also recommended in patients with a clinical diagnosis, two *SMN1* copies, and a consanguineous background.

Muscle biopsy is used more selectively in patients showing equivocal or negative genetic findings. The muscle biopsy in infancy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle. Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers of both histochemical types (Fig. 652.3). Scattered immature myofibers resembling myotubes also are demonstrated. In juvenile SMA, the pattern may be more similar to adult muscle that has undergone many cycles of denervation and reinnervation. Neurogenic changes in muscle also may be demonstrated by EMG, but the results are less definitive than by muscle biopsy in infancy. Sural nerve biopsy is performed only occasionally, but shows mild sensory neuropathic changes, and the sensory nerve conduction velocity may be slowed; hypertrophy of unmyelinated axons also is seen. At autopsy, mild degenerative changes are seen in sensory neurons of dorsal root ganglia and in somatosensory nuclei of the thalamus, but these alterations are not perceived clinically as a sensory loss or paresthesias. The most pronounced neuropathologic lesions are the extensive neuronal degeneration and gliosis in the ventral horns of the spinal cord and brainstem motor nuclei, especially the hypoglossal nucleus. On rare instances, the clinical features of an SMA-like presentation may be a feature of mitochondrial diseases (*SCO2, DGUOK,* and *TK2* gene variants). *SCO2* encodes one of the COX assembly proteins, and the latter two gene variants are associated with mitochondrial DNA depletion syndromes. Unexpectedly elevated serum CK levels at some point in the clinical course of these patients, and cognitive developmental delay, can be clues to considering a mitochondrial disease in the differential diagnosis. Depending on the stage and progression of the disease, a muscle biopsy demonstrating ragged red fibers and COX-deficient fibers, may help in the differential diagnosis.

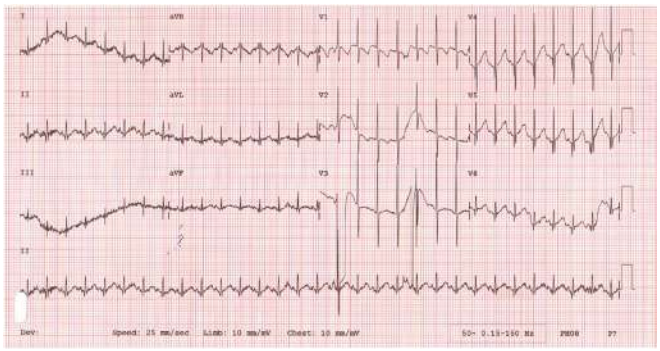

Fig. 652.2 Standard 12-lead EKG (25 mm/s, 10 mV/mm, diagnostic filter 0.05-150 Hz) showed diffuse somatic muscle fibrillations and baseline tremor, more prominent on lead II.

GENETICS

The genetic locus for all three of the common forms of SMA is on chromosome 5, a deletion at the 5q11-q13 locus, confirming that they are variants of the same disease rather than different diseases. The affected *SMN1* gene has a molecular weight of 38 kDa and contains 8 exons that span 20 kb and telomeric and centromeric exons that differ only by 5 bp and produce a transcript encoding 294 amino acids. *SMN1* is duplicated in a highly homologous gene called *SMN2,* and both genes are transcribed. *SMN2* remains present in all patients with SMA but cannot fully compensate for the *SMN1* defect. However, a molecular basis for correlation between the *SMN2* copy number and clinical severity of the SMA is the capability of *SMN2* to encode a small amount of an identical *SMN* protein. The critical difference between *SMN1* and *SMN2* is a cytosine (C) to thymine (T) transition in exon 7 of *SMN2* (Fig. 652.4).

The SMN complex has a role in the formation of small nuclear ribonucleoproteins (snRNPs), through assembly of Sm-proteins (a distinctive family of RNA-associated small proteins) onto small nuclear RNAs (SnRNAs). SMN deficiency and reduced snRNP assembly capacity are hypothesized to cause aberrant splicing or transport of RNPs to motor neurons. Dysregulation of genes involved

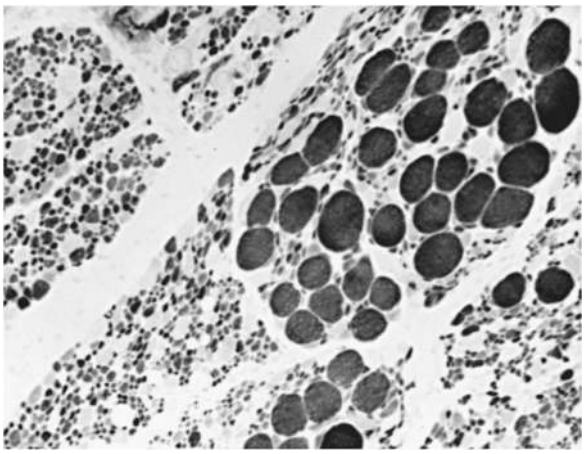

Fig. 652.3 Muscle biopsy of neonate with infantile spinal muscular atrophy. Groups of giant type I (darkly stained) fibers are seen within muscle fascicles of severely atrophic fibers of both histochemical types. This is the characteristic pattern of perinatal denervation of muscle. Myofibrillar adenosine triphosphatase, preincubated at pH 4.6 (×400).

Table 652.9 Molecular Genetic Tests in Spinal Muscular Atrophy

TYPE OF VARIANT	TEST APPLIED	VARIANT DETECTION RATE
Homozygous deletion of exon 7*	*SMN1* Targeted variant analysis Polymerase chain reaction/restriction enzyme analysis or multiplex ligation probe amplification methodologies	Approximately 95–98%
Compound heterozygosity (deletion of *SMN1* exon 7 [allele 1] and an intragenic variant of *SMN1*† [allele 2])	Targeted variant analysis combined with *SMN1* sequence analysis‡	2–5%
SMN2 copy number#	Quantitative polymerase chain reaction analysis and other methodologies¶	Not available

*Testing for exon 8 deletion is not necessary.
†Small intragenic deletions/insertions and nonsense, missense, and splice site variants.
‡Whole-gene deletions/duplications are not detected.
#*SMN2* copy number ranges from 0 to 5.
¶Multiplex ligation-dependent probe amplification (MLPA), long-range polymerase chain reaction (PCR), chromosomal microarray analysis (CMA) that includes the *SMN1, SMN2* chromosomal segment.
From Darras BT. Spinal muscular atrophies. *Pediatr Clin North Am.* 2015;62:743–766; Adapted from Markowitz JA, Singh P, Darras BT. Spinal muscular atrophy: a clinical and research update. *Pediatr Neurol.* 2012;46:1–12.

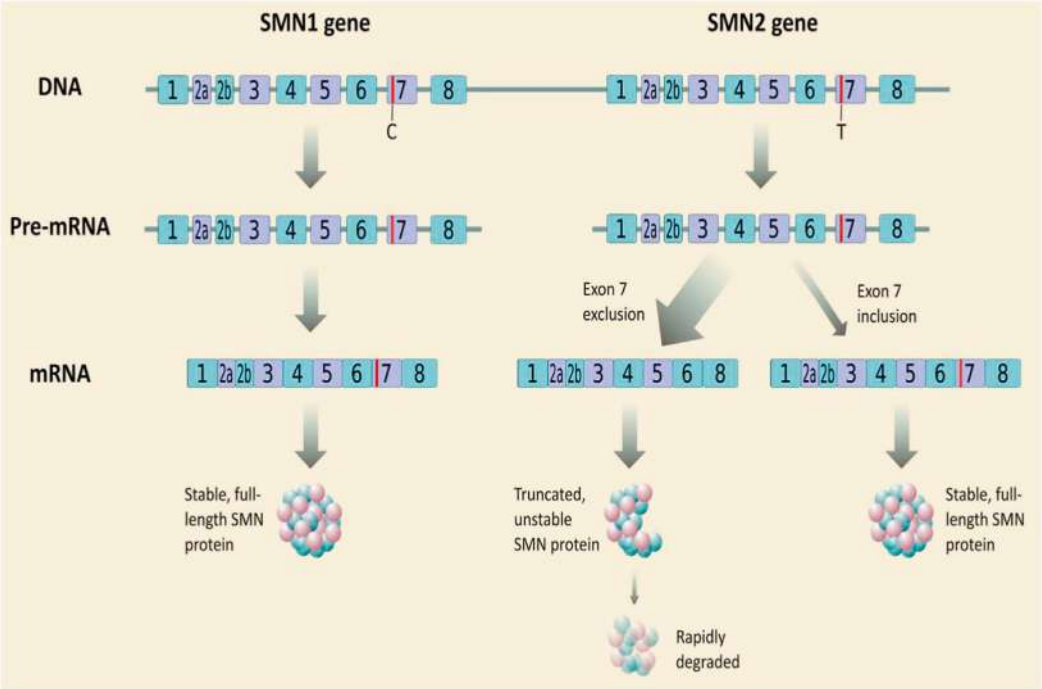

Fig. 652.4 Genetics of spinal muscular atrophy. In humans, the SMN protein is encoded by the *SMN1* and *SMN2* genes. The C to T substitution in exon 7 of *SMN2* is translationally silent but alters splicing such that the majority of *SMN2* transcripts lack exon 7 and the truncated protein is unstable. Normally, *SMN1* produces abundant SMN protein. In SMA, homozygous variants of *SMN1* result in only a small amount of functional SMN protein contributed by the varying copy numbers of *SMN2*. mRNA, messenger RNA; SMN, survival motor neuron. *(From Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017;81:355–368.)*

in synaptogenesis and the maintenance of neuromuscular junctions in animal studies possibly explains the special vulnerability of motor neurons. A second view is that, independent from snRNPs assembly, SMN may have a motor neuron–specific role such as mRNA transport along the axon. Considering the length of axons, integrity of neuromuscular junctions, and interactions with skeletal muscle, SMN protein deficiency may be detrimental for motor neurons. SMN is localized in bright-dot–like structures, called gems (gemini of Cajal bodies) in the nucleus. It is also present in other cellular structures such as Golgi bodies, cell membranes, and especially the axon and growth cone compartments of motor neurons. Due to its localization in ribonucleoprotein granules in neurites and growth cones in neurons, SMN modulates axonal growth and localization of β-actin messenger ribonucleic acid (mRNA) in growth cones of motor neurons. Early functional impairment of sensory-motor connectivity in animal models showed that motor neuron loss follows afferent synapse loss with the same temporal and topographic pattern, with changes occurring first in motor neurons innervating the proximal muscles and axial muscles, and then the distal muscles. The third view connects SMN function, in a direct or indirect manner, to actin dynamics and actin-dependent processes. There is an expansion in the spectrum of SMN function, including actin dynamics, vesicular transport, protein translation and trafficking, mRNA transport, apoptosis, and many others, which are reflected to widespread pathophysiologic findings described in humans and animal models (Fig. 652.5).

The severity of the disease is inversely correlated with the amount of functional SMN protein. In that sense, other than the *SMN2* copy number, which is the major protective modifier, the severity of the phenotype can be also influenced by other genetic modifiers, including plastin 3 and neurocalcin. Nutritional deficiency, oxidative stress, and hypoxia may contribute to widespread splicing alterations, including *SMN2,* and affect the disease progression.

Carrier testing by dose analysis is available and is based on semiquantitative real-time PCR or MLPA. In this context, limitations of the molecular testing, difficulties in predicting the offspring's phenotype based solely on the *SMN2* copy number, and the effect on reproductive planning should be considered.

Newborn screening is aimed at identifying presymptomatic SMA patients. DNA extraction from newborn blood spots, followed by either liquid microbead array or real-time PCR techniques, helps to identify *SMN1* homozygous deletions. Challenges in newborn screening include the inability to detect carriers of heterozygous deletions of *SMN1*, and *SMN2* copy numbers.

MANAGEMENT

A multidisciplinary and supportive approach is the key in the management of a patient with SMA along with published updated standards of care. Follow-up coordination should be managed by an expert in neuromuscular disorders, and the team ideally should include a pediatric and an adult neurologist, respiratory physicians, geneticists, gastroenterologists, palliative care physicians, rehabilitation specialists, orthopedic surgeons, and allied healthcare professionals. The consensus statement for the standard of care in SMA includes ethical and palliative care sections. Despite increased standards and technologic advances, there is a high variability in terms of ventilatory support, nutritional support, and scoliosis surgery. In terms of advances in disease-modifying treatments that will change the natural course of the disease, care and treatment options should be discussed clearly with the family and/or patients to define expectations, the quality of life, and palliative care issues. Because SMA is a dynamic disease by nature, a proactive plan should be introduced in almost every care subtopic (Table 652.10). Overall, supportive therapy should aim to help the patient to be as functionally independent as possible.

THERAPEUTIC ADVANCES

The prognosis, especially for SMA type I, has been improved due to the use of genetically based treatments with three drugs, nusinersen, onasemnogene, and risdiplam (Table 652.11). These drugs are expensive and may not be available in all countries.

SMN-antisense oligonucleotide (ASO), **nusinersen**, administered intrathecally is approved by the FDA and by the European Medicines Agency for all types of SMA patients. It modifies the splicing of *SMN2* by inducing an increase in exon 7 retention in *SMN2* pre-mRNA, which finally allows a protein product similar to *SMN1*. The initial

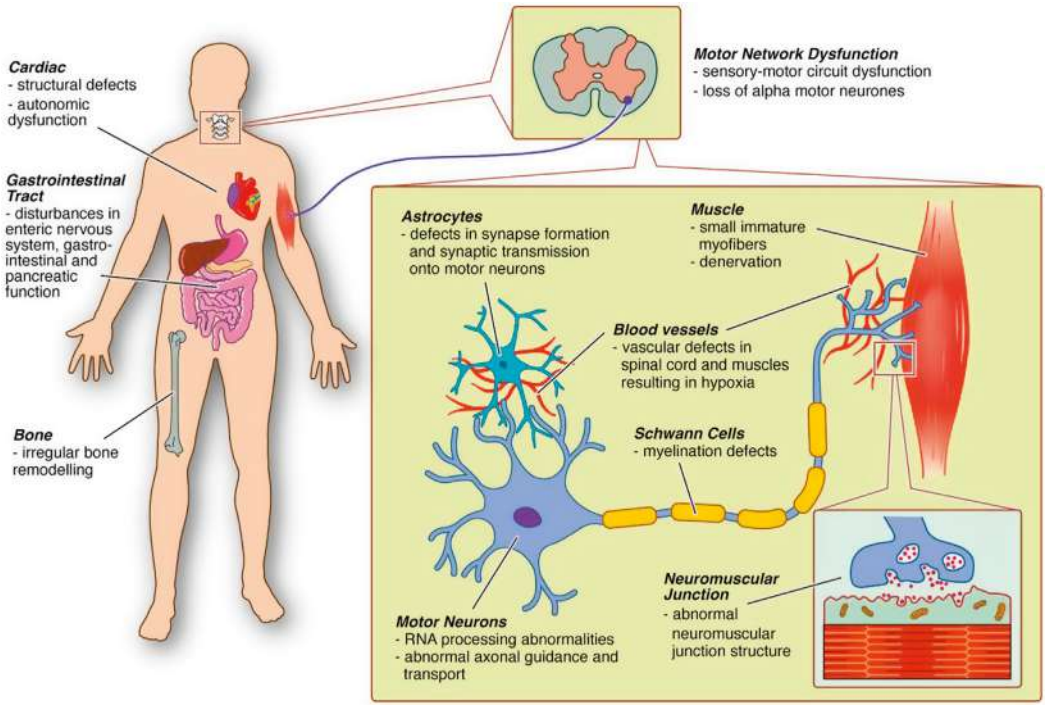

Fig. 652.5 Pathophysiologic findings in spinal muscular atrophy (SMA). Multiple functional abnormalities in motor networks have been identified in SMA mice and humans, including defects in astrocytes, Schwann cells, motor neurons, and skeletal muscle. Disease-associated phenotypes have also been reported across a range of other organs in SMA mice (in some cases supported by data from human patients), including cardiac structural and functional abnormalities, gastrointestinal tract dysfunction, and irregular bone remodeling. One potential unifying factor may be a deficiency in the development of the vasculature in SMA, with the resulting hypoxia likely impacting a range of cell types. *(From Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017;81:355–368.)*

Table 652.10 Management of Spinal Muscular Atrophy

	PROBLEMS	ASSESSMENTS	INTERVENTIONS
Respiratory	• Respiratory muscle weakness • Paradoxical breathing, bell-shaped chest • Weak cough • Difficulties in mobilization of mucus • Recurrent pulmonary infections • Mucus plugs • Atelectasis • Respiratory failure	• Cough effectiveness • Respiratory muscle function tests • Overnight oximetry • Forced vital capacity (>6 yr) • Overnight polysomnography if disordered breathing suspected • Acute respiratory infections	• Referral to respiratory specialist • Routine immunizations • Annual influenza vaccination • Airway clearance techniques and cough assistance (chest physiotherapy, postural drainage, mechanical or manual cough assistance) • Respiratory devices: noninvasive ventilation (nocturnal and/or daytime if indicated)* • Antibiotics intensified airway clearance • Increased ventilation support*
Nutritional	• Swallowing dysfunction • Failure to thrive • Prolonged feeding times • Gastroesophageal reflux • High risk for aspiration pneumonia • Constipation • Delayed gastric emptying • Increased fat mass and particular risk for becoming overweight (nonambulatory SMA type II patients) • Decreased bone mineral density	• Feeding and swallowing assessment • Assess caloric intake • Assess for signs of reflux or aspiration • Assess for constipation • Assess calcium and vitamin D status	• Nutritional supplementation • Modifying food consistency • Optimizing oral intake • Positioning and seating alterations • Nasogastric, nasojejunal, or percutaneous gastrostomy (as soon as reduced oral intake is recognized) • Nissen fundoplication (if indicated) • Hydration, regular oral aperients • Calcium and vitamin D supplementation (if indicated)
Orthopedic physiotherapy	• Scoliosis, hip subluxation, joint contractures (nonambulatory SMA type II patients) • Pain • Limited mobility	• Posture, mobility, function • Contractures • Scoliosis • Hip subluxation/dislocation	• Equipment to assist with mobility, self-care, and function • Physiotherapy, standing frames, orthoses • Spinal surgery† • Stretching, adequate positioning • Exercises with low resistance or high repetition • Evaluation with functional motor scales developed for SMA patients

Continued

Table 652.10 Management of Spinal Muscular Atrophy—cont'd

	PROBLEMS	ASSESSMENTS	INTERVENTIONS
Other organ involvement	• Reduced muscle mass • Higher risk of hypoglycemia during fasting • Congenital heart failure (SMA type 0) • Obesity, hyperinsulinemia with insulin resistance, and/or impaired glucose metabolism (nonambulatory type II SMA patients)	• Consider hypoglycemia during surgery and febrile episodes • Assess glucose metabolism if indicated	• Appropriate treatment if indicated • Referral to cardiologist • Referral to endocrinologist
Psychologic	• Issues related to quality-of-life index • Evaluation of family matrix	• Assess for depression/anxiety	• Counseling, pharmacotherapy • Appropriate referrals

*The appropriate level of interventional support to prolong life, particularly in spinal muscular atrophy (SMA) type I, is controversial, and the consensus statement recognizes the importance of discussions with the family to explore and define the potential quality of life and palliative care issues. The philosophy and introduction of proactive respiratory support in patients with SMA type I varies considerably and practice varies internationally.

†There is no consensus on management of scoliosis or hip subluxation/dislocation in nonambulant patients. If there is no fast progression of scoliosis, surgery should be delayed until at least 10-12 yr of age to allow for optimum growth. Otherwise, growing rods and vertical expandable prosthetic titanium ribs should be considered. Possibility of intrathecal administration of drugs should be taken into account.

The management of SMA incorporates a multidisciplinary and supportive approach, including neurologists (adult and pediatric), respiratory physicians, geneticists, gastroenterologists, palliative care physicians, rehabilitation specialists, orthopedic surgeons, and allied healthcare professionals.

Modified from Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol.* 2017;81:355–368; and from Pechman A, Kirschner J. Diagnosis and new treatment avenues in spinal muscular atrophy. *Neuropediatrics.* 2017;48(4):273–281.

Table 652.11 US Food and Drug Administration Approved SMA Therapeutics

MEDICATIONS	APPROVED FOR AGES	ROUTE/DOSING FREQUENCY	MECHANISM OF ACTION	ADVERSE EVENTS
Nusinersen (Spinraza)	All	IT/Loading dose (4 doses in 2 mo), then q 4 mo	ASO promoting inclusion of exon 7 in *SMN2* pre-mRNA	*Common*: LP-related, thrombocytopenia,* proteinuria* *Rare*: Hydrocephalus†
Onasemnogene abeparvovec-xioi (Zolgensma)	≤2 yr 0 d	IV/one-time dose	GRT using AAV9 vector	*Common*: asymptomatic thrombocytopenia, moderate elevation LFTs *Rare*: acute liver failure, TMA
Risdiplam (Evrysdi)	≥2 mo	PO/daily	Small molecule splice modifier promoting inclusion of exon 7 in *SMN2* pre-mRNA	*Common*: fever, diarrhea, rash, oral ulcers *Rare* (animal models only): retinal toxicity, testicular toxicity

*Associated with ASOs.

†Hydrocephalus has rarely been reported in individuals treated with either nusinersen or onasemnogene abeparvovec, and it remains unclear whether this is a rare consequence of SMA or is related to treatment.

AAV, Adeno-associated virus; ASO, antisense oligonucleotide; GRT, gene replacement therapy; IT, intrathecal; IV, intravenous; LFT, liver function test; LP, lumbar puncture; PO, oral; TMA, thrombotic microangiopathy.

From Klotz J, Rocha CT, Young SD, et al. Advances in the therapy of spinal muscular atrophy. *J Pediatr.* 2021;236:13–20. Table 1.

"loading" regime is with four intrathecal doses of nusinersen over the first 2 months, and this is followed by an intrathecal dose every 4 months, anticipated to be continued for life for maintenance of benefit. Nusinersen in phase 1 to phase 3 studies in SMA type I (0-6 months) showed favorable safety and tolerability with statistically significant improvement in survival and motor milestones. Two-year follow-up data on "real-world use" of an Italian clinical cohort reported that sitting was achieved in all the seven patients treated before 210 days of age (100%), in 11 of 23 treated between 210 days and 2 years (55%), and in 3 of 14 treated between 2 and 4 years of age (17.6%). Only one child achieved independent walking. The NURTURE study group has also reported a cohort of 25 presymptomatic infants (15 with two copies of SMN2, and 10 with three copies of SMN2) with a median follow-up of approximately 3 years: all participants achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently. Long-term follow-up is necessary to evaluate the effect of this treatment at different stages of the disease. Scoliosis, surgical interventions, and severe respiratory disease may complicate the lumbar puncture procedure.

The clinical trial data of the use of nusinersen in SMA type II/III patients (2-14 years) has also been very positive, with statistically significant improvement in functional assessment scores and motor milestones. Real-world cohort data from multiple studies of intrathecal nusinersen has reported improvement in walking ability or 6-minute walk distance in SMA3.

Risdiplam is an orally administered small molecule drug that modifies SMN2 pre-mRNA splicing and has been approved by the FDA for the treatment of patients with SMA who are 2 months of age or older. Risdiplam promotes the inclusion of exon 7, thereby increasing the expression of full-length SMN2 mRNA and functional SMN protein.

A phase 2-3 open-label study of risdiplam SMA1 infants age 1-7 months reported that sitting was achieved in 30% of the treated infants. Another study was in open-label extension, with optimized dose of risdiplam; 41 infants were enrolled and after 12 months of treatment, 12 infants (29%) were able to sit without support for at least 5 seconds, a milestone not attained in the natural history of SMA1.

Onasemnogene abeparvovec is a single-dose intravenously administered SMN gene replacement therapy (GRT) to replace *SMN1* and thus increase the production of the full-length SMN protein. It has FDA license for use up to 2 years of age and European medicines Agency approval children up to 21 kg bodyweight, so it primarily addresses the SMA1 population. The adeno-associated viral vector (AAV9) is used to transport a functional copy of *SMN1*, crossing the blood-brain barrier. The phase I clinical trial of intravenously administered GRT in SMA type I patients established a safety profile, but alanine transaminase (ALT) and aspartate transaminase (AST) elevation was noted in the

first month after treatment, indicating an immune-mediated "hepatitis," which requires treatment with prednisolone starting the day before treatment, and weaned off over a period of 3-4 months. *Thrombotic angiopathy* is a rare but life-threatening adverse effect.

The efficacy of onasemnogene has completely altered the natural history of SMA1. In an open-label study, 12 infants received the high (therapeutic) dose of onasemnogene at mean age of 3.4 months and follow-up was reported at median age 25 months; 11 patients sat unassisted, 11 were fed orally and could speak, and 2 walked independently. Five-year follow-up data were available for 10 of the 12 patients in the therapeutic-dose cohort (families of 2 infants refused participation in the follow-up study). All these patients remained alive and without the need for permanent ventilation (permanent ventilation is defined as need for ventilatory support for more than 16 hours per day) and maintained previously acquired motor milestones. Two patients attained the new milestone of "standing with assistance" without the use of nusinersen.

The outcome of single-dose onasemnogene gene therapy for *symptomatic* infantile-onset SMA1 has demonstrated that 14 of 32 patients achieved independent sitting at 18 months of age. Only 1 patient achieved walking. This study had broader inclusion and exclusion criteria compared with others, which resulted in inclusion of patients with more severe disease at baseline, at least in part explaining why the results were not as positive. There are no randomized controlled trials or systematic reviews comparing nusinersen, risdiplam, and onasemnogene, and their use is dictated by patient age, SMA categorization and severity, availability and funding, and patient choice.

Genetic counseling, depending on carrier screening tests, or in the presence of a previously affected child with SMA, may help with reproductive planning (prenatal diagnosis or preimplantation diagnosis). **Prenatal diagnosis** should be offered to families with an index patient in the family (recurrence risk is 25%), and antenatal screening by chorionic villus sampling between the 10th and 12th gestational week of pregnancy may serve for *SMN1* deletion/variant analysis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

652.3 Other Motor Neuron Diseases

Adnan Y. Manzur

Motor neuron diseases (MNDs) are a heterogeneous group of *progressive neurodegenerative* disorders characterized by upper and lower neuron dysfunction, with an onset from birth to adulthood. A variety of causes, including hereditary, immune-mediated, infectious, paraneoplastic, and sporadic diseases, should be considered.

Acute flaccid paralysis is the most common presentation of MND in children; it may occur in outbreaks. *Poliomyelitis* used to be a major cause of chronic disability, but with the routine use of polio vaccine, this viral infection is rare (see Chapter 296). Other enteroviruses, such as coxsackievirus and echovirus, or the live polio vaccine virus can also cause an acute infection of motor neurons, with symptoms and signs similar to poliomyelitis, although usually milder. Specific PCR tests and viral cultures of cerebrospinal fluid are diagnostic. A clustering of cases of acute flaccid paralysis has been reported during outbreaks of enterovirus D68 in multiple states in children (mean age 7-11 years). Limb weakness is often *asymmetric* and includes bulbar weakness, as well as cranial nerve VI and VII involvement. MRI may demonstrate longitudinal spinal cord lesions with dominant anterior horn cell involvement (Fig. 652.6). Cerebrospinal fluid pleocytosis and elevated protein are common. Treatments have included steroids and intravenous immunoglobulin; persistent paresis is a common sequela. Motor neuron infection with the West Nile virus also occurs.

In children, an insidious onset, slow progression, and family history can be clues for a genetic basis. Although the most common MND in children is 5q13-associated SMA, with a typical or predominant lower motor neuron phenotype, there is a clinically and genetically heterogeneous group of MNDs that overlap with **hereditary spastic paraplegias (HSPs), hereditary sensory-motor neuropathies (HSMNs),** and **juvenile forms of amyotrophic lateral sclerosis (ALS).**

A less common group of MNDs, not associated with *SMN1,* are called **non–5q13-associated SMAs;** this heterogeneous group can be associated with X-linked, autosomal dominant or autosomal recessive SMAs, **distal SMAs, segmental SMAs,** or **distal hereditary motor neuropathies** or **neuronopathies.** Additional features, such as deafness; epilepsy; encephalopathy; spasticity; visual impairment; or brainstem, cerebellar, gastrointestinal, or rheumatologic disorders may be indicative of a widespread involvement. These **atypical SMA** phenotypes can also be called **SMA-plus syndromes,** and they show extensive phenotypic overlap and molecular genetic heterogeneity (see Table 652.7). Primary involvement of the upper motor neuron, with a progressive upper and lower motor neuron loss, characterize **juvenile amyotrophic lateral sclerosis,** which is rare and ultimately fatal.

There has been an increase in the molecular diagnostic yield and expansion of these clinical phenotypes. This further helps not only to understand the natural course and common pathophysiologic mechanisms involved, but also indicates the appropriate genetic counseling and prenatal diagnosis.

A pattern of weakness, amyotrophy, and progression (proximal or distal, bulbar or respiratory involvement), the presence of spasticity, deep tendon reflexes, and the family history should be evaluated. In contrast to typical SMA, electrophysiologic studies and EMG may serve as important tools to demonstrate a neurogenic basis. Multisystem assessment, including vision, hearing, and cognitive development, is required. Clinical evaluation and recognition of distinctive features will help to classify MND and consider treatable MND forms in the differential diagnosis.

SMA with respiratory distress (SMARD) is a rare autosomal recessive disease due to pathogenic variants in the gene encoding IGHMBP2 on chromosome 11q13. In contrast to classical SMA type I, *predominant distal weakness* with *diaphragmatic palsy* results in severe respiratory failure. There is usually an early presentation between 6 weeks and 6 months of age, with intrauterine growth restriction, a weak cry and suck, and congenital foot deformities. Routine chest x-ray may reveal *diaphragmatic eventration,* which causes early respiratory failure. Atypical patients with peripheral neuropathy and no respiratory involvement have also been described. Beyond the core symptoms, sensory and autonomic dysfunction (excessive sweating, urinary retention, constipation, and cardiac arrhythmia), seizures, and progressive cranial nerve involvement can be additional features.

Brown-Vialetto-Van Laere (BVVL) syndrome is a rare heterogeneous neurodegenerative disorder characterized by involvement of cranial nerves VII-XII, progressive facial weakness, sensorineural deafness, dysphagia, tongue amyotrophy, fasciculations, bulbar palsy, and respiratory insufficiency. It may present at all ages. Weakness of the arms and hands, optic atrophy, and ataxia may be additional presentations. The clinical presentation of **Fazio-Londe syndrome** is the same and characterized by progressive bulbar palsy resulting from motor neuron degeneration more in the brainstem than the spinal cord, *without sensorineural deafness.*

Identification of pathogenic variants in the riboflavin transporter genes provided a targeted therapeutic strategy with oral or intravenous *high-dose riboflavin supplementation* with the starting dose being 10 mg/kg/day. The oral riboflavin dose may need to be sequentially increased to 50 mg/kg/day in pediatric patients and 1500 mg/day in adult patients for maximum benefit. The clinical response in this group may be variable, ranging from a rapid response to gradual improvement over 12 months, clinical stabilization, or rarely no response. Recognition of *abnormal acylcarnitine profiles* mimicking *multiple acyl-CoA dehydrogenase deficiency* in BVVL should also be considered. A biochemical response to treatment is also evident. The common core phenotype of this treatable MND includes progressive axonal sensorimotor neuropathy (manifesting with sensory ataxia and severe weakness of the upper limbs and axial muscles with distinctly preserved muscle power of the lower limbs), hearing loss, optic atrophy, and respiratory insufficiency.

The classic form of **pontocerebellar hypoplasia with SMA (PCH1)** is characterized by severe hypotonia, areflexia, muscle weakness, central visual impairment, dysphagia, respiratory insufficiency, and acquired microcephaly, with a presentation in the first months of life and death in infancy. There is a wide clinical spectrum, with a severe antenatal onset representing the severe end of the spectrum with arthrogryposis and polyhydramnios.

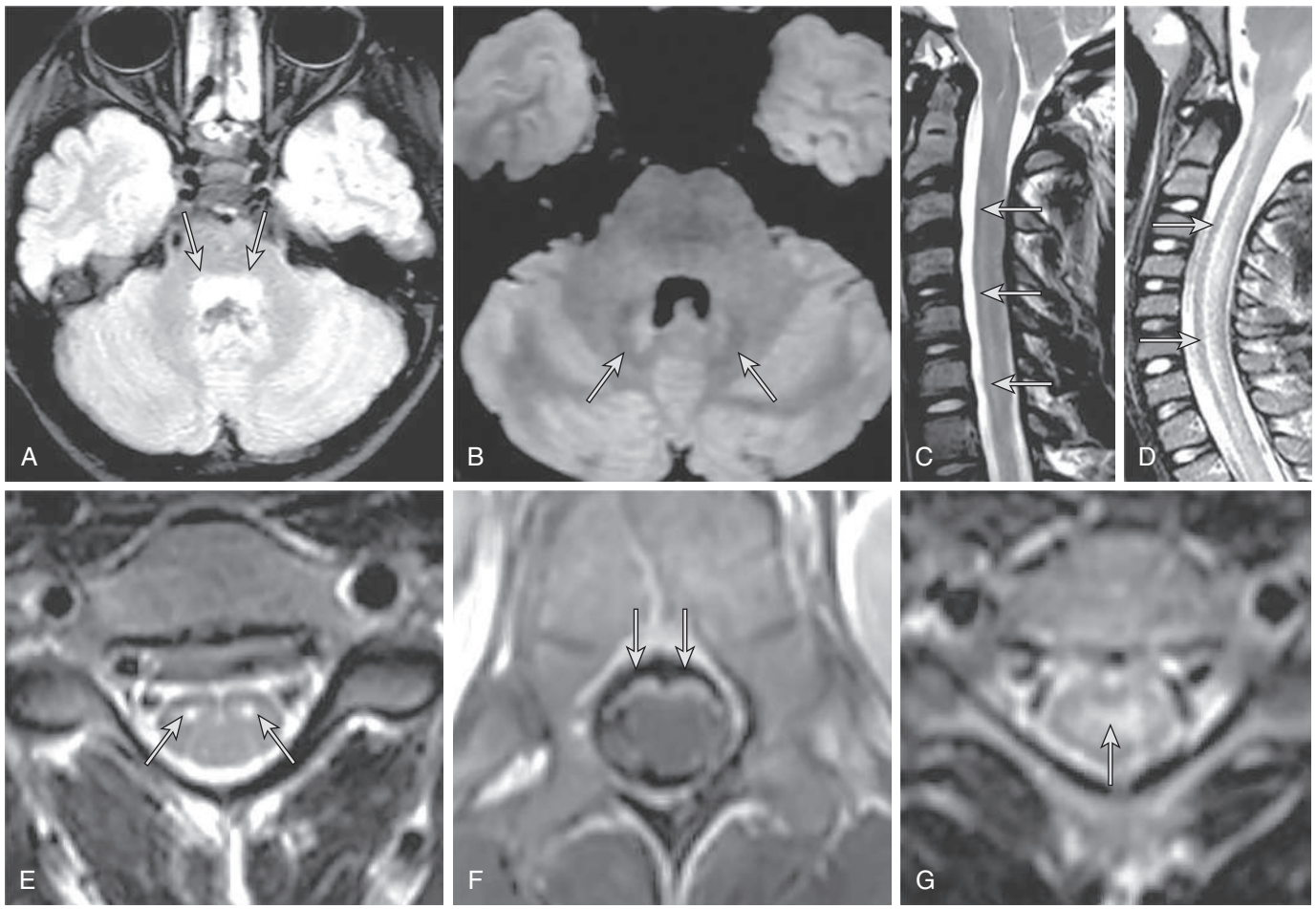

Fig. 652.6 Acute flaccid paralysis. Brain and spinal cord MRI. Axial fluid-attenuated inversion recovery (FLAIR) image at the level of the pons showing increased signal in the tegmentum (**A**; case 2). Axial FLAIR image at the level of the pons showing increased signal in the dentate nuclei, right greater than left, and sagittal T2 weighted image of the cervical spine shows long segment hyperintensity in the ventral cord (**B, C**; case 5). Sagittal T2 weighted image shows extensive increased signal in the central cord and cord swelling (**D**) at presentation (**D-F**; case 1). Five weeks after presentation, axial T2 weighted imaging of the cervical spine shows residual increased signal in the anterior horns (**E**) and an axial T1 weighted postcontrast image shows ventral nerve root enhancement at the level of the conus medullaris (**F**). Axial T2 weighted image of the cervical spine showing increased signal in the central gray matter (**G**; case 6). Cases 2, 5, and 6 were children with enterovirus D68 identified in the nasopharynx. *(From Messacar K, Schreiner TL, Maloney JA, et al. A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA. Lancet. 2015;385:1662–1671. Fig. 3.)*

SMA with progressive myoclonic epilepsy (SMAPME) is characterized by treatment-resistant progressive myoclonic epilepsy combined with proximal muscle weakness, areflexia, atrophy, progressive weakness, and dysphagia, followed by normal developmental milestones. Mild facial weakness, tongue fasciculations, sensorineural hearing loss, and tremor may be additional features. Rare variants include *polyarticular arthritis with SMA, mild SMA without seizures, eyelid myoclonic status epilepticus,* and *absence and atonic seizures* in adolescence.

Lethal arthrogryposis with anterior horn cell disease (LAAHD) and SMA with congenital arthrogryposis and fractures are atypical SMA forms within the fetal akinesia/hypokinesia spectrum (see Chapter 648.10).

A variety of **mitochondrial diseases** may present with an SMA-like clinical phenotype. In addition to hypotonia, weakness, and respiratory failure, there is a more extensive spectrum of multisystem involvement, such as infantile hypertrophic cardiomyopathy, hepatic failure, spasticity, Leigh-like syndrome, encephalopathy, seizures, brainstem dysfunction, global developmental delay, ptosis, and ophthalmoplegia. Lactic acidosis and increased serum CK levels may further help to include genes involved in *COX assembly proteins* and *mitochondrial depletion syndromes* in the molecular genetic workup.

SMA with lower extremity predominance (SMALED) is characterized by congenital or early-onset, proximal lower limb–predominant muscle weakness and atrophy. There is again a wide range of clinical presentations from the antenatal to adulthood periods. Spasticity and cognitive impairment can be a part of the clinical picture in some patients. The most common gene responsible for this phenotype is *DYNC1H1,* and its phenotypic spectrum spans lower extremity–predominant SMA, axonal Charcot-Marie-Tooth disease type 2, neurodevelopmental disorders, malformations of cortical development, learning disability, epilepsy, HSP, and phenotypes may overlap. *DYNC1H1*-related SMALED has a distinctive pattern of lower limb muscle MRI abnormalities, which are of diagnostic help.

Scapuloperoneal SMA is an autosomal dominant condition defined by its selective muscle involvement, progressive distal weakness, and atrophy. Laryngeal palsy, sensorineural deafness, short stature, scoliosis, and mild limb and skeletal dysplasia may accompany the picture.

Motor neurons become involved in several metabolic diseases of the nervous system, such as gangliosidosis (Tay-Sachs disease), ceroid lipofuscinosis (Batten disease), and glycogenosis II (Pompe disease), but the signs of denervation may be minor or obscured by the more prominent involvement of other parts of the central nervous system or of muscle. Amyotrophy related to lower motor neuron degeneration is a prominent future of some multisystem disorders, such as infantile neuroaxonal dystrophy (INAD), achalasia-addisonianism-alacrima (AAA, triple A, or Allgrove syndrome), and Chédiak-Higashi syndrome (CHS).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 653

Hereditary Motor-Sensory Neuropathies

Adnan Y. Manzur*

The hereditary motor-sensory neuropathies (HMSNs) are a group of progressive diseases of peripheral nerves of genetic (and syndrome) etiology (Tables 653.1 and 653.2). HMSNs are the most common group of hereditary neuropathies and the term Charcot-Marie-Tooth disease (CMT) is used interchangeably, and more commonly. Motor components generally dominate the clinical picture, but sensory and autonomic involvement is expressed later. Sural nerve biopsy used to be the most definitive means of diagnosis, but with the expanded knowledge of the molecular genetics of this group of diseases, the diagnosis of most can be confirmed by less invasive genetic testing. Electromyography (EMG) remains a useful adjunct to clinical diagnosis and helps distinguish between **demyelinating** or **hypomyelinating** and **axonal** forms. Clinical clues are noted in Tables 653.3-653.5.

Classification of HMSNs is difficult because no simple unifying scheme is capable of incorporating all the clinical presentations and overlapping genetics (see Tables 653.1 and 653.2). More than 140 genes have been described as causing the HMSN/CMT spectrum. In some neuropathies, a diverse genotype with pathogenic variants in different genes at different chromosomal loci may produce a similar phenotype. One classification identifies the following:

I. Hereditary neuropathies secondary to general diseases
II. Primary neuropathies
  IIa. Hereditary motor sensory neuropathies
  IIb. Distal hereditary motor neuropathies
  IIc. Hereditary sensory ± autonomic neuropathies
III. Syndromic neuropathies, including congenital hypomyelinating neuropathies
IV. Hereditary sensory neuropathy (Refsum disease)

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.1 Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease, HMSN Type IIa)

Adnan Y. Manzur

CMT is the most common genetically determined neuropathy and the most common demyelinating variant, also described as CMT1A, and has an overall prevalence of 3.8/100,000 population and accounts for >50% of cases of HMSN overall. It is transmitted as an autosomal dominant trait with 83% expressivity; the 17p11.2 locus is the site of the abnormal gene. Autosomal recessive transmission also is described but is rarer. The gene product is peripheral myelin protein 22 (PMP22). A much rarer X-linked HMSN type I results from a defect at the Xq13.l locus, causing pathogenic variants in the gap junction protein connexin-32. Other forms, caused by >40 genes, have been reported (see Table 653.1). Both fatty acid binding by PMP22 and the kinetics of its membrane interactions are affected by mutations.

CLINICAL MANIFESTATIONS

Most patients are asymptomatic until late childhood or early adolescence, but young children sometimes manifest gait disturbance as early as the second year of life. The peroneal and tibial nerves are the earliest and most severely affected. Children with the disorder are often described as being clumsy, falling easily, or tripping over their own feet. Application of the Cumberland Ankle Instability Tool for Youth is a means of objectively documenting and following this manifestation. The onset of symptoms may be delayed until after the fifth decade.

Muscles of the anterior compartment of the lower legs become wasted, and the legs have a characteristic storklike contour. The muscular atrophy is accompanied by progressive weakness of dorsiflexion of the ankle and eventual foot drop. The process is bilateral but may be slightly asymmetric. Pes cavus deformities invariably develop as a result of denervation of intrinsic foot muscles, further destabilizing the gait. A small minority of individuals with CMT1A have hip dysplasia. Atrophy of muscles of the forearms and hands is usually not as severe as that of the lower extremities, but in advanced cases contractures of the wrists and fingers produce a claw hand. Proximal muscle weakness is a late manifestation and is usually mild. Axial muscles are not involved.

The disease is slowly progressive throughout life, but patients occasionally show accelerated deterioration of function over a few years. Most patients remain ambulatory and have normal longevity, although orthotic appliances are required to stabilize the ankles.

Sensory involvement mainly affects large, myelinated nerve fibers that convey proprioceptive information and vibratory sense, but the threshold for pain and temperature can also increase. Some children complain of tingling or burning sensations of the feet, but pain is rare. Because the muscle mass is reduced, the nerves are more vulnerable to trauma or compression. Autonomic manifestations may be expressed as poor vasomotor control with blotching or pallor of the skin of the feet and inappropriately cold feet.

Nerves often become palpably enlarged. Tendon stretch reflexes are lost distally. Cranial nerves are not affected. Sphincter control remains well preserved. Autonomic neuropathy does not affect the heart, gastrointestinal tract, or bladder. Intelligence is normal. A unique point variant in *PMP22* causes progressive auditory nerve deafness in addition, but this is usually later in onset than the peripheral neuropathy. X-linked CMT disease (*GJB1* variant) has been associated with an acute disseminated encephalitis-like illness.

Davidenkow syndrome is a variant of HMSN type I with a scapuloperoneal distribution.

LABORATORY FINDINGS AND DIAGNOSIS

Motor and sensory nerve conduction velocities are greatly reduced, sometimes as slow as 20% of the normal conduction time. In new cases without a family history, both parents should be examined, and nerve conduction studies should be performed.

EMG and muscle biopsy are not usually required for diagnosis, but they show evidence of many cycles of denervation and reinnervation. The serum creatine kinase level is normal. The cerebrospinal fluid (CSF) protein may be elevated, but no cells appear in the CSF.

Sural nerve biopsy is diagnostic. Large- and medium-size myelinated fibers are reduced in number, collagen is increased, and characteristic **onion bulb formations** of proliferated Schwann cell cytoplasm surround axons. This pathologic finding is called **interstitial hypertrophic neuropathy.** Extensive segmental demyelination and remyelination also occur. The definitive molecular genetic diagnosis may be made in blood.

TREATMENT

Stabilization of the ankles is a primary concern. In early stages, stiff boots that extend to the midcalf often suffice, particularly when patients walk on uneven surfaces such as ice and snow or stones. As the dorsiflexors of the ankles weaken further, lightweight plastic splints may be custom-made to extend beneath the foot and around the back of the ankle. They are worn inside the socks and are not visible, reducing self-consciousness. External short-leg braces may be required when foot drop becomes complete. Soft tissue/bony foot surgery, or surgical fusion of the ankle may be considered in cases of progressive foot deformity, depending upon age and severity.

* The editors are grateful to Dr. Harvey B. Sarnat and Dr. Diana X. Bharucha-Goebel, much of whose work on previous editions of this chapter is retained here.

Table 653.1 Nonsyndromic Inherited Neuropathies

DISEASE	INHERITANCE PATTERN	GENE OR LOCUS	CLINICAL FEATURES
HEREDITARY MOTOR AND SENSORY NEUROPATHIES (HMSNs)			
Demyelinating			Forearm NCV usually <38 m/sec
CMT1	AD		Young adult onset, NCV 10-35 m/sec
CMT1A		*PMP22* (usually duplication)	Most common (70% of all CMT1) Pathogenic variants also cause CMT3
CMT1B		*MPZ* (P_0)	Pathogenic variants also cause CMT2 and CMT3
CMT1C		*LITAF/SIMPLE*	
CMT1D		*EGR2*	Broad clinical spectrum (also CMT3)
CMT1F		*NEFL*	DSS phenotype common
CMT1 plus		*FBLN5*	Macular degeneration; cutis laxa
CMT1		*PMP2*	Classic CMT1
SNCV/CMT1		*ARHGEF10*	Asymptomatic slowed NCVs
HNPP	AD	*PMP22* (usually deletion)	Adult-onset episodic entrapment neuropathies, mild slowing (NCV 40-50 m/sec)
CMT3			Severe, early-onset demyelinating
DSS	AD/X AR	*CMT1* genes *PRX, MTMR2*	Onset before age 3 yr old
CHN	AD AR	*PMP22, MPZ* *EGR2*	Congenital onset AR-CHN, also known as CMT4E
CMT4	AR		Childhood onset, usually severe
CMT4A		*GDAP1*	Both axonal and demyelinating types
CMT4B1		*MTMR2*	Biopsy shows focally folded myelin
CMT4B2		*SBF2/MTMR13*	Same as above ± early-onset glaucoma
		SBF1/MTMR5	
CMT4C		*SH3TC2*	Scoliosis often severe, also axonal types
CMT4D		*NDRG1*	Dysmorphic features, deafness
CMT4E		*EGR2*	
CMT4F		*PRX*	DSS phenotype
CMT4G		*HK1*	
CMT4H		*FGD4*	
CMT4J		*FIG4*	
		SURF-1	
		CTDP1	
Slow NCV	AD	*ARHGEF10*	Asymptomatic NCV slowing
Intermediate			NCV 25-45 m/sec
CMTX	X		
CMTX1		*GJB1/Cx32*	Similar to CMT1, but males more severely affected, CNS involvement common
CMTX2, Cowchock syndrome		*AIFM1*	MR, deafness, axonal
CMTX5		*PRPS1*	Axonal CMT, deafness, optic atrophy
CMTX6		*PDK3*	Axonal CMT
CMTX		*DRP2*	Intermediate MCVs
CMTDI	AD		
DI-CMTA		10q24	
DI-CMTB		*DNM2*	Neutropenia
DI-CMTC		*YARS*	

Continued

Table 653.1 Nonsyndromic Inherited Neuropathies—cont'd

DISEASE	INHERITANCE PATTERN	GENE OR LOCUS	CLINICAL FEATURES
DI-CMTD		*MPZ*	
DI-CMTE		*IFN2*	Focal segmental glomerulosclerosis
DI-CMTF		*GNB4*	
CMTRI	AR		
CMTR1A		*GDAP1*	
CMTR1B		*KARS*	
CMTR1C		*PLEKHG5*	
CMTR1D		*COX6A1*	
Axonal			NCV >38 m/sec
CMT2	AD		Young adult onset
CMT2A		*MFN2* *KIF1B (rare)*	Most common; also HMSN V (optic atrophy), VI (spasticity), and early onset
CMT2B		*RAB7*	Severe sensory loss like HSAN-1
CMT2C		*TRPV4*	Vocal cord/diaphragm weakness
CMT2D		*GARS*	Arm > leg, motor predominant, similar to dHMN caused by BSCL2 mutations
CMT2E		*NEFL*	Allelic with CMT1E; variable phenotype
CMT2F		*HSP27 (HSPB1)*	Motor predominant
CMT2G		12q12-13.3	Proximal > distal weakness
CMT2H, K		*GDAP1*	Allelic with CMT4A
CMT2I, J		*MPZ (P0)*	Cough, pain, autonomic/pupil, deafness
CMT2L		*HSP22 (HSPB8)*	Motor predominant, allelic with HMNIIa
CMTDIB, CMT2M		*DNM2*	Intermediate or CMT2; cataracts; ophthalmoplegia; ptosis
CMT2N		*AARS*	
CMT2P		*LRSAM1*	
CMT2Q		*DHTKD1*	
CMT2U		*MARS*	Late onset
CMT2V		*NAGLU*	Late-onset painful sensory predominant
CMT2W		*HARS*	
CMT2Y		*VCP*	
CMT2Z		*MORC2*	Pyramidal signs
CMT2			
CMT2 with giant axons		*DCAF8*	Childhood onset
CMT2		*TUBB3*	
CMT2		*DGAT2*	
CMT2		*JAG1*	Vocal fold paralysis
SPG10, CMT2		*KIF5A*	
HMSNP		*TFG*	Proximal > distal
AR-CMT2	AR		
CMT2B1		*LMNA*	Also called CMT2B1 and CMT4C1
CMT2B2		*MED25*	
NMAN		*HINT1*	
CMT2R		*TRIM2*	
CMT2S		*IGHMBP2*	

Table 653.1 Nonsyndromic Inherited Neuropathies—cont'd

DISEASE	INHERITANCE PATTERN	GENE OR LOCUS	CLINICAL FEATURES
CMT2T		*HSJ1*	
CMT2X		*KIAA1840*	
AR-CMT2	AR/AD	*MME*	Dominant pathogenic variants cause late onset
HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES (HSANS)			
HSAN			Sensory (± autonomic) neuropathy
HSAN1A	AD	*SPTLC1*	Late-onset, slowly progressive sensory axonal neuropathy ± SNHL, weakness
HSAN1B	AD	3p24-p22	Variant with cough, GERD, deafness
HSAN1C	AD	*SPTLC2*	
HSAN1D/SPG3A	AD	*ATL1*	
HSAN2A	AR	*HSN2*	Congenital sensory loss, acral mutilation
HSAN3	AR	*IKBKAP*	Severe dysautonomia, Ashkenazi Jews
HSAN4	AR	*TRKA*	Anhidrosis, acral mutilation, ± CNS
HSAN5	AR	*NGFB*	Congenital insensitivity to pain
HSAN6	AR	*DST*	Severe autonomic dysfunction, death by age 2
HSAN7	AD	*SCN11A*	Congenital insensitivity to pain, hyperhidrosis, GI dysfunction
HSAN8	AR	*PRDM12*	Congenital insensitivity to pain
HEREDITARY MOTOR NEUROPATHIES/NEURONOPATHIES (HMNS)			
HMN/dSMA			Distal wasting and weakness
HMNIIa	AD	*HSPB8(HSP22)*	Adult onset, allelic with CMT2L
HMNIIb	AD	*HSP27(HSPB1)*	Allelic with CMT2F
HMNVa	AD	*GARS*	Upper limb predominant
HMNVb	AD	*BSCL2*	Allelic with SPG17/Silver syndrome
HMNVI	AR	*IGHMBP2*	Severe infantile respiratory distress/SMARD
HMNVIIa	AD	2q14	Adult onset, vocal cord paralysis
HMNVIIb	AD	*DCTN1*	Same as above
HMNX	X	Xq13.1-q21	
HMNJ	AR	9p21.1-p12	Childhood-onset (Jerash type)
SBMA	X	Androgen Receptor (CAG rpt)	Adult-onset bulbar symptoms, proximal weakness, sensory neuronopathy, gynecomastia

This table lists the inherited neuropathies that are generally considered to affect the peripheral nerve exclusively or predominantly, although as shown in the Clinical Features column, many of these diseases affect the CNS and other tissues. For the columns, in the Disease column, the name is usually abbreviated, with full names below; inheritance pattern is listed as autosomal dominant (AD), autosomal recessive (AR), or X-linked (X); and for gene or locus, the affected gene(s) is listed if known; otherwise, the chromosomal locus is listed. In cases where the variant is not a missense variant, the type of variant is listed in parentheses (duplication, deletion, or CAG repeat). The diseases are grouped according to phenotype: HMSN, hereditary motor and sensory neuropathy; HS(A)N, hereditary sensory and (±autonomic) neuropathy; HMN, hereditary motor neuropathy, also called dSMA (distal spinal muscular atrophy); SBMA, spinal bulbar and muscular atrophy. The HMSNs are further divided into demyelinating, axonal, and intermediate forms based on the usual range of nerve conduction velocity (NCV).

CHN, Congenital hypomyelinating neuropathy; CMT, Charcot-Marie-Tooth disease; CMTDI, dominant intermediate CMT; CNS, central nervous system; DSS, Déjèrine-Sottas disease; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HNPP, hereditary neuropathy with liability to form pressure palsies; MCV, motor conduction velocity; MR, mental retardation; rpt, repeat; SMARD, spinal muscular atrophy with respiratory distress; SNHL, sensorineural hearing loss; SPG, hereditary spastic paraplegia (see Table 653.2).

From Motley W, Chaudry V, Lloyd TE. Treatment and management of hereditary neuropathies. In: Bertorini TE, ed. *Neuromuscular Disorders Treatment and Management*, 2nd ed. Philadelphia: Elsevier; 2022: Table 14.2, p. 280–282.

Table 653.2 Syndromic Neuropathies

DISEASE	INHERITANCE PATTERN	GENE OR LOCUS	CLINICAL FEATURES
HNA	AD	*SEPT9*	Recurrent brachial neuritis, dysmorphic features in some
Friedreich ataxia (FRDA)	AR	*Frataxin-GAA repeats*	Ataxia, sensory large fiber axonal neuropathy, positive Babinski sign, cardiomyopathy
AVED	AR	*TTPA*	FRDA-like, vitamin E deficiency
SCAN1	AR	*TDP1*	Spinocerebellar ataxia, sensory neuropathy

Continued

Table 653.2 Syndromic Neuropathies—cont'd

DISEASE	INHERITANCE PATTERN	GENE OR LOCUS	CLINICAL FEATURES
Ataxia-telangiectasia	AR	*ATM*	Ataxia, telangiectasias, malignancy, infections
SCA			Sensory neuropathy variable in most
SCA3/MJD	AD	*ATXN3*	Ataxia, spasticity, severe axonal neuropathy
SCA4	AD	*PLEKHG4*	Prominent axonal sensory neuropathy
SCA10	AD	*ATXN10*	± Sensorimotor neuropathy
SCA25	AD	2p21-p13	Prominent axonal sensory neuropathy
SCA27	AD	*FGF-14*	Mild axonal sensory neuropathy
HSP			"Complicated HSP" with neuropathy
SPG2	X	*PLP*	CNS white matter disease ± neuropathy
SPG7	AR	Paraplegin	± Neuropathy, dysarthria, dysphagia
SPG9	AD	10q23.3-24.1	Amyotrophy, cataracts, GERD
SPG10	AD	*KIF5A*	± Distal atrophy
SPG11	AR	*Spatacsin*	MR, nystagmus, thin corpus callosum
SPG14	AR	3q27-q28	Distal motor neuropathy, MR, visual agnosia
SPG15	AR	*Spastizin*	Pigmented maculopathy, MR, dysarthria
SPG17	AD	*BSCL2*	(Silver syndrome) hand atrophy prominent
SPG20	AR	*Spartin*	(Troyer syndrome) distal atrophy, dysarthria
FAP TTR	AD	*TTR*	Early adult-onset painful sensorimotor and autonomic neuropathy, entrapment neuropathy, cardiomyopathy, GI symptoms
(Iowa)		*ApoAI*	Similar to TTR, but progressive renal failure
(Finnish)		*Gelsolin*	Cranial neuropathies, corneal dystrophy
Fabry	X	*α-Gal-A*	Child-onset painful SFSN, renal failure, cardiac disease, strokes
Leukodystrophies			Some associated with demyelinating neuropathy
GLD/Krabbe	AR	*GALC*	Progressive MR, hyperreflexia, sz, optic atrophy
MLD	AR	*ARSA*	Same as above, though CNS sx less severe
PCWH/Waardenburg	AD	*SOX10*	CHN, central dysmyelination, Waardenburg and Hirschsprung syndrome
Adrenomyeloneuropathy	X	*ABCD1*	Spastic paraparesis, large fiber sensory loss, bowel and bladder incontinence
Merosin deficiency	AR	*LAMA2*	Neuropathy and muscular dystrophy
Refsum disease	AR	*PAHX* *PEX7*	Ataxia, retinitis pigmentosa, demyelinating neuropathy, cardiac, deafness, ichthyosis
AMACR deficiency	AR	*AMACR*	Adult-onset sensory and motor neuropathy, retinitis pigmentosa, seizures, ataxia, developmental delay, acute and relapsing encephalopathy with headache
Mitochondrial diseases			Neuropathy common, axonal or demyelinating
Leigh disease	ARmito	Multiple genes	Early onset CPEO, ptosis, ataxia, MR, pyramidal signs, demyelinating neuropathy
NARP	Mito	*MTATP6*	Sensory neuropathy, ataxia, retinitis pigmentosa
MNGIE	AR	*ECGF1* *POLG*	Ptosis, CPEO, leukoencephalopathy, neuropathy, myopathy, GI dysmotility
Porphyria	AD		
AIP		*PBGD*	Acute neuropathy, abdominal pain, psychosis, sz
Copro		*CPO*	Similar to AIP, but also skin photosensitivity
Variegate		*PPOX*	Similar to AIP, but also skin photosensitivity
Tangiers disease	AR	*ABC1*	Orange tonsils, organomegaly, low HDL, atherosclerosis
Abetalipoproteinemia	AR	*MTTP*	Ataxia, acanthocytosis, steatorrhea, low LDL

Table 653.2 Syndromic Neuropathies—cont'd

DISEASE	INHERITANCE PATTERN	GENE OR LOCUS	CLINICAL FEATURES
Hypobetalipoproteinemia	AD	*Apo-B*	Ataxia, sensory axonal polyneuropathy
GAN	AR	Gigaxonin	MR, kinky hair, biopsy shows giant axons
ACCPN	AR	*KCC3*	Agenesis of corpus callosum, French Canadian
CCFDN	AR	*CTDP1*	Congenital cataracts, facial dysmorphism

This table lists the inherited neuropathies in which the neuropathy is part of a systemic disease. For the columns, in Disease, the name is usually abbreviated, with full names below; in the column Inheritance Pattern, data are listed as autosomal dominant (AD), autosomal recessive (AR), X-linked (X), or mitochondrial (maternal) (mito); and for in the Gene or Locus column, the affected gene(s) is listed if known; otherwise, the chromosomal locus is listed.

ACCPN, Agenesis of the corpus callosum and peripheral neuropathy, also known as Anderman syndrome; AIP, acute intermittent porphyria; AMACR , alpha-methylacyl-CoA racemase; AVED, ataxia with isolated vitamin E deficiency; CCFDN, congenital cataracts, facial dysmorphism, neuropathy; CHN, congenital hypomyelinating neuropathy; CNS, central nervous system; Copro, coproporphyria; CPEO, chronic progressive external ophthalmoplegia; FAP, familial amyloidotic polyneuropathy; GAN, giant axonal neuropathy; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GLD, globoid-cell dystrophy; HDL, high-density lipoprotein; HNA, hereditary neuralgic amyotrophy; HSP, hereditary spastic paraplegia; LDL, low-density lipoprotein; MLD, metachromatic leukodystrophy; MJD, Machado-Joseph disease; MNGIE, mitochondrial neurogastrointestinal encephalopathy syndrome; MR, mental retardation; NARP, neuropathy, ataxia, and retinitis pigmentosa; PCWH, peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease; SCA, spinocerebellar ataxia; SCAN1, spinocerebellar ataxia with axonal neuropathy 1; SFSN, small fiber sensory neuropathy; SPG, spastic gait; sx, symptoms; sz, seizures; TTR, transthyretin; Variegate, variegate porphyria.

From Motley W, Chaudry V, Lloyd TE. Treatment and management of hereditary neuropathies. In: Bertorini TE, ed,. *Neuromuscular Disorders Treatment and Management,* 2nd ed. Philadelphia: Elsevier; 2022: Table 14.3, p. 283–284.

Table 653.3 Polyneuropathies with Onset in Infancy

SALIENT CLINICAL FEATURE	CLINICAL PHENOTYPE	GENE	MODE OF INHERITANCE
AXONAL NEUROPATHIES			
Pes cavus with footdrop	CMT2E	*NEFL*	AD, AR
Optic atrophy	CMT2A	*MFN2*	AD, AR
	CMT4A	*GDAP1*	AR
	IOSCA	*C10orf2*	AR
	Infantile neuroaxonal dystrophy	*PLA2G6*	AR
Ophthalmoparesis	Mitochondrial disorders	*SCO2* *C10orf2* *TK2*	AR
Skeletal abnormalities	CMT2C, SPSMA, congenital dSMA	*TRPV4*	AD
Arthrogryposis	Congenital dSMA	*TRPV4*	AD
	SMARD1	*IGHMBP2*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	*TRIP4* *ASCC1*	Presumed AR
Congenital fractures	X-linked SMA	*UBE1*	X-linked
	SMA with congenital fractures	*TRIP4* *ASCC1*	Presumed AR
Vocal cord paresis	CMT2A	*MFN2*	AD, AR
	CMT2C, SPSMA, congenital dSMA	*TRPV4*	AD
	CMT4A	*GDAP1*	AR
	BVVL/Fazio-Londe disease	*SLC52A3*	AR
Early infantile respiratory failure	SMA1	*SMN1*	AR
	SMARD1	*IGHMBP2*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	*TRIP4* *ASCC1*	Presumed AR
	Lethal neonatal AR axonal sensorimotor polyneuropathy	Unknown	AR
	Congenital axonal neuropathy with encephalopathy	Unknown	Unknown, presumed AR

Continued

Table 653.3 Polyneuropathies with Onset in Infancy—cont'd

SALIENT CLINICAL FEATURE	CLINICAL PHENOTYPE	GENE	MODE OF INHERITANCE
AXONAL NEUROPATHIES			
Predominant motor involvement	Congenital dSMA, SPSMA	*TRPV4*	AD
	SMA1	*SMN1*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	*TRIP4* *ASCC1*	Presumed AR
	Mitochondrial disorders	*SCO2, TK2*	AR
Kinky hair hepatopathy	Giant axonal neuropathy	*GAN*	AR
	Mitochondrial disorders	*DGUOK* *C10orf2*	AR
	MTP/LCHAD deficiency	*HADHA/HADHB*	AR
Cardiomyopathy	Mitochondrial disorders	*SCO2*	AR
		TK2	AR
		DGUOK	AR
	MTP/LCHAD deficiency	*HADHA/HADHB*	AR
CNS involvement	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	Giant axonal neuropathy	*GAN*	AR
	Infantile neuroaxonal dystrophy	*PLA2G6*	AR
	HMSN/ACC	*KCC3*	AR
	IOSCA	*C10orf2*	AR
	CMTX1	*GJB1*	X-linked
	Mitochondrial disorders	*SCO2*	AR
		TK2	AR
		DGUOK	AR
	Adrenoleukodystrophy	*ABCD1*	X-linked
Developmental regression	Adrenoleukodystrophy	*ABCD1*	X-linked
Dysautonomia, chronic skin ulceration	HSAN III (Riley-Day syndrome)	*IKBKAP*	AR
DEMYELINATING NEUROPATHIES			
Acute sensory ataxia, walking difficulties in a previously well child	GBS		
Slowly progressive weakness, ataxia in a previously well child; responsive to steroids	CIDP		
Developmental regression	MLD	*ARSA*	AR
	Krabbe disease	*GALC*	AR
Irritable, stiff, crying infant; occasional unexplained fevers	Krabbe disease	*GALC*	AR
Pes cavus with footdrop, marked difficulties walking	CMT1A	*PMP22* point variants or duplication	De novo (AD), AR
	CMT1B	*MPZ*	De novo (AD)
	CMT1F	*NEFL*	AD, AR
	CMT4C	*SH3TC2*	AR
	CMT4E	*EGR2*	AR, AD
	CMT4F	*PRX*	AR
	CMT4H	*FGD4*	AR

Table 653.3 Polyneuropathies with Onset in Infancy—cont'd

SALIENT CLINICAL FEATURE	CLINICAL PHENOTYPE	GENE	MODE OF INHERITANCE
AXONAL NEUROPATHIES			
Early respiratory insufficiency	CMT1A	*PMP22* point variants or duplication	De novo (AD), AR
	CMT1B	*MPZ*	De novo (AD)
	CMT4C	*SH3TC2*	AR
	CMT4E	*EGR2*	AR, AD
Severe scoliosis requiring surgery in infancy	CMT1B	*MPZ*	De novo (AD)
	CMT4C	*SH3TC2*	AR
Facial weakness	CMT4B1	*MTMR2*	AR
	CMT4B2	*SBF2*	AR
	CMT4C	*SH3TC2*	AR
Sensorineural hearing loss	CMT1A	*PMP22* point variants or duplication	De novo (AD), AR
	CMT4C	*SH3TC2*	AR
	CMT4F	*PRX*	AR
Congenital nystagmus	CMT1B	*MPZ*	De novo (AD)
	CMT4C	*SH3TC2*	AR

AD, Autosomal dominant; AR, autosomal recessive; BVVL, Brown-Vialetto-Van Laere syndrome; CMT, Charcot-Marie-Tooth disease; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; dSMA, distal spinal muscular atrophy; GBS, Guillain-Barré syndrome; HMSN/ACC, hereditary motor and sensory neuropathy with agenesis of the corpus callosum; HSAN, hereditary sensory and autonomic neuropathy; IOSCA, infantile-onset spinocerebellar ataxia; MLD, metachromatic leukodystrophy; MTP/LCHAD, mitochondrial trifunctional protein/long-chain 3-hydroxyacyl-CoA dehydrogenase; SMA, spinal muscular atrophy; SMARD, spinal muscular atrophy with respiratory distress type 1; SPSMA, scapuloperoneal spinal muscular atrophy.

From Konersman C. Hypotonia, weakness, and stroke. In: Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Symptom-Based Diagnosis.* Philadelphia: Elsevier; 2018: Table 29.19.

Table 653.4 Infantile Demyelinating Neuropathies with CNS Involvement

	INHERITANCE	GENE	OTHER FEATURES
ASSOCIATED WITH CNS HYPOMYELINATION			
Hypomyelination with congenital cataracts (HCC)	AR	*DRCTNNBIA*	Congenital cataracts, pyramidal signs, cerebellar signs, intellectual disability
Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH)	AD	*SOX10*	Waardenburg syndrome, Hirschsprung disease, spasticity, ataxia, dysautonomia, intellectual disability
Pelizaeus-Merzbacher disease	X-linked	*PLP1**	Early nystagmus and titubation, ataxia, spasticity, movement disorder, intellectual disability
Pelizaeus-Merzbacher–like disease	AR	*GJA12*	Nystagmus, ataxia, delayed development
Cockayne syndrome	AR	*ERCC6, ERCC8*	Growth failure, photosensitivity, retinopathy, progressive neurologic impairment
ASSOCIATED WITH ABNORMAL CNS WHITE MATTER			
Metachromatic leukodystrophy	AR	*ARSA*	Psychomotor regression, spasticity, seizures
Krabbe disease	AR	*GALC*	Extreme irritability, spasticity, psychomotor regression
Niemann-Pick disease type C†	AR	*NPC1, NPC2*	Hepatomegaly, vertical gaze palsy, progressive ataxia, dystonia, cataplexy
Merosin-deficient congenital muscular dystrophy	AR	*LAMA2*	Proximal weakness, raised creatine kinase, muscular dystrophy
Navajo neurohepatopathy	AR	*MPV17*	Liver disease, corneal scarring, recurrent metabolic acidosis, recurrent infections, failure to thrive
ASSOCIATED WITH OTHER CNS INVOLVEMENT			
Congenital disorders of glycosylation	AR	Multiple genes	Variable features
Congenital cataracts, facial dysmorphism and neuropathy (CCFDN)	AR	*CTDP1*	Congenital cataracts, microretina, intellectual disability, facial dysmorphism, short stature, hypogonadism

Continued

Table 653.4 Infantile Demyelinating Neuropathies with CNS Involvement—cont'd

	INHERITANCE	GENE	OTHER FEATURES
POLG-related hepatocerebral mtDNA deletion syndromes	AR	*POLG1*	Encephalopathy, refractory seizures, liver dysfunction
Leigh syndrome	AR, X-linked, mitochondrial	Multiple genes	Psychomotor regression, brainstem and basal ganglia signs, raised lactate levels

*Peripheral neuropathy associated with *PLP1* null mutations only.
†Peripheral neuropathy rarely seen in Niemann-Pick disease type.
AD, Autosomal dominant; AR, autosomal recessive; CNS, central nervous system; mtDNA, mitochondrial DNA.
From Yiu EM, Ryan MM. Demyelinating prenatal and infantile developmental neuropathies. *J Peripher Nerve Syst*. 2012;17:32–52. Table 4.

Table 653.5 Characterization of Inherited Loss of Pain Perception Syndrome

GENE (PROTEIN)	PROTEIN FUNCTION	INHERITANCE	CLASSIFICATION	TYPICAL ONSET	PROMINENT AND DISTINGUISHING FEATURES
ARL6IP1 (ARL6IP1)	Organization of endoplasmic reticulum and mitochondrial networks	AR	NC	Congenital	Spastic paraplegia and severe acromutilations
ATL1 (ATL)	Membrane-shaping molecule	AD	HSAN1 (allelic with spastic paraplegia: SPG 3 A)	Adulthood	Impaired sensation of touch, involvement of upper motor neurons (some cases), fractures, and osteomyelitis
ATL3 (ATL3)	Membrane-shaping molecule	AD	HSAN1	Adulthood	Spasticity (some cases), fractures, osteomyelitis, and severely delayed wound healing
*CLTCL*1 (CH22,CLH-22)	Clathrin-coated vesicles	AR	NC	Congenital	Inability to feel touch and developmental delay
DNMT1 (DNMT1)	Epigenetic regulation	AD	HSAN1 (allelic with autosomal dominant cerebellar ataxia, deafness, and narcolepsy: ADCADN)	Adulthood	Sensorineural hearing loss, progressive dementia, and sleep disorder
DST (DST)	Organization of the cytoskeleton	AR	HSAN6 (allelic with epidermolysis bullosa, isoform-dependent)	Congenital	Severe psychomotor delay, joint contractures, alacrima, feeding difficulties, cardiovascular instability, hypomimia, and muscle weakness
ELP1 (ELP1/1KAP)	Transcription elongation factor complex	AR	HSAN3 (allelic with medulloblastoma predisposition syndrome)	Congenital	Loss of proprioception leading to spinal deformities, alacrima, gastrointestinal dysfunction, cardiovascular instability, and autonomic crises
FAAH-OUT (non-coding RNA. FAAHPl)	Endocarmabinoid signaling	AD/AR	CIP	Congenital	Impaired anxiety
FLVCR1 (FLVCR1)	Heme metabolism	AR	NC (allelic with posterior column ataxia with retinitis pigmentosa: PCARP)	Congenital	Psychomotor delay, delayed wound healing, anemia, and retinitis pigmentosa
GMPPA (GMPPA)	Protein glycosylation	AR	Alacrima, achalasia, and mental retardation syndrome (AAMR)	Congenital	Psychomotor delay, achalasia (swallowing disorder), and alacrima (lack of tears)
KIF1A (KIF1A)	Axonal transport	AR	HSAN2	Childhood	Muscle weakness and autonomic involvement
MADD (MADD)	TNF signaling	AR	Developmental delay with endocrine, exocrine, autonomic, and hematologic abnormalities (DEEAH)	Congenital	Psychomotor delay, exocrine and endocrine dysfunction, and pancreatic insufficiency

Table 653.5 Characterization of Inherited Loss of Pain Perception Syndrome—cont'd

GENE (PROTEIN)	PROTEIN FUNCTION	INHERITANCE	CLASSIFICATION	TYPICAL ONSET	PROMINENT AND DISTINGUISHING FEATURES
MPV17	Maintenance of mitochondrial DNA (mtDNA)	AR	CMT2EE (allelic with mitochondrial DNA depletion syndrome 6: MTDPS6)	Juvenile, adulthood	Distal sensory impairment signs of CMT, restrictive lung disease, steatosis, and muscle weakness
NCF (NGF)	Neurotrophin signaling	AR	HSAN5	Congenital	Variable degree of intellectual disability, fractures, osteomyelitis, corneal lesions, and anhidrosis (lack of sweating leading to hyperthermia and fever episodes)
NTRK1 (TRKA)	Neurotrophin signaling	AR	HSAN4	Congenital	Variable degree of intellectual disability, painless fractures, osteomyelitis, corneal lesions, and anhidrosis (lack of sweating leading to hyperthermia and fever episodes)
PRDM 12 (PRDM12)	Epigenetic regulation	AR	HSAN8	Congenital	Normal intellect, but in a few cases intellectual disability, facial injuries, corneal lesions, and hypohidrosis
RAB7A (RAB7)	Axonal transport	AD	HSAN (also classified as Charcot-Marie-Tooth; CMT2B)	Adulthood	Strong motor involvement
RETREG1 (RETREG1/ FAM134B)	Selective autophagy of the ER (ER-phagy), Golgi	AR	HSAN2	Childhood	Spasticity: muscle weakness may occur, osteomyelitis, and hyper- hidrosis
RFC1 (RFC 1)	DNA synthesis during replication or after damage	AR	Chronic idiopathic axonal polyneuropathy (CIAP)/ HSAN (allelic with CANVAS)	Adulthood	Large clinical spectrum: sensory neuropathy, numbness (sometimes with pain), chronic cough, cerebellar and vestibular dysfunction, afferent ataxia/proprioceptive loss
SCN9A (Na, 1.7)	Voltage-gated sodium channel (neuron excitability)	AR	CIP/HSAN2	Congenital	Anosmia (absent sense of smell) and fractures
SCN11A (Nav l.9)	Voltage-gated sodium channel (neuron excitability)	AR	CIP/HSAN7	Congenital	Pruritus, delayed motor development, joint hypermobility, skin ulcers (cervical region), intestinal dysmotility, and sometimes abdominal pain
SPTLC1 (SPTLCl)	Sphingolipid metabolism	AD	HSAN1 (allelic with ALS)	Adulthood	Mild motor involvement (some cases more pronounced), osteomyelitis, amputations, autonomic involvement rare, shooting and lancinating pain
SPTLC2 (SPTLC2)	Sphingolipid metabolism	AD	HSAN1	Adulthood	Mild motor involvement (some cases more pronounced), osteomyelitis, amputations, autonomic involvement rare, shooting and lancinating pain
TECPR2 (TECPR2)	Autophagy	AR	HSAN9 (allelic with spastic paraplegia: SPG49)	Congenital	Dysautonomia and respiratory failure
WNKl (WNK1)	Kinase activity, ion transport and ER function	AR	HSAN 2	Childhood	Severe acral mutilations
ZFHX2 (ZFHX2)	Transcription	AD	CIP	Congenital	Normal intellect

AD, Autosomal dominant; AR, autosomal recessive; CANVAS, cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; CIP, congenital insensitivity to pain; CMT, Charcot-Marie-Tooth; ALS, amyotrophic lateral sclerosis; ER, endoplasmic reticulum; HSAN, hereditary sensory and autonomic neuropathy; NC, not classified.

From Lischka A, Lassuthova P, Çakar A, et al. Genetic pain loss disorders. *Nat Rev Dis Primers*. 2022;8:41. Table 1.

The leg should be protected from traumatic injury. In advanced cases, compression neuropathy during sleep may be prevented by placing soft pillows beneath or between the lower legs. Burning paresthesias of the feet are not common but are often abolished by phenytoin, carbamazepine, or gabapentin. Progressive resistance exercise for foot dorsiflexion may attenuate the progression of weakness.

Hereditary sensory autonomic neuropathy 1 (HSAN1) has, in preliminary studies, been treated with oral L-serine, with biochemical improvements (lowering of toxic metabolites). Multiple gene replacement therapies for CMT disease are in the experimental stage.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.2 Peroneal Muscular Atrophy (Axonal Type)

Adnan Y. Manzur

Peroneal muscular atrophy is clinically similar to HMSN type I, but the rate of progression in the disability is variable. EMG shows denervation of muscle. Sural nerve biopsy reveals axonal degeneration rather than the demyelination and whorls of Schwann cell processes typical in the demyelinating type I. The most common form of axonal HMSN is caused by pathogenic variants in the *MFN2* gene with locus on chromosome 1 at 1p36. More than 40 genes have been described as causing axonal HMSN, and the inheritance can be dominant or recessive.

An autosomal recessive infantile motor axonal neuropathy can closely mimic infantile spinal muscular atrophy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.3 Congenital Hypomyelinating Neuropathy and Déjèrine-Sottas Disease (HMSN Type III)

Adnan Y. Manzur

Congenital hypomyelinating neuropathy is an interstitial hypertrophic neuropathy of autosomal dominant transmission, clinically similar to HMSN type I but more severe. Symptoms develop in early infancy and are rapidly progressive, with hypotonia and breathing and feeding difficulties. Pupillary abnormalities, such as lack of reaction to light and *Argyll Robertson pupil,* are common. Kyphoscoliosis and pes cavus deformities complicate approximately 35% of cases. Nerves become palpably enlarged at an early age. Déjèrine-Sottas disease is a more slowly progressive variant with onset usually before age 5 years.

An autosomal recessive form of congenital hypomyelinating neuropathy also is known and may be caused by various pathologic genetic variants, including *MTMR2, PMP22, EGR2,* and *MPZ.* A secondary variant in the *EGR2* gene may intensify the clinical manifestation of Déjèrine disease. Neonatal hypotonia and developmental delay in infancy are hallmark clinical features. Many patients exhibit congenital insensitivity to pain. Cranial nerves are inconsistently involved, and respiratory distress and dysphagia are rare complications. Tendon reflexes are absent. **Arthrogryposis** is present at birth in at least half of the cases.

The onion bulb formations seen in the sural nerve biopsy specimen are pronounced. Hypomyelination also occurs. In the recessive form, hypomyelination may not be accompanied by interstitial hypertrophy in all cases.

The genetic locus of 17p11.2 is identical to that of HMSN type I or CMT disease. Monoallelic variants in *MPZ* (myelin protein zero), *PMP22,* or *EGR2* (early grow response 2) are the most frequent genetic causes. The clinical and pathologic differences may be phenotypic variants of the same disease, analogous to the situation in Duchenne and Becker muscular dystrophies. An autosomal recessive form of Déjèrine-Sottas disease is incompletely documented.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.4 Roussy-Lévy Syndrome

Adnan Y. Manzur

Roussy-Lévy syndrome is defined as a combination of HMSN type II and cerebellar deficit resembling Friedreich ataxia, but it does not have cardiomyopathy.

653.5 Refsum Disease (HMSN Type IV) and Infantile Refsum Disease

Adnan Y. Manzur

See also Chapter 106.2.

Refsum disease is a rare autosomal recessive disease caused by an enzymatic block in β-oxidation of phytanic acid to pristanic acid. Phytanic acid is a branched-chain fatty acid that is derived mainly from dietary sources, such as spinach, nuts, and coffee. Levels of phytanic acid are greatly elevated in plasma, CSF, and brain tissue. Phytanic and very long-chain fatty acids may be lipotoxic by impairing mitochondrial function in the central and peripheral nervous systems. The CSF shows an albuminocytologic dissociation, with a protein concentration of 100-600 mg/dL. Genetic linkage studies identify two distinct loci at 10p13 and 6q22-q24 with *PHYH* and *PEX7* pathogenic variants, respectively. The infantile form also can be caused by the *PEX1, PEX2,* or *PEX26* genes, which produce both clinical and biochemical differences from the classic form, and include minor facial dysmorphism, retinitis pigmentosa, sensorineural hearing loss, hypercholesterolemia, hepatomegaly, and failure to thrive. Phytanic acid accumulation in infantile Refsum disease is secondary to a primary peroxisomal disorder; hence, autosomal recessive Refsum disease is really a different disease.

The clinical onset of classic Refsum disease is usually between 4 and 7 years of age, with intermittent motor and sensory neuropathy. Ataxia, progressive neurosensory hearing loss, retinitis pigmentosa with loss of night vision, ichthyosis, and liver dysfunction also develop in various degrees. Skeletal malformations from birth and cardiac findings of conduction disturbances and cardiomyopathy appear in the majority. Motor and sensory nerve conduction velocities are delayed. Sural nerve biopsy shows loss of myelinated axons. Treatment is by dietary management and periodic plasma exchange. With careful management, life expectancy can be normal. Hearing loss due to acoustic nerve involvement may sometimes be improved with cochlear implantation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.6 Fabry Disease

Adnan Y. Manzur

See also Chapter 106.4.

Fabry disease, a rare X-linked recessive trait, results in storage of ceramide trihexoside because of deficiency of the enzyme ceramide trihexosidase, which cleaves the terminal galactose from ceramide trihexoside (ceramide-glucose-galactose-galactose), resulting in tissue accumulation of this trihexoside lipid in central nervous system neurons, Schwann cells and perineurial cells, ganglion cells of the myenteric plexus, skin, kidneys, blood vessel endothelial and smooth muscle cells, heart, sweat glands, cornea, and bone marrow. It results from a missense pathogenic variant disrupting the crystallographic structure of α-galactosidase A.

CLINICAL MANIFESTATIONS

The presentation is in late childhood or adolescence, with recurrent episodes of burning pain and paresthesias of the feet and lower legs so severe that patients are unable to walk. These episodes are often precipitated by fever or by physical activity. Objective sensory and motor deficits are not demonstrated on neurologic examination, and reflexes are preserved. Autonomic nerve involvement is almost universal and may cause cardiac rhythm abnormalities, cutaneous mottling, and gastrointestinal peristaltic abnormalities; autonomic expression is variable between patients. Cardiac involvement is not limited to autonomic abnormalities of arrhythmias and conduction defects, but may also include left ventricular hypertrophy, coronary artery disease, and valvular infiltrative myopathy. Characteristic skin lesions are seen in the perineal region, scrotum, buttocks, and periumbilical zone as flat or raised red-black telangiectasias known as **angiokeratoma corporis diffusum.** Hypohidrosis may be present. Corneal opacities, cataracts, and necrosis of the femoral heads are inconstant features. Tortuosity of retinal vessels and of the vertebral and basilar arteries can occur. The disease is progressive. Hypertension and renal failure are usually delayed until early adult life. Recurrent strokes result from vascular wall involvement. Untreated, death often occurs in the fifth decade due to cerebral infarction or renal insufficiency, but a significant morbidity already occurs in childhood despite the absence of major organ failure. Heterozygous female carriers may be asymptomatic or less severely affected than symptomatic males; corneal opacities involve 70–80%, though cataracts are rare.

LABORATORY FINDINGS

Motor and sensory nerve conduction velocities are normal to only mildly slow, showing preservation of large, myelinated nerve fibers. CSF protein is normal. Proteinuria is present early in the course. An electrochemical skin conductance test is abnormal in the majority of Fabry patients as an indication of small sensory nerve and autonomic nerve involvement. Cardiac evaluation should include ECG, echocardiography, and coronary artery assessment in selected cases.

Calcifications often are seen in the pulvinar of the thalamus, as demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI), and are specific imaging findings, believed caused by cerebral hyperperfusion. Positron tomography, by contrast, shows reduced cerebral blood flow velocity and impaired autoregulation because of the glycosphingolipid storage in vascular endothelial cells.

Pathologic features are usually first detected in skin or sural nerve biopsy specimens. Electron microscopy demonstrates crystalline glycosphingolipids, appearing as *zebra bodies,* in lysosomes of endothelial cells, in smooth myocytes of arterioles, and in Schwann cells. Nerves show a selective loss of small, myelinated fibers and relative preservation of large- and medium-sized axons, in contrast to most axonal neuropathies, in which large, myelinated fibers are most involved.

An assay for the deficient enzyme, α-galactosidase-A, may be performed from blood leukocytes, skin fibroblasts, and other tissues. This test may permit detection of the female carrier state; for females, gene sequencing is preferred.

TREATMENT

See Chapter 106.4 for the specific therapy of Fabry disease, including enzyme replacement.

Medical therapy of painful neuropathies includes management of the initiating disease and therapy directed to the neuropathic pain independent of the etiology. Pain may be burning or associated with paresthesia, hyperalgesia (abnormal response to noxious stimuli), or allodynia (induced by nonnoxious stimuli; see Chapter 93). Neuropathic pain is often successfully managed by tricyclic antidepressants; selective serotonin reuptake inhibitors are less effective. Anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine) are effective, as are narcotic and nonnarcotic analgesics. **Enzyme replacement therapy** has improved the short- and long-term prognosis of the clinical neuropathy and also reverses the increased blood flow velocity in the brain. Chaperone therapy with migalastat facilitates trafficking and stabilization of the abnormal enzyme.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.7 Giant Axonal Neuropathy

Adnan Y. Manzur

Giant axonal neuropathy is a rare autosomal recessive disease with onset in early childhood. It is a progressive mixed peripheral neuropathy and degeneration of central white matter similar to leukodystrophies (Table 653.6). Ataxia and nystagmus are accompanied by signs of progressive peripheral neuropathy. A large majority of affected children have frizzy or kinky hair, which microscopically shows variation in the diameter of the shaft and twisting, similar to that in Menkes disease; microscopic examination of a few scalp hairs provides a simple screening tool in suspected cases. Focal axonal enlargements are seen in both the peripheral nervous system and the central nervous system, but the myelin sheath is intact. The disease is a general proliferation of intermediate filaments, including neurofilaments in axons, glial filaments (i.e., Rosenthal fibers) in brain, cytokeratin in hair, and vimentin in Schwann cells and fibroblasts.

Nonsense, missense gene variants, splice site variants, or deletions occur in *GAN,* with allelic heterogeneity at 16q24. These gene variants are responsible for defective synthesis of the protein gigaxonin, a member of the cytoskeletal BTB/kelch superfamily, crucial to linkage between intermediate proteins and the cell membrane. MRI shows white matter lesions of the brain similar to leukodystrophies (Fig. 653.1A,B), and MR spectroscopy demonstrates increased ratios of choline:creatine and myoinositol:creatine, with decreased *N*-acetyl aspartate, indicating demyelination and glial proliferation, as well as axonal loss. Gigaxonin is expressed in a wide variety of neuronal cell types and is localized to the Golgi apparatus and endoplasmic reticulum. *GAN* gene variants have been demonstrated in human cell lines of neoplastic cells and also in a variety of tumors.

The diagnosis is suspected clinically based upon a childhood onset of ataxic gait, findings of neuropathy, and kinky or curly hair (see Fig. 653.1C); it is genetically confirmed by testing of the *GAN* gene. Pathologic findings of enlarged or swollen axons from peripheral nerve biopsy are characteristic. Clinically, the onset of symptoms occurs within the first 5 years of life, and there is progressive ataxia and weakness. As the disease progresses, patients also develop dysphagia, dysarthria, optic neuropathy, respiratory insufficiency, scoliosis (see Fig. 653.1E), and some in later stages will develop seizures. A gene variant of *BAG3,* one of several genes associated with myofibrillar myopathy (see Chapter 648.5), also can cause the finding of giant axons histologically, but clinically it is distinguished from giant axonal neuropathy caused by pathologic variants in the *GAN* gene.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.8 Hypermyelinating (Tomaculous) Neuropathy; Hereditary Neuropathy with Liability to Pressure Palsies

Adnan Y. Manzur

This hereditary neuropathy is characterized by redundant overproduction of myelin around each axon in an irregular segmental fashion so that tomaculous (sausage-shaped) bulges occur in the individual myelinated nerve fibers. Other sections of the same nerve can show loss of myelin. Such nerves are particularly prone to pressure palsies, and patients, usually beginning in adolescence, present with recurrent or intermittent mononeuropathies secondary to minor trauma or entrapment neuropathies, such as carpal tunnel syndrome, peroneal

Table 653.6 Clinical Features of Human Disorders Caused by Pathogenic Variants in Ion Channel and Inflammatory Genes That Lead to Altered Pain Perception and Are Inherited in a Mendelian Manner

DISORDER	GENE (PROTEIN)	TYPE AND EFFECT OF GENE	MAIN PHENOTYPE	ADDITIONAL FEATURES
ION CHANNELS				
Inherited erythromelalgia (primary)	*SCN9A* ($Na_v1.7$)	Heterozygous, activating GOF, AD	Onset by age 20 yr; episodic pain triggered by warmth; feet affected more frequently than hands; burning distal extremity pain initiated by heat or physical activity	Erythema and warmth; cold relieves symptoms (see Chapter 211.5)
Paroxysmal extreme pain disorder	*SCN9A* ($Na_v1.7$)	Heterozygous, activating GOF	Onset at birth; episodic pain; sacral region is affected most frequently; face is affected more often than the limbs; physical triggers include defecation	Erythema of the sacrum; tonic attacks
Small-fiber neuropathy	*SCN9A* ($Na_v1.7$)	Heterozygous, activating GOF	Onset at any age but more common in early adulthood; persistent burning pain; feet affected more frequently than hands	Could be autonomic features
Small-fiber neuropathy	*SCN10A* ($Na_v1.8$)	Heterozygous, activating GOF	Persistent burning pain	Could be autonomic features
Familial episodic pain syndrome type I	*TRPA1* (TRPA1)	Heterozygous, activating GOF	Onset at birth or in infancy; episodic chest or arm pain; triggers are hunger and cold	—
Familial episodic pain syndrome type III	*SCN11A* ($Na_v1.9$)	Heterozygous, activating GOF	Onset in first decade; episodic hand and foot pain; triggers are intercurrent illness or exercise	—
INFLAMMATION				
STING-associated vasculopathy infantile onset (SAVI)	*TMEM173 (STING1)* GOF	AD	Onset in infancy Rash → ulcers-necrosis, nose, fingers, toes, ears Exacerbated by cold	Lung and joint involvement
Aicardi-Goutières syndrome	*TREX1* *RNASEH2A* *RNASEH2B* *RNASEH2C* *IFIN1*	AR; rarely AD	Inconsolable crying, jittery, seizures, microcephaly, rashes, poor feeding	—
Familial chilblain lupus	*TREX1* *SAMHD1* *LOF; rarely GOF* *STING*	AD	Cold-induced erythema, onset early childhood Papules, plaques on fingers, nose, toes, ear, cheeks	—

AD, Autosomal dominant; AR, autosomal recessive; GOF, gain of function; LOF, loss of function; Na_v, sodium ion channel.
Modified from Rabbitt AL. The irritable infant. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 30.7, p. 511.

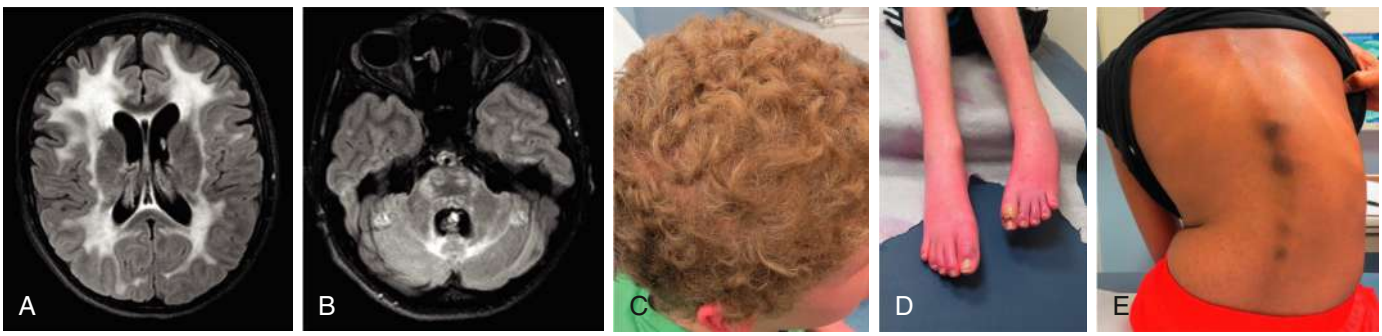

Fig. 653.1 Giant axonal neuropathy (GAN). **A** and **B,** White matter abnormalities on T2/fluid-attenuated inversion recovery (FLAIR) sequences seen diffusely and including the brainstem and cerebellum in a more advanced patient with GAN. There is also mild ex vacuo dilatation of the ventricles due to progressive atrophy. **C,** Typical kinky hair in GAN (i.e., dry and tight curly hair) often evident in patients from birth or early childhood. **D,** Patients with GAN develop distal atrophy and contractures and may have pedal erythema. **E,** Children with GAN often develop scoliosis by 8-10 yr of age.

palsies, and even writer's cramp. Phenotype expression is somewhat variable. It is transmitted as an autosomal dominant trait, with loci identified at 17p11.2 and 17p12, and deletion of exons in *PMP22* (in some patients, only microdeletions). Duplication of the same 17p12 locus leads to CMT disease type 1A, *MPZ* gene variants. Sural nerve biopsy is diagnostic, but special teased fiber preparations should be made to demonstrate the myelin abnormalities most clearly. Skin or conjunctival biopsies also may be diagnostic. Electrophysiologic nerve conduction studies are abnormal but nonspecific. Genetic studies are definitive.

Treatment is supportive and includes avoiding trauma and prolonged nerve compression, including postures when sitting or lying. Surgical release of entrapped nerves is indicated at times, particularly of the ulnar nerve.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.9 Leukodystrophies

Adnan Y. Manzur

Several hereditary degenerative diseases of white matter of the central nervous system also cause peripheral neuropathy. The most important are Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, and adrenoleukodystrophy (see Chapters 106 and 639). Within the brain, they produce progressive but selective demyelination, affecting the deep white matter of the centrum semiovale with relative sparing of U-fibers around each gyrus. Additional metabolic disorders associated with peripheral neuropathy are noted in Table 653.2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

653.10 Congenital Hereditary Sensory Pain Syndromes

Adnan Y. Manzur

Nociception is the result of complex activity in sensory pathways, whereas *pain* is the interaction between nociception, cognition, emotion, and social learning. There are genetic disorders of "nociception," which encompass a range of rare conditions and several genes. These are labeled as "pain" syndromes, which may make clinical assessment difficult.

In understanding genotype-phenotype pathophysiology, there are genes encoding the voltage-dependent sodium channel (Nav channel) 1.7, which is expressed selectively in sensory and autonomic neurons. Inactivating gene variants in SCN9A Nav1.7 result in congenital insensitivity to pain (see Table 653.5), whereas gain-of-function gene variants produce distinct pain syndromes such as inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and small-fiber neuropathy (see Table 653.6).

GENETIC DISORDERS WITH INCREASED PAIN THRESHOLD OR INSENSITIVITY TO PAIN

Congenital insensitivity to pain disorders are diagnosed in infancy or early childhood (see Chapter 655). Table 653.5 provided a summary of some of the phenotypes presenting with abnormal deficiencies in autonomic nervous system function like anhidrosis, recurrent fever, defective tears, and feeding problems.

The collective term *congenital insensitivity to pain* has five underlying causative HSAN. Each are associated with unique clinical features, and all are autosomal recessive, apart from HSAN I, which is autosomal dominant. Figure 653.2 is a composite illustration of clinical images of patients with HSAN. These disorders can involve ion channels (channelopathies) or other key elements of nociception transduction pathways, such as modulators.

HSAN-I

HSAN-I is the most common type of HSAN, and it affects all nerve fiber types. The consequent clinical and sensory deficits are diminished or absent reflexes, distal loss of proprioception, light touch, and sensitivity to noxious thermal stimuli. HSAN-I has an autosomal dominant pattern of inheritance with different causative pathologic gene variants, which mostly involve the *SPTLC1* gene (HSAN-IA) and lead to reduced activity of serine palmitoyltransferase (a key enzyme in sphingolipid synthesis).

The disease is evident in late adolescence to the early thirties and features pupillary abnormalities, loss of corneal reflex and abrasions, deafness, restless legs, cramps, absent reflexes, Charcot joints, and development of painless injuries of the tongue and limbs. The clinical picture may also be complicated with the occurrence of osteomyelitis and sepsis. In this instance, the sensory disturbances of nociception are not a consequence of an ion channel or receptor defect, but down to membrane impairment in signal transduction and variants in the *SPTLC2* gene. Gene variants in the *ATL1* and *ATL3* genes (altered synthesis of axonal proteins), as well as the *DNMT1* gene (DNA methylation protein) have also been reported in HSAN-I.

HSAN-II

HSAN-II has an autosomal recessive inheritance pattern. The age of clinical onset is during infancy. HSAN-II affects all myelinated fibers,



Fig. 653.2 Clinical images of patients with HSAN. These patients may present with a variety of severe clinical symptoms and signs including self-inflicted mutilations of the tongue, lips, and distal phalanges, as well as corneal opacities, foot ulcers, and deformities. Excessive scratching may occur, leading to painless tissue damage. Recurring fractures can result in malposition of bones and joints, here represented by a knee joint in a patient with *SCN11A* gene variant. The affected genes are indicated, respectively. *(From Lischka A, Lassuthova P, Cakar A, et al. Genetic pain loss disorders. Nat Rev Dis Primer. 2022;8:41. Fig. 4; ATL3 from Kornak U, Mademan I, Schinke M, et al. Sensory neuropathy with bone destruction due to a mutation in the membrane-shaping atlastin GTPase 3. Brain. 2014;137(Pt 3):683–692. Fig 3; PRDM12 from Chen YC, Auer-Grumbach M, Matsukawa S, et al. Transcriptional regulator PRDM12 is essential for human pain perception [published correction appears in Nat Genet. 2015 Aug;47(8):962]. Nat Genet. 2015;47(7):803–808. Fig 2; RETREG1 (right panel) from Kurth I, Pamminger T, Hennings JC, et al. Mutations in FAM134B, encoding a newly identified Golgi protein, cause severe sensory and autonomic neuropathy. Nat Genet. 2009;41(11):1179–1181. Fig 1; SCN11A from Leipold E, Liebmann L, Korenke GC, et al. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. Nat Genet. 2013;45(11):1399–1404. Fig 1.)*

and so the clinical and sensory deficits that characterize this condition are diminished or absent reflexes, distal loss of proprioception, light touch, and sensitivity to noxious thermal stimuli.

The four gene variants described are *WNK1, FAM134B, KIF1A,* and *SCN9A*; each are associated with different subtypes of HSAN-II. The *WNK1* gene variant leads to the HSAN-IIA phenotype with marked loss of sensitivity to pressure, proprioception, vibration sensation, and areflexia, decreased corneal reflexes, diffuse hypotonia, and episodic hyperhidrosis. *WNK1* is involved with organizing sodium and chloride ion fluxes and cell membrane excitability, as well as coordinating the expression of *TRPV4,* which is an important cation channel involved in nociception. Recessive gene variants in *KIF1A,* encoding kinesin proteins (axonal transport of synaptic vesicles), can cause other HSAN-II disorders with a more complex neurologic picture.

HSAN-III

HSAN-III includes **Riley-Day syndrome (familial dysautonomia)** and is typically identified during infancy (see Chapter 655). It affects both unmyelinated fibers and large myelinated fibers leading to autonomic deficits including hyperhidrosis, defective tears, postural hypotension, recurrent fevers, and significant feeding problems. Reflexes may be diminished or absent, and the sensory deficits include a general inability to detect noxious stimuli and a diffuse thermal insensitivity.

Riley-Day syndrome (familial dysautonomia) is a neurodevelopmental genetic autosomal recessive disorder due to variants in the *IKBKAP* or *ELP1* gene (9q31.3), which encodes the elongator complex protein 1 (ELP1). ELP1 is a scaffold protein for the transcription of neural key proteins and a regulator for different kinases involved in proinflammatory signaling. There are diffuse changes in pathology that affect myelinated terminals (usually small nerve fibers), dorsal root ganglia, spinal cord lateral root entry zones, Lissauer tracts, and parasympathetic afferents.

HSAN-IV

HSAN-IV is a rare condition and typically diagnosed in infancy because of autonomic dysfunction including anhidrosis and repeated episodes of fever, and sometimes developmental difficulty. HSAN-IV affects both unmyelinated and small myelinated fibers. The reflexes may be diminished, or absent, and sensory deficits include an inability to detect noxious stimuli and diffuse thermal insensitivity. This condition is also referred to as congenital insensitivity to pain with anhidrosis (CIPA). Other possible signs and symptoms are bone lesions, facial dysmorphology, microcephaly, mandibular osteolysis, dental caries and premature tooth loss, recurrent soft tissue and bone infections, urine and fecal incontinence, and growth disturbances.

CIPA is an autosomal recessive condition with a loss-of-function pathogenic variant in the *TRKA* gene encoding the high-affinity tyrosine kinase receptor *NTRK1* for nerve growth factor (NGF). This gene is located on chromosome 1 (1q21-q22) and several mutations have been reported.

HSAN-V

HSAN-V is a very rare autosomal recessive disease that affects only small-myelinated fibers; hence, the condition is characterized by distal insensitivities to noxious and thermal stimuli. HSAN-V is caused by a pathologic variant in the *NGF-β* gene (chromosome 1p13.2). Because the *NGF-β* gene also binds with the *TRKA* gene (HSAN-IV), and is involved with signaling apoptosis of nociceptive sensory neurons, the HSAN-V phenotype can encompass characteristics of HSAN-IV. There may be other phenotypes caused by changes in the NGF/TRKA signaling pathway.

GENETIC DISORDERS WITH PAINFUL PERIPHERAL NEUROPATHIES

The familial forms of painful peripheral neuropathy result from a pathologic gain of function in ion channel gene variants, i.e., some the autosomal dominant channelopathies and some inflammatory disorders (see Table 653.6). The other conditions resulting in pain syndromes are listed below.

Familial Episodic Pain Syndrome Type 1

Familial episodic pain syndrome type 1 (FEPS type 1) is an autosomal dominant disorder due to pathologic variants in the *TRPA1* gene.

It has only been reported in one family, in Colombia in South America. The family has 21 affected members over 4 generations. Onset is evident during infancy and characterized by arm and chest pain, tachycardia, and diaphoresis, which is triggered by cold, hunger (fasting), or physical stress (exertion). Episodes last around 1-2 hours. There is no altered pain sensitivity outside the episodes in the affected individuals.

FEPS type 2 is seen in adults: only three reported, from two independent families. The episodes of pain are in the feet. One case developed episodes of burning and intense itch in the feet in middle age; the patient's son developed a similar phenotype with allodynia and hyperalgesia at an earlier age. The third case from a different family developed stabbing pain in both feet, lower legs, and hands in middle age. These pain attacks of are not associated with cold or other triggering factors, but warmth sometimes relieves the attack.

FEPS type 3 is an autosomal dominant disorder due to pathologic variants in the *SCN11A* gene, producing a small-fiber painful neuropathy, again seen predominantly in adults. It has been reported in over 20 families. Infants may present with recurrent episodes of crying due to limb and distal joint pain. Fatigue, intercurrent illnesses, and weather changes are common triggers. The pain is sometimes relieved by nonsteroidal antiinflammatory drugs (NSAIDs). Most affected individuals report that the severe pain episodes diminish with age.

Paroxysmal Extreme Pain Disorder

PEFD (sometimes called **familial rectal pain syndrome**) is an autosomal dominant condition with painful neuropathy due to pathologic gain-of-function variants in the *SCN9A* gene. Pain may begin from birth and is often stimulated by defecation or perineal stimulation during wiping or use of rectal thermometer. Jaw pain may be provoked by cold fluids, spicy foods, and emotion; ocular pain may be caused by cold wind blowing on the face. The pain is severe, paroxysmal, and associated with harlequin color change, tears, rhinorrhea, and tonic stiffening episodes, which may be confused with seizures, syncope, or hyperekplexia. The painful episodes last seconds to a few minutes. Treatment is difficult and may include carbamazepine, mexiletine, topical lidocaine, and stool softeners (see later).

Inherited Erythromelalgia

IEM, sometimes called erythermalgia, is due to pathologic gain-of-function variants in the *SCN9A* gene and is characterized by recurrent episodes of bilateral burning pain, erythema, and swelling primarily of the feet and hands (see Chapter 211.5). Over time, the face and ears are involved, and the pain may become constant. It is more commonly evident during childhood, but episodes may begin during infancy. Triggers include a warm environment or prolonged standing. Figure 653.3 illustrates some of the clinical and physiologic features in a patient. Treatment includes cooling with a fan or ice; but be aware that ice may produce cold injury if used too often. Medical therapy is similar to that for PEPD. The differential diagnosis includes Fabry disease (which may initially present in infancy with painful feet and hands) and secondary autoimmune causes of erythromelalgia.

Other Pathologic Genetic Variants in SCN2A

Other variants in *SCN2A* can cause benign familial infantile seizures, febrile seizures plus syndrome, and intractable epilepsy of infancy. A gain-of-function gene variant is associated with neonatal seizures, episodic ataxia, myoclonus, and pain.

STING-Associated Vasculopathy Infantile Onset

STING-associated vasculopathy infantile onset (SAVI) is a severe autosomal dominant autoinflammatory disorder due to a pathologic gain-of-function variant in *TMEM173,* which encodes the STING protein (stimulator of interferon genes). Interferon-driven inflammation (**interferonopathy**) results in painful ulcerating lesions (digits, face, nose, ears) that become eschars and necrotic. The associated features

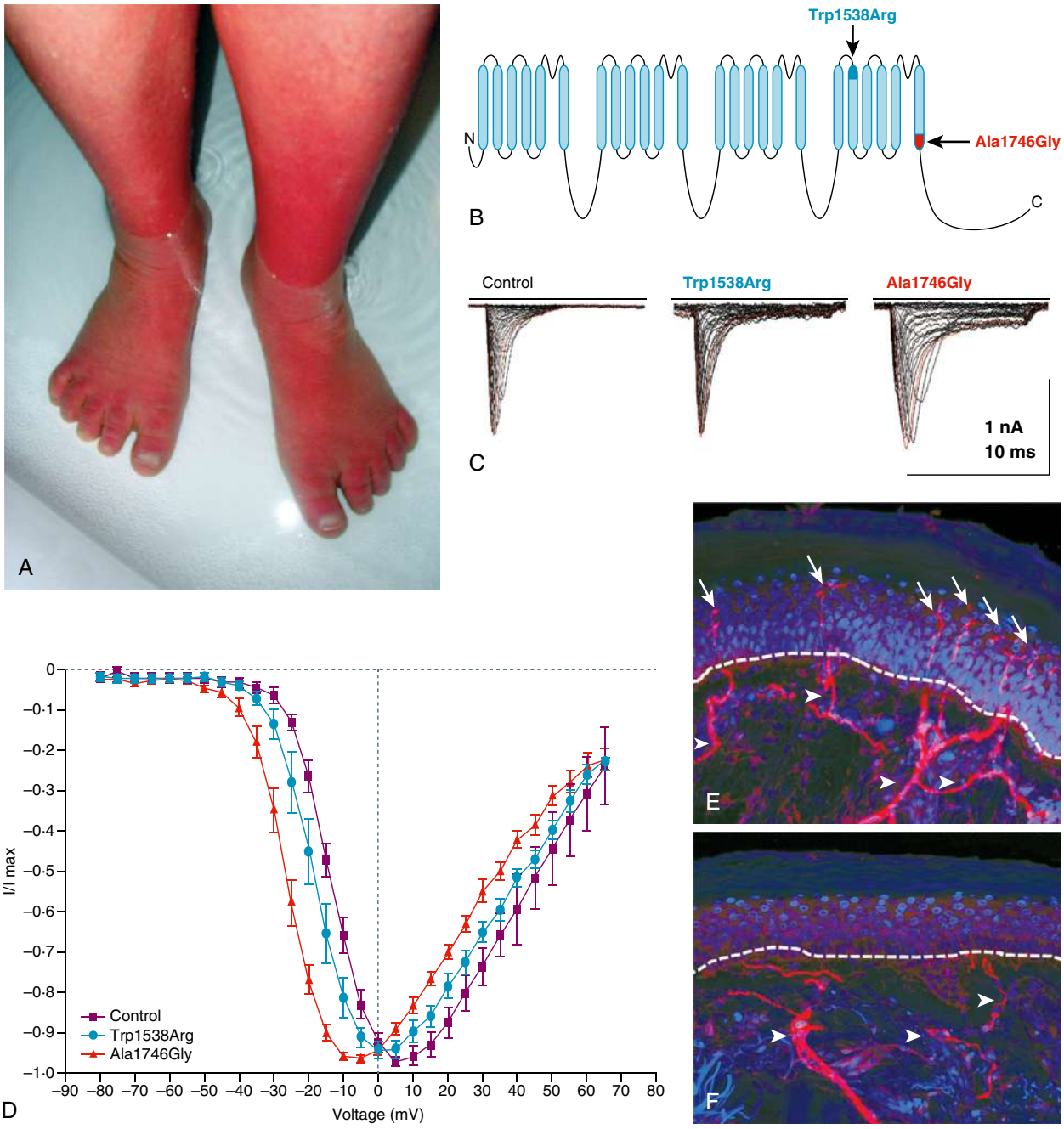

Fig. 653.3 Clinical characteristics and genetic and physiologic features of inherited erythromelalgia and small-fiber neuropathy. **A,** Patient with inherited erythromelalgia and erythema cools feet in cold water in an attempt to relieve pain, which is exacerbated by warmth. **B,** Schematic diagram of the Nav1.7 α subunit. Two mutations are shown in the fourth domain (Trp1538Arg in transmembrane segment 2 and Ala1746Gly in transmembrane segment 6) that cause erythromelalgia with varying clinical phenotypes and that have been characterized biophysically. **C,** Whole cell voltage-clamp recordings in HEK293 cells expressing wild-type Nav1.7 or mutant channels. From a holding potential of −120 mV, currents were evoked by voltage increments of 5 mV from −80 to 40 mV. **D,** Normalized current–voltage plots from recordings in **(C)** show a hyperpolarizing shift in the voltage dependence of activation. This shift is more pronounced in the mutation causing early onset (first decade) of inherited erythromelalgia (Ala1746Gly) rather than late onset (sixth decade; Trp1538Arg). **E,** Inherited erythromelalgia is not associated with sensory nerve-fiber degeneration, in contrast with small-fiber neuropathy. Epidermal innervations in a healthy individual are detected by immunostaining with the pan-neuronal marker PGP9.5 *(red).* Intraepidermal fibers *(arrows)* and dermal fibers *(arrowheads)* are seen. **F,** Gain-of-function mutations in Nav1.7 (distinct from mutations causing inherited erythromelalgia) or Nav1.8 can cause small-fiber neuropathy characterized by degeneration and loss of intraepidermal nerve fibers as shown here. *(**A, E, F** from Bennett DIH, Woods CG. Painful and painless channelopathies. Lancet Neurol. 2014;13:587–599. Fig. 3; **B-D** from Cregg R, Laguda B, Werdehausen R, et al. Novel mutations mapping to the fourth sodium channel domain of Nav1.7 result in variable clinical manifestations of primary erythromelalgia. Neuromolecular Med. 2013;15:265–278.)*

include interstitial lung disease, livedo reticularis, Raynaud phenomenon, and elevated inflammatory biomarkers (e.g., erythrocyte sedimentation rate and C-reactive protein). The differential diagnosis includes juvenile idiopathic arthritis, granulomatosis with polyangiitis, and other infant-onset autoinflammatory diseases.

Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is an autosomal recessive (occasionally autosomal dominant), systemic autoinflammatory interferonopathy that presents in infancy with irritability and progresses to dystonia, seizures, developmental delay, and progressive microcephaly.

Some patients may develop systemic lupus erythematosus (SLE)-like symptoms as well as cold-induced chilblains.

Familial Chilblain Lupus

Familial chilblain lupus (FCL) is another interferonopathy with early childhood onset of acral lesions (i.e., involving fingers, toes, nose, cheeks, ears). This disorder is a monogenetic form of cutaneous lupus with autosomal dominant inheritance (*TREX1, SAMHD1, STING* gene variants)

DIAGNOSIS

All HSANs are characterized by absence of the normal axon flare response to intradermal injection of histamine phosphate (see Chapter 655 for details). There are also descriptions of using nerve conduction studies in the pain disorders. However, the combination of any concerning clinical features (see Tables 653.5 and 653.6) should prompt genetic testing. In developed medical settings a combined panel for mendelian disorders of pain perception, as well as insensitivity to pain or increased pain perception, should include gene testing for the following disorders: congenital insensitivity to pain, IEM, PEPD, small fiber neuropathy, FEPs, HSAN, and forms of HSAN with prominent sensory loss.

TREATMENT

Symptomatic Management of Insensitivity to Pain Syndromes

Treatment is primarily supportive for conditions like HSAN (see Chapter 655). Neuropathic pain medications like pregabalin or gabapentin can improve burning, lancinating pains, and symptoms of restless legs syndrome. Carbidopa, an inhibitor of DOPA-decarboxylase, blocks dopamine synthesis outside the brain and is effective in dysautonomic crisis, and better than benzodiazepines. Unstable hypertension occurring with dysautonomic crisis can be treated with α_2-adrenergic agonists like clonidine and intranasal dexmedetomidine, or diazepam.

Outside of dysautonomic crisis, fluctuations in blood pressure and orthostatic hypotension require head of the bed elevation to avoid supine hypertension, while sufficient water and salt intake, compression devices, exercise, and adrenergic agents like midodrine and droxidopa can improve postural hypotension. Counseling is needed to avoid overheating with the use of cold pack, regular rest, and staying in cool areas for those with prominent anhidrosis, especially in HSAN-IV.

Multidisciplinary management is recommended with involvement of neurology, dermatology, physical and occupational therapy, prosthetics, and orthopedic surgery for optimal skin and limb care. These teams can provide guidance on foot care including daily examinations and cleaning, protective footwear with well-fitted shoes, splinting, stretching, guided exercise programs, and early treatment of injuries. For those with tongue ulceration, smoothing incisors is preferable to dental extraction. Artificial tears, moisture chamber glasses, scleral lenses, tarsorrhaphy, and cautery of tear ducts should be evaluated by ophthalmology to protect anesthetic corneas and increase baseline moisture. Those with early cognitive impairment may benefit from early special education school programs.

Therapies for Genetic Disabling Pain Syndromes

In general, the disabling pain syndromes do not have effective treatments. However, some patients with voltage-gated sodium channel–related FEPS experience pain attacks that may gradually weaken and diminish with age. A similar age-dependent reduction in painful events is seen in patients with *TRPA1*-related FEPS type 1. In contrast, episodic pain does not gradually weaken with age in patients with Nav1.8-related FEPS type 2 and Nav1.9-related FEPS type 3 disorder.

To date, medications such as mexiletine, lidocaine, and carbamazepine have been used as nonselective sodium channel blocking analgesics. There may also be some efficacy in certain pain channelopathies (e.g., Nav1.7-related PEPD). Other antiepilepsy medications have been used with varying effectiveness including lamotrigine, topiramate, tiagabine, and sodium valproate. However, there are no proven positive outcomes for these nonselective anti-epilepsy drugs in FEPS patients; there is also the problem that analgesic dosing may be accompanied by central nervous system side effects such as ataxia, confusion, and sedation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 654
Toxic Neuropathies

*Adnan Y. Manzur**

Many chemicals (organophosphates), toxins, and drugs can cause peripheral neuropathy (Tables 654.1-654.3). The clinical features may differ depending on the agent (Table 654.4). **Heavy metals** are well-known neurotoxins. Lead poisoning, especially if chronic,

Table 654.1 Toxic Neuropathies

METALS
Arsenic (insecticide, herbicide)
Gold
Lead (paint, batteries, pottery)
Lithium (batteries)
Mercury (metallic, vaporized)
Thallium (rodenticides)
Zinc (chronic excessive intake)
OCCUPATIONAL OR INDUSTRIAL CHEMICALS
Acrylamide (grouting, flocculation)
Carbon disulfide (solvent)
Cyanide
Dichlorophenoxyacetate
Dimethylaminopropionitrite
Ethylene oxide (gas sterilization)
Nitrous oxide (vitamin B12 deficiency)
Hexacarbons (glue, solvents)
Organophosphates (insecticides, petroleum additive)
Polychlorinated biphenyls
Tetrachlorobiphenyl
Trichloroethylene
METABOLIC DISORDERS
Fabry disease
Krabbe disease
Leukodystrophies
Porphyria
Tangier disease
Tyrosinemia
Uremia
BIOLOGIC AND INFECTIOUS NEUROPATHIES
COVID-19
Diphtheria
Herpesviruses
HIV
Leprosy
Lyme disease
Rabies
Serum sickness
West Nile virus
Zika virus

* The editors are grateful to Dr. Harvey B. Sarnat, much of whose work on previous editions of this chapter is retained here.

Table 654.2 Chemotherapy Drugs Commonly Associated with Peripheral Neuropathy

CLASS	DRUG	TYPICAL CLINICAL FEATURES OF NEUROPATHY	ADDITIONAL FEATURES/ NOTES
Platinum compounds	Oxaliplatin*	Pure sensory with ataxia	Acute paresthesias, cramps, fasciculation common after each dose
	Cisplatin*	Pure sensory with ataxia	Coasting common (continued worsening after stopping chemotherapy for 2–3 months) Can cause ototoxicity
Taxanes	Paclitaxel*	Predominantly sensory, often painful	Acute arthralgia and myalgia in 10–30%
	Docetaxel*	Predominantly sensory, often painful	Acute arthralgia and myalgia in 10–30%
Vinca alkaloids	Vincristine*	Distal weakness and sensory symptoms	Autonomic involvement common
Immunomodulatory agents	Thalidomide*	Predominantly sensory, sometimes painful	Cramps may occur Constipation common
Proteasome inhibitors	Bortezomib*	Painful, small-fiber predominant sensory	Autonomic involvement can occur and rarely non–length-dependent patterns
Epothilones	Ixabepilone*	Predominantly sensory, sometimes painful	Not used in UK outside clinical trial setting
Antibody–drug conjugates	Brentuximab vedotin*	Predominantly sensory with ataxia	
	Ado-trastuzumab emtansine†	Predominantly sensory	Limited clinical information in the literature
Immune checkpoint inhibitors	Nivolumab, pembrolizumab, ipilimumab‡	Acute or subacute polyradiculoneuropathy	Usually respond to corticosteroids
BRAF/MEK inhibitors	Dabrafenib, vemurafenib, trametinib†	Length-dependent sensory predominant, or acute/subacute polyradiculopathy	May respond to immunotherapy

*Neuropathy is dose related (more likely with increasing cumulative dose).
†Relationship to dose is unclear/not reported.
‡Neuropathy is likely to be idiosyncratic and unrelated to dose.
MEK, Mitogen-activated protein kinase kinase (or MAP2K).
Modified from Smyth D, Kramarz C, Carr AS, et al. Toxic neuropathies: a practical approach. *Pract Neurol.* 2023;23:120–130. Table 2.

Table 654.3 Medications Associated with Peripheral Neuropathy

DRUG/CLASS	TYPICAL PATTERN OF NEUROPATHY	NOTES/ADDITIONAL FEATURES
IMMUNOSUPPRESANTS		
Tumor necrosis factor inhibitors	Acute or subacute polyradiculoneuropathy (axonal or demyelinating)	Some of the conditions being treated with these drugs are also associated with a neuropathy
Calcineurin inhibitors (tacrolimus, cyclosporine)	Acute or subacute polyradiculoneuropathy (axonal or demyelinating)	Almost exclusively reported in posttransplant patients
Interferon-alpha	Acute, subacute or chronic demyelinating polyradiculoneuropathy	Initial course of immunomodulation usually needed; however, most recover after single course
Leflunomide	Length-dependent sensory or sensorimotor axonal	Renal failure increases risk
ANTIBIOTICS		
Linezolid	Painful predominantly sensory axonal	Dose dependent—mainly with prolonged courses May also cause optic neuropathy
Metronidazole	Painful length-dependent sensory axonal	Dose dependent—mainly with prolonged courses (≥4 weeks) May coexist with ataxia or encephalopathy
Nitrofurantoin	Length-dependent sensorimotor axonal, often rapid onset with clinical weakness	
Dapsone	Motor-predominant axonal	Dose dependent—mainly with prolonged courses

Continued

Table 654.3 Medications Associated with Peripheral Neuropathy—cont'd

DRUG/CLASS	TYPICAL PATTERN OF NEUROPATHY	NOTES/ADDITIONAL FEATURES
Fluoroquinolones (e.g., ciprofloxacin, norfloxacin)	Sensory symptoms, however, detailed clinical features not well documented	Likely to be extremely rare with short courses
ANTITUBERCULOSIS DRUGS		
Isoniazid	Sensory predominant axonal	Prevented with pyridoxine (B_6) supplementation Occasionally causes optic neuropathy
Ethambutol	Sensory predominant axonal (uncommon)	Optic neuropathy
ANTIFUNGALS		
Some triazoles (itraconazole, voriconazole, posaconazole)	Sensory predominant axonal	May also increase risk of neuropathy with vinca alkaloids and calcineurin inhibitors due to CYP3A4 inhibition
ANTIRETROVIRALS		
Some nucleoside reverse transcriptase inhibitors (stavudine, didanosine, zalcitabine)	Sensory predominant axonal	Have largely been superseded by nonneurotoxic agents
CARDIAC DRUGS		
Amiodarone	Distal predominant sensorimotor, often with both sensory ataxia and distal weakness Nerve conduction studies may show demyelinating or axonal changes	Tremor, cerebellar ataxia, optic neuropathy, myopathy may develop
Perhexiline	Severe, demyelinating polyradiculoneuropathy	Very common No longer available in the UK
OTHER DRUGS		
Phenytoin	Mild axonal or demyelinating sensory or sensorimotor Commonly asymptomatic signs or nerve conduction abnormalities	Occasional cases of more significant neuropathy associated with high doses/phenytoin concentrations, often without cerebellar signs Folate supplementation should be given
Levodopa/carbidopa intestinal gel	Sensory predominant axonal neuropathy	Due to impaired absorption/metabolism of pyridoxine and other B vitamins
Colchicine	Mild sensory predominant axonal	Myopathy usually more prominent
Chloroquine	Mild sensory predominant axonal	Myopathy usually more prominent
Disulfiram	Sensorimotor axonal, often with clinical muscle weakness	
Nitrous oxide	Usually length-dependent sensorimotor Can also cause a pure motor/motor-predominant neuropathy	Myelopathy often more prominent
Pyridoxine (vitamin B_6)	Sensory ganglionopathy with prominent large-fiber loss and ataxia	Pyridoxine deficiency can also lead to a sensory predominant neuropathy. Mild elevation in plasma concentration (2-3 times upper limit of normal) common with multivitamin supplementation

From Smyth D, Kramarz C, Carr AS, et al. Toxic neuropathies: a practical approach. *Pract Neurol*. 2023;23:120–130. Table 3.

causes mainly a motor neuropathy selectively involving large nerves, such as the common peroneal, radial, and median nerves, a condition known as mononeuritis multiplex (see Chapter 761). Arsenic produces painful burning paresthesias and motor polyneuropathy. Exposure to industrial and agricultural chemicals is a less common cause of toxic neuropathy in children than in adults, but insecticides are neurotoxins for both insects and humans, and if they are used as sprays in closed spaces, they may be inhaled and induce lethargy, vomiting, seizures, and neuropathy, particularly with recurrent or long-term exposure. Working adolescents and children in developing countries are also at risk. Lithium is widely used in batteries, as well as in medication for the treatment of psychosis and other psychiatric conditions, but can be neurotoxic, especially cumulatively over time. **Puffer fish poisoning,** which can be acquired even when fish contaminated with the venom has been cooked, produces a Guillain-Barré–like syndrome. Ethanol abuse can be neurotoxic and particularly affects the optic nerves, but optic neuritis is not a peripheral neuropathy.

The most frequent cause of toxic neuropathies in children is **prescribed medications,** though street drugs and even some legal over-the-counter products also can be neurotoxic. Antimetabolic and immunosuppressive drugs, such as vincristine, cisplatin, and paclitaxel, produce polyneuropathies as complications of chemotherapy for neoplasms and immunologic disorders, such as juvenile idiopathic arthritis. This *iatrogenic* cause is usually an axonal degeneration rather than primary demyelination, unlike primary autoimmune neuropathies. Excessive vitamin intake of *megavitamins* can be neurotoxic. Zinc compounds are widely sold without prescription as dietary supplements and promoted for treatment of a variety of disorders, both neurologic (e.g., hyposmia) and immunologic, and for various visceral organ systems; most claims are not evidence based. Zinc ions are essential for the conservation of postsynaptic membranes

Table 654.4 Clinical Features of Toxic Neuropathies

NEUROPATHY PHENOTYPE	TOXIC CAUSES TO CONSIDER
Sensory predominant	*Commonly cause predominant sensory ataxia:* Mercury, nitrous oxide, acrylamide Pyridoxine (vitamin B_6), platinum compounds, brentuximab vedotin, amiodarone *Other causes of sensory predominant neuropathy:* Alcohol, cadmium, *n*-hexane/glue-sniffing, allyl chloride, carbon disulfide, ethylene oxide Taxanes, bortezomib, thalidomide, *BRAF*/MEK inhibitors, leflunomide, linezolid, metronidazole, calcineurin inhibitors, isoniazid, ethambutol, triazole antifungals, amiodarone, phenytoin, colchicine, chloroquine, levodopa/carbidopa intestinal gel, fluoroquinolones
Can involve significant distal motor weakness	Nitrous oxide, lead, arsenic, thallium, *n*-hexane/glue-sniffing, organophosphates Vinca alkaloids, *BRAF*/MEK inhibitors, dapsone, nitrofurantoin, disulfiram, amiodarone
Predominant neuropathic pain	Alcohol, mercury, thallium, ciguatoxin Taxanes, bortezomib, thalidomide, linezolid, metronidazole, nitrofurantoin, disulfiram, cotrimoxazole
Acute/subacute sensorimotor neuropathy ("GBS like")	Arsenic, thallium, seafood toxins (saxitoxin, tetrodotoxin), diethylene glycol, *n*-hexane/glue-sniffing (if acute high doses) Immune checkpoint inhibitors, tumor necrosis factor inhibitors, *BRAF*/MEK inhibitors, calcineurin inhibitors, nitrofurantoin, bortezomib (rarely), amiodarone (rarely)
Encephalopathy	Alcohol, lead (mainly in children), arsenic, mercury, *n*-hexane/glue-sniffing, industrial agents (acrylamide, carbon disulfide, diethylene glycol, ethylene oxide). Metronidazole, disulfiram, phenytoin
Tremor	Mercury Calcineurin inhibitors, amiodarone, phenytoin
Optic neuropathy	Nitrous oxide, lead, mercury, thallium Vincristine, calcineurin inhibitors, linezolid, ethambutol, isoniazid, amiodarone, chloroquine, dapsone, disulfiram
Myelopathy	Nitrous oxide
Myopathy	Taxanes, immune checkpoint inhibitors, amiodarone, colchicine, chloroquine
Gastrointestinal disturbance	Lead, arsenic, thallium, seafood toxins, organophosphates
Renal failure	Lead, mercury, cadmium, diethylene glycol Calcineurin inhibitors
Anemia	Chemotherapy drugs, lead (microcytic anemia, basophilic stippling), arsenic, nitrous oxide (megaloblastic anemia)
Mees lines	Arsenic, thallium
Hyperkeratosis	Arsenic, thallium

GBS, Guillain-Barré syndrome; MEK, mitogen-activated protein kinase kinase (or MAP2K).
Modified from Smyth D, Kramarz C, Carr AS, et al. Toxic neuropathies: a practical approach. *Pract Neurol.* 2023;23:120–130. Table 1.

and mitochondria. Chronic excessive zinc intake is cumulative and becomes toxic by impairing synaptic activity and mitochondrial respiratory chain enzymes, especially complex I enzymes, resulting in polyneuropathy, myopathy, and encephalopathy. Mitochondrial dysfunction also is a frequent basis of neuropathy in many other toxic neuropathies.

Chronic uremia is associated with toxic neuropathy and myopathy. The neuropathy is caused by excessive levels of circulating parathyroid hormone (see Chapter 650). Reduction in serum parathyroid hormone levels is accompanied by clinical improvement and a return to normal of nerve conduction velocity. Peripheral nerve axonal damage, particularly of small fibers, can be secondary to mitochondrial loss or dysfunction in toxic neuropathies. Abnormal toxic complex lipids, generated in Schwann cells by deficient mitochondrial respiration, are capable of damaging or destroying neighboring axons, a secondary mitochondrial toxic neuropathy. Small heat-shock proteins can be provoked that also may contribute to toxic neuropathy.

Biologic neurotoxins associated with diphtheria, Lyme disease, West Nile virus disease, leprosy, herpesviruses (Bell palsy), and rabies also produce peripheral nerve–induced or ventral horn cell–induced weakness or paralysis. Human immunodeficiency virus (HIV) infections also produce neuropathy, and this infection is particularly prevalent in children in several African countries, including those who emigrate to western countries as refugees. Tick paralysis, botulism, and paralytic shellfish poisoning cause neuromuscular junction blockade rather than true neuropathy. During the 2020/2021 COVID-19 pandemic, Guillain Barré syndrome and peripheral neuropathy were described in association with SARS-CoV-2 infection. The SARS-CoV-2–associated peripheral neuropathy was considered to be multifactorial and immune mechanisms, preexisting risk factors, antiviral drugs, and bedding-related nerve compression were considered contributing factors. Various inborn errors of metabolism are also associated with peripheral neuropathy from metabolite toxicity or deficiencies (see Part XI and Table 654.1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 655

Autonomic Neuropathies

Monique M. Ryan

Involvement of small, lightly, or unmyelinated autonomic nerve fibers is seen in many peripheral neuropathies, but their autonomic manifestations are usually mild or subclinical. Some autonomic neuropathies are more symptomatic, causing disturbances of autonomic regulation of the cardiovascular, gastrointestinal, genitourinary, thermoregulatory, sudomotor, and pupillomotor systems.

The differential diagnosis is noted in Table 653.1 (in Chapter 653) and Tables 655.1-655.3. Table 655.4 lists the tests useful in assessing autonomic nervous system function. The treatment of acquired autonomic dysfunction includes both management of the primary disorder (Guillain-Barré syndrome, diabetes) and symptomatic management of organ-specific manifestations (Table 655.5).

655.1 Familial Dysautonomia

Monique M. Ryan

Familial dysautonomia **(Riley-Day syndrome)** is an autosomal recessive disorder most common in Eastern European Jews, in whom its incidence is 1 in 10,000-20,000. It is very rare in other ethnic groups but is, overall, the most common hereditary sensory autonomic neuropathy (HSAN). The variant gene, *IKBKAP* (IκB kinase–associated protein), is at the 9q31-q33 locus. Variants in *IKBKAP* affect the development and maturation of peripheral nerves. This and other autonomic neuropathies are often regarded as **neurocristopathies** because the abnormal tissues are largely derived from the neural crest.

PATHOLOGY

This disease of the peripheral nerves is characterized pathologically by a reduced number of the small unmyelinated nerve fibers that carry pain, temperature, and taste sensation and mediate autonomic functions, including baroreceptors. There is also loss of small and large myelinated fibers from peripheral nerves. The dorsal root ganglia are small, with reduced neurons. The number of parasympathetic ganglion cells in the myenteric plexuses is reduced. Optic nerve involvement, with predominant loss of papillomacular nerve fibers, may impair visual acuity. Fungiform and circumvallate papillae (taste buds) are absent or reduced in the tongue (Fig. 655.1).

CLINICAL MANIFESTATIONS

Clinical manifestations are highly variable. Affected infants and children may be hypotonic, with motor delay and feeding difficulties. Breath-holding spells, followed by syncope, are common in the first 5 years of life. Responses to hypoxia and hypercapnia are reduced. Recurrent pneumonia often leads to chronic lung disease. Affected persons may experience profound postural hypotension without compensatory tachycardia but can also develop extreme hypertension and tachycardia when under emotional and/or physical stress. Temperature dysregulation is reflected by the development of hyperthermia or hypothermia with infections and environmental stressors.

When affected children become older, insensitivity to pain becomes evident and traumatic injuries are frequent. Pain and temperature sensation are reduced, although to a lesser degree than in other HSANs (see Table 655.2). **Alacrima** (absence of tears with emotional crying) is a universal finding. Corneal ulcerations result from decreased corneal sensation and xerophthalmia. Newly erupting teeth cause tongue ulcerations and, in older children, dental trauma; soft tissue mutilation may be prominent. Walking is delayed and appears ataxic, probably as a result of a combination of poor sensory feedback from muscle spindles, vestibular nerve dysfunction, and cerebellar involvement. The deep tendon reflexes are absent. Scoliosis or kyphosis, or both, is seen in most patients and is usually progressive. There is an increased incidence of urinary incontinence. Bradycardia and other cardiac arrhythmias can occur; some patients require a cardiac pacemaker.

Approximately 40% of patients experience seizures; some are triggered by hypoxia during breath holding and some by fever, but some have no obvious precipitants. Emotional lability and learning disabilities are common in school-age children with familial dysautonomia. Puberty is often delayed, especially in females. Short stature can occur but is responsive to treatment with growth hormone.

After 3 years of age, **dysautonomic crises** begin, usually with attacks of cyclic vomiting lasting 24-72 hours or even longer. These repeated episodes of retching and vomiting are associated with tachycardia, hypertension, profuse sweating, blotching of the skin, apprehension, and irritability. Prominent gastric distention can occur, causing abdominal pain and even respiratory distress. Hematemesis can complicate pernicious vomiting.

LABORATORY FINDINGS

ECG shows prolonged corrected QT intervals with lack of appropriate shortening with exercise, reflecting aberrant autonomic regulation of cardiac conduction. Chest radiographs may show atelectasis and chronic inflammatory changes. The urinary vanillylmandelic acid level is decreased, and the homovanillic acid level is increased. The plasma level of dopamine β-hydroxylase (the enzyme that converts dopamine to epinephrine) is diminished. Sural nerve biopsy shows loss of unmyelinated fibers, but nerve conduction studies and electromyography are often normal, because they reflect only the function of large myelinated fibers. Electroencephalography is useful for evaluating seizures.

DIAGNOSIS

All HSANs are characterized by absence of the normal axon flare response to intradermal injection of histamine phosphate. Because the skin of a normal infant reacts more intensely to histamine, a 1:10,000 dilution should be used. Instillation of 2.5% methacholine into the conjunctival sac produces miosis in patients with familial dysautonomia but no detectable effect on a normal pupil; this is a nonspecific sign of parasympathetic denervation from any cause. Methacholine is applied to only one eye in this test, with the other eye serving as a control; the pupils are compared at 5-minute intervals for 20 minutes. The combination of alacrima, absent fungiform papillae, decreased patellar reflexes, and an abnormal histamine test with Ashkenazi Jewish lineage is diagnostic. Because of variable expression and potential overlap with other HSANs, genetic testing should be used to confirm the diagnosis.

TREATMENT

Symptomatic treatment includes special attention to the respiratory and gastrointestinal systems to prevent aspiration and malnutrition, topical ocular lubricants to prevent corneal ulceration, orthopedic management of scoliosis and joint problems, and anticonvulsants where required. Gastrostomy, with or without fundoplication, should be considered in those with recurrent aspiration. Hyperpyrexia from anhidrosis can be life-threatening and should be treated aggressively. Chronic lung disease should be treated symptomatically. Patients should be warned that their insensitivity to hypoxia may place them at risk of complications with underwater swimming, air travel, and travel to high altitudes. Protection from injuries is important because of the lack of pain as a protective mechanism. Some children require a cardiac pacemaker.

Dysautonomic crises respond poorly to standard antiemetics and are usually treated with centrally acting medications such as diazepam and clonidine. Carbidopa, a DOPA decarboxylase inhibitor, is also effective in dysautonomic crises.

PROGNOSIS

Sixty percent of patients die before the age of 20 years, usually of chronic respiratory failure or aspiration. Older patients often develop chronic renal disease related to vasomotor instability and hypertension. The prognosis is improved by treatment in a center familiar with this

Table 655.1 Classifications of Pediatric Autonomic Disorders

ETIOLOGY	TOPOGRAPHY	FREQUENCY	NEUROTRANSMISSION
FUNCTIONAL	GENERALIZED	COMMON	PANDYSAUTONOMIA (ADRENERGIC AND CHOLINERGIC FAILURE)
Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia	Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Hereditary sensory autonomic neuropathies Other rare genetic disorders Immune-mediated	Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Obesity Diabetes Anorexia nervosa Other metabolic disorders	Autoimmune autonomic ganglionopathy Acute autonomic and sensory neuropathy Guillain-Barré syndrome Paraneoplastic neuropathies Porphyria
INHERITED			
Hereditary sensory autonomic neuropathies Other rare genetic disorders			
METABOLIC	PUPIL	RARE	PURE ADRENERGIC FAILURE
Obesity Diabetes Anorexia Other metabolic disorders	Argyll Robertson pupil Adie pupil Horner syndrome Pourfour du Petit syndrome	Immune-mediated Traumatic Hereditary sensory autonomic neuropathies Other rare genetic disorders	Dopamine-beta hydroxylase deficiency Pure adrenergic neuropathy
IMMUNE-MEDIATED	FACE		PURE CHOLINERGIC FAILURE
Autoimmune autonomic ganglionopathy Guillain-Barré syndrome Anti-NMDA receptor encephalitis Paraneoplastic autonomic neuropathy Sjögren disease	Cluster headache Harlequin syndrome Gustatory sweating		Botulism Lambert-Eaton syndrome Adie pupil Chagas disease Acute cholinergic neuropathy
INFECTIOUS	LIMBS		
Chagas disease HIV Tetanus	Raynaud phenomenon Acrocyanosis Primary idiopathic hyperhidrosis		
NEOPLASIA			
Catecholamine-secreting tumors Brainstem and posterior fossa tumors			
TRAUMA AND MALFORMATIONS			
Spinal cord injury Traumatic brain injury Syringomyelia Arnold-Chiari malformation			
DRUGS			
POSTSURGICAL OR POSTRADIOTHERAPY USAGES			
Acquired baroreflex failure			

From Palma JA, Norcliffe-Kaufmann, Fuente-Mora C, et al. Disorders of the autonomic nervous system: autonomic dysfunction in pediatric practice. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Table 154-1.

disease. Measures to better control vasomotor stability and vomiting improve quality of life, but their effect on longevity is not yet known.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

655.2 Other Autonomic Neuropathies

Monique M. Ryan

CONGENITAL INSENSITIVITY TO PAIN AND ANHIDROSIS

Congenital insensitivity to **pain** and **anhidrosis,** or HSAN type IV, is an autosomal recessive disorder with onset in infancy (see Table 655.2 and Chapter 653.10). Affected children usually present with episodes of overheating related to warm environmental temperatures because they have absent or reduced sweating. Infantile hypotonia improves with age. Frequent burns and traumatic injuries result from the lack of pain perception, which also causes poor healing of fractures and a tendency for development of chronic osteomyelitis and Charcot joints. Temperature sensation is also markedly impaired. Anhidrosis causes a thick, calloused appearance of the skin, with lichenification of the palms and chronic dystrophic changes in the nails. There is no alacrima, but corneal ulceration may result from hypoesthesia. Almost all patients have behavioral and cognitive deficits. Nerve biopsy reveals an almost total absence of unmyelinated nerve fibers, which usually convey pain, temperature, and autonomic sensation. The diagnosis is confirmed by targeted genetic testing.

Table 655.2 Hereditary Sensory and Autonomic Neuropathies

TYPE	GENE	INHERITANCE	ONSET	AUTONOMIC FEATURES	SENSORY FEATURES	OTHER FEATURES
HSAN 1A	*SPTLC1*	AD	Adult	Varying degrees of distal anhidrosis	Progressive loss of pain, temperature, and fine-touch sensation Varying degrees of sensorineural hearing loss Episodes of lancinating limb pain	One case with congenital presentation reported with severe growth and mental retardation, microcephaly, hypotonia, and respiratory insufficiency
HSAN 1B	3p24-p22 locus					Cough and gastroesophageal reflux
HSAN 1C	*SPTLC2*					Varying degrees of distal muscle weakness
HSAN 1D	*ALT1*			None		—
HSAN 1E	*DMNT1*			None		Early-onset dementia
HSAN 1F	*ATL3*			None		—
HSAN 2A	*WNK1*	AR	Childhood or adolescence	None	Varying degrees of progressive loss of pain, temperature, and fine-touch sensation	
HSAN 2B	*FAM134B*			Varying degrees of hyperhidrosis, urinary incontinence, and pupillary abnormalities		—
HSAN 2C	*KIF1A*			None		—
HSAN 2D	*SCN9A*			Urinary and fecal incontinence, reduced sweating		Lack of fungiform lingual papillae, hyposmia, hearing loss, hypogeusia, and bone dysplasia
HSAN 3	*IKAP (ELP-1)*	AR	Newborn	Impaired lacrimation Orthostatic hypotension Paroxysmal hypertension and vomiting episodes with skin blotching Normal or increased sweating	Impaired pain and temperature sensation with preserved fine-touch sensation	Described in Ashkenazi Jewish ancestry Neonatal hypotonia Respiratory and feeding difficulties Neuropathic joints Optic neuropathy, chronic lung disease, scoliosis, rhabdomyolysis Renal failure Varying degrees of cognitive and behavioral problems
HSAN 4	*NTRK (TRKA)*	AR	Newborn	Anhidrosis Episodic hyperthermia Undetectable plasma norepinephrine	Loss of pain and temperature sensation Preserved fine-touch and vibration sensation	Frequent fractures Neuropathic joints Slow-healing wounds Varying degrees of cognitive and behavioral problems
HSAN 5	*NGFβ*	AR	Newborn	Variable degree of anhidrosis	Loss of pain and temperature sensation Preserved fine-touch and vibration sensation	Frequent fractures Neuropathic joints Tooth loss from gingival disease

Table 655.2 Hereditary Sensory and Autonomic Neuropathies—cont'd

TYPE	GENE	INHERITANCE	ONSET	AUTONOMIC FEATURES	SENSORY FEATURES	OTHER FEATURES
HSAN 6	*DST*	AR	Newborn	Impaired lacrimation Labile blood pressure and heart rate Hyperthermia and skin-blotching episodes	Loss of pain and temperature sensation	Described in Ashkenazi Jewish ancestry Neonatal hypotonia Respiratory and feeding difficulties, delayed psychomotor development, neuropathic joints All described patients died before age 3
HSAN 7	*SCN11A*	AD (only a heterozygous de novo variant described)	Newborn	Hyperhidrosis and gastrointestinal dysfunction	Loss of pain and temperature sensation	Frequent fractures Neuropathic joints Slow-healing wounds

AD, Autosomal dominant; AR, autosomal recessive.
From Palma JA, Norcliffe-Kaufmann, Fuente-Mora C, et al. Disorders of the autonomic nervous system: autonomic dysfunction in pediatric practice. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology,* 6th ed. Philadelphia: Elsevier; 2018: Table 154-2.

Table 655.3 Other Genetic and Metabolic Disorders Causing Autonomic Dysfunction

DISEASE	AUTONOMIC FEATURES
Dopamine beta-hydroxylase deficiency	Ptosis, hypotension, hypothermia; treatment with droxidopa
Aromatic L-amino acid decarboxylase deficiency	Ptosis, poor feeding, hypotension, hypotonia; treatment with dopamine agonists/monoamine oxidase inhibitors
Menkes disease	Orthostatic hypotension; treatment with subcutaneous copper injections
Fabry disease	Hypohidrosis or hyperhidrosis, decreased salivation; treatment by enzyme replacement
Acute intermittent porphyria (AIP)	Tachycardia, hypotension or hypertension; treatment as for AIP
Porphyria variegata	As for AIP
Hirschsprung disease	Tachycardia, hypertension, hyperthermia; treatment symptomatic (see Table 655.5)
Congenital central hypoventilation syndrome (CCHS)	Constipation, pupillary abnormalities, hypothermia; treatment symptomatic
Pitt-Hopkins syndrome	As for CCHS
Rett syndrome	Irregular breathing, abnormal heart rate variability, sudden death; treatment symptomatic
Alexander disease	Constipation, hypothermia, sleep-disordered breathing; treatment symptomatic
Hyperbradykininism	Orthostatic hypotension, purple legs; treatment symptomatic (see Table 655.5)
Panayiotopoulos syndrome	Hypertension, tachycardia, cardiac arrest; treatment symptomatic (see Table 655.5)
Cold-induced sweating syndrome	Unexplained fevers, impaired thermoregulation; treatment symptomatic (see Table 655.5)

Table 655.4 Autonomic Function Testing

The sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function

CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION
Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments
Heart rate response to the Valsalva maneuver
Heart rate response to standing

SYMPATHETIC ADRENERGIC FUNCTION
Blood pressure response to upright posture (standing or tilt table)
Blood pressure response to Valsalva maneuver
Microneurography

SYMPATHETIC CHOLINERGIC FUNCTION
Thermoregulatory sweat testing
Quantitative sudomotor-axon reflex test
Sweat imprint methods
Sympathetic skin response

From Freeman R. Autonomic peripheral neuropathy. *Lancet.* 2005;365:1259–1270.

Table 655.5 Symptomatic Management of Autonomic Dysfunction

PROBLEM	TREATMENT
Orthostatic hypotension	Volume and salt supplements Adequate hydration Pressure garments Fludrocortisone (mineralocorticoid) Midodrine (α agonist)
Aspiration pneumonitis	Gastrostomy with/without fundoplication
Dysautonomic crises	Clonidine, diazepam, carbidopa
Gastroparesis	Prokinetic agents (metoclopramide, domperidone, erythromycin)
Hypomotility	Fiber, laxatives
Urinary dysfunction	Timed voiding; bladder catheterization
Hyperhidrosis	Anticholinergic agents (glycopyrrolate, propantheline) Intracutaneous botulism toxin
Anhidrosis	Cool baths, cooling vests

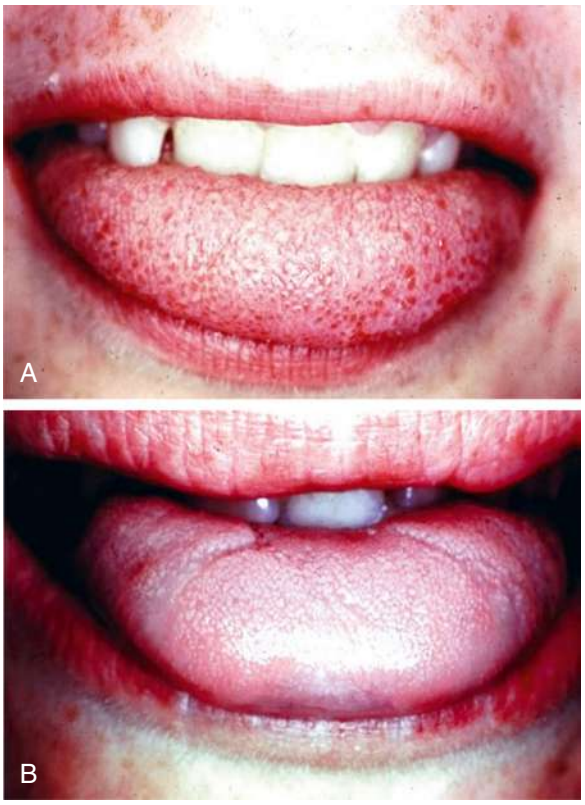

Fig. 655.1 A, Normal tongue with fungiform papillae present on the tip. B, Dysautonomic tongue. Note absence of the highly vascularized fungiform papillae from the tongue tip, which gives the appearance of a smooth tongue. *(From Axelrod FB, Gold-von Simson G. Hereditary sensory and autonomic neuropathies: Types II, III, and IV. Orphanet J Rare Dis. 2007;2:39. Fig. 4.)*

ALLGROVE SYNDROME (TRIPLE A SYNDROME)

Allgrove syndrome is a rare autonomic neuropathy characterized by early-onset alacrima, feeding difficulties and achalasia, autonomic dysfunction with orthostatic hypotension, altered heart rate variability, hyperreflexia, ataxia, muscle weakness, sensorimotor polyneuropathy, and adrenocorticotropic hormone–resistant adrenal insufficiency, which develops in the first decade. The gene *AAAS* (alacrima-achalasia-adrenal insufficiency neurologic disorder) is located on chromosome 12q13.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 656

Guillain-Barré Syndrome

Monique M. Ryan

Guillain-Barré syndrome (GBS) is an autoimmune disorder that is thought to be a **postinfectious polyneuropathy,** involving mainly motor but also sensory and sometimes autonomic nerves. This syndrome affects people of all ages and is not hereditary. Most GBS patients in the United States and Europe have a demyelinating neuropathy, but primarily axonal degeneration is apparent in some forms of GBS seen mainly in China, Mexico, Bangladesh, and Japan.

CLINICAL MANIFESTATIONS

The onset of weakness usually follows a nonspecific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal (especially *Campylobacter jejuni,* but also *Helicobacter pylori*), respiratory (especially *Mycoplasma pneumoniae*), or systemic (Zika virus, COVID-19) symptoms. Consumption of undercooked poultry, unpasteurized milk, and contaminated water are the main sources of gastrointestinal infections. West Nile virus also can mimic Guillain-Barré–like syndrome, but more often causes a motor neuron disease similar to poliomyelitis. GBS may follow administration of vaccines against rabies, influenza, and conjugated meningococcal vaccine, particularly serogroup C. Other infectious precursors of GBS include mononucleosis, Lyme disease, cytomegalovirus, the Zika virus and, most recently, COVID-19 infection.

Initial symptoms include numbness and paresthesia, followed by weakness (Fig. 656.1). Radicular back pain and myalgia are common in the initial stages; affected children can be very irritable. Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and finally the bulbar muscles, but weakness is sometimes proximally prominent. Extraocular muscle involvement is rare, but many children develop facial weakness. In most cases weakness is essentially symmetric. Weakness progresses over days or weeks, the clinical nadir occurring in less than 4 weeks. Approximately 60% of children lose the ability to walk at some point in their illness; a small proportion progress to flaccid tetraplegia. The maximal severity of weakness is reached by 4 weeks after onset. The differential diagnosis of GBS is shown in Tables 656.1 and 656.2.

Bulbar involvement occurs in about 50% of cases and can result in respiratory insufficiency (see Fig. 656.1; Table 656.3). Dysphagia and facial weakness can be signs of impending respiratory failure, interfere with saliva control and swallowing, and increase the risk of aspiration. Vocal cord paralysis may cause dyspnea or a hoarse voice. Severe bulbar and respiratory muscle involvement can lead to death if GBS is not recognized and treated.

The **autonomic nervous system** is also involved in some cases. Lability of blood pressure and heart rate, postural hypotension, episodes of profound bradycardia or tachycardia, and occasional asystole occur more commonly in younger patients or those with severe weakness. Cardiovascular monitoring is important, especially early in the disease course, when rapid progression of weakness, respiratory insufficiency, and autonomic instability can be life-threatening. The tendon reflexes are lost in GBS, usually early, but are sometimes preserved until later; areflexia is more common but hyporeflexia may be seen. As many as 10% of affected children retain their reflexes throughout their course.

Subtypes of GBS include an acute inflammatory demyelinating polyneuropathy and an acute motor axonal neuropathy; these are distinguished by findings on nerve conduction studies and an associated pattern of antiganglioside antibodies (see Table 656.3). Localized forms of GBS also occur and include a pattern of facial diplegia with paresthesias and a pattern of pharyngeal-cervical-brachial weakness. **Miller Fisher syndrome (MFS)** is an uncommon GBS variant associated with acute external (and occasionally internal) ophthalmoplegia, ataxia, and areflexia. The cranial nerve VI is most often involved in MFS. Although areflexia is seen in MFS, patients have no or only very mild lower extremity weakness, compared with GBS. Distal paresthesias are common in MFS. Urinary incontinence or retention is seen in approximately 20% of cases but is usually transient. MFS overlaps clinically with Bickerstaff brainstem encephalitis, which has similar findings with an associated encephalopathy.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP, sometimes called *chronic inflammatory relapsing polyneuritis*) is a more chronic, slowly progressive, acquired inflammatory neuropathy with some clinical overlap with GBS (Table 656.4). Symptoms such as weakness and paresthesias develop over more than 4-6 weeks, recur intermittently (relapsing), or progress slowly over periods of months to years. Weakness is generally both proximal and distal, and variably severe. Hyporeflexia or areflexia is almost universal. Motor deficits occur in 94% of cases and sensory paresthesias in 64%, but cranial

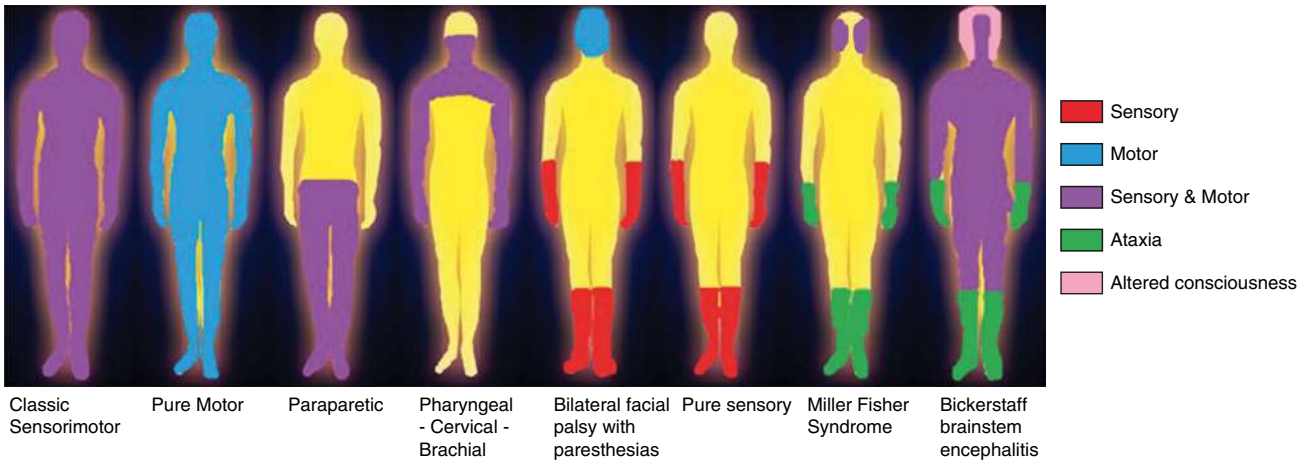

Fig. 656.1 Pattern of symptoms in variants of Guillain-Barré syndrome (GBS). Graphic representation of the pattern of symptoms typically observed in the different clinical variants of GBS. Symptoms can be purely motor, purely sensory (rare), or a combination of motor and sensory. Ataxia can be present in patients with Miller Fisher syndrome, and both decreased consciousness and ataxia can be present in patients with Bickerstaff brainstem encephalitis. Symptoms can be localized to specific regions of the body, and the pattern of symptoms differs between variants of GBS. Although rare, bilateral facial palsy with paresthesias, the pure sensory variant, and Miller Fisher syndrome are included in the GBS spectrum, but they do not fulfill the diagnostic criteria for GBS. *(From El-Abassi RN, Soliman M, Levy MH, et al. Treatment and management of autoimmune neuropathies. In: Bertorini TE, ed. Neuromuscular Disorders Treatment and Management, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 15.1, p. 313.)*

Table 656.1 Differential Diagnosis of Childhood Guillain-Barré Syndrome

SPINAL CORD LESIONS
Acute transverse myelitis (may occur with GBS)
Epidural abscess
Tumors
Poliomyelitis
Enteroviral myelitis
Acute flaccid myelitis
Hopkins syndrome
Vascular malformations
Cord infarction
Fibrocartilaginous embolism
Cord compression from tumors
Acute disseminated encephalomyelitis
Bickerstaff brainstem encephalitis
Anterior spinal artery syndrome

PERIPHERAL NEUROPATHIES
Toxic (See Chapter 654)
- Vincristine
- Thalidomide
- Glue sniffing
- Heavy metal: gold, arsenic, lead, thallium, mercury
- Organophosphate pesticides
- Fluoroquinolones
- Isoniazid
- Dapsone
- Nitrous oxide
- Snake venom
- Puffer fish
- Buckthorn toxin
- Carbon monoxide
- Immune checkpoint inhibitors

Infections
- HIV
- Diphtheria
- West Nile virus
- Cytomegalovirus (radiculitis)
- Leprosy
- Lyme disease
- Zika virus
- COVID-19

Inborn errors of metabolism/hereditary
- Leigh disease
- Tangier disease
- Porphyria
- Fabry disease
- Tyrosinemia
- Mitochondrial neuropathies

Critical illness: polyneuropathymyopathy
Eosinophilic granulomatosis with polyangiitis
Granulomatosis with polyangiitis
Sarcoidosis
Systemic lupus erythematosus
Microscopic polyangiitis
Other vasculitides
Nutritional deficiencies
- Vitamin B1, B6, B12, E
- Riboflavin

NEUROMUSCULAR JUNCTION DISORDERS
Tick paralysis
Myasthenia gravis
Acute flaccid myelitis
Botulism
Hypercalcemia

MYOPATHIES
Periodic paralyses (hypokalemic or hyperkalemic)
Dermatomyositis
Critical illness myopathy/polyneuropathy

OTHER
Conversion disorder
Chronic inflammatory demyelinating polyneuritis (acute onset)

Table 656.2 Differential Diagnosis of Guillain-Barré Syndrome by Anatomic Site and Illness

	DISTINGUISHING CLINICAL FEATURES	CSF FINDINGS	ELECTROMYOGRAPHY FINDINGS	OTHER SUPPORTIVE TESTS
BRAIN				
Encephalitis	Drowsiness, seizures	Pleocytosis	Normal	Brain MRI for hyperintense lesions, EEG for slowing epileptiform discharges
Brainstem stroke	Hyperacute sudden onset, cranial and limb weakness	Normal	Normal	Brain MRI and magnetic resonance angiography for corresponding infarct and vascular occlusion
SPINAL CORD				
Transverse myelitis	Sensory level, brisk reflexes	Normal	Normal	Abnormal spine MRI for hyperintense lesions
Malignant infiltration	Cauda equina syndrome	Malignant cells	Normal	Abnormal spine MRI for enhancing lesions, investigations for primary lesions
ANTERIOR HORN CELL				
Infection with poliovirus, enterovirus 71, or enterovirus D68	Fever, flaccid paralysis	Pleocytosis	Motor neuronopathy	Presence of virus
PLEXUS				
Neuralgic amyotrophy	Asymmetry, pain, and findings limited to affected nerves	Normal	Abnormal in affected nerves	Brachial plexus MRI for nerve enhancement
NERVE ROOTS				
Cytomegalovirus and HIV radiculitis	Subacute presentation	Pleocytosis	Delayed or absent F waves and H waves	HIV and cytomegalovirus serology
Chronic inflammatory demyelinating polyneuropathy	Subacute presentation and relapsing–remitting pattern	Albumin-cytologic dissociation	Demyelinating neuropathy	Nerve ultrasound for enlarged nerve roots
PERIPHERAL NERVES				
Chronic inflammatory demyelinating polyneuropathy	Subacute presentation and relapsing–remitting pattern	Albumin-cytologic dissociation	Demyelinating neuropathy	Nerve ultrasound for enlarged nerve roots, and proximal and distal nerves
Porphyria	Family history, concomitant psychiatric and abdominal pain	Normal	Axonal neuropathy	Increased urinary porphobilinogen
Lyme disease or other tick-borne diseases	History of exposure, characteristic rash (erythema migrans in Lyme disease)	Normal	Axonal neuropathy	Antibodies against *Borrelia burgdorferi* (Lyme disease) or the related tick species
Thiamine deficiency	Predisposing factors (e.g., hyperemesis gravidarum, alcohol misuse, nutritional deficiency, and other neurologic features such as Wernicke encephalopathy)	Normal	Axonal neuropathy	Reduced blood thiamine and erythrocyte transketolase activity
Diphtheria	Laryngeal infection	Increased total protein	Demyelinating neuropathy	Isolation of *Corynebacterium diphtheriae* on cultures
Critical illness polyneuropathy	Prolonged illness or ventilation	Normal	Axonal neuropathy	Overlap with myopathy
Metabolic or electrolyte imbalance	Predisposing factors	Normal	Normal	Low serum concentrations of abnormal electrolyte
NEUROMUSCULAR JUNCTION				
Myasthenia gravis	Fatigable weakness, relapsing–remitting pattern	Normal	Repetitive nerve stimulation for a decremental response	Acetylcholine receptor antibodies
Botulism	Rapid progression, pupillary abnormalities, dysautonomia, and descending paralysis	Normal	Rapid repetitive nerve stimulation for an incremental increase	Botulism toxin

Table 656.2 Differential Diagnosis of Guillain-Barré Syndrome by Anatomic Site and Illness—cont'd

	DISTINGUISHING CLINICAL FEATURES	CSF FINDINGS	ELECTROMYOGRAPHY FINDINGS	OTHER SUPPORTIVE TESTS
Lambert-Eaton syndrome	Proximal weakness, depressed tendon reflexes, and autonomic changes	Normal	Repetitive nerve stimulation for post-tetanic facilitation	Antibodies against voltage-gated calcium channels
MUSCLE				
Inflammatory myositis	Proximal weakness, normal reflexes and sensation	Normal	Normal sensory potentials Myopathic	Increased serum creatine kinase
Critical illness myopathy	Prolonged illness or ventilation	Normal	Normal sensory potentials	Overlap with neuropathy
Hypokalemic periodic paralysis	Transient weakness, family history, triggering factors (e.g., fasting, exercise, and carbohydrate-rich meals)	Normal	Abnormal exercise test	Low serum potassium concentrations, genetic mutation
MISCELLANEOUS				
Functional disorder	Inconsistent, variable presentation	Normal	Normal	Psychologic evaluation

From Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barre syndrome. *Lancet*. 2021;397:1214–1226. Table 2.

Table 656.3 Clinical Classification of Guillain-Barré Syndrome

	PATTERNS OF LIMB WEAKNESS	SENSORY INVOLVEMENT	CRANIAL NERVE INVOLVEMENT	CNS INVOLVEMENT	SERIAL NEURAL CONDUCTION	IgG AGAINST GANGLIOSIDE TYPE	PROPORTION OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME
GUILLAIN-BARRÉ SYNDROME SPECTRUM							
Classic							
Demyelinating	Upper and lower limbs	Yes	Yes	No	AIDP	Unknown	69–90%
Axonal	Upper and lower limbs	Yes in AMSAN, no in AMAN	Yes	No	AMSAN, RCF	GM1, GD1a	<22%
Pure motor	Upper and lower limbs	No	Yes	No	AMAN, RCF	GM1, GD1a	5–70%
Pure sensory	None	Yes	No	No	Abnormal SNAPs	GD1b	<1%
Paraparetic	Lower limbs	Yes	No	No	Axonal	GM1, GD1b	5–10%
Facial diplegia and paresthesia	None	Yes (distal)	Facial	No	AIDP	Unknown	<5%
Pharyngeal, cervical, brachial	Proximal upper limbs	Supportive	Bulbar	No	Equivocal	GT1a, GQ1b	<5%
Acute bulbar palsy	None	Supportive	Bulbar	No	Equivocal	GT1a	<1%
Guillain-Barré syndrome with hyperreflexia	Upper and lower limbs	Yes	Yes	No	Axonal	GM1	<1%
MILLER FISHER SYNDROME SPECTRUM							
Classic	None	Ataxia	Ocular motor nerves	No	Abnormal SNAPs	GQ1b, GT1a	4–25%
Acute ophthalmoplegia	None	Supportive	Ocular motor nerves	No	Normal	GQ1b	<1%
Acute ataxic neuropathy	None	Ataxia	No	No	Axonal	GM1	<5%
Acute ptosis	None	Supportive	Ptosis only	No	Normal	GQ1b	<1%
Acute mydriasis	None	Supportive	Dilated pupils	No	Normal	Unknown	<1%
Acute vestibular syndrome	None	Supportive	Nystagmus	Nystagmus	Normal	GQ1b	<1%

Continued

Table 656.3 Clinical Classification of Guillain-Barré Syndrome—cont'd

	PATTERNS OF LIMB WEAKNESS	SENSORY INVOLVEMENT	CRANIAL NERVE INVOLVEMENT	CNS INVOLVEMENT	SERIAL NEURAL CONDUCTION	IgG AGAINST GANGLIOSIDE TYPE	PROPORTION OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME
BICKERSTAFF BRAINSTEM ENCEPHALITIS							
Classic	None	Supportive	Ocular motor nerves	Yes	Axonal	GQ1b, GT1a	<5%
Acute ataxic hypersomnolence	None	Ataxia	No	Yes	Normal	GQ1b	<1%

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory neuropathy; RCF, reversible conduction failure; SNAP, sensory nerve action potential.
From Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barre syndrome. *Lancet*. 2021;397:1214–1226. Table 3.

Table 656.4 Differential Diagnosis CIDP

TYPICAL CIDP
- AL amyloidosis, ATTRv polyneuropathy
- Chronic ataxic neuropathy ophthalmoplegia M-protein agglutination disialosyl antibodies (CANOMAD)
- Guillain-Barré syndrome
- Hepatic neuropathy
- HIV-related neuropathy
- Multiple myeloma
- Osteosclerotic myeloma
- POEMS syndrome
- Uremic neuropathy
- Vitamin B12 deficiency—actual or functional (e.g., nitrous oxide poisoning)
- Riboflavin transporter deficiency (*SLC52A2*)

DISTAL CIDP
- Anti-MAG IgM neuropathy
- Diabetic neuropathy
- Hereditary neuropathies (CMT1, CMTX1, CMT4, metachromatic leukodystrophy, Refsum disease, adrenomyeloneuropathy, ATTRv polyneuropathy)
- POEMS syndrome
- Vasculitic neuropathy

MULTIFOCAL AND FOCAL CIDP
- Diabetic radiculopathy/plexopathy
- Entrapment neuropathies
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Multifocal motor neuropathy (MMN)
- Neuralgic amyotrophy
- Peripheral nerve tumors (such as lymphoma, perineurioma, schwannoma, neurofibroma)
- Vasculitic neuropathy (mononeuritis multiplex)

MOTOR CIDP
- Hereditary motor neuropathies (such as distal hereditary motor neuropathies, spinal muscular atrophy, porphyria)
- Inflammatory myopathies
- Motor neuron disease
- Neuromuscular junction disorders (such as myasthenia gravis, Lambert-Eaton syndrome)

SENSORY CIDP
- Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)
- Chronic immune sensory polyradiculopathy (CISP)
- Dorsal column lesions (such as syphilis, paraneoplastic, copper deficiency, vitamin B_{12} deficiency)
- Hereditary sensory neuropathies
- Idiopathic sensory neuropathy
- Sensory neuronopathy
- Toxic neuropathies (such as chemotherapy and vitamin B_6 toxicity)

AL, amyloid light chain; ATTRv, hereditary transthyretin amyloidosis; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MAG, antimyelin-associated glycoprotein; POEMS, polyneuropathy,organomegaly, endocrinopathy, M-protein, skin changes.
Modified from Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force-second version. *J Peripher Nerv Syst*. 2021;26:242–268. Table 4.

nerve and autonomic involvement is uncommon. The cerebrospinal fluid (CSF) shows no pleocytosis, but the CSF protein is almost always elevated. Nerve conduction studies show variable slowing of nerve conduction; where required, sural nerve biopsy shows patchy myelin loss and focal inflammatory changes. Acute-onset CIDP may be difficult to distinguish from GBS; CIDP may also be difficult to distinguish from GBS with treatment-related symptom fluctuations.

Congenital GBS is very rare, manifesting as generalized hypotonia, weakness, and areflexia in an affected neonate, fulfilling all electrophysiologic and CSF criteria and in the absence of maternal neuromuscular disease. Treatment is not always required.

LABORATORY FINDINGS AND DIAGNOSIS

CSF studies are helpful in diagnosing GBS. The CSF protein is usually elevated to more than twice the upper limit of normal, the glucose level is normal, and there is no pleocytosis; there should be fewer than 10 white blood cells/mm^3. Bacterial cultures are negative, whereas viral studies rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response (cytoalbuminologic dissociation) in a patient with an acute or subacute polyneuropathy is essentially diagnostic of GBS. These findings may not be apparent in the first week after the onset of symptoms (Table 656.5).

On MRI of the spinal cord in GBS, typical findings include thickening of the cauda equina and intrathecal nerve roots with gadolinium enhancement (Fig. 656.2). Atypical findings should prompt consideration of the alternative diagnoses listed in Table 656.1. Imaging in CIDP is similar but may show greater enhancement of spinal nerve roots (Fig. 656.3).

Nerve conduction studies and electromyography are sensitive to early signs of peripheral nerve inflammation in GBS. Motor and sensory nerve conduction velocities are reduced to a variable extent, reflecting the patchy nature of nerve involvement in this disorder, which is also reflected by focal conduction block and dispersed responses. Electromyography may show acute denervation of muscle. Serum creatine kinase levels may be mildly elevated or normal. Serum antiganglioside antibodies against GM_1 and GD_1 are sometimes elevated in GBS, particularly in cases with primarily axonal rather than demyelinating neuropathy, suggesting that they might play a role in disease propagation and/or recovery in some cases (see Table 656.3). Sural nerve biopsy shows segmental demyelination, focal inflammation, and Wallerian degeneration, but is almost never required for diagnosis.

Serologic testing for *Campylobacter* and *Helicobacter* infections helps establish causation if results are positive but does not alter treatment. Stool cultures are rarely positive because the infection is generally self-limited, and the neuropathy follows the acute gastroenteritis.

TREATMENT

Patients in early stages of GBS should be admitted to the hospital for observation because the ascending paralysis can rapidly cause (potentially life-threatening) respiratory failure and autonomic instability (Fig. 656.4). The respiratory effort (measured by bedside testing or spirometry) *must* be monitored for changes predicting onset of hypoventilation and respiratory failure. Patients with milder weakness and slow progression may be treated expectantly, with observation for stabilization and spontaneous remission. Severe or rapidly

Table 656.5 Diagnostic Criteria for Guillain-Barré Syndrome*

FEATURES NEEDED FOR DIAGNOSIS OF GUILLAIN-BARRÉ SYNDROME IN CLINICAL PRACTICE

- Progressive weakness in legs and arms (sometimes initially only in legs)
- Areflexia (or decreased tendon reflexes) in weak limbs

ADDITIONAL SYMPTOMS

- Progressive phase lasts days to 4 wk (often 2 wk)
- Relative symmetry
- Mild sensory symptoms or signs (not present in acute motor axonal neuropathy)
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain (common)

FEATURES THAT SHOULD RAISE DOUBT ABOUT THE DIAGNOSIS OF GUILLAIN-BARRÉ SYNDROME

- CSF: increased number of mononuclear cells or polymorphonuclear cells (>50 cells/μL)
- Severe pulmonary dysfunction with little or no limb weakness at onset
- Severe sensory signs with little or no weakness at onset
- Bladder or bowel dysfunction at onset
- Fever at onset
- Sharp spinal cord sensory level
- Marked, persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- Slow progression of weakness and without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or acute-onset chronic inflammatory demyelinating polyneuropathy)

NERVE CONDUCTION STUDIES

- Can be helpful in clinical practice but are generally not required to diagnose Guillain-Barré syndrome
- Essential for classification of Guillain-Barré syndrome as acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy
- Acute inflammatory demyelinating polyneuropathy: features of demyelination (decreased motor nerve conduction velocity, prolonged distal motor latency, increased F-wave latency, conduction blocks, and temporal dispersion)
- Acute motor axonal neuropathy: no features of demyelination (one demyelinating feature in one nerve, if distal CMAP amplitude is less than 10% LLN, can be found; distal CMAP amplitude less than 80% LLN in at least two nerves. Transient motor nerve conduction block might be present.

*Classification of Guillain-Barré syndrome as either acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy is not required for the diagnosis of Guillain-Barré syndrome. Whether acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy require different treatments is unknown. The amount of conduction slowing required to define demyelination differs between classification systems.

CSF, Cerebrospinal fluid; CMAP, compound muscle action potential; LLN, lower limit of normal.

From Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet.* 2016;388:717–727. Panel 1.

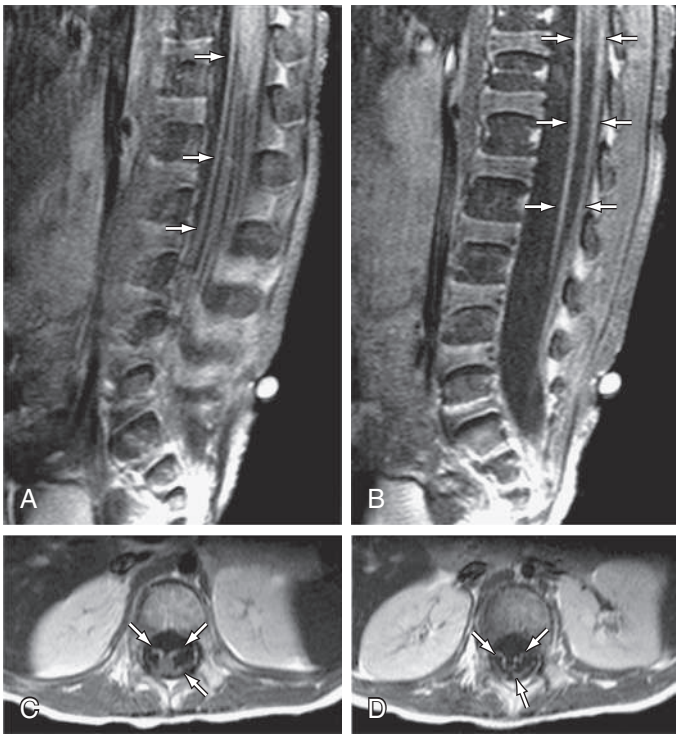

Fig. 656.2 Guillain-Barré syndrome. Sagittal off-midline (**A**) and midline (**B**) postgadolinium T1 weighted fat-saturated images through the lumbar spine of a patient who could not ambulate. **C** and **D**, Axial post-contrast T1 weighted images through the conus medullaris and proximal lumbar nerve roots, respectively. The images show extensive contrast enhancement of nerve roots (*arrows* in **A-D**), in keeping with changes of Guillain-Barré syndrome. *(From Slovis TL, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 65-6.)*

progressive muscle weakness is treated with intravenous immunoglobulin (IVIG); common protocols include IVIG 0.4 g/kg/day for 5 consecutive days or 1 g/kg/day for 2 days. Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are not effective for weakness but may help with pain. Supportive care, such as respiratory support, prevention of pressure sores and constipation, nutritional support, pain management, prevention of deep vein thrombosis, and treatment of secondary bacterial infections is important.

Neuropathic pain in GBS should be treated aggressively, with narcotic analgesics where necessary, and with medications such as gabapentin.

CIDP can be treated with either oral or pulsed steroids or IVIG, with refractory cases often requiring use of other immunosuppressive medications. Children with relapsing or slowly progressive weakness often need months to years of therapy, but most eventually achieve a sustained remission. The outcome is generally good, but some children have permanent deficits.

PROGNOSIS

GBS is usually a monophasic illness; spontaneous recovery begins within 2-3 weeks but can take months. Therapy with IVIG hastens recovery but not does alter the long-term outcome. As many as 60% of affected children become nonambulant during their illness, but most eventually regain full strength. A minority has some residual weakness, most often of the ankle dorsiflexors. Improvement usually follows a gradient opposite the direction of involvement, with bulbar function recovering first and lower extremity weakness resolving last. The tendon reflexes are usually the last function to recover. Clinical features predicting a severe course and slow (possibly incomplete) recovery include cranial nerve involvement, the need for ventilatory support, and maximum disability at the time of presentation. Neurophysiologic studies do not necessarily predict the long-term outcome, but children with demyelinating forms of GBS generally recover more quickly than those with axonal forms. Bulbar and respiratory muscle involvement can lead to death from GBS if the syndrome is not recognized and treated. Fatigue is the most common long-term residuum of GBS. Relapses occur in about 4% of children with GBS and are generally responsive to immunomodulatory treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

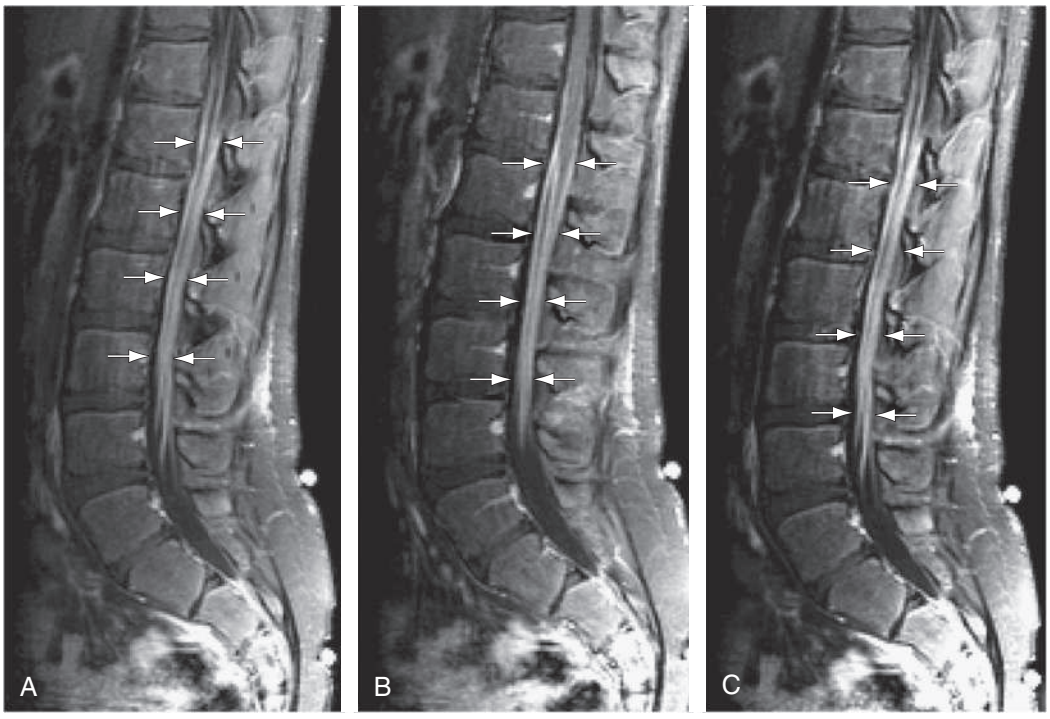

Fig. 656.3 Chronic inflammatory demyelinating polyneuropathy (CIDP) in a 13-yr-old male with peripheral neuropathy and gait disturbance. Sagittal fat-saturated T1 weighted images off the midline to the right **(A)**, at the midline **(B)**, and off the midline to the left **(C)**. *(From Slovis TL, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 65-7.)*

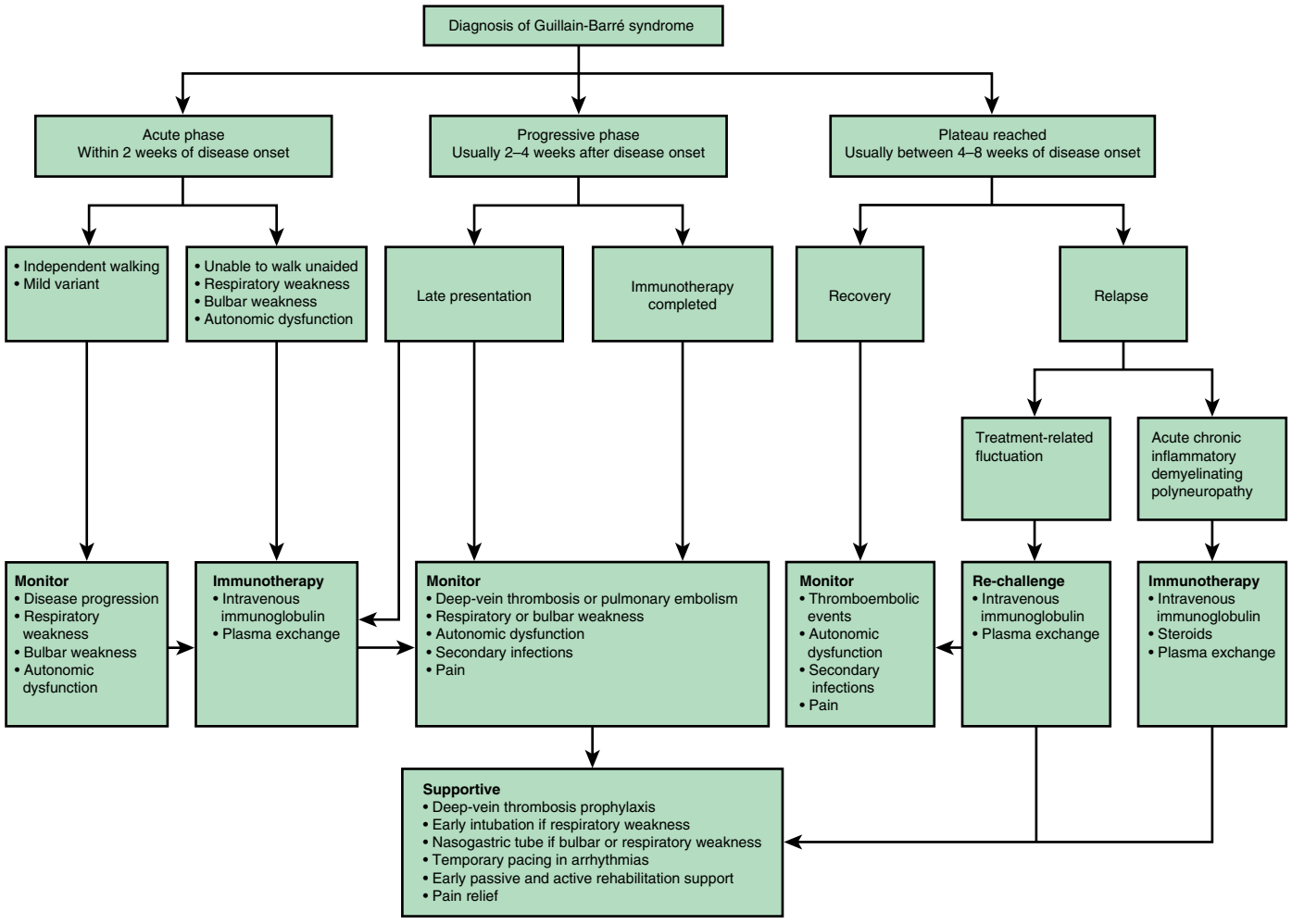

Fig. 656.4 Management algorithm for Guillain-Barré syndrome. Depending on the time of symptom presentation from disease onset, patients can be managed according to the disease phase. Immunotherapy with either intravenous immunoglobulin or plasma exchange is recommended when the patient cannot walk unaided. Supportive management includes monitoring for disease progression and early intervention when there is evidence of autonomic dysfunction, respiratory weakness, or bulbar weakness. Due to prolonged immobility, patients are also at risk of deep vein thrombosis and pulmonary embolism, warranting preventive prophylaxis. After plateau is reached, some patients can have a relapse, which could be due to treatment-related fluctuation, or an acute onset of chronic inflammatory demyelinating polyneuropathy. *(From Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barre syndrome. Lancet. 2021;397:1214–1226. Fig. 3.)*

Chapter 657

Bell Palsy

Monique M. Ryan

Bell palsy is an *acute-onset* peripheral facial nerve palsy that is not associated with any other cranial nerve neuropathies or brainstem dysfunction. It is a common disorder at all ages from infancy through adolescence, usually developing suddenly about 2 weeks after a presumed viral infection. Numerous viruses have been linked with Bell palsy (Table 657.1). Active or reactivation of herpes simplex or varicella-zoster virus are the most common causes of Bell palsy (Fig. 657.1). In **Ramsay Hunt syndrome** (herpes zoster oticus), an acute facial nerve palsy is associated with painful vesicles in the external auditory canal or auricle. Hereditary forms of Bell palsy are rare. Bell palsy rarely occurs in the context of systemic hypertension or type 1 diabetes mellitus. *Unilateral or bilateral facial nerve palsy is often a sign of Lyme disease.* In addition, Lyme-associated facial palsy is often preceded by fever, malaise, headache, myalgias or arthralgias, all symptoms uncommon in idiopathic Bell palsy.

CLINICAL MANIFESTATIONS

Pain behind the ear may precede weakness, which develops acutely. Both the upper and lower portions of the face are paretic, and the corner of the mouth droops. Patients are unable to close the eye on the affected side and are hence at risk of exposure keratitis. Taste on the anterior two thirds of the tongue is lost on the involved side in approximately 50% of cases; this finding helps establish the anatomic limits of the lesion as being proximal or distal to the chorda tympani branch of the facial nerve. Lacrimation is spared. Facial numbness and paresthesias are rare, but when present suggest concomitant involvement of the trigeminal nerve. The blood pressure should always be checked in a child with acute facial weakness.

Imaging is not required for *typical* Bell palsy. In children less than 2 years of age or those in whom there is suspicion of other pathologies because of atypical findings or chronic or recurrent weakness, MRI of the facial nerve excludes structural lesions causing facial nerve dysfunction. Serology and other viral studies are generally noncontributory. A full blood count should be considered to exclude leukemia in younger patients or those with atypical findings. Lyme antibody testing is indicated in children from endemic areas.

In patients who do not recover within a few weeks, neurophysiologic examination of the facial nerve helps to determine the severity of the facial neuropathy and the likely speed of recovery. In chronic cases, other causes of facial neuropathy should be considered, including hypertension, diabetes, facial nerve tumors such as schwannomas and neurofibromas, infiltration of the facial nerve by leukemic cells or by a rhabdomyosarcoma of the middle ear, brainstem infarcts or tumors, and traumatic injury of the facial nerve.

Table 657.1 Etiologies of Acute Peripheral Facial Palsy

COMMON
Idiopathic
Herpes simplex virus type 1*
Varicella-zoster virus*
Lyme disease (may be bilateral)
LESS COMMON INFECTIOUS CAUSES
Otitis media ± cholesteatoma
Epstein-Barr virus
Cytomegalovirus
Mumps
Human herpesvirus 6
Intranasal influenza vaccine
Mycoplasma
Toxocara
Rickettsia
AIDS/HIV
OTHER LESS COMMON ASSOCIATIONS
Trauma
Schwannoma of facial nerve
Infiltrative tumor
Aneurysm or vascular malformation
Anomalous narrowing of facial nerve canal
Hypertension
Sjögren syndrome
Diabetes mellitus, type 1
Guillain-Barré syndrome
Sarcoidosis
Kawasaki syndrome
Melkersson-Rosenthal syndrome†
Treatment with ribavirin or interferon

*Implicated in idiopathic Bell palsy.
†Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

TREATMENT

In contrast to adults, the outcome of pediatric Bell palsy is so good that benefit from treatment with corticosteroids, with or without acyclovir, has not been established, although many centers recommend a brief course of oral prednisone. In adults, treatment may include steroids *plus* an antiviral agent (valacyclovir, famciclovir) although this is controversial, and steroids alone have been beneficial, whereas antiviral agents alone have had no benefit. The combination may provide improved outcomes. Protection of the cornea with an ocular lubricant is especially important at night.

PROGNOSIS

Most children experience complete spontaneous recovery from Bell palsy within a few weeks from onset. A small proportion (<10%) has some residual facial weakness. Bilateral Bell palsy is rare, but as many as 15% of children experience recurrent episodes of facial weakness.

Nerve regrowth is occasionally misdirected, resulting in **synkinesis,** where activation of one muscle group may produce activation of another inappropriate muscle group; blinking may result in mouth twitching, smiling may cause eye blinking, and lacrimation (crocodile tears) may occur while eating. This complication is much less common in children than adults.

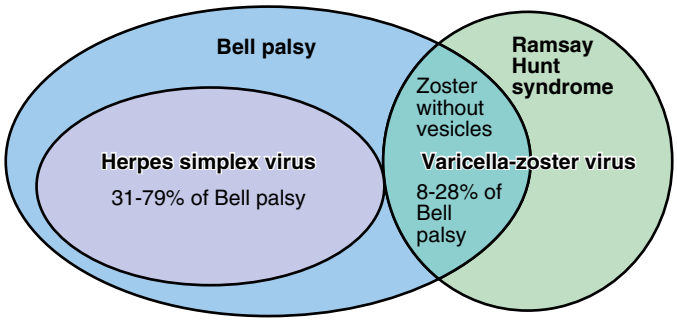

Fig. 657.1 Involvement of herpes simplex and varicella-zoster viruses in acute facial palsy. *(Modified from Hato N, Murakami S, Gyo K. Steroid and antiviral treatment for Bell's palsy. Lancet. 2008;371:1818–1820.)*

Disorders of the Eye

PART XXVII

Chapter 658
Growth and Development of the Eye

Scott E. Olitsky and Justin D. Marsh

The eye of a normal full-term infant at birth is approximately 65% of adult size. Postnatal growth is maximal during the first year, proceeds at a rapid but decelerating rate until the third year, and continues at a slower rate thereafter until puberty, after which little change occurs. The anterior structures of the eye are relatively large at birth but thereafter grow proportionately less than the posterior structures. This results in a progressive change in the shape of the globe such that it becomes more spherical.

In an infant, the sclera is thin and translucent, with a bluish tinge. The cornea is relatively large in newborns (averaging 10 mm) and attains adult size (nearly 12 mm) by the age of 2 years or earlier. Its curvature tends to flatten with age, resulting in a progressive change in the refractive properties of the eye. A normal cornea is perfectly clear. In infants born prematurely, however, the cornea may have a transient opalescent haze. The anterior chamber in a newborn appears shallow, and the angle structures, important in the maintenance of normal intraocular pressure, must undergo further differentiation after birth. The iris, typically light blue or gray at birth in White individuals, undergoes progressive change of color as the pigmentation of the stroma increases in the first 6 months of life. The pupils of a newborn infant tend to be small and are often difficult to dilate. This is the result of an immature iris dilator muscle. Remnants of the **pupillary membrane** (anterior vascular capsule) are often evident on ophthalmoscopic examination, appearing as cobweb-like lines crossing the pupillary aperture, especially in preterm infants.

The lens of a newborn infant is more spherical than that of an adult; its greater refractive power helps to compensate for the relative shortness of the young eye. The lens continues to grow throughout life, as new peripheral fibers continually push older fibers toward the center of the lens. With age, the lens becomes progressively denser and more resistant to the change of shape that occurs during accommodation (focusing of the lens).

The fundus of a newborn's eye is less pigmented than that of an adult; the choroidal vascular pattern is highly visible, and the retinal pigment pattern often has a fine peppery or mottled appearance. In some darkly pigmented infants, the fundus has a gray or opalescent sheen. In a newborn, the macular landmarks, particularly the foveal light reflex, are less well defined due to incomplete maturation of the retinal layers. The peripheral retina appears pale or grayish, and the peripheral retinal vasculature is immature, especially in premature infants. The optic nerve head color varies from pink to slightly pale, sometimes grayish. Within 4-6 months, the appearance of the fundus approximates that of the mature eye.

Superficial retinal hemorrhages may be observed in many newborn infants. These are usually absorbed promptly and rarely leave any permanent effect. The majority of birth-related retinal hemorrhages resolve within 2 weeks, with complete resolution of all such hemorrhages within 4-6 weeks of birth. Conjunctival hemorrhages also may occur at birth and are resorbed spontaneously without consequence.

Remnants of the primitive **hyaloid vascular system** may appear as small tufts or wormlike structures projecting from the disc (Bergmeister papilla) or as a fine strand traversing the vitreous; in some cases, only a small dot (Mittendorf dot) remains on the posterior aspect of the lens capsule.

An infant's eye is somewhat **hyperopic** (farsighted). The general trend is for hyperopia to increase from birth until age 7 years. Thereafter, the level of hyperopia tends to decrease rapidly until age 14 years. Elimination of the hyperopic state may occur during this time. If the process continues, a child may become **myopic** (nearsighted). A slower continuation of the decrease in hyperopia, or increase in myopia, continues into the third decade of life. The refractive state at any time in life depends on the net effect of many factors: the size of the eye, the state of the lens, and the curvature of the cornea.

Newborn infants tend to keep their eyes closed much of the time, but normal newborns can see, respond to changes in illumination, and fixate points of contrast. The visual acuity in newborns is estimated to be approximately 20/400. This poor vision is a result of the immature, multilayered foveal anatomy. Retinal development continues postnatally, maturing completely during the first few years of life. One of the earliest responses to a formed visual stimulus is an infant's regard for the mother's face, evident especially during feeding. By 2 weeks of age, an infant shows more sustained interest in large objects, and by 8-10 weeks of age, a normal infant can follow an object through an arc of 180 degrees. The acuity improves rapidly and may reach 20/30-20/20 by the age of 2-3 years.

Many normal infants may have imperfect coordination of the eye movements and alignment during the early days and weeks, but proper coordination should be achieved by 3-6 months, usually sooner. Persistent deviation of an eye in an infant at 6 months of age requires evaluation.

Tears often are not present with crying until after 1-3 months. Preterm infants have reduced reflex and basal tear secretion, which may allow topically applied medications to become concentrated and lead to rapid drying of their corneas.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 659
Examination of the Eye

Scott E. Olitsky and Justin D. Marsh

The eye exam is a routine part of pediatric well childcare, which begins in the newborn period. The primary care physician plays a critical role in the detection of both obvious and insidious asymptomatic eye diseases. School and community screening programs can also be effective in identifying problems at an early age. The American Academy of Ophthalmology recommends preschool vision screening during well child visits as a means of reducing preventable visual loss (Table 659.1). Referrals to an ophthalmologist should be

made when a significant ocular abnormality or visual acuity deficit is suspected. An ophthalmologist should also examine high-risk children, such as those with a family history of eye disease, or various systemic or genetic disorders, such as Down syndrome or juvenile idiopathic arthritis.

The basic eye exam, whether performed by a pediatrician or an ophthalmologist, must include visual acuity and visual field testing, assessment of pupils, ocular motility and alignment, a general external/facial examination, and finally, examination of the media and fundus via ophthalmoscopy.

The periodicity for visual assessment should occur beginning in the newborn to 6 month age group and continue at ages 6-12 months, 1-3 years, 4-5 years, and 6 years and older. The assessments include an ocular history, inspection of the lids and eyes, red reflex testing, pupil examination, ocular motility testing, and assessment of visual acuity.

When indicated, biomicroscopy (slit-lamp examination), cycloplegic refraction, and tonometry are performed by an ophthalmologist. Special diagnostic procedures, such as ultrasound, fluorescein angiography, electroretinography, or visual evoked response testing, are also indicated for specific conditions.

VISUAL ACUITY

There are various means of assessing visual acuity in the pediatric population. A child's age and ability to cooperate, as well as clinician preference, all factor into deciding which test to use. The most common visual acuity test in infants is an assessment of their ability to fixate and follow a target. If appropriate targets are used, this response can be demonstrated by approximately 6 weeks of age.

The test begins by seating the child comfortably in the caretaker's lap. The object of visual interest, usually a bright-colored toy or target with lights, is slowly moved to the right and to the left. The examiner observes whether the infant's eyes turn toward the object and follow its movements. The examiner can use a thumb or palm of the hand to occlude one of the infant's eyes to test each eye separately. Although a sound-producing object might compromise the purity of the visual stimulus, in practice, toys that squeak or rattle heighten an infant's awareness and interest in the test.

The human face is a better target than test objects. The examiner can exploit this by moving his or her face slowly in front of the infant's face. If the appropriate following movements are not elicited, the test should be repeated with the caretaker's face as the test stimulus. It should be remembered that even children with poor vision can follow a large object without apparent difficulty, especially if only one eye is affected.

An objective measurement of visual acuity is usually possible when children reach the age of 2.5-3 years. Children this age are tested using a schematic picture or other illiterate eye chart. Examples include Allen or Lea symbols and tumbling E. Each eye should be tested separately. It is essential to prevent peeking. The examiner should hold the occluder in place and observe the child throughout the test. The child should be reassured and encouraged throughout the test because many children are intimidated by the process and fear a "bad grade" or punishment for errors. In addition, many children may be too timid to verbally identify figures being tested and may be more willing to participate if given the opportunity to match the presented symbols to identical symbols provided on a handout during the exam. Matching is often preferred at this age, particularly in randomized control trials, because it also allows the clinician to test visual acuity using letters instead of figures, even if a child has not yet learned the alphabet.

An adult-type **Snellen acuity chart** can be used at 5-6 years of age if the child knows letters. A visual acuity of 20/40 is generally accepted as normal for 3-year-old children. At 4 years of age, 20/30 is acceptable. By 5 or 6 years of age, most children attain 20/20 vision.

Optokinetic nystagmus (the response to a sequence of moving targets; "railroad" nystagmus) can also be used to assess vision; this can be calibrated by targets of various sizes (stripes or dots) or by a rotating drum (known as an OKN drum) at specified distances.

The visual evoked response, an electrophysiologic method of evaluating the response to light and special visual stimuli, such as calibrated stripes or a checkerboard pattern, can also be used to study visual function in selected cases.

Preferential looking tests are used for evaluating vision in infants and children who cannot respond verbally to standard acuity tests. This is a behavioral technique based on the observation that, given a choice, an infant prefers to look at patterned rather than unpatterned stimuli. Because these tests require the presence of a skilled examiner, their use is often limited to research protocols involving preverbal children.

VISUAL FIELD ASSESSMENT

Visual field assessment must be geared to a child's age and abilities. Formal visual field examination (perimetry and scotometry) can often be accomplished in school-age children. In younger children and in the pediatrician's office, the examiner must often rely on confrontation techniques and finger counting in quadrants of the visual field. In many such children, only testing by attraction can be accomplished; the examiner observes a child's response to familiar objects brought into each of the four quadrants of the visual field of each eye in turn. The child's bottle, a favorite toy, and lollipops are particularly effective attention-getting items. These gross methods can often detect diagnostically significant field changes such as the bitemporal hemianopia of a chiasmal lesion or the homonymous hemianopia of a cerebral lesion.

COLOR VISION TESTING

Color vision testing can be accomplished when a child is able to name or trace the test figures, which include numbers, shapes, or other symbols. The common color vision testing tools include Ishihara color plates or Hardy Rand Littler. Color vision testing is not frequently necessary in young children; however, parents may request testing, particularly if their child seems to be slow in learning colors or if there is a family history of color vision deficiency. It is important to keep in mind and reassure parents that "color-deficient" children do not misname colors, and that true "color blindness" is very rare and not compatible with normal vision. **Color deficiency** is common in male patients but rare in females because the gene is transmitted in an X-linked manner. **Achromatopsia**, which may be encountered occasionally, is a condition of complete color blindness associated with subnormal visual acuity, nystagmus, and photophobia.

Color discrimination is a means of assessing the intensity of a hue, typically red. Patients describe the intensity of red depicted from the test object. A change in color discrimination (often referred to as color "desaturation") can be a sign of optic nerve or retinal disease.

PUPILLARY EXAMINATION

The pupil exam includes evaluations of both the direct and consensual responses to light, accommodation (a near target), and reduced illumination, noting the size and symmetry of the pupils under each testing condition. Special care must be taken to differentiate the reaction to light from the reaction to near gaze. A child's natural tendency is to look directly at the approaching light, inducing the near gaze reflex when one is attempting to test only the reaction to light; accordingly, every effort must be made to control fixation on a distance target. The swinging flashlight test is especially useful for detecting unilateral or asymmetric prechiasmatic afferent defects in children (see "Marcus Gunn Pupil" in Chapter 662).

OCULAR MOTILITY

Ocular motility testing assesses alignment and extraocular muscle function. This is tested by having a child follow an object in various positions of gaze, known as the *cardinal positions*. The cardinal positions are those in which one extraocular muscle predominantly functions and a deficit can be identified if present. Movements of each eye individually **(ductions)** and of the two eyes together (**versions**, conjugate movements, and convergence) are assessed.

Alignment can be assessed in two ways. The first is symmetry of the corneal light reflexes. The second method is to occlude each eye in an

Table 659.1 Vision Screening Guidelines

FUNCTION	RECOMMENDED TESTS	REFERRAL CRITERIA	COMMENTS
AGES 3-5 YEARS			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test (contains only these 4 letters)	<4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., <10/20 or 20/40), or Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and 10/20 or 20/25 and 20/40)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, Lea symbols or the HOTV test should be used for ages 3-5 years and Snellen letters or numbers for ages 6 years and older
	Picture tests		Testing distance of 3 m (10 ft) is recommended for all visual acuity tests
	Allen figures		A line of figures is preferred over a single figure
	Lea symbols		The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to eye; the examiner must ensure that it is not possible to peek with the nontested eye
Ocular alignment	Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)	Any eye movement <4 of 6 correct	
	Simultaneous red reflex test (Bruckner test)	Any asymmetry of pupil color, size, brightness	Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2-3 ft away; detects asymmetric refractive errors as well
Ocular media clarity (cataracts, tumors, etc.)	Red reflex	White pupil, dark spots, absent reflex	Direct ophthalmoscope, darkened room. View eyes separately at 12-18 inches; white reflex indicates possible retinoblastoma
AGES 6 YEARS AND OLDER			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test	<4 of 6 correct on 4.5 m (15 ft) line with either eye tested at 3 m (10 ft) monocularly (i.e., <10/15 or 20/30)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, Lea symbols or the HOTV test should be used for ages 3-5 years and Snellen letters or numbers for ages 6 years and older
	Picture tests	Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30)	Testing distance of 3 m (10 ft) is recommended for all visual acuity tests
	Allen figures		A line of figures is preferred over a single figure
	Lea symbols		The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner must ensure that it is not possible to peek with the nontested eye
Ocular alignment	Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)	Any eye movement <4 of 6 correct	

alternating fashion and observe for a change in fixation of the viewing eye (see discussion on cover testing for strabismus in Chapter 663).

BINOCULAR VISION

Attaining binocular visual function is one of the primary goals of amblyopia therapy and ocular realignment surgery. Just as there are multiple methods for assessing visual acuity, there are various means of testing the level of binocular vision. The Titmus test is probably the most frequently used test; a series of three-dimensional images are shown to the child while he or she wears a set of polarized glasses. The level of difficulty with which these images can be detected correlates with the degree of binocular vision present.

EXTERNAL EXAMINATION

The external examination begins with general inspection, paying close attention to size, shape, and symmetry of the orbits, in addition to the position and movement of the lids and position and symmetry of the globes. Viewing the eyes and lids in such a manner aids in detecting orbital asymmetry, lid masses, proptosis (exophthalmos), and abnormal pulsations. Palpation is also important in detecting orbital and lid masses. Orbital dermoids and capillary hemangiomas are frequently evaluated during the external examination.

The lacrimal system is assessed by looking for evidence of tear deficiency, overflow of tears (epiphora), erythema, and swelling in the region of the tear sac or gland. The lacrimal gland is located in the superotemporal orbit, beneath the eyebrow. The tear drainage system, which includes the lacrimal sac, is located within the medial wall of the orbit, where the eyelids meet the bridge of the nose. The sac is massaged to check for reflux when obstruction is suspected. The presence and position of the puncta are also checked.

The lids and conjunctivae are specifically examined for focal lesions, foreign bodies, and inflammatory signs; loss and misdirection of lashes should also be noted. When necessary, the lids can be everted in the following manner: (1) instruct the patient to look down; (2) grasp the lashes of the patient's upper lid between the thumb and index finger of one hand; (3) place a probe, a cotton-tipped applicator, or the thumb of the other hand at the upper margin of the tarsal plate; and (4) pull the lid down and outward and evert it over the probe, using the instrument as a fulcrum. Foreign bodies commonly lodge in the concavity just above the lid margin and are exposed only by fully everting the lid.

The anterior segment of the eye is then evaluated with oblique focal illumination, noting the luster and clarity of the cornea, the depth and clarity of the anterior chamber, and the features of the iris. Transillumination of the anterior segment aids in detecting opacities and in demonstrating atrophy or hypopigmentation of the iris; these latter signs are important when ocular albinism is suspected. When necessary, fluorescein dye can be used to aid in diagnosing abrasions, ulcerations, and foreign bodies.

BIOMICROSCOPY (SLIT-LAMP EXAMINATION)

The slit-lamp exam provides a highly magnified view of the various structures of the eye and an optical section through the media of the eye—the cornea, aqueous humor, lens, and vitreous. Lesions can be identified and localized according to their depth within the eye; the resolution is sufficient to detect individual inflammatory cells in the aqueous and anterior vitreous. With the addition of special lenses and prisms, the angle of the anterior chamber and components of the fundus also can be examined with a slit lamp. Biomicroscopy is often crucial in trauma and in examining for iritis. It is also helpful in diagnosing many metabolic and genetic diseases of childhood.

FUNDUS EXAMINATION (OPHTHALMOSCOPY)

The ideal setting for ophthalmoscopy is with a well-dilated pupil unless there are neurologic or other contraindications. Tropicamide (Mydriacyl) 0.5–1% and phenylephrine (Neo-Synephrine) 2.5% are recommended as mydriatics of short duration. These are safe for most children, but the possibility of adverse systemic effects must be recognized. For very small infants, especially 6 months or younger, more dilute preparations may be advisable. Beginning with posterior landmarks, the disc, the macula, and the four quadrants are systematically examined by following each of the major vessel groups to the periphery. Retinal hemorrhages, vascular anomalies, and posterior uveitis are often appreciated during this segment of the examination. Color, cup, and contour of the optic nerve should be noted as well. Abnormalities are frequently followed with further imaging studies such as a CT or MRI or diagnostic testing such as automated perimetry (see "Visual Field Assessment" earlier). The midperipheral retina can be seen if a child is directed to look up and down and to the right and left. Even with care, only a limited fraction of the fundus can be seen with a direct or handheld ophthalmoscope. For examination of the far periphery, an indirect ophthalmoscope is used, and full dilation of the pupil is essential.

REFRACTION

Refraction determines the focusing power of the eye: the degree of nearsightedness (myopia), farsightedness (hypermetropia), or astigmatism. Retinoscopy provides an objective determination of the amount of correction needed and can be performed at any age, including the newborn period. In young children, it is best done with cycloplegia using cyclopentolate 1% eye drops in an ophthalmologist's office. Subjective refinement of refraction involves asking patients for preferences in the strength and axis of corrective lenses; it can be accomplished in many school-age children. Refraction and determination of visual acuity with appropriate corrective lenses in place are essential steps in deciding whether a patient has a visual defect or amblyopia. Photoscreening cameras aid ancillary medical personnel in screening for refractive errors in preverbal children. The accuracy and practical usefulness of these devices are still being investigated.

TONOMETRY

Tonometry is the method of assessing intraocular pressure. It may be performed with a portable, stand-alone instrument or by the applanation method during slit-lamp examination. Alternative methods are pneumatic, electronic, or rebound tonometry. When accurate measurement of the pressure is necessary in a child who cannot cooperate, it may be performed with sedation or general anesthesia. A gross estimate of pressure can be made by palpating the globe with the index fingers placed side by side on the upper lid above the tarsal plate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 660

Abnormalities of Refraction and Accommodation

Scott E. Olitsky and Justin D. Marsh

Emmetropia is the normal state in which parallel rays of light come to focus on the retina with the eye at rest (nonaccommodating). Even though such an ideal optical state is common, the opposite condition, ametropia, often occurs. Three principal types of **ametropia** exist: **hyperopia** (farsightedness), **myopia** (nearsightedness), and **astigmatism** (Fig. 660.1). Most children are physiologically hyperopic at birth. Nevertheless, myopia and astigmatism may develop early in childhood, particularly when associated with previous prematurity or numerous medical diagnoses. With growth, the refractive state tends to change and should be evaluated periodically.

Measurement of the refractive state of the eye (refraction) can be accomplished both objectively and subjectively. The objective method involves directing a beam of light from a retinoscope onto a patient's retina. Using loose lenses of various strengths held in front of the eye, the retinal light reflex (viewed through the pupil) can be neutralized, yielding a precise refraction. An objective refraction is obtainable at any age because it requires no response from the patient. In infants and children, it is generally more accurate to perform a refraction after instillation of eye drops that produce **mydriasis** (dilation of the pupil) and **cycloplegia** (paralysis of accommodation); those used most commonly are tropicamide (Mydriacyl), cyclopentolate (Cyclogyl), and atropine sulfate. A subjective refraction involves placing lenses in front of the eye and having the patient report which lenses provide the clearest image of the letters on a chart. This method is dependent on a patient's ability to discriminate and communicate, but it can be used for some children and may be helpful in determining the best refractive correction for children who are developmentally capable.

HYPEROPIA

If parallel rays of light come to focus posterior to the retina with the eye in a neutral state, hyperopia or farsightedness exists. This may result from a shorter anteroposterior diameter of the eye or a lower refractive power of the cornea or lens.

In hyperopia, the additional refracting power needed to bring objects into focus at distance and near is generated through the accommodative mechanism. If the accommodative effort required for focus is within that child's accommodative amplitude, the vision is clear. In

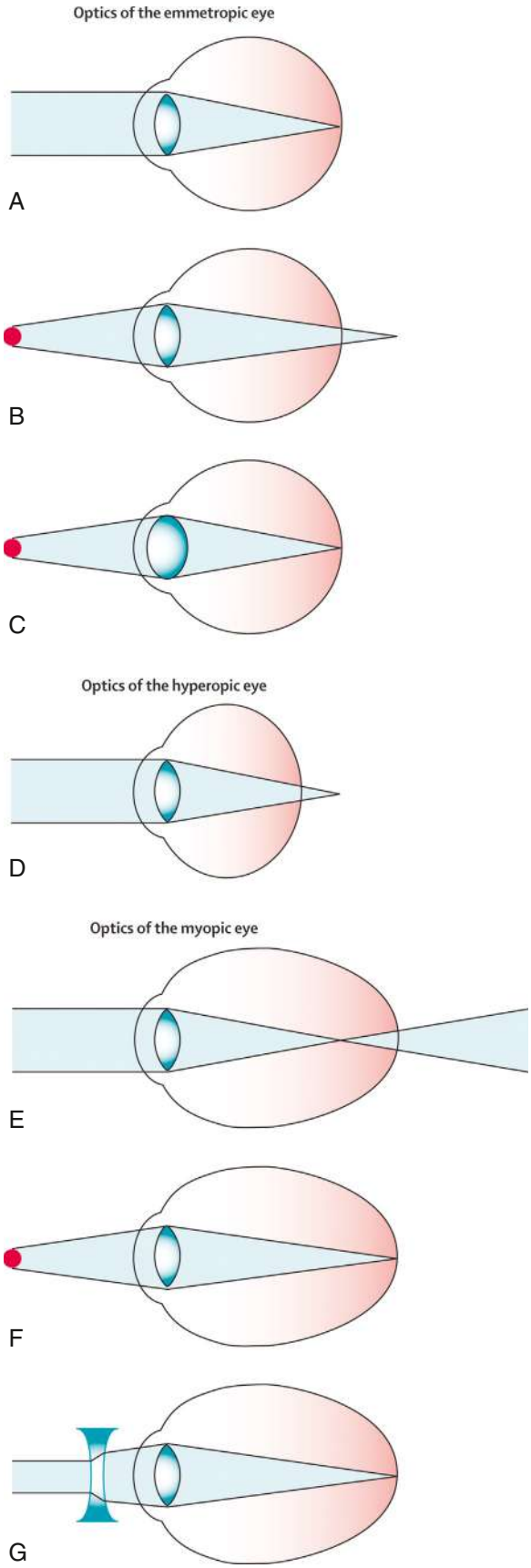

Fig. 660.1 Schematic optics of the eye. **A-C,** Emmetropic eyes. **D,** Hyperopic eyes. **E-G,** Myopic eyes. **A,** In emmetropic eyes, the parallel rays of a distant object are focused on the photoreceptors. **B,** When a closer object is viewed, the image is in focus behind the photoreceptors. The image can be brought forward into focus on the photoreceptors by the process of accommodation—increasing the optical power of the lens **(C).** In hyperopic eyes **(D),** the eye is too short, and the image of a distant object is focused behind the photoreceptors and can be brought into focus by accommodation. Myopic eyes are eyes that have grown too long **(E),** and the image of a distant object falls in front of the photoreceptors and cannot be brought into focus by accommodation. When closer objects are viewed, the image moves back toward the photoreceptors, and at a certain distance (the far point), which is related inverse to the severity of the myopia, it comes into focus **(F).** Closer objects can then be brought into focus using accommodation. Optical correction for myopia is achieved with concave (diverging) lenses, which move the image into focus on the photoreceptors (G). Contact lenses work in a similar way, whereas refractive surgery reduces the power of the cornea to bring the image of distant objects into focus. For equal corneal power, myopic eyes have longer axial lengths than emmetropic eyes, with deeper anterior and vitreal chambers. Their lenses tend to be thinner and of lower power than those of emmetropic eyes. *(From Morgan IG, Ohno-Matusi K, Saw SM. Myopia. Lancet. 2012;379:1739-1746, Fig. 1, p. 1740.)*

high degrees of hyperopia requiring greater accommodative effort, vision may be blurred, and the child may complain of eyestrain, headaches, or fatigue. Squinting, eye rubbing, and lack of interest in reading are frequent manifestations. If the induced discomfort is great enough, a child may not make the effort to focus and may develop bilateral amblyopia (ametropic amblyopia). Esotropia may also be associated (see discussion on convergent strabismus, accommodative esotropia in Chapter 663). Convex lenses (spectacles or contact lenses) of sufficient strength to provide clear vision and comfort are prescribed when indicated. Even children who have high degrees of hyperopia but who have good vision will happily wear glasses because they provide comfort by eliminating the excessive accommodation required to see well. Preverbal children should also be given glasses for high levels of hyperopia to prevent the development of esotropia or amblyopia. Children with normal levels of hyperopia do not require correction in the majority of cases.

MYOPIA

In myopia, parallel rays of light come to focus anterior to the retina. This is a result of either a long anteroposterior diameter of the eye or a higher refractive power of the cornea or lens. The principal symptom is blurred vision for distant objects. The far point of clear vision varies inversely with the degree of myopia; as the myopia increases, the far point of clear vision moves closer to the eye. For example, an individual with one diopter of myopia has a far point of clear focus that is 1 m from the eye. Any object located farther than 1 m from the eye will begin to appear blurry. Similarly, for an individual with 3 diopters of myopia, the far point of clear vision is now ⅓ m from the eye, as the far point is the inverse of the power of myopia, as measured in meters. Thus myopic children tend to hold objects and reading material closer, prefer to be close to the blackboard, and may be uninterested in distant activities. Squinting is common because the visual acuity is improved when the lid aperture is reduced, also known as the *pinhole effect*.

Myopia is infrequent in infants and preschool-age children. It is more common in infants with a history of **retinopathy of prematurity.** A hereditary tendency to myopia is also observed, and children of myopic parents should be examined at an early age. Nonsyndromic myopia is associated in some families with variants in the high-grade myopia-1 locus *(MYP1)* as well as in *SLITRK6* and *RASGRF1* genes. The incidence of myopia increases during the school years, especially during the preteen and teen years. The degree of myopia also increases with age during periods of rapid growth.

Concave lenses (spectacles or contact lenses) of appropriate strength are provided to allow for clear vision. Changes are usually needed periodically, from every few months to every 1-2 years. Globally the prevalence of myopia appears to be increasing, leading to heightened interest in myopia prevention treatment. Numerous therapies, including cycloplegic agents (topical atropine sulfate), peripheral defocus contact lenses, and reading addition spectacle lenses (bifocal lenses) are under investigation in an attempt to prevent or slow the progression of myopia.

Excimer laser correction for myopia has been approved for adults since 1995. The laser is applied to the corneal stroma to reshape the cornea, changing its refractive power (Fig. 660.2). Laser-assisted in situ keratomileusis (LASIK) uses either a microkeratome or a femtosecond laser to produce an epithelial-stromal flap, permitting the underlying corneal tissue to be ablated. The flap is then reseated and assumes the altered corneal shape. Photorefractive keratectomy (PRK) requires manual removal of the epithelium after treatment with alcohol to expose the Bowman layer and stroma, allowing the corneal surface to then be treated by the excimer laser. The epithelium regenerates to cover the defect over a period of 4-10 days. Reduction or elimination of refractive error is usually significant and remains stable over time. Risks are greatest with high degrees of myopia (>10 diopters) and include starbursts, halos, and distorted images or multiple images (usually at night). Refractive surgery is not approved for pediatric patients but is occasionally used off-label to treat certain forms of amblyopia or other high refractive error states in children who are unable to wear proper refractive correction.

In most cases, myopia is not a result of pathologic alteration of the eye and is referred to as simple or physiologic myopia. Some children may have **pathologic myopia**, a rare condition caused by a pathologically abnormal axial length of the eye; this is usually associated with thinning of the sclera, choroid, and retina and often with some degree of uncorrectable visual impairment. Tears or breaks in the retina may occur as it becomes increasingly thin, leading to the development of retinal detachments. Myopia may also occur as a result of other ocular abnormalities, such as keratoconus, ectopia lentis, congenital stationary night blindness, and glaucoma. Myopia is also a major feature of Stickler syndrome, a genetic disorder of connective tissue involving problems with vision, hearing, and facial and skeletal development; it is also common in Marfan syndrome, homocystinuria, and Weill-Marchesani syndrome.

ASTIGMATISM

In astigmatism, the refractive powers of the various meridians of the eye differ. Most cases are caused by irregularity in the curvature of the cornea, although some astigmatism results from changes in the lens. Mild degrees of astigmatism are common and may produce no symptoms. With greater degrees, distortion of vision can occur. To achieve a clearer image, a person with astigmatism uses accommodation or squints to obtain a pinhole effect. Symptoms include eyestrain, headache, and fatigue. Cylindrical or spherocylindrical lenses are used to provide optical correction when indicated. Glasses may be needed constantly or only part time, depending on the degree of astigmatism and the severity of the attendant symptoms. In some cases, contact lenses are used.

Infants and children with corneal irregularity resulting from injury, ptosis, or hemangiomas of the periorbita or eyelid are at increased risk of astigmatism and associated amblyopia.

ANISOMETROPIA

When the refractive state of one eye is significantly different from the refractive state of the other eye, **anisometropia** exists. If uncorrected, one eye may always be out of focus, leading to the development of amblyopia. Early detection and correction are essential if normal visual development in both eyes is to be achieved.

ACCOMMODATION

During accommodation, the ciliary muscle contracts, the suspensory fibers of the lens relax, and the lens assumes a more rounded shape, adding power to the lens. The amplitude of accommodation is greatest during childhood and gradually diminishes with age. The physiologic decrease in accommodative ability that occurs with age is called **presbyopia**.

Disorders of accommodation in children are relatively rare. Premature presbyopia is occasionally encountered in young children. The most common cause of paralysis of accommodation in children is

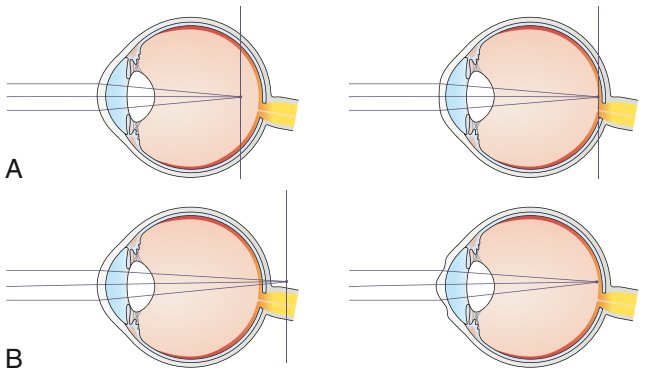

Fig. 660.2 Refractive errors before *(left)* and after *(right)* surgery. A, Refractive eye surgery corrects myopia using central ablation to flatten the corneal curvature (B) and corrects hyperopia using mid-peripheral ablation to steepen the corneal curvature. *(Modified from Kim T, Alió del Barrio, Wilkins M, et al. Refractive surgery. Lancet. 2019;393:2085-2094, Fig. 1, p. 2086.)*

intentional or inadvertent use of cycloplegic substances, topically or systemically; included are all the anticholinergic drugs and poisons, as well as plants and plant substances having these effects. Neurogenic causes of accommodative paralysis include lesions affecting the oculomotor nerve (third cranial nerve) along any part of its course. Differential diagnoses include tumors, degenerative diseases, vascular lesions, trauma, and infectious etiologies. Systemic disorders that may cause impairment of accommodation include botulism, diphtheria, Wilson disease, diabetes mellitus, and syphilis. Adie tonic pupil may also lead to a deficiency of accommodation after some viral illnesses (see Chapter 662). An apparent defect in accommodation may be psychogenic in origin; it is common for a child to feign inability to read when it can be demonstrated that visual acuity and ability to focus are normal.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 661

Disorders of Vision

Scott E. Olitsky and Justin D. Marsh

Severe visual impairment (corrected vision poorer than **6/60**) and blindness in children have many etiologies and may be caused by multiple defects affecting any structure or function along the visual pathways (Tables 661.1, 661.2, 661.3). The overall incidence is approximately 2.5/100,000 children; the incidence is higher in developing countries, in low birthweight infants, and in the first year of life. The most common causes occur during the prenatal and perinatal time periods; the cerebral-visual pathways, optic nerve (hypoplasia, atrophy), and retinal (Leber amaurosis) sites are most often affected. Important prenatal causes include microphthalmia/anophthalmia as well as autosomal recessive (most common), autosomal dominant, and X-linked genetic disorders and hypoxia or chromosomal syndromes. Perinatal/neonatal causes include retinopathy of prematurity, hypoxia-ischemia, and infection. Severe visual impairment starting in older children may be due to central nervous system or retinal tumors, infections, hypoxia-ischemia, injuries, neurodegenerative disorders, or juvenile idiopathic arthritis.

AMBLYOPIA

This is a decrease in visual acuity, unilateral or bilateral, that occurs in visually immature children as a result of a lack of a clear image projecting onto the retina. The unformed retinal image may occur secondary to a deviated eye **(strabismic amblyopia)**, an unequal need for vision correction between the eyes **(anisometropic amblyopia)**, a high refractive error in both eyes **(ametropic amblyopia)**, or a media opacity within the visual axis **(deprivation amblyopia)**.

The development of visual acuity normally proceeds rapidly in infancy and early childhood. Anything that interferes with the formation of a clear retinal image during this early developmental period can produce amblyopia. Amblyopia occurs only during the critical period of development before the cortex has become visually mature, within the first decade of life. The younger the child, the more susceptible he or she is to the development of amblyopia.

The **diagnosis** of amblyopia is confirmed when a complete ophthalmologic examination reveals reduced acuity that is unexplained by an organic abnormality. If the history and ophthalmologic examination do not support the diagnosis of amblyopia in a child with poor vision, consideration must be given to other causes (neurologic, psychologic). *Amblyopia is usually asymptomatic and can avoid detection until vision screening, which may delay diagnosis as screening programs often target school-age children.* This is problematic because amblyopia is more resistant to treatment at an older age, being reversed more rapidly in younger children whose visual system is less mature. Thus one key to the successful treatment of amblyopia is early detection and prompt intervention.

Most often, **treatment** first consists of removing any media opacity or prescribing appropriate glasses, if needed, so that a well-focused retinal image can be produced in each eye. The sound eye is then covered (occlusion therapy) or blurred with glasses (fogging) or drops (penalization therapy) to stimulate proper visual development of the more severely affected eye. Occlusion therapy may provide a more rapid improvement in vision, but some children may better tolerate atropine penalization. The best treatment for any one patient should be selected on an individual basis. The goals of treatment should be thoroughly understood and the treatment carefully supervised. Close monitoring of amblyopia therapy by an ophthalmologist is essential, especially in the very young, to avoid deprivation amblyopia in the good eye. Many families need reassurance and support throughout the trying course of treatment. Although full-time occlusion has historically been considered the best way to treat children with amblyopia, a series of prospective studies has shown that some children can achieve similar results with part-time patching, or the use of atropine drops. Historical thought was that older children would not respond to amblyopia therapy. Studies suggest older children and adolescents deemed visually mature who demonstrate amblyopia, particularly refractive or anisometropic in etiology, can demonstrate improvement in vision with appropriate therapy.

DIPLOPIA

Diplopia, or double vision, is generally a result of a misalignment of the visual axes. Occluding either eye relieves the diplopia if it is binocular in origin. Affected children commonly squint, cover one eye with a hand, or assume an abnormal head posture (a face turn or head tilt) to alleviate the bothersome sensation. These behaviors, especially in preverbal children, are important clues to diplopia. *The onset of diplopia in any child warrants prompt evaluation; it may signal the onset of a serious problem such as increased intracranial pressure, a brain tumor, infection (Lyme disease), migraine, Guillain-Barré syndrome, or an orbital mass* (Fig. 661.1).

Monocular diplopia is less common and results from refractive error, dislocation of the lens, cataract, dry eyes, or some defect in the media or macula. With this type of diplopia, occluding the nondiplopic eye will not relieve the symptoms. Monocular diplopia may also often have psychologic causes.

SUPPRESSION

In the presence of strabismus, diplopia occurs secondary to the same image falling on different regions of the retina in each eye. In a visually immature child, a process may occur in the cortex that eliminates the disability of seeing double. This is an active process and is termed **suppression**. It typically only develops in children. Although suppression eliminates the annoying symptom of diplopia, frequent suppression may not only place the patient at risk for amblyopia but also increase the risk for worsening strabismus. Once suppression develops, it may allow an intermittent strabismus to become constant or strabismus to redevelop later in life, even after successful treatment during childhood.

AMAUROSIS

Amaurosis is partial or total loss of vision; the term is usually reserved for profound impairment, blindness, or near blindness. When amaurosis exists from birth, primary consideration in the differential diagnosis must be given to developmental malformations, damage consequent to gestational or perinatal infection, anoxia or hypoxia, perinatal trauma, and the genetically determined diseases that can affect the eye itself or the visual pathways (see Table 661.3). Often the reason for amaurosis can be readily determined by objective ophthalmic examination; examples are severe microphthalmia, corneal opacification, dense cataracts, chorioretinal scars, macular defects, retinal dysplasia, and severe optic nerve hypoplasia. In other cases, an intrinsic retinal disease may not be apparent on initial ophthalmoscopic examination, or the defect may involve the brain and not the eye. Neuroradiologic (MRI or CT) and electrophysiologic (electroretinography) evaluation are helpful in these cases.

Amaurosis that develops in a child who once had useful vision has different implications. In the absence of obvious ocular disease (cataract, chorioretinitis, retinoblastoma, retinitis pigmentosa), consideration must be given to many neurologic and systemic disorders that can affect the visual pathways (see Table 661.1). Amaurosis of rather

Table 661.1 Causes of Childhood Severe Visual Impairment or Blindness

CONGENITAL
- Optic nerve hypoplasia or aplasia
- Holoprosencephaly
- Septo-optic dysplasia
- Optic coloboma
- Congenital hydrocephalus
- Hydranencephaly
- Porencephaly
- Microcephaly
- Encephalocele, particularly occipital
- Morning glory disc
- Aniridia
- Microphthalmia/anophthalmia syndromes
- Persistent pupillary membrane
- Cataracts
- Persistent hyperplastic primary vitreous
- Anterior segment dysgenesis syndromes
- Peters anomaly
- Axenfeld-Rieger anomaly
- Glaucoma syndromes (see Table 661.2)

PHAKOMATOSES
- Tuberous sclerosis
- Neurofibromatosis (special association with optic glioma)
- Sturge-Weber syndrome
- von Hippel-Lindau disease

TUMORS
- Retinoblastoma
- Optic glioma
- Perioptic meningioma
- Craniopharyngioma
- Cerebral glioma
- Astrocytoma
- Posterior and intraventricular tumors when complicated by hydrocephalus
- Pseudotumor cerebri

NEURODEGENERATIVE DISEASES
- Cerebral storage disease
- Gangliosidoses, particularly Tay-Sachs disease, Sandhoff variant, generalized gangliosidosis
- Other lipidoses and ceroid lipofuscinoses, particularly the late-onset disorders such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt
- Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome
- Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease
- Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica
- *Special types:* Dawson disease, Leigh disease, the Bassen-Kornzweig syndrome, Refsum disease
- *Retinal degenerations:* retinitis pigmentosa and its variants and Leber congenital type (see Table 661.3)
- *Optic atrophies:* congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias: Behr, Marie, and Sanger-Brown

INFECTIOUS/INFLAMMATORY PROCESSES
- Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii*, cytomegalovirus, rubella virus, *Treponema pallidum*, herpes simplex virus, Zika virus
- Meningitis or arachnoiditis
- Chorioretinitis
- Endophthalmitis
- Trachoma
- Keratitis
- Uveitis
- Sarcoidosis
- Optic neuritis
- Hemophagocytic lymphohistiocytosis
- Granulomatosis with polyangiitis

HEMATOLOGIC DISORDERS
- Leukemia with central nervous system involvement
- Langerhans cell histiocytosis

VASCULAR AND CIRCULATORY DISORDERS
- Collagen vascular diseases
- Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage
- Central retinal occlusion
- Retinal vasculitis
- Coats disease
- Susac syndrome

TRAUMA
- Contusion or avulsion of optic nerves, chiasm, globe, cornea
- Cerebral contusion or laceration
- Intracerebral, subarachnoid, or subdural hemorrhage
- Retinal detachment
- Laser injury

DRUGS AND TOXINS
- Quinine
- Ethambutol
- Methanol
- Many others

OTHER
- Retinopathy of prematurity
- Sclerocornea
- Conversion reaction
- Osteopetrosis
- Susac syndrome: branch retinal artery occlusions, hearing loss, CNS dysfunction
- Coats disease: poor vision, retinal telangiectasias and exudation

Modified from Kliegman R. *Practical Strategies in Pediatric Diagnosis and Therapy*. Philadelphia: WB Saunders;1996.

rapid onset may indicate an encephalopathy (hypertension), infectious or inflammatory (optic neuritis) processes, vasculitis, migraine, leukemia, drugs or toxins, eclampsia, or trauma. It may be caused by acute demyelinating disease affecting the optic nerves, chiasm, or cerebrum. In some cases, precipitous loss of vision is a result of increased intracranial pressure, rapidly progressive hydrocephalus, or dysfunction of a ventricular shunt. More slowly progressive visual loss suggests tumor or neurodegenerative disease. Gliomas of the optic nerve and chiasm and craniopharyngiomas are primary diagnostic considerations in children who show progressive loss of vision.

Clinical manifestations of impairment of vision vary with the age and abilities of a child, the mode of onset, and the laterality and severity of the deficit. The first clue to amaurosis in an infant may be **nystagmus** or **strabismus,** with the vision deficit itself passing undetected for some time. Timidity, clumsiness, or behavioral change may be the initial clues in the very young. Deterioration in school progress and indifference to school activities are common signs in an older child. School-age children often try to hide their disability and, in the case of very slowly progressive disorders, may not themselves realize the severity of the problem; some detect and promptly report small changes in their vision.

Any evidence of loss of vision requires prompt and thorough ophthalmic evaluation. Complete delineation of childhood amaurosis and its cause may require extensive investigation involving neurologic evaluation, electrophysiologic tests, neuroradiologic procedures, and sometimes metabolic and genetic studies. Furthermore, attendant special educational, social, and emotional needs must be met.

Table 661.2 Congenital Glaucoma and Anterior Segment Dysgenesis*

OMIM NUMBER	GENE SYMBOL	PROTEIN	PHENOTYPE	MODE OF INHERITANCE	SYNDROMIC (S) OR ISOLATED (I)
105650	*RPS19*	Ribosomal protein S19	Diamond-Blackfan anemia 1	AD	S
137600	*PITX2*	Paired like homeodomain 2	Anterior segment dysgenesis 4	AD	I
175780	*COL4A1*	Collagen type IV alpha 1 chain	Brain small vessel disease with or without ocular anomalies including congenital glaucoma	AD	S
180849	*CREBBP*	CREB binding protein	Rubinstein-Taybi syndrome 1	AD	S
236670	*POMT1*	Protein O-mannosyltransferase 1	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 1; muscular dystrophy-dystroglycanopathy (congenital with cognitive disabilities), type B, 1; muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 1	AR	S
249420	*SH3PXD2B*	SH3 and PX domains 2B	Frank-Ter Haar syndrome with or without glaucoma	AR	S
251750	*LTBP2*	Latent transforming growth factor beta binding protein 2	Weill-Marchesani syndrome 3; glaucoma 3, primary congenital, D; microspherophakia and/or megalocornea, with ectopia lentis and with or without secondary glaucoma	AR	S or I
253280	*POMGNT1*	Protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-)	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 3	AR	S
600221	*TEK*	TEK receptor tyrosine kinase	Glaucoma 3, primary congenital, E; Venous malformations, multiple cutaneous and mucosal	AD	S or I
601090	*FOXC1*	Forkhead box C1	Anterior segment dysgenesis 3, multiple subtypes; Axenfeld-Rieger syndrome, type 3	AD	S or I
601631	*FOXC1*	Forkhead box C1	Anterior segment dysgenesis 3, multiple subtypes; Axenfeld-Rieger syndrome, type 3	AD	S or I
601652	*MYOC*	Myocilin	Glaucoma 1A, primary open angle	AD	I
601771	*CYP1B1*	Cytochrome P450 family 1 subfamily B member 1	Anterior segment dysgenesis 6, multiple subtypes; glaucoma 3A, primary open angle, congenital, juvenile, or adult onset	AR	I
602091	*LTBP2*	Latent transforming growth factor beta binding protein 2	Weill-Marchesani syndrome 3; Glaucoma 3, primary congenital, D; microspherophakia and/or megalocornea, with ectopia lentis and with or without secondary glaucoma	AR	S or I
603474	*RPS19*	Ribosomal protein S19	Diamond-Blackfan anemia 1	AD	S
604563	*SBF2*	SET binding factor 2	Charcot-Marie-Tooth disease, type 4B2	AR	S
607423	*POMT1*	Protein O-mannosyltransferase 1	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 1; muscular dystrophy-dystroglycanopathy (congenital with cognitive disabilities), type B, 1; muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 1	AR	S
610192	*GLIS3*	GLIS family zinc finger 3	Diabetes mellitus, neonatal, with congenital hypothyroidism. Additional features include congenital glaucoma	AR	S
610199	*GLIS3*	GLIS family zinc finger 3	Diabetes mellitus, neonatal, with congenital hypothyroidism. Additional features include congenital glaucoma	AR	S

Continued

Table 661.2 Congenital Glaucoma and Anterior Segment Dysgenesis*—cont'd

OMIM NUMBER	GENE SYMBOL	PROTEIN	PHENOTYPE	MODE OF INHERITANCE	SYNDROMIC (S) OR ISOLATED (I)
613150	*POMT2*	Protein O-mannosyltransferase 2	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 2	AR	S
613293	*SH3PXD2B*	SH3 and PX domains 2B	Frank-Ter Haar syndrome with or without glaucoma	AR	S
617315	*CYP1B1*	Cytochrome P450 family 1 subfamily B member 1	Anterior segment dysgenesis 6, multiple subtypes; glaucoma 3A, primary open angle, congenital, juvenile, or adult onset	AR	I

*There are 55 entries in Online Mendelian Inheritance in Man (OMIM, https://www.ncbi.nlm.nih.gov/omim) for congenital glaucoma. This table only lists those with strong association to congenital glaucoma or diseases with congenital glaucoma as one of the major clinical features.
AD, Autosomal dominant; AR, autosomal recessive.
From Chen HY, Lehmann OJ, Swaroop A. Genetics and therapy for pediatric eye diseases. *EBioMedicine*. 2021;67:103360(Table 1b)

Table 661.3 Leber Congenital Amaurosis (LCA)*

OMIM NUMBER	GENE SYMBOL	PROTEIN	PHENOTYPE	MODE OF INHERITANCE	SYNDROMIC (S) OR ISOLATED (I)
204000	*GUCY2D*	Guanylate cyclase 2D, retinal	Leber congenital amaurosis 1	AD or AR	I
601777			Cone-rod dystrophy 6		
204100	*RPE65*	Retinoid isomerohydrolase RPE65	Leber congenital amaurosis 2	AR	I
613794			Retinitis pigmentosa 20		
618697			Retinitis pigmentosa 87 with choroidal involvement	AD	
604232	*SPATA7*	Spermatogenesis associated 7	Leber congenital amaurosis 3; Retinitis pigmentosa, juvenile	AR	I
604393	*AIPL1*	Aryl hydrocarbon receptor interacting protein like 1	Cone-rod dystrophy; Retinitis pigmentosa, juvenile; Leber congenital amaurosis 4	AD or AR	I
604537	*LCA5*	Lebercilin LCA5	Leber congenital amaurosis 5	AR	I
613826	*RPGRIP1*	RPGR interacting protein 1	Leber congenital amaurosis 6	AR	I
613829	*CRX*	Cone-rod homeobox	Leber congenital amaurosis 7	AD	I
613835	*CRB1*	Crumbs cell polarity complex component 1	Leber congenital amaurosis 8	AR	I
600105			Retinitis pigmentosa-12		
608553	*NMNAT1*	Nicotinamide nucleotide adenylyltransferase 1	Leber congenital amaurosis 9	AR	I
611755	*CEP290*	Centrosomal protein 290	Leber congenital amaurosis 10	AR	I or S
610188			Joubert syndrome 5		
610189			Senior-Loken syndrome 6		
613837	*IMPDH1*	Inosine monophosphate dehydrogenase 1	Leber congenital amaurosis 11	AR	I
180105			Retinitis pigmentosa 10	AD	
610612	*RD3*	RD3 regulator of GUCY2D	Leber congenital amaurosis 12	AR	I
612712	*RDH12*	Retinol dehydrogenase 12	Leber congenital amaurosis 13	AD or AR	I
613341	*LRAT*	Lecithin retinol acyltransferase	Retinitis pigmentosa, juvenile; Leber congenital amaurosis 14; Retinal dystrophy, early-onset severe	AR	I
613843	*TULP1*	TUB like protein 1	Leber congenital amaurosis 15	AR	I
600132					

Table 661.3 Leber Congenital Amaurosis (LCA)*—cont'd

OMIM NUMBER	GENE SYMBOL	PROTEIN	PHENOTYPE	MODE OF INHERITANCE	SYNDROMIC (S) OR ISOLATED (I)
614186	*KCNJ13*	Potassium inwardly rectifying channel subfamily J member 13	Leber congenital amaurosis 16	AR	I
615360	*GDF6*	Growth differentiation factor 6	Leber congenital amaurosis 17	AR	I
608133	*PRPH2*	Peripherin 2	Leber congenital amaurosis 18; Retinitis pigmentosa 7 and digenic form	AD or AR	I or S
169150			Macular dystrophy, patterned, 1		
618513	*USP45*	Ubiquitin specific peptidase 45	Leber congenital amaurosis 19	AR	I
617879	*TUBB4B*	Tubulin beta 4B class IVb	Leber congenital amaurosis with early-onset deafness	AD	S
609237	*IQCB1*	IQ motif-containing protein B1	Leber congenital amaurosis	AR	I or S
609254			Senior-Loken syndrome 5	AR	

*There are 101 entries in Online Mendelian Inheritance in Man (OMIM; https://www.ncbi.nlm.nih.gov/omim) for LCA. This table only lists the genes with strong association to LCA or diseases with LCA as one of the major clinical attributes.
AD, Autosomal dominant; AR, autosomal recessive; DR, digenic recessive.
From Chen HY, Lehmann OJ, Swaroop A. Genetics and therapy for pediatric eye diseases. *EBioMedicine* .2021;67:103360(Table 1c)

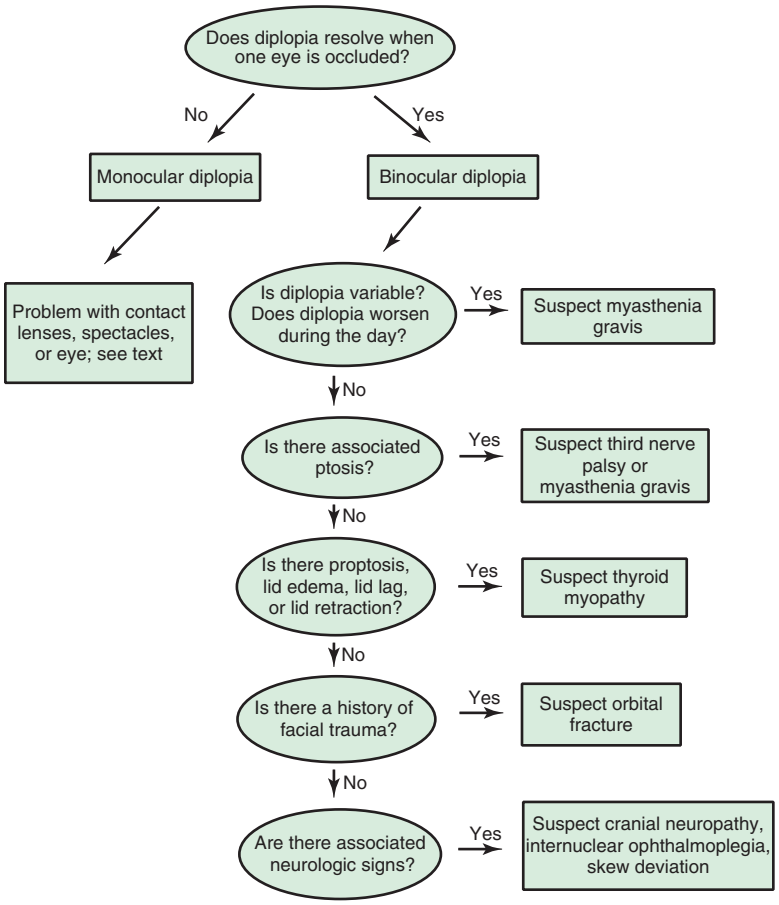

Fig. 661.1 General approach to diplopia. The clinician should first distinguish monocular from binocular diplopia and, in patients with binocular diplopia, address the five questions on the right side of the figure. Only then should the clinician identify which muscle is weak, although this is unnecessary if the clinician already suspects myasthenia (from fatigability) or full third nerve palsy (from weakness of the medial rectus, superior rectus, inferior rectus, and inferior oblique muscles, with or without a dilated pupil). Uncommon causes of diplopia and associated ptosis, not presented in the figure, are botulism, the Fisher variant of Guillain-Barre syndrome, and aberrant regeneration of the third nerve. Uncommon causes of diplopia and associated orbital findings (e.g., proptosis) are carotid-cavernous fistula (which causes an orbital bruit), orbital tumor, and pseudotumor. *(From McGee S. Evidence-Based Physical Diagnosis, 3rd ed. Elsevier; 2012. Fig. 57.1, p. 522.)*

NYCTALOPIA

Nyctalopia, or night blindness, is vision that is defective in reduced illumination. It generally implies impairment in function of the rods, particularly in dark adaptation time and perceptual threshold. Stationary congenital night blindness may occur as an autosomal dominant, autosomal recessive, or X-linked recessive condition. It may be associated with myopia and nystagmus. Children may have excessive problems going to sleep in a dark room, which may be mistaken for a behavioral problem. Progressive night blindness usually indicates primary or secondary retinal, choroidal, or vitreoretinal degeneration (see Chapter 670); it occurs also in vitamin A deficiency or as a result of retinotoxic drugs such as quinine.

PSYCHOGENIC DISTURBANCES

Vision problems of psychogenic origin are common in school-age children. Both conversion reactions and willful feigning are encountered. The usual manifestation is a report of reduced visual acuity in one or both eyes. Another common manifestation is constriction of the visual field. In some cases, the symptom is diplopia or polyopia (see Chapters 35 and 38).

Important clues to the diagnosis are inappropriate affect, excessive grimacing, inconsistency in performance, and suggestibility. A thorough ophthalmologic examination is essential to differentiate organic from functional visual disorders.

Affected children usually fare well with reassurance and positive suggestions. In some cases, mental health care is indicated. In all cases, the approach must be supportive and nonpunitive.

DYSLEXIA

This is the inability to develop the capability to read at an expected level despite an otherwise normal intellect (see Chapter 51). The terms *reading disability* and *dyslexia* are often used interchangeably. Most dyslexic individuals also display poor writing ability. Dyslexia is a primary reading disorder and should be differentiated from secondary reading difficulties caused by intellectual disability, environmental or educational deprivation, and systemic physical or other organic brain or eye diseases. Because there is not one standard test for dyslexia, the diagnosis is usually made by comparing reading ability with intelligence and standard reading expectations. Dyslexia is a language-based disorder and is not caused by any defect in the eye or visual acuity per se, nor is it attributable to a defect in ocular motility or binocular alignment. Although ophthalmologic evaluation of children with a reading problem is recommended to diagnose and correct any concurrent ocular problems such as a refractive error, amblyopia, or strabismus, treatment directed to the eyes themselves cannot be expected to correct developmental dyslexia (see Chapter 51).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 662

Abnormalities of Pupil and Iris

Scott E. Olitsky and Justin D. Marsh

ANIRIDIA

The term *aniridia* is a misnomer because some iris tissue is usually present, although it is hypoplastic (Fig. 662.1). Two-thirds of the cases are dominantly transmitted with a high degree of penetrance. The other third of cases are sporadic and are considered new pathologic genetic variants. The condition is bilateral in 98% of all patients, regardless of the means of transmission, and is found in approximately 1/50,000 persons. Pathologic variants in *PAX6* on 11p13 are typically implicated, and aniridia may be associated with other ocular findings.

Aniridia is a panocular disorder and should not be thought of as an isolated iris defect. Macular and optic nerve hypoplasia are commonly present and lead to decreased vision and sensory nystagmus. The visual acuity is approximately 20/200 in most patients, although the vision may occasionally be better. Other ocular deformities are common and may involve the lens and cornea. The cornea may be small, and a cellular infiltrate (pannus) occasionally develops in the superficial layers of the peripheral cornea (keratopathy). Clinically this appears as a gray opacification. Lens abnormalities include cataract formation and partial or total lens dislocation. **Glaucoma** develops in as many as 75% of individuals with aniridia.

One-fifth of sporadic aniridic patients may develop **Wilms tumor** (see Chapter 548.1). Because of their proximity in location, large deletions may include both *PAX6* and *WT1*, leading to this association. Although it has traditionally been taught that only patients with sporadic aniridia are at risk for developing Wilms tumor, it has also been reported in individuals with familial aniridia. Additionally, genitourinary abnormalities and intellectual disability, when present with aniridia, are strongly associated with Wilms tumor (WAGR syndrome). Wilms tumor usually presents before the fifth year, and these children should be screened using renal ultrasonography every 3-6 months until approximately 5 years of age if there is an 11p13 region deletion placing the child at risk for Wilms tumor.

COLOBOMA OF THE IRIS

A **coloboma** is the defect formed when the embryonic fissure fails to close completely. This unilateral or bilateral developmental defect may present as a defect in a sector of the iris, a hole in the substance of the iris, or a notch in the pupillary margin (Fig. 662.2). Simple (isolated) colobomas may be sporadic but are frequently transmitted as an autosomal dominant trait and may occur alone or in association with other anomalies and syndromes (syndromic) (Table 662.1). Because of the anatomic location of the embryonic fissure, an iris coloboma is always located inferiorly, giving the iris a keyhole appearance. An iris coloboma may be the only externally visible part of a more extensive coloboma that also involves the choroid, retina, and optic nerve. When this occurs, vision is likely to be severely affected. Complications include retinal detachment, cataract formation, and choroidal neovascularization. All children with an iris coloboma should undergo a full ophthalmologic examination.

MICROCORIA

Microcoria (congenital miosis) appears as a small pupil that does not react to light or accommodation and that dilates poorly, if at all, with medication. The condition may be unilateral or bilateral. In bilateral cases, the degree of miosis may be different in each eye. The eye may be otherwise normal or may demonstrate other abnormalities of the

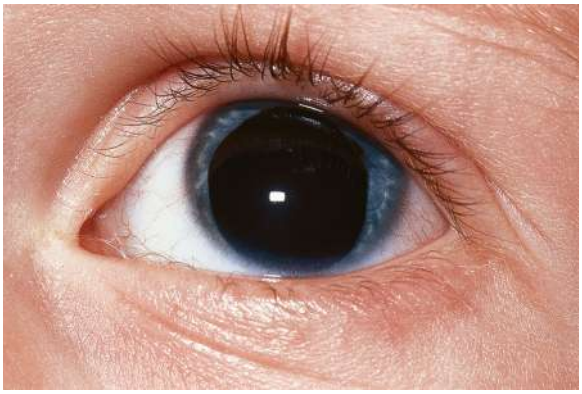

Fig. 662.1 Partial aniridia in a member of an autosomal dominant pedigree. *(From Hoyt CS, Taylor D, eds. Pediatric Ophthalmology and strabismus. 4th ed. Elsevier; 2013; Fig. 32.22, p. 304.)*

NYCTALOPIA

Nyctalopia, or night blindness, is vision that is defective in reduced illumination. It generally implies impairment in function of the rods, particularly in dark adaptation time and perceptual threshold. Stationary congenital night blindness may occur as an autosomal dominant, autosomal recessive, or X-linked recessive condition. It may be associated with myopia and nystagmus. Children may have excessive problems going to sleep in a dark room, which may be mistaken for a behavioral problem. Progressive night blindness usually indicates primary or secondary retinal, choroidal, or vitreoretinal degeneration (see Chapter 670); it occurs also in vitamin A deficiency or as a result of retinotoxic drugs such as quinine.

PSYCHOGENIC DISTURBANCES

Vision problems of psychogenic origin are common in school-age children. Both conversion reactions and willful feigning are encountered. The usual manifestation is a report of reduced visual acuity in one or both eyes. Another common manifestation is constriction of the visual field. In some cases, the symptom is diplopia or polyopia (see Chapters 35 and 38).

Important clues to the diagnosis are inappropriate affect, excessive grimacing, inconsistency in performance, and suggestibility. A thorough ophthalmologic examination is essential to differentiate organic from functional visual disorders.

Affected children usually fare well with reassurance and positive suggestions. In some cases, mental health care is indicated. In all cases, the approach must be supportive and nonpunitive.

DYSLEXIA

This is the inability to develop the capability to read at an expected level despite an otherwise normal intellect (see Chapter 51). The terms *reading disability* and *dyslexia* are often used interchangeably. Most dyslexic individuals also display poor writing ability. Dyslexia is a primary reading disorder and should be differentiated from secondary reading difficulties caused by intellectual disability, environmental or educational deprivation, and systemic physical or other organic brain or eye diseases. Because there is not one standard test for dyslexia, the diagnosis is usually made by comparing reading ability with intelligence and standard reading expectations. Dyslexia is a language-based disorder and is not caused by any defect in the eye or visual acuity per se, nor is it attributable to a defect in ocular motility or binocular alignment. Although ophthalmologic evaluation of children with a reading problem is recommended to diagnose and correct any concurrent ocular problems such as a refractive error, amblyopia, or strabismus, treatment directed to the eyes themselves cannot be expected to correct developmental dyslexia (see Chapter 51).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 662

Abnormalities of Pupil and Iris

Scott E. Olitsky and Justin D. Marsh

ANIRIDIA

The term *aniridia* is a misnomer because some iris tissue is usually present, although it is hypoplastic (Fig. 662.1). Two-thirds of the cases are dominantly transmitted with a high degree of penetrance. The other third of cases are sporadic and are considered new pathologic genetic variants. The condition is bilateral in 98% of all patients, regardless of the means of transmission, and is found in approximately 1/50,000 persons. Pathologic variants in *PAX6* on 11p13 are typically implicated, and aniridia may be associated with other ocular findings.

Aniridia is a panocular disorder and should not be thought of as an isolated iris defect. Macular and optic nerve hypoplasia are commonly present and lead to decreased vision and sensory nystagmus. The visual acuity is approximately 20/200 in most patients, although the vision may occasionally be better. Other ocular deformities are common and may involve the lens and cornea. The cornea may be small, and a cellular infiltrate (pannus) occasionally develops in the superficial layers of the peripheral cornea (keratopathy). Clinically this appears as a gray opacification. Lens abnormalities include cataract formation and partial or total lens dislocation. **Glaucoma** develops in as many as 75% of individuals with aniridia.

One-fifth of sporadic aniridic patients may develop **Wilms tumor** (see Chapter 548.1). Because of their proximity in location, large deletions may include both *PAX6* and *WT1*, leading to this association. Although it has traditionally been taught that only patients with sporadic aniridia are at risk for developing Wilms tumor, it has also been reported in individuals with familial aniridia. Additionally, genitourinary abnormalities and intellectual disability, when present with aniridia, are strongly associated with Wilms tumor (WAGR syndrome). Wilms tumor usually presents before the fifth year, and these children should be screened using renal ultrasonography every 3-6 months until approximately 5 years of age if there is an 11p13 region deletion placing the child at risk for Wilms tumor.

COLOBOMA OF THE IRIS

A **coloboma** is the defect formed when the embryonic fissure fails to close completely. This unilateral or bilateral developmental defect may present as a defect in a sector of the iris, a hole in the substance of the iris, or a notch in the pupillary margin (Fig. 662.2). Simple (isolated) colobomas may be sporadic but are frequently transmitted as an autosomal dominant trait and may occur alone or in association with other anomalies and syndromes (syndromic) (Table 662.1). Because of the anatomic location of the embryonic fissure, an iris coloboma is always located inferiorly, giving the iris a keyhole appearance. An iris coloboma may be the only externally visible part of a more extensive coloboma that also involves the choroid, retina, and optic nerve. When this occurs, vision is likely to be severely affected. Complications include retinal detachment, cataract formation, and choroidal neovascularization. All children with an iris coloboma should undergo a full ophthalmologic examination.

MICROCORIA

Microcoria (congenital miosis) appears as a small pupil that does not react to light or accommodation and that dilates poorly, if at all, with medication. The condition may be unilateral or bilateral. In bilateral cases, the degree of miosis may be different in each eye. The eye may be otherwise normal or may demonstrate other abnormalities of the

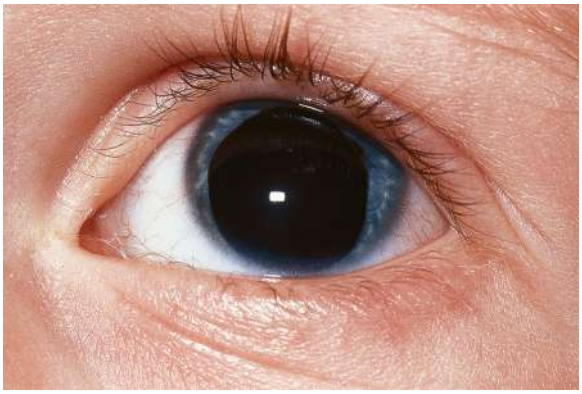

Fig. 662.1 Partial aniridia in a member of an autosomal dominant pedigree. *(From Hoyt CS, Taylor D, eds. Pediatric Ophthalmology and strabismus. 4th ed. Elsevier; 2013; Fig. 32.22, p. 304.)*

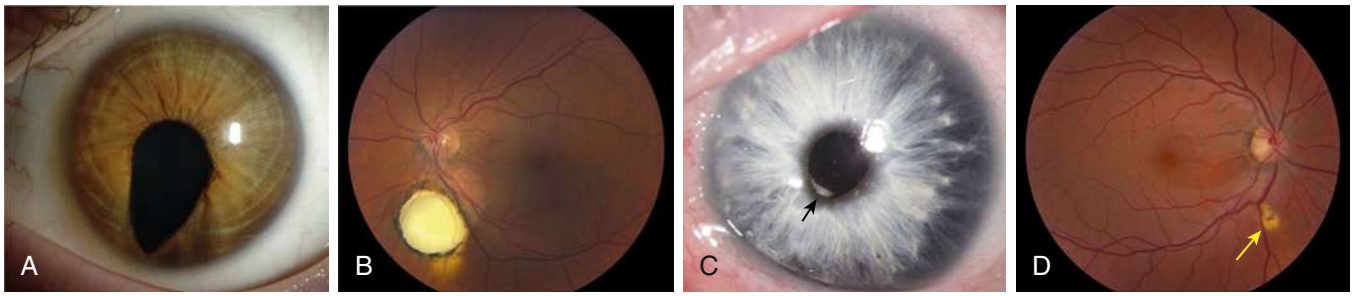

Fig. 662.2 Clinical presentations of uveal coloboma. **A,** Typical iris coloboma of a left eye. Note the inferonasal positioning of the coloboma, corresponding to the position of the optic fissure. **B,** Typical chorioretinal coloboma inferior to the optic nerve in a patient with excellent visual acuity. **C,** Microform of iris coloboma in a patient with Waardenburg syndrome, type 2A. Note slight peaking of the pupil of the inferonasal quadrant *(arrow).* **D,** Microform of a chorioretinal coloboma in the asymptomatic mother of a patient with bilateral nonsyndromic coloboma. *(From George A, Cogliati T, Brooks BP. Genetics of syndromic ocular coloboma: CHARGE and COACH syndromes. Exp Eye Res. 2020;193:107940; Fig. 2).*

Table 662.1 Syndromes Associated with Coloboma

Cat eye syndrome
CHARGE association
COACH
Coloboma with agenesis of corpus callosum
Congenital colobomatous microphthalmia iris coloboma and anal atresia
Congenital disorder of glycosylation type IV
Deletion 4p, 7p, 13q, 2q31.1, 14q24.3, 15q24
Glotz
Goldenhar
Jacobsen
Joubert
Klippel Feil 1,3
Meckel Gruber
Morning glory anomaly
Noonan
Renpenning
Rieger
Rubinstein-Taybi
SOX2-related eye disorders
Temtamy
Trisomy 13, 18, 22
Warburg

Plus >40 single gene pathologic variants.
COACH, Cerebral vermis hypoplasia, oligophrenia, ataxia, coloboma, hepatic fibrosis; CHARGE, coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies, deafness.

anterior segment. Congenital microcoria is usually transmitted as an autosomal dominant trait, although it may occur sporadically.

CONGENITAL MYDRIASIS

In this disorder, the pupils appear dilated, do not constrict significantly to light or near gaze, and respond minimally to miotic agents. The iris is otherwise normal, and affected children are usually healthy. Trauma, pharmacologic mydriasis, and neurologic disorders should be considered. Congenital mydriasis is one component of the **multisystemic smooth muscle dysfunction syndrome**; associated features include a patent ductus arteriosus and dilation of the aorta. Many apparent cases of congenital mydriasis show abnormalities of the central iris structures and may be considered a form of aniridia.

DYSCORIA AND CORECTOPIA

Dyscoria is abnormal shape of the pupil, and corectopia is abnormal pupillary position. They may occur together or independently as congenital or acquired anomalies.

Congenital corectopia is usually bilateral and symmetric and rarely occurs as an isolated anomaly; it is often accompanied by dislocation of the lens (ectopia lentis et pupillae), and the lens and pupil are commonly dislocated in opposite directions. **Ectopia lentis et pupillae** is transmitted as an autosomal recessive disorder; consanguinity is common. It is associated with pathologic variants in *ADAMTSL4*, which encodes a secreted glycoprotein widely distributed in the eye, which binds fibrillin-1 microfibrils and accelerates microfibril biogenesis.

When acquired, distortion and displacement of the pupil are frequently a result of trauma or intraocular inflammation. Prolapse of the iris after perforating injuries of the eye leads to peaking of the pupil in the direction of the perforation. Posterior synechiae (adhesions of the iris to the lens) are commonly seen when inflammation from any cause occurs in the anterior segment.

ANISOCORIA

Anisocoria occurs when the pupils are of different sizes. This may be a result of local or neurologic disorders. As a rule, if the inequality is more pronounced in the *presence of bright focal illumination* or on near gaze, there is a defect in pupillary constriction and the larger pupil is abnormal. If the anisocoria is worse in *reduced illumination*, a defect in dilation exists and the smaller pupil is abnormal (Figs. 662.3 and 662.4). Neurologic causes of anisocoria (parasympathetic or sympathetic lesions) must be differentiated from local causes such as synechiae (adhesions), congenital iris defects (colobomas, aniridia), and pharmacologic effects. **Horner syndrome** is an important cause of anisocoria (see later). Simple central anisocoria may occur in otherwise healthy individuals.

DILATED FIXED PUPIL

A dilated, unreactive pupil may be caused by internal ophthalmoplegia, Hutchinson pupil of transtentorial herniation, tonic pupil, pharmacologic blockade, and iridoplegia secondary to ocular trauma (see Fig. 662.3).

The most common cause of a dilated unreactive pupil is purposeful or accidental instillation of a cycloplegic agent, particularly atropine and related substances. Central nervous system lesions, such as a pinealoma, may cause internal ophthalmoplegia in children. Because the external surface of the oculomotor nerve carries the fibers responsible for pupillary constriction, compression of the nerve along its intracranial course may be associated with internal ophthalmoplegia, even before the development of ptosis or an ocular motility deficit. Although ophthalmoplegic migraine is a common cause of a third nerve palsy with pupillary involvement in children, an intracranial aneurysm must also be considered in the differential diagnosis. The blown pupil of transtentorial herniation, occurring with increasing intracranial pressure, is generally unilateral, and patients usually are obviously ill. The **pilocarpine test** can help differentiate neurologic iridoplegia from pharmacologic blockade. In the case of neurologic iridoplegia, the dilated pupil constricts within minutes after instillation of 1 or 2 drops of 0.5–1% pilocarpine; if the pupil has been dilated with atropine, pilocarpine has no effect. Because pilocarpine is a long-acting drug, this test is not to be used in acute situations in which pupillary signs must be carefully monitored. Because of the consensual pupil response to light, even complete uniocular blindness does not cause a unilaterally dilated pupil.

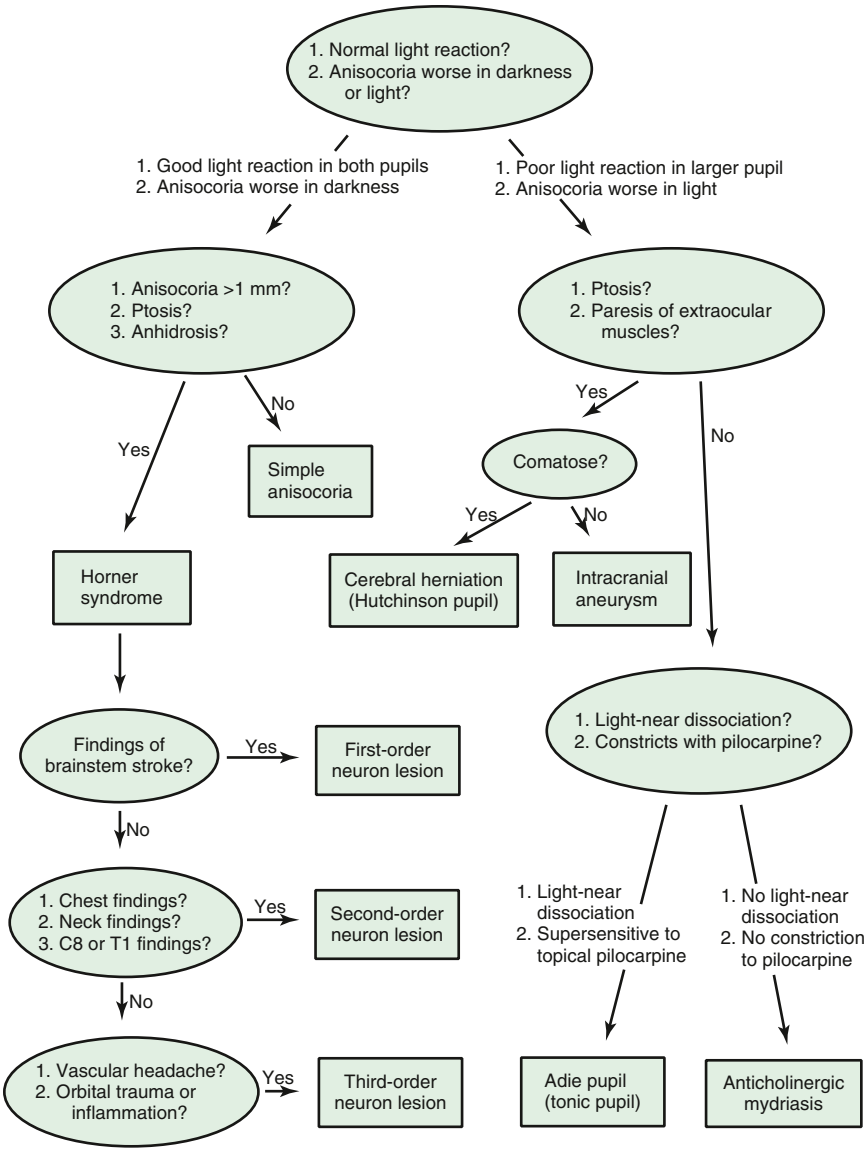

Fig. 662.3 Approach to anisocoria. The first two questions (Is there normal light reaction? And is anisocoria worse in darkness or light?) distinguish problems with the pupillary dilator muscle (i.e., Horner syndrome, simple anisocoria; *left side of figure*) from problems with the pupillary constrictor muscle (i.e., third cranial nerve, iris; *right side of figure*). Two other tests distinguish Horner syndrome from simple anisocoria: the cocaine test and pupillary dilator lag (i.e., the pupil dilates slowly in darkness, as documented in photographs). *(From Czarnecki JSC, Pilley SFJ, Thompson HS. The analysis of anisocoria: the use of photography in the clinical evaluation of unequal pupils. Can J Ophthalmol. 1979;14:297-302; and Thompson HS, Pilley SFJ. Unequal pupils: a flow chart for sorting out the anisocorias. Surv Ophthalmol. 1976;21[1]:45-48.)*

TONIC PUPIL

This is typically a large pupil that reacts poorly to light (the reaction may be very slow or even absent), reacts poorly and slowly to accommodation, and redilates in a slow, tonic manner. The features of tonic pupil are explained by cholinergic supersensitivity of the sphincter after peripheral (postganglionic) denervation and imperfect reinnervation. A distinctive feature of a tonic pupil is its sensitivity to dilute cholinergic agents. Instillation of 0.125% pilocarpine causes significant constriction of the involved pupil and has little or no effect on the unaffected side. The condition is usually unilateral.

Tonic pupil may develop after the acute stage of a partial or complete iridoplegia. It can be seen after trauma to the eye or orbit and may occur in association with toxic or infectious conditions. For those in the pediatric age group, tonic pupil is uncommon. Infectious processes (primarily viral syndromes) and trauma are the primary causes. Features of tonic pupil may also be seen in infants and children with familial dysautonomia (Riley-Day syndrome), although the significance of these findings has been questioned. Tonic pupil has also been reported in young children with Charcot-Marie-Tooth disease. Tonic pupil and other pupillary abnormalities may be noted in ROHHAD syndrome (rapid onset obesity, hypoventilation, hypothalamic dysfunction, and autonomic dysregulation). The occurrence of tonic pupil in association with decreased deep tendon reflexes in young women is referred to as **Adie syndrome.**

Ross syndrome is similar to Adie syndrome and includes decreased deep tendon reflexes and hypohidrosis.

MARCUS GUNN PUPIL

A **relative afferent pupillary defect** (Marcus Gunn pupil) indicates an asymmetric, *prechiasmatic*, afferent conduction defect. It is best demonstrated by the swinging flashlight test, which allows comparison of the direct and consensual pupillary responses in both eyes (Fig. 662.5). With patients fixing on a distant target (to control accommodation), a bright focal light is directed alternately into each eye in turn. In the presence of an afferent lesion, both the direct response to light in the affected eye and the consensual response in the other eye are subnormal. Swinging the light to the better or normal eye causes both pupils to react (constrict) normally. Swinging the light back to the affected eye causes both pupils to redilate to some degree, reflecting the defective conduction. This is a very sensitive and useful test for detecting and confirming optic nerve and retinal disease. This test is only abnormal if there is a "relative" difference in the conduction properties of the optic nerves. Therefore patients with bilateral and symmetric optic nerve

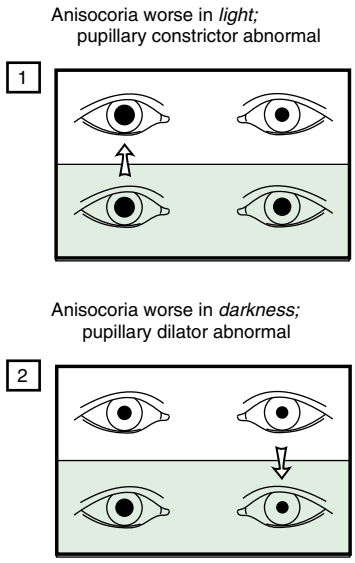

Fig. 662.4 Patient 1 *(top)* has more prominent anisocoria in light than darkness, indicating that the pupillary constrictor of the larger pupil is abnormal (i.e., it fails to constrict in light, *arrow*). Patient 2 has more prominent anisocoria in darkness than light, indicating that the pupillary dilator of the smaller pupil is abnormal (i.e., it fails to dilate in darkness, *arrow*). The diagnosis in patient 1 (abnormal pupillary constrictor) could be a third nerve palsy, tonic pupil, pharmacologic mydriasis, or a disorder of the iris. The diagnosis in patient 2 (abnormal pupillary dilator) could be Horner syndrome or simple anisocoria. In patient 2, both pupils will react to light, whereas the larger pupil of patient 1 does not react well to light. *(From McGee S. Evidence-Based Physical Diagnosis. 3rd ed. Elsevier; 2012; Fig. 20.4, p. 170.)*

disease will not demonstrate an afferent pupillary defect. A subtle relative afferent defect may be found in some children with amblyopia.

HORNER SYNDROME

The principal signs of oculosympathetic paresis (Horner syndrome) are homolateral miosis, mild ptosis, and apparent enophthalmos with slight elevation of the lower lid as a result of the ptosis. Patients may also have decreased facial sweating, increased amplitude of accommodation, and transient decrease in intraocular pressure. If paralysis of the ocular sympathetic fibers occurs before the age of 2 years, heterochromia iridis with hypopigmentation of the iris may occur on the affected side (Fig. 662.6).

Oculosympathetic paralysis may be caused by a lesion (tumor, trauma, infarction) in the midbrain, brainstem, upper spinal cord, neck, middle fossa, or orbit (Table 662.2). Congenital oculosympathetic paresis, often as part of **Klumpke brachial palsy**, is common, although the ocular signs, particularly the anisocoria, may pass undetected for years. Horner syndrome is also seen in some children after thoracic surgery. *Congenital* Horner syndrome may occur in association with vertebral anomalies and with enterogenous cysts. In some infants and children, Horner syndrome is the presenting sign of tumor in the mediastinal or cervical region—specifically neuroblastoma. Rare causes of Horner syndrome, such as vascular lesions or ectopic thymus tissue, also occur in the pediatric age group. In many cases, no cause of congenital Horner syndrome can be identified. Occasionally the condition is familial.

When the cause of Horner syndrome is in question, investigative procedures should be implemented and may include imaging of the head, neck, and chest, as well as 24-hour urinary catecholamine assay. Examining old photographs and old records can sometimes be helpful in establishing the age at onset of Horner syndrome.

The cocaine test is useful in diagnosing oculosympathetic paralysis; a normal pupil dilates within 20-45 minutes after instillation of one or two drops of 4% cocaine, whereas the miotic pupil of an oculosympathetic paresis dilates poorly, if at all, with cocaine. In some cases, there is also denervation supersensitivity of the affected eye to dilute

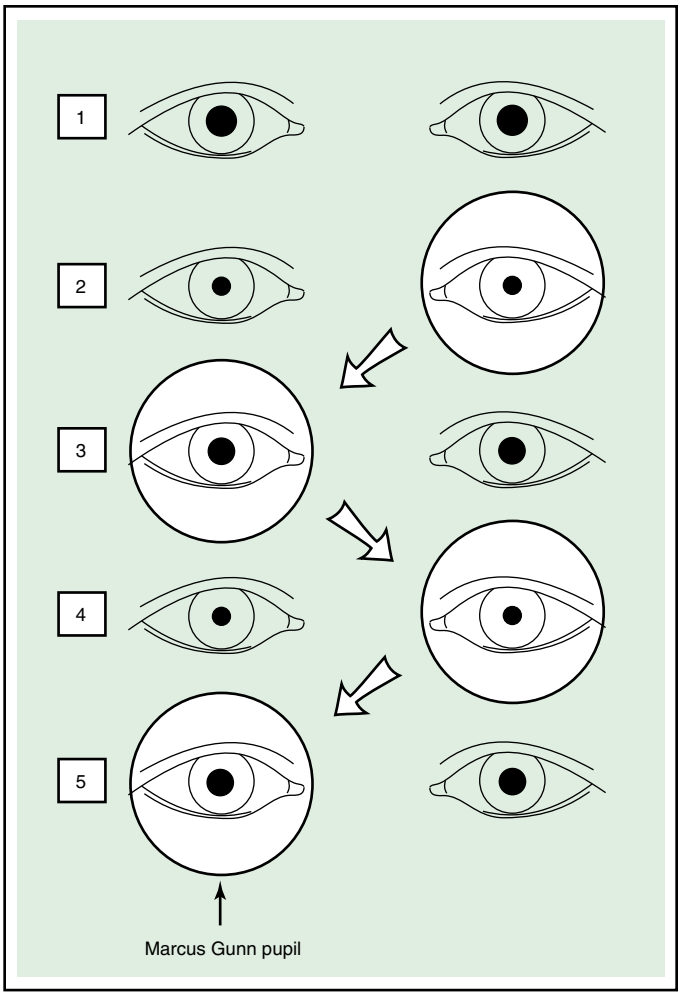

Fig. 662.5 The relative afferent pupillary defect (Marcus Gunn pupil). The figure depicts a patient with an abnormal right optic nerve. Under normal room light illumination (row 1), the pupils are symmetrical. During the swinging flashlight test, the pupils constrict when the normal eye is illuminated (rows 2 and 4) but dilate when the abnormal eye is illuminated (rows 3 and 5). Although both pupils constrict or dilate simultaneously, the clinician is usually focused on just the illuminated pupil. The pupil that dilates during the swinging flashlight test has the "relative afferent pupillary defect" and is labeled the Marcus Gunn pupil. *(From McGee S. Evidence-Based Physical Diagnosis. 3rd ed. Elsevier; 2012; Fig. 20.2, p. 165.)*

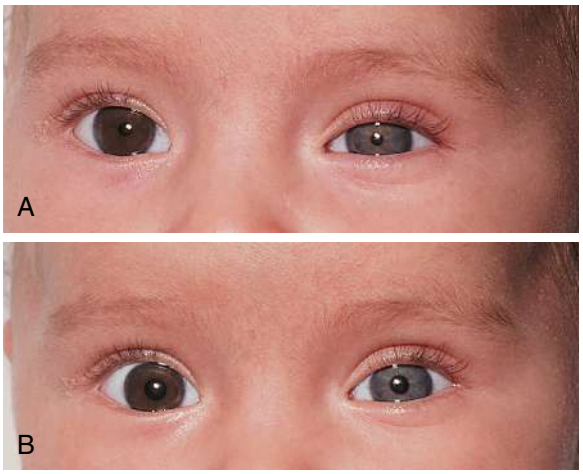

Fig. 662.6 Left congenital Horner syndrome showing upper- and lower-lid ptosis and an iris heterochromia, with the lighter eye being the affected eye. In bright light (**A**) and in the dark (**B**). *(From Hoyt CS, Taylor D, eds. Pediatric Ophthalmology and strabismus. 4th ed. Elsevier; 2013; Fig. 63.9, p. 661.)*

Table 662.2	Causes of Horner Syndrome
CENTRAL (FIRST-ORDER NEURON)	
Brainstem disease – commonly stroke (e.g. lateral medullary infarction), but also tumor, demyelination	
Syringomyelia	
Lateral medullary (Wallenberg) syndrome	
Cervical spinal cord lesion	
Diabetic autonomic neuropathy	
PREGANGLIONIC (SECOND-ORDER NEURON)	
Pancoast tumor	
Carotid and aortic aneurysm and dissection	
Thoracic spinal cord lesion	
Miscellaneous neck lesions (thyroid tumour, enlarged lymph nodes, trauma, postsurgical)	
POSTGANGLIONIC (THIRD-ORDER NEURON)	
Internal carotid artery dissection	
Nasopharyngeal tumour	
Cavernous sinus mass	
Otitis media	
CLUSTER HEADACHE (MIGRAINOUS NEURALGIA)	

From Salman JF: Kanski's Clinical Ophthalmology, 9th ed. London: Elsevier, 2020. Table 19.4

phenylephrine or similar agents. When present, the topical administration of a weak alpha$_1$ agonist may dilate only the affected pupil, leading to a "reversal" of the apparent miosis. Furthermore, instillation of 1% hydroxyamphetamine hydrobromide can help determine the location of sympathetic lesion because it only dilates the pupil if the postganglionic sympathetic neuron is intact.

PARADOXICAL PUPIL REACTION

Some children exhibit paradoxical constriction of the pupils to darkness. An initial brisk constriction of the pupils occurs when the light is turned off, followed by slow redilation of the pupils. The response to direct light stimulation and the near response are normal. The mechanism is not clear, but paradoxical constriction of the pupils in reduced light can be a sign of retinal or optic nerve abnormalities. The phenomenon has been observed in children with congenital stationary night blindness, albinism, retinitis pigmentosa, Leber congenital retinal amaurosis, and Best disease. It has also been observed in those with optic nerve anomalies, optic neuritis, optic atrophy, and possibly amblyopia. Thus children with paradoxical pupillary constriction to darkness should have a thorough ophthalmologic examination.

PERSISTENT PUPILLARY MEMBRANE

Involution of the pupillary membrane and anterior vascular capsule of the lens is usually completed during months 5-6 of fetal development. It is common to see some remnants of the pupillary membrane in newborns, particularly in premature infants. These membranes are nonpigmented strands of obliterated vessels that cross the pupil and may secondarily attach to the lens or cornea. The remnants tend to atrophy in time and usually present no problem. In some cases, however, significant remnants that remain obscure the pupil and interfere with vision. In rare cases, there is patency of the vascular elements; hyphema may result from rupture of persistent vessels.

Intervention must be considered to minimize amblyopia in infants with extensive persistent pupillary membrane of sufficient degree to interfere with vision in the early months of life. In some cases, mydriatics and occlusion therapy may be effective, but in others, surgery may be needed to provide an adequate pupillary aperture.

HETEROCHROMIA

In heterochromia, the two irises are of different color (heterochromia iridium) or a portion of an iris differs in color from the remainder (heterochromia iridis). Simple heterochromia may occur as an autosomal dominant characteristic. Congenital heterochromia is also a feature of Waardenburg syndrome, an autosomal dominant condition characterized principally by lateral displacement of the inner canthi and puncta, pigmentary disturbances (usually a median white forelock and patches of hypopigmentation of the skin), and defective hearing. Change in the color of the iris may occur as a result of trauma, hemorrhage, intraocular inflammation (iridocyclitis, uveitis), intraocular tumor (especially retinoblastoma), intraocular foreign body, glaucoma, iris atrophy, or oculosympathetic palsy (Horner syndrome), which may be associated with a cervical neuroblastoma, melanosis oculi, previous intraocular surgery, and some glaucoma medications.



Fig. 662.7 Red reflex. Normal red reflex in the left eye and white reflex in the right eye. This patient was later diagnosed with retinoblastoma in the right eye. *(From Martin RJ, Fanaroff AA, Walsch MC eds. Fanaroff & Martin's Neonatal-Perinatal Medicine. 10th ed. Vol 2, Elsevier; 2015; Fig. 103.7, p. 1739.)*

OTHER IRIS LESIONS

Discrete nodules of the iris, referred to as **Lisch nodules**, are commonly seen in patients with neurofibromatosis (see Chapter 636.1). Lisch nodules represent melanocytic hamartomas of the iris and vary from slightly elevated pigmented areas to distinct ball-like excrescences. The nodules cause no visual disturbance. Lisch nodules are found in 92–100% of individuals older than 5 years of age who have neurofibromatosis but are rare in infancy. Slit-lamp identification of these nodules may help fulfill the criteria required to confirm the diagnosis of neurofibromatosis.

In leukemia (see Chapter 544), there may be infiltration of the iris, sometimes with **hypopyon**, an accumulation of white blood cells in the anterior chamber, which may herald relapse or involvement of the central nervous system.

The lesion of **juvenile xanthogranuloma** (nevoxanthoendothelioma; see Chapter 711) may occur in the eye as a yellowish fleshy mass or plaque of the iris. Spontaneous **hyphema** (blood in the anterior chamber), glaucoma, or a red eye with signs of uveitis may be associated. A search for the skin lesions of xanthogranuloma should be made in any infant or young child with spontaneous hyphema, although the iris lesions may be present without cutaneous manifestations. In many cases, the ocular lesion responds to topical corticosteroid therapy.

LEUKOCORIA

This includes any white pupillary reflex, or so-called *cat's-eye reflex*. Primary diagnostic considerations in any child with leukocoria are cataract, persistent hyperplastic primary vitreous, cicatricial retinopathy of prematurity, retinal detachment, retinoschisis, larval granulomatosis, and retinoblastoma (Fig. 662.7). Also to be considered are endophthalmitis, organized vitreous hemorrhage, leukemic ophthalmopathy, exudative retinopathy (as in Coats disease), and less-common conditions such as medulloepithelioma, massive retinal gliosis, the retinal pseudotumor of Norrie disease, the so-called *pseudoglioma of the Bloch-Sulzberger syndrome*, retinal dysplasia, and the retinal lesions of the phakomatoses. A white reflex may also be seen with fundus coloboma, large atrophic chorioretinal scars, and ectopic medullation of retinal nerve fibers. *Leukocoria is an indication for prompt and thorough evaluation.*

The diagnosis can often be made by direct examination of the eye by ophthalmoscopy and biomicroscopy. Ultrasonographic and radiologic examinations are often helpful. In some cases, the final diagnosis rests with a pathologist.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 663

Disorders of Eye Movement and Alignment

Scott E. Olitsky and Justin D. Marsh

STRABISMUS

Strabismus, or misalignment of the eyes, is one of the most common eye problems encountered in children, affecting approximately 4% of children younger than 6 years of age. Strabismus can result in vision loss (amblyopia) and can have significant psychologic effects. Early detection and treatment of strabismus are essential to prevent permanent visual impairment. Of children with strabismus, 30–50% develop amblyopia. Restoration of proper alignment of the visual axis must occur at an early stage of visual development to allow these children a chance to develop normal binocular vision. The word strabismus means "to squint or to look obliquely." Many terms are used in discussing and characterizing strabismus (Table 663.1).

Orthophoria is the ideal condition of exact ocular balance. It implies that the oculomotor apparatus is in perfect equilibrium so that the eyes remain coordinated and aligned in all positions of gaze and at all distances. Even when binocular vision is interrupted, as by occlusion of one eye, truly orthophoric individuals maintain perfect alignment. Orthophoria is seldom encountered because the majority of individuals have a small latent deviation (heterophoria).

Heterophoria is a latent tendency for the eyes to deviate. This latent deviation is normally controlled by fusional mechanisms that provide binocular vision or avoid diplopia (double vision). The eye deviates only under certain conditions, such as fatigue, illness, or stress, or during tests that interfere with maintenance of these normal fusional abilities (such as covering one eye). If the amount of heterophoria is large, it may give rise to bothersome symptoms, such as transient diplopia (double vision), headaches, or asthenopia (eyestrain). Some degree of heterophoria is found in normal individuals; it is usually asymptomatic.

Heterotropia is a misalignment of the eyes that is constant. It occurs because of an inability of the fusional mechanism to control the deviation. Tropias may be unilateral or may alternate between either eye, depending on the patient. In an alternating tropia, there is no preference for fixation of either eye, and both eyes drift with equal frequency. Because each eye is used periodically, vision usually develops normally. A unilateral tropia is a more serious situation because only one eye is constantly misaligned. The undeviated eye becomes the preferred eye, resulting in loss of vision or amblyopia of the deviated eye.

It is common in ocular misalignments to describe the type of deviation. This helps to make decisions on the cause and treatment of the strabismus. The prefixes *eso-*, *exo-*, *hyper-*, and *hypo-* are added to the terms *phoria* and *tropia* to further delineate the type of strabismus. Esophorias and esotropias are inward or convergent deviations of the eyes, commonly known as *crossed eyes*. Exophorias and exotropias are divergent or outward-facing eye deviations, *walleyed* being the lay term. Hyperdeviations and hypodeviations designate upward or downward, respectively, deviations of an eye. In cases of unilateral strabismus, the deviating eye is often part of the description of the misalignment (left esotropia).

Diagnosis

Many techniques are used to assess ocular alignment and movement of the eyes to aid in diagnosing strabismic disorders. In a child with strabismus or any other ocular disorder, assessment of visual acuity is mandatory. Decreased vision in one eye requires evaluation for a strabismus or other ocular abnormalities, which may be difficult to discern on a brief screening evaluation. Even strabismic deviations of only a few degrees in magnitude, too small to be evident by gross inspection, may lead to amblyopia and significant vision loss.

Corneal light reflex tests are perhaps the most rapid and easily performed diagnostic tests for strabismus. They are particularly useful in children who are uncooperative and in those who have poor ocular fixation. To perform the **Hirschberg corneal reflex test,** the examiner projects a light source onto the cornea of both eyes simultaneously as a child looks directly at the light. Comparison should then be made of the placement of the corneal light reflex in each eye. In straight eyes, the light reflection appears symmetric and, because of the relationship between the cornea and the macula, slightly nasal to the center of each pupil. If strabismus is present, the reflected light is asymmetric and appears displaced in one eye. The Krimsky method of the corneal reflex test uses prisms placed over one or both eyes to align the light reflections. The amount of prism needed to align the reflections is used to measure the degree of deviation. Although it is a useful screening test, corneal light reflex testing may not detect a small angle or an intermittent strabismus.

Cover tests for strabismus require a child's attention and cooperation, good eye movement capability, and reasonably good vision in each eye (Fig. 663.1). If any of these are lacking, the results of these tests may not be valid. These tests consist of the cover-uncover test and the alternate cover test. In the cover-uncover test, a child looks at an object in the distance, preferably 6 m away. An eye chart is commonly used for fixation in children older than 3 years of age. For younger children, a noise-making toy or movie helps hold their attention for the test. As the child looks at the distant object, the examiner covers one eye and watches for movement of the uncovered eye. If no movement occurs, there is no apparent misalignment of that eye. After one eye is tested, the same procedure is repeated on the other eye. When performing the alternate cover test, the examiner rapidly covers and uncovers each eye, shifting back and forth from one eye to the other. If the child has an ocular deviation, the eye rapidly moves as the cover is shifted to the other eye. Both the cover-uncover test and the alternate cover test should be performed at both distance and near fixation. The cover-uncover test differentiates tropias, or manifest deviations, from latent deviations, called **phorias**.

Clinical Manifestations and Treatment

The etiologic classification of strabismus is complex, and the causative types must be distinguished; there are comitant and noncomitant forms of strabismus.

Comitant Strabismus

Comitant strabismus is the most common type of strabismus. The individual extraocular muscles usually have no defect, and extraocular motility is full in all positions of gaze. The amount of deviation is constant, or relatively constant, in the various directions of gaze.

Pseudostrabismus is one of the most common reasons a pediatric ophthalmologist is asked to evaluate an infant. This condition is characterized by the false appearance of strabismus when the visual axes are aligned accurately. This appearance may be caused by a flat, broad nasal bridge, prominent epicanthal folds, or a narrow interpupillary distance, giving the appearance of esotropia despite the eyes being aligned (pseudoesotropia). The observer may see less white sclera nasally than would be expected, and the impression is that the eye is turned in toward the nose, especially when the child gazes to either side. Parents frequently comment that when their child looks to the side, the eye almost disappears from view. Pseudoesotropia can be differentiated from a true misalignment of the eyes when the corneal light reflex is centered in both eyes and when the cover-uncover test shows no refixation movement. Once pseudoesotropia has been confirmed, parents can be reassured that the child will outgrow the appearance of esotropia. As the child grows, the bridge of the nose becomes more prominent and displaces the epicanthal folds, and the medial sclera becomes proportional to the amount visible on the lateral aspect. It is the appearance of crossing that the child will outgrow. Because true esotropia can develop later in children with pseudoesotropia, parents and pediatricians should

be cautioned that reassessment is required if the apparent deviation does not improve.

Esodeviations are the most common type of ocular misalignment in children and represent >50% of all ocular deviations. *Congenital esotropia* is a confusing term. Few children who are diagnosed with this disorder are actually born with an esotropia. For this reason, infants with confirmed onset earlier than 6 months are typically considered to have what was previously classified as congenital esotropia, although the term **infantile esotropia** is perhaps a more accurate description.

Between 2-4 months of age, many infants will exhibit strabismus, including esotropia, which typically resolve spontaneously. Esotropia that resolves without treatment do so before 10-12 weeks of age and have intermittent or variable deviations. Those most likely to benefit from active treatment have persistent esotropia (10 weeks-6 months of age) and constant esotropia (40 PD), in combination with a refractive error ≤ +3.00 D, and the absence of prematurity, developmental delay, meningitis, nystagmus, eye anomalies, and incomitant or paralytic strabismus. The evaluation is noted in Figure 663.2.

Table 663.1 Description of Alignment and Movement

NORMAL OCULAR ALIGNMENT: ORTHOPHORIA
LATENCY
phoria: development of abnormality only during certain conditions (fatigue, illness, cover test)
tropia: abnormality present during normal conditions; deviation may be constant or intermittent
DIRECTION OF DEVIATION
Eso-: inward, horizontal deviation ("crossing")
Exo-: outward, horizontal deviation ("wall eye")
Hyper-: upward, vertical deviation
Hypo-: downward, vertical deviation
Incyclo-: nasal torsional deviation of the superior pole of the cornea
Excyclo-: temporal torsional deviation of the superior pole of the cornea
EQUALITY OF DEVIATION
Concomitant: misalignment is equal in all positions of gaze
Noncomitant: misalignment varies significantly in different positions of gaze
NEUROMUSCULAR DYSFUNCTION
Paralytic: misalignment secondary to a cranial nerve palsy, muscle weakness, or mechanical restriction (usually noncomitant)
Nonparalytic: no underlying neuromuscular dysfunction; usually concomitant but can be noncomitant
TANDEM MOVEMENTS OF BOTH EYES
version: both eyes move in same direction (conjugate); direction of movement: levo- (left), dextro- (right), supra- (up), infra- (down)
vergence: eyes move in opposite directions (disconjugate); convergence (inward movement), divergence (outward movement)

From Costakos D. Eye disorders. In: Kliegman RM, Bordini BJ, Toth H, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis.* 2nd ed, Philadelphia: Elsevier; 2022: Table 43.2, p. 787.

The characteristic angle of infantile esodeviations is large and constant (Fig. 663.3). Because of the large deviation, cross-fixation is frequently encountered. This is a condition in which the child looks to the right with the left eye and to the left with the right eye. With cross-fixation, there is no need for the eye to turn away from the nose (abduction) as the adducting eye is used in side gaze; this condition simulates a sixth nerve palsy. Abduction can be demonstrated by the doll's-head maneuver or by patching one eye for a short time. Children with infantile esotropia tend to have refractive errors similar to those of normal children of the same age. This contrasts with the characteristic high level of farsightedness associated with accommodative esotropia. **Amblyopia** is common in children with infantile esotropia.

The primary goal of **treatment** in infantile esotropia is to eliminate or reduce the deviation as much as possible. Ideally this results in normal sight in each eye, in straight-looking eyes, and in the development of binocular vision. Early treatment (before age 2 years) is more likely to lead to the development of binocular vision, which helps maintain long-term ocular alignment. Once any associated amblyopia is treated, surgery is performed to align the eyes. Even with successful surgical alignment, it is common for vertical deviations to develop in children with a history of infantile esotropia. The two most common forms of vertical deviations to develop are inferior oblique muscle overaction and dissociated vertical deviation. In inferior oblique muscle overaction, the overactive inferior oblique muscle produces an upshoot of the eye closest to the nose when the patient looks to the side (Fig. 663.4). In dissociated vertical deviation, one eye drifts up slowly with no movement of the other eye. Surgery may be necessary to treat either or both of these conditions.

It is important that parents realize that early successful surgical alignment is only the beginning of the treatment process. Because many children may redevelop strabismus or amblyopia, they need to be monitored closely during the visually immature period of life.

Accommodative esotropia is defined as a "convergent deviation of the eyes associated with activation of the accommodative (focusing) reflex." It usually occurs in a child who is between 2-3 years of age and who has a history of acquired intermittent or constant crossing. Amblyopia occurs in the majority of cases.

The mechanism of accommodative esotropia involves uncorrected hyperopia, accommodation, and accommodative convergence. The image entering a hyperopic (farsighted) eye is blurred. If the amount of hyperopia is not significant, the blurred image can be sharpened by accommodating (focusing of the lens of the eye). Accommodation is closely linked with convergence (eyes turning inward) because both are required to view an object at near. If a child's hyperopic refractive error

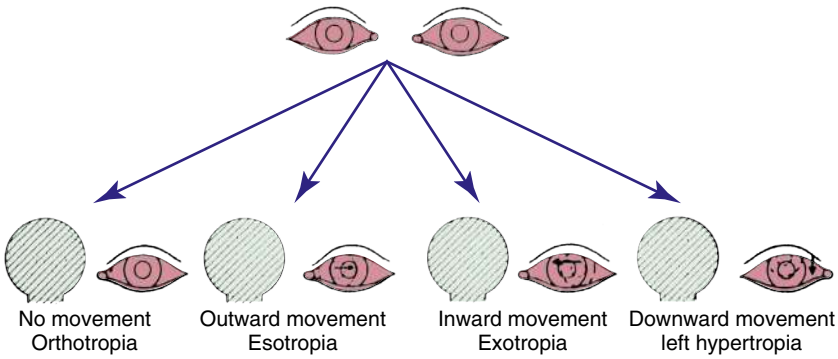

Fig. 663.1 The cover test. In each instance, the occluder is placed over the right eye while the patient is viewing a fixation target and the examiner is watching for movement of the patient's left eye. If the left eye is not aligned, it will need to move to look at the fixation target. If there is no movement of the left eye, the test needs to be repeated by occluding the left eye and watching for movement of the right eye. *(From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. Elsevier; 2018: Fig. 32.6, p. 567).*

is large or if the amount of convergence that occurs in response to each unit of accommodative effort is great, esotropia may develop.

The **treatment** for accommodative esotropia is to prescribe the full hyperopic (farsighted) correction. These glasses eliminate a child's need to accommodate and therefore correct the esotropia (Fig. 663.5). Although many parents are initially concerned that their child will not want to wear glasses, the benefits of binocular vision and the decrease in the focusing effort required to see clearly provide a strong stimulus to wear glasses, and they are generally accepted well. The full hyperopic correction sometimes straightens the eye position at distance fixation but leaves a residual deviation at near fixation. This may be observed, treated with bifocal lenses, or treated with surgery.

It is important to warn parents of children with accommodative esotropia that the esodeviation may appear to increase without glasses after the initial correction is worn. Parents frequently state that before wearing glasses, their child had a small esodeviation, whereas after removal of the glasses, the esodeviation becomes quite large. Parents often blame the increased esodeviation on the glasses. This apparent increase is a result of the child using the appropriate amount of accommodative effort after the glasses have been worn. When these children remove their glasses, they continue to use an accommodative effort to bring objects into proper focus and increase the esodeviation.

Most children maintain straight eyes once initially treated. Because hyperopia generally decreases with age, patients may outgrow the need to wear glasses to maintain alignment. In some patients, a residual esodeviation persists even when wearing their glasses. This condition commonly occurs when there is a delay between the onset of accommodative esotropia and treatment. In others, the esotropia may initially be eliminated with glasses, but crossing redevelops and is not correctable with glasses. Any residual component of esotropia that is not fully correctable with glasses is typically referred to as "nonaccommodative," and a child with both accommodative and nonaccommodative components of esotropia is often referred to as having "partially accommodative" esotropia. Surgery for the nonaccommodative portion of the crossing may be indicated to restore binocular vision.

Exodeviations are the second most common type of misalignment. The divergent deviation may be intermittent or constant. Intermittent exotropia is the most common exodeviation in childhood. It is characterized by outward drifting of one eye, which usually occurs when a child is fixating at distance. The deviation is generally more frequent with fatigue or illness. Exposure to bright light may cause reflex closure of the exotropic eye. Because the eyes initially can be kept straight most of the time, visual acuity tends to be good in both eyes and binocular vision is initially normal.

The age at onset of intermittent exotropia varies but is often between age 6 months and 4 years. The decision to perform eye muscle surgery is based on the amount and frequency of the deviation. If the deviation is small and infrequent, it is reasonable to observe the child. If the exotropia is large or increasing in frequency, surgery is indicated to maintain normal binocular vision.

Constant exotropia may rarely be congenital. Congenital exotropia may be associated with neurologic disease or abnormalities of the bony orbit, as in Crouzon syndrome. Exotropia that occurs later in life may represent a deterioration of an intermittent exotropia that was present in childhood. Surgery can restore binocular vision even in long-standing cases.

Noncomitant Strabismus

When an eye muscle is paretic, palsied, or restricted, a muscle imbalance occurs in which the deviation of the eye varies according to the direction of gaze. Recent onset of a paretic muscle can be suggested by the symptom of double vision that increases in one direction, the findings of an ocular deviation that increases in the field of action of the paretic muscle, and an increase in the deviation when the child fixates with the paretic eye. It is important to differentiate a noncomitant strabismus from a comitant deviation because noncomitant forms

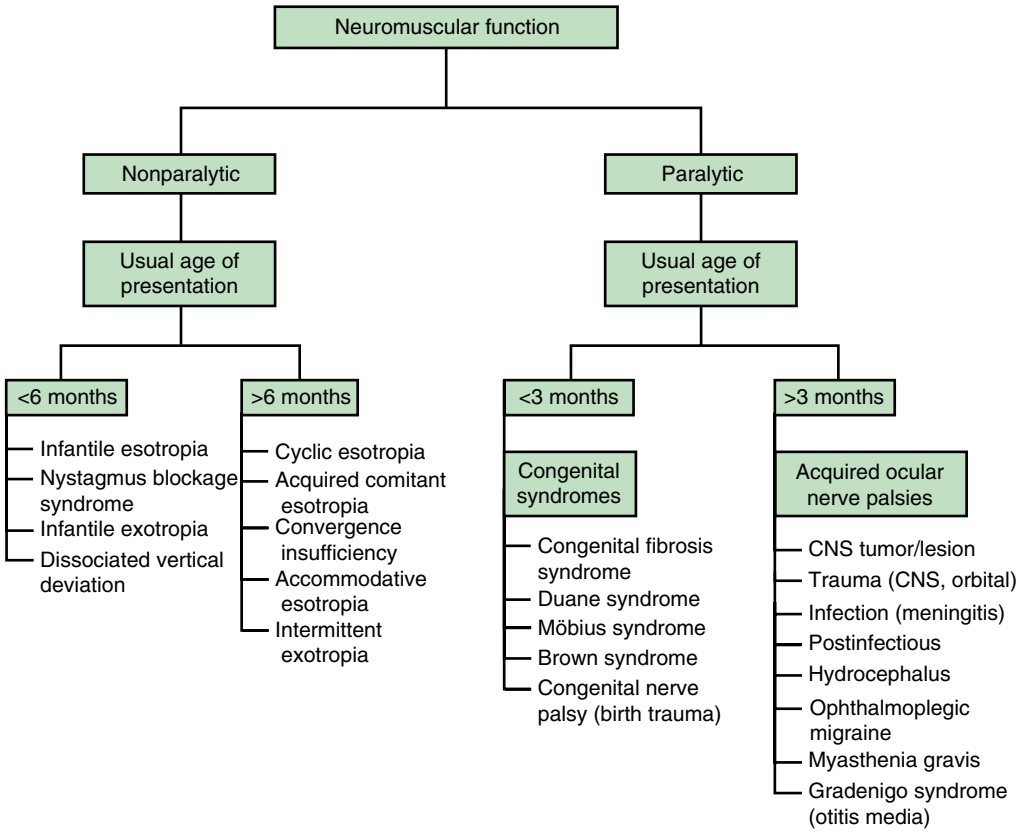

Fig. 663.2 Evaluation of strabismus. CNS, Central nervous system. *(From Costakos D. Eye disorders. In: Kliegman RM, Bordini BJ, Toth H, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. 2nd ed. Philadelphia: Elsevier; 2022: Fig. 43.9, p. 789).*



Fig. 663.3 Congenital esotropia. Note the large angle of crossing.

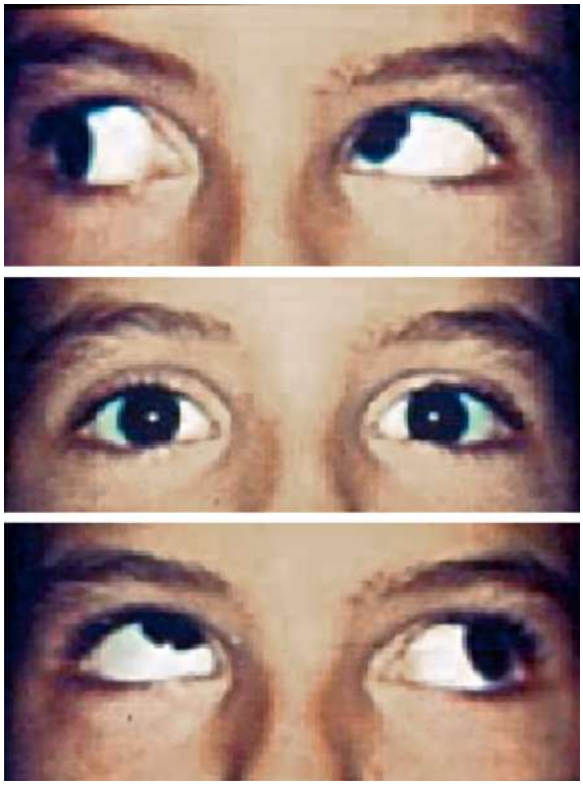

Fig. 663.4 Inferior oblique muscle overaction.

of strabismus are often associated with trauma, systemic disorders, or neurologic abnormalities (Table 663.2).

Third Nerve Palsy

In the pediatric population, third nerve palsies are usually congenital. The congenital form is often associated with a developmental anomaly or birth trauma. Acquired third nerve palsies in children can be an ominous sign and may indicate a neurologic abnormality such as increased intracranial pressure (ICP) and an intracranial neoplasm or aneurysm. Other, less serious causes include an inflammatory or infectious lesion, head trauma, postviral syndromes, and migraines.

A third nerve palsy, whether congenital or acquired, usually results in an exotropia and a hypotropia, or downward deviation of the affected eye, as well as complete or partial ptosis of the upper lid. This characteristic strabismus results from the action of the normal, unopposed muscles, the lateral rectus muscle, and the superior oblique muscle. If



Fig. 663.5 Accommodative esotropia. Control of deviation with corrective lenses.

the internal branch of the third nerve is involved, pupillary dilation may be noted as well. Eye movements are usually limited nasally, in elevation, and in depression. In addition, clinical findings and treatment may be complicated in congenital and traumatic cases of third nerve palsy, owing to misdirection of regenerating nerve fibers, referred to as *aberrant regeneration*. This results in anomalous and paradoxical eyelid, eye, and pupil movement such as elevation of the eyelid, constriction of the pupil, or depression of the globe on attempted medial gaze.

Fourth Nerve Palsy

These palsies can be congenital or acquired. Because the fourth nerve has a long intracranial course, it is susceptible to damage resulting from head trauma. In children, however, fourth nerve palsies are more frequently congenital than traumatic. A palsied fourth nerve results in weakness in the superior oblique muscle, which causes an upward deviation of the affected eye, a hypertropia. Because the antagonist muscle, the inferior oblique, is relatively unopposed, the affected eye demonstrates an upshoot when looking toward the nose. Children typically present with a head tilt to the shoulder opposite the affected eye and may also position their chin down and face turned away from the affected side. This head position places the eye away from the area of greatest action of the affected muscle and therefore minimizes the deviation and the associated double vision. Because the abnormal head posture maintains the child's ocular alignment, amblyopia is uncommon. Because no abnormality exists in the neck muscles, attempts to correct the head tilt by exercises and neck muscle surgery are ineffective. Recognition of a superior oblique paresis can be difficult because deviation of the head and the eye may be minimal. **Treatment** may include eye muscle surgery to improve the ocular alignment and eliminate the abnormal head posture.

Sixth Nerve Palsy

These palsies produce markedly crossed eyes with limited ability to move the afflicted eye laterally. Children frequently present with their head turned toward the palsied muscle, a position that helps preserve binocular vision. The esotropia is largest when the eye is moved toward the affected muscle.

Congenital sixth nerve palsies are rare. Decreased lateral gaze in infants is often associated with other disorders, such as infantile esotropia or Duane retraction syndrome. In neonates, a transient sixth nerve paresis can occur; it usually clears spontaneously by 6 weeks. It

Table 663.2 Less Common Forms of Strabismus

TYPE OF STRABISMUS	PRESENTING SYMPTOMS AND SIGNS	CAUSE	TREATMENT
Duane syndrome	Esotropia with deficient abduction or exotropia with deficient adduction of one eye; head turn	Absence of sixth nerve nucleus and aberrant innervation of lateral rectus muscle from third cranial nerve	Strabismus surgery for correction of large deviations or abnormal head position
Dissociated vertical deviation	One eye turns up intermittently, especially with fatigue	Eye movement abnormality related most commonly to congenital esotropia	Eye muscle surgery on superior rectus and inferior oblique muscles
Brown syndrome	Head tilt; inability to elevate eye in adduction	Restriction of free passage of superior oblique tendon through trochlea	Observation if not severe; superior oblique tendon surgery if severe
Möbius syndrome	Masklike facies; inability to abduct both eyes; difficulty closing eyes	Bilateral sixth and seventh nerve palsies	Protect corneas from exposure; strabismus surgery
Congenital fibrosis syndrome	Chin-up head position; inability to elevate eyes; ptosis	Autosomal dominant gene on chromosome 16 in some patients; superior division of third nerve in others	Surgical release of tight extraocular muscles
Third nerve palsy	Exotropia and hypertropia; ptosis; dilated, nonreactive pupil	Congenital absence of third nerve; trauma; tumor	Ptosis and strabismus surgery
Double elevator palsy	Chin-up head posture; inability to elevate one eye	Paresis of superior rectus muscle	Transposition strabismus surgery
Orbital floor fracture	Vertical diplopia; chin-up head position	Entrapment of orbital tissues in fracture	Repair of floor fracture; release of inferior rectus muscle restriction
Myasthenia: congenital or acquired	Variable ptosis and eye movement abnormalities	Blockage of acetylcholine receptor sites by immune complexes	Treatment of systemic myasthenia; strabismus surgery if patient is stable
Mitochondrial disorders	Ptosis, progressive external ophthalmoplegia, optic neuropathy, cardiomyopathy, peripheral myopathy	Various mitochondrial variants	Supportive

From Costakos D. Eye disorders. In: Kliegman RM, Bordini BJ, Toth H, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis.* 2nd ed. Philadelphia: Elsevier; 2022: Table 43.3, p. 790.

is believed that increased ICP associated with labor and delivery is the contributing factor.

Acquired sixth nerve palsies in childhood are often an ominous sign because the sixth nerve is susceptible to increased ICP associated with hydrocephalous and intracranial tumors. Other causes of sixth nerve defects in children include trauma, vascular malformations, meningitis, and Gradenigo syndrome. A benign sixth nerve palsy, which is painless and acquired, can be noted in infants and older children. This is frequently preceded by a febrile illness or upper respiratory tract infection and may be recurrent. Complete resolution of the palsy is common in this scenario, although other causes of an acute sixth nerve palsy should be eliminated before this diagnosis is made.

Strabismus Syndromes

Special types of strabismus have unusual clinical features. Most of these disorders are caused by structural anomalies of the extraocular muscles or adjacent tissues. Most strabismus syndromes produce noncomitant misalignments.

Monocular Elevation Deficiency

A monocular elevation deficit in both abduction and adduction is referred to as *monocular elevation deficiency* (previously called *double-elevator palsy*). It may represent a paresis of both elevators, the superior rectus and inferior oblique muscles, or a possible restriction to elevation from a fibrotic inferior rectus muscle. When an affected child fixates with the nonparetic eye, the paretic eye is hypotropic and the ipsilateral upper eyelid may appear ptotic. Fixation with the paretic eye causes a hypertropia of the nonparetic eye and a disappearance of the ptosis (Fig. 663.6). Because the apparent ptosis is actually secondary to the strabismus, correction of the hypotropia treats the pseudoptosis.

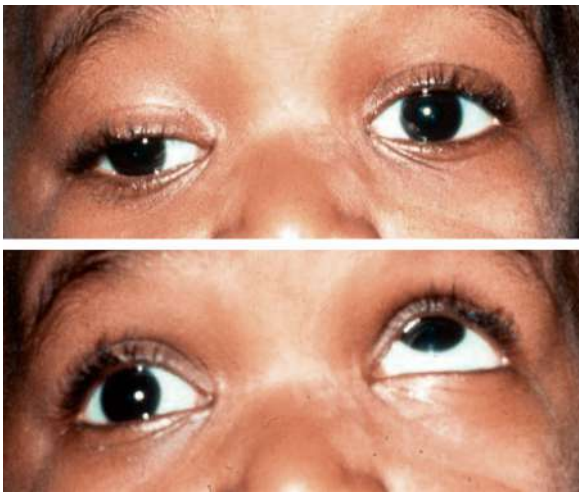

Fig. 663.6 Double-elevator palsy of the right eye. Note the disappearance of the apparent ptosis when fixating with the involved eye.

Duane Syndrome

This congenital disorder of ocular motility is characterized by retraction of the globe on adduction. Duane syndrome occurs more frequently in females and involves the left eye more commonly than the right eye. It is caused by the absence of the sixth nerve nucleus and subsequent anomalous innervation of the lateral rectus muscle, which results in co-contraction of the medial and lateral rectus muscles on attempted adduction of the affected eye. Within the spectrum of Duane syndrome, patients may exhibit impairment of abduction, impairment

of adduction, or upshoot or downshoot of the involved eye on adduction. They may have esotropia, exotropia, or relatively straight eyes. Many children exhibit a compensatory head posture to maintain single vision. Some develop amblyopia. Surgery to improve alignment or to reduce a noticeable face turn can be helpful in selected cases. Duane syndrome usually occurs sporadically, but it can be inherited as an autosomal dominant trait. While typically occurring as an isolated condition, some patients may have various associated ocular and systemic anomalies.

Möbius Syndrome

The distinctive features of Möbius syndrome are congenital facial paresis and abduction weakness. The facial palsy is commonly bilateral, frequently asymmetric, and often incomplete, tending to spare the lower face and platysma. Ectropion, epiphora, and exposure keratopathy may develop. The abduction defect may be unilateral or bilateral. Esotropia is common. The cause is unknown. Whether the primary defect is maldevelopment of cranial nerve nuclei, hypoplasia of the muscles, or a combination of central and peripheral factors is unclear. Some familial cases have been reported. Associated developmental defects may include ptosis, palatal and lingual palsy, hearing loss, pectoral and lingual muscle defects, micrognathia, syndactyly, supernumerary digits, and the absence of hands, feet, fingers, or toes. Surgical correction of the esotropia is indicated and any attendant amblyopia should be treated.

Brown Syndrome

In this syndrome, elevation of the eye in the adducted position is restricted (Fig. 663.7). An associated downward deviation of the affected eye in adduction may also occur. A compensatory head posture may be evident. Brown syndrome occurs as a result of restriction of the superior oblique tendon as it moves through the trochlea. Cases may be congenital or acquired. Acquired Brown syndrome may follow trauma to the orbit involving the region of the trochlea or sinus surgery. It may also occur with inflammatory processes, particularly sinusitis and juvenile idiopathic arthritis.

Acquired inflammatory Brown syndrome may respond to treatment with either nonsteroidal medications or corticosteroids. Surgery may be helpful for selected cases of Brown syndrome.

Parinaud Syndrome

This eponym designates a palsy of vertical gaze, isolated or associated with pupillary or nuclear oculomotor (third cranial nerve) paresis. It indicates a lesion affecting the mesencephalic tegmentum. The ophthalmic signs of midbrain disease include vertical gaze palsy, dissociation of the pupillary responses to light and to near focus, general pupillomotor paralysis, corectopia, dyscoria, accommodative disturbances, pathologic lid retraction, ptosis, extraocular muscle paresis, and convergence paralysis. Some cases have associated spasms of convergence, convergent retraction nystagmus, and vertical nystagmus, particularly on attempted vertical gaze. Combinations of these signs are referred to as the **sylvian aqueduct syndrome**.

A principal cause of vertical gaze palsy and associated mesencephalic signs in children is tumor of the pineal gland or third ventricle. Differential diagnosis includes trauma and demyelinating disease. In children with hydrocephalus, impairment of vertical gaze and pathologic lid retraction are referred to as the *setting-sun sign*. A transient supranuclear disorder of gaze is sometimes seen in healthy neonates.

CONGENITAL OCULAR MOTOR APRAXIA

This congenital disorder of conjugate gaze is characterized by a defect in voluntary horizontal gaze, compensatory jerking movement of the head, and retention of slow pursuit and reflexive eye movements. Additional features are absence of the fast (refixation) phase of optokinetic nystagmus and obligate contraversive deviation of the eyes on rotation of the body. Affected children typically are unable to look quickly to either side voluntarily in response to a command or in response to an eccentrically presented object but may be able to follow a slowly moving target to either side. To compensate for the defect in purposive lateral eye movements, children jerk their head to bring the eyes into the desired position and may also blink repetitively in an attempt to change fixation. The signs tend to become less conspicuous with age.

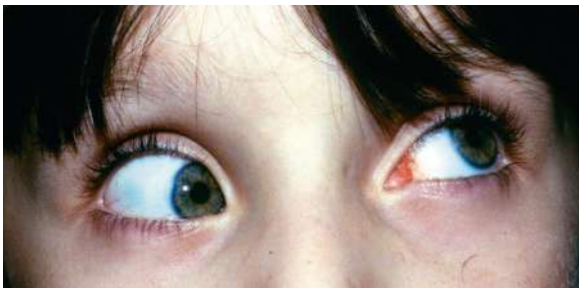

Fig. 663.7 Brown syndrome of the right eye.

The pathogenesis of congenital ocular motor apraxia is unknown. It may be a result of delayed myelination of the ocular motor pathways. Structural abnormalities of the central nervous system (CNS) have been found in a few patients, including agenesis of the corpus callosum and cerebellar vermis, porencephaly, hamartoma of the foramen of Monro, and macrocephaly. Many children with congenital ocular motor apraxia show delayed motor and cognitive development.

NYSTAGMUS

Nystagmus (rhythmic oscillations of one or both eyes) may be caused by an abnormality in any one of the three basic mechanisms that regulate position and movement of the eyes: the fixation, conjugate gaze, or vestibular mechanism. In addition, physiologic nystagmus may be elicited by appropriate stimuli (Table 663.3).

Congenital sensory nystagmus is generally associated with ocular abnormalities that lead to decreased visual acuity; common disorders that lead to early-onset nystagmus include albinism, aniridia, achromatopsia, congenital cataracts, congenital macular lesions, congenital optic atrophy, and congenital optic nerve hypoplasia. In some instances, nystagmus occurs as a dominant or X-linked characteristic without obvious ocular abnormalities.

Congenital idiopathic motor nystagmus is characterized by horizontal jerky oscillations, often with gaze preponderance. There are no ocular anatomic defects that cause the nystagmus, and the visual acuity is generally near normal. There may be a null point in which the nystagmus damps and the vision improves; a compensatory head posture will develop that places the eyes into the position of least nystagmus. The cause of congenital idiopathic motor nystagmus is unknown; in some instances, this is familial. Eye muscle surgery may be performed to eliminate an abnormal head posture by bringing the point of best vision into straight-ahead gaze.

Acquired nystagmus requires prompt and thorough evaluation. Spontaneous nystagmus is often associated with either peripheral or central vestibular disorders. Peripheral disorders are often acute and benign, but the severity of symptoms is often problematic to the patient (room spinning, unsteady gait, tinnitus, diaphoresis). Central vestibular lesions are more concerning for CNS disorders (vestibular nuclei, brainstem, cerebellum, cortex); symptoms are more chronic and less severe. Worrisome pathologic types are the gaze-paretic or gaze-evoked oscillations of cerebellar, brainstem, or cerebral disease.

Nystagmus retractorius or **convergent nystagmus** is repetitive jerking of the eyes into the orbit or toward each other. It is usually seen with vertical gaze palsy as a feature of Parinaud (sylvian aqueduct) syndrome. The causal condition may be neoplastic, vascular, or inflammatory. In children, nystagmus retractorius suggests particularly the presence of pinealoma or hydrocephalus.

A diagnostic approach to nystagmus is noted in Figures 663.8 and 663.9 and Table 663.4.

Table 663.3 Specific Patterns of Nystagmus

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Latent nystagmus	Conjugate jerk nystagmus toward viewing eye	Congenital vision defects, occurs with occlusion of eye
Manifest latent nystagmus	Fast jerk to viewing eye	Strabismus, congenital idiopathic nystagmus
Periodic alternating	Cycles of horizontal or horizontal-rotary that change direction	Caused by both visual and neurologic conditions
Seesaw nystagmus	One eye rises and intorts as other eye falls and extorts	Usually associated with optic chiasm defects
Nystagmus retractorius	Eyes jerk back into orbit or toward each other	Caused by pressure on mesencephalic tegmentum (Parinaud syndrome)
Gaze-evoked nystagmus	Jerk nystagmus in direction of gaze	Caused by medications, brainstem lesion, or labyrinthine dysfunction
Gaze-paretic nystagmus	Eyes jerk back to maintain eccentric gaze	Cerebellar disease
Downbeat nystagmus	Fast phase beating downward	Posterior fossa disease, drugs
Upbeat nystagmus	Fast phase beating upward	Brainstem and cerebellar disease; some visual conditions
Vestibular nystagmus	Horizontal-torsional or horizontal jerks	Vestibular system dysfunction
Asymmetric or monocular nystagmus	Pendular vertical nystagmus	Disease of retina and visual pathways
Spasmus nutans	Fine, rapid, pendular nystagmus	Torticollis, head nodding; idiopathic or gliomas of visual pathways

From Kliegman R. *Practical Strategies in Pediatric Diagnosis and Therapy.* Philadelphia: WB Saunders;1996.

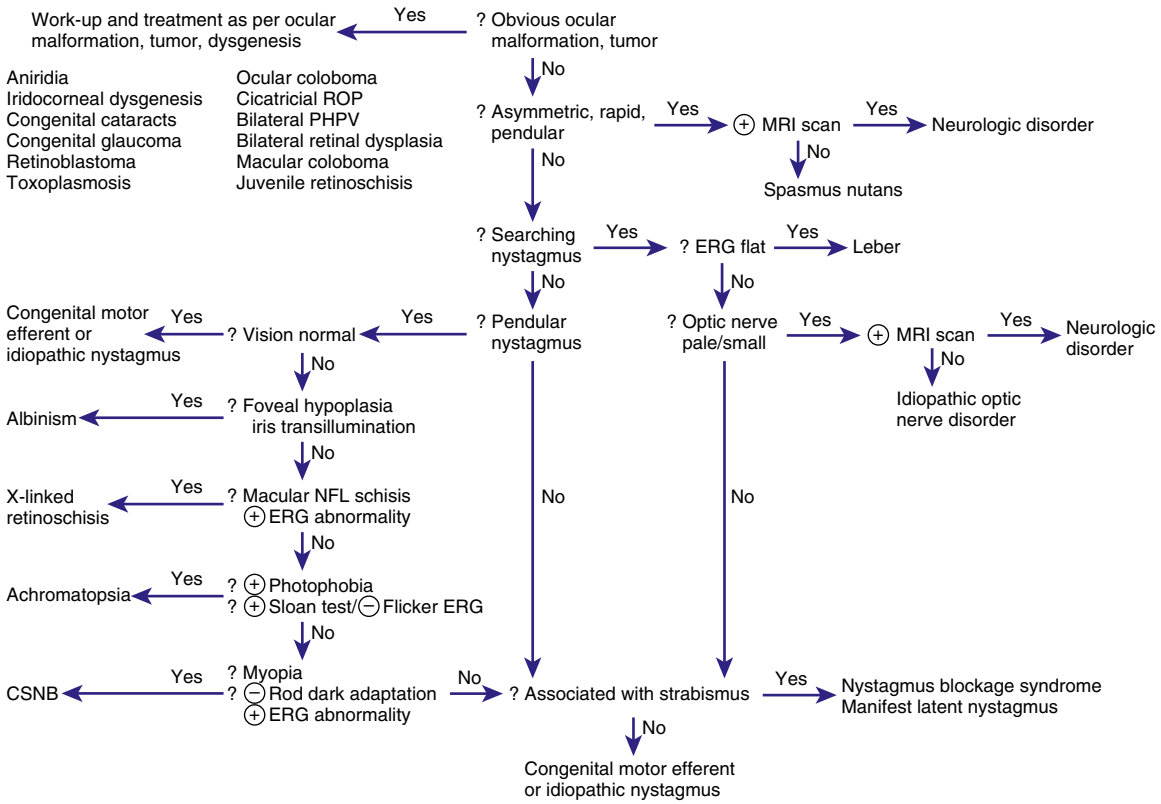

Fig. 663.8 Algorithm for the work-up of an infant with nystagmus. ⊕, Positive; ⊖, negative; CSNB, congenital stationary night blindness; ERG, electroretinogram; NFL, nerve fiber layer; PHPV, persistent hyperplastic primary vitreous; ROP, retinopathy of prematurity. *(From Nelson LB. Harley's Pediatric Ophthalmology. 4th ed. Philadelphia: Saunders; 1998: p. 470.)*

Spasmus nutans is a special type of acquired nystagmus in childhood (see also Chapter 637). In its complete form, it is characterized by the **triad** of pendular nystagmus, head nodding, and torticollis. The nystagmus is characteristically very fine, very rapid, horizontal, and pendular; it is often asymmetric, sometimes unilateral. Signs usually develop within the first year or two of life. Components of the triad may develop at various times. In many cases, the condition is benign and self-limited, usually lasting a few months, sometimes years. The cause of this classic type of spasmus nutans, which usually resolves spontaneously, is unknown. Some children exhibiting signs resembling

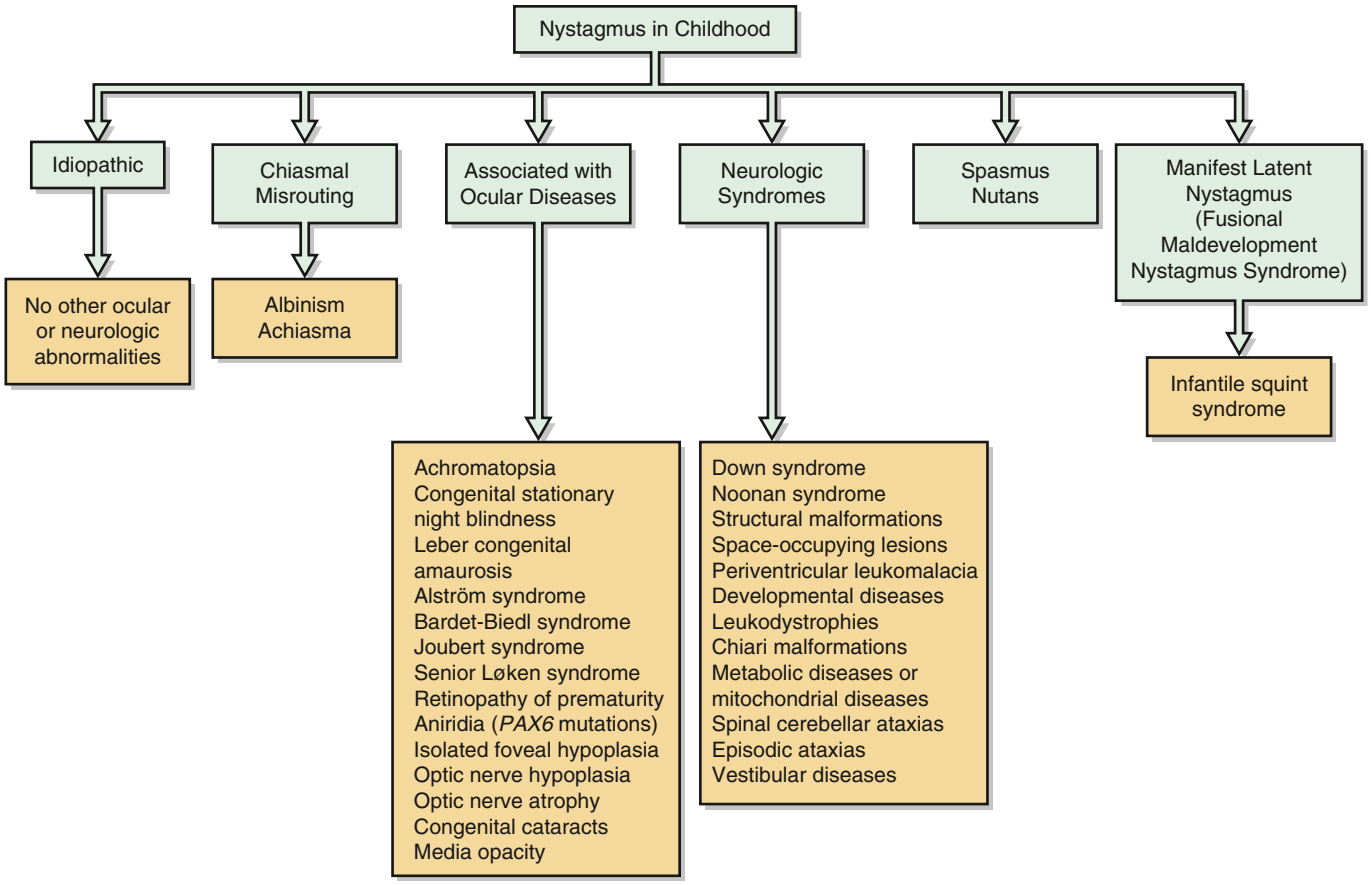

Fig. 663.9 Classification of nystagmus based on associated diseases. *(From Hoyt CS, Taylor D, eds. Pediatric ophthalmology and strabismus. 4th ed. Philadelphia: Elsevier; 2013: Fig. 89.2, p. 910.)*

Table 663.4 Key Distinguishing Features of Peripheral and Central Types of Spontaneous and Positional Nystagmus

TYPE OF NYSTAGMUS	PERIPHERAL (END ORGAN AND NERVE)	CENTRAL (BRAINSTEM AND CEREBELLUM)
Spontaneous	Unidirectional, fast phase away from the lesion, combined horizontal torsional, inhibited with fixation	Bidirectional or unidirectional; often pure horizontal, vertical, or torsional; *not* inhibited with fixation
Static positional	Fixed or changing direction, inhibited with fixation	Fixed or changing direction, *not* inhibited with fixation
Paroxysmal positional	Vertical-torsional, occasionally horizontal-torsional, vertigo prominent, fatigability, latency	Often pure vertical, vertigo less prominent, no latency, nonfatigable

From Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 25 ed. Philadelphia: Elsevier; 2016: Table 424.5, p. 2579.

those of spasmus nutans have underlying brain tumors, particularly hypothalamic and chiasmal optic gliomas. Appropriate neurologic and neuroradiologic evaluation and careful monitoring of infants and children with nystagmus are therefore recommended.

OTHER ABNORMAL EYE MOVEMENTS

To be differentiated from true nystagmus are certain special types of abnormal eye movements, particularly opsoclonus, ocular dysmetria, and flutter (Table 663.5).

Opsoclonus

Opsoclonus and ataxic conjugate movements are spontaneous, nonrhythmic, multidirectional, chaotic movements of the eyes. The eyes appear to be in agitation, with bursts of conjugate movement of varying amplitude in varying directions. Opsoclonus is most often associated with infectious or autoimmune encephalitis. It may be the first sign of neuroblastoma or other tumors producing a paraneoplastic syndrome.

Ocular Motor Dysmetria

This is analogous to dysmetria of the limbs. Affected individuals show a lack of precision in performing movements of refixation, characterized by an overshoot (or undershoot) of the eyes with several corrective to-and-fro oscillations on looking from one point to another. Ocular motor dysmetria is a sign of cerebellar or cerebellar pathway disease.

Table 663.5 Specific Patterns of Nonnystagmus Eye Movements

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Opsoclonus	Multidirectional conjugate movements of varying rate and amplitude	Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome
Ocular dysmetria	Overshoot of eyes on rapid fixation	Cerebellar dysfunction
Ocular flutter	Horizontal oscillations with forward gaze and sometimes with blinking	Cerebellar disease, hydrocephalus, or central nervous system neoplasm
Ocular bobbing	Downward jerk from primary gaze, remains for a few seconds, then drifts back	Pontine disease
Ocular myoclonus	Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement	Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus

From Kliegman R. *Practical Strategies in Pediatric Diagnosis and Therapy.* Philadelphia: Saunders; 1996.

Flutter-Like Oscillations

These intermittent to-and-fro horizontal oscillations of the eyes may occur spontaneously or on change of fixation. They are characteristic of cerebellar disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 664

Abnormalities of the Lids

Scott E. Olitsky and Justin D. Marsh

PTOSIS

In blepharoptosis, the upper eyelid droops below its normal level. **Congenital ptosis** is usually a result of a localized dystrophy of the levator muscle in which the striated muscle fibers are replaced with fibrous tissue. The condition may be unilateral or bilateral and can be familial, transmitted as a dominant trait (Figs. 664.1 and 664.2).

Parents often comment that the eye looks smaller because of the drooping eyelid. The lid crease is decreased or absent where the levator muscle would normally insert below the skin surface. Because the levator is replaced by fibrous tissue, the lid does not move downward fully in downgaze (lid lag). If the ptosis is severe, affected children often attempt to raise the lid by lifting their brow or adapting a chin-up head posture to maintain binocular vision.

Marcus Gunn jaw-winking ptosis (maxillopalpebral synkinesis) accounts for 5% of ptosis in children. In this syndrome, an abnormal synkinesis exists between the fifth and third cranial nerves; this causes the eyelid to elevate with movement of the jaw. The wink is produced by chewing or sucking and may be more noticeable than the ptosis itself (Fig. 664.3).

Although ptosis in children is often an isolated finding, it may also be acquired and occur in association with other ocular or systemic disorders (Fig. 664.4). Systemic disorders include myasthenia gravis, muscular dystrophy, Miller Fisher variant of Guillain Barré syndrome, and botulism. Ocular disorders include mechanical ptosis secondary to lid tumors, blepharophimosis syndrome, congenital fibrosis syndrome, combined levator/superior rectus maldevelopment, and congenital or acquired third nerve palsy. Ptosis may be a sign of cerebral herniation. A small degree of ptosis is seen in Horner syndrome (see Chapter 662). A complete ophthalmic and systemic examination is therefore important in the evaluation of a child with ptosis.

Amblyopia may occur in children with ptosis. The amblyopia may be secondary to the lid covering the visual axis (deprivation) or induced astigmatism (anisometropia). When amblyopia occurs, it should generally be treated before treating the ptosis.

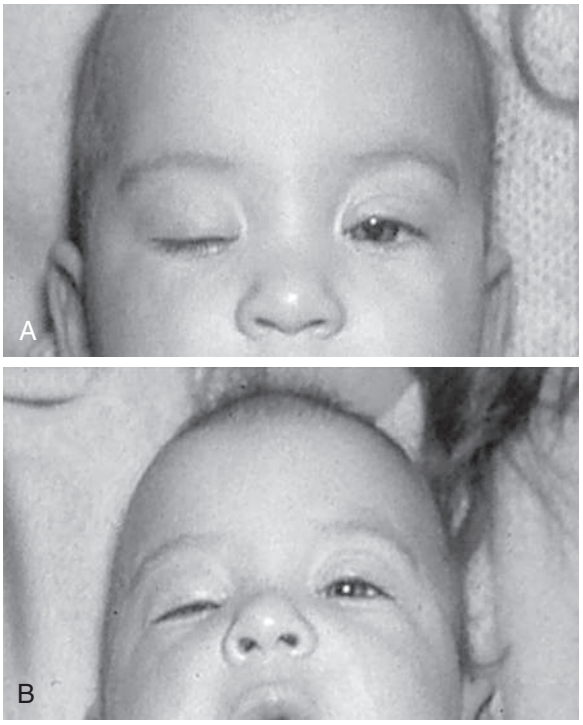

Fig. 664.1 A, Congenital ptosis of the right upper eyelid. B, The child adopted a compensatory chin-up head posture to allow use of both eyes together and did not have amblyopia. *(From Costakos DM. Eye disorders In Kliegman RM, Bordini BJ, Toth H, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. 2nd ed. Philadelphia: Elsevier; 2022: Fig. 43.20, p. 805.)*

Treatment of ptosis in a child is indicated for elimination of an abnormal head posture, improvement in the visual field, prevention of amblyopia, and restoration of a normal eyelid appearance. The timing of surgery depends on the degree of ptosis, its cosmetic and functional severity, the presence or absence of compensatory posturing, the wishes of the parents, and the discretion of the surgeon. Surgical treatment is determined by the amount of levator function that is present. A levator resection may be used in children with moderate to good function. In patients with poor or absent function, a frontalis suspension procedure may be necessary. This technique requires that a suspension material be placed between the frontalis muscle and the tarsus of the eyelid. It allows patients to use their brow and frontalis muscle more effectively to raise their eyelid. Amblyopia may still exist even after surgical correction and should be treated if present.

Table 663.5 Specific Patterns of Nonnystagmus Eye Movements

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Opsoclonus	Multidirectional conjugate movements of varying rate and amplitude	Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome
Ocular dysmetria	Overshoot of eyes on rapid fixation	Cerebellar dysfunction
Ocular flutter	Horizontal oscillations with forward gaze and sometimes with blinking	Cerebellar disease, hydrocephalus, or central nervous system neoplasm
Ocular bobbing	Downward jerk from primary gaze, remains for a few seconds, then drifts back	Pontine disease
Ocular myoclonus	Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement	Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus

From Kliegman R. *Practical Strategies in Pediatric Diagnosis and Therapy.* Philadelphia: Saunders; 1996.

Flutter-Like Oscillations

These intermittent to-and-fro horizontal oscillations of the eyes may occur spontaneously or on change of fixation. They are characteristic of cerebellar disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 664

Abnormalities of the Lids

Scott E. Olitsky and Justin D. Marsh

PTOSIS

In blepharoptosis, the upper eyelid droops below its normal level. **Congenital ptosis** is usually a result of a localized dystrophy of the levator muscle in which the striated muscle fibers are replaced with fibrous tissue. The condition may be unilateral or bilateral and can be familial, transmitted as a dominant trait (Figs. 664.1 and 664.2).

Parents often comment that the eye looks smaller because of the drooping eyelid. The lid crease is decreased or absent where the levator muscle would normally insert below the skin surface. Because the levator is replaced by fibrous tissue, the lid does not move downward fully in downgaze (lid lag). If the ptosis is severe, affected children often attempt to raise the lid by lifting their brow or adapting a chin-up head posture to maintain binocular vision.

Marcus Gunn jaw-winking ptosis (maxillopalpebral synkinesis) accounts for 5% of ptosis in children. In this syndrome, an abnormal synkinesis exists between the fifth and third cranial nerves; this causes the eyelid to elevate with movement of the jaw. The wink is produced by chewing or sucking and may be more noticeable than the ptosis itself (Fig. 664.3).

Although ptosis in children is often an isolated finding, it may also be acquired and occur in association with other ocular or systemic disorders (Fig. 664.4). Systemic disorders include myasthenia gravis, muscular dystrophy, Miller Fisher variant of Guillain Barré syndrome, and botulism. Ocular disorders include mechanical ptosis secondary to lid tumors, blepharophimosis syndrome, congenital fibrosis syndrome, combined levator/superior rectus maldevelopment, and congenital or acquired third nerve palsy. Ptosis may be a sign of cerebral herniation. A small degree of ptosis is seen in Horner syndrome (see Chapter 662). A complete ophthalmic and systemic examination is therefore important in the evaluation of a child with ptosis.

Amblyopia may occur in children with ptosis. The amblyopia may be secondary to the lid covering the visual axis (deprivation) or induced astigmatism (anisometropia). When amblyopia occurs, it should generally be treated before treating the ptosis.

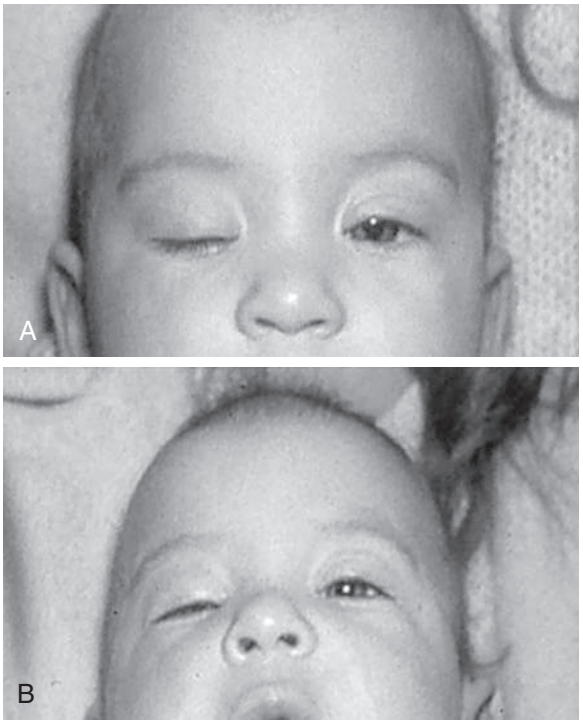

Fig. 664.1 A, Congenital ptosis of the right upper eyelid. B, The child adopted a compensatory chin-up head posture to allow use of both eyes together and did not have amblyopia. *(From Costakos DM. Eye disorders In Kliegman RM, Bordini BJ, Toth H, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. 2nd ed. Philadelphia: Elsevier; 2022: Fig. 43.20, p. 805.)*

Treatment of ptosis in a child is indicated for elimination of an abnormal head posture, improvement in the visual field, prevention of amblyopia, and restoration of a normal eyelid appearance. The timing of surgery depends on the degree of ptosis, its cosmetic and functional severity, the presence or absence of compensatory posturing, the wishes of the parents, and the discretion of the surgeon. Surgical treatment is determined by the amount of levator function that is present. A levator resection may be used in children with moderate to good function. In patients with poor or absent function, a frontalis suspension procedure may be necessary. This technique requires that a suspension material be placed between the frontalis muscle and the tarsus of the eyelid. It allows patients to use their brow and frontalis muscle more effectively to raise their eyelid. Amblyopia may still exist even after surgical correction and should be treated if present.

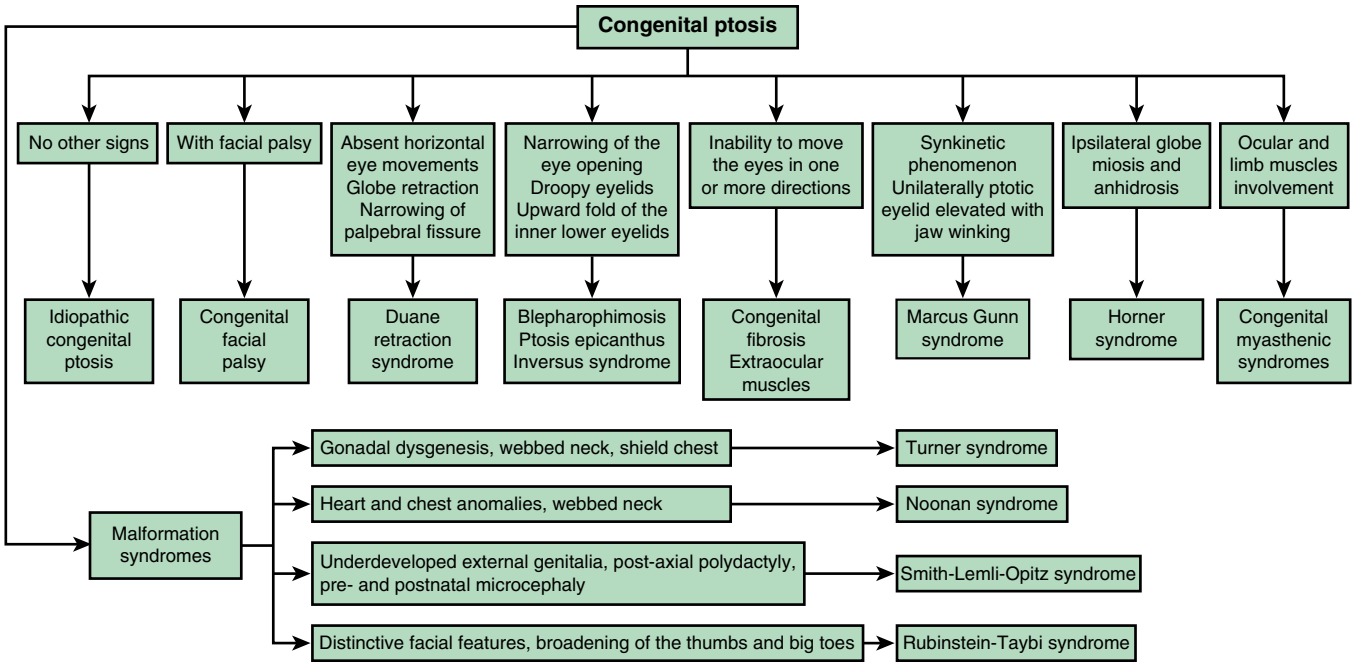

Fig. 664.2 Flow chart outlining congenital types of ptosis. *(From Pavone P, Cho YC, Pratico AD, et al. Ptosis in childhood: A clinical sign of several disorders. Medicine. 2018 Sep;97[36]:e12124, Fig. 8A.)*

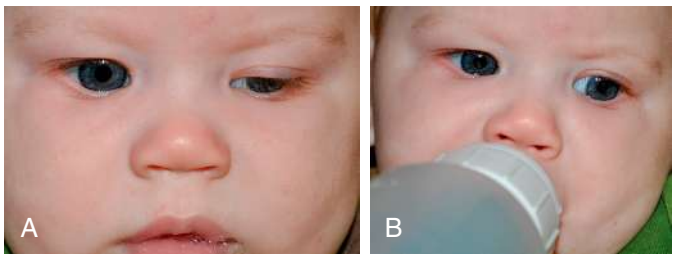

Fig. 664.3 Marcus Gunn jaw-winking phenomenon. A, Left upper lid ptosis. B, The left lid raises up while the patient sucks from the bottle. *(From Martin RJ, Fanaroff AA, Walsch MC, eds. Fanaroff & Martin's Neonatal-Perinatal Medicine. 10th ed. Philadelphia: Elsevier; 2015: Fig. 103.2.)*

EPICANTHAL FOLDS

These vertical or oblique folds of skin extend on either side of the bridge of the nose from the brow or lid area, covering the inner canthal region. They are present to some degree in most young children and become less apparent with age. The folds may be sufficiently broad to cover the medial aspect of the eye, making the eyes appear crossed (pseudoesotropia). Epicanthal folds are a common feature of many syndromes, including chromosomal aberrations (trisomies) and disorders of single genes.

LAGOPHTHALMOS

This is a condition in which complete closure of the lids over the globe is difficult or impossible. It may be paralytic because of a facial palsy involving the orbicularis muscle, or spastic, as in thyrotoxicosis. It may be structural when retraction or shortening of the lids results from scarring or atrophy consequent to injury (burns) or disease. Children with various craniosynostosis syndromes can have problematic lagophthalmos. Infants with congenital ichthyosis may have lagophthalmos caused by the restrictive effect of the lids. Lagophthalmos may accompany proptosis or **buphthalmos** (enlarged cornea because of elevated intraocular pressure) when the lids, although normal, cannot effectively cover the enlarged or protuberant eye. A degree of physiologic lagophthalmos may occur normally during sleep, but functional lagophthalmos in an unconscious or debilitated patient can be a problem.

In patients with lagophthalmos, exposure of the eye may lead to drying, infection, corneal ulceration, or perforation of the cornea; the result may be loss of vision, even loss of the eye. In lagophthalmos, protection of the eye by artificial tear preparations, ophthalmic ointment, or moisture chambers is essential. Gauze pads are to be avoided because the gauze may abrade the cornea. In some cases, surgical closure of the lids (tarsorrhaphy) may be necessary for long-term protection of the eye.

LID RETRACTION

Pathologic retraction of the lid may be myogenic or neurogenic. Myogenic retraction of the upper lid occurs in **thyrotoxicosis**, in which it is associated with three classic signs: a staring appearance (Dalrymple sign), infrequent blinking (Stellwag sign), and lag of the upper lid on downward gaze (von Graefe sign).

Neurogenic retraction of the lids may occur in conditions affecting the anterior mesencephalon. Lid retraction is a feature of the **syndrome of the sylvian aqueduct**. In children, it is commonly a sign of hydrocephalus. It may occur with meningitis. Paradoxical retraction of the lid is seen in the Marcus Gunn jaw-winking syndrome. It may also be seen with attempted eye movement after recovery from a third nerve palsy if aberrant regeneration of the oculomotor nerve fibers has occurred.

Simple staring and the physiologic or reflexive lid retraction ("eye popping"), in contrast to pathologic lid retractions, occur in infants in response to a sudden reduction in illumination or as a startle reaction.

ECTROPION, ENTROPION, AND EPIBLEPHARON

Ectropion is eversion of the lid margin; it may lead to overflow of tears (epiphora) and subsequent maceration of the skin of the lid, inflammation of exposed conjunctiva, or superficial exposure keratopathy. Common causes are scarring consequent to inflammation, burns, or trauma and weakness of the orbicularis muscle as a result of facial palsy; these forms may be corrected surgically. Protection of the cornea is essential. Ectropion is also seen in certain children who have faulty development of the lateral canthal ligament; this may occur in Down syndrome.

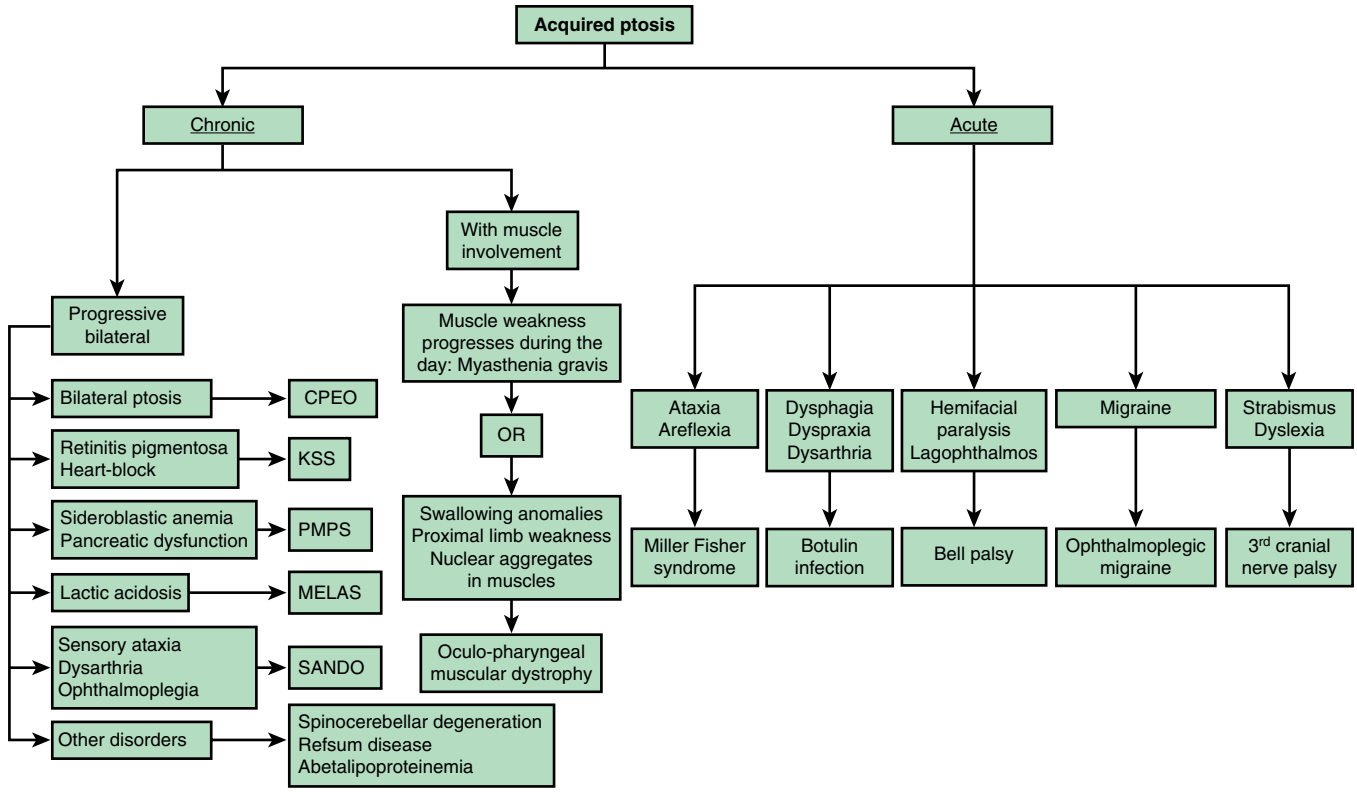

Fig. 664.4 Flow chart outlining acquired types of ptosis. CPEO, Chronic progressive external ophthalmoplegia; KSS, Kearns-Sayre syndrome; MELAS, mitochondrial encephalopathy, lactic acidosis, and strokelike episodes; PMPS, Pearson marrow pancreas syndrome; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis. *(From Pavone P, Cho YC, Pratico AD, et al. Ptosis in childhood: A clinical sign of several disorders. Medicine. 2018 Sep;97[36]:e12124, Fig. 8B.)*

Entropion is inversion of the lid margin, which may cause discomfort and corneal damage because of the inward turning of the lashes (trichiasis). A principal cause is scarring secondary to inflammation, such as occurs in trachoma or as a sequela of Stevens-Johnson syndrome. There is also a rare congenital form. Surgical correction is effective in many cases.

Epiblepharon is commonly seen in childhood and may be confused with entropion. In epiblepharon, a roll of skin beneath the lower eyelid lashes causes the lashes to be directed vertically and to touch the cornea (Fig. 664.5). Unlike entropion, the eyelid margin itself is not rotated toward the cornea. Epiblepharon usually resolves spontaneously. When mild symptoms are present, such as mild ocular irritation, lubrication is typically recommended. Rarely, corneal scarring may occur, and surgery may be necessary.

BLEPHAROSPASM

This spastic or repetitive closure of the lids may be caused by irritative disease of the cornea, conjunctiva, or facial nerve; fatigue or uncorrected refractive error; or common tic. Thorough ophthalmic examination for pathologic causes, such as trichiasis, keratitis, conjunctivitis, or foreign body, is indicated. Local injection of botulinum toxin may give relief but frequently must be repeated.

BLEPHARITIS

This inflammation of the lid margins is characterized by erythema and crusting or scaling; the usual symptoms are irritation, burning, and itching. The condition is commonly bilateral and chronic or recurrent. The two main types are **staphylococcal** and **seborrheic.** In staphylococcal blepharitis, ulceration of the lid margin is common, the lashes tend to fall out, and conjunctivitis and superficial keratitis are often associated. In seborrheic blepharitis, the scales tend to be greasy, the lid margins are less red, and ulceration usually does not occur. Commonly blepharitis presents as a combination of the two.

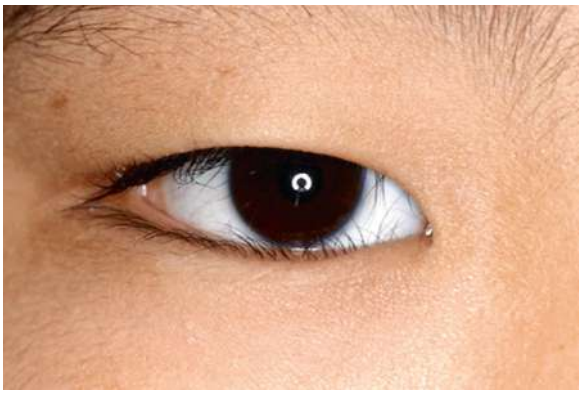

Fig. 664.5 Epiblepharon.

Thorough daily cleansing of the lid margins with a cloth or moistened cotton applicator to remove scales and crusts is important in the **treatment** of both forms. Staphylococcal blepharitis is treated with an antistaphylococcal antibiotic applied directly to the lid margins. When a child also has seborrhea, concurrent treatment of the scalp is important.

Pediculosis of the eyelashes may produce a clinical picture of blepharitis. The lice can be smothered with ophthalmic-grade petrolatum ointment applied to the lid margin and lashes. Nits should be mechanically removed from the lashes. It should be remembered that pediculosis can represent a sexually transmitted disease.

Mites (*Demodex* spp.) are an increasingly recognized cause of blepharitis, including in children and adolescents. Close inspection of the eyelashes often reveals sheathing of the lash at its base. Tea tree oil or products containing tea tree oil may be helpful, in addition to diligent lid hygiene.

HORDEOLUM (STYE)

Infection of the glands of the lid may be acute or subacute; tender focal swelling and redness are noted. The usual agent is *Staphylococcus aureus.* When the meibomian glands are involved, the lesion is referred to as an internal hordeolum; the abscess tends to be large and may point through either the skin or the conjunctival surface. When the infection involves the glands of Zeis or Moll, the abscess tends to be smaller and more superficial and points at the lid margin; it is then referred to as an *external hordeolum* or *stye*.

Treatment is frequent warm compresses and, if necessary, surgical incision and drainage. In addition, topical antibiotic preparations are often used. Untreated, the infection may progress to cellulitis of the lid or orbit, requiring the use of systemic antibiotics.

CHALAZION

A chalazion is a granulomatous inflammation of a meibomian gland characterized by a firm, nontender nodule in the upper or lower lid. This lesion tends to be chronic and differs from internal hordeolum in the absence of acute inflammatory signs. Although many chalazia subside spontaneously, incision and drainage may be necessary if they become large enough to distort vision (by inducing astigmatism by exerting pressure on the globe) or become cosmetically unacceptable. Patients who experience frequent chalazia formation, or those who have significant corneal changes secondary to the underlying blepharitis, may benefit from systemic, low-dose erythromycin or azithromycin treatment.

COLOBOMA OF THE EYELID

This cleftlike deformity may vary from a small indentation or notch of the free margin of the lid to a large defect involving almost the entire lid. If the gap is extensive, ulceration and corneal opacities may result from exposure. Early surgical correction of the lid defect is recommended. Other deformities frequently associated with lid colobomas include dermoid cysts or dermolipomas on the globe; they often occur in a position corresponding to the site of the lid defect. Lid colobomas may also be associated with extensive facial malformation, as in mandibulofacial dysostosis (Franceschetti or Treacher Collins syndrome).

TUMORS OF THE LID

A number of lid tumors arise from surface structures (the epithelium and sebaceous glands). Nevi may appear in early childhood; most are junctional. Compound nevi tend to develop in the prepubertal years and dermal nevi at puberty. Malignant epithelial tumors (basal cell carcinoma, squamous cell carcinoma) are rare in children, but the basal cell nevus syndrome and the malignant lesions of xeroderma pigmentosum and of Rothmund-Thomson syndrome may develop in childhood.

Other lid tumors arise from deeper structures (the neural, vascular, and connective tissues). **Capillary hemangiomas** are especially common in children (Fig. 664.6). Many tend to regress spontaneously, although they may show alarmingly rapid growth in infancy. In many cases, the best management of such hemangiomas is patient observation, allowing spontaneous regression to occur (see Chapter 691). In the case of a rapidly expanding lesion, which may cause amblyopia by obstructing the visual axis or inducing astigmatism, **treatment** should be considered. Systemic propranolol is an effective treatment without the risks associated with corticosteroid use. Other treatment options include topical timolol, corticosteroids (systemically or by direct injection), and surgical excision. Cutaneous capillary malformations (e.g., port-wine stain) can occur as an isolated lesion or in association with other signs of Sturge-Weber syndrome. Affected patients should be monitored for the development of glaucoma. **Lymphangiomas** (lymphatic malformations) of the lid appear as firm masses at or soon after birth and tend to enlarge slowly during the growing years. Associated conjunctival involvement, appearing as a clear, cystic, sinuous conjunctival mass, may provide a clue to the diagnosis. In some cases, there is also orbital involvement. The **treatment** may include sclerosant therapy, percutaneous drainage, or surgical excision.



Fig. 664.6 Capillary hemangioma of the eyelid. *(Courtesy Amy Nopper, MD, and Brandon Newell, MD.)*

Plexiform neuromas of the lids occur in children with neurofibromatosis, often with ptosis as the first sign. The lid may take on an S-shaped configuration. The lids may also be involved by other tumors, such as retinoblastoma, neuroblastoma, and rhabdomyosarcoma of the orbit; these conditions are discussed elsewhere.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 665

Disorders of the Lacrimal System

Scott E. Olitsky and Justin D. Marsh

THE TEAR FILM

The tear film, which bathes the eye, is a complex structure composed of three layers. The innermost mucin layer is secreted by the goblet and epithelial cells of the conjunctiva and the acinar cells of the lacrimal gland. It adds stability and provides an attachment for the tear film to the conjunctiva and cornea. The middle aqueous layer constitutes 98% of the tear film and is produced by the main lacrimal gland and accessory lacrimal glands. It contains various electrolytes and proteins as well as antibodies. The outermost lipid layer is produced largely from the sebaceous meibomian glands of the eyelid and retards evaporation of the tear film. Tears drain medially into the punctal openings of the lid margin and flow through the canaliculi into the lacrimal sac and then through the nasolacrimal duct into

the nose (Fig. 665.1). Preterm infants have reduced tear secretion. This may mask the diagnosis of a nasolacrimal duct obstruction and concentrate topically applied medications. Tear production reaches adult levels at 1-3 months.

DACRYOSTENOSIS

Congenital nasolacrimal duct obstruction (CNLDO), or dacryostenosis, is the most common disorder of the lacrimal system, occurring in up to 20% of newborn infants. It is usually caused by a failure of canalization of the epithelial cells (resulting in membrane formation) that form the nasolacrimal duct as it enters the nose beneath the inferior turbinate (valve of Hasner). Signs of CNLDO may be present at the time of birth, although the condition may not become evident until normal tear production develops. Signs of CNLDO include an excessive tear lake, overflow of tears onto the lid and cheek, and reflux of mucoid material that is produced in the lacrimal sac. Erythema or maceration of the skin may result from irritation and rubbing produced by dripping of tears and discharge. If the blockage is complete, these signs may be severe and continuous. If obstruction is only partial, the nasolacrimal duct may be capable of draining the basal tear film that is produced. However, under periods of increased tear production (exposure to cold, wind, sunlight) or increased closure of the distal end of the nasolacrimal duct (nasal mucosal edema), tear overflow may become evident or may increase.

Infants at increased risk for CNLDO include those with trisomy 21, EEC (ectrodactyly, ectodermal dysplasia, clefting) syndrome, branchiooculofacial syndrome, craniometaphyseal or craniodiaphyseal dysplasias, LADD (lacrimo-auriculo-dento-digital) syndrome, CHARGE (coloboma, heart anomaly, choanal atresia, retardation, genital, and ear anomalies) syndrome, and Goldenhar syndrome (Table 665.1).

Infants with CNLDO may develop acute infection and inflammation of the nasolacrimal sac **(dacryocystitis)**, inflammation of the surrounding tissues **(pericystitis)**, or, rarely, periorbital cellulitis. With dacryocystitis, the sac area is swollen, red, and tender, and patients may have systemic signs of infection such as fever and irritability.

The primary **treatment** of uncomplicated nasolacrimal duct obstruction is a regimen of nasolacrimal massage, usually two or three times daily, accompanied by cleansing of the lids with warm water. Topical antibiotics are used for control of mucopurulent drainage. A bland ophthalmic ointment may be used on eyelids if the skin is macerated. Most cases of CNLDO resolve spontaneously; 96% resolve before 1 year of age. For cases that do not resolve by 1 year, the nasolacrimal duct may be probed, with a cure rate of approximately 80%. Some ophthalmologists intubate the nasolacrimal system at the same time because this may improve the outcome of the procedure.

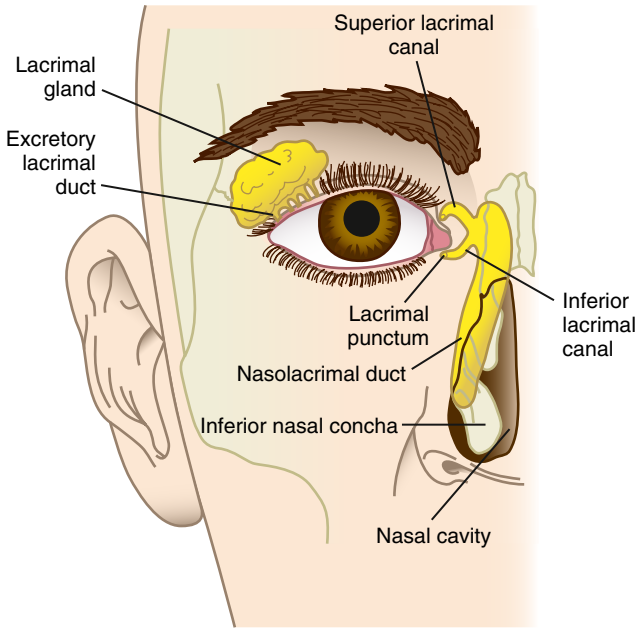

Fig. 665.1 The lacrimal apparatus.

Acute dacryocystitis (Fig. 665.2) requires prompt treatment with systemic antibiotics. In such cases, some form of definitive surgical intervention is usually indicated.

A **dacryocystocele** (mucocele) is an unusual presentation of a nonpatent nasolacrimal sac that is obstructed both proximally and distally. Dacryocystoceles can be seen at birth or shortly after birth as a bluish subcutaneous mass just below the medial canthal tendon (Figs. 665.3 and 665.4). Initial **treatment** of dacryocystocele is usually conservative, involving massage/digital decompression of the lacrimal sac. If resolution of the dacryocystocele is not achieved with conservative management, surgical probing may be beneficial. At times, the intranasal portion of the nasolacrimal duct becomes distended, causing respiratory compromise. In one study, 9.5% of infants with dacryocystocele had related respiratory compromise, and this may be more common when dacryocystoceles are present bilaterally. These infants benefit from early probing. When left untreated, dacryocystocele may progress to dacryocystitis/cellulitis, requiring systemic antibiotics and often hospitalization. Once the cellulitis has improved, the nasolacrimal system should be probed if spontaneous resolution has not occurred.

Not all tearing in infants and children is caused by nasolacrimal obstruction. Tearing may also be a sign of glaucoma, intraocular inflammation, or external irritation, such as that from a corneal abrasion or foreign body.

ALACRIMA AND "DRY EYE"

Alacrima refers to a wide spectrum of disorders with reduced or absent tear secretion. Occasionally normal basal tearing occurs with an absence of emotional tearing. Etiologies can be divided into syndromes that have a pathologic association or are inherited. Associated syndromes include familial dysautonomia (Riley-Day syndrome), anhidrotic ectodermal dysplasia, and triple-A syndrome (Allgrove syndrome: achalasia, alacrima, adrenal insufficiency). Examples of pathologic association include aplasia of cranial nerve nuclei and lacrimal gland aplasia/hypoplasia. Both autosomal recessive and autosomal dominant inheritance have been reported in isolated congenital alacrima. In addition, medications with anticholinergic side effects can decrease tear production. The patients with alacrima have variable presentation, including no symptoms, photophobia, foreign body sensation, eye pain, and decreased vision. The symptoms, if present, often occur early in life. Because the dryness can be severe, damage to the cornea and subsequent loss of vision may occur. The goal of treatment is to minimize corneal irritation, corneal scarring, and loss of vision. Aggressive ocular lubrication is used to prevent these sequelae.

An **acquired abnormality** of any layer of the tear film may produce a dry eye. Commonly acquired disorders that may lead to a decreased or unstable tear film include Sjögren syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, vitamin A deficiency, viral infections of the lacrimal gland, ocular pemphigoid, trachoma, chemical burns, irradiation, isotretinoin treatment of acne, graft-versus-host disease, and meibomian gland dysfunction. Corneal exposure as a consequence of poor lid closure or other pathologic states can quickly lead to pathologically dry eyes. Examples of conditions leading to such exposure include ichthyosis, xeroderma pigmentosum, and certain

Table 665.1 Syndromes Associated with Congenital Lacrimal Drainage Anomalies

Down syndrome	Branchio-oto-renal syndrome
Ectrodactyly-ectodermal dysplasia clefting (EEC) syndrome	Crouzon syndrome
Treacher Collins syndrome	Klinefelter syndrome
Rubinstein-Taybi syndrome	Fraser syndrome
Lacrimo-auriculo-dento-digital (LADD) or Levy-Hollister syndrome	Goltz-Gorlin syndrome
	Wolf-Hirschhorn or 4p-syndrome
Hay-Wells syndrome	Congenital rubella syndrome
ADULT syndrome	Turner syndrome
Limb-mammary syndrome	Fetal alcohol syndrome
Rapp-Hodgkin syndrome	Hallermann-Streiff syndrome
Split-hand/split-foot syndrome	Fetal valproate syndrome
Aplasia of the lacrimal and salivary glands (ALSG) syndrome	HPPD syndrome (hypertelorism, preauricular sinus, punctal pits, deafness)
Apert syndrome	
Saethre-Chotzen syndrome	Velocardiofacial (VCFS) syndrome
CHARGE syndrome	Poland-Möbius syndrome
Branchio-oculo-facial (BOF) syndrome	Robinow syndrome
Goldenhar syndrome	Angelman syndrome
Cornelia de Lange syndrome	Waardenburg-Klein syndrome
Congenital arhinia-microphthalmia syndrome	PHACE syndrome
Johanson Blizzard syndrome	Williams-Beuren syndrome
Pashayan syndrome	Peter's plus syndrome
Millers syndrome	Kabuki syndrome
Kallmann syndrome	Angora hair nevus syndrome
Nager syndrome	TARP syndrome
Blepharophimosis syndrome	11q trisomy syndrome
VACTERL association	Barber-Say syndrome

ADULT, acro-dermato-ungual-lacrimal-tooth; CHARGE, coloboma, heart, atresia choanae, growth retardation, genital ear; PHACE, posterior fossa, hemangioma, arterial, cardiac, eye or endocrine; TARP, talipes equinovarus, atrial septal defects, Robin syndrome, persistent left superior vena cava; VACTERL, vertebral, anal atresia, cardiac, tracheo-esophageal atresia, renal, limb.

Modified from Ali MJ. Updates on congenital lacrimal drainage anomalies and their association with syndromes and systemic disorders: A major review. *Ann Anatomy.* 2021;233:151613: Table 665.1.

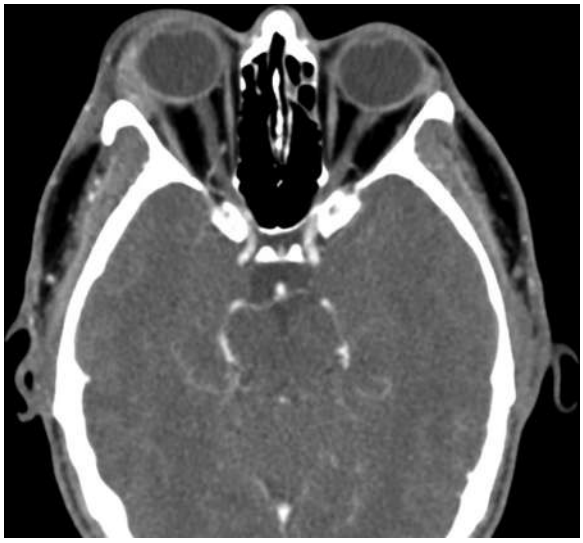

Fig. 665.2 Noncontrast axial CT study exhibiting right acute dacryoadenitis with inflammation adjacent to the lateral orbital wall and lateral rectus muscle. *(From Maamari RN, Couch SM. Nonspecific orbital inflammation. Adv Ophthalmol Optom. 2018;3[1]:315-335, Fig. 3.)*



Fig. 665.3 Dacryocystocele below inner canthus of the right eye.

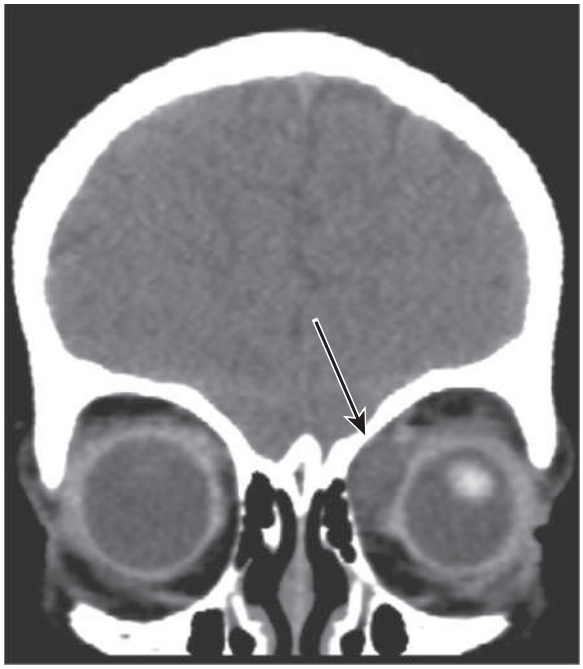

Fig. 665.4 Coronal CT shows a left dacryocystocele *(arrow)*. *(Modified from Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 5.23, p. 36.)*

craniosynostoses syndromes, such as Crouzon, Apert, or Pfeiffer. Any tear deficiency can lead to corneal ulceration, scarring, or infection. **Treatment** includes correction of the underlying disorder when possible and frequent instillation of an ocular lubricant. In some cases, occlusion of the lacrimal puncta is helpful. In severe cases, tarsorrhaphy may be necessary to protect the cornea.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 666

Disorders of the Conjunctiva

Scott E. Olitsky and Justin D. Marsh

CONJUNCTIVITIS

The conjunctiva reacts to a wide range of bacterial and viral agents, allergens, irritants, toxins, and systemic diseases. Conjunctivitis is common in childhood and may be infectious or noninfectious. The differential diagnosis of a red-appearing eye includes conjunctival disease, as well as other ocular sites (Table 666.1).

Ophthalmia Neonatorum

This form of conjunctivitis, occurring in infants younger than 4 weeks of age, is the most common eye disease of newborns. Its many different causal agents vary greatly in their virulence and outcome. Silver nitrate instillation may result in a mild self-limited chemical conjunctivitis, whereas *Neisseria gonorrhoeae* and *Pseudomonas* are capable of causing corneal perforation, blindness, and death. The risk of conjunctivitis in newborns depends on frequencies of maternal infections, prophylactic measures, circumstances during labor and delivery, and postdelivery exposure to microorganisms.

Epidemiology

Conjunctivitis during the neonatal period is usually acquired during vaginal delivery and reflects the sexually transmitted infections prevalent in the community. The incidence of gonococcal ophthalmia neonatorum can be reduced by widespread use of topical silver nitrate or erythromycin prophylaxis, prenatal screening, and treatment of maternal gonorrhea. Gonococcal ophthalmia neonatorum has an incidence of 0.3/1,000 live births in the United States. In comparison, *Chlamydia trachomatis* is the most common organism causing ophthalmia neonatorum in the United States, with an incidence of 8.2/1,000 births.

Clinical Manifestations

The clinical manifestations of the various forms of ophthalmia neonatorum are not specific enough to allow an accurate diagnosis. Although the timing and character of the signs are somewhat typical for each cause of this condition, there is considerable overlap, and physicians should not rely solely on clinical findings. Regardless of its cause, ophthalmia neonatorum is characterized by redness and chemosis (swelling) of the conjunctiva, edema of the eyelids, and discharge, which may be purulent.

Neonatal conjunctivitis is a potentially blinding condition. The infection may also have associated systemic manifestations that require treatment. Any newborn infant who develops signs of conjunctivitis needs a prompt and comprehensive systemic and ocular evaluation to determine the agent causing the infection and the appropriate treatment.

The onset of inflammation caused by silver nitrate drops usually occurs within 6-12 hours after birth, with clearing by 24-48 hours. The usual incubation period for conjunctivitis caused by *N. gonorrhoeae* is 2-5 days, and for that caused by *C. trachomatis*, 5-14 days. Gonococcal infection may be present at birth owing to prolonged rupture of amniotic membranes or be delayed beyond 5 days of life because of partial suppression by ocular prophylaxis. Gonococcal conjunctivitis may also begin in infancy after inoculation by the contaminated fingers of adults. The time of onset of disease with other bacteria is highly variable.

Gonococcal conjunctivitis begins with mild inflammation and a serosanguineous discharge. Within 24 hours, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If proper treatment is delayed, the infection may spread to involve the deeper layers of the conjunctivae and the cornea. Complications include corneal ulceration and perforation, iridocyclitis, anterior synechiae, and, rarely, panophthalmitis. Conjunctivitis caused by *C. trachomatis* (inclusion blennorrhea) may vary from mild inflammation to severe swelling of the eyelids with copious purulent discharge. The process involves mainly the tarsal conjunctivae; the corneas are rarely affected. Conjunctivitis caused by *Staphylococcus aureus* or other organisms is similar to that produced by *C. trachomatis.* Conjunctivitis caused by *Pseudomonas aeruginosa* is uncommon, acquired in the nursery, and a potentially serious process. It is characterized by the appearance on days 5-18 of edema, erythema of the lids, purulent discharge, pannus formation, endophthalmitis, sepsis, shock, and death.

Diagnosis

Conjunctivitis appearing after 48 hours should be evaluated for a possibly infectious cause. Gram stain of the purulent discharge should be performed and tested by polymerase chain reaction (PCR) for gonococcus. If a viral cause is suspected, a swab should be submitted for PCR testing. In chlamydial conjunctivitis, the diagnosis is made by tests for chlamydial antigen or DNA. The differential diagnosis of ophthalmia neonatorum includes dacryocystitis caused by congenital nasolacrimal duct obstruction with lacrimal sac distention (dacryocystocele; see Chapter 665).

Treatment

Treatment of infants in whom gonococcal ophthalmia is suspected where the Gram stain shows the characteristic intracellular Gram-negative diplococci should be initiated immediately with ceftriaxone, 25-50 mg/kg/24 hr for one dose IV or IM, not to exceed 125 mg. The eye should also be irrigated initially with saline every 10-30 minutes, gradually increasing to 2-hour intervals until the purulent discharge has cleared. Treatment (ceftriaxone 25-50 mg/kg/day, IM or IV in a single daily dose for 7 days, with cefotaxime 25 mg/kg q 12 hr substituted if the patient has hyperbilirubinemia) is extended if sepsis or other extraocular sites are involved. Associated meningitis is treated for 10-14 days. Neonatal conjunctivitis secondary to chlamydial infections is treated with oral erythromycin (50 mg/kg/24 hr in four divided doses) for 2 weeks. This cures conjunctivitis and may prevent subsequent chlamydial pneumonia. *Pseudomonas* neonatal conjunctivitis is treated with systemic antibiotics, including an aminoglycoside, plus local saline irrigation and gentamicin ophthalmic ointment. Staphylococcal conjunctivitis is treated with parenteral methicillin and local saline irrigation.

Prognosis and Prevention

Before the institution of topical ophthalmic prophylaxis at birth, gonococcal ophthalmia was a common cause of blindness or permanent eye damage. If properly applied, this form of prophylaxis is highly effective unless infection is present at birth. Drops of 0.5% erythromycin or 1% silver nitrate are instilled directly into the open eyes at birth using wax or plastic single-dose containers. Saline irrigation after silver nitrate application is unnecessary. Silver nitrate is ineffective against active infection and may have limited use against *Chlamydia*. Povidone-iodine (2% solution) may also be an effective prophylactic agent, especially in developing countries.

Identification of maternal gonococcal infection and appropriate treatment has become a standard element of routine prenatal care. An infant born to a woman who has untreated gonococcal infection should receive a single dose of ceftriaxone, 50 mg/kg (maximum 125 mg) IV or IM, in addition to topical prophylaxis. The dose should be reduced for premature infants. Penicillin (50,000 units) should be used if the mother's gonococcal isolate is known to be penicillin sensitive.

Neither topical prophylaxis nor topical treatment prevents the afebrile pneumonia that occurs in 10–20% of infants exposed to *C. trachomatis.* Although chlamydial conjunctivitis is often a self-limiting disease, chlamydial pneumonia may have serious consequences. It is important that infants with chlamydial disease receive systemic treatment. Treatment of colonized pregnant people with erythromycin may prevent neonatal disease.

Table 666.1 The Red Eye

CONDITION	CAUSE	SIGNS/SYMPTOMS	TREATMENT
Bacterial conjunctivitis	*Haemophilus influenzae*, *H. influenzae aegyptius*, *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Yersinia* species, cat-scratch bacillus less common	Mucopurulent unilateral or bilateral discharge, normal vision, photophobia usually absent Conjunctival injection and edema (chemosis); gritty sensation	Topical antibiotics: systemic ceftriaxone for gonococcus, *H. influenzae*
Viral conjunctivitis	Adenovirus, ECHO virus, coxsackievirus, herpes simplex virus, coronavirus	As above; may be hemorrhagic, unilateral enlarged preauricular lymph nodes	Self-limited
Neonatal conjunctivitis	*Chlamydia trachomatis*, gonococcus, chemical (silver nitrate), *S. aureus*	Palpebral conjunctival follicle or papillae; as above	Ceftriaxone for gonococcus and oral erythromycin for *C. trachomatis*
Allergic conjunctivitis	Seasonal pollens or allergen exposure	Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae	Antihistamines, steroids, cromolyn
Keratitis	Herpes simplex, adenovirus, *S. pneumoniae*, *S. aureus*, *Pseudomonas* species, *Acanthamoeba* species, chemicals	Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection	Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes
Endophthalmitis	*S. aureus*, *S. pneumoniae*, *Candida albicans*, associated surgery or trauma	Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze	Antibiotics
Anterior uveitis (iridocyclitis)	JIA, reactive arthritis, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease	Unilateral/bilateral; erythema, ciliary flush (in circumcorneal area), irregular pupil, iris adhesions; pain, marked photophobia, small pupil, poor vision, no discharge	Topical steroids, plus therapy for primary disease
Posterior uveitis (choroiditis)	Toxoplasmosis, histoplasmosis, *Toxocara canis*	No sign of erythema, decreased vision, no discharge	Specific therapy for pathogen
Episcleritis/ scleritis	Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura)	Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation, no discharge	Episcleritis is self-limiting; topical steroids for fast relief
Foreign body	Occupational exposure	Unilateral, red, gritty feeling; visible or microscopic size	Irrigation, removal; check for ulceration
Blepharitis	*S. aureus*, *S. epidermidis*, seborrheic, blocked lacrimal duct: rarely, molluscum contagiosum, *Pthirus pubis*, *Pediculosis capitis*	Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins	Topical antibiotics, warm compresses
Dacryocystitis	Obstructed lacrimal sac: *S. aureus*, *H. influenzae*, pneumococcus	Pain, tenderness, erythema, and exudate in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis	Systemic, topical antibiotics; surgical drainage
Dacryoadenitis	*S. aureus*, *Streptococcus* species, CMV, measles, EBV, enteroviruses, trauma, sarcoidosis, leukemia	Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis	Systemic antibiotics; drainage of orbital abscesses
Orbital cellulitis	Paranasal sinusitis: *H. influenzae*, *S. aureus*, *S. pneumoniae*, other *Streptococcus* species Trauma: *S. aureus* Fungi: *Aspergillus*, *Mucor* species if immunodeficient	Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis	Systemic antibiotics (postseptal cellulitis), drainage of orbital abscesses
Periorbital cellulitis	Trauma: *S. aureus*, *Streptococcus* species Bacteremia: *H. influenzae*, pneumococci, *S. pyogenes*, *S. aureus*	Cutaneous erythema, warmth, normal vision, minimal involvement of orbit, fever, leukocytosis, toxic appearance	Systemic antibiotics (preseptal cellulitis)

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; ECHO, enteric cytopathogenic human orphan; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.
Modified from Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics*. 3rd ed. Philadelphia: WB Saunders; 1998; with data from Rosenbaum JT, Nozik RA. Uveitis: many diseases, one diagnosis. *Am J Med*. 1985;79:545–547; Elkington AR, Khaw PT. The red eye. *BMJ*. 1988;296:1720–1724; Wilhemus KR. The red eye. Infectious conjunctivitis, keratitis, endophthalmitis, and periocular cellulitis. *Infect Dis Clin North Am*. 1988;2:99–116; Forrester JV. Uveitis: pathogenesis. *Lancet*. 1991;338:1498–1501; Gioliotti F. Acute conjunctivitis of childhood. *Pediatr Ann*. 1993;22:353–356.

Acute Purulent Conjunctivitis

This is characterized by more or less generalized (bilateral in 50–75%) conjunctival hyperemia, edema, mucopurulent exudate, glued eyes (lids stuck together after sleeping), and various degrees of ocular pain and discomfort. It is usually a result of bacterial infection. In addition, there is usually little or no pruritus or periauricular lymph node enlargement; the peak season is between December and April. Bacterial conjunctivitis is more common in young children (<5 years), whereas viral conjunctivitis is more common among adolescents and adults. The most frequent causes are nontypeable *Haemophilus influenzae* (60–80%; associated with ipsilateral otitis media), pneumococci (20%), and staphylococci (5–10%). Bacterial purulent conjunctivitis, especially that caused by

pneumococcus or *H. influenzae,* may occur in epidemics. Conjunctival smear and culture are helpful in differentiating specific types. These common forms of acute purulent conjunctivitis usually respond well to warm compresses and topical instillation of antibiotic drops, which shortens the duration of illness and hastens return to school. Topical antibiotics include aminoglycosides (gentamicin, tobramycin), quinolones (ciprofloxacin, ofloxacin, moxifloxacin), and combinations of antibiotics and chloramphenicol (Table 666.2). Brazilian purpuric fever caused by *Haemophilus aegyptius* manifests as conjunctivitis and sepsis. **Hyperacute bacterial conjunctivitis** is caused by gonococcal or meningococcal infection and requires systemic, not topical, antimicrobial therapies. Concerning symptoms that should require an ophthalmology referral include vision loss, severe purulent discharge, corneal involvement, conjunctival scarring, cutaneous-conjunctival involvement (Stevens-Johnson syndrome), recurrent symptoms, severe pain, herpes simplex virus infection, severe photophobia, and involvement with a contact (cosmetic or prescription) lens.

Viral Conjunctivitis

This is generally characterized by a watery discharge. Follicular changes (small aggregates of lymphocytes) are often found in the palpebral conjunctiva. Involvement is often unilateral and associated with periauricular nodes. Viral conjunctivitis occurs more often in the summer and in older children (>5 years). Conjunctivitis resulting from adenovirus infection is relatively common, sometimes with corneal involvement as well as pharyngitis or pneumonia. Outbreaks of conjunctivitis caused by enterovirus are also encountered; this type may be hemorrhagic (Fig. 666.1). Acute hemorrhagic conjunctivitis may be epidemic because of enterovirus CA24 or 70 and is characterized by red, swollen, and painful eyes with a hemorrhagic watery discharge. Conjunctivitis is commonly associated with such systemic viral infections as childhood exanthems, particularly measles. Viral conjunctivitis is usually self-limited.

Epidemic Keratoconjunctivitis

This is caused by adenovirus serotypes 8, 19, or 37, and is transmitted by direct contact. It initially presents as a sensation of a foreign body beneath the lids, with itching and burning. Edema (chemosis) and photophobia develop rapidly, and large oval follicles appear within the conjunctiva. Preauricular adenopathy and a pseudomembrane on the conjunctival surface occur frequently. Subepithelial corneal infiltrates may develop and may cause blurring of vision; these usually disappear but may permanently reduce visual acuity. Corneal complications are less common in children than in adults. Children may have associated upper respiratory tract infection and pharyngitis. No specific medical therapy is available to decrease the symptoms or shorten the course of the disease. Emphasis must be placed on prevention of spread of the disease. A replicating virus is present in 95% of patients 10 days after the appearance of symptoms.

Pharyngoconjunctival fever presents with high fever, pharyngitis, bilateral conjunctivitis, and periauricular lymphadenopathy. It is highly contagious.

Membranous and Pseudomembranous Conjunctivitis

These types of conjunctivitis can be encountered in a number of diseases. The classic membranous conjunctivitis is that of diphtheria, accompanied by a fibrin-rich exudate that forms on the conjunctival surface and permeates the epithelium; the membrane is removed with difficulty and leaves raw bleeding areas. In pseudomembranous conjunctivitis, the layer of fibrin-rich exudate is superficial and can often be stripped easily, leaving the surface smooth. This type occurs with



Fig. 666.1 Acute hemorrhagic conjunctivitis (AHC) is a highly contagious conjunctivitis that presents with symptoms of pain, redness, and tearing. Ocular findings include extensive subconjunctival hemorrhages, follicles, and chemosis. Causative agents include coxsackie group A24 (CA24) and enterovirus E70 (EV70). *(From Krachmer JH, Palay DA. Cornea Atlas. 3rd ed. London: Elsevier, 2014: Fig 7-23))*

Table 666.2 Topical Antibiotics Used to Treat Bacterial Conjunctivitis: Adult Dosages

DRUG	DOSAGE
Bacitracin (AK-Tracin, Bacticin) ointment	Apply 0.5 inch in eye q3-4hr
Ciprofloxacin (Ciloxan) 0.3% ophthalmic solution	1-2 gtt in eye q15min × 6 hr, then q30min × 18h, then q1hr × 1 day, then q4hr × 12 days*
Gatifloxacin (Zymar) 0.3% ophthalmic solution	1 gt in eye q2h up to 8 × per day × 2 days, then 1 gt qid × 5 days
Gentamicin (Gentak, Gentasol) 0.3% ophthalmic solution or ointment	Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4hr
Levofloxacin (Quixin) 0.5% ophthalmic solution	1-2 gtt in eye q2hr × 2 days while awake, then q4hr × 5 days while awake
Moxifloxacin (Vigamox) 0.5% ophthalmic solution	1 gt in eye tid × 7 days
Neomycin/polymyxin B/gramicidin (Neosporin) ophthalmic solution	1-2 gtt in eye q4hr × 7-10 days
Ofloxacin (Ocuflox) 0.3% ophthalmic solution	1-2 gtt in eye q2-4hr × 2 days, then 1-2 gtt in eye qid × 5 days
Polymyxin B and trimethoprim (Polytrim) ophthalmic solution	1 gt in eye q3hr × 7-10 days
Sulfacetamide (Isopto Cetamide, Ocusulf-10, Sodium Sulamyd, Sulf-10, AK-Sulf) 10% ophthalmic solution, ointment	Ointment: 0.5-inch ribbon in eye q3-4hr and qhr × 7 days Solution: 1-2 gtt in eye q2-3hr × 7-10 days
Tobramycin (AK-Tob, Tobrex) 0.3% ophthalmic solution	1-2 gtt in eye q4hr

*Exceeds dosage recommended by the manufacturer.
From Bope ET, Kellerman RD, eds. *Conn's Current Therapy.* Philadelphia: Elsevier; 2014: Table 2, p. 321.

many bacterial and viral infections, including staphylococcal, pneumococcal, streptococcal, or chlamydial conjunctivitis, and in epidemic keratoconjunctivitis. It is also found in vernal conjunctivitis and in Stevens-Johnson disease.

Allergic Conjunctivitis

This is usually accompanied by intense itching, clear watery discharge, and conjunctival edema (chemosis) (see Chapter 188). It is commonly seasonal (spring-summer). Cold compresses and topical antihistamine drops give symptomatic relief. Topical mast cell stabilizers or prostaglandin inhibitors may also help. In selected cases, topical corticosteroids are used under an ophthalmologist's supervision but should not be used routinely or for a long time.

Vernal Conjunctivitis

This usually begins in the prepubertal years and may recur for many years. Atopy appears to have a role in its origin, but the pathogenesis is uncertain. Extreme itching and tearing are the usual complaints. Large, flattened, cobblestone-like papillary lesions of the palpebral conjunctivae are characteristic (Fig. 666.2). A stringy exudate and a milky conjunctival pseudomembrane are frequently present. Small elevated lesions of the bulbar conjunctiva adjacent to the limbus (Horner-Trantas dots) may be found. Smear of the conjunctival exudate reveals many eosinophils. Topical corticosteroid therapy and cold compresses afford some relief. Topical mast cell stabilizers or prostaglandin inhibitors are useful when long-term control is needed. The long-term use of corticosteroids should be avoided.

Parinaud Oculoglandular Syndrome

This represents a form of cat-scratch disease and is caused by *Bartonella henselae,* which is transmitted from cat to cat by fleas (see Chapter 255). Kittens are more likely than adult cats to be infected. Humans can become infected when they are scratched by a cat. In addition, bacteria may pass from a cat's saliva to its fur during grooming. The bacteria can then be deposited on the conjunctiva after rubbing one's eyes after handling the cat. Lymphadenopathy and conjunctivitis are hallmarks of the disease. Conjunctival granulomas may develop (Fig. 666.3). The course is generally self-limited, but antibiotics may be used in some cases.

Chemical Conjunctivitis

This can result when an irritating substance enters the conjunctival sac (as in the acute but benign conjunctivitis caused by silver nitrate in newborns). Other common offenders are household cleaning substances (including detergent pods), sprays, smoke, smog, metal halide bulbs, and industrial pollutants. Alkalis tend to linger in the conjunctival tissues and continue to inflict damage for hours or days. Acids precipitate the proteins in tissues and so produce their effect immediately. In either case, prompt, thorough, and copious irrigation is crucial. Extensive tissue damage, even loss of the eye, can result, especially if the offending agent is an alkali.



Fig. 666.2 Vernal conjunctivitis.

OTHER CONJUNCTIVAL DISORDERS

Subconjunctival hemorrhage is manifested by bright or dark red patches in the bulbar conjunctiva and may result from injury or inflammation. It commonly occurs spontaneously. It may occasionally result from severe sneezing or coughing. Rarely, it may be a manifestation of a blood dyscrasia. Subconjunctival hemorrhages are self-limiting and require no treatment.

Pinguecula is a yellowish white, slightly elevated mass on the bulbar conjunctiva, usually in the interpalpebral region (Fig. 666.4). It represents elastic and hyaline degenerative changes of the conjunctiva. No treatment is required except for cosmetic reasons, in which case simple excision suffices.

Pterygium is a fleshy triangular conjunctival lesion that may encroach on the cornea. It typically occurs in the nasal interpalpebral region (Fig. 666.5). The pathologic findings are similar to those

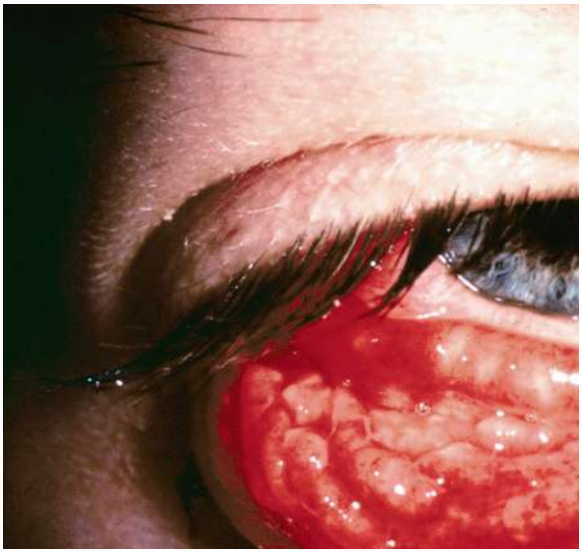

Fig. 666.3 Conjunctival granulomas in Parinaud oculoglandular syndrome.



Fig. 666.4 Pinguecula. These lesions are found at the 3 o'clock and 9 o'clock positions and are extremely common, especially in older patients. *(From Palay DA, Krachmer JH. Primary Care Ophthalmology, 2nd ed, Philadelphia: Elsevier Mosby; 2005: Fig. 3.49, p 62.)*



Fig. 666.5 Pterygium. These lesions are found in the horizontal meridian, most common nasally. *(From Palay DA, Krachmer JH. Primary Care Ophthalmology. 2nd ed. Philadelphia: Elsevier Mosby; 2005: Fig. 3.50, p 62.)*

of a pinguecula. The development of pterygia is related to exposure to ultraviolet light, and it therefore is more commonly found among people who live near the equator. Removal is suggested when the lesion encroaches far onto the cornea. Recurrence after removal is common.

Dermoid cyst and **dermolipoma** are benign lesions, clinically similar in appearance. They are smooth, elevated, round to oval lesions of various sizes. The color varies from yellowish white to fleshy pink. The most frequent site is the upper outer quadrant of the globe; they also commonly occur near or straddling the limbus. Dermolipoma is composed of adipose and connective tissue. Dermoid cysts may also contain glandular tissue, hair follicles, and hair shafts. Excision for cosmetic reasons is feasible. Dermolipomas are often connected to the extraocular muscles, making their complete removal impossible without sacrificing ocular motility.

Conjunctival nevus is a small, slightly elevated lesion that may vary in pigmentation from pale salmon to dark brown. It is usually benign, but careful observation for progressive growth or changes suggestive of malignancy is advised.

Symblepharon is a cicatricial adhesion between the conjunctiva of the lid and the globe; the lower lid is usually affected. It follows operation or injuries, especially burns from lye, acids, or molten metals. It is a serious complication of Stevens-Johnson syndrome. It may interfere with motion of the eyeball and may cause diplopia. The adhesions should be separated and the raw surfaces kept from uniting during healing. Grafts of oral mucous membrane may be necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 667

Abnormalities of the Cornea

Scott E. Olitsky and Justin D. Marsh

MEGALOCORNEA

This is a nonprogressive symmetric condition characterized by an enlarged cornea (>12 mm in diameter) and an anterior segment in which there is *no evidence* of previous or concurrent ocular hypertension (glaucoma). High myopia is frequently present and may lead to reduced vision. A frequent complication is the development of lens opacities in adult life. All modes of inheritance have been described, although X-linked recessive is the most common. Systemic abnormalities that may be associated with megalocornea include Marfan syndrome, craniosynostosis, and Alport syndrome. The cause of the enlargement of the cornea and the anterior segment is unknown, but possible explanations include a defect in the growth of the optic cup and an arrest of congenital glaucoma.

Pathologic corneal enlargement caused by glaucoma is to be differentiated from this anomaly. Any progressive increase in the size of the cornea, especially when accompanied by photophobia, lacrimation, or haziness of the cornea, requires prompt ophthalmologic evaluation.

MICROCORNEA

Microcornea, or anterior microphthalmia, is an abnormally small cornea in an otherwise relatively normal eye. It may be familial, with transmission being dominant more often than recessive. More commonly, a small cornea is just one feature of an otherwise developmentally abnormal or microphthalmic eye; associated defects include colobomas, microphakia, congenital cataract, glaucoma, and aniridia.

KERATOCONUS

This is a disease of unclear pathogenesis characterized by progressive thinning and bulging of the central cornea, which becomes cone shaped. Although familial cases are known, most cases are sporadic. It is a common ocular condition with an incidence of 1 in 2,000 adults. Eye rubbing and contact lens wear have been implicated as pathogenic, but the evidence to support this is equivocal. The incidence is increased in individuals with atopy, Down syndrome, Marfan syndrome, and retinitis pigmentosa.

Most cases are bilateral, but involvement may be asymmetric. The disorder usually presents and progresses rapidly during adolescence; progression then slows and stabilizes when patients reach full growth. Descemet's membrane may occasionally be stretched beyond its elastic breaking point, causing an acute rupture in the membrane with resultant sudden and marked corneal edema (acute hydrops, Fig. 667.1) and decrease in vision. The corneal edema resolves as endothelial cells cover the defective area. Some degree of corneal scarring occurs, but the visual acuity is often better than before the initial incident. Signs of keratoconus include Munson sign (bulging of the lower eyelid on looking downward) and the presence of a Fleischer ring (a deposit of iron in the epithelium at the base of the cone). Glasses and contact lenses are the first step in treating the visual distortion caused by keratoconus. Corneal cross-linking is a procedure using riboflavin and UV light and may arrest the progression of keratoconus. If the cornea vaults too severely for the vision to be corrected with contact lenses, then a corneal transplant must be performed to restore vision.

NEONATAL CORNEAL OPACITIES

Loss of the normal transparency of the cornea in neonates may occur secondary to either intrinsic hereditary or extrinsic environmental causes (Table 667.1).

SCLEROCORNEA

In sclerocornea, the normally translucent cornea is replaced by sclera-like tissue. Instead of a clearly demarcated cornea, white, feathery, often ill-defined, and vascularized tissue develops in the peripheral cornea, appearing to blend with and extend from the sclera. The central cornea is usually clearer, but total replacement of the cornea with sclera may occur. The curvature of the cornea is often flatter, similar to the sclera. Potentially coexisting abnormalities include a shallow anterior chamber, iris abnormalities, and microphthalmos. This condition is usually bilateral. In approximately 50% of cases, a dominant or recessive inheritance has been described. Sclerocornea has been reported in association with numerous systemic abnormalities including limb deformities, craniofacial defects, and genitourinary disorders. In generalized sclerocornea, especially if bilateral, early corneal transplantation should be considered in an effort to provide vision.

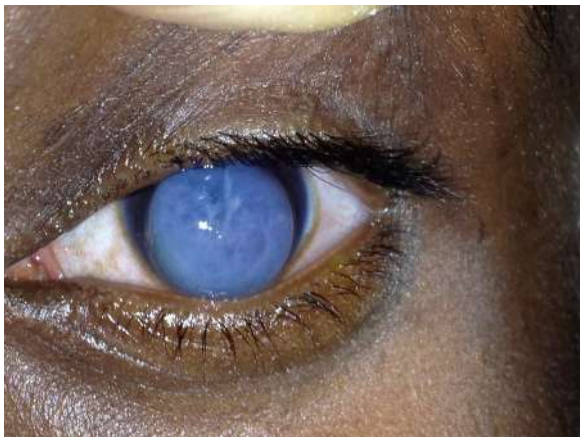

Fig. 667.1 Acute hydrops from keratoconus with significant corneal edema.

Sclerocornea is classified into one of the congenital corneal opacity disorders with cornea plana if it involves peripheral scleralization or a total sclerocornea disorder such as Peters anomaly.

PETERS ANOMALY

Peters anomaly (irido-corneo-trabecular dysgenesis) is a bilateral central corneal opacity (leukoma) that is present at birth (Fig. 667.2). It is often associated with iridocorneal adhesions that extend from the iris collarette to the border of the corneal opacity. Approximately 50% of patients have other ocular abnormalities, which may include cataracts, glaucoma, and microphthalmia. As many as 80% of cases may be bilateral, and 60% are associated with systemic malformations **(Peters plus syndrome)**, which may include short stature, developmental delay, cleft lip and/or palate, dysmorphic facial features, and cardiac, genitourinary, and central nervous system malformations. Peters plus syndrome is an autosomal recessive (*B3GLCT* gene) disorder.

Some investigators have divided Peters anomaly into two types: a mesodermal or neuroectodermal form (type 1), which does not show

Table 667.1 STUMPED: Differential Diagnosis of Neonatal Corneal Opacities

DIAGNOSIS	LATERALITY	OPACITY	OCULAR PRESSURE	OTHER OCULAR ABNORMALITIES	NATURAL HISTORY	INHERITANCE
S—Sclerocornea	Unilateral or bilateral	Vascularized, blends with sclera, clearer centrally	Normal (or elevated)	Cornea plana	Nonprogressive	Sporadic
T—Tears in endothelium and Descemet's membrane						
Birth trauma	Unilateral	Diffuse edema	Normal	Possible hyphema, periorbital ecchymoses	Spontaneous improvement in 1 mo	Sporadic
Infantile glaucoma	Bilateral	Diffuse edema	Elevated	Megalocornea, photophobia and tearing, abnormal angle	Progressive unless treated	Autosomal recessive
U—Ulcers						
Herpes simplex keratitis	Unilateral	Diffuse with geographic epithelial defect	Normal	None	Progressive	Sporadic
Congenital rubella	Bilateral	Disciform or diffuse edema, no frank ulceration	Normal or elevated	Microphthalmos, cataract, pigment epithelial mottling	Stable, may clear	Sporadic
Neurotrophic exposure	Unilateral or bilateral	Central ulcer	Normal	Lid anomalies, congenital sensory neuropathy	Progressive	Sporadic
M—Metabolic (rarely present at birth) (mucopolysaccharidoses IH, IS; mucolipidosis type IV)*	Bilateral	Diffuse haze, denser peripherally	Normal	Few	Progressive	Autosomal dominant
P—Posterior corneal defect	Unilateral or bilateral	Central, diffuse haze or vascularized leukoma	Normal or elevated	Anterior chamber cleavage syndrome	Stable, sometimes early clearing or vascularization	Sporadic, autosomal recessive
E—Endothelial dystrophy						
Congenital hereditary endothelial dystrophy	Bilateral	Diffuse corneal edema, marked corneal thickening	Normal	None	Stable	Autosomal dominant or recessive
Posterior polymorphous dystrophy	Bilateral	Diffuse haze, normal corneal thickness	Normal	Occasional peripheral anterior synechiae	Slowly progressive	Autosomal dominant
Congenital hereditary stromal dystrophy	Bilateral	Flaky, feathery stromal opacities; normal corneal thickness	Normal	None	Stable	Autosomal dominant
D—Dermoid	Unilateral or bilateral	White vascularized mass, hair, lipid arc	Normal	None	Stable	Sporadic

*Mucopolysaccharidosis IH (Hurler syndrome); mucopolysaccharidosis IS (Scheie syndrome).
From Nelson LB, Calhoun JH, Harley RD. *Pediatric Ophthalmology*. 3rd ed. Philadelphia: WB Saunders; 1991, p. 210.



Fig. 667.2 Peters anomaly. Central opacity in a patient with Peters anomaly.

associated lens changes, and a surface ectodermal form (type 2), which does. Histologic findings include a focal absence of Descemet's membrane and corneal endothelium in the region of the opacity. Peters anomaly may be caused by incomplete migration and differentiation of the precursor cells of the central corneal endothelium and Descemet's membrane, or a defective separation between the primitive lens and cornea during embryogenesis. Peters anomaly may be autosomal recessive (*CYP1B1* gene) or autosomal dominant (*FOXC1*, *PAX6*, *PITX2* genes).

CORNEAL DYSTROPHIES

These are rare inherited disorders that may present at birth, during childhood, or during early adulthood with bilateral involvement (although severity may be asymmetric) and that progress with time (Table 667.2). In most, inheritance is autosomal dominant with variable expression; the most common pathogenic variant is in *TGFB1*, which is associated with the granular corneal dystrophy types 1 and 2, as well as lattice corneal dystrophy. Congenital hereditary endothelial dystrophy is both an autosomal recessive and dominant disorder; the recessive form presents at birth and is more severe (Fig. 667.3; see also Table 667.2); three variants are X-linked.

DERMOIDS

Epibulbar dermoids are choristomas. They are often present at birth and may increase in size with age. They occur most frequently in the lower temporal quadrant. They most commonly straddle the limbus and extend into the peripheral cornea (Fig. 667.4). Rarely, they may be confined entirely to the cornea or conjunctiva. Epibulbar (or limbal) dermoids may cause visual disturbance by encroaching on the visual axis or by contributing to the development of astigmatism, which may lead to amblyopia.

A dermoid usually appears as a well-circumscribed, rounded or oval, gray or pinkish-yellow mass with a dry surface from which short hairs may protrude. It may affect only the superficial layers of the cornea, although full-thickness involvement is common. Associated ocular anomalies include eyelid and iris colobomas, microphthalmos, and retinal and choroidal defects. A total of 30% of dermoids are associated with systemic abnormalities. Many of the associated anomalies involve developmental defects of the first branchial arch (vertebral anomalies, dysostosis of the facial bones, ear anomalies and dental anomalies, and Goldenhar syndrome). Epibulbar dermoids are found in 75% of cases of Goldenhar syndrome.

DENDRITIC KERATITIS

Infection of the cornea with the herpes simplex virus produces a characteristic lesion of the corneal epithelium, referred to as a dendrite; it has a branching, treelike pattern that can be demonstrated by fluorescein staining (Fig. 667.5). The acute episode is accompanied by pain, photophobia, tearing, blepharospasm, and conjunctival injection. Specific treatment may include mechanical debridement of the involved corneal epithelium to remove the source of infection and eliminate an antigenic stimulus to inflammation in the adjacent stroma. Medical treatment may include the use of topical trifluridine, topical ganciclovir, or systemic acyclovir/valacyclovir. In addition, a cycloplegic agent is useful to relieve pain from spasm of the ciliary muscle. Overly aggressive topical antiviral treatment itself can be toxic to the cornea and should be avoided. Recurrent infection and deep stromal involvement can lead to corneal scarring and loss of vision.

Topical use of corticosteroids causes exacerbation of superficial herpetic disease of the eye and may lead to corneal perforation; eye drops combining steroids and antibiotics are therefore to be avoided in treatment of red eye, unless there are clear-cut indications for their use and close supervision during therapy.

Infants born to mothers infected with herpes simplex virus should be examined carefully for signs of ocular involvement. Intravenous acyclovir is required for treatment of ocular herpes in newborns.

CORNEAL ULCERS

The usual signs and symptoms are focal or diffuse corneal haze, hyperemia, lid edema, pain, photophobia, tearing, and blepharospasm. It is important to distinguish a corneal ulcer from that of a corneal abrasion. Although a corneal abrasion involves loss of the epithelial layer of the cornea and subsequently stains with topical fluorescein, a corneal ulcer also has underlying stromal infiltration and appears white or hazy on examination. Corneal ulcers can be infectious or noninfectious in origin. **Hypopyon** (pus in the anterior chamber) is common, particularly when the cause is infection. Regardless of cause, corneal ulcers require prompt treatment. Infectious cases result most frequently from contact lens wear and traumatic lesions that become secondarily infected. Although many organisms are capable of infecting the cornea, *Pseudomonas aeruginosa* can be particularly devastating because it can rapidly destroy stromal tissue and lead to corneal perforation. *Neisseria gonorrhoeae* also is particularly damaging to the cornea. Indolent ulcers may be caused by fungi, often in association with the use of contact lenses. In each case, scrapings of the cornea must be studied in an effort to identify the infectious agent and determine the best therapy. Although aggressive local treatment is generally needed to save the eye, systemic treatment may be necessary in some cases as well. Perforation or scarring resulting from corneal ulceration is an important cause of blindness throughout the world and is estimated to be responsible for 10% of blindness in the United States.

Unexplained corneal ulcers in infants and young children should raise the question of a sensory defect, as in Riley-Day or Goldenhar-Gorlin syndrome, or of a metabolic disorder, such as tyrosinemia (Fig. 667.6). Corneal ulceration can also occur as a consequence of severe vitamin deficiencies, such as those seen with malabsorption in cystic fibrosis or restrictive eating disorders. Peripherally located inflammatory ulcers are commonly associated with blepharitis and typically require both topical antibiotic and corticosteroid treatment.

PHLYCTENULES

These are small, yellowish, slightly elevated lesions usually located at the corneal limbus; they may encroach on the cornea and extend centrally. A small corneal ulcer is often found at the head of the advancing lesion, with a fascicle of blood vessels behind the head of the lesion. Although once thought to represent a sign of systemic tuberculin infection, phlyctenular keratoconjunctivitis is a morphologic expression of delayed hypersensitivity to diverse antigens. In children, it commonly occurs as a result of a hypersensitivity reaction to nonpathogenic staphylococcal strains at the eyelid margin. Treatment usually consists of eliminating the underlying disorder, usually staphylococcal blepharitis or meibomianitis, and suppressing the immune response with the use of topical corticosteroid therapy. A superficial stromal pannus and scarring sometimes remain after treatment.

Table 667.2 Corneal Dystrophies Classified According to IC3D, Second Edition

NAME	LOCUS	GENE	INHERITANCE
EPITHELIAL AND SUBEPITHELIAL DYSTROPHIES			
Epithelial basement membrane dystrophy	5q31	*TGFBI*	AD Mostly sporadic
Epithelial recurrent erosion dystrophies	10q25.1	*COL17A1*	AD
Subepithelial mucinous corneal dystrophy	Unknown	Unknown	AD
Meesmann corneal dystrophy	12 q13 17q12	*KRT3* *KRT12*	AD
Lisch epithelial corneal dystrophy	Xp22.3	Unknown	XLD
Gelatinous drop–like corneal dystrophy	1p32	*TACSTD2*	AR
EPITHELIAL—STROMAL *TGFBI* DYSTROPHIES			
Reis-Bückler corneal dystrophy	5q31	*TGFBI*	AD
Thiel-Behnke corneal dystrophy	5q31	*TGFBI*	AD
Lattice corneal dystrophy	5q31	*TGFBI*	AD
Granular corneal dystrophy type 1	5q31	*TGFBI*	AD
Granular corneal dystrophy type 2	5q31	*TGFBI*	AD
STROMAL DYSTROPHIES			
Macular corneal dystrophy	16q22	*CHST6*	AR
Schnyder corneal dystrophy	1p36	*UBIAD1*	AD
Congenital stromal corneal dystrophy	12q21.33	*DCN*	AD
Fleck corneal dystrophy	2q34	*PIKFYVE*	AD
Posterior amorphous corneal dystrophy	12q21.33	*DCN* *KERA* *LUM* *EPYC*	AD
Central cloudy dystrophy of Francois	Unknown	Unknown	AD
Pre-Descemet's corneal dystrophy	Xp22.31 Unknown	*STS* Unknown	XLR (when associated with x-linked ichthyosis) AD (in isolated corneal dystrophy)
ENDOTHELIAL DYSTROPHIES			
Fuchs endothelial corneal dystrophy (FECD)	1p34.3-p32 18q21.2 10p11.22 20p13	*COL8A2* *TCF4* *ZEB1* *SLC4A11*	AD (early-onset FECD)
Posterior polymorphous corneal dystrophy	20p11.2-q11.2 1p34.3-p32.3 10p11.22	Unknown *COL8A2* *ZEB1*	AD
Congenital hereditary endothelial dystrophy	20p13	*SLC4A11*	AR
X-linked endothelial corneal dystrophy	Xq25	Unknown	XLD

IC3D, International Committee for Classification of Corneal Dystrophies; AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant.
From Bitar M, Hara Y, Sethi D, Couser NL. Genetic abnormalities of the cornea. In Couser NL, ed. *Ophthalmic Genetic Diseases*. Elsevier; 2019: Table 5.1, p. 62.

INTERSTITIAL KERATITIS

This denotes nonulcerative inflammation of the corneal stroma. There is a diverse list of causes of interstitial keratitis (IK), including bacterial, viral, parasitic, and inflammatory etiologies (Table 667.3). In the United States, herpesvirus infections and congenital syphilis account for the majority of cases of IK. Although the corneal findings may regress with time, "ghost vessels," which represent the previous vascular changes, and patchy corneal scarring remain and serve as permanent stigmata of the disease.

Cogan syndrome is an autoimmune IK associated with hearing loss and vestibular symptoms. Although its cause is unknown, a systemic vasculitis is suspected. Prompt treatment is required to avoid permanent hearing loss. Both the corneal changes and the auditory involvement may respond to the use of corticosteroids and immunosuppressive agents.

CORNEAL MANIFESTATIONS OF SYSTEMIC DISEASE

Several metabolic diseases produce distinctive corneal changes in childhood. Refractile polychromatic crystals are deposited throughout the cornea in cystinosis (see Chapter 105.4). Corneal deposits producing various degrees of corneal haze also occur in certain types

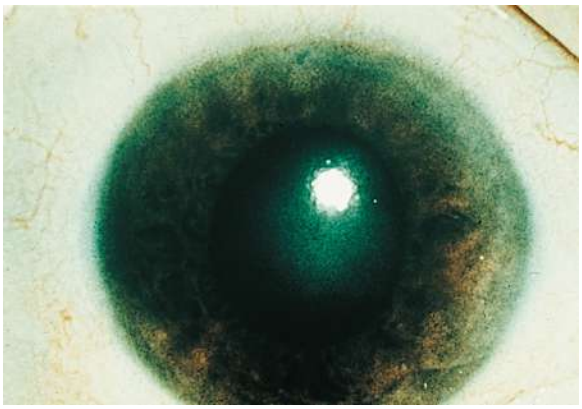

Fig. 667.3 Congenital hereditary endothelial dystrophy. This cornea is markedly edematous but has no enlargement. Intraocular pressure was normal. Patient has since undergone corneal transplantation with excellent results. *(From Stamper RL, Lieberman MF, Drake MV, eds. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. 8th ed. Philadelphia: Mosby; 2009: Fig. 19-21, p. 30).)*



Fig. 667.4 Limbal dermoid. Inferotemporal lesion in a patient with Goldenhar syndrome.

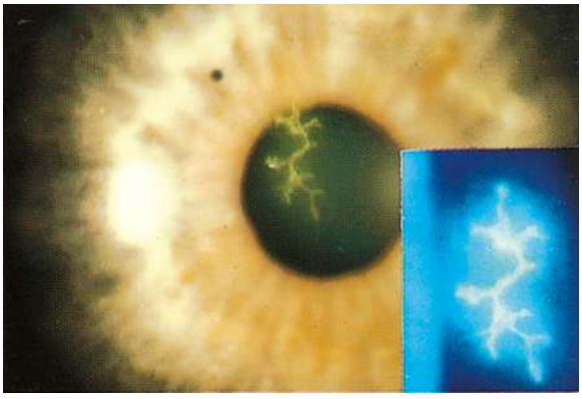

Fig. 667.5 Herpes simplex corneal epithelial keratitis in diffuse light and in light passed through a cobalt blue filter after fluorescein staining *(inset)*. Note the dendritic staining pattern characteristic of herpes simplex. *(From Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 25th ed. Philadelphia: Elsevier; 2016: Fig. 423.19.)*

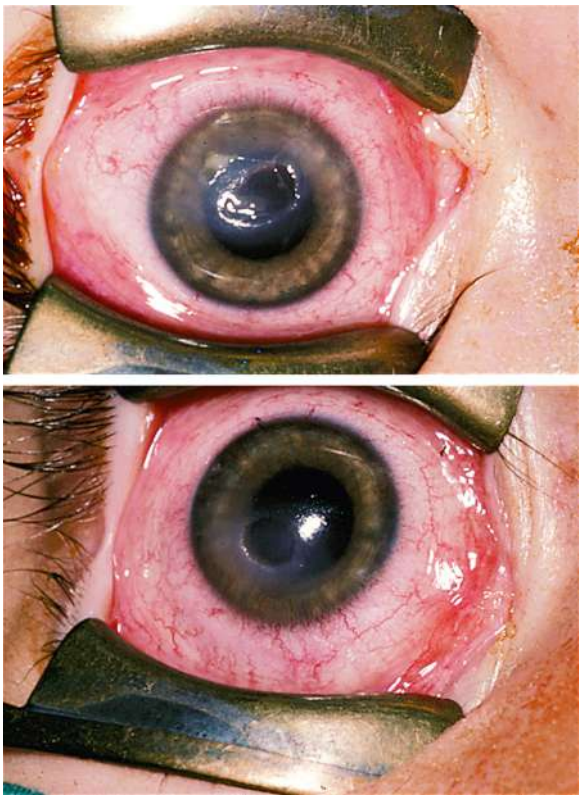

Fig. 667.6 Riley-Day syndrome. This child had a combination of anesthetic corneas and dry eyes that had been treated for several months by topical wetting agents without success. He responded well to a bilateral tarsorrhaphy and lubricant ointment. Later, punctal occlusion allowed enough wetting of his eyes to allow the tarsorrhaphies to be undone. *(From Hoyt CS, Taylor D, eds. Pediatric Ophthalmology and Strabismus, 4th ed. Philadelphia: Elsevier; 2013: Fig. 33.9, p. 315.)*

of mucopolysaccharidosis (MPS; see Chapter 109), particularly MPS IH (Hurler), MPS IS (Scheie), MPS I H/S (Hurler-Scheie compound), MPS IV (Morquio), MPS VI (Maroteaux-Lamy), and sometimes MPS VII (Sly). Corneal deposits may develop in patients with GM_1 (generalized) gangliosidosis (see Chapter 106.4). In Fabry disease, fine opacities radiating in a whorl or fanlike pattern occur, and corneal changes can be important in identifying the carrier state (see Chapter 106.4). A spraylike pattern of corneal opacities may also be seen in the Bloch-Sulzberger syndrome (incontinentia pigmenti; see Chapter 636.7). In Wilson disease (see Chapter 405.2), the distinctive corneal sign is the Kayser-Fleischer ring, a golden-brown ring in the peripheral cornea resulting from changes in Descemet's membrane. Pigmented corneal rings may develop in neonates with cholestatic liver disease. Corneal changes may occur in autoimmune hypoparathyroidism and band keratopathy in patients with hypercalcemia (see Chapters 611 and 613.1). Transient keratitis may occur with measles and sometimes with rubella (see Chapter 294).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 667.3 Partial List of Causative Agents in Microbial Keratitis

BACTERIA

Gram-Positive Cocci

- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae, Streptococcus pyogenes,* viridans streptococci
- *Enterococcus faecalis*
- *Peptostreptococcus* spp.

Gram-Positive Bacilli

- *Bacillus coagulans, Bacillus cereus, Bacillus licheniformis*
- *Brevibacillus (Bacillus) brevis, Brevibacillus (Bacillus) laterosporus*
- *Corynebacterium diphtheriae*
- *Clostridium perfringens, Clostridium tetani*

Gram-Negative Coccobacilli

- *Neisseria gonorrhoeae*
- *Moraxella lacunata, Moraxella nonliquefaciens, Moraxella catarrhalis*
- *Acinetobacter calcoaceticus*
- *Pasteurella multocida*
- *Achromobacter xylosoxidans*

Gram-Negative Bacilli

- *Pseudomonas aeruginosa, Pseudomonas stutzeri, Pseudomonas fluorescens*
- *Burkholderia (Pseudomonas) mallei*
- *Proteus mirabilis*
- *Serratia marcescens*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Morganella morganii*
- *Aeromonas hydrophila*
- *Bartonella henselae*

Mycobacteria

- *Mycobacterium tuberculosis, Mycobacterium chelonae, Mycobacterium gordonae, Mycobacterium mucogenicum*

Actinomycetes

- *Nocardia* spp.

Spirochetes

- *Treponema pallidum*
- *Borrelia burgdorferi*

VIRUSES

- Herpes simplex virus
- Varicella-zoster virus
- Adenovirus
- Vaccinia virus
- Epstein-Barr virus
- Rubeola
- Enteroviruses
- Coxsackievirus

FUNGI

- *Fusarium* spp.
- *Candida* spp.
- *Aspergillus* spp.
- *Acremonium* spp.
- *Alternaria* spp.
- *Penicillium* spp.
- *Bipolaris* spp.
- *Nosema* spp.
- *Vittaforma (Nosema) corneae*
- *Encephalitozoon* spp.
- *Edenia gomezpompae*
- *Exophiala phaeomuriformis*

CHLAMYDIA

- *Chlamydia trachomatis*

PARASITES

- *Acanthamoeba polyphaga, Acanthamoeba castellanii*
- *Onchocerca volvulus*
- *Leishmania brasiliensis*
- *Trypanosoma* spp.

From Azar DT, Hallak J, Barnes SD, et al. Microbial keratitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases.* 9th ed. Saunders; 2020: Table 113.1, p. 1509.

Chapter 668

Abnormalities of the Lens

Scott E. Olitsky and Justin D. Marsh

CATARACTS

A cataract is any opacity of the lens (Fig. 668.1). Some are clinically unimportant; others significantly affect visual function. The incidence of infantile cataracts is approximately 2-13/10,000 live births. Approximately 60% of cataracts are an isolated defect, 22% are part of a syndrome, and the remaining cases are associated with other unrelated major birth defects. Cataracts are more common in low birthweight infants. Infants who weigh at or below 2,500 g have a three- to fourfold increased odds of developing infantile cataracts. Some cataracts are associated with other ocular or systemic diseases.

Differential Diagnosis

The differential diagnosis of cataracts in infants and children includes a wide range of developmental disorders, infectious and inflammatory processes, metabolic diseases, and toxic and traumatic insults (Table 668.1). Cataracts may also develop secondary to intraocular processes, such as retinopathy of prematurity, persistent hyperplastic primary vitreous, retinal detachment, retinitis pigmentosa, and uveitis. Finally, a fraction of cataracts in children are inherited (Fig. 668.2).

Developmental Variants

Early developmental processes may lead to various congenital lens opacities. Discrete dots or white plaquelike opacities of the lens capsule are common and sometimes involve the contiguous subcapsular region. Small opacities of the posterior capsule may be associated with persistent remnants of the primitive hyaloid vascular system (the common Mittendorf dot), whereas those of the anterior capsule may be associated with persistent strands of the pupillary membrane or vascular sheath of the lens. Congenital cataracts of this type are usually stationary and rarely interfere with vision, but in some cases, progression occurs.

Prematurity

A special type of lens change seen in some preterm newborn infants is the so-called *cataract of prematurity*. The appearance is of a cluster of tiny vacuoles in the distribution of the Y sutures of the lens. They can be visualized with an ophthalmoscope and are best seen with the pupil well dilated. The pathogenesis is unclear. In most cases, the opacities disappear spontaneously, often within a few weeks.

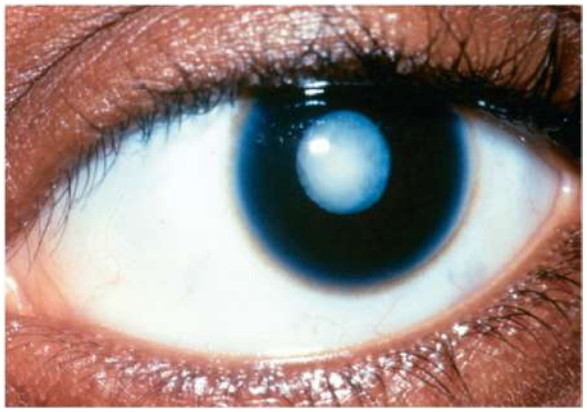

Fig. 668.1 Leukocoria secondary to cataract.

Mendelian Inheritance

Many isolated, idiopathic cataracts unassociated with other diseases are hereditary. There are ~35 genes associated with isolated pediatric cataracts; ~40% are inherited as autosomal dominants, ~20% are autosomal recessive, and ~35% have both dominant and recessive traits. Twelve crystallin gene pathologic variants are the most frequently identified genetic etiologies for both autosomal dominant and recessive inheritance patterns. Other involved genes include transcription factors, membrane proteins, and cytoskeletal proteins.

Congenital Infection Syndrome

Cataracts in infants and children can be a result of prenatal infection. Lens opacity may occur in any of the major congenital infection syndromes (e.g., toxoplasmosis, cytomegalovirus, syphilis, rubella, herpes simplex virus). Cataracts may also occur secondary to other perinatal infections, including measles, poliomyelitis, influenza, varicella-zoster, and vaccinia.

Metabolic Disorders

Cataracts are a prominent manifestation of many metabolic diseases, particularly certain disorders of carbohydrate, amino acid, calcium, and copper metabolism. A primary consideration in any infant with cataracts is the possibility of **galactosemia** (see Chapter 107.2). In classic infantile galactosemia, galactose-1-phosphate uridyltransferase deficiency, the cataract is typically of the zonular type, with haziness or opacification of one or more of the perinuclear layers of the lens. Haziness or clouding of the nucleus also often occurs. In its early stages, the cataract generally has a distinctive oil droplet appearance and is best detected with the pupil fully dilated. Progression to complete opacification of the lens may occur within weeks. With early treatment (galactose-free diet), the lens changes may be reversible.

In **galactokinase deficiency**, cataracts are the sole clinical manifestation. The cataracts are usually zonular and may appear in the first few months of life, first few years of life, or later in childhood.

In children with juvenile-onset diabetes mellitus, lens changes are uncommon. Some develop snowflake-like white opacities and vacuoles of the lens. Others develop cataracts that may progress and mature rapidly, sometimes in a matter of days, especially during adolescence. An antecedent event may be the sudden development of myopia caused by changes in the optical density of the lens. Congenital lens opacities may be seen in children of diabetic and prediabetic mothers (see Chapter 147).

Hypoglycemia in neonates can also be associated with early development of cataracts. Ketotic hypoglycemia is also associated with cataracts.

An association between cataracts and hypocalcemia is well established. Various lens opacities may be seen in patients with hypoparathyroidism (see Chapter 611).

The **oculocerebral renal syndrome of Lowe** is associated with cataracts in infants. Affected male children frequently have dense bilateral cataracts at birth, often in association with glaucoma and miotic pupils. Punctate lens opacities are frequently present in heterozygous females.

The distinctive sunflower cataract of **Wilson disease** is not commonly seen in children. Various lens opacities may be seen in children with certain of the sphingolipidoses, mucopolysaccharidoses, and mucolipidoses, particularly Niemann-Pick disease, mucosulfatidosis, Fabry disease, and aspartylglycosaminuria.

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive metabolic storage disease involving a pathogenic variant in an enzyme used during bile acid synthesis, leading to accumulation of cholesterol in the brain and elsewhere. In addition to cataract formation in childhood, patients may develop chronic diarrhea in infancy and progressive cognitive and neurologic impairment later in life. Early detection is vital as cataract formation may occur before permanent neurologic impairment, providing a window of time to treat the condition. Treatment typically consists of oral chenodeoxycholic acid.

Table 668.1 Differential Diagnosis of Cataracts

DEVELOPMENTAL VARIANTS
Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity
Mittendorf dot (remnant of hyaloid artery)
Persistent pupillary membrane (remnant of embryonic lens vasculature)

GENETIC DISORDERS
Simple Mendelian Inheritance
Autosomal dominant (most common)
Autosomal recessive
X-linked

Major Chromosomal Defects
Trisomy disorders (13, 15, 18, 21)
Turner syndrome (45X)
Deletion syndromes (1p36, 1q43-44, 5p, 11p13, 18p, 18q, 22q11.2)
Duplication syndromes (3q, 20p, 10q)

Multisystem Syndromic Disorders
Alport syndrome (hearing loss, renal disease)
Alström syndrome (nerve deafness, diabetes mellitus)
Apert disease (craniosynostosis, syndactyly)
Branchiooculofacial syndrome
Cerebrooculofacial skeletal syndrome
Cockayne syndrome (premature senility, skin photosensitivity)
Congenital cataracts–facial dysmorphism–neuropathy (CCFDN) syndrome
Conradi disease (chondrodysplasia punctata)
Crouzon disease (dysostosis craniofacialis)
Ectodermal dysplasia
Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, and hypotrichosis)
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis)
Ichthyosis (keratinizing disorder with thick, scaly skin)
Incontinentia pigmenti (dental anomalies, mental retardation, cutaneous lesions)
Laurence Moon Bardet Biedl Syndrome
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease)
Marfan syndrome
Meckel-Gruber syndrome (renal dysplasia, encephalocele)
Myotonic dystrophy
Nail-patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella)
Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia)
Martsolf syndrome
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood)
Norrie disease
Oculofaciocardiodental syndrome
Progeria
Rothmund-Thomson syndrome (poikiloderma: skin atrophy)
Rubinstein-Taybi syndrome (broad great toe, mental retardation)
Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation)
Sotos syndrome (cerebral gigantism)
Spondyloepiphyseal dysplasia (dwarfism, short trunk)
Warburg-Micro syndrome types 1-4
Werner syndrome (premature aging in second decade of life)

INBORN ERRORS OF METABOLISM
Abetalipoproteinemia (absent chylomicrons, retinal degeneration)
Fabry disease (α-galactosidase A deficiency)
Galactokinase deficiency
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Homocystinemia (subluxation of lens, mental retardation)
Infantile neuronal ceroid lipofuscinosis
Mannosidosis (acid α-mannosidase deficiency)
Niemann-Pick disease (sphingomyelinase deficiency)
Refsum disease (phytanic acid α-hydrolase deficiency)
Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms)
Zellweger syndrome

ENDOCRINOPATHIES
Albright hereditary osteodystrophy
Hypocalcemia (hypoparathyroidism)
Hypoglycemia
Diabetes mellitus

CONGENITAL INFECTIONS
Toxoplasmosis
Cytomegalovirus infection
Syphilis
Rubella
Perinatal herpes simplex infection
Measles (rubeola)
Poliomyelitis
Influenza
Varicella-zoster

OCULAR ANOMALIES
Peters' anomaly (corneal opacifications with iris-corneal dysgenesis)
Rieger syndrome (iris dysplasia, myotonic dystrophy)
Microphthalmia
Coloboma
Aniridia
Mesodermal dysgenesis
Norrie disease
Posterior lenticonus
Persistent hyperplastic primary vitreous
Primitive hyaloid vascular system
Retinitis pigmentosa

MISCELLANEOUS DISORDERS
Atopic dermatitis
Drugs (corticosteroids)
Radiation
Trauma
Juvenile idiopathic arthritis
Retinopathy of prematurity
Spherocytosis

IDIOPATHIC

Chromosomal Defects

Lens opacities of various types may occur in association with chromosomal defects, including trisomies 13, 18, and 21; Turner syndrome; and a number of deletion and duplication syndromes (Table 668.1).

Drugs, Toxic Agents, and Trauma

Of the various drugs and toxic agents that may produce cataracts, corticosteroids are of major importance in the pediatric age group. Steroid-related cataracts characteristically are posterior subcapsular lens opacities. The incidence and severity vary. The relative significance of dose, mode of administration, duration of treatment, and individual susceptibility is controversial, and the pathogenesis of steroid-induced cataracts is unclear. The effect on vision depends on the extent and density of the opacity. In many cases, the acuity is only minimally or moderately impaired. Reversibility of steroid-induced cataracts may occur in some cases. All children receiving long-term steroid treatment should have periodic eye examinations.

Trauma to the eye is a major cause of cataracts in children (Fig. 668.3). Opacification of the lens may result from blunt or penetrating injury. Cataracts can be an important manifestation of child abuse.

Cataract formation after exposure to therapeutic radiation is dose and duration dependent. Adult research shows 50% occurrence in lens dose of 15 Gy. Delayed onset is the rule.

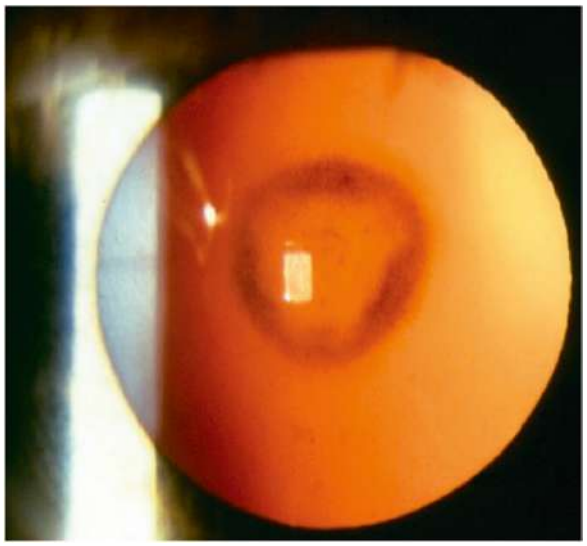

Fig. 668.2 Central lamellar cataract.

Miscellaneous Disorders

The list of multisystem syndromes and diseases associated with lens opacities and other eye anomalies is extensive (see Table 668.1).

Treatment

The treatment of cataracts that significantly interfere with vision includes the following: (1) surgical removal of lens material to provide an optically clear visual axis; (2) correction of the resultant aphakic refractive error with spectacles, contact lenses, or intraocular lens implantation; and (3) correction of any associated sensory deprivation amblyopia. Because the use of spectacles may not be possible in children after cataract removal, the use of contact lenses for visual rehabilitation is sometimes a medical necessity. Intraocular lens implantation is the mainstay for visual rehabilitation in children 2 years or older. A multicenter trial studied the visual outcomes in very young children treated with a contact lens versus an intraocular lens implant. One year after treatment, the children randomized into the intraocular lens implant group had more intraoperative complications, adverse events, and need for additional intraocular surgery. Although the median visual acuity was better in the contact lens group, the difference did not reach statistical significance. Treatment of the amblyopia may be the most demanding and difficult step in the visual rehabilitation of infants or children with cataracts. Not all cataracts require surgical intervention. Cataracts that are not visually significant should be monitored for change, and the child should be monitored for the development of amblyopia.

Prognosis

Prognosis depends on many factors, including the nature of the cataract, the underlying disease, age at onset, age at intervention, duration and severity of any attendant amblyopia, and presence of any associated ocular abnormalities (e.g., microphthalmia, retinal lesions, optic atrophy, glaucoma, nystagmus, and strabismus). Persistent amblyopia is the most common cause of poor visual recovery after cataract surgery in children. Secondary conditions and complications may develop in children who have had cataract surgery, including inflammatory sequelae, secondary membranes, glaucoma, retinal detachment, and changes in the axial length of the eye. All of these should be considered in planning treatment.

ECTOPIA LENTIS

Normally the lens is suspended in place behind the iris diaphragm by the zonular fibers of the ciliary body. Abnormalities of the suspensory system resulting from a developmental defect, disease, or trauma may result in instability or displacement of the lens. Displacement of the lens is classified as luxation, which is complete displacement of the lens (also known as dislocation) (Fig. 668.4), or as subluxation, which is a partial displacement (Fig. 668.5). Symptoms include blurring of vision, which is often the result of refractive changes such as myopia, astigmatism, or aphakic hyperopia. Some patients experience diplopia (double vision). An important sign of displacement is **iridodonesis**, a tremulousness of the iris caused by the loss of its usual support. Also, the anterior chamber may appear deeper than normal. Sometimes the equatorial region ("edge") of the displaced lens may be visible in the pupillary aperture. On ophthalmoscopy, this may appear as a black crescent. Also, the difference between the phakic and aphakic portions can be appreciated when focusing on the fundus.

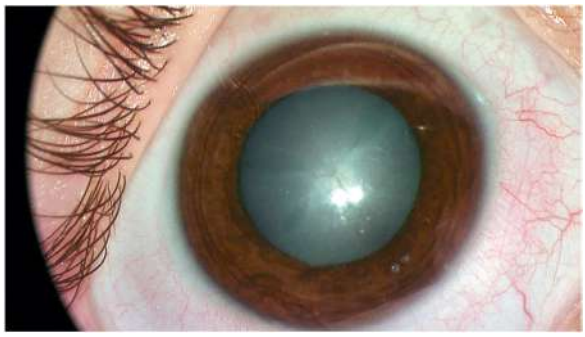

Fig. 668.3 Diffuse cataract related to blunt trauma.

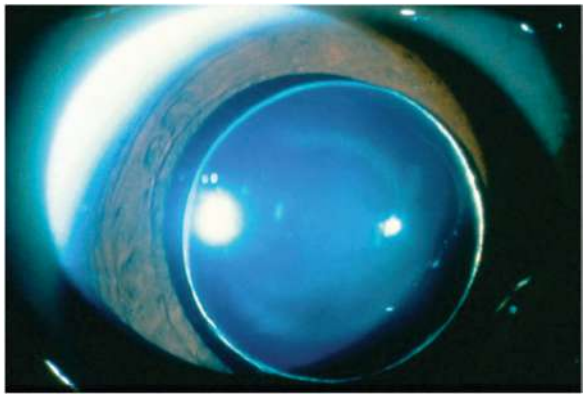

Fig. 668.4 Complete dislocation of lens into the anterior chamber seen in Weill-Marchesani syndrome.

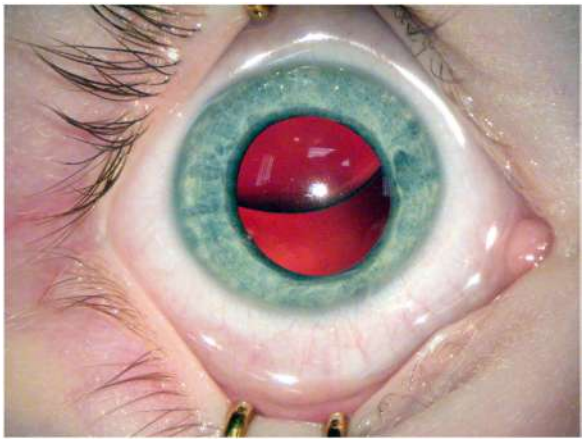

Fig. 668.5 Marfan syndrome. Upward lens subluxation. *(From Hoyt CS, Taylor D. Pediatric Ophthalmology and Strabismus. 4th ed. Philadelphia: Elsevier; 2013: Fig. 35.9A, p. 333.)*

Differential Diagnosis

A major cause of lens displacement is trauma. Displacement may also occur as a result of ocular disease, such as uveitis, intraocular tumor, congenital glaucoma, high myopia, megalocornea, or aniridia, or in association with cataract. Ectopia lentis may also be inherited or associated with systemic disease.

Displacement of the lens occurring as a heritable ocular condition unassociated with systemic abnormalities is referred to as *simple ectopia lentis*. Simple ectopia lentis is usually transmitted as an autosomal dominant condition. The lens is generally displaced upward and temporally. The ectopia may be present at birth or may appear later in life. Another form of heritable dislocation is ***ectopia lentis et pupillae*** (see Chapter 662). In this condition, both the lens and pupil are displaced, usually in opposite directions. This condition is generally bilateral, with one eye being almost a mirror image of the other. *Ectopia lentis et pupillae* is an autosomal recessive condition, although variable expression with some intermingling with simple ectopia lentis has been reported.

Systemic disorders associated with displacement of the lens include Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, and sulfite oxidase deficiency. Ectopia lentis occurs in approximately 80% of patients with Marfan syndrome. In approximately 50% of patients with Marfan syndrome, the ectopia is evident by 5 years of age. In most cases, the lens is displaced superiorly and temporally; it is almost always bilateral and relatively symmetric. In homocystinuria, the lens is usually displaced inferiorly and somewhat nasally. The subluxation of the lens occurs early in life and is often evident by 5 years of age. In Weill-Marchesani syndrome, the displacement of the lens is often downward and forward, and the lens tends to be small and round.

Ectopia lentis is also associated occasionally with other conditions, including Ehlers-Danlos, Sturge-Weber, Crouzon, and Klippel-Feil syndromes; oxycephaly; and mandibulofacial dysostosis. A syndrome of dominantly inherited blepharoptosis, high myopia, and ectopia lentis has also been described.

Treatment and Prognosis

Displacement of the lens often results only in optical problems. In some cases, however, more serious complications may develop, such as glaucoma, uveitis, retinal detachment, or cataract. Management must be individualized according to the type of displacement, its cause, and the presence of any complicating ocular or systemic conditions. For many patients, optical correction by spectacles or contact lenses can be provided. Manipulation of the iris diaphragm with mydriatic or miotic drops may sometimes help improve vision. In selected cases, the best treatment is surgical removal of the lens. In many children, treatment of any associated amblyopia must be instituted early. In addition, for children with ectopia lentis, safety precautions should be taken to prevent injury to the eye.

OTHER DISORDERS OF THE LENS

Microspherophakia

The term *microspherophakia* refers to a small, round lens that may occur as an isolated anomaly (probably autosomal recessive) or in association with other ocular abnormalities, such as ectopia lentis, myopia, or retinal detachment (possibly autosomal dominant). Microspherophakia may also occur in association with various systemic disorders, including Marfan syndrome, Weill-Marchesani syndrome, Alport syndrome, mandibulofacial dysostosis, and Klinefelter syndrome.

Anterior Lenticonus

Anterior lenticonus is a rare bilateral condition in which the anterior capsule of the lens thins, allowing the lens to bulge forward centrally. It may be accompanied by lens opacities or other eye anomalies and is a prominent feature of Alport syndrome. The increased curvature of the central area may cause high myopia. Spontaneous rupture of the anterior capsule may occur, requiring prompt surgical intervention.

Posterior Lenticonus

Posterior lenticonus, which occurs more commonly than anterior lenticonus, is characterized by a circumscribed round or oval bulge of the posterior lens capsule and cortex, involving the central region of the lens. In the early stages, by the red reflex test, this may look like an oil droplet. It occurs in infants and young children and tends to increase with age. Usually the lens material within and surrounding the capsular bulge eventually becomes opacified. Posterior lenticonus usually occurs as an isolated ocular anomaly. It is generally unilateral but may be bilateral. It is believed to be sporadic, although autosomal dominant and X-linked inheritance has been suggested in some cases. Infants or children with posterior lenticonus may require optical correction, amblyopia treatment, and surgery for progressive cataract.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 669

Disorders of the Uveal Tract

Scott E. Olitsky and Justin D. Marsh

UVEITIS (IRITIS, CYCLITIS, CHORIORETINITIS)

The uveal tract (the inner vascular coat of the eye, consisting of the iris, ciliary body, and choroid) (Fig. 669.1) is subject to inflammatory involvement in numerous systemic diseases, both infectious and noninfectious, and in response to exogenous factors, including trauma and toxic agents (Table 669.1). Inflammation may affect any one portion of the uveal tract preferentially or all parts together. Uveitis may be classified as anterior (iris, ciliary body), intermediate (vitreous-choroid locations), posterior (choroid, retina) or panuveitis, with subclassification as infectious, inflammatory, or systemic disease associated and eye limited.

Iritis may occur alone or in conjunction with inflammation of the ciliary body as iridocyclitis or in association with pars planitis. Pain, photophobia, and lacrimation are the characteristic symptoms of acute anterior uveitis, but the inflammation may develop insidiously without disturbing symptoms. Signs of anterior uveitis include conjunctival hyperemia, particularly in the perilimbal region (ciliary flush), and cells and protein ("flare") in the aqueous humor (Figs. 669.2 and 669.3). Inflammatory deposits on the posterior surface of the cornea (keratic precipitates) and congestion of the iris may also be seen. More chronic cases may show degenerative changes of the cornea (band keratopathy), lenticular opacities (cataract), development of glaucoma, and impairment of vision. The cause of anterior uveitis is often idiopathic; primary considerations in children are rheumatoid disease, particularly pauciarticular arthritis, Kawasaki disease, postinfectious reactive arthritis syndrome, tubulointerstitial nephritis (TINU), HLA-B27 associated syndromes, and sarcoidosis. Iritis may be secondary to corneal disease, such as herpetic keratitis or a bacterial or fungal corneal ulcer, or to a corneal abrasion or foreign body. Traumatic iritis and iridocyclitis are especially common in children.

Iridocyclitis that occurs in children with juvenile idiopathic arthritis deserves special mention. Unlike most forms of anterior uveitis, it rarely creates pain, photophobia, or conjunctival hyperemia. Loss of vision may not be noticed until severe and irreversible damage has occurred. Because of the lack of symptoms and the high incidence of uveitis in these children, routine periodic screening is necessary. Ophthalmic screening guidelines are based on 3 factors that predispose children with arthritis to uveitis (Fig. 669.4):

1. Type of arthritis
2. Age of onset of arthritis
3. Antinuclear antibody (ANA) status

Choroiditis, inflammation of the posterior portion of the uveal tract, invariably also involves the retina; when both are obviously affected, the condition is termed *chorioretinitis*. The causes of posterior uveitis are numerous; the more common are toxoplasmosis, histoplasmosis, cytomegalovirus, sarcoidosis, syphilis, tuberculosis, and toxocariasis

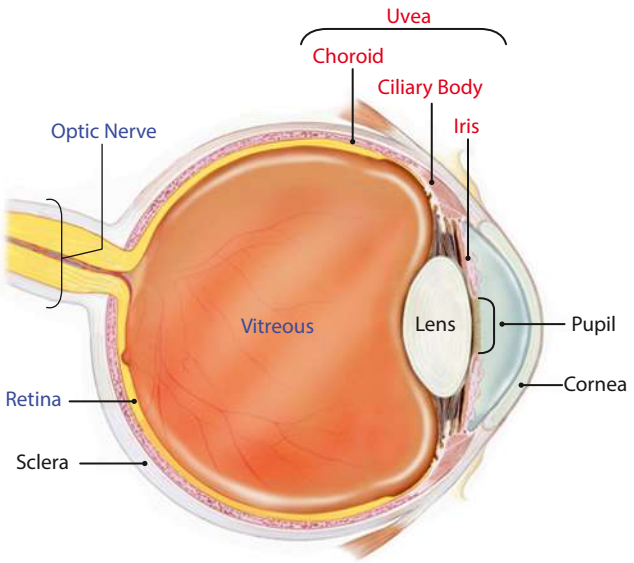

Fig. 669.1 Anatomic locations for uveitis. *(From National Eye Institute: Uveitis. Courtesy National Eye Institute, National Institutes of Health, Bethesda, Maryland.* https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/uveitis*)*

(Fig. 669.5). Depending on the etiology, the inflammatory signs may be diffuse or focal. Vitreous reaction often occurs as well. With many types, the result is atrophic chorioretinal scarring demarcated by pigmentation, often with visual impairment. Secondary complications include retinal detachment, glaucoma, and phthisis.

Panophthalmitis is inflammation involving all parts of the eye. It is frequently suppurative, most often as a result of a perforating injury or of septicemia. It produces severe pain, marked congestion of the eye, inflammation of the adjacent orbital tissues and eyelids, and loss of vision. In many cases, the eye is lost despite intensive treatment of the infection and inflammation. Enucleation of the eye or evisceration of the orbit may be necessary.

Sympathetic ophthalmia is a rare type of uveal inflammatory response that affects the uninjured eye after a perforating injury to the other eye. It may occur weeks, months, or even years after the injury. A hypersensitivity phenomenon is the most probable cause. Loss of vision in the uninjured (sympathizing) eye may result. Removal of the injured eye prevents the development of sympathetic ophthalmia but does not stop the progression of the disease once it has occurred. High-dose intravenous methylprednisolone is the initial treatment of choice. Immune therapy (immune suppression or modulators) may need to be added to steroids; these agents include cyclosporine, azathioprine, mycophenolate mofetil, cytoxan and TNF-alpha blocking agents (infliximab, adalimumab).

Treatment

The various forms of intraocular inflammation are treated according to their underlying systemic causal factors. When infection is proved or suspected, appropriate systemic antimicrobial or antiviral therapy is used. In some cases, intravitreal injection is indicated.

Elimination of the intraocular inflammation is important to reduce the risk of severe, and often permanent, vision loss. Untreated, the inflammatory process may lead to the development of band keratopathy (calcium deposition in the cornea), cataracts, glaucoma, and irreversible retinal damage. Anterior inflammation may respond well to topical corticosteroid treatment. Posterior cases often require systemic therapy. The use of topical and systemic corticosteroids can lead to the development of glaucoma and cataracts. To reduce the need for topical and systemic corticosteroids, systemic immunosuppression is often used in patients requiring long-term treatment. Immunosuppressive agents include methotrexate, cyclosporine, and tumor necrosis factor inhibitors. Multiple agents may be needed in recalcitrant cases.

Table 669.1 Uveitis in Childhood

ANTERIOR UVEITIS
Juvenile idiopathic arthritis (pauciarticular)
Sarcoidosis including Blau syndrome
Trauma
Tuberculosis
Kawasaki disease
MIS-C
Ulcerative colitis
Crohn syndrome
HLA-B27 associated
Reactive postinfectious (enteric or genital) with arthritis and rash
Spirochetal (syphilis, leptospiral)
Lyme disease
Brucellosis
Heterochromic iridocyclitis (Fuchs)
Viral (herpes simplex, herpes zoster)
Ankylosing spondylitis
Stevens-Johnson syndrome
Chronic infantile neurologic cutaneous arthritis syndrome (CINCA)
Familial Mediterranean fever
Hyperimmunoglobulin D syndrome
Tumor necrosis factor receptor–associated periodic syndrome
Muckle-Wells syndrome
Celiac disease
Psoriasis
Multiple sclerosis
Cyclic neutropenia
Chronic granulomatous disease
X-linked lymphoproliferative disease
Hypocomplementemic vasculitis
Tubulointerstitial nephritis and uveitis syndrome
Idiopathic
Drugs (rifabutin, anti-tumor necrosis factor agents, interferon)
INTERMEDIATE AND POSTERIOR UVEITIS (CHOROIDITIS—MAY INVOLVE RETINA)
Toxoplasmosis
Toxocariasis
Sarcoidosis including Blau syndrome
Cat-scratch disease
Tuberculosis
Histoplasmosis
Viral (rubella, herpes simplex, HIV, cytomegalovirus, West Nile)
Subacute sclerosing panencephalitis
Tubulointestinal nephritis and uveitis syndrome
Diffuse unilateral subacute neuroretinitis (DUSN) secondary to *Ancylostoma caninum* or *Baylisascaris procyonis*
Idiopathic
ANTERIOR AND/OR POSTERIOR (PAN) UVEITIS
Sympathetic ophthalmia (trauma to other eye)
Vogt-Koyanagi-Harada syndrome (uveootocutaneous syndrome: poliosis, vitiligo, alopecia, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)
Behçet syndrome
Juvenile xanthogranulomatosis
Lyme disease
Sarcoidosis
UVEO-MENINGEAL SYNDROMES
Vogt-Koyanagi-Harada disease
Behçet
Sarcoidosis
Granulomatosis with polyangiitis
Cat-scratch disease
Whipple disease
Syphilis
Lyme disease
Acute posterior multifocal placoid pigment epitheliopathy
Lymphoma, leukemia
Herpes simplex
Cytomegalovirus

MIS-C, Multisystem inflammatory system in children associated with COVID-19

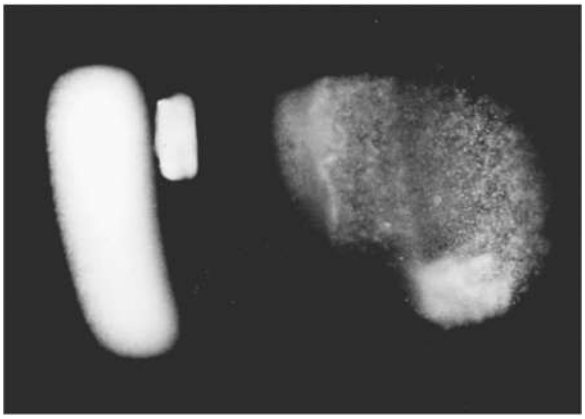

Fig. 669.2 Cell and flare in the anterior chamber. The flare represents protein leakage. *(Courtesy Peter Buch, CRA.)*

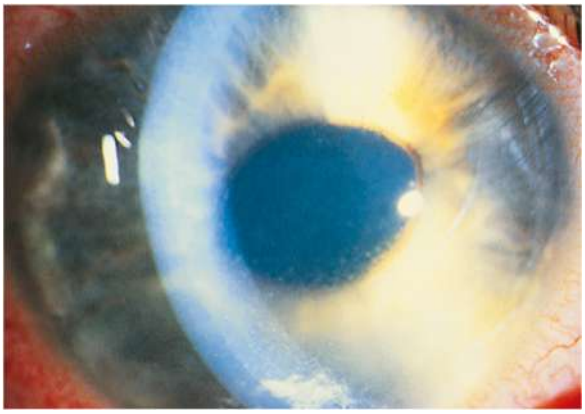

Fig. 669.3 Iritis. Conjunctival injection is most marked immediately around the cornea (ciliary flush). *(From Zitelli BJ, McIntire SC, Nowald AJ, Garrison J, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis. 8th ed. Philadelphia: Elsevier; 2023: Fig. 20.88, p. 721)*

Noninfectious inflammatory uveitis in adolescents has been treated with adalimumab, a human antitumor necrosis factor-α monoclonal antibody resulting in improved vision, lack of disease progression, and an ability to wean steroids. Cycloplegic agents, particularly atropine, are also used to reduce inflammation and to prevent adhesion of the iris to the lens (posterior synechiae), especially in anterior uveitis. Extensive posterior synechiae formation can lead to acute angle closure glaucoma. Other complications are noted in Table 669.2.

Surgery may be required for patients who develop glaucoma because of the underlying disease process or the need for corticosteroid treatment. Cataract surgery should be delayed until the inflammation has been under control for a period of time. Cataract surgery in children with a history of prolonged uveitis can carry significant risk. There is no universal agreement concerning the use of intraocular lenses in these patients.

Pars planitis is an uncommon idiopathic form of intermediate uveitis characterized by anterior chamber involvement, anterior vitreous cells and condensations, and peripheral retinal vasculitis. The average age of onset is 9 years. It is predominately bilateral and seen more frequently in males. Painless decreased vision is the usual presenting sign. The prognosis is good when adequate medical treatment is sought early in the course of the disease.

Masquerade syndromes can sometimes mimic intraocular inflammation. Retinoblastoma, leukemia, retained intraocular foreign body, juvenile xanthogranuloma, and peripheral retinal detachments may produce signs similar to those seen in uveitis. These syndromes should be kept in mind when evaluating a patient with suspected uveitis or if a patient does not respond as anticipated to appropriate treatment.

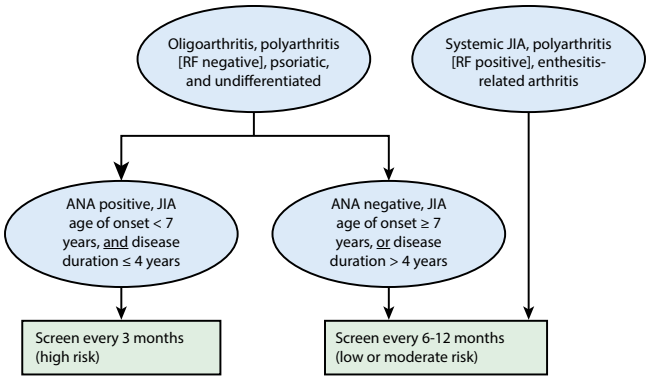

Fig. 669.4 Ophthalmology screening recommendations. ANA, Antinuclear antibody; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor. *(From Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. Arthritis Care Res (Hoboken). 2019;71:703–716.)*

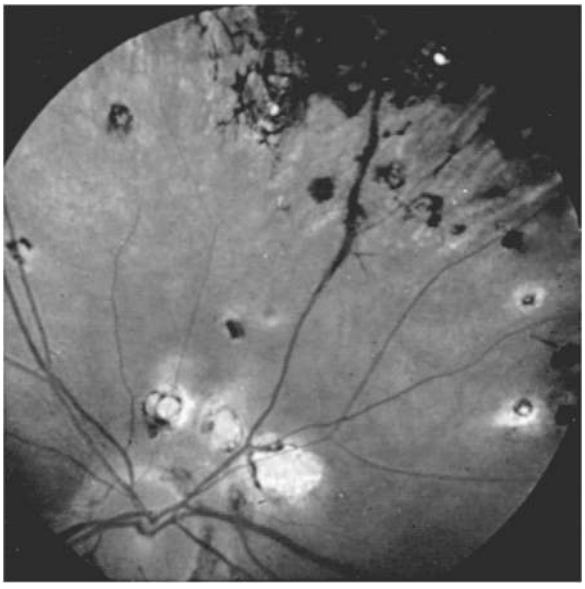

Fig. 669.5 Focal atrophic and pigmented scars of chorioretinitis.

Table 669.2 Comorbidities and Complications of Uveitis in Pediatric Group

Band keratopathy
Posterior synechia
Peripheral anterior synechia
Cataract
Ocular hypertension
Glaucoma
Ocular hypotension
Cystoid macular edema (CME)
Vitreous hemorrhage
Tractional and rhegmatogenous retinal detachment
Epiretinal membrane
Neovascularization of cornea
Neovascular or fibrovascular proliferation on retina or in vitreous
Phthisis bulbi

From Maleki A, Anesi SD, Look-Why S, Manhapra A, Foster CS. Pediatric uveitis: A comprehensive review. *Surv Ophthalmol.* 2022;67(2):510–529. Table 4.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 670

Disorders of the Retina and Vitreous

Scott E. Olitsky and Justin D. Marsh

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in infants born prematurely. It may be acute (early stages) or chronic (late stages). Clinical manifestations range from mild, usually transient changes of the peripheral retina to severe progressive vasoproliferation, scarring, and potentially blinding retinal detachment. ROP includes all stages of the disease and its sequelae.

Pathogenesis

Beginning at 16 weeks of gestation, retinal angiogenesis normally proceeds from the optic disc to the periphery, reaching the outer rim of the retina (ora serrata) nasally at about 36 weeks and extending temporally by approximately 40 weeks. Injury to this process results in various pathologic and clinical changes. The first observation in the acute phase is cessation of vasculogenesis. Rather than a gradual transition from a vascularized to avascular retina, there is an abrupt termination of the vessels marked by a line in the retina. The line may then grow into a ridge composed of mesenchymal and endothelial cells. Cell division and differentiation may later resume, and vascularization of the retina may proceed. Alternatively, there may be progression to an abnormal proliferation of vessels out of the plane of the retina, into the vitreous, and over the surface of the retina. Cicatrization and traction on the retina may follow, leading to retinal detachment.

The risk factors associated with ROP are not fully known, but prematurity and the associated retinal immaturity at birth represent the major factors. Oxygenation, respiratory distress, apnea, bradycardia, heart disease, infection, hypercarbia, acidosis, anemia, and the need for transfusion are thought by some to be contributory factors. Generally, the lower the gestational age, the lower the birthweight, and the sicker the infant, the greater the risk for ROP.

The basic pathogenesis of ROP is still unknown. Exposure to the extrauterine environment, including the necessarily high inspired oxygen concentrations, produces cellular damage, perhaps mediated by free radicals. Later in the course of the disease, peripheral hypoxia develops and vascular endothelial growth factors (VEGFs) are produced in the nonvascularized retina. These growth factors stimulate abnormal vasculogenesis, causing neovascularization to occur. Because of poor pulmonary function, a state of relative retinal hypoxia occurs. This causes upregulation of VEGF, which, in susceptible infants, can cause abnormal fibrovascular growth. This neovascularization may then lead to scarring and loss of vision.

Classification

The international classification of ROP describes the location, extent, and severity of the disease. To delineate location, the retina is divided into three concentric zones centered on the optic disc (Fig. 670.1). Zone I, the posterior or inner zone, extends twice the disc-macular distance, or 30 degrees in all directions from the optic disc. Zone II, the middle zone, extends from the outer edge of zone I to the ora serrata nasally and to the anatomic equator temporally. Zone III, the outer zone, is the residual crescent that extends from the outer border of zone II to the ora serrata temporally. The extent of involvement is described by the number of circumferential clock hours involved.

The phases and severity of the disease process are classified into five stages. Stage 1 is characterized by a demarcation line that separates vascularized from avascular retina. This line lies within the plane of the retina and appears relatively flat and white. Often noted is abnormal branching or arcading of the retinal vessels leading into the line. Stage 2 is characterized by a ridge; the demarcation line has grown, acquiring height, width, and volume and extending up and out of the plane of the retina. Stage 3 is characterized by the presence of a ridge and the development of extraretinal fibrovascular tissue (Fig. 670.2A). Stage 4 is characterized by subtotal retinal detachment caused by traction from the proliferating tissue in the vitreous or on the retina. Stage 4 is subdivided into two phases: (1) subtotal retinal detachment not involving the macula and (2) subtotal retinal detachment involving the macula. Stage 5 is total retinal detachment.

When signs of posterior retinal vascular changes accompany the active stages of ROP, the term *plus disease* is used (see Fig. 670.2B and C). Patients reaching the point of dilation and tortuosity of the retinal vessels also frequently demonstrate the associated findings of engorgement of the iris, pupillary rigidity, and vitreous haze.

The Early Treatment for Retinopathy of Prematurity Cooperative has described types 1 and 2 ROP as follows:

Type 1 ROP

- Zone I: Any stage with plus
- Zone I: Stage 3 without plus
- Zone II: Stage 2 to three with plus type 2 ROP
- Zone I: Stage 1 to two without plus
- Zone II: Stage 3 without plus

Clinical Manifestations and Prognosis

In more than 90% of at-risk infants, the course is one of spontaneous arrest and regression, with little or no residual effects or visual disability. Fewer than 10% of infants have progression toward severe disease, with significant extraretinal vasoproliferation, cicatrization, detachment of the retina, and impairment of vision.

Some children with arrested or regressed ROP are left with demarcation lines, undervascularization of the peripheral retina, or abnormal branching, tortuosity, or straightening of the retinal vessels. Some are left with retinal pigmentary changes, dragging of the retina, ectopia of the macula, retinal folds, or retinal breaks. Others proceed to total retinal detachment, which commonly assumes a funnel-like configuration. The clinical picture is often that of a retrolental membrane, producing leukocoria (a white reflex in the pupil). Some patients develop cataract, glaucoma, and signs of inflammation. The end stage is often a painful blind eye or a degenerated phthisical eye. The spectrum of ROP also includes myopia, which is often progressive and of significant degree in infancy. The incidence of anisometropia, strabismus, amblyopia, and nystagmus may also be increased.

Diagnosis

Systematic serial screening ophthalmologic examinations of infants at risk are recommended. Infants with a birthweight of less than 1,500 g or gestational age of 32 weeks or less and selected infants with a birthweight between 1,500 and 2,000 g or gestational age of more than 32 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their pediatrician or neonatologist to be at high risk, should have retinal screening examinations. The timing of the initial screening exam is based on the infant's age. Table 670.1 was developed from an evidence-based analysis of the Multicenter Trial of Cryotherapy for ROP. The examination can be stressful to fragile preterm infants, and the dilating drops can have untoward side effects. Infants must be carefully monitored during and after the examination. Some neonatologists and ophthalmologists advocate the use of topical tetracaine and/or oral sucrose to reduce the discomfort and stress to the infant. Follow-up is based on the initial findings and risk factors but is usually 2 weeks or less.

Treatment

In selected cases, laser photocoagulation of the avascular retina reduces the more severe complications of progressive ROP (Table 670.2). Advances in vitreoretinal surgical techniques have had limited success in reattaching the retina in infants with total retinal detachment (stage 5 ROP), but the visual results are often disappointing. The Early Treatment for Retinopathy of Prematurity Cooperative study did find

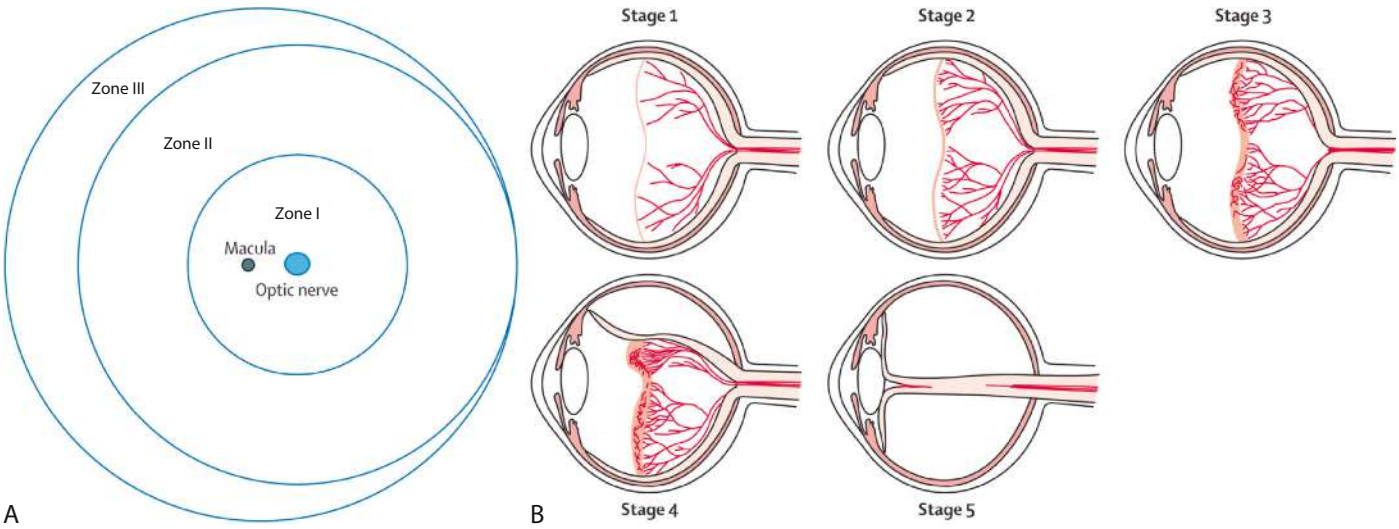

Fig. 670.1 The retina is divided into three zones and the extent or severity of retinopathy in these zones is classified in terms of five stages. **A,** Diagram of right eye. **B,** Stage 1 is characterized by a thin demarcation line between vascularized and nonvascularized retina, stage 2 by a ridge, stage 3 by extraretinal fibrovascular proliferation, stage 4 by partial retinal detachment, and stage 5 by total retinal detachment. In stage 3, extraretinal neovascularization can become severe enough to cause retinal detachment (stages 4-5), which usually leads to blindness. *(***A** *from Hellström A, Smith LEH, Dammann O. Retinopathy of prematurity. Lancet. 2013;382:1445–1454, Fig. 3, p. 1450;* **B** *courtesy Lisa Hård.)*

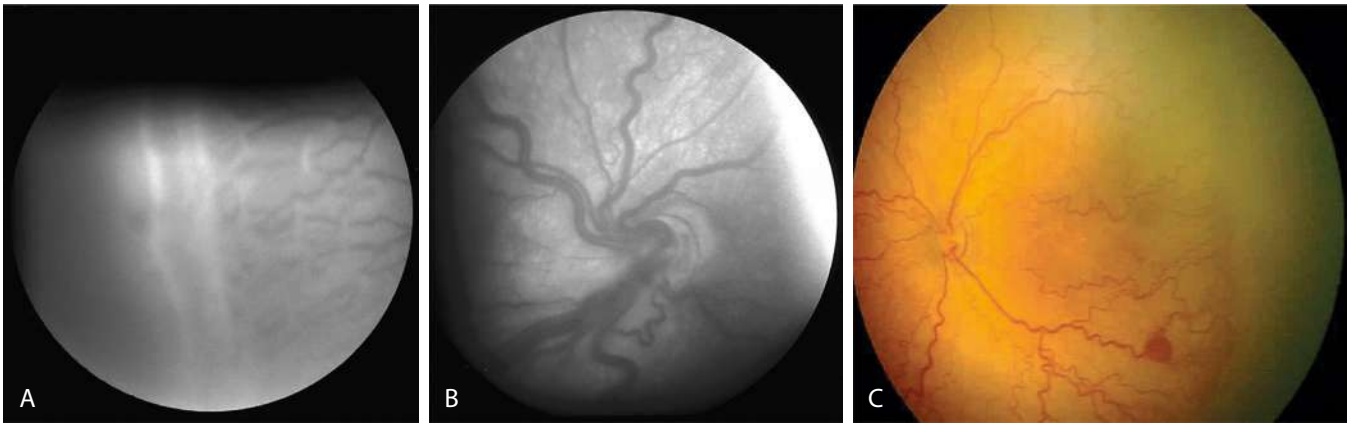

Fig. 670.2 Retinopathy of prematurity (ROP). **A,** In stage 3, there is a ridge and extraretinal vascular tissue. **B,** Retinal vessels are dilated and tortuous in active zone I ROP with plus disease. **C,** Zone I ROP with plus disease.

Table 670.1 Timing of First Eye Examination Based on Gestational Age at Birth

GESTATIONAL AGE AT BIRTH	AGE AT INITIAL EXAMINATION IN WEEKS	
	POSTMENSTRUAL	CHRONOLOGICAL
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

Table 670.2 Criteria for Peripheral Ablative Therapy for Retinopathy of Prematurity

1. Zone II: Plus disease with stage 2 or 3 ROP
2. Zone I: Plus disease with stage 1 or 2 ROP
3. Zone I: Stage 3 ROP

ROP, Retinopathy of prematurity.
Data from Early Treatment for Retinopathy of Prematurity Cooperative Group: Revised indications for the treatment of retinopathy of prematurity: Results of the Early Treatment for Retinopathy of Prematurity Randomized Trial. *Arch Ophthalmol* 2003;121:1684.

improved structural and visual outcomes with a redefined threshold for treatment. It demonstrated the importance of plus disease and the presence of posterior retinal involvement in the determination of when to treat ROP. Treatment should be considered for any eye with type 1 ROP. Serial examinations are indicated for any eye with type 2 ROP; treatment is considered if type 2 progresses to type 1 or if threshold ROP develops.

Intravitreal injections of VEGF antagonists may be recommended as first or second therapy for ROP, particularly in neonates with disease in zone 1. This treatment rapidly reduces intravitreal VEGF levels, often

improving plus disease and extraretinal fibrovascular tissue (stage 3 disease) within days of treatment. Theoretical advantages of these agents include not only the potential for improved peripheral retinal vascularization after treatment but also an apparent reduction in myopia later in childhood. Because the effects of intravitreal VEGF antagonists are temporary, neonates treated in this manner must be followed closely, often for months, after treatment to ensure additional therapy is not warranted.

Prevention

Prevention of ROP ultimately depends on the prevention of premature birth and its attendant problems (see Chapters 116 and 119.2). However, a number of other potential factors have been studied to decrease the occurrence of ROP in these premature infants. Ambient light had been considered by some to be a potential agent that could hopefully be manipulated. The LIGHT-ROP study definitively found that ambient light reduction had no impact on ROP. The association between ROP and oxygen saturation has been studied for decades. Recent research has focused on maintaining oxygen saturation levels for severely premature infants at levels sufficiently low to minimize the risk of ROP and sufficiently high to optimize survival.

PERSISTENT FETAL VASCULATURE

Persistent fetal vasculature (PFV; formerly called *persistent hyperplastic primary vitreous*) includes a spectrum of manifestations caused by the persistence of various portions of the fetal hyaloid vascular system and associated fibrovascular tissue.

Pathogenesis

During development of the eye, the hyaloid artery extends from the optic disc to the posterior aspect of the lens; it sends branches into the vitreous and ramifies to form the posterior portion of the vascular capsule of the lens. The posterior portion of the hyaloid system normally regresses by the seventh fetal month and the anterior portion by the eighth fetal month. Small remnants of the system, such as a tuft of tissue at the disc (Bergmeister papilla) or a tag of tissue on the posterior capsule of the lens (Mittendorf dot), are common findings in healthy persons. More extensive remnants and associated complications constitute PFV. Two major forms are described: anterior PFV and posterior PFV. Variability is great, and mixed or intermediate forms occur.

Clinical Manifestations

The usual clinical feature of anterior PFV is the presence of a vascularized plaque of tissue on the back surface of the lens in an eye that is microphthalmic or slightly smaller than normal. The condition is usually unilateral and may occur in infants with no other abnormalities and no history of prematurity. The fibrovascular tissue tends to undergo gradual contracture. The ciliary processes become elongated, and the anterior chamber may become shallow. The lens is usually smaller than normal and may be clear, but it often becomes cataractous and may swell or absorb fluid. Large or anomalous vessels of the iris may be present. The anterior chamber angle may have abnormalities. In time, the cornea may become cloudy.

Anterior PFV is usually noted in the first weeks or months of life. The most frequent presenting signs are leukocoria (white pupillary reflex), strabismus, and nystagmus. The course is usually progressive, and the outcome is poor. Major complications are spontaneous intraocular hemorrhage, swelling of the lens caused by rupture of the posterior capsule, and glaucoma. The eye may eventually deteriorate. The spectrum of posterior PFV includes fibroglial veils around the disc and macula, vitreous membranes and stalks containing hyaloid artery remnants projecting from the disc, and meridional retinal folds. Traction detachment of the retina may occur. Vision may be impaired, but the eye is usually retained.

Treatment

Surgery is performed to prevent complications, to preserve the eye and a reasonably good cosmetic appearance, and, in some cases, to salvage vision. Surgical treatment usually involves aspirating the lens and excising the abnormal tissue. If useful vision is to be attained, refractive correction and aggressive amblyopia therapy are required. In some cases, the affected eye is enucleated because distinguishing between this white mass and retinoblastoma can be difficult. Ultrasonography and CT are valuable diagnostic aids.

RETINOBLASTOMA

Retinoblastoma (Fig. 670.3) is the most common primary malignant intraocular tumor of childhood. It occurs in approximately 1/15,000 live births; 250-300 new cases are diagnosed in the United States annually. Hereditary and nonhereditary patterns of transmission occur; there is no predilection for gender or race. The hereditary form occurs earlier and is usually bilateral and multifocal, whereas the nonhereditary form is generally unilateral and unifocal. Fifteen percent of unilateral cases are hereditary. Bilateral cases often present earlier than unilateral cases. Unilateral tumors are often large by the time they are discovered. The average age at diagnosis is 15 months for bilateral cases compared with 27 months for unilateral cases. It is unusual for a child to present with a retinoblastoma after 3 years of age. Rarely, the tumor is discovered at birth, during adolescence, or even in early adulthood.

Clinical Manifestations

The clinical manifestations of retinoblastoma vary depending on the stage at which the tumor is detected. The initial sign in the majority of patients is a white pupillary reflex (leukocoria). Leukocoria results because of the reflection of light off the white tumor. The second most frequent initial sign of retinoblastoma is strabismus. Less frequent presenting signs include pseudohypopyon (tumor cells layered inferiorly in front of the iris) caused by tumor seeding in the anterior chamber of the eye, hyphema (blood layered in front of the iris) secondary to iris neovascularization, vitreous hemorrhage, and signs of orbital cellulitis. On examination, the tumor appears as a white mass, sometimes small and relatively flat, sometimes large and protuberant. It may appear nodular. Vitreous haze or tumor seeding may be evident.

The retinoblastoma gene is a recessive suppressor gene located on chromosome 13 at the 13q14 region. Because of the hereditary nature of retinoblastoma, family members of affected children should undergo a complete ophthalmologic examination and genetic counseling. Newborn siblings and children of affected patients should be referred to an ophthalmologist shortly after birth, when the peripheral retina can be evaluated without the need for an examination under anesthesia.

Diagnosis

Retinoblastoma is diagnosed by direct observation by an experienced ophthalmologist. Ancillary testing such as CT or ultrasonography may help to confirm the diagnosis and demonstrate calcification within the mass. MRI may better detect the presence of an associated pineoblastoma (trilateral retinoblastoma). A definitive diagnosis occasionally cannot be made, and removal of the eye must be considered to avoid the possibility of lethal metastasis of the tumor. Because a biopsy can lead to spread of the tumor, histologic confirmation before enucleation is not possible in most cases. Therefore removal of a blind eye in which the diagnosis of retinoblastoma is likely may be appropriate.

Treatment

Therapy varies, depending on the size and location of the tumor as well as whether it is unilateral or bilateral. Advanced tumors may be treated by enucleation. Other treatment modalities include the use of external beam irradiation, radiation plaque therapy, laser or cryotherapy, and chemoreduction (systemic chemotherapy) followed by local therapies (i.e., laser therapy, cryotherapy, and brachytherapy). During the last decade, there has been a dramatic shift in the treatment of retinoblastomas. Intraarterial chemotherapy involves delivery of chemotherapeutic agents via the ophthalmic artery and has dramatically reduced the need for enucleation in many cases of retinoblastoma.

Nonocular secondary tumors are common in patients with germinal pathogenic variants; they are estimated to occur with an incidence of 1% per years of life. The most common secondary tumor is osteogenic sarcoma of the skull and long bones; the risk is higher in patients

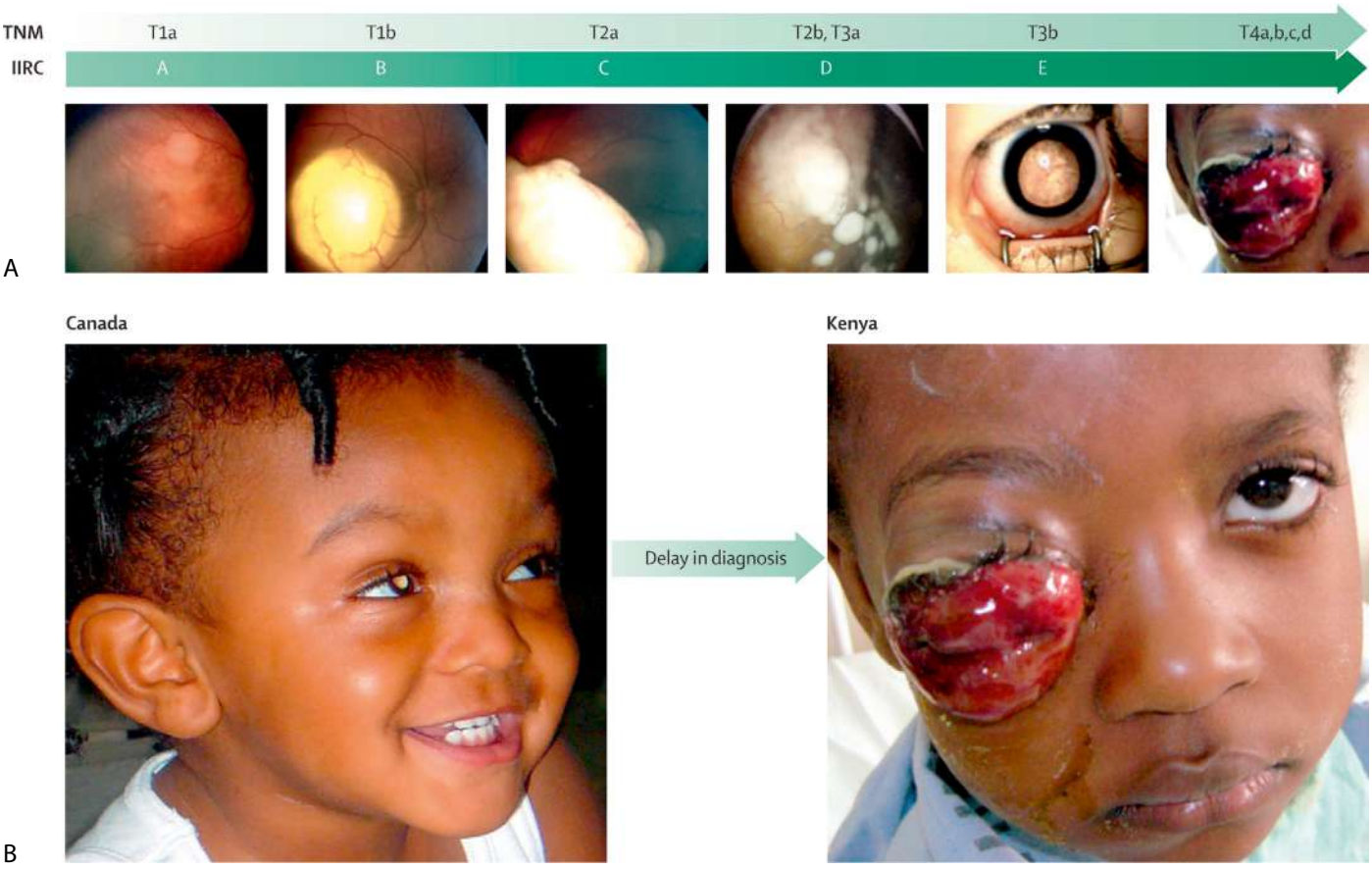

Fig. 670.3 Progression of retinoblastoma from small intraretinal tumors to a massive orbital retinoblastoma probably extending into the brain. A, Progression of retinoblastoma from small intraretinal tumors that can be cured by laser treatment and cryotherapy (TNM T1a, IIRC A) to massive orbital retinoblastoma probably extending into the brain (TNM T4a-b). B, A difference in age at diagnosis recorded between Canada and Kenya could mean the difference between possible cure and certain death. The Canadian child with leukocoria was diagnosed because of the left-hand image, which was taken by his sister with his mother's mobile phone. IIRC, International Intraocular Retinoblastoma Classification; TNM, tumor node metastasis cancer staging. *(From Dimaras H, Kimani K, Dimba EAO, et al. Retinoblastoma. Lancet. 2012;379:1436–1444, Fig. 1, p. 1438.)*

treated with radiation. Other malignancies include lung, brain, soft tissue, and skin.

The prognosis for children with retinoblastoma depends on the size and extension of the tumor. When confined to the eye, most tumors can be cured. The prognosis for long-term survival is poor when the tumor has extended into the orbit or along the optic nerve.

INHERITED RETINAL DYSTROPHIES

Inherited retinal dystrophies (IRDs) represent a wide spectrum of disorders (~280 affected genes) causing loss of photoreceptors and involving various locations (peripheral vs. macular or central) (Fig. 670.4) and affecting ~1/3,000 people. Most cases are monogenetic or isolated and nonsyndromic (~75%). Inheritance may be autosomal recessive or dominant, X-linked, mitochondrial, uniparental disomy, or digenic. There is significant genetic heterogenicity and overlap of the involved genes (Fig. 670.5). The IRDs are classified as retinitis pigmentosa, macular dystrophies, cone, or cone-rod dystrophies, syndromic (Usher syndrome with deafness), and the Leber congenital amaurosis disorders (>20 genes).

Retinitis Pigmentosa

This progressive peripheral retinal degeneration is the most common IRD and is characterized by pigmentary changes, arteriolar attenuation, usually some degree of optic atrophy, and progressive

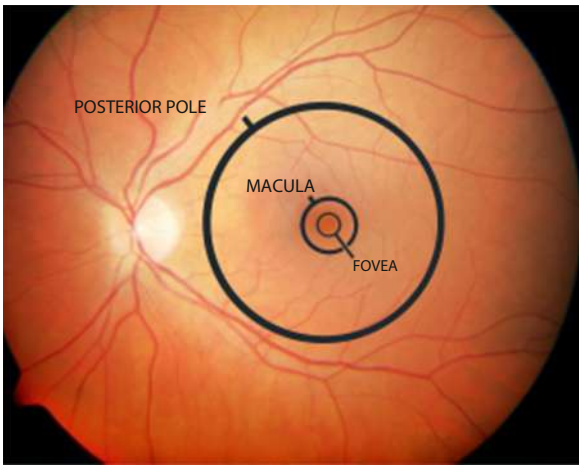

Fig. 670.4 Fundus image of a normal retina. The macula contains a high proportion of cone cells, which are most densely clustered in the fovea. The posterior pole marks the area of the retina between the optic disc (the *bright yellow oval* on the left of the image) and the macula. *(From Broadgate S, Yu J, Downes SM, Halford S. Unraveling the genetics of inherited dystrophies: Past, present, and future. Prog Retinal Eye Res. 2017;59:53–96. Fig. 1, p. 55).*

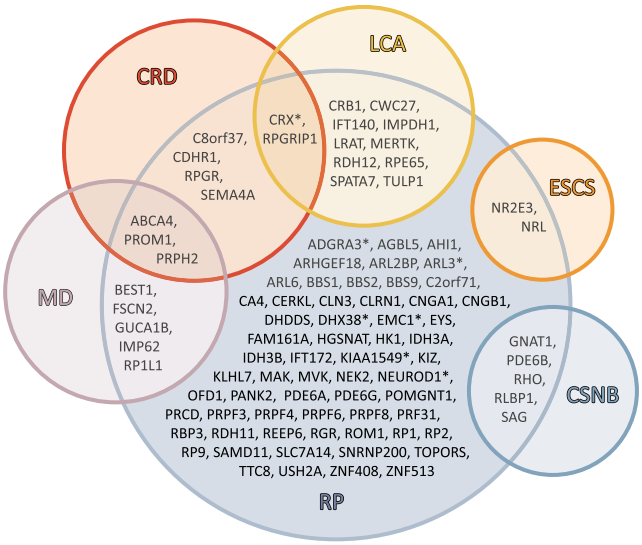

Fig. 670.5 Venn diagram summarizing the genetic overlap between retinitis pigmentosa and other inherited retinal dystrophies. Each circle represents a specific clinical diagnosis. The gene names listed in the overlapping areas indicate that mutations in these genes can lead to different phenotypes. Genes marked with an asterisk are candidate genes for nonsyndromic RP. CRD, cone-rod dystrophy; CSNB, congenital stationary night blindness; ESCS, enhanced S-cone syndrome; LCA, Leber congenital amaurosis; MD, macular dystrophy; RP, retinitis pigmentosa. *(From Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. Prog Retin Eye Res. 2018;66:157–186. Fig 1.)*

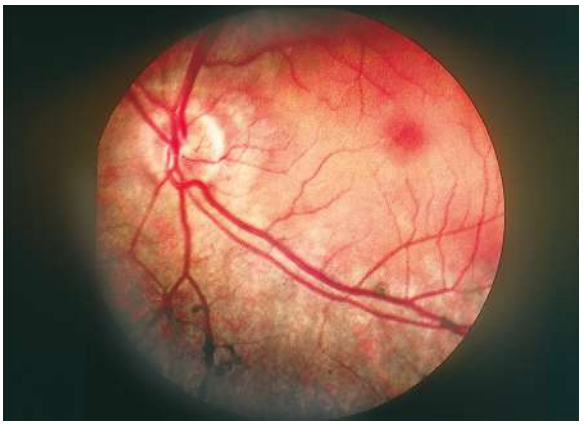

Fig. 670.6 Retinitis pigmentosa. Fundus photograph shows "bone spicule" pigmentation of the midperipheral fundus, waxy pallor of the optic disc, and attenuated retinal vessels, the most consistent finding in retinitis pigmentosa. *(Courtesy Dr. John I. Loewenstein.)*

impairment of visual function. Dispersion and aggregation of the retinal pigment produce various ophthalmoscopically visible changes ranging from granularity or mottling of the retinal pigment pattern to distinctive focal pigment aggregates with the configuration of bone spicules (Fig. 670.6). Other ocular findings include subcapsular cataract, glaucoma, and keratoconus.

Impairment of night vision (nyctalopia) or dark adaptation is often the first clinical manifestation. Progressive loss of peripheral vision (tunnel vision), often in the form of an expanding ring scotoma or concentric contraction of the field, is usual. There may also be loss of central vision. Retinal function, as measured by electroretinography (ERG), is characteristically reduced. The disorder may be autosomal recessive, autosomal dominant, or X-linked with ~70 affected genes (see Fig. 670.5). Children with autosomal recessive retinitis pigmentosa are more likely to become symptomatic at an earlier age (median age 10.7 years). Those with autosomal dominant retinitis pigmentosa are more likely to present in their 20s.

Another form of nonsyndromic IRD is **Leber congenital retinal amaurosis** (LCA), in which the retinal changes tend to be pleomorphic, with various degrees of pigment disorder, arteriolar attenuation, and optic atrophy. The incidence is approximately 1/81,000 births. Patients develop poor vision, nystagmus, poor pupillary response to light, and a behavioral pattern of eye rubbing. There are pathogenic variants in ~20 different genes producing this early (infancy) onset autosomal recessive severe retinal degenerative disease (see Fig. 670.5). Ten percent have pathogenic variants in the *LRAT* or *RPE65* genes, involved in retinoid metabolism. Although the retina may initially appear normal during infancy, the child typically shows evidence of visual impairment, nystagmus, and poor pupillary reaction soon after birth. ERG findings are abnormal early and confirm the diagnosis. Visual loss can be profound and may progress with age.

Gene replacement therapy via subretinal injections shows promise for *RPE65*-related IRDs, including those phenotypes of retinitis pigmentosa, Leber congenital amaurosis, and other IRD with this pathologic gene variant. Individuals who received subretinal injection of vector genomes of voretigene neparvovec improved in their ability to navigate a dimly lit course when compared with controls, with outcomes measured at 1 year. Similar gene replacement studies have been conducted or are being conducted for other retinal dystrophies, including choroideremia, Stargardt disease, cone-rod dystrophy, and X-linked retinoschisis.

Usher syndrome, an autosomal recessive disorder, is the most common cause of syndromic IRD *and* sensorineural deafness (incidence, 1/25,000). Type 1 Usher syndrome presents at birth with profound hearing loss and poor balance; vision loss progresses more slowly and begins during adolescence. Patients with type 3 disease have normal hearing at birth but develop hearing loss and night blindness around puberty. To date, 11 genetic loci have been located (5 for type 1, 3 for type 2; 1 for type 3).

A similar clinical picture may occur in the setting of secondary pigmentary retinal degenerations, which must be differentiated from retinitis pigmentosa, when associated with a wide variety of metabolic diseases, neurodegenerative processes, and multifaceted syndromes. Examples include the progressive retinal changes of the mucopolysaccharidoses (particularly Hurler, Hunter, Scheie, and Sanfilippo syndromes; see Chapter 109) and certain of the late-onset gangliosidoses (Batten-Mayou, Spielmeyer-Vogt, and Jansky-Bielschowsky diseases; see Chapters 106.4 and 639.2), the progressive retinal degeneration associated with progressive external ophthalmoplegia (Kearns-Sayre syndrome; see Chapter 638.2), and the retinitis pigmentosa–like changes in the Laurence-Moon and Bardet-Biedl syndromes. The retinal manifestations of abetalipoproteinemia (Bassen-Kornzweig syndrome; see Chapter 106) and Refsum disease (see Chapter 106.2) are also similar to those found in retinitis pigmentosa. The diagnosis of the latter two disorders in a patient with presumed retinitis pigmentosa is important because treatment is possible. There is also an association of retinitis pigmentosa and congenital hearing loss, as in Usher syndrome.

STARGARDT DISEASE (FUNDUS FLAVIMACULATUS)

This autosomal recessive IRD/macular dystrophy is characterized by slowly progressive bilateral macular degeneration and impairment of vision. It usually appears at 8-14 years of age, and affected children are often initially misdiagnosed as having functional visual loss. The foveal reflex becomes obtunded or appears grayish, pigment spots develop in the macular area, and macular depigmentation and chorioretinal atrophy eventually occur. Macular hemorrhages may also develop. Some patients also have white or yellow spots beyond the macula or pigmentary changes in the periphery; the term *fundus flavimaculatus* is commonly used for this condition. It is now recognized that Stargardt disease and fundus flavimaculatus represent different entities on the spectrum of the same disease. Central visual acuity is reduced, often to 20/200, but total loss of vision does not occur. ERG findings vary. The condition is not associated with central nervous system abnormalities and is to be differentiated from the macular changes of many

progressive metabolic neurodegenerative diseases. The most common (95%) genetic pathogenic variant (autosomal recessive) responsible for Stargardt macular dystrophy involves the *ABCA4* gene. Pathologic variants in *ELOVL4* are less common and are inherited as an autosomal dominant trait. Gene replacement therapy is being investigated for this condition.

BEST VITELLIFORM DEGENERATION

This macular dystrophy is characterized by a distinctive yellow or orange discoid subretinal lesion in the macula, resembling the intact yolk of a fried egg. Diagnosis is usually made at 3-15 years of age, with a mean age of presentation of 6 years. Vision is usually normal at this stage. The condition may be progressive; the yolklike lesion may eventually degenerate ("scramble") and result in pigmentation, chorioretinal atrophy, and vision impairment. The condition is usually bilateral. There is no association with systemic abnormalities. Inheritance is usually autosomal dominant. The vitelliform macular dystrophy gene *(VMD2)* has been identified, and DNA testing is available. In vitelliform macular degeneration, the ERG response is normal. Electrooculographic findings are abnormal in affected patients and carriers, and this test is useful in diagnosis and genetic counseling.

CHERRY-RED SPOT

Because of the special histologic features of the macula, certain pathologic processes affecting the retina produce an ophthalmoscopically visible sign referred to as a *cherry-red spot*, a bright to dull red spot at the center of the macula surrounded and accentuated by a grayish-white or yellowish halo (Fig. 670.7). The halo is a result of a loss of transparency of the retinal ganglion cell layer secondary to edema, lipid accumulation, or both. Because ganglion cells are not present in the fovea, the retina surrounding the fovea is opacified but the fovea transmits the normal underlying choroidal color (red), accounting for the presence of the cherry-red spot. A cherry-red spot typically occurs in certain sphingolipidoses, principally in Tay-Sachs disease (GM_2 type 1), in the Sandhoff variant (GM_2 type 2), and in generalized gangliosidosis (GM_1 type 1). Similar but less distinctive macular changes occur in some cases of metachromatic leukodystrophy (sulfatide lipidosis), in some forms of neuronopathic Niemann-Pick disease, in galactosialidosis, and in certain mucolipidoses. The cherry-red spot that characteristically occurs as a result of retinal ischemia secondary to vasospasm, ocular contusion, or occlusion of the central retinal artery must be differentiated from the cherry-red spot of neurodegenerative disease (see Chapters 106.4 and 639).

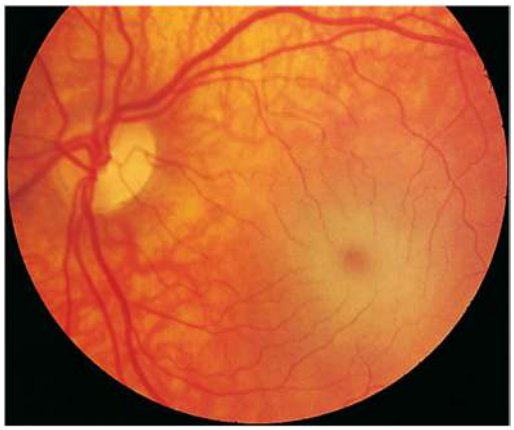

Fig. 670.7 Cherry-red spot seen in a case of Tay-Sachs disease. Because the parafoveal area has many retinal ganglion cells and the fovea has none, the fovea retains its orange-red color but is surrounded by a retina that is whitish. This produces the cherry-red spot in the macula. *(From Cheng KP, Biglan AW. Ophthalmology. In Zitelli BJ, McIntire SC, Nowald AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th ed. Philadelphia: Saunders, 2012. Fig. 19.102.)*

PHAKOMATOSIS

See also Chapter 636.

These are the herald lesions of the hamartomatous disorders. **Tuberous sclerosis**, the distinctive ocular lesion is a refractile, yellowish, multinodular cystic lesion arising from the disc or retina; the appearance of this typical lesion is often compared with that of an unripe mulberry (Fig. 670.8). Equally characteristic and more common in tuberous sclerosis are flatter, yellow to whitish retinal lesions that vary in size from minute dots to large lesions approaching the size of the disc. These lesions are benign astrocytic proliferations. Rarely, similar retinal phakomas occur in neurofibromatosis. In **von Hippel-Lindau disease** (angiomatosis of the retina and cerebellum), the distinctive fundus lesion is a hemangioblastoma; this vascular lesion usually appears as a reddish globular mass with large, paired arteries and veins passing to and from the lesion. In **Sturge-Weber syndrome** (encephalofacial angiomatosis), the fundus abnormality is a choroidal hemangioma; the hemangioma may impart a dark color to the affected area of the fundus, but the lesion is best seen with fluorescein angiography.



Fig. 670.8 Retinal phakoma of tuberous sclerosis.

RETINOSCHISIS

Congenital hereditary retinoschisis, also referred to as juvenile X-linked retinoschisis, is a bilateral vitreoretinal dystrophy that has a bimodal age of presentation. The first group presents with strabismus and nystagmus at a mean age of 1.5-2 years and is the most severely affected. The second group presents at 6-7 years with poor vision. Retinoschisis is characterized by splitting of the retina into inner and outer layers. The usual ophthalmoscopic finding in affected males is an elevation of the inner layer of the retina, most commonly in the inferotemporal quadrant of the fundus, often with round or oval holes visible in the inner layer. Schisis of the fovea is virtually pathognomonic and is found in almost 100% of patients. Ophthalmoscopically, this appears in early stages as small, fine striae in the internal limiting membrane. These striae radiate outward in a petaloid or spoke-wheel configuration. In some cases, frank retinal detachment or vitreous hemorrhage occurs.

Vision impairment varies from mild to severe; visual acuity may worsen with age, but good vision is often retained. Carrier females are asymptomatic, but linkage studies may be useful to help detect carriers. In some cases, treatment with a topical carbonic anhydrase inhibitor may improve visual acuity.

RETINAL DETACHMENT

A retinal detachment is a separation of the outer layers of the retina from the underlying retinal pigment epithelium (RPE). During embryogenesis, the retina and RPE are initially separated. During ocular development, they join together and are held in apposition to each other by various physiologic mechanisms. Pathologic events leading to a retinal

detachment return the retina–RPE to its former separated state. The detachment can occur as a congenital anomaly but more commonly arises secondary to other ocular abnormalities or trauma. Three types of detachment are described, and each may occur in children. Rhegmatogenous detachments result from a break in the retina that allows fluid to enter the subretinal space. In children, these are usually a result of trauma (such as child abuse) but may occur secondary to myopia or ROP or after surgery for congenital cataract. Tractional retinal detachments result when vitreoretinal membranes pull on the retina. They can occur in diabetes, sickle cell disease, and ROP. Exudative retinal detachments result when exudation exceeds absorption. This can be seen in Coats disease, retinoblastoma, and ocular inflammation.

The presenting sign of retinal detachment in an infant or child may be loss of vision, secondary strabismus or nystagmus, or leukocoria (white pupillary reflex). In addition to direct examination of the eye, special diagnostic studies such as ultrasonography and neuroimaging (CT, MRI) may be necessary to establish the cause of the detachment and the appropriate treatment. Prompt treatment is essential if vision is to be salvaged.

COATS DISEASE

This idiopathic, nonfamilial exudative retinopathy is characterized by telangiectasia of retinal vessels with leakage of plasma to form intraretinal and subretinal exudates and by retinal hemorrhages and detachment (Fig. 670.9). The condition is usually unilateral. It predominantly affects previously healthy males, usually appearing in the first decade. The most frequent presenting signs are blurring of vision, leukocoria, and strabismus. Rubeosis of the iris, glaucoma, and cataract may develop. The differential diagnosis includes retinoblastoma, ROP, Norrie disease, angiomatosis, chorioretinitis (see Table 669.1), systemic vasculitis, and Coats plus syndrome (leukodystrophy, osteopenia, anemia, retinitis) due to pathogenic variants in *CTC1* (autosomal recessive). **Treatment** with photocoagulation, cryotherapy, or VEGF inhibitors may be helpful.

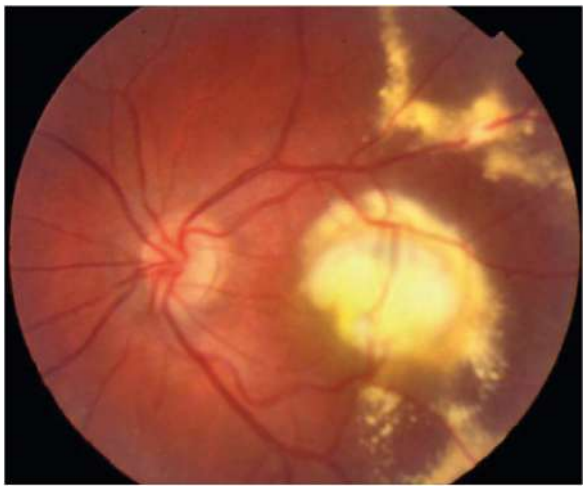

Fig. 670.9 Coats disease with massive retinal exudation.

FAMILIAL EXUDATIVE VITREORETINOPATHY

This progressive genetic retinal vascular disorder has clinical and angiographic findings that suggest an aberration of vascular development. Avascularity of the peripheral temporal retina is a significant finding in most cases, with abrupt cessation of the retinal capillary network in the region of the equator. The avascular zone often has a wedge- or V-shaped pattern in the temporal meridian. Glial proliferation or well-marked retinochoroidal atrophy may be found in the avascular zone. Excessive branching of retinal arteries and veins, dilation of the capillaries, arteriovenous shunt formation, neovascularization, and leakage from retinal vessels of the farthest vascularized retina occur. Vitreoretinal adhesions are usually present at the peripheral margin of the vascularized retina. Traction, retinal dragging and temporal displacement of the macula, falciform retinal folds, and retinal detachment are common. Intraretinal or subretinal exudation, retinal hemorrhage, and recurrent vitreous hemorrhages may develop. Patients may also develop cataracts and glaucoma. Vision impairment of varying severity occurs. The condition is usually bilateral. Familial exudative vitreoretinopathy (FEVR) is usually an autosomal dominant condition (*FZD4* or *LRP5*) with incomplete penetrance. Autosomal recessive *(LRP5)* and X-linked *(CNDP)* have also been reported. Asymptomatic family members often display a zone of avascular peripheral retina.

The findings in FEVR may resemble those of ROP in the cicatricial stages, but unlike ROP, the neovascularization of FEVR seems to develop years after birth, and most patients with FEVR have no history of prematurity, oxygen therapy, prenatal or postnatal injury or infection, or developmental abnormalities. FEVR is also to be differentiated from Coats disease, angiomatosis of the retina, peripheral uveitis, and other disorders of the posterior segment.

HYPERTENSIVE RETINOPATHY

In the early stages of hypertension, no retinal changes may be observable. Generalized constriction and irregular narrowing of the arterioles are usually the first signs in the fundus. Other alterations include retinal edema, flame-shaped hemorrhages, cotton-wool spots (retinal nerve fiber layer infarcts), and papilledema (Fig. 670.10). These changes are reversible if the hypertension can be controlled in the early stages, but in long-standing hypertension, irreversible changes may occur. Thickening of the vessel wall may produce a silver- or copper-wire appearance. Hypertensive retinal changes in a child should alert the physician to renal disease, pheochromocytoma, collagen disease, and cardiovascular disorders, particularly coarctation of the aorta.

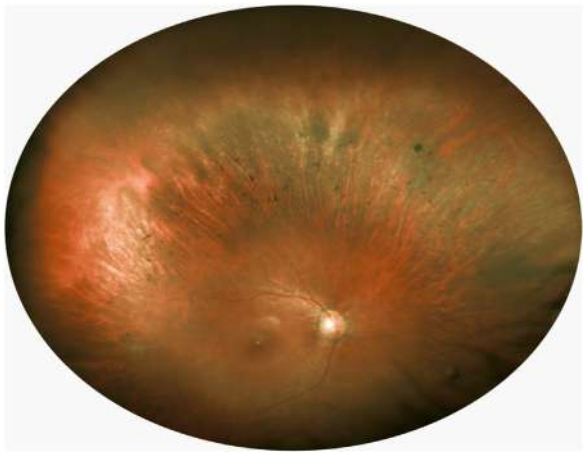

Fig. 670.10 Hypertension retinopathy with narrowed arterioles whose sclerosed walls create the appearance of "nicking" when the arterioles cross venules. *(From Yanoff M, Duker JS, eds. Ophthalmology. Elsevier, 2009.)*

DIABETIC RETINOPATHY

The retinal changes of diabetes mellitus are classified as nonproliferative or proliferative. Nonproliferative diabetic retinopathy is characterized by retinal microaneurysms, venous dilation, retinal hemorrhages, and exudates. The microaneurysms appear as tiny red dots. The hemorrhages may be of both the dot and blot type, representing deep intraretinal bleeding, and the splinter or flame-shaped type, involving the superficial nerve fiber layer. The exudates tend to be deep and to appear waxy. There may also be superficial nerve fiber infarcts called cytoid bodies or cotton-wool spots, as well as retinal edema. These signs may wax and wane. They are seen primarily in the posterior pole, around the disc and macula, or well within the range of direct ophthalmoscopy. Involvement of the macula may lead to decreased vision.

Proliferative retinopathy, the more serious form, is characterized by neovascularization and proliferation of fibrovascular tissue on the

retina, extending into the vitreous. Neovascularization may occur on the optic disc, elsewhere on the retina, or on the iris and in the anterior chamber angle (or rubeosis irides) (Fig. 670.11). Traction on these new vessels leads to hemorrhage and, eventually, scarring. The vision-threatening complications of proliferative diabetic retinopathy are retinal and vitreous hemorrhages, cicatrization, traction, and retinal detachment. Neovascularization of the iris may lead to secondary glaucoma if not treated promptly.

Diabetic retinopathy involves the alteration and nonperfusion of retinal capillaries, retinal ischemia, and neovascularization, but its pathogenesis is not yet completely understood, either in terms of location of the primary pathogenetic mechanism (retinal vessels vs surrounding neuronal or glial tissue) or the specific biochemical factors involved. The better the degree of long-term metabolic control, the lower the risk of diabetic retinopathy.

The prevalence and course of retinopathy relate to a patient's age and to disease duration. Detectable microvascular changes are rare in prepubertal children, with the prevalence of retinopathy increasing significantly after puberty, especially after the age of 15 years. The incidence of retinopathy is low during the first 5 years of disease and increases progressively thereafter, with the incidence of proliferative retinopathy becoming substantial after 10 years and with increased risk of visual impairment after 15 years or more.

Ophthalmic examination guidelines have been proposed by the American Academy of Pediatrics. An initial exam is recommended at age 9 years if the diabetes is poorly controlled. If the diabetes is well controlled, an initial exam 3 years after puberty with annual follow-up is recommended.

In addition to retinopathy, patients with juvenile-onset diabetes may develop optic neuropathy, characterized by swelling of the disc and blurring of vision. Patients with diabetes may also develop cataracts, even at an early age, sometimes with rapid progression.

Treatment

Macular edema is the leading cause of visual loss in diabetic persons. Photocoagulation may be used to decrease the risk of continued vision loss in patients with macular edema.

Proliferative retinopathy causes the most severe vision loss and can lead to total loss of vision and even loss of the eye. Patients who have proliferative disease and who display certain high-risk characteristics should undergo panretinal photocoagulation to preserve their central vision. Neovascularization of the iris is also treated with panretinal photocoagulation to stop the development of neovascular glaucoma.

Vitrectomy and other intraocular surgery may be necessary in patients with nonresolving vitreous hemorrhage or traction retinal detachment. The value of technologic advances, such as insulin infusion pumps and pancreatic transplants, in preventing ocular complications is under investigation (see Chapter 629).

SUBACUTE BACTERIAL ENDOCARDITIS

At some time during the disease, retinopathy is present in approximately 40% of cases of subacute bacterial endocarditis (see Chapter 486). The lesions include hemorrhages, hemorrhages with white centers (Roth spots), papilledema, and, rarely, embolic occlusion of the central retinal artery (Fig. 670.12).

BLOOD DISORDERS

In primary and secondary anemias, retinopathy in the form of hemorrhages and cotton-wool patches may occur. Vision can be affected if hemorrhage occurs in the macular area. The hemorrhages may be light and feathery or dense and preretinal. In polycythemia vera, the retinal veins are dark, dilated, and tortuous. Retinal hemorrhages, retinal edema, and papilledema may be observed. In leukemia, the veins are characteristically dilated, with sausage-shaped constrictions; hemorrhages, particularly white-centered hemorrhages and exudates, are common during the acute stage. In the sickling disorders, fundus changes include vascular tortuosity, arterial and venous occlusions, "salmon patches," refractile deposits, pigmented lesions, arteriolar-venous anastomoses, and neovascularization (with "sea-fan" formations), sometimes leading to vitreous hemorrhage and retinal detachment. Individuals with sickle cell hemoglobin C and sickle cell hemoglobin β-thalassemia hemoglobinopathies are at a higher risk of the development of retinopathy than are those with homozygous hemoglobin S disease. It is thought that the more anemic state of those patients with homozygous hemoglobin S disease offers protection from vascular occlusions in the retina.

TRAUMA-RELATED RETINOPATHY

Retinal changes may occur in patients who suffer trauma to other parts of the body. The occurrence of retinal hemorrhages in infants who have been physically abused is well documented (Fig. 670.13; see Chapter 17). Retinal, subretinal, subhyaloid, and vitreous hemorrhages have been described in infants and young children with inflicted neurotrauma. Often there are no signs of direct trauma to the eye, periocular region, or head. Such cases may result from violent shaking of an infant, and permanent retinal damage may result.

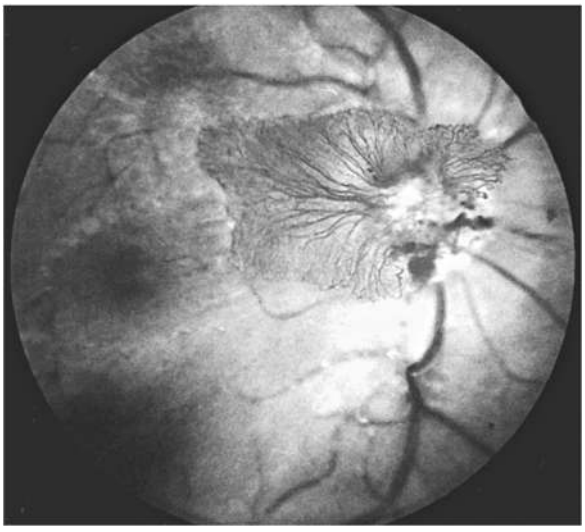

Fig. 670.11 Proliferative diabetic retinopathy with neovascularization of the disc.

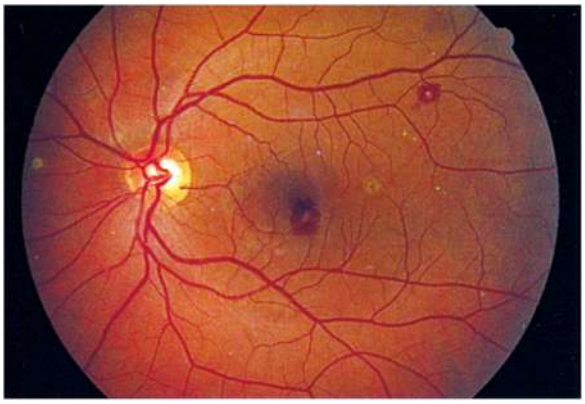

Fig. 670.12 Roth's spots. Multiple white-centered hemorrhages in a man with recurrent subacute bacterial endocarditis. White-centered hemorrhages are also seen with leukemia and diabetes. The small white scars are probably the residua of previous episodes. *(From Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 25th ed. Philadelphia: Elsevier, 2016. Fig. 423.28, p. 2569.)*

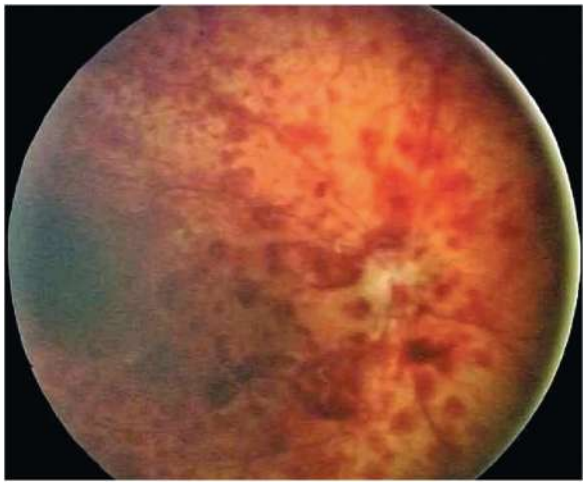

Fig. 670.13 Shaken baby syndrome (inflicted neurotrauma). Retinal hemorrhages in multiple layers too numerous to count into the far periphery.

In patients with severe head or chest compressive trauma, a traumatic retinal angiopathy known as **Purtscher retinopathy** may occur. This is characterized by retinal hemorrhage, cotton-wool spots, possible disc swelling, and decreased vision. The pathogenesis is unclear, but there is evidence of arteriolar obstruction in this condition. A Purtscher-like fundus picture may also occur in several nontraumatic settings, such as acute pancreatitis, lupus erythematosus, and childbirth. **Laser pointers** may produce vision loss with varying findings depending on the retinal area exposed to the nonionizing radiation.

MYELINATED NERVE FIBERS

Myelination of the optic nerve fibers normally terminates at the level of the disc, but in some individuals, ectopic myelination extends to nerve fibers of the retina. The condition is most commonly seen adjacent to the disc, although more peripheral areas of the retina may be involved. The characteristic ophthalmoscopic picture is a focal white patch with a feathered edge or brushstroke appearance. Because the macula is generally unaffected, the visual prognosis is good. A relative or absolute visual field defect corresponding to areas of ectopic myelination is usually the only associated ocular abnormality. Extensive unilateral involvement, however, is associated with ipsilateral myopia, amblyopia, and strabismus. If unilateral high myopia and amblyopia are present, appropriate optical correction and occlusion therapy should be instituted. For unknown reasons, the disorder is more commonly encountered in patients with craniofacial dysostosis, oxycephaly, neurofibromatosis, and Down syndrome.

CHORIORETINAL COLOBOMA

The term *coloboma* describes a defect such as a gap, notch, fissure, or hole (see Chapter 662). The typical fundus coloboma is a result of malclosure of the embryonic fissure, which leaves a gap in the retina, RPE, and choroid, thus baring the underlying sclera. The defect may be extensive, involving the optic nerve, ciliary body, and iris and even the lens, or it may be localized to one or more portions of the fissure. The usual appearance is of a well-circumscribed, wedge-shaped white area extending inferonasally below the disc, sometimes involving or engulfing the disc. In some cases, there is ectasia or cyst formation in the area of the defect. Less extensive colobomatous defects may appear as only single or multiple focal punched-out chorioretinal defects or anomalous pigmentation of the fundus in the line of the embryonic fissure. Colobomas may occur in one or both eyes. A visual field defect usually corresponds to the chorioretinal defect. Visual acuity may be impaired, particularly if the defect involves the disc or macula.

Fundus colobomas may occur in isolation as sporadic defects or as an inherited condition. Isolated colobomatous anomalies are commonly inherited in an autosomal dominant manner with highly variable penetrance and expressivity. Family members of affected patients should receive appropriate genetic counseling. Colobomas may also be associated with such abnormalities as microphthalmia, glioneuroma of the eye, cyclopia, or encephalocele. They occur in children with various chromosomal disorders, including trisomies 13 and 18, triploidy, cat-eye syndrome, and 4p−. Ocular colobomas also occur in many multisystem disorders, including the CHARGE (*C,* coloboma; *H,* heart disease; *A,* atresia choanae; *R,* retarded growth, and development and/or central nervous system anomalies; *G,* genetic anomalies and/or hypogonadism; *E,* ear anomalies and/or deafness) association; Joubert, Aicardi, Meckel, Warburg, and Rubinstein-Taybi syndromes; linear sebaceous nevus; Goldenhar and Lenz microphthalmia syndromes; and Goltz focal dermal hypoplasia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 671

Abnormalities of the Optic Nerve

Scott E. Olitsky and Justin D. Marsh

OPTIC NERVE APLASIA

This rare congenital anomaly of unknown etiology is typically unilateral. The optic nerve, retinal ganglion cells, and retinal blood vessels are absent. A vestigial dural sheath usually connects with the sclera in a normal position, but no neural tissue is present within this sheath. Optic nerve aplasia typically occurs sporadically in an otherwise healthy person.

OPTIC NERVE HYPOPLASIA

Hypoplasia of the optic nerve is a nonprogressive, idiopathic condition characterized by a subnormal number of optic nerve axons with normal mesodermal elements and glial supporting tissue. In typical cases, the nerve head is small and pale, with a pale or pigmented peripapillary halo or double ring sign (Fig. 671.1).

This anomaly is associated with defects of vision and of visual fields of varying severity, ranging from blindness to normal or near-normal vision. It may be associated with systemic anomalies that most commonly involve the central nervous system (CNS). CNS defects such as hydranencephaly or anencephaly or more focal lesions compatible with continued development may accompany optic nerve hypoplasia, but unilateral or bilateral optic nerve hypoplasia may be found without any concomitant defects.

Optic nerve hypoplasia is a principal feature of **septo-optic dysplasia (SOD),** a developmental disorder characterized by the association of anomalies of the midline structures of the brain

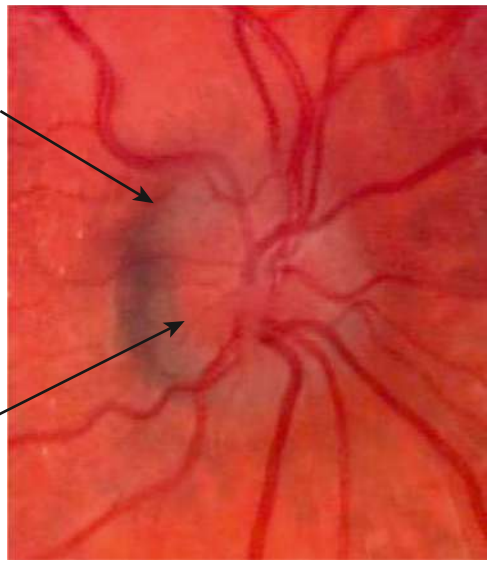

Fig. 671.1 Optic nerve hypoplasia: the "double ring sign." The first ring shows the border of the nerve sheath, and the second ring is formed by the actual border of the optic nerve tissue edge. *(From Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff & Martin's Neonatal-Perinatal Medicine. 10th ed. Philadelphia: Elsevier; 2015: Fig. 103.24, p. 1753.)*

with hypoplasia of the optic nerves, optic chiasm, and optic tracts; typically noted are agenesis of the septum pellucidum, partial or complete agenesis of the corpus callosum, and malformation of the fornix, with a large chiasmatic cistern. Patients may have hypothalamic abnormalities and endocrine defects ranging from panhypopituitarism to isolated deficiency of growth hormone, hypothyroidism, or diabetes insipidus. Neonatal hypoglycemia and seizures are important presenting signs in affected infants. In some patients with SOD, pathologic variants in *HESX1*, *SOX2*, *SOX3*, *OTX2*, and *PROKR2* have been identified.

MRI is preferred for evaluating CNS abnormalities in patients with optic nerve hypoplasia. During MRI, special attention should be directed to the pituitary infundibulum, where ectopia of the posterior pituitary may be found. Posterior pituitary ectopia appears on MRI as an absence of the pituitary infundibulum with an abnormal bright spot at the upper infundibulum area. This abnormality is present in approximately 15% of patients and suggests a posterior pituitary hormone deficiency, requiring further endocrinologic workup. Endocrine function should be watched closely in patients with optic nerve hypoplasia. The cause of optic nerve hypoplasia remains unclear.

Children with **periventricular leukomalacia** display an unusual form of optic nerve hypoplasia. The optic nerve demonstrates a large cup within a normal-size optic disc. This form of optic nerve hypoplasia occurs secondary to transsynaptic degeneration of optic axons caused by the primary bilateral lesion in the optic radiation (periventricular leukomalacia).

OPTIC NERVE COLOBOMA

Optic nerve colobomas can be unilateral or bilateral. The visual acuity can range from normal to complete blindness. The coloboma develops secondary to incomplete closure of the embryonic fissure. The defect may produce a partial or total excavation of the optic disc (Fig. 671.2). Chorioretinal and iris colobomas may also occur (see Chapter 662). Optic nerve colobomas may be seen in a multitude of ocular and systemic abnormalities, including the CHARGE (*C*, coloboma; *H*, heart disease; *A*, atresia choanae; *R*, retarded growth and development and/or CNS anomalies; *G*, genetic anomalies and/or hypogonadism; *E*, ear anomalies and/or deafness) association.

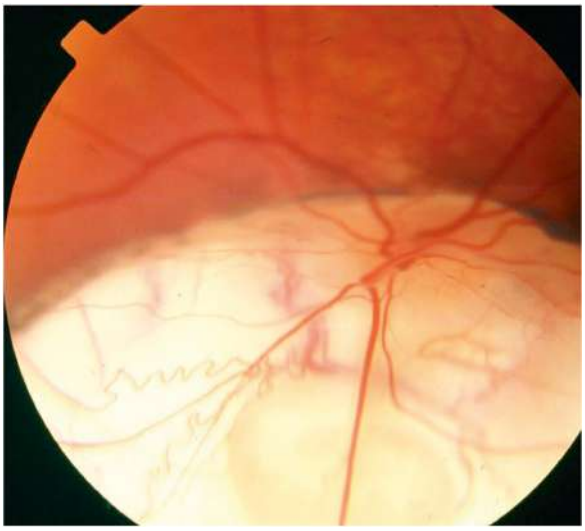

Fig. 671.2 Optic nerve coloboma.

MORNING GLORY DISC ANOMALY

This term describes a congenital malformation of the optic nerve characterized by an enlarged, excavated, funnel-shaped disc with an elevated rim resembling a morning glory flower. White glial tissue is present in the central part of the disc (Fig. 671.3). The retinal vessels are abnormal and appear at the peripheral disc, coursing over the elevated pink rim in a radial fashion. Pigmentary mottling of the peripapillary region is usually seen. Most cases are unilateral. Females are affected twice as often as males. Visual acuity is usually severely reduced. Morning glory disc anomaly has been associated with basal encephalocele in patients with midfacial anomalies. Abnormalities of the carotid circulation can also be seen in patients with morning glory anomaly. Moyamoya disease is a well-described associated finding.

TILTED DISC

In this congenital anomaly, the vertical axis of the optic disc is directed obliquely, so that the upper temporal portion of the nerve head is more prominent and anterior to the lower nasal portion of the disc. The retinal vessels emerge from the upper temporal portion of the disc rather than from the nasal side. Often noted is a peripapillary crescent or conus. Associated visual field defects and myopic astigmatism may be found. Clinical recognition of the tilted disc syndrome is important to avoid confusion of its disc and visual field signs with those of papilledema and intracranial tumor.

DRUSEN OF THE OPTIC NERVE

These globular, acellular bodies are thought to arise from axoplasmic derivatives of disintegrating nerve fibers. Drusen may be buried within the optic nerve, producing elevation of the optic nerve head (pseudopapilledema), or they may be partially or completely exposed, appearing as refractile bodies at the surface of the disc (Fig. 671.4). Visual field defects and spontaneous hemorrhages of the peripapillary nerve fiber layer may occur in association with drusen. Drusen may occur as an autosomal dominant condition with incomplete penetrance. B-scan ultrasonography can help to positively identify drusen suspected on clinical ophthalmic exam in some cases, although drusen in young children may be less likely to be visible with ultrasonography than in adults.

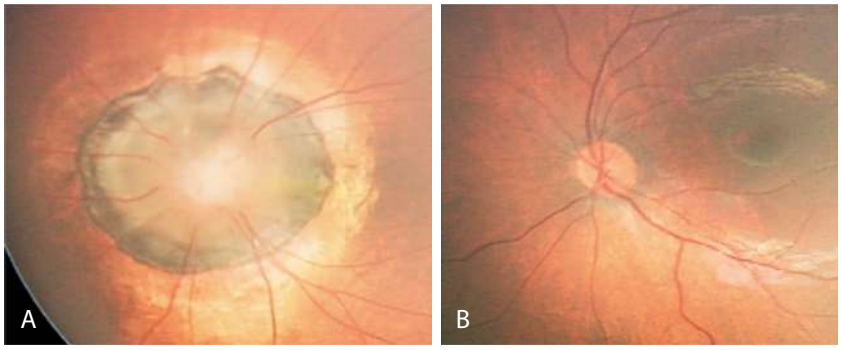

Fig. 671.3 A, Morning glory disc anomaly. The defect looks like a fully opened morning glory flower. B, Normal appearance of scaled fundus photography. *(From Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff & Martin's Neonatal-Perinatal Medicine. 10th ed. Philadelphia: Elsevier; 2015: Fig. 103.25, p. 1754.)*

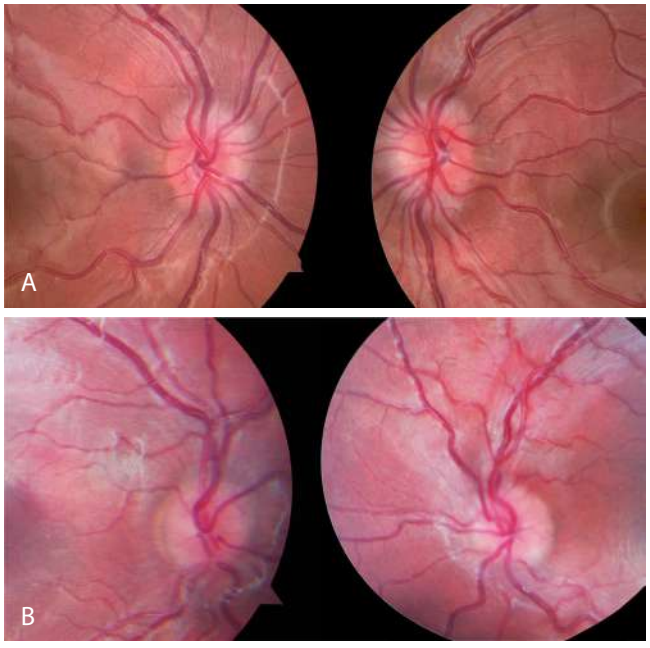

Fig. 671.4 Comparison of optic disc in children with optic disc drusen and papilledema. A, Optic disc photos of a 10-year-old child with bilateral buried optic disc drusen. The disc margins are blurred, but there are no hemorrhages, exudates, or vessel obscuration. B, Optic disc photos of a 5-year-old child with mild papilledema due to increased intracranial pressure. Disc margins are blurred with mild obscuration of vessels, but no hemorrhages or exudates. *(From Chang MY, Pineles SL. Optic disc drusen in children. Surv Ophthalmol. 2016;61:745–758: Fig. 1).*

PAPILLEDEMA

The term *papilledema* is reserved to describe swelling of the nerve head secondary to increased intracranial pressure (ICP). Clinical manifestations of papilledema include edematous blurring of the disc margins, fullness or elevation of the nerve head, partial or complete obliteration of the disc cup, capillary congestion and hyperemia of the nerve head, generalized engorgement of the veins, loss of spontaneous venous pulsation, hemorrhages in the nerve fiber layer around the disc, and peripapillary exudates (see Fig. 671.4 and 630.2). In some cases, edema extending into the macula may produce a fan- or star-shaped figure. In addition, concentric peripapillary retinal wrinkling (Paton lines) may be noted. Transient obscuration of vision may occur, lasting seconds, and is associated with postural changes. Vision, however, is usually normal in acute papilledema. Normally, when the ICP is relieved, the papilledema resolves and the disc returns to a normal or nearly normal appearance within 6-8 weeks. Sustained chronic papilledema or longstanding unrelieved increased ICP may, however, lead to permanent nerve fiber damage, atrophic changes of the disc, macular scarring, and impairment of vision.

The *pathophysiology* of papilledema is probably as follows: elevation of intracranial subarachnoid cerebrospinal fluid (CSF) pressure, elevation of CSF pressure in the sheath of the optic nerve, elevation of tissue pressure in the optic nerve, stasis of axoplasmic flow and swelling of the nerve fibers in the optic nerve head, and secondary vascular changes and the characteristic ophthalmoscopic signs of venous stasis. Associated neuro-ophthalmic signs of increased ICP in infants and children include sixth cranial nerve palsy and attendant esotropia, lid retraction, paresis of upward gaze, tonic downward deviation of the eyes, and convergent nystagmus.

The common **etiologies** of papilledema in childhood are intracranial tumors and obstructive hydrocephalus, intracranial hemorrhage, the cerebral edema of trauma, meningoencephalitis, toxic encephalopathy, idiopathic intracranial hypertension, and certain metabolic diseases. Regardless of the cause, the optic disc signs of increased ICP in early childhood may occasionally be modified by the distensibility of the young skull. In the absence of conditions associated with early closure of sutures and early obliteration of the fontanel (craniosynostosis, Crouzon disease, and Apert syndrome), infants with increased ICP may not develop papilledema.

The **differential diagnosis** of papilledema includes structural changes of the disc (pseudopapilledema, pseudoneuritis, drusen, and myelinated nerve fibers; see Fig. 671.4), with which it may be confused, and the disc swelling of papillitis associated with optic neuritis in addition to the disc changes of hypertension and diabetes mellitus. Unless retinal hemorrhage or edema involves the macular area, the preservation of good central vision and the absence of an afferent pupillary defect (Marcus Gunn pupil) help to differentiate acute papilledema from the edema of the optic nerve head found in acute optic neuritis.

Papilledema is a neurologic emergency. It can be accompanied by other signs of increased ICP, including headaches, nausea, and vomiting. Neuroimaging should be performed; if no intracranial masses are detected, a lumbar puncture and determination of CSF pressure should follow.

OPTIC NEURITIS

This is any inflammation or demyelinization of the optic nerve with attendant impairment of function (see Chapter 640.2). The process is usually acute, with rapidly progressive loss of vision. It may be unilateral or bilateral. Pain on movement or palpation of the globe may precede or accompany the onset of visual symptoms. There is decreased visual activity, decreased color vision and contrast sensitivity, a relative afferent pupillary defect, and a normal macula and peripheral retina.

When the retrobulbar portion of the nerve is affected without ophthalmoscopically visible signs of inflammation at the disc, the term *retrobulbar optic neuritis* is applied. When there is ophthalmoscopically visible evidence of inflammation of the nerve head, the term *papillitis* or *intraocular optic neuritis* is used. When there is involvement of both the retina and the papilla, the term *optic neuroretinitis* is used.

In childhood, optic neuritis may occur as an isolated condition or as a manifestation of a neurologic or systemic disease. Optic neuritis may be secondary to inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Behçet disease); infections (tuberculosis, syphilis, Lyme disease, meningitis, viral encephalitis, HIV, or postinfectious disease); and toxic or nutritional disorders (methanol, ethambutol, vitamin B_{12} deficiency). It may signify one of the many demyelinating diseases of childhood (see Chapter 640.2). Although a significant percentage of adults who experience an episode of optic neuritis eventually develop other symptoms associated with multiple sclerosis (MS), young children with optic neuritis are seemingly at less risk (risk of MS is 19% within 20 years). High-risk features suggestive of MS include visual acuity better than no light perception, periocular pain, acutely normal-appearing optic nerve, no retinal abnormalities, and abnormal MRI suggesting a demyelinating disease. Bilateral optic neuritis in children may be associated with **acute disseminated encephalomyelitis (ADEM)** or **neuromyelitis optica (NMO or Devic disease).** NMO is characterized by rapid and severe bilateral visual loss accompanied by transverse myelitis and paraplegia. Involvement of the brain stem and occasionally the cortex may be seen on MRI. NMO-specific immunoglobulin G (directed to the aquaporin 4 water channel) is the diagnostic test of choice for Devic syndrome. Antibody-negative NMO patients may have anti-MOG (myelin oligodendrocyte glycoprotein) antibodies, suggesting another form of demyelinating optic neuritis. Optic neuritis may also be secondary to an exogenous toxin or drug, as with lead poisoning or as a complication of long-term high-dose treatment with chloramphenicol or vincristine. Extensive pediatric neurologic and ophthalmic investigation, including MRI and lumbar puncture, is usually required. Idiopathic NMO is associated with anti–aquaporin 4 antibodies, otherwise known as NMO antibodies.

In most cases of acute optic neuritis, some improvement in vision begins within 1-4 weeks after onset, and vision may improve to normal or near normal within weeks or months. The course varies with cause. Although central vision may recover fully, it is common to find permanent defects in other areas of visual function (contrast sensitivity, color, brightness sense, and motion perception). Recurrences may occur especially, but not universally, in patients who go on to develop MS.

A **treatment** trial has demonstrated that high-dose intravenous methylprednisolone may help to speed the visual recovery in young adults, and it may prevent the development of MS in those at risk. It is unknown to what degree the results of the aforementioned trial may be extrapolated to optic neuritis in childhood.

LEBER HEREDITARY OPTIC NEUROPATHY

Leber hereditary optic neuropathy (LHON) is characterized by an acute to subacute painless loss of central vision primarily affecting young males (male to female ratio 2.5:1). The incidence is 1:30,000-50,000 people. A characteristic peripapillary telangiectatic microangiopathy occurs not only in the presymptomatic phase of involved eyes but also in a number of asymptomatic females (Fig. 671.5). Disc hyperemia and edema mark the acute phase of central visual loss. One eye is usually affected before the other; the second eye involvement begins 2-3 months later. Visual field loss (blurring, clouding) and impaired color vision are also present. In time, progressive optic atrophy and vision loss usually ensue. The tortuous angiopathy becomes less obvious. Although visual function after the initial loss generally remains stable, partial or less often complete recovery may occur in as many as 20–30% of affected individuals. This recovery may take place years or decades after the initial episode of acute vision loss. The peripapillary angiopathy, the lack of short-term remission and inflammation and MRI, as well as the degree of symmetry or peripheral motor or sensory deficits, serve to distinguish most cases of Leber disease from the optic neuritis of MS.

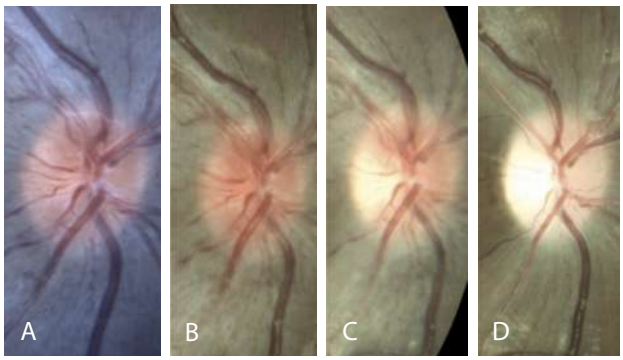

Fig. 671.5 A 9-year-old child with Leber hereditary optic neuropathy (LHON) m.11778 presents with best-corrected visual acuity of 20/20 in the right eye and no symptoms **(A).** At age 12, retinal nerve fiber layer swelling is observed before reduction in vision **(B).** His visual acuity rapidly decreases 1 month later to 20/50 and subtle temporal optic nerve pallor is visible **(C).** Three months later, his visual acuity is <20/400 and diffuse optic nerve pallor is present **(D).** Notice that peripapillary telangiectasia was present at age 9, 3 years before his visual symptoms started. The patient's left eye progressed similarly to the right eye. *(From Pilz YL, Bass SJ, Sherman J. A review of mitochondrial optic neuropathies: from inherited to acquired forms. J Optometry. 2016;10:205–214: Fig. 1, p. 208).*

LHON is maternally inherited and is caused by pathogenic gene variants in mitochondrial DNA (Fig. 671.6). Multiple point variants in the mitochondrial DNA have been identified. Pathogenic variants in *MTND1*, *MTND4* (~70%), and *MTND6* represent ~90% of cases. **LHON plus** is a related mitochondrial disorder affecting skeletal and cardiac muscle disorders, including electrocardiographic abnormalities. Only ~50% of males and 15% of females with a pathogenic gene variant develop symptomatic LHON.

The differential diagnosis includes optic neuritis (Chapter 640.2), other genetic optic neuropathies (Table 671.1; see also Fig. 671.6) and toxic or nutritional neuropathies (Table 671.2).

Gene therapy with intravitreal injection of a vector-*ND4* gene has had success improving vision in patients with LHON.

OPTIC ATROPHY

This term denotes degeneration of optic nerve axons, with attendant loss of function. The ophthalmoscopic signs of optic atrophy are pallor of the disc and loss of substance of the nerve head, sometimes with enlargement of the disc cup. The associated vision defect varies with the nature and site of the primary disease or lesion.

Optic atrophy is the common expression of a wide variety of congenital or acquired pathologic processes (Table 671.3). The cause may be traumatic, inflammatory, degenerative, neoplastic, or vascular; intracranial tumors and hydrocephalus are principal causes of optic atrophy in children. In some cases, progressive optic atrophy is hereditary. **Dominantly inherited infantile optic atrophy** is a relatively mild heredodegenerative type that tends to progress through childhood and adolescence. **Autosomal recessively inherited congenital optic atrophy** is a rare condition that is evident at birth or develops at

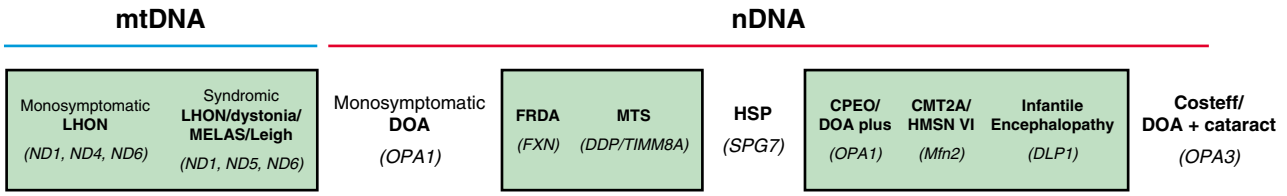

Fig. 671.6 Mitochondrial and nuclear DNA etiologies of inherited optic neuropathies. LHON, Leber hereditary optic neuropathy; DOA, dominant optic atrophy; FRDA, Friedreich ataxia; MTS, Mohr-Tranebjaerg syndrome; HSP, hereditary spastic paraplegia; CPEO, chronic progressive external ophthalmoplegia; CMT2A, Charcot Marie tooth; HMSN VI, hereditary motor and sensory neuropathy; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; MELAS, mitochondrial encephalopathy, lactic acidosis, stroke. *(Modified from Carelli V, La Morgia C, Valentino ML, et al. Retinal ganglion cell neurodegeneration in mitochondrial inherited disorders. Biochim et Biophysic Acta. 2009;1787:518–528: Fig. 2).*

Table 671.1 Genetic and Clinical Features of Primary Hereditary Optic Atrophies and Their Respective Genes

	OPA1	*LHON*	*OPA3*	*TMEM126A*	*WFS1*
Inheritance	Autosomal dominant	Maternal	Autosomal dominant	Autosomal recessive	Autosomal dominant
Age of onset	Childhood	Young adult, male > female	Late childhood	Childhood	Childhood to adult
Ophthalmologic features	Slowly progressive, tritanomaly	Sudden visual loss. Frequently beginning unilateral	Often additional cataract	Early manifestation and progression	Highly variable
Loss of visual acuity	Moderate to severe	Pronounced visual impairment	Moderate	Severe visual loss	Variable
Possible extraocular signs	~20% of patients have neurologic symptoms (e.g., ataxia, neuropathy)	Mild neurologic symptoms possible; multiple sclerosis–like symptoms	Late in life; mild neurologic signs possible late in life	Subclinical hearing impairment	Hearing impairment, disturbed glucose tolerance, behavioral abnormalities

LHON, Leber hereditary optic neuropathy (*mt-ND1, mt-ND4, mt-ND46, mt-ND6*); OPA1, optic atrophy type 1; OPA3, optic atrophy type 3; TMEM126A, optic atrophy type 7; WFS1, Wolfram syndrome (diabetes mellitus, diabetes insipidus, optic neuropathy, deafness).
Modified from Neuhann T, Rautenstrauss B. Genetic and phenotypic variability of optic neuropathies. *Expert Rev Neurother.* 2013;13(4):357–367.

Table 671.2 Causes of Acquired Optic Neuropathies

TOXINS	MEDICATIONS	NUTRITIONAL DEFICIENCIES
Methanol	Ethambutol	Thiamine (Vitamin B_1)
Ethanol	Isoniazid	Riboflavin (Vitamin B_2)
Tobacco	Chloramphenicol	Pyridoxine (Vitamin B_6)
Arsenics	Linezolid	Folic Acid (Vitamin B_9)
Cobalt	Erythromycin	Cobalamin (Vitamin B_{12})
Thallium	Streptomycin	
Carbon disulfide	Ciprofloxacin	
Tetrachloride	Dapsone	
Cyanide	Antiretrovirals	
Ethylene glycol	Amiodarone	
Toluene	Infliximab	
Styrene	Clioquinol	
Perchloroethylene	Pheniprazine	
	Suramin	
	Quinine	

From Pilz YL, Bass SJ, Sherman J. A review of mitochondrial optic neuropathies: From inherited to acquired forms. *J Optometry.* 2016;10:205–214: Table 2.

a very early age; the visual defect is usually profound. **Behr optic atrophy** is a hereditary type associated with hypertonia of the extremities, increased deep tendon reflexes, mild cerebellar ataxia, some degree of mental deficiency, and possibly external ophthalmoplegia. This disorder principally afflicts boys 3-11 years of age. Some forms of heredodegenerative optic atrophy are associated with sensorineural hearing loss, as may occur in some children with juvenile-onset (insulin-dependent) diabetes mellitus. In the absence of an obvious cause, optic atrophy in an infant or child warrants extensive etiologic investigation.

OPTIC NERVE GLIOMA

Optic nerve glioma, more properly referred to as **juvenile pilocytic astrocytoma,** is the most frequent tumor of the optic nerve in childhood (Fig. 671.7). This neuroglial tumor may develop in the intraorbital, intracanalicular, or intracranial portion of the nerve; the chiasm is often involved.

The tumor is a cytologically benign hamartoma that is generally stationary or only slowly progressive. The principal *clinical manifestations* when the tumor occurs in the intraorbital portion of the nerve are unilateral loss of vision, proptosis, and deviation of the eye; optic atrophy or congestion of the optic nerve head may occur. Chiasmal involvement may be attended by defects of vision and visual fields (often bitemporal hemianopia), increased ICP, papilledema or optic atrophy, hypothalamic dysfunction, pituitary dysfunction, and sometimes nystagmus or strabismus. Juvenile pilocytic astrocytomas occur with increased frequency in patients with neurofibromatosis (see Chapter 636.1).

Treatment of optic pathway gliomas is controversial. The best management is usually periodic observation with serial radiography

Table 671.3 Causes of Childhood Optic Atrophy

Compressive intracranial lesions
Compressive bony disorders
Craniosynostosis
Fibrous dysplasia
Hydrocephalus
Postpapilledema optic atrophy
Infectious
Hereditary
Leber hereditary optic neuropathy
Dominant optic atrophy (Kjer)
Recessive optic atrophy
Behr optic atrophy
DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) (Wolfram) optic atrophy
Toxic or nutritional optic neuropathy
Hypoxia
Trauma
Postoptic neuritis
Radiation optic neuropathy
Paraneoplastic syndromes
Neurodegenerative disorders with optic atrophy
Krabbe disease
Canavan disease
Leigh disease
Mitochondrial encephalomyopathy, lactic acidosis, and strokelike (MELAS) episodes
Neonatal adrenoleukodystrophy
Metachromic leukodystrophy
Riley-Day syndrome
Lactic acidosis
Spinocerebellar degeneration
Mucopolysaccharidosis
Ocular disorders
Glaucoma
Retinal disease
Vascular disease
Uveitis
Optic nerve hypoplasia

From Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine.* 10th ed. Philadelphia: Elsevier; 2015. Box 103.5.

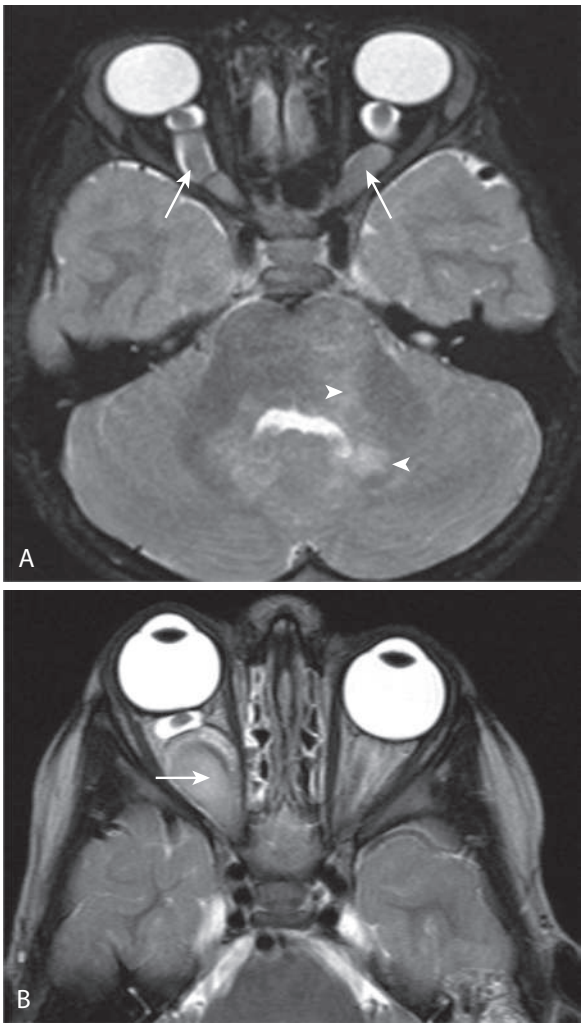

Fig. 671.7 Optic nerve glioma (ONG). **A,** ONG in a patient with neurofibromatosis NF1. Axial fat-saturated T2-weighted MR image of the orbits demonstrates bilaterally symmetrically enlarged and tortuous intracanalicular portions of the optic nerves associated *(arrows).* Areas of signal abnormality within the cerebellar white matter indicate spongiform changes of NF1 *(arrowheads).* **B,** Isolated right ONG. Axial T2-weighted MR image of the orbits demonstrates an ONG *(arrow)* with similar expansion and tortuosity of the optic nerve to the case in **A** but with unilateral involvement of the right optic nerve and without additional imaging findings of NF1. *(From Coley BD [ed]. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier, 2019: Fig. 7.8, p. 48.)*

(preferably MRI). Only symptomatic and radiographically progressing optic nerve gliomas require strong consideration for treatment. If a patient has unsightly proptosis with complete or nearly complete loss of vision of the affected eye, surgical removal may be appropriate when the tumor is confined to the intraorbital, intracanalicular, or prechiasmal portion of the nerve. When the chiasm is involved, resection is not usually indicated, and radiation and chemotherapy may be necessary.

TRAUMATIC OPTIC NEUROPATHIES

Injury to the optic nerve may result from both direct and indirect trauma. Direct trauma to the optic nerve is a result of a penetrating injury to the orbit with transection or contusion of the nerve. Blunt trauma to the orbit may also lead to severe visual loss if the traumatic force is transmitted to the optic canal and causes disruption of the blood supply to the intracanalicular portion of the nerve. Treatment with high-dose corticosteroids has not proved to be effective; it has been shown that similar regimens involve an increased relative risk of death when they are given to patients who have experienced significant head injuries.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 672

Childhood Glaucoma

Scott E. Olitsky and Justin D. Marsh

Glaucoma is a general term used to indicate damage to the optic nerve with visual field loss that is caused by or related to elevated pressure within the eye. It is classified according to the age of the affected individual at presentation and the association of other ocular or systemic conditions. Glaucoma that begins within the first 5 years of life is called

Table 672.1 Primary and Secondary Childhood Glaucomas

I. PRIMARY GLAUCOMAS
A. Congenital open-angle glaucoma
  1. Congenital
  2. Infantile
  3. Late recognized
B. Autosomal dominant juvenile glaucoma
C. Primary angle-closure glaucoma
D. Associated with systemic abnormalities
  1. Sturge-Weber syndrome
  2. Neurofibromatosis type I (NF-1)
  3. Stickler syndrome
  4. Oculocerebrorenal (Lowe) syndrome
  5. Rieger syndrome
  6. Hepatocerebrorenal syndrome
  7. Marfan syndrome
  8. Rubinstein-Taybi syndrome
  9. Infantile glaucoma associated with cognitive disability and paralysis
  10. Oculodentodigital dysplasia
  11. Open-angle glaucoma associated with microcornea and absence of frontal sinuses
  12. Mucopolysaccharidosis
  13. Trisomy 13
  14. Cutis marmorata telangiectasia congenita
  15. Warburg syndrome
  16. Kniest syndrome (skeletal dysplasia)
  17. Michel syndrome
  18. Nonprogressive hemiatrophy
E. Associated with ocular abnormalities
  1. Congenital glaucoma with iris and pupillary abnormalities
  2. Aniridia
    a. Congenital glaucoma
    b. Acquired glaucoma
  3. Congenital ocular melanosis
  4. Sclerocornea
  5. Iridotrabecular dysgenesis
  6. Peters syndrome
  7. Iridotrabecular dysgenesis and ectropion uveae
  8. Posterior polymorphous dystrophy
  9. Idiopathic or familial elevated episcleral venous pressure
  10. Anterior corneal staphyloma
  11. Congenital microcornea with myopia
  12. Congenital hereditary endothelial dystrophy
  13. Congenital hereditary iris stromal hypoplasia

II. SECONDARY GLAUCOMAS
A. Traumatic glaucoma
  1. Acute glaucoma
    a. Angle concussion
    b. Hyphema
    c. Ghost cell glaucoma
  2. Late-onset glaucoma with angle recession
  3. Arteriovenous fistula
B. Secondary to intraocular neoplasm
  1. Retinoblastoma
  2. Juvenile xanthogranuloma
  3. Leukemia
  4. Melanoma
  5. Melanocytoma
  6. Iris rhabdomyosarcoma
  7. Aggressive nevi of the iris
C. Secondary to uveitis
  1. Open-angle glaucoma
  2. Angle-blockage glaucoma
    a. Synechial angle closure
    b. Iris bombé with pupillary block
D. Lens-induced glaucoma
  1. Subluxation-dislocation and pupillary block
    a. Marfan syndrome
    b. Homocystinuria
  2. Spherophakia and pupillary block
  3. Phacolytic glaucoma
E. Secondary to surgery for congenital cataract
  1. Lens material blockage of the trabecular meshwork (acute or subacute)
  2. Pupillary block
  3. Chronic open-angle glaucoma associated with angle defects
F. Steroid-induced glaucoma
G. Secondary to rubeosis
  1. Retinoblastoma
  2. Coats disease
  3. Medulloepithelioma
  4. Familial exudative vitreoretinopathy
H. Secondary angle-closure glaucoma
  1. Retinopathy of prematurity
  2. Microphthalmos
  3. Nanophthalmos
  4. Retinoblastoma
  5. Persistent hyperplastic primary vitreous
  6. Congenital pupillary iris-lens membrane
I. Glaucoma associated with increased venous pressure
  1. Carotid or dural-venous fistula
  2. Orbital disease
J. Secondary to maternal rubella
K. Secondary to intraocular infection
  1. Acute recurrent toxoplasmosis
  2. Acute herpetic iritis

From Nelson LB. *Harley's Pediatric Ophthalmology*. 4th ed. Philadelphia: Saunders; 1998: p. 294.

infantile (congenital); that which begins between the ages of 5 and 30 years is called juvenile.

Primary glaucoma indicates that the cause is an isolated anomaly of the drainage apparatus of the eye (trabecular meshwork). More than 50% of infantile cases are primary glaucoma. In secondary glaucoma, other ocular or systemic abnormalities are associated, even if a similar developmental defect of the trabecular meshwork is also present. Primary infantile glaucoma occurs with an incidence of 0.03% (Table 672.1).

CLINICAL MANIFESTATIONS

The symptoms of infantile glaucoma include the classic triad of epiphora (tearing), photophobia (sensitivity to light), and blepharospasm (eyelid squeezing; Fig. 672.1). Each can be attributed to corneal irritation. Only approximately 30% of affected infants demonstrate the classic symptom complex. Signs of glaucoma include corneal edema, corneal and ocular enlargement, and conjunctival injection (Fig. 672.2).

The sclera and cornea are more elastic in early childhood than later in life. An increase in intraocular pressure (IOP) therefore leads to an expansion of the globe, including the cornea, and the development of buphthalmos ("ox eye"). If the cornea continues to enlarge, breaks occur in the endothelial basement membrane (Descemet's membrane) and may lead to permanent corneal scarring. These breaks in Descemet's membrane (Haab striae) are visible as horizontal edematous lines that cross or curve around the central cornea. They rarely occur beyond 3 years of age or in corneas <12 mm in diameter. The cornea also becomes edematous and cloudy, with increased IOP. The corneal edema leads to tearing and photophobia. If any of these other signs or symptoms are present, glaucoma should be considered in a child suspected of having a nasolacrimal duct obstruction.

Children with unilateral glaucoma generally present early because the difference in the corneal size between the eyes can be noticed. When the disease is bilateral, parents may not recognize the increased corneal size.

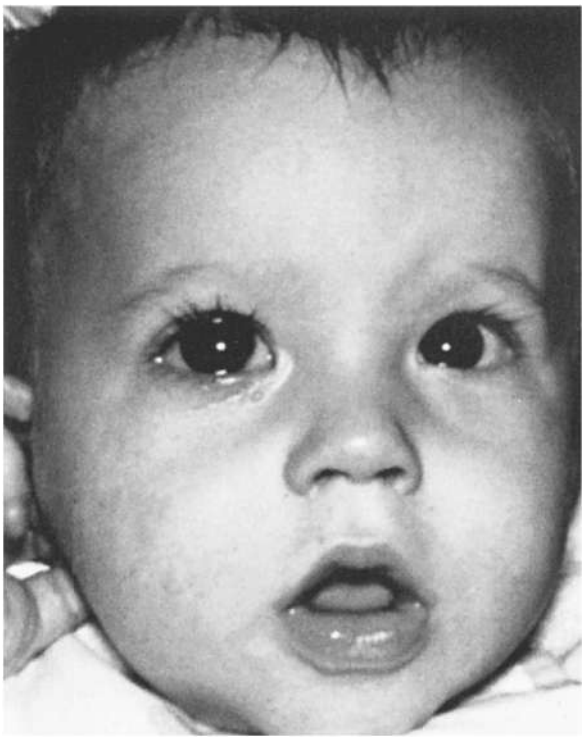

Fig. 672.1 Tearing of the right eye caused by glaucoma. Note the increased corneal diameter of the right eye. *(From Nelson LB. Harley's Pediatric Ophthalmology. 4th ed. Philadelphia: WB; 1998; p. 285.)*



Fig. 672.2 Infantile glaucoma. The left cornea is enlarged and edematous.

Many parents view the large eyes as attractive and do not seek help until other symptoms develop.

Cupping of the optic nerve head is detected by ocular examination. The optic nerve of an infant is easily distended by excessive pressure. Deep central cupping readily occurs and may regress with normalization of pressure.

Some infants and children with early-onset glaucoma have more extensive maldevelopment of the anterior segment of the eye. The neurocristopathies, particularly those involving the anterior segment (Axenfeld-Rieger syndrome: *FOXC1, PITX2, CYP1B1, PRDM5* genes), produce early-onset glaucoma. They are usually bilateral and may include abnormalities of the iris, cornea, and lens. Other ocular anomalies that may be associated with glaucoma in infants and children are aniridia, cataract, spherophakia, and ectopia lentis. Glaucoma may also develop secondary to persistent hyperplastic primary vitreous or retinopathy of prematurity.

Trauma, intraocular hemorrhage, ocular inflammatory disease, and intraocular tumor are also important causes of glaucoma in the pediatric population. Systemic disorders associated with glaucoma in infants and children are Sturge-Weber syndrome (see Chapter 636.3), neurofibromatosis (see Chapter 636.1), Lowe syndrome, Marfan syndrome (see Chapter 743), congenital rubella (see Chapters 149 and 294), and a number of chromosomal syndromes (see Chapter 99).

Table 672.2 Differential Diagnosis of Primary Congenital Glaucoma

I. OTHER GLAUCOMAS
- A. Glaucoma associated with congenital anomalies
- B. Secondary glaucoma

II. OTHER CAUSES OF CORNEAL ENLARGEMENT OR CLOUDING
- A. Megalocornea
- B. Sclerocornea
- C. High myopia
- D. Metabolic diseases
  1. Cystinosis
  2. Mucopolysaccharidoses
     - a. MPS I H = Hurler's syndrome
     - b. MPS I S = Scheie's syndrome
     - c. MPS II = Hunter's syndrome
     - d. MPS IV = Morquio's syndrome
     - e. MPS VI = Maroteaux-Lamy syndrome
     - f. MPS VII = b-Glucuronidase deficiency
  3. Hand-Schüller-Christian disease (histiocytosis)
  4. Acrodermatitis enteropathica
  5. Peroxisomal disorders
  6. Zellweger syndrome
- E. Posterior polymorphous dystrophy
- F. Congenital hereditary endothelial dystrophy
- G. Obstetric trauma
- H. Inflammation (keratitis, iridocyclitis)

III. OTHER CAUSES OF EPIPHORA OR PHOTOPHOBIA
- A. Nasolacrimal duct obstruction
- B. Conjunctivitis
- C. Corneal abrasion
- D. Meesmann's corneal dystrophy
- E. Reis-Buckler's dystrophy

IV. OTHER CAUSES OF OPTIC NERVE ABNORMALITIES
- A. Pit
- B. Coloboma
- C. Hypoplasia
- D. Tilted disc
- E. Large physiologic cup

From Stamper RL, Lieberman MF, Drake MV, eds. *Becker-Shaffer's Diagnosis and Therapy of the Glaucomas.* 8th ed. Philadelphia: Mosby, 2009: Box 19.3, p. 307.

Glaucoma occurs frequently in children with a history of congenital cataracts. Glaucoma may develop in up to 25% of children who have undergone cataract surgery early in life. The cause of aphakic glaucoma is not known but is thought to be the result of a coexistent anterior chamber deformity. Children treated for cataracts must be monitored closely for this complication, which may threaten vision.

DIAGNOSIS AND TREATMENT

The diagnosis of infantile glaucoma is made on recognition of the signs and symptoms. Once the diagnosis is established, treatment is started promptly. Unlike adult glaucoma, in which medication is often the first line of therapy, for infantile glaucoma the treatment is primarily surgical. The differential diagnosis is noted in Table 672.2.

Procedures used to treat glaucoma in children include surgery to establish a more normal anterior chamber angle (goniotomy and trabeculotomy), to create a site for aqueous fluid to exit the eye (trabeculectomy and Seton surgery), or to reduce aqueous fluid production (cyclocryotherapy and cyclophotocoagulation). Many children frequently require several operations to lower and maintain their IOP adequately, and long-term medical therapy may be necessary as well. Patients with multiple ocular abnormalities and those with aphakic glaucoma generally require more surgeries to achieve and maintain adequate IOP control. Although vision may be reduced secondary to glaucomatous optic nerve damage or corneal scarring, amblyopia is the most common cause of loss of vision in these children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 673

Orbital Abnormalities

Scott E. Olitsky and Justin D. Marsh

HYPERTELORISM AND HYPOTELORISM

Hypertelorism is wide separation of the eyes or an increased interorbital distance, which may occur as a morphogenetic variant, a primary deformity, or a secondary phenomenon in association with developmental abnormalities, such as frontal meningocele or encephalocele or the persistence of a facial cleft. Often-associated conditions are strabismus, exotropia, and sometimes optic atrophy.

Hypotelorism refers to narrowness of the interorbital distance, which may occur as a morphogenetic variant alone or in association with other anomalies, such as epicanthus or holoprosencephaly, or secondary to a cranial dystrophy, such as scaphocephaly.

EXOPHTHALMOS AND ENOPHTHALMOS

Protrusion of the eye is referred to as *exophthalmos* or *proptosis* and is a common indicator of orbital disease. It may be caused by shallowness of the orbits, as in many craniofacial malformations, or by increased tissue mass within the orbit, as with neoplastic, vascular, and inflammatory disorders. Ocular complications include exposure keratopathy, ocular motor disturbances, and optic atrophy with loss of vision.

Posterior displacement or sinking of the eye back into the orbit is referred to as *enophthalmos*. This may occur with orbital fracture or with atrophy of orbital tissue.

ORBITAL INFLAMMATION

Nonspecific Orbital Inflammation/Idiopathic Orbital Inflammation/Orbital Pseudotumor

Nonspecific orbital inflammation (NSOI) is an acute or subacute, usually benign, idiopathic inflammatory process of unknown etiology manifesting in specific orbital structures but usually with no systemic features. After thyroid-associated disease and lymphoproliferative disorders, it is the third most common noninfectious masslike inflammatory lesion of the orbit. It is unilateral in ~80% of patients, who often present with periorbital edema, ptosis, limited extraocular motion, pain, proptosis, conjunctival injection, chemosis or, less often, decreased visual acuity. There are five categories involving specific orbit tissues: dacryoadenitis (Fig. 673.1A), myositis (see Fig. 673.1B), anterior orbit (see Fig. 673.1C), posterior orbit apex (optic nerve; Fig. 673.2), and diffuse. Lacrimal gland inflammation and orbital myositis are the most common manifestations. The apical (**orbital apex syndrome**) often affects visual acuity and cranial nerves III, IV, and VI, as well as the first division of CN V. There is an association with a sclerosing IgG4-related disease variant, which may also manifest with inflammation and fibrosis in extraorbital tissue (pancreas, retroperitoneal); systemic IgG4-related disease is more common in patients with bilateral lacrimal gland involvement.

The differential diagnosis of NSOI includes sarcoidosis, granulomatosis with polyangiitis, lymphoma, and thyroid orbitopathy (Fig. 673.3). In addition, **Tolosa Hunt syndrome** may mimic NSOI; manifestations include unilateral headache, brow and eye pain, and cranial nerve palsies with associated cavernous sinus granulomatosis (Fig. 673.4). Biopsy is not initially needed for patients with NSOI who have a typical presentation (usually myositis) or a higher biopsy risk (orbital apex-optic nerve). Therapy is usually initiated with systemic corticosteroids.

Thyroid-related ophthalmopathy (see Chapter 601) is believed to be secondary to an immune mechanism, leading to inflammation and deposition of mucopolysaccharides and collagen in the extraocular muscles and orbital fat. Involvement of the extraocular muscles may lead to a restrictive strabismus. Lid retraction and exophthalmos may cause corneal exposure and infection or perforation. Involvement of the posterior orbit can compress the optic nerve. Treatment of thyroid-related ophthalmopathy may include the use of systemic corticosteroids, radiation of the orbit, eyelid surgery, strabismus surgery, or orbital decompression to eliminate symptoms and protect vision. The degree of orbital involvement is often independent of the status of the systemic disease.

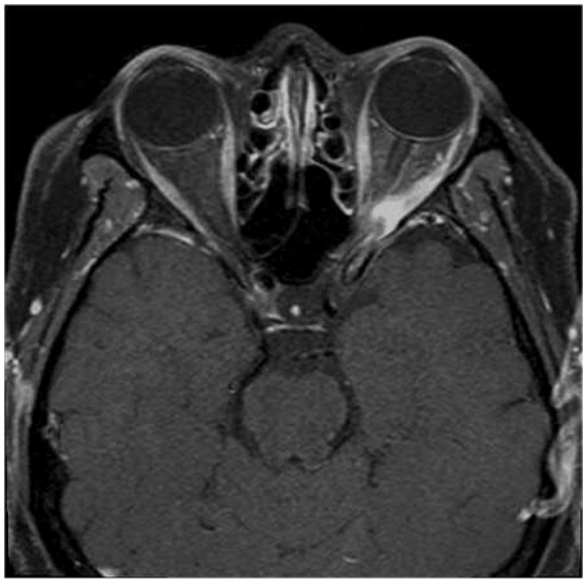

Fig. 673.2 Nonspecific orbital inflammation involving the orbital apex. Contrast-enhanced T1-weighted axial MRI with fat suppression showing inflammatory tissue at the left orbital apex resulting in compression and obliteration of the optic nerve. *(From Maamari RN, Couch SM. Nonspecific orbital inflammation. Adv Ophthalmol Optom. 2018;3:315–335: Fig. 7.)*



Fig. 673.1 Anatomic localization of nonspecific orbital inflammation. **A,** Lacrimal gland (right eye). **B,** Extraocular muscle (left lateral rectus). **C,** Orbital fat (left inferomedial extraconal space). *(From Lee MJ, Planck SR, Choi D, et al. Non-specific orbital inflammation: current understanding and unmet needs. Prog Retinal Eye Res. 2021;81:100885: Fig. 5).*

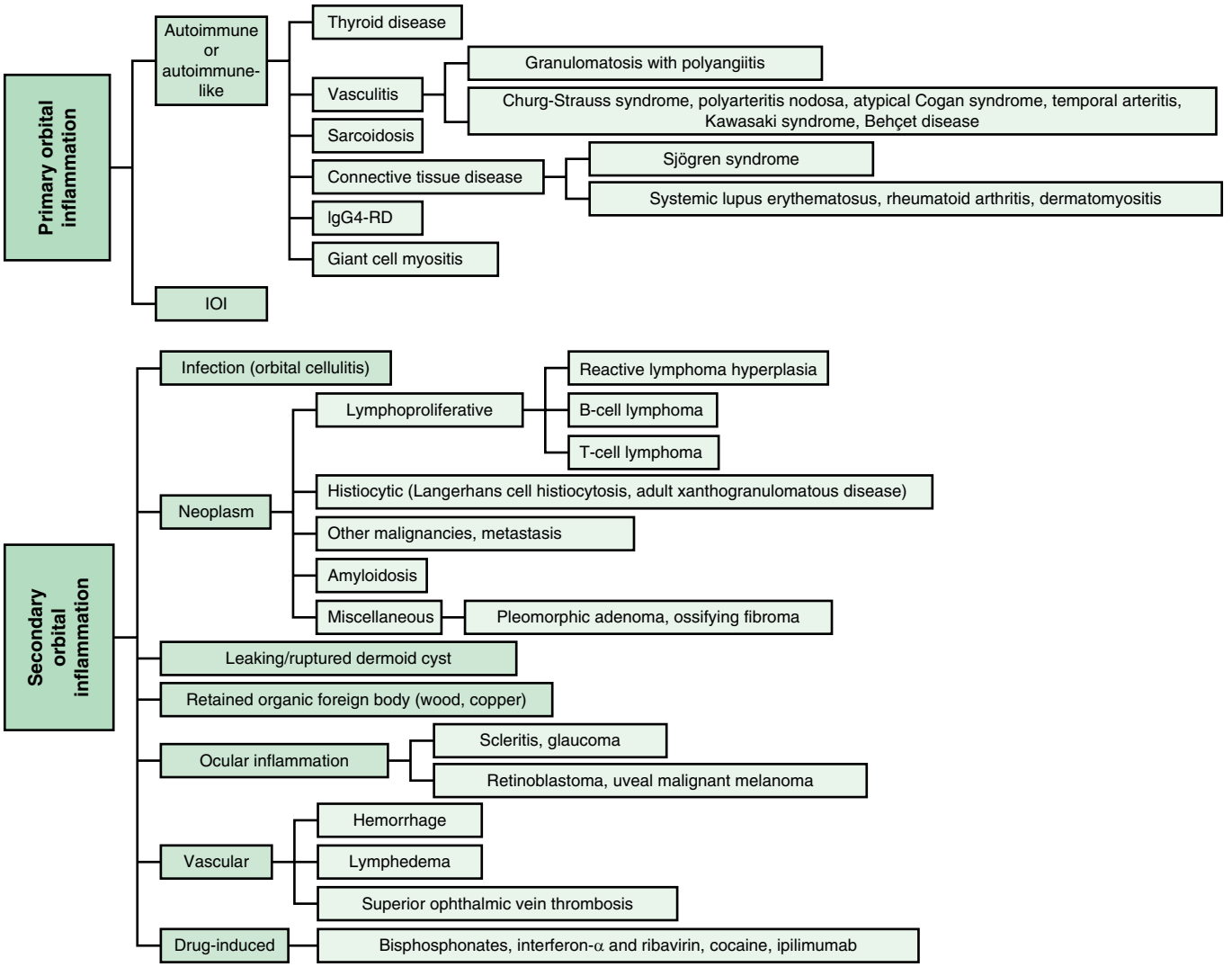

Fig. 673.3 Classification for possible causes of orbital inflammation. NSOI, nonspecific orbital inflammation. *(From Mombaerts I, Rose GE, Garrity JA. Orbital inflammation: biopsy first. Surv Ophthalmol. 2016;61:664–669: Table 1.)*

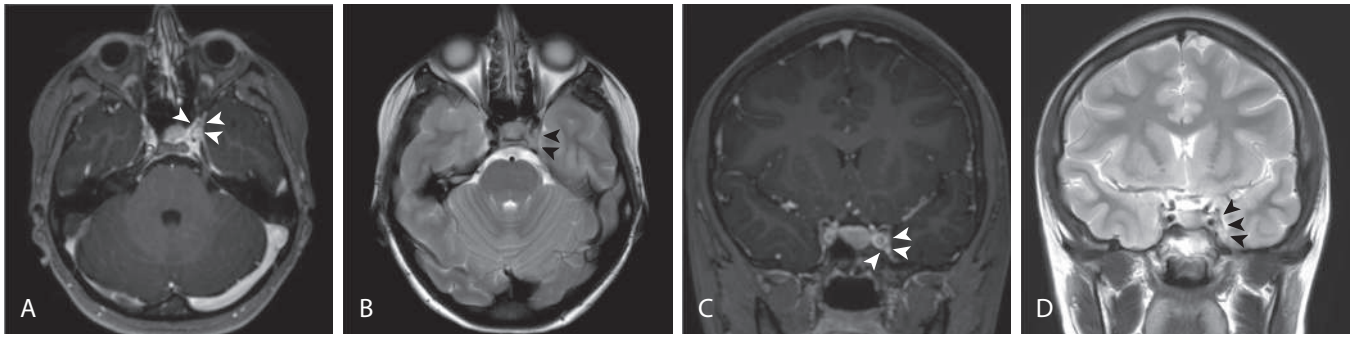

Fig. 673.4 MR scan of the brain showing an enhancing space-occupying lesion within the left cavernous sinus *(arrowheads)*. Postgadolinium T1-weighted (**A**) and T2-weighted (**B**) axial views. Postgadolinium T1-weighted (**C**) and T2-weighted (**D**) coronal views. *(From Pérez CA, Evangelista M. Evaluation and management of Tolosa-Hunt syndrome in children: a clinical update. Pediatr Neurol. 2016;62:18–26: Fig. 2.)*

Other systemic disorders that may cause inflammatory disease within the orbit include lymphoma (see Chapter 545), sarcoidosis (see Chapter 209), amyloidosis (see Chapter 206), polyarteritis nodosa (see Chapter 210.3), systemic lupus erythematosus (see Chapter 199), dermatomyositis (see Chapter 200), granulomatosis with polyangiitis (see Chapter 210), and juvenile xanthogranuloma (see Chapter 556).

TUMORS OF THE ORBIT

Various tumors occur in and about the orbit in childhood. Among benign tumors, the most common are vascular lesions (principally hemangiomas; Fig. 673.5) and dermoids. Among malignant neoplasms, rhabdomyosarcoma, lymphosarcoma, and metastatic neuroblastoma are the most frequent. Optic nerve gliomas (see Chapter 671)



Fig. 673.5 Orbital hemangioma. **A**, Note the proptosis. **B**, CT scan. *(Courtesy Amy Nopper, MD, and Brandon Newell, MD.)*

are most commonly seen in patients with neurofibromatosis and may present with poor vision or proptosis. Retinoblastoma (see Chapter 551) may extend into the orbit if it is discovered late or goes untreated. Teratomas are rare tumors that typically grow rapidly after birth and exhibit explosive proptosis.

The effects of orbital tumors vary with their locations and growth patterns. The principal signs are proptosis, resistance to retroplacement of the eye, and impairment of eye movement. A palpable mass may be found. Other significant signs are ptosis, optic nerve head congestion, optic atrophy, and loss of vision. Bruit and visible pulsation of the globe are important clues to vascular lesions.

Evaluation of orbital tumors includes ultrasonography, MRI, and CT. Pseudotumor of the orbit also must be considered in children with signs of a mass lesion. In selected cases, an incisional or excisional biopsy of the lesion may be warranted.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 674

Orbital Infections

Scott E. Olitsky, Justin D. Marsh, and Mary Anne Jackson

Orbital infections are common in children. It is important to be able to distinguish the different forms of infection that occur in the orbital region to allow rapid diagnosis and treatment to prevent loss of vision or spread of the infection to the nearby intracranial structures (Table 674.1).

DACRYOADENITIS

Dacryoadenitis is inflammation of the lacrimal gland; it most commonly occurs in the pediatric population and in some young adults and is related to a variety of infectious pathogens or inflammatory processes (see Chapter 673). Pain, redness, swelling, increase in tearing, and discharge over the lacrimal gland are noted and usually visible at the lateral one third of the upper eyelid; concurrent preauricular lymphadenopathy may be noted (Fig. 674.1). It may occur with mumps (in which case it is usually acute and bilateral, subsiding in a few days or weeks), with influenza, infectious mononucleosis, and herpes zoster. *Staphylococcus aureus* may produce a suppurative dacryoadenitis, and other bacterial causes include streptococci and *Neisseria gonorrhoeae*. Chronic dacryoadenitis is associated with certain systemic diseases, particularly sarcoidosis, tuberculosis, and syphilis. Some systemic diseases may produce enlargement of the lacrimal and salivary glands (Mikulicz syndrome).

DACRYOCYSTITIS

Dacryocystitis is an infection of the lacrimal sac and generally requires obstruction of the nasolacrimal system to allow its development. Acute, subacute, and chronic forms are described. Most patients with dacryocystitis present with redness and swelling over the region of the lacrimal sac (Fig. 674.2). It is treated with warm compresses and systemic antibiotics. This helps control the infection, but the obstruction usually requires definitive treatment to reduce the risk of recurrence.

Dacryocystitis may occur in newborns as a complication of a congenital dacryocystocele (see Chapter 665). If present, systemic antibiotics and digital pressure for decompression are recommended. The obstruction of the nasolacrimal system may resolve once the infection clears. If spontaneous resolution does not occur, probing should be considered within a short time frame. An intranasal cyst may be present in conjunction with the dacryocystocele. If this occurs, marsupialization of the cyst may be needed at the time of the probing.

PRESEPTAL CELLULITIS

Inflammation of the lids and periorbital tissues without signs of true orbital involvement (such as proptosis or limitation of eye movement) is generally referred to as *periorbital* or *preseptal cellulitis* and is a form of facial cellulitis. This is a common entity in young children, usually under age 5 years, and may rarely be caused by direct seeding related to bacteremia (usually seen in those <3 years), or more often sinusitis,

Table 674.1 Manifestations of Orbital Cellulitis Associated with Ethmoid Sinusitis

MANIFESTATIONS	CLINICAL AND CT IMAGING DESCRIPTION
1: Inflammatory edema	Eyelid edema and erythema; eye may be swollen shut Fever Painless extraocular muscle movement; full range of motion Visual acuity normal Edema of orbit without abscess formation
2: Orbital cellulitis	Inflammation of orbital contents without discrete abscess formation Fever, malaise
3: Subperiosteal abscess	Purulent exudate beneath medial orbital periosteum of lamina papyracea Pain on extraocular muscle movement Fever, malaise, may have pain with extraocular muscle movement Displacement of globe (down and out)
4: Orbital abscess/ orbital apex syndrome	Purulent collection within orbit Proptosis, chemosis Ophthalmoplegia; pain on extraocular muscle movement Decreased vision Fever, malaise
5: Septic cavernous sinus thrombophlebitis	Bilateral (contralateral) eye findings; ptosis, proptosis, swelling, ophthalmoplegia Severe headaches Meningismus, fever, severe malaise Decreased vision

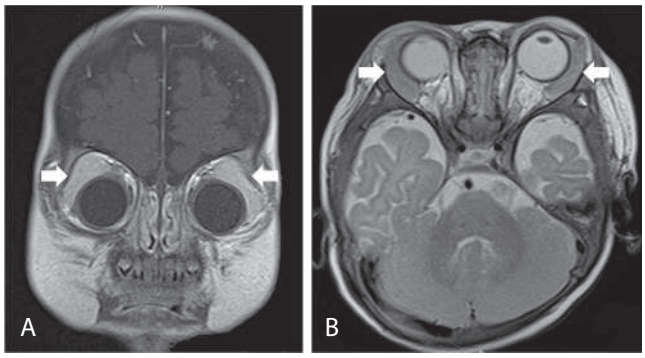

Fig. 674.1 MRI of the bilateral lacrimal glands. **A,** Coronal T1-weighted image. **B,** Axial T2-weighted image. The bilateral lacrimal glands are markedly enlarged *(arrows)*. *(From Hoshino A, Fujii T, Hibino S, Abe Y. Acute infantile dacryoadenitis. J Pediatr. 2014;164:425: Fig. 2))*



Fig. 674.2 Dacrycystitis in a child previously treated for nasolacrimal duct obstruction.

trauma, or other infected wounds in the periorbital region, or an abscess of the lid or periorbital region (pyoderma, hordeolum, conjunctivitis, dacryocystitis, insect bite). Brown recluse spider bites are often associated with considerable local swelling, and in the first 24 hours, the bite itself may not be obvious to the parent or the examiner.

Patients present with eyelid swelling; the edema may be so intense as to make it difficult to evaluate the globe. Before the *Haemophilus influenzae* type B (Hib) vaccine, the most common cause of pediatric preseptal (facial) cellulitis was bacteremia caused by Hib. Group A streptococcus (GAS), pneumococcus, and *S. aureus* (especially if related to an infected wound or bite) are the most common identifiable etiologic agents. Occasionally, young children with herpes simplex virus infection of the periorbital tissues will present first with swelling and redness, followed by the appearance of discrete tiny ulcers.

Clinical examination will show **lack of** proptosis, with normal painless ocular movements, normal vision, and normal pupil responses. CT imaging can demonstrate edema of the lids and subcutaneous tissues anterior to the orbital septum (Fig. 674.3); imaging is not necessary in those without signs of an orbital process. Antibiotic therapy and careful clinical monitoring and evaluation to identify signs of local progression are essential. In well-appearing children with infected traumatic wounds or insect bites associated with periorbital cellulitis, oral antibiotics that target *S. aureus* and GAS may be considered. For young children in whom a hematogenous process is suspected, or in any toxic, ill-appearing child, blood cultures should be obtained, and hospitalization and intravenous antibiotics are required. Most recommend intravenous ampicillin with sulbactam or intravenous clindamycin plus cefotaxime (or ceftriaxone) for hospitalized patients.



Fig. 674.3 CT scan of a patient with preseptal cellulitis.

Periorbital necrotizing fasciitis is a severe, rapidly spreading form of periorbital bacterial infection, involving both superficial and deep fascial planes. The disease may have no preceding events or may follow trauma to the periorbital skin. Initial symptoms resemble periorbital/facial cellulitis but rapidly progress to tissue necrosis, blistering, and significant systemic toxicity. Streptococci and *S. aureus* are the most common pathogens. Treatment includes broad spectrum antibiotics, surgical debridement, and, when available, hyperbaric oxygen therapy.

ORBITAL CELLULITIS

Inflammation of the tissues of the orbit, characterized by the triad of proptosis, painful limitation of movement of the eye (ophthalmoplegia), and potentially decreased visual acuity, is termed *orbital cellulitis* (see Table 674.1). Edema of the conjunctiva (chemosis) and inflammation and swelling of the eyelids may be seen. The mean age is ~7 years, ranges from 1 week to 18 years, and has a 2:1 predilection in males. An increased risk is seen in the winter because complicated obligatory sinusitis often follows respiratory viral infection (e.g., influenza). Patients often feel ill, are febrile, and appear toxic, and leukocytosis sometimes but not always may be appreciated. Practitioners should have an increased clinical suspicion for intracranial extension in those with headache, vomiting, and any focal neurologic findings.

Orbital cellulitis may follow direct infection of the orbit from a wound, hematogenous seeding of organisms during bacteremia, or *more often* direct extension or venous spread of infection from contiguous sites such as the lids, conjunctiva, globe, lacrimal gland, nasolacrimal sac, or *more commonly* from the paranasal (ethmoid) sinuses. The **differential diagnosis** includes idiopathic orbital inflammation, myositis, sarcoidosis, granulomatous vasculitis, leukemia, lymphoma, histiocytic disorders, rhabdomyosarcoma, ruptured dermoid cyst, orbital trauma, and orbital foreign body (see Chapter 673). In some cases, primary or metastatic tumor in the orbit can produce the clinical picture of orbital cellulitis.

Although the most common cause of orbital cellulitis in children is direct extension or venous spread from infected paranasal sinuses, an antecedent history of sinusitis requiring antibiotic therapy is generally not reported. The spread of infection to the orbit from the sinuses is more prevalent in children because of their thinner bony septa and sinus wall, greater porosity of bones, open suture lines, and larger vascular foramina (Fig. 674.4). The spread of infection is also facilitated by the venous and lymphatic communication between the sinuses and surrounding structures, which allow flow in either direction, facilitating retrograde thrombophlebitis. Frequently noted pathogenic organisms include *S. aureus,* streptococcus species (especially *Streptococcus anginosus* also known as the *Streptococcus milleri* group, and *S. pyogenes*), *Streptococcus pneumoniae*, and anaerobes (e.g., *Bacteroides* spp., *Prevotella* spp.).

The potential for complications is high. Visual loss can occur secondary to an increase in orbital pressure that causes retinal artery or ophthalmic vein occlusion or optic neuritis. This is more likely to occur in the presence of an orbital abscess. Extension of infection from the orbit into the cranial cavity may lead to cavernous sinus thrombosis or meningitis, epidural or subdural empyema, or brain abscesses (Fig. 674.5). Additional complications include optic atrophy, exposure keratitis, and retinal or choroidal ischemia. An interdisciplinary team involving an infectious disease specialist, ophthalmologist, otolaryngologist, and, where indicated, a pediatric neurosurgeon should be involved in the care of the patient with orbital infection.

Orbital cellulitis must be recognized promptly and treated aggressively. Hospitalization and systemic antibiotic therapy are indicated. All patients with suspected orbital cellulitis should undergo contrast CT imaging of the orbit, paranasal sinuses, and adjacent cortex. Lumbar puncture should not be considered unless there is a meningitis presentation (and only after CT imaging), assuming there are no signs of elevated intracranial pressure or focal neurologic findings on examination. Parenteral antibiotics should be initiated immediately. Antimicrobial agents should begin with intravenous ampicillin with sulbactam or intravenous clindamycin plus ceftriaxone, cefepime (or cefotaxime); in cases where there is suspicion for intracranial extension, vancomycin plus cefotaxime (or ceftriaxone) plus metronidazole should be given.

If the patient does not show evidence of improvement or if there are signs of progression, sinus and abscess drainage should be considered. The presence of an orbital or unresponsive subperiosteal abscess (see Fig. 674.4) may require urgent drainage of the orbit. The clinical presentation and course of each individual patient should dictate the need and timing of abscess drainage.

Most children (especially those <9 years of age) with a medial **subperiosteal abscess** can initially be managed with intravenous antibiotics, which usually are sufficient for resolution of the subperiosteal abscess. Adjunctive use of corticosteroids is controversial but may hasten resolution. Patients should be examined frequently for signs of visual deterioration or pupillary abnormalities. Most will become afebrile within 48 hours and have examination improvement by 72 hours. If there are pupillary abnormalities, decreased vision, or failure to improve, the subperiosteal abscess should be drained.

Many recommend drainage for a subperiosteal abscess and an orbital abscess in older children. Additionally, abscesses involving the orbital roof with associated frontal sinus disease may require more frequent surgical intervention. Operative procedures should be coordinated with the otolaryngologist to allow for sinus drainage at the same time that the subperiosteal abscess is drained, and cultures should be obtained from the sinus and the abscess. Similarly, if neurosurgical intervention is required, operative coordination should occur with ophthalmology and otolaryngology.

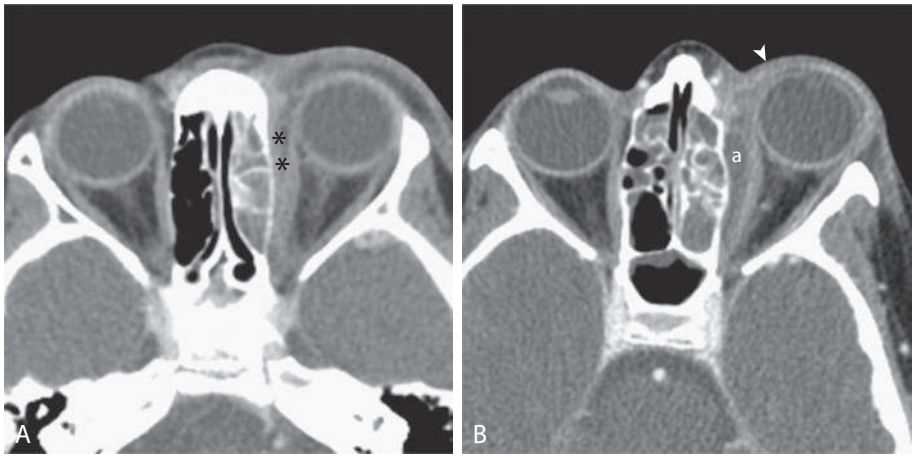

Fig. 674.4 Orbital complications of sinusitis. **A,** Orbital phlegmon and orbital cellulitis. Axial contrast-enhanced computed tomography (CECT) shows left preseptal periorbital soft tissue swelling (STS) and left ethmoid air cell opacification. There is increased density of the left medial extraconal orbital fat *(asterisks)*, consistent with phlegmon. The adjacent medial rectus muscle is thickened. There is subtle increased density of the intraconal orbital fat, consistent with orbital cellulitis. **B,** Orbital subperiosteal abscess. Axial CECT shows preseptal periorbital STS *(arrowhead)*, extensive left ethmoid air cell opacification, and an elliptical low-density, peripherally enhancing, medial subperiosteal abscess *(a)*. *(Modified from Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017. Fig. 10.37, p. 377.)*

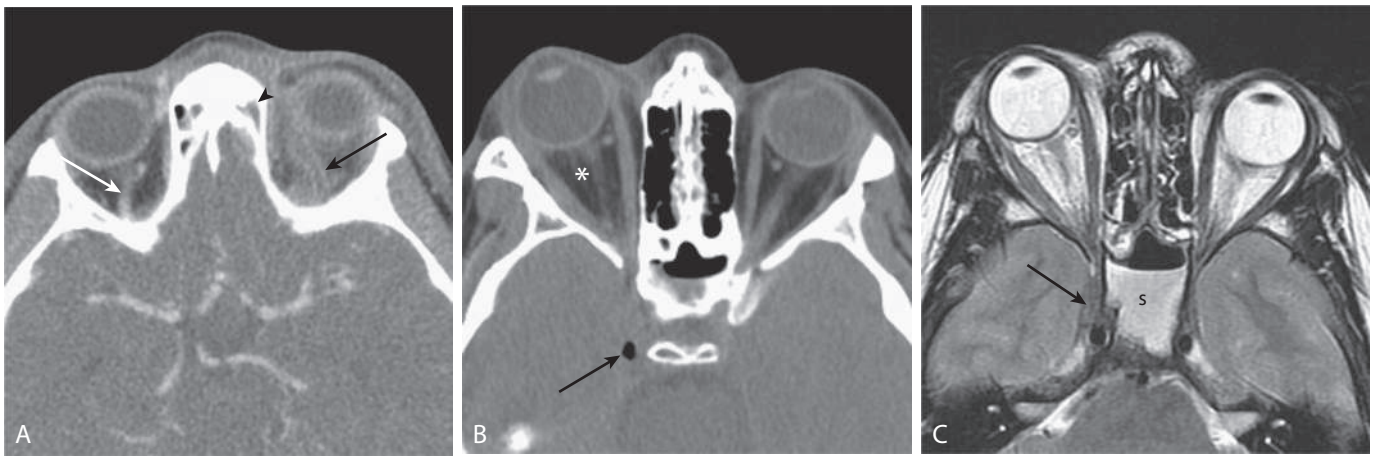

Fig. 674.5 Superior ophthalmic vein (SOV) and cavernous sinus thrombosis (CST). **A,** SOV thrombosis. Axial contrast-enhanced computed tomography (CECT) shows opacification of the partially visualized paranasal sinuses *(arrowhead)*. There is a tram-track sign due to lack of enhancement of the thrombosed left SOV *(black arrow)*. Compare with the normally enhancing right SOV *(white arrow)*. **B,** CST (new patient). Axial computed tomography image demonstrates a sphenoid sinus air–fluid level caused by sphenoid sinusitis. Gas is present within the right cavernous sinus *(arrow)* due to CST. There is resultant right ocular proptosis with minimal reticulation of the right intraconal orbital fat *(asterisk)*. **C,** Axial T2-weighted magnetic resonance (same patient) shows low signal intensity within the right cavernous sinus with lateral convexity of its lateral margin *(arrow)*, consistent with CST. Note the sphenoid sinus air–fluid level *(s)*. *(From Walters MM, Robertson RL [eds]. Pediatric Radiology: The Requisites. 4th ed. Philadelphia: Elsevier, 2017: Fig. 10.38, p. 377.)*

Table 674.2 Endophthalmitis Categories and the Most Common Pathogens in Each

CATEGORY	COMMON PATHOGENS
Acute postoperative	Coagulase-negative staphylococci
Chronic postcataract	*Propionibacterium acnes*
Postinjection	Viridans streptococci, coagulase-negative staphylococci
Bleb-related	Streptococci, *Haemophilus influenzae*
Posttraumatic	*Bacillus cereus*
Keratitis related	Molds (e.g., *Fusarium*)
Endogenous	*Staphylococcus aureus*, streptococci, gram-negative bacilli
Fungal	Candida, Aspergillus, Fusarium

From Durand ML. Endophthalmitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* Philadelphia: Elsevier, 2020: Table 114.1, p. 1524.

ENDOPHTHALMITIS

Endophthalmitis is infection of the aqueous and/or vitreous humors and is rare in children; major predisposing factors are noted in Table 674.2. Endogenous hematogenous bacterial (*S. aureus*, streptococci, gram-negative bacilli) and fungal (candida, *Aspergillus* spp., *Fusarium*) may be seen in immunosuppressed and neutropenic patients, whereas histoplasmosis, blastomycosis, coccidiomycosis, and cryptococcus endophthalmitis may rarely be seen as part of disseminated systemic mycotic infection. In addition, ocular toxocariasis may mimic bacterial or fungal endophthalmitis.

The diagnosis requires vitreous sampling because aqueous samples are often negative. The pathogen may be identified by staining, culture, and molecular methods.

Treatment of bacterial endophthalmitis requires intravitreal antibiotics; systemic antibiotics alone are ineffective. Fungal disease often requires combined intraocular and systemic antifungal agents.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 675

Injuries to the Eye

Scott E. Olitsky and Justin D. Marsh

Approximately 30% of all blindness in children results from trauma. Children and adolescents account for a disproportionate number of episodes of ocular trauma. Males ages 11-15 years are the most vulnerable; their injuries outnumber those in females by a ratio of about 4:1. The majority of injuries are related to sports, sticks, stones, fireworks, paint balls, air-powered BB guns, and other projectiles. High-velocity projectiles and fireworks cause particularly devastating ocular and orbital injuries. Much of the trauma is avoidable (see Chapter 14). Any part of the orbit or globe may be affected (Figs. 675.1 and 675.2).

ECCHYMOSIS AND SWELLING OF THE EYELIDS

Ecchymosis and edema of the eyelids are common after blunt trauma (Fig. 675.3). These disorders are self-limiting, absorb spontaneously, and can be treated with iced compresses and analgesics. Periorbital

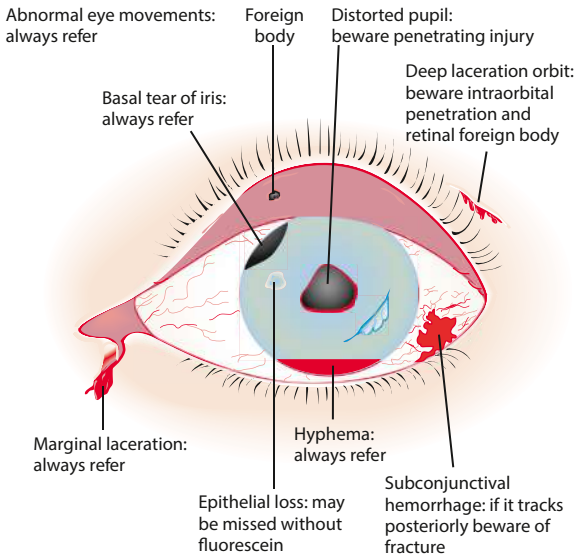

Fig. 675.1 The injured eye. *(From Khaw PT, Shah P, Elkington AR. Injury to the eye. BMJ. 2004;328:36–38.)*

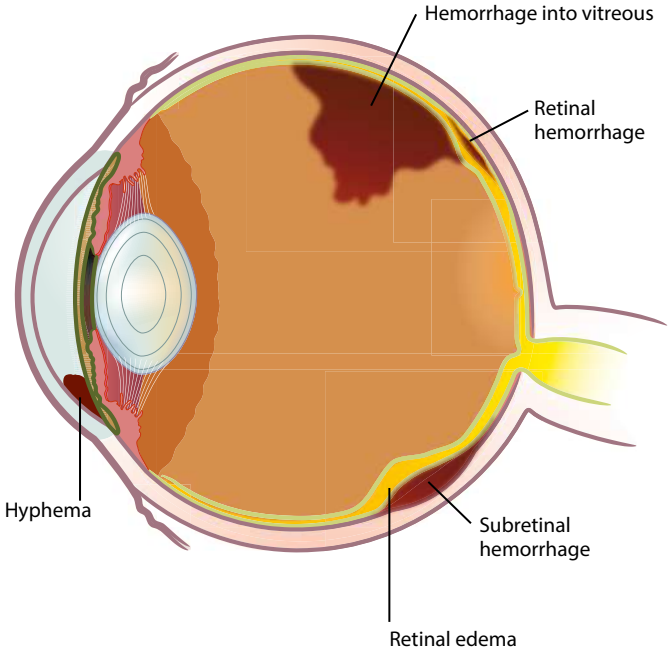

Fig. 675.2 Various types of ocular hemorrhage after blunt trauma to the globe. *(From Reilly BM. Practical Strategies in Outpatient Medicine. 2nd ed. Philadelphia: WB Saunders; 1991:68.)*



Fig. 675.3 Eyelid ecchymosis and subconjunctival hemorrhage.

ecchymosis should prompt careful examination of the eye and surrounding structures for more serious injuries such as orbital bone fracture, intraocular hemorrhage, or rupture of the globe.

LACERATIONS OF THE EYELIDS

Eyelid lacerations may vary from simple to complex. When evaluating an eyelid laceration, key findings include the depth of the laceration, its location, and whether there is involvement of the canaliculus (lacrimal ducts). Most superficial eyelid lacerations may be closed by the primary caregiver, but if a laceration is deep, involves the lid margin, or involves the canaliculus, it should be evaluated by an ophthalmologist. The levator muscle is responsible for elevation of the upper eyelid and runs deep to the skin and orbicularis oculi muscle. If the levator muscle is compromised and not recognized at initial repair, ptosis will occur. Therefore, if orbital fat is visible in the laceration, the laceration has compromised the skin, orbicularis oculi, levator muscles, and orbital septum and must be meticulously repaired to avoid ptosis. Eyelid margin involvement (Fig. 675.4) also requires careful repair to avoid lid malposition and notch formation. These can lead to ocular surface problems in the future, resulting in corneal scarring and loss of vision. Lacerations involving the canaliculus require intubation of the nasolacrimal system, in addition to repair of the laceration of the eyelid to avoid future tearing problems. Proper primary repair of eyelid lacerations often achieves a superior outcome to secondary repair at a later date. As with any eyelid injury, careful examination of the eye and surrounding tissue is required.

SUPERFICIAL ABRASIONS OF THE CORNEA

When the corneal epithelium is scratched, abraded, or denuded, it exposes the underlying epithelial basement layer and superficial corneal nerves. This is accompanied by pain, tearing, photophobia, and decreased vision. Corneal abrasions are detected by instilling fluorescein dye and inspecting the cornea using a blue-filtered light (Fig. 675.5). A slit lamp is ideal for this examination, but a direct ophthalmoscope with a blue filter or a handheld Wood lamp is adequate for young children.

Treatment of a corneal abrasion is directed at promoting healing and relieving pain. Abrasions are treated with frequent applications of a topical antibiotic ointment until the epithelium is completely healed. The use of a semipressure patch does not improve healing time or decrease pain. An improperly applied patch may itself abrade the cornea. A topical cycloplegic agent (cyclopentolate hydrochloride 1%) can relieve the pain from ciliary spasm in patients with large abrasions. Topical anesthetics should not be given at home because they retard epithelial healing and inhibit the natural blinking reflex.

FOREIGN BODY INVOLVING THE OCULAR SURFACE

This usually produces acute discomfort, tearing, and inflammation. Most foreign bodies can be detected by examination in good light with the aid of magnification (Fig. 675.6) or a direct ophthalmoscope set on a high plus lens (+10 or +12). In many cases, slit-lamp examination is necessary, especially if the particle is deep or metallic. Some conjunctival foreign bodies tend to lodge under the upper eyelid, causing the sensation of corneal foreign body, as they make contact with the globe on eyelid movement; they may also produce vertically oriented linear corneal abrasions (Fig. 675.7). Finding these abrasions should lead to a suspicion of such a foreign body, and eversion of the lid may be necessary (see Chapter 659). If a foreign body is suspected but not found, further examination is indicated. If the history suggests injury with a high-velocity particle, radiologic examination of the eye may be needed to explore the possibility of an intraocular foreign body.

Removal of a foreign body can be facilitated by instillation of a drop of topical anesthetic. Many foreign bodies can be removed by irrigation or by gently wiping them away with a moistened cotton-tipped applicator. Embedded foreign bodies or foreign bodies in the central cornea should be treated by an ophthalmologist. Removal of corneal foreign bodies may leave epithelial defects, which are treated as corneal abrasions. Metallic foreign bodies may cause rust to form in the corneal tissues; examination



Fig. 675.4 Eyelid margin laceration.

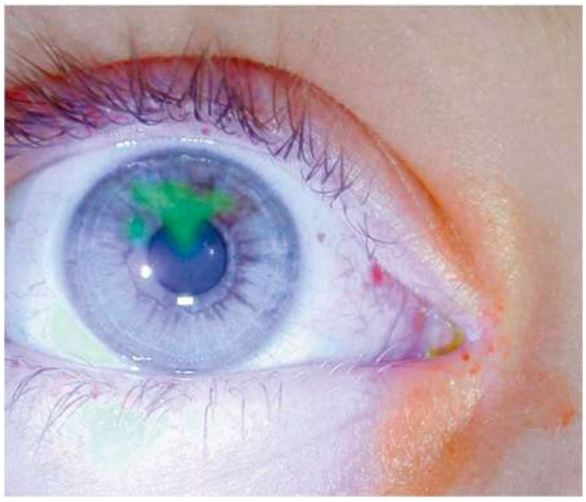

Fig. 675.5 Corneal abrasion with fluorescein staining.

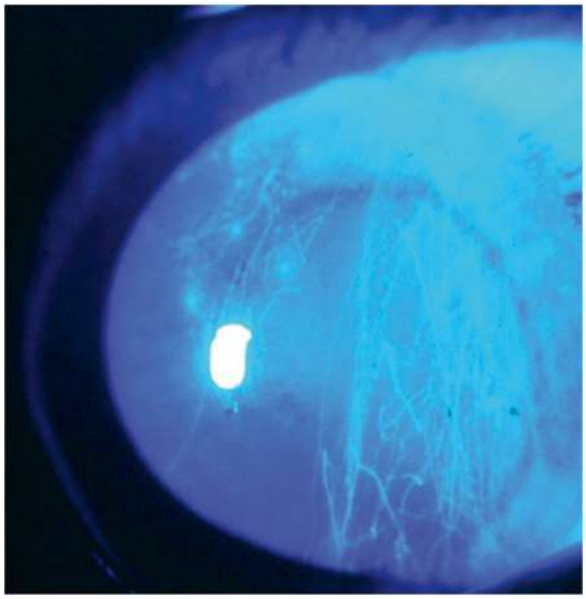

Fig. 675.6 Vertically oriented linear corneal abrasions secondary to a foreign body underneath the upper eyelid.

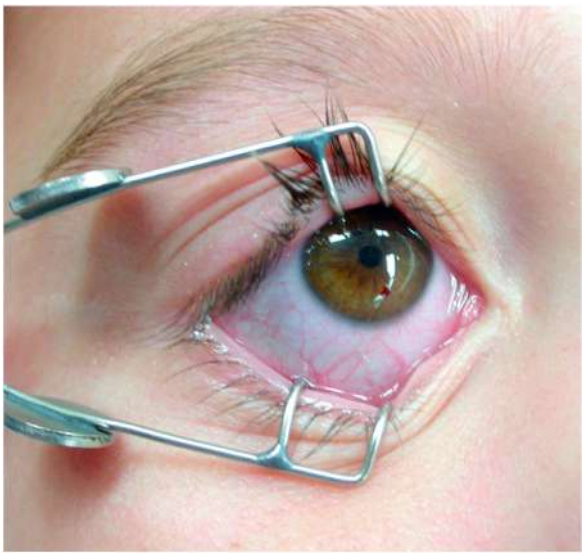

Fig. 675.7 Superficial corneal foreign body.

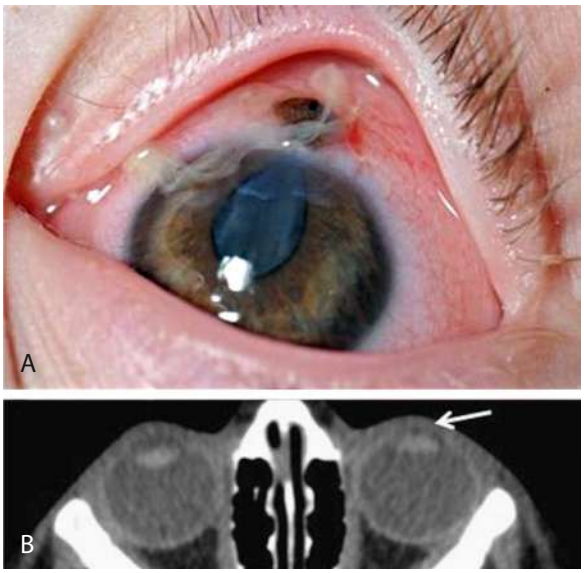

Fig. 675.8 A, Photograph of an open globe injury with a peaked pupil because of iris prolapse through the sclera, a shallow anterior chamber, and a traumatic cataract. B, CT imaging demonstrating a shallow left anterior chamber when compared to the right *(arrow)* but without evidence of an intraocular foreign body. *(From Hwang RY, Schoenberger SD. Imaging a peaked pupil in a traumatic open globe injury. J Pediatr. 2013;163:1517: Figs. A and B.)*

by an ophthalmologist 1 or 2 days after removal of a foreign body is recommended because a rust ring might require further treatment.

HYPHEMA

This is the presence of blood in the anterior chamber of the eye. It may occur with either a blunt or perforating injury and represents a situation that may threaten vision. Hyphema appears as a bright or dark red fluid level between the cornea and iris, or as a diffuse murkiness of the aqueous humor. Children with hyphema present with acute loss of vision, with or without pain. The treatment of hyphema involves efforts to minimize the vision-threatening sequelae, such as rebleeding, glaucoma, and corneal blood staining. Bedrest is necessary, ideally with elevation of the head of the bed to 30 degrees. A shield (without underlying patch) is placed on the affected eye to prevent repeat trauma, and a cycloplegic agent is used to immobilize the iris. In addition, topical or systemic steroids are used to minimize intraocular inflammation. Antiemetics should be considered if the patient is experiencing nausea. All nonsteroidal anti-inflammatories and aspirin must be avoided. Rarely, hospitalization and sedation may be necessary to ensure compliance in some children. If the intraocular pressure is elevated, topical and systemic pressure-lowering medications are used. If the pressure is not controllable by such measures, then surgical evacuation of the clot may be required to minimize the risk of permanent vision loss. Patients with sickle cell disease or trait are at higher risk of acute loss of vision secondary to elevated intraocular pressure or optic nerve infarction and may require more aggressive intervention. Individuals with a history of traumatic hyphema have an increased incidence of glaucoma later in life and should be monitored on a regular basis throughout their lives.

OPEN GLOBE

A penetrating, perforating, or blunt injury resulting in compromise of the cornea or sclera of the eye is one of the most sight-threatening injuries that can be sustained (Fig. 675.8). An open globe is a true ophthalmologic emergency that requires prompt, careful evaluation and immediate repair to minimize vision loss. Permanent vision loss can result from corneal scarring, loss of intraocular contents, or infection. Evaluation involves careful history, including time and mechanism of the injury, as well as visual acuity and inspection of the eye. A full-thickness corneal wound will often present with prolapsed iris tissue through the wound. If this is not immediately evident, a peaked or irregular pupil may be a sign of full-thickness laceration. Scleral compromise may be more difficult to identify because of overlying structures. The thinnest part of the sclera is at the corneoscleral junction (the limbus) and just posterior to the insertion of the rectus muscles. When an open globe is caused by blunt force injury, these are the two areas most likely involved. A ruptured globe occurs when the compressive traumatic force is high enough to lead to a rupture of the globe itself. Although the term *ruptured globe* is frequently used to describe any open eye, the term should be reserved for this specific form of trauma. The force required to rupture the globe often is severe enough to lead to other permanent injuries to the eye with a resultant poor prognosis even when the rupture itself can be repaired. This specific term denotes a poorer prognosis than many other forms of open globe injuries.

The overlying conjunctiva may not be compromised but a subconjunctival hemorrhage may be present, obscuring the view. In these cases, look for a shallow anterior chamber, low intraocular pressure, or pigment within the involved area. If the patient has been diagnosed with an open globe, the examination should be stopped, an eye shield placed immediately, and the ophthalmologist contacted to minimize further ocular compromise.

OPTIC NERVE TRAUMA

The optic nerve may be injured in both penetrating and blunt trauma. The injury may occur at any point between the globe and the chiasm. Traumatic injury to the optic nerve, regardless of cause or location, results in reduced vision and a pupillary defect. Direct trauma to the intraorbital optic nerve may cause transection, partial transection, or optic sheath hemorrhage. Fractures involving the skull base may cause injury to the intracranial portions of the optic nerve. Treatment decisions are difficult because there are no universally accepted guidelines, and the prognosis for good visual outcome is often poor. Medical management involves observation and the use of high-dose corticosteroids, although the use of corticosteroids has not been proven to improve visual outcomes and has been shown to increase the risk of death in patients with significant head injury. Surgical intervention involves optic nerve sheath decompression for nerve sheath hemorrhages. If compression of the optic nerve is secondary to orbital hemorrhage, prompt lateral canthotomy and cantholysis should be performed to relieve intraorbital pressure. Decompression of the optic canal may be performed if there is compression of the optic nerve by a bone fragment. Optic canal decompression is controversial in the absence of direct bone compression.

CHEMICAL INJURIES

Chemical burns of the cornea and adnexal tissue are among the most urgent of ocular emergencies, and they are most common in toddler and preschool-age children and men. Laundry detergent pods have become an increasingly common source of ocular injury to young children over the last decade. Alkali burns are usually more destructive than acid burns because they react with fats to form soaps, which damage cell membranes, allowing further penetration of the alkali into the eye. Acids generally cause less severe, more localized tissue damage. The corneal epithelium offers moderate protection against weak acids, and little damage occurs unless the pH is 2.5 or less. Most stronger acids precipitate tissue proteins, creating a physical barrier against their further penetration.

Mild acid or alkali burns are characterized by conjunctival injection and swelling and mild corneal epithelial erosions. The corneal stroma may be mildly edematous, and the anterior chamber may have mild to moderate cell and flare reactions. With strong acids, the cornea and conjunctiva rapidly become white and opaque. The corneal epithelium may slough, leaving a relatively clear stroma; this appearance may initially mask the severity of the burn. Severe alkali burns are characterized by corneal opacification.

Emergency treatment of a chemical burn begins with immediate, copious irrigation with water or saline. Local debridement and removal of foreign particles should be performed as irrigation continues. If the nature of the chemical injury is unknown, the use of pH test paper is helpful in determining whether the agent was basic or acidic. Irrigation should continue for at least 30 minutes or until 2 L of irrigant has been instilled in mild cases and for 2-4 hours or until 10 L of irrigant has been instilled in severe cases. At the end of irrigation, the pH should be within a normal range (7.3-7.7). The pH should be checked again approximately 30 minutes after irrigation to ensure that it has not changed. The goal of treatment is to minimize sequelae that may threaten vision, such as conjunctival scarring, corneal scarring/opacification, glaucoma, cataract, and phthisis.

ORBITAL FRACTURES

The orbit is the bony structure surrounding the eye. Any of these bones may fracture in a traumatic incident. Superior and lateral wall fractures are the least common of the fracture sites, but superior orbital fracture is the most significant because of the potential of intracranial injury. The medial wall of the orbit is very susceptible to fracture because of the thin nature of the lamina papyracea. Perhaps the most common site of fracture from blunt trauma is the orbital floor. This is often referred to as blowout fracture. At times, the fracture may act as a trapdoor, entrapping orbital contents within the fracture site. In some cases, there may be very little external evidence of trauma, the so called "white-eyed blow-out fracture."

The patient often presents with a recent history of periorbital trauma and pain. Diplopia, eyelid swelling, eye movement restriction, or hypesthesia may or may not be present. Eye symptoms may be associated with nausea and bradycardia if the inferior rectus is entrapped in the fracture site. A complete ophthalmic examination, including visual acuity, examination of the pupil for ocular alignment, ocular motility, anterior segment, and fundus status, as well as the history of the injury, is required because there are often accompanying ocular injuries. The diagnosis of fracture is suspected if eye misalignment, eye movement restriction, or enophthalmos (sunken eye) are present. The diagnosis can be verified by orbital CT scan, although small areas of entrapped muscle may easily be missed if careful attention is not directed toward the fracture site.

Medical management includes iced compresses to the orbit and elevation of the head of the bed for the first 24-48 hours. Broad-spectrum antibiotics are sometimes recommended for 14 days because of the exposure of the orbital contents to the sinus cavity. In medial wall fractures, instructions not to blow one's nose should be given to the patient to avoid orbital emphysema and subsequent optic nerve compression. Consider neurosurgical consultation in orbital roof fractures. Indications for surgical repair of orbital fractures are diplopia in primary gaze or downgaze that persists for 2 weeks, enophthalmos, or fracture of the orbital floor involving more than half of the floor. Extraocular muscle entrapment often requires prompt surgical repair because affected patients have significant pain, nausea, and vomiting that are difficult to control. Rarely, extraocular muscle entrapment can cause activation of the oculocardiac reflex, requiring urgent fracture repair.

PENETRATING WOUNDS OF THE ORBIT

These demand careful evaluation for possible damage to the eye, optic nerve, orbital contents, or brain. Examination should include investigation for a retained foreign body. Orbital hemorrhage and infection are common with penetrating wounds of the orbit; such injuries must be treated as emergencies.

CHILD ABUSE

See Chapter 17.

This is a major cause of injuries to the eye and orbital region. The possibility of nonaccidental trauma must be considered in any child with ecchymosis or laceration of the lids, hemorrhage in or about the eye, cataract or dislocated lens, retinal detachment, or fracture of the orbit. Inflicted childhood neurotrauma (shaken baby syndrome) occurs secondary to violent, nonaccidental, repetitive, unrestrained acceleration-deceleration head and neck movements, with or without blunt head trauma in children typically younger than 3 years of age. Inflicted childhood neurotrauma accounts for approximately 10% of all cases of child abuse and carries a mortality rate of up to 25%. Detection of abuse is not only important to treat the pathology that is discovered but also to prevent further abuse or even death. The ocular manifestations are numerous and may have a prominent role in recognition of this syndrome. Retinal hemorrhage is the most common ophthalmic finding and occurs at all levels of the retina. The pattern of hemorrhage helps distinguish this disorder from other causes of retinal hemorrhage or from accidental injuries (Fig. 675.9). Retinal hemorrhages can occur without associated intracranial pathology.

FIREWORKS-RELATED INJURIES

Injuries related to the use of fireworks can be the most devastating of all ocular traumas that occur in children. At least 20% of emergency department visits for fireworks-related injuries are for ocular trauma. In the United States, a majority of these injuries take place around Independence Day, and most occur despite adult supervision.

SPORTS-RELATED OCULAR INJURIES AND THEIR PREVENTION

Although sports injuries occur in all age-groups, far more children and adolescents participate in high-risk sports than adults. The greater number of participating children, their athletic immaturity, and the increased likelihood of their using inadequate or improper eye protection account for their disproportionate share of sports-related eye injuries (see Chapter 734).

The sports with the highest risk of eye injury are those in which no eye protection can be worn, including boxing, wrestling, and martial arts. Other high-risk sports include those that use a rapidly moving ball or puck, bat, stick, racquet, or arrow (baseball, hockey, lacrosse, racquet sports, and archery) or involve aggressive body contact (football and basketball). Related to both risk and frequency of participation, the highest percentage of eye injuries are in basketball and baseball.

Protective eyewear, designed for a specific activity, is available for most sports. For basketball, racquet sports, and other recreational activities that do not require a helmet or face mask, molded polycarbonate sports goggles that are secured to the head by an elastic strap are suggested. For hockey, football, lacrosse, and baseball (batter), specific helmets with polycarbonate face shields and guards are available. Children should also wear sports goggles under their helmets. For baseball, goggles and helmets should be worn for batting, catching, and base running; goggles alone are usually sufficient for other positions.

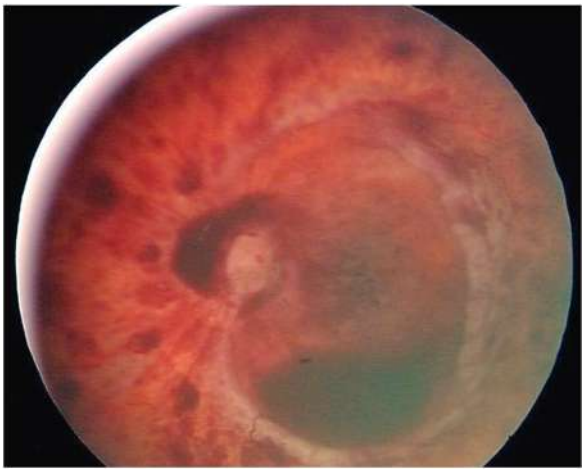

Fig. 675.9 Retinal hemorrhages in an abused child.

HANDHELD LASER RETINAL INJURY

Handheld laser pointers, often purchased to light cigarettes or for other purposes, may produce significant retinal damage if the power output is ≥150 mW. If a person looks directly at the light, direct foveal injury may occur before they have time to blink. Central (foveal) blurring and decreased visual activity are the chief complaints. Retinal injuries include retinal disruption, subretinal edema, and macular holes (Fig. 675.10), which usually require surgical repair.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

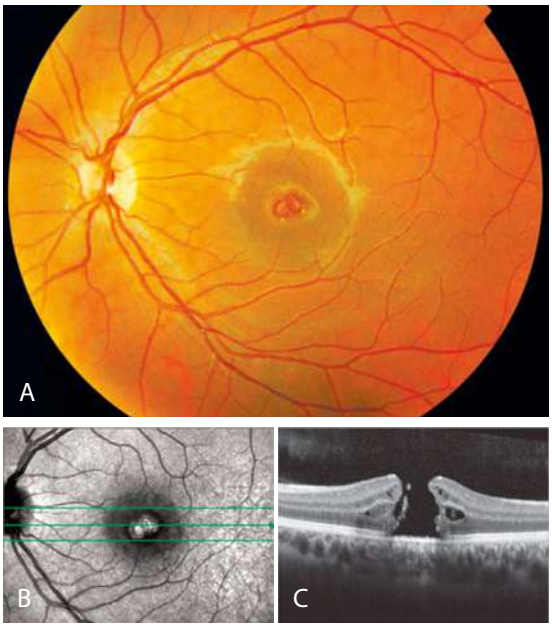

Fig. 675.10 Laser damage to the left eye. **A,** Color photo of the fundus of the left eye showing a macular hole. Note the changes at the retinal pigment epithelium. **B,** Infrared photo of the left fundus. **C,** Optical coherence tomography of the left eye showing the macular hole. *(From Petrou P, Patwary S, Banerjee PJ, et al. Bilateral macular hole from a handheld laser pointer. Lancet. 2014;383:1780.)*

The Ear

PART XXVIII

Chapter 676

General Considerations and Evaluation of the Ear

Joseph Haddad Jr.

CLINICAL MANIFESTATIONS

Diseases of the ear and temporal bone typically manifest with one or more of eight clinical signs and symptoms.

Otalgia usually is associated with inflammation of the middle ear (about 50% of cases) or external ear, but it can represent pain referred from involvement of the teeth, temporomandibular joint, or pharynx (Table 676.1). In young infants, pulling or rubbing the ear along with general irritability or poor sleep, especially when associated with fever, may be the only signs of ear pain. Ear pulling alone is not diagnostic of ear pathology.

Purulent otorrhea is a sign of otitis externa, otitis media (OM) with perforation of the tympanic membrane (TM), drainage from the middle ear through a patent tympanostomy tube, or, rarely, drainage from a first branchial cleft sinus. Bloody drainage may be associated with acute or chronic inflammation (often with granulation tissue and/or an ear tube), trauma, neoplasm, foreign body, or blood dyscrasia. Clear drainage suggests a perforation of the TM with a serous middle-ear effusion or, rarely, a cerebrospinal fluid leak draining through defects (congenital or traumatic) in the external auditory canal or from the middle ear.

Hearing loss results either from disease of the external or middle ear (conductive hearing loss) or from pathology in the inner ear, retrocochlear structures, or central auditory pathways (sensorineural hearing loss [SNHL]); the underlying etiology can be genetic or nongenetic, syndromic or nonsyndromic, or idiopathic. The most common cause of hearing loss in children is OM.

Swelling around the ear most commonly is a result of inflammation (e.g., external otitis, perichondritis, mastoiditis), trauma (e.g., hematoma), benign cystic masses, or neoplasm.

Vertigo is a specific type of dizziness that is defined as any illusion or sensation of motion. **Dizziness** is less specific than vertigo and refers to a sensation of altered orientation in space. Vertigo is an uncommon complaint in children; the child or parent might not volunteer information about balance unless asked specifically. The most common cause of dizziness in young children is eustachian tube–middle-ear disease, but true vertigo also may be caused by labyrinthitis, perilymphatic fistula between the inner and middle ear as a result of trauma or a congenital inner ear defect, cholesteatoma in the mastoid or middle ear, vestibular neuronitis, benign paroxysmal vertigo, Meniere disease, or disease of the central nervous system. Older children might describe a feeling of the room spinning or turning; younger children might express the dysequilibrium only by falling, stumbling, or clumsiness.

Nystagmus may be unidirectional, horizontal, or jerk nystagmus. It is vestibular in origin and usually is associated with vertigo.

Tinnitus rarely is described spontaneously by children, but it is common, especially in patients with eustachian tube–middle-ear disease or SNHL. Children can describe tinnitus if asked directly about it, including laterality and the quality of the sound.

FACIAL PARALYSIS

The facial nerve may be dehiscent in its course through the middle ear as a normal variant in as many as 50% of people. Infection with local inflammation, most commonly in acute OM, can lead to a temporary paralysis of the facial nerve. It also can result from Lyme disease, cholesteatoma, Bell palsy, Ramsay Hunt syndrome (herpes zoster oticus), fracture, neoplasm, or infection of the temporal bone. Congenital facial paralysis can result from birth trauma or congenital abnormality of the seventh nerve or from a syndrome such as Möbius or CHARGE (coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, and ear anomalies), or it may be associated with other cranial nerve abnormalities and craniofacial anomalies.

PHYSICAL EXAMINATION

Complete examination with special attention to the head and neck can reveal a condition that can predispose to or be associated with ear disease in children. The facial appearance and the character of speech can give clues to an abnormality of the ear or hearing. Many craniofacial anomalies, such as cleft palate, mandibulofacial dysostosis (Treacher Collins syndrome), and trisomy 21 (Down syndrome), are associated with disorders of the ear and eustachian tube. Mouth breathing and hyponasality can indicate intranasal or postnasal obstruction. **Hypernasality** is a sign of velopharyngeal insufficiency. Examining the oropharyngeal cavity might uncover an overt cleft palate or a submucous cleft (usually associated with a bifid uvula), both of which predispose to OM with effusion. A nasopharyngeal tumor with nasal and eustachian tube blockage may be associated with OM.

The position of the patient for examination of the ear, nose, and throat depends on the patient's age and ability to cooperate, the clinical setting, and the examiner's preference. The child can be examined on an examination table or on the parent's lap. The presence of a parent or assistant usually is necessary to minimize movement and provide better examination results. An examining table may be desirable for uncooperative older infants or when a procedure, such as microscopic evaluation or tympanocentesis, is performed. Lap examination is adequate in most infants and young children; the parent may assist in restraining the child by folding the child's wrists and arms over the child's own abdomen with one hand and holding the child's head against the parent's chest with the other hand. If necessary, the child's legs can be held between the parent's knees. To avoid ear trauma with movement, the examiner should hold the otoscope with the hand placed firmly against the child's head or face, so that the otoscope moves with the head. Pulling up and out on the pinna straightens the ear canal and allows better exposure of the TM.

When examining the ear, inspecting the auricle and external auditory meatus for infection can aid in evaluating complications of OM. External otitis can result from acute OM with discharge, or inflammation of the posterior auricular area can indicate a periostitis or subperiosteal abscess extending from the mastoid air cells. The presence of preauricular pits or skin tags also should be noted because affected children have a slightly higher incidence of SNHL; ear pits can develop chronic infection.

Cerumen is a protective, waxy, water-repellent coating in the ear canal that can interfere with examination. Cerumen usually is removed using the surgical head of the otoscope, which allows passage of a wire loop or a blunt curette under direct visualization. Other methods include gentle irrigation of the ear canal with warm water, which should be performed only if the TM is intact, or instillation of a solution such as diluted hydrogen peroxide in the ear canal (with intact TM only) for a few minutes to soften the wax for suction removal or irrigation. Commercial preparations such as trolamine polypeptide oleate–condensate (Cerumenex) may cause dermatitis of the external canal with chronic use and should be used only under a physician's supervision.

Inflammation of the ear canal with associated pain often indicates external otitis. Abnormalities of the external auditory canal include

Table 676.1 Causes of Otalgia and Sources for Referred Pain

INTRINSIC
External Ear
External otitis
Cerumen impaction
Foreign body
Perichondritis
Preauricular cyst or sinus
Impacted insects
Myringitis
Trauma
Tumor
Middle Ear, Eustachian Tube, and Mastoid
Barotrauma
Middle ear effusion
Negative intratympanic pressure (eustachian tube dysfunction)
Acute otitis media
Mastoiditis
Aditus block
Complication of otitis media
Gradenigo syndrome (otorrhea, CN VI palsy, pain in CN V distribution, petrositis)
Tumor
Eosinophilic granuloma
Granulomatosis with polyangiitis
EXTRINSIC
Trigeminal Nerve
Dental
Jaw
Temporomandibular joint
Oral cavity (tongue)
Infratemporal fossa tumors
Facial Nerve
Bell palsy
Tumors
Herpes zoster
Glossopharyngeal Nerve
Tonsil
Oropharynx
Nasopharynx
Vagus Nerve
Laryngopharynx
Esophagus
Gastroesophageal reflux
Thyroid
Cervical Nerves
Lymph nodes
Cysts
Cervical spine
Neck infections
Miscellaneous
Migraine
Neuralgias
Paranasal sinuses
Central nervous system
Drug induced (mesalazine, sulfasalazine)
Factitious disorder by proxy

From Bluestone CD, Stool SE, Alper CM, et al. *Pediatric Otolaryngology*, 4th ed., vol. 1. Philadelphia: Saunders; 2003:288.

stenosis (common in children with trisomy 21), bony exostoses, otorrhea, and the presence of foreign bodies. Cholesteatoma of the middle ear can manifest in the canal as intermittent foul-smelling drainage, sometimes associated with white debris; cholesteatoma of the external canal can appear as a white, pearl-like mass in the canal skin. White or gray debris of the canal suggests fungal external otitis. Newborn ear canals are filled with vernix caseosa, which is soft and pale yellow and should disappear shortly after birth.

The TM and its mobility are best assessed with a pneumatic otoscope. The normal TM is in a neutral position; a bulging TM may be caused by increased middle-ear air pressure, with or without pus or effusion in the middle ear; a bulging drum can obscure visualization of the malleus and annulus. Retraction of the TM usually indicates negative middle-ear pressure, but it also can result from previous middle-ear disease with fixation of the ossicles, ossicular ligaments, or TM. When retraction is present, the bony malleus appears more prominent, and the incus may be more visible posterior to the malleus.

The normal TM has a silvery gray, "waxed paper" appearance. A white or yellow TM can indicate a middle-ear effusion. A red TM alone might not indicate pathology, because the blood vessels of the membrane may be engorged as a result of crying, sneezing, or nose blowing, though hemorrhagic redness is associated with acute OM. A normal TM is translucent, allowing the observer to visualize the middle-ear landmarks: incus, promontory, round window niche, and often the chorda tympani nerve. If a middle-ear effusion is present, an air-fluid level or bubbles may be visible (Fig. 676.1). Inability to visualize the middle-ear structures indicates opacification of the drum, usually caused by thickening of the TM or a middle-ear effusion or both. Assessment of the light reflex often is not helpful, because a middle ear with effusion reflects light as well as a normal ear. Bullae (blister of the TM) formation is associated with acute OM.

TM mobility is helpful in assessing middle-ear pressures and the presence or absence of fluid (see Fig. 676.1). To best perform pneumatic otoscopy, a speculum of adequate size is used to obtain a good seal and allow air movement in the canal. A rubber ring around the tip of the speculum can help obtain a better canal seal. Normal middle-ear pressure is characterized by a neutral TM position and brisk TM movement to both positive and negative pressures.

Eardrum retraction is most common when negative middle-ear pressure is present; with even moderate negative middle-ear pressure, there is no visible inward movement with applied positive pressure in the ear canal. However, negative canal pressure, which is produced by releasing the rubber bulb of the pneumatic otoscope, can cause the TM to bounce out toward the neutral position. The TM can retract in both the presence and absence of middle-ear fluid, and if the middle-ear fluid is mixed with air, the TM might still have some mobility. Outward eardrum movement is less likely in the presence of severe negative middle-ear pressure or middle-ear effusion.

The TM that exhibits fullness (bulging) moves to applied positive pressure but not to applied negative pressure if the pressure within the middle ear is positive. A full TM and positive middle-ear pressure without an effusion may be seen in young infants who are crying during the otoscopic examination, in older infants and children with nasal obstruction, and in the early stage of acute OM. When the middle-ear–mastoid air cell system is filled with an effusion and little or no air is present, the mobility of the TM is severely decreased or absent in response to both applied positive and negative pressures.

Tympanocentesis, or aspiration of the middle ear, is the definitive (but not usually needed) method of verifying the presence and type of a middle-ear effusion and is performed by inserting an 18-gauge spinal needle attached to a syringe or a collection trap through the inferior portion of the TM (Fig. 676.2). Culturing of the ear canal and alcohol cleansing should precede tympanocentesis and culture of the middle-ear aspirate; a canal culture is taken first to help determine whether organisms cultured from the middle ear are contaminants from the external canal or true middle-ear pathogens.

Further diagnostic studies of the ear and hearing include audiometric evaluation, impedance audiometry (tympanometry), acoustic reflectometry, and specialized eustachian tube function studies. Diagnostic imaging studies, including CT and MRI, often provide further information about anatomic abnormalities and the extent of inflammatory processes or neoplasms. Specialized assessment of labyrinthine function should be considered in the evaluation of a child with a suspected vestibular disorder (see Chapter 682).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

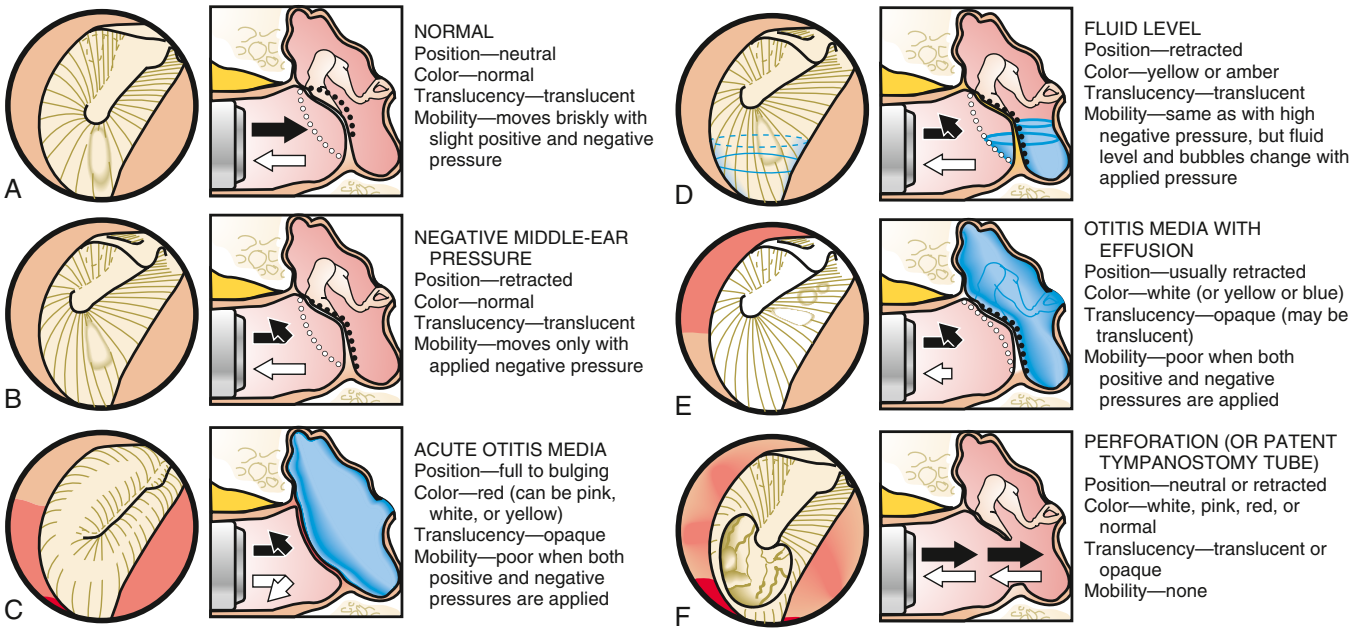

Fig. 676.1 A–F, Common conditions of the middle ear, as assessed with the otoscope. *(From Bluestone CD, Klein JO. Otitis Media in Infants and Children, 3rd ed. Philadelphia: Saunders; 2001:131.)*

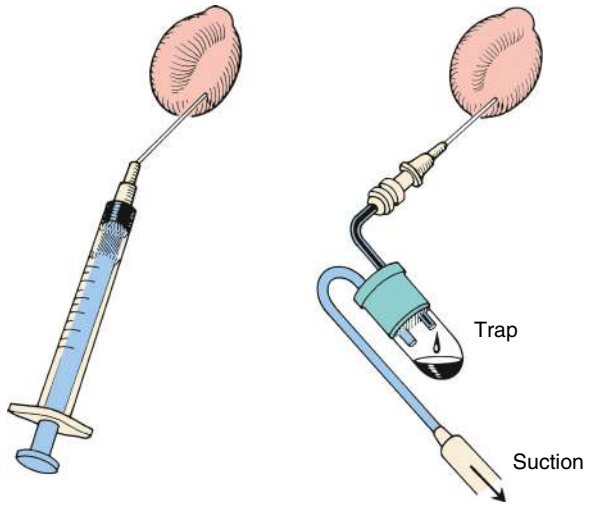

Fig. 676.2 Tympanocentesis can be performed with a needle attached to a tuberculin syringe *(left)* or by using an Alden-Senturia collection trap (Storz Instrument Co, St. Louis). *(From Bluestone CD, Klein JO. Otitis Media in Infants and Children, 2nd ed. Philadelphia: Saunders; 1995:127.)*

Chapter 677

Hearing Loss

Joseph Haddad Jr.

See also Chapter 55.

INCIDENCE AND PREVALENCE

Bilateral neural hearing loss is categorized as **mild** (20-30 dB hearing level [HL]), **moderate** (30-50 dB HL), **moderately severe** (50-70 dB HL), **severe** (75-85 dB HL), or **profound** (>85 dB). The World Health Organization estimates that approximately 360 million people (5% of the world's population, including 32 million children) have disabling hearing loss. An additional 364 million people have mild hearing loss. Half of these cases could have been prevented. In the United States, the average incidence of neonatal hearing loss is 1.6 per 1,000 infants; the rate by state varies from 0.22 to 3.61 per 1,000. Among children and adolescents, the prevalence of mild or greater hearing loss is 3.1% and is higher among persons from lower-income families.

Onset of hearing loss in children can occur at any time in childhood. When less severe hearing loss or the transient hearing loss that commonly accompanies middle-ear disease in young children is considered, the number of affected children increases substantially.

TYPES OF HEARING LOSS

Hearing loss can be peripheral or central in origin. Peripheral hearing loss can be conductive, sensorineural, or mixed. **Conductive hearing loss (CHL)** is the most common type of hearing loss in children and occurs when sound transmission is physically impeded in the external and/or middle ear, most commonly by otitis media (OM) with effusion. **Sensorineural hearing loss (SNHL)** is caused by damage to or maldevelopment of structures of the inner ear, including hair cell destruction, cochlear malformation; perilymphatic fistula of the round or oval window membrane, and failure in development or lesions of the acoustic division of the eighth nerve. Coexistent CHL and SNHL is considered a **mixed hearing loss**.

An auditory deficit originating along the central auditory nervous system pathways from the proximal eighth nerve to the cerebral cortex usually is considered **central** (or **retrocochlear**) **hearing loss**. Tumors or demyelinating disease of the eighth nerve and cerebellopontine angle can cause hearing deficits but spare the outer, middle, and inner ear. These causes of hearing loss are rare in children. Functional disorders of the eighth nerve and/or brainstem pathways may manifest in a variety of clinical defects known collectively as *auditory neuropathy spectrum disorder* (ANSD) or *auditory dyssynchrony,* without abnormalities demonstrable on imaging. Other forms of central auditory deficits, known as **central auditory processing disorders**, include those that make it difficult even for children with normal hearing sensitivity to listen selectively in the presence of noise, to combine information from the two ears properly, to process speech when it is slightly degraded, and to integrate auditory information when it is delivered faster, although they can process it when delivered at a slow rate. These deficits can manifest as specific language disorders or poor attention or as academic or behavior problems

in school. Strategies for coping with such disorders are available for older children, and identification and documentation of the central auditory processing disorder allow parents and teachers to make appropriate accommodations to enhance learning.

ETIOLOGY

Most CHL is acquired, with middle-ear fluid the most common cause. Congenital causes include anomalies of the pinna, external ear canal, tympanic membrane (TM), and ossicles. Rarely congenital cholesteatoma or other masses in the middle ear manifest as CHL. TM perforation (e.g., trauma, OM), ossicular discontinuity (e.g., infection, cholesteatoma, trauma), tympanosclerosis, acquired cholesteatoma, or masses in the ear canal or middle ear (Langerhans cell histiocytosis, salivary gland tumors, glomus tumors, rhabdomyosarcoma) also can manifest as CHL. Uncommon diseases that affect the middle ear and temporal bone and can manifest with CHL include otosclerosis, osteopetrosis, fibrous dysplasia, and osteogenesis imperfecta. Rare autoimmune or inflammatory syndromes may include hearing loss. **Susac syndrome** is manifest as a subacute encephalopathy, visual impairment, and hearing loss. **Cogan syndrome** presents with interstitial keratitis, sudden hearing loss, and vestibular impairment.

SNHL may be congenital or acquired. Acquired SNHL may be caused by genetic, infectious, autoimmune, anatomic, traumatic, ototoxic, and idiopathic factors (Tables 677.1-677.4). The recognized risk factors account for approximately 50% of cases of moderate to profound SNHL.

Infectious Causes

The most common infectious cause of congenital SNHL is **cytomegalovirus (CMV)**, which infects 1 in 100 newborns in the United States (see Chapters 149 and 302). Of these, 6,000-8,000 infants each year have clinical manifestations, including approximately 75% with SNHL. Congenital CMV warrants special attention because it is associated with hearing loss in its symptomatic and asymptomatic forms with bilateral and unilateral hearing loss, respectively; the hearing loss may be progressive. Some children with congenital CMV have suddenly lost residual hearing at 4-5 years of age. Much less common congenital infectious causes of SNHL include toxoplasmosis and syphilis. Congenital CMV, toxoplasmosis, and syphilis also can manifest with delayed onset of SNHL months to years after birth. Rubella, once the most common viral cause of congenital SNHL, is very uncommon because of effective vaccination programs. In utero infection with herpes simplex virus is rare, and hearing loss is not an isolated manifestation.

Other postnatal infectious causes of SNHL include neonatal group B streptococcal sepsis and bacterial meningitis at any age. *Streptococcus pneumoniae* is the most common cause of bacterial meningitis that results in SNHL after the neonatal period and has become less common with the routine administration of pneumococcal conjugate vaccine. *Haemophilus influenzae* type b, once the most common cause of meningitis resulting in SNHL, is rare owing to the *H. influenzae* type b conjugate vaccine. Uncommon infectious causes of SNHL include Lyme disease, parvovirus B19, and varicella. Mumps, rubella, and measles, all once common causes of SNHL in children, are rare owing to vaccination programs. When these infectious etiologies occur, the resulting hearing loss is frequently bilateral and severe.

Genetic Causes

Genetic causes of SNHL probably are responsible for as many as 50% of SNHL cases (see Tables 677.3 and 677.4). These disorders may be associated with other abnormalities, may be part of a named syndrome, or can exist in isolation. SNHL often occurs with abnormalities of the ear and eye and with disorders of the metabolic, musculoskeletal, integumentary, renal, and nervous systems.

Autosomal dominant hearing losses account for approximately 10% of all cases of childhood SNHL. Waardenburg (types I and II) and branchiootorenal syndromes represent two of the most common autosomal dominant syndromic types of SNHL. Types of SNHL are coded with a four-letter code and a number, as follows: **DFN** = deafness, A = dominant, B = recessive, and number = order of discovery (e.g., DFNA 13). Autosomal dominant conditions in addition to those just discussed include DFNA 1-18, 20-25, 30, 36, 38, and pathologic variants in the crystallin gene *(CRYM)*.

Autosomal recessive genetic SNHL, both syndromic and nonsyndromic, accounts for approximately 80% of all childhood cases of

Table 677.1 Indicators Associated with Hearing Loss

INDICATORS ASSOCIATED WITH SENSORINEURAL AND/OR CONDUCTIVE HEARING LOSS

Neonates (Birth to 28 Days) When Universal Screening Is Not Available

- Family history of hereditary childhood sensorineural hearing loss
- In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
- Craniofacial anomalies, including those with morphologic abnormalities of the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
- Birth weight <1,500 g (3.3 lb)
- Hyperbilirubinemia at a serum level requiring exchange transfusion
- Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics
- Bacterial meningitis
- Apgar scores of 0-4 at 1 min or 0-6 at 5 min
- Mechanical ventilation lasting ≥5 days; extracorporeal membrane oxygenation
- Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; white forelock

Infants and Toddlers (Age 29 Days to 2 Yr) When Certain Health Conditions Develop that Require Rescreening

- Parent or caregiver concern regarding hearing, speech, language, and/or developmental delay
- Bacterial meningitis and other infections associated with sensorineural hearing loss
- Head trauma associated with loss of consciousness or skull fracture
- Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; neurofibromatosis, osteopetrosis, and Usher Hunter, Waardenburg, Alport, Pendred, or Jervell and Lange-Nielsen syndrome
- Ototoxic medications, including but not limited to chemotherapeutic agents or aminoglycosides used in multiple courses or in combination with loop diuretics
- Recurrent or persistent otitis media with effusion for 3 mo or longer
- Skeletal dysplasia

Infants and Toddlers (Age 29 Days to 3 Yr) Who Require Periodic Monitoring of Hearing

- Some newborns and infants pass initial hearing screening but require periodic monitoring of hearing to detect delayed-onset sensorineural and/or conductive hearing loss. Infants with these indicators require hearing evaluation at least every 6 mo until age 3 yr and at appropriate intervals thereafter

INDICATORS ASSOCIATED WITH DELAYED-ONSET SENSORINEURAL HEARING LOSS

- Family history of hereditary childhood hearing loss
- In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
- Neurofibromatosis type 2 and neurodegenerative disorders
- Cogan syndrome (vasculitis: keratitis, uveitis, vertigo, arthritis, dermatitis)

INDICATORS ASSOCIATED WITH CONDUCTIVE HEARING LOSS

- Recurrent or persistent otitis media with effusion
- Anatomic deformities and other disorders that affect eustachian tube function
- Neurodegenerative disorders

Note: At all ages, parents' concern about hearing loss must be taken seriously even in the absence of risk factors.

Adapted from American Academy of Pediatrics, Joint Committee on Infant Hearing. Joint Committee on Infant Hearing 1994 position statement. *Pediatrics.* 1995;95:152.

Table 677.2 Infectious Pathogens Implicated in Sensorineural Hearing Loss in Children

CONGENITAL INFECTIONS
Cytomegalovirus
Lymphocytic choriomeningitis virus
Rubella virus
Toxoplasma gondii
Treponema pallidum
ACQUIRED INFECTIONS
Borrelia burgdorferi (Lyme disease)
Cytomegalovirus
Epstein-Barr virus
Haemophilus influenzae
Herpes simplex
Lassa fever virus
Measles virus
Mumps virus
Neisseria meningitidis
Nonpolio enteroviruses
Plasmodium falciparum
Rubella
Streptococcus pneumoniae
Syphilis
Varicella-zoster virus

From Smith RJH, Bale JF Jr., White KR. Sensorineural hearing loss in children. *Lancet.* 2005;365:879–890.

SNHL. Usher syndrome (types 1, 2, and 3: all associated with blindness and retinitis pigmentosa), Pendred syndrome, and Jervell and Lange-Nielsen syndrome (one form of long QT syndrome) are three of the most common syndromic recessive types of SNHL. Other autosomal recessive conditions include Alström syndrome, type 4 Bartter syndrome, biotinidase deficiency, and DFNB 1-18, 20-23, 26-27, 29-33, 35-40, 42, 44, 46, 48, 49, 53, and 55.

Unlike children with an easily identified syndrome or with anomalies of the outer ear, who may be identified as being at risk for hearing loss and consequently monitored, children with nonsyndromic hearing loss present greater diagnostic difficulty. Pathogenic variants of the connexin-26 and -30 genes are identified in autosomal recessive (DNFB 1) and autosomal dominant (DNFA 3) SNHL and in sporadic patients with nonsyndromic SNHL; up to 50% of nonsyndromic SNHLs may be related to a pathogenic variation of connexin-26. Pathologic variants of the *GJB2* gene co-localize with DFNA 3 and DFNB 1 loci on chromosome 13, are associated with autosomal nonsyndromic susceptibility to deafness, and are associated with as many as 30% of cases of sporadic severe to profound congenital deafness and 50% of cases of autosomal recessive nonsyndromic deafness. In addition, pathogenic variants in *GJB6* are associated with approximately 5% of recessive nonsyndromic deafness. Sex-linked disorders associated with SNHL, thought to account for 1–2% of SNHLs, include Norrie disease, otopalatal digital syndrome, Nance deafness, and Alport syndrome. Chromosomal abnormalities such as trisomy 13-15, trisomy 18, and trisomy 21 also can be accompanied by hearing impairment. Patients with Turner syndrome have monosomy for all or part of one X chromosome and can have CHL, SNHL, or mixed hearing loss. The hearing loss may be progressive. Mitochondrial genetic abnormalities (MELAS, MERRF) also can result in SNHL (see Table 677.3).

Many genetically determined causes of hearing impairment, both syndromic and nonsyndromic, do not express themselves until sometime after birth. Alport, Alström, Down, and Hunter-Hurler syndromes and von Recklinghausen disease are genetic diseases that can have SNHL as a late manifestation.

Physical Causes

Agenesis or malformation of cochlear structures may be genetic; these include Scheibe, Mondini (Fig. 677.1), Alexander, and Michel anomalies, enlarged vestibular aqueducts (in isolation or associated with Pendred syndrome), and semicircular canal anomalies. These anomalies most likely develop before the eighth week of gestation and result from arrest in normal development, aberrant development, or both. Many of these anomalies also have been described in association with other congenital conditions such as intrauterine CMV and rubella infections. These abnormalities are quite common; in as many as 20% of children with SNHL, obvious or subtle temporal bone abnormalities are seen on high-resolution CT scanning or MRI.

Conditions, diseases, or syndromes that include craniofacial abnormalities may be associated with CHL and possibly with SNHL. Pierre Robin sequence, Stickler syndrome, and Treacher Collins, Klippel-Feil, Crouzon, and branchiootorenal syndromes and osteogenesis imperfecta often are associated with hearing loss. Congenital anomalies causing CHL include malformations of the ossicles and middle-ear structures and atresia of the external auditory canal.

SNHL also can occur secondary to exposure to toxins, chemicals, antimicrobials, and noise exposure. Early in pregnancy, the embryo is particularly vulnerable to the effects of toxic substances. Ototoxic drugs, including aminoglycosides, loop diuretics, and chemotherapeutic agents (cisplatin) also can cause SNHL. Congenital SNHL can occur secondary to exposure to these drugs as well as to thalidomide and retinoids. Certain chemicals, such as quinine, lead, and arsenic, can cause hearing loss both prenatally and postnatally. Among adolescents, the use of personal listening devices at high volume settings has been found to be correlated with hearing loss.

Trauma, including temporal bone fractures, inner ear concussion, head trauma, iatrogenic trauma (e.g., surgery, extracorporeal membrane oxygenation), radiation exposure, and noise, also can cause SNHL. Other uncommon causes of SNHL in children include autoimmune disease (systemic or limited to the inner ear), metabolic abnormalities, and neoplasms of the temporal bone.

EFFECTS OF HEARING IMPAIRMENT

The effects of hearing impairment depend on the nature and degree of the hearing loss and on the individual characteristics of the child. Hearing loss may be unilateral or bilateral, conductive, sensorineural, or mixed; mild, moderate, severe, or profound; of sudden or gradual onset; stable, progressive, or fluctuating; and affecting a part or all of the audible spectrum. Other factors, such as intelligence, medical or physical condition (including accompanying syndromes), family support, age at onset, age at time of identification, and promptness of intervention, also affect the impact of hearing loss on a child (see Chapter 55).

Most hearing-impaired children have some useable hearing. Only 6% of those in the hearing-impaired population have bilateral profound hearing loss. Hearing loss very early in life can affect the development of speech and language, social and emotional development, behavior, attention, and academic achievement. Some cases of hearing impairment are misdiagnosed because affected children have sufficient hearing to respond to environmental sounds and can learn some speech and language but when challenged in the classroom cannot perform to full potential.

Even mild or unilateral hearing loss can have a detrimental effect on the development of a young child and on school performance. Children with such hearing impairments have greater difficulty when listening conditions are unfavorable (e.g., background noise and poor acoustics), as can occur in a classroom. The fact that schools are auditory-verbal environments is unappreciated by those who minimize the impact of hearing impairment on learning. Hearing loss should be considered in any child with speech and language difficulties or below-par performance, poor behavior, or inattention in school (Table 677.5).

Children with moderate, severe, or profound hearing impairment and those with other impairing conditions often are educated in classes or schools for children with special needs. There is a strong trend toward integrating a child with hearing loss into the least restrictive learning environment; this approach can only be successful if there are sufficient supportive services available for auditory and other learning needs. The auditory management and choices regarding modes of communication

Table 677.3 Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss

LOCUS	GENE	AUDIO PHENOTYPE
DFN3*	*POU3F4*	Conductive hearing loss as a result of stapes fixation mimicking otosclerosis; superimposed progressive SNHL.
DFNA1	*DIAPH1*	Low-frequency loss beginning in the first decade and progressing to all frequencies to produce a flat audio profile with profound losses throughout the auditory range.
DFNA2	*KCNQ4* *GJB3*	Symmetric high-frequency sensorineural loss beginning in the first decade and progressing over all frequencies. Symmetric high-frequency sensorineural loss beginning in the third decade.
DFNA3	*GJB2* *GJB6*	Childhood-onset, progressive, moderate to severe high-frequency sensorineural hearing impairment. Childhood-onset, progressive, moderate to severe high-frequency sensorineural hearing impairment.
DFNA6, 14, and 38	*WFS1*	Early-onset low-frequency sensorineural loss; approximately 75% of families dominantly segregating this audio profile carry missense mutations in the C-terminal domain of wolframin.
DFNA8, and 12	*TECTA*	Early-onset stable bilateral hearing loss affecting mainly mid to high frequencies.
DFNA10	*EYA4*	Progressive loss beginning in the second decade as a flat to gently sloping audio profile that becomes steeply sloping with age.
DFNA11	*MYO7A*	Ascending audiogram affecting low and middle frequencies at young ages and then affecting all frequencies with increasing age.
DFNA13	*COL11A2*	Congenital midfrequency sensorineural loss that shows age-related progression across the auditory range.
DFNA15	*POU4F3*	Bilateral progressive sensorineural loss beginning in the second decade.
DFNA20, and 26	*ACTG1*	Bilateral progressive sensorineural loss beginning in the second decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases.
DFNA22	*MYO6*	Postlingual, slowly progressive, moderate to severe hearing loss.
DFNB1	*GJB2, GJB6*	Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying 1 35delG allele and any other *GJB2* SNHL-causing allele variant; in children carrying 2 *GJB2* SNHL-causing missense mutations, severe to profound deafness is not observed.
DFNB3	*MYO7A*	Severe to profound sensorineural hearing loss.
DFNB4	*SLC26A4*	DFNB4 and Pendred syndrome (see Table 677.5) are allelic. DFNB4 hearing loss is associated with dilation of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss also is common.
DFNB7, and 11	*TMC1*	Severe to profound prelingual hearing impairment.
DFNB9	*OTOF*	*OTOF*-related deafness is characterized by two phenotypes: prelingual nonsyndromic hearing loss and, less frequently, temperature-sensitive nonsyndromic auditory neuropathy spectrum disorder. The nonsyndromic hearing loss is bilateral severe to profound congenital deafness.
DFNB12	*CDH23*	Depending on the type of mutation, recessive mutations of *CDH23* can cause nonsyndromic deafness or type 1 Usher syndrome (USH1), which is characterized by deafness, vestibular areflexia, and vision loss as a result of retinitis pigmentosa.
DFNB16	*STRC*	Early-onset, nonsyndromic, autosomal recessive sensorineural hearing loss.
mtDNA	*MTRNR1* *MTTS1*	Degree of hearing loss varies from mild to profound but usually is symmetric; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy; variable penetrance.

*Approximately 45 DFNA genes are inherited as autosomal recessive or dominant and, less often, X-linked.
SNHL, Sensorineural hearing loss.
Adapted from Smith RJH, Bale JF Jr,. White KR. Sensorineural hearing loss in children. *Lancet*. 2005;365:879–890.

and education for children with hearing impairments must be individualized, because these children are not a homogeneous group. A team approach to individual case management is essential because each child and family unit have unique needs and abilities (see Chapter 55).

HEARING SCREENING

Hearing impairment can have a major impact on a child's development, and because early identification improves prognosis, screening programs have been widely and strongly advocated. The National Center for Hearing Assessment and Management estimates that the detection and treatment at birth of hearing loss saves $400,000 per child in special education costs; screening costs approximately $8-$50/child. Data from the Colorado newborn screening program suggest that if hearing-impaired infants are identified and treated by age 6 months, these children (with the exception of those with bilateral profound impairment) should develop the same level of language as their age-matched peers who are not hearing impaired. These data provide compelling support for establishing mandated newborn hearing screening programs for all children. The American Academy of Pediatrics endorses the goal of universal detection of hearing loss in infants before 3 months of age, with appropriate intervention no later than 6 months of age. The Centers for Disease Control and Prevention estimates that of the approximately 4 million infants born in the United States in 2014, 97.9% were screened for hearing loss.

Table 677.4 Common Types of Syndromic Sensorineural Hearing Loss

SYNDROME	GENE	PHENOTYPE
DOMINANT		
Waardenburg (WS1) (may also be recessive)	*PAX3*	Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected first-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Waardenburg (WS2) (WS2D) (WS2E) (WS4A) (WS4B)	*MITF*, others *SNAI12* *SOX10* *EDNRB* *EDN3*	Major diagnostic criteria are as for WS1 but without dystopia canthorum. Approximately 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Branchiootorenal	*EYA1* *SIX1* *SIX5*	Diagnostic criteria include hearing loss (98%); preauricular pits (85%); and branchial (70%), renal (40%), and external ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed and mild to profound in degree.
CHARGE syndrome	*CHD7*	Choanal atresia, colobomas, heart defect, retardation, genital hypoplasia, ear anomalies, deafness. Can lead to sensorineural or mixed hearing loss. Can be autosomal dominant or isolated cases.
Goldenhar syndrome	Unknown	Part of the hemifacial microsomia spectrum. Facial hypoplasia, ear anomalies, hemivertebrae, and parotid gland dysfunction. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic.
Stickler	*COL2A1* *COL11A1* *COL11A2* *COL9A1*	Myopia, cleft palate, hearing loss, joint hypermobility, micrognathia.
RECESSIVE		
Pendred syndrome	*SLC26A4*	Diagnostic criteria include sensorineural hearing loss that is congenital, nonprogressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goiter.
Alport syndrome	*COL4A3, COL4A4,* and *COL4A5* (X-linked)	Nephritis, deafness, lens defects, retinitis. Can lead to bilateral sensorineural hearing loss in the 2,000-8,000 Hz range. The hearing loss develops gradually and is not generally present in early infancy.
Usher syndrome type 1 (USH1)	*USH1A, MYO7A, USH1C, CDH23, USH1E, PCDH15, USH1G*	Diagnostic criteria include congenital, bilateral, and profound hearing loss; vestibular areflexia; and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nyctalopia become severe enough to be noticeable).
Usher syndrome type 2 (USH2)	*USH2A, USH2B, USH2C, WHRN, ADGRV1*	Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading.
Usher syndrome type 3 (USH3)	*USH3* *CLRN1*	Diagnostic criteria include postlingual, progressive sensorineural hearing loss; late-onset retinitis pigmentosa; and variable impairment of vestibular function.
Jervell and Lange-Nielsen syndrome	*KCNQ1* *KCNE1*	Severe hearing loss, prolonged QT interval (ECG), and sudden death.

Adapted from Smith RJH, Bale JF Jr., White KR. Sensorineural hearing loss in children. *Lancet.* 2005;365:879–890.

Hearing screening is mandated in at least 45 states, but until screening programs are universally mandated, some hospitals will continue to use other criteria to screen for hearing loss. Some use the high-risk criteria (see Table 677.1) to decide which infants to screen, some screen all infants who require intensive care, and some do both. The problem with using high-risk criteria to screen is that 50% of cases of hearing impairment will be missed, either because the infants are hearing impaired but do not meet any of the high-risk criteria or because they develop hearing loss after the neonatal period.

The recommended hearing screening techniques are either otoacoustic emissions (OAE) testing or auditory brainstem evoked responses (ABRs). The ABR test, an auditory evoked electrophysiologic response that correlates highly with hearing, has been used successfully and cost-effectively to screen newborns and to identify further the degree and type of hearing loss. OAE tests, used successfully in most universal newborn screening programs, are quick, easy to administer, and inexpensive, and they provide a sensitive indication of the presence of hearing loss. Results are relatively easy to interpret. OAE tests elicit no response if hearing is worse than 30-40 dB, no matter what the cause; children who fail OAE tests undergo an ABR for a more definitive evaluation, as ABR has a higher sensitivity and specificity. It is recommended that both OAE measurement and ABR screening be used in the intensive care unit setting. Screening methods such as observing behavioral responses to uncalibrated noisemakers or using automated systems such as the Crib-o-gram (Canon) or the auditory response cradle (in which movement of the infant in response to sound is recorded by motion sensors) *are not recommended.*

Many children become hearing impaired after the neonatal period and therefore are not identified by newborn screening programs. Often it is not until children are in preschool or kindergarten that further hearing screening takes place; an evidence-based systematic review has identified pure-tone and OAE screening to be effective, with pure-tone screening having higher sensitivity. Among adolescents, high-frequency hearing loss is associated with exposure to loud noises, so

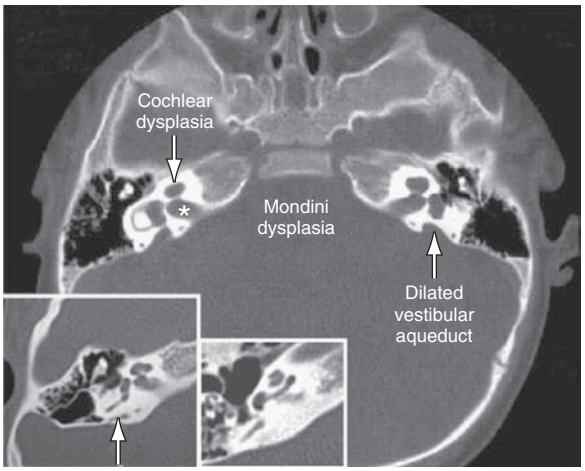

Fig. 677.1 Mondini dysplasia shown by CT of the temporal bone in a child with Pendred syndrome. Both dilation of the vestibular aqueduct and cochlear dysplasia are present in this section. In the larger of the two inset images of a normal temporal bone, the vestibular aqueduct is visible but much smaller *(arrow)*. The cochlea appears normal, and in the smaller inset image of a more inferior axial section, the expected number of cochlear turns can be clearly counted. Internal auditory canal *(asterisk)*. *(From Smith RJH, Bale JF Jr., White KR. Sensorineural hearing loss in children. Lancet. 2005;365:879–890.)*

attention should be paid to those frequencies on a hearing screen; most noise-induced hearing loss is around 4 kHz. Figure 677.2 provides recommendations for postneonatal screening.

IDENTIFICATION OF HEARING IMPAIRMENT

The impact of hearing impairment is greatest on an infant who has yet to develop language; consequently, identification, diagnosis, description, and treatment should begin as soon as possible. Infants with a prenatal or perinatal history that puts them at risk (see Table 677.3) or those who have failed a formal hearing screening should be evaluated by an experienced clinical audiologist until a reliable assessment of auditory sensitivity has been obtained. Primary care clinicians should encourage families to cooperate with the follow-up plan. Infants who are born at risk but who were not screened as neonates (e.g., because of transfer from one hospital to another) should have a hearing screening by age 3 months.

Hearing-impaired infants who are born at risk or are screened for hearing loss in a neonatal hearing screening program account for only a portion of hearing-impaired children. Children who are congenitally deaf because of autosomal recessive inheritance or subclinical congenital infection often are not identified until 1-3 years of age. Usually those with more severe hearing loss are identified at an earlier age, but identification often occurs later than the age at which intervention can provide an optimal outcome, especially in countries lacking technologic resources. Children who hear normally develop extensive receptive and expressive language by 3 years of age (Table 677.6) and exhibit behavior reflecting normal auditory

Table 677.5 Hearing Impairment as a Function of Average Hearing Threshold Level of the Better Ear

AVERAGE THRESHOLD LEVEL (dB) AT 500-2,000 Hz (ANSI)	DESCRIPTION	COMMON CAUSES	WHAT CAN BE HEARD WITHOUT AMPLIFICATION	DEGREE OF IMPAIRMENT (IF NOT TREATED IN FIRST YEAR OF LIFE)	PROBABLE NEEDS
0-15	Normal range	Conductive hearing loss	All speech sounds	None	None
16-25	Slight hearing loss	Otitis media, TM perforation, tympanosclerosis; eustachian tube dysfunction; some SNHL	Vowel sounds heard clearly, may miss unvoiced consonant sounds	Mild auditory dysfunction in language learning Difficulty in perceiving some speech sounds	Consideration of need for hearing aid, speech reading, auditory training, speech therapy, appropriate surgery, preferential seating
26-30	Mild	Otitis media, TM perforation, tympanosclerosis, severe eustachian dysfunction, SNHL	Hears only some speech sounds, the louder voiced sounds	Auditory learning dysfunction Mild language retardation Mild speech problems Inattention	Hearing aid Lip reading Auditory training Speech therapy Appropriate surgery
31-50	Moderate hearing loss	Chronic otitis, ear canal/middle ear anomaly, SNHL	Misses most speech sounds at normal conversational level	Speech problems Language retardation Learning dysfunction Inattention	All of the above, plus consideration of special classroom situation
51-70	Severe hearing loss	SNHL or mixed loss due to a combination of middle-ear disease and sensorineural involvement	Hears no speech sound of normal conversations	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes
71+	Profound hearing loss	SNHL or mixed	Hears no speech or other sounds	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes or schools

ANSI, American National Standards Institute; *SNHL*, sensorineural hearing loss; *TM*, tympanic membrane.
Modified from Northern JL, Downs MP. *Hearing in Children*, 4th ed. Baltimore: Williams & Wilkins; 1991.

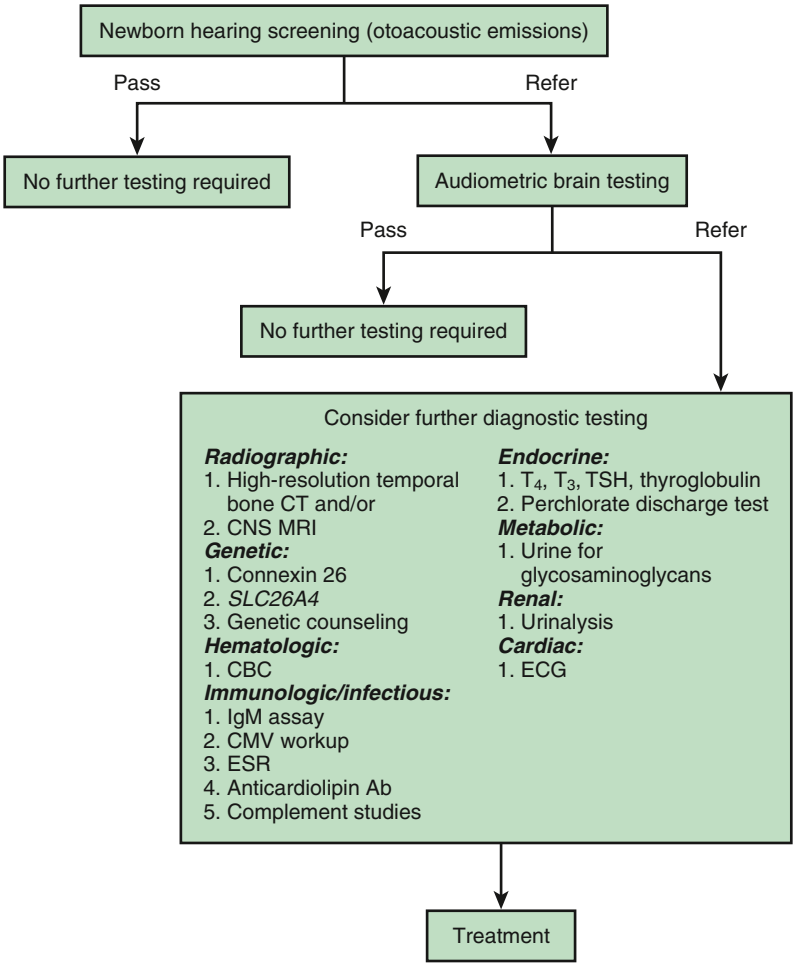

Fig. 677.2 Algorithm for newborn hearing screening. Ab, Antibody; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; MRI, magnetic resonance imaging; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone. *(From Norton SJ, Bhama PK, Perkins JA. Early detection and diagnosis of infant hearing impairment. In: Flint PW, Haughey BH, Lund VJ, et al., eds. Cummings Otolaryngology–Head and Neck Surgery, 5th ed. Philadelphia: Mosby; 2010: Fig. 190.1.)*

Table 677.6 Criteria for Referral for Audiologic and Speech and Language Evaluation

SHOULD ABSOLUTELY REFER FOR A SPEECH-LANGUAGE EVALUATION IF:		
AT AGE (mo)	**RECEPTIVE**	**EXPRESSIVE**
15	Does not look/point at 5-10 objects/people named by parent	Not using three words
18	Does not follow simple directions ("get your shoes.")	Not using Mama, Dada, or other names
24	Does not point to pictures or body parts when they are named	Not using 25 words
30	Does not verbally respond or nod/shake head to questions	Not using unique two-word phrases, including noun-verb combinations
36	Does not understand prepositions or action words; does not follow two-step directions	Vocabulary <200 words; does not ask for things by name; echolalia to questions; regression of language after acquiring two-word phrases

From Schum RL. Language screening in the pediatric office setting. *Pediatr Clin North Am.* 2007;54(3):425–436.

Table 677.7 Guidelines for Referral of Infants/Toddlers with Suspected Hearing Loss

AGE (mo)	NORMAL DEVELOPMENT
0-4	Should startle to loud sounds, quiet to mother's voice, momentarily cease activity when sound is presented at a conversational level
5-6	Should correctly localize to sound presented in a horizontal plane, begin to imitate sounds in own speech repertoire or at least reciprocally vocalize with an adult
7-12	Should correctly localize to sound presented in any plane Should respond to name, even when spoken quietly
13-15	Should point toward an unexpected sound or to familiar objects or persons when asked
16-18	Should follow simple directions without gestural or other visual cues; can be trained to reach toward an interesting toy at midline when a sound is presented
19-24	Should point to body parts when asked; by 21-24 mo, can be trained to perform play audiometry

From Matkin ND. Early recognition and referral of hearing-impaired children. *Pediatr Rev.* 1984;6:151–156.

function (Table 677.7). Failure to fulfill these criteria should be the reason for an audiologic evaluation. Parents' concern about hearing and any delayed development of speech and language should alert the pediatrician, because parents' concern usually precedes formal identification and diagnosis of hearing impairment by 6-12 months.

CLINICAL AUDIOLOGIC EVALUATION

When hearing impairment is suspected in a young child, reliable and valid estimates of auditory function can be obtained using electrophysiologic and age-appropriate behavioral measurement. Successful treatment strategies for hearing-impaired children rely on prompt identification and ongoing assessment to define the dimensions of auditory function. Cooperation among primary care providers and specialists in areas such as audiology, speech and language pathology, education, and child development is necessary to optimize auditory-verbal development. Therapy for hearing-impaired children may include an amplification device, a **frequency modulation** (FM) system in the classroom, close monitoring of hearing and auditory skills, speech and language therapy, counseling of parents and families, advising teachers, and dealing with public agencies.

Audiometry

Audiologic evaluation technique varies as a function of the age and developmental level of the child, the reason for the evaluation, and the child's otologic condition or history. An audiogram provides the fundamental description of hearing sensitivity (Fig. 677.3). Hearing thresholds are assessed as a function of frequency using pure tones (single-frequency stimuli) at octave intervals from 250 to 8,000 Hz. When the child is old enough to accept their placement, earphones typically are used to assess each ear independently. Before this stage, testing may be performed in a sound-treated environment with stimuli delivered via speakers; this approach permits description only of the better-hearing ear.

Air-conducted signals are presented through earphones (or loudspeakers) and are used to provide information about the sensitivity of the entire auditory system. These same test sounds can be delivered to the ear through an oscillator that is placed on the head, usually on the mastoid. Such signals are considered bone-conducted because the bones of the skull transmit vibrations as sound energy directly to the inner ear, essentially bypassing the outer and middle ears. In a normal ear, and also in children with SNHL, the air- and bone-conduction thresholds are equivalent. In those with CHL, bone-conduction thresholds are more sensitive than air- conducted responses; this is called the **air-bone gap**, which indicates the amount of hearing loss attributable to dysfunction in the outer and/or middle ear. In mixed hearing loss, both the bone- and air-conduction thresholds are abnormal, and there is additionally an air-bone gap.

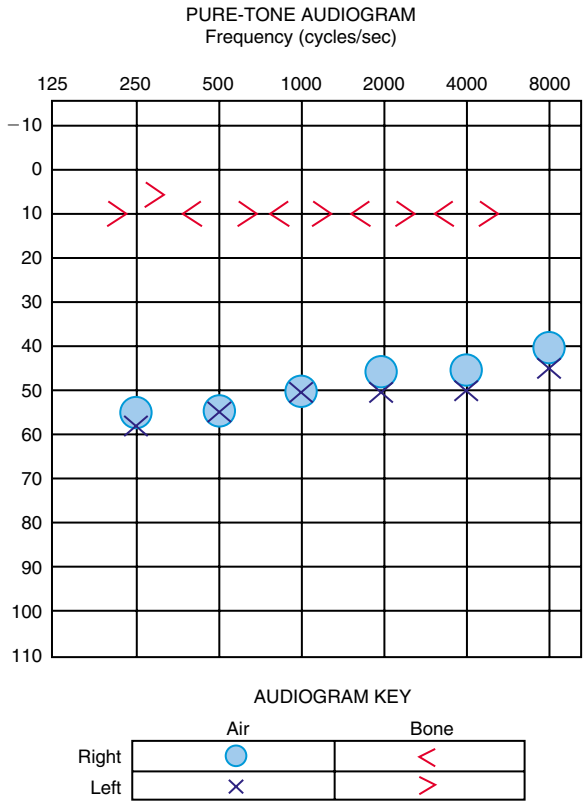

Fig. 677.3 Audiogram showing bilateral conductive hearing loss.

Speech-Recognition Threshold

Another measure useful for describing auditory function is the **speech-recognition threshold (SRT)**, which is the lowest intensity level at which a score of approximately 50% correct is obtained on a task of recognizing spondee words. Spondee words are 2-syllable words or phrases that have equal stress on each syllable, such as *baseball, hotdog,* and *pancake*. Listeners must be familiar with all the words for a valid test result to be obtained. The SRT should correspond to the average of pure-tone thresholds at 500, 1,000, and 2,000 Hz, the pure-tone average. The SRT is relevant as an indicator of a child's potential for development and use of speech and language; it also serves as a check of the validity of a test because children with nonorganic hearing loss (malingerers) might show a discrepancy between the pure-tone average and SRT. An SRT may be obtained in a child with expressive speech or language limitations using modified techniques, such as picture-pointing responses.

The basic battery of hearing tests concludes with an assessment of a child's ability to understand monosyllabic words when presented at a comfortable listening level. Performance on such word recognition tests assists in the differential diagnosis of hearing impairment and provides a measure of how well a child performs when speech is presented at loudness levels similar to those encountered in conversation. For speech recognition as well, a picture-pointing response may be obtained with standardized tests.

Play Audiometry

Hearing testing technique is age dependent. For children at or above the developmental level of a 5- to 6-year-old, conventional test methods can be used. For children 30 months to 5 years of age, play audiometry can be used. Responses in play audiometry usually are conditioned motor activities associated with a game, such as dropping blocks in a bucket, placing rings on a peg, or completing a puzzle. The technique can be used to obtain a reliable audiogram for a preschool child.

Visual Reinforcement Audiometry

For children between the ages of about 6 and 30 months, **visual reinforcement audiometry (VRA)** is commonly used. In this technique, the child is conditioned to turn the head in response to a tonal signal from a speaker in the same location as an animated (mechanical) toy or video reinforcer. If infants are properly conditioned, by presenting sounds associated with the reinforcer, VRA can provide reliable estimates of hearing sensitivity for tonal signals and speech sounds. In most applications of VRA, sounds are presented by loudspeakers in a sound field, so *ear-specific* information is not obtained. Assessment of an infant often is designed to rule out hearing loss that would be sufficient to affect the development of speech and language. Normal sound-field response levels of infants indicate sufficient hearing for this purpose despite the possibility of different HLs in the two ears. When ear-specific information is needed in this age-group, the ABR is conducted under sleep-deprived or sedated conditions.

Behavioral Observation Audiometry

Used as a screening device for infants <5 months of age, **behavioral observation audiometry** is limited to unconditioned, reflexive

responses to complex (not frequency-specific) test sounds such as warble tones, narrow-band noise, speech, or music presented using calibrated signals from a loudspeaker. Response levels can vary widely within and among infants and usually do not provide a reliable estimate of hearing sensitivity. The types of responses observed during this testing may include alterations in sucking behavior, initiation or cessation in crying, pupillary dilatation, and alterations in respiration.

Assessment of a child with suspected hearing loss is not complete until pure-tone hearing thresholds and SRTs (a reliable audiogram) have been obtained in each ear. Behavioral observation audiometry and VRA in sound-field testing give estimates of hearing responsivity in the *better-hearing ear*. When significant hearing loss is suspected in infants, electrophysiologic assessments must be conducted to permit early intervention.

Acoustic Immittance Testing

Acoustic immittance testing is a standard part of the clinical audiologic test battery and includes tympanometry, acoustic reflex threshold measurement, and acoustic reflex decay testing. It is a useful objective assessment technique that provides information about the status of the TM, middle ear, and acoustic reflex arc. Tympanometry can be performed in a physician's office and is helpful in the diagnosis and management of OM with effusion, a common cause of mild to moderate hearing loss in young children.

Tympanometry

Tympanometry provides a graph (tympanogram) of the middle ear's ability to transmit sound energy (admittance or compliance) or impede sound energy (impedance) as a function of air pressure in the external ear canal. Because most immittance test instruments measure acoustic admittance, the term *admittance* is used here. The principles apply to whatever units of measurement are used.

A probe is inserted into the entrance of the external ear canal so that an airtight seal is obtained. A manometer in the probe varies air pressure, while a sound generator presents a tone, and a microphone measures the sound pressure level reflected back. The sound pressure measured in the ear canal relative to the known intensity of the probe signal is used to estimate the acoustic admittance of the ear canal and middle-ear system. Admittance can be expressed in a unit called a millimho (mmho) or as a volume of air (mL) with equivalent acoustic admittance. Additionally, an estimate can be made of the volume of air enclosed between the probe tip and TM. The acoustic admittance of this volume of air is deducted from the overall admittance measure to obtain a measure of the admittance of the middle-ear system alone. Estimating ear canal volume also has a diagnostic benefit, because an abnormally large value is consistent with the presence of an opening in the TM (perforation, pressure equalization tube, or surgical defect).

Once the admittance of the air mass in the external auditory canal has been eliminated, it is assumed that the remaining admittance measure accurately reflects the admittance of the entire middle-ear system. Its value is controlled largely by the dynamics of the TM. Abnormalities of the TM can dictate the shape of tympanograms, thus obscuring abnormalities medial to the TM. In addition, the frequency of the probe tone, the speed and direction of the air pressure change, and the air pressure at which the tympanogram is initiated can all influence the outcome. The effect of the probe tone frequency is well documented, and in young children (<4-6 months) with small ear canals, use of a high-frequency probe tone, either 678 or 1,000 Hz, is recommended.

When air pressure in the ear canal is equal to that in the middle ear, the middle-ear system is functioning optimally. That is, the pressure equalization function of the eustachian tube permits the middle ear to rest at atmospheric pressure, equivalent to the condition in the ear canal. Therefore the ear canal pressure at which there is the greatest flow of energy (admittance) should be a reasonable estimate of the air pressure in the middle-ear space. This pressure is determined by finding the maximum or **peak admittance** on the tympanogram and obtaining its value on the *x* axis. The value on the *y* axis at the tympanogram peak is an estimate of peak admittance based on admittance tympanometry (Table 677.8). This peak measure sometimes is referred to as **static acoustic admittance**, even though it is estimated from a dynamic measure. Normative values for peak admittance as a function of air pressure are well established.

Table 677.8 Norms for Peak (Static) Admittance Using a 226-Hz Probe Tone for Children and Adults

AGE GROUP	ADMITTANCE (mL)	SPEED OF AIR PRESSURE SWEEP	
		≤50 daPa/sec*	200 daPa/sec†
Children (3-5 yr)	Lower limit	0.30	0.36
	Median	0.55	0.61
	Upper limit	0.90	1.06
Adults	Lower limit	0.56	0.27
	Median	0.85	0.72
	Upper limit	1.36	1.38

*Ear canal volume measurement based on admittance at lowest tail of tympanogram.
†Ear canal measurement based on admittance at lowest tail of tympanogram for children and at +200 daPa for adults.
daPa, decaPascals.
Adapted from Margolis RH, Shanks JE. Tympanometry: basic principles of clinical application. In: Rintelman WS, ed. *Hearing Assessment*, 2nd ed. Austin: PRODED; 1991: pp. 179–245.

Tympanometry in Otitis Media with Effusion

Children who have OM with effusion often have reduced peak admittance or high negative tympanometric peak pressures (see Fig. 680.5C). However, in the diagnosis of effusion, the tympanometric measure with the greatest sensitivity and specificity is the shape of the tympanogram rather than its peak pressure or admittance. The tympanogram is classified based on shape and peak admittance location. The greater the stiffening of the TM and ME, the lower the peak. As negative pressure within the middle ear increases, the peak becomes more negatively displaced. The more rounded the peak (or, in an absent peak, a flat tympanogram), the higher is the probability that an effusion is present (see Fig. 680.5B). The stage of OM may affect the tympanometric findings. An immobile TM/ME system based on significant effusion, as reflected in flat tympanogram, may evolve into findings of negative ME pressure and later positive pressure as the OM resolves, returning to a normal tympanogram.

Acoustic Reflex Threshold Test

The acoustic reflex threshold test also is part of the immittance test battery. With a properly functioning middle-ear system, admittance at the TM decreases due to the stiffening action of the middle ear muscles (stapedius and, to a lesser extent, tensor tympani). In healthy ears, the stapedial reflex occurs after exposure to loud sounds as a protective mechanism. Admittance instruments are designed to present reflex-activating signals (pure tones of various frequencies or noise), either to the same ear or the contralateral ear, while measuring the concomitant changes in admittance. Very small admittance changes that are time locked to presentations of the signal are considered to be a result of middle-ear muscle reflexes. Admittance changes may be absent when the hearing loss is sufficient to prevent the signal from reaching the loudness level necessary to elicit the reflex or when a middle-ear condition affects HLs or introduces sufficient stiffening to obscure reading the reflex activity. The acoustic reflex test also is used in the assessment of SNHL and the integrity of the neurologic components of the reflex arc, including crossed and uncrossed activity of cranial nerves VII and VIII.

Auditory Brainstem Response

The auditory brainstem response (ABR) test is used to screen newborn hearing, confirm hearing loss in young children, obtain

ear-specific information in young children, and test children who cannot, for whatever reason, cooperate with behavioral test methods. It also is important in the diagnosis of auditory dysfunction (i.e., estimation of hearing thresholds) and of disorders of the auditory nervous system. The ABR test is a far-field recording of minute electrical discharges from numerous neurons. The stimulus therefore must be able to cause synchronous discharge of the large numbers of neurons involved. Stimuli with very rapid onset, such as clicks or tone bursts, must be used. Unfortunately, the rapid onset required to create a measurable ABR also causes energy to be spread in the frequency domain, reducing the frequency specificity of the response.

The ABR result is not affected by sedation or general anesthesia. Infants and children from about 4 months to 4 years of age routinely are sedated to minimize electrical interference caused by muscle activity during testing. The ABR also can be performed in the operating room when a child is anesthetized for another procedure. Children younger than 4 months of age might sleep for a long enough period after feeding to allow an ABR to be done.

The ABR is recorded as 5-7 waves. Waves I, III, and V can be obtained consistently in all age-groups; waves II and IV appear less consistently. The latency of each wave (time of occurrence of the wave peak after stimulus onset) increases and the amplitude decreases with reductions in stimulus intensity; latency also decreases with increasing age, with the earliest waves reaching mature latency values earlier in life than the later waves. Age-specific normative data have been obtained in several studies.

The ABR test has two major uses in a pediatric setting. As an audiometric test, it provides information on the ability of the peripheral auditory system to transmit information to the auditory nerve and beyond. It also is used in the differential diagnosis or monitoring of central nervous system pathology. For hearing threshold estimation, the goal is to find the minimum stimulus intensity that yields an observable ABR, generally relying on wave V, the most robust aspect of morphology. Plotting latency versus intensity for various waves also aids in the differential diagnosis of hearing impairment. A major advantage of auditory assessment using the ABR test is that ear-specific threshold estimates can be obtained on infants or patients who are difficult to test. ABR thresholds using click stimuli correlate best with behavioral hearing thresholds in the higher frequencies (1,000-4,000 Hz); responsivity in the low frequencies requires different stimuli (tone bursts/pips or filtered clicks) or the use of masking, neither of which isolates the low-frequency region of the cochlea in all cases, and this can affect interpretation.

The ABR test does not assess "hearing." It reflects auditory neuronal electrical responses that can be correlated to behavioral hearing thresholds, but a normal ABR result only suggests that the auditory system, up to the level of the midbrain, is responsive to the stimulus used. Conversely, a failure to elicit an ABR indicates an impairment of the system's synchronous response but does not necessarily mean that there is no "hearing." The behavioral response to sound sometimes is normal when no ABR can be elicited, such as in neurologic demyelinating disease.

Hearing losses that are sudden, progressive, or unilateral are indications for ABR testing. Although it is believed that the different waves of the ABR reflect activity in increasingly rostral levels of the auditory system, the neural generators of the response have not been precisely determined. Each ABR wave beyond the earliest waves probably is the result of neural firing at many levels of the system, and each level of the system probably contributes to several ABR waves. High-intensity click stimuli are used for the neurologic application. The morphology of the response and wave, interwave latencies, and interaural latency differences are examined with respect to age-appropriate forms. Delayed or missing waves in the ABR result often have diagnostic significance.

The ABR and other electrical responses are extremely complex and difficult to interpret. A number of factors, including instrumentation design and settings, environment, degree and configuration of hearing loss, and patients' characteristics, can influence the quality of the recording. Therefore testing and interpretation of electrophysiologic activity as it possibly relates to hearing should be carried out by trained audiologists to avoid the risk that unreliable or erroneous conclusions will affect a patient's care.

Otoacoustic Emissions

During normal hearing, OAEs originate from the outer hair cells in the cochlea and are detected by sensitive amplifying processes. They travel from the cochlea through the middle ear to the external auditory canal, where they can be detected using miniature microphones. Transient evoked OAEs (TEOAEs) may be used to check the integrity of the cochlea. In the neonatal period, detection of OAEs can be accomplished during natural sleep, and TEOAEs can be used as screening tests in infants and children for hearing down to the 30 dB level of hearing loss. They are less time consuming and elaborate than ABRs and may be used when behavioral tests cannot be accomplished. TEOAEs are reduced or absent owing to various dysfunctions in the middle and inner ears. They are absent in patients with >30 dB of hearing loss and are not used to determine the hearing threshold; rather, they provide a screen for whether hearing is present at >30-40 dB. CHL, such as OM or congenitally abnormal middle-ear structures, reduces the transfer of TEOAEs and may be incorrectly interpreted as a cochlear hearing disorder. If a hearing loss is suspected based on the absence of OAEs, the ears should be examined for the evidence of pathology, tympanometry should be conducted, and then ABR testing should be used for confirmation and identification of the type, degree, and laterality of hearing loss.

TREATMENT

With widespread hearing screening within the United States, early diagnosis and treatment of children with hearing loss are common. Testing for hearing loss is possible even in very young children, and it should be done if parents suspect a problem. Any child with a known risk factor for hearing loss should be evaluated in the first 6 months of life.

Once a hearing loss is identified, a full developmental and speech and language evaluation is needed. Counseling and involvement of parents are required in all stages of the evaluation and treatment or rehabilitation. A CHL often can be corrected through treatment of a middle-ear effusion (i.e., ear tube placement) or surgical correction of the abnormal sound-conducting mechanism. Dependent on the level of hearing loss, children with SNHL should be evaluated for possible hearing aid use by a pediatric audiologist. Current guidelines indicate that within 1 month of diagnosis of SNHL, children should be fitted with **hearing aids**, and hearing aids may be fitted for children as young as 1 month of age. Compelling evidence from the hearing screening program in Colorado shows that identification and amplification before age 6 months make a very significant difference in the speech and language abilities of affected children compared with cases identified and amplified after the age of 6 months. In these children, repeat audiologic testing is needed to reliably identify the degree of hearing loss and to fine-tune the use of hearing aids. Hearing aids remain the rehabilitative device of choice, in the context of an individually designed treatment plan, for children with mild, moderate, or moderately severe CHL, mixed HL, or SNHL. For children with severe or profound SNHL, a trial with hearing aids is needed to determine if this approach is sufficient for the development of language; other options may need to be explored if there are indications that speech and language are delayed with a hearing aid in this HL group. Importantly, efficacy of hearing aids depends on their consistent use. There is great variability in how often children wear their hearing aids. Though there is no specific recommendation regarding the minimal number of hours per day that the hearing aids should be worn, parents should be encouraged to have their child use hearing aids full-time in order to facilitate speech and language development.

When it is clear that hearing aids are not providing the auditory stimulation needed to support language development, the parents require counseling to consider alternative treatments. A **cochlear implant** may be necessary to facilitate intelligible oral communication (i.e., oralism). This approach requires years of intensive speech and language training and is dependent on providing the best possible auditory stimulation. This option is very attractive to parents with hearing because it is the most familiar form of communication to them. Although there is a heavy emphasis in the medical world valuing the development of oral language (speech production), parents should also be provided with information about alternatives such as sign language, total communication, and cued speech (see Chapter 55). Each of these communication modalities has advantages and disadvantages. **Sign language** allows the child to develop a language system early and can support academic training. The consequence of this option is that the dominant hearing world does not interact easily with users of sign language, and the child may face significant challenges integrating into hearing society. Such possibilities as academic success and college/graduate school training are not excluded by the use of sign language, but a narrower set of venues may be available to accommodate the child's learning needs. Whereas this option may be acceptable to deaf parents already in the deaf community, many hearing parents are uncomfortable with this path for their child. This option also requires that the parents become fluent in sign language.

Total communication is an educational philosophy in which both sign and oral language as well as other forms of communication are encouraged. In theory, the two systems support and clarify information transfer and enhance academic progress. Depending on the particular school and/or teachers, one system may be emphasized over the other. **Cued speech** is an approach in which the development of oral language is supported by a system of hand gestures near the mouth and throat to disambiguate confusions that result from lip reading alone. This system can be highly successful in supporting spoken language and requires that parents become fluent in the use of the cues. Other factors should be considered in making the choice of communication modality. Significant comorbidities, such as visual impairment or other developmental delays, may limit the ability of a child to derive benefit from some choices. Support for the parents in making this decision may require counseling from an audiologist, social worker, deaf educator, and/or psychologist. Organizations of parents of deaf children, such as the A.G. Bell Association and the John Tracy Clinic, can provide a wealth of support and information to parents in this process.

Infants and young children with profound congenital or prelingual onset of deafness have benefited from **multichannel cochlear implants** (Fig. 677.4). Cochlear implants are systems that combine internal (surgically implanted) and externally worn components. These implants consist of 4 main components: the externals—which include a microphone, a minicomputer sound (speech) processor, and a transmitter—and the internal—an electrode array. These implants bypass injury to the organ of Corti and provide neural stimulation through the digitization of auditory stimuli into digital radiofrequency impulses. Specifically, sound is initially detected by the microphone and then is processed by the speech processor. The speech processor is programmed by an audiologist to implement the manufacturer's proprietary speech processing strategies that are highly sophisticated manipulations of the input signal. Signals from the speech processor are transmitted across the skin by an FM signal to the internal receiver, which converts these signals into electrical impulses. Finally, these electrical impulses are sent to the electrode array located in the cochlea, where electrical fields are created that act on the cochlear nerve. This contrasts with the transmission of sound in a healthy ear, which involves the transmission of sound vibrations to the hair cells of the cochlea, the release of ions and neurotransmitters in the cochlea, and the transmission of neural impulses to the cochlear nerve and then the brain.

Surgical implantation is done under general anesthesia and involves mastoidectomy and widening of the facial recess because the approach to the cochlea is through the facial recess. After fastening the internal stimulator package in the mastoid process, the cochlea must be opened to insert the electrode array, which is most commonly done through an opening made in the round window. Care is taken to avoid contamination of the cochlear fluids by bone dust or blood. After the cochlea is closed, generally with fascia, the wound is closed. An audiologist performs testing in the operating room to verify the functional integrity of the implanted device. These electrophysiologic responses from cranial nerve VIII are critical to determining a starting point for programming the external device after the wound has healed. A plain x-ray is often performed in the operating room as well to document placement of the array in the scala tympani.

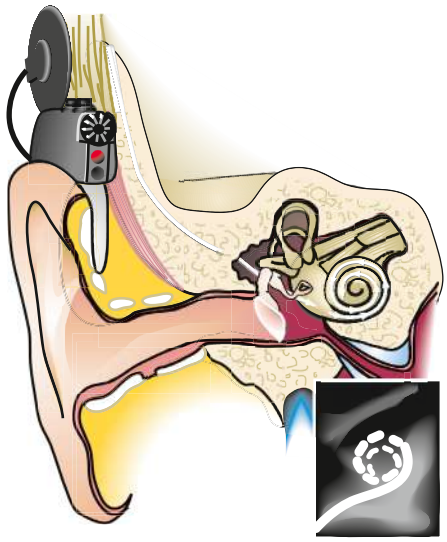

Fig. 677.4 All cochlear implants share key components, including a microphone, speech processor, and transmitter coil, shown in a behind-the-ear position in this diagram. The microphone and speech processor pick up environmental sounds and digitize them into coded signals. The signals are sent to the transmitter coil and relayed through the skin to the internal device embedded in the skull. The internal device converts the code to electronic signals, which are transmitted to the electrode array wrapping around the cochlea. The inset shows the radiographic appearance of the stimulating electrode array. *(From MED-EL Corporation, Innsbruck, Austria. From Smith RJH, Bale JF Jr., White KR. Sensorineural hearing loss in children. Lancet. 2005;365:879–890.)*

The healing process after surgery is approximately 3-4 weeks for a child. During this time, the child cannot hear. When the child is brought in for the first stimulation using the external equipment, programs are developed that provide the first access to sound. The methods to create the programs entail a combination of electrophysiologic measures and behavioral testing that is like the pediatric audiologic assessments described earlier. The initial programs are a starting point, followed by modifications and enhancements that are based on the parents' and audiologist's observations of changing auditory awareness and vocalization.

When parents elect to pursue cochlear implantation for their child, a long-term commitment is necessary to ongoing engagement with a team of rehabilitation specialists. Audiologic management entails consistent monitoring of the child's response to the implant and impact on emerging language skills. Speech and language therapy is necessary to stimulate language and to teach parents skills to support speech development. The child should be in a preschool setting in which speech, language, social, and academic precursor skills are fostered. For some parents, this engagement is very challenging, not only in terms of time required but also in terms of the emotional consequences of attempting to minimize the impact of hearing loss on their child's future; support for the parents is often needed in this process from the team.

Table 677.9 Recommended Pneumococcal Vaccination Schedule for Persons with Cochlear Implants

AGE AT FIRST PCV13 DOSE (mo)*	PCV12 PRIMARY SERIES	PCV13 ADDITIONAL DOSE	PPV23 DOSE
2-6	3 doses, 2 mo apart†	1 dose at 12-15 mo of age‡	Indicated at ≥24 mo of age§
7-11	2 doses, 2 mo apart†	1 dose at 12-15 mo of age‡	Indicated at ≥24 mo of age§
12-23	2 doses, 2 mo apart¶	Not indicated	Indicated at ≥24 mo of age§
24-59	2 doses, 2 mo apart¶	Not indicated	Indicated§
≥60	Not indicated	Not indicated**	Indicated

*A schedule with a reduced number of total 13-valent pneumococcal conjugate vaccine (PCV13) doses is indicated if children start late or are incompletely vaccinated. Children with a lapse in vaccination should be vaccinated according to the catch-up schedule (see Chapter 228).
†For children vaccinated at younger than age 1 yr, minimum interval between doses is 4 wk.
‡The additional dose should be administered 8 wk or more after the primary series has been completed.
§Children younger than age 5 yr should complete the PCV13 series first; 23-valent pneumococcal polysaccharide vaccine (PPV23) should be administered to children 24 mo of age or older 8 wk or more after the last dose of PCV13 (see Chapter 228) (Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Preventing pneumococcal disease among infants and young children: Recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Recomm Rep*. 2000;49[RR-9]:1–35, and Licensure of a 13-valent pneumococcal conjugate vaccine [PCV13] and recommendations for use among children—Advisory Committee on Immunization Practices [ACIP]. *MMWR Morb Mortal Wkly Rep*. 2010;59[9]:258–261.)
¶Minimum interval between doses is 8 wk.
**PCV13 is not recommended generally for children age 5 yr or older.
PCV, Pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.
From Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Pneumococcal vaccination for cochlear implant candidates and recipients: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2003;52(31):739–740.

A serious possible complication of cochlear implantation is pneumococcal meningitis. All children receiving a cochlear implant must be vaccinated with the pneumococcal polyvalent vaccine PCV13 (Table 677.9), and rates of pneumococcal meningitis have declined considerably since implementation of the vaccine.

The Food and Drug Administration (FDA) has approved cochlear implantation in patients over 9 months of age with severe to profound bilateral hearing loss not benefitting from hearing aids; off-label use of cochlear implants has demonstrated efficacy in younger children and those with residual hearing. Cochlear implantation before age 2 years improves hearing and speech, enabling more than 90% of children to be in mainstream education. Most develop age-appropriate auditory perception and oral language skills. There is increasing evidence to support expansion of the candidacy for cochlear implantation in children to be based on outcomes of advanced testing using speech stimuli, especially in noise. To date, implantation of children with devices that combine acoustic input (like a hearing aid) with electric stimulation from a cochlear implant has not been approved by the FDA. These devices, called *electroacoustic cochlear implants,* or *hybrids,* may offer hope for children using hearing aids but struggling with noise in the classroom or social contexts.

Valganciclovir has been effective in treating hearing deficits in children with congenital CMV and isolated SNHL (see Chapter 302).

GENETIC COUNSELING

Families of children with the diagnosis of SNHL or a syndrome associated with SNHL and/or CHL should be referred for genetic counseling. This will give the parents an idea of the likelihood of similar diagnoses in future pregnancies, and the geneticist can assist in the evaluation and testing of the patient to establish a diagnosis.

677.1 Idiopathic Sudden Sensorineural Hearing Loss

Joseph Haddad Jr.

Sudden SNHL in a previously healthy child is uncommon but may be from OM or other cochlear pathologies such as autoimmunity (Cogan syndrome, others). Usually, these causes are obvious from the history and physical examination. Sudden loss of hearing in the absence of obvious causes may also be the result of a vascular event affecting the cochlear apparatus or nerve, such as embolism or thrombosis (secondary to prothrombotic conditions) or hemorrhage. Additional causes include perilymph fistula, medications, trauma, and the first episode of Meniere syndrome. In adults, sudden SNHL is often idiopathic and unilateral; it may be associated with a sensation of ear fullness, tinnitus, and vertigo. Identifiable causes of sudden SNHL include infections (Epstein-Barr virus, varicella-zoster virus, herpes simplex virus) (see Table 677.2), vascular injury to the cochlea, enlarged vestibular aqueduct, endolymphatic hydrops, and autoimmune inflammatory diseases. In most (~75%) patients with sudden SNHL, no etiology is discovered, and it is termed **idiopathic sudden SNHL**. This entity is defined by a rapid (≤72 hours) onset that may be unilateral (bilateral in 25%) and associated with a hearing loss of ≥30 dB. Patients should be evaluated immediately to exclude other etiologies and obtain a focused MRI of the auditory vestibular region.

Management of **idiopathic sudden SNHL** has included oral prednisone, intratympanic (also called transtympanic) dexamethasone perfusion, or a combination of both; the latter combination may be the most useful. Recovery of hearing is more likely in patients with early treatment and with mild or moderate hearing loss and those with unilateral involvement.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 678

Congenital Malformations of the Ear

Joseph Haddad Jr.

The external and middle ears, derived from the first and second branchial arches and grooves, grow throughout puberty, but the inner ear, which develops from the otocyst, reaches adult size and shape by midfetal development. The ossicles are derived from the first and second arches (malleus and incus), and the stapes arises from the second arch and the otic capsule. The malleus and incus achieve adult size and shape by the 15th week of gestation, and the stapes achieves adult size and shape by the 18th week of gestation. Although the pinna, ear canal, and tympanic membrane (TM) continue to grow after birth, congenital abnormalities of these structures develop during the first half of gestation. Malformed external and middle ears may be associated with serious renal anomalies, mandibulofacial dysostosis, hemifacial microsomia, and other craniofacial malformations (Table 678.1). Facial nerve abnormalities may be associated with any of the congenital abnormalities of the ear and temporal bone. Malformations of the external and middle ears also may be associated with abnormalities of the inner ear and both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL).

Congenital ear problems may be either minor and mainly cosmetic or major, affecting both appearance and function. Any child born with an abnormality of the pinna, external auditory canal, or TM should have a complete audiologic evaluation in the neonatal period. Imaging studies are necessary for evaluation and treatment; in the patient with other craniofacial abnormalities, a team approach with other specialists can assist in guiding therapy.

PINNA MALFORMATIONS

Severe malformations of the external ear are rare, but minor deformities are common. Isolated abnormalities of the external ear occur in approximately 1% of children (Fig. 678.1). A **pitlike** depression just in front of the helix and above the tragus may represent a cyst or an epidermis-lined fistulous tract (Fig. 678.2). These are common, with an incidence of approximately 8 in 1,000 children, and may be unilateral or bilateral and familial. The pits require surgical removal only if there is recurrent infection. Accessory **skin tags**, with an incidence of 1-2/1,000 live births, can be removed for cosmetic reasons by simple ligation if they are attached by a narrow pedicle. If the pedicle is broad based or contains cartilage, the defect should be corrected surgically. An unusually prominent or "lop" ear results from lack of bending of the cartilage that creates the antihelix. It may be improved cosmetically in the neonatal period by applying a firm framework (sometimes soldering wire is used) attached by Steri-Strips to the pinna and worn continuously for weeks to months. Otoplasty for cosmetic correction can be considered in children older than 5 years of age, when the pinna has reached approximately 80% of its adult size.

The term **microtia** may indicate subtle abnormalities of the size, shape, and location of the pinna and ear canal or major abnormalities with only small nubbins of skin and cartilage and the absence of the ear canal opening; **anotia** indicates complete absence of the pinna and ear canal (Fig. 678.3). Microtia can have a genetic or environmental predisposition. Several hereditary forms of microtia have been identified that exhibit either autosomal dominant or recessive mendelian inheritance. In addition, some forms due to chromosomal aberrations have been reported. Most of the responsible genes that have been identified are homeobox genes, which are involved in the development of pharyngeal arches. Microtic ears often are more anterior and inferior in placement than normal auricles, and the location and function of the facial nerve may be abnormal. Surgery to correct microtia is considered for both cosmetic and functional reasons; children who have some pinna can wear regular glasses, a hearing aid, and earrings and feel more normal in appearance. If the microtia is severe, some patients may opt for creation and attachment of a prosthetic ear, which cosmetically closely

Table 678.1 Diseases with Anomalies of the External and Middle Ears Listed by Pathologic Defect and Traditional Name

PATHOLOGIC NAME	EPONYM
4p-syndrome	Wolf-Hirschhorn syndrome
Acrocephalosyndactyly type I	Apert syndrome
Acrocephalosyndactyly type III	Saethre-Chotzen syndrome
Acrocephalosyndactyly type V	Pfeiffer syndrome
Anus imperforate with hand, foot, and ear anomalies	Townes-Brocks syndrome
Arteriohepatic dysplasia	Alagille syndrome
Branchio-oto-renal syndrome	Melnick Fraser syndrome
Brevicollis	Klippel-Feil syndrome
Cervico-oculoacoustic syndrome	Wildervanck syndrome
Cleft palate, microcephaly, large ears, and short stature	Say syndrome
Cleft palate, micrognathia, and glossoptosis	Pierre Robin sequence
Congenital contractural arachnodactyly	Beals syndrome
Congenital facial diplegia	Möbius syndrome
Constitutional aplastic pancytopenia with multiple anomalies	Fanconi syndrome
Craniofacial dysostosis	Crouzon disease
Craniometaphyseal dysplasia	Pyle disease
Dyschondrosteosis	Léri-Weill syndrome
Exomphalos-macroglossia-gigantism syndrome	Beckwith-Wiedemann syndrome
Faciodigitogenital syndrome	Aarskog syndrome
Gargoylism	Hurler syndrome
Gonadal aplasia	Turner syndrome
Hemifacial microsomia (oculoauriculovertebral dysplasia)	Goldenhar syndrome
Lacrimoauriculodentodigital syndrome	Levy-Hollister syndrome
Mandibulofacial dysostosis	Treacher Collins syndrome
Orofaciodigital syndrome type II	Mohr syndrome
Osteodysplasty	Melnick-Needles syndrome
Osteopetrosis	Albers-Schönberg disease
Renal agenesis, bilateral	Potter syndrome
Third and fourth pharyngeal pouch syndrome	DiGeorge syndrome
Trisomy 13-15 syndrome	Patau syndrome
Trisomy 18 syndrome	Edwards syndrome
Trisomy 21 syndrome	Down syndrome

From Lesperance MM, Flint PW, eds. *Cummings Pediatric Otolaryngology.* Philadelphia: Elsevier; 2015, Table 15.1, p. 197.

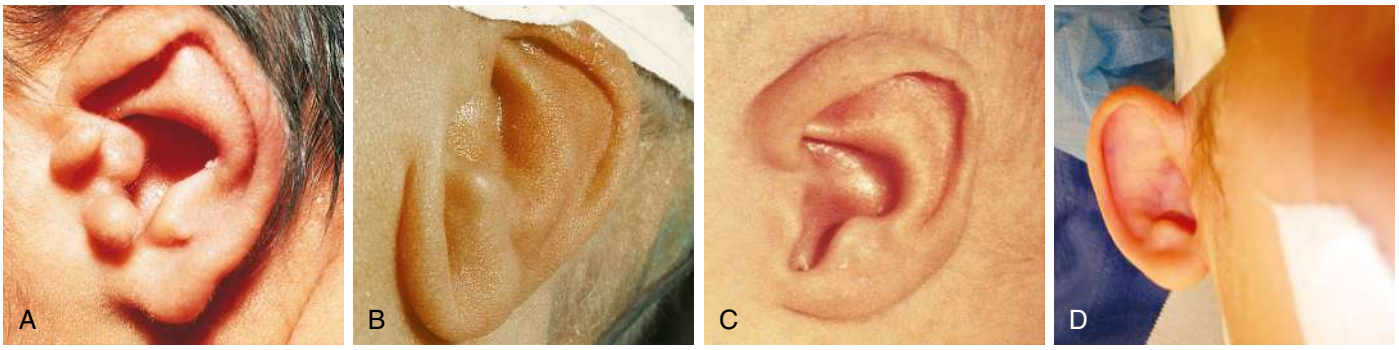

Fig. 678.1 Minor congenital auricular deformities. **A,** In this infant, the superior portion of the helix is folded over, obscuring the triangular fossa; the antihelix is sharply angulated; and there are three preauricular skin tags. **B,** This neonate with orofaciodigital and Turner syndromes has a simple helix and a redundant folded lobule. The ear is low set and posteriorly rotated, and the antitragus is anteriorly displaced. **C,** This infant with Rubinstein-Taybi syndrome has an exaggerated elongated intertragal notch. **D,** Prominent ear in an otherwise normal child. The auricular cartilage is abnormally contoured, making the ear protrude forward. *(**C** courtesy Dr. Michael E. Sherlock, Lutherville, Maryland; from Zitelli BJ, McIntire SC, Nowalk AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 7th ed. Philadelphia: Elsevier; 2018: Fig. 24.17, p. 875.)*

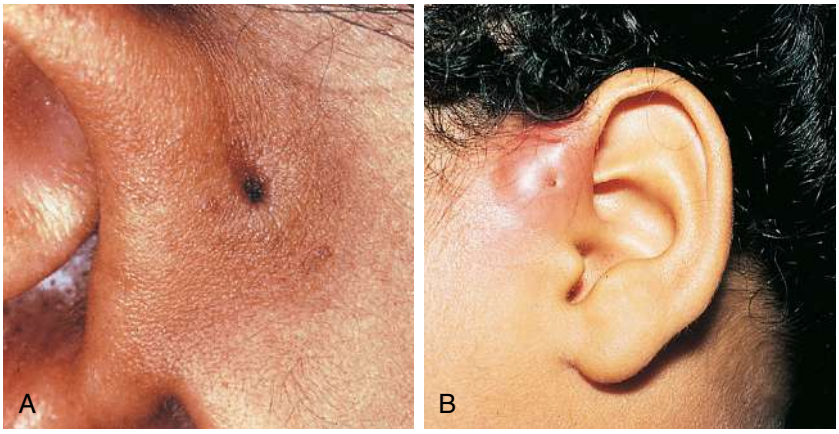

Fig. 678.2 Preauricular sinuses. **A,** These congenital remnants are located anterior to the pinna and have an overlying surface dimple. **B,** In this child, the sinus has become infected, forming an abscess. *(**A** courtesy Michael Hawke, MD; from Zitelli BJ, McIntire SC, Nowalk AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 7th ed. Philadelphia: Elsevier; 2018: Fig. 24.18, p. 876.)*

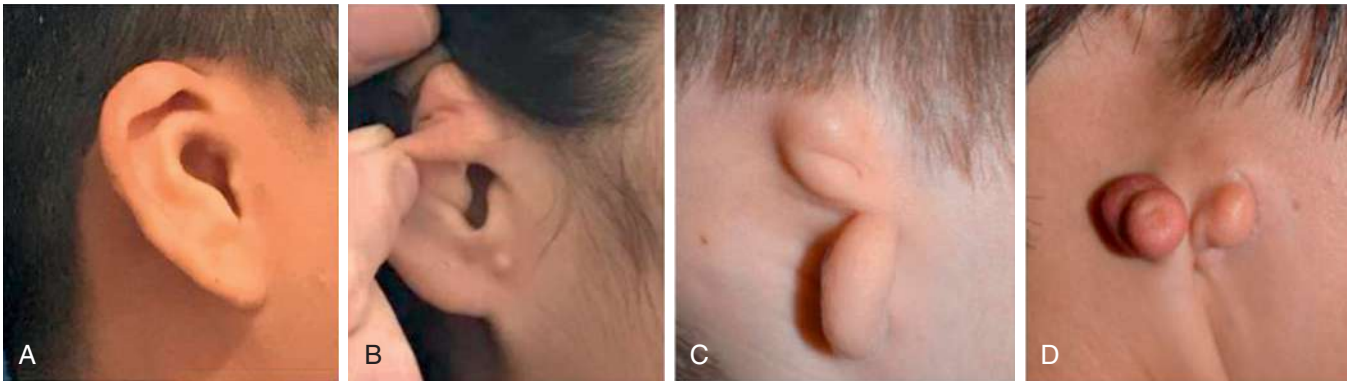

Fig. 678.3 A, Type I microtia with constricted ear and minimal tissue deficiency. **B,** Type II microtia, conchal type: absence of superior portions of the ear and preservation of inferior conchal anatomy. **C,** Type III microtia, lobular type: markedly deformed and no identifiable concha and preservation of the lobule. **D,** Type IV, anotia. *(From Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed, Philadelphia: Elsevier; 2022: Fig. 18.2, p. 250.)*

resembles a real ear. Surgery to correct severe microtia may involve a multistage procedure, including carving and transplantation of autogenous cartilage rib grafts and local soft tissue flaps. Cosmetic reconstruction of the auricle usually is performed between 5 and 7 years of age and is performed before canal atresia repair in children deemed appropriate for this surgery.

CONGENITAL STENOSIS OR ATRESIA OF THE EXTERNAL AUDITORY CANAL

Stenosis or atresia of the ear canal often occurs in association with malformation of the auricle and middle ear. Malformations can occur in isolation or as part of a genetic syndrome. For example, the ear canal is narrow in trisomy 21, and external canal stenosis or atresia is common in branchiooculofacial syndrome, leading to CHL. Audiometric evaluation of these children should be undertaken as early in life as possible. Most children with significant CHL secondary to bilateral atresia wear bone conduction hearing aids for the first several years of life. Diagnosis, evaluation, and surgical planning often are aided by CT, and sometimes MRI, of the temporal bone. Mild cases of ear canal stenosis do not require surgical enlargement unless the patient develops chronic external otitis or severe cerumen impaction that affects hearing.

Reconstructive ear canal and middle-ear surgery for atresia usually is considered for children older than 5 years of age who have bilateral deformities resulting in significant CHL. The aim of reconstructive surgery is to improve hearing to a point where the child may not need a hearing aid or to provide an ear canal and pinna so that the child can derive improved benefit from an air-conduction hearing aid. Hearing results for atresiaplasty range from fair to excellent. CT evidence of an adequate middle-ear cleft, ossicles, and mastoid is required to perform the surgery; the position of the facial nerve, which often is in an abnormal location in these children, also must be considered (Fig. 678.4). The use of bone-anchored hearing aids is a safe, reliable, and low-risk alternative to atresiaplasty, and hearing results are generally excellent. Bone-anchored hearing aids may also be useful for rehabilitation of nonoptimal atresiaplasty hearing results. These devices are approved by the US Food and Drug Administration for surgical placement in children age 5 years and older; before age 5 years, they can be worn with a soft band around the head. Disadvantages include the fact that cosmesis is not very good (a bone-anchored hearing aid has a visible titanium abutment and snap-on hearing aid) and frequent wound care is required. Middle ear implants are effective alternatives for those who cannot tolerate foreign bodies in the ear for medical reasons or rely on good perception of high-frequency sounds.

CONGENITAL MIDDLE-EAR MALFORMATIONS

Children may have congenital abnormalities of the middle ear as an isolated defect or in association with other abnormalities of the temporal bone, especially the ear canal and pinna, or as part of a syndrome. Affected children usually have CHL but may have mixed CHL and SNHL. Most malformations involve the ossicles, with the incus most commonly affected. Other less common abnormalities of the middle ear include persistent stapedial artery, high-riding jugular bulb, and abnormalities of the shape and volume of the aerated portion of the middle ear and mastoid; all present problems for a surgeon. Depending on the type of abnormality and the presence of other anomalies, surgery may be considered to improve hearing.

CONGENITAL INNER EAR MALFORMATIONS

Congenital inner ear malformations are classified as a result of improvements in imaging modalities (Table 678.2). As many as 20% of children with SNHL may have anatomic abnormalities identified on CT or MRI. Congenital malformations of the inner ear usually are associated with SNHL of various degrees, from mild to profound. These malformations are most commonly found in infants and may occur as isolated anomalies or in association with other syndromes, genetic abnormalities, or structural abnormalities of the head and neck (Table 678.3). High-resolution temporal bone CT can identify enlarged vestibular aqueducts and cochlear nerve canal stenosis in association with SNHL. Although no therapy exists for this condition, it may be associated with progressive SNHL in some children; therefore diagnosis may have some prognostic value.

Congenital perilymphatic fistula of the oval or round window membrane may present as a rapid-onset, fluctuating, or progressive SNHL with or without vertigo and often is associated with congenital inner ear abnormalities. Middle-ear exploration may be required to confirm this

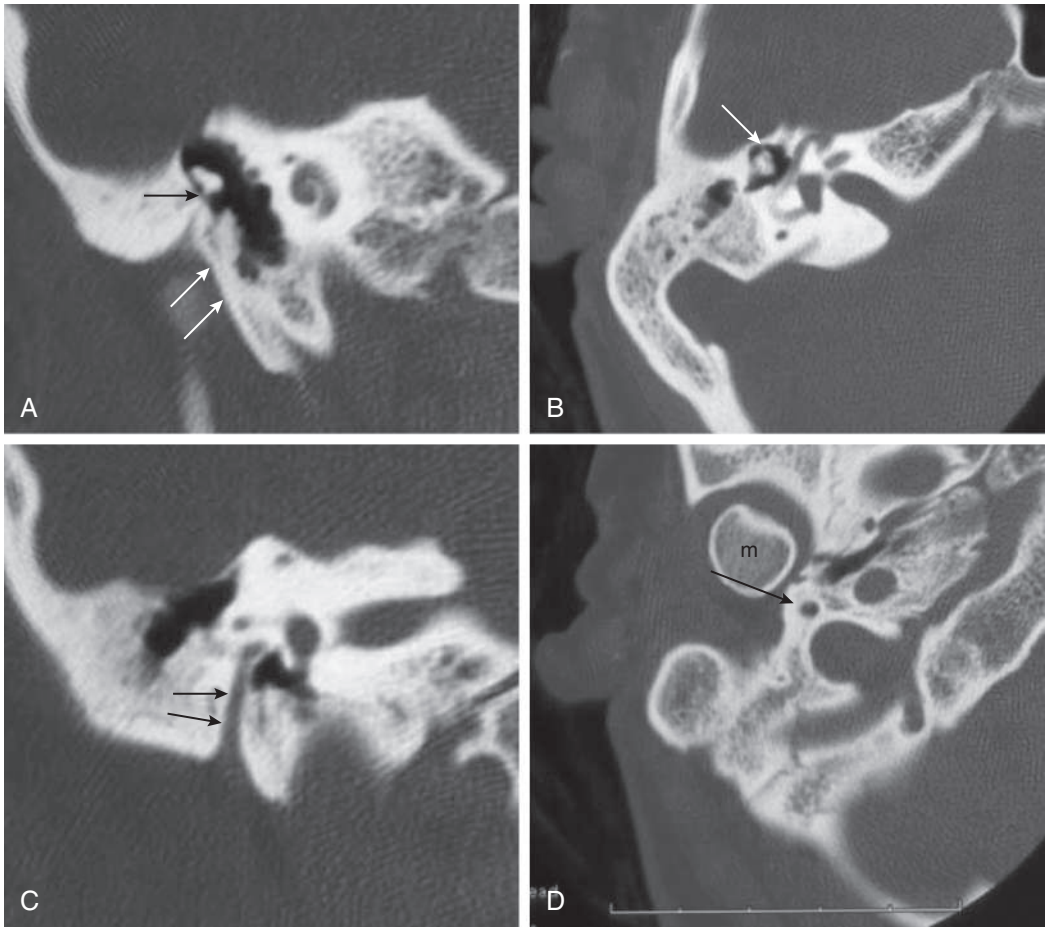

Fig. 678.4 External auditory canal atresia on CT scans. **A,** Coronal scan of right ear shows absent external auditory canal with thick bony atresia plate *(white arrows).* Malleus neck is rotated and fused to superior portion of atresia plate *(black arrow).* **B,** Axial scan through attic shows fused ossicular mass *(arrow).* **C,** Coronal scan more posterior to **(A)** shows mastoid segment of facial nerve canal positioned more anteriorly than normal *(arrows).* **D,** Axial scan more inferior to **(B)** shows anterior-posterior mastoid segment of the facial nerve en face *(arrow).* Note abnormally close relationship to mandibular condyle. *(From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 44.7, p. 584.)*

diagnosis, because no reliable nonoperative diagnostic test exists. It may be necessary to repair a perilymphatic fistula to prevent possible spread of infection from the middle ear to the labyrinth or meninges, to stabilize hearing loss, and to improve vertigo when present.

Table 678.2 Classification of Congenital Inner Ear Malformations

MALFORMATIONS LIMITED TO THE MEMBRANOUS LABYRINTH
Complete membranous labyrinthine dysplasia
Limited membranous labyrinthine dysplasia
Cochleosaccular dysplasia (Scheibe)
Cochlear basal turn dysplasia
MALFORMATIONS OF THE OSSEOUS AND MEMBRANOUS LABYRINTH
Complete labyrinthine aplasia (Michel)
Cochlear anomalies
Cochlear aplasia
Cochlear hypoplasia
Incomplete partition (Mondini)
Common cavity
Labyrinthine anomalies
Semicircular canal dysplasia
Semicircular canal aplasia
Aqueductal anomalies
Enlargement of the vestibular aqueduct
Enlargement of the cochlear aqueduct
Internal auditory canal anomalies
Narrow internal auditory canal
Wide internal auditory canal
Eighth cranial nerve anomalies
Hypoplasia
Aplasia

From Lesperance MM, ed. *Cummings Pediatric Otolaryngology*, 2nd ed, Philadelphia: Elsevier; 2022: Box 13.1, p. 178.

CONGENITAL CHOLESTEATOMA

A congenital cholesteatoma (approximately 2–5% of all cholesteatomas) is a nonneoplastic, destructive, cystic lesion that usually appears as a white, round, cystlike structure medial to an intact TM. Cysts are seen most commonly in boys and in the anterior-superior portion of the middle ear, although they can present in other locations and within the TM or in the skin of the ear canal. They can be classified as "open," meaning in direct continuity with mucosa of the middle ear, or "closed." Affected children often have no prior history of otitis media. One theory for the pathogenesis is that the cyst derives from a congenital rest of epithelial tissue that persists beyond 33 weeks of gestation, when it ordinarily would disappear. Other theories include squamous metaplasia of the middle ear, entrance of squamous epithelium through a nonintact eardrum into the middle ear, ectodermal implants between the first and second branchial arch remnants, and residual amniotic fluid squamous debris. Congenital or acquired cholesteatoma should be suspected when deep retraction pockets, keratin debris, chronic drainage, aural granulation tissue, or a mass behind or involving the TM is present. Congenital cholesteatoma is often asymptomatic, whereas acquired cholesteatoma commonly presents with otorrhea. Besides acting as a benign tumor causing local bone destruction, the keratinaceous debris of a cholesteatoma serves as a culture medium, leading to chronic otitis media. Complications include ossicular erosion with hearing loss, bone erosion into the inner ear with dizziness, or exposure of the dura, with consequent meningitis or a brain abscess. Evaluation includes a CT scan (Fig. 678.5) to detect bone erosion and audiometry to assess air and bone conduction and speech reception and discrimination. Treatment includes cholesteatoma removal, repair of damaged small middle ear bones, and mastoidectomy in 50% of congenital and >90% of acquired cholesteatoma cases. A second-look procedure 6-9 months after primary surgery is usually recommended to detect and remove small amounts of residual disease before more extensive recurrence or development of complications. Higher initial stage of disease, erosion of ossicles, cholesteatoma abutting or enveloping the incus or stapes,

Table 678.3 Inner Ear Malformations in Syndromic Hearing Loss

SYNDROME	GENETIC ABNORMALITY	RADIOGRAPHIC ANOMALIES	ASSOCIATED ANOMALIES
Apert	*FGFR2*	Vestibular dysplasia, high-riding jugular bulb	Stapes footplate fixation
Branchio-oto-renal	*EYA1*	Hypoplastic cochlea, enlarged VA	Malleus or incus dysplasia, aberrant facial nerve
CHARGE	*CHD7*	Hypoplastic or absent SCC	Coloboma, heart defects, choanal atresia, growth retardation, genital/urinary abnormalities
Down	Trisomy 21	Hypoplastic cochlea, SCC dysplasia, cochlear nerve canal hypoplasia	Narrow external auditory canal, eustachian tube dysfunction
Edwards	Trisomy 18	Hypoplastic cochlea, absent SCC	Microtia, low-set ears
Pendred	*SLC26A4*	Hypoplastic cochlea, enlarged VA, modiolar deficiency	Goiter, hypothyroidism
Waardenburg type I	*PAX3*	Hypoplastic cochlea and/or SCC, enlarged VA	Telecanthus, white forelock, heterochromia iridum
Waardenburg type II	*MITF, SNAI2, SOX10*	Enlarged vestibule, hypoplastic SCC	White forelock, heterochromia iridum
Waardenburg type III	*PAX3*	Hypoplastic cochlea and/or SCC, enlarged VA	Upper limb abnormalities, white forelock, heterochromia iridum
Waardenburg type IV	*EDNRB, EDN3, SOX10*	Enlarged vestibule, hypoplastic SCC	Hirschsprung disease, white forelock, heterochromia iridum

SCC, Semicircular canal; VA, vestibular aqueduct.
Modified from Lesperance MM, ed. *Cummings Pediatric Otolaryngology,* 2nd ed. Philadelphia: Elsevier; 2022: Table 13.2, p. 189.

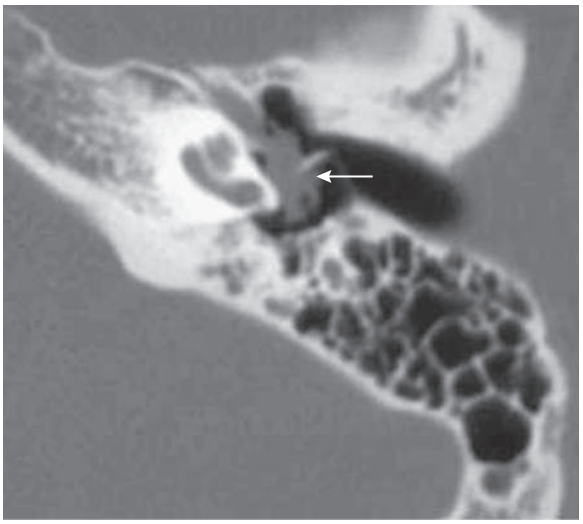

Fig. 678.5 Congenital cholesteatoma. Axial CT of left ear shows soft tissue mass *(arrow)* in the middle ear. This mass was noted otoscopically behind an intact membrane. *(From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 44.31, p. 598.)*

and need for removal of the ossicles are associated with increased likelihood of residual cholesteatoma, which occurs in ~10% of congenital and ~25% of acquired cases. More extensive disease at initial surgery is associated with poorer hearing outcomes. Children with significant inflammation or extensive scarring may require a 2-stage procedure with initial removal of the cholesteatoma and subsequent repair of damaged middle ear structures.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 679

External Otitis (Otitis Externa)

Joseph Haddad Jr.

In an infant, the outer two thirds of the ear canal is cartilaginous and the inner one third is bony. In an older child and adult, the outer one third is cartilaginous and the inner two thirds is bony. The epithelium is thinner in the bony portion than in the cartilaginous portion, there is no subcutaneous tissue, and epithelium is tightly applied to the underlying periosteum; hair follicles, sebaceous glands, and apocrine glands are scarce or absent. The skin in the cartilaginous area has well-developed dermis and subcutaneous tissue and contains hair follicles, sebaceous glands, and apocrine glands. The highly viscid secretions of the sebaceous glands and the watery, pigmented secretions of the apocrine glands in the outer portion of the canal combine with exfoliated surface cells of the skin to form **cerumen**, a protective, waxy, water-repellent coating.

The normal flora of the external canal consists mainly of aerobic bacteria and includes coagulase-negative staphylococci (see Chapter 227.3), *Corynebacterium* (diphtheroids; see Chapter 233), *Micrococcus,* and occasionally *Staphylococcus aureus* (see Chapter 227.1), viridans streptococci (see Chapter 231), and *Pseudomonas aeruginosa* (see Chapter 251.1). **Excessive wetness** (swimming, bathing, increased environmental humidity), **dryness** (dry canal skin and lack of cerumen), the presence of other skin pathologic conditions (previous infection, eczema, or other forms of dermatitis), and trauma (due to digital or foreign body, use of cotton-tipped swabs) make the skin of the canal vulnerable to infection by the normal flora or exogenous bacteria and predispose to colonization with gram-negative bacteria.

ETIOLOGY

External otitis (**swimmer's ear**, although it can occur without swimming) is caused most by *P. aeruginosa* (up to 60%), but *S. aureus*, *Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae,* streptococci, coagulase-negative staphylococci and diphtheroids, and fungi such as *Candida* and *Aspergillus* also may rarely be isolated. External otitis results from chronic irritation and maceration from excessive moisture in the canal. The loss of protective cerumen may play a role, as may trauma, but cerumen impaction with trapping of water also can cause infection. Inflammation of the ear canal due to herpesvirus, varicella-zoster virus, other skin exanthems, and eczema also may predispose to external otitis.

CLINICAL MANIFESTATIONS

The predominant symptom is acute rapid onset (typically within 48 hours) of ear pain (otalgia), often severe, accentuated by manipulation of the pinna or by pressure on the tragus and by jaw motion. The severity of the pain and tenderness (tragus or pinna, or both) may be disproportionate to the degree of inflammation, because the skin of the external ear canal is tightly adhered to the underlying perichondrium and periosteum. Itching often is a precursor of pain and usually is characteristic of chronic inflammation of the canal or resolving acute otitis externa. Conductive hearing loss (CHL) may result from edema of the skin and tympanic membrane (TM), serous or purulent secretions, or the canal skin thickening associated with chronic external otitis.

Edema of the ear canal, erythema, and thick, clumpy otorrhea are prominent signs of acute disease. The cerumen usually is white and soft in consistency, as opposed to its usual yellow color and firmer consistency (Fig. 679.1). The canal often is so tender and swollen that the entire ear canal and TM cannot be adequately visualized, and complete otoscopic examination may be delayed until the acute swelling subsides. If the TM can be visualized, it may appear either normal or opaque. TM mobility may be normal, or, if the TM is thickened, mobility may be reduced in response to positive and negative pressure.

Other physical findings may include palpable and tender lymph nodes in the periauricular region and erythema and swelling of the pinna and periauricular skin. Rarely, facial paralysis, other cranial nerve abnormalities, vertigo, and/or sensorineural hearing loss are present. If these occur, **necrotizing (malignant) otitis externa**, an invasive infection of the temporal bone and skull base, is probable. Fortunately, this disease is rare in children and is seen only in association with immunocompromise or severe malnourishment. In adults, it is associated with diabetes mellitus.

DIAGNOSIS

Diffuse external otitis may be confused with **furunculosis**, **otitis media (OM)**, and **mastoiditis** (Table 679.1). Furuncles occur in the lateral hair-bearing part of the ear canal; furunculosis usually causes a localized swelling of the canal limited to one quadrant, whereas external otitis is associated with concentric swelling and involves the entire ear canal. In OM, the TM may be perforated, severely retracted, or bulging and immobile; hearing usually is impaired. If the middle ear is draining through a perforated TM or tympanostomy tube, secondary external otitis may occur; if the TM is not visible owing to drainage or ear canal swelling, it may be difficult to distinguish acute OM with drainage from an acute external otitis. Pain on manipulation of the

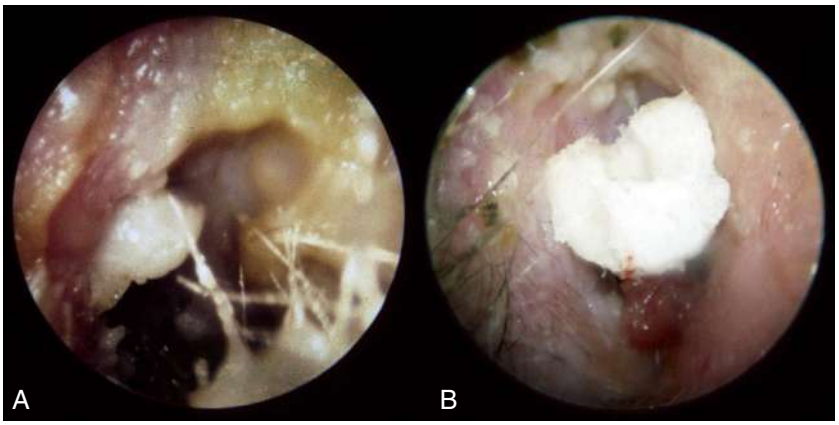

Fig. 679.1 Acute otitis externa. **A,** Erythema, edema, and copious purulent debris. **B,** In some cases an edematous canal with granulation tissue necessitates the placement of an ear wick to assist with topical drug delivery in the acute setting. *(Courtesy Dr. John W. House, Los Angeles.)*

Table 679.1 Differential Diagnosis of Painful External Ear and Auditory Canal Disorders

DISORDER	CLINICAL FEATURES
Acute otitis externa	Diffuse redness, swelling, and pain of the canal with greenish to whitish exudate; often very tender pinna
Necrotizing (malignant) otitis externa (± skull base osteomyelitis)	Rapidly progressive, severe swelling and redness of pinna; pinna may be laterally displaced; risk factors include diabetes mellitus, congenital or acquired immunodeficiency, severe neutropenia
Dermatitis	
Eczema	History of atopy, presence of lesions elsewhere; lesions are scaly, red, pruritic, and weeping
Contact	History of cosmetic use or irritant exposure; lesions are scaly, red, pruritic, and weeping
Seborrhea	Scaly, red, papular dermatitis; scalp may have thick, yellow scales
Psoriasis	History or presence of psoriasis elsewhere; erythematous papules that coalesce into thick, white plaques
Cellulitis	Diffuse redness, tenderness, and swelling of the pinna
Furuncles	Red, tender papules in areas with hair follicles (distal third of the ear canal)
Infected periauricular cyst	Discrete, palpable lesions; history of previous swelling at same site; cellulitis may develop, obscuring cystic structure
Insect bites	History of exposure; lesions are red, tender papules
Herpes zoster oticus	Painful, vesicular lesions in the ear canal and tympanic membrane, hearing loss, vestibulitis; with addition of seventh cranial nerve palsy—Ramsay Hunt syndrome
Perichondritis	Inflammation of the cartilage, usually secondary to cellulitis
Relapsing polychondritis	Recurrent episodes, involves other cartilage sites (nose)
Granulomatosis with polyangiitis	Fever, weight loss, respiratory and/or renal manifestations
Tumors including Langerhans cell histiocytosis	Palpable mass, destruction of surrounding structures
Foreign body	Foreign body may cause secondary trauma to the ear canal or become a nidus for an infection of the ear canal
Trauma	Bruising and swelling of external ear; there may be signs of basilar skull fracture (cerebrospinal fluid otorrhea, hemotympanum)
Red ear syndrome	Paroxysmal unilateral or bilateral burning and reddening. Associated with migraines or trigeminal cephalgias
Erythromelalgia	Burning, erythema from heat exposure relieved by cold; isolated ear involvement unusual

Modified from Kliegman R, Bordini B, Toth H, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2022: Table 5.2.

auricle and significant lymphadenitis are not common features of OM, and these findings assist in the differential diagnosis. In some patients with external otitis, the periauricular edema is so extensive that the auricle is pushed forward, creating a condition that may be confused with acute mastoiditis and a subperiosteal abscess. In mastoiditis, the postauricular fold is obliterated, whereas in external otitis, the fold is usually better preserved. In acute mastoiditis, a history of OM and hearing loss is usual; tenderness is noted over the mastoid and not on movement of the auricle; and otoscopic examination may show sagging of the posterior canal wall.

Referred otalgia may come from disease in the paranasal sinuses, teeth, pharynx, parotid gland, neck and thyroid, and cranial nerves

(trigeminal neuralgia; herpes simplex virus, varicella-zoster virus; see Table 676.1).

TREATMENT

Topical otic preparations containing acetic acid, with or without hydrocortisone, or neomycin (active against gram-positive organisms and some gram-negative organisms, notably *Proteus* spp.), polymyxin (active against gram-negative bacilli, notably *Pseudomonas* spp.), or a quinolone (ciprofloxacin), with or without hydrocortisone, are all highly effective in treating most forms of acute external otitis. A nonototoxic (quinolone) antibiotic should be chosen in the setting of known TM perforation or tympanostomy tube. If canal edema is marked, the patient may need referral to a specialist for cleaning and possible wick placement. An otic antibiotic and corticosteroid eardrop is often recommended. A wick can be inserted into the ear canal and topical antibiotics applied to the wick 3 times a day for 24-48 hours. The wick can be removed after 2-3 days, at which time the edema of the ear canal usually is markedly improved and the ear canal and TM are better seen. Topical antibiotics are then continued by direct instillation. When the pain is severe, oral analgesics (e.g., ibuprofen, acetaminophen) may be necessary for a few days.

Someone other than the patient should place the drops in the ear canal while the patient is recumbent with the affected ear facing up. The drops should fill the canal, and the patient should remain in place for 3-5 minutes. Gently moving the ear to and fro may enhance the drops to fill the ear canal. Patients should respond to initial therapeutics in 48-72 hours. Failure to improve in this time frame should prompt assessment of drug delivery and adherence to therapy, consideration for change in therapy, and consideration of alternative diagnoses. Careful evaluation for underlying conditions should also be undertaken in patients with severe or recurrent otitis externa. Figure 679.2 outlines an approach to managing acute external otitis.

As the inflammatory process subsides, cleaning the canal with a suction or cotton-tipped applicator to remove the debris enhances the effectiveness of the topical medications. In subacute and chronic infections, periodic cleansing of the canal is essential. In severe acute external otitis associated with fever and lymphadenitis, oral or parenteral antibiotics may be indicated; an ear canal culture should be done, and empirical antibiotic treatment can then be modified if necessary, based on susceptibility of the organism cultured. A fungal infection of the external auditory canal, or **otomycosis**, is characterized by fluffy white debris, sometimes with black spores seen; treatment includes cleaning and application of antifungal solutions such as clotrimazole or nystatin; other antifungal agents include boric acid powder, m-cresyl acetate 25%, gentian violet 2%, and thimerosal 1:1,000.

Necrotizing otitis externa, commonly caused by *P. aeruginosa* (see Chapter 251.1), requires immediate culture, intravenous antibiotics,

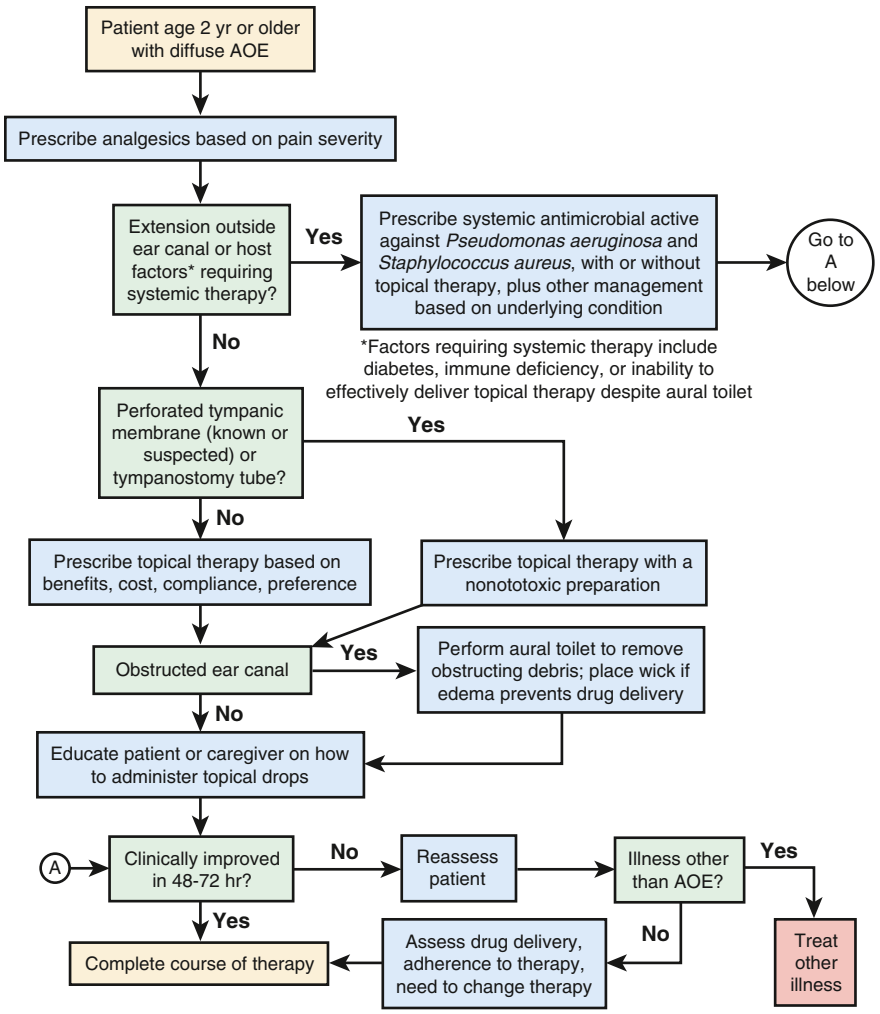

Fig. 679.2 Management algorithm for acute otitis externa (AOE). *(From Rosenfeld RM, Brown L, Cannon CR, et al. Clinical practice guideline: acute otitis externa. Otolaryngol Head Neck Surg. 2006;134:S4–S23. Copyright 2006 American Academy of Otolaryngology—Head and Neck Surgery Foundation, Inc.)*

and imaging studies to evaluate the extent of the disease. Surgical intervention to obtain cultures or debride devitalized tissue may be necessary.

PREVENTION

Preventing external otitis may be necessary for individuals susceptible to recurrences, especially children who swim. The most effective prophylaxis is instillation of dilute alcohol or acetic acid (2%) immediately after swimming or bathing. During an acute episode of otitis externa, patients should not swim, and the ears should be protected from excessive water during bathing. A hair dryer may be used to clear moisture from the ear after swimming as a method of prevention. Cotton-tipped swabs (or another material) may cause trauma to the ear canal, including tympanic membrane perforation, cerumen impaction, or retained foreign body and should be avoided.

OTHER DISEASES OF THE EXTERNAL EAR

Furunculosis

Furunculosis, caused by *S. aureus,* affects only the hair-containing outer third of the ear canal and typically occurs at the inferior entrance to the meatus. Mild forms are treated with oral antibiotics active against *S. aureus*. If an abscess develops, incision and drainage may be necessary.

Acute Cellulitis

Acute cellulitis of the auricle and external auditory canal usually is caused by group A streptococcus and occasionally by *S. aureus*. The skin is red, hot, and indurated, without a sharply defined border. Fever may be present with little or no exudate in the canal. Parenteral administration of penicillin G or a penicillinase-resistant penicillin is the therapy of choice.

Perichondritis and Chondritis

Perichondritis is an infection involving the skin and perichondrium of the auricular cartilage; extension of infection to the cartilage is termed **chondritis**. The ear canal, especially the lateral aspect, also may be involved. Early perichondritis may be difficult to differentiate from cellulitis because both are characterized by skin that is red, edematous, and tender. The main cause of perichondritis/chondritis and cellulitis is trauma (accidental or iatrogenic, laceration or contusion), including ear piercing, especially when done through the cartilage. The most commonly isolated organism in perichondritis and chondritis is *P. aeruginosa,* although other gram-negative and, occasionally, gram-positive organisms may be found. Treatment involves systemic, often parenteral, antibiotics; surgery to drain an abscess or remove nonviable skin or cartilage may also be needed. Removal of all ear jewelry is mandatory in the presence of infection.

Dermatoses

Various dermatoses (seborrheic, contact, infectious eczematoid, or neurodermatoid) are common causes of inflammation of the external canal; scratching and the introduction of infecting organisms cause acute external otitis in these conditions.

Seborrheic dermatitis is characterized by greasy scales that flake and crumble as they are detached from the epidermis; associated changes in the scalp, forehead, cheeks, brow, postauricular areas, and concha are usual.

Contact dermatitis of the auricle or canal may be caused by earrings or by topical otic medications such as neomycin, which may produce erythema, vesiculation, edema, and weeping. Poison ivy, oak, and sumac also may produce contact dermatitis. Hair care products have been implicated in sensitive individuals.

Infectious eczematoid dermatitis is caused by a purulent infection of the external canal, middle ear, or mastoid; the purulent drainage infects the skin of the canal or auricle, or both. The lesion is weeping, erythematous, or crusted.

Atopic dermatitis occurs in children with a familial or personal history of allergy; the auricle, particularly the postauricular fold, becomes thickened, scaly, and excoriated.

Neurodermatitis is recognized by intense itching and erythematous, thickened epidermis localized to the concha and orifice of the meatus.

Treatment of these dermatoses depends on the type but should include application of an appropriate topical medication, elimination of the source of infection or contact when identified, and management of any underlying dermatologic problem. In addition to topical antibiotics (or antifungals), topical steroids are helpful if contact dermatitis (see Chapter 696.1), atopic dermatitis (see Chapter 696), or eczematoid dermatitis is suspected.

Herpes Simplex Virus

See Chapter 299.

Herpes simplex virus may appear as vesicles on the auricle and lips. The lesions eventually become encrusted and dry and may be confused with impetigo. Topical application of a 10% solution of carbamide peroxide in anhydrous glycerol is symptomatically helpful. **Ramsay Hunt syndrome** (herpes zoster oticus with facial paralysis) may present initially with otalgia, with subsequent appearance of vesicles in the ear canal and on the pinna and with facial paralysis and pain. Other cranial nerves may be affected as well, especially the eighth nerve. Treatment of herpes zoster oticus includes systemic antiviral agents, such as acyclovir, and systemic corticosteroids. As many as 50% of patients with Ramsay Hunt syndrome do not completely recover their facial nerve function.

Bullous Myringitis

Commonly associated with an acute upper respiratory tract infection, bullous myringitis presents as an ear infection with more severe pain than usual. On examination, hemorrhagic or serous blisters (bullae) may be seen on the TM. The disease sometimes is difficult to differentiate from acute OM because a large bulla may be confused with a bulging TM. The organisms involved are the same as those that cause acute OM, including both bacteria and viruses. Treatment consists of empiric antibiotic therapy and pain medications. In addition to ibuprofen or codeine for severe pain, a topical anesthetic eardrop may also provide some relief. Incision of the bullae, although not necessary, promptly relieves the pain.

Exostoses and Osteomas

Exostoses represent benign hyperplasia of the perichondrium and underlying bone. Those involving the auditory canal tend to be found in people who swim often in cold water. Exostoses are broad based, often multiple, and bilateral. Osteomas are benign bony growths in the ear canal of uncertain cause (see Chapter 550.2). They usually are solitary and attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line. Both are more common in males; exostoses are more common than osteomas. Surgical treatment is recommended when large masses cause cerumen impaction, ear canal obstruction, or hearing loss.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 680

Otitis Media

Brittany Player

The term **otitis media (OM)** has two main categories: acute infection, which is termed suppurative or **acute otitis media (AOM)**, and inflammation accompanied by **middle-ear effusion (MEE)**, termed nonsuppurative or **secretory OM**, or **otitis media with effusion (OME)**. These two main types are interrelated: acute infection usually is succeeded by residual inflammation and effusion that, in turn, predispose children to recurrent infection. MEE is a feature of both AOM and OME and is an expression of the underlying middle-ear mucosal inflammation. MEE results in the conductive hearing loss associated with OM, ranging from none to as much as 50 dB of hearing loss (moderate hearing loss).

The peak incidence and prevalence of OM are during the first 2 years of life. More than 80% of children experience at least one episode of OM by the age of 3 years. Conservative estimates for OM-related costs place the annual burden at $3-5 billion per year. Accounting for >10% of pediatric primary care encounters, OM is a leading reason for pediatric visits and use of antibiotics and figures importantly in the differential diagnosis of fever. Recurrent OM is defined as a minimum of three episodes of AOM in 6 months or four episodes of AOM in 12 months with at least one of those episodes occurring in the preceding 6 months. It often serves as the main justification for myringotomy with insertion of tympanostomy tubes and adenoidectomy, the most frequently performed operations in infants and young children. OM is also the most common cause of acquired hearing loss in children. OM has a propensity to become chronic and recur. The earlier in life a child experiences the first episode, the greater the frequency of recurrence, severity, and persistence of MEE.

Accurate diagnosis of AOM in infants and young children may be difficult (Figs. 680.1-680.3). Symptoms may not be apparent, especially in early infancy and in chronic stages of the disease. Accurate visualization of the tympanic membrane (TM) and middle-ear space may be difficult because of anatomy, patient cooperation, or blockage by cerumen, removal of which may be arduous and time consuming. Abnormalities of the eardrum may also be subtle or difficult to appreciate. In the face of these difficulties, both underdiagnosis and overdiagnosis occur.

EPIDEMIOLOGY

Several factors affect the occurrence of OM, including age, gender, genetic background, socioeconomic status, breast milk feeding, degree of exposure to tobacco smoke, degree of exposure to other children, presence or absence of respiratory allergy, season of the year, and pneumococcal vaccination status. Children with certain types of immune deficiencies and congenital craniofacial anomalies (i.e., cleft palate, Down syndrome) are particularly prone to OM.

Age

The age of onset of OM is an important predictor of the development of recurrent and chronic OM, with earlier age of onset having an increased risk for exhibiting these difficulties later in life. The development of at least one episode of OM is reported as 63–85% by 12 months and 66–99% by 24 months of age. The percentage of days with MEE is 5–27% during the first year of life and 6–18% during the second year of life. Across groups, rates are highest at 6-20 months of age. After the age of 2, the incidence and prevalence of OM decline progressively, although the disease remains relatively common into the early school-age years. The most likely reasons for the higher rates in infants and younger children include less well-developed immunologic defenses and less favorable eustachian tubal structure and function.

Gender

Epidemiologic data suggest an incidence of OM greater in males than in females, although some studies have found no gender-related differences in the occurrence of OM.

Genetic Background

That middle-ear disease tends to run in families is a commonplace observation, suggesting that OM may have a heritable component. The degree of concordance for the occurrence of OM is much greater among monozygotic than among dizygotic twins. OM is especially prevalent and severe among Native American, Inuit, and Indigenous Australian children.

Socioeconomic Status

Elements contributing to the association of poverty with OM include crowding, limited hygienic facilities, suboptimal nutritional status, limited access to medical care, and limited resources for complying with prescribed medical regimens.

Breast Milk Compared with Formula Feeding

Most studies have found a protective effect of breast milk feeding against OM. This protective effect may be greater in socioeconomically

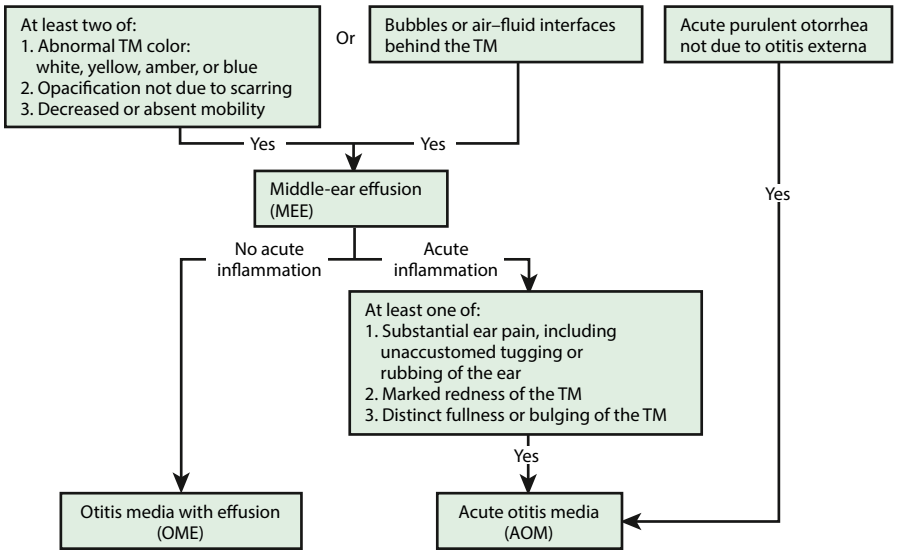

Fig. 680.1 Algorithm for distinguishing between acute otitis media and otitis media with effusion. TM, Tympanic membrane.

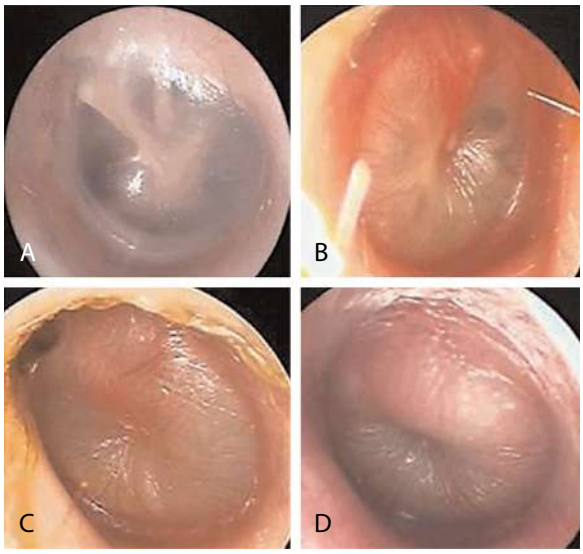

Fig. 680.2 Examples of normal tympanic membrane (A) and of mild bulging (B), moderate bulging (C), and severe bulging (D) of the tympanic membrane from middle-ear effusion. *(Courtesy Alejandro Hoberman, MD.)*



Fig. 680.3 Tympanic membrane in acute otitis media.

disadvantaged children than in more advantaged children. The protective effect is attributable to the milk itself rather than to the mechanics of breastfeeding.

Exposure to Tobacco Smoke

Tobacco smoke exposure is an important preventable risk factor in the development of OM. Studies that have used objective measures to determine infant exposure to secondhand tobacco smoke, such as cotinine levels, have consistently identified a significant linkage between tobacco smoke and OM.

Exposure to Other Children

OM is more common with repeated exposure to other children, whether at home or in out-of-home group daycare. Together, but independently, family socioeconomic status and the extent of exposure to other children appear to constitute two of the most important identifiable risk factors for developing OM.

Season

In keeping with the pattern of occurrence of upper respiratory tract infections in general, the highest rates of occurrence of OM are observed during cold weather months and the lowest rates during warm weather months. In OM, it is likely that these findings strongly depend on the significant association of OM with viral respiratory illnesses.

Congenital Anomalies

OM is universal among infants with unrepaired palatal clefts and is also highly prevalent among children with submucous cleft palate, other craniofacial anomalies, and Down syndrome (see Chapter 57). The common feature in these congenital anomalies is a deficiency in eustachian tube function, which predisposes these children to middle-ear disease.

Other Factors

Pacifier use is linked with an increased incidence of OM and recurrence of OM, although the effect is small. Neither maternal age nor birthweight nor season of birth appears to influence the occurrence of OM once other demographic factors are accounted for. Some suggest an association of OM with bottle feeding in the recumbent position (propped bottle). Children with HIV infection have a high risk for recurrent OM.

ETIOLOGY

Acute Otitis Media

Pathogenic bacteria can be isolated by standard culture techniques from middle-ear fluid in most documented AOM cases. Three pathogens predominate in AOM: *Streptococcus pneumoniae* (see Chapter 228), nontypeable *Haemophilus influenzae* (see Chapter 240), and *Moraxella catarrhalis* (see Chapter 242). The overall incidence of these organisms has changed with the use of the conjugate pneumococcal vaccine. Widespread use of the expanded serotype coverage 13-valent as compared with the 7-valent pneumococcal conjugate vaccine has further reduced the prevalence of *S. pneumoniae* as a cause of AOM, particularly the virulent 19A serotype. Less common pathogens include group A streptococcus (see Chapter 229), *Staphylococcus aureus* (see Chapter 227.1), and gram-negative organisms. Gram-negative organisms and *S. aureus* are found most commonly in neonates and very young infants who are hospitalized; in outpatient settings, the distribution of pathogens in these young infants is similar to that in older infants. Molecular techniques to identify nonculturable bacterial pathogens have suggested the importance of other bacterial species such as *Alloiococcus otitidis.*

Respiratory viruses may also be identified in MEEs of children with AOM, either alone or, more commonly, in association with pathogenic bacteria. Of these viruses, rhinovirus (see Chapter 310) and respiratory syncytial virus (RSV; see Chapter 307) are found most often. AOM is a known complication of bronchiolitis; middle-ear aspirates in children with bronchiolitis regularly contain bacterial pathogens, suggesting that RSV is rarely, if ever, the sole cause of their AOM. Viral pathogens have a negative impact on eustachian tube function, can impair local immune function and increase bacterial adherence, and can change the pharmacokinetic dynamics, reducing the efficacy of antimicrobial medications. However, it remains uncertain whether viruses alone can cause AOM or whether their role is limited to setting the stage for bacterial invasion, and perhaps also to amplify the inflammatory process, thereby interfering with resolution of the bacterial infection.

Otitis Media with Effusion

Using standard culture techniques, the pathogens typically found in AOM are recoverable in only 30% of children with OME. However, using polymerase chain reaction (PCR), MEEs contain evidence of bacterial DNA and viral RNA in much larger proportions of these children. Biofilms of pathogenic bacteria are present on the middle-ear mucosa and adenoid pad in most children with chronic OM. Biofilms consist of aggregated and adherent bacteria, embedded in an extracellular matrix and in neutrophil extracellular traps, allowing for

protection against antimicrobials; their presence may contribute to the persistence of pathogens and the recalcitrance of chronic OM to antibiotic treatment.

PATHOGENESIS

A multifactorial disease process, risk profile, and host-pathogen interactions play important roles in the pathogenesis of OM. Such events as alterations in mucociliary clearance through repeated viral exposure experienced in daycare settings or through exposure to tobacco smoke may tip the balance of pathogenesis in less virulent OM pathogens in their favor, especially in children with a unique host predisposition.

Anatomic Factors

Patients with significant craniofacial abnormalities affecting eustachian tube function have an increased incidence of OM. During the pathogenesis of OM, the eustachian tube demonstrates decreased effectiveness in ventilating the middle-ear space.

Under usual circumstances the eustachian tube is passively closed and is opened by contraction of the tensor veli palatini muscle. In relation to the middle ear, the tube has three main functions: ventilation, protection, and clearance. The middle-ear mucosa depends on a continuing supply of air from the nasopharynx delivered by way of the eustachian tube. Interruption of this ventilatory process by tubal obstruction initiates an inflammatory response that includes secretory metaplasia, compromise of the mucociliary transport system, and effusion of liquid into the tympanic cavity. Measurements of eustachian tube function have demonstrated that the tubal function is suboptimal during the events of OM with increased opening pressures.

Eustachian tube obstruction may result from extraluminal blockage via hypertrophied nasopharyngeal adenoid tissue or tumor or may result from intraluminal obstruction via inflammatory edema of the tubal mucosa, most commonly as a consequence of a viral upper respiratory tract infection. Progressive reduction in tubal wall compliance with increasing age may explain the progressive decline in the occurrence of OM as children grow older. The protection and clearance functions of the eustachian tube may also be involved in the pathogenesis of OM. Thus, if the eustachian tube is patulous or excessively compliant, it may fail to protect the middle ear from reflux of infective nasopharyngeal secretions, whereas impairment of the mucociliary clearance function of the tube might contribute to both the establishment and persistence of infection. The shorter and more horizontal orientation of the tube in infants and young children may increase the likelihood of reflux from the nasopharynx and impair passive gravitational drainage through the eustachian tube.

Children with **craniofacial abnormalities** experience an increased incidence of OM associated with the abnormal eustachian tube function. In children with cleft palate, where OM is a universal finding, a main factor underlying the chronic middle-ear inflammation appears to be impairment of the opening mechanism of the eustachian tube. Possible factors include muscular changes, tubal compliance factors, and defective velopharyngeal valving, which may result in disturbed aerodynamic and hydrodynamic relationships in the nasopharynx and proximal portions of the eustachian tubes. In children with other craniofacial anomalies and with Down syndrome, the high prevalence of OM has also been attributed to structural and/or functional eustachian tubal abnormalities.

Host Factors

The effectiveness of a child's immune system in response to the bacterial and viral infections of the upper airway and middle ear during early childhood probably is the most important factor in determining which children are otitis prone. The maturation of this immune system during early childhood is most likely the primary event leading to the decrease in incidence of OM with increased age. Immunoglobulin A (IgA) deficiency is found in some children with recurrent AOM, but the significance is questionable; many children with IgA deficiency do not experience recurrent episodes of AOM. Selective immunoglobulin G (IgG) subclass deficiencies (despite normal total serum IgG) may be found in children with recurrent AOM in association with recurrent sinopulmonary infection, and these deficiencies probably underlie the susceptibility to infection. Children with HIV infection have recurrent and difficult-to-treat episodes of AOM in the first and second year of life. Children with recurrent OM that is not associated with recurrent infection at other anatomic sites rarely have a readily identifiable immunologic deficiency. Evidence that subtle immune deficits play a role in the pathogenesis of recurrent AOM is provided by studies involving antibody responses to various types of infection and immunization; by the observation that breast milk feeding, as opposed to formula feeding, confers some protection against the occurrence of OM in infants with cleft palate; and by studies in which young children with recurrent AOM achieved a measure of protection from intramuscularly administered bacterial polysaccharide immunoglobulin or intravenously administered polyclonal immunoglobulin. This evidence, along with the documented decrease in incidence of upper respiratory tract infections and OM as children's immune systems develop and mature, is indicative of the importance of a child's innate immune system in the pathogenesis of OM (see Chapter 164).

Viral Pathogens

Although OM may develop and persist in the absence of apparent respiratory tract infection, many, if not most, episodes are initiated by viral or bacterial upper respiratory tract infection. Among children in group daycare, AOM was observed in approximately 30–40% of children with respiratory illness caused by RSV (see Chapter 307), influenza viruses (see Chapter 305), or adenoviruses (see Chapter 309) and in approximately 10–15% of children with respiratory illness caused by parainfluenza viruses (see Chapter 306), rhinoviruses (see Chapter 310), or enteroviruses (see Chapter 297). Viral infection of the upper respiratory tract results in release of cytokines and inflammatory mediators, some of which may cause eustachian tube dysfunction.

Respiratory viruses also may enhance nasopharyngeal bacterial colonization and adherence and impair host immune defenses against bacterial infection.

CLINICAL MANIFESTATIONS

Symptoms of AOM are variable, especially in infants and young children. In young children, evidence of ear pain may be manifested by irritability or a change in sleeping or eating habits and, occasionally, holding or tugging at the ear. *Pulling at the ear alone has a low sensitivity and specificity.* Fever may also be present and may occasionally be the only sign. Rupture of the TM with purulent otorrhea is uncommon. Systemic symptoms and symptoms associated with upper respiratory tract infections also occur; occasionally there may be no symptoms, with the disease having been discovered at a routine health examination. The Acute Otitis Media Severity of Symptom (AOM-SOS) scale is a five-item validated symptom score that has proven beneficial as a tool to monitor AOM symptoms in patients and studies of antimicrobial effectiveness in OM. OME often is not accompanied by overt complaints of the child but can be accompanied by hearing loss. This hearing loss may manifest as changes in speech patterns but often goes undetected if unilateral or mild in nature, especially in younger children. Balance difficulties or disequilibrium can rarely be associated with OME, and older children may complain of mild discomfort or a sense of fullness in the ear.

EXAMINATION OF THE TYMPANIC MEMBRANE

Otoscopy

Two types of otoscope heads are available: **surgical** or **operating** and **diagnostic** or **pneumatic**. The surgical head embodies a lens that can swivel over a wide arc and an unenclosed light source, thus providing ready access of the examiner's instruments to the external auditory canal and TM. Use of the surgical head is optimal for removing cerumen or debris from the canal under direct observation and is necessary for satisfactorily performing tympanocentesis or myringotomy. The

diagnostic head incorporates a larger lens, an enclosed light source, and a nipple for the attachment of a rubber bulb and tubing. When an attached speculum is fitted snugly into the external auditory canal, an airtight chamber is created comprising the vault of the otoscope head, the bulb and tubing, the speculum, and the proximal portion of the external canal. Although examination of the ear in young children is a relatively invasive procedure that is often met with lack of cooperation by the patient, this task can be enhanced if done with as little pain as possible. The outer portion of the ear canal contains hair-bearing skin and subcutaneous fat and cartilage that allow a speculum to be placed with relatively little discomfort. Closer to the TM the ear canal is made of bone and is lined only with skin and no adnexal structures or subcutaneous fat; a speculum pushed too far forward and placed in this area often causes skin abrasion and pain. Using a rubber-tipped speculum or adding a small sleeve of rubber tubing to the tip of the plastic speculum may serve to minimize patient discomfort and enhance the ability to achieve a proper fit and an airtight seal, facilitating pneumatic otoscopy.

Learning to perform **pneumatic otoscopy** is a critical skill in being able to assess a child's ear and in making an accurate diagnosis of AOM. The degree of TM mobility in response to both positive and negative pressure can be estimated by observing as the bulb is alternately squeezed gently and released, thus providing a critical assessment of middle-ear fluid, which is a hallmark sign of both AOM and OME (see Fig. 680.1). With both types of otoscope heads, bright illumination is also critical for adequate visualization of the TM.

Clearing the External Auditory Canal

Children's ears are "self-cleaning" because of squamous migration of ear canal skin. Cleaning of cerumen with cotton-tipped swabs should be avoided, as it often worsens impaction by pushing cerumen deeper into the canal, compacting it. If the TM is obscured by cerumen, the cerumen should be removed. This can be accomplished through direct visualization using a headlight or through the surgical head of the otoscope by using an ear curette or gentle suction with a No. 5 or 7 French ear suction tube. During this procedure, it may be most advantageous to restrain the infant or young child in the prone position, turning the child's head to the left or right as each ear is cleared. In children old enough to cooperate, clearing of the external canal may be achieved more easily and less traumatically by lavage than by mechanical removal, provided one can be certain that a TM perforation is not present.

Tympanic Membrane Findings

Important characteristics of the TM consist of contour, color, translucence, structural changes, if any, and mobility. The TM is anatomically divided into the pars tensa and pars flaccida. The pars tensa comprises the lower two thirds of the drum inferior to the lateral process of the malleus. Its contour is normally **slightly concave**; abnormalities consist of fullness or bulging or, conversely, extreme retraction. The normal color of the pars tensa is **pearly gray**, with the pars flaccida being slightly more vascular in nature. Erythema may be a sign of inflammation or infection, but unless intense, erythema alone may result from crying or vascular flushing. Abnormal whiteness of the membrane may result from either scarring or the presence of effusion in the middle-ear cavity; this effusion also may impart an amber, pale yellow, or, rarely, bluish color. Rarely a persistent focal white area may be indicative of a congenital cholesteatoma in the middle-ear space. Normally, the membrane is translucent, although some degree of opacity may be normal in the first few months of life; later, opacification denotes either scarring or, more commonly, underlying effusion. Structural changes include scars, perforations, and retraction pockets. Retractions or perforations, especially in the posterior-superior quadrant, or pars flaccida, of the TM may be a sign of cholesteatoma formation. Of all the visible characteristics of the TM, mobility is the most sensitive and specific in determining the presence or absence of MEE. Mobility is generally not an all-or-none phenomenon. A total absence of mobility does exist with a TM perforation that can develop after a substantial increase in middle-ear pressure associated with effusion. When a perforation is not present, substantial impairment of mobility is the more common finding with MEE. Bulging of the TM is the most specific finding of AOM (97%) but has lower sensitivity (51%) (see Figs. 680.2 and 680.3).

Diagnosis

A **diagnosis of AOM** should be made in children who present with:

- Moderate to severe bulging of the TM or new-onset otorrhea not caused by otitis externa
- Mild bulging of the TM and recent (<48 hours) onset of ear pain or intense TM erythema

A **diagnosis of AOM** should ***not*** be made in children without MEE.

AOM and OME may evolve into the other without any clearly differentiating physical findings; any schema for distinguishing between them is to some extent arbitrary. In an era of increasing bacterial resistance, distinguishing between AOM and OME is important in determining treatment, because OME in the absence of acute infection does not require antimicrobial therapy. Purulent otorrhea of recent onset is indicative of AOM. Difficulty in distinguishing clinically between AOM and OME is limited to circumstances in which purulent otorrhea is not present. Both AOM without otorrhea and OME are accompanied by physical signs of MEE, namely, the presence of at least two of three TM abnormalities: white, yellow, amber, or (rarely) blue discoloration; opacification other than that caused by scarring; and decreased or absent mobility. Alternatively, in OME, either air-fluid levels or air bubbles outlined by small amounts of fluid may be visible behind the TM, a condition often indicative of impending resolution (see Fig. 680.4).

To support a diagnosis of AOM instead of OME in a child with MEE, distinct fullness or bulging of the TM may be present, with or without accompanying erythema, or, at a minimum, MEE should be accompanied by ear pain that appears clinically important. Unless intense, erythema alone is insufficient because erythema, without other abnormalities, may result from crying or vascular flushing. In AOM, the malleus may be obscured, and the TM may resemble a bagel without a hole but with a central depression (see Fig. 680.3). Rarely, the TM may be obscured by surface bullae or may have a cobblestone appearance. Bullous myringitis is a physical manifestation of AOM and not an etiologically discrete entity. Within days after onset, fullness of the membrane may diminish, even though infection may still be present.

In OME, bulging of the TM is absent or slight or the membrane may be retracted (Fig. 680.4); erythema also is absent or slight but may increase with crying or with superficial trauma to the external auditory canal incurred in clearing the canal of cerumen.

Both before and after episodes of OM and also in the absence of OM, the TM may be retracted as a consequence of negative middle-ear air pressure. The presumed cause is diffusion of air from the middle-ear



Fig. 680.4 Tympanic membrane in otitis media with effusion.

cavity more rapidly than it is replaced via the eustachian tube. Mild retraction is generally self-limited, although in some children it is accompanied by mild conductive hearing loss. More extreme retraction is of concern, as discussed later in the section on sequelae of OM.

Conjunctivitis-Associated Otitis Media

Simultaneous appearance of purulent and erythematous conjunctivitis with an ipsilateral OM is a well-recognized presentation, caused by nontypeable *H. influenzae* in most children. The disease often is present in multiple family members and affects young children and infants. Topical ocular antibiotics are ineffective. In an era of resistant organisms, this clinical association can be important in antibiotic selection, with oral antibiotics (see later) effective against resistant forms of nontypeable *H. influenzae.*

Asymptomatic Purulent Otitis Media

Rarely, a child will present during a routine exam without fever, irritability, or other overt signs of infection, but on exam, the patient will demonstrate an obvious purulent MEE and bulging TM. Although an uncommon presentation of "acute" OM, the bulging nature of the TM and the obvious purulence of the effusion do warrant antimicrobial therapy.

Tympanometry

Tympanometry, or **acoustic immittance testing**, is a simple, rapid, atraumatic test that, when performed correctly, offers objective evidence of the presence or absence of MEE. The tympanogram provides information about **TM compliance** in electroacoustic terms that can be thought of as approximately equivalent to TM mobility as perceived visually during pneumatic otoscopy. The absorption of sound by the TM varies inversely with its stiffness. The stiffness of the membrane is least, and its compliance is greatest, when the air pressures impinging on each of its surfaces—middle-ear air pressure and external canal air pressure—are equal. Anything tending to stiffen the TM, such as TM scarring or middle-ear fluid, reduces the TM compliance, which is recorded as a flattening of the curve of the tympanogram. An ear filled with middle-ear fluid generally has a very noncompliant TM and therefore a flattened tympanogram tracing.

Tympanograms may be grouped into one of three categories (Fig. 680.5). Tracings characterized by a relatively steep gradient, sharp-angled peak, and middle-ear air pressure (location of the peak in terms of air pressure) that approximates atmospheric pressure (see Fig. 680.5A) (type A curve) are assumed to indicate normal middle-ear status. Tracings characterized by a shallow peak or no peak are often termed "flat" or type B (see Fig. 680.5B) and usually are assumed to indicate the presence of a middle-ear abnormality that is causing decreased TM compliance. The most common such abnormality in infants and children is MEE. Tracings characterized by intermediate findings—somewhat shallow peak, often in association with a gradual gradient (obtuse-angled peak) or negative middle-ear air pressure peak (often termed type "C"), or combinations of these features (see Fig. 680.5C)—may or may not be associated with MEE and must be considered nondiagnostic or equivocal with respect to OM. However, type C tympanograms do suggest eustachian tube dysfunction and some ongoing pathology in the middle ear and warrant follow-up.

When reading a tympanogram, it is important to look at the volume measurement. The type B tympanometric response is analyzed within the context of the recorded volume. A flat, "low"-volume (≤1 mL) tracing typically reflects the volume of the ear canal only, representing MEE, which impedes the movement of an intact eardrum. A flat, high-volume (>1 mL) tracing typically reflects the volume of the ear canal and middle-ear space, representing a perforation (or patent tympanostomy tube) in the TM. In a child with a tympanostomy tube present, a flat tympanogram with a volume <1 mL would suggest a plugged or nonfunctioning tube and middle-ear fluid, whereas a flat tympanogram with a volume >1 mL would suggest a patent tympanostomy tube.

Although tympanometry is quite sensitive in detecting MEE, it can be limited by patient cooperation, the skill of the individual administering the test, and the age of the child, with less reliable results in very young children. Use of tympanometry may be helpful in office screening, may supplement the examination of difficult-to-examine patients, and may help to identify patients who require further attention because their tympanograms are abnormal. Tympanometry also may be used to help confirm, refine, or clarify questionable otoscopic findings; to objectify the follow-up evaluation of patients with known middle-ear disease; and to validate otoscopic diagnoses of MEE. Even though tympanometry can predict the probability of MEE, it cannot distinguish the effusion of OME from that of AOM.

PREVENTION

General measures to prevent OM that have been supported by numerous investigations include avoiding exposure to individuals with respiratory infection, appropriate vaccination strategies against pneumococci and influenzae, avoiding environmental tobacco smoke, and breast milk feeding.

IMMUNOPROPHYLAXIS AND VACCINATION STATUS

Heptavalent pneumococcal conjugate vaccine (PCV7) reduced the overall number of episodes of AOM by only 6–8% but with a 57% reduction in serotype-specific episodes. Reductions of 9–23% are seen in children with histories of frequent episodes, and a 20% reduction is seen in the number of children undergoing tympanostomy tube insertion. The 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) contains the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and six additional serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A). Early data indicate a significant reduction in the number of invasive pneumococcal mastoiditis cases since the introduction of PCV13. With the widespread use of PCV13,

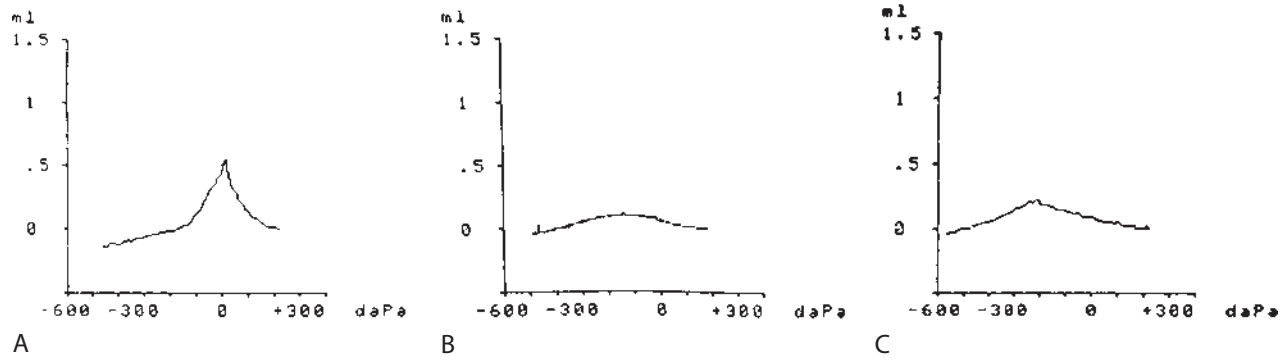

Fig. 680.5 Tympanograms obtained with a Grason-Stadler GSI 33 Middle Ear Analyzer, exhibiting (**A**) high admittance, steep gradient (i.e., sharp-angled peak), and middle-ear air pressure approximating atmospheric pressure (0 decaPascals [daPa]); (**B**) low admittance and indeterminate middle-ear air pressure; and (**C**) somewhat low admittance, gradual gradient, and markedly negative middle-ear air pressure.

continued surveillance will be necessary to detect other emerging serotypes, which are also demonstrating increasing resistance. Although the influenza vaccine also provides a measure of protection against OM, the relatively limited time during which individuals and even communities are exposed to influenza viruses limits the vaccine's effectiveness in broadly reducing the incidence of OM. Limitation of OM disease is only a portion of the benefit realized from the vaccinations for pneumococci and influenza viruses.

TREATMENT

Management of Acute Otitis Media

AOM can be very painful. Whether or not antibiotics are used for treatment, pain should be assessed and, if present, treated (Table 680.1). Individual episodes of AOM have traditionally been treated with antimicrobial drugs, and a sharp decline in complications from AOM during the last half-century seems, at least in part, attributable to the widespread routine use of antimicrobials. However, concerns about increasing bacterial resistance have prompted consideration for withholding antimicrobial treatment in certain, well-defined clinical situations (Table 680.2). Although viral and bacterial pathogens have been cultured from middle-ear fluid obtained by tympanocentesis, two factors may argue in favor of prescribing antimicrobial therapy for children who have AOM. First, symptomatic improvement and resolution of infection may occur more promptly and more consistently with antimicrobial treatment than without, even though most untreated cases eventually resolve. Second, prompt and adequate antimicrobial treatment may prevent the development of suppurative complications. Whereas data from the Netherlands in the 1990s suggested an increased incidence of acute mastoiditis with watchful waiting as the initial approach to treatment of AOM, other studies from several countries have contradicted these findings, demonstrating no increased incidence in acute mastoiditis with changes in recommendations for more conservative antimicrobial prescribing practices.

Given that most episodes of OM will spontaneously resolve, consensus guidelines have been published to assist clinicians who wish to consider a period of "watchful waiting" or observation before treating AOM with antibiotics (see Table 680.2 and Table 680.3; Fig. 680.6). The most important aspect of these guidelines is that close follow-up of the patient must be ensured to assess for lack of spontaneous resolution or worsening of symptoms and that patients should be provided with adequate analgesic medications (acetaminophen, ibuprofen) during the period of observation. When pursuing the practice of watchful waiting in patients with AOM, the certainty of the diagnosis, the patient's age, and the severity of the disease should be considered. For patients <2 years of age, it is recommended to treat all confirmed diagnoses of AOM. In patients, <6 months of age, even presumed episodes of AOM should be treated because of the increased potential of significant morbidity from infectious complications. In children between 6 and 24 months of age who have a questionable diagnosis of OM but severe disease, defined as temperature of >39°C (102°F), significant otalgia, or toxic appearance, antibiotic therapy is also recommended. Children in this age-group with a questionable diagnosis and nonsevere disease can be observed for a period of 2-3 days with close follow-up. In children older than 2 years of age, observation might be considered in all episodes of nonsevere OM or episodes of questionable diagnosis, whereas antibiotic therapy is reserved for confirmed, severe episodes of AOM. Information from Finland suggests that the "watchful waiting" or delayed treatment approach does not worsen the recovery from AOM or increase the complication rates.

Accurate diagnosis is the most crucial aspect of the treatment of OM. In studies using stringent criteria for diagnosis of AOM, the benefit of antimicrobial treatment is enhanced. In addition, subpopulations of patients clearly receive more benefit from oral antimicrobial therapy than others. *Younger children, children with otorrhea, and children with bilateral AOM have a significantly enhanced benefit from antimicrobial therapy in comparison with older children, children without otorrhea, or children with unilateral AOM.*

Table 680.1 Therapy for Otalgia in Acute Otitis Media

APPROACH	RECOMMENDATIONS
Acetaminophen, ibuprofen	Preferred therapy
Benzocaine, antipyrine (topical)	Brief, benefit over acetaminophen in patients older than 5 yr
Topical antibiotics (fluoroquinolones) with or without steroids for chronic suppurative otitis (perforated tympanic membrane)	Preferred treatment with ear canal cleaning; must culture
Homeopathic agents	Not recommended
Narcotic analgesia with codeine or analogs	Not recommended
Tympanostomy/myringotomy	Not recommended for initial approach; an option for otitis media unresponsive to antibiotic therapy

Bacterial Resistance

Persons at greatest risk of harboring resistant bacteria are those who are younger than 2 years of age; who are in regular contact with large groups of other children, especially in daycare settings; or who recently have received antimicrobial treatment. The development of resistant bacterial strains and their rapid spread have been fostered and facilitated by selective pressure resulting from extensive use of antimicrobial drugs, the most common target of which in children is OM. Many strains of each of the pathogenic bacteria that commonly cause AOM are resistant to commonly used antimicrobial drugs.

Although antimicrobial resistance rates vary between countries, in the United States approximately 40% of strains of nontypeable *H. influenzae*

Table 680.2 Recommendations for Initial Management for Uncomplicated Acute Otitis Media*

AGE	OTORRHEA WITH AOM*	UNILATERAL OR BILATERAL AOM* WITH SEVERE SYMPTOMS†	BILATERAL AOM* WITHOUT OTORRHEA	UNILATERAL AOM* WITHOUT OTORRHEA
6 mo to 2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation‡

*Applies only to children with well-documented AOM with high certainty of diagnosis.
†A toxic-appearing child, persistent otalgia more than 48 hours, temperature ≥39°C (102.2°F) in the past 48 hours, or if there is uncertain access to follow-up after the visit.
‡This plan of initial management provides an opportunity for shared decision-making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.
NOTE: For infants younger than age 6 mo, a suspicion of AOM should result in antibiotic therapy.
AOM, Acute otitis media.
From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964–e999, Table 4.

Table 680.3 Suggested Antibiotics for Treatment of Otitis Media and for Patients Who Have Failed First-Line Antibiotic Treatment

INITIAL IMMEDIATE OR DELAYED ANTIBIOTIC TREATMENT		ANTIBIOTIC TREATMENT AFTER 48-72 HR OF FAILURE OF INITIAL ANTIBIOTIC TREATMENT	
RECOMMENDED FIRST-LINE TREATMENT	**ALTERNATIVE TREATMENT (IF PENICILLIN ALLERGY OR SUSPICION OF β-LACTAMASE–PRODUCING ORGANISMS)**	**RECOMMENDED TREATMENT**	**ALTERNATIVE TREATMENT**
Amoxicillin (pathogens include *Pneumococcus, H. influenzae* non–type B, *Moraxella)*	Cefdinir	Amoxicillin-clavulanate	Ceftriaxone
or	*or*	*or*	
Amoxicillin-clavulanate Ceftriaxone	Cefpodoxime Ceftriaxone Levofloxacin (type I hypersensitivity to penicillin) Clindamycin + third generation cephalosporin (non–type I hypersensitivity to penicillin)	Ceftriaxone	Tympanocentesis*

ANTIBIOTIC DOSAGE

- Amoxicillin 80-90 mg/kg/day bid for 10 days**
- Amoxicillin-clavulanate (ratio 14:1) 80-90 mg/kg/day of amoxicillin component bid for 10 days**
- Ceftriaxone 50 mg/kg/day daily IM or IV for 1-3 days
- Cefdinir 14 mg/kg/day daily for 10 days**
- Cefpodoxime 10 mg/kg/day bid for 10 days**
- Levofloxacin 20 mg/kg/day bid if ≤5 yr for 10 days; 10 mg/kg/day bid if >5 yr for 10 days

*Tympanocentesis for those who fail second-line therapy.
**Durations of antibiotic therapy may vary based on symptom severity and patient age. For patients 2-5 yr old with mild or moderate disease severity, a 7-day course may be appropriate. For patients 6 yr and older, a 5- to 7-day course may be adequate for mild to moderate symptoms.
IM, Intramuscular; IV intravenous; bid, twice daily.

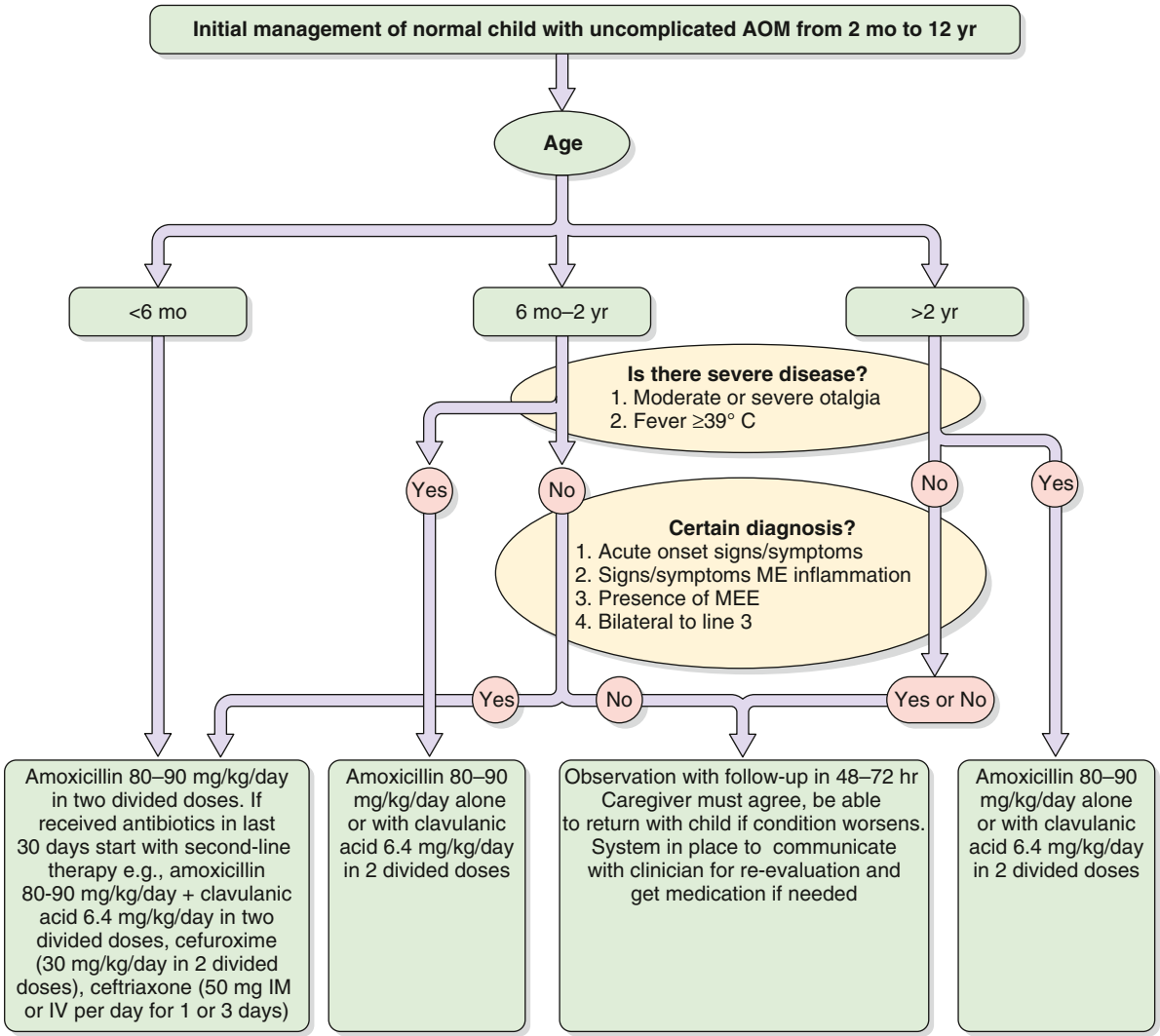

Fig. 680.6 Algorithm for management of acute otitis media. *(From Mazer BD: Otitis media. In: Leung DYM, Szefler SJ, Bonilla FA, et al., eds. Pediatric Allergy: Principles and Practices, 3 ed, Philadelphia: Elsevier; 2016: Fig. 25-3.)*

and almost all strains of *M. catarrhalis* are resistant to aminopenicillins (e.g., ampicillin and amoxicillin). In most cases the resistance is attributable to production of β-lactamase and can be overcome by combining amoxicillin with a β-lactamase inhibitor (clavulanate) or by using a β-lactamase–stable antibiotic. Occasional strains of nontypeable *H. influenzae* that do not produce β-lactamase are resistant to aminopenicillins and other β-lactam antibiotics by virtue of alterations in their penicillin-binding proteins. It is worth noting that bacterial resistance rates in Northern European countries where antibiotic use is not routine are lower (β-lactamase resistance in 6–10% of isolates) than in the United States.

In the United States, approximately 50% of strains of *S. pneumoniae* are penicillin-nonsusceptible, divided approximately equally between penicillin-intermediate and, even more difficult to treat, penicillin-resistant strains. A much higher incidence of resistance is seen in children attending daycare. Resistance by *S. pneumoniae* to the penicillins and other β-lactam antibiotics is mediated not by β-lactamase production but by alterations in penicillin-binding proteins. This mechanism of resistance can be overcome if higher concentrations of β-lactam antibiotics at the site of infection can be achieved for a sufficient time interval. Many penicillin-resistant strains of *S. pneumoniae* are also resistant to other antimicrobial drugs, including sulfonamides, macrolides, and cephalosporins. In general, as penicillin resistance increases, so also does resistance to other antimicrobial classes. Resistance to macrolides, including azithromycin and clarithromycin, by *S. pneumoniae* has increased, rendering these antimicrobials far less effective in treating AOM. One mechanism of resistance to macrolides also results in resistance to clindamycin, which otherwise is effective against resistant strains of *S. pneumoniae.* Unlike resistance to β-lactam antibiotics, macrolide resistance cannot be overcome by increasing the dose.

First-Line Antimicrobial Treatment

Amoxicillin remains the drug of choice for uncomplicated AOM under many circumstances because of its excellent safety record, relative efficacy, palatability, and low cost. Amoxicillin is the most efficacious of available oral antimicrobial drugs against both penicillin-susceptible and penicillin-nonsusceptible strains of *S. pneumoniae*. Increasing the dose from the traditional 40-45 mg/kg/day to 80-90 mg/kg/day will generally provide efficacy against penicillin-intermediate and some penicillin-resistant strains. This higher dose should be used particularly in children younger than 2 years old, in children who have recently received treatment with β-lactam drugs, and in children who are exposed to large numbers of other children because of their increased likelihood of an infection with a nonsusceptible strain of *S. pneumoniae*. A limitation of amoxicillin is that it may be inactivated by the β-lactamases produced by many strains of nontypeable *H. influenzae* and most strains of *M. catarrhalis*. However, episodes of AOM caused by these two pathogens often resolve spontaneously.

Allergies to penicillin antibiotics should be categorized into type I hypersensitivity, consisting of urticaria or anaphylaxis, and those that fall short of type I reactions, such as rash formation. For children with a non–type I reaction in which cross reactivity with cephalosporins is less of a concern, first-line therapy with cefdinir would be an appropriate choice. In children with a type I reaction or known sensitivity to cephalosporin antibiotics, there are far fewer choices. Resistance to trimethoprim-sulfamethoxazole by many strains of both nontypeable *H. influenzae* and *S. pneumoniae* and a reported high clinical failure rate in children with AOM treated initially with this antimicrobial argue against its use. Similarly, increasing rates of macrolide resistance argue against the efficacy of azithromycin. Because of concerns for arthropathy and damage to weight-bearing bones in animal models, fluoroquinolone use in children has been limited; fluoroquinolone use is recommended in certain clinical situations and/or when alternative therapies are deemed suboptimal. Early alternative management in allergic patients with tympanostomy tubes can allow for lessening of the severity of their disease and the use of topical antimicrobials.

Duration of Treatment

The duration of treatment of AOM has historically been set at 10 days, and most efficacy studies examining antimicrobial treatment in AOM have used this duration as a benchmark. Studies comparing shorter with longer durations of antimicrobial treatment have reported higher treatment failure rates in younger children, particularly those younger than 2 years old. Antibiotic courses shorter than 10 days, more severe disease, exposure to larger groups of other children, such as in daycare settings, and in children with a history of OME are also associated with higher treatment failure rates. The clinical practice guidelines published in 2013 by the American Academy of Pediatrics suggest shorter durations of antibiotic therapy may be adequate for treatment of AOM in children older than 2 years. However, compelling evidence substantiating the efficacy of shorter antibiotic courses to treat AOM in older children is limited.

Most patients improve within 72 hours; however, patients should not stop therapy. If there are persistent symptoms after 72 hours of therapy, the child should be reexamined for persistent OM or a complication such as mastoiditis (see Chapter 681).

Follow-Up

The principal goals of follow-up are to assess the outcome of treatment and to differentiate between inadequate response to treatment and early recurrence. The appropriate interval for follow-up should be individualized. Follow-up within days is advisable in the young infant with a severe episode or in a child of any age with continuing pain. Follow-up within 2 weeks is appropriate for the infant or young child who has been having frequent recurrences. At that point, the TM is not likely to have returned to normal, but substantial improvement in its appearance should be evident. In the child with only a sporadic episode of AOM and prompt symptomatic improvement, follow-up 1 month after initial examination is early enough, or in older children, no follow-up may be necessary. The continuing presence of MEE alone after an episode of AOM is not an indication for additional or second-line antimicrobial treatment. However, persisting MEE does warrant additional follow-up to ensure that the effusion resolves and does not lead to persisting hearing loss or other complications.

Unsatisfactory Response to First-Line Treatment

AOM is essentially a closed-space infection, and its resolution depends both on eradication of the offending organism and restoration of middle-ear ventilation. Factors contributing to unsatisfactory response to first-line treatment, in addition to inadequate antimicrobial efficacy, include poor compliance with treatment regimens, concurrent or intercurrent viral infection, persistent eustachian tube dysfunction and middle-ear under-aeration, reinfection from other sites or from incompletely eradicated middle-ear pathogens, and immature or impaired host defenses. The identification of biofilm formation in the middle ear of children with chronic OM also indicates that, in some children, eradication with standard antimicrobial therapy is likely to be unsuccessful. Despite these many potential factors, switching to an alternative or second-line drug is reasonable when there has been inadequate improvement in symptoms or in middle-ear status as reflected in the appearance of the TM or when the persistence of purulent nasal discharge suggests that the antimicrobial drug being used has less-than-optimal efficacy. Second-line drugs may also appropriately be used when AOM develops in a child already receiving antimicrobial therapy, or in an immunocompromised child, or in a child with severe symptoms whose previous experience with OM has been problematic.

Second-Line Treatment

When treatment of AOM with a first-line antimicrobial drug has proven inadequate, numerous second-line alternatives are available (see Table 680.3). Drugs chosen for second-line treatment should be effective against β-lactamase–producing strains of nontypeable *H. influenzae* and *M. catarrhalis* and against susceptible and most nonsusceptible strains of *S. pneumoniae.* Because high-dose amoxicillin (80-90 mg/kg/day) is effective against most strains of *S. pneumoniae* and because the addition of clavulanate extends the effective antibacterial spectrum of amoxicillin to include β-lactamase–producing bacteria, high-dose amoxicillin-clavulanate is particularly well-suited as a

second-line drug for treating AOM. The 14:1 amoxicillin-clavulanate formulation contains twice as much amoxicillin as the previously available 7:1 formulation. Diarrhea, especially in infants and young children, is a common adverse effect and usually is not severe enough to require cessation of treatment. Cefdinir has demonstrated efficacy in treatment, is generally well tolerated with respect to taste, and can be given as a once-daily regimen. The ability to also use cefdinir in most children with mild type I hypersensitivity reactions has further added to its favorable selection as a second-line agent. Intramuscular ceftriaxone has important limitations for use in young children; treatment entails both the pain of intramuscular injection and substantial cost, and the injection may need to be repeated once or twice at 2-day intervals to achieve the desired degree of effectiveness. Nonetheless, use of ceftriaxone is appropriate in severe cases of AOM when oral treatment is not feasible, in highly selected cases after treatment failure using orally administered second-line antimicrobials, or when highly resistant *S. pneumoniae* is found in aspirates obtained from diagnostic tympanocentesis.

Clarithromycin and azithromycin have only limited activity against nonsusceptible strains of *S. pneumoniae* and against β-lactamase–producing strains of nontypeable *H. influenzae*. Macrolide use also appears to be a major factor in causing increases in rates of resistance to macrolides by group A streptococcus and *S. pneumoniae*. Clindamycin is active against most strains of *S. pneumoniae,* including resistant strains, but is not active against nontypeable *H. influenzae* or *M. catarrhalis*.

Other antimicrobial agents that have been traditionally used in the management of AOM have such significant lack of effectiveness against resistant organisms that use seldom outweighs the potential side effects or complications. This includes cefaclor, loracarbef, cefixime, trimethoprim-sulfamethoxazole, and erythromycin-sulfisoxazole. Cefpodoxime has demonstrated reasonable effectiveness in some investigations but is generally poorly tolerated because of its taste.

ANTIMICROBIAL PROPHYLAXIS

In children who have developed frequent episodes of AOM, antimicrobial prophylaxis with subtherapeutic doses of an aminopenicillin or a sulfonamide has been used in the past to provide protection against recurrences of AOM (although not of OME). However, because of the increased incidence of resistant organisms and the contribution of antimicrobial usage to bacterial resistance, the risks of sustained antimicrobial prophylaxis clearly outweigh potential benefits.

Myringotomy and Tympanocentesis

Myringotomy is a long-standing treatment for AOM but is not commonly needed in children receiving antimicrobials. **Indications for myringotomy** in children with AOM include severe, refractory pain; hyperpyrexia; complications of AOM such as facial paralysis, mastoiditis, labyrinthitis, or central nervous system infection; and immunologic compromise from any source. Myringotomy should be considered as third-line therapy in patients who have failed two courses of antibiotics for an episode of AOM. In children with AOM in whom clinical response to vigorous, second-line treatment has been unsatisfactory, either diagnostic tympanocentesis or myringotomy is indicated to enable identification of the offending organism and its sensitivity profile. Either procedure may be helpful in effecting relief of pain. Tympanocentesis with culture of the middle-ear aspirate may also be indicated as part of the sepsis workup in very young infants with AOM who show systemic signs of illness such as fever, vomiting, or lethargy and whose illness accordingly cannot be presumed to be limited to infection of the middle ear. Performing tympanocentesis can be facilitated by use of a specially designed tympanocentesis aspirator. Studies reporting the use of strict, individualized criteria for the diagnosis of AOM that include office tympanocentesis with bacterial culture followed by culture-guided antimicrobial therapy demonstrate significant reduction in the frequency of recurrent AOM episodes and tympanostomy tube surgery. However, many primary care physicians do not feel comfortable performing this procedure, there is the potential for complications, and parents may view this procedure as traumatic. Often, children requiring this intervention have a strong enough history of recurrent OM to warrant the consideration of tympanostomy tube placement, so that the procedure can be performed under general anesthesia.

Early Recurrence After Treatment

Recurrence of AOM after apparent resolution may be caused by either incomplete eradication of infection in the middle ear or upper respiratory tract reinfection by the same or a different bacteria or bacterial strain. Recent antibiotic therapy predisposes patients to an increased incidence of resistant organisms, which should also be considered in choosing therapy, and, generally, initiating therapy with a second-line agent is advisable (see Table 680.3).

Myringotomy and Insertion of Tympanostomy Tubes

When AOM is recurrent, despite appropriate medical therapy, consideration of surgical management of AOM with tympanostomy tube insertion is warranted. Although this surgical procedure may improve the quality of life in patients with recurrent AOM, some studies have suggested the procedure is effective at reducing the rate of AOM, whereas others found postprocedure rates of AOM were no different than patients managed with antibiotics. Individual patient factors, including the risk profile, severity of AOM episodes, child's development and age, presence of a history of adverse drug reactions, concurrent medical problems, and parental wishes, will affect the timing of a decision to consider referral for this procedure. When a patient experiences three episodes of AOM in a 6-month period or four episodes in a 12-month period with one episode in the preceding 6 months, potential surgical management of the child's AOM should be discussed with the parents. Guidelines on tympanostomy tube placement indicate that if MEE is persistent in one or two ears and present at the time of evaluation by the otolaryngologist, then myringotomy is indicated. However, if MEE has cleared, the guidelines recommend holding off on myringotomy and offering observation unless there are additional considerations such as difficulty with tolerating antibiotic therapy (allergic concerns or other tolerance difficulties), severe episodes of acute OM, or other developmental considerations. Not infrequently, one or more of these additional considerations do affect a child's care.

AOM-Associated Tube Otorrhea

Although tympanostomy tubes may reduce the incidence of AOM in some children, patients with tympanostomy tubes may still develop AOM. One advantage of tympanostomy tubes in children with recurrent AOM is that if patients do develop an episode of AOM with a functioning tube in place, these patients will manifest purulent drainage from the tube. By definition, children with functioning tympanostomy tubes without otorrhea do not have bacterial AOM as a cause for a presentation of fever or behavioral changes and should not be treated with oral antibiotics. If tympanostomy tube otorrhea develops, ototopical treatment, and not oral antibiotics, should be considered as first-line therapy. With a functioning tube in place, the infection is able to drain, there is usually negligible pain associated with the infection, and the possibility of developing a serious complication from an episode of AOM is remote. Importantly, strict water precautions after tympanostomy tube placement do not appear to affect the occurrence of posttympanostomy otorrhea, and as such, water precautions are no longer recommended in children with myringotomy tubes. However, when otorrhea does occur, it is important to keep the ear canal dry while ototopical treatment is administered. The current quinolone otic drops approved by the U.S. Food and Drug Administration for use in the middle-ear space in children are formulated with ciprofloxacin/dexamethasone (Ciprodex) and ofloxacin (Floxin). The topical delivery of these otic drops allows them to use a higher antibiotic concentration than can be tolerated by administering oral antibiotics, and they have excellent coverage of even the most resistant strains of common middle-ear pathogens, as well as coverage of *S. aureus* and *Pseudomonas aeruginosa*. The high rate of success of these topical preparations, their broad coverage, the lower likelihood of their contributing to the

development of resistant organisms, the relative ease of administration, the lack of significant side effects, and the lack of ototoxicity make them the first choice for tube otorrhea. Oral antibiotic therapy should be reserved for cases of tube otorrhea that have other associated systemic symptoms, patients who have difficulty in tolerating the use of topical preparations, or, possibly, patients who have failed an attempt at topical otic drops. Despite these advantages of ototopical therapy, survey data have indicated that, compared with otolaryngologists, primary care practitioners are less likely to prescribe ototopicals as first-line therapy in tympanostomy tube otorrhea.

As a result of the relative ease in obtaining fluid for culture and the possibility of the development of fungal otitis, which has shown an increase with the use of broad-spectrum quinolone ototopicals, patients who fail topical therapy should also have culture performed. Other otic preparations are available; although these either have some risk of ototoxicity or have not received approval for use in the middle ear, many of these preparations were widely used before the development of the current quinolone drops and were generally considered reasonably safe and effective. In all cases of tube otorrhea, attention to aural toilet (e.g., cleansing the external auditory canal of secretions and avoidance of external ear water contamination) is important. In some cases, with very thick, tenacious discharge, topical therapy may be inhibited due to lack of delivery of the medication to the site of infection. Suctioning and removal of the secretions, often done through referral to an otolaryngologist, may be quite helpful. When children with tube otorrhea fail to improve satisfactorily with conventional outpatient management, they may require tube removal, hospitalization to receive parenteral antibiotic treatment, or both.

MANAGEMENT OF OTITIS MEDIA WITH EFFUSION

Management of OME depends on an understanding of its natural history and its possible complications and sequelae. Children with OME should be assessed for any baseline sensory, physical, cognitive, or behavioral factors that may portend risk of learning problems from MEE. Moreover, clinicians should evaluate developmentally at-risk children for OME at the time of diagnosis of an at-risk condition such as Down syndrome, autism, speech and language delay, permanent hearing loss, craniofacial syndromes, cleft palate, blindness, or global developmental delay and at 12-18 months of age (if diagnosed as being at risk before this time). However, children who do not have symptoms that could be attributed to OME, such as hearing difficulties, ear discomfort, balance (vestibular) problems, poor school performance, or behavioral problems, and are not at developmental risk should not be routinely screened for OME. When MEE persists for longer than 3 months, an age-appropriate hearing test and consideration of referral to an otolaryngologist are appropriate. In older children (generally older than 4 years) and depending on the expertise in the primary care office, hearing screening may be achieved in primary care. For any child who fails a hearing screening in the primary care office, referral to an otolaryngologist is warranted. In considering the decision to refer the patient for consultation, the clinician should attempt to determine the impact of the OME on the child and educate the family in this regard. Most cases of OME resolve without treatment within 3 months. For children with OME being managed expectantly, the guidelines for management of OME recommend examination should be performed at 3- to 6-month intervals, until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected. Although hearing loss may be of primary concern, OME causes several other difficulties in children that should also be considered. These include predisposition to recurring AOM, pain, disturbance of balance, and tinnitus. In addition, long-term sequelae that have been demonstrated to be associated with OME include pathologic middle-ear changes, atelectasis of the TM and retraction pocket formation, adhesive OM, cholesteatoma formation and ossicular discontinuity, and conductive and sensorineural hearing loss. Long-term adverse effects on speech, language, cognitive, and psychosocial development have also been demonstrated. This impact is related to the duration of effusion present, whether the effusion is unilateral or bilateral, the degree of underlying hearing loss, and other developmental and social factors affecting the child. In considering the impact of OME on development, it is especially important to take into consideration the overall presentation of the child. Although it is unlikely that OME causing unilateral hearing loss in the mild range will have long-term negative effects on an otherwise healthy and developmentally normal child, even a mild hearing loss in a child with other developmental or speech delays certainly has the potential to compound this child's difficulties (Table 680.4). At a minimum, children with OME persisting longer than 3 months deserve close monitoring of their hearing levels with skilled audiologic evaluation, frequent assessment of developmental milestones, including speech and language assessment, and attention paid to their rate of recurrent AOM.

Variables Influencing Otitis Media with Effusion Management Decisions

Patient-related variables that affect decisions on how to manage OME include the child's age, the frequency and severity of previous episodes of AOM and interval since the last episode, the child's current speech and language development, presence of a history of adverse drug reactions, concurrent medical problems, or risk factors such as daycare attendance, and parental wishes. In considering surgical management of OME with tympanostomy tubes, particular benefit is seen in patients with persisting OME punctuated by episodes of AOM, because the tubes may provide resolution of both conditions. Persistence of MEE after recurrent AOM (three episodes in 6 months or four in 12 months) may be treated with tympanostomy tube placement. Disease-related variables that most otolaryngologists consider in the treatment of OME include whether the effusion is unilateral or bilateral, the apparent quantity of effusion, the duration if known, the degree of hearing impairment, the presence or absence of other possibly related symptoms (such as tinnitus, vertigo, or disturbance of balance), and the presence or absence of mucopurulent or purulent rhinorrhea, which, if sustained for longer than 2 weeks, would suggest that concurrent nasopharyngeal or paranasal sinus infection is contributing to continuing compromise of middle-ear ventilation.

Medical Treatment

Antimicrobials have demonstrated limited efficacy in resolving OME, presumably because they help to eradicate nasopharyngeal infection, unapparent middle-ear infection, or both. The most significant effects of antibiotics for OME have been shown with treatment durations of 4 weeks and 3 months. However, with the risk of bacterial antimicrobial resistance, the small potential benefit of antimicrobial therapy is outweighed by the negative potential of treatment and is not recommended. Instead, antibiotic treatment should be limited to cases in which there is evidence of associated bacterial upper respiratory tract infection or untreated middle-ear infection. For this purpose, the most broadly effective drug available should be used as recommended for AOM.

Table 680.4 Sensory, Physical, Cognitive, or Behavioral Factors that Place Children Who Have Otitis Media with Effusion at an Increased Risk for Developmental Difficulties (Delay or Disorder)

Permanent hearing loss independent of otitis media with effusion
Suspected or diagnosed speech and language delay or disorder
Autism spectrum disorder and other pervasive developmental disorders
Syndromes (e.g., Down) or craniofacial disorders that include cognitive, speech, and language delays
Blindness or uncorrectable visual impairment
Cleft palate with or without associated syndrome
Developmental delay

From Rosenfeld RM, Shin JJ, Schwartz SJ, et al. American Academy of Otolaryngology-Head and Neck Surgery Foundation. Clinical practice guideline. Otitis media with effusion (update). *Otolaryngol Head Neck Surg.* 2016;154(2):201–214, Table 3.

The efficacy of corticosteroids in the treatment of OME has been demonstrated to be short term. Therefore the risk-to-benefit ratio for steroids is such that they are no longer recommended for treatment of OME. Antihistamine-decongestant combinations are not effective in treating children with OME and are not indicated. Antihistamines alone, decongestants alone, and mucolytic agents are also ineffective and not recommended. The risk profile for decongestants and antihistamines in children are such that, unless there is some other medical condition such as documented allergic disease for antihistamine therapy, these medications are contraindicated for OME treatment. Randomized controlled trials do not support the use of topical intranasal steroid sprays to treat the manifestations of eustachian tube dysfunction, and their use for OME resolution is also not recommended. Inflation of the eustachian tube by the Valsalva maneuver or other means has not demonstrated long-term efficacy. Other "alternative" therapies, including spinal manipulation, currently have no demonstrated efficacy or role in children with OME.

Myringotomy and Insertion of Tympanostomy Tubes

When OME persists despite an ample period of watchful waiting, generally 3-6 months or perhaps longer in children with unilateral effusion, consideration of surgical intervention with tympanostomy tubes is appropriate. Myringotomy alone, without tympanostomy tube insertion, permits evacuation of MEE and may sometimes be effective, but often the incision heals before the middle-ear mucosa returns to normal, and the effusion soon reaccumulates. Inserting a tympanostomy tube offers the likelihood that middle-ear ventilation will be sustained for at least as long as the tube remains in place and functional. Tympanostomy tubes have a variable duration of efficacy based on design. Tubes that are designed for a shorter duration, 6-12 months, have a lesser impact on disease-free middle-ear spaces in children. Some studies comparing the efficacy of tympanostomy tube types, including shorter-acting tubes, with watchful waiting provide a less helpful assessment of the differences between these approaches. Tubes that are somewhat longer acting, effective for 12-18 months, are generally more appropriate for most children undergoing tube placement. Regardless of type, tympanostomy tube placement nearly uniformly reverses the conductive hearing loss associated with OME. Occasional episodes of obstruction of the tube lumen and premature tube extrusion may limit the effectiveness of tympanostomy tubes, and tubes can also be associated with otorrhea. However, placement of tympanostomy tubes is generally quite effective in providing resolution of OME in children. Tympanostomy tubes generally extrude on their own but rarely require surgical removal after several years in place. Sequelae after tube extrusion include residual perforation of the eardrum, tympanosclerosis, localized or diffuse atrophic scarring of the eardrum (which may predispose to the development of a retraction pocket), residual conductive hearing loss, and cholesteatoma. The more serious of these sequelae are quite infrequent. Recurrence of MEE after the extrusion of tubes does develop, especially in younger children. However, most children without underlying craniofacial abnormalities require only one set of tympanostomy tubes. In developed countries, immunologic maturity and other developmental changes provide improved middle-ear health and resolution of chronic OME by the time of tube extrusion. However, in some populations, including Australian Aboriginal people, Indigenous Nations in the United States, and Alaskan Natives, even with an absence of craniofacial abnormalities, there is a preponderance of chronic OME; these patients should have increased follow-up after tube extrusion. Because persistent OME may clear spontaneously during the summer months, watchful waiting through the summer season may be advisable in children with OME who are otherwise well and without developmental or speech concerns. In considering surgical management of OME in children, primarily in those with bilateral disease and hearing loss, it has been demonstrated that placement of tympanostomy tubes results in a significant improvement in their quality of life.

Adenoidectomy

Adenoidectomy may reduce the risk of subsequent recurrences of both AOM and OME in older children who have undergone tube insertion and in whom, after extrusion of tubes, OM continues to be a problem. Efficacy appears to be independent of adenoid size and probably derives from removal of the focus of infection in the nasopharynx as a site of biofilm formation, chronic inflammation affecting eustachian tube function, and recurrent seeding of the middle ear via the eustachian tube. Current guidelines state that adenoidectomy should not be performed at the time of tympanostomy tube insertion in children younger than 4 years old unless a distinct indication exists (nasal obstruction, chronic adenoiditis). However, in children older than 4 years, one should recommend tympanostomy tubes, adenoidectomy, or both when surgery is performed for OME.

Complications of Acute Otitis Media

Most complications of AOM consist of the spread of infection to adjoining or nearby structures, the development of chronicity, or both. Suppurative complications are relatively uncommon in children in developed countries but occur not infrequently in disadvantaged children whose medical care is limited. The complications of AOM may be classified as either intratemporal or intracranial (Table 680.5).

Intratemporal Complications

Direct but limited extension of AOM leads to complications within the local region of the ear and temporal bone. These complications include dermatitis, TM perforation, chronic suppurative OM (CSOM), mastoiditis, petrositis, brain abscess, hearing loss, facial nerve paralysis, cholesteatoma formation, and labyrinthitis.

Infectious Dermatitis

This is an infection of the skin of the external auditory canal resulting from contamination by purulent discharge from the middle ear. The skin is often erythematous, edematous, and tender. Management consists of proper hygiene combined with systemic antimicrobials and ototopical drops as appropriate for treating AOM and tube otorrhea.

Tympanic Membrane Perforation

Rupture of the TM can occur with episodes of either AOM or OME. Although damage to the TM from these episodes generally heals spontaneously, chronic perforations can develop in a small number of cases and require further surgical intervention.

Chronic Suppurative Otitis Media

CSOM consists of persistent middle-ear infection with discharge through a TM perforation. The disease is initiated by an episode of AOM with rupture of the membrane. The mastoid air cells are invariably involved. The most common etiologic organisms are *P. aeruginosa* and *S. aureus;* however, the typical AOM bacterial pathogens may also be the cause, especially in younger children or in the winter months. Treatment is guided by the results of microbiologic investigation. If an associated cholesteatoma is not present, parenteral antimicrobial treatment combined with assiduous aural cleansing is likely to be successful in clearing the infection, but in refractory cases, tympanomastoidectomy can be required.

Mastoiditis

Mastoiditis is an important complication associated with OM (see Chapter 681).

Facial Paralysis

As it traverses the middle ear and mastoid bone, the facial nerve may be affected by adjacent infection. Facial paralysis occurring as a complication of AOM is uncommon and often resolves after myringotomy and parenteral antibiotic treatment. Facial paralysis in the presence of AOM requires urgent attention because prolonged infection can result in the development of permanent facial paralysis, which can have a devastating effect on a child. Facial paralysis in an infant or child requires complete and unequivocal examination of the TM and middle-ear space. Any difficulty in examination requires urgent consultation with an otolaryngologist. Any examination that demonstrates an ear abnormality also requires urgent referral to an otolaryngologist. If facial paralysis

Table 680.5 Manifestations of the Sequelae and Complications of Otitis Media

COMPLICATION	CLINICAL FEATURES
ACUTE	
Perforation with otorrhea	Immobile tympanic membrane secondary to visible perforation, exudate in ear canal
Acute mastoiditis with periostitis	Tenderness and erythema over mastoid process, no destruction of bony trabeculae
Acute mastoid osteitis	Destruction of bony trabeculae; tenderness and erythema over mastoid process coupled with outward displacement of pinna
Petrositis	Infection of perilabyrinthine cells; may present with otitis, paralysis of lateral rectus, and ipsilateral orbital or facial pain (Gradenigo syndrome)
Facial nerve palsy	Peripheral cranial nerve VII paralysis
Labyrinthitis	Vertigo, fever, ear pain, nystagmus, hearing loss, tinnitus, nausea and vomiting
Lateral (or transverse) sinus thrombosis	Headache, fever, seizures, altered states of consciousness, septic emboli
Meningitis	Fever, headache, nuchal rigidity, seizures, altered states of consciousness
Extradural empyema	Fever, headache, seizures, altered states of consciousness
Subdural empyema	Fever, headache, seizures, altered states of consciousness
Brain abscess	Fever, headache, seizures, altered states of consciousness, focal neurologic examination
Gradenigo syndrome	OM, sixth cranial nerve palsy, pain in first and second distribution of trigeminal nerve.
NONACUTE	
Chronic perforation	Immobile tympanic membrane secondary to perforation
Otitis media with effusion (OME)	Immobile, opaque tympanic membrane
Adhesive otitis	Irreversible conductive hearing loss secondary to chronic OME
Tympanosclerosis	Thickened white plaques may cause conductive hearing loss
Chronic suppurative otitis media	After acute otitis media with perforation, secondary infection with *Staphylococcus aureus, Pseudomonas aeruginosa*, or anaerobes develops, causing chronic otorrhea
Cholesteatoma	White, pearl-like destructive tumor with otorrhea arising near or within tympanic membrane; may be secondary to chronic negative middle ear pressure
Otitic hydrocephalus	Increased intracranial pressure secondary to AOM; signs and symptoms include severe headaches, blurred vision, nausea, vomiting, papilledema, diplopia (abducens paralysis)

AOM, Acute otitis media.
From Kliegman RM, Bordini BJ, Toth H, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*. Philadelphia: Elsevier; 2022: Table 5.6.

develops in a child with mastoid osteitis or with CSOM, mastoidectomy should be undertaken urgently.

Cholesteatoma

Cholesteatoma is a cystlike growth originating in the middle ear, lined by keratinized, stratified squamous epithelium and containing desquamated epithelium and/or keratin (see Chapter 678; Fig. 680.7).

Acquired cholesteatoma develops most often as a complication of long-standing chronic OM. The condition also may develop from a deep retraction pocket of the TM or as a consequence of epithelial implantation in the middle-ear cavity from traumatic perforation of the TM or insertion of a tympanostomy tube. Cholesteatomas tend to expand progressively, causing bony resorption, often extend into the mastoid cavity, and may extend intracranially with potentially life-threatening consequences. Acquired cholesteatoma commonly presents as a chronically draining ear in a patient with a history of previous ear disease. Cholesteatoma should be suspected if otoscopy demonstrates an area of TM retraction or perforation with white, caseous debris persistently overlying this area. Along with otorrhea from this area, granulation tissue or polyp formation identified in conjunction with this history and presentation should prompt suspicion of cholesteatoma. The most common location for cholesteatoma development is in the superior portion of the TM *(pars flaccida)*. Most patients also present with conductive hearing loss on audiologic evaluation. When cholesteatoma is suspected, otolaryngology consultation should be sought immediately. Delay in recognition and treatment can have significant long-term consequences, including the need for more extensive surgical treatment, permanent hearing loss, facial nerve injury, labyrinthine damage with loss of balance function, and intracranial extension. The required treatment for cholesteatoma is tympanomastoid surgery.

Congenital cholesteatoma is an uncommon condition generally identified in younger patients (Fig. 680.8). The etiology of congenital cholesteatoma is thought to be a result of epithelial implantation in the middle-ear space during otologic development in utero. Congenital cholesteatoma most commonly presents in the anterior-superior quadrant of the TM but can be found elsewhere. Congenital cholesteatoma appears as a discrete, white opacity in the middle-ear space on otoscopy. Unlike patients with acquired cholesteatoma, there is generally not a strong history of OM or chronic ear disease, history of otorrhea, or changes in the TM anatomy such as perforation or retraction. Similar to acquired cholesteatoma, many patients do have some degree of abnormal findings on audiologic evaluation, unless identified very early. Congenital cholesteatoma also requires surgical resection.

Labyrinthitis

Labyrinthitis occurs uncommonly as a result of the spread of infection from the middle ear and/or mastoid to the inner ear (see Chapter 682). Cholesteatoma or CSOM is the usual source. Symptoms and signs include vertigo, tinnitus, nausea, vomiting, hearing loss, nystagmus, and clumsiness. Treatment is directed at the underlying condition and must be undertaken promptly to preserve inner-ear function and prevent the spread of infection.

INTRACRANIAL COMPLICATIONS

Meningitis, epidural abscess, subdural abscess, focal encephalitis, brain abscess (see Chapters 643, 644, and 681), transverse (lateral) and sigmoid sinus thrombosis and otitic hydrocephalus each may develop as a complication of acute or chronic middle-ear or mastoid infection through direct extension, hematogenous spread, or thrombophlebitis. Bony destruction adjacent to the dura is often involved, and a cholesteatoma may be present. In a child with middle-ear or mastoid infection, the presence of any systemic symptom, such as high spiking fevers, headache, or lethargy of extreme degree or a finding of meningismus or of any abnormal central nervous system sign on physical examination should prompt suspicion of an intracranial complication.

When an intracranial complication is suspected, lumbar puncture should be performed only after imaging studies establish that there is no evidence of mass effect or hydrocephalus. In addition to examination

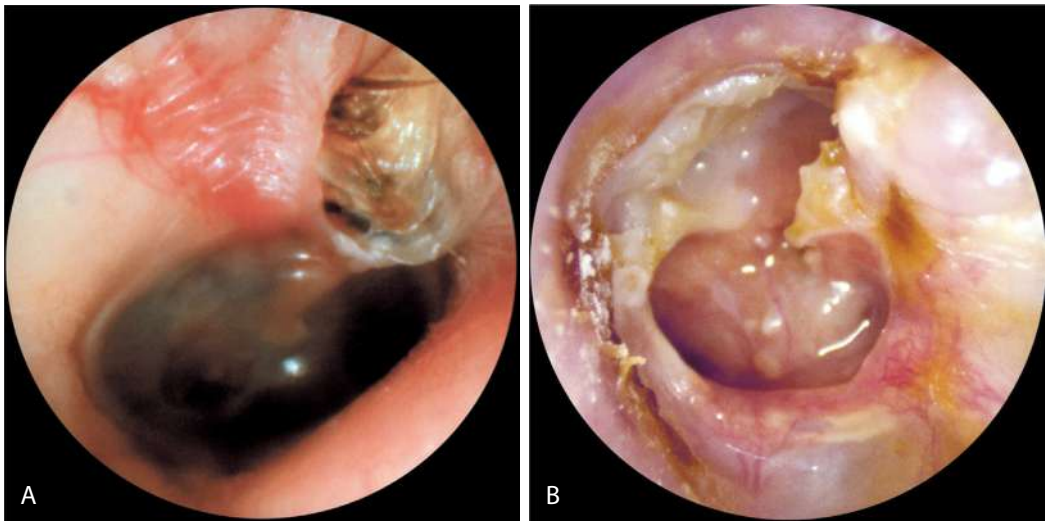

Fig. 680.7 A, Primary acquired cholesteatoma in the region of the pars flaccida with scutum erosion. B, Cholesteatoma developing at the margin of perforation (secondary acquired cholesteatoma) with secondary infection. *(From Chole RA, Sudhoff HH. Chronic otitis media, mastoiditis, and petrositis. In: Flint PW, Haughey BH, Lund VJ, et al, eds. Cummings Otolaryngology—Head and Neck Surgery, 5th ed. Philadelphia: Elsevier; 2010: Figs. 139-4, 139-5.)*



Fig. 680.8 Congenital chronic otitis media with cholesteatoma. *(From Chole RA, Sudhoff HH. Chronic otitis media, mastoiditis, and petrositis. In: Flint PW, Haughey BH, Lund VJ, et al., eds. Cummings Otolaryngology—Head and Neck Surgery, 5th ed. Philadelphia: Elsevier; 2010: Fig. 139-6.)*

of the cerebrospinal fluid, culture of middle-ear exudate obtained via tympanocentesis may identify the causative organism, thereby helping to guide the choice of antimicrobial medications. Myringotomy should be performed to permit middle-ear drainage. Concurrent tympanostomy tube placement is preferable to allow for continued decompression of the "infection under pressure" that is the causative event leading to intracranial spread of the infection.

Treatment of intracranial complications of OM requires urgent, otolaryngologic, and often, neurosurgical consultation, intravenous antibiotic therapy, drainage of mastoiditis, and tympanomastoidectomy in patients with coalescent mastoiditis. Many brain abscesses may be managed without drainage but require long-term broad-spectrum antibiotic therapy (see Chapter 644).

Lateral (transverse) or sigmoid sinus thrombosis may be complicated by dissemination of infected thrombi with resultant development of septic infarcts in various organs. Diagnosis is confirmed by MRI. Mastoidectomy may be required even in the absence of osteitis or coalescent mastoiditis, especially in the case of propagation or embolization of infected thrombi. In the absence of coalescent mastoiditis, sinus thrombosis can often be treated with tympanostomy tube placement, anticoagulation, and intravenous antibiotics. Otolaryngology consultation should be obtained before initiating this anticoagulation to coordinate the possible need for surgical intervention before anticoagulation.

Otitic hydrocephalus, a form of **idiopathic intracranial hypertension**, or **pseudotumor cerebri** (see Chapter 645), is an uncommon condition that consists of increased intracranial pressure without dilation of the cerebral ventricles occurring in association with acute or chronic OM or mastoiditis. The condition is commonly also associated with lateral sinus thrombosis, and the pathophysiology is thought to involve obstruction by thrombus of intracranial venous drainage into the neck, producing a rise in cerebral venous pressure and a consequent increase in cerebrospinal fluid pressure. Symptoms are those of increased intracranial pressure. Signs may include, in addition to evidence of OM, paralysis of one or both lateral rectus muscles and papilledema with or without visual acuity loss. MRI can confirm the diagnosis. Treatment measures include the use of antimicrobials and medications such as acetazolamide or furosemide to reduce intracranial pressure, mastoidectomy, repeated lumbar puncture, lumboperitoneal shunt, and ventriculoperitoneal shunt. If left untreated, otitic hydrocephalus may result in loss of vision secondary to optic atrophy.

Physical Sequelae

The physical sequelae of OM consist of structural middle-ear abnormalities resulting from long-standing middle-ear inflammation. In most instances, these sequelae are consequences of severe and/or chronic infection, but some may also result from the noninfective inflammation of long-standing OME. The various sequelae may occur singly or interrelatedly in various combinations.

Tympanosclerosis consists of whitish plaques in the TM and nodular deposits in the submucosal layers of the middle ear. The changes involve hyalinization with deposition of calcium and phosphate crystals. Uncommonly, there may be associated conductive hearing loss. In developed countries, probably the most common cause of tympanosclerosis is tympanostomy tube insertion.

Atelectasis of the TM is a descriptive term applied to either severe retraction of the TM caused by high negative middle-ear pressure or loss of stiffness and medial prolapse of the membrane from long-standing retraction or severe or chronic inflammation. A **retraction pocket** is a localized area of atelectasis. Atelectasis is often transient and usually unaccompanied by symptoms, but a deep retraction pocket may lead to erosion of the ossicles and adhesive otitis and may serve as the nidus of a cholesteatoma. For a deep retraction pocket, and for the unusual instance in which atelectasis is accompanied by symptoms

such as otalgia, tinnitus, or conductive hearing loss, the required treatment is tympanostomy tube insertion and, at times, tympanoplasty. Patients with persisting atelectasis and retraction pockets should have referral to an otolaryngologist.

Adhesive OM consists of proliferation of fibrous tissue in the middle-ear mucosa, which may, in turn, result in severe TM retraction, conductive hearing loss, impaired movement of the ossicles, ossicular discontinuity, and cholesteatoma. The hearing loss may be amenable to surgical correction.

Cholesterol granuloma is an uncommon condition in which the TM may appear to be dark blue secondary to middle-ear fluid of this color. Cholesterol granulomas are rare, benign cysts that occur in the temporal bone. They are expanding masses that contain fluids, lipids, and cholesterol crystals surrounded by a fibrous lining and generally require surgical removal. Tympanostomy tube placement will not provide satisfactory relief. This lesion requires differentiation from bluish middle-ear fluid, which can also rarely develop in patients with the more common OME.

Chronic perforation may rarely develop after spontaneous rupture of the TM during an episode of AOM or from acute trauma, but more commonly results as a sequela of CSOM or as a result of failure of TM closure after extrusion of a tympanostomy tube. Chronic perforations are generally accompanied by conductive hearing loss. Surgical repair of a TM perforation is recommended to restore hearing, prevent infection from water contamination in the middle-ear space, and prevent cholesteatoma formation. Chronic perforations are almost always amenable to surgical repair, usually after the child has been free of OM for an extended period.

Permanent **conductive hearing loss** (see Chapter 677) may result from any of the conditions just described. Rarely, permanent sensorineural hearing loss may occur in association with acute or chronic OM, secondary to spread of infection or products of inflammation through the round window membrane, or as a consequence of suppurative labyrinthitis.

POSSIBLE DEVELOPMENTAL SEQUELAE

Permanent hearing loss in children has a significant negative impact on development, particularly in speech and language. The degree to which OM affects long-term development in children is difficult to assess, and there have been conflicting studies examining this question. Developmental impact is most likely to be significant in children who have greater levels of hearing loss, hearing loss that is sustained for longer periods, or hearing loss that is bilateral and in children who have other developmental difficulties or risk factors for developmental delay (see Table 680.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 681

Acute Mastoiditis

Brittany Player

Mastoiditis, a suppurative infection of the mastoid air cell system, is the most common infectious complication of acute otitis media (AOM), typically affecting younger children. Coalescent mastoiditis occurs when the suppurative infection leads to bony breakdown of the fine bony septa separating individual mastoid air cells.

ANATOMY

The temporal bone forms a portion of the skull base and has multiple complex anatomic functions. The mastoid process is a pyramid-shaped outgrowth of the temporal bone. The inferior extent is attached to the sternocleidomastoid muscle. The mastoid process borders the middle cranial fossa, posterior cranial fossa, and sigmoid sinus. It is composed of a system of interlinked mucosa-lined air cells that communicate with the middle ear space and contains the fallopian canal, which includes the facial nerve, the chorda tympani supplying taste to the anterior two thirds of the tongue, and the semicircular canal system. Because the mastoid cavity is anatomically adjacent to the meninges, brain, venous sinuses of the brain, facial nerve, and cervical lymph nodes, mastoiditis often accompanies or precedes intracranial complications of AOM (see Chapter 680).

EPIDEMIOLOGY

In the preantibiotic era, acute mastoiditis was a much more common complication of AOM with high rates of intracranial infectious complications, morbidity, and mortality. Currently, mastoiditis is a rare complication, occurring in approximately 1-4 cases per 100,000 population of children <2 years old and less commonly among older children. A multicenter study with 223 consecutive cases of acute mastoiditis reported 28% of patients were younger than 1 year old, 38% of patients were between 1 and 4 years old, 22% of patients were between 4 and 8 years old, and 8% of patients were between 8 and 18 years old. Some studies reported decreased incidence of acute mastoiditis after introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), whereas others reported no change or nominal increases. One study reported a sharp decrease in acute mastoiditis beginning in 2010, which coincided with licensure and widespread use of the 13-valent pneumococcal conjugate vaccine (PCV13). Another study, which included data from eight hospitals, found that the proportion of PCV13 serotypes isolated from cases of mastoiditis decreased from 50% in 2011 to 29% in 2013, with most of the decrease attributable to decreases in serotype 19A. Changes in rates of mastoiditis are likely related to changing incidence of AOM in response to pneumococcal conjugate vaccines. Other factors influencing the occurrence of mastoiditis include rates of antibiotic prescriptions for AOM, access to healthcare, and rates of antimicrobial resistance. Whereas groups in countries such as the Netherlands and Iceland reported adherence to a watchful waiting strategy for treatment of AOM, this resulted in slightly increased rates of acute mastoiditis compared with countries where antibiotics are routinely used to treat AOM. Other studies from several countries have contradicted these findings, demonstrating no increased incidence in acute mastoiditis, with changes in recommendations for more conservative antimicrobial prescribing practices. Despite large differences in antibiotic prescription rates in different countries, because of the overall low incidence of acute mastoiditis, the number of children needed to be treated with antibiotics to prevent one case of acute mastoiditis ranges from 2,500 to 4,800. Some studies have reported an increase in incidence, which has correlated with an increase in infections with drug-resistant bacteria. All-cause mortality among children with mastoiditis is 0.03%.

MICROBIOLOGY

Streptococcus pneumoniae remains the most common pathogen cultured from cases of acute mastoiditis (Table 681.1). After introduction of PCV7, pneumococcal serotype 19A was commonly associated with acute mastoiditis. This serotype is frequently resistant to

Table 681.1 Etiology of Acute Mastoiditis

BACTERIA	FREQUENCY
Streptococcus pneumoniae	10–51%
Streptococcus pyogenes	0–12%
Staphylococcus aureus	2–10%
Pseudomonas aeruginosa	10%
Haemophilus influenzae	2–3%
No growth	20–40%

penicillin and macrolide antibiotics. PCV13 use has been associated with fewer serotype 19A infections overall; its impact on the etiology of mastoiditis is less clear. Other bacteria commonly cultured include *Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa, Fusobacterium necrophorum,* and *Haemophilus influenzae*. *P. aeruginosa* is more likely in patients with chronic otitis media and/or cholesteatoma, older children, and those with previous tympanostomy tubes, though higher rates of *P. aeruginosa* recovery should suggest consideration of the method of sample collection when interpreting this culture result.

CLINICAL MANIFESTATIONS

Acute mastoiditis and AOM present similarly in children. Ninety-seven percent of children with an acute mastoiditis have a coexisting AOM on the affected side. The remaining 3% of children with acute mastoiditis either had a serous middle ear effusion at the time of presentation or had a history of AOM within the past 2 weeks. Other clinical manifestations include protrusion of the ear (87%), retroauricular swelling and tenderness (67%), retroauricular erythema (87%), fever (60%), otalgia, and hearing loss (Tables 681.2 and 681.3). Prolonged symptoms during the treatment of AOM may suggest concurrent mastoiditis. Children with acute mastoiditis were less likely to have bilateral infection. Some children do not have external signs of infection.

DIAGNOSIS AND IMAGING

Acute mastoiditis is usually diagnosed based on history and clinical findings (see Table 681.2). CT scan of the temporal bone can confirm the diagnosis, whereas head CT can identify intracranial complications (see Chapter 680), including epidural abscess or subdural empyema. Findings of acute mastoiditis include bony demineralization, loss of bony septations in the mastoid cavity (Fig. 681.1), and, occasionally, subperiosteal abscess (Fig. 681.2). CT scans have the advantage of being readily available in most emergency rooms, can quickly evaluate for intracranial complications, and can identify whether there is bony destruction or a drainable fluid collection. Contrast-enhanced CT scan or MRI allows evaluation for vascular thrombosis (Fig. 681.3) and abscess formation. MRI is generally reserved for patients in whom there is a suspected intracranial complication (Figs. 681.4 and 681.5). Incidental detection of mastoid air cell opacification occurs in more than 20% of children (and in 40% of children <2 years old) undergoing MRI for other reasons, so imaging findings must be interpreted in the appropriate clinical context.

There is a limited role for ultrasound in the diagnosis of acute mastoiditis. Ultrasound can be used as a screening test when a postauricular subperiosteal abscess is suspected due to clinical findings such as protrusion of the pinna and retroauricular erythema. If there is a fluid collection on ultrasound or concern for a defect in the cranial vault, further imaging with a CT and/or MRI would be recommended. Because ultrasound cannot identify intracranial complications, its use must be limited to a highly selected patient population.

MANAGEMENT

Acute mastoiditis is a rare complication of AOM, and there is a large degree of overlap between the presentations of children with both disease processes. For the pediatrician confronted with a majority of uncomplicated AOM, it is difficult to decide when to initiate a more extensive evaluation. Any time there is a purulent middle-ear effusion along with postauricular findings, acute mastoiditis needs to be in the differential diagnosis. In general, children with acute mastoiditis will appear sicker than children with uncomplicated AOM, and many of them have already failed to respond to appropriate antibiotic therapy for AOM. Focal neurologic deficits, including facial paresis, in a child with AOM or mastoiditis suggest intracranial spread of infection. In a child with suspected mastoiditis, it is critical to document normal facial nerve function at the time of the initial exam so that if this complication does develop during treatment, the treating team is able to document this complication.

Table 681.2 Diagnosis of Acute Mastoiditis

Fever, otalgia, postauricular swelling plus redness
- Older child: ear up and out
- Infant: ear down and out

Tympanic membrane: acute otitis media
Radiograph: mastoid air cells coalescent or clouded
Computed tomography, magnetic resonance imaging, or bone scan as needed

From Wald ER, Conway JH. Mastoiditis. In: Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases,* 5th ed. Philadelphia: Elsevier; 2018: p. 227.

Table 681.3 Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periostitis/Abscess

	POSTAURICULAR SIGNS AND SYMPTOMS					
DISEASE	**CREASE***	**ERYTHEMA**	**MASS**	**TENDERNESS**	**EXTERNAL CANAL INFECTION**	**MIDDLE-EAR EFFUSION**
Acute mastoiditis with periostitis	May be absent	Yes	No	Usually	No	Usually
Acute mastoiditis with subperiosteal abscess	Absent	Maybe	Yes	Yes	No	Usually
Periostitis of pinna with postauricular extension	Intact	Yes	No	Usually	No	No
External otitis with postauricular extension	Intact	Yes	No	Usually	Yes	No
Postauricular lymphadenitis	Intact	No	Yes†	Maybe	No	No

*Postauricular crease (fold) between pinna and postauricular area.
†Circumscribed.
From Bluestone CD, Klein JO, eds. *Otitis Media in Infants and Children,* 3rd ed. Philadelphia: WB Saunders; 2001: p. 333.

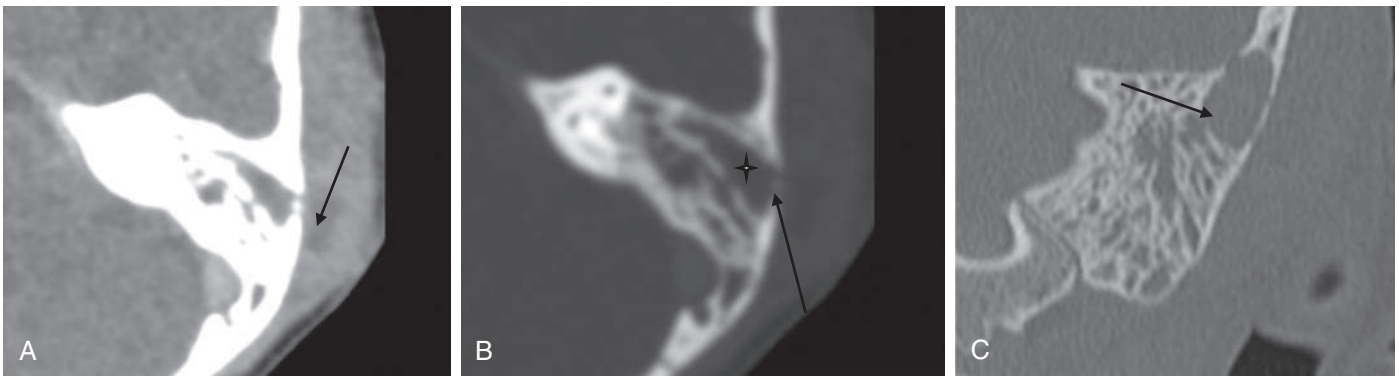

Fig. 681.1 Coalescent mastoiditis with subperiosteal abscess formation. **A** and **B**, Axial CT images with soft tissue windows and bone windows, respectively. *Arrow* in **A** points to the subperiosteal abscess. *Star* in **B** shows the loss of bony septations in the mastoid cavity, and the *arrow* points to the erosion of the bony cortex. **C**, Coronal image shows demineralization of the mastoid tegmen abutting the middle cranial fossa, a precursor to epidural abscess formation.

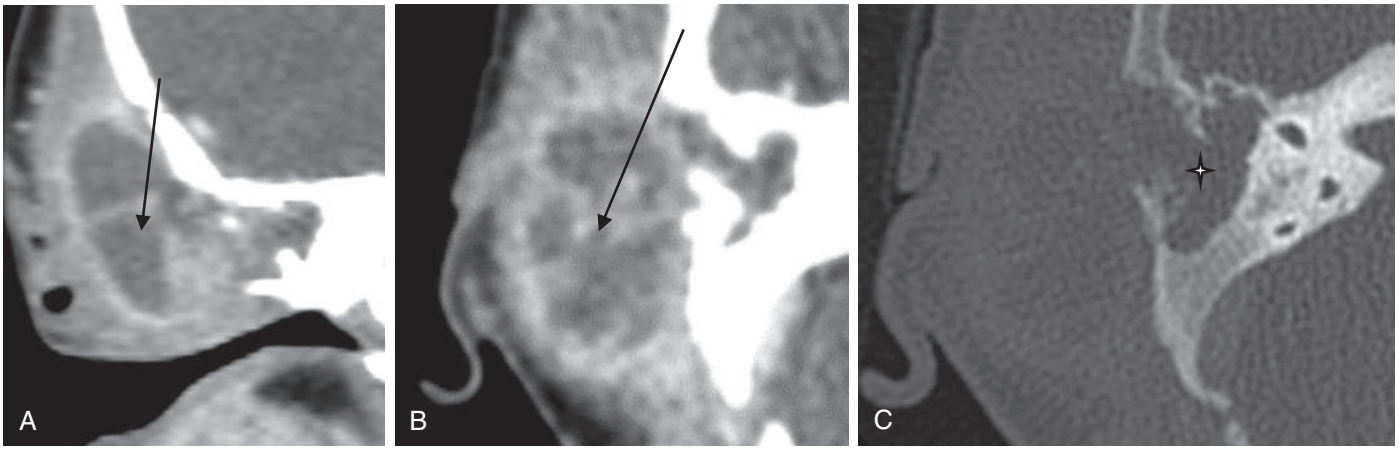

Fig. 681.2 Advanced case of coalescent mastoiditis with subperiosteal abscess formation. Axial (**A**) and coronal (**B**) images; *arrow* points to the subperiosteal abscess **C**, Extensive loss of bony septations in the mastoid cavity (*star).*

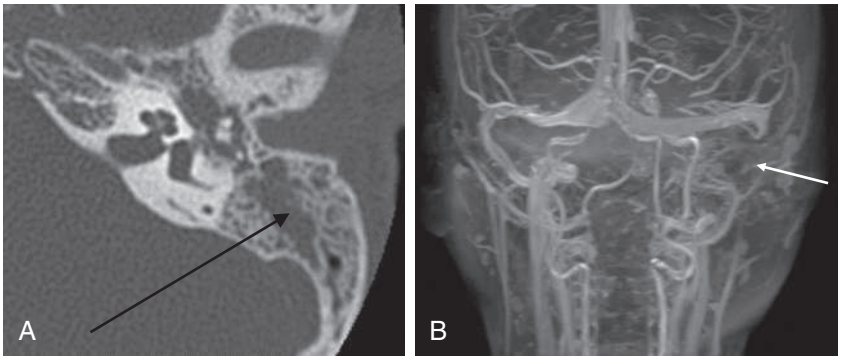

Fig. 681.3 **A**, Axial CT scan with bone windows shows opacification of the mastoid air cells, a small region of coalescence (*arrow),* and opacification of the middle ear space. **B**, CT venogram with a sigmoid sinus thrombosis. The *arrow* points to the area where a patent sigmoid sinus should be present.

Complete blood count typically reveals leukocytosis with neutrophil predominance. C-reactive protein is often highly elevated. If otorrhea is present, implying a perforated tympanic membrane, the fluid should be sent for Gram stain and culture. Blood culture should be considered in any child appearing toxic. For children with postauricular findings consistent with acute mastoiditis, admission to the hospital for intravenous antibiotic therapy and serial exams is recommended.

In highly selected cases, ultrasound may be helpful to differentiate postauricular erythema from a postauricular abscess and avoids the risk of ionizing radiation exposure. However, ultrasound is not as sensitive as CT scanning and will underdiagnose postauricular abscess formation and will provide no information as to whether there is an intracranial complication present such as a brain abscess. Some authors advocate deferring CT scanning in patients with clinically suspected acute mastoiditis and without focal neurologic

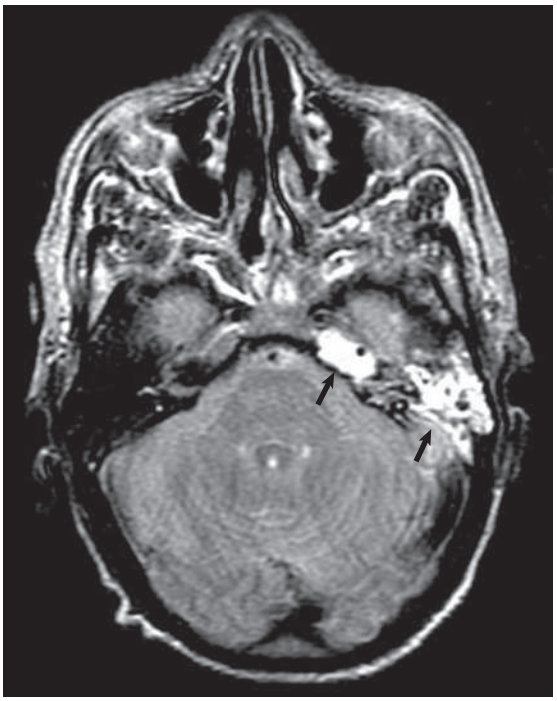

Fig. 681.4 Axial T2-weighted MRI showing left mastoiditis and petrous apicitis *(arrows)* as high signal in mastoid and petrous apex. *(From Budenz CL, El-Kashlan HK. Complications of temporal bone infections. In: Flint PW, Francis HW, Haughey BH, et al, eds. Cummings Otolaryngology Head & Neck Surgery, 7th ed., vol. 2. Philadelphia: Elsevier; 2021: Fig 141.17A.)*

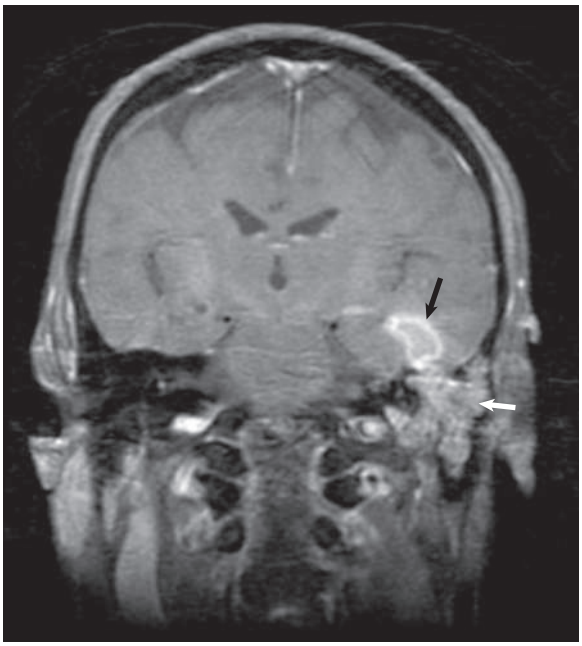

Fig. 681.5 Coronal enhanced T1-weighted MRI of the patient showing enhancing tissue in left mastoid *(white arrow)* and temporal lobe abscess with enhancing capsule *(black arrow)*. *(From Budenz CL, El-Kashlan HK. Complications of temporal bone infections. In: Flint PW, Francis HW, Haughey BH, et al, eds. Cummings Otolaryngology Head & Neck Surgery, 7th ed., vol. 2. Philadelphia: Elsevier; 2021: Fig 141.17D)*

findings to allow for an initial 24- to 48-hour period of inpatient intravenous antibiotic therapy. If there is any concern about the possibility of an intracranial complication, a contrasted CT scan is the most sensitive readily available test and should be ordered upon presentation.

Antibiotic therapy should initially be administered intravenously. Empiric antibiotic selection may include a β-lactam/β-lactamase inhibitor combination (e.g., ampicillin-sulbactam, piperacillin-tazobactam) or third-generation cephalosporin (e.g., cefotaxime, ceftriaxone). In children with chronically draining ears or concern for cholesteatoma, there is an increased incidence of gram-negative infection, and coverage should include antibiotics with activity against *Pseudomonas* spp. (e.g., ceftazidime, cefepime). If intracranial infection is suspected, broader-spectrum antimicrobial coverage (e.g., vancomycin plus a third-generation cephalosporin) should be initiated. In cases of uncomplicated acute mastoiditis (e.g., absence of intracranial complications or localized abscess formation), a 24- to 48-hour trial of intravenous antibiotics may yield clinical improvement without surgical intervention. Therapy should be adjusted when cultures and susceptibilities are available. The total duration of therapy is 4 weeks, with transition from intravenous to oral therapy at discharge for those without intracranial complications. The optimal duration of intravenous therapy is unknown, but some experts recommend a minimum of 7-10 days of intravenous therapy before oral transition, whereas others transition once the patient demonstrates clinical improvement and surgical intervention is no longer required.

Otolaryngology consultation can be helpful to assist with management and to determine whether surgical intervention would be beneficial. Many patients will benefit from tympanostomy tube placement at the time of the acute infection to allow localized ototopical antibiotic treatment and aspiration of middle-ear fluid for culture and sensitivity. In a patient with an additional extracranial complication such as facial paresis, drainage of the middle-ear space with placement of a tympanostomy tube is required and should take place urgently. A small group of patients may necessitate mastoidectomy—surgical removal of diseased bone and granulation tissue in the mastoid cavity. At the time of surgery, a drain is often placed to allow purulent secretions an egress. Indications for mastoidectomy include coalescent mastoiditis, postauricular abscess formation, infectious intracranial complication, and failure to respond to appropriate IV antibiotics. When intracranial complications occur or there are mental status changes, evaluation by otolaryngology and neurosurgery and emergent mastoidectomy are indicated. Most children with mastoiditis make a full recovery. Long-term otologic complications like sensorineural or conductive hearing loss are uncommon. A posttreatment audiogram is often obtained to evaluate the hearing status after an infection.

SPECIAL SITUATIONS

When treating acute mastoiditis, several uncommon situations require particular attention. Selecting empiric antibiotics for unvaccinated and undervaccinated children is challenging, and in this patient population, it is especially important to obtain a sample of middle-ear fluid for Gram stain and culture to guide antibiotic therapy. There is an increased incidence of acute mastoiditis in children with autism spectrum disorder. Immunocompromised patients should be treated with more aggressive and prolonged courses of antibiotic; they may benefit from more aggressive surgical treatment to remove infected tissue. Sigmoid sinus thrombosis can occur secondary to acute mastoiditis. If this does occur, in addition to the standard treatment for acute mastoiditis, consideration should be given to involving hematology and for administering systemic anticoagulation. Otitic hydrocephalus, which is elevated intracranial pressure after middle-ear infection, manifests with emesis, headache, and visual impairment and is associated with lateral or sigmoid sinus thrombosis; management requires antibiotics, anticoagulation, treatment of increased intracranial pressure, and surgical decompression with drainage of the mastoid infection.

Children with **cochlear device implantation** may have a 3.5% incidence of acute mastoiditis. Despite having a foreign body present in the middle ear and inner ear space, the majority of these

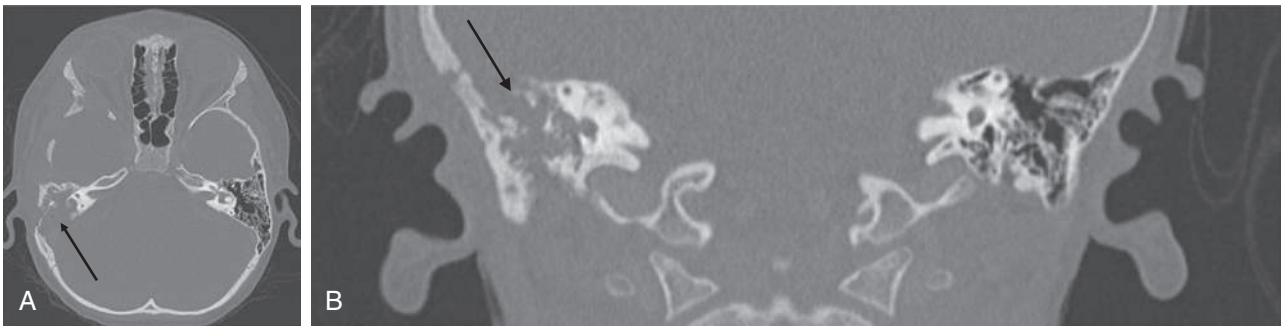

Fig. 681.6 Axial (A) and coronal (B) CT scans of a patient with Langerhans cell histiocytosis of the right temporal bone. A, Opacification of the mastoid with loss of bony septations and erosion of the bone separating the cranial fossa from the mastoid cavity *(arrow)*. B, Bony erosion caused by the tumor and the erosion of the mastoid tegmen *(arrow)*.

acute mastoiditis cases can be managed with tympanostomy tube placement, intravenous antibiotic therapy, and incision and drainage of an abscess without removal of the device.

Although very rare, benign and malignant tumors can affect the temporal bone of children. The presentation mimics that of chronic otitis media and chronic mastoiditis, and this often leads to a delay in diagnosis. Hearing loss, otalgia, and otorrhea are common symptoms. The main differentiating factor is the protracted course of otorrhea and refractory nature of symptoms despite appropriate medical therapy. Aural polyps or a mass lesion may be present on physical exam. Potential causes include rhabdomyosarcoma, nonrhabdomyosarcomatous sarcoma (including chondrosarcoma, chordoma, osteosarcoma, Ewing sarcoma, fibrosarcoma, angiosarcoma, and chloroma), Langerhans cell histiocytosis (formerly histiocytosis X) (Fig. 681.6), lymphoma, and metastasis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 682

The Inner Ear and Diseases of the Bony Labyrinth

Joseph Haddad Jr.

Genetic factors can affect the anatomy and function of the inner ear. Infectious agents, including viruses, bacteria, and protozoa, also can cause abnormal function, most commonly as sequelae of congenital infection (see Table 677.2) or bacterial meningitis (see Chapter 643.1). Other acquired diseases of the labyrinthine capsule include otosclerosis, osteopetrosis, Langerhans cell histiocytosis (see Chapter 556.1), fibrous dysplasia, and other types of bony dysplasia. All of these can cause both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL), as well as vestibular dysfunction.

OTHER DISEASES OF THE INNER EAR

Labyrinthitis (also called **vestibular neuritis**) may be a complication of direct spread of infection from acute or chronic otitis media or mastoiditis and also can complicate bacterial meningitis as a result of organisms entering the labyrinth through the internal auditory meatus, endolymphatic duct, perilymphatic duct, vascular channels, or hematogenous spread. Clinical manifestations of vestibular neuritis can include a sudden onset of rotatory vertigo, dysequilibrium, postural imbalance (furniture walking) with falls to the affected side, deep-seated ear pain, nausea, vomiting, and spontaneous horizontal (occasionally rotary) nystagmus.

The dizziness may last a few days, but balance issues, particularly after rapid head movements toward the affected ear, may last for months. Vestibular neuritis is usually unilateral and is not associated with other neurologic defects; subjective hearing loss is unusual in vestibular neuritis. If hearing loss is present, idiopathic SNHL should be considered, as well as classical labyrinthitis (vestibular and cochlear nerves). Treatment of vestibular neuritis may include prednisone and vestibular rehabilitative exercises. Recurrent episodes should suggest another diagnosis such as vestibular migraine or benign paroxysmal positional vertigo.

In children, viral labyrinthitis is often associated with hearing loss. **Acute serous labyrinthitis**, characterized by mild symptoms of vertigo and hearing loss, most commonly develops secondary to middle-ear infection without direct invasion. **Acute suppurative labyrinthitis**, characterized by abrupt, severe onset of these symptoms, may be caused by bacterial meningitis or acute middle-ear or mastoid infection via a dehiscent horizontal semicircular canal. In these latter cases, a cholesteatoma is almost always present. Treatment of acute infectious labyrinthitis includes antimicrobial agents in cases of bacterial infection or antiviral agents (acyclovir, valacyclovir) in cases of herpes zoster oticus. Oral corticosteroids reduce labyrinthine inflammation and may prevent sequelae. A short course (≤3 days) of vestibular suppressants (dimenhydrinate 1-2 mg/kg) alleviates acute symptoms such as nausea. If it is secondary to otitis media, otologic surgery may be required to remove underlying cholesteatoma or drain the middle ear and mastoid. **Chronic labyrinthitis**, most often associated with cholesteatoma, manifests with SNHL and vestibular dysfunction that develops over time; surgery is required to remove the cholesteatoma. Chronic labyrinthitis also occurs uncommonly secondary to long-standing otitis media, with the slow development of SNHL, usually starting in the higher frequencies, and possibly with vestibular dysfunction. In addition, and more commonly, children with chronic middle-ear fluid often are unsteady or off balance, a situation that improves immediately when the fluid resolves.

Vertigo and dizziness are common among older children and adolescents. Benign **paroxysmal vertigo**, the most common cause of vertigo in pediatric patients, is characterized by short periods of vertigo or dizziness lasting seconds to a few minutes and associated with imbalance and nystagmus; tinnitus or hearing loss is unusual. **Basilar/vestibular migraine** is a common cause of episodic vertigo or dizziness and is associated with headache (50–70% of patients), rotary or to-and-fro nystagmus, and sensitivity to noise and bright light (see Chapter 635.1). **Benign paroxysmal positional vertigo** is less common in young children and more common with increasing age into adulthood. Particles form in the semicircular canals (canalithiasis), most often the

posterior canal; symptoms occur with position changes of the head and may last seconds to minutes. Vertigo and nystagmus may be demonstrated by changing position (sitting to lying down on the right or left). Treatment involves canalith repositioning maneuvers to shift the debris from the canals into the utricle. Additional etiologies of vertigo include vestibular migraine, trauma, superior semicircular canal dehiscence, isolated autoimmune inner ear disease or syndrome-associated autoimmune diseases including Cogan syndrome (interstitial keratitis, vertigo, hearing loss), Vogt-Koyanagi-Harada syndrome (uveomeningitis, vitiligo, vertigo, hearing loss), Susac syndrome (microangiopathy with retinopathy, encephalopathy, deafness), granulomatosis with polyangiitis, mixed connective tissue disease, and, most rarely, CNS tumor.

Otosclerosis, an autosomal dominant disease that affects only the temporal bones, causes abnormal bone growth that can result in fixation of the stapes in the oval window, leading to progressive hearing loss. In one series in North America, otosclerosis was found in 0.6% of temporal bones of children younger than 5 years of age and 4% of those ages 5-18 years. The hearing loss is usually conductive at first, but SNHL can develop. Females are affected most commonly, with onset of otosclerosis in teenagers or young adults, often associated with pregnancy. Corrective surgery to replace the stapes with a mobile prosthesis often is successful.

Osteogenesis imperfecta is a systemic disease that can involve both the middle and inner ears (see Chapter 742). Hearing loss occurs in approximately 20% of young children and as many as 50% of adults by the age of 50 with this disease. The hearing loss most commonly is conductive but can be sensorineural or mixed. Etiologies of hearing loss include otosclerosis, ossicle fractures, or neural degeneration. If the hearing loss is severe enough, a hearing aid may be a preferable alternative to surgical correction of the fixed stapes, because stapedectomy in children with osteogenesis imperfecta can be technically very difficult, and the disease and the hearing loss may be progressive.

Osteopetrosis, a very uncommon skeletal dysplasia, can involve the temporal bone, including the middle ear and ossicles, usually resulting in a moderate to severe CHL. Recurrent facial nerve paralysis also can occur because of excess bone deposition; with each recurrence, less facial function might return (see Chapter 740).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 683

Traumatic Injuries of the Ear and Temporal Bone

Joseph Haddad Jr.

AURICLE AND EXTERNAL AUDITORY CANAL

Auricle trauma is common in certain sports. Hematoma, with accumulation of blood between the perichondrium and the cartilage, can follow trauma to the pinna and is especially common in teenagers involved in wrestling or boxing. Prompt drainage of a hematoma can prevent irreversible damage. Immediate needle aspiration or, when the hematoma is extensive or recurrent, incision and drainage and a pressure dressing are necessary to prevent perichondritis, which can result in cartilage loss and a "cauliflower ear deformity." Sports helmets should be worn when appropriate during activities when head trauma is possible.

Frostbite of the auricle should be managed by rapidly rewarming the exposed pinna with warm irrigation or warm compresses.

Foreign bodies in the external canal are common in childhood. Often these can be removed in the office setting without general anesthesia if the child is mature enough to understand and cooperate and is properly restrained; if an adequate headlight, surgical head otoscope, or otomicroscope is used for visualizing the object; and if appropriate instruments such as alligator forceps, wire loops or a blunt cerumen curette or suction are used, depending on the shape of the object. Gentle irrigation of the ear canal with body-temperature water or saline may be used to remove very small objects, but only if the tympanic membrane (TM) is intact. Attempts to remove an object from a struggling child or with poor visualization and inadequate tools result in a terrified child with a swollen and bleeding ear canal and can then mandate general anesthesia to remove the object. Difficult foreign bodies, especially those that are large, deeply embedded, or associated with canal swelling, are best removed by an otolaryngologist and/or under general anesthesia. Disk batteries are removed emergently because they leach a basic fluid that can cause severe tissue destruction. Insects in the canal are first killed with mineral oil or lidocaine and are then removed under otomicroscopic examination. Objects retained in the external auditory canal can lead to complications such as otalgia, conductive hearing loss, infection, and aural drainage.

After a foreign body is removed from the external canal, the TM should be inspected carefully for traumatic perforation, middle-ear effusion, abrasions, and bleeding. If a foreign body has resulted in acute inflammation of the canal, topical otic medications as described for acute external otitis should be instituted (see Chapter 679).

TYMPANIC MEMBRANE AND MIDDLE EAR

Traumatic perforation of the TM usually results from sudden external compression, such as a slap, or penetration by a foreign object such as a stick or cotton-tipped swab. The perforation may be linear or stellate. It is most commonly in the anterior portion of the pars tensa when it is caused by compression, and it may be in any quadrant of the TM when caused by a foreign object. Systemic antibiotics and topical otic medications are not required unless suppurative otorrhea is present. Small traumatic TM perforations often heal spontaneously, but it is important to evaluate and monitor the patient's hearing to ensure that spontaneous healing occurs. If the TM does not heal within several months, surgical graft repair should be considered. If a perforation is present, otorrhea can occur from water entering the middle ear from the ear canal during swimming or bathing; appropriate precautions should be taken. Perforations resulting from penetrating foreign bodies are less likely to heal than those caused by compression. Audiometric examination reveals a conductive hearing loss, with larger air-bone gaps seen in larger perforations. Immediate surgical exploration may be indicated if the injury is accompanied by one or more of the following: vertigo, nystagmus, severe tinnitus, moderate to severe hearing loss, or cerebrospinal fluid (CSF) otorrhea. At the time of exploration, it is necessary to inspect the ossicles, especially the stapes, for possible dislocation or fracture and to clear sharp objects that might have penetrated the oval or round windows. Sensorineural hearing loss results if the stapes subluxates or dislocates into the oval window or if either the oval or round window is penetrated. Children should not be given access to cotton-tipped applicators, because the applicators commonly cause ear trauma. Contact with small objects should be limited to times of parental supervision.

Perilymphatic fistula can occur after barotrauma or an increase in CSF pressure. It should be suspected in a child who develops a sudden SNHL or vertigo after physical exertion, deep water diving, air travel, playing a wind instrument, or significant head trauma. The leak characteristically is at the oval (Fig. 683.1) or the round window and may be associated with congenital abnormalities of these structures or an anatomic abnormality of the cochlea or semicircular canals. Perilymphatic fistulas occasionally close

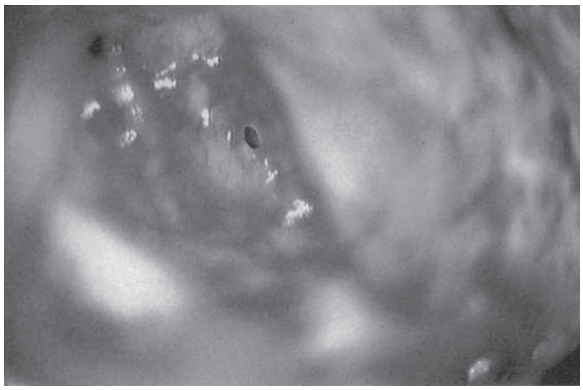

Fig. 683.1 Intraoperative view of traumatic oval window perilymphatic fistula. *(From Kim SH, Kazahaya K, Handler SD. Traumatic perilymphatic fistulas in children: etiology, diagnosis and management. Int J Pediatr Otorhinolaryngol. 2001;60:147–153, Fig. 2.)*

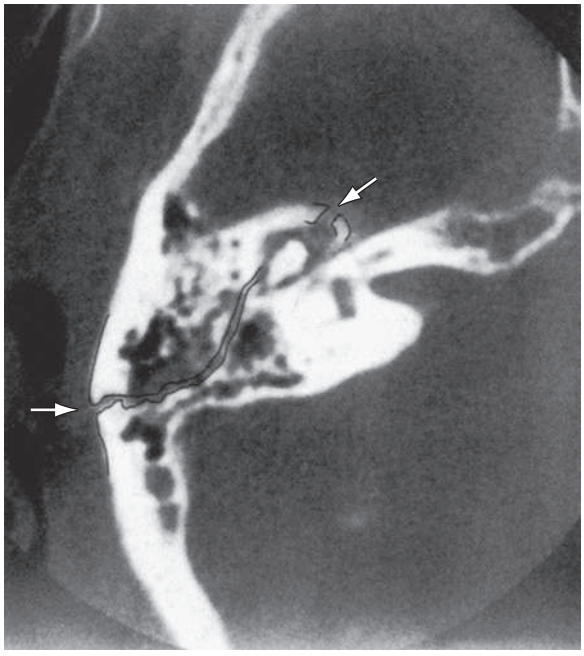

Fig. 683.2 High-resolution axial CT of uncomplicated longitudinal fracture *(arrows)*. A hematoma is present. The course of the fracture has been highlighted. *(From Schubiger O, Valavanis A, Stuckman G, et al. Temporal bone fractures and their complications: examination with high resolution CT. Neuroradiology. 1986;28:93–99.)*

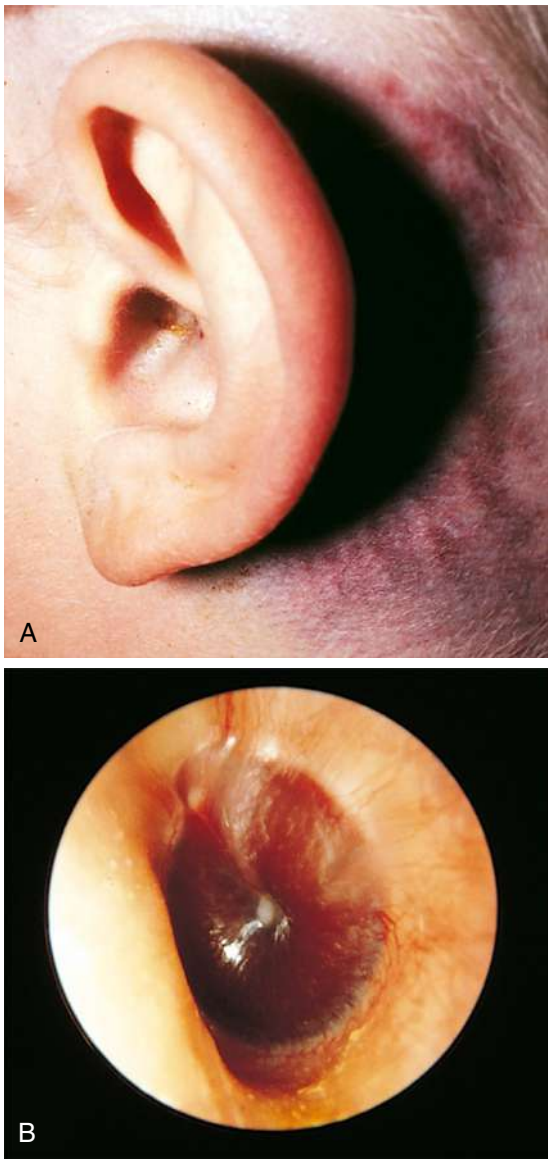

Fig. 683.3 Basilar skull fracture. **A,** Basilar skull fracture involving the temporal bone is often signaled by postauricular ecchymotic discoloration, termed the *Battle sign*. **B,** The force of the blow may also cause tearing of the ear canal or, as shown here, middle ear hemorrhage with hemotympanum. Depending on the timing of examination, this may appear red or blue. *(**B** courtesy Michael Hawke, MD; from Zitelli BJ, McIntire SC, Nowalk AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 7th ed. Philadelphia: Elsevier; 2018: Fig. 24-15, p. 874.)*

spontaneously, but immediate surgical repair of the fistula is recommended to control vertigo and to stop any progression of the SNHL; even timely surgery does not usually restore the SNHL. No reliable test is known for perilymphatic fistula, so middle-ear exploration is required for diagnosis and treatment.

TEMPORAL BONE FRACTURES

Children are particularly prone to basilar skull fractures, which usually involve the temporal bone. Temporal bone trauma should be considered in head injuries, and the status of the ear and hearing should be evaluated. Temporal bone fractures are divided into longitudinal (70–80%), transverse (10–20%), and mixed. Longitudinal fractures (Fig. 683.2) are commonly manifested by bleeding from a laceration of the external canal or TM; postauricular ecchymosis **(Battle sign)**; **hemotympanum** (blood behind an intact TM); conductive hearing loss resulting from TM perforation, hemotympanum, or ossicular injury; delayed onset of facial paralysis (which usually improves spontaneously); and temporary CSF otorrhea or rhinorrhea (from CSF running down the eustachian tube) (Fig. 683.3). Transverse fractures of the temporal bone have a graver prognosis than longitudinal fractures and are often associated with immediate facial paralysis and damage to the labyrinth or internal auditory canal. Facial paralysis might improve if caused by edema, but surgical decompression of the nerve is often recommended if there is no evidence of clinical recovery and facial nerve studies are unfavorable. If the facial nerve has been transected, surgical decompression and anastomosis offer the possibility of some functional recovery. Transverse fractures are also associated with severe SNHL, vertigo, nystagmus, tinnitus, nausea, and vomiting associated with

loss of cochlear and vestibular function; hemotympanum; rarely, external canal bleeding; and CSF otorrhea, either in the external auditory canal or behind the TM, which can exit the nose via the eustachian tube.

If temporal bone fracture is suspected or seen on radiographs, gentle examination of the pinna and ear canal is indicated; lacerations or avulsion of soft tissue is common with temporal bone fractures. Vigorous removal of external auditory canal blood clots or tympanocentesis is not indicated, because removing the clot can further dislodge the ossicles or reopen CSF leaks. The effectiveness of prophylactic antibiotics to prevent meningitis in patients with basilar skull fractures and CSF otorrhea or rhinorrhea cannot be determined because studies to date are flawed by biases. If a patient is afebrile and the drainage is not cloudy, watchful waiting without antibiotics is indicated. Surgical intervention is reserved for children who require repair of a nonhealing TM perforation, who have suffered dislocation of the ossicular chain, or who need decompression of the facial nerve. SNHL can also follow a blow to the head without an obvious fracture of the temporal bone (labyrinthine concussion).

ACOUSTIC TRAUMA

Acoustic trauma results from exposure to high-intensity sound (fireworks, gunfire, loud music, heavy machinery) and is initially manifested by a temporary decrease in the hearing threshold, most commonly at 4,000 Hz on an audiometric examination, and tinnitus. If the sound is between 85 and 140 dB, the loss is usually temporary (after a rock concert), but both the hearing loss and the tinnitus can become permanent with chronic noise exposure; the frequencies from 3,000-6,000 Hz are most often involved. Sudden, extremely loud (>140 dB), short-duration noises with loud peak components (gunfire, bombs) can cause permanent hearing loss after a single exposure. Noise-induced hearing loss results from interactions between genes and the environment. A meta-analysis demonstrated that loud music exposure resulted in increased hearing thresholds and decreased otoacoustic emissions in children and adolescents. Ear protection and avoidance of chronic exposure to loud noise are preventive measures. Hearing loss from chronic noise exposure should be entirely preventable. Parents should be made aware of the dangers of acoustic trauma, from the environment and from the use of headphones, and should take measures to minimize exposure. Treatment with high-dose steroids for 1-2 weeks should be considered to treat acute hearing loss related to noise trauma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 684

Tumors of the Ear and Temporal Bone

Joseph Haddad Jr.

Benign tumors of the external canal include osteomas and monostotic and polyostotic fibrous dysplasia. Osteomas are usually unilateral and located lateral in the bony canal; they require removal only if hearing is impaired or external otitis results. Exostoses (see Chapter 550.2), or localized bony hyperplasias, may be confused with osteomas; however, exostoses are usually bilateral and located in the region of the annulus of the tympanic membrane. Masses occurring over the mastoid bone, such as first branchial cysts, dermoid cysts, and lipomas, may be confused with primary mastoid tumors; imaging can help with the diagnosis and treatment plan.

Eosinophilic granuloma, which can occur in isolation or as part of systemic Langerhans cell histiocytosis (see Chapter 556.1), should be suspected in patients with otalgia, otorrhea (sometimes bloody), hearing loss, abnormal tissue within the middle ear or ear canal, and roentgenographic findings of a sharply delineated destructive lesion of the temporal bone. Definitive diagnosis is made by biopsy. Treatment depends on the site of the lesion and histology. Depending on the site, it may be treated by surgical excision, curettage, or local radiation. If the lesion is part of a systemic presentation of Langerhans cell histiocytosis, chemotherapy in addition to local therapy (surgery with or without radiation) is indicated. Long-term follow-up is necessary whether the temporal bone lesion is a single isolated lesion or part of a multisystem disease.

Rhabdomyosarcoma is the most common malignancy of the temporal bone in children. Symptoms and signs of rhabdomyosarcoma (see Chapter 549) originating in the middle ear or ear canal include a mass or polyp in the middle ear or ear canal, bleeding from the ear, otorrhea, otalgia, facial paralysis, and hearing loss. Other cranial nerves also may be involved. Diagnosis is based on biopsy, but the extent of disease is determined by both CT and MRI of the temporal and facial bones, skull base, and brain (Fig. 684.1).

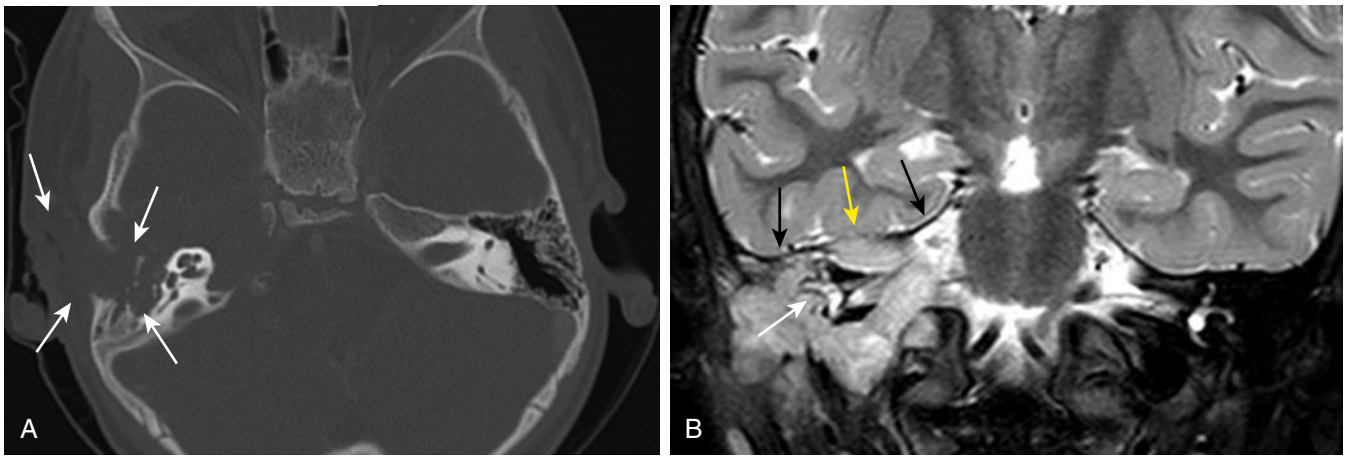

Fig. 684.1 Rhabdomyosarcoma in a 2-yr-old male with hearing loss and right periauricular swelling. A, Axial CT shows a large soft tissue mass of the right temporal bone *(arrows)* with extensive osseous destruction. B, Coronal STIR MR image shows hyperintense mass of the right temporal bone. Focal loss of integrity of the floor of the right middle cranial fossa *(yellow arrow)* and intact dura *(black arrows)* are shown. Destruction of the bony labyrinth *(white arrow)* by the mass. *(Modified from Koral K. Neoplasia. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed, Philadelphia: Elsevier; 2019: Fig. 12.1.)*

Management usually involves a combination of chemotherapy, radiation, and surgery.

Non-Hodgkin lymphoma (see Chapter 545.2) and leukemia (see Chapter 544) also occur rarely in the temporal bone. Although primary neoplasms of the middle ear are very uncommon in children, they include adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma. Benign tumors of the temporal bone include glomus tumors. The initial signs and symptoms of the more common nasopharyngeal neoplasms (angiofibroma, rhabdomyosarcoma, epidermoid carcinoma) may be associated with insidious onset of chronic otitis media with effusion (often unilateral). A high index of suspicion is needed for diagnosing these tumors early.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

The Skin

PART XXIX

Chapter 685

Morphology of the Skin

Julie M. Dhossche and Yvonne E. Chiu

EPIDERMIS

The mature epidermis is a stratified epithelial tissue composed predominantly of keratinocytes (Fig. 685.1). The epidermis protects the organism from the external environment through physical, chemical, and immunologic barrier functions and prevents water loss. Epidermal differentiation results in the formation of a functional barrier to the external world. The epidermis comprises four histologically recognizable layers, described here from deepest to most superficial. The first or **basal layer** consists of columnar cells that rest on the dermal-epidermal junction. Basal keratinocytes are connected to the dermal-epidermal junction by hemidesmosomes. Basal keratinocytes are attached to themselves and to the cells in the spinous layer by desmosomal, tight, gap, and adherens junctions. The role of the basal keratinocyte is to serve as a continuing supply of keratinocytes for the normally differentiating epidermis and as a reservoir of cells to repair epidermal damage. The second layer is the **spinous layer**, composed of three to four layers of spinous cells. Their role is to synthesize keratin, which makes up the keratin intermediate filament network. The third layer is the **granular layer**, which consists of two to three layers of granular cells. Granular cells contain keratohyalin and lamellar granules, containing the protein and lipid components that make up the cornified layer. The fourth layer, or **cornified layer**, is composed of multiple layers of dead, highly compacted cells. The dead cells are composed mainly of disulfide-bonded keratins cross-linked by filaggrins. The intercellular spaces are composed of hydrophobic lipids, predominantly ceramides, cholesterol, and fatty acids, serving as an effective barrier against water and salt loss as well as permeation of water-soluble substances. As the cornified layer is replenished, the oldest or most superficial layer is shed in a highly regulated process. The normal process of epidermal differentiation, from basal cell to shedding of the cornified layer, takes 28 days.

The epidermis also contains three other cell types. The **melanocytes** are pigment-forming cells, which are responsible for skin color and protection from ultraviolet radiation. Epidermal melanocytes are derived from the neural crest and migrate to the skin during embryonic life. They reside in the interfollicular epidermis and in the hair follicles. Melanocytes produce intracellular organelles (melanosomes) containing melanin, which they transfer via dendrites to the keratinocytes to protect the keratinocyte nucleus from ultraviolet damage. **Merkel** cells are type I slow-adapting mechanosensory receptors for touch that differentiate within the epidermis from epidermal progenitor cells. **Langerhans** cells are dendritic cells of the mononuclear phagocyte system and are uniquely characterized by a specific organelle, the Birbeck granule, which resembles a tennis racket on electron microscopy. These cells are derived from bone marrow and participate in immune reactions in the skin, playing an active part in antigen presentation and processing.

The junction of the epidermis and dermis is the basement membrane zone. This complex structure is a result of contributions from both epidermal and mesenchymal cells. The dermal-epidermal junction extends from the basal cell plasma membrane to the uppermost region of the dermis. Ultrastructurally, the basement membrane appears as a trilaminar structure, consisting of a lamina lucida immediately adjacent to the basal cell plasma membrane, a central lamina densa, and the subbasal lamina on the dermal side of the lamina densa. Several structures within this zone act to anchor the epidermis to the dermis. The plasma membrane of basal cells contains electron-dense plates known as *hemidesmosomes;* tonofilaments course within basal cells to insert at these sites. The **hemidesmosomes** are composed of 180- and 230-kDa bullous pemphigoid antigens (BP180 [BPAG2, type XVII collagen] and BP230 [BPAG1], respectively), $\alpha_6\beta_4$ and $\alpha_3\beta_1$ integrins, and plectin. Anchoring filaments originate in the plasma membrane, primarily near the hemidesmosomes, and insert into the lamina densa. Anchoring fibrils, composed predominantly of type VII collagen, extend from the lamina densa into the uppermost dermis, where they loop through collagen fibrils before reinserting into the lamina densa.

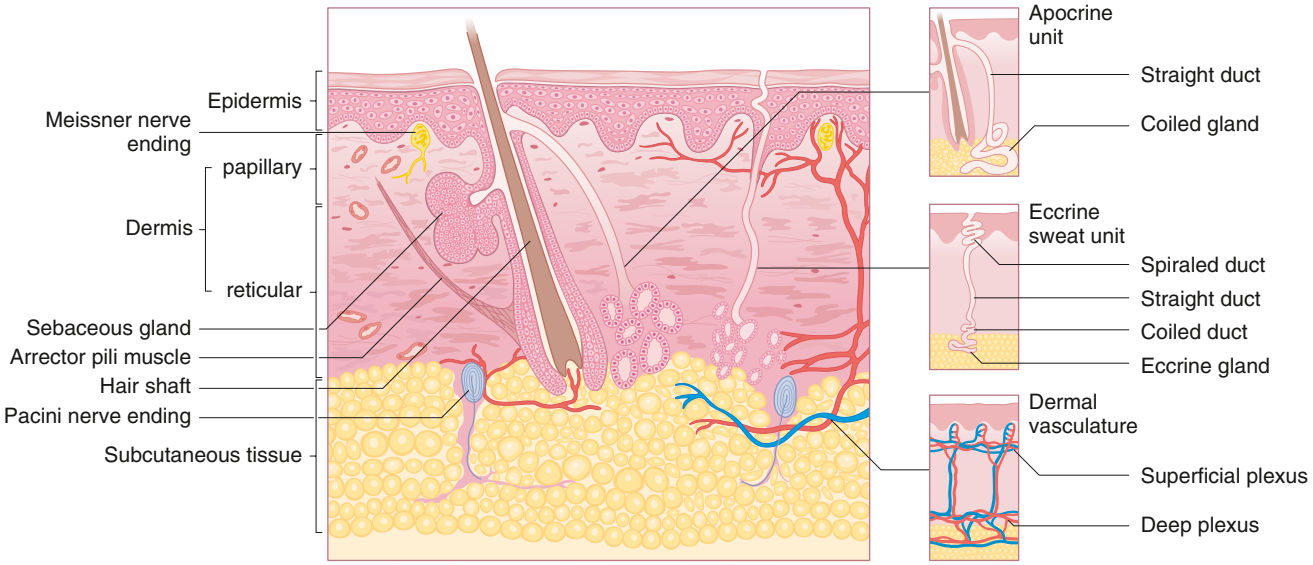

Fig. 685.1 Schematic of skin structure. *(From James WD, Berger T, Elston D. Andrews' Diseases of the Skin: Clinical Dermatology, 12th ed. Philadelphia: Elsevier; 2016: Fig. 1.1.)*

DERMIS

The dermis provides the skin with most of its mechanical properties (see Fig. 685.1). The dermis forms a tough, pliable, fibrous supporting structure between the epidermis and the subcutaneous fat. The predominant dermal cell is a spindle-shaped fibroblast that is responsible for the synthesis of collagen, elastic fibers, and mucopolysaccharides. Phagocytic histiocytes, mast cells, and motile leukocytes are also present. Within the dermis are blood vessels, lymphatics, neural structures, eccrine and apocrine sweat glands, hair follicles, sebaceous glands, and smooth muscle. Morphologically, the dermis can be divided into two layers: the superficial papillary layer that interdigitates with the rete ridges of the epidermis and the deeper reticular layer that lies beneath the papillary dermis. The papillary layer is less dense and more cellular, whereas the reticular layer appears more compact because of the coarse network of interlaced collagen and elastic fibers.

The extracellular matrix of the dermis consists of collagen and elastic fibers embedded in an amorphous ground substance. Collagen provides strength and stability to the dermis, and elastic fibers allow for elasticity. The gelatinous ground substance serves as a supporting medium for the fibrillar and cellular components and as a storage place for a substantial portion of body water.

SUBCUTANEOUS TISSUE

The **panniculus**, or subcutaneous tissue, consists of fat cells and fibrous septa that divide it into lobules and anchor it to the underlying fascia and periosteum (see Fig. 685.1). Blood vessels and nerves are also present in this layer, which serves as a storage depot for lipid, an insulator to conserve body heat, and a protective cushion against trauma.

APPENDAGEAL STRUCTURES

Appendageal structures are derived from aggregates of epidermal cells that become specialized during early embryonic development. Small buds (primary epithelial germs) appear in the third fetal month and give rise to hair follicles, sebaceous and apocrine glands, and the attachment bulges for the arrector pili muscles. Eccrine sweat glands are derived from separate epidermal downgrowths that arise in the second fetal month and are completely formed by the fifth month. Formation of nails is initiated in the third intrauterine month.

Hair Follicles

The pilosebaceous unit includes the hair follicle, sebaceous gland, arrector pili muscle, and, in areas such as the axillae, an apocrine gland. Hair follicles are distributed throughout the skin, except in the palms, soles, lips, and glans penis. Individual follicles extend from the surface of the epidermis to the deep dermis (see Fig. 685.1). The hair follicle is divided into four segments: the infundibulum, which extends from the skin surface to the opening of the sebaceous duct; the isthmus, extending from the sebaceous duct opening to the bulge; the lower follicle between the bulge and the hair bulb; and the hair bulb. The bulge is at the insertion of the arrector pili muscle and is a focus of epidermal stem cells. The bulb is where the matrix cells and the dermal papilla are involved in formation and maintenance of the hair. The growing hair consists of the hair shaft, made of dead keratinocytes, and its supporting inner and outer root sheaths.

Human hair growth is cyclic, with alternate periods of growth (anagen), transition (catagen), and rest (telogen). The length of the anagen phase varies from months to years, whereas catagen and telogen last approximately 3 weeks and 3 months, respectively. At birth, all hairs are in the anagen phase. Subsequent generative activity lacks synchrony, so an overall random pattern of growth and shedding prevails. At any time, approximately 85% of hairs are in the anagen phase. Scalp hair usually grows about 1 cm per month.

The types of hair are lanugo, vellus, and terminal hairs. **Lanugo hair** is thin and short; this hair is shed in utero and is replaced by vellus hair by 36-40 weeks of gestation. **Vellus hair** is short, soft, frequently unpigmented, and distributed over the body. **Terminal hair** is long and coarse and is found on the scalp, beard, eyebrows, eyelashes, and axillary and pubic areas. During puberty, androgenic hormone stimulation causes pubic, axillary, and beard hair to change from vellus hair to terminal hair.

Sebaceous Glands

Sebaceous glands occur in all areas except the palms, soles, and dorsal feet and are most numerous on the head, upper chest, and back (see Fig. 685.1). Their ducts open into the hair follicles except on the eyelids, lips, nipples, prepuce, and labia minora, where they emerge directly onto the skin surface. These holocrine glands are saccular structures that are often branched and lobulated and consist of a proliferative basal layer of small flat cells peripheral to the central mass of lipidized cells. The latter cells disintegrate as they move toward the duct and form the lipid secretion known as *sebum,* which consists of triglycerides, wax esters, squalene, and cholesterol esters. The purpose of sebum production likely relates to hydrophobic skin barrier function. Sebaceous glands depend on hormonal stimulation and are activated by androgens at puberty. Fetal sebaceous glands are stimulated by maternal androgens, and their lipid secretion, together with desquamated stratum corneum cells, constitutes the vernix caseosa.

Apocrine Glands

The apocrine glands are located in the axillae, areolae, perianal and genital areas, and periumbilical region (see Fig. 685.1). These large, coiled, tubular structures continuously secrete an odorless milky fluid that is discharged in response to adrenergic stimuli, usually because of emotional stress. Bacterial biotransformation of apocrine sweat components (fatty acids, thioalcohols, and steroids) accounts for the unpleasant odor associated with perspiration. Apocrine glands remain dormant until puberty, when they enlarge and secretion begins in response to androgenic activity. The secretory coil of the gland consists of a single layer of cells enclosed by a layer of contractile myoepithelial cells. The duct is lined with a double layer of cuboidal cells and opens into the pilosebaceous complex.

Eccrine Sweat Glands

Eccrine sweat glands are distributed over the entire body surface and are most abundant on the palms and soles (see Fig. 685.1). Those on the hairy skin respond to thermal stimuli and serve to regulate body temperature by delivering water to the skin surface for evaporation; in contrast, sweat glands on the palms and soles respond mainly to psychophysiologic stimuli.

Each eccrine gland consists of a secretory coil located in the reticular dermis or subcutaneous fat and a secretory duct that opens onto the skin surface. Sweat pores can be identified on the epidermal ridges of the palm and fingers with a magnifying lens but are not readily visualized elsewhere. Two types of cells constitute the single-layered secretory coil: small dark cells and large clear cells. These rest on a layer of contractile myoepithelial cells and a basement membrane. The glands are supplied by sympathetic nerve fibers, but the pharmacologic mediator of sweating is acetylcholine rather than epinephrine. Sweat from these glands consists of water; sodium; potassium; calcium; chloride; phosphorus; lactate; and small quantities of iron, glucose, and protein. The composition varies with the rate of sweating but is always hypotonic in normal children.

Nails

Nails are specialized protective epidermal structures that form convex, translucent, tight-fitting plates on the distal dorsal surfaces of the fingers and toes. The nail plate, which is derived from a metabolically active matrix of multiplying cells situated beneath the posterior nail fold, is composed of anucleate keratinocytes. Nail growth is relatively slow; complete fingernail regrowth takes 6 months, and complete toenail regrowth requires 12-18 months. The nail plate is bounded by the lateral and posterior nail folds; a thin eponychium (the cuticle) protrudes from the posterior fold over a crescent-shaped white area called the *lunula.* The eponychium serves as a sealant barrier to protect the germinal matrix of the nail plate. The hyponychium refers to the volar surface epithelium of the distal digit and seals the nail bed distally. The pink color beneath the nail reflects the underlying vascular bed. Nail health relies on several factors, including nutrition, hydration, local infection/irritation, and systemic disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 686

Dermatologic Evaluation of the Patient

Julie M. Dhossche and Yvonne E. Chiu

HISTORY AND PHYSICAL EXAMINATION

A history and careful physical examination are often necessary for accurate assessment of skin disorders. A good skin exam is essential in dermatologic evaluation and should be performed under adequate illumination. In addition to the skin covering the entire body surface, mucous membranes (conjunctiva, oropharynx, nasal mucosa, and anogenital mucosa), hair, and nails should be examined when appropriate. The color, turgor, texture, temperature, and moisture of the skin and the growth, texture, caliber, and luster of the hair and nails should be noted. Erythema or other color changes may be challenging to appreciate in children with darker skin tones, and other features of the disorder should be relied upon to make the diagnosis. Skin lesions should be palpated, inspected, and classified on the basis of morphology, size, color, texture, firmness, configuration, location, and distribution. One must also decide whether the changes are those of the *primary* lesion itself or whether the clinical pattern has been altered by a *secondary* factor such as infection, trauma, or therapy.

Primary lesions are classified as macules, papules, patches, plaques, nodules, tumors, vesicles, bullae, pustules, wheals, and cysts. A **macule** represents an alteration in skin color but cannot be felt. When the lesion is >1 cm, the term **patch** is used. **Papules** are palpable solid lesions <1 cm. **Plaques** are palpable lesions >1 cm in size and have a flat surface. **Nodules** are palpable lesions >1 cm with a rounded surface. The word **tumor** may be used for a large nodule that is suspected to be neoplastic in origin. **Vesicles** are raised, fluid-filled lesions <1 cm in diameter; when larger, they are called **bullae**. **Pustules** are fluid-filled lesions containing purulent material. **Wheals** are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collections of edema fluid. **Cysts** are circumscribed, thick-walled lesions; they are covered by a normal epidermis and contain fluid or semisolid material.

Primary lesions may change into secondary lesions, or secondary lesions may develop over time where no primary lesion existed. Primary lesions are usually more helpful for diagnostic purposes than secondary lesions. Secondary lesions include scales, purpura, petechiae, ulcers, erosions, excoriations, fissures, crusts, and scars. **Scales** consist of compressed layers of stratum corneum cells that are retained on the skin surface. **Purpuras** are the result of bleeding into the skin and have a red-purple color; they may be flat or palpable. **Petechiae** are small (<2-3 mm) purpura. **Erosions** involve focal loss of the epidermis, and they heal without scarring. **Ulcers** extend into the dermis and tend to heal with scarring. Ulcerated lesions inflicted by scratching are often linear or angular in configuration and are called **excoriations**. **Fissures** are caused by splitting or cracking. **Crusts** consist of matted, retained accumulations of blood, serum, pus, and epithelial debris on the surface of a weeping lesion. **Scars** are end-stage lesions that can be thin, depressed, and atrophic; raised and hypertrophic; or flat and pliable. **Lichenification** is a thickening of skin with accentuation of normal skin lines that is caused by chronic irritation (rubbing, scratching) or inflammation.

If the diagnosis is not clear after a thorough examination, one or more diagnostic procedures may be indicated.

BIOPSY OF SKIN

Biopsy of skin is occasionally required for diagnosis. The two most commonly used approaches are the shave biopsy and the punch biopsy. A shave biopsy is primarily used for superficial, raised lesions, whereas a punch biopsy is used when it is indicated to sample the dermis and subcutaneous tissue, as with most inflammatory dermatoses. Both are simple, relatively painless procedures and usually provide adequate tissue for examination if the appropriate lesion is sampled. The selection of a fresh, well-developed primary lesion is extremely important to obtain an accurate diagnosis. In cases of a punch biopsy, the site of the biopsy should have relatively low risk for damage to underlying dermal structures. After cleansing of the site, the skin is anesthetized by intradermal injection of 1–2% lidocaine, with or without epinephrine, with a 27- or 30-gauge needle. For a shave biopsy, a double-edged razor or scalpel is used to remove a thin disk of tissue down to the upper dermis. Hemostasis can be obtained with 20% aluminum chloride solution, and the biopsy site is then covered with petroleum jelly and a bandage. In the case of a punch biopsy, after anesthetizing the skin, a punch tool, usually 3 or 4 mm in diameter, is pressed firmly against the skin and rotated until it sinks to the proper depth. All three layers (epidermis, dermis, and subcutis) should be contained in the plug. The plug should be lifted gently with forceps or extracted with a needle and separated from the underlying tissue with iris scissors. Bleeding abates with firm pressure and with suturing. The biopsy specimen should be placed in 10% formaldehyde solution (Formalin) for appropriate processing.

WOOD LAMP

A Wood lamp emits ultraviolet light mainly at a wavelength of 365 nm. A skin examination under a Wood lamp, which is performed in a darkened room, is useful in accentuating changes in pigmentation and detecting fluorescence in certain infectious disorders. Discrete areas of altered pigment can often be visualized more clearly by using a Wood lamp, particularly if the pigmentary change is epidermal. Hyperpigmented lesions appear darker, and hypopigmented lesions (e.g., those seen in **tuberous sclerosis**) lighter than the surrounding skin. Blue-green fluorescence is detectable at the base of each infected hair shaft in ectothrix infections, such as tinea capitis caused by *Microsporum* species. Scales and crusts may appear pale yellow, but this color is not evidence of a fungal infection. Dermatophyte lesions of the skin (tinea corporis) do not fluoresce; macules of tinea versicolor have a golden fluorescence under a Wood lamp. **Erythrasma**, an intertriginous infection caused by *Corynebacterium minutissimum,* may fluoresce pink-orange, whereas *Pseudomonas aeruginosa* is yellow-green under a Wood lamp.

POTASSIUM HYDROXIDE PREPARATION

Potassium hydroxide (KOH) preparation is a rapid and reliable method for detecting fungal elements of both yeasts and dermatophytes. Scaly lesions should be scraped at the active border for optimal recovery of mycelia and spores. Vesicles should be unroofed, and the blister roof should be clipped and placed on a slide for examination. In tinea capitis, infected hairs must be plucked from the follicle; scales from the scalp do not usually contain mycelia. A few drops of 20% KOH are added to the specimen. Dimethyl sulfoxide is usually in solution with the KOH, negating the need to heat the specimen. If using KOH without dimethyl sulfoxide, the specimen is gently heated over an alcohol lamp or on a hot plate until the KOH begins to bubble. Alternatively, sufficient time (10-20 minutes) can be allowed for dissolution of the keratin at room temperature. The preparation is examined under low-intensity light microscopy for fungal elements.

TZANCK SMEAR

Tzanck smear had been useful in the diagnosis of infections caused by herpes simplex virus or varicella-zoster virus and for the detection of acantholytic cells in pemphigus. An intact, fresh vesicle is ruptured and drained of fluid. The roof and base of the blister are then carefully scraped with a No. 15 scalpel blade, with care taken to avoid drawing a significant amount of blood; the material is smeared on a clear glass slide and air dried. Staining with Giemsa stain is preferable, but Wright stain is acceptable. Balloon cells and multinucleated giant cells are diagnostic of herpes virus infection; acantholytic epidermal cells—large round epidermal cells with hypertrophic nuclei—are characteristic of pemphigus.

Table 686.1 Immunofluorescence Findings in Immune-Mediated Cutaneous Diseases

DISEASE	INVOLVED SKIN	UNINVOLVED SKIN	DIRECT IF FINDINGS	INDIRECT IF FINDINGS	CIRCULATING ANTIBODIES
Dermatitis herpetiformis	Negative	Positive	Granular IgA ± C in papillary dermis	None	IgA antiendomysial and transglutaminase antibodies
Bullous pemphigoid	Positive	Positive	Linear IgG and C band in BMZ, occasionally IgM, IgA, IgE	IgG to BMZ	IgG anti-BP180 and anti-BP230
Pemphigus (all variants)	Positive	Positive	IgG in intercellular spaces of epidermis between keratinocytes	IgG to intercellular spaces of epidermis between keratinocytes	IgG antidesmoglein 1 and 3 (pemphigus vulgaris and foliaceus). IgA antidesmocollin 1 (IgA pemphigus)
Linear IgA bullous dermatosis (chronic bullous dermatosis of childhood)	Positive	Positive	Linear IgA at BMZ, occasionally C	Low titer, rare IgA, anti-BP180	None
Discoid lupus erythematosus	Positive	Negative	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	Usually ANA-negative
Systemic lupus erythematosus	Positive	Variable; 30–50% of sun-exposed skin; 10–30% of photoprotected skin	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	ANA Anti-Ro (SSA), anti-La (SSB) Anti-RNP Anti-dsDNA Anti-Sm
IgA vasculitis (Henoch-Schönlein purpura)	Positive	Positive	IgA around vessel walls	None	None

ANA, Antinuclear antibody; BMZ, basement membrane zone at the dermal-epidermal junction; BP, bullous pemphigoid; C, complement; dsDNA, double-stranded deoxyribonucleic acid; IF, immunofluorescence; Ig, immunoglobulin; Sm, Smith; SSA/SSB, Sjögren syndrome A/B; RNP, ribonucleoprotein.

Direct fluorescent assay and polymerase chain reaction tests have largely replaced Tzanck smears in the diagnosis of herpes simplex and varicella-zoster infections. Both of these are rapid, sensitive, and specific, with the polymerase chain reaction even more so. When obtaining specimens for these tests, the vesicles should be ruptured before sample collection with the swab.

IMMUNOFLUORESCENCE STUDIES

Immunofluorescence studies of skin can be used to detect tissue-fixed antibodies to skin components and complement; characteristic staining patterns are specific for certain skin disorders (Table 686.1). Direct immunofluorescence detects autoantibodies bound to cutaneous antigens in the skin, and indirect immunofluorescence detects circulating autoantibodies present in the serum.

Skin biopsy specimens for direct immunofluorescence should be obtained from involved sites except in those diseases for which perilesional skin or uninvolved skin is required. A punch biopsy sample is obtained, and the tissue is placed in a special transport medium or immediately frozen in liquid nitrogen for transport or storage. Thin cryostat sections of the specimen are incubated with fluorescein-conjugated antibodies to the specific antigens.

Serum of patients can be examined by indirect immunofluorescence techniques using sections of normal human skin, guinea pig lip, or monkey esophagus as substrate. The substrate is incubated with fresh or thawed frozen serum and then with fluorescein-conjugated antihuman globulin. If the serum contains antibody to epithelial components, its specific staining pattern can be seen on fluorescence microscopy. By serial dilution, the titer of circulating antibody can be estimated.

686.1 Cutaneous Manifestations of Systemic Diseases

Julie M. Dhossche and Yvonne E. Chiu

Selected diseases have signature skin findings, often as the presenting signs of illness, which can facilitate the assessment of patients with complex medical states (Table 686.2).

CONNECTIVE TISSUE DISEASES

Lupus Erythematosus

Lupus erythematosus (LE; see Chapter 199) is an idiopathic autoimmune inflammatory disease that may be multisystemic (i.e., systemic LE or SLE) or confined to the skin. Distinct cutaneous lupus subtypes seen in children include acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE (including discoid LE, discussed under "Discoid Lupus Erythematosus"), and neonatal LE (discussed under "Neonatal Lupus Erythematosus").

Systemic Lupus Erythematosus

SLE is a chronic inflammatory multisystem disease with approximately 15–20% of cases diagnosed in childhood. It is diagnosed when 4 of 11 well-defined clinical and 6 immunologic criteria are present (see Chapter 199), where both one clinical and one immunologic criterion each must be met. Four of the clinical criteria are skin findings. **Criterion 1** is acute cutaneous lupus, which may involve the classic malar or "butterfly" rash (Fig. 686.1), bullous lupus lesions, psoriasiform and/or annular polycyclic lupus lesions that resolve without scarring, and photosensitive erythematous macular or papular eruption (Fig. 686.2).

Table 686.2 Characteristics of Cutaneous Signs of Systemic Diseases

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIATED SYMPTOMS/ SIGNS	DIFFERENTIAL DIAGNOSIS
Systemic lupus erythematosus	Any	Erythematous patches and plaques; palpable purpura; livedo reticularis; Raynaud phenomenon; urticaria	Photodistribution; "malar" face	ANA panel Anti-dsDNA Leukopenia/ lymphopenia Thrombocytopenia Complement levels Urinalysis	Arthritis Nephritis Cerebritis Serositis	Seborrheic dermatitis Atopic dermatitis Juvenile dermatomyositis
Discoid lupus erythematosus	Any	Annular, scaly plaques; atrophy; dyspigmentation	Photodistribution	ANA	Scarring	Subacute cutaneous lupus Polymorphous light eruption Juvenile dermatomyositis
Neonatal lupus erythematosus	Newborn	Annular, erythematous, scaly plaques	Head/neck	ANA Anti-Ro (SSA), anti-La (SSB)	Heart block Thrombocytopenia	Tinea capitis Atopic dermatitis Seborrheic dermatitis
Juvenile dermatomyositis	Any	Erythematous to violaceous scaly macules; discrete papules overlying joints	Periocular face; shoulder girdle; extensor extremities	ANA AST ALT Aldolase Creatine kinase Lactate dehydrogenase	Fatigue Proximal muscle weakness Calcifications Vasculopathy	Atopic dermatitis Allergic contact dermatitis Lupus erythematosus
Morphea	Any	Sclerotic plaques; resolve with hyperpigmentation and atrophy	Variable	Skin biopsy MRI brain if head and neck involvement	Neurologic (seizures, migraine headaches, focal neurologic deficits, asymptomatic MRI abnormalities) Musculoskeletal (joint contractures, limb length discrepancy, arthritis, arthralgias)	Systemic sclerosis
IgA vasculitis (Henoch-Schönlein purpura)	Childhood and adolescence	Purpuric papules and plaques	Buttocks; lower extremities	Urinalysis Blood urea nitrogen/ creatinine ratio Skin biopsy	Abdominal pain Arthritis	Vasculitis Drug eruption Infantile hemorrhagic edema Viral exanthem
Kawasaki disease	Infancy, childhood	Erythematous maculopapular to urticarial plaques; acral and groin erythema, edema, desquamation, digital cyanosis / gangrene	Diffuse	Leukocytosis ESR C-reactive protein Thrombocytosis	Strawberry tongue Conjunctivitis Lymphadenopathy Cardiovascular complications	Viral syndrome Drug eruption Staphylococcal/ streptococcal illness
Inflammatory bowel disease	Childhood and adolescence	Aphthae; erythema nodosum; pyoderma gangrenosum; lip swelling	Oral and perianal predominate	Skin biopsy Fecal calprotectin, ESR, CRP Gastroenterology evaluation	Abdominal pain Diarrhea Cramping Arthritis Conjunctivitis	Behçet syndrome Vasculitis *Yersinia* colitis
Sweet syndrome	Any	Infiltrated erythematous, edematous plaques	Head and neck predominate	Skin biopsy Leukocytosis ESR	Fever Flulike illness Conjunctivitis	Infection Urticaria Erythema multiforme Urticarial vasculitis Systemic autoinflammatory diseases*

Continued

Table 686.2 Characteristics of Cutaneous Signs of Systemic Diseases—cont'd

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIATED SYMPTOMS/ SIGNS	DIFFERENTIAL DIAGNOSIS
Graft-versus-host disease	Any	Acute: erythema, papules, vesicles, bullae	Diffuse with predilection for head/neck and palms/soles	Skin biopsy Liver function tests	Fever Mucositis Hepatitis	Drug eruption Infectious exanthem
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Any	Erythema; urticarial macules and plaques	Diffuse	Liver function Eosinophilia Atypical lymphocytosis	Facial edema Lymphadenopathy Fever Hepatitis	Stevens-Johnson syndrome Infectious exanthem
Serum sickness-like reaction (SSLR)	Any	Edematous, urticarial plaques	Diffuse	None	Fever Lymphadenopathy Arthritis, nephritis	Kawasaki disease Urticaria
Multisystem inflammatory syndrome in children (MIS-C) (see Table 686.3)						
Autoinflammatory diseases (see Table 686.4)						

*NOMID, Neonatal-onset multisystem inflammatory disease and other recurrent fever syndromes.
ALT, Alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; SSA/SSB, Sjögren syndrome A/B.



Fig. 686.1 Malar rash of systemic lupus erythematosus.



Fig. 686.2 Photosensitive rash of systemic lupus erythematosus.

The malar rash must be distinguished from other causes of a "red face," most notably seborrheic dermatitis, atopic dermatitis, and rosacea. **Criterion 2** is chronic cutaneous lupus, which includes discoid lupus lesions, hypertrophic (verrucous) lupus lesions, and lupus panniculitis, among others. **Criterion 3** is oral or nasal ulcers in the absence of other causes such as vasculitis, Behçet disease, infection (herpes simplex virus [HSV]), or inflammatory bowel disease. **Criterion 4** is nonscarring alopecia, which may include diffuse thinning or hair fragility in the absence of other causes such as alopecia areata, drugs, or iron deficiency. Patients may meet full SLE criteria based on skin findings alone with one immunologic criterion (such as positive antinuclear antibodies [ANA] or anti-dsDNA). Other associated but not diagnostic cutaneous findings include purpuric lesions, livedo reticularis, Raynaud phenomenon, and urticaria.

On histology, cutaneous LE demonstrates varying degrees of epidermal atrophy, plugging of hair follicles, and a vacuolar alteration at an inflamed dermal-epidermal junction. Deposition of immunoglobulins (IgM, IgG) and complement in lesional skin may help confirm the diagnosis. Immune deposits in nonlesional sun-exposed skin are found in the majority of patients with SLE (lupus band test), although clinical use of this test has been mostly abandoned in favor of serologic testing.

The skin lesions often respond to treatment of the SLE with systemic agents. Oral hydroxychloroquine is used most commonly, but many other systemic therapies are effective, including both classic and biologic immunosuppressants. Low- to mid-potency topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroid injection may be considered for adjunctive therapy for skin lesions. A multispecialty approach is recommended, as pediatric patients are at significantly higher risk for long-term morbidity than adults.

Neonatal Lupus Erythematosus

Neonatal LE (see Chapter 199.1) manifests at birth or during the first few weeks of life as annular, erythematous, scaly plaques, typically on the head, neck, and upper trunk (Fig. 686.3). Telangiectasias are also common. Ultraviolet light may exacerbate or initiate cutaneous lesions. Passive transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies causes the transient skin lesions, though most infants are born to mothers without a known rheumatologic diagnosis.

Table 686.3 Mucocutaneous Findings in Multisystem Inflammatory Syndrome in Children

LOCATION	DESCRIPTORS
Generalized, including: Perineal Trunk Face Ears Periorbital area Extremities	Urticarial Papular Maculopapular Macular Morbilliform Desquamative Edematous Erythematous Purpuric Targetoid Retiform Reticular Scarlatiniform Petechiae Livedoid EM-like RIME-like Lipschultz ulcer
Hands and Feet	Edematous Erythematous Desquamative Purpuric Petechiae
Tongue	Papillitis Strawberry tongue De-epithelialized
Lips	Cracked/fissured Erythematous
Eyes	Injected Swollen Nonpurulent discharge

RIME, Reactive infectious mucocutaneous eruption.
From Neale H, Hawryluk EB. COVID-19 pediatric dermatology. *Dermatol Clin.* 39(4):505–519, Table 1, p. 509.

Table 686.4 Dermatologic Manifestations of Monogenic Autoinflammatory Diseases

I. NONSPECIFIC MACULOPAPULAR RASHES WITH RECURRENT EPISODIC FEVER AND ABDOMINAL PAIN (HEREDITARY PERIODIC FEVER SYNDROME)
A. Recurrent fever attacks of short duration (typically ≤7 days)
1. Familial Mediterranean fever
2. Hyperimmunoglobulinemia D with periodic fever syndrome/ mevalonate kinase deficiency
B. Recurrent fever attacks of longer duration (typically >7 days)
1. Tumor necrosis factor receptor–associated periodic syndrome
II. NEUTROPHILIC URTICARIA (CAPS)
A. Recurrent fever attacks of short duration (typically <24 hours)
1. CAPS/familial cold autoinflammatory syndrome
2. CAPS/Muckle-Wells syndrome
B. Continuous low-grade fever
1. CAPS/neonatal-onset multisystem inflammatory disease/ CINCA
2. IL-18–mediated AID and IL-1–mediated AID: NLRC4-related macrophage activation syndrome
III. PUSTULAR SKIN RASHES AND EPISODIC FEVERS
A. IL-1–mediated pyogenic disorders with sterile osteomyelitis
1. Deficiency of IL-1 receptor antagonist
2. Majeed syndrome
B. Partially IL-1–mediated pyogenic disorders
1. Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome
2. Haploinsufficiency of A20 (monogenic form of Behçet disease)
C. Pyogenic disorders caused by non–IL-1 cytokine dysregulation
1. Deficiency of IL-36 receptor antagonist
2. CARD14-mediated psoriasis (monogenic form of psoriasis)
3. Early-onset inflammatory bowel disease
IV. VASCULOPATHY AND PANNICULITIS/LIPOATROPHY SYNDROMES
A. Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome or proteasome-associated autoinflammatory syndrome
V. VASCULOPATHY AND/OR VASCULITIS WITH LIVEDO RETICULARIS SYNDROMES
A. Without significant CNS disease
1. STING-associated vasculopathy with onset in infancy
B. With severe CNS disease
1. Aicardi-Goutières syndrome
2. Deficiency of adenosine deaminase 2
3. Spondyloenchondrodysplasia with immune dysregulation
VI. AUTOINFLAMMATORY DISORDERS WITH GRANULOMATOUS SKIN DISEASES
A. Without significant immunodeficiency
1. Blau syndrome (pediatric granulomatous arthritis, pediatric granulomatous arthritis)
B. With variable features of immunodeficiency and significant CNS disease
2. PLCγ2-associated antibody deficiency and immune dysregulation: cold-induced urticaria and/or granulomatous rash
VII. OTHER INFLAMMATORY SYNDROMES
A. LACC1-mediated monogenic Still disease

AID, Autoinflammatory disorder; CAPS, cryopyrin-associated periodic syndromes; CINCA, chronic infantile neurologic cutaneous and articular syndrome; CNS, central nervous system; STING, stimulator of interferon genes.
From Shwin KW, Lee CCR, Goldbach-Mansky. Dermatologic manifestations of monogenic autoinflammatory diseases. *Dermatol Clin.* 2017;35:21–38, Box 1, p. 24–25.

Antibody levels wane by 6 months old, generally resulting in clearance of the rash. Congenital heart block occurs in 30% of affected infants, but only 10% of affected infants have both skin and cardiac abnormalities. Noncardiac extracutaneous manifestations, such as anemia, thrombocytopenia, and cholestatic liver disease, are less common. Neonatal LE is often misdiagnosed as infantile eczema, seborrheic dermatitis, or tinea corporis. Skin lesions are typically managed conservatively, given the transient nature of neonatal LE, and strict sun avoidance and protection are important. If necessary, low- to mid-potency topical corticosteroids may be used. Systemic agents should be avoided. Maternal ANA testing is indicated.

Discoid Lupus Erythematosus

Discoid LE (DLE) is uncommon in early childhood and manifests in late adolescence. The signature skin findings in DLE are chronic, erythematous, scaly, atrophic plaques (Fig. 686.4) on sun-exposed skin that frequently heal with scarring and dyspigmentation. Extracutaneous features may include involvement of the nasal and oral mucosa, eyes, and nails. The differential diagnosis includes other photodermatoses, such as polymorphous light eruption, juvenile springtime eruption, and juvenile dermatomyositis (JDM). There is a distinct overlap between SLE and DLE, with common histopathologic features and photoexacerbation; most patients with DLE have normal laboratory results and do not progress to systemic disease.

First-line treatment of DLE consists of low- to mid-potency topical corticosteroids. Other topical options include calcineurin inhibitors and retinoids. Intralesional corticosteroid injection is also effective for severe localized lesions. Oral hydroxychloroquine is used first-line for severe skin disease or as a second-line agent when lesions are not controlled with topical or local agents. Strict ultraviolet light avoidance is important.

Juvenile Dermatomyositis

Characteristic skin findings are often the presenting sign of JDM (see Chapter 200). An ill-defined, erythematous to violaceous, scaly,



Fig. 686.3 Annular plaque in neonatal lupus erythematosus.



Fig. 686.4 Erythematous scaly plaque of discoid lupus erythematosus.



Fig. 686.5 Gottron papules in juvenile dermatomyositis.

minimally pruritic eruption occurs in photodistributed areas such as the face, upper trunk, and extensor extremities. Circumscribed periocular involvement of this **heliotrope** rash involving the eyelids may take the appearance of "raccoon eyes," particularly in young children. Distinctive erythematous, scaly papules overlying the knuckles and other joints **(Gottron papules)** are helpful in suggesting the diagnosis in the absence of associated muscle weakness (Fig. 686.5). Other cutaneous features include nail fold and gingival margin telangiectasia, palmar hyperkeratosis ("mechanic's hands"), ulceration resulting from vasculopathy or underlying calcinosis, lipodystrophy, and a poikilodermatous (dyspigmentation and telangiectasia) eruption over the shoulder girdle ("shawl sign"). Cutaneous features may precede the systemic illness, which is primarily characterized by muscle weakness and pain. The differential diagnosis includes atopic dermatitis, other connective tissue diseases, lichen planus, medication reactions, and infectious exanthems. Pathology of lesional skin demonstrates epidermal atrophy and vacuolar degeneration at the dermal-epidermal junction, often similar to LE. JDM is distinct from adult dermatomyositis in both presentation and prognosis. Pediatric patients have more difficulty with gastrointestinal (GI) vasculopathy and cutaneous calcifications, and JDM is not a paraneoplastic phenomenon as in adults. A rare clinical variant known as **amyopathic dermatomyositis** occurs when only skin, and not muscle, is involved.

Skin lesions benefit from systemic immunosuppressive therapy, as discussed in detail in Chapter 200. Adjunctive treatment options for skin disease include topical corticosteroids and calcineurin inhibitors. The cutaneous calcinosis of JDM is difficult to manage, with a variety of agents showing limited benefit, and no treatment consensus exists. Strict photoprotection and sunlight avoidance are vital to prevent cutaneous exacerbations.

Systemic Sclerosis

Systemic sclerosis is characterized by diffuse skin hardening and thickening, along with systemic features. It frequently manifests as acral (sclerodactyly, ulceration, nail fold telangiectasia, or Raynaud phenomenon) and facial changes (pinched nose, furrowed perioral skin, or "scleroderma facies") (see Chapter 201). Overlap syndromes such as **mixed connective tissue disease** may include some physical and laboratory features of scleroderma.

Morphea

Morphea, also called *localized scleroderma* (see Chapter 201), is another autoimmune connective tissue disease characterized by skin hardening and thickening. The lesions of morphea are generally more localized, and it is a distinct disorder from systemic sclerosis. There are five subtypes of morphea, including circumscribed (plaque), linear, generalized, pansclerotic, and mixed. Though morphea is not characterized by the degree of systemic involvement that systemic sclerosis has, it can have extracutaneous manifestations. Neurologic findings such as seizures, migraine headaches, focal neurologic deficits, and asymptomatic MRI abnormalities are seen in some patients, predominately those with linear morphea of the head and neck. Musculoskeletal complications can include joint contractures, limb length and girth discrepancies, arthritis, and arthralgias, and these are most common in children with linear morphea of a limb.

VASCULITIDES

The vasculitides (see Chapter 210) encompass a broad group of disorders having considerable overlap with connective tissue diseases. Immune-mediated inflammation of blood vessels of varying size may be caused by an underlying inflammatory state, infection, medication, or malignancy. Common clinical features include **palpable nonthrombocytopenic purpuric** skin lesions, arthritis, fever, myalgia, fatigue, and weight loss as well as an elevated erythrocyte sedimentation rate. Extracutaneous organs that may be involved include the joints, lungs, kidneys, and central nervous system.

Henoch-Schönlein Purpura (Immunoglobulin A Vasculitis)

Henoch-Schönlein purpura (see Chapter 210.1) is a vasculitis that manifests in school-age children as palpable purpuric lesions in gravity-dependent areas, predominantly the buttocks and lower extremities (Fig. 686.6). **Infantile hemorrhagic edema (IHE**; also called *acute hemorrhagic edema of infancy*) shares some clinical features with Henoch-Schönlein purpura but appears in infants and toddlers. IHE is characterized by the sudden onset of circumscribed edema with purpuric papules and plaques on the trunk and extremities but, unlike Henoch-Schönlein purpura, commonly affects the face and lacks other organ involvement. Henoch-Schönlein purpura must also be differentiated from infectious causes of purpuric skin lesions, such as meningococcemia, Rocky Mountain spotted fever, and purpuric viral exanthems such as those caused by enteroviruses, as well as from juvenile rheumatoid arthritis and other vasculitides. Diagnosis is



Fig. 686.6 Purpura of the lower leg in IgA vasculitis (Henoch-Schönlein purpura).



Fig. 686.7 Clinical picture of idiopathic Sweet syndrome. *(From Prat L, Bouaziz JD, Wallach D, et al. Neutrophilic dermatoses as systemic diseases. Clin Dermatol. 2014;32:376–388, Fig. 1.)*

confirmed by histologic confirmation of a small vessel vasculitis with the immunofluorescence finding of IgA in blood vessel walls. Skin lesions are generally managed conservatively and self-resolve in 3–4 weeks. Systemic treatment is discussed in detail in Chapter 210.1.

Kawasaki Disease

Kawasaki disease (see Chapter 208) is a common vasculitis usually seen in children younger than age 5 years. The skin eruption of Kawasaki disease is polymorphic, manifesting variously as maculopapular or morbilliform eruptions, urticaria, targetoid lesions, or psoriasiform lesions on the trunk and extremities. Early involvement with erythema and peeling in the perineum/inguinal region may be an initial clue to the diagnosis. Acral edema and desquamation are also prominent features but typically occur later. Classic mucocutaneous features include erythematous cracked lips, nonpurulent conjunctivitis with sparing of the limbus, and lingual plaques ("white strawberry tongue") that shed to produce denuded, erythematous patches with prominent papilla ("strawberry tongue"). Extracutaneous features include high fever, cervical lymphadenopathy, arthritis, and occasionally cardiac or GI disease. First-line treatment is with aspirin and intravenous immunoglobulin, as discussed in Chapter 208. **Multisystem inflammatory syndrome in children (MIS-C)** (Chapter 311) may resemble Kawasaki disease; cutaneous manifestations are noted in Table 686.3.

Behçet Disease

Behçet disease (see Chapter 202) is a multisystem disease that includes oral and genital ulceration and ocular disease (uveitis, relapsing iridocyclitis) in older children and adults. Recurrent aphthous stomatitis is present in almost all patients and is commonly the presenting symptom. Genital ulcerations may resemble aphthae; can occur on the penis, scrotum, or vulva; and may be particularly painful in females. Perianal ulceration is more common in children than in adults. Additional skin findings may include folliculitis, purpuric lesions, erythema nodosum, and pustule formation after venipuncture or skin trauma **(pathergy)**. Differential diagnosis of oral lesions includes recurrent aphthous stomatitis, herpes simplex, and rare oculocutaneous syndromes (e.g., MAGIC [mouth and genital ulcers with inflamed cartilage] syndrome). Skin biopsy demonstrates nongranulomatous vasculitis in all vessel sizes. Oral lesions may respond to swish and spit/swallow preparations variably, including corticosteroids, antihistamines, antibiotics, and analgesics. Skin lesions are managed with topical corticosteroids, topical anesthetics such as sucralfate, and systemic agents as outlined in Chapter 202.

GASTROINTESTINAL DISEASES

Inflammatory Bowel Disease

Inflammatory bowel disease includes ulcerative colitis (see Chapter 382.1) and Crohn disease (see Chapter 382.2). Skin lesions of inflammatory bowel disease are classified as specific or reactive. Specific cutaneous manifestations have the same histologic features and pathologic mechanism as the underlying inflammatory bowel disease lesions and include aphthous ulcers, granulomatous cheilitis, perianal fistulas and fissures, and metastatic Crohn disease (discussed later). Reactive cutaneous manifestations occur secondary to immune-mediated antigen cross reactivity between gut and skin components; examples include erythema nodosum and pyoderma gangrenosum.

Up to 30% of patients with **ulcerative colitis** present with cutaneous manifestations. Aphthous ulcers are common and may worsen with gastrointestinal exacerbations. Erythema nodosum, occurring in up to 10% of patients, manifests as warm, erythematous nodules, often on the distal lower extremities. Pyoderma gangrenosum is a focal, ulcerative process that has distinctive, inflamed, undermined borders and a purulent, boggy center. Thrombophlebitis also occurs at an increased rate in patients with ulcerative colitis.

Crohn disease classically manifests as perianal fissures and skin tags, abscesses, sinuses, and fistulas; these may be presenting signs. Enlargement of the lips and a cobblestone appearance of oral mucosa may also be present, known as *orofacial granulomatosis* or *cheilitis granulomatosa.* As in ulcerative colitis, aphthae, erythema nodosum, and pyoderma gangrenosum occur with increased frequency and may improve with treatment of the underlying disease. Noncaseating granulomatous inflammation is seen on routine histopathology, and when found in skin not contiguous with the intestinal tract, is labeled **metastatic Crohn disease**. Metastatic lesions may appear as solitary or multiple localized plaques or nodules and may be located on perianal, perioral, or other cutaneous surfaces, including scars and ileostomy sites. In most cases of inflammatory bowel disease–associated skin disease, treatment of the underlying condition improves the cutaneous sequelae.

Rarely, these associated skin findings may be seen without the classic GI manifestations, warranting continued GI surveillance for subsequent disease development. Isolated cutaneous involvement is treated similarly with systemic steroid-sparing and biologic agents with or without topical or intralesional corticosteroids. Azathioprine, a common treatment, causes increased risk for nonmelanoma skin cancers.

CUTANEOUS MANIFESTATIONS OF MALIGNANCY

Skin disease associated with malignancy has a wide variety of presentations, including both metastatic lesions and nonmalignant paraneoplastic conditions. Cutaneous metastases manifest as firm nodules and occur at any cutaneous site. Paraneoplastic reaction patterns are often distinctive and can aid in the diagnosis of the underlying malignancy. Some genetic syndromes have an increased malignancy risk that may be suggested initially by cutaneous signs. Other cutaneous findings that may signal an underlying malignancy include pruritus, ichthyosis, acanthosis nigricans, urticaria, pemphigus, and erythroderma.

Sweet Syndrome

Also known as **acute febrile neutrophilic dermatosis**, Sweet syndrome (see Chapter 213) occurs in several forms, including classical (usually idiopathic or infection-related, Fig. 686.7), malignancy-associated,

immunodeficiency-related, autoinflammatory (recurrent fever) syndromes, and drug-induced. Pathogenesis for all four forms remains unclear; however, new data are emerging implicating a potential interleukin (IL)-1–mediated pathway. Malignancy-associated Sweet syndrome is most commonly associated with hematologic malignancies, especially **acute myelogenous leukemia**. It manifests abruptly before, during, or after the malignancy course and is characterized by tender, erythematous, edematous plaques or nodules that may be pustular or targetoid, often accompanied by fever, anemia, and leukocytosis. Oral ulcers are more common in malignancy-associated Sweet syndrome than in other forms of the disease, and extracutaneous manifestations involving various organ systems may also occur. Diagnosis is confirmed by the presence of a dense neutrophilic infiltrate without evidence of vasculitis. The differential diagnosis includes other neutrophilic dermatoses such as pyoderma gangrenosum as well as cellulitis, erythema multiforme, Behçet disease, and erythema nodosum. First-line treatment for both malignancy-associated and nonmalignancy-associated Sweet syndrome is oral glucocorticoids (prednisone 1-2 mg/kg/day for 2-4 weeks) in combination with high-potency topical or intralesional corticosteroids. Systemic steroid-sparing agents include colchicine and dapsone.

Cutaneous manifestations of other autoinflammatory diseases are noted in Table 686.4.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH, see Chapter 556.1) is a neoplastic disorder characterized by proliferation of myeloid dendritic cells. Once thought to be Langerhans cells, which are skin-resident dendritic cells, the cells of LCH are now understood to represent a distinct cell type. LCH can be a single-system or multisystem disease, with the neoplastic infiltrate in organs such as the skin, bone, central nervous system, lung, hematopoietic system, liver, and spleen. When present on the skin, the lesions of LCH can be crusted erosions, scaly papules, or purpura. There is a predilection for the scalp, palms, soles, and intertriginous areas such as axillae and groin. Prognosis and treatment are variable depending on the organ systems involved.

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

Necrolytic migratory erythema is a distinctive migratory erythema that often signals an underlying neoplasm, usually an α-cell pancreatic tumor. Polycyclic, weeping, erythematous patches and plaques on the face, extremities, and groin occur in association with glossitis and cheilitis. The lesions are painful or pruritic, enlarge and coalesce over time, and may develop central clearing with vesicles, crusts, and scales peripherally. Skin biopsy reveals superficial necrolysis with perivascular infiltrate. Elevated glucagon levels, hyperglycemia, and hypoaminoacidemia confirm the diagnosis, and tumor resection leads to resolution of the rash. Other treatments for necrolytic migratory erythema include somatostatin analogs (octreotide) and nutritional support; however, these measures do not affect the underlying tumor burden.

ERYTHROMELALGIA

This disorder may be primary (caused by pathogenic genetic variants in *SCN9A*) or secondary (myeloproliferative disorders, paraneoplastic, autoimmune) and is characterized by the triad of recurrent extremity pain, warmth, and redness. Warmth, exercise, sitting, or wearing shoes or gloves may initiate the episode. Cooling and elevation may relieve symptoms (see Chapter 211.5).

CUTANEOUS REACTIONS IN THE SETTING OF IMMUNOSUPPRESSION

Medication reactions, infectious etiologies, and graft-versus-host disease (GVHD) are included in the differential diagnosis in skin eruptions in immunosuppressed patients; cutaneous and histologic similarities can be confounding.

Medication Reactions

The majority of medication reactions are mild morbilliform or exanthematous eruptions of little clinical consequence. Identifying the suspect medication may be difficult owing to the many medications used in immunosuppressed patients. Features that may help identify suspect medications include rash onset relative to exposure, character of distribution and spread, associated symptoms, and laboratory data. Medication eruptions usually begin on the trunk **7-10 days after exposure**; they spread peripherally and are associated with pruritus and, less commonly, with fever, arthralgia, and lymphadenopathy. Eosinophilia may support a diagnosis of drug eruption but may be absent in the setting of bone marrow suppression. Penicillins, sulfa drugs, cephalosporins, nonsteroidal antiinflammatory drugs (NSAIDs), anticonvulsants, and aminoglycosides are common offenders. Medication eruptions may resolve despite continued use of the offending agent, or they may progress to more severe involvement. A careful drug history, elimination of all nonessential, suspect medications or change to medications of dissimilar class, and treatment of pruritus with emollients, topical steroids, antihistamines, and antipruritics are indicated. Skin biopsies are rarely useful in distinguishing medication eruptions from viral exanthems, although GVHD, if sufficiently advanced, may have signature histopathologic findings.



Fig. 686.8 Lichenoid eruption in chronic graft-versus-host disease.

Graft-Versus-Host Disease

GVHD (see Chapter 179) may have florid cutaneous expression in addition to characteristic extracutaneous features such as fever, mucositis, diarrhea, and hepatitis. It may be either acute or chronic. **Acute GVHD** occurs in 20–70% of hematopoietic stem cell transplants, depending on histocompatibility differences. It may be mistaken for a medication reaction or infectious exanthem because of the nonspecific erythematous maculopapular (morbilliform) eruption that often starts focally and then generalizes. Features that suggest acute GVHD include timing of eruption (typically 1-3 weeks after transplantation, at the time of hematopoietic reconstitution); initial involvement of the head and neck including the ears; and subsequent spread to the trunk, extremities, palms, and soles. In severe cases of acute GVHD, blistering, necrolysis, and erythroderma occur. **Chronic GVHD** occurs in approximately 65% of long-term transplant survivors, who may or may not have experienced prior acute GVHD. Cutaneous manifestations of chronic GVHD are distinctive, with sclerotic, poikilodermic scaly plaques and lichen planus–like papules predominating on the trunk and distal extremities (Fig. 686.8). Sclerotic areas are prone to contracture and chronic wound development. Involvement of the hair, nails, and oral mucosa is also common in chronic GVHD. First-line treatment for GVHD includes systemic glucocorticoids and other immunosuppressants supplemented by mid- to high-potency topical corticosteroids. In mild disease, topical corticosteroids or topical calcineurin inhibitors alone may be effective. Second-line treatment approaches include phototherapy (narrow-band UVB or UVA1) and extracorporeal photopheresis. All patients with GVHD benefit from sunlight protection, emollient use, and topical or oral antipruritics.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

686.2 Multisystem Medication Reactions

Julie M. Dhossche and Yvonne E. Chiu

See also Chapter 193.

Most cutaneous reactions that result from the use of systemic medications are confined to the skin and resolve without sequelae after discontinuation of the offending agent (Table 686.5). More severe drug eruptions may be life-threatening, making rapid recognition vital (Table 686.6 and see Chapter 695). Genetics and, particularly, ethnicity appear to play a major role in determination of the occurrence of multisystem medication reactions, particularly to anticonvulsants.

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is also called *drug hypersensitivity syndrome* or *anticonvulsant hypersensitivity syndrome.* It is classically seen **2-6 weeks after initial exposure** to an anticonvulsant (carbamazepine, phenobarbital, phenytoin, lamotrigine) or other drugs (allopurinol, minocycline, sulfonamides [dapsone, sulfasalazine], other antibiotics) and often manifests as the triad of **fever**, **rash**, and **hepatitis** (Fig. 686.9). The skin rash is initially located on the head, upper trunk, and arms. A diffuse exanthem of pruritic, morbilliform papules

Table 686.5 Drug Eruptions in Pediatric Patients

ERUPTION	KEY DRUGS	LESIONAL PATTERN	MUCOSAL CHANGES
Urticaria	Penicillins, cephalosporins, sulfonamides, minocycline, aspirin/NSAIDs, antiepileptics, monoclonal antibodies, radiocontrast media	Pruritic erythematous wheals (Fig. 686.12)	None
Angioedema	Aspirin/NSAIDs, ACE inhibitors	Swelling of subcutaneous and deep dermal tissues	May be present
Serum sickness–like reaction	Cephalosporins, penicillins, minocycline, sulfonamides, macrolides, rifampin, ciprofloxacin, griseofulvin, itraconazole, bupropion, fluoxetine, rituximab, H1N1 vaccine	Urticarial or erythema multiforme–like (see Fig. 686.11)	None
Exanthematous	Penicillins, sulfonamides, cephalosporins, antiepileptics	Erythematous macules and/or papules	None
Drug hypersensitivity syndrome	Sulfonamides, phenytoin, phenobarbital, carbamazepine, lamotrigine, amoxicillin, allopurinol, sulfonamides, dapsone, minocycline, aspirin, vancomycin, azithromycin, abacavir, nevirapine, Chinese medicine	Edema (especially periorbital); erythematous macules and/or papules; sometimes vesicles or bullae (see Fig. 686.10)	May be present
Lichenoid	Captopril, enalapril, labetalol, nifedipine, propranolol, gold salts, hydrochlorothiazide, furosemide, spironolactone, hydroxychloroquine, ketoconazole, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs, hydroxyurea, imatinib, dapsone, sulfasalazine, allopurinol, iodides and radiocontrast media, IFN-γ, omeprazole, TNF inhibitors, sildenafil, leflunomide, human growth hormone	Discrete flat-topped, reddish-purple papules and plaques	May be present
Fixed drug	Sulfonamides, ibuprofen, acetaminophen, salicylates, tetracyclines, pseudoephedrine, loratadine, teicoplanin, metronidazole, macrolides, barbiturates, lamotrigine, potassium iodide, quinine, phenolphthalein, foods and food flavorings (especially tartrazine)	Solitary to few erythematous, hyperpigmented plaques (see Fig. 686.13)	Unusual
Pustular (AGEP)	β-Lactam antibiotics, cephalosporins, macrolides, clindamycin, terbinafine, paroxetine, hydroxychloroquine, contrast agents	Generalized small pustules and papules (see Fig. 686.14)	None
Acneiform	Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, methotrexate	Follicular-based inflammatory papules and pustules predominate	None
Pseudoporphyria	NSAIDs, COX-2 inhibitors, tetracyclines, furosemide	Photodistributed blistering and skin fragility	None
Vasculitis	Penicillins, NSAIDs, sulfonamides, cephalosporins	Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers	Rarely
Stevens-Johnson/ toxic epidermal necrolysis	Sulfonamides, antiepileptics (especially phenytoin, carbamazepine, and lamotrigine), NSAIDs, acetaminophen, allopurinol, dapsone, barbiturates	Target lesions, bullae, epidermal necrosis with detachment (see Figs. 695.3 and 695.4)	Present
Drug-induced lupus	Minocycline, procainamide, hydralazine, isoniazid, penicillamine	Urticarial, vasculitic, erythematous	Rare

ACE, Angiotensin converting enzyme; AGEP, acute generalized exanthematous pustulosis; COX-2, cyclooxygenase-2; IFN, interferon; NSAID, Nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

Adapted from Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology*, 6th ed. St Louis: Elsevier; 2022: p. 541.

Table 686.6 Main Clinical and Histologic Characteristics of Severe Cutaneous Adverse Reactions

DRUG TO SCAR INTERVAL	GENERAL SYMPTOMS	SKIN FEATURES	LABORATORY VALUES	MAIN ORGANS INVOLVED	HISTOLOGIC FEATURES
SJS and TEN	4-28 days	Fever ≥38°C, Influenza- like syndrome, respiratory tract symptoms	Blisters, large skin detachment, confluent erythema, atypical target lesions, purpura, Nikolsky sign; skin detachment Stevens-Johnson syndrome <10%, toxic epidermal necrolysis ≥30%, SJS-TEN 10–30%; two or more mucous membranes involved	Lymphopenia, transitory neutropenia, mild cytolysis, renal impairment	Full-thickness epidermal necrosis, focal adnexal necrosis, necrotic keratinocytes, mild mononuclear cell dermal infiltrate, negative direct immunofluorescence test
DRESS syndrome	2-6 wk	Fever ≥38°C, Influenza- like syndrome	Maculopapular rash Erythroderma, facial or extremity edema, pustules, focal monopolar mucous membrane involvement	Eosinophilia >700 cells/μL Atypical lymphocytes, elevated transaminase concentration, impaired renal function, herpesvirus reactivation (HHV-6, HHV-7, EBV, CMV), parvovirus B19 reactivation	Lichenoid infiltrate or Eczematous pattern (spongiosis, edema), focal necrotic keratinocytes, mononuclear infiltrate, focal eosinophil and neutrophil infiltrates, mild vasculitis
AGEP	1-11 days	Fever ≥38°C	Intertriginous erythema, edema, widespread nonfollicular sterile pustules, postpustular pinpoint desquamation, Nikolsky sign, rare oral mucous membrane involvement	Hyperleukocytosis, neutrophils ≥7,000 cells/μL, mild eosinophilia	Subcorneal or intraepidermal spongiform or nonspongiform pustules with or without papillary edema, focal necrotic keratinocytes, neutrophilic, sometimes with eosinophils, mild vasculitis

*General symptoms can precede or occur at the same time as skin manifestations.
AGEP, Acute generalized exanthematous pustulosis; CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; HHV, human herpesvirus; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
From Duong TA, Valeyrie-Allanore L, Wolkenstein P, et al. Severe cutaneous adverse reactions to drug. *Lancet.* 2017;390: 1996–2011. Table 1.

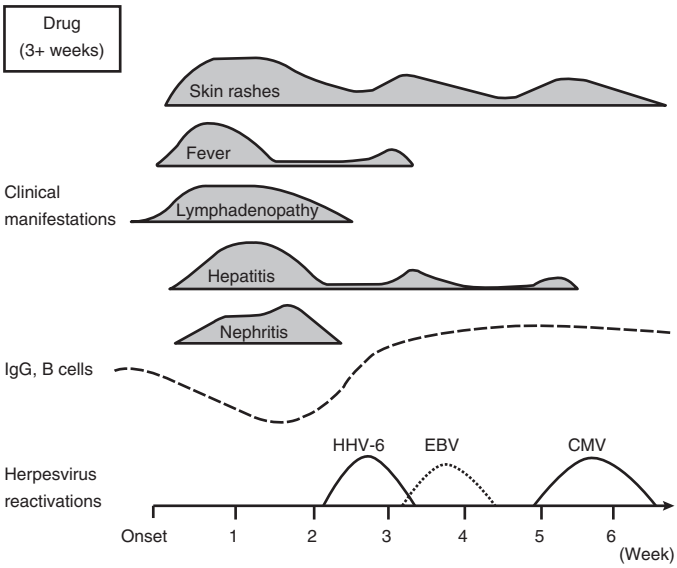

Fig. 686.9 Clinical symptoms and laboratory findings of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus. *(From Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. Med Clin N Am. 2010;94:743–759, Fig. 1, p. 745).*

are most common, though any morphology may be present (Fig. 686.10). Exfoliation early in the course, as seen in toxic epidermal necrolysis, is uncommon. If mucous membrane involvement occurs, it is usually mild. Prominent periocular or facial edema, cervical lymphadenopathy, pharyngitis, and malaise accompany this dramatic cutaneous eruption. *Eosinophilia (≥500/μL) and atypical lymphocytosis are common but not always present.* Hepatitis ranging from mild elevation of liver transaminase values to frank hepatic failure may also be accompanied by interstitial nephritis, pneumonitis, myocarditis, shock, and encephalitis; mortality rate from these complications approaches 10%. Late-onset thyroiditis and hypothyroidism may occur months later as a result of antimicrosomal antibodies directed against thyroid peroxidases involved in drug metabolism.

DRESS syndrome is caused by a T-cell response specific to the drug. Reactivation of herpesviruses, especially human herpesvirus 6, also contributes to DRESS syndrome via an unknown pathogenic mechanism. Genetic predisposition with particular HLA allele types has also been implicated with specific ethnic groups and drugs, such as HLA-A*3101 with carbamazepine. The differential diagnosis includes Stevens-Johnson syndrome, viral exanthem, macrophage activation, hemophagocytic syndromes, and GVHD in the appropriate clinical setting. DRESS syndrome is often distinguished from other medication reactions by its later onset after drug exposure and more persistent course.

Withdrawal of the medication is the primary therapeutic intervention. Lymphocyte transformation tests and patch testing may be



Fig. 686.10 A 9-yr-old with cerebral palsy and seizures treated with carbamazepine. Seventeen days after start of therapy he demonstrated fever, rash (exanthematous), lymphadenopathy, and nephritis, all part of a drug-induced hypersensitivity syndrome. *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 2003: p. 1269.)*

helpful for identifying the offending drug when multiple suspect agents are present, but drug discontinuation should not be delayed while awaiting results. Symptomatic treatment of pruritus and pain can be accomplished with emollients and mid- to high-potency topical corticosteroids (twice daily for 1-2 weeks). Systemic corticosteroid therapy is necessary in the setting of rapidly evolving or severe hepatic or renal involvement. Counseling about increased risk with similar medications and in family members is important. DRESS syndrome can have a relapsing course, both in the skin and other organ systems, well after the medication has been withdrawn and initial improvement achieved, necessitating close follow-up for several months.

SERUM SICKNESS–LIKE REACTION

Serum sickness–like reaction (SSLR) manifests as annular, urticarial, sharply marginated, coalescing plaques, often with a lavender hue to the center (Fig. 686.11). In addition, acral erythema/edema, arthritis/arthralgia, lymphadenopathy, and fever are often present. Unlike with true serum sickness (see Chapter 191), laboratory evidence of circulating immune complexes and multisystem involvement of vasculitis are typically absent. The differential diagnosis includes Kawasaki disease, connective tissue diseases, acute annular urticaria, and DRESS syndrome. SSLR is most commonly seen 10-14 days after exposure to various drugs (especially cephalosporins, penicillins, minocycline, and other antibiotics), as well as after certain infections and vaccinations. The cause of drug-related SSLR is unknown, but a toxic metabolite is suspected. In contrast to DRESS syndrome, SSLR typically occurs after repeated drug exposures.



Fig. 686.11 Serum sickness–like reaction is composed of urticarial plaques with an erythematous border and violaceous centers.



Fig. 686.12 Urticaria. Transient well-circumscribed, erythematous wheals occurred in this girl as a reaction to administration of cefixime. Note the edematous center and halo of erythema. Circling a lesion and noting whether it is clear 24 hours later facilitates diagnosis. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2016: Fig. 20-2, p. 469.)*



Fig. 686.13 Multiple fixed-drug eruption.

Medication withdrawal and symptomatic treatment with oral antihistamines and analgesics are recommended. Systemic glucocorticoids are indicated for severe joint involvement or extensive rashes.



Fig. 686.14 Acute generalized exanthematous pustulosis is characterized by the acute onset of fever and generalized erythema with numerous small, discrete, sterile, nonfollicular pustules. Pustules may appear in a few days after the drug therapy is started. Pustules resolve in <15 days, followed by desquamation. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004: p. 490.)*

FIXED-DRUG ERUPTION

Fixed-drug eruption (FDE) occurs minutes to hours after exposure to a drug and is characterized by mild pruritus or burning of a well-circumscribed, dusty red, brown, gray or, if severe, violaceous patch appearing on the extremities, trunk, lips, or genitals (Fig. 686.13). There is usually one lesion that, on reexposure to the drug, appears in the same (fixed) location as the previous episode, often appearing more rapidly. On occasion, there may be two or more lesions. Stopping the offending agent is required; the FDE will then resolve within 10-14 days, often with residual hyperpigmentation. Offending medications include sulfonamides, tetracyclines, NSAIDs, and acetaminophen.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis is often drug-related (most commonly aminopenicillins, macrolides, sulfonamides), occurring **within hours to days after drug exposure**. It is characterized by many nonfollicular sterile pustules with underlying edema and erythema, typically beginning on the face and intertriginous regions (Fig. 686.14). Neutrophilia and fever are common, whereas eosinophilia is less common than in DRESS syndrome. The rash may burn or itch; mucous membrane involvement is rare and often mild. Internal organ involvement is not common and often is asymptomatic. A pustular smear is always indicated to rule out infection in the setting of leukocytosis, fever, and a pustular rash. Differential diagnosis includes generalized pustular psoriasis, bullous impetigo, IgA pemphigus, and subcorneal pustular dermatosis. Therapy consists of stopping the causative drug and offering symptomatic relief with moist dressings, emollients, and mid-potency topical corticosteroids (applied twice daily for 1-2 weeks).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 687

Principles of Dermatologic Therapy

Stephen R. Humphrey

Competent skin care requires an appreciation of primary versus secondary lesions, a specific diagnosis, and knowledge of the natural course of the disease. If the diagnosis is uncertain, it is better to err on the side of less aggressive rather than more aggressive treatment.

In the use of topical medication, consideration of vehicle is as important as the specific therapeutic agent. Acute **weeping lesions** respond best to wet compresses, followed by lotions or creams. For **dry, thickened,** scaly skin, or for treatment of a contact allergic reaction possibly the consequence of a component of a topical medication, an ointment base is preferable, as it helps to occlude and moisten the affected area. Gels and solutions are most useful for the scalp and other hairy areas because of their faster absorption. The site of involvement is of considerable importance because the most desirable vehicle may not be cosmetically or functionally appropriate, such as an ointment on the face or hands. A patient's preference should also play a part in the choice of vehicle because compliance is poor if a medication is not acceptable to a patient. Ointments tend to sting less and are the least irritating. Cosmetically acceptable foam delivery systems have been developed, and the number of products and formulations available is increasing.

Most **lotions** are mixtures of water and oil that can be poured. After the water evaporates, the small amount of remaining oil covers the skin. Some shake lotions are a suspension of water and insoluble powder; as the water evaporates, cooling the skin, a thin film of powder covers the skin. **Creams** are emulsions of oil and water that are viscous and do not pour (more oil than in lotions). **Ointments** have oils and a small amount of water or no water at all; they feel greasy, lubricate dry skin, trap water, and aid in occlusion. Ointments without water usually require no preservatives because microorganisms require water to survive. Because of this, ointments often have the lowest number and concentration of ingredients, decreasing the risk of sensitizing the skin.

Therapy should be kept as simple as possible, and specific written instructions about the frequency and duration of application should be provided. Physicians should become familiar with one or two preparations in each category and should learn to use them appropriately. Prescribing nonspecific proprietary medications that may contain sensitizing agents should be avoided. Certain preparations, such as topical antihistamines and sensitizing anesthetics, are never indicated.

WET DRESSINGS

Wet dressings cool and dry the skin by evaporation and cleanse it by removing crusts and exudate, which would cause further irritation if permitted to remain. The dressings decrease pruritus, burning, and stinging sensations and are indicated for acutely inflamed moist or oozing dermatitis. Although various astringent and antiseptic substances may be added to the solution, cool or tepid tap water compresses are just as effective. Dressings of multiple layers of Kerlix, gauze, or soft cotton material may be saturated with water and remoistened as often as necessary. Compresses should be applied for 10-20 minutes at least every 4 hours and should usually be continued for 24-48 hours.

Alternatively, cotton pajamas can be soaked in water and then wrung as dry as possible. These are placed on the child and covered with dry pajamas, preferably sleeper pajamas with feet. The child should sleep in these overnight. This type of dressing can be used nightly for up to 1 week.

Wet dressings or wet wraps in conjunction with topical steroids may also be used in more severe cases of dermatitis (e.g., atopic dermatitis). In this method, a thin layer of the topical steroid is applied to the affected areas, which are then covered with warm, wet wraps



Fig. 686.14 Acute generalized exanthematous pustulosis is characterized by the acute onset of fever and generalized erythema with numerous small, discrete, sterile, nonfollicular pustules. Pustules may appear in a few days after the drug therapy is started. Pustules resolve in <15 days, followed by desquamation. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004: p. 490.)*

FIXED-DRUG ERUPTION

Fixed-drug eruption (FDE) occurs minutes to hours after exposure to a drug and is characterized by mild pruritus or burning of a well-circumscribed, dusty red, brown, gray or, if severe, violaceous patch appearing on the extremities, trunk, lips, or genitals (Fig. 686.13). There is usually one lesion that, on reexposure to the drug, appears in the same (fixed) location as the previous episode, often appearing more rapidly. On occasion, there may be two or more lesions. Stopping the offending agent is required; the FDE will then resolve within 10-14 days, often with residual hyperpigmentation. Offending medications include sulfonamides, tetracyclines, NSAIDs, and acetaminophen.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis is often drug-related (most commonly aminopenicillins, macrolides, sulfonamides), occurring **within hours to days after drug exposure**. It is characterized by many nonfollicular sterile pustules with underlying edema and erythema, typically beginning on the face and intertriginous regions (Fig. 686.14). Neutrophilia and fever are common, whereas eosinophilia is less common than in DRESS syndrome. The rash may burn or itch; mucous membrane involvement is rare and often mild. Internal organ involvement is not common and often is asymptomatic. A pustular smear is always indicated to rule out infection in the setting of leukocytosis, fever, and a pustular rash. Differential diagnosis includes generalized pustular psoriasis, bullous impetigo, IgA pemphigus, and subcorneal pustular dermatosis. Therapy consists of stopping the causative drug and offering symptomatic relief with moist dressings, emollients, and mid-potency topical corticosteroids (applied twice daily for 1-2 weeks).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 687

Principles of Dermatologic Therapy

Stephen R. Humphrey

Competent skin care requires an appreciation of primary versus secondary lesions, a specific diagnosis, and knowledge of the natural course of the disease. If the diagnosis is uncertain, it is better to err on the side of less aggressive rather than more aggressive treatment.

In the use of topical medication, consideration of vehicle is as important as the specific therapeutic agent. Acute **weeping lesions** respond best to wet compresses, followed by lotions or creams. For **dry, thickened,** scaly skin, or for treatment of a contact allergic reaction possibly the consequence of a component of a topical medication, an ointment base is preferable, as it helps to occlude and moisten the affected area. Gels and solutions are most useful for the scalp and other hairy areas because of their faster absorption. The site of involvement is of considerable importance because the most desirable vehicle may not be cosmetically or functionally appropriate, such as an ointment on the face or hands. A patient's preference should also play a part in the choice of vehicle because compliance is poor if a medication is not acceptable to a patient. Ointments tend to sting less and are the least irritating. Cosmetically acceptable foam delivery systems have been developed, and the number of products and formulations available is increasing.

Most **lotions** are mixtures of water and oil that can be poured. After the water evaporates, the small amount of remaining oil covers the skin. Some shake lotions are a suspension of water and insoluble powder; as the water evaporates, cooling the skin, a thin film of powder covers the skin. **Creams** are emulsions of oil and water that are viscous and do not pour (more oil than in lotions). **Ointments** have oils and a small amount of water or no water at all; they feel greasy, lubricate dry skin, trap water, and aid in occlusion. Ointments without water usually require no preservatives because microorganisms require water to survive. Because of this, ointments often have the lowest number and concentration of ingredients, decreasing the risk of sensitizing the skin.

Therapy should be kept as simple as possible, and specific written instructions about the frequency and duration of application should be provided. Physicians should become familiar with one or two preparations in each category and should learn to use them appropriately. Prescribing nonspecific proprietary medications that may contain sensitizing agents should be avoided. Certain preparations, such as topical antihistamines and sensitizing anesthetics, are never indicated.

WET DRESSINGS

Wet dressings cool and dry the skin by evaporation and cleanse it by removing crusts and exudate, which would cause further irritation if permitted to remain. The dressings decrease pruritus, burning, and stinging sensations and are indicated for acutely inflamed moist or oozing dermatitis. Although various astringent and antiseptic substances may be added to the solution, cool or tepid tap water compresses are just as effective. Dressings of multiple layers of Kerlix, gauze, or soft cotton material may be saturated with water and remoistened as often as necessary. Compresses should be applied for 10-20 minutes at least every 4 hours and should usually be continued for 24-48 hours.

Alternatively, cotton pajamas can be soaked in water and then wrung as dry as possible. These are placed on the child and covered with dry pajamas, preferably sleeper pajamas with feet. The child should sleep in these overnight. This type of dressing can be used nightly for up to 1 week.

Wet dressings or wet wraps in conjunction with topical steroids may also be used in more severe cases of dermatitis (e.g., atopic dermatitis). In this method, a thin layer of the topical steroid is applied to the affected areas, which are then covered with warm, wet wraps

for approximately 30 minutes to 1 hour 2-3 times daily. This method is especially effective in children with extensive and severe dermatitis.

BATH OILS, COLLOIDS, AND SOAPS

Bath oil has little benefit in the treatment of children. It offers little moisturizing effect but increases the risk of injury during a bath. Bath oil may lubricate the surface of the bathtub, causing an adult or child to fall when stepping into the tub. Tar bath solutions can be prescribed and may be helpful for psoriasis and atopic dermatitis. Colloids such as starch powder and colloidal oatmeal are soothing and antipruritic for some patients when added to the bathwater. Oilated colloidal oatmeal contains mineral oil and lanolin derivatives for lubrication if the skin is dry. These can also lubricate the bathtub surface. Ordinary bath soaps may be irritating and drying if patients have dry skin or dermatitis. Synthetic soaps are much less irritating. Fragrance-free soaps and cleansers are often better tolerated and less likely to irritate skin. Additionally, solid soaps tend to be less irritating, as they do not have as many preservatives as liquid soap might. When skin is acutely inflamed, avoidance of soap is advised.

LUBRICANTS

Lubricants, such as lotions, creams, and ointments, can be used as moisturizers for dry skin and as vehicles for topical agents such as corticosteroids and keratolytics. In general, ointments are the most effective emollients. Numerous commercial preparations are available. Some patients do not tolerate ointments, and some may be sensitized to a component of the lubricant; some preservatives in creams are also sensitizers. These preparations can be applied several times a day if necessary and tolerated. Maximal effect is achieved when they are applied to dry skin 2 or 3 times daily. Lotions containing menthol and camphor in an emollient vehicle can help control pruritus and dryness, but the use of moisturizers in addition to these products is best to decrease skin dryness.

SHAMPOOS

Special shampoos containing sulfur, salicylic acid, zinc, and selenium sulfide are useful for conditions in which there is scaling of the scalp, such as seborrheic dermatitis or psoriasis. Tar-containing shampoos are useful in these conditions. Most shampoos also contain surfactants and detergents. They should be used as frequently as necessary to control scaling. Patients should be instructed to leave the lathered shampoo in contact with the scalp for 5-10 minutes before thorough rinsing.

POWDERS

Powders are hygroscopic and serve as absorptive agents in areas of excessive moisture. When dry, powders decrease friction between two surfaces. They are most useful in the intertriginous areas and between the toes, where maceration and abrasion may result from friction on movement. Coarse powders may cake; therefore they should be of fine particle size and inert, unless medication has been incorporated in the formulation. The use of cornstarch-based powders in inflamed or broken skin may serve as a good growth environment for microorganisms and should be avoided.

PASTES

Pastes contain fine powder in ointment vehicles and are not often prescribed in current dermatologic therapy; in certain situations, however, they can be used effectively to protect vulnerable or damaged skin. A stiff zinc oxide paste is bland and inert and can be applied to the diaper area to prevent further irritation caused by diaper dermatitis. Zinc oxide paste should be applied in a thick layer, completely obscuring the skin, and is removed more easily with mineral oil than with soap and water.

KERATOLYTIC AGENTS

Urea-containing agents are hydrophilic; they hydrate the stratum corneum and make the skin more pliable. In addition, because urea dissolves hydrogen bonds and epidermal keratin, it is effective in treating scaling disorders. Concentrations of 10–40% are available in several commercial lotions and creams, which can be applied once or twice daily as tolerated. Salicylic acid is an effective keratolytic agent and can be incorporated into various vehicles in concentrations up to 6% to be applied 2 or 3 times daily. Salicylic acid preparations should not be used in treating small infants or on large surface areas or denuded skin; percutaneous absorption may result in salicylism. The α-hydroxy acids, particularly lactic acid and glycolic acid, are available in commercial preparations or can be incorporated in an ointment vehicle in concentrations up to 12%. Some creams contain both urea and lactic acid. The α-hydroxy acid preparations are useful for the treatment of keratinizing disorders and may be applied once or twice daily. Some patients complain of burning with the use of these agents; in such cases, the frequency of application should be decreased.

Table 687.1 Potency of Topical Glucocorticosteroids

CLASS 1—SUPER-POTENT
Betamethasone dipropionate, 0.05% gel, ointment
Clobetasol propionate cream, ointment, 0.05%
Halobetasol propionate cream, ointment, 0.05%
CLASS 2—POTENT
Betamethasone dipropionate cream 0.05%
Desoximetasone cream, ointment, gel 0.05% and 0.25%
Fluocinonide cream, ointment, gel, 0.05%
CLASS 3—UPPER MID-STRENGTH
Betamethasone dipropionate cream, 0.05%
Betamethasone valerate ointment, 0.1%
Fluticasone propionate ointment, 0.005%
Mometasone furoate ointment, 0.1%
Triamcinolone acetonide cream, 0.5%
CLASS 4—MID-STRENGTH
Desoximetasone cream, 0.05%
Fluocinolone acetonide ointment, 0.025%
Triamcinolone acetonide ointment, 0.1%
CLASS 5—LOWER MID-STRENGTH
Betamethasone valerate cream/lotion, 0.1%
Fluocinolone acetonide cream, 0.025%
Fluticasone propionate cream, 0.05%
Triamcinolone acetonide cream/lotion, 0.1%
CLASS 6—MILD STRENGTH
Desonide cream, 0.05%
CLASS 7—LEAST POTENT
Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone

From Weston WL, Lane AT, Morelli JG. *Color Textbook of Pediatric Dermatology*, 4th ed. St. Louis: Mosby; 2007: p. 418.

TAR COMPOUNDS

Tars are obtained from bituminous coal, shale, petrolatum (coal tars), and wood. They are antipruritic and astringent and appear to promote normal keratinization. They may be useful for chronic eczema and psoriasis, and their efficacy may be increased if the affected area is exposed to UV light after the tar has been removed. Tars should not be used for acute inflammatory lesions. Tars are often messy and unacceptable because they may stain and they have an odor. They may be incorporated into shampoos, bath oils, lotions, and ointments. A useful preparation for pediatric patients is liquor carbonis detergens (LCD) 2–5% in a cream or ointment vehicle. Tar gel and tar in light body oil are relatively pleasant cosmetic preparations that cause minimal staining of skin and fabrics. Tars can also be incorporated into a vehicle with a topical corticosteroid. The frequency of application varies from 1-3 times daily, according to tolerance. Many children refuse to use tar preparations because of their odor and staining characteristics.

ANTIFUNGAL AGENTS

Antifungal agents are available as powders, lotions, creams, ointments, and solutions for the treatment of dermatophyte and yeast infections. Nystatin, naftifine, and amphotericin B are specific for *Candida albicans* and are ineffective in other fungal disorders. Tolnaftate is effective against dermatophytes but not against yeast. The spectrum for ciclopirox olamine includes the dermatophytes, *Malassezia furfur,* and *C. albicans.* The azoles clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, and sulconazole have a similar broad spectrum. Butenafine has a similar broad

spectrum and also has antiinflammatory properties. Terbinafine has greater activity against dermatophytes but poorer activity against yeasts than the azoles. The topical antifungal agents should be applied 1-2 times a day for most fungal infections. All have low sensitizing potential; additives such as preservatives and stabilizers in the vehicles may cause allergic contact dermatitis. Ointments containing 6% benzoic acid and 3% salicylic acid are potent keratolytic agents that have also been used for the treatment of dermatophyte infections. Irritant reactions are common.

TOPICAL ANTIBIOTICS

Topical antibiotics have been used for many years to treat local cutaneous infections, although their efficacy, with the exception of mupirocin, fusidic acid, and retapamulin, has been questioned. Ointments are the preferred vehicles (except in the treatment of acne vulgaris; see Chapter 710), and combinations with other topical agents such as corticosteroids are, in general, inadvisable. Whenever possible, the etiologic agent should be identified and treated specifically. Antibiotics in wide use as systemic preparations should be avoided because of the risk of bacterial resistance. The sensitizing potential of certain topical antibiotics, such as neomycin and nitrofurazone, should be kept in mind and avoided when possible. Mupirocin, fusidic acid, and retapamulin are the most effective topical agents currently available and are as effective as oral erythromycin in treatment of mild to moderate impetigo. Polysporin and bacitracin are not as effective.

TOPICAL CORTICOSTEROIDS

Topical corticosteroids are potent antiinflammatory agents and effective antipruritic agents. Successful therapeutic results are achieved in a wide variety of skin conditions. Corticosteroids can be divided into seven different categories on the basis of strength (Table 687.1), but for practical purposes, four categories can be used: low, moderate, high, and super. Low-potency preparations include hydrocortisone, desonide, and hydrocortisone butyrate. Medium-potency compounds include betamethasone, flurandrenolide, fluocinolone, mometasone furoate, and triamcinolone. High-potency topical steroids include fluocinonide and halcinonide. Betamethasone dipropionate, halobetasol, and clobetasol propionate are superpotent preparations and should be prescribed with care. Some of these compounds are formulated in several strengths according to clinical efficacy and degree of vasoconstriction. Physicians using topical steroids should become familiar with preparations within each class.

All corticosteroids can be obtained in various vehicles, including creams, ointments, solutions, gels, and aerosols. Some are available in a foam vehicle. Absorption is enhanced by an ointment or gel vehicle, but the vehicle should be selected on the basis of the type of disorder and the site of involvement. Frequency of application should be determined by the potency of the preparation, the location on the body, and the severity of the eruption. Applying a thin film 2 times daily usually suffices. Adverse local effects include cutaneous atrophy, striae, telangiectasia, acneiform eruptions, purpura, hypopigmentation, and increased hair growth. Systemic adverse effects of high-potency and superpotent topical steroids occur with long-term use and include poor growth, cataracts, and suppression of adrenal function.

The relative skin thickness should be considered in regard to the selection of class of steroid (see Table 687.1). Thin skin such as the eyelids, face, groin, and genitalia will absorb a substantial amount of medication compared to the thickest skin on the palms and soles. One adult fingertip's worth of medication is enough to cover an area the size of an adult palm and is approximately half a gram of medication. Knowing the area being treated and which medication class to prescribe can decrease the potential for side effects.

In selected circumstances, corticosteroids may be administered by intralesional injection (acne cysts, keloids, psoriatic plaques, alopecia areata, persistent insect bite reactions). Only experienced physicians should use this method of administration.

TOPICAL NONSTEROIDAL ANTIINFLAMMATORY AGENTS

Calcineurin-inhibiting antiinflammatory agents that inhibit T-cell activation may be used instead of topical steroids for the treatment of atopic dermatitis and other inflammatory conditions. These agents are pimecrolimus and tacrolimus. They do not have the adverse local effects seen with topical steroids. Stinging with application is the most common complaint and may be lessened by mixing the medication with an ointment such as petrolatum jelly for the initial applications. These agents are only as strong as medium-potency topical steroids. In 2006, the FDA issued a boxed warning for topical calcineurin inhibitors because data from animal experiments and case reports suggested potential for an increased risk of lymphoma with systemic use. No clear link between topical calcineurin inhibitor use and lymphoma risk has been established despite multiple epidemiologic and clinical studies. Crisaborole, a novel PDE4 inhibitor, is now approved for mild to moderate atopic dermatitis, and is another option for nonsteroidal treatments.

SUNSCREENS

Sunscreens are of two general types: (1) those, such as zinc oxide and titanium dioxide, that absorb all wavelengths of the UV and visible spectrums and (2) a heterogeneous group of chemicals that selectively absorb energy of various wavelengths within the UV spectrum. In addition to the spectrum of light that is blocked, other factors to be considered include cosmetic acceptance, sensitizing potential, retention on skin while swimming or sweating, required frequency of application, and cost. Sunscreen ingredients include para-aminobenzoic acid (PABA) with ethanol, PABA esters, cinnamates, and benzophenone. These block transmission of the majority of solar UVB and some UVA wavelengths. Avobenzone and ecamsule are more effective in blocking UVA. Antioxidants may also be found in some sunscreens. Lip protectants that absorb in the UVB range are also available. Some chemical sunscreens (oxybenzone, octocrylene, and octinoxate) have been implicated in harming coral reefs and are banned in certain areas of the world.

Sunscreens are designated by sun protection factor (SPF). The SPF is defined as the amount of time to develop a mild sunburn with the sunscreen compared with the amount of time without the sunscreen. A minimum SPF factor of 30 should be recommended most often. The higher the SPF, the better the protection is against UVB rays. Sunscreens do not include any measurement of the efficacy in blocking UVA. The efficacy of these agents depends on careful attention to instructions for use. Chemical sunscreens should be applied at least 30 minutes before sun exposure to permit penetration into the epidermis, again on arrival at the destination, and every subsequent hour when exposed to direct sunlight. Most patients with photosensitivity eruptions require protection by agents that absorb both UVB and UVA wavelengths (see Chapter 697).

Although sunscreens do confer photoprotection and may decrease the development of nevi, protection is incomplete against all harmful UV light. Midday (10 AM to 4 PM) sun avoidance is the primary method of photoprotection. Clothing, hats, and staying in the shade offer additional sun protection.

LASER THERAPY

The vascular-specific pulsed dye laser therapy is used mainly for the treatment of capillary malformations (port-wine stains). Spider telangiectasia, small facial pyogenic granulomas, superficial and ulcerated hemangioma, and warts may also be treated. Vascular-specific pulsed dye lasers produce light that is readily absorbed by oxyhemoglobin, producing selective photothermolysis of vascular lesions.

Ultraviolet Phototherapy

Phototherapy can be a useful treatment for many cutaneous inflammatory disorders, including atopic dermatitis, psoriasis, pityriasis lichenoides, vitiligo, and a few others. Some benefits of phototherapy include the fact that it is well tolerated, may treat a large area of the body, and may enable a patient to avoid systemic immunosuppressive agents. There are two traditional modalities of treatment: psoralen (a photosensitizer) + UVA (PUVA) or narrow-band UVB phototherapy (NBUVB). NBUVB phototherapy is most often used, typically dosed between 1 and 3 times per week, depending on the condition. There is an increased risk of skin cancers with long-term use of PUVA, but there does not seem to be an increased risk for NBUVB. Risks include burns, though this is quite rare if performed properly.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 688

Dermatologic Diseases of the Neonate

Sarah B. Younger and Kari L. Martin

Minor evanescent lesions of newborn infants, particularly when florid, may cause undue concern. Most of these entities are relatively common, benign, and transient and do not require therapy.

SEBACEOUS HYPERPLASIA

Minute, profuse, yellow-white papules are frequently found on the forehead, nose, upper lip, and cheeks of a term infant; they represent hyperplastic sebaceous glands (Fig. 688.1). These tiny papules diminish gradually in size and disappear entirely within the first few weeks of life; no treatment is required.

MILIA

Milia are superficial epidermal inclusion cysts that contain laminated keratinized material. The lesion is a firm cyst, 1-2 mm in diameter, and pearly, opalescent white. Milia may occur at any age, but in neonates are most frequently scattered over the face and gingivae and on the midline of the palate, where they are called *Epstein pearls.* Milia exfoliate spontaneously in most infants and may be ignored; those that appear in scars or sites of trauma in older children may be gently unroofed and the contents extracted with a fine-gauge needle.

SUCKING BLISTERS

Solitary or scattered superficial bullae present at birth on the upper limbs of infants are presumably induced by vigorous sucking on the affected part in utero. Common sites are the radial aspect of the forearm, thumb, and index finger. These bullae resolve rapidly without sequelae. They may occur in conjunction with sucking pads (calluses), which are found on the lips and are a result of combined intracellular edema and hyperkeratosis. No treatment is required.

CUTIS MARMORATA

When a newborn infant is exposed to low environmental temperatures, an evanescent, lacy, reticulated red and/or blue cutaneous vascular pattern appears over most of the body surface. This vascular change represents an accentuated physiologic vasomotor response that disappears with increasing age, although it is sometimes discernible even in older children. No treatment is needed.

Cutis marmorata telangiectatica congenita presents in a similar fashion but is a vascular anomaly in which the lesions are more intense, may be segmental, and are persistent despite warming of the infant. They may be associated with loss of dermal tissue, epidermal atrophy, and ulceration (Fig. 688.2). The lower extremities are usually affected, with limb atrophy noted on the affected side. Gradual fading of the livid erythema occurs over 3-5 years, but limb asymmetry is permanent. Extracutaneous findings such as ocular and neurologic abnormalities may be associated in 20–80% of cases. There is no specific treatment.



Fig. 688.1 Sebaceous hyperplasia. Minute white-yellow papules on the nose of a newborn.

HARLEQUIN COLOR CHANGE

A dramatic vascular event, harlequin color change occurs transiently in up to 10% of newborns, most commonly on days 2-52 of life. It probably reflects an imbalance in the autonomic vascular regulatory mechanism. When the infant is placed on one side, the body is bisected longitudinally into a pale upper half and a deep red dependent half. The color change lasts only for a few minutes and occasionally affects only a portion of the trunk or face. Changing the infant's position may reverse the pattern. Muscular activity causes generalized flushing and obliterates the color differential. Repeated episodes may occur but do not indicate permanent autonomic imbalance. There is generally no need for treatment. This disorder should be readily distinguishable from harlequin syndrome, which is associated with paroxysmal hemifacial flushing and sweating with or without a Horner syndrome. Symptoms are induced by heat, stress, or exercise. Some cases are secondary to trauma, cervical cord syrinx, or neuroblastoma. Although rarely congenital, most cases occur in older children.

NEVUS SIMPLEX (SALMON PATCH)

Nevus simplex is a small, pale pink, ill-defined, vascular macule that occurs most commonly on the glabella, eyelids, upper lip, and nuchal area of 40–60% of normal newborn infants. These lesions persist for several months and may become more visible during crying or changes in environmental temperature. Most lesions on the face eventually fade and disappear completely, although lesions occupying the entire central forehead often do not. Those on the posterior neck and occipital areas usually persist. Treatment is not usually indicated, though pulsed dye laser treatment can be helpful in lightening lesions that are persistent and cosmetically bothersome. Lesions located in the midline lumbosacral area and associated with other changes such as a sinus or pit, patch of hair, or asymmetric gluteal cleft warrant imaging with ultrasound to evaluate the underlying spinal cord for spinal dysraphism.

Nevus simplex should not be confused with a port-wine stain (capillary malformation), which is a permanent lesion and may be associated with Sturge-Weber syndrome. Nevus simplex is usually symmetric, with lesions on both eyelids or on both sides of the midline. Port-wine stains are often larger and unilateral, and they usually end along the midline (see Chapter 691).



Fig. 688.2 Newborn girl with reticulate erythema/livedo on legs, right arm, and cheeks. *(From Pleimes M, Gottler S, Weibel L. Characteristic congenital reticular erythema: cutis marmorata telangiectatica congenital. J Pediatr. 2013;163:604, Fig. 1.)*

CONGENITAL DERMAL MELANOCYTOSIS (SLATE GRAY NEVUS)

Congenital dermal melanocytosis, which appears as blue or slate-gray macular lesions, has variably defined margins. It occurs most commonly in the sacral area but may be found over the posterior thighs, legs, back, and shoulders (Fig. 688.3). The spots may be solitary or numerous and often involve large areas. The peculiar hue of these macules is a result of the dermal location of melanin-containing melanocytes (mid-dermal melanocytosis) that are presumably arrested in their migration from neural crest to epidermis. They usually fade during the first few years of life as a result of darkening of the overlying skin; no therapy is required. If lesions persist, they may be treated with lasers, if desired. Malignant degeneration does not occur. The characteristic appearance and congenital onset distinguish these spots from the bruises of child abuse. Rarely dermal melanocytosis is associated with Hurler or Hunter syndrome, GM1 gangliosidosis, Niemann-Pick disease, mucolipidosis, and mannosidosis. These lesions have previously been referred to as "Mongolian spots." This term should be avoided, as it derives from racist terminology.

ERYTHEMA TOXICUM

A benign, self-limited, evanescent eruption, erythema toxicum occurs in approximately 50% of full-term infants; preterm infants are affected less commonly. The lesions are firm, yellow-white, 1- to 2-mm papules or pustules with a surrounding erythematous flare (Fig. 688.4). At times, splotchy erythema is the only manifestation. Lesions may be sparse or numerous and either clustered in several sites or widely dispersed over much of the body surface. The palms and soles are usually spared. Peak incidence occurs on the second day of life, but new lesions may erupt during the first few days as the rash waxes and wanes. Onset may occasionally be delayed for a few days to weeks in premature infants. Eosinophils can be demonstrated in Wright-stained smears of the intralesional contents. Cultures are sterile.

The cause of erythema toxicum is unknown. The lesions can mimic pyoderma, candidiasis, herpes simplex, transient neonatal pustular melanosis, and miliaria but can be differentiated by the characteristic infiltrate of eosinophils and the absence of organisms on a stained smear. The course is brief (3-7 days), and lesions generally resolve without pigmentation. No therapy is required. Incontinentia pigmenti and eosinophilic pustular folliculitis also have eosinophilic infiltration but can be distinguished by their distribution, histologic type, and chronicity.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

Pustular melanosis is a transient, benign, self-limited dermatosis of unknown etiology that is characterized by three types of lesions: (1) evanescent superficial pustules, (2) ruptured pustules with a collarette of fine scale, at times with a central hyperpigmented macule, and (3) hyperpigmented macules (Fig. 688.5). Lesions are present at birth, and one or all types of lesions may be found in a profuse or sparse distribution. Pustules represent the early phase of the disorder, and macules, the late phase. The pustular phase rarely lasts more than 2-3 days; hyperpigmented macules may persist for as long as 3 months. Sites of predilection are the anterior neck, forehead, and lower back, although the scalp, trunk, limbs, palms, and soles may be affected.

The active phase shows an intracorneal or subcorneal pustule filled with polymorphonuclear leukocytes, debris, and an occasional eosinophil. The macules are characterized only by increased melanization of epidermal cells. Cultures and smears can be used to distinguish these pustules from those of pyoderma and erythema toxicum, because the lesions of pustular melanosis do not contain bacteria or dense aggregates of eosinophils. No therapy is required.

INFANTILE ACROPUSTULOSIS

Onset of infantile acropustulosis generally occurs at 2-10 months of age; lesions are occasionally noted at birth (Fig. 688.6). The cause is unknown. The lesions are initially discrete erythematous papules that become vesiculopustular within 24 hours and subsequently crust over before healing.



Fig. 688.3 Extensive dermal melanocytosis on the back of a newborn. *(Courtesy Fitzsimons Army Medical Center teaching file.)*



Fig. 688.4 Erythema toxicum on the trunk of a newborn infant.



Fig. 688.5 Transient neonatal pustular melanosis. Multiple papules present at birth on the arm of an infant. *(From Weston WL, Lane AT, Morelli JG, eds. Color Textbook of Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 2002:331.)*



Fig. 688.6 Acropustulosis of infancy. Multiple tense erythematous papules and pustules on the palm of this 4-mo-old girl. *(From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. Philadelphia: Elsevier; 2017: Fig. 47.3, p. 854.)*

They are intensely pruritic. Preferred sites are the palms of the hands and the soles and sides of the feet, where the lesions may be extensive. A less dense eruption may be found on the dorsum of the hands and feet, ankles, and wrists. Pustules occasionally occur elsewhere on the body. Each episode lasts 7-14 days, during which time pustules continue to appear in crops. After a 2- to 4-week remission, a new outbreak follows. This cyclic pattern continues for approximately 2 years; permanent resolution is often preceded by longer intervals of remission between periods of activity. Infants with acropustulosis are otherwise well.

Wright-stained smears of intralesional contents show abundant neutrophils or, occasionally, a predominance of eosinophils. Histologically, well-circumscribed, subcorneal, neutrophilic pustules, with or without eosinophils, are noted.

The differential diagnosis in neonates includes transient neonatal pustular melanosis, erythema toxicum, milia, cutaneous candidiasis, and staphylococcal pustulosis. In older infants and toddlers, additional diagnostic considerations include scabies, dyshidrotic eczema, pustular psoriasis, subcorneal pustular dermatosis, and hand-foot-and-mouth disease. A therapeutic trial of a scabicide is warranted in equivocal cases.

Therapy is directed at minimizing discomfort for infants. Topical mid- to high-potency corticosteroids and/or oral antihistamines may decrease the severity of the pruritus and an infant's irritability. Dapsone (1-2 mg/kg/day by mouth, divided in one to two doses) is effective but has potentially serious side effects, notably, hemolytic anemia and methemoglobinemia; its use should be limited to particularly severe cases.

EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis is defined as recurrent crops of pruritic, coalescing, follicular papulopustules on the face, trunk, and extremities. Fifty percent of patients have peripheral eosinophilia, with eosinophil counts exceeding 5%, and approximately 30% have leukocytosis (>10,000 leukocytes/mm^3).

Infants account for <10% of all cases of eosinophilic pustular folliculitis. The clinical and histologic appearances of this disorder in infants closely resemble those in immunocompetent adults, with minor exceptions. In infants, the lesions are most prominent on the scalp, although they also occur on the trunk and extremities and occasionally are found on the palms and soles. The classic annular and polycyclic appearance with centrifugal enlargement is not seen in infants. The differential diagnosis includes erythema toxicum neonatorum, infantile acropustulosis, localized pustular psoriasis, pustular folliculitis, and transient neonatal pustular melanosis. High-potency topical corticosteroids are the most effective treatment (see Table 687.1).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 689

Cutaneous Defects

Kari L. Martin

SKIN DIMPLES

Cutaneous depressions over bony prominences and in the sacral area, at times associated with pits and creases, may occur both in normal children and in association with dysmorphic syndromes. Skin dimples may develop in utero because of interposition of tissue between a sharp bony point and the uterine wall, which leads to decreased subcutaneous tissue formation.

Dimples may also be present overlying an area of bone hypoplasia. Bilateral acromial skin dimples are usually an isolated finding, but they are also seen in association with deletion of the long arm of chromosome 18. Dimples tend to occur over the patella in congenital rubella, over the lateral aspects of the knees and elbows in prune-belly syndrome, on the pretibial surface in campomelic syndrome, and in the shape of an H on the chin in Freeman-Sheldon ("whistling face") syndrome.

Sacral dimples are common and usually are isolated findings. They may be seen in multiple syndromes or in association with spina bifida occulta and diastematomyelia. Association with a mass or other cutaneous stigma (hair, aplasia cutis, lipoma, hemangioma) should increase concern for underlying **spinal dysraphism** (see Chapter 631). Simple sacral dimples do not predict underlying spinal cord malformations, and spinal ultrasounds should not be performed in these cases because most of the abnormal findings reported in them are of no clinical significance. In infants younger than 3 months who warrant imaging, ultrasound is an initial, cost-effective, noninvasive method. If there is serious concern of an underlying defect, MRI is indicated. *MRI of the spine is the imaging modality of choice for patients older than 3 months if there is a strong suspicion of a spinal dysraphism.*

REDUNDANT SKIN

Loose folds of skin must be differentiated from a congenital defect of elastic tissue or collagen such as cutis laxa, Ehlers-Danlos syndrome, or pseudoxanthoma elasticum. Redundant skin over the posterior part of the neck is common in Turner, Noonan, Down, and Klippel-Feil syndromes and monosomy 1p36; more generalized folds of skin occur in infants with trisomy 18 and short-limbed skeletal dysplasia.

AMNIOTIC CONSTRICTION BANDS

Partial or complete constriction bands that produce defects in extremities and digits are found in 1 in 10,000-45,000 otherwise normal infants. Constrictive tissue bands are caused by primary amniotic rupture, with subsequent entanglement of fetal parts, particularly limbs, in shriveled fibrotic amniotic strands. This event is probably sporadic, with negligible risk of recurrence. Formation of constrictive tissue bands is associated with maternal history of abdominal trauma, amniocentesis, and hereditary defects of collagen such as Ehlers-Danlos syndrome and osteogenesis imperfecta. Treatment traditionally involves multiple surgical elongating procedures such as Z- and W-plasties. A surgical alternative uses lipoinjection and multiple internal incisions on the deep surface of the band.

Adhesive bands involve the craniofacial area and are associated with severe defects such as encephalocele and facial clefts. Adhesive bands result from broad fusion between disrupted fetal tissue and an intact amniotic membrane. The craniofacial defects appear not to be caused by constrictive amniotic bands, but to result from a vascular disruption sequence with or without cephaloamniotic adhesion (see Chapter 100).

The limb–body wall complex involves vascular disruption early in development, affecting several embryonic structures; it includes at least two of the following three characteristics: exencephaly or encephalocele with facial clefts, thoracoschisis and/or abdominoschisis, and limb defects.

PREAURICULAR SINUSES AND PITS

Pits and sinus tracts anterior to the pinna may be a result of imperfect fusion of the tubercles of the first and second branchial arches. These anomalies may be unilateral or bilateral, may be familial, and at times are associated with other anomalies of the ears and face. **Preauricular pits** are present in **branchiootorenal dysplasia 1 syndrome** (*EYA-1* gene), an autosomal dominant disorder that consists of external ear malformations, branchial fistulas, hearing loss, and renal anomalies. When the tracts become chronically infected, retention cysts may form and drain intermittently; such lesions may require excision.

ACCESSORY TRAGI

An accessory tragus typically appears as a single pedunculated, flesh-colored papule in the preauricular region anterior to the tragus. Less commonly, accessory tragi are multiple or bilateral and may be located in the preauricular area, on the cheek along the line of the mandible (Fig. 689.1), or on the lateral aspect of the neck anterior to the sternocleidomastoid muscle. In contrast to the rest of the pinna, which develops from the second branchial arch, the tragus and accessory tragi derive from the first branchial arch. Accessory tragi may occur as isolated defects or in chromosomal first branchial arch syndromes that include anomalies of the ears and face, such as cleft lip, cleft palate, and mandibular hypoplasia. An accessory tragus is consistently found in oculoauriculovertebral syndrome (Goldenhar syndrome). Other associated syndromes include mandibulofacial dysostosis (Treacher Collins syndrome), Townes-Brocks, VACTERL, and Wolf-Hirschhorn syndrome. Surgical excision is appropriate if cosmetically desired.

Studies are controversial on whether patients with accessory tragi and preauricular pits have a higher prevalence of hearing loss and urinary tract anomalies. *Renal ultrasound should be performed when found with at least one of the following: other malformations or dysmorphic features; family history of deafness, auricular, and/or renal malformation; or a maternal history of gestational diabetes.*

BRANCHIAL CLEFT AND THYROGLOSSAL CYSTS AND SINUSES

Cysts and sinuses in the neck may be formed along the course of the first, second, third, or fourth branchial clefts as a result of improper closure during embryonic life. Second branchial cleft cysts are the most common. The lesions may be unilateral or bilateral (2–3%) and may open onto the cutaneous surface or drain into the pharynx. Secondary infection is an indication for systemic antibiotic therapy. These anomalies may be inherited as autosomal dominant traits.

Thyroglossal cysts and fistulas are similar defects located in or near the midline of the neck; they may extend to the base of the tongue. A pathognomonic sign is vertical motion of the mass with swallowing and tongue protrusion. In nearly 50% of affected children, the cyst or fistula manifests as an infected midline upper neck mass. Cysts in the tongue base may be differentiated from an undescended lingual thyroid by radionuclide scanning. Unlike branchial cysts, a thyroglossal duct cyst often appears after an upper respiratory infection (see Chapter 601).



Fig. 689.1 Accessory tragus on cheek along jaw line.

PILONIDAL SINUS AND ABSCESS

The etiology of pilonidal disease remains unknown; three hypotheses explaining its origin have been proposed. The first states that trauma, such as can occur with prolonged sitting, impacts hair into the subcutaneous tissue, which serves as a nidus for infection. The second suggests that in some patients, hair follicles exist in the subcutaneous tissues, perhaps the result of some embryologic abnormality, and that they serve as a focal point for infection, especially with secretion of hair oils. The third speculates that motion of the buttocks disturbs a particularly deep midline crease and works bacteria and hair beneath the skin. This theory arises from the apparent improved short-term and long-term results of operations that close the wound off the midline, obliterating the deep natal cleft.

Pilonidal disease usually manifests in adolescents or young adults with significant hair over the midline sacral and coccygeal areas. It can occur as an acute abscess with a tender, warm, flocculent, erythematous swelling or as draining sinus tracts. This disease does not resolve with nonoperative treatment. An acute abscess should be drained and packed open, using appropriate anesthesia. Oral broad-spectrum antibiotics covering the usual isolates (*Staphylococcus aureus* and *Bacteroides* species) are prescribed, and the patient's family withdraws the packing over the course of a week. When the packing has been totally removed, the area can be kept clean by a bath or shower. The wound usually heals completely in 6 weeks. Once the wound is healed, most pediatric surgeons feel that elective excision should be scheduled to avoid recurrence. There are some reports, however, that this is only necessary if the disease recurs. Usually, patients who present with sinus tracts are managed with a single elective excision.

Most surgeons carefully identify the extent of each sinus tract and excise all skin and subcutaneous tissue involved to the fascia covering the sacrum and coccyx. Some close the wound in the midline; others leave it open and packed for healing by secondary intention. This method has been modified by the application of a vacuum-assisted (VAC sponge) dressing. This is a system that applies continuous suction to a porous dressing. It is usually changed every 3 days and can be done at home with the assistance of a nurse. Some marsupialize the wound by suturing the skin edges down to the exposed fascia covering the sacrum and coccyx. There appears to be improved success with excision and closure in such a way that the suture line is not in the midline. Currently there appears to be enthusiasm for the less radical methods that Bascom has introduced, treating simple sinus tracts with small local procedures and limiting excision to only diseased tissues, while still keeping the incision off the midline. Recurrence or wound-healing problems are relatively common, occurring in 9–27% of cases. The variety of treatments and procedures currently being described indicates that all are associated with significant complications and delays in return to normal activity. Still, it is rare for problems to persist beyond 1-2 years. Recalcitrant cases are treated by a large, full-thickness gluteal flap or skin grafting.

SUPERNUMERARY NIPPLES

Solitary or multiple accessory nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. Accessory nipples may or may not have areolae and may be mistaken for congenital nevi. They may be excised for cosmetic reasons, but otherwise, treatment is not necessary. Renal or urinary tract anomalies, malignancies—especially genitourinary cancers—and hematologic abnormalities may rarely occur in children with this finding (see Chapter 588).

APLASIA CUTIS CONGENITA (CONGENITAL ABSENCE OF SKIN)

Developmental absence of skin is usually noted on the scalp as multiple or solitary (70%), noninflammatory, well-demarcated, oval or circular 1- to 2-cm ulcers (Table 689.1). The appearance of lesions varies, depending on when they occurred during intrauterine development. Those that form early in gestation may heal before delivery and appear as atrophic, fibrotic scars with associated alopecia, whereas more recent defects may

Table 689.1 Freiden's Classification of Aplasia Cutis Congenita

GROUP	DEFINITION	INHERITANCE
1	Isolated scalp involvement; may be associated with single defects	AD
2	Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocele	AD
3	Scalp ACC with epidermal nevus	Sporadic
4	ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocele	Sporadic
5	ACC with placental infarcts and/or fetus papyraceus (disappearing twin syndrome)	Sporadic
6	ACC with epidermolysis bullosa; Bart phenotype*	AD or AR
7	ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet	AD or AR
8	ACC caused by teratogens (e.g., varicella, herpes, methimazole, valproic acid, misoprostol)	Sporadic
9	ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p−, deletion Xp22.1, ectodermal dysplasia, Johanson-Blizzard syndrome, Adams-Oliver syndrome)	Variable

*Bart phenotype ACC with epidermolysis bullosa and dystrophic nails.
ACC, Aplasia cutis congenital; AD, autosomal dominant; AR, autosomal recessive.
Modified from Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol.* 1986;14:646–660.

manifest as ulcerations. Most occur at the vertex of the scalp just lateral to the midline, but similar defects may also occur on the face, trunk, and limbs, where they are often symmetric and usually associated with an intrauterine fetal demise of a twin **(fetus papyraceus)**. The depth and size of the ulcer vary. Only the epidermis and upper dermis may be involved, resulting in minimal scarring or hair loss, or less often, the defect may extend to the deep dermis; to the subcutaneous tissue; and, rarely, to the periosteum, skull, and dura. Lesions may be surrounded by a ring of hair known as the **hair collar sign** (Fig. 689.2). The hair collar sign may also be associated with an encephalocele, meningocele, heterotopic glial tissue, or a meningothelial hamartoma.

Diagnosis is made on physical findings indicative of in utero disruption of skin development. Lesions are sometimes mistakenly attributed to scalp electrodes or obstetric trauma. Most are sporadic, but autosomal dominant and recessive cases also occur; some are caused by pathogenic variants in *BMS1*.

Although most individuals with aplasia cutis congenita have no other abnormalities, these lesions may be associated with isolated physical anomalies or with malformation syndromes, including Opitz, Adams-Oliver, oculocerebrocutaneous, Johanson-Blizzard, and 4p(−), X-p22 microdeletion syndromes; trisomy 13-15; and chromosome 16-18 defects (see Table 689.1). Aplasia cutis congenita may also be found in association with an overt or underlying embryologic malformation, such as congenital pulmonary malformations, meningomyelocele, gastroschisis, omphalocele, or spinal dysraphism. Aplasia cutis congenita in association with the vanishing twin syndrome (fetus papyraceus) is apparently caused by ischemic or thrombotic events in the placenta and fetus such as the hypovolemia that occurs with acute transfusion from a surviving to a dying twin. Blistering or skin fragility and/or absence or deformity of nails in association with aplasia cutis congenita is a well-recognized manifestation of epidermolysis bullosa.



Fig. 689.2 Solitary scalp vertex lesion of aplasia cutis congenita with hair collar sign.



Fig. 689.3 An elastic protruding hairless nodule measuring up to 1.5 cm in diameter, with a ring of dark, coarse, long hairs surrounding the nodule forming a "hair collar." *(From Chien MM, Chen KL, Chiu HC. The "hair collar" sign. J Pediatr. 2016;168:246.)*

Major complications are rare and more often associated with large, stellate lesions of the midline parietal scalp. Hemorrhage, secondary local infection, and meningitis have been reported. If the defect is small, recovery is uneventful, with gradual epithelialization and formation of a hairless atrophic scar over a period of several weeks. Small bony defects usually close spontaneously in the first year of life. Large or numerous scalp defects may require repair, but care must be taken, as abnormal underlying venous structures have complicated surgical repair. Truncal and limb defects, despite being large, usually epithelialize and form atrophic scars, which can later be revised.

Although the hair collar sign is often associated with aplasia cutis, it may also be seen with encephaloceles, meningoceles, heterotopic glial elements, or hamartoma. Brain MRI is often indicated to evaluate for these lesions in patients with the hair collar sign without aplasia cutis (Fig. 689.3).

FOCAL FACIAL DERMAL DYSPLASIAS

The focal facial dermal dysplasias (FFDDs) are a rare group of conditions sharing bitemporal or preauricular lesions resembling scars or aplasia cutis congenita. FFDD1 **(Brauer syndrome)** is inherited in an autosomal dominant fashion and typically has mild associated facial features. FFDD2 **(Brauer-Setleis syndrome)** and FFDD3 **(Setleis syndrome)** are associated with thin, puckered periorbital skin, distichiasis

and/or absent eyelashes, upslanting palpebral fissures, flat nasal bridge, large lips, and redundant facial skin. FFDD2 is inherited in an autosomal dominant fashion, whereas FFDD3 is autosomal recessive and caused by pathogenic variants in *TWIST2;* autosomally dominant cases of FFDD3 have been reported and are caused by chromosome duplication/triplication of the 1p36.22p36.21 region. FFDD4 has no other related skin findings; it is inherited both in autosomal dominant and recessive manners and is caused by pathogenic variants in *CYP26C1*.

FOCAL DERMAL HYPOPLASIA (GOLTZ-GORLIN SYNDROME)

A rare congenital mesoectodermal and ectodermal disorder, focal dermal hypoplasia is characterized by dysplasia of connective tissue in the skin and skeleton. This disorder is an X-linked dominant disorder caused by pathogenic variants in the *PORCN* gene. It manifests as numerous soft tan papillomas. Other cutaneous findings include linear atrophic lesions, reticulated hypopigmentation and hyperpigmentation, telangiectasias, congenital absence of skin, angiofibromas presenting as verrucous excrescences, and papillomas of the lips, tongue, circumoral region, vulva, anus, and the inguinal, axillary, and periumbilical areas. Partial alopecia, sweating disorders, and dystrophic nails are additional, less common ectodermal anomalies. The most frequent skeletal defects are syndactyly, clinodactyly, polydactyly, and scoliosis. **Osteopathia striata** are fine parallel vertical stripes noted on radiographs in the metaphyses of long bones of patients with this disorder; these are highly characteristic of focal dermal hypoplasia but are not pathognomonic. Many ocular abnormalities, the most common of which are colobomas, strabismus, nystagmus, and microphthalmia, are also characteristic. Small stature, enamel hypoplasia, soft tissue anomalies, and peculiar dermatoglyphic patterns are also common. Cognitive impairment occurs occasionally. There is no specific treatment.

DYSKERATOSIS CONGENITA (ZINSSER-ENGMAN-COLE SYNDROME)

Dyskeratosis congenita (DKC), a rare familial syndrome, consists classically of the triad of reticulated hyperpigmentation of the skin (Fig. 689.4), dystrophic nails, and mucous membrane leukoplakia in association with immunologic and hematologic abnormalities. Patients with DKC also show signs of premature aging and increased occurrence of cancer, especially squamous cell carcinoma. DKC may be X-linked recessive (*DKC-1* gene), autosomal dominant (*hTERC* and *TINF2* genes), or autosomal recessive (*NOLA3* gene). Onset occurs in childhood, most commonly as nail dystrophy. The nails become atrophic and ridged longitudinally with progression to pterygia and complete nail loss. Skin changes usually appear after onset of nail changes and consist of reticulated gray-brown pigmentation, atrophy, and telangiectasia, especially on the neck, face, and chest. Hyperhidrosis and hyperkeratosis of the palms and soles, sparse scalp hair, and easy blistering of the hands and feet are also characteristic. Blepharitis, ectropion, and excessive tearing because of atresia of the lacrimal ducts are occasional manifestations. Oral leukokeratosis may give rise to squamous cell carcinoma. Other mucous membranes, including conjunctival, urethral, and genital, may be involved. Infection, malignancy, pulmonary fibrosis, and bone marrow failure are common, and death before age 40 years is typical. No effective treatment exists. Allogenic hemopoietic stem cell transplantation is curative treatment when bone marrow failure occurs.



Fig. 689.4 Reticulated dyspigmentation on neck of patient with dyskeratosis congenita.

CUTIS VERTICIS GYRATA

Cutis verticis gyrata, an unusual alteration of the scalp that is more common in males, may be present from birth or may develop during adolescence. The scalp is characterized by convoluted elevated folds, 1-2 cm in thickness, usually in the fronto-occipital axis. Unlike the lax skin of other disorders, the convolutions cannot generally be flattened by traction. **Primary cutis gyrata** may be associated with intellectual disability, retinitis pigmentosa, sensorineural deafness, and thyroid aplasia. **Secondary cutis gyrata** may be the result of chronic inflammatory diseases, tumors, nevi, and acromegaly.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 690

Ectodermal Dysplasias

Kari L. Martin

Ectodermal dysplasia (ED) is a heterogeneous group of disorders characterized by a constellation of findings involving defects of two or more of the following: teeth, skin, and appendageal structures, including hair, nails, and eccrine and sebaceous glands. Although more than 150 EDs have been described, the majority are rare, with an estimated incidence of 3.5 in 10,000 individuals.

Individuals presenting with a constellation of abnormalities involving the teeth, skin, and nails should raise suspicion for a diagnosis of ED. Table 690.1 provides a general list of abnormalities that may be seen in patients with EDs. Further specifying the specific type of ED can be challenging because there are a large number of subtypes and most are extremely rare (Table 690.2). Exome sequencing may enhance the identification of these rare subtypes.

Table 690.1 Clinical Abnormalities in Ectodermal Dysplasia

Teeth	Small primary teeth, anodontia or hypodontia of secondary teeth, conical or peg teeth, premature loss of teeth, delayed eruption of teeth, defective enamel, small widely spaced teeth, elongated pulp chamber in teeth
Skin	Atopic dermatitis, xerosis, photosensitivity, palmoplantar keratoderma, facial telangiectasias
Hair	Abnormal quantity, structure and quality: thin, brittle, slow-growing, kinky or wooly, fragile, dry, and lusterless hair. Often involves scalp, eyebrows and eyelashes.
Nails	Brittle, dystrophic, absent, ridging, pitting
Sweat	Hypohidrosis, hyperhidrosis of palms and soles
Other	Recurrent sinus infection, nasal congestion, hoarse voice, wheezing

Normal phenotype is also possible for any of these categories.

Table 690.2 Classification for Ectodermal Dysplasias*

DISORDER†	INHERITANCE	GENE	PROTEIN	FUNCTION
EDA/NF-κB PATHWAY				
Hypohidrotic ectodermal dysplasia	XLR	*EDA1*	Ectodysplasin (EDA)	Membrane ligand
Hypohidrotic ectodermal dysplasia	AD	*EDAR*	EDA receptor (EDAR)	Receptor of EDA
		EDARADD	EDAR-associated death domain	Adaptor molecule
Hypohidrotic ectodermal dysplasia	AR	*EDAR*	EDAR	Receptor of EDA
		EDARADD	EDAR-associated death domain	Adaptor molecule
		TRAF6	TNF receptor–associated factor 6	Activates IKK
Hypohidrotic ectodermal dysplasia with immune deficiency (males) ± osteopetrosis (males) ± lymphedema	XLR	*NEMO/IKBKG*	NF-kB essential modulator	NF-kB activation
Incontinentia pigmenti (females)	XLD	*NEMO/IKKγ*	NF-κB essential modulator	NF-κB activation
Hypohidrotic ectodermal dysplasia with immune deficiency	AR	*IkBα*	IkBα	NF-kB activation
P63 PATHWAY				
Ectrodactyly-ectodermal dysplasia-clefting syndrome	AD	*p63*	p63	Transcription factor
Rapp-Hodgkin syndrome	AD	*p63*	p63	Transcription factor
Ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC)	AD	*p63*	p63	Transcription factor
Acrodermatoungual-lacrimal-tooth (ADULT)	AD	*p63*	p63	Transcription factor
Limb-mammary syndrome	AD	*p63*	p63	Transcription factor
Curly hair, ankyloblepharon, and nail dystrophy (CHAND) syndrome	AR	*RIPK4*	RIPK4	Serine/threonine protein kinase
Popliteal pterygium syndromes (spectrum)	AR, AD	*IRF6*	IRF6	Transcription factor
Popliteal pterygium	AR	*RIPK4*	RIPK4	Kinase
Bartsocas-Papas (Cocoon syndrome)	AR	*CHUK*	CHUK	Kinase
Ectodermal dysplasia	AD	*KDF1*	KDF1	Keratinocyte differentiation factor
Trichodentoosseous syndrome (TDO)	AD	*DLX3*	DLX3	Transcription factor
Clefting-ectodermal dysplasia	AR	*PVRL1*	Nectin 1	Interacts with cadherins, especially at adherens junctions
Ectodermal dysplasia-syndactyly syndrome	AR	*PVRL4*	Nectin 4	Interacts with cadherins, especially at adherens junctions
Hypotrichosis with juvenile macular dystrophy ± ectrodactyly/other ectodermal defects	AR	*CDH3*	Cadherin 3/P-cadherin	Adhesion molecule for cell-cell binding
WNT PATHWAY				
Witkop syndrome	AD	*MSX1*	MSX1	Transcription factor
Focal dermal hypoplasia	X-linked dominant	*PORCN*	PORCN	Regulates Wnt signaling
Oculodentodigital dysplasia (ODDD)	AD	*WNT10A*	Wnt10A	Wnt pathway
Hypohidrotic ectodermal dysplasia	AR, AD	*WNT10A*	Wnt10A	β-catenin-mediated signaling
Schöpf-Schulz-Passarge syndrome	AR	*WNT10A*	Wnt10A	β-catenin-mediated signaling

Table 690.2 Classification for Ectodermal Dysplasias*—cont'd

DISORDER†	INHERITANCE	GENE	PROTEIN	FUNCTION
Ectodermal dysplasia	AR	*KREMEN1*	KREMEN1	Receptor involved in Wnt regulation
STRUCTURAL ELEMENT				
Clouston syndrome	AD	*GJB6*	Connexin 30	Intercellular junctions
Ectodermal dysplasia	AR	*GRHL2*	Grainyhead-like 2	Transcription factor
Oculodentodigital dysplasia (ODDD)	AR	*GJA1*	Connexin 43	Intercellular junctions
Ellis van Creveld syndrome	AR	*EVC, EVC2*	EVC, EVC2	Ciliopathy
Ectodermal dysplasia 4, hair/nail type (ECTD4)	AR	*KRT85*	KRT85	Keratin
Keratitis-ichthyosis-deafness syndrome, autosomal dominant (KID)	AR	*GJB2*	Connexin 26	Intercellular junctions
Ectodermal dysplasia: skin fragility syndrome	AR	*PKP1*	Plakophilin 1	Desmosomal plaque/ stability
Naegeli- Franceschetti-Jadassohn syndrome	AD	*KRT14*	KRT14	Keratin
Pachyonychia congenita	AD	*KRT 6a, 6b, 6c, 16, 17*	KRT 6a, 6b, 6c, 16, 17	Keratin

*Many forms of ectodermal dysplasia remain unclassified.
†Some more recently described forms of ectodermal dysplasia are not yet named.
AD, Autosomal dominant; AR, autosomal recessive; IKK, inhibitor of kappa light polypeptide gene enhancer in B-cell kinase; TNF, tumor necrosis factor; XLD, X-linked dominant; XLR, X-linked recessive.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 6th ed. Philadelphia: Elsevier; 2022: Table 7.1, p. 165.

HYPOHIDROTIC ECTODERMAL DYSPLASIA

The syndrome known as hypohidrotic ectodermal dysplasia (HED) manifests as a triad of defects: partial or complete absence of sweat glands, anomalous dentition, and hypotrichosis. There are many recognized types of HED; HED-1 (X-linked recessive) is most common, with a frequency of 1 per 17,000 live births.

In HED, affected patients are unable to sweat and may experience episodes of high fever in warm environments, which may be mistakenly considered to be **fevers of unknown origin**. This error is particularly common in infancy when the facial changes are not easily appreciated. Diagnosis at this time may be made using the starch-iodine test or palmar or scalp biopsy. Scalp biopsy is the most sensitive and is 100% specific. It shows a complete lack of eccrine structures. Infants and older children must be protected from high temperatures given their inability to sweat. Cooling devices and clothing can be helpful to increase participation in activities and sports. Aside from patients with *WNT10A* pathogenic variants—who do not have facial dysmorphism—the typical facies are characterized by frontal bossing; malar hypoplasia; a flattened nasal bridge; recessed columella; thick, everted lips; wrinkled, hyperpigmented periorbital skin; and prominent, low-set ears (Fig. 690.1). The skin over the entire body is dry, finely wrinkled, and hypopigmented, often with a prominent venous pattern. Extensive peeling of the skin is a clinical clue to diagnosis in the newborn period. The paucity of sebaceous glands may account for the dry skin. The scalp hair is sparse, fine, and lightly pigmented, and eyebrows and lashes are sparse or absent. Other body hair is also sparse or absent. Sexual hair growth is normal. Anodontia or hypodontia with widely spaced, conical teeth is a consistent feature (see Fig. 690.1). *Co-management with pediatric dentistry familiar with ectodermal dysplasias is critical for oral health, nutrition, and maintenance of the facial bones.* Otolaryngic and ophthalmologic abnormalities secondary to decreased saliva and tear production are seen. The incidence of atopic diseases in children with HED is high. Gastroesophageal reflux is common and may play a role in failure to thrive, which is seen in 20% of cases. Sexual development is usually normal. Historically, the infant mortality rate has been 30%. Carrier females of X-linked HED may have no or less severe clinical manifestations.

Prenatal therapy of X-linked HED with a recombinant protein containing the EDA receptor binding domain has been successful in three patients.

Hypohidrotic ED with immune deficiencies causes similar findings in sweating and hair and nail development, in association with a dysgammaglobulinemia. Significant mortality is seen from recurrent infections. A variety of pathogenic variants of the genes encoding the tumor necrosis factor α (TNFα)–related signaling pathway proteins—key in signal transduction from ectoderm to mesoderm during development—are the molecular basis for this disorder (see Table 690.2).

Treatment of children with HED includes protecting them from exposure to high ambient temperatures. Early dental evaluation is necessary so that prostheses can be provided for cosmetic reasons and for adequate nutrition. The use of artificial tears prevents damage to the cornea in patients with defective lacrimation. Alopecia may necessitate the wearing of a wig to improve appearance.

HIDROTIC ECTODERMAL DYSPLASIA (CLOUSTON SYNDROME)

The salient features of the autosomal dominant disorder hidrotic ED are dystrophic, hypoplastic, or absent nails; sparse hair; and hyperkeratosis of the palms and soles (Table 690.3). Conjunctivitis and blepharitis are common. The dentition and sweating are always normal. Absence of eyebrows and eyelashes, clubbing of the fingers, and hyperpigmentation over the knees, elbows, and knuckles have been noted in some affected individuals. Pathogenic variants in the *GJB6* gene encoding the gap junction protein connexin 30 are responsible for this disorder. A similar disorder associated with deafness has been described with pathogenic variants in the *GJB2* gene encoding the connexin 26 protein. Pathogenic variants in *GJB1* have also been implicated.



Fig. 690.1 Hypohidrotic ectodermal dysplasia is characterized by pointed ears, fine hair, periorbital hyperpigmentation, midfacial hypoplasia, and pegged teeth. *(Courtesy the Fitzsimons Army Medical Center teaching file.)*

Table 690.3 Common Ectodermal Dysplasias: Inheritance and Characteristic Clinical Findings

TYPE	INHERITANCE(S)	CHARACTERISTIC CLINICAL FINDINGS
Hypohidrotic ED	XLR, AD, AR	Distinctive facies: prominent forehead, thick lips and flattened nasal bridge; collodion-like membrane; eczema Hypotrichosis of scalp and trunk, light/brittle/slow-growing hair Hypodontia, conical teeth Hypohidrosis
Hypohidrotic ED-immune deficiency (EDA-ID)	XLR, AD	Seborrheic dermatitis–like rash, intertrigo Hypotrichosis Hypodontia, pointed teeth Hypohidrosis/anhidrosis Recurrent infections Decreased immunoglobulin levels
Hidrotic ED (Clouston)	AD	Hyperpigmented skin over joints; palmoplantar keratoderma, conjunctivitis, blepharitis Milky-white nails in early childhood, nail dystrophy, clubbing Sparse, wiry, brittle, pale scalp hair to total alopecia Normal sweating
Witkop tooth and nail syndrome	AD	Usually normal hair, rarely sparse or fine Normal sweating Small primary teeth, hypodontia causing lower lip eversion ("pouting lower lip") Thin, slow growing hypoplastic nails (toes > fingers), koilonychia
EEC	AD	Dry skin, aplasia or hypoplasia of skin Normal sweating Coarse, lightly pigmented hair; thick eyebrows Hypodontia (reduced number), taurodontia, premature loss of teeth, dental enamel abnormalities Ectrodactyly more common than syndactyly Nail dystrophy, transverse ridging and pitting Corneal erosion, lacrimal duct abnormality, blepharitis, GU defects, cleft lip or palate

Continued

Table 690.3 Common Ectodermal Dysplasias: Inheritance and Characteristic Clinical Findings—cont'd

TYPE	INHERITANCE(S)	CHARACTERISTIC CLINICAL FINDINGS
AEC (Hay-Wells syndrome) and RHS	AD	Erosive dermatitis, neonatal erythroderma (e.g., scalp, hands), dyspigmentation of skin Coarse, wiry, lightly pigmented hair, patchy alopecia ± Hypohidrosis Hypodontia, conical teeth Nail absence or dystrophy with thickened nails Ectrodactyly more common than syndactyly Lacrimal duct abnormality, hearing loss, cleft lip/palate, ankyloblepharon, reflux
Limb-mammary	AD	Normal hair Hypodontia ± Hypohidrosis Nail dystrophy Ectrodactyly more common than syndactyly Bifid uvula, hypoplastic nipples, joint contracture of hand, lacrimal duct atresia, cleft palate
ADULT	AD	Dry skin, photosensitivity, lentigines Hypodontia, premature loss of teeth Normal sweating Pitting and longitudinal ridging of nails Ectrodactyly and syndactyly No cleft palate or lip Hypoplastic nipples, lacrimal duct atresia,

AD, Autosomal dominant; ADULT, acro-dermato-ungal-lacrimal-tooth; AEC, ankyloblepharon-ectodermal dysplasia-clefting; AR, autosomal recessive; ED, ectodermal dysplasia; EEC, ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome; RHS, Rapp-Hodgkin syndrome; XLR, X-linked recessive.

Table 690.4 Disorders Associated with Decreased Sweat Production

CUTANEOUS LESIONS
Congenital absence of sweat glands without ectodermal dysplasia
Incontinentia pigmenti
Burns
MULTISYSTEM DISORDERS
Fabry disease
Crisponi syndrome
Chronic graft-versus-host disease
Sjögren syndrome
NEUROLOGIC DISORDERS
Spinal cord injury
Guillain-Barré syndrome
Hereditary sensory autonomic neuropathy type I, II, IV
Complex regional pain syndrome
Multiple sclerosis
Multiple system atrophy
Ross syndrome
Shy-Drager syndrome
MEDICATIONS
Anticholinergic drugs
Opioids
Botulism toxin
Clonidine
Barbiturate overdose
α_2-Receptor antagonists
OTHER
Idiopathic acquired generalized anhidrosis
Hypothyroidism
Conversion disorder
Heat shock
Sympathectomy

In addition to the EDs, other disorders are associated with absent or decreased sweat production (Table 690.4).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 691

Vascular Anomalies

Kari L. Martin

Nearly all vascular lesions of childhood may be divided into vascular malformations and vascular tumors (Table 691.1). Vascular malformations are developmental disorders of blood vessel formation. Malformations do not regress, but slowly enlarge. They should be named after the predominant vessel(s) forming the lesion: arterial, capillary, lymph, venous, or combinations of these. Vascular tumors exhibit endothelial cell hyperplasia and proliferation. The International Society for the Study of Vascular Anomalies (ISSVA) continues to update the classification structure for vascular disorders as new disorders are identified and as the biology and genetic causes for established disorders are found. The complete classification, associated syndromes, and causative pathogenic variants can be found at www.issva.org.

VASCULAR MALFORMATIONS

Capillary Malformation (Port-Wine Stain)

Capillary malformations (CMs) are present at birth. These vascular malformations consist of mature dilated dermal capillaries. The lesions are macular, sharply circumscribed, pink to purple, and tremendously varied in size (Fig. 691.1). The head and neck region is the most common site of predilection; most lesions are unilateral. The mucous membranes can be involved. As a child matures into adulthood, the CM may become darker in color and pebbly in consistency; it may occasionally develop papules that bleed spontaneously. CM may occur in isolation or in combination with other vessel malformations.

True CM should be distinguished from **nevus simplex**, which, in contrast, is a relatively transient lesion often located in the midline (see Chapter 688). When a CM is lateral and localized to the forehead and upper eyelid, the diagnosis of **Sturge-Weber syndrome** (glaucoma, leptomeningeal venous angioma, seizures, hemiparesis contralateral to the facial lesion, intracranial calcification) must be considered (see Chapter 636.3). Early screening for glaucoma is important to

Table 691.1 Contemporary Classification of Vascular Anomalies (ISSVA 2014 Classification)

VASCULAR TUMORS
Benign
Infantile hemangioma/hemangioma of infancy
Congenital hemangiomas (RICH, NICH, PICH)
Tufted angioma
Spindle cell hemangioma
Epithelioid hemangioma
Pyogenic granuloma
Locally Aggressive or Borderline
Kaposiform hemangioendothelioma
Retiform hemangioendothelioma
Papillary intralymphatic angioendothelioma (Dabska tumor)
Composite hemangioendothelioma
Kaposi sarcoma
Malignant
Angiosarcoma
Epithelioid hemangioendothelioma
VASCULAR MALFORMATIONS
Simple
Capillary (CM) (e.g., port-wine stain, telangiectasia, CMTC, salmon patch/nevus simplex)
Venous (VM) (includes common, familial, glomuvenous, others)
Lymphatic (LM) (includes macrocystic, microcystic, primary lymphedema, others)
Arteriovenous (AVM) and arteriovenous fistula (sporadic or syndromal)
Combined
CM + VM, CM + LM, CM + AVM
LM + VM
CM + LM + VM
CM + LM + AVM, CM + VM + AVM
CM + LM + VM + AVM
Of major named vessels
Affect veins, arteries or lymphatics; usually of large caliber
Associated with other anomalies
Associated with anomalies of bone, soft tissue (usually overgrowth, rarely undergrowth) or viscera

CMTC, Cutis marmorata telangiectatica congenita; *NICH*, noninvoluting congenital hemangioma; *PICH*, partially involuting congenital hemangioma; *RICH*, rapidly involuting congenital hemangioma.

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Box 12.1, p. 327. Created with data from Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: Recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics.* 2015;136(1):e203–e214.



Fig. 691.1 Capillary malformation. Pink macule on the cheek of an infant.

Table 691.2 Port-Wine Stain–Associated Syndromes

- Sturge-Weber syndrome
- Klippel-Trenaunay syndrome
- Parkes-Weber syndrome
- Phakomatosis pigmentovascularis
- Macrocephaly–capillary malformation (M-CM) syndrome
- Capillary malformation–arteriovenous malformation (CM-AVM) syndrome
- Diffuse capillary malformation with overgrowth (DCMO)
- Bannayan-Riley-Ruvalcaba syndrome
- Von Hippel-Lindau disease
- Rubinstein-Taybi syndrome
- Wyburn-Mason syndrome
- Roberts syndrome
- Coat disease

Modified from Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Elsevier: Philadelphia; 2022: Box 12.4, p. 347.



Fig. 691.2 Nodular venous malformation on the leg of an adolescent.

prevent additional damage to the eye. CMs also occur as a component of **Klippel-Trenaunay syndrome** and with moderate frequency in other syndromes, including megalencephaly, capillary malformation, polymicrogyria (MCAP), Cobb (spinal arteriovenous malformation [AVM], port-wine stain), congenital lipomatous, overgrowth, vascular malformations, epidermal nevi, skeletal anomalies (CLOVES), Proteus, Beckwith-Wiedemann, and Bonnet-Dechaume-Blanc syndromes, and others (Table 691.2). In the absence of associated anomalies, morbidity from these lesions may include a poor self-image, hypertrophy of underlying structures, and traumatic bleeding.

The most effective treatment for CM is with the pulsed-dye laser. This therapy is targeted to hemoglobin within the lesion and minimizes thermal injury to the surrounding normal tissue. After such treatment, the texture and pigmentation of the skin are generally improved with low risks of scarring. Therapy can begin in infancy when the surface area of involvement is smaller. There may be advantages to treating within the first year of life. Although this approach is quite effective, redarkening of the stain may occur over time, making ongoing treatments useful. Camouflaging cosmetics may also be used.

Venous Malformation

Venous malformations include vein-only malformations and combination malformations. Malformations consisting of veins only range from nodules containing a mass of venules (Fig. 691.2) to diffuse large vein abnormalities that may consist of either a superficial component resembling varicose veins, deeper venous malformations, or both. Most venous malformations are sporadic, although inherited forms exist as well. Inherited forms and up to 40% of sporadic venous malformations are caused by *TIE2* pathogenic variants. Treatment is reserved for painful or symptomatic lesions. Surgical excision is best for small

or superficial nodular lesions; sclerotherapy or laser ablation is used for larger, diffuse lesions. Localized intravascular coagulopathy can be problematic in these lesions because of the chronic slow flow. This leads to both painful thrombotic episodes and the risk of progression to systemic disseminated intravascular coagulopathy. Pulmonary embolus has been reported in patients with large venous malformations.

LYMPHATIC MALFORMATIONS

See Chapter 538.

ARTERIOVENOUS MALFORMATION

AVMs are direct connections of artery to vein that bypass the capillary bed (Fig. 691.3). AVMs of the skin are very rare. Skin changes are often noted at birth, but they tend to be very subtle, presenting as a red-pink patch. Over time the lesions deepen in color and often result in thickening of the skin and surrounding tissue. They are diagnosed from their obvious arterial palpation. Some AVMs are progressive and can lead to significant morbidity and even mortality, so early diagnosis and evaluation by an experienced multidisciplinary team are essential.

KLIPPEL-TRENAUNAY AND PARKES-WEBER SYNDROMES

Klippel-Trenaunay syndrome is a term historically used to describe complex mixed vascular malformation with overgrowth of bone and soft tissue (Figs. 691.4 and 691.5). The anomaly is present at birth and usually involves a lower limb but may involve more than one limb, as well as portions of the trunk or face. Enlargement of the soft tissues may be gradual and may involve the entire extremity, a portion of it, or selected digits. The vascular lesion most often is a capillary malformation, generally localized to the hypertrophied area. The deep venous system may be absent or hypoplastic. Venous blebs and/or vesicular lymphatic lesions may be present on the malformation's surface. Thick-walled venous varicosities typically become apparent ipsilateral to the vascular malformation after the child begins to ambulate. If there is an associated AVM, the disorder is called **Parkes-Weber syndrome**.



Fig. 691.3 Arteriovenous malformation in conjunction with a port-wine stain of the scalp of a newborn.



Fig. 691.4 Overgrowth of the right arm and hand in an adolescent with Klippel-Trenaunay syndrome.

Somatic pathogenic activating variants in multiple genes have been associated with vascular malformations and limb overgrowth (Fig. 691.6 and Table 691.3).

These disorders can be confused with Maffucci syndrome or, if the surface vascular lesion is minimal, with Milroy disease. Pain, limb swelling, and cellulitis may occur. Thrombophlebitis, dislocations of joints, hematuria secondary to angiomatous involvement of the urinary tract, rectal bleeding from lesions of the gastrointestinal tract, pulmonary lesions, and malformations of the lymphatic vessels are infrequent complications. MRI may delineate the extent of the anomaly, but surgical correction or palliation is often difficult. Sclerotherapy or endovenous laser ablation may be of benefit when a venous component is the dominant vessel in the malformation. The indications for radiologic studies of viscera and bones are best determined by clinical evaluation. Supportive care includes compression bandages for varicosities; surgical treatment may help carefully selected patients. Leg-length differences should be treated with orthotic devices to prevent the development of spinal deformities. Corrective bone surgery may eventually be needed to treat significant leg-length discrepancy.

Angiokeratoma Circumscriptum

Several forms of angiokeratoma have been described. Angiokeratomas are characterized by ectasia of superficial lymphatic vessels and capillaries with hyperkeratosis of the overlying epidermis. Angiokeratoma circumscriptum is a rare disorder consisting of a solitary lesion or multiple lesions that manifest as a plaque or plaques of blue-red crusted papules or nodules. The limbs are the sites of predilection. **If therapy is desired, surgical excision is the treatment of choice.**

Cutis Marmorata Telangiectatica Congenita

Cutis marmorata telangiectatica congenita, a benign vascular anomaly apparent at birth, is composed of dilated superficial capillaries and veins. Involved areas of skin have a reticulated red or purple hue that resembles physiologic cutis marmorata but is more pronounced and relatively unvarying (Fig. 691.7). The lesions may be restricted to a single limb and a portion of the trunk or may be more widespread. The lesions become more pronounced during changes in environmental temperature, physical activity, or crying. In some cases, the underlying subcutaneous tissue is atrophic, and ulceration may occur within the reticulated bands. Rarely, defective growth of bone and other congenital abnormalities may be present. No specific therapy is indicated. Mild vascular-only cases may show gradual improvement. Cutis marmorata telangiectatica congenita may be associated with CM, Adams-Oliver syndrome, patent ductus arteriosus, and a variety of other anomalies. It must be differentiated from reticulate CM and physiologic cutis marmorata.

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus is a rare syndrome consisting of numerous venous malformations of the skin, mucous membranes, and gastrointestinal tract caused by somatic pathogenic variants in *TEK* in some patients. Typical lesions are blue-purple and rubbery in consistency; they vary in size from a few millimeters to a few centimeters in diameter. They are sometimes painful or tender. The compressible nodules may be present at birth but usually are progressive during childhood. New lesions may continue to develop throughout life. Large disfiguring and irregular blue marks may also occur. The lesions, which can rarely be located in the liver, spleen, and central nervous system in addition to the skin and gastrointestinal tract, do not involute spontaneously. Recurrent gastrointestinal hemorrhage caused by lesions in the gastrointestinal tract may lead to severe anemia. Palliation can be achieved by excision of involved bowel.



Fig. 691.5 Parkes-Weber syndrome. **A**, Three-dimensional volume-rendering CT angiography image of the limbs shows overgrowth of the right limb *(arrows)* with an arterial blush adjacent to the posterior tibial artery (*arrowhead*), consistent with a high-flow vascular malformation. **B**, Three-dimensional volume-rendering CT angiography image of the limbs shows arterial blush adjacent to the posterior tibial artery *(arrowhead)*. **C**, Coronal CT angiography image of the limb shows arterial blush adjacent to the posterior tibial artery *(arrowhead)*. **D**, Venous phase CT of the limb reveals varicose veins in the right limb. *(From Ufuk F. Limb overgrowth with vascular anomalies. J Pediatr. 2020;240:308–309, Fig, p. 309)*

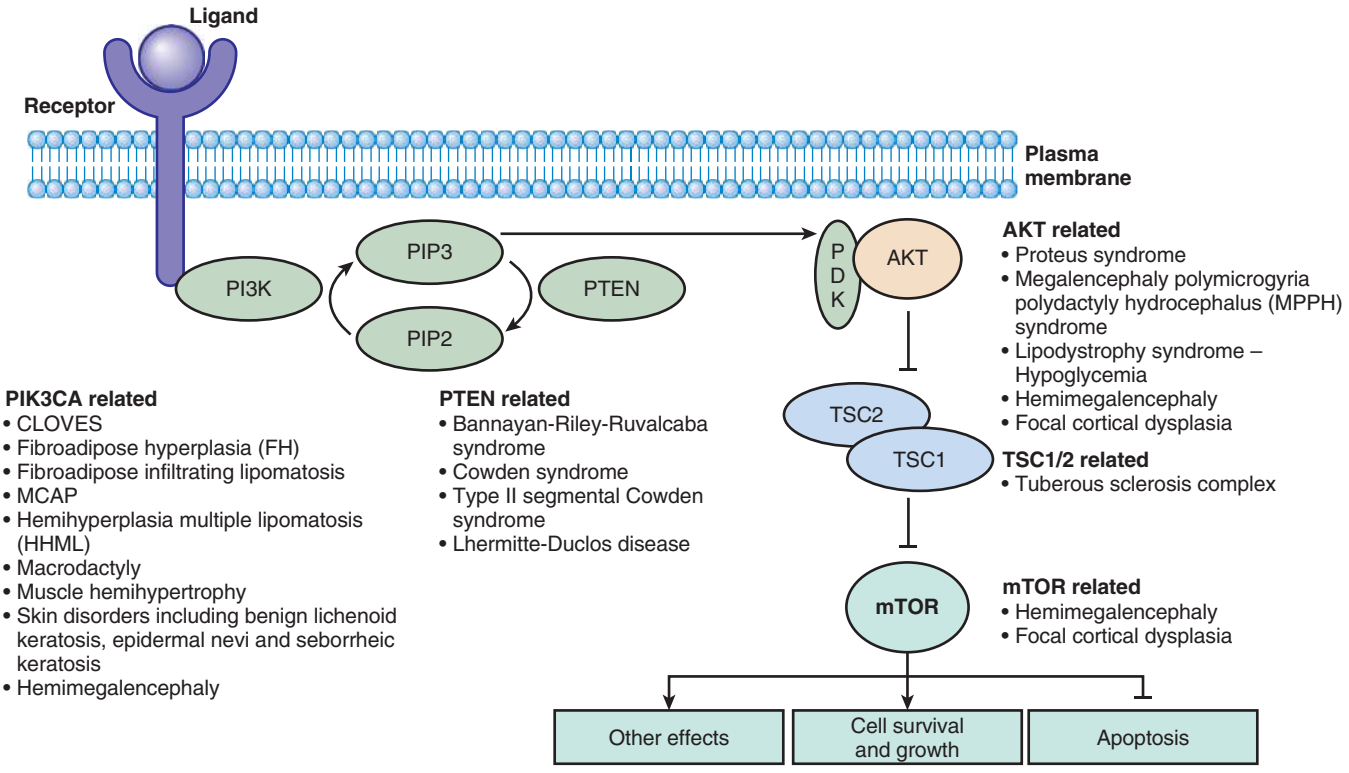

Fig. 691.6 Simplified PIK3CA-AKT-mTOR pathway and associated clinical overgrowth disorders. PIP, Phosphatidylinositol polyphosphate; PTEN, phosphatase and tensin homolog; PDK, phosphatidylinositol-dependent kinase. *(From Kang HC, Baek ST, Song S, Gleeson JG. Clinical and genetic aspects of the segmental overgrowth spectrum due to somatic mutations in PIK3CA. J Pediatr. 2015;167[5]:957–962, Fig, p. 959)*

PHAKOMATOSIS PIGMENTOVASCULARIS

Phakomatosis pigmentovascularis is a rare disorder characterized by the association of a capillary malformation and melanocytic lesions. Typically, the capillary malformation is extensive, and associated pigmentary lesions may include dermal melanocytosis, café-au-lait macules, or a nevus spilus (speckled nevus). Nonpigmented skin lesions that may occur in this setting include nevus anemicus and epidermal nevi. Systemic anomalies are seen in rare cases.

NEVUS ANEMICUS

Although present at birth, nevus anemicus may not be detectable until early childhood. The nevus consists of solitary or numerous sharply

Table 691.3 Clinical Diagnostic Criteria for *PIK3CA*-Related Overgrowth Spectrum (PROS)

REQUIRED CRITERIA

1. The presence of somatic *PIK3CA* pathogenic variant (if the pathogenic variant cannot be defined, then the disease is regarded as a presumptive PROS disorder)
2. Congenital or early childhood onset
3. Sporadic, without family history and mosaic distribution
4. Affected patients can have one or more findings from category A or B

CATEGORY A (MORE THAN 2 FEATURES)*	CATEGORY B (ISOLATED FEATURES)
1. Adipose, muscle, nerve, and skeletal overgrowth	1. Large, isolated LM
2. Capillary, venous, arteriovenous, and/or LMs	2. Isolated macrodactyly,† overgrown and splayed feet/hands, or overgrown limbs
3. Epidermal nevus	3. Truncal adipose overgrowth
	4. Hemi- or bilateral dysplastic megalencephaly or focal cortical dysplasia type 2
	5. Epidermal nevus
	6. Seborrheic keratosis
	7. Benign lichenoid keratoses

*Typically progressive. Can manifest as scoliosis (kyphosis), limb overgrowth, central nervous system (hydrocephalus, cerebellar tonsillar ectopia, Chiari, megalencephaly, mega corpus callosum), regional lipomatous undergrowth with overgrowth, infiltrating lipomatosis, or Wilms tumor/ovarian cystadenoma.

†Other terms include macrodystrophia lipomatosa, macrodactylia fibrolipomatosis, and gigantism.

From Kang HC, Baek ST, Song S, Gleeson JG. Clinical and genetic aspects of the segmental overgrowth spectrum due to somatic mutations in *PIK3CA*. *J Pediatr*. 2015;167(5):957–962, Table 1.



Fig. 691.7 Mottled pattern of cutis marmorata telangiectatica congenita on the right hand.

delineated, pale macules or patches that are most often on the trunk but may also occur on the neck or limbs. These nevi may simulate plaques of vitiligo, leukoderma, or nevoid pigmentary defects, but they can be readily distinguished because of their response to firm stroking. Stroking evokes an erythematous line and flare in normal surrounding skin, but the skin of a nevus anemicus does not redden. They can also be diagnosed by diascopy, in which pressure of the skin with a glass slide will obscure the borders of a nevus anemicus. Although the cutaneous vasculature appears normal histologically, the blood vessels within the nevus do not respond to injection of vasodilators. It has been postulated that the persistent pallor may represent a sustained localized adrenergic vasoconstriction.

VASCULAR TUMORS

Vascular tumors include infantile hemangiomas (IHs), tufted angiomas, kaposiform hemangioendotheliomas (KHEs), congenital hemangiomas, and additional more rare entities.

Infantile Hemangioma

IHs are proliferative benign vascular tumors of vascular endothelium that may be present at birth or, more commonly, may become apparent in the first or second week of life, predictably enlarge, and then spontaneously involute. IHs are the most common tumor of infancy, occurring in 5% of newborns. Risk factors include prematurity, low birthweight, female gender, and White race. IHs should be classified as superficial, deep, or mixed (Fig. 691.8). The terms *strawberry* and *cavernous* should not be used to describe hemangiomas. The immunohistochemical marker GLUT-1 is specifically expressed in an IH, which helps distinguish it histologically from other vascular anomalies. Superficial IHs are bright red, protuberant, compressible, sharply demarcated lesions that may occur on any area of the body (Fig. 691.9, see also Fig. 691.8). Although sometimes present at birth, they more often appear in the first or second month of life and are heralded by an erythematous or blue mark or an area of pallor, which subsequently develops a fine telangiectatic pattern before the growth phase (see Fig. 691.9). The presenting sign may occasionally be an ulceration of the perineum or lip. Favored sites are the face, scalp, back, and anterior chest; lesions may be solitary or multiple. Patterns of facial involvement include frontotemporal, maxillary, mandibular, and frontonasal regions. IHs that are more deeply situated are more diffuse and are less defined than superficial IHs. The lesions are cystic, firm, or compressible, and the overlying skin may appear normal in color or may have a bluish hue (Fig. 691.10).

Most IHs are mixed, having both superficial and deep components. IHs undergo a phase of rapid expansion, followed by a stationary period and finally by spontaneous involution (Fig. 691.11). Regression may be anticipated when the lesion develops pale gray areas centrally. The course of a particular lesion is unpredictable, but approximately 60% of these lesions reach maximal involution by 5 years of age and 90–95% by 9 years. Spontaneous involution cannot be correlated with size or site of involvement, but lip lesions seem to persist most often. Complications include impairment of a vital function, ulceration, secondary infection, and permanent disfigurement. The location of a lesion may interfere with a vital function (e.g., on an eyelid interfering with vision, on the urethra with urination, on the airway with respiration). IHs in a "beard" distribution may be associated with upper airway or subglottic involvement. Stridor should suggest a tracheobronchial lesion. Large visceral (hepatic) IHs may be complicated by coexistent hypothyroidism because of type 3 iodothyronine deiodinase; symptoms may be difficult to detect in this age-group. Table 691.4 lists other concerning features.

In the usual patient with an IH who has no serious complications or extensive growth resulting in tissue destruction and severe disfigurement, treatment consists of expectant observation. Because almost all lesions regress spontaneously, therapy is rarely indicated. Parents require repeated reassurance and support. After spontaneous involution, many patients are left with small cosmetic defects, such as telangiectasia, hypopigmentation, fibrofatty deposits, and scars if the lesion has ulcerated. Residual telangiectasias may be treated with pulsed dye laser therapy. Other defects can be treated or minimized by judicious surgical repair if desired.

In the rare case in which intervention is required, topical timolol solution (1 drop of 0.5% gel-forming solution applied twice each day) is effective, especially in small, superficial, nonulcerating, and nonmucosal IH. Topical timolol treatment is a very safe alternative to observation alone for a superficial IH. Timolol solution may also be used with caution in the treatment of an ulcerated IH, with or without occlusion.

In a disfiguring, life- or vision-threatening, or ulcerated IH that is not responding to other treatment, oral propranolol is the first-line treatment. IHs typically respond with growth arrest and often early signs of involution within a couple of weeks of treatment initiation. Dosing varies ranging from 1 to 3 mg/kg/day, though best outcomes occur at 3 mg/kg/day with no increase in side effects. Some recommend inpatient initiation of propranolol for infants younger than 8 weeks gestational age or those with comorbid conditions. The dose is initiated at 1 mg/kg/day divided into three doses with heart rate and blood pressure monitoring at 1 and 2 hours after each dose. If that dose is tolerated, the dose is increased to 2 mg/kg/day divided



Fig. 691.8 Types of infantile hemangiomas according to anatomic location. **A,** Bright red, superficial hemangioma. **B,** Bluish, deep hemangioma. **C,** Mixed type. *(From Léaute-Labréze C, Harper JI, Hieger PH. Infantile haemangioma. Lancet. 2017;390:85–94, Fig. 4, p. 88.)*

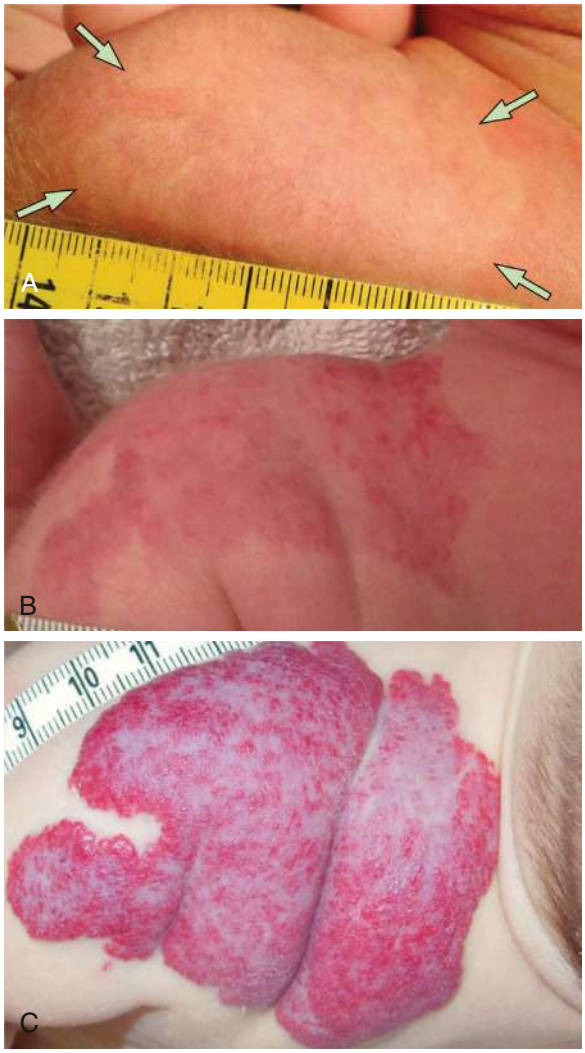

Fig. 691.9 Precursor lesions of infantile hemangioma. Figure shows a sharply demarcated, so-called anemic spot on the left shoulder. **A,** Day 3. **B,** Day 21. **C,** Day 90. *(From Léaute-Labréze C, Harper JI, Hieger PH. Infantile haemangioma. Lancet. 2017;390:85–94, Fig. 3, p. 87.)*



Fig. 691.10 Deep infantile hemangioma of the chest.



Fig. 691.11 Spontaneous regression of infantile hemangioma. **A,** Hemangioma on right lower arm, age 14 wk. **B,** Residual telangiectasia at age 23 mo. *(From Léaute-Labréze C, Harper JI, Hieger PH. Infantile haemangioma. Lancet. 2017;390:85–94, Fig. 5, p. 88.)*

into three doses. The outpatient initiation assumes good social support and access to the hospital. The initial dose and monitoring are similar to the inpatient plan; if the dose is tolerated for 3-7 days, the dose is increased to 1.5 mg/kg/day. If the latter dose is tolerated after 3-7 days, the dose is increased to 2 mg/kg/day. In all situations, propranolol must be given a minimum of 6 hours after the last dose. Risks of propranolol treatment include hypoglycemia, bradycardia, hypotension, gastroesophageal reflux disease or

Table 691.4 Clinical "Red Flags" Associated with Hemangiomas

CLINICAL FINDING	RECOMMENDED EVALUATION
Facial hemangioma involving significant area of face (>5 cm)	Evaluate for PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities): MRI and MRA of brain, neck, orbit
	Cardiac, ophthalmologic evaluation
	Evaluate for midline abnormality: supraumbilical raphe, sternal atresia, cleft palate, thyroid abnormality
Cutaneous hemangiomas in beard distribution	Evaluate for airway hemangioma, especially if manifesting with stridor
Periocular hemangioma	MRI of orbit Ophthalmologic evaluation
Paraspinal midline vascular lesion	Ultrasonography or MRI to evaluate for occult spinal dysraphism
Multifocal infantile hemangiomas (>5 cm)	Evaluate for parenchymal hemangiomas, especially hepatic/central nervous system Guaiac stool test, liver ultrasound
Large hemangioma, especially hepatic	Ultrasonography with Doppler flow study
	MRI
	TSH to detect associated hypothyroidism
Thrill and/or bruit associated with hemangioma	Consider cardiac evaluation and echocardiography to rule out diastolic reversal of flow in aorta
	MRI to evaluate extent and flow characteristics
Perineal segmental hemangioma	MRI of spine, kidneys to detect LUMBAR/PELVIS/SACRAL syndrome

LUMBAR, Lower body infantile hemangiomas and other skin defects, urogenital anomalies and ulceration, myelopathy, bony deformities, anorectal malformations and arterial anomalies, renal anomalies; PELVIS, perineal hemangioma, external genital malformations, lipomyelomeningocele, vesicorenal anomalies, imperforate anus, skin tag; SACRAL, spinal dysraphism, anogenital anomalies, cutaneous anomalies, renal/urologic anomalies, angioma in lumbosacral location.
Modified from Blei F. Vascular anomalies: from bedside to bench and back again. *Curr Probl Pediatr Adolesc Health*. 2002;32:67–102.



Fig. 691.12 Large segmental infantile hemangioma of the face in a 2-mo-old infant with definite PHACE. *(From Garzon MC, Epstein LG, Heyer GL, et al. PHACE syndrome: consensus-derived diagnosis and care recommendations. J Pediatr. 2016;178:24–33, Fig. 1, p. 25.)*

worsening of existing disease, hyperkalemia, and bronchospasm/wheezing. Nonetheless, reports of side effects of propranolol used for IH treatment are rare. Increased propranolol levels occur with inhibitors of CYP2D6 (cimetidine, amiodarone, fluoxetine, quinidine, ritonavir) and CPY1A2 (cimetidine, ciprofloxacin, isoniazid, ritonavir, theophylline); decreased blood levels occur with inducers of hepatic drug metabolism (rifampin, phenytoin, phenobarbital).

In patients unable to tolerate propranolol, or if the IH has not responded after a couple of weeks of treatment, systemic oral corticosteroids may be used. Termination of growth and sometimes regression may be evident after 2-4 weeks of therapy. When a response is obtained, the dose should be decreased gradually, though most patients will require treatment until about 1 year of age.

Intralesional corticosteroid injection by an experienced physician can also induce rapid involution of a localized IH but has risks of ulceration, tissue atrophy, and blindness if used near the orbit. Vincristine is used by some oncologists to treat significant IH. Interferon-α therapy may also be effective, but spastic diplegia is seen in 10% of cases. Use of these therapies has become less necessary since the introduction of propranolol.

In patients with large segmental IH of the face, **PHACES** syndrome should be considered (Fig. 691.12 and Table 691.5). PHACES stands for **p**osterior fossa brain defects such as Dandy-Walker malformation or cerebellar hypoplasia, large segmental facial infantile **h**emangioma, **a**rterial cerebrovascular abnormalities such as aneurysms and stroke, **c**oarctation of the aorta, and **e**ye abnormalities. **S**ternal raphe defects such as pits, scars, or **s**upraumbilical raphe are infrequently observed. Evaluation of children at risk for PHACES is important both to detect any underlying abnormalities and before starting systemic therapy, which may be indicated given the size and location of the IH typically associated with this syndrome. PHACES children with cervical and intracranial arterial abnormalities are at increased risk of cerebrovascular accidents, and specialized care by an experienced multidisciplinary team is essential.

Multifocal Infantile Hemangioma

Diffuse neonatal hemangiomatosis (or benign neonatal hemangiomatosis) is a historical term to describe a condition in which numerous or multifocal vascular lesions are widely distributed (Fig. 691.13). Several distinct diagnoses have been previously lumped together under this clinical phenotype with mortality cited as high as 60–80%. Upon further analysis, this group of disorders has been found to comprise several distinct entities, which are important to distinguish from one another, given their varying prognoses and management strategies. Therefore the term *multifocal IH* is more accurate and leads to correct treatments and prognosis for these patients with more than one cutaneous (and/or visceral) IH.

Multifocal IHs may occur in the skin and visceral organs, but remain GLUT-1–positive when biopsied, have a relatively good prognosis with low morbidity, and respond to systemic propranolol just as solitary cutaneous IH. Patients with more than five cutaneous IH should undergo an abdominal physical exam and possibly liver ultrasound to detect liver IH, which can grow quite large (Fig. 691.14).

Multifocal lymphangioendotheliomatosis (also known as cutaneovisceral angiomatosis) also presents with many vascular tumors in the skin and visceral organs but is GLUT-1–negative and complicated by

Table 691.5 PHACES Diagnostic Criteria: Revised

ORGAN SYSTEMS	MAJOR CRITERIA	MINOR CRITERIA
Arterial anomalies	Anomaly of major cerebral or cervical arteries* Dysplasia† of the large cerebral arteries Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
Structural brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid and/or hind brain	Midline brain anomalies Malformation of cortical development
Cardiovascular	Aortic arch anomalies Coarctation of the aorta Dysplasia* Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch/double aortic arch Systemic venous anomalies
Ocular	Posterior segment abnormalities Persistent hyperplastic primary vitreous Persistent fetal vasculature Retinal vascular anomalies Morning glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormalities Microphthalmia Sclerocornea Coloboma Cataracts
Ventral/midline	Anomaly of the midline chest and abdomen • Sternal defect • Sternal pit • Sternal cleft • Supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma

DEFINITE PHACE

Hemangioma >5 cm in diameter of the head including scalp PLUS one major criteria or two minor criteria	Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS two major criteria

POSSIBLE PHACE

Hemangioma >5 cm in diameter of the head including scalp PLUS one minor criteria	Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS one major or two minor criteria	No hemangioma PLUS two major criteria

*Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
†Includes kinking, looping, tortuosity, and/or dolichoectasia.
From Garzon MC, Epstein LG, Heyer GL, et al. PHACE syndrome: consensus-derived diagnosis and care recommendations. *J Pediatr.* 2016;178:24–33, Table II.

severe thrombocytopenia and gastrointestinal bleeding with high mortality. Accurate diagnosis in patients who present with multifocal vascular tumors is critical so early, appropriate management may be initiated.

Congenital Hemangioma

Congenital hemangiomas are benign vascular tumors that are present typically at birth. They are most often red or blue hued with telangiectasia and may have a ring of pallor. They do not undergo further growth after delivery as IHs do. Changes after delivery occur along a spectrum, and the lesion may stay stable **(noninvoluting congenital hemangiomas [NICH])**, partially involute (**partially involuting congenital hemangiomas [PICH]**), or decrease rapidly in size, leaving fibrofatty residual tissue behind **(rapidly involuting congenital hemangiomas [RICH])**. They are distinguishable from IH because of their clinical course and negative GLUT-1 markers on histopathology. It is also important to note the difference because CH do not respond to propranolol.

Kaposiform Hemangioendothelioma

KHE is a rare and potentially life-threatening vascular tumor. KHE classically presents as a red to purple firm plaque on the lateral neck, axilla, trunk, or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. Tufted angioma, once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 691.15). The main complication of these tumors is the development of **Kasabach-Merritt phenomenon (KMP)**, which may be fatal; therefore early diagnosis and treatment are important. Oral sirolimus may be helpful to stabilize and sometimes shrink these tumors. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

Kasabach-Merritt Phenomenon

KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute

or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. Thrombocytopenia is present, but the bone marrow contains increased numbers of normal or immature megakaryocytes. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 533.6).

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. Initial studies of sirolimus therapy have been promising. The mortality rate overall once patients have KMP is significant.



Fig. 691.13 Multifocal cutaneous and systemic (liver) infantile hemangiomas. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology, 2nd ed. Philadelphia: Saunders; 2008:359.)*

Pyogenic Granuloma (Lobular Capillary Hemangioma)

A pyogenic granuloma (PG) is a small, red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (Fig. 691.16). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily



Fig. 691.15 Nodular tufted angioma on the left thigh.

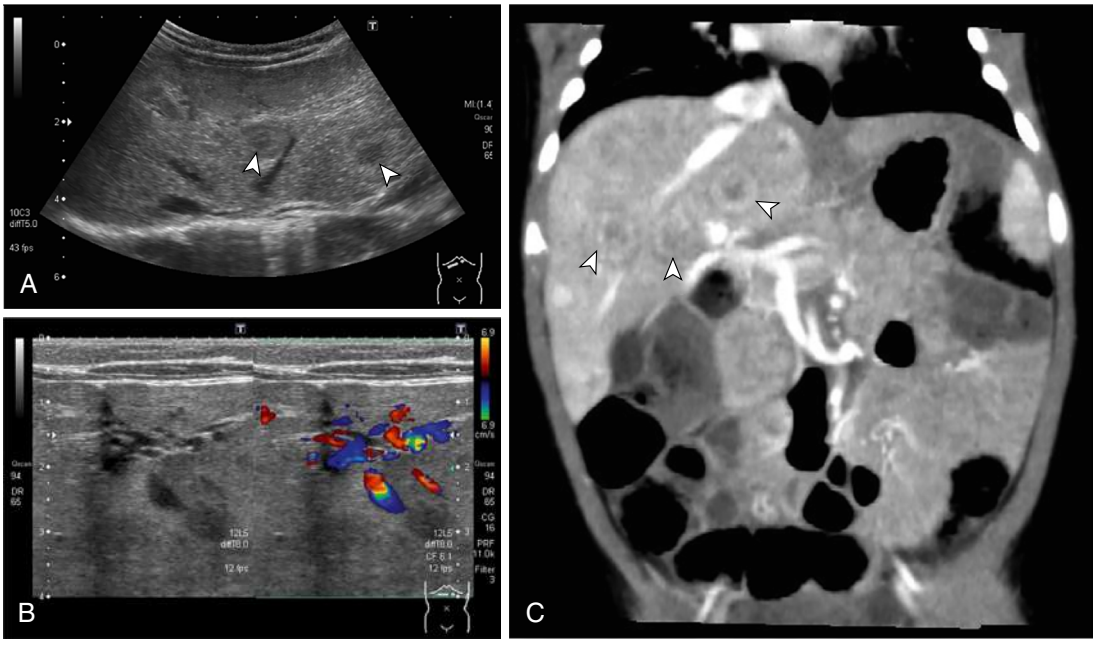

Fig. 691.14 Multifocal infantile hemangioma. **A,** Multiple hypoechoic lesions *(arrowheads)*. **B,** Arteriovenous shunting on ultrasound. **C,** Multiple hypervascular masses in the liver on computed tomography *(arrowheads)*. *(From Uda K, Okubo Y, Matushima T, et al. Multifocal infantile hemangioma. J Pediatr. 2019;210:238, Fig. 2, p. 238.e1.)*



Fig. 691.16 Pyogenic granuloma on the left cheek.



Fig. 691.17 Spider angioma with visible central arteriole component.

when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauterization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with pulsed dye laser therapy.

Angiokeratoma of Mibelli

Angiokeratoma of Mibelli is characterized by 1- to 8-mm red, purple, or black scaly, verrucous, occasionally crusted papules and nodules that appear on the dorsum of the fingers and toes and on the knees and the elbows. Less commonly, palms, soles, and ears may be affected. In many patients, onset has followed frostbite or chilblains. These nodules bleed freely after injury and may involute in response to trauma. They may be effectively eradicated by cryotherapy, electrofulguration, excision, or laser ablation.

Spider Angioma

A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (Fig. 691.17). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region, lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.



Fig. 691.18 Hereditary hemorrhagic telangiectasia. Telangiectases are found on the lips, oral mucosa, nasal mucosa, skin, and conjunctiva. Epistaxis is the most common manifestation of the disease. Blood transfusions may be required. *(From Habif TP. Clinical Dermatology: A Color Guide to Diagnosis and Therapy, 4th ed. Philadelphia: Mosby; 2004: Fig. 23.22, p. 831.)*

Maffucci Syndrome

The association of spindle cell hemangiomas with nodular enchondromas in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as *Maffucci syndrome.* Maffucci syndrome is caused by somatic mosaic pathogenic variants in the *IDH1* and *IDH2* genes. Vascular lesions are typically soft, compressible, asymptomatic, blue to purple subcutaneous masses that grow in proportion to a child's growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 550).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Hereditary hemorrhagic telangiectasia (HHT), which is inherited as an autosomal dominant trait, occurs in two types. The gene in **HHT-1** encodes *ENG,* a membrane glycoprotein on endothelial cells that binds transforming growth factor-β. **HHT-2** is caused by pathogenic variants in the *ACVRL1* gene and is associated with increased risk for hepatic involvement and pulmonary hypertension. **HHT-juvenile polyposis syndrome** is caused by a pathogenic variant in *SMAD4.*

Affected children usually experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions. The mucocutaneous lesions, which usually develop at puberty, are 1- to 4-mm, sharply demarcated, red to purple macules, papules, or spider-like projections, each composed of a tightly woven mat of tortuous telangiectatic vessels (Fig. 691.18). The nasal mucosa, lips, and tongue are usually involved; less commonly, cutaneous lesions occur on the face, ears, palms, and nail beds. Vascular ectasias may also arise in the conjunctivae, larynx, pharynx, gastrointestinal tract, bladder, vagina, bronchi, brain, and liver. Diagnostic criteria include spontaneous recurrent epistaxis, telangiectasias (oral, nose, fingers), visceral lesions (gastrointestinal telangiectasias,

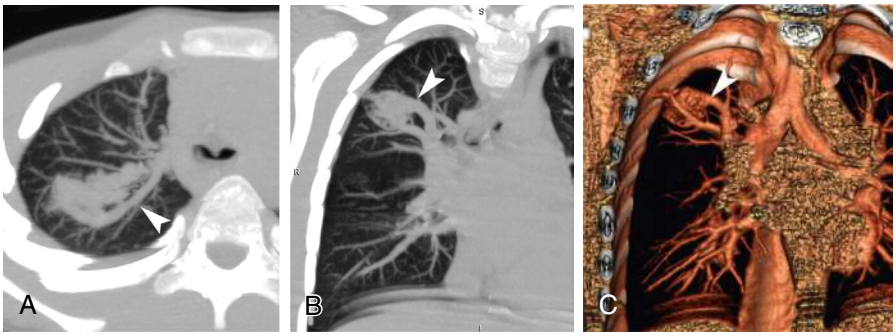

Fig. 691.19 Chest multislice spiral CT in a patient showing a large pulmonary arteriovenous malformation in the posterior segment of right upper lobe *(arrowhead)*. **A**, Axial maximum intensity projection image. **B**, Coronal maximum intensity projection image. **C**, Three-dimensional volume rendering. *(From Giordano P, Lenato GM, Suppressa P, et al. Hereditary hemorrhagic telangiectasia: arteriovenous malformations in children. J Pediatr. 2013;163:179–186, Fig. 1, p. 182.)*



Fig. 691.20 Infant with CM-AVM syndrome and a typical-appearing CM-AVM stain of the left chest. This lesion demonstrates high flow on Doppler evaluation, differentiating it from classic CM. In CM-AVM syndrome, the lesions tend to be multifocal, with more arising over time. *(From Eichenfield LF, Frieden IJ, eds. Neonatal and Infant Dermatology, 3rd ed. Philadelphia: Elsevier; 2015: Fig. 22.14, p. 363.)*

pulmonary or hepatic or cerebral AVMs), and first-degree relative with HHT.

Massive hemorrhage is the most serious complication of HHT and may result in severe anemia. Bleeding may occur from the nose, mouth, gastrointestinal tract, genitourinary tract, or lungs; epistaxis is often the only complaint, occurring in 80% of patients. Approximately 15–20% of patients with AVMs in the lungs present with stroke due to embolic abscesses (Fig. 691.19). Hepatic encephalopathy in the presence of normal liver function may occur with a hepatic AVM. Persons with HHT have normal levels of clotting factors and an intact clotting mechanism. In the absence of serious complications, the life span of a person with HHT is normal. Local lesions may be ablated temporarily with chemical cautery or electrocoagulation. More drastic surgical measures may be required for lesions in critical sites, such as the lung or gastrointestinal tract. Bevacizumab, an anti–vascular endothelial growth factor agent, has been effective in treating affected patients with HHT who have high cardiac output secondary to hepatic AVMs. The nasal spray form of bevacizumab may be beneficial therapy for epistaxis.

Capillary Malformation–Arteriovenous Malformation Syndrome (CM-AVM)

CM-AVM is an autosomal dominant disorder caused by pathogenic variants in *RASA1* (CM-AVM-1) or *EPHB4* (CM-AVM-2) and is characterized by multiple atypical-appearing macules or patches that are present at birth, suggestive of microcutaneous AVMs that look like capillary malformations (Fig. 691.20). Lesions that are present at birth will enlarge and darken with increasing age. Some lesions have peripheral pallor (**halo effect**). In addition, associated high-flow AVMs may be present in the brain, spinal cord, or skin. Arteriovenous fistulas have also been reported. Pulse dye laser treatment may be effective for cutaneous lesions, whereas embolization is indicated for AVMs.

Ataxia-Telangiectasia

See Chapter 637.1.

Ataxia-telangiectasia is transmitted as an autosomal recessive trait because of a pathogenic variant in the *ATM* gene. The characteristic telangiectasias develop at approximately 3 years of age, first on the bulbar conjunctivae and later on the nasal bridge, malar areas, external ears, hard palate, upper anterior chest, and antecubital and popliteal fossae. Additional cutaneous stigmata include café-au-lait spots, premature graying of the hair, and sclerodermatous changes. Progressive cerebellar ataxia, neurologic deterioration, sinopulmonary infections, and malignancies are also seen.

Angiokeratoma Corporis Diffusum (Fabry Disease)

See Chapter 106.4.

An inborn error of glycolipid metabolism (α-galactosidase), angiokeratoma corporis diffusum is an X-linked recessive disorder that is fully penetrant in males and is of variable penetrance in carrier females. Angiokeratomas appear before puberty and occur in profusion over the genitalia, hips, buttocks, and thighs and in the umbilical and inguinal regions. They consist of 0.1- to 3.0-mm, red to blue-black papules that may have a hyperkeratotic surface. Telangiectasias are seen in the mucosa and conjunctiva. On light microscopy, these angiokeratomas appear as blood-filled, dilated, endothelium-lined vascular spaces. Granular lipid deposits are demonstrable in dermal macrophages, fibrocytes, and endothelial cells.

Additional clinical manifestations include recurrent episodes of fever and agonizing pain, cyanosis and flushing of the acral limb areas, paresthesias of the hands and feet, corneal opacities detectable on slit-lamp examination, and hypohidrosis. Renal involvement and cardiac involvement are the usual causes of death. The biochemical defect is a deficiency of the lysosomal enzyme α-galactosidase, with accumulation of ceramide trihexoside in tissues, particularly vascular endothelium, and excretion in urine (see Chapter 106.4 for therapy). Similar cutaneous lesions have also been described in another lysosomal enzyme disorder, α-L-fucosidase deficiency, and in sialidosis, a storage disease with neuraminidase deficiency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 692

Cutaneous Nevi

Kari L. Martin

Nevus skin lesions are characterized histopathologically by collections of well-differentiated cell types normally found in the skin. Vascular nevi are described in Chapter 691. Melanocytic nevi are subdivided into two broad categories: those that appear after birth (acquired nevi) and those that are present at birth (congenital nevi).

ACQUIRED MELANOCYTIC NEVUS

Melanocytic nevi are benign clusters of melanocytic nevus cells that arise as a result of alteration and proliferation of melanocytes at the epidermal-dermal junction.

Epidemiology

The number of *acquired* melanocytic nevi increases gradually during childhood and more slowly in early adulthood. The number reaches a plateau in the third or fourth decade and then slowly decreases thereafter. The mean number of melanocytic nevi in an adult varies depending on genetics, skin color, and sun exposure. The greater the number of nevi present, the greater the risk for development of melanoma, though the majority of melanomas arise de novo. Sun exposure during childhood, particularly intermittent, intense exposure of an individual with light skin, and a propensity to burn and freckle rather than tan are important determinants of the number of melanocytic nevi that develop. Red-haired children, despite their light skin and propensity to freckle and sunburn, have fewer nevi than other children. Increased numbers of nevi are also associated with immunosuppression and administration of chemotherapy.

Clinical Manifestations

Melanocytic nevi have a well-defined life history and are classified as junctional, compound, or dermal in accordance with the location of the nevus cells in the skin. In childhood, >90% of nevi are junctional; melanocyte proliferation occurs at the junction of the epidermis and dermis to form nests of cells. Junctional nevi appear anywhere on the body in various shades of brown; they are relatively small, discrete, flat, and variable in shape. Although some nevi, particularly those on the palms, soles, and genitalia, remain junctional throughout life, most become compound as melanocytes migrate into the papillary dermis to form nests at both the epidermal-dermal junction and within the dermis. If the junctional melanocytes stop proliferating, nests of melanocytes remain only within the dermis, forming an intradermal nevus. With maturation, compound and intradermal nevi may become raised, dome-shaped, verrucous, or pedunculated. Slightly elevated lesions are usually compound. Distinctly elevated lesions are usually intradermal. With age, the dermal melanocytic nests regress and nevi gradually disappear.

Prognosis and Treatment

Acquired pigmented nevi are benign, but a very small percentage undergo malignant transformation. Suspicious changes are indications for excision and histopathologic evaluation. This includes rapid increase in size; unusual colors such as red, black, varying shades of brown, gray, and white; bleeding; textures such as scaling, erosion, ulceration, and induration; and regional lymphadenopathy. Most of these changes are from irritation, infection, or maturation; darkening and gradual increase in size and elevation normally occur during adolescence and should not be cause for concern. Two common benign changes are clonal nevi (fried-egg moles) and eclipse nevi. A **clonal nevus** is light brown with a dark, raised center representing a clonal change of a subset of nevus cells within the lesion. **Eclipse nevi** are flat and light brown with dark brown rims. They are seen primarily in the scalp (Fig. 692.1). Consideration should be given to the presence of risk factors for development of melanoma and the patient's parents' wishes about removal of the nevus. If doubt remains about the benign nature of a nevus, excision is a safe and simple outpatient procedure that may be justified to allay anxiety.

ATYPICAL MELANOCYTIC NEVUS

Atypical melanocytic nevi occur both in an autosomal dominant familial melanoma-prone setting (familial mole–melanoma syndrome, dysplastic nevus syndrome, BK mole syndrome) and as a sporadic event. Only 2% of all pediatric melanomas occur in individuals with a familial syndrome; melanoma develops before age 20 years in 10% of individuals with the syndrome. Malignant melanoma has been reported in children with dysplastic nevus syndrome as young as 10 years old. Risk for development of melanoma is essentially 100% in individuals with dysplastic nevus syndrome who have two family members who have had melanomas. The term *atypical mole syndrome* describes lesions in those individuals without an autosomal dominant familial history of melanoma but with more than 50 nevi, some of which are atypical. The lifetime risk of melanoma associated with dysplastic nevi in this context is estimated to be 5–10%.

Atypical nevi tend to be large (5-15 mm) and round to oval. They have irregular margins and variegated color, and portions of them are elevated. These nevi are most common on the posterior trunk, suggesting that intermittent, intense sun exposure has a role in their genesis. They may also occur in sun-protected areas such as the breasts, buttocks, and scalp. Atypical nevi do not usually develop until puberty, although scalp lesions may be present earlier. Atypical nevi demonstrate disordered proliferation of atypical intraepidermal melanocytes, lymphocytic infiltration, fibroplasia, and angiogenesis. It may be helpful to obtain histopathologic documentation of dysplastic change by biopsy to identify these individuals. It is prudent to excise borderline atypical nevi in immunocompromised children or in those treated with irradiation or chemotherapeutic agents. Although chemotherapy is associated with the development of a greater number of melanocytic nevi, it has not been directly linked to increased risk for development of melanoma. The threshold for removal of clinically atypical nevi is also lower at sites that are difficult to observe, such as the scalp. Children with atypical nevi should undergo a complete skin examination every 6-12 months. In these children, photographic mole mapping serves as a useful adjunct in following nevus change. Parents must be counseled about the importance of sun protection and avoidance and should be instructed to look for early signs of melanoma on a regular basis, approximately every 3-4 months.

CONGENITAL MELANOCYTIC NEVUS

Congenital melanocytic nevi are present in 2–3% of newborn infants. These nevi have been categorized by size: giant congenital nevi are >40 cm in diameter (adult size) or >5% of the body surface; large nevi are 20-40 cm, medium nevi are 1.5-20 cm, and small nevi are <1.5 cm in diameter (Fig. 692.2). Congenital nevi are characterized by the



Fig. 692.1 Eclipse nevi (rim moles) in the scalp.

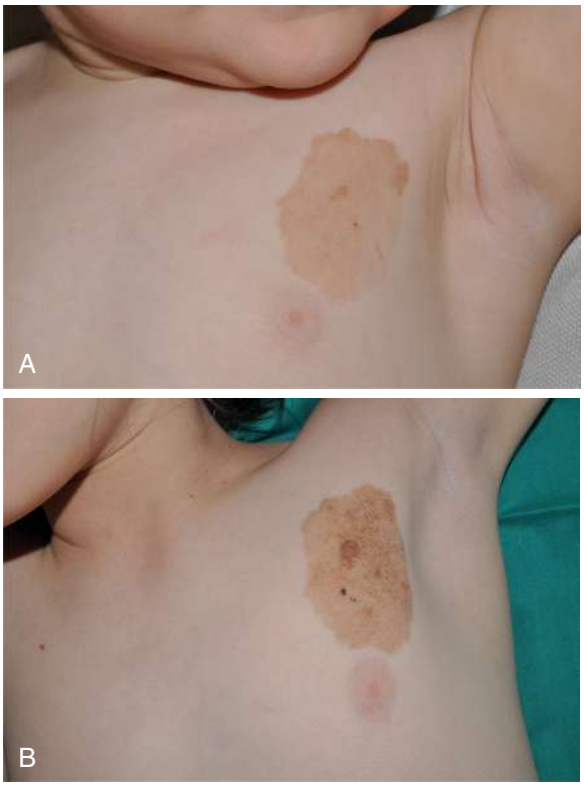

Fig. 692.2 Congenital melanocytic nevus. Changing appearance with time of a congenital melanocytic nevus of small-to-medium size on the trunk when the patient was 9 months old (A) and 10 years old (B). *(From Anderson-Vildosola J, Hernandez-Martin A. Addressing frequently asked questions and dispelling myths about melanocytic nevi in children. Dermatol Clin. 2022;40:51–59, Fig. 5)*

presence of nevus cells in the lower reticular dermis; between collagen bundles; surrounding cutaneous appendages, nerves, and vessels in the lower dermis; and occasionally extending to the subcuticular fat. Large and giant congenital nevi often harbor *NRAS* pathogenic variants, and *BRAF* pathogenic variants typically seen in regular melanocytic nevi are most common in small or medium congenital nevi. Identification is often uncertain, however, because they may have the histologic features of ordinary junctional, compound, or intradermal nevi. Some nevi that were not present at birth display histopathologic features of congenital nevi; these should not be considered congenital, but may be called congenital nevus–like nevi (CNLN). Furthermore, congenital nevi may be difficult to distinguish clinically from other types of pigmented lesions, adding to the difficulty that parents may have in identifying nevi that were present at birth. The clinical differential diagnosis includes dermal melanocytosis, café-au-lait macules, and smooth muscle hamartomas.

Sites of predilection for small congenital nevi are the lower trunk, upper back, shoulders, chest, and proximal limbs. The lesions may be flat, elevated, verrucous, or nodular and may be various shades of brown, blue, or black. Given the difficulty in identifying small congenital nevi with certainty, data regarding their malignant potential are controversial and likely overstated. The true incidence of melanoma in congenital nevi, especially small and medium-sized lesions, is unknown. Removal of all small congenital nevi is not warranted because the development of melanoma in a small congenital nevus is an exceedingly rare event before puberty. A number of factors must be weighed in the decision about whether or not to remove a nevus, including its location, the ability to monitor it clinically, the potential for scarring, the presence of other risk factors for melanoma, and the presence of atypical clinical features.

Giant congenital pigmented nevi (<1 in 20,000 births) occur most commonly on the posterior trunk (Fig. 692.3) but may also appear on the head or extremities. These nevi are of special significance because



Fig. 692.3 "Bathing suit" large congenital melanocytic nevus.

of their association with leptomeningeal melanocytosis (neurocutaneous melanocytosis) and their predisposition for development of malignant melanoma.

Leptomeningeal involvement occurs most often when the nevus is located on the head or midline on the trunk, particularly when associated with multiple "satellite" melanocytic nevi (>20 lesions). Nevus cells within the leptomeninges and brain parenchyma may cause increased intracranial pressure, hydrocephalus, seizures, intellectual disability, and motor deficits and may result in melanoma. Malignancy can be identified by careful cytologic examination of the cerebrospinal fluid for melanin-containing cells. MRI demonstrates asymptomatic leptomeningeal melanosis in 30% of individuals with giant congenital nevus of the type described earlier. The overall incidence of malignant melanoma arising in a giant congenital nevus is 1–2%. The median age at diagnosis of the melanomas that arise within a giant congenital nevus is 7 years. The mortality rate approaches 100%. The risk of melanoma is greater in patients in whom the predicted adult size of the nevus is >40 cm, lesions are on the trunk, and satellite lesions are present. Management of giant congenital nevi remains controversial and should involve the parents, pediatrician, dermatologist, and plastic surgeon. If the nevus lies over the head or spine, MRI may allow detection of neural melanosis**,** the presence of which makes gross removal of a nevus from the skin a futile effort. In the absence of neural melanosis, early excision and repair aided by tissue expanders or grafting may reduce the burden of nevus cells and thus the potential for development of melanoma, but at the cost of many potentially disfiguring operations. Nevus cells deep within subcutaneous tissues may evade excision. Random biopsies of the nevus are not helpful, but biopsy of newly expanding nodules is indicated. Follow-up every 6 months for 5 years and every 12 months thereafter is recommended. Serial photographs of the nevus may aid in detecting changes.

MELANOMA

Malignant melanoma is the most common skin cancer in children, and approximately 1% of all melanomas occur before 20 years of age. An estimated 400 cases of pediatric melanoma are diagnosed each year. The incidence of melanoma in the pediatric population increases with age, from 1-2 cases per 1 million in children under age 10 to 16.9 cases in children age 15-19 years. The incidence of pediatric melanoma has increased by an average of 2% per year between 1973 and 2009. This increase was especially notable in females between the ages of 15 and 19. In this age-group, melanoma accounts for 6% of all childhood cancers. Melanoma develops primarily in White individuals, on the head and trunk in males, and on the extremities in females. In preadolescent patients, melanoma is more likely to present on the head and neck than in other locations. Risk factors for the development of melanoma include the presence of familial atypical mole–melanoma syndrome or xeroderma pigmentosum; an increased number of acquired melanocytic nevi, or atypical nevi; fair complexion; excessive sun exposure, especially intermittent exposure to intense sunlight; a personal or family (first-degree relative) history of a previous melanoma; giant

congenital nevus; and immunosuppression (Table 692.1). In previously well children, UV radiation is responsible for most melanomas. Less than 5% of childhood melanomas develop within giant congenital nevi or in individuals with familial atypical mole–melanoma syndrome. Approximately 40–50% of the time, melanoma develops at a site where there was no apparent nevus. The mortality rate from melanoma is related primarily to tumor thickness and the level of invasion into the skin. About 75% of pediatric cases are localized and have an excellent outcome. Ninety percent of pediatric patients diagnosed with melanoma are expected to be alive in 5 years. In patients with nodal disease, the outcomes are intermediate, with about 60% expected to survive long-term.

There is variability in prognosis depending on the age of diagnosis in pediatric patients. Children younger than 10 with melanoma often have poor prognostic features. They are more often non-White, have head and neck primary tumors, thicker primary lesions, a higher incidence of spitzoid morphology, vascular invasion and nodal metastases, and more often have syndromes that predispose them to melanoma. The treatment of melanomas, as in adult patients, is surgical excision with 1-cm margins for tumors <1 mm deep, 1- to 2-cm margins for tumors >1 mm and <2 mm deep, and 2-cm margins for tumors >2 mm deep. Sentinel lymph node biopsy has become a widespread practice in pediatric melanoma. It should be considered in lesions >1 mm and in thin lesions with ulceration, mitotic rate greater than 1 mm^2, and young age. Though pediatric patients are more likely to have nodal metastases than their adolescent counterparts, this has not been associated with a decrease in overall survival. Alternatively, in adolescents, nodal disease is a significant negative prognostic factor. Increased tumor thickness and ulceration are associated with lymph node positivity. If the sentinel node is positive, a lymph node dissection can be considered. Patients with regional lymph node involvement can be offered treatment with interferon alfa-2b or ipilimumab (FDA approved for 12 years of age and older). *BRAF* and *MEK* inhibitors are not currently available for pediatric patients; however, phase 1 and 2 clinical trials are currently ongoing for adolescent patients.

Given the lack of effective therapy for melanoma, prevention and early detection are the most effective measures. Emphasis should be given to avoidance of intense midday sun exposure between 10 AM and 3 PM; wearing of protective clothing such as a hat, long sleeves, and pants; and use of sunscreen. Adolescents should be counseled not to use tanning booths. Early detection includes frequent clinical and photographic examinations of patients at risk (dysplastic nevus syndrome) and prompt response to rapid changes in nevi (size, shape, color, inflammation, bleeding or crusting, and sensation). The ABCDE rule (asymmetry, border irregularities, color variability, diameter >6 mm, evolving), which is a useful screening tool for adults, may not be as effective for children. Unlike adult melanomas, which are usually pigmented, pediatric melanomas are often amelanotic and can mimic benign lesions such as warts and pyogenic granulomas. They are also more likely to have regular borders and to be less than 6 mm in diameter. They often present as papules or papulonodules. To highlight these differences from adult melanomas, an **ABCDE rule for pediatric melanoma** has been proposed: **A**melanotic, **B**leeding, **B**umps, uniform **C**olor, small **D**iameter, **D**e novo, and in **E**volution.

HALO NEVUS

Halo nevi occur primarily in children and young adults, most commonly on the back (Fig. 692.4). Development of the lesion may coincide with puberty or pregnancy. Several pigmented nevi frequently develop halos simultaneously. Subsequent disappearance of the central nevus over several months is the usual outcome, and the depigmented area usually repigments. Excision and histopathologic examination of the lesion is indicated only when the nature of the central lesion is in question. An acquired melanocytic nevus occasionally develops a peripheral zone of depigmentation over a period of days to weeks. There is a dense inflammatory infiltrate of lymphocytes and histiocytes in addition to the nevus cells. The pale halo reflects disappearance of the melanocytes. This phenomenon is associated with congenital nevi, blue nevi, Spitz nevi, dysplastic nevi, neurofibromas, primary and secondary malignant melanoma, and occasionally with poliosis, **Vogt-Koyanagi-Harada** syndrome, and pernicious anemia. Patients with vitiligo have an increased incidence of halo nevi. Individuals with halo nevi have circulating antibodies against the cytoplasm of melanocytes and nevus cells.

SPITZ NEVUS (SPINDLE AND EPITHELIOID CELL NEVUS)

Spitz nevus manifests most commonly in the first 2 decades of life as a pink to red, smooth, dome-shaped, firm, hairless papule on the face, shoulder, or upper limb (Fig. 692.5). Most are <1 cm in diameter, but they can achieve a size of 3 cm. Rarely, they occur as numerous grouped lesions. Visually similar lesions include pyogenic granuloma, hemangioma, nevocellular nevus, juvenile xanthogranuloma, and basal cell carcinoma, but these entities are histologically distinguishable. Classic-appearing Spitz nevi can be monitored with regular clinical and dermoscopic examination, and multiple dermoscopy studies

Table 692.1 Summary of Clinical and Histologic Features by Subtypes of Pediatric Melanoma

	SPITZOID MELANOMA	MELANOMA ARISING IN CMN	CONVENTIONAL MELANOMA
Clinical	Papule or nodule; frequently amelanotic, but can be any color (e.g., pink-red to blue-black); distribution is not limited to sun-exposed skin	New, rapidly growing nodule arising in the deep dermis or subcutaneous tissues of a CMN; commonly solitary and ulcerated; by comparison, proliferative nodules commonly occur in multiples and are not ulcerated	Children: typically papules or nodules of any color, but often amelanotic; most do not follow ABCD criteria; nodular subtype most common Adolescents: similar to presentation in adults with lesions having ABCD criteria
Histologic	Primary differential diagnosis is Spitz nevus vs atypical Spitz tumor; most cells have abundant eosinophilic cytoplasm and characteristic spitzoid cytomorphology; nuclear atypia is typically high grade; growth in the form of expansile nodules or sheets; ulceration, epidermal consumption, brisk deep mitotic activity, and poor maturation are often seen; epidermal hyperplasia might be seen on the surface, but Kamino bodies are relatively uncommon	The primary differential diagnosis is benign proliferative nodules arising in congenital nevi; compared with benign proliferative nodules, melanomas typically have epithelioid or small, blue cell, tumor-like morphology, with sheets of melanocytes with high-grade nuclear atypia; mitotic activity is high (often >3/mm^2); zones of necrosis or ulceration can be helpful in establishing a diagnosis	Nodular melanoma: similar to adult nodular melanoma; no horizontal growth phase present; superficial spreading melanoma: similar to superficial spreading melanoma in adults with a preceding horizontal growth phase, pagetosis, lentiginous growth, and junctional confluence with frequent alteration of the epidermal contour; precursor nevus is common

CMN, Congenital melanocytic nevi; ABCD, asymmetry, border irregularity, color variegation, diameter >6 mm.
From Merkel EA, Mohan LS, Shi K, et al. Paediatric melanoma: clinical update, genetic basis, and advances in diagnosis. *Lancet Child Adoles.* 2019;3:646–654, Table 1).



Fig. 692.4 Well-developed halo nevus.



Fig. 692.5 Dome-shaped red Spitz nevus.

have demonstrated a tendency for these benign lesions to develop a reticular or homogeneous pattern and/or regress over time. Guidelines recommend excision be reserved for suspicious lesions (>8-10 mm, with excessive growth, asymmetry, or ulceration) in children over 12 years of age and for suspicious lesions in all ages when melanoma cannot be excluded. If a nevus arouses clinical suspicion that it may be a melanoma, an excisional biopsy of the entire lesion is recommended. If the margins of excision of a Spitz nevus are positive but the biopsy sample suggested a typical Spitz nevus, reexcision of the site is no longer routinely recommended. Because Spitz nevi may be difficult to distinguish histopathologically from malignant melanoma, immunohistochemistry and genomic alteration studies can be useful adjunct tools. Atypical Spitz tumors are Spitz nevi with atypical histologic features or unknown malignant potential. Management for these tumors is not clearly defined and may range from clinical monitoring to yearly nodal ultrasonography to potentially sentinel lymph node biopsy and lymphadenectomy. Improving genetic profiling of these tumors may provide better prognostic information soon. Prognostic implication of positive sentinel lymph node biopsy has not been established, and given the potential morbidity of the procedure, it is often avoided.

ZOSTERIFORM LENTIGINOUS NEVUS (AGMINATED LENTIGINES)

Zosteriform lentiginous nevus is a unilateral, linear, bandlike collection of numerous 2- to 10-mm brown or black macules on the face, trunk, or limbs. The nevus may be present at birth or may develop during childhood. There are higher numbers of melanocytes in elongated rete ridges of the epidermis.

NEVUS SPILUS (SPECKLED LENTIGINOUS NEVUS)

Nevus spilus is a flat brown patch within which are darker flat or raised brown melanocytic elements with a prevalence of 2–3% (Fig. 692.6). It varies considerably in size and can occur anywhere on the body. The color of the macular component may vary from light to dark brown,



Fig. 692.6 Nevus spilus.

and the number of darker lesions may be low or high. Nevus spilus is rare at birth and is commonly acquired in late infancy or early childhood. Dark elements within the nevus are usually present initially and tend to increase in number gradually over time. The darker macules represent nevus cells in a junctional or dermal location; the patch has increased numbers of melanocytes in a lentiginous epidermal pattern. The malignant potential of these nevi is uncertain; nevus spilus is found more commonly in individuals with melanoma than in matched control subjects. Like congenital melanocytic nevi, the risk of melanoma developing within a nevus spilus is thought to be proportionate to the size of the lesion as a whole. The nevi need not be excised unless atypical features or recent clinical changes are noted.

NEVUS OF OTA AND NEVUS OF ITO

Nevus of Ota is more common among females and Asian and Black patients. This nevus consists of a permanent patch composed of partially confluent blue, black, and brown macules. Enlargement and darkening may occur with time. Occasionally, some areas of the nevus are raised. The macular nevi resemble the more common dermal melanocytosis of the lower back and buttocks in color and occur unilaterally in the areas supplied by the first and second divisions of the trigeminal nerve. Nevus of Ota differs from a more common dermal melanocytosis patch not only by its distribution but also by having a speckled rather than a uniform appearance. Both are forms of mid-dermal melanocytosis. Nevus of Ota also has a greater concentration of elongated, dendritic dermal melanocytes located in the upper rather than the lower portion of the dermis. This nevus is sometimes present at birth; in other cases, it may arise during the first or second decade of life. Patchy involvement of the conjunctiva, hard palate, pharynx, nasal mucosa, buccal mucosa, or tympanic membrane occurs in some patients. Malignant change is exceedingly rare. Laser therapy may effectively decrease the pigmentation but can be unpredictable.

Nevus of Ito is localized to the supraclavicular, scapular, and deltoid regions. This nevus tends to be more diffuse in its distribution and less mottled than nevus of Ota. It is also a form of mid-dermal melanocytosis. The only available treatments are masking with cosmetics and laser therapy.

BLUE NEVI

The common blue nevus is a solitary, asymptomatic, smooth, dome-shaped, blue to blue-gray papule <10 mm in diameter on the dorsal aspect of the hands and feet. Rarely, common blue nevi form large plaques. Blue nevus is nearly always acquired, often during childhood and more commonly in females. Microscopically, it is characterized by groups of intensely pigmented, spindle-shaped melanocytes in the dermis. This nevus is benign.

The cellular blue nevus is typically 1-3 cm in diameter and occurs most frequently on the buttocks and in the sacrococcygeal area. In addition to collections of deeply pigmented dermal dendritic melanocytes, cellular islands composed of large spindle-shaped cells are noted in the dermis and may extend into the subcutaneous fat. A histologic continuum may be seen from blue nevi to cellular blue nevi. A combined nevus is the association of a blue nevus with an overlying melanocytic nevus.

The blue-gray color that is characteristic of these nevi is an optical effect caused by dermal melanin. Longer wavelengths of visible light penetrate to the deep dermis and are absorbed there by melanin; shorter-wavelength blue light cannot penetrate deeply but instead is reflected back to the observer.

NEVUS DEPIGMENTOSUS (ACHROMIC NEVUS)

Nevi depigmentosi are usually present at birth; they are localized macular hypopigmented patches or streaks, often with irregular borders (Fig. 692.7). They can resemble hypomelanosis of Ito clinically, except that they are more localized and often unilateral. Small lesions may also resemble the ash leaf macules of tuberous sclerosis. Nevi depigmentosi appear to represent a focal defect in transfer of melanosomes to keratinocytes.

EPIDERMAL NEVI

Epidermal nevi may be visible at birth or may develop in the first few months or years of life. They affect both sexes equally and usually occur sporadically. Epidermal nevi are hamartomatous lesions characterized by hyperplasia of the epidermis and/or adnexal structures in a focal area of the skin.

Epidermal nevi are classified into a number of variants, depending on the morphology and extent of the individual nevus and the predominant epidermal structure (Table 692.2). An epidermal nevus may appear initially as a discolored, slightly scaly patch that, with maturation, becomes more linear, thickened, verrucous, and hyperpigmented. *Systematized* refers to a diffuse or extensive distribution of lesions, and *ichthyosis hystrix* indicates that the distribution is extensive and bilateral (Fig. 692.8). Morphologic types include pigmented papillomas, often in a linear distribution; unilateral hyperkeratotic streaks involving a limb and perhaps a portion of the trunk; velvety hyperpigmented plaques; and whorled or marbled hyperkeratotic lesions in localized plaques or over extensive areas of the body along Blaschko lines. An inflammatory linear verrucous variant is markedly pruritic and tends to become erythematous, scaling, and crusted. Many have *RAS* pathogenic variants.



Fig. 692.7 Large nevus depigmentosus of the abdomen.

The histologic pattern evolves as an epidermal nevus matures, but epidermal hyperplasia of some degree is apparent in all stages of development. One or another dermal appendage may predominate in a particular lesion. These nevi must be distinguished from lichen striatus, lymphangioma circumscriptum, shagreen patch of tuberous sclerosis, congenital hairy nevi, linear porokeratosis, linear lichen planus, linear psoriasis, the verrucous stage of incontinentia pigmenti, and nevus sebaceus (Jadassohn). Keratolytic agents such as retinoic acid and salicylic acid may be moderately effective in reducing scaling and controlling pruritus, but definitive treatment requires full-thickness excision; recurrence is usual if more superficial removal is attempted. Alternatively, the nevus may be left intact. Epidermal nevi are occasionally associated with other abnormalities of the skin and soft tissues; eyes; and nervous, cardiovascular, musculoskeletal, and urogenital systems. In these instances, the disorder is referred to as epidermal nevus syndrome. This syndrome, however, is not a distinct clinical entity.

Nevus Sebaceus (Jadassohn)

A relatively small, sharply demarcated, oval or linear, elevated, yellow-orange plaque that is usually devoid of hair, nevus sebaceus occurs on the head and neck of infants (Fig. 692.9). Although the lesion is characterized histopathologically by an abundance of sebaceous glands, all elements of the skin are represented. It is frequently flat and inconspicuous in early childhood. With maturity, usually during adolescence, the lesions become verrucous and studded with large rubbery nodules. The changing clinical appearance reflects the histologic pattern, which is characterized by a variable degree of hyperkeratosis, hyperplasia of the epidermis, malformed hair follicles, and often a profusion of sebaceous glands and

Table 692.2 Epidermal Nevi and Their Associated Genetic Syndromes

LESION	PATHOGENIC GENE VARIANT
KERATINOCYTIC NEVI	
Epidermal nevus	*FGFR3* *FGFR2* *HRAS* *KRAS* *NRAS* *PIK3CA*
Epidermolytic ichthyosis	*KRT1* *KRT10* *KRT2*
CHILD syndrome	*NSDHL*
PTEN nevus	*PTEN*
Proteus syndrome and epidermal nevi	*AKT1*
PIK3CA-related overgrowth spectrum/ CLOVES	*PIK3CA*
Acantholytic dyskeratotic epidermal nevus	*ATP2A2* *GJB2*
Inflammatory linear verrucous epidermal nevus	*Not identified to date*
ADNEXAL NEVI	
Nevus sebaceous/nevus sebaceous syndrome	*FGFR2* *HRAS* *KRAS* *NRAS*
Porokeratotic adnexal ostial nevus	*GJB2 (connexin 26)*
Nevus comedonicus/nevus comedonicus syndrome	*NEK9* *FGFR2*
Becker nevus/Becker nevus syndrome	*ACTB (beta-actin)*

CHILD, Congenital hemidysplasia with ichthyosiform erythroderma and limb defects; CLOVES, congenital lipomatous overgrowth and vascular and skeletal anomalies.



Fig. 692.8 Epidermal nevus (ichthyosis hystrix type).



Fig. 692.9 Orange-yellow nevus sebaceus of the scalp.



Fig. 692.10 Becker nevus on the shoulder of an adolescent male.



Fig. 692.11 Large smooth muscle hamartoma of the buttock.

the presence of ectopic apocrine glands. Sebaceous nevi are caused by somatic mosaic pathogenic variants in *HRAS* and *KRAS*. The disruption of these oncogenes helps explain the 14% incidence of these lesions developing tumors throughout a patient's lifetime. Most tumors are benign (trichoblastomas, syringocystadenoma papilliferum, trichilemmomas), but basal cell carcinoma can occur as well. Lesions may be monitored or excised if the family is unable to or uncomfortable with monitoring alone. Sebaceous nevi associated with central nervous system, skeletal, and ocular defects represent a variant of the epidermal nevus syndrome.

Becker Nevus (Becker Melanosis)

Becker nevus develops predominantly in males, during childhood or adolescence, initially as a hyperpigmented patch. The lesion commonly develops hypertrichosis, limited to the area of hyperpigmentation, and evolves into a unilateral, slightly thickened, irregular, hyperpigmented plaque. The most common sites are the upper torso and upper arm (Fig. 692.10). The nevus shows an increased number of basal melanocytes and variable epidermal hyperplasia. Becker melanosis is commonly associated with a smooth muscle hamartoma, which may appear as slight perifollicular papular elevations or slight induration. Stroking of such a lesion may induce smooth muscle contraction and make the hairs stand up **(pseudo-Darier sign)**. The nevus is benign, has no risk for malignant change, and is rarely associated with other anomalies.

NEVUS COMEDONICUS

An uncommon organoid nevus of epithelial origin, nevus comedonicus consists of linear plaques of plugged follicles that simulate comedones; they may be present at birth or may appear during childhood. The horny plugs represent keratinous debris within dilated, malformed pilosebaceous follicles. The lesions are most often unilateral and may develop at any site. Rarely, they are associated with other congenital malformations, including skeletal defects, cerebral anomalies, and cataracts. Although these lesions are often asymptomatic, some affected individuals experience recurrent inflammation, resulting in cyst formation, fistulas, and scarring. There is no effective treatment except full-thickness excision; palliation of larger lesions may be achieved by regular applications of a retinoic acid preparation.

CONNECTIVE TISSUE NEVUS

Connective tissue nevus is a hamartoma of collagen, elastin, and/or glycosaminoglycans of the dermal extracellular matrix. It may occur as a solitary defect or as a manifestation of an associated disorder. These nevi may occur at any site but are most common on the back, buttocks, arms, and thighs. They are skin-colored, ivory, or yellow plaques, 2-15 cm in diameter, composed of many tiny papules or grouped nodules that are frequently difficult to appreciate visually because of the subtle color changes. The plaques have a rubbery or cobblestone consistency on palpation. Biopsy findings are variable and include increased amounts and/or degeneration or fragmentation of dermal collagen, elastic tissue, or ground substance. Similar lesions occurring with tuberous sclerosis are called shagreen patches; however, shagreen patches consist only of excessive amounts of collagen. The association of many small papular connective tissue nevi with osteopoikilosis is called *dermatofibrosis lenticularis disseminata* **(Buschke-Ollendorff syndrome)**.

SMOOTH MUSCLE HAMARTOMA

Smooth muscle hamartoma is a developmental anomaly resulting from hyperplasia of the smooth muscle (arrector pili) associated with hair follicles. It is usually evident at birth or shortly thereafter as a flesh-colored or lightly pigmented plaque with overlying hypertrichosis on the trunk or limbs (Fig. 692.11). Transient elevation or a rippling movement of the lesion, caused by contraction of the muscle bundles, can sometimes be elicited by stroking of the surface (pseudo-Darier sign). Smooth muscle hamartoma can be mistaken for congenital pigmented nevus, but the distinction is important because the former has no risk for malignant melanoma and need not be removed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 693

Hyperpigmented Lesions

Joel C. Joyce

DISORDERS OF PIGMENTATION

Pigmentation of the skin requires migration of melanoblasts from the neural crest to the dermal-epidermal junction, enzymatic processes to form pigment, structural components to contain the pigment (melanosomes), and transfer of pigment to the surrounding keratinocytes. Increased skin color may be generalized or localized and may result from various defects in any of these requirements. Some of these aberrations are a manifestation of systemic disease, others represent generalized or focal developmental or genetic defects, and still others may be nonspecific and the result of cutaneous inflammation.

EPHELIDES (FRECKLES)

Ephelides (freckles) are well-demarcated macules—light or dark brown, round, oval, or irregularly shaped—that occur in sun-exposed areas such as the face, upper back, arms, and hands. They are usually less than 3 mm in diameter and are induced by exposure to sun, particularly during the summer, and may fade or disappear during the winter. They are a result of increased sun-induced melanogenesis and melanosome transport from melanocytes to keratinocytes and not from increased numbers of melanocytes. They are more common in redheads and fair-haired individuals and first appear in the preschool years. Histologically, they are marked by increased melanin pigment in epidermal basal cells, which have more numerous and larger dendritic processes than the melanocytes of the surrounding paler skin. The lack of melanocytic proliferation or elongation of epidermal rete ridges distinguishes them from **lentigines**. Ephelides have been identified as a marker for increased risk for ultraviolet (UV)-induced neoplasia and hence melanoma independent of melanocytic nevi. Treatment is not required, but regular and consistent sun protection can slow ephelis development.

LENTIGINES

Lentigines, often mistaken for ephelides or junctional nevi, are small (usually <5 mm but occasionally 1-2 cm), round, dark-brown macules that can appear anywhere on the body. They can be solitary or grouped. Onset can be at an early age, particularly when associated with genetic syndromes, but can appear at any age. They are more common in darkly pigmented than in lightly pigmented individuals. They do not vary in coloration seasonally and remain permanently. Histologically they have elongated, club-shaped epidermal rete ridges with increased numbers of melanocytes and dense epidermal deposits of melanin. No nests of melanocytes are found. Lentigines are benign and, when few, may be viewed as a normal occurrence. They are seen most commonly on the lower lip and sun-exposed skin but may occur elsewhere, particularly when associated with syndromes, inadvertent or therapeutic radiation exposure, or patterned (inherited-tendency).

Eruptive/generalized lentiginosis (lentiginosis profusa) involves innumerable small pigmented macules that are present at birth or appear during childhood. There are no associated abnormalities, and mucous membranes are spared. Carney complex is an autosomal dominant syndrome characterized by multiple lentigines and neoplasms, including myxomas of the skin, heart (atrial), and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosae; growth hormone–producing pituitary adenomas; and testicular Sertoli cell tumors. Components of the Carney complex have been described previously as the NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides) and LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) syndromes. The complex is inherited in an autosomal dominant pattern and caused by an inactivating pathogenic variant of the *PRKAR1A* gene.

Multiple lentigines syndrome (formerly LEOPARD) is an autosomal dominant entity consisting of a generalized, symmetric distribution of *l*entigines (Fig. 693.1) in association with *e*lectrocardiographic *a*bnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals (cryptorchidism, hypogonadism, hypospadias), growth *r*etardation, and sensorineural *d*eafness (type 1, *PTPN11* gene; type 2, *RAF1* gene). Other features include hypertrophic obstructive cardiomyopathy and pectus excavatum or carinatum.

Peutz-Jeghers syndrome is characterized by melanotic macules on the lips and mucous membranes and by gastrointestinal (GI) polyposis. It is inherited as an autosomal dominant trait caused by pathogenic variants of *STK11*. Onset is noted in infancy and early childhood when pigmented macules appear on the lips and buccal mucosa. The macules are usually a few millimeters in size but may be as large as 1-2 cm. Macules also occasionally appear on the palate, gums, tongue, and vaginal mucosa. Cutaneous macules may develop on the nose, hands, and feet; around the mouth, eyes, and umbilicus; and as longitudinal bands or diffuse hyperpigmentation of the nails. Pigmented macules often fade from the lips and skin during puberty and adulthood but generally do not disappear from mucosal surfaces. Buccal mucosal macules are the most constant feature of the disorder; in some families, occasional members may be affected only with the pigmentary changes. Indistinguishable pigmentary changes beginning in adult life, without intestinal involvement, also occur sporadically in individuals.

Polyposis usually involves the jejunum and ileum but may also occur in the stomach, duodenum, colon, and rectum (see Chapter 393). Episodic abdominal pain, diarrhea, melena, and intussusception are frequent complications. Patients have a significantly increased risk of GI tract and non–GI tract tumors at a young age. GI cancer has been reported in 2–3% of patients; the lifetime relative risk for GI malignancy is 13-15. The relative risk of non–GI tract malignancies, including ovarian, cervical, and testicular tumors, is 9. **Peutz-Jeghers syndrome** must be differentiated from other syndromes associated with multiple lentigines (Laugier-Hunziker syndrome), from ordinary freckling, from Gardner syndrome, and from Cronkhite-Canada syndrome, a disorder characterized by GI polyposis, alopecia, onychodystrophy, and diffuse pigmentation of the palms, volar aspects of the fingers, and dorsal hands. Treatment of Peutz-Jeghers melanotic macules is not required, but various lasers have been effective for cosmesis in some cases.

CAFÉ-AU-LAIT MACULES

Café-au-lait macules (CALMs) are uniformly hyperpigmented, sharply demarcated macular lesions, the hues of which vary with the normal degree of pigmentation of the individual: they are tan or light brown in White individuals and may be dark brown in Black children (Figs. 693.2 and 693.3). CALMs vary tremendously in size and may be large, covering a significant portion of the trunk or limb. The borders are usually



Fig. 693.1 Multiple lentigines in LEOPARD (*l*entigines in association with *e*lectrocardiographic *a*bnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals [cryptorchidism, hypogonadism, hypospadias], growth *r*etardation, and sensorineural *d*eafness) syndrome.

smooth (ovoid), but some have exceedingly irregular borders. They are characterized by increased numbers of melanocytes and melanin in the epidermis but lack the clubbed rete ridges that typify lentigines. One to three CALMs are common in the general population, and up to 27% of children have a solitary CALM, depending on ancestry. The spots may be present at birth or may develop during childhood. The spots themselves are benign and may fade with age.

Large, often asymmetric café-au-lait spots with irregular borders are characteristic of patients with **McCune-Albright syndrome** (*GNAS1* gene; see Chapter 600.6). This disorder includes polyostotic fibrous dysplasia of bone, leading to pathologic fractures; precocious puberty; and numerous hyperfunctional endocrinopathies. The macular hyperpigmentation has an irregular border and may be present at birth or may develop late in childhood (see Fig. 693.3). The lesions are often unilateral and migrate along the lines of Blaschko. Cutaneous pigmentation is typically most extensive on the side showing the most severe bone involvement.



Fig. 693.2 Multiple café-au-lait macules on a child with neurofibromatosis type 1. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001:372.)*

Neurofibromatosis Type 1 (Von Recklinghausen Disease)

The CALM is the most familiar cutaneous hallmark of the autosomal dominant neurocutaneous syndrome known as **neurofibromatosis type 1** (*NF1*, see Fig. 693.2 and Chapter 636.1). Included in the criteria for this diagnosis is the presence of six or more CALMs (>5 mm in diameter in prepubertal patients and >15 mm in diameter in postpubertal patients; Table 693.1). Multiple CALMs commonly produce a freckled appearance of non–sun-exposed areas such as the axillae (Crowe sign), the inguinal and inframammary regions, and under the chin. CALMs can also be seen in segmental NF1, which results from somatic mosaicism arising from postzygotic pathogenic genetic variants in the *NF1* gene such that the clinical manifestations of NF1 are present only in a localized body segment. Another variant of NF1 is hereditary spinal neurofibromatosis, which is a rare disorder that generally presents with multiple CALM and multiple symmetric spinal root neurofibromas, but other stigmata of NF1 are typically absent.

CALM may be seen in **Watson syndrome**, an NF1 allelic variant (CALM, pulmonic stenosis intellectual disability, short stature), mosaic NF1, and **Legius syndrome** *(SPRED1)*. Differentiation of these disorders is noted in Figure 693.4 and Table 693.2.

CALMs also occur with certain other disorders, including other types of neurofibromatosis, but in many of these disorders the CALMs are not the defining diagnostic feature (see Table 693.2).

INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER DISEASE)

See Chapter 636.7.

POSTINFLAMMATORY PIGMENTARY CHANGES

Either hyperpigmentation or hypopigmentation can occur as a result of cutaneous inflammation. Alteration in pigmentation usually follows a severe inflammatory reaction but may result from mild dermatitis. Dark-skinned individuals are more likely than fair-skinned children to show these changes. Although altered pigmentation may persist for weeks to months, patients can be reassured that these lesions are usually temporary. Sun protection and treatment of the underlying dermatitis can shorten duration.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 693.3 Coast of Maine café-au-lait macules. Irregularly bordered café au lait macules that tend not to cross the midline are characteristic of McCune-Albright syndrome. *(Modified from Collins MT, Singer FR, Rugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012;7[Suppl. 1]:S4, Fig. 2.)*

Table 693.1 Previous and Recently Updated National Institutes of Health Diagnostic Criteria for Neurofibromatosis Type 1

CARDINAL CLINICAL FEATURES (ANY TWO OR MORE ARE REQUIRED FOR DIAGNOSIS)	NEW CHANGES
1. Six or more café-au-lait macules more than 5 mm in greatest diameter in prepubertal individuals and more than 15 mm in greatest diameter in postpubertal individuals	Must be bilateral (both sides of the body)*
2. Freckling in the axillary or inguinal regions	Must be bilateral (both sides of the body)*
3. Two or more neurofibromas of any type or one plexiform neurofibroma	No change
4. Two or more Lisch nodules	Or two or more choroidal abnormalities
5. Optic pathway glioma	No change
6. A distinctive osseous lesion such as sphenoid wing dysplasia	Added anterolateral bowing of tibia (tibial dysplasia) or pseudarthrosis of a long bone
7. First-degree relative (e.g., mother, father, sister, brother) with NF1	Changed to a parent with NF1 by the aforementioned criteria
	New criteria: A pathogenic NF1 variant

*If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1, but exceptionally, the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
NIH, National Institutes of Health.
From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. *Dermatol Clin.* 2022;40:9–23, Table 1.

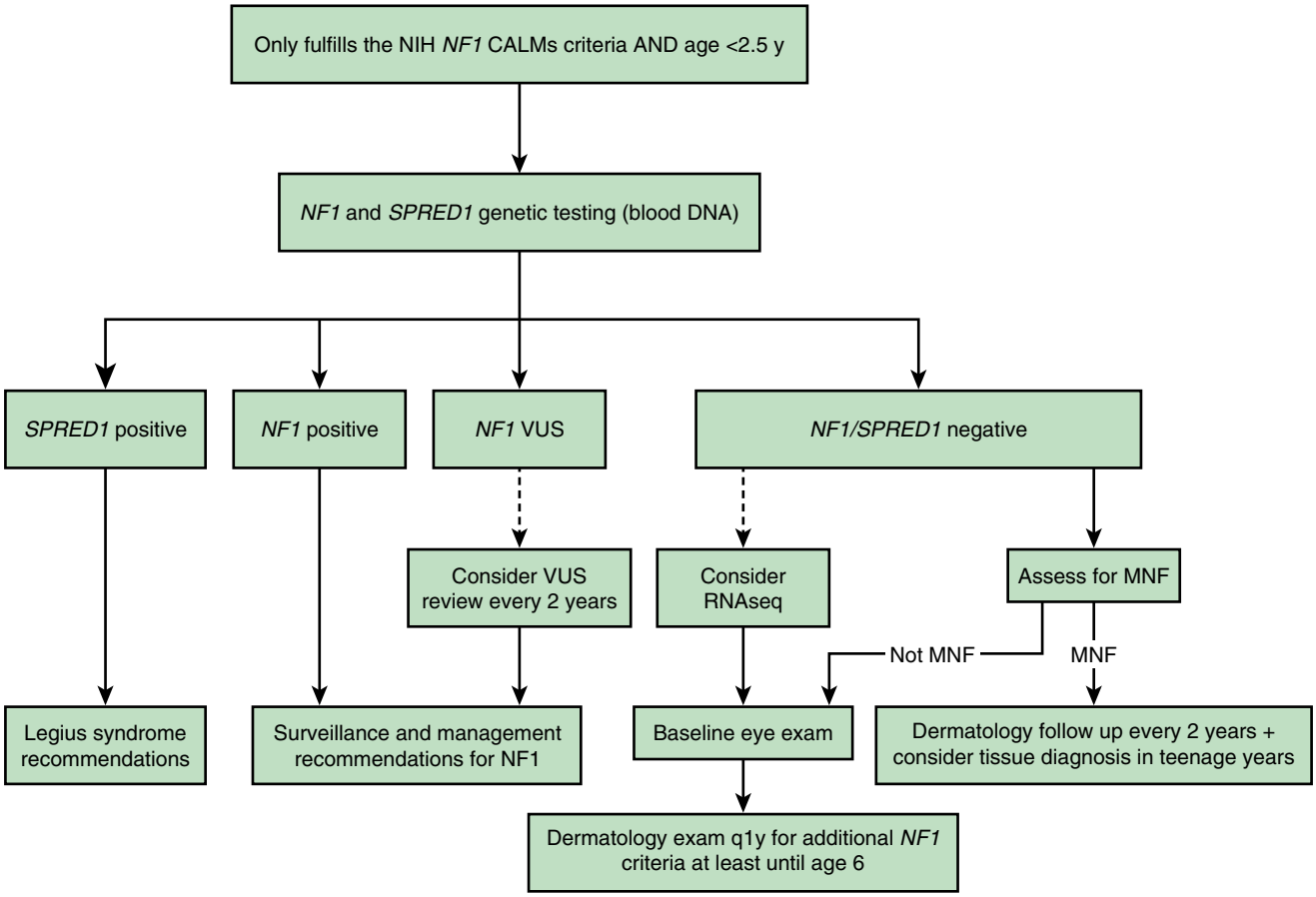

Fig. 693.4 Approach to the genetic diagnosis of young children who solely meet the CALM NIH criteria. MNF, Mosaic neurofibromatosis; NFI, neurofibromatosis; RNAseq, RNA sequencing; SPRED1, sprouty-related EVH1 domain-containing 1; VUS, variant of unknown significance. *(From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. Dermatol Clin. 2022;40:9–23, Fig. 7.)*

Table 693.2 Conditions Featuring Café au Lait Macules

CONDITION	GENE (INHERITANCE)	ASSOCIATED FEATURES*	ADDITIONAL TESTING TO CONSIDER
Ataxia telangiectasia	*ATM* (AR)	Progeric changes in skin and hair, hypopigmented macules, progressive neurologic impairment, cerebellar ataxia, radiosensitivity, malignancy, immunocompromise, premature aging, and oculocutaneous telangiectasia	Karyotype* Serum AFP*
Cardiofaciocutaneous syndrome	*BRAF, MAP2K1/2* (AD)	Follicular hyperkeratosis, sparse, slow-growing, curly hair, ulerythema ophryogenes, melanocytic nevi, infantile hemangiomas, distinctive craniofacial features, cardiac anomalies, psychomotor delay, failure to thrive, and skin abnormalities	Gene panel for RASopathies
Constitutional mismatch repair deficiency syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM* (AR)	Adenomatous colonic polyps, multiple malignancies including colonic adenocarcinoma, glioblastoma, medulloblastoma, lymphoma, and a positive family history of Lynch syndrome–associated malignancies on both sides of the family	Gene panel for Lynch syndrome genes
Multiple café-au-lait spots	N/A (AD)	Six or more CALMs in multiple generations without NF1-associated features	No genetic testing available
Familial progressive hyperpigmentation and hypopigmentation syndrome	*KITLG* (AR)	Progressive, diffuse, partly blotchy, hyperpigmented lesions with scattered hypopigmented spots and lentigines	*KITLG* gene testing
Fanconi anemia	*FANCA* and other genes (AR)	Faint, ill-defined CALMs "shadow spots," hypopigmented macules, skinfold freckle-like macules, progressive bone marrow failure, short stature, hypogonadism, thumb or other radial ray abnormalities, and skeletal malformations	DNA breakage studies Gene panel for bone marrow failure syndromes
Legius syndrome	*SPRED1* (AD)	Six or more CALMs, intertriginous freckling, lipomas, macrocephaly, and learning disabilities	*SPRED1* gene testing
Noonan syndrome with lentigines	*PTPN11* (AD)	Small brown lentigines, café noir spots, CALMs, dysmorphic facial features, obstructive cardiomyopathy, pulmonary stenosis, growth abnormalities, and sensorineural hearing loss	*PTPN11* gene testing
McCune-Albright syndrome	*GNAS* (sporadic)	Coast of Maine CALMs associated with the lines of Blaschko, fibrous dysplasia, and endocrinopathies	*GNAS* gene testing from affected tissue (not blood)
Neurofibromatosis type 1	*NF1* (AD)	Six or more CALMs, skinfold freckling, neurofibromas, plexiform neurofibromas, Lisch nodules, optic gliomas, skeletal dysplasia, macrocephaly, nevus anemicus, and juvenile xanthogranuloma	*NF1* gene testing (DNA) ± RNA sequencing
Neurofibromatosis type 2	*NF2* (AD)	Schwannomas, cutaneous plaques with hypertrichosis, light irregularly bordered CALMs, subcutaneous nodular tumors, peripheral neuropathy, and ophthalmologic lesions	*NF2* gene testing (DNA) ± RNA sequencing
Noonan syndrome	*PTPN11, SOS2,* and other genes (AD)	Skin hyperlaxity, easy bruising, keratosis pilaris, temporal alopecia, distinctive facial features, developmental delay, learning difficulties, short stature, congenital heart disease, renal anomalies, lymphatic malformations	Gene panel for RASopathies
Piebaldism	*KIT* (AD)	Hypopigmented patches of skin and hair, hyperpigmentation of skin, CALMs, and axillary/inguinal freckling	*KIT* gene testing
PTEN hamartoma tumor syndrome	*PTEN* (AD)	Hamartomas, trichilemmomas, papillomatous papule, acral and plantar keratoses, lipomas, autism spectrum disorder, and macrocephaly	*PTEN* gene testing
Ring chromosome syndrome 7, 11, 12, 15, and 17	Sporadic	Depends on which chromosome but may include CALMs, nevus flammeus, dark pigmented nevi, patchy hypopigmented areas, microcephaly, mental delay, short stature, and skeletal abnormalities	Karyotype

Continued

Table 693.2 Conditions Featuring Café au Lait Macules—cont'd

CONDITION	GENE (INHERITANCE)	ASSOCIATED FEATURES*	ADDITIONAL TESTING TO CONSIDER
RSS	11p15 locus Chromosome 7 (sporadic) *CDKN1C, IGF2, PLAGL2, HMGA2* (AD)	Growth restriction, relative macrocephaly, craniofacial abnormalities, mild cognitive impairment, and delay	Molecular and methylation testing of 11p15 and uniparental disomy 7 ± RSS gene panel testing
Tuberous sclerosis	*TSC1, TSC2* (AD)	Facial angiofibromas, ash leaf macules, thumbprint-like macules, confetti-like skin lesions, shagreen patch, Koenen tumors, hamartomas, multisystem lymphangioleiomyomatosis, epilepsy, cognitive deficits	*TSC1* and *TSC2* gene testing

*All disorders listed have had multiple CALMs associated with them.

AD, Autosomal dominant; AFP, alpha fetoprotein; AR, autosomal recessive; ATM, ataxia telangiectasia variant gene; BRAF, B-RAF proto-oncogene; CDKN1C, cyclin-dependent kinase inhibitor 1C; EPCAM, epithelial cell adhesion molecule; FANCA, FA complementation group A; GNAS, GNAS complex locus; HMGA2, high mobility group AT-hook 2; IFG2, insulin-like growth factor 2; KIT, KIT proto-oncogene receptor tyrosine kinase; KITLG, *KIT* ligand; MAP2K1/2; mitogen-activated protein kinase 1, MLH1; MutL, *Escherichia coli* homolog of 1; MSH2; MutS, *E. coli* homolog of 2; MSH6, MutS , *E. coli* homolog of 6; NF1, neurofibromin 1; NF2, neurofibromin 2; PLAGL2, PLAG1-like zinc finger 2; PTEN, phosphate and tensin homolog; *PMS2*, postmeiotic segregation increased *Saccharomyces cerevisiae* 2; PTPN11, protein tyrosine phosphatase nonreceptor type 11; RSS, Russel-Silver syndrome; SPRED 1, sprouty-related EVH1 domain-containing protein 1; SOS2, SOS RAS/RAC guanine nucleotide exchange factor 2; TSC1, TSC1 gene; TSC2, TSC2 gene.

From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. *Dermatol Clin*. 2022;40:9–23, Table 2.

Chapter 694

Hypopigmented Lesions

Joel C. Joyce

ALBINISM

Congenital oculocutaneous albinism (OCA) consists of partial or complete failure of melanin production in the skin, hair, and eyes despite the presence of normal number, structure, and distribution of melanocytes. These disorders are autosomal recessive in inheritance and result from pathogenic variants in genes related to melanin synthesis or the transport and storage of melanin within cells (Table 694.1). Tyrosinase is the copper-containing enzyme that catalyzes multiple steps in melanin biosynthesis (see Chapter 105.2), and gene variants resulting in abnormal function of tyrosinase and associated transporter proteins result in various OCA phenotypes. Gene variants resulting in abnormal structure and function of several cellular organelles may result in OCA with other extracutaneous complications.

Oculocutaneous Albinism with Abnormal Melanin Production

Oculocutaneous albinism type 1 (OCA1) is characterized by great reduction in or absence of tyrosinase activity caused by pathogenic gene variants in *TYR*. OCA1-A, the most severe form, is characterized by a lack of visible pigment in hair, skin, and eyes (Fig. 694.1). This manifests as photophobia, nystagmus, defective visual acuity, white hair, and white skin. The irises are blue-gray in oblique light and prominent pink in reflected light. OCA1-B, or yellow **albinism**, manifests at birth as white hair, pink skin, and gray eyes. This type is particularly prevalent in Amish communities. Progressively the hair becomes yellow-red, the skin tans lightly on exposure to the sun, and the irises may accumulate some brown pigment, with a resultant improvement in visual acuity. Photophobia and nystagmus are present but mild. OCA-TS is a temperature-sensitive type of albinism. The abnormal tyrosinase has decreased activity at 35–37°C (95–98.6°F). Therefore cooler regions of the body such as the limbs and head pigment to some degree, whereas other areas remain depigmented.

Oculocutaneous albinism type 2 (OCA2) ranges from nearly normal to closely resembling type 1 albinism. This is the most common form of albinism seen worldwide. Little or no melanin is present at birth, but pigment, particularly red-yellow pigment, may accumulate during childhood to produce straw-colored or light brown skin in White individuals. Pigmented nevi may develop. Progressive improvement in visual acuity and nystagmus occurs with aging. Black individuals may have yellow-brown skin, dark-brown freckles in sun-exposed areas, and brown coloration of the irises. Brown OCA is an allelic variant of OCA2. Prader-Willi and Angelman syndromes, which include hypopigmentation, have deletions that include the gene *(OCA2)* involved in OCA2.

Oculocutaneous albinism type 3 (OCA3), also known as *rufous albinism,* is seen predominantly in patients of African descent. It is characterized by red hair, reddish-brown skin, pigmented nevi, freckles, reddish-brown to brown eyes, nystagmus, photophobia, and decreased visual acuity. Vision abnormalities tend to be milder than in other forms of OCA. Abnormal gene variants in *TYRP1* are typically associated with development of OCA3.

Oculocutaneous albinism type 4 (OCA4) is a rare OCA with clinical findings similar to those in OCA2. Gene variants in *SLC45A2* are known to cause OCA4.

Additional rare variants of OCA exist that may present with similar clinical features to those noted earlier. See Table 694.1.

Cross-McKusick-Breen syndrome consists of tyrosinase-positive albinism with ocular abnormalities, cognitive impairment, spasticity, and athetosis. The genetic defect is unidentified.

Because of the absence of normal protection by adequate amounts of epidermal melanin, persons with albinism are predisposed to development of actinic keratoses and cutaneous carcinoma secondary to skin damage by ultraviolet light. Protective clothing and a broad-spectrum sunscreen (see Chapter 697) should be worn during exposure to sunlight.

Oculocutaneous Albinism with Organelle Dysfunction

Hermansky-Pudlak syndrome is a collection of autosomal recessive genetic disorders characterized by OCA, ceroid accumulation in lysosomes, and platelet dysfunction, resulting in prolonged bleeding time (Table 694.2). Ceroid accumulation over time can cause damage to the lung, kidneys, and gastrointestinal tract, with risk of development of granulomatous colitis and/or pulmonary fibrosis. Abnormalities in the development of platelet-dense granules lead to platelet dysfunction.

Table 693.2 Conditions Featuring Café au Lait Macules—cont'd

CONDITION	GENE (INHERITANCE)	ASSOCIATED FEATURES*	ADDITIONAL TESTING TO CONSIDER
RSS	11p15 locus Chromosome 7 (sporadic) *CDKN1C, IGF2, PLAGL2, HMGA2* (AD)	Growth restriction, relative macrocephaly, craniofacial abnormalities, mild cognitive impairment, and delay	Molecular and methylation testing of 11p15 and uniparental disomy 7 ± RSS gene panel testing
Tuberous sclerosis	*TSC1, TSC2* (AD)	Facial angiofibromas, ash leaf macules, thumbprint-like macules, confetti-like skin lesions, shagreen patch, Koenen tumors, hamartomas, multisystem lymphangioleiomyomatosis, epilepsy, cognitive deficits	*TSC1* and *TSC2* gene testing

*All disorders listed have had multiple CALMs associated with them.

AD, Autosomal dominant; AFP, alpha fetoprotein; AR, autosomal recessive; ATM, ataxia telangiectasia variant gene; BRAF, B-RAF proto-oncogene; CDKN1C, cyclin-dependent kinase inhibitor 1C; EPCAM, epithelial cell adhesion molecule; FANCA, FA complementation group A; GNAS, GNAS complex locus; HMGA2, high mobility group AT-hook 2; IFG2, insulin-like growth factor 2; KIT, KIT proto-oncogene receptor tyrosine kinase; KITLG, *KIT* ligand; MAP2K1/2; mitogen-activated protein kinase 1, MLH1; MutL, *Escherichia coli* homolog of 1; MSH2; MutS, *E. coli* homolog of 2; MSH6, MutS , *E. coli* homolog of 6; NF1, neurofibromin 1; NF2, neurofibromin 2; PLAGL2, PLAG1-like zinc finger 2; PTEN, phosphate and tensin homolog; *PMS2*, postmeiotic segregation increased *Saccharomyces cerevisiae* 2; PTPN11, protein tyrosine phosphatase nonreceptor type 11; RSS, Russel-Silver syndrome; SPRED 1, sprouty-related EVH1 domain-containing protein 1; SOS2, SOS RAS/RAC guanine nucleotide exchange factor 2; TSC1, TSC1 gene; TSC2, TSC2 gene.

From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. *Dermatol Clin*. 2022;40:9–23, Table 2.

Chapter 694

Hypopigmented Lesions

Joel C. Joyce

ALBINISM

Congenital oculocutaneous albinism (OCA) consists of partial or complete failure of melanin production in the skin, hair, and eyes despite the presence of normal number, structure, and distribution of melanocytes. These disorders are autosomal recessive in inheritance and result from pathogenic variants in genes related to melanin synthesis or the transport and storage of melanin within cells (Table 694.1). Tyrosinase is the copper-containing enzyme that catalyzes multiple steps in melanin biosynthesis (see Chapter 105.2), and gene variants resulting in abnormal function of tyrosinase and associated transporter proteins result in various OCA phenotypes. Gene variants resulting in abnormal structure and function of several cellular organelles may result in OCA with other extracutaneous complications.

Oculocutaneous Albinism with Abnormal Melanin Production

Oculocutaneous albinism type 1 (OCA1) is characterized by great reduction in or absence of tyrosinase activity caused by pathogenic gene variants in *TYR*. OCA1-A, the most severe form, is characterized by a lack of visible pigment in hair, skin, and eyes (Fig. 694.1). This manifests as photophobia, nystagmus, defective visual acuity, white hair, and white skin. The irises are blue-gray in oblique light and prominent pink in reflected light. OCA1-B, or yellow **albinism**, manifests at birth as white hair, pink skin, and gray eyes. This type is particularly prevalent in Amish communities. Progressively the hair becomes yellow-red, the skin tans lightly on exposure to the sun, and the irises may accumulate some brown pigment, with a resultant improvement in visual acuity. Photophobia and nystagmus are present but mild. OCA-TS is a temperature-sensitive type of albinism. The abnormal tyrosinase has decreased activity at 35–37°C (95–98.6°F). Therefore cooler regions of the body such as the limbs and head pigment to some degree, whereas other areas remain depigmented.

Oculocutaneous albinism type 2 (OCA2) ranges from nearly normal to closely resembling type 1 albinism. This is the most common form of albinism seen worldwide. Little or no melanin is present at birth, but pigment, particularly red-yellow pigment, may accumulate during childhood to produce straw-colored or light brown skin in White individuals. Pigmented nevi may develop. Progressive improvement in visual acuity and nystagmus occurs with aging. Black individuals may have yellow-brown skin, dark-brown freckles in sun-exposed areas, and brown coloration of the irises. Brown OCA is an allelic variant of OCA2. Prader-Willi and Angelman syndromes, which include hypopigmentation, have deletions that include the gene *(OCA2)* involved in OCA2.

Oculocutaneous albinism type 3 (OCA3), also known as *rufous albinism,* is seen predominantly in patients of African descent. It is characterized by red hair, reddish-brown skin, pigmented nevi, freckles, reddish-brown to brown eyes, nystagmus, photophobia, and decreased visual acuity. Vision abnormalities tend to be milder than in other forms of OCA. Abnormal gene variants in *TYRP1* are typically associated with development of OCA3.

Oculocutaneous albinism type 4 (OCA4) is a rare OCA with clinical findings similar to those in OCA2. Gene variants in *SLC45A2* are known to cause OCA4.

Additional rare variants of OCA exist that may present with similar clinical features to those noted earlier. See Table 694.1.

Cross-McKusick-Breen syndrome consists of tyrosinase-positive albinism with ocular abnormalities, cognitive impairment, spasticity, and athetosis. The genetic defect is unidentified.

Because of the absence of normal protection by adequate amounts of epidermal melanin, persons with albinism are predisposed to development of actinic keratoses and cutaneous carcinoma secondary to skin damage by ultraviolet light. Protective clothing and a broad-spectrum sunscreen (see Chapter 697) should be worn during exposure to sunlight.

Oculocutaneous Albinism with Organelle Dysfunction

Hermansky-Pudlak syndrome is a collection of autosomal recessive genetic disorders characterized by OCA, ceroid accumulation in lysosomes, and platelet dysfunction, resulting in prolonged bleeding time (Table 694.2). Ceroid accumulation over time can cause damage to the lung, kidneys, and gastrointestinal tract, with risk of development of granulomatous colitis and/or pulmonary fibrosis. Abnormalities in the development of platelet-dense granules lead to platelet dysfunction.

Table 694.1 Forms of Oculocutaneous Albinism

TYPE	PERCENTAGE OF PATIENTS WORLDWIDE	GENETIC VARIANT	FUNCTION OF AFFECTED GENE	COMMENTS
OCA1A	50%	TYR (absence) = tyrosinase negative	Rate-limiting steps in melanin formation; hydroxylates L-tyrosine to L-DOPA and L-DOPA to DOPA-quinone	1:40,000; most severe cutaneous and ocular defects; highest risk of skin cancer; most common type in Whites
OCA1B		TYR (decreased)	Critical enzyme in melanin formation	Subtypes: yellow (yellow hair); platinum (metallic tinge); minimal pigment (only eyes darken)
OCA1-TS		TYR (variant site functions at higher temperatures)	Temperature sensitive	Melanin at cooler sites (arms, legs) Occurs in Siamese cats
OCA2	30%	P protein	Transmembrane protein that is key for melanosome biogenesis and normal processing and transport of TYR and *TRYP1*	1:36,000 (Whites); TYR-positive; includes brown albinism (1:3,900-1:10,000; most common form in patients of African origin; more pigment with advancing age); also includes red OCA2 with concomitant *MC1R* pathogenic variant and red hair
OCA3 (Rufous)	3%	*TRYP1*	Catalyzes oxidation of 5,6-dihydroxyindole-2-carboxylic acid monomers into melanin and stabilizes TYR so it can leave endoplasmic reticulum for incorporation into melanosomes	1:8,500 Africans; reddish-bronze color to skin and hair
OCA4	17%	*MATP/SLC45A2*	Membrane transporter in melanosomes and regulates pH	Rare (Whites); 27% of OCA in Japan; resembles OCA2
OCA5		Unknown (4q24)	—	One Pakistani family
OCA6		*SLC24A5*	$Na^+/K^+/Ca^+$ + solute carrier protein involved in melanosome maturation and melanin biosynthesis	Heterogeneous extent of pigmentation
OCA7		*LRMDA*	Melanocyte differentiation	Rare; skin color lighter only when compared with relatives

LRMDA, Leucine-rich melanocyte differentiation associated protein; MATP, membrane-associated transporter protein; OCA, oculocutaneous albinism; P protein, pink-eyed dilution protein; TS, temperature sensitive; TYR, tyrosinase; TRYP1, tyrosinase-related protein 1.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 11.1, p. 291.



Fig. 694.1 White hair and skin in oculocutaneous albinism type 1 (OCA1).

Chédiak-Higashi syndrome (see Chapter 170) is another genetic abnormality associated with dysfunction of lysosome-related organelles. Patients with Chédiak-Higashi syndrome have hypopigmentation of the skin, eyes, and hair; prolonged bleeding times and easy bruising; recurrent infections; abnormal natural killer cell function; and peripheral neuropathy. Chédiak-Higashi syndrome is caused by pathogenic gene variants in the *CHS1/LYST* gene, which is a lysosomal trafficking regulatory gene.

MELANOBLAST MIGRATION ABNORMALITIES

Piebaldism

A congenital autosomal dominant disorder, piebaldism is characterized by sharply demarcated amelanotic patches that occur most frequently on the forehead, anterior scalp (producing a white forelock), ventral trunk, elbows, and knees. Islands of normal or darker-than-normal pigmentation may be present within the amelanotic areas (Fig. 694.2). The plaques are a result of a permanent localized absence of melanocytes as a result of a defect in the *KIT* protooncogene, which encodes the cell surface receptor transmembrane tyrosine kinase. The pattern of depigmentation arises from defective melanoblast migration from the neural crest during development. The reason that piebaldism is a localized and not a generalized process remains unknown. Piebaldism must be differentiated from vitiligo, which may be progressive and is not usually congenital, nevus depigmentosus, and Waardenburg syndrome.

Waardenburg Syndrome

Waardenburg syndrome also manifests at birth as localized areas of depigmented skin and hair. There are four main types of Waardenburg syndrome with additional subtypes identified. The hallmark of **Waardenburg type 1** (WS1) is the white forelock, which is seen in

Table 694.2 Clinical Features of Hermansky-Pudlak Syndrome

TYPE	PATHOGENIC VARIANT	UNDERLYING CAUSE	FINDINGS ASSOCIATED WITH THE CUTANEOUS PIGMENT DILUTION
HPS-1 HPS-4	*HPS1* (82% of HPS in Puerto Ricans; 37% in non–Puerto Ricans) *HPS4*	BLOC-3 deficiency: HPS1 and HPS4 associate in a complex (BLOC-3) that regulates biogenesis of melanosomes, platelet-dense bodies, and the lung lamellar body	Nystagmus, decreased visual acuity; prolonged bleeding; pulmonary fibrosis (typical onset in young adults); granulomatous colitis (up to one third of patients)
HPS-2 HPS-10	*AP3B1* (~10% of non–Puerto Ricans) and *AP3D1* (rare)	AP-3 deficiency: *AP3B1* and APSD1 encode subunits of AP-3, which mediates protein trafficking into transport vesicles of the lysosome (and is thus also involved in immune function)	Nystagmus, decreased visual acuity; prolonged bleeding; congenital neutropenia and impaired NK cell cytotoxicity; recurrent bacterial and viral infections; conductive hearing loss; fibrosing lung disease (30–50%) beginning during childhood; seizures in HPS-10
HPS-3 HPS-5 HPS-6	*HPS3* (~20% in Puerto Ricans and ~12% in non–Puerto Ricans) *HPS5* (~9% in non–Puerto Ricans) *HPS6* (~16% in non–Puerto Ricans)	BLOC-2 deficiency: HPS3, HPS5, and HPS6 are associated in a complex (BLOC-2) that localizes tyrosinase and *TRYP1*, allowing them to function normally	Nystagmus, decreased visual acuity; mild extraocular manifestations (bleeding, skin pigmentation)
HPS-7 HPS-8 HPS-9	*DTNBP1* *BLOC1S3* *BLOC1S6/PLDN*	BLOC-1 deficiency: Dysbindin, BLOC1S3, and BLOC1S6 are subunits of BLOC-1 and also involved in skin melanosome biogenesis and platelet function	Nystagmus, decreased visual acuity; prolonged bleeding (may not be a feature with *BLOC1S6* pathogenic variant)

BLOC, Biogenesis of lysosome-related organelles complex; DTNBP1, dystrobrevin binding protein 1; HPS, Hermansky-Pudlak syndrome.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 6th ed. Philadelphia: Elsevier; 2022: Table 11.2, p. 295.



Fig. 694.2 Depigmented macule with islands of hyperpigmentation in piebaldism.

20–60% of patients. Only 15% of patients have areas of depigmented skin. Deafness occurs in 9–37%, heterochromia irides in 20%, and unibrow (synophrys) in 17–69% of those affected. Dystopia canthorum (i.e., telecanthus) is seen in all patients with WS1. **Waardenburg type 2** is similar to type 1, except that patients with type 2 lack dystopia canthorum, but they also have a higher incidence of deafness. **Waardenburg type 3** is similar to WS1, except that patients also have limb abnormalities. It is also called *Klein-Waardenburg syndrome.* **Waardenburg type 4** is also called *Shah-Waardenburg syndrome.* Patients with this type all have Hirschsprung disease. Dystopia canthorum is seldom seen in these patients. Multiple pathogenic variants in multiple genes have been identified as causative of the various types of **Waardenburg syndrome** (Table 694.3).

Tuberous Sclerosis Complex (*TSC1*, *TSC2* Genes)

See Chapter 636.2 for a discussion of this complex.

Hypomelanosis of Ito

Hypomelanosis of Ito is a rare congenital skin disorder affecting children that can have associated defects in several organ systems. There is no evidence for genetic transmission; chromosomal mosaicism and chromosomal translocations have been reported. Hypomelanosis of Ito is a descriptive diagnosis. Blaschkoid or mosaic hypomelanosis may be better descriptive terms. It is also known as *incontinentia pigmenti achromians.*

The skin lesions of hypomelanosis of Ito are generally present at birth but may be acquired in the first 2 years of life. The lesions are similar to a negative image of those present in incontinentia pigmenti, consisting of patterned, hypopigmented macules arranged over the body surface in sharply demarcated whorls, streaks, and patches that follow the lines of Blaschko (Fig. 694.3). The palms, soles, and mucous membranes are spared. The hypopigmentation remains unchanged throughout childhood but fades during adulthood. The degree of depigmentation varies from hypopigmented to achromic. Neither inflammatory nor vesicular lesions precede the development of the pigmentary changes as in incontinentia pigmenti. The hypopigmented areas demonstrate fewer and smaller melanocytes and a decreased number of melanin granules in the basal cell layer than normal. Inflammatory cells and pigment incontinence are lacking.

The majority of patients with hypomelanosis of Ito have no associated abnormalities, but involvement of other organ systems can rarely occur. The most commonly associated abnormalities involve the nervous system, including intellectual disability (70%), seizures (40%), microcephaly (25%), and muscular hypotonia (15%). The musculoskeletal system is the second most frequently involved system, affected by scoliosis and thoracic and limb deformities. Minor ophthalmologic defects (strabismus, nystagmus) are present in 25% of patients, and 10% have cardiac defects. These frequencies are likely to be overestimated because patients with isolated skin disease often do not seek further evaluation. The differential diagnosis includes systematized nevus depigmentosus, which is a stable leukoderma not associated with systemic manifestations. Differentiation from incontinentia pigmenti, particularly the hypopigmented fourth stage, is critical for genetic counseling because incontinentia pigmenti, unlike hypomelanosis of Ito, is inherited.

Table 694.3 Subtypes of Waardenburg Syndrome

DISORDER	INHERITANCE	GENE(S)	OTHER COMMENTS
WS1	AD	*PAX3*	Most common form; dystopia canthorum
WS2	AD	*MITF, SOX10, SLUG, KITLG, KIT*	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS3	AD/AR	*PAX3*	Associated limb abnormalities
WS4A	AD/AR	*EDNRB*	Aganglionic megacolon
WS4B	AD/AR	*EDN3*	Aganglionic megacolon
WS4C	AD	*SOX10*	Aganglionic megacolon
PCWH	AD	*SOX10*	Severe hypotonicity with central nervous system and peripheral nerve abnormalities

AD, Autosomal dominant; AR, autosomal recessive; EDN, endothelin; EDNRB, endothelin receptor beta; PCWH, peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 11.4, p. 298.



Fig. 694.3 Marbled hypopigmented streaks on the abdomen in hypomelanosis of Ito.

Vitiligo

Epidemiology and Etiology

Vitiligo is an *acquired* macular depigmentation disorder associated with the destruction of melanocytes. The disorder represents a clinical end-point resulting from a complex interaction of environmental, genetic, and immunologic factors. Autoimmune, genetic, autocytotoxic, and neural theories have been postulated. The prevalence is 0.5–2% of most populations.

There is an autoimmune component to vitiligo. Eighty percent of patients with active disease have anti-melanocyte antibodies to one of several antigens on melanocytes. These antibodies appear to be cytotoxic for melanocytes. There is also a correlation between disease activity and the titer of serum anti-melanocyte antibody. Melanocyte-specific $CD8^+$ T lymphocytes are also involved in the pathogenesis of vitiligo. These antibodies and T cells recognize a variety of melanocyte enzymatic and structural proteins.

The genetic epidemiology of vitiligo is part of a broader genetically determined autoimmune and autoinflammatory diathesis. Between 15 and 20% of patients with generalized vitiligo have one or more affected first-degree relatives. In these families the genetic pattern is suggestive of polygenic, multifactorial inheritance. In the other patients, the disease occurs sporadically. Genome-wide association studies in patients with vitiligo have identified a substantial number of associated genes, of which consistent association is seen with *DDR1, XBP1, NLRP1, PTPN22,* and *COMT,* although many other genes have been implicated.

Table 694.4 Vitiligo Subgroups

DERMATOMAL OR SEGMENTAL	NONDERMATOMAL OR NONSEGMENTAL
Onset in childhood	Can begin in childhood; 50% before 20 yr of age
Less common	More common
Rapid onset; stabilizes in ~1 yr	Progressive, with flare-ups; lifelong
Involves hair after onset	Involves hair in later stages
Autoimmune diseases uncommon	Personal or family history of autoimmunity* common
Often occurs on the face or upper extremities	Occurs at sites sensitive to pressure, friction, or trauma; Koebner phenomenon
Responsive to autologous grafting, with repigmentation	Relapses after autologous grafting
Difficult to distinguish from nevus depigmentosus	Associated with halo nevus formation

*Autoimmune thyroid diseases, type 1 diabetes, psoriasis, pernicious anemia, systemic lupus erythematosus, Addison disease, alopecia areata.



Fig. 694.4 Sharply demarcated, symmetric, depigmented areas of vitiligo.

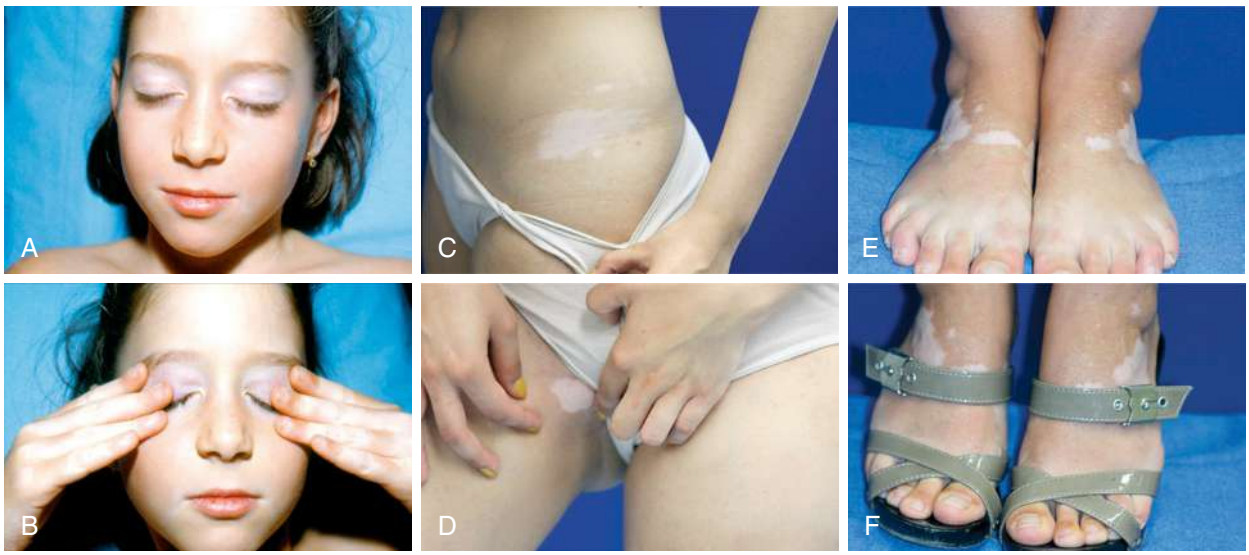

Fig. 694.5 Koebner phenomenon in relation to daily living activities. **A** and **B**, Eye rubbing. **C** and **D**, Underwear print. **E** and **F**, Shoe print. *(From Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet. 2015;386:74–82, Fig. 5.)*

Many authorities believe that the cause of melanocyte destruction in vitiligo is an interferon gamma–based immune destruction and melanocyte apoptosis. It has also been suggested that melanocytes are destroyed because of the accumulation of a toxic melanin synthesis intermediate and/or lack of protection from hydrogen peroxide and other oxygen radicals. There is in vitro evidence that some of these metabolites may be lethal to melanocytes.

Clinical Manifestations

There are two subtypes of vitiligo, generalized (nonsegmental) and segmental, which likely are distinctly different diseases (Table 694.4). Generalized vitiligo (85–90% of cases) may be divided into widespread (type A) and localized (type B). Approximately 50% of all patients with vitiligo have onset before 18 years of age, and 25% demonstrate depigmentation before age 8 years. Most children have the generalized form, but the segmental type is more common among children than among adults. Patients with the generalized form usually present with a remarkably symmetric pattern of white macules and patches (Fig. 694.4); the margins may be somewhat hyperpigmented. The patches tend to be acral and/or periorificial. Occasionally, almost the entire skin surface becomes depigmented. Vitiligo lesions may develop in areas of traumatized skin (Koebner phenomenon) (Fig. 694.5).

There are several varieties of localized vitiligo. One form is halo nevus phenomenon, whereby benign moles develop depigmented rings at the periphery (see Chapter 692). Premature graying of scalp hair (canities) has also been considered a form of localized vitiligo. In segmental vitiligo, depigmented areas are typically limited to a dermatomal distribution. This type of vitiligo has a rapid onset and progression in a localized area without the development of depigmentation in other areas.

A number of **autoimmune diseases** occur in up to 20% of patients with vitiligo, including Addison disease, Hashimoto thyroiditis, pernicious anemia, diabetes mellitus, hypoparathyroidism, and polyglandular autoimmune syndrome with selective immunoglobulin A deficiency. In addition, other diseases with possible immune defects, such as alopecia areata and morphea, have been seen in patients with vitiligo.

Vogt-Koyanagi-Harada syndrome is vitiligo associated with uveitis, dysacusia, meningoencephalitis, and depigmentation of the skin, scalp hair, eyebrows, and eyelashes. In **Alezzandrini syndrome**, vitiligo is associated with tapetoretinal degeneration and deafness. It is typically unilateral. Light microscopic examination of early lesions shows mild inflammatory change. Over time, degenerative changes occur in melanocytes, leading to their complete disappearance.

The differential diagnosis of vitiligo includes other causes of widespread acquired leukoderma. The two most common alternative diagnoses are pityriasis versicolor and postinflammatory hypopigmentation.

Treatment

Localized areas of vitiligo may respond to a potent topical steroid (class I or II) and/or topical calcineurin inhibitor (tacrolimus or pimecrolimus), depending on the location of involvement. Therapy with Janus kinase inhibitors has been effective in adults with vitiligo. In patients with more extensive involvement, narrow-band ultraviolet light B (NBUVB) [UVB311] is the treatment of choice. Treatment with NBUVB is often undertaken simultaneously with topical therapy. Systemic therapy and whole-body depigmentation are rarely used in children, although systemic corticosteroids can be given to slow the rate of change in rapidly progressive depigmentation. In all forms of vitiligo, response to therapy may be slow, taking many months to years. For those not interested in treatment, cover-up cosmetics may be used. All areas of vitiligo are susceptible to sun damage, and care should be taken to minimize sun exposure of affected areas. Spontaneous remission may be seen in a small percentage of cases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 695

Vesiculobullous Disorders

Joel C. Joyce

Many diseases are characterized by vesiculobullous lesions; they vary considerably in cause, age of onset, and pattern. The morphology and distribution of the blisters in these **blistering disorders** often provides a visual clue to the location of the lesion within the skin. Blisters localized to the epidermal layers are thin-walled, relatively flaccid, and easily ruptured. Subepidermal blisters are tense, thick-walled, and more durable. Biopsies of blisters can be diagnostic because the level of cleavage within the skin and associated findings, such as the nature of the inflammatory infiltrate, are characteristic for a particular disorder. Other diagnostic procedures, such as direct immunofluorescence on affected tissue and indirect immunofluorescence from a patient's serum to detect circulating antibodies, can often help to distinguish vesiculobullous disorders that have nearly identical histopathologic findings (Table 695.1).

695.1 Erythema Multiforme

Joel C. Joyce

ETIOLOGY

Among the numerous factors implicated in the etiology of erythema multiforme (EM), infection with herpes simplex virus (HSV) is the most common. Other viral infections, as well as vaccinations, have been implicated as triggers. Infection with *Mycoplasma pneumoniae* and other pathogens may produce a similar lesion, particularly in children and young adults; differentiation from Stevens-Johnson syndrome and reactive infectious mucocutaneous eruptions (RIMEs; see Chapter 695.2) can be difficult. HSV labialis and, less commonly, HSV genitalis are implicated in 60–70% of episodes of EM and are believed to trigger nearly all episodes of *recurrent* (six or more episodes per year) EM, frequently in association with sun exposure. HSV antigens and DNA are present in skin lesions of EM but are absent in nonlesional skin. The presence of the human leukocyte antigens A33, B62, B35, DQw3 (DQB1*0301 split), and DR53 is associated with an increased risk of HSV-induced EM, particularly the recurrent form. Most patients experience a single self-limited episode of EM. Lesions of HSV-induced recurrent EM typically develop 10-14 days after onset of recurrent HSV eruptions and have a similar appearance from episode to episode, but they may vary in frequency and duration in a given patient. Not all episodes of recurrent HSV evolve into EM in susceptible patients.

Drug-related EM is less common (<10% of patients) and may be associated with nonsteroidal antiinflammatory agents, including acetaminophen, sulfonamides, and other antibiotics. The differential diagnosis in drug-related EM should include severe cutaneous adverse reactions such as Stevens-Johnson syndrome (see Chapter 695.3) and drug hypersensitivity syndrome (sometimes called drug reaction [rash] with eosinophilia and systemic symptoms [DRESS] or drug-induced hypersensitivity syndrome [DIHS]) (see Chapter 686.2).

CLINICAL MANIFESTATIONS

EM has numerous morphologic manifestations on the skin, varying from erythematous macules, papules, vesicles, bullae, or urticarial plaques to patches of confluent erythema. The eruption appears most commonly in patients between the ages of 10 and 40 years (with highest incidence in males in the second decade) and usually is asymptomatic, although a burning sensation or pruritus may be present. The diagnosis of EM is established by finding the classic lesion: doughnut-shaped, **targetoid** (target-like, iris, or bull's-eye) papules with an erythematous outer border, an inner pale ring, and a dusky purple to necrotic center (which sometimes blisters and erodes; Figs. 695.1 and 695.2).

EM is characterized by an abrupt, symmetric cutaneous eruption, most commonly on the extensor upper extremities; lesions are relatively sparse on the face, trunk, and legs. Lesions can be seen on the palms and soles. The eruption often appears initially as red macules or urticarial plaques that evolve and expand centrifugally to form lesions up to 2 cm in diameter with a dusky to necrotic center. Lesions of a particular episode typically appear within 72 hours and remain fixed in place (average duration: 7 days). Oral lesions may occur with a predilection for the vermilion border of the lips and the buccal mucosa, but other mucosal surfaces are usually spared. EM may manifest initially as urticaria-like lesions, but in contrast to urticaria, a given lesion of EM does not fade within 24 hours. Prodromal symptoms are generally absent. Prognosis is favorable with limited long-term morbidity. Lesions typically resolve without sequelae in approximately 2 weeks, but in darker pigmented individuals, pigmentary alterations at the site of lesions can be long-standing. *Progression to Stevens-Johnson syndrome does not occur.* Many authors distinguish between **EM minor** (mainly cutaneous typical or atypical **targetoid** lesions affecting <10% body surface area plus no or limited mucosal involvement, often limited to one site, such as the mouth) and **EM major** (same cutaneous involvement pattern as EM minor plus two or more mucosal sites with more severe oral involvement). EM major and Stevens-Johnson syndrome are separate entities.



Fig. 695.1 Early fixed papules with a central dusky zone on the dorsum of the hand of a child with erythema multiforme caused by herpes simplex virus. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002:156.)*



Fig. 695.2 "Target" or "iris" lesions with characteristic central dusky zone on palms of a child with erythema multiforme caused by herpes simplex virus. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002:156.)*

Table 695.1 Sites of Blister Formation and Diagnostic Studies for the Vesiculobullous Disorders

DISORDER	BLISTER CLEAVAGE SITE	DIAGNOSTIC STUDIES
Acrodermatitis enteropathica	IE	Serum zinc level
Bullous impetigo	GL	Smear, culture
Bullous pemphigoid	SE (junctional)	Direct and indirect immunofluorescence
Candidiasis	SC	KOH preparation, culture
Dermatitis herpetiformis	SE	Direct immunofluorescence
Dermatophytosis	IE	KOH preparation, culture
Dyshidrotic eczema	IE	Routine histopathology
EB simplex	IE	Electron microscopy, immunofluorescence mapping, genetic testing
Junctional EB	SE (junctional)	Electron microscopy, immunofluorescence mapping, genetic testing
Recessive dystrophic EB	SE	Electron microscopy, immunofluorescence mapping, genetic testing
Dominant dystrophic EB	SE	Electron microscopy, immunofluorescence mapping, genetic testing
Epidermolytic ichthyosis	IE	Routine histopathology
Erythema multiforme	SE	Routine histopathology
Erythema toxicum	SC, IE	Smear for eosinophils
Incontinentia pigmenti	IE	Smear for eosinophils Routine histopathology
Insect bites	IE	Routine histopathology
Kindler syndrome	IE, SE	Electron microscopy, immunofluorescence mapping, genetic testing
Linear IgA dermatosis	SE	Direct immunofluorescence
Mastocytosis	SE	Routine histopathology
Miliaria crystallina	IC	Routine histopathology
Neonatal pustular melanosis	SC, IE	Smear for neutrophils
Pemphigus foliaceus	GL	Direct and indirect immunofluorescence studies
		Tzanck smear
Pemphigus vulgaris	Suprabasal	Direct and indirect immunofluorescence studies
		Tzanck smear
Scabies	IE	Skin scraping
Staphylococcal scalded skin syndrome	GL	Routine histopathology
Toxic epidermal necrolysis	SE	Routine histopathology
Viral blisters	IE	Viral PCR (preferred) or direct immunofluorescence testing for HSV and VZV Routine histopathology

EB, Epidermolysis bullosa; GL, granular layer; HSV, herpes simplex virus; IC, intracorneal; IE, intraepidermal; KOH, potassium hydroxide; PCR, polymerase chain reaction; SC, subcorneal; SE, subepidermal; VZV, varicella-zoster virus.

Pathogenesis

The pathogenesis of EM is unclear, but it may be a host-specific, cell-mediated immune response to an antigenic stimulus, resulting in damage to keratinocytes. The HSV *Pol1* gene expressed in HSV-induced recurrent EM lesions upregulates/activates the transcription factor SP1 and inflammatory cytokines. These cytokines, released by activated mononuclear cells and keratinocytes, may contribute to epidermal cell death and constitutional symptoms.

Pathology

Microscopic findings in EM are variable but may aid in diagnosis. Early lesions typically have slight intercellular edema, rare dyskeratotic keratinocytes, and basal vacuolation in the epidermis, as well as a perivascular lymphohistiocytic infiltrate with edema in the upper dermis. More mature lesions demonstrate accentuation of these characteristics and the development of lymphocytic exocytosis, as well as an intense, perivascular, and interstitial mononuclear infiltrate in

the upper third of the dermis. In severe cases, the entire epidermis becomes necrotic.

Differential Diagnosis

The differential diagnosis of EM also includes RIME, bullous pemphigoid, pemphigus vulgaris, linear immunoglobulin (Ig) A dermatosis, graft-versus-host disease, fixed-drug eruption, bullous drug eruption, urticaria, viral infections such as HSV, reactive arthritis syndromes, Kawasaki disease, Sweet syndrome, Behçet disease, vasculitis, erythema annulare centrifugum, and polymorphous drug eruption. EM that primarily involves the oral mucosa may be confused with Stevens-Johnson syndrome, bullous pemphigoid, pemphigus vulgaris, vesiculobullous or erosive lichen planus, Behçet syndrome, recurrent aphthous stomatitis, and primary herpetic gingivostomatitis. In contrast to EM, Stevens-Johnson syndrome manifests with erythematous or purpuric macules (no papules) and usually begins on the trunk. Serum sickness–like reaction to cefaclor (or other antibiotics) may also manifest as EM-like lesions; the lesions may develop a dusky to purple center, but in most cases, the eruption of cefaclor-induced serum sickness–like reaction is pruritic, transient, and migratory and is probably urticarial rather than true EM.

Treatment

Treatment of EM is supportive. If secondary to underlying infection, the infection should be treated. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory agents do not alter the course of the disease but may provide symptomatic relief. For individuals with severe mucosal disease, opioids can be used to control pain, and diligent oral hygiene is essential. No controlled, prospective studies support the use of corticosteroids in the management of EM. Prophylactic oral acyclovir given for 6 months may be effective in controlling *recurrent episodes of HSV-associated EM*. On discontinuation of acyclovir, both HSV and EM may recur, although episodes may be less frequent and milder. For recurrent cases not responsive to antiviral therapy, steroid-sparing agents used to decrease frequency of recurrence include azathioprine, mycophenolate mofetil, and dapsone. Appropriate laboratory monitoring is recommended. See Chapter 695.2.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

695.2 Reactive Infectious Mucocutaneous Eruption

Joel C. Joyce

Originally named *Mycoplasma*-induced rash and mucositis (MIRM), RIME may also be caused by other infectious agents such as *Chlamydophila,* enterovirus, COVID-19, and others. It is believed to be a distinct entity not classified as EM or Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN).

RIME presents 1-2 weeks after a prodrome characterized by fever, malaise, headache, and cough or features more characteristic of a specific infection (pneumonia secondary to *M. pneumoniae* or COVID-19). The dominant feature is severe mucositis (Fig. 695.3, Table 695.2) most often involving the oral (~95%), ocular (~80%), and urogenital mucosa. Rash may be absent in ~30%, but when present is sparse; lesions are vesiculobullous (~75%) or atypical targeted (~45%), papules, macules, or morbilliform. Lesions involve <10% of body surface area but rarely may be extensive in severe RIME.

The differential diagnosis includes EM, which manifests with an acral rash that evolves from macules to papules to plaques and target lesions. In addition, severe RIME may resemble SJS/TEN, which presents with macules, purpura, erythroderma, atypical target lesions, and extensive blistering.

Treatment includes mouth care and pain management. Azithromycin is used when there is evidence of *Mycoplasma* infection (positive PCR plus IgM) or *Chlamydophila* infection. Steroids have been used, as has etanercept, for more severe disease. In general, RIME is a self-limiting disease that heals without residua. Recurrences are rare.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

695.3 Stevens-Johnson Syndrome

Joel C. Joyce

ETIOLOGY

Drugs, particularly sulfonamides, nonsteroidal antiinflammatory agents, antibiotics (particularly β-lactams), and anticonvulsants, are the most common precipitants of the blistering drug rashes known as Stevens-Johnson syndrome (SJS) and toxic epidermal **necrolysis** (TEN). SJS and TEN exist along a spectrum: SJS is defined as affected body surface area <10%, SJS-TEN overlap syndrome as affected body surface area between 10% and 30%, and TEN as affected body surface area >30%. TEN is the most severe disorder in the clinical spectrum of the disease, involving considerable constitutional toxicity and extensive necrolysis of the mucous membranes and >30% of the body surface area. Approximately 80% of cases are classified as SJS. In children in the United States, the risk of death is 0.3–1.5%. Human leukocyte antigen (HLA)-B*1502 and HLA-B*5801 are implicated in the development of these two disorders in Han Chinese patients receiving carbamazepine and in Japanese patients receiving allopurinol, respectively. Current thinking defines most cases of classic SJS as secondary to medications.

Clinical Manifestations

Cutaneous lesions in SJS generally consist initially of erythematous macules that rapidly and variably develop central necrosis to form vesicles, bullae, and areas of denudation on the face, trunk, and extremities. The **Nikolsky sign** (denudation of the skin with gentle



Fig. 695.3 Manifestations of mycoplasma-induced rash and mucositis. **A,** Bilateral conjunctivitis. **B,** Oral mucositis. **C,** Cutaneous targetoid vesicles; sutures are visible at sites where skin biopsy sample was taken. *(From Sandhu R, Mareddy C, Itskowitz M, et al. Mycoplasma-induced rash and mucositis in a young patient with red eyes, oral mucositis, and targetoid cutaneous vesicles. Lancet Infect Dis. 2017;17:562.)*

Table 695.2	Mucocutaneous Lesions of *Mycoplasma pneumoniae*–Induced Rash and Mucositis
ORAL	
Erosions	
Ulcers	
Vesiculobullae	
Denudation	
Hemorrhagic crusting	
OCULAR	
Conjunctival injection	
Conjunctivitis	
Photophobia	
Eyelid edema	
Lid margin ulceration	
Conjunctival pseudomembranes	
Corneal involvement (rare)	
UROGENITAL	
Erosions	
Ulcerations	
Vesiculobullae	
Oro-esophageal	
Mucositis	
ANAL	
Mucositis	
CUTANEOUS	
Vesiculobullae	
Targetoid	
Papules	
Macules	
Morbilliform	

From Ramien ML. Reactive infectious mucocutaneous eruption: Mycoplasma pneumoniae-induced rash and mucositis and other parainfectious eruptions. *Clin Exper Dermatol.* 2021;46:420–429.

tangential pressure) may be positive. The skin lesions are typically more widespread than in EM and are accompanied by involvement of two or more mucosal surfaces, namely the eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa (Fig. 695.4). A burning sensation, edema, and erythema of the lips and buccal mucosa are often the presenting signs, followed by development of bullae, ulceration, and hemorrhagic crusting. Lesions may be preceded by a flulike upper respiratory illness. Pain from mucosal ulceration is often severe, but skin tenderness is minimal to absent in SJS, in contrast to pain in TEN. Corneal ulceration, anterior uveitis, panophthalmitis, bronchitis, pneumonitis, myocarditis, hepatitis, enterocolitis, polyarthritis, hematuria, and acute tubular necrosis leading to renal failure may occur. Disseminated cutaneous bullae and erosions may result in increased insensible fluid loss and a high risk of bacterial superinfection and sepsis. New lesions occur in crops, and complete healing may take 4-6 weeks, and ocular scarring, visual impairment, and strictures of the esophagus, bronchi, vagina, urethra, or anus may remain. Nonspecific laboratory abnormalities in SJS include leukocytosis, elevated erythrocyte sedimentation rate, and, occasionally, increased liver transaminase levels and decreased serum albumin values.

Pathogenesis

Pathogenesis is related to drug-specific $CD8^+$ cytotoxic T cells, with perforin/granzyme B and granulysin triggering keratinocyte apoptosis. This process is followed by expanded enactment of apoptosis involving the interaction of soluble Fas ligand with Fas receptor. Consideration has been given to the role that macrophages/monocytes play in the development of SJS/TEN via tumor necrosis factor-α, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor–inducer of apoptosis weak (TWEAK) signaling pathways. It is likely that many affected individuals have yet unrecognized underlying genetic predispositions.



Fig. 695.4 Bullae are present on the conjunctivae (A) and in the mouth (B) with Stevens-Johnson syndrome. C, Sloughing, ulceration, and necrosis in the oral cavity interfere with eating. Genital lesions cause dysuria and interfere with voiding. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:631.)*

Differential Diagnosis

The differential diagnosis of SJS includes TEN, urticaria, RIME, DRESS (sometimes called DIHS; see Chapter 686), other drug eruptions, and viral exanthems, as well as Kawasaki disease. SJS has rarely been reported in patients with systemic lupus erythematosus.

Treatment

Management of SJS is supportive and symptomatic. Potentially offending drugs must be discontinued as soon as possible. *Ophthalmologic consultation is mandatory because ocular sequelae such as corneal scarring can lead to vision loss.* Application of cryopreserved amniotic membrane to the ocular surface during the acute phase of the disease limits the destructive and long-term sequelae. Early topical steroid treatment may also reduce ocular sequelae. Oral lesions should be managed with mouthwashes and glycerin swabs. Urogenital lesions should be observed closely and treated to prevent stricture or fusion. Topical (oral) anesthetics (diphenhydramine, dyclonine, viscous lidocaine) may provide relief from pain, particularly when applied before eating. Denuded skin lesions can be cleansed with saline or Burrow solution compresses. Treatment may require admission to an intensive care unit, IV fluids,

nutritional support, sheepskin or air-fluid bedding, daily saline or Burrow solution compresses, paraffin gauze or colloidal gel (Hydrogel) dressing of denuded areas, saline compresses on the eyelids, lips, or nose, analgesics, and urinary catheterization (when needed). A daily examination for infection and ocular lesions, which constitute the major cause of long-term morbidity, is essential. Systemic antibiotics are indicated for documented urinary or cutaneous infections and for suspected bacteremia (*Staphylococcus aureus* or *Pseudomonas aeruginosa*) because infection is the leading cause of death. Prophylactic systemic antibiotics are not necessary. Systemic antiinflammatory and immunosuppressive therapies have been controversial. A large systematic review concluded that patients who received IV immunoglobulin (IVIG) and systemic corticosteroids had better outcomes than supportive care alone. Other publications have found that these agents have not improved outcomes such as decreased time to healing or shortened hospital stay. Nevertheless, advocates for use remain, and IVIG (1.5-2.0 g/kg/day × 3 days) may be considered in early disease. Total dose >2 g/kg has shown improved but not statistically significant outcomes in children compared with adults. Case reports/series have demonstrated rapid efficacy with cyclosporine (3 mg/kg/day divided twice daily), as well as with infliximab (5 mg/kg intravenously for one dose) or with etanercept (0.8 mg/kg injection once and then a second dose 1 week later). Emerging evidence has supported the use of anti–tumor necrosis factor therapy in the acute setting, particularly in adults but also in children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

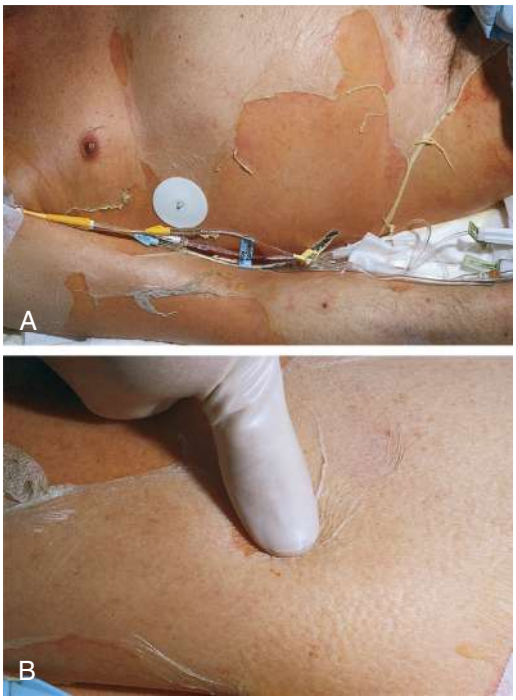

Fig. 695.5 A, Large sheets of full-thickness epidermis are shed. B, Toxic epidermal necrolysis begins with diffuse, hot erythema. In hours the skin becomes painful, and with slight thumb pressure, the skin wrinkles, slides laterally, and separates from the dermis (Nikolsky sign). *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:633.)*

695.4 Toxic Epidermal Necrolysis

Joel C. Joyce

EPIDEMIOLOGY AND ETIOLOGY

The pathogenesis of toxic epidermal necrolysis (TEN) is not proven but may involve a hypersensitivity phenomenon that results in damage primarily to the basal cell layer of the epidermis. Epidermal damage appears to result from keratinocyte apoptosis. This condition, typically attributed as a drug rash, is triggered by many of the same factors that are thought to be responsible for SJS (see Chapter 695.3), principally drugs such as the sulfonamides, β-lactam antibiotics, anticonvulsants, and allopurinol. TEN is defined by (1) widespread blister formation and morbilliform or confluent erythema, associated with skin tenderness; (2) absence of target lesions; (3) sudden onset and generalization within 24-48 hours; and (4) histologic findings of full-thickness epidermal necrosis and a minimal-to-absent dermal infiltrate. Skin involvement should be 30% or greater in contrast to SJS (10% or less) or SJS-TEN overlap (10–30%). These criteria categorize TEN as a separate entity from EM.

CLINICAL MANIFESTATIONS

The prodrome consists of fever, malaise, localized skin tenderness, and diffuse erythema. Inflammation of the eyelids, conjunctivae, mouth, and genitals may precede skin lesions. Flaccid bullae may develop, although this is not a prominent feature. Characteristically, full-thickness epidermis is lost in large sheets (Fig. 695.5). The **Nikolsky sign** (denudation of the skin with gentle tangential pressure) is present, but only in the areas of erythema (see Fig. 695.5). Healing takes place over 14 or more days. Scarring, particularly of the eyes, may result in corneal opacity. The course may be relentlessly progressive, complicated by severe dehydration, electrolyte imbalance, shock, and secondary localized infection and septicemia. Loss of nails and hair may also occur. Long-term morbidity includes alterations in skin pigmentation, eye problems (lack of tears, conjunctival scarring, loss of lashes), and strictures of mucosal surfaces.

Differential Diagnosis

The differential diagnosis includes staphylococcal scalded skin syndrome, in which the blister cleavage plane is intraepidermal; graft-versus-host disease; chemical burns; drug eruptions; toxic shock syndrome; and **pemphigus**. The use of skin histopathology to differentiate SJS-TEN from other similar **blistering disorders** can be difficult, but early full-thickness epidermal necrosis tends to portend a worse clinical prognosis.

Drug hypersensitivity syndrome (sometimes called DRESS or DIHS; see Chapter 686), is a multisystem reaction that appears approximately several weeks to 3 months after the start of therapy with the offending agent. The skin eruption is variable but can be a red-pink morbilliform eruption often associated with facial swelling; lymphadenopathy; fever; hepatic, renal, and pulmonary disease; eosinophilia; atypical lymphocytosis; and leukocytosis.

TREATMENT

Appreciation of the specific etiologic factor is crucial in the treatment of TEN. Because most cases are drug-induced, cessation of the offending agent as soon as possible is critical. Management is similar to that for severe burns and may be best accomplished in a burn unit (see Chapter 89). It may include strict reverse isolation, meticulous fluid and electrolyte therapy, use of an air-fluid bed, and daily cultures. Systemic antibiotic therapy is indicated when secondary infection is evident or suspected. Skin care consists of cleansing with isotonic saline or Burrow solution. Biologic or colloid gel (Hydrogel) dressings alleviate pain and reduce fluid loss. Opiates are often required for pain relief. Mouth and eye care, as for EM major and SJS, may be necessary. Similar considerations as in the treatment of SJS (see Chapter 695.3) with systemic agents may be considered, although controversies remain over relative efficacy and best treatment regimens.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

695.5 Mechanobullous Disorders

Joel C. Joyce

EPIDERMOLYSIS BULLOSA

Diseases categorized under the general term epidermolysis bullosa (EB) are a heterogeneous group of congenital, genetic **blistering disorders**. They differ in severity and prognosis, clinical and histologic features, and inheritance patterns but are all characterized by induction of blisters by trauma and exacerbation of blistering in warm weather. The disorders can be categorized under three major headings with multiple subgroupings: **epidermolysis bullosa simplex** (EBS), **junctional epidermolysis bullosa** (JEB), and **dystrophic epidermolysis bullosa** (DEB) (Tables 695.3-695.8). **Kindler syndrome**, which includes poikiloderma and photosensitivity, as well as easy blistering, is also considered a separate form of EB. **Epidermolysis bullosa acquisita** is an autoimmune disorder producing antibodies to the α chain of type VII collagen. It is rare in children. It is often acquired secondary to other autoimmune diseases or malignancy but has rare congenital forms. Affected mothers may pass the autoantibody to the fetus, resulting in similar but transient lesions in the newborn.

EPIDERMOLYSIS BULLOSA SIMPLEX

EBS is a nonscarring, autosomal dominant or recessive disorder. The defect in *most common* types of EBS is in keratin 5 or 14, which makes up intermediate filaments of the basal keratinocytes (see Table 695.6). The intraepidermal bullae result from cytolysis of the basal cells. There are multiple other rare variants with defects that also result in intraepidermal blistering (see Table 695.3).

Table 695.3 Epidermolysis Bullosa Simplex (EBS) Clinical Subtypes

MOST COMMON EBS CLINICAL SUBTYPES	TARGETED PROTEIN(S)
AUTOSOMAL DOMINANT EBS	
Localized	Keratin 5, keratin 14
Intermediate	Keratin 5, keratin 14
Severe	Keratin 5, keratin 14
With mottled pigmentation	Keratin 5*
Migratory circinate erythema	Keratin 5
Intermediate	Plectin
Intermediate with cardiomyopathy	**Kelch-like member 24**
AUTOSOMAL RECESSIVE EBS	
Intermediate or severe	Keratin 14, keratin 5
Intermediate	Plectin
Localized or intermediate with BP230 deficiency	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e)
Localized or intermediate with exophilin-5 deficiency	Exophilin-5 (syn. Slac2-b)
Intermediate with muscular dystrophy	**Plectin**
Severe with pyloric atresia	**Plectin**
Localized with nephropathy	**CD151 (CD151 antigen) (syn. tetraspanin 24)**

*Typical recurrent mutation in keratin 5, but cases with other keratin 5, keratin 14 or exophilin-5 mutations have been reported; syndromic EBS subtypes in **bold**.

From Has C, Bauer JW, Bodemer C, et al: Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-617; Table 3, p. 617.)

Localized EBS (formerly Weber-Cockayne disease) predominantly affects the hands and feet and often manifests when a child begins to walk; onset may be delayed until puberty or early adulthood, when heavy shoes are worn or the feet are subjected to increased trauma. Bullae are usually restricted to the hands and feet (Fig. 695.6); rarely, they occur elsewhere, such as the dorsal aspect of the arms and the shins. The disorder ranges from mildly incapacitating to crippling at times, with severe exacerbations. Blisters should be drained by puncturing, but the blister top should be left intact to protect the underlying skin. Erosions may be covered with a semipermeable dressing. Diligent wound care and protection of areas subject to pressure are beneficial. Observation for infection is important and should be treated promptly.

In **intermediate EBS (formerly Koebner type)**, blisters are usually present at birth or during the neonatal period. Sites of predilection are the hands, feet, elbows, knees, legs, and scalp. Intraoral lesions are minimal, nails rarely become dystrophic and usually regrow even when they are shed, and dentition is normal. Bullae heal with minimal to no scar or milia formation. Secondary infection is the primary complication. The propensity to blister decreases with age, and the long-term prognosis is good. Treatment is similar to that noted earlier.

Severe EBS (formerly EBS Dowling-Meara or EBS herpetiformis) is characterized by grouped blisters resembling those of herpes simplex (Fig. 695.7). During infancy, blistering may be severe and extensive, may involve mucous membranes, and may result in shedding of nails, formation of milia, and mild pigmentary changes, without scarring. After the first few months of life, warm temperatures do not appear to exacerbate blistering. Hyperkeratosis and hyperhidrosis of the palms and soles may develop, but generally, the condition improves with age. Maintenance of nutritional status and treatment of infections is important, particularly in infancy. Day-to-day management may involve wound care techniques as described.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

Severe JEB (formerly Herlitz syndrome) is an autosomal recessive condition that is life threatening (see Tables 695.5 and 695.6). Blisters appear at birth or develop during the neonatal period, particularly on the perioral area, scalp, legs, diaper area, and thorax. Nails eventually become dystrophic and then often permanently lost. Mucous membrane involvement may be severe, and ulceration of the respiratory, gastrointestinal, and genitourinary epithelium has been documented in many affected children, although less frequently than in severe recessive DEB. Healing is delayed, and vegetating granulomas may persist for a long time. Large, moist, erosive plaques (Fig. 695.8) may provide a portal of entry for bacteria, and septicemia is a frequent cause of death. Mild atrophy may be seen in areas of recurrent blistering. Defective dentition with early loss of teeth as a result of rampant caries is characteristic. Growth retardation and recalcitrant anemia are almost invariable. In addition to infection, cachexia and circulatory failure are common causes of death. Most patients die within the first years of life.

Intermediate JEB (formerly non-Herlitz syndrome) is a heterogeneous group of disorders. Blistering may be severe in the neonatal period, making differentiation from severe JEB difficult. All conditions associated with severe JEB may be seen but are usually milder. **Localized JEB** and **JEB with pyloric atresia** are similar disorders.

In all types of JEB, a subepidermal blister is found on light microscopic examination, and electron microscopy demonstrates a cleavage plane in the lamina lucida, between the plasma membranes of the basal cells and the basal lamina. Absence or a great reduction of hemidesmosomes is seen on electron micrographs in severe JEB and some cases of intermediate JEB. The defect in severe JEB is in laminin 332 (pathogenic gene variants in *LAMA3, LAMB3,* or *LAMC2*), a glycoprotein associated with anchoring filaments beneath the hemidesmosomes. In intermediate JEB, defects have also been described in other hemidesmosomal components, such as type XVII collagen (BP180) (gene variants of *COL17A1*). In JEB with pyloric atresia, the defect is in the $\alpha_6\beta_4$ integrin (gene variants of *ITGA6* or *ITGB4*).

Treatment for JEB is supportive. The diet should provide adequate calories and *supplemental iron*. Infections should be treated promptly. Transfusions of packed red blood cells may be required if the patient shows no response to iron and erythropoietin therapy. Strict adherence to wound care regimens is essential. Wound care regimens include highly specialized nonadherent bandages designed specifically for children with chronic skin fragility. Tissue-engineered skin grafts (artificial skin derived from human keratinocytes and fibroblasts) may be beneficial. Birch bark extract topical gel containing betulin is approved by the European Union and promotes wound healing and controls inflammation.

Table 695.4 Characteristics of Major Forms of Epidermolysis Bullosa Simplex

TYPE	CLINICAL MANIFESTATIONS
Localized EBS (formerly Weber-Cockayne)	Easy blistering on palms and soles May be focal keratoderma of palms and soles in adults 25% show oral mucosal erosions Rarely show reticulated pigmentation, especially on arms and trunk and punctate keratoderma (EBS with mottled pigmentation)
Intermediate EBS (formerly Koebner)	Generalized blistering Variable mucosal involvement Focal keratoderma of palms and soles Nail involvement in 20% Improves with advancing age
Severe EBS (formerly Dowling-Meara or EB herpetiformis)	Most severe in neonate, infant; improves beyond childhood Large, generalized blisters; later, smaller (herpetiform) blisters Mucosal blistering, including esophageal Nails thickened, shed but regrow May have natal teeth
EBS with mottled pigmentation	Reticulated hyperpigmentation, especially on arms and trunk Punctate keratoses and keratoderma

EBS, Epidermolysis bullosa simplex.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 13.2, p. 319.

Table 695.6 Characteristics of Major Forms of Junctional Epidermolysis Bullosa

TYPE	CLINICAL MANIFESTATIONS
JEB, severe (formerly Herlitz)	50% of patients die by 2 yr old Blisters heal with atrophic scarring but no milia Periungual and fingerpad blistering, erythema Blistering of oral and esophageal mucosae Laryngeal and airway involvement with early hoarseness Later, perioral granulation tissue with sparing of lips Anonychia Dental enamel hypoplasia, excessive caries Growth retardation Anemia
JEB, intermediate (formerly non-Herlitz)	Less severe, but similar manifestations to Herlitz type, including dental, nail, and laryngeal involvement Granulation tissue is rare Perinasal cicatrization Less mucosal involvement Alopecia Anemia but not as severe as JEB, generalized severe
JEB, localized	Localized blisters without residual scarring or granulation tissue Minimal mucosal involvement Dental and nail abnormalities as in JEB, generalized severe
JEB, with pyloric atresia	Usually lethal in neonatal period Generalized blistering, leading to atrophic scarring May be born with large areas of cutis aplasia No granulation tissue Nail dystrophy or anonychia Pyloric atresia, genitourinary malformations Rudimentary ears Dental enamel hypoplasia (survivors) Variable anemia, growth retardation, mucosal blistering

JEB, Junctional epidermolysis bullosa.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 13.4, p. 321.

Table 695.5 Junctional Epidermolysis Bullosa (JEB) Clinical Subtypes

MOST COMMON JEB CLINICAL SUBTYPES	TARGETED PROTEIN(S)
Severe	Laminin 332*
Intermediate	Laminin 332
Intermediate	Type XVII collagen
With pyloric atresia	**Integrin α6β4**
Localized	Laminin 332, type XVII collagen, integrin α6β4, integrin α3 subunit
Inversa	Laminin 332
Late onset	Type XVII collagen
LOC syndrome	Laminin α3A
With interstitial lung disease and nephrotic syndrome	**Integrin α3 subunit**

*JEB severe is rarely caused by pathogenic variants affecting the type XVII collagen gene; syndromic JEB subtypes in **bold**.
LOC, laryngo–onycho–cutaneous.
From Has C, Bauer JW, Bodemer C, et al: Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-617; Table 4, p. 617.)

Table 695.7 Dystrophic Epidermolysis Bullosa (DEB) Clinical Subtypes

DEB SUBTYPES	TARGETED PROTEIN
AUTOSOMAL DOMINANT DEB (DDEB)	
Intermediate	Type VII collagen
Localized	
Pruriginosa	
Self-improving	
AUTOSOMAL RECESSIVE DEB (RDEB)	
Severe	Type VII collagen
Intermediate	
Inversa	
Localized	
Pruriginosa	
Self-improving	
DOMINANT AND RECESSIVE (COMPOUND HETEROZYGOSITY)	
DEB, severe	Type VII collagen

bold, most common subtypes.
From Has C, Bauer JW, Bodemer C, et al: Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-617; Table 5, p. 617.)

Table 695.8 Characteristics of Major Forms of Dystrophic Epidermolysis Bullosa

TYPE	CLINICAL MANIFESTATIONS
Dominant dystrophic	Onset at birth to early infancy Blistering predominates on dorsum of hands, elbows, knees, and lower legs Milia associated with scarring Some patients develop scarlike lesions, especially on the trunk 80% have nail dystrophy
Recessive dystrophic, severe generalized	Present at birth Widespread blistering, scarring, milia Deformities: pseudosyndactyly, joint contractures Severe involvement of mucous membranes, nails; alopecia Growth retardation, poor nutrition Anemia Mottled, carious teeth Osteoporosis, delayed puberty, cardiomyopathy, glomerulonephritis, renal amyloidosis, IgA nephropathy Predisposition to squamous cell carcinoma in heavily scarred areas
Recessive dystrophic, generalized intermediate	Generalized blisters from birth with milia, scarring Less anemia, growth retardation, mucosal but more esophageal issues with advancing age

IgA, Immunoglobulin A.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 13.6, p. 323.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

All forms of DEB result from pathogenic variants in collagen VII, a major component of anchoring fibrils that tether the basement membrane and overlying epidermis to its dermal foundation (see Tables 695.7 and 695.8). The blister is subepidermal in all types of DEB. The type and location of the pathogenic gene variant within *COL7A1* dictate the severity of the phenotype.

Dominant DEB is the most common type. The spectrum of dominant DEB is varied. Blisters may be manifest at birth and are often limited and characteristically form over acral bony prominences.



Fig. 695.6 Bullae of the feet in localized epidermolysis bullosa simplex.



Fig. 695.7 Grouped vesicle on an erythematous base in severe epidermolysis bullosa simplex.



Fig. 695.8 Nonhealing granulation tissue in junctional epidermolysis bullosa.

The lesions heal promptly, with the formation of soft, wrinkled scars; milia; and alterations in pigmentation (Fig. 695.9). Abnormal nails and nail loss are common. In many cases, the blistering process is mild, causing little restriction of activity and not impairing growth and development. Mucous membrane involvement tends to be minimal.

Recessive DEB, severe generalized (formerly recessive DEB–Hallopeau-Siemens syndrome) is the most incapacitating form of EB, although the clinical spectrum is wide. Some patients have blisters, scarring, and milia formation primarily on the hands, feet, elbows, and knees (Fig. 695.10). Others have extensive erosions and blister formation at birth that seriously impede their care and feeding. Mucous membrane lesions are common and may cause severe nutritional



Fig. 695.9 Scarring with milia formation over the knee in dominant dystrophic epidermolysis bullosa.



Fig. 695.10 Severe scarring of the hands and knees in recessive dystrophic epidermolysis bullosa.

deprivation, even in older children, whose growth may be restricted. During childhood, esophageal erosions and strictures, scarring of the buccal mucosa, flexion contractures of joints secondary to scarring of the integument, development of cutaneous squamous cell carcinomas, and the development of digital fusion may significantly limit the quality of life (Fig. 695.11). Squamous cell carcinomas and infection are major causes of morbidity and mortality.

Although the skin becomes less sensitive to trauma with aging in patients with recessive DEB, the progressive and permanent deformities complicate management, and the overall prognosis is poor. *Foods that traumatize the buccal or esophageal mucosa should be avoided.* If esophageal scarring develops, a semiliquid diet and esophageal dilatations may be required. Stricture excision or colonic interposition may be needed to relieve esophageal obstruction. In infants, severe oropharyngeal involvement may necessitate the use of special feeding devices such as a gastrostomy tube. Iron therapy for anemia, intermittent antibiotic therapy for secondary infections, and periodic surgery for release of digits may reduce morbidity. Wound care dressings, including nonstick dressings made from silicone, are a mainstay of treatment and the daily maintenance of the skin barrier to reduce new skin trauma and promote healing. Compounds for treating itch, reducing inflammation, and fighting infection, particularly with antimicrobial peptides, aid in promoting more effective wound healing when dressings are used, therefore reducing morbidity.

Beyond wound care and care of comorbid conditions in EB, a number of new technologies offer a wider array of practical and hypothetical treatment options for EB patients. Tissue-engineered skin grafts containing keratinocytes and fibroblasts are of some benefit. Skin grafts that have undergone gene editing may show promise. Pluripotent stem cells, taken from areas of revertant mosaicism of a patient's own skin, provide personalized options



Fig. 695.11 Mitten-hand deformity of recessive dystrophic epidermolysis bullosa.

for treatments for affected patients. Redosable gene therapy with a herpes simplex virus type 1 vector carrying the *COL7A1* gene is FDA approved for patients ≥6 months of age. The therapy is applied directly to wounds and produces normal collagen type VII alpha chains. Allogeneic bone marrow transplantation has been shown to be beneficial in some cases but warrants further study.

KINDLER SYNDROME

Kindler syndrome, often considered a distant subtype of EB, contains features of both EB, such as congenital blistering, and congenital poikilodermas, such as Rothmund-Thomson syndrome and Bloom syndrome (see Chapter 697), which include photosensitivity, congenital poikiloderma, and progressive cutaneous atrophy. Blisters tend to appear on acral sites in infancy or early childhood and are provoked by trauma. Photosensitivity can appear as increased susceptibility to sunburn. Both blistering and photosensitivity can improve greatly with advancing age, but poikilodermatous changes can be progressive. Sclerodermoid-like changes and nail abnormalities of the hands and feet, as well as dental abnormalities, have been reported.

Kindler syndrome is an autosomal recessive disorder caused by pathogenic gene variants in *KIND1* (also known as *FERMT1*), which encodes kindlin-1, a protein thought to regulate interactions between the extracellular matrix and actin filaments. Blister formation has been shown to occur within the epidermis, within the basement membrane zone, and below the basement membrane. Because Kindler syndrome is often confused with EB, at least initially, it can be confirmed by electron microscopy, immunostaining for anti–kindlin-1 antibodies within the skin, or genetic analysis of the *KIND1* gene.

Treatment is similar to that for EB, with efforts to reduce trauma to the skin, meticulous wound care, and treatment of skin infections. In addition, sun avoidance measures are beneficial because they can slow the rate of the development of poikiloderma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

695.6 Pemphigus

Joel C. Joyce

PEMPHIGUS VULGARIS

Etiology/Pathogenesis

Pemphigus vulgaris (PV) is a rare autoimmune blistering disorder caused by circulating antibodies to desmoglein III that results in suprabasal cleaving with consequent blister formation. Desmoglein III is a 30-kDa glycoprotein that is complexed with plakoglobin, a plaque protein of desmosomes. The desmogleins are a subfamily of the cadherin family of cell adhesion molecules.

Clinical Manifestations

PV usually first appears as painful oral ulcers, which may be the only evidence of the disease for weeks or months. Subsequently, large, flaccid bullae emerge on nonerythematous skin, most commonly on the face, trunk, pressure points, groin, and axillae. The **Nikolsky sign** is present. The lesions rupture and enlarge peripherally, producing painful, raw, denuded areas that have little tendency to heal. When healing occurs, it is without scarring, but hyperpigmentation is common. Malodorous, verrucous, and granulomatous lesions may develop at sites of ruptured bullae, particularly in the skinfolds; as this pattern becomes more pronounced, the condition may be more properly referred to as **pemphigus vegetans**. Because the course may rapidly lead to debility, malnutrition, and death, prompt diagnosis is essential. **Neonatal PV** develops in utero as a result of placental transfer of maternal antidesmoglein antibodies from women who have active PV, although it may occur when the mother is in remission. High antepartum maternal titers of PV antibodies and increased maternal disease activity correlate with a poor fetal outcome, including demise.

Pathology

Biopsy of a fresh small blister reveals a suprabasal (intraepidermal) blister containing loose, acantholytic epidermal cells that have lost their intercellular bridges and thus their contact with one another. Immunofluorescence staining with an IgG antibody produces a characteristic pattern ("chicken wire") on direct immunofluorescence preparations of both involved and uninvolved skin of essentially all patients. Serum IgG antibody titers to desmoglein correlate with the clinical course in many patients; thus serial determinations may have predictive value.

Differential Diagnosis

PV must be differentiated from EM, bullous pemphigoid (BP), SJS, and TEN.

Treatment

The disease is best treated initially with systemic methylprednisolone 1-2 mg/kg/day. Azathioprine, cyclophosphamide, mycophenolate mofetil, and methotrexate therapy all have been useful in maintenance regimens. IVIG given in cycles may be beneficial to patients whose disease does not respond to steroids. Rituximab with IVIG replacement has been very effective in the management of severe PV. Excellent control of the disease may be obtained, but relapse is common. It has been successfully used in children.

PEMPHIGUS FOLIACEUS

Etiology/Pathogenesis

Pemphigus foliaceus is caused by circulating antibodies to a 50-kDa portion of the 160-kDa desmosomal glycoprotein desmoglein I, which result in subcorneal cleavage leading to superficial erosions. This extremely rare disorder is characterized by subcorneal blistering; the site of cleavage is high in the epidermis rather than suprabasal as in PV.

Clinical Manifestations

The superficial blisters rupture quickly, leaving erosions surrounded by erythema that heal with crusting and scaling (Fig. 695.12). The



Fig. 695.12 Superficial erosions in pemphigus foliaceus.

Nikolsky sign is present. Focal lesions are usually localized to the scalp, face, neck, and upper trunk. Mucous membrane lesions are minimal or absent. Pruritus, pain, and a burning sensation are frequent complaints. The clinical course varies but is generally more benign than that of PV. **Fogo selvagem (endemic pemphigus foliaceus)**, which is endemic in certain areas of Brazil, is identical clinically, histopathologically, and immunologically to pemphigus foliaceus. Anti–desmoglein-1 antibodies in individuals with fogo selvagem cross react with sand fly (*Lutzomyia* sp.) salivary proteins, suggesting an environmental trigger for this autoimmune disease.

Pathology

An intraepidermal acantholytic bulla high in the epidermis is diagnostic. It is imperative to select an early lesion for biopsy. Immunofluorescent staining with an IgG antibody reveals a characteristic intercellular staining pattern similar to that of PV but higher in the epidermis.

Differential Diagnosis

When generalized, pemphigus foliaceus may resemble an exfoliative dermatitis or any of the chronic blistering disorders; localized erythematous plaques simulate seborrheic dermatitis, psoriasis, impetigo, eczema, and systemic lupus erythematosus.

For localized disease, super-potent topical corticosteroids used twice a day may be all that is needed for control until remission. For more generalized disease, long-term remission is usual after suppression of the disease by systemic methylprednisolone (1 mg/kg/day) therapy. Dapsone (25-100 mg/day) also may be used, with appropriate laboratory monitoring.

BULLOUS PEMPHIGOID

Etiology/Pathogenesis

BP is caused by circulating antigens to either the 180-kDa or 230-kDa BP antigen that result in a subepidermal blister. The 230-kDa protein (BP230) is part of the hemidesmosome, whereas the 180-kDa protein (BP180, now known as type XVII collagen) localizes to both the hemidesmosome and the upper lamina lucida and is a transmembrane collagenous protein.

Clinical Manifestations

The blisters of BP typically arise in crops on a normal, erythematous, eczematous, or urticarial base. Bullae appear predominantly on the flexural aspects of the extremities, in the axillae, and on the groin and central abdomen. Infants have involvement of the palms, soles, and face more frequently than older children do. Individual lesions vary greatly in size, are tense, and are filled with serous fluid that may become hemorrhagic or turbid. Oral lesions occur less frequently and are less severe than in PV. Pruritus, a burning sensation, and subcutaneous edema may accompany the eruption, but constitutional symptoms are not prominent.

Pathology

Biopsy material should be taken from an early bulla arising on an erythematous base. A subepidermal bulla and a dermal

inflammatory infiltrate, predominantly of eosinophils, can be identified histopathologically. In sections of a blister or perilesional skin, a band of Ig (usually IgG) and C3 can be demonstrated in the basement membrane zone by direct immunofluorescence. Indirect immunofluorescence studies of serum have positive results in ~70% of cases for IgG antibodies to the basement membrane zone; however, the titers do not correlate well with the clinical course.

Diagnosis and Differential Diagnoses

BP rarely occurs in children but must be considered in the differential diagnosis of any chronic blistering disorder. The differential diagnosis includes bullous EM, PV, linear IgA dermatosis, bullous drug eruption, dermatitis herpetiformis (DH), herpes simplex infection, and bullous impetigo, which can be differentiated by histologic examination, immunofluorescence studies, and cultures. The large, tense bullae of BP can generally be distinguished from the smaller, flaccid bullae of PV.

Treatment

Localized BP can be successfully suppressed with super-potent topical corticosteroids (clobetasol propionate) twice a day. Generalized disease usually requires systemic methylprednisolone (1 mg/kg/day) therapy. Doxycycline has some benefits but is not as effective as prednisone. Rarely are other immunosuppressive treatments necessary, such as azathioprine or mycophenolate mofetil. Refractory cases have been treated with rituximab, but the condition usually remits within a year in most children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

695.7 Dermatitis Herpetiformis

Joel C. Joyce

ETIOLOGY/PATHOGENESIS

In dermatitis herpetiformis (DH), IgA antibodies are directed at epidermal transglutaminase (transglutaminase 3). **Gluten-sensitive enteropathy (celiac disease)** is found in all patients with DH, although the majority are asymptomatic or have minimal gastrointestinal symptoms (see Chapter 384). The severity of the skin disease and the responsiveness to gluten restriction do not correlate with the severity of the intestinal inflammation. An antibody to smooth muscle endomysium is found in 70–90% of patients with DH. Ninety percent of patients with the disease express HLA-DQ2. HLA-DQ2–negative patients with DH usually express HLA-DQ8.

CLINICAL MANIFESTATIONS

DH is characterized by symmetric, grouped, small, tense, erythematous, stinging, intensely pruritic papules and vesicles. The eruption is pleomorphic, including erythematous, urticarial, papular, vesicular, and bullous lesions. Sites of predilection are the knees, elbows, shoulders, buttocks, forehead, and scalp; mucous membranes are usually spared. Hemorrhagic lesions may develop on the palms and soles. When pruritus is severe, excoriations may be the only visible sign (Fig. 695.13).

PATHOLOGY

Subepidermal blisters composed predominantly of neutrophils are found in dermal papillae. The presence of granular IgA on direct immunofluorescence in the dermal papillary tips is diagnostic.

DIFFERENTIAL DIAGNOSIS

DH may mimic other chronic blistering disorders and may also resemble scabies, papular urticaria, insect bites, contact dermatitis, and papular eczema.



Fig. 695.13 Multiple excoriations around the elbows in dermatitis herpetiformis.

TREATMENT

Patients with DH show response within weeks to months to a gluten-free diet. Oral administration of dapsone (0.5-2.0 mg/kg/day daily or divided twice daily) provides immediate relief from the intense pruritus but must be used with caution because of possible serious side effects (methemoglobinemia, hemolysis, and drug hypersensitivity syndrome [sulfone syndrome]). Dapsone alone may not relieve the intestinal inflammation of celiac disease. Local antipruritic measures may also be useful. Jejunal biopsy is indicated to diagnose gluten-sensitive enteropathy because cutaneous manifestations may precede malabsorption. The disease is chronic, and either a gluten-free diet or dapsone must be continued indefinitely to prevent relapse.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

695.8 Linear Immunoglobulin A (IgA) Dermatosis (Chronic Bullous Dermatosis of Childhood)

Joel C. Joyce

ETIOLOGY/PATHOGENESIS

Linear IgA dermatosis is a heterogeneous autoimmune disorder with antibodies targeting multiple antigens. It has been reported to be the most common autoimmune blistering disorder in children. It is caused by circulating IgA antibodies, most commonly to LABD97 and LAD-1, which are degradation proteins of BP180 (type XVII collagen). Linear IgA dermatosis may also be seen as a drug eruption. Most cases of drug-induced linear IgA dermatosis are related to vancomycin, although anticonvulsants, ampicillin, cyclosporine, and captopril are implicated.

CLINICAL MANIFESTATIONS

This rare dermatosis is most common in the first decade of life, with a peak incidence during the preschool years. The eruption consists of many large, symmetrically located, tense bullae filled with clear or hemorrhagic fluid. The bullae are often clustered together and develop on a normal or erythematous urticarial base. Areas of predilection are the genitals and buttocks (Fig. 695.14), the perioral region, and the scalp. Sausage-shaped bullae may be arranged in an annular or rosette-like fashion around a central crust (Fig. 695.15). Erythematous plaques with gyrate margins bordered by intact bullae may develop over larger areas. Pruritus may be absent or very intense, and systemic signs or symptoms are absent.

PATHOLOGY

The subepidermal bullae are infiltrated with a mixture of inflammatory cells. Neutrophilic abscesses may be noted in the dermal papillary tips,



Fig. 695.14 Erosion on an erythematous base after loss of blister roof in linear IgA dermatosis.



Fig. 695.15 Linear IgA bullous dermatitis. *(Modified from Gouveia AI, Teixeira A, Freitas JP, et al. Linear immunoglobulin A bullous dermatosis. J Pediatr. 2016;170:338, Fig. 1A.)*

indistinguishable from those of DH. The infiltrate may also be largely eosinophilic, resembling that in BP. Therefore direct immunofluorescence studies are required for a definitive diagnosis of linear IgA dermatosis; perilesional skin demonstrates linear deposition of IgA and sometimes IgG and C3 at the dermal-epidermal junction. Immunoelectron microscopy has localized the immunoreactants to the sublamina densa, although a combined sublamina densa and lamina lucida pattern has also been seen.

DIFFERENTIAL DIAGNOSIS

The eruption can be distinguished by histopathologic and immunofluorescence studies from PV, BP, DH, scabies, and EM. Gram stain and culture preclude the diagnosis of bullous impetigo.

TREATMENT

Many cases of linear IgA dermatosis respond favorably to oral dapsone (see treatment of DH) or sulfapyridine. Other antibiotics, including erythromycin and dicloxacillin, have been used, but the response is often transient. Children who show no response to dapsone may benefit from oral therapy with methylprednisolone (1 mg/kg/day) or a combination of these drugs. The usual course is 2-4 years, although some children have persistent or recurrent disease; there are typically no long-term sequelae. IgA nephropathy is a rare complication.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 696

Eczematous Disorders

Julie M. Dhossche and Yvonne E. Chiu

Eczematous disorders are a broad group of cutaneous eruptions characterized by erythema, edema, and pruritus. Acute eczematous lesions demonstrate erythema, weeping, oozing, and the formation of microvesicles within the epidermis. Chronic lesions are generally thickened, dry, and scaly, with coarse skin markings (lichenification) and altered pigmentation. Many types of eczema occur in children; the most common is **atopic dermatitis** (see Chapter 186), although seborrheic dermatitis, allergic and irritant contact dermatitis, nummular eczema, and acute palmoplantar eczema (dyshidrosis) are also relatively common in childhood.

Once the diagnosis of eczema has been established, it is important to further classify the eruption more specifically for proper management. Pertinent historical data often provide the clue. In some instances, the subsequent course and character of the eruption permit classification. Histologic changes are relatively nonspecific, but all types of eczematous dermatitis are characterized by intraepidermal edema known as *spongiosis*.

696.1 Contact Dermatitis

Julie M. Dhossche and Yvonne E. Chiu

The form of eczema known as contact dermatitis can be subdivided into irritant dermatitis, in which nonspecific injury to the skin causes immediate inflammation, and allergic contact dermatitis, resulting from a delayed hypersensitivity reaction. Irritant dermatitis is more frequent in children, particularly during the early years of life. Allergic reactions increase in frequency upon maturation of the immune system.

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis can result from prolonged or repetitive contact with physical, chemical, or mechanical irritants, including saliva, urine, feces, fragrance, detergents, dyes, henna, plants, caterpillars, abrasive materials, and chafing.

Irritant contact dermatitis may be difficult to distinguish from atopic dermatitis or allergic contact dermatitis. A detailed history and consideration of the sites of involvement, the age of the child, and contactants usually provide clues to the etiologic agent. The propensity for development of irritant dermatitis varies considerably among children; some may respond to minimal injury, making it difficult to identify the offending agent through history. Children with atopic dermatitis are more prone to irritant contact dermatitis as an exacerbating factor. Irritant contact dermatitis usually clears after removal of the stimulus and temporary treatment with a topical corticosteroid preparation (see Chapter 687). Education of patients and parents about the causes of contact dermatitis is crucial to successful therapy.

Dry skin dermatitis results from repetitive wet-to-dry behaviors such as lip licking (Fig. 696.1), thumb sucking, frequent handwashing, or excessive sweating. Involved skin is erythematous and fissured, localized to the area of exposure. Treatment of dry skin dermatitis begins with eliminating the offending wet-to-dry behavior. A thick moisturizer (cream or ointment based) applied twice daily decreases transepidermal water loss and replenishes skin lipids to improve hydration. A topical steroid is usually necessary to treat the inflammation.

Juvenile plantar dermatosis occurs mainly in prepubertal children with hyperhidrosis who wear occlusive synthetic footwear. Weight-bearing surfaces of the foot may be pruritic or painful and develop a fissured or glazed appearance (Fig. 696.2). Immediate application of a thick emollient when socks and shoes are removed or immediately after swimming usually minimizes juvenile plantar dermatosis. Severe inflammatory cases may require short-term (1-2 weeks) application of a medium- to high-potency topical steroid.



Fig. 696.1 Perioral irritant contact dermatitis from lip licking.



Fig. 696.2 Red, scaly juvenile plantar dermatosis.

DIAPER DERMATITIS

Diaper dermatitis refers to any rash in the diaper region; the most common of these is irritant diaper dermatitis. Elevated pH in the diaper area and synergistic activity of urinary and fecal enzymes lead to inflammation, which disrupts the normal skin barrier and increases susceptibility to other irritants and organisms. Additional factors are occlusion, friction, and use of diaper wipes and topical preparations. Loose or frequent stooling predisposes an infant to diaper dermatitis. Diaper dermatitis presents with erythema and scaling in a patchy or confluent pattern and, in severe cases, may have papulovesicular or bullous lesions, fissures, and/or erosions (Fig. 696.3). The genitocrural folds are often spared because concave areas are relatively protected. Chronic hypertrophic, flat-topped papules and infiltrative nodules may occur. **Candidal infection** typically represents a secondary process. It is characterized by "beefy" red-pink, tender skin that has numerous 1- to 2-mm pustules and satellite papules and involves both concave and convex areas. Discomfort may be marked because of intense inflammation. Allergic contact dermatitis, seborrheic dermatitis, psoriasis, candidiasis, atopic dermatitis, child abuse, and rare disorders such as Langerhans cell histiocytosis, nutritional deficiencies, and acrodermatitis enteropathica should be considered when the eruption is persistent or is recalcitrant to simple therapeutic measures (Table 696.1).

Diaper dermatitis often responds to simple measures; some infants are predisposed to diaper dermatitis, and management may be difficult. The damaging effects of overhydration of the skin and prolonged contact with feces and urine can be obviated by frequent changing of the diapers and periods of "rest" free of diaper use. Cleansing of affected skin is best accomplished with a soft cloth and lukewarm water, patted dry. Overwashing should be avoided because it leads to chapping and may worsen the dermatitis. Disposable diapers containing a superabsorbent material may help to maintain a relatively dry environment. First-line therapy for diaper dermatitis is application of a protective barrier agent (ointment or paste)



Fig. 696.3 Severe, erosive diaper dermatitis.

containing petroleum or zinc oxide at every diaper change. Topical sucralfate is an effective barrier with some antibacterial activity and is useful for recalcitrant cases. Low-potency nonhalogenated topical corticosteroids, such as 2.5% hydrocortisone, may be used for short periods (3-5 days). Treatment with a topical anticandidal agent is indicated for secondary candidal infection. Topical preparations containing triamcinolone-nystatin and betamethasone dipropionate-clotrimazole are generally inappropriate for diaper dermatitis in infants because of the higher potency of the corticosteroid component. If using multiple topical agents, the protective barrier should be applied last. When diaper dermatitis does not respond to typical prevention and treatment strategies, non–diaper-associated causes must be considered.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is a delayed hypersensitivity cutaneous reaction to environmental allergens and should be considered in any child with recalcitrant eczema. It has been estimated to affect 16.4% of all children in the United States, though children are likely underdiagnosed, especially those with concomitant atopic dermatitis. Children of all ages may develop allergic contact dermatitis, though it is more common in older children. Allergic contact dermatitis is a T-cell–mediated hypersensitivity reaction that is provoked by application of an antigen to the skin surface. The antigen penetrates the skin, where it is conjugated with a cutaneous protein, and the hapten-protein complex is transported to the regional lymph nodes by antigen-presenting Langerhans cells. A primary immunologic response occurs locally in the nodes and becomes generalized, presumably because of dissemination of sensitized T cells. Sensitization requires several days and, when followed by a fresh antigenic challenge, manifests as allergic contact dermatitis. Generalized distribution may also occur if enough antigen finds its way into the circulation, such as by consumption. Once sensitization has occurred, each new antigenic challenge may provoke an inflammatory reaction within 8-12 hours; sensitization to a particular antigen usually persists for many years.

Acute allergic contact dermatitis is an erythematous, intensely pruritic, eczematous dermatitis. Acute cases may be edematous and vesiculobullous. The chronic condition has the features of long-standing eczema: lichenification, scaling, fissuring, and pigmentary change. Distinguishing allergic contact dermatitis from other eczematous disorders can be challenging, especially with irritant contact dermatitis, which can be clinically identical. The distribution of the eruption often provides a clue to the diagnosis. Airborne sensitizers usually affect exposed areas, such as the face and arms. Jewelry, topical agents, shoes, clothing, henna tattoo dyes, plants,

Table 696.1 Diaper Dermatitis

DISEASE	CLINICAL MANIFESTATION	OTHER FEATURES	TREATMENT
Friction	Inner surface of thighs, genitalia, buttocks, abdomen	Course waxes and wanes Aggravated by talc	Responds well to diaper changes Avoidance of diapers
Irritant	Mild erythema with shiny surface and occasional papules Confined to convex surfaces Spares intertriginous areas	Exacerbated by heat, moisture, and sweat retention	Gentle cleansing Regular diaper changes Barrier creams (zinc oxide, Vaseline) Low-potency topical steroids can help
Allergic contact	Typically confined to convex surfaces Skin involved is in direct contact with offending agent *Mild cases:* diffuse erythema, papules, vesicles, scaling *Severe cases:* papules, plaques, psoriasiform lesions, ulcerations, infiltrative nodules	Often related to topical antibiotics (neomycin, bacitracin) Certain emulsifiers in topical products Preservatives in wet wipes can be an offender	Remove offending agent Judicious use of low-potency topical steroids Barrier creams/ointments
Seborrheic dermatitis	Salmon-colored patches Often have yellow, greasy scale Fissures, erosions, maceration, and weeping can be seen	Axillae, ear creases, and neck are often involved "Cradle cap" on scalp Hypopigmentation often seen in patients with darker skin tones	Low-potency topical steroids If coexistent infection—antifungal or antibacterial agents
Candidiasis	Usually involves intertriginous areas and convex surfaces Bright-red papules and plaques Satellite lesions on abdomen and thighs	Oral thrush may be present Often occurs after treatment with systemic antibiotics or local topical steroid use	Topical anticandidal agent, including nystatin
Intertrigo	Well-demarcated, macerated plaques with weeping Gluteal cleft and fleshy folds of thighs	May be associated with miliaria	Avoiding excessive heat Cool clothing
Psoriasis	Bright red, scaly, well-demarcated plaques Can persist for months Less responsive to topical treatment	Red, sometimes scaly Can be present on extremities or trunk Nail changes seen Family history	Low-potency topical steroids Moisturizers
Staphylococcal infection	Many thin-walled pustules with pink-red base Collarette of scale after rupturing		Antistaphylococcal therapy
Acrodermatitis enteropathica (zinc deficiency)	Early lesions are vesicular and pustular Become confluent, pink, dry, scaly, crusty plaques	Perioral skin typically also involved Irritability or listlessness Failure to thrive, alopecia, diarrhea	Secondary to zinc deficiency or inborn error of zinc transporter Treat with zinc replacement
Langerhans cell histiocytosis	May mimic candidiasis or seborrheic dermatitis Persistent, does not improve with standard treatments Clusters of infiltrative, crusted, hemorrhagic papules Ulceration can be seen	Involvement of groin, axillae, periauricular skin, hairline, and scalp Anemia, thrombocytopenia, hepatosplenomegaly, and osseous lesions	Chemotherapy

From Humphrey S. Congenital cutaneous lesions and infantile rashes. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 60.2, p. 1144.

and even toilet seats cause dermatitis at points of contact. Careful evaluation of environmental exposures, cultural customs, daily activity, animal exposures, ear piercing, tattooing, and personal product usage in the patient and all caregivers is essential. Other potential diagnoses to consider include herpes simplex virus, impetigo, cellulitis, and dermatophytoses.

Rhus dermatitis (poison ivy, poison sumac, poison oak), a response to the plant allergen urushiol, is the most common allergic contact dermatitis. It is often vesiculobullous and may be distinguished by linear streaks of vesicles where the plant leaves have brushed against the skin (Fig. 696.4). Fluid from ruptured cutaneous vesicles does not spread the eruption; antigen retained on skin, clothing, or under fingernails initiates new plaques of dermatitis if not removed by washing with soap and water. Antigen may also be carried by animals on their fur. "Black spot" poison ivy dermatitis is a rare variant that results from oxidation of concentrated urushiol left on the skin and manifests as small discrete black lacquer–like glossy papules with surrounding erythema and edema. Sensitization to one plant produces cross reactions with the others. Spontaneous resolution occurs in 1-3 weeks, with the most common complication being secondary bacterial infection with normal skin flora. Exposure avoidance and thorough washing after exposure are the mainstays for prevention. Barrier creams or organoclay compounds such as bentoquatam may be effective if applied before expected exposure.

Nickel dermatitis develops from contact with jewelry, metal closures on clothing, or even cell phones. Metal closures on pants frequently cause periumbilical dermatitis (Fig. 696.5). Some children are exquisitely sensitive to nickel, with even the trace amounts found in gold jewelry provoking eruptions. The most frequently involved sites from jewelry are the earlobes from nickel-containing earrings. Early ear piercing increases risk of sensitization, and it is recommended to delay piercing until after 10 years of age. Patch testing for nickel sensitivity is unreliable in infants and toddlers and should only be performed if there is high clinical suspicion.

Shoe dermatitis typically affects the dorsum or soles of the feet and toes, sparing the interdigital spaces; it is usually symmetric. Other forms of allergic contact dermatitis, in contrast to irritant dermatitis, rarely involve the palms and soles. Common allergens are the antioxidants and accelerators in shoe rubber, adhesives, and the chromium salts in tanned leather or shoe dyes. Excessive sweating often leaches these substances from their source.

Apparel contains a number of sensitizers, including dyes, dye fixative, fabric finishes, fibers, resins, and cleaning solutions. Dye may be poorly



Fig. 696.4 Linear lesions in poison ivy.



Fig. 696.5 Chronic periumbilical nickel dermatitis.

fixed to clothing and so may be leached out with sweating, as can partially cured formaldehyde resins. The elastic in garments is a frequent cause of clothing dermatitis, and contact allergy to the ink "tag" of tagless baby clothing has been reported. Exposure to other items with fabric, such as infant car seats, may induce reactions similar to clothing.

Topical medications and cosmetics may be unsuspected as allergens, particularly if a medication is being used for a preexisting dermatitis. The most common offenders are neomycin, topical antihistamines, topical anesthetics, fragrances, topical corticosteroids, oxybenzone and octocrylene in chemical sunscreens, preservatives, dye in temporary tattoos, and ethylenediamine, a stabilizer present in many medications. All types of cosmetics can cause facial dermatitis; involvement of the eyelids is characteristic for nail polish sensitivity. Another pediatric allergen has been methylisothiazolinone (MI), a chemical preservative found in rinse-off products including liquid soaps and shampoos, as well as paints and glues, which may be used in making homemade "slime" and lead to hand dermatitis.

Neomycin sulfate is present in many nonprescription topical antibiotic preparations, and thus children are frequently exposed at an early age. It is one of the most common causes of allergic contact dermatitis, and use of combination products of neomycin with other antibiotics, antifungals, or corticosteroids may induce co-reactivity with these chemically unrelated substances.

As mentioned previously, diagnosis of allergic contact dermatitis is usually based on history; however, patch testing may be helpful, especially in older children. Identification and avoidance of the offending agent is the mainstay of managing allergic contact dermatitis. First-line treatment for acute eruption is a mid-potency topical corticosteroid ointment for 2-3 weeks and symptom management with nonsensitizing and fragrance-free emollients/moisturizers, wet dressings, and sedating antihistamines to allow for sleep. Systemic corticosteroids are used when >10% of skin is involved (0.5-1.0 mg/kg prednisone to a maximum of 60 mg/day for 7-10 days, followed by a 7-10 day taper). More chronic allergic contact dermatitis is treated with low- to mid-potency topical corticosteroids. Desensitization therapy is rarely indicated. Topical calcineurin inhibitors, such as tacrolimus, may be a potential steroid-sparing alternative agent in select patients.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

696.2 Nummular Eczema

Julie M. Dhossche and Yvonne E. Chiu

Nummular eczema is characterized by coin-shaped, severely pruritic, eczematous plaques, commonly involving the extensor surfaces of the extremities (Fig. 696.6), buttocks, and shoulders with facial sparing. The plaques are relatively discrete, boggy, vesicular, slightly scaly, and exudative; when chronic, they often become thickened and lichenified and may develop central clearing. Nummular eczema may be an atypical morphology in someone with underlying atopic dermatitis or may be an independent disorder. Flares are generally sporadic but may be precipitated by xerosis, irritants, allergens, or occult staphylococcal infection. Most frequently, these lesions are mistaken for tinea corporis, but plaques of nummular eczema are distinguished by the lack of a raised, sharply circumscribed border, the lack of fungal organisms on a potassium hydroxide (KOH) preparation, and frequent weeping or bleeding when scraped. First-line treatment is with emollients, wet dressings, and potent topical corticosteroids. Steroid-impregnated tapes may simultaneously treat and provide barrier protection to these circumscribed eczematous plaques. An oral antihistamine may be helpful, particularly a sedating antihistamine at night. Antibiotics are indicated for secondary infection. Methotrexate and dupilumab have been described as systemic treatments.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

696.3 Pityriasis Alba

Julie M. Dhossche and Yvonne E. Chiu

Pityriasis alba occurs mainly in children and causes lesions that are hypopigmented, ill-defined, round or oval patches (Fig. 696.7). They may be mildly erythematous and finely scaly. Lesions occur on the face, neck, upper trunk, and proximal portions of the arms and are most pronounced on darker skin tones or after tanning of surrounding skin. Itching



Fig. 696.6 Discrete, boggy plaque of nummular dermatitis.

is minimal or absent. The cause is unknown, but the eruption appears to be exacerbated by dryness and is often regarded as a mild form of atopic dermatitis. Pityriasis alba is frequently misdiagnosed as vitiligo, tinea versicolor, or tinea corporis. The lesions wax and wane but eventually disappear, and normal pigmentation often takes months to return. Application of a lubricant or emollient may ameliorate the condition, and avoidance of sun exposure and daily sunscreen use can help reduce the appearance of existing lesions by allowing for natural lightening of adjacent unaffected skin. If pruritus is troublesome or if the lesions are active with erythema and fine scale, a low-potency topical steroid or calcineurin inhibitor may be used.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

696.4 Lichen Simplex Chronicus

Julie M. Dhossche and Yvonne E. Chiu

Lichen simplex chronicus is a secondary skin disorder resulting from excessive scratching or rubbing. It is characterized by a chronic pruritic, eczematous, circumscribed plaque that is usually lichenified and hyperpigmented (Fig. 696.8). All affected areas must be accessible to scratching, with the most common sites being the posterior neck, genitalia, wrists, ankles, and dorsal feet. Although the initiating event may be a transient lesion such as an insect bite, trauma from rubbing and scratching accounts for persistence of the plaque. Lichen simplex chronicus may also be seen in other chronic eczematous dermatoses such as atopic dermatitis, typically when poorly controlled. Pruritus must be controlled to permit healing; thus a covering to prevent scratching may be necessary. A high-potency topical corticosteroid under occlusion is often helpful and hastens resolution. Second-line therapy includes adding 6% salicylic acid gel to the topical corticosteroid preparation.

696.5 Acute Palmoplantar Eczema

Julie M. Dhossche and Yvonne E. Chiu

A recurrent, sometimes seasonal, blistering disorder of the hands and feet, acute palmoplantar eczema (also known as dyshidrotic eczema or pompholyx) occurs in all age-groups but is uncommon in infancy. The pathogenesis is unknown, although possible predisposing factors include a history of atopy, exposure to contact allergens (especially metals) or irritants, or IV immunoglobulin therapy. The disease is characterized by recurrent crops of small, deep-seated, "tapioca-like" vesicles, which are intensely pruritic and may coalesce into tense bullae (Fig. 696.9). Sites of predilection are the palms, soles, and lateral aspects of the fingers and toes. Primary lesions are noninflammatory and are filled with clear fluid, which, unlike sweat, has a physiologic pH and contains protein. Maceration and secondary infection are frequent because of scratching. The chronic phase is characterized by thickened, fissured plaques that may cause considerable discomfort and dystrophic nails. Although acute



Fig. 696.7 Patchy hypopigmented lesions with diffuse borders characteristic of pityriasis alba.



Fig. 696.8 Thickened plaque of lichen simplex chronicus.

palmoplantar eczema is frequently seen in patients with hyperhidrosis, histologic examination reveals an eczematous reaction around sweat ducts, without any structural or functional abnormalities of the sweat ducts themselves. The diagnosis is made clinically. The disorder may be confused with allergic contact dermatitis, which usually affects the dorsal rather than the volar surfaces, and with dermatophytosis, which can be distinguished by a KOH preparation of the roof of a vesicle and by appropriate cultures.

Acute palmoplantar eczema responds to wet dressings, liberal emollient use, and potent topical corticosteroid ointment applied twice daily for 2-4 weeks. Weeping skin benefits from twice-daily soaking in an astringent solution, such as aluminum subacetate. Second-line treatment includes phototherapy and systemic immunomodulators. Severe disease may require oral corticosteroids with a 2-week taper. Secondary bacterial infection should be treated systemically with an appropriate antibiotic. Patients should be told to expect recurrence and should protect their hands and feet from the damaging effects of excessive sweating, chemicals, harsh soaps, and adverse weather. Unfortunately, it is impossible to prevent recurrence or to predict its frequency.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

696.6 Seborrheic Dermatitis

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY

Seborrheic dermatitis is a chronic inflammatory disease most common in infancy and adolescence that parallels the distribution, size, and activity of the sebaceous glands. The cause is unknown, as is the role of the sebaceous glands in the disease. *Malassezia furfur* is implicated as a causative agent,



Fig. 696.9 Vesicular palmar lesions of acute palmoplantar eczema with large bullae.



Fig. 696.10 Cradle cap in an infant.

although it remains unclear whether dermatitis results from the action of the fungus, its by-products, or an exaggerated response of the host. In adolescence, seborrheic dermatitis typically occurs after puberty, indicating a possible role for sex hormones.

It is also unknown whether infantile seborrheic dermatitis and adolescent seborrheic dermatitis are the same or different entities. There is no evidence that children with infantile seborrheic dermatitis will experience seborrheic dermatitis as adolescents.

CLINICAL MANIFESTATIONS

The disorder may begin in the first month of life and typically self-resolves by 1 year. Diffuse or focal scaling and crusting of the scalp, sometimes called *cradle cap* (Fig. 696.10), may be the initial and, at times the only, manifestation. A greasy, scaly, erythematous papular dermatitis, which is usually nonpruritic in infants, may involve the face, neck, retroauricular areas, axillae, umbilicus, and diaper area. The dermatitis may be patchy and focal or may spread to involve almost the entire body (Fig. 696.11). Postinflammatory pigmentary changes are common, particularly in infants with darker skin. When the scaling becomes pronounced, the condition may resemble psoriasis and, at times, can be distinguished only with difficulty. The possibility of coexistent atopic dermatitis must be considered when there is an acute weeping dermatitis with pruritus, and the two are often clinically inseparable at an early age. An intractable seborrhea-like dermatitis with chronic diarrhea and failure to thrive may reflect systemic dysfunction of the immune system. A chronic treatment-resistant seborrhea-like pattern may also result from cutaneous histiocytic infiltrates in infants with Langerhans cell histiocytosis. Seborrheic dermatitis is a common cutaneous manifestation of AIDS in young adults and is characterized by thick, greasy scales on the scalp and large hyperkeratotic erythematous plaques on the face, chest, and genitals.

During adolescence, seborrheic dermatitis is more localized and may be confined to the scalp, chest, and intertriginous areas. Also noted may be marginal blepharitis and involvement of the external auditory canal. Scalp changes vary from diffuse, brawny scaling to focal areas of thick, oily, yellow crusts with underlying erythema. Loss of hair is uncommon, and pruritus may be absent to marked. When the dermatitis is severe, erythema and scaling occur at the frontal hairline, the medial aspects of the eyebrows, and in the nasolabial and retroauricular folds. Red, scaly plaques may appear in the axillae, inguinal region, gluteal cleft, and umbilicus. On the extremities, seborrheic plaques may be more eczematous and less erythematous and demarcated. Unlike infantile seborrheic dermatitis, adolescent seborrheic dermatitis generally does not self-resolve and has a chronic relapsing course.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of seborrheic dermatitis includes psoriasis, atopic dermatitis, dermatophytosis, Langerhans cell histiocytosis, and candidiasis. Secondary bacterial infections and superimposed candidiasis are common.

TREATMENT

Initial management for infantile seborrheic dermatitis is generally conservative given the self-limited nature of this condition.



Fig. 696.11 Seborrheic dermatitis may occasionally be more widespread. *(From Tom WL, Eichenfield LF. Eczematous disorders. In: Eichenfield LF, Frieden IJ, eds. Neonatal and Infant Dermatology, 3rd ed. Philadelphia: Elsevier; 2015: Fig. 15.11, p. 225.)*

Emollients, baby oil, gentle shampooing with nonmedicated baby shampoo, and gentle use of a soft brush to remove scales are usually effective measures. Persistent lesions may be treated with low-potency topical corticosteroids if inflamed (applied once daily for 1 week) and a topical antifungal (e.g., ketoconazole 2% cream twice daily). Antifungal shampoos such as ketoconazole 2% shampoo should be used cautiously because they are not tear-free.

First-line therapy for children and adolescents with scalp seborrheic dermatitis is antifungal shampoo used several times weekly to daily (selenium sulfide, ketoconazole, ciclopirox, zinc pyrithione, salicylic acid, or tar). Mid-potency topical corticosteroids such as fluocinolone 0.01% oil or triamcinolone 0.1% lotion may also be used for inflamed lesions, applied once daily for 2-4 weeks. Nonscalp lesions are treated with topical corticosteroid cream (low-potency for facial lesions, mid-potency elsewhere), as well as topical antifungals such as ketoconazole 2% cream or ketoconazole 2% shampoo used as a body or face wash. Second-line therapy for seborrheic dermatitis includes topical calcineurin inhibitors and keratolytic agents such as urea. Severe adult cases improve with oral antifungal agents; however, pediatric studies are lacking. Once acute disease is controlled, antifungal shampoo used on a twice-weekly basis is effective maintenance to reduce the risk of relapse.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 697

Photosensitivity

Julie M. Dhossche and Yvonne E. Chiu

Photosensitivity denotes an abnormal cutaneous reaction to UV radiation, either in sunlight or artificial light. The UV light spectrum contains UVA (320-400 nm wavelength), UVB (290-320 nm wavelength), and UVC (100-290 nm wavelength) subtypes. Transmitted radiation <300 nm is largely absorbed in the epidermis, whereas >300 nm is mostly transmitted to the dermis after variable epidermal melanin absorption. Children vary in susceptibility to UV radiation, depending on their skin type (i.e., its amount of pigment; Table 697.1).

ACUTE SUNBURN REACTION

The most common photosensitive reaction seen in children is acute sunburn, which is caused mainly by UVB radiation. Sunlight contains many times more UVA than UVB radiation, but UVA must be encountered in much larger quantities than UVB radiation to produce sunburn. Immediate pigment darkening is caused by UVA radiation–induced photo-oxidative darkening of existing melanin and its transfer from melanocytes to keratinocytes. This effect generally lasts for a few hours and is not photoprotective. UVB-induced effects appear 6-12 hours after initial exposure and reach a peak in 24 hours. Effects include redness, tenderness, edema, and blistering (Fig. 697.1). Severe sunburn induces systemic symptoms of fever, nausea, and headache. Reactive oxidation species generated by UVB induce keratinocyte membrane damage and are involved in the pathogenesis of sunburn. A portion of the vasodilation seen in UVB-induced erythema is mediated by prostaglandins E_2, E_3, and F_{2A}. Other inflammatory cytokines induced by UVB include interleukins 1, 6, and 8 and tumor necrosis factor-α. Acute sunburn is a self-limited condition that resolves within 1 week with desquamation and without scarring. Delayed melanogenesis as a result of UVB radiation begins in 2-3 days and lasts several days to a few weeks. Manufacture of new melanin in melanocytes, transfer of melanin from melanocytes to keratinocytes, increase in size and arborization of melanocytes, and activation of quiescent melanocytes produce delayed melanogenesis and pigment darkening (tanning). This effect reduces skin sensitivity to future UV-induced erythema. The amount of protection afforded depends on the skin type of the patient. Additional effects and possible complications of sun exposure include increased thickness of the stratum corneum, recurrence or exacerbation of herpes simplex labialis, lupus erythematosus, and many other conditions (Table 697.2).

Acute sunburn should be managed conservatively with cool compresses, aloe vera products, and calamine lotion. Oral analgesics such as ibuprofen and acetaminophen may decrease pain. Topical corticosteroids are only helpful in the acute phase and generally should not be used to treat sunburn once peak erythema has been reached (~24 hours). Topical anesthetics are relatively ineffective and potentially hazardous because of their propensity to cause contact dermatitis. A bland emollient, such as plain petrolatum, is effective in the desquamative phase.

Table 697.1 Sun-Reactive Skin Types

FITZPATRICK SKIN TYPE	SUNBURN, TANNING HISTORY
I	Always burns easily, no tanning
II	Usually burns, minimal tanning
III	Sometimes burns, gradual light brown tan
IV	Minimal to no burning, always tans
V	Rarely burns, tans profusely dark brown
VI	Never burns, pigmented black

The long-term sequelae of chronic and intense sun exposure are not often seen in children, but most individuals receive >50% of their lifetime UV dose by age 20 years; therefore pediatricians have a pivotal role in educating patients and their parents about the harmful effects, potential malignancy risks, and irreversible skin damage that result from prolonged exposure to the sun and tanning lights. Premature aging, senile elastosis, actinic keratoses, squamous and basal cell carcinomas, and melanomas all occur with greater frequency in sun-damaged skin. In particular, blistering sunburns in childhood and adolescence significantly increase the risk for development of malignant melanoma.

Sun protection is best achieved by sun avoidance, which includes minimizing time in the midday sun (10 AM to 4 PM), staying in the shade, and wearing protective clothing including wide-brimmed hats. Protection is enhanced by a wide variety of sunscreen agents. Physical sunscreens (zinc oxide, titanium dioxide) that block UV light are preferred, whereas chemical sunscreens (para-aminobenzoic acid [PABA], PABA esters, salicylates, benzophenones, avobenzone, cinnamates, and ecamsule) absorb damaging radiation. Some of these products may be systemically absorbed and achieve levels higher than permitted by the FDA. Most chemical sunscreens are effective for only UVB wavelengths but benzophenones and avobenzone provide protection in both the UVA and UVB ranges; ecamsule is a UVA sunscreen. Stabilizers such as octocrylene and diethyl 2,6-naphthalate increase the time of function of the chemical sunscreens. "Broad-spectrum" sunscreens are combination products that absorb both UVA and UVB, and families should be advised to use products labeled as "broad spectrum" with a sun protective factor (SPF) of at least 30, reapply liberally at least every 2 hours while outdoors, and reapply after swimming. Infants younger than 6 months of age should not be exposed to direct sunlight but may have SPF 15 physical sunscreens applied to small areas of skin if sunlight avoidance is not possible. SPF is defined as the minimal dose of sunlight required to produce cutaneous erythema after application of a sunscreen, divided by the dose required with no use of sunscreen. SPF applies only to UVB protection; there is no associated rating for UVA protection in the United States aside from the "broad spectrum" designation.

PHOTOSENSITIVE REACTIONS

Photosensitizers in combination with a particular wavelength of light (typically UVA) cause dermatitis that can be classified as phototoxic or photoallergic reactions. Contact with the photosensitizer may occur externally on the skin, internally by enteral or parenteral administration, or through host synthesis of photosensitizers in response to an administered drug.

Photoallergic reactions occur in only a small percentage of persons exposed to photosensitizers and light and require a time interval for sensitization to take place. Thereafter, dermatitis appears within 24 hours of reexposure to the photosensitizer and light. Typically, patients present with an eczematous eruption in sun-exposed areas with sparing behind the ear, under the chin, and under clothing. Photoallergic dermatitis is a T-cell–mediated delayed hypersensitivity reaction in which the drug, acting as a hapten, may combine with a skin protein to form the antigenic substance. Table 697.2 lists some of the important classes of drugs and chemicals responsible for photosensitivity reactions. The most common photoallergens are chemicals present in sunscreens.

Phototoxic reactions occur in all individuals who accumulate adequate amounts of a photosensitizing drug or chemical within the skin. UV radiation excites the agent to a state capable of causing cell or tissue damage through reactive oxygen species formation. Prior sensitization is not required. Dermatitis develops within hours after exposure to radiation in the range of 285-450 nm. The eruption is confined to light-exposed areas and often resembles exaggerated sunburn, but it



Fig. 697.1 Sunburn. Well-demarcated, severe erythema.

may be urticarial or bullous. It results in postinflammatory hyperpigmentation. All the drugs that cause photoallergic reactions may also cause a phototoxic dermatitis if given in sufficiently high doses. Several additional drugs and contactants cause phototoxic reactions (see Table 697.2). Postinflammatory hyperpigmentation develops rapidly and can be the presenting sign. Contact with furocoumarin-containing plants causes a nonallergic disorder called **phytophotodermatitis** (Figs. 697.2 and 697.3). The most common phytophotodermatitis seen in children is caused by lime juice, which presents as hyperpigmentation in streaky patterns on sun-exposed skin consistent with dripping juice or handprints (see Table 697.2).

Diagnosis of photosensitive reactions caused by drugs or chemicals relies on a high index of suspicion, an appreciation of the distribution pattern of the eruption, and a history of application or ingestion of a known photosensitizing agent. Phototesting and photopatch testing are also helpful when available. First-line treatment for both photoallergy and phototoxicity consists of discontinuation of the offending agent and good sun protection practices, including avoidance of sun exposure. Photoallergic reactions are treated similarly to contact dermatitis, with a topical corticosteroid to alleviate pruritus when necessary. Severe reactions may necessitate a 2- to 3-week course of systemic corticosteroid therapy. Phototoxic reactions are treated similarly to sunburn, with comfort measures such as cool compresses, emollients, and oral analgesics.

PORPHYRIAS

See Chapter 112.

Porphyrias are acquired or inborn disorders due to genetic variants of specific enzymes in the heme biosynthetic pathway. Some have childhood photosensitivity as a consistent feature. The pathogenesis of photosensitivity in porphyria relates to deposition of excess porphyrins in the skin; UV radiation excites these molecules, causing cell and tissue damage via generation of reactive oxygen species. Signs and symptoms may be negligible during the winter, when sun exposure is minimal.

Congenital erythropoietic porphyria (Günther disease) is a rare autosomal recessive disorder affecting the enzyme uroporphyrinogen III synthase. It may cause hydrops fetalis, but more typically manifests in the first few months of life as hemolytic anemia and exquisite sensitivity to light, which may induce repeated severe bullous eruptions that result in mutilating scars (Fig. 697.4). Hyperpigmentation, hyperkeratosis, vesiculation, and fragility of skin, as well as various nail changes, develop in light-exposed areas. Light therapy for an affected neonate presenting with jaundice may inadvertently induce skin manifestations. Hirsutism in areas of mild involvement, scarring alopecia in severely affected areas, pink to red urine, brown teeth (erythrodontia), splenomegaly, and corneal ulceration are additional characteristic manifestations. Laboratory findings include uroporphyrin I and coproporphyrin I in urine, plasma, and erythrocytes and coproporphyrin I in feces. Teeth and urine from affected patients fluoresce reddish pink under a Wood lamp as a result of the presence of porphyrins. **Hepatoerythropoietic porphyria**, a separate entity, has skin findings that closely resemble those seen in congenital erythropoietic porphyria; this extremely rare disorder presents in early childhood and is discussed in greater depth in Chapter 112.

Table 697.2 Cutaneous Reactions to Sunlight

Sunburn
Photoallergic Drug Eruptions
• Systemic drugs include tetracyclines, psoralens, chlorothiazides, sulfonamides, barbiturates, griseofulvin, thiazides, quinidine, phenothiazines
• Topical agents include coal tar derivatives, psoralens, halogenated salicylanilides (soaps), perfume oils (e.g., oil of bergamot), sunscreens (e.g., PABA, cinnamates, benzophenones)
Phototoxic Drug Eruptions
• Systemic agents include nalidixic acid, furosemide, nonsteroidal antiinflammatory agents (naproxen, piroxicam), and high doses of agents causing photoallergic eruptions
• Topical agents include 5-fluorouracial, furocoumarins and high doses of agents causing photoallergic eruptions
Phytophotodermatosis
• Furocoumarin-containing plants: fig tree leaves and sap, limes, celery, fennel, carrots, parsley, dill, parsnips
Genetic Disorders with Photosensitivity
• Xeroderma pigmentosum
• Bloom syndrome
• Cockayne syndrome
• Rothmund-Thomson syndrome
• Trichothiodystrophy
• Smith-Lemli-Opitz syndrome
• Kindler syndrome
Inborn Errors of Metabolism
• Porphyrias
• Hartnup disease and pellagra
Infectious Diseases Associated with Photosensitivity
• Recurrent herpes simplex infection
• Viral exanthems (accentuated photodistribution; e.g., varicella)
Skin Diseases Exacerbated or Precipitated by Light
• Lichen planus
• Darier disease
• Lupus erythematosus, including neonatal
• Dermatomyositis
• Psoriasis
• Erythema multiforme
• Atopic dermatitis
• Hailey-Hailey disease
Deficient Protection Because of a Lack of Pigment
• Vitiligo
• Oculocutaneous albinism
• Phenylketonuria
• Chédiak-Higashi syndrome
• Hermansky-Pudlak syndrome
• Waardenburg syndrome
• Piebaldism

PABA, para-aminobenzoic acid.

Erythropoietic protoporphyria may be autosomal dominant, autosomal recessive, or X-linked and most commonly involves the enzyme ferrochelatase (FECH), the final enzyme in the heme synthetic pathway. Symptoms develop in early childhood and manifest as intense pain, tingling, or pruritus within 30 minutes of sun exposure, followed by erythema, edema, urticaria, or mild systemic symptoms; these acute manifestations resolve completely within days. The absence of blistering distinguishes erythropoietic protoporphyria from the other cutaneous porphyrias. Nail changes consist of opacification of the nail plate, onycholysis, pain, and tenderness. Recurrent sun exposure produces a subtle chronic eczematous dermatitis with thickened, lichenified skin, especially over the finger joints (Fig. 697.5A), as well as mild facial scarring (see Fig. 697.5B). Pigmentation, hypertrichosis, skin fragility, and mutilation are not seen. Gallstones develop frequently; however, severe liver disease occurs in <5% of patients. Protoporphyrin is detected in plasma, erythrocytes, and feces. **X-linked protoporphyria**

is a similar disorder to erythropoietic protoporphyria but is due to a pathogenic genetic variant in 5-aminolevulinic acid synthetase (the first and rate-controlling enzyme of heme synthesis) and therefore does not have iron overload or associated anemia.

The wavelengths of light mainly responsible for eliciting cutaneous reactions in porphyria are in the region of 400 nm (UVA light). Window glass, including that in automobiles, transmits wavelengths >320 nm and is not protective, and fluorescent indoor lights may be pathogenic. Patients must avoid direct sunlight, wear protective clothing, and use a sunscreen agent that effectively blocks UVA light. Oral beta-carotene also provides some photoprotective benefit. Afamelanotide, an alpha-melanocyte–stimulating hormone (α-MSH) analog, is approved by the FDA for treatment of erythropoietic protoporphyria to increase pain-free light exposure. This drug serves to increase skin pigmentation by increasing melanin production by melanocytes, resulting in increased UV tolerance.

Cutaneous porphyria symptoms are typically constant throughout life, and secondary bacterial infections commonly complicate the disease course. Cutaneous porphyrias do not appear to increase the risk for skin malignancies. Additional diagnostic and treatment recommendations for the porphyrias are outlined in Chapter 112.



Fig. 697.2 Phytophotodermatitis (fig tree leaves). *(From Papazoglou A, Mantadakis E. Fig tree leaves phytophotodermatitis. J Pediatr. 2021;239:244–245, Fig.1A.)*

Pseudoporphyria is a porphyria-like reaction characterized by erythema, blistering, and scarring on sun-exposed skin seen occasionally in patients with juvenile idiopathic arthritis taking nonsteroidal anti-inflammatory agents.

COLLOID MILIUM

Colloid milium is a rare, asymptomatic disorder that occurs on the face (nose, upper lip, and upper cheeks) and may extend to the dorsum of the hands and the neck as a profuse eruption of tiny, ivory to yellow, firm, grouped papules. Lesions appear before puberty on otherwise normal skin, unlike the adult variant that develops on sun-damaged skin. Onset may follow an acute sunburn or long-term sun exposure. Most cases reach maximal severity within 3 years and remain unchanged thereafter, although the condition may remit spontaneously after puberty. Treatment is usually not necessary.

HYDROA VACCINIFORME

Hydroa vacciniforme is a vesiculobullous disorder with unclear etiology, although chronic or latent Epstein-Barr virus infections or lymphoproliferative disorders have been implicated. It begins in early childhood and may remit at puberty, with peak incidence in the spring and summer. Erythematous, pruritic macules develop symmetrically within hours of sun exposure over the ears, nose, lips, cheeks, and dorsal surfaces of the hands and forearms. Lesions progress to stinging tender papules and hemorrhagic vesicles and bullae, resembling chickenpox. They become umbilicated, ulcerated, and crusted, eventually healing with pitted scars and telangiectasias. Associated features are rare but include fever, malaise, hypersensitivity to mosquito bites, conjunctivitis, and other ocular symptoms. This eruption should be distinguished



Fig. 697.4 Crusted ulcerations in an infant with congenital erythropoietic porphyria.

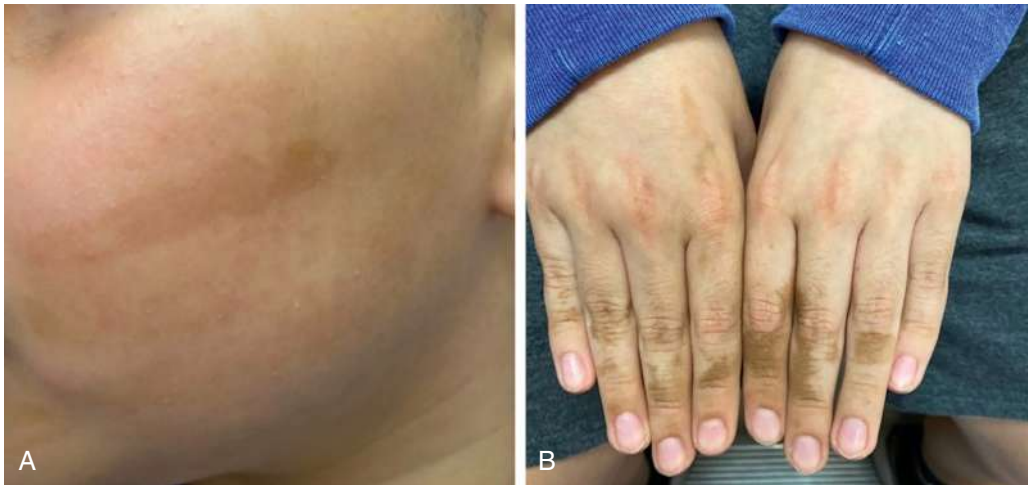

Fig. 697.3 Phytophotodermatitis (lime). **A,** Linear hyperpigmentation on the left cheek. **B,** A linear streak of hyperpigmentation on the right dorsal hand along with irregular hyperpigmentation of the bilateral dorsal fingers. *(From Dreher K, Evans MS. Linear hyperpigmentation in chronic phytophotodermatitis from limes. J Pediatr. 2021;239:245–246.)*



Fig. 697.5 Erythropoietic protoporphyria. **A**, Erythematous thickening over the metacarpal phalangeal joints. **B**, Linear crusts and scarring.

from erythropoietic protoporphyria, which rarely shows vesicles. Typical lesions have been reproduced with repeated doses of UVA or UVB light. First-line treatment includes sun avoidance, broad-spectrum sunscreens, and other sun-protective habits. Other potential therapies include mid-potency topical corticosteroids for inflamed lesions, low-dose courses of narrow-band UVB (NB-UVB) therapy, beta-carotene, hydroxychloroquine, or antiviral agents such as acyclovir.

SOLAR URTICARIA

Solar urticaria is a rare disorder induced by UV or visible irradiation. The disorder is mediated by immunoglobulin E antibodies to either an abnormal photoallergen present only in affected patients (type I) or a normal photoallergen ordinarily present in skin (type II), leading to mast cell degranulation and histamine release. Classic urticarial lesions consisting of erythematous pruritic wheals develop on sun-exposed skin (Fig. 697.6) within 5-10 minutes of sun exposure and fade within 24 hours. Severe reactions involving large areas of skin may lead to systemic symptoms or anaphylaxis. Diagnosis is achieved by history alone or with phototesting. First-line treatment is an oral H_1 antihistamine, plus sun avoidance and protection. Second-line therapy possibilities include oral or topical corticosteroids, photodesensitization using NB-UVB, omalizumab, or intravenous immunoglobulin.

POLYMORPHOUS LIGHT ERUPTION

Polymorphous light eruption (PMLE) is a common photosensitivity reaction that develops most commonly in females. The first eruption typically appears in the spring after the first episode of prolonged sun exposure of the season. Onset of the eruption is delayed by hours to days after sun exposure and lasts for days to sometimes weeks. PMLE usually resolves with increased sun exposure throughout the spring and summer. Areas of involvement tend to be symmetric and are characteristic for a given patient, including some, but not all, of the exposed or lightly covered skin on the face, neck, upper chest, and distal extremities. Lesions have various morphologies but most commonly are pruritic, 2- to 5-mm, grouped, erythematous papules or papulovesicles or >5-cm edematous plaques; lesions are nonscarring. A PMLE variant known as **juvenile spring eruption** characteristically occurs



Fig. 697.6 Urticaria after 5 min of exposure to artificial ultraviolet A radiation.

on affected boys' ears each spring, and **pinpoint papular PMLE** is a variant characterized by pinpoint-sized lesions occurring in darker-skinned individuals. Most PMLE cases involve sensitivity to UVA radiation, although some are UVB induced. PMLE most likely results from a delayed-type hypersensitivity reaction to a photo-induced antigen within the skin, with individuals having a genetic predisposition. Provocative phototesting, as well as skin biopsy (showing epidermal spongiosis and superficial and deep lymphocytic infiltrate), aid in diagnosis. Treatment is aimed at prevention with sun avoidance, protective clothing, and broad-spectrum sunscreens. Topical corticosteroids (low-potency for facial lesions, high-potency for lesions elsewhere) can be used for mild eruptions. Second-line approaches include prophylactic NB-UVB phototherapy or hydroxychloroquine in early spring and short-course systemic glucocorticoids for severe flares.

ACTINIC PRURIGO

Actinic prurigo, often classified as a variant of PMLE, is a chronic familial photodermatitis inherited as an autosomal dominant trait seen most commonly in Native Americans of North and South America. Human leukocyte antigen (HLA) DRB1*0407 (60–70%) and HLA DRB1*0401 (20%) are strongly associated with actinic prurigo. Most patients are female and are sensitive to UVA radiation. The first episode generally occurs in early childhood, several hours to 2 days after intense sun exposure. The papulonodular lesions are intensely pruritic, erythematous, and crusted. Areas of predilection include the face (Fig. 697.7), lower lip, distal extremities, and, in severe cases, buttocks. Facial lesions may heal with minute pitted or linear scarring. Lesions often become chronic, without periods of total clearing, merging into eczematous plaques that become lichenified and occasionally secondarily infected. Associated features that distinguish this disorder from other photoeruptions and atopic dermatitis include cheilitis, conjunctivitis, and traumatic alopecia of the outer half of the eyebrows. Actinic prurigo is a chronic condition that generally persists into adult life, although it may improve spontaneously in the late teenage years. Sun avoidance, protective clothing, and broad-spectrum sunscreens may be helpful in preventing the eruption. Mid- to high-potency topical corticosteroids and antihistamines palliate the pruritus and inflammation. Severe acute eruptions may require oral glucocorticoids. Treatment with NB-UVB beginning in springtime has shown improved tolerance of sunlight during summer months; however, it may induce symptoms in some patients. Thalidomide 50-100 mg/day is very effective, but its use is limited by toxicity, especially severe birth defects when taken by pregnant females. Dupilumab is described in case reports to be helpful.

COCKAYNE SYNDROME

Cockayne syndrome is a rare autosomal recessive disorder. Onset occurs at 1 year of age and is characterized by facial erythema in a butterfly distribution after sun exposure. Later characteristics include loss of adipose tissue and development of thin, atrophic, hyperpigmented



Fig. 697.7 Erythematous, excoriated papules in actinic prurigo.



Fig. 697.8 Dyspigmentation and actinic keratoses in child with xeroderma pigmentosum.

skin, particularly over the face. Associated features include stunted growth; dwarfism; microcephaly; progressive neurologic dysfunction (caused by leukodystrophy); mental retardation; progressive dementia; distinct facies (aged look, pinched nose, sunken eyes, large protuberant ears); long limbs; disproportionately large hands and feet; cool and cyanotic extremities; carious teeth; unsteady gait with tremor; limitation of joint mobility; progressive deafness; cataracts; retinal degeneration; optic atrophy; decreased sweating and tearing; and premature graying of the hair. Complications include diabetes and hepatic or renal impairment. Diffuse extensive demyelination of the peripheral and central nervous systems ensues, and patients generally die of atheromatous vascular disease or infections (especially pneumonia) before the third decade. There are two types of Cockayne syndrome. **Type I (*CSA* gene)** is less severe than **type II (*CSB* gene)**. Patients may have xeroderma pigmentosum–Cockayne syndrome overlap, which is phenotypically more like Cockayne syndrome and is due to genetic variants in *XPB, XPD,* or *XPG* genes. Photosensitivity in Cockayne syndrome is a result of deficient nucleotide excision repair of UV-induced damage, specifically within actively transcribing regions of DNA (transcription-coupled DNA repair). The etiology of neurologic and other associated features remains unclear; however, evidence points toward a mitochondriopathy. The syndrome is distinguished from progeria (see Chapter 111) by the presence of photosensitivity and ocular abnormalities and from xeroderma pigmentosum by the fact that patients with Cockayne syndrome do not develop sun-induced pigmentation or increased risk of skin cancers. Diagnosis is accomplished by genetic testing and performing various tests on cultured fibroblasts. The mainstay of treatment for the photosensitivity of Cockayne syndrome is strict sunlight avoidance and protective measures.

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum is a rare autosomal recessive disorder that results from a defect in nucleotide excision repair. Eight genetic groups have been recognized on the basis of each group's separate defect in ability to repair (xeroderma pigmentosum A through G) or replicate (xeroderma pigmentosum V [variant]) damaged DNA. The wavelength of light that induces the DNA damage ranges from 280 to 340 nm. Skin changes are first noted during infancy or early childhood in sun-exposed areas, though lesions may occur at other sites, including the scalp. The skin lesions consist of erythema, scaling, bullae, crusting, ephelides (freckles), telangiectasia, keratoses (Fig. 697.8), basal and squamous cell carcinomas, and malignant melanomas. Interestingly, although most patients experience exaggerated acute sunburn reactions after minimal UV exposure, up to half of affected patients do not and instead develop progressive freckling. This difference in presentation depends on genetic subtype. Ocular manifestations include photophobia, lacrimation, blepharitis, symblepharon, keratitis, corneal opacities, tumors of the lids, and possible eventual blindness. Neurologic abnormalities such as cognitive deterioration and sensorineural deafness develop in approximately 20% of patients.

This disease is a serious mutilating disorder, and the life span of an affected patient is often brief. Affected families should have genetic counseling. Xeroderma pigmentosum is detectable in cells cultured from amniotic fluid or DNA analysis of chorionic villous samples. Cultured skin fibroblast tests and genetic testing after birth also confirm diagnosis. Affected children should be totally protected from sun exposure; protective clothing, sunglasses, and opaque broad-spectrum sunscreens should be used even for mildly affected children. Light from unshielded fluorescent bulbs and sunlight passing through glass windows (including vehicle windows) are also harmful; thus applied window films are recommended. Early detection and removal of malignancies is mandatory, and oral isotretinoin may be used to prevent nonmelanoma skin cancers. Average age of death of these patients is 32 years. There is crossover between several subtypes of xeroderma pigmentosum and both Cockayne syndrome and trichothiodystrophy.

ROTHMUND-THOMSON SYNDROME

Rothmund-Thomson syndrome is also known as **poikiloderma congenitale** because of the striking skin changes (Fig. 697.9). It is inherited as an autosomal recessive trait. Pathogenic genetic variants in the *RECQL4* gene, which encodes a DNA helicase involved in repair and replication of DNA and telomeres, are found in approximately 65% of patients. The other genetic variants causing Rothmund-Thomson syndrome are unknown. Skin changes are noted as early as 3 months of age and begin on the face. Plaques of erythema and edema appear in a butterfly distribution and on the forehead, ears, neck, dorsal portions of the hands, extensor surfaces of the arms, and buttocks. These are replaced gradually by **poikiloderma** (reticulated, atrophic, hyperpigmented, and hypopigmented telangiectatic patches or plaques). Palmoplantar hyperkeratosis develops in one third of patients. Light sensitivity is present in many cases, and exposure to the sun may provoke formation of bullae. Areas of involvement, however, are not strictly photodistributed. Short stature; small hands and feet; sparse eyebrows, eyelashes, and pubic and axillary hair and sparse, fine, prematurely gray scalp hair or alopecia; dystrophic nails; various tooth and skeletal abnormalities; and hypogonadism are common. One of the more distinguishing features is an increased incidence of juvenile subcapsular bilateral cataracts. Most patients have normal mental development. Keratoses and later squamous cell carcinomas may develop on exposed skin. The most worrisome association is osteosarcoma, which occurs in 30% of those patients with Rothmund-Thomson syndrome and *RECQL4* pathogenic genetic variants. Genetic testing aids in diagnosis. Management of dermatologic findings begins with sun avoidance and protection behaviors, and telangiectatic lesions have been shown to respond to pulsed dye laser therapy. In the absence of malignancy, life expectancy is normal.



Fig. 697.9 Poikiloderma on the arm of an infant with Rothmund-Thomson syndrome.

BLOOM SYNDROME

Bloom syndrome is inherited in an autosomal recessive manner, most commonly in the Ashkenazi Jewish population. It is caused by pathogenic genetic variants in the *BLM/RECQL3* gene encoding a DNA helicase. Patients are sensitive to UV radiation, with increased rates of chromosomal breaks and sister chromatid exchanges. Erythema and telangiectasia develop during infancy in a butterfly distribution on the face after exposure to sunlight. A bullous eruption on the lips and telangiectatic erythema on the cheeks, hands, and forearms may develop. Café-au-lait spots and hypopigmented macules may be present. Intrauterine growth deficiency developing into short stature, referred to as "proportionate dwarfism," and a distinctive facies consisting of a prominent nose and ears and a small, narrow face are generally found. Intellect is average to low average. Immunodeficiency is seen in all patients, manifesting as recurrent ear and pulmonary infections. Gastrointestinal malabsorption, gastroesophageal reflux, and hypogonadism are common. Affected children have an unusual tendency to develop both solid tumors (especially of the skin) and lymphoreticular malignancies, which often result in death during childhood or early adulthood. Sister chromatid exchange analysis is generally performed to confirm diagnosis. The only effective measures to reduce skin disease are sun protection and avoidance.

HARTNUP DISEASE

See Chapter 105.5.

Hartnup disease is a rare inborn error of metabolism with autosomal recessive inheritance. Neutral amino acids, including tryptophan, are not transported across the brush border epithelium of the intestine and kidneys due to a pathogenic variant in the *SLC6A19* gene encoding the transporter. This results in deficiency of nicotinamide synthesis and causes a photo-induced **pellagra-like syndrome**. The urine contains increased amounts of monoamine monocarboxylic amino acids, distinguishing Hartnup disease from dietary pellagra. Cutaneous signs, which precede neurologic manifestations, initially develop during the early months of life. An eczematous, occasionally vesiculobullous, eruption occurs on the face and extremities in a glove-and-stocking photodistribution. Hyperpigmentation and hyperkeratosis may supervene and are intensified by further exposure to sunlight. Episodic flares may be precipitated by febrile illness, sun exposure, emotional stress, and poor nutrition. In most cases, mental development is normal, but some patients display emotional instability and episodic cerebellar ataxia. Neurologic symptoms are fully reversible. Administration of nicotinamide and protection from sunlight result in improvement of both cutaneous and neurologic manifestations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 698
Diseases of the Epidermis

698.1 Psoriasis

Julie M. Dhossche and Yvonne E. Chiu

Psoriasis affects 2–4% of the U.S. population, and pediatric psoriasis accounts for approximately one third of all cases.

ETIOLOGY/PATHOGENESIS

Psoriasis is an inflammatory autoimmune-related disease characterized by inflammation and keratinocyte proliferation (Fig. 698.1). Within the dermis, dendritic cells are activated by self-antigens and release cytokines such as interferon-γ, tumor necrosis factor, and interleukin (IL)-12, IL-17, IL-22, and IL-23, which recruit T cells. Once activated, the T cells release cytokines that induce proliferation and abnormal differentiation of epidermal keratinocytes; in turn, more cytokines are produced to perpetuate the cycle. Psoriasis has a complex multifactorial genetic basis. Family history of psoriasis is present in ~50% of patients, typically a first-degree relative. The major psoriasis-susceptibility gene *(PSORS1)* is human leukocyte antigen (HLA)-CW*0602, encoding a class I major histocompatibility complex protein involved in recognition of self-antigens. Numerous other psoriasis susceptibility genes have been identified.

Factors contributing to disease onset/flares in some patients include bacterial and viral infections, trauma, physical or emotional stress, tobacco use/secondhand exposure, and certain medications.

CLINICAL MANIFESTATIONS

This common chronic skin disorder is first evident within the first 2 decades of life for approximately 30% of affected individuals. **Plaque psoriasis**, the most common (>80%) subtype, is characterized by erythematous papules that coalesce to form plaques with sharply demarcated, irregular borders (Fig. 698.2A-D). If they are unaltered by treatment, a thick silvery or yellow-white scale (resembling mica) develops (see Fig. 698.2A). Removal of the scale may result in pinpoint bleeding **(Auspitz sign)**. The **Koebner phenomenon**, in which new lesions appear at sites of trauma, is a valuable diagnostic feature. Lesions may occur anywhere, but preferred sites are the scalp, knees, elbows, umbilicus, superior intergluteal fold, genitalia, and ear canal. Nail involvement, a valuable diagnostic sign, is characterized by pitting of the nail plate, detachment of the plate (onycholysis), yellowish-brown subungual discoloration, and accumulation of subungual debris (see Fig. 698.2G, H, and M). Plaques are generally asymptomatic; however, pruritus is more common in children than in adults.

Guttate psoriasis, a variant that occurs predominantly in children, is characterized by an acute eruption of many oval or round papules smaller than 1.5 cm that are morphologically identical to the larger plaques of psoriasis (see Fig. 698.2N-Q). Sites of predilection are the trunk, face, and proximal portions of the limbs. The onset usually follows a few weeks after a **streptococcal** infection such as pharyngitis; thus throat culture and serologic titers should be obtained. Guttate psoriasis has also been observed after perianal streptococcal infection, viral infections, sunburn, and withdrawal of systemic corticosteroid therapy or tumor necrosis factor (TNF)-α inhibitors. Clinical course ranges from spontaneous resolution to chronic disease.

Pustular psoriasis is a multisystem autoinflammatory disease characterized by recurrent episodes with the sudden onset of fever, malaise, extracutaneous organ involvement, and a diffuse erythematous-pustular exanthema. It may be associated with plaque psoriasis in some patients; unregulated cytokine production as a result of pathogenic genetic variants in the *IL36RN, AP1S3,* and *CARD14* genes are implicated in a subset of patients.

Psoriasis is rare in infants but may be severe and recalcitrant and may pose a diagnostic problem. Psoriatic diaper rash is a common

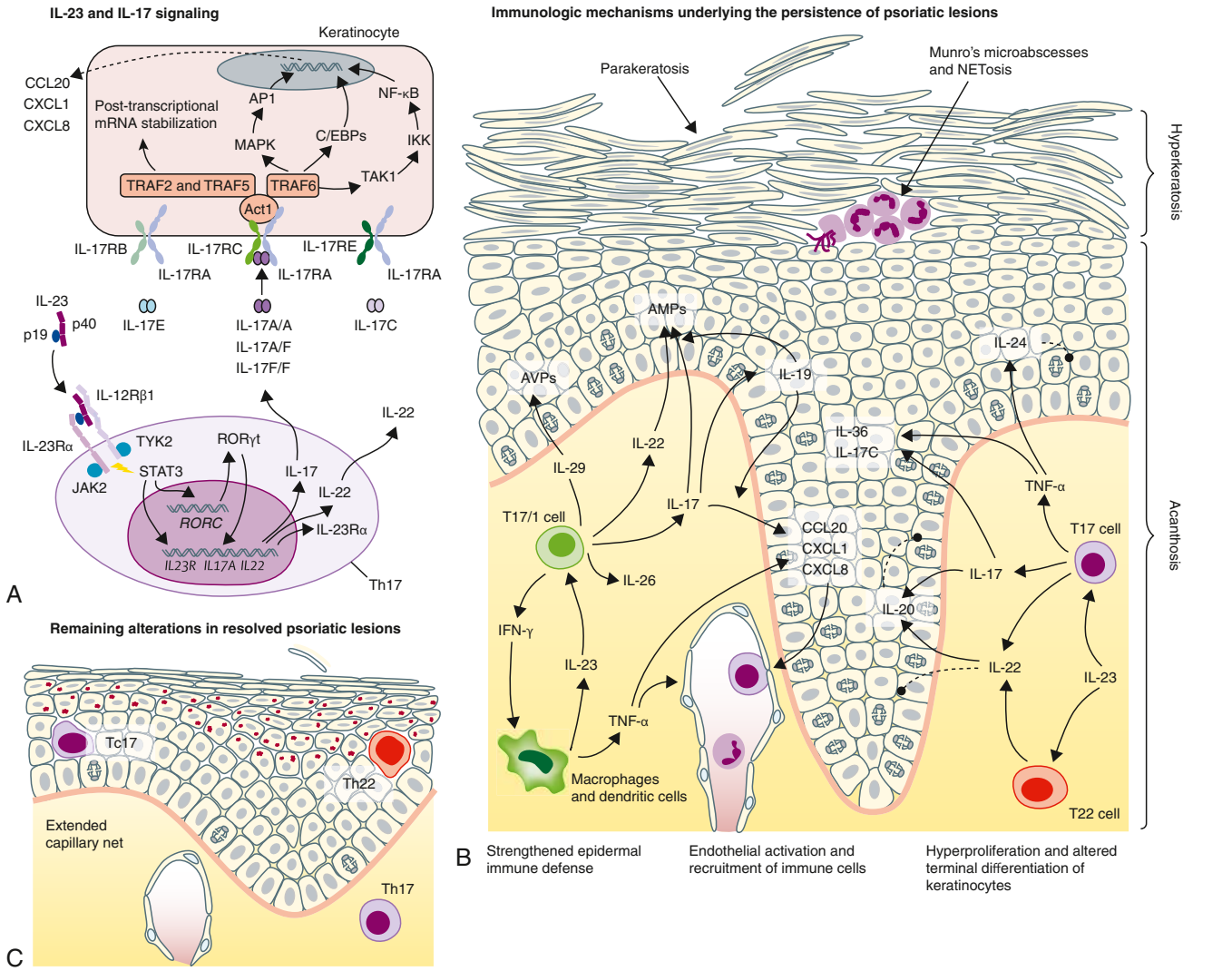

Fig. 698.1 Immune pathogenesis of psoriasis. The IL-23 and IL-17 pathway in psoriasis with elements of their signaling. **A**, IL-23 acts on Th17 cells via the transmembrane receptor complex composed of IL-12Rβ1 and IL-23Rα and intracellular JAK–STAT signaling and induces the expression of IL-17A, IL-17F, and IL-22, which act on epithelial cells through distinct receptor and signaling pathways. **B**, In psoriatic skin IL-23 is essential for the stabilization of the phenotype of IL-17–producing lymphocytes, activates these cells, and enhances their cytokine production and pathogenicity. IL-17 mostly acts synergistically with other cytokines, leading to massive activation of immunologic pathways and cytokines such as IL-22, IL-20, and IL-24, promoting the epidermal changes. **C**, After successful antipsoriatic treatment, potentially pathogenetic T cells remain in the resolved psoriatic skin. Blood capillaries extend during psoriatic inflammation by angiogenic signals and recede slowly. AMP, antimicrobial protein; AVP, antiviral protein; C/EBP, CCAAT-enhancer-binding protein; T17, Th17 and Tc17; T1, Th1 and Tc1; T22, Th22 and Tc22; Th, T helper cell; Tc, cytotoxic T cell; NETosis, activation and release of neutrophil extracellular traps. *(From Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet. 2021;397:754–766, Fig. 2.)*

presentation in children younger than 2 years old. Other rare forms include psoriatic erythroderma (>90% body surface area involvement), linear psoriasis, palmoplantar psoriasis, and inverse psoriasis (occurring in intertriginous areas). Children may also develop juvenile psoriatic arthritis, with or without skin lesions.

Psoriasis may be triggered by mild trauma (piercing, tattoos), sun or chemical burns, medications (β blockers, NSAIDs), or HIV infection. Comorbid conditions include arthritis, Crohn disease, depression, and nonalcoholic fatty liver disease.

DIFFERENTIAL DIAGNOSIS

Psoriasis is a clinical diagnosis. The differential diagnosis of plaque-type psoriasis includes nummular dermatitis, tinea corporis, seborrheic dermatitis, postinfectious arthritis syndromes, and pityriasis rubra pilaris. Scalp lesions may be confused with seborrheic dermatitis, atopic dermatitis, or tinea capitis. Diaper area psoriasis may mimic seborrheic dermatitis, eczematous diaper dermatitis, perianal streptococcal disease, candidiasis, or allergic contact dermatitis. Guttate psoriasis can be confused with viral exanthems, secondary syphilis, pityriasis rosea, and pityriasis lichenoides chronica (PLC). Nail psoriasis must be differentiated from onychomycosis, lichen planus, and other causes of onychodystrophy.

PATHOLOGY

When the diagnosis is in doubt, histopathologic examination of an untreated lesion can be helpful. Characteristic changes of psoriasis include parakeratosis, acanthosis, elongated rete ridges, neutrophilic infiltrate in the epidermis sometimes forming microabscesses, dilated dermal blood vessels, and lymphocytic infiltrate in the dermis.



Fig. 698.2 Clinical manifestations of psoriasis. Typical erythematous plaques with silvery scales (**A**) can be scattered (**B**, psoriasis nummularis), cover larger areas of the skin (**C**, psoriasis geographica), or affect the entire body surface (**D**, erythrodermic psoriasis). Scalp involvement might be accompanied by nonscarring alopecia (**E**). Psoriatic arthritis affects up to 30% of all patients (**F**, thumb interphalangeal joint). Nail changes are frequent and range from pitting and yellow or brown discoloration (**G**) to complete dystrophy (**H**). Psoriasis inversa occurs in intertriginous areas and is usually devoid of scales (**I**). Pustular psoriasis might occur in a generalized form (**J** and **K**) or localized (**L**, palmoplantar type and **M**, acrodermatitis continua suppurativa type). In children, the onset as guttate psoriasis might follow streptococcal infection of the upper respiratory tract (**N**) and affect any site of the body (**O-Q**). *(From Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386:983–992, Fig. 1, p. 984.)*

TREATMENT

The therapeutic approach varies with the age of the child, type of psoriasis, sites of involvement, and extent of the disease. Physical and chemical trauma to the skin should be avoided as much as possible to prevent Koebner-response lesions. The treatment of psoriasis should be viewed as a four-tier process. Efficacy varies with each therapy (Table 698.1).

The first tier is topical therapy. The first-line topical agents for lesions on the body are emollients, vitamin D analogs (calcipotriene or calcitriol, although calcitriol is less irritating for children), and mid- to high-potency corticosteroids (see Chapter 687). A proprietary formulation containing both calcipotriene and betamethasone dipropionate (a high-potency topical corticosteroid) exists in ointment and solution forms. The preparation that is least potent but effective should be applied twice a day. Second-line topical options for lesions on the body include retinoids (tazarotene), tar preparations, anthralin, and keratolytics (salicylic acid or urea). Facial or intertriginous lesions may be treated with low-potency topical corticosteroids and/or topical vitamin D analogs or calcineurin inhibitors as corticosteroid-sparing agents. For scalp lesions, applications of a phenol and saline solution (e.g., Baker Cummins P&S liquid) or salicylic acid shampoo followed by a tar shampoo are effective in the removal of scales. A high-potency to superpotency corticosteroid in a foam, solution, or lotion base may be applied when the scaling is diminished. Nail lesions are difficult to treat topically; the first-line approach is a high-potency topical corticosteroid to the proximal nail fold.

The second tier of therapy is phototherapy. Narrow-band ultraviolet B (311 nm; NB-UVB) is an effective and well-tolerated alternative in pediatric patients with plaque and guttate psoriasis poorly controlled with topical treatments. Excimer (308 nm) laser UVB irradiation may be used for localized treatment-resistant plaques. Exposure to natural sunlight is often effective for less severe psoriasis.

The third tier is systemic therapy for children with moderate to severe, recalcitrant or generalized psoriasis. Methotrexate (0.2-0.7 mg/kg/wk to a maximum of 25 mg/week) is the first-line systemic agent for children; other options include oral retinoids (0.5-1.0 mg/kg/day to a maximum of 50 mg/day) and cyclosporine (modified formulation, 3-5 mg/kg/day). Oral retinoids may be cautiously combined with phototherapy, although doses may need to be decreased because of the photosensitizing effects of the medication. Oral retinoids are also considered for generalized pustular and diffuse guttate psoriasis.

Biologic response modifiers are increasingly used in place of traditional oral agents. TNF-α inhibitors such as etanercept, infliximab, and adalimumab have increasingly been used for pediatric psoriasis. Etanercept has FDA approval for those 4 years and older with psoriasis. One study reported a significant improvement in psoriatic lesions at 12 weeks with 57% versus 11% of patients receiving etanercept or placebo, respectively, achieving a 75% improvement in Psoriasis Area and Severity Index-75 (PASI-75, a metric to evaluate psoriasis severity). Ustekinumab, a human monoclonal antibody that blocks IL-12 and IL-23 and their cell-surface receptors, is approved for those 6 years and older with moderate to severe psoriasis. Biologic IL-17 inhibitors

Table 698.1 Recommendations for Pediatric Psoriasis

RECOMMENDATION	STRENGTH OF RECOMMENDATION	LEVEL OF EVIDENCE
Topical corticosteroids are recommended for the treatment of pediatric psoriasis as an off-label therapy	B	II
The use of ultra-high-potency topical corticosteroids as monotherapy is effective for short-term treatment of localized psoriasis in pediatric patients	C	II
Tacrolimus 0.1% ointment is recommended for off-label use as monotherapy for pediatric psoriasis of the face and genital region	C	II-III
Calcipotriene/calcipotriol is recommended as a treatment option for childhood plaque psoriasis	B	II
Because of the theoretical risk of increased calcium absorption and systemic effects of hypercalcemia, occlusion of calcipotriene/calcipotriol applied to large body surface areas is not recommended	B	III
Monitoring of vitamin D metabolites may be considered during calcipotriene/calcipotriol therapy when applied to a large body surface area	B	I-II
The combination of calcipotriol/betamethasone dipropionate ointment applied once daily for up to 4 weeks at a time is recommended as a safe and effective treatment for children ages 12 yr and older with mild to moderate plaque psoriasis	B	I-II
The combination of calcipotriol/betamethasone dipropionate suspension applied once daily for up to 8 wk at a time is recommended as a safe and effective treatment for children ages 12 yr and older with mild to moderate plaque psoriasis of the scalp	B	II
The use of emollients (at the same time or different time of day) with topical calcipotriene may be considered to reduce irritation and enhance the efficacy of calcipotriene	C	III
Rotational therapy with topical vitamin D analogues, topical calcineurin inhibitors, emollients, tar-based therapies, and topical corticosteroids may be considered in children as steroid-sparing regimens that may reduce potential adverse effects from overreliance on topical steroid therapy	C	II
The off-label use of topical tazarotene may be recommended as monotherapy or in combination with topical corticosteroids for the treatment of localized pediatric skin or nail psoriasis	C	III
Long-term use (12 wk or longer) of topical anthralin is recommended for the treatment of mild to moderate psoriasis. Short-contact anthralin protocols are recommended to limit adverse effects	B	II
Coal tar preparations can be used as a monotherapy or combined with other topical therapies for the treatment of pediatric psoriasis	C	II-III
The use of coal tar preparations in conjunction with phototherapy is effective for the treatment of psoriasis in children but may be limited by the theoretical long-term risk of carcinogenesis	B	II-III
NB-UVB is recommended as a treatment option for moderate to severe pediatric plaque and guttate psoriasis	B	II-III
The use of excimer laser or PUVA therapy in children with psoriasis may be efficacious and well tolerated but has limited supporting evidence	C	III
Methotrexate is recommended as an effective systemic therapy for moderate to severe plaque psoriasis and other psoriasis subtypes in children	B	II-III
Methotrexate is recommended as an effective systemic therapy for pustular psoriasis in children	B	III
Methotrexate weight-based dosing is recommended in younger children, ranging from 0.2 to 0.7 mg/kg/wk (maximum, 25 mg/wk)	B	III
Folic acid supplementation daily or six times weekly during treatment with methotrexate is recommended	B	II
Routine clinical and laboratory monitoring is recommended before and during treatment with methotrexate	B	III
Cyclosporine is recommended as an effective systemic therapy for moderate to severe plaque psoriasis in children	B	II-III
Cyclosporine is recommended as an effective systemic therapy for moderate to severe pustular psoriasis in children	B	III
Cyclosporine is recommended for short-term crisis management of severe or unstable plaque, erythrodermic, or pustular psoriasis until the patient can be transitioned to a medication appropriate for long-term use	C	III
Routine blood pressure clinical and laboratory monitoring is recommended during therapy with cyclosporine	A	III
Modified cyclosporine (for microemulsion in capsules or solution) is recommended for use and is not interchangeable with unmodified forms of cyclosporine	C	III

Continued

Table 698.1 Recommendations for Pediatric Psoriasis—cont'd

RECOMMENDATION	STRENGTH OF RECOMMENDATION	LEVEL OF EVIDENCE
Acitretin is recommended as an effective, nonimmunosuppressive systemic therapy for children with extensive guttate or moderate to severe (ideally thin plaque) psoriasis vulgaris at a dosage of 0.1-1 mg/kg/d	B	II
Acitretin is recommended as an effective systemic therapy for pustular psoriasis in children	B	II-III
Acitretin combined with NB-UVB therapy may be synergistic for plaque and pustular psoriasis in childhood and allows for a reduction in dosing of both agents	C	III
Acitretin may be combined with other systemic therapies such as methotrexate or cyclosporine, or biologics, depending on the individual clinical situation	C	III
Routine clinical and laboratory monitoring is recommended during therapy with acitretin	C	III
Fumaric acid esters may be considered as a potentially effective alternative therapy for pediatric patients with moderate to severe psoriasis who are candidates for systemic therapy	C	II-III
Clinical and laboratory monitoring is recommended during treatment with fumaric acid esters	C	III
Etanercept is recommended as an effective therapy for moderate to severe psoriasis in children 6 yr of age and older	A	I-III
Etanercept dosing is typically once weekly and is dosed subcutaneously at 0.8 mg/kg with a maximum of 50 mg weekly	A	I, III
Adalimumab is recommended for off-label use as an effective therapy in children and adolescents with moderate to severe psoriasis	B	I, III
The dose of adalimumab is 0.8 mg/kg (maximum, 40 mg) at weeks 0 and 1 and then is given every other week; adalimumab administered at a dose of 0.8 mg/kg is more efficacious than at a dose of 0.4 mg/kg	B	I
Infliximab can be recommended as monotherapy or in combination with methotrexate for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening	C	III
The starting dose of infliximab is an infusion of 5 mg/kg administered on weeks 0, 2, and 6 and then every 8 weeks	C	III
Ustekinumab is recommended as an effective therapy for adolescents 12 yr and older with moderate to severe plaque psoriasis	A	I, III
Ustekinumab can be used as an effective therapy for pediatric patients younger than 12 yr old with moderate to severe plaque psoriasis	C	III
Ustekinumab is given at weeks 0, 4, and 16 and then every 12 weeks with weight-based dosing as follows: 0.75 mg/kg if < 60 kg, 45 mg if 60 to 100 kg, and 90 mg if > 100 kg	B	I
Biologics may be safely combined with topical corticosteroids, with or without a vitamin D analogue, to augment effectiveness for the treatment of moderate to severe plaque psoriasis	C	III
The major risk for biologics in children is injection site reaction, but patients should be monitored for their increased risk of infection	B	II

Data from Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol.* 2020;82(1):161–201, Tables XX–XLVIII, pp. 173–189.

secukinumab and ixekizumab are also FDA approved for those 6 and older. The safety and efficacy data of these biologic agents show they are generally well tolerated and efficacious in the treatment of moderate to severe plaque psoriasis. The primary risk is injection site reaction. A small-molecule inhibitor of phosphodiesterase 4, apremilast, is also used for pediatric psoriasis. IL-23 inhibitors may also have a role in the treatment of severe disease and are being studied in pediatric populations.

PROGNOSIS

Prognosis is best for children with limited disease. Psoriasis is a lifelong disease characterized by remissions and exacerbations. Arthritis or various eye diseases may be extracutaneous complications. Metabolic and cardiovascular disorders also occur with increased frequency in patients with psoriasis. For example, an increasing degree of obesity and the associated metabolic syndrome (hyperglycemia, hyperlipidemia, and hypertension) correlates with psoriasis severity. Patients with psoriasis also have increased rates of stroke, myocardial infarction, and other vascular diseases later in adult life. A proposed mechanism involves the systemic proinflammatory state induced by both psoriasis and these associated conditions, although the direction of causality remains unclear. Furthermore, children suffering from psoriasis have a greater risk of taking psychotropic medications for anxiety or depression and are more likely to report impairment in quality of life due to their chronic disease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.2 Pityriasis Lichenoides

Julie M. Dhossche and Yvonne E. Chiu

Pityriasis lichenoides encompasses a disease spectrum ranging from PLC to pityriasis lichenoides et varioliformis acuta (PLEVA; Mucha-Habermann disease). The designation of pityriasis



Fig. 698.3 Widespread plaques with fine scale in pityriasis lichenoides chronica.



Fig. 698.4 Necrotic lesion with erythematous halo in pityriasis lichenoides et varioliformis acuta.

lichenoides as acute or chronic refers to the morphologic appearance of the lesions rather than to the duration of the disease. No correlation is found between the type of lesion at the onset of the eruption and the duration of the disease. Many patients have both acute and chronic lesions simultaneously, and transition of lesions from one form into another occurs occasionally. As a result, some authors advocate using pityriasis lichenoides as the general diagnosis rather than differentiating between PLC and PLEVA. Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare subtype of PLEVA that is more severe and potentially life-threatening.

ETIOLOGY/PATHOGENESIS

Two main theories exist for the etiology of pityriasis lichenoides. The first is that it arises in a genetically susceptible individual as a hypersensitivity reaction to an infection. The second is that it represents a monoclonal T-cell lymphocytic proliferation on the pathway to cutaneous T-cell dyscrasia.

CLINICAL MANIFESTATIONS

Pityriasis lichenoides most commonly manifests in the second and third decades of life; 30% of cases manifest before age 20 years, with peaks of incidence at 5 and 10 years of age. The overall eruption persists for months to years with a tendency to eventually remit.

PLC manifests gradually as generalized, multiple, brown-red papules to plaques that are covered by a fine grayish scale (Fig. 698.3). Lesions may be asymptomatic or may cause minimal pruritus and occasionally become vesicular, hemorrhagic, crusted, or superinfected. Individual papules become flat and brownish in 2-6 weeks, ultimately leaving hyperpigmented or hypopigmented macules and patches. Scarring is unusual. Various stages of lesions are present, most commonly on the trunk and extremities and generally spare the face, palmoplantar surfaces, scalp, and mucous membranes.

PLEVA manifests as an abrupt eruption of numerous 2- to 3-mm papules that have a vesiculopustular and then a purpuric center, are covered by a dark adherent hemorrhagic or necrotic crust, and are surrounded by an erythematous halo (Fig. 698.4). Constitutional symptoms, such as fever, malaise, headache, and arthralgias, may be present for 2-3 days after the initial outbreak. Lesions are distributed diffusely on the trunk and extremities, as in PLC. Individual lesions heal within a few weeks, sometimes leaving a varioliform scar, and successive crops of papules produce the characteristic polymorphous appearance of the eruption, with lesions in various stages of evolution.

FUMHD manifests as high fever and ulceronecrotic nodules up to a few centimeters in diameter, which are most common on the anterior trunk and flexor surfaces of the proximal upper extremities. Histopathology of lesions is consistent with PLEVA. Hemorrhagic bullae, mucosal ulcers, arthritis, cardiomyopathy, vasculitis, abdominal complaints, hematologic abnormalities (megaloblastic anemia, pancytopenia, and diffuse intravascular coagulation), and superinfection of cutaneous lesions with *Staphylococcus aureus* may also develop. These patients may have a history of previous PLEVA diagnosis. Although there is no reported standardized treatment and there have been reports of fatalities, typically the ulceronecrotic lesions heal with hypopigmented scarring in a few weeks.

PATHOLOGY

PLC histologically shows a parakeratotic, thickened corneal layer; epidermal spongiosis; a superficial perivascular infiltrate of macrophages and predominantly CD8 lymphocytes that may extend into the epidermis; and small numbers of extravasated erythrocytes in the papillary dermis.

The histopathologic changes of PLEVA and FUMHD reflect their more severe nature. Intercellular and intracellular edema in the epidermis may lead to degeneration of keratinocytes. A dense perivascular mononuclear cell infiltrate, endothelial cell swelling, and extravasation of erythrocytes into the epidermis and dermis are additional characteristic features.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pityriasis lichenoides includes guttate psoriasis, pityriasis rosea, drug eruptions, secondary syphilis, viral exanthems, lymphomatoid papulosis, and lichen planus. The chronicity of pityriasis lichenoides helps preclude pityriasis rosea, viral exanthems, and some drug eruptions. A skin biopsy can help distinguish pityriasis lichenoides from other entities in the differential diagnosis.

TREATMENT

Pityriasis lichenoides should be considered a benign condition that does not alter the health of the child. A lubricant to remove excessive scaling may be all that is necessary if the patient is asymptomatic. If treatment is required, first-line agents are oral antiinflammatory antibiotics such as erythromycin (30-50 mg/kg/day to a maximum of 4000 mg/day for 2-3 months) or doxycycline for children >8 years. Topical corticosteroids (mid-potency, applied twice daily) and topical calcineurin inhibitors may help the pruritus and inflammation but do not alter the course of the disease. Phototherapy (NB-UVB) is the second-line treatment option. Methotrexate should be reserved for severely symptomatic cases. The rare FUMHD usually requires inpatient treatment; initially, systemic corticosteroids, methotrexate, intravenous immunoglobulin, or cyclosporine may be necessary, with eventual transition to another form of treatment, as mentioned earlier, once the disease improves and stabilizes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 698.5 Keratotic follicular plugs with surrounding erythema in keratosis pilaris.

698.3 Keratosis Pilaris

Julie M. Dhossche and Yvonne E. Chiu

Keratosis pilaris is a common papular eruption resulting from keratin plugging of hair follicles. It displays an autosomal dominant transmission with variable penetrance. Typical areas of involvement include the upper extensor surfaces of the arms and thighs, cheeks, and buttocks. The lesions may resemble gooseflesh; they are noninflammatory, scaly, follicular papules that do not coalesce. They are generally asymptomatic but may be pruritic. Irritation of the follicular plugs occasionally causes erythema surrounding the keratotic papules (Fig. 698.5). A subset of patients has keratosis pilaris associated with facial telangiectasia and ulerythema ophryogenes, a rare cutaneous disorder characterized by inflammatory keratotic facial papules that may result in scars, atrophy, and alopecia. Because the lesions of keratosis pilaris are associated with and accentuated by dry skin, they are often more prominent during the winter. Keratosis pilaris is more frequent in patients with atopic dermatitis and is most common during childhood and early adulthood, tending to subside in the third decade of life. Treatment of keratosis pilaris is optional. Measures to decrease pruritus include moisturization with a bland emollient. Regular applications of a 10–40% urea cream or an alpha-hydroxy acid preparation such as 12% lactic acid cream or lotion can improve the appearance of keratosis pilaris but may further contribute to pruritus and irritation. Therapy may improve the condition but does not cure it.

698.4 Lichen Spinulosus

Julie M. Dhossche and Yvonne E. Chiu

Lichen spinulosus is an uncommon disorder that occurs principally in children and more frequently in boys. The cause is unknown. The lesions consist of sharply circumscribed irregular plaques of spiny, keratotic, follicular plugs. Plaques may occur anywhere on the body and are often distributed symmetrically on the trunk, elbows, knees, and extensor surfaces of the limbs. Although sometimes erythematous or pruritic, the lesions are usually skin colored and asymptomatic.

Treatment is usually unnecessary. For patients who regard the eruption as a cosmetic defect, urea-containing lubricants (10–40%) are often effective in flattening the projections. The plaques usually disappear spontaneously after several months or years.

698.5 Pityriasis Rosea

Julie M. Dhossche and Yvonne E. Chiu

Pityriasis rosea is a common benign papulosquamous disorder typically affecting adolescents and young adults 15-30 years of age. The disease is more commonly seen in the winter and is usually self-limited.



Fig. 698.6 Herald patch and surrounding pityriasis rosea.

ETIOLOGY/PATHOGENESIS

The cause of pityriasis rosea is unknown; a viral agent is suspected, with a current focus on human herpesviruses 6 and 7. Supporting evidence for an infectious etiology includes the tendency for it to occur in (familial) case clusters, presence of a prodrome and seasonal variation, and infrequent recurrences, although the rash itself does not appear to be contagious.

CLINICAL MANIFESTATIONS

This benign, common eruption occurs most frequently in children and young adults. Although a prodrome of fever, malaise, arthralgia, and pharyngitis may precede the eruption, children rarely complain of such symptoms. A **herald patch** classically precedes the generalized eruption and may occur anywhere on the body. Herald patches are generally larger than other lesions and vary from 1 to 10 cm in diameter; they are annular in configuration and have a raised border with fine, adherent scales. Approximately 5-10 days after the appearance of the herald patch, a widespread, symmetric eruption involving mainly the trunk and proximal limbs becomes evident (Fig. 698.6). In the inverse form of pityriasis rosea, the face, scalp, and distal limbs may be preferentially involved. Lesions may appear in crops for several days. Typical lesions are oval or round, <1 cm in diameter, slightly raised, and pink to brown. The developed lesion is covered by a fine scale, which gives the skin a crinkly appearance. Some lesions clear centrally and produce a collarette of scale that is attached only at the periphery. Papular, vesicular, urticarial, hemorrhagic, large annular, and mucosal lesions are unusual variants. The long axis of each lesion is usually aligned with the cutaneous cleavage lines, a feature that creates the so-called **Christmas tree pattern** on the back. Conformation to skin lines is often more discernible in the anterior and posterior axillary folds and supraclavicular areas. The lesions most commonly are asymptomatic but may be mildly to severely pruritic. Duration of the eruption varies from 2 to 12 weeks, with self-resolution. After the eruption has resolved, postinflammatory hypopigmentation or hyperpigmentation may be pronounced, particularly in dark-skinned patients. These changes disappear in subsequent weeks to months.

DIFFERENTIAL DIAGNOSIS

The herald patch may be mistaken for tinea corporis, a pitfall that can be avoided if microscopic evaluation of a potassium hydroxide preparation of scrapings of the lesion is performed. The generalized eruption resembles a number of other diseases; secondary syphilis is the most important. Drug eruptions, viral exanthems, guttate psoriasis, PLC, and nummular dermatitis can also be confused with pityriasis rosea.

TREATMENT

Therapy is unnecessary for asymptomatic patients with pityriasis rosea. If scaling is prominent, a bland emollient may suffice. Pruritus may be suppressed by a lubricating lotion containing menthol and camphor or by an oral antihistamine for sedation, particularly at night, when itching may be troublesome. Occasionally, a mid-potency topical corticosteroid preparation may be necessary to alleviate pruritus. Exposure to natural sunlight and NB-UVB phototherapy may reduce disease duration and severity. Acyclovir has been used in some cases to treat symptoms and shorten duration.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.6 Pityriasis Rubra Pilaris

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The cause of pityriasis rubra pilaris remains unclear. Pityriasis rubra pilaris can be subdivided into six clinical subtypes based on age of onset, characteristics, and other features. Most cases are sporadic, but familial forms are commonly seen in the fifth subtype, with gain-of-function variants in the *CARD14* gene. The sixth subtype occurs in those with HIV infection. Some studies have indicated a role for TNF-α in disease development, whereas other hypotheses for causal factors include abnormal vitamin A metabolism, trauma, infections, immunosuppression, and UV light exposure.

CLINICAL MANIFESTATIONS

This rare inflammatory dermatosis is known for its variability in clinical presentation and course of disease. It often has an insidious onset with diffuse scaling and erythema of the scalp, which is indistinguishable from the findings in seborrheic dermatitis, and with thick hyperkeratosis of the palms and soles (Fig. 698.7A). Lesions over the elbows and knees are also common (see Fig. 698.7B), and generalized erythroderma develops in some patients. The characteristic primary lesion is a firm, dome-shaped, tiny, acuminate, pink to red papule, which has a central keratotic plug pierced by a vellus hair. Masses of these papules coalesce to form large, erythematous, sharply demarcated orange-pink plaques with overlying scale, within which islands of normal skin can be distinguished. Typical papules on the dorsum of the proximal phalanges are readily palpated. Gray plaques or papules resembling lichen planus may be found in the oral cavity. Dystrophic changes in the nails may occur and mimic those of psoriasis. Lesions are commonly pruritic. In childhood, the prognosis for eventual resolution is relatively good.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes ichthyosis, seborrheic dermatitis, keratoderma of the palms and soles, and psoriasis. The "Wong" variant of dermatomyositis may present with a pityriasis rubra pilaris–like eruption.

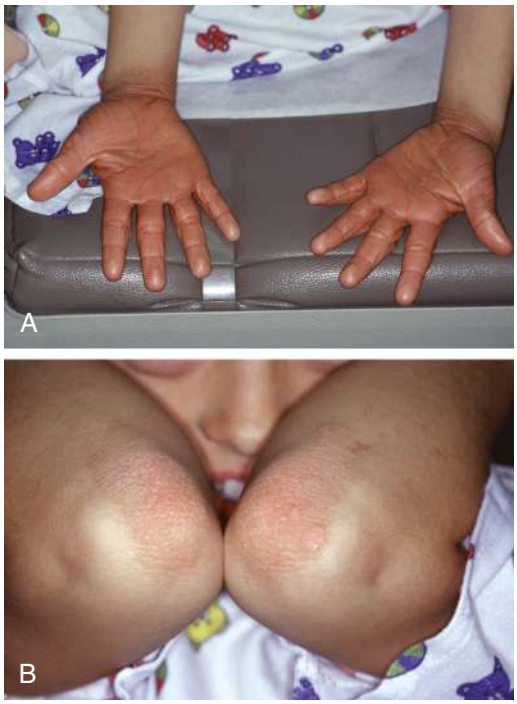

Fig. 698.7 Pityriasis rubra pilaris. A, Orange palmar hyperkeratosis. B, Elbow lesions.

HISTOLOGY

Skin biopsy revealing follicular plugging, epidermal acanthosis, perivascular infiltrate, checkerboard pattern of orthokeratosis and parakeratosis, and an intact granular layer may differentiate this condition from psoriasis and seborrheic dermatitis.

TREATMENT

The numerous therapeutic regimens recommended are difficult to evaluate because pityriasis rubra pilaris has a capricious course with exacerbations and remissions. Moisturization alone is useful in mild cases. Topical agents, such as mid- to high-potency corticosteroids, keratolytics (urea, salicylic acid), vitamin D analogs (calcipotriene), retinoids (tazarotene, tretinoin), and tar, are used in combination with systemic agents for widespread disease and as monotherapy for localized disease. When further treatment is necessary, oral retinoids (isotretinoin or acitretin 0.5-1 mg/kg/day; maximum daily dose of isotretinoin is 80 mg/day and acitretin is 50 mg/day) are used as first-line agents, whereas methotrexate is used as a second-line agent. Third-line treatment options include biologic TNF-α inhibitors, cyclosporine, azathioprine, and NB-UVB phototherapy. Ustekinumab and secukinumab have also been described as efficacious.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.7 Darier Disease (Keratosis Follicularis)

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

A rare genetic disorder, Darier disease is inherited as an autosomal dominant trait and is caused by pathogenic genetic variants in the *ATP2A2* gene. This gene encodes a cellular calcium pump, SERCA2, and dysfunction results in loss of adhesion between epidermal cells and abnormal keratinization.

CLINICAL MANIFESTATIONS

Onset usually occurs in late childhood and persists throughout life. Typical lesions are small, firm, skin-colored, warty papules that are not always follicular in location. The lesions eventually acquire yellow, malodorous, greasy crusts and coalesce to form large, gray-brown, vegetative plaques (Fig. 698.8). The scalp, face, neck, shoulders, chest, back, axillae, limb flexures, and groin are symmetrically involved. Papules, fissures, crusts, and ulcers may appear on the mucous membranes of the lips, tongue, buccal mucosa, pharynx, larynx, and vulva. Hyperkeratosis of the palms and soles and nail dystrophy with subungual hyperkeratosis and longitudinal red and white banding are variable features. Severe pruritus, secondary infection, offensive odor, and pain may occur. Several exacerbating triggers have been identified: sweating, UV light exposure, heat, friction, surgery, and infections; thus Darier disease has a chronic relapsing course that usually worsens in summertime.

HISTOLOGY

Histologic changes seen in Darier disease are diagnostic. Hyperkeratosis with keratin plugging, intraepidermal separation (acantholysis) with formation of suprabasal clefts, and dyskeratotic epidermal cells are characteristic features.

DIFFERENTIAL DIAGNOSIS

Darier disease is most likely to be confused with seborrheic dermatitis, acanthosis nigricans, flat warts, or Hailey-Hailey disease.

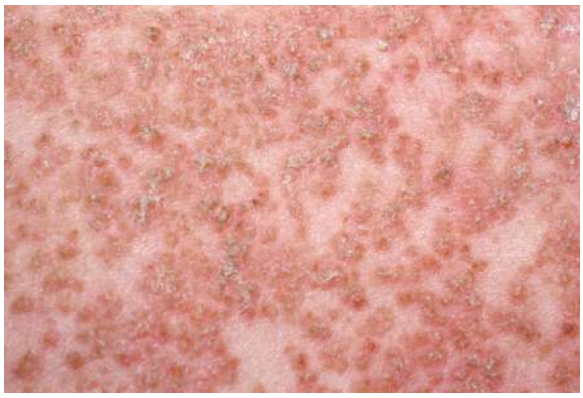

Fig. 698.8 Papules coalescing into a large plaque on the back of a patient with Darier disease.

TREATMENT

Treatment is nonspecific and begins with emollients and avoidance of triggers. First-line treatment for mild/localized disease is low- to mid-potency corticosteroids; second-line treatment are topical retinoids. Further treatment options include topical keratolytic agents (urea, lactic acid), antiseptic washes (triclosan, chlorhexidine gluconate, or bleach), or calcineurin inhibitors. More severe/generalized disease is treated with oral isotretinoin or acitretin (0.5-1.0 mg/kg/day for 3-4 months; maximum daily dose of isotretinoin is 80 mg/day and acitretin is 50 mg/day). Secondary infections are common and must be treated appropriately. Novel treatments currently being investigated include anti–IL-6 antibodies, cyclooxygenase-2 (COX2) inhibitors and miglustat (a glucosylceramide synthase inhibitor).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.8 Lichen Nitidus

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The etiology of lichen nitidus is unknown but has been linked to immune alteration.

CLINICAL MANIFESTATIONS

This uncommon, chronic, benign, papular eruption is characterized by minute (1-2 mm), flat-topped, shiny, firm papules of uniform size. The papules are most often skin-colored but may be pink or red. In darker-skinned individuals, they are usually hypopigmented (Fig. 698.9). Sites of predilection are the genitals, abdomen, chest, forearms, wrists, and inner aspects of the thighs. The lesions may be sparse or numerous and may form large plaques; careful examination usually discloses linear papules in a line of a scratch (Koebner phenomenon), a valuable clue to the diagnosis because it occurs in only a few diseases. Lichen nitidus occurs in all age-groups but is most prevalent in school-age children and young adults. Patients with lichen nitidus are usually asymptomatic and constitutionally well, although pruritus may be severe. The lesions may be confused with those of lichen planus, and lichen nitidus can rarely occur concurrently with lichen planus.

DIFFERENTIAL DIAGNOSIS

Widespread keratosis pilaris can also be confused with lichen nitidus, but the follicular localization of the papules and the absence of Koebner phenomenon in the former distinguish them. Verruca plana (flat warts), if small and uniform in size, may occasionally resemble lichen nitidus.



Fig. 698.9 Slightly hypopigmented, uniform papules of lichen nitidus.

HISTOLOGY

Although the diagnosis can be made clinically, a biopsy is occasionally indicated. The lichen nitidus papule consists of sharply circumscribed nests of lymphocytes and histiocytes in the upper dermis enclosed by clawlike epidermal rete ridges.

TREATMENT

The course of lichen nitidus spans months to years, but the lesions eventually involute completely. No treatment is necessary, but mid- to high-potency topical steroids may be used for pruritus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.9 Lichen Striatus

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Lichen striatus is hypothesized to be caused by a combination of a genetic predisposition present in a mosaic manner in the skin (following the lines of Blaschko) and an infectious trigger.

CLINICAL MANIFESTATIONS

A benign, self-limited eruption, lichen striatus consists of a continuous or discontinuous linear band of papules in a Blaschkoid distribution. The primary lesion is a flat-topped, hypopigmented or pink papule covered with fine scale. Aggregates of these papules form multiple bands or plaques. The papules are gradually replaced by hypopigmented macules, which may be the presenting lesion in some cases. The eruption evolves over a period of days or weeks in an otherwise healthy child, remains stationary for weeks to months, and finally remits without sequelae, usually within 2 years. Symptoms are usually absent, although some children complain of itching. Nail dystrophy may occur when the eruption involves the proximal nail fold and matrix (Fig. 698.10).

DIFFERENTIAL DIAGNOSIS

Lichen striatus is occasionally confused with other disorders. The initial plaque may resemble papular eczema or lichen nitidus until the linear configuration becomes apparent. Linear lichen planus and linear psoriasis are usually associated with typical individual lesions elsewhere on the body. Linear epidermal nevi are permanent lesions that often become more hyperkeratotic and hyperpigmented than those of lichen striatus.

TREATMENT

Treatment is not necessary and generally not very effective. A low-potency topical corticosteroid preparation or topical calcineurin



Fig. 698.10 Lichen striatus with nail dystrophy.

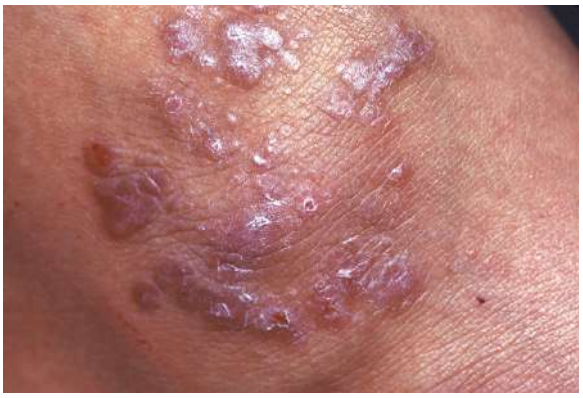

Fig. 698.11 Flat-topped, purple polygonal papules of lichen planus.

inhibitor can be used when pruritus is a problem in a patient with lichen striatus.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.10 Lichen Planus

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The cause of lichen planus is unknown, but an immune attack on the skin by cytotoxic T cells is postulated. A genetic predisposition may exist, and other proposed triggers include metal exposure, certain medications, liver disease, vaccinations (especially hepatitis B vaccination), and infections (especially hepatitis C virus).

CLINICAL MANIFESTATIONS

This is a rare disorder in young children and uncommon in older ones. The classic form of lichen planus is the most common subtype in children, often exhibiting an acute eruptive onset. The lesions erupt in an explosive fashion, much like a viral exanthem, and spread to involve most of the body surface. The primary lesion is a violaceous, sharply demarcated, polygonal papule with fine white lines (Wickham's striae) or scale on the surface. Papules may coalesce to form large plaques (Fig. 676.11). The papules are intensely pruritic, and additional papules are often induced by scratching (Koebner phenomenon) so that lines of them are detected. Sites of predilection are the flexor surfaces of the wrists, the forearms, the inner aspects of the thighs, and the ankles.

Hypertrophic, linear, bullous, atrophic, annular, follicular, erosive, ulcerative, and actinic forms of lichen planus may also occur in children. Characteristic lesions of mucous membranes consist of pinhead-size white papules that coalesce to form reticulated and lacy patterns on the buccal mucosa. Erosive ulcers are also common in the oral mucosa and may also involve the gastrointestinal tract. Nail involvement causes nail dystrophy. The disorder may persist for months to years, but self-resolution eventually occurs in most cases. Intense hyperpigmentation frequently persists for a long time after the resolution of lesions.

HISTOLOGY

The histopathologic findings in lichen planus are specific, consisting of hyperkeratosis, irregular acanthosis, wedge-shaped hypergranulosis, apoptotic keratinocytes in the lower epidermis and upper dermis, and basal cell degeneration with a bandlike lymphocytic infiltrate at the epidermal-dermal junction. Pigment incontinence is frequently seen. Biopsy is indicated if the diagnosis is unclear.

TREATMENT

Treatment is directed at alleviation of the intense pruritus and amelioration of the skin lesions. First-line treatment with a high-potency topical corticosteroid applied twice daily is effective for localized disease on the trunk or extremities; lesions on the face and genitals may be treated with low- to mid-potency corticosteroids. Alternatives to topical steroids include topical calcineurin inhibitors or vitamin D analogs. Thick lesions may require intralesional corticosteroid injection. Oral antihistamines (hydroxyzine) are often added for the pruritus. Short courses of systemic glucocorticoids or phototherapy (NB-UVB) are used as second-line approaches for rare cases of widespread, intractable lesions. Other medications with reported efficacy include oral retinoids (acitretin), dapsone, metronidazole, griseofulvin, and methotrexate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.11 Porokeratosis

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Porokeratoses are a group of uncommon dermatoses due to abnormal epidermal keratinization. Genetic variants in the mevalonate pathway with autosomal dominant transmission, chronic sun exposure (particularly with the disseminated superficial actinic form), and immunosuppression (particularly organ transplantation) may contribute.

CLINICAL MANIFESTATIONS

Porokeratosis is a rare, chronic, progressive disease of keratinization. The prototypical lesion is an atrophic papule or plaque with a surrounding ridge of hyperkeratosis, called *cornoid lamella.* Several forms have been delineated: solitary plaques, linear porokeratosis, hyperkeratotic lesions of the palms and soles, disseminated eruptive lesions, and superficial actinic porokeratosis. **Classic porokeratosis of Mibelli** begins in childhood and is more common in males. Sites of predilection are the limbs, face, genitals, mucous membranes, palms, and soles. The primary lesion is a small, keratotic papule that slowly enlarges peripherally so that the center becomes depressed, with the edge forming an elevated wall or collar (Fig. 698.12). The configuration of the plaque may be round, oval, or gyrate. The elevated border is split by a thin groove from which minute cornified projections protrude. The central atrophic area is yellow, gray, or tan and sclerotic, smooth, and dry, whereas the hyperkeratotic border is a darker gray, brown, or black. **Linear porokeratosis** is also more common in childhood and typically follows the lines of Blaschko. The disease is slowly progressive but relatively asymptomatic; some patients experience pruritus or pain.



Fig. 698.12 Large plaque of porokeratosis of Mibelli with raised border and depressed center.

HISTOLOGY

A skin biopsy is usually unnecessary but will disclose the characteristic cornoid lamella (plug of stratum corneum cells with retained nuclei), which is responsible for the invariable linear ridge of the lesion. The granular layer is absent beneath the cornoid lamella.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of porokeratosis includes warts, epidermal nevi, lichen planus, granuloma annulare, tinea corporis, nummular eczema, pityriasis rosea, and elastosis perforans serpiginosa.

TREATMENT

No treatment is uniformly successful; thus therapeutic decisions depend largely on lesion size, location, symptoms, and patient preference. Most lesions are asymptomatic and do not require any intervention; however, when treatment is necessary, options include pharmacologic management (topical vitamin D analogs, topical retinoids, topical 5-fluorouracil, topical imiquimod, or oral retinoids [severe cases only]); destructive therapy (liquid nitrogen cryotherapy, electrodessication and curettage, or various lasers); and surgical removal. In general, the less invasive topical agents should be attempted first. Good UV protection should also be encouraged. Patients should be monitored for malignant transformation.

PROGNOSIS

Typically, the course of porokeratosis is slowly progressive, with an increase in size and number of individual lesions. Some cases undergo spontaneous resolution, and infrequently porokeratosis lesions may undergo malignant transformation into squamous cell carcinoma. At-risk lesions appear to be long-standing (average 33.5 years duration), large size, and location on limbs.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.12 Gianotti-Crosti Syndrome (Papular Acrodermatitis)

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The pathogenesis of Gianotti-Crosti syndrome, also known as *papular acrodermatitis,* is unclear, but an immunologic reaction to viral infections and immunizations has been postulated. Historically, the most common associations are with Epstein-Barr virus, hepatitis B virus (primarily in countries without routine childhood vaccination programs), coxsackievirus A16, and parainfluenza virus, as well as with many childhood immunizations.



Fig. 698.13 Numerous flat-topped, red papules in Gianotti-Crosti syndrome.

CLINICAL MANIFESTATIONS

This distinctive eruption is benign and predominantly occurs in children younger than 5 years old about 1 week after a viral illness. Cases are usually sporadic, but epidemics have been recorded. Skin lesions are monomorphic, firm, dusky, or coppery red papules ranging in size from 1 to 10 mm (Fig. 698.13), although there is considerable variation in lesion appearance between patients. The papules often have the appearance of vesicles; however, when opened, no fluid is obtained. The papules sometimes become hemorrhagic. Lines of papules **(Koebner phenomenon)** may be noted on the extremities after minor local trauma. The papules occur in crops and may become profuse and coalesce into plaques, forming a symmetric eruption on the face, ears, buttocks, and limbs, including the palms and soles. The trunk is relatively spared, as are the scalp and mucous membranes. The eruption is occasionally associated with malaise and low-grade fever but few other constitutional symptoms. The underlying viral infection may cause signs and symptoms, such as lymphadenopathy and hepatomegaly in patients with hepatitis B viremia. The eruption resolves spontaneously but may take up to 2 months. Some residual pigment change may occur but is not scarring.

HISTOLOGY

Skin biopsy in Gianotti-Crosti syndrome is not specific, being characterized by a dermal perivascular mononuclear cell infiltrate, capillary endothelial swelling, and epidermal spongiosis and parakeratosis.

DIFFERENTIAL DIAGNOSIS

Gianotti-Crosti syndrome can be confused with other viral exanthems, erythema infectiosum, lichen planus, erythema multiforme, and Henoch-Schönlein purpura (IgA vasculitis).

TREATMENT

The lesions are typically asymptomatic and resolve spontaneously, thus requiring no treatment. If present, pruritus may be relieved by emollients or calamine lotion. Mid-potency topical steroids may relieve pruritus but do not alter disease course. Sedating antihistamines at bedtime are also helpful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

698.13 Acanthosis Nigricans

Julie M. Dhossche and Yvonne E. Chiu

See also Chapter 65.

ETIOLOGY/PATHOGENESIS

The skin lesions of acanthosis nigricans may be genetic due to variants in the fibroblast growth factor receptor gene or acquired as a manifestation of insulin resistance. In familial cases, acanthosis nigricans



Fig. 698.14 Velvety hyperpigmentation of the axilla in acanthosis nigricans.



Fig. 698.15 Confluent and reticulated papillomatosis. Reticulate tan papules, patches, and plaques involving the epigastrium, inframammary areas, and sternum. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022, Fig. 23.34, p. 641.)*

is inherited as an autosomal dominant trait and develops in infancy. Insulin resistance with compensatory hyperinsulinism may lead to insulin binding to and activation of insulin-like growth factor receptors, promoting epidermal and fibroblast growth. Common causes of insulin resistance in children are obesity and diabetes mellitus, with acanthosis nigricans seen in >60% of children with a body mass index >98%. Other endocrinopathies such as pituitary hypogonadism, Cushing syndrome, polycystic ovarian syndromes, thyroid disease, and acromegaly, as well as certain drugs (insulin, oral contraceptives and other sex hormones, nicotinic acid, corticosteroids, and heroin) are also implicated as potential underlying causes. In the paraneoplastic form (rare in children), tumor-secreted growth factors induce acanthosis nigricans.

CLINICAL MANIFESTATIONS

Acanthosis nigricans is characterized by symmetric, hyperpigmented, velvety, hyperkeratotic plaques with exaggerated skin lines in intertriginous areas. The most common locations are the posterior neck and axillae (Fig. 698.14), but it is also seen in the inframammary areas, groin, inner thighs, and anogenital region. Before plaque development, patients notice a "dirty" appearance of affected skin that does not wash clean. Skin lesions remain asymptomatic unless maceration or secondary infection occurs. The clinical severity and histopathologic features of acanthosis nigricans correlate positively with the degree of hyperinsulinism and with the degree of obesity. The differential diagnosis includes **confluent and reticulated papillomatosis (CARP)**, Addison disease, pellagra, and erythrasma. CARP is an idiopathic disorder characterized by hyperpigmented papules with reticulation peripheral to the papules and is commonly distributed in the intermammary region (Fig. 698.15) and the epigastrium and upper back; less often it involves the axilla (Fig. 698.16) or neck and face.



Fig. 698.16 Confluent and reticulated papillomatosis. Hyperpigmented thin plaques, which were confluent centrally and reticulated at the periphery, were present in the bilateral axillae of this 16-year-old male patient who also had classic acanthosis nigricans affecting the neck folds. These axillary changes resolved completely with oral minocycline and lactic acid–containing emollients. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022, Fig. 23.35, p. 641.)*

HISTOLOGY

The histologic changes are those of papillomatosis and hyperkeratosis rather than acanthosis or excessive pigment formation. A mild dermal inflammatory infiltrate may be present.

TREATMENT

Treatment is aimed at the underlying disorder. Acanthosis nigricans in the obese child is associated with risk factors for glucose homeostasis abnormalities, and counseling families on its causes and consequences may motivate them to make healthy lifestyle changes that can decrease the risk for development of cardiac disease and diabetes mellitus. In children with obesity-related acanthosis nigricans, weight loss should be the primary goal. If a drug or malignancy is suspected, removal of that agent or treatment of cancer typically results in resolution. Appearance of skin lesions responds poorly to local medical management; some patients benefit from topical keratolytic agents (40% urea cream or 12% ammonium lactate cream) and agents that inhibit keratinocyte proliferation (topical retinoids and vitamin D analogs).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 699

Disorders of Keratinization

Kari L. Martin

DISORDERS OF CORNIFICATION

Mendelian disorders of cornification (ichthyoses) are a primary group of inherited conditions characterized clinically by patterns of scaling and histopathologically by hyperkeratosis. They are usually distinguishable by inheritance patterns, clinical features, associated defects, and histopathologic changes (Tables 699.1, 699.2, and 699.3). The two main categories of ichthyotic diseases are whether they are limited to the skin or have syndromic associations.

COLLODION BABY

Collodion baby is not a single entity, but a newborn phenotype that is most often seen in babies who eventually demonstrate lamellar ichthyosis or congenital ichthyosiform erythroderma (CIE). Less commonly, collodion babies evolve into babies with Gaucher disease or neutral lipid storage disease with ichthyosis, Loricrin keratoderma, trichothiodystrophy, Sjögren-Larsson syndrome, Conradi-Hünerman syndrome, or harlequin ichthyosis. A small subset become otherwise healthy babies without chronic skin disease (self-healing collodion baby).

Collodion babies are covered at birth by a thick, taut membrane resembling oiled parchment or collodion (Fig. 699.1), which is subsequently shed. Affected neonates have ectropion (eversion of the eyelid away from the globe), flattening of the ears and nose, and fixation of the lips in an O-shaped configuration. Hair may be absent or may perforate the abnormal covering. The membrane cracks with initial respiratory efforts and, shortly after birth, begins to desquamate in large sheets. Admission to a neonatal intensive care unit and a high-humidity environment and application of nonocclusive lubricants facilitate shedding of the membrane. Complete shedding may take several weeks, and a new membrane may occasionally form in localized areas.

Neonatal morbidity and mortality may be due to cutaneous infection, aspiration pneumonia (squamous material), hypothermia, or hypernatremic dehydration from excessive transcutaneous fluid losses as a result of increased skin permeability. The outcome is uncertain, and accurate prognosis depends on identification of the underlying ichthyosis.

NONSYNDROMIC ICHTHYOSES

Ichthyosis Vulgaris

Etiology/Pathogenesis

Autosomal dominant or recessive pathogenic variants in the filaggrin gene cause ichthyosis vulgaris. Filaggrin is a filament-aggregating protein that assembles the keratin filament cytoskeleton, causing collapse of the granular cells into a classic flattened squamous cell shape. Pathogenic variants in filaggrin lead to absence of or marked reductions in keratohyalin granules (see Table 699.2).

Clinical Manifestations

Ichthyosis vulgaris is *the most common* of the disorders of keratinization, with an incidence of 1/250 live births. Onset generally occurs in the first year of life. In most cases, it is trivial, consisting only of slight roughening of the skin surface. Scaling is most prominent on the extensor aspects of the extremities, particularly the legs (Fig. 699.2). Flexural surfaces are spared, and the abdomen, neck, and face are relatively uninvolved. Keratosis pilaris—particularly on the upper arms and thighs, accentuated markings, and hyperkeratosis on the palms and soles—and atopy are relatively common. Scaling is most pronounced during the winter months and may abate completely during warm weather. There is no accompanying disorder of hair, teeth, mucosal surfaces, or other organ systems; however, patients are at increased risk of atopy.

Treatment

Scaling may be diminished by daily applications of an emollient or a lubricant containing urea (10–40%), salicylic acid, or an alpha-hydroxy acid such as lactic acid (5–12%).

X-Linked Ichthyosis

Etiology/Pathogenesis

X-linked ichthyosis involves a deficiency of steroid sulfatase, which hydrolyzes cholesterol sulfate and other sulfated steroids to cholesterol. Cholesterol sulfate accumulates in the stratum corneum and plasma. In the epidermis this accumulation causes malformation of intercellular lipid layers, leading to barrier defects and delay of corneodesmosome degradation, resulting in corneocyte retention.

Clinical Manifestations

Skin peeling may be present at birth but typically begins at 3-6 months of life. Scaling is most pronounced on the sides of the neck, lower face, preauricular areas, anterior trunk, and the limbs, particularly the legs. The elbow (Fig. 699.3) and knee flexures are generally spared but may be mildly involved. The palms and soles may be slightly thickened but are also usually spared. The condition gradually worsens in severity and extent. Keratosis pilaris is not present, and there is no increased incidence of atopy. Deep corneal opacities that do not interfere with vision develop in late childhood or adolescence and are a useful marker for the disease because they may also be present in carrier females. Some patients have larger deletions on the X chromosome that encompass neighboring genes, generating *contiguous gene deletion syndromes*. These include Kallmann syndrome (*KAL1* gene), which consists of hypogonadotrophic hypogonadism and anosmia, X-linked chondroplasia punctata (*ARSE* gene), short stature, and ocular albinism. The rate of testicular cancer may be increased in patients with coexistent Kallmann syndrome. There is also an increased risk of attention-deficit/hyperactivity disorder and autism owing to a contiguous gene defect in neuroligin 4.

Reduced steroid sulfatase enzyme activity can be detected in fibroblasts, keratinocytes, and leukocytes and, prenatally, in amniocytes or chorionic villus cells. In affected families, an affected male can be detected by restriction enzyme analysis of cultured chorionic villus cell DNA or amniocytes or by in situ hybridization, which identifies steroid sulfatase gene deletions prenatally in chorionic villus cells. A placental steroid sulfatase deficiency in carrier mothers may result in low urinary and serum estriol values, prolonged labor, and insensitivity of the uterus to oxytocin and prostaglandins.

Treatment

Daily application of emollients and a urea-containing lubricant (10–40%) is usually effective. Glycolic or lactic acid (5–12%) in an emollient base and propylene glycol (40–60%) in water with occlusion overnight are alternative forms of therapy.

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSES

Harlequin Ichthyosis

Etiology/Pathogenesis

Harlequin ichthyosis is caused by pathogenic variants in the *ABCA12* gene. Pathogenic variants in the gene lead to defective lipid transport, and *ABCA12* activity is required for the generation of long-chain ceramides that are essential for the development of the normal skin barrier.

Clinical Manifestations

At birth, markedly thickened, ridged, and cracked skin forms horny plates over the entire body, disfiguring the facial features and constricting the digits. Severe ectropion and chemosis obscure the orbits, the nose and ears are flattened, and the lips are everted and gaping. Nails

Table 699.1 Inherited Ichthyoses – Syndromic

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRACUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
X-LINKED ICHTHYOSIS SYNDROMES							
RXLI (recessive X-linked ichthyosis) syndromic presentation		308100	XR	Large, dark scales Sparing of body folds	Prolongation of labor Cryptorchidism Corneal opacities, asymptomatic	*STS* Larger deletions with contiguous gene defects	Steroid sulfatase
IFAP syndrome (ichthyosis-follicularis-atrichia-photophobia)		398205	XR	Spiny follicular ichthyosis Nail dystrophy Alopecia	Photophobia Psychomotor delay Short stature	*MBTPS2*	Membrane-bound transcription factor peptidase, site 2
Conradi-Hünermann-Happle syndrome (CDPX2)	X-linked chondrodysplasia punctata (Conradi-Hünermann syndrome)	302960	XD	Striated ichthyosiform hyperkeratosis Follicular atrophoderma Alopecia	Cataracts Frontal bossing Short proximal limbs	*EBP*	Emopamil-binding protein
CHILD syndrome		308050	XD	Unilateral ichthyosiform erythroderma	Chondrodysplasia punctata Cataracts Limb reduction defects Asymmetric organ hypoplasia	*NSDHL*	3-β-hydroxysteroid-Δ8,Δ7-isomerase
AUTOSOMAL ICHTHYOSIS SYNDROMES WITH PROMINENT HAIR ABNORMALITIES							
NS (Netherton syndrome)		256500	AR	Erythroderma in infancy Ichthyosis linearis circumflexa Alopecia	Atopic diathesis Food allergies Structural hair defects (trichorrhexis invaginata) Growth delay	*SPINK5*	LETKI
IHS (ichthyosis hypotrichosis syndrome)		610765	AR	Adherent platelike scale Hypohidrosis Hypotrichosis	Photophobia Pingueculum	*ST14*	Serine protease 14
IHSC syndrome (ichthyosis-hypotrichosis-sclerosing cholangitis)		607626	AR	Fine thin scale Hypotrichosis with coarse thick hair	Sclerosing cholangitis Congenital paucity of bile ducts	*CLDN1*	Claudin 1
TTD (trichothiodystrophy)		601675	AR	May have collodion membrane Can vary from mild scaling to marked adherent plaques	Photosensitivity Brittle hair with "tiger tail" pattern Decreased fertility Short stature Susceptibility to infection	*ERCC2, XPD ERCC3, XPB GTF2H5, TTDA*	Xeropigmentosum group D protein Xeropigmentosum group B protein
TTD (not associated with congenital ichthyosis)		234050	AR	Delayed onset Fine scale	Nonphotosensitive Brittle hair Short stature Decreased fertility	*C7Orf11, (TTDN1)*	M-phase–specific PLK1-interacting protein, (TTD non-photosensitive 1 protein)
AUTOSOMAL ICHTHYOSIS SYNDROMES WITH FATAL DISEASE COURSE							
Gaucher syndrome, type 2		230900	AR	Collodion baby, mild scaling later	Hepatosplenomegaly retroflexion of the head, strabismus, dysphagia, choking spells, hypertonicity Death usually occurs in the first year	*GBA*	Acid β-glucosidase

Continued

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 22, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 699.1 Inherited Ichthyoses – Syndromic—cont'd

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRACUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
Multiple sulfatase deficiency		272200	AR	Mild scale	Mental retardation Mucopolysaccharidosis Metachromatic leukodystrophy Death within first year of life	*SUMF1*	Sulfatase-modifying factor-1
CEDNIK syndrome (cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma)		609528	AR	Coarse platelike white scale Fine, sparse hair	Sensorineural deafness Cerebral dysgenesis Neuropathy Microcephaly Neurogenic muscle atrophy Optic nerve atrophy Cachexia Lethal within first decade	*SNAP29*	Synaptosomal-associated protein, 29kDA
ARC syndrome (arthrogryposis-renal dysfunction-cholestasis)		208085	AR	Fine scale	Arthrogryposis Intrahepatic bile duct hypoplasia with cholestasis Renal tubular degeneration Metabolic acidosis Abnormal platelet function Death within first year of life	*VPS33B*	Vacuolar protein sorting–associated protein 33B
AUTOSOMAL ICHTHYOSIS SYNDROMES WITH OTHER ASSOCIATED SIGNS							
SLS (Sjögren-Larsson syndrome)		270200	AR	Fine lamellar scale	Diplegia or tetraplegia Retinal glistening white dots	*ALDH3A2*	Long-chain aldehyde dehydrogenase
RS (Refsum syndrome) (HMSN4: hereditary motor sensory neuropathy type 4)	Refsum disease	266500	AR	Late onset, fine scale	Retinitis pigmentosa Cardiac failure	*PAHX* or *PHYH* *PEX7*	Phytanoyl-CoA hydroxylase Peroxin-7
KID syndrome (keratitis-ichthyosis-deafness syndrome)	KID; includes HID syndrome	242150 602540	AD	Verrucous plaques Stippled pattern of keratoderma	Keratitis Sensorineural deafness	*GJB2 (GJB6)*	Connexin 26
Neutral lipid storage disease with ichthyosis	Chanarin-Dorfman syndrome (also termed NCIE2)	275630	AR	Fine scales with occasional background erythema	Myopathy Hepatosplenomegaly	*ABHD5*	CGI-58
IPS (ichthyosis prematurity syndrome)		608649	AR	White caseous scale, attenuated on scalp and eyebrows Follicular keratosis	Atopic manifestations	*SLC27A4*	Long-chain fatty acid transport protein 4
CHIME syndrome		280000	AR	Ichthyotic erythema Occasionally migratory plaques	Colobomas Conductive hearing loss Mental retardation	NK	NK
MEDNIK syndrome (mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratodermia)		Not on OMIM	AR	Rough, thickened skin	Congenital sensorineural deafness Psychomotor and growth retardation Chronic diarrhea	*AP1S1*	Adapter-related protein complex 1 sigma-1A subunit

AD, Autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive.
Modified from Foley CC, Paller AS, Irvine AD. Disorders of cornification (ichthyosis). In: Eichenfield LF, Frieden IJ, eds. *Neonatal and Infant Dermatology,* 3rd ed. Philadelphia: Elsevier; 2015: Table 19.1, p. 283–284.

Downloaded for mohamed ahmed (dr.mms2020@gmail.com) at University of Southern California from ClinicalKey.com by Elsevier on April 22, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Table 699.2 Inherited Ichthyoses – Nonsyndromic

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRA-CUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
COMMON ICHTHYOSES							
IV (ichthyosis vulgaris)		146700	AD (autosomal semidominant)	Fine, white scale Accentuated palmoplantar markings	Strong association with atopic manifestations	*FLG*	Filaggrin
RXLI (recessive X-linked ichthyosis) (nonsyndromic presentation)		308100	XR	Large, dark scales Sparing of body folds	Prolongation of labor Cryptorchidism Corneal opacities, asymptomatic	*STS*	Steroid sulfatase
AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS (ARCI)							
MAJOR TYPES							
HI (harlequin ichthyosis)		242500	AR	Rigid plates Severe erythema Hypohidrosis Scarring alopecia	Ectropion Eclabion Contractures Failure to thrive Short stature	*ABCA12*	ATP-binding cassette, subfamily a, member 12
LI (lamellar ichthyosis)		242300 601277 604777	AR	Large adherent plates Hypohidrosis	Ectropion Eclabium Short stature if severe	*TGM1, ABCA12, PNPLA1, LIPN*	Transglutaminase 1, ABCA12 transporter, PNPLA1, lipase N
CIE (congenital ichthyosiform erythroderma)		242100	AR	Fine white scales Background erythema Hypohidrosis Mild PPK White nails	Failure to thrive Short stature if severe Occasional neurologic deficits	*TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4*	Transglutaminase 1 Arachidonate lipoxygenases, cytochrome P450 enzyme, ichthyin, ABCA12 transporter
MINOR VARIANTS							
SHCB (self-healing collodion baby)		242300	AR	Collodion baby at birth, not subsequent ichthyotic phenotype	None	*TGM1, ALOX12B, ALOXE3*	Keratinocyte transglutaminase 1
Acral SHCB (self-healing collodion baby)		242300	AR	Acral collodion membranes that heal	None	*TGM1*	Transglutaminase 1
BSI (bathing suit ichthyosis)		242300	AR	Collodion membrane at birth, extremities heal	None	*TGM1*	Transglutaminase 1
KERATINOPATHIC ICHTHYOSIS (KPI)							
MAJOR TYPES							
EI (epidermolytic ichthyosis)	BCIE/EH	113800	AD, rarely AR	Widespread skin blistering in neonates Warty hyperkeratosis	Growth failure if severe	*KRT1, KRT10*	Keratins 1 and 10
SEI (superficial EI)	Ichthyosis bullosa of Siemens	146800	AD	Mild flexural hyperkeratosis Adherent fine scale Pruritus	None	*KRT2E*	Keratin 2
MINOR VARIANTS							
AEI (annular epidermolytic ichthyosis)		607602	AD	Intermittent annular, polycyclic erythematous scaly plaques		*KRT1, KRT10*	Keratins 1 and 10
ICM (ichthyosis Curth-Macklin)	Ichthyosis hystrix	146590 146600	AD	Spiky hyperkeratosis	None	*KRT1*	Keratin 1
Epidermolytic epidermal nevi		Not in OMIM	Somatic pathogenic variants			*KRT1, KRT10*	Keratins 1 and 10

Continued

Table 699.2 Inherited Ichthyoses – Nonsyndromic—cont'd

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRA-CUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
OTHER FORMS							
LK (loricrin keratoderma)		604117	AD	Collodion baby Mild, fine, white scale Diffuse PPK	None	*LOR*	Loricrin
EKV (erythrokeratoderma variabilis)		133200	AD	Transient, migratory erythematous patches Hyperkeratosis Diffuse PPK	None	*GJB3, GJB4*	Connexins 31, 30.3
PSD (peeling skin disease)		270300	AR		None	*CDSN, TGM5*	Corneodesmin, Transglutaminase 5
CRIE (congenital reticular ichthyosiform erythroderma)		609165	AD (isolated cases)		None	*KRT10*	Keratin
KLICK (keratosis linearis-ichthyosis congenita-keratoderma)		Not in OMIM	AR	Linear keratoses in skin folds Sclerosing PPK	None	*POMP*	Proteasome maturation protein

AD, Autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.
Modified from Foley CC, Paller AS, Irvine AD. Disorders of cornification (ichthyosis). In: Eichenfield LF, Frieden IJ, eds. *Neonatal and Infant Dermatology,* 3rd ed. Philadelphia: Elsevier; 2015: Table 19.2, p. 285–286.

Table 699.3 Differential Diagnosis of Netherton Syndrome: Disorders with Ichthyosis and Alopecia (Hereditary Disorders Only)*

DISORDER	INHERITANCE	GENE	FEATURES RESEMBLING NETHERTON SYNDROME	DIFFERENTIATION FROM NETHERTON SYNDROME
SAM syndrome	AR Loss-of-function pathogenic variants	*DSG1*	CIE with PPK, no collodion membrane; failure to thrive; hypernatremia; barrier defect; dermatitis; high IgE; malabsorption; eosinophilic esophagitis; multiple food allergies; recurrent infections; hypotrichosis; hypoalbuminemia	May have microcephaly, growth hormone deficiency, developmental delay, cardiac defects; psoriasiform dermatitis with acantholysis in skin sections; absence of desmoglein
ADAM17 deficiency	AR Loss-of-function pathogenic variants	*ADAM17*	Psoriasiform erythroderma/widespread pustules; failure to thrive; malabsorption; short, broken hair; recurrent infections	Bloody diarrhea; cardiomyopathy/ cardiomyositis
EGFR deficiency	AR Loss-of-function pathogenic variants	*EGFR*	Erythema, scaling, and widespread pustules; alopecia; failure to thrive, watery diarrhea, high IgE and eosinophils, hypernatremia, hypoalbuminemia; recurrent bronchiolitis	Cardiovascular issues
Trichothiodystrophy	AR Loss-of-function pathogenic variants	*ERCC2, ERCC3, GTF2H5, C7Orf11*	CIE-like ichthyosis; short, brittle hair; "tiger tail" hair shaft defect under polarized microscopy	May have impaired intelligence, decreased fertility, short stature, and photosensitivity
IHS (also called autosomal recessive ichthyosis with hypotrichosis [ARIH] syndrome)	AR Loss-of-function pathogenic variants	*ST14* (encodes matriptase); abnormal filaggrin processing	Generalized, congenital ichthyosis with sparing of face, palms, and soles; diffuse nonscarring alopecia of scalp, eyelashes, and eyebrows from birth, but improves to sparse, unruly hair during adolescence and merely recession of the frontal hair line by adulthood	May have patchy follicular atrophoderma and hypohidrosis; photophobia from corneal abnormalities; blepharitis; dental abnormalities; hair microscopy may show pili torti or pili bifurcati
IHSC (or NISCH) syndrome	AR Loss-of-function pathogenic variants	*CLDN1* (encodes claudin 1, structural protein of tight junctions)	Congenital generalized scaling, predominantly on the limbs and abdomen and sparing skinfolds, palms, and soles; coarse, curly hair with frontotemporal cicatricial alopecia	Congenital paucity of bile ducts or sclerosing cholangitis leads to neonatal jaundice with hepatomegaly; oligodontia, and enamel dysplasia; blood smears show small eosinophils and keratinocyte vacuoles without lipid contents

*Netherton syndrome must also be distinguished from severe atopic dermatitis and immunodeficiency disorders.
AR, Autosomal recessive; CIE, congenital ichthyosiform erythroderma; Ig, immunoglobulin; IHS, ichthyosis hypotrichosis syndrome; IHSC, ichthyosis-hypotrichosis-sclerosing cholangitis; NISCH, neonatal ichthyosis sclerosing cholangitis; PPK, palmoplantar keratoderma; SAM, severe dermatitis, multiple allergies, and metabolic wasting.



Fig. 699.1 Typical appearance of a collodion baby.



Fig. 699.2 Scale over the shin in ichthyosis vulgaris.



Fig. 699.3 Sparing of the antecubital fossa in X-linked ichthyosis.

and hair may be absent. Joint mobility is restricted, and the hands and feet appear fixed and ischemic. Affected neonates have respiratory difficulty, suck poorly, and are subject to severe cutaneous infection. Harlequin ichthyosis used to be uniformly fatal in the neonatal period, but with the use of oral retinoids, more patients survive (~80%) beyond infancy and have severe ichthyosis usually resembling lamellar ichthyosis or nonbullous CIE as adolescents and adults. Those with a compound heterozygous genotype have a better prognosis. Prenatal diagnosis has been accomplished by fetoscopy, fetal skin biopsy, and microscopic examination of cells from amniotic fluid.

Treatment

Initial treatment includes high fluid intake to avoid dehydration from transepidermal water loss and use of a humidified heated incubator, emulsifying ointments, careful attention to hygiene, and oral retinoids.



Fig. 699.4 Generalized scaling of lamellar ichthyosis.

Intubation may be required until nares are patent and parenteral nutrition required until eclabium has resolved. Consultation with ophthalmology is often required given the extensive ectropion. If constrictive bands are around the digits, debridement may be performed to prevent ischemia.

Lamellar Ichthyosis and Congenital Ichthyosiform Erythroderma (Nonbullous Congenital Ichthyosiform Erythroderma)

Lamellar ichthyosis and CIE (nonbullous congenital ichthyosiform erythroderma; non-harlequin ichthyosis autosomal recessive congenital ichthyoses [ARCI]) are the most common types of autosomal recessively inherited ichthyosis. Both forms are present at or shortly after birth. Most infants with these forms of ichthyosis present with erythroderma and scaling, but among collodion babies, most turn out to have one of these ichthyosis variants.

Etiology/Pathogenesis

Six genes have been identified that cause non-harlequin ichthyosis ARCI: *TGM* (the gene encoding transglutaminase), *ABCA12, NIPAL4* (also known as *ICHTHYIN*), *CYP4F22,* and the lipoxygenase genes *ALOX12B* and *ALOXE3*. Transglutaminase pathogenic variants lead to abnormalities in the cornified envelope, whereas defects in *ABCA12* cause abnormal lipid transport and those in *CYP4F22* produce abnormal lamellar granules. The lipoxygenases are likely to play a role in epidermal barrier formation by affecting lipid metabolism.

Clinical Manifestations

After shedding of the collodion membrane, if present, lamellar ichthyosis evolves into large, quadrilateral, dark scales that are free at the edges and adherent at the center. Scaling is often pronounced and involves the entire body surface, including flexural surfaces (Fig. 699.4). The face is often markedly involved, including ectropion and small, crumpled ears. The palms and soles are generally hyperkeratotic. The hair may be sparse and fine, but the teeth and mucosal surfaces are normal. Unlike in CIE, there is little erythema.

In CIE, erythroderma tends to be persistent, and scales, although they are generalized, are finer and whiter than in lamellar ichthyosis (Fig. 699.5). Hyperkeratosis is particularly noticeable around the knees, elbows, and ankles. Palms and soles are uniformly hyperkeratotic. Patients have sparse hair, cicatricial alopecia, and nail dystrophy. Neither form includes blistering.

Treatment

Pruritus may be severe and responds minimally to antipruritic therapy. The unattractive appearance of the child and the bad odor from bacterial colonization of macerated scales may cause severe emotional distress. A high-humidity environment in winter and air conditioning in summer reduce discomfort. Generous and frequent applications of emollients and keratolytic agents such as lactic or glycolic acid (5–12%), urea (10–40%), tazarotene (0.1% gel), and retinoic acid (0.1% cream) may lessen the scaling to some extent, although these agents



Fig. 699.5 Prominent erythema and scale in congenital ichthyosiform erythroderma.



Fig. 699.6 Superficial erosions and hyperkeratosis in epidermolytic hyperkeratosis.

produce stinging if applied to fissured skin. Oral retinoids have a beneficial effect in these conditions but do not alter the underlying defect and therefore must be administered indefinitely. The long-term risks of these compounds (teratogenic effects and toxicity to bone) may limit their usefulness. Ectropion requires ophthalmologic care and, at times, plastic surgical procedures.

KERATINOPATHIC ICHTHYOSES

Epidermolytic Ichthyosis (Bullous Congenital Ichthyosiform Erythroderma; Epidermolytic Hyperkeratosis)

Etiology/Pathogenesis

Epidermolytic ichthyosis is an autosomal dominant trait that has been shown to be due to defects in either keratin 1 or keratin 10. These keratins are required to form the keratin-intermediate filaments in cells of the suprabasilar layers of the epidermis.

Clinical Manifestations

The clinical manifestations are initially characterized by the onset at birth of widespread blisters and erosions on a background of generalized erythroderma (Fig. 699.6). Recurrent blistering may be widespread in neonates and may cause diagnostic confusion with other blistering disorders. With time, the blister formation ceases, erythema decreases, and generalized hyperkeratosis develops. The scales are small, hard, and verrucous. Distinctive, parallel hyperkeratotic ridges develop over the joint flexures, including the axillary, popliteal, and antecubital fossae, and on the neck and hips. Palmoplantar keratoderma (PPK) is associated with keratin 1 defects. The hair, nails, mucosa, and sweat glands are normal. Malodorous secondary bacterial infection is common and requires appropriate antibiotic therapy.



Fig. 699.7 Erythrokeratoderma variabilis. **A**, Fixed, hyperkeratotic plaques. **B**, Migratory, erythematous lesion.

Histopathology

The histopathology is diagnostic of epidermolytic ichthyosis, consisting of hyperkeratosis, degeneration of the epidermal granular layer with an increased number of keratohyalin granules, clear spaces around nuclei, and indistinct cellular boundaries of cells in the upper epidermis. On electron microscopic examination, keratin-intermediate filaments are clumped, and many desmosomes are attached to only one keratinocyte instead of connecting neighboring keratinocytes. Localized forms of the disease may resemble epidermal nevi or keratoderma of the palms and soles but share the distinctive histopathologic changes of epidermolytic ichthyosis.

Treatment

Treatment of epidermolytic ichthyosis is difficult. Morbidity is increased in the neonatal period as a result of prematurity, sepsis, and fluid and electrolyte imbalance. Bacterial colonization of macerated scales produces a distinctive bad odor that can be controlled somewhat by use of an antibacterial cleanser. Intermittent oral antibiotics are generally necessary. Keratolytic agents are often poorly tolerated. Oral retinoids may produce significant improvement. Prenatal diagnosis for affected families is possible by examination of DNA extracts from chorionic villus cells or amniocytes, provided that the specific pathogenic variant in the affected parent is known.

OTHER NONSYNDROMIC ICHTHYOSES

Erythrokeratoderma Variabilis

Etiology/Pathogenesis

An autosomal dominant disorder, erythrokeratoderma variabilis (EKV), is caused by pathogenic variants in connexins 31 and 30.3. Connexins are proteins that form gap junctions between cells that allow for transport and signaling between neighboring epidermal cells.

Clinical Manifestations

EKV usually manifests in the early months of life, progresses in childhood, and stabilizes in adolescence. It is characterized by two distinctive manifestations: sharply demarcated, hyperkeratotic plaques (Fig. 699.7A)

and transient figurate erythema (see Fig. 699.7B). The distribution is generalized but sparse; sites of predilection are the face, buttocks, axillae, and extensor surfaces of the limbs. The palms and soles may be thickened, but hair, teeth, and nails are normal.

Treatment
There are case reports that topical tazarotene gel 0.1% and oral retinoids are effective for treatment of EKV.

Symmetric Progressive Erythrokeratoderma
Etiology/Pathogenesis
Symmetric progressive erythrokeratoderma is an autosomal dominant disorder caused by pathogenic variants in the gene encoding loricrin. Loricrin is a major component of the epidermal cornified cell envelope.

Clinical Manifestations
The disorder manifests in childhood as large, fixed, geographic and symmetric, fine, scaling, hyperkeratotic, erythematous plaques primarily on the extremities, buttocks, face, ankles, and wrists. The primary feature distinguishing this disorder from EKV is the lack of variable erythema seen in the latter condition.

Treatment
Symmetric progressive erythrokeratoderma is a very rare disorder, but reports of response to topical and oral retinoids exist.

SYNDROMIC ICHTHYOSES
Sjögren-Larsson Syndrome
Etiology/Pathogenesis
The autosomal recessive inborn error of metabolism known as Sjögren-Larsson syndrome is an abnormality of fatty alcohol oxidation that results from a deficiency of fatty aldehyde dehydrogenase *(FALDH3A2)*, a component of the fatty alcohol–nicotinamide adenine dinucleotide oxidoreductase enzyme complex (see Table 699.1).

Clinical Manifestations
The clinical picture of Sjögren-Larsson syndrome consists of ichthyosis, cognitive impairment, and spasticity. The ichthyosis is generalized but is accentuated on the flexures and the lower abdomen and consists of erythroderma, fine scaling, larger platelike scales, and dark hyperkeratosis. The degree of scale varies markedly from patient to patient. Most individuals have palmoplantar hyperkeratosis. The skin changes may be identical to the other forms of ichthyosis, and diagnosis is often delayed until the onset of neurologic symptoms. Pruritus is severe, and hypohidrosis is common. Glistening dots in the foveal area are a cardinal ophthalmologic sign. About half the patients have primary retinal degeneration. Motor and speech developmental delays are usually noted before 1 year of age, and spastic diplegia or tetraplegia, epilepsy, and intellectual disability generally become evident in the first to third years of life. Some patients may walk with the aid of braces, but most are confined to wheelchairs. This deficiency can be demonstrated in cultured skin fibroblasts of affected patients and carriers and, prenatally, in cultured chorionic villus cells and amniocytes from affected fetuses. Elevation of urinary leukotriene B4 (LTB4) may provide an easier approach to diagnosis.

Treatment
Treatment is similar to the other forms of ichthyosis (humectants, emollients, topical or oral retinoids); 5-lipoxygenase inhibitors have been used to decrease pruritus.

Netherton Syndrome
Etiology/Pathogenesis
A rare autosomal recessive disorder, Netherton syndrome is caused by pathogenic variants in the *SPINK 5* gene, which encodes a serine protease inhibitor *(LEKT1)*.

Clinical Manifestations
Netherton syndrome is characterized by ichthyosis (usually ichthyosis linearis circumflexa, but occasionally the lamellar or congenital types of ichthyosiform erythroderma), trichorrhexis invaginata and other hair shaft anomalies, and atopic diathesis. The disorder manifests at birth or in the first few months of life as generalized erythema and scaling. The trunk and limbs have diffuse erythema and superimposed migratory, polycyclic, and serpiginous hyperkeratotic lesions (Fig. 699.8), some with a distinctive double-edged margin of scale. Lichenification or hyperkeratosis tends to persist in the antecubital and popliteal fossae. The face and scalp may remain erythematous and scaling. Many hair shaft deformities, most notably trichorrhexis invaginata, have been described in most patients with Netherton syndrome.



Fig. 699.8 Serpiginous, erythematous, hyperkeratotic lesions of ichthyosis linearis circumflexa.



Fig. 699.9 Very short scalp hair and thick scale in Netherton syndrome.

The ichthyosis is present in the first 10 days of life and may be especially marked around the eyes, mouth, and perineal area. The erythroderma is often intensified after infection. Infants may suffer from failure to thrive, recurrent bacterial and candidal infections, elevated serum immunoglobulin IgE values, and marked hypernatremic dehydration. The most frequent allergic manifestations are urticaria, angioedema, atopic dermatitis, and asthma. Scalp hair is sparse and short and fractures easily (Fig. 699.9); eyebrows, eyelashes, and body hair are also abnormal. The characteristic hair abnormality can be identified with light microscopy; in the newborn, it may best be identified in eyebrow hair. The differential diagnosis is noted in Table 699.3.

Treatment
Owing to the inflammatory nature of the skin disease, oral antihistamines and topical steroids, as used in the treatment of atopic dermatitis, are helpful for Netherton syndrome.

Refsum Syndrome
See Chapters 106.2 and 653.5.

Etiology/Pathogenesis
There are two types of Refsum syndrome. The classic form is autosomal recessive and caused by pathogenic variants in the *PAHX* gene that result in an increase in phytanic acid. The infantile forms of Refsum syndrome are also autosomal recessive and caused by pathogenic variants in the *PEX1, PEX2,* or *PEX26* genes. These are peroxisomal abnormalities that lead to an increase in very long-chain fatty acids, di- and tri-hydroxycholestanoic acid, and pipecolic acid, as well as phytanic acid.

Clinical Manifestations
Refsum syndrome is a multisystem disorder that becomes symptomatic in the second or third decade of life. The ichthyosis may be generalized, is relatively mild, and resembles ichthyosis vulgaris. The ichthyosis may also be localized to the palms and soles. Chronic polyneuritis with progressive paralysis and ataxia, retinitis pigmentosa, anosmia, deafness, bony abnormalities, and electrocardiographic changes are the most characteristic features. The condition is diagnosed through lipid analysis of the blood or skin, which shows elevated phytanic acid values.

The infantile form begins, as suggested by the name, early in life, and in addition to the changes seen in the classic form, affected patients have hepatomegaly, abnormal bile acid profiles, developmental delay, and cognitive impairment.

Treatment
Phytanic acid is exclusively derived from dietary chlorophyll. Lifelong dietary avoidance of phytanic acid–containing products leads to clinical improvement in classic Refsum syndrome.

Chondrodysplasia Punctata
See Chapter 106.2.

Etiology/Pathogenesis
Chondrodysplasia punctata (CPD) is a clinically and genetically heterogeneous condition. X-linked dominant CPD, also known as *Conradi-Hünermann syndrome,* is the best-characterized form. There is also an X-linked recessive form caused by a pathogenic variant in the *ARSE* gene. Rhizomelic CPD type 1 is an autosomal recessive disorder caused by pathogenic variants in the *PEX7* gene, which encodes the *PTS2* receptor. CPD can also be caused by maternal vitamin K deficiency or warfarin teratogenicity.

Clinical Manifestations
These heterogeneous disorders are marked by ichthyosis and bone changes. Nearly all patients with the X-linked dominant form and approximately 25% of those with the recessive type have cutaneous lesions, ranging from severe, generalized erythema and scaling to mild hyperkeratosis. Rhizomelic CPD is associated with cataracts, hypertelorism, optic nerve atrophy, disproportionate shortening of the proximal extremities, psychomotor retardation, failure to thrive, and spasticity; most affected patients die in infancy. Patients with the X-linked dominant form have asymmetric, variable shortening of the limbs and a distinctive ichthyosiform eruption at birth. Thick, yellow, tightly adherent, keratinized plaques are distributed in a whorled pattern over the entire body. The eruption typically resolves in infancy and may be superseded by a follicular atrophoderma and patchy alopecia.

Additional features in all variants include cataracts and abnormal facies with saddle nose and frontal bossing. The pathognomonic defect, termed CPD, is stippled epiphyses in the cartilaginous skeleton. This defect, which is seen in various settings and inherited disorders, often in association with peroxisomal deficiency and disturbance of cholesterol biosynthesis, disappears by 3-4 years of age.



Fig. 699.10 Limb dysplasia and ichthyosiform eruption in CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome.



Fig. 699.11 Palmar keratoderma with epidermolytic changes seen on biopsy.

OTHER SYNDROMES WITH ICHTHYOSIS
A number of other rare syndromes with ichthyosis as a consistent feature include the following: keratitis with ichthyosis and deafness (KID syndrome, connexin 26 gene), ichthyosis with defective hair having a banded pattern under polarized light and a low sulfur content (trichothiodystrophy), multiple sulfatase deficiency, neutral lipid storage disease with ichthyosis (Chanarin-Dorfman syndrome; *CGI58* gene), and CHILD syndrome (Fig. 699.10; congenital hemidysplasia with ichthyosiform erythroderma and limb defects; *NSDHL* gene).

Palmoplantar Keratodermas
Excessive hyperkeratosis of the palms and soles may occur as a manifestation of a focal or generalized congenital hereditary skin disorder or may result from such chronic skin diseases as psoriasis, eczema, pityriasis rubra pilaris, lupus erythematosus, or postinfectious arthritis syndrome.

Diffuse Hyperkeratosis of Palms and Soles (Unna-Thost, Vorner)
Unna-Thost and Vorner type PPKs, although clinically inseparable, were thought to be separate entities. They were separated histologically by the presence (Vorner) or absence (Unna-Thost) of epidermolytic hyperkeratosis. They represent the clinical spectrum of the same disease caused by pathogenic variants in keratin (*KRT1* and *KRT9* genes). This autosomal dominant disorder manifests in the first few months of life as erythema that

gradually progresses to sharply demarcated, hyperkeratotic, scaling plaques over the palms (Fig. 699.11) and soles. The margins of the plaques often remain red; plaques may extend along the lateral aspects of the hands and feet and onto the volar wrists and the heels. Hyperhidrosis is usually present, but hair, teeth, and nails are usually normal. Striate (*DSG1*, *DSP*, *KRT1* genes) and punctate forms of palmar and plantar hyperkeratosis represent distinct entities.

Mal De Meleda (*SLURP-1* Gene)

A rare, progressive autosomal recessive condition, mal de Meleda is characterized by erythema and thick scales on the palms, fingers, soles, and flexor aspects of the wrists, knees, and elbows. Hyperhidrosis, nail thickening or koilonychia, and eczema may also occur.

Vohwinkel Palmoplantar Keratoderma (Mutilating Keratoderma)

Vohwinkel PPK is a progressive autosomal dominant disease consisting of honeycombed hyperkeratosis of palms and soles, sparing the arches; starfish-like and linear keratoses on the dorsum of the hands, fingers, feet, and knees; and ainhum-like constriction of the digits that sometimes leads to autoamputation. Varying degrees of alopecia may be seen. Two forms have been identified. Vohwinkel PPK with ichthyosis is caused by pathogenic variants in the loricrin gene, and Vohwinkel PPK with deafness by pathogenic variants in connexin 26.

Papillon-Lefèvre Syndrome (Cathepsin C Gene)

An autosomal recessive erythematous hyperkeratosis of the palms and soles, Papillon-Lefèvre syndrome sometimes extends to the dorsal hands and feet, elbows, and knees later in childhood. The PPK may be either diffuse, striate, or punctuate. This syndrome is characterized by periodontal inflammation, leading to loss of teeth by age 4-5 years if untreated.

Other Syndromes

Keratoderma of palms and soles also occurs as a feature of some forms of ichthyosis and ectodermal dysplasia. Richner-Hanhart syndrome is an autosomal recessive focal PPK with corneal ulcers, progressive mental impairment, and a deficiency of tyrosine aminotransferase, which leads to tyrosinemia. **Pachyonychia congenita** is transmitted as an autosomal dominant trait with variable expressivity. The classic type I form (Jadassohn-Lewandowski syndrome) is due to pathogenic variants in the gene for keratin 16. Major features of the syndrome are onychogryphosis; PPK; follicular hyperkeratosis, especially of the elbows and knees; and oral leukokeratosis. The nail dystrophy is the most striking feature and may be present at birth or develop early in life. The nails are thickened and tubular, projecting upward at the free edge to form a conical roof over a mass of subungual keratotic debris. Repeated paronychial inflammation may result in shedding of the nails. The feature seen most consistently among patients with this condition is keratoderma of the palms and soles. Additional associated features include hyperhidrosis of the palms and soles and bullae and erosions on the palms and soles. Some patients have shown a selective cell-mediated defect in recognition and processing of *Candida.* Surgical removal of the nails and excision of the nail matrix have been helpful in some patients.

Treatment

Treatment for PPK is the same no matter what its cause. In mild cases, emollient therapy may suffice. Keratolytic agents such as salicylic acid, lactic acid, and urea creams may be required. Oral retinoids are the treatment of choice for severe cases unresponsive to topical therapy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 700

Diseases of the Dermis

Jacquelyn R. Sink and Yvonne E. Chiu

KELOID

Etiology and Pathogenesis

Keloids are usually induced by trauma and commonly follow ear piercing, burns, scalds, and surgical procedures. The resulting keloid is larger than the initial area of trauma to the skin. Certain individuals are predisposed to keloid formation; a familial tendency (recessive or dominant inheritance) or the presence of foreign material in the wound may have a pathogenic role. Keloids are a rare feature of Ehlers-Danlos syndrome, Rubinstein-Taybi syndrome, and pachydermoperiostosis. Keloids result from an abnormal fibrous wound-healing response in which tissue repair and regeneration-regulation control mechanisms are lost. Collagen production is 20 times that seen in normal scars, and the type I:III collagen ratio is abnormally high. In keloids, tissue levels of tumor growth factor-β and platelet-derived growth factor are elevated; fibroblasts are more sensitive to their effects, and their degradation rate is decreased.

Clinical Manifestations

A *keloid* is a sharply demarcated, benign, dense growth of connective tissue that forms in the dermis after trauma. The lesions are firm, raised, pink to hyperpigmented, and rubbery; they may be tender or pruritic. Sites of predilection are the face, earlobes (Fig. 700.1), neck, shoulders, upper trunk, sternum, and lower legs. Unlike hypertrophic scars, keloids frequently recur after attempted removal and outgrow the original boundaries of the wound.

Histology

A keloid consists of whorled and interlaced hyalinized collagen fibers.

Differential Diagnosis

Keloids should be differentiated from *hypertrophic scars,* which remain confined to the site of injury and may involute over time.



Fig. 700.1 Keloid of earlobe after piercing.

Treatment
Treatment of keloids is difficult. Young keloids may diminish in size if injected intralesionally at 4-week intervals with triamcinolone suspension (10-40 mg/mL). At times, a more concentrated suspension is required. Large or old keloids may require surgical excision followed by serial intralesional injections of corticosteroid; however, recurrence rates are high. Earlobe keloids may respond favorably to surgical excision followed by use of pressure earrings and serial intralesional steroid injections. Silicone scar sheeting may help in some patients. Other therapeutic modalities that have been used with variable success include laser therapy, radiation therapy, and intralesional injection of bleomycin, interferon, verapamil, or fluorouracil.

STRIAE CUTIS DISTENSAE (STRETCH MARKS)
Etiology and Pathogenesis
Striae formation is common in adolescence. The most frequent causes are rapid growth, pregnancy, obesity, Cushing disease, and prolonged use of systemic or topical corticosteroid therapy. They may also be seen in patients with Ehlers-Danlos syndrome. The pathogenesis is unknown, but alterations in collagen and elastic fibers are thought to play a role.

Clinical Manifestations
Striae appear as linear, depressed, pink bands of atrophic skin that eventually become silvery, opalescent, and smooth. They occur most frequently in areas subject to distention, such as the lower back (Fig. 700.2), buttocks, thighs, breasts, abdomen, and shoulders.

Differential Diagnosis
Striae distensae resemble atrophic scars.

Treatment
Striae tend to spontaneously become less conspicuous as the color fades with time, and treatment is not necessary.

CORTICOSTEROID-INDUCED ATROPHY
Etiology and Pathogenesis
Both topical and systemic corticosteroid treatment can result in cutaneous atrophy. This is particularly common when a potent or superpotent topical corticosteroid is applied under occlusion or to an intertriginous area for a prolonged period. Keratinocyte growth is decreased, but epidermal maturation is accelerated, resulting in thinning of the epidermis and stratum corneum. Fibroblast growth and function are also decreased, leading to dermal changes. The mechanism involves inhibition of synthesis of collagen type I, noncollagenous proteins, and total protein content of the skin, along with progressive reduction of dermal proteoglycans and glycosaminoglycans.

Clinical Manifestations
Affected skin is thin, fragile, smooth, and semitransparent, with telangiectasia, prominent veins, and loss of normal skin markings.

Histology
On histology, thinning of the epidermis is present. Spaces between dermal collagen and elastic fibers are small, producing a more compact yet thin dermis.

Treatment
Optimal treatment is prevention by monitoring and educating on the proper use of topical steroids to avoid side effects.

GRANULOMA ANNULARE
Etiology and Pathogenesis
The cause of granuloma annulare (GA) is unknown. A possible association with diabetes mellitus has been proposed, particularly with the generalized form of GA; however, this hypothesis is controversial and has not been confirmed in children.

Clinical Manifestations
This common dermatosis occurs predominantly in healthy children and young adults. Typical lesions begin as firm, smooth, erythematous papules. They gradually enlarge to form annular plaques with a papular border and a normal, slightly atrophic or discolored central area up to several centimeters in size. Lesions may occur anywhere on the body, but mucous membranes are notably spared. Favored sites include the dorsum of the hands (Fig. 700.3) and feet. The disseminated papular form is rare in children. Subcutaneous GA tends to develop on the scalp and limbs, particularly in the pretibial area. These lesions are firm, usually nontender, skin-colored nodules. Perforating GA is characterized by the development of grouped papules, some with a yellowish, crusted, or scaly center, and occur because of transepidermal elimination of altered collagen.

Differential Diagnosis
Annular lesions are often mistaken for tinea corporis due to the elevated, advancing border; however, GA characteristically lacks scale. Papular lesions may simulate rheumatoid nodules, particularly when grouped on the fingers and elbows.

Histology
The lesions of GA demonstrate granuloma formation on histology with a central area of necrotic collagen, mucin deposition, and a peripheral palisading infiltrate of lymphocytes, histiocytes, and foreign body giant cells. The pattern resembles that of necrobiosis lipoidica and rheumatoid nodules, but subtle histologic differences usually permit differentiation.

Treatment
The eruption persists for months to years, but spontaneous resolution without residual change is typical; approximately 50% of lesions clear within 2 years. Application of a potent or superpotent topical corticosteroid preparation or intralesional injections (5-10 mg/mL)



Fig. 700.2 Striae on the back of an adolescent.



Fig. 700.3 Annular lesion with a raised papular border and depressed center, characteristic of granuloma annulare.

of corticosteroid may hasten involution, but nonintervention is also appropriate.

NECROBIOSIS LIPOIDICA

Etiology and Pathogenesis

The cause of necrobiosis lipoidica (NL) is unclear, but 50–75% of patients have diabetes mellitus, though NL occurs in less than 1% of all diabetic patients. NL has also been noted in patients with obesity, hypertension, and dyslipidemias. Its presence may signify a higher risk for diabetic complications such as nephropathy and retinopathy.

Clinical Manifestations

This disorder manifests as erythematous papules that evolve into irregularly shaped, sharply demarcated, erythematous to yellow, sclerotic plaques with central telangiectasias and a violaceous border. Scaling, crusting, and ulceration may occur. Lesions develop most commonly on the anterior tibial surfaces (Fig. 700.4). Slow extension of a given lesion over the years is usual, but long periods of quiescence or complete healing with scarring may occur.

Histology

Poorly defined areas of necrobiotic collagen are seen on microscopic evaluation, primarily low in the dermis with mucin deposition. Surrounding the necrobiotic, disordered areas of collagen is a palisading lymphohistiocytic granulomatous infiltrate. Some lesions are more characteristically granulomatous, with limited necrobiosis of collagen.

Differential Diagnosis

NL must be differentiated clinically from xanthomas, morphea, GA, erythema nodosum, and pretibial myxedema.

Treatment

The lesions of NL usually persist despite good control of the diabetes but may improve minimally after applications of high-potency topical steroids or local injection of a corticosteroid. Ulcerated areas should be managed with meticulous wound care. Pentoxifylline and antiplatelet therapy with aspirin have also been used.

LICHEN SCLEROSUS

Etiology and Pathogenesis

Lichen sclerosus (LS) is a chronic inflammatory dermatosis whose cause is largely unknown. Several studies have identified the presence of autoantibodies against the glycoprotein extracellular matrix protein 1 (ECM-1).

Clinical Manifestations

Lichen sclerosus (LS) manifests as shiny, ivory-colored, flat-topped papules, often with a violaceous halo. The surface shows prominent dilated pilosebaceous or sweat duct orifices that may contain yellow or brown follicular plugs. The papules coalesce to form irregular plaques of variable size, and hemorrhagic bullae can be seen in the margins. In the later stages, atrophy results in a depressed plaque with a wrinkled surface. This disorder occurs more commonly in girls than in boys. Sites of predilection in girls are the vulvar (Fig. 700.5), perianal, and perineal skin. Extensive involvement may produce an atrophic plaque of hourglass configuration; shrinkage of the labia and stenosis of the introitus may result. Erythema and purpura are possible. Vaginal discharge precedes vulvar lesions in approximately 20% of patients. In boys, the prepuce and glans penis are often involved, usually in association with phimosis *(balanitis xerotica obliterans)*; most boys with the disorder were not circumcised early in life. Commonly involved extragenital sites include the upper trunk, neck, axillae, flexor surfaces of wrists, and areas around the umbilicus and the eyes. Pruritus, pain, and dysuria may be severe, and constipation due to withholding may occur.

Differential Diagnosis

In children, LS is most frequently confused with focal morphea (see Chapter 201), with which it may coexist. In the genital area, it may be mistakenly attributed to sexual abuse, irritant dermatitis, or vulvovaginitis. The vitiligoid form associated with depigmentation must be differentiated from vitiligo or postinflammatory hypopigmentation.

Histology

Biopsy is rarely necessary but shows hyperkeratosis with follicular plugging, hydropic degeneration of basal cells, a bandlike dermal lymphocytic infiltrate, homogenized collagen, and thinned elastic fibers in the upper dermis.

Treatment

Vulvar LS in childhood usually improves with puberty but does not always resolve completely, and symptoms can recur throughout life. Long-term observation for the development of squamous cell carcinoma is necessary in patients with later disease onset or persistence beyond puberty. Superpotent topical corticosteroids are the treatment of choice, including for the genital area, providing relief from pruritus and producing clearing of lesions. Topical tacrolimus and pimecrolimus have also been used. It is not known how response to treatment affects long-term cancer risk.

MORPHEA

Etiology and Pathogenesis

Morphea is an autoimmune sclerosing condition of the dermis and subcutaneous tissue of unknown etiology.

Clinical Manifestations

Morphea is characterized by solitary, multiple, or linear circumscribed areas of erythema that evolve into indurated, sclerotic, atrophic plaques, with or without a lilac border (Fig. 700.6). Affected areas may resolve



Fig. 700.4 Yellow sclerotic plaque of necrobiosis lipoidica on the shin.



Fig. 700.5 Ivory-colored perivaginal plaque with hemorrhage.



Fig. 700.6 Erythematous, hyperpigmented plaque of early morphea.



Fig. 700.7 Linear morphea with involvement over the ankle.

without sequelae or with subsequent atrophy and/or pigment change. Morphea is seen more commonly in females. Five types of morphea have been described: circumscribed, linear, generalized, mixed, and pansclerotic; the most common types in children are circumscribed and linear. Morphea can affect any area of skin. When confined to the frontal scalp, forehead, and midface in a linear band, it is referred to as **en coup de sabre**. When located on one side of the face, it is termed **progressive hemifacial atrophy**, also known as **Parry-Romberg syndrome**. These forms of morphea carry a poorer prognosis because of the associated underlying central nervous system involvement or musculoskeletal atrophy that can be cosmetically disfiguring. Linear morphea over a joint may lead to limb undergrowth or restriction of mobility (Fig. 700.7). Pansclerotic morphea is a rare, severe, disabling variant.

Differential Diagnosis

The differential diagnosis of morphea includes GA, NL, LS, and late-stage European Lyme borreliosis (acrodermatitis chronica atrophicans).

Histology

Thickening or sclerosus of the dermis with collagen degeneration is seen.

Treatment

Morphea tends to persist, with gradual outward expansion for months to years until spontaneous cessation of the inflammatory phase occurs. Topical calcipotriene, alone or in combination with high-potency to superpotency topical steroids or topical tacrolimus, has been used for less severe disease. For severe morphea, methotrexate with or without pulsed intravenous or oral glucocorticosteroids may halt progression and help shorten the disease course. Ultraviolet A-1 (UVA-1) phototherapy, mycophenolate mofetil, and other therapies are also used. Physical therapy is recommended in linear morphea involving a joint to maintain mobility. Significant postinflammatory pigment alteration may persist for years.

SCLEREDEMA (SCLEREDEMA ADULTORUM, SCLEREDEMA OF BUSCHKE)

Etiology and Pathogenesis

The cause of scleredema is unknown. There are three types. **Type 1** (55% of cases) is preceded by a febrile illness, often related to an upper or lower respiratory infection (most commonly streptococcus). **Type 2** (25%) is associated with paraproteinemia, including multiple myeloma. **Type 3** (20%) is seen in diabetes mellitus.

Clinical Manifestations

Fifty percent of patients with scleredema are younger than 20 years old. Onset of type 1 is sudden, with brawny edema of the face and neck that spreads rapidly to involve the thorax and arms in a sweater distribution; the abdomen and legs are usually spared. The face acquires a waxy, masklike appearance. The involved areas feel indurated and woody, are nonpitting, and are not sharply demarcated from normal skin. The overlying skin is normal in color and is not atrophic.

Type 2 and type 3 scleredema may occur insidiously. Systemic involvement, which is uncommon and usually associated with types 2 and 3, is marked by thickening of the tongue, dysarthria, dysphagia, restriction of eye and joint movements, and pleural, pericardial, and peritoneal effusions. Electrocardiographic changes may also be observed. Laboratory data are not helpful.

Differential Diagnosis

Scleredema must be differentiated from scleroderma (see Chapter 201), morphea, myxedema, trichinosis, dermatomyositis, sclerema neonatorum, and subcutaneous fat necrosis.

Histology

Skin biopsy demonstrates an increase in dermal thickness due to swelling and homogenization of the collagen bundles, which are separated by large interfibrous spaces. Special stains can identify increased amounts of mucopolysaccharides in the dermis of patients with scleredema.

Treatment

In type 1 scleredema, the active phase of the disease persists for 2-8 weeks. Spontaneous and complete resolution usually occurs after 6 months to 2 years. Recurrent attacks are unusual. In types 2 and 3, the disease is slowly progressive. There is no specific therapy.

LIPOID PROTEINOSIS (URBACH-WIETHE DISEASE, HYALINOSIS CUTIS ET MUCOSAE)

Etiology and Pathogenesis

Lipoid proteinosis is an autosomal recessive disorder caused by pathogenic variants in the *ECM-1* gene, which encodes ECM-1. ECM-1 has a functional role in the structural organization of the dermis by binding to perlecan, matrix metalloproteinase 9, and fibulin. Pathogenesis involves infiltration of hyaline material into the skin, oral cavity, larynx, and internal organs.

Clinical Manifestations

Lipoid proteinosis presents initially in early infancy as hoarseness due to vocal cord involvement. Skin lesions appear during childhood and consist of yellowish papules and nodules that may coalesce to form plaques. The classic sign is a string of beaded papules on the eyelids. Lesions also occur on the face, forearms, neck, genitals, dorsum of the fingers, and scalp, where they result in patchy alopecia. Similar deposits are found on the lips, leading to eversion of the lips, as well as the undersurface of the tongue, fauces, uvula, epiglottis,

and vocal cords. The tongue becomes enlarged and feels firm on palpation. The patient may be unable to protrude the tongue. Pocklike, atrophic scars may develop on the face. Hypertrophic, hyperkeratotic nodules and plaques occur at sites of friction, such as the elbows and knees; the palms may be diffusely thickened. The disease progresses until early adult life, but the prognosis is good. Symmetric calcification lateral to the sella turcica in the medial temporal region, identifiable roentgenographically as bilateral bean-shaped opacities, is pathognomonic but is not always present. Involvement of the larynx can lead to respiratory compromise, particularly in infancy, necessitating tracheostomy. Associated anomalies include dental abnormalities, epilepsy, and recurrent parotitis because of infiltrates in the Stensen duct. Virtually any organ can be involved.

Histology

The distinctive histologic pattern in lipoid proteinosis includes dilation of dermal blood vessels and infiltration of homogeneous eosinophilic extracellular hyaline material along capillary walls and around sweat glands. Hyaline material in homogeneous bundles, diffusely arranged in the upper dermis, produces a thickened dermis. The infiltrates appear to contain both lipid and mucopolysaccharide substances.

Treatment

There is no specific treatment for lipoid proteinosis.

MACULAR ATROPHY (ANETODERMA)

Etiology and Pathogenesis

Anetoderma is characterized by circumscribed areas of slack skin associated with loss of dermal substance. This disorder may have no associated underlying disease (primary macular atrophy) or may develop after an inflammatory skin condition. Secondary macular atrophy may be a result of direct destruction of dermal elastin or elastolysis on an immunologic basis, especially in the presence of antiphospholipid antibodies, which are related to autoimmune disorders. The elastolysis may then be a result of release of elastase from inflammatory cells.

Clinical Manifestations

Lesions vary from 0.5 to 1.0 cm in diameter and, if inflammatory, may initially be erythematous. They subsequently become thin, wrinkled, and blue-white or hypopigmented. The lesions often protrude as small outpouchings that, on palpation, may be readily indented into the subcutaneous tissue because of the dermal atrophy. Sites of predilection include the trunk, thighs, upper arms, and, less commonly, the neck and face. Lesions remain unchanged for life; new lesions often continue to develop for years.

Histology

All types of macular atrophy show focal loss of elastic tissue on histopathologic examination, a change that may not be recognized unless special stains are used.

Differential Diagnosis

Lesions of anetoderma occasionally resemble morphea, LS, focal dermal hypoplasia, atrophic scars, or end-stage lesions of chronic bullous dermatoses.

Treatment

There is no effective therapy for macular atrophy.

PSEUDOXANTHOMA ELASTICUM

Etiology and Pathogenesis

Pseudoxanthoma elasticum (PXE) is a genetic metabolic disease linked to pathogenic variants in the *ABCC6* gene. The primary abnormality seen in PXE is mineralization of tissue in the skin, Bruch membrane in the retina, and vessel walls. Cutaneous manifestations of PXE may be present in generalized arterial calcification of infancy.



Fig. 700.8 Confluent plaque of pebbly skin in pseudoxanthoma elasticum.

Clinical Manifestations

Onset of skin manifestations often occurs during childhood, but the changes produced by early lesions are subtle and may not be recognized. The characteristic pebbly, "plucked chicken skin" cutaneous lesions are 1- to 2-mm, asymptomatic, yellow papules arranged in a linear or reticulated pattern or in confluent plaques. Preferred sites are the flexural neck (Fig. 700.8), axillary and inguinal folds, umbilicus, thighs, and antecubital and popliteal fossae. As the lesions become more pronounced, the skin acquires a velvety texture and droops in lax, inelastic folds. The face is usually spared. Mucous membrane lesions may involve the lips, buccal cavity, rectum, and vagina. There is involvement of the connective tissue of the media and intima of blood vessels, Bruch membrane of the eye, and endocardium or pericardium, which may result in visual disturbances, angioid streaks in the Bruch membrane, irregular mottling of the retinal epithelium, intermittent claudication, cerebral and coronary occlusion, hypertension, and hemorrhage from the gastrointestinal tract, uterus, or mucosal surfaces. Women with PXE have an increased risk of miscarriage in the first trimester. Arterial involvement generally manifests in adulthood, but claudication and angina have occurred in early childhood.

Pathology

Histopathologic examination shows fragmented, swollen, and clumped elastic fibers in the middle and lower third of the dermis. The fibers stain positively for calcium. Collagen near the altered elastic fibers is reduced in amount and is split into small fibers. Aberrant calcification of the elastic fibers of the internal elastic lamina of arteries in PXE leads to narrowing of vessel lumina.

Treatment

There is no effective treatment for PXE, although laser therapy, with or without intravitreal injection of vascular endothelial growth factor antagonists, may help prevent retinal hemorrhage. The use of oral phosphate binders has shown mixed results in decreasing calcification of elastic fibers.

ELASTOSIS PERFORANS SERPIGINOSA

Etiology and Pathogenesis

Elastosis perforans serpiginosa (EPS) is characterized by the extrusion of altered elastic fibers through the epidermis. The primary abnormality is probably in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue.

Clinical Manifestations

This is an unusual skin disorder in which 1- to 3-mm, firm, skin-colored, keratotic papules tend to cluster in arcuate and annular patterns on the posterolateral neck and limbs (Fig. 700.9) and occasionally on the face and trunk. Onset usually occurs in childhood or



Fig. 700.9 Arcuate keratotic papule of elastosis perforans serpiginosa.



Fig. 700.10 Hyperkeratotic papules in reactive perforating collagenosis.

adolescence. A papule consists of a circumscribed area of epidermal hyperplasia that communicates with the underlying dermis by a narrow channel. There is a great increase in the amount and size of elastic fibers in the upper dermis, particularly in the dermal papillae. Approximately 30% occur in association with osteogenesis imperfecta, Marfan syndrome, PXE, Ehlers-Danlos syndrome, Rothmund-Thomson syndrome, scleroderma, acrogeria, and Down syndrome. EPS has also occurred in association with penicillamine therapy.

Histology
Histopathology reveals a hyperplastic epidermis with extrusion of abnormal elastic fibers and a lymphocytic superficial infiltrate.

Differential Diagnosis
The differential diagnosis of EPS includes tinea corporis, perforating GA, reactive perforating collagenosis, lichen planus, creeping eruption, and porokeratosis of Mibelli.

Treatment
Treatment of EPS is ineffective; however, the lesions are asymptomatic and may disappear spontaneously.

REACTIVE PERFORATING COLLAGENOSIS
Etiology and Pathogenesis
The primary process in reactive perforating collagenosis represents transepidermal elimination of altered collagen. A familial autosomal recessive form has been described.

Clinical Manifestations
Reactive perforating collagenosis usually manifests in early childhood as small papules on the dorsal areas of the hands and forearms, elbows, knees, and, sometimes, the face and trunk. Over a period of several weeks, the papules enlarge to 5-10 mm, become umbilicated, and develop keratotic plugs centrally (Fig. 700.10). Individual lesions resolve spontaneously in 2-4 months, leaving hypopigmented macules or scars. Lesions may recur in crops, linearly as a part of the Koebner phenomenon, or in response to cold temperatures or superficial trauma such as abrasions, insect bites, and acne lesions.

Histology
Collagen in the papillary dermis is engulfed within a cup-shaped perforation in the epidermis. The central crater contains pyknotic inflammatory cells and keratinous debris.

Differential Diagnosis
EPS and Kyrle disease may mimic reactive perforating collagenosis.

Treatment
Reactive perforating collagenosis resolves spontaneously in 6-8 weeks. Narrow-band ultraviolet B (UVB) light may help with pruritus and hasten resolution.

XANTHOMAS
See Chapter 105.

FABRY DISEASE
See Chapter 653.6.

MUCOPOLYSACCHARIDOSES
See Chapter 109.

Several of the mucopolysaccharidoses are characterized by thickened, rough, inelastic skin, particularly on the extremities, and generalized hypertrichosis but are nonspecific features. Extensive and persistent dermal melanocytosis has been described in children with Hurler and Hunter syndromes. Telangiectasias on the face, forearms, trunk, and legs have been observed in Scheie and Morquio syndromes. In some patients with Hunter syndrome, ivory-colored, distinctive, firm dermal papules and nodules with corrugated surface texture are grouped into symmetric plaques on the upper trunk (Fig. 700.11), arms, and thighs. Onset of these unusual lesions occurs in the first decade of life, and spontaneous disappearance has been noted.

MASTOCYTOSIS
Etiology and Pathogenesis
Mastocytosis encompasses a clinical spectrum of disorders that range from solitary cutaneous nodules to diffuse infiltration of skin associated with involvement of internal organs (Table 700.1). All of the disorders are characterized by aggregates of mast cells in the dermis. There are four types of mastocytosis: mastocytomas (three or fewer lesions), urticaria pigmentosa (more than three lesions, also known as *maculopapular cutaneous mastocytosis*), diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans (TMEP). Increased expression of stem cell factor (also called *kit ligand* or *mast cell growth factor*) stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. Some forms of mastocytosis are associated with activating pathogenic variants (most commonly the *D816V* variant) in the *KIT* gene. The local and systemic manifestations of the disease are at least partly a result of the release of histamine and heparin from mast cell granules; although heparin is present in significant amounts in mast cells, coagulation disturbances occur only rarely. The vasodilator prostaglandin D_2 or its metabolite appears to exacerbate the flushing response. Serum tryptase values may be elevated, but not consistently.



Fig. 700.11 Ivory-colored papules on the upper back in Hunter syndrome.

Table 700.1	Mastocytosis Classification
CUTANEOUS MASTOCYTOSIS	
Urticaria pigmentosa/maculopapular cutaneous mastocytosis	
Diffuse cutaneous mastocytosis	
Solitary mastocytoma	
SYSTEMIC MASTOCYTOSIS	
Indolent mastocytosis	
Smoldering mastocytosis	
Aggressive mastocytosis	
Systemic mastocytosis with associated hematologic non–mast cell lineage (AHN) disease	
Mast cell leukemia	
MAST CELL SARCOMA	

Modified from Valent P, Akin C, Metcalfe D. Mastocytosis: 2016 Updated WHO classification and novel emerging treatment concepts. *Blood.* 2017;129:1420–1427, Table 2.

Clinical Manifestations

Mastocytomas are usually 1-5 cm in diameter. Lesions may be present at birth or may arise in early infancy at any site. The lesions may manifest as recurrent, evanescent wheals or bullae; in time, an infiltrated, pink, yellow, or tan, rubbery plaque develops at the site of whealing or blistering (Fig. 700.12). The surface acquires a pebbly, orange peel–like texture, and hyperpigmentation may become prominent. Mechanical irritation of the lesion may lead to urtication (Darier sign) within a few minutes due to local histamine release; rarely, systemic signs of histamine release become apparent.

Urticaria pigmentosa is the most common form of mastocytosis in children. In the first type of urticaria pigmentosa, the **classic infantile type**, lesions may be present at birth but more often erupt in crops in the first several months to 2 years of age. New lesions seldom arise after age 3-4 years. In some cases, early bullous or urticarial lesions fade, only to recur at the same site, ultimately becoming fixed and hyperpigmented. In others, the initial lesions are hyperpigmented. Vesiculation usually abates by 2 years of age. Individual lesions range in size from a few millimeters to several centimeters and may be macular, papular, or nodular. They range in color from yellow-tan to red-brown and often have ill-defined borders (see Fig. 700.12). Larger nodular lesions, like solitary mastocytomas, may have a characteristic *peau d'orange* (orange peel–like) texture. Lesions of urticaria pigmentosa may be sparse or numerous and are often symmetrically distributed. Palms, soles, and face are usually spared, as are the mucous membranes. The rapid appearance of erythema and wheals in response to vigorous stroking of a lesion can usually be elicited; dermographism of intervening normal skin is also common. Affected children can have intense pruritus. Systemic signs of histamine release, such as anaphylaxis-like episodes, hypotension, syncope, headache, episodic flushing, tachycardia, wheezing, colic, and diarrhea, are uncommon and occur most frequently in the more severe types of mastocytosis. Flushing is by far the most common symptom.

The **second type** of urticaria pigmentosa may begin in childhood but typically develops in adulthood. This type does not resolve, and new lesions continue to develop throughout life. Patients with this type of mastocytosis may develop systemic involvement.

Systemic mastocytosis is marked by an abnormal increase in the number of mast cells in numerous organ systems and is uncommon in children. Bone lesions are often silent (but may be painful) and are detectable radiologically as osteoporotic or osteosclerotic areas, principally in the axial skeleton. Gastrointestinal tract involvement may lead to abdominal pain, nausea, vomiting, diarrhea, steatorrhea, and bloating. Mucosal infiltrates may be detectable by barium studies or by small bowel biopsy. Peptic ulcers also occur. Hepatosplenomegaly due to mast cell infiltrates and fibrosis has been described, as has mast cell proliferation in lymph nodes, kidneys, periadrenal fat, and bone marrow. Abnormalities in the peripheral blood, such as anemia, leukocytosis, and eosinophilia, are noted in approximately 30% of patients. Mast cell leukemia may occur.

Diffuse cutaneous mastocytosis is characterized by diffuse involvement of the skin rather than discrete hyperpigmented lesions. Affected patients are usually normal at birth and demonstrate features of the disorder after the first few months of life. Rarely, the condition may present with intense generalized pruritus in the absence of visible skin changes. The skin usually appears thickened, pink to yellow in color, doughy, or with a *peau d'orange* texture. Surface changes are accentuated in flexural areas. Recurrent bullae (see Fig. 700.12), intractable pruritus, and flushing attacks are common, as is systemic involvement.

Telangiectasia macularis eruptiva perstans (TMEP) is a variant of mastocytosis that consists of telangiectatic, hyperpigmented macules usually localized to the trunk. These lesions do not urticate when stroked. This form of the disease is seen primarily in adolescents and adults.

Differential Diagnosis

The differential diagnosis of solitary mastocytomas includes recurrent bullous impetigo, herpes simplex, congenital melanocytic nevi, and juvenile xanthogranuloma.

Urticaria pigmentosa can be confused with drug eruptions, postinflammatory pigmentary change, juvenile xanthogranuloma, pigmented nevi, ephelides, xanthomas, chronic urticaria, insect bites, and bullous impetigo. Diffuse cutaneous mastocytoma may be confused with epidermolytic hyperkeratosis. TMEP must be differentiated from other causes of telangiectasia.

The systemic manifestations of mastocytosis may mimic pheochromocytoma, carcinoid syndrome, vasoactive intestinal peptide–secreting tumors, vasculitis, autoinflammatory diseases, hyper-IgE syndrome, somatization disorder, autonomic dysfunction, angioedema, chronic urticaria, and anaphylaxis.

Prognosis

Spontaneous involution usually occurs in patients with solitary mastocytomas and classic infantile urticaria pigmentosa. The incidence of systemic manifestations in these patients is very low. The mean duration of urticaria pigmentosa is around 10 years. A larger number of lesions early in life may lead to later resolution.

Treatment

Solitary mastocytomas usually do not require treatment. Lesions that blister may be treated with topical steroids after each blistering episode.

In urticaria pigmentosa, flushing can be precipitated by excessively hot baths, vigorous rubbing of the skin, and certain drugs, such as

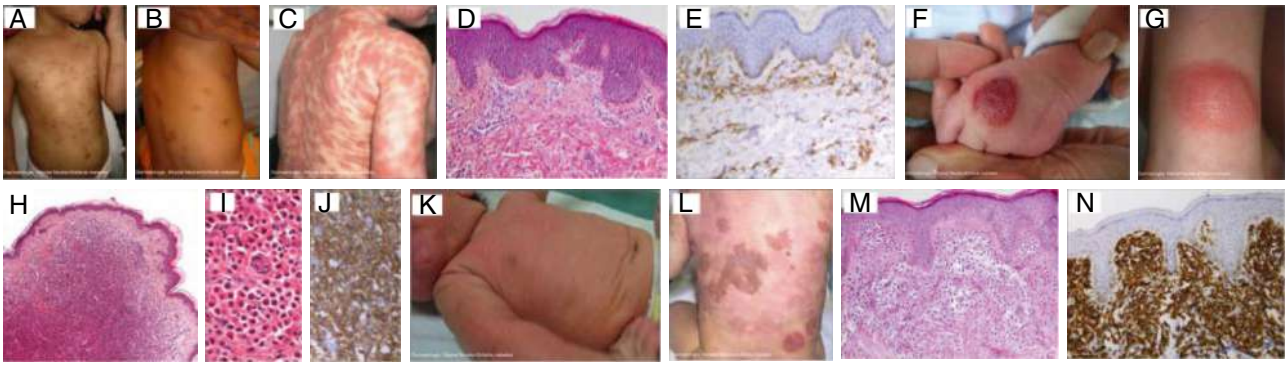

Fig. 700.12 Clinical features and histologic findings in childhood mastocytosis. Diagnosis of mastocytosis in children is often obvious, and skin biopsy is rarely performed. The histologic diagnosis of cutaneous mastocytosis must consider the increased number and proportion of mast cells compared to other inflammatory cells. Mast cells can be rounded, cuboidal, fusiform, or histiocyte-like. Eosinophils may be observed in all mastocytosis subtypes. The epidermis may be hyperpigmented in urticaria pigmentosa (UP) and diffuse cutaneous mastocytosis (DCM), whereas it is normal in mastocytoma. **A-E,** Types of urticaria pigmentosa. **A,** Maculopapular UP. **B,** Plaque-type UP. **C,** Extensive UP with plaques and macules. **D,** Skin biopsy: increased number and proportion of mast cells around the vessels or scattered into the dermis, dilatation of the capillaries of the superficial dermis. **E,** c-Kit staining. **F-J,** Mastocytoma. **F,** Mastocytoma localized on the hand. **G,** Mastocytoma localized on the forearm. **H, I,** Skin biopsy: abundant and diffuse infiltration of mast cells throughout the dermis. Mast cells are always recognizable, with a large, pink, and granular cytoplasm and a round, dense, central nucleus. **J,** c-Kit staining. **K-N,** DCM. **K,** Diffuse infiltration of skin. **L,** Extensive bullous lesions associated with infiltration on the back. **M,** Skin biopsy: diffuse dermal infiltration of mast cells associated with some fibrosis and dilated capillaries. **N,** c-Kit staining. *(From Méni C, Bruneau J, Georgin-Lavialle S, et al. Paediatric mastocytosis: a systematic review of 1747 cases. Br J Dermatol. 2015;172:642–651, Fig. 1, p. 643.)*

Table 700.2 Pharmacologic Agents and Physical Stimuli that May Exacerbate Mast Cell Mediator Release in Patients with Mastocytosis

Venoms (bee stings, jellyfish stings, snake bites)
Complement-derived anaphylatoxins
Biologic peptides (substance P, somatostatin, vasoactive intestinal polypeptide)
Polymers (dextran)
Physical stimuli (heat, cold, exertion, friction, trauma, vibration, sunlight)
Acetylsalicylic acid (aspirin), ibuprofen, and related nonsteroidal analgesics*
Alcohol
General anesthetics (D-tubocurarine, scopolamine, decamethonium, gallamine, pancuronium)
Polymyxin B
Local anesthetics (lidocaine, tetracaine procaine, methylparaben preservative)
Sympathomimetics
Opiates (codeine, morphine)*
Radiographic dyes (iodine-containing)
Other drugs (papaverine, dipyridamole, trimethaphan, amphotericin B, quinine, thiamine, dextromethorphan, lactam, antibiotics, vancomycin)
Stress (sleep deprivation, anxiety, pain)

*Appears to be a problem in <10% of patients.
Modified from Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child.* 2002;86:315–319, Table 4.

codeine, aspirin, morphine, atropine, ketorolac, alcohol, tubocurarine, iodine-containing radiographic dyes, and polymyxin B (Table 700.2). Avoidance of these triggering factors is advisable; it is notable that general anesthesia may be safely performed with appropriate precautions.

For patients who are symptomatic, oral antihistamines may be palliative. H_1 receptor antagonists are the initial drugs of choice for systemic signs of histamine release. If H_1 antagonists are unsuccessful, H_2 receptor antagonists may be helpful in controlling pruritus or gastric hypersecretion. Topical steroids are of benefit in controlling skin urtication and blistering. Oral mast cell–stabilizing agents, such as cromolyn sodium or ketotifen, may also be effective for diarrhea or abdominal cramping and with systemic symptoms such as headache or muscle pain. Midostaurin, an inhibitor of receptor tyrosine kinase KIT, may be effective in patients with systemic mastocytosis associated with hematologic malignancy. A premeasured epinephrine pen kit may be considered for those individuals at higher risk for anaphylaxis such as systemic disease, extensive cutaneous disease, high baseline tryptase levels, and known allergies.

For patients with diffuse cutaneous mastocytosis, treatment is similar to urticaria pigmentosa. Phototherapy with narrow-band UV (UVB or UVA-1) or psoralen with UVA treatment may be useful.

Lesions of TMEP may be cautiously treated with vascular pulsed dye lasers.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

700.1 Mast Cell Activation Syndrome

James J. Nocton

Mast cell activation (MCA) occurs in several defined conditions, including primary mast cell disorders, allergic reactions, systemic inflammatory diseases, and drug reactions, and results in the release of multiple proinflammatory mediators, including tryptase, histamine, prostaglandins, and leukotrienes. The effects of these mediators lead to the clinical symptoms of MCA, which may range from mild to severe and may involve multiple organ systems, including the cutaneous, gastrointestinal, respiratory, and cardiovascular systems (Table 700.3). The term *mast cell activation syndrome (MCAS)* has been used to describe a condition associated with symptoms, signs, and laboratory abnormalities that are consistent with the effects of mast cell mediators; it is recurrent, usually severe, and involves multiple organ systems and responds to treatment with medications that are known to inhibit mast cells or secreted mast cell mediators. Consensus criteria for the diagnosis and

Table 700.3 Common Symptoms in Patients with Mast Cell Mediator Disorders

Cardiovascular: chest pain, hypotension, hypotensive syncope, tachycardia
Dermatologic: angioedema, dermatographism, flushing, pruritus, urticaria pigmentosa
Gastrointestinal: abdominal cramping/pain, bloating, diarrhea, esophagitis, nausea, vomiting
Musculoskeletal: bone/muscle pain, degenerative disc disease, osteoporosis/osteopenia
Naso-ocular: nasal congestion, pruritus, tearing
Neurologic: headache, memory and concentration difficulties (brain fog), paresthesia, peripheral neuropathy
Respiratory: hoarseness, sore throat, stridor, throat swelling, wheezing
Systemic: anaphylaxis, fatigue

From Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders? *Expert Rev Clin Immunol.* 2019;15(6):639–656, Table 1.

Table 700.4 Consensus Criteria for the Diagnosis of Mast Cell Activation Syndrome (MCAS)*

Criterion A: Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in the form of anaphylaxis) (definition of systemic: involving at least two organ systems)
Criterion B: Involvement of MC is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to plus 20% + 2 ng/mL†
Criterion C: Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production or drugs blocking mediator release or effects of MC-derived mediators‡

*All three MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS.
†Other MC-derived markers of MCA (histamine and histamine metabolites, PGD_2 metabolites, and heparin) have also been proposed but are less specific compared to tryptase.
‡Example: histamine receptor blockers.
From Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome (MCAS). *J Allergy Clin Immunol Pract.* 2019;7(4):1125–1133, Table I, p. 1126.

Table 700.5 Facial Flushing Etiologies

FLUSHING WITH FOOD
- Alcohol
- Monosodium glutamate (MSG)
- Sulfites
- Scrombroidosis
- Auriculotemporal syndrome (Frey syndrome gustatory flushing)
- Postherpetic gustatory flushing
- Nitrates
- Capsaicin
- Tyramine-containing foods

ENDOCRINE
- Carcinoid
- Pheochromocytoma and paraganglioma
- Medullary thyroid carcinoma
- Pancreatic neuroendocrine tumors (VIP)
- Cushing syndrome
- Perimenopause
- Thyrotoxicosis

OTHER
- Mastocytosis
- Urticaria pigmentosa
- Mast cell activation syndrome
- Harlequin syndrome
- Congenital Horner syndrome
- Idiopathic anaphylaxis
- Panic attacks
- Blushing/anxiety
- Spinal cord injury/autonomic dysregulation
- Niacin supplements

classification of MCAS have been developed (Table 700.4). Under this classification, MCAS is designated primary when it is associated with a defined mast cell disorder such as systemic or cutaneous **mastocytosis**; it is termed secondary when it is recognized in the context of an allergen or another disease known to be associated with MCA; and it is designated idiopathic when neither a primary mast cell disorder nor another associated disease is present.

Patients fulfilling the consensus criteria for MCAS must have *recurrent* clinical manifestations *consistent with MCA*. Cutaneous symptoms have included urticaria, angioedema, itching, and frequent skin **flushing** (Table 700.5). Gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea are common. Tachycardia, sometimes with hypotension and syncope, may be frequent, and some patients have wheezing episodes and rhinitis. Nonspecific and constitutional symptoms have also been described, including headache, fatigue, chronic pain, paresthesias, anxiety, and depression. These nonspecific symptoms most likely represent comorbidities.

Patients diagnosed with MCAS have biochemical evidence indicating mast cell mediator release. **Laboratory abnormalities** that might indicate MCA include elevated serum tryptase and increases in 24-hour urinary histamine metabolites (N-methylhistamine), the prostaglandin D_2 metabolite 2,3-dinor-11-β-$PGF_{2\text{-}\alpha}$, or the leukotriene metabolite LTE_4. The current consensus criteria for the diagnosis of MCAS includes an increase in serum tryptase as the preferred measurement documenting mast cell mediator release (see Table 700.4). Additional biochemical markers have been proposed but remain either of unknown or questionable reliability as markers of MCA.

MCAS has been classified into three groups: primary, secondary, and idiopathic. Primary MCAS refers to patients with *clonal proliferation* of mast cells resulting from pathogenic variants in the *KIT* gene and is usually associated with systemic or cutaneous mastocytosis. A small percentage of those with primary MCAS have clonal proliferation of mast cells but may not completely fulfill the criteria to diagnose systemic or cutaneous mastocytosis. Secondary MCAS refers to patients with either an IgE-dependent allergy, a non–IgE-mediated hypersensitivity disorder, or another inflammatory disease associated with MCA. Idiopathic MCAS refers to patients who do not have clonal mast cells and who do not have an underlying disorder but who nonetheless fulfill the consensus criteria for MCAS with characteristic clinical symptoms and signs, specific abnormal laboratory test results, and a response to treatment that inhibits mast cells or the effect of mast cell mediators.

The **differential diagnosis** of MCAS is broad, reflecting the protean symptoms and signs that have been associated with the syndrome. Cardiovascular conditions may be considered in those with syncope; thyroid disease, adrenal insufficiency, infectious diseases, intoxications, chronic pain syndromes, somatization secondary to anxiety or depression, hypereosinophilic syndromes, hereditary angioedema, and dysautonomias are also considerations in patients with symptoms that appear to be potentially related to MCA. There is also an overlap with idiopathic anaphylaxis and MCAS (see Chapter 190 and Fig. 190.4).

When episodes of cutaneous flushing are the primary symptom and sign, the differential diagnosis is likewise broad. Flushing refers to transient episodes of erythema, most commonly on the face, accompanied by a sensation of warmth. Wet flushing is associated with *increased sweating* and is typical of autonomic nervous system activation, whereas dry flushing occurs without sweating. Wet flushing is more likely caused by panic attacks, pain syndromes, dysautonomia, medications, or toxins. Dry flushing is associated with a more extensive list of

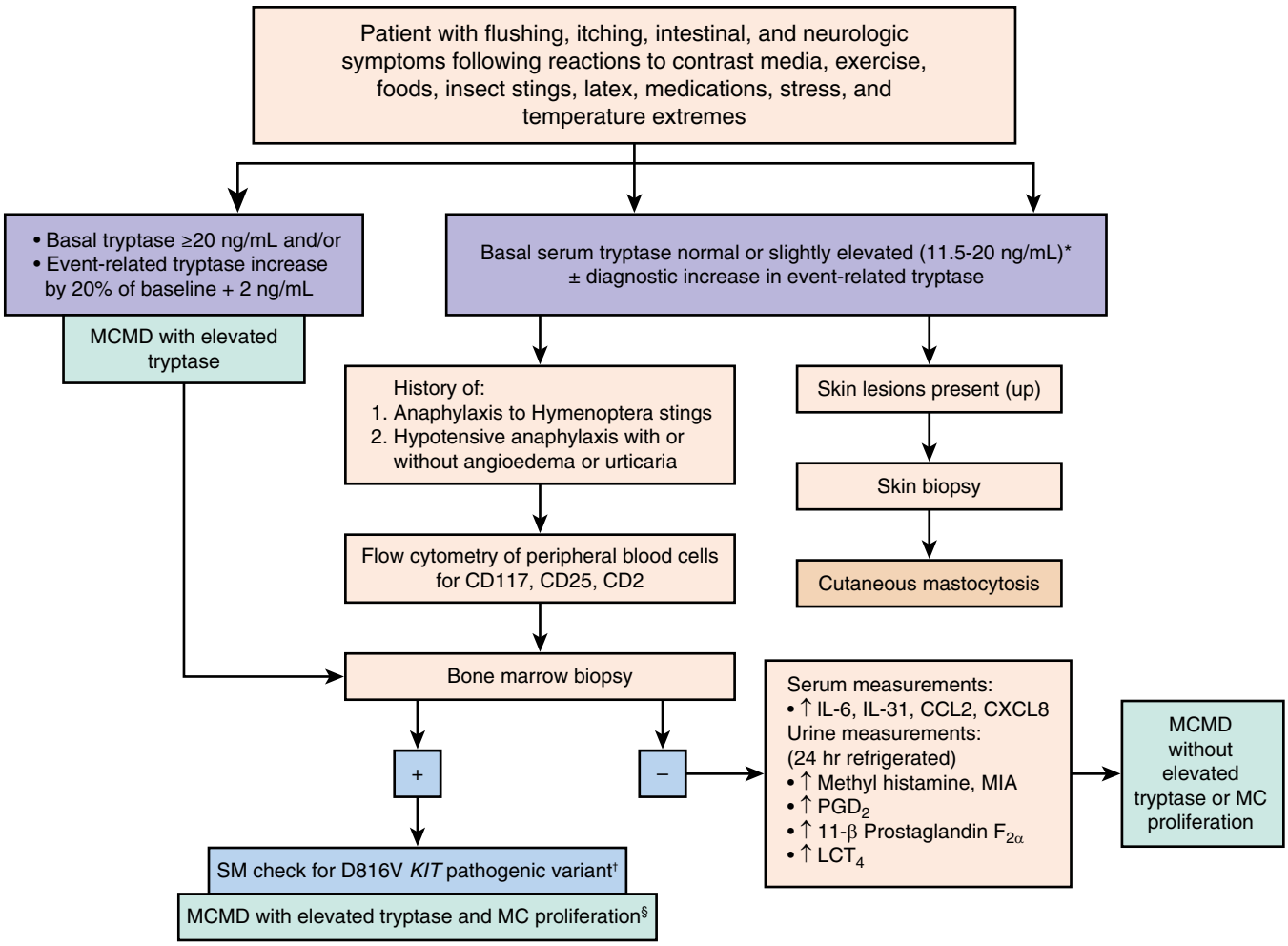

Fig. 700.13 Diagnostic algorithm for mast cell disorders. Diagrammatic representation of a proposed diagnostic rubric for mast cell mediator disorders with emphasis on clonal and nonclonal subtypes and the presence or absence of elevated serum tryptase. MC, Mast cells; MCMD, mast cell mediator disorder; SM, systemic mastocytosis. *This range varies among different laboratories. †KIT pathogenic variants should be investigated. §A patient with elevated basal tryptase should also have BM biopsy; most of these patients have SM. *(From Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders? Expert Rev Clin Immunol. 2019;15[6]:639–656, Fig. 1.)*

possible diagnoses, including MCAS, thyroid disease, foods and other ingestions, some interferonopathies and channelopathies, and tumors such as pheochromocytoma, neuroendocrine tumors, and medullary carcinoma of the thyroid.

When evaluating a patient with symptoms consistent with MCA, if the symptoms are severe, episodic, and respond to mast cell–directed therapy, then the likelihood of MCAS is high. In this setting, further evaluation with serum tryptase measurements should be performed. If the patient fulfills all three diagnostic criteria for MCAS (see Table 700.4), a potential underlying cause should then be sought. This investigation might include genetic analysis of the *KIT* gene in those suspected of having clonal disease such as cutaneous or systemic mastocytosis, a search for potential allergens, or further evaluation for an underlying chronic inflammatory disease (Fig. 700.13). The MCAS can then be classified as primary, secondary, or idiopathic and appropriate management initiated.

The management of MCAS includes medications that interfere with the effects of mast cell mediators, such as the antihistamines cetirizine, loratadine, and fexofenadine; the antileukotrienes montelukast and zafirlukast; and medications that interfere with degranulation such as the mast cell stabilizer cromolyn. Recently, the tyrosine kinase inhibitor midostaurin has also demonstrated efficacy by inhibiting histamine release and increasing apoptosis of mast cells. Management of any identified associated disease is paramount. Prognosis is favorable for most individuals with MCAS but is also dependent on potential associated disease and comorbidities.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 701

Diseases of Subcutaneous Tissue

Jacquelyn R. Sink and Yvonne E. Chiu

Diseases involving the subcutis are usually characterized by necrosis and/or inflammation; they may occur either as a primary event or as a secondary response to various stimuli or disease processes. The principal diagnostic criteria relate to the appearance and distribution of the lesions, associated symptoms, results of laboratory studies, histopathology, and natural history and exogenous provocative factors of these conditions.

CORTICOSTEROID-INDUCED ATROPHY

Intradermal or subcutaneous injection of a corticosteroid can produce deep atrophy accompanied by surface pigmentary changes and telangiectasia (Fig. 701.1). These changes occur approximately 2-8 weeks after injection and may last for months.

RAYNAUD PHENOMENON

An exaggerated vascular response to cold temperatures or emotional stress, Raynaud phenomenon is characterized by sudden-onset, sharply demarcated, transient color changes of the skin of the digits (see Chapter 201). This condition can occur as a primary condition or may be associated with an underlying disorder, such as systemic lupus erythematosus (SLE) or systemic sclerosis. It is thought to be caused by abnormal vasoconstriction of the digital blood vessels.

701.1 Panniculitis and Erythema Nodosum

Jacquelyn R. Sink and Yvonne E. Chiu

Inflammation of the fibrofatty subcutaneous tissue may primarily involve the fat lobule (lobular panniculitis) or the fibrous septum that compartmentalizes the fatty lobules (septal panniculitis). Histopathologic evaluation is usually necessary to confirm the diagnosis. Lobular panniculitis that spares the subcutaneous vasculature includes infectious panniculitis, traumatic panniculitis (including cold and post-steroid panniculitis), connective tissue disease panniculitis, pancreatic panniculitis, α_1 antitrypsin deficiency, subcutaneous fat necrosis (SCFN) of the newborn, sclerema neonatorum, subcutaneous sarcoidosis, and factitial panniculitis. Lobular panniculitis associated with vasculitis occurs in erythema induratum and occasionally as a feature of Crohn's disease (see Chapter 382.2). Septal panniculitis, sparing the vasculature, may be seen in erythema nodosum (Table 701.1 and Fig. 701.2), necrobiosis lipoidica, progressive systemic sclerosis (see Chapter 201), and subcutaneous granuloma annulare (see Chapter 700). Septal panniculitis that includes inflammation of the vessels is found primarily in leukocytoclastic vasculitis and polyarteritis nodosa (see Chapter 210).



Fig. 701.1 Localized fat atrophy with overlying erythema after steroid injection.

ERYTHEMA NODOSUM

Etiology and Pathogenesis

No underlying cause is found in 30–50% of pediatric cases of erythema nodosum; Table 701.1 lists numerous potential etiologies. The most common etiology in children is group A β-hemolytic streptococcal infection. Other causes include *Yersinia enterocolitica* gastroenteritis, medications (cephalosporins, penicillins, macrolides), and inflammatory disorders (inflammatory bowel disease); sarcoidosis should be considered in young adults.

Clinical Manifestations

Erythema nodosum is a nodular erythematous hypersensitivity reaction that typically appears as multiple lesions on the lower legs (favoring the pretibial area) and less often in other areas, including the extensor surfaces of the arms and thighs. The lesions vary in size from 1 to 6 cm and are symmetric and oval, with the longer axis parallel to the extremity. Lesions initially appear bright or dull red but progress to a brown or purple; they are painful and usually do not ulcerate (see Fig. 701.2). Initial lesions may resolve in 1-2 weeks, but new lesions may continue to appear for 2-6 weeks. Repeat episodes may occur over weeks to months. Before or immediately at the onset of lesions, there may be systemic manifestations, including fever, malaise, arthralgias (50–90%), and rheumatoid factor–negative arthritis.

Histology

A septal panniculitis occurs acutely with thickening of the septa and an inflammatory cell infiltrate composed of neutrophils. Monocytes and histiocytes predominate in chronic erythema nodosum.

Treatment

Treatment is directed at the underlying cause. Nonsteroidal antiinflammatory agents (ibuprofen, naproxen, salicylates) may be prescribed for symptomatic relief, along with bed rest and leg elevation. Supersaturated solution of potassium iodide (oral), colchicine, and intralesional corticosteroids can be considered as alternative treatments for persistent symptoms. Oral steroids have been employed for the treatment of severe, persistent, or recurrent lesions. The idiopathic form

Table 701.1 Etiology of Erythema Nodosum

VIRUSES
Epstein-Barr, hepatitis B, mumps
FUNGI
Coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis, *Trichophyton mentagrophytes*
BACTERIA AND OTHER INFECTIOUS AGENTS
Group A streptococcus,* tuberculosis,* *Yersinia, Shigella, Escherichia coli,* cat-scratch disease, leprosy, leptospirosis, tularemia, mycoplasma, Whipple disease, lymphogranuloma venereum, psittacosis, brucellosis, meningococcosis, neisserial infection, syphilis
OTHER
Sarcoidosis, inflammatory bowel disease,* estrogen-containing oral contraceptives,* systemic lupus erythematosus, Behçet syndrome, severe acne, celiac disease, Hodgkin disease, lymphoma, sulfonamides, bromides, echinacea, Sweet syndrome, pregnancy, idiopathic*

*Common.



Fig. 701.2 Tender red nodules with indistinct borders in a teenage girl with erythema nodosum. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002, p. 212.)*

is a self-limited disorder. Protracted or recurrent cases may warrant further workup, including antistreptolysin O/deoxyribonuclease ASO/(DNase) B titer, complete blood count (CBC), throat culture, QuantiFERON-TB gold assay but not a tuberculosis (TB) skin test, chest radiograph, erythrocyte sedimentation rate, and C-reactive protein.

POST-STEROID PANNICULITIS

Etiology and Pathogenesis

The mechanism of the inflammatory reaction in the fat in post-steroid panniculitis is unknown.

Clinical Manifestations

Most cases of post-steroid panniculitis have been reported in children. The disorder occurs in children who have received high-dose corticosteroids, particularly after rapid discontinuation. Within 1-2 weeks after discontinuation of the drug, multiple subcutaneous nodules usually appear on the cheeks, although other areas may be involved. Nodules range in size from 0.5 to 4.0 cm, are erythematous or skin-colored, and may be pruritic or painful.

Histology

A lobular panniculitis is seen with a mixed infiltrate of lymphocytes, histiocytes, and neutrophils. Scattered, swollen adipocytes with eosinophilic, needle-shaped crystals are also seen. The epidermis, dermis, and fibrous septa of the fat are normal. Vasculitis is not seen.

Treatment

Treatment of post-steroid panniculitis is unnecessary because the lesions remit spontaneously over a period of months without scarring.

LUPUS ERYTHEMATOSUS PROFUNDUS (LUPUS ERYTHEMATOSUS PANNICULITIS)

Etiology and Pathogenesis

The pathophysiology of lupus erythematosus profundus is largely unknown. This variant of chronic cutaneous lupus erythematosus is rare in childhood. Only 2–5% of patients with lupus erythematosus profundus have associated SLE. It can occur in association with other forms of cutaneous lupus or as an isolated condition. The mean age of onset in reported pediatric cases is 9.8 years.



Fig. 701.3 Deep nodule of lupus profundus with overlying hyperkeratotic lesion of discoid lupus erythematosus.

Clinical Manifestations

Lupus erythematosus profundus manifests as one to several firm, tender, well-defined, purple plaques or nodules 1-3 cm in diameter. Most pediatric cases involve the head/neck and proximal extremities. This condition may precede or follow the development of other cutaneous lesions and/or SLE. The overlying skin is usually normal but may be erythematous, atrophic, poikilodermatous, ulcerated, or hyperkeratotic (Fig. 701.3). On healing, a shallow depression generally remains or, rarely, soft pink areas of anetoderma result.

Histology

The histopathologic changes in lupus erythematosus profundus are distinctive and may allow the clinician to make the diagnosis in the absence of other cutaneous features of lupus erythematosus. The panniculitis is characterized by a mostly nodular, dense infiltrate of lymphocytes and plasma cells. Necrosis of the fat lobule is characteristic. A dense perivascular and periappendiceal lymphocytic infiltrate is seen in the dermis. Lichenoid changes may be identified at the epidermal-dermal junction. Histopathologic differentiation from subcutaneous panniculitis–like T-cell lymphoma may be difficult and requires T-cell rearrangement studies.

Treatment

Nodules tend to be persistent and frequently ulcerate. Long-term follow-up to evaluate for systemic disease is warranted; approximately 5–10% of patients with lupus erythematosus profundus will have SLE. There is no consensus on the utility of laboratory testing. Antinuclear antibody is positive in only a small subset of patients. A few case reports show slight neutropenia, leukopenia, and mildly elevated liver function tests. Hydroxychloroquine (2-5 mg/kg/day) is the treatment of choice for lupus erythematosus profundus. Systemic corticosteroids may be helpful, but topical corticosteroids are typically ineffective. Intralesional corticosteroids may worsen the lipoatrophy and lead to ulceration. Immunosuppressive agents are indicated only for the treatment of other severe manifestations of SLE. Avoidance of sun exposure and trauma is also important.

α_1-ANTITRYPSIN DEFICIENCY

Etiology and Pathogenesis

Individuals with α_1-antitrypsin deficiency have severe homozygous deficiency (ZZ genotype) or, rarely, a partial deficiency of the protease inhibitor α_1-antitrypsin, which inhibits trypsin activity and the activity of elastase, serine proteases, collagenase, factor VIII, and kallikrein (see Chapter 442). Panniculitis is rare and usually occurs with severe α_1-antitrypsin deficiency.

Clinical Manifestations

Cellulitis-like areas or one or more warm, tender, red nodules occur on the trunk or proximal extremities. Nodules tend to ulcerate

spontaneously and discharge an oily yellow fluid. Panniculitis may be associated with other manifestations of the disease, such as panacinar emphysema, noninfectious hepatitis, cirrhosis, persistent cutaneous vasculitis, cold contact urticaria, and acquired angioedema. Diagnosis can be substantiated by a decreased level of serum α_1-antitrypsin activity.

Histology
Extensive septal and lobular neutrophilic infiltrate with necrosis of the fat is observed.

Treatment
Panniculitis associated with α_1-antitrypsin deficiency typically resolves over several weeks after treatment with intravenous exogenous enzyme replacement therapy.

PANCREATIC PANNICULITIS
Etiology and Pathogenesis
The pathogenesis of pancreatic panniculitis appears to be multifactorial, involving liberation of the lipolytic enzymes lipase, trypsin, and amylase into the circulation, which leads to adipocyte membrane damage and intracellular lipolysis. There is no correlation, however, between the occurrence of panniculitis and the serum concentration of pancreatic enzymes.

Clinical Manifestations
Pancreatic panniculitis manifests most commonly on the pretibial regions, thighs, or buttocks as tender, erythematous nodules that may be fluctuant and occasionally discharge an oily brown or yellowish liquid. It appears most often in males with alcoholism but may also occur in patients with pancreatitis because of cholelithiasis or abdominal trauma, rupture of pancreatic pseudocysts, pancreatic ductal adenocarcinoma, or pancreatic acinar cell carcinoma. Associated features may include polyarthritis **(pancreatitis-panniculitis-polyarthritis syndrome)**. In almost 65% of patients, abdominal signs are absent or mild, making the diagnosis difficult.

Histology
Characteristic histopathologic changes include lobular panniculitis with necrosis of fat cells and ghost cells with thick, shadowy walls and no nuclei.

Treatment
The primary pancreatic disorder must be treated. The arthritis may be chronic and responds poorly to treatment with nonsteroidal antiinflammatory drugs and oral corticosteroids.

SUBCUTANEOUS FAT NECROSIS
Etiology and Pathogenesis
SCFN in infants may be a result of ischemic injury from various perinatal complications, such as maternal preeclampsia, birth trauma, asphyxia, meconium aspiration, and prolonged hypothermia. Whole-body cooling for neonatal hypoxemic-ischemic encephalopathy is increasingly associated with SCFN. Susceptibility is attributed to differences in composition between the subcutaneous tissue of young infants and that of older infants, children, and adults. Neonatal fat solidifies at a relatively high temperature because of its relatively greater concentration of high-melting-point saturated fatty acids, such as palmitic and stearic acids.

Clinical Manifestations
This benign, self-limited inflammatory disorder of adipose tissue occurs primarily in the first few days to weeks of life in apparently healthy, full-term or postterm infants. Some lesions may be present at birth. Typical lesions are asymptomatic, indurated, erythematous to violaceous, sharply demarcated plaques or nodules located primarily on the cheeks, buttocks, back, thighs, or upper arms (Fig. 701.4). Lesions may be focal or extensive and are generally asymptomatic, although they may be tender during the acute phase. Uncomplicated



Fig. 701.4 Red-purple nodular infiltration of the skin of the chest caused by subcutaneous fat necrosis.

lesions involute spontaneously within weeks to months, usually without scarring or atrophy. Calcium deposition may occasionally occur within areas of fat necrosis, which may sometimes result in rupture and drainage of liquid material. These areas may heal with atrophy. A potentially serious complication of SCFN is **hypercalcemia**. It typically manifests before 2 months of age, but can present up to 6 months of age, with lethargy, poor feeding, vomiting, failure to thrive, irritability, seizures, shortening of the QT interval on electrocardiography, and/or renal failure. The origin of the hypercalcemia is unknown, but an accepted hypothesis is that macrophages produce 1,25-dihydroxyvitamin D_3 which, in turn, increases calcium uptake. Infants with SCFN should be monitored for several months after lesion resolution for delayed-onset hypercalcemia.

Histology
Histopathologic changes in SCFN are diagnostic, consisting of necrosis of fat; a granulomatous cellular infiltrate composed of lymphocytes, histiocytes, multinucleated giant cells, and fibroblasts; and radially arranged clefts of crystalline triglyceride within fat cells and multinucleated giant cells. Calcium deposits are commonly found in areas of fat necrosis.

Differential Diagnosis
SCFN can be confused with sclerema neonatorum, panniculitis, cellulitis, and hematoma.

Treatment
Because the lesions are self-limited, therapy is not required for uncomplicated cases of SCFN. Needle aspiration of fluctuant lesions may prevent rupture and subsequent scarring but is rarely needed. Treatment of hypercalcemia is aimed at enhancing renal calcium excretion with hydration and furosemide (1-2 mg/kg/dose) and at limiting dietary intake of calcium and vitamin D. Reduction of intestinal calcium absorption and alteration of vitamin D metabolism may be accomplished by administering corticosteroids (0.5-1.0 mg/kg/day). Bisphosphonates have been used in severe cases.

SCLEREMA NEONATORUM
Etiology and Pathogenesis
Although the cause of sclerema neonatorum remains unknown, multiple theories have been proposed. The hardening of the subcutaneous fat may occur as a response to a decrease in body temperature because of circulatory shock, a defect in lipolytic enzymes or in lipid transport, association with an underlying severe disease, or a special form of edema affecting the connective tissue supporting the adipocytes.

Clinical Manifestations
This uncommon panniculitis manifests abruptly in preterm, gravely ill infants as diffuse, yellowish white, woody indurations of the skin. It begins on the legs and buttocks and then quickly progresses to other areas, sparing the palms and soles. Affected skin becomes stony in

consistency, cold, and nonpitting. The face assumes a masklike expression, and joint mobility may be compromised because of inflexibility of the skin.

Histology
Histopathologic changes in sclerema neonatorum consist of increased size of fat cells and width of the fibrous connective tissue septa. In contrast to SCFN, fat necrosis, inflammation, giant cells, and calcium crystals are generally absent.

Treatment
Sclerema neonatorum is almost always associated with serious illness, such as sepsis, congenital heart disease, multiple congenital anomalies, or hypothermia. The appearance of sclerema in a sick infant should be regarded as an ominous prognostic sign. There is no specific therapy for the condition. The outcome depends on the response of the underlying disorder to treatment.

COLD PANNICULITIS
Etiology and Pathogenesis
The pathogenic mechanism of cold panniculitis may be likened to that of SCFN, involving a greater propensity of fat to solidify in infants than in older children and adults because of the higher percentage of saturated fatty acids in the subcutaneous fat of infants. Lesions occur in infants after prolonged cold exposure, especially on the cheeks, or after prolonged application of a cold object such as an ice cube, ice bags, cooling blankets, or popsicles to any area of the skin.

Clinical Manifestations
Ill-defined, erythematous to bluish, painful, indurated plaques or nodules arise within hours to a few days in areas exposed to cold (face, arms, legs); the lesions persist for 2-3 weeks and heal without residua.

Histology
Histopathologic examination reveals an infiltrate of lymphoid and histiocytic cells around blood vessels at the dermal-subdermal junction and in the fat lobules; by the third day, some of the fat cells in the subcutis may have ruptured and coalesced into cystic structures.

Differential Diagnosis
Cold panniculitis may be confused with facial cellulitis caused by *Haemophilus influenzae* type b. As opposed to buccal cellulitis, the area may be cold to the touch, and the patient is afebrile and appears well. **Familial cold autoinflammatory syndrome** manifests with urticaria on exposure to cold environments; associated features include conjunctivitis, myalgias, fatigue, and elevated inflammatory markers. **Cold urticaria**, in contrast, occurs on direct contact with cold objects, resulting in urticaria at the site, which can be reproduced with the ice cube test.

Treatment
Treatment is unnecessary because cold panniculitis resolves spontaneously. Recurrence of the lesions is common, emphasizing the importance of parental education.

CHILBLAINS (PERNIO)
Etiology and Pathogenesis
Vasospasm of arterioles from damp cold exposure with resultant hypoxemia and localized perivascular mononuclear inflammation appears to be responsible for chilblains (see Chapter 90). The disease is most commonly idiopathic but may be associated with cryoglobulins, antiphospholipid antibodies, anorexia nervosa, or a thin body habitus. There are reports of chilblain-like rash occurring during the COVID-19 pandemic.

Clinical Manifestations
The condition is characterized by initial blanching followed by localized, symmetric, erythematous to violaceous, edematous plaques and nodules in areas exposed to cold, typically acral sites (distal hands and feet, ears, face). Lesions develop 12-24 hours after cold exposure and may be associated with numbness, tingling, itching, burning, or pain. Blister formation and ulceration are rare (see Chapter 90).

Histology
Histopathologic examination reveals marked dermal edema and a perivascular and periappendiceal, predominantly T-cell lymphocytic infiltrate in the papillary and reticular dermis.

Differential Diagnosis
Raynaud phenomenon is a more acute condition than chilblains, with characteristic color changes and no chronic lesions. Frostbite due to extreme cold exposure is painful and involves freezing of the tissue, with resultant tissue necrosis.

Treatment
Most cases of chilblains resolve spontaneously, but the condition can last up to 2-3 weeks. Prevention is the treatment of choice. Nifedipine (0.25-0.5 mg/kg 3 times a day, maximum 10 mg/dose) may be used in severe cases. Unusual or persistent cases of perniosis in children may warrant further workup, including antinuclear antibody titer, cryoglobulins, antiphospholipid antibodies, CBC with differential, and cold agglutinins.

FACTITIAL PANNICULITIS
Etiology and Pathogenesis
Factitial panniculitis results from subcutaneous injection of a foreign substance by the patient or a proxy. The most common substances are organic materials such as milk and feces; drugs, such as the opiates and pentazocine; oily materials, such as mineral oil and paraffin; and the synthetic polymer povidone.

Clinical Manifestations
Indurated plaques, ulcers, or nodules that liquefy and drain may be noted clinically in factitial panniculitis.

Histology
The histopathology is variable, depending on the injected substance, but may include the presence of birefringent crystals, oil cysts surrounded by fibrosis and inflammation, and an acute inflammatory reaction with fat necrosis. Vessels are characteristically spared.

Treatment
Treatment of factitial panniculitis must address the primary reason for the performance of this self-destructive act. Munchausen syndrome by proxy should be considered in young children (see Chapter 17.2).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

701.2 Lipodystrophy
Leah Lalor

Lipodystrophies are conditions that share a common finding of reduction in subcutaneous fat, often with accompanying lipohypertrophy in other areas. They may be inherited or acquired. Several lipodystrophy syndromes have been described, which are extremely rare disorders of deficient body fat associated with many metabolic complications. Lipoatrophy is selective loss of fat (whereas lipodystrophy is redistribution of fat) and is associated with medications, HIV infection, trauma or pressure, autoimmune disorders, and after inflammation of fat.

Lipodystrophies are defined by etiology (congenital or acquired) and distribution of fat loss (generalized or partial). This results in four main types of lipodystrophy: congenital generalized lipodystrophy, familial partial lipodystrophy, acquired generalized lipodystrophy, and acquired partial lipodystrophy.

GENERALIZED LIPODYSTROPHY
Generalized lipodystrophy may be congenital or acquired and is characterized by loss of fat affecting the whole body.

Congenital generalized lipodystrophy (CGL): This is an autosomal recessive disorder characterized by nearly complete lack of subcutaneous fat starting at birth or in infancy with prominent musculature, phlebomegaly, acanthosis nigricans, hepatomegaly, umbilical prominence, and voracious appetite in childhood. There are several known genetic causes, each with unique clinical features. Metabolic complications are frequent and may be severe.

Acquired generalized lipodystrophy (AGL): This typically presents before adolescence with progressive fat loss of the whole body, including palms and soles, and is more common in females (3:1 female:male). There may be fat accumulation in the face, neck, and/or axillae. There are frequent and often severe metabolic complications, and this is associated with autoimmune disease.

PARTIAL LIPODYSTROPHY

Partial lipodystrophy is when part of the body has loss of fat with frequent excess fat accumulation elsewhere in the body. It may be inherited or acquired.

Familial partial lipodystrophy (FPLD): This is a group of autosomal dominant disorders in which fat loss affects the limbs, buttocks, and hips with excess fat accumulation in other areas dependent on particular subtype. Fat distribution is often normal in childhood with development of progressive loss of fat around puberty. There is often associated muscular hypertrophy and metabolic complications in adulthood, particularly cardiac.

Acquired partial lipodystrophy (APL): As in AGL, this is more common in females (4:1 female:male) and begins in childhood with progressive loss of fat in a cranial-to-caudal distribution. Fat accumulation may appear in the hips, buttocks, and legs. Metabolic complications are uncommon, but it is associated with autoimmune diseases, in particular, membranoproliferative glomerulonephritis.

Diagnosis

Diagnosis of lipodystrophy is based on history, physical examination, body composition, and metabolic status, and confirmatory genetic testing may be helpful in suspected familial cases, but formal diagnostic criteria have not been established. Lipodystrophy should be suspected in patients with regional or generalized lack of adipose tissue outside the normal range and in children with failure to thrive. Additional physical features include prominent muscles and veins; severe acanthosis nigricans; eruptive xanthomas; and Cushingoid, acromegaloid, or progeroid appearance. Familial forms can be suspected when there is a clear familial pattern.

Differential diagnosis includes other conditions that present with severe weight loss, including malnutrition, eating disorders, uncontrolled diabetes mellitus, thyrotoxicosis, adrenocortical deficiency, cancer cachexia, HIV-associated wasting, and chronic infections.

Screening for Comorbidities

Metabolic comorbidities are common in many forms of lipodystrophy, and all patients should be screened for dyslipidemia, diabetes, nonalcoholic fatty liver disease, and cardiovascular and reproductive dysfunction. Those with APL are at lower risk for metabolic issues.

Dyslipidemia: Triglycerides should be measured at least annually and with new-onset abdominal pain or appearance of cutaneous xanthomas. Fasting lipid panel should be measured at diagnosis and yearly after age 10 years.

Diabetes mellitus: Screening should be formed annually following the guidelines of the American Diabetes Association, which includes fasting plasma glucose, oral glucose tolerance test, or glycosylated hemoglobin.

Liver disease: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be measured yearly with liver ultrasound performed at diagnosis and then clinically as indicated based on symptoms or laboratory abnormalities. Liver biopsy should be performed as indicated clinically.

Reproductive dysfunction: Early adrenarche, true precocious puberty, or central hypogonadism may occur in children with generalized lipodystrophy, and oligo/amenorrhea, decreased fertility, and polycystic ovary syndrome are common in women with lipodystrophy. Measurement of gonadal steroids and gonadotropins, and pelvis ultrasonography should be performed as clinically indicated with pubertal staging performed annually for children.

Cardiac disease: Hypertension is common in lipodystrophy syndromes, even in children. Blood pressure should be measured at least yearly. ECG and echocardiogram should be done yearly in CGL and progeroid disorders and at diagnosis and as clinically indicated in FPLD and AGL.

Kidney disease: Protenuria is common. Urine protein should be measured yearly using 24-hour collection or spot urine protein-to-creatinine ratio. Kidney biopsy should be done as indicated clinically.

Malignancy: Lymphomas occur in AGL. Appropriate screening has not been established but could include yearly skin and lymph node exam. Generalized lipodystrophy has been reported as a paraneoplastic phenomenon in pilocytic astrocytoma in some children who recovered body fat after treatment. Some progeroid syndromes are associated with increased malignancy risk.

Treatment of Lipodystrophy

There is no cure for lipodystrophy, and no treatment that can regrow lost adipose tissue; however, there are some ways to prevent or improve the associated comorbidities. Diet is the cornerstone of therapy for the metabolic complications of lipodystrophies, and a dietician should be consulted for children with these diagnoses. Medium-chain triglyceride oil formulas can provide energy and reduce triglycerides in infants. Most patients with lipodystrophy should be encouraged to be physically active, though some should have a cardiac evaluation before engaging in an intense exercise regimen.

Metreleptin is recombinant human methionyl leptin and is the only approved medication for lipodystrophy. It is a first-line treatment for metabolic and endocrine abnormalities in generalized lipodystrophy and may be used for prevention of these complications in children. Treatment for specific metabolic complications can be reviewed elsewhere.

Consideration should be given to referral to plastic surgeons and/or cosmetic dermatologists for patients with distress related to their body appearance. Mental health professionals may also be helpful.

HIV/ART-ASSOCIATED LIPODYSTROPHY

This is the most common form of *nonlocalized* lipodystrophy and is linked to protease inhibitors and nucleoside analogue reverse transcriptase inhibitors. It may affect up to 40% of patients within 1-2 years of antiretroviral therapy (ART) initiation. Typical manifestations include lipoatrophy of peripheral sites (face, limbs, heel pads, buttocks), central lipohypertrophy (particularly dorsocervical, supraclavicular, breast, intraabdominal, and visceral), and metabolic abnormalities (insulin resistance, type 2 diabetes mellitus, dyslipidemia, hypertension, lactic acidosis). These changes are progressive and largely irreversible, can be disfiguring and stigmatizing, and may result in a lack of adherence to treatment.

LOCALIZED LIPOATROPHY

Localized lipoatrophy can be idiopathic or secondary to subcutaneous medication injections, pressure, and panniculitis. Unlike generalized or partial lipodystrophy, localized lipoatrophy involves a small part of the body and has no accompanying metabolic derangements. Idiopathic and pressure-induced lipoatrophy manifest as annular atrophy at the ankles; a bandlike semicircular depression 2-4 cm in diameter on the thighs, abdomen, and/or upper groin; or a centrifugally spreading, depressed, bluish plaque with an erythematous margin. Medication-induced lipoatrophy is most common with insulin and injected corticosteroids, though others have been reported. **Insulin lipoatrophy** usually occurs approximately 6 months to 2 years after the initiation of relatively high doses of insulin. A dimple or well-circumscribed depression at or surrounding the site of injection is typically seen. Lesions may be prevented by frequent rotation of injection sites or a switch to insulin pump.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 702

Disorders of the Sweat Glands

Kari L. Martin

Eccrine glands are found over nearly the entire skin surface and provide the primary means, through evaporation of the water in sweat, of cooling the body. These glands, which have no anatomic relationship to hair follicles, secrete a relatively large amount of odorless aqueous sweat. In contrast, apocrine sweat glands are limited in distribution to the axillae, anogenital skin, mammary glands, ceruminous glands of the ear, Moll glands in the eyelid, and selected areas of the face and scalp. Each apocrine gland duct enters the pilosebaceous follicle at the level of the infundibulum and secretes a small amount of a complex, viscous fluid that, on alteration by microorganisms, produces a distinctive body odor. Some disorders of these two types of sweat glands are similar pathogenetically, whereas others are unique to a given gland.

ANHIDROSIS

Neuropathic anhidrosis results from a disturbance in the neural pathway from the control center in the brain to the peripheral efferent nerve fibers that activate sweating. Disorders in this category, which are characterized by generalized anhidrosis, include **congenital insensitivity to pain with anhidrosis (CIPA)**, tumors of the hypothalamus, and damage to the floor of the third ventricle. Pontine or medullary lesions may produce anhidrosis of the ipsilateral face or neck and ipsilateral or contralateral anhidrosis of the rest of the body. Peripheral or segmental neuropathies, caused by leprosy, amyloidosis, diabetes mellitus, alcoholic neuritis, or syringomyelia, may be associated with anhidrosis of the innervated skin. Various autonomic disorders are also associated with altered eccrine sweat gland function.

At the level of the sweat gland, anticholinergics (drugs such as atropine and scopolamine) may paralyze the sweat glands. Acute intoxication with barbiturates or diazepam has produced necrosis of sweat glands, resulting in anhidrosis with or without erythema and bullae. Eccrine glands are largely absent throughout the skin or are present in a localized area among patients with **hypohidrotic ectodermal dysplasia (HED)** or **localized congenital absence of sweat glands**, respectively. Infiltrative or destructive disorders that may produce atrophy of sweat glands by pressure or scarring include scleroderma, acrodermatitis chronica atrophicans, radiodermatitis, burns, Sjögren syndrome, multiple myeloma, and lymphoma. Obstruction of sweat glands may occur in miliaria and in a number of inflammatory and hyperkeratotic disorders, such as the ichthyoses, psoriasis, lichen planus, pemphigus, porokeratosis, atopic dermatitis, and seborrheic dermatitis. Occlusion of the sweat pore may also occur with the topical agents aluminum and zirconium salts, formaldehyde, or glutaraldehyde.

Diverse disorders that are associated with anhidrosis by unknown mechanisms include dehydration, uremia, cirrhosis, endocrine disorders such as Addison disease, diabetes mellitus, diabetes insipidus, and hyperthyroidism, toxic overdose with lead, arsenic, thallium, fluorine, or morphine, and inherited conditions such as autonomic neuropathies, Fabry disease, Franceschetti-Jadassohn syndrome, which combines features of incontinentia pigmenti and HED, CIPA, and familial anhidrosis with neurolabyrinthitis.

Anhidrosis may be complete, but in many cases, what appears clinically to be anhidrosis is actually hypohidrosis caused by anhidrosis of many, but not all, eccrine glands. Compensatory, localized hyperhidrosis of the remaining functional sweat glands may occur, particularly in diabetes mellitus and miliaria. The primary complication of anhidrosis is *hyperthermia,* seen primarily in anhidrotic ectodermal dysplasia or in otherwise normal preterm or full-term neonates who have immature eccrine glands.

HYPERHIDROSIS

Etiology and Pathogenesis

Hyperhidrosis is excessive sweating beyond what is physiologically necessary for temperature control and occurs in 3% of the population, with about half having axillary hyperhidrosis. The numerous disorders that can be associated with increased production of eccrine sweat may also be classified into those with neural mechanisms involving an abnormality in the pathway from the neural regulatory centers to the sweat gland and those that are nonneurally mediated and occur by direct effects on the sweat glands (Table 702.1).

Clinical Manifestations

The average age at onset of hyperhidrosis is 14-25 years. The excess sweating may be continuous or may occur in response to emotional stimuli. In severe cases, sweat may be seen to drip constantly from the hands.

Treatment

Excessive sweating of the palms and soles (volar hyperhidrosis) and axillary sweating may respond to 20% aluminum chloride in anhydrous ethanol applied under occlusion for several hours, iontophoresis, injection with botulinum toxin, therapy with oral anticholinergics and antimuscarinic drugs (oxybutynin), or in severe, refractory cases, cervicothoracic or lumbar sympathectomy. Reports of successful treatment of hyperhidrosis with ultrasound and microwave technology are available, but studies are faulted with small sample size and/or lack of controls.

MILIARIA

Etiology and Pathogenesis

Miliaria results from retention of sweat in occluded eccrine sweat ducts. The eruption is most often induced by hot, humid weather, but it may also be caused by high fever. Infants who are dressed too warmly may demonstrate this eruption indoors, even during the winter.

Clinical Manifestations

In miliaria crystallina, asymptomatic, noninflammatory, pinpoint, clear vesicles may suddenly erupt in profusion over large areas of the body surface, leaving brawny desquamation on healing (Fig. 702.1). This type of miliaria occurs most frequently in newborn infants because of the relative immaturity and delayed patency of the sweat duct and the tendency for infants to be nursed in relatively warm, humid conditions. It may also occur in older patients with hyperpyrexia or hypernatremia.

Miliaria rubra is a less superficial eruption characterized by erythematous, minute papulovesicles that may impart a prickling sensation. The lesions are usually localized to sites of occlusion or to flexural areas, such as the neck, groin, and axillae, where friction may have a role in their pathogenesis. Involved skin may become macerated and eroded. However, lesions of miliaria rubra are extrafollicular.

Repeated attacks of miliaria rubra may lead to miliaria profunda, which is caused by rupture of the sweat duct deeper in the skin, at the level of the dermal-epidermal junction. Severe, extensive miliaria rubra or miliaria profunda may result in disturbance of heat regulation. Lesions of miliaria rubra may become infected, particularly in malnourished or debilitated infants, leading to development of **periporitis staphylogenes**, which involves extension of the process from the sweat duct into the sweat gland.

Histology

Histologically, miliaria crystallina reveals an intracorneal or subcorneal vesicle in communication with the sweat duct, whereas in miliaria rubra, one sees focal areas of spongiosis and spongiotic vesicle formation in close proximity to sweat ducts that generally contain a keratinous plug.

Table 702.1 Causes of Hyperhidrosis

CORTICAL
- Emotional
- Familial dysautonomia
- Congenital ichthyosiform erythroderma
- Epidermolysis bullosa
- Nail-patella syndrome
- Jadassohn-Lewandowsky syndrome
- Pachyonychia congenita
- Palmoplantar keratoderma
- Stroke

HYPOTHALAMIC

Drugs
- Alcohol
- Antipyretics
- Cocaine
- Emetics
- Insulin
- Opiates (including withdrawal)
- Ciprofloxacin
- Exercise

Infection
- Defervescence
- Chronic illness

Metabolic
- Carcinoid syndrome
- Debility
- Diabetes mellitus
- Hyperpituitarism
- Hyperthyroidism
- Hypoglycemia
- Obesity
- Pheochromocytoma
- Porphyria
- Pregnancy
- Rickets
- Infantile scurvy

Cardiovascular
- Heart failure
- Shock
- Vasomotor
- Cold injury
- Raynaud phenomenon
- Rheumatoid arthritis

Neurologic
- Abscess
- Familial dysautonomia
- Postencephalitic
- Tumor
- Absence of corpus callosum

Miscellaneous
- Chédiak-Higashi syndrome
- Compensatory
- Lymphoma
- Phenylketonuria
- Vitiligo
- Frey syndrome

MEDULLARY
- Physiologic gustatory sweating
- Encephalitis
- Granulosis rubra nasi
- Syringomyelia
- Thoracic sympathetic trunk injury

SPINAL
- Cord transection
- Syringomyelia

CHANGES IN BLOOD FLOW
- Maffucci syndrome
- Arteriovenous fistula
- Klippel-Trénaunay syndrome
- Glomus tumor
- Blue rubber-bleb nevus syndrome

Differential Diagnosis

The clarity of the fluid, superficiality of the vesicles, and absence of inflammation permit differentiation of miliaria crystalline from other blistering disorders. Miliaria rubra may be confused with or superimposed on other diaper area eruptions, including candidiasis and folliculitis.

Treatment

All forms of miliaria respond dramatically to cooling of the patient by regulation of environmental temperatures and by removal of excessive clothing; administration of antipyretics is also beneficial to patients with fever. Topical agents are usually ineffective and may exacerbate the eruption.

BROMHIDROSIS

Bromhidrosis, characterized by excessive odor, may result from alteration of either apocrine or eccrine sweat. Apocrine bromhidrosis develops after puberty as a result of the formation of short-chain fatty acids and ammonia by the action of anaerobic diphtheroids on axillary apocrine sweat. Eccrine bromhidrosis is caused by microbiologic degradation of stratum corneum that has become softened by excessive eccrine sweat. The soles of the feet and the intertriginous areas are the primary affected sites. Hyperhidrosis, warm weather, obesity, intertrigo, and diabetes mellitus are predisposing factors. Treatments that may be helpful include cleansing with germicidal soaps, topical clindamycin or erythromycin, or topical application of aluminum or zirconium. In addition, more invasive surgical and laser treatments have been used. Treatment of any associated hyperhidrosis is mandatory.



Fig. 702.1 Superficial clear vesicles of miliaria crystallina.

HIDRADENITIS SUPPURATIVA

Etiology and Pathogenesis

Hidradenitis suppurativa (HS) is a disease of the apocrine gland–bearing areas of the skin. The pathogenesis of hidradenitis suppurativa is controversial. It is believed that it is a primary inflammatory disorder of the hair follicle and not solely an alteration of apocrine glands. It is considered a part of the follicular occlusion tetrad, along with acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus. The natural history of the disease involves progressive dilation below the follicular obstruction, leading to rupture of the duct, inflammation, sinus tract formation, and destructive scarring. It has been associated with Sjögren syndrome, inflammatory bowel disease, obesity, smoking, diabetes mellitus, and thyroid disease. It is also known to occur in other family members and may be associated with loss-of-function pathogenic variants in multiple genes in some patients (Fig. 702.2). HS has been one manifestation of autoinflammatory syndromes, including pyoderma gangrenosum-acne-HS (PASH) (*PSTPIP1* promoter), pyoderma gangrenosum-acne-pyogenic arthritis-HS (PAPASH) (*PSTPIP1*), and psoriatic arthritis-pyoderma gangrenosum-acne-HS (PsAPASH).

Clinical Manifestations

HS is a chronic, inflammatory, suppurative disorder of the follicular units in the axillae, anogenital area, and, occasionally, the scalp, posterior aspect of the ears, inframammary folds (female), and periumbilical area (Fig. 702.3). Onset of clinical manifestations is sometimes preceded by pruritus or discomfort and usually occurs during puberty or early adulthood. Solitary or multiple painful erythematous nodules, deep abscesses, and contracted scars are sharply confined to areas of skin containing apocrine glands. When the disease is severe and chronic, sinus tracts, ulcers, and thick, linear fibrotic bands develop. HS tends to persist for many years, punctuated by relapses and partial remissions. Complications include cellulitis, ulceration, and burrowing abscesses that may perforate adjacent structures, forming fistulas to the urethra, bladder, rectum, or peritoneum. Episodic inflammatory arthritis develops in some patients. Obesity and smoking may worsen or trigger symptoms. Patients with HS have an increased risk of adverse cardiovascular outcomes and a long-term risk of squamous cell carcinoma.

The autoinflammatory associated disorders present with fever, joint pain, cutaneous lesions (severe painful acne), and elevated inflammatory markers (ESR, CRP).

Differential Diagnosis

Early lesions of HS are often mistaken for infected epidermal cysts, furuncles, scrofuloderma, actinomycosis, cat-scratch disease, granuloma inguinale, or lymphogranuloma venereum. However, sharp localization to areas of the body that bear apocrine glands should suggest hidradenitis. When involvement is limited to the anogenital region, the condition may be difficult to distinguish from Crohn's disease.

Treatment

Conservative management includes cessation of smoking, weight loss, and avoidance of irritation of the affected area. Warm compresses and topical antiseptic or antibacterial soaps may also be helpful. For mild, early disease, topical clindamycin 1% may be helpful. For more severe disease, therapy may be initiated with doxycycline (100 mg bid) or minocycline (100 mg bid) in adolescents and young adults. Some patients require intermittent or long-term antibiotic treatment. Combination therapy with clindamycin and rifampin is helpful in some patients. Oral retinoids for 5-6 months may also be effective, although disease may recur. Oral contraceptive agents, which contain a high estrogen:progesterone ratio and low androgenicity of the progesterone, are another alternative along with spironolactone. Laser hair ablation has proven helpful in some studies as well. Systemic immunosuppressants (infliximab, adalimumab, cyclosporine, anakinra) and medications targeted at glucose metabolism and metabolic syndrome (metformin) have been helpful in patients resistant to more traditional measures. Adalimumab, a tumor necrosis factor-alpha (TNF-α) inhibitor, is the only FDA-approved medication for the treatment of moderate-to-severe HS. Surgical measures, including deroofing procedures and full excision, may be a helpful adjuvant to medical therapy, especially in recalcitrant cases.

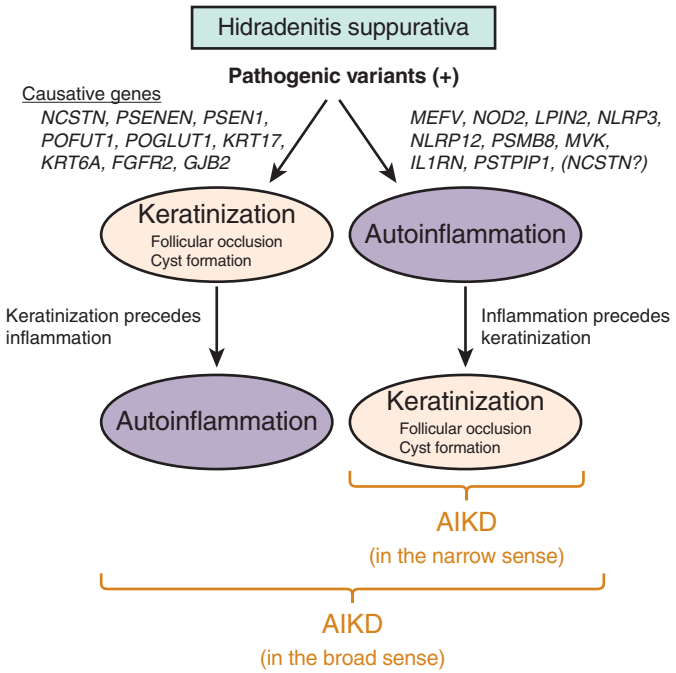

Fig. 702.2 Hidradenitis suppurativa and autoinflammatory keratinization disease (AIKD). Genes responsible for hidradenitis suppurativa can be divided into two groups. One includes *NCSTN, PSENEN, PSEN1, POFUT1, POGLUT1, KRT17, KRT6A, FGFR2,* and *GJB2*, whose pathogenic variants result in autoinflammation preceded by keratinization. This hidradenitis suppurativa subtype can be regarded as an autoinflammatory keratinization disease in the broad sense. The other group includes *MEFV, NOD2, LPIN2, NLRP3, NLRP12, PSMB8, MVK, IL1RN, PSTPIP1,* and possibly *NCSTN*, whose pathogenic variants lead to keratinization preceded by autoinflammation. This hidradenitis suppurativa subtype can be regarded as an autoinflammatory keratinization disease in the narrow sense. *(From Nomura T. Hidradenitis suppurativa as a potential subtype of autoinflammatory keratinization disease. Front Immunol. 2020;11:847, Fig. 1.).*

FOX-FORDYCE DISEASE

Etiology and Pathogenesis

The cause of Fox-Fordyce disease is unknown, but it is related to blockage of apocrine sweat glands.

Clinical Manifestations

This disease is most common in females and manifests during puberty to the third decade of life as pruritus primarily in the axillae, although the areolae, pubic, and perineal regions can also be affected. Pruritus is exacerbated by emotional stress and stimuli that induce apocrine sweating. Dome-shaped, skin-colored to slightly hyperpigmented, follicular papules develop in the pruritic areas.

Treatment

Fox-Fordyce disease is difficult to treat. Oral contraceptive pills and topical treatments, including corticosteroids, antibiotics, or retinoids, may help some patients. Systemic isotretinoin and ablative lasers have shown varying efficacy. Mechanical destruction and removal of apocrine glands have been used in recalcitrant cases. Partial response has been seen in one study using botulinum toxin type A.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.



Fig. 702.3 Hidradenitis suppurativa. **A,** This young man had recurrent inflammatory papules and nodulocystic lesions in the axillae and groin for 5 years. Although lesions initially improved with oral antibiotics, he subsequently developed draining sinus tracts. **B,** This young woman had multiple indurated sinus tracts, nodules, and ulcers with purulent and necrotic drainage in her axillae. *(From Rachidi S, Bender AM, Cohen BA. Disorders of the hail and nails. In: Cohen BA, ed. Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2022, Fig. 8.42.)*

Chapter 703

Disorders of Hair

Kari L. Martin

Disorders of hair in infants and children may be a result of intrinsic disturbances of hair growth, underlying biochemical or metabolic defects, inflammatory dermatoses, or structural anomalies of the hair shaft. Excessive and abnormal hair growth is referred to as hypertrichosis or hirsutism. **Hypertrichosis** is excessive hair growth at inappropriate locations; **hirsutism** is an androgen-dependent male pattern of hair growth in women (see Chapter 589). **Hypotrichosis** is deficient hair growth. Hair loss, partial or complete, is called **alopecia**. Alopecia may be classified as nonscarring or scarring; the latter type is rare in children and, if present, is most often caused by prolonged or untreated inflammatory conditions such as pyoderma and tinea capitis.

HYPERTRICHOSIS

Hypertrichosis is rare in children and may be localized or generalized and permanent or transient. Tables 703.1 and 703.2 list some of the many causes of hypertrichosis.

HYPOTRICHOSIS AND ALOPECIA

Table 703.3 lists some of the disorders associated with hypotrichosis and alopecia. True alopecia is rarely congenital; it is more often related to an inflammatory dermatosis, mechanical factors, drug ingestion, infection, endocrinopathy, nutritional disturbance, or disturbance of the hair cycle. Any inflammatory condition of the scalp, such as atopic dermatitis or seborrheic dermatitis, if severe enough, may result in partial alopecia. Unless the hair follicle has been permanently damaged, hair growth returns to normal if the underlying condition is treated successfully.

Hair loss in childhood should be divided into the following four categories: congenital diffuse, congenital localized, acquired diffuse, and acquired localized.

Table 703.1 Causes of Hypertrichosis and Associated Conditions

INTRINSIC FACTORS
Racial and familial forms such as hairy ears, hairy elbows, intraphalangeal hair, or generalized hirsutism
EXTRINSIC FACTORS
Local trauma Malnutrition Anorexia nervosa Long-standing inflammatory dermatoses Drugs: Diazoxide, phenytoin, corticosteroids, Cortisporin, cyclosporine, androgens, anabolic agents, hexachlorobenzene, minoxidil, psoralens, penicillamine, streptomycin, danazol, omeprazole, valproic acid
HAMARTOMAS OR NEVI
Congenital pigmented nevocytic nevus, hair follicle nevus, Becker nevus, congenital smooth muscle hamartoma, fawn-tail nevus associated with diastematomyelia
ENDOCRINE DISORDERS
Virilizing ovarian tumors, Cushing syndrome, acromegaly, hyperthyroidism, hypothyroidism, congenital adrenal hyperplasia, adrenal tumors, gonadal dysgenesis, male pseudohermaphroditism, nonendocrine hormone–secreting tumors, polycystic ovary syndrome, pigmentary hypertrichosis with non-autoimmune diabetes mellitus *(SLC29A3)*
CONGENITAL AND GENETIC DISORDERS (SEE TABLE 703.2)

Acquired localized hair loss is the most common type of hair loss in childhood. Three conditions—traumatic alopecia, alopecia areata, and tinea capitis—are predominantly seen (Tables 703.4 and 703.5).

TRAUMATIC ALOPECIA (TRACTION ALOPECIA, HAIR PULLING, TRICHOTILLOMANIA)

Traction Alopecia

Traction alopecia is common and is seen in almost 20% of school-aged females with coily or kinky hair. It is caused by trauma to the hair follicles from tight braids or ponytails, headbands, rubber bands, curlers, weaves, or rollers (Fig. 703.1). There is a greater risk of traction alopecia if hair trauma is combined with chemically relaxed hair. Broken hairs and inflammatory follicular papules in circumscribed patches at the scalp margins are characteristic and may be accompanied by regional lymphadenopathy. Children and parents must be encouraged to avoid devices that cause trauma to the hair and, if necessary, to alter the hairstyle. Otherwise scarring of hair follicles may occur. Treatment with topical phenylephrine, an α_1-adrenergic receptor agonist, facilitates contraction of arrector pili smooth muscle and shows promise in decreasing hair loss and increasing the force needed for epilation.

Hair Pulling

Hair pulling in childhood is usually an acute reactional process related to emotional stress, or it may be a habit (especially in young children). It may also be seen in trichotillomania (obsessive-compulsive disorder) and as part of more severe psychiatric disorders, usually in adolescents.

Table 703.2 Congenital Syndromes Associated with Generalized Hypertrichosis

Acromegaloid facial appearance syndrome (affected genes: *PGM1, GLO1, IGHG3, HP*)
Barber-Say syndrome *(KMT2A)*
Cantú syndrome (hypertrichosis with osteochondrodysplasia) (*ABCC9, KCNJ8*)
Coffin-Siris syndrome (BAF complex genes)
Cornelia de Lange (Brachmann-de Lange) syndrome (*NIPBL, SMC1A, SMC3, RAD21, HDAC8*)
Craniofacial dysostosis
Eye disorders • With amaurosis congenital, cone-rod type • With congenital lamellar cataracts and mental retardation • With pigmentary retinopathy
Gorlin-Chaudhry-Moss (oculo-facio-cardio-dental) syndrome *(BCOR)*
Gingival hyperplasia • Congenital generalized hypertrichosis with gingival hyperplasia • Zimmerman-Laband syndrome
Hemimaxillofacial dysplasia
Lipodystrophies • Berardinelli-Seip syndrome (*BSCL*) • Donohue syndrome (leprechaunism) (*INSR*)
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome
Mucopolysaccharidoses • Hunter syndrome • Hurler syndrome • Sanfilippo syndrome
Porphyrias • Erythropoietic porphyria (Gunther disease) • Familial porphyria cutanea tarda • Hepatoerythropoietic porphyria
Rubinstein-Taybi syndrome (*CREBBP, EP300*)
Schinzel-Giedion syndrome (*SETBP1* [MAJ359])
Stiff skin syndrome
Toxin exposure • Fetal alcohol syndrome • Fetal hydantoin syndrome
Weidemann-Steiner syndrome (*KMT2A*)
Winchester (Torg-Winchester) syndrome (*MMP2*)

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022, Box 7.8, p. 191.

Trichotillomania

Etiology and Pathogenesis. The *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5) classifies trichotillomania in the category of obsessive-compulsive and related disorders. The diagnostic criteria for trichotillomania include visible hair loss attributable to pulling; mounting tension preceding or during hair pulling; gratification or release of tension after hair pulling; and absence of hair pulling attributable to hallucinations, delusions, or an inflammatory skin condition.

Clinical Manifestations. Compulsive pulling, twisting, and breaking of hair produces irregular areas of incomplete hair loss, most often on the crown and in the occipital and parietal areas of the scalp. Occasionally eyebrows, eyelashes, and body hair are traumatized. Trichotillomania often begins during periods of inactivity (going to bed, watching TV) and is frequently unobserved by the parents. Some plaques of alopecia may have a linear outline. The hairs remaining within the areas of loss are of various lengths (Fig. 703.2) and are typically blunt-tipped because of breakage. The scalp usually appears normal, although hemorrhage, crusting (Fig. 703.3), and chronic folliculitis may also occur. Long-term repeated trauma may result in irreversible damage and permanent alopecia. Trichophagy, resulting in trichobezoars, may complicate this disorder.

Differential Diagnosis. Acute reactional hair pulling, tinea capitis, and alopecia areata must be considered in the differential diagnosis of trichotillomania (see Tables 703.4 and 703.5).

Treatment. Trichotillomania is closely related to obsessive-compulsive disorder and may be an expression of it for some children. When trichotillomania occurs secondary to obsessive-compulsive disorder, clomipramine 50-150 mg/day or a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine may be helpful, particularly when combined with behavioral interventions (see Chapter 37). *N*-Acetylcysteine may also be helpful.

Table 703.3 Disorders Associated with Alopecia and Hypotrichosis

Congenital total alopecia: Atrichia with papules, Moynahan alopecia syndrome
Congenital localized alopecia: Aplasia cutis, triangular alopecia, sebaceous nevus
Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis (Mari type), ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia, "pure" hair and nail and other ectodermal dysplasias
Diffuse alopecia of endocrine origin: Hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism
Alopecia of nutritional origin: Marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency
Disturbances of the hair cycle: Telogen effluvium
Toxic alopecia: Anagen effluvium
Autoimmune alopecia: Alopecia areata
Traumatic alopecia: Traction alopecia, trichotillomania
Cicatricial alopecia: Lupus erythematosus, lichen planopilaris, pseudopelade, morphea (*en coup de sabre*) dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis
Hair shaft abnormalities: Monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, trichodento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi)

ALOPECIA AREATA

Etiology and Pathogenesis

Alopecia areata is a T-cell–driven autoimmune disorder producing nonscarring alopecia. The cause is unknown. It is hypothesized that in genetically susceptible individuals, loss of immune privilege of the hair follicle allows for T-cell inflammation against anagen hairs and follicles, leading to stoppage of hair growth.

Clinical Manifestations

Alopecia areata is characterized by rapid and complete loss of hair in round or oval patches on the scalp (Fig. 703.4), eyebrows, eyelashes, and on other body sites. In alopecia totalis, all the scalp hair is lost (Fig. 703.5); alopecia universalis involves all body and scalp hair. The lifetime incidence of alopecia areata is 0.1–0.2% of the population. More than half of affected patients are younger than 20 years of age.

The skin within the plaques of hair loss appears normal. Alopecia areata is associated with atopy and with nail changes such as pits (Fig. 703.6), longitudinal striations, and leukonychia. Autoimmune diseases such as Hashimoto thyroiditis, Addison disease, pernicious anemia, ulcerative colitis, myasthenia gravis, collagen vascular diseases, and vitiligo may also be seen. An increased incidence of alopecia areata has been reported in patients with Down syndrome (5–10%).

Differential Diagnosis

Tinea capitis, seborrheic dermatitis, trichotillomania, traumatic alopecia, and lupus erythematosus should be considered in the differential diagnosis of alopecia areata (see Tables 703.4 and 703.5).

Treatment

The course is unpredictable, but spontaneous resolution in 6-12 months is usual, particularly when relatively small, stable patches of alopecia are present. Recurrences are common. Onset at a young age, extensive or prolonged hair loss, and numerous episodes are usually poor prognostic signs. Alopecia universalis, alopecia totalis, and alopecia ophiasis (Fig. 703.7)—a type of alopecia areata in which hair loss is circumferential—are also less likely to resolve. Therapy is difficult to evaluate because the course is erratic and unpredictable. The use of highly potent or superpotent topical corticosteroids is effective in

Table 703.4 Helpful Historical Clues in the Diagnosis of Hair Disorders

HISTORICAL CONSIDERATIONS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Are the spots itchy?	Negative	Negative	Positive	Usually negative
Do the spots come and go?	Negative	Sometimes positive	Negative	Sometimes positive
Is the hair falling out in clumps?	Positive	Negative	Negative	Usually negative
Are there any anxiety disorders or obsessive-compulsive tendencies?	Negative	Positive	Negative	Negative

From Lio PA. What's missing from this picture? An approach to alopecia in children. *Arch Dis Child Educ Pract Ed.* 2007;92:193–198.

Table 703.5 Helpful Physical Examination Clues in the Diagnosis of Hair Disorders

PHYSICAL FINDINGS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Scarring?	Negative	Negative	Usually negative	Negative
Exclamation-point hairs?	Negative	Negative	Negative	Positive
Irregular pattern with mixed length and stubbly hairs?	Negative	Positive	Negative	Negative
Scaling, pustules, or kerion?	Negative	Negative	Positive	Negative
Positive hair-pull test result?	Positive	Negative	Negative	Usually negative
Nail pitting or grooves?	Negative	Negative	Negative	Positive

From Lio PA. What's missing from this picture? An approach to alopecia in children. *Arch Dis Child Educ Pract Ed.* 2007;92:193–198.



Fig. 703.1 Traction alopecia.



Fig. 703.2 Hair pulling. Hairs are broken off at various lengths.



Fig. 703.3 Hemorrhage and crusting secondary to hair pulling.



Fig. 703.4 Circular patch of alopecia areata with normal-appearing scalp.



Fig. 703.5 Alopecia totalis: total loss of scalp hair.



Fig. 703.6 Multiple nail pits in alopecia areata.



Fig. 703.7 Ophiasis pattern of alopecia areata.

some patients. Intradermal injections of steroid (triamcinolone 5 mg/mL) every 4-6 weeks may also stimulate hair growth locally, but this mode of treatment is impractical in young children or in patients with extensive hair loss. Systemic corticosteroid therapy (prednisone 1 mg/kg/day) is associated with good results; the permanence of cure is questionable, however, and the side effects of chronic oral corticosteroids are a serious deterrent. Some patients may maintain hair growth by switching to a more appropriate long-term immunosuppressant such as methotrexate. Additional therapies that are sometimes effective include short-contact anthralin, topical minoxidil, and contact sensitization with squaric acid dibutylester or diphenylcyclopropenone. Janus kinase inhibitors, both oral and topical, may also be used. In general, parents and patients can be reassured that spontaneous remission of alopecia areata usually occurs. New hair growth may initially be of finer caliber and lighter color, but replacement by normal terminal hair can be expected.

ACQUIRED DIFFUSE HAIR LOSS

Telogen Effluvium

Telogen effluvium manifests as sudden loss of large amounts of hair, often with brushing, combing, and washing of hair. Diffuse loss of scalp hair occurs from premature conversion of growing, or anagen, hairs, which normally constitute 80–90% of hairs, to resting, or telogen, hairs. Hair loss is noted 6 weeks to 3 months after the precipitating cause, which may include childbirth; a febrile episode; surgery; acute blood loss, including blood donation; sudden severe weight loss; discontinuation of high-dose corticosteroids or oral contraceptives; hypothyroidism or hyperthyroidism; and psychiatric stress. Telogen effluvium also accounts for the loss of hair by infants in the first few months of life; friction from bed sheets, particularly in infants with pruritic, atopic skin, may exacerbate the problem. There is no inflammatory reaction; the hair follicles remain intact, and telogen bulbs can be demonstrated microscopically on shed hairs. Because >50% of the scalp hair is rarely involved, alopecia is usually not severe. Parents should be reassured that normal hair growth will return within approximately 3-6 months.

Toxic Alopecia (Anagen Effluvium)

Anagen effluvium is an acute, severe, diffuse inhibition of growth of anagen follicles, resulting in the loss of >80–90% of scalp hair. Hairs become dystrophic, and the hair shaft breaks at the narrowed segment. Loss is diffuse, rapid (1-3 weeks after treatment), and temporary, as regrowth occurs after the offending agent is discontinued. Causes of anagen effluvium include radiation; cancer chemotherapeutic agents such as antimetabolites, alkylating agents, and mitotic inhibitors; thallium; thiouracil; heparin; the coumarins; boric acid; and hypervitaminosis A (see Table 703.6).

Table 703.6 Possible Etiology of Anagen Effluvin

CANCER THERAPY
Chemotherapy
Radiation therapy
TOXIC METAL (SEE CHAPTER 760)
Lead (see Chapter 761)
Mercury
Arsenic (rat, insect poison)
Thallium (rat poison)
Bismuth
TOXIC CHEMICALS
Boric acid (pesticide, cleaning agent)
Warfarin
Colchicine

CONGENITAL DIFFUSE HAIR LOSS

Congenital diffuse hair loss is defined as congenitally thin hair diffusely related to either hypoplasia of hair follicles or to structural defects in hair shafts.

Structural Defects of Hair

Structural defects of the hair shaft may be congenital, reflect known biochemical aberrations, or be related to damaging grooming practices. All the defects can be demonstrated by microscopic examination of affected hairs, particularly with scanning and transmission electron microscopy, although many can even be seen by simple trichography done in the office.

Trichorrhexis Nodosa

Congenital trichorrhexis nodosa is an autosomal dominant condition. The hair is dry, brittle, and lusterless, with irregularly spaced, grayish white nodes on the hair shaft. Microscopically, the nodes have the appearance of two interlocking brushes (Fig. 703.8A). The defect results from a fracture of the hair shaft at the nodal points caused by disruption of the cells in the hair cortex. Trichorrhexis nodosa has also been observed in some infants with Menkes syndrome, trichothiodystrophy, citrullinemia, and argininosuccinic aciduria.

Acquired Trichorrhexis Nodosa

Acquired trichorrhexis nodosa, the most common cause of hair breakage, occurs in two forms. Proximal defects are found most frequently in children with coily or kinky hair, whose complaint is not of alopecia but of failure of the hair to grow. The hair is short, and longitudinal splits, knots, and whitish nodules can be demonstrated in hair mounts. Easy breakage is demonstrated by gentle traction on the hair shafts. A history of other affected family members may be obtained. The problem may be caused by a combination of genetic predisposition and the cumulative mechanical trauma of rough combing and brushing, hair-straightening procedures, and "permanents." Patients must be cautioned to avoid damaging grooming techniques. A soft, natural-bristle brush and a wide-toothed comb should be used. The condition is self-limited, with resolution in 2-4 years, if patients avoid damaging practices. Distal trichorrhexis nodosa is seen more frequently in children with loose curly or straight hair types. The distal portion of the hair shaft is thinned, ragged, and faded; white specks, sometimes mistaken for nits, may be noted along the shaft. Hair mounts reveal the paintbrush defect and the sites of excessive fragility and breakage. Localized areas of the moustache or beard may also be affected. Avoidance of traumatic grooming, regular trimming of affected ends, and the use of cream rinses to lessen tangling ameliorate this condition.

Pili Torti

Patients with pili torti present with spangled, brittle, coarse hair of different lengths over the entire scalp. There is a structural defect in which the hair shaft is grooved and flattened at irregular intervals and is twisted on its axis to various degrees. Minor twists that occur in normal hair should not be misconstrued as pili torti. Curvature of the hair follicle apparently leads to the flattening and rotation of the



Fig. 703.8 A, Microscopic hair fracture in trichorrhexis nodosa. B, Beading of hair in monilethrix. C, Cuplike abnormality of hair in Netherton syndrome.

hair shaft. The genetic defect in isolated pili torti is unknown, and both autosomal dominant and recessive forms have been described. Syndromes in which the hair shaft abnormalities of pili torti are seen in association with other cutaneous and systemic abnormalities include Menkes kinky hair syndrome, Björnstad syndrome (pili torti with deafness; *BCS1L* gene), and multiple ectodermal dysplasia syndromes.

Menkes Kinky Hair Syndrome (Trichopoliodystrophy)

Males with Menkes kinky hair syndrome, an X-linked recessive trait, are born to an unaffected mother after a normal pregnancy. Neonatal problems include hypothermia, hypotonia, poor feeding, seizures, and failure to thrive. Hair is normal to sparse at birth but is replaced by short, fine, brittle, light-colored hair that may have features of trichorrhexis nodosa, pili torti, or monilethrix. The skin is hypopigmented and thin, cheeks typically appear plump, and the nasal bridge is depressed. Progressive psychomotor retardation is noted in early infancy. Pathogenic variants in the *ATP7A* gene, encoding a copper-transporting adenosine triphosphatase protein, cause Menkes kinky hair syndrome. It is a result of maldistribution of the copper in the body. Copper uptake across the brush border of the small intestine is increased, but copper transport from these cells into the plasma is defective, resulting in low total body copper stores. Parenteral administration of copper-histidine is helpful if begun in the first 2 months of life.

Monilethrix

The hair shaft defect known as monilethrix is inherited as an autosomal dominant trait with variable age of onset, severity, and course. Pathogenic variants in the hair keratins *KRT81* (hHb1), *KRT83* (hHb3), and *KRT86* (hHb6) have been identified in autosomal dominant cases, and pathogenic variants in desmoglein 4 are found in autosomal recessive cases. The hair appears dry, lusterless, and brittle, and it fractures spontaneously or with mild trauma. Eyebrows, lashes, body and pubic hair, and scalp hair may be affected. Monilethrix may be present at birth, but the hair is usually normal at birth and is replaced in the first few months of life by abnormal hairs; the condition is sometimes first apparent in childhood. Follicular papules may appear on the nape of the neck and the occiput and, occasionally, over the entire scalp. Short, fragile beaded hairs that emerge from the horny follicular plugs give a distinctive appearance. Keratosis pilaris and koilonychia of fingernails and toenails may also be present. Microscopically, a distinctive, regular beading pattern of the hair shaft is evident, characterized by elliptic nodes that are separated by narrower internodes (see Fig. 703.8B). Not all hairs have nodes, and both normal and beaded hairs may break. Patients should be advised to handle the hair gently to minimize breakage. Treatment is generally ineffective, although oral retinoids and topical minoxidil have produced some improvement.

Trichothiodystrophy

Hair in trichothiodystrophy is sparse, short, brittle, and uneven; the scalp hair, eyebrows, or eyelashes may be affected. Microscopically, the hair is flattened, folded, and variable in diameter; it has longitudinal grooving and nodal swellings that resemble those seen in trichorrhexis nodosa. Under a polarizing microscope, distinctive alternating dark and light bands are seen. The abnormal hair has a cystine content that is <50% of normal because of a major reduction in and altered composition of constituent high-sulfur matrix proteins. Trichothiodystrophy is caused by pathogenic variants in DNA repair/transcription genes (*XPD, XPB, TTDN1,* and *TTDA*) and may occur as an isolated finding or in association with various syndrome complexes that include intellectual impairment, short stature, ichthyosis, nail dystrophy, dental caries, cataracts, decreased fertility, neurologic abnormalities, bony abnormalities, and immunodeficiency. Some patients are photosensitive and have impaired DNA repair mechanisms, similar to that seen in groups B and D xeroderma pigmentosum; the incidence of skin cancers, however, is not increased. Patients with trichothiodystrophy tend to resemble one another, with a receding chin, protruding ears, raspy voice, and sociable, outgoing personality. Trichoschisis, a fracture perpendicular to the hair shaft, is characteristic of the many syndromes that are associated with trichothiodystrophy. Perpendicular breakage of the hair shaft has also been described in association with other hair abnormalities, particularly monilethrix.

Trichorrhexis Invaginata (Bamboo Hair)

Short, sparse, fragile hair without apparent growth is characteristic of trichorrhexis invaginata, which is found primarily in association with Netherton syndrome (see Chapter 699). It has also been reported in other ichthyosiform dermatoses. The distal portion of the hair is invaginated into the cuplike proximal portion, forming a fragile nodal swelling (see Fig. 703.8C).

Pili Annulati

Alternating light and dark bands of the hair shaft characterize pili annulati. When viewed under the light microscope, the region of the hair shaft that appeared bright in reflected light instead appears dark in the transmitted light as a result of focal aggregates of abnormal air-filled cavities within the shaft. The hair is not fragile. The defect may be autosomal dominant or sporadic in inheritance and usually begins after age 2. Pseudopili annulati is a variant of normal blond hair; an optical effect caused by the refraction and reflection of light from the partially twisted and flattened shaft creates the impression of banding.

Woolly Hair Disease

Woolly hair diseases manifest at birth as peculiarly tight, curly, abnormal hair in a person who is not Black. Autosomal dominant and recessive (*PKRY5* gene) types have been described along with the genodermatoses Naxos disease and Carvajal syndrome, which are associated with cardiomyopathy. Woolly hair nevus, a sporadic form, involves only a circumscribed portion of the scalp hair. The affected hair is fine, tightly curled, and light-colored, and it grows poorly. Microscopically, an affected hair is oval and shows twisting of 180 degrees on its axis.

Uncombable Hair Syndrome (Spun-Glass Hair)

The hair of patients with uncombable hair syndrome appears disorderly, is often silvery blond (Fig. 703.9), and may break because of



Fig. 703.9 Complicated combing. Blond, frizzy, and glistening hair in uncombable hair syndrome. *(From Drivenes JL, Betz RC, Bygum A. A girl with unruly locks: molecular genetics makes a diagnosis of uncombable hair syndrome. Lancet. 2022;399:1079.)*

repeated, futile efforts to control it. Eyebrows and eyelashes are normal. A longitudinal depression along the hair shaft is a constant feature, and most hair follicles and shafts are triangular (pili trianguli et canaliculi). The shape of the hair varies along its length, however, preventing the hairs from lying flat.

The disorder is associated with pathogenic variants in *PAD13, TCHH,* and *TGM3* genes. Most patients have no other findings, but in some there may be associated brachydactyly, ectodermal dysplasia, cataracts, and oligodontia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 704.1 White Nail or Nail Bed Changes

DISEASE	CLINICAL APPEARANCE
Anemia	Diffuse white
Arsenic	Mees lines: transverse white lines
Cirrhosis	Terry nails: most of nail, zone of pink at distal end (see Fig. 704.6)
Congenital leukonychia (autosomal dominant; variety of patterns)	Syndrome of leukonychia, knuckle pads, deafness; isolated finding; partial white
Darier disease	Longitudinal white streaks
Half-and-half nail	Proximal white, distal pink azotemia
High fevers (some diseases)	Transverse white lines
Hypoalbuminemia	Muehrcke lines: stationary paired transverse bands
Hypocalcemia	Variable white
Malnutrition	Diffuse white
Pellagra	Diffuse milky white
Punctate leukonychia	Common white spots
Tinea and yeast	Variable patterns
Thallium toxicity (rat poison)	Variable white
Trauma	Repeated manicure: transverse striations
Zinc deficiency	Diffuse white

From Habif TP, ed. *Clinical Dermatology,* 4th ed. Philadelphia: Mosby; 2004:887.

Table 704.2 Congenital Diseases with Nail Defects

Large nails	Pachyonychia congenita, Rubinstein-Taybi syndrome, hemihypertrophy
Smallness or absence of nails	Ectodermal dysplasias, nail-patella, dyskeratosis congenita, focal dermal hypoplasia, cartilage-hair hypoplasia, COIF, Ellis–van Creveld, Larsen, epidermolysis bullosa, incontinentia pigmenti, Rothmund-Thomson, Turner, Coffin-Siris, popliteal web, trisomies (8, 13, 18), Apert, Gorlin-Pindborg, long arm 21 deletion, otopalatodigital, elfin facies, anonychia, Noonan, acrodermatitis enteropathica, teratogens (alcohol, warfarin, hydantoin)
Other	Congenital malalignment of the great toenails, familial dystrophic shedding of the nails

COIF, Congenital onychodysplasia of index fingers.

Chapter 704
Disorders of the Nails

Kari L. Martin

Nail abnormalities in children may be manifestations of generalized skin disease, skin disease localized to the periungual region, systemic disease, drugs, trauma, or localized bacterial and fungal infections (Table 704.1). Nail anomalies are also common in certain congenital disorders (Table 704.2).

ABNORMALITIES IN NAIL SHAPE OR SIZE

Anonychia is absence of the nail plate, usually a result of a congenital disorder or trauma. It may be an isolated finding or may be associated with malformations of the digits. **Koilonychia** is flattening and concavity of the nail plate with loss of normal contour, producing a spoon-shaped nail (Fig. 704.1). Koilonychia occurs as an autosomal dominant trait or in association with iron-deficiency anemia, Plummer-Vinson syndrome, hemochromatosis, various genodermatoses, and occupational trauma. The nail plate is relatively thin for the first year or two of life and, consequently, may be spoon-shaped in otherwise normal children.

Congenital nail dysplasia, an autosomal dominant disorder, manifests at birth as longitudinal streaks and thinning of the nail plate. There is platyonychia and koilonychia, which may overgrow the lateral folds and involve all nails of the toes and fingers.

Nail-patella syndrome is an autosomal dominant disorder in which the nails are 30–50% of their normal size and often have triangular or pyramidal lunulae. The thumbnails are always involved, although in some cases only the ulnar half of the nail may be affected or may be missing. Nail involvement is symmetric, and the nails from the index finger to the little finger are progressively less damaged. The patella is also smaller than usual or absent, and this anomaly may lead to knee instability. Iliac horns, bony spines arising from the posterior aspect of the iliac bones; overextension of joints; skin laxity; ocular anomalies;



Fig. 704.1 Spoon nails (koilonychia). Most cases are a variant of normal. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:885.)*



Fig. 704.2 Finger clubbing. The distal phalanges are enlarged to a rounded bulbous shape. The nail enlarges and becomes curved, hard, and thickened. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:885.)*

Table 704.3 Clubbing in Children*

HISTORY	SYMPTOM	DISEASE
ACQUIRED		
Generalized	Pulmonary	Cystic fibrosis Bronchiectasis Tuberculosis, aspergillosis Asthma complicated by lung infections Sarcoidosis Pulmonary fibrosis Tumors
	Cardiovascular	Cyanotic congenital heart disease Subacute bacterial endocarditis Myxomas
	Gastrointestinal	Inflammatory bowel disease Gardner's syndrome Parasitosis Cirrhosis Chronic active hepatitis
	Endocrine	Diamond's syndrome (myxedema, exophthalmos and clubbing) Hypervitaminosis A Malnutrition
Limited to one or more digits		Aortic/subclavian artery aneurysm Brachial plexus injury Trauma Maffucci's syndrome Gout Sarcoidosis Severe herpetic whitlow
Hereditary		Pachydermoperiostosis Familial, isolated
Pseudoclubbing*		Apert's syndrome Pfeiffer's syndrome Rubinstein-Taybi syndrome

*Broad distal phalanges with normally shaped nails.
Modified from Baran R, Dawber RPR. *Diseases of the Nails and Their Management.* Oxford: Blackwell Science; 1984:29.

and nephropathy, the most serious feature, may also be present. Nail-patella syndrome is caused by pathogenic variants in the transcription factor *LMX1B* gene.

For a discussion of pachyonychia congenita, see Chapter 699.

Habit tic deformity consists of a depression down the center of the nail with numerous horizontal ridges extending across the nail from it. One or both thumbs are usually involved as a result of chronic rubbing and picking at the nail with an adjacent finger. Treatment aims at cessation of trauma to the nail via massaging with bland ointments, physical barriers, or cyanoacrylate adhesive.

Clubbing of the nails is characterized by swelling of each distal digit, an increase in the angle between the nail plate and the proximal nail fold (Lovibond angle) to >180 degrees, and a spongy feeling when one pushes down and away from the interphalangeal joint because of an increase in fibrovascular tissue between the matrix and the phalanx (Fig. 704.2). The pathogenesis is not known. Nail clubbing is seen in association with diseases of numerous organ systems, including pulmonary, cardiovascular (cyanotic heart disease), gastrointestinal (celiac disease, inflammatory bowel disease), and hepatic (chronic hepatitis) systems, and in healthy individuals as an idiopathic or familial finding (Table 704.3).

CHANGES IN NAIL COLOR

Leukonychia is a white opacity of the nail plate that may involve the entire plate or may be punctate or striate (see Table 704.1). The nail plate itself remains smooth and undamaged. Leukonychia can be traumatic or associated with infections such as leprosy and tuberculosis, dermatoses such as lichen planus and Darier disease, malignancies such as Hodgkin disease, anemia, and arsenic poisoning (Mees lines). Leukonychia of all nail surfaces is an uncommon hereditary autosomal dominant trait that may be associated with congenital epidermal cysts and renal calculi. Paired parallel white bands that do not change position with growth of the nail, fade with pressure, and thus reflect a change in the nail bed are associated with hypoalbuminemia and are called *Muehrcke lines.* When the proximal portion of the nail is white and the distal 20–50% of the nail is red, pink, or brown, the condition is called *half-and-half nails* or *Lindsay nails;* this is seen most commonly in patients with renal disease but may occur as a normal variant. White nails of cirrhosis, or Terry nails (Fig. 704.3), are characterized by a white ground-glass appearance of the entire or the proximal end of the nail and a normal pink distal 1-2 mm of the nail; this finding can also be associated with congestive heart failure and adult-onset diabetes and can be normal in children less than 4 years old.



Fig. 704.3 Terry nails. The nail bed is white with only a narrow zone of pink at the distal end. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:885.)*



Fig. 704.4 Green/black discoloration at the edge of the nails secondary to *Pseudomonas* infection.

Black pigmentation of an entire nail plate or linear bands of pigmentation **(melanonychia striata)** is most common in individuals with Fitzpatrick type IV-VI skin. Most often, the pigment is melanin, which is produced by melanocytes of a junctional nevus in the nail matrix and nail bed and is of no consequence. Extension or alteration in the pigment should be evaluated by biopsy because of the possibility of malignant change.

Bluish black to greenish nails may be caused by *Pseudomonas* infection (Fig. 704.4), particularly in association with onycholysis or chronic paronychia. The coloration is caused by subungual debris and pyocyanin pigment from the bacterial organisms.

Yellow nail syndrome manifests as thickened, excessively curved, slow-growing yellow nails without lunulae. All nails are affected in most cases. Associated systemic diseases include bronchiectasis, recurrent bronchitis, chylothorax, and focal edema of the limbs and face. Deficient lymphatic drainage, caused by hypoplastic lymphatic vessels, is believed to lead to the manifestations of this syndrome.

Splinter hemorrhages most often result from minor trauma but may also be associated with subacute bacterial endocarditis, vasculitis, Langerhans cell histiocytosis, severe rheumatoid arthritis, peptic ulcer disease, hypertension, chronic glomerulonephritis, cirrhosis, scurvy, trichinosis, malignant neoplasms, and psoriasis (Fig. 704.5 and Table 704.4).

NAIL SEPARATION

Onycholysis indicates separation of the nail plate from the distal nail bed. Common causes are trauma, long-term exposure to moisture, hyperhidrosis, cosmetics, psoriasis, fungal infection (distal onycholysis), atopic or contact dermatitis, porphyria, drugs (bleomycin, vincristine, retinoid agents, indomethacin, chlorpromazine [Thorazine]), and drug-induced phototoxicity from tetracyclines (Fig. 704.6) or chloramphenicol (Table 704.5).



Fig. 704.5 Splinter hemorrhage of the distal nail bed due to trauma. *(From Hordinsky M, Sawaya ME, Scher RK. Atlas of Hair and Nails. London: Churchill Livingstone; 1999.)*

Table 704.4 Disorders Associated with Subungual Hemorrhage

	SPLINTER-SHAPED	HEMATOMAS
Normal variant	+	–
Blood dyscrasias	+	+
Collagen diseases (lupus erythematosus)	+	+
Trichinosis	+	–
Trauma	+	+
Child abuse	+	+
Cryoglobulinemia	+	–
Drug eruptions	+	–
Dialysis	+	–
Endocarditis (SBE)	+	–
Emboli	+	+
Langerhans cells histiocytosis	+	–
Arterial lines or punctures	+	–
Sarcoidosis	+	–
Sepsis	+	–
Thyroid disease	+	–
Vasculitis	+	–
Phototoxicity (tetracyclines)	+	–

From Silverman R, Baran R. Nail and appendageal abnormalities. In: Schachner LA, Hansen RC, eds. *Pediatric Dermatology,* 4th ed. Philadelphia: Mosby; 2011, Table 12.9, p. 813.

Beau lines are transverse grooves in the nail plate (Fig. 704.7) that represent a temporary disruption of formation of the nail plate. The lines first appear a few weeks after the event that caused the disruption in nail growth. A single transverse ridge appears at the proximal nail fold in most 4- to 6-week-old infants and works its way distally as the nail grows; this line may reflect metabolic changes after delivery. At



Fig. 704.6 Distal onycholysis secondary to oral tetracycline usage and ultraviolet light exposure.

Table 704.5 Underlying Causes of Onycholysis

CHEMICAL IRRITANTS
Cosmetics, especially with formaldehyde
Depilatories
Detergents
Nail polish removers
Organic solvents
INFLAMMATORY DISORDERS
Alopecia areata
Atopic dermatitis
Contact dermatitis
Lichen planus
Psoriasis
INFECTIOUS DISORDERS
Bacterial paronychia
Candidiasis
Herpes simplex (whitlow)
Onychomycosis
Verrucae
MEDICATIONS
Anticonvulsants (valproic acid)
Chemotherapeutic agents (especially taxanes)
Griseofulvin
Retinoids (isotretinoin)
Tetracyclines (photoonycholysis)
Thiazides (photoonycholysis)
SYSTEMIC DISORDERS
Iron-deficiency anemia
Rheumatic disease
Thyroid disease (hyperthyroidism or hypothyroidism)
Kawasaki disease
MIS-C
TRAUMA
Compulsive subungual cleaning
Sportsman toe

MIS-C, multisystem inflammatory syndrome in children.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022, Box 7.9, p. 201.

other ages, Beau lines are usually indicative of periodic trauma or episodic shutdown of the nail matrix secondary to a systemic disease such as hand-foot-and-mouth disease, measles, mumps, pneumonia, or zinc deficiency. Onychomadesis is an exaggeration of Beau lines leading to proximal separation of the nail bed (Fig. 704.8).

NAIL CHANGES ASSOCIATED WITH SKIN DISEASE

Nail changes may be particularly associated with various other diseases. Nail changes of psoriasis most characteristically include pitting, onycholysis, yellow-brown discoloration, and thickening. Nail changes in lichen planus include violaceous papules in the proximal nail fold and nail bed,



Fig. 704.7 Beau lines. Longitudinal disruption of the nail.



Fig. 704.8 Onychomadesis. Proximal nail bed separation.

leukonychia, longitudinal ridging, thinning of the entire nail plate, and pterygium formation, which is abnormal adherence of the cuticle to the nail plate or, if the plate is destroyed focally, to the nail bed. Postinfectious reactive arthritis syndromes may include painless erythematous induration of the base of the nail fold; subungual parakeratotic scaling; and thickening, opacification, or ridging of the nail plate. Dermatitis that involves the nail folds may produce dystrophy, roughening, and coarse pitting of the nails. Nail changes are more common in atopic dermatitis than in other forms of dermatitis that affect the hands. Darier disease is characterized by red or white streaks that extend longitudinally and cross the lunula. Where the streak meets the distal end of the nail, a V-shaped notch may be present. Total leukonychia may also occur. Transverse rows of fine pits are characteristic of alopecia areata. In severe cases, the entire nail surface may be rough. Patients with acrodermatitis enteropathica may have transverse grooves (Beau lines) and nail dystrophy as a result of periungual dermatitis.

TRACHYONYCHIA (20-NAIL DYSTROPHY)

Trachyonychia is characterized by longitudinal ridging, pitting, fragility, thinning, distal notching, and opalescent discoloration of all the nails (Fig. 704.9). Patients can have no associated skin or systemic diseases and no other ectodermal defects. Its occasional association with alopecia areata has led some authorities to suggest that trachyonychia may reflect an abnormal immunologic response to the nail matrix, whereas histopathologic studies have suggested that it may be a manifestation of lichen planus, psoriasis, or spongiotic (eczematous) inflammation of the nail matrix. The disorder must be differentiated from fungal infections, psoriasis, nail changes of alopecia areata, and nail dystrophy secondary to eczema. Eczema and fungal infections rarely produce changes in all the nails simultaneously. The disorder is self-limited, can be treated with potent topical steroids or topical retinoids, and eventually remits by adulthood.

NAIL INFECTION

Fungal infection **(onychomycosis)** of the nails has been classified into four types. White superficial onychomycosis manifests as diffuse or speckled white discoloration of the surface of the toenails. It is caused primarily by *Trichophyton mentagrophytes,* which invades the nail plate. The organism



Fig. 704.9 Dystrophy of all nails in trachyonychia.



Fig. 704.10 Discoloration, hyperkeratosis, and crumbling of nail secondary to dermatophyte infection.

may be scraped off the nail plate with a blade, but treatment is best accomplished by the addition of a topical azole antifungal agent. Distal subungual onychomycosis, the most common type, involves foci of onycholysis under the distal nail plate or along the lateral nail groove, followed by development of hyperkeratosis and yellow-brown discoloration. The process extends proximally, resulting in nail plate thickening, crumbling (Fig. 704.10), and separation from the nail bed. *Trichophyton rubrum* and, occasionally, *T. mentagrophytes* infect the toenails; fingernail disease is almost exclusively caused by *T. rubrum,* which may be associated with superficial scaling of the plantar surface of the feet and often of one hand. The dermatophytes are found most readily at the most proximal area of the nail bed or adjacent ventral portion of the involved nail plates. Topical therapies such as ciclopirox 8% lacquer, amorolfine 5% lacquer, or bifonazole-urea 1%/40% ointment may be effective for solitary nail infection. Topical efinaconazole 10% and topical tavaborole 5% solution may also be effective; laser treatment is an expensive but safe alternative to oral therapy. Because of its long half-life in the nail, oral itraconazole may be effective when given as pulse therapy (1 week of each month for 3-4 months). Dosage is weight-dependent. Oral daily terbinafine is also quite effective. Either agent is superior to griseofulvin, fluconazole, or ketoconazole. The risks, the most concerning of which is hepatic toxicity, and costs of oral therapy are minimized with the use of pulsed dosing.

Proximal white subungual onychomycosis occurs when the organism, generally *T. rubrum,* enters the nail through the proximal nail fold, producing yellow-white discoloration of portions of the undersurface of the nail plate. The surface of the nail is unaffected. This occurs almost exclusively in immunocompromised patients and is a well-recognized manifestation of AIDS. Treatment includes oral terbinafine or itraconazole.

Candidal onychomycosis involves the entire nail plate in patients with chronic mucocutaneous candidiasis. It is also commonly seen in patients with AIDS. The organism, generally *Candida albicans,* enters distally or along the lateral nail folds; rapidly involves the entire thickness of the nail plate; and produces thickening, crumbling, and deformity of the plate. Topical azole antifungal agents may be sufficient for treatment of candidal onychomycosis in an immunocompetent host, but oral antifungal agents are necessary for treatment of patients with immune deficiencies. Table 704.6 outlines the differential diagnosis of onychomycosis.

Table 704.6 Differential Diagnosis of Onychomycosis

Psoriasis
- As in onychomycosis: onycholysis, subungual hyperkeratosis, splinter hemorrhages, leukonychia, dystrophy
- Pitting
- Oil drop sign (a translucent yellow-red discoloration seen in the nail bed)
- Other cutaneous features of psoriasis, family history of psoriasis

Lichen planus
- Cutaneous disease at other sites
- Thin nail plate and ridging
- Dorsal pterygium—scarring at proximal aspect of nail

Trauma
- Nail plate can appear abnormal
- Nail bed should be normal
- Distal onycholysis with repeated trauma
- Single nail affected, shape of nail changed, homogenous alteration of nail color

Eczema
- Irregular buckled nails with ridging
- Cutaneous signs of eczema

Yellow nail syndrome
- Nail plate is discolored green-yellow
- Nails are hard with elevated longitudinal curvature
- Nails may be shed, painful
- Associations with bronchiectasis, lymphedema, and chronic sinusitis

Lamellar onychoschizia (lamellar splitting)
- History of repeated soaking in water
- Usually distal portion of nail
- Periungual squamous cell carcinoma/Bowens disease
- Single nail, warty changes of nail fold; ooze from edge of nail

Malignant melanoma
- Black discoloration of nail plate or nail bed
- Pigment can extend onto nail fold
- Can get associated bleeding

Myxoid (mucous) cyst
- Cyst at base of nail, groove in nail extending length of nail

Alopecia areata
- Pits, longitudinal ridging, brittleness
- Hair loss

From Eisman S, Sinclair R. Fungal nail infection: diagnosis and management. *BMJ.* 2014;348:g1800.

PARONYCHIAL INFLAMMATION

Paronychial inflammation may be acute or chronic and generally involves one or two nail folds on the fingers. Acute paronychia manifests as erythema, warmth, edema, and tenderness of the proximal nail fold, most commonly as a result of pathogenic staphylococci, streptococci, or *Candida* (Fig. 704.11). Warm soaks and oral agents are generally effective; incision and drainage may occasionally be necessary. Development of chronic paronychia follows prolonged immersion in water (Fig. 704.12), such as occurs in finger or thumb sucking; exposure to irritating solutions; nail fold trauma; or diseases including Raynaud phenomenon, collagen vascular diseases, and diabetes. Swelling of the proximal nail fold is followed by separation of the nail fold from the underlying nail plate and suppuration. Foreign material, embedded in the dermis of the nail fold, becomes a nidus for inflammation and secondary infection with *Candida* species and mixed bacterial flora. A combination of attention to predisposing factors, meticulous drying of the hands, and long-term topical antifungal agents and potent topical corticosteroids may be required for successful treatment of chronic paronychia.

Ingrown nail occurs when the lateral edge of the nail, including spicules that have separated from the nail plate, penetrates the soft tissue of



Fig. 704.11 Acute paronychia secondary to *Staphylococcus aureus.*



Fig. 704.12 Chronic paronychia with erythema and lateral nail fold separation.



Fig. 704.13 Clinical features of an 8-yr-old boy upon initial presentation to a dermatology clinic. Findings included yellowish-brown discoloration, hyperkeratosis, transverse ridging, and lateral deviation of the bilateral great toenails. *(From Pollack K, Zlotoff B, Wilson B. Hyperkeratosis and discoloration of the toenails in an 8-year-old. J Pediatr. 2017;189:233.)*

the lateral nail fold. Erythema, edema, and pain, most often involving the lateral great toes, are noted acutely; recurrent episodes may lead to formation of granulation tissue. Predisposing factors include (1) congenital malalignment (especially of the great toes) (Fig.704.13); (2) compression of the side of the toe from poorly fitting shoes, particularly if the great toes are abnormally long and the lateral nail folds are prominent; and (3) improper cutting of the nail in a curvilinear manner rather than straight across. Management includes proper fitting of shoes; allowing the nail to grow out beyond the free edge before cutting it straight across; warm water soaks; oral antibiotics if cellulitis affects the lateral nail fold; and, in severe, recurrent cases, application of silver nitrate to granulation tissue, nail avulsion, or excision of the lateral aspect of the nail followed by matricectomy.

PARONYCHIAL TUMORS

Tumors in the paronychial area include pyogenic granulomas, mucous cysts, subungual exostoses, and junctional nevi. Periungual fibromas that appear in late childhood should suggest a diagnosis of tuberous sclerosis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 705
Disorders of the Mucous Membranes

Leah Lalor

The mucous membranes may be involved in developmental disorders, genodermatoses, infections, acute and chronic skin diseases, and benign or malignant tumors. This chapter includes some of the more common and more distinctive conditions of the mucous membranes, but is not exhaustive (see also Chapter 695 for erythema multiforme, Stevens-Johnson syndrome, and reactive infectious mucocutaneous eruption [RIME]).

ANGULAR CHEILITIS

Angular cheilitis **(perlèche)** is characterized by inflammation and fissuring at the corners of the mouth, often with associated erosion, maceration, and crusting (Fig. 705.1). Chapping or moisture collection at the angles of the mouth predispose children to developing angular cheilitis. Children who are chronic lip lickers or who have excessive salivation or drooling related to neurologic deficits, orthodontic appliances, or mouth breathing are at increased risk. Atopic dermatitis or contact dermatitis related to toothpaste, chewing gum, mouthwash, or cosmetics are also common causes. Nutritional deficiencies are a less frequent etiology. Protection can be provided by frequent application of a bland ointment such as petrolatum. Candidiasis should be treated with an appropriate antifungal agent, and contact dermatitis of the perioral skin should be treated with a low-potency topical corticosteroid ointment preparation and frequent use of petrolatum or a similar emollient along with avoidance of the offending agent. Correction of the underlying predisposing factors (if possible) will prevent recurrence.

APHTHOUS STOMATITIS (CANKER SORES)

Aphthous stomatitis consists of solitary or multiple painful ulcerations occurring on the labial (Fig. 705.2), buccal, lingual, sublingual, palatal, or gingival mucosa (see Chapter 361). Lesions may manifest initially as erythematous, indurated papules that erode rapidly to form sharply circumscribed, necrotic ulcers with a gray fibrinous exudate and an erythematous halo. Minor aphthous ulcers are 2-10 mm in diameter and heal spontaneously in 7-10 days. Major aphthous ulcers are >10 mm in diameter, take from 10 to 30 days to heal, and may heal with scarring. A third type of aphthous ulceration is herpetiform in appearance,



Fig. 705.1 Angular cheilitis.



Fig. 705.2 Aphthous ulceration on lower lip.

manifesting as a few to numerous grouped 1- to 2-mm lesions, which tend to coalesce into plaques and heal over 7-10 days. Approximately 30% of patients with recurrent lesions have a family history of the disorder (see Chapter 361 for the differential diagnosis).

The etiology of aphthous stomatitis is multifactorial; the condition probably represents an oral manifestation of a number of conditions, including viral infection, inflammatory bowel disease, cyclic neutropenia, and others. Altered local regulation of the cell-mediated immune system, after activation and accumulation of cytotoxic T cells, may contribute to the localized mucosal breakdown. It is a common misconception that aphthous stomatitis is a manifestation of herpes simplex virus infection. Recurrent herpes infections remain localized to the lips and rarely cross the mucocutaneous junction; involvement of the oral mucosa occurs only in primary infections.

Treatment of aphthous stomatitis is supportive. The majority of mild cases do not require therapy. Relief of pain, particularly before eating, may be achieved with the use of a topical anesthetic such as viscous lidocaine or an oral rinse with a combined solution of elixir of diphenhydramine, viscous lidocaine, and an oral antacid. Caution must be taken to avoid hot food and drink after topical anesthetic use. A superpotent topical corticosteroid in a mucosa-adhering agent may help to reduce inflammation, and topical tetracycline mouthwash may also hasten healing. In severe, debilitating cases, systemic therapy with corticosteroids, colchicine, dapsone, or thalidomide may be helpful.

FORDYCE SPOTS

Fordyce spots (Fordyce granules) are clusters of asymptomatic, 1- to 3-mm, yellow-white macules and papules on the vermilion lips and buccal mucosa. They are a common clinical finding and represent a normal anatomic variant of sebaceous glands. They can present in either sex from infancy to adulthood and may become more prominent during puberty due to the influence of androgens. No therapy is required.



Fig. 705.3 Mucocele on lower lip.

EPSTEIN PEARLS (GINGIVAL CYSTS OF THE NEWBORN)

Epstein pearls are white, keratin-containing cysts on the palatal or alveolar mucosa of approximately 60–85% of neonates. They are epidermal inclusion cysts that form when the soft and hard palates fuse and are analogous to facial milia. They cause no symptoms and are generally shed within a few weeks; no therapy is necessary.

MUCOCELE

Mucus retention cysts are painless, fluctuant, tense, 2- to 10-mm, bluish papules on the lips (Fig. 705.3), tongue, palate, or buccal mucosa. Traumatic severance of the duct of a minor salivary gland leads to submucosal retention of mucus secretion. Lesions on the floor of the mouth are known as *ranulas* when the sublingual or submandibular salivary gland ducts are involved. Fluctuations in size are typical, and the lesions may disappear temporarily after traumatic rupture. Recurrence is prevented by surgical excision of the mucus deposit and associated salivary gland(s).

FISSURED TONGUE

Fissured tongue (scrotal tongue, or lingua plicata) is a common benign developmental anomaly of the tongue. The dorsal tongue has many folds with deep grooves and a pebbled appearance. Fissured tongue can be seen in individuals with Melkersson-Rosenthal syndrome and Down syndrome, and it is often seen in association with geographic tongue. Food particles and debris may become trapped in the fissures, resulting in irritation, inflammation, and halitosis. Careful cleansing with a mouth rinse and soft-bristled toothbrush is recommended.

GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS)

Geographic tongue consists of single or multiple sharply demarcated, irregular, smooth, red patches surrounded by an elevated yellowish-white serpiginous border on the dorsum of the tongue. Onset is rapid, and the pattern may change over hours to days. The smooth patches correspond to atrophic filiform papillae, and the elevated margins represent hypertrophic papillae (Fig. 705.4). The etiology of this condition remains unclear, though it is associated with some inflammatory disorders of the skin like psoriasis. Lesions are typically asymptomatic, but some patients may experience a burning sensation or sensitivity to spicy, hot, or cold foods. No therapy other than reassurance is necessary.



Fig. 705.4 Geographic tongue.

BLACK HAIRY TONGUE

Black hairy tongue is a dark coating on the dorsum of the tongue caused by hyperplasia and elongation of the filiform papillae; overgrowth of chromogenic bacteria and fungi and entrapped pigmented residues that adsorb to microbial plaque and desquamating keratin may contribute to the dark coloration. Changes often begin posteriorly and extend anteriorly on the dorsum of the tongue. The condition is most common in adults but may also manifest during adolescence. Poor oral hygiene, lack of oral feeding, treatment with systemic antibiotics such as tetracycline (which promote the growth of *Candida* spp.), and smoking are predisposing factors. Improved oral hygiene and brushing with a soft-bristled toothbrush may be all that is necessary for treatment.

ORAL HAIRY LEUKOPLAKIA

Oral hairy leukoplakia occurs in approximately 25% of patients with AIDS but is rare in the pediatric population. It manifests as corrugated and shaggy white plaques on the lateral margins of the tongue, which cannot be removed by rubbing. The lesions occasionally may spread to the ventral tongue surface, floor of the mouth, tonsillar pillars, and pharynx. The condition is caused by Epstein-Barr virus, which is present in the upper layer of the affected epithelium. The plaques have no malignant potential. The disorder occurs predominantly in HIV-infected patients but may also be found in individuals who are immunosuppressed for other reasons, such as organ transplantation, leukemia, chemotherapy, and long-term use of inhaled steroids. The condition is generally asymptomatic and does not require therapy.

ACUTE NECROTIZING ULCERATIVE GINGIVITIS (VINCENT STOMATITIS, FUSOSPIROCHETAL GINGIVITIS, TRENCH MOUTH)

Acute necrotizing ulcerative gingivitis manifests as painful, punched-out ulceration, necrosis, and bleeding of the interdental papillae. A grayish-white pseudomembrane may cover the ulcerations. Lesions may spread to involve the buccal mucosa, lips, tongue, tonsils, and pharynx and may be associated with dental pain, a bad taste, low-grade fever, and lymphadenopathy. It occurs most commonly in the second or third decade, particularly in the context of poor dental hygiene, poor nutrition, smoking, and stress.

NOMA

Noma is a severe form of fusospirillary gangrenous stomatitis that occurs primarily in malnourished, impoverished children 2-5 years of age who have had a preceding illness such as measles, scarlet fever, tuberculosis, malignancy, or immunodeficiency. The disease is most prevalent in Africa but also occurs in Asia and Latin America. Sporadic cases associated with immunodeficiency have been reported in developed countries. It manifests as a painful, red, indurated papule on the alveolar margin, followed by ulceration and mutilating gangrenous destruction of tissue in the oronasal region. The process may also involve the scalp, neck, shoulders, perineum, and vulva. Noma neonatorum manifests in the first month of life as gangrenous lesions of the lips, nose, mouth, and anal regions. Affected infants are usually small for gestational age, malnourished, premature, and frequently ill (particularly with *Pseudomonas aeruginosa* sepsis). Care consists of nutritional support, conservative debridement of necrotic soft tissues, empirical broad-spectrum antibiotics such as penicillin and metronidazole, and, in the case of noma neonatorum, antipseudomonal antibiotics (see Chapter 62).

PTEN HAMARTOMA SYNDROME (COWDEN SYNDROME)

PTEN hamartoma syndrome is an autosomal dominant condition caused by loss-of-function pathogenic variants in the *PTEN* tumor-suppressor gene. Mucocutaneous lesions typically appear in the second or third decade. Oral papillomas are 1- to 3-mm, smooth, pink or whitish papules on the palatal, gingival, buccal, and labial mucosae and may coalesce into a cobblestone appearance. Numerous flesh-colored papules also develop on the face, particularly around the mouth, nose, and ears. These papules are most commonly trichilemmomas, a benign neoplasm of the hair follicle. Associated findings may include acral keratoses, thyroid adenoma, goiter, gastrointestinal polyps, fibrocystic breast nodules, and carcinoma of the breast or thyroid.

Herpes Simplex Virus Infection

Herpes simplex virus (HSV) types 1 and 2 commonly cause primary and recurrent infection, resulting in grouped vesicles on oral, nasal, and genital mucosae.

Erythema Multiforme

Erythema multiforme (EM) is an uncommon disorder of mucocutaneous blistering typically on the labial mucosa and acral skin as a reaction to HSV infection. Please see Chapter 695.1 for more detail.

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) is an uncommon disorder of skin sloughing that occurs primarily after exposure to a medication. It can have extensive mucosal involvement in addition to skin. Please see Chapter 695.3 for more detail.

Reactive Infectious Mucocutaneous Eruption (Formerly Mycoplasma-Induced Rash and Mucositis)

This condition is on the spectrum of SJS and toxic epidermal necrolysis (TEN), but tends to be triggered by various infections and has more mucosal involvement than cutaneous. Please see Chapter 695.2 for more detail.

Lichen Sclerosus

Lichen sclerosus is a rare disorder of genital mucosa typically seen in young girls and elderly women. It manifests as pink and white atrophic genital mucosa that can be associated with pain, dysuria, constipation, and bleeding. Please see Chapter 586 for more details.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 706

Cutaneous Bacterial Infections

706.1 Impetigo

Stephen R. Humphrey

ETIOLOGY/PATHOGENESIS

Impetigo is the most common skin infection in children throughout the world. Invasive *Staphylococcus aureus* has a global incidence of approximately 20-50 cases/100,000 population per year. There are two classic forms of impetigo: nonbullous and bullous.

S. aureus is the predominant organism of **nonbullous impetigo** in the United States (see Chapter 227); group A β-hemolytic streptococci (GABHS) are implicated in the development of some lesions (see Chapter 229). The staphylococcal types that cause nonbullous impetigo are variable but are not generally from phage group 2, the group that is associated with scalded skin and toxic shock syndromes. Staphylococci generally spread from the nose to normal skin and then infect the skin. In contrast, the skin becomes colonized with GABHS an average of 10 days before development of impetigo. The skin serves as the source for acquisition of GABHS and is the probable primary source for the spread of impetigo. Lesions of nonbullous impetigo that grow staphylococci in culture cannot be distinguished clinically from those that grow pure cultures of GABHS.

Bullous impetigo is always caused by *S. aureus* strains that produce exfoliative toxins. The staphylococcal exfoliative toxins (ETA, ETB, ETD) blister the superficial epidermis by hydrolyzing human desmoglein 1, resulting in a subcorneal vesicle. This is also the target antigen of the autoantibodies in pemphigus foliaceus.

CLINICAL MANIFESTATIONS

Nonbullous Impetigo

Nonbullous impetigo accounts for more than 70% of cases. Lesions typically begin on the skin of the face or on extremities that have been traumatized. The most common lesions that precede nonbullous impetigo are insect bites, abrasions, lacerations, chickenpox, scabies pediculosis, and burns. A tiny vesicle or pustule forms initially and rapidly develops into a honey-colored crusted plaque that is generally <2 cm in diameter (Fig. 706.1). The infection may be spread to other parts of the body by the fingers, clothing, and towels. Lesions are associated with little to no pain or surrounding erythema, and constitutional symptoms are generally absent. Pruritus occurs occasionally, regional adenopathy is found in up to 90% of cases, and leukocytosis is present in approximately 50%.



Fig. 706.1 Multiple crusted and oozing lesions of impetigo.

Bullous Impetigo

Bullous impetigo is mainly an infection of infants and young children. Flaccid, transparent bullae develop most commonly on skin of the face, buttocks, trunk, perineum, and extremities. **Neonatal bullous impetigo** can begin in the diaper area. Rupture of a bulla occurs easily, leaving a narrow rim of scale at the edge of a shallow, moist erosion. Surrounding erythema and regional adenopathy are generally absent. Unlike those of nonbullous impetigo, lesions of bullous impetigo are a manifestation of localized staphylococcal scalded skin syndrome and develop on intact skin.

Differential Diagnosis

The differential diagnosis of **nonbullous impetigo** includes viruses (herpes simplex, varicella-zoster), fungi (tinea corporis, kerion), arthropod bites, and parasitic infestations (scabies, pediculosis capitis), all of which may become impetiginized.

The differential diagnosis of **bullous impetigo** in neonates includes epidermolysis bullosa, bullous mastocytosis, herpetic infection, and early staphylococcal scalded skin syndrome. In older children, allergic contact dermatitis, burns, erythema multiforme, linear immunoglobulin A dermatosis, pemphigus, and bullous pemphigoid must be considered, particularly if the lesions do not respond to therapy.

COMPLICATIONS

Potential but *very rare* complications of either nonbullous or bullous impetigo include bacteremia with subsequent osteomyelitis, septic arthritis, pneumonia, and septicemia. Positive blood culture results are *very rare* in otherwise healthy children with localized lesions. Cellulitis has been reported in up to 10% of patients with nonbullous impetigo and rarely follows the bullous form. Lymphangitis, suppurative lymphadenitis, guttate psoriasis, and scarlet fever occasionally follow streptococcal disease. There is no correlation between the number of lesions and clinical involvement of the lymphatics or development of cellulitis in association with streptococcal impetigo.

Infection with nephritogenic strains of GABHS may result in **acute poststreptococcal glomerulonephritis** (see Chapter 559.4). The clinical character of impetigo lesions does not predict the development of poststreptococcal glomerulonephritis. Children 3-7 years of age are most commonly affected. The latent period from onset of impetigo to development of poststreptococcal glomerulonephritis averages 18-21 days, which is longer than the 10-day latency period after pharyngitis. Poststreptococcal glomerulonephritis occurs epidemically after either pharyngeal or skin infection. Impetigo-associated epidemics have been caused by M groups 2, 49, 53, 55, 56, 57, and 60. Strains of GABHS that are associated with endemic impetigo in the United States have little or no nephritogenic potential. Acute rheumatic fever does not occur as a result of impetigo.

TREATMENT

The decision on how to treat impetigo depends on the number of lesions and their locations. Topical therapy with mupirocin 2% and retapamulin 1% 2-3 times a day for 10-14 days is acceptable for localized disease caused by *S. aureus,* though there are resistant strains to these topical antibiotics.

Systemic therapy with oral antibiotics should be prescribed for patients with streptococcal or widespread involvement of staphylococcal infections; when lesions are near the mouth, where topical medication may be licked off; or in cases with evidence of deep involvement, including cellulitis, furunculosis, abscess formation, or suppurative lymphadenitis. Cephalexin 25-50 mg/kg/day in three to four divided doses for 7 days is an excellent choice for initial therapy. A culture should be performed, as the emergence of methicillin-resistant *S. aureus* (MRSA) typically requires a different antibiotic choice based on antibiotic susceptibility patterns. If MRSA is suspected, clindamycin, doxycycline, or sulfamethoxazole-trimethoprim is indicated. No evidence suggests that a 10-day course of therapy is superior to a 7-day course; twice-daily

sulfamethoxazole trimethoprim for 3 days has been comparable to once daily for 5 days. Benzathine benzylpenicillin IM has been used when compliance with multiple-dose and -day oral antibiotics may be poor.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

706.2 Subcutaneous Tissue Infections

Stephen R. Humphrey

The principal determinations for soft tissue infection are whether it is *nonnecrotizing* or *necrotizing* and *purulent* or *nonpurulent*. Nonnecrotizing, nonpurulent lesions respond to antibiotic therapy alone, whereas necrotizing or purulent (abscess) lesions require prompt surgical removal of all devitalized tissue in addition to antimicrobial therapy. Necrotizing soft tissue infections are life-threatening conditions that are characterized by rapidly advancing local tissue destruction and systemic toxicity, including shock. Tissue necrosis distinguishes soft tissue infections from cellulitis. In cellulitis, an inflammatory infectious process involves subcutaneous tissue but does not destroy it. Necrotizing soft tissue infections may initially manifest with a paucity of early cutaneous signs relative to the rapidity and degree of destruction of the subcutaneous tissues.

CELLULITIS

Etiology

Cellulitis is characterized by infection and inflammation of loose connective tissue, with limited involvement of the dermis and relative sparing of the epidermis. A break in the skin from previous trauma, insect bite, surgery, or an underlying skin lesion predisposes to cellulitis. Cellulitis is also more common in individuals with lymphatic stasis, diabetes mellitus, or immunosuppression.

S. aureus and *Streptococcus pyogenes* (group A streptococcus) are the most common etiologic agents. In patients who are immunocompromised or have diabetes mellitus, other bacterial or fungal agents may be involved, notably *Pseudomonas aeruginosa; Aeromonas hydrophila* and, occasionally, other Enterobacteriaceae; *Legionella* spp.; the Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp.; and *Cryptococcus neoformans.* Children with relapsed nephrotic syndrome may experience cellulitis caused by *Escherichia coli.* In children 3 months to 5 years of age, *Haemophilus influenzae* type b was once an important cause of facial cellulitis, but its incidence has declined significantly since the institution of immunization against this organism.

Environmental risk factors include exposure to fish, shellfish, and meats *(Erysipelothrix rhusiopathiae)*; salt water, or brackish inland waterways *(Vibrio vulnificus)*; penetrating trauma (mixed pathogens including *Clostridium perfringens*); and human or animal bites (see Chapter 765) (Table 706.1).

Table 706.1 Special Considerations for Causes of Cellulitis

SETTING OR EXPOSURE	CAUSES OF CELLULITIS
Cat or dog bites	*Pasteurella* species, *Capnocytophaga canimorsus*
Penetrating trauma	*Staphylococcus aureus*
Freshwater immersion	*Aeromonas hydrophila*
Saltwater immersion	*Vibrio* species
Freshwater, saltwater fish	*Streptococcus iniae*
Swine, poultry, fish	*Erysipelothrix rhusiopathiae*
Periorbital or facial cellulitis	*Haemophilus influenzae, Streptococcus pneumoniae*
Neutropenia	*Pseudomonas aeruginosa*, other gram-negative bacilli
Human immunodeficiency virus infection	*Helicobacter cinaedi*
Acute varicella	*Streptococcus pyogenes*
Immunosuppression	*Cryptococcus neoformans*

From Long SS, Prober CG, Fischer M. *Principles and Practice of Pediatric Infectious Diseases*, 5th ed. Philadelphia: Elsevier; 2018: Table 68.3, p. 444.

Clinical Manifestations

Cellulitis manifests clinically as a localized area of edema, warmth, erythema, and tenderness. The lateral margins tend to be indistinct because the process is deep in the skin, primarily involving the subcutaneous tissues in addition to the dermis. Application of pressure may produce pitting. Although distinction cannot be made with certainty in any particular patient, cellulitis due to *S. aureus* tends to be more localized and may suppurate, whereas infections caused by *S. pyogenes* (group A streptococci) tend to spread more rapidly and may be associated with lymphangitis. Regional adenopathy and constitutional signs and symptoms such as fever, chills, and malaise are common. Complications of cellulitis are uncommon but include subcutaneous abscess, bacteremia, osteomyelitis, septic arthritis, thrombophlebitis, endocarditis, and necrotizing fasciitis. Lymphangitis or glomerulonephritis can also follow infection with *S. pyogenes.*

Diagnosis

Cellulitis in a neonate should prompt assessment for invasive bacterial infection, including blood culture; lumbar puncture is also usually performed, though its necessity for mild cases of cellulitis is controversial in this age-group. In older children, cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended. However, blood cultures should be considered if the patient is younger than 1 year of age, if signs of systemic toxicity are present, if an adequate examination cannot be carried out, or if an immunocompromising condition (e.g., malignancy, neutropenia, or neutrophil functional defects) is present. Aspirates from the site of inflammation, skin biopsy, and blood cultures allow identification of the causal organism in approximately 25% of cases of cellulitis. Yield of the causative organism is approximately 30% when the site of origin of the cellulitis is apparent, such as an abrasion or ulcer. An aspirate taken from the point of maximum inflammation yields the causal organism more often than a leading-edge aspirate. Lack of success in isolating an organism stems primarily from the low number of organisms present within the lesion. Ultrasonography can be performed if an associated subcutaneous abscess is suspected and may be helpful in cases where there is uncertainty if there a drainable fluid collection is present.

The differential diagnosis includes an exuberant immune-allergic reaction to insect bites, particularly mosquito bites (Skeeter syndromes) (see Chapter 187). **Skeeter syndrome** is characterized by swelling disproportionate to erythema; there is pruritus but usually no tenderness. In addition, **cold panniculitis** may appear as an erythematous, but usually nontender, swelling after exposure to cold, such as sledding or eating a cold Popsicle (see Chapter 701.1).

Treatment

Empirical antibiotic therapy for cellulitis and the initial route of administration should be guided by the age and immune status of the patient, history of the illness, and location and severity of the cellulitis.

Neonates should receive an intravenous antibiotic with a β-lactamase–stable antistaphylococcal antibiotic such as nafcillin, cefazolin, or vancomycin, and an aminoglycoside such as gentamicin or a third-generation cephalosporin such as cefotaxime.

In infants and children older than 2 months with mild to moderate infections, particularly if fever, lymphadenopathy, and other constitutional signs are absent, treatment of cellulitis may be initiated orally on an outpatient basis with a penicillinase-resistant penicillin such as dicloxacillin or a first-generation cephalosporin such as cephalexin or, if MRSA is suspected, with clindamycin. Some recommend trimethoprim-sulfamethoxazole, although it does not provide ideal

coverage against *S. pyogenes,* a potential cause of cellulitis *without* abscess.

Intravenous antibiotics may be necessary if improvement is not noted or the disease progresses significantly in the first 24-48 hours of therapy. Infants and children older than 2 months with signs of systemic infection, including fever, lymphadenopathy, or constitutional signs, also require hospitalization and treatment with intravenous antibiotics effective against *S. pyogenes* and *S. aureus,* such as clindamycin or a first-generation cephalosporin (cefazolin). If the child is severely ill or toxic appearing, consideration should be given to the addition of clindamycin or vancomycin if these antibiotics were not started initially. Other agents for complicated skin and skin structure infections caused by MRSA or *S. pyogenes* have been approved by the U.S. Food and Drug Administration (FDA) in adults, including dalbavancin (IV given once weekly), ceftaroline (IV), telavancin (IV), linezolid (oral or IV), tedizolid (oral or IV), and oritavancin (IV). Dalbavancin also provides activity against vancomycin-resistant enterococci.

In unimmunized patients, antibiotic treatment may include a third-generation cephalosporin (cefepime, ceftriaxone, or, if available, cefotaxime) or a β-lactam/β-lactamase inhibitor combination (e.g., ampicillin-sulbactam), which provides coverage for *H. influenzae* type b and *Streptococcus pneumoniae*.

Once the erythema, warmth, edema, and fever have decreased significantly, a 5- to 7-day total course of treatment may be completed on an outpatient basis, though treatment should be extended if the infection has not substantially improved with this period. Elevation of an affected limb, particularly early in the course of therapy, may help reduce swelling and pain. If present, a subcutaneous abscess should be drained.

NECROTIZING FASCIITIS

Etiology

Necrotizing fasciitis is a subcutaneous tissue infection that involves the deep layer of superficial fascia but may spare adjacent epidermis, deep fascia, and muscle.

Relatively few organisms possess sufficient virulence to cause necrotizing fasciitis when acting alone. Most (55–75%) cases of necrotizing fasciitis are polymicrobial **(synergistic or type 1 necrotizing fasciitis)**, with an average of four different organisms isolated. The organisms most commonly isolated in polymicrobial necrotizing fasciitis are *S. aureus,* streptococcal species, *Klebsiella* species, *E. coli,* and anaerobic bacteria.

The rest of the cases **(type 2)** and the most fulminant infections, associated with toxic shock syndrome and a high case-fatality rate, are usually caused by *S. pyogenes* (group A streptococcus) (see Chapter 229). Streptococcal necrotizing fasciitis may occur in the absence of toxic shock-like syndrome and is potentially fatal and associated with substantial morbidity. Necrotizing fasciitis can occasionally be caused by *S. aureus; C. perfringens; Clostridium septicum; P. aeruginosa; Vibrio* spp., particularly *V. vulnificus;* and fungi of the order Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp. Necrotizing fasciitis has also been reported on rare occasions to result from nongroup A streptococci such as group B, C, F, or G streptococci; *S. pneumoniae;* or *H. influenzae* type b.

Infections caused by any organism or combination of organisms cannot be distinguished clinically from one another, although development of *crepitus* signals the presence of gas-forming organisms: *Clostridium* spp. or gram-negative bacilli such as *E. coli, Klebsiella, Proteus,* or *Aeromonas.*

Clinical Manifestations

Necrotizing fasciitis may occur anywhere on the body but most often on the extremities or areas of trauma. The incidence of necrotizing fasciitis is highest in hosts with systemic or local tissue immunocompromise, such as those with diabetes mellitus, neoplasia, or peripheral vascular disease, and those who have recently undergone surgery, who use IV drugs, or who are undergoing immunosuppressive treatment, particularly with corticosteroids. The infection can also occur in healthy individuals after minor puncture wounds, abrasions, or lacerations; blunt trauma; surgical procedures, particularly of the abdomen, gastrointestinal or genitourinary tracts, or the perineum; or hypodermic needle injection.

There is a resurgence of fulminant necrotizing soft tissue infections caused by *S. pyogenes,* which may occur in previously healthy individuals. Streptococcal necrotizing fasciitis is classically located on an extremity. There may be a history of recent trauma to or operation in the area. Necrotizing fasciitis due to *S. pyogenes* may also occur after superinfection of varicella lesions. Children with this disease have tended to display onset, recrudescence, or persistence of high fever and signs of toxicity after the third or fourth day of varicella. Common predisposing conditions in neonates are omphalitis and balanitis after circumcision.

Necrotizing fasciitis begins with acute onset of local, and at times tense, edema with erythema, tenderness, and heat. Fever is usually present, and pain, tenderness, and constitutional signs are disproportionate to cutaneous signs, especially with involvement of fascia and muscle. Tachycardia is out of proportion to the fever. Lymphangitis and lymphadenitis may or may not be present. The infection advances along the superficial fascial plane, and initially there may be few cutaneous signs to herald the serious nature and extent of the subcutaneous tissue necrosis that is occurring. Skin changes may appear over 24-48 hours as nutrient vessels are thrombosed and cutaneous ischemia develops. Early clinical findings include ill-defined cutaneous erythema and edema that extends beyond the area of erythema. *There is intense pain on movement.* Additional signs include formation of bullae filled initially with straw-colored and later bluish to hemorrhagic fluid and darkening of affected tissues from red to purple to blue. Skin anesthesia and, finally, frank tissue gangrene and slough develop owing to the ischemia and necrosis. Vesiculation or bulla formation, ecchymoses, crepitus, anesthesia, and necrosis are ominous signs indicative of advanced disease. Children with varicella lesions may initially show no cutaneous signs of superinfection with invasive *S. pyogenes,* such as erythema or swelling. Significant systemic toxicity may accompany necrotizing fasciitis, including shock, organ failure, and death. Advance of the infection in this setting can be rapid, progressing to death within hours. Patients with involvement of the superficial or deep fascia and muscle tend to be more acutely and systemically ill and have more rapidly advancing disease than those with infection confined solely to subcutaneous tissues above the fascia. There is often hyponatremia (<135 mg/L), an elevated CRP (>20 mg/L), and extreme leukocytosis. In an extremity, **compartment syndrome** may develop, manifesting as tight edema, pain on motion, and loss of distal sensation and pulses; this is a surgical emergency (see Chapter 80).

Diagnosis

Definitive diagnosis of necrotizing fasciitis is made by surgical exploration, which should be undertaken as soon as the diagnosis is suspected. Necrotic fascia and subcutaneous tissue are gray and offer little resistance to blunt probing. Although MRI aids in delineating the extent and tissue planes of involvement, these procedures should not delay surgical intervention. Frozen-section incisional biopsy specimens obtained early in the course of the infection can aid management by decreasing the time to diagnosis and helping to establish the margins of involvement. Gram staining of tissue can be particularly useful if chains of gram-positive cocci, indicative of infection with *S. pyogenes,* are seen.

Treatment

Early supportive care, surgical debridement, and parenteral antibiotic administration are mandatory for necrotizing fasciitis. All devitalized tissue should be removed to freely bleeding edges, and repeat exploration is generally indicated within 24-36 hours to confirm that no necrotic tissue remains. This procedure may need to be repeated on several occasions until devitalized tissue has ceased to form. Meticulous daily wound care is also paramount.

Parenteral antibiotic therapy should be initiated as soon as possible with broad-spectrum agents against all potential pathogens. Initial empirical therapy should be instituted with vancomycin, linezolid,

or daptomycin to cover gram-positive organisms and piperacillin-tazobactam to cover gram-negative organisms. An alternative is to add ceftriaxone with metronidazole to cover mixed aerobic-anaerobic organisms. Definitive therapy should then be based on sensitivity of isolated organisms. Penicillin with clindamycin is indicated for necrotizing fasciitis caused by either group A streptococcus or *Clostridium* spp. For group A streptococcus infections, clindamycin is administered until the patient is hemodynamically stable and no longer requires surgical debridement. Unlike penicillin, the effectiveness of clindamycin is not influenced by the infectious burden or bacterial stage of growth; thus its addition early in the course of infection may lead to more rapid bacterial killing. Doxycycline plus either ciprofloxacin or ceftazidime is recommended for *V. vulnificus* necrotizing fasciitis. Duration of therapy for necrotizing fasciitis depends on the course of the illness. Antibiotics are generally continued for at least 5 days after signs and symptoms of local signs and symptoms have resolved; the typical duration of therapy is 4 weeks. Many centers employ hyperbaric oxygen therapy, although it should not delay resuscitation of shock or surgical debridement.

Prognosis

The combined case-fatality rate among children and adults with necrotizing fasciitis and syndrome due to polymicrobial infection or *S. pyogenes* has been as high as 60%. However, death is less common in children and in cases not complicated by toxic shock–like syndrome.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

706.3 Staphylococcal Scalded Skin Syndrome (Ritter Disease)

Stephen R. Humphrey

ETIOLOGY AND PATHOGENESIS

Staphylococcal scalded skin syndrome is caused predominantly by phage group 2 staphylococci, particularly strains 71 and 55, which are present at localized sites of infection. Foci of infection include the nasopharynx and, less commonly, the umbilicus, urinary tract, a superficial abrasion, conjunctivae, and blood. The clinical manifestations of staphylococcal scalded skin syndrome are mediated by hematogenous spread in the absence of specific antitoxin antibody of staphylococcal epidermolytic or exfoliative toxins A or B. The toxins have reproduced the disease in both animal models and human volunteers. Decreased renal clearance of the toxins may account for the fact that the disease is most common in infants and young children, as well as a lack of protection from antitoxin antibodies. Epidermolytic toxin A is heat stable and is encoded by bacterial chromosomal genes. Epidermolytic toxin B is heat labile and is encoded on a 37.5-kb plasmid. The site of blister cleavage is subcorneal. The epidermolytic toxins produce the split by binding to and cleaving desmoglein 1. Intact bullae are consistently sterile, unlike those of bullous impetigo, but culture specimens should be obtained from all suspected sites of localized infection and from the blood to identify the source for elaboration of the epidermolytic toxins.

CLINICAL MANIFESTATIONS

Staphylococcal scalded skin syndrome, which occurs predominantly in infants and children younger than 5 years of age, includes a range of disease from localized bullous impetigo to generalized cutaneous involvement with systemic illness. Onset of the rash may be preceded by malaise, fever, irritability, and exquisite tenderness of the skin. **Scarlatiniform erythema** develops diffusely and is accentuated in flexural and periorificial areas. The conjunctivae are inflamed and occasionally become purulent. The brightly erythematous skin may rapidly acquire a wrinkled appearance, and in severe cases, sterile, flaccid blisters and erosions develop diffusely. Circumoral erythema is characteristically prominent, as is radial crusting and fissuring around the eyes, mouth, and nose. At this stage, areas of the epidermis may separate in response to gentle shear force (Nikolsky sign; Fig. 706.2). As large sheets of epidermis peel away, moist, glistening, denuded areas become apparent, initially in the flexures and subsequently over much of the body surface (Fig. 706.3). This development may lead to secondary cutaneous infection, sepsis, and fluid and electrolyte disturbances. The desquamative phase begins after 2-5 days of cutaneous erythema; healing occurs without scarring in 10-14 days. Patients may have pharyngitis, conjunctivitis, and superficial erosions of the lips, but intraoral mucosal surfaces are spared. Although some patients appear ill, many are reasonably comfortable except for the marked skin tenderness.

DIFFERENTIAL DIAGNOSIS

A presumed forme fruste of the disease manifests as diffuse, scarlatiniform, tender erythroderma that is accentuated in the flexural areas but does not progress to blister formation. In patients with this form, Nikolsky sign may be absent. Although the exanthem is similar to that of streptococcal scarlet fever, strawberry tongue and palatal petechiae are absent. Staphylococcal scalded skin syndrome may be mistaken for a number of other blistering and exfoliating disorders, including



Fig. 706.2 Nikolsky sign. With slight thumb pressure the skin wrinkles, slides laterally, and separates from the dermis. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004.)*



Fig. 706.3 Infant with staphylococcal scalded skin syndrome.

bullous impetigo, epidermolysis bullosa, epidermolytic hyperkeratosis, pemphigus, drug eruption, erythema multiforme, and drug-induced toxic epidermal necrolysis. Toxic epidermal necrolysis can often be distinguished by a history of drug ingestion, the presence of Nikolsky sign only at sites of erythema, the absence of perioral crusting, full-thickness epidermal necrosis, and a blister cleavage plane in the lowermost epidermis.

HISTOLOGY

A subcorneal, granular layer split can be identified on skin biopsy. Absence of an inflammatory infiltrate is characteristic. Histology is identical to that seen in pemphigus foliaceus, bullous impetigo, and subcorneal pustular dermatosis.

TREATMENT

Systemic therapy, given either orally in cases of localized involvement or parenterally with a semisynthetic antistaphylococcal penicillin (e.g., nafcillin), first-generation cephalosporin (e.g., cefazolin), clindamycin, or vancomycin if MRSA is considered, should be prescribed. Clindamycin is typically used *in addition* to other agents to inhibit bacterial protein (toxin) synthesis; however, it may not provide any additional coverage compared with cephalosporins unless there is high MRSA community prevalence. The skin should be gently moistened and cleansed. Application of an emollient provides lubrication and decreases discomfort. Topical antibiotics are unnecessary. In neonates, or in infants or children with severe infection, hospitalization is mandatory, with attention to fluid and electrolyte management, infection control measures, pain management, and meticulous wound care with contact isolation. In particularly severe disease, care in an intensive care or burn unit is required. Recovery is usually rapid, but complications, such as excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, septicemia, and cellulitis, may cause increased morbidity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

706.4 Ecthyma

Stephen R. Humphrey

See also Chapters 227, 229, and 251.

Ecthyma resembles nonbullous impetigo in onset and appearance but gradually evolves into a deeper, more chronic infection. The initial lesion is a vesicle or vesicular pustule with an erythematous base that erodes through the epidermis into the dermis to form an ulcer with elevated margins. The ulcer becomes obscured by a dry, heaped-up, tightly adherent crust (Fig. 706.4) that contributes to the persistence of the infection and scar formation. Lesions may be spread by autoinoculation, may be as large as 4 cm, and occur most frequently on the legs. Predisposing factors include the presence of pruritic lesions, such as insect bites, scabies, or pediculosis, that are subject to frequent scratching; poor hygiene; and malnutrition. Complications include lymphangitis, cellulitis, and, rarely, poststreptococcal glomerulonephritis. The causative agent is usually GABHS; *S. aureus* is also cultured from most lesions but is probably a secondary pathogen. Crusts should be softened with warm compresses and removed. Systemic antibiotic therapy, as for impetigo, is indicated; almost all lesions are responsive to treatment with penicillin.

Ecthyma gangrenosum is a necrotic ulcer covered with a gray-black eschar. It is usually a sign of *P. aeruginosa* infection, most often occurring in immunosuppressed patients. Neutropenia is a risk factor for ecthyma gangrenosum, including variants such as chronic, cyclic, and transient neutropenia. Ecthyma gangrenosum occurs in up to 6% of patients with systemic *P. aeruginosa* infection but can also occur as a primary cutaneous infection by inoculation. The lesion begins as a red or purpuric macule that vesiculates and then ulcerates. There is a surrounding rim of pink to violaceous skin. The punched-out ulcer develops raised edges with a dense, black, depressed, crusted center.

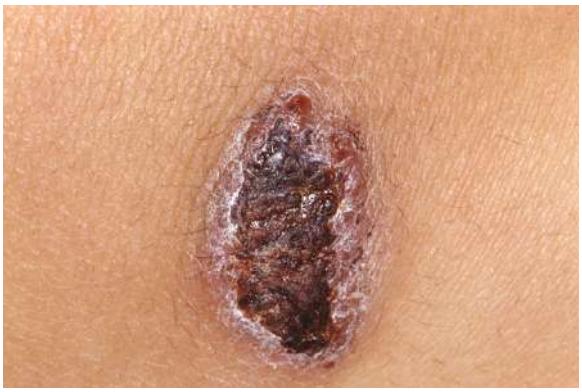

Fig. 706.4 Dry, tightly adherent crust in ecthyma.

Lesions may be single or multiple. Patients with bacteremia commonly have lesions in apocrine areas. Clinically similar lesions may also develop as a result of infection with other agents, such as *S. aureus, A. hydrophila, Enterobacter* spp., *Proteus* spp., *Burkholderia cepacia, Serratia marcescens, Aspergillus* spp., Mucorales, *E. coli,* and *Candida* spp. There is bacterial invasion of the adventitia and media of dermal veins but not arteries. The intima and lumina are spared. Blood and skin biopsy specimens for culture should be obtained, and empirical broad-spectrum, systemic therapy that includes coverage for *P. aeruginosa* (e.g., antipseudomonal penicillin or cephalosporin and an aminoglycoside) should be initiated as soon as possible.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

706.5 Other Cutaneous Bacterial Infections

Stephen R. Humphrey

BLASTOMYCOSIS-LIKE PYODERMA (PYODERMA VEGETANS)

Blastomycosis-like pyoderma is an exuberant cutaneous reaction to bacterial infection that occurs primarily in children who are malnourished and immunosuppressed. The organisms most commonly isolated from lesions are *S. aureus* and group A streptococcus, but several other organisms have been associated with these lesions, including *P. aeruginosa, Proteus mirabilis,* diphtheroids, *Bacillus* spp., and *C. perfringens.* Crusted, hyperplastic plaques on the extremities are characteristic, sometimes forming from the coalescence of many pinpoint, purulent, crusted abscesses (Fig. 706.5). Ulceration and sinus tract formation may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and microabscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The differential diagnosis includes deep fungal infection, particularly blastomycosis (Fig. 706.6) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

BLISTERING DISTAL DACTYLITIS

Blistering distal dactylitis is a superficial blistering infection of the volar fat pad on the distal portion of the finger or thumb that typically affects infants and young children (Fig. 706.7). More than one finger may be involved, as may the volar surfaces of the proximal phalanges, palms, and toes. Blisters are filled with a watery purulent fluid; polymorphonuclear leukocytes and gram-positive cocci are identified on Gram stain. Patients commonly have no preceding history of trauma, and systemic symptoms are generally absent. Poststreptococcal



Fig. 706.5 Large vegetating lesion of pyoderma vegetans.



Fig. 706.6 Cutaneous blastomycosis. Verrucous, crusted, erythematous plaque on the chin in a 15-yr-old boy with respiratory symptoms and bone pain. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006, Fig. 14.13.)*



Fig. 706.7 Blistering dactylitis. Edema and a tense bulla on the thumb of this 7-yr-old girl. Culture of the blister fluid yielded *Staphylococcus aureus* rather than the more commonly seen group A β-hemolytic streptococcus. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006, Fig. 14.14.)*

glomerulonephritis has not occurred after blistering distal dactylitis. The infection is caused most commonly by group A streptococcus but has also occurred as a result of infection with *S. aureus.* If left untreated, blisters may continue to enlarge and extend to the paronychial area. The infection responds to incision and drainage and a 10-day course of an antibiotic effective against group A streptococcus and *S. aureus* (e.g., amoxicillin-clavulanate, clindamycin, cephalexin); patients may require initial IV antibiotic therapy.



Fig. 706.8 Perianal streptococcal dermatitis. Bright red erythema with a moist, tender surface. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006, Fig. 17.38.)*

PERIANAL INFECTIOUS DERMATITIS

Perianal infectious dermatitis presents most commonly in boys (70% of cases) between the ages of 6 months and 10 years as perianal dermatitis (90% of cases) and pruritus (80% of cases; Fig. 706.8). The incidence of perianal infectious dermatitis is not known precisely but ranges from 1 in 2,000 to 1 in 218 patient visits. When GABHS is suspected, it is often referred to as *perianal streptococcal dermatitis.* The rash is superficial, erythematous, well marginated, nonindurated, and confluent from the anus outward. Acutely (<6 weeks), the rash tends to be bright red, moist, and tender to touch. At this stage, a white pseudomembrane may be present. As the rash becomes more chronic, the perianal eruption may consist of painful fissures, a dried mucoid discharge, or psoriasiform plaques with yellow peripheral crust. In girls, the perianal rash may be associated with vulvovaginitis. In boys, the penis may be involved. Approximately 50% of patients have rectal pain, most commonly described as burning inside the anus during defecation, and 33% have blood-streaked stools. Fecal retention is a frequent behavioral response to the infection. Patients also have presented with guttate psoriasis. Although local induration or edema may occur, constitutional symptoms, such as fever, headache, and malaise, are absent, suggesting that subcutaneous involvement, as in cellulitis, is absent. Familial spread of perianal infectious dermatitis is common, particularly when family members bathe together or use the same water.

Perianal infectious dermatitis is usually caused by GABHS, but it may also be caused by *S. aureus.* The index case and family members should undergo culture; follow-up cultures to document bacteriologic cure after a course of treatment are recommended.

The differential diagnosis of perianal infectious dermatitis includes psoriasis, seborrheic dermatitis, candidiasis, pinworm infestation, sexual abuse, and inflammatory bowel disease.

For GABHS perianal infectious dermatitis, treatment with a 7-day course of cefuroxime (20 mg/kg/day in two divided doses) is superior to treatment with penicillin. Concomitant topical mupirocin ointment two to three times a day also may be used. If *S. aureus* is cultured, treatment should be based on sensitivities.

ERYSIPELAS

See Chapter 229.



Fig. 706.9 Folliculitis. Multiple follicular pustules.

FOLLICULITIS

Folliculitis, or superficial infection of the hair follicle, is most often caused by *S. aureus*. The lesions are typically small, discrete, dome-shaped pustules with an erythematous base, located at the ostium of the pilosebaceous canals (Fig. 706.9). Hair growth is unimpaired, and the lesions heal without scarring. Favored sites include the scalp, buttocks, and extremities. Poor hygiene, maceration, drainage from wounds and abscesses, and shaving of the legs can be provocative factors. Folliculitis can also occur as a result of tar therapy or occlusive wraps. The moist environment encourages bacterial proliferation. In HIV-infected patients, *S. aureus* may produce confluent erythematous patches with satellite pustules in intertriginous areas and violaceous plaques composed of superficial follicular pustules in the scalp, axillae, or groin. The differential diagnosis includes *Candida,* which may cause satellite follicular papules and pustules surrounding erythematous patches of intertrigo (particularly in groin/buttocks), and *Malassezia furfur,* which produces 2- to 3-mm, pruritic, erythematous, perifollicular papules and pustules on the back, chest, and extremities, particularly in patients who have diabetes mellitus or are taking corticosteroids or antibiotics. Diagnosis is made by examining potassium hydroxide–treated scrapings from lesions. Detection of *Malassezia* may require a skin biopsy, demonstrating clusters of yeast and short, branching hyphae ("macaroni and meatballs") in widened follicular ostia mixed with keratinous debris.

Topical antibiotic therapy (e.g., clindamycin 1% lotion or solution twice a day) is usually all that is needed for mild cases, but more severe cases may require the use of a systemic antibiotic such as dicloxacillin or cephalexin. Bacterial culture should be performed in treatment-resistant cases. In chronic recurrent folliculitis, daily application of a benzoyl peroxide 5% gel or wash may facilitate resolution. Dilute bleach baths may also be effective in reducing recurrence.

Folliculitis barbae (sycosis barbae) is a deeper, more severe recurrent inflammatory form of folliculitis caused by *S. aureus* that involves the entire depth of the follicle. Erythematous follicular papules and pustules develop on the chin, upper lip, and angle of the jaw, primarily in young Black males. Papules may coalesce into plaques, and healing may occur with scarring. Affected individuals are frequently found to be *S. aureus* carriers. Treatment with warm saline compresses and topical antibiotics, such as mupirocin, generally clear the infection. More extensive, recalcitrant cases may require therapy with β-lactamase–resistant systemic antibiotics for several weeks and elimination of *S. aureus* from the sites of carriage.

Pseudomonal folliculitis (hot tub folliculitis) is attributable to *P. aeruginosa,* predominantly serotype O-11. It occurs after exposure to poorly chlorinated hot tubs/whirlpools and swimming pools and to a contaminated water slide or loofah sponge. The lesions are pruritic papules and pustules or deeply erythematous to violaceous nodules that develop 8-48 hours after exposure and are most dense in areas covered by a bathing suit (Fig. 685.10). Patients occasionally experience fever, malaise, and lymphadenopathy. The organism is readily cultured from pus. The eruption usually resolves spontaneously in 1-2 weeks, often leaving postinflammatory hyperpigmentation. Consideration should be given to the use of systemic antibiotics (ciprofloxacin) in adolescent patients with constitutional symptoms. Immunocompromised children are susceptible to complications of *Pseudomonas* folliculitis (cellulitis) and should avoid hot tubs.

ABSCESSES AND FURUNCLES

Etiology

The causative agent in furuncles ("boils") and carbuncles is usually *S. aureus,* which penetrates abraded perifollicular skin. Furuncles are nodules that develop from a single follicle, whereas carbuncles are a coalescence of multiple follicles and are more extensive. Conditions predisposing to furuncle formation include obesity, hyperhidrosis, maceration, friction, and preexisting dermatitis. Furunculosis is also more common in individuals with low serum iron levels, diabetes, malnutrition, HIV infection, or other immunodeficiency states. Recurrent furunculosis is frequently associated with carriage of *S. aureus* in the nares, axillae, or perineum or close contact with someone such as a family member who is a carrier. Other bacteria or fungi may occasionally cause furuncles or carbuncles.

Community-acquired MRSA **abscesses** can also complicate folliculitis-related carbuncles or are acquired from penetrating cutaneous trauma unrelated to folliculitis. Community-acquired MRSA infections commonly affect children and young adults, especially athletes, where spread of the infection is enhanced by skin-to-skin contact. Infection can also be spread by crowding conditions, shared personal hygiene items, and a compromised skin barrier. They may occur in any location; however, they are most common on the lower abdomen, buttocks, and legs.

Clinical Manifestations

This follicular lesion may originate from a preceding folliculitis or may arise initially as a deep-seated, tender, erythematous, perifollicular nodule. Although lesions are initially indurated, central necrosis and suppuration follow, leading to rupture and discharge of a central core of necrotic tissue and destruction of the follicle (Fig. 706.11). Healing occurs with scar formation. Sites of predilection are the hair-bearing areas on the face, neck, axillae, buttocks, and groin. Pain may be intense if the lesion is situated in an area where the skin is relatively fixed, such as in the external auditory canal or over the nasal cartilages. Patients with furuncles usually have no constitutional symptoms; bacteremia may occasionally ensue. Rarely, lesions on the upper lip or cheek may lead to cavernous sinus thrombosis. Infection of a group of contiguous follicles, with multiple drainage points, accompanied by inflammatory changes in surrounding connective tissue is a carbuncle. Carbuncles may be accompanied by fever, leukocytosis, and bacteremia. Hidradenitis suppurativa should be considered in individuals who have recurrent abscesses.

Treatment

Treatment for furuncle and carbuncle includes regular bathing with antimicrobial soaps (chlorhexidine) and wearing of loose-fitting clothing to minimize predisposing factors for furuncle formation. Frequent application of a hot, moist compress may facilitate the drainage of lesions. Large lesions should be drained by a small incision. Carbuncles and large or numerous furuncles should be treated with systemic antibiotics chosen based on culture and sensitivity testing results.

Abscesses are treated with incision and drainage and oral antibiotics for 7-10 days. Antibiotics with coverage against MRSA are recommended and commonly include oral clindamycin (10-30 mg/kg/day in divided doses) or trimethoprim-sulfamethoxazole (8-10 mg trimethoprim/kg/day in divided doses every 12 hours). Children older than 8 years may receive doxycycline. To reduce colonization and hence reinfection in children with recurrent infections, mupirocin intranasally (twice daily) and either chlorhexidine (in lieu of soap during showers) or diluted bleach baths (1 teaspoon per gallon of water or 1/4 cup per 1/4 tub [~13 gallons] of water) once daily for 5 days in patients and in family members has been recommended. Recolonization often occurs, typically within 3 months of the decolonization attempt.



Fig. 706.10 Papules and pustules in hot tub folliculitis.



Fig. 706.11 Rupture and discharge of pus in a furuncle.

PITTED KERATOLYSIS

Pitted keratolysis occurs most frequently in humid tropical and subtropical climates, particularly in individuals whose feet are moist for prolonged periods, for example, as a result of hyperhidrosis, prolonged wearing of boots, or immersion in water. It occurs most commonly in young males from early adolescence to the late 20s. The lesions consist of 1- to 7-mm, irregularly shaped, superficial erosions of the horny layer on the soles, particularly at weight-bearing sites (Fig. 706.12). Brownish discoloration of involved areas may be apparent. A rare variant manifests as thinned, erythematous to violaceous plaques in addition to the typical pitted lesions. The condition is frequently malodorous and is painful in approximately 50% of cases. The most likely etiologic agent is *Corynebacterium (Kytococcus) sedentarius.* Treatment of hyperhidrosis is mandatory with prescription-strength aluminum chloride products or 40% formaldehyde in petrolatum ointment. Avoidance of moisture and maceration produces slow, spontaneous resolution of the infection. Topical or systemic erythromycin and topical imidazole creams are standard therapy.

ERYTHRASMA

Erythrasma is a benign chronic superficial infection caused by *Corynebacterium minutissimum.* Predisposing factors include heat, humidity, obesity, skin maceration, diabetes mellitus, and poor hygiene. Approximately 20% of affected patients have involvement of the toe webs. Other frequently affected sites are moist, intertriginous areas such as the groin and axillae. The inframammary and perianal regions are occasionally involved. Sharply demarcated, irregularly bordered, slightly scaly, brownish red patches are characteristic of the disease. Mild pruritus is the only constant symptom. *C. minutissimum* is a complex of related organisms that produce porphyrins that fluoresce brilliant coral red under ultraviolet light. The diagnosis is readily made, and erythrasma is differentiated from dermatophyte infection and from tinea versicolor on Wood lamp examination. However, bathing within 20 hours of Wood lamp examination may remove the water-soluble porphyrins. Staining of skin scrapings with methylene blue or Gram stain reveals the pleomorphic, filamentous coccobacillary forms.

Effective treatment can be achieved with topical erythromycin, clindamycin, miconazole, or a 10- to 14-day course of oral erythromycin or an oral tetracycline (in those older than 8 years of age).



Fig. 706.12 Superficial erosions of the horny layer in pitted keratolysis.

ERYSIPELOID

A rare cutaneous infection, erysipeloid is caused by inoculation of *E. rhusiopathiae* from handling contaminated animals, birds, fish, or their products. The localized cutaneous form is most common, characterized by well-demarcated, diamond-shaped, erythematous to violaceous patches at sites of inoculation. Local symptoms are generally not severe, constitutional symptoms are rare, and the lesions resolve spontaneously after weeks but can recur at the same site or develop elsewhere weeks to months later. The diffuse cutaneous form manifests as lesions at several areas of the body in addition to the site of inoculation. It is also self-limited. The systemic form, caused by hematogenous spread, is accompanied by constitutional symptoms and may include endocarditis, septic arthritis, cerebral infarct and abscess, meningitis, and pulmonary effusion. Diagnosis is confirmed by skin biopsy, which reveals the gram-positive organisms, and culture. The treatment of choice for localized cutaneous infection is oral penicillin for 7 days; ciprofloxacin or a combination of erythromycin and rifampin may be used for penicillin-allergic patients. Severe diffuse cutaneous or systemic infection may require parenteral penicillin or ceftriaxone.

TUBERCULOSIS OF THE SKIN

See Chapters 261 and 263.

Cutaneous tuberculosis infection occurs worldwide, particularly in association with HIV infection, malnutrition, and poor sanitary conditions. Primary cutaneous tuberculosis is rare in the United States. Cutaneous disease is caused by *Mycobacterium tuberculosis, Mycobacterium bovis,* and, occasionally, by the bacillus Calmette-Guérin (BCG), an attenuated vaccine form of *M. bovis.* The manifestations caused by a given organism are indistinguishable from one another. After invasion of the skin, mycobacteria either multiply intracellularly within macrophages, leading to progressive disease, or are controlled by the host immune reaction.

Primary cutaneous tuberculosis (tuberculous chancre) results when *M. tuberculosis* or *M. bovis* gains access to the skin or mucous membranes through trauma in a previously uninfected individual without immunity to the organism. Sites of predilection are the face, lower extremities, and genitals. The initial lesion develops 2-4 weeks after introduction of the organism into the damaged tissue. A red-brown papule gradually enlarges to form a shallow, firm, sharply demarcated ulcer. Satellite abscesses may be present. Some lesions acquire a crust resembling impetigo, and others become heaped up and verrucous at the margins. The primary lesion can also manifest as a painless ulcer on the conjunctiva, gingiva, or palate and occasionally as a painless acute paronychia. Painless regional adenopathy may appear several

weeks after the development of the primary lesion and may be accompanied by lymphangitis, lymphadenitis, or perforation of the skin surface, forming **scrofuloderma**. Untreated lesions heal with scarring within 12 months but may reactivate, may form lupus vulgaris (sharply defined red-brown nodules with a gelatinous consistency that represent progressive infection), or, rarely, may progress to the acute miliary form. Therefore antituberculous therapy is indicated (see Chapter 261).

M. tuberculosis or *M. bovis* can be cultured from the skin lesion and local lymph nodes, but acid-fast staining of histologic sections, particularly of a well-controlled infection, often does not reveal the organism. The differential diagnosis is broad, including a syphilitic chancre; deep fungal or atypical mycobacterial infection; leprosy; tularemia; cat-scratch disease; sporotrichosis; nocardiosis; leishmaniasis; reaction to foreign substances such as zirconium, beryllium, silk or nylon sutures, talc, and starch; papular acne rosacea; and lupus miliaris disseminatus faciei.

Scrofuloderma results from enlargement, cold abscess formation, and breakdown of a lymph node, most frequently in a cervical chain, with extension to the overlying skin from underlying foci of tuberculous infection. Linear or serpiginous ulcers and dissecting fistulas and subcutaneous tracts studded with soft nodules may develop. Spontaneous healing may take years, eventuating in cordlike keloid scars. Lupus vulgaris may also develop. Lesions may also originate from an underlying infected joint, tendon, bone, or epididymis. The differential diagnosis includes syphilitic gumma, deep fungal infections, actinomycosis, and hidradenitis suppurativa. The course is indolent, and constitutional symptoms are typically absent. Antituberculous therapy is indicated (see Chapter 261).

Direct cutaneous inoculation of the tubercle bacillus into a previously infected individual with a moderate to high degree of immunity initially produces a small papule with surrounding inflammation. **Tuberculosis verrucosa cutis** (warty tuberculosis) forms when the papule becomes hyperkeratotic and warty, and several adjacent papules coalesce or a single papule expands peripherally to form a brownish red to violaceous, exudative, crusted verrucous plaque. Irregular extension of the margins of the plaque produces a serpiginous border. Children have the lesions most commonly on the lower extremities after trauma and contact with infected material such as sputum or soil. Regional lymph nodes are involved only rarely. Spontaneous healing with atrophic scarring takes place over months to years. Healing is also gradual with antituberculous therapy.

Lupus vulgaris is a rare, chronic, progressive form of cutaneous tuberculosis that develops in individuals with a moderate to high degree of tuberculin sensitivity induced by previous infection. The incidence is greater in cool, moist climates, particularly in females. Lupus vulgaris develops as a result of direct extension from underlying joints or lymph nodes; through lymphatic or hematogenous spread; or, rarely, by cutaneous inoculation with the BCG vaccine. It most commonly follows cervical adenitis or pulmonary tuberculosis. Approximately 33% of cases are preceded by scrofuloderma, and 90% of cases manifest on the head and neck, most commonly on the nose or cheek. Involvement of the trunk is uncommon. A typical solitary lesion consists of a soft, brownish red papule that has an apple-jelly color when examined by diascopy. Peripheral expansion of the papule or, occasionally, the coalescence of several papules forms an irregular lesion of variable size and form. One or several lesions may develop, including nodules or plaques that are flat and serpiginous, hypertrophic and verrucous, or edematous in appearance. Spontaneous healing occurs centrally, and lesions characteristically reappear within the area of atrophy. Chronicity is characteristic, and persistence and progression of plaques over many years are common. Lymphadenitis is present in 40% of those with lupus vulgaris, and 10–20% have infection of the lungs, bones, or joints. Extensive deformities may be caused by vegetative masses and ulceration involving the nasal, buccal, or conjunctival mucosa; the palate; the gingiva; or the oropharynx. Squamous cell carcinoma, with a relatively high metastatic potential, may develop, usually after several years of the disease. After a temporary impairment in immunity, particularly after measles infection (lupus exanthematicus), multiple lesions may form at distant sites as a result of hematogenous spread from a latent focus of infection. The histopathology reveals a tuberculoid granuloma without caseation; organisms are extremely difficult to demonstrate. The differential diagnosis includes sarcoidosis, atypical mycobacterial infection, blastomycosis, chromoblastomycosis, actinomycosis, leishmaniasis, tertiary syphilis, leprosy, hypertrophic lichen planus, psoriasis, lupus erythematosus, lymphocytoma, and Bowen disease. Small lesions can be excised. Antituberculous drug therapy usually halts further spread and induces involution.

Orificial tuberculosis (tuberculosis cutis orificialis) appears on the mucous membranes and periorificial skin after autoinoculation of mycobacteria from sites of progressive infection. It is a sign of advanced internal disease and carries a poor prognosis, and it occurs in a sensitized host with impaired cellular immunity. Lesions appear as painful, yellowish or red nodules that form punched-out ulcers with inflammation and edema of the surrounding mucosa. Treatment consists of identification of the source of infection and initiation of antituberculous therapy.

Miliary tuberculosis (hematogenous primary tuberculosis) rarely manifests cutaneously and occurs most commonly in infants and in individuals who are immunosuppressed after chemotherapy or infection with measles or HIV. The eruption consists of crops of symmetrically distributed, minute, erythematous to purpuric macules, papules, or vesicles. The lesions may ulcerate, drain, crust, and form sinus tracts or may form subcutaneous gummas, especially in malnourished children with impaired immunity. Constitutional signs and symptoms are common, and a leukemoid reaction or aplastic anemia may develop. Tubercle bacilli are readily identified in an active lesion. A fulminant course should be anticipated, and aggressive antituberculous therapy is indicated.

Single or multiple metastatic tuberculous abscesses **(tuberculous gummas)** may develop on the extremities and trunk by hematogenous spread from a primary focus of infection during a period of decreased immunity, particularly in malnourished and immunosuppressed children. The fluctuant, nontender, erythematous subcutaneous nodules may ulcerate and form fistulas.

Vaccination with BCG characteristically produces a papule approximately 2 weeks after vaccination. The papule expands in size, typically ulcerates within 2-4 months, and heals slowly with scarring. In 1-2 per million vaccinations, a complication caused specifically by the BCG organism occurs, including regional lymphadenitis, lupus vulgaris, scrofuloderma, and subcutaneous abscess formation. Delayed reactivation with inflammation at the site of BCG vaccination has been reported with Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C), as well as immunization with the COVID-19 and influenza vaccines.

Tuberculids are skin reactions that exhibit tuberculoid features histologically but do not contain detectable mycobacteria. The lesions appear in a host who usually has moderate to strong tuberculin reactivity, has a history of previous tuberculosis of other organs, and usually shows a therapeutic response to antituberculous therapy. The cause of tuberculids is poorly understood. Most affected patients are in good health with no clear focus of disease at the time of the eruption. The most commonly observed tuberculid is the papulonecrotic tuberculid. Recurrent crops of symmetrically distributed, asymptomatic, firm, sterile, dusky-red papules appear on the extensor aspects of the limbs, the dorsum of the hands and feet, and the buttocks. The papules may undergo central ulceration and eventually heal, leaving sharply delineated, circular, depressed scars. The duration of the eruption is variable, but it usually disappears promptly after treatment of the primary infection. Lichen scrofulosorum, another form of tuberculid, is characterized by asymptomatic, grouped, pinhead-sized, often follicular pink or red papules that form discoid plaques, mainly on the trunk. Healing occurs without scarring.

Atypical mycobacterial infection may cause cutaneous lesions in children. Interestingly, there may be some seasonable variation in incidence. It has been postulated that vitamin D may play a role. *Mycobacterium marinum* is found in saltwater, freshwater, and diseased fish. In the United States, it is most commonly acquired from tropical fish tanks and swimming pools. Traumatic abrasion of the skin serves as a portal of entry for the organism. Approximately 3 weeks after inoculation, a single reddish papule develops and enlarges slowly to form a violaceous nodule or, occasionally, a warty plaque (Fig. 706.13). The lesion occasionally breaks down to form a crusted ulcer or a suppurating



Fig. 706.13 Violaceous, warty plaque of *Mycobacterium marinum* infection.

abscess. Sporotrichoid erythematous nodules along lymphatics may also suppurate and drain. Lesions are most common on the elbows, knees, and feet of swimmers and on the hands and fingers in persons with aquarium-acquired infection. Systemic signs and symptoms are absent. Regional lymph nodes occasionally become slightly enlarged but do not break down. Rarely, the infection becomes disseminated, particularly in an immunosuppressed host. A biopsy specimen of a fully developed lesion demonstrates a granulomatous infiltrate with tuberculoid architecture. Treatment with two active agents is generally recommended, with a combination of clarithromycin and ethambutol providing a reasonable balance between effectiveness and tolerability. Rifampin should be added to clarithromycin and ethambutol for deep tissue involvement. Other agents with activity against *M. marinum* include trimethoprim-sulfamethoxazole, doxycycline, minocycline, and ciprofloxacin. Although azithromycin has been used as an alternative to clarithromycin for some mycobacterial infections, its effectiveness against *M. marinum* is not known. Treatment should continue for 1-2 months after resolution of lesions with a minimum treatment duration of 6 months. The application of heat to the affected site may be a useful adjunctive therapy (see Chapter 263).

Mycobacterium kansasii primarily causes pulmonary disease; skin disease is rare, often occurring in an immunocompromised host. Most commonly, sporotrichoid nodules develop after inoculation of traumatized skin. Lesions may develop into ulcerated, crusted, or verrucous plaques. The organism is relatively sensitive to antituberculous medications, which should be chosen on the basis of susceptibility testing.

Mycobacterium scrofulaceum causes cervical lymphadenitis (scrofuloderma) in young children, typically in the submandibular region. Nodes enlarge over several weeks, ulcerate, and drain. The local reaction is nontender and circumscribed, constitutional symptoms are absent, and there generally is no evidence of lung or other organ involvement. Other atypical mycobacteria may cause a similar presentation, including *Mycobacterium avium* complex, *M. kansasii,* and *Mycobacterium fortuitum.* Treatment is accomplished by excision and administration of antituberculous drugs (see Chapter 263).

Mycobacterium ulcerans (Buruli ulcer or Bairnsdale ulcers) causes a painless subcutaneous nodule after inoculation of abraded skin. Most infections occur in children in tropical rainforests. The nodule usually ulcerates, develops undermined edges, and may spread over large areas, most commonly on an extremity. Local necrosis of subcutaneous fat, producing a septal panniculitis, is characteristic. Ulcers persist for months to years before healing spontaneously with scarring, sometimes with contractures (if over a joint) and lymphedema. Constitutional symptoms and lymphadenopathy are absent. Diagnosis is made by culturing the organism at 32–33°C (89.6–91.4°F). **Treatment of choice** is an 8-week course of rifampin and streptomycin with surgical debridement for larger lesions. Local heat therapy and oral chemotherapy may benefit some patients.

M. avium complex, composed of more than 20 subtypes, most commonly causes chronic pulmonary infection. Cervical lymphadenitis and osteomyelitis occur occasionally, and papules or purulent leg ulcers occur rarely by primary inoculation. Skin lesions may be an early sign of disseminated infection. The lesions may take various forms, including erythematous papules, pustules, nodules, abscesses, ulcers, panniculitis, and sporotrichoid spread along lymphatics. For treatment, see Chapter 263.

M. fortuitum complex causes disease in an immunocompetent host principally by primary cutaneous inoculation after traumatic injury, injection, or surgery. A nodule, abscess, or cellulitis develops 4-6 weeks after inoculation. In an immunocompromised host, numerous subcutaneous nodules may form, break down, and drain. Treatment is based on identification and susceptibility testing of the organism. Isolates are usually susceptible to fluoroquinolones, doxycycline, minocycline, sulfonamides, cefoxitin, and imipenem; macrolides should be used with caution because many *M. fortuitum* isolates have the erythromycin methylase *(erm)* gene, which confers inducible resistance to macrolides despite "susceptible" minimum inhibitory concentrations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 707

Cutaneous Fungal Infections

Stephen R. Humphrey

TINEA VERSICOLOR

A common, innocuous, chronic fungal infection of the stratum corneum, tinea versicolor is most often caused by the dimorphic yeast *Malassezia globosa,* with *Malassezia furfur* and *Malassezia sympodialis* as less frequent causative agents. The synonyms *Pityrosporum ovale* and *Pityrosporum orbiculare* were used previously to identify the causal organism.

Etiology

M. globosa is part of the normal indigenous skin flora, predominantly in the yeast form, and is found particularly in areas of skin that are rich in sebum production. Proliferation of filamentous forms occurs in the disease state. Predisposing factors include a warm, humid environment, excessive sweating, occlusion, high plasma cortisol levels, immunosuppression, malnourishment, and genetically determined susceptibility. The disease is most prevalent in adolescents and young adults.

Clinical Manifestations

The lesions of tinea versicolor vary widely in color. In lighter skin, they are typically reddish brown, whereas in darker skin, they may be either hypopigmented or hyperpigmented. The characteristic macules are covered with a fine scale. They often begin in a perifollicular location, enlarge, and merge to form confluent patches, most commonly on the neck, upper chest, back, and upper arms (Fig. 707.1). Facial lesions are common in adolescents; lesions occasionally appear on the forearms, dorsum of the hands, and pubis. There may be little or no pruritus. Involved areas do not tan after sun exposure. A papulopustular perifollicular variant of the disorder may occur on the back, chest, and sometimes the extremities. These pustules tend to be monomorphic.

Differential Diagnosis

Examination with a Wood lamp discloses a yellowish gold fluorescence. A potassium hydroxide (KOH) preparation of scrapings is diagnostic, demonstrating groups of thick-walled spores and myriad short, thick,



Fig. 707.1 Hyperpigmented, sharply demarcated macules of varying sizes on the upper trunk characteristic of tinea versicolor.



Fig. 707.2 Id reaction. Papular eruption of the face associated with severe tinea infection of the hand.

angular hyphae resembling macaroni/spaghetti and meatballs. Skin biopsy, including culture and special stains for fungi (periodic acid–Schiff), are often necessary to make the diagnosis in cases of primarily follicular involvement. Microscopically, organisms and keratinous debris can be seen within dilated follicular ostia.

Tinea versicolor must be distinguished from dermatophyte infections, seborrheic dermatitis, pityriasis alba, pityriasis rosea, and secondary syphilis. Tinea versicolor may mimic nonscaling pigmentary disorders, such as postinflammatory pigmentary change, if a patient has removed the scales by scrubbing. *M. globosa* folliculitis must be distinguished from the other forms of folliculitis.

Treatment

Many therapeutic agents can be used to treat this disease successfully. The causative agent, a normal human saprophyte, is not eradicated from the skin, however, and the disorder recurs in predisposed individuals. Appropriate topical therapy may include one of the following: selenium 2% shampoo applied for 10 minutes before rinsing for 1 week, ketoconazole 2% shampoo once daily for 3 days, and terbinafine spray once to twice daily for 1-2 weeks. Antifungal creams are available and can be used; however, these can be impractical to apply given the large surface of skin involved. Oral therapy may be more convenient and may be achieved successfully with fluconazole 300 mg/wk for 2-4 weeks or itraconazole 200 mg/24 hr for 5-7 days. Recurrent episodes continue to respond promptly to these agents. Oral therapy is particularly helpful in those with severe disease or recurrent disease or in those where topical therapies have failed. Maintenance therapy with selenium sulfide shampoo or ketoconazole 2% shampoo once a week may be used.

DERMATOPHYTOSES

Dermatophytoses are caused by a group of closely related filamentous fungi with a propensity for invading the stratum corneum, hair, and nails. The three principal genera responsible for infections are *Trichophyton, Microsporum,* and *Epidermophyton.*

Etiology

Trichophyton spp. cause lesions of all keratinized tissue, including skin, nails, and hair. *Trichophyton rubrum* is the most common dermatophyte pathogen. *Microsporum* spp. principally invade the hair, and the *Epidermophyton* spp. invade the intertriginous skin. Dermatophyte infections are designated by the word **tinea** followed by the Latin word for the anatomic site of involvement. The dermatophytes are also classified according to source and natural habitat. Fungi acquired from the soil are called *geophilic*. They infect humans sporadically, inciting an inflammatory reaction. Dermatophytes that are acquired from animals are *zoophilic*. Transmission may be through direct contact or indirectly by infected animal hair or clothing. Infected animals are frequently asymptomatic. Dermatophytes acquired from humans are referred to as *anthropophilic*. These infestations range from chronic low-grade to acute inflammatory disease. *Epidermophyton* infections are transmitted only by humans, but various species of *Trichophyton* and *Microsporum* can be acquired from both human and nonhuman sources.

Epidemiology

Host defense has an important influence on the severity of the infection. Disease tends to be more severe in individuals with diabetes mellitus, lymphoid malignancies, immunosuppression, and states with high plasma cortisol levels, such as Cushing syndrome. Some dermatophytes, most notably the zoophilic species, tend to elicit more severe, suppurative inflammation in humans. Some degree of resistance to reinfection is acquired by most infected persons and may be associated with a delayed hypersensitivity response. However, no relationship has been demonstrated between antibody levels and resistance to infection. The frequency and severity of infection are also affected by the geographic locale, the genetic susceptibility of the host, and the virulence of the strain of dermatophyte. Additional local factors that predispose to infection include trauma to the skin, hydration of the skin with maceration, occlusion, and elevated temperature.

Occasionally, a secondary skin eruption, referred to as a dermatophytid or "id" reaction, appears in sensitized individuals and has been attributed to circulating fungal antigens derived from the primary infection. The eruption is characterized by grouped papules (Fig. 707.2) and vesicles and, occasionally, by sterile pustules. Symmetric urticarial lesions and a more generalized maculopapular eruption also can occur. Id reactions are most often associated with tinea pedis, but they also occur with tinea capitis.

Tinea Capitis

Clinical Manifestations

Tinea capitis is a dermatophyte infection of the scalp most often caused by *Trichophyton tonsurans,* occasionally by *Microsporum canis*, and, much less commonly, by other *Microsporum* and *Trichophyton* spp. It is particularly common in children age 3-7 years old. In *Microsporum* and some *Trichophyton* infections, the spores are distributed in a sheathlike fashion around the hair shaft (**ectothrix** infection), whereas *T. tonsurans* produces an infection within the hair shaft (endothrix). **Endothrix** infections may continue past the anagen phase of hair growth into telogen and are more chronic than infections with ectothrix organisms that persist only during the anagen phase. *T. tonsurans* is an anthropophilic species acquired most often by contact with infected hairs and epithelial cells that are on such surfaces as theater seats, hats, and combs. Dermatophyte spores may also be airborne within the immediate environment, and high carriage rates have been demonstrated in noninfected schoolmates and household members. *M. canis* is a zoophilic species that is acquired from cats and dogs.

The clinical presentation of tinea capitis varies with the infecting organism. Endothrix infections such as those caused by *T. tonsurans* create a



Fig. 707.3 Black-dot ringworm with hairs broken off at the scalp.



Fig. 707.4 Tinea capitis mimicking seborrheic dermatitis.



Fig. 707.5 Lymphadenopathy associated with tinea capitis.

pattern known as "black-dot ringworm," characterized initially by many small circular patches of alopecia in which hairs are broken off close to the hair follicle (Fig. 707.3). Another clinical variant manifests as diffuse scaling, with minimal hair loss secondary. It strongly resembles seborrheic dermatitis, psoriasis, or atopic dermatitis (Fig. 707.4). *T. tonsurans* may also produce a chronic and more diffuse alopecia. Lymphadenopathy is common (Fig. 707.5). A severe inflammatory response produces elevated, boggy granulomatous masses **(kerion)**, which are often studded with pustules (Fig. 707.6A). Fever, pain, and regional adenopathy are common, and permanent scarring and alopecia may result (see Fig. 707.6B). The zoophilic organism *M. canis* or the geophilic organism *Microsporum gypseum* also may cause kerion formation. The pattern produced by



Fig. 707.6 A, Kerion. Boggy granulomatous mass of the scalp. B, Scarring after kerion.

Microsporum audouinii, the most common cause of tinea capitis in the 1940s and 1950s, is characterized initially by a small papule at the base of a hair follicle. The infection spreads peripherally, forming an erythematous and scaly circular plaque **(ringworm)** within which the infected hairs become brittle and broken. Numerous confluent patches of alopecia develop, and patients may complain of severe pruritus. *M. audouinii* infection is no longer common in the United States. **Favus** is a chronic form of tinea capitis that is rare in the United States and is caused by the fungus *Trichophyton schoenleinii*. Favus starts as yellowish red papules at the opening of hair follicles. The papules expand and coalesce to form cup-shaped, yellowish, crusted patches that fluoresce dull green under a Wood lamp. Other species, such as *Trichophyton violaceum* and *Trichophyton soudanense* are becoming more common with resettlement and emigration.

Differential Diagnosis

Tinea capitis can be confused with seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania, and certain dystrophic hair disorders. When inflammation is pronounced, as in kerion, primary or secondary bacterial infection must also be considered. In adolescents, the patchy, moth-eaten type of alopecia associated with secondary syphilis may resemble tinea capitis. If scarring occurs, discoid lupus erythematosus and lichen planopilaris must also be considered in the differential diagnosis.

The important diagnostic procedures for the various dermatophyte diseases include examination of infected hairs with a Wood lamp, microscopic examination of KOH preparations of infected material, and identification of the etiologic agent by culture. Hairs infected with common *Microsporum* spp. fluoresce a bright blue-green. Most *Trichophyton*-infected hairs do not fluoresce.

Microscopic examination of a KOH preparation of infected hair from the active border of a lesion discloses tiny spores surrounding the hair shaft in *Microsporum* infections and chains of spores within the hair shaft in *T. tonsurans* infections. Fungal elements are not usually seen in scales. A specific etiologic diagnosis of tinea capitis may be obtained by planting broken-off infected hairs on Sabouraud medium with reagents to inhibit growth of other organisms. Such identification may require 2 weeks or more.

Treatment

Oral administration of griseofulvin microcrystalline (20-25 mg/kg/day with a maximum daily dose of 1000 mg, or 10-15 mg/kg/day with a maximum daily dose of 750 mg if the ultramicrosize form is used) is typically the recommended treatment for all forms of tinea capitis. Absorption of griseofulvin is enhanced by the ingestion of a fatty meal and should be recommended for the patient. A minimum of 8 weeks of treatment is usually required, though longer courses are sometimes needed. Repeat fungal cultures may help guide treatment length. Treatment for 1 month after a negative culture result minimizes the risk of recurrence. Adverse reactions to griseofulvin are rare but include nausea, vomiting, headache, blood dyscrasias, phototoxicity, and hepatotoxicity. Terbinafine dosing is weight-based. Off-label use is 125 mg daily for 6 weeks if under 25 kg. From 25 to 35 kg, the dose is 187.5 mg daily for 6 weeks. For patients greater than 35 kg, the dose is 250 mg daily for 6 weeks. It is possibly effective in pulse therapy, although it has limited activity against *M. canis*, but better activity than griseofulvin for *T. tonsurans.* The oral granule formulation of terbinafine is approved by the U.S. Food and Drug Administration (FDA) for tinea capitis in children 4 years of age and older. Oral itraconazole is useful in instances of griseofulvin resistance, intolerance, or allergy. Itraconazole is given for 4-6 weeks at a dosage of 5 mg/kg/24 hr with food. This is off-label and length of course depends on organism. Capsules are preferable to the syrup, which may cause diarrhea. Itraconazole is not approved by the FDA for treatment of dermatophyte infections in the pediatric population. Topical therapy alone is ineffective, but it may be an important adjunct because it may decrease the shedding of spores and should be recommended in all patients. Asymptomatic dermatophyte carriage in family members is common. Because one in three families have at least one member who is a carrier, treatment of both patient and potential carriers with a sporicidal shampoo may hasten clinical resolution. Vigorous shampooing with a 2.5% selenium sulfide, zinc pyrithione, or ketoconazole shampoo is helpful. It is not necessary to shave the scalp.

Tinea Corporis

Clinical Manifestations

Tinea corporis, defined as infection of the glabrous skin, excluding the palms, soles, and groin, can be caused by most of the dermatophyte species, although *T. rubrum* and *Trichophyton mentagrophytes* are the most prevalent etiologic organisms. In children, infections with *M. canis* are also common. Tinea corporis can be acquired by direct contact with infected persons or by contact with infected scales or hairs deposited on environmental surfaces. *M. canis* infections are usually acquired from infected pets.

The most typical clinical lesion begins as a dry, mildly erythematous, elevated, scaly papule or plaque that spreads centrifugally and clears centrally to form the characteristic annular lesion responsible for the designation of ringworm (Fig. 707.7). At times, plaques with advancing borders may spread over large areas. Grouped pustules are another variant. Most lesions clear spontaneously within several months, but some may become chronic. Central clearing does not always occur (Fig. 707.8), and differences in host response may result in wide variability in the clinical appearance; for example, granulomatous lesions called **Majocchi granuloma**, which are caused by the penetration of organisms along the hair follicle to the level of the dermis, produce a fungal folliculitis and perifolliculitis (Fig. 707.9) and the kerion-like lesions referred to as *tinea profunda.* Majocchi granuloma is more common after inappropriate treatment with topical corticosteroids, especially the superpotent class.

Differential Diagnosis

Many skin lesions, both infectious and noninfectious, must be differentiated from the lesions of tinea corporis. Those most frequently confused are granuloma annulare, nummular eczema, pityriasis rosea, psoriasis, seborrheic dermatitis, erythema chronicum migrans, and tinea versicolor. Microscopic examination of KOH wet mount preparations and cultures should always be performed when fungal infection is considered. Tinea corporis usually does not fluoresce with a Wood lamp.



Fig. 707.7 Annular plaque of tinea corporis with central clearing.



Fig. 707.8 Minimal central clearing with tinea corporis.



Fig. 707.9 Follicular papule and pustule in Majocchi granuloma after use of a superpotent topical steroid.

Treatment

Tinea corporis usually responds to treatment with one of the topical antifungal agents (e.g., imidazoles, terbinafine, butenafine, naftifine) twice daily for 2-4 weeks. In unusually severe or extensive disease, a course of therapy with oral griseofulvin microcrystalline may be required for 4 weeks. Terbinafine for 2 weeks can also be used. Itraconazole has produced excellent results in many cases with a 1- to 2-week course of oral therapy. Combination topical corticosteroid/antifungal preparations should not be used, as they may result in worsening or persistent infection.

Tinea Cruris

Clinical Manifestations

Tinea cruris, or infection of the groin, occurs most often in adolescent males and is usually caused by the anthropophilic species *Epidermophyton floccosum* or *T. rubrum,* but occasionally by the zoophilic species *T. mentagrophytes.*

The initial clinical lesion is a small, raised, scaly, erythematous patch on the inner aspect of the thigh. This spreads peripherally, often developing numerous tiny vesicles at the advancing margin. It eventually forms bilateral, irregular, sharply bordered patches with hyperpigmented scaly centers. In some cases, particularly in infections with *T. mentagrophytes,* the inflammatory reaction is more intense and the infection may spread beyond the crural region. The scrotum and labia are usually not involved in the infection, which is an important distinction from candidiasis. Pruritus may be severe initially but abates as the inflammatory reaction subsides. Bacterial superinfection may alter the clinical appearance, and erythrasma or candidiasis may coexist. Tinea cruris is more prevalent in obese persons and in persons who perspire excessively and wear tight-fitting clothing. It is a good idea to examine a patient's feet, which can be a source for tinea cruris.

Differential Diagnosis

The diagnosis of tinea cruris is confirmed by culture and by demonstration of septate hyphae on a KOH preparation of epidermal scrapings. The disorder must be differentiated from intertrigo, allergic contact dermatitis, candidiasis, and erythrasma. Bacterial superinfection must be precluded when there is a severe inflammatory reaction.

Treatment

Patients should be advised to wear loose cotton underwear. Topical treatment with an imidazole twice a day for 3-4 weeks is recommended for severe infection, especially because these agents are effective in mixed candidal-dermatophytic infections. Oral treatments, as mentioned earlier, may also be used.

Tinea Pedis

Clinical Manifestations

Tinea pedis (athlete's foot), infection of the toe webs and soles of the feet, is uncommon in young children but occurs with some frequency in preadolescent and adolescent males. The usual etiologic agents are *T. rubrum, T. mentagrophytes,* and *E. floccosum.*

Most commonly, the lateral toe webs (third to fourth and fourth to fifth interdigital spaces) and the subdigital crevice are fissured, with maceration and peeling of the surrounding skin (Fig. 707.10). Severe tenderness, itching, and a persistent foul odor are characteristic. These lesions may become chronic. This type of infection may involve overgrowth by bacterial flora, including *Kytococcus sedentarius, Brevibacterium epidermidis,* and gram-negative organisms. Less commonly, a chronic diffuse hyperkeratosis of the sole of the foot occurs with only mild erythema (Fig. 707.11). In some cases, two feet and one hand are involved. This type of infection is more refractory to treatment and tends to recur. An inflammatory vesicular type of reaction may occur with *T. mentagrophytes* infection. This type is most common in young children. The lesions involve any area of the foot, including the dorsal surface, and are usually circumscribed. The initial papules progress to vesicles and bullae that may become pustular (Fig. 707.12). A number of factors, such as occlusive footwear and warm, humid weather, predispose to infection. Tinea pedis may be transmitted in shower facilities and swimming pool areas.

Differential Diagnosis

Tinea pedis must be differentiated from simple maceration and peeling of the interdigital spaces, which is common in children. Infection with *Candida albicans* and various bacterial organisms (erythrasma) may cause confusion or may coexist with primary tinea pedis. Contact dermatitis, vesicular foot dermatitis, atopic dermatitis, and juvenile plantar dermatitis also simulate tinea pedis. Fungal mycelia can be seen on microscopic examination of a KOH preparation or by culture.

Treatment

Treatment for mild infections includes simple measures such as avoidance of occlusive footwear, careful drying between the toes after bathing, and the use of an absorbent antifungal powder such as zinc undecylenate. Topical therapy with an imidazole is curative in most cases. Each of these agents is also effective against candidal infection. Several weeks of therapy may be necessary, and low-grade, chronic infections, particularly those caused by *T. rubrum,* may be refractory. In refractory cases, oral griseofulvin therapy may effect a cure, but recurrences are common.



Fig. 707.11 Diffuse, minimally erythematous tinea pedis.



Fig. 707.10 Interdigital tinea pedis.



Fig. 707.12 Vesicobullous tinea pedis.

Tinea Unguium

Clinical Manifestations

Tinea unguium (onychomycosis) is a dermatophyte infection of the nail plate. It occurs most often in patients with tinea pedis, but it may occur as a primary infection. It can be caused by a number of dermatophytes, of which *T. rubrum* and *T. mentagrophytes* are the most common.

The most superficial form of tinea unguium (i.e., white superficial onychomycosis) is caused by *T. mentagrophytes.* It manifests as irregular single or numerous white patches on the surface of the nail unassociated with paronychial inflammation or deep infection. *T. rubrum* generally causes a more invasive, subungual infection that is initiated at the lateral distal margins of the nail and is often preceded by mild paronychia. The middle and ventral layers of the nail plate, and perhaps the nail bed, are the sites of infection. The nail initially develops a yellowish discoloration and slowly becomes thickened, brittle, and loosened from the nail bed (Fig. 707.13). In advanced infection, the nail may turn dark brown to black and may crack or break off.

Differential Diagnosis

Tinea unguium must be differentiated from various dystrophic nail disorders. Changes as a result of trauma, psoriasis, lichen planus, eczema, and trachyonychia can all be confused with tinea unguium. Nails infected with *C. albicans* have several distinguishing features; most prominently, a pronounced paronychial swelling. Thin shavings taken from the infected nail, preferably from the deeper areas, should be examined microscopically with KOH and cultured. Repeated attempts may be required to demonstrate the fungus. Histologic evaluation of nail clippings with special stains for dermatophytes can be diagnostic.

Treatment

Systemic antifungals are more effective at treating onychomycosis than topical antifungals. The long half-life of itraconazole in the nail has led to promising trials of intermittent short courses of therapy (double the normal dose for 1 week of each month for 3-4 months). Oral terbinafine is also used for the treatment of onychomycosis. Terbinafine once daily for 12 weeks is more effective than itraconazole pulse therapy. Pulse terbinafine treatment has also been used in adults and has been effective. Topical antifungals may be an acceptable treatment for mild disease without matrix involvement, and typically children have a better response to topical therapy than adults, likely because of faster growth of the nails. Several topical agents have been FDA approved for the treatment of onychomycosis in adults, including ciclopirox, efinaconazole, and tavaborole. Small clinical trials have demonstrated efficacy of ciclopirox in children. Efinaconazole and tavaborole can be used in children 6 and older as well.

Tinea Nigra Palmaris

Tinea nigra palmaris is a rare but distinctive superficial fungal infection that occurs principally in children and adolescents. It is caused by the dimorphic fungus *Phaeoannellomyces werneckii,* which imparts a gray-black color to the affected palm. The characteristic lesion is a well-defined hyperpigmented macule. Scaling and erythema are rare, and the lesions are asymptomatic. Tinea nigra is often mistaken for a junctional nevus, melanoma, or staining of the skin by contactants. Treatment is with an imidazole antifungal. *Keratolytic agents, such as salicylic acid, once to twice daily* can also be used.



Fig. 707.13 Hyperkeratotic nail in onychomycosis.

CANDIDAL INFECTIONS (CANDIDIASIS AND MONILIASIS)

See Chapter 280.

The dimorphic yeasts of the genus *Candida* are ubiquitous in the environment, but *C. albicans* usually causes candidiasis in children. This yeast is not part of the indigenous skin flora, but it is a frequent transient on skin and may colonize the human alimentary tract and the vagina as a saprophytic organism. Certain environmental conditions, notably elevated temperature and humidity, are associated with an increased frequency of isolation of *C. albicans* from the skin. Many bacterial species inhibit the growth of *C. albicans,* and alteration of normal flora by the use of antibiotics may promote overgrowth of the yeast.

Chronic mucocutaneous candidiasis is associated with a diverse group of primary immunodeficiency diseases (Table 707.1). Chronic mucocutaneous candidiasis is characterized by chronic or recurrent *Candida* infections of the oral cavity, esophagus, genitals, nails, and skin. Chronic mucocutaneous candidiasis may also be seen as an acquired infection in patients with HIV infection and during immunosuppressive treatments.

Oral Candidiasis (Thrush)

See Chapter 280.

Vaginal Candidiasis

See Chapters 163 and 280.

C. albicans is an inhabitant of the vagina in 5–10% of women, and vaginal candidiasis is not uncommon in adolescent girls. A number of factors can predispose to this infection, including antibiotic therapy, corticosteroid therapy, diabetes mellitus, pregnancy, and the use of oral contraceptives. The infection manifests as cheesy white plaques on an erythematous vaginal mucosa and a thick white-yellow discharge. The disease may be relatively mild or may produce pronounced inflammation and scaling of the external genitals and surrounding skin with progression to vesiculation and ulceration. Patients often complain of severe itching and burning in the vaginal area. Before treatment is initiated, the diagnosis should be confirmed by microscopic examination and/or culture. The infection may be eradicated by insertion of nystatin or imidazole vaginal tablets, suppositories, creams, or foam. If these products are ineffective, the addition of one dose of fluconazole (150 mg) is effective for adolescents.

Congenital Cutaneous Candidiasis

See Chapter 280.

Candidal Diaper Dermatitis

Candidal diaper dermatitis is a ubiquitous problem in infants and, although relatively benign, is often frustrating because of its tendency to recur. Predisposed infants usually carry *C. albicans* in their intestinal tracts, and the warm, moist, occluded skin of the diaper area provides an optimal environment for its growth. A seborrheic, atopic, or primary irritant contact dermatitis usually provides a portal of entry for the yeast.

The primary clinical manifestation consists of an intensely erythematous, confluent plaque with a scalloped border and a sharply demarcated edge. It is formed by the confluence of numerous papules and vesicular pustules. Satellite pustules, those that stud the contiguous skin, are a hallmark of localized candidal infections. The perianal skin, inguinal folds, perineum, and lower abdomen are usually involved (Fig. 707.14). In males, the entire scrotum and penis may be involved, with an erosive balanitis of the perimeatal skin. In females, the lesions may be found on the vaginal mucosa and labia. In some infants, the process is generalized, with erythematous lesions distant from the diaper

Table 707.1 Primary Immunodeficiencies Underlying Candida and Other Fungal Infections

DISEASE	ASSOCIATED INFECTIONS	IMMUNOLOGIC PHENOTYPE	GENE, TRANSMISSION
CMC			
SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and/or NK cell lymphopenia	>30 genes: *IL2RG*, X-linked; *JAK3*, autosomal recessive; *RAG1*, autosomal recessive; *RAG2*, autosomal recessive; *ARTEMIS*, autosomal recessive; *ADA*, autosomal recessive; *CD3*, autosomal recessive, etc.
CID			
CD25 deficiency	Viruses and bacteria	T-cell defect	*IL2RA*, autosomal recessive
NEMO or iκBγ deficiency	Pyogenic bacteria, mycobacteria, viruses		*NEMO* or *IKBG* X-linked
IκBα GOF pathogenic variant			*IKBA*, autosomal dominant
DOCK8 deficiency	Viruses, bacteria and fungi		*DOCK8*, autosomal recessive
TCR-α deficiency	Viruses and bacteria		*TCRA*, autosomal recessive
CRACM1 deficiency	Viruses, mycobacteria, bacteria and fungi		*CRACM1*, autosomal recessive
MST1/STK4 deficiency	Viruses and bacteria		*MST1/STK4*, autosomal recessive
MHC class II deficiency	Viruses, bacteria and fungi		*CIITA, RFXANK, RFXC, RFXAP*, all autosomal recessive
Idiopathic CD4 lymphopenia	*Pneumocystis, Cryptococcus*, virus	CD4 T cells <300 cells/mm^3	*UNC119*, autosomal dominant, *MAGT1* X-linked, *RAG1*, autosomal recessive
SYNDROMIC CMC			
Interleukin-12Rβ1 and interleukin-12p40 deficiencies	*Mycobacteria, Salmonella*	Deficit of interleukin-17–producing T cells	*IL12RB1*, autosomal recessive, *IL12B*, autosomal recessive
STAT3 deficiency (autosomal dominant-HIES)	*Staphylococcus aureus, Aspergillus*	Hyperimmunoglobulin E, deficit of interleukin-17–producing T cells	*STAT3*, autosomal dominant
APECED/APS-1	No	Neutralizing antiinterleukin-17A, antiinterleukin-17F, and/or antiinterleukin-22 autoantibodies	*AIRE*, autosomal recessive
CARD9 deficiency	Dermatophytes, *Candida*, brain abscess	Deficit of interleukin-17–producing T cells	*CARD9*, autosomal recessive
CMCD			
Complete interleukin-17RA deficiency	*S. aureus*	No interleukin-17 response	*IL17RA*, autosomal recessive
Partial interleukin-17F deficiency	*S. aureus*	Impaired interleukin-17F, interleukin-17A/F function	*IL17F*, autosomal dominant
STAT1 GOF pathogenic variants	Bacteria, viruses, fungi, mycobacteria	Low interleukin-17–producing T cells	*STAT1*, autosomal dominant

CMC, Chronic mucocutaneous candidiasis; SCID, severe combined immunodeficiency; NK, natural killer; CID, combined immunodeficiency; NEMO, nuclear factor κβ essential modulator; iκBγ, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B cells, gamma; IκBα, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B cells, alpha; GOF, gain-of-function; DOCK8, dedicator of cytokinesis 8; TCR, T-cell receptor; CRACM1, calcium release-activated calcium modulator 1; MST1, macrophage stimulating 1; STK4, serine/threonine protein kinase 4; MHC, major histocompatibility complex; STAT, signal transducer and activator of transcription; HIES, hyperimmunoglobulin E syndrome; APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; APS-1, autoimmune polyendocrinopathy syndrome type 1; AIRE, autoimmune regulator; CARD9, caspase recruitment domain-containing protein 9; CMCD, chronic mucocutaneous candidiasis disease.

From Lanternier F, Cypowyj S, Picard, C, et al. Primary immunodeficiencies underlying fungal infections. *Curr Opin Pediatr.* 2013;25:736–747.

area. In some cases, the generalized process may represent a fungal id (hypersensitivity) reaction.

The differential diagnosis of candidal diaper dermatitis includes other eruptions of the diaper area that may coexist with candidal infection. For this reason, it is important to establish a diagnosis by means of KOH preparation or culture.

Treatment consists of applications of an imidazole cream 2 times daily. The combination of a corticosteroid and an antifungal agent may be justified if inflammation is severe but may confuse the situation if the diagnosis is not firmly established. Corticosteroids should not be continued for more than a few days. Protection of the diaper area by an application of thick zinc oxide paste overlying the anticandidal preparation may be helpful. The paste is more easily removed with mineral oil than with soap and water. Fungal id reactions gradually abate with successful treatment of the diaper dermatitis or may be treated with a mild corticosteroid preparation. When



Fig. 707.14 Erythematous confluent plaque caused by candidal infection.



Fig. 707.15 Intertriginous candidiasis of the neck.

recurrences of diaper candidiasis are frequent, it may be helpful to prescribe a course of oral anticandidal therapy to decrease the yeast population in the gastrointestinal tract. Some infants seem to be receptive hosts for *C. albicans* and may reacquire the organism from a colonized adult.

Intertriginous Candidiasis

Intertriginous candidiasis occurs most often in the axillae and groin, on the neck (Fig. 707.15), under the breasts, under pendulous abdominal fat folds, in the umbilicus, and in the gluteal cleft. Typical lesions are large, confluent areas of moist, denuded, erythematous skin with an irregular, macerated, scaly border. Satellite lesions are characteristic and consist of small vesicles or pustules on an erythematous base. With time, intertriginous candidal lesions may become lichenified, dry, scaly plaques. The lesions develop on skin subjected to irritation and maceration. Candidal superinfection is more likely to occur under conditions that lead to excessive perspiration, especially in obese children and in children with underlying disorders, such as diabetes mellitus. A similar condition, interdigital candidiasis, commonly occurs in individuals whose hands are constantly immersed in water. Fissures occur between the fingers and have red denuded centers, with an overhanging white epithelial fringe. Similar lesions between the toes may be secondary to occlusive footwear. Treatment is the same as for other candidal infections.

Perianal Candidiasis

Perianal dermatitis develops at sites of skin irritation as a result of occlusion, constant moisture, poor hygiene, anal fissures, and pruritus from pinworm infestation. It may become superinfected with *C. albicans,* especially in children who are receiving oral antibiotic or corticosteroid medication. The involved skin becomes erythematous, macerated, and excoriated, and the lesions are identical to those of candidal intertrigo or candidal diaper rash. Application of a topical antifungal agent in conjunction with improved hygiene is usually effective. Underlying disorders such as pinworm infection must also be treated (see Chapter 339).

Candidal Paronychia and Onychia

See Chapter 704.

Candidal Granuloma

Candidal granuloma is a rare response to an invasive candidal infection of skin. The lesions appear as crusted, verrucous plaques and hornlike projections on the scalp, face, and distal limbs. Affected patients may have single or numerous defects in immune mechanisms, and the granulomas are often refractory to topical therapy. A systemic anticandidal agent may be required for palliation or eradication of the infection.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 708

Cutaneous Viral Infections

Lamiaa Hamie and Stephen R. Humphrey

WART (VERRUCA)

Etiology

Human papillomaviruses (HPVs) cause a spectrum of diseases from warts (verrucae vulgaris) to squamous cell carcinoma of the skin and mucous membranes, including the larynx (see Chapter 438.2). The HPVs are classified by genus, species, and type. More than 200 types are known, and the entire genomes of approximately 100 are completely sequenced. The incidence of all types of warts is highest in children and adolescents. HPV is spread by direct contact and autoinoculation; transmission within families and by fomites also occurs. The clinical manifestations of infection develop 1 month or longer after inoculation and depend on the HPV type, the size of the inoculum, the immune status of the host, and the anatomic site.

Clinical Manifestations

Cutaneous warts develop in 5–10% of children. **Common warts** (verruca vulgaris), caused most commonly by HPV types 2 and 4, occur most frequently on the fingers, dorsum of the hands (Fig. 708.1), paronychial areas, face, knees, and elbows. They are well-circumscribed papules with an irregular, roughened, keratotic surface. When the surface is pared away, many black dots representing thrombosed dermal capillary loops are often visible. **Periungual warts** are often painful and may spread beneath the nail plate, separating it from the nail bed (Fig. 708.2). **Plantar warts (verruca plantaris)**, although similar to the common wart, are caused by HPV type 1 and are usually flush with the surface of the sole because of the constant pressure from weight bearing. When plantar warts become hyperkeratotic (Fig. 708.3), they may be painful. Similar lesions (palmar-verruca palmaris) can also occur on the palms. They are sharply demarcated, often with a ring of thick callus. The surface keratotic material must sometimes be removed before the boundaries of the wart can be appreciated. Several



Fig. 708.1 Verrucous papules on the back of the hand.



Fig. 708.2 Periungual wart with disruption of nail growth.



Fig. 708.3 Hyperkeratotic plantar wart.



Fig. 708.4 Multiple flat warts on the face with lesions in line of trauma.



Fig. 708.5 Condylomata acuminata in the perianal area of a toddler.

contiguous warts (HPV type 4) may fuse to form a large plaque, known as the *mosaic wart*. **Flat warts (verruca plana)**, caused by HPV types 3 and 10, are slightly elevated, minimally hyperkeratotic papules that usually remain <3 mm in diameter and vary in color from pink to brown. They may occur in profusion on the face, arms, dorsum of the hands, and knees. The distribution of several lesions along a line of cutaneous trauma (koebnerization) is a helpful diagnostic feature (Fig. 708.4). Lesions may be disseminated in the beard area and on the legs by shaving and from the hairline onto the scalp by combing the hair. **Epidermodysplasia verruciformis** (*EVER1, EVER2* genes), caused primarily by HPV types 5 and 8 (β-papillomaviruses, species 1), manifests as many diffuse verrucous papules. Wart types 9, 12, 14, 15, 17, 25, 36, 38, 47, and 50 may also be involved. Inheritance is thought to be primarily autosomal recessive, but an X-linked recessive form has also been postulated. Warts progress to **squamous cell carcinoma** in 10% of patients with epidermodysplasia verruciformis.

Genital HPV infection occurs in sexually active adolescents, most commonly as a result of infection with HPV types 6 and 11. **Condylomata acuminata** (mucous membrane warts) are moist, fleshy, papillomatous lesions that occur on the perianal mucosa (Fig. 708.5), labia, vaginal introitus, and perineal raphe and on the shaft, corona, and glans penis. Occasionally, they can obstruct the urethral meatus or the vaginal introitus. Because they are located in intertriginous areas, they may become moist and friable. When left untreated, condylomata proliferate and become confluent, at times forming large cauliflower-like masses. Lesions can also occur on the lips, gingivae, tongue, and conjunctivae. Genital warts in children may occur after inoculation during birth through an infected birth canal, as a consequence of sexual abuse, or from incidental spread from cutaneous warts. A significant proportion of genital warts in children contain HPV types that are usually isolated from cutaneous warts. HPV infection of the cervix is a major risk factor for the development of carcinoma, particularly if the infection is caused by HPV type 16, 18, 31, 33, 35, 39, 45, 52, 59, 67, 68, or 70. Immunization against types 6, 11, 16, 18, 31, 33, 45, 52, and 58 is available (see Chapter 438.2). Laryngeal (respiratory) papillomas contain the same HPV types as in anogenital papillomas. Transmission is believed to occur from mothers with a genital HPV infection to

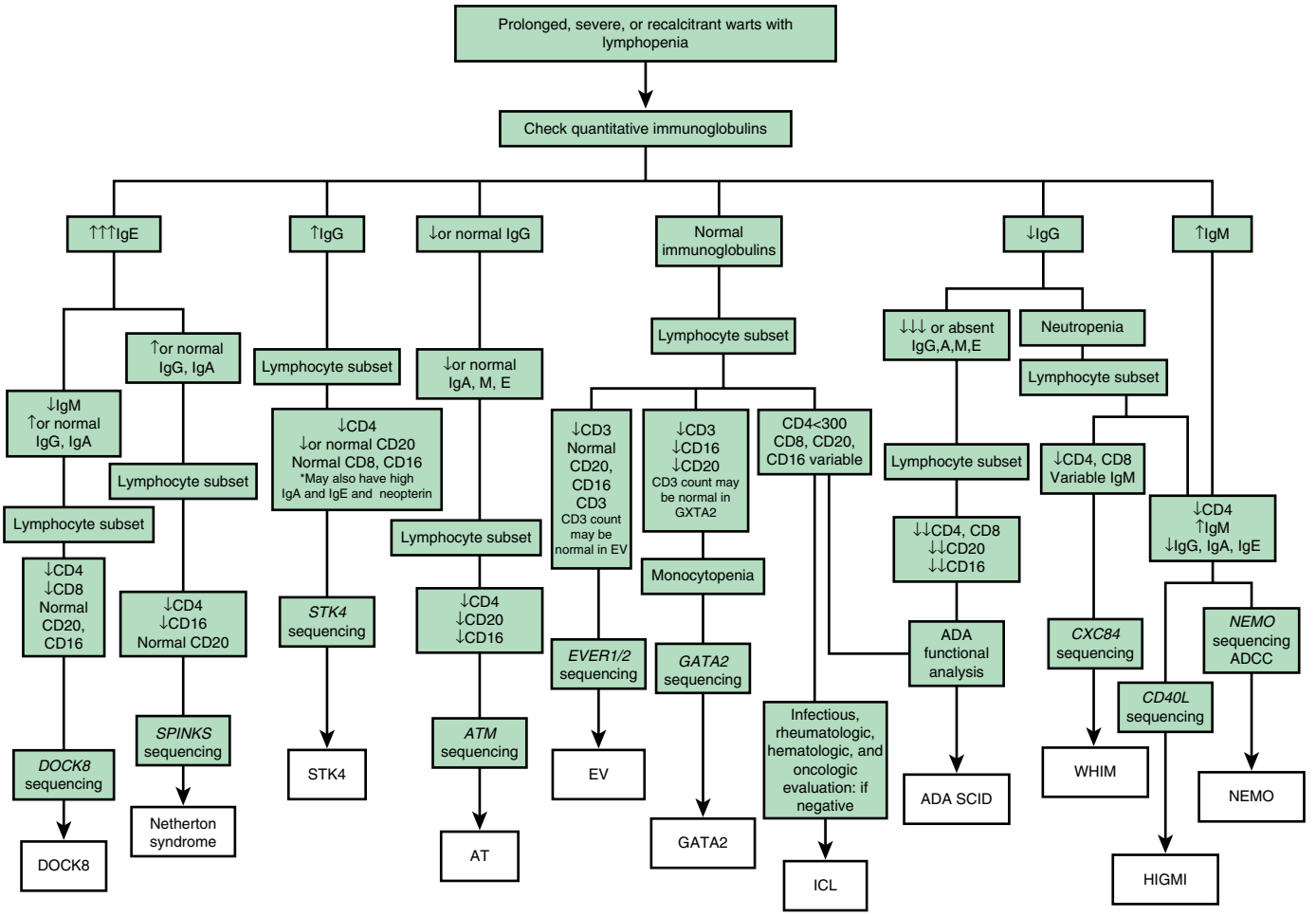

Fig. 708.6 Algorithm for diagnosis of primary immune deficiency with warts and lymphopenia. ADA SCID, adenosine deaminase severe combined immunodeficiency; AT, ataxia-telangiectasia; DOCK8, Dedicator of cytokinesis 8; EV, epidermodysplasia verruciformis; ICL, idiopathic CD4 lymphopenia; NEMO, nuclear factor κB essential modulator deficiency; STK4, serine/threonine kinase 4 deficiency; WHIM, warts, hypogammaglobulinemia, recurrent bacterial infections, and myelokathexis; XHIGM1, x-linked hyper IgM syndrome type 1/CD40L deficiency. *(From Lieding JW, Holland SM. Warts and all: HPV in primary immunodeficiencies. J Allergy Clin Immunol. 2012;130[5]:1030–1048, Fig. 3, p. 1043.)*

neonates who aspirate infectious virus during birth and may subsequently develop laryngeal papillomatosis.

Differential Diagnosis

Common warts are most often confused with molluscum contagiosum. Plantar and palmar warts may be difficult to distinguish from punctate keratoses, corns, and calluses. In contrast to calluses, warts obliterate normal skin markings. Juvenile flat warts mimic lichen planus, lichen nitidus, angiofibromas, syringomas, milia, and acne. Condylomata acuminata may resemble condylomata lata of secondary syphilis. Patients with recurrent, multiple, difficult-to-treat or disseminated warts may have a primary immune deficiency disorder (Fig. 708.6).

Treatment

Various therapeutic measures are effective in the treatment of warts. More than 65% of warts disappear spontaneously within 2 years. Warts are epidermal lesions and do not produce scarring unless subjected to surgical procedures or overly aggressive treatments. Hyperkeratotic lesions (common, plantar, and palmar warts) are more responsive to therapy if the excess keratotic debris is gently pared with a scalpel until thrombosed capillaries are apparent; further paring may induce bleeding. Treatment is most successful when performed regularly and frequently (every 2-4 weeks).

Common warts can be eradicated by applications of liquid nitrogen or by laser therapy, such as carbon dioxide or pulsed dye laser. Daily application of salicylic acid in flexible collodion or as a stick is a slow but painless method of removal that is effective in some patients. Plantar and palmar warts may be treated with 40% salicylic acid plasters. These should be applied for 5 days at a time with a 2-day rest period between applications. After removal of the plaster and prolonged soaking in hot water, keratotic debris can be removed with an emery board or pumice stone. Condylomata respond best to weekly applications of 25% podophyllin in tincture of benzoin. The medication should be left on the warts for 4-6 hours and then removed by bathing. Keratinized warts near the genitals (buttocks) do not respond to podophyllin. Imiquimod (5% cream) applied 3 times weekly is also beneficial. Imiquimod is not only indicated for genital warts but also has been used successfully to treat warts in other locations; however, it can cause inflammation and irritation, particularly in occluded areas. For nongenital warts, imiquimod should be applied daily. Cimetidine 30-40 mg/kg/day by mouth has been used in children with multiple warts unresponsive to other treatment, though its efficacy remains unclear. Immunotherapy with intralesional candida, MMR (measles, mumps, and rubella)



Fig. 708.7 Grouped molluscum.



Fig. 708.8 Molluscum with surrounding dermatitis.

vaccine or *Trichophyton* antigen may also be employed, especially when lesions are numerous or resistant to other therapies. Immunotherapy is performed in clinic, and multiple treatments at 1-month intervals (at least three to four) are usually required. With all types of therapy, care should be taken to protect the surrounding normal skin from irritation. Other treatments include 5-fluorouracil, a chemotherapy agent, which can be helpful, particularly when used with occlusion and sometimes in combination with salicylic acid. Topical cidofovir, an antiviral agent, and intralesional bleomycin, have also been used in refractory cases.

MOLLUSCUM CONTAGIOSUM

Etiology

The poxvirus that causes molluscum contagiosum is a large double-stranded DNA virus that replicates in the cytoplasm of host epithelial cells. Type 1 virus causes most infections. The disease is acquired by direct contact with an infected person or from fomites and is spread by autoinoculation. Children age 2-6 years who are otherwise well and individuals who are immunosuppressed are most commonly affected. The incubation period is estimated to be 2 weeks or longer.

Clinical Manifestations

Discrete, pearly, skin-colored, smooth, dome-shaped papules vary in size from 1 to 5 mm. They typically have a central umbilication from which a plug of cheesy material can be expressed. Although these papules can emerge anywhere on the body, they have a predilection for sites such as the face, eyelids, neck, axillae, and thighs (Fig. 708.7). They may be found in clusters on the genitals or in the groin of adolescents and may be associated with other venereal diseases in sexually active individuals. Lesions commonly involve the genital area in children but are not acquired by sexual transmission in most cases. Mild surrounding erythema or an eczematous dermatitis may accompany the papules (Fig. 708.8). Lesions on patients with AIDS tend to be large and numerous, particularly on the face. Exuberant lesions may also be found in children with leukemia and other immunodeficiencies. Children with atopic dermatitis are susceptible to widespread involvement in areas of dermatitis. A pustular eruption can develop at the site of individual molluscum lesions (Fig. 708.9). It is not a secondary bacterial infection, but rather an immunologic reaction to the molluscum virus; hence treatment with antibiotics is unnecessary. Atrophic scars may often follow this type of reaction.

Differential Diagnosis

The differential diagnosis of molluscum contagiosum includes trichoepithelioma, basal cell carcinoma, ectopic sebaceous glands, syringoma, hidrocystoma, keratoacanthoma, juvenile xanthogranulomas, and warty dyskeratoma. In individuals with AIDS, cryptococcosis may be indistinguishable clinically from molluscum contagiosum. Rarely, coccidioidomycosis, histoplasmosis, or *Penicillium marneffei* infection masquerades as molluscum-like lesions in an immunocompromised host.



Fig. 708.9 Inflamed molluscum. Crusted papule at the site of a previous molluscum.

Treatment

Molluscum contagiosum is a self-limited disease, with an average duration of 6-9 months. However, lesions can persist for years, spreading to distant sites and potentially transmitting to others. Affected patients should be advised to avoid shared baths and towels until the infection is clear. In cases of atopic dermatitis or immunodeficiency, infection may rapidly spread, leading to the development of hundreds of lesions in children. *Immunotherapy with either* Candida *or* Trichophyton *antigen is the most commonly used treatment*. This is repeated every 4 weeks until resolution. If lesions are limited in number, then depending on the age of the patient, individual lesions can be treated with liquid nitrogen cryotherapy. For younger children, cantharidin may be applied to the lesions and covered with adhesive bandages to prevent unwanted spread of the blistering agent. A blister forms at the application site, facilitating the removal of the molluscum. However, it's important to note that cantharidin should not be applied to the face. Cantharidin availability is either very limited or completely unavailable in the United States. Imiquimod has not been proven more effective than placebo in randomized trials. Considering that molluscum is an epidermal disease, caution should be exercised to avoid excessive treatment that may result in scarring.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 709

Arthropod Bites and Infestations

709.1 Arthropod Bites

Lamiaa Hamie and Stephen R. Humphrey

Arthropod bites are a common affliction of children and occasionally pose a problem in diagnosis. A patient may be unaware of the source of the lesions or may deny being bitten, making interpretation of the eruption difficult. In these cases, knowledge of the habits, life cycle, and clinical signs of the more common arthropod pests of humans may help lead to a correct diagnosis (Table 709.1).

CLINICAL MANIFESTATIONS

The type of reaction that occurs after an arthropod bite depends on the insect species and the age-group and reactivity of the human host. Arthropods may cause injury to a host by various mechanisms, including mechanical trauma, such as the lacerating bite of a tsetse fly; invasion of host tissues, as in myiasis; contact dermatitis, as seen with repeated exposure to cockroach antigens; granulomatous reaction to retained mouthparts; transmission of systemic disease; injection of irritant cytotoxic or pharmacologically active substances, such as hyaluronidase, proteases, peptidases, and phospholipases in sting venom; and induction of anaphylaxis. Most reactions to arthropod bites depend on antibody formation to antigenic substances in saliva or venom. The type of reaction is determined primarily by the degree of previous exposure to the same or a related species of arthropod. When someone is bitten for the first time, no reaction develops. An immediate petechial reaction is occasionally seen. After repeated bites, sensitivity develops, producing a pruritic papule (Fig. 709.1) approximately 24 hours after the bite. This is the most common reaction seen in young children. With prolonged, repeated exposure, a wheal develops within minutes after a bite, followed 24 hours later by papule, vesicle, or bullae formation. By adolescence or adulthood, only a wheal may form, unaccompanied by the delayed papular reaction. Thus adults in the same household as affected children may be unaffected. Ultimately, as a person becomes insensitive to the bite, no reaction occurs at all. This stage of nonreactivity is maintained only as long as the individual continues to be bitten regularly. Individuals in whom papular urticaria develops are in the transitional phase between development of a primarily delayed papular reaction and development of an immediate urticarial reaction.

Arthropod bites may occur as solitary, numerous, or profuse lesions, depending on the feeding habits of the perpetrator. Fleas tend to sample their host several times within a small localized area, whereas mosquitoes tend to attack a host at more randomly scattered sites. Delayed



Fig. 709.1 Pruritic papules after bed bug bites.

Table 709.1 Bed Bugs Versus Other Arthropod Bites: Main Clinical and Epidemiologic Features*

ARTHROPOD	CLINICAL FEATURES ON EXAMINATION	LOCATION	TIMING OF PRURITUS	CONTEXT
Bed bugs	3-4 bites in a line or curve	Uncovered areas	Morning	Traveling
Fleas	3-4 bites in a line or curve	Legs and buttocks	Daytime	Pet owners or rural living
Mosquitoes	Nonspecific urticarial papules	Potentially anywhere	*Anopheles* spp. night; *Culex* spp. night; *Aedes* spp. day	Worldwide distribution
Head lice	Live lice on the head associated with itchy, scratched lesions	Scalp, ears, and neck	Any	Children, parents, or contact with children
Body lice	Excoriated papules and hyperpigmentation; live lice inside clothes	Back	Any	Unhoused people
Sarcoptes scabiei mites (scabies)	Vesicles, burrows, nodules, and nonspecific secondary lesions	Interdigital spaces, forearms, breasts, genitals	Night	Sexually transmitted, households or institutions
Ticks	Erythema migrans or ulcer	Potentially anywhere	Asymptomatic	Pet owners or hikers
Pyemotes ventricosus	Comet sign, a linear, erythematous, macular tract	Under clothes	Any time when inside habitat	People exposed to woodworm-contaminated furniture (*Pediculoides ventricosus* is a woodworm parasite)
Spiders	Necrosis (uncommon)	Face and arms	Immediate pain, no itching	Rural living

*It is difficult to diagnose a bite. Diagnosis relies on an array of arguments, none of which is specific by itself; it is the association of elements that is suggestive. Any arthropod bite can be totally asymptomatic.

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O. Bed bug infestation [published correction appears in *BMJ*. 2013;346:F1044]. *BMJ*. 2013;346:f138.



Fig. 709.2 Red-brown papules in papular urticaria.

hypersensitivity reactions to insect bites—the predominant lesions in the young and uninitiated—are characterized by firm, persistent papules that may become hyperpigmented and are often excoriated and crusted. Pruritus may be mild or severe, transient or persistent. A central punctum is usually visible but may disappear as the lesion ages or is scratched. The immediate hypersensitivity reaction is characterized by an evanescent, erythematous wheal. If edema is marked, a tiny vesicle may surmount the wheal. Certain beetles produce bullous lesions through the action of cantharidin, and various insects, including beetles and spiders, may cause hemorrhagic nodules and ulcers. Bites on the lower extremities are more likely to be severe or persistent or become bullous than those located elsewhere. Complications of arthropod bites include development of impetigo, folliculitis, cellulitis, lymphangitis, and severe anaphylactic hypersensitivity reactions, particularly after the bite of certain hymenopterans. The histopathologic changes are variable, depending on the arthropod, the age of the lesion, and the reactivity of the host. Acute urticarial lesions tend to show central vesiculation in which eosinophils are numerous. Papules most commonly show dermal edema and a mixed superficial and deep perivascular inflammatory infiltrate, often including a number of eosinophils. At times, however, the dermal cellular infiltrate is so dense that a lymphoma is suspected. Many young children demonstrate extensive dermal but nonerythematous, nontender edema in response to mosquito bites **(Skeeter syndrome)**, which responds to oral antihistamines; this must be distinguished from cellulitis, which tends to be painful, tender, and red. Retained mouthparts may stimulate a foreign body type of granulomatous reaction.

Papular urticaria occurs principally in the first decade of life. It may occur at any time of the year. The most common culprits are species of fleas, mites, bed bugs, gnats, mosquitoes, chiggers, and animal lice. Individuals with papular urticaria have predominantly transitional lesions in various stages of evolution between delayed-onset papules and immediate-onset wheals. The most characteristic lesion is an edematous, red-brown papule (Fig. 709.2). An individual lesion frequently starts as a wheal that, in turn, is replaced by a papule. A given bite may incite an id reaction at distant sites of quiescent bites in the form of erythematous macules, papules, or urticarial plaques. After a season or two, the reaction progresses from a transitional to a primarily immediate hypersensitivity urticarial reaction.

One of the most commonly encountered arthropod bites is that resulting from human, cat, or dog fleas (family Pulicidae). Eggs, which are generally laid in dusty areas and cracks between floorboards, give rise to larvae that then form cocoons. The cocoon stage can persist for up to 1 year, and the flea emerges in response to vibrations from footsteps, accounting for the assaults that frequently befall the new owners of a recently reopened dwelling. Adult dog fleas can live without a blood meal for approximately 60 days. Attacks from fleas are more likely to occur when the fleas do not have access to their usual host; cat or dog fleas are more voracious and problematic when one visits an area frequented by the pet than when the pet is encountered directly. Flea bites tend to be grouped in lines or irregular clusters on the lower extremities. Fleas are often not seen on the body of a pet. Diagnosis of flea bites is aided by examination of debris from the animal's bedding material. The debris is collected by shaking the bedding into a plastic bag and examining the contents for fleas or their eggs, larvae, or feces.

Table 709.2 Patient Education to Eliminate Bed Bugs

DETECTION
• Look for brown insects no bigger than apple seeds on the mattress, sofa, and curtains and in darker places in the room (especially cracks in the walls, crevices in box springs, and furniture)
• Look for black spots on the mattress or blood traces on the sheets
ELIMINATION
• Contact a pest management company
• Wash clothes at 60°C (140°F) or freeze delicate clothing, vacuum, and clean your home before the pest manager visits
• Collaborate with professionals who are used to dealing with bed bug infestation to increase eradication efficacy
PREVENTION
• Carefully examine secondhand furniture to assure the absence of bed bugs before purchase so as not to contaminate your home
• When sleeping in a hotel, even an upmarket establishment, lift mattresses to look for bed bugs or black spots
• Do not leave luggage in dark places, near furniture, or close to your bed. Before going to bed, close suitcases and put them in the bathroom—in the bathtub or shower stall

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O. Bed bug infestation [published correction appears in *BMJ*. 2013;346:F1044]. *BMJ*. 2013;346:f138.

TREATMENT

Treatment is directed at alleviation of pruritus by oral antihistamines and cool compresses. Potent topical corticosteroids are helpful. Topical antihistamines are potent immunologic sensitizers and have no role in the treatment of insect bite reactions. A short course of systemic steroids may be helpful if many severe reactions occur, particularly around the eyes. Insect repellents containing *N,N*-diethyl-3-methylbenzamide (DEET) may afford moderate protection against mosquitoes, fleas, flies, chiggers, and ticks, but are relatively ineffective against wasps, bees, and hornets. DEET must be applied to exposed skin and clothing to be effective. The most effective protection against mosquitoes, the human body louse, and other blood-feeding arthropods is the use of DEET and permethrin-impregnated clothing. However, these measures are not effective against the phlebotomine sand fly, which transmits leishmaniasis. Because of the potential for toxicity, the lowest effective DEET dose should be selected. Additional insect repellents include picaridin (flies, mosquitoes, chiggers, ticks), IR3535 (mosquitoes), oil of lemon, eucalyptus (mosquitoes), and citronella (mosquitoes). Table 709.2 lists methods to eliminate bed bugs.

An effort should be made to identify and eradicate the etiologic agent. Pets should be carefully inspected. Crawl spaces, eaves, and other sites of the house or outbuildings frequented by animals and birds should be decontaminated, and baseboard crevices, mattresses, rugs, furniture, and animal sleeping quarters should be decontaminated. Agents that are effective for ridding the home of fleas include lindane, pyrethroids, and organic thiocyanates. Flea-infested pets may be treated with powders containing rotenone, pyrethroids, malathion, or methoxychlor. Lufenuron, an agent that prevents fleas from reproducing, is effective for animals in oral and injectable formulations. Fipronil is effective as a topical agent for the prevention of flea infestation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

709.2 Scabies

Lamiaa Hamie and Stephen R. Humphrey

Scabies is caused by burrowing and release of toxic or antigenic substances by the female mite *Sarcoptes scabiei* var. *hominis*. The most

Table 709.3 Different Presenting Forms of Scabies

PRESENTING FORMS OF SCABIES	SPECIFIC HIGH-RISK POPULATIONS	CLINICAL MANIFESTATIONS	LIMITED DIFFERENTIAL DIAGNOSES
Classic scabies (scabies vulgaris)	Infants and children; sexually active adults; men who have sex with men	Intense generalized pruritus, worse at night; inflammatory pruritic papules localized to finger webs, flexor aspects of wrists, elbows, axillae, buttocks, genitalia, female breasts; lesions and pruritus spare the face, head, and neck; secondary lesions include eczematization, excoriation, impetigo	Dermatitis herpetiformis, drug reactions, eczema, pediculosis corporis, lichen planus, pityriasis rosea
Scalp scabies	Infants and children; institutionalized older adults; AIDS patients; patients with preexisting crusted scabies	Atypical crusted papular lesions of the scalp, face, palms, and soles	Dermatomyositis, ringworm, seborrheic dermatitis
Crusted scabies (Norwegian scabies, scabies norvegica, scabies crustosa)	Institutionalized older adults; institutionalized developmentally disabled (Down syndrome); unhoused persons, especially HIV-positive; all immunocompromised patients, particularly those with AIDS or positive for HIV or HTLV-1; transplant recipients; patients on prolonged systemic corticosteroids and chemotherapy	Psoriasiform hyperkeratotic papular lesions of the scalp, face, neck, hands, feet, with extensive nail involvement; eczematization and impetigo common	Contact dermatitis, drug reactions, eczema, erythroderma, ichthyosis, psoriasis
Nodular scabies	Sexually active adults; men who have sex with men; HIV-positive men > HIV-positive women	Violaceous pruritic nodules localized to male genitalia, groin, axillae, representing hypersensitivity reaction to mite antigens	Acropustulosis, atopic dermatitis, Darier disease, lupus erythematosus, lymphomatoid papulosis, papular urticaria, necrotizing vasculitis, secondary syphilis

HTLV-1, Human T-cell lymphotropic virus type 1.
From Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 8th ed. Philadelphia: Saunders; 2015: Table 295.1, p. 3252.

important factor that determines spread of scabies is the extent and duration of physical contact with an affected individual. Children and sexual partners of affected individuals are most at risk. Scabies is transmitted only rarely by fomites because the isolated mite dies within 2-3 days.

ETIOLOGY AND PATHOGENESIS

An adult female mite measures approximately 0.4 mm in length; has four sets of legs; and has a hemispheric body marked by transverse corrugations, brown spines, and bristles on the dorsal surface. A male mite is approximately half her size and is similar in configuration. After impregnation on the skin surface, a gravid female exudes a keratolytic substance and burrows into the stratum corneum, often forming a shallow well within 30 minutes. She gradually extends this tract by 0.5-5.0 mm/24 hours along the boundary with the stratum granulosum. She deposits 10-25 oval eggs and numerous brown fecal pellets (scybala) daily. When egg laying is completed, in 4-5 weeks, she dies within the burrow. The eggs hatch in 3-5 days, releasing larvae that move to the skin surface to molt into nymphs. Maturity is achieved in approximately 2-3 weeks. Mating occurs, and the gravid female invades the skin to complete the life cycle.

CLINICAL MANIFESTATIONS

In an immunocompetent host, scabies is frequently heralded by intense pruritus, particularly at night (Table 709.3). The first sign of the infestation often consists of 1- to 2-mm red papules, some of which are excoriated, crusted, or scaling. Threadlike burrows are the classic lesion of scabies (Figs. 709.3 and 709.4) but may not be seen in infants. In infants, bullae and pustules are relatively common. The eruption may also include wheals, papules, vesicles, and a superimposed eczematous dermatitis (Fig. 709.5). The palms, soles, and scalp are often affected. In older



Fig. 709.3 Classic scabies burrow.

children and adolescents, the clinical pattern is similar to that in adults, in whom preferred sites are the interdigital spaces; wrist flexors; anterior axillary folds; ankles, buttocks, umbilicus and belt line; groin; genitals in men; and areolas in women. The head, neck, palms, and soles are generally spared. Infants will often have a diffuse eczematous eruption that will involve the scalp, neck, and face. Red-brown nodules, most often located in covered areas such as the axillae, groin, and genitals, predominate in the less common variant called *nodular scabies.* Additional clues include facial sparing, affected family members, poor response to topical antibiotics, and transient response to topical steroids. Untreated, scabies may lead to eczematous dermatitis, impetigo, ecthyma, folliculitis, furunculosis,

cellulitis, lymphangitis, and id reaction. Glomerulonephritis has developed in children from streptococcal impetiginization of scabies lesions. In some tropical areas, scabies is the predominant underlying cause of pyoderma. A latent period of approximately 1 month follows an initial infestation. Thus itching may be absent and lesions may be relatively inapparent in contacts who are asymptomatic carriers. However, on reinfestation, reactions to mite antigens are noted within hours.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of scabies can often be made clinically but is confirmed by microscopic identification of mites (Fig. 709.6A), ova, and scybala (see Fig. 709.6B) in epithelial debris. Scrapings most often test positive when obtained from burrows or fresh papules. A reliable method is application of a drop of mineral oil on the selected lesion, scraping of it with a No. 15 blade, and transferring the oil and scrapings to a glass slide.

The differential diagnosis depends on the types of lesions present. **Burrows** are virtually pathognomonic for human scabies. **Papulovesicular lesions** are confused with papular urticaria, canine scabies, chickenpox, viral exanthems, drug eruptions, dermatitis herpetiformis, and folliculitis. **Eczematous lesions** may mimic atopic dermatitis and seborrheic dermatitis, and the less common bullous disorders of childhood may be suspected in infants with predominantly bullous lesions. **Nodular scabies** is frequently misdiagnosed as urticaria pigmentosa and Langerhans cell histiocytosis. The histopathologic appearance of nodular scabies, consisting of a deep, dense, perivascular infiltrate of lymphocytes, histiocytes, plasma cells, and atypical mononuclear cells, may mimic malignant lymphoid neoplasms.

TREATMENT

The treatment of choice for scabies is permethrin 5% cream (Elimite) applied to the entire body from the neck down, with particular attention to intensely involved areas, which is also standard therapy (Table 709.4). Scabies is frequently found above the neck in infants (younger than 2



Fig. 709.4 Scabies. Felt-tipped ink pen has penetrated and highlighted a burrow. The ink is retained after the surface is wiped clean with an alcohol swab. *(From Habif TP, ed. Clinical Dermatology, 6th ed. Philadelphia: Mosby; 2016: Fig 15-16.)*



Fig. 709.6 A, Human scabies mite obtained from scraping. B, Scabies ova and scybala.



Fig. 709.5 A, Diffuse scabies on an infant. The face is clear. The lesions are most numerous around the axillae, chest, and abdomen. B, Scabies. Infestation of the palms and soles is common in infants. The vesicular lesions have all ruptured. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004: Figs. 15.8 and 15.9.)*

Table 709.4 Currently Recommended Treatment for Scabies

SCABICIDES	FDA APPROVED?	PREGNANCY CATEGORY*	DOSING SCHEDULE	SAFETY PROFILE	CONTRAINDICATIONS
5% Permethrin cream (Actin, Nix, Elimite)	Yes	B	Apply from neck down; wash off after 8-14 hr; good residual activity, but second application recommended after 1 wk	Excellent; itching and stinging on application	Prior allergic reactions; infants <2 mo of age; breastfeeding
1% Lindane lotion or cream	Yes	B	Apply 30-60 mL from neck down; wash off after 8-12 hr; no residual activity; increasing drug resistance	Potential for central nervous system toxicity from organochloride poisoning, usually manifesting as seizures, with overapplication and ingestions	Preexisting seizure disorder; infants and children <6 mo of age; pregnancy; breastfeeding
10% Crotamiton cream or lotion (Eurax)	Yes	C	Apply from neck down on 2 consecutive nights; wash off 24 hr after second application	Excellent; not very effective; exacerbates pruritus	None
2–10% Sulfur in petrolatum ointments	No	C	Apply for 2-3 days, then wash	Excellent; not very effective	Preexisting sulfur allergy
10–25% Benzoyl benzoate lotion	No	None	Two applications for 24 hr with 1-day to 1-wk interval	Irritant; exacerbates pruritus; can induce contact irritant dermatitis and pruritic cutaneous xerosis	Preexisting eczema
0.5% Malathion lotion (Ovide), 1% malathion shampoo (unavailable in the United States)	No	B	95% ovicidal; rapid (5 min) killing; good residual activity; increasing drug resistance	Flammable 78% isopropyl alcohol vehicle stings eyes, skin, mucosa; increasing drug resistance; organophosphate poisoning risk with overapplication and ingestions	Infants and children <6 mo of age; pregnancy; breastfeeding
Ivermectin (Stromectol)	Yes	C	200-μg/kg single PO dose, may be repeated in 14-15 days; not ovicidal, second dose on day 14 or 15 highly recommended; recommended for endemic or epidemic scabies in institutions and refugee camps	Excellent; may cause nausea and vomiting; take on empty stomach with water	Safety in pregnancy uncertain; probably safe during breastfeeding; not recommended for children younger than 5 yr of age or weighing <15 kg

*U.S. Food and Drug Administration safety in pregnancy categories: A, safety established; B, presumed safe; C, uncertain safety; D, unsafe; X, highly unsafe.
From Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 295.2, p. 3253.

years old), necessitating treatment of the scalp. The medication is left on the skin for 8-12 hours and should be reapplied in 1 week for another 8- to 12-hour period. Additional therapies include sulfur ointment 5–10%, and crotamiton 10% lotion or cream. Lindane 1% lotion or cream should only be used as an alternative therapy, given the risk of systemic toxicity. For severe infestations or in immunocompromised patients, ivermectin 200 μg/kg per dose given orally for two doses 2 weeks apart can be used (off-label use). Single-dose ivermectin (200 μg/kg) has also been effective in immunocompetent patients, with improvement (cure) noted in 60% at 2 weeks and 89% at 4 weeks after treatment (see Table 709.4).

Transmission of mites is unlikely more than 24 hours after treatment. Pruritus, which is a result of hypersensitivity to mite antigens, may persist for a number of days to weeks, and may be alleviated by a topical corticosteroid preparation. If pruritus persists for >2 weeks after treatment and new lesions are occurring, the patient should be reexamined for mites. Nodules are extremely resistant to treatment and may take several months to resolve. The entire family should be treated, as should caretakers of the infested child. Clothing, bed linens, and towels should be washed in hot water and dried using high heat. Clothing or other items (e.g., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 week, as the mite will die when separated from the human host.

CRUSTED SCABIES

The Norwegian variant of human scabies is highly contagious and occurs mainly in individuals who are cognitively and physically debilitated, particularly those who are institutionalized and those with Down syndrome; in patients with poor cutaneous sensation (leprosy, spina bifida); in patients who have severe systemic illness (leukemia, diabetes); and in immunosuppressed patients (HIV infection). Affected individuals are infested by a myriad of mites that inhabit the crusts and exfoliating scales of the skin and scalp (Fig. 709.7). The nails may become thickened and dystrophic. The subungual debris is densely populated by mites. The infestation is often accompanied by generalized lymphadenopathy and eosinophilia. There is massive orthokeratosis and parakeratosis with numerous interspersed mites, psoriasiform epidermal hyperplasia, foci of spongiosis, and neutrophilic abscesses. Norwegian scabies is thought to represent a deficient host immune response to the organism. Management is difficult, requiring scrupulous isolation measures, removal of the thick scales, and repeated but careful applications of permethrin 5% cream. Ivermectin (200-250 μg/kg) has been used successfully as single-dose therapy in refractory cases, particularly in HIV-infected patients. A second dose may be needed a week later. The U.S. Food and Drug Administration has not approved this agent for the treatment of scabies.



Fig. 709.7 Norwegian scabies. A and B, Right side of the head and neck and right leg before treatment showing diffuse, scaly hyperkeratotic rash, crusts, and fissures with areas of skin erythema *(arrow)* caused by hyperinfestation after infection with *Sarcoptes scabiei* in a patient with Down syndrome. *(Modified from Lee K, Heresi G, Hammond RA. Norwegian scabies in a patient with Down syndrome. J Pediatr. 2019;209:253.)*

CANINE SCABIES

Canine scabies is caused by *S. scabiei* var. *canis,* the dog mite that is associated with mange. The eruption in humans, which is most frequently acquired by cuddling an infested puppy, consists of tiny papules, vesicles, wheals, and excoriated eczematous plaques. Burrows are not present because the mite infrequently inhabits human stratum corneum. The rash is pruritic and has a predilection for the arms, chest, and abdomen, the usual sites of contact with dogs. Onset is sudden and usually follows exposure by 1-10 days, possibly resulting from development of a hypersensitivity reaction to mite antigens. Recovery of mites or ova from scrapings of human skin is rare. The disease is self-limited because humans are not a suitable host. Bathing and changing clothes are generally sufficient. Removal or treatment of the infested animal is necessary. Symptomatic therapy for itching is helpful. In rare cases in which mites are demonstrated in scrapings from an affected child, they can be eradicated by the same measures applicable to human scabies.

OTHER TYPES OF SCABIES

Other mites that occasionally bite humans include the chigger or harvest mite *(Eutrombicula alfreddugesi),* which prefers to live on grass, shrubs, vines, and stems of grain. Larvae have hooked mouthparts, which allow the chigger to attach to the skin, but not to burrow, to obtain a blood meal, most commonly on the lower legs. Avian mites may affect those who come into close contact with chickens or pet gerbils. Humans may occasionally be assaulted by avian mites that have infested a nest outside a window, an attic, heating vents, or an air conditioner. The dermatitis is variable, including grouped papules, wheals, and vesicular lesions on the wrists, neck, breasts, umbilicus, and anterior axillary folds. A prolonged investigation is often undertaken before the cause and source of the dermatitis are discovered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

709.3 Pediculosis

Lamiaa Hamie and Stephen R. Humphrey

Three types of lice are obligate parasites of the human host: body or clothing lice *(Pediculus humanus corporis),* head lice *(Pediculus humanus capitis),* and pubic or crab lice *(Phthirus pubis).* Only the body louse serves as a vector of human disease (typhus, trench fever, relapsing fever). Body and head lice have similar physical characteristics. They are approximately 2-4 mm in length. Pubic lice are only 1-2 mm in length and are greater in width than in length, giving them a crablike appearance. Female lice live for approximately 1 month and deposit 3-10 eggs daily on the human host. However, body lice generally lay eggs in or near the seams of clothing. The ova or nits are glued to hairs or fibers of clothing but not directly on the body. Ova hatch in 1-2 weeks and require another week to mature. Once the eggs hatch, the nits remain attached to the hair as empty sacs of chitin. Freshly hatched larvae die unless a meal is obtained within 24 hours and every few days thereafter. Both nymphs and adult lice feed on human blood, injecting their salivary juices into the host and depositing their fecal matter on the skin. Symptoms of infestation do not appear immediately but develop as an individual becomes sensitized. The hallmark of all types of pediculosis is pruritus.

Pediculosis corporis is rare in children except under conditions of poor hygiene, especially in colder climates when the opportunity to change clothes on a regular basis is lacking. The parasite is transmitted mainly on contaminated clothing or bedding. The primary lesion is a small, intensely pruritic, red macule or papule with a central hemorrhagic punctum, located on the shoulders, trunk, or buttocks. Additional lesions include excoriations, wheals, and eczematous, secondarily infected plaques. Massive infestation may be associated with constitutional symptoms of fever, malaise, and headache. Chronic infestation may lead to "vagabond's skin," which manifests as lichenified, scaling, hyperpigmented plaques, most commonly on the trunk. Lice are found on the skin only transiently when they are feeding. At other times, they inhabit the seams of clothing. Nits are attached firmly to fibers in the cloth and may remain viable for up to 1 month. Nits hatch when they encounter warmth from the host's body when the clothes are worn again. Therapy consists of improved hygiene and hot water laundering of all infested clothing and bedding. A uniform temperature of 65°C (149°F), wet or dry, for 15-30 minutes kills all eggs and lice. Alternatively, eggs hatch and nymphs starve if clothing is stored for 2 weeks at 23.9–29.4°C (75–85°F).

Pediculosis capitis is an intensely pruritic infestation of lice in the scalp hair. It is the most common form of lice to affect children, in particular those between the ages of 3 and 12 years. Fomites and head-to-head contact are important modes of transmission. In summer months in many areas of the United States and in the tropics at all times of the year, shared combs, brushes, or towels have a more important role in louse transmission. Translucent 0.5-mm eggs are laid near the proximal portion of the hair shaft and become adherent to one side of the shaft (Fig. 709.8). A nit cannot be moved along or knocked off the hair shaft with the fingers. Secondary pyoderma, after trauma from scratching, may result in matting together of the hair and cervical and occipital lymphadenopathy. Hair loss does not result from pediculosis but may accompany the secondary pyoderma. Head lice are a major cause of numerous pyodermas of the scalp, particularly in tropical environments. Lice are not always visible, but nits are detectable on the hairs, most commonly in the occipital region and above the ears, rarely on beard or pubic hair. Dermatitis may also be noted on the neck and pinnae. An **id reaction**, consisting of erythematous patches and plaques, may develop, particularly on the trunk.

In cases of resistance (which is common) of head lice to pyrethroids, malathion 0.5% in isopropanol is the treatment of choice and should be applied to dry hair until hair and scalp are wet and left on for 12 hours. A second application 7-9 days after the initial treatment may be necessary. This product is flammable, so care should be taken to avoid open flames. Malathion, like lindane shampoo, is not indicated for use in neonates and infants; however, additional approved therapies include spinosad (if >6 months), benzyl alcohol lotion (if >6 months), and ivermectin for difficult-to-treat head lice (Table 709.5). All household members should be treated at the same time. Nits can be removed

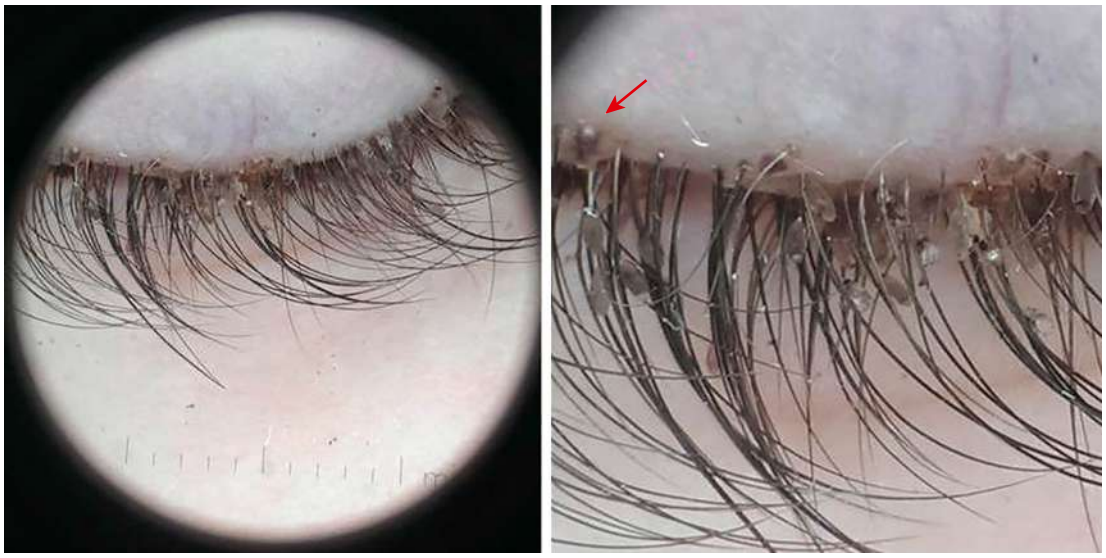

Fig. 709.8 Phthiriasis palpebrarum. Dermoscopy examination of eyelashes in a 27-mo-old boy, showing nits and parasites *(arrow)*. *(From Ouedraogo M, Ventejou S, Leducq S, et al. Crusts on the eyelashes. J Pediatr. 2019;209:254.)*

Table 709.5 Drugs for Head Lice

DRUG	RESISTANCE	FDA-APPROVED LOWER AGE OR WEIGHT LIMIT	DOSAGE AND ADMINISTRATION	COST*/SIZE
Ivermectin 0.5% lotion—Sklice (Arbor)	No	6 mo	Apply to dry hair and scalp for 10 min, then rinse†	$297.60/4 oz
Ivermectin tablets‡—Stromectol (MSD)	No	15 kg§	200-400 µg/kg PO once; repeat 7-10 days later	$9.30#
Spinosad 0.9% suspension—Natroba (ParaPro)	No	6 mo	Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary¶	$246.10/4 oz
Benzyl alcohol 5% lotion—Ulesfia (Lachlan)	No	6 mo	Apply to dry hair for 10 min, then rinse; repeat 7 days later**	$181.30/8 oz
Pyrethrins with piperonyl butoxide shampoo‡—Generic Rid (Bayer)	Yes	2 yr	Apply to dry hair for 10 min, then shampoo; repeat 7-10 days later	$15.00/8 oz‡‡ $20.00/8 oz‡‡
Permethrin 1% creme rinse‡—Generic Nix (Insight)	Yes	2 mo	Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later	$18.00/4 oz‡‡ $21.00/4 oz‡‡
Malathion 0.5% lotion—Generic Ovide (Taro)	Not in the United States	6 yr§§	Apply to dry hair for 8-12 hr, then shampoo; repeat 7-9 days later if necessary##,¶¶	$221.70/2 oz $246.40/2 oz
Abametapir lotion 0.74% (Xeglyze)	No	6 mo	Apply to dry hair for 10 min on day 0 and then rinse with water	Not available yet

*Approximate WAC for the indicated size. WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource Monthly. November 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. Copyright 2016. www.fdbhealth.com/policies/drug-pricing-policy. Total cost of treatment may vary based on hair length and number of applications required to completely eradicate lice.

†The manufacturer recommends using up to one single-use, 4-oz tube of topical ivermectin lotion per application.

‡Not FDA approved for treatment of head lice.

§The safety and effectiveness of oral ivermectin have not been established in children weighing <15 kg.

#Cost of two 3-mg tablets (one dose for a 30-kg child at the lowest dosage).

¶The manufacturer recommends using up to one 4-oz (120-mL) bottle of spinosad 0.9% suspension per application.

**The amount of benzoyl alcohol 5% lotion recommended per application depends on hair length.

‡‡Approximate cost according to Walgreens.com. Accessed November 10, 2016.

§§The safety and effectiveness of malathion lotion have not been established in children <6 yr old; it is contraindicated in children <24 mo old.

##In clinical trials, patients used a maximum of 2 fl oz of malathion lotion per application.

¶¶One or two 20-min applications have also been effective (Meinking TL, Vicaria M, Eyerdam DH, et al: Efficacy of a reduced application time of Ovide lotion [0.5% malathion] compared to Nix creme rinse [1% permethrin] for the treatment of head lice. *Pediatr Dermatol* 21:670–674, 2004.)

††Available without a prescription.

FDA, U.S. Food and Drug Administration; MSD, Merck Sharp Dohme; WAC, wholesaler acquisition cost or manufacturer's published price to wholesalers.

From The Medical Letter. Drugs for head lice. *Med Lett Drugs Ther.* 2016;58:150–152.



Fig. 709.9 Intact nits on human hairs.

with a fine-toothed comb after application of a damp towel to the scalp for 30 minutes. Clothing and bed linens should be laundered in very hot (54.4°C [>130°F]) water and then dried for at least 10 minutes at the highest setting or dry-cleaned; brushes and combs should be discarded or coated with a pediculicide for 15 minutes and then thoroughly cleaned in boiling water. If the object cannot be washed, it can be sealed in a plastic bag for 48 hours. Children may return to school after the initial treatment.

Pediculosis pubis is transmitted by skin-to-skin or sexual contact with an infested individual; the chance of acquiring the lice with one sexual exposure is 95%. The infestation is usually encountered in adolescents, although small children may occasionally acquire pubic lice on the eyelashes (see Fig. 709.8). Patients experience moderate to severe pruritus and may develop a secondary pyoderma from scratching. Excoriations tend to be shallow, and the incidence of secondary infection is lower than in pediculosis corporis. Maculae ceruleae are steel-gray spots, usually <1 cm in diameter, which may appear in the pubic area and on the chest, abdomen, and thighs. Oval translucent nits, which are firmly attached to the hair shafts, may be visible to the naked eye or may be readily identified by a hand lens or by microscopic examination (Fig. 709.9). Grittiness, as a result of adherent nits, may sometimes be detected when the fingers are run through infested hair. Adult lice are more difficult to detect than head or body lice because of their lower level of activity and smaller, translucent bodies. Because pubic lice occasionally may wander or may be transferred to other sites on fomites, terminal hair on the trunk, thighs, axillary region, beard area, and eyelashes should be examined for nits. The coexistence of other venereal diseases should be considered. Treatment with a 10-minute application of a pyrethrin preparation is usually effective. Retreatment may be required in 7-10 days. Infestation of eyelashes is eradicated by petrolatum applied 3-5 times per 24 hours for 8-10 days. Clothing, towels, and bed linens may be contaminated with nit-bearing hairs and should be thoroughly laundered or dry-cleaned.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

709.4 Seabather's Eruption

Lamiaa Hamie and Stephen R. Humphrey

Seabather's eruption is a severely pruritic dermatosis of inflammatory papules that develops within about 12 hours of bathing in saltwater, primarily on body sites that were covered by a bathing suit. The eruption has been described primarily in connection with bathing in the waters of Florida and the Caribbean. Lesions, which may include pustules, vesicles, and urticarial plaques, are more numerous in individuals who keep their bathing suits on for an extended period after leaving the water. The eruption may be accompanied by systemic symptoms of fatigue, malaise, fever, chills, nausea, and headache; in one large series, ~40% of children younger than 16 years of age had fever. Duration of the pruritus and skin eruption is 1-2 weeks. Lesions consist of a superficial and deep perivascular and interstitial infiltrate of lymphocytes, eosinophils, and neutrophils. The eruption appears to be caused by an allergic hypersensitivity reaction to venom from larvae of the thimble jellyfish *(Linuche unguiculata)*. Treatment is largely symptomatic. Potent topical corticosteroids have been shown to provide relief to some patients.

Chapter 710
Acne

Leah Lalor

ACNE VULGARIS

Acne is a chronic inflammatory disorder of the pilosebaceous unit with a multifactorial pathogenesis that affects at least 85% of adolescents but can occur in any age-group.

Pathogenesis

There are four main pathogenic factors leading to the development of acne: (1) increased sebum production; (2) abnormal keratinization of the follicular infundibulum; (3) *Cutibacterium acnes* (formerly *Propionibacterium acnes*)–mediated responses; and (4) inflammation.

The initial lesion of acne is a microcomedone, which progresses to a comedone. A comedone is a dilated, epithelium-lined follicular sac filled with lamellated keratinaceous material, lipid, and bacteria. An open comedone, known as a **blackhead**, has a patulous pilosebaceous orifice that permits visualization of the plug. An open comedone becomes inflammatory less commonly than does a closed comedone, or **whitehead**, which has only a pinpoint opening. An inflammatory papule or nodule develops from a comedone that has ruptured and extruded its follicular contents into the subadjacent dermis, inducing a neutrophilic inflammatory response. If the inflammatory reaction is close to the surface, a **papule or pustule** develops. If the inflammatory infiltrate develops deeper in the dermis, a **nodule** forms. Suppuration and an occasional giant cell reaction to keratin and hair are the cause of **nodulocystic** lesions. These are not true cysts but liquefied masses of inflammatory debris.

Comedonal acne (Fig. 710.1), particularly of the forehead and central face, is frequently the first sign of pubertal maturation. Most patients with acne do not have endocrine abnormalities. Many women with acne (25–50%) note acne flares about 1 week before menstruation.



Fig. 710.1 Primarily comedonal acne in a 7-yr-old female.



Fig. 710.2 Inflammatory papules and pustules.



Fig. 710.3 Severe nodulocystic acne.

Clinical Manifestations

Acne vulgaris is characterized by four basic types of lesions: open and closed comedones, papules, pustules (Fig. 710.2), and nodulocystic lesions (Fig. 710.3 and Table 710.1). One or more types of lesions may predominate. In its mildest form, which is often seen early in adolescence, lesions are limited to comedones on the central area of the face. Lesions may also involve the chest, upper back, and deltoid areas. A predominance of lesions on the forehead, particularly closed comedones, is common in early acne but can also be seen with prolonged use of greasy hair preparations (pomade acne) (Fig. 710.4). Marked involvement on the trunk is most often seen in males. Lesions often heal with temporary postinflammatory erythema and hyperpigmentation. Pitted, atrophic, or hypertrophic scars may be interspersed, depending on the severity, depth, and chronicity of the process.

Diagnosis of acne is rarely difficult, although flat warts, folliculitis, and other types of acne (drug-induced or exacerbated: glucocorticoid agents, anabolic steroids, gold, dactinomycin, isoniazid, iodides, bromides, cyclosporin, interferon beta, epidermal growth factor inhibitors, lithium, phenobarbital, phenytoin, progestins/Depo-Provera) may be confused with acne vulgaris. Definable autoinflammatory syndromes and androgen excess disorders are often associated with difficult-to-treat acne or when acne is noted with other cutaneous or systemic symptoms (Fig. 710.5). The differential diagnosis includes sarcoidosis, angiofibromas, keratosis pilaris, chloracne, rosacea, and fibrofolliculomas.

Treatment

An effective treatment strategy targets multiple pathogenic factors. There is no single treatment that addresses all four pathogenic factors other than the systemic retinoid isotretinoin; thus a **combination approach is typically preferred**. Therapy must be individualized based on acne lesion assessment and severity and aimed at preventing comedone formation. Inflammatory acne is frequently underdiagnosed in people of color, as the characteristic erythema may be masked by darker skin pigment. Careful evaluation of acne type is warranted to ensure appropriate treatment is selected.

Initial control requires 10-12 weeks of regular daily use of medications. Acne can be controlled and severe scarring prevented by judicious maintenance therapy that is continued until the disease process has abated spontaneously (Table 710.2 and Fig. 710.6).

It is also important to address the potentially severe emotional impact of acne on adolescents. The pediatrician must be aware of the frequently poor correlation between acne severity and psychosocial impact, particularly in adolescents. As adolescents become preoccupied with their appearance, offering treatment even to the youngster whose acne is mild may enhance self-image.

Table 710.1 One Approach to the Classification of Acne

SEVERITY	DESCRIPTION
Mild	Comedones (noninflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally <10).
Moderate	Moderate numbers of papules and pustules (10-40) and comedones (10-40) are present. Mild disease of the back and trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40-100), usually with many comedones (40-100) and occasional larger, deeper nodular inflammatory lesions (up to 5). Widespread affected areas usually involve the face, chest, and back.
Severe	Nodulocystic acne and conglobate acne, including many large inflammatory, painful nodular or pustular lesions along with many smaller papules, pustules, and comedones.

The American Academy of Dermatology acknowledges that there is no universally agreed upon grading/severity classification for acne.
Modified from James WD. Clinical practice: Acne. *N Engl J Med.* 2005;352:1463–1472.

Diet

Little evidence shows that the ingestion of particular foods can trigger acne flares, though high nonfat milk ingestion and high-glycemic-load diets may be contributory. When a patient is convinced that certain

dietary items exacerbate acne, it is prudent for the patient to omit those foods, provided that such omissions do not lead to excessive dietary restrictions.

Climate

Climate appears to influence acne in that improvement frequently occurs in summer and flares are more common in winter. Remission in summer may relate partly to the relative absence of stress. Emotional tension and fatigue seem to exacerbate acne in many individuals; the mechanism is unclear but has been proposed to relate to an increased adrenocortical response.

Cleansing

Cleansing with soap and water removes surface lipid and renders the skin less oily in appearance. It is generally recommended to wash with a gentle cleanser twice daily, followed by moisturizing with a noncomedogenic emollient, for all acne patients. Repetitive cleansing can be harmful because it irritates the skin, and use of harsh scrubs is not recommended. Greasy cosmetic and hair preparations must be discontinued because they exacerbate preexisting acne and cause further plugging of follicular pores. Manipulation and squeezing of facial lesions can lead to scarring and should be avoided.



Fig. 710.4 Pomade acne along the hairline.

Topical Therapy

All topical preparations must be used for 10-12 weeks before their effectiveness can be assessed (Table 710.3). Retinoids are first-line therapy and may be used alone for mild acne, but combination therapy is frequently more effective. A popular and effective combination is use of a benzoyl peroxide preparation in the morning and a retinoid at night. Recommendations for specific acne presentations are presented in Tables 710.2 and 710.3.

Retinoids. A topical retinoid should be the primary treatment for acne vulgaris. Topical retinoids have multiple actions, including inhibition of the formation and number of microcomedones, reduction of mature comedones, reduction of inflammatory lesions, and production of normal desquamation of the follicular epithelium. Retinoids should be applied nightly to all affected areas. The main side effects of retinoids are irritation and dryness. Not all patients initially tolerate daily use of a retinoid. It may be prudent to begin therapy every other or every third day and slowly increase the frequency of application as tolerated. Tretinoin, adapalene, tazarotene, and trifarotene (Table 710.4) are the available retinoids. They vary in strength and efficacy, although adapalene tends to be less irritating and tazarotene is more irritating but may be more effective.

Benzoyl Peroxide. Benzoyl peroxide is primarily an antimicrobial agent and does have mild comedolytic activity. It has an advantage over topical antibiotics in that it does not enhance antimicrobial resistance. It is available in multiple formulations and concentrations. The gel formulations are preferred, owing to better stability and more consistent release of the active ingredient. Washes and cleansers are useful for covering large surface areas such as the chest and back. As with retinoids, the main side effects are irritation and drying. Benzoyl peroxide can also bleach clothing, which sometimes limits the use of leave-on preparations like gels.

Topical Antibiotics. Topical antibiotics are indicated for the treatment of inflammatory acne. Clindamycin is the most commonly used. It is not as effective as oral antibiotics. It should never be used as monotherapy because it does not inhibit microcomedone formation and has the potential to induce antimicrobial resistance. Irritation and dryness are generally less than with retinoids or benzoyl peroxide. Topical antibiotics should not be used as monotherapy and can be prescribed as a combination product or separately. The most common combination product is benzoyl peroxide/clindamycin. A combination tretinoin/clindamycin product may also be used.

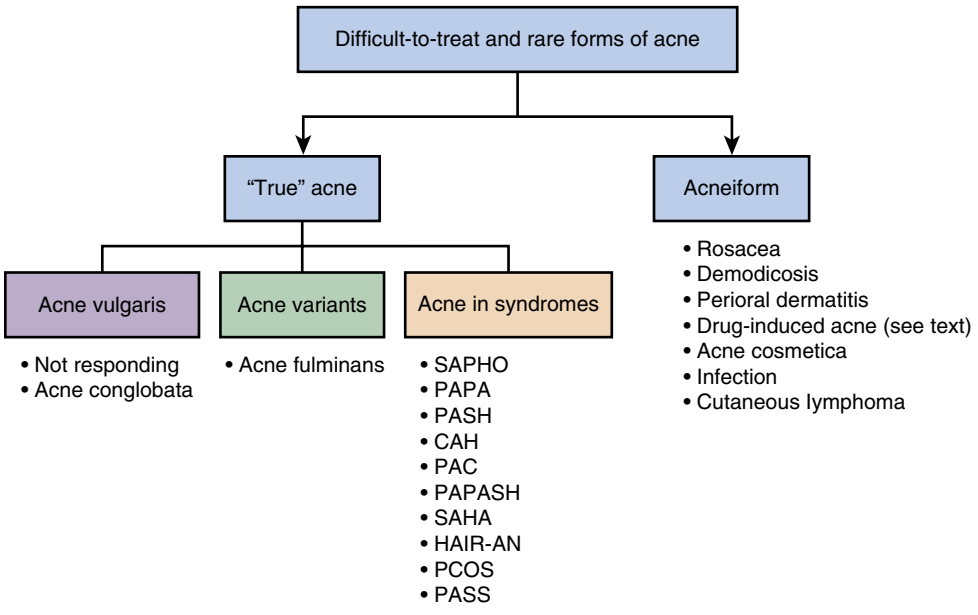

Fig. 710.5 Rare and difficult forms of acne. CAH, Congenital adrenal hyperplasia; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PASH, pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; PAC, pyoderma gangrenosum, acne, ulcerative colitis; PAPASH, pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis; SAHA, seborrhea, acne, hirsutism, androgenic alopecia; HAIR-AN, hyperandrogenism, insulin resistance, acanthosis nigricans; PCOS, polycystic ovarian syndrome; PASS, pyoderma gangrenosum acne, spondyloarthritis. *(Modified from Dessinioti C, Katsambas A. Difficult and rare forms of acne. Clin Dermatol. 2017;35[2]:138–146.)*

Table 710.2 Acne Treatment Algorithm

THERAPY	SEVERITY (LESION TYPE)				
	MILD (COMEDONAL)	MILD (INFLAMMATORY/ MIXED)	MODERATE (INFLAMMATORY/ MIXED)	SEVERE (INFLAMMATORY/ MIXED)	SEVERE (NODULAR/ SCARRING)
Initial therapy options*,†	Topical retinoid BP Salicylic acid cleanser	BP/retinoid combo BP/antibiotic combo Antibiotic/retinoid combo + BP	BP/retinoid combo BP/antibiotic combo ± topical retinoid Antibiotic/retinoid combo + BP ± oral antibiotic	BP/retinoid combo + oral antibiotic BP/antibiotic combo + topical retinoid + oral antibiotic Antibiotic/retinoid combo + BP + oral antibiotic	Isotretinoin
Alternative therapy options*,†,‡	Add BP or retinoid if not already prescribed BP/antibiotic combo BP/retinoid combo Antibiotic/retinoid combo	Substitute another combo product Add missing component (e.g., topical retinoid, BP, topical antibiotic) Change type, strength, or formulation of topical retinoid	Substitute another combo product Add missing component (i.e., topical retinoid, BP, topical antibiotic, oral antibiotic) Change type, strength, or formulation of topical retinoid Consider hormonal therapy§ for female patients Consider oral isotretinoin	Consider changing oral antibiotic Consider isotretinoin Consider hormonal therapy§ for female patients	Consider hormonal therapy§ for female patients
Maintenance therapy	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo

*If combination products not available to patient, consider substitution of individual components as separate prescriptions.
†Topical dapsone may be considered in place of topical antibiotic.
‡If needed as determined by physician assessment and patient satisfaction.
§Combined oral contraceptive or oral spironolactone.
BP, Benzoyl peroxide.
Adapted from Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics* 2006;118(3):1188–1199; Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. *J Am Acad Dermatol.* 2009;60:S1–50; Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131(3):S163–S186; Thiboutot DM, Gollnick HP. Treatment considerations for inflammatory acne: Clinical evidence for adapalene 0.1% in combination therapies. *J Drugs Dermatol.* 2006;5(8):785–794; Gollnick H, Cunliffe W, Berson D, et al. Management of acne: A report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(Suppl 1):S1–S37; and Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74:945–973. From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022, Table 8.1, p. 210.

Azelaic Acid. Azelaic acid (20% cream) has mild antimicrobial and keratolytic properties. It can also help expedite resolution of postinflammatory hyperpigmentation and is less irritating than many other topical acne treatments.

Clascoterone. Clascoterone 1% cream is a topical androgen antagonist, a first in its class, and is approved for use in males and females 12 years and older. It has shown efficacy in improving both inflammatory and noninflammatory acne in trials, but how this medication will be used under real-world circumstances is yet to be determined.

Systemic Therapy

Antibiotics, especially tetracycline and its derivatives (see Table 710.4), are indicated for the treatment of patients whose acne has not responded to topical medications, who have moderate to severe inflammatory papulopustular and nodulocystic acne, and who have a propensity for scarring (Table 710.5). Tetracycline and its derivatives act by reducing the growth and metabolism of *C. acnes*. They also have antiinflammatory properties. For most adolescent patients, therapy may be initiated twice daily, for at least 6-8 weeks, in combination with a judicious topical regimen, and should not be used for longer than 3-6 months. The drugs should always be administered in combination with a topical retinoid and topical benzoyl peroxide but not with topical antibiotics. Doxycycline is the preferred oral antibiotic in acne because of its high efficacy and lower risk of long-term side effects compared with similar medications. Minocycline and doxycycline should be taken with food. Side effects of tetracycline and derivatives are rare and include vaginal candidiasis, particularly in those who take tetracycline concurrently with oral contraceptives; gastrointestinal irritation; phototoxic reactions, including onycholysis and brown discoloration of nails; esophageal ulceration; inhibition of fetal skeletal growth; and staining of growing teeth, precluding its use during pregnancy and in those younger than 8 years of age. Doxycycline is the most photosensitizing of the tetracycline derivatives and is also more likely to cause pill esophagitis. Rarely, minocycline causes dizziness, intracranial hypertension, bluish discoloration of the skin and mucous membranes, hepatitis, a lupus-like syndrome, and drug hypersensitivity. A possible complication of prolonged systemic antibiotic use is proliferation of gram-negative organisms—particularly *Enterobacter, Klebsiella, Escherichia coli,* and *Pseudomonas aeruginosa*—producing severe refractory folliculitis.

Females who have acne and hormonal abnormalities, whose acne is unresponsive to antibiotic therapy, or who are not candidates for isotretinoin therapy should be considered for a trial of hormonal therapy. Combined oral contraceptive pills are the primary form of hormonal therapy. Spironolactone has also shown effectiveness. Young women with acne that is refractory to conventional therapy and have other signs of hyperandrogenism should be evaluated for polycystic ovarian syndrome.

Isotretinoin (13-*cis*-retinoic acid) is indicated for *severe nodulocystic acne and moderate to severe acne that has not responded to conventional*

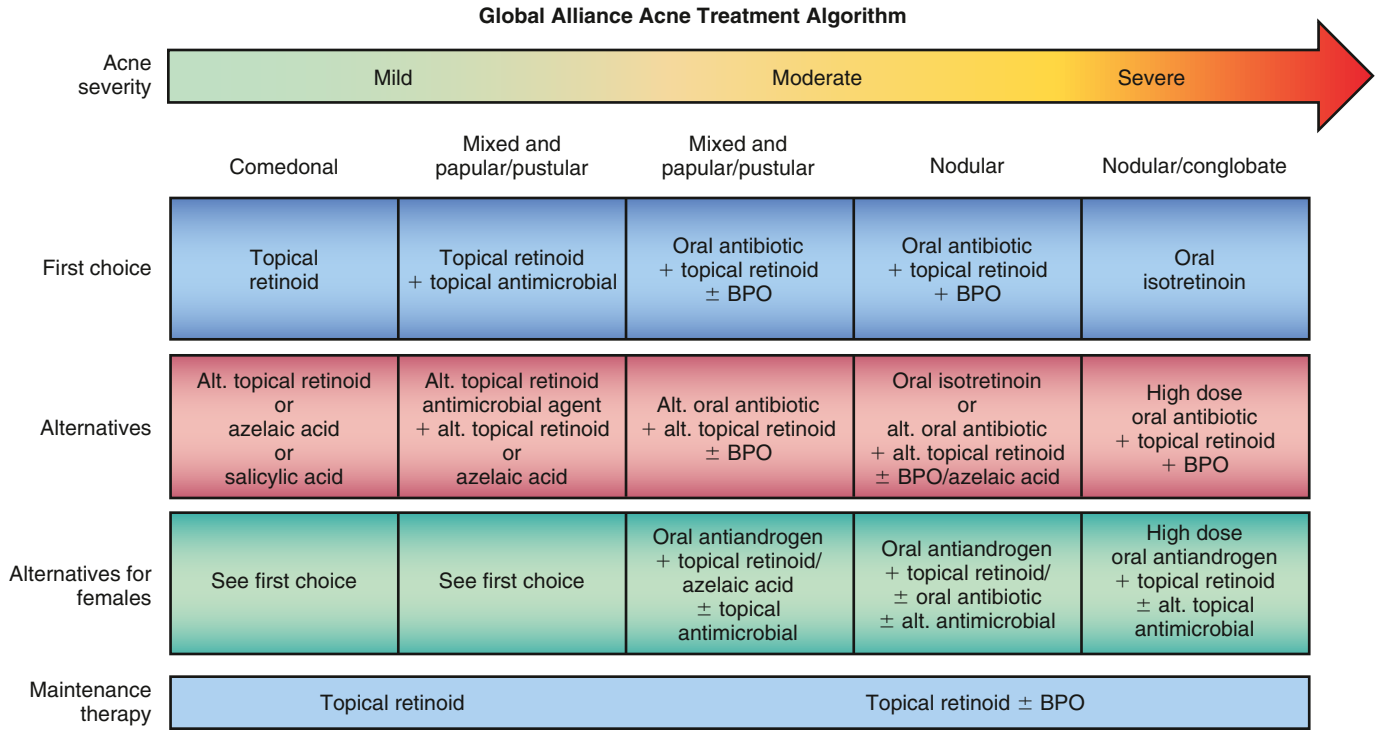

Fig. 710.6 Acne treatment algorithm. BPO, Benzoyl peroxide. *(From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al. New insights into the management of acne: an update from the Global Allegiance to Improve Outcomes in Acne. J Am Acad Dermatol. 2009;60:S1–S50.)*

Table 710.3 Recommendations for Topical Therapies

- Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne.
- Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy.
- Topical antibiotics (e.g., erythromycin and clindamycin) are effective acne treatments but are not recommended as monotherapy because of the risk of bacterial resistance.
- Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions.
- Treatment with multiple topical agents that affect different aspects of acne pathogenesis can be useful. Combination therapy should be used in the majority of patients with acne.
- Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children.
- Azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation.
- Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne.
- There is limited evidence to support recommendations for sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc in the treatment of acne.

From Zaenglein AL, Pathy AL, Scholsser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945–973, Table V, p. 951.

therapy. The recommended dosage is 0.5-1.0 mg/kg/day. A standard course in the United States lasts 16-20 weeks or until acne is clear. At the end of one course of isotretinoin, 70–80% of patients are cured, 10–20% need conventional topical and/or oral medications to maintain adequate control, and 10–20% have relapses and need an additional course of isotretinoin. Isotretinoin addresses all four pathogenic mechanisms of acne, is highly effective, and only has very rare treatment failures.

Isotretinoin use has many side effects. It is highly **teratogenic** and is **absolutely contraindicated** in pregnancy. Pregnancy should be avoided for 4 weeks after discontinuation of therapy. Two forms of birth control are required, or a confirmation of total abstinence, as are monthly pregnancy tests. *Concerns over cases of pregnancy despite warnings have prompted a manufacturer registration program, iPLEDGE (www.ipledgeprogram.com), which requires physician enrollment and careful patient pregnancy screening to prescribe isotretinoin.* Many patients also experience cheilitis, xerosis, periodic epistaxis, and blepharoconjunctivitis. Increased serum triglyceride and cholesterol levels are also common. It is important to rule out preexisting liver disease and hyperlipidemia before initiating therapy and to recheck laboratory values when the dosage is established. Less common but significant side effects include arthralgias, myalgias, temporary thinning of the hair, paronychia, increased susceptibility to sunburn, formation of pyogenic granulomas, and colonization of the skin with *Staphylococcus aureus,* leading to impetigo, secondarily infected dermatitis, and scalp folliculitis. Rarely, hyperostotic lesions of the spine develop after more than one course of isotretinoin. Concomitant use of an oral tetracycline and isotretinoin is contraindicated because either drug, but particularly when they are used together, can cause benign intracranial hypertension. Although no cause-and-effect relationship has been established, drug-induced mood changes and depression and/or suicide have mandated close attention to psychiatric well-being before and during isotretinoin prescription. An increased risk of inflammatory bowel disease with the use of isotretinoin is debated.

Surgical Therapy

Intralesional injection of low-dose (3-5 mg/mL) midpotency glucocorticoids (e.g., triamcinolone) with a 30-gauge needle on a tuberculin syringe may hasten the healing of individual painful nodulocystic lesions. Dermabrasion or laser peel to minimize scarring should be considered only after the active process is quiescent. Figure 710.7 describes the management of scarring.

The role of pulsed dye laser in the treatment of inflammatory acne is controversial and inconclusive.

Table 710.4 Medications for the Treatment of Acne

DRUG	DOSE	SIDE EFFECTS	OTHER CONSIDERATIONS
TOPICAL AGENTS			
Retinoids			
Tretinoin	Applied once nightly; strengths of 0.025–0.1% available*	Irritation (redness and scaling)	Generics available.
Adapalene	Applied once daily, at night or in the morning; 0.1% and 0.3%*	Minimal irritation	0.1% generic available.
Tazarotene†	Applied once nightly; 0.05% and 0.1%*	Irritation	Limited data suggest tazarotene is more effective than alternatives.
Trifarotene	Applied once nightly; 0.005% cream	Mild irritation	Labeled for trunk use.
Antimicrobials			
Benzoyl peroxide, 2.5–10%	Applied once or twice daily	Benzoyl peroxide can bleach clothing and bedding	Available over the counter; 2.5–5% concentrations as effective as and less drying than 10% concentration.
Clindamycin, erythromycin‡	Applied once or twice daily	Propensity to resistance	Most effective for inflammatory lesions (rather than comedones); resistance a concern when used alone.
Minocycline	Applied once or twice daily; 4% foam	None	Brand name, expensive.
Combination benzoyl peroxide and clindamycin or erythromycin; combination tretinoin and clindamycin	Applied once or twice daily	Side effects from benzoyl peroxide (bleach clothing or bedding) and from topical antibiotics (propensity to resistance)	Combination more effective than topical antibiotics alone; limits development of resistance; use of individual products in combination less expensive and appears similarly effective.
Other Topical Agents			
Azelaic acid‡	Applied twice daily; 20% cream	Well tolerated	Helpful for postinflammatory dyspigmentation; 10% cream available over the counter
Salicylic acid	Applied once or twice daily	Peeling, irritation	Low efficacy
Dapsone	Applied once daily; 5% and 7.5% gel	Mild irritation	Evidence of particular efficacy in skin of color
Clascoterone	Applied twice daily; 1% cream	Mild irritation	Brand name, expensive.
ORAL ANTIBIOTICS§			
Tetracycline#	250-500 mg once or twice daily	Gastrointestinal upset, intracranial hypertension	Inexpensive; dosing limited by need to take on empty stomach.
Doxycycline#	50-100 mg once or twice daily	Phototoxicity, intracranial hypertension, pill esophagitis, gastrointestinal upset	20-mg dose antiinflammatory only; limited data on efficacy.
Minocycline#	50-100 mg once or twice daily	Hyperpigmentation of teeth, oral mucosa, and skin; lupus-like reactions with long-term treatment, intracranial hypertension, drug hypersensitivity	
Sarecycline	Daily for 12 wk based on weight; 60-mg, 100-mg, 150-mg tablets	Intracranial hypertension, lightheadedness, candidiasis, nausea	Newest antimicrobial agent
Trimethoprim-sulfamethoxazole	One dose (160 mg trimethoprim, 800 mg sulfamethoxazole) twice daily	Toxic epidermal necrolysis and allergic eruptions	Trimethoprim may be used alone in a 300-mg dose twice daily; limited data available; not generally recommended.
Erythromycin‡	250-500 mg twice daily	Gastrointestinal upset	Resistance problematic; efficacy is limited.

Table 710.4 Medications for the Treatment of Acne—cont'd

DRUG	DOSE	SIDE EFFECTS	OTHER CONSIDERATIONS
HORMONAL AGENTS[¶]			
Spironolactone[#]	50-200 mg in 1-2 divided doses	Temporary menstrual irregularities and breast tenderness; possible potassium elevations in those with renal or cardiac disease	Higher doses more effective but cause more side effects; best given in combination with oral contraceptives.
Estrogen-containing oral contraceptives	Daily	Potential side effects include thromboembolism	Several approved specifically for acne, but all COCs have efficacy in acne treatment
ORAL RETINOID			
Isotretinoin[**]	0.5-1.0 mg/kg/day in 2 divided doses	Birth defects; adherence to pregnancy prevention program outlined by drug manufacturer, including two initial negative pregnancy tests, is essential; hypertriglyceridemia, elevated results on liver function tests, abnormal night vision, benign intracranial hypertension, dryness of the lips, ocular, nasal, and oral mucosa and skin, secondary staphylococcal infections, arthralgias, and mood disturbances are possible common or important side effects; laboratory testing of lipid profiles and liver function tests when dosage established	Relapse rate higher if patient is younger than age 16 yr at initial treatment, if acne is of high severity and involves the trunk, or if drug is used in adult women

*As cream or gel.
[†]Tazarotene is in pregnancy category X: contraindicated in pregnancy.
[‡]Clindamycin, erythromycin, and azelaic acid are in pregnancy category B: no evidence of risk in humans.
[§]Oral antibiotics are indicated for moderate to severe disease; for the treatment of acne on the chest, back, or shoulders; and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.
[#]This drug is in pregnancy category D: positive evidence of risk in humans.
[¶]Hormonal agents are for use in women only.
**Isotretinoin is in pregnancy category X: contraindicated in pregnancy. It should be used only in patients with severe acne that does not clear with combined oral and topical therapy.
Modified from James WD. Clinical practice: Acne. *N Engl J Med.* 2005;352:1463–1472.

Table 710.5 Recommendations for Systemic Antibiotics

- Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments.
- Doxycycline and minocycline are more effective than tetracycline.
- Although oral erythromycin or azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children <8 years of age). Erythromycin use should be restricted because of its increased risk of bacterial resistance.
- Use of systemic antibiotics other than the tetracyclines and macrolides is discouraged because there are limited data for their use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracyclines or to treatment-resistant patients.
- The use of systemic antibiotics should be limited to the shortest possible duration. Reevaluate at 3-4 mo to minimize the development of bacterial resistance. Monotherapy with systemic antibiotics is not recommended.
- Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy.

From Zaenglein AL, Pathy AL, Scholsser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945–973, Table VI, p. 952.

DRUG-INDUCED ACNE

Pubertal and postpubertal patients who are receiving systemic corticosteroid therapy are predisposed to steroid-induced acne. This monomorphous folliculitis occurs primarily on the face, neck, chest (Fig. 710.8), shoulders, upper back, arms, and, rarely, on the scalp. Onset follows the initiation of steroid therapy by approximately 2 weeks. The lesions are small, erythematous papules or pustules that may erupt in profusion and are all in the same stage of development. Comedones may occur subsequently, but nodulocystic lesions and scarring are rare. Pruritus is occasional. Although steroid acne is relatively refractory if the medication is continued, the eruption may respond to the use of tretinoin and a benzoyl peroxide gel.

Other drugs that can induce acneiform lesions in susceptible individuals include isoniazid, phenytoin, phenobarbital, trimethadione, lithium carbonate, androgens (anabolic steroids), and vitamin B_{12}.

Other causes of acne, including halogens and chloracne, are rare and typically obvious with judicious history-taking.

NEONATAL CEPHALIC PUSTULOSIS (FORMERLY NEONATAL ACNE)

Approximately 20% of normal neonates demonstrate pustules and red papules on the face in the first 6 weeks of life. Small inflammatory papules and pustules predominate on the cheeks and forehead (Fig. 710.9); comedones are absent. The cause of neonatal acne is unknown, but it has been theorized that it may be an inflammatory reaction to *Pityrosporum* species rather than true acne. Other theories include placental transfer of maternal androgens, hyperactive neonatal adrenal glands, and a hypersensitive neonatal end-organ response to androgenic hormones. The eruption involutes spontaneously over a few months. Treatment is usually unnecessary. If desired, the lesions can be treated effectively with topical antifungals and/or benzoyl peroxide.



Icepick (V)	Rolling (U)	Boxcar (M)	Keloids	Hypertrophic
Punch excision (deep bases) Elevation and grafting Laser resurfacing/ dermabrasion (many scars close together) Spot TCA peel	**Combined therapy** Micrograft and subcision + ± Filler Resurfacing microdermabrasion Deep-spot TCA peel	**Shallow** ≤3 mm diameter-laser skin resurfacing >3 mm diameter-laser skin resurfacing ± punch elevation **Deep** ≤3 mm diameter-punch excision >3 mm diameter-punch excision or punch elevation Fractional thermolysis (deep or shallow) Dermabrasion CO_2 laser resurfacing	Intralesional corticosteroids Intralesional 5-FU Intralesional bleomycin Compression Imiquimod after intralesional excision Cryotherapy Pulsed-dye laser Excision + electrotherapy	Intralesional steroids Intralesional 5-FU Vascular laser Intralesional bleomycin Compression Imiquimod after intralesional excision
Adjunctive treatment: Topical retinoids 2 wk before and after treatment, sunscreens, moisturizers				
Nonablative lasers for mild disease; ablative and fractional lasers for moderate scarring				

Fig. 710.7 Treatment options for acne scars. CO_2, Carbon dioxide; FU, fluorouracil; TCA, trichloroacetic acid. *(From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al. New insights into the management of acne: an update from the Global Allegiance to Improve Outcomes in Acne. J Am Acad Dermatol. 2009;60:S1–S50.)*

INFANTILE ACNE

Infantile acne usually manifests between 6 weeks and 2 years of age, more commonly in males than in females (Fig. 710.10). Open and closed comedones predominate on the face. Papules and pustules occur frequently, but only occasionally do nodulocystic lesions develop. Pitted scarring is seen in 10–15%. The course may be relatively brief, or the lesions may persist for many months or years, although the eruption generally resolves by 4 years of age. Use of topical benzoyl peroxide gel and topical retinoid, as would be recommended for typical acne, is effective but off-label. Some acne medications are approved down to age 9 years but none for infants. Oral erythromycin is occasionally necessary, and isotretinoin can be used in severe cases. A child with refractory acne or other signs of pubertal development warrants a search for an abnormal source of androgens, such as a virilizing tumor or congenital adrenal hyperplasia.

MID-CHILDHOOD ACNE

Acne that begins between 1 and 7 years of age is not considered normal. Although the neonatal adrenal gland secretes high levels of androgens through the first year of life, it becomes quiescent until adrenarche, which occurs around age 7. Underlying endocrine abnormality should be investigated in those presenting with acne in middle childhood. Precocious puberty, late-onset congenital adrenal hyperplasia, or an androgen-secreting tumor may underlie acne in this age-group. Workup for androgen excess is indicated.

ACNE FULMINANS (ACUTE FEBRILE ULCERATIVE ACNE)

Acne fulminans is characterized by abrupt onset of extensive inflammatory, tender, ulcerative acneiform lesions in typically male teenagers and may be related to recent initiation of isotretinoin. The distinctive feature is the tendency for large nodules to form exudative, necrotic, ulcerated, crusted plaques. Lesions heal with extensive scarring. A preceding history of mild papulopustular or nodular acne is noted in most patients. Constitutional symptoms and signs are common, including fever, debilitation, arthralgias, myalgias, weight loss, and leukocytosis. Blood cultures are sterile. Lesions of erythema nodosum sometimes develop on the shins. Osteolytic bone lesions may develop in the clavicle, sternum, and epiphyseal growth plates; affected bones appear normal or have slight sclerosis or thickening on healing. Salicylates may be helpful for the myalgias, arthralgias, and fever. Treatment should be directed by a dermatologist and includes systemic corticosteroids and isotretinoin. Antibiotics are not indicated unless there is evidence of secondary infection.



Fig. 710.8 Monomorphous papular eruption of steroid acne.



Fig. 710.9 Comedonal acne in a neonate.



Fig. 710.10 Inflammatory infantile acne.

Pyogenic Arthritis with Pyoderma Gangrenosum and Acne (PAPA Syndrome) (see Fig. 710.5, Chapter 204, and Chapter 702).

Chronic Recurrent Multifocal Osteomyelitis/Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome (see Chapter 204).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 711

Tumors of the Skin

Kari L. Martin

See also Chapter 636.

INFUNDIBULAR FOLLICULAR CYST

Infundibular follicular cysts (more commonly referred to as *epidermoid cysts* or *sebaceous cysts*) are the nodules most commonly seen in children. Such a cyst is a sharply circumscribed, dome-shaped, firm, freely movable, skin-colored nodule (Fig. 711.1), often with a central dimple or punctum that is a plugged, dilated pore of a pilosebaceous follicle. Follicular cysts form most frequently on the face, neck, chest, or upper back and may periodically become inflamed and infected secondarily, particularly in association with acne vulgaris. The cyst wall may also rupture and induce an inflammatory reaction in the dermis. The wall of the cyst is derived from the follicular infundibulum. A mass of layered keratinized material that may have a cheesy consistency fills the cavity. Cysts may arise from occlusion of pilosebaceous follicles (acneiform cysts), implantation of epidermal cells into the dermis as a result of an injury that penetrates the epidermis (epidermal inclusion cysts), and rests of epidermal cells (epidermoid cysts). Multiple epidermoid cysts may be present in Gardner syndrome and nevoid basal cell carcinoma syndrome. Excision of the cyst with removal of the entire sac and its contents is indicated, particularly if the cyst becomes recurrently inflamed. A fluctuant cyst should be incised and drained and, if there is surrounding erythema, treated with antibiotics or intralesional corticosteroids. After the inflammation subsides, the cyst may be removed.

MILIUM

A milium is a 1- to 2-mm, firm, pearly white or yellowish subepidermal keratin cyst. Milia in newborns are discussed in Chapter 688. Secondary milia occur in association with subepidermal blistering diseases and after dermabrasion or other injury to the skin. They are retention cysts caused by hyperproliferation of injured epithelium and are indistinguishable histopathologically from primary milia. Those that develop after blistering usually arise from the eccrine sweat duct, but they may develop from the hair follicle, sebaceous duct, or epidermis. A milium body differs from an infundibular follicular cyst only in its small size and superficial location.

FIBROFOLLICULOMAS

These lesions usually appear in late adolescence or in young adults and are characterized by multiple dome-shaped, clear-white papules appearing on the nose, cheeks, and neck, and at times the trunk or ears (Fig. 711.2). They are associated with the familial cancer syndrome of **Birt-Hogg-Dubé**, an autosomal dominant disorder that results from a pathogenic variant in the folliculin *(FLCN)* tumor suppressor gene. Associated features include pulmonary cysts, pneumothorax, renal cell carcinoma, and other benign or malignant tumors.

PILAR CYST (TRICHILEMMAL CYST)

A pilar cyst may be clinically indistinguishable from an infundibular follicular cyst. It manifests as a smooth, firm, mobile nodule, predominantly on the scalp (Fig. 711.3). Pilar cysts occasionally develop on the face, neck, or trunk. A cyst may become inflamed and may occasionally suppurate and ulcerate. The cyst wall is composed of stratified squamous epithelium with indistinct intercellular bridges. The peripheral cell layer of the wall shows a palisade arrangement, which is not seen in an epidermoid cyst. No granular layer is present. The cyst cavity contains dense homogeneous eosinophilic keratinous material, and foci of calcification are seen in 25% of cases. The propensity for development of pilar cysts may be inherited in an autosomal dominant manner. More than one cyst generally develops in a patient. Numerous pilar and epidermoid cysts, desmoid tumors, fibromas, lipomas, or osteomas may be associated with colonic polyposis or adenocarcinoma in Gardner syndrome. Pilar cysts shell out easily from the dermis.

PILOMATRICOMA (PILOMATRIXOMA)

The second most common nodule seen in children, pilomatricoma is a benign tumor that manifests as a 3- to 30-mm, firm, solitary, deep dermal or subcutaneous tumor on the head, neck, or upper extremities. The overlying epidermis is usually normal. The tumor may occasionally be located more superficially, however, tinting the overlying skin blue-red (Fig. 711.4). Multiple pilomatricomas are seen in myotonic dystrophy, Gardner syndrome, Rubinstein-Taybi syndrome, and Turner syndrome. In general, however, pilomatricomas are not hereditary. Histopathologically, irregularly shaped islands of epithelial cells with eosinophilic, anucleate "ghost cells" are embedded in a cellular stroma. Calcium deposits are found in 75% of tumors. Pilomatricomas are caused by pathogenic variants in β-catenin.

TRICHOEPITHELIOMA

A 2- to 8-mm, smooth, round, firm, skin-colored papule, trichoepithelioma is derived from an immature hair follicle.



Fig. 711.1 Flesh-colored cyst on the forehead.



Fig. 711.2 Multiple dome-shaped, whitish papules on the nose and cheeks in a 31-yr-old carrier of an *FLCN* pathogenic variant. *(From Menko FH, van Steensel MAM, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet. 2009;10:1199–1206, Fig. 1.)*



Fig. 711.3 Pilar cyst of the anterior scalp.

Trichoepitheliomas generally occur singly on the face in childhood or early adulthood. Multiple trichoepitheliomas are inherited autosomal dominantly (type 1: *CYLD* gene; type 2: 9p21 gene currently unidentified), appear in childhood or at puberty, and gradually increase in number on the nasofacial folds, nose, forehead, and upper lip; occasionally they occur on the scalp, neck, and upper trunk. Microscopically, these benign tumors are characterized by horn cysts composed of a fully keratinized center surrounded by basophilic cells in an adenoid network. Topical imiquimod therapy may be beneficial. Surgical excision has been used for therapy, as have cryotherapy, electrosurgery, and laser vaporization.



Fig. 711.4 Pilomatricoma. Firm tumor with overlying bluish discoloration of the skin.

ERUPTIVE VELLUS HAIR CYSTS

Eruptive vellus hair cysts are 1- to 3-mm, asymptomatic, soft, skin-colored follicular papules on the central chest (Fig. 711.5). They may become crusted or umbilicated. Abnormal vellus hair follicles become occluded at the level of the infundibulum, resulting in retention of hairs within an epithelium-lined cystic dilation of the proximal part of the follicle. Most cases are chronic, but spontaneous regression has been reported.

STEATOCYSTOMA MULTIPLEX

An autosomal dominant (*KRT17* gene) condition, steatocystoma multiplex usually manifests in adolescence or early adulthood as numerous soft to firm cystic nodules that are adherent to the underlying skin and are 3 mm to 3 cm in diameter. When punctured, the cysts may drain oily or cheesy material. Sites of predilection include the sternal region, axillae, arms, and scrotal skin. The multiply folded cyst wall is lined on the luminal side with a thick, homogeneous, eosinophilic horny layer; there is no granular layer. Flattened sebaceous gland lobules are often visible in the cyst wall, and lanugo hairs may be present in a cystic cavity that appears otherwise empty (a processing artifact).

SYRINGOMA

The benign tumors known as syringomas are soft, small, skin-colored or yellowish-brown papules that develop on the face, particularly in the periorbital regions (Fig. 711.6). Other sites of predilection include the axillae and umbilical and pubic areas. They often develop during puberty and are more frequent in females. Eruptive syringomas develop in crops over the anterior trunk during childhood or adolescence. A syringoma is derived from an intraepidermal sweat gland duct. Syringomas are of cosmetic significance only. Sparse lesions may be excised, but they are often too numerous to remove.

INFANTILE DIGITAL FIBROMA

Infantile digital fibroma is a smooth, firm, erythematous or skin-colored nodule on the dorsal or lateral surface of a distal phalanx of a finger or toe. More than 80% of tumors occur in infancy or may be present at birth. Lesions may be solitary or multiple and may manifest as "kissing" tumors on opposing digits. They are usually asymptomatic, but flexion deformity of the digits may occur. Clinically the lesion resembles a fibroma, leiomyoma, angiofibroma, acquired digital fibrokeratoma, accessory digit, or mucous cyst. The diagnosis is confirmed by the finding of numerous spindle-shaped fibroblasts that contain small, round, dense eosinophilic cytoplasmic inclusion bodies composed of collections of actin microfilaments. Local recurrence after simple excision of this tumor has been reported in 75% of patients. Because the tumor does not metastasize and may regress spontaneously in 2-3 years, a course of expectant observation is advised. If functional impairment or flexion deformity of the digit becomes apparent, prompt full excision of the tumor is indicated.



Fig. 711.5 Eruptive vellus hair cysts. Multiple papules on the chest.



Fig. 711.7 Dermatofibroma. Red-brown nodular variant.



Fig. 711.6 Syringomas. Multiple yellow papules near the eye.

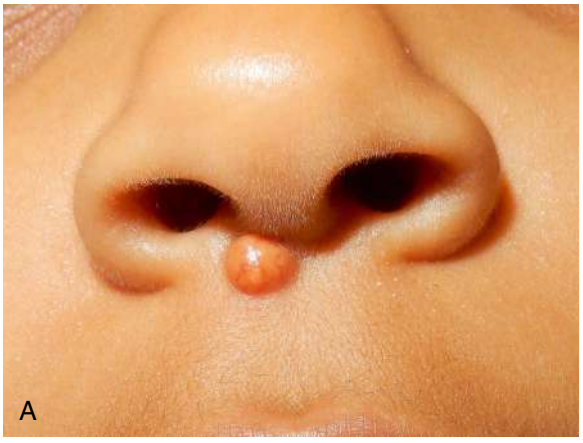



Fig. 711.8 A, Juvenile xanthogranuloma. A 4-mm, apricot-colored, dome-shaped, firm papule with overlying telangiectasias below the nasal columella. B, Pink-red rim in a "setting-sun" pattern seen by dermoscopy. *(From Bell KA, Marathe K, Burke KT, Cardis MA. A persistent pimple in a 5-year-old girl. J Pediatr. 2020;224:172–173, Figs. 1 and 2, p. 172).*

DERMATOFIBROMA

A benign dermal tumor, dermatofibroma may be pedunculated, nodular (Fig. 711.7), or flat and is usually well circumscribed and firm but occasionally feels soft on palpation. The overlying skin is usually hyperpigmented; it may be shiny or keratotic and dimples when the tumor is pinched. Dermatofibromas range in size from 0.5 to 10.0 mm, arise most frequently on the limbs, and are usually asymptomatic but may occasionally be pruritic. They are composed of fibroblasts, young and mature collagen, capillaries, and histiocytes in varying proportions, forming a nodule in the dermis that has poorly defined edges. The cause of these tumors is unknown, but trauma such as an insect bite or folliculitis appears to induce reactive fibroplasia. The differential diagnosis includes epidermal inclusion cyst, juvenile xanthogranuloma, hypertrophic scar, and neurofibroma. Dermatofibromas may be excised or left intact, according to the patient's preference. They usually persist indefinitely.

JUVENILE XANTHOGRANULOMA

A firm, dome-shaped, yellow, pink, or orange papule or nodule (Fig. 711.8), juvenile xanthogranuloma varies from 5 mm to approximately 4 cm in diameter. The average age at onset is 2 years. These nodules are 10 times more common in White than in Black individuals. Sites of predilection are the scalp, face, and upper trunk, where they may erupt in profusion or remain as solitary lesions. Nodular lesions may appear on the oral mucosa. The diagnosis is usually made clinically. Mature lesions are characterized histopathologically by a dermal infiltrate of lipid-laden histiocytes, admixed inflammatory cells, and Touton giant cells. Clinically the lesions may resemble papulonodular urticaria pigmentosa, dermatofibromas, or xanthomas of hyperlipoproteinemia, but they can be distinguished from these entities histopathologically.

Affected infants are nearly always otherwise normal, and blood lipid values are not elevated. Café-au-lait macules are found on 20% of

patients with juvenile xanthogranuloma. Xanthogranulomatous infiltrates occur occasionally in the iris or other ocular tissues. This process may result in glaucoma, hyphema, uveitis, heterochromia iridis, iritis, or sudden proptosis. When seen in patients <2 years of age, multiple lesions and periocular location may heighten concerns for intraocular involvement. There appears to be an association among juvenile xanthogranuloma, neurofibromatosis, and childhood leukemia, most frequently juvenile chronic myelogenous leukemia. There is no need to remove the benign lesions of juvenile xanthogranuloma because most of them regress spontaneously in the first few years. Residual dyspigmentation and atrophy may result.

LIPOMA

A benign collection of fatty tissue, lipoma appears on the trunk, neck, or proximal portions of the limbs. Lipomas are soft, compressible, lobulated subcutaneous masses. Multiple lesions may occur occasionally, as in Gardner syndrome. Atrophy, calcification, liquefaction, or xanthomatous change may sometimes complicate their course. A lipoma is composed of normal fat cells surrounded by a thin connective tissue capsule. Lipomas represent a cosmetic defect and may be surgically excised. Multiple lipomas, identical to those that occur singly, are inherited in an autosomal dominant fashion and often appear by the third decade in patients with familial multiple lipomatosis. Lipomas may appear intraabdominally, intramuscularly, and subcutaneously. Congenital lipomatosis manifests in the first few months of life as large subcutaneous fatty masses on the chest with extension into skeletal muscle. Congenital lipomatosis can also be a manifestation of **Proteus syndrome** (overgrowth/hyperplasia skin, connective tissue, pathogenic variant in *AKT1*). Angiolipomas usually manifest as numerous painful subcutaneous nodules on the arms and trunk.

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies) is usually a sporadic disorder caused by a pathogenic variant in the ***PIK3CA*** gene with an asymmetric truncal lipomatous mass present at birth. Additional features include macrodactyly, vascular malformations (low flow), linear epidermal nevus, and renal anomalies. The differential diagnosis includes Proteus, Klippel-Trenaunay, and Bannayan-Riley-Ruvalcaba syndromes.

PIK3CA somatic pathogenic variants and those in the related AKT-mTOR pathway (*PIK3CA*-related overgrowth spectrum [PROS]) are associated with segmental overgrowth syndromes (Fig. 711.9; see also Fig. 691.6). In addition to regional/localized tissue overgrowth, there is a spectrum of malformations (hemimegaloencephaly, macrodactyly, lymphatic, muscle hemihypertrophy, epidermal nevi, capillary, polydactyly, syndactyly).

BASAL CELL CARCINOMA

Basal cell carcinoma is very rare in children in the absence of a predisposing condition, such as nevoid basal cell carcinoma syndrome, xeroderma pigmentosum, nevus sebaceus of Jadassohn, arsenic intake, or exposure to irradiation. The lesions are smooth, pearly, pink telangiectatic papules that enlarge slowly and may bleed or ulcerate. Sites of predilection are the face, scalp, and upper back. The differential diagnosis includes pyogenic granuloma, nevocellular nevus, epidermal inclusion cyst, closed comedo, dermatofibroma, and adnexal tumor. Depending on the site of occurrence and associated disease of the host, electrodesiccation and curettage or simple excision of basal cell carcinoma is usually curative. When the tumor is recurrent, >2 cm in diameter, located on problematic anatomic areas such as the midface or ears, or is an aggressive histopathologic type, Mohs microscopically controlled surgery may be the most appropriate treatment.

NEVOID BASAL CELL CARCINOMA SYNDROME (BASAL CELL NEVUS SYNDROME, GORLIN SYNDROME)

The autosomal dominant entity known as nevoid basal cell carcinoma syndrome is caused by pathogenic variants in the *PTCH1*, *PTCH2* ("patched"), and *SUFU* genes. These tumor-suppressor genes, part of the hedgehog signaling pathway, are important in determining embryonic patterning and cell fate in a number of structures in the developing embryo. Pathogenic variants in these genes produce dysregulation of several genes involved in organogenesis and

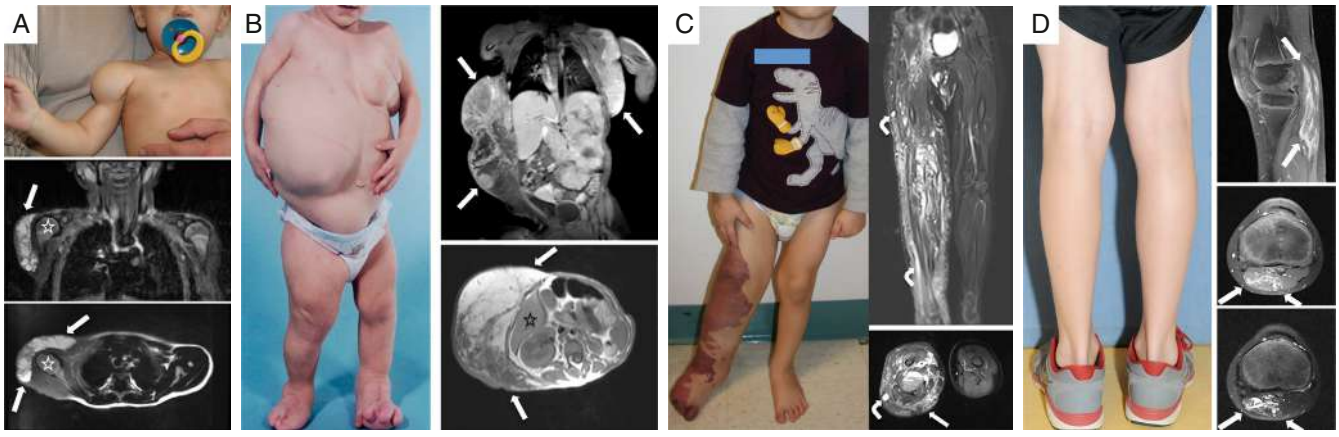

Fig. 711.9 Photographs and MRIs of participants with isolated LM, CLOVES, KTS, and FAVA. **A,** An 8-mo-old boy (LM1) with isolated LM. Note swelling in deltoid region without cutaneous vascular signs. Coronal and sagittal fat-saturated T2-weighted MRI demonstrates macrocystic LM (a multilocular cystic mass) involving the anterolateral aspects of the right shoulder without muscular infiltration *(arrows)*; humeral head *(asterisk)*. **B,** A 19-mo-old female (CL12) with CLOVES syndrome. Note asymmetric distribution of truncal lipomatous masses and bilateral lower extremity involvement. Coronal fat-saturated T1-weighted MRI after contrast administration demonstrates moderate heterogeneous enhancement of the bilateral truncal masses *(arrows)*. Axial T1-weighted MRI without contrast depicts truncal lipomatous overgrowth *(arrows)*; segment VI of the liver *(asterisk)*. **C,** A 3-yr-old boy (KT4) with KTS. Note capillary LM and overgrowth involving the right lower extremity. Coronal and axial fat-saturated T2-weighted MRI shows the persistent marginal vein system *(bent arrows)* and marked enlargement of the subcutaneous tissues due to a combination of lymphatic fluid and fat *(straight arrow)*. There are also intramuscular venous malformations. **D,** A 9-yr-old boy (F8) with FAVA of the left gastrocnemius muscle; note absence of overgrowth and cutaneous vascular anomalies. Sagittal fat-saturated T1-weighted MRI after contrast administration demonstrates the longitudinal distribution of the diffuse FAVA *(arrows)*. Axial fat-saturated T2-weighted MRI with *(upper)* and without *(lower)* contrast. Note that the right head of the gastrocnemius muscle is diffusely replaced by a contrast-enhancing heterogeneous soft tissue lesion *(arrows)*. CLOVES, Congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies; FAVA, fibroadipose vascular anomaly; KTS, Klippel-Trenaunay syndrome; LM, lymphatic malformation. *(From Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic pathogenic variants in PIK3CA. J Pediatr. 2015;166:1048–1054, Fig. 1, p. 1051.)*

carcinogenesis. Consequently, the syndrome includes a wide spectrum of defects involving the skin, eyes, central nervous and endocrine systems, and bones. The predominant features are early-onset basal cell carcinomas and mandibular cysts. Approximately 20% of those in whom a basal cell carcinoma develops before age 19 years have this syndrome. Basal cell carcinomas appear between puberty and age 35 years, erupting in crops of tumors that vary in size, color, and number; they may be difficult to distinguish from other types of skin lesions. Sites of predilection are the periorbital skin, nose, malar areas, and upper lip, but the lesions can also develop on the trunk and limbs and are not restricted to sun-exposed areas. Ulceration, bleeding, crusting, and local invasion can occur. Small milia, epidermal cysts, pigmented lesions, hirsutism, and palmar and plantar pits are additional cutaneous findings.

The facies of patients with this syndrome are characterized by temporoparietal bossing, prominent supraorbital ridges, a broad nasal root, ocular hypertelorism or dystopia canthorum, and prognathism. Keratinized cysts (odontogenic keratocysts) in the maxilla and mandible occur in most patients. These cysts range in size from a few millimeters to several centimeters; may result in maldevelopment of the teeth; and cause pain, swelling of the jaw, facial deformity, bone erosion, pathologic fractures, and suppurating sinus tracts. Osseous defects such as anomalous rib development, spina bifida, kyphoscoliosis, and brachymetacarpalism occur in 60% of patients, and ocular abnormalities—including cataracts, glaucoma, coloboma, strabismus, and blindness—occur in approximately 25%. Some males have hypogonadism, and the testes are absent or undescended. Kidney malformations have also been reported. Neurologic manifestations include calcification of the falx, seizures, mental retardation, partial agenesis of the corpus callosum, hydrocephalus, and nerve deafness. The incidence of medulloblastoma, ameloblastoma of the oral cavity, fibrosarcoma of the jaw, teratoma, cystadenoma, cardiac fibroma, ovarian fibroma, and fetal-onset rhabdomyoma is higher in patients with nevoid basal cell carcinoma syndrome.

Treatment of these patients requires the participation of various specialists according to individual clinical problems. Basal cell carcinomas should not be treated with irradiation. Most of the basal cell carcinomas have a clinically benign course, and it is often impossible to remove them all. Those with an aggressive growth pattern and those on the central areas of the face, however, should be removed promptly. Treatment options include surgery, Mohs micrographic surgery, laser ablation, cryotherapy, photodynamic therapy, topical 5% imiquimod and oral retinoids (0.5-1.0 mg/kg/day). Vismodegib, which inhibits smoothened protein in the hedgehog pathway, is a targeted therapy available for unresectable basal cell carcinomas. Genetic counseling is also indicated.

MELANOMA

See Chapter 692.

MUCOSAL NEUROMA SYNDROME (MULTIPLE ENDOCRINE NEOPLASIA TYPE IIB)

Mucosal neuroma syndrome, an autosomal dominant trait, is characterized by an asthenic or marfanoid habitus with scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The syndrome is caused by pathogenic variants in the tyrosine kinase domain of the *RET* gene. Patients have thick, patulous lips and soft tissue prognathism simulating acromegaly. Multiple mucosal neuromas or neurofibromas appear as pink, pedunculated, or sessile nodules on the anterior third of the tongue, at the commissures of the lips, and on the buccal mucosa and palpebral conjunctiva. Various ophthalmologic defects and intestinal ganglioneuromatosis with recurrent diarrhea are additional common findings. There is a high incidence of medullary thyroid carcinoma in association with high calcitonin levels, pheochromocytoma, and hyperparathyroidism in patients with this syndrome. Periodic screening tests for the associated malignant tumors are mandatory.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 712 Nutritional Dermatoses

Joel C. Joyce

OVERVIEW

There are many cutaneous manifestations of nutritional deficiencies (Table 712.1). For more details see Chapters 64-72.

ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by an inability to absorb sufficient zinc from the diet. The genetic variant is in the intestinal zinc-specific transporter gene *SLC39A4*. Initial signs and symptoms usually occur in the first few months of life, often after weaning from breast milk to cow's milk. The cutaneous eruption consists of vesiculobullous, eczematous, dry, scaly, or psoriasiform skin lesions symmetrically distributed in the perioral, acral, and perineal areas (Fig. 712.1) and on the cheeks, knees, and elbows (Fig. 712.2). The hair often has a peculiar, reddish tint, and alopecia of some degree is characteristic. Ocular manifestations include photophobia, conjunctivitis, blepharitis, and corneal dystrophy detectable by slit-lamp examination. Associated manifestations include chronic diarrhea, stomatitis, glossitis, paronychia, nail dystrophy, growth retardation, irritability, delayed wound healing, intercurrent bacterial infections, and superinfection with *Candida albicans*. Lymphocyte function and free radical scavenging are impaired. Without treatment the course is chronic and intermittent but often relentlessly progressive. When the disease is less severe, only growth retardation and delayed development may be apparent.

The diagnosis is established by the constellation of clinical findings and detection of a low plasma zinc concentration. A serum zinc level less than 50 μg/dL is suggestive, but not diagnostic, of **acrodermatitis enteropathica**. Levels of alkaline phosphatase, a zinc-dependent enzyme, may also be decreased. Histopathologic changes in the skin are nonspecific and include parakeratosis and pallor of the upper epidermis. The variety of manifestations of the syndrome may stem from the fact that zinc has a role in numerous metabolic pathways—including those of copper, protein, essential fatty acids, and prostaglandins—and that zinc is incorporated into many zinc metalloenzymes. Other nutritional deficiencies may produce similar findings (see Table 712.1), although the classic findings are highly suggestive of acrodermatitis enteropathica.

Oral therapy with zinc compounds is the treatment of choice. Replacement for individuals with inherited acrodermatitis enteropathica is with elemental zinc 3 mg/kg/24 hr in the form of zinc sulfate, gluconate, or acetate (i.e., 220 mg of zinc sulfate contains 50 mg of elemental zinc). Zinc gluconate carries less risk of gastrointestinal distress. However, plasma zinc levels should be monitored every 3-6 months so as to individualize the dosage. Zinc therapy rapidly abolishes the manifestations of the disease. Supplementation is for life. A syndrome resembling acrodermatitis enteropathica has been observed in patients with secondary zinc deficiency resulting from long-term total parenteral nutrition without supplemental zinc or to chronic malabsorption syndromes. A rash similar to acrodermatitis enteropathica has also been reported in infants fed breast milk that is low in zinc and in those with maple syrup urine disease, organic aciduria, methylmalonic acidemia, biotinidase deficiency, essential fatty acid deficiency, severe protein malnutrition (kwashiorkor), and cystic fibrosis. Cutaneous manifestations tend to appear in more severe forms. For those individuals with acquired zinc deficiency, oral replacement with elemental zinc, 0.5-1.0 mg/kg/24 hr, should be undertaken and the cause of underlying malnutrition should be addressed.

Table 712.1 Distinctive Skin Changes of Nutritional Disorders and Selected Differential Diagnosis

SKIN CHANGE	NUTRITIONAL DISORDER	SELECTED DIFFERENTIAL DIAGNOSIS
Exfoliative erythroderma	Kwashiorkor	Atopic dermatitis, psoriasis, staphylococcal scalded skin syndrome
Phrynoderma	Vitamin A deficiency, vitamin B–complex deficiencies, vitamin C deficiency, essential fatty acid deficiency	Keratosis pilaris, pityriasis rubra pilaris
Petechiae, purpura	Vitamin K deficiency, vitamin C deficiency (perifollicular petechiae)	Consumptive coagulopathy, coagulation disorder, thrombocytopenia, vascular fragility syndrome (Ehlers-Danlos), cutaneous vasculitis (e.g., Henoch-Schoenlein purpura)
Yellow-orange discoloration	Carotenemia	Jaundice, quinacrine-induced
Hyperpigmentation	Vitamin B12 deficiency, folate deficiency	Addison disease
Photodistributed dermatitis	Vitamin B3 deficiency (pellagra), vitamin B6 deficiency	Connective tissue disease (systemic lupus erythematosus, dermatomyositis), polymorphous light eruption
Seborrheic dermatitis–like changes	Vitamin B–complex deficiencies	Seborrheic dermatitis, psoriasis
Angular stomatitis	Vitamin B–complex deficiencies, iron deficiency	Angular cheilitis with candidal overgrowth
Glossitis	Vitamin B–complex deficiencies, zinc deficiency, iron deficiency	Sjogren syndrome, oral lichen planus, syphilis
Diaper dermatitis	Zinc deficiency, vitamin B–complex deficiencies	Irritant or allergic contact dermatitis, seborrheic dermatitis, inverse psoriasis, Langerhans cell histiocytosis
Lightening of hair	Kwashiorkor, marasmus, vitamin B–complex deficiencies, copper deficiency	Poliosis, vitiligo
Corkscrew hairs	Vitamin C deficiency	
Nail changes	Koilonychia: iron deficiency Longitudinal hyperpigmented streaks: vitamin B3 deficiency (pellagra)	Koilonychia: chronic irritant, lichen planus, psoriasis, Plummer–Vinson syndrome, transient in young children Longitudinal hyperpigmented streaks: physiologic, drug-induced, trauma

From Wong CY, Chu DH. Cutaneous signs of nutritional disorders. *Inter J Women Dermatol*. 2021;7:647–652: Table 1, p. 649.

ESSENTIAL FATTY ACID DEFICIENCY

Essential fatty acid deficiency causes a generalized scaly dermatitis composed of thickened, erythematous, desquamating plaques. Individuals may also show failure to thrive, growth retardation, alopecia, thrombocytopenia, and poor wound healing. The eruption has been induced experimentally in animals fed a fat-free diet and has been observed in patients with chronic severe malabsorption, as in short-gut syndrome, and in those sustained on a fat-free diet or fat-free parenteral alimentation. Linoleic acid (18:2 n-6) and arachidonic acid (20:4 n-6) are deficient, and an abnormal metabolite, 5,8,11-eicosatrienoic acid (20:3 n-9), is present in the plasma. Alterations in the triene/tetraene ratio are diagnostic (arachidonic acid/eicosatrienoic acid ratio >0.4 or linoleic acid/arachidonic acid ratio >2.3). The horny layer of the skin contains microscopic cracks, the barrier function of the skin is disturbed, and transepidermal water loss is increased. Topical application of linoleic acid, which is present in sunflower seed and safflower oils, may ameliorate the clinical and biochemical skin manifestations, although absorption can be inconsistent. Oral and/or parenteral therapy can also be considered. Appropriate nutrition should be provided, with the recommendation that 1–4% of total calories should be from linoleic acid.

KWASHIORKOR

Severe protein and essential amino acid deprivation in association with adequate caloric intake can lead to **kwashiorkor**, particularly at the time of weaning to a diet that consists primarily of corn, rice (or rice milk), or beans (see Chapter 64). Children can be fed such a restricted diet for cultural reasons or because of misdiagnosis on the part of the child's parents or healthcare providers of perceived food allergies. Diffuse, fine, reddish-brown scaling (enamel/flaky paint sign) is the classic cutaneous finding. In severe cases, erosions and linear fissures develop (Fig. 712.3). Nails are thin and soft, and hair is sparse, thin, and depigmented, sometimes displaying a "flag sign" consisting of alternating light and dark bands that reflect alternating periods of adequate and inadequate nutrition. The cutaneous manifestations may closely resemble those of acrodermatitis enteropathica; however, edema of the extremities and face ("moon facies") and a protuberant abdomen ("pot belly") are key features uniformly observed in kwashiorkor. The serum zinc level is often deficient; in some cases, skin lesions of kwashiorkor heal more rapidly when zinc is applied topically. See Chapter 64 for treatment recommendations.

CYSTIC FIBROSIS

See Chapter 454.

Protein-calorie malnutrition develops in 5–10% of patients with cystic fibrosis. Rash in infants with cystic fibrosis and malnutrition is rare but may appear by age 6 months. The initial eruption consists of scaling, erythematous papules and progresses in 1-3 months to extensive desquamating plaques. The rash is accentuated around the mouth and perineum and on the extremities (lower greater than upper). Alopecia may be present, but mucous membranes and nails are uninvolved.



Fig. 712.1 A, Periorificial eruption. B, Diaper rash. The skin findings are typical of zinc deficiency, in this case caused by low levels of zinc in breast milk. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001: Fig. 14.14.)*

PELLAGRA

See Chapter 67.3.

Pellagra manifests as edema, erythema, and burning of sun-exposed skin on the face, neck, and dorsal aspects of the hands, forearms, and feet. Lesions of pellagra may also be provoked by burns, pressure, friction, and inflammation. The eruption on the face frequently follows a butterfly distribution, and the dermatitis encircling the neck has been termed "Casal's necklace." Blisters and scales develop, and the skin increasingly becomes dry, rough, thickened, cracked, and hyperpigmented. Skin infections may be unusually severe. Pellagra develops in patients with insufficient dietary intake or malabsorption of niacin and/or tryptophan. Administration of isoniazid, 6-mercaptopurine, or 5-fluorouracil may also produce **pellagra**. **Hartnup disease** (see Chapter 105), caused by a pathogenic gene variant in *SLC6A19,* which encodes a neutral amino acid transporter, is a rare autosomal recessive disorder that presents in infancy with a "pellagra-like syndrome" as a result of decreased absorption of tryptophan. Nicotinamide supplementation and sun avoidance are the mainstays of therapy in pellagra. See Chapter 67.3 for treatment recommendations.



Fig. 712.3 Erosions and scaling in kwashiorkor.



Fig. 712.2 A, Psoriasiform lesion of zinc deficiency dermatitis on the ankles. B, Similar lesions on the elbows.

SCURVY (VITAMIN C OR ASCORBIC ACID DEFICIENCY)

See Chapter 68.

Scurvy manifests initially as follicular hyperkeratosis, or coiling of the hair on the upper arms, back, buttocks, and lower extremities (Fig. 712.4). Other features are perifollicular erythema and hemorrhage, particularly on the legs and advancing to involve large areas of hemorrhage; swollen, erythematous gums (Fig. 712.5); stomatitis; and subperiosteal hematomas. In children, the most common risk factors are behavioral or psychiatric disease resulting in poor nutrition. The best method of confirmation of a clinical diagnosis of scurvy is a trial of vitamin C supplementation. Treatment is with 100-200 mg/day of vitamin C supplementation orally or parenterally for up to 3 months.

VITAMIN A DEFICIENCY

See Chapter 66.



Fig. 712.4 Scurvy. *(Photo courtesy Albert Yan, MD.)*



Fig. 712.5 Clinical photograph showing inflamed marginal gingiva in scurvy. *(From Agarwal A, Shaharyar A, Kumar A, et al. Scurvy in pediatric age group – a disease often forgotten? J Clin Ortho Trauma. 2015;6:101–107, Fig. 1, p. 103.)*

Vitamin A deficiency manifests initially as impairment of visual adaptation to the dark. Cutaneous changes include xerosis and hyperkeratosis and hyperplasia of the epidermis, particularly the lining of hair follicles and sebaceous glands. In severe cases, desquamation may be prominent. See Chapter 66 for treatment recommendations.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Bone and Joint Disorders

PART XXX

Section 1

Orthopedic Problems

Chapter 713

Orthopedic Growth and Development

Brendan A. Williams and Lawrence Wells

There is a wide spectrum of normal orthopedic growth and development in children. Normal values are often defined as those that fall within 2 standard deviations of the mean value for the population, a range that accounts for approximately 95% of values. *Statistically normal* should not be confused with *ideal* in any given person's or parent's mind. Table 713.1 lists terms used to describe some common deviations from normal. Congenital anomalies can be categorized into production problems and packaging problems. Production problems include abnormalities caused by malformation, dysplasia, or disruption that will not spontaneously resolve (see Chapter 100). Packaging problems include deformations caused by mechanical causes, including in utero positioning and molding, and they usually resolve with time.

Table 713.1 Terminologies for Deviations

TERMINOLOGY	DESCRIPTION
Congenital	Anomaly that is apparent at birth
Deformation	A normally formed structure that is pushed out of shape by mechanical forces
Deformity	A body part altered in shape from normal, outside the normal range
Developmental	A deviation that occurs over time; one that might not be present or apparent at birth
Disruption	A structure undergoing normal development that stops developing or is destroyed or removed
Dysplasia	A tissue that is abnormal or wrongly constructed
Malformation	A structure that is wrongly built; failure of embryologic development or differentiation resulting in abnormal or missing structures

IN UTERO POSITIONING

In utero positioning produces temporary joint and muscle contractures and affects the torsional alignment of the long bones, particularly those of the lower extremities. Normal full-term newborns can have up to 20- to 30-degree hip and knee flexion contractures. These contractures tend to resolve by 4-6 months of age. The newborn hip externally rotates in extension up to 80-90 degrees and has limited internal rotation to approximately 0-10 degrees. The lower leg often has inward rotation (internal tibial torsion). The face may also be distorted; the spine and upper extremities are less affected by the in utero position. The effects of in utero positioning, therefore, are physiologic in origin and resolve by 3-4 months of age.

GROWTH AND DEVELOPMENT

Consideration of growth and development helps formulate treatment strategies designed to preserve or restore normal growth potential. Growth is subject to many variables, including genetics, nutrition, general health, endocrine status, mechanical forces, and physiologic age. Growth also varies between two anatomic regions and even between two bones of the same region.

Bone formation or ossification occurs in two different ways. In **endochondral ossification**, mesenchymal cells undergo chondrogenesis to form cartilage that matures to become bone. Most bones in the axial and appendicular skeleton are formed in this manner. In **intramembranous ossification**, osteoblasts are formed by direct differentiation of mesenchymal cells into bone. Flat bones of the skull and clavicle are examples of this pattern of bone formation.

CENTERS OF OSSIFICATION

At the beginning of the fetal period, the chondrocytes in the midshaft of the long bones form the **primary** centers of growth from which the bone eventually lengthens. **Secondary** centers of ossification appear in the chondroepiphysis and mostly appear postnatally. They direct the formation of bone throughout growth, particularly joint development. The ossification centers that are typically present at birth are the distal femur, proximal tibia, calcaneus, and talus (Fig. 713.1).

Anatomic Locations: Descriptive Terms

Typical **long bones** are divided into the physis, epiphysis, metaphysis, diaphysis, and perichondrial ring (Figs. 713.2 and 713.3). The physis is the growth plate located at the end of bone. The epiphysis is typically a secondary ossification center that contributes to joint development. The metaphysis is the bone adjacent to the physis on the side away from the joint. The diaphysis is the central part or shaft of long bones. The perichondrial ring contributes to appositional growth.

The articular cartilage also contributes to the growth of the epiphysis. The perichondrial ring, which surrounds the physes, and the perichondrium around the epiphyses and periosteum, which surrounds the metaphysis and diaphyseal regions of the bone, contribute to appositional or circumferential growth. Bones without physes (pelvis, scapulae, carpals, tarsals) grow by appositional bone growth from their surrounding perichondrium and periosteum. Other bones (metacarpals, metatarsals, phalanges, spine) grow by a combination of appositional and endochondral ossification.

Important Growth and Developmental Milestones

Table 713.2 summarizes some important musculoskeletal growth considerations.

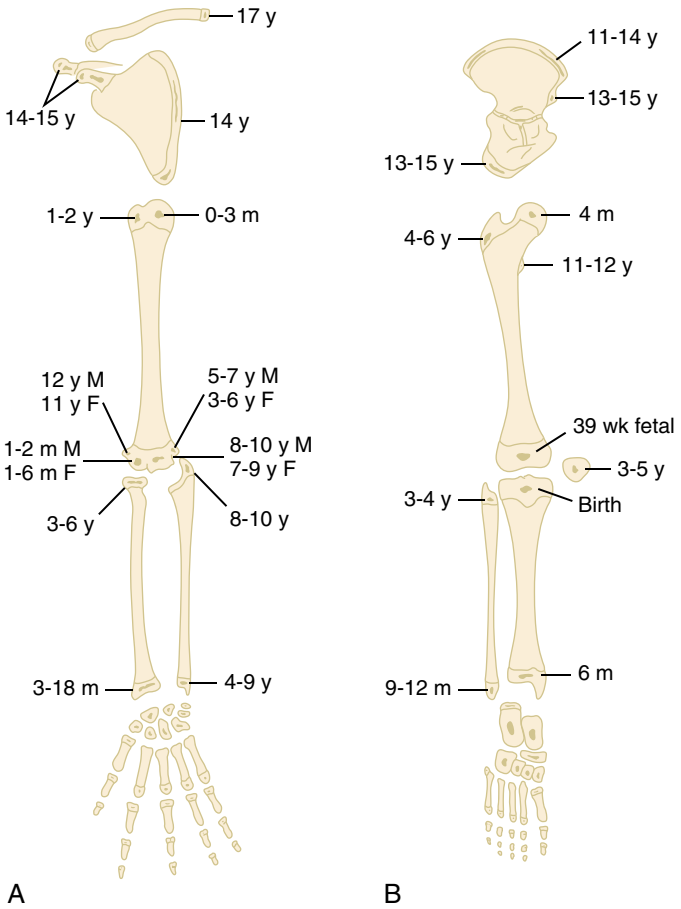

Fig. 713.1 Ages of onset of secondary (epiphyseal and apophyseal) ossification of the major bones of the upper (A) and lower (B) extremity. F, Female; M, male; m, month; wk, week; y, year. *(From Caffey J. Pediatric X-ray Diagnosis, 8th ed. Chicago: Year Book, 1985.)*

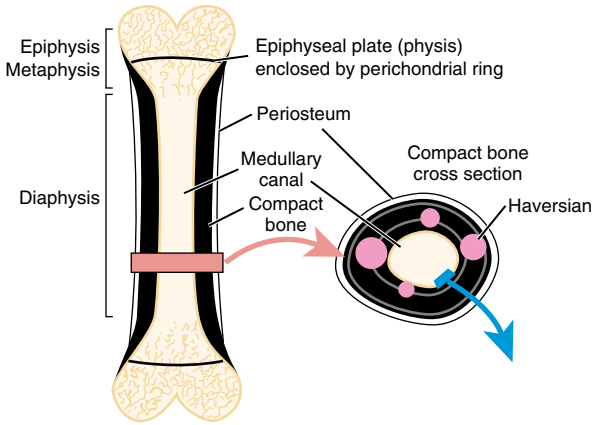

Fig. 713.2 Diagram showing typical long bone divisions.

Growth Patterns in Upper and Lower Extremities

The upper extremity grows longitudinally, primarily from physes of the proximal humeral physis and the distal radial and ulnar physes. In the lower extremity, most of the longitudinal growth occurs around the knee, in the distal femoral and the proximal tibial physes (Fig. 713.4).

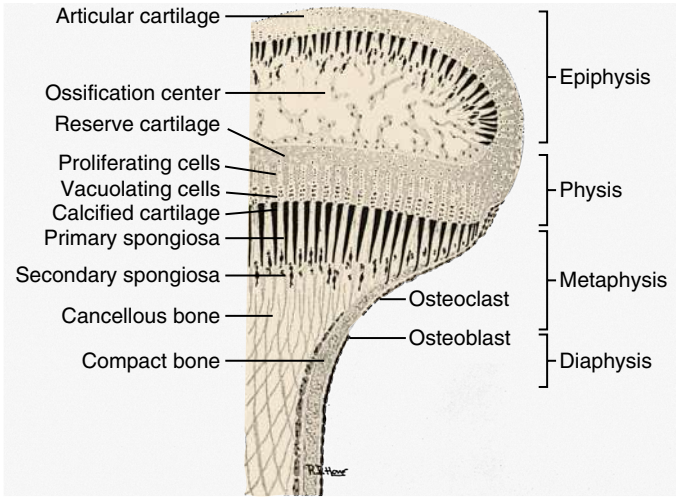

Fig. 713.3 Functional components of the growing end of a tubular bone and their anatomic substrate. *(From Kan JH, Strouse PJ. Embryology, anatomy, and normal findings. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier, 2019: Fig. 128.5)*

Table 713.2 Skeletal Growth Considerations

- Abnormal stature can be assessed as "proportionate" or "disproportionate" based on comparing the ratio of sitting height with sub-ischial height (lower limbs).
- Normally the arm span is almost equal to standing height.
- The head is disproportionately large at birth, and the ratio of head height to total height is approximately 1:4 at birth, which changes to 1:7.5 at skeletal maturity.
- Lower extremities account for approximately 15% of height at birth and 30% at skeletal maturity.
- The rate of height and growth increase is not constant and varies with growth spurts.
- By age 5, birth height usually doubles, and the child is approximately 60% of adult height. The child is approximately 80% of final height at 9 yr old. During puberty, the standing height increases by approximately 1 cm/mo.
- Bone age is more important than chronological age in determining future growth potential.

In the hip joint, the acetabulum forms with the convergence of three primary ossification centers: ischium, ilium, and pubis.

GAIT/FUNCTIONAL MATURATION

Functional mobility develops in infants in a predictable fashion (Table 713.3). Failure to achieve functional milestones is an indication for referral to a neurologist to determine if a central nervous system (CNS) problem exists. CNS maturation contributes significantly to the development of gait. In early ambulation (at 8-15 months), the child usually has a wide-based gait with hyperflexion of hips and knees, and initial contact with the heel. By the age of 2 years, the wide gait diminishes, reciprocal arm swing begins, and there is increased stride length and velocity. Adult fluid gait patterns usually start developing by 3 years and mature to an adult-like pattern by age 7 years.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

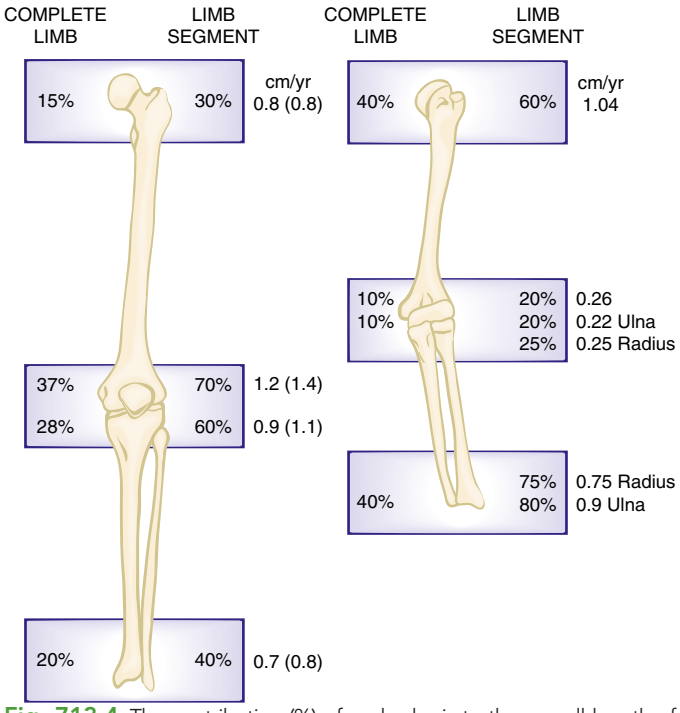

Fig. 713.4 The contribution (%) of each physis to the overall length of the extremities. *(From Morrissy R, Weinstein S, eds. Lovell and Winter's Pediatric Orthopedics, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)*

Table 713.3 Functional Milestones

MILESTONE	ACHIEVED BY
Head control	3-6 mo
Sitting	6-9 mo
Crawling	8 mo
Pulling to stand	8-12 mo
Ambulating	12-18 mo

Chapter 714

Orthopedic Evaluation of the Child

Kathleen J. Maguire and Lawrence Wells

A detailed history and thorough physical examination are critical to the evaluation of a child with an orthopedic problem. The child's family and acquaintances are important sources of information, especially in younger children and infants. Appropriate radiographic imaging and, occasionally, laboratory testing may be necessary to support the clinical diagnosis.

HISTORY

A comprehensive history should include details about the prenatal, perinatal, and postnatal periods. Prenatal history should include information about maternal health, including smoking history, use of prenatal vitamins, use of drugs or opiates, alcohol consumption, diabetes, immunization status (including receipt of rubella vaccine), and sexually transmitted infections. The child's prenatal and perinatal history should include information about the length of pregnancy, length of labor, type of labor (induced or spontaneous, Cesarean or vaginal delivery), presentation of fetus (cephalic or breech), birth trauma, evidence of any fetal distress at delivery, requirement for supplemental oxygen after the delivery, birth length and weight, Apgar score, muscle tone at birth, feeding history, and period of hospitalization. In older infants and young children, evaluation of developmental milestones for posture, locomotion, dexterity, social activities, and speech are important. Specific orthopedic questions should focus on joint, muscular, appendicular, or axial skeleton complaints. Information regarding pain or other symptoms in any of these areas should be elicited (Table 714.1). The family history can give clues to heritable disorders. It also can forecast expectations of the child's future development and allow appropriate interventions as necessary.

Table 714.1 Characterization of Pain and Presenting Symptom

Location: Whether pain is localized to a particular segment or involves a larger area.
Intensity: Usually on a pain scale of 1-10 to indicate severity.
Quality: Tumor pain is often unrelenting, progressive, and present during the night. Pain at night particularly suggests osteoid osteoma. Pain in inflammation and infection is usually continuous.
Onset: Was it acute and related to specific trauma or was it insidious? Acute pain and history of trauma are more commonly associated with fractures.
Duration: Whether transient, only lasting for minutes, or lasting for hours or days. Pain lasting for longer than 3-4 weeks suggests a serious underlying problem.
Progress: Whether static, increasing, or decreasing.
Radiation: Pain radiating to upper or lower extremities or complaints of numbness, tingling, or weakness require appropriate workup.
Aggravating factors: Relationship to any activities, movements, or particular positions.
Alleviating factors: Is the pain relieved by rest, heat/ice, and/or medication? Conditions such as spondylolysis, Scheuermann disease, inflammatory spondyloarthropathy, muscle pulls, or overuse are improved by bed rest.
Gait and posture: Disturbances associated with pain.

PHYSICAL EXAMINATION

The orthopedic physical examination includes a thorough examination of the musculoskeletal system along with a comprehensive neurologic examination. The examination may vary depending on the age of the child. The musculoskeletal examination includes inspection, palpation, and evaluation of motion, strength, stability, and gait. A basic neurologic examination includes sensory examination, motor function, and reflexes. The orthopedic physical examination requires basic knowledge of anatomy of joint range of motion, alignment, and stability. Many common musculoskeletal disorders can be diagnosed by the history and physical examination alone. One screening tool that has been useful in children is the pediatric gait, arms, legs, spine (pGALS) test, the components of which are shown in Figure 714.1.

Inspection

Initial examination of the child begins with inspection. The patient should be *comfortable with adequate exposure and well-lit surroundings* (lest some important physical findings be missed). Infants or young children may be examined on their parent's lap so that they feel more secure and are more likely to be cooperative. The clinician should use the guidelines listed in Table 714.2 during inspection.

Palpation

Palpation of the involved region should include assessment of local temperature and tenderness; assessment for a swelling or mass, lymphadenopathy, spasticity or contracture, and bone or joint deformity; and evaluation of anatomic axis of limb and of limb lengths.

Gait



A "Walk on your tip-toes." *Observe the child walking



B "Walk on your heels." *Observe the child walking

Arms



C "Put your hands out in front of you."



D "Turn your hands over and make a fist. Pinch your index finger and thumb together."



E "Touch the tips of your fingers with your thumb."



F Squeeze metacarpophalangeal joints



G "Put your hands together."*



H "Put your hands back to back."*



I "Reach up and touch the sky.* Look at the ceiling."



J "Put your hands behind your neck."

Legs



K Feel for effusion at the knee



L "Bend and then straighten your knee." (active movement of knees and examiner feels for crepitus)



M Passive flexion (90 degrees) with internal rotation of hip

Spine



N "Open your mouth and put 3 of your (child's own) fingers in your mouth."*



O Lateral flexion of cervical spine: "Try and touch your shoulder with your ear."



P Observe spine from behind



Q "Can you bend and touch your toes?" Observe curve of spine from side and behind

Fig. 714.1 The components of pediatric gait, arms, legs, spine (pGALS) screen, with illustration of movement. Screening questions: (1) Do you have any pain or stiffness in your joints, muscles, or back? (2) Do you have any difficulty getting yourself dressed without any help? (3) Do you have any difficulty going up and down stairs? *Additions and amendments to the original adult gait, arms, legs, spine screen. *(From Foster HE, Kay LJ, Friswell M, et al. Musculoskeletal screening examination [pGALS] for school-age children based on the adult GALS screen. Arthritis Rheum. 2006;55:709–716.)*

Table 714.2 Guidelines During Inspection of a Child with Musculoskeletal Problem

- It is important to inspect how the patient moves about in the room before and during the examination, as well as during various maneuvers. *Balance, posture,* and *gait pattern* should also be evaluated.
- *General examination* findings should include inspection for skin rashes, café-au-lait spots, hairy patches, dimples, cysts, tuft of hair, or evidence of spinal midline defects that can indicate serious underlying problems that need review.
- *General body habitus,* including signs of cachexia, pallor, and nutritional deficiencies, should be noted.
- *In the setting of trauma,* inspection of the injured limb should note deformity, swelling, erythema, and ecchymosis about a joint and/or long bone of the appendicular skeleton.
- Inspect the appendicular skeleton for evidence of *deformity.* Note if the deformity appears centered at a joint, bone, or within soft tissue. Attempt correction of the deformity to assess if it is correctible/flexible or fixed.
- Note any obvious spinal asymmetry, axial deformities, trunk decompensation, and evidence of muscle spasm or contractures. The *forward bending test* is valuable in assessing asymmetry and movement of the spine.
- Any *discrepancies in limb lengths,* as well as *muscle atrophy,* should be recorded.

Table 714.3 Beighton Grading for Hypermobility

DESCRIPTION	BILATERAL TESTING	SCORE (MAX. POINTS)
Passive dorsiflexion of the fifth metacarpophalangeal joint to >90 degrees	Yes	2
Passive hyperextension of the elbow >10 degrees	Yes	2
Passive hyperextension of the knee >10 degrees	Yes	2
Passive apposition of the thumb to the flexor side of the forearm, while shoulder is flexed 90 degrees, elbow is extended, and hand is pronated	Yes	2
Forward flexion of the trunk, with the knees straight, so that the palms of the hands rest easily on the floor	No	1
Total		9

From Smits-Engelsman, B, Klerks M, Kirby A. Beighton Score: a valid measure for generalized hypermobility in children. *J Pediatr.* 2011;158:119–123. Table 1.

Contractures are a loss of mobility of a joint from congenital or acquired causes and are caused by periarticular soft tissue fibrosis or involvement of muscles crossing the joint. Congenital contractures are common in **arthrogryposis** (see Chapter 723). Spasticity is an abnormal increase in tone associated with hyperreflexia and is common in cerebral palsy.

Deformity of the bone or joint is an abnormal fixed shape or position from congenital or acquired causes. It is important to assess the type of deformity, its location, and degree of deformity on clinical examination. It is also important to assess whether the deformity is fixed or can be passively or actively corrected, and whether there is any associated muscle spasm, local tenderness, or pain on motion. Classification of the deformity depends on the plane of deformity: **varus** (apex away from midline) or **valgus** (apex toward midline), or **flexion and extension** (in the sagittal plane). In the axial skeleton, especially the spine, deformity can be defined as scoliosis, kyphosis, hyperlordosis, and kyphoscoliosis (see Chapter 720).

Range of Motion

Active and passive joint motion should be assessed, recorded, and compared with the opposite side. Baseline flexibility or hypermobility beyond the range of normal motion should be noted. The **Beighton score** for hyperflexibility has been validated in children and serves to establish underlying laxity in the pediatric population (Table 714.3). Objective evaluation should be done with a goniometer and recorded.

Vocabulary for direction of joint motion is as follows:

Abduction: Away from the midline
Adduction: Toward the midline
Flexion: Movement of bending from the starting position
Extension: Movement from bending to the starting position
Hyperextension: Movement in extension beyond the starting position
Supination: Rotating the forearm to face the palm upward
Pronation: Rotating the forearm to face the palm downward
Inversion: Turning the hindfoot inward
Eversion: Turning the hindfoot outward
Plantar flexion: Pointing the toes away from the body (toward the floor)
Dorsiflexion: Pointing the toes toward the body (toward the ceiling)
Internal rotation: Turning inward toward the axis of the body
External rotation: Turning outward away from the axis of the body

Table 714.4 Normal Upper Extremity Motion in Children in Degrees

MOTION	VALUE (IN DEGREES)
Shoulder elevation	180
Shoulder internal rotation	50-60
Shoulder external rotation	40-45
Shoulder extension	45-55
Shoulder internal rotation at 90 degrees of abduction	70
Shoulder external rotation at 90 degrees of abduction	100
Elbow flexion	145-150
Elbow extension	4-7

Adapted from Payares-Lizano M, Pino C. Pediatric orthopedic examination. *Pediatr Clin North Am.* 2020;67(1):1–21. Table 5; with additional data from McKay MJ, Baldwin JN, Ferreira P, et al. Normative reference values for strength and flexibility of 1,000 children and adults. *Neurology.* 2017;88(1):36–43.

Normal ranges of motion for the appendicular skeleton are noted in Table 714.4 (upper extremity), Table 714.5 (hip), and Table 714.6 (lower extremity).

NEUROLOGIC EVALUATION

A careful neurologic evaluation is part of every pediatric musculoskeletal examination (see Chapter 630). The assessment should include evaluation of developmental milestones, muscle strength (Table 714.7), sensory assessment, muscle tone, and deep tendon reflexes. The neurologic evaluation should also assess the spine and identify any deformity, such as scoliosis and kyphosis, or abnormal spinal mobility. The hips and feet should also be examined specifically, along with torsional

Table 714.5 Normal Hip Range of Motion in Children in Degrees

MOTION	AGE 2-5 (MALE/FEMALE)	AGE 6-10 (MALE/FEMALE)	AGE 11-17 (MALE/FEMALE)
Abduction	51/53	43/51	34/44
Adduction	17/18	15/18	14/17
Flexion	118/121	118/122	113/120
Extension	21/21	19/21	15/22
Internal rotation in flexion	45/47	40/41	35/35
External rotation in flexion	51/49	44/48	40/46
Internal rotation in extension	47/51	42/47	36/42
External rotation in extension	47/50	42/45	39/44

From Sankar WN, Laird CT, Baldwin KD. Hip range of motion in children: what is the norm? *J Pediatr Orthop*. 2012;32(4):399–405. Table 1.

Table 714.6 Normal Lower Extremity Motion in Children in Degrees

MOTION	AGE 3-9 (MALE/FEMALE)	AGE 10-19 (MALE/FEMALE)
Knee flexion	145/144	140/142
Knee extension	4/4	2/2
Ankle dorsiflexion	33/31	32/31
Ankle plantarflexion	63/63	58/63

Adapted from McKay MJ, Baldwin JN, Ferreira P, et al. Normative reference values for strength and flexibility of 1,000 children and adults. *Neurology*. 2017;88(1):36–43. Table e-4.

Table 714.7 Medical Research Council (MRC) Scale for Muscle Strength

MUSCLE GRADE	DESCRIPTION
Grade 5	Normal
Grade 4	Movement against gravity and resistance
Grade 3	Movement against gravity over (almost) full range
Grade 2	Movement of the limb with gravity eliminated
Grade 1	Visible contraction without movement of the limb
Grade 0	No visible contraction

Data from Medical Research Council.

Table 714.8 Ashworth Scale of Spasticity

0	No increase in muscle tone
1	Slight increase in muscle tone, usually a catch or minimal resistance at end range of motion
2	Moderate tone throughout range of motion
3	Considerable increase in tone; passive range of motion difficult
4	Rigid in flexion or extension

Table 714.9 Clinical Scale of Extremity Motor Control

GRADE	DEFINITION
1	Hypotonic, no volitional motion
2	Hypertonic, no volitional motion
3	Mass flexion or extension in response to a stimulus
4	Patient can initiate movement but results in mass flexion or extension
5	Slow volitional movement; stress or rapid movement results in mass action
6	Volitional control of specific joints/muscles

abnormalities of the lower extremity, which are vastly more common in the neurologically involved population. Specific peripheral nerve examinations may be necessary.

When the nervous system matures, the developing cerebral cortex normally inhibits rudimentary reflexes that are often present at birth (see Chapter 630). Therefore, persistence of these reflexes can indicate neurologic abnormality. The most commonly performed deep tendon reflex tests include biceps, triceps, quadriceps, and gastrocnemius and soleus tendons. Upper motor neuron signs should also be noted. The **Ashworth scale** is often used to grade spasticity (Table 714.8). Upper-extremity motor control is often graded, and these grades are useful both diagnostically and prognostically. Passive range of motion should be assessed to determine extremity motor control (Table 714.9). Localized or diffuse weakness must be determined and documented. A thorough assessment and grading of muscle strength is mandatory in all cases of neuromuscular disorders (see Table 714.7).

Gait Assessment

Children typically begin walking between 8 and 16 months of age. Early ambulation is characterized by short stride length, a fast cadence, and slow velocity with a wide-based stance. The gait cycle is a single sequence of functions that starts with heel strike, foot flat, heel off, toe off, and swing. These events describe one gait cycle and include two phases: stance and swing. The stance phase is the period during which the foot is in contact with the ground. The swing phase is the portion of the gait cycle during which a limb is being advanced forward without ground contact. Normal gait is a symmetric and smooth process. Deviation from the norm indicates potential abnormality and should trigger investigation.

Neurologic maturation is necessary for the development of gait and the normal progression of developmental milestones. A child's

Table 714.10 Causes of Gait Disturbances

MECHANICAL
Acute injuries (accidental or nonaccidental)
Overuse conditions (mainly sports-related)
Dysplastic lesions
Limb length discrepancy
OSSEOUS
Legg-Calvé-Perthes disease
Osteochondritis dissecans of knee and talus
Slipped capital femoral epiphysis
Osteomyelitis
Spondylodiscitis
Osteoid osteoma or other primary bone tumor
ARTICULAR
Developmental hip dysplasia
Septic arthritis
Transient synovitis
Rheumatic disease (juvenile idiopathic arthritis, systemic lupus erythematosus)
Hemophilia-related hemorrhage
Ankylosis of a joint
NEUROLOGIC
Guillain-Barré syndrome and other peripheral neuropathies
Intoxication
Cerebellar ataxia
Brain tumor
Lesion occupying spinal cord space
Posterior column spinal cord disorders
Myopathy
Hemiplegia
Complex regional pain syndrome
Cerebral palsy
HEMATOLOGIC/ONCOLOGIC
Sickle cell pain crisis
Leukemia, lymphoma
Metastatic tumor
Langerhans cell histiocytosis
OTHER
Soft tissue infection
Myositis
Fasciitis
Bursitis
Kawasaki disease
Conversion disorder
Gaucher disease
Phlebitis
Scurvy
Rickets
Peritonitis

From Kliegman RM, Lye PS, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*. Philadelphia: Elsevier, 2018: Table 34.1, p. 615.

Table 714.11 Differential Diagnosis of Limping in Children by Age

AGE GROUP	DIAGNOSTIC CONSIDERATIONS
Early walker: 1-3 yr	**PAINFUL LIMP** Septic arthritis and osteomyelitis Transient synovitis Fracture Occult trauma (toddler's fracture) Intervertebral diskitis Malignancy Abuse (nonaccidental trauma) Rheumatologic disorders (e.g., juvenile idiopathic arthritis) **PAINLESS LIMP** Developmental dysplasia of the hip Neuromuscular disorder Polio Cerebral palsy Lower extremity length inequality
Child: 3-10 yr	**PAINFUL LIMP** Septic arthritis, osteomyelitis, myositis Transient synovitis Trauma, fracture Rheumatologic disorders Spondylodiscitis Malignancy **PAINLESS LIMP** Developmental dysplasia of the hip Legg-Calvé-Perthes disease Lower extremity length inequality Neuromuscular disorder (e.g., muscular dystrophy) Polio Cerebral palsy
Adolescent: 11 yr to maturity	**PAINFUL LIMP** Septic arthritis, osteomyelitis, myositis Trauma (including overuse injuries and fractures) Rheumatologic disorder Slipped capital femoral epiphysis (acute, unstable) Malignancy Osteochondritis dissecans **PAINLESS LIMP** Slipped capital femoral epiphysis (chronic, stable) Developmental dysplasia of the hip (acetabular dysplasia) Lower extremity length inequality Neuromuscular disorder

Modified from Marcdante K, Kliegman R, eds. *Nelson Essentials of Pediatrics*, 7th ed. Philadelphia: Saunders, 2015.

gait changes with neurologic maturation. Toddlers normally walk with greater hip and knee flexion, flexed arms, and a wider base of gait than older children. As the neurologic system continues to develop in the cephalocaudal direction, the efficiency and smoothness of gait increase. The gait characteristics of a 7-year-old child are similar to those of an adult. When the neurologic system is abnormal (e.g., cerebral palsy), gait can be disturbed, exhibiting pathologic reflexes and abnormal movements.

Deviations from normal gait occur in a variety of orthopedic conditions. Disorders that result in muscle weakness (e.g., spina bifida, muscular dystrophy), spasticity (e.g., cerebral palsy), or contractures (e.g., arthrogryposis) lead to abnormalities in gait. Other causes of gait disturbances include limp, pain, torsional variations (in-toeing and out-toeing), toe walking, joint abnormalities, and leg-length discrepancy (Tables 714.10 and 714.11).

LIMPING

A thorough history and clinical examination are the first steps toward early identification of the underlying problem causing a limp. Limping can be considered either *painful* ***(antalgic)*** or *painless*, with the differential diagnosis ranging from benign to serious causes (e.g., septic hip, tumor). In a painful gait, the stance phase is shortened as the child decreases the time spent on the painful extremity. In a painless gait, which indicates underlying proximal muscle weakness or hip instability, the stance phase is equal between the involved and uninvolved sides, but the child leans or shifts the center of gravity over the involved extremity for balance. A bilateral disorder produces a waddling gait. **Trendelenburg gait** (i.e., trunk lists to the affected side with each step) is produced by weak abnormal hip abductors. When the patient stands on one foot, a **Trendelenburg sign** (i.e., sagging rather than rising of

the unsupported buttock) can often be elicited when abductors are weak.

Disorders most commonly responsible for an abnormal gait generally vary based on the age of the patient. The differential diagnosis of limping varies based on age group (see Table 714.11) or mechanism. Neurologic disorders, especially spinal cord, muscle, or peripheral nerve disorders, can also produce limping and difficulty walking. Antalgic gait is predominantly a result of trauma, infection, or pathologic fracture. Trendelenburg gait is generally caused by congenital, developmental, or muscular disorders. In some cases, limping also may be caused by nonskeletal causes, such as testicular torsion, inguinal hernia, and appendicitis.

BACK PAIN

Children frequently have a specific skeletal pathology as the cause of back pain. The most common causes of back pain in children are trauma, spondylolysis, spondylolisthesis, and infection (see Chapter 720.5). Tumor and tumor-like lesions that cause back pain in children are likely to be missed unless a thorough clinical assessment and adequate workup are performed when required. Nonorthopedic causes of back pain include urinary tract infections, nephrolithiasis, and pneumonia.

RADIOGRAPHIC ASSESSMENT

Plain radiographs are the first step in evaluation of most musculoskeletal disorders. Advanced imaging includes MRI, nuclear bone scans, ultrasonography, CT, and positron emission tomography. Rapid short tau inversion recovery (STIR) MRI is a valuable screening test if a specific location is not well defined.

Plain Radiographs

Routine radiographs consist of anteroposterior and lateral views of the involved area with inclusion of one joint above and below the site of symptoms. Comparison views of the opposite side, if uninvolved, may be helpful in difficult situations but are not always necessary. Specialized views for each joint, such as oblique views, may offer more specific and tailored imaging for an individual fracture or other condition. It is important for the clinician to be aware of normal radiographic variants of the immature skeleton, including when to expect to see development and ultimately closure of growth centers about the joints. Several synchondroses may be mistaken for fractures. A patient with "normal" plain radiographic appearance but having persistent pain or symptoms might need to be evaluated further with additional imaging studies.

Ultrasonography

Ultrasonography is useful to evaluate suspected fluid-filled lesions such as popliteal cysts and hip joint effusions. Major indications for ultrasonography are fetal studies of the extremities and spine (including detection of congenital anomalies like spondylocostal dysostosis or osteogenesis imperfecta), developmental dysplasia of the hip in children 6 weeks to 6 months of age, joint effusions, occult neonatal spinal dysraphism, foreign bodies in soft tissues, and popliteal cysts of the knee.

Magnetic Resonance Imaging

MRI is the imaging modality of choice for defining the exact anatomic extent of most musculoskeletal lesions (particularly if the structure is soft tissue). MRI avoids ionizing radiation and does not cause any known harmful effects. It produces excellent anatomic images of the musculoskeletal system, including the soft tissue, bone marrow cavity, spinal cord, and brain. It is especially useful for defining the extent of soft tissue lesions, infections, and injuries. Tissue planes are well delineated, allowing more accurate assessment of tumor invasion into adjacent structures. Cartilage structures can be visualized and differentiated (e.g., articular cartilage of the knee can be distinguished from the fibrocartilage of the meniscus). MRI is also helpful in visualizing unossified joints in the pediatric population, including the shoulders, elbows, and hips of young infants.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) has largely replaced routine angiography in the preoperative assessment of vascular lesions and bone tumors. MRA provides good visualization of peripheral vascular branches and tumor neovascularity in patients with primary bone tumors.

Computed Tomography

CT has enhanced the evaluation of multiple musculoskeletal disorders. Coronal, sagittal, and axial imaging is possible with CT, including three-dimensional reconstructions that can be beneficial in evaluating complex lesions of the axial and appendicular skeleton. It allows for visualization of the detailed bone anatomy and the relationship of bones to contiguous structures. CT is useful to readily evaluate tarsal coalition, accessory navicular bone, infection, growth plate arrest, osteoid osteoma, pseudoarthrosis, femoroacetabular impingement, complex fracture patterns (periarticular and intra-articular), bone and soft tissue tumors, spondylolysis, and spondylolisthesis. CT is superior to MRI for assessing bone involvement and cortical destruction (even subtle changes), including calcification or ossification and fracture (particularly if displacement of an articular fracture is suspected).

Nuclear Medicine Imaging

A bone scan displays physiologic information rather than pure anatomy and relies on the emission of energy from the nucleotide injected into the patient. Indications include early septic arthritis, osteomyelitis, avascular necrosis, tumors (osteoid osteoma), metastatic lesions, occult and stress fractures, and cases of nonaccidental trauma.

Total-body radionuclide scan (technetium-99) is useful to identify bony lesions, inflammatory tumors, and stress fractures. Tumor vascularity can also be inferred from the flow phase and the blood pool images. Gallium or indium scans have high sensitivity for local infections. Thallium-201 chloride scintiscans have >90% sensitivity and 80–90% accuracy in detecting malignant bone or soft tissue tumors. *MRI has supplanted nuclear medicine imaging in many circumstances.*

LABORATORY STUDIES

Laboratory tests are occasionally necessary in the evaluation of a child with musculoskeletal disorder. These may include a complete blood cell count; erythrocyte sedimentation rate; C-reactive protein assay; Lyme titers; and blood, wound, joint, periosteum, or bone cultures for infectious conditions such as septic arthritis or osteomyelitis. Rheumatoid factor, antinuclear antibodies, and human leukocyte antigen B27 may be necessary for children with suspected rheumatologic disorders. Creatine kinase, aldolase, aspartate aminotransferase, and dystrophin testing are indicated in children with suspected disorders of striated muscle, such as Duchenne muscular dystrophy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 715

The Foot and Toes

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Abnormalities affecting the osseous and articular structures of the foot may be congenital, developmental, neuromuscular, inflammatory, or acquired. Problems with the foot and/or toes may be associated with a host of connective tissue diseases and syndromes, and overuse syndromes are commonly observed in young athletes. Symptoms may include pain and difficulty with shoe wear, and cosmetic concerns are common. The foot may be divided into the **forefoot** (toes and metatarsals), the **midfoot** (cuneiforms, navicular, cuboid), and the **hindfoot** (talus and calcaneus). Although the tibiotalar joint (ankle) provides plantarflexion and dorsiflexion, the subtalar joint (between the talus and calcaneus) is oriented obliquely, providing inversion and eversion. Inversion represents a combination of plantarflexion and varus, whereas eversion involves dorsiflexion and valgus. The subtalar joint is especially important for walking on uneven surfaces. Inversion of the transverse tarsal (Chopart) joint locks the midfoot to provide a stable base on which to perform toe-off during the gait cycle. Eversion of the transverse tarsal joint unlocks the **hindfoot** to provide accommodation during heel strike of the of the gait cycle. The talonavicular and calcaneocuboid joints connect the midfoot with the hindfoot.

715.1 Metatarsus Adductus

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Metatarsus adductus involves adduction of the forefoot relative to the hindfoot. When the forefoot is adducted, and sometimes in supination, the deformity is termed *metatarsus varus* (Fig. 715.1). The disorder is common in newborns, most frequently caused by intrauterine molding (deformation); the deformity is bilateral in 50% of cases. A careful hip and neck examination must always be performed to look for other abnormalities associated with intrauterine positioning.

CLINICAL MANIFESTATIONS

The forefoot is adducted (occasionally supinated), whereas the midfoot and hindfoot are normal. The lateral border of the foot is convex, and the base of the fifth metatarsal appears prominent. Range of motion at the ankle and subtalar joints is normal. Both the magnitude and the degree of flexibility should be documented. When the normal foot is viewed from the plantar surface, a line through the midpoint of (and parallel to) the heel should extend through the second toe. In metatarsus adductus, the line extends laterally to the second toe. Flexibility is assessed by stabilizing the hindfoot and midfoot in a neutral position with one hand and applying pressure over the first metatarsal head with the other. Correction with little pressure is indicative of a more flexible deformity. In the walking child with an uncorrected metatarsus adductus deformity, an in-toe gait and abnormal shoe wear may occur. A subset of patients will also have a dynamic adduction deformity of the great toe (hallux varus), which is often most noticeable during ambulation. This usually improves spontaneously and does not require treatment.

RADIOGRAPHIC EVALUATION

Radiographs are not performed routinely in infants with metatarsus adductus. Older children with residual deformity should have anteroposterior (AP) and lateral weight-bearing or simulated weight-bearing radiographs. The AP radiographs demonstrate adduction of the metatarsals at the tarsometatarsal articulation and an increased intermetatarsal angle between the first and second metatarsals.

TREATMENT

The treatment of metatarsus adductus is based on the rigidity of the deformity, but most children respond to nonoperative treatment. Deformities that are flexible and overcorrect into abduction with passive manipulation may be observed. Those feet that correct just to a neutral position may benefit from stretching exercises, which can be demonstrated to the parents in the office. In a walking child, the parents can try reversing the shoes as well. If this is not effective, reverse-last shoes can be prescribed to maintain the abducted position of foot. These are worn full-time (22 hours/day), and the condition is reevaluated in 4-6 months. The position of the heel bisector can be followed over the course of observation or treatment to monitor for improvement. If improvement occurs, treatment can be continued for an additional year or more. If there is no improvement, serial plaster casts should be considered. When stretching a foot with metatarsus adductus, care should be taken to maintain the hindfoot in neutral to slight varus alignment to avoid creating hindfoot valgus. Feet that cannot be corrected to a neutral position may benefit from initial serial casting; the best results are obtained when treatment is started before 8 months of age. In addition to stretching the soft tissues, the goal is to alter physeal growth and stimulate remodeling, resulting in permanent correction. Once flexibility and alignment are restored, orthoses, corrective shoes, or wearing shoes on opposite feet is generally recommended for 6-12 months. A dynamic hallux varus usually improves spontaneously, and no active treatment is required.

Surgical treatment may be considered in the small subset of patients with symptomatic residual deformities who have not responded to treatment. Surgery is generally delayed until children are 4-6 years of age. Cosmesis is often a concern, and pain and/or the inability to wear certain types of shoes may occasionally lead patients to consider surgery.

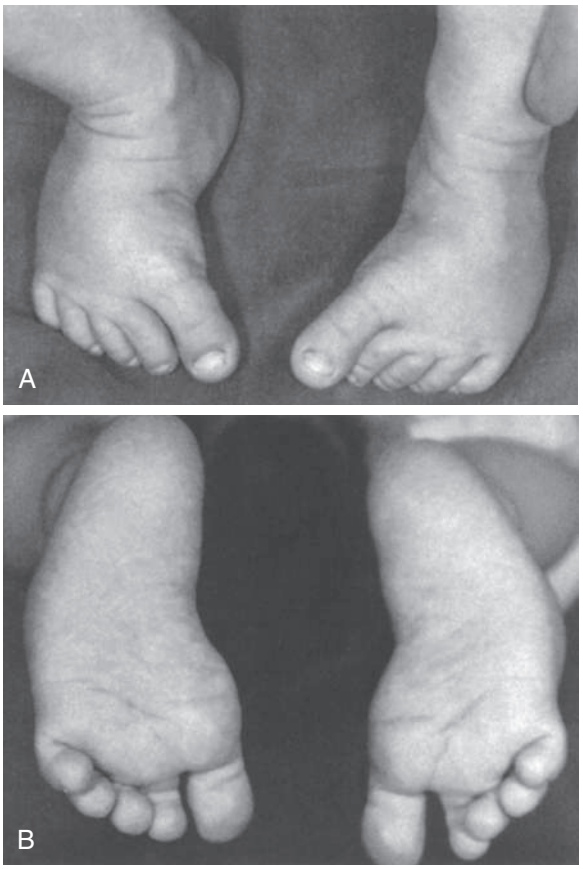

Fig. 715.1 Bilateral mild metatarsus adductus. **A,** Dorsal view showing medial deviation of all the metatarsals. **B,** Plantar view showing the "bean-shaped" foot. This type of foot is easily corrected with serial casting. *(From Ricco AI. Disorders of the foot. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 19-19.)*

Options for surgical treatment include either soft tissue releases or osteotomies depending on age, anatomy, deformity flexibility, and other patient-specific factors. An osteotomy (midfoot or multiple metatarsals) is most likely to result in permanent restoration of alignment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.2 Calcaneovalgus Feet

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

A common finding in the newborn, the calcaneovalgus foot occurs secondary to in utero positioning (deformation). Excessive dorsiflexion and eversion are observed in the hindfoot, and the forefoot may be abducted. There may be an associated external tibial torsion (see Chapter 716).

CLINICAL MANIFESTATIONS

The infant typically presents with the foot dorsiflexed and everted, and occasionally the dorsum of the foot or toes will be in contact with the anterolateral surface of the lower leg (Fig. 715.2). Dimpling may be indicative of reduced subcutaneous fat at the dorsolateral ankle. Plantarflexion and inversion are often restricted. A careful hip examination should be performed, and if there is any concern, hip ultrasonography should be considered. When comparing risk for developmental dysplasia of the hip (DDH) with other congenital foot deformities, congenital calcaneovalgus has the highest association, with 6.1–19.4% of patients having coexisting DDH. The calcaneovalgus foot may be confused with a congenital vertical talus and may rarely be associated with a posteromedial bow of the tibia. A calcaneovalgus deformity also may be seen in older patients, typically those with a neuromuscular imbalance involving weakness or paralysis of the gastrocsoleus muscle (e.g., polio, myelomeningocele).

RADIOGRAPHIC EVALUATION

Radiographs are usually not required but should be ordered if the deformity fails to correct spontaneously or with early treatment. AP and lateral radiographs along with a lateral radiograph of the foot in maximal plantarflexion may help distinguish calcaneovalgus from a congenital vertical talus or congenital oblique talus. Evaluation of the position of the talus in relation to the navicular in both the lateral and maximally plantarflexed lateral view can help to diagnose congenital vertical or oblique talus. If a posteromedial bow of the tibia is suspected, AP and lateral radiographs of the tibia and fibula are necessary. In posteromedial bowing of the tibia, the deformity is located in the tibia with the apex of deformity positioned posterior and medial. All three conditions may be confused clinically with calcaneovalgus feet.

TREATMENT

Mild cases of calcaneovalgus foot, in which full passive range of motion is present at birth, require no active treatment. These usually resolve within the first few weeks of life. A gentle stretching program focusing on plantarflexion and inversion is recommended for cases with some restriction in motion. For cases with a greater restriction in mobility, serial casts may be considered to restore motion and alignment, although casting is rarely required in the treatment of calcaneovalgus feet. Unresponsive cases should be evaluated for associated neuromuscular or other etiologies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.3 Talipes Equinovarus (Clubfoot)

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Clubfoot or congenital talipes equinovarus (CTEV) is the term used to describe a deformity involving malalignment of the calcaneotalar-navicular complex. Components of this deformity may be best understood using the mnemonic **CAVE** (cavus:midfoot, adductus:forefoot, varus:heel, equinus:hindfoot). Although this is predominantly a hindfoot deformity, it involves plantarflexion (cavus) of the first ray (the first metatarsal and first cuneiform) and adduction of the forefoot/midfoot on the hindfoot. The hindfoot is in varus and equinus. The clubfoot deformity may be positional, congenital, associated with a variety of underlying diagnoses (neuromuscular or syndromic), or a focal dysplasia of musculoskeletal tissue distal to the knee.

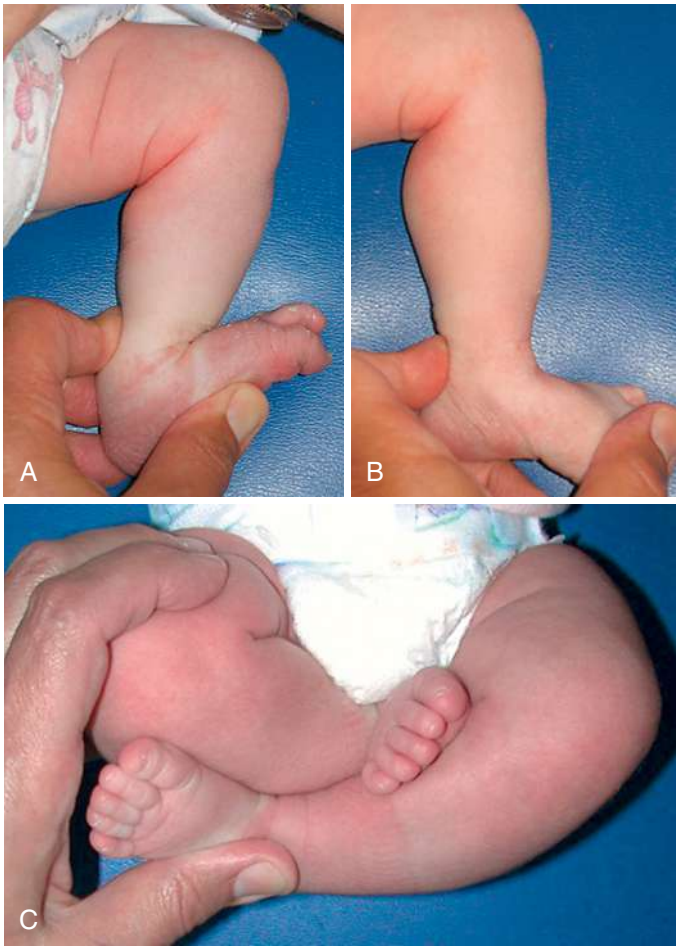

Fig. 715.2 Clinical picture of calcaneovalgus foot (A) that is passively correctable (B) and is due to intrauterine positioning (C).

The **positional (or postural) clubfoot** is a normal foot that has been held in a deformed position in utero and is found to be flexible on examination in the newborn nursery. The nonpositional **congenital clubfoot** can either be idiopathic or syndromic. There is a spectrum of severity, but clubfoot associated with neuromuscular diagnoses or syndromes is typically rigid and more difficult to treat. Clubfoot is also extremely common in patients with myelodysplasia, arthrogryposis, and chromosomal syndromes such as trisomy 18 and chromosome 22q11 deletion syndrome (see Chapter 99).

Congenital clubfoot is seen in approximately 1-2 in 1,000 births and most likely results from a complex multifactorial polygenic inheritance. The risk is ~25% when both a parent and one sibling have clubfeet. It occurs more commonly in males (2:1) and is bilateral in 50% of cases. The pathoanatomy involves both abnormal tarsal morphology (plantar and medial deviation of the head and neck of the talus) and abnormal relationships between the tarsal bones in all three planes, as well as associated contracture of the soft tissues on the plantar and medial aspects of the foot.

CLINICAL MANIFESTATIONS

A complete physical examination should be performed to rule out coexisting musculoskeletal and neuromuscular problems. The spine should be inspected for signs of occult dysraphism. Examination of the infant

clubfoot demonstrates forefoot cavus and adductus and hindfoot varus and equinus (Fig. 715.3). The degree of flexibility varies, and all patients will exhibit calf atrophy. Internal tibial torsion, foot length shortening, and leg-length discrepancy (shortening of the ipsilateral extremity) will be observed in a subset of cases. Although classically not associated with DDH (see Chapter 719.1), there is a higher association of CTEV and DDH than in the general population.

RADIOGRAPHIC EVALUATION

AP and lateral radiographs are not recommended for idiopathic clubfoot. For arthrogrypotic or syndromic feet, x-rays may be helpful but must be performed with the foot held in the maximally corrected position. The lateral x-ray should be a trans-malleolar view. Multiple radiographic measurements can be made to describe malalignment between the tarsal bones. The navicular bone does not ossify until 3-6 years of age, so the focus of radiographic interpretation is the relationship between segments of the foot, forefoot to hindfoot. A common radiographic finding is "parallelism" between lines drawn through the axis of the talus and the calcaneus on the lateral radiograph, indicating hindfoot varus. X-ray may be particularly useful for older children with persistent or recurrent deformities that are difficult to assess.

TREATMENT

Nonoperative treatment is initiated in all infants and should be started as soon as possible following birth. Techniques have included taping and strapping, manipulation and serial casting, and functional treatment. Historically, a significant percentage of patients treated by manipulation and casting required a surgical release, which was usually performed between 3 and 12 months of age. Although many feet remain well aligned after surgical releases, a significant percentage of patients require additional surgery for recurrent or residual deformities, and stiffness remains a concern at long-term follow-up. While pain is uncommon in childhood and adolescence, symptoms may appear during adulthood. These concerns have led to considerable interest in less-invasive methods for treating the deformity.

The Ponseti method of clubfoot treatment, which is the standard of initial treatment, involves a specific technique for manipulation and serial casting, and may be best described as minimally invasive rather than nonoperative (Fig. 715.4). The order of correction follows the mnemonic CAVE. Weekly cast changes are performed; 5-10 casts are typically required. The most difficult deformity to correct is the hindfoot equinus, and ~90% of patients will require a percutaneous tenotomy of the heel cord under local anesthesia as an outpatient. Following the tenotomy, a long leg cast with the knee flexed 90 degrees and the foot in maximal abduction (up to 70 degrees) with 0-10 degrees of dorsiflexion is worn for 3-4 weeks. The patient then begins a bracing program. An abduction brace (bars and shoes) is worn 22 hours a day for 3 months and then at nighttime until the age of 3-5 years. A small subset of patients (up to 20%) with recurrent, dynamic supination deformity will require transfer of the tibialis anterior tendon to the lateral cuneiform. The results of the Ponseti method are excellent at up to 40 years of follow-up. Despite casting, children do not have much dysfunction or delay in achieving normal motor milestones. Compliance with the bracing program is essential as recurrence is common if the brace is not worn as recommended. Minimally invasive methods are most successful when treatment is begun at birth or during the first few months of life, and with good compliance with postmanipulation bracing.

Aggressive surgical realignment has a definite role in the management of clubfeet, especially in the minority of *congenital* clubfeet that have failed nonoperative or minimally invasive methods, and for the neuromuscular and rigid syndromic clubfeet. In such cases, minimally invasive methods such as the Ponseti technique may potentially be of value in decreasing the need for surgery or the magnitude of surgery required. Common surgical approaches include a release of the involved joints (realignment of the tarsal bones), a lengthening of the shortened posteromedial musculotendinous units, and usually pinning of the foot in the corrected position. The "a la carte" method allows the surgeon to apply the principles of deformity correction to be tailored to the unique characteristics of each deformity. For older children with untreated clubfeet or those in whom a recurrence or residual deformity is observed, bony procedures (osteotomies) may be required in addition to soft tissue surgery. Triple arthrodesis is reserved as salvage for painful, deformed feet in adolescents and adults.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.4 Congenital Vertical Talus

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Congenital vertical talus is an uncommon foot deformity in which the midfoot is dorsally dislocated on the hindfoot and the ankle is in fixed equinus. A variant form, called oblique talus, refers to subluxation of

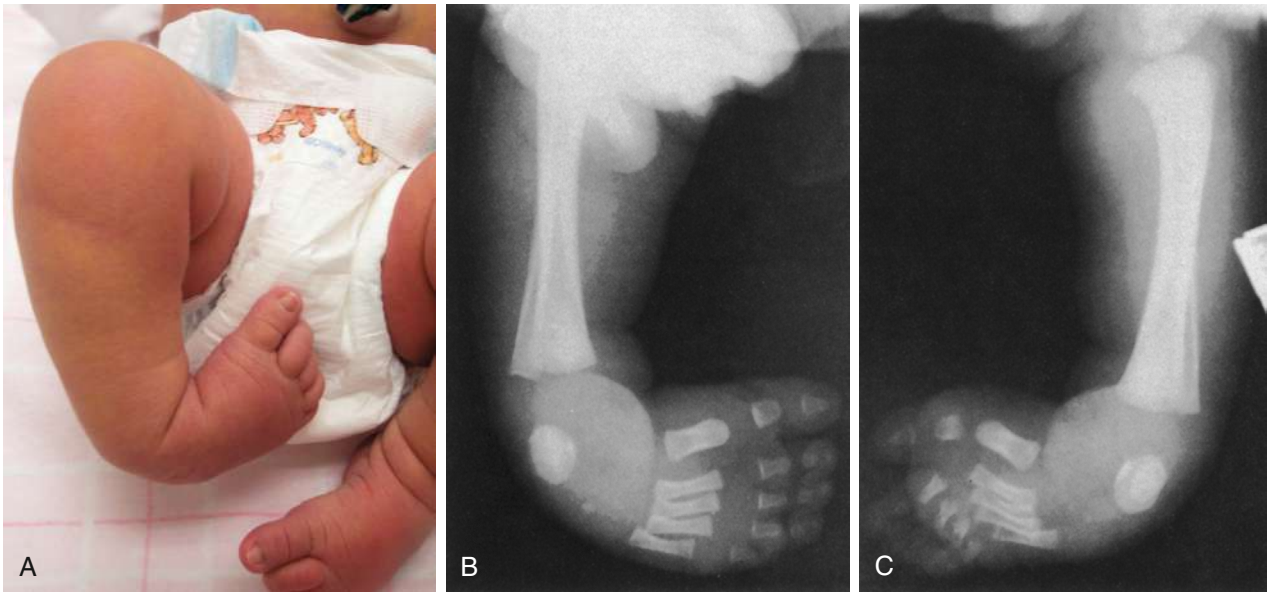

Fig. 715.3 Talipes equinovarus in a newborn. **A**, Clinical appearance of an untreated clubfoot. **B** and **C**, Initial radiographic appearance of bilateral untreated clubfeet. *(From Ricco AI. Disorders of the foot. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 19-42.)*



Fig. 715.4 Ponseti method of clubfoot treatment. Ponseti casts show *serial* correction of the patient (**A-F**). The last cast (**E** and **F**) was applied after percutaneous heel cord tenotomy. *(From Ricco AI. Disorders of the foot. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 19.47, p. 717.)*

the talonavicular joint and is usually neuromuscular in origin. There is nearly an even split between idiopathic cases and cases with an underlying neuromuscular condition or a syndrome. Neurologic causes include myelodysplasia, tethered cord, and sacral agenesis. Other associated conditions include arthrogryposis, Larsen syndrome, multiple pterygium syndrome, and chromosomal abnormalities (trisomy 13-15, 19; see Chapter 99). Depending on the age at diagnosis, the differential diagnosis may include a calcaneovalgus foot, oblique talus (talonavicular joint reduces passively), flexible flatfoot with a tight Achilles tendon, and tarsal coalition.

CLINICAL MANIFESTATIONS

Congenital vertical talus has also been described as a **rocker-bottom foot** (Fig. 715.5). The plantar surface of the foot is convex, and the talar head is prominent along the medial border of the midfoot. The forefoot is dorsiflexed (dorsally dislocated) and abducted relative to the hindfoot, and the hindfoot is in equinus and valgus. There is an associated contracture of the anterolateral (toe extensors) and the posterior (Achilles tendon, peroneals) soft tissues, which may overpower a weakened posterior tibialis and toe flexors. The deformity is typically rigid in vertical talus and flexible in oblique talus. Physical examination is required to identify any coexisting neurologic and/or musculoskeletal abnormalities.

RADIOGRAPHIC EVALUATION

AP, lateral, and maximal plantarflexion, and dorsiflexion lateral radiographs should be obtained when the diagnosis is suspected. The maximum plantarflexion view helps determine whether the dorsal subluxation or dislocation of the midfoot on the hindfoot can be reduced passively, that is, if the navicular can be aligned with the talus. The dorsiflexion lateral view confirms the equinus contracture of the ankle. Although the navicular does not ossify until 3-6 years of age, in younger patients the relationship between the talus and the first metatarsal may be evaluated.

TREATMENT

The initial management consists of serial manipulation and casting, which is started shortly after birth. A *reverse* Ponseti method of casting is particularly useful in stretching out the dorsiflexion and valgus deformities. Open reduction and pin fixation can then stabilize the midfoot, allowing simultaneous heel cord tenotomy and dorsiflexion with casting to correct the ankle equinus.

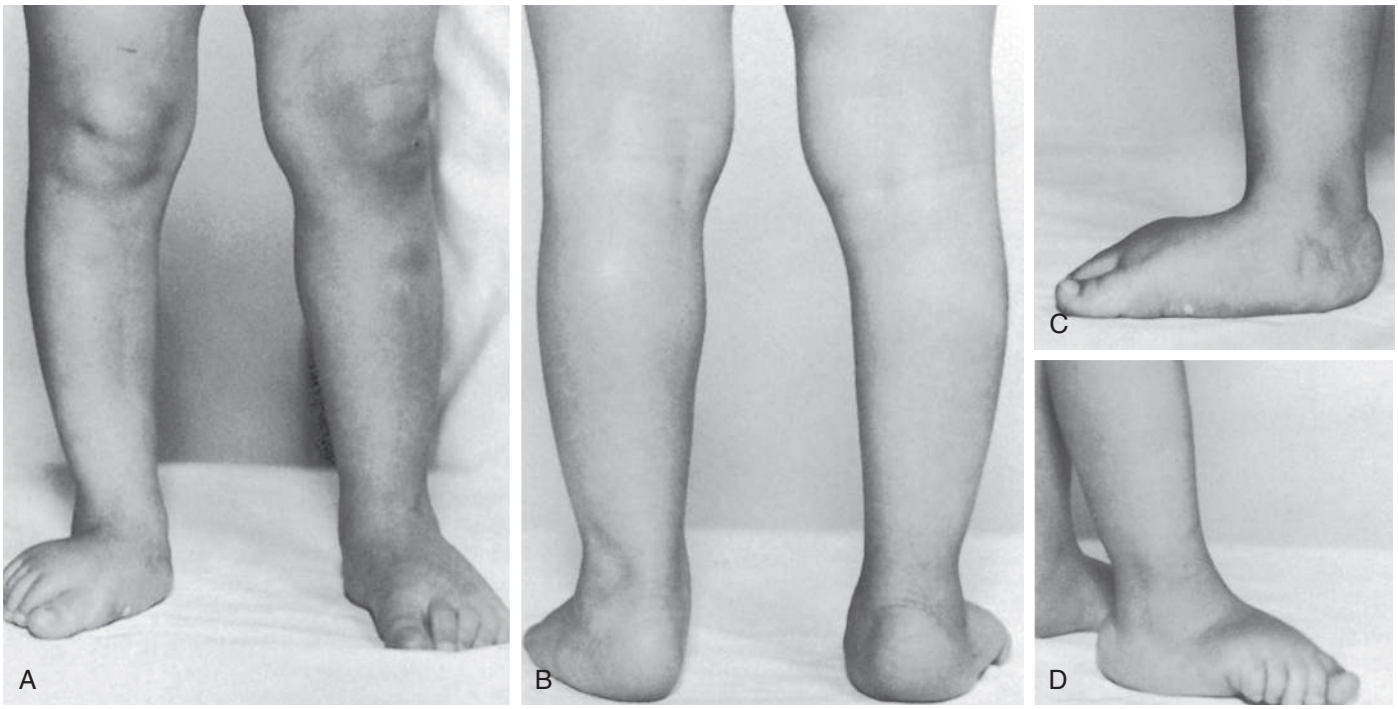

Fig. 715.5 Congenital vertical talus. **A,** Pronation of the forefoot. **B,** Valgus of the heel. **C,** Absence of an arch, the rocker bottom deformity. **D,** Elevation of the lateral toes and tight peroneal tendons. *(From Ricco AI. Disorders of the foot. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 19-67.)*

In recalcitrant cases, the competing deformities of the midfoot and the hindfoot make conservative treatment difficult. Initially an attempt is made to reduce the dorsal dislocation of the forefoot/midfoot on the hindfoot. Once this has been achieved, attention can be directed toward stretching the hindfoot contracture. These deformities are typically rigid, and surgical intervention is required in the majority of cases. In such cases, casting still helps to stretch out the contracted soft tissues to minimize the magnitude of surgical correction required. Surgery is generally performed between 3 and 12 months of age as a one-stage procedure. This involves release/lengthening of the contracted anterior soft tissues in concert with an open reduction and wire fixation of the talonavicular joint, followed by a posterior release with lengthening of the contracted musculotendinous units. Fixation with Kirschner wires is commonly performed to maintain alignment. Postoperatively, casting is employed for a variable period of time, and afterward patients often require the use of an orthosis for extended periods, depending on the underlying diagnosis. Salvage options for recurrent or residual deformities in older children include a subtalar or triple arthrodesis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.5 Hypermobile Pes Planus (Flexible Flatfeet)

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Flatfoot is a common diagnosis, and it has been estimated that up to 23% of the public may be affected, depending on the diagnostic criteria employed. Three types of flatfeet may be identified: a flexible flatfoot, a flexible flatfoot with a tendo-Achilles contracture, and a rigid flatfoot. Flatfoot describes a change in foot shape, and there are several abnormalities in alignment between the tarsal bones. There is eversion of the subtalar complex, valgus alignment of the hindfoot, and midfoot sag at the naviculocuneiform and/or the talonavicular joints. Additionally, the forefoot is abducted relative to the hindfoot, and the head of the talus is uncovered and prominent along the plantar and medial border of the midfoot/hindfoot. Although hypermobile or flexible pes planus represents a common source of concern for parents, these children are rarely symptomatic. Flatfeet are common in neonates and toddlers and are associated with physiologic ligamentous laxity. Improvement or correction is seen as the longitudinal arch develops between 5 and 10 years of age in the vast majority of children. Flexible flatfeet persisting into adolescence and adulthood are usually associated with **familial ligamentous laxity (hypermobility syndromes)** and often can be identified in other family members.

Patients typically have a normal longitudinal arch when examined in a non–weight-bearing position or standing on the toes, but the arch flattens when weight-bearing. The hindfoot collapses into valgus, and the midfoot sag becomes evident. The forefoot is supinated in weight-bearing. Generalized hypermobility and ligamentous laxity are often observed. Range of motion should be assessed at both the subtalar and the ankle joints. If the heel cord is tight, the flexible flatfoot may become painful. When assessing range of motion at the ankle, the hindfoot should always be inverted while testing dorsiflexion to lock subtalar eversion and apparent dorsiflexion. If the foot is neutral or everted, spurious dorsiflexion may occur through the midfoot, masking a tendo-Achilles contracture. If subtalar motion is restricted, the flatfoot is considered "rigid," and other diagnoses, such as tarsal coalition and juvenile rheumatoid arthritis, must be considered. On occasion, there may be tenderness and/or callus formation under the talar head medially. The shoes should be assessed as well and may have evidence of excessive wear along the medial border.

RADIOGRAPHIC EVALUATION

Routine radiographs of asymptomatic flexible flatfeet are usually not indicated. If obtained for diagnostic reasons, weight-bearing radiographs (AP and lateral) are required to assess the deformity. The foot should be positioned in the child's normal stance as medial rotation and hindfoot inversion may falsely correct the flatfoot. On the AP radiograph, there is widening of the angle between the longitudinal axis of the talus and the calcaneus, indicating excessive heel valgus, as well as talonavicular uncoverage and forefoot abduction. The lateral

view shows decreased calcaneal pitch to the tibia and distortion of the normal straight-line relationship between the long axis of the talus and the first metatarsal (i.e., Meary angle) with sag, either of the talonavicular or naviculocuneiform joint, resulting in flattening of the normal medial longitudinal arch (Fig. 715.6).

TREATMENT

Although the natural history of the flexible flatfoot remains unknown, there is little evidence to suggest that this condition results in long-term problems or disability. As such, treatment is reserved for the small subset of patients who develop symptoms. Patients may complain of hindfoot pain, difficulty with shoe wear, or fatigue after long walking. These patients may benefit from a nonprescription orthosis, such as a medial arch support. However, tight heel cords, when present, must be corrected before using arch supports. Severe cases, often associated with an underlying connective tissue disorder such as Ehlers-Danlos syndrome (see Chapter 744) or Down syndrome (see Chapter 99), may benefit from a custom orthosis such as the UCBL (University of California Biomechanics Laboratory) orthosis to better control the hindfoot and prevent collapse of the arch. Although an orthosis may relieve symptoms, there is no evidence to suggest any permanent change in the shape of the foot or alignment of the tarsal bones. Patients with a flexible flatfoot and a tight tendo-Achilles should be treated with stretching exercises. Often patients are referred to physical therapy to ensure that they are stretching appropriately. For the few patients with persistent pain despite conservative measures, surgical correction of the flatfoot can be considered. This typically involves a lateral column lengthening, which addresses all components of the deformity. The procedure involves an osteotomy of the calcaneus, with placement of a trapezoidal bone graft. A lengthening of the tendo-Achilles is often required, sometimes with a plantarflexion osteotomy of the medial cuneiform if the first ray remains supinated or in varus to restore the tripod surface of the foot. This procedure preserves the mobility of the hindfoot joints, in contrast to a subtalar or triple arthrodesis. Although a hindfoot arthrodesis may correct the deformity adequately, the subsequent stress transfer to neighboring joints may result in late-onset, painful degenerative changes.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.6 Tarsal Coalition

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Tarsal coalition, also known as **peroneal spastic flatfoot**, is characterized by a painful, rigid flatfoot deformity and peroneal (lateral calf) muscle spasm without true spasticity. It represents a congenital fusion or failure of segmentation between two or more tarsal bones. Any condition that alters the normal gliding and rotatory motion of the subtalar joint may produce the clinical appearance of a tarsal coalition. Thus congenital malformations, arthritis, inflammatory disorders, infection, neoplasms, and trauma can be possible causes.

The most common tarsal coalitions occur between the talus and calcaneus at the medial talocalcaneal facet (subtalar or talocalcaneal coalition) and between the calcaneus and navicular (calcaneonavicular coalition). Coalitions can be fibrous, cartilaginous, or osseous. Tarsal coalition occurs in approximately 1% of the general population and appears to be inherited as an autosomal dominant trait with nearly full penetrance. Approximately 60% of calcaneonavicular and 50% of medial facet talocalcaneal coalitions are bilateral.

CLINICAL MANIFESTATIONS

Approximately 25% of patients will become symptomatic, typically during the second decade of life. Although the flatfoot and a decrease in subtalar motion may have been present since early childhood, the onset of symptoms may correlate with the additional restriction in motion that occurs as a cartilaginous bar ossifies, reducing flexibility. Recurrent "ankle sprains" often accompany the presenting symptoms. The timing of ossification varies between the talonavicular (3-5 years of age), the calcaneonavicular (8-12 years of age), and the talocalcaneal (12-16 years of age) coalitions. Hindfoot pain is commonly observed, especially in the region of the sinus tarsi and under the head of the talus. Symptoms are activity related and are often increased with running or prolonged walking, especially on uneven surfaces. There may be tenderness over the site of the coalition and/or pain with testing of subtalar motion. The clinical appearance of a flatfoot is seen in both the weight-bearing and non–weight-bearing positions. There is a restriction in subtalar motion.

RADIOGRAPHIC EVALUATION

AP and lateral weight-bearing radiographs and an oblique radiograph of the foot should be obtained as well as a Harris or "heel" view (Table 715.1). A calcaneonavicular coalition is seen best on the oblique radiograph. On the lateral radiograph, there may be elongation of the anterior process of the calcaneus, known as the "anteater sign" (Fig. 715.7). A talocalcaneal coalition may be seen on a Harris (axial) view of the heel. On the lateral radiograph, there may be narrowing of the posterior facet of the subtalar joint or a C-shaped line along the medial outline of the talar dome and the inferior outline of the sustentaculum tali ("C sign"; Fig. 715.8). Beaking (or spur formation) of the anterior aspect of the talus on the lateral view is seen with some frequency and results from an alteration in the distribution of stress. Irregularity in the subchondral bony surfaces may be seen in patients with a cartilaginous coalition, in contrast to a well-formed bony bridge in those with an osseous coalition. A fibrous coalition may require additional imaging studies to diagnose. Although plain films may be diagnostic, a CT scan is considered the "gold standard" imaging modality when a coalition is suspected (see Fig. 715.8). In addition to securing the diagnosis, this study helps define the degree of joint involvement in patients with a talocalcaneal coalition. Although uncommon, more than one tarsal coalition may be observed in the same patient. MRI is also very accurate at detecting tarsal coalition, with a high rate of agreement with CT, and



Fig. 715.6 Lateral weight-bearing radiograph demonstrating features of flatfoot.

Table 715.1 Radiographic Secondary Signs Associated with Tarsal Coalition

Talar beaking
Posterior subtalar facet narrowing
Rounding and flattening of the lateral talar process
Hypoplasia of the talus, shortening of the talar neck
Anterior nose sign
Ball-and-socket ankle joint
Continuous C-sign
Flatfoot deformity
Altered navicular morphology (wide or laterally tapering)
Dysmorphic sustentaculum tali (enlarged and ovoid on lateral radiograph)

From Slovis T, ed. *Caffey's Pediatric Diagnostic Imaging,* 11th ed. Philadelphia: Mosby; 2008: p. 2604.

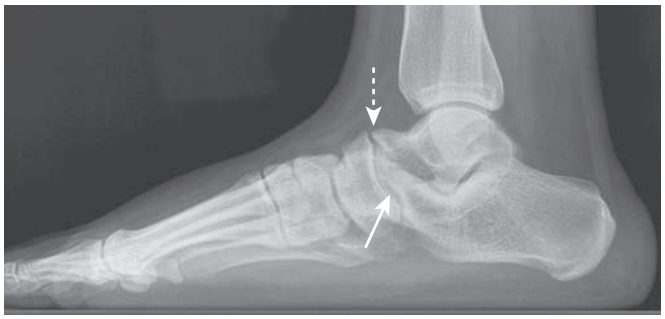

Fig. 715.7 Calcaneonavicular coalition in a child with the anteater sign *(arrow)* and talar beak *(dashed arrow)*. Elongation of the anterior calcaneus resembling the nose of an anteater is present. *(From Kan JH, Laor T. Congenital anomalies of bone. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 131.11, p. 1250.)*

may be useful when other diagnoses for pain are suspected and CT is diagnostically suboptimal, or in young children whose tarsal bones are not ossified. MRI offers less radiation exposure but requires more time and may necessitate sedation.

TREATMENT

The treatment of symptomatic tarsal coalitions varies according to the type and extent of coalition, the age of the patient, and the presence and magnitude of symptoms. Treatment is required only for symptomatic coalitions, and the initial management consists of activity restriction and nonsteroidal antiinflammatory medications, often with a shoe insert such as the UCBL orthosis. Immobilization in a short leg walking cast for 4-6 weeks may be required in patients with more pronounced symptoms or those who do not respond to initial measures. For patients with chronic pain despite an adequate trial of nonoperative therapy, surgical treatment should be considered as persistently symptomatic patients who are treated surgically are less likely to report persistent problems at long-term follow-up. Options include resection of the coalition, osteotomy, and/or, in extensive coalitions, arthrodesis. For the calcaneonavicular coalition, resection, and interposition of fat, bone wax, or of the extensor digitorum brevis muscle has been successful. Often, concomitant hindfoot valgus and contracture of the gastrocnemius-soleus are present. In these patients, more reliable pain relief can be obtained with resection of the coalition, correction of the hindfoot valgus by calcaneal lengthening osteotomy with bank bone graft and lengthening of the gastrocnemius-soleus complex. For those with extensive involvement of the joint and/or degenerative changes, a triple arthrodesis may be the best option; this is rarely needed in adolescents.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.7 Cavus Feet

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Cavus is a deformity involving plantarflexion of the forefoot or midfoot on the hindfoot and may involve the entire forepart of the foot or just the medial column. The result is an elevation of the medial longitudinal arch (Fig. 715.9). A deformity of the hindfoot will often develop to compensate for the primary forefoot abnormality. Although familial cavus may occur, most patients with this deformity will have an underlying neuromuscular etiology. The initial goal is to rule out, and if present, treat, any underlying causes. These diagnoses may relate to abnormalities of the spinal cord (occult dysraphism, tethered cord, polio, myelodysplasia, etc.) and peripheral nerves (hereditary motor and sensory neuropathies [see Chapter 653], such as Charcot-Marie-Tooth [CMT] disease, Dejerine-Sottas disease, or

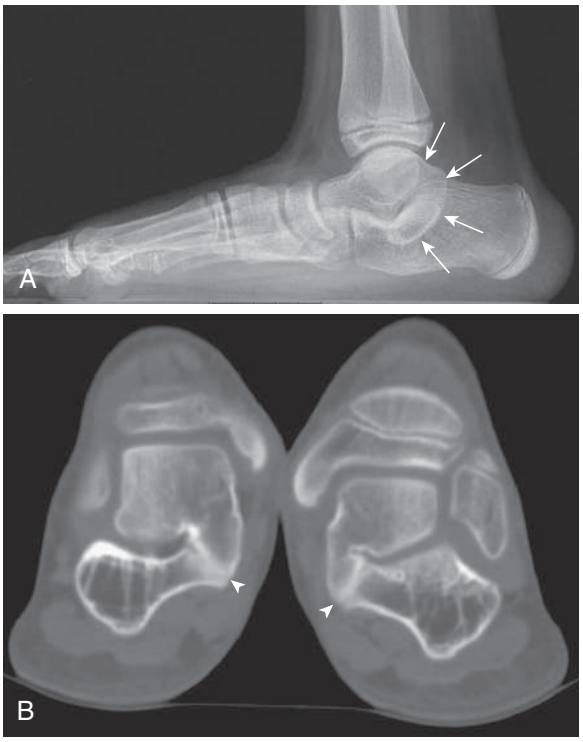

Fig. 715.8 Talocalcaneal coalition. **A**, A lateral radiograph demonstrates the C sign *(arrows)*, ovoid, elongated sustentaculum tali, and pes planus. **B**, Computed tomography with coronal reformats in a different patient demonstrates bilateral middle facet subtalar coalitions *(arrowheads)*. *(From Laor T, Kan JH. Congenital anomalies of bone. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 131-13.)*

Refsum disease). Although a unilateral cavus foot is most likely to result from an occult intraspinal anomaly, bilateral involvement usually suggests an underlying nerve or muscle disease. Cavus is commonly observed in association with a hindfoot deformity. Two thirds of patients with pes cavovarus have CMT, and conversely, 80% of CMT patients have pes cavovarus. In patients with hereditary motor and sensory neuropathies, progressive weakness and muscle imbalance result in plantarflexion of the first ray and medial column. To obtain a plantigrade foot, the hindfoot must roll into varus. With equinocavus, the hindfoot is in equinus, whereas in calcaneocavus (usually seen in polio or myelodysplasia), the hindfoot is in calcaneus (excessive dorsiflexion).

TREATMENT

Any underlying diagnosis must be identified, as this knowledge also helps address the specific disorder and formulate the proper management strategy. With mild deformities, stretching through physical therapy or serial casting of the plantar fascia and contracted muscles with exercises to strengthen weakened muscles may help delay progression. An ankle-foot orthosis may be necessary to stabilize the foot and improve ambulation. Surgical treatment is indicated for progressive or symptomatic deformities that have failed to respond to nonoperative measures or in the foot that is no longer braceable. The specific procedures recommended depend on the degree of deformity and the underlying diagnosis. In the case of a progressive neuromuscular condition, recurrence of deformity is commonly observed, and additional procedures may be required to maintain a plantigrade foot. Families should be counseled in detail regarding the disease process and the expected gains from the surgery. The goal of surgery is to restore motion and alignment, and to improve muscle balance. For milder deformities, a soft tissue release of the plantar fascia, often combined with a tendon transfer, may suffice. For patients with a fixed bony deformity of the forefoot, midfoot, and/or hindfoot, one or more osteotomies may be required for realignment. A triple arthrodesis (calcaneocuboid,



Fig. 715.9 Clinical picture demonstrating pes cavus.

talonavicular, and subtalar) may be required for severe or recurrent deformities in older patients. Long-term bracing is usually helpful in preventing recurrence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.8 Osteochondroses/Apophysitis

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Osteochondroses are idiopathic avascular necroses of bones, which may involve tarsal bones as well. Although rare, they may be observed in the tarsal navicular **(Köhler disease)** or the second or third metatarsal head **(Freiberg infraction**; Fig. 715.10). These are generally self-limited conditions that commonly result in activity-related pain, which can at times be disabling. The treatment is based on the degree of symptoms and most often includes restriction of activity. The diagnosis is made by history and physical examination in conjunction with concordant radiographic findings. The navicular is particularly sensitive, as it is the last tarsal bone to ossify, which may lead to compression from adjacent ossified bones. For patients with Köhler disease, nonsurgical treatment with a short leg cast or controlled ankle motion (CAM) boot for 6-8 weeks may provide significant relief. Patients with Freiberg infraction may benefit from a period of casting and/or shoe modifications such as a rocker-bottom sole, a stiff-soled shoe, or a metatarsal bar (not pads) to offload the forefoot. Degenerative changes and collapse of the metatarsal head will occasionally occur following the gradual healing process, and surgical intervention is required in a small subset of cases. Procedures have included joint debridement, bone grafting, redirectional osteotomy, subtotal or complete excision of the metatarsal head, and joint replacement.

Apophysitis represents inflammation or stress injury to the areas on or around growth plates in children and adolescents from repetitive tensile loading and is most often observed during periods of rapid growth. Enthesopathy refers to injury or inflammation at attachment points of tendons to bones. Calcaneal apophysitis **(Sever disease)** is the most common cause of heel pain in children; treatment includes activity modification, nonsteroidal antiinflammatory medications, heel cord stretching exercises, and heel cushions or arch supports. **Iselin disease** represents an apophysitis at the fifth metatarsal base where the peroneus brevis attaches and is less common. Even though the mandate for imaging heel pain in all children remains controversial, radiographs should be considered when the symptoms are unilateral or fail to respond to treatment. Gentle stretching, a period of rest (6-8 weeks), and avoidance of sports will often resolve symptoms, although recurrence is common until maturity when the apophyses close.

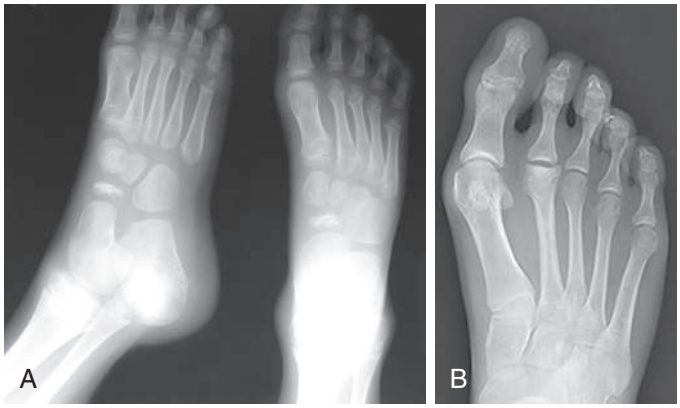

Fig. 715.10 Radiographs of Köhler disease (A) and Freiberg infraction (B).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.9 Puncture Wounds of the Foot

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Most puncture wound injuries to the foot may be adequately managed in the clinic or emergency department. Treatment involves a thorough irrigation and a tetanus booster, if appropriate, and many clinicians will recommend antibiotics. Using this approach, the majority will heal without complication. A subset of cases may develop cellulitis, most often caused by *Staphylococcus aureus*, and require intravenous antibiotics with or without surgical drainage if an abscess develops. Persistent signs of infection should be investigated more thoroughly. Deep infection is uncommon and may be associated with septic arthritis, infectious chondritis, or osteomyelitis. The most common organisms are *S. aureus* and *Pseudomonas aeruginosa*; the treatment involves a thorough surgical debridement followed by a short course (10-14 days) of systemic antibiotics. Although plain radiographs will demonstrate any metallic fragments or other radiopaque foreign bodies, ultrasonography (or CT or MRI) may be necessary to identify radiolucent objects such as glass, plastic, or wood. Routine empiric exploration and removal of foreign bodies is not required but may be necessary when symptoms are present or when an infection is suspected. Pain and/or gait disturbance is more likely with superficial objects under the plantar surface of the foot.

A special situation occurs when a puncture wound from a nail comes through a rubber sneaker or running shoe. This situation presents a high risk of a *Pseudomonas* infection, and consideration should be given to a thorough irrigation and debridement under general anesthesia followed by systemic antibiotics for 10-14 days. Foreign-body entrapment of rubber may also occur.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

715.10 Toe Deformities

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

JUVENILE HALLUX VALGUS (BUNION)

Juvenile hallux valgus is approximately 10-fold more common in females than in males. A family history is common and is typically associated with familial ligamentous laxity. The etiology is multifactorial, and important factors include genetic factors, ligamentous laxity, pes planus, wearing shoes with a narrow toe box, and occasionally spasticity (e.g., in the setting of cerebral palsy). Bunion refers to the

bump that occurs with chronic rubbing against the prominent first metatarsal head medially.

Clinical Manifestations

There is prominence of the first metatarsophalangeal (MTP) joint medially and often erythema and callus from chronic irritation (Fig. 715.11). The great toe metatarso-phalangeal joint is in valgus and is usually pronated. There is splaying (widening) of the forefoot. Pes planus, with or without an associated heel cord contracture, is also observed commonly. Although cosmesis is perhaps the most common concern, patients may have pain in the region of the first MTP joint and/or difficulty with shoe wear.

Radiographic Evaluation

Weight-bearing AP and lateral radiographs of the feet should be obtained. On the AP view, common measurements include the angular relationships between the first and second metatarsals (intermetatarsal angle, <10 degrees is normal) and between the first metatarsal and the proximal phalanx (hallux valgus angle, <25 degrees is normal) (see Fig. 715.11). The orientation of the first metatarsal–medial cuneiform joint is also documented. On the lateral radiograph, the angular relationship between the talus and the first metatarsal helps identify a midfoot break associated with pes planus. Radiographs are more helpful in surgical planning than in establishing the diagnosis.

Treatment

Conservative management of adolescent bunions consists primarily of shoe modifications. It is important that footwear accommodate the width of the forefoot, or pressure on the medial prominence can lead to callouses and pain. Patients should avoid wearing shoes with a narrow toe box and/or a high heel. Shoe modifications, such as a soft upper, bunion last, or heel cup, also may be recommended. In the presence of flexible pes planus, an orthotic to restore the medial longitudinal arch may be beneficial. If the flatfoot is rigid, further evaluation for tarsal coalition should be pursued. If a tendo-Achilles contracture is present, stretching exercises are recommended. The value of night splinting remains unproven. Surgical treatment is reserved for those patients with persistent and disabling pain who have failed a course of nonoperative therapy. Surgery is not advised purely for cosmesis. Surgery is usually delayed until skeletal maturity to decrease the risk of either recurrence or overcorrection, although guided growth via hemiepiphysiodesis in skeletally immature symptomatic patients is gaining popularity. Radiographs are essential in preoperative planning to assess both the magnitude of deformity (hallux valgus angle, intermetatarsal angle, distal metatarsal articular angle) and associated features such as obliquity of the first metatarsal–medial cuneiform joint. Surgical treatment often involves a soft tissue release and/or rebalancing procedure at the first MTP joint, and a single or double osteotomy of the first metatarsal to decrease foot width and realign the joints along the medial column of the forefoot. If there is deformity in the medial cuneiform, medial cuneiform opening wedge osteotomy and bone graft placement can correct the proximal alignment. An arthrodesis of the first MTP joint may be indicated in patients with spasticity to prevent recurrence.

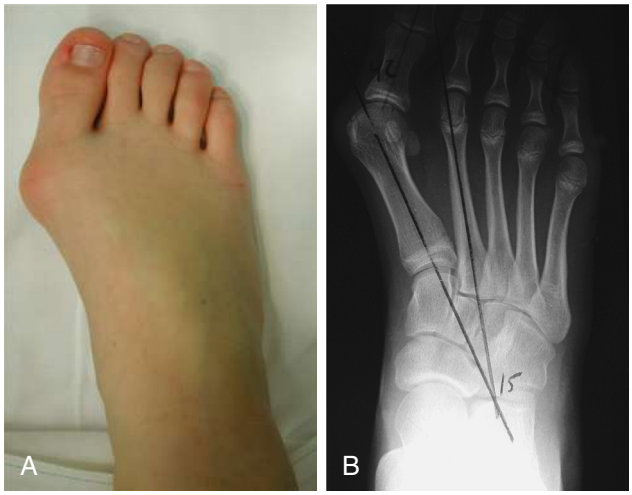

Fig. 715.11 Juvenile hallux valgus (bunion). **A,** Clinical appearance of the right foot of an 11-yr-old with hallux valgus. **B,** Radiograph shows an intermetatarsal angle of 15 degrees. The hallux valgus angle measures 42 degrees. It is the angle formed by a line drawn along the axis of the proximal phalanx and a second line drawn along the shaft of the first metatarsal. *(From Ricco AI. Disorders of the foot. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier, 2022; Fig. 19-111.)*

CURLY TOES

Curly toes, or varus deformity, is caused by contracture of the flexor digitorum longus resulting in flexion at the MTP and interphalangeal (IP) joints and medial deviation of the toe. It is extremely common and is often seen in the parents of affected patients. The toe usually lies underneath its neighbor, and the third, fourth, and fifth toes are most commonly involved (Fig. 715.12). The deformity very rarely causes symptoms, and active treatment (stretching, splinting, or taping) is not required. Most cases improve over time, and a subset will resolve completely. For the rare case in which there is chronic pain or skin irritation, release of the flexor digitorum longus tendon at the distal IP joint may be considered. Osteotomy in the older child may rarely be considered.

OVERLAPPING FIFTH TOE

Congenital digitus minimus varus, or varus fifth toe, involves dorsiflexion and adduction of the fifth toe. The fifth toe typically overlaps the fourth. There is also a rotatory deformity of the toe, and the nail tends to point outward. Mild congenital shortness of the fifth metatarsal is common. The deformity is usually bilateral and may have a genetic basis. Symptoms are frequent and involve pain over the dorsum of the toe from shoe wear. Nonoperative treatment has not been successful. For symptomatic patients, several different options for reconstruction have been described. Common features of operative intervention include releasing the contracted extensor tendon and the MTP joint capsule (dorsal, dorsomedial, or complete), and plastic alteration of the tight skin. An alternative procedure involves creation of a syndactyly between the fourth and fifth toes.

POLYDACTYLY

Polydactyly is the most common congenital toe deformity and is seen in approximately 2 in every 1,000 births; it is bilateral in 50% of cases. Polydactyly may be preaxial (great toe) or postaxial (fifth toe), and occasionally one of the central toes is duplicated. Associated anomalies are found in approximately 10% of postaxial and 20% of preaxial polydactyly and may be present in over half of patients with more rare forms of polydactyly. One third of patients will also have polydactyly of the hand. Conditions that may be associated with polydactyly include Ellis-Van Creveld (chondroectodermal dysplasia), longitudinal deficiency of the tibia, and Down syndrome. The extra digit may be either rudimentary or well formed, and plain radiographs of the foot help define the anatomy and evaluate any coexisting bony anomalies. Treatment is indicated for cosmesis and to allow for fitting with standard shoes. This involves surgical removal of the extra digit, and the procedure is generally performed between 9 and 12 months of age. Rudimentary digits may be surgically excised earlier but should not be "tied off," as this may leave painful residual scars or bone masses. For surgical treatment, radiographic evaluation is critical to properly plan reconstruction for a properly shaped and stable foot at maturity.

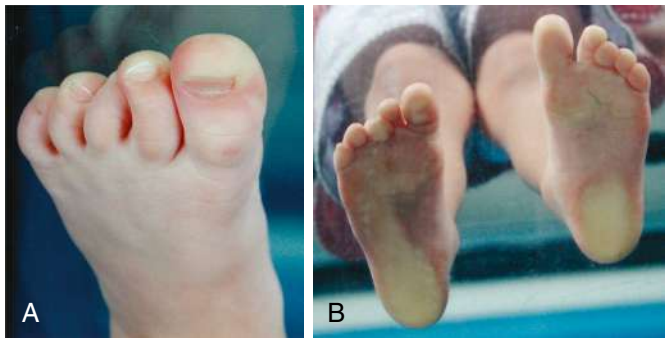

Fig. 715.12 Curly third, fourth, and fifth toes. *(From Ricco AI. Disorders of the foot. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022. Fig. 19-133.)*



Fig. 715.13 Clinical picture of polysyndactyly involving the great toe.

SYNDACTYLY

Syndactyly involves webbing of the toes, which may be simple (soft tissue only) or complex (involving bone). The syndactyly may be incomplete or complete (extends to the tip of the toes), and the toenails may be confluent. There is often a positive family history, and the third and fourth toes are most frequently involved. Symptoms are extremely rare, and cosmetic concerns are infrequent. Treatment is only required for a subset of cases in which there is an associated polydactyly (Fig. 715.13). Complex syndactyly may be seen in patients with Apert syndrome.

HAMMER TOE

A hammer toe is a flexion deformity of the lesser toes that involves the proximal IP (PIP) joint. This deformity may be distinguished from a curly toe by the absence of rotation. The second toe is most often involved, and a painful callus may develop over the dorsum of the toe where it rubs on the shoe or the tip of the toe which is directed against the sole of the shoe. Nonoperative therapy is rarely successful, and surgery is recommended for symptomatic cases. A release of the flexor tendons will suffice in most cases. Some authors recommend a transfer of the flexor tendon to the extensor tendon. For severe cases with significant rigidity, especially in older patients, a partial or complete resection of the proximal phalanx and a PIP joint fusion may be required.

MALLET TOE

Mallet toe involves a flexion contracture at the distal IP (DIP) joint and results from congenital shortening of the flexor digitorum longus tendon. Patients may develop a painful callus on the plantar surface of the tuft or dorsal aspect of the DIP joint. As nonoperative therapy is usually unsuccessful, surgery is required for patients with chronic symptoms. For flexible deformities in younger children, stretching or release of the flexor digitorum longus tendon is recommended. For stiffer deformities in older patients, resection of the head of the middle phalanx, or arthrodesis of the DIP joint, may be considered.

CLAW TOE

A claw toe deformity involves hyperextension at the MTP joint and flexion at both the PIP and DIP joints, often associated with dorsal subluxation of the MTP joint. *This condition must be distinguished from hyperextension of the MTP joint due to ground reaction where the stiff flexed toe in stance pushes the MTP joint into hyperextension. If the MTP does hyperextend, this is a claw toe.* The majority are associated with an underlying neurologic disorder and must be evaluated. The etiology is usually muscle imbalance, and the extensor tendons are recruited to substitute for weakening of the tibialis anterior muscle. If treatment is elected, surgery is required. Transfer of the extensor digitorum (or hallucis) tendon to the metatarsal neck is commonly performed along with a dorsal capsulotomy of the MTP joint and fusion of the PIP joint (IP joint of the great toe).

ANNULAR BANDS

Bands of amniotic tissue associated with amniotic disruption syndrome (early amniotic rupture sequence, congenital constriction band syndrome, annular band syndrome) may become entwined along the extremities, resulting in a spectrum of problems from in utero amputation (Fig. 715.14) to a constriction ring along a digit (Fig. 715.15; see Chapter 100). These rings, if deep enough, may result in impairment of arterial or venous blood flow as well as severe damage to the muscles, tendons, and bone growth distal to the band. Even though concerns regarding tissue viability are less common, swelling from impairment in venous return is often an urgent problem. The treatment of annular bands usually involves observation; however, circumferential release of the band may be required emergently if arterial inflow is obstructed or electively to relieve venous congestion. Physical therapy and bracing may help prevent future contractures and deformities.

MACRODACTYLY

Macrodactyly represents an enlargement of the toes and may occur as an isolated problem or in association with a variety of other conditions such as Proteus syndrome (Fig. 715.16), neurofibromatosis, tuberous sclerosis, and Klippel-Trenaunay-Weber syndrome. This condition results from a deregulation of growth, and there is hyperplasia of one or more of the underlying tissues (osseous, nervous, lymphatic, vascular, fibrofatty). Macrodactyly of the toes may be seen in isolation (localized gigantism) or with enlargement of the entire foot or leg. In addition to cosmetic concerns, patients may have difficulty wearing standard shoes. The initial treatment is observation, if possible. This is a difficult condition to treat surgically, and complications are frequent. For involvement of a single toe, the best option may be a resection of the ray (including the metatarsal). For greater degrees of involvement, debulking of the various tissues is required. Often a growth arrest of the underlying osseous structures is performed. Stiffness and wound problems are common. The rate of recurrence is high, and more than one debulking may be required. Patients may elect to have an amputation if the process cannot be controlled by less extensive procedures. Leg length inequality is common and must be looked for and treated if needed.

SUBUNGUAL EXOSTOSIS

A subungual exostosis is a benign bone mass that projects out from the dorsal and medial surface of a distal toe phalanx, under the nail. The etiology is unknown but may relate to minor, repetitive trauma. The great toe is involved most often. Patients present with discomfort, and the toenail may be deformed and elevated. The lesion may be demonstrated on plain radiographs and histologically involves normal bone with a fibrocartilaginous cap. The treatment for symptomatic lesions is excision, and the recurrence rate is approximately 10%.

INGROWN TOENAIL

Ingrown toenails are relatively common in infants and young children and usually involve the medial and/or lateral border of the great toe. Symptoms include chronic irritation and discomfort. Recurrent infection is seen in some cases. Parents should be instructed when cutting toenails to cut straight across the distal aspect of the nail, rather than



Fig. 715.14 Constriction band syndrome with congenital amputation.



Fig. 715.15 Constriction band syndrome with foot involvement.



Fig. 715.16 Macrodactyly of the great toe in a case of Proteus syndrome.

curve inward at the nail edges. If conservative measures, including shoe modifications, warm soaks, and appropriate nail trimming fail to control the symptoms, surgical removal of a portion of the nail should be considered.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 715.2 Differential Diagnosis of Foot Pain According to Age

AGE GROUP	DIAGNOSTIC CONSIDERATIONS
0-6 yr	Poorly fitting shoes Fracture Puncture wound Foreign body Osteomyelitis Cellulitis Juvenile idiopathic arthritis Hair tourniquet Dactylitis Leukemia
6-12 yr	Poorly fitting shoes Trauma (fracture, sprain) Juvenile idiopathic arthritis (enthesopathy) Puncture wound Sever disease (calcaneal apophysitis) Accessory tarsal navicular bone Hypermobile flatfoot Tarsal coalition Oncologic (Ewing sarcoma, leukemia)
12-18 yr	Poorly fitting shoes Stress fracture Trauma (fracture, sprain) Foreign body Ingrown toenail Metatarsalgia Plantar fasciitis Achilles tendinopathy Accessory ossicles (navicular, os trigonum) Tarsal coalition Avascular necrosis of metatarsal (Freiberg infarction) or navicular (Köhler disease) bones Plantar warts

From Marcdante KJ, Kliegman RM, Schuh AM. *Nelson Essentials of Pediatrics*, 9th ed. Philadelphia: Elsevier; 2023.

715.11 Painful Foot

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

Table 715.2 shows a differential diagnosis for foot pain in different age ranges. In addition to the history and physical examination, plain radiographs are most helpful in establishing the diagnosis. Occasionally more sophisticated imaging modalities such as CT or MRI will be required.

715.12 Shoes

Christine M. Goodbody, Jennifer J. Winell, and Richard S. Davidson

In toddlers and children, a well-fitting shoe with flexible soles is recommended. This recommendation is in part based on studies suggesting that the development of the longitudinal arch seems to be best in societies in which shoes are not worn, and flatfeet are more common in shod children. Well-cushioned, shock-absorbing shoes are helpful in the child and adolescent athlete to decrease the chances of developing an overuse injury. Otherwise, shoe modifications are generally reserved for abnormalities in either alignment between segments of the foot or symptoms from an underlying condition (e.g., a limb-length discrepancy). Numerous modifications are available.

As a rule, shoes protect the foot from abnormal temperature as well as rough surfaces and sharp objects but have not been shown to help the normal foot develop. Poorly fitting shoes may create problems.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 716

Torsional and Angular Deformities of the Limb

Brendan A. Williams, Jennifer J. Winell, and Lawrence Wells

716.1 Normal Limb Development

Brendan A. Williams, Jennifer J. Winell, and Lawrence Wells

During the seventh week of intrauterine life, the lower limb rotates medially to bring the great toe toward the midline. The hip joint forms by the eleventh week; the proximal femur and acetabulum continue to develop until physeal closure in adolescence. The first component of rotation is the femoral neck, which is rotated approximately 40 degrees anteriorly at birth. This anterior rotation is referred to as **anteversion** (the angle between the axis of the femoral neck and the transcondylar axis). The increased anteversion results in increased internal rotation of the hip. In most children, femoral anteversion decreases to 15-20 degrees by 8-10 years of age. Conditions such as cerebral palsy that involve spasticity of the lower extremities can result in the persistence of fetal anteversion. This results in torsional abnormalities of the lower limb and gait disturbances. The second component of limb rotation is found in the tibia. Tibial torsion is the angular difference between the axis of the knee and the transmalleolar axis. Infants can have 30 degrees of medial rotation of the tibia. When skeletally mature, the rotation is between 5 degrees of medial rotation and 15 degrees of lateral rotation (Fig. 716.1). Excessive medial rotation of the tibia is referred to as **medial tibial torsion**. This is very common and, although concerning to parents, very rarely requires treatment. The medial or lateral rotation beyond ±2 SDs from the mean is considered abnormal rotation. The third component of rotational (axial) abnormalities of the lower extremity derives from the foot. Metatarsus adductus can cause the foot to curve medially, pointing the toes inward. It is assessed by observing the medial and lateral borders of the foot.

Torsional deformity may be simple, involving a single component, or complex, involving multiple components. Complex deformities may be additive (internal tibial torsion and internal femoral torsion are additive) or compensatory (external tibial torsion and internal femoral torsion are compensatory).

The normal tibiofemoral angle at birth is 10-15 degrees of physiologic varus. The alignment changes to 0 degrees by 18 months, and physiologic valgus up to 12 degrees is reached in between 3 and 4 years of age. The normal valgus of 7 degrees is achieved by 5-8 years of age (Fig. 716.2). Persistence of varus beyond 2 years of age may be pathologic and is seen in conditions such as Blount disease. Overall, 95% of developmental physiologic genu varum and genu valgum cases resolve with growth. Persistent genu valgum or valgus into adolescence is considered pathologic and deserves further evaluation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

716.2 Limb Evaluation

Brendan A. Williams, Jennifer J. Winell, and Lawrence Wells

When evaluating concerns regarding the limb, the provider should obtain a history documenting onset, progression, functional limitations, previous treatment, evidence of neuromuscular disorder, and any significant family history. The examination should assess the exact torsional profile and include (1) foot progression angle, (2) femoral anteversion, (3) tibial version with thigh-foot angle, and (4) assessment of foot adduction and abduction.

FOOT PROGRESSION ANGLE

Limb position during gait is expressed as the **foot progression angle** and represents the angular difference between the axis of the foot with the direction in which the child is walking. Its value is usually estimated by asking the child to walk in the clinic hallway (Fig. 716.3). Inward rotation of the foot is assigned a negative value, and outward rotation is designated with a positive value. The normal foot progression angle in children and adolescents is 10 degrees (range: −5 to 20 degrees). The foot progression angle delineates whether there is an in-toeing or out-toeing gait.

FEMORAL ANTEVERSION

Hip rotation is measured with the child in the prone position, the hip in neutral flexion or extension, thighs together, and the knees flexed to 90 degrees (Fig. 716.4). Both hips are assessed at the same time. Internal rotation of the hip is measured by rotating the leg ipsilaterally, and external rotation is measured by rotating the leg contralaterally. Excessive anteversion has increased internal rotation, whereas retroversion has increased external rotation. The amount of anteversion can be approximately estimated by palpating the greater trochanter of the hip while internally rotating the limb. Femoral anteversion should be measured at the point when the greater trochanter is most prominent laterally during this rotation (Craig test).

TIBIAL ROTATION

Tibial rotation is measured using the **transmalleolar angle.** The transmalleolar angle is the angle between the longitudinal axis of the thigh with a line perpendicular to the axis of the medial and lateral malleolus (Fig. 716.5). In the absence of foot deformity, the **thigh-foot angle** is preferred (Fig. 716.6). It is measured with the child lying prone. The angle is formed between the longitudinal axis of the thigh and the longitudinal axis of the foot. It measures the tibial and hindfoot rotational status. Inward rotation is assigned a negative value, and outward rotation is assigned a positive value. Inward rotation indicates medial tibial torsion, whereas outward rotation represents lateral tibial torsion. Infants have a mean angle of −5 degrees (range: −35 to 40 degrees) as a consequence of normal in utero position. In mid-childhood through adult life, the mean thigh-foot angle is 10 degrees (range: −5 to 30 degrees).

FOOT SHAPE AND POSITION

The foot is observed for any deformities in prone and standing position. The **heel bisector line** (HBL) is used to evaluate the foot adduction and abduction deformities. The HBL is a line that divides the heel in two equal halves along the longitudinal axis (Fig. 716.7). It normally extends through the center of the second toe. When the HBL points medial to the second toe, the forefoot is abducted, and when the HBL is lateral to the second toe, the forefoot is adducted. Other lower-extremity problems, such as heel varus or valgus, can make assessment of axial plane issues more difficult.

It is also important to screen children with these foot deformities for associated hip dysplasia and neuromuscular problems (e.g., cerebral palsy).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

716.3 Torsional Deformities

Brendan A. Williams, Jennifer J. Winell, and Lawrence Wells

FEMORAL ANTEVERSION

In-toeing gait most commonly results from excessive femoral anteversion. It occurs more commonly in females than males (2:1) in children 3-6 years of age and is congenital, resulting from persistent infantile

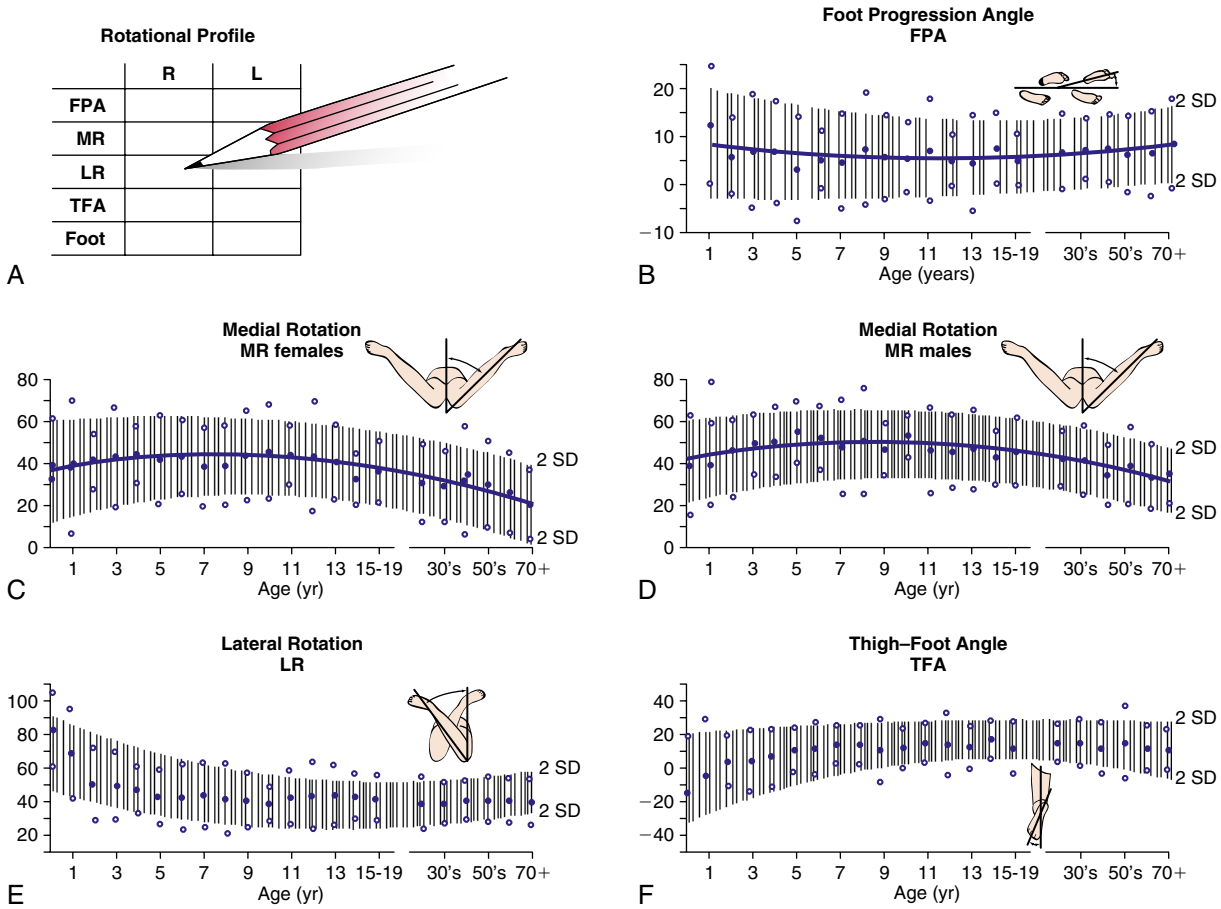

Fig. 716.1 A-F, The rotational profile from birth to maturity is depicted graphically. All graphs include 2 SD from the mean for the foot progression angle *(FPA)* for femoral medial rotation *(MR)* and lateral rotation *(LR)* (for males and females), and the thigh-foot angle *(TFA)*. *(From Morrissey RT, Weinstein SL, eds. Lovell and Winter's Pediatric Orthopaedics, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1990.)*

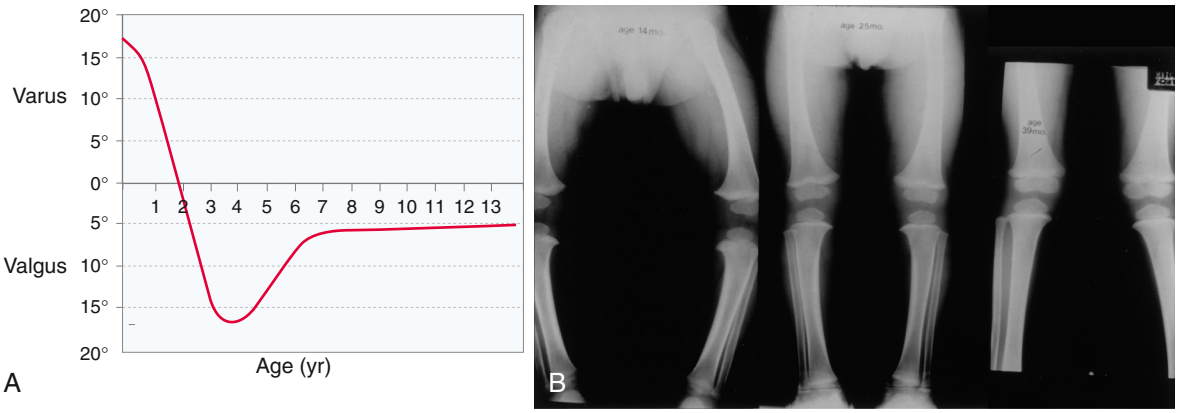

Fig. 716.2 A, Development of the tibiofemoral angle during growth (after Salenius). B, Serial radiographs demonstrating normal transition from varus alignment at 14 months to neutral position at 25 months to valgus tibiofemoral alignment at 39 months. *(From Wimberly RL. Disorders of the leg. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig 18.13.)*

anteversion. On examination, many children with this condition will have **generalized ligamentous laxity**. Gait examination reveals that the entire leg is inwardly rotated. Internal hip rotation is increased beyond 70 degrees, and consequently the external rotation is restricted to 10-20 degrees. Clinically, the patellae point inward when the foot is straight, and compensatory external rotation of the tibia is demonstrated. This is frequently mistaken as "genu valgum." The amount of anteversion can be roughly estimated by palpating the greater trochanter of the hip while internally rotating the limb. The point of maximal prominence of the greater trochanter laterally during this rotation corresponds to the degree of femoral anteversion.

Diagnosis is made clinically on examination; CT can provide objective measurements but is rarely indicated. The treatment is predominantly observation and reassurance. The torsion usually corrects with longitudinal growth by 8-10 years of age. Although rare, persistent deformity, unacceptable cosmesis, functional impairment, anteversion

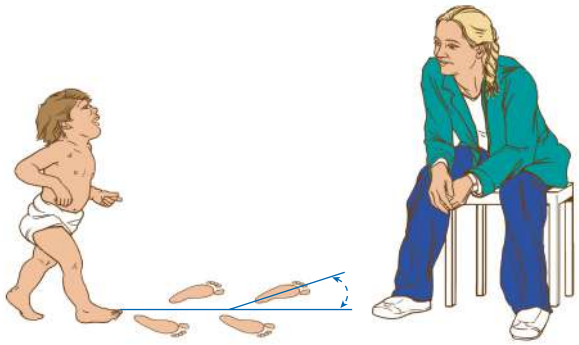

Fig. 716.3 Foot progression angle. The long axis of the foot is compared with the direction in which the child is walking. If the long axis of the foot is directed outward, the angle is positive. If the foot is directed inward, the angle is negative and indicates in-toeing. *(From Thompson GH. Gait disturbances. In: Kliegman RM, ed. Practical Strategies in Pediatric Diagnosis and Therapy. Philadelphia: WB Saunders; 2004.)*



Fig. 716.4 Anteversion measured by medial rotation of hip (A) and lateral rotation of hip (B). In this patient, internal rotation is nearly 90 degrees, suggestive of excessive femoral anteversion.

>45 degrees, and no external rotation beyond neutral are indications for operative intervention. Surgery involves a derotation osteotomy of the femur.

MEDIAL TIBIAL TORSION

Medial (internal) tibial torsion manifests with **in-toeing gait.** It is commonly associated with metatarsus adductus, genu valgum, or femoral anteversion. This condition is usually seen during the second year of life. It is often noticed after the child begins to walk independently. Many parents are concerned with a "bowed" appearance of the legs. Normally at birth, the medial malleolus lies behind the lateral



Fig. 716.5 Measurement of transmalleolar angle (TMA). *(From Guler O, Isyar M, Karataş D, et al. Investigating the relationship between internal tibial torsion and medial collateral ligament injury in patients undergoing knee arthroscopy due to tears in the posterior one third of the medial meniscus. Knee. 2016;23[4]:655–658, Fig 2.)*

malleolus, but by adulthood, it is reversed, with the tibia in 15 degrees of external rotation. The treatment is observation and reassurance because spontaneous resolution with normal growth and development can be anticipated. Correction can be seen as early as 4 years of age and in some children by 8-10 years of age. Persistent deformity with functional impairment is treated with supramalleolar derotation osteotomy, but this is rarely necessary.

EXTERNAL FEMORAL TORSION

Femoral retrotorsion, when of idiopathic origin, is usually bilateral. The disorder is associated with an **out-toeing gait** and increased incidence of degenerative arthritis. The clinical examination of external femoral torsion shows excessive hip external rotation and limitation of internal rotation. The hip will externally rotate up to 70-90 degrees and internally rotate to only 0-20 degrees. External femoral torsion can also follow a **slipped capital femoral epiphysis (SCFE)**. There should be a low threshold to perform radiographs of the hips in children older than 10 years of age who present with hip or knee pain and decreased internal rotation of the hip on clinical examination. If a SCFE is detected, it is treated surgically. Occasionally, persistent femoral retroversion after SCFE can produce functional impairment resulting in a severe out-toed gait and difficulty opposing one's knees in the sitting position. The latter can be disabling to adolescent females. Should this occur, a Southwick osteotomy or surgical realignment might be necessary.

LATERAL TIBIAL TORSION

Lateral (external) tibial torsion is less common than medial rotation and is often associated with a **calcaneovalgus foot**. It can be compensatory to persistent femoral anteversion or secondary to a tight iliotibial band. Natural growth rotates the tibia externally, and therefore external tibial torsion can become worse with time. Clinically, the patella faces outward when the foot is straight. The thigh-foot angle and the transmalleolar angle are increased. There may be associated patellofemoral instability with knee pain. Although some correction can occur with growth, extremely symptomatic children may need a supramalleolar osteotomy, which is usually done by 10-12 years of age.

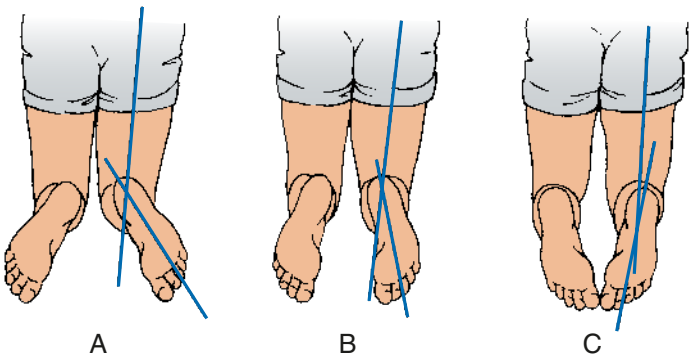

Fig. 716.6 Thigh-foot angle. With the child in the prone position and the knees flexed and approximated, the long axis of the foot can be compared with the long axis of the thigh. The long axis of the foot bisects the heel and the third or middle toe. **A,** External tibial torsion produces excessive outward rotation. **B,** Normal alignment is characterized by slight external rotation. **C,** Internal tibial torsion produces inward rotation. *(From Zolkoske AC, Fehr SD. Gait disturbances. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Fig 45.6.)*

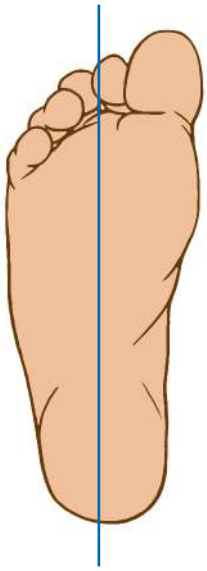

Fig. 716.7 Schematic demonstration of heel bisector line.

METATARSUS ADDUCTUS

Metatarsus adductus (see Chapter 715.1) manifests with forefoot adduction and medial rotation of all metatarsals. Of children with metatarsus adductus, 10–15% have hip dysplasia. The prognosis is good because the majority get better with nonoperative intervention. Feet that correct actively with stimulation of the lateral border of the foot are treated with stretching exercises alone. Feet that are flexible and correctable to neutral with manipulation are treated with stretching, reverse last shoes, or serial casting. Feet that do not correct fully with conservative care or rigid deformities are treated with medial capsulotomy of the first metatarsal cuneiform joint and soft tissue release by 2 years of age. Osteotomies of the base of the metatarsal may be performed after 6 years of age.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

716.4 Coronal Plane Deformities

Brendan A. Williams, Jennifer J. Winell, and Lawrence Wells

Genu varum and genu valgum are common pediatric deformities of the knee. Figure 716.2 presents the age-appropriate normal values for knee angle. Tibial bowing is common during the first year, bowlegs are common during the second year, and knock-knees are most prominent between 3 and 4 years of age.

GENU VARUM

Physiologic bowleg is a common torsional combination that is secondary to normal in utero positioning (Fig. 716.8). Spontaneous resolution with normal growth and development can be anticipated. Persistence of varus beyond 2 years of age may be pathologic. Causes of pathologic bowing include metabolic bone disease (vitamin D deficiency, rickets, hypophosphatasia), asymmetric growth arrest (trauma, infection, tumor, Blount disease), bone dysplasia (dwarfism, metaphyseal dysplasia), and congenital and neuromuscular disorders (Table 716.1). It is important to differentiate physiologic bowing from Blount disease (Table 716.2). Physiologic bowing should also be differentiated from rickets and skeletal dysplasia. Rickets has classic bony changes seen on plain radiographs with trumpeting widening and fraying of the metaphysis along with widening of the physis (see Chapter 69).

TIBIA VARA

Idiopathic tibia vara, or **Blount disease**, is a developmental deformity resulting from abnormal endochondral ossification of the medial aspect of the proximal tibial physis leading to varus angulation and medial rotation of the tibia (Fig. 716.9). The incidence is greater in Black patients and in overweight toddlers. It is also higher in patients who have an affected family member or started walking early in life. Idiopathic tibia vara has been classified into three types, depending on the age at onset: infantile (1-3 years of age), juvenile (4-10 years of age), and adolescent (11 years or older). The juvenile and adolescent forms are commonly combined as late-onset tibia vara. The exact cause of tibia vara remains unknown, although it is thought to result from abnormal growth of the physis due to excessive weight.

The **infantile** form of tibia vara is the most common. There is a predominance in Black females. Approximately 80% are bilateral with a prominent medial metaphyseal beak, internal tibial torsion, and leg-length discrepancy. The characteristics of the **juvenile** and **adolescent** (late-onset) forms include predominance in Black males, obesity, normal or greater than normal height, less frequent bilateral involvement (approximately 50%), slowly progressive genu varum deformity, pain rather than deformity as the primary initial complaint, no palpable proximal medial metaphyseal beak, minimal internal tibial torsion, mild medial collateral ligament laxity, and mild lower extremity length discrepancy. The infantile group has the greatest potential for progression.

An anteroposterior (AP) standing radiograph of both lower extremities with patellae facing forward and a lateral radiograph of the involved extremity should be obtained (Fig. 716.10). Weight-bearing radiographs are preferred and allow maximal presentation of the clinical deformity. The metaphyseal-diaphyseal angle (Drennan angle) can be measured and is useful in distinguishing between physiologic genu varum and early tibia vara (Fig. 716.11). This angle can aid in predicting the risk of progression. Angles greater than 16 degrees carry an increased risk of progression, whereas those less than 10 degrees are likely to resolve spontaneously. Patients with Drennan angles of 11-16 degrees should be monitored for progressive tibia vara.

The Langenskiöld classification, which describes six stages on radiographs for infantile Blount disease (Fig. 716.12), is the most widely

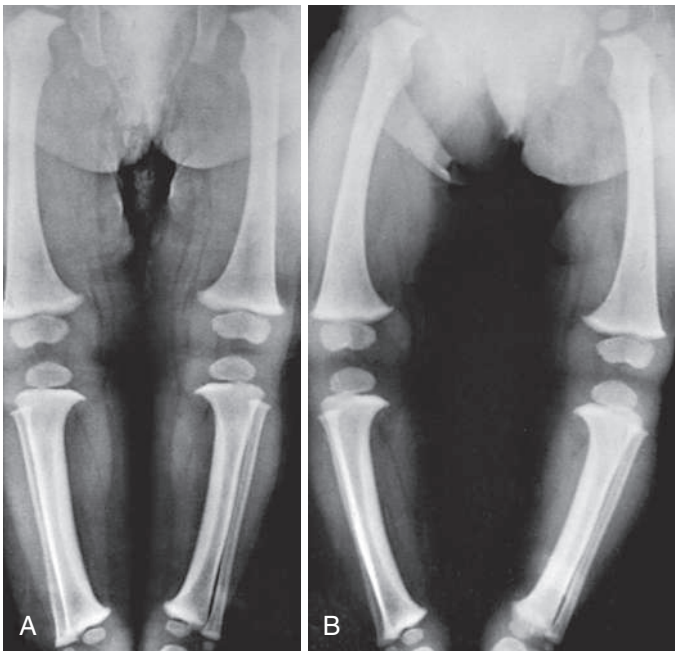

Fig. 716.8 Genu varum. **A,** In recumbent position, tibia and femora are bowed, but the legs do not appear bowed. **B,** In erect position during weight bearing and with ankles in apposition, the legs are bowed. *(From Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019.)*

Table 716.1 Classification of Genu Varum (Bowlegs)

PHYSIOLOGIC
Asymmetric growth
Tibia vara (Blount disease)
• Infantile
• Juvenile
• Adolescent
Focal fibrocartilaginous dysplasia
Physeal injury
Trauma
Infection
Tumor
METABOLIC DISORDERS
Vitamin D deficiency (nutritional rickets)
Vitamin D–resistant rickets
Hypophosphatasia
SKELETAL DYSPLASIA
Metaphyseal dysplasia
Achondroplasia
Enchondromatosis

Modified from Thompson GH. Angular deformities of the lower extremities. In: Chapman MW, ed. *Operative Orthopedics*, 2nd ed. Philadelphia: JB Lippincott; 1993: Table 222-1, p. 3132.

Table 716.2 Differentiation of Leg Bowing

PHYSIOLOGIC BOWING	BLOUNT DISEASE
Gentle and symmetric deformity	Asymmetric, abrupt, and sharp angulation
Metaphyseal-diaphyseal angle <11 degrees	Metaphyseal-diaphyseal angle >11 degrees
Normal appearance of the proximal tibial growth plate	Medial sloping of the epiphysis Widening of the physis Fragmentation of the metaphysis
No significant lateral thrust	Significant lateral thrust

cited classification system, although other radiographic and MRI-based systems have been described. Langenskiöld differentiates based on fragmentation of the epiphysis, beaking of the medial tibial epiphysis, depression of the medial tibial plateau, and formation of a bony bar. CT with three-dimensional reconstructions and MRI can also be useful to assess the meniscus; the articular surface of the proximal tibia, including the posteromedial slope; or the integrity of the proximal tibial physis.

Management is based on the stage of the disease, the age of the child, and the nature of presentation (primary or recurrent deformity). In children younger than 3 years and Langenskiöld stage <3, bracing is effective and can prevent progression in 50% of patients. A maximal trial of 1 year of orthotic management is recommended. If complete correction is not obtained after 1 year or if progression occurs during this time, a corrective osteotomy is indicated. Surgical treatment is also indicated in children >4 years of age, those at Langenskiöld stage >3, and those with severe deformities. A proximal tibial valgus osteotomy and associated fibular diaphyseal osteotomy are usually the procedures of choice. In late-onset tibia vara, correction is also necessary to restore the mechanical axis of the knee. Hemiplateau elevation with correction of posteromedial slope has been established as a treatment modality in relapsed cases.

GENU VALGUM (KNOCK-KNEES)

The appearance of symmetric bilateral genu valgum most pronounced around age 4 years of age is part of the normal physiologic process of leg development. However, variation of up to 15 degrees of valgus is possible until 6 years of age. The majority of physiologic valgus has a good chance of correction until this age. The intermalleolar distance with the knees approximated is normally <2 cm, and in a severe valgus deformity, it could measure >10 cm. Pathologic conditions leading to valgus are metabolic bone disease (e.g., rickets or renal osteodystrophy), skeletal dysplasia, posttraumatic physeal arrest, tumors, and infection. The increased valgus at the knee causes lateral deviation of the mechanical axis with stretching of the medial aspect of the knee leading to knee pain. Deformities >15 degrees and occurring after 6 years of age are unlikely to correct with growth and require surgical management. In the skeletally immature, medial tibial epiphyseal hemiepiphysiodesis or stapling (guided growth) is attempted for correction. In the skeletally mature, osteotomy is necessary at the center of rotation of angulation and is usually situated in the distal femur. Long-length AP radiographs of the leg in a weight-bearing stance are necessary for preoperative planning.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

716.5 Congenital Angular Deformities of the Tibia and Fibula

Brendan A. Williams, Jennifer J. Winell, and Lawrence Wells

POSTEROMEDIAL TIBIAL BOWING

Congenital posteromedial bowing is typically associated with a calcaneovalgus foot and rarely with secondary valgus of the tibia. The exact cause is unknown. Early operative intervention is not indicated because this bowing generally corrects with growth. However, despite the correction of angulation, there can be residual shortening in the tibia and fibula. The mean growth inhibition is 12–13% (range: 5–27%). The mean leg length discrepancy at maturity is 4 cm (range: 3-7 cm). The diagnosis of bowing is confirmed on radiographs, which show the posteromedial angulation without any other osseous abnormalities. The calcaneovalgus deformity of the foot improves with stretching or modified shoe wear and occasionally ankle-foot orthosis. Predicted leg length discrepancy <4 cm is managed with age-appropriate epiphysiodesis of the normal leg. Leg length discrepancy >4 cm is managed with combination of contralateral epiphysiodesis and ipsilateral lengthening. A corrective osteotomy for distal valgus may be required and can be done in the same setting while correcting leg length discrepancy.

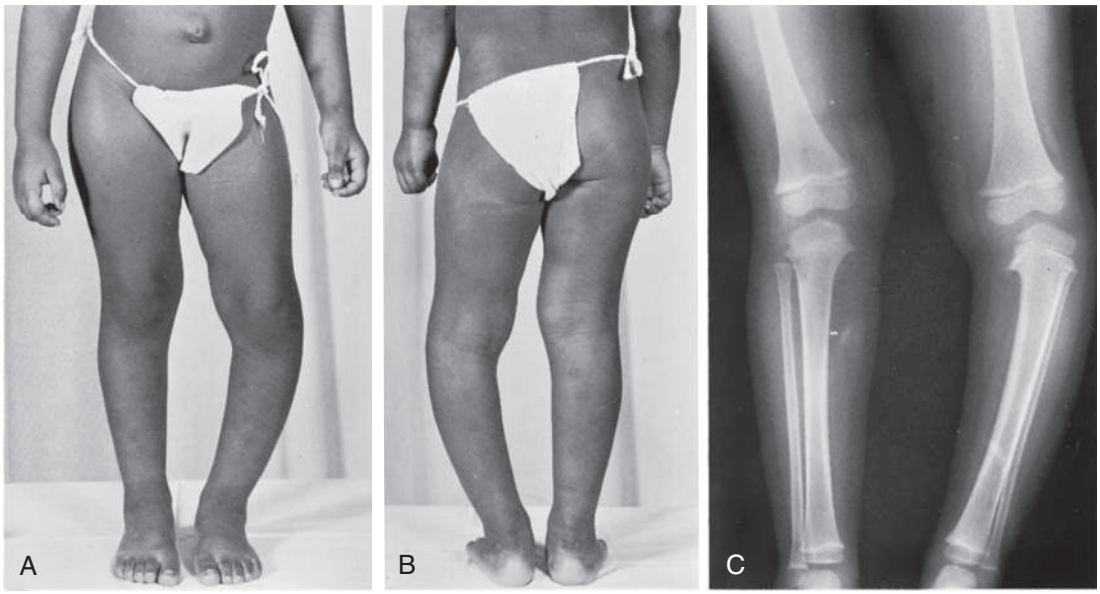

Fig. 716.9 Blount disease in a 5-year-old child. **A** and **B**, Preoperative clinical appearance. Note the abrupt medial deviation of the tibia just below the knee. Lateral "thrust" of the knee during weight bearing exacerbates the "limp." **C**, Radiograph demonstrating abrupt angulation at the epiphyseal-metaphyseal junction and medial metaphyseal radiolucency and beaking with apparent lateral subluxation of the proximal end of the tibia. *(From Johnston CE, Young M. Disorders of the leg. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig 18.14.)*



Fig. 716.10 Anteroposterior radiograph of both knees in Blount disease.

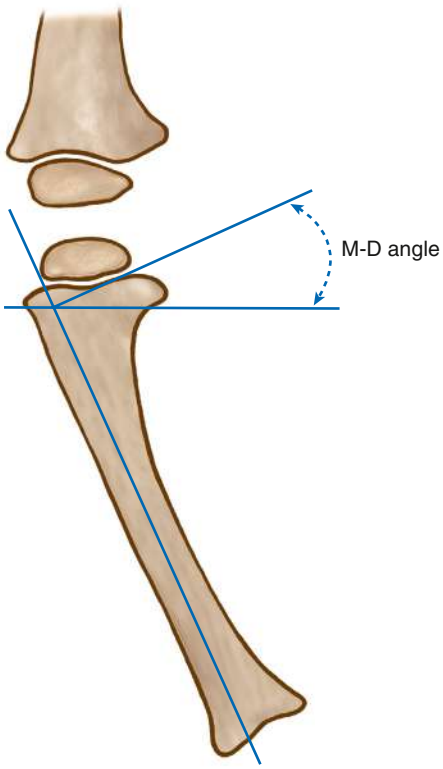

Fig. 716.11 Metaphyseal-diaphyseal *(M-D)* angle. Draw a line on the radiograph through the proximal tibial physis. Draw another line along the lateral tibial cortex. Last, draw a line perpendicular to the shaft line as demonstrated in the diagram. *(From Morrissey RT, Weinstein SL, eds. Lovell and Winter's Pediatric Orthopaedics, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1990.)*

ANTEROMEDIAL TIBIAL BOWING (POSTAXIAL HEMIMELIA)

Fibular hemimelia is the most common cause of anteromedial bowing of the tibia. The fibular deficiency can occur with complete absence of fibula or with partial fibular development both proximally and distally. It is associated with deformities of femur, knee, tibia, ankle, and foot. The femur is short and has lateral condylar hypoplasia, causing patellar instability and genu valgum deformity. The tibia has anteromedial bowing with reduced growth potential. The keys for management are addressing the ankle stability and foot deformities. The ankle resembles a ball-and-socket joint with lateral instability. The foot deformities are characterized by the absence of lateral digits, equinocavovarus foot, and tarsal coalition.

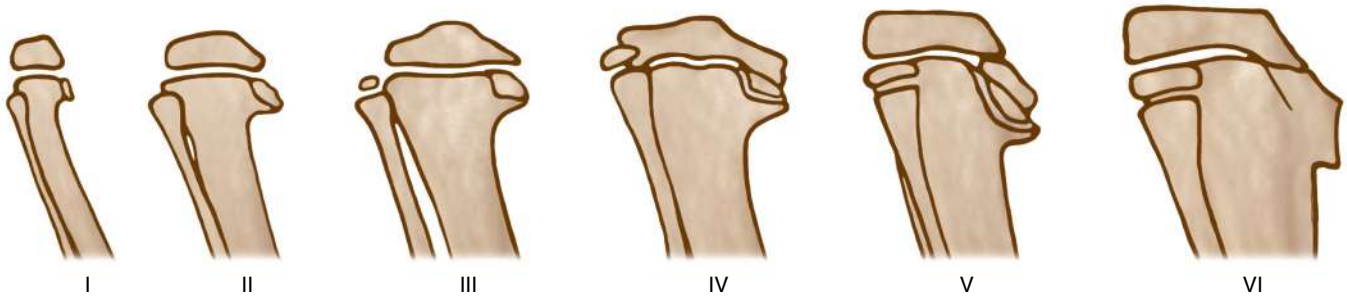

Fig. 716.12 Depiction of the stages of infantile Blount disease. *(From Langeskiöld A. Tibia vara [osteochondrosis deformans tibiae]: a survey of 23 cases. Acta Chir Scand. 1952;103:1.)*

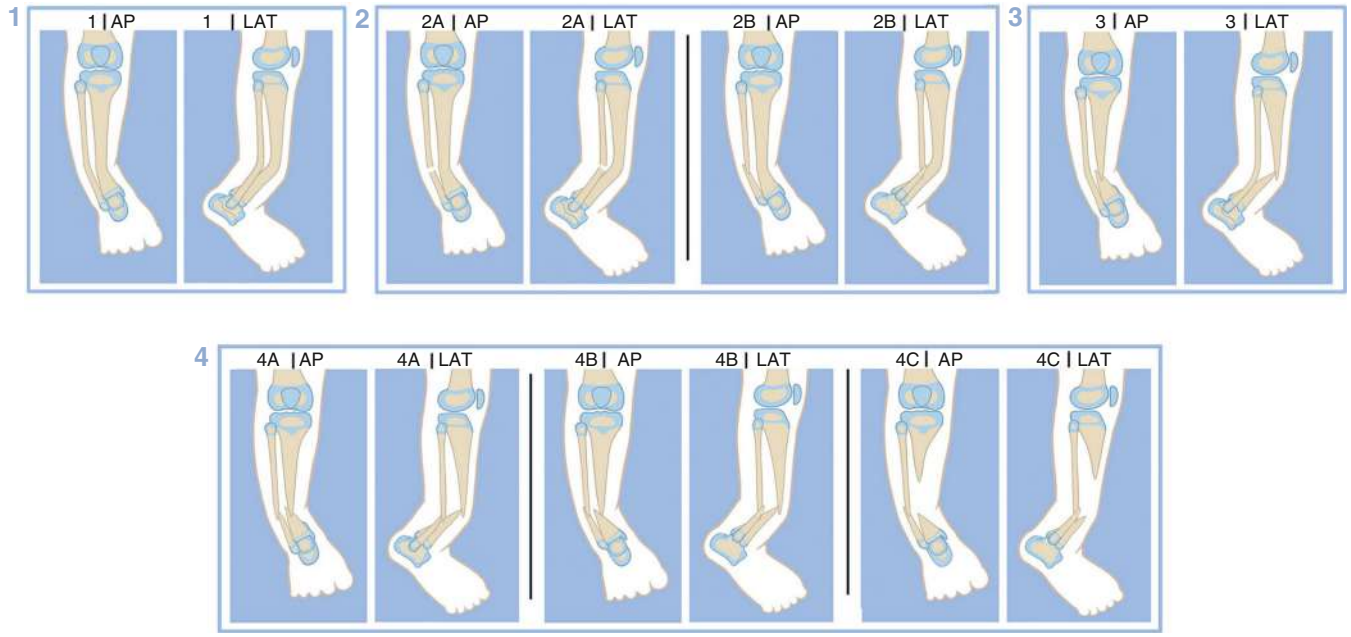

Fig. 716.13 Paley classification of congenital pseudoarthrosis of the tibia. Paley: type 1, no fractures; type 2, no fracture tibia, fracture fibula with fibula *(2A)* at station *(2B)* proximal migration; type 3, fracture tibia, no fracture fibula; type 4, fracture tibia and fibula with fibula *(4A)* at station *(4B)* proximal migration *(4C)* bone defect tibia with proximal migration fibula AP, Anteroposterior; LAT, lateral. (Reproduced with permission by the Paley Foundation.) *(From Paley D. Congenital pseudarthrosis of the tibia: biological and biomechanical considerations to achieve union and prevent refracture. J Child Orthop. 2019;13:120–133.)*

Various surgical options have been described, and the treatment is tailored to the patient's needs and parents' acceptance. A severely deformed foot may be best managed with Syme or Boyd amputation and prosthesis as early as 1 year of age. In the salvageable foot, leg length discrepancy can be treated with contralateral leg epiphysiodesis or ipsilateral limb lengthening.

ANTEROLATERAL TIBIAL BOWING

Anterolateral tibial bowing is associated with **congenital pseudarthrosis of the tibia (CPT)**. Previous estimates suggest that 50–60% of patients with CPT have **neurofibromatosis**; however, this prevalence may be underestimated as the diagnostic criteria for neurofibromatosis often become evident after CPT has been diagnosed. Overall, less than 10% of patients with neurofibromatosis have this lesion. The pseudarthrosis or site of nonunion is typically situated at the middle third and distal third of the tibia. The Boyd's classification identifies six types of CPT with increasing severity depending on the presence of cystic and dysplastic changes. The Paley classification is another frequently employed system (Fig. 716.13). The treatment for this condition has been very frustrating with poor results. Bracing has been recommended to prevent fracture early in the course but does not usually obviate need for later surgical intervention. Numerous treatment protocols and surgical procedures have been described to achieve union, such as single- and dual-onlay grafting with rigid internal fixation, intramedullary nailing with or without bone grafting, and circular frame fixation. With the growing use of microsurgery in orthopedics, vascularized fibular autograft also has been used with varying results. Due to the rate of complications occurring during reconstructive treatment, a below-knee amputation with early rehabilitation is also an accepted treatment strategy for some of these patients.

TIBIAL LONGITUDINAL DEFICIENCY

Tibial longitudinal deficiency, or tibial hemimelia, follows an autosomal dominant inheritance pattern. Multiple classification systems have been described, all of which largely categorize patients based on which portion(s) of the tibia is deficient. The other associated anomalies are foot deformities, hip dysplasia, and symphalangism of the hand. Traditionally, treatment has been guided by the Jones classification, which describes presence of a proximal tibial anlage and a functional quadriceps mechanism. In type Ia deformity, the proximal tibial anlage is absent, and knee disarticulation with prosthesis is recommended. In types Ib and II, the tibial anlage is present, and the management consists of an early Syme amputation, followed later by synostosis of the fibula with the tibia, and a below-knee prosthesis. Type III is rare, and the principal management is with Syme amputation and a prosthesis. Type IV deformity is associated with ankle diastasis, which requires stabilization of the ankle and correction of leg length discrepancy at a later stage. Due to the varied pathology of this condition and its rarity, treatment options and recommendations continue to evolve.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 717

Leg-Length Discrepancy

Christine M. Goodbody and Richard S. Davidson

A discrepancy in leg lengths may result from a variety of congenital or acquired conditions (Table 717.1). Although up to 25% of adults may have a difference of more than 1 cm, only a small percentage have more than a 2 cm difference, for which the main consequence is gait asymmetry. An increase in vertical pelvic motion is observed, and more energy must be expended during ambulation. Although a small compensatory lumbar curvature may develop, a small leg-length discrepancy (<2 cm) is unlikely to result in back pain, structural scoliosis, or degenerative arthritis. There is some evidence to suggest that larger, long-standing discrepancies may be associated with hip or knee arthritis, structural scoliosis, and spine degenerative changes. The goal of treatment is to have a discrepancy of <2-2.5 cm at skeletal maturity, and several treatment methods are available to achieve this objective. Knowledge of the underlying etiology, coupled with regular follow-up to assess limb growth and skeletal maturity, allows the treating physician to project the discrepancy at skeletal maturity and to plan treatment. A subset of patients will have coexisting abnormalities in the viscera or musculoskeletal system that must also be identified and treated.

DIAGNOSIS AND CLINICAL FINDINGS

Gait asymmetry is the most frequent complaint. The long leg is often kept flexed at the knee and hip in stance to level the pelvis. The diagnosis is made on physical examination, and specialized radiographs help to quantify the existing discrepancy and predict what the discrepancy will be at maturity. The discrepancy may be caused by hypoplasia, hyperplasia, or angular deformity (structural discrepancy), by soft-tissue contracture at the hips, knees, or ankles (apparent or functional shortening), or by a combination of these conditions. Other contributing factors include joint subluxation or dislocation (hip), a decrease in the height of the foot (congenital or neuromuscular), or structural disorders of the pelvis. A careful physical examination is required to identify all factors contributing to the discrepancy. Muscle contracture about the hip will also create the appearance of leg-length inequality. For example, to bear weight on an abducted hip, the patient must hike up the contralateral hip and pelvis, making the contralateral leg appear short.

There are several clinical methods for measuring the extent of the limb-length discrepancy. The preferred method is to perform a standing examination in which blocks of various sizes are placed under the short leg until the pelvis is leveled (Fig. 717.1). An alternate method is to measure the length of each leg with the patient supine; the examiner first extends the patient's legs and examines the soles of the feet for asymmetry before flexing the patient's hip to 90 degrees to evaluate for discrepant knee height (Galeazzi sign). Using a tape measure is very inaccurate because of several variables, including the line of measurement used, muscle atrophy, and moving patients. The range of motion at the hip, knee, and ankle must also be assessed to identify any causes of apparent discrepancy. A 10-degree fixed abduction (or adduction) contracture of the hip may create an apparent leg-length discrepancy of 2-3 cm. Similarly, a flexion contracture of the hip and/or knee will create apparent shortening of the extremity, whereas an equinus contracture at the ankle will create apparent lengthening of the extremity. A rigid lumbar scoliosis (suprapelvic contracture) will create pelvic obliquity and an associated apparent limb length inequality. Once a discrepancy is quantified in a child, it must be followed at regular intervals until maturity. Assessments at 6- to 12-month intervals are most common depending on the rate of change.

Leg-length discrepancy may be associated with various **genetic overgrowth syndromes** (see Table 717.1). If there are features other than leg-length discrepancy, specific diagnostic tests for Beckwith-Wiedemann syndrome and *PIK3CA* pathogenic variants must be included in the patient's evaluation. In these disorders, the leg overgrowth tends to increase over time.

RADIOGRAPHIC EVALUATION

Radiologic evaluation complements the clinical examination; both are typically used when making treatment decisions. For an accurate assessment, it is important that the child not move and keep their legs extended; a lift may help. Five different techniques are available. The **teleoroentgenogram** is a single radiographic exposure of both lower extremities (standing) and requires a long cassette. A ruler is placed on the film, and direct measurements are made, factoring in a 6% magnification error, which is usually accounted for using a radiographic marker of known diameter to calibrate the image. One advantage is that angular deformities may be assessed. Its primary indication is for young children. Unfortunately, because only one exposure is used for the leg and because the ankle is less dense than the hip, it may be difficult to "see" the whole leg. In addition, because the x-ray source is at the knee projecting up to the hip and down to the ankle, this method projects the hip and ankle along the ruler, making the leg appear longer than it really is, particularly in obese patients. The **orthoroentgenogram** consists of three separate exposures of the hips, knees, and ankles on a long cassette. The patient is supine, and a ruler is placed on the cassette for measurement of bone length. However, the patient must lie still for the three exposures, which is often difficult to achieve in younger children. Because the x-ray beam is pointed at the hip, knee, and ankle in each of the three exposures, the length measurement is accurate and each of the three joints can be exposed properly. The x-rays expose from the top of the pelvis to the mid femur, from the mid femur to the mid tibia, and from the mid tibia to below the foot for each of the three exposures, respectively, permitting angular deformity assessment in the frontal plane only. The **scanogram** also consists of separate exposures of the hips, knees, and ankles on a cassette with a radiographic ruler; a chest-sized film cassette is used (Fig. 717.2). There is no magnification error; patients must remain still for the three exposures, and angular deformities cannot be assessed. Although CT is an accurate technique, the assessment is time-consuming, and the patient receives a larger dose of radiation. In addition, a radiologist must normalize the axis of the leg to the screen to accurately measure the limbs. An advantage of CT is that limb and segment lengths can be measured even if there are soft tissue contractures or deformity in the sagittal plane. Another popular technique is called **EOS**. EOS is a proprietary low-dose x-ray scanner that can simultaneously take orthogonal full-body images in a standing position and is therefore able to reconstruct three-dimensional (3D) images of the bony anatomy in question (Fig. 717.3). The advantages of EOS are that it has a much lower radiation dose than standard x-rays, it can capture frontal and sagittal planes quickly and simultaneously, and there is no magnification error. The disadvantages are that it requires a trained radiology technician to correctly align the limbs for computer measurement, and not all centers have access to the technology at this time. Regardless of the technique, it is critical that the patellae be pointed forward, that measurements be made in the plane of the limb, that the legs be extended, and that the same method be used in sequential measurements to be compared.

In the presence of flexion or extension deformities where 3D imaging is not employed, each bone should be x-rayed individually with a ruler where the x-ray beam is perpendicular to the bone and the ruler parallel to the bone.

In addition to quantifying the discrepancy, it is essential to determine skeletal age (bone age) to assess how much growth a patient has left and to assist in estimating the size of discrepancy at maturity. An anteroposterior radiograph of the hand and wrist is usually obtained at each visit and compared with the standards in the Greulich and Pyle Atlas to estimate skeletal age. Although more accurate techniques are available, most are time-consuming and impractical for routine clinical

Table 717.1 Causes of Lower Extremity Length Discrepancy

SHORTENING	LENGTHENING
CONGENITAL Hemiatrophy* Skeletal dysplasias Short femur Proximal focal femoral deficiency* Fibular, tibial hemimelia Developmental dysplasia of the hip*	CONGENITAL Hemihypertrophy* Local vascular malformation
TUMOR Developmental Neurofibromatosis Multiple exostosis Enchondromatosis (Ollier disease) Osteochondromatosis Fibrous dysplasia (Albright syndrome) Punctate epiphyseal dysplasia Dysplasia epiphysealis hemimelica (Trevor disease) Radiation therapy before skeletal maturity (physeal arrest)* Resection of benign or malignant neoplasm	TUMOR Developmental Neurofibromatosis Soft tissue hemangioma Arteriovenous malformation Hemihypertrophy with Wilms tumor Aneurysm
INFECTION Osteomyelitis* Septic arthritis Tuberculosis	INFECTION Inflammation Metaphyseal osteomyelitis Rheumatoid arthritis Hemarthrosis (hemophilia)
TRAUMA Physeal injury* Failed joint replacement Osteotomy, atrophic nonunion Overlapping, malposition of fracture fragments* Burns	TRAUMA Metaphyseal, diaphyseal fracture Diaphyseal operations (bone grafts, osteosynthesis, periosteal stripping)

SHORTENING	LENGTHENING
NEUROMUSCULAR DISEASE Poliomyelitis Cerebral palsy* Myelomeningocele Peripheral neuropathy Focal cerebral lesions (hemiplegia)	
OTHER Legg-Calvé-Perthes disease* Slipped capital femoral epiphysis	LATERALIZED OVERGROWTH (HEMIHYPERTROPHY / HEMIHYPERPLASIA SYNDROMES) Beckwith-Wiedemann syndrome *PIK3CA* related overgrowth spectrum (PROS) Klippel-Trenaunay syndrome CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal, spinal) Isolated lymphatic malformation Fibroadipose vascular anomaly Megalencephaly—capillary malformation Hemimegalencephaly /dysplastic megalencephaly/focal cortical dysplasia Muscular hemihyperplasia Fibroadipose hyperplasia or overgrowth CLAPO syndrome (capillary malformation of lower lip, lymphatic malformation of face and neck, asymmetry of face and limbs and partial or generalized overgrowth)

*Common.
Modified from Moseley C. Leg-length discrepancy. *Pediatr Clin North Am.* 1986;33(6):1385.

application. The range of variability using the atlas is approximately 9 months, so the method is most accurate when multiple data points have been collected. Apps to calculate the discrepancy at maturity and timing of treatment are available.

TREATMENT

Options for treatment include observation, a shoe lift or custom orthosis, a limb-shortening procedure (acute shortening and internal fixation versus gradual shortening by growth arrest or guided growth), a limb-lengthening procedure (with internal or external fixation), or a combination of these. Deformity correction is often accomplished simultaneously. In the congenital deficiencies (femur, tibia, fibula) in which the predicted limb-length inequality will require more than three lengthening operations (more than 20 cm), an early foot amputation may be the best option to achieve an optimal functional outcome. In addition to the magnitude of discrepancy predicted at skeletal maturity, both the anticipated adult height of the patient (estimated from family members) and the desires of the patient and the patient's family are important considerations.

Discrepancies of up to 2.5 cm may be treated by observation or a shoe lift. With regard to a shoe lift, up to 1 cm may be placed within the shoe, and up to 5 cm may be placed on the outside of the shoe. Complete correction of inequality is not required, and the height of the lift should be adjusted based on the patient's gait and comfort. An orthotic may be used as a temporizing measure before definitive treatment. For extended discrepancies, "foot in foot" extension prostheses are a reasonable alternative until limb lengthening can be accomplished or for patients who cannot or do not wish to undergo surgical correction.

For patients with a predicted ultimate discrepancy between 2 and 5 cm, an **epiphysiodesis** is offered in skeletally immature patients, and an acute shortening may be performed in a skeletally mature patient. Epiphysiodesis refers to a temporary or permanent cessation of growth at one or more physes. A permanent growth arrest is most commonly performed when sufficient data are available with which to accurately predict when to perform the procedure. Approximately 65% of the growth of the lower extremity comes from the distal femur (37%, 9 mm/year) and proximal tibia (28%, 6 mm/year). Males typically grow until 16 years of age, whereas females grow until 14 years of age. As such, performing an epiphysiodesis of both the distal femur and the proximal tibia in a patient with 3 years of growth remaining should achieve approximately 4.5 cm of correction. Techniques used to determine the timing of epiphysiodesis are the Menelaus method ("rule of thumb"), the Green and Anderson method, the Moseley straight-line graph, and the multiplier method (Figs. 717.4-717.6). Apps to make calculations are available. The most common surgical technique for permanent growth arrest is the percutaneous epiphysiodesis, in which the physis is ablated with a drill and curetted under image intensification. This is an outpatient procedure with few complications. Insertion of plates and screws or just screws across the physis is an alternative but usually requires a second operation to remove the hardware. For patients for whom sufficient data are unavailable or those for whom the underlying diagnosis is associated with an unpredictable pattern

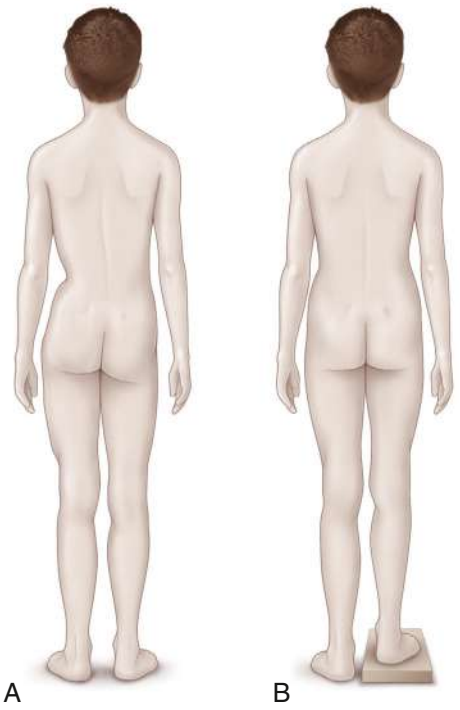

Fig. 717.1 Clinical assessment of limb length inequality with the aid of graduated blocks. (A) True leg length inequality (or fixed functional discrepancy) results in asymmetric iliac crest or posterior iliac spine heights with the patient standing erect. The examiner must be sure that the patient is standing evenly on the legs, with the knees straight and the feet flat on the floor. (B) A reasonably accurate estimation of leg length inequality can be made by having the patient stand erect on sufficient graduated blocks under the shorter limb to level the pelvis. *(From Podeszwa D. Limb length discrepancy. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier, 2022: Fig 20.3.)*

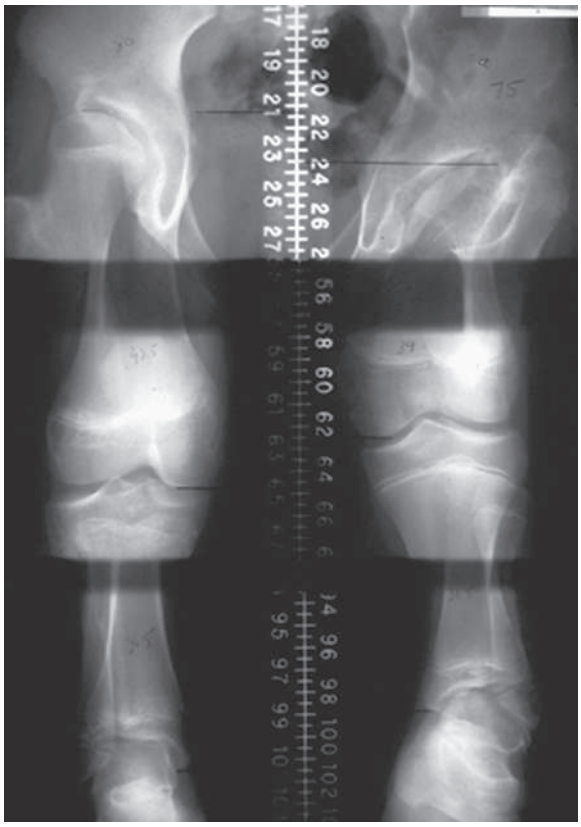

Fig. 717.2 Scanogram to demonstrate exact leg-length discrepancy.



Fig. 717.3 2D Biplanar Whole Body EOS Imaging. *(From Garg B, Mehta N, Bansal T, Malhotra R. EOS Imaging: concept and current applications in spinal disorders. J Clin Orthop Trauma. 2020;11:786–793. Fig. 2.)*

of growth, then a reversible technique, such as staples, plates, and/or screws, may be considered. Once equalization has been achieved, the hardware can be removed, allowing growth to resume. When the patient is skeletally mature or if it is deemed appropriate to wait until maturity before treatment, depending on the magnitude of deformity and patient/family preference, acute shortening may be the best option. Acute shortening is typically performed at the femur (several techniques have been described), given the increased risk of complications associated with shortening of the tibia and fibula including compartment syndrome and neurovascular problems.

For discrepancies >5 cm after maturity, or for smaller ones depending on patient/family preference, lengthening of the short limb is the procedure of choice. An exception would be a discrepancy secondary to overgrowth of one limb, in which acute or gradual shortening of the abnormal limb would be preferred so as to preserve body proportions. Patients with anticipated discrepancies >8-10 cm often require one or more limb-lengthening procedures (several years apart), with or without an epiphysiodesis to mitigate the size of the ultimate discrepancy and need for more than one lengthening. The most common technique used for limb lengthening involves placement of an intramedullary magnetic lengthening nail or an external fixator, either a ring fixator such as the Ilizarov device or a monolateral device (Fig. 717.7). The bone is cut at the metaphyseal-diaphyseal junction, and lengthening is achieved gradually through distraction at the corticotomy. The usual rate

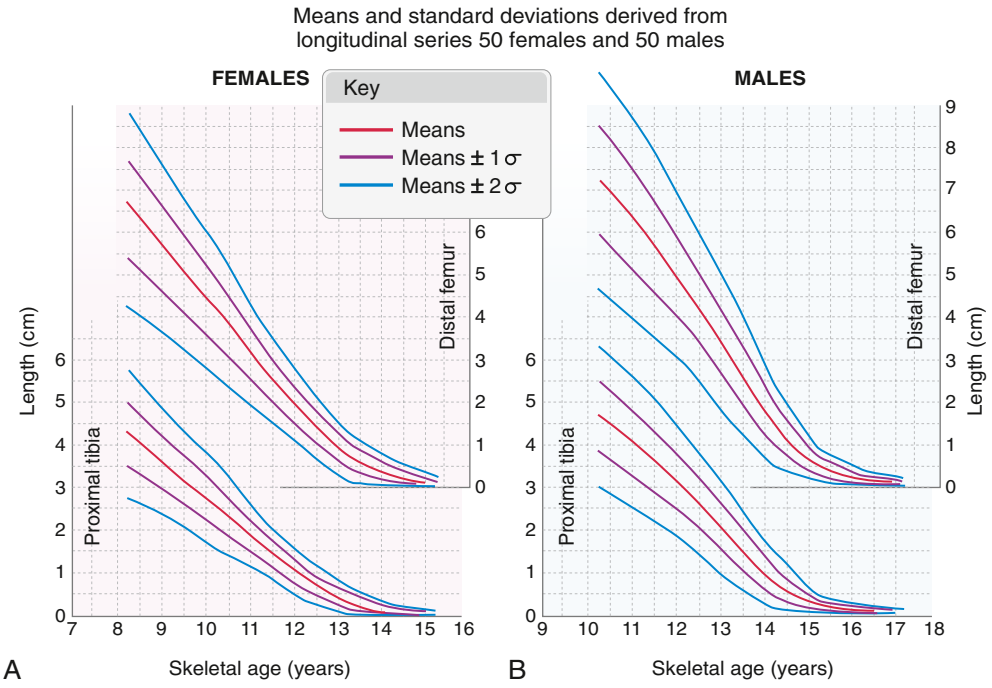

Fig. 717.4 Growth remaining charts for the distal femur and proximal tibia for females (A) and males (B). These charts are based on the growth data and an estimate of the contribution to growth of the distal femur (70%) and the proximal tibia (56%) to the total length of the respective bone. Data are presented relative to skeletal age from age 8 yr to skeletal maturity. *(From Podeszwa D. Limb length discrepancy. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier, 2022: Fig 20.13.)*

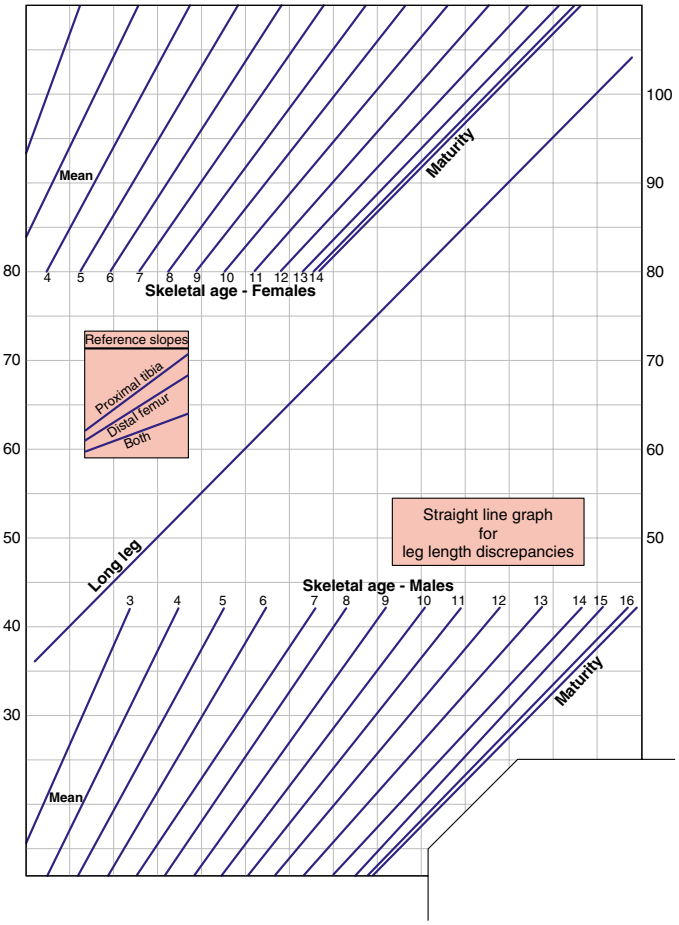

Fig. 717.5 The Moseley straight-line graph for the assessment of leg-length inequalities. This allows simultaneous correlation of the normal leg, short leg, and bone age of the child. It will accurately predict lengths of each extremity at skeletal maturity. The reference slopes are used as a guide in determining when appropriate treatment should be performed. *(From Moseley CF. A straight-line graph for leg-length discrepancies. J Bone Joint Surg Am. 1977;59:174–179.)*

Multiplier for Males and Females (Paley et al, 1999)

Males		Females	
Age	**Multiplier**	**Age**	**Multiplier**
0	5.08	0	4.63
0.4	4.01	0.3	4.01
1	3.24	1	2.97
1.3	2.99	2	2.39
2	2.59	3	2.05
3	2.23	3.3	2.00
4	2.00	4	1.83
5	1.83	5	1.66
6	1.68	6	1.53
7	1.57	7	1.43
8	1.47	8	1.33
9	1.38	9	1.26
10	1.31	10	1.19
11	1.24	11	1.13
12	1.18	12	1.07
13	1.12	13	1.03
14	1.07	14	1.00
15	1.03	15	1.00
16	1.01	16	1.00
17	1.00		
18	1.00		

LLD Prediction Formulas

Prenatal LLD (congenital)
$\Delta_m = \Delta \times M$

Postnatal LLD (developmental)
$\Delta_m = \Delta + I \times G$

Inhibition $\approx I = 1 - \frac{S - S^{\bullet}}{L - L^{\bullet}}$

Growth remaining = $G = L(M - 1)$

Δ_m = LLD at maturity

Δ = Current LLD

L & S = Current length of long and short leg

$L^{\bullet}$ & $S^{\bullet}$ = Length of long and short leg at any other date since LLD began

Fig. 717.6 Paley multiplier. This is a simple method of determining the leg-length discrepancy (LLD) at maturation. This is applicable for shortening conditions in which growth retardation is consistent. *(From Paley D, Bhave A, Herzenberg JE, et al. Multiplier methods for predicting limb-length discrepancy. J Bone Joint Surg Am. 2000;82;1432–1446.)*

of lengthening is 1 mm/day in the femur and 0.75 mm/day in the tibia, and it takes approximately 1 month of wearing the fixator for each centimeter of length gained with a minimum of 3 months in the fixator. Additional time in the fixation device may be required for pathologic bone or for metabolic diseases affecting bone formation. A maximum of 15–25% of the original length of the bone may be gained at each session and is limited by tolerance of the soft tissues and nearby neurovascular structures. An advantage of



Fig. 717.7 Ilizarov device demonstrating bone lengthening by distraction osteogenesis.

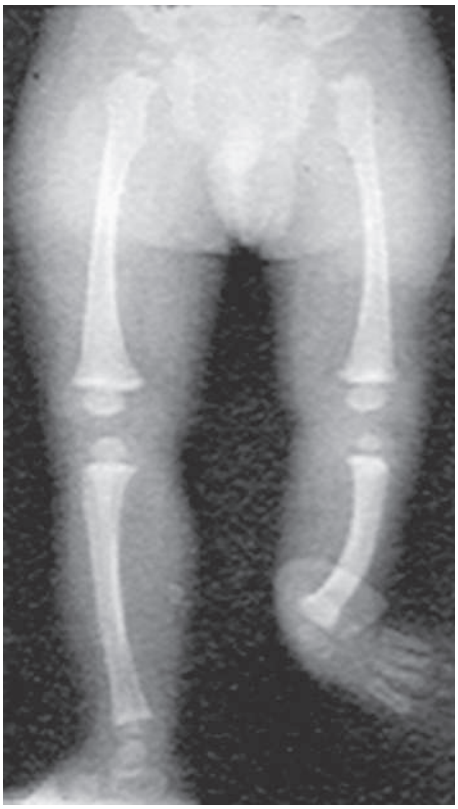

Fig. 717.9 Anteroposterior radiograph of fibular hemimelia with leg-length discrepancy.



Fig. 717.8 Extension prosthesis leg-length discrepancy (A) and compensated with extension prosthesis (B).

the circular fixator or multiaxial external fixators is the ability to correct coexisting angular deformities at the same time. Technologic advances have allowed the development of totally implantable intramedullary lengthening rods driven by external magnets. Internal lengthening has become the procedure of choice for patients whose age and anatomy are appropriate for the procedure, especially in the femur where external fixation is more poorly tolerated. These devices may provide improvements in patient satisfaction and reduced complications, including a lower rate of contracture and absence of pin site infection. New technologies for internal lengthening in skeletally immature patients whose physes cannot safely be violated by a rigid nail are actively under study. Complications of limb lengthening include pin tract infection (most common), wound infection, hypertension, joint subluxation, muscle contracture, stretch-induced nerve palsy, premature consolidation, delayed union, implant-related problems, and fractures after implant removal.

Early amputation and prosthetic fitting may provide the best long-term function in patients with projected discrepancies in excess of 18-20 cm, especially when there are coexisting deformities or deficiencies of the ipsilateral foot (Figs. 717.8 and 717.9). The alternative would be multiple reconstructive procedures throughout childhood and adolescence. The cultural and personal values of the child and family, as well as the impact of multiple procedures on the child's psychosocial development, must also be kept in mind when formulating the treatment plan in these complex cases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 718

The Knee

Anne M. Coyle and J. Todd R. Lawrence

NORMAL DEVELOPMENT OF THE KNEE

The knee is a synovial joint and forms between the third and fourth months of fetal development. Secondary ossification centers form between the sixth and ninth fetal months at the distal femur and between the eighth fetal month and the first postnatal month at the proximal tibia. The patellar ossification center does not appear until 2-4 years of age in females and 3-5 years of age in males.

ANATOMY AND RANGE OF MOTION

The knee is the largest joint in the body and acts primarily as a modified hinge. The distal femur is cam shaped, with the medial and lateral femoral condyles having slightly different shapes. The shape of the articular surfaces allows the femur to glide posteriorly on the tibial plateau during knee flexion and also permits approximately 8-12 degrees of rotation through the flexion and extension arc. The normal range of motion of the knee is from neutral (or fully straight) to 140 degrees of flexion. Increased ligament laxity, including hyperextension of up to 10-15 degrees, can be normal in many children. Most activities can be performed in the flexion arc of 0-70 degrees.

The knee consists of three articulations: *patellofemoral*, *tibiofemoral*, and *tibiofibular*. The anterior and posterior cruciate ligaments as well as medial and lateral collateral ligaments stabilize the knee during movement. The medial and lateral menisci provide support under compressive forces, helping to redistribute the forces from the more rounded distal femur to the flatter proximal tibia. The medial patellofemoral ligament is the primary static soft tissue restraint against lateral patellar displacement. There are also several bursae located about the knee to cushion and reduce friction on tendons acting across the knee joint.

718.1 Discoid Lateral Meniscus

Anne M. Coyle and J. Todd R. Lawrence

Discoid lateral meniscus (DLM) is a congenital anatomic variation of the lateral meniscus that may be asymptomatic or cause the classic **snapping knee syndrome**. Many cases are asymptomatic for years, making the true incidence difficult to determine. DLM is estimated to occur in 3–5% of children and adolescents and is bilateral in about 20% of cases.

Anatomically, the normal meniscus (Fig. 718.1A) is attached around its periphery and at the tips of the "C" anteriorly and posteriorly onto the tibia. During knee motion, the meniscus translates anteriorly and posteriorly to match the slight rollback of the lateral femoral condyle on the tibia with knee flexion. However, with DLM, the meniscal tissue trapped between the articular surfaces is pushed anteriorly as the knee flexes. These abnormal forces, over time, result in tears in the meniscal tissue, the peripheral attachments, or both. Tearing or stretching of this tissue allows for excessive meniscal displacement during knee range of motion. Usually a pop is heard or sensed when flexing at about 90-120 degrees of knee flexion as the meniscus is extruded anteriorly and a loud click or clunk is heard when extending the knee in the last 30 degrees of extension as the meniscus reduces back between the joint surfaces.

The **Watanabe classification system** defines three types of DLM based on arthroscopic appearance. A type I, or **complete discoid lateral meniscus**, is characterized by a thickened lateral meniscus with complete coverage of the tibial surface (see Fig. 718.1B). Because meniscus tissue is always between the joint surfaces with this type of discoid meniscus, it is the type most commonly associated with the knee snapping characteristic of DLM. A type II, or **incomplete discoid lateral meniscus**, is of variable size and covers a lower percentage of the tibial surface (see Fig. 718.1C) compared to the complete type. Although the meniscus can become stretched or torn over time, both the complete and the incomplete types are thought to develop with normal peripheral attachments. A type III, or **Wrisberg variant lateral meniscus**, has no peripheral attachments posteriorly. Instead, it is stabilized posteriorly only by a prominent meniscofemoral ligament, or ligament of Wrisberg, that secures the posterior horn of the lateral meniscus to the lateral surface of the medial femoral condyle (see Fig. 718.1D). As a result, the Wrisberg ligament type of DLM is extremely mobile. Although its shape is not necessarily discoid, the hypermobility of the posterior portion of the meniscus allows it to be extruded anteriorly with flexion and for it to pop back into place with extension, allowing it to present with the same snapping knee pain characteristic of the other DLM variants.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

All types of DLM can be asymptomatic, especially if they have stable peripheral attachments and no tears (see Fig. 718.1). Patients with *symptomatic* DLM usually present with complaints of lateral knee pain and examination findings consistent with a meniscal tear or meniscal instability because of absent peripheral attachments, allowing for anterior extrusion during flexion and reduction with extension thus producing the classic snapping knee. Although patients can present as early as 2 years of age, presentation after 6 years of age is typical, with the highest incidence of presentation during the teenage years.

Younger children usually present with no history of trauma or acute inciting event but rather with a complaint of popping in the knee with occasional swelling as a result of peripheral tears or instability of the meniscus. Older children and adolescents often can recall an inciting event and will sometimes report a history of the mechanical popping. However, they more often note lateral joint line pain and knee swelling. Weight gain during the adolescent growth spurt places increased static and dynamic loads on the tissue, especially during high-level sports. In these patients, degeneration in the central portion of the DLM with direct weight-bearing makes the meniscus highly susceptible to injury and tears, producing the lateral pain and swelling in the knee. Often, the classic popping is not appreciated in these patients.

Physical examination often shows a mild effusion and tenderness over the lateral joint line. For patients with an unstable meniscus, when the knee is fully flexed, a pop with a slight protuberance along the lateral joint line anteriorly can sometimes be appreciated as the meniscus is extruded anteriorly. When the knee is brought back into extension at approximately 20-30 degrees short of full extension, the meniscus can be felt to snap back in place and the protuberance at the lateral joint line disappears.

A high level of suspicion is necessary based on history and clinical examination findings because many patients will present with a complaint that their knee is "dislocating." Radiographs including standard anteroposterior (AP), lateral, merchant (patellar), and 45 degrees flexed posteroanterior (PA) (tunnel) views should be obtained if this diagnosis is considered. Radiographs may appear normal or show findings that include widening of the lateral aspect of the knee joint, flattening of the lateral femoral condyle (resulting in a squared-off appearance), lateral tibial spine hypoplasia, and cupping of the lateral aspect of the tibial plateau. Because these findings are very nonspecific, with any history or physical examination findings suggestive of DLM, evaluation using MRI will provide a definitive diagnosis. Diagnosis on MRI is made if the ratio of the minimal meniscal width to the maximal tibial width in the coronal plane is >20% and/or if continuity between the anterior and posterior horns of the meniscus is present on three or more consecutive slices in the sagittal plane.

TREATMENT

Patients with asymptomatic or incidentally found DLM without evidence of a tear or meniscal instability do not require treatment. They should be educated on symptoms to anticipate, but activity restriction

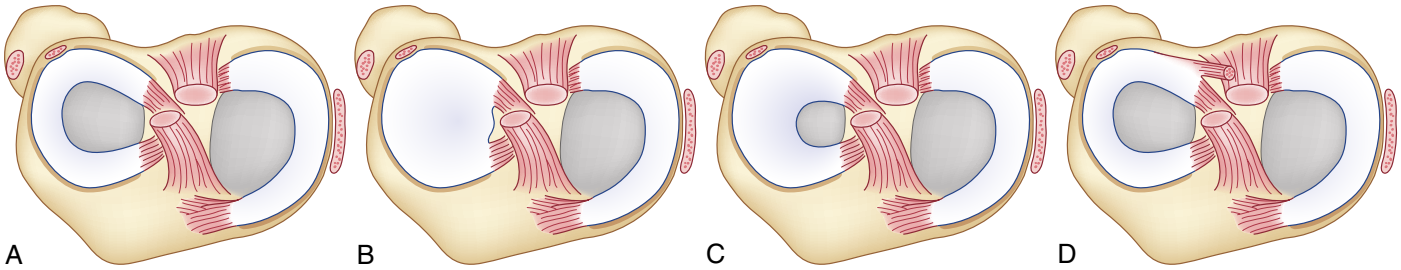

Fig. 718.1 The anatomy of the normal meniscus and discoid variants. A, The lateral meniscus normally has a C shape with circumferential and root attachments. B, A type I, or complete, discoid lateral meniscus covers the entire tibial plateau and has normal attachments. C, A type II, or incomplete, discoid lateral meniscus partially covers the tibial plateau and also has normal attachments. D, A type III, or Wrisberg ligament type, appears similar in shape to a normal lateral meniscus but lacks sufficient attachments posteriorly resulting in a hypermobile meniscus. The ligament of Wrisberg secures the posterior horn of the meniscus to the lateral aspect of the medial femoral condyle.

is not usually necessary. If knee pain or mechanical symptoms are persistent and limit activity or if a meniscal tear develops, surgical intervention should be considered. Partial meniscectomy, referred to as **saucerization**, is often performed to reshape the meniscus arthroscopically with the goal of obtaining an anatomically normal-appearing meniscus (Fig. 718.2). Tears remaining in what would be the normal rim of meniscal tissue are either repaired or excised. Meniscal instability is also addressed with repairs as appropriate. Because tears that extend from the center of the meniscal tissue all the way to the peripheral rim are difficult to repair and removing this much meniscal tissue leaves the joint surfaces unprotected, leading to early osteoarthritis, addressing DLM tears as soon as they develop and before they extend to the periphery is preferred. Approximately 9–17% of patients require repeat operation, which is almost always due to repeated tear of the meniscus. Patients with symptomatic DLM are 4.5 times more likely to eventually require surgical treatment on their other knee.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

718.2 Popliteal Cysts (Baker Cysts)

Anne M. Coyle and J. Todd R. Lawrence

Popliteal cysts or Baker cysts are simple cystic masses filled with gelatinous material that develops in the popliteal fossa, the shallow depression located at the posterior part of the knee. They are considered rare in children. They most commonly occur in the region of the medial head of the gastrocnemius and semimembranosus muscles as an isolated fluid-filled bursa or via herniation through the posterior joint capsule of the knee into this same location. Histologically, the cysts are classified as fibrous, synovial, inflammatory, or transitional. Typically, popliteal cysts resolve spontaneously, although the process may take several years.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients commonly present with a unilateral mass behind the knee that may be fairly large when first noted. Typically, there is no associated history of trauma or knee injury. Physical examination reveals a firm but compressible mass in the popliteal fossa, often medially located and distal to the popliteal crease. The mass is usually most prominent when the knee is extended. Transillumination of the cyst on physical examination is a simple diagnostic test. Knee radiographs are normal but should be obtained to rule out other lesions, such as osteochondromas, osteochondritis dissecans, and malignancies. Ultrasonography, MRI, or aspiration may confirm the diagnosis. Ultrasound can be used to confirm a simple cystic lesion in the expected anatomic location and is often the only diagnostic test necessary with these reassuring findings. However, if a solid mass, vascular lesion, or complex cystic lesion is identified on ultrasound, an MRI may be used to further evaluate the mass. Additionally, in the presence of a knee effusion, an MRI should be considered to evaluate for knee intraarticular pathology that may be causing the swelling. These children should also be assessed for other pathology that may cause recurrent or intermittent knee effusions, including Lyme disease, juvenile idiopathic arthritis, or other autoimmune processes. The presence of a solid mass detected on ultrasound or MRI warrants additional diagnostic testing and referral for biopsy.

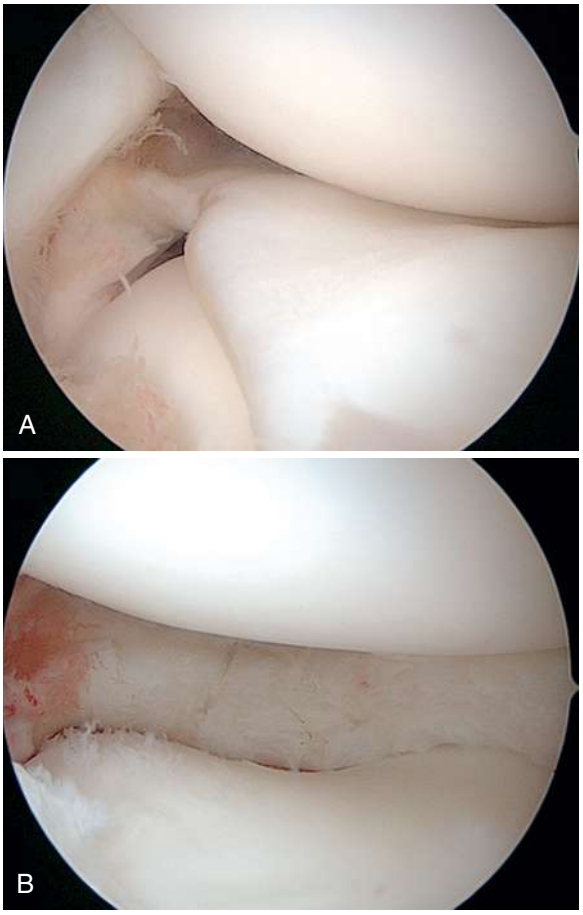

Fig. 718.2 Surgical treatment of discoid lateral meniscus. Arthroscopic images of a complete discoid lateral meniscus before (A) and after (B) partial meniscectomy.

TREATMENT

In most cases, reassurance is all that is needed for popliteal cysts because they often resolve spontaneously. Rest and leg elevation can be suggested to promote drainage of the fluid accumulating within the cyst. In rare cases in which the cyst is persistently symptomatic, treatment options include aspiration to reduce the size of the cyst and/or corticosteroid injection to reduce inflammation. However, because

cysts often recur after treatment, the risk of these procedures is not usually worth the benefits. Surgical excision of a popliteal cyst is indicated only when symptoms are debilitating and have not resolved after an extended period of conservative treatment. If surgical excision is pursued, concurrent arthroscopic treatment of underlying joint pathology is typically recommended to significantly decrease recurrence rates.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

718.3 Juvenile Osteochondritis Dissecans

Anne M. Coyle and J. Todd R. Lawrence

Osteochondritis dissecans (OCD) is a localized pathologic process of the subchondral bone that secondarily affects the overlying articular cartilage and can progress to instability of the lesion with cartilage separation and fragmentation. Although OCD may occur in different joints, including the elbow and ankle, 75% of lesions are seen in the knee. Emerging evidence suggests that the cause of OCD is vascular insult to the developing knee that is unable to heal because of repetitive microtrauma. The disorder is being seen with rising frequency in children and adolescents, with a higher incidence in patients >12 years old, likely in large part because of the increased sports participation of young athletes. OCD is more common in active children, and about 60% of cases occur in participants of high-level athletics. The natural history of juvenile OCD is not the same as that seen in adults. In the knee, OCD most commonly affects the lateral aspect of the medial femoral condyle; however, the lateral femoral condyle and patella may also be affected. Failure of both the bone and the cartilage surface to heal completely is associated with an increased risk for developing premature osteoarthritis. Although the exact incidence of OCD is unknown, it is estimated to occur bilaterally in 14–20% of patients.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common presenting complaint is a vague or deep knee pain that is often activity related with no history of significant trauma to the knee. If the osteochondral fragment becomes unstable, the patient may also develop mechanical symptoms, such as catching or locking. Physical examination findings include effusion, tenderness to palpation over the femoral condyles, quadriceps atrophy, and diminished range of motion. It is important to conduct a thorough history and physical examination because several other conditions can present similarly in the pediatric population, including torn meniscus, patellofemoral pain syndrome, and hip pathologies such as Legg-Calvé-Perthes disease and slipped capital femoral epiphysis.

Imaging evaluation of OCD typically includes plain radiographs and MRI. Radiographs can establish the diagnosis and can be used to evaluate the treatment response. Because most OCD lesions are located more on the posterior aspect of the femoral condyle, a PA radiograph with a 45-degree flexed knee (tunnel view) is often required to evaluate for the presence of an OCD. Many of these patients also have some degree of patellar-related pain, necessitating merchant (patellar) view plain films. Thus standard radiographic evaluation of nontraumatic adolescent knee pain should routinely include AP, lateral, tunnel, and merchant radiographs of the knee. An early lesion may appear as a small radiolucency at the articular surface. A more advanced lesion may have a well-demarcated segment of subchondral bone with a lucent line demonstrating separation from the condyle. The clinical significance of irregularities in the ossification center of the developing epiphysis in children younger than 10 years is unclear.

MRI is useful for both diagnosing and characterizing OCD lesions. It can be used to determine the size and stability of the OCD, the integrity of the articular cartilage, and the presence of loose bodies. Fluid observed between the fragment and subchondral bone suggests an unstable lesion and a high risk for detachment. Any linear signal through the articular cartilage or displacement of the fragment indicates a potentially unstable lesion as well. Cysts surrounding the OCD can indicate instability if there are multiple or they are large in size. However, when deciding treatment, it is important to consider both the clinical and radiographic findings as the ability of MRI to predict OCD stability in the pediatric population has been reported to be only 30–92% accurate. For an unstable-appearing OCD, based on either the patients' symptoms and signs or the imaging, arthroscopy is considered the gold standard to determine stability and should be performed to evaluate the status of the lesion.

TREATMENT

Treatment for juvenile OCD includes nonoperative and surgical management, with treatment decisions being based on many factors, including the growth status and skeletal maturity of the patient, the presence of symptoms, the size of the lesion, whether the lesion appears intact and stable, or if there is any suggestion of instability. The rate of juvenile OCD healing without surgical intervention is estimated to be 30–60%. Skeletal immaturity (i.e., younger age), smaller lesion size, and the absence of mechanical symptoms or pain have been associated with a higher likelihood of OCD healing with nonoperative treatment. Unstable OCD lesions will not usually heal with conservative treatment and thus almost always require surgical intervention.

Young patients with stable lesions, as evidenced by an intact articular surface on imaging (Fig. 718.3A), are deemed to have an acceptable probability of healing and are often initially managed conservatively with a period of restricted weight-bearing and immobilization, followed by a period of strict activity restriction and physical therapy for 3-6 months. OCD healing is followed with radiographs, usually at intervals of approximately 1.5-3 months, until lesion healing has been noted. If healing has not been radiographically confirmed in 3-6 months, surgical intervention is often considered. Because of the low rate of healing in skeletally mature patients, even intact lesions are not usually managed conservatively in this patient population, and surgery is recommended.

Although nonsurgical treatment may be successful in stable lesions, surgical treatment of these lesions is often more successful. Surgery also seems to induce healing at a faster rate than conservative treatment. Because surgical treatment has a very low complication rate and a time frame of recovery that closely parallels a course of conservative treatment, some patients may choose to pursue early surgical intervention instead of trying nonoperative treatment first. For stable and intact lesions, surgical management involves arthroscopic evaluation of the joint followed by either a transarticular or retroarticular drilling to stimulate bony healing by creating channels in the subchondral bone that allow revascularization to occur.

More advanced and unstable lesions with findings of edema beneath the fragment, subchondral cyst formation, and partial (see Fig. 718.3B) or complete (see Fig. 718.3C) fragment detachment on arthroscopy are potentially salvageable and should be treated surgically. Treatment involves drilling or fixation with possible bone grafting. OCD lesions may progress and become unstable and dislodge into the joint space (see Fig. 718.3D). Removal of the loose body in addition to cartilage repair and restoration are typically performed for unstable, unsalvageable lesions. In the postoperative period, patients usually require physical therapy to regain strength and range of motion, with a gradual return to baseline activity levels once full healing has been observed. Early identification and treatment of OCD lesions often prevents recurrent symptoms in adulthood and reduces the risk of early-onset osteoarthritis.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

718.4 Osgood-Schlatter Disease and Sinding-Larsen-Johansson Syndrome

Anne M. Coyle and J. Todd R. Lawrence

In skeletally immature patients, the tibial tubercle apophysis is an extension of the proximal tibial epiphysis. As the femur rapidly grows in length, patients often develop tight musculature, particularly of the quadriceps, across the knee joint. These patients also develop

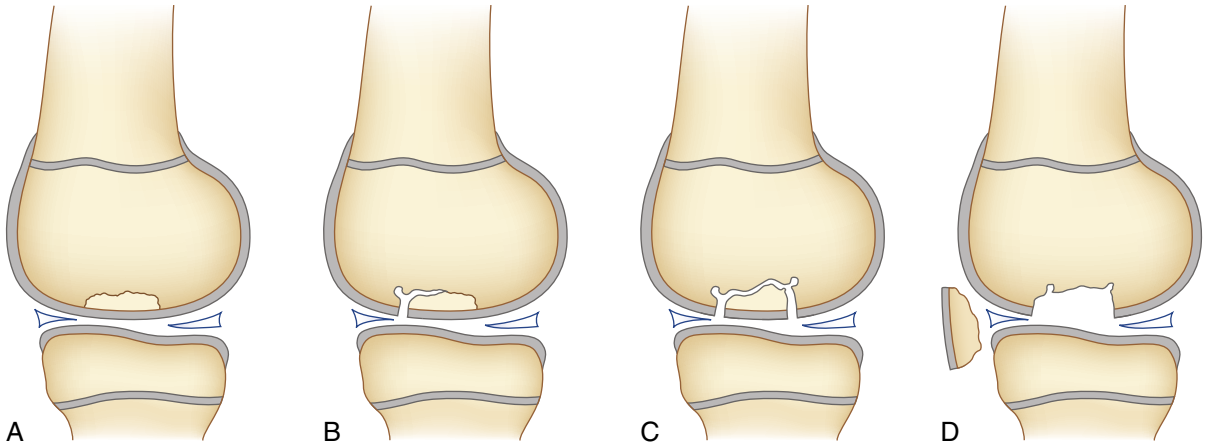

Fig. 718.3 The spectrum of osteochondritis dissecans (OCD) pathology of the knee. A, A stable and intact lesion without breach of the overlying articular cartilage. B, An OCD with fluid beneath the fragment, subchondral cyst formation, and partial fragment detachment. C, An unstable but located lesion with fluid beneath the fragment, multiple subchondral cysts, and complete fragment detachment. D, A dislodged OCD lesion, resulting in a loose body within the knee joint space.

movement patterns that preferentially place stress on the knees during physical activity instead of distributing that stress across other joints in the lower extremity. The repetitive tensile microtrauma sustained during sports or other athletic activities creates traction injuries at the weak points in the extensor mechanism at the knee, as the stress exceeds the developing skeleton's ability to repair the damage.

Sinding-Larsen-Johansson (SLJ) syndrome and **Osgood Schlatter (OS) disease** are *overuse injuries* that occur at the most common "weak points" in the system and are two of the most common causes of anterior knee pain in children and adolescents. SLJ syndrome is an **insertional periostitis** at the inferior pole of the patella. OS disease is an irritation of the patellar tendon at its insertion into the tibial tubercle or a **traction apophysitis** of the tibial tubercle growth plate. These conditions typically present during periods of relative accelerated growth and self-resolve within 12-24 months. SLJ syndrome tends to occur in a slightly younger patient population most commonly ages 9-13 years, whereas OS disease presents in slightly older patients with most symptomatic between the ages of 10-15 years. These conditions are most common in very physically active children particularly those that participate in sports such as basketball, volleyball, and soccer, in which jumping, kicking, and squatting puts repetitive strain on the patellar tendon.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Anterior knee pain, very specifically localized to the inferior pole of the patella (SLJ syndrome) or over the tibial tubercle (OS disease), is the most common patient complaint. Localized soft tissue swelling, along with an eventual firm and fixed increased prominence at the tibial tubercle, may occur with OS disease and may also be part of the initial complaint (Fig. 718.4). There is typically no acute traumatic inciting event, and the history of an acute traumatic onset of symptoms should raise the possibility of a tibial tubercle fracture or patellar sleeve fracture. The pain is aggravated by sports activities but may often persist with regular daily activities and even at rest. Physical examination reveals point tenderness over the inferior pole of the patella (SLJ) or over the tibial tubercle (OS disease). The presence of a knee effusion should raise the possibility of other intraarticular pathology. Diagnosis is usually made clinically, but radiographs may reveal fragmentation of the tibial tubercle and soft tissue swelling consistent with OS disease (Fig. 718.5) and be used to rule out other pathologies.

Another cause of patellar pain is **fat pad impingement syndrome** (Hoffa disease), which is characterized by inflammation and swelling of the infrapatellar fat pad, most often due to trauma or recent surgery. Patients may have pain when extending the knee against resistance.

TREATMENT

In most patients, SLJ syndrome and OS disease are self-limited processes and resolve with rest. Patients are treated with increasing levels

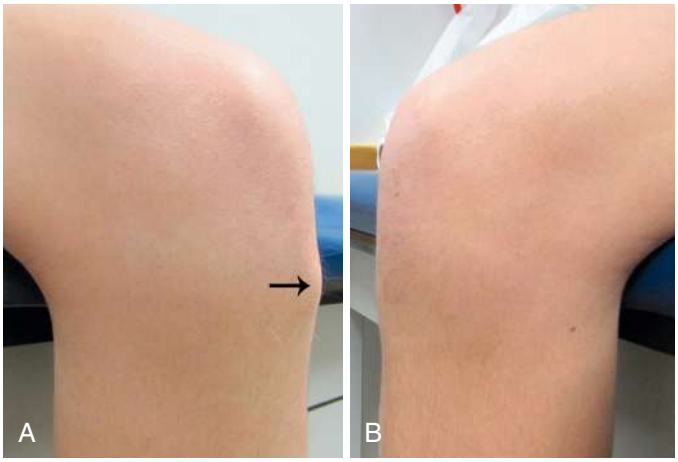

Fig. 718.4 Clinical manifestations of Osgood-Schlatter disease. The increased prominence of the tibial tubercle, indicated by the *arrow,* (A) from traction apophysitis in a 15-yr-old male's knee is contrasted with the normal appearance of the tibial tubercle (B) in his contralateral, unaffected knee.

of activity restriction or immobilization to get them to a pain-free state before advancing their activities. For instance, if they have pain only with running, but are pain free with normal daily activities, they may be restricted from running but perform daily activities for 2 weeks before advancing. In more severe cases, a knee immobilizer or even crutches with restricted weight-bearing are required to help the patient reach a pain-free state. Patients are usually advised to maintain this pain-free level of activity for 1-2 weeks before attempting to advance their activities. Sports and other dynamic activities are restricted until the patient is pain free with palpation and during daily activities for at least 2 weeks. During this rest period, addressing some of the contributing factors, such as muscular tightness, can help prevent a recurrence with activity resumption. A self-directed stretching regimen, concentrating on the quadriceps and hamstrings, may be provided. Some patients and resistant cases may benefit from formal instruction in these exercises with a physical therapist. Adjunctive therapy with ice (20 minutes every 2-4 hours and after activity) and NSAIDs (topical or oral) is common.

Communication with the patient and family members about the disease and prognosis is an important component of treatment. Reassurance may be appropriate because some patients and parents fear that the swollen tubercle may be a sign of a more significant pathology. Patients and family members should be advised that the tibial tubercle swelling will likely not fully resolve. Additionally, some evidence has suggested that a subgroup of patients who are competitive athletes may

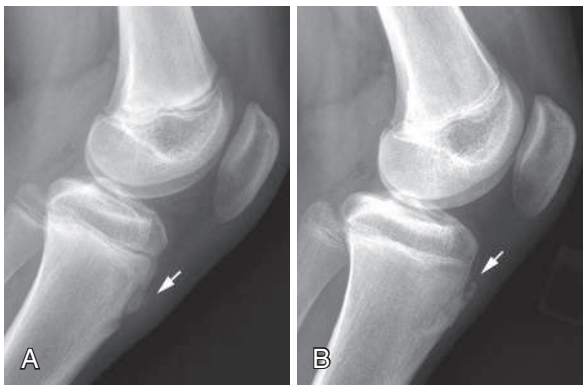

Fig. 718.5 Radiographic findings of Osgood-Schlatter disease. **A,** Lateral radiograph of the knee of a 13-yr-old male demonstrates a sliver of new bone formation *(arrow)* at the tibial tubercle. **B,** Lateral radiograph of the same child at 15 yr of age demonstrates characteristic fragmentation *(arrow)* of the tibial tubercle.

experience long-term pain, and therefore options of treatment strategies and goals regarding participation in competitive sports may need to be discussed.

Treatment with hyperosmolar dextrose local injections may improve outcomes in patients with recalcitrant OS disease. However, corticosteroid injections are not recommended because of the risk of rupture of the patellar tendon due to steroid-induced atrophy. In the rare situation in which young adults have persistent and disabling symptoms, surgical removal of ossicles from the tubercle or reduction of an enlarged tibial tubercle may be warranted. Complications are rare and include early closure of the tibial tubercle with recurvatum or hyperextension, deformity, and, rarely, patellar tendon rupture or avulsion fracture of the tibial tubercle. Although rare, these complications can have significant long-term consequences and should thus prompt counseling to avoid playing through the pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

718.5 Patellofemoral Pain Syndrome

Anne M. Coyle and J. Todd R. Lawrence

Also known as **anterior knee pain syndrome**, patellofemoral pain syndrome (PFPS) is one of the most common causes of knee pain and is characterized by pain located around or behind the patella that is elicited during activities that load the patella during knee flexion and weight-bearing such as squatting and running. PFPS affects 6–7% of the general adolescent population and up to 25% of teens who participate in sports. Females are estimated to account for 55–62% cases. Previously, PFPS was thought to arise from a deranged patellar articular surface; however, increasing evidence shows that anterior knee pain is frequently present even with normal articular cartilage of the patella. Even though abnormal patellar tracking may have a role in in the pathogenesis, the precise etiology of the knee pain remains unknown and is likely multifactorial. In adolescents, repetitive loading of the knee joint without adequate time for recovery is thought to be a key factor in developing PFPS.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pain is usually described as being beneath or near the patella. The pain is worse with bent knee activities, such as walking up and down stairs, because these activities put the patella under high compressive loads. Squatting, running, and other vigorous physical activities also exacerbate the anterior knee pain. Sitting in a flexed knee position for an extended period of time, the so-called **theater sign**, is another common complaint and is often relieved through knee extension. The onset of symptoms in usually gradual, with no history of trauma. If a traumatic etiology is noted, consideration for other etiologies should be entertained. Buckling or a sense of the knee *giving way* can occur, but there is rarely any true patellar or knee instability. Swelling is not common and, if present, should prompt further investigation.

On physical examination, reproduction of the patient's pain with palpation about the medial or lateral aspects of the patella and pain during squatting have the highest sensitivity for PFPS. With the knee extended and the quadriceps relaxed, placing pressure on the patella and translating it distally into the top of the trochlear groove, the **grind test**, often also causes pain. Two tests, the patellar tilt test and the patellar apprehension test, have been found to have low sensitivity but the highest specificity for PFPS. The **patellar tilt test** is performed while holding the patella between two fingers, and with the knee extended, the medial patella is compressed posteriorly while simultaneously trying to elevate the lateral aspect of the patella. A fixed lateral aspect of the patella indicates tight lateral structures. With the **patellar apprehension test**, there is resistance to forced lateral displacement of the patella. Reproduction of the patient's pain with these maneuvers is an important component of the examination. Active and passive range of motion of the knee, alignment of the lower extremity, knee ligamentous stability, patellar tracking, and gait should be evaluated to identify any obvious causes of malalignment or an unstable patella. These patients often have tight quadriceps, hamstrings, and heel cords, along with weak hip musculature and poor overall balance. A single leg squat can often highlight the hip weakness and balance and alignment issues that contribute to this condition.

Radiographs are not required for diagnosis as there are no structural defects in PFPS; however, routine radiographs of the knee, including AP, lateral, tunnel (PA with 45-degree flexed knee), and merchant (patellar) views, are sometimes obtained to eliminate other etiologies of vague knee pain, such as OCD. Radiographs of the hip should be considered to rule out hip pathology, such as a slipped capital femoral epiphysis, which can manifest as ill-defined knee pain in adolescents as well. An MRI is not routinely required for evaluation but should be considered in any patient with a history of mechanical symptoms or an effusion. MRI should be considered in cases refractory to standard treatments as well.

TREATMENT

Several methods of nonoperative treatment are used to address PFPS. The mainstay of treatment is continued physiotherapy, involving overall lower-extremity stretching and strengthening, including short-arc quadriceps strengthening, hip and core strengthening, and exercises designed to address balance and overall body positioning during dynamic activities. Home exercise programs can be effective for the properly disciplined and motivated patient, but formal physical therapy should be considered in resistant cases or in patients who are unable to adhere to a self-directed program. Combining physiotherapy with activity modification and load management during treatment is associated with an increased rate of return to sports. Orthoses, including patellar taping, knee sleeves, customized knee braces, or even shoe inserts are often used in conjunction with physical therapy. Knee taping alone does not improve pain; however, exercise therapy in combination with knee taping has a greater reduction in pain than exercise therapy alone. Evidence for long-term benefit from other orthotic use is unclear. Treatment with botulinum toxin injections, nonsteroidal antiinflammatory medications, or therapeutic ultrasound is not substantiated. Despite these efforts, 40% of adolescents will have some pain that continues into early adulthood and significantly affects their quality of life, knee function, and physical activity. Surgical treatment of PFPS is rarely necessary.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

718.6 Patellofemoral Instability

Anne M. Coyle and J. Todd R. Lawrence

The stable tracking of the patellofemoral joint in the front of the knee depends on a balance of the static restraints and the dynamic forces

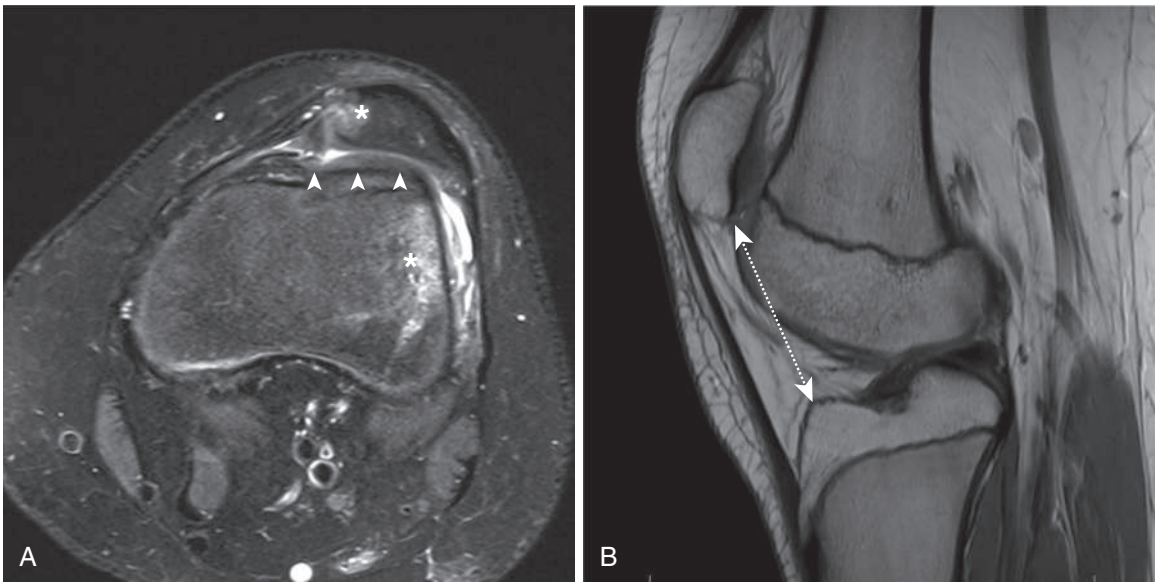

Fig. 718.6 A 14-yr-old female with patellar instability. A, A T2-weighted fat suppression axial image through the mid-patella and proximal trochlea demonstrates the characteristic bone bruise pattern on the medial patella and along the lateral femoral condyle that occurs when the dislocated medial patella impacts the lateral femur *(asterisks)*. Injury to the patellar attachment of the medial patellofemoral ligament is also visible at the medial patella. The patella is laterally subluxated in a dysplastic trochlea that is flat to slightly convex *(arrowheads)* instead of having a normal concave shape. B, A proton density weighted sagittal image through the center of the knee and patella demonstrates patella alta, with the distance from the anterior tibia to the inferior aspect of the patellar cartilage *(dotted line)* being much longer than the length of the patellar cartilage.

acting on the patella. These include the restraining ligaments and the articular anatomy of the patellofemoral groove that serve to balance the dynamic forces of the quadriceps mechanism and overall limb positioning. During knee flexion, the pull of the quadriceps mechanism tends to place an overall lateral displacing force at the patella. The **Q angle** refers to the deviation between the angle of the patellar tendon and the line of the quadriceps. Wider hips and valgus (knock-kneed) positioning increase the Q angle and thus the lateral force applied at the patella. In extension, the static restraints, including the medial restraining ligaments, primarily the medial patellofemoral ligament, are responsible for guiding the patella into the trochlear groove in the distal femur. Once in the trochlea, the bony congruity becomes the primary restraint to the net lateral forces.

Factors that contribute to patellofemoral instability are multifactorial, including ligamentous laxity; trochlear dysplasia, creating a shallow sulcus; condylar hypoplasia; patella alta (a high-riding patella); or malalignment that effectively increases the Q angle, such as genu valgum, increased femoral anteversion, or a lateralized tibial tubercle.

Acute patellofemoral dislocation is the most common acute knee disorder in children and adolescents between ages 10-19 years and often occurs after a sudden valgus strain during sports participation, but it may also be the result of direct trauma. **Recurrent patellofemoral subluxation** is more than one episode of patellar subluxation without frank dislocation. Lateral malalignment of the extensor mechanism and trochlear dysplasia are the most common etiologic factors. **Habitual dislocation of the patella** describes patellar dislocation occurring during every knee flexion/extension cycle. A dysplastic knee with contracture of the lateral portion of the quadriceps mechanism is often associated. Several syndromes are associated with patellar instability, including Down syndrome (see Chapter 57), Turner syndrome (see Chapter 626.1), Kabuki syndrome (see Chapter 102.2), and Rubinstein-Taybi syndrome (see Chapter 102.3).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

With an **acute patellar dislocation**, patients will recall the acute event and the sensation that their kneecap was out of place. A focused, detailed history is important for characterizing the instability. Straightening the knee is all that is usually required to reduce the patella, but sometimes this requires medical attention. Swelling is typically apparent immediately after the injury and appreciable on examination as a large effusion. Pain along the knee from the medial patella to the medial epicondyle of the femur is common. Lateral patellar translocation with the knee extended should be tested with the **patellar apprehension test**. In the acute setting, there will be increased translation and pain and a feeling of insecurity. Patellar tracking is also an important component of the examination but may not be possible due to pain in the acute setting. The **J sign** refers to the inverted J-path the patella takes, beginning in a laterally subluxated position and then suddenly shifting medially to engage the femoral groove with early knee flexion. The torsional profile of the extremity is also important to assess to rule out possible rotational abnormalities of the femur or tibia.

Radiographs of a patient with patellar instability should include AP, lateral, and merchant views (obtained with the knee bent 45 degrees, with the beam of the x-ray through the knee from head to toe) of the patella. In children and adolescents with acute patellar dislocations, osteochondral injuries are present in up to 75% of cases. Radiographs should also be carefully examined for occult fractures. In the presence of a significant knee effusion, mechanical symptoms, acute traumatic patellar dislocation, or uncertainty in the diagnosis, further investigation should include an MRI to evaluate for loose bodies or cartilage damage. MRI will demonstrate bone bruise patterns typical of patellar dislocation at the medial patellar facet and at the lateral femoral condyle and a tear in the medial patellofemoral ligament (Fig. 718.6). Risk factors for recurrent instability include skeletal immaturity, ligamentous laxity, patella alta (see Fig. 718.6), trochlear dysplasia (see Fig. 718.6), and lateralized tibial tubercle (particularly one situated outside the lateral trochlear ridge).

TREATMENT

Nonoperative management that includes activity restriction, bracing, and physical therapy with return to full activity within in 3-4 months is initially recommended for first-time, acute patellar dislocation and recurrent patellar subluxation, unless a large osteochondral fracture or additional intraarticular pathology is seen on imaging studies. Short-term immobilization for 3 weeks in extension with a posterior splint has been shown to significantly decrease the risk of redislocation. After this, transition to a patellar stabilizing brace usually improves symptoms. Successful treatment is usually achieved with formal physical therapy aimed at improving extensor muscle tone, particularly the vastus medialis obliquus, activity-related body positioning, stretching the iliotibial band, and hip and core

muscle strengthening. Current criteria to return to full activity after conservative management requires absence of pain, recurring patellar instability, and knee effusion, as well as full range of motion, adequate core strength and endurance, psychologic readiness, hop test showing limb symmetry >85%, and satisfactory performance on sport-specific drills. Recurrent, ipsilateral patellofemoral instability is reported in up to 36% of skeletally mature patients. However, the reported redislocation rate in skeletally immature patients is as high as 69%. Risk factors for recurrence include younger age at time of first dislocation, ligamentous laxity, open physes, trochlear dysplasia (shallow trochlea), and extensor mechanism malalignment. Patients at high risk for recurrent dislocation may elect to undergo surgical stabilization early to prevent additional traumatic cartilage damage from a repeat dislocation, but early stabilization after the first dislocation is not currently a mainstay of treatment.

Failure to improve after nonoperative treatment and persistent patellar subluxation or experiencing a recurrent dislocation are the major indications for surgical intervention. Patients are considered surgical candidates for early intervention if there are loose bodies, osteochondral fractures, or chondral damage to prevent mechanical blocking of motion. Many different types of surgical procedures exist to prevent dislocation of the patella, but almost all include reconstruction of the medial patellofemoral ligament. Distal realignment of the patellar tendon insertion with a tibial tubercle osteotomy can help improve overall alignment and is often included as part of the stabilization procedure in skeletally mature adolescents. In skeletally immature patients, surgical reconstruction with physeal-sparing techniques can be performed. Guided growth techniques can be used in patients with growth remaining (typically 6 months–1 year) to correct overall alignment. The surgical approach should be patient specific depending on the pathoanatomy contributing to the recurrent instability for best outcomes. Return to full activity criteria is similar to that for nonsurgical management but the timeline may be adjusted based on underlying pathology and bone healing. Recurrence of patellofemoral instability after surgical intervention is estimated to be around 20%.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

718.7 Anterior Cruciate Ligament Rupture

Anne M. Coyle and J. Todd R. Lawrence

Anterior cruciate ligament (ACL) tears account for more than half of all knee injuries. Young age is a known risk factor with peak incidence at 16-18 years old. Pediatric ACL reconstruction has become more prevalent as ACL tears in skeletally immature patients have greatly increased in recent years. This increase is likely due to increased sports participation, increased intensity of training and competition, and participation on multiple teams. Heightened awareness and improved methods for diagnosis are also likely contributing factors to the growing awareness of ACL injuries in children and adolescents.

Females are known to have up to a twofold increased risk for ACL injury compared to males playing the same sport. The gender-specific discrepancy appears to be caused mostly by insufficient neuromuscular activation patterns in females, resulting in increased dynamic **genu valgum** (knock-knee), biased limb alignment when landing, and therefore a heightened tendency toward landing or stopping in an injury-prone position. Other nonmodifiable risk factors include generalized joint laxity, knee recurvatum (hyperextension), femoral anteversion, and contralateral ACL injury. Various pediatric ACL injury prevention programs have shown benefits in not only reducing the rate of injuries but also in increasing athletic strength and performance. Studies also indicate that universal implementation of injury prevention programs can be a cost-effective prevention strategy.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most ACL tears occur as a result of a noncontact injury involving a rapid pivoting, cutting, landing, or stopping maneuver. Patients with an acute knee injury from one of these activities who present with knee effusion and report a "pop" have a 70% chance of an ACL tear. The pop sensation occurs at the time of injury with later development of swelling, limited range of motion, and sometimes a sensation of instability. After the initial injury, patients may have surprisingly little pain. On physical examination, the **anterior drawer sign** or **Lachman test** may indicate increased anterior tibial translation. The Lachman examination is performed by applying an anteriorly directed force to the proximal tibia with the femur stabilized and the knee flexed 20-30 degrees. The amount of translation and the end point are assessed, with increased translation and an indistinct end point indicating a positive test. A **pivot shift test** can also be performed to confirm the diagnosis, but it is rarely tolerated in the conscious patient. It is conducted by gently bending the knee while just supporting the lower leg. A gentle valgus stress and slight internal rotation can enhance the shift. Assessment for concurrent injury to the medial collateral ligament and medial or lateral menisci should be considered as concurrent tears can be present in up to 45% of ACL tears.

Radiographs of the knee are performed, including AP, lateral, tunnel (PA with 45 degrees flexed knee), and merchant (patellar) views, to assess for other potential injuries common in pediatric and adolescent patients, such as tibial spine avulsion fractures or OCD. In acute traumatic injuries, internal and external oblique radiographs can also be helpful. Ultimately, knee MRI is usually necessary to confirm the presence of an intrasubstance ACL tear and any associated meniscal or chondral pathology (Fig. 718.7). Arthroscopic evaluation is the gold standard for diagnosis and treatment.

TREATMENT

The management of ACL injury in this patient population can be challenging, and the severity of the ACL tear and the degree of knee instability are important in directing treatment. Incomplete or partial ACL tears with a firm endpoint on examination may be treated nonoperatively, and the patient's and family's understanding and willingness to adhere to a protocol of bracing and activity restriction are important factors in optimizing outcomes. For complete tears of the ACL, surgical reconstruction is the preferred treatment for patients who are physically, mentally, and emotionally capable of maintaining precautions and complying with the long rehabilitation course after the procedure. Increasing evidence suggests that optimal timing for surgical intervention is within 3 months of injury to reduce the likelihood of additional damage occurring in the knee. While timing does not seem to affect recovery of knee stability, the risk of meniscal injury is up to 4.5 times higher when surgical intervention is delayed. Use of autologous tissue for ACL reconstruction is usually recommended for young active patients due to a lower risk of reinjury compared to allograft tissue. Growth-respecting ACL reconstruction techniques, such as all-epiphyseal, partial transphyseal, or traditional transphyseal reconstruction techniques, are used based on the skeletal maturity of the patient to minimize the risk for growth disturbance across the distal femoral and proximal tibial physes. The ultimate treatment course is an individual decision for the patient and family to make in consultation with their physician.

Depending on the technique used for reconstruction and any associated meniscal pathology addressed, weight-bearing is initially restricted, and a brace is used for the first 4-6 weeks postoperatively. Physical therapy is started postoperatively and continued until strength and functional testing are equal to the contralateral, unaffected limb. Injury prevention through neuromuscular training is built into the final phases of the rehabilitation and final screening tests to try to minimize the risk of reinjury. Most patients regain full range of motion and report no pain by 12 weeks after surgery. Patients return to sports typically at a minimum of 9-12 months postoperatively and are followed on a yearly basis thereafter until skeletal maturity to monitor progress and for any signs of growth disturbance. The majority of athletes are able to return to their same level of competition. The role of using a brace following ACL reconstruction is not established. Rehabilitation programs focused on strengthening, proximal control exercises, and incorporation of various exercise genres have significantly reduced the recurrence in female athletes. However, despite extensive prevention

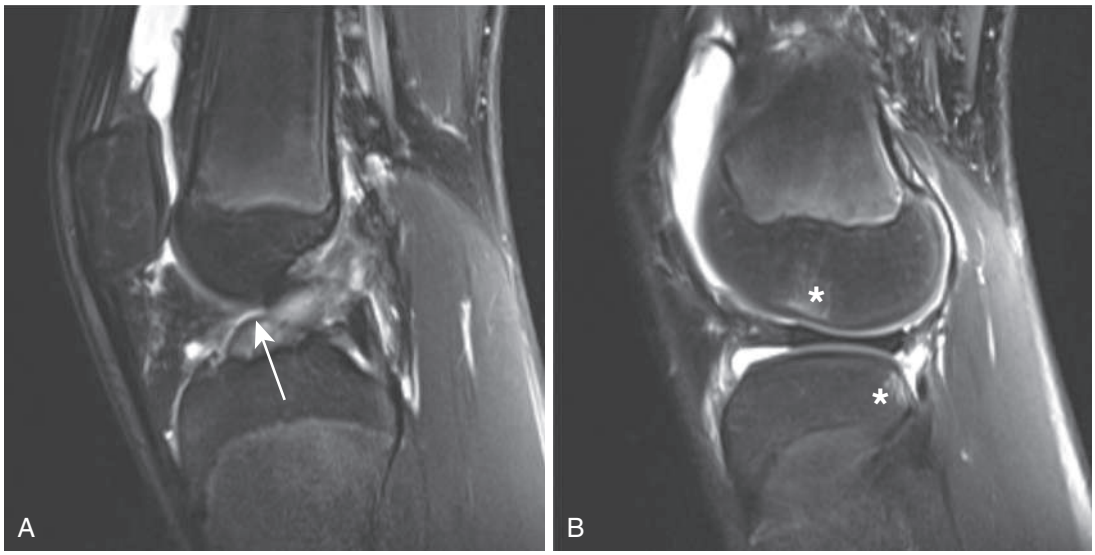

Fig. 718.7 A 14-yr-old female with full-thickness anterior cruciate ligament (ACL) tear. A, A T2-weighted fat-suppression sagittal image through the center of the knee demonstrates a full-thickness tear of the ACL with a folded stump near the tibial attachment. *(arrow)*. B, A T2-weighted fat-suppression sagittal image through the lateral compartment demonstrates the characteristic kissing contusion pattern in the distal femoral condyle and posterior tibial plateau related to the anterior pivot shift that occurs during the ACL injury *(asterisks)*.

efforts, secondary injury rates within 24 months of ACL reconstruction remain very high when patients elect to return to risky sports. The sports with the greatest risk for ACL tears are soccer, basketball, and lacrosse for females and football, soccer, and lacrosse for males. Revision of ACL reconstructions has been associated with increased complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 719

The Hip

Wudbhav N. Sankar, Jennifer J. Winell, B. David Horn, and Lawrence Wells

Anatomically, the hip joint is a ball-and-socket articulation between the femoral head and acetabulum. The hip joint is a pivotal joint of the lower extremity, and its functional demands require both stability and flexibility.

GROWTH AND DEVELOPMENT

The hip joint begins to develop at about the seventh week of gestation, when a cleft appears in the mesenchyme of the primitive limb bud. These precartilaginous cells differentiate into a fully formed cartilaginous **femoral head** and **acetabulum** by the eleventh week of gestation (see Chapter 21). At birth, the neonatal acetabulum is completely composed of cartilage, with a thin rim of fibrocartilage called the **labrum**.

The very cellular hyaline cartilage of the acetabulum is continuous with the triradiate cartilages, which divide and interconnect the three osseous components of the pelvis (the **ilium**, **ischium**, and **pubis**). The concave shape of the hip joint is determined by the presence of a spherical femoral head.

Several factors determine acetabular depth, including interstitial growth within the acetabular cartilage, appositional growth under the perichondrium, and growth of adjacent bones (the ilium, ischium, and pubis). In the neonate, the entire proximal femur is a cartilaginous structure, which includes the femoral head and the greater and lesser trochanters. The three main growth areas are the physeal plate, the growth plate of the greater trochanter, and the femoral neck isthmus. Between the fourth and seventh month of life, the proximal femoral ossification center (in the center of the femoral head) appears. This ossification center continues to enlarge, along with its cartilaginous anlage, until adult life, when only a thin layer of articular cartilage remains. During this period of growth, the thickness of the cartilage surrounding this bony nucleus gradually decreases, as does the thickness of the acetabular cartilage. The growth of the proximal femur is affected by muscle pull, the forces transmitted across the hip joint with weight bearing, normal joint nutrition, circulation, and muscle tone. Alterations in these factors can cause profound changes in the development of the proximal femur.

VASCULAR SUPPLY

The blood supply to the capital femoral epiphysis is complex and changes with growth of the proximal femur. The proximal femur receives its arterial supply from intraosseous (primarily the medial femoral circumflex artery) and extraosseous vessels (Fig. 719.1). The **retinacular vessels** (extraosseous) lie on the surface of the femoral neck but are intracapsular because they enter the epiphysis from the periphery. This makes the blood supply vulnerable to damage from septic arthritis, trauma, thrombosis, and other vascular insults. Interruption of this tenuous blood supply can lead to avascular necrosis of the femoral head and permanent deformity of the hip.

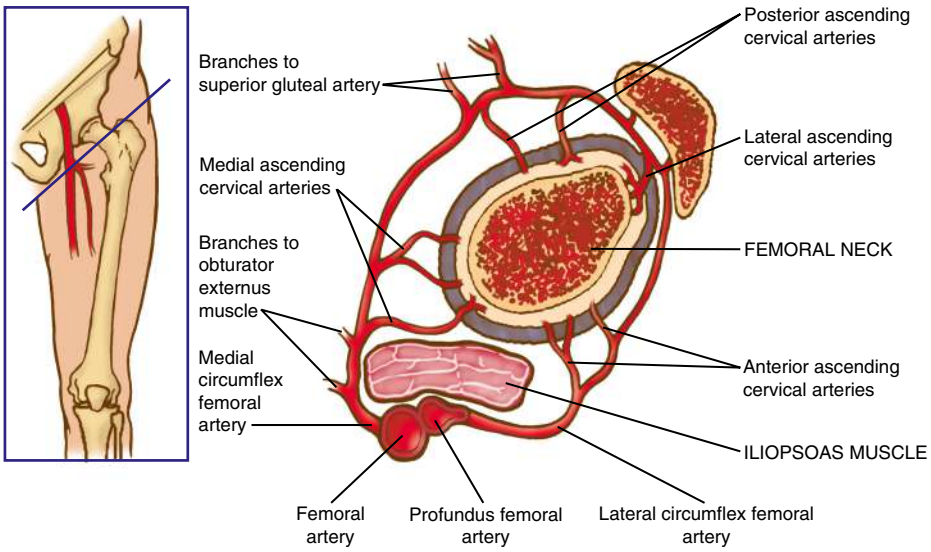

Fig. 719.1 Diagram of vascular anatomy of the proximal femur.

719.1 Developmental Dysplasia of the Hip

Wudbhav N. Sankar, B. David Horn, Jennifer J. Winell, and Lawrence Wells

Developmental dysplasia of the hip (DDH) refers to a spectrum of pathology in the development of the immature hip joint. Formerly called *congenital dislocation of the hip*, DDH more accurately describes the variable presentation of the disorder, encompassing mild dysplasia as well as frank dislocation.

CLASSIFICATION

Acetabular **dysplasia** refers to abnormal morphology and development of the acetabulum. Hip **subluxation** is defined as only partial contact between the femoral head and acetabulum. Hip **dislocation** refers to a hip with no contact between the articulating surfaces of the hip. DDH is classified into two major groups: typical and teratologic. **Typical DDH** occurs in otherwise normal patients or those without defined syndromes or genetic conditions. **Teratologic hip dislocations** usually have identifiable causes, such as arthrogryposis or a genetic syndrome, and occur before birth.

ETIOLOGY AND RISK FACTORS

Although the etiology remains unknown, the final common pathway in the development of DDH is increased laxity of the joint, which fails to maintain a stable femoroacetabular articulation. This increased laxity is probably the result of a combination of hormonal, mechanical, and genetic factors. A positive family history for DDH is found in 12–33% of affected patients. DDH is more common among female patients (80%), which is thought to be because of the greater susceptibility of female fetuses to maternal hormones, such as relaxin, which increases ligamentous laxity. Although only 3–4% of all babies are born in breech presentation, the incidence of DDH in these patients is 16–25%.

Any condition that leads to a tighter intrauterine space and, consequently, less room for normal fetal motion may be associated with DDH. These conditions include oligohydramnios, large birth weight, and first pregnancy. The high rate of association of DDH with other intrauterine molding abnormalities, such as torticollis and metatarsus adductus, supports the theory that the *crowding phenomenon* has a role in the pathogenesis. The left hip is the most commonly affected hip. In the most common fetal position, the left hip is usually forced into adduction by the mother's sacrum.

Tight swaddling with the hips in the extended position has been identified as an important risk factor for the development of hip dysplasia. Population studies of cultures that prefer immobilizing children in hip extension have shown that swaddling in such a way that prevents an infant from naturally drawing their hips to their chest (so called "M" position) is detrimental for hip development.

EPIDEMIOLOGY

Although most newborn screening studies suggest that some degree of hip instability can be detected in 1 in 100 to 1 in 250 babies, actual dislocated or dislocatable hips are much less common, being found in 1-1.5 of 1,000 live births.

There is marked geographic and racial variation in the incidence of DDH. These differences may result from environmental factors, such as child-rearing practices, rather than genetic predisposition. African and Asian caregivers have traditionally carried babies against their bodies in a shawl so that a child's hips are flexed, abducted, and free to move. This keeps the hips in the optimal position for stability and for dynamic molding of the developing acetabulum by the cartilaginous femoral head. Children in Native American and Eastern European cultures, which have a relatively high incidence of DDH, have historically been swaddled in confining clothes that bring their hips into extension. This position increases the tension of the psoas muscle-tendon unit and might predispose the hips to displace and eventually dislocate laterally and superiorly.

PATHOANATOMY

In DDH, several secondary anatomic changes can prevent reduction. Both the fatty tissue in the depths of the socket, known as the pulvinar, and the ligamentum teres can hypertrophy, blocking reduction of the femoral head. The transverse acetabular ligament usually thickens as well, which effectively narrows the opening of the acetabulum. In addition, the shortened iliopsoas tendon becomes taut across the front of the hip, creating an hourglass shape to the hip capsule, which limits access to the acetabulum. Over time, the dislocated femoral head places pressure on the acetabular rim and labrum, causing the labrum to infold and become thick.

The shape of a normal femoral head and acetabulum depends on a concentric reduction between the two. The more time that a hip spends dislocated, the more likely that the acetabulum will develop abnormally. Without a femoral head to provide a template, the acetabulum will become progressively shallow, with an oblique acetabular roof and a thickened medial wall.

CLINICAL FINDINGS

The Neonate

DDH in the neonate is asymptomatic and must be screened for in all newborns by specific maneuvers. Physical examination must be carried out with the infant unclothed and placed supine in a warm, comfortable setting on a flat examination table.

The **Barlow** provocative maneuver assesses the potential for dislocation of an initially nondisplaced hip. The examiner adducts the flexed hip and gently pushes the thigh posteriorly in an effort to dislocate the femoral head (Fig. 719.2). In a positive test, the hip is felt to slide out of the acetabulum. As the examiner relaxes the proximal push, the hip can be felt to slip back into the acetabulum.

The **Ortolani** test is the reverse of the Barlow test: The examiner attempts to reduce a hip that is dislocated at rest (Fig. 719.3). The examiner grasps the child's thigh between the thumb and index finger and, with the fourth and fifth fingers, lifts the greater trochanter while simultaneously abducting the hip. When the test is positive, the femoral head will slip into the socket with a delicate clunk that is palpable but usually not audible. It should be a gentle, nonforced maneuver.

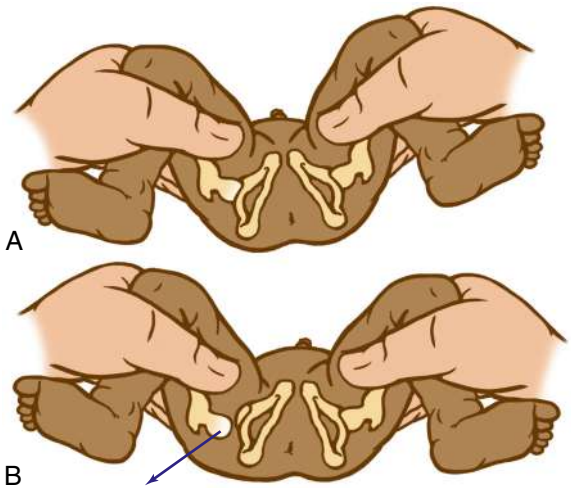

Fig. 719.2 The Barlow provocative test is performed with the patient's knees and hips flexed. A, Holding the patient's limbs gently, with the thigh in adduction, the examiner applies a posteriorly directed force. B, This test is positive in a dislocatable hip.

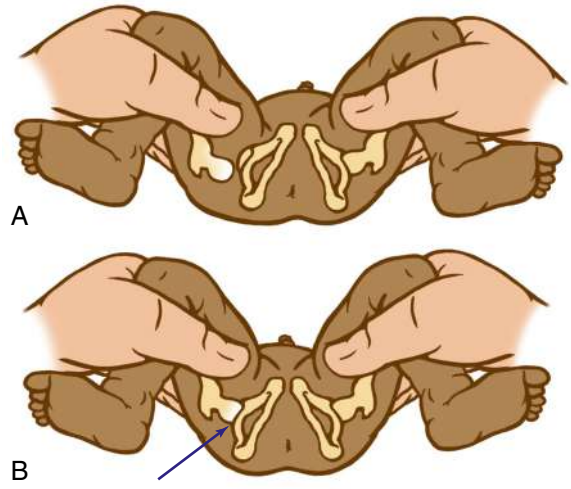

Fig. 719.3 The Ortolani maneuver is the sign of the ball of the femoral head moving in and out of the acetabulum. A, The examiner holds the patient's thigh and gently abducts the hip while lifting the greater trochanter with two fingers. B, When the test is positive, the dislocated femoral head falls back into the acetabulum with a palpable clunk as the hip is abducted.

A **hip click** is the high-pitched sensation (or sound) felt at the very end of abduction during testing for DDH with Barlow and Ortolani maneuvers. A hip click can be differentiated from a **hip clunk**, which is felt as the femoral head goes in and out of joint. Hip clicks usually originate in the ligamentum teres or occasionally in the fascia lata or psoas tendon and do not indicate a significant hip abnormality.

The Infant

As the baby enters the second and third month of life, the soft tissues begin to tighten, and the Ortolani and Barlow tests are no longer reliable. In this age-group, the examiner must look for other specific physical findings, including limited hip abduction, apparent shortening of the thigh, proximal location of the greater trochanter, asymmetry of the gluteal or thigh folds (Fig. 719.4), and positioning of the hip. Limitation of abduction is the most reliable sign of a dislocated hip in this age-group.

Shortening of the thigh, the **Galeazzi sign**, is best appreciated by placing both hips in 90 degrees of flexion and comparing the height of the knees, looking for asymmetry (Fig. 719.5). Asymmetry of gluteal skin creases may be a sign of hip dysplasia. Another helpful test is the **Klisic test**, in which the examiner places the third finger over the greater trochanter and the index finger of the same hand on the anterior superior iliac spine. In a normal hip, an imaginary line drawn between the two fingers points to the umbilicus. In the dislocated hip, the trochanter is elevated, and the line projects halfway between the umbilicus and the pubis (Fig. 719.6).



Fig. 719.4 Asymmetry of thigh folds in a child with developmental dysplasia of the hip.



Fig. 719.5 Positive Galeazzi sign noted in a case of untreated developmental dysplasia of the hip.

The Walking Child

The walking child often presents to the physician after the family has noticed a limp, a waddling gait, or a leg-length discrepancy. The affected side appears shorter than the normal extremity, and the child toe-walks on the affected side. The **Trendelenburg sign** (see Chapter 714) is positive in these children, and an abductor lurch is usually observed when the child walks. As in the younger child, there is limited hip abduction on the affected side and the knees are at different levels when the hips are flexed (the Galeazzi sign). Excessive lordosis, which develops secondary to altered hip mechanics, is common and is often the presenting complaint.

DIAGNOSTIC TESTING

Ultrasonography

Because it is superior to radiographs for evaluating cartilaginous structures, ultrasonography is the diagnostic modality of choice for DDH before the appearance of the femoral head ossific nucleus (4-6 months). During the early newborn period (0-4 weeks), however, physical examination is preferred over ultrasonography because there is a high incidence of false-positive sonograms in this age-group. Therefore, waiting to obtain an ultrasound until the infant is at least 6 weeks of age is recommended unless the child has a strongly positive physical examination. In addition to elucidating the static relationship of the femur to the acetabulum, ultrasonography provides dynamic information about the stability of the hip joint. The ultrasound examination can be used to monitor acetabular development, particularly of infants in Pavlik harness treatment; this method can minimize the number of radiographs taken and might allow the clinician to detect treatment failure earlier.

In the Graf technique, the transducer is placed over the greater trochanter, which allows visualization of the ilium, the bony acetabulum, the labrum, and the femoral epiphysis (Fig. 719.7). The angle formed by the line of the ilium and a line tangential to the bony roof of the acetabulum is termed the α **angle** and represents the depth of the acetabulum. Values >60 degrees are considered normal, and those <60 degrees imply acetabular dysplasia. The **β angle** is formed by a line drawn tangential to the labrum and the line of the ilium; this represents the cartilaginous roof of the acetabulum. A normal β angle is <55 degrees; as the femoral head subluxates, the β angle increases. Another useful test is to evaluate the position of the center of the head compared with the vertical line of the ilium. If the line of the ilium falls lateral to the center of the head, the epiphysis is considered reduced. If the line falls medial to the center of the head, the epiphysis is uncovered and is either subluxated or dislocated.

Screening for DDH with ultrasound remains controversial. Although routinely performed in Europe, meta-analyses indicate that data are insufficient to give clear recommendations. In the United States, the current recommendations are that every newborn undergo a clinical examination for hip instability. Children who have findings suspicious for DDH should be followed up with ultrasound. Most authors agree that infants with risk factors for DDH (breech position, family history, torticollis) should be screened with ultrasound regardless of the clinical findings.

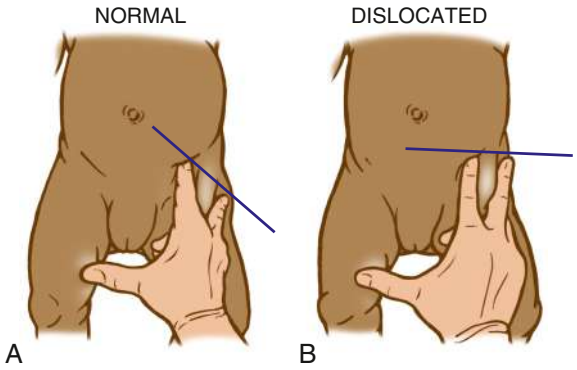

Fig. 719.6 Klisic test. **A,** In a normal hip, an imaginary line drawn down through the tip of an index finger placed on the patient's iliac crest and the tip of the long finger placed on the patient's greater trochanter should point to the umbilicus. **B,** In a dislocated hip, this line drawn through the two fingertips runs below the umbilicus because the greater trochanter is abnormally high.

Radiography

Radiographs are recommended for an infant once the proximal femoral epiphysis ossifies, usually by 4-6 months. In infants of this age, radiographs have proven to be more effective, less costly, and less operator dependent than an ultrasound examination. An anteroposterior (AP) view of the pelvis can be interpreted with the aid of several classic lines drawn on it (Fig. 719.8).

Hilgenreiner's line is a horizontal line drawn through the top of both triradiate cartilages (the clear area in the depth of the acetabulum). **Perkins line** is a vertical line through the most lateral ossified margin of the roof of the acetabulum, drawn perpendicular to Hilgenreiner's line. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these two lines. **Shenton's line** is a curved line drawn from the medial aspect of the femoral neck to the lower border of the superior pubic ramus. In a child with normal hips, this line is a continuous contour. In a child with hip subluxation or dislocation, this line consists of two separate arcs and is described as "broken."

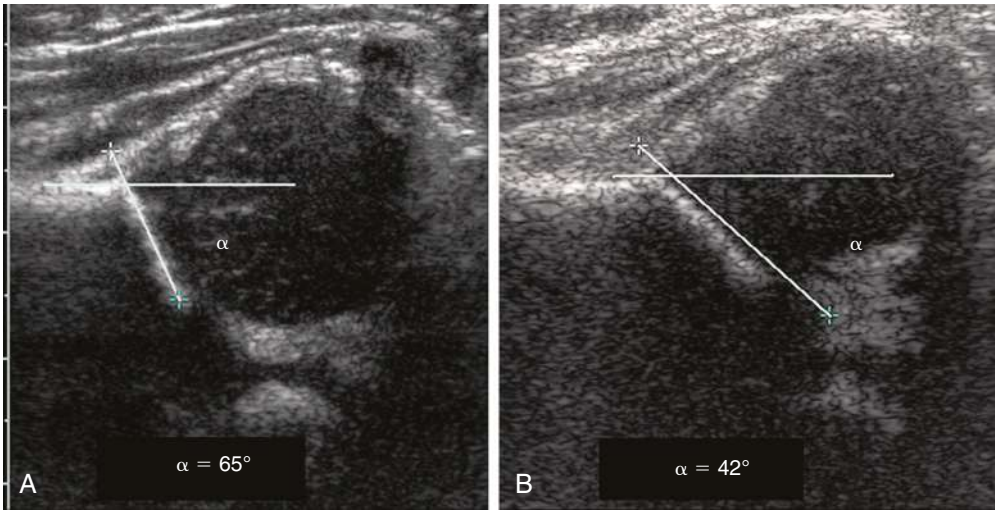

Fig. 719.7 **A,** Normal ultrasonographic image of the hip in an infant. The α angle is >60 degrees. Note that a line drawn tangential to the ilium falls lateral to the center of the femoral head. **B,** In this child with developmental dysplasia of the hip, the left hip demonstrates an α angle of 42 degrees, and a line drawn tangential to the ilium shows that <50% of the femoral head is contained within the acetabulum.

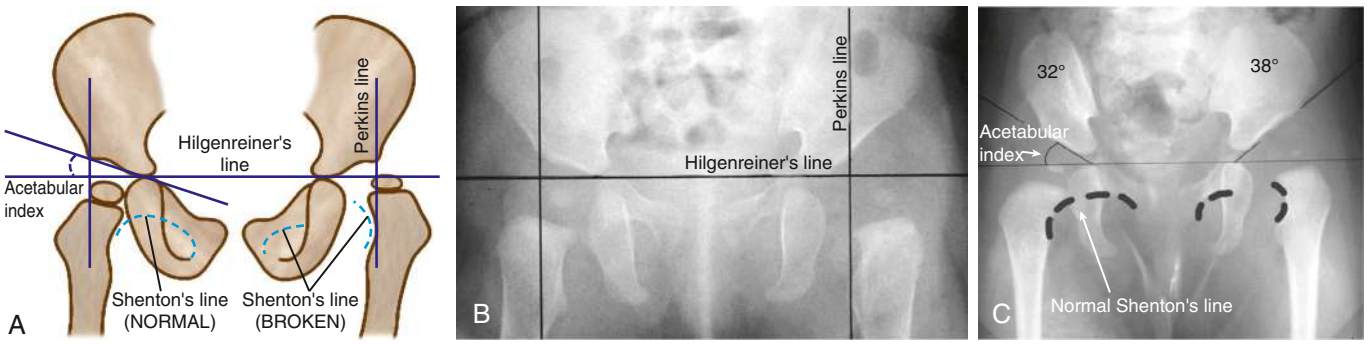

Fig. 719.8 A-C, Radiographic measurements are useful in evaluating developmental dysplasia of the hip. Hilgenreiner's line is drawn through the triradiate cartilages. Perkins line is drawn perpendicular to Hilgenreiner's line at the lateral edge of the acetabulum. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these two lines. Shenton's line curves along the femoral metaphysis and connects smoothly to the inner margin of the pubis. In a child with hip subluxation or dislocation, this line consists of two separate arcs and is described as broken. The acetabular index is the angle between a line drawn along the margin of the acetabulum and Hilgenreiner's line; in normal newborns, it averages 27.5 degrees and decreases with age.

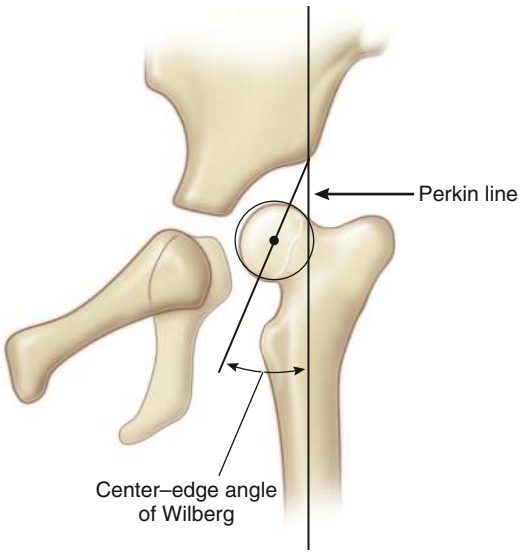

Fig. 719.9 Center–edge angle of Wilberg, which is the angle that is formed between the Perkin's line and a line drawn from the lateral lip of the acetabulum through the center of the femoral head. This angle, which is a useful measure of hip position in older children, is considered normal if it is more than 19 degrees in children between the ages of 6 and 13 years. It increases with age. *(From Kim HK, Herring JA. Developmental dysplasia of the hip. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig.13.31.)*

The **acetabular index** is the angle formed between Hilgenreiner's line and a line drawn from the depth of the acetabular socket to the most lateral ossified margin of the roof of the acetabulum. This angle measures the development of the osseous roof of the acetabulum. In the newborn, the acetabular index can be up to 40 degrees; by 4 months in the normal infant, it should be no more than 30 degrees. In the older child, the **center-edge angle of Wilberg** is a useful measure of femoral head coverage. This angle is formed at the juncture of the Perkins line and a line connecting the lateral margin of the acetabulum to the center of the femoral head (Fig. 719.9). In children 6-13 years, an angle >19 degrees is normal, whereas in children 14 years and older, an angle >25 degrees is considered normal.

TREATMENT

The goals in the management of DDH are to obtain and maintain a concentric reduction of the femoral head within the acetabulum to provide the optimal environment for the normal development of both the femoral head and acetabulum. The later the diagnosis of DDH is made, the more difficult it is to achieve these goals, the less potential there is for acetabular and proximal femoral remodeling, and the more complex the required treatments.

Newborns and Infants Younger Than 6 Months

Newborns' hips that are Barlow positive (reduced but dislocatable) or Ortolani positive (dislocated but reducible) should generally be treated with a Pavlik harness as soon as the diagnosis is made. The management of newborns with dysplasia who are younger than 4 weeks of age is less clear. A significant proportion of these hips normalize within 3-4 weeks; consequently, many physicians prefer to reexamine these newborns after a few weeks before making treatment decisions. A study of newborns with mildly dysplastic hips based on the results of an ultrasound (alpha angles between 43 and 50 degrees) and who were randomly assigned to receive immediate abduction splinting or active sonographic surveillance from birth with Frejka splinting (if treatment was subsequently needed) revealed no difference in radiologic findings at 6 years of age.

Triple diapers or abduction diapers have *no place* in the treatment of DDH in the newborn; they are usually ineffective and give the family a false sense of security. Acetabular dysplasia, subluxation, or dislocation can all be readily managed with the Pavlik harness. Although other braces are available (von Rosen splint, Ilfeld splint, Frejka pillow), the Pavlik harness remains the most commonly used device worldwide (Fig. 719.10). By maintaining the Ortolani-positive hip in a Pavlik harness on a full-time basis for 6 weeks, hip instability resolves in approximately 75% of cases. After 6 months of age, the failure rate for the Pavlik harness is >50% because it is difficult to maintain the increasingly active and crawling child in the harness. Frequent examinations and readjustments are necessary to ensure that the harness is correctly fitted. The anterior straps of the harness should be set to maintain the hips in flexion (usually ~90-100 degrees); excessive flexion is discouraged because of the risk of femoral nerve palsy. The posterior straps are designed to encourage abduction. These are generally set to allow adduction just to neutral, because forced abduction by the harness can lead to avascular necrosis of the femoral epiphysis.

If follow-up examinations and ultrasounds do not demonstrate concentric reduction of the hip after 3-4 weeks of Pavlik harness treatment, the harness should be abandoned. Continued use of the harness beyond this period in a persistently dislocated hip can cause **Pavlik harness disease** or wearing away of the posterior aspect of the acetabulum, which can make the ultimate reduction less stable.

Children 6 Months to 2 Years of Age

The principal goals in the treatment of late-diagnosed dysplasia are to obtain and maintain reduction of the hip without damaging the femoral head. Closed reductions are performed in the operating room under general anesthesia. The hip is moved to determine the range of motion (ROM) in which it remains reduced. This is



Fig. 719.10 Photograph of a Pavlik harness.

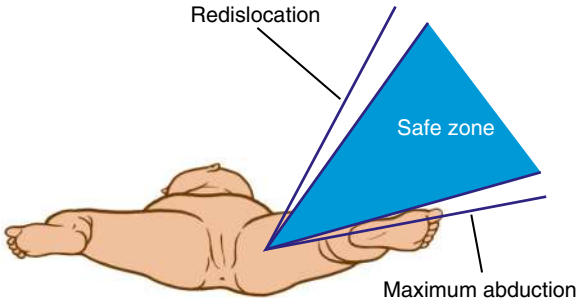

Fig. 719.11 Diagram of the safe zone of Ramsey.

compared to the maximal ROM to construct a "safe zone" (Fig. 719.11). An arthrogram obtained at the time of reduction is very helpful for evaluating the depth and stability of the reduction (Fig. 719.12). The reduction is maintained in a well-molded spica cast, with the "human position" of moderate flexion and abduction being the preferred position. After the procedure, single-cut CT or MRI may be used to confirm the reduction. Twelve weeks after closed reduction, the plaster cast is removed; an abduction orthosis is often used at this point to encourage further remodeling of the acetabulum. Failure to obtain a stable hip with a closed reduction indicates the need for an open reduction. In patients younger than 18 months of age, a concomitant acetabular or femoral procedure is rarely required. The potential for acetabular development after closed or open reduction is excellent and continues for 4-8 years after the procedure.

Children Older Than 2 Years

Children 2-6 years of age with a hip dislocation usually require an open reduction. In this age-group, a concomitant femoral shortening osteotomy is often performed to reduce the pressure on the proximal femur and minimize the risk of osteonecrosis. Because the potential for acetabular development is markedly diminished in these older children, a pelvic osteotomy is usually performed in conjunction with the open reduction. Postoperatively, patients are immobilized in a spica cast for 6-12 weeks.

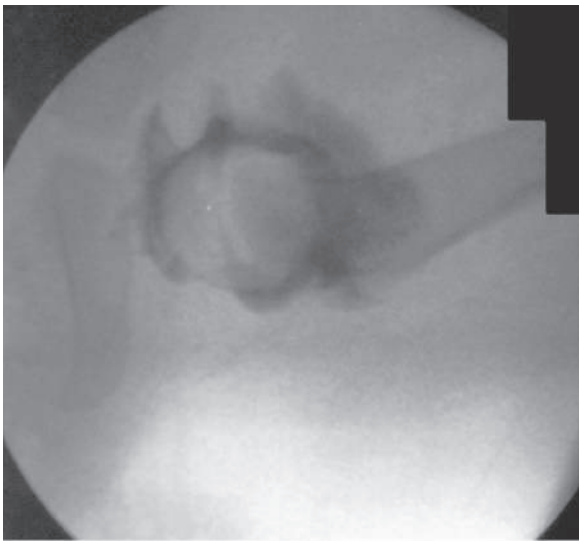

Fig. 719.12 Arthrogram of a reduced hip for evaluating the stability of reduction.

COMPLICATIONS

The most important complication of DDH is **avascular necrosis** of the femoral epiphysis. Reduction of the femoral head under pressure or in extreme abduction can result in occlusion of the epiphyseal vessels and produce either partial or total infarction of the epiphysis. Revascularization soon follows, but if the physis is severely damaged, abnormal growth and development can occur. Management, as previously outlined, is designed to minimize this complication. With appropriate treatment, the incidence of avascular necrosis for DDH is reduced to 5–15%. Other complications in DDH include redislocation, residual subluxation, acetabular dysplasia, pressure ulcers from prolonged casting, and postoperative complications, including wound infections.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

719.2 Transient Monoarticular Synovitis (Toxic Synovitis)

Wudbhav N. Sankar, Jennifer J. Winell, B. David Horn, and Lawrence Wells

Transient synovitis (toxic synovitis) is thought to be a reactive arthritis and is one of the most common causes of hip pain in young children.

ETIOLOGY

The cause of transient synovitis remains unknown. It has been variously described as a nonspecific inflammatory condition or as a postviral immunologic synovitis because it tends to follow recent viral illnesses.

CLINICAL MANIFESTATIONS

Although transient synovitis can occur in all age-groups, it is most prevalent in children between 3 and 8 years of age, with a mean onset at age 6 years. Approximately 70% of all affected children have had a nonspecific upper respiratory tract infection the 7-14 days before symptom onset. Symptoms often develop acutely (~3 days) and usually consist of pain in the groin, anterior thigh, or knee, which may be referred from the hip. These children are usually able to bear weight on the affected limb and typically walk with an antalgic gait with the foot externally rotated. The hip is not held flexed, abducted, or laterally rotated unless a significant effusion is present. They are often afebrile or have a low-grade fever (≤38°C).

DIAGNOSIS

Transient synovitis is a diagnosis of exclusion, and laboratory and radiographic tests can be useful to rule out other more serious conditions. In transient synovitis, infection laboratory tests (ESR: <20 mm/hr, serum CRP: normal or ≤2 mg/dL, and WBC: <12,000 cells/mm^3) are relatively normal, but on occasion a mild elevation in the ESR is observed. AP and Lauenstein (frog-leg) lateral radiographs of the pelvis may be acquired and are also usually found to be normal. Ultrasonography of the hip is the preferred imaging modality and often demonstrates a small joint effusion.

The most important condition to exclude before confirming a diagnosis of toxic synovitis is septic arthritis. Children with septic arthritis usually appear more systemically ill and have more pain than those with transient synovitis, often refusing to walk or move their hip at all. High fever, refusal to walk, and elevations of the ESR, serum CRP, and WBC all suggest a diagnosis of septic arthritis. If the clinical scenario is suspicious for septic arthritis, an ultrasound-guided aspiration of the hip joint should be performed to make the definitive diagnosis (see Chapter 726). An exception to these criteria is hip septic arthritis due to *Kingella kingae or Lyme disease*, which may have minimal inflammation and low-grade or no fever. Synovial fluid white blood cell counts are low in toxic synovitis (<25,000) and much higher in Lyme and septic arthritis (50,00-200,000). MRI may be needed to evaluate for an associated osteomyelitis if the patient has concerning examination or laboratory findings (see Chapter 725).

TREATMENT

The treatment of transient monoarticular synovitis of the hip is symptomatic. Recommended therapies include activity limitation and relief of weight bearing until the pain subsides. Antiinflammatory agents and analgesics can shorten the duration of pain. Most children improve in 5-7 days and recover completely within 3-6 weeks.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

719.3 Legg-Calvé-Perthes Disease

Wudbhav N. Sankar, Jennifer J. Winell, B. David Horn, and Lawrence Wells

Legg-Calvé-Perthes disease (LCPD) is a hip disorder of unknown etiology that results from temporary interruption of the blood supply to the proximal femoral epiphysis, leading to osteonecrosis and femoral head deformity.

ETIOLOGY

Although the underlying etiology remains obscure, most authors agree that the final common pathway in the development of LCPD is disruption of the vascular supply to the femoral epiphysis, which results in ischemia and osteonecrosis. Infection, trauma, and transient synovitis have all been proposed as causative factors but are unsubstantiated. Factors leading to thrombophilia, an increased tendency to develop thrombosis, and a reduced ability to lyse thrombi have been identified. Factor V Leiden mutation, deficiency of proteins C and S, lupus anticoagulant, anticardiolipin antibodies, antitrypsin, and plasminogen activator might play a role in the abnormal clotting mechanism. These abnormalities in the clotting cascade are thought to increase blood viscosity and the risk for venous thrombosis. Poor venous outflow leads to increased intraosseous pressure, which, in turn, impedes arterial inflow, causing ischemia and cell death. LCPD is rarely due to pathogenic variants in *COL2A1*, which is usually sporadic (de novo) and manifests as an autosomal dominant trait.

EPIDEMIOLOGY

The incidence of LCPD in the United States is 1 in 1,200 children, with males 4-5 times more likely to be affected than females. The peak incidence of the disease is between the ages of 4 and 8 years. Bilateral involvement is seen in approximately 10% of the patients, but the hips are usually in different stages of collapse.

PATHOGENESIS

Early pathologic changes in the femoral head are the result of ischemia and necrosis; subsequent changes result from the repair process. The disease course may have four stages, although variations have been described. The **initial stage** of the disease, which lasts an average of 6 months, is characterized by synovitis, joint irritability, and early necrosis of the femoral head. Revascularization then leads to osteoclastic-mediated resorption of the necrotic segment. The necrotic bone is replaced by fibrovascular tissue rather than new bone, which compromises the structural integrity of the femoral epiphysis. The second stage is the **fragmentation stage**, which typically lasts 8 months. During this stage, the femoral epiphysis begins to collapse, usually laterally, and begins to extrude from the acetabulum. The **healing stage**, which lasts approximately 4 years, begins with new bone formation in the subchondral region. Reossification begins centrally and expands in all directions. The degree of femoral head deformity depends on the severity of collapse and the amount of remodeling that occurs. The final stage is the **residual stage**, which begins after the entire head has reossified. A mild amount of remodeling of the femoral head still occurs until the child reaches skeletal maturity. LCPD often damages the proximal femoral physis, leading to a short neck (coxa breva) and trochanteric overgrowth.

CLINICAL MANIFESTATIONS

The most common presenting symptom is a limp of varying duration. Pain, if present, is usually activity related and may be localized in the groin or referred to the anteromedial thigh or knee region. *Failure to recognize that thigh or knee pain in a child may be secondary to hip pathology can cause further delay in the diagnosis.* Less commonly, the onset of the disease may be much more acute and may be associated with a failure to ambulate.

Antalgic gait (a limp characterized by a shortening of gait phase on the injured side to alleviate weight-bearing pain) may be particularly prominent after strenuous activity at the end of the day. Hip motion, primarily internal rotation and abduction, is limited. Early in the course of the disease, the limited abduction is secondary to synovitis and muscle spasm in the adductor group; however, with time and the subsequent deformities that can develop, the limitation of abduction can become permanent. A mild hip flexion contracture of 10-20 degrees may be present. Atrophy of the muscles of the thigh, calf, or buttock from disuse secondary to pain may be evident. An apparent leg-length inequality may be caused by an adduction contracture or true shortening on the involved side from femoral head collapse.

DIAGNOSIS

Routine plain radiographs are the primary diagnostic tool for LCPD. AP and Lauenstein (frog-leg) lateral views are used to diagnose, stage, provide prognosis for, and follow the course of the disease (Fig. 719.13). It is important when evaluating disease progression that all radiographs be viewed sequentially and compared with previous radiographs to assess the stage of the disease and to determine the true extent of epiphyseal involvement.

In the initial stage of LCPD, the radiographic changes include a decreased size of the ossification center, lateralization of the femoral head with widening of the medial joint space, a subchondral fracture, and physeal irregularity. In the fragmentation stage, the epiphysis appears fragmented, and there are scattered areas of increased radiolucency and radiodensity. During the reossification stage, the bone density returns to normal via new (woven) bone formation. The residual stage is marked by the reossification of the femoral head, gradual remodeling of head shape until skeletal maturity, and remodeling of the acetabulum.

In addition to these radiographic changes, several classic radiographic signs have been reported that describe a "head at risk" for severe deformity. Lateral extrusion of the epiphysis, a horizontal physis, calcification lateral to the epiphysis, subluxation of the hip, and a

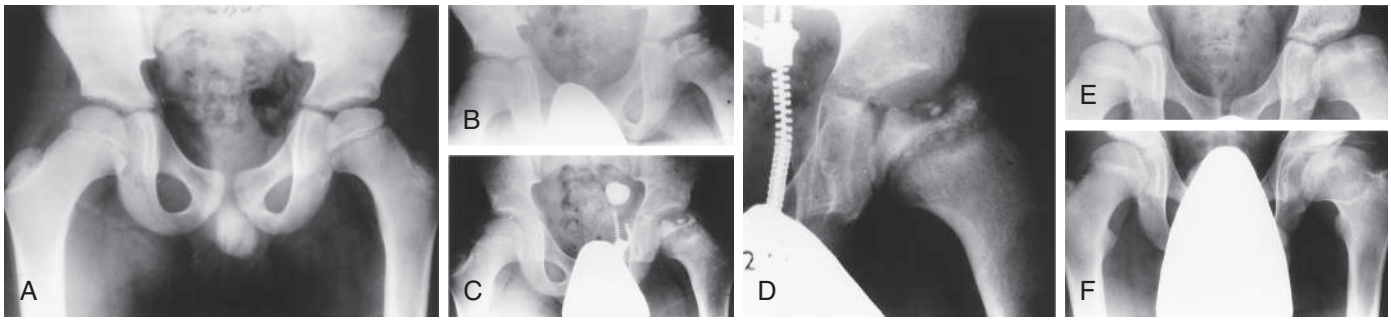

Fig. 719.13 Radiographic evolution of Legg-Calvé-Perthes disease, with onset in a male at 10-yr, 11-mo of age. Despite the late age of onset, the femoral head remodels well as the patient approaches skeletal maturity. **A,** Anteroposterior (AP) radiograph obtained at onset of the disorder shows increased density in the femoral head and apparent widening of the joint space (Waldenström's initial stage). **B,** AP radiograph obtained 9 mo after onset shows the head entering the fragmentation stage. The central fragment remains dense and has collapsed relative to the lateral portion (lateral pillar) of the femoral head. The lateral pillar is lucent but has not collapsed, and the hip is classified as group B in the lateral pillar classification system. The joint space has widened further. **C,** AP radiograph obtained 17 mo after onset shows early reossification of the femoral head (the healing stage). **D,** A closer view of the femoral head at 22 mo after onset of disease. There is still widening of the joint space, and the acetabulum has a bicompartmental appearance. **E,** AP radiograph obtained 4 yr after onset. The femoral head is healed and in the residual state. There is still widening of the joint space and incongruity of the head with the acetabulum. **F,** AP radiograph obtained 6 yr after onset shows improved roundness of the femoral head and better joint congruity. *(From Kim HK, Herring JA. Legg-Calvé-Perthes disease. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 14.19.)*

radiolucent horizontal V in the lateral aspect of the physis (Gage's sign) are all associated with a poor prognosis.

In the absence of changes on plain radiographs, particularly in the early stages of the disease, MRI is useful to diagnose early infarction and determine the degree of impaired perfusion. It is being used more in early stages to help determine prognosis. During the remodeling or residual stages, MRI is extremely helpful to define the abnormal anatomy and determine the extent of intraarticular injury. Arthrography can be useful to dynamically assess the shape of the femoral head, demonstrate whether a hip can be contained, and diagnose hinge abduction. Table 719.1 outlines the differential diagnosis.

CLASSIFICATION

A four-group classification is based on the amount of femoral epiphysis involvement and a set of radiographic "head at-risk" signs**. Group I** hips have anterior femoral head involvement of 25%, no sequestrum (an island of dead bone within the epiphysis), and no metaphyseal abnormalities. **Group II** hips have up to 50% involvement and a clear demarcation between involved and uninvolved segments. Metaphyseal cysts may be present. **Group III** hips display up to 75% involvement and a large sequestrum. In **group IV**, the entire femoral head is involved. Use of this classification system has been limited because of a high degree of interobserver variability.

The **Herring lateral pillar classification** is the most widely used radiographic classification system for determining treatment and prognosis during the active stage of the disease (Fig. 719.14). The Herring classification has a high degree of interobserver reliability. Classification is based on several radiographs taken during the early fragmentation stage. The lateral pillar classification system for LCPD evaluates the shape of the femoral head epiphysis on AP radiograph of the hip. The head is divided into three sections or pillars. The lateral pillar occupies the lateral 15–30% of the head width, the central pillar is approximately 50% of the head width, and the medial pillar is 20–35% of the head width. The degree of involvement of the lateral pillar can be subdivided into three groups. In **group A**, the lateral pillar is radiographically normal. In **group B**, the lateral pillar has some lucency, but >50% of the lateral pillar height is maintained. In **group C**, the lateral pillar is more lucent than in group B, and <50% of the pillar height remains. Herring has added a B/C border group to the classification system to describe patients with approximately 50% collapse of the lateral pillar.

Table 719.1 Differential Diagnosis of Legg-Calvé-Perthes Disease

OTHER CAUSES OF AVASCULAR NECROSIS
Sickle cell disease
Other hemoglobinopathies (e.g., thalassemia)
Chronic myelogenous leukemia
Steroid medication
Sequela of traumatic hip dislocation
Treatment of developmental dysplasia of the hip
Septic arthritis
Systemic lupus erythematosus (SLE)
SKELETAL DYSPLASIAS MIMICKING PERTHES
Multiple epiphyseal dysplasia
Spondyloepiphyseal dysplasia
Mucopolysaccharidoses
Hypothyroidism
OTHER SYNDROMES
Osteochondromatosis
Metachondromatosis
Schwartz-Jampel syndrome
Trichorhinophalangeal syndrome
Maroteaux-Lamy syndrome
Martsolf syndrome
Stickler syndrome

From Kim HKW, Herring JA. Legg-Calvé-Perthes disease. In: Herring JA, ed. *Tachdjian's Pediatric Orthopaedics,* 6th ed. Philadelphia: Elsevier; 2022: Box 14.6, p. 561.

NATURAL HISTORY AND PROGNOSIS

Children who develop signs and symptoms of LCPD before the age of 6 years tend to recover with fewer residual problems. Patients older than 9 years of age at presentation usually have a poor prognosis. The reason for this difference is that the remodeling potential of the femoral head is higher in younger children. Greater extent of femoral head involvement and duration of the disease process are additional factors associated with a poor prognosis. Hips classified as Catterall groups III and IV and lateral pillar group C generally have a poor prognosis.

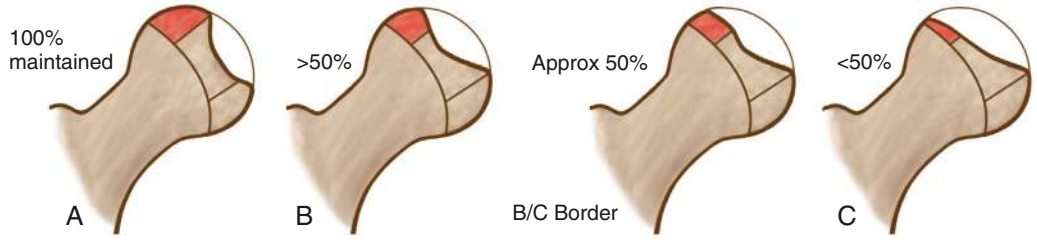

Fig. 719.14 Lateral pillar classification for Legg-Calvé-Perthes disease. **A,** There is no involvement of the lateral pillar. **B,** More than 50% of the lateral pillar height is maintained. **B/C Border,** Lateral pillar is narrowed or poorly ossified with approximately 50% height maintained. **C,** Less than 50% of the lateral pillar height is maintained.

TREATMENT

The goal of treatment in LCPD is preservation of a spherical, well-covered femoral head and maintenance of hip ROM that is close to normal. Although the treatment of LCPD remains controversial, most authors agree that the general approach to these patients should be guided by the principle of containment. This principle is predicated on the fact that while the femoral head is fragmenting, and therefore in a softened condition, it is best to contain it entirely within the acetabulum; by doing so, the acetabulum acts as a mold for the regenerating femoral head. Conversely, failure to contain the head permits it to deform, with resulting extrusion and impingement on the lateral edge of the acetabulum. To be successful, containment must be instituted early while the femoral head is still moldable; once the head has healed, repositioning the femoral epiphysis will not aid remodeling and can, in fact, worsen symptoms.

Initial options to manage symptoms include activity limitation, protected weight bearing, and nonsteroidal antiinflammatory medications. Nonoperative containment can be achieved by using a Petrie cast to restore abduction and to direct the femoral head deeper into the acetabulum. Petrie casts are two long-leg casts that are connected by a bar and can be helpful to keep the hips in abduction and internal rotation (the best position for containment). Casting is generally done in conjunction with an arthrogram to confirm containment and a tenotomy of the adductor tendons. After 6 weeks, patients can be transitioned into an abduction orthosis with limited weight bearing. Several older studies did not support the efficacy of casting and long-term bracing as a means of containment, but a subsequent large series reported excellent results with this form of treatment.

Surgical containment may be approached from the femoral side, the acetabular side, or both sides of the hip joint. A varus osteotomy of the proximal femur is the most common procedure. Pelvic osteotomies in LCPD are divided into three categories: acetabular rotational osteotomies, shelf procedures, and medial displacement or Chiari osteotomies. Any of these procedures can be combined with a proximal femoral varus osteotomy when severe deformity of the femoral head cannot be contained by a pelvic osteotomy alone.

After healing of the epiphysis, surgical treatment shifts from containment to management of the residual deformity. Patients with hinge abduction or joint incongruity might benefit from a valgus-producing proximal femoral osteotomy. Coxa breva and overgrowth of the greater trochanter can be managed by performing an advancement of the trochanter. This helps restore the length-tension relationship of the abductor mechanism and can alleviate abductor fatigue. Patients with femoroacetabular impingement from irregularity of the femoral head often can be helped with an osteoplasty or cheilectomy of the offending prominence.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

719.4 Slipped Capital Femoral Epiphysis

Wudbhav N. Sankar, Jennifer J. Winell, B. David Horn, and Lawrence Wells

Slipped capital femoral epiphysis (SCFE) is a hip disorder that affects adolescents, most often between 10-16 years of age, and involves failure of the physis and displacement of the femoral head relative to the neck.

CLASSIFICATION

SCFEs may be classified temporally, according to onset of symptoms (acute, chronic, acute-on-chronic); functionally, according to the patient's ability to bear weight (stable or unstable); or morphologically, as the extent of displacement of the femoral epiphysis relative to the neck (mild, moderate, or severe), as estimated by measurement on radiographic or CT images.

An **acute** SCFE is characterized as one occurring in a patient who has prodromal symptoms for ≤3 weeks and should be distinguished from a purely traumatic separation of the epiphysis in a previously normal hip (a true Salter-Harris type I fracture; see Chapter 724). The patient with an acute slip usually has some prodromal pain in the groin, thigh, or knee, and usually reports a relatively minor injury (a twist or fall) that is not sufficiently violent to produce an acute fracture of this severity.

Chronic SCFE is the most common form of presentation. Typically, an adolescent presents with a few months' history of vague groin, thigh, or knee pain and a limp. Radiographs show a variable amount of posterior and inferior migration of the femoral epiphysis and remodeling of the femoral neck in the same direction.

Children with **acute-on-chronic** SCFE can have features of both acute and chronic conditions. Prodromal symptoms have been present for >3 weeks with a sudden exacerbation of pain. Radiographs demonstrate femoral neck remodeling and further displacement of the capital epiphysis beyond the remodeled point of the femoral neck.

The stability classification separates patients based on their ability to ambulate and is more useful in predicting prognosis and establishing a treatment plan. The SCFE is considered *stable* when the child is able to walk with or without crutches. A child with an *unstable* SCFE is unable to walk with or without walking aids. Patients with unstable SCFE have a much higher prevalence of osteonecrosis (up to 50%) compared to those with stable SCFE (nearly 0%). This is most likely because of the vascular injury caused at the time of initial displacement.

SCFE may also be categorized by the degree of displacement of the epiphysis on the femoral neck. The head-shaft angle difference is <30 degrees in mild slips, between 30 and 60 degrees in moderate slips, and >60 degrees in severe slips, compared to the normal contralateral side.

SCFE is one of many etiologies of acquired **coxa vara** defined by an abnormal decrease in the femoral neck shaft angle (Table 719.2).

Table 719.2 Classification of Coxa Vara

ACQUIRED COXA VARA
Slipped capital femoral epiphysis
Sequela of avascular necrosis of the femoral epiphysis
Legg-Calvé-Perthes disease
Traumatic coxa vara
Femoral neck fracture
Traumatic hip dislocation
Sequela of reduction for developmental dysplasia of the hip
Septic necrosis
Other causes of avascular necrosis of the immature femoral head
Coxa vara associated with pathologic bone disorders
Osteogenesis imperfecta
Fibrous dysplasia
Renal osteodystrophy
Osteopetrosis
Other bone-softening conditions affecting the femoral neck
Congenital femoral deficiency with coxa vara
DEVELOPMENTAL COXA VARA
Isolated (may be bilateral)
Associated with a skeletal dysplasia
Cleidocranial dysostosis
Metaphyseal dysostosis
Other skeletal dysplasias

From Sucato DJ. Congenital coxa vara. In: Herring JA, ed. *Tachdjian's Pediatric Orthopaedics*, 6th ed. Philadelphia: Elsevier; 2022: Box 16.1, p. 617.



Fig. 719.15 Clinical examination of a patient with a stable slipped capital femoral epiphysis. Hip flexion and external rotation are limited. With flexion of the affected hip, the limb rotates externally. *(From Podesczwa D. Slipped capital femoral epiphysis. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig.15.5.)*

ETIOLOGY AND PATHOGENESIS

SCFEs are most likely caused by a combination of mechanical and endocrine factors. The plane of cleavage in most SCFEs occurs through the hypertrophic zone of the physis. During normal puberty, the physis becomes more vertically oriented, which converts mechanical forces from compression to shear. In addition, the hypertrophic zone becomes elongated in pubertal adolescents due to high levels of circulating hormones. This widening of the physis decreases the threshold for mechanical failure. Normal ossification depends on a number of different factors, including the thyroid hormone, vitamin D, and calcium. Consequently, it is not surprising that SCFEs occur with increased incidence in children with medical disorders, such as hypothyroidism, hypopituitarism, and renal osteodystrophy. Obesity, one of the largest risk factors for SCFE, affects both the mechanical load on the physis and the level of circulating hormones. The combination of mechanical and endocrine factors results in gradual failure of the physis, which allows posterior and inferior displacement of the head in relation to the femoral neck.

EPIDEMIOLOGY

The annual incidence of SCFE is 2 per 100,000 in the general population. Obesity is the most closely associated risk factor in the development of SCFE; approximately 65% of the patients are in the >90th percentile in weight-for-age profiles. There is a predilection for males to be affected more often than females and for the left hip to be affected more often than the right. Bilateral involvement has been reported in as many as 60% of cases, nearly half of which may be present at the time of initial presentation.

CLINICAL MANIFESTATIONS

The classic patient presenting with a SCFE is an obese male between the ages of 11 and 16 years. Females present earlier, usually between 10 and 14 years of age. Patients with chronic and stable SCFEs tend to present after weeks to months of symptoms. Patients usually limp to some degree and have an externally rotated lower extremity. Physical examination of the affected hip reveals a restriction of internal rotation, abduction, and flexion. Commonly, the examiner notes that as the affected hip is flexed, the thigh tends to rotate progressively into more external rotation with increased flexion (Fig. 719.15). Most patients complain of groin symptoms, but isolated thigh or knee pain is a common presentation from referred pain along the course of the obturator nerve. Missed or delayed diagnosis often occurs in children who present with knee pain and do not receive appropriate imaging of the hip. Patients with unstable SCFEs usually present in an urgent fashion. Children typically refuse to allow any ROM of the hip; much like a hip fracture, the extremity is shortened, abducted, and externally rotated.

DIAGNOSTIC STUDIES

AP and frog-leg lateral radiographic views of both hips are usually the only imaging studies needed to make the diagnosis. Because approximately 25% of patients have a contralateral slip on initial presentation, it is critical that both hips be carefully evaluated by the treating physician. Radiographic findings include widening and irregularity of the physis, a decrease in epiphyseal height in the center of the acetabulum, a crescent-shaped area of increased density in the proximal portion of the femoral neck, and the "blanch sign of Steel" corresponding to the double density created from the anteriorly displaced femoral neck overlying the femoral head. In an unaffected patient, Klein's line, a straight line drawn along the superior cortex of the femoral neck on the AP radiograph, should intersect some portion of the lateral capital femoral epiphysis. With progressive displacement of the epiphysis, Klein's line no longer intersects the epiphysis (Fig. 719.16). Although some of these radiographic findings can be subtle, most diagnoses can be readily made on the frog-leg lateral view, which reveals the characteristic posterior and inferior displacement of the epiphysis in relation to the femoral neck (Fig. 719.17).

TREATMENT

Once the diagnosis is made, the patient should be admitted to the hospital immediately and placed on bed rest. Allowing the child to go home without definitive treatment increases the risk that a stable SCFE will become an unstable SCFE and that further displacement will occur. Children with atypical presentations (younger than 10 years of age, thin body habitus) should have screening labs sent to rule out an underlying endocrinopathy.

The goal of treatment is to prevent further progression of the slip and to stabilize (i.e., close) the physis. Although various forms of treatment have been used in the past, including spica casting, the current gold standard for the treatment of SCFE is in situ pinning with a single large screw (Fig. 719.18). The term *in situ* implies that no attempt is made to reduce the displacement between the epiphysis and femoral neck because doing so increases the risk of

osteonecrosis. Screws are typically placed percutaneously under fluoroscopic guidance. Postoperatively, most patients are allowed partial weight bearing with crutches for 4-6 weeks, followed by a gradual return to normal activities. Patients should be monitored with serial radiographs to be sure that the physis is closing and that the slip is stable. After healing from the initial stabilization, patients with severe residual deformity may be candidates for proximal femoral osteotomy to correct the deformity, reduce impingement, and improve range of motion.

Because 20–40% of children will develop a contralateral SCFE at some point, many orthopedists advocate prophylactic pin fixation of the contralateral (normal) side in patients with a unilateral SCFE. The benefits of preventing a possible slip must be balanced with the risks of performing a potentially unnecessary surgery. Several recent studies have attempted to analyze decision models for prophylactic pinning, but controversy remains regarding the optimal course of treatment. If prophylactic pinning is not performed, patients and their families must be instructed to return immediately if they develop contralateral hip or leg pain.

COMPLICATIONS

Osteonecrosis and chondrolysis are the two most serious complications of SCFE. Osteonecrosis, or avascular necrosis, usually occurs as a result of injury to the retinacular vessels. This can be caused by an initial force of injury, particularly in unstable slips, forced manipulation of an acute or unstable SCFE, compression from intracapsular hematoma, or as a direct injury during surgery. Partial forms of osteonecrosis can also appear after internal fixation; this can be caused by a disruption of the intraepiphyseal blood vessels. Chondrolysis, on the other hand, is an acute dissolution of articular cartilage in the hip. There are no clear causes of this complication, but it is thought to be associated with more severe slips, to occur more commonly in females, and to be associated with pins or screws protruding out of the femoral head.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

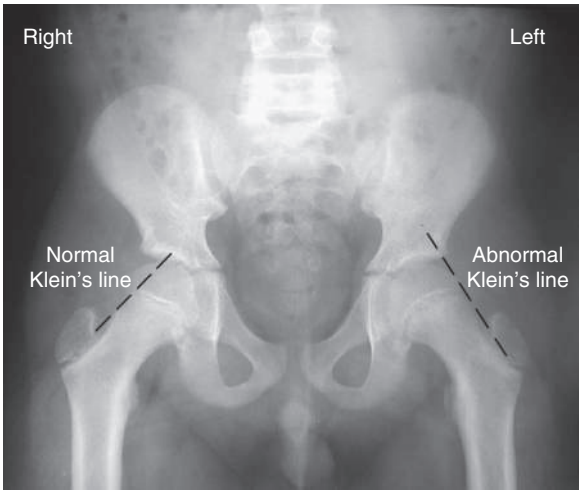

Fig. 719.16 Illustration of Klein's line.

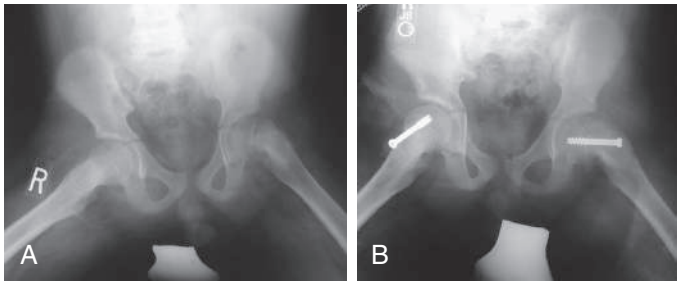

Fig. 719.18 Preoperative (A) and postoperative (B) radiographs demonstrating the in situ pinning in a case of slipped capital femoral epiphysis.

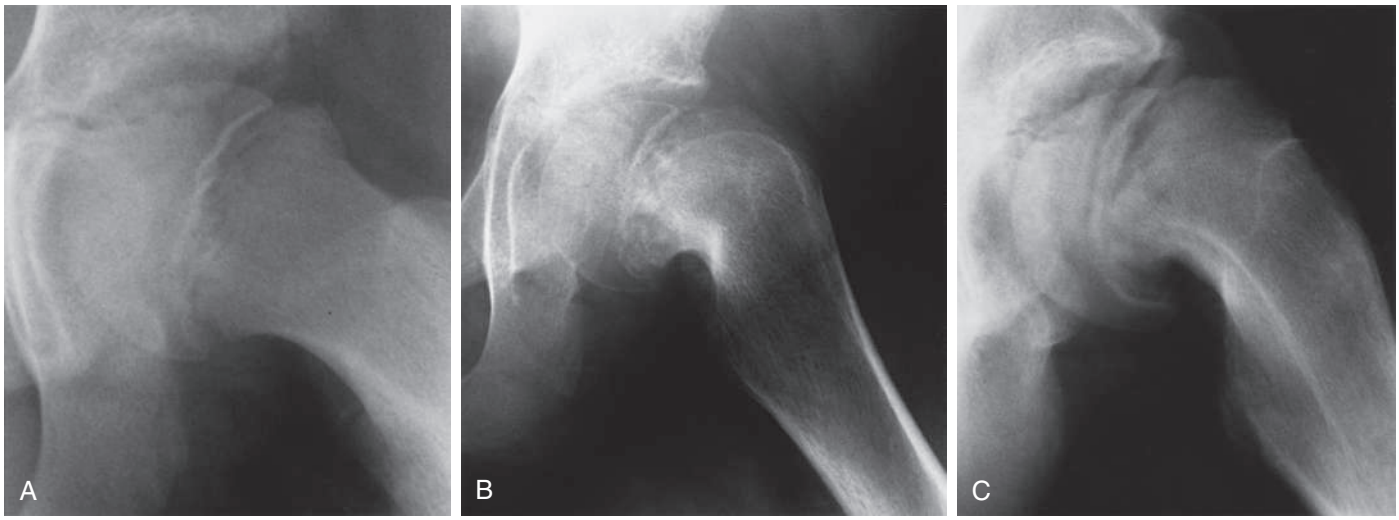

Fig. 719.17 Radiographic appearance of slipped capital femoral epiphysis (SCFE) on presentation. **A,** Appearance of acute SCFE on a frog-leg lateral view. The displacement of the epiphysis is suggestive of a Salter-Harris type I fracture of the upper femoral physis. There are no secondary adaptive changes noted in the femoral neck. **B,** Frog-leg lateral radiographs in a patient with many months of thigh discomfort and a chronic slipped epiphysis. Adaptive changes in the femoral neck predominate, and the epiphysis is centered on the adapted femoral neck. **C,** Frog-leg lateral radiographs of a patient with acute-on-chronic SCFE. The patient had several months of vague thigh pain, with sudden, severe exacerbation of that pain. The acute displacement of the epiphysis is evident. Unlike in acute SCFE (see **A**), secondary adaptive remodeling changes are also present in the femoral neck, beyond which the epiphysis has acutely displaced. *(From Podeszwa D. Slipped capital femoral epiphysis. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 15.1, p. 583.)*

Chapter 720

The Spine

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Abnormalities of the spine can result from a variety of causes, including congenital, developmental, and traumatic. In addition to spinal deformities, back pain is also prevalent in children and adolescents and may be caused by a number of serious or relatively benign pathologies.

NORMAL SPINAL CURVATURES

A normal spinal column is straight in the anteroposterior (AP, coronal) plane but has curvatures in the lateral (sagittal) plane. Normal cervical lordosis, thoracic kyphosis, and lumbar lordosis regions are biomechanically advantageous as they maintain relationships of the body relative to the forces of gravity, which is important for balance. These curvatures also help to conserve energy by minimizing the amount of muscular activity required to maintain an upright posture.

Abnormalities affecting these normal curvatures, termed *sagittal plane imbalances*, can be measured on a lateral spine radiograph. A vertical line, or *plumb line*, drawn from the center of the seventh cervical vertebra should normally fall through the posterosuperior corner of the sacrum. Disorders affecting sagittal alignment include thoracic hyperkyphosis and lumbar hyperlordosis. In contrast, although scoliosis is *actually* a three-dimensional deformity not limited to a single anatomic plane, it is most commonly *described* as a frontal or coronal plane deformity with curvatures away from the midline in this plane.

OVERVIEW OF ABNORMAL SPINAL CURVATURES

The most common spinal deformities are scoliosis and kyphosis. Early diagnosis is important, as a subset of patients may be candidates for early interventions to prevent curve progression. Bracing has been proven to reduce the number of patients with curve progressing to require surgery in **adolescent idiopathic scoliosis (AIS).**

Scoliosis may be idiopathic, due to congenital bony deformities, or may be associated with a variety of underlying conditions, including neuromuscular diseases, connective tissue diseases, or genetic syndromes. Oftentimes, the pediatrician is the first to diagnose these conditions.

Although parents and families are often most concerned about potential cosmetic abnormalities, the physician diagnosing a patient with a spinal deformity must carefully consider both the potential for underlying causes requiring treatment and the patient's long-term prognosis. Progressive curvatures in the neuromuscular population may result in respiratory insufficiency in addition to a loss of sitting balance. Other conditions such as neurofibromatosis are associated with a specific dystrophic curve pattern that can rapidly progress. Sometimes, a spinal deformity might be the first sign of an underlying syndrome. Parents and the patient need an understanding of the deformity, how it may progress, and potential complications associated with the diagnosis. A classification of common spinal abnormalities is presented in Table 720.1.

720.1 Idiopathic Scoliosis

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Scoliosis is a complex, three-dimensional spinal deformity, defined in the coronal plane as a curve of at least 10 degrees on a posteroanterior (PA) radiograph of the spine. Affected vertebrae are axially rotated, causing a visible prominence to be noted on the **Adams forward bend test**. The sagittal plane is also affected, leading to abnormalities such as decreased thoracic kyphosis.

ETIOLOGY

By definition, the etiology of idiopathic scoliosis remains unknown despite a considerable body of research. It is likely that the disease is multifactorial, with genetic, hormonal, cellular, and anatomic contributions.

A genetic link has been proposed with sex-linked dominant, autosomal dominant, and polygenetic inheritance patterns all suggested. Genetic involvement has been substantiated in studies of twins, demonstrating a 73% concordance rate for AIS in monozygotic twins compared to a 36% concordance rate in dizygotic twins.

AIS is 2 to 10 times more common in females than males. Investigators have attempted to explain this difference as a genetic effect: it has been hypothesized that males are not as susceptible to the involved genes as females. Therefore, affected males must inherit a larger number of susceptibility genes to have a scoliosis phenotype. Males would pass more susceptibility genes onto their children and would therefore have more affected children. Fathers with AIS transmit the gene to 80% of their children, but mothers with AIS transmit it to only 56% of their children.

Exome sequencing has identified pathogenic variants in the *COL11A2* collagen gene in 32% of AIS cases. COMP promotor methylation has been correlated with a younger age and larger main curve magnitude. Other gene variants have been found to demonstrate an association with AIS, including *PAX1*, *POC5*, the Bsml polymorphism in the vitamin D receptor gene, and *FBN1*. Additionally, females who have first-degree relatives with AIS have been found to have more severe curves and longer arm spans than females who have a spontaneous case.

Cellular structures may be involved in the disease process. Calmodulin, a regulator of the contractile properties of muscle, occurs at increased levels in the platelets of patients with progressive AIS. On a more cellular level, differences in the mRNA expression of H19 and ADIPOQ have been described in the paraspinal musculature from the concave to the convex side of a curvature. Other functional evaluations of patients with AIS have noted abnormalities in proprioception and postural balance.

MRI studies of the brain in patients with AIS versus controls have found that the cerebellum of affected patients is hypertrophied in areas involving the somatosensory tracts, motor control, and response to visual stimulation. These areas of hypertrophy may be a compensation for impaired balance resulting from malalignment of the spine.

Approximately 30% of females with AIS have osteopenia on DEXA studies, and of these, 80% will have lifelong osteopenia. Osteopenia has been linked to an increased risk of curve progression. Insufficient vitamin D levels have been reported in over 90% of patients with operative AIS.

EPIDEMIOLOGY

Idiopathic scoliosis is the most common type of spinal curvature; 80% of cases are idiopathic. The overall prevalence of idiopathic scoliosis in skeletally immature patients ranges from 1–3% of the population. Most curves are mild and do not require treatment, with only 0.5% being >20 degrees and 0.3% exceeding 30 degrees. Curves of ≤10 degrees occur equally between males and females; however, those requiring an intervention occur in a 7:1 female-to-male ratio.

CLASSIFICATION OF IDIOPATHIC SCOLIOSIS

Idiopathic scoliosis is classified according to the age at onset. Patients with curves that are present before age 8-10 years have **early-onset scoliosis (EOS)**. Although EOS can have several etiologies, young patients without a clearly identified cause are classified as having idiopathic EOS. The subgroup of *infantile idiopathic EOS* refers to patients diagnosed before age 3 years and accounts for only 0.5–4% of cases of AIS. AIS affects patients 10 years of age and older and comprises 70–80% of all cases of idiopathic scoliosis.

Table 720.1 Classification of Spinal Deformities

SCOLIOSIS
Idiopathic
Infantile
Juvenile
Adolescent
Congenital
Failure of formation
Wedge vertebrae
Hemivertebrae
Failure of segmentation
Unilateral bar
Block vertebra
Mixed
Neuromuscular
Neuropathic diseases
Upper motor neuron
Cerebral palsy
Spinocerebellar degeneration (Friedreich ataxia, Charcot-Marie-Tooth disease)
Syringomyelia
Spinal cord tumor
Spinal cord trauma
Lower motor neuron
Poliomyelitis
Spinal muscular atrophy
Myopathies
Duchenne muscular dystrophy
Arthrogryposis
Other muscular dystrophies
Syndromes
Neurofibromatosis
Marfan syndrome
Compensatory
Leg-length discrepancy
KYPHOSIS
Postural kyphosis (flexible)
Scheuermann disease
Congenital kyphosis
Failure of formation
Failure of segmentation
Mixed

Adapted from the Terminology Committee, Scoliosis Research Society. A glossary of scoliosis terms. *Spine*. 1976;1:57.

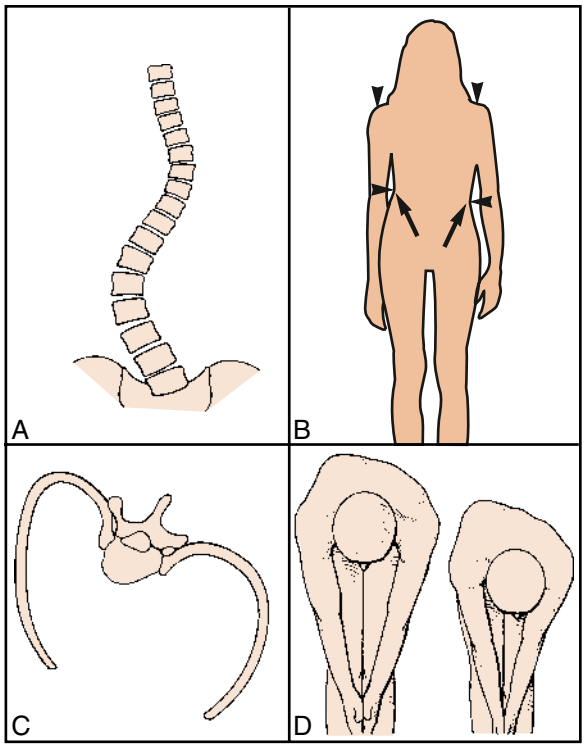

Fig. 720.1 Structural changes in idiopathic scoliosis. **A,** As curvature increases, alterations in body configuration develop in both the primary and compensatory curve regions. **B,** Asymmetry of shoulder height, waistline, and elbow-to-flank distance are common findings. **C,** Vertebral rotation and associated posterior displacement of the ribs on the convex side of the curve are responsible for the characteristic deformity of the chest wall (rib hump) in scoliosis patients. **D,** In the school screening examination for scoliosis, the patient bends forward at the waist. Rib asymmetry of even a small degree is obvious. *(From Scoles PV. Spinal deformity in childhood and adolescence. In: Behrman RE, Vaughn VC III, eds. Nelson Textbook of Pediatrics, update 5. Philadelphia: WB Saunders; 1989.)*

CLINICAL PRESENTATION OF IDIOPATHIC SCOLIOSIS

When evaluating a patient with a structural spinal curvature, a thorough history and physical examination are required because idiopathic scoliosis is a diagnosis of exclusion. All other potential causes, including congenital bone malformations, neuromuscular and syndromic diseases, and tumors must systematically be excluded.

The curvature is frequently found on a positive screening by primary care physicians, through a school screening program, or because patients (or their family or friends) have noticed a cosmetic deformity. Citing the need for early identification of scoliosis to reduce the risk of operative complications with correction of large, neglected curves, the Scoliosis Research Society advocates for school screening. The BrAIST study, which definitively demonstrated that patients treated with Boston braces for 18 hours a day have a significantly lower incidence of curves progressing to the surgical range, supports the potential value of early detection through screening programs. Although the United States Preventive Services Task Force previously recommended against school screening programs, their updated 2018 recommendation statement concluded that evidence was insufficient to recommend for or against screening.

Back pain is not commonly a primary presenting complaint of patients with scoliosis, though when questioned, at least 30% of adolescents with idiopathic scoliosis will report some degree of back discomfort at some point in time. To keep this finding in perspective, a similar number of healthy adolescents complain of episodes of low back pain and discomfort. If a child presents with back pain associated with a curvature, it is important to do a careful history and physical exam, check spine radiographs, and rule out any diagnostic red flags (see Chapter 720.5). Look for other causes of pain in these patients, including spondylosis, spondylolisthesis, tethered cord, syrinx, herniated disk, or tumor such as osteoid osteoma or spinal cord tumor.

PHYSICAL EXAMINATION OF IDIOPATHIC SCOLIOSIS

Evaluate the patient in the standing position, from both the front and the side, to identify any asymmetry in the chest wall, trunk, or shoulders.

Begin the examination focusing on the back. The earliest abnormality noted on physical exam in patients with scoliosis is asymmetry of the posterior chest wall on forward bending. This test, called the Adams forward-bending test (Fig. 720.1), is performed by observing the patient's back while he or she is bending 45 degrees forward. This test can also be augmented with a scoliometer placed at the apex of the deformity. An inclination measuring 7 degrees or more has been suggested as the cutoff for orthopedic referral. Scoliosis is a three-dimensional deformity; patients develop a posterior rib hump on the convex side of the spinal curve as a result of the rotational component of the deformity. The anterior chest wall may be prominent on the

concavity of the curve due to outward rib rotation. Other associated findings may include shoulder imbalance, a lateral shift of the trunk, or an apparent leg-length discrepancy due to pelvic obliquity. A primary **limb length discrepancy** may also present as a lumbar spinal deformity. This lumbar curvature is compensatory and flexible, with the apex toward the shorter leg.

Next, examine the patient from the side to evaluate the degree of kyphosis and lordosis. The upper thoracic spine normally has a smooth, gently rounded kyphotic curve with an apex in the midthoracic region. The cervical spine and lower lumbar spine have concave, or lordotic curves. The magnitude of these sagittal contours varies with age. Children have less cervical lordosis and more lumbar lordosis than do adults or adolescents. When examining a patient with idiopathic scoliosis, a common finding is a loss of the normal thoracic kyphosis, resulting in what is called a relative thoracic lordosis or hypokyphosis.

Another common, benign finding in normal adolescent thoracic spines not associated with scoliosis is a flexible round back, or postural kyphosis. This can be corrected voluntarily when the patient extends his or her spine. This is different from sharp, abrupt, or accentuated forward angulation in the thoracic or thoracolumbar region, which is indicative of a pathologic kyphotic deformity.

The final exam component is a careful neurologic examination because scoliosis may be associated with an underlying neurologic diagnosis. Check superficial abdominal reflexes, extremity deep tendon reflexes, muscle strength, and atrophy and examine for clonus. Also, remember to examine the patient's feet because a cavovarus foot can be associated with a tethered cord. A high suspicion is necessary in patients with infantile and juvenile idiopathic scoliosis because up to 25% have an associated intraspinal abnormality such as a tethered spinal cord or syringomyelia. The index of suspicion for neurologic involvement is further raised in the presence of back pain or neurologic symptoms, bowel or bladder symptoms, café-au-lait spots, a sacral dimple, midline cutaneous abnormalities such as a hair patch or skin tag, unilateral foot deformity, or an atypical curve pattern.

RADIOGRAPHIC EVALUATION OF IDIOPATHIC SCOLIOSIS

Standing, high-quality PA and lateral radiographs of the *entire* spine are recommended at the initial evaluation for patients with clinical findings suggestive of a spinal deformity. Many children's hospitals have low-dose stereoradiographic imaging systems rather than conventional radiographs, which can minimize radiation exposure and also provide three-dimensional reconstructions of spinal deformity. On the PA radiograph, the degree of curvature is determined by the **Cobb angle**, in which the angle between the superior and inferior vertebrae most tilted into the curve is measured (Fig. 720.2).

Although the indications for performing an MRI are variable, it is helpful when an *underlying* cause for scoliosis such as a spinal cord abnormality is being considered. Patients with early-onset scoliosis have a higher incidence of associated cord anomalies. Other considerations include abnormal findings on the history or physical examination and atypical radiographic features, including abnormal curve patterns. Atypical radiographic findings include curve patterns such as a left thoracic curve, double thoracic curves, or high thoracic curves. Other radiographic abnormalities include widening of the spinal canal and erosive or dysplastic changes in the vertebral body or ribs. On the lateral radiograph, an increase in thoracic kyphosis or an absence of segmental lordosis may be suggestive of an underlying neurologic abnormality.

NATURAL HISTORY OF IDIOPATHIC SCOLIOSIS

Treatment decisions are based on the natural history of idiopathic scoliosis. Infantile idiopathic early-onset scoliosis may spontaneously resolve in 20–90% of cases. Patients with infantile scoliosis who have cognitive disabilities, curves presenting after 1 year of age, and larger magnitude curves are more likely to progress. A radiographic parameter called the Mehta angle can also be used to predict curve progression in infantile scoliosis. This measurement examines the vertebra at the apex of the thoracic curve. It measures the angle formed by a line

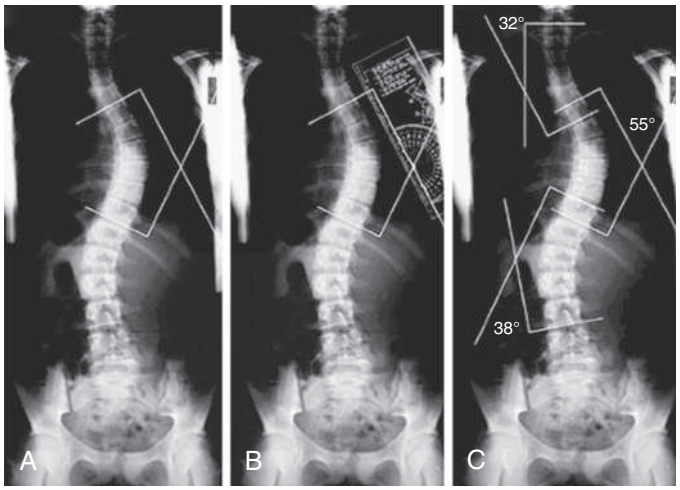

Fig. 720.2 A-C, Cobb angles measurements. *(From Morrissey RT, Weinstein SL, eds. Lovell and Winter's Pediatric Orthopaedics, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1990.)*

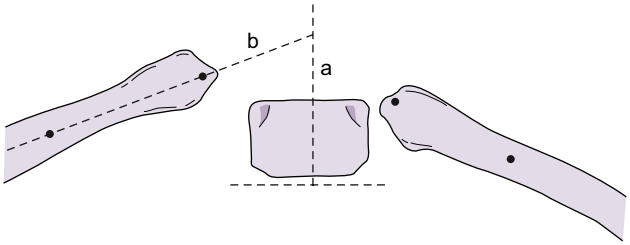

Fig. 720.3 Measuring the rib-vertebra angle difference (RVAD). A line is drawn perpendicular to the inferior end plate of the apical thoracic vertebra. Another line is drawn between two points that bisect the head and neck of the rib articulating with the apex. The angle between the perpendicular line *(a)* and the rib line *(b)* is measured. The same procedure is repeated for the rib on the opposite side. The concave–convex side angles are equal to the RVAD. *(Modified from Mehta MH. The rib-vertebra angle in the early diagnosis between resolving and progressive infantile scoliosis. J Bone Joint Surg Br. 1972;54[2]:230–243.)*

perpendicular from the vertebral end plate and a line down the center of the rib. The measurement is calculated on the convex and concave side, and the final **rib vertebral angle difference** (RVAD) is calculated by subtracting the convex side from the concave side (Fig. 720.3). A curve with an RVAD <20 degrees will resolve in about 80% of cases, whereas one with an RVAD >20 degrees will progress in over 80% of cases. Curves that resolve typically do so before 2 years of age.

Several factors affect the rate of curve progression in patients with AIS. Curves are more likely to progress in more skeletally immature patients with significant growth remaining. Findings associated with significant growth remaining are younger age, premenarchal status, Tanner stage I or II, Risser sign (a radiographic measurement of ossification of the iliac crest) of 0 or 1, and Sanders Maturity Scale values of 1-4. The Sanders Skeletal Maturity Staging System examines skeletal maturity using a single PA radiograph of the left hand and associates this value with current curve magnitude. Patients are staged from S1-S8, with S1 being the most immature and S8 indicating early maturity. Higher magnitude curves in more skeletally immature patients are more likely to progress.

Other factors affecting curve progression are the current curve magnitude, curve pattern, and patient sex. Three-dimensional spinal measurements of vertebral wedging, axial rotation, and torsion have been correlated to curve progression. In general, female patients are more likely than males to have curves that progress. Younger, premenarchal

females with curves between 20 and 30 degrees have a significantly higher risk of progression than do females 2 years after menarche with similar curves, demonstrating the significance of age on progression. In fact, the older group is unlikely to have any progression at all whereas premenarchal females with the same curve are likely to progress. Thoracic curves <30 degrees rarely progress after skeletal maturity, while those >45 degrees may progress approximately 1-2 degrees annually past skeletal maturity, and surgical stabilization is commonly offered.

Functionally, there are not many significant, clinically detrimental effects of smaller curves. There is conflicting literature regarding the exact curve magnitude and curve morphology in idiopathic thoracic scoliosis that leads to cardiopulmonary impairment. Thoracic curves of 50-70 degrees and greater have been associated with pulmonary impairment, although magnitude of curve alone cannot fully predict pulmonary function. Exercise capacity indicators, including heart rate, peak oxygen intake, and work rate, were not affected by thoracic curve magnitude, while FEV_1 was influenced in a prospective study of AIS patients. Factors such as thoracic kyphosis, curve stiffness, location of curve apex, and degree of vertebral rotation may also impact pulmonary function. Surgical correction is correlated with improved total lung capacity in patients with severe restrictive pulmonary function preoperatively.

Long-term studies have demonstrated that back pain is common in patients with scoliosis, although there is no definitive connection between pain and the curve magnitude or location. Furthermore, nearly 70% of patients with pain reported low or moderate severity of symptoms, stating that the pain does not interfere with normal activities.

TREATMENT OF IDIOPATHIC SCOLIOSIS

Treatment options include observation for small curves, bracing, and surgical care. Vitamin D deficiency is common in patients with adolescent idiopathic scoliosis, so evaluation and supplementation if appropriate should be considered. Brace treatment decreases the incidence of curve progression. The BrAIST study, examining the effect of Boston braces in patients treated for 18 hours a day, was stopped before study completion because the benefits of bracing became so clear that it was unethical to continue patients in the nonbraced control arm of the study. Treatment success (preventing curve progression to 50 degrees) in the bracing group was 72%, whereas only 48% of those patients observed without bracing avoided progression to the surgical range. Other types of bracing have also been used, including the Providence night bending brace and the Rigo Chêneau Brace. When discussing bracing with families, is important to understand that bracing in AIS does not lead to curve resolution or other measures of decreased magnitude but rather limits further progression. Additionally, while ~30% of patients who are braced will still require surgery, this does not necessarily mean that bracing was unsuccessful: without a brace, the curve may have progressed more rapidly or to an even higher magnitude, potentially requiring either an earlier surgery or more extensive fusion.

The bracing success rate depends on the amount of growth remaining. For example, patients with infantile or juvenile scoliosis are much more likely to require a surgical procedure than those with adolescent scoliosis and limited remaining growth. Patients at Risser 0 who are very skeletally immature are at a higher risk of surgery even if they are braced. It is recommended that these skeletally immature patients with curves that are otherwise thought of as small magnitude (>30 degrees) should be braced full time for a minimum of 18 hours daily. In addition to the effect of skeletal maturity, adherence with the recommended protocol for wearing the brace will influence the outcome. Adherence can be a challenge in the adolescent population. To better counsel parents and patients on their adherence, braces can be fitted with sensors to monitor duration of wear, and surgeons can review this data with families during follow-up appointments.

Braces are offered for treatment of skeletally immature patients with curves >30 degrees at the first visit or in patients who are being followed and have developed progression of their curvature beyond 25 degrees. Bracing is ineffective in curvatures >45 degrees because these patients have already reached the threshold for surgical intervention. The brace is worn until complete cessation of growth in males, but in females, weaning from the brace may be considered when the patient is more than 2 years postmenarchal, is a Risser 4 or greater, and has grown less than a centimeter over the previous 6 months. Some practitioners will continue with the bracing beyond these parameters and base their weaning on the Sanders scale and/or assessment of the maturity of the distal radius and ulna, especially when the curve is more than 40 degrees because these curves are thought to have a significant incidence of progression after bracing has been completed. There also has been interest in using the Schroth method, which involves physical therapy in addition to a bracing program. While several studies have suggested that the Schroth method may enhance the success of a bracing program, further study will be required to make definitive recommendations.

Serial body casting **(Mehta casting)** can be performed in patients with early-onset scoliosis to minimize the risk of curve progression and potentially delay the necessity of growing spine procedures. In some cases, the scoliosis can be permanently corrected without the need for long-term bracing or surgery. Although most patients can tolerate casting well, the treatment is labor intensive, and there may be a negative impact on health-related quality of life for patients and their caregivers during and potentially after casting. Nonetheless, this quality-of-life effect must be carefully weighed against the risk of increased complications in patients who begin earlier growth-sparing spine surgery. One study found the risk of unplanned reoperation was 3 times higher in those who had growth-sparing spine surgery before age 3 when compared with those who were able to delay surgery.

Traditional surgical treatment involves spinal instrumentation and fusion and is usually recommended for skeletally immature patients with progressive curves >45 degrees and skeletally mature patients with curves >50 degrees. Some surgeons will also consider surgery for lumbar curves >35 degrees, particularly if associated with truncal imbalance. The goals of surgery are to arrest progression of the deformity, to improve cosmesis, and to achieve a balanced spine, all while minimizing the number of vertebral segments that are stabilized and thereby preserving as much motion as possible.

Implants including pedicle screws, sublaminar wires or bands, and hooks are attached to two longitudinal rods (Fig. 720.4). All implants function by allowing the application of mechanical forces to the spine, correcting the deformity in both the frontal and lateral planes to achieve normal frontal and sagittal spinal balance. Pedicle screw constructs also allow for derotational maneuvers, correcting the rib prominences associated with the axial component of the deformity. After instrumentation, the spine is decorticated, and bone graft is placed for the fusion portion of the procedure. The strength of modern spinal implants maintains correction without requiring a postoperative brace in most cases.

Most procedures are performed posteriorly using pedicle screw fixation, which affords excellent correction, especially of the rotational component of the deformity. Posterior osteotomies are often added to enhance flexibility and improve the degree of correction in stiffer curves. Anterior spinal releases requiring a thoracotomy are performed infrequently as a result of the efficacy of pedicle screw instrumentation. Open anterior thoracic and thoracolumbar procedures violate the chest wall and often the diaphragm. Pulmonary function may take up to 2 years to return to normal values. Although thoracoscopic techniques may be used to perform anterior spinal release with or without instrumentation and fusion, their use has been limited because of the efficacy of posterior pedicle screw constructs. However, patients with conditions such as neurofibromatosis and myelomeningocele have a higher likelihood of achieving a nonunion of their fusion, and an anterior fusion may be considered in addition to the posterior fusion in these groups. Additionally, patients with severe, neglected deformities may still benefit from combined anterior and posterior procedures.

Younger patients, in whom the triradiate cartilage remains open, are at risk for "crank shafting," or progressive deformity due to continued anterior spinal growth, after a posterior fusion. Traditionally, these patients were treated by simultaneous anterior fusion to remove this growth potential; however, the rigidity of pedicle screw constructs has negated the need for this additional surgery. While an anterior fusion

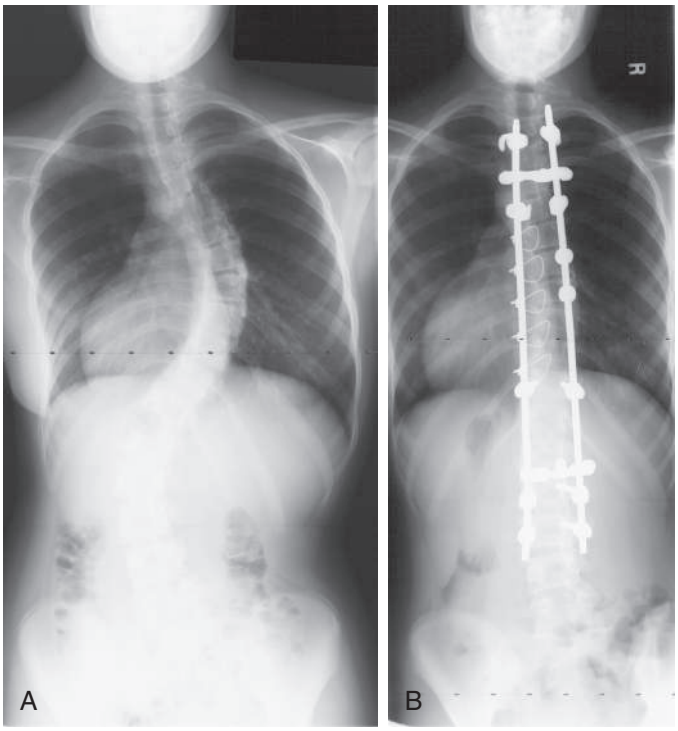

Fig. 720.4 Preoperative standing posteroanterior radiograph of a 14-yr-old female who was skeletally immature and developed a 68-degree right thoracic and a 53-degree left lumbar scoliosis (A). Her trunk was shifted to the right, and the left shoulder was slightly depressed. Based on the risk of future progression, she was treated by an instrumented posterior spinal fusion from T3 to L3 with correction of the right thoracic curve to 20 degrees and the left lumbar curve to 10 degrees (B). Coronal spinal balance was restored, and shoulder height was maintained.

with instrumentation can be considered for idiopathic thoracolumbar and lumbar curves, the posterior approach with pedicle screw fixation is being used more frequently to avoid the need for anterior surgery and chest wall violation.

Very young patients with growing spines are not candidates for definitive **posterior spinal fusion**, as this will limit their lung capacity. A commonly employed simple measurement of thoracic height (a vertical line drawn from T1-T12) can help guide treatment decisions, with fusion not recommended for patients with a thoracic height <22 cm.

In patients with remaining thoracic growth, growing spine procedures are recommended when surgical intervention is required. The most commonly used implants are **growing rods** (traditional and magnetic) and the **vertical expandable prosthetic titanium rib (VEPTR)**.

Growing rods have fixation points placed at the proximal and distal ends of the spinal deformity, which are then linked to subcutaneous expandable rods, spanning the length of the deformity (Fig. 720.5). These fixation points can be pedicle screws or hooks that affix to the posterior elements of the spine. Traditional growing rods require additional minor operations to lengthen the rods, performed about every 6-8 months. **Magnetically controlled growing rods (MCGRs)**, once inserted, can be lengthened in the clinic using an external device, thereby eliminating the need for further surgeries. Even with MCGR, complications are relatively common, with 39% of patients experiencing at least one complication, including rod breakage, screw/hook failure, failure of the rod to lengthen, and surgical site infection (though the risk of infection is lower than in traditional growing rods). Whether patients have traditional or magnetic growing rods, a final fusion is usually necessary once they have sufficient thoracic height or attain skeletal maturity. In selected cases in which the device is stable and the curve is well controlled once patients have achieved adequate pulmonary maturity and chest wall growth, observation

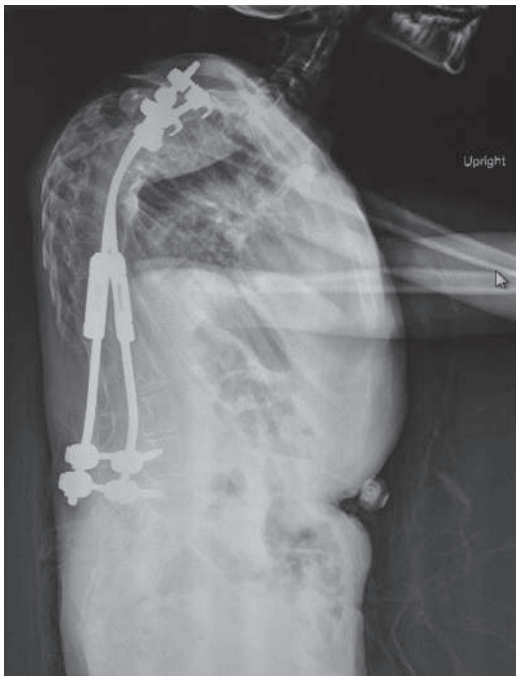

Fig. 720.5 A postoperative lateral radiograph of a skeletally immature patient with severe syndromic scoliosis after placement of growing rods.

has been selected rather than definitive fusion. Minimal correction is achieved when converting growth sparing implants to definitive spinal fusion because there is local osteopenia and usually fibrous or osseous fusions at a subset of spinal segments. In patients who have elected observation rather than conversion to a fusion, the indications for conversion would include implant failure/loss of correction and/or progression of curvature.

The VEPTR (Fig. 720.6) helps young children with thoracic insufficiency syndrome and is also used for early-onset scoliosis in patients with congenital or neuromuscular diagnoses. Long-term survival rates are favorable for these extremely severe deformity patients treated by VEPTR, though the risk of implant-related complications is substantial. Surgery in these young syndromic patients carries a substantial risk of complications, and one study reported a complication rate of nearly 85% with a mortality rate of over 15% over the entire course of operative treatment for early-onset scoliosis.

Significant interest remains in developing surgical techniques to treat AIS that can avoid spinal fusion. One fusionless technique currently used is anterior vertebral body tethering, consisting of a flexible cord attached with screws to affected vertebrae, allowing for correction of a curve dynamically by limiting growth on the curve convexity. Although the device most certainly limits motion to some extent, one would expect greater motion than patients treated with fusion. The ideal indications for tethering remain unclear, though commonly employed criteria are patients age 9-15 years with thoracic curves of 40-67 degrees and Risser stage of ≤1.

A meta-analysis of tethering found that pooled complication rates were 26% for patients treated with a tether versus 0.6% for those treated with a standard posterior spinal fusion. Additionally, the mean reoperation rates in studies that had at least 3 years of follow-up were 24.7% in patients treated with tethers versus 1.8% in posterior spinal fusion patients. Patients treated with posterior spinal fusion have a mean revision rate at 10 years of 7.5% (i.e., >90% are definitively treated with a single procedure).

Another novel fusionless treatment is the ApiFix, which is an expandable, ratcheting, hinged rod connected to a cluster of pedicle screws above and below a curve. The device is placed posteriorly and can allow more motion than traditional fusion techniques, but this has been associated with a 50% complication rate within 2 years, including

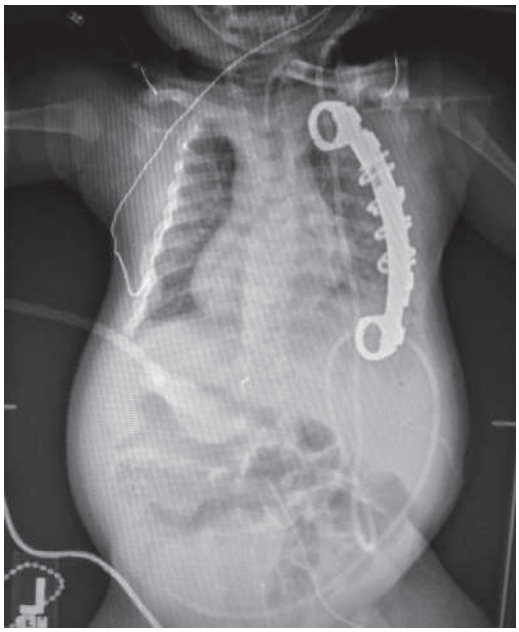

Fig. 720.6 A postoperative posteroanterior radiograph of a patient with Jeune syndrome after placement of a right rib-to-rib VEPTR (vertical expandable prosthetic titanium rib).

implant breakage, failure of the ratchet mechanism, osteolysis, and bacterial seeding of implants.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.2 Congenital Scoliosis

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Congenital scoliosis is a spinal deformity that results from abnormal development of the vertebrae. Asymmetric spinal growth due to one or more vertebral anomalies leads to spinal curvature. Although the malformation is present at birth, it may not become clinically apparent until a later time as growth progresses.

ETIOLOGY

Embryologic development of the spine begins at the fifth week of gestation. An insult to the normal developmental process occurs, resulting in abnormal growth of one or more vertebrae. Oftentimes, this abnormal development is associated with additional developmental anomalies or known syndromic conditions, including Alagille, Jarcho-Levin, Klippel-Fiel, Goldenhar, and VACTERL syndromes.

ASSOCIATED CONDITIONS

It is common for children with congenital scoliosis to have associated malformations in other organ systems that must be ruled out. Genitourinary abnormalities are identified in 20–40% of children with congenital scoliosis and include unilateral renal agenesis, ureteral duplication, horseshoe kidney, and genital anomalies. Approximately 2% of these patients have a silent obstructive uropathy. Renal ultrasonography should be performed early on in all children with congenital scoliosis; other studies such as CT or MRI may also be required.

Cardiac anomalies are identified in 10–54% of patients. A thorough cardiac examination should be performed as well as a referral to pediatric cardiology for consideration of echocardiography.

Intraspinal anomalies are identified in approximately 15–40% of patients. Spinal dysraphism is the general term applied to such lesions (see Chapters 631 and 689). Examples include diastematomyelia, split cord malformations, intraspinal lipomas, arachnoid cysts, teratomas, dermoid sinuses, fibrous bands, and a tight filum terminale. **Cutaneous findings** that may be seen in patients with closed spinal dysraphism include hair patches, skin tags or dimples, sinuses, and hemangiomas. Infants with these cutaneous abnormalities overlying the spine may benefit from ultrasonography to rule out an occult spinal dysraphic condition. MRI is often delayed in older patients until a clinical indication is present, such as tethering of the spinal cord, which may present as back or leg pain, calf atrophy, progressive unilateral foot deformity (especially cavovarus), and problems with bowel or bladder function.

CLASSIFICATION OF CONGENITAL SCOLIOSIS

Congenital scoliosis is classified by the type of developmental abnormality: either a **failure of formation** or a **failure of segmentation**. The deformities are then further described by the anatomic features of the affected vertebrae. Failure of formation results in wedge vertebrae or hemivertebrae. Failure of segmentation results in unilateral bar vertebrae or block vertebrae. Some instances of congenital scoliosis result from a combination of both failure of formation and failure of segmentation (Fig. 720.7). One or more bony anomalies may occur in isolation or in combination.

NATURAL HISTORY OF CONGENITAL SCOLIOSIS

The risk of progression depends on the growth potential of each anomaly, which may vary considerably. Close radiographic follow-up is required. Progression of these curves is most pronounced during periods of rapid growth associated with the first 2-3 years of life and adolescence.

The anatomic characteristics of the malformed vertebra play a significant role in the progression of deformity. The most severe form of congenital scoliosis is a *unilateral* unsegmented bar with a contralateral hemivertebra. In this anomaly, the spine is fused to the side of the unsegmented bar but also has a growth center on the other side at the location of the hemivertebra at the same level. This combination of deformities in the bony spine results in a rapidly progressive curve. All affected patients usually require surgical stabilization. A unilateral unsegmented bar is also associated with significant progression and in most cases will require surgical intervention. An isolated hemivertebra must be followed closely, and many, but not all, of these will be associated with a progressive deformity that requires surgical intervention. In contrast, an isolated block vertebra has little growth potential and rarely requires treatment.

TREATMENT OF CONGENITAL SCOLIOSIS

Early diagnosis and prompt treatment of progressive curves are essential. Bracing is not traditionally indicated for most congenital curves due to their structural nature, except in rare cases to control additional curves not associated with the bony abnormality or to attempt to delay surgery until a safer age for a surgical procedure. Once a bony abnormality is identified that is likely to progress, surgery is recommended before progression occurs, preventing development or further inevitable progression of spinal deformity. If the deformity has already developed, surgical correction is difficult to achieve and the risk of neurologic complications is high.

Surgical techniques depend on the curve anatomy, flexibility, patient age, and surgeon preference. Young patients with growing spines may benefit from a growing spine procedure to allow further growth while limiting curve progression. In terms of definitive fusion, an anterior and posterior spinal fusion was often historically required, though with pedicle screw constructs, a posterior fusion can be sufficient. A convex hemiepiphysiodesis is an option for selected cases with milder curves and younger patients, fusing only one side of the spine to allow some correction of the deformity by permitting growth on the noninvolved side of the curve. Complete excision of a hemivertebra along with fusion of a short segment of the spine through a posterior approach has been performed with greater frequency and often in early childhood. A definitive fusion is still required for many progressive curvatures at skeletal maturity.

Adolescents with a congenital etiology of their spinal deformities are at higher risk of developing in-hospital complications than those with

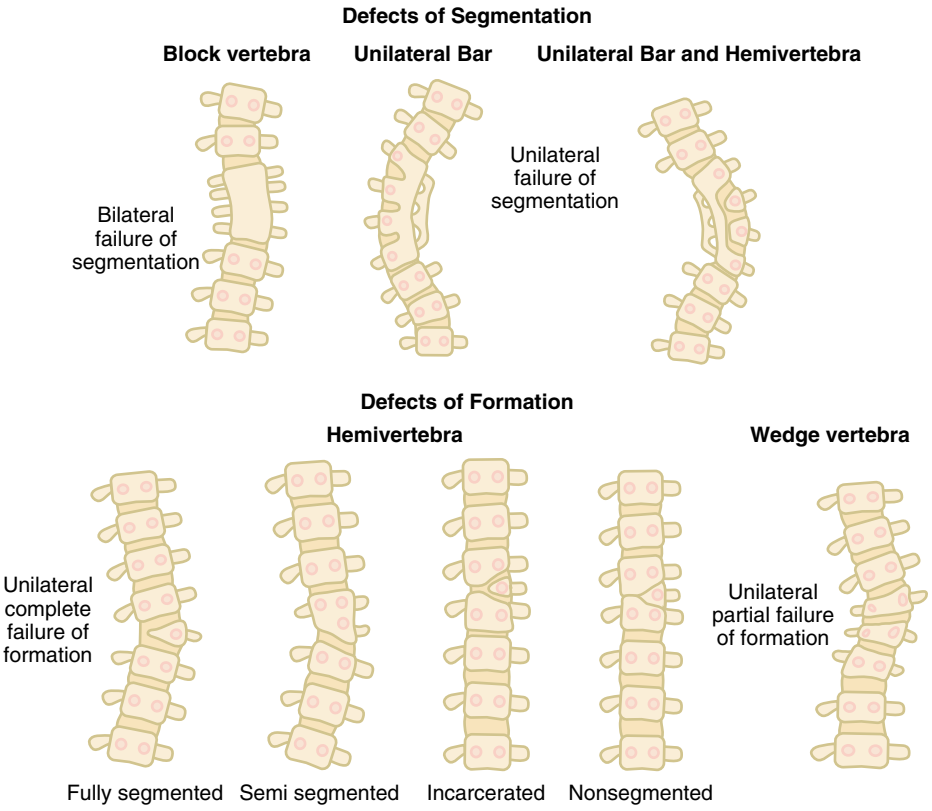

Fig. 720.7 The defects of segmentation and formation that can occur during spinal development. *(From McMaster MJ. Congenital scoliosis. In Weinstein SL, ed. The Pediatric Spine: Principles and Practice, 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:163.)*

idiopathic scoliosis, including shock, infection, and acute respiratory distress syndrome.

SPECIAL CIRCUMSTANCE: THORACIC INSUFFICIENCY SYNDROME

When multiple levels of the thoracic spine are involved in the presence of fused ribs, a progressive three-dimensional deformity of the chest wall may impair lung development and function. This development is termed **thoracic insufficiency syndrome**, when the chest wall is unable to support normal respiration, which can result in decreased life expectancy (Chapter 467.5).

Thoracic insufficiency syndrome may be seen in patients with several recognized conditions such as **Jarcho-Levin syndrome** (spondylocostal or **spondylothoracic dysplasia**) and **Jeune syndrome** (asphyxiating thoracic dystrophy) as well as patients with early-onset scoliosis (idiopathic, neuromuscular, or congenital) and severe spinal deformities in older patients. These difficult cases are treated with **expansion thoracoplasty**, in which the thoracic cage is gradually expanded over time by progressive lengthening of the chest wall on the concavity of the spinal deformity (or in some cases on both sides of the spine). The procedure involves an opening wedge thoracostomy, followed by placement of a VEPTR. The implant is then lengthened at regular intervals (Fig. 720.8). The primary goal is to gradually correct the chest wall deformity to improve pulmonary function, and a secondary goal is correction of an associated spinal deformity. In patients with associated fused ribs, insertion of a VEPTR with an opening wedge thoracostomy results in improved pulmonary function. VEPTR also has been used successfully in patients with early-onset congenital scoliosis. Complications are frequent, and multiple procedures are required; however, this strategy offers hope for many patients with complex, challenging cases. The decision of whether to proceed with a final spinal arthrodesis once chest wall and pulmonary development are thought to be adequate will depend on the specifics of each case. Some patients may elect to be followed even after skeletal maturity if the implant remains in stable position. Further research will be required to answer this and other questions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.3 Neuromuscular Scoliosis, Genetic Syndromes, and Compensatory Scoliosis

R. Justin Mistovich and David A. Spiegel

NEUROMUSCULAR SCOLIOSIS

Scoliosis is frequently identified in children with neuromuscular diseases such as cerebral palsy, muscular dystrophies, myopathies, spinal muscular atrophy, Friedreich's ataxia, myelomeningocele, polio, and arthrogryposis. Children with spinal cord injuries are also at high risk to develop a progressive curvature. The etiology and natural history of these patients differ from idiopathic and congenital scoliosis. Most cases result from weakness and/or imbalance of the trunk musculature. Spasticity may also contribute to spinal curvatures. In some cases, such as myelomeningocele, coexisting congenital vertebral anomalies may be present, further contributing to curve development.

A spinal deformity is more common in patients with higher degrees of neurologic impairment, particularly those who are nonambulatory with inadequate control of their trunk. It is diagnosed in more than 70% of nonambulatory patients with cerebral palsy and over 90% of patients with Duchenne muscular dystrophy.

The diagnosis is suspected on physical examination. In nonambulatory patients, the most common curve pattern is a long, sweeping C-shaped thoracolumbar or lumbar curve (Fig. 720.9). The curve is typically associated with pelvic obliquity, which may have an impact on seating balance. In contrast, ambulatory patients with diagnoses such as Friedreich ataxia may have curve patterns more similar to that of idiopathic scoliosis.

In ambulatory patients, the examination is similar to the physical examination for idiopathic scoliosis. In nonambulatory patients, the back is inspected with the patient sitting upright. Any asymmetry should be noted. These patients often need manual support to maintain an upright position. If any progressive asymmetry is observed, sitting

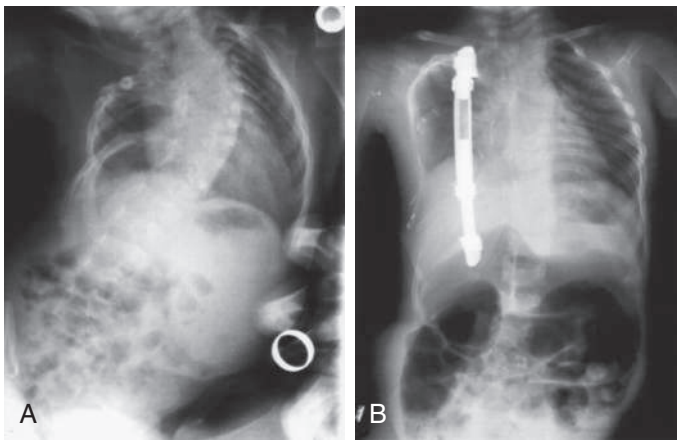

Fig. 720.8 A, Anteroposterior preoperative radiograph of a 7-mo-old infant with congenital scoliosis and fused ribs. A three-dimensional reconstruction of a CT scan of the chest of this infant estimated his lung volume to be 173.2 mL^3. B, Anteroposterior radiograph after implantation of a vertically expandable prosthetic titanium rib and several expansions over 33 mo. The lung volume now measures 330.3 mL^3, an increase of 90.7%. *(From Gollogly S, Smith JT, Campbell RM. Determining lung volume with three-dimensional reconstructions of CT scan data: a pilot study to evaluate the effects of expansion thoracoplasty on children with severe spinal deformities. J Pediatr Orthop. 2004;23:323–328.)*



Fig. 720.9 Imaging shows a long C-shaped curve with convexity to the left side and significant pelvic obliquity, a curve pattern often seen in patients with neuromuscular scoliosis. *(From Pruthi S. Scoliosis. In: Coley BD, ed. Caffey' Pediatric Diagnostic Imaging, 12th ed. Philadelphia: WB Saunders; 2013: Fig 135-10B.)*

PA and lateral radiographs should be obtained. Because prophylactic treatment or bracing cannot alter the natural history of the disease, our own preference is to establish the diagnosis clinically and obtain radiographs if the curve is noted to progress.

The clinical course of patients with neuromuscular scoliosis depends on the severity of neuromuscular involvement as well as the nature of the underlying disease process. Progressive diseases are often associated with progressive curvatures. The consequences of a progressive scoliosis in the neuromuscular population involve function, especially sitting and standing balance, and ease of hygiene and personal care. Pulmonary dysfunction may be expected with the gradual deformation of the rib cage and vertebra-pelvic axis, as well as collapse of the spine with the pelvis impinging on the rib cage. Diaphragmatic function is impaired, and changes in chest volume and chest wall architecture will undoubtedly exacerbate the pulmonary dysfunction owing to underlying muscle weakness. Pulmonary function may be difficult to document in some patient populations, especially those with severe cerebral palsy. Additionally, patients with initial marginal ambulatory function may lose the ability to walk altogether as their scoliosis advances. Curves associated with pelvic obliquity result in asymmetric seating pressures, which may limit sitting endurance and may cause skin breakdown and decubitus ulcers. Patients may also experience pain from impingement of the rib cage on the iliac crest.

The treatment of neuromuscular scoliosis depends on the age of the patient, the underlying diagnosis, and the magnitude of the deformity. The goal is to achieve or maintain a straight spine over a level pelvis, especially in the nonambulatory population, and to intervene early before curve magnitude and rigidity become severe. Neuromuscular curves often continue to progress after skeletal maturity. Curves of >40-50 degrees will continue to worsen over time. Brace treatment does not affect the natural history of neuromuscular scoliosis, and standard braces used for idiopathic scoliosis are poorly tolerated in neuromuscular patients. A **soft spinal orthosis** may improve sitting balance and ease of care, although it does not ultimately change the natural history of the curvature.

A spinal **arthrodesis** should be offered to patients with progressive curvatures over 40-50 degrees. The indications will differ somewhat based on the underlying diagnosis. For example, patients with Duchenne muscular dystrophy are often offered surgery when their curves progress beyond 20-30 degrees, before their anticipated decline in pulmonary or cardiac function makes the procedure riskier or precludes their ability to tolerate surgery. Ambulatory patients with curvatures similar to those seen in idiopathic scoliosis are managed by principles similar to those used with idiopathic etiologies. Patients who are nonambulatory with pelvic obliquity are usually managed by a long spinal fusion extending from the upper thoracic spine to the pelvis, or the lower lumbar spine in selected cases. A brace is not required after this procedure. Treatment decisions must be individualized in nonambulatory patients with spastic quadriplegia and are based on loss of function, the potential to improve hygiene or personal care, and the desires of the family and/or caregivers. These treatment decisions are complex, and research has demonstrated the benefit of formal decision aids for families to assist with understanding treatment risks and benefits.

Although complications are relatively frequent in comparison to patients with nonneuromuscular curves, the available literature suggests that most patients benefit in terms of function and ease of care. Additionally, data suggest that corrective surgery for patients with neuromuscular scoliosis may improve weight gain postoperatively. It is important to identify risk factors for perioperative complications. Research studies have identified nonambulatory patients and those with curves ≥60 degrees as having a significantly increased risk of postoperative major complications, including ileus, pneumonia, infection, and wound problems. Gastrostomy (G)-tube dependence and increased blood loss were also found to be risk factors for postoperative complications. Baclofen pumps have not been associated with increased risk of complications. ASA classification ≥3, BMI ≥95th percentile, and extension of fusion to the pelvis have been found to be associated with postoperative infections. One study subclassified patients with Gross Motor Function Classification System (GMFCS) level 5 in terms of their risk for complications from spinal fusion. These patients have severe functional limitations and are at a high risk of perioperative complications, although not all are identical in terms of risk factors. They identified four subgroups, based on the associated presence of a G-tube, tracheostomy, history of seizures, and nonverbal status. Patients with none of these risk factors were subclassified as 5.0; one associated risk factor was 5.1; two were 5.2; and three or more were 5.3. The rate of major complications for patients with 5.0 GMFCS levels

was 12%, whereas patients with 5.3 GMFCS level had a 49% rate of major complications.

SYNDROMES AND GENETIC DISORDERS

This diverse group of diagnoses includes **neurofibromatosis** (see Chapter 636.1), **osteogenesis imperfecta** (see Chapter 742), connective tissue diseases such as **Marfan syndrome** (see Chapter 743) and **Ehlers-Danlos syndrome** (see Chapter 744), and **Prader-Willi syndrome** (see Chapter 99). Patients with these diagnoses should have their spine examined routinely during visits to their primary care physician. The follow-up and treatment are based on the age of the patient, the degree of deformity, whether progression has been documented, and the underlying diagnosis. Growth-sparing surgical strategies are appropriate in these diverse patient populations depending on curve onset. Each has unique aspects to their medical and surgical care, often with anatomic abnormalities such as dysplastic bone and dural ectasia, and as a group these diseases have a higher rate of complications related to bleeding, wound healing, infection, neurologic dysfunction, nonunion, and the development of progressive curvatures above or below the instrumented segments in comparison with patients requiring surgery for idiopathic scoliosis. Knowledge of the patient's genetic disorder, including prognosis and life expectancy, is important when determining whether surgical correction is appropriate.

COMPENSATORY SCOLIOSIS

Leg-length inequality is a common clinical diagnosis and is usually associated with a small compensatory lumbar curvature (see Chapter 717). This is one cause of false-positive screening examinations. Patients with leg-length inequality may have the pelvis become tilted toward the shorter limb and subsequently develop an associated lumbar curve. The apex of the curve points toward the short leg. There is little evidence to suggest that a small compensatory lumbar curve places the patient at risk of progression or back pain. However, children with leg-length inequality may also have idiopathic or congenital scoliosis. A standing radiograph may be obtained with a block under the foot on the short side, which corrects the leg-length discrepancy and levels the pelvis. If the curvature disappears when the limb-length discrepancy is corrected, a diagnosis of a compensatory curve is made. An alternative imaging study is a PA radiograph with the patient seated.

In neuromuscular disorders such as polio (see Chapter 296) or cerebral palsy (see Chapter 638.1), an adduction or abduction contracture of the hip, described as a fixed infrapelvic contracture, may have an associated compensatory lumbar scoliosis to maintain standing balance. For patients who ambulate, a 10-degree fixed contracture will result in up to 3 cm of apparent leg-length discrepancy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.4 Kyphosis

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

The normal thoracic spine has 20-50 degrees of kyphosis from T3-T12 using the Cobb method on a standing lateral radiograph of the spine. A thoracic kyphosis in excess of the normal range of values is termed **hyperkyphosis**. Patients with hyperkyphosis may present with cosmetic concerns, back pain, or both. A flexible or postural kyphosis may be overcorrected voluntarily or with postural adjustment; however, a rigid kyphosis cannot be corrected passively. Causes of rigid kyphosis include **Scheuermann disease** and congenital kyphosis, among others. Table 720.2 lists conditions associated with hyperkyphosis.

Table 720.2 Conditions Associated with Hyperkyphosis

- Trauma causing spinal fractures
- Spinal infections resulting from bacteria, tuberculosis, and fungi
- Metabolic diseases such as osteogenesis imperfecta or osteoporosis
- Iatrogenic (laminectomy, spinal irradiation)
- Neuromuscular diseases
- Neoplasms
- Congenital/developmental
  - Disorders of collagen such as Marfan syndrome
  - Dysplasias such as neurofibromatosis, achondroplasia, and mucopolysaccharidoses

The evaluation and treatment depend on the underlying diagnosis, the degree of deformity, curve flexibility, whether the deformity is progressive, and severity of associated symptoms.

FLEXIBLE KYPHOSIS (POSTURAL KYPHOSIS)

Postural kyphosis is a common cosmetic concern and is most often recognized by parents or peers. Adolescents with postural kyphosis can correct the curvature voluntarily. A standing lateral radiograph will show an increase in kyphosis but no pathologic changes of the involved vertebrae. There is no evidence that postural kyphosis progresses to a structural deformity. Although mild aching discomfort is sometimes reported, there is no evidence that the condition leads to long-term symptoms, alterations in function, or reduced quality of life. The mainstay of treatment is reassurance. Physical therapy can be considered for muscular discomfort. Although core strengthening is certainly beneficial to most patients, no data suggest that a permanent alteration in alignment can be maintained. Neither bracing nor surgery plays a role in the management of this condition.

STRUCTURAL KYPHOSIS

Scheuermann Disease

Scheuermann disease is the most common form of structural hyperkyphosis and is defined by wedging of >5 degrees of three or more consecutive vertebral bodies at the apex of the deformity on a lateral radiograph. In addition, the apex of the thoracic kyphosis is lower than expected. Other radiographic findings include irregularities of the vertebral end plates and **Schmorl nodes**, which are herniations of the vertebral disk into the surface of the vertebral body. The etiology remains unknown but most likely involves the influence of mechanical forces in a genetically susceptible individual. Histologic specimens taken of patients with Scheuermann disease have shown a disordered pattern of endochondral ossification. However, it remains unclear whether these findings are the primary result of a genetic or metabolic pathologic process, or simply the secondary result of mechanical overload. The reported incidence varies from 0.4% to 10%, affecting males three times more frequently than females.

Physical Exam and Clinical Manifestations

The patient should be examined from the side. Hyperkyphosis of the thoracic spine will typically be associated with a sharp contour. The apex of the deformity will often be in the lower thoracic spine. Patients are unable to correct the deformity voluntarily. Pain is a relatively common complaint. It is typically mild and near the apex of the kyphosis. The symptoms are intermittent, rarely severe, and occasionally limit certain activities. Neurologic symptoms are uncommon.

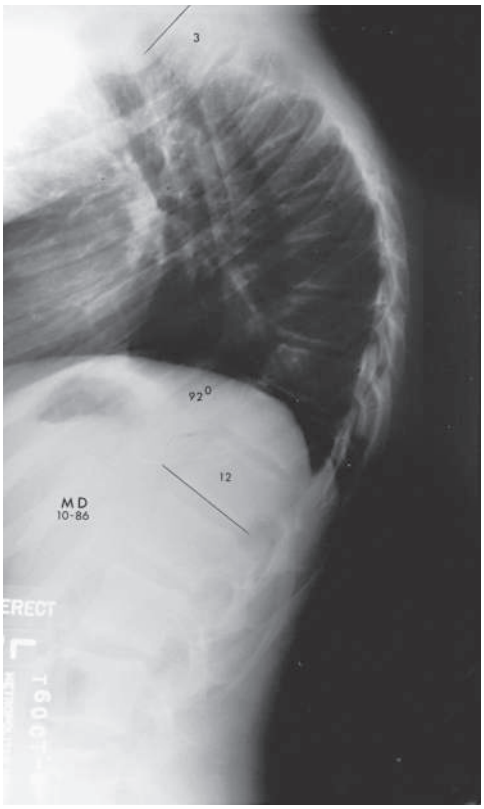

Fig. 720.10 Standing lateral radiograph of a 14-yr-old boy with severe Scheuermann kyphosis. This measures 92 degrees between T3 and T12. Note the wedging of the vertebrae at T6, T7, T8, and T9. The normal thoracic kyphosis is ≤40 degrees.

Radiographic Evaluation

The standard imaging protocol includes standing PA and lateral radiographs (Fig. 720.10). A specific, standardized technique in which the arms are folded across the chest is recommended for the lateral view. In addition to the diagnostic findings noted earlier, a mild scoliosis is commonly seen. Less frequently, a spondylolisthesis may be identified on the lateral radiograph.

Natural History

Treatment depends on the age of the patient, the degree of deformity, and whether any symptoms are present. Adolescent patients with Scheuermann kyphosis may have more complaints of back pain compared to other adolescents, but this often improves after skeletal maturity. A long-term follow-up study noted continued curve progression at about half a degree annually and poorer health-related quality of life compared to normative population values. Kyphotic deformities >90 degrees are more likely to be esthetically unacceptable, symptomatic, and progressive. Deformities more than 100 degrees may be associated with restrictive pulmonary dysfunction.

Treatment

There are few absolute guidelines for treatment, and decisions must therefore be individualized. Skeletally immature patients with mild deformity may benefit from a hyperextension exercise program, but the effects of this strategy on pain relief and spinal alignment, or the natural history, remain unknown. Patients with more than 1 year of growth remaining and a kyphosis of >55-60 degrees may benefit from a bracing program. A Milwaukee brace, which extends up to the neck, is recommended for curves with an apex above T7, whereas curves with a lower apex may often be treated by a thoracolumbar orthosis. The brace should be worn for up to 23 hours daily. Consideration may also be given to a serial casting or stretching program to gain flexibility before instituting the brace program. The goal of the brace is to prevent progression. A permanent improvement in alignment is seen less frequently. Skeletally mature patients with little or no pain and acceptable cosmesis are not treated. In patients with progressive deformity >70-80 degrees who are dissatisfied with their cosmetic appearance or have persistent back pain despite nonoperative measures, a spinal fusion may be considered. Patients treated operatively have less pain and greater satisfaction with their outcome compared to those treated nonoperatively.

An instrumented posterior spinal fusion from the upper thoracic to the mid-lumbar spine is commonly performed, with spinal osteotomies to allow compression of the posterior elements to facilitate deformity correction. These osteotomies allow for shortening of the spine, which should reduce the risks of neurologic complications. An alternative that was used with frequency in the past is combining an anterior spinal release (diskectomies and fusion) with the posterior spinal fusion. This strategy has been used less frequently because of increased complications, length of stay, and costs, in addition to the satisfactory outcomes associated with posterior only surgery. Procedures for kyphosis carry a higher risk than fusions performed for AIS.

CONGENITAL KYPHOSIS

Congenital kyphosis results from congenital anomalies of the vertebrae. In an anterior failure of formation **(type I),** a portion of the vertebral body fails to form. The resulting kyphosis is typically identified after birth and carries a high risk of progression and neurologic dysfunction. Spinal cord dysfunction commonly results from compression at the apex of the deformity. The second type of congenital kyphosis involves an anterior failure of segmentation, in which two vertebrae are fused **(type II)**. The posterior elements of the spine continue to grow, but the anterior spine does not, resulting in a variably progressive kyphosis and a much lower risk of neurologic dysfunction. Patients must be followed closely, and treatment is required in a significant number of cases. Similar to congenital scoliosis, abnormalities of other organ systems should be ruled out.

The treatment depends on the type of malformation, the degree of deformity, and whether neurologic symptoms are present. Bracing is ineffective, and surgical treatment is the only option for progressive curves. Because the natural history is poor for type I deformities and neurologic deterioration is likely, spinal fusion is usually performed shortly after the diagnosis is made. The surgical goals are to prevent or treat kyphotic deformities to restore adequate spinal alignment, while avoiding neurologic deterioration and complications and maximizing spinal growth to the extent possible. This usually involves some form of limited spinal fusion, which may include anterior and/or posterior components, with or without resection of the vertebral remnant, and spinal instrumentation. Ideally, only a short segment of the spine will be fused to try to maximize trunk height. Deformities resulting from anterior failure of segmentation also require spinal stabilization in some cases, but progression is typically slower, and patients are often followed over years to determine whether surgical stabilization will be required.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.5 Back Pain in Children

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Back pain is a frequent complaint in pediatric and adolescent patients, with studies demonstrating single-year prevalence rates between 7% and 58% of adolescents. An epidemiologic cross-sectional survey found 33.7% of children 10-18 years old experienced back pain within the prior year, with 8.9% of them describing the pain as severe. Risk factors for back pain include increasing growth, female sex, family history, overuse injury resulting from sport participation, manual labor, mobile phone usage of more than 10 hours per week (back and neck pain), and possibly carrying a heavy backpack. Patients with scoliosis commonly have back pain; up to 25% may rate this as severe. The pain may be linked to anxiety, depression, and/or substance misuse (smoking, alcohol); psychosocial factors are often underappreciated. Younger patients are felt to have a greater likelihood of a pathologic diagnosis, and therefore a more aggressive workup has been suggested. The incidence of both pediatric and adolescent back pain has increased, whereas the proportion of patients having diagnosable pathology is decreasing, with 75–80% of patients having a negative workup. These trends add further complexity to determining the proper approach to diagnosis and treatment. The differential diagnosis is extensive (Table 720.3). Although the likelihood of serious pathology is low, a complete history and careful physical exam must be performed on all patients (Table 720.4).

CLINICAL EVALUATION

Providers should take a full history, identifying the location, character, and duration of symptoms. Any history of acute trauma or repetitive physical activities should be sought. It is important to identify patients with at-risk athletic pursuits, including football linemen or gymnasts who have a high incidence of spondylolysis and spondylolisthesis. Symptoms consistent with a neoplastic or infectious etiology include pain that is constant or unrelenting, not relieved by rest, and wakes the patient from sleep. Fevers, chills, night sweats, or constitutional symptoms of weight loss or malaise are additional red flags for infectious or neoplastic processes (see Table 720.4).

Symptoms of neurologic dysfunction must also be uncovered. Patients should be questioned about the presence of any radicular symptoms, gait disturbance, muscle weakness, alterations in sensation, muscle atrophy, and changes in bowel or bladder function.

The physical examination includes a complete musculoskeletal and neurologic assessment. The patient should be adequately undressed for the clinical exam. The provider should inspect the patient from the back and the side, identifying any changes in alignment in the frontal or sagittal plane. Assessment of range of motion in flexion, extension, and lateral bending should be performed. Recall that pain with extension suggests pathology within the posterior elements of the spine, such as spondylolysis. Forward flexion will exacerbate pain linked to abnormalities of the anterior column of the spine (vertebral body or disk), such as a herniated disk or diskitis.

Palpation will reveal any areas of point tenderness over the posterior bony elements of the spinal column or the muscles and identify muscle spasm or strain.

Because pain may be referred from a nonspine region, an abdominal examination should be performed, and a gynecologic evaluation should also be considered. Pathology at the sacroiliac joint may also mimic low back pain. This joint should be stressed by compression of the iliac wings or by external rotation at the hip (Faber test).

A detailed neurologic examination should be performed, including manual muscle testing, sensation, proprioception, and reflexes. The patient should be examined for myelopathy by performing the Babinski test, assessing for hyperreflexia, and checking for sustained (more than three beats) of clonus. The superficial cutaneous abdominal reflex should be tested by gently stroking the skin on each of the four quadrants surrounding the umbilicus. Normally, the umbilicus will move toward the area stimulated. A normal examination includes symmetry in the response on both sides of the midline, even if the reflex cannot be elicited on either side. An abnormal test suggests the presence of a subtle abnormality of spinal cord function, most commonly syringomyelia. A straight leg

Table 720.3 Differential Diagnosis of Back Pain

INFECTIOUS AND INFLAMMATORY DISEASES
Spondylodiscitis*
Vertebral osteomyelitis (pyogenic, tuberculosis)
Spinal epidural abscess
Transverse myelitis
Pyelonephritis*
Perinephric abscess
Pancreatitis
Paraspinal muscle abscess, myositis
Psoas abscess
Endocarditis
Pelvic osteomyelitis or myositis
Pelvic inflammatory disease
RHEUMATOLOGIC DISEASES
Pauciarticular juvenile idiopathic arthritis*
Reactive arthritis
Ankylosing spondylitis
Psoriatic arthritis
Inflammatory bowel disease
Fibrositis, fibromyalgia
DEVELOPMENTAL DISEASES
Spondylolysis*
Spondylolisthesis*
Scheuermann kyphosis*
Scoliosis
Chiari malformation type 1 with or without syringomyelia
Spinal dysraphism
Cauda equina syndrome
MECHANICAL TRAUMA AND ABNORMALITIES
Muscle strain/sprain*
Hip/pelvic anomalies (sacroiliac joint dysfunction)
Herniated disk (rare)
Juvenile osteoporosis (rare)
Overuse syndromes (facet syndrome)*
Vertebral stress fractures
Vertebral compression fractures
Limbus vertebra
Lumbosacral sprain*
Seatbelt injury
Trauma (direct injury; e.g., motor vehicle crash)*
Strain from heavy knapsacks
Radiculopathy (sciatica)
NEOPLASTIC DISEASES
Primary vertebral tumors (osteogenic sarcoma, Ewing sarcoma)
Metastatic tumor (neuroblastoma, rhabdomyosarcoma)
Primary spinal tumor (neuroblastoma, lipoma, cysts, astrocytoma, ependymoma)
Malignancy of bone marrow (ALL, lymphoma)
Benign tumors (eosinophilic granuloma, osteoid osteoma, osteoblastoma, bone cyst)
OTHER
Disk space calcification (idiopathic, after diskitis)
Conversion reaction
Sickle cell anemia*
Nephrolithiasis
Hemolysis (acute)
Hematocolpos
Postprocedure pain after lumbar puncture

*Common.
ALL, Acute lymphocytic leukemia.
Modified from Marcdante KJ, Kliegman RM, Schuh AM. *Nelson Essentials of Pediatrics*, 9th ed. Philadelphia: Elsevier; 2023:774.

Table 720.4 Red Flags: Most Common Indications from History and Examination for Pathologic Findings Needing Special Attention and Sometimes Immediate Action

- Children younger than 18 yr old with considerable pain
- History of violent trauma
- Nonmechanical nature of pain (i.e., constant pain not affected by movement; pain at night)
- History of cancer
- Systemic steroid use
- Drug use
- HIV infection or other immunocompromised patients
- Unintentional weight loss
- Systemically ill, particularly signs of infections such as fever or night sweats
- Persisting severe restriction of motion or intense pain with minimal motion
- Structural deformity including scoliosis, Chiari malformation, tethered cord
- Difficulty with micturition (urinary retention)
- Loss of anal sphincter tone or fecal incontinence
- Progressive motor weakness or gait disturbance, paresthesias, pes cavus, foot drop, saddle anesthesia
- Marked morning stiffness
- Peripheral joint involvement
- Iritis, skin rashes, colitis, urethral discharge, or other symptoms of rheumatologic disease
- Inflammatory disorder such as ankylosing spondylitis suspected
- Family history of rheumatologic disease or structural abnormality

raise test should be done to check for nerve root tension secondary to a herniated disk, slipped vertebral apophysis, or other pathology. This examination should reproduce any neurologic symptoms distal to the knee.

MEDICAL DECISION-MAKING

A detailed history and physical exam are the most important components of the initial evaluation and should focus on identifying "red flags" and differentiating between mechanical and nonmechanical back pain (see Table 720.4). Findings consistent with a nonmechanical etiology warrant a more aggressive evaluation and/or prompt referral.

Patients with mechanical or muscular back pain and symptoms that are activity related and improve with rest are typically treated by rest for a few days or activity restrictions and nonnarcotic analgesics. Physical therapy for core strengthening should be considered if the acute symptoms do not resolve or if the pain is chronic. The patient should be asked to return for a follow-up appointment after 4-6 weeks. Plain radiographs are commonly obtained at the discretion of individual practitioners. However, if no red flags are present, providers may defer radiographs because of the cumulative adverse effects of radiation exposure. Patients presenting with red flags or those who have not improved after 6 weeks of conservative care necessitate further investigation.

RADIOGRAPHIC AND LABORATORY EVALUATION

When further workup is indicated, PA and lateral radiographs of the involved region of the spine are the initial images of choice. Some clinicians will also use oblique radiographs of the lumber spine when spondylolysis is in the differential diagnosis. If plain radiographs are normal, advanced imaging modalities should be considered, including a three-phase technetium bone scan, a bone scan with single-photon emission computed tomography (SPECT) if spondylolysis is suspected, CT for viewing osseous detail, and MRI for viewing soft tissue detail or bony areas of inflammation.

When systemic signs or constitutional symptoms are present, a CBC, ESR, and CRP should be ordered. In certain cases, laboratory tests to evaluate for inflammatory diseases such as juvenile idiopathic arthritis, seronegative spondyloarthropathies, and ankylosing spondylitis are indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.6 Spondylolysis and Spondylolisthesis

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Spondylolysis represents a defect in the pars interarticularis, the segment of bone connecting the superior and inferior articular facets in the vertebra. It is thought to result from repetitive hyperextension stresses, in which compressive forces are transmitted from the inferior articular facet of the superior vertebra to the pars interarticularis of the inferior vertebra. Supporting the mechanical theory, spondylosis has never been described in nonambulatory adults. However, there may be a genetic association with 19–69% of affected patients having a first-degree relative also affected. A stress fracture, unilateral or bilateral, may progress to a spondylolysis. In many cases, this stress fracture does not heal, resulting in a pseudarthrosis, or false joint, and thereby allowing motion through this bony area where motion should not normally exist.

Spondylolysis is common in athletes who engage in repetitive spinal hyperextension, especially gymnasts, football interior linemen, weightlifters, and wrestlers. Approximately 4–8% of the entire pediatric population is affected, making it the most common cause of back pain in adolescents when a diagnosis can be established. Patients with excessive lordosis in the lumbar spine may be predisposed to developing a spondylolysis, and a genetic component has also been suggested. The lesion is most common at L5, but it may be identified at upper lumbar levels as well.

Spondylolisthesis represents a forward slippage of one vertebra on another and is identified in approximately 4–5% of the population. The multiple causes of spondylolisthesis include dysplastic/congenital defects, isthmic (due to a pars stress fracture), trauma, and neoplasm. In children and adolescents, the most common types are dysplastic and isthmic. Between 5% and 15% of patients with spondylolysis will develop spondylolisthesis.

Spondylolisthesis is assessed on a standing lateral radiograph of the lumbosacral junction according to (1) the percentage of forward translation of one vertebra on the other, (2) the slip angle, measuring the rotation of the involved vertebrae in the sagittal plane, and (3) relative position of the sacrum during upright posture. A grade 1 slip of L5 on S1 has <25% of the width of the vertebral body of L5 translated anteriorly on S1. Similarly, grade 2 is 25–50%, grade 3 is 50–75%, and grade 4 is 75–100%. **Spondyloptosis,** or grade 5 spondylolisthesis, describes a complete displacement of one vertebral body on the level below. The slip angle, which demonstrates the degree to which the superior vertebra is flexed forward relative to the underlying vertebra, and the verticality of the sacrum both have a significant effect on sagittal balance or the relationship of the sagittal weight-bearing axis to the body segments. Abnormalities in sagittal spinal balance may be associated with compensatory flexion of the knees during ambulation, hamstring spasm and/or contracture, and back pain.

CLINICAL MANIFESTATIONS

Spondylolysis may occasionally be asymptomatic and diagnosed incidentally on imaging obtained for other reasons. It usually presents with mechanical low back pain that may radiate to the buttocks, with or without spasm of the hamstring muscles. Neurologic symptoms are rare in patients with spondylolysis. However, patients with spondylolisthesis may experience neurologic symptoms from compression or stretching of the nerve roots, causing radiculopathy or even the surgical emergency of cauda equina in which bowel and bladder function is affected.

PHYSICAL EXAM

Patients with spondylolysis often have discomfort with spinal extension or hyperextension. Provocative testing may include keeping the spine extended for 10-20 seconds to see if back pain can be reproduced. There may be discomfort with palpation of the spinous process of the involved vertebra. Patients with higher grades

of spondylolisthesis demonstrate loss of lumbar lordosis, flattening of the buttocks on visual inspection, and a vertical sacrum resulting from posterior rotation of the pelvis. A step-off may be palpated between the spinous processes of the involved vertebrae. Hamstring contracture is tested by measuring the popliteal angle. The hip is flexed to 90 degrees while fully extending the contralateral hip to the level the pelvis. The knee is then passively extended, and the popliteal angle represents the angle between the thigh (vertical) and the lower leg axis. A careful, complete neurologic examination is essential because diagnosis of spondylolysis and spondylolisthesis is often delayed.

RADIOGRAPHIC EVALUATION

The initial evaluation of the lumbar region should include high-quality AP and lateral radiographs. Some authors also prefer to obtain oblique radiographs, which demonstrate the classic "Scotty dog" finding on the pars interarticularis. The lumbar spine in oblique radiograph projections normally appears to form the figure of a "Scotty dog" (i.e., Scottish terrier), with the transverse process forming the nose, the pedicle forming the eye, and the pars interarticularis forming the neck; in spondylolysis, the pars interarticularis will have a defect or a break, mimicking a "collar" on the radiograph. Standing PA and lateral radiographs of the entire spine are obtained if findings suggestive of scoliosis or hyperkyphosis are also present (Figs. 720.11 and 720.12). In patients with normal plain films, traditional imaging studies included a bone scan with SPECT to diagnose a spondylolysis during the earliest stage of a stress reaction, before the formation of a stress fracture or an established pseudarthrosis. The radiation exposure from this test, though, is substantial—bone scans have 7-9 times the radiation dose of two-view plain films. In comparison, CT scans carry only 2 times the radiation dose of two-view plain films. The sensitivity of MRI using STIR imaging is comparable to SPECT and led to a recommendation for MRI STIR rather than bone scans in acute cases in which plain films could not make a diagnosis. MRI sequences will demonstrate inflammation associated with an acute spondylolysis while avoiding radiation exposure. A CT scan with thin cuts may provide additional information to establish the presence of a pars defect and may be indicated in chronic, refractory cases. MRI is also indicated in the presence of signs or symptoms of cauda equina or nerve root involvement.

TREATMENT

The asymptomatic patient with spondylolysis requires no treatment. Patients with pain are treated initially by activity modification, physical therapy for core strengthening, and analgesic medications. The use of a lumbosacral orthosis, which immobilizes the spine in slight flexion to decompress the posterior elements, may lead to a faster resolution of symptoms, though a recent SRS Evidence Based Medicine Committee report determined that the benefit of bracing is not well established. This orthosis is typically worn for 3-4 months. Participation in sports or other activities that exacerbate pain should be restricted until the symptoms have resolved. Providers should consider checking a vitamin D level in patients with spondylolysis and treating if deficient.

Most patients experience resolution of their symptoms even though the spondylolysis heals in only a small number of patients. Surgery should be offered for chronic, refractory back pain when conservative measures have failed. For those with spondylolysis at L5, a posterior spinal fusion from L5 to S1 is indicated as the mobility at this joint is limited relative to that observed at higher levels in the spine. For the infrequent cases in which the defect is at higher levels in the lumbar spine, techniques for repairing the pseudarthrosis without fusion are considered.

Recommendations for the management of spondylolisthesis depend on the age of the patient, the presence of pain or neurologic symptoms, and the degree of deformity. For low-grade lesions, the management is similar to that for spondylolysis. Significant progressive slippage may occur in 3–5% of skeletally immature patients, and patients must be followed through skeletal maturity. Progression of deformity is increased in higher grade slips and in cases of dysplastic spondylolisthesis. However, there is only a 1.4% incidence of progression after adolescence. Guidelines for the timing of follow-up, and whether or not to obtain routine radiographs at each follow-up, differ between individuals and institutions; we typically follow asymptomatic patients yearly with a standing lateral of the lumbosacral junction. Nonoperative management in minimally symptomatic or asymptomatic patients is appropriate, and delaying surgical treatment does not appear to worsen outcomes.

For low-grade slips with persistent symptoms despite nonoperative measures, an in situ posterior spinal arthrodesis is suggested. Additionally, patients with a more kyphotic slip angle have been shown to have poorer prognosis, although operative treatment did not significantly improve their outcome. The surgical approach for high-grade slips varies between surgeons and institutions. The main

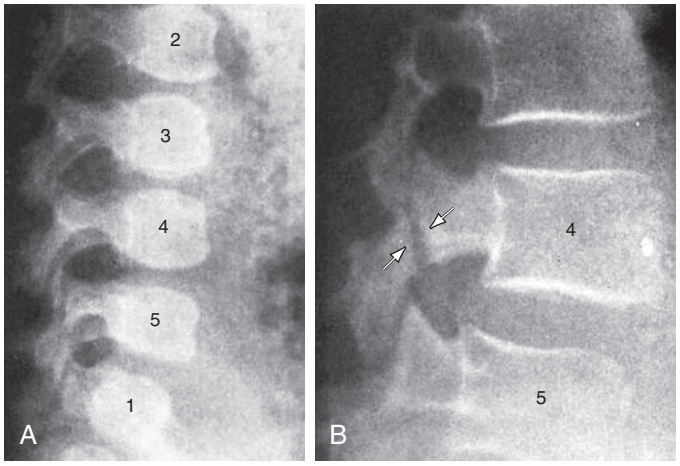

Fig. 720.11 A, Normal spine at 9 months of age. B, Spondylolysis in the L4 vertebra at 10 yr of age. *(From Silverman FN, Kuhn JP. Essentials of Caffrey's Pediatric X-ray Diagnosis. Chicago: Year Book Medical Publishers; 1990:94.)*

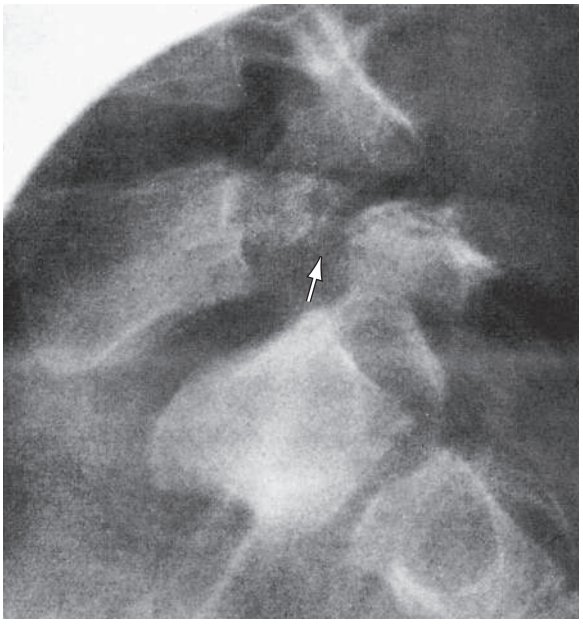

Fig. 720.12 Defect in the pars interarticularis *(arrow)* of the neural arch of L5 (spondylolysis) that has permitted the body of L5 to slip forward (spondylolisthesis) on the body of S1. *(From Silverman FN, Kuhn JP. Essentials of Caffrey's Pediatric X-ray Diagnosis. Chicago: Year Book Medical Publishers; 1990:95.)*

principle is to stabilize the unstable segment of the spine, avoid neurologic complications, and restore adequate sagittal balance to the spine. The typical components of these complex procedures include (1) posterior decompression of the L5 and S1 nerve roots (laminectomy and takedown of pseudarthrosis), (2) instrumented posterior spinal fusion from L4 or L5 to S1 and occasionally the pelvis is included in the instrumentation, (3) diskectomy at L5-S1 with placement of anterior column support (transforaminal cage or fibular allograft from sacrum to L5), and (4) reduction of the slippage by positioning the hips in extension or by an "instrumented reduction" using the spinal implants. Adding the anterior column support enhances rates of fusion. Reduction improves radiographic outcomes but may increase the risk of unplanned surgeries, pseudarthrosis (failure of fusion), and neurologic complications.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.7 Spine Infection

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Spondylitis, meaning inflammation of the vertebrae, is most commonly due to infectious or autoimmune processes. **Spondylodiscitis** is defined as a primary infection of the intervertebral disk **(diskitis)** with spread to the vertebrae **(osteomyelitis)**. Based on MRI, some think the infection begins in the vertebral body with subsequent rupture into the disk space. The most common etiology is hematogenous seeding of bacteria, with the original infection of the well-perfused end plate extending into the disk and vertebral body. Spondylodiscitis is more commonly seen in children younger than 5 years of age but can occur at any age; it is often associated with vertebral body osteomyelitis. Patients in the younger age range have vascular channels between the vertebral end plate and the disk space, explaining the prevalence of diskitis with osteomyelitis.

Staphylococcus aureus is the most common organism causing spine infections. Other organisms include ***Kingella kingae*** and less often group A streptococcus and *Escherichia coli*. Rare causes of vertebral bone infection include tuberculosis (often multiple vertebral bodies), *Serratia marcescens*, brucellosis, and cat-scratch disease. Blood cultures have a sensitivity of only 30%. Percutaneous or less often open biopsy of the disk space is positive only 50–85% of the time; polymerase chain reaction is indicated for the diagnosis of *Kingella*. The differential diagnosis includes chronic recurrent multifocal osteomyelitis.

CLINICAL MANIFESTATIONS

A high index of suspicion is required to establish the diagnosis of infectious spondylodiscitis. Patients may experience back pain, abdominal pain, fever, or malaise. Fever is less common and may be present in only 30% of patients. Toddlers may develop a limp or refuse to walk, stand, or sit. In an effort to reduce the pain associated with spinal motion, the child will hold the spine in a rigid position. There may also be a paraspinal muscle spasm. Local point tenderness over the affected spinous process is common. There may be a "list" or leaning of the trunk when the patient is viewed from the front or back, and from the side there may be a loss of lumbar lordosis. Neurologic manifestations are rare and, if present, suggest that an epidural abscess may be present. The infection may drain beyond the spine to the paravertebral space and psoas muscles.

Spine flexion compresses the anterior elements of the spine and will elicit an increase in pain. Asking a child to pick up an object from the ground is a simple way to elicit this provocative test.

Although the white blood count may remain normal, the ESR is elevated in 80% of cases, and the CRP is also elevated.



Fig. 720.13 Spondylodiscitis. Sagittal T2-weighted (**A**) and coronal short tau inversion recovery (**B**) images demonstrate destruction of T7-T8 intervertebral disk with abnormal marrow signal in the adjacent vertebral bodies and associated paravertebral soft tissue phlegmon. *(From Bosemani T, Huisman TAGM. Spine imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 9.31, p. 345.)*

RADIOGRAPHIC EVALUATION

The earliest radiographic finding is a postural loss of lumbar lordosis. Later characteristic features on plain radiographs are disk space narrowing, or loss of disk height, and irregularity of the adjacent vertebral end plates. However, these findings do not develop until 2-3 weeks after the onset of symptoms. The diagnosis may be established earlier using MRI. MRI is the most sensitive and specific imaging to diagnose osteomyelitis and to identify abscesses and/or neural compression (Figs. 720.13 and 720.14).

TREATMENT

Once the diagnosis is suspected clinically, the treatment involves symptomatic care and empiric anti-staphylococcal antibiotics, as *S. aureus* is the most common pathogen isolated. *Kingella kingae* is recognized as a common pathogen in patients from 6 months to 4 years of age. A first-generation cephalosporin (e.g., cefazolin) or semisynthetic antistaphylococcal penicillin (e.g., oxacillin) is recommended in areas where methicillin-resistant *S. aureus* (MRSA) is not prevalent. Clindamycin should be considered in areas where MRSA is more common. Some areas of the world report increasing clindamycin resistance among both methicillin-resistant and methicillin-susceptible *S. aureus* isolates, leading to consideration of vancomycin or linezolid. Blood cultures should be obtained *before* the administration of antibiotics. The antibiotic agent may be modified if blood cultures are positive. Symptomatic care includes rest and analgesics, antiinflammatory medications, and a spinal orthosis may also be considered. The typical antibiotic course is from 4-6 weeks. Data in osteomyelitis suggest that conversion from intravenous to oral agents may be acceptable after several days depending on the clinical course (see Chapter

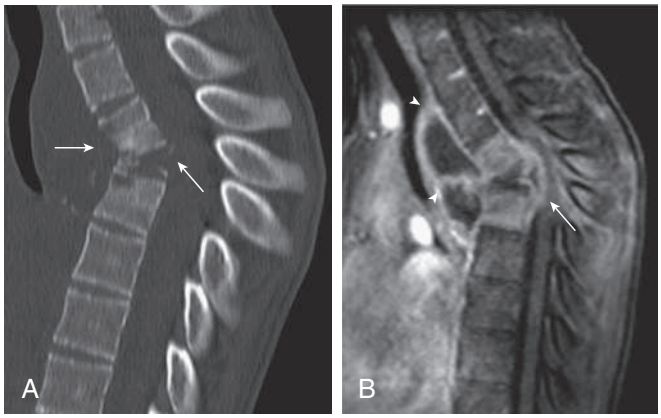

Fig. 720.14 Tuberculous vertebral osteomyelitis in 13-yr-old female with progressive loss of strength and coordination in legs. (A) Sagittal reformatted soft-tissue window images from a CT of the spine (B) sagittal fat-saturated postcontrast T1-weighted MR images of the thoracic spine demonstrate marked kyphosis at site of bony collapse at the level of the midthoracic spine (*arrows* in A and B), as well as surrounding soft tissue abscess (*arrowheads* in B) predominately anteriorly, at the same level. *(Modified from Maddocks ABR, Pollock AN. Infections of the spine and spinal cord. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 44.8AC, p. 422.)*

725). A CT-guided needle biopsy of the disk space can be considered. Although the diagnostic yield on cultures is low (20–40%), the pathologic findings may show acute inflammatory cells to establish the diagnosis (≥1 neutrophil per high power field). This intervention is often reserved for patients who do not respond to empiric antibiotics or when there are questionable diagnostic features. Surgical treatment is rarely required, and indications include establishing the diagnosis in patients who fail to respond to empiric antibiotics, and those in whom an abscess and/or neurologic involvement are identified.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.8 Intervertebral Disk Herniation/ Slipped Vertebral Apophysis

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Intervertebral disk herniation is the result of a tear in the outer layer of the vertebral disk, called the annulus fibrosus, which then allows for protrusion of the inner nucleus pulposus. At times, a free fragment of disk can rupture and compress the nerve roots or spinal cord. Bulging of the annulus without rupture may also be observed, resulting in back pain and occasionally radicular symptoms. Symptoms are due to either direct mechanical compression or a local inflammatory response.

Slipped vertebral apophysis, also called a posterior ring apophysis separation, is due to an injury and is only found in skeletally immature patients. A small fragment of bone from the posterior corner of the vertebral body apophysis avulses and may cause direct mechanical compression to the spinal cord or nerve root, similar to a disk herniation. (An apophysis is a normal outgrowth of bone with its own physis, or growth plate. Another example is the tibial tubercle.) Both disk herniations and ring apophysis separations can cause back pain, radicular symptoms (nerve root compression or irritation), or spinal cord compression.

ETIOLOGY

Predisposing activities for both conditions include heavy lifting, repetitive axial loading activities, and occasionally traumatic injury such as a fall. Approximately 30–60% of patients with symptomatic herniated disks have a history of a trauma or sports-related injury. Other associations include preexisting disk degeneration, congenital malformation, and genetic or environmental factors. There may be a potential association between disk degeneration and the herpes virus. Missense pathogenic variants in collagen-encoding genes may be present in 80% of young patients with symptomatic lumbar disk herniations.

CLINICAL MANIFESTATIONS

Symptoms of intervertebral disk herniation or slipped vertebral apophysis in adolescents are similar to adult herniated disk symptoms. The major complaint is back pain, present in nearly 90% of patients. Over 30% of patients complain of **radicular symptoms** or radiating sciatic-type pain into the legs. The back pain is often made worse by coughing, a Valsalva maneuver, or sitting. Pain may be relieved by standing or back extension, which increases the disk space between vertebral bodies. Providers should inquire about weight loss, fever, or other constitutional symptoms to rule out an infectious or neoplastic etiology.

On physical examination, both paraspinal muscle spasm and a generalized spinal stiffness are common. Patients may lean toward the unaffected side to increase the size of the affected neural foramen, thereby partially relieving symptoms. This results in a reactive scoliosis—not a true spinal curve—that improves with symptom resolution. Although overt signs of neurologic involvement are absent in most patients, a positive straight leg raise test, causing radicular pain to shoot down the affected leg, is usually present. Pain is also worsened by spinal flexion.

It is critical to perform a full neurologic evaluation, including sensation to light touch, pinprick, and proprioception; muscle strength; and reflexes. Providers must also evaluate for perineal numbness, or saddle anesthesia. This finding, combined with changes in bowel or bladder function, is indicative of cauda equina syndrome, a surgical emergency in which the nerve roots at the caudal end of the spinal cord are compressed or damaged.

RADIOGRAPHIC EVALUATION

Radiographs often show loss of lumbar lordosis, which is due to muscle spasm, and sometimes a mild lumbar scoliosis. Other radiographic findings include degenerative changes and a loss of intervertebral disk height. MRI is the best study to establish the diagnosis of a disk herniation (Fig. 720.15). CT is especially helpful to visualize a partially ossified fragment associated with a slipped apophysis.

TREATMENT

The initial treatment is nonoperative in the vast majority of patients—even if symptoms or findings of radiculopathy are observed. Treatment focuses on rest, activity modification, NSAIDs, and physical therapy. An orthosis may provide additional symptomatic relief. Complete bed rest is not recommended. Epidural steroid injection (ESI) may be discussed with patients after approximately 6 weeks of symptomatic treatment if symptoms persist, though the evidence is not yet definitive. However, if patients elect to undergo an ESI, they should not have more than a single injection if the first did not provide any relief. Clinical experience has demonstrated that multiple injections are no more likely to provide relief than a single injection and expose patients to additional risks of infection, scarring, and neural injury. If a patient experiences substantial relief from an ESI and has a later recurrence of symptoms, consideration may be given for a repeat injection after performing a complete physical exam and ruling out any new pathology.

Surgical treatment should be considered when nonoperative measures have failed or when a profound neurologic deficit such as cauda equina syndrome is present or evolving. Unfortunately, children and adolescents respond less favorably to nonoperative therapy compared with adults, and a significant percentage will require surgical intervention. Although patients with disk herniation may improve with reduction in the local inflammatory response around the nerve root and also as the disk material loses water volume and shrinks, which eliminates mechanical compression, patients with symptomatic ring apophyseal separations have a bony fragment causing their symptoms and are unlikely to improve spontaneously.

The surgical technique involves removing a small area of the lamina via a posterior approach, called a **laminotomy**, which allows exposure

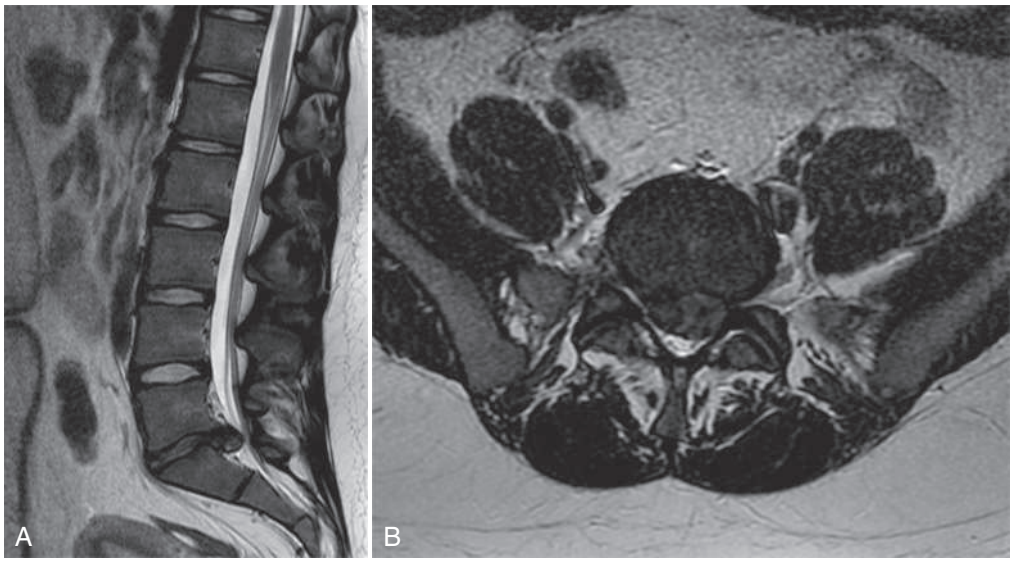

Fig. 720.15 Lumbar disk herniation. Sagittal (A) and axial T2-weighted (B) images demonstrate a disk extrusion at L5-S1 level with near-complete infilling of bilateral lateral recesses, left greater than right, and effacement of the thecal sac. *(From Bosemani T, Huisman TAGM. Spine imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 9.30, p. 345.)*

of the neural elements and underlying disk. Any loose fragments are removed. A bulging disk may also be opened surgically to decompress the area compressing the neural elements, although a complete diskectomy is inadvisable. The surgical approach is similar in the case of a slipped vertebral apophysis, in which fragments of bone and cartilage must also be removed. This often requires a bilateral laminotomy to completely address the pathology. Patients with congenital lumbar spinal stenosis may be more likely to require surgical treatment and also may require a posterior decompression in addition to the discectomy.

The initial results are excellent in the majority of patients. Approximately 30% may have recurrent herniations and resultant symptoms of back or leg pain at longer-term follow-up. These recurrences are initially treated nonoperatively; however, repeat discectomy may be required, and if so, a significant number of patients may require a spinal arthrodesis to stabilize the damaged motion segment. A spinal fusion may also be required for instability associated with spondylolisthesis or other etiology.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

720.9 Tumors

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Back pain may be the most common presenting complaint in children who have a tumor involving the vertebral column or the spinal cord. Other associated symptoms may include weakness of the lower extremities, scoliosis, and loss of sphincter control. The majority of tumors are benign (see Chapter 550), including osteoid osteoma, osteoblastoma, aneurysmal bone cyst, and eosinophilic granuloma. Malignant tumors involving the vertebral column may be osseous, such as osteosarcoma or Ewing sarcoma. They may involve the spinal cord and sympathetic or parasympathetic nerves in cases of ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. Tumors from other primary sites can also metastasize to the spine.

High-quality plain radiographs may show **vertebra plana**, or symmetric collapse of a single vertebra with preserved disk space; this is most commonly seen with eosinophilic granuloma (Fig. 720.16). Other useful imaging modalities include bone scans, which help with localization and identification of other lesions; MRI, which is helpful to identify soft tissue extension and neurologic compression; and CT, which provides excellent bony detail.

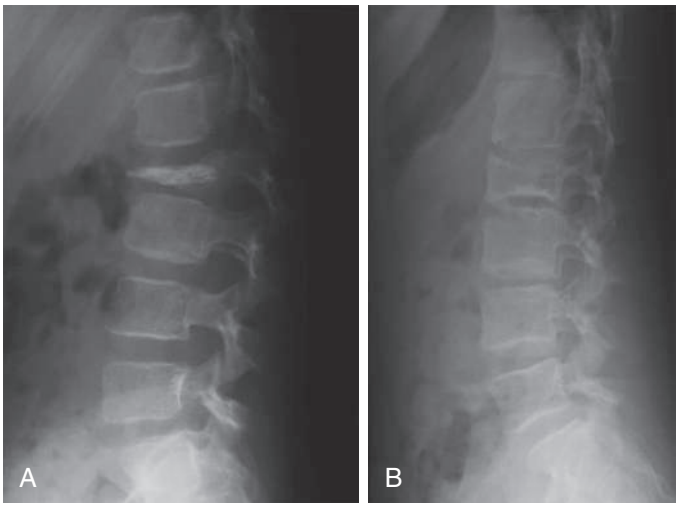

Fig. 720.16 (A) Lateral radiograph of the lumbar spine of a 6-yr-old female with a painful osteolytic lesion of the L2 vertebral body with vertebral plana deformity. CT-guided frozen section biopsy showed eosinophilic granuloma; intralesional methylprednisolone injection was performed. (B) Lateral radiograph of the lumbar spine shows complete reconstitution of the lesion 7 years after diagnosis and treatment. *(From Angelini A, Mavrogenis AF, Rimondi E, et al. Current concepts for diagnosis and management of eosinophilic granuloma of bone. J Orthop Traumatol. 2017;18:83-90. Fig. 3.)*

A biopsy is usually required to establish the diagnosis. Treatment of tumors of the spinal column may require a multidisciplinary approach. These cases should ideally be managed in centers with experience in the care of patients with these lesions. Many lesions are surgically treated by laminectomy, and postoperative surveillance is essential to identify cases of postlaminectomy kyphosis or other spinal deformities, which when progressive may require an instrumented spinal fusion to stabilize.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 721

The Neck

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

721.1 Torticollis

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Torticollis, literally meaning "twisted neck," is not a diagnosis but rather a clinical manifestation of a variety of underlying conditions (Table 721.1). Common names associated with this condition include "wry-neck" and "cock-robin" deformity. Although congenital muscular torticollis is the most common diagnosis in cases presenting at or close to the time of birth, the differential diagnosis for acquired torticollis is large. Therefore a thorough evaluation is required to identify the underlying cause.

CONGENITAL MUSCULAR TORTICOLLIS

Congenital muscular torticollis (CMT) is due to a contracture of the sternocleidomastoid (SCM) muscle, which results in a *tilting* of the head and neck *toward* the side of the contracted muscle with *rotation* of the head to the *opposite* side (Fig. 721.1). In most cases (75%), the right SCM muscle is involved, causing the patient's face and chin to point to the left side.

CMT is thought to result from an intrauterine deformation or compression and is more common in children of primigravida mothers. CMT may be associated with the presence of a palpable mass or nodule of fibrous tissue within the substance of the SCM muscle in approximately 50% of cases (Figs. 721.2 and 721.3). Findings on muscle biopsies and MRI studies led to the hypothesis that SCM muscle injury from compression or stretch may create localized ischemia, which in turn results in fibrosis and subsequent contracture—essentially an intramuscular compartment syndrome. In rare cases, the condition can result from hereditary muscle aplasia.

Associated findings with CMT include plagiocephaly, facial asymmetry, and positional musculoskeletal deformities such as metatarsus adductus (15%) and calcaneovalgus feet. Hip dysplasia may be identified in 8–20% of affected patients. In addition to routine screening by physical examination for hip dysplasia, providers should consider obtaining either an ultrasound at 6 weeks of age or a plain radiograph of the pelvis at 4-6 months of age in children with CMT even if the physical exam is normal and there are no other risk factors for DDH.

The cornerstone of treatment for CMT is physical therapy and a home stretching program in which caregivers are instructed to gently stretch the contracted SCM by rotating the infant's chin to the ipsilateral shoulder and simultaneously tilting the head toward the contralateral shoulder. The best results occur when treatment is started within the first 3 months of life, leading to resolution in nearly all cases. Patients who start their physical therapy later can expect a more prolonged course, and a subset will not achieve a normal range of motion. Recently, single frequency microcurrent has been used as an adjunct to physical therapy with the goal of reducing the time of treatment and also addressing the challenges of patients presenting at a later age. Botulinum toxin injections may also be considered as an adjunct, especially in resistant cases in older patients. Plagiocephaly commonly accompanies CMT, and patients may be referred to a craniofacial clinic or specialist for discussion of treatment with a cranial remolding helmet. Early restoration of motion reduces the likelihood that patients will have persistent facial asymmetry or cranial molding abnormalities.

Although firm guidelines for imaging the cervical spine have not been established, anteroposterior (AP) and lateral radiographs of the cervical spine may be obtained when the typical clinical features associated with congenital muscular torticollis are absent or if the deformity does not respond to the stretching treatment, because torticollis in infants may also be due to **congenital vertebral anomalies**.

Surgical release of the SCM is considered in patients with *persistent deformity* after failure of conservative treatment. The muscle may be released at its insertion on the clavicle (unipolar release) or at both its origin and insertion (bipolar release). There is no agreement as to the most appropriate time for the surgical release, but surgical treatment is typically delayed until at least 18 months of age; some even suggest waiting until the child is approaching school age. Although range of motion can be improved after surgical release even during the teenage years, remodeling of facial asymmetry and plagiocephaly may be less predictable in patients older than infancy. Surgical management results in satisfactory function and acceptable cosmesis in more than 90% of patients; however, with early diagnosis and treatment, surgery should be required in only a minority of cases. Patients who have residual or untreated CMT beyond a year of age may develop secondary skeletal abnormalities such as a mild cervicothoracic scoliosis or rotational malalignment and tilting of upper and lower cervical vertebrae (especially at the atlantoaxial joint). It is presumed that such malalignment will improve with release of contracture, but in older patients, skeletal deformities may persist.

Table 721.1 Differential Diagnosis of Torticollis

CONGENITAL
Muscular torticollis
Positional deformation
Hemivertebra (cervical spine)
Unilateral atlanto-occipital fusion
Klippel-Feil syndrome
Unilateral absence of sternocleidomastoid
Pterygium colli
TRAUMA
Muscular injury (cervical muscles)
Fibromatosis coli (sternocleidomastoid tumor of infancy)
Atlanto-occipital subluxation
Atlantoaxial subluxation
C2-3 subluxation
Rotary subluxation
Fractures
Foreign body
INFLAMMATION
Cervical lymphadenitis
Retropharyngeal abscess
Cervical vertebral osteomyelitis
Grisel syndrome (nontraumatic subluxation of the atlantoaxial joint due to local inflammation)
Juvenile idiopathic arthritis
Lemierre syndrome
Upper lobe pneumonia
NEUROLOGIC
Visual disturbances (nystagmus, superior oblique or lateral rectus paresis)
Dystonic drug reactions (phenothiazines, haloperidol, metoclopramide)
Cervical cord tumor
Posterior fossa brain tumor
Syringomyelia
Wilson disease
Dystonia musculorum deformans
OTHER
Acute cervical disk calcification
Sandifer syndrome (gastroesophageal reflux, hiatal hernia)
Benign paroxysmal torticollis
Bone tumors (eosinophilic granuloma)
Soft tissue tumor
Psychogenic



Fig. 721.1 Congenital muscular torticollis. **A,** Torticollis secondary to a contracted left sternocleidomastoid (SCM) muscle. **B,** Mass in right SCM *(arrow)* of a newborn. Note intrauterine folding deformity of the right ear. **C,** Flattening of the left occipital area and left ear formation resulting from supine positioning of a child with right congenital torticollis. *(From Johnson CE. Disorders of the neck. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig 8.6, p. 93.)*



Fig. 721.2 Clinical presentation of a 2- × 2-cm firm, left-sided neck mass. *(From Baik G, Blask A, Reilly BK. Unilateral neck mass in a neonate. J Pediatr. 2018;202:329, Fig. 1.)*

OTHER CAUSES OF TORTICOLLIS

The evaluation of torticollis becomes more complex when the typical findings associated with CMT are absent, the usual clinical response is not observed, or the deformity presents at a later age. In addition to a careful history and physical examination, consultation with an ophthalmologist and neurologist will be helpful. Plain radiographs should be obtained, and MRI of the brain and cervical spine will be required in a subset of cases.

The differential diagnosis is extensive (see Table 721.1). **Neurogenic torticollis** is uncommon and results from tumors of the posterior fossa or brainstem, syringomyelia, and Arnold-Chiari malformation. In addition to the neurologic examination, MRI of the brain and cervical spine is required to establish the diagnosis. **Benign paroxysmal torticollis** of infancy is also uncommon and may be due to vestibular dysfunction. Episodes may last from minutes to days, and the side of the deformity may alternate. The condition is self-limiting, and no specific treatment is required other than ruling out other treatable causes. Torticollis may also be seen in association with diskitis or vertebral osteomyelitis; juvenile idiopathic arthritis; cervical disk calcification; visual problems, such as congenital nystagmus or paresis of the superior oblique or lateral rectus muscle; benign or malignant bone tumors; and in cerebral palsy and chronic gastroesophageal reflux from a hiatal hernia **(Sandifer syndrome).**

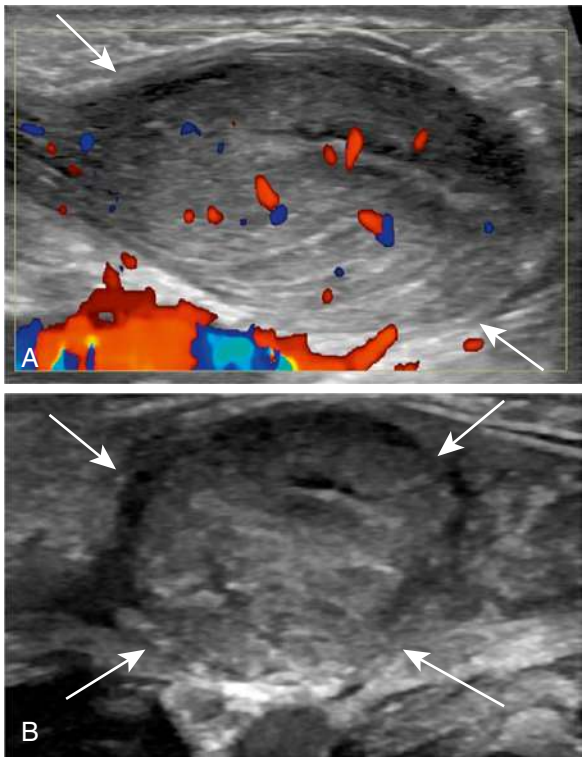

Fig. 721.3 Sonographic image of the symptomatic left neck in a 3-wk-old neonate with fibromatosis colli of the left sternocleidomastoid muscle. **A,** Longitudinal image of the sternocleidomastoid muscle showing enlargement with a fusiform configuration and masslike focus within the expanded segment of the muscle *(arrows).* The echotexture of the mass is mildly heterogenous and echogenic compared with the normal muscle on the contralateral side. Color flow is preserved within the mass. **B,** The mass has a more rounded configuration on the transverse ultrasound image *(arrows). (From Baik G, Blask A, Reilly BK. Unilateral neck mass in a neonate. J Pediatr. 2018;202:329, Fig. 2.)*

ATLANTOAXIAL ROTATORY DISPLACEMENT

Atlantoaxial rotatory displacement (AARD) represents a spectrum of pathology involving axial alignment (rotational) and motion between C1 and C2. The vertebrae may be partially displaced (subluxated) or completely displaced (dislocated) in the neutral or resting position with head facing forward. Motion between the vertebrae may

be normal (reducible with full range of motion), "sticky" (partially reducible with loss of motion), or fixed (irreducible with no motion between C1 and C2). Loss of motion at the C1-C2 joint results in 50% loss of cervical rotation. Prompt diagnosis and treatment are essential as the malalignment may become irreducible after several weeks. If the displacement persists, the facet of C2 will become deformed (resulting in increased forward slope), which increases the risk of C1 facet sliding off of the C2 facet leading to relapse of deformity.

AARD may complicate infection or inflammation of the tissues of the upper airway, neck, or pharynx **(Grisel syndrome)**, minor traumatic injuries, and surgical procedures in the oropharynx, ear, or nose. The diagnosis is most often made clinically, with the SCM muscle on the *contralateral* side (away from the head tilt) in spasm and prominent. Additionally, patients with AARD often have pain at rest and with head manipulation, features not seen with CMT. Plain radiographs are difficult to interpret given the head tilt, and AARD is best appreciated on a dynamic rotational CT scan, in which axial images are obtained through the upper cervical spine with the head at neutral and rotated maximally toward both the right and the left. The patient must be relaxed and comfortable for images to be successfully obtained. MRI may demonstrate edema or inflammation of the supporting ligaments. Clinicians may choose to treat a patient empirically if the history and clinical findings are characteristic, reserving advanced imaging for patients who have not responded clinically. If the patient is seen within a few days of the onset of symptoms, a trial of analgesics and a soft collar may be attempted. Patients with symptoms that persist or have been present for more than a week are often admitted to the hospital for analgesia, muscle relaxants, and a period of soft cervical traction. If this fails to reduce the displacement, halo traction may be attempted. If the joint can be reduced, patients are typically immobilized for at least 6 weeks in a halo vest. The treatment course is more challenging and outcomes less favorable for patients presenting more than 4 weeks after symptom onset. In such cases traction is typically employed to reduce the joint and then a halo vest used for up to 3-4 months to maintain the reduction. Some have used manipulation under anesthesia to obtain reduction before manipulation. The longer period of immobilization in these chronic cases allows for remodeling of the C2 facet, therefore reducing the risks of relapse after treatment. For those who fail these nonoperative treatment strategies, the most common treatment is a C1-C2 arthrodesis. A less common approach has been to perform an open reduction of the joint followed by either immobilization or by surgical fusion.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

721.2 Klippel-Feil Syndrome

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Klippel-Feil syndrome (KFS) includes the classic triad of a low posterior hairline, short neck, and decreased cervical range of motion (Fig. 721.4). However, these clinical findings are present in <50% of patients with KFS. Limited cervical motion may be the most common finding, present in 64.5% of patients, whereas only 9.7% of patients had all three findings. Patients have a congenital fusion **(failure of segmentation)** of one or more cervical motion segments at the craniocervical junction and/or in the subaxial spine and often have additional associated congenital anomalies of the cervical spine and other organ systems.

Additional findings in the cervical spine include occipitocervical synostosis, odontoid abnormalities, basilar invagination (proximal migration of the C2 vertebra above the foramen magnum), and Chiari malformation. Other associations include **Sprengel's deformity** (congenital elevation of the scapula), congenital scoliosis, genitourinary anomalies (25–35%), sensorineural hearing loss (5%), and congenital heart disease (5–10%). Renal abnormalities include double collecting systems, renal aplasia, and horseshoe kidney. The cervical spine anomalies seen in patients with KFS may also be seen with Goldenhar syndrome, Mohr syndrome, VACTERL syndrome, and fetal alcohol syndrome. Clinical problems are more common in adults and include pain or neurologic symptoms from spinal instability or stenosis. Although the incidence has been estimated at 1 in 40,000-42,000 births, many patients with this condition are undiagnosed

ETIOLOGY AND CLASSIFICATION

Most cases are sporadic, but four genetic forms have been described, two of which are autosomal dominant and two are autosomal recessive. A number of chromosomal abnormalities have also been associated with KFS. Pathogenic variants have been reported in the mesenchymal homeobox 1 gene (*MEOX1*, regulates segmentation of vertebrae), the growth differentiating factor 3 or 6 genes *(GDF)*, and the myosin 18 *(MYO18B)* gene.

One classification system is the most practical and has three types, namely a single fused segment (I), multiple noncontiguous fusions (II), and multiple contiguous fused segments (III). Patients with type I tend to have axial pain, whereas while those with types II/III are more likely to have neurologic symptoms.

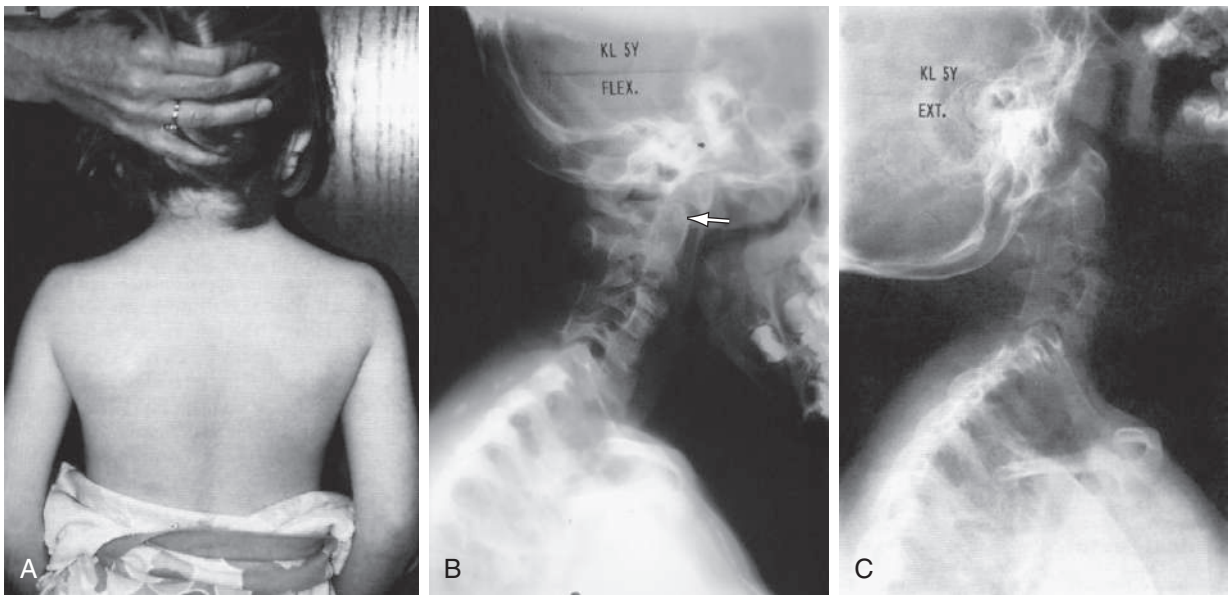

Fig. 721.4 Clinical picture of a 5-yr-old with Klippel-Feil syndrome. **A,** Note short neck and low hairline. **B** and **C,** Radiographs of the cervical spine (**B**, flexion; **C**, extension) demonstrate congenital fusion and evidence of spinal instability *(arrow). (From Drummond DS. Pediatric cervical instability. In: Weisel SE, Boden DS, Wisnecki RI, eds. Seminars in Spine Surgery. Philadelphia: WB Saunders; 1996;292–309.)*

CLINICAL PRESENTATION

KFS is present at birth but does not usually become clinically apparent until the second or third decades. Patients at this point present with pain, loss of motion, or neurologic symptoms. Pain is extremely common by adulthood and may be referred to the neck, occiput, and shoulders/upper back. The source of discomfort may be musculoskeletal and/or neurologic. The pain is greater in patients with more extensive involvement. Headache, dizziness, and fatigue have also been reported. Given that the same physiologic stresses are applied to a smaller number of mobile spinal segments, patients are at risk for the development of hypermobility and often instability, especially at motion segments adjacent to the fused vertebrae. Weakness or clumsiness consistent with **myelopathy** may be the presenting symptoms.

PHYSICAL EXAMINATION

A comprehensive musculoskeletal and neurologic examination is required, given associated anomalies in the musculoskeletal and visceral systems. **Scoliosis** is present in more than 50% of patients with KFS, and congenital anomalies may be identified in other regions of the spine as well. The neurologic exam focuses on identifying any signs of radiculopathy or myelopathy. Spinal cord compression, or myelopathy, may result from stenosis or instability. A physical exam will demonstrate upper motor neuron signs such as hyperreflexia, Hoffman's sign, Babinski's sign, and sustained clonus, with more than three beats considered pathologic. Nerve root compression, or radiculopathy, may be due to stenosis and is identified by weakness or decreased sensation in the muscles or dermatomes served by a particular nerve root.

RADIOLOGIC INVESTIGATION

Initial radiologic evaluation should include an AP, lateral, and oblique view of the cervical spine. The characteristic finding is a congenital fusion of two or more vertebrae resulting from a failure of segmentation; however, multiple vertebrae may be involved. Because congenital anomalies may exist in more than one region of the spine, radiographs of the thoracic and lumbosacral spine should be routinely obtained. Flexion-extension lateral views of the cervical spine may help to identify segments with excessive motion. Referral to an orthopedist is appropriate once the diagnosis is established. Patients with this condition usually undergo CT and MRI of the spine to accurately characterize the bony anomalies and also identify any coexisting neural pathology. A renal ultrasound is routinely obtained to identify associated anomalies (e.g., duplicated collecting system, absence of a kidney, horseshoe kidney). Additional imaging, such as echocardiogram, may identify cardiovascular anomalies, mainly septal defects.

Audiologic evaluation is indicated for patients diagnosed with KFS; hearing impairment may be identified in up to one third of affected patients.

TREATMENT

The three patterns commonly associated with instability include (1) C2/C3 fusion with occipitocervical synostosis, (2) extensive fusion over multiple levels with an abnormal occipitocervical junction, and (3) two fused segments separated by an open joint space.

Pain may often be controlled by activity restriction, intermittent immobilization, or other nonoperative modalities. Patients who are chronically symptomatic, have instability with positive neurologic symptoms or exam findings, or are thought to be at increased risk for neurologic deterioration are candidates for surgical treatment. Operative interventions include decompression of nerve roots or the spinal cord itself and/or spinal fusion to address cervical spinal instability.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 721.2 Causes of Pediatric Cervical Instability

CAUSES	SUBTYPES
Congenital	Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas)
	Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process)
	Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis)
	Syndromic disorders (e.g., Down syndrome, Klippel-Feil syndrome, 22q11.2 deletion syndrome, Larsen syndrome, Marfan syndrome, Ehlers-Danlos syndrome)
Acquired	Trauma
	Infection (pyogenic/granulomatous)
	Tumor (including neurofibromatosis)
	Inflammatory conditions (e.g., juvenile idiopathic arthritis)
	Osteochondrodysplasias (e.g., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia)
	Storage disorders (e.g., mucopolysaccharidoses)
	Metabolic disorders (rickets)
	Miscellaneous (including osteogenesis imperfecta, after surgery)

721.3 Cervical Anomalies and Instabilities

R. Justin Mistovich, Keith D. Baldwin, and David A. Spiegel

Anomalies of the craniovertebral junction or lower cervical spine may be seen in isolation or in association with other conditions. These include genetic syndromes, skeletal dysplasias, connective tissue disorders, and metabolic disorders. These anomalies may be congenital or developmental. Although most anomalies remain asymptomatic and undiagnosed, a subset will place the patient at risk of neurologic injury as a result of instability or spinal canal stenosis. The most frequently encountered causes of cervical spine instability in children can be categorized etiologically (Table 721.2). Patients with conditions that have known associations involving the cervical spine should have a complete evaluation, including history, physical examination, and initial radiographic examination. Lateral radiographs in flexion and extension may be helpful to evaluate instability, and advanced imaging such as CT or MRI may be required to further characterize any abnormalities noted on plain radiographs.

Patients may complain of neck pain or neurologic symptoms. Radicular symptoms include pain, weakness, and numbness within the distribution of a nerve root. Myelopathic symptoms include generalized weakness, gait disturbance, increased fatigue with ambulation, upper extremity clumsiness, and abnormalities in bowel or bladder function. Other symptoms such as headaches, dizziness, or vertigo have also been described. Physical exam findings may include restricted cervical mobility, cervical tenderness or spasm, and neurologic abnormalities.

Although the upper cervical spine has limited flexion and extension, roughly 50% of cervical rotation occurs at the atlantoaxial (C1-2) joint. The main constraints to motion in the upper cervical spine are soft tissue (ligaments and joint capsules) rather than osseous. Excessive motion or instability may result in a compressive injury to the brainstem or spinal cord. Anomalies at the craniovertebral junction include congenital fusion of the occiput to C1 (**occipitalization** of the atlas), basilar impression and invagination (proximal migration of the C2 vertebra as the result of softening of the bones and with normal bones, respectively), and accessory vertebrae. Aplasia or hypoplasia of the atlas or the axis may result in atlantoaxial instability.

OS ODONTOIDEUM

Os odontoideum is the most common anomaly of the odontoid, or dens, and radiographically appears as an oval-shaped, well-corticated bony ossicle that is positioned cephalad to the body of the axis. There is a discontinuity, and the upper portion of the dens moves with the ring of C1, narrowing the space available for the spinal cord and placing it at risk for injury. The body of the dens is mesenchymal in origin and originates from the first cervical vertebra. Subsequent separation allows it to then fuse with the C2 vertebra. It is formed by two separate ossification centers, one on either side of the midline that eventually fuse and are visible at birth. The os odontoideum may be in a normal anatomic position (orthotopic) or adjacent to the occipital bone (dystopic). Although the etiology remains unclear, both traumatic (nonunion of a fracture, repetitive shear stresses from hypermobility on growing cartilage) and developmental (failure of fusion of the ossification centers) theories have been proposed.

Symptoms may include pain and/or neurologic dysfunction. Myelopathy may develop from neural stretch, ischemia, or bony impingement, whereas vertebrobasilar findings may result from ischemia due to stretching or thrombosis of the vertebral arteries. Neurologic examination may reveal a combination of both upper and lower motor neuron signs. Some patients are completely asymptomatic with the anomaly noted incidentally on a lateral cervical spine radiograph.

The radiographic evaluation begins with AP, lateral, and open mouth odontoid views, which may be supplemented by flexion and extension lateral radiographs. CT provides the best bony detail and is useful in defining each anomaly. MRI, including dynamic images in flexion and extension, is best for evaluating neurologic impingement.

Patients who are asymptomatic with no instability may be managed by observation with serial radiographs, activity restriction, and taking special precautions if they require intubation/general anesthesia. Those with neurologic symptoms and instability require surgical stabilization by an instrumented posterior arthrodesis between C1 and C2.

Down Syndrome

Ligamentous hyperlaxity is a characteristic feature of Down syndrome and may result in hypermobility or instability at the occipitoatlantal or the atlantoaxial joints in 4–30% of patients (see Chapter 57). These patients may also have coexisting congenital or developmental anomalies of the cervical spine, such as occipitalization of the atlas, atlantal arch hypoplasia, basilar invagination, and os odontoideum.

Although the natural history of this spectrum of pathology remains unknown, a small subset of patients will develop instability with neurologic dysfunction. The clinical diagnosis of neurologic dysfunction may be challenging because patients often present with subtle findings such as decreased exercise tolerance, tripping/falling, or other gait abnormalities. The challenge lies in the early identification of such cases, especially in patients who plan to participate in activities with increased risk of trauma to the head or neck such as tumbling or other sports.

All patients with Down syndrome require screening by history and physical examination at regular intervals. The guidelines for health supervision for children with Down syndrome suggest that routine radiographic screening is not indicated in asymptomatic patients and that a lateral radiograph in neutral alignment should be obtained for all patients with symptoms of possible atlantoaxial instability (neck pain, radicular pain, weakness, spasticity/change in tone, gait difficulties, hyperreflexia, or change in bowel or bladder function). Dynamic images are suggested when abnormalities

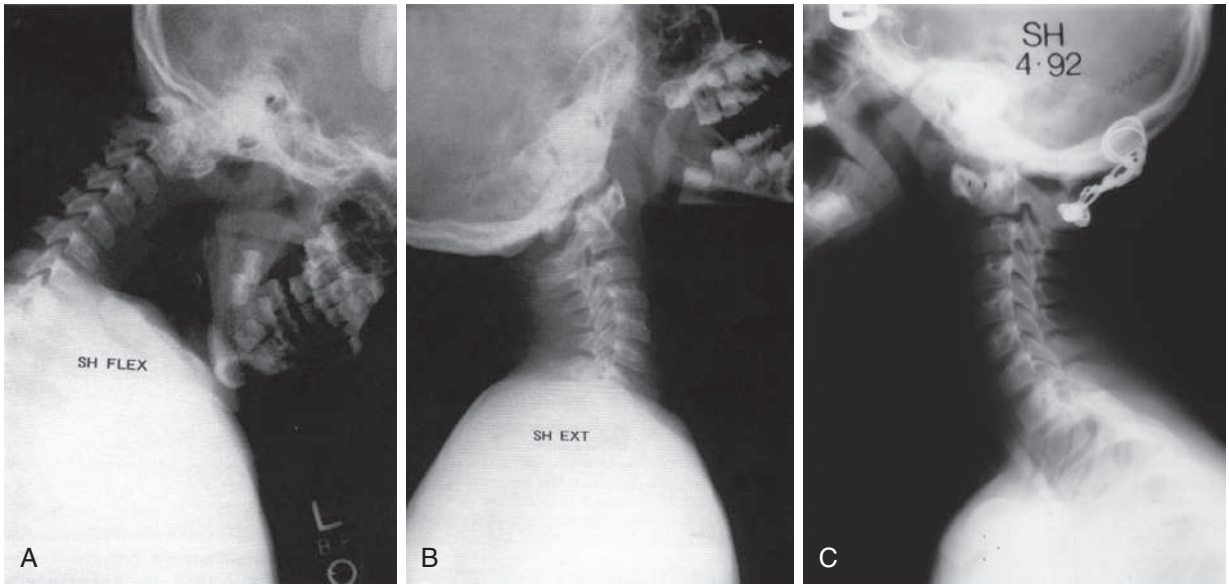

Fig. 721.5 Flexion (A) and extension (B) radiographs of a case of Down syndrome demonstrating atlanto-occipital hypermobility and subluxation. C, Instability and symptoms were relieved by an occipitoaxial arthrodesis.



Fig. 721.6 Radiographs of the cervical spine in a child with 22q11.2 deletion syndrome showing evidence of platybasia, occipitocervical, and atlantoaxial instability. **A,** Neutral radiograph. **B,** Flexion. **C,** Extension. *(From Drummond DS. Pediatric cervical instability. In: Weisel SE, Boden DS, Wisnecki RI, eds. Seminars in Spine Surgery. Philadelphia: WB Saunders; 1996:292–309.)*

are present on the initial lateral radiograph. Although variations in practice patterns likely exist and recommendations may vary between states, radiographic screening is required before participation in the Special Olympics. Patients with coexisting os odontoideum are candidates for routine radiographic surveillance because they are at greater risk for progression of displacement and neurologic injury.

Plain radiographs are ideally obtained in children older than 3 years unless clinical findings mandate earlier evaluation, consisting of an AP and lateral in neutral alignment, usually supplemented by a lateral view in flexion and extension. The atlanto-dens interval (ADI) is used to evaluate the relationship between C1 and C2 (atlantoaxial joint) and is measured as the space between the dens and the anterior ring of C1 on lateral radiographs in neutral, flexion, and extension (Fig. 721.5). Although the ADI should be 3 mm or less in the population without Down syndrome, a normal ADI in children with Down syndrome is <4.5 mm. Hypermobility is diagnosed as an ADI between 6 and 10 mm, whereas an ADI >10 mm represents frank instability and carries greater risk of neurologic injury. Evaluating the space available for the spinal cord is also important, and a measurement of ≤14 mm between the posterior odontoid and posterior arch is felt to be abnormal. Progression from hypermobility to instability on surveillance radiographs is uncommon. In one series of patients with Down syndrome screened routinely, an ADI of ≥6 mm was identified in 4.4%, and 1.6% were noted to progress to hypermobility/instability over 4 years. MRI in flexion and extension is indicated to evaluate for impingement and/or neurologic injury in patients with appropriate clinical symptoms or findings and/or those with radiographic instability, and an increase in signal intensity within the spinal cord at the level of excessive motion is diagnostic of neurologic injury.

Although hypermobility at the occipitoatlantal joint is present in >50% of children with Down syndrome, most patients do not develop instability or neurologic symptoms. The relationships at this articulation are difficult to measure reliably on plain radiographs. An MRI in flexion and extension is required to evaluate any questionable radiographic findings, especially in the presence of clinical symptoms. Involvement of the subaxial spine is less common and is typically encountered in the adult population of patients with Down syndrome. Degenerative changes or instability may result in pain, radiculopathy, and/or myelopathy.

Specific treatment recommendations have not been standardized, but patients diagnosed with hypermobility may be restricted from participation in contact sports and other activities that increase the risk of trauma to the cervical spine. Patients with C1-2 instability with or without neurologic findings are candidates for an atlantoaxial fusion.

22Q11.2 Deletion Syndrome

The chromosome deletion of 22q11.2 is a common genetic syndrome, with an overall prevalence of 1 in 5,950 births and encompasses a wide spectrum of abnormalities. There are characteristic facial features, cleft palate, and cardiac anomalies. Cervical spine anomalies are also common. At least one developmental variation of the occiput or cervical spine is noted in all patients. The occipital variations observed include **platybasia**, an abnormal flattening of the base of the skull, and **basilar impression**. Variations in anatomy of C1 include dysmorphic shape, an open posterior arch, and occipitalization, while axis variations include a dysmorphic dens and "C2 swoosh" (upswept lamina and posterior elements). A range of cervical vertebral fusions is noted in these patients, the most common being at the C2-3 level. Increased segmental motion is commonly observed, but symptomatic instability is quite uncommon. With frequent occurrence of upper cervical spine anomalies in patients with 22q11.2 deletion syndrome (Fig. 721.6), advanced imaging of the upper cervical spine is suggested to characterize the anomalies. Regular follow-up is required as a small subset of patients may develop instability. A flexion-extension MRI of the cervical spine may be considered for evaluation of symptomatic patients to rule out instability and/or neurologic injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 722

The Upper Limb

Robert B. Carrigan

SHOULDER

The shoulder is a ball-and-socket joint that is similar to the hip; however, there are several anatomic differences between the two. The shoulder is a very shallow ball-and-socket joint compared to the hip and is more prone to dislocation than the hip. In addition, shoulder

range of motion (ROM) is much greater than that of the hip. This is due to the size of the humeral head relative to the glenoid and the presence of scapulothoracic motion. The shoulder positions the hand along the surface of a theoretical sphere in space, with its center at the glenohumeral joint.

Sprengel Deformity

Sprengel deformity, or congenital elevation of the scapula, is a disorder of development that involves a high scapula and limited scapulothoracic motion. The scapula originates in early embryogenesis at a level posterior to the fourth cervical vertebra. It descends during development to below the seventh cervical vertebra. Failure of this descent, either unilateral or bilateral, is the Sprengel deformity. The severity of the deformity depends on the location of the scapula and associated anomalies. The scapula in mild cases is simply rotated, with a palpable or visible bump corresponding to the superomedial corner of the scapula. Function is generally good. In moderate cases, the scapula is higher on the neck and connected to the spine with an abnormal omovertebral ligamentous or bony connection. Shoulder motion, particularly abduction, is limited. In severe cases, the scapula is small and positioned on the posterior neck. The neck may be webbed. Most patients with Sprengel deformity have associated anomalies of the musculoskeletal system, especially in the spine (Klippel-Feil syndrome), making spinal evaluation important.

Treatment

In mild cases, treatment is generally unnecessary. A prominent and unsightly superomedial corner of the scapula can be excised. In more severe cases, surgical repositioning of the scapula with rebalancing of parascapular muscles can significantly improve both function and appearance.

Congenital Pseudarthrosis of the Clavicle

The clavicle is a tubular S-shaped bone that articulates with the sternum and acromion. It acts as a strut to keep the shoulder from protracting forward. Congenital pseudoarthrosis of the clavicle is a failure of the two primary ossification centers of the clavicle to fuse during embryogenesis (Fig. 722.1). The condition presents exclusively on the right side and may be confused for an acute clavicle fracture sustained during birth. A thorough history and physical exam will help to distinguish between the two conditions. Although both a birth-related clavicle fracture and a congenital pseudoarthrosis will present with a bump or prominence over the midclavicle, a birth-related clavicle fracture will be tender to palpation on exam. The parents may also report that the child is fussy with feeding and changing. Congenital pseudoarthrosis of the clavicle will be painless on exam. Radiographically the congenital pseudoarthrosis clavicle will have two rounded edges at the midportion with signs of hypertrophy.

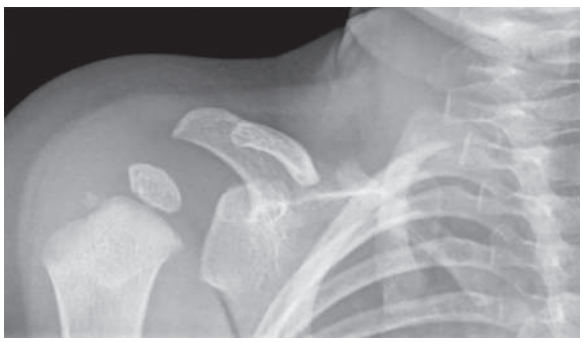

Fig. 722.1 Radiograph of congenital pseudoarthrosis of the clavicle.

Treatment

There is not a clear consensus regarding treatment of congenital pseudoarthrosis of the clavicle. Surgery is indicated for patients with symptoms of **thoracic outlet syndrome** (impingement of the clavicle on the brachial plexus and subclavian vessels). However, most patients are asymptomatic with few functional limitations and do not require surgical repair. Surgical treatment may be considered for patients with unacceptable cosmetic deformity, pain, or functional deficits.

The operative treatment of congenital pseudoarthrosis of the clavicle consists of opening the pseudoarthrosis site, preserving the periosteum, debriding the hypertrophic ends, bone grafting, and stabilization.

ELBOW

The elbow is the most congruent joint in the body. The stability of the elbow is imparted via this bony congruity and through the medial and radial collateral ligaments. Where the shoulder positions the hand along the surface of a theoretical sphere, the elbow positions the hand within that sphere. The elbow allows extension and flexion through the ulnohumeral articulation and pronation and supination through the radiocapitellar articulation.

Panner Disease and Osteochondritis of the Capitellum

Panner disease is a disruption of the blood flow to the subchondral bone and articular cartilage of the capitellum (Fig. 722.2). It typically occurs in males between the ages of 5 and 13 years. Presenting symptoms include lateral elbow pain, loss of motion, and, in advanced cases, mechanical symptoms of the elbow (loose bodies).

The mechanism of injury can be impaction or overloading of the joint, as seen with sports such as gymnastics and baseball. It can also be idiopathic. Radiographs of the elbow may be normal or may show a small lucency within the subchondral bone of the capitellum. MRI is the study of choice to evaluate a suspected capitellar lesion. MRI can demonstrate the extent of the involvement in the subchondral bone and the integrity of the cartilage of the articular surface.

Treatment

Treatment is typically conservative. Rest, activity modification, and patient education are initial treatment options. In cases in which the articular cartilage fragments and loose bodies form, arthroscopy of the elbow is warranted to remove the loose bodies. When the cartilage defect in the capitellum is large and symptomatic, procedures for restoration of the articular cartilage may be considered. These procedures include drilling of the subchondral bone (microfracture) to promote scar cartilage and osteochondral autograft transplantation (OATS).

Radial Longitudinal Deficiency

Radial longitudinal deficiency of the forearm comprises a spectrum of conditions and diseases that have resulted in hypoplasia or absence of the radius (Table 722.1). Clinical characteristics consist of a small, shortened limb with the hand and wrist in excessive radial deviation. Partial or complete absence of the radial structures of the forearm and hand are observed (Fig. 722.3).

Radial longitudinal deficiency can range in severity from mild to severe and has been classified into four types according to Bayne and Klug (Table 722.2). Radial longitudinal deficiency can be associated with other syndromes such as **Holt-Oram** and **Fanconi anemia**. Complete and thorough workup of these associated conditions is important for the long-term health of the child.

Treatment

The goals for the treatment of radial longitudinal deficiency include centralizing the hand and wrist on the forearm, balancing the wrist, and maintaining appropriate thumb and digital motion. Shortly after

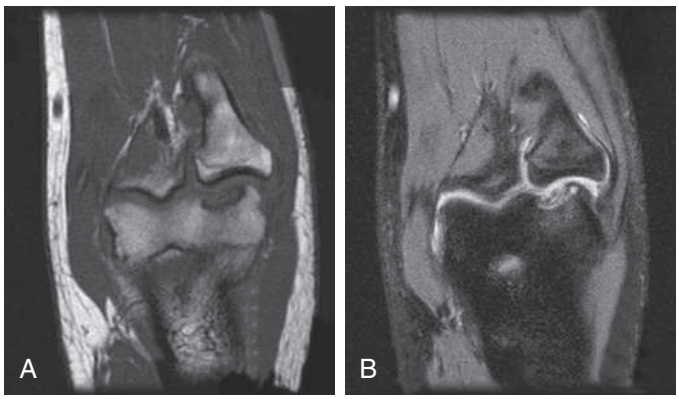

Fig. 722.2 T1 (A) and T2 (B) coronal MRI images of the elbow depicting Panner disease of the elbow.

Table 722.1 Syndromes Commonly Associated with Radial Deficiency

SYNDROME	CHARACTERISTICS
Holt-Oram syndrome	Heart defects, most commonly atrial septal defects Absent thumb or long finger-like thumb
Thrombocytopenia-absent radius syndrome	Thrombocytopenia present at birth but improves over time Thumbs present, radii absent
VACTERL association	Vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula, esophageal atresia, renal defects, radial dysplasia, lower limb abnormalities
Fanconi anemia	Aplastic anemia does not present at birth, develops about 6 yr of age; fatal without bone marrow transplant Chromosomal breakage challenge test and genetic testing available for early diagnosis Thumb hypoplasia but present

From Trumble T, Budoff J, Cornwall R, eds. *Core Knowledge in Orthopedics: Hand, Elbow, Shoulder.* Philadelphia: Elsevier; 2005:425.

birth, stretching and splinting of the wrist and hand should be started to elongate the contracted radial soft tissues.

Surgery for correction of the wrist deformity is focused on addressing the tight structures and varies by age and level of involvement. The classic surgical technique for children with good elbow motion is centralization of the wrist on the forearm, which is often associated with recurrence of the deformity. When considering a centralization procedure, the preoperative plan begins with careful examination of the patient; considerations regarding thumb and elbow function must be made before surgery. The surgery typically occurs when the child is 1 year of age. Correction of the radial deviation as well as centralization of the wrist can be accomplished with a variety of different surgical techniques. These techniques include open release, capsular reefing, and tendon rebalancing. External fixation techniques and free tissue transfers also have been described.

Nursemaid's Elbow

Nursemaid's elbow is a subluxation and interposition of the annular ligament of the elbow. It is often confused for a subluxation or dislocation of the radial head. The proximal end of the radius, or radial head, is anchored to the proximal ulna by the annular ligament. It wraps around like a leash from the ulna, around the radial head, and back to the ulna. If the radius is pulled distally, the annular ligament can slip proximally off the radial head and into the joint between the radial head and the humerus (Fig. 722.4). The injury is typically produced when a longitudinal traction force is applied to the arm, such as when a falling child is caught by the hand, or when a child is pulled by the hand. The injury usually occurs in toddlers and rarely occurs in children older than 5 years of age. Subluxation of the annular ligament produces immediate pain and limitation of supination. Flexion and extension of the elbow are not limited. Swelling is generally absent. The diagnosis is made by history and physical examination because radiographs are typically normal.

Treatment

The annular ligament is reduced by rotating the forearm into supination while holding pressure over the radial head. A palpable click or clunk can be felt. The child recovers active supination and usually has relief of discomfort. Sometimes pain may persist after reduction maneuvers. Immobilization is not required, but recurrence can happen. Parents should avoid activities that apply traction to the elbows. Parents can learn reduction maneuvers for recurrent episodes to avoid trips to the emergency department or pediatrician's office. Recurrence beyond 5 years of age is rare.

WRIST

The wrist is composed of the two forearm bones (radius and ulna) as well as the eight carpal bones. The wrist allows flexion, extension, and radial and ulnar deviation through the radiocarpal and midcarpal articulations. Pronation and supination occur at the wrist through the distal radial ulnar joint (DRUJ). The wrist is a complex joint with numerous ligamentous and soft tissue attachments. It has complex kinematics that allows for its generous ROM, but when these kinematics are altered, significant dysfunction can occur.

Madelung Deformity

Madelung deformity is a deformity of the wrist that is characterized as radial and palmar angulations of the distal aspect of the radius (Fig. 722.5). Growth arrest of the palmar and ulnar aspect of the distal radial physis is the underlying cause of this deformity. Bony physeal lesions and an abnormal radiolunate ligament **(Vicker's ligament)** have been implicated. The deformity can be bilateral and affects females more than males.

Treatment

Treatment of Madelung deformity is typically observation. Mild deformities can be observed until skeletal maturity. Moderate to severe deformities that either are painful or limit function may be candidates for surgical intervention. Surgical treatment for Madelung deformity is often motivated by appearance. Patients and their families may be concerned about the palmar angulation of the wrist and the resulting prominent distal ulna.

There are a multitude of surgical options for treating Madelung deformity. For the skeletally immature patient, resection of the tethering soft tissue (Vicker's ligament) and physiolysis (fat grafting of any bony lesion seen within the physis) is often the first option. When Madelung deformity is encountered in skeletally mature patients, an osteotomy may be considered. Dorsal closing wedge, dome, and ulnar shortening osteotomies may be used alone or in combination to achieve the desired result.

Long-term considerations of Madelung deformity concern the incongruity of the DRUJ and resulting premature DRUJ arthritis.

Gymnast's Wrist

Gymnast's wrist refers to the changes observed in the physis of the distal radius in the setting of repetitive stress associated with gymnastics

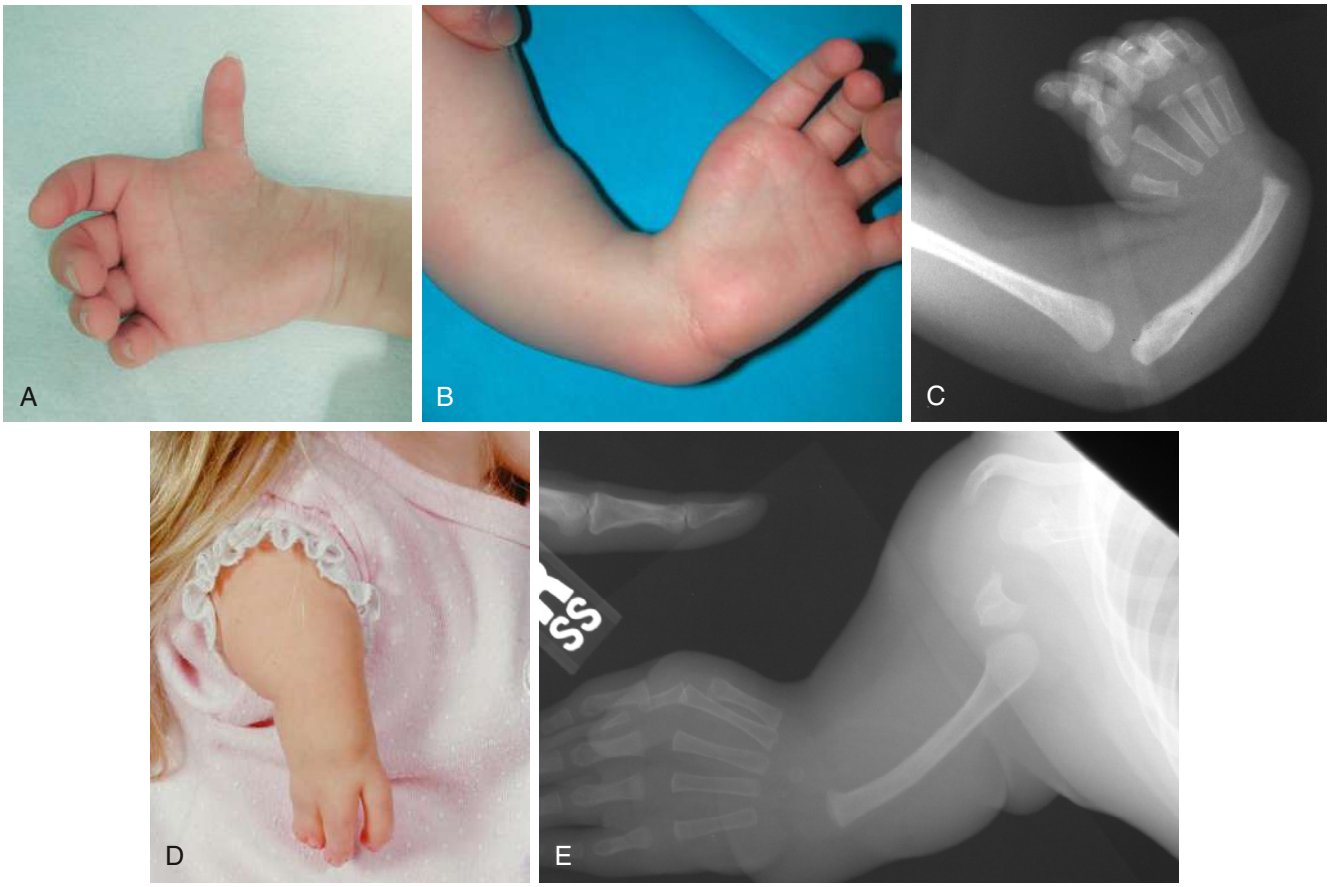

Fig. 722.3 Spectrum of phenotypes of radial dysplasia. **A,** Type 1 radius with a hypoplastic thumb. **B,** Type IV radius with an absent thumb. **C,** Radiograph of a type IV radius. **D** and **E,** Phocomelic radial deficiency. *(From Oishi S, Stutz C, Lake A. Disorders of the upper extremity. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 2022: Fig. 12.72, p. 337.)*

Table 722.2 Modified Classification of Radial Longitudinal Deficiency

TYPE	THUMB	CARPUS	DISTAL RADIUS	PROXIMAL RADIUS
N	Hypoplastic or absent	Normal	Normal	Normal
0	Hypoplastic or absent	Absence, hypoplasia, or coalition	Normal	Normal, radioulnar synostosis, or congenital dislocation of the radial head
1	Hypoplastic or absent	Absence, hypoplasia, or coalition	>2 mm shorter than the ulna	Normal, radioulnar synostosis, or congenital dislocation of the radial head
2	Hypoplastic or absent	Absence, hypoplasia, or coalition	Hypoplasia	Hypoplasia
3	Hypoplastic or absent	Absence, hypoplasia, or coalition	Physis absent	Variable hypoplasia
4	Hypoplastic or absent	Absence, hypoplasia, or coalition	Absent	Absent

From James MA, McCarroll HR Jr, Manske PR. The spectrum of radial longitudinal deficiency: a modified classification. *J Hand Surg Am.* 1999;24:1145–1155.

(Fig. 722.6). Symptoms include pain with weight bearing, swelling, and loss of motion (mainly wrist extension). The pain is typically mild at first and worsens with time and increased activity. Children will have pain over the distal radial physis on palpation. The child should also be examined for coexisting wrist pathology including DRUJ instability and triangular fibrocartilage complex (TFCC) tears. Radiographs are often normal but may show chronic changes in the distal radial physis, including widening, sclerosis, and partial physeal arrest. Ulnar positive variance may also be observed because of partial growth arrest of the radius. MRI may be useful to examine the extent of physeal involvement as well as TFFC pathology

Treatment

Treatment of gymnast's wrist begins with rest. Typically, the child is prohibited from weight-bearing activities for a period of 6 weeks or until symptoms resolve. The child is slowly progressed back to their routine. If symptoms return during the recovery phase, rest is reinitiated. It is not uncommon for relapses to occur when returning to competition. This may be difficult for the child and parents to understand, as gymnasts and gymnast's families are often very motivated to continue their sport. Use of braces, such as Tiger Paws, may help limit the amount of force transmitted to the wrist and in turn help with injury prevention.

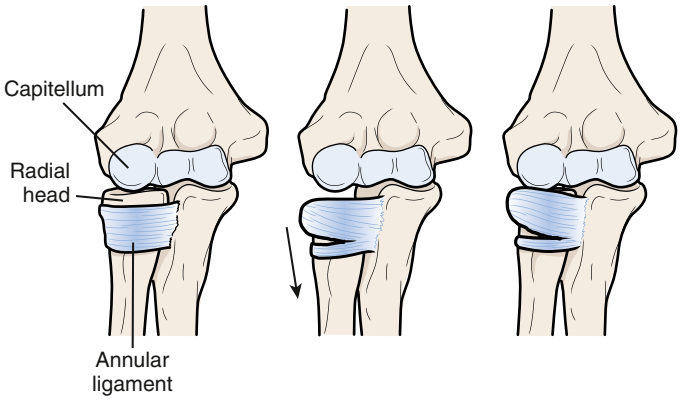

Fig. 722.4 Nursemaid's elbow. Illustration depicting subluxation of the radial head inferior to the annular ligament, with interposition of the ligament to the radiocapitellar joint space. This entity is sometimes in the differential in the setting of upper extremity injury in a small child. Radiographs are negative and serve only to exclude the presence of bony injury when the diagnosis is not clear. *(From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.102.)*



Fig. 722.5 Radiograph of an adolescent with Madelung deformity.

In cases where significant damage is seen in the distal radius physis, surgery may be indicated to prevent future morphologic changes in the wrist. Surgery may include epiphysiodesis of the radius and ulna, shortening of the ulna, and TFCC repair.

Ganglion

The wrist joint articulation is lubricated with synovial fluid, which is produced by the synovial lining of the joint and maintained within the joint by the joint capsule. A defect in the capsule can allow fluid to leak from the joint into the soft tissues, resulting in a ganglion. The term *cyst* is a misnomer, because this extraarticular collection of fluid does not have its own true lining. The defect in the capsule can occur as a traumatic event, although trauma is rarely a feature of the presenting history. The fluid usually exits the joint in the interval between the scaphoid and lunate, resulting in a ganglion located at the dorsoradial aspect of the wrist. Ganglia can occur at other locations, such as the volar aspect of the wrist, or in the palm because of leakage of fluid from the flexor tendon sheaths. Pain is not commonly associated with ganglia in children, and when it is, it is unclear whether the cyst is the cause of the pain. The diagnosis is usually evident on physical examination, especially if the lesion transilluminates. Extensor tenosynovitis and anomalous muscles can mimic ganglion cysts, but radiography or MRI is not routinely required. Ultrasonography is an effective, noninvasive tool to support the diagnosis and reassure the patient and family.

Treatment

Regarding the treatment of ganglia in children, consider the vowels AEIOU.

Aspiration: Simple aspiration of the fluid has a high recurrence rate and is painful for children given the large-bore needle required to aspirate the gelatinous fluid. However, in older children who would like to try and decompress the cyst before considering surgery, this may be reasonable.

Excision: Surgical excision, including excision of the stalk connecting the ganglion to its joint of origin, has a high success rate, although the ganglion can recur.

Injection: Aspiration of the cyst and a simultaneous injection of a corticosteroid have been shown to be effective in treating recurrence in children.

Observation: Up to 80% of ganglia in children <10 years of age resolve spontaneously within 1 year of being noticed. If the ganglion is painful or bothersome and the child is >10 years of age, treatment may be warranted.

Ultrasound: For children's parents who are concerned about the mass and want a radiographic study to confirm the diagnosis, ultrasound is a noninvasive test to confirm the diagnosis.

HAND

The hand and fingers allow for complex and fine manipulations. An intricate balance among extrinsic flexors, extensors, and intrinsic

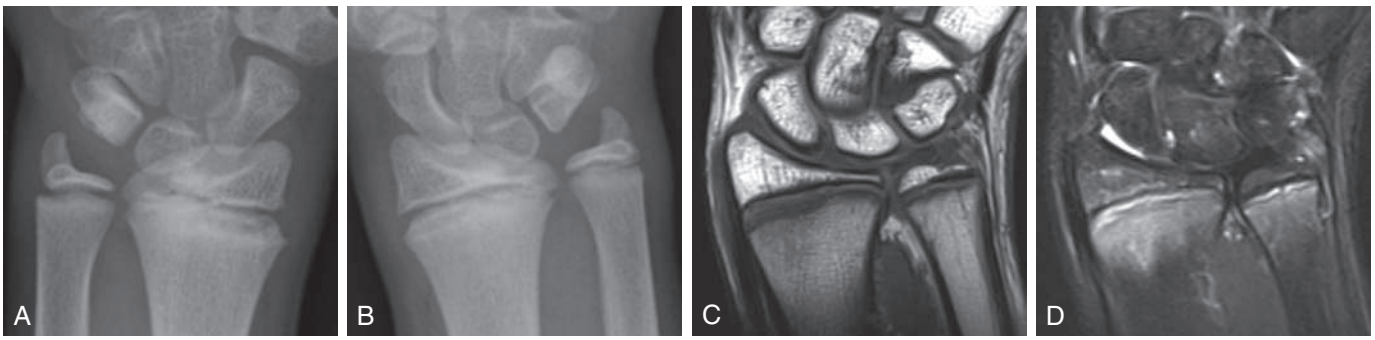

Fig. 722.6 Gymnast's wrist. **A** and **B,** Posteroanterior radiographs of the bilateral wrists show widening and irregularity of the distal radial physis. Abnormal linear lucency is seen in the metaphyses, with surrounding sclerosis noted. Findings reflect disrupted growth at the physes. **C,** Coronal T1 and **D,** coronal T2 magnetic resonance images with fat saturation show similar abnormality at the distal radial physis, along with abnormal increased fluid signal along the metaphysis. *(From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.107.)*

Table 722.3 Classification of Camptodactyly

TYPE	CHARACTERISTICS
I	Congenital, no sex bias, small finger only
II	Acquired between 7-11 yr, typically progressive
III	Severe, significant contracture, bilateral and associated with other musculoskeletal syndromes

Adapted from Kozin SH. Pediatric hand surgery. In: Beredjiklian PK, Bozentka DJ, eds. *Review of Hand Surgery*. Philadelphia: WB Saunders; 2004:223–245.

muscles allows these complex motions to occur. Congenital anomalies of the hand and upper extremity rank just behind cardiac anomalies in incidence. Like cardiac anomalies, if they are not properly identified and remedied, may have long-term consequences.

Camptodactyly

Camptodactyly is a nontraumatic flexion contracture of the proximal interphalangeal joint that is often progressive. The small and ring fingers are most often affected. Bilateralism is observed two thirds of the time. The etiology of camptodactyly is varied. Several different hypotheses have been offered as to the cause of this condition. Camptodactyly can be divided into three different types (Table 722.3).

Treatment

Nonsurgical treatment is the primary treatment of camptodactyly. Mild contractures of less than 30 degrees are usually well tolerated and do not need treatment. Serial casting or static and dynamic splinting can prevent contractures from worsening.

Surgical treatment is limited to the treatment of severe contractures. At the time of surgery, all contracted and anomalous structures are released. Results of contracture release for camptodactyly are mixed; often a loss of flexion results from an attempt to improve extension.

Clinodactyly

Angular deformity of the digit in the coronal plane, distal to the metacarpophalangeal joint is clinodactyly. The most observed finding is a mild radial deviation of the small finger at the level of the distal interphalangeal joint. This is often due to a triangular or trapezoidal middle phalanx. In some cases, a disruption of the physis at the middle phalanx produces a longitudinal epiphysial bracket. This bracket is thought to be the underlying cause for the formation of the "delta phalanx" that is often observed in clinodactyly. Clinodactyly has been observed in other fingers, including the thumb (Fig. 722.7) and ring finger.

Treatment

The initial treatment for clinodactyly is observation. For severe deformities and for those affecting the thumb, surgery may be indicated. Surgery is technically demanding. Bracket resections, corrective osteotomies, and growth plate ablations are the most common procedures performed to correct the observed angular deformities. Results are good, and recurrences are few.

Polydactyly

Polydactyly or duplication of a digit can occur either as a radial deformity (involving the thumb), central (index, middle, or ring), or as an ulnar deformity (involving the small finger) (Table 722.4). Each has an inherited and genetic component. Transmission is typically in an autosomal dominant pattern and has been linked to differences in genes localized to chromosome 2.

Duplication of the thumb has been subdivided into seven types by Flatt and Wassel based on the degree of duplication (Table 722.5). Small finger duplication has been further subdivided into two types.

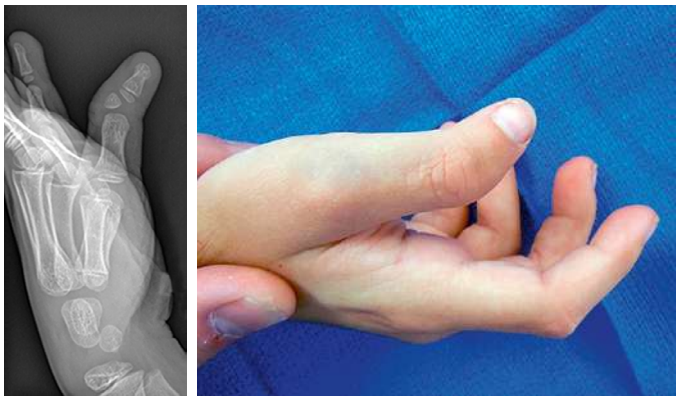

Fig. 722.7 Clinodactyly of the thumb.

Table 722.4 Syndromes Associated with Polydactyly*

Carpenter syndrome
Ellis-van Creveld syndrome
Meckel-Gruber syndrome
Polysyndactyly
Trisomy 13
Orofaciodigital syndrome
Rubinstein-Taybi syndrome
Bardet-Biedl syndrome
Meckel-Gruber syndrome
Pallister-Hall syndrome
Short Rib-polydactyly syndromes (type I, II)

*There are many syndromes with polydactyly; this is a partial list.

Table 722.5 Wassel Classification of Thumb Duplication

TYPE	CHARACTERISTICS
I	Bifid distal phalanx
II	Duplicate distal phalanx
III	Bifid proximal phalanx
IV	Duplicate proximal phalanx
V	Bifid metacarpal
VI	Duplicate metacarpal
VII	Triphalangeal component

Data from Wassel, HD. The results of surgery for polydactyly of the thumb: a review. *Clin Orthop*. 1969;125:175–193.

Type A is a well-formed digit. Type B is a small, often underdeveloped supernumerary digit.

Treatment

Thumb and small finger duplication are typically treated with ablation of the supernumerary digit. Treatment options vary based on the degree of involvement. Less well-formed digits can be treated with suture ligation. Well-formed digits require reconstructive procedures that preserve important structures such as the collateral ligaments and nail folds (Fig. 722.8).

Thumb Hypoplasia

Hypoplasia of the thumb is a challenging condition for both the patient and the doctor. The thumb represents ~40% of hand function. A less-than-optimal thumb can severely limit a patient's function as they grow and develop. Hypoplasia of the thumb can range from being mild with slight shortening and underdeveloped musculature to complete

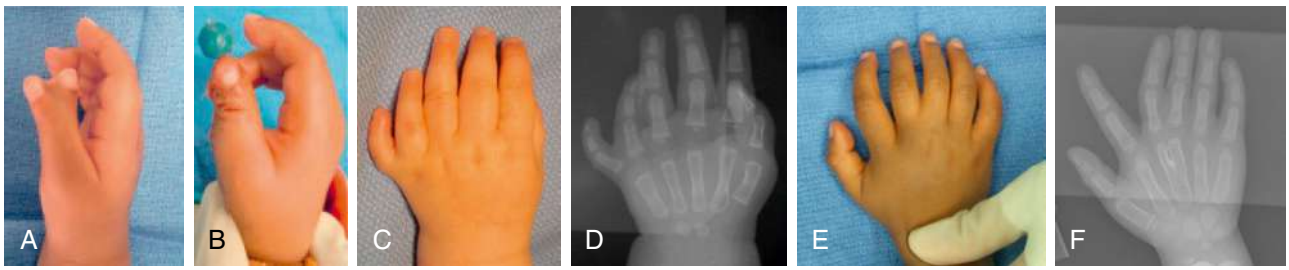

Fig. 722.8 A and B, Preoperative and postoperative pictures of a Wassel II thumb duplication. C, Clinical photograph. D, Radiograph postaxial polydactyly. E, Clinical photograph. F, Radiograph of central polydactyly.

absence of the thumb. Radiographs are useful to help determine osseous abnormalities. The most important finding on physical exam is the presence or absence of a stable carpometacarpal (CMC) joint. This finding helps guide surgical treatment.

Treatment

If the thumb has a stable CMC joint, reconstruction is advised. Key elements of thumb reconstruction include rebuilding the ulnar collateral ligament of the metacarpophalangeal joint, tendon transfers to aid thumb abduction, and procedures to deepen the web space.

If a stable CMC joint is not present or the thumb is completely absent (Fig. 722.9A), pollicization (surgical construction of a thumb from a finger) is the definitive treatment (see Fig. 722.9B). Pollicization is a complex procedure rotating the index finger along its neurovascular pedicle to form a thumb. This procedure is typically performed at around 1 year of age and may be followed by subsequent procedures to deepen the web space or augment abduction.

Syndactyly

Failure of the individual digits to separate during development produces syndactyly. Syndactyly is one of the more common anomalies observed in the upper limb (Table 722.6). It is seen in 0.5 of 1,000 live births. Syndactyly can be classified as simple (skin attachments only), complicated (bone and tendon attachments), complete (fusion to the tips, including the nail), or incomplete (simple webbing).

Treatment

Division of conjoined digits should be considered before the second year of life. Border digits should be divided earlier (3-6 months) because of concern for tethered growth of digits of unequal length. Digits of similar size, such as the index, middle, and ring, may wait until the child is older to consider separation. Reconstruction of the web space and nail folds as well as appropriate skin-grafting techniques must be used to ensure the best possible functional and cosmetic result (Fig. 722.10).

Fingertip Injuries

Young children commonly sustain crush injuries to the fingertips from doorjambs, car doors, and other tight spaces. Injury can range from a simple subungual hematoma to complete amputation of part or the entire fingertip. Radiographs are important to rule out fractures. Physeal fractures associated with nailbed injuries are open fractures with a high risk of osteomyelitis, growth arrest, and deformity if not treated correctly.

The treatment of the soft tissue injury depends on the type of injury. For suture repairs, only absorbable sutures should be used. Removal of sutures from a young child's fingertip can be difficult and may require sedation or general anesthesia. If a subungual hematoma exists but the nail is normal and no displaced fracture is present, the nail need not be removed for nailbed repair. If the nail is torn or avulsed, the nail should be removed, and the nailbed and skin should be inspected and repaired with absorbable sutures where appropriate

If the fingertip is completely amputated, treatment depends on the level of amputation and the age of the child. Distal amputations



Fig. 722.9 A, Congenital absence of the thumb. B, Postsurgical image after pollicization.

of skin and fat in children <2 years of age can be replaced as a composite graft with a reasonable chance of surviving. Similar amputations in older children can heal without replacing the skin if no bone is exposed and the amputated area is small. A variety of coverage procedures exist for amputations through the midportion of the nail. Amputations at or proximal to the proximal edge of the fingernail should be referred emergently to a replant center for consideration for microvascular replantation. When referring, all amputated parts should be saved, wrapped in saline-soaked gauze, placed in a watertight bag, and then placed in ice water. Ice should never directly contact the part because it can cause severe osmotic and thermal injury.

Trigger Thumb and Fingers

The flexor tendons for the thumb and fingers pass through fibrous tunnels made up of a series of pulleys on the volar surface of the digits.

These tunnels can become tight at the most proximal or first annular pulley. Swelling of the underlying tendon occurs, and the tendon no longer glides under the pulley. In children, the most common digit involved is the thumb. Trigger thumbs are not congenital deformities but rather are developmental and most frequently occur before 2 years of age. The incidence of trigger thumb is approximately 3 per 1,000 children at 1 year of age. A history of trauma is rare, and the condition is often painless. Overall function is rarely impaired. A trigger thumb typically manifests with the inability to fully extend the thumb interphalangeal joint. A palpable nodule can be felt in the flexor pollicis longus tendon at the base of the thumb metacarpal phalangeal joint volarly. Other conditions can mimic trigger thumb, including the thumb-in-palm deformity of cerebral palsy. Similar findings in the fingers (index through small) are much less common and may be associated with inflammatory conditions such as juvenile idiopathic arthritis (Fig. 722.11).

Table 722.6 Syndromes Associated with Syndactyly*

Apert syndrome
Carpenter syndrome
Chotzen syndrome
de Lange syndrome
Fanconi pancytopenia
Fetal hydantoin syndrome
Holt-Oram syndrome
Laurence-Moon-Biedl syndrome
Noack syndrome
Orofaciodigital syndrome
Pfeiffer syndrome
Poland syndrome
Polysyndactyly
Trisomy 13
Trisomy 18
Trisomy 21

*There are many more syndromes associated with syndactyly; this list is not all-inclusive.

Treatment

Trigger thumbs spontaneously resolve in up to 30% of children who are diagnosed before 1 year of age. Spontaneous resolution beyond that age is uncommon. Corticosteroid injections are effective in adults but are not effective in children and risk injury to the nearby digital nerves. Surgical release of the first annular pulley is curative and is generally performed between 1 and 3 years of age. Treatment of trigger fingers other than the thumb in children involves evaluation and treatment of any underlying inflammatory process and in some cases surgical decompression of the flexor sheath and possible flexor tendon partial excision.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

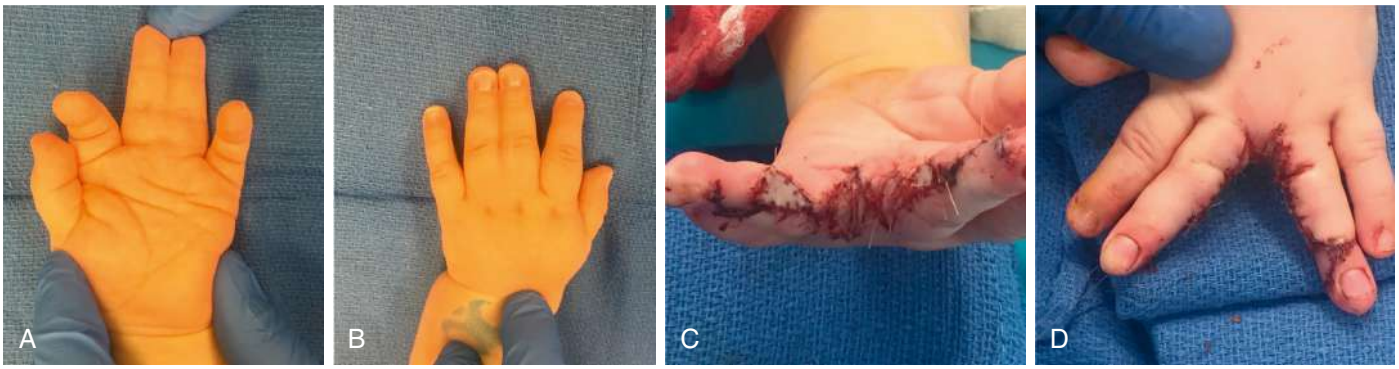

Fig. 722.10 Preoperative (A and B) and postoperative (C and D) pictures of a simple syndactyly.

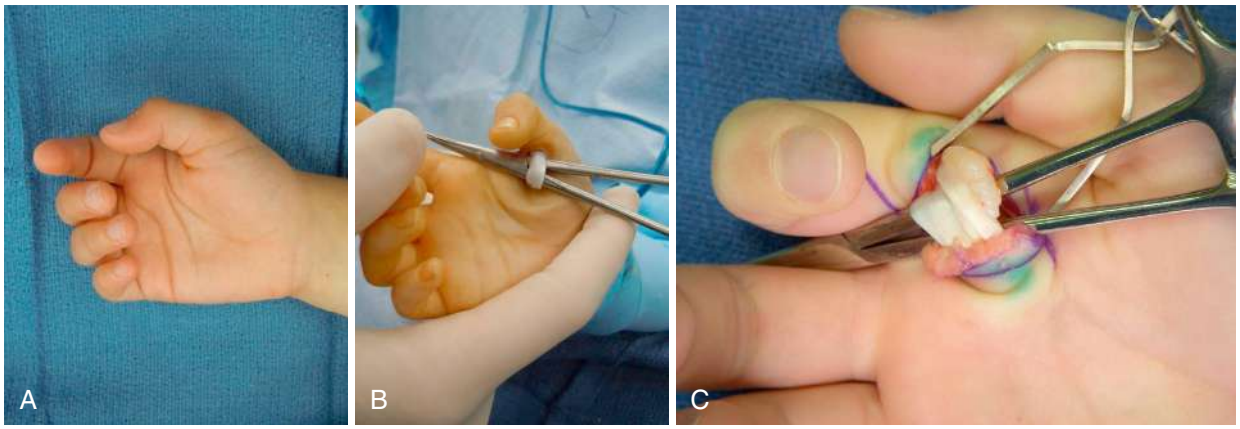

Fig. 722.11 A, Clinical picture of trigger thumb in a 2 yr old; note flexed posture of the interphalangeal joint. B, Intraoperative picture of flexor tendon following release of A1 pulley. C, Intraoperative picture of benign growth along flexor tendon causing triggering in an index finger.

Chapter 723

Arthrogryposis

Christine M. Goodbody, Helen M. Horstmann, and Richard S. Davidson

Arthrogryposis multiplex congenita refers to a heterogeneous group of muscular, neurologic, and connective tissue anomalies that present with two or more joint nonprogressive contractures at birth, as well as muscle weakness. It is associated with abnormal contraction of muscle fibers, causing reduced mobility with a decreased active and passive arc of motion. Arthrogryposis is not a specific diagnosis but a descriptive term with various etiologies and complex clinical features, including multiple congenital contractures of various limb joints. It is associated with over 300 different disorders encompassing malformation, malfunction, and neurologic deficiency (see Chapter 648.10).

Approximately 1% of all births show some form of contractures of the joints ranging from unilateral clubfoot to amyoplasia (the most severe), a condition characterized by pervasive, crippling contractures involving many joints. The overall incidence of arthrogryposis is 1/5,000-10,000 live births with equal gender ratios.

Although children with arthrogryposis may have many other problems, such as micrognathia and feeding issues, focus is on the orthopedic problems frequently seen in this group of children. In the absence of central nervous system lesions, many children have normal intelligence.

ETIOLOGY

The main cause of arthrogryposis is fetal akinesia or decreased fetal movement. The associated pattern of abnormalities is often referred to as the **fetal akinesia deformation sequence**. This sequence manifests as multiple joint contractures, oligohydramnios, craniofacial anomalies (e.g., micrognathia), and pulmonary hypoplasia because of lack of movement of the diaphragm and intercostal muscles. Intrinsic and extrinsic causes of fetal akinesia are categorized into six groups (Fig. 723.1) and include a multitude of disorders (Table 723.1).

Neurologic Abnormalities

Neurologic abnormalities are present in 70–80% of cases. Patchy damage to the anterior horn cells of the spinal cord can lead to characteristic limb posturing of arthrogryposis. Neurologic disorders, such as spinal muscular atrophy and anterior horn disease, are associated with arthrogryposis; however, the type of anterior horn cell involvement is usually not from spinal muscular atrophy syndrome. Other less common neurologic disorders include neonatal myasthenia, myotonic dystrophy, olivo-ponto-cerebellar disorders, and neuronal migration anomalies.

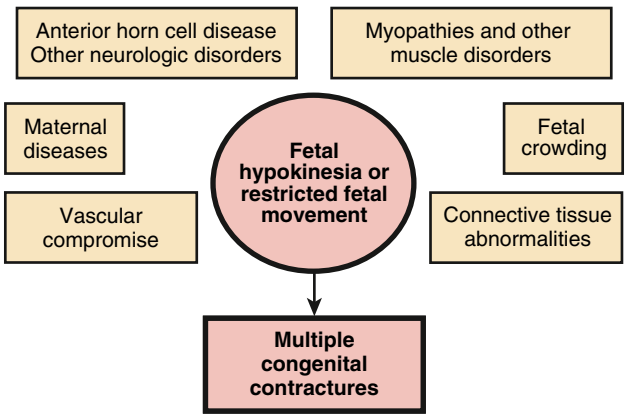

Fig. 723.1 Etiology of arthrogryposis. *(Data from Hall JG. Arthrogryposis multiplex congenital: etiology, genetics, classification, diagnostic approach, and general aspects. J Pediatr Orthop B. 1996;6:159–166.)*

Muscular Abnormalities

These rare abnormalities affect the function and structure of the muscles. **Amyoplasia**, the most common form of arthrogryposis, is associated with abnormally decreased fetal movement and is characterized by underdeveloped, contracted muscles causing joint deformity. The involved skeletal muscle is replaced by fatty or fibrous tissue. Some muscular diseases associated with arthrogryposis are muscular dystrophies, congenital myopathies (central core, nemaline, centronuclear), intrauterine myositis, and mitochondrial diseases.

Limited Intrauterine Spacing

Uterine constraint is rarely the primary cause of arthrogryposis. Maternal uterine anomalies will occasionally increase contractures of fetal limbs with arthrogryposis already existing. Other known causes are lack of amniotic fluid within the uterus, and tumors, such as fibroids, that can prevent movement by impinging on uterine space.

Connective Tissue Abnormalities

When the tendons, bones, joints, and joint lining develop atypically, the resulting decrease in fetal movement causes congenital contractures. Diseases such as **diastrophic dysplasia**, **campomelic dysplasia**, and **metatropic dysplasia** result from connective tissue not developing properly. These are specific diagnoses resulting in limited joint motion and not true distal arthrogryposis. In some cases, the connective tissue develops normally but does not attach to the proper location around a bone or joint, and the subsequent abnormal movement results in distal joint involvement.

Maternal Diseases

Maternal diseases, such as multiple sclerosis, diabetes mellitus, myasthenia gravis, maternal hyperthermia, infection (Zika virus), drugs, and trauma, are associated with an increased incidence of arthrogryposis. In approximately 10% of neonates born to mothers with myasthenia gravis, maternal antibodies enter the fetal circulation through the placenta, causing transient myasthenia gravis; this inhibits fetal acetylcholine receptors, which leads to damaged fetal muscles.

Intrauterine Vascular Compromise

Abnormal fetal blood supply may be associated with arthrogryposis. This occurs when inadequate vascular supply to the fetus causes fetal hypoxia resulting in anterior horn cell death, which, in turn, decreases neurologic and myologic function. The result is fetal akinesia and secondary joint contractures. Multiple congenital contractures have been reported in individuals after bleeding throughout pregnancy or after a failed attempt at terminating the pregnancy.

CLASSIFICATION

Arthrogryposis multiplex congenita is divided into subgroups with different signs, symptoms, and causes as a practical way to make a differential diagnosis. However, given the wide spectrum of disease presentation and etiology, no one classification system exists that is entirely comprehensive. Disorders involving primarily the limbs, such as amyoplasia and distal arthrogryposis, are the most common subgroups. Disorders involving limbs and other body parts typically represent a form of **multiple pterygium syndrome**, which is characterized by weblike membranes that form across joints, affecting a child's ability to extend those joints and causing fixed flexion deformities. Disorders with limb involvement and abnormal neurologic function are caused by atypical central nervous system development, peripheral nervous system abnormalities, damaged or absent anterior horn cells, or a combination thereof.

Amyoplasia, also known as *classic arthrogryposis,* is a sporadic symmetric disorder that causes fibrotic replacement of the muscles. Symptoms include internally rotated and adducted shoulders, extended

Table 723.1 Associated Etiologies of Arthrogryposis

ARTHROGRYPOSIS CAUSED BY NERVOUS SYSTEM DISORDERS
• Focal anterior horn cell deficiency
• Generalized anterior horn cell deficiency
• Structural brain disorder/damage
• Uncertain location
(Spastic conditions are excluded)
DISTAL ARTHROGRYPOSIS SYNDROMES
• Type I dominant distal
• Type IIa dominant distal (Freeman-Sheldon syndrome)
• Digitotalar dysmorphism
• Trismus pseudocamptodactyly
• Distal distribution, type not specified
PTERYGIUM SYNDROMES
• Multiple pterygium syndrome
• Lethal multiple pterygium syndrome
• Popliteal pterygium syndrome
• Ptosis, scoliosis, pterygia
• Antecubital webbing syndrome (Liebenberg)
MYOPATHIES
• Emery-Dreifuss muscular dystrophy
• Hypotonia, myopathy, mild contractures
ABNORMALITIES OF JOINTS AND CONTIGUOUS TISSUE
• Congenital contractural arachnodactyly
• Freeman-Sheldon syndrome
• Laxity or hypertonicity with intrauterine dislocation and contractures
• Larsen syndrome
• Spondyloepimetaphyseal dysplasia with joint laxity
• Trisomy 18, extended breech position with bilateral hip dislocation
• Siblings with bifid humeri, hypertelorism, and hip and knee joint dislocations
SKELETAL DISORDERS
• Diastrophic dysplasia
• Parastremmatic dysplasia
• Kniest dysplasia
• Metatropic dysplasia
• Campomelic dysplasia
• Schwartz syndrome
• Fetal alcohol syndrome with synostoses
• Osteogenesis imperfecta with bowing/contractures
INTRAUTERINE/MATERNAL FACTORS
• Fetal alcohol syndrome with contractures
• Infections
• Untreated maternal systemic lupus erythematosus
• Intrauterine fetal constraint
• Deformity (pressure)
• Amniotic fluid leakage
• Multiple pregnancies
• Intrauterine tumors
• Disruption (bands)
MISCELLANEOUS
• Pseudotrisomy 18 with contractures
• Roberts pseudothalidomide syndrome
• Deafness with distal contractures
• VACTERL association
• Multiple abnormalities and contractures not otherwise specified
• ARC
SINGLE JOINT
• Campomelia
• Symphalangism
• "Trigger" finger

ARC, Arthrogryposis, renal tubular acidosis, cholestasis; VACTERL, vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects.

Modified from Mennen U, Van Heest A, Ezaki MB, et al. Arthrogryposis multiplex congenita. *J Hand Surg Br.* 2005;30(5):468–474. Copyright 2005 The British Society for Surgery of the Hand.

elbows, pronated forearms, flexed fingers and wrists, dislocated hips, feet with severe equinovarus contractures, and extended knees. Involved muscles are hypoplastic and fibrotic. Often, patients have midfacial hemangioma. Intelligence is usually normal (Figs. 723.2 and 723.3).

Distal arthrogryposis is an autosomal dominant disorder that primarily affects the distal joints of the limbs. Characteristics of the upper limbs are medially overlapping fingers, clenched fists, ulnar deviation of fingers, camptodactyly, and hypoplasia. Lower limbs show talipes equinovarus, calcaneovalgus, vertical talus, or metatarsus varus (Fig. 723.4), in addition to limited motion at the involved joints. Ten different types of distal arthrogryposis have been categorized based on specific traits they share with each other (Table 723.2).

MANAGEMENT OF ORTHOPEDIC PROBLEMS OF ARTHROGRYPOSIS

When a child is born with arthrogryposis, the many stiff or dislocated joints pose issues of timing and best practices of management. The overarching goal of management in the lower extremities are plantigrade feet and joints that function to optimize ambulatory potential, whereas in the upper extremity, the aim is largely the ability to grasp, feed, and toilet independently. A child may have stiff elbows, dislocated hips; dislocated, hyperextended, or contracted knees; and clubfeet (Fig. 723.5). The stiffness and deformity need to be aggressively addressed through a combination of modalities. A team of clinicians, including therapists for the upper and lower extremities, orthotists, and orthopedic surgeons, will be involved.

Initially, passive range-of-motion exercises and judicious splinting directed and assisted by physical and occupational therapy will help to address the various deformities. Splinting and casting can be augmented by a taping program that can be taught to the family so that the taping can be redone frequently to take advantage of improved range of motion. The ingenuity of the therapists and/or orthotists to create the right splints and braces using appropriate thermoplastics, neoprene, Velcro, and other materials can be effective (Fig. 723.6).

The therapeutic and orthopedic goal for the child with arthrogrypotic limb deformities is to achieve maximal joint motion and to optimize joint position for function. In the lower extremities, the foot needs to be plantigrade. The knees need to have optimal motion for sitting and standing. Hips need to be stabilized, especially if the child has walking potential. In the upper extremities, in cases where there is extreme stiffness, the goals should include positioning of one arm for feeding and the other for toileting. Two-handed activities require some symmetry, which can be a challenging goal with extreme contractures and limited muscle strength. Serial casting may be beneficial in correcting joint contractures. Although scoliosis is common, it usually does not become a problem until adolescence (see Chapter 720).

FOOT PROBLEMS

Clubfoot deformities are the most commonly seen deformities with arthrogryposis (Fig. 723.7). A clubfoot has components of hindfoot equinus, midfoot varus, and forefoot adduction. Clubfeet in arthrogryposis tend to be more resistant to improvement than in idiopathic cases, but the traditional methods of treatment are nevertheless employed. Casting is begun shortly after birth in a method known as the Ponseti method. Casts are changed weekly until a plateau is reached, then heel cord lengthening is needed. Other deformities such as vertical talus are also seen and are addressed in a similar approach, although with case-appropriate differences in casting techniques (see Chapter 715).

Persistent stiffness often leads to more comprehensive soft tissue releases. This is typically done around age 6-12 months and is followed by 3 months of further casting and additional bracing as needed, especially as the foot is growing. When deformities are not corrected in early childhood, additional bony surgery may be needed later. Some of the approaches to this involve bony wedge osteotomies, lateral column lengthening, bone decancellation, or talectomy. Ring or multiaxial monolateral external fixation with or without osteotomies are used in late correction of residual deformities.



Fig. 723.2 Infant with stiff elbows, wrists, fingers, dislocated left hip, valgus stiff knees, and clubfeet.



Fig. 723.3 Infant with stiff elbows, wrists, fingers, dislocated left hip, clubfeet, and micrognathia.

Children with significant deformities are often in ankle foot orthoses through much of their lives to avoid deformity recurrence and to augment the standing base caused by weak leg muscles. A plantigrade, pain-free, stable foot is the goal of foot management. Foot stiffness is anticipated and unavoidable in arthrogryposis involving the foot.



Fig. 723.4 Infant with club feet, stiff knees, dislocated hips, stiff fingers, and facial hemangioma.

KNEE PROBLEMS

Knee issues in patients with arthrogryposis may include knee extension or flexion contracture, subluxation, and stiffness. Knee flexion contracture is more common in arthrogryposis and is often resistant to nonsurgical treatment. It can be structurally complex and associated with skin webbing known as pterygiums, which require Z-plasty lengthenings. In the case of a flexion contracture, the quadriceps musculature is often deficient and weak. When a trial of casting and splinting of the knee contractures is insufficient, surgical intervention with hamstring lengthenings and posterior knee capsular releases are often needed. Soft tissue relaxation by femoral shortening has also shown benefit.

In the case of knee hyperextension, the quadriceps are sometimes fibrotic and weak despite seeming to overpower the hamstrings. Casting and splinting should begin shortly after birth, which can be done in conjunction with clubfoot casting as needed following the principles of Ponseti. If splinting and therapy fail, lengthening of the quadriceps can be achieved through a number of surgical techniques that may include detachment of the rectus femoris and lengthening of the quadriceps either percutaneously or through a mini open procedure, which may minimize scarring.

Long-standing stiffness may lead to joint surface flattening and other bony abnormalities that can permanently reduce the arc of motion. Repositioning the arc of motion through bony osteotomies may improve sitting or standing. Follow-up bracing can help to compensate for weak, fibrotic muscles of the legs. Use of guided growth plates and screws may also be of benefit.

HIP PROBLEMS

Teratologic hip dislocations are common within the spectrum of arthrogryposis and usually require open reduction of the hip. Hips in a child with less upper-extremity involvement and more supple hips that are not pathologically stiff may respond to early treatment with a Pavlik harness. Coexisting knee hyperextension should

Table 723.2 A Classification System and Clinical Features of Distal Arthrogryposes

TYPE	DESCRIPTION
I	Characteristic clinical features are camptodactyly and talipes equinovarus with possible concomitant shoulder and hip contractures. The DA1 variant is determined by a gene located on chromosome 9.
II	The phenotype was first described in 1938 as the Freeman-Sheldon syndrome, where contractures of fingers and toes are accompanied by kyphosis, scoliosis, and malformations of the facial skeleton with characteristic facial appearance: narrow mouth, wide cheeks, an H-shaped chin dimple, small wide-based nose, high palate, and small tongue. Growth retardation, inguinal hernia, and cryptorchidism have also been reported. Another name of this syndrome is "whistling face" syndrome. The Freeman-Sheldon syndrome is currently classified as DA2A, as a separate DA2B subtype, known as Sheldon-Hall syndrome has been described; this syndrome combines clinical features of DA1 (hand and foot contractures) and some features of DA2 (prominent nasolabial folds, slanted down-facing eyes, and narrow mouth) and is currently considered to be probably the most common type of distal arthrogryposis.
III	Also known as Gordon syndrome, this rare syndrome is characterized by low stature and palatoschisis.
IV	Rare. Contractures with severe scoliosis.
V	Contractures with ocular signs and symptoms such as limited eye motion, ptosis, strabismus, and the absence of typical hand flexion creases. Chest wall muscle abnormalities have also been observed, potentially causing restricted respiratory movements and, consequently, pulmonary hypertension.
VI	Similar to DA3, DA4; very rare, characterized by sensorineural auditory abnormalities.
VII	Difficulties in mouth opening (trismus) and pseudocamptodactyly: wrists position in palmar flexion with MCP joints in extension. Sometimes accompanied by low stature and knee flexion contractures.
VIII	Autosomal dominant multiple pterygium syndrome.
IX	Beals syndrome, i.e., congenital arachnodactyly with contractures of small joints of the fingers. Patients with this type of arthrogryposis are tall and slender, phenotypically resembling Marfan syndrome but without cardiovascular abnormalities.
X	Congenital plantar flexion contractures of the foot.

From Kowalczyk B, Feluś J. Arthrogryposis: an update on clinical aspects, etiology, and treatment strategies. *Arch Med Sci.* 2016;12(1):10–24. Table 1.



Fig. 723.5 Child with stiff elbows, wrists, knees, and clubfeet.



Fig. 723.6 Infant with splints to extend metatarsophalangeal joints, wrists, and knees.

first be treated with physical therapy and serial casting to allow for appropriate Pavlik harness fitting. However, careful observation of the hip during knee flexion is necessary because tightening of the quadriceps and hip flexors can push the hip into posterior dislocation. Once some knee flexion has been achieved, the Pavlik harness can be useful in further flexing the knee and maintaining hip stability in the infant. Most often, the hips are stiff and not reducible by closed means. For these, open reduction with pelvic reconstruction and femoral osteotomy are commonly required, typically at 1 year of age. There is some controversy about reducing bilateral hip dislocations because a high failure rate can result in asymmetry of the pelvis, pain, leg length inequality, and stiffness. If a child has little



Fig. 723.7 Clubfeet in infant with arthrogryposis.

ambulatory potential, they may do as well retaining the bilateral hip dislocations and positioning the hips for sitting. Management decisions should be made in conjunction with the family and guided by a pediatric hip surgeon.

Ambulation

As would be expected, walking is more difficult for children with arthrogryposis because of the muscle weakness and limited joint motion. Children with arthrogryposis who walk have lower activity levels and take fewer steps than their peers. Not surprisingly, muscle fatigue and pain on exertion are common.

UPPER EXTREMITY PROBLEMS

If splinting and a movement exercise program do not result in optimally functional upper extremities, surgical management may improve use of the arms of the child with arthrogryposis. A typical child with arthrogrypotic involvement of the upper extremities has internally rotated arms, extended elbows, flexed wrists, and thumb-in-palm or clasp-thumb deformities (see Figs. 723.2 and 723.3).

Treatment is geared toward optimizing use of the arms and hands, particularly for critical activities of daily living, such as feeding and toileting. Therapy to improve motion of the joints is started immediately after birth. Pediatric hand therapists are the optimal leaders of the mobility treatment program. Therapy is augmented by use of splints so that less-extensive surgery will ultimately be required. The elbow is the critical length adjuster of the arm, allowing the arm to reach out as is necessary for toileting or to approach the mouth for feeding. If necessary, lack of these motions can be compensated for with modified silverware and other adaptive equipment, including arm extenders for grabbing.

Surgery of the Upper Extremity

Surgical correction of arthrogrypotic upper extremity contractures should be started after 1-3 months and completed by age 12 months so that the child can optimize his or her motor development. This allows for improved results by optimizing the joint growth remodeling plasticity. One-stage procedures yield the best results. Delays in surgery result in more problems of intraarticular adhesions as well as fixed joint incongruity.

Shoulder

Because of the rotational capacity of the shoulder, derotation osteotomy of the humerus is only occasionally needed. This is usually done in later childhood.

Elbow

A stiff elbow that does not respond to therapy requires surgical intervention starting with soft tissue and capsular release. Capsulotomy of the posterior elbow combined with a V-Y or Z reconstructive lengthening of the triceps allows improved elbow flexion. Muscle transfer to the forearm can permit active elbow flexion; however, each child needs individual assessment as to an available flexor source. The triceps is commonly used, but caution must be exerted into the overall muscle balance because use of the triceps can create elbow flexion overpowering and an opposite contracture.

Wrist

Wrist flexion deformity is improved with soft tissue balancing as well as partial carpectomies. The carpectomies need to be trapezoidal with more removed from the dorsum and the radial side to balance the wrist flexion contracture as well as the tendency for ulnar deviation. Thumb adduction may require an adductor release with an opponensplasty. Tendon transfers such as transfer of the extensor indicis pollicis to the extensor pollicis longus is helpful for improved function of the thumb in clasp thumb deformity.

Finger stiffness and wrist contractures often respond to therapy and bracing without need for surgery.

Scoliosis

Scoliosis develops in some children with arthrogryposis, with the reported incidence ranging from 2.5–66%. Scoliosis can be congenital or paralytic. It is often accompanied by hip contractures associated with hip dislocation and compensatory lumbar lordosis. Curves <30 degrees can be treated initially with bracing in a thoracolumbar spinal orthosis (TLSO brace). After 40 degrees, spinal fusion is generally warranted.

Surgical Staging

Surgical treatment of the lower limbs usually begins distally and works proximally. The feet are corrected around 6 months of age, the knees around 8 months of age, and the hips around 12 months of age because pelvic osteotomy is often needed to stabilize the hips properly.

The upper extremities are corrected during infancy when the child is seen early. Hand, physical, and occupational therapy are a critical part of the team to optimize function before and after surgery. Further surgery during childhood may be needed to optimize functional use of the upper and lower extremities.

Prognosis

Although most patients with arthrogryposis are ambulatory into adulthood, fewer are entirely independent, and many have pain or limitations in walking and standing. Surgical advancements in upper extremity positioning have improved function, and procedures to correct lower extremity contractures, including not only surgery but also casting for clubfeet, have increased long-term ambulatory potential. However, there is significant variability in this population, and further work must be done to optimize intervention techniques and their appropriate utilization.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 724

Common Fractures

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

Trauma is a leading cause of death and disability in children older than 1 year of age (see Chapter 14). Several factors make fractures of the immature skeleton different from those involving the mature skeleton. The anatomy, biomechanics, and physiology of the pediatric skeletal system differ from those of adults, resulting in different fracture patterns (Fig. 724.1), diagnostic challenges, and management techniques. Children have a high functional demand and expectations while carrying concerns regarding remaining skeletal growth and development.

Epiphyseal lines, rarefaction, dense growth lines, congenital fractures, and pseudofractures may appear on radiographs, which make it challenging to identify and differentiate an acute fracture. Although most fractures in children heal well, some fractures have poor outcomes if handled with insufficient expertise. The differences in the pediatric skeletal system predispose children to injuries different from those of adults. Important differences are the presence of periosseous cartilage, **physes**, and a thicker, stronger, more osteogenic periosteum that produces new bone, called **callus**, more rapidly and in greater amounts. The pediatric bone is less dense and more porous than adult bone. The low density is from lower mineral content, and the increased porosity is the result of an increased number of haversian canals and vascular channels. These differences result in a comparatively lower modulus of elasticity and lower bending strength. The bone in children can fail either in tension or in compression; because the fracture lines do not propagate as in adults, there is less chance of comminuted fractures. Hence, pediatric bone can crush, splinter, and break incompletely (e.g., buckle fracture, greenstick fracture), as opposed to adult bone which generally breaks like glass and may comminute.

A common teaching is that joint injuries, dislocation, and ligament disruptions are infrequent in children. Damage to the physis is more likely. Although this is generally true, MRI studies show that ligament damage in ankle injuries may be more common than once thought. Interdigitating mammillary bodies and the perichondrial ring enhance the strength of the physes. Biomechanically, the physes are not as strong as the ligaments or metaphyseal bone. The physis is most resistant to traction and least resistant to torsional forces. The periosteum is loosely attached to the shaft of bone and adheres densely to the physeal periphery. The periosteum is essentially injured in all fractures, but it is less likely to have complete circumferential rupture because of its loose attachment to the shaft. This intact hinge or sleeve of periosteum lessens the extent of fracture displacement and assists in reduction and maintenance of fracture reduction. The thick periosteum, however, may act as an impediment to reduction, particularly if the fracture has penetrated the periosteum, or in reduction of a displaced growth plate fracture.

724.1 Unique Characteristics of Pediatric Fractures

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

FRACTURE REMODELING

Remodeling is the third and final phase in the biology of fracture healing; it is preceded by the inflammatory and reparative phases. This occurs from a combination of appositional bone deposition on the concavity of deformity, resorption on the convexity, and asymmetric physeal growth. Thus reduction accuracy is somewhat less important than it is in adults (exceptions include intraarticular fractures) (Fig. 724.2). The three major factors that have a bearing on the potential for angular correction are skeletal age, distance from the physis, and orientation to the joint axis. Rotational deformity and angular deformity not in the axis of the joint motion have less potential for remodeling. Remodeling is greatest when the child has many years of growth remaining and when the fracture occurs close to the physis, has less deformity to remodel, and is adjacent to a rapidly growing physis (e.g., the proximal humerus or distal radius). Remodeling typically occurs over several months after the fracture until skeletal maturity. Generally, skeletal maturity is reached in postmenarchal females between 13 and 15 years of age and in males between 15 and 17 years of age.

OVERGROWTH

Physeal stimulation from the hyperemia associated with fracture healing may also cause overgrowth. It is usually more prominent in lower extremity long bones such as the femur. The growth acceleration is usually present for 6 months to 1 year after the injury. Femoral fractures in children younger than 10 years of age may overgrow up to 1-3 cm. If external fixation or casting is employed, bayonet apposition of bone may be preferred for younger children to compensate for the expected overgrowth. This overgrowth phenomenon will result in equal or near equal limb lengths at the conclusion of fracture remodeling if the fracture shortens less than 2 cm. After 10 years of age, overgrowth does not tend to occur, and anatomic alignment is recommended. In physeal injuries, growth stimulation is associated with use of implants or fixation hardware that can cause stimulus for longitudinal growth.

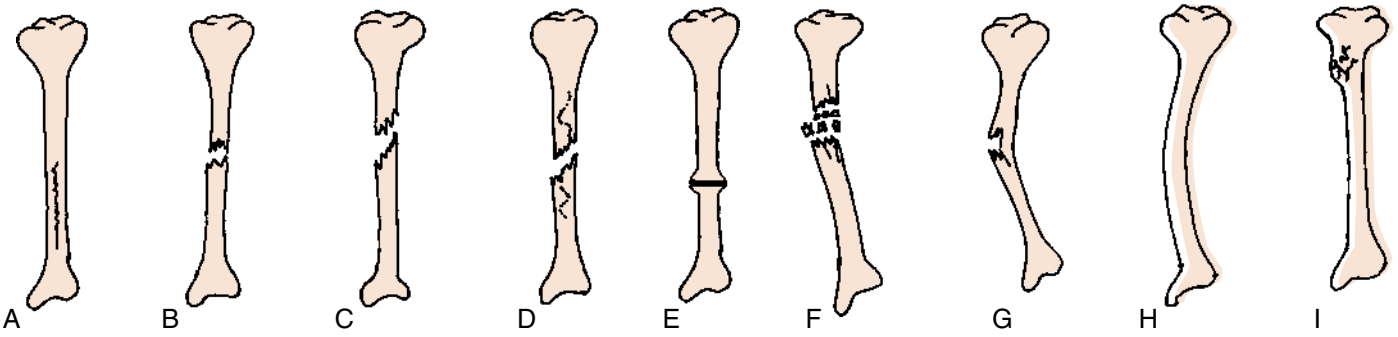

Fig. 724.1 Illustration of fracture patterns. **A,** Longitudinal fracture line parallel to bony axis. **B,** Transverse fracture line perpendicular to bony axis. **C,** Oblique fracture line at angle to bony axis. **D,** Spiral fracture line runs a curvilinear course to the bony axis. **E,** Impacted fractured bone ends compressed together. **F,** Comminuted fragmentation of bone into three or more parts. **G,** Greenstick bending of bone with incomplete fracture of convex side. **H,** Bowing bone plastic deformation. **I,** Torus buckling fracture. *(From White N, Sty R. Radiological evaluation and classification of pediatric fractures. Clin Pediatr Emerg Med. 2002;3:94–105.)*

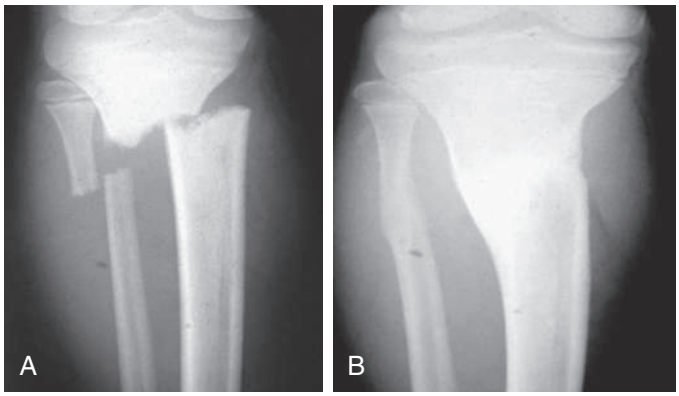

Fig. 724.2 Remodeling in children is often extensive, as in this proximal tibial fracture (A) and as seen 1 yr later (B). *(From Dormans JP. Pediatric Orthopedics: Introduction to Trauma. Philadelphia: Mosby; 2005:38.)*

PROGRESSIVE DEFORMITY

Injuries to the physes can be complicated by permanent or temporary growth arrest, leading to progressive limb deformity. The most common cause is complete or partial closure of the growth plate. This can occur in any long bone but is particularly seen in fractures involving the distal ulna, distal femur, and proximal tibia growth plates. An MRI is helpful for early diagnosis of growth arrest, as well as measurement of the percent of physeal closure after such an injury. Harris growth arrest lines may be observed in the setting of asymmetric growth and will point toward the area of growth arrest (Fig. 724.3). If these lines are parallel to the physis, this finding indicates that the growth plate is healthy. As a consequence of growth arrest, angular deformity or shortening, or both, can occur. The partial arrest may be peripheral, central, or combined. The magnitude of deformity depends on the specific physis involved, the degree of involvement, and the amount of growth remaining.

RAPID HEALING

Children's fractures heal more quickly than adults as a result of children's growth potential and thicker, more active periosteum. When children approach adolescence and maturity, the rate of healing slows and mirrors that of an adult.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

724.2 Pediatric Fracture Patterns

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

The different pediatric fracture patterns are the reflection of a child's characteristic skeletal system. The majority of pediatric fractures can be managed by closed methods and heal well.

PLASTIC DEFORMATION

Plastic deformation is unique to children. It is most commonly seen in the forearm and occasionally the fibula. The fracture results from a force that produces microscopic failure on the tensile side of bone and does not propagate to the concave side (Fig. 724.4). The concave side of bone also shows evidence of microscopic failure in compression. The bone is angulated beyond its elastic limit, but the energy is insufficient to produce a fracture. Thus no fracture line is visible radiographically (Fig. 724.5). Although the plastic deformation is permanent, it is important to remember that children have great remodeling capability; for example, a 20-degree bend in the ulna of a 4-year-old child is expected to correct completely with growth. These findings inform "acceptability" of fracture alignment.



Fig. 724.3 A, Harris growth arrest lines on either side of the femur pointing centrally in the femur indicating a central growth arrest. B, Corresponding MRI image showing central growth arrest. *(A, Courtesy Dr. Keith D. Baldwin, Children's Hospital of Philadelphia.)*

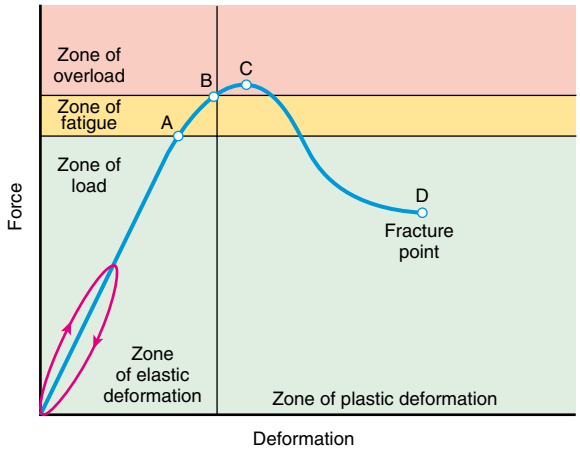

Fig. 724.4 Graphic relation of bony deformation (bowing) and force (longitudinal compression) showing that the limit of an elastic response is not a fracture but plastic deformation. If the force continues, a fracture results. *A,* Reversible bowing with stress; *B,* microfractures occur; *C,* point of maximal strength; between C and *D,* bowing fractures; and *D,* linear fracture occurs. *(Modified from Borden S IV. Roentgen recognition of acute plastic bowing of the forearm in children. Am J Roentgenol Radium Ther Nucl Med. 1975;125:524–530.)*

BUCKLE OR TORUS FRACTURE

Buckle, or torus, fractures represent a failure in compression of the bone, usually occurring at the junction of the metaphysis and diaphysis. The distal radius is the most common location, but it may occur in other areas as well (Fig. 724.6). They are inherently stable, usually associated with an acceptable amount of angulation, and heal in 3-4 weeks with simple immobilization.

GREENSTICK FRACTURE

These fractures occur when the bone is bent and there is failure on the tensile (convex) side of the bone. The fracture line does not propagate to the concave side of the bone (Fig. 724.7). The concave side shows evidence of microscopic failure with plastic deformation. If the angulation at the fracture site is unacceptable, it is usually necessary to break the bone on the concave side because the plastic deformation recoils it back to the deformed position. It is important to distinguish this unicortical fracture pattern from buckle fractures, as these fractures are at greater risk of loss of reduction and often require a longer period of immobilization.

COMPLETE FRACTURES

Fractures that propagate completely through the bone are called complete fractures. These fractures may be classified as spiral, transverse, or oblique, depending on the direction and shape of the fracture lines. A rotational force is responsible for spiral fractures. Most spiral fractures



Fig. 724.5 Plastic deformation is a microfailure in tension without a visible fracture line. *(Courtesy Dr. John Flynn, Children's Hospital, Philadelphia.)*

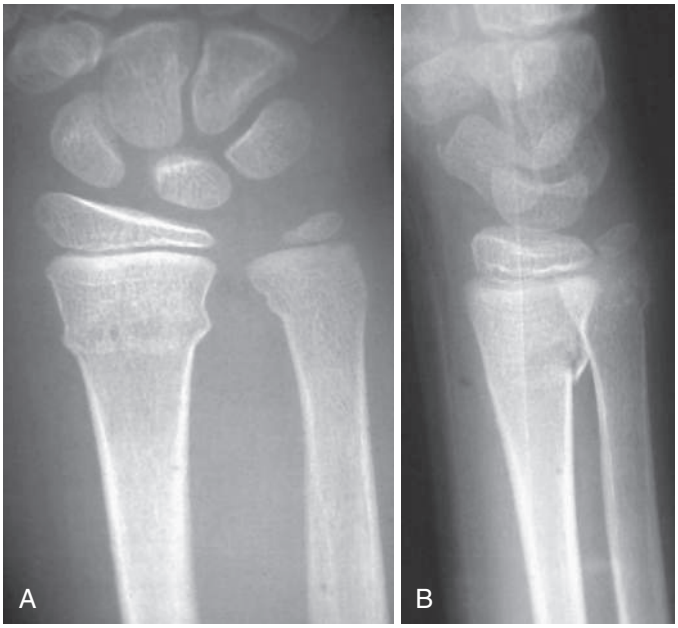

Fig. 724.6 Buckle fracture is a partial failure in compression. Anteroposterior (**A**) and lateral (**B**) radiographs of the distal radius. *(From Dormans JP. Pediatric Orthopedics: Introduction to Trauma. Philadelphia: Mosby; 2005:37.)*

are stable and heal quickly due to the large surface area; however, spiral fractures occurring as a result of a high-energy trauma may present with shortening of the bone and loss of alignment. Oblique fractures are defined by a 30-degree angle to the axis of the bone and are often unstable. The transverse fracture pattern occurs following a three-point bending force and is amenable to successful reduction by using the intact periosteum from the concave side as a hinge.



Fig. 724.7 Greenstick fractures of the radial and ulnar diaphyses in an 8-yr-old boy. The fracture lines only extend through part of the cortex. *(From Pai DR, Strouse PJ. Skeletal trauma. In: Coley BD ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 142.5, p. 1435.)*

Table 724.1 Salter-Harris Classification

SALTER-HARRIS TYPE	CHARACTERISTICS
I	Separation through the physis, usually through the zones of hypertrophic and degenerating cartilage cell columns
II	Fracture through a portion of the physis but extending through the metaphyses
III	Fracture through a portion of the physis extending through the epiphysis and into the joint
IV	Fracture across the metaphysis, physis, and epiphysis
V	Crush injury to the physis

EPIPHYSEAL FRACTURES

Fractures involving the epiphysis often involve the growth plate (physis); therefore the potential for growth disturbance leading to deformity or discrepancy exists, and long-term observation is necessary. The distal radial physis is the most injured physis. Salter and Harris (SH) classified physeal injuries into five groups (Table 724.1 and Fig. 724.8). This classification helps to predict the outcome of the injury and offers guidelines in formulating treatment. Most SH type I and II fractures usually can be managed by closed reduction techniques and do not require perfect alignment because they tend to remodel with growth, as long as there is enough growth remaining. One classic exception is the distal femur, where SH type II fractures are unstable and require anatomic reduction with adequate fixation. The SH type III and IV epiphyseal fractures involve the articular surface and require anatomic alignment (<2 mm displacement) to prevent any step off and realign the growth cells of the physis. SH type V fractures are usually not diagnosed initially. They manifest in the future with growth disturbance. Other injuries to the epiphysis are avulsion injuries of the tibial spine and muscle attachments to the pelvis. Osteochondral fractures are also defined as physeal injuries that do not involve the growth plate.

CHILD ABUSE

See also Chapter 17.

Fractures are the second most common manifestation of child abuse after skin injury (bruises, burns/abrasions). The orthopedic surgeon sees 30–50% of all nonaccidental traumas. Child abuse should be suspected in nonambulatory children with lower-extremity long-bone fractures. No fracture pattern or types are pathognomonic for

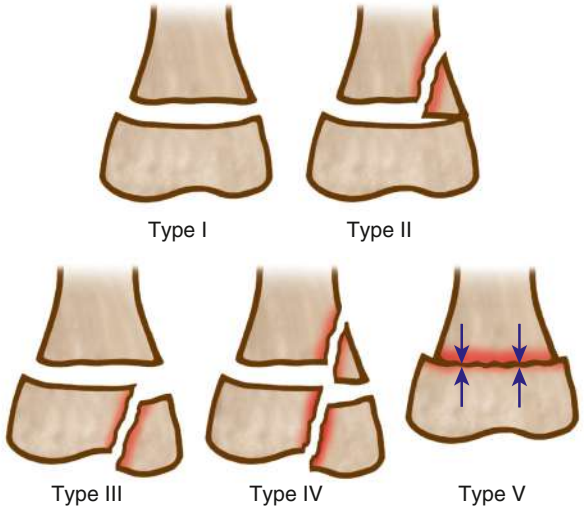

Fig. 724.8 Salter-Harris classification of physeal fractures, types I-V.

child abuse; any type of fracture can result from nonaccidental trauma (Table 724.2). **Transverse fractures** in long bones are the most prevalent, and **corner fractures** in the metaphysis are the most classic. The fractures that suggest nonaccidental injury include femur fractures in nonambulatory children (younger than age 18 months), distal femoral metaphyseal corner fractures, posterior rib fractures, scapular spinous process fractures, and proximal humeral fractures. Fractures that were unwitnessed or carry a suspicious or changing story or delayed presentation also warrant investigation. A full skeletal survey is essential in every suspected case of child abuse because it can demonstrate other fractures in different stages of healing. Radiographically, some systemic diseases mimic signs of child abuse, such as osteogenesis imperfecta, osteomyelitis, Caffey disease, vitamin C deficiency, and fatigue fractures. Many hospitals have a multidisciplinary team to evaluate and treat patients who are victims of child abuse; these teams are critical to engage early and preferably in the emergency room setting, as difficulty arises managing these emotionally charged issues in a clinic setting. Dedicated teams are most well equipped to identify and manage these issues. It is mandatory to report these cases to social welfare agencies.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 724.2 Skeletal Injuries from Child Abuse

HIGH-SPECIFICITY FINDINGS
• Classic metaphyseal lesions • Posterior rib fracture • Scapular fracture • Sternal fracture • Spinous process fracture • First rib fracture
MODERATE-SPECIFICITY FINDINGS
• Multiple fractures • Fractures of differing age • Spine fracture • Complex skull fracture • Physeal fractures of the long bones • Digital fractures
LOW-SPECIFICITY FINDINGS
• Diaphyseal fractures of the long bones • Simple skull fractures • Clavicle fracture • Subperiosteal new bone formation

From Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging,* 13th ed. Philadelphia: Elsevier; 2019: Box 143.2, p. 1455; modified from Kleinman PK. *Diagnostic Imaging of Child Abuse,* 2nd ed. St. Louis, MO: Mosby; 1998.

724.3 Upper Extremity Fractures

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

PHALANGEAL FRACTURES

Finger fractures are among the most common fracture types in children. The different phalangeal fracture patterns in children include physeal, diaphyseal, and tuft fractures. The mechanism of injury varies from a direct blow to the finger to a finger trapped in a door (see Chapter 722). Crush injuries of the distal phalanx manifest with severe comminution of the underlying bone (tuft fracture), disruption of the nail bed, and significant soft tissue injury. These injuries are best managed with irrigation, tetanus prophylaxis, and antibiotic prophylaxis; antibiotics effective against staphylococci (e.g., first-generation cephalosporins) are usually appropriate, although the mechanism of injury may warrant other antibiotic coverage. Radiographs in patients with fingertip crush injuries should be scrutinized for evidence of a **Seymour fracture**, an open physeal fracture of the distal phalanx with possible interposition of the nail matrix. These patients are at higher risk of nail plate deformity and infection without surgical treatment. A **mallet finger** deformity is the inability to extend the distal portion of the digit and is caused by a hyperflexion injury. It represents an avulsion fracture of the physis of the distal phalanx. The treatment is continuous splinting of the digit in extension for 6 weeks. The physeal injuries of the proximal and middle phalanx are similarly treated with cast immobilization. The most common physeal finger fracture results from an abduction injury to the small finger. These fractures often require a closed reduction before immobilization. Diaphyseal fractures may be oblique, spiral, or transverse in fracture geometry. They are assessed for angular and rotational deformity with the finger in flexion. The patient should be asked to make a fist. All fingers should point toward the scaphoid. If they do not, a malrotation is suspected, even in the presence of x-rays in which the bones appear minimally displaced. Malrotation or angular deformity may require correction to avoid finger crossover and to optimize hand function. These deformities are corrected with closed reduction, and, if unstable, they need surgical fixation with a percutaneous pin.

HAND FRACTURES

Metacarpal fractures are commonly seen in children or adolescents who strike a person or object with a closed fist. When metacarpal fractures are not displaced, they can be managed with splinting and/or casting. Displaced fractures are typically managed with closed reduction and casting. If reduction cannot be maintained, surgical stabilization may be required.

Fractures of carpal bones are rare in young children but become more common in adolescence. Most carpal bones are stable and can be treated with immobilization in a splint or cast. The scaphoid is the most commonly fractured carpal bone and presents with tenderness at the anatomic snuffbox. **Scaphoid fractures** may be difficult to visualize on initial radiographs; if clinical suspicion for fracture is high, the patient with negative initial radiographs should be placed in a thumb spica splint with a plan to repeat imaging in 14-21 days.

FOREARM FRACTURES

Fractures of the wrist and forearm are very common in children, accounting for nearly half of all fractures seen in the skeletally immature. The most common mechanism of injury is a fall on the outstretched hand. Of forearm fractures, 80% involve the distal radius and ulna, 15% involve the middle third, and the rest are rare fractures of the proximal third of the radius or ulnar shaft (Fig. 724.9). Most forearm fractures in younger children are torus or greenstick fractures. The torus fracture is an impacted fracture, and there is minimal soft tissue swelling or hemorrhage. They may be managed in either a short

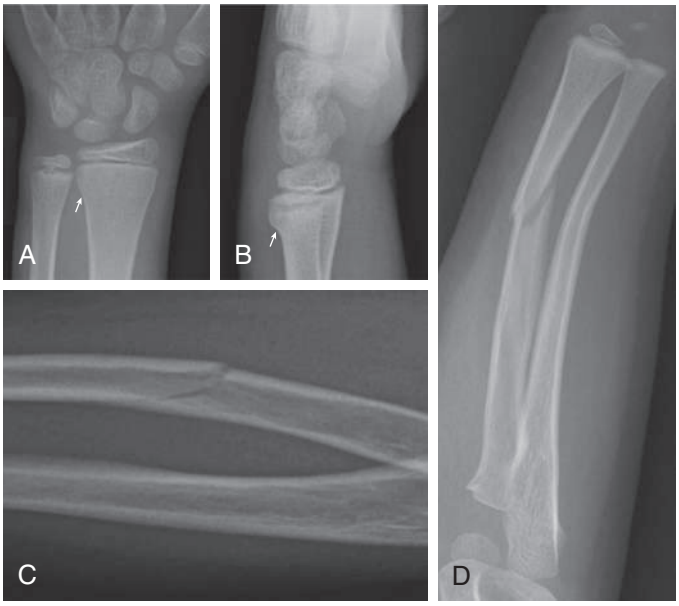

Fig. 724.9 Common pediatric fracture patterns. **A,** Posteroanterior and (**B**) lateral radiographs of the wrist demonstrate a buckle fracture of the distal radial metaphysis *(arrows).* **C,** Radiograph of the forearm demonstrates a greenstick fracture of the radial shaft, with the fracture extending through a single cortex. **D,** Anteroposterior radiograph of the forearm shows an oblique fracture through the distal radial shaft, with plastic bowing deformity of the adjacent distal ulna. *(From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.90.)*

arm (below the elbow) cast or removable wrist splint and usually heal within 3-4 weeks.

Diaphyseal fractures can be more difficult to treat because the limits of acceptable reduction are much more stringent than for distal radial fractures. A significant malunion of a forearm diaphyseal fracture can lead to a permanent loss of pronation and supination, leading to functional difficulties. This is particularly true with malrotation of the fragments. Diaphyseal fractures are vulnerable to rotational malalignment because of insertion of the pronator muscle groups and the supinator groups. This malalignment is particularly hard to assess because the deformity is in the axial plane and is evaluated with anteroposterior (AP) and lateral radiographs (Fig. 724.10). The physical examination focuses on soft tissue injuries and ruling out any neurovascular involvement. The AP and lateral radiographs of the forearm and wrist confirm the diagnosis. Displaced and angulated fractures require manipulative closed reduction under general anesthesia or conscious sedation. They are immobilized in an above-elbow cast for at least 6 weeks. Bone fractures in older children and adolescents (>10 years of age) must be followed carefully as they often lose reduction. Loss of reduction and unstable fractures require open reduction and internal fixation. Fixation may be with intramedullary nails or plate fixation, which yield similar results.

DISTAL HUMERAL FRACTURES

Fractures around the elbow receive more attention because more aggressive management is needed to achieve an excellent result. Many injuries are intraarticular, involve the physeal cartilage, and can result in malunion or nonunion. Because the distal humerus develops from a series of ossification centers, these ossification centers can be mistaken for fractures by inexperienced eyes. Careful radiographic evaluation is an essential part of diagnosing and managing distal humeral injuries. It is important to remember that the distal humerus is only responsible for 20% of the growth of the humerus; therefore there is very low potential for remodeling. Observation of soft tissue swelling and tenderness is critical to pick up subtle injuries. Common fractures include separation of the distal humeral epiphysis (transphyseal



Fig. 724.10 A rotationally malaligned forearm fracture that initially had good alignment but lost reduction in the cast. Note that the radial styloid is visible, but the biceps tuberosity is not. The two should normally be 180 degrees from one another. These landmarks are sometimes hard to appreciate in children but were visible on other views in this child.

fracture), **supracondylar fractures** of the distal humerus, and epiphyseal fractures of the lateral condyle or medial epicondyle. The mechanism of injury is most frequently a fall on an outstretched arm. The physical examination includes noting the location and extent of soft tissue swelling, ruling out any neurovascular injury, specifically anterior interosseous nerve involvement or evidence of compartment syndrome. *A transphyseal fracture in a very young child who does not have the reflex to keep the arm outstretched to break a fall should raise suspicion of child abuse.* AP and lateral radiographs of the involved extremity are necessary for the diagnosis. If the fracture is not visible, but there is an altered relationship between the humerus and the radius and ulna or the presence of a posterior fat pad sign, a transphyseal fracture or an occult fracture should be suspected (Fig. 724.11). Imaging studies such as oblique radiographs, CT, MRI, and ultrasonography may be required for further confirmation. Displaced supracondylar fractures may be associated with concomitant neurovascular injury (Fig. 724.12) or, rarely, a compartment syndrome. Ulnar nerve injury is identified by decreased sensation over the cutaneous innervation of the lateral aspects of the hand as well as a motor deficit of abduction and adduction of the fingers. Neurologic injury may also appear in the postoperative period. Careful neurologic examination of the hand before and after is needed to document and treat nerve injury. Most nerve injuries associated with displaced supracondylar fractures are neuropraxias and will resolve in several months.

In general, distal humeral fractures need restoration of anatomic alignment. This is necessary to prevent deformity and to allow for normal growth and development. Closed reduction alone, or in association with percutaneous fixation, is the preferred method. Open reduction is indicated for fractures that cannot be reduced by closed methods, fractures with vascular compromise after closed reduction, open fractures, or interarticular fractures, particularly in older children. Inadequate reductions can lead to loss of motion, cubitus varus, cubitus valgus, and rare nonunion or elbow instability. Elbow stiffness is not as common as in adult fractures but may occur with fractures which are severe or intraarticular.

PROXIMAL HUMERUS FRACTURES

Fractures of the proximal humerus account for <5% of fractures in children. They usually result from a fall onto an outstretched arm or direct trauma. The fracture pattern tends to vary with the age group. Physeal and metaphyseal fractures are both common. Among physeal fractures of the proximal humerus, children younger than 5 years of age most commonly have SH I injuries, those 5-10 years of age have metaphyseal fractures, and children older than 11 years of age have SH II injuries. Examination includes a thorough neurologic evaluation, especially of the axillary nerve. The diagnosis is made on AP radiographs of the shoulder. An axillary view is obtained to rule out

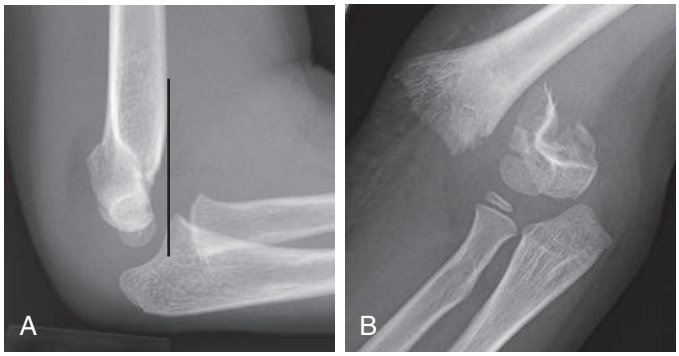

Fig. 724.11 Supracondylar humerus fracture. **A,** Lateral radiograph of the elbow demonstrates a type II supracondylar humerus fracture, with disruption of the anterior humeral line *(black line)*. This line normally passes through the middle third of the capitellum. Here the capitellum is displaced behind the line. A large joint effusion is noted. **B,** Anteroposterior radiograph of the elbow shows a type III supracondylar humerus fracture. There is no cortical continuity and significant displacement and overlap of fracture fragments. *(From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.97.)*

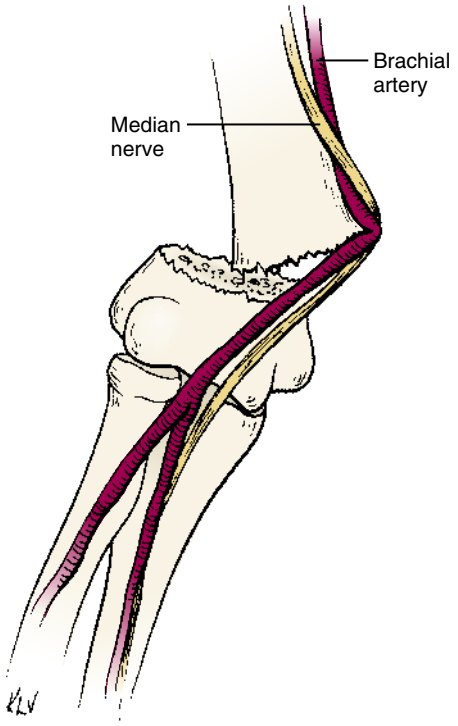

Fig. 724.12 Posterolaterally displaced type III (extension-type) supracondylar humeral fracture. The proximal fragment displaces anteromedially, thus placing the brachial artery and median nerve at risk. *(From Ho C. Upper extremity injuries. In: Herring JA, ed. Tachdjian's Pediatric Orthopaedics, 6th ed. Philadelphia: Elsevier; 202: Fig. 29.30, p. 1194.)*

any dislocation, whereas a scapular-Y view or an axillary view assesses angular deformity in an orthogonal plane. Many children are too uncomfortable to tolerate an axillary view; thus, in this case, a Velpeau axillary can be obtained while the arm remains in a sling. SH I injuries do not require reduction because they have excellent remodeling capacity, and simple immobilization in a sling for 2-3 weeks is sufficient. Metaphyseal fractures usually do not need reduction unless the angulation is >50 degrees. In general, sling immobilization is all that is required. SH II fractures with <30 degrees of angulation and <50% displacement are managed in a sling. Displaced fractures are treated with closed reduction and further stabilization if unstable. Occasionally, open reduction is required because of button-holing of the fracture spike through the deltoid or interposition of the tendon of biceps. The majority of longitudinal growth (80%) of the limb comes from the proximal humeral physis. Additionally, the glenohumeral joint is capable of a large amount of motion. As such, this area is extremely tolerant to deformity. Indications for open reduction are rare. However, as adolescents approach adulthood, these fractures will remodel less.

CLAVICULAR FRACTURES

Neonatal fractures occur as a result of direct trauma during birth, most often through a narrow pelvis or following shoulder dystocia. They can be missed initially and can appear with pseudoparalysis. Childhood fractures are usually the result of a fall on the affected shoulder or direct trauma to the clavicle. The most common site for fracture is the junction of the middle and lateral third clavicle. Tenderness over the clavicle will make the diagnosis. *A thorough neurovascular examination is important to diagnose any associated brachial plexus injury.* Biceps function is critical to assess, as it is a prognostic indicator for future function.

An AP radiograph of the clavicle demonstrates the fracture and can show overlap of the fragments. Physeal injuries occur through the medial or lateral growth plate and are sometimes difficult to differentiate from dislocations of the acromioclavicular or sternoclavicular joint. Further imaging such as a CT scan may be necessary to further define the injury. Posterior medial clavicular physeal injuries are particularly problematic due to their proximity to the great vessels and the trachea. Closed versus open reduction with a cardiac/thoracic team on standby is necessary. This can be delayed if there is no sign of vascular or respiratory compromise.

The treatment of most clavicle fractures consists of an application of a figure-of-8 clavicle strap or a simple sling. A figure-of-8 strap will extend the shoulders and minimize the amount of overlap of the fracture fragments. Evidence exists for adults that fractures that are shortened or displaced result in strength loss of the shoulder without anatomic reduction and fixation. Many centers are extending that indication to older adolescents; however, a 2019 report suggests similar satisfaction and outcomes with less complications in nonoperatively treated adolescent clavicle fractures when compared with operatively treated injuries. If a fracture is open, tenting the skin, or resulting in neurovascular compromise, surgery is indicated. The physeal fractures are treated with simple sling immobilization without any reduction attempt. Often, anatomic alignment is not achieved, nor is it necessary. Clavicle fractures heal rapidly, typically in 3-6 weeks. A palpable mass of callus is usually visible in thin children, and this remodels satisfactorily in 6-12 months. Complete restoration of shoulder motion and function is uniformly achieved.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

724.4 Lower Extremity Fractures

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

HIP FRACTURES

Hip fractures in children account for <1% of all pediatric fractures. These injuries result from high-energy trauma and can be associated with injury to the chest, head, or abdomen. Treatment of hip fractures in children is associated with a complication rate of up to 60%, including an overall avascular necrosis rate of 50% and a malunion rate of up to 30%. The unique blood supply to the femoral head accounts for the high rate of avascular necrosis. Fractures are classified by the Delbet classification as transphyseal separations, transcervical fractures, cervicotrochanteric fractures, and intertrochanteric fractures. The management principles include urgent anatomic reduction (either open or closed), stable internal fixation (avoiding the physis if possible), and

spica casting if the child is younger. Urgent management has been associated with a lower rate of avascular necrosis and superior overall outcomes. Capsular decompression also has been advocated as decreasing overall pressure on the epiphyseal vessels and has been demonstrated experimentally; the clinical results, however, remain mixed.

FEMORAL SHAFT FRACTURES

Fractures of the femur in children are common. All age groups, from early childhood to adolescence, can be affected. The mechanism of injury varies from low-energy twisting type injuries to high-velocity injuries in vehicular accidents. *Femur fractures in children younger than age 2 years should raise concern for child abuse.* A thorough physical examination is necessary to rule out other injuries and assess the neurovascular status. In the case of high-energy trauma, any signs of hemodynamic instability should prompt the examiner to look for other sources of bleeding. AP and lateral radiographs of the femur demonstrate the fracture. An AP radiograph of the pelvis is obtained to rule out any associated pelvic fracture. Treatment of shaft fractures varies with the age group, as described in Table 724.3.

PROXIMAL TIBIA FRACTURES

Proximal tibia fractures can be physeal injuries, metaphyseal injuries, or avulsion injuries of the tibial spine or tubercle. Physeal injuries can be either isolated or as part of tibial tubercle fracture. If the distal segment is displaced posteriorly the trifurcation of the popliteal vessels may be involved. Careful neurovascular examination is warranted both pre- and postreduction. Anatomic reduction and pin fixation is preferred with unstable fractures or displaced SH III or IV fractures.

Proximal tibial metaphyseal fractures, or the Cozen fracture, are most common in the 3- to 6-year-old age group. They may result in a late valgus deformity even if anatomically reduced. This deformity tends to remodel within 1-2 years but can cause great distress to parents and treating clinicians.

Tibial eminence fractures are fractures of the bony prominence that is the attachment of the anterior cruciate ligament. The mechanism of injury is similar to an anterior cruciate ligament tear in an adult. Displaced fractures require surgical reduction and fixation. This may be done either open or arthroscopically.

Tibial tubercle fractures are common in patients with Osgood-Schlatter syndrome. Care must be taken to observe for compartment syndrome as the injury is associated with injury of the recurrent anterior tibial artery. The injury may be treated nonoperatively if the fracture is displaced <2 mm and the patient has no extensor lag (rare). Open reduction and internal fixation is preferred otherwise.

TIBIA AND FIBULA SHAFT FRACTURES

The tibia is the most commonly fractured bone of the lower limb in children. This fracture generally results from a direct injury. Most tibial fractures are associated with a fibular fracture, and the mean age of presentation is 8 years. The child presents with pain, swelling, and deformity of the affected leg and is unable to bear weight. Distal neurovascular examination is important in assessment. The AP and lateral radiographs should include the knee and ankle. Closed reduction and immobilization are the standard method of treatment. Most fractures heal well, and children usually have excellent results. Open fractures need to undergo irrigation and debridement as well as antibiotic treatment. The tibia is a subcutaneous bone, so if severe soft tissue loss occurs with an open fracture, the patient may need plastic surgery consultation. Definitive external fixation versus internal fixation and simultaneous soft tissue coverage are alternative treatment strategies to minimize infection. Tibia fractures are associated with compartment syndrome. Vigilance is necessary to avoid disastrous outcomes associated with missed compartment syndrome. *Emergent fasciotomy is indicated as soon as compartment syndrome is diagnosed.* Several return trips to the operating room are often necessary to close, versus cover, the fasciotomy wounds.

TODDLER FRACTURES

Toddler fractures occur in young ambulatory children. The age range for this fracture is typically around 1-4 years (Fig. 724.13). The injury often occurs after a seemingly harmless twist or fall and is often unwitnessed. It is a result of a torsional injury. The children in this age group are usually unable to articulate the mechanism of injury clearly or to describe the area of injury well. The radiographs may show no fracture; in these cases, the diagnosis is made by physical examination. The classic symptom is refusal to bear weight, which can manifest as pulling up the affected extremity or florid display of protest. The other common sign is point tenderness at the fracture site. The AP and lateral views of the tibia-fibula might show a nondisplaced spiral fracture of the distal tibial metaphysis. An oblique view is often helpful because the fracture line may be visible in only one of the three views. Often the fracture

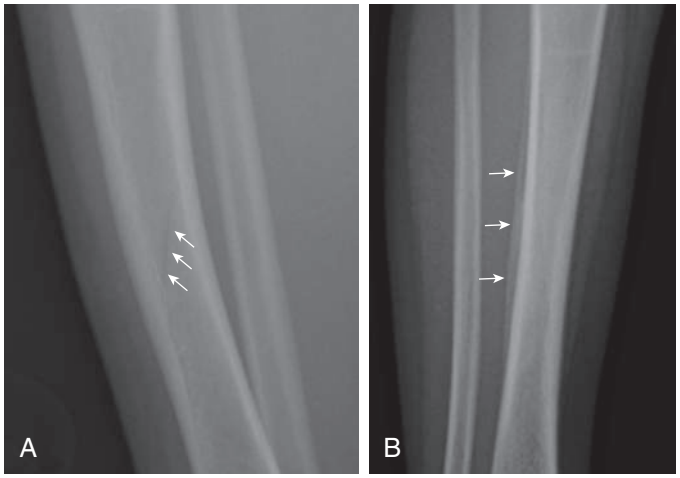

Fig. 724.13 Toddler's fracture of the tibia in a 2-yr-old child presenting with a limp and no history of trauma. **A,** Lateral radiograph of the lower leg shows a subtle, nondisplaced, oblique fracture through the tibial shaft *(arrows).* **B,** Anteroposterior radiograph obtained 10 days later shows healing, with subperiosteal new bone formation along the tibial shaft *(arrows). (From Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.117, p. 256.)*

Table 724.3 Femoral Shaft Fracture: Treatment Options by Age

TREATMENT OPTIONS	0-2 YR	3-5 YR	6-10 YR	>11 YR
Spica cast	x	x		
Traction and spica cast		x	x	x
Intramedullary rod		x	x	x
External fixator		x*	x*	x*
Screw or plate		x	x	x

*Open fracture.
Modified from Wells L. Trauma related to the lower extremity. In: Dormans JP, ed. *Pediatric Orthopaedics: Core Knowledge in Orthopaedics.* Philadelphia: Mosby; 2005:93.

line is not visualized until 2-3 weeks later, when periosteal reaction and resorption at the fracture site allow better visualization. Inflammatory markers may be ordered to rule out infectious processes if the diagnosis is in doubt. Bone scans were employed in the past but impart a large amount of radiation to the child. The fracture can be safely treated with a below-knee cast or a controlled ankle motion (CAM) walking boot for approximately 3 weeks.

TRIPLANE AND TILLAUX FRACTURES

Triplane and Tillaux fracture patterns occur at the end of the growth period and are based on relative strength of the bone-physis junction and asymmetric closure of the tibial physis. The triplane fractures are so named because the injury has coronal, sagittal, and transverse components (Fig. 724.14). The Tillaux fracture is an avulsion fracture of the anterolateral aspect of the distal tibial epiphysis. Radiographs and further imaging with CT and three-dimensional reconstructions are necessary to analyze the fracture geometry. The triplane fracture involves the articular surface and hence anatomic reduction is necessary. The reduction is further stabilized with internal fixation. The Tillaux fracture is treated by closed reduction. Open reduction is recommended if a residual intraarticular step-off persists.

METATARSAL FRACTURES

Metatarsal fractures are common in children. They usually result from direct trauma to the dorsum of the foot. High-energy trauma or multiple fractures of the metatarsal base are associated with significant swelling. A high index for compartment syndrome of the foot must be maintained and compartment pressures must be measured if indicated. Diagnosis is obtained by AP, lateral, and oblique radiographs of the foot. Most metatarsal fractures can be treated by closed methods in a below-knee cast or walking boot. Weight-bearing is allowed as tolerated. The Jones fracture of the proximal fifth metatarsal is an exception as it lies at a watershed area of vascular supply and thus has an increased risk of nonunion. Patients with Jones fractures should initially be nonweightbearing and should be referred to an orthopedics specialist. Displaced fractures can require closed or open reduction with internal fixation. Percutaneous, smooth Kirschner wires (K-wires) generally provide sufficient internal fixation for these injuries.

TOE PHALANGEAL FRACTURES

Fractures of the lesser toes are common and are usually secondary to direct blows. They commonly occur when the child is barefoot. The toes are swollen, ecchymotic, and tender. There may be a mild deformity. Diagnosis is made radiographically. Bleeding suggests the possibility of an open fracture. The lesser toes usually do not require closed reduction unless significantly displaced. If necessary, reduction can usually be accomplished with longitudinal traction on the toe. Casting is not usually necessary. Buddy taping of the fractured toe to an adjacent stable toe usually provides satisfactory alignment and relief of symptoms. Crutches and heel walking may be beneficial for several days until the soft tissue swelling and the discomfort decrease.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

724.5 Operative Treatment of Fractures

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

Surgery is required for 4–5% of pediatric fractures. The common indications for operative treatment in children and adolescents include displaced physeal fractures, displaced intraarticular fractures, unstable fractures, multiple injuries, open fractures, failure to achieve adequate reduction in older children, failure to maintain an adequate reduction, and certain pathologic fractures.

The aim of operative intervention is to obtain anatomic alignment and relative stability. Rigid fixation is not necessary as it is in adults for early mobilization. The relatively stable construct can be supplemented with external immobilization such as a cast, splint, or CAM walking boot. SH types III and IV injuries require anatomic alignment, and if they are unstable, internal fixation is used (smooth K-wires, preferably avoiding the course across the growth plate). Multiple closed reductions of an epiphyseal fracture are contraindicated because they can cause permanent damage to the physis.

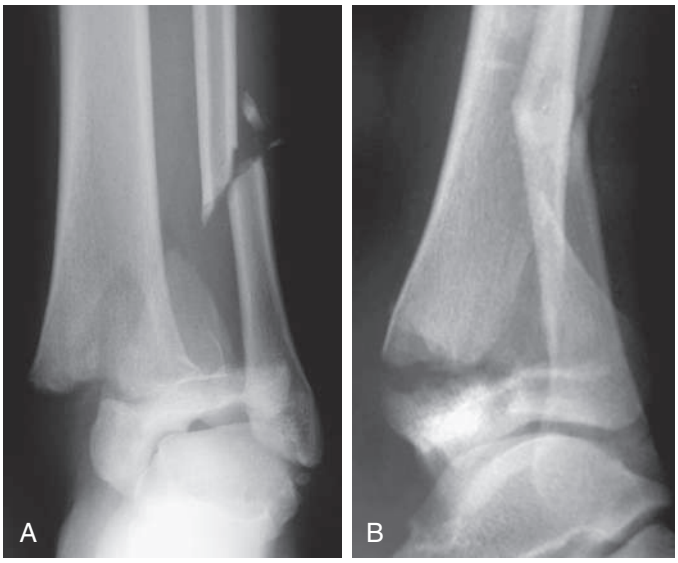

Fig. 724.14 The triplane fracture is a transitional fracture: anteroposterior (A) and lateral (B) radiographs. *(From Dormans JP. Pediatric Orthopedics: Introduction to Trauma. Philadelphia: Mosby; 2005:38.)*

Table 724.4 Common Indications for External Fixation in Pediatric Fractures

Grades II and III open fractures
Fractures associated with severe burns
Fractures with soft tissue loss requiring free flaps or skin grafts
Fractures requiring distractions such as those with significant bone loss
Unstable pelvic fractures
Fractures in children with associated head injuries and spasticity
Fractures associated with vascular or nerve repairs or reconstruction

SURGICAL TECHNIQUES

It is important to take great care with soft tissues and skin. The other indications for open reduction and internal fixation are unstable fractures of the spine, ipsilateral fractures of the femur and tibia, neurovascular injuries requiring repair, and open fractures. Closed reduction and minimally invasive fixation are specifically used for supracondylar fractures of the distal humerus and most phalangeal fractures. Failure to obtain anatomic alignment by closed means is an indication for an open reduction. Percutaneous techniques such as intramedullary fixation and minimally invasive plate osteosynthesis are increasingly popular as well.

As children become older, surgical techniques become more similar to adult techniques. The classic example of this is the femoral shaft fracture. Newborns may be treated with a soft dressing or Pavlik harness; young children may have a spica cast; older children will often be treated with flexible nails. Adolescents will frequently be treated with rigid intramedullary fixation similar to their adult counterparts.

Table 724.4 summarizes the main indications for external fixation. The advantages of external fixation include rigid immobilization of the fractures, access to open wounds for continued management, and easier patient mobilization for treatment of other injuries and transportation for diagnostic and therapeutic procedures. The majority of

complications with external fixation are pin tract infections, chronic osteomyelitis, and refractures after pin removal.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

724.6 Complications of Fractures in Children

Jason B. Anari, Alexandre Arkader, and Lawrence Wells

Complications of fractures in children can be categorized as (1) complications of the injury itself, (2) complications of treatment, and (3) late complications resulting from growth disturbance or deformity.

COMPLICATIONS RESULTING FROM INJURY

Growth arrest is possible in physeal fractures, particularly widely displaced physeal fractures about the distal femur, proximal tibia, or distal ulna. Fractures about the hip may cause **avascular necrosis** or premature physeal closure, particularly when the fracture involves the proximal femoral physis. Unacceptable alignment may cause loss of motion or limb malalignment. Fracture malunion may cause cosmetically unappealing bumps or curves in the limb, and at times functional impairment. **Compartment syndrome** can occur, particularly in diaphyseal tibia fractures or high energy or open both bone forearm fractures. Supracondylar humerus fractures, distal femur fractures, and proximal tibia fractures may result in neurovascular compromise. Nonunions are rare in children but can be seen with intraarticular fractures, such as distal humerus lateral condyle fractures. Malunions or missed Monteggia fracture dislocations about the elbow can cause permanent stiffness and loss of function if the deformity is not corrected. Displaced intraarticular fractures can result in posttraumatic arthritis and early joint degeneration. Open fractures can result in infection and osteomyelitis if inadequately treated. Older children with severe injuries of the lower extremity can be vulnerable to **deep vein thrombosis**.

COMPLICATIONS OF TREATMENT

Treatment may complicate fractures. Cast immobilization can result in **cast ulcers**, either from inadequate padding of bony prominences or from patients placing objects in the cast. Casts that are too tight can cause neurovascular compromise and compartment syndrome. Patients can get cast saw burns from using cast saws that are too dull to remove the cast. Safe operation of a cast saw requires monitoring of blade temperature. The saw blade should be intermittently cooled by taking a break to avoid overheating and thermal injury to the skin. Improperly placed casts can promote fracture displacement and malunion. Surgical treatment can be complicated by blood loss, neurovascular compromise, iatrogenic physeal damage, and hardware complications such as infection or hardware failure. Symptomatic hardware may require later removal.

LATE COMPLICATIONS OF TRAUMA

Late effects of trauma can be from partial or complete closure of the physis or malunion of the fracture. This can lead to limb angular deformity, shortening, or incongruency. Angular deformities can be treated by hemiepiphysiodesis or osteotomy. Joint incongruency may be a very difficult problem to deal with and may ultimately lead to early degenerative joint disease. Reflex sympathetic dystrophy is another poorly understood late effect of trauma but can be debilitating. Distal radius fractures have an above average rate of reflex sympathetic dystrophy relative to other injuries. Physical and occupational therapists are very helpful in managing this condition. Limited evidence exists that vitamin C may be useful in the acute setting of high-risk injuries to prevent this complication.

Chapter 725 Osteomyelitis

Samir S. Shah

Osteomyelitis, or infection of the bone, may be classified as acute or chronic. These clinical definitions correspond with treatment recommendations. **Acute osteomyelitis** is defined as the diagnosis of bone infection within 4 weeks after onset of clinical signs or symptoms in a previously uninfected bone. **Chronic osteomyelitis** is defined as a protracted and indolent disease process with presence of a sequestrum or relapse of infection at the same site following apparently successful treatment; sequestra may arise as a complication of treated or untreated acute hematogenous osteomyelitis.

ETIOLOGY

Bacteria are the most common pathogens in acute skeletal infections. *Staphylococcus aureus* (see Chapter 227.1) is the most common infecting organism in osteomyelitis among all age groups, including newborns. The prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) as a cause of osteomyelitis varies substantially by region.

Group B streptococcus (see Chapter 230) and gram-negative enteric bacilli (*Escherichia coli,* see Chapter 246) are prominent pathogens in neonates; group A streptococcus (see Chapter 229) constitutes <10% of all cases in this group. After 6 years of age, most cases of osteomyelitis are caused by *S. aureus,* group A streptococci, or *Pseudomonas aeruginosa* (see Chapter 251.1). Cases of *Pseudomonas* infection are related almost exclusively to puncture wounds of the foot, with direct inoculation of *P. aeruginosa* from the foam padding of the shoe into bone or cartilage, which develops as osteochondritis. *Salmonella* spp. (see Chapter 244) and *S. aureus* are the two most common causes of osteomyelitis in children with sickle cell disease (see Chapter 511.1). *Streptococcus pneumoniae* (see Chapter 228) most commonly causes osteomyelitis in children younger than 24 months of age and in children with sickle cell disease, but its frequency has declined because of pneumococcal conjugate vaccines. *Bartonella henselae* (see Chapter 255) can cause osteomyelitis of any bone but is most often seen in pelvic and vertebral bones.

Kingella kingae (see Chapter 239) is the second most common cause of osteomyelitis in children younger than 4 years of age. The organism causes osteomyelitis, spondylodiscitis, and septic arthritis (see Chapter 726) in this age group, especially when there is a subacute presentation. *K. kingae* can be difficult to detect unless polymerase chain reaction (PCR) testing is used.

Infection with atypical mycobacteria (see Chapter 263), *S. aureus,* or *Pseudomonas* can occur after penetrating injuries. These organisms, as well as coagulase-negative staphylococci or gram-negative enteric bacteria, may cause bone infection related to implanted materials such as orthopedic hardware. Fungal infections usually occur as part of multisystem disseminated disease; *Candida* (see Chapter 280) osteomyelitis sometimes complicates fungemia in neonates with or without indwelling vascular catheters. Blastomycosis causes multiple bone lesions in endemic areas.

EPIDEMIOLOGY

The median age of children with musculoskeletal infections is approximately 6 years. Bone infections are more common in males than females.

Minor closed trauma is a common preceding event in cases of osteomyelitis, occurring in approximately 30% of patients. Impaired host defenses (e.g., hemoglobinopathies, human immunodeficiency virus, or chronic granulomatous disease) also increase the risk of skeletal infection. Table 725.1 lists other risk factors.

Table 725.1 Microorganisms Isolated from Patients with Osteomyelitis and Their Clinical Associations

MOST COMMON CLINICAL ASSOCIATION	MICROORGANISM
Frequent microorganism in any type of osteomyelitis	*Staphylococcus aureus* (susceptible or resistant to methicillin)
Associated with septic arthritis, spondylodiscitis, long or unusual bones, age <4 yr, mild symptoms	*Kingella kingae*
Foreign body–associated infection	Coagulase-negative staphylococci, other skin flora, atypical mycobacteria, fungi
Common in nosocomial infections	*Enterobacteriaceae, Pseudomonas aeruginosa, Candida* spp.
Decubitus ulcer or ulceration associated with sensory autonomic neuropathies	*S. aureus*, streptococci, gram-negative enterics, and/or anaerobic bacteria; polymicrobial infections are common
Sickle cell disease	*Salmonella* spp., *S. aureus*, or *Streptococcus pneumoniae*
Exposure to kittens	*Bartonella henselae*
Human or animal bites	*Pasteurella multocida* or *Eikenella corrodens*
Immunocompromised patients	*Aspergillus* spp., *Candida albicans*, or *Mycobacteria* spp.
Populations in which tuberculosis is prevalent	*Mycobacterium tuberculosis*
Populations in which these pathogens are endemic	*Brucella* spp., *Coxiella burnetii*, fungi found in specific geographic areas (coccidioidomycosis, blastomycosis, histoplasmosis)

Modified from Lew DP, Waldvogel FA. Osteomyelitis. *Lancet.* 2004;364:369–379.

PATHOGENESIS

Bacteria reach bone matrices most commonly via hematogenous spread (primary bacteremia). Less common mechanisms include direct inoculation (i.e., trauma or procedures) or contiguous spread from infection of adjacent sites such as synovial fluid or soft tissues.

The unique anatomy and circulation of the ends of long bones result in the predilection for localization of bloodborne bacteria. In the metaphysis, nutrient arteries branch into non-anastomosing capillaries under the physis, which make a sharp loop before entering venous sinusoids draining into the marrow. Low-velocity blood flow in this area predisposes to bacterial invasion. Once a bacterial focus is established, phagocytes migrate to the site and produce an inflammatory exudate (metaphyseal abscess). The generation of proteolytic enzymes, toxic oxygen radicals, and cytokines results in decreased oxygen tension, decreased pH, osteolysis, and tissue destruction. As the inflammatory exudate progresses, pressure increases spread through the porous metaphyseal space via the Haversian system and Volkmann canals into the subperiosteal space. Purulence beneath the periosteum may lift the periosteal membrane of the bony surface, further impairing blood supply to the cortex and metaphysis.

In newborns and young infants, transphyseal blood vessels connect the metaphysis and epiphysis, so it is common for pus from the metaphysis to enter the joint space. This extension through the physis has the potential to result in abnormal growth and bone or joint deformity. During the latter part of the first year of life, the physis forms, obliterating the transphyseal blood vessels. Joint involvement can occur where the metaphysis is intraarticular (hip, ankle, shoulder, and elbow), and subperiosteal pus ruptures into the joint space.

In later childhood, the periosteum becomes more adherent, favoring pus to decompress through the periosteum. Once the growth plate closes in late adolescence, hematogenous osteomyelitis more often begins in the diaphysis and can spread to the entire intramedullary canal. Septic arthritis contiguous with a site of osteomyelitis is also seen in older children with *S. aureus* osteomyelitis, which may be related to simultaneous hematogenous inoculation of bone and joint space. Septic arthritis may also result from infected material entering the synovial space from an adjacent osteomyelitis.

CLINICAL MANIFESTATIONS

The earliest signs and symptoms of acute osteomyelitis, often subtle and nonspecific, generally depend on patient age. Neonates might exhibit *pseudoparalysis* or pain with movement of the affected extremity (e.g., diaper changes). Half of neonates do not have fever and might not appear ill. Older infants and children are more likely to have pain, fever, and localizing signs such as edema, erythema, and warmth. With involvement of the lower extremities, limp or refusal to walk is seen in approximately half of patients.

Focal tenderness over a long bone can be an important finding. Local swelling and redness with osteomyelitis suggests spread of infection beyond the metaphysis and into the subperiosteal space, representing a secondary soft tissue inflammatory response. Pelvic osteomyelitis can manifest with subtle findings such as hip, thigh, groin, or abdominal pain. Vertebral osteomyelitis typically presents as back pain with or without tenderness to palpation over the vertebral processes (Chapter 720.7).

Long bones are principally involved in osteomyelitis (Table 725.2); the femur and tibia are equally affected and together constitute almost half of all cases. The bones of the upper extremities account for 25% of all cases. Flat bones are less commonly affected.

Usually, a single site of bone or joint is involved, although multifocal osteomyelitis may be noted in up to 20% of children with *S. aureus* infections. In neonates, two or more bones are involved in almost half of the cases. Multifocal disease may also be seen with tuberculosis, cat-scratch disease, and brucellosis. Clinical manifestations of chronic infection are more indolent, and fever is unusual. Children with *subacute* symptoms and focal findings in the metaphyseal area (usually of the tibia) might have a **Brodie abscess**, with a well-defined radiographic lucency and surrounding reactive bone. The contents of Brodie abscesses are often sterile, but *S. aureus* is often the most common pathogen (Fig. 725.1).

Some patients with osteomyelitis due to *S. aureus* infection develop a deep venous thrombosis adjacent to the affected bone that can produce septic pulmonary emboli; these patients are often critically ill. Uncomplicated disease should be distinguished from more complicated osteomyelitis (Table 725.3).

DIAGNOSIS

The diagnosis of osteomyelitis begins with clinical suspicion and requires appropriate cultures and imaging studies. *Blood cultures should be performed in all suspected cases before administration of antibiotic therapy.* Blood cultures are positive in ~30% of patients. Blood culture contamination rates are low, generally <5%; microbes such as coagulase-negative staphylococci, α-streptococci (except *S. pneumoniae* and *S. anginosus* group), *Bacillus* species, *Corynebacterium*, and *Cutibacterium* are usually considered contaminants when identified in blood culture from a patient with acute or subacute hematogenous osteomyelitis.

Depending on the results of imaging studies, aspiration or biopsy of bone or subperiosteal abscess for Gram stain, standard bacterial culture, PCR for *K. kingae,* and possibly bone histology provides the optimal specimen for culture to confirm the diagnosis and significantly increases the yield compared with blood culture alone. These specimens, which identify a causative bacteria in ~60% of cases, are often obtained by the interventional radiologist or at the time of surgical

Table 725.2 Site of Involvement in Acute Hematogenous Osteomyelitis

SITE	%
TUBULAR BONE	
Femur	25
Tibia	24
Humerus	13
Phalanges	5
Fibula	4
Radius	4
Ulna	2
Metatarsal	2
Clavicle	0.5
Metacarpal	0.5
CUBOIDAL BONE	
Calcaneus	5
Talus	0.8
Carpals	0.5
Cuneiform	0.5
Cuboid	0.3
IRREGULAR BONE	
Ischium	4
Ilium	2
Vertebra	2
Pubis	0.8
Sacrum	0.8
FLAT BONE	
Skull	1
Rib	0.5
Sternum	0.5
Scapula	0.5
Maxilla	0.3
Mandible	0.3

Data from Krogstad P. Osteomyelitis. In: Cherry JD, Harrison GJ, Kaplan SL, et al., eds. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*, 8th ed. Philadelphia: Elsevier, 2019: Table 55.2.

drainage by the orthopedic surgeon. Direct inoculation of clinical specimens into aerobic blood culture bottles can improve the recovery of *K. kingae,* particularly if held for 1 week. PCR is the most sensitive technique to detect *K. kingae*, even up to 6 days after antibiotics are initiated. Anaerobic, fungal, and mycobacterial cultures may be performed if risk factors are identified by history or physical examination.

There are no specific laboratory tests for osteomyelitis. Laboratory evaluation of children with suspected osteomyelitis may include a complete blood count and C-reactive protein (CRP). A complete blood count may contribute to assessment of infection severity (e.g., anemia, thrombocytopenia) and suggest an alternative diagnosis (e.g., hematologic malignancy). The initial CRP is elevated in most children with acute osteomyelitis. CRP is nonspecific and does not establish the diagnosis of osteomyelitis, but serial monitoring of an elevated CRP may be of value in assessing response to therapy or identifying complications. Erythrocyte sedimentation rate (ESR) is no longer routinely recommended in cases of acute hematogenous osteomyelitis. Data on procalcitonin are insufficient.

RADIOGRAPHIC EVALUATION

Radiographic studies play a crucial role in the evaluation of osteomyelitis. Conventional radiographs and MRI are the primary modalities. Ultrasonography, CT, and radionuclide studies can also contribute to establishing the diagnosis in selected cases.

Plain Radiographs

Within 72 hours of onset of symptoms of osteomyelitis, plain radiographs of the involved site using soft tissue technique and compared with the opposite extremity, if necessary, can show displacement of the deep muscle planes from the adjacent metaphysis caused by deep-tissue edema. Lytic bone changes are not visible on radiographs until 30–50% of the bony matrix is destroyed. Tubular long bones do not show lytic changes for 7-14 days after onset of infection. Infection in flat and irregular bones can take longer to appear. Radiographs in children with possible osteomyelitis are important to exclude other possible causes (e.g., fracture) of the presenting symptoms and signs.

Magnetic Resonance Imaging and Computed Tomography

MRI is more sensitive than CT or radionuclide imaging in acute osteomyelitis and is the best radiographic imaging technique for identifying abscesses and for differentiating between bone and soft tissue infection. MRI provides precise anatomic detail of subperiosteal pus and accumulation of purulent debris in the bone marrow and metaphyses for possible surgical intervention. In acute osteomyelitis, purulent debris and edema appear dark, with decreased signal intensity on T1-weighted images, with fat appearing bright (Figs. 725.2 and 725.3). The opposite is seen in T2-weighted images. The signal from fat can be diminished with fat-suppression techniques to enhance visualization. Gadolinium administration can also enhance MRI. Cellulitis and sinus tracts appear as areas of high signal intensity on T2-weighted images. Short tau inversion recovery (STIR) MRI is a rapid imaging modality for osteomyelitis (Fig. 725.4). MRI can also demonstrate contiguous or isolated septic arthritis, pyomyositis, or venous thrombosis. *Whole body rapid STIR MRI is an effective alternative to radionuclide imaging where multiple sites of infection are suspected or the site of infection cannot be clearly localized on exam.* CT can demonstrate osseous and soft tissue abnormalities and is ideal for detecting gas in soft tissues but has poor sensitivity for detecting the presence of osteomyelitis.

Radionuclide Studies

Radionuclide imaging, an alternative to MRI, may be useful if multiple foci are suspected. Technetium-99 (^{99m}Tc) methylene diphosphonate, which accumulates in areas of increased bone turnover, is the preferred agent for radionuclide bone imaging (three-phase bone scan). Any areas of increased blood flow or inflammation can cause increased uptake of ^{99m}Tc in the first and second phases, but osteomyelitis causes increased uptake of ^{99m}Tc in the third phase (4-6 hours). Three-phase imaging with ^{99m}Tc has excellent sensitivity (84–100%) and specificity (70–96%) in hematogenous osteomyelitis and can detect osteomyelitis within 24-48 hours after onset of symptoms. The sensitivity in neonates is much lower because of poor bone mineralization. Advantages include infrequent need for sedation and the ability to image the entire skeleton for detection of multiple foci. Disadvantages include exposure to radiation, inability to image surrounding soft tissues, and overall lack of detail, which limits the tests' utility for preoperative planning.

DIFFERENTIAL DIAGNOSIS

Distinguishing osteomyelitis from cellulitis or trauma (unintentional or abuse) may be difficult, particularly when the history is limited. Myositis or pyomyositis can also appear similar to osteomyelitis with fever, warm and swollen extremities, and limping; tenderness to palpation of the affected soft tissue area is generally more diffuse than noted in acute osteomyelitis. Myositis and pyomyositis may be isolated but are often found adjacent to an osteomyelitis on MRI. **Pyomyositis** is most often caused by *S. aureus,* followed by group A streptococcus. The pelvic muscles are a common site of pyomyositis and can mimic a pelvic osteomyelitis. MRI is the definitive

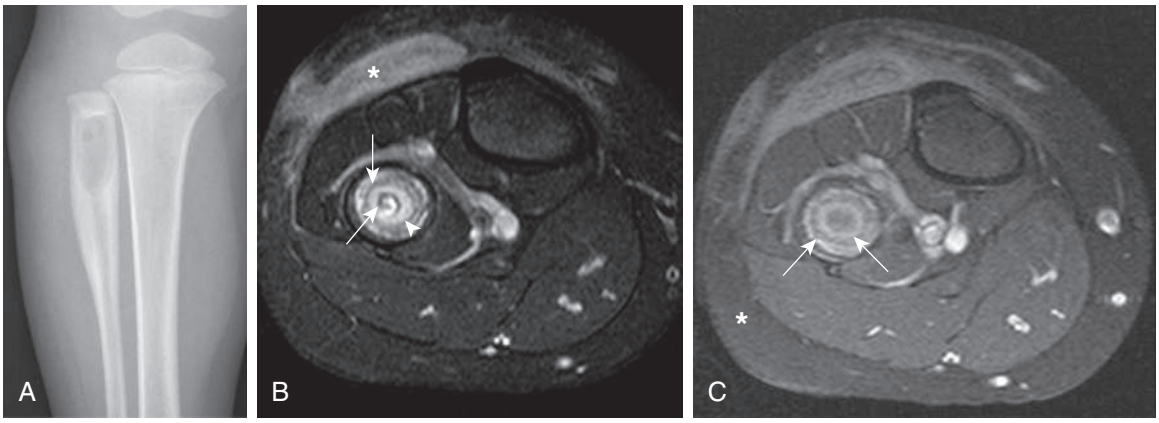

Fig. 725.1 A, Radiograph demonstrates a lytic lesion in the proximal fibula with laminated thick periostitis. Axial T2-weighted fat-saturated MR image (B) shows a layered appearance with intermediate signal *(arrowhead)* between inner and outer rims of lower signal intensity *(arrows)* and a more central hyperintense region. Also note the soft tissue phlegmon/early abscess formation *(asterisk)*. On an axial T1-weighted, fat-saturated, postgadolinium MR image (C), a rim of low signal sclerosis *(outer arrow)* surrounds an inner rim of enhancing granulation tissue *(inner arrow)*, which surrounds the nonenhancing abscess. *(From Kan JH, Meyers AB, Azouz EM. Musculoskeletal infections. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 137.17.)*

Table 725.3 Characteristics of Uncomplicated vs Complicated Osteomyelitis*

CHARACTERISTIC	UNCOMPLICATED	COMPLICATED
Sites of infection	Single bone	Two or more bones involved Additional soft tissue sites of infection beyond the bone (e.g., muscle [myositis or pyomyositis], pneumonia, and liver abscess)
Clinical response to medical and surgical treatment	Rapid (within 3-5 days), including signs of sepsis or septic shock	Slow, prolonged response, or lack of clinical response Need for more than one surgery for source control
Course of bacteremia when present	Rapid resolution of bacteremia (serial blood cultures become negative when obtained within 1-2 days after the initiation of therapy and source control)	Prolonged bacteremia (3 or more days), suggestive of uncontrolled infection/distant site(s) of infection
Acute sequelae of infection	None	Venous thrombosis or septic thrombophlebitis Endocarditis
Late sequelae of infection	No findings that suggest risk of physis injury or other short- or long-term osteoarticular sequelae of infection	Findings concerning for physeal injury with potential impacts on bone growth with long-term sequelae Presence of or concern for pathologic fracture

*This set of criteria is consensus based with primary focus on clinical findings and course. It may be reasonable to include additional laboratory tests such as the serum C-reactive protein (CRP) in making a determination of an uncomplicated vs complicated course. Concepts such as (1) rapid fall of the CRP concentration within 48 hr of initiation of treatment or (2) a 50% or more decline from peak CRP concentration within 3-5 days of admission or first surgical debridement may be considered. Further research into the various components and functionality of this definition, and any added utility of the CRP or other laboratory markers, will have value and is encouraged.

From Woods CR, Bradley JS, Chatterjee A, et al. Clinical practice guideline by the Pediatric Infectious Diseases Society of America: 2021 guideline on diagnosis and management of acute hematogenous osteomyelitis in pediatrics. *J Pediatric Infect Dis Soc.* 2021;10(8):801–844. Table 1.

study to identify and localize pelvic pyomyositis (Fig. 725.5). An **iliopsoas abscess** can manifest with thigh pain, limp, and fever and must be considered in the differential diagnosis of osteomyelitis. The iliopsoas abscess may be primary (hematogenous: *S. aureus*) or secondary to infection in adjacent bone *(S. aureus)*, kidney *(E. coli)* or intestine (*E. coli*, *Bacteroides* spp.). *Mycobacterium tuberculosis* has been reported in patients with HIV infection. Any child with negative x-ray imaging and a negative hip aspiration who presents with fever, limp, and elevated inflammatory markers should be evaluated for pyomyositis.

Appendicitis, urinary tract infection, and gynecologic disease are among the conditions in the differential diagnosis of pelvic osteomyelitis. Children with leukemia commonly have bone pain or joint pain as an early symptom. Neuroblastoma with bone involvement may be mistaken for osteomyelitis. Primary bone tumors need to be considered, but fever and other signs of illness are generally absent except in Ewing sarcoma. In patients with sickle cell disease, distinguishing bone infection from infarction may be challenging.

Chronic recurrent multifocal osteomyelitis (CRMO) (also called chronic nonbacterial osteomyelitis, CNO) is a nonpyrogenic, sterile inflammatory bone disease that is considered an autoinflammatory disorder (see Chapter 204). It may also be associated with a family history of autoimmune disease; the affected patient may have other inflammatory diseases such as Crohn disease, Sweet syndrome, psoriasis, and palmar plantar pustulosis. CRMO in children has many similarities with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO), seen in adults. CRMO also has similarities to Majeed syndrome, an autosomal recessive disorder with a microcytic dyserythropoietic anemia, and with a deficiency of interleukin-1 receptor antagonist (DIRA), an autosomal recessive autoinflammatory disease.

In contrast to infectious osteomyelitis, CRMO is multifocal, recurrent, and may involve bones not typical of osteomyelitis (spine, pelvis, clavicle, mandible, and calcaneus). Plain radiographs reveal osteolytic lesions or sclerosis; whole body STIR MRI imaging is the diagnostic study of choice (Fig. 725.6).

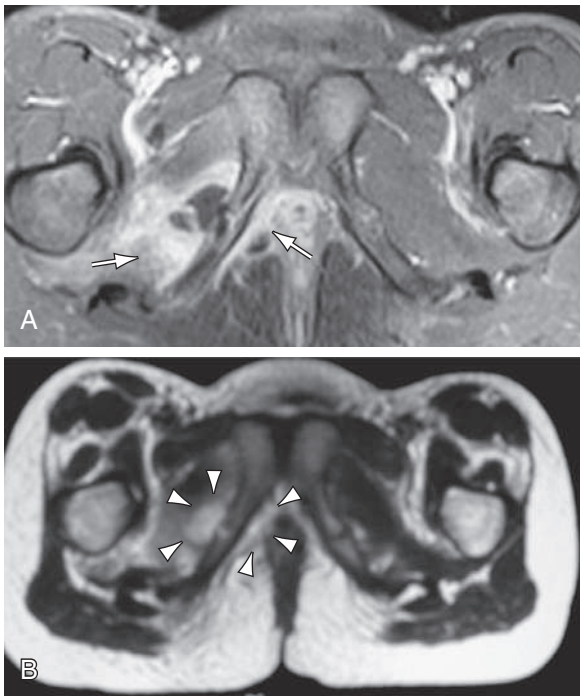

Fig. 725.2 MRI of an 8-year-old female with acute pelvic hematogenous osteomyelitis. **A,** Axial T1-weighted contrast-enhanced MRI with fat saturation reveals a nonenhancing fluid collection adjacent to the inflamed pubic synchondrosis. **B,** The fluid collection appears hyperintense on the corresponding T2-weighted image *(arrowheads)*. In addition, a contrast enhancement within the adjacent internal obturator muscle is seen *(arrow)*, indicating acute pelvic hematogenous osteomyelitis with complicating adjacent abscess formation and soft tissue inflammation. *(From Weber-Chrysochoou C, Corti N, Goetschel P, et al. Pelvic osteomyelitis: a diagnostic challenge in children. J Pediatr Surg. 2007;42:553–557.)*

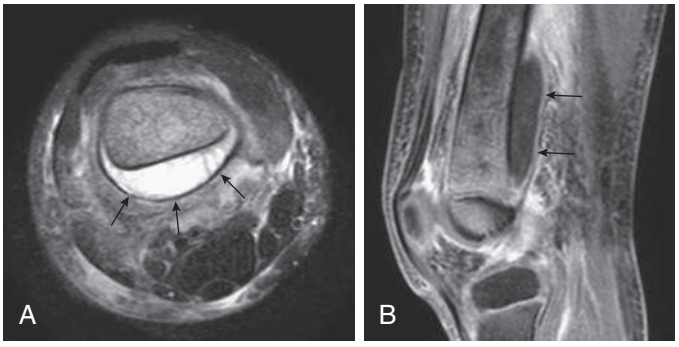

Fig. 725.3 Acute osteomyelitis of the distal femur in a 5-yr-old male. **A,** T2-weighted fat-saturated axial MRI shows a large subperiosteal abscess *(arrows)* at the posterior aspect of the femur. Increased signal is seen within the bone, and there is adjacent soft tissue edema. **B,** T1-weighted fat-saturated postgadolinium sagittal MRI shows the longitudinal extent of the subperiosteal abscess with enhancing wall *(arrows)*. *(From Kan JH, Azouz EM. Musculoskeletal infections. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 137.13.)*

Pain in CRMO is usually insidious and noted at night; fever is not always present. The mean age of onset is 10 years. The CRP may be elevated but is not as high as in bacterial osteomyelitis. Pain usually responds to nonsteroidal antiinflammatory drugs. Second-line treatments include systemic corticosteroids or tumor necrosis factor-α inhibitors.

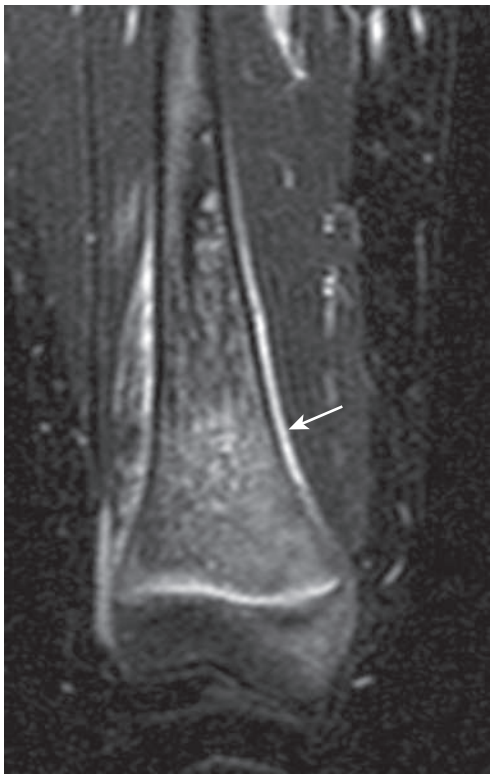

Fig. 725.4 Coronal STIR MR image demonstrates a salt-and-pepper appearance of marrow edema and periosteal reaction *(arrow)*. *(From Kan JH, Azouz EM. Musculoskeletal infections. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 137.14.)*

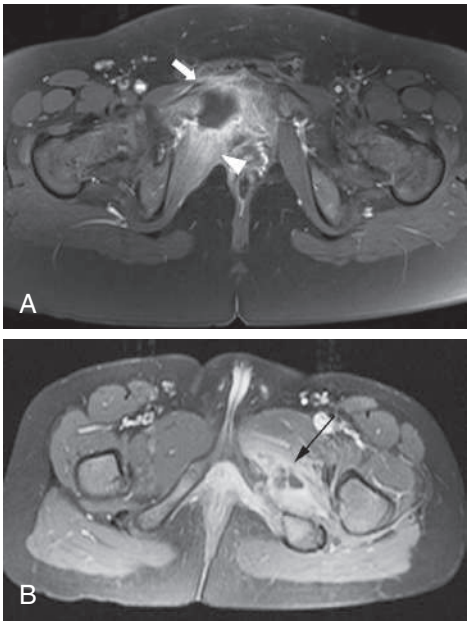

Fig. 725.5 **A,** Pelvic pyomyositis in a 10-yr-old male presenting with limping. Pelvis MRI demonstrates an avid contrast enhancement of the internal obturator muscle *(arrowhead)* with an abscess on T1-weighted fat-saturated postcontrast axial image *(arrow)*. **B,** Pyomyositis in a 7-yr-old male with left pelvic pain and fever. Axial T1 fat-saturated postcontrast image through the inferior ramus of the obturator ring demonstrates multiloculated, rim-enhancing fluid collections in the adductor muscles *(arrow)*, which is characteristic of pyomyositis. *(**A** from Bartoloni A, Gómez A, Pilar M, et al. Imaging of the limping child. Eur J Radiol. 2018;109:155–170. Fig 13; **B** from Pruthi S, Thapa MM. Infectious and inflammatory disorders. Magn Reson Imaging Clin North Am. 2009;17:423. Fig 7.)*



Fig. 725.6 MRI in a patient with chronic recurrent multifocal osteomyelitis. **A,** Whole body image showing multiple foci of osteomyelitis *(arrows)*, some of which are distributed symmetrically. **B,** Image of the ankle showing inflammatory metaphyseal and epiphyseal lesions. **C,** Image of the left femur showing involvement of the diaphysis with a soft tissue reaction. *(From Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C. Chronic recurrent multifocal osteomyelitis. Joint Bone Spine. 2011;78:555–560. Fig. 3, p. 557.)*

TREATMENT

Optimal treatment of skeletal infections requires collaborative efforts of pediatricians, orthopedic surgeons, and interventional radiologists. Obtaining a blood culture *before* antibiotics are given is essential. Most patients with osteomyelitis have an indolent, non–life-threatening condition, and in these circumstances antibiotics may be deferred until a decision about whether to obtain additional diagnostic cultures (periosteal abscess, bone) has been made. A short duration of antibiotic pretreatment (<48 hours) for osteomyelitis caused by *S. aureus* has minimal impact on culture yield from abscess or bone specimens. In critically ill patients, empirical antimicrobial therapy should be initiated without delay.

Antimicrobial Therapy

The initial empirical antimicrobial therapy is based on knowledge of likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations (Table 725.4). In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (100-200 mg/kg/24 hr divided q6hr IV), and a broad-spectrum cephalosporin, such as cefepime (100-150 mg/kg/24 hr divided q12hr IV), provide coverage for the methicillin-susceptible *S. aureus* (MSSA), group B streptococcus, and gram-negative bacilli. If methicillin-resistant *Staphylococcus* (MRSA) is suspected, clindamycin or vancomycin is substituted for nafcillin. If the neonate is a premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (gram-negative enteric, *Pseudomonas,* or *S. aureus*) or fungi (*Candida* spp.) should be considered. In older infants and children, the principal pathogens are *S. aureus, K. kingae,* and group A streptococcus.

Cefazolin (100-150 mg/kg/24 hr divided q6hr IV) or nafcillin (100-200 mg/kg/24 hr divided q6hr) is the agent of choice for parenteral treatment of osteomyelitis caused by MSSA and is the backbone of empirical treatment for acute hematogenous osteomyelitis. A major factor influencing the selection of empirical therapy is the rate of methicillin resistance among community *S. aureus* isolates. In areas where the prevalence of CA-MRSA is >10–20%, clindamycin (30-40 mg/kg/24 hr divided q6-8hr) or vancomycin (40-60 mg/kg/24 hr divided q6-8hr IV) should be used as empirical treatment. Clindamycin is often preferred over vancomycin when the rate of clindamycin resistance is low among community *S. aureus* isolates given the renal toxicity associated with vancomycin. Because β-lactams are superior to clindamycin and vancomycin for the treatment of MSSA, dual drug therapy in critically ill children should be continued until the causative organism is identified and susceptibilities are known. Rapid molecular diagnostic tests that can accurately differentiate MRSA from MSSA within hours of blood culture positivity can help to avoid prolonged exposure to multiple agents. Clindamycin is the best studied alternative therapy for susceptible isolates of MRSA and for MSSA when a β-lactam cannot otherwise be used.

Penicillin is first-line therapy for treating osteomyelitis caused by susceptible strains of *S. pneumoniae* and all group A streptococci. Cefotaxime or ceftriaxone is recommended for pneumococcal isolates with resistance to penicillin and for most *Salmonella* spp.

Special situations dictate deviations from the usual empirical antibiotic selection. In patients with sickle cell disease with osteomyelitis, gram-negative enteric bacteria *(Salmonella)* are common pathogens, as well as *S. aureus,* so a broad-spectrum cephalosporin such as cefepime (150 mg/kg/24 hr q8hr IV) is used in addition to clindamycin or vancomycin. Clindamycin is a useful alternative drug for patients allergic to β-lactam drugs. In addition to good antistaphylococcal activity, clindamycin has broad activity against anaerobes and is useful for treating infections secondary to penetrating injuries or compound fractures. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime, cefepime, or piperacillin-tazobactam, with or without an aminoglycoside. *K. kingae* responds to β-lactam antibiotics, including penicillin and cephalosporins, but some isolates produce a β-lactamase. Thus a first-generation cephalosporin (cefazolin) is a reasonable component of empirical therapy in children younger than 4 years of age. Although

Table 725.4 Antibiotic Choice and Duration of Therapy for Uncomplicated Pediatric Acute Hematogenous Osteomyelitis Caused by *Staphylococcus aureus*[*,†]

PATHOGEN	PARENTERAL THERAPY	ORAL CONVALESCENT THERAPY	DURATION[‡]
Staphylococcus aureus, methicillin susceptible	*Preferred:*[§] Cefazolin Semisynthetic penicillin,[#] e.g., oxacillin and nafcillin	*Preferred:* Cephalexin	3-4 weeks if uncomplicated
	Alternatives:[#] Clindamycin Vancomycin Ceftaroline	*Alternative:* Clindamycin	3-4 weeks if uncomplicated
S. aureus, methicillin resistant, susceptible to clindamycin	*Preferred:* Clindamycin	*Preferred:* Clindamycin	3-4 weeks if uncomplicated
	Alternatives: Vancomycin Daptomycin Ceftaroline Linezolid	*Alternatives:*[¶] Linezolid	No data
S. aureus, methicillin resistant, resistant to clindamycin	*Preferred:* Vancomycin	*Preferred:* Linezolid	No data
	Alternatives: Daptomycin Ceftaroline Linezolid	*Alternatives:* Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against *S. aureus*	No data

*Uncomplicated AHO is defined as the presence of infection in a single site with rapid clinical response to antimicrobial therapy (i.e., resolution of fever and marked improvement in clinical signs within 3-5 days), with no more than a single early surgical procedure required as source control for the infection. Complicated infections may require a longer duration of treatment than uncomplicated infections, particularly if multiple surgeries are needed to establish source control.

†Not all antibiotics listed have been prospectively evaluated in clinical trials of acute bacterial osteomyelitis. Prospective studies to evaluate the effectiveness of a range of antibiotic doses in various degrees of severity of uncomplicated and complicated osteomyelitis, with or without surgery, have not been performed, although retrospective data have been reported for many antibiotics in the treatment of pediatric osteomyelitis.

‡The suggested duration of therapy should be based on clinical course (pace of resolution of fever and clinical signs and symptoms, noting the need for surgical intervention[s] required, if any), supported by decline of inflammatory markers.

§Preferred and alternative agents are selected based on published data regarding in vitro activity, clinical efficacy, and safety. Agents are generally listed in order of preference.

#Many of the β-lactamase-stable penicillins cause significant phlebitis in peripheral veins with infusion; administration through a central venous catheter is preferred.

¶Alternative antibiotics that may display in vitro activity against *S. aureus* have not been evaluated prospectively in AHO. However, linezolid has been evaluated in prospective controlled clinical trials for invasive methicillin-resistant *S. aureus* nosocomial pneumonia in adults and is more likely to provide adequate therapy of invasive *S. aureus* AHO, compared with trimethoprim-sulfamethoxazole, which is not recommended for children with AHO by the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children.

AHO, Acute hematogenous osteomyelitis.

From Woods CR, Bradley JS, Chatterjee A, et al. Clinical practice guideline by the Pediatric Infectious Diseases Society of America: 2021 guideline on diagnosis and management of acute hematogenous osteomyelitis in pediatrics. *J Pediatric Infect Dis Soc.* 2021;10(8):801–844. Table 4.

the efficacy of treating osteomyelitis caused by *B. henselae* is uncertain, azithromycin plus rifampin may be considered.

When the pathogen is identified and antibiotic susceptibilities are determined, appropriate adjustments should be made to use the antibiotic with the narrowest spectrum, lowest adverse effect profile, and most favorable host tolerance. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the initially selected antibiotic or an agent with a comparable spectrum of coverage. This selection is more complicated owing to the presence of MRSA isolates in the community. If a pathogen is not identified and a patient's condition is not improving, repeat aspiration or biopsy and the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and clinical course. Most acute cases of osteomyelitis, including those caused by *S. aureus,* can be treated with antibiotics for 21-28 days provided that the patient shows prompt resolution of signs and symptoms (within 5-7 days) and the CRP has normalized; a total of 4-6 weeks of therapy may be required for those with substantially slower resolution of symptoms or normalization of CRP. For group A streptococcus, *S. pneumoniae,* or *Haemophilus influenzae* type b, treatment duration may be shorter. A total of 7-10 postoperative days of treatment is adequate for *Pseudomonas* osteochondritis from a foot puncture wound, when curettage of infected tissue has been performed. Immunocompromised patients generally require prolonged courses of therapy, as do patients with mycobacterial or fungal infection.

For typical cases, antimicrobial agents may be changed from intravenous to oral administration when a patient's condition clearly has improved, the child is afebrile, and bacteremia has resolved. Oral cephalexin (75-100 mg/kg/24 hr divided q8hr) may be used for susceptible staphylococcal or streptococcal infections. Oral clindamycin (30-40 mg/kg/24 hr divided q6-8hr) can be used to complete therapy for children with clindamycin-susceptible CA-MRSA or for patients who are seriously allergic or cannot tolerate β-lactam antibiotics. The oral regimen decreases the risk of complications related to prolonged intravenous therapy, is more comfortable for patients, and permits treatment outside the hospital if adherence to treatment can be ensured. Outpatient intravenous antibiotic therapy via a central venous catheter can be used for completing therapy at home for (1) patients unable or unwilling to take oral medication; (2) patients with underlying medical conditions that make enteral

drug absorption unreliable; (3) patients without comparable oral antibiotic options (e.g., resistant bacteria, drug allergy); and (4) patients with disseminated infection (e.g., endocarditis, pulmonary septic emboli). Catheter-related complications, including infection or mechanical problems, can lead to readmission or emergency department visits.

In children with venous thrombosis complicating osteomyelitis, administration of anticoagulants under the supervision of a hematologist until the thrombus has resolved is a generally accepted practice, although high-quality evidence to support this practice is lacking; antibacterial therapy alone may be sufficient.

Surgical Therapy

When frank pus is obtained from subperiosteal or metaphyseal aspiration or is suspected based on MRI findings, a surgical drainage procedure is usually indicated. Surgical intervention is also often indicated after a penetrating injury and when a retained foreign body is possible. In selected cases, catheter drainage performed by an interventional radiologist is adequate.

Treatment of chronic osteomyelitis consists of surgical removal of sinus tracts and sequestrum, if present. Surgical implantation of antibiotics is not generally recommended. Antimicrobial therapy, typically administered orally, is continued for several months or longer until clinical and radiographic findings suggest that healing has occurred. Normalization of CRP and ESR is expected in successful treatment of chronic osteomyelitis but does not by itself indicate clearance of the underlying infection. Many patients with chronic osteomyelitis have a normal CRP and ESR even at the onset of illness.

Physical Therapy

The major role of physical therapy is a preventive one. If a child is allowed to lie in bed with an extremity in flexion, limitation of extension can develop within a few days. The affected extremity should be kept in extension with sandbags, splints, or, if necessary, a temporary cast. Casts are also indicated when there is a potential for pathologic fracture. After 2-3 days, when pain is easing, passive range-of-motion exercises are started and continued until the child resumes normal activity. In neglected cases with flexion contractures, prolonged physical therapy is required.

Prognosis

When pus is drained and appropriate antibiotic therapy is given, the improvement in signs and symptoms is rapid. Failure to improve or worsening by 48-72 hours requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, or the accuracy of the diagnosis. Acute phase reactants may be useful as monitors. In acute osteomyelitis, the serum CRP typically decreases below 2 mg/dL within 7-10 days after starting treatment, whereas the ESR typically rises for 5-7 days and then falls slowly, dropping sharply after 10-14 days. Failure of CRP to follow the usual course should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Because children are in a dynamic state of growth, sequelae of skeletal infections might not become apparent for months or years; therefore long-term follow-up is necessary, with close attention to range of motion of joints and bone length. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 week of onset of symptoms provides a better prognosis than delayed treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 726

Septic Arthritis

Samir S. Shah

Without early recognition and prompt institution of appropriate medical and surgical therapy, septic arthritis in infants and children has the potential to damage the synovium, adjacent cartilage, and bone and may cause permanent disability.

ETIOLOGY

Staphylococcus aureus (see Chapter 227.1) is the most common cause of bacterial arthritis in all age groups. Methicillin-resistant *S. aureus* (MRSA) accounts for a high proportion (>25%) of community *S. aureus* isolates in many areas of the United States and throughout the world. Group A streptococcus (see Chapter 229) and ***Streptococcus pneumoniae*** (pneumococcus; see Chapter 228) historically cause 10–20%; *S. pneumoniae* is most likely in the first 2 years of life, but its frequency has declined since the introduction of the pneumococcal conjugate vaccines. ***Kingella kingae*** is recognized as a relatively common etiology with improved culture and polymerase chain reaction (PCR) methods in children younger than 4 years (see Chapters 239 and 725). In sexually active adolescents, **gonococcus** (see Chapter 238) is a common cause of septic arthritis and tenosynovitis, usually of small joints or as a monoarticular infection of a large joint (knee). ***Neisseria meningitidis*** (see Chapter 237) can cause either a septic arthritis that occurs in the first few days of illness or a reactive arthritis that is typically seen several days after antibiotics have been initiated. **Group B streptococcus** (see Chapter 230) is an important cause of septic arthritis in neonates. Q fever and brucellosis should be considered in endemic areas and with an exposure risk.

Fungal infections usually occur as part of multisystem disseminated disease; *Candida* arthritis can complicate systemic infection in neonates with or without indwelling vascular catheters. Primary viral infections of joints are rare, but arthritis accompanies many viral (parvovirus, mumps, rubella live vaccines) syndromes, suggesting an immune-mediated pathogenesis.

A microbial etiology is confirmed in approximately 65% of cases of septic arthritis. In addition, some cases treated as bacterial arthritis are actually postinfectious (gastrointestinal or genitourinary) **reactive arthritis** (see Chapter 198) rather than primary infection. **Lyme disease** produces an arthritis more like a rheumatologic disorder and not typically suppurative.

EPIDEMIOLOGY

Septic arthritis is more common in young children. Half of all cases occur by 2 years of age, and 75% of all cases occur by 5 years of age. Adolescents and neonates are at risk of gonococcal septic arthritis.

Most infections in otherwise healthy children arise hematogenously. Less commonly, infection of joints can follow penetrating injuries or procedures such as trauma, arthroscopy, prosthetic joint surgery, intraarticular steroid injection, and orthopedic surgery. Immunocompromised patients and those with rheumatologic joint disease are also at increased risk of joint infection.

PATHOGENESIS

Septic arthritis primarily occurs as a result of hematogenous seeding of the synovial space. Less often, organisms enter the joint space by direct inoculation or extension from a contiguous focus. The synovial membrane has a rich vascular supply and lacks a basement membrane, providing an ideal environment for hematogenous seeding. The presence of bacterial products (endotoxin or other toxins) within the

joint space stimulates cytokine production (tumor necrosis factor-α, interleukin-1) within the joint, triggering an inflammatory cascade. The cytokines stimulate chemotaxis of neutrophils into the joint space, where proteolytic enzymes and elastases are released by neutrophils, damaging the cartilage. Proteolytic enzymes released from the synovial cells and chondrocytes also contribute to destruction of cartilage and synovium. Bacterial hyaluronidase breaks down the hyaluronic acid in the synovial fluid, making the fluid less viscous and diminishing its ability to lubricate and protect the joint cartilage. Damage to the cartilage can occur through increased friction, especially for weight-bearing joints. The increased pressure within the joint space from accumulation of purulent material can compromise the vascular supply and induce pressure necrosis of the cartilage. Synovial and cartilage destruction results from a combination of proteolytic enzymes and mechanical factors.

CLINICAL MANIFESTATIONS

Most septic arthritides are monoarticular. The signs and symptoms of septic arthritis depend on the age of the patient. Early signs and symptoms may be subtle, particularly in neonates. As with osteomyelitis, neonates might exhibit **pseudoparalysis** or pain that limits voluntary movement of the affected extremity (e.g., diaper changes). Septic arthritis in neonates and young infants is often associated with adjacent osteomyelitis caused by transphyseal spread of infection, although osteomyelitis contiguous with an infected joint can be seen at any age (see Chapter 725).

Older infants and children might have fever and pain, with localizing signs such as swelling, erythema, and warmth of the affected joint. With involvement of joints of the pelvis and lower extremities, limp or refusal to walk often occurs.

Erythema and edema of the skin and soft tissue overlying the site of infection are seen earlier in septic arthritis than in osteomyelitis because the bulging infected synovium is usually more superficial, whereas the metaphysis is located more deeply. Septic arthritis of the hip is an exception because of the deep location of the hip joint. With Lyme arthritis, joint swelling is typically quite prominent and may be disproportionate to the relatively lesser degree of pain and limited range of motion when compared with suppurative arthritis. Lyme arthritis has a predilection for large joints, particularly the knees and hips, and may be either monoarticular or pauciarticular at presentation.

Joints of the lower extremity constitute 75% of all cases of septic arthritis (Table 726.1). The elbow, wrist, and shoulder joints are involved in approximately 25% of cases, and small joints are uncommonly infected, except in gonococcal arthritis. Suppurative infections of the hip, shoulder, elbow, and ankle in infants and children may be associated with an adjacent osteomyelitis of the proximal femur, proximal humerus, proximal radius, and distal tibia because the metaphysis extends intraarticularly. Concomitant osteomyelitis is less common in older children and adolescents as their anatomy and physiology become more adult-like.

Table 726.1 Distribution of Hematogenous Bacterial Arthritis*

BONE	PERCENT (%)
Knee	~35
Hip	~25
Ankle	~10
Elbow	~10
Wrist	~4
Shoulder	~5
Small joints	~1–2

*Excludes Lyme disease and immune-complex postinfectious arthritis. Viral (rubella, mumps, chikungunya) infectious arthritis is often small and multiple joints. Septic bursitis (shoulder, prepatellar) may be confused with bacterial joint infections.

DIAGNOSIS

The white blood cell count (WBC) and differential, ESR, and CRP are generally elevated in children with joint infections, but elevations are nonspecific and might not be helpful in distinguishing between infection and other inflammatory processes. Most children with septic arthritis will have normal leukocyte counts and ESR at presentation, and normal test results do not preclude the diagnosis of septic arthritis. A CBC, however, may assist with assessment of illness severity (e.g., anemia, thrombocytopenia) or with identification of other causes of the patient's symptoms (e.g., leukemia).

Blood cultures should be performed in all cases of suspected septic arthritis but are positive in ~20% of proven or probable septic arthritis. Cervical, anal, and throat cultures should be obtained when gonococcus is suspected. Aspiration of the joint fluid provides the optimal specimen to confirm the diagnosis. Most large joint spaces are easy to aspirate, but the hip can pose technical problems; ultrasound guidance facilitates aspiration. Although yield for joint aspirate cultures is higher than from blood cultures, the overall culture yield when combining both methods remains less than 50%. Multiplex bacterial PCR panels have a yield around 50% from joint fluid specimens, but this increase over culture is almost entirely because of their enhanced ability to detect *K. kingae*. Other strategies to increase detection of *K. kingae* include prompt inoculation onto solid media and inoculation of the joint fluid in blood culture bottles. A diagnosis of Lyme arthritis is made via a two-step test of an ELISA or IFA followed by a reflex Western blot for samples that are positive or equivocal by the first methodology. Patients with Lyme arthritis are seropositive because arthritis is a late manifestation of infection. PCR is rarely necessary but can detect *Borrelia burgdorferi* in joint aspirate specimens in cases of Lyme arthritis.

Synovial fluid analysis for cell count, differential, protein, and glucose has limited utility in diagnosing infectious arthritis. Joint fluid WBC counts >50,000 cells/mm^3 (often >100,000 cells/mm^3) suggest bacterial infection as the most likely etiology, but this finding is neither sensitive nor specific enough to exclude or confirm a bacterial infection in isolation. When the results of joint aspirate cell counts and culture are not strongly suggestive of a joint infection, but the clinical presentation is worrisome for a bacterial etiology, infectious causes of sympathetic joint effusions such as adjacent pyomyositis and osteomyelitis should be investigated by MRI (see Chapter 725).

Monitoring elevated CRP may be of value in assessing response to therapy or identifying complications. In addition, patients with adjacent infections complicating septic arthritis more frequently have a CRP >10-13 mg/dL compared with patients with septic arthritis alone. Other findings such as older age, prolonged symptoms, bacteremia, alterations in other lab values (such as elevated absolute neutrophil count or thrombocytopenia), and failure to rapidly improve with therapy have been less consistently associated with adjacent infection. Nonetheless, adjacent infection should be considered in patients demonstrating multiple risk factors.

Radiographic Evaluation

Radiographic studies play a crucial role in evaluating septic arthritis. Conventional radiographs and ultrasonography are performed as part of the routine workup. CT, MRI, and radionuclide studies can all contribute to establishing the diagnosis in selected cases (Fig. 726.1).

Plain Radiographs

Plain films can suggest the diagnosis of septic arthritis by showing widening of the joint capsule, soft tissue edema, and obliteration of normal fat lines. Plain films can also help to exclude other causes of joint pain such as fractures. Plain films of the hip can show medial displacement of the obturator muscle into the pelvis (the obturator sign), lateral displacement or obliteration of the gluteal fat lines, and elevation of Shenton's line with a widened arc.



Fig. 726.1 MRI of staphylococcal septic arthritis of left hip, with fluid collections between planes of gluteal muscles. *Arrows* indicate fluid collection. *(From Matthews CJ, Weston VC, Jones A, et al. Bacterial septic arthritis in adults. Lancet. 2010;375:846–854.)*

Ultrasonography

Ultrasonography is included with plain films in routine evaluations because it is particularly helpful in detecting joint effusion and fluid collection in the soft tissue and subperiosteal regions. Ultrasonography is highly sensitive in detecting joint effusion, particularly for the hip joint, where plain radiographs are normal in more than 50% of cases of septic arthritis of the hip. Ultrasonography can serve as an aid in performing hip aspiration.

Magnetic Resonance Imaging and Computed Tomography

MRI and CT can confirm the presence of joint fluid in patients with suspected osteoarthritis infections but are not routinely indicated. MRI is useful in evaluating for adjacent osteomyelitis or pyomyositis but is typically reserved for cases when the index of suspicion for these conditions is high. Considerations include patient factors such as younger age, the clinical presentation (e.g., protracted pain preceding joint swelling), the results of laboratory investigations such as joint aspiration and CRP, and response to therapy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of septic arthritis depends on the joint or joints involved and the age of the patient. For the hip, transient synovitis, pyomyositis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, psoas abscess, and proximal femoral, pelvic, or vertebral osteomyelitis, as well as diskitis, should be considered. Transient synovitis (toxic synovitis) is a postinfectious arthritis of the hip that is often seen in young children after a viral infection (see Chapter 719.2). For the knee, distal femoral or proximal tibial osteomyelitis, pauciarticular rheumatoid arthritis, and referred pain from the hip should be considered. Knee or thigh pain may be referred from the hip. Other conditions such as trauma, cellulitis, pyomyositis, sickle cell disease, hemophilia, Lyme arthritis, leukemia, serum sickness, and IgA vasculitis (Henoch-Schönlein purpura) can mimic purulent arthritis. When several joints are involved, serum sickness, collagen vascular disease, rheumatic fever, and IgA vasculitis should be considered. Arthritis is one of the extraintestinal manifestations of inflammatory bowel disease. Reactive arthritis after a variety of bacterial (gastrointestinal or genital) and parasitic infections, streptococcal pharyngitis, or viral hepatitis can resemble acute septic arthritis (see Chapter 198).

TREATMENT

Optimal treatment of septic arthritis requires coordination between primary care physicians, orthopedic surgeons, and radiologists.

Surgical Therapy

Drainage and irrigation of the infected joint via arthroscopy or arthrotomy is typically performed to decompress the joint and remove inflammatory debris. The decision to proceed to one of these procedures after arthrocentesis is based on the gross appearance of the joint fluid, or joint fluid WBC and differential, in the context of the clinical presentation and the specific joint that is infected. Infection of the hip is generally considered a surgical emergency because of the vulnerability of the blood supply to the head of the femur. For joints other than the hip, daily aspirations of synovial fluid may be required. In general, one or two subsequent aspirations suffice. If fluid continues to accumulate after 4-5 days, arthrotomy or video-assisted arthroscopy is needed. At the time of surgery, the joint is flushed with sterile saline solution. Antibiotics are not instilled because they are irritating to synovial tissue, and adequate amounts of antibiotic are achieved in joint fluid with systemic administration.

Antimicrobial Therapy

Empiric antimicrobial therapy should be started immediately in a child with presumed septic arthritis who is ill-appearing or has a rapidly progressive infection. Antibiotic therapy may be deferred until initial joint aspirate has been collected for diagnostic purposes in a child with presumed septic arthritis who does not appear clinically ill.

The initial empirical antimicrobial therapy is based on likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (100-200 mg/kg/24 hr divided q6hr IV), and a broad-spectrum cephalosporin, such as cefepime (100-150 mg/kg/24 hr divided q12hr IV), provide coverage for the *S. aureus,* group B streptococcus, and gram-negative bacilli. If MRSA is a concern, clindamycin or vancomycin is selected instead of nafcillin or oxacillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (*S. aureus*, gram-negative enterics, or *Pseudomonas aeruginosa*) or fungi *(Candida)* should be considered.

In children with septic arthritis, empirical therapy to cover for *S. aureus* and streptococci includes at minimum nafcillin (100-200 mg/kg/24 hr divided q6hr). In preschool-age children (i.e., 6 months to 4 years), empiric therapy should include an antibiotic with activity against *Kingella kingae* as well as *S. aureus*, such as cefazolin (100-150 mg/kg/24 hr divided q8hr).

In areas where methicillin resistance is noted in ≥10–15% of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains, adding an antimicrobial that is effective against local CA-MRSA isolates is suggested. Vancomycin (15 mg/kg q6hr IV) is preferred in patients who are ill-appearing, suspected to be bacteremic, or if local clindamycin resistance is more than 10–15%. Clindamycin (30-40 mg/kg/24 hr divided q6-8hr) is a good alternative when treating CA-MRSA infections. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime, cefepime, or piperacillin/tazobactam, with or without an aminoglycoside. Adjunct therapy with dexamethasone has been shown in some studies to decrease the duration of fever and promote a more rapid decline in inflammatory markers, but this is not yet part of routine care. **Lyme arthritis** is treated with oral doxycycline (4.4 mg/kg/24 hr divided q12hr) for 28 days in children >8 years old. For children <8 years old, oral amoxicillin (50 mg/kg/24 hr divided q8hr) or cefuroxime (30 mg/kg/24 hr divided q12hr) is recommended. A second 28-day course may be considered for patients with persistent or recurrent symptoms after completing the initial course of treatment. Intravenous ceftriaxone (50 mg/kg q24hr IV) for 14-28 days may be considered as an initial or second course of therapy for severe or refractory cases.

Empirical antimicrobials are narrowed to targeted therapy when the pathogen is identified. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the antibiotic selected

initially. If a pathogen is not identified and a patient's condition is not improving, consideration should be given to the need for repeat aspiration, the presence of an extraarticular infection requiring surgical debridement, or the possibility of a noninfectious etiology. In such cases, MRI may be performed to assist with subsequent management decisions.

Duration of antibiotic therapy is individualized depending on the organism isolated and the clinical course. A total of 10-14 days is usually adequate for streptococci, *S. pneumoniae*, and *K. kingae;* longer therapy may be needed for *S. aureus* and gram-negative infections (3 weeks), concomitant osteomyelitis (4 weeks), extensive disease, or slow response to treatment. Normalization of CRP in addition to a normal examination supports discontinuing antibiotic therapy. The prognostic significance of an improved but still minimally elevated ESR in the third or fourth week of therapy is not clear if all other clinical and laboratory parameters are favorable. In selected patients, obtaining a plain radiograph of the joint before completing therapy can provide evidence (typically periosteal new bone) of a previously unappreciated contiguous site of osteomyelitis that would likely prolong antibiotic treatment. Oral antibiotics can be used to complete therapy once the patient is afebrile for 48-72 hours and is clearly improving.

Surgically administered intraarticular antibiotics are not recommended.

PROGNOSIS

Improvement in signs and symptoms occurs rapidly after joint drainage and antibiotic administration. Failure to improve or worsening by 48-72 hours requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, and the correctness of the diagnosis. CRP may be useful to monitor response to therapy. Failure of CRP to decline should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Septic arthritis can lead to numerous long-term sequelae in children, including leg-length discrepancy or angular deformity from growth arrest, limitations in range of motion due to chondral damage, and avascular necrosis of the femoral head from septic arthritis of the hip. The overall rate of these sequelae with current therapies is <5%. However, children are in a dynamic state of growth, so these abnormalities might not become apparent for months or years; therefore long-term follow-up is necessary, with close attention to range of motion of joints and bone length. Involvement of the hip is associated with a higher rate of sequelae. Initiation of medical and surgical therapy within 1 week of onset of symptoms provides a better prognosis than delayed treatment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 2
Sports Medicine

Chapter 727
Prevention of Injuries

Gregory L. Landry and Andrew M. Watson

The Centers for Disease Control and Prevention, the American College of Sports Medicine, and the American Academy of Pediatrics all recommend daily moderate to vigorous physical activity for all adolescents. Physical activity has favorable effects on blood pressure, body composition, and serum lipid levels in youths and is associated with lower rates of cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and colon and breast cancer among adults.

Pediatricians should promote physical activity to their patients, especially those with lower rates of physical activity and sports participation, including children with special healthcare needs (see Chapter 756) and those from lower socioeconomic groups. Physicians also have the responsibility of providing medical clearance for participation in physical activity and sports as well as for the diagnosis and rehabilitation of injuries.

Approximately 30 million children and adolescents participate in organized sports in the United States. Around 3 million sport-related injuries occur annually in young athletes, if injury is defined as time lost from the sport. Deaths in sports are rare, with the majority of nontraumatic deaths caused by cardiac diseases (see Chapter 485). Nonetheless, approximately 30% of life-threatening injuries in children presenting to an emergency room are sports related. Overall, injury rates and injury severity in sports increase with age and pubertal development, related to the greater speed, strength, and intensity of competition.

Identifying mechanisms of injury and establishing and enforcing rules that reduce the likelihood of that mechanism of injury, including penalizing dangerous play, have reduced catastrophic injury rates. Injury rates also have been reduced by removing environmental hazards, such as trampolines in gymnastics and stationary (versus breakaway) bases in softball, and by modifying heat injury rates in soccer tournaments by adding water breaks and reducing the playing time. Certain types of equipment can mitigate the risk of some injuries, such as the use of mouth guards to reduce dental injuries. The most consistently identified risk factor for injury is prior injury. In other words, although reinjury may often be due to insufficient recovery and rehabilitation of a prior injury, appropriate rehabilitation reduces injury risk. Preseason training for adolescent athletes, with an emphasis on speed, agility, core strength, landing mechanics, and flexibility, is associated with lower injury rates in soccer and fewer serious knee injuries in female athletes. Traditional stretching maneuvers or massage have not been demonstrated to reduce the risk of injury or muscle soreness, but ankle taping and use of lace-up ankle braces are helpful in preventing ankle injuries. One setting for implementing some of these prevention strategies and for detecting unrehabilitated injuries and medical problems that could affect participation in sports is the preparticipation sports examination (PSE).

PREPARTICIPATION SPORTS EXAMINATION

The PSE is performed with a directed history and physical examination, including a screening musculoskeletal examination (see Table 485.2 in Chapter 485). It identifies possible problems in 1–8% of athletes and excludes fewer than 1% from participation. The PSE is not a substitute for the recommended comprehensive annual evaluation, which looks at behaviors that are potentially harmful to teens, such as sexual activity, drug use, and violence, and assesses for depression and suicidal ideation and addresses broader issues of prevention. Table 727.1 identifies the purposes of the PSE. If possible, the PSE should be combined with the comprehensive annual health visit with an emphasis on preventive healthcare (see Chapters 13 and 28).

State requirements for how often a young athlete needs a PSE differ, ranging from annually to entry to a new school level (middle school, high school, college). At a minimum, a focused, annual interim evaluation should be done on an otherwise healthy young athlete. The PSE is optimally performed 3-6 weeks before the start of practice.

History and Physical Examination

The essential components of the PSE are the history and focused medical and musculoskeletal screening examinations. Identified problems require more investigation (Table 727.2). While many medical conditions should not limit sports participation, many specialty organizations have released recommendations regarding sports participation (Table 727.3). In the absence of symptoms, no screening laboratory tests are required. Return to sports after COVID-19 infection is based on the severity of infection (mild, moderate, or ICU admission and/or MIS-C), and the intensity of follow-up, especially for those with active cardiac involvement during the acute phase of the illness (Fig. 727.1).

Seventy-five percent of significant findings are identified by the history; a standardized questionnaire given to the parent and athlete is important

Table 727.1 Objectives of the Preparticipation Sports Examination

- Determination of the general health of the athlete
- Disclosure of defects that may limit participation
- Detection of conditions that may predispose the athlete to injury
- Determination of optimal level of performance
- Classification of the athlete according to individual qualifications
- Fulfillment of legal and insurance requirements for organized athletic programs
- Evaluation of size and level of maturation of younger athletes
- Improvement of fitness and performance
- Provision of opportunities for students to compete who have either physiologic or pathologic health conditions that may preclude blanket approval
- Provision of the opportunity to counsel youths and answer health and personal questions
- Entry of the athlete into the local sports medicine system, establishing a doctor-patient relationship that continues

From Sanders B, Blackburn TA, Boucher B. Preparticipation screening-the sports physical therapy perspective. *Int J Sports Phys Ther*. 2013;8(2):180–193. Table 1.

Table 727.2 Preparticipation Sports Examination

COMPONENT OF THE PHYSICAL EXAMINATION	CONDITION TO BE DETECTED
Vital signs	Hypertension, cardiac disease, bradycardia or tachycardia
Height and weight	Obesity, eating disorders, malabsorption
Vision and pupil size	Legal blindness, absent eye, anisocoria, amblyopia
Lymph node	Infectious diseases, malignancy
Cardiac (performed standing and supine)	Heart murmur, prior surgery, dysrhythmia, femoral pulses
Pulmonary	Recurrent and exercise-induced bronchospasm, chronic lung disease
Abdomen	Organomegaly, abdominal mass
Skin	Contagious diseases (impetigo, herpes, staphylococcal, streptococcal)
Genitourinary	Varicocele, undescended testes, tumor, hernia
Musculoskeletal	Acute and chronic injuries, physical anomalies (scoliosis)

Table 727.3 Sports Participation Recommendations by Condition

CONDITION	RECOMMENDATION
Hemophilia	Restrict contact or collision sports until evaluation by a hematologist who can assess degree of hemostatic abnormality and the sport-specific risk
Sickle cell disease	Individual decision-making given variation in phenotypic expression
Diabetes mellitus	No restrictions
Skin infections (herpes gladiatorum, tinea gladiatorum, impetigo, molluscum contagiosum, warts, and MRSA)	Prevent transmission by: • Covering infected site • Using prophylactic medications as prescribed • No sharing of personal items • Thorough cleaning of equipment
Mononucleosis infection	Light, noncontact activity may be introduced as tolerated 3 weeks after illness onset with avoidance of contact/collision sports until 4 weeks after illness onset
Blood-borne infections (hepatitis B, hepatitis C, HIV)	No restrictions
COVID-19 infection	See Fig. 727.1
Heat illness, history of	Gradual acclimatization to heat over 7-14 days, avoid participation while ill (fever, skin rash, viral symptoms), ensure free access to fluids at all times, consume sodium-containing food/fluids to replace insensible losses, rest periods of at least 3 hours before practice or games
Down syndrome	Individual decision-making based on the presence of congenital heart disease or atlantoaxial instability

Data from Herman D, Gadi N, Peck E. Team medical coverage. In Miller MD, Thompson SR, eds. *DeLee, Drez, & Miller's Sports Medicine*, 5th ed. Philadelphia: Elsevier, 2020.

because the young athlete might not know or might forget important aspects of the history. The questionnaire should include questions about the family history and the patient's previous medical, surgical, cardiac, pulmonary, neurologic, dermatologic, visual, psychologic, musculoskeletal, and endocrinologic problems, as well as about prior heat illness, medications, allergies, immunizations, and diet. The most commonly identified problems are *unrehabilitated injuries*. An investigation of previous injuries, including diagnostic tests, treatment, and present functional status, is indicated.

Sudden death during sports can result from undetected cardiac disease, such as hypertrophic or other **cardiomyopathies** (see Chapter 488), **anomalous coronary vessels** (see Chapter 481.2), or a ruptured aorta in **Marfan syndrome** (see Chapter 743). In many cases, the underlying heart disease is not suspected, and death is the first sign of underlying heart disease (see Chapter 485). However, in approximately 25–50% of cases, preceding symptoms of dizziness, chest pain, syncope, palpitations, shortness of breath, and/or a family history of early, unexpected death are identified retrospectively. Chest radiographs, electrocardiograms, and echocardiograms are not recommended as routine screening tests in the United States, but screening electrocardiograms are recommended in a number of other countries and are becoming more commonly used among higher risk groups in the United States, such as collegiate and professional athletes. If there is a suspicion of heart disease, such as a history of syncope, presyncope, palpitations, or excessive dyspnea with exercise, or a family history of a condition such as hypertrophic cardiomyopathy or prolonged QT or Marfan syndrome, the evaluation should be complete and include a 12-lead electrocardiogram, an echocardiogram, Holter or event-capture monitoring, and a stress test with electrocardiographic monitoring. Recommendations for participation with identified cardiac disease should be made in consultation with a cardiologist.

Sports may also be classified by intensity (Fig. 727.2) and contact (Table 727.4). Athletes may seek to participate in sports against medical advice and have done so successfully for professional sports. Section 504(a) of the Rehabilitation Act of 1973 prohibits discrimination against disabled athletes if they have the capabilities or skills required to play a competitive sport. This was reinforced through the Americans with Disabilities Act of

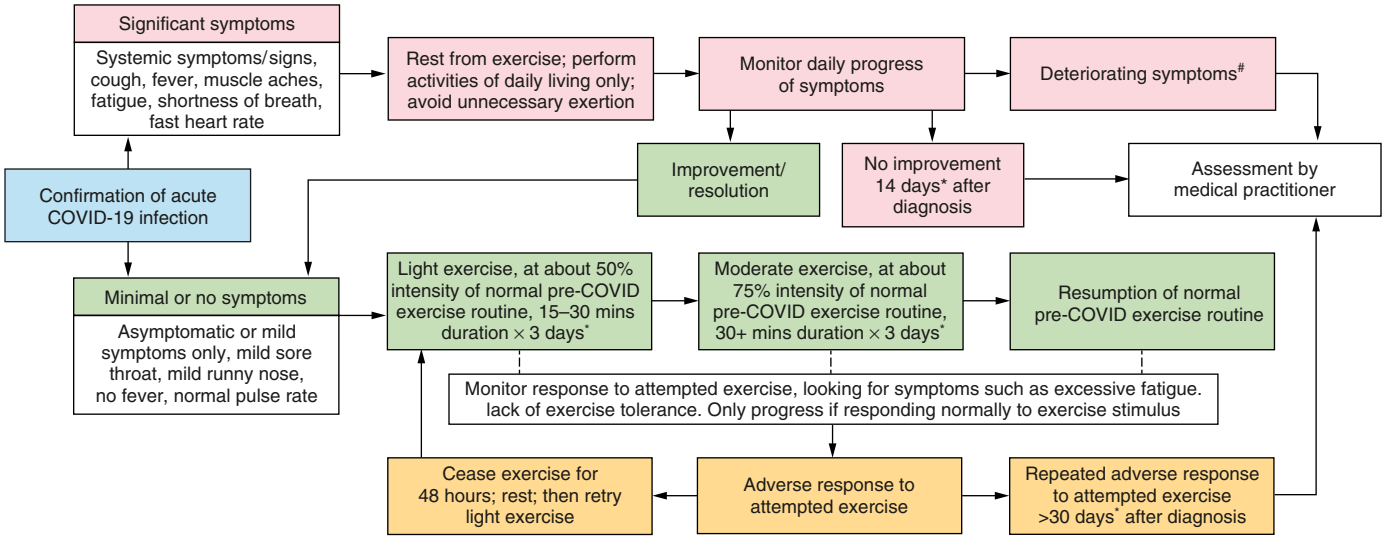

- Dry, post-viral cough may persist beyond the acute COVID-19 infection
- Individuals should be 10 days post diagnosis or onset of symptoms (or have negative RAT on days 6 & 7), before rejoining group / team activities
- *Number of days at each step may be modified in high performance sport, where athletes have the benefit of close medical supervision
- Those with medical comorbidities should adopt a more cautious approach to return to exercise
- # **Cardiac symptoms should be treated as a medical emergency: Pressure, tightness, squeezing pain in chest, arms, neck, jaw, or back, cold sweat, difficulty breathing, collapse, sudden dizziness**

Fig. 727.1 Graduated return to exercise after COVID-19 infection. RAT, rapid home antigen test. *(From Hughes DC, Orchard JW, Partridge EM, et al. Return to exercise post-COVID-19 infection: a pragmatic approach in mid-2022. J Sci Med Sport. 2022;25:544–547. Fig. 1.)*

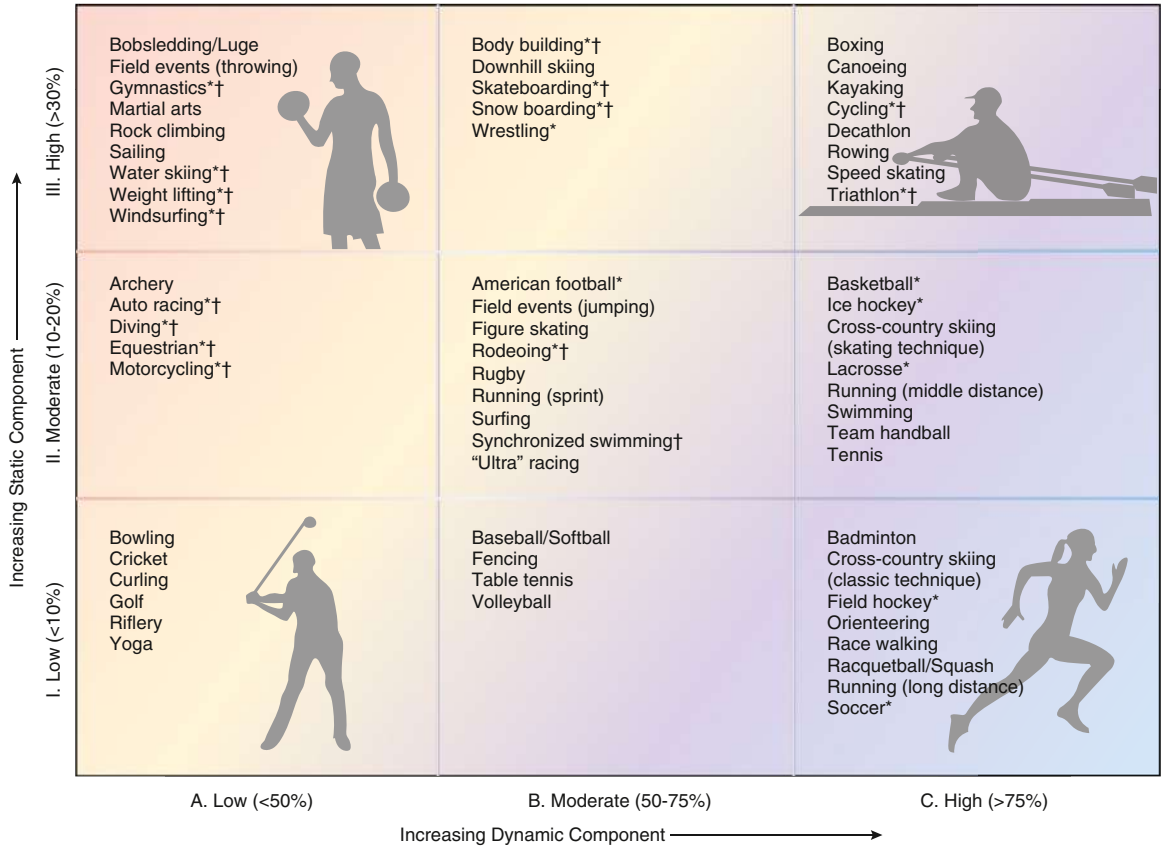

Fig. 727.2 Classification of sports. This classification is based on peak static and dynamic components achieved during competition; however, higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake ($\dot{V}o_{2max}$) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in the palest color, with increasing dynamic load depicted by increasing blue intensity and increasing static load by increasing red intensity. Note the graded transition between categories, which should be individualized on the basis of player position and style of play. *Danger of bodily collision (see Table 727.4 for more detail on collision risk). †Increased risk if syncope occurs. *(Modified from Mitchell JH, Haskell W, Snell P, et al. 36th Bethesda conference. Task force 8: classification of sports. J Am Coll Cardiol. 2005;45:1364–1367.)*

Table 727.4	Sports According to Risk of Impact and Educational Background	
	JUNIOR HIGH SCHOOL	**HIGH SCHOOL/COLLEGE**
Impact expected	American football Ice hockey Lacrosse Wrestling Karate/judo Fencing Boxing	American football Soccer Ice hockey Lacrosse Basketball Wrestling Karate/judo Downhill skiing Squash Fencing Boxing
Impact may occur	Soccer Basketball Field hockey Downhill skiing Equestrian Squash Cycling	Field hockey Equestrian Cycling Baseball/softball Gymnastics Figure skating
Impact not expected	Baseball/softball Cricket Golf Riflery Gymnastics Volleyball Swimming Track and field Tennis Figure skating Cross-country skiing Rowing Sailing Archery Weightlifting Badminton	Cricket Golf Riflery Volleyball Swimming Track and field Tennis Cross-country skiing Rowing Sailing Archery Weightlifting Badminton

From Levine BD, Baggish AL, Kovacs RJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task force 1: classification of sports: dynamic, static, and impact: a scientific statement from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol.* 2015;66(21):2350–2355.

1990. Participation in competitive sports is considered a privilege, not a right. *Knapp v Northwestern University* established that "difficult medical decisions involving complex medical problems can be made by responsible physicians exercising prudent judgment (which will be necessarily conservative when definitive scientific evidence is lacking or conflicting) and relying on the recommendations of specialist consultants or guidelines established by a panel of experts."

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 728

Management of Musculoskeletal Injury

Gregory L. Landry and Andrew M. Watson

MECHANISM OF INJURY

Acute Injuries

Sprains, strains, and contusions account for the majority of musculoskeletal injuries. A **sprain** is an injury to a ligament or joint capsule. Most sprains are graded I-III. A *grade I* sprain is defined as mild damage to a ligament or ligaments without instability of the affected joint. A *grade II* sprain is considered a partial tear to the ligament, such that it exhibits excessive laxity but has a firm endpoint on examination. A *grade III* sprain is a complete tear of the ligament with instability to the affected joint and without a firm endpoint on examination. A **strain** is an injury to a muscle or tendon, and these are also graded I-III. *Grade I* muscle strains involve disruption of only a few muscle fibers, pain is mild to moderate, and range of motion and strength are at or near normal. *Grade II* strains represent a more significant, partial tear of the muscle and frequently involve loss of range of motion and strength. *Grade III* strains are defined as complete rupture of the musculotendinous unit. On examination, *grade III* strains, and often *grade II* strains, present with ecchymosis and a palpable step-off at the site of injury. A **contusion** is a crush injury to any soft tissue. The history of the injury is especially helpful in assessing musculoskeletal trauma. More severe injuries, including fractures or internal derangement of a joint, may have acute signs and symptoms such as immediate swelling, deformity, numbness or "give-way" weakness, a loud painful pop, mechanical locking of the joint, or instability.

Overuse Injuries

Overuse injuries are caused by repetitive microtrauma that exceeds the body's rate of repair. This can occur in muscles, tendons, bone, bursae, cartilage, and nerves. Overuse injuries can occur in all sports but are more commonly seen in sports emphasizing repetitive motion such as swimming, running, tennis, baseball pitching, and gymnastics. Factors leading to overuse injuries can be categorized as extrinsic (i.e., training errors, poor equipment, or workout surface) and intrinsic (i.e., athlete's anatomy or medical conditions). Training error is the most commonly identified factor. For example, at the beginning of the training program, athletes might violate the "10% rule" by increasing the duration or intensity of workouts by more than 10% per week. This may exceed the body's capacity to recover between bouts of activity, leading to accumulated microtrauma that manifests as an overuse injury. Intrinsic factors include abnormal biomechanics that may be due to underlying anatomic causes (e.g., leg-length discrepancy, pes planus, pes cavus, tarsal coalition, valgus heel, external tibial torsion, and femoral anteversion), muscle imbalance, inflexibility, and medical conditions (deconditioning, nutritional deficits, amenorrhea, and obesity). To identify the cause of an overuse injury, the athlete should be questioned about the specifics of their training. Specifically, runners, for example, should be asked about their shoes, orthotics, running surface, weekly mileage or time spent running per week, speed or hill workouts, and previous injuries and rehabilitation. When causative factors are identified, they can be modified or eliminated so that after rehabilitation the athlete does not suffer a recurrent overuse injury.

For athletes engaged in excessive training that causes an overuse injury, curtailing all exercise may not be necessary. Treatment incorporates a reduction of training load (relative rest) combined with a rehabilitation program designed to return athletes to their sport as soon as possible while minimizing risk of re-injury. Early identification of an overuse injury requires less alteration of the workout regimen. In addition, proper sleep, nutrition, and stress management can optimize recovery between bouts of activity, promoting physiologic adaptation and reducing the risk of accumulated damage that leads to injury.

It has become more commonplace for young athletes to *specialize* in a single sport and engage in year-round training. Families should be advised about the risks of specialization in young athletes because this is associated with burnout, decreased motivation and enjoyment, and increased risk of overuse injuries. This is especially evident among baseball pitchers, in whom repeated exposure to the highly repetitive and forceful throwing motion can damage the tissues in the elbow and shoulder in a growing athlete. These athletes and their parents should be counseled to diversify their sport participation at younger ages, which may increase their enjoyment and performance in sport, as well as reduce the risk of overuse injury.

The goals of treatment in overuse injuries are to control pain and spasm to rehabilitate flexibility, strength, endurance, and proprioceptive deficits (Table 728.1). In many overuse injuries, the role of inflammation in the process is minimal. For most injuries to tendons, the term

Table 728.1 Staging of Overuse Injuries

GRADE	GRADING SYMPTOMS	TREATMENT
I	Pain only after activity Does not interfere with performance or intensity Generalized tenderness Disappears before next session	Modification of activity, consider cross-training, home rehabilitation program
II	Minimal pain with activity Does not interfere with performance More localized tenderness Disappears before next session	Modification of activity, cross-training, home rehabilitation program
III	Pain interferes with activity and performance Definite area of tenderness Usually disappears between sessions	Significant modification of activity, strongly encourage cross-training, home rehabilitation program, and outpatient physical therapy
IV	Pain with activities of daily living Pain does not disappear between sessions Marked interference with performance and training intensity	Discontinue activity temporarily, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy
V	Pain interferes with activities of daily living Signs of tissue injury (e.g., edema) Chronic or recurrent symptoms	Prolonged discontinuation of activity, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy

tendinitis is no longer used because there is little or no inflammation on histopathology of the affected tendons. Rather, there is evidence of microscopic trauma to the tissue and a disorientation of the tendon fibers. Most of these entities are more appropriately called **tendinosis**; when the tendon tissue is scarred and when markedly abnormal, **tendinopathy**. With tendinosis, there is less of a role for antiinflammatory medication in the treatment, except as an analgesic.

Novel treatments are emerging for the effective treatment of chronic tendinopathies. Under ultrasound guidance, pathologic areas of tendon tissue can be targeted with injections of autologous blood or platelet-rich plasma to stimulate a proinflammatory and more robust healing response. Platelet-rich plasma is a controversial therapy with a mixed body of evidence related to its effectiveness for certain acute and chronic tendinopathies; there is a lack of consensus regarding its role in the standard of care. Pathologic tissue can also be targeted with percutaneous needle fenestration or tenotomy, and tendon-fat pad adhesions can also be addressed through mechanical needle scraping or hydrodissection techniques using ultrasound.

INITIAL EVALUATION OF THE INJURED EXTREMITY

Initially, the examiner should determine the quality of the peripheral pulses and capillary refill rate, as well as the gross motor and sensory function to assess for neurovascular injury. The first priorities are to maintain vascular integrity and skeletal stability.

Criteria for immediate attention and rapid orthopedic consultation include vascular compromise, nerve compromise, and open fracture. With the latter, the exposed wound should be covered with sterile saline-soaked gauze, the injured limb should be padded and splinted, and systemic antibiotics should be administered. Pressure should be applied to any site of excessive bleeding. Additional criteria include deep laceration over a joint, unreducible dislocation, grade III (complete) tear of a muscle-tendon unit, and displaced, significantly angulated fractures.

TRANSITION FROM IMMEDIATE MANAGEMENT TO RETURN TO PLAY

Rehabilitation of a musculoskeletal injury should be initiated on the day of the injury.

Phase 1

Limit further injury, control swelling and pain, and minimize strength and flexibility losses. **PRICE** principles (**P**rotection, **R**est, **I**ce, **C**ompression, and **E**levation) need to be applied. Crutches, air stirrups for ankle sprains, slings for arm injuries, and elastic wraps (4-8 inches) for compression are a helpful inventory of medical supplies. Ice can be placed directly over the injury as tolerated for 20 minutes continuously 3 or 4 times per day until the swelling resolves. Compression limits further bleeding and swelling but should not be so tight that it limits perfusion. Elevation of the extremity promotes venous return and limits swelling. A nonsteroidal antiinflammatory drug (NSAID) or acetaminophen are indicated for analgesia.

Pain-free isometric strengthening and range of motion exercises should be initiated as soon as tolerable. Pain inhibits full muscle contraction; deconditioning results if the pain and resultant disuse persist for days to weeks, thus delaying recovery. Education about the nature of the injury and the specifics of rehabilitation exercises, including handouts with written instructions and drawings demonstrating the exercises, are helpful.

Phase 2

Improve strength and range of motion (e.g., flexibility) while allowing the injured structures to heal. Protective devices are removed when the patient's strength and flexibility improve and activities of daily living are pain-free. Flexibility can then be addressed by a program of specific stretches, held for 15-30 seconds for three to five repetitions, once or twice daily. A physical therapist or athletic trainer is invaluable in guiding the athlete through this process. Protective devices might need to be used upon return to sports participation. Swimming, water jogging, and stationary cycling are good, low-impact aerobic exercises that can allow the injured lower extremity to be used pain-free while maintaining cardiovascular fitness.

Phase 3

Achieve near-normal strength and flexibility of the injured structures and further improve or maintain cardiovascular fitness. Strength and endurance are improved under controlled conditions using elastic bands and closed kinetic chain exercises (movement of multiple joints and limb segments with foot fixed to a static surface, such as the floor or wall) at this point and then progressing next to using exercise equipment followed by free weights. Additional sensory proprioceptive training allows the athlete to redevelop the kinesthetic sense critical to joint function and stability during activity.

Phase 4

Return to exercise or competition without restriction. When the athlete has reached normal range of motion, strength, proprioception, and endurance, the athlete can initiate sports-specific exercises. The athlete will transition from the rehabilitation program to functional rehabilitation appropriate for the sport. Substituting sports participation for rehabilitation is inappropriate; rather, there should be progressive stepwise

functional return to a full activity or play program. For instance, a basketball player recovering from an ankle injury might begin a walk-run-sprint-cut program before returning to competition. At any point in this progression, if pain is experienced, the athlete needs to stop, apply ice, avoid running for 1-2 days, continue to perform ankle stabilizing exercises, and then resume running at a lower intensity and progress accordingly.

Relative Rest and Return-to-Play Guidelines

Relative rest refers to the concept that the athlete participates in rehabilitation and return to sport activities provided the injured structures do not hurt during or within 24 hours of the activity. Exercising beyond the pain threshold delays recovery.

IMAGING

Traditional imaging modalities such as x-ray, ultrasound, MRI, and CT are well-established in the routine diagnostic workup of musculoskeletal injury. An obvious advantage of ultrasound is a lack of radiation. It is also better tolerated by younger children who may have difficulty complying with MRI or CT protocols. Dynamic movement or stressing of a limb, joint, or structure can provide valuable diagnostic information and can easily be compared to the contralateral side for comparison. Snapping or popping sensations, suspected intramuscular hematomas, stress fractures, and prognostic scrutiny of strains, sprains, and tendinopathies are all high-yield applications of diagnostic musculoskeletal sonography. Ultrasound imaging can also increase the accuracy of therapeutic injections, improving injection efficacy while simultaneously reducing adverse outcomes by erroneous needle placement.

DIFFERENTIAL DIAGNOSES OF MUSCULOSKELETAL PAIN

Traumatic, rheumatologic, infectious, hematologic, psychologic, congenital, and oncologic processes—especially under the age of 12 years old —can result in a presenting complaint of musculoskeletal pain. Symptoms such as fatigue, weight loss, rash, multiple joint complaints, fever, chronic or recent illness, pain out of proportion to the nature of the injury, and persistent pain despite conservative care suggest a diagnosis other than sports-related trauma. The possibility of child abuse, including sexual abuse, should not be overlooked. Incongruity between the patient's history and physical examination findings should lead to further evaluation. A negative review of systems with an injury history consistent with the physical findings suggests a sports-related etiology.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.1 Growth Plate Injuries

Gregory L. Landry and Andrew M. Watson

Approximately 20% of pediatric sports injuries seen in the emergency department are fractures, and 25% of those fractures involve an epiphyseal growth plate or physis (see Chapter 724). Growth in long bones occurs in three areas and is susceptible to injury. Immature bone can be acutely injured at the physis (e.g., Salter-Harris fractures, see Chapter 724.2), the articular surface (e.g., osteochondritis dissecans [OCD]), or the apophysis (e.g., avulsion fractures). Males suffer nearly twice as many physeal fractures as females, with the highest incidence of fracture occurring during peak height velocity (females: age 12 ± 2.5 years; males: age 14 ± 2 years). The physis is a pressure growth plate and is responsible for longitudinal growth in bone. The apophysis is a bony outgrowth at the attachment of a tendon and is a traction physis. The epiphysis is the end of a long bone, distal or proximal to the long bone, and contains articular cartilage at the joint.

Physeal injuries of the upper extremity are most commonly seen at the distal radius in the growing child or adolescent and are typically due to excessive force applied to the upper extremity. Injuries of this nature can be seen in athletes, including those participating in gymnastics, cheerleading, ice skating, hockey, and weightlifting. Mechanisms of injury include falls onto an outstretched hand or repetitive dorsiflexion and axial loading through the distal radius (see Chapter 734). Chronic wrist pain can be seen in up to 79% of young gymnasts—particularly female gymnasts between the ages of 12-14 years—and is commonly termed **gymnasts' wrist** (see Chapter 722). With repetitive axial loading, temporary metaphyseal ischemia may be induced, preventing cartilage calcification and causing the physis to widen. With widening of the distal radial physis, microfractures can develop. Clinical features include radial wrist pain (particularly dorsal) that is aggravated with passive and active hyperextension activities and relieved with suspension of the offending activity. Tenderness or focal pain around the circumference of the distal radius is often noted. Differential diagnosis includes metacarpal fractures, scaphoid fracture and, in the older child or adolescent, de Quervain tenosynovitis. Juvenile idiopathic arthritis, malignancy, and infection need to be considered in a child with a painful, swollen wrist without a history of trauma. X-rays of the wrist can be helpful, particularly when compared to the contralateral extremity. Radiographs can show physeal widening with cystic changes involving the metaphyseal segment, breaking of the distal epiphysis, and, in later stages, positive ulnar variance (longer ulna compared to the radius). MRI is often helpful for stress fractures when radiographs are inconclusive and will show signs of stress reaction (bone marrow edema, periosteal reaction, etc.), even if a fracture line is not evident. PRICE principles are followed with nonnarcotic pain management. Salter-Harris fractures types I and II can be treated with closed reduction and immobilization. Ulnar-shortening osteotomy may be necessary in the athlete with significant ulnar positive variance. Physeal injuries at the knee (distal femur, proximal tibia) are rare, whereas those at the ankle (distal fibula most commonly) are more frequent—typically occurring as a result of an inversion injury—and predominantly consist of Salter-Harris I fractures.

Growth disturbance following a growth plate injury is a function of location of the physeal fracture. This influences the probability that a physeal bar will form, resulting in growth arrest. In the upper extremity, the areas making the largest contribution to longitudinal growth are the proximal humerus and distal radius and ulna; in the lower extremities, the distal femur and the proximal tibia and fibula are the greatest contributors to longitudinal growth. Injuries to these areas are more likely to cause growth disturbance compared with physeal injuries at the other end of these long bones. The type of physis fracture relative to the risk of growth disturbance is described by the Salter-Harris classification system (see Table 724.1). A grade I injury is least likely to result in growth disturbance, and grade V is the most likely fracture to result in growth disturbance.

Osteochondritis dissecans (OCD) affects the subchondral bone and overlying articular surface (see Chapter 718.3). With avascular necrosis of subchondral bone, the articular surface can flatten, soften, or break off in fragments. The etiology may be related to repetitive stress injury in some patients. OCD most commonly presents in the lower extremities at the knee, affecting the lateral aspect of the medial femoral condyle in 70% of patients, the lateral femoral condyle in 20%, and the patella in 10%. In the upper extremities, it is most frequently seen at the elbow (Fig. 728.1)—affecting the capitellum—and is often associated with repetitive overhead throwing or swinging activities (e.g., baseball). Other sites where OCD lesions are seen are the ankle (talus) and radial head. OCD classically affects athletes in their second decade. The most common presentation is poorly localized, vague joint pain. There is rarely a history of recent acute trauma. Some OCD lesions are asymptomatic and incidental—diagnosed on "routine" radiographs—whereas others manifest as joint effusion, pain, decreased range of motion, and mechanical symptoms (e.g., locking, popping, or catching). Activity usually worsens the pain.

Physical examination might show no specific findings. Sometimes tenderness over the involved condyle can be elicited by deep palpation. Diagnosis is usually made with plain radiographs. Treatment of OCD includes both nonoperative and surgical management (Chapter 718.3). Long-term sequelae can be seen in up to 25% with atypical lesions, older age, effusion, and lesions of large size.

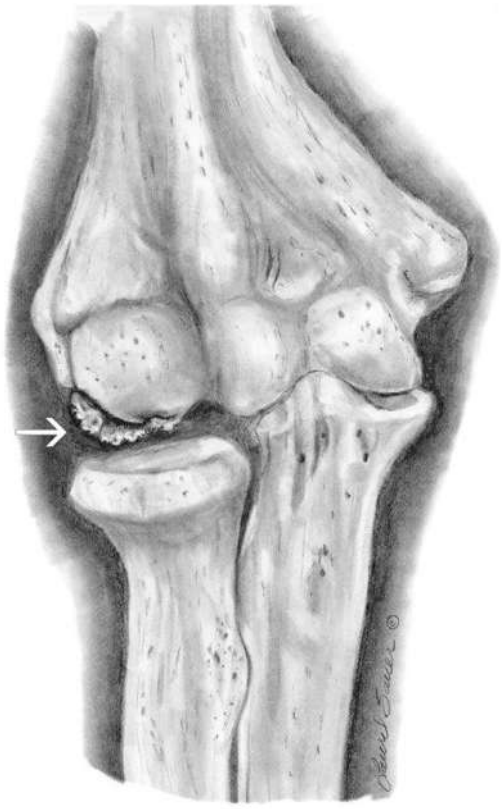

Fig. 728.1 Osteochondritis dissecans in the elbow. *(Copyright Laurel Sauer, 2017.)*

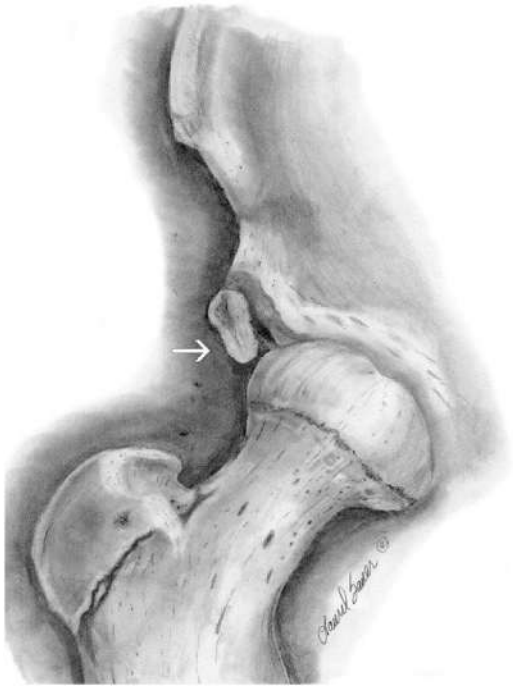

Fig. 728.2 Anterior inferior iliac spine avulsion. *(Copyright Laurel Sauer, 2017.)*



Fig. 728.3 Calcaneal apophysitis (Sever disease). *(Copyright Laurel Sauer, 2017.)*

Avulsion fractures occur when a forceful muscle contraction dislodges the apophysis from the bone. They occur most commonly around the hip (Fig. 728.2) and are typically treated nonsurgically if no significant displacement of the avulsed fragment is present. Acute fractures to other apophyses (i.e., knee and elbow) require urgent orthopedic consultation. Chronically increased traction at the muscle-apophysis attachment can lead to repetitive microtrauma and pain at the apophysis. The most common areas affected are the knee (**Osgood-Schlatter** and **Sinding-Larsen-Johansson disease**), the ankle **(Sever disease)** (Fig. 728.3), the proximal fifth metatarsal **(Iselin disease)**, and the medial epicondyle **(Little Leaguer's elbow)**. Traction apophysitis of the knee and ankle can often be treated in a primary care setting. The main goal of treatment is to minimize the intensity and incidence of pain and disability. Exercises that increase the strength, flexibility, and endurance of the muscles attached at the apophysis, using the relative rest principle, are appropriate. The use of a patellar strap can provide benefit in reducing the traction force placed upon the tibial apophysis during activity. Symptoms can last for 12-24 months if untreated. As growth slows, symptoms abate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.2 Shoulder Injuries

Gregory L. Landry and Andrew M. Watson

Shoulder pain associated with radiating symptoms down the arm should raise the possibility of a neck injury (see Chapter 730). Neck pain and tenderness or limitation of cervical range of motion requires cervical spine immobilization and transfer of the athlete for further evaluation. If there is no neck pain, tenderness, or limitation of motion of the cervical spine, the shoulder is likely the site of the primary injury.

CLAVICLE FRACTURES

Clavicle fracture is one of the most common shoulder injuries (see Chapter 724.3). Injury is usually sustained by a fall on the lateral side of an adducted shoulder, on an outstretched hand, or by direct blow. Approximately 80% of fractures occur in the middle third of the clavicle. With younger children, plastic bowing of the clavicle may be present instead of an overt fracture but should be treated in the same fashion. Treatment is conservative and includes the use of an arm sling or figure-of-8 brace for comfort and protection. An arm sling is preferred because it is generally more comfortable and easier to apply with similar clinical outcomes. Healing time is shorter in comparison to that in adults—generally 3-6 weeks. An additional 2- to 3-week period of protection from contact/collision activities is recommended after clinical and radiographic healing is achieved to prevent re-injury. If nondisplaced, most medial and lateral clavicular fractures can be managed similar to middle-third clavicular fractures. Displaced lateral and medial third fractures require orthopedic consultation because of a higher incidence of acromioclavicular (AC) osteoarthritis (lateral), and physeal involvement (medial). **Distal clavicular osteolysis** is likely an overuse injury associated with slow dissolution and resorption of

bone. The cause of injury is unclear, appearing most consistent with a stress reaction or fracture at the site of considerable force. This lesion is commonly seen in weightlifting athletes and can be seen in older children. Nonoperative treatment, including activity limitations, ice, NSAIDs, and cortisone injections, can be helpful. For weightlifters, narrowing their hand spacing on the barbell and slowing descent phase of the bench press to end 4-6 cm above the chest are recommended activity modifications. For those not willing to modify weightlifting activity or those with persistent symptoms despite conservative care, surgery can be very successful and involves removal of the distal clavicle (approximately 1 cm) with no loss of strength and full return to activity anticipated.

ACROMIOCLAVICULAR JOINT SEPARATION

An AC joint separation most commonly occurs when an athlete sustains a direct blow to the acromion with the humerus in an adducted position, forcing the acromion inferiorly and medially. Force is directed toward the AC joint and coracoclavicular ligaments because of the inherent stability of the sternoclavicular joint. Patients have point tenderness at the AC joint, pain with lifting their arms above the level of their shoulder, and possibly an apparent step-off between the distal clavicle and the acromion (Fig. 728.4).

Type I AC joint injuries involve isolated sprain of the AC ligament with the periosteal sleeve intact (Fig. 728.5). There is no visible deformity, and the radiographs are normal. Pain is elicited with adduction of the humerus across the chest and palpation of the AC joint. **Type II** injuries involve disruption of the AC and coracoclavicular ligaments, as well as partial disruption of the periosteal sleeve. Radiographs may show slight widening of the AC joint, though the distance between the clavicle and the coracoid process is unchanged in comparison to the uninjured shoulder. Treatment of type I and type II AC injuries is conservative and consists of ice, NSAIDs, and a sling for immobilization. Shoulder range of motion exercises and strengthening of the rotator cuff, deltoid, and trapezius musculature are incorporated early in the rehabilitative course once pain-free range of motion is achieved in order to prevent residual joint stiffness. A short course of physical therapy may be helpful if range of motion limitations are present 2-4 weeks out from injury. Consideration for return to play is made when the patient no longer has focal AC joint tenderness, exhibits full, painless range of motion, has strength sufficient to be functionally protected from a collision or fall, and can perform maneuvers required within their sport. Typically, return to play from a type I AC injury is 1-2 weeks, and 2-4 weeks for type II.

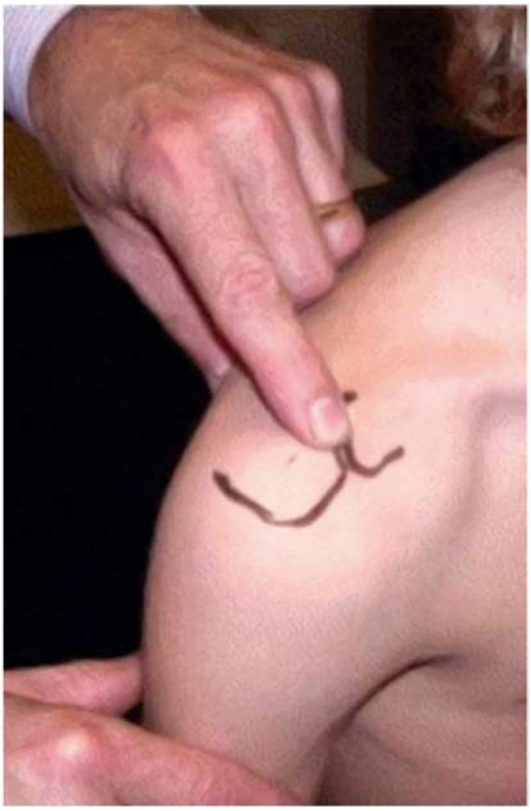

Fig. 728.4 Palpitation of acromioclavicular joint. *(From Anderson SJ. Sports injuries. Curr Probl Pediatr Adolesc Health. 2005;35:105–176.)*

Type III AC joint injury is more severe, involving further tearing of the AC and coracoclavicular ligaments and disruption of the periosteal sleeve with instability of the distal clavicle because of deltotrapezial fascial detachment. Radiographs will commonly show superior displacement of the distal clavicle from the coracoid of 25–100%. The treatment of type III AC injuries is controversial. Many can be treated nonoperatively—similar to that described for types I and II AC injuries—if there is no damage to the overlying skin or neurovascular compromise to the injured limb. The patient should be counseled that this injury is likely to result in a noticeable defect to ascertain whether this is acceptable. Surgery for type III AC injuries is uncommon and primarily for athletes involved with throwing sports or for cosmesis. **Types IV**, **V**, **and VI** AC joint injuries have progressive worsening of ligamentous and fascial disruption with varied locations of the clavicular displacement. These injuries should be referred to an orthopedist for consultation and operative repair.

ANTERIOR GLENOHUMERAL DISLOCATION

The most common mechanism of injury causing an anterior glenohumeral dislocation is contact with the shoulder abducted to 90 degrees and forcefully externally rotated. Patients complain of severe pain and that their shoulder "popped out of place" or "shifted." Patients with an unreduced anterior dislocation have a hollow region inferior to the acromion and a bulge in the anterior portion of the shoulder caused by anterior displacement of the humeral head. Abnormal sensation of the lateral deltoid region and the extensor surface of the proximal forearm should be assessed to evaluate for concomitant injury to the radial or musculocutaneous nerves, respectively.

Reduction of a dislocated shoulder should be made expediently, assuming that there is no crepitus to suggest a fracture. Numerous safe methods for closed reduction have been described, including the traction–counter traction technique, the **Stimson maneuver**, and the abduction maneuver. Postreduction radiographs are helpful and may show evidence of a posterior lateral humeral head impaction fracture **(Hill-Sachs lesion)**. Injuries to the surrounding soft tissues, including the anterior capsule and labrum, are best evaluated by MRI—often with an accompanying arthrogram of the glenohumeral joint. Once reduced, initial treatment of a dislocation includes placing the patient into an arm sling for comfort and protection. The duration of immobilization is controversial and may last from a few days to 6 weeks. The most significant risk after an acute traumatic dislocation is recurrence. Most sports medicine practitioners encourage early range of motion and strengthening exercises as tolerated. Rehabilitation focuses on progressive strengthening of the rotator cuff, deltoid, and periscapular muscles at increasing degrees of abduction and external rotation. Strengthening of the rotator cuff muscles is extremely important because they are the dynamic stabilizers of the glenohumeral joint and are integral to the prevention of future dislocation. Plyometric exercises also may be incorporated near the end of rehabilitation to improve proprioceptive function in preparation for return to athletics. Patients can return to play when strength, range of motion, and proprioception are equal to the uninjured shoulder to the extent that they are able to protect the shoulder and perform sports-specific activities without pain. Surgery is to be considered in cases of recurrent dislocations or in those individuals that fail to heal adequately after prolonged rehabilitation. Additionally, early operative repair should be considered for athletes participating in contact or collision sports that inherently have higher recurrence rates.

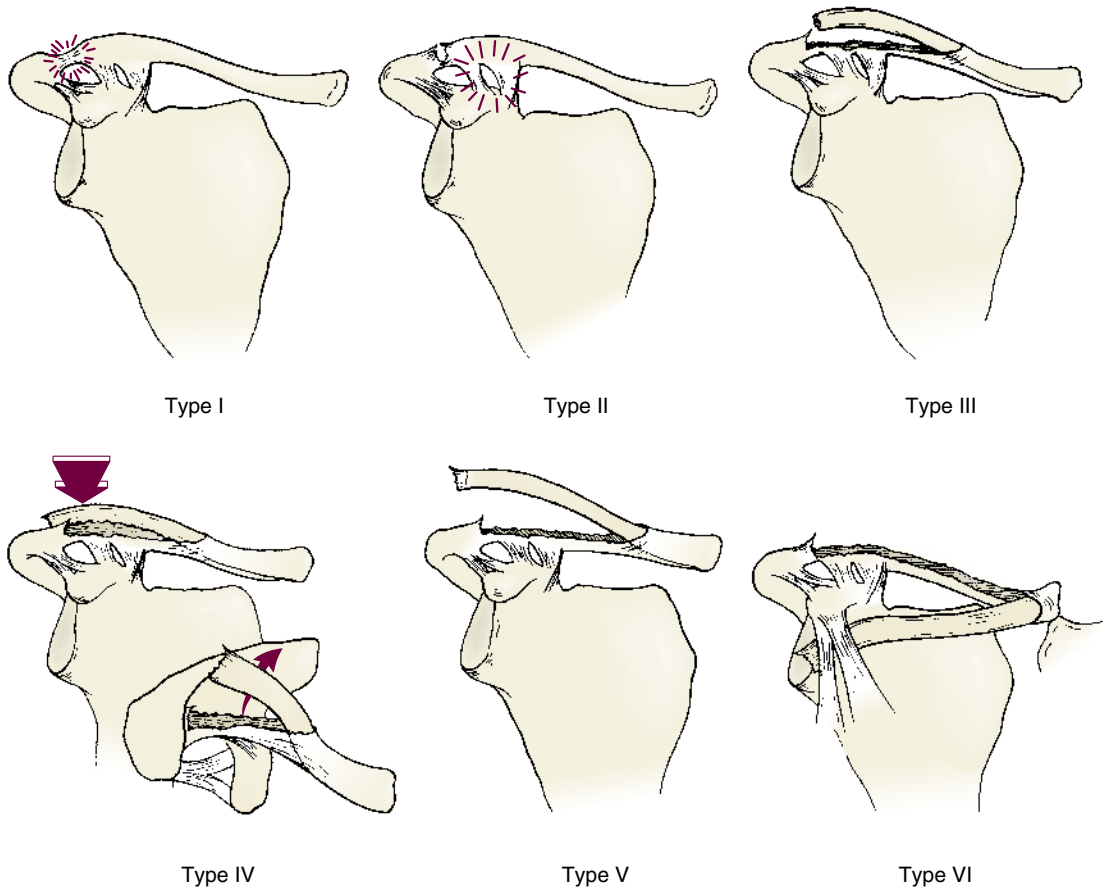

Fig 728.5 Rockwood's classification of acromioclavicular (AC) joint injuries in children. *Type 1*, sprain of the AC ligaments without disruption of the periosteal tube. *Type II*, partial disruption of the periosteal tube. This may produce some AC instability. *Type III*, large split in the periosteal tube allowing superior displacement of the lateral clavicle. *Type IV*, large split in the periosteal tube *(large arrow)* with posterior displacement of the lateral clavicle through the trapezius muscle *(curved arrow)*. *Type V*, complete disruption of the periosteal tube with displacement of the clavicle through the deltoid and trapezius muscles into the subcutaneous tissues. *Type VI*, inferior dislocation of the distal clavicle below the coracoid process. *(Redrawn from Sanders JO, Rockwood CA, Curtis RJ. Fractures and dislocations of the humeral shaft and shoulder. In Rockwood CA, Wilkins KE, Beaty JH, eds. Fractures in Children. Vol 3. Philadelphia, PA: Lippincott-Raven; 1996:974.)*

ROTATOR CUFF INJURY

The muscles of the rotator cuff consist of the supraspinatus, infraspinatus, teres minor, and subscapularis. The function of these muscles is to rotate the humerus and stabilize the humeral head against the glenoid. The supraspinatus is most commonly injured, either by an acute traumatic injury or chronic tendinosis from overuse. Specifically, rotator cuff tendinosis commonly presents with the complaint of pain with overhead arc of motion, such as with throwing, lifting, or reaching for objects above one's head. Pain is often poorly localized about the shoulder, although it may be referred to the deltoid. The onset of pain is often insidious and is commonly associated with increased frequency or duration of overhead throwing or lifting activities. Pain is exacerbated with overhead activities but is often present at rest as well; nighttime pain occurs in more severe cases. On exam, manual muscle testing of the rotator cuff muscles often produces pain and in some cases weakness in comparison to the uninjured shoulder. Supraspinatus tendinosis produces pain with active abduction against resistance in which the patient abducts the arm to 90 degrees, forward flexes to 30 degrees anterior to the parasagittal plane, and internally rotates the humerus.

The treatment of rotator cuff tendinosis includes relative rest from athletics or activities causing pain as well as the use of ice, analgesia, and/or NSAIDs. Strengthening of the rotator cuff and scapular stabilizer musculature, modifications of technique, and core strengthening are important components of rehabilitation often supervised by a physical therapist. In the young athlete, rotator cuff pain is most commonly a result of glenohumeral instability and not rotator cuff impingement syndrome. The latter is more commonly seen in adults and is caused by impingement of the rotator cuff by the bony structures superior to it. As a result, treatment focusing on stretching alone can make symptoms worse. Return to play often includes gradual increases in load placed upon the rotator cuff as the patient resumes prior activities, such as an interval throwing program in baseball.

Glenoid labrum tears may present in similar insidious fashion to rotator cuff tendinosis or may be associated with an acute traumatic dislocation. This frequently manifests with pain in the glenohumeral joint and may be associated with mechanical sensations of clicking or catching in the shoulder. This can frequently be reproduced on exam. One of the most common lesions is a superior labrum anterior and posterior (SLAP) lesion. Throwing athletes are at particular risk. The mechanism of injury is thought to be related to a traction injury along the long head of the biceps at its attachment at the superior glenoid labrum, occurring during the throwing cycle. Radiographs are usually normal. MRI with arthrogram is the best study to identify glenoid labrum pathology (Fig. 728.6).

Proximal humeral stress fracture (epiphysiolysis) is an uncommon cause of proximal shoulder pain and is suspected when shoulder pain does not respond to routine measures. Gradual onset of deep shoulder pain occurs in a young athlete involved in repetitive overhead motion, such as in baseball, tennis, or swimming, but with no history of trauma. Tenderness is noted over the proximal humerus; the diagnosis is confirmed by detecting a widened epiphyseal plate on plain



Fig. 728.6 Coronal intermediate-weighted MRI showing superior labral tear *(arrow)* and tendinosis of the supraspinatus tendon *(arrowhead)*. There is no adjacent perilabral edema, suggesting chronic injury. *(From Chang, I-Yuan J, Polster JM. Pathomechanics and magnetic resonance imaging of the thrower's shoulder. Radiol Clin N Am. 2016;54[5]:801-805. Fig. 13.)*

radiographs, increased uptake on nuclear scan, or edema of the physis on MRI. Treatment is total rest from throwing for at least 6-8 weeks.

Non–sports-related conditions that need to be considered in any child with a painful shoulder include an undiagnosed Sprengel deformity. This deformity involves the scapula, which fails to descend from its cervical region overlying the first through fifth ribs. Children often present with a shortened neckline and a lack of normal scapular thoracic motion. Malpositioning of a glenoid can cause limited forward flexion and abduction of the shoulder. An omovertebral bar is present in up to 50% of cases. This bar connects the superior medial angle of the scapula and the cervical spine and consists of fibrous cartilaginous tissue or bone. Other regional abnormalities can include scoliosis with a prominent scapula on the convex side, congenital rib anomalies, and undiagnosed Klippel-Feil syndrome. Winging of the scapula raises the question of facioscapulohumeral muscular dystrophy. Family histories can be most helpful. Primary bone tumors (see Chapter 550) common to the upper extremities include Ewing sarcoma of the scapula and osteogenic sarcoma of the proximal humerus, in addition to osteoblastomas and chondroblastomas common to the diaphysis and epiphysis of long bones. The most common presenting manifestations of osteosarcoma are pain, upper limb dysfunction, and swelling. Similar presentations can be seen in Ewing sarcoma, along with weight loss and fever. Symptoms not responding to conservative treatment require further investigation and specialty consultation.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.3 Elbow Injuries

Gregory L. Landry and Andrew M. Watson

ACUTE INJURIES

The most commonly dislocated joint in childhood is the elbow. Radial head subluxation, or "nursemaid's elbow," comprises the majority of these (see Chapter 722). Posterior dislocation is the next most common type of **elbow dislocation**, typically resulting from falling backward onto an outstretched arm with the elbow in extension. The dislocation may be complete or incomplete—termed "perched"—with the trochlea subluxed upon the top of the coronoid process. The ulnar collateral ligament (UCL) is commonly disrupted along with other components of the soft tissue capsule about the elbow. Fractures of the olecranon (>80% occurrence) or medial epicondyle may be present as well. An obvious deformity is visualized with the olecranon process displaced prominently behind the distal humerus. Careful examination of the distal radius and ulnar pulses to assess vascular integrity of the distal upper arm is important because of the potential for injury to the brachial artery. Sensation to the distal extremity should also be assessed because of possible injury to the radial, median, and ulnar nerves. Reduction should be performed as soon as possible before significant swelling and muscle spasm potentially complicate the procedure. Longitudinal traction is applied to the forearm with gentle upward pressure on the distal humerus so that the coronoid process clears the trochlea. If reduction is unable to be performed, the arm should be placed in a padded splint and sling and the patient transported to an emergency facility.

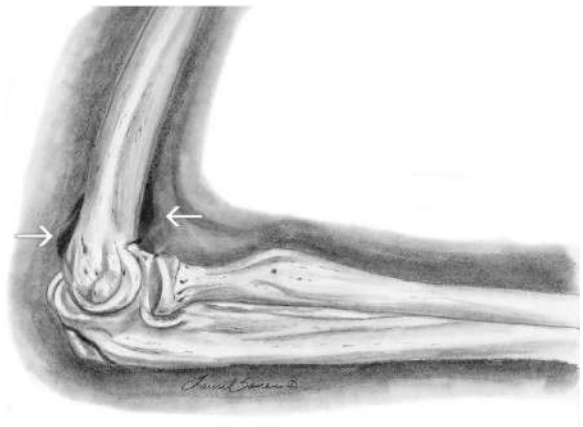

Fig. 728.7 Deflection of the supracondylar fat pad with a joint effusion (fat pad sign) *(arrows)* showing evidence of a fracture. *(Copyright Laurel Sauer, 2017.)*

Supracondylar humeral fractures can result from the same mechanism of injury as elbow dislocations and can be difficult to distinguish on exam from a posterior dislocation because of significant swelling about the elbow joint. These, too, can be complicated by concomitant injury to the brachial artery and to a lesser extent the median, radial, and ulnar nerves. The injury typically occurs in the first decade of life, which is associated with peak hyperlaxity of the elbow joint in children between the ages of 5-8 years. An acute compartment syndrome can develop after these fractures, which is associated with a fat pad sign on radiographs (Fig. 728.7). These fractures should be referred for orthopedic consultation and are discussed in more depth in Chapter 724.

Direct trauma to the elbow can cause bleeding and inflammation in the olecranon bursa resulting in **olecranon bursitis**. Aspiration is rarely required, and this injury can be managed with ice, compressive dressing, and analgesia (PRICE principles). An overlying elbow pad provides comfort during activity and prevents re-injury.

Chronic Injuries

Overuse injuries in the upper extremities occur primarily in throwing sports, sports that require repetitive wrist flexion or extension, or sports that demand weight-bearing on hands (gymnastics).

Little Leaguer's elbow is a broad term for several different elbow problems. Throwing overhand creates valgus stress to the elbow with medial opening of the joint and lateral compressive forces. **Medial elbow pain** is a common complaint of young throwers, resulting from repetitive valgus overload of the wrist flexor-pronator muscle groups and their attachment on the medial apophysis. In preadolescents who still have maturing secondary ossification centers, traction apophysitis of the medial epicondyle is likely. Patients have tenderness along the medial epicondyle; pain is exacerbated by valgus stress or resisted wrist flexion and pronation. Wrist pain may be present in more severe cases. Radiographs may show widening of the growth plate at the medial

apophysis in comparison to the uninjured elbow. Treatment includes no throwing for 4-6 weeks and pain-free strengthening and stretching of the flexor-pronator group followed by a 1-2 week progressive functional throwing program with careful rehabilitation. Incorporation of core strengthening and scapular stabilizing exercises, as well as addressing proper throwing mechanics (to reduce the load upon the medial elbow), are important components of the rehabilitation program. Little Leaguer's elbow has to be treated with a period of rest from throwing because of the risk of nonunion of the apophysis and chronic pain. If pain occurs acutely, an avulsion fracture of the medial epicondyle must be considered. Radiographs should be taken in any thrower with acute elbow pain. If the medial epicondyle is avulsed (Fig. 728.8), orthopedic consultation is indicated.

In older adolescents and young adults with a fused apophysis, the structure at the elbow vulnerable to injury is the UCL. UCL sprains/tears are common in sports requiring high-velocity throwing or overhead activities. Medial elbow pain that is worst during the acceleration phase of throwing is common. A loss of throwing velocity and control, as well as a sensation of elbow joint "opening" during throwing is also frequently described. On exam, focal tenderness to palpation over the UCL is present. Additionally, laxity may be appreciated with valgus stress of the elbow when flexed to 30 and/or 90 degrees. Radiographs are generally unremarkable. Diagnostic ultrasonography or MRI with arthrography is often necessary to assess the integrity of the UCL. Partial tears can be treated with a period of time off from throwing (2-4 weeks) followed by careful progressive rehabilitation as discussed earlier for medial elbow pain. If there is a complete tear, surgical repair is indicated if the athlete desires to continue a pitching career.



Fig. 728.8 The many faces of little Leaguer's elbow in a 14-yr-old pitcher. A, AP radiograph and coronal oblique fat-saturated T2-weighted MRI demonstrate features of chronic medial epicondyle stress injury *(yellow arrow)* as well as findings of capitellar osteochondritis dissecans *(white arrowhead)*. Proximal medial ulnar collateral ligament edema/grade 1 sprain also noted at the humeral attachment *(red arrow)*. B, Sagittal short tau inversion recovery and fat-saturated T1-weighted MR arthrogram images emphasize the classic features of injury to the "metaphyseal equivalent" bone deep to the disorganized and obliterated secondary physis of the ossifying capitellum. *(From Braithwaite KA, Marshall KW. The skeletally immature and newly mature throwing athlete. Radiol Clin N Am. 2016;54[5]:841–855. Fig. 11.)*

Medial epicondylitis, or golfer's elbow**,** is another common cause of medial elbow pain in the individual with fused apophyses. It is commonly caused by overuse of the flexor pronator muscle groups at their origin at the medial humeral epicondyle. This occurs frequently in athletics or activities with repetitive wrist flexion. Tenderness is noted over the medial epicondyle and exacerbated by passive wrist extension or resisted wrist flexion. Treatment includes rest from the inciting activity, ice, stretching and strengthening of the wrist flexors, forearm straps, counterforce bracing, and analgesia. Local injection of corticosteroids can be considered as an adjunctive treatment if initial conservative measures fail. Ulnar nerve dysfunction can be a complication of valgus overload and can occur with any of the diagnoses previously discussed. Persisting paresthesia or motor weakness in the ulnar nerve distribution should be evaluated with electromyography and nerve conduction studies. Diagnostic ultrasonography can also be of use to assess for focal thickening of the nerve, as a sign of irritation, as well as dynamically visualizing the nerve through the arc of elbow flexion to assess for subluxation over the medial epicondyle (Fig. 728.9).

Lateral elbow pain can be caused by compression during the throwing motion at the radiocapitellar joint. **Panner disease** is osteochondrosis of the capitellum that occurs between ages 7 and 12 years (Fig. 728.10). **OCD** of the capitellum occurs at age 13-16 years (see Fig. 728.1). Although patients with both conditions present with insidious onset of lateral elbow pain exacerbated by throwing, patients with OCD have mechanical symptoms (popping, locking) and, more commonly, decreased range of motion. Patients with Panner disease have no mechanical symptoms and often have normal range of motion. The prognosis of Panner disease is excellent, and treatment consists of relative rest (no throwing), brief immobilization, and repeat radiographs in 6-12 weeks to assess bone remodeling. In OCD, radiographs show a more focal lesion in the capitellum with eventual flattening and potentially fragmentation. MRI can be very helpful in early diagnosis and with subsequent staging. A diagnosis of OCD requires orthopedic consultation, with treatment depending on the severity of the lesion and fragmentation.

Lateral epicondylitis, or "tennis elbow," is the most common overuse elbow injury in adults but is relatively uncommon in children and adolescents (Fig. 728.11). It is a tendinosis of the extensor muscle origin at the lateral humeral epicondyle, which is commonly found in individuals performing activities requiring repetitive or prolonged grip. Tenderness is localized over the upper lateral epicondyle and is worsened with passive wrist flexion or resisted wrist extension. Treatment includes relative rest, analgesia, and specific stretching and strengthening exercises for the elbow and forearm. As with medial epicondylitis, corticosteroid injection can be considered as an adjunctive treatment if initial conservative measures fail. Improper equipment (i.e., wrong grip size or overstrung racket) and poor technique can contribute to the onset of symptoms. Return to play should be gradual and progressive to prevent re-injury.

Elbow injuries can be minimized but not necessarily prevented by preseason stretching and strengthening exercises. The importance of core strengthening and scapular stabilization with respect to preventing elbow and shoulder injuries in the throwing athlete cannot be overstated. The most important consideration for preventing elbow injuries in throwers is limitation of the number of pitches and advising players, coaches, and athletes that they should stop immediately when they experience elbow pain. If it persists, they need medical evaluation. It has been recommended that a young pitcher have age-specific limits

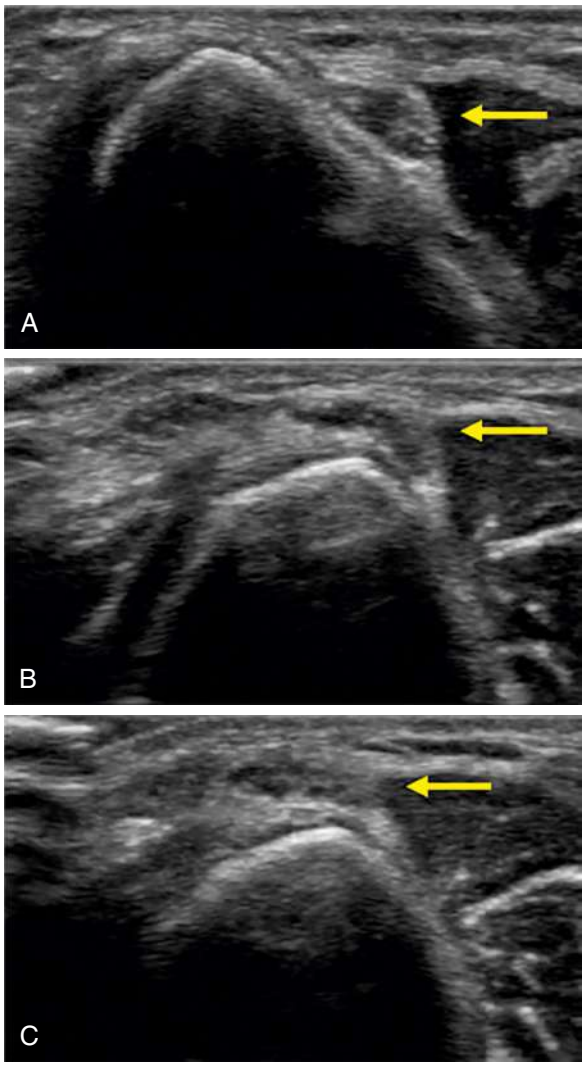

Fig. 728.9 Ulnar nerve subluxation. Dynamic ultrasound imaging of the ulnar nerve (arrow) in the ulnar groove at the elbow. A, The ulnar nerve positioned appropriately in the ulnar groove with the elbow extended. With elbow flexion, (B) the nerve becomes perched upon the medial epicondyle. As the elbow moves into terminal flexion, (C) the nerve is completely dislocated anteriorly over the medial epicondyle. *(Courtesy Nicholas Goyeneche, MD, ultrasound clinic files, Ochsner Clinic Medical Center.)*

on pitch counts, including the number of pitches thrown per game and per week, as well as maintaining appropriate days off between games pitched. A good rule of thumb is that the maximal number of pitches per game should be approximately 6 times the pitcher's age in years.

Other less-common problems that cause elbow pain are ulnar neuropathy/subluxation, tricipital or bicipital tendonitis (distal), olecranon apophysitis, and loose bodies. Non–sports-related injuries that need to be considered in the child with a painful elbow include undiagnosed congenital conditions such as radial dysplasia, including radial ulnar synostosis and mild persistent brachial plexus palsy. The elbow is not an uncommon site for inflammatory arthritides, including juvenile idiopathic arthritis, sepsis, hemophilia, and sickle cell disease. Neoplasia to consider includes osteoblastomas and chondroblastomas, which are common in the diaphysis and epiphysis of longer bones, in addition to osteosarcoma. As always, in the child with persistent symptoms who is not responding to conservative care, further diagnostic workup is indicated.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

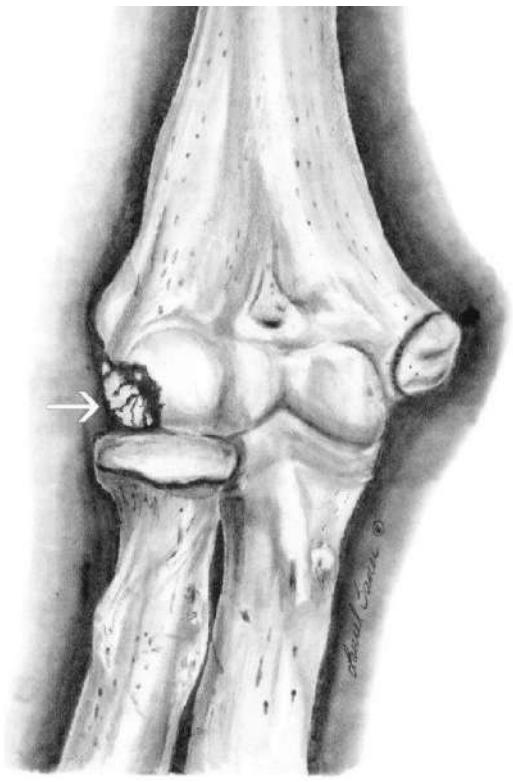

Fig. 728.10 Panner disease. Note fragmentation of the humeral capitellum and flattening of the articular surface *(arrow). (Copyright Laurel Sauer, 2017.)*

728.4 Low Back Injuries

Gregory L. Landry and Andrew M. Watson

SPONDYLOLYSIS, SPONDYLOLISTHESIS, AND FACET SYNDROME

Spondylolysis

Spondylolysis, a common cause of back pain in athletes, is a stress fracture of the pars interarticularis (see Chapter 720.6). It can occur at any vertebral level but is most likely at L5. Complete spondylolysis has never been found in the newborn. Its occurrence increases between the ages of 5.5 and 6.5 years to a rate of 5%. Prevalence in adolescent athletes evaluated for low back pain is 13–47%. Besides hyperextension that causes an acute fracture, the mechanism of injury is either a congenital defect or hypoplastic pars. This is exacerbated by repetitive lumbar extension loading. Ballet, weightlifting, gymnastics, and football are examples of sports in which repetitive extension loading of the lumbar spine frequently occurs.

Patients often present with pain of insidious onset. However, there may be a precipitating injury, such as a fall, or a single episode of hyperextension. The pain is worse with extension, may radiate to the buttocks, and can eventually affect activities of daily living. Rest or supine positioning usually alleviates the pain.

On examination, the pain is reproduced with lumbar extension while standing, especially when standing on one leg (single-leg hyperextension test). Limited forward spinal flexion and tight hamstrings may be seen. Neurologic examination is generally normal. There is often well-localized tenderness to deep palpation just lateral to the involved spinous process.

The diagnosis can be confirmed by finding a pars defect on an oblique lumbar spine radiograph. The defect is rarely seen on anteroposterior

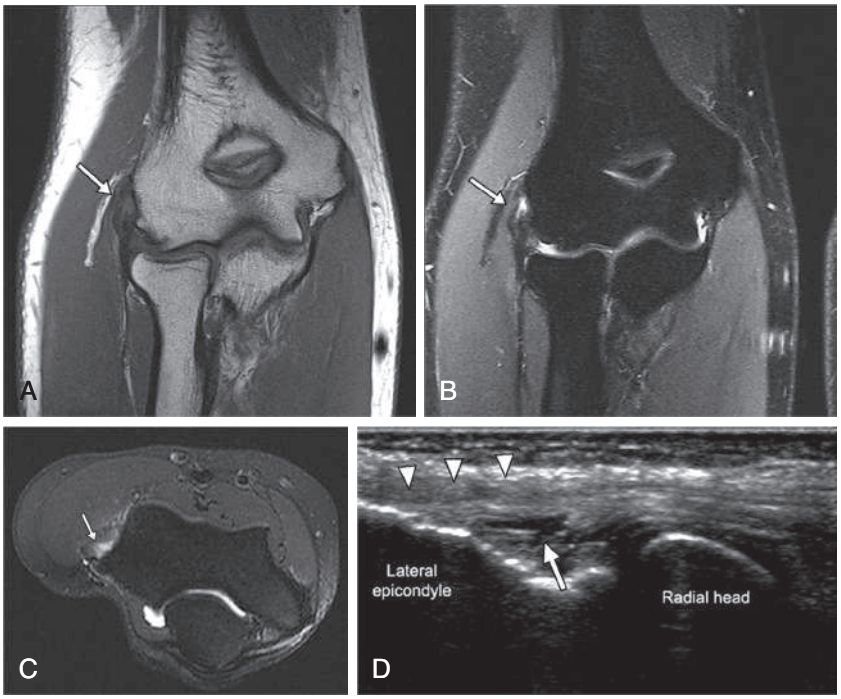

Fig. 728.11 A 22-yr-old tennis player with persistent lateral elbow pain despite 3 months of physical therapy. **A,** Coronal T1 sequence shows thickening and intermediate signal in the common extensor tendon (CET; *arrow*). **B,** Coronal T2 fat suppression (FS) (CET; *arrow*) and **(C)** axial proton density FS sequences reveal fluid signal within the CET and discontinuity of tendon fibers, consistent with a partial-thickness tear (CET; *arrow*). **D,** Corresponding long axis ultrasound image shows an anechoic fluid cleft *(arrow)* in the undersurface of the CET *(arrowheads). (From Gustas CN, Lee KS. Current imaging concepts and image-guided treatments for the injured thrower's elbow. Radiol Clin N Am. 2016;54[5]:817–839. Fig. 2.)*

(AP) and lateral views. MRI or bone single-photon emission CT (SPECT) is needed to confirm diagnosis if radiographs are normal and spondylolysis is suspected. A plain CT scan can help identify the degree of bony involvement and is sometimes used to assess healing.

Treatment includes pain relief and activity restriction. Rehabilitation consisting of trunk strengthening, hip flexor stretching, and hamstring stretching is important in most cases. A thoracic lumbar sacral orthotic may be considered for symptom management in cases in which conservative measures fail, but the overall benefit of bracing on healing is unclear.

Spondylolisthesis and Facet Syndrome

Spondylolysis, spondylolisthesis, and facet syndrome are injuries to the posterior elements of the vertebrae. Spondylolisthesis occurs when bilateral pars defects exist and forward displacement or slippage of a vertebra occurs upon the vertebra inferior to it (see Chapter 720.6). Facet syndrome has history and physical examination findings similar to those of spondylolysis. It is caused by instability or injury to the facet joint, posterior to the pars interarticularis and at the interface of the inferior and superior articulating processes. Facet syndrome can be established by identifying facet abnormalities on CT or by exclusion, if a radiograph and MRI rule out spondylolysis.

Treatment of posterior element injuries is conservative and directed at reducing the extension-loading activity, often for 2-3 months. Body mechanics, posture principals, core strengthening, and lumbar pelvic stabilization routines can be very helpful in the functional recovery of the motivated athlete. Walking, swimming, and cycling can be appropriate exercises during the rehabilitation phase. Rarely, spinal segmental fusion can be indicated in the athlete with spondylolisthesis and persistent symptomatic segmental instability despite conservative care.

LUMBAR DISK HERNIATION, STRAIN, AND CONTUSION

Intervertebral disk injury in children and adolescents is uncommon. Symptoms include pain with prolonged standing and prolonged periods of lumbar flexion, such as sitting in a car. Presentation is variable, and patients may report an acute pain onset with an obvious inciting event or an insidious onset with a history of heavy lifting or repetitive axial load activities. In contrast to the selective motor and sensory deficits often observed in adults with disk herniation, athletes younger than 20 years of age less commonly have pain or tenderness over the course of the sciatic nerve. Physical examination findings may be minimal but usually include pain with forward flexion and lateral bending. It is unusual to have a positive straight leg test or any neurologic deficit in the young athlete with an injured disk. There may be tenderness of the vertebral spinous process at the level of the disk injury. A general aching sensation in the lower back or upper buttocks may be present. MRI usually confirms a clinical diagnosis. Assuming the herniation is not large and the pain is not intractable, treatment is conservative with analgesia and physical therapy. Surgery is rarely necessary.

Acute lumbar strain or contusion can be seen in the younger athlete and is usually associated with precipitating activity often outside of the normal routine. Physical examination reveals tenderness in the paraspinal and lateral soft tissues often associated with recreating the mechanism of injury. Thoracic and lumbar strain in the school-age child is frequently associated with obesity, deconditioning, positive family history, and poorly supervised and equipped recreational activity. Up to 20% of youths have experienced back pain at some point in their life before the age of 15 years. The backpack is the most common cause of back pain of a benign nature in children, with up to 74% of school backpack–wearers experiencing pain. Back pain is more common with the heavy backpack (>10–20% of body weight), female sex, large body mass index, and single shoulder strap.

Treatment is conservative and includes analgesia, myofascial release, massage, and physical therapy, as tolerated. The natural history of acute back strain in adults is that 50% are better in 1 week, 80% in 1 month, and 90% in 2 months, regardless of therapy. The course of back pain in young athletes is likely similar given the elimination of obvious precipitating influence and/or activities, as discussed previously.

Sacroiliitis manifests as pain over the sacroiliac joints; it is usually chronic but is occasionally associated with a history of trauma. Patients

have a positive result with the **Patrick test**, performed in the supine position by resting the foot of the affected side across the opposite knee ("figure-4" position), stabilizing the contralateral iliac crest, and externally rotating the hip on the affected side (pushing the knee down and lateral). Symptomatic improvement with knee-to-chest maneuvers and subsequent posterior pelvic tilt may be present. A radiograph of the sacroiliac joints is indicated, and if results are positive, exploration for a rheumatologic disease (ankylosing spondylitis [see Chapter 197], juvenile idiopathic arthritis [see Chapter 196], or inflammatory bowel disease [see Chapter 382]) is warranted.

Treatment is with relative rest, NSAIDs, and physical therapy. Ankylosing spondylitis is more likely if the onset of lower back pain is before 40 years of age, if there is morning stiffness demonstrating improvement with activity, a family history is present, there is clear benefit from antiinflammatory medication, and if the pain has a gradual onset having lasted longer than 3 months.

OTHER CAUSES

Non–sports-related causes of low back pain in the young athlete are numerous and include infection (osteomyelitis, diskitis) and neoplasia (see Chapter 720.5). These should be considered in patients with fever, weight loss, other constitutional signs, or lack of response to initial therapy. Osteomyelitis of the lower back or pelvis is often, but not always, associated with fever. Undiagnosed Scheuermann disease needs to be considered with a history of chronic back pain; it is more common in males and younger adolescents and should be distinguished from symptomatic postural roundback and congenital decompensating kyphosis. Atypical Scheuermann disease or thoracolumbar apophysitis can progress and become the pediatric equivalent of an adult compression fracture. Benign tumors of the spine include osteoid osteoma, which presents with intense focal nighttime pain that is not activity related and is almost always relieved by aspirin or NSAIDs. Undiagnosed osteoblastoma, eosinophilic granuloma, aneurysmal bone cyst, and fibrous dysplasia are additional benign tumors not to be excluded. Malignant spinal tumors include Ewing sarcoma (onion skin appearance) and osteogenic sarcoma (sunburst pattern); both are associated with the *Codman triangle*, which is the triangular area of new subperiosteal bone seen on radiographs when a tumor raises the periosteum away from the bone. Metastatic tumors of the spine include neuroblastoma, spinal cord tumors, leukemia, and lymphoma. Wilms tumor can also metastasize to the spine and be associated with hemihypertrophy. Referred pain to the spine always needs to be considered. Conditions that can refer pain include pyelonephritis, renal osteodystrophy, pneumonia, endocarditis, cholecystitis, nephrolithiasis, pancreatitis, megacolon, constipation/ileus, hiatal hernia/reflux, pelvic inflammatory disease, and sickle cell crisis. Undiagnosed pregnancy is a consideration in the age-appropriate female. Psychogenic pain and fibromyalgia can be seen in children. Child abuse can present in the spine, with soft tissue injuries more common than fractures. Posterior rib and spinous process fractures can be seen in up to 30% of abused children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.5 Hip and Pelvis Injuries

Gregory L. Landry and Andrew M. Watson

Injuries to the hip and pelvis represent a small percentage of sports injuries, but they are potentially severe and require prompt diagnosis. Hip pathology can manifest as knee pain with normal findings on knee examination.

In children, **transient synovitis** (see Chapter 719.2) is the most common nontraumatic cause of hip pain. It usually manifests with acute onset of a limp, with the child refusing to use the affected leg and painful range of motion on examination. There may be a history of minor trauma or a recent viral infection. This is a self-limiting condition that usually resolves in 48-72 hours.

Legg-Calvé-Perthes disease (avascular necrosis of the femoral head) also presents in childhood with insidious onset of limp and hip pain (see Chapter 719.3).

Until skeletal maturity (Table 728.2), younger athletes are susceptible to apophyseal injuries (e.g., the anterior superior iliac spine). **Apophysitis** develops from overuse or from direct trauma. **Avulsion fractures** occur in adolescents playing sports requiring sudden, explosive bursts of speed (see Fig. 728.2). Large muscles contract and create force greater than the strength of the attachment of the muscle to the apophysis. Biomechanical susceptibility of the pelvis allows separation to occur in the cartilaginous region between the apophysis and the adjoining bone. The most common sites of pelvic avulsion fractures are the anterior superior iliac spine (sartorius and tensor fasciae lata), anterior inferior iliac spine (rectus femoris), lesser femoral trochanter (iliopsoas), ischial tuberosity (hamstrings), and the iliac crest (abdominal muscles). Symptoms include localized pain and swelling with decreased strength and range of motion. Bilateral radiographs are important for comparison to assess for displacement, if any, of the fracture fragment. Significant displacement or the presence of a large fragment may require orthopedic consultation. Initial treatment includes ice, analgesics, rest, and pain-free range of motion exercises. Crutches are usually needed initially for ambulation. Surgery is not typically indicated because most of these fractures—even large or displaced ones—heal well. Direct contact to the bone around the hip and pelvis causes exquisitely tender subperiosteal hematomas called "**hip pointers**." These injuries are more commonly seen around the anterior superior iliac spine and the iliac crest. Limited active range of motion can be identified about the hip, brought on by contracture of locally attached musculature such as hip flexors and hip abductors. Symptomatic care includes rest, ice, analgesia, and protection from re-injury.

Slipped capital femoral epiphysis usually occurs among 11- to 15-year-olds during the time of rapid linear bone growth (see Chapter 719.4) and often presents with complaints of pain in the groin area or, on occasion, referred pain felt at the knee. Bilateral hip radiographs confirm the diagnosis.

A **femoral neck stress fracture** can manifest as vague progressive hip pain in an endurance athlete. Females are at higher risk. This diagnosis should be suspected in the running athlete with vague anterior

Table 728.2 Age of Appearance and Fusion of Apophyses in Hip and Pelvis

APOPHYSIS	APPEARANCE (YR)	FUSION (YR)	RELATED MUSCLE GROUP(S)
Anterior inferior iliac spine	13-15	16-18	Quadriceps
Anterior superior iliac spine	13-15	21-25	Sartorius
Lesser trochanter	11-12	16-17	Iliopsoas
Greater trochanter	2-3	16-17	Gluteal
Ischial tuberosity	13-15	20-25	Hamstrings
Iliac crest	13-15	21-25	Abdominal obliques Latissimus dorsi

From Waite BL, Krabak BJ. Examination and treatment of pediatric injuries of the hip and pelvis. *Phys Med Rehabil Clin N Am.* 2008;19:305–318.

thigh pain without a history of trauma or acute injury. On examination, there may be pain with passive stretch of the hip flexors and pain with hip rotation. If radiographs do not demonstrate a periosteal reaction consistent with a stress fracture, MRI may be indicated to confirm the suspected diagnosis and determine the location of the fracture. Orthopedic consultation is necessary in femoral neck stress fractures because of their predisposition to nonunion and displacement with minor trauma or continued weight-bearing. These fractures carry increased risk of avascular necrosis of the femoral head. Whereas compression (inferomedial) side femoral neck stress fractures can typically be treated conservatively with non–weight-bearing, tension side (superolateral femoral neck) fractures may be at particular risk of progression and often require surgical fixation.

Osteitis pubis is an inflammation at the pubic symphysis that may be caused by excessive side-to-side rocking of the pelvis. It can be seen in an athlete in any running sport and is more common in sports requiring additional use of the adductor muscles such as ice hockey, soccer, and inline skating. Athletes typically present with vague groin pain that may be unilateral or bilateral. On physical examination, there is tenderness over the symphysis and sometimes over the proximal adductors. Adduction strength testing causes discomfort. Radiographic evidence (irregularity, sclerosis, widening of the pubic symphysis with osteolysis) may not be present until symptoms are present for 6-8 weeks; MRI is more sensitive to early changes. Relative rest for 6-12 weeks may be required. Some patients require corticosteroid injection as adjunctive therapy. Ultrasound needle guidance may be used to improve the accuracy of the injection while simultaneously avoiding injury to surrounding structures, such as the bladder, and vascular structures of the genitalia.

Acetabular labrum tears can occur in the hip, similar to glenoid labrum tears in the shoulder. Athletes may have a history of trauma and complain of sharp anterior hip pain associated with a clicking or catching sensation. Clinical diagnosis is often difficult; magnetic resonance arthrography is the gold standard for diagnosis, but MRI may be useful as well.

Snapping hip syndrome is caused by the iliopsoas musculotendinous unit riding over the pectineal eminence of the pelvis, anterior hip capsule, or the iliotibial band (ITB) over the greater trochanter. Lack of flexibility in these muscles results in snapping, as the musculotendinous unit slides over the associated bony prominence. It is most commonly seen in ballet dancers and runners, and it can occur as an acute or, more commonly, overuse injury. Athletes present with either a painful or painless click or snap in the hip, usually located lateral or anterior and deep within the joint. Examination often reproduces the symptoms. Radiographs are not usually needed in the workup. Ultrasound examination can be useful to visualize the anatomic structures in question causing the snapping sensation. Core weakness may be present, leading to excessive movement about the hip girdle contributing to increased sliding of the tight muscle over the boney prominence. Treatment involves analgesia, relative rest, biomechanical assessment, core flexibility, and stretching/strengthening of the involved soft tissue. Patients with concomitant greater trochanteric bursitis may benefit from a corticosteroid injection into the inflamed bursa to improve pain control and facilitate rehabilitation. The athlete may return to activity as tolerated. Common soft tissue injuries around the hip and pelvis include strain and tendinosis of the hip flexors (groin) and hamstrings in addition to quadriceps contusions and greater trochanteric bursitis.

The term **athletic pubalgia** is commonly used to describe a number of different pathologies that may cause lower abdominal or groin pain. Often called a sports hernia, this is a source of confusion as no true hernia exists through the inguinal canal or abdominal wall. The pathophysiology stems from tissue injury to the structures that comprise the pubic aponeurosis, most commonly the tendinous attachment of the abdominal and hip adductor musculature. Like a true hernia, pain may radiate into the anterior thigh, inguinal region, perineum, and/or scrotum. Physical exam may exhibit tenderness over, or adjacent to, the pubic ramus and/or reproduction of pain with resisted abdominal flexion or hip adduction. MRI, CT scan, and bone scan can be helpful in ruling out other diagnoses but usually are negative. Some radiology departments may have MRI protocols specific for athletic pubalgia that provide more detailed imaging of the pathologic area. Patients who continue with symptoms despite conservative care, such as physical therapy, may be candidates for surgical intervention.

Femoroacetabular impingement (FAI) may coexist with athletic pubalgia to produce groin pain. FAI is defined as an abnormal contact between the femoral neck and the acetabulum as a result of excessive bone on the acetabular rim, the femoral neck, or both. X-rays and MRI can be diagnostic. As in athletic pubalgia, a period of rest and rehabilitation should be attempted, and those who fail conservative treatment should be referred to a sports medicine specialist.

Undiagnosed **non–sports-related conditions** need to be considered. Differential diagnoses may include the epiphyseal dysplasias, congenital or developmental hip dysplasia, additional causes of avascular necrosis, including sickle cell disease, Gaucher disease, rheumatoid arthritis, and other collagen disorders and steroid therapy. Inguinal hernia should be recognized in those patients with groin pain exacerbated with coughing/Valsalva maneuver and a palpable mass in the groin. Traumatic hip dislocations are relatively rare in children but should not be overlooked. Leg-length discrepancies (usually >1 cm) can be symptomatic at the hip in an otherwise healthy child. Common tumors in the lower extremities include osteosarcoma along with osteoblastoma, aneurysmal bone cysts, and fibrous dysplasia (more common in the pelvis). Metastatic tumors to the lower extremities include neuroblastoma, lymphoma, and leukemic infiltration with joint arthralgia. Child abuse always needs to be considered in a young patient with musculoskeletal pain.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.6 Knee Injuries

Gregory L. Landry and Andrew M. Watson

Knee pain is common among adolescents. Acute knee injuries that cause immediate disability and/or effusion are likely to be due to fracture, patellar dislocation, anterior or posterior cruciate ligament injury, or meniscal tear. The mechanism of injury is usually a weight-bearing event. Physeal injuries tend to predominate in younger patients, whereas more skeletally mature adolescents tend to sustain ligamentous injuries. If the knee swells more immediately (within several hours of injury), the swelling is likely caused by a hemarthrosis and more severe injury. The injury most likely to occur with a hemarthrosis is an **anterior cruciate ligament (ACL)** injury. This injury (rare in children younger than 12 years) is usually caused by direct contact, landing off-balance from a jump, quickly changing direction while running, or hyperextension. Instability is often present but may be hard to detect in the presence of significant swelling. Females are more than twice as likely as males to disrupt their ACL, often during sports such as basketball or soccer. Occasionally, these injuries are associated with an avulsion injury of the anterior tibial spine. Most athletes with significant ACL injury need orthopedic consultation with consideration of ACL reconstruction. Chronic ACL insufficiency may increase the risk of meniscal injury, early osteoarthritis, and further joint dysfunction. Physeal-sparing reconstructions with minimal risk of growth arrest or angular deformity have been reported with success in children younger than 12 years and adolescents.

Posterior cruciate ligament (PCL) injury occurs from a direct blow to the region of the proximal tibia when the knee is flexed, such as might occur with a dashboard injury or a fall to the knees in volleyball. PCL injuries are rare and are usually treated nonsurgically.

Medial collateral ligament injuries typically result from a valgus blow to the outside of the knee. Isolated **lateral collateral ligament** injuries are uncommon and result from significant varus knee stress. Because they are extra-articular, lateral collateral and medial collateral ligament injuries should not produce a significant knee effusion and

are generally less disabling. Isolated medial and lateral collateral injuries are generally managed nonsurgically with conservative care and appropriate rehabilitation.

Meniscal tears generally occur by the same mechanisms as ACL injuries. They are often associated with less hemarthrosis, significant joint line pain, and increased pain with full knee flexion. MRI will usually yield the diagnosis; conservative care, including PRICE principles, is therapeutic for smaller injuries. Orthopedic consultation is indicated for meniscus tears in children and adolescents, and surgery may be indicated for larger tears, displaced tears, or those not healing with conservative care over 6-8 weeks. An isolated meniscal tear in a child younger than 10 years of age is unusual. The surgical choice is often repair of the meniscus rather than resection because of the increased potential in children for cartilaginous healing. Discoid meniscus (an anatomic variant covering lateral tibial plateau) should be considered in children younger than 12 years of age and those with a suspected meniscus injury without a history of notable trauma.

Patellar dislocation occurs most often as a noncontact injury when the quadriceps muscles forcefully contract to extend the knee while the tibia is externally rotated in relation to the femur. Patellar dislocation is the second most common cause of hemarthrosis. The patella is almost always dislocated laterally, and this motion tears the medial patellar retinaculum, causing bleeding in the joint. Recurrent episodes of patellar instability are associated with less swelling. Patellar dislocations are often associated with genu valgum, external tibial torsion, and general ligamentous hyperlaxity. Exercises to strengthen the quadriceps, particularly the vastus medialis, and the use of patella-tracking braces may be helpful. Recurrent instability can require surgical intervention. Surgical stabilization of the medial patellar tissues and lateral retinacular release can be helpful in more difficult cases.

INITIAL TREATMENT OF ACUTE KNEE INJURIES

The physician should inspect for an effusion and obvious deformities; if any deformity is present, the physician should assess neurovascular status and transfer the patient for emergency care as indicated. If no gross deformities are present and neurovascular integrity is intact, initial maneuvers include full passive extension and gentle valgus and varus stress to the knee while in extension. *Any laxity to varus or valgus stress in full extension implies a multiligamentous injury*. Comparison to the noninjured knee is always helpful for assessing degrees of laxity and range of motion. The patient's ability to contract the quadriceps should be noted. Pain occurring with quadriceps contraction, or the inability to contract the quadriceps muscle, implies an injury to the extensor mechanism. Tenderness over the medial patella, medial retinaculum, or above the adductor tubercle is associated with a patellar dislocation (usually lateral). Point tenderness is consistent with fracture or injury to the underlying structure. Meniscal tears usually manifest as tenderness along the joint line, accentuated with flexion of the knee beyond 90 degrees. Pain or limitation in either flexion or extension while rotating the tibia implies a meniscal injury. Ligament injury is manifested as pain or laxity with the appropriate maneuver (Fig. 728.12).

If a patient cannot weight-bear without pain, or has clinical signs of instability, significant swelling, or any other major concern, the knee should be immobilized and crutches provided. The Ottawa knee rule, which has been validated for children over 5 years of age, helps determine which patients with mild knee injuries require radiographs. X-rays should be obtained if *any* of the following apply: 55 years or older, point tenderness of fibular head, tenderness of the patella, inability to flex knee to 90 degrees, or inability to bear weight (inability to take four steps) both immediately after the injury and in the emergency department.

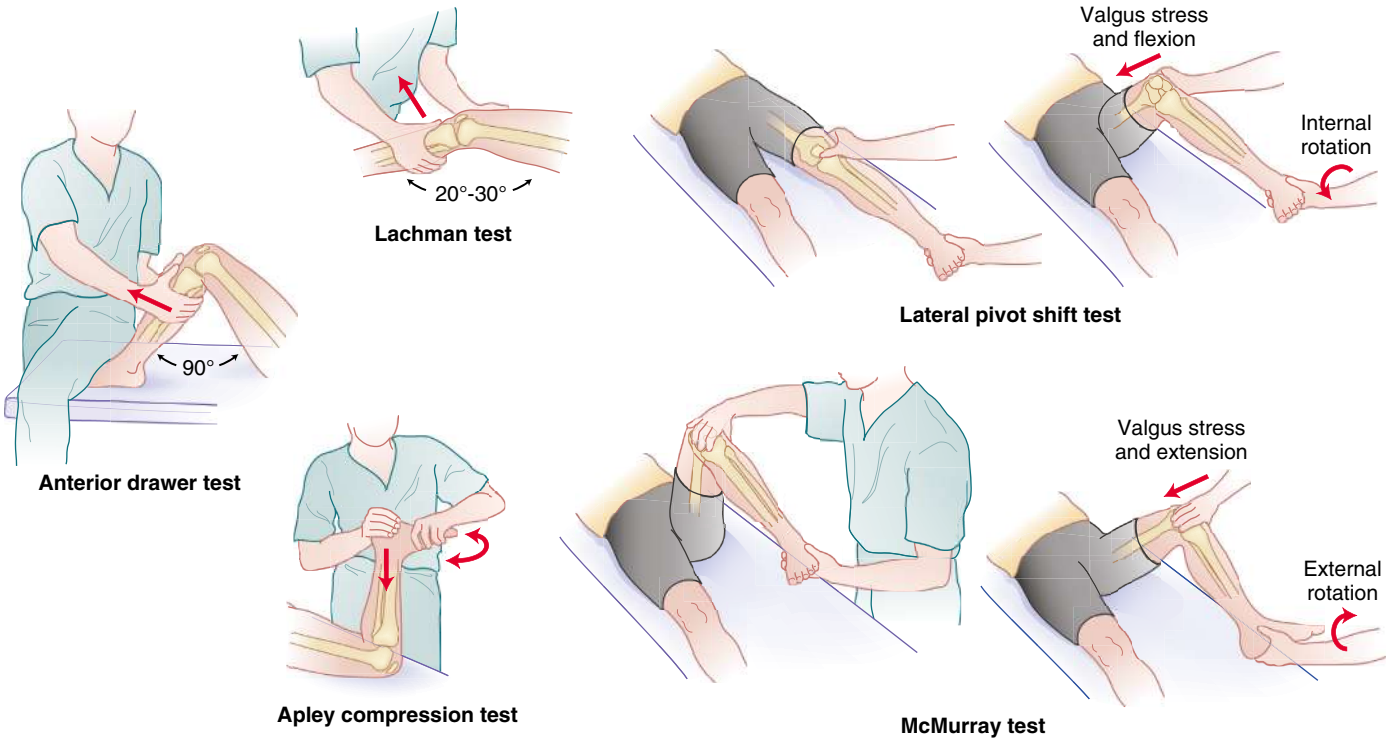

Fig. 728.12 Examination maneuvers include the Lachman, anterior drawer, lateral pivot shift, Apley compression, and McMurray tests. The Lachman test, performed to detect anterior cruciate ligament (ACL) injuries, is conducted with the patient supine and the knee flexed 20-30 degrees. The anterior drawer test detects ACL injuries and is performed with the patient supine and the knee in 90 degrees of flexion. The lateral pivot shift test is performed with the patient supine, the hip flexed 45 degrees, and the knee in full extension. Internal rotation is applied to the tibia while the knee is flexed to 40 degrees under a valgus stress (pushing the outside of the knee medially). The Apley compression test, used to assess meniscal integrity, is performed with the patient prone and the examiner's knee over the patient's posterior thigh. The tibia is externally rotated while a downward compressive force is applied over the tibia. The McMurray test, used to assess meniscal integrity, is performed with the patient supine and the examiner standing on the side of the affected knee.

If the patella is dislocated, reduction may be achieved with gentle active assistive knee extension. Straight-leg immobilizers offer no structural support and are only used for comfort and reminding the patient to be careful with any weight-bearing. A derotational hinge brace may be indicated for stabilization, such as after an injury involving both the ACL and medial collateral ligament. The leg should be elevated, and an elastic wrap can be applied for compression (PRICE principles).

CHRONIC INJURIES

Patellofemoral Stress Syndrome

Patellofemoral stress syndrome (PFSS), or runner's knee, is the most common cause of anterior knee pain. PFSS is also known as **patellofemoral pain syndrome** or **patellofemoral dysfunction** (see Chapter 718.5). It is a diagnosis of exclusion used to describe anterior knee pain that has no other identifiable pathology. Chondromalacia may be seen in association with softening of the articular cartilage underneath the patellar surface. Pain is usually difficult to localize. Patients indicate a diffuse area over the anterior knee as the source, or they might feel as if the pain is originating from underneath the patella. Bilateral pain is common, and pain is often worse going up stairs, after sitting for prolonged periods, or after squatting or running. There should be a negative history for significant swelling or true mechanical symptoms, which would indicate a more serious injury. History of change in activity is common, such as altered training surface or terrain, increased training regimen, or performance of new tasks.

Examination should include evaluation of stance and gait for lower limb alignment, musculature, and midfoot hyperpronation. Flexibility of the hamstrings, iliotibial band, and gastrocnemius should be assessed, because stress is increased across the patellofemoral joint when these structures are excessively tight. Hip range of motion should be assessed to rule out hip pathology. Medial patellar tenderness or pain with compression of the patellofemoral joint confirms the diagnosis in the absence of a significant effusion and other positive findings. PFSS is a clinical diagnosis usually managed without imaging.

Treatment focuses on assessing and improving flexibility, strength, and gait abnormalities. In the presence of midfoot hyperpronation (ankle valgus), new shoes or the use of arch supports can improve patellofemoral mechanics and alleviate pain. Ice and analgesics can be used to help control pain. Reduced overall activity or training is important initially in rehabilitation. Short arc quadriceps strengthening exercises can be helpful: active knee extension with or without resistance between 0 and 30 degrees of knee flexion. Hip and core strengthening exercises are also beneficial. Therapeutic taping techniques to improve patella tracking within the trochlear groove can be helpful with the assistance of a sports physical therapist. The use of a patellar stabilizing brace with a lateral buttress to maintain patellar alignment may be of benefit in more chronic cases as well.

Osgood-Schlatter Disease

Osgood-Schlatter disease is a traction apophysitis occurring at the insertion of the patellar tendon on the tibial tuberosity (see Chapter 718.4). Because it is also related to overuse of the extensor mechanism, Osgood-Schlatter disease is treated like PFSS. A protective pad to protect the tibial tubercle from direct trauma can be used. Therapeutic taping of the tibial tubercle may provide comfort, along with well-fitted knee sleeves and/or straps. NSAIDs are often prescribed for comfort. Stretching focused on the quadriceps and hamstrings is recommended, and PRICE principles apply. Patients and parents should be made aware that resolution is usually slow, often requiring 12-18 months. Complications are rare and can include growth arrest with recurvatum deformity and rupture or avulsion of the patellar tendon/tibial tubercle.

Other Chronic Injuries

Sinding-Larsen-Johansson disease is a traction apophysitis occurring at the inferior pole of the patella. It occurs most often in volleyball and basketball athletes. Treatment is similar to PFSS and Osgood-Schlatter disease.

Patellar tendinosis, or jumper's knee, is caused by repetitive microtrauma of the patellar tendon, usually at the inferior pole of the patella. In approximately 10% of cases, the quadriceps tendon above the patella is affected. It is associated with jumping sports but may occur in runners as well. Treatment is similar to that for PFSS, with an emphasis on eccentric strengthening in physical therapy. Relative rest is more important in patellar tendinosis because chronic pain can be associated with irreversible changes in the tendon. In these cases, recalcitrant to rest, activity modifications, and physical therapy, there may be a role of biologic injections such as platelet-rich plasma to the pathologic area. Surgical techniques also have a good success rate if needed.

Iliotibial band (ITB) friction syndrome is the most common cause of chronic lateral knee pain. Generally, it is not associated with swelling or instability. It is from friction of the ITB along the lateral knee, resulting in bursitis. Tenderness is elicited along the ITB as it courses over the lateral femoral condyle or at its insertion at Gerdy's tubercle along the lateral tibial plateau. Tightness of the ITB is also noted using the Ober test. To perform an Ober test, the athlete lies on one side, the inferior hip is flexed, and the superior hip is extended with the knee flexed. The examiner holds the superior foot in midair, and if the superior knee drops inferiorly toward the exam table, it implies a flexible ITB and a negative Ober test. If the knee and leg stay in midair, the Ober test is positive, suggesting a tight ITB. Treatment principles follow those for PFSS, except the emphasis is on improving flexibility of the ITB.

Other soft tissue injuries to be considered include prepatellar and pes anserine **bursitis**, plical syndromes, and Hoffa syndrome. The pes anserine bursa lies just under the conjoined tendon of the sartorius, gracilis, and semitendinosus muscles as it attaches medially to the proximal tibia. In **Hoffa syndrome**, the fat pad beneath the patella and posterior to the patella ligament becomes pinched with anterior pain on knee extension. These conditions are generally more common in adolescents, those with genu recurvatum, and long-distance runners. Undiagnosed non–sports-related conditions always need to be considered in the context of any child with a painful knee, particularly those younger than 12 years old. These include conditions such as OCD (see Chapter 718.3), which is most common on the lateral aspect of the medial femoral condyle. Inflammatory and infectious arthritis, Baker cyst (see Chapter 718.2), and hip pain referred to the knee are additional considerations. Tumors more common to the knee joint include osteogenic sarcoma (distal femoral and proximal tibial), Langerhans cell histiocytosis in the diaphysis, and eosinophilic granuloma in the epiphysis of long bones. Metastatic tumors to the lower extremities include neuroblastoma and lymphoma. As with any musculoskeletal injury in a child not responding to conservative care, more in-depth diagnostic pursuit for alternative pathology is mandatory.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.7 Lower Leg Exertional Pain: Shin Splints, Stress Fractures, and Chronic Compartment Syndrome

Gregory L. Landry and Andrew M. Watson

Stress injury to the bones of the lower leg occurs on a continuum from mild injury (shin splints) to stress fracture. All occur by an overuse mechanism.

Medial tibial stress syndrome, or shin splints, manifests with pain along the medial tibia and is the most common overuse injury of the lower leg. The pain initially appears toward the end of exercise, and if exercise continues without rehabilitation, the pain worsens and occurs earlier in the exercise period. There is diffuse tenderness over the lower third to half of the distal medial tibia. Any focal tenderness of the tibia is suspicious for a **tibial stress fracture**. A stress fracture tends to be associated with more severe pain and is painful during the entire workout. Shin splints and stress fractures represent a continuum of stress injury to the tibia and are thought to be related to traction of the soleus

on the tibia. Eccentric contraction of the medial aspect of the soleus is required to control pronation from initial contact to mid-stance with running. This contraction increases the stress of the fascial origin of the soleus, possibly through Sharpey fibers, causing disruption to the tibial periosteum and fibrocartilaginous attachments.

The diagnosis can be made by history and physical examination. Findings on plain radiographs of the tibia are typically unremarkable with shin splints, as well as with tibial stress fractures within the first 2 weeks of injury. Beyond this time frame, radiographs may demonstrate periosteal reaction if a stress fracture is present but may still be unremarkable. Sensitivity of plain radiographs can be increased by obtaining four views of the tibia: AP, lateral, and both oblique views. MRI is the most sensitive test to diagnose stress injuries as it can reveal both a stress fracture and stress reaction in the affected bone. Stress reactions may include bone marrow edema or periosteal reaction without a fracture line but represent an impending progression to a fracture if the offending stress is not reduced or eliminated.

The treatment of shin splints involves relative rest, correcting training errors, and addressing muscle imbalances and abnormal mechanical alignment. Orthotics and/or new shoes may be useful in patients who hyperpronate. Fitness can be maintained with non–weight-bearing activities, such as swimming, cycling, and water jogging. With shin splints, after 7-10 days, patients can usually start on the walk-jog program. If pain worsens, 2-3 pain-free days are required before resuming the walk-jog program. Ice should be used daily, and an analgesic should be used for pain control. Stretching the plantar flexors and hamstrings and strengthening the ankle dorsiflexors may be useful. Therapeutic taping and wrapping techniques to support the soft tissue attachments have been useful in some when directed by a skilled sports therapist. Being pain free for 7-10 days is recommended before exercises are commenced. Individuals with pain at rest and who are not responsive to treatment require continued evaluation for stress fracture. Treatment of tibial stress fractures is similar but requires more prolonged avoidance of running and jumping, usually 6-8 weeks.

Chronic compartment syndrome occurs in an athlete in a running sport, usually during a period of heavy training. It is caused by muscle hypertrophy and increased intracompartmental pressure with exercise. There is typically a pain-free period of about 10 minutes at the beginning of a workout before onset of constant throbbing pain that is difficult to localize. It lasts for minutes to hours after exercise and is relieved by ice and elevation. Classically, there is numbness of the foot associated with high pressure within the corresponding muscle compartment. The most common compartment affected is the anterolateral compartment with compression of the fibular nerve followed by the deep posterior compartment. The physical examination in the office is often normal, but weakness of the extensor hallucis longus (anterolateral compartment) and decreased sensation between the first and second toe may be present. Symptoms may be elicited through exercise in or near the examination room (jogging in place, stair climbing, etc.), and prompt evaluation after symptom onset may aid in diagnosis. Radiologic evaluation is typically negative and used primarily to rule out other conditions. Compartment pressure measurements are the test of choice. Treatment involves reduction of activity, antiinflammatory medication, orthotics (hyperpronation), heel cord stretching, light strengthening of distal musculature, optimal footwear, and cross-training (swimming, cycling, and water jogging). Cryotherapy and superficial heat can also be of help. Persistent systems, despite conservative care, may require fasciotomy.

Popliteal artery entrapment syndrome occurs when the popliteal artery is compressed by the medial head of the gastrocnemius muscle and the fascial band of the soleus with activity; the entrapment may be anatomic or functional (from hypertrophy). Patients may have claudication and paresthesia (involvement of the tibial nerve), and calf swelling (primary venous obstruction). Most patients have exertional leg pain with no symptoms at rest; pain may be unilateral or bilateral depending on the type of entrapment syndrome. The tibial or dorsalis pedis pulse may be reduced or absent with passive ankle dorsiflexion with the knee extended. Doppler exam in the neutral and flexion position confirms the diagnosis in most patients; magnetic resonance angiography or CT angiography may be needed if the Doppler exam is inconclusive. Surgical correction is the treatment of choice and involves medical gastrocnemius fasciotomy, take down of the soleus tibial attachments, and resection of the fibula soleus band. If the artery is injured, it requires bypass surgery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

728.8 Ankle Injuries

Gregory L. Landry and Andrew M. Watson

Ankle injuries are the most common acute athletic injury. Approximately 85% of ankle injuries are ankle sprains, and 85% of these are inversion injuries (foot planted with the lateral fibula moving toward the ground), 5% are eversion injuries (foot planted with the medial malleolus moving toward the ground), and 10% are combined.

EXAMINATION AND INJURY GRADING SCALE

In obvious cases of fracture or dislocation, evaluating neurovascular status with as little movement as possible is the initial priority. If no deformity is obvious, the next step is inspection for edema, ecchymosis, and anatomic variants. Key sites to palpate for tenderness are the entire length of the fibula; the medial malleolus; the base of the fifth metatarsal; the anterior, medial, and lateral joint lines; the navicular; and the Achilles tendon complex. Assessment of active range of motion (patient alone) in dorsiflexion, plantar flexion, inversion, and eversion along with gentle resisted range of motion can be helpful.

Provocative testing attempts to evaluate the integrity of the ligaments. In a patient with a markedly swollen, painful ankle, provocative testing is difficult because of muscle spasm and involuntary guarding. It is more useful on the field before much bleeding and edema have occurred. The anterior drawer test assesses for anterior translation of the talus and competence of the anterior talofibular ligament. The inversion stress test examines the competence of the anterior talofibular and calcaneofibular ligaments (Fig. 728.13). In the acute setting, the integrity of the tibiofibular ligaments and syndesmosis can be examined by the syndesmosis squeeze test. Pain at the ankle joint with squeezing the superior aspect of the lower leg implies injury to the interosseous membrane and syndesmosis between the tibia and fibula—suspicious for a high ankle sprain or more severe injury. Athletes with this injury cannot bear any weight and have severe pain with dorsiflexion and external rotation of the foot. Occasionally, the peroneal tendon dislocates from the fibular groove simultaneously with an ankle sprain. To assess for peroneal tendon instability, the examiner applies pressure from behind the peroneal tendon with resisted eversion and plantar

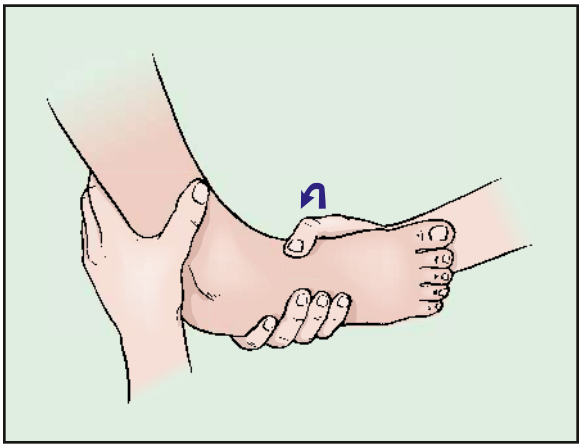

Fig. 728.13 Inversion stress tilt test for ankle instability. *(From Hergenroeder AC. Diagnosis and treatment of ankle sprains: a review. Am J Dis Child. 1990;144:809–814.)*

flexion, and the tendon pops anteriorly. If either a significant syndesmotic injury or an acute peroneal dislocation is suspected, orthopedic consultation should be sought.

RADIOGRAPHS

AP, lateral, and mortise views of the ankle are obtained when patients have pain in the area of the malleoli, are unable to bear weight, or have focal bone tenderness over the distal tibia or fibula. The **Ottawa ankle rules** help define who requires radiographs (Fig. 728.14). A foot series (AP, lateral, and oblique views) should be obtained when patients have pain in the area of the midfoot or bone tenderness over the navicular or fifth metatarsal, and/or an inability to bear weight. It is important to differentiate an **avulsion fracture** of the fifth metatarsal base (dancer's fracture) from the more distal **Jones fracture** of the proximal fifth metatarsal (located about 2 cm distal to the proximal end). The former is treated like an ankle sprain; the latter fracture has an increased risk of nonunion and requires orthopedic consultation. Injury to the deltoid ligament of the medial ankle is rare but should raise the question of proximal fibular fracture. In this circumstance more proximal tibial imaging may be necessary. A **talar dome fracture** may present as an ankle sprain that does not improve. Radiographs on initial presentation can have subtle abnormalities. Any suspicion on the initial radiographs of a talar dome fracture warrants orthopedic consultation and further imaging. In the early adolescent, always look carefully at the tibial epiphysis. Nondisplaced Salter III fractures can be subtle and need to be recognized early and referred to an orthopedic surgeon promptly. Diagnostic ultrasound, when available at the point of care, can efficiently provide prognostic information by direct visualization of injured ligaments. Additionally, dynamic stress can be applied during ligament visualization to assess for gaping of the joint, which is indicative of more complete tearing with an increased duration of expected recovery.

INITIAL TREATMENT OF ANKLE SPRAINS

Ankle sprains need to be treated with PRICE principles. This should be followed for the first 48-72 hours after the injury to minimize bleeding and edema. For an ankle injury, this may consist of crutches and an elastic wrap, although other compression devices, such as an air stirrup splint, are also effective. This allows early weight-bearing with protection and can be removed for rehabilitation. It is important to start a rehabilitation program as soon as possible.

Rehabilitation

Rehabilitation should begin the day of injury; for patients who have pain with movement, isometric strengthening can be started. Early-phase intervention includes restoration of functional range of motion, strengthening with emphasis on peroneal musculature, and early sensory proprioceptive training. Later intervention includes higher-level balance activities, advanced proprioception exercises, and endurance training. When determining when an athlete is ready for running, there must be full range of motion and nearly full strength compared to the uninjured side. While standing on the uninjured side only, the athlete is instructed to hop 8-10 times, if possible. When this can be achieved without pain on the injured side, the athlete can begin to run, starting out with jogging and gradually progressing in speed. The athlete must stop if there is significant pain or limp. Finally, before returning to sport, the athlete must be able to sprint and change directions off the injured ankle comfortably. Performing some sport-related tasks is also helpful in determining readiness for return to play.

Recurrent ankle injuries are more likely in patients who have not undergone complete rehabilitation. Ankle sprains are less likely in players wearing high-top shoes or lace-up ankle braces. Proper taping of the ankle with adhesive tape can provide functional support but loosens with use and is often unavailable. Surgery is a consideration for chronic mechanical instability with lateral complex ligamentous laxity in the failure of more conservative care. Salter-Harris grade I distal fibular fractures need careful consideration, particularly in the child younger than 12 years of age. The physeal plates are generally the weakest link in the musculoskeletal chain and tend to slide or pull apart before the surrounding soft tissue and/or ligaments tear in this younger population.

OTHER CAUSES OF ANKLE PAIN

Toddler's fracture needs to be considered in young children with ankle pain, especially in those younger than 6 years (see Chapter 724.4). The proposed mechanism involves sheer stress with lack of displacement because of the periosteum that is relatively strong compared to the elastic bone in younger children. Initial radiographs may be inconspicuous (a faint spiral oblique line) or even normal. The condition can be mistaken for osteomyelitis, transient synovitis, or even child abuse. Toddler's fracture usually occurs in the lower third of the tibia, whereas nonaccidental injury typically affects the upper two-thirds or midshaft

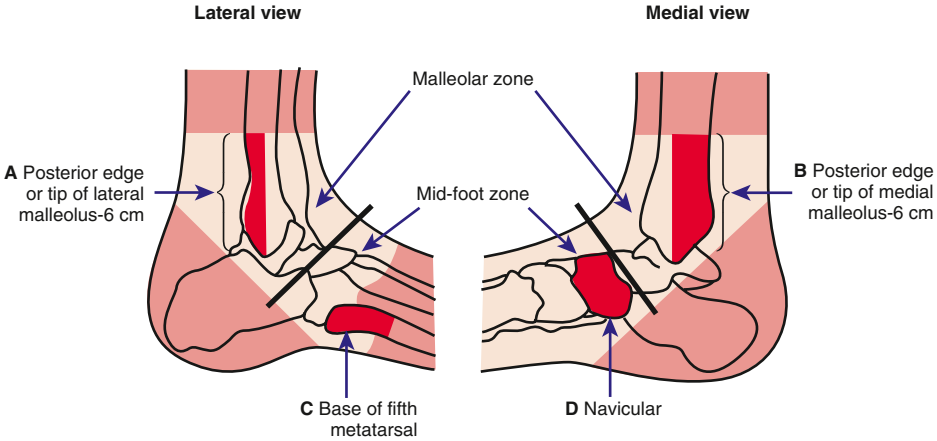

Fig. 728.14 Ottawa ankle rules. *(From Bachmann LM, Kolb E, Koller MT, et al. Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot; systematic review. BMJ. 2003;326:417–419.)*

of the tibia. Other less common conditions that cannot be excluded include os fibulare, a congenital unfused secondary ossification center of the distal fibula. This can be seen in younger patients with recurrent ankle sprains, particularly as their body weight and activity increase during the early academic years. Undiagnosed tarsal coalitions can also be seen in the presence of ankle sprains in younger children (most commonly talocalcaneal and calcaneal navicular). Muscular strains and/or tendinoses are more prevalent in the older child and adolescent, and include peroneal, posterior tibialis, and gastrocnemius/Achilles types. Tarsal tunnel syndrome (entrapment of the posterior tibial nerve) is more prevalent in the adolescent/younger adult and is commonly associated with medial ankle pain and burning or tingling into the sole of the foot.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for a complete Bibliography.

728.9 Foot Injuries

Gregory L. Landry and Andrew M. Watson

Metatarsal stress fractures can occur in any running athlete. The history is often one of insidious pain with activity that is getting worse. Examination reveals point tenderness over the mid-shaft of the metatarsal, most commonly the second or third metatarsal. Radiographs might not show the periosteal reaction before pain has been present for 2 weeks or more. Treatment is relative rest for 6-8 weeks. Shoes with good arch supports reduce stress to the metatarsals.

Vague dorsal foot pain in an athlete in a running sport can represent a **navicular stress fracture**. Unlike other stress fractures, it might not localize well on examination. If there is any tenderness around the navicular, a stress fracture should be suspected. This stress fracture can take many weeks to show up on plain radiographs, so MRI should be done to confirm the diagnosis. Because this fracture is at high risk of nonunion, immobilization and non–weight-bearing for 8-12 weeks is the usual treatment. A CT scan should be obtained to document full healing after the period of immobilization.

Sever disease (calcaneal apophysitis) occurs at the insertion of the Achilles tendon on the calcaneus and manifests as activity-related pain (see Fig. 728.3). It is more common in males, is often bilateral, and usually occurs between ages 8 and 13 years. Tenderness is elicited at the insertion of the Achilles tendon into the calcaneus, especially with squeezing the heel (positive squeeze test). Sever disease is associated with tight Achilles tendons and mid-foot hyperpronation that puts more stress on the plantar flexors of the foot. Treatment includes relative rest, ice, massage, stretching, and strengthening the Achilles tendon. Correcting the mid-foot hyperpronation with orthotics, arch supports, or stabilizing shoe wear is important in most athletes with Sever disease. If the foot is neutral or there is mild hyperpronation, cushioned heel lifts can be helpful to unload the Achilles tendon and its insertion. With optimal management, symptoms frequently improve in 4-8 weeks. Generally, if there is no limp during the athletic activity, young athletes with Sever disease should be allowed to play.

Plantar fasciitis is an overuse injury resulting in degeneration of the plantar aponeurosis. Rare in prepubertal children, this diagnosis is more likely seen in the adolescent or young adult. Athletes report heel pain with activity that is worse with the first steps of the day or after several hours of non–weight-bearing. Tenderness is elicited on the medial calcaneal tuberosity. Relative rest from weight-bearing activity is helpful. Athletes get plantar fasciitis when shoes are worn with inadequate arch supports. New shoes or use of semirigid arch supports often lessen the pain. Stretching the calves and plantar fascia helps, assisted at times with therapeutic ultrasound treatment. Some patients benefit from night splints even though they can make sleep difficult. As long as there is no limping with athletic activity, the athlete may continue participation. Complete recovery is usually seen at 6 months. Corticosteroid injection, extracorporeal shock-wave therapy, or injections of platelet-rich plasma can be considered in those cases recalcitrant to conservative treatments.

Calcaneal stress fracture is seen in the older adolescent or young adult involved in a running sport. There is heel pain with any weight-bearing activity. The physical examination reveals pain with squeezing the calcaneus. Sclerosis can show up on the AP and lateral radiographs after 2-3 weeks of pain. MRI may need to be performed to confirm the diagnosis in some cases. The calcaneus is an uncommon location for a stress fracture and is often associated with osteopenia. Treatment is rest from running and other weight-bearing activity for at least 8 weeks. Immobilization is rarely necessary.

Pes planus, or "flat feet," may be termed "flexible" or "rigid." Flexible pes planus is usually asymptomatic and is the most common type found in children (see Chapter 715.5). Foot orthotics may be helpful for older children with foot pain or associated muscle cramping. Rigid pes planus is a congenital deformity associated with other anomalies in 50% of cases. It is caused by failure of the tarsal bones to separate, leaving a bony cartilaginous or fibrous bridge or coalition between two or more tarsal bones (see Chapter 715.6). Talocalcaneal coalitions are more symptomatic between 12 and 16 years of age, whereas calcaneonavicular coalitions are more symptomatic between 8 and 12 years of age. Symptoms are insidious with occasional acute arch, ankle, and mid-foot pain, which is at times brought on with sports-related activities. The hindfoot often does not align in its normal varus position on tiptoe maneuvers. Patients are predisposed to ankle sprains secondary to limited subtalar motion, and stress to the subtalar and transverse tarsal joints frequently causes pain. CT scans are diagnostic, and initial treatment is conservative with short leg casting and/or molded orthoses and rest. In the case of failure of conservative care, surgical intervention is usually necessary. Rigid cavus feet can also be associated with metatarsalgia, clawing, and intrinsic muscle atrophy, which are all possible in the young athlete (see Chapter 715.7). With a cavus foot, undiagnosed neurologic conditions, such a Charcot-Marie-Tooth disease, spinal dysraphism, Friedrich ataxia, or spinal tumor, need to be considered. Custom-molded orthotics may be helpful, and family history can be critical. Symptomatic, accessory navicular bones and sesamoiditis can be considered when these areas are painful and do not have evidence of fracture or prior trauma. These conditions are more common in the adolescent or younger adult and can be exacerbated with sporting activities.

Other conditions causing foot pain include **Lisfranc sprain** and/or dislocation, which is more common in football linemen or other athletes requiring heavy loading on the mid-foot and forefoot joints, and gymnasts using the balance beam. The Lisfranc joint is the tarsal metatarsal articulation of the three cuneiform bones and the cuboid with the five proximal metatarsals. Turf toe can be seen, particularly in the older child and/or adolescent running on artificial or synthetic surfaces. It results from hyperextension through the first metatarsal phalangeal joint, spraining the ligaments surrounding the joint often in a football and/or soccer activity.

Iselin apophysitis is an apophysitis that occurs at the tuberosity of the fifth metatarsal. The apophysis at this site appears between the ages of 9 and 14 years and is located within the insertion of the peroneus brevis tendon. This condition can be a predisposing factor to dancer's fracture (see Chapter 728.8). **Freiberg disease**, which involves the collapse of the articular service and subchondral bone, usually of the second metatarsal, and **Kohler disease**, which involves irregular ossification of the tarsal navicular joint with localized pain and increased density, should always be considered in the evaluation **osteochondroses of the foot** (see Chapter 715.8). Freiberg disease is more common in girls between the ages of 12 and 15 years, whereas Kohler disease occurs in younger individuals, age 2-9 years, and is frequently reversible with conservative care, including orthoses and casting.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com Bibliography.

Chapter 729

Sports-Related Traumatic Brain Injury (Concussion)

Alex M. Taylor, William P. Meehan III, and Mark R. Proctor

Concussion is a form of **traumatic brain injury** (TBI) caused by sudden acceleration, deceleration, or rotational forces to the brain, which can occur with a blow to the head, neck, face, or body. The resulting pathophysiologic state is associated with a constellation of signs and symptoms that, for **sport-related concussions (SRCs)**, typically self-resolve within 7-10 days. A minority of children can experience **persistent postconcussion symptoms** (PPCS) that extend beyond 28 days and limit functional ability, cause social isolation, reduce school attendance and performance, and can lead to anxiety, mood alteration, and lower quality of life. Accurate diagnosis and appropriate management of concussion is needed to safely return children to school and sports and to avoid the potential for worse outcomes.

DEFINITION/TERMINOLOGY

The spectrum of TBI ranges from mild to severe. Classification is typically determined by score on the Glasgow Coma Scale (see Chapter 79), with severe = ≤8, moderate = 9-12, and mild = 13-15. Although concussion and **mild TBI (mTBI)** are sometimes used interchangeably, concussion may be best understood as the *clinical syndrome* that is associated with mTBI. There are several agreed on features:

- Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.
- Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously. However, in some cases, signs and symptoms may evolve over minutes to hours.
- Concussion may result in neuropathologic changes, but the acute clinical signs and symptoms largely reflect a *functional* disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.
- Concussion results in a range of clinical signs and symptoms that may or may not involve loss of consciousness (Fig. 729.1). Resolution of the clinical and cognitive features typically follows a sequential course. However, in some cases, symptoms may be prolonged.

To be defined as a concussion, the clinical signs and symptoms cannot be explained by drug, alcohol, or medication use, other injuries (such as cervical injuries, peripheral vestibular dysfunction), or other comorbidities (e.g., psychologic factors or coexisting medical conditions).

EPIDEMIOLOGOY

According to the Centers for Disease Control and Prevention (CDC), as many as 3.8 million sport-related TBIs may occur in the United States annually with 70–90% of these injuries classified as concussion. One study suggested that current surveillance systems may capture only one out of every nine concussions.

Approximately 20% of middle and high school children report a lifetime prevalence of concussion. Sports participation is the most common mechanism of injury. An estimated 1.1-1.9 million recreational and sports-related concussions occur each year in children 18 years or younger. In gender comparable sports, female athletes report higher rates of concussion than males, and both groups are more likely to suffer a concussion in competition than at practice. Among males, the incidence of concussion is highest in collision (contact) sports, including rugby, American football, ice hockey, lacrosse, basketball, soccer, and wrestling. Among females, the incidence of concussion is highest in soccer, lacrosse, and field hockey. Other sports and recreational activities in which concussions frequently occur include bicycling, skateboarding, skiing, and snowboarding. Younger children may have playground-associated concussions.

PATHOPHYSIOLOGY

The constellation of symptoms associated with concussion are not caused by observable structural injury or hemorrhage; clinical imaging studies (MRI/CT) typically are normal. However, there is a proposed cascade of events that lead to the clinical syndrome. A sudden acceleration, deceleration, or rotation of the brain is thought to result in parenchymal shear stress and strain that disrupts neuronal function in a cascade of ionic and metabolic fluctuations. Affected neurons experience massive depolarization and then require additional adenosine triphosphate (ATP) to restore cellular homeostasis. Glucose levels dramatically increase to fuel ATP production, which ultimately causes lactic acid accumulation. At the same time this process occurs, there is a decrease in cerebral blood flow, which may persist for several weeks. Consequently, less glucose is available when it is most needed to fuel ATP for ionic recovery. The signs and symptoms of concussion are thought to reflect the energy crisis or mismatch between the demand and availability of fuel in the brain after trauma.

SIGNS AND SYMPTOMS

Signs and symptoms of concussion can be classified into five categories, including somatic, vestibular, cognitive, emotional, and sleep related (Table 729.1). Acutely, headache is the most commonly reported symptom, followed by dizziness, difficulty concentrating, and confusion. Sleep disturbance, anxiety, and mood-related symptoms are more likely to occur several weeks post-injury. Brief loss of consciousness occurs in less than 5% of SRCs and is not associated with injury severity or time to recover. The most reliable predictor of recovery is initial symptom burden; children who experience greater symptom load and severity are at increased risk of PPCS. However, several noninjury–related factors can also affect recovery, including female sex, history of migraines, history of prior concussion, poorer preinjury child adjustment, family dysfunction, neurodevelopmental disorder (e.g., learning disability, attention-deficit/hyperactivity disorder [ADHD]), and psychiatric illness (e.g., anxiety, depression).

Although concussion typically results in an immediate onset of short-lived neurologic dysfunction that resolves spontaneously, signs and symptoms may develop over several minutes to hours. The diagnosis can be challenging and further complicated by the presence of concussion-like symptoms in noninjured athletes. Children with preexisting neurodevelopmental disorders, mental health concerns, history of prior concussion, or headaches/migraines may endorse concussion-like symptoms in the absence of injury. A reasonable mechanism of injury needs to be identified as well as a measurable change from baseline symptoms. To this end, age-appropriate symptom scales or checklists may be useful in assessing SRC and monitoring recovery (Table 729.1). Many symptom rating scales are available, and some are incorporated into sideline assessment tools, including the Sport Concussion Assessment Tool version 6 (SCAT6), which is approved for age 13 years and older. It is important to use a developmentally appropriate scale for younger children (e.g., Child-SCAT6 for children age 5-12 years) and to use the same tool in subsequent assessments to allow for tracking of symptoms over time.

INITIAL ASSESSMENT AND TOOLS

The initial diagnosis and management of concussion often begins on the field, rink, or court. Whether on the sideline and/or at a medical clinic, the first step is to rule out an injury that requires immediate attention. Acute care should include cervical spine stabilization, evaluation of airway, breathing, and circulation, and motor and sensory neurologic testing. Once a spinal cord injury or more severe injury to the brain is ruled out, it is important to: (1) perform a detailed evaluation of the athlete's mental status, (2) assess signs and symptoms, and (3) identify risks for delayed recovery (i.e., neurodevelopmental disorders, mental health concerns, history of prior concussion, or headaches/migraines). *This process is facilitated by use of a validated sideline*

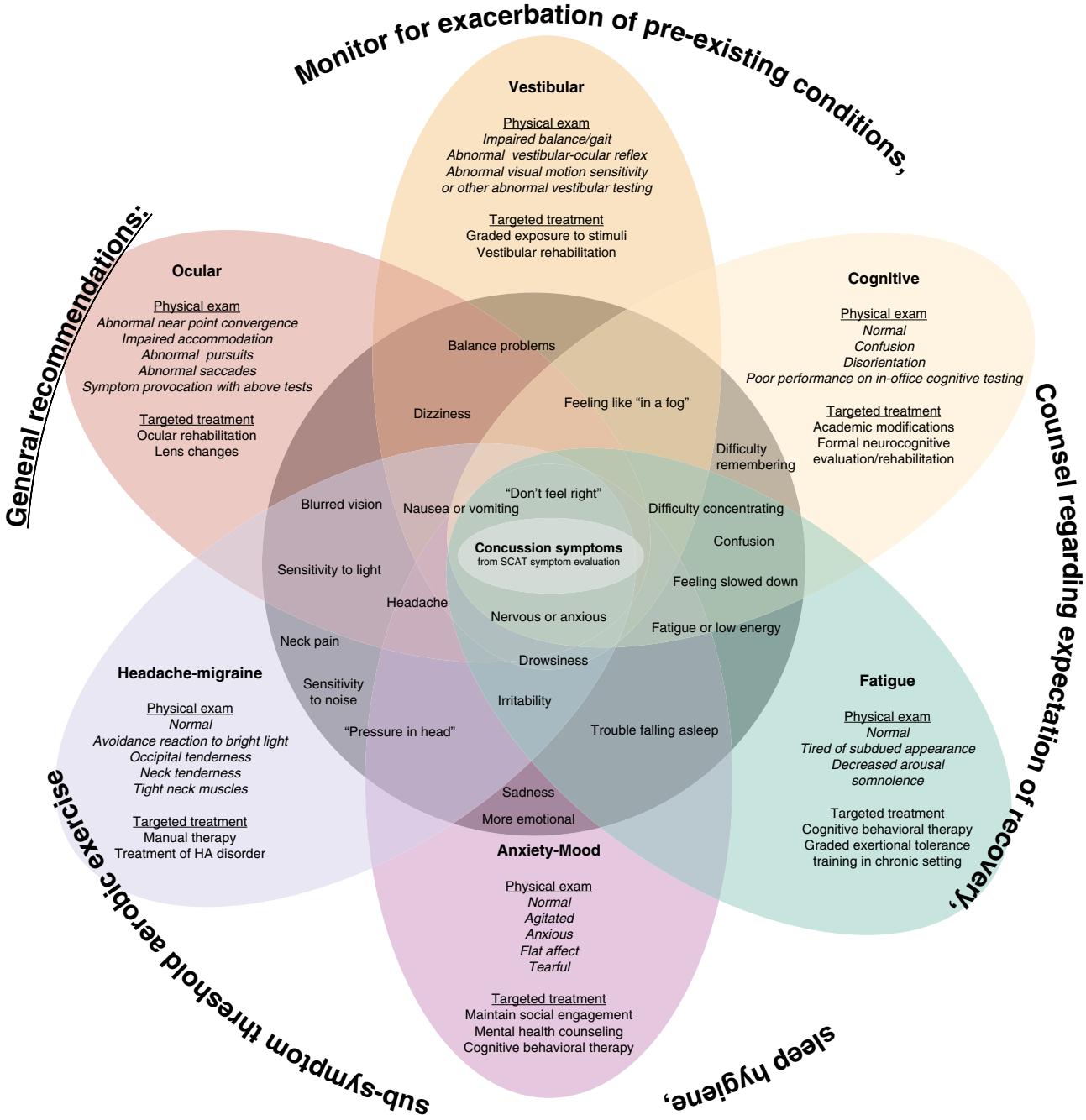

Fig. 729.1 Constellation of symptoms after concussion. Overlapping clinical domains to monitor and facilitate individualized management after concussion. *(From Harmon KG, Clugston JR, Dec K, et al. American Medical Society for Sports Medicine position statement on concussion in sport. Br J Sports Med. 2019;53[4]:213–225.)*

assessment tool. SCAT6 is recommended and includes standardized methods for recording relevant demographics, observable signs of injury, postconcussion symptoms, and memory function (excluding children <12 years), as well as the GCS, cervical spine assessment, brief neurologic exam, and the modified Balance Error Scoring System (m-BESS). Another often-used sideline assessment is the Sideline Assessment of Concussion, which includes a mental status exam, brief neurologic exam, and cognitive screen.

The Balance Error Scoring System (BESS) measures postural stability or balance and consists of six stances, three on a firm surface and the same three stances on an unstable (medium density foam) surface. The modified BESS (m-BESS) is frequently used because it does not rely on availability of medium-density foam for administration. Both include three stances: feet shoulder width apart, a tandem stance (one foot in front of the other), and a single-leg stance on the person's nondominant leg, which are performed for 20 seconds with eyes closed and hands on the iliac crests. An error is recorded each time athletes lift their hands off their hips, open their eyes, step, stumble, fall, remain out of the test position for more than 5 seconds, move hips into more than 30 degrees of flexion or abduction, or lift their forefoot or heel. Normative data are available for comparison, although preseason balance screening provides more precise, individualized data. Furthermore, most evidence suggests that balance impairments generally resolve within 3 days postinjury.

Clinicians should screen for vision problems after concussion. In addition to visual acuity and visual field testing, the Vestibular Ocular Motor Screening Assessment (VOMS) is another tool that is increasingly used to evaluate concussion. It involves a standardized method to

Table 729.1 Postconcussion Symptom Scale

	NONE	MILD		MODERATE		SEVERE	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or anxious	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6

From Echemendia RJ, Meeuwisse W, McCrory P, et al. Sport concussion assessment tool—5th edition. *Br J Sports Med*. 2017;51:851–858.

assess smooth pursuits, horizontal and vertical saccades, convergence, horizontal vestibular ocular reflex, and visual motion sensitivity. Findings on the VOMS have been shown to distinguish children with concussion from uninjured controls, and vestibular-ocular dysfunction may have a particularly deleterious effect on academics.

Neuropsychologic assessment quantifies cognitive symptoms of concussion and can help to identify comorbidities that can complicate the diagnosis. The areas identified as most vulnerable to injury include attention and executive function (e.g., speed of processing), new learning and memory, and reaction time. Obtaining preseason or "baseline" data enables clinicians to accurately detect cognitive impairment after injury and aids interpretation of data for athletes with preexisting or contextual factors that affect cognitive function (e.g., neurodevelopmental disorder, sleep, anxiety, and depression). Computer-administered neurocognitive tests are frequently used because the cost and availability of trained neuropsychologists to administer and interpret more comprehensive tests are prohibitive. Further, testing may be of additional benefit in determining appropriate school and home interventions for children who go on to experience PPCS.

The application of neuropsychologic assessment varies depending on the time of referral. Research generally supports the use of brief cognitive screens acutely (~3 days postinjury) such as those incorporated into the SCAT and SAC. Computerized administered neurocognitive assessment or a hybrid approach that includes paper and pencil measures of function are most often administered subacutely (~4-30 days postinjury) to assist in return-to-play decision-making, documenting lingering cognitive deficits, and providing rationale for academic supports or accommodations. The purpose of neuropsychologic assessment for patients with prolonged or chronic postconcussion symptoms (30+ days) is to provide the referring clinician and patient with additional insight into injury and noninjury factors affecting recovery, as well as their impact on cognitive function. Symptoms of comorbidities, including sleep deprivation, deconditioning, and pain, closely resemble postconcussion symptoms and similarly influence health-related status and cognition. Research also indicates that anxiety and depression, family functioning, and caregiver adjustment, as well as neurodevelopmental disorders (e.g., learning disability or ADHD) are strong predictors of prolonged symptoms.

In addition to ruling out more severe injury, the primary goal of both sideline assessment and/or office-based assessment is to prevent concussed athletes from returning to play prematurely. The brain is likely more vulnerable to reinjury immediately after concussion and until ionic and metabolic functioning normalizes. Consistent with this, most reinjuries occur within the first 10 days of an initial concussion. Thus, if a concussion is suspected, it is often wise to remove younger athletes from play for 24 hours or until the diagnosis of concussion can be confidently ruled out. Athletes who experience prolonged loss of consciousness, focal neurologic deficits, excessive somnolence, progressively worsening headache pain, repeated vomiting, slurred speech, and significant confusion may need to be seen in the emergency department where brain imaging can be conducted to rule out more severe head injury.

A blood test (Brain Trauma Indicator) is FDA approved for patients ≥18 years of age with concussion who have normal mental status) to help identify patients in need of cranial imaging. The test measures brain proteins, glial fibrillary acid protein, and ubiquitin C-terminal hydroclase-1, and may also be useful in detecting concussion in children.

MANAGEMENT

After diagnosis and removal from play, the initial management strategy is education of the child and parents about concussion, including the signs and symptoms, effects on cognition, and expected trajectory of recovery. Early limited, subsymptom levels of physical activity may improve recovery, whereas complete rest beyond 2-3 days is associated with delayed recovery. Children (symptomatic or asymptomatic) who can tolerate light exercise soon after injury should be encouraged to do so because it prevents deconditioning and can help with sleep and mood regulation. Importantly, early moderate and intense exercise is associated with symptom exacerbation and longer recovery times, and exercise of any intensity is deferred if it provokes symptoms in the first few days postinjury. Most children will begin to achieve some level of activity tolerance within 2-3 days. Management plans should then focus on gradually and progressively resuming noncontact, low-risk physical activity until full recovery (Table 729.2).

Most children who sustain a concussion will experience full recovery with adherence to relative rest, followed by graduated return to physical and cognitive activity. Nonetheless, some athletes require targeted symptom management, particularly when they are slow to improve (Table 729.3; see Fig. 729.1). Acetaminophen or NSAIDs may help to reduce acute headache pain. Prescription medications are sometimes warranted, including topiramate, amitriptyline, or cyproheptadine for posttraumatic headaches, peripheral nerve blocks for occipital or cervicogenic headaches, and gabapentin for headaches with a neuropathic component. Otolaryngology referral or vestibular therapy is recommended for management of dizziness, vertigo, and imbalance. For children with visual disturbance, assessment and visual rehabilitation therapy managed by an optometrist or ophthalmologist is appropriate. Psychologic assessment and intervention, particularly cognitive behavioral therapy, is recommended

Table 729.2 Graduated Return to Play Protocol

STAGE	AIM	ACTIVITY	GOAL OF EACH STEP
1	Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2	Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase heart rate
3	Sport-specific exercise	Running or skating drills. No head impact activities	Add movement
4	Noncontact training drills	Harder training drills (e.g., passing drills). May start progressive resistance training	Exercise, coordination, and increased thinking
5	Full contact practice	After medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6	Return to sport	Normal game play	

NOTE: An initial period of 24-48 hr of both relative physical rest and cognitive rest is recommended before beginning the return to sport progression.
There should be at least 24 hr (or longer) for each step of the progression. If any symptoms worsen during exercise, the athlete should go back to the previous step. Resistance training should be added only in the later stages (stage 3 or 4 at the earliest). If symptoms are persistent (e.g., more than 10-14 days in adults or more than 1 mo in children), the athlete should be referred to a healthcare professional who is an expert in the management of concussion.
From Patricios JS, Schneider KJ, Dvorak J, et al. Consensus statement on concussion in sport: the 6th International Conference on Concussion in Sport–Amsterdam, Oct 2022. *Br J Sports Med.* 2023;57:695.

Table 729.3 Common Potential Interventions for Specific Symptoms After Pediatric Concussion

SPECIFIC SYMPTOMS	POTENTIAL INTERVENTIONS
Headache	Lifestyle modifications (water intake, meal schedule, sleep, and exercise), cervicovestibular therapy, acute medications, preventive medications, and avoiding overuse of acute medications
Light-Headedness or Exercise Intolerance	Increase water and salt intake and gradual increase in exercise
Dizziness or Neck Pain	Vestibular therapy and cervical spine therapy
Balance or Coordination Difficulties	Neuromuscular training
Sleep Difficulties	Lifestyle modifications (bedtime routine, white noise, avoid caffeine, and exercise earlier), and melatonin
Anxiety or Mood Problems	Counselling, antidepressants, and anxiolytics
Cognitive Difficulties	Cognitive testing and academic accommodations

From Beauchamp MH, Degeilh F, Rose SC: Improving outcome after paediatric concussion: challenges and possibilities. *Lancet Child Adolesc* 2023;7:728-738 (Panel 2, p. 733).

for athletes who experience worsening or newly developed symptoms of anxiety or depression. Both are potentially heightened as a direct consequence of concussion as well as the resulting limitations on everyday activities and social interaction. A multidisciplinary and collaborative approach to target specific treatments is advised for children whose symptoms do not show improvement with standard behavioral interventions.

Return to School

Of particular importance to children and their families is the effect of concussion on cognitive function and school performance. Children and adolescents exposed to greater levels of cognitive stress endorse worse symptoms and experience longer recovery after concussion. Students who experience postconcussion symptoms report difficulty in school. There is also evidence that overly restricting cognitive exertion and school participation can delay recovery. Current recommendations focus on using self-reported symptoms to determine school readiness, followed by increasing exposure to classroom learning, tests, and assignments (Table 729.3). In general, children and adolescents are encouraged to attend school, even if on a modified schedule, in 2-3 days or sooner, with a program of academic adjustments and modifications that allow for ongoing learning to occur with minimal symptom provocation. Clinicians should provide documentation to schoolteachers and administrators requesting compressed assignments, more time to complete tests or assignments, deferred examinations, rest breaks, audiobooks, oral teaching, large font printed material, or preprinted notes where indicated.

Return to Play

There is a six-stage return-to-play (RTP) protocol for a safe return to activities (see Table 729.2). Starting with physical rest, athletes are progressed to light aerobic exercise, moderate levels of sport-specific exercise, noncontact training drills, full contact practice, and normal game play. Athletes should be completely asymptomatic, free of medications used to treat concussion symptoms, at full school, and back to baseline functioning on all domains tested before the injury before returning to contact or collision sports. Children and adolescents should remain at each stage of rehabilitation for no less than 24 hours before advancing to the next level. Thus a minimum of 5 days should pass before consideration of full return to competition. If symptoms return at any stage of exertion, the athlete should rest until the symptoms resolve and then return to the previous level of exertion. The final decision for RTP should be made by a licensed clinical provider with experience in the evaluation and management of sports-related concussions. Note that some states or schools require an extended minimum number of symptom-free days before RTP, so clinicians need to be aware of the laws or local recommendations regarding RTP.

Risks for Persistent Postconcussion Symptoms

From 80–90% of children and adolescents diagnosed with concussion will clinically recover within 4 weeks. Factors associated with prolonged recovery include a history of prior concussions, female

Table 729.4 Graduated Return to School Strategy

STAGE	AIM	ACTIVITY	GOAL OF EACH STEP
1	Daily activities at home that do not give the child symptoms	Typical activities of the child during the day as long as they do not increase symptoms (e.g., reading, texting, screen time). Start with 5-15 min at a time and gradually build up	Gradual return to typical activities
2	School activities	Homework, reading, or other cognitive activities outside of the classroom	Increase tolerance to cognitive work
3	Return to school part-time	Gradual introduction of schoolwork. May need to start with a partial school day or with increased breaks during the day	Increase academic activities
4	Return to school full time	Gradually progress school activities until a full day can be tolerated	Return to full academic activities and catch up on missed work

From Patricios JS, Schneider KJ, Dvorak J, et al. Consensus statement on concussion in sport: the 6th International Conference on Concussion in Sport–Amsterdam, Oct 2022. *Br J Sports Med.* 2023;57:695.

sex, history of migraines, neurodevelopmental disorder (e.g., ADHD, learning disability), successive concussion soon after recovery, and acute symptom severity and burden. Female sex and initial symptom severity are the factors associated with more persistent symptoms in adolescents.

Retiring Young Athletes

Retirement from contact sports is rare but sometimes indicated, even in younger athletes. Indications for retirement include chronic neuropsychologic deficit, increased recovery times for successive injuries, decreased threshold for repeat concussions, and multiple concussions over the course of an athletic career.

COMPLICATIONS/LONG-TERM EFFECTS

Second impact syndrome, seen more frequently in younger athletes than adults, refers to a rare, catastrophic neurologic injury involving diffuse cerebral swelling that purportedly occurs in athletes who sustain a second head injury before full recovery from a concussion. Although second impact syndrome is rare, its occurrence highlights the importance of removing children with concussion from play and other activities that place them at increased risk of head injury until fully recovered. Pathogenic variants in *CACNA1A* have been associated with delayed and severe cerebral edema after minor head trauma.

Some literature suggests that young athletes who suffer repetitive head impacts and multiple concussions may be at risk for neurodegenerative diseases, such as chronic traumatic encephalopathy (CTE) or Alzheimer disease. CTE describes pathologic changes in the brain observed postmortem, which are hypothesized to be associated with changes in mood, behavior, and cognition function. At present, there is no way to diagnose CTE in living persons and its incidence and prevalence are unknown.

PREVENTION

The strongest evidence for concussion prevention is in support of concussion education initiatives, age limits on contact, fair play, and adherence to rules of the game or competition. Additionally, there is some evidence that neck strengthening may reduce the risk of concussion. Current research shows no proven benefit to personal protective equipment (i.e., helmets, mouthguards) or dietary supplements in reducing the risk of concussion or its severity, although it is important for athletes to wear properly fitted sport specific protective equipment to prevent *more serious* head injury and maxillofacial and dental trauma.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 730

Cervical Spine Injuries

Julie M. Kerr and Joseph A. Congeni

Sports participation has surpassed motor vehicle crashes as the number one cause of cervical spine injuries (primarily involving soft tissue) in youth older than 8 years of age. American football, hockey, wrestling, and gymnastics have the highest incidence in the United States; internationally, rugby is nearly as high. Catastrophic cervical spine injuries fortunately are rare but can occur as a result of the scrum or tackling in rugby and tackling plays in American football.

The normal cervical spine has a lordotic curve, allowing it to absorb shock and dissipate force with application of an axial force. When the neck is flexed forward, the spine straightens, losing this shock-absorbing property. An axial load to the top of the head in this flexed position transmits force through the spine.

SOFT TISSUE INJURY

The most frequent injury resulting from trauma to the head and neck involves the muscles, tendons, and ligamentous structures. Even though strains, sprains, and contusions are common and are managed with cervical, scapulothoracic, and shoulder-strengthening exercises, thorough evaluation is required to rule out more serious injuries. Even without bony abnormalities, the cervical spine may become unstable secondary to soft tissue injury.

Spinal laxity results when most restraining ligaments are injured. When compared with adjacent vertebra, laxity should horizontally be less than 3.5 mm and angular displacement less than 11 degrees on plain flexion/extension films. However, younger athletes have more baseline laxity, making the criteria less applicable, and muscle spasm can acutely mask instability. If subluxation is remotely suspected, a hard cervical collar should be placed and flexion/extension views obtained again at 2-4 weeks when inflammation and spasm have subsided. A loss of lordosis on lateral x-ray is associated with significant weakness of cervical muscles, particularly the cervical extensors. Disk injuries are rare in pediatric patients. Rupture or herniation must be considered in any cervical pain differential (see Chapter 81).

SPEAR TACKLER'S SPINE

This clinical entity is characterized by progressive spinal changes secondary to incorrect tackling form. Findings on plain x-ray consist of (1) narrowing of cervical spinal canal, (2) loss or reversal of normal cervical lordosis, and (3) preexisting minor posttraumatic x-ray evidence of bony

or ligamentous injury. Although rule changes in collision and contact sports have limited the practice of contacting an opponent with a "head-down" neck position, this condition persists. Most experts argue that this condition disqualifies athletes from return to play.

CERVICAL FRACTURES

All significant neck injuries should be treated seriously until cleared with appropriate examination and imaging. Although many cervical fractures are stable, improper management or inadequate evaluation could produce catastrophic results. *Until formally evaluated, the patient should be immobilized and treated as if the patient has an unstable cervical fracture* (see Chapter 81).

STINGERS (BURNERS)

Stingers are unilateral *(never bilateral)* peripheral nerve injuries occurring at an anatomic location between the cervical nerve root and the brachial plexus. Three proposed mechanisms include traction or tensile stretch injury, compressive injury, and direct trauma. A typical presentation is a transient episode of unilateral burning pain, with or without numbness, that radiates from the shoulder, down the upper arm, and into the hand. Symptoms of C5 and C6 root injury with deltoid and biceps weakness are the most common presentation. These symptoms may last for several minutes to days but do not result in permanent neurologic deficit or abnormal imaging evaluations. Examination should assess for weakness, especially shoulder abduction, external rotation, and elbow flexion. The cervical spine should have full and pain-free range of motion and no tenderness to palpation.

The Spurling Compression test helps to assess for cervical radiculopathy as a cause of upper extremity pain. The patient is seated with their neck tilted to the affected side. In a positive test, the pain is reproduced with gentle axial compression. The test has high specificity (~93%) but relatively low sensitivity (~30%), meaning that positive tests indicate likely cervical radiculopathy but many patients with cervical radiculopathy will not have a positive test.

Return to play may be considered the same day if the exam is reassuring. This requires complete resolution of symptoms, full range of motion, and normal strength. Multiple stingers, bilateral symptoms, or symptoms persisting for longer than one hour should prompt further evaluation with cervical spine radiographs and other imaging modalities as indicated before resumption of any physical activities.

BURNING HANDS SYNDROME

The athlete with this syndrome presents with intense paresthesia and associated hand and arm weakness in both upper extremities. This is suggestive of a central cord syndrome with cord compression of the spinothalamic and corticospinal tracts. As with stingers, most of these episodes resolve in minutes to days. Persistent symptoms or repeated episodes warrant further evaluation and imaging.

TRANSIENT QUADRIPARESIS

Transient quadriparesis is a temporary neurologic episode encompassing sensory symptoms with or without motor changes. Transient quadriparesis is also known as *cervical cord neurapraxia*, *commotio spinalis*, and *spinal cord concussion*. Transient quadriparesis can be divided into three types: plegia (complete loss of motor function), paresis (motor weakness), and paresthesia (sensory symptoms only). There is also a three-part grading system: grade 1 symptoms lasting less than 15 minutes, grade 2 symptoms lasting 15 minutes to 24 hours, and grade 3 symptoms persisting beyond 24 hours. Transient quadriparesis must be differentiated from a stinger, and the player should be removed from activity and spinal cord injury considered.

Mechanisms of injury include hyperextension, hyperflexion, and axial loading. Anatomically, when the neck is hyperflexed or hyperextended, the spinal canal is narrowed by up to 30%, increasing the likelihood of cord injury.

Evaluation should start with plain flexion and extension films if stable. CT should be used if cervical fracture is suspected. MRI should then be used to evaluate for intrinsic spinal cord abnormalities or ongoing cord or root compression.

Table 730.1 Return to Play

NO CONTRAINDICATION TO RTP	
Healed fractures	Healed C1 or C2 fracture with normal cervical spine ROM Healed subaxial fracture without sagittal plane deformity Asymptomatic clay-shoveler's (C7) spinous process avulsion fracture
Congenital conditions	Klippel-Feil (single-level anomaly not C0/C1 articulation) Spina bifida occulta
Degenerative/ postsurgical conditions	Cervical disk disease (no change in baseline neurologic status) Single-level ACF with/without instrumentation Single- or multiple-level posterior cervical laminotomy
Recurrent stingers	Fewer than three episodes lasting <24 hours Must have full cervical range of motion No persisting neurologic deficit
Transient quadriparesis	Single episode Full cervical range of motion Normal neurologic exam No radiologic instability Normal spinal reserve (as evidenced on MRI)
RELATIVE CONTRAINDICATION TO RTP	
Stingers/burners	Prolonged symptomatic burner/stinger Three or more stingers
Transient quadriparesis	Transient quadriparesis lasting >24 hours More than 1 episode with symptoms of any duration
Postsurgical	Healed two-level ACF PCF with/without instrumentation
ABSOLUTE CONTRAINDICATION TO RTP	
Transient quadriparesis and any one or more of	Cervical myelopathy Continued neck discomfort Reduced ROM Neurologic deficit from baseline after injury
Surgical procedures	C1 + C2 fusion Cervical laminectomy Three-level ACF or PCF
Soft tissue injuries	Asymptomatic ligamentous laxity (>11 degrees of kyphotic deformity) C1 + C2 hypermobility with anterior dens >3.5 mm (adult), >4 mm (child), i.e., Down syndrome Symptomatic cervical disk herniation
Other conditions	Spear tackler's spine Multilevel Klippel-Feil anomaly (see Chapter 721.2) Healed subaxial fracture with sagittal kyphosis, coronal plane abnormality, or cord encroachment Ankylosing spondylitis Rheumatoid arthritis with spinal abnormalities Spinal cord abnormality (cord edema, compression, etc.) Arnold-Chiari syndrome Basilar invagination Occipital-C1 assimilation (occipitalization or connection) Spinal stenosis (canal width <13 mm between C3 and C7)

ACF, Anterior cervical fusion; PCF, posterior cervical fusion; ROM, range of motion; RTP, return to play.

Adapted from Cantu R, Li YM, Abdulhamid M, et al. Return to play after cervical spine injury in sports. *Curr Sports Med Rep*. 2013;12:14–17.



Fig. 730.1 An MRI (sagittal) demonstrating spinal cord contusion (edema in central portion of spinal cord). *(From Krabak BJ, Kanarek SL. Cervical spine pain in the competitive athlete. Phys Med Rehabil Clin N Am. 2011;22:459–471. Fig. 2).*

Return to play for transient quadriparesis is heavily debated and lacks data to guide decision-making. Some experts argue that one episode is a contraindication to return to contact sports, whereas others agree with using the Return to Play Table (Table 730.1) for absolute and relative contraindications for return. If allowed to return to play and a second episode of transient quadriparesis occurs, the complete workup must be repeated.

CONGENITAL SPINAL STENOSIS

Developmental narrowing of the cervical spinal canal predisposes an athlete to higher risk of spinal cord injury. This condition can be found incidentally while working up other conditions. Currently, the "gold standard" imaging modality is an MRI measuring a canal width of <13 mm between C3 and C7 to define stenosis, with "normal" being greater than 15 mm.

Functional stenosis can be seen with dynamic MRI in flexion and extension to determine whether the canal space decreases with movement. The positioning of the canal in flexion or extension causes narrowing from movement of the vertebra and ligament, respectively. The measured diameter may be irrelevant if disk protrusion or ligament hypertrophy causes compression. This narrow "reserve space" around the spinal cord puts the athlete at greater risk for injury as compared with the same force applied to a normal spine.

SPINAL CORD INJURY

Spinal cord injury is the most devastating complication of cervical trauma. Hemorrhage and transection are considered irreversible and associated with complete cord injury, whereas contusion and edema are considered to have more potential for recovery (Fig. 730.1). These severe injuries should be managed by providers with expertise in this area.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 731

Heat Injuries

Gregory L. Landry and Andrew M. Watson

Heat illness is among the leading causes of death in U.S. high school athletes. It is a continuum of clinical signs and symptoms that can be mild (heat stress) to fatal (heat stroke). Children are more vulnerable to heat illness than adults because they have a greater ratio of surface area to body mass and produce greater heat per kilogram of body weight during activity. The sweat rate is lower in children, and the temperature at which sweating occurs is higher. Although there is considerable interindividual variability, children can take longer to acclimatize to warmer, more humid environments (typically 8-12 near-consecutive days of 30- to 45-minute exposures). Children also have a blunted thirst response compared with adults and might not consume enough fluid during exercise in hot, humid environments to prevent dehydration. In addition, certain medications may predispose to heat-related injury (Table 731.1).

Three major categories for heat illness are generally used: heat cramps, heat exhaustion, and heat stroke (Table 731.2). However, symptoms of heat illness overlap and progress as the core temperature rises. **Heat cramps** are the most common heat injury and usually occur in mild dehydration and/or salt depletion, typically affecting the calf and hamstring muscles. They tend to occur later in activity, as muscle fatigue is reached and water loss and sodium loss worsen. Heat cramps will normally respond to oral rehydration with electrolyte solution and with gentle stretching. The athlete can return to play when the ability to perform is not impaired. Other minor heat illnesses include heat syncope, heat edema, and heat tetany. **Heat syncope** is fainting after prolonged exercise, attributed to poor vasomotor tone and depleted intravascular volume; it responds to fluids, cooling, and supine positioning. **Heat edema** is mild edema of the hands and feet during initial exposure to heat; it resolves with acclimatization. **Heat tetany** is carpopedal tingling or spasms caused by heat-related hyperventilation during short periods of exposure to intense heat. It responds to moving to a cooler environment and decreasing respiratory rate (or rebreathing by breathing into a bag).

Heat exhaustion is a moderate illness with a core temperature of 37.7–40°C (100–104°F). It is manifested as weakness, fatigue, headache, nausea, vomiting, dizziness, orthostasis, piloerection, and possibly syncope. Central nervous system dysfunction is mild, if present. Treatment includes moving to a cool environment, cooling the body with fans, removing excess clothing, and placing ice over the groin and axillae. If a patient is not able to tolerate oral rehydration, IV fluids are indicated. Patients should be monitored, including rectal temperature, for signs of heat stroke. If rapid improvement is not achieved, transport to an emergency facility is recommended.

Heat stroke is a severe illness manifested by central nervous system disturbances and potential tissue damage. It is a medical emergency; *the mortality rate is up to 50%*. Sports-related heat stroke is characterized by profuse sweating and is related to intense exertion, whereas "classic" heatstroke with dry, hot skin is of slower onset (days) in elderly or chronically ill persons. Rectal temperature is usually >40°C (104°F). Significant damage to the heart, brain, liver, kidneys, and muscle occurs, with possible fatal consequences if untreated. Treatment is immediate whole-body cooling via cold water immersion (Table 731.3). Airway, breathing, circulation, core temperature, and central nervous system status should be monitored constantly. Rapid cooling should be ceased when core temperature is approximately 38.3–38.9°C (101–102°F). IV fluid at a rate of 800 mL/m^2 in the first hour with normal saline or lactated Ringer solution improves

Table 731.1 Medications and Drugs That May Increase the Risk of Heat-Related Injury

MEDICATIONS
Anticholinergic agents (including antihistamines)
β Blockers
Antipsychotics (including SSRIs, TCAs)
Lithium
Diuretics
Salicylates
Sympathomimetic agents
Calcium channel blockers
Antiseizure medications (topiramate, zonisamide)
DRUGS OF MISUSE/SUPPLEMENTS
Amphetamines (including ephedra)
Cocaine
Ecstasy
Phencyclidine
Cathinone (synthetic marijuana) agents
LSD
Alcohol
Anabolic steroids

SSRI, selective serotonin reuptake inhibitors; LSD, lysergic acid diethylamide; TCA, tricyclic antidepressants.

Table 731.2 Spectrum of Heat Illness

HEAT CRAMPS AND DEHYDRATION: *CAUTIOUS RETURN TO PLAY*
Muscle cramps
Thirst
Fatigue
Light-headedness
Sweating
Flushed face
HEAT EXHAUSTION: *REMOVE FROM PLAY*
Dizziness
Rapid pulse
Headaches
Nausea
Vomiting
Loss of coordination
Profuse sweating
Core temperature less than 40°C (104°F)
HEAT STROKE: *MEDICAL EMERGENCY, CALL 911*
Core temperature of 40°C (104°F) or higher
Hot dry skin
Multiple system failure
Delirium
Convulsions
Abnormal vital signs

From Merkel DL, Molony JT Jr. Medical sports injuries in the youth athlete: emergency management. *Int J Sports Phys Ther.* 2012;7:242–251. Table 4.

Table 731.3 Current Therapy for Heat-Related Illness

- Acclimatization is key for prevention of exertional heat illness.
- Heat illness is most effectively managed by immediate recognition of the signs and symptoms and proper diagnosis.
- Core body temperature measurement *must* be done with a rectal thermometer.

EXERCISE-ASSOCIATED COLLAPSE

- Continue walking after race to prevent development.
- Position the patient in the supine or Trendelenburg position and start fluid administration.

HEAT EXHAUSTION

- Provide rapid cooling with ice bags to areas adjacent to large vasculature (groin, neck, axilla).
- Administer oral or intravenous (IV) fluid to correct for hydration deficit.

HEAT STROKE

- Ensure the ability to maintain adequate circulation, airway, and breathing.
- *Ice-water immersion is the most effective way to provide rapid cooling.*
- The goal of cooling is to reduce and maintain a temperature below 38.3°C (101°F).
- Transport to the hospital may be required if the patient's temperature is not reduced effectively or the patient does not return to normal mental status after 30 minutes of medical treatment.

From Cleland P. Heat illness. In: Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier, 2023: p. 1390.

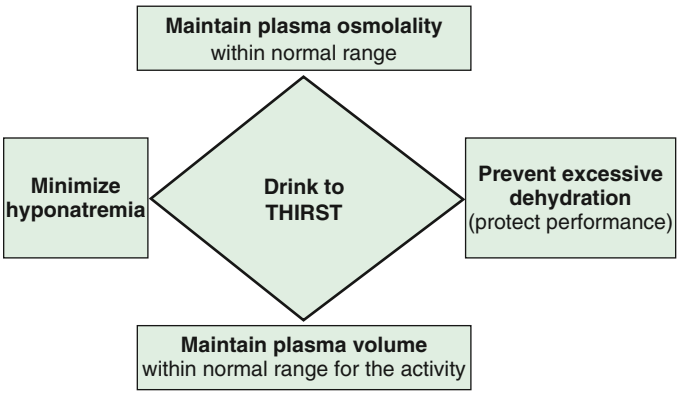

Fig. 731.1 Primary recommended fluid intake strategy to prevent symptomatic exercise-associated hyponatremia. *(From Hew-Butler T, Rosner MH, Fowkes-Godek S, et al. Statement of the third international exercise-associated hyponatremia consensus development conference, Carlsbad, California, 2015. Clin J Sport Med. 2015;25:303–320. Fig. 1.)*

intravascular volume and the body's ability to dissipate heat. Immediate transport to an emergency facility is necessary. Physician clearance is required before return to exercise.

Dehydration is common to all heat illness; consequently, measures to prevent dehydration may also prevent heat illness. Thirst is usually an adequate indicator of hydration status; excessive hypotonic fluid replacement beyond sweat and urine losses can lead to hyponatremia. Endurance athletes should be cautioned not to drink beyond thirst. Mild dehydration (2–3%) does not usually affect performance and itself does not cause cramping, fatigue, or heat stroke.

Exercise-associated hyponatremia (Na < 135 mmol/L) may be asymptomatic or symptomatic (lightheadedness, nausea, headache, confusion, cerebral edema) and is often seen in endurance sports (marathon, triathlon, cycling, swimming), hiking, football, and police or military drills. Major risk factors include overdrinking water or hypotonic sports drinks, weight gain during exercise, exercise duration >4 hours, readily available fluids, and inexperienced or slow pace. Athletes are advised to be hydrated before exercise and should drink to thirst (Fig. 731.1). Fluids should contain sodium and not be ingested in excess.

During a football practice, for example, scheduled breaks every 20-30 minutes with helmets off can decrease the cumulative amount of heat exposure. Practices and competitions should be scheduled in the early morning or late afternoon to avoid the hottest part of the day. Guidelines have been published about modifying activity related to temperature and humidity (Fig. 731.2). Proper clothing such as shorts and T-shirts without helmets can improve heat dissipation. Prepractice and postpractice weight can be helpful in determining the amount of fluid necessary to replace (8 oz for each pound of weight loss). When practicing or performing in a warm environment, gradual acclimatization is recommended.

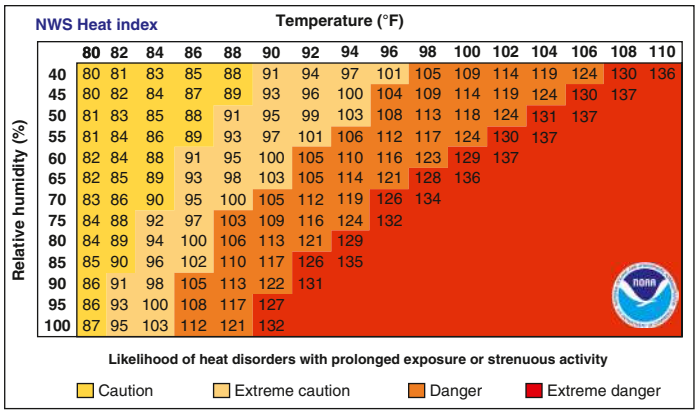

Classification	Heat index	Effect on the body
Caution	80°F - 90°F	Fatigue possible with prolonged exposure and/or physical activity
Extreme danger	90°F - 103°F	Heat stroke, heat cramps, or heat exhaustion possible with prolonged exposure and/or physical activity
Danger	103°F - 124°F	Heat cramps or heat exhaustion likely, and heat stroke possible with prolonged exposure and/or physical activity
Extreme danger	125°F or higher	Heat stroke highly likely

Fig. 731.2 Heat index. To determine the heat index using this chart, air temperature and the relative humidity need to be known. For example, if the air temperature is 100°F and the relative humidity is 55%, the heat index will be 124°F. When the relative humidity is low, the apparent temperature can actually be lower than the air temperature. *(Courtesy National Weather Service, United States National Oceanic and Atmospheric Administration. https://www.weather.gov/ama/heatindex.)*

Fluids with electrolytes and carbohydrates are important during exercise lasting longer than 1 hour. Salt supplements should not be used by most people because of the risk of causing hypernatremia and delayed gastric emptying. If excessive fluid intake contributes to hyponatremia, salt supplements will not avoid the decline in serum sodium. They may be useful in a person with a high sweat rate or recurrent heat cramps.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 732

Nutrition and Endocrine Conditions in Athletes

Gregory L. Landry and Andrew M. Watson

Excessive physical training in young women can adversely affect reproductive function and bone mineral status, especially when combined with calorie restriction (Fig. 732.1; see Chapters 41 and 159).

The majority of bone mass is acquired by the end of the second decade of life (see Chapter 749). Approximately 60–70% of adult bone mass is genetically determined, and the remaining is influenced by three modifiable factors: exercise, calcium intake, and sex steroids (primarily estrogen). Exercise promotes bone mineralization in the majority of young women and should be encouraged. In females with eating disorders and those who exercise to the point of excessive weight loss with **amenorrhea** or **oligomenorrhea**, exercise can be detrimental to bone mineral acquisition, resulting in reduced bone mineral content, or **osteopenia**. In males, prolonged negative energy balance can similarly result in bone demineralization, although this may be more occult without the obvious sign of menstrual cycle disruption.

Specifically, bone mineralization is negatively affected by amenorrhea (absence of menstruation for 3 or more consecutive months). This may be influenced by abnormal eating patterns, or disordered eating, that results in insufficient caloric intake. When occurring together, disordered eating, amenorrhea, and osteoporosis represent the **female athlete triad**. A more inclusive definition refers to the interrelationships among energy availability, endocrine function, and bone mineral

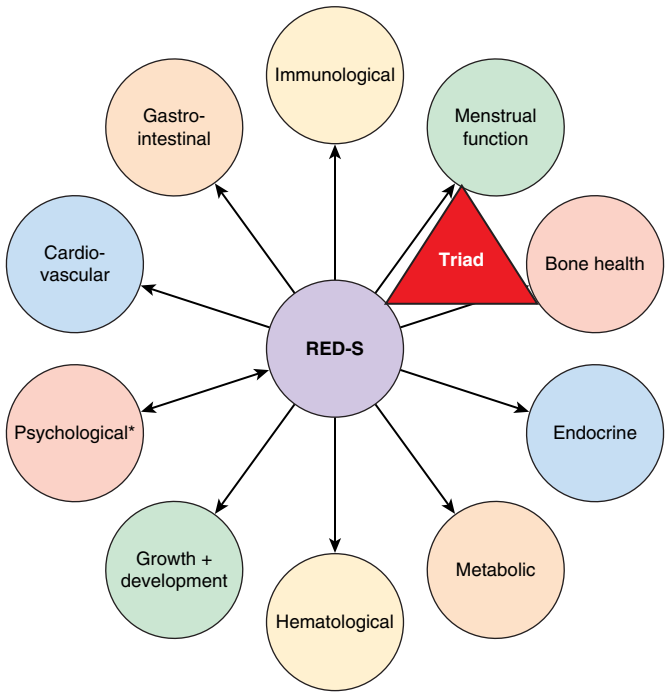

Fig. 732.1 Health consequences of relative energy deficiency in sport (RED-S) showing an expanded concept of the Female Athlete Triad to acknowledge a wider range of outcomes and the application to male athletes. *Psychologic consequences can either precede RED-S or be the result of RED-S. *(Courtesy Dr. Naama W. Constantini, Shaare Zedek Medical Center, Hebrew University, Israel.)*

density, as athletes are distributed along a spectrum of health and disease. The **male athlete triad** describes the impact of these interrelated problems in male athletes. In addition, the International Olympic Committee introduced the concept of **relative energy deficiency in sport** (RED-S), outlining the myriad physiologic, psychologic, and performance consequences of low energy availability in both male and female athletes (see Fig 732.1). At health supervision visits and the preparticipation physical examination, special attention should be given to screening for any unhealthy features of the female or male athlete triads (Tables 732.1 and 732.2).

In both male and female athletes, low energy availability can result in disruption of the hypothalamic-pituitary-gonadal axis. Menstrual abnormalities (including amenorrhea) result from

Table 732.1 Recommended Screening Questions for the Female Athlete Triad*

- Have you ever had a menstrual period?
- How old were you when you had your first menstrual period?
- When was your most recent menstrual period?
- How many periods have you had in the past 12 months?
- Are you presently taking any female hormones (estrogen, progesterone, birth control pills)?
- Do you worry about your weight?
- Are you trying to or has anyone recommended that you gain or lose weight?
- Are you on a special diet or do you avoid certain types of foods or food groups?
- Have you ever had an eating disorder?
- Have you ever had a stress fracture?
- Have you ever been told you have low bone density (osteopenia or osteoporosis)?

*The Triad Consensus Panel recommends asking these screening questions at the time of the sport preparticipation evaluation.

From Constantini NW. Medical concerns of the dancer. Book of Abstracts. XXVII FIMS World Congress of Sports Medicine, Budapest, Hungary, 2002. p. 151.

Table 732.2 Recommended Screening Questions for the Male Athlete Triad

- Do you worry about your weight?
- Are you trying or has anyone recommended that you lose or gain weight?
- Are you on a special diet, or do you avoid certain types of foods or food groups?
- Have you ever had an eating disorder?
- Have you ever had a stress fracture?
- Have you ever been told that you have low bone density or osteoporosis?
- Have you ever been diagnosed with low testosterone levels?
- Do you have low libido (sex drive)?
- Do you have morning erections?*
- Do you need to shave your facial hair less frequently?*

*Recommend inclusion on only preparticipation physical examinations for postpubertal athletes.

From Fredericson M, Kussman A, Misra M, et al. The male athlete triad – a consensus statement from the Female and Male Athlete Triad Coalition part II: diagnosis, treatment, and return-to-play. *Clin J Sport Med.* 2021;31(4):349–366. Box 1.

suppression of the spontaneous hypothalamic pulsatile secretion of gonadotropin-releasing hormone (Fig. 732.2; see Chapter 159.1). It is believed that the amenorrhea results from reduced energy availability, defined as energy intake minus expenditure. Energy availability below a threshold of 30 kcal/kg/day lean body mass is thought to result in menstrual disturbances, whereas availability at or above 45 kcal/kg/day is generally considered sufficient for optimal physiologic function. Other causes of menstrual cycle irregularities to be ruled out are pregnancy (see Chapter 161), pituitary tumors, thyroid abnormalities, polycystic ovary syndrome (see Chapter 589), anabolic-androgenic steroid use (see Chapters 157 and 733), and other medication side effects. Negative energy balance also appears to disrupt thyroid function and appetite-regulating hormones (e.g., leptin, ghrelin), increase resistance to growth hormone, decrease insulin and insulin-like growth factor 1, and increase cortisol levels. Although a threshold has yet to be established, low energy availability in males may also lead to decreased levels of testosterone and luteinizing hormone.

The low estrogen state of amenorrhea predisposes the female athlete to osteopenia and increases the risk of stress fractures, especially of the spine and lower extremity. If left unchecked, bone loss may be partially irreversible despite resumed menses, estrogen replacement, or calcium supplements. Similarly, low energy availability in males reduces bone turnover and can contribute to bone demineralization. Routine bone mineral density screening is not recommended but can help guide treatment and return to activity in severe cases.

Three eating disorders can occur in athletes, contributing to low energy availability. **Anorexia nervosa** manifests as weight <85% of estimated ideal body weight with evidence of starvation manifesting as bradycardia, hypothermia, and orthostatic hypotension or orthostatic tachycardia. **Bulimia nervosa** manifests as recurrent episodes (at least once weekly) of binge eating with a sense of lack of control over eating during an episode with recurrent episodes of compensatory behaviors, such as induced vomiting or excessive exercise. A third category, **unspecified feeding or eating disorder (UFED)**, is a general description for disorders failing to meet the criteria for the two previous disorders. Many young people who previously were diagnosed with UFED have a specific diagnosis of anorexia or bulimia. Signs of an eating disorder are weight loss, food restriction, depression, fatigue, worsened athletic performance, and preoccupation with calories and weight. The athlete might avoid events surrounding food consumption or might hide and discard food. Signs and symptoms include fat depletion, muscle wasting, bradycardia worsened from baseline, orthostatic hypotension, constipation, cold intolerance, hypothermia, gastric motility problems, and in some cases lanugo (see Chapter 41). Electrolyte abnormalities can lead to cardiac dysrhythmias. Psychiatric problems (depression [see Chapter 39], anxiety [see Chapter 38], and suicide risk [see Chapter 40]) are of higher incidence in this population.

For treatment of eating disorders, control of the symptoms is a central theme. The first step is confronting the athlete about the abnormal behavior and unhealthy weight. In general, exercise is not recommended if body weight is <85% of estimated ideal body weight, although there are exceptions, especially if the athlete is eumenorrheic. If the athlete is unable to gain weight with nutrition and medical counseling alone, then psychologic consultation is sought (Fig. 732.3).

Most athletes will not initially admit a problem, and many are unaware of the serious physical consequences. In some cases, athletes may have pursued athletic participation (e.g., in endurance activities) as a means to reduce or maintain a low body weight. A helpful technique in talking to these athletes is to sensitively point out performance issues. Education about decreased strength, endurance, and concentration can be a motivating factor for treatment. Often, the athlete's family needs to be involved, and the athlete should be encouraged to reveal necessary information to them. Psychology or psychiatry referral is important in the multidisciplinary approach to treatment of disordered eating. It is important for the physician to monitor the athlete's physical health while the mental health professional is caring for the mental aspects of the eating disorder.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

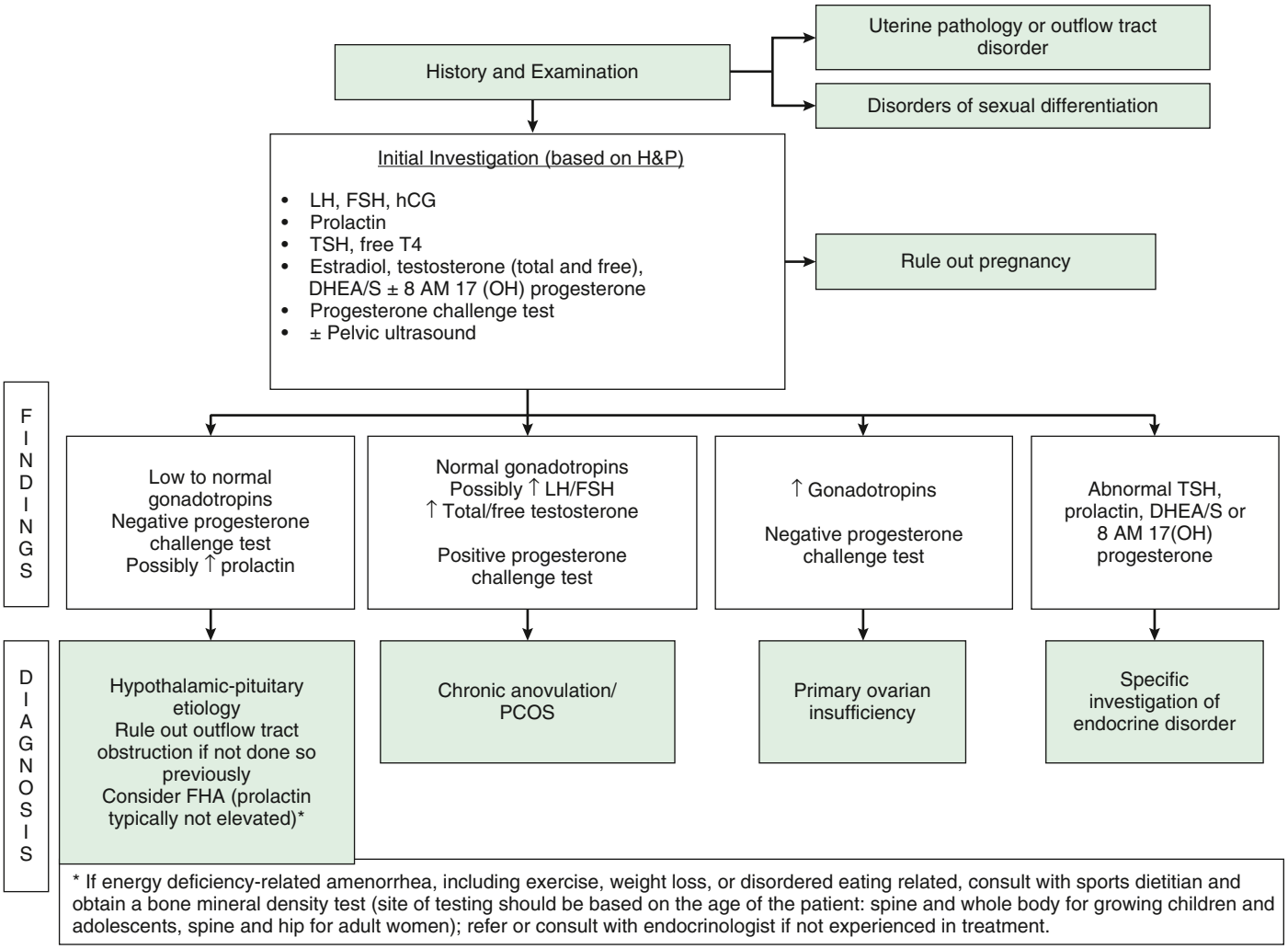

Fig. 732.2 Amenorrhea algorithm. Recommended clinical evaluation of an athlete with primary or secondary amenorrhea, or prolonged oligomenorrhea, includes a history and physical examination, initial and follow-up laboratory testing, and diagnosis by a physician. Referral or consultation with endocrinology is recommended if the diagnosing physician is not experienced with treatment of functional hypothalamic amenorrhea or other etiologies of amenorrhea. DHEA/S, Dehydroepiandrosterone sulfate; FHA, functional hypothalamic amenorrhea; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; PCOS, polycystic ovarian syndrome; TSH, thyroid-stimulating hormone. *(Modified from Jameson JL, De Groot LJ, Illingworth P. Amenorrhea, anovulation, and dysfunctional uterine bleeding. In: Jameson JL, De Groot LJ, eds. Endocrinology Adult and Pediatric, 6th ed. St. Louis: Saunders, 2010: pp. 2341–2355.)*

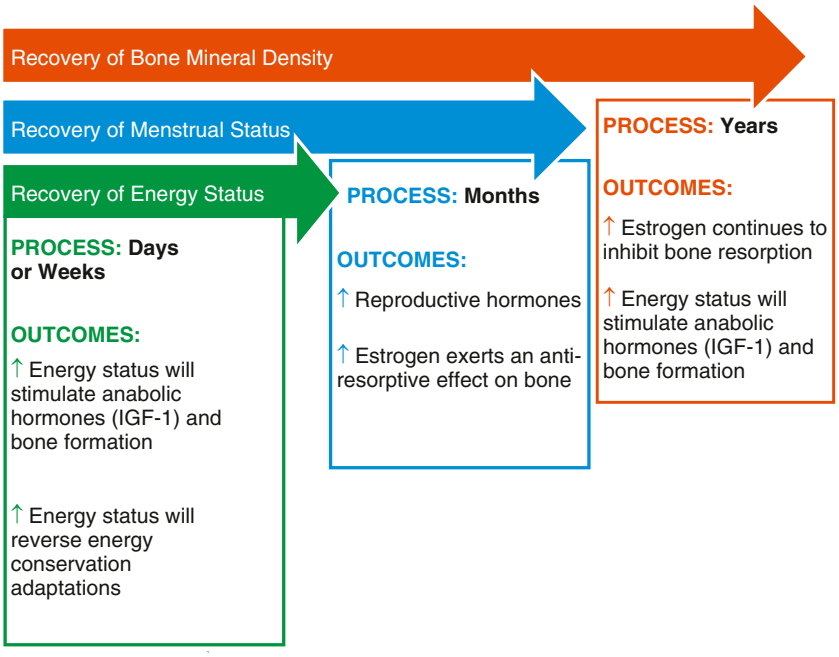

Fig. 732.3 Treatment of the female athlete triad. The three components of the triad recover at different rates with the appropriate treatment. Recovery of energy status is typically observed after days or weeks of increased energy intake and/or decreased energy expenditure. Recovery of menstrual status is typically observed after months of increased energy intake and/or decreased energy expenditure, which improves energy status. Recovery of bone mineral density may not be observed until years after recovery of energy status and menstrual status has been achieved. IGF-1, Insulin-like growth factor-1. *(From De Souza MJ, Nattiv A, Joy E, et al. 2014 Female Athlete Triad Coalition consensus statement on treatment and return to play of the female athlete triad. Br J Sports Med. 2014;48:289. Fig. 3.)*

Chapter 733

Performance-Enhancing Aids

Gregory L. Landry and Andrew M. Watson

See also Chapter 157.

Ergogenic aids are substances used for performance enhancement, most of which are unregulated supplements (Table 733.1). Many agents have significant side effects without proven ergogenic properties. The 2004 Controlled Substance Act outlawed the purchase of steroidal supplements, such as androstenediol and androstenedione, with the exception of dehydroepiandrosterone (DHEA).

The prevalence of lifetime steroid use is highest among males in the United States; among a large representative sample, 3–4% of males in middle school and 5–6% of those in high school report having used steroids for muscle enhancement. The European School Survey Project on Alcohol and Other Drugs found that 1% of European youth reported any use of steroids. Steroids in oral, injectable, and skin cream form are taken in various patterns. *Cycling* is a term used to describe taking multiple doses of steroids for a period, ceasing, and then starting again. *Stacking* refers to the use of different types of steroids in both oral and injectable forms. *Pyramiding* involves slowly increasing the steroid dose to a peak amount and then gradually tapering down.

Anabolic-androgenic steroids have been used in supraphysiologic doses for their ability to increase muscle size and strength and decrease body fat. An evidence base does support the increase in muscle mass and strength; the effects appear to be related to the myotrophic action at androgen receptors, as well as competitive antagonism at catabolism-mediating corticosteroid receptors. However, they have significant endocrinologic side effects, such as decreased sperm count and testicular atrophy in men and menstrual irregularities and virilization in women. Hepatic problems include elevated aminotransaminases and γ-glutamyl transferase, cholestatic jaundice, peliosis hepatitis, and a variety of tumors, including hepatocellular carcinoma. There is evidence that anabolic-androgenic steroids might predispose to a number of cardiovascular risk factors as well, including higher blood pressure, lower high-density lipoprotein, higher low-density lipoprotein, higher homocysteine, and decreased glucose tolerance. The possible psychologic effects include aggression, several personality disorders, and a variety of other psychologic problems (anxiety, paranoia, mania, depression, psychosis). Physical findings that may accompany anabolic-androgenic steroid use in males include gynecomastia, testicular shrinkage, jaundice, male pattern baldness, acne, and marked striae. Women can develop hirsutism, voice deepening, clitoral hypertrophy, male-pattern baldness, acne, and marked striae.

Testosterone precursors (also known as *prohormones*) include androstenedione and DHEA. Their use in the adolescent population has increased markedly in conjunction with reports of high-profile athletes' use. They are androgenic but have not been proven to be anabolic. If they are anabolic at all, they work by increasing the production of testosterone. They also increase production of estrogenic metabolites. The side effects are similar to those of anabolic-androgenic steroids and far outweigh any ergogenic benefit. These substances cannot be sold without prescription.

Creatine is an amino acid mostly stored in skeletal muscle as creatine phosphate or phosphocreatine. Phosphocreatine has the ability to rephosphorylate adenosine diphosphate through the donation of its phosphate group, yielding creatine and adenosine triphosphate. Creatine phosphate is then reconstituted through oxidative phosphorylation. The exogenous provision of creatine can therefore allow for a greater concentration of phosphocreatine in muscle, increasing muscle performance. The use of creatine as an ergogenic aid has increased, especially since other supplements have been withdrawn from the market. Thirty percent of high school football players have used creatine. There is evidence that creatine, as a source of increased energy, enhances strength and maximal exercise performance when used during training.

Caffeine is an active ingredient in energy drinks and some endurance sport supplements that has been shown to have ergogenic effects in both aerobic and anaerobic efforts. It acts primarily as an antagonist at the adenosine receptor, resulting in a number of potentially ergogenic effects such as reduced fatigue and increased muscle power. Although moderate doses of caffeine are considered relatively safe, when included in an energy drink combined with alcohol, excessive caffeine ingestion may result in tachycardia, gastritis, nausea, vomiting, and central nervous system excitation. Overdoses of caffeine may result in seizures, arrhythmias, and hypotension.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 733.1 Characteristics of Common Performance-Enhancing Substances

PERFORMANCE-ENHANCING SUBSTANCE	DESIRED EFFECTS	MAJOR ADVERSE EFFECTS	MINOR ADVERSE EFFECTS	STATUS	ROUTE OF ADMINISTRATION
Anabolic-androgenic steroids*	Increase muscle size, strength, lean body mass; decrease body fat	Testicular atrophy, CV disease, atherosclerosis, myocardial disease, liver dysfunction, cancer	Acne, gynecomastia	Banned by IOC and all major sporting bodies	Oral, topical, injectable
Creatine	Increase in strength, power output, sprint performance, total work to fatigue, peak force/power; decrease lactate threshold; increase weight and lean body mass	Heatstroke	Dehydration	Allowed	Oral

Continued

Table 733.1 Characteristics of Common Performance-Enhancing Substances—cont'd

PERFORMANCE-ENHANCING SUBSTANCE	DESIRED EFFECTS	MAJOR ADVERSE EFFECTS	MINOR ADVERSE EFFECTS	STATUS	ROUTE OF ADMINISTRATION
Human growth hormone[†]	May increase lean body mass and decrease fat mass	Carpal tunnel syndrome, intracranial hypertension, CV disease, hyperlipidemia, insulin resistance	Arthralgias	Banned by IOC and International Federations	Injectable
Amphetamines/ stimulants[‡,§]	Increase in alertness and metabolism; may increase strength, muscular power, speed, acceleration, aerobic power, anaerobic capacity, endurance	Arrhythmias, heat exhaustion, seizures, myocardial infarction, sudden death	Agitation, GI upset, nausea, headaches, insomnia, hallucinations	Banned by IOC, NCAA, NFL	Oral, injectable, inhalable
Erythropoietin/blood doping	Increase in oxygen-carrying capacity, endurance	Hypertension, myocardial infarction, pulmonary embolism, immune reaction	Headaches	Banned by IOC and all major sporting bodies	Injectable
Beta-hydroxy-beta-methylbutyrate	May increase lean body mass, muscle strength, power; enhance recovery	Unknown	Unknown	Allowed	Oral
Protein supplements	Increase lean body mass, improve healing	Unknown in previously healthy athletes	Unknown	Allowed	Oral

*Including selective androgen receptor modulators and aromatase inhibitors or estrogen receptor modulators.
[†]Including various growth factors (IGF-1, etc.).
[‡]Caffeine is commonly used and remains permitted by WADA.
[§]Includes various beta-2-agonists prohibited by WADA, except when needed for therapy of asthma but within therapeutic limits.
CV, Cardiovascular; GI, gastrointestinal; IOC, International Olympic Committee; LDH, lactate dehydrogenase; N/A, not applicable; NCAA, National Collegiate Athletic Association; NFL, National Football League; WADA, World Anti-Doping Agency.
Modified from Momaya A, Fawal M, Estes R. Performance-enhancing substances in sports: a review of the literature. *Sports Med.* 2015;45:517–531. Table 1.

Chapter 734

Specific Sports and Associated Injuries

Gregory L. Landry and Andrew M. Watson

SPORTS PARTICIPATION, EARLY SPECIALIZATION, INJURY RISK, AND BURNOUT

It is estimated that 60 million youth, age 6-18 years, participate in organized athletics, with 44 million participating in multiple sports. It has also been estimated that 69% of females and 75% of males age 8-17 years participate in at least one organized sport team or club. Participating in sport gives children the opportunity to develop self-esteem and leadership skills, promote peer socialization, and improve general health and fitness. Some parents encourage their children to participate in a *single sport* because they think this will allow the athlete more time to focus on sport-specific skills and will increase the likelihood that their child will be selected for elite teams, a college scholarship, or professional contract. They may also feel pressure from coaches. However, only 0.2–0.5% of U.S. high school athletes rise to the professional level; Olympic-level athletes start training in their main sport at an older age than their less elite peers and on average participate in two other sports before, or in parallel with, their main sport. A study at the collegiate level revealed that 70% of surveyed athletes did not specialize in their sport until 12 years of age, and 88% participated in more than one sport at some point during childhood. *Multisport* athletes, in general, have a more diverse skill set, can transfer skills from one sport to another, have a decreased risk of **overuse injury**, have lower rates of **burnout**, and thus are less likely to quit sports at a younger age. Exposure to multiple sports also allows these athletes to identify the sport they most enjoy.

Risk of injury in sports increases with age and training volume. In general, there is an increased risk of injury if young athletes participate in more weekly organized sport hours than their age. When young athletes exceed a 2:1 ratio of weekly hours in organized sports to weekly hours in unorganized free play, they are more likely to suffer a serious overuse injury. Overuse injuries unique to young athletes include apophyseal injuries and physeal stress injuries secondary to decreased muscle mass, increased joint hypermobility, and imbalances in growth and strength (see Chapter 728). Overuse injuries and fractures are more likely to occur during adolescent growth spurts as physes, apophyses, and articular surfaces in a rapid phase of growth are less resistant to tensile, shear, and compressive forces than either mature bone or more immature prepubescent bone, and because of decreased blood flow to

the physes. When this underlying vulnerable physiology is combined with overscheduling secondary to participation in a large number of competitive events at young ages, the risk of overuse injury increases. These events often include tournaments, which may consist of multiple games in a short period of time. This type of schedule does not allow enough time for rest and recovery.

Sports specialization is traditionally defined as "participating in a single sport for greater than eight months per year, choosing a single main sport, and/or quitting all other sports to focus on one sport." Athletes who specialize early sometimes report increased anxiety and stress secondary to worrying about failure, trying to meet adult expectations, or experiencing parental pressure to participate or perform at a certain level, and often feel as though they have a lack of control in sport decision-making. These feelings can contribute to burnout, which can lead to quitting sports early and ultimately increased inactivity as an adult. To reduce the risk of overuse injury and burnout, one should limit weekly and yearly participation time, limit sport-specific repetitive movements, and ensure adequate rest and recovery periods. Thus it has been recommended that "intense training in a single sport to the exclusion of others should be delayed until adolescence in order to optimize success while minimizing injury, stress, and burnout."

FOOTBALL

Football is the sport with the greatest number of participants in the United States, especially at the high school level, and with the highest number and rate of injuries. Most of these injuries are relatively minor, and compared with injuries in many other sports, are less severe, as evidenced by fewer days lost from injury. Age, weight, and position played contribute to injury risk, with older and heavier players, running backs, and linebackers having higher injury rates. The most common football injuries include joint sprains, muscle strains, and contusions, with the lower extremities injured most frequently.

Although the majority of catastrophic sports injuries in the United States have occurred in football, these injuries are rare. Catastrophic injury is defined as a fatal injury or a severe injury with or without permanent severe functional disability. Disabling injuries include cervical spine and cerebral injuries.

Head and neck injuries in football include concussion, neck sprain, and brachial plexopathy. Compared to other sports, brain injury (concussion) (see Chapter 729) occurs with the highest rate in football, a result of the frequent exposure to contact during practices and games, although more concussions occur in games than practices. When compared to other sports, cervical spine injuries occur at higher rates in football given the increased risk of high-velocity contact, neck flexion, and axial loading. Proper blocking and tackling form with the neck extended rather than flexed is essential to help reduce the risk of cervical spine injury. Although not shown to reduce the concussion rate, helmets can help reduce facial and dental trauma and provide some protection from side head blows. A **"stinger"** or **"burner"** represents a brachial plexus neurapraxia (see Chapter 730). This is the most common nerve injury in football and results from traction, compression, or a direct blow to the upper cervical nerve roots of the brachial plexus caused by forceful lateral neck bending.

Heat illness is possible in pediatric athletes given physiologic factors, including increased heat production per body weight, less efficient heat dissipation, and higher body temperatures associated with dehydration. Dehydration and associated electrolyte abnormalities and poor acclimatization increase the risk of heat illness. Heat illness risk can be reduced with proper hydration prepractice, during, and postpractice, avoiding practice in high heat or humidity, wearing breathable, light-colored clothing, removing the helmet between plays, and avoiding certain medications such as antihistamines, anticholinergics, stimulants, and supplements (see Chapter 731).

Contusions to the arm or thigh muscles can result in the development of a large hematoma if not treated aggressively in the acute stage, resulting in prolonged time away from football. Large hematomas and those allowed to persist are at risk for development of **myositis ossificans**.

Low back pain can be caused by **spondylolysis**, especially in players with repetitive hyperextension of the spine (see Chapter 720.6). Education on tackling mechanics, core strengthening, and hamstring flexibility are important in prevention of and/or recovery from a spondylolysis injury. Shoulder trauma can cause glenohumeral joint dislocations, the majority of which are anterior dislocations and have a high rate of recurrence; acromioclavicular joint sprains; and fractures to the clavicle or humerus (see Chapter 724). Knee injuries (see Chapter 728.6) are common and include **anterior cruciate ligament (ACL)** tears and, less frequently, medial collateral ligament (MCL) tears. Knee bracing in high school football players is controversial and lacks significant evidence.

Ankle sprains occur frequently, with lateral ankle sprains resulting in less time away from the sport than high ankle sprains. The risk of re-injury may be reduced by rehabilitation, including strengthening and range of motion, and the use of a lace-up ankle brace (see Chapter 728.8). **Turf toe**, a sprain to the first metatarsophalangeal joint, is caused by forceful dorsiflexion of the toe while wearing soft, lightweight, flexible shoes. Calcaneal apophysitis at the insertion of the Achilles tendon on the calcaneus, also known as **Sever disease**, is an overuse injury that typically presents as heel pain in a cleated athlete who is still growing (typically age 7-10 years).

BASEBALL/SOFTBALL

Baseball- and softball-related injury sites are most commonly the shoulder, elbow, ankle, and hip. Facial injuries and concussions are also seen. The most common mechanisms of injury include pitching repetition and being hit by a ball or a bat.

Throwing injuries of the shoulder and elbow are typically seen in pitchers secondary to overuse, with contributory factors, including high pitch count, pitch type, and inadequate rest. **Little League shoulder** is a repetitive microtrauma injury to the open proximal humeral physis, and **Little League elbow** is a repetitive microtrauma injury to one or more of the six ossification centers in the elbow (see Chapter 728.3). Little League shoulder is the most common injury seen in softball windmill pitching, with similar shoulder stress as seen in overhand pitching. Poor core strength and alteration in biomechanics, especially when fatigued, may contribute to injury risk (Fig. 734.1). Age-related **pitch count** and rest guidelines, "Pitch Smart," are available online and are endorsed by the Little League. Curve balls and sliders should not be thrown by players younger than 14 years of age. Current recommendations also advise against participating in multiple leagues and participating in year-round baseball, given the increased risk of injury with this volume of play. Adherence to the guidelines is the responsibility of the athlete, parents, and coaches. Counseling athletes (and coaches) to stop all throwing activities if the player experiences shoulder or elbow pain, with medical evaluation if no resolution with rest, is essential. If injured, a gradual return to throwing protocol under the direction of a physical therapist with additional focus on strengthening and throwing mechanics should be considered. Catchers are more vulnerable to traumatic sprains of the interphalangeal and metacarpal phalangeal joints, head injuries, including concussions from the ball striking the mask, and knee injuries associated with the deep squatting posture. Knee savers are pads attached to the shin guards that increase the angle between the knee and thigh and prevent hyperflexion of the knees. No scientific studies have been done to assess their effectiveness.

Death or serious injury in baseball is rare but may result from direct contact by the ball or bat, causing serious head injury or **commotio cordis**, which is a direct blow to the chest during a critical time in the cardiac cycle resulting in a possibly fatal arrhythmia. Batting helmets, with consideration of faceguards, must be worn properly to help prevent face and head injuries. Modifications to the hardness of baseballs used with younger athletes may also be helpful. Chest protectors have not been shown to reduce the risk of commotio cordis.

Sliding causes the most injuries in base runners, including head injury and lower limb injuries. If sliding is allowed, correct sliding technique must be taught because many injuries are secondary to timing

issues. Head-first sliding is controversial and is not recommended for players younger than 10 years of age.

BASKETBALL/VOLLEYBALL

When combining male and female sports participation, basketball has one of the highest injury rates, even though it is considered a "safe sport" from a contact perspective. Common maneuvers of basketball and volleyball include jumping, pivoting, running, and sudden acceleration and deceleration, which increase the risk for knee and ankle injuries. Similarly, injury to the fingers may result from the passing, catching, and striking of the ball inherent in these sports. Scaphoid fractures may result from falling on an outstretched hand. Injuries to the face and eyes can also occur.

Ankle sprains are the most common injury and are usually caused by inversion with plantar flexion, placing the lateral ligaments at risk. An avulsion fracture of the base of the fifth metatarsal at the insertion of the peroneus brevis tendon is another sequela of inversion ankle injuries. A **high ankle sprain** or syndesmosis ligament injury typically results from an excessive external rotation in a dorsiflexed position, and these athletes have pain out of proportion to examination findings.

Foot pain may be secondary to calcaneal apophysitis (Sever disease), retrocalcaneal bursitis, posterior tibialis tendinosis, accessory tarsal navicular, sesamoiditis, blisters, subungual hematoma, and paronychia (see Chapter 704). Achilles tendinosis is also a common overuse injury.

Knee injuries include those caused by overuse, such as traction apophysitis at the insertion of the patella tendon on the tibial tubercle **(Osgood-Schlatter disease)** (see Chapter 718.4), traction apophysitis at the distal patella **(Sinding-Larsen-Johansson syndrome)** and patellar tendinosis **(jumper's knee)** (see Chapter 728.6).

ACL injury occurs in both male and female participants; however, among children 12-17 years old, the frequency of ACL injury in female participants is slightly higher. The exact reason for this discrepancy is unclear; however, some data suggest that female athletes do not exhibit the same neuromuscular adaptions that male athletes exhibit during pubertal growth spurts. Multiple studies on the effect of neuromuscular training and strengthening programs focused on ACL injury prevention in females suggest that these types of programs may reduce the risk of ACL injury. As with other jumping sports, other acute ligament sprains (MCL with or without ACL) can occur. For all participants, a program focused on the sport-specific strengthening of hip, core, and hamstring muscles to prevent dynamic valgus when landing can help to reduce knee injury rates.

The overhead nature of volleyball can result in overuse shoulder injuries, including rotator cuff tendinosis, shoulder impingement syndrome, labral tears, and glenohumeral instability. Players may want to limit the number of overhead spikes and serves they perform, similar to pitch count limits in baseball, to help reduce the risk of overuse injuries. Finger injuries seen in both basketball and volleyball participants include sprains, dislocations, and fractures.

Eye injuries, although rare, can be reduced by wearing protective eyewear. Facial injuries typically result from an elbow or hand hitting the opponent's face during rebounding or defending. Head injury can occur in both sports when the player makes contact with another player, the floor, or equipment (such as the net pole in volleyball).

TENNIS

Injury rates in high-level youth tennis players are higher than in adults. Tennis injuries occur twice as often in the lower extremity as in the upper extremity. Lower extremity injuries tend to be more acute, whereas upper extremity and trunk injuries tend to be more chronic, and the incidence of overuse injury is high. Overall injury rates are similar for males and females. However, male players age 5-10 years were more likely to sustain injuries to the head and neck and suffer injuries as a result of contact with the net, ball, or racket than other groups.

The most common injury in tennis players is to the ankle, although the knee and thigh are vulnerable as well. Lower extremity injuries are related to the frequent directional changes, creating significant concentric and eccentric loads. Overuse injuries include iliopsoas tendonitis or bursitis, patellofemoral stress syndrome, patellar tendinosis, Osgood-Schlatter disease, medial gastrocnemius strain (**"tennis leg"**), Achilles tendonitis, and Sever disease. Stress fractures in the lower extremity in elite players are most common at the tarsal navicular, metatarsals, and tibia.

In the upper extremities, **tennis elbow** (lateral epicondylosis with extensor carpi radialis brevis tendinosis) and **extensor carpi ulnaris (ECU) tendinosis** with or without subluxation, are particularly prevalent in the recreational player and are thought to be most likely related to overuse and improper technique (see Fig. 728.11). With repetitive overload of the wrist flexor–pronator muscle groups, traction apophysitis at the medial humeral epicondyle and medial epicondylar fragmentation of the humerus, especially in younger males, can occur. This can secondarily involve the ulnar collateral ligament and ulnar nerve. Shoulder pain often results from **labral injury**, a common site of injury for overhead athletes. Anteroposterior glenohumeral instability, glenohumeral internal rotation deficit with impingement, rotator cuff strain, and scapular dyskinesis are all possible. Wrist problems include an enlarged dorsal ganglion cyst, radiocarpal joint capsular impingement or synovitis, chronic degenerative tears of the triangular fibrocartilage complex, and acute fracture of the hook of the hamate. Stress fractures may occur in the metacarpals (second metacarpal in particular) and less commonly in the humerus, ulna, and radius.

It has been hypothesized that repeated loading during service, particularly using a "topspin" serve at a young age, may contribute to the

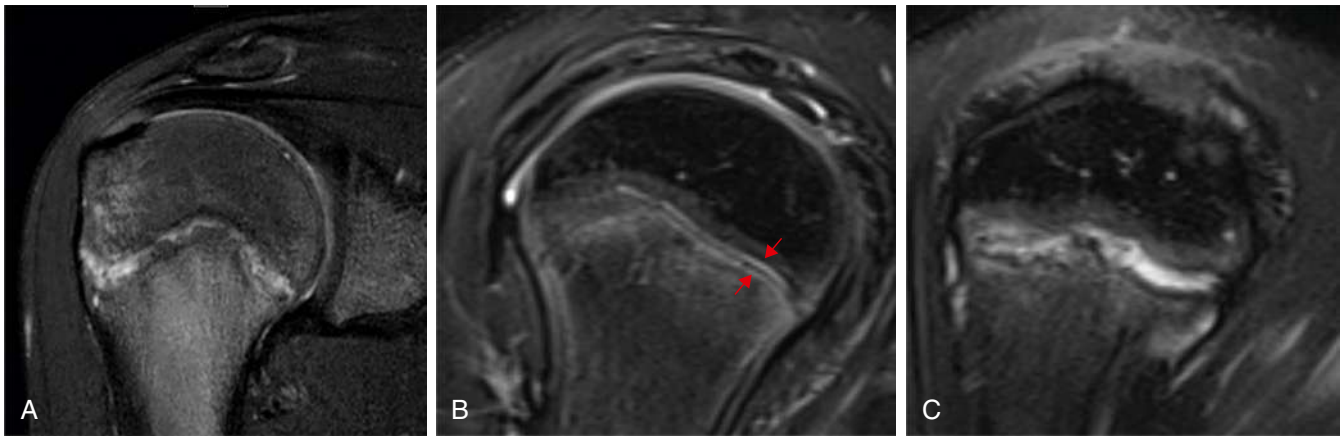

Fig. 734.1 Little League shoulder MRI findings. A, Coronal oblique fat-saturated T2 weighted image in a 12-yr-old pitcher demonstrates diffuse proximal humeral primary physeal widening and undulation with bone marrow edema within the metaphysis and lateral epiphysis. B and C Sagittal oblique fat-saturated T2 weighted images obtained in a 13-yr-old pitcher demonstrate preservation of the normal anterior medial humeral physis *(arrows)* in contrast to the widened irregular physis posteriorly and laterally. *(From Braithwaite KA, Marshall KW. The skeletally immature and newly mature throwing athlete. Radiol Clin N Am. 2016;54:841–855.)*

development of **spondylolysis (pars interarticularis fracture)** or spondylolisthesis. However, the most common back injury in tennis is lumbar muscle strain.

LACROSSE

Lacrosse is one of the fastest growing sports for both male and female youth, high school, and college level athletes. Protective equipment and rules are different for male and female players. Required equipment for male players includes mouth guard, helmet, gloves, and elbow and shoulder pads. Required equipment for female players includes eye wear and mouth guard. **Checking** is allowed in men's lacrosse but is not permitted in youth or women's games.

Injury rates are nearly three times higher in competition than in practice. The most common injuries for all players include lower extremity injuries, primarily ankle and knee sprains, and head injuries. Ankle sprains typically occur in the setting of cutting, dodging, and twisting activities. The likelihood of subsequent injury may be reduced with bracing. ACL tears are a common knee injury and typically occur in noncontact cutting or pivoting. Prepractice training should include balance, lower extremity strengthening, and neuromuscular feedback activities, as these have been proven to help reduce the ACL injury rate.

Head injury occurs in both male and female players. Player-to-player contact is the typical mechanism for head injury in male players. Incidental contact with the stick is the typical mechanism for head injury in female players. Eyewear for female athletes has been shown to reduce the risk of significant eye injury.

Upper extremity injuries include **acromioclavicular sprains** and hand and thumb fractures, particularly in games that permit contact and checking. Shoulder and elbow injuries are typically secondary to contact injury.

As with any sport with significant protective equipment that impedes heat loss, heat illness can occur. Players and coaches should be mindful of hydration, temperature, humidity, and duration of play. Commotio cordis is a rare but possible risk. The use of chest protectors has been evaluated and has not been shown to reduce risk.

SWIMMING/DIVING

In competitive swimming, injuries to the shoulder are most common and are generally a result of chronic overuse. **Swimmer's shoulder** is a general term for shoulder overuse in a swimmer and is typically a combination of subacromial impingement/bursitis and tendinosis of the rotator cuff and long head of the bicep tendon. Commonly, a narrowed subacromial space, increased laxity of the shoulder capsule, and relative weakness of the scapular stabilizers result in protracted shoulder posture, which contributes over time to the insidious onset of shoulder pain and possible **scapulohumeral dyskinesis**. Freestyle, back, and butterfly strokes tend to exacerbate the pain. Prevention includes monitoring training load, proper technique, and strengthening exercises. The multiaxial instability of the glenohumeral joint common in swimmers is addressed with rehabilitation focusing on strengthening of the rotator cuff and scapular stabilizer musculature. Knee and hip/groin pain can be exacerbated with breaststroke given the whip kick motion required in this stroke.

Swimmer's ear, or **otitis externa**, presents with pain and often drainage from the external auditory canal. It is caused by bacterial, or less commonly, fungal infection of the external auditory canal as a result of chronic, excessive wetness (see Chapter 679).

Diving is a sport that many athletes start at a young age with early sport-specific, specialized training. The most common injury for divers is shoulder strain, given overhead activity and the significant force taken by the shoulder, which is dependent on the angle of entry into the water. Low back pain can be seen in divers and may be associated with lumbar hyperextension to compensate for limited shoulder flexibility when entering the water, which can lead to spondylolysis. Diving is also associated with a risk of cervical spinal cord injury secondary to axial loading; according to the National Spinal Cord Injury Statistical Center, diving is the fifth leading cause of spinal cord injury in the United States.

SOCCER

Soccer enjoys a very high level of popularity and participation among youth worldwide. In the United States, the annual rate of injury in soccer more than doubled between 1990 and 2014, and almost three million children were seen in U.S. emergency departments for injuries related to soccer during those years. Mechanisms of injury include noncontact, body-to-body contact, falls, or ball-to-body contact. Although lower extremity injuries are by far the most common, younger children are more likely to injure an upper extremity, and upper extremity injuries are most likely to be fractures. Torso and significant abdominal injuries can occur. Low back symptoms are relatively less common and are most often muscular in nature.

Injuries in youth soccer occur predominately in the lower extremity and include joint and ligament injuries, abrasions, contusions, muscle strains, and fractures of the ankle, knee, and thigh. Ligamentous injuries to the ACL and MCL at the knee and the **anterior talofibular ligament** at the ankle can occur because of the cutting and pivoting maneuvers required during play or as a result of contact with another player. ACL injuries, particularly in females, have gained attention in recent years. ACL injuries are more common in high school girls' soccer than in other girls' sports. Risk factors may include genetics, hormones, age, sex, previous injury, and anthropomorphic factors. **Overuse syndromes** such as patellofemoral dysfunction, Osgood-Schlatter, Sinding-Larsen-Johansson, and Sever disease frequently occur. Hip problems include the **hip pointer (iliac crest contusion)**, iliac crest apophysitis, and chronic groin pain (muscle strain, **sports hernia**, **osteitis pubis**). The terms *sportsman's hernia, inguinal insufficiency,* and *conjoint tendon tear* may comprise a constellation of different pathologic processes producing similar groin pain. These injuries may occur with the combined forceful rotation of the torso and kicking motion. Femoral neck stress fractures, slipped femoral capital epiphysis, and avulsion fractures of the pelvis or femur should also be considered in the differential. Neuromuscular factors, such as quadriceps dominance, muscle activation patterns and dynamic stability, may be modifiable; thus the American Academy of Pediatrics (AAP), and other organizations support neuromuscular training programs aimed at risk reduction for both sexes.

Concussion is common in soccer, primarily as a result of contact between players, player and goal post, and player and ground. Recent evidence suggests that intentional heading of the ball rarely results in a concussion, although the long-term effect of repeated subconcussive impacts for intentional heading remains unknown. The U.S. Soccer Concussion Initiative updated recommendations to reduce head injury risk in youth soccer players, including a ban on heading the ball for age 10 and under and limited heading of the ball for 11-13 year olds. It remains unknown if this has reduced the number or severity of concussions. Padded headbands have not been shown to reduce the risk of concussion in youth soccer players.

ICE HOCKEY

Ice hockey is a fast-paced collision sport associated with injuries caused by contact from other players, the ice, or the boards, as well as from the puck or stick. With injury rates similar to other high school full-contact sports, concussions, contusions, fractures, ligament sprains, muscle strains, lacerations, joint separations, dislocations, and subluxations are commonly reported. Injuries are more likely to occur in competition than in practice, and overall injury rates appear to be on the rise, possibly related to increased participation.

Concussion was the most commonly reported injury in U.S. high school ice hockey athletes, with head and face injuries accounting for 34% of all of the reported injuries. Injuries to the shoulder and arm are also common and include contusions, strains, acromioclavicular separations, and clavicle fractures. Over 50% of upper extremity fractures occur in the forearm, wrist, and hand. Other specific hockey injuries include hip pain secondary to **femoroacetabular impingement (FAI)**, high ankle sprains, hip adductor strain, and osteitis pubis.

The role of factors such as age, size, level of skill, player position, and sex in injury risk is inconclusive, although evidence suggests that concussion may be more frequent in females and fractures more common in males.

Body checking is the single most common mechanism of injury. In Canada, 11- and 12-year-old Pee Wee hockey players who were allowed

to body check had a threefold greater risk of injury than those who were not. USA Hockey rules of play do not allow body checking in the 12-year and under youth leagues. Body checking is not allowed in girls'/women's leagues of any age. The AAP recommends the expansion of nonchecking programs and the restriction of body checking to elite levels of boys' play after 15 years of age. AAP recommendations also include the use of protective equipment (helmets and full-face shields or cages), rules to eliminate dangerous play with a zero-tolerance policy for head contact and body contact from behind, and safer play education for coaches and athletes.

FIELD HOCKEY

Field hockey is played worldwide by both male and female athletes. Protective equipment, including mouth, shin, and ankle guards, is recommended but not required. Players are twice as likely to be injured in game versus practice. Lower limb injuries, particularly inversion ankle sprains, are the most common. Bracing may help with ankle re-injury rates. Other lower extremity injuries include hamstring strain, ACL tears, and contusions. The most common upper limb injury occurs when the hand is struck by a stick or a ball, as field hockey does not require the use of padded gloves for protection. Head injury and facial lacerations occur at a very high rate and are typically caused by contact with the stick or ball. Injury types and rates may differ based on the position played; however, specific data are lacking.

Injury prevention is important in this sport and can be attained via the use of protective equipment, including permitted head or face protection, and sport-specific training, including balance, strengthening, and proprioceptive training activities.

SKIING AND SNOWBOARDING

Injury frequency in skiing, snowboarding, and related winter sports has declined over the past several decades, largely secondary to improved equipment (boots, bindings, poles) and slope conditions. Of concern, however, is that severe head and spinal cord injuries are on the rise due to increased speed and the addition of acrobatic maneuvers (terrain parks, half pipes, aerial tricks). Head and neck injuries are the primary cause of fatal injury. Of the World Cup events, freestyle skiers (particularly aerials and slope style) have a higher incidence of head injury than snowboard and alpine events. Overall, the risk of injury is higher in snowboarders, males, beginners, and those with improper equipment.

Lower extremity injuries are more commonly associated with skiing, while head, internal organ, upper extremity, and ankle injuries are more common in snowboarders. The most common lower extremity injury in skiing is ligamentous (ACL, MCL, and LCL) at the knee. Lower-extremity injuries in skiers also include contusions, knee dislocation, femur fractures, spiral fractures of the tibia **("boot top" fractures)**, and high ankle sprains. Snowboarders are at a unique risk for fracture of the lateral process of the talus, which is often initially misdiagnosed as an ankle sprain.

Upper-extremity injuries are more common in snowboarding because both of the snowboarder's feet are strapped onto the same board and, without poles, there is an increased risk of falls on outstretched arms. Common injuries include distal radial, ulnar, and metacarpal fractures, sprains, and contusions. Other high-incidence upper extremity injuries in snowboarding include shoulder soft tissue injuries, clavicle fractures, acromioclavicular sprains, and glenohumeral joint dislocations. A unique skiing injury is **skier's thumb**, a sprain of the ulnar collateral ligament of the thumb, which typically results from a fall with the thumb in abduction and hyperextension around a ski pole. Phalanx fractures and bony avulsions can also be associated with this injury.

Snow sport athletes may experience visceral injuries to the spleen, liver, and kidney. Spine injuries, including fracture and strain, may also occur.

It is strongly advised that individuals of all ages wear helmets for skiing and snowboarding. Wrist protectors are also recommended for snowboarders. Care should be taken to ensure up-to-date and properly fitted and adjusted equipment. Preventive measures endorsed by the AAP include participation in formal instruction, such as in a ski school, having adequate supervision, and exercising responsible speed and technique. Cardiovascular fitness, endurance, and muscle strength are believed to be critical components in injury prevention; however, there is limited supportive literature.

SKATEBOARDING

Injuries associated with skateboarding are predominantly acute, including contusions, lacerations, sprains, and fractures, affecting the wrists, forearms, and to a lesser extent, the ankles and head. Fractures involving the upper extremities are more common in younger skateboarders, often from a fall onto an outstretched arm. Lower-extremity fractures and head injuries predominate in the adolescent population, which is likely because of higher complexity of the airborne maneuvers and tricks often attempted. Loss of balance leading to a fall when failing to perform a particular maneuver, especially when catching a wheel, is generally the primary cause of injury. These falls can occur at high velocities (up to 40 mph), placing the skateboarder at risk for serious injuries.

Traumatic brain injuries do occur within this sport; the incidence increases with age and is more common in males than females. In older children and adolescents, the neglected use of helmets and the increased speed of their skating contribute to this fact.

In addition to helmet use, other safety measures recommended include wrist guards as well as elbow and knee pads. The building of skateboard parks has been a recent strategy to remove skateboarders from pedestrians, bicyclists, and motor vehicle traffic, while also encouraging adult supervision.

CYCLING AND MOTOCROSS

Bicycle riding has been a beloved childhood recreational activity for decades. Cycling options have expanded to include a variety of events such as track and road racing as well as mountain biking, mountain bike terrain parks or "free-riding," cyclo-cross, and freestyle BMX. As increased speed, jumps, and other human-made obstacles have been added, risk for injury has increased. Motocross, beginning as early as 4 years of age, adds further complexity as it uses two-wheeled motorized cycles racing through designed outdoor courses.

Recreational bicycling injuries include abrasions, lacerations, contusions, and fractures. Head and face as well as genitourinary injuries are common. Helmet use is strongly encouraged to reduce the risk of serious head injury. Upper extremity fractures predominate in mountain bikers and mountain terrain park riders. Risk of injury is increased in mountain biking males between 10 and 14 years and in those who admit to riding faster than usual. Motocross riders sustain more serious injuries. Head injuries include skull fractures and a variety of intracranial bleeds that may occur even when using a helmet.

WRESTLING

Wrestlers may have great fluctuations in weight to meet weight-matched competition standards. Such fluctuations are sometimes associated with fasting, dehydration, and then binging. Counseling wrestlers and their parents regarding impaired performance from these components of disordered eating, especially with respect to decreased speed and strength, is important to deter athletes from incorporating them into routine practice. Most states have rules in place to mitigate this risk by limiting the amount of weight loss for each wrestler.

Wrestling moves apply a variety of torques or forces to the extremities and spine, potentially resulting in a number of common injuries. Takedown maneuvers and subsequent impact with the mat can produce concussions, neck strain/sprain, or spinal cord injury. Spondylolysis (see Chapter 720.6) is a concern in wrestlers given repetitive lumbar extension.

Stingers and **burners**—also seen among football players—are caused by stretching or pinching of the brachial plexus (see Chapter 730). Overall, the two most common sites of injury in wrestling are the shoulder and knee.

At the shoulder, subluxation is common. This generally occurs anteriorly with the shoulder forcibly abducted and extended. Patients are commonly aware of their shoulder slipping in and out. Injuries to the hand are less common and typically include metacarpophalangeal and proximal interphalangeal joint sprains.

Knee injuries (see Chapter 728.6) are also common, and include **prepatellar bursitis**, medial and lateral collateral ligament sprains, and medial and lateral meniscus tears. Acute or recurrent traumatic impact to the mat can result in prepatellar bursitis. If the overlying skin is broken, septic bursitis may occur, resulting in swelling, redness, and warmth over the anterior knee.

Dermatologic problems associated with wrestling include herpes simplex (see Chapter 299: **herpes gladiatorum**), impetigo (see Chapter 706.1), staphylococcal furunculosis or folliculitis, superficial fungal infections, and contact dermatitis. Herpes gladiatorum and superficial bacterial skin infections are contraindications to wrestling until the lesions have resolved. Washing of the wrestling mats with appropriate antibacterial and antifungal solution is required after daily wrestling sessions to keep the mats disinfected and prevent the spread of dermatologic contagion.

Auricular hematoma is caused by friction or direct trauma to the auricle (see Chapter 683). If allowed to remain without evacuation, irreversible deformity of the auricle often results, termed cauliflower ear. Properly fitted headgear is the best means of prevention, and early aspiration of the accumulated blood may reduce the risk of deformity.

RUNNING

Running for sport and exercise has increased in popularity for children and adolescents. Running problems are typically caused by overuse injury related to muscle imbalance; a minor skeletal deformity; repetitive overload; and/or poor flexibility, strength, endurance, or proprioception. With each step while running, the foot impact ranges from 3-8 times the athlete's body weight. Errors in training, including increasing the distance or intensity of workouts too rapidly, often result in injury to the runner. Minor variations (e.g., malalignment) in anatomy that do not cause problems at rest can predispose to injury at specific sites, such as **over-pronation** contributing to increased **patellofemoral stress**. Muscle fatigue, environmental temperature (see Chapter 731), and running surface (grass vs unyielding concrete) also contribute to injury. **Barefoot** or **minimalist running** shoes may promote greater weight distribution through the forefoot during running, and biomechanical research suggests reduced joint forces through the knee and hip. However, increased forces can occur through the foot, ankle, and lower leg in individuals not accustomed to this style of running. Prevention of injuries is possible by muscle-strengthening exercises, incorporating periods of rest into training plans, and the use of good-quality running shoes that match an athlete's foot type.

Shin splints, or **medial tibial stress syndrome**, is a descriptive term for pain located diffusely over the distal medial tibia and should be distinguished from tibia stress fracture and chronic exertional compartment syndrome. Medial tibial stress syndrome is a periosteal stress reaction at the insertion of the soleus muscle. It can be seen in new runners, runners that have markedly increased their training duration in a short period of time, and runners with higher body mass indices (BMIs). Continued loading and stress of medial tibial stress syndrome can lead to a **stress fracture**. Stress fractures in runners (see Chapter 724.4) have been documented at the femoral neck, inferior pubic rami, subtrochanteric area, proximal femoral shaft, proximal tibia, fibula, calcaneus, tarsal navicular, metatarsals, and sesamoids. The most common are in the metatarsals, tibia, and fibula. The anterior proximal tibia, femoral neck (tension or superior side), tarsal navicular, and sesamoids are most at risk for nonunion.

Muscle strains most frequently affect the hamstrings, followed by the quadriceps, hip adductors, soleus, and gastrocnemius muscles. Lower extremity tendon injuries are more common than apophyseal injuries in young, skeletally immature runners. Tendon injury is most common in the Achilles tendon, followed by the posterior tibial, peroneal, iliopsoas, and proximal hamstring tendons. Achilles tendinosis should be distinguished from retrocalcaneal bursitis.

Knee pain in the runner is frequently anterior in location and is commonly caused by **patellofemoral pain syndrome (runner's knee**), which results from excessive dynamic, usually lateral, motion of the patella in relationship to the femoral intracondylar groove (see Chapter 728.6). The athlete's body habitus (i.e., increased Q-angle, over-pronation) and presence of core and hip abductor weakness may contribute to this overuse injury. Posterior knee pain can be caused by gastrocnemius strain, while posteromedial pain may be caused by proximal tibial stress fracture or semimembranosus/semitendinosus tendinosis. Lateral knee pain is commonly caused by **iliotibial band syndrome** and less so by **popliteal tendinosis**, which may be precipitated by running downhill. Iliotibial band syndrome may combine a component of both bursitis and tendinosis owing to mechanical friction of the iliotibial band (an extension of the tensor fasciae latae) over the lateral femoral epicondyle. Vague knee pain that worsens with activity or traumatic event, particularly if associated with joint swelling, should raise suspicion for **osteochondritis dissecans**, most commonly located at the lateral aspect of the medial femoral condyle.

Chronic exertional compartment syndrome can involve any of the muscle compartments, but the most common is the anterior compartment. There is typically poorly localized throbbing pain that begins 10-15 minutes into a run. Pain typically prevents further training, thus limiting the risk of nerve injury (see Chapter 728.7).

Plantar fasciitis is an inflammation of the supporting structures of the longitudinal arch of the foot due to repetitive cyclic loading with foot strike. Pain is typically worst with the first step out of bed in the morning and with running and is located on the medial aspect of the heel. Pes planus and over-pronation are common in these patients. Calcaneal stress fracture should be considered, especially in the amenorrheic distance runner (see Chapter 732).

The **female and male athlete triads (or relative energy deficiency in sport)**, referring to abnormalities in energy availability, endocrine function, and bone health, are well documented in adolescent running literature and are important education topics for the runner, parents, and coaches (see Chapter 732).

CHEERLEADING

Like other sports, cheerleading has become increasingly popular and evolved to become more competitive and athletic. Cheerleading can begin as early as 3-6 years of age and includes skill levels ranging from recreational to sideline, competition to professional. The sport includes advanced gymnastic tumbling and "stunts" involving athletes lifting and throwing other athletes overhead. This requires repetitive flexion, hyperextension, and rotation of the spine as well as compressive loading on landings, and the risk of athlete contact and falls.

Stunting injuries account for the majority of injuries, with bases (the athletes who lift, throw, and catch another athlete) at higher risk of injury than fliers (athletes who are lifted and thrown). The primary mechanism of injury is contact with another athlete. Injuries sustained in tumbling are the second most common.

The overall injury rate in cheerleading is low at 1/1,000 athletic exposures. However, injuries may be severe; of all female sports, the risk of catastrophic injury is the highest in cheerleading. Following a period of increasing incidence of injury, it appears that injury rates have stabilized.

Head and facial injury accounts for almost one third of injuries sustained. Head trauma primarily results from falls while stunting or from a pyramid formation, which includes the base cheerleaders as well. After concussion, strains and sprains account for the most likely injuries, with ankle the most common site followed by wrist and trunk. Fractures are more likely to occur in the upper extremity. Overuse injuries are common.

Strategies to reduce the risk of injury include designating cheerleading as an official sport, ensuring athletes undergo preparticipation exams, participating in conditioning and strength training, using proper lifting technique, avoiding stunting over hard surfaces, and educating coaches and trainers about sport safety, including specific rules for the execution of technical skills. The American Association of Cheerleading Coaches and Administrators and others have also set up rules to limit the type of stunts performed, and the National Federation of State High School Associations annually updates rules for spirit events with the intent of improving cheerleading safety.

GYMNASTICS

Typically, males and females begin gymnastics participation at 4-5 years of age. The highest level of competition is in the mid-teens followed by retirement, often by 20 years of age for females and mid-20s for males. Both acute and chronic injuries, with a high incidence of overuse-related injuries, are seen in gymnasts and commonly involve the wrists, shoulders, ankles, and back. Injury types and rates in the acrobatic and circus arts are similar to those seen in traditional gymnastics.

The injury rate is similar in male versus female gymnasts. Lower-extremity injuries are more common in female gymnasts, whereas upper body injuries occur with higher frequency in male gymnasts.

Apparatus competed upon accounts for this discrepancy, such as the horizontal bar and ring exercises for male gymnasts, which place a great deal of stress upon the shoulders, and floor exercise, vault, and balance beam for female gymnasts, stressing the feet and ankles. In addition to mechanical or traumatic injuries, female gymnasts may have delayed menarche and can be at risk for hypothalamic amenorrhea or oligomenorrhea, as well as low body weight for height, which is related to disordered eating. Despite the presence of these two components of the **female athlete triad** (see Chapter 732), the third component, reduced bone density or osteoporosis, is not commonly seen. In fact, bone density tends to be high in most gymnasts, which is thought to be secondary to their performance involving repetitive high-impact activities. Nevertheless, **stress fractures**, in both the upper and lower extremities, are a significant problem. The short stature associated with male and female gymnasts is probably caused by selection bias and not the result of gymnastics training.

The amount of weight bearing through the upper extremities in gymnastics can contribute to the development of both traumatic and overuse injuries. During upper extremity weight bearing, the wrist, particularly over the radial physis, is subjected to a force almost twice the athlete's body weight and up to 16 times the body weight during high-impact loading activities. This, along with repetitive motion, axial compression, and torsional forces, contributes to the increasing frequency of wrist pain and injury in gymnastics and acrobatics. Wrist pain and injury is also correlated with training intensity, based on skill level and number of hours of training per week. Wrist injuries typically seen include **distal radial epiphysitis (gymnast's wrist)**, triangular fibrocartilage complex tears, scaphoid fractures, **scapholunate dissociation**, dorsal ganglion cysts, and wrist sprains (see Chapter 722). Individualized training regimens, including gradual increase in training load and reduced training during growth spurts, as well as the use of wrist orthoses, should be considered for these athletes.

Ankle sprain remains the most common injury in gymnastics, secondary to forces seen in landing and dismounting. Ankle sprains that have not responded to conservative management should be further evaluated for osteochondral defects of the talar dome. Heel pain may be secondary to plantar fasciitis, Sever disease, or calcaneal stress fracture. Patellar tendinopathy may contribute to knee pain in a gymnast.

Spine injuries are notable for a high incidence of **spondylolysis**, a stress fracture of the pars interarticularis, and, in less frequent cases, spondylolisthesis, both related to repetitive extension loading of spine (see Chapter 720.6). Other potential sources of back pain in a gymnast include intervertebral disk pathology, **Scheuermann disease** (juvenile kyphosis) (see Chapter 720.4), and mechanical back pain secondary to biomechanical imbalances.

DANCE

Dance, including ballet, modern dance, or drill line, is a highly demanding activity that may be associated with delayed menarche in females and disordered eating in both female and male dancers (see Chapter 732). Acute injuries commonly involve the lower extremities. Overuse injuries are common, due to the repetitive nature of maneuvers incorporated into training and performance and occur at the same rate in amateur male and female dancers. Injuries seen in modern/contemporary dance are similar in type and incidence to those seen in traditional ballet.

Frequently, kinetic chain dysfunction contributes to injury and should be considered when evaluating the dancer. Common mistakes in technique can cause injury, such as forcing excessive "turnout" (external rotation at the hip) in ballet resulting in undue stress placed upon the hip and knees (see Chapter 728.6).

Foot problems are common and include metatarsal stress fractures, subungual hematomas, **sesamoiditis**, **tenosynovitis** (especially of the flexor digitorum longus), plantar fasciitis, Achilles tendinitis, retrocalcaneal bursitis, calluses, and bunions (see Chapter 728.7). A **dancer's fracture** is an avulsion fracture of the distal shaft of the fifth metatarsal. This fracture is at risk for delayed healing as a result of the tenuous blood supply in the area and may necessitate surgical fixation. Common ankle injuries and pain include acute sprains, anterior and posterior impingement syndromes, and osteochondral defects of the talus. Soft tissue impingement between the lateral malleolus and talus can cause persistent pain after an inversion injury. Medial tibial stress syndrome ("shin splints") and tibial stress fractures are noted in the lower leg. Achilles tendinopathy is seen due to the demands of running and jumping. Patellar malalignment or hypermobility can result in patellofemoral pain syndrome or, less frequently, patellar subluxation/dislocation. Patellar tendinopathy is widely reported. **Internal snapping hip syndrome**, caused by the iliopsoas tendon riding over the anterior hip capsule and iliopectineal eminence, and hip flexor (rectus femoris and iliopsoas) tendinosis are commonly noted in traditional ballet. Gluteal region pain with sciatica may be a result of piriformis syndrome, which occurs because of the repetitive external hip rotation required in ballet (see Chapter 728.5).

The proper time to allow a ballet dancer to go en pointe is a common question asked by dancers and parents alike. The average age to go en pointe is 12 years. A functional test should be part of that decision: if the young dancer is able to perform a passé steadily away from the barre and maintain an en pointe position without pain or instability, the dancer is likely ready to begin dancing en pointe. **Posterior impingement syndrome** of the ankle can be seen with dancing en pointe, given compression between bony or soft tissue structures during terminal plantarflexion. An **os trigonum** is commonly the cause of bony-related posterior impingement syndrome.

ADAPTIVE SPORTS

Participation in sports and recreational activities helps to minimize deconditioning; improve strength, endurance, and cardiopulmonary fitness; and promote companionship, sense of achievement, and self-esteem (see Chapter 756). Participation can also support the development of the child's motor coordination and adjustment to physical limitations. However, children with disabilities tend to participate less in physical activity for myriad reasons, including lack of access to activities or opportunities for participation, lack of self-confidence, and fear of injury by the child, parent, or physician. Direction into appropriate sports/physical activity rather than excluding them should be guided by the child's physical or mental challenge, physical abilities, preparticipation exam, and consideration of the American Academy of Orthopedic Surgeons "participation possibility chart," which outlines recommended sports and recreation based on physical disability.

Fear of injury remains a barrier to participation for many; however, the risk of injury for an adaptive sport athlete is no greater than for an athlete without disability. Injuries in the adaptive sport athlete are influenced by the specific disability, equipment used, and prosthetic or orthotics worn. Acute soft tissue injuries, including skin abrasions, contusions, sprains, and strains, tend to be the most common injuries; fractures and dislocations tend to be uncommon, given the lower participation in contact sports. Overuse injuries commonly occur in this athlete population. Lower limb injuries are more common in athletes with amputations or cerebral palsy, and upper limb injuries are more common in spinal cord injury and wheelchair-based athletes. Appropriate training to support muscle balance and avoid muscle imbalance, as well as the management of **spasticity** and properly fitting prosthetics and orthotics can help to reduce the risk of overuse injuries. Pressure sores are common in wheelchair-based athletes and can be avoided with vigilant skin care and monitoring and weight shifting.

Consideration of the athlete's disability and medications is essential because they may have increased propensity for abnormalities in, for example, thermoregulation, resulting in heat illness, and fluid and electrolyte derangements. This should be discussed and monitored with the athlete, parents, athletic trainers, and coaches, as appropriate.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 3

The Skeletal Dysplasias

Chapter 735

General Considerations in Skeletal Dysplasias

Julie E. Hoover-Fong and Daniah Albokhari

Genetic skeletal disorders include skeletal dysplasias, as well as metabolic bone conditions, dysostoses, and other skeletal malformations (Table 735.1).

The **chondroosteodysplasias**, also known as **skeletal dysplasias** or bone dysplasias, are a genetically and clinically heterogeneous group of disorders with an estimated prevalence of 1/4,000 births. The chondroosteodysplasias can be divided into the chondrodysplasias and osteodysplasias. The former includes genetic disorders of cartilage and results in deficient linear growth, typified by achondroplasia. The **osteodysplasias** are marked by abnormal bone structure, with a classic example of osteogenesis imperfecta (see Chapter 742). The clinical picture of the chondroosteodysplasias is dominated by generalized skeletal abnormalities with frequent involvement of nonskeletal elements. The disorders range in severity from lethal in utero to such mild features as to go undetected. Metabolic bone conditions, such as rickets or hypophosphatasia, are because of abnormal bone mineralization, whereas the dysostoses affect a single bone (e.g., craniosynostosis). Many complex genetic syndromes include skeletal malformations as part of the overall phenotype.

The chondrodysplasias are distinguished from other forms of short stature by skeletal disproportion between the length of the torso and the limbs. There are two basic categories of skeletal dysplasias: those with predominantly short limbs versus short trunks. Figure 735.1 notes the importance of cartilage in bone formation. Efforts to define the extent of clinical heterogeneity has resulted in the delineation of well

Table 735.1 Nosology of Genetic Skeletal Disorders: 2023

GROUP #	NAME	EXAMPLES*
01	FGFR3 chondrodysplasias	Achondroplasia, hypochondroplasia, thanatophoric dysplasia type 1, 2
02	Type 2 collagen disorders	Achondrogenesis (*COL2A1*), Kniest dysplasia, Stickler syndrome (*COL2A1* related)
03	Type 11 collagen	Stickler syndrome (*COL11A1*, *COL11A2*), Marshall syndrome
04	Sulfation disorders	Achondrogenesis (*SLC26A2*), diastrophic dysplasia, spondyloepimetaphyseal dysplasia
05	Dysplasias with multiple joint dislocations	Ehlers-Danlos syndrome types 1 and 2, SEMD with joint laxity
06	Filamins and related disorders	Frontometaphyseal dysplasias (multiple types), Larsen syndrome
07	Proteoglycan core protein disorders	Spondyloepiphyseal dysplasias (multiple types)
08	TRPV4 disorders	Metatropic dysplasia, spondyloepiphyseal dysplasia, SEMD
09	Pseudoachondroplasia and the multiple epiphyseal dysplasias	Sticker syndromes (multiple types), MED (multiple types)
10	Skeletal disorders caused by abnormalities of cilia or ciliary signaling	Short-rib polydactyly syndromes (Jeune syndromes multiple types), Ellis-Van-Creveld syndrome, Meckel syndrome
11	Metaphyseal dysplasias	Metaphyseal dysplasia (multiple types)
12	Spondylometaphyseal dysplasias	Spondylometaphyseal dysplasias (multiple types)
13	Spondyloepi(meta)physeal dysplasias	Multiple types
14	Severe spondylodysplastic dysplasias	Achondrogenesis (*TRIP11*), spondylometaphyseal dysplasia (*GPX4*, *SBDS*, *PAM16*)
15	Mesomelic and rhizo-mesomelic dysplasias	Robinow syndrome (multiple types), mesomelic dysplasia (multiple types)
16	Acromesomelic dysplasias	Multiple types
17	Acromelic dysplasias	Geleophysic dysplasias, acromicric dysplasias, Weill-Marchesani syndrome (multiple types)
18	Brachydactylies (isolated)	Multiple types
19	Brachydactylies (syndromic)	Multiple types, Coffin-Siris syndrome (multiple types)
20	Bent bones dysplasias	Campomelic dysplasia, bent bone dysplasia
21	Primordial dwarfism and slender bones	Microcephalic osteodysplastic primordial dwarfism (multiple types)
22	Lysosomal storage diseases with skeletal involvement	Mucopolysaccharidosis types 1, 2, 3, 4, 6, 7, 10
23	Chondrodysplasia punctata (CDP)	Rhizomelic CDP (multiple types)

Continued

Table 735.1 Nosology of Genetic Skeletal Disorders: 2023—cont'd

GROUP #	NAME	EXAMPLES*
24	Osteopetrosis and related osteoclast disorders	Osteopetrosis (multiple types)
25	Osteosclerotic disorders	Caffey disease and dysplasia, craniometaphyseal dysplasias
26	Osteogenesis imperfecta (OI) and bone fragility	OI (multiple types), osteoporosis (multiple types)
27	Disorders of bone mineralization	Hypophosphatasia, hypophosphatemic rickets (multiple types)
28	Skeletal disorders of parathyroid hormone signaling	Metaphyseal dysplasia (*PTHR1*, *SIK3*)
29	Osteolysis	Progeria, mandibuloacral dysplasias (multiple types)
30	Disorganized development of skeletal components	Cherubism, fibrodysplasia ossificans progressiva
31	Overgrowth and segmental overgrowth	Marfan syndrome, Loey-Dietz syndrome, Sotos syndrome, Proteus syndrome
32	Genetic inflammatory or rheumatoid-like osteoarthropathies	Neonatal onset multisystem inflammatory disease
33	Cleidocranial dysplasias (CD)	CD (*RUNX2*, *CBFB*)
34	Syndromes with craniosynostosis	Carpenter syndromes, Crouzon syndromes, Pfeiffer syndromes
35	Craniofacial dysostosis	Treacher Collins syndrome (multiple types), frontonasal dysplasias; mandibulofacial dysostosis (multiple types)
36	Vertebral and costa dysostosis	Spondylocostal dysostosis (multiple types), Klippel-Feil syndrome (multiple types)
37	Patellar dysostosis	Nail patella syndrome, Holt-Oram syndromes
38	Limb hypoplasia (reduction defects)	Holt-Oram, Cornelia de Lange syndrome (multiple types) Rothmund-Thompson syndrome, Poland syndrome, TAR syndrome
39	Split hand / foot ± other manifestations	Ectrodactyly-ectodermal dysplasia-cleft palate, split hand-foot malformation (multiple types)
40	Polydactyly-syndactyly triphalangism	Preaxial polydactyly (multiple types), syndactyly types 1, 3, 4, 5
41	Defects in joint formation and synostosis	Multiple synostosis syndrome (multiple types), radio-ulnar synostosis (multiple types)

*Examples are not all inclusive; incomplete list.
SEMD, spondyloepimetaphyseal dysplasia; MED multiple epiphyseal dysplasia; ( ) gene notations in italics; TAR, thrombocytopenia absent radius.
Data from Unger S, Ferreira CR, Mortier GR, et al. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet* 2023;1-46 (Table 1).

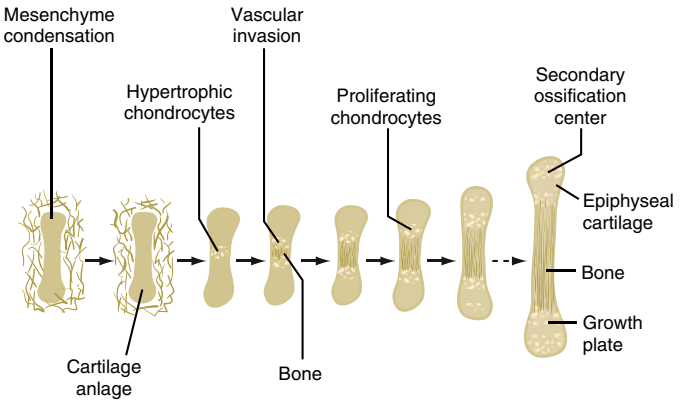

Fig. 735.1 The importance of cartilage in bone formation. *(From Horton WA. Skeletal development: insights from targeting the mouse genome. Lancet. 2005;362:560.)*

over 200 distinct entities (Table 735.2). Many of these disorders result from pathogenic variants of a relatively small group of genes, the *chondrodysplasia genes*. The better-defined chondrodysplasia groups, such as the *FGFR3* and type II collagenopathy groups, contain graded series of disorders that range from severe to mild. This severity spectrum is increasingly appreciated in other skeletal dysplasia groups as more pathogenic variants have been discovered and their associated phenotypes defined. For some genes, such as *COL2A1*, pathogenic variants are distributed throughout the gene, and the clinical phenotypes merge into one another across a broad range. There is much less phenotypic overlap in other genes, such as *FGFR3*, in which the distribution of pathogenic variants is more discrete.

Most chondrodysplasias require the analysis of information from the history, physical examination, skeletal radiographs, family history, and laboratory testing to make a diagnosis. The process involves recognizing complex patterns that are characteristic of the different disorders (Tables 735.3-735.6). Metaphyseal dysplasias, for example, often are characterized by short stature, bowing of the legs, and a waddling gait. Most metaphyseal dysplasias have normal serum levels of calcium and phosphate, alkaline phosphatase activity, and vitamin D metabolites. In addition, subtypes of metaphyseal dysplasias exist and have their own unique features. Metaphyseal chondrodysplasia (**Jansen type;** see Chapter 737) is typified by cupped and ragged metaphyses, which develop mottled calcification at the distal ends of bone over time (Fig. 735.2). Hypercalcemia can occur. The **Schmid type** of metaphyseal chondrodysplasia is less severe, although the radiographic appearance of the knees and extreme bowing of the lower limbs resemble that in patients with familial hypophosphatemia. This condition is associated with defects in collagen type X (*COL10A1*), and the hip abnormalities are more debilitating than in Jansen metaphyseal chondrodysplasia. Patients with both types of metaphyseal chondrodysplasia have short stature.

Table 735.2 Genetics of Some Skeletal Dysplasias

GENE LOCUS	PROTEIN	PROTEIN FUNCTION	CLINICAL PHENOTYPE	INHERIT
COL2A1	Type II collagen α_1 chain	Cartilage matrix protein	Achondrogenesis II	AD*
			Hypochondrogenesis	AD*
			SED congenita	AD
			Kniest dysplasia	AD
			Late-onset SED	AD
			Stickler dysplasia	AD
ACG1	Aggrecan	Cartilage matrix protein	SED Kimberley	AD
			SEMD Aggrecan type	AR
SEDL	Sedlin	Intracellular transporter	X-linked SED tarda	XLR
COL11A1	Type XI collagen α_1 chain	Cartilage matrix protein	OSMEDA	AD
COL11A2	Type XI collagen α_2 chain	Cartilage matrix protein	OSMEDB	AR
COMP	Cartilage oligomeric matrix protein	Cartilage matrix protein	Pseudoachondroplasia	AD
			EDM1 (MED)	AD
COL9A2	Type IX collagen α_2 chain	Cartilage matrix protein	EDM2 (MED)	AD
COL9A3	Type IX collagen α_3 chain	Cartilage matrix protein	EDM3 (MED)	AD
MATN3	Matrilin-3	Cartilage matrix protein	EDM5 (MED)	AD
COL10A1	Type X collagen α_1 chain	Hypertrophic cartilage matrix protein	Schmid metaphyseal chondrodysplasia	AD
FGFR3	FGF receptor 3	Tyrosine kinase receptor for FGFs	Thanatophoric dysplasia I	AD*
			Thanatophoric dysplasia II	AD*
			Achondroplasia	AD
			Hypochondroplasia	AD
PTHR1	PTHrP receptor	G protein–coupled receptor for PTH and PTHrP	Jansen metaphyseal chondrodysplasia	AD
DTDST	DTD sulfate transporter	Transmembrane sulfate transporter	Achondrogenesis 1B	AR*
			Atelosteogenesis II	AR*
			Diastrophic dysplasia	AR
SOX9	SRY box 9	Transcription factor	Campomelic dysplasia	AD
RUNX2†	Runt-related transcription factor 2	Transcription factor	Cleidocranial dysplasia	AD
LMX1B		Transcription factor	Nail-patella dysplasia	AD
CTSK	Cathepsin K	Enzyme	Pyknodysostosis	AR
RMPR	Mitochondrial RNA-processing endoribonuclease	RNA-processing enzyme	CHH	AR
DYNC2H1	Dynein, cytoplasmic two, heavy chain 1	Cytoplasmic cilia-related protein	ATD	AR
			SRPIII	AR
TRPV4	Calcium-permeable TRP ion channel	Transmembrane channel protein	Brachyolmia type 3	AD
			SMDK	AD
			Metatropic dysplasia	AD

*Usually lethal.
†Also called CBFA1.
AD, Autosomal dominant; SED, spondyloepiphyseal dysplasia; SEMD, spondyloepimetaphyseal dysplasia; AR, autosomal recessive; EDM (MED), multiple epiphyseal dysplasia; FGF, fibroblast growth factor; OSMEDA, otospondylomegaepiphyseal dysplasia autosomal dominant; OSMEDB, otospondylomegaepiphyseal dysplasia autosomal recessive; PTHrP, parathyroid hormone-related protein; PTH, parathyroid hormone; DTD, diastrophic dysplasia; SRY, sex-determining region of the Y chromosome; CHH, cartilage-hair hypoplasia; ATD, Jeune asphyxiating thoracic dystrophy; SRPIII, short rib polydactyly syndrome type III; TRPV4, transient receptor potential vanilloid family 4; SMDK, spondyloepimetaphyseal dysplasia Kozlowski type.

Table 735.3 Major Problems Associated with Skeletal Dysplasias

PROBLEM	EXAMPLE
Lethality*	Thanatophoric dysplasia
Associated anomalies†	Ellis-van Creveld syndrome
Short stature	Common to almost all
Cervical spine dislocations	Larsen syndrome
Severe limb bowing	Metaphyseal dysplasia, Schmid type
Spine curvatures	Metatropic dysplasia
Clubfeet	Diastrophic dysplasia
Fractures	Osteogenesis imperfecta
Pneumonias, aspirations	Campomelic dysplasia
Spinal cord compression	Achondroplasia
Joint problems (hips, knees)	Most skeletal dysplasias
Hearing loss	Common (greatest with cleft palate)
Myopia/cataracts	Stickler syndrome
Immunodeficiency	Cartilage-hair hypoplasia, Schimke immunoosseous dysplasia, spondyloenchondromatosis, pathogenic variants in *PEM3, EXTL3, ADA*
Poor body image	Variable, but common to all
Sex reversal	Campomelic dysplasia

*Mostly a result of severely reduced size of thorax.
†See Table 735.4.

Table 735.4 Associated Anomalies in Skeletal Dysplasias

ANOMALY	EXAMPLE
Heart defects	Ellis-van Creveld syndrome, Jeune syndrome
Polydactyly	Short rib polydactyly, Majewski type
Cleft palate	Diastrophic dysplasia
Ear cysts	Diastrophic dysplasia
Spinal cord compression	Achondroplasia
Encephalocele	Dyssegmental dysplasia
Hemivertebrae	Dyssegmental dysplasia
Micrognathia	Campomelic dysplasia
Nail dysplasia	Ellis-van Creveld syndrome
Conical teeth, oligodontia	Ellis-van Creveld syndrome
Multiple oral frenula	Ellis-van Creveld syndrome
Dentinogenesis imperfecta	Osteogenesis imperfecta
Pretibial skin dimples	Campomelic dysplasia
Cataracts, retinal detachment	Stickler syndrome
Intestinal atresia	Saldino-Noonan syndrome
Renal cysts	Saldino-Noonan syndrome
Camptodactyly	Diastrophic dysplasia
Craniosynostosis	Thanatophoric dysplasia
Ichthyosis	Chondrodystrophia punctata
Hitchhiker thumb	Diastrophic dysplasia
Sparse scalp hair	Cartilage-hair hypoplasia
Hypertelorism	Robinow syndrome
Hypoplastic nasal bridge	Acrodysostosis
Clavicular agenesis	Cleidocranial dysplasia
Genital hypoplasia	Robinow syndrome
Tail	Metatropic dysplasia
Omphalocele	Beemer-Langer syndrome
Blue sclera	Osteogenesis imperfecta

Comprehensive descriptions of disorders and references can be found at the Online Mendelian Inheritance in Man (OMIM) website (http://omim.org/about), along with the most recent nosology for genetic skeletal conditions.

CLINICAL MANIFESTATIONS

Growth

The hallmark of the chondrodysplasias is disproportionate short stature. Although this refers to a disproportion between the limbs and the trunk, most disorders exhibit some shortening of both, and subtle degrees of disproportion may be difficult to appreciate, especially in premature, obese, or edematous infants. Disproportionate shortening of the limbs should be suspected if the upper limbs do not reach the mid-pelvis in infancy or the upper thigh after infancy. Disproportionate shortening of the trunk is indicated by a short neck, small chest, and protuberant abdomen. Skeletal disproportion is usually accompanied by short stature (length and height below the third percentile); these measurements are occasionally within the low-normal range early in the course of certain conditions.

There may also be disproportionate shortening of different segments of the limbs; the specific pattern can provide clues for diagnoses. Shortening is greatest in the proximal segments (upper arms and legs) in achondroplasia; this is termed **rhizomelic shortening.** Disproportionate shortening of the middle segments (forearms and lower legs) is called **mesomelic shortening; acromelic** shortening involves the hands and feet.

With some exceptions, there is a strong correlation between the age when shortening is appreciated and the clinical severity of the condition. Many of the lethal neonatal chondrodysplasias are evident during routine fetal ultrasound examinations performed at the end of the first trimester of gestation (see Table 735.5). Gestational standards exist for long-bone lengths, and discrepancies are often detected between biparietal diameter of the skull and long-bone lengths. Many disorders become apparent around the time of birth whereas others manifest during the first year of life. A number of disorders manifest in early childhood and a few in late childhood or later.

Non–Growth-Related Manifestations

Most patients also have problems unrelated to growth. Skeletal deformities, such as abnormal joint mobility, protuberances at and around joints, and angular deformities, are common and usually symmetric. Skeletal abnormalities can adversely affect nonskeletal tissues. Impaired growth at the base of the skull and of vertebral pedicles reduces the size of the spinal canal in achondroplasia and can contribute to spinal cord compression. Short ribs reduce thoracic volume, which can compromise breathing in patients with short trunk chondrodysplasias. Cleft palate (see Chapter 356) is common to many disorders, presumably reflecting defective palatal growth.

Manifestations may be unrelated to the skeleton; they reflect the expression of pathogenic gene variants in nonskeletal tissues. Examples include retinal detachment in spondyloepiphyseal

Table 735.5 Lethal Neonatal Skeletal Dysplasias

USUALLY FATAL*
Achondrogenesis (different types)
Thanatophoric dysplasia
Short rib polydactyly (different types)
Homozygous achondroplasia
Campomelic dysplasia
Dyssegmental dysplasia, Silverman-Handmaker type
Osteogenesis imperfecta, type II
Hypophosphatasia (perinatal form)
Chondrodysplasia punctata (rhizomelic form)
OFTEN FATAL
Asphyxiating thoracic dysplasia (Jeune syndrome)
OCCASIONALLY FATAL
Ellis-van Creveld syndrome
Diastrophic dysplasia
Metatropic dwarfism
Kniest dysplasia

*A few prolonged survivors have been reported in most of these disorders.

Table 735.6 Usually Nonlethal Dwarfing Conditions Recognizable at Birth or Within the First Few Months of Life

MOST COMMON
Achondroplasia
Osteogenesis imperfecta (types I, III, IV)
Spondyloepiphyseal dysplasia congenita
Diastrophic dysplasia
Ellis-van Creveld syndrome
LESS COMMON
Chondrodysplasia punctata (some forms)
Kniest dysplasia
Metatropic dysplasia
Langer mesomelic dysplasia

dysplasia congenita, sex reversal in campomelic dysplasia, congenital heart malformations in Ellis-van Creveld syndrome, immunodeficiency in cartilage-hair hypoplasia, and renal dysfunction in asphyxiating thoracic dysplasia. These nonskeletal problems provide valuable clues to specific diagnoses and must be managed clinically (see Table 735.4).

Family and Reproductive History

A family history might identify relatives with the condition, and a Mendelian inheritance pattern may be elicited. Because the presentation can vary in some disorders within and among families, features that might be related to the disorder should be identified. Special attention should be given to mild degrees of short stature, disproportion, deformities, and other manifestations (e.g., precocious osteoarthritis) because they may be overlooked. Physical examination of relatives may be useful, as may the review of their photographs, radiographs, and medical and laboratory records.

A reproductive history might reveal previous stillbirths, fetal losses, and other abnormal pregnancy outcomes resulting from a skeletal dysplasia. Pregnancy complications, such as polyhydramnios or reduced fetal movement, are common in bone dysplasias, especially neonatal lethal variants.

Even though most of the skeletal dysplasias are genetic, it is common for an affected individual to be the first in their family to have the diagnosis. New pathogenic variants are common for autosomal dominant disorders, especially lethal disorders in the perinatal period (e.g., thanatophoric dysplasia, osteogenesis imperfecta). In achondroplasia, the most common short stature skeletal dysplasia, ~80% of all individuals have a new pathogenic variant in *FGFR3*. Germ cell mosaicism, in which a parent has clones of mutant germ cells, has been observed in osteogenesis imperfecta, achondroplasia, and in other dominant disorders. A negative family history is usually seen in recessive disorders unless consanguinity is present. A few of the short stature skeletal dysplasias are X-linked in origin. Prenatal diagnosis is available for disorders that have a known genetic etiology. Appropriateness of the testing depends on many factors, and genetic counseling is warranted for these families.

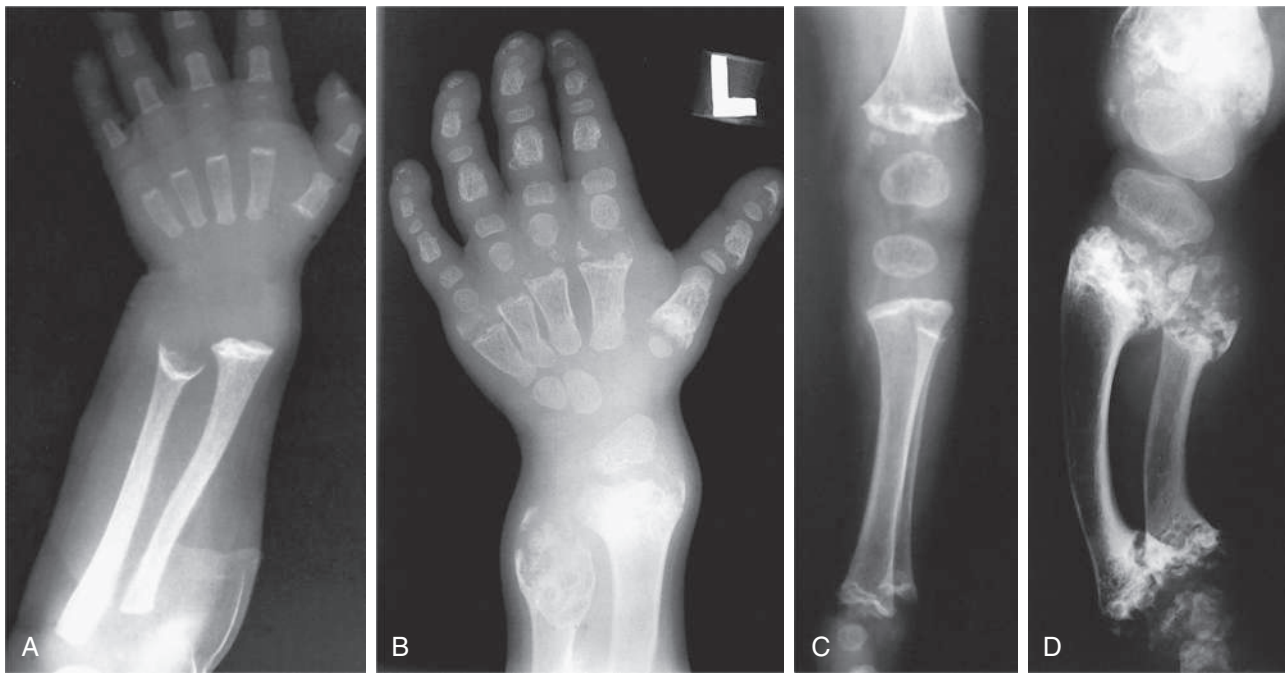

Fig. 735.2 Radiographic findings in Jansen-type metaphyseal chondrodysplasia. **A,** At age 1 yr, there is severe metaphyseal cupping and splaying at the wrists and also in the hand bones. **B,** At age 7 yr, there is increasing metaphyseal change at the wrists with enlarged epiphysis; enlarged epiphyses with wide epiphyseal plates are also present in the hands. **C,** At age 1 yr, there are severe metaphyseal irregularities at the knees and ankles (femur, tibia, and fibula) and enlarged, rounded epiphyses. **D,** At age 7 yr, there are severely fragmented, sclerotic metaphyses, wide epiphyseal plates, and enlarged epiphyses. Radiographic findings in Jansen-type metaphyseal chondrodysplasia. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby, 2008.)*

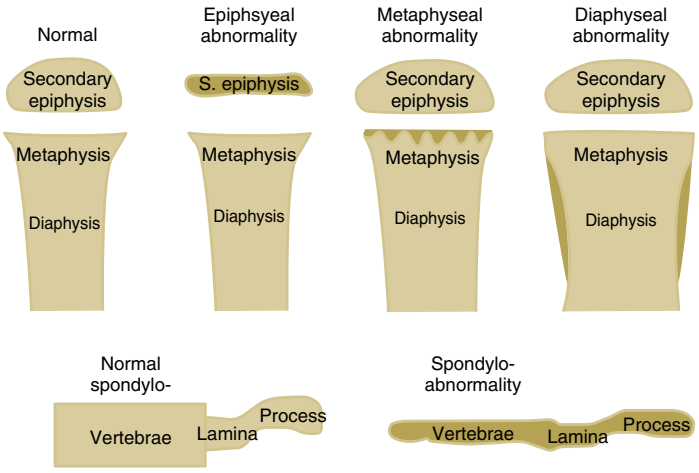

Fig. 735.3 Demonstration of the different portions of the appendicular skeleton that manifest radiographic abnormalities that aid in the clinical classification of the skeletal dysplasias. *(From Krakow D, Rimoin DL. The skeletal dysplasias. Genet Med. 2010;12:327–341. Fig. 2.)*

Table 735.7 Dynamic Classification of Bone Dysplasias

I. EPIPHYSEAL DYSPLASIAS
A. Epiphyseal hypoplasias
1. Failure of articular cartilage: spondyloepiphyseal dysplasia congenita and tarda
2. Failure of ossification center: multiple epiphyseal dysplasia congenita and tarda
B. Epiphyseal hyperplasia
1. Excess of articular cartilage; dysplasia epiphysealis hemimelica
II. PHYSEAL DYSPLASIAS
A. Cartilage hypoplasias
1. Failure of proliferating cartilage: achondroplasia congenita and tarda
2. Failure of hypertrophic cartilage: metaphyseal dysostosis congenita and tarda
B. Cartilage hyperplasias
1. Excess of proliferating cartilage: hyperchondroplasia
2. Excess of hypertrophic cartilage: enchondromatosis
III. METAPHYSEAL DYSPLASIAS
A. Metaphyseal hypoplasias
1. Failure to form primary spongiosa: hypophosphatasia congenita and tarda
2. Failure to absorb primary spongiosa: osteopetrosis congenita and tarda
3. Failure to absorb secondary spongiosa: craniometaphyseal dysplasia congenita and tarda
B. Metaphyseal hyperplasias
1. Excessive spongiosa: multiple exostoses
IV. DIAPHYSEAL DYSPLASIAS
A. Diaphyseal hypoplasias
1. Failure of periosteal bone formation: osteogenesis imperfecta congenita and tarda
2. Failure of endosteal bone formation: idiopathic osteoporosis congenita and tarda
B. Diaphyseal hyperplasias
1. Excessive periosteal bone formation: progressive diaphyseal dysplasia
2. Excessive endosteal bone formation: hyperphosphatasemia

From Rubin P. *Classification of bone dysplasias*. Chicago: Year Book Medical Publishers, 1964. p. 82.

Radiographic Features

Radiographic evaluation for a chondrodysplasia should include plain films of the entire skeleton. Efforts should be made to identify which bones and which parts of bones (i.e., epiphyses, metaphyses, diaphyses) are most affected (Figs. 735.3 and Fig. 735.4 and Table 735.7). If possible, films taken at different ages should be examined because the radiographic changes evolve with time. Films taken before puberty are generally more informative because pubertal closure of the epiphyses obliterates many of the signs needed for a radiographic diagnosis. Prenatal diagnosis may also be possible with fetal ultrasound.

DIAGNOSIS

If an infant or child is short with disproportionate features, a diagnosis is established by matching the observed clinical picture (defined primarily from clinical, family, and gestational histories; physical examination; and radiographic evaluation) with clinical phenotypes of well-documented disorders. A number of reference texts and online databases provide information about the disorders and comprehensive lists of current references (http://www.ncbi.nlm.nih.gov/books/NBK1116/). Consultation with experts in medical genetics, orthopedics, endocrinology, or the bone dysplasia field is recommended.

Genetic testing for chondrodysplasias is very useful, especially for disorders in which recurrent pathogenic variants occur (typical achondroplasia has the same *FGFR3* pathogenic variant). Pathogenic variant testing for achondroplasia is available, although the diagnosis can be made clinically. The greatest utility for testing may be for prenatal diagnosis for couples where both parents have typical *(heterozygous)* achondroplasia. Their children are at a 25% risk of the much more severe *homozygous* achondroplasia (also known as *double dominant*), which can be detected by pathogenic variant analysis. Preimplantation genetic testing can be used to identify zygotes with two pathogenic variants in *FGFR3*. Another example of the utility of genetic testing is in disorders resulting from pathogenic variants in *DTDST*. These disorders are inherited in an autosomal recessive manner, and a limited number of mutant alleles have been found. If the pathogenic variants are identified in the patient, they should be detectable in the parents and potentially used for prenatal diagnosis. Pathogenic variant analysis is commercially available for many of the skeletal dysplasias and is increasingly used to confirm clinical diagnosis and for future pregnancy planning.

Many of the chondrodysplasias have distinct histologic changes of the skeletal growth plate. Sometimes, such tissues obtained at biopsy or discarded from a surgical procedure are helpful diagnostically. It is uncommon to make a diagnosis histologically if it was not already suspected on clinical or radiographic grounds.

MOLECULAR GENETICS OF SKELETAL DYSPLASIAS

A number of chondrodysplasia genes have been identified (see Table 735.2). They encode several categories of proteins, including cartilage matrix proteins, transmembrane receptors, ion transporters, and transcription factors. The number of identified gene loci is smaller than anticipated from the number of recognized clinical phenotypes. The majority of patients have disorders that map to fewer than 10 loci, and

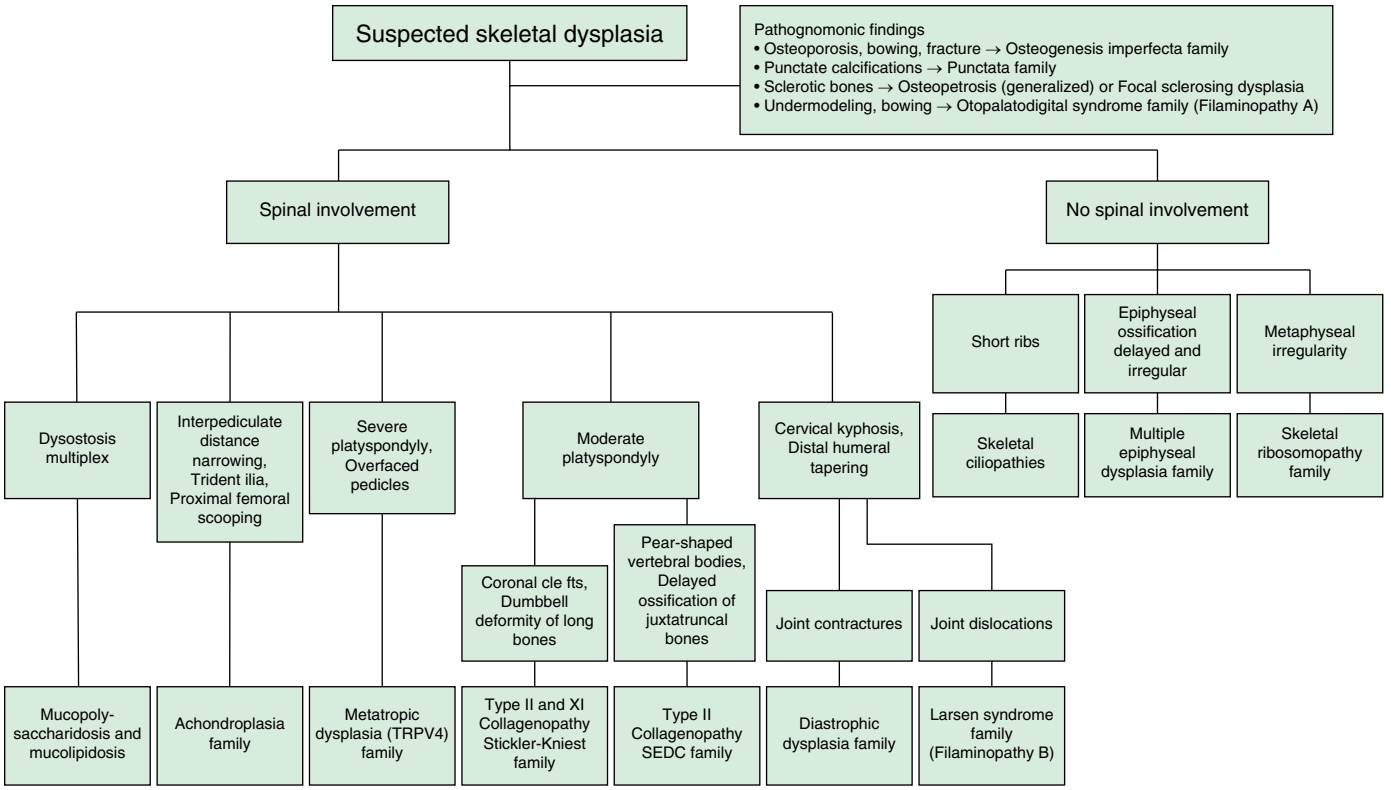

Fig. 735.4 Diagnostic algorithm for the major skeletal dysplasias. TRPV4, transient receptor potential vanilloid 4. *(From Handa A, Grigelioniene G, Nishimura G: Skeletal dysplasia families: a stepwise approach to diagnosis. RadioGraphics 2023;43(5), Fig. 1.)*

pathogenic variants at two loci (*COL2A1* and *FGFR3*) account for more than half of all cases. There may be a limited number of genes whose function is critical to skeletal development, especially linear bone growth, and pathogenic variants in these genes give rise to a wide range of chondrodysplasia clinical phenotypes. New genes harboring pathogenic variants that cause chondrodysplasias continue to be identified with advances in technology.

Pathogenic variants of *COL2A1* and *FGFR3* illustrate different genetic characteristics. *COL2A1* pathogenic variants are distributed throughout the gene, with few instances of recurrence in unrelated persons. In contrast, *FGFR3* pathogenic variants are restricted to a few locations within the gene, and the occurrence of new pathogenic variants at these same sites in unrelated persons is the rule. There is a strong correlation between clinical phenotype and pathogenic variant site for *FGFR3,* but not *COL2A1*.

PATHOPHYSIOLOGY

Chondrodysplasias are caused by pathogenic variants in genes that encode abnormal proteins and disrupt normal endochondral ossification, the biologic process responsible for the development and linear growth of the skeleton (see Fig. 735.1). These genetic variants act through different mechanisms. Most pathogenic variants involving cartilage matrix proteins cause disease when only one of the two copies (alleles) of the relevant gene is mutated. These pathogenic variants usually act through a *dominant negative mechanism* in which the protein products of the mutant allele interfere with the assembly and function of multimeric molecules that contain the protein products of both the normal and mutant alleles. The type II collagen molecule is a triple helix composed of three collagen chains, which are the products of the type II collagen gene *COL2A1*. When chains from both normal and mutant alleles are combined to form triple helices, most molecules contain at least one mutant chain. It is not known how many mutant chains are required to produce a dysfunctional molecule, but, depending on the pathogenic variant, it theoretically could be as few as one.

Pathogenic variants in the gene encoding type X collagen differ from the model above. They map to the region of the chain that is responsible for chain recognition; the chains must recognize each other before they can assemble into collagen molecules. Disease-causing variants are thought to disrupt this process. As a result, none of the mutant chains are incorporated into molecules. This mechanism is *haploinsufficiency* because the products of the mutant allele are functionally absent, and the normal allele is insufficient for normal function. Genetic variants involving ion transport genes also act through a *loss of function* of the transporters. Pathogenic variants of transmembrane receptors studied to date appear to act through a *gain of function*; the mutant receptors initiate signals in a constitutive manner independent of their normal ligands. A pathogenic variant in *FGFR3* is another example of a *gain of function* mechanism of disease. At baseline, *FGFR3* is a negative regulator of endochondral bone formation. If the pathogenic variant associated with achondroplasia is present in this gene, the clinical manifestations of this condition are caused by enhanced inhibition of endochondral bone formation and growth, independent of normal ligands.

TREATMENT

The first step is to establish the correct diagnosis. This allows one to provide a prognosis and to anticipate the medical and surgical problems associated with a particular disorder. Establishing a diagnosis helps to distinguish between lethal disorders and nonlethal disorders in a premature or newborn infant (see Tables 735.5 and 735.6). A poor prognosis for long-term survival might argue against initiating extreme lifesaving measures for thanatophoric dysplasia or achondrogenesis types Ib or II, whereas such measures may be indicated for infants with spondyloepiphyseal dysplasia congenita or diastrophic dysplasia, which have a good prognosis if the infant survives the newborn period.

Overall, management of patients with short stature skeletal dysplasias is directed at preventing and correcting skeletal deformities (spinal stenosis, kyphosis, scoliosis), treating nonskeletal complications (other anomalies, immunodeficiencies), providing genetic counseling, and

helping patients and families learn to cope. Each disorder has its own unique set of problems, and consequently, management must be tailored to each disorder.

There are a number of problems common to many chondrodysplasias for which general recommendations can be made. Children with most chondrodysplasias should avoid contact sports and other activities that cause injury or stress to joints. Good dietary habits should be established in childhood to prevent or minimize obesity in adulthood. Dental care should be started early to minimize the crowding and malalignment of teeth. Children and relatives should be given the opportunity to participate in support groups, such as the Little People of America (http://www.lpaonline.org) and Human Growth Foundation (http://www.hgfound.org).

Three controversial approaches have been used to increase bone length. Surgical limb lengthening has been employed for a few disorders. Its greatest success has been in achondroplasia in which nonskeletal tissues tend to be redundant and easily stretched. The procedure is usually performed during adolescence. Pharmacologic doses of human growth hormone comparable to those used to treat Turner syndrome have also been tried in several disorders; the results have been equivocal. Animal studies suggest that C-type natriuretic peptide (CNP) promotes linear bone growth in achondroplasia. One CNP analogue (vosoritide) is approved to increase height in children with achondroplasia (≥5 years old) before the growth plates are closed. Palovarotene is undergoing clinical trials for fibrodysplasia ossificans and resveratrol for pseudoachondroplasia. Enzyme replacement therapy is available for hypophosphatasia and Morquio A syndrome. Many new therapies are based on the gene or pathway involved in the specific disease (see Chapters 736-742). Clinicaltrials.gov is a resource to access information about these and all other clinical trials.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 736

Disorders Involving Cartilage Matrix Proteins

Daniah Albokhari and Julie E. Hoover-Fong

Disorders of cartilage matrix proteins resulting in bone and joint disorders can be classified according to the defective proteins: collagens (types 2, 9, 10, 11) and the noncollagenous proteins COMP (cartilage oligomeric matrix protein), matrilin-3, and aggrecan. The clinical phenotypes and clinical severity differ between and within the groups, especially the spondyloepiphyseal dysplasia (SED) group, which is made up largely of type collagenopathies (see also Table 735.1).

TYPE 2 COLLAGENOPATHIES

The term *spondyloepiphyseal dysplasia* refers to a heterogeneous group of disorders characterized by shortening of the trunk and, to a lesser extent, the limbs. Severity ranges from most severe and often lethal perinatally, such as achondrogenesis type II, hypochondrogenesis, and platyspondylic dysplasia, Torrance type, to severe/moderately severe neonatal presentation, such as Kniest dysplasia (which is apparent at birth and usually nonlethal) and SED congenita, to mild SED with premature-onset arthrosis (which might not be detected until adolescence or later) (Table 736.1). The radiographic hallmarks are abnormal development of the vertebral bodies and of epiphyses, the extent of which corresponds with clinical severity. Most of the SEDs result from heterozygous pathogenic variants of *COL2A1* and are autosomal dominant disorders. The pathogenic variants are dispersed throughout the gene with imperfect correlation between the variant location and resultant clinical phenotype. Molecular testing/confirmation is readily available commercially. Prenatal diagnosis is possible if the pathogenic variant is known.

Lethal Spondyloepiphyseal Dysplasias

Achondrogenesis type II is characterized by severe shortening of the neck and trunk and especially the limbs, and by a large, soft head. Fetal hydrops and prematurity are common, and infants are stillborn or die shortly after birth. **Hypochondrogenesis** refers to a clinical phenotype intermediate between achondrogenesis type II and SED congenita. It is typically lethal in the newborn period. **Platyspondylic dysplasia, Torrance type** is characterized by disproportionate short stature, short limbs, and coarse facial features. The majority of infants die at or shortly after birth.

The severity of radiographic changes correlates with clinical severity. These conditions manifest short, broad tubular bones with cupped metaphyses. The cranial bones are not well mineralized, and the vertebral bodies are poorly ossified in the entire spine in achondrogenesis type II, and in the cervical and sacral spine in hypochondrogenesis. In both conditions, the pelvic bones are hypoplastic, and the pedicles are ossified. In Torrance type, the platyspondyly is strikingly severe, with iliac hypoplasia, short sacrosciatic notches, and preserved ossification of the pubic bones. The three types can be detected prenatally and confirmed by molecular testing.

KNIEST DYSPLASIA

The Kniest dysplasia variant of SED manifests at birth with a short trunk and limbs associated with a flat face, prominent eyes, enlarged joints, cleft palate, and clubfoot (Fig. 736.1). Radiographs show vertebral defects and short tubular bones with epiphyseal irregularities and metaphyseal enlargement that gives rise to a dumbbell appearance.

Motor development is often delayed because of the joint deformities, although intelligence is normal. Hearing loss and myopia commonly develop during childhood, and retinal detachment is a common complication. Joint enlargement progresses during childhood and becomes painful. It is accompanied by flexion contractures and muscle atrophy, which may be incapacitating by adolescence.

Spondyloepiphyseal Dysplasia Congenita

The phenotype of this group, SED congenita, is apparent at birth. The hands and feet are usually normal. Craniofacial features may present, including malar hypoplasia, hypertelorism, and cleft palate. The neck is short, and the chest is barrel shaped (Fig. 736.2). Kyphosis and exaggeration of the normal lumbar lordosis are common. The proximal segments of the limbs are shorter than the hands and feet, which often appear normal. Some infants have clubfoot and/or exhibit hypotonia.

Skeletal radiographs of the newborn reveal short tubular bones, delayed ossification of vertebral bodies, and proximal limb bone epiphyses (Fig. 736.3). Hypoplasia of the odontoid process, a short, square pelvis with a poorly ossified symphysis pubis, and mild irregularity of metaphyses are apparent.

Infants usually have normal developmental milestones with a waddling gait typically appearing in early childhood. Childhood complications include respiratory compromise from tracheomalacia, spinal deformities, and spinal cord compression because of cervicomedullary instability. The disproportion and shortening become progressively worse with age, and adult heights range from 95-128 cm. Myopia is typical; adults are predisposed to retinal detachment. Precocious osteoarthritis (OA) occurs in early adulthood and requires surgical joint replacement.

Table 736.1 Collagen Disorders

DISORDER	INHERITANCE	GENE
TYPE 2 COLLAGEN DISORDERS		
Achondrogenesis (formerly type 2, type Langer-Saldino)	AD	*COL2A1*
Hypochondrogenesis	AD	*COL2A1*
Platyspondylic dysplasia, type Torrance	AD	*COL2A1*
Spondyloepiphyseal dysplasia congenita	AD, AR	*COL2A1*
Spondyloepimetaphyseal dysplasia	AD	*COL2A1*
Kniest dysplasia	AD	*COL2A1*
Spondyloperipheral dysplasia	AD	*COL2A1*
SED with metatarsal shortening	AD	*COL2A1*
Stickler syndrome	AD	*COL2A1*
Dysplasia of the proximal femoral epiphyses	AD	*COL2A1*
TYPE 11 COLLAGEN DISORDERS		
Stickler syndrome	AD, MOS	*COL11A1*
Marshall syndrome	AS	*COL11A1*
Stickler syndrome (nonocular type)	AD	*COL11A2*
Fibrochondrogenesis	AR, AD	*COL11A1*
Fibrochondrogenesis	AR, AD	*COL11A2*
Otospondylomegaepiphyseal dysplasia	AR	*COL11A2*
Otospondylomegaepiphyseal dysplasia	AD	*COL11A2*

Data from Unger S, Ferreira CR, Mortier GR, et al. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet*. 2023;191A:1164-1209 (Table 1, Group 2 and 3, pp 1166-1167).

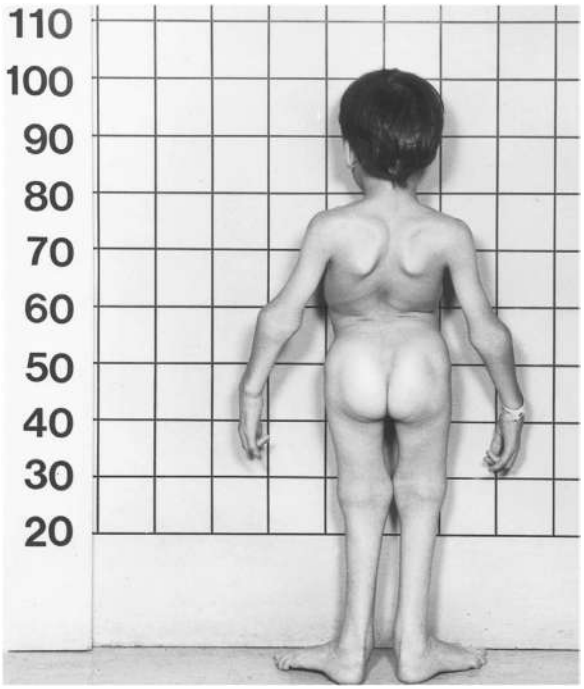

Fig. 736.1 Patient with Kniest dysplasia. The trunk is short, the epiphyses are broad, and there is contracture of the fingers. *(From Traboulsi EI. Skeletal and connective tissue disorders with anterior segment manifestations. In Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea, 3rd ed. Philadelphia: Elsevier, 2011. Fig. 60.9.)*

Mild Spondyloepiphyseal Dysplasia with Premature-Onset Arthrosis

Late-onset SED is a mild clinical phenotype characterized by slightly short stature, progressive joint pain, and diminished range of movement, associated with mild epiphyseal and vertebral abnormalities on radiographs. It is typically detected during childhood or adolescence but can go unrecognized until adulthood when precocious OA appears. The vision and hearing are usually normal. This designation is nosologically distinct from SED tarda, which is clinically similar but results from pathogenic variant of the X-linked gene *SEDL (TRAPPC2)*.

Stickler Syndrome/Dysplasia (Hereditary Progressive Arthro-Ophthalmopathy)

Short stature is not a feature of Stickler dysplasia. This condition resembles SED because of its joint and eye manifestations. Pathogenic variants of genes encoding type II *(COL2A1)*, type XI *(COL11A1, COL11A2)*, and type IX *(COL9A1, COL9A2, COL9A3)* collagens have been identified in Stickler-like disorders. Stickler dysplasia is often identified in the newborn because of cleft palate and micrognathia (**Pierre Robin** anomaly; see Chapter 357). Of patients with Stickler syndrome, 25% have Pierre Robin anomaly, and 18% of patients with Pierre Robin anomaly have Stickler syndrome. Children with Stickler syndrome are often identified in craniofacial clinics. Infants typically have severe myopia and additional ophthalmologic complications, including cataracts, glaucoma, and choroidoretinal and vitreous degeneration, with retinal detachment common during childhood requiring multiple surgical interventions (Fig. 736.4). Special attention must be given to eye complications even in childhood to preserve vision for these individuals. Hearing loss is a common feature that arises during adolescence. Sensorineural hearing loss is the most common form; however, conductive hearing loss may also be seen. Osteoarticular manifestations include joint hypermobility (especially hip), which resolves in adulthood, metaphyseal broadening of the femoral neck, hypoplastic iliac wings, Schmorl nodes, muscle hypotonia, metaphyseal-epiphyseal dysplasia, precocious progressive OA of the spine and peripheral joints (which may require hip replacement surgery before age 30 years), and decreased bone density. Similar manifestations may be seen in other diseases with pathogenic variants in type II and XI collagen genes (Table 736.2).

PSEUDOACHONDROPLASIA AND MULTIPLE EPIPHYSEAL DYSPLASIA

Pseudoachondroplasia and the most common form of multiple epiphyseal dysplasia (MED) are two distinct phenotypes that are grouped together because they result from pathogenic variants of the gene encoding COMP. The pathogenic variants are heterozygous in both, and they are autosomal dominant traits. The clinical phenotypes are restricted to musculoskeletal tissues. Newborns with pseudoachondroplasia are average in size and appearance. Gait abnormalities and short stature mainly affect the limbs and become apparent in late infancy. Short stature becomes marked as the child grows and is associated with generalized joint laxity (Fig. 736.5). The hands are short, broad, and deviated in an ulnar direction; the forearms are bowed. Developmental milestones and intelligence are usually normal. Lumbar lordosis and deformities of the knee develop during childhood; the latter often requires surgical correction. Pain is common in weight-bearing joints during childhood and adolescence, and OA develops late in the second decade of life, which may require hip replacement by mid-30s. Adult height ranges from 105-128 cm. Skeletal radiographs show distinctive abnormalities of vertebral bodies and of both epiphyses and metaphyses of tubular bones (Fig. 736.6).

The MED phenotype has skeletal abnormalities that predominantly affect the epiphyses as noted on radiographs. Two forms, the severe Fairbank type and the mild Ribbing type, are no longer used in classification. Because of overlap in clinical features, and because COMP pathogenic variants are found in both types, they are now considered part of a clinical spectrum. The more severe clinical

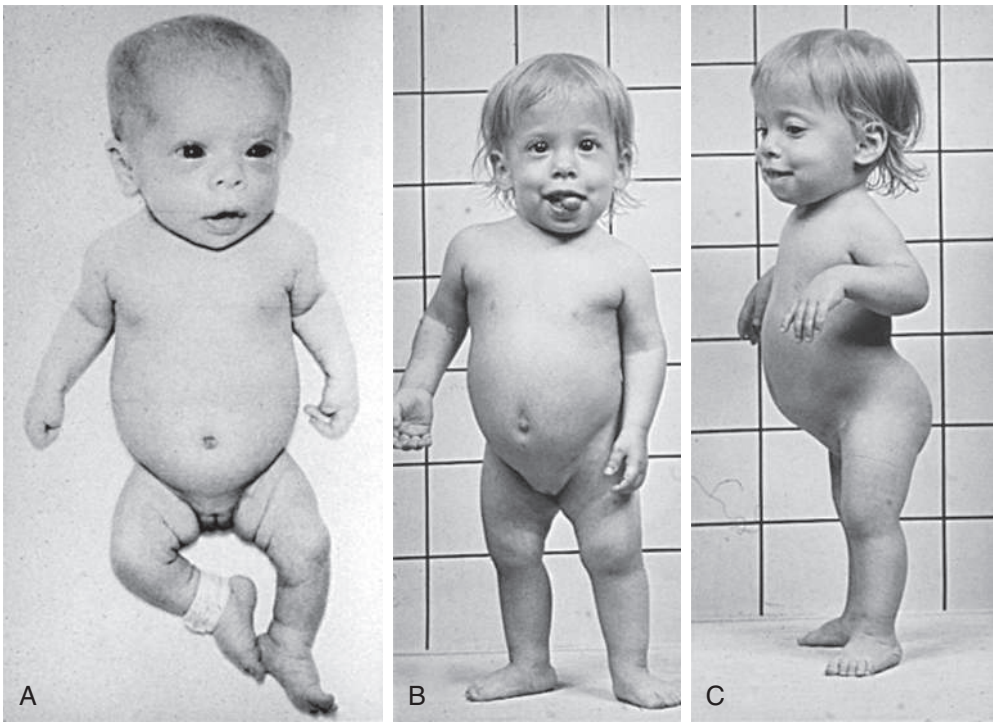

Fig. 736.2 Spondyloepiphyseal dysplasia congenita is shown in infancy (**A**) and early childhood (**B, C**). Note the short extremities, relatively normal hands, flat facies, and exaggerated lordosis.



Fig. 736.3 Spondyloepiphyseal dysplasia. Platyspondyly, delayed epiphyseal ossification (especially femoral heads), dens hypoplasia. *(From Campeau P, Schlesinger AE. Skeletal dysplasias. [Updated 2017 Jan 30]. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. Endotext [internet]. South Dartmouth, MA, 2000, MDText.com, Inc. Fig. 5. Available from https://www.ncbi.nlm.nih.gov/books/NBK279130/.)*

phenotype of MED has its onset during childhood, with mild short-limbed short stature, pain in weight-bearing joints, and a waddling gait. Radiographs show delayed and irregular ossification of epiphyses. A typical finding is the double-layered patella (pathognomonic). In more mildly affected patients, the disorder might not be recognized until adolescence or adulthood. Radiographic changes may be limited to the capital femoral epiphyses. In the latter case, mild MED must be distinguished from bilateral Legg-Calvé-Perthes disease (see Chapter 719.3). Precocious OA of hips and knees is the major complication in adults with MED. Adult heights range from 136-151 cm.

There are families with clinical and radiographic manifestations of MED that are not caused by pathogenic variants of COMP. Pathogenic variants in the genes encoding all three of the type IX collagen chains have been reported. It has been suggested that COMP and type IX collagen interact functionally in cartilage matrix, thus explaining why pathogenic variants of different genes produce similar pictures. Pathogenic variants of the genes coding for another cartilage matrix protein, matrilin-3 *(MATN3)*, and the diastrophic dysplasia sulfate transporter *(SLC26A)* have also been found in patients with autosomal dominant and recessive MED, respectively. For familial cases of pseudoachondroplasia and MED resulting from pathogenic variant in COMP, prenatal diagnosis is available.

Spondyloepimetaphyseal dysplasia, Borochowitz-Cormier-Daire type

Spondyloepimetaphyseal dysplasia, Borochowitz-Cormier-Daire type is a rare more severe spondylo-epi-metaphyseal dysplasia (SEMD)-like phenotype characterized by short-limb dwarfism with spinal,



Fig. 736.4 Face and profile of a mother and daughter with Stickler syndrome type I. Note in the daughter the flat nasal bridge, the mild epicanthal folds, and discrete micrognathia. At first sight, the mother shows no clear facial characteristics of Stickler syndrome. *(From Baijens LWJ, De Leenheer EMR, Weekamp HH, et al. Stickler syndrome type I and Stapes ankylosis. Int J Pediatr Otorhinolaryngol. 2004;68:1573–1580. Fig. 2.)*

Table 736.2 Other Genetic Diseases Associated with Pathogenic Variants in Type II and Type XI Collagen Genes, with Clinical Presentations Similar to That of Stickler Syndrome

PHENOTYPES ASSOCIATED WITH *COL2A1* PATHOGENIC VARIANTS
Achondrogenesis type II
Hypochondrogenesis
Spondyloepiphyseal dysplasia congenita
Spondyloepimetaphyseal dysplasia, Strudwick type
Kniest dysplasia
Platyspondylic skeletal dysplasia, Torrance type
Spondyloperipheral dysplasia
Czech dysplasia
Spondyloepiphyseal dysplasia, Stanescu type
Dysplasia with altered vertebral contours
Some of the juvenile joint diseases
PHENOTYPES ASSOCIATED WITH *COL11A1* PATHOGENIC VARIANTS
Marshall syndrome
Fibrochondrogenesis 1
Autosomal dominant deafness
PHENOTYPES ASSOCIATED WITH *COL11A2* PATHOGENIC VARIANTS
Otospondylometaphyseal dysplasia
Weissenbacher-Zweymüller syndrome
Fibrochondrogenesis 2
Some cases of isolated sensorineural deafness

Table adapted from Couchouron T, Masson C. Early-onset progressive osteoarthritis with hereditary progressive ophthalmology or Stickler syndrome. *Joint Bone Spine.* 2011;78:45–49. Table 1, p. 48; with additional data from Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. *Am J Med Genet A.* 2019;179(12):2393–2419.

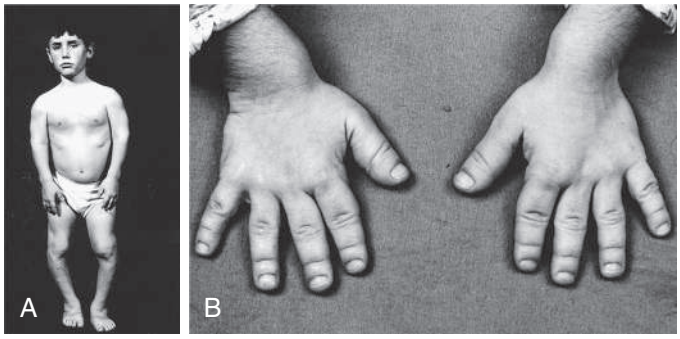

Fig. 736.5 Pseudoachondroplasia in an adolescent male. **A,** The facies and head circumference are normal. There is shortening of all extremities and bowing of the lower extremities. **B,** Photograph of hands, demonstrating short stubby fingers.

epiphyseal, and metaphyseal abnormalities. There are only three families described in the literature caused by autosomal recessive pathogenic variant in the gene encoding matrilin-3 (*MATN3*). Radiographic examination showed flat, ovoid vertebral bodies, short with a stocky appearance, long tubular bones, wide metaphysis with lateral spurs, irregular epiphysis of knee, unossified proximal femur epiphysis, squaring of pelvis, and narrow greater sciatic notch.

SCHMID METAPHYSEAL DYSPLASIA

Schmid metaphyseal dysplasia is one of several chondrodysplasias in which metaphyseal abnormalities dominate the radiographic features. It typically manifests in early childhood with mild short stature, bowing of the legs, and a waddling gait (Fig. 736.7). Joints, such as the wrist, may be enlarged. Radiographs show flaring and irregular mineralization of the metaphyses of tubular bones of the proximal

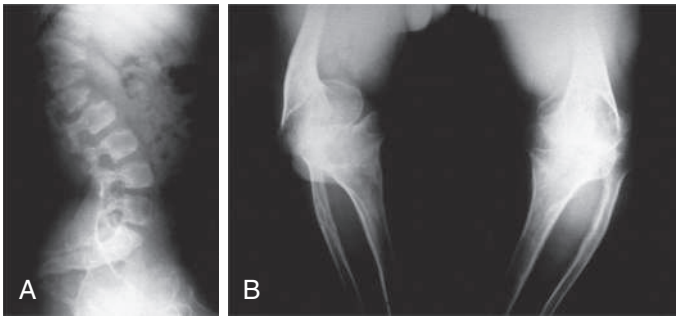

Fig. 736.6 A, Lateral thoracolumbar spine radiograph of a patient with pseudoachondroplasia showing central protrusion (tonguing) of the anterior aspect of upper lumbar and lower thoracic vertebrae. Note reduced vertebral body heights (platyspondyly) and secondary lordosis. B, Lower-extremity radiograph of a patient with pseudoachondroplasia showing large metaphyses, poorly formed epiphyses, and marked bowing of the long bones.



Fig. 736.7 Female patient with metaphyseal dysplasia, type Schmid. The facies are normal, and the stature is mildly reduced. Mild tibia vara is present.

limbs (Fig. 736.8). Coxa vara is usually present and can require surgical correction. Short stature becomes more evident with age and affects the lower extremities more than the upper extremities. Overall, manifestations are limited to the skeleton. Schmid metaphyseal chondrodysplasia is caused by heterozygous pathogenic variants



Fig. 736.8 Radiograph of lower extremities in Schmid metaphyseal dysplasia showing short tubular bones and metaphyseal flaring and irregularities, abnormal capital femoral epiphyses, and femoral necks. The epiphyses are normal. Coxa vara is present.

in the gene encoding type X collagen *(COL10A1)* as an autosomal dominant condition. The distribution of type X collagen is restricted to the region of growing bone in which cartilage is converted into bone. This might explain why radiographic changes are confined to the metaphyses.

Aggrecan-Related Spondyloepiphyseal Dysplasias

Pathogenic variants of aggrecan have been detected in three SED-like conditions. SED-Kimberley is relatively mild, with short stature, stocky build, and early-onset OA of weight-bearing joints. Autosomal dominant pathogenic variants are etiologic. Autosomal recessive pathogenic variants cause a more severe and generalized clinical phenotype, **spondyloepimetaphyseal dysplasia–aggrecan type**. Radiographic changes include irregular epiphyses and widened metaphyses. A mild condition, **familial osteochondritis dissecans,** is characterized by multiple osteochondritic lesions (separation of cartilage and subchondral bone from the surrounding tissue and primarily affecting the knee, ankle, and elbow joints) in knees and/or hips and/or elbows, disproportionate short stature, and early-onset OA. Autosomal dominant pathogenic variants have been found in familial cases.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 737

Disorders Involving Transmembrane Receptors

Daniah Albokhari and Julie E. Hoover-Fong

Heterozygous pathogenic variants of genes encoding *FGFR3* (fibroblast growth factor receptor 3) and *PTHR1* (parathyroid hormone-1 receptor) result in disorders involving transmembrane receptors. The pathogenic variants cause the receptors to become activated in the absence of physiologic ligands, which accentuates normal receptor function of negatively regulating bone growth. The pathogenic variants act by gain of negative function. In the *FGFR3* pathogenic variant group, in which the clinical phenotypes range from severe to mild, the severity appears to correlate with the extent to which the receptor is activated. *PTHR1* and especially *FGFR3* pathogenic variants tend to recur in unrelated individuals (Table 737.1; see also Table 735.1).

FGFR3 CHONDRODYSPLASIA GROUP

The achondroplasia group represents a substantial percentage of patients with chondrodysplasias and contains thanatophoric dysplasia (TD), the most common lethal chondrodysplasia, with a birth prevalence of 1 in 35,000 births and achondroplasia, the most common nonlethal chondrodysplasia, with a birth prevalence of 1 in 15,000–25,000 births. Also in this group are severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), hypochondroplasia, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL). All five have pathogenic variants in a small number of locations in the *FGFR3* gene. There is a strong correlation between the pathogenic variant site and the clinical phenotype.

Thanatophoric Dysplasia

TD manifests before or at birth. In the former situation, ultrasonographic examination in mid-gestation or later reveals a large head and very short limbs; the pregnancy is often accompanied by polyhydramnios and premature delivery. Very short limbs, short neck, long narrow thorax, and large head with midfacial hypoplasia dominate the clinical phenotype at birth (Fig. 737.1). The cloverleaf skull deformity known as **kleeblattschädel** is sometimes found. If the affected fetus survives pregnancy, the newborn will have severe respiratory distress because of the small thorax. Although this distress can be treated by intense respiratory care, the long-term prognosis is poor.

Skeletal radiographs distinguish two slightly different forms called TD I and TD II. In the more common TD I, radiographs show large calvarium with a small cranial base, marked thinning and flattening of vertebral bodies (platyspondyly) visualized best on lateral view, very short ribs, severe hypoplasia of pelvic bones, and very short and bowed tubular bones with flared metaphyses (Fig. 737.2). The femurs are curved and shaped like a telephone receiver. TD II differs mainly in that there are longer and straighter femurs.

The TD II clinical phenotype is associated with pathogenic variants that map to codon 650 of *FGFR3*, causing the substitution of a lysine with glutamic acid. This activates the tyrosine kinase activity of a receptor that transmits signals to intracellular pathways. The pathogenic variant of the same lysine 650 to methionine is also associated with a clinical phenotype intermediate between TD and achondroplasia, referred to as **SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans)**, where affected cases often do not require ventilatory support and survive beyond infancy. Pathogenic variants of the TD I phenotype mainly map to two regions in the extracellular domain of the receptor, where they substitute cysteine residues for other amino acids. Free cysteine residues are thought to form disulfide bonds promoting dimerization of receptor molecules, leading to activation and signal transmission. TD I and TD II typically present as new pathogenic variants in offspring born to unaffected, average stature parents. The recurrence risk is low. Because the variant codons in TD are pathogenic for unknown reasons and because of the theoretical risk of germ cell mosaicism, parents are offered prenatal diagnosis for subsequent pregnancies.

Table 737.1 *FGFR3* Chondrodysplasia Group

GROUP/NAME OF DISORDER	INHERITANCE	OMIM	GENE
Thanatophoric dysplasia type I (TD I)	AD	187600	*FGFR3*
Thanatophoric dysplasia type II (TD II)	AD	187601	*FGFR3*
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	616482	*FGFR3*
Achondroplasia	AD	100800	*FGFR3*
Hypochondroplasia	AD	146000	*FGFR3*
Camptodactyly, tall stature, and hearing loss syndrome (CATSHL)	AD	610474	*FGFR3*

Please also refer to group 33 from Mortier et al nosology for craniosynostoses syndromes linked to FGFR3 pathogenic variants, as well as LADD syndrome in group 41 for another FGFR3-related phenotype.

OMIM, Online Mendelian Inheritance in Man (omim.org).

From Campeau P, Schlesinger AE: Skeletal dysplasias. [Updated 2017 Jan 30]. In: De Groot LJ, Chrousos G, Dungan K, et al. (eds). *Endotext [internet]*. South Dartmouth, MA, 2000, MDText.com, Inc. Available from https://www.ncbi.nlm.nih.gov/books/NBK279130/.

Achondroplasia

Achondroplasia is the prototype chondrodysplasia. It typically manifests at birth with short limbs, a long narrow trunk, and a large head with midfacial hypoplasia and prominent forehead (Fig. 737.3). The limb shortening is greatest in the proximal segments (rhizomelia), and the fingers often display a trident configuration. Most joints are hyperextensible, but extension is restricted at the elbow. A thoracolumbar gibbus is typically found in newborns but improves as they start walking with no intervention in 90% of the cases. Birth length may be slightly less than normal but often plots within the low-normal range.

Diagnosis

Skeletal radiographs confirm the diagnosis (Fig. 737.4; see also Fig. 737.3). The calvarial bones are large, whereas the cranial base and facial bones are small. The vertebral pedicles are short throughout the spine as noted on a lateral radiograph. The interpedicular distance, which normally increases from the first to the fifth lumbar vertebra, decreases in achondroplasia. The iliac bones are short and round, and the acetabular roofs are flat. The tubular bones are short with mildly irregular and flared metaphyses. The fibula is disproportionately long compared with the tibia, which is often bowed, causing genu varum.

Clinical Manifestations

Infants usually exhibit delayed motor milestones, often not walking alone until 18-24 months. This is because of hypotonia and mechanical difficulty balancing the large head on a normal-sized trunk and short extremities. Intelligence is normal unless central nervous system complications develop. As the child begins to walk, the gibbus usually gives way to an exaggerated lumbar lordosis.

Infants and children with achondroplasia progressively fall below normal standards for length and height. They can be plotted against standards established for achondroplasia. Adult heights typically are 118-145 cm for men and 112-136 cm for women. C-type natriuretic



Fig. 737.1 Identical twins with type I thanatophoric dysplasia. Disproportionately large head, bell-shaped chest, and micromelia. *(From Gilbert-Barness E, Kapur RP, Oligny LL, Siebert JR, eds. Potter's Pathology of the Fetus, Infant and Child, 2nd ed. Philadelphia: Elsevier, 2007. Fig. 20-47.)*

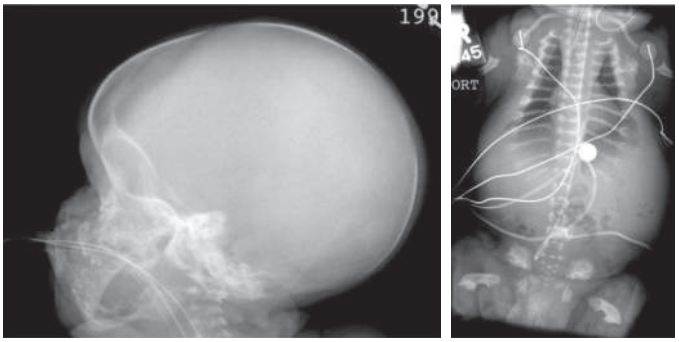

Fig. 737.2 Thanatophoric dysplasia type I. Severe platyspondyly, very short ribs, narrow thorax, short broad pelvis, large skull, very short and bent long bones. *(From Campeau P, Schlesinger AE. Skeletal dysplasias. [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al., eds. Endotext [internet]. South Dartmouth, MA, 2000, MDText.com, Inc., Fig. 1. Available from https://www.ncbi.nlm.nih.gov/books/NBK279130/.)*



Fig. 737.3 Achondroplasia phenotype at different ages. **A**, Infant with achondroplasia with macrocephaly, frontal bossing, midface hypoplasia, small chest, rhizomelic shortening of all the limbs, redundant skinfolds, and extreme joint laxity. Note the trident hand with short fingers and abducted hips. **B**, Typical radiographic findings from a child with achondroplasia. All of the tubular bones are short, but the fibula is relatively long compared with the tibia. There is protrusion of the epiphysis into the metaphysis of the distal femur, creating the chevron deformity, and—to a lesser extent—of the proximal tibia. The iliac bones are rounded, the acetabular roof is horizontal, and the sacrosciatic notches are small. **C**, A 3-yr-old with achondroplasia with the typical features shown in **(A)**. Note that the redundant skinfolds are no longer present and that joint laxity has improved. Rhizomelic shortening of the extremities is more pronounced and accompanied by tibial bowing. *(From Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007;370:162–172.)*

peptide analogue (vosoritide), administered as a daily subcutaneous injection is the first approved treatment for children ≥5 years of age with achondroplasia; treatment with vosoritide produced an increase of annual growth velocity with no significant side effect. In addition, vosoritide maintains this annual growth velocity up to 2 years along with an improvement in body segment proportion. Clinical trials are underway to study other compounds such as soluble FGFR3 decoy receptors, and tyrosine kinase inhibitors, which may restore bone growth in achondroplasia based on studies in animal models. Other possible future treatments of achondroplasia include fibroblast growth factor aptamers and meclizine, which showed improvement of the skeletal phenotype of the mutant mice. Surgical limb lengthening and human growth hormone treatment have been used to increase height; however, both are controversial.

Virtually all infants and children with achondroplasia have large heads, although only a fraction have true hydrocephalus. Head circumference should be carefully monitored using standards developed for achondroplasia, as should neurologic function in general. The spinal canal is stenotic, and spinal cord compression can occur at the foramen magnum and in the lumbar spine. The former usually occurs in infants and small children and may be associated with hypotonia, failure to thrive, quadriparesis, central and obstructive apnea, and sudden death. Surgical correction may be required for severe stenosis. Lumbar spinal stenosis usually does not occur until early adulthood. Symptoms include paresthesias, numbness, and claudication in the legs. Loss of bladder and bowel control may be late complications. Bowing of the legs is common in patients with achondroplasia and might need to be corrected surgically. Other common problems include dental crowding, articulation difficulties, obesity, and frequent episodes of otitis media, which can contribute to hearing loss.

Genetics

All patients with typical achondroplasia have pathogenic variants at *FGFR3* codon 380. This pathogenic variant is located in the transmembrane domain of the receptor and is thought to stabilize receptor dimers that enhance receptor signals, the consequences of which inhibit linear bone growth. Achondroplasia behaves as an autosomal dominant condition; most cases arise from a new pathogenic variant to average stature parents.

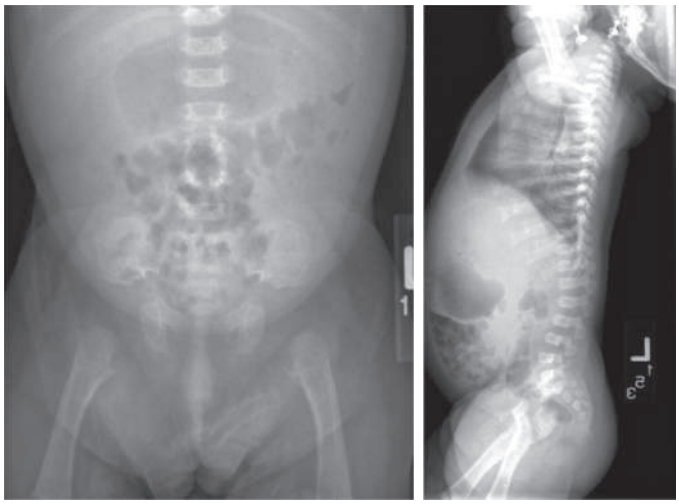

Fig. 737.4 Achondroplasia. Small rounded iliac bones, horizontal acetabula, decreasing interpediculate distance, normal vertebral body height, short ribs. *(From Campeau P, Schlesinger AE. Skeletal dysplasias. [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al., eds. Endotext [internet]. South Dartmouth, MA, 2000, MDText.com, Inc., Fig. 2. Available from https://www.ncbi.nlm.nih.gov/books/NBK279130/.)*

Because of the high frequency of achondroplasia among short stature skeletal dysplasias, it is relatively common for adults with achondroplasia to marry. Such couples have a 50% risk of transmitting their condition, heterozygous achondroplasia, to each offspring, as well as a 25% risk of **homozygous achondroplasia**. The latter condition exhibits intermediate severity between TD and heterozygous achondroplasia and is usually lethal in the newborn period and is often referred to as "double dominant" inheritance. Prenatal diagnosis is available and has been used to diagnose homozygous achondroplasia. Preimplantation genetic testing can be used to identify double dominant pathogenic variants.

Hypochondroplasia

Hypochondroplasia resembles achondroplasia but is milder. Usually, it is not apparent until childhood, when mild short stature affecting the limbs becomes evident. Children have a stocky build, disproportionately short extremities, and slight frontal bossing of the head. Learning disabilities may be more common in this condition. Radiographic changes are mild and consistent with the mild achondroplastic phenotype. Complications are rare; in some patients, the condition is never diagnosed. Adult heights range from 131-154.5 cm for men and 124-138 cm for women. An *FGFR3* pathogenic variant at codon 540 is the most pathogenic variant found in patients with more severe hypochondroplasia. Genetic heterogeneity exists in hypochondroplasia; that is, *SHOX* pathogenic variants are associated with a very similar clinical phenotype. Recombinant growth hormone therapy may enhance growth and improve body disproportion but is still considered controversial with limited evidence of increased final adult height.

JANSEN METAPHYSEAL DYSPLASIA

Jansen metaphyseal chondrodysplasia is a rare, dominantly inherited chondrodysplasia characterized by severe shortening of limbs associated with an unusual facial appearance (see Chapter 735). Sometimes it is accompanied by clubfoot and **hypercalcemia** with serum calcium values of 13-15 mg/dL. At birth, a diagnosis can be made from these clinical findings, and radiographs that show short tubular bones with characteristic metaphyseal abnormalities that include flaring, irregular mineralization, fragmentation, and widening of the physeal space. The epiphyses are normal. The joints become enlarged and limited in mobility with age. Flexion contractures develop at the knees and hips, producing a bent-over posture. The spine can also be deformed by the irregular growth of vertebrae. Intelligence is normal, although there may be hearing loss.

Jansen metaphyseal chondrodysplasia is caused by activating pathogenic variants of *PTHR1*. This G-protein–coupled transmembrane receptor serves as a receptor for both parathyroid hormone and parathyroid hormone-related peptide. Signaling through this receptor serves as a brake on the terminal differentiation of cartilage cells at a critical step in bone growth. Because the pathogenic variants activate the receptor, they enhance the braking effect and thereby slow bone growth. In contrast, loss-of-function pathogenic variants of *PTHR1* are observed in Blomstrand chondrodysplasia, whose clinical features are the mirror image of Jansen metaphyseal chondrodysplasia.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 738

Disorders Involving Ion Transporters

Daniah Albokhari and Julie E. Hoover-Fong

Five genes related to ion transporters have been reported to be involved in skeletal dysplasia conditions, including the *SLC39A13* gene causing Ehlers-Danlos syndrome, spondylodysplastic type, the *SLCO2A1* gene causing hypertrophic osteoarthropathy (OA), the *SLC10A7* gene causing multiple joint dislocations with amelogenesis imperfecta, and the *SLC34A3* gene causing hypophosphatemic rickets with hypercalciuria (HHRH). This chapter will focus on pathogenic variants in the sulfate transporter gene *(SLC26A2)*, also known as **diastrophic dysplasia sulfate transporter *(DTDST),*** which is the most common ion transporter gene causing sulphation disorders skeletal dysplasia. It encompasses a spectrum of both lethal and nonlethal chondrodysplasia, including, in order of decreasing severity, achondrogenesis type 1B, atelosteogenesis type II, diastrophic dysplasia, and a rare recessive form of multiple epiphyseal dysplasia (rMED). The gene product sulfate transporter is important to uptake sulfate ions into cells and is important for cartilage cells that add sulfate moieties to newly synthesized proteoglycans destined for cartilage extracellular matrix. Matrix proteoglycans are responsible for many of the properties of cartilage that allow it to serve as a template for skeletal development. The clinical manifestations result from defective sulfation of cartilage proteoglycans (see also Table 735.1).

A number of pathogenic alleles have been found for the *DTDST* gene; they variably disturb transporter function. The disorders are recessive traits requiring the presence of bi-allelic pathogenic variants. The phenotype is determined by the combination of abnormal alleles with some alleles present in more than one disorder.

Achondrogenesis Type 1B and Atelosteogenesis Type 2

Achondrogenesis type 1B and atelosteogenesis type 2 are rare recessive lethal chondrodysplasias. The most serious is achondrogenesis type 1B, which demonstrates a severe lack of skeletal development usually detected in utero or after a miscarriage. The limbs are extremely short, the head is soft, the thorax is narrow, and the abdomen protuberant. Skeletal radiographs show poor to missing ossification of skull bones, vertebral bodies, fibulas, and ankle bones. The pelvis is hypoplastic, and the ribs are short and slightly thin. The femurs are short and exhibit a trapezoid shape with irregular metaphyses.

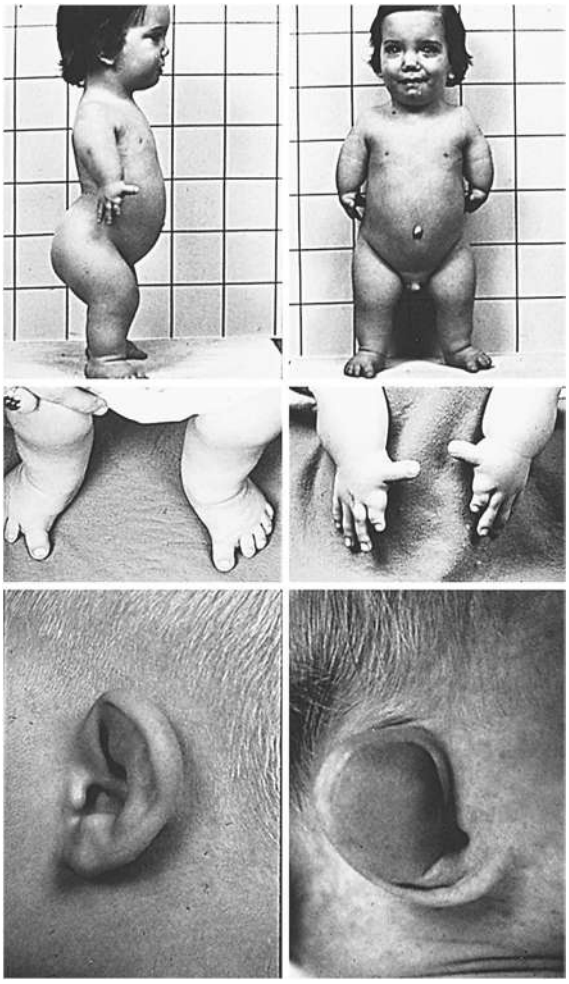

Fig. 738.1 Child with diastrophic dysplasia. The extremities are dramatically shortened *(top)*. Clubfoot is commonly observed *(middle left)*. The fingers are short, especially the index finger; the thumb characteristically is proximally placed and has a hitchhiker appearance *(middle right)*. The upper helix of the ears becomes swollen 3-4 wk postnatally *(lower left)*, and this inflammation spontaneously resolves, leaving a cauliflower deformity of the pinnae *(lower right)*.

Infants with atelosteogenesis type II are stillborn or die soon after birth; prematurity is common. They exhibit very short limbs, especially the proximal segments with normal size head and midface hypoplasia. Clubfoot and dislocations of the elbows and knees may be detected. Hypoplasia of vertebral bodies, especially in the cervical and lumbar spine, and hypoplastic ilia with flat acetabulum are found on radiographs. The femora and humeri are hypoplastic and display a club-shaped appearance. The distal limb bones, including the ulna and fibula, are poorly ossified.

Both disorders have a 25% recurrence risk and are potentially detectable in utero by pathogenic variant analysis if the mutant alleles are identified in the parents. Prenatal diagnosis is possible with fetal imaging and/or pathogenic variant testing, which is commercially available.

Diastrophic Dysplasia

Diastrophic dysplasia is a well-characterized disorder recognized at birth by the presence of very short extremities, normal head size, clubfoot, and short hands, with proximal displacement of the thumb producing a hitchhiker appearance (Fig. 738.1). The hands are usually deviated in an ulnar direction. Bony fusion of the metacarpophalangeal joints (symphalangism) is common, as is restricted movement of many joints, including the hips, knees, and elbows. The external ears often become inflamed soon after birth. The inflammation resolves spontaneously but leaves the ears fibrotic and contracted (cauliflower ear deformity). Many newborns have a cleft palate.



Fig. 738.2 Radiograph of hands in diastrophic dysplasia. The metacarpals and phalanges are irregular and short. The first metacarpal is ovoid.

Radiographs reveal short and broad tubular bones with flared metaphyses and flat, irregular epiphyses (Fig. 738.2). The capital femoral epiphyses are hypoplastic, and the femoral heads are broad. The ulnas and fibulas are disproportionately short. Carpal centers may be developmentally advanced with the first metacarpal typically ovoid, and the metatarsals twisted medially. There may be vertebral abnormalities, including clefts of cervical vertebral lamina and narrowing of the interpedicular distances in the lumbar spine.

Complications are primarily orthopedic and tend to be severe and progressive, leading to joint contractures, spine deformity and early onset OA. The clubfoot deformity in the newborn resists usual treatments, and multiple corrective surgeries are common. Scoliosis typically develops during early childhood. It often requires multiple surgical procedures to control, and it sometimes compromises respiratory function in older children. Despite the orthopedic problems, patients typically have normal intelligence, have normal life span, and reach adult heights in the 105-130 cm range, depending on the severity of scoliosis. Growth curves are available for diastrophic dysplasia. Respiratory insufficiency may present in neonates because of the small rib cage and tracheal instability and collapsibility. In these cases, supportive measures such as mechanical ventilation may be required. Cervical kyphosis is seen in most newborns, which improves spontaneously in childhood. However, some may experience severe cervical kyphosis leading to spinal cord compression.

Some patients are mildly affected and exhibit slight short stature and joint contractures, no clubfoot or cleft palate, and correspondingly mild radiographic changes. The mild phenotype tends to recur within families. The recurrence risk of this autosomal recessive condition is 25%. Ultrasonographic examination can be employed for prenatal diagnosis, but if *DTDST* pathogenic variants can be identified in the patients or parents, molecular genetic diagnosis is possible.

AUTOSOMAL RECESSIVE MULTIPLE EPIPHYSEAL DYSPLASIA

Although previously regarded as a multiple epiphyseal dysplasia, according to the new nosology, rMED is now classified among other sulfation disorders. rMED typically presents during adolescence with the gradual onset of hip and knee pain that might resemble rheumatoid arthritis. Later on, patients present with hand, feet, and knee deformities and scoliosis. Fifty percent of individuals present during infancy with club feet and external ear abnormalities. Stature is normal during childhood, but final height might be slightly decreased compared with unaffected siblings and ranges from 150-180 cm. Radiographic findings include flat epiphysis, mild brachydactyly, and double-layered patella. Diagnosis is clinical, based on presentation and radiologic findings, but molecular confirmation is available with a detection rate over 90%. Management includes physical therapy, pain control, and orthopedic interventions.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 739

Disorders Involving Transcription Factors

Julie E. Hoover-Fong and Daniah Albokhari

Transcription factors are proteins that control the transcription of DNA into RNA to make proteins essential for cellular function. Pathogenic variants in the genes that make transcription factors can result in disease by "turning on" or "turning off" downstream genes to result in disease. Of the estimated 1,500 known transcription factors in humans, four are associated with well-delineated bone dysplasias. Campomelic dysplasia (CD), cleidocranial dysplasia (CCD), and SHOX gene-related conditions are considered dysplasias, whereas nail-patella syndrome (NPS) is classified as a dysostosis (meaning a skeletal disorder limited to individual bones or group of bone rather than the entire skeleton, as in a skeletal dysplasia) (see also Table 735.1).

Pathogenic variants in genes that encode transcription factors that cause disease are *SOX9, RUNX2 (CBFA1)*, *SHOX,* and *LMX1B*, respectively. *SOX9* is a member of the SOX family of transcription factors related to the SRY (sex-determining region of the Y chromosome) gene; *RUNX2 (CBFA1)* belongs to the runt family of transcription factor genes; *SHOX* is part of the homeobox gene family; and *LMX1B* is part of the LIM homeodomain gene family. Each results in a disorder caused by haploinsufficiency of the respective gene products. CD, CCD, and NPS are all autosomal dominant conditions, whereas *SHO*X-related conditions are inherited in a pseudoautosomal fashion.

CAMPOMELIC DYSPLASIA

Campomelic dysplasia is apparent in newborn infants and characterized by short, bowed long bones (especially in the lower legs), respiratory distress, cervical spine anomalies, Pierre-Robin sequence, and variable involvement of the central nervous system, heart, and kidneys. In some cases, femoral bowing is minimal (i.e., acampomelic campomelic dysplasia). Additionally, 75% of XY individuals have some degree of gonadal dysgenesis that ranges from normal female phenotype through ambiguous genitalia and lack of determination of testicular tissue with undervirilization. 46,XX individuals have an expected female phenotype with normal ovarian differentiation. *Therefore karyotype analysis is indicated in every female with campomelia*. These features are because of the role of *SOX9* in the differentiation of testicular tissue downstream of *SRY*. Compared with SOX9 haploinsufficiency, duplications cause gonadal tissue to differentiate into testicular tissue in 46,XX individuals, highlighting the dosage sensitivity of *SOX9* in gonadal differentiation. Radiographs confirm long bone bowing and often show hypoplasia of the scapulae and pelvic bones (Fig. 739.1). Affected infants often die of respiratory distress in the neonatal period because of tracheomalacia, small thoracic volume, and early scoliosis. Complications in children and adolescents who survive include cervical instability, short stature with progressive kyphoscoliosis, recurrent apnea and respiratory infections, hearing loss, and learning difficulties. Because of a deficiency of gonadal differentiation, 46,XY individuals with female genitalia often present with absent thelarche and primary amenorrhea. Pathogenic variant testing is commercially available and has a >95% detection rate. Nearly all individuals with CD represent a de novo pathogenic variant in *SOX9*.

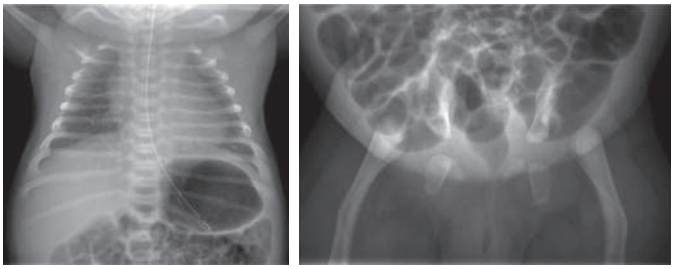

Fig. 739.1 Campomelic dysplasia. Bell-shaped thorax, hypoplastic scapula, bowed femurs, widely spaced ischial bones. *(From Campeau P, Schlesinger AE. Skeletal dysplasias [Fig. 12]. [Updated 2017 Jan 30]. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. Endotext [internet]. South Dartmouth, MA, 2000, MDText.com, Inc. Fig 12. Available at https://www.ncbi.nlm.nih.gov/books/NBK279130/.)*

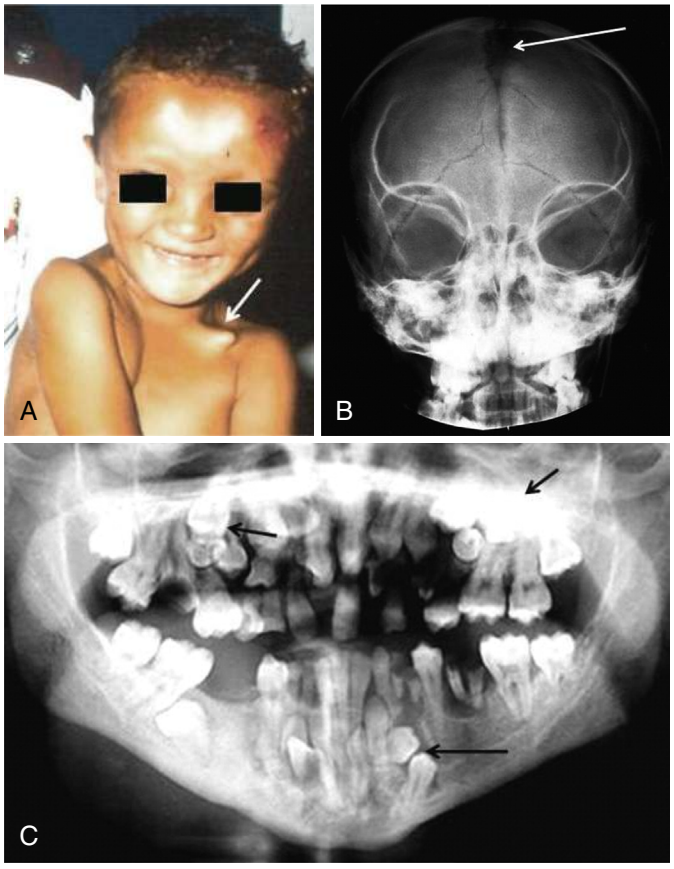

Fig. 739.2 Features of cleidocranial dysplasia displayed. **A,** The forehead is bulky with a central depression, the eyes are widely spaced, and the jaw is pointed. The clavicle is misshapen *(arrow)*. **B,** Note patency of the anterior fontanelle. **C,** Hyperdontia pantomogram of an affected male showing supernumerary teeth. *(From Roberts T, Stephen L, Beighton P. Cleidocranial dysplasia: a review of the dental, historical, and practical implications with an overview of the South African experience. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115[1]:46–55. Figs. 1, 4, and 6.)*

CLEIDOCRANIAL DYSPLASIA

Cleidocranial dysplasia can be recognized in infants because of sloping shoulders, wide fontanelles, and prominent forehead. Birth length is normal, but mild short stature and dental abnormalities are evident during childhood (Fig. 739.2). The shoulders of patients



Fig. 739.3 Nail-patella syndrome. **A,** Adolescent showing nail hypoplasia, especially of thumbs, and displacement of small patellae. **B,** Two affected children showing nail dysplasia. **C,** Incomplete extension of the elbows. *(From Jones KL, Jones MC, Del Campo M, eds. Smith's Recognizable Patterns of Human Malformation, 7th ed. Philadelphia: Saunders, 2013. Fig. 1, p. 574.)*

with CD can collapse to meet in the midline because of hypoplasia or absence of the clavicles. Radiographs will reveal the abnormal clavicles, delayed ossification of cranial bones with multiple ossification centers (Wormian bones), and delayed ossification of pelvic bones. The anterior fontanelle is wide and may remain open into adulthood. The course is relatively uncomplicated except for dislocations and variable diffuse joint pain (especially of the shoulders), dental anomalies (e.g., supernumerary and/or retained primary teeth) that require dental treatment, and risk of hearing loss because of infections. Affected individuals are shorter than unaffected siblings and have an increased risk of genu valgum, pes planus, and scoliosis. Diagnosis is based on clinical and radiographic presentation, but molecular confirmation is available with a detection rate of >70%. The proportion of cases caused by de novo pathogenic variants is high. Management includes prevention of ear infections, speech therapy, dental, and orthopedic interventions as indicated.

SHOX GENE-RELATED CONDITIONS

The *SHOX* gene is located on the pseudoautosomal region of the X and Y chromosomes (i.e., Xp22.33/Yp11.32). Because of crossover during meiotic replication, a *SHOX* variant can segregate on both sex chromosomes, thereby allowing inheritance to occur from male to male, male to female, female to female, and female to male (i.e., sex chromosome gene location while appearing to have autosomal inheritance; pseudoautosomal). Haploinsufficiency of the *SHOX* gene (i.e., loss of one copy of the gene) through deletion, single nucleotide variant, or abnormal regulation of adjacent genes causes Leri-Weill dyschondrosteosis (LWD) and idiopathic short stature (ISS) and contributes to Turner syndrome features when included in the absent X-chromosome material. Features of LWD include short stature, mesomelia, and Madelung deformity of the wrists. ISS does not have other phenotypic features of an abnormal *SHOX* gene other than short stature. This distinguishes ISS from Turner syndrome in which the entire X chromosome is typically missing in affected females, causing short stature, pubertal delay/absence, cardiac anomalies, nuchal folds, and other anomalies. Growth hormone injections can provide effective treatment for short stature associated with a *SHOX* gene abnormality.

NAIL-PATELLA SYNDROME

Dysplasia of the nails, absence or hypoplasia of the patella, abnormalities of the elbow, and spurs or "horns" extending from the iliac bones characterize NPS, also called *osteo-onychodysostosis*. Penetrance is high, but clinical presentation is extremely variable with a wide spectrum of severity. Some patients present in early childhood, whereas others are asymptomatic as adults. Nail abnormalities are almost universal with a wide variety of manifestations, including absence, hypoplasia, clefts, ridged, thin, or hypertropic nails, all of which may worsen in severity moving in the ulnar to radial direction. Elbow abnormalities include limitation of movement, cubits valgus, and pterygium. The patella can be hypoplastic or absent (Fig. 739.3). Iliac horns project posterior-laterally from the center of the iliac bone. A total of 30% of patients have nephritis that resembles chronic glomerulonephritis that presents with proteinuria with or without hematuria; 5% of cases progress to end-stage renal disease. There is an increased risk of glaucoma for NPS patients. NPS is often inherited with 12% of cases being *de novo*. Diagnosis is based on clinical presentation, and molecular confirmation is available with a 95% detection rate. Management includes treatment of orthopedic complications, surveillance and treatment of renal disease, and ophthalmologic follow-up.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 740

Osteopetrosis and Other Disorders Involving Defective Bone Resorption

Julie E. Hoover-Fong and Daniah Albokhari

Bone dysplasias displaying increased bone density are rare. Osteopetrosis, which has many subtypes, pycnodysostosis, and dysosteosclerosis are the principal members of this disease category. The clinical features and complications of these conditions are the result of abnormal osteoclast formation and function, resulting in defective bone resorption (Table 740.1).

Table 740.1 Osteopetrosis and Related Osteoclast Disorders

GROUP / DISORDER	INHERITANCE	GENE OR LOCUS
Osteopetrosis, neonatal or infantile form	AR	*TCIRG, CLCN, SNX10*
Osteopetrosis, infantile form, with nervous system involvement	AR	*OSTM1*
Osteopetrosis, infantile form, osteoclast-poor with immunoglobulin deficiency	AR	*TNFRSF11A*
Osteopetrosis, intermediate form	AR	*TCIRG1, TNFSF11, PLEKHM1, CLCN7*
Osteopetrosis, late-onset, dominant form	AD	*CLCN7*
Osteopetrosis with renal tubular acidosis	AR	*CA2*
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	XL	*IKBKG*
Osteopetrosis, moderate form	AR	*SLC4A2*
Osteopetrosis, moderate form with defective leucocyte adhesion	AR	*FERMT3, RASGRP2*
Osteosclerotic metaphyseal dysplasia	AR	*LRRK1*
Pyknodysostosis	AR	*CTSK*
Dysosteosclerosis	AR	*SLC29A3, TNFRSF11A*
Dysosteosclerosis with degenerative encephalopathy and brain malformation	AR	*CSF1R*

Data from Unger S, Ferreira CR, Mortier GR, et al. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet* 2023;191A:1164-1209 (Table 1, Group 24, pp 1184-1185).

OSTEOPETROSIS

The term *osteopetrosis* derives from the Greek root "osteo," meaning bone, and "petrosis," meaning stone. Osteopetrosis is marked by *increased* bone mass caused by abnormal osteoclast formation or function. The dense bone in osteopetrosis invades the marrow space, causing anemia and pancytopenia, and impinges on nerves traversing cranial and other skeletal foramina, causing deafness, blindness, and palsies. Although the skeleton is dense in osteopetrosis, the bone quality is poor and may be prone to fracture because of imbalanced bone turnover.

To date, genes known to cause osteopetrosis include: *CLCN7, TCIRG1, OSTM1, SNX10, CA2, PLEKHM1, TNFRSF11A, TNFSF11, IKBKG, SLC4A2, FERMT3, and RASGRP2.* Pathogenic variants in *CLCN7, TCIRG1, OSTM1, SNX10, CA2,* and *PLEKHM1* prevent normal osteoclast function to resorb bone while *TNFRSF11A, TNFSF11* encode proteins (RANK and RANKL, respectively) that are essential to the formation of osteoclasts. Pathogenic variants in *CLCN7* may cause disease in an autosomal dominant or recessive fashion and variants in *IKBKG* are X-linked, whereas all others here cause recessive osteopetrosis. CLCN7-related autosomal dominant osteopetrosis occurs in 1 in 20,000 births, while collectively, the recessive form of osteopetrosis occurs in 1 in 250,000 births. Pathogenic variants in *CLCN7* are the most common cause of osteopetrosis overall, causing a wide spectrum of disease severity ranging from late childhood/adolescent-onset autosomal dominant osteopetrosis II (ADOII) to more involved intermediate autosomal osteopetrosis (IAO) to the most severe autosomal recessive osteopetrosis (ARO) with onset at birth. In general, the other recessive forms of osteopetrosis are also severe, usually detected in infancy because of macrocephaly, hepatosplenomegaly, deafness, blindness, and severe anemia.

CLINICAL MANIFESTATIONS

Most of the manifestations of osteopetrosis are because of failure to remodel growing bones. This leads to narrowing of cranial nerve foramina and encroachment on marrow spaces, which results in secondary complications, such as optic and facial nerve dysfunction, and anemia accompanied by compensatory extramedullary hematopoiesis in the liver and spleen (Table 740.2). The unusually dense bones are weak, leading to increased risk of fractures.

In the severe recessive infancy-onset form, patients present with macrocephaly, hepatosplenomegaly, deafness, blindness, and severe anemia. Radiographs reveal diffuse bone sclerosis and *hypocalcemia* may be present. Later radiographs show the characteristic bone-within-bone appearance throughout the skeleton (Figs. 740.1 and 740.2). With time, infants typically fail to thrive and show psychomotor delay and worsening of cranial neuropathies and anemia. Dental problems, osteomyelitis of the mandible, and pathologic fractures are common. The most severely affected patients die during infancy; less severely affected patients rarely survive beyond the second decade but often only after treatment with bone marrow transplant. Those who survive beyond infancy usually have learning disabilities but might have normal intelligence despite hearing and vision loss.

The autosomal dominant form of osteopetrosis (Albers-Schönberg disease, osteopetrosis tarda, or marble bone disease) usually manifests during childhood or adolescence with fractures and mild anemia and, less often, as cranial nerve dysfunction, dental abnormalities, or osteomyelitis of the mandible. Skeletal radiographs reveal a generalized increase in bone density and clubbing of metaphyses. Alternating lucent and dense bands produce a sandwich appearance to vertebral bodies. The radiographic changes are sometimes incidental findings in otherwise asymptomatic adolescents and adults.

Table 740.2 Complications of Osteopetrosis by Subspeciality

SUBSPECIALTY	COMPLICATION
Endocrinology	Osteopetrorickets Hypocalcemia
Ophthalmology	Papilledema Ptosis Strabismus Paralysis of extraocular muscles Optic nerve atrophy Exophthalmos Nystagmus Retinal degeneration Tearing (from nasolacrimal duct obstruction)
Dentistry	Delay/failure of tooth eruption Malformed crowns/roots Periodontal ligament defects Odontoma Tooth agenesis Enamel hypoplasia Tooth decay/caries Thickened lamina dura Osteomyelitis (most frequently of the mandible)
Orthopedics	Skeletal deformities Scoliosis Spondylolisthesis Fractures (particularly of the long bones) Delayed union/nonunion Degenerative arthritis Spondylolysis
Neurology/ neurosurgery	Compressive cranial neuropathies (often optic and facial nerves, but can involve any of cranial nerves I–VIII) Increased intracranial pressure Craniosynostosis Arnold–Chiari I malformation Neuromuscular scoliosis Developmental delay/regression, seizures (*OSTM1* mutation) Calcifications of the basal ganglia, thalami (*CAII* deficiency) Hydrocephalus Cerebrovascular stenosis/occlusion Acquired encephalocele
Otolaryngology	Conductive hearing loss Recurrent otitis media Chronic congestion (poorly pneumatized sinuses) Rhinorrhea Choanal atresia Rhinosinusitis Obstructive sleep apnea
Hematology	Thrombocytopenia with bleeding Anemia Leukopenia with frequent infections Hepatosplenomegaly Transfusion dependence
Nephrology	Renal tubular acidosis, nephrocalcinosis, and nephrolithiasis (*CAII* deficiency)

From Wu CC, Econs MJ, DiMeglio LA, et al. Diagnosis and management of osteopetrosis: consensus guidelines from the osteopetrosis working group. *J Clin Endocrinol Metab* 2017;102(9):3111-3123 (Table 2, p. 3116).

TREATMENT

Most of the bone manifestations in severe osteopetrosis caused by intrinsic osteoclast defects can be prevented or reversed by hematopoietic stem cell transplantation (HSCT), if carried out before development of irreversible secondary complications, such as visual impairment. RANKL replacement therapy may be useful in patients with RANKL deficiency caused by *TNFSF11* bi-allelic pathogenic variants, who do not benefit from HSCT. Interferon-γ is used to delay progression in patients with severe malignant infantile osteopetrosis. Symptomatic care, such as dental care, transfusions for anemia, and antibiotic treatment of infections, is important for patients who survive infancy.



Fig. 740.1 Osteopetrosis. Thick dense bones, alternating bands of sclerosis, and normal density bone in long bones, rugger jersey spine, dense base of skull. *(From Campeau P, Schlesinger AE. Skeletal dysplasias. [Updated 2017, Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al, eds. Endotext [internet]. South Dartmouth, MA, 2000, MDText.com, Inc. Fig. 14. Available at https://www.ncbi.nlm.nih.gov/books/NBK279130/.)*

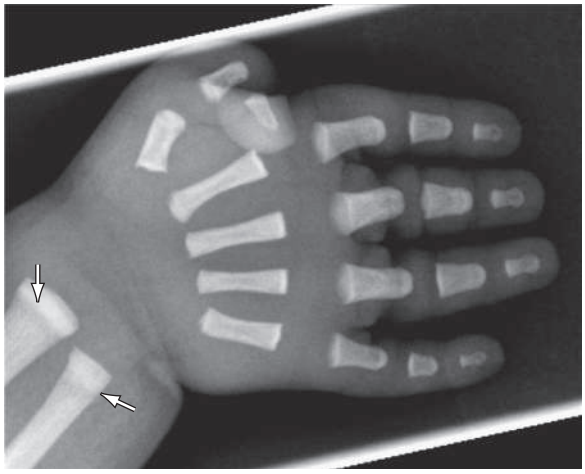

Fig. 740.2 Osteopetrosis. Right-hand radiograph obtained at 2 weeks of age. Note metaphyseal lucent bands in the distal ulna and radius *(arrows)* and short tubular bones. *(From Stark Z, Savarirayan R. Osteopetrosis. Orphanet J Rare Dis. 2009;4:5.)*

PYCNODYSOSTOSIS AND DYSOSTEOSCLEROSIS

Pycnodysostosis

An autosomal recessive bone dysplasia related to osteopetrosis, pycnodysostosis manifests in early childhood with short limbs, characteristic facies, an open anterior fontanel, a large skull with frontal and occipital bossing, acroosteolysis, and dental abnormalities. The hands and feet are short and broad, and the nails may be dysplastic. The sclerae may be blue. Minimal trauma often leads to fractures. Treatment is symptomatic and focused mainly on the management of dental problems and fractures. Although some patients have a persistently open anterior fontanelle (i.e., even into adulthood), others with pycnodysostosis have craniosynostosis. The overall prognosis for these patients is generally good, and they typically reach 130-150 cm in height. Skeletal radiographs show a generalized increase in bone density. In contrast to many disorders in this group, the metaphyses are normal. Other changes include wide sutures and Wormian bones in the skull, a small mandible, and osteolysis of the distal phalanges. Homozygous or compound heterozygous missense, nonsense, insertions, deletions, and splicing variants have been described in the gene *CTSK*, which encodes cathepsin K. This is a lysosomal protease that is involved in bone resorption and remodeling. *CTSK* is highly expressed in osteoclasts, and pathogenic variants prevent degradation of bone matrix proteins (e.g., type I and II collagen), which is necessary for normal bone remodeling and resorption. Growth hormone therapy has been used to improve growth.

Dysosteosclerosis

Dysosteosclerosis is another rare bone disease with generalized increased bone density plus widening of tubular bones and vertebral flattening. It is caused by pathogenic variants in three genes: *SLC9A3*, *CSF1R*, and *TNFRSF11A* (which is allelic with osteopetrosis). Affected individuals have short stature and cranial nerve involvement caused by impingement of the foramina by the abnormally dense bone. No disease-specific treatment has been developed.

There are several other conditions marked by hyperostotic and fragile bones but also other anomalies or conditions distinguishing them from osteopetrosis, pycnodysostosis, and dysosteosclerosis (Table 740.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Table 740.3 Other Conditions with Hyperostotic Fragile Bones

GENE	DISORDER	CLINICAL CHARACTERISTICS	FEATURES DISTINGUISHING THIS DISORDER FROM *CLCN7*-RELATED ARO
CA2	ARO w/renal tubular acidosis (RTA) (OMIM 259730)	Generalized osteosclerosis. Cerebral calcifications are typical and may be associated with ID.	Onset of ARO with RTA is usually later than in infantile malignant form of ARO and disease course is milder.
OSTM1	*OSTM1*-related ARO (OMIM 259720)	~4% of ARO is caused by pathogenic variants in *OSTM1*. Extremely severe form of ARO with CNS involvement that is indistinguishable from most severe forms of *CLCN7*-related ARO.	*OSTM1*-related ARO is frequently associated with structural brain anomalies.
PLEKHM1	*PLEKHM1*-related ARO (OMIM 611497)	Very rare, can look like ADOII.	*PLEKHM1*-related ARO appears to be very mild and can regress with ↑ age. One person with *PLEKHM1*-related ARO caused by a heterozygous pathogenic variant has been described.
SNX10	*SNX10*-related ARO (OMIM 615085)	~4% of ARO is caused by pathogenic variants in *SNX10*; in particular, "Västerbottenian osteopetrosis" is caused by *SNX10* pathogenic variants. Loss of vision, anemia, and bone fragility are frequently observed, warranting use of HSCT.	*SNX10*-related ARO appears to be slightly less severe than *CLCN7*-related ARO.
TCIRG1	*TCIRG1*-related ARO (OMIM 259700)	>50% of ARO is caused by pathogenic variants in *TCIRG1*.	Higher frequency of neurodevelopmental delay and seizures in *CLCN7*-related ARO than in *TCIRG1*-related ARO. Noncoding *TCIRG1* variants can cause milder phenotype that resembles ADOII.
TNFRSF11A	Osteoclast-poor ARO (OMIM 612301)	Characterized by onset within first year of life and typical ARO manifestations. Investigation of bone biopsy is prerequisite for reliable diagnosis.	*TNFSF11* pathogenic variants cause a slight T-cell defect, and *TNFRSF11A* pathogenic variants can lead to hypogammaglobulinemia similar to a common variable immune deficiency. It is crucial to rule out *TNFSF11*- and *TNFRSF11A*-related ARO, as HSCT is not successful in these persons.
TNFSF11	Osteoclast-poor ARO (OMIM 259710)		

ADOII, Autosomal dominant osteopetrosis type II; ARO, autosomal recessive osteopetrosis; CNS, central nervous system; ID, intellectual disability; HSCT, hematopoietic stem cell transplantation

From Sobacchi C, Villa A, Schulz A, Kornak U. *CLCN7*-Related Osteopetrosis. 2007 Feb 12 [updated 2022 Jan 20]. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

Chapter 741

Other Inherited Disorders of Skeletal Development

Julie E. Hoover-Fong and Daniah Albokhari

Advances in understanding have led to the delineation of the genetic basis of disorders that were previously poorly understood. Some of these conditions are now classified into gene families based on their molecular and clinical findings, as outlined in the most recent nosology and classification of genetic skeletal disorders and previous chapters. Additional important skeletal dysplasias that do not fit into one of the previous categories are discussed in this chapter.

ELLIS-VAN CREVELD SYNDROME

The Ellis-van Creveld syndrome, also known as **chondroectodermal dysplasia**, is a skeletal *and* an ectodermal dysplasia. This skeletal dysplasia presents at birth with short limbs, especially the middle and distal segments, accompanied by postaxial polydactyly of the hands and sometimes of the feet (Fig. 741.1). Nail dysplasia and dental anomalies (including neonatal, absent, premature loss of teeth, and upper lip defects) constitute the ectodermal dysplasia. Additional common manifestations include atrial septal defects and other congenital heart defects.

Skeletal radiographs reveal short tubular bones with clubbed ends, especially the proximal tibia and ulna (Fig. 741.2). Carpal bones display extra ossification centers and fusion; cone-shaped epiphyses are evident in the hands. A bony spur is often noted above the medial aspect of the acetabulum.

Ellis-van Creveld syndrome is an autosomal recessive condition that occurs with increased frequency in the Amish and Finnish founder populations than in the general population. Pathogenic variants have been identified in one of two genes, *EVC (EVC1)* or *EVC2 (LIMBIN)*, which map in a head-to-head configuration to chromosome 4p. Disease-causing variants of *EVC2* are detected in the allelic condition **Weyers acrofacial dysostosis**. EVC and EVC2 proteins are thought to influence hedgehog signaling in cilia by constitutively associating in a ringlike pattern in the ciliary transition zone and transducing extracellular signals to the nucleus via hedgehog signaling. Fgf18 may also play a significant role. This disorder is classified under the **ciliopathies** with major skeletal involvement (see Chapter 101.3).

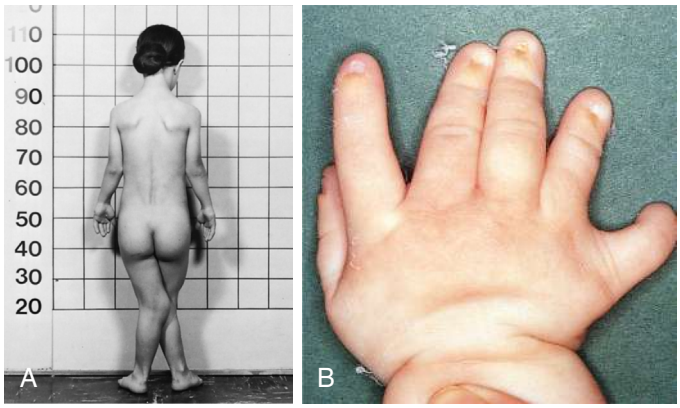

Fig. 741.1 **A,** Ellis-van Creveld syndrome in a young female. Note short stature, joint contractures at the elbows, and marked genu valgum. **B,** Multiple digits (polydactyly) in a different patient with Ellis-van Creveld syndrome. (**A** *from Zipes DP, Libby P, Bonow R, Braunwald E, eds. Braunwald's Heart Disease: a textbook of cardiovascular medicine, 7th ed. Philadelphia: WB Saunders, 2004. Fig 70.6;* **B** *from Beerman LB, Kreutzer J, Allada V. Cardiology. In: Zitelli BJ, McIntire SC, Nowalk AJ, eds. Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th ed. Philadelphia: Elsevier, 2012. Fig 5.6.)*



Fig. 741.2 Radiograph of lower extremities in Ellis-van Creveld syndrome. Tubular bones are short, and proximal fibula is short. Ossification is retarded in lateral tibia epiphyses, causing a knock-knee deformity.

Approximately 30% of patients die of cardiac or respiratory problems during infancy. Life span is otherwise normal; adult heights range from 119-161 cm.

ASPHYXIATING THORACIC DYSTROPHY

See also Chapter 467.3.

Asphyxiating thoracic dystrophy, or **Jeune syndrome**, is an autosomal recessive chondrodysplasia. Newborn infants present with a long, narrow thorax and respiratory insufficiency associated with pulmonary hypoplasia. Neonates often die. Other neonatal manifestations include slightly short limbs and postaxial polydactyly. This condition results from a disturbance of primary cilia, most often from pathogenic variants of the gene encoding cytoplasmic dynein 2 heavy chain 1 *(DYNC2H1)*. This disorder is classified under **ciliopathies** with major skeletal involvement (see Chapter 101.3).

Skeletal radiographs show very short ribs with anterior expansion. Tubular limb bones are short with bulbous ends; cone-shaped epiphyses occur in hand bones. The iliac bones are short and square with a spur above the medial aspect of the acetabulum (Fig. 741.3).

If infants survive the neonatal period, respiratory function usually improves as the rib cage grows. Surgery that produces lateral thoracic expansion improves rib growth and enhances chest wall dimensions. Progressive renal dysfunction often develops during childhood. Intestinal malabsorption and hepatic dysfunction have also been reported.

SHORT-RIB POLYDACTYLY SYNDROMES

These conditions, which share the clinical features of constricted thoracic cage, short ribs, polydactyly, very short extremities, lethality during the newborn period and autosomal recessive inheritance. Pathogenic variants that map to cilia-related genes—*DYNC2H1, IFT80, IFT81, WDR34, WDR60, DYNC2LI1, NEK1, IFT122, WDR19, INTU, TRAF3IP1*—are found in this group of disorders.

CARTILAGE-HAIR HYPOPLASIA-ANAUXETIC SPECTRUM DISORDERS

Cartilage-hair hypoplasia (CHH), also known as **metaphyseal chondrodysplasia–McKusick type,** is part of a spectrum of disorders with metaphyseal involvement that includes metaphyseal dysplasia without hypotrichosis and anauxetic dysplasia. All disorders are characterized by severe disproportionate short stature, which is usually recognized at birth; the short limbs can lead to prenatal detection. They all show autosomal recessive inheritance and are caused by pathogenic variants in *RMRP*, a gene coding for a large untranslated RNA component of an enzyme complex involved in processing mitochondrial RNA. Loss of this gene product interferes with processing of both messenger RNA and ribosomal RNA and correlates with the extent of bone dysplasia, whereas loss of messenger RNA processing correlates with the degree of hair hypoplasia, immunodeficiency, and hematologic abnormality. Molecular testing confirms the diagnosis, and prenatal diagnosis is available if the pathogenic variant is identified either in the patient or the parents.

CHH is recognized during the second year because of growth deficiency affecting the limbs, accompanied by flaring of the lower rib cage, a prominent sternum, and bowing of the legs. The hands and feet are short, and the fingers are very short with extreme ligamentous laxity. The hair is thin, sparse, and light colored; the nails are hypoplastic; and the skin can be hypopigmented.

Radiographs show short tubular bones with flared, irregularly mineralized, and cupped metaphyses (Fig. 741.4). The knees are more affected than are the hips, and the fibula is disproportionately longer than the tibia. The metacarpals and phalanges are short and broad. Spinal radiographs reveal mild platyspondyly.

Nonskeletal manifestations associated with CHH include immunodeficiency (T-cell abnormalities, neutropenia, leukopenia, and susceptibility to varicella zoster virus infections; children also may have complications from smallpox and polio vaccinations), malabsorption, celiac disease, and Hirschsprung disease. Adults are at risk for malignancy, especially non-Hodgkin lymphoma and skin tumors. Adult height ranges from 107-157 cm.

The highest birth prevalence is in the Amish and Finnish populations because of a founder effect. Carrier frequency in the Amish is 1:19 with 1 per 1,300 births affected compared to a carrier frequency of 1:76 and 1 per 23,000 births affected in Finland. The exact prevalence in the general population is not known, but CHH

is relatively rare. However, two allelic conditions, metaphyseal dysplasia without hypotrichosis and anauxetic dysplasia, expand the phenotypic spectrum. Children with a growth disorder and abnormal hair should be evaluated for *RMRP* pathogenic variants.

TRPV4-SPECTRUM DISORDERS

Pathogenic variants in *TRPV4* cause a spectrum of conditions including metatropic dysplasia, spondylometaphyseal dysplasia (SMD), Kozlowski type, brachyolmia, and familial digital arthropathy with brachydactyly. Metatropic dysplasia and SMD, Kozlowski type are expanded on next. **Brachyolmia** is dominated by progressive scoliosis and platyspondyly on x-rays and familial digital arthropathy with brachydactyly, which is characterized by deforming painful osteoarthritis of the interphalangeal, metacarpophalangeal, and metatarsophalangeal joints starting after the first decade of life. The rest of the skeleton is unaffected in this condition. It should also be noted that pathogenic variants in *TRPV4* are also responsible for a large group of neuromuscular disorders including **Charcot-Marie-Tooth disease type 2C**, scapuloperoneal spinal muscular atrophy, and congenital distal spinal muscular atrophy. Though there is considerable overlap of the phenotypes of the conditions within the skeletal group and the neuromuscular group, there are only rare instances currently recognized of individual patients with both features.

METATROPIC DYSPLASIA

Metatropic dysplasia is an autosomal dominant disorder resulting from heterozygous pathogenic variants of transient receptor potential vanilloid family 4 (TRPV4), which encodes a calcium-permeable cation channel. Newborn infants present with a long narrow trunk and short extremities. A tail-like appendage sometimes extends from the base of the spine. Odontoid hypoplasia is common and may be associated with cervical instability. Kyphoscoliosis appears in late infancy and progresses through childhood, often becoming severe enough to compromise cardiopulmonary function. The joints are large and become progressively restricted in mobility, except in the hands. Contractures often develop in the hips and knees during childhood. Although severely affected infants can die at a young age from respiratory failure, patients usually survive, although they can become disabled as adults from the progressive musculoskeletal deformities. Adult heights range from 110-120 cm.

Skeletal radiographs show characteristic changes dominated by severe platyspondyly and short tubular bones with expanded and deformed metaphyses that exhibit a dumbbell appearance (Fig. 741.5). The pelvic bones are hypoplastic and exhibit a halberd appearance because of a small sacrosciatic notch and a notch above the lateral margin of the acetabulum.



Fig. 741.4 Radiograph of lower extremities in cartilage-hair hypoplasia. The tubular bones are short, and the metaphyses are flared and irregular. The fibula is disproportionately long compared with the tibia. The femoral necks are short.



Fig. 741.3 Asphyxiating thoracic dystrophy. Short ribs, long and narrow chest, small pelvis, trident acetabula, no platyspondyly (helps differentiate from thanatophoric dysplasia), cystic renal disease. *(From Campeau P, Schlesinger AE. Skeletal dysplasias. [Updated 2017 Jan 30]. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. Endotext [internet]. South Dartmouth, MA, 2000,* MDText.com, *Inc., Fig 6. Available at:* https://www.ncbi.nlm.nih.gov/books/NBK279130/*)*

SPONDYLOMETAPHYSEAL DYSPLASIA, KOZLOWSKI TYPE

Kozlowski type of spondylometaphyseal dysplasia is an autosomal dominant allelic disorder to metatropic dysplasia caused by *TRPV4* variants.

Kozlowski type of spondylometaphyseal dysplasia manifests in early childhood with mild short stature involving mostly the trunk and a waddling gait. The hands and feet may be short and stubby. Radiographs show flattening of vertebral bodies. The metaphyses of tubular bones are widened and irregularly mineralized, especially at the proximal femur. The pelvic bones manifest mild hypoplasia. Scoliosis can develop during adolescence. The disorder is otherwise uncomplicated, and manifestations are limited to the skeleton. Adults reach heights of 130-150 cm.

DISORDERS INVOLVING FILAMINS

Pathogenic variants of genes encoding filamin A and filamin B proteins have been detected in diverse disorders of skeletal development: filamin A pathogenic variants in otopalatodigital syndromes type 1 and 2, frontometaphyseal dysplasia, Melnick-Needles syndrome and terminal osseous dysplasia with pigmentary defects and filamin B pathogenic variants in Larsen syndrome and perinatal lethal atelosteogenesis types 1 and 3, spondylo-carpal-tarsal dysplasia and Boomerang dysplasia. Filamins functionally connect extracellular to intracellular structural proteins, thereby linking cells to their local microenvironment, which is essential for skeletal development and growth.

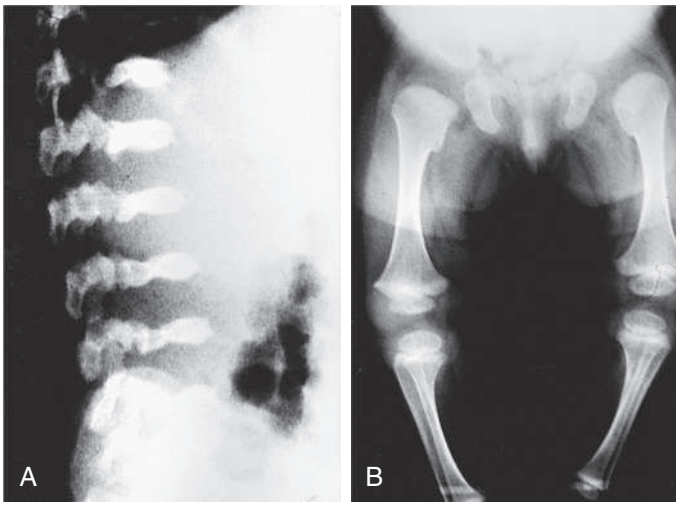

Fig. 741.5 A, Radiograph of the lateral thoracolumbar spine in metatropic dysplasia showing severe platyspondyly. B, Radiograph of lower extremities in metatropic dysplasia showing short tubular bones with widened metaphyses. The femurs have a dumbbell appearance.

JUVENILE OSTEOCHONDROSES

The juvenile osteochondroses are a heterogeneous group of disorders in which regional disturbances in bone growth cause noninflammatory arthropathies. Table 741.1 summarizes the juvenile osteochondroses. Some have localized pain and tenderness (Freiberg disease, Osgood-Schlatter disease [see Chapter 718.4], osteochondritis dissecans [see Chapter 718.3]), whereas others present with painless limitation of joint movement (Legg-Calvé-Perthes disease [see Chapter 719.3], Scheuermann disease [see Chapter 720.4]). Bone growth may be disrupted, leading to deformities. The diagnosis is usually confirmed radiographically, and treatment is symptomatic. The pathogenesis of these disorders is believed to involve ischemic necrosis of primary and secondary ossification centers. Although familial forms have been reported, these disorders usually occur sporadically.

CAFFEY DISEASE (INFANTILE CORTICAL HYPEROSTOSIS)

This is a rare disorder of unknown etiology characterized by cortical hyperostosis with inflammation of the contiguous fascia and muscle. It is often sporadic, but both autosomal dominant and autosomal recessive forms have been reported. Pathogenic variants in *FAM111A* and *TBCE* have been identified in the autosomal dominant and recessive forms, respectively. **Sanjad-Sakati syndrome** (hypoparathyroidism, intellectual disability, dysmorphism) is also caused by pathogenic variants in *TBCE*. Caffey dysplasia is classified in the slender bone dysplasia group.

Prenatal and more often postnatal onsets have been described. Prenatal onset may be mild (autosomal dominant) or severe (autosomal recessive). Severe prenatal disease is characterized by typical bone lesions, polyhydramnios, hydrops fetalis, severe respiratory distress, prematurity, and high mortality. Onset in infancy (younger than 6 months; average: 10 weeks) is most common; manifestations include the sudden onset of irritability, swelling of contiguous soft tissue that precedes the cortical thickening of the underlying bones, fever, and anorexia. The swelling is painful with a woodlike induration but with minimal warmth or redness; suppuration is absent. There are unpredictable remissions and relapses; an episode can last 2 weeks to 3 months. The most common bones involved include the mandible (75%) (Fig. 741.6), the clavicle, and the ulna. If swelling is not prominent or visible, the diagnosis might not be evident.

Laboratory features include elevated erythrocyte sedimentation rate and serum alkaline phosphatase as well as, in some patients, increased serum prostaglandin E levels. There may be

Table 741.1 Juvenile Osteochondroses

EPONYM	AFFECTED REGION	AGE AT PRESENTATION
Legg-Calvé-Perthes disease	Capital femoral epiphysis	3-12 yr
Osgood-Schlatter disease	Tibial tubercle	10-16 yr
Sever disease	Os calcaneus	6-10 yr
Freiberg disease	Head of second metatarsal	10-14 yr
Scheuermann disease	Vertebral bodies	Adolescence
Blount disease	Medial aspect of proximal tibial epiphysis	Infancy or adolescence
Osteochondritis dissecans	Subchondral regions of knee, hip, elbow, and ankle	Adolescence



Fig. 741.6 Facies in infantile cortical hyperostosis. In almost all cases, the changes have appeared before the fifth month of life. Unilateral swelling of the left cheek and left side of the jaw in an infant 12 weeks of age. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby, 2008.)*

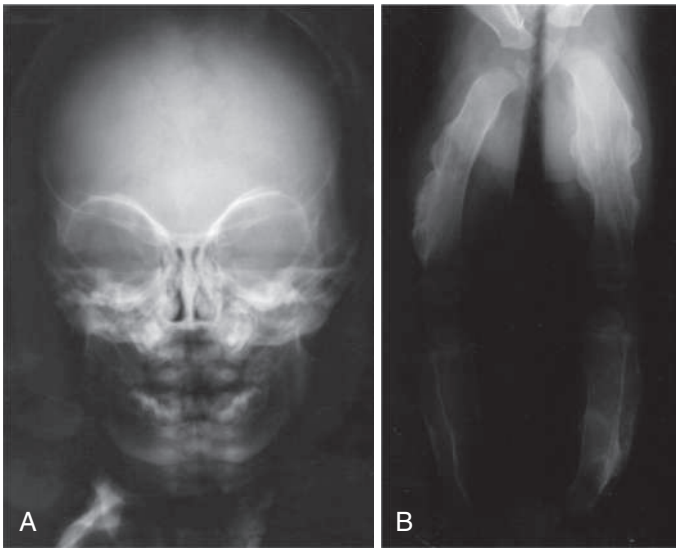

Fig. 741.7 A, Radiograph of a 5-mo-old infant showing hyperostosis of the mandible. B, Radiograph of a 5-mo-old infant showing hyperostosis of both legs. *(From Kamoun-Goldrat A, le Merrer M. Infantile cortical hyperostosis [Caffey disease]: a review. J Oral Maxillofac Surg. 2008;66:2145–2150. Figs. 1 and 2.)*

thrombocytosis and anemia. The radiographic features include soft tissue swelling and calcification and cortical hyperostosis (Fig. 741.7). All bones may be affected except the phalanges or vertebral bodies. The differential diagnosis includes other causes of hyperostosis such as chronic vitamin A intoxication, prolonged prostaglandin E infusion in children with ductal dependent congenital heart disease, primary bone tumors, and scurvy.

Complications are unusual but include pseudoparalysis with limb or scapula involvement, pleural effusions (rib), torticollis (clavicle), mandibular asymmetry, bone fusion (ribs or ulna and radius), and bone angulation deformities (common with severe prenatal onset). Treatment includes indomethacin and prednisone (if there is a poor response to indomethacin).

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Fibrodysplasia ossificans progressiva (FOP) is a rare and severely disabling disorder characterized by progressive extraskeletal heterotopic bone formation in soft connective tissues including muscles, tendons, ligaments, fascia, and aponeuroses. With the exception of deformity of the large toes, infants are normal at birth. Episodes of painful soft tissue swelling with inflammation usually begin in early childhood initially involving the upper back and neck, and later the entire trunk and extremities. Repeated episodes (flare-ups) slowly transform the soft tissues into bands or plates of bone that span joints and progressively limit movement and mobility. Episodes are often triggered by injury, intramuscular injections, and viral infection. Most patients are wheelchair bound by their late teens. The average life span is approximately 40 years, with death usually resulting from complications of thoracic insufficiency.

FOP results from heterozygous activating pathogenic variants of the gene *(ACVR1)* encoding the bone morphogenetic protein (BMP) type I receptor, activin A receptor type I *(ALK2)*. Patients with classic FOP have the same missense *ACVR1* pathogenic variant, which enhances BMP signaling, which, in turn, induces inflammation and aberrant endochondral ossification through mechanisms that are poorly understood. Environmental factors, such as injury, play an important role in triggering these events. *ACVR1* pathogenic variants usually occur sporadically, but autosomal dominant transmission has rarely been observed. FOP is classified in the disorganized development of skeletal components group.

There is currently no definitive treatment for FOP. Supportive care includes avoidance of injury-prone physical activities, intramuscular injections including immunizations, and overstretching of the jaw during dental procedures. Corticosteroids and other anti-inflammatory agents reduce inflammation and pain during flare-ups but are unable to prevent heterotopic bone formation. Studies in FOP animal models suggest that BMP type I kinase inhibitors and retinoic acid receptor γ agonists, which block chondrogenesis—the initial step in endochondral ossification—may be useful therapies in the future. An animal FOP study has indicated that mutant ALK2 responds to activin A, induces canonical BMP signaling, and leads to heterotopic bone formation, providing an additional possible therapeutic target. The retinoic acid receptor γ agonist palovarotene was approved by the US Food and Drug Administration in 2023 for treatment of FOP for females ages 8 years and older and for males ages 10 years and older.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 742

Osteogenesis Imperfecta

Joan C. Marini

Osteoporosis is fragility of the skeletal system and a susceptibility to fractures of the long bones or vertebral compressions from mild or inconsequential trauma (see Chapter 749). **Osteogenesis imperfecta (OI)** (brittle bone disease), the most common genetic cause of osteoporosis, is a generalized disorder of connective tissue. The spectrum of OI is extremely broad, ranging from forms that are lethal in the perinatal period to a mild form in which the diagnosis may be equivocal in an adult (Table 742.1).

ETIOLOGY

Structural or quantitative defects in type I collagen cause the full clinical spectrum of OI (types I-IV). Defects in processing either the N- or C-terminal propeptides of type I collagen cause distinctive bone fragility syndromes. Type I collagen is the primary component of the extracellular matrix of bone and skin. Between 15% and 20% of patients clinically indistinguishable from OI do not have a molecular defect in type I collagen. These cases are typically caused by defects in genes whose protein products interact with type I collagen. One group of patients has overmodified collagen, with similar biochemical findings to those with collagen structural defects and severe or lethal OI bone dysplasia. These cases are caused by recessive null pathogenic variants in any of the three components of the collagen prolyl 3-hydroxylation complex, prolyl 3-hydroxylase 1 (encoded by *LEPRE1*) or its associated protein, CRTAP, or cyclophilin B (CyPB, encoded by *PPIB*). A second set of cases without collagen defects have biochemically normal collagen. Defects in *IFITM5* and *SERPINF1* account for defects in mineralization in types V and VI OI, while pathogenic variants in *SERPINH1*, encoding the collagen chaperone HSP47, and *FKBP10*, encoding the peptidyl-prolyl *cis-trans* isomerase FKBP65, cause types X and XI OI, respectively. Rare pathogenic variants in *BMP1,* the enzyme that processes the C-propeptide of type I collagen, also cause a recessive form of OI (type XIII). The newest set of genes added to the recessive OI causative panel (*SP7*, type XII OI; *TMEM38B*, type XIV OI; *WNT1*, type XV OI; *CREB3L1*, type XVI OI, *SPARC*, type XVII OI, and *MBTPS2*, type XVIII OI) are not only involved in osteoblast differentiation but also affect collagen synthesis and cross linking. There are currently very few individuals with OI whose genetic defect is not in a known causative gene.

EPIDEMIOLOGY

The autosomal dominant forms of OI occur equally in all racial and ethnic groups, whereas recessive forms occur predominantly in ethnic groups with consanguineous marriages or as a founder effect in an isolated population. The West African founder pathogenic variant for type VIII OI has a carrier frequency of 1 in 200-300 among Black individuals. The collective incidence of all types of OI detectable in infancy is approximately 1 in 20,000. There is a similar incidence of the mild form OI type I.

PATHOLOGY

The pathogenic structural collagen variants in OI cause the bones to be globally abnormal. The bone matrix contains abnormal type I collagen fibrils and relatively increased levels of types III and V collagen. Several noncollagenous proteins of bone matrix are also reduced. Bone cells also contribute to OI pathology, with abnormal osteoblast differentiation and increased numbers of active bone resorbing osteoclasts. The hydroxyapatite crystals deposited on this matrix are poorly aligned with the long axis of fibrils, and there is paradoxical hypermineralization of bone.

PATHOGENESIS

Type I collagen is a heterotrimer composed of two α_1(I) chains and one α_2(I) chain. The chains are synthesized as procollagen molecules with short globular propeptide extensions on both ends of the central helical domain. The helical domain is composed of uninterrupted repeats of the sequence Gly-X-Y, where Gly is glycine, X is often proline, and Y is often hydroxyproline. The presence of glycine at every third residue is crucial to helix formation because its small side chain can be accommodated in the interior of the helix. The chains are assembled into trimers at their carboxyl ends, and helix formation then proceeds linearly in a carboxyl to amino direction. Concomitant with helix assembly and formation, helical proline and lysine residues are hydroxylated by prolyl 4-hydroxylase and lysyl hydroxylase 1, and some of the hydroxylysine residues are subsequently glycosylated. After secretion, the propeptides are cleaved in the pericellular space by specific N- and C-terminal propeptidases.

Collagen structural defects are predominantly of two types: 80% are pathogenic missense variants causing substitutions of helical glycine residues or crucial residues in the C-propeptide by other amino acids, and 20% are single exon splicing defects. The clinically mild OI type I has a quantitative defect, with null pathogenic variants in one α_1(I) allele leading to a reduced amount of normal collagen. Deficiency of type I procollagen caused by a C-propeptide removal causes a paradoxical high bone mass form of OI with mild or severe skeletal fragility depending on whether the defect is in the cleavage site or the cleaving peptidase. Impaired removal of the N-propeptide causes an overlap syndrome of Ehlers-Danlos and OI (OI/EDS) with variable skeletal fragility.

Glycine substitutions in the two α chains have distinct genotype-phenotype relationships, but there is also striking phenotype variability caused by independent pathogenic variants at the same site. In general, glycine substitutions in the α_1 chain are more lethal than those in the α_2(I) chain. Two lethal regions in α_1(I) align with major ligand binding regions of the collagen helix.

Classical OI (Sillence types I-IV) is an autosomal dominant disorder, as is type V OI. Some familial recurrences of OI are caused by parental mosaicism for dominant collagen pathogenic variants. Recessive OI accounts for 10–15% of newly diagnosed OI in North America. Three recessive types are caused by null pathogenic variants in the genes coding for the components of the collagen prolyl 3-hydroxylation complex in the endoplasmic reticulum (*LEPRE1*, *CRTAP,* or *PPIB)*. Murine models indicate that it is the absence of the complex components, rather than the absence of the Pro986 modification, that is critical for development of OI. Other recessive types are caused by null pathogenic variants in genes whose products are involved in collagen folding *(SERPINH1, FKBP10)*, bone mineralization *(SERPINF1)*, or defects in osteoblast differentiation and function *(SP7, TMEM38B, WNT1, CREB3L1, SPARC, MBTPS2)*.

CLINICAL MANIFESTATIONS

Classical OI was described with the triad of fragile bones, blue sclerae, and early deafness, although most cases do not have all three features. The Sillence classification divides OI into four types based on clinical and radiographic criteria. Types V and VI were later proposed based on histologic distinctions. Subsequent types VII-XVIII were based on identification of the molecular defect, followed by clinical description.

Osteogenesis Imperfecta Type I (Mild)

OI type I is sufficiently mild that it is often found in large pedigrees. Many type I families have blue sclerae, recurrent fractures in childhood, and presenile (i.e., beginning in early adulthood) hearing loss (30–60%). Both types I and IV are divided into A and B subtypes, depending on the absence (A) or presence (B) of **dentinogenesis imperfecta,** a type of dentin dysplasia resulting in discolored (often blue-gray or amber), translucent teeth that wear down rapidly or break. Other possible connective tissue abnormalities include hyperextensible joints, easy bruising, thin skin, joint laxity, scoliosis, wormian bones, hernia, and mild short stature compared with family members. Fractures result from mild to moderate trauma but decrease after puberty.

Table 742.1 Osteogenesis Imperfecta

DISORDER	INHERITANCE	GENE	PREVIOUS NAMES / NOTATION
Osteogenesis imperfecta, non-deforming (Sillence type 1)	AD	*COL1A1, COL1A2*	OMIM as OI type I
Osteogenesis imperfecta, severe perinatal form (Sillence type 2)	AD	*COL1A1, COL1A2*	OMIM as OI type II
	AR	*CRTAP*	OMIM as OI type VII
	AR	*P3H1*	OMIM as OI type VIII
	AR	*PPIB*	OMIM as OI type IX
Osteogenesis imperfecta, progressively deforming (Sillence type 3)	AD	*COL1A1, COL1A2, IFITM5*	OMIM as OI type III
	AD	*SERPINF1*	In OMIM as OI type VI
	AR	*CRTAP, P3H1*	OMIM as OI type VII
	AR	*PPIB*	OMIM as OI type IX
	AR	*SERPINH1*	OMIM OI as type X
	AR	*FKBP10*	OMIM as OI type XI
	AR	*TMEM38B*	OMIM as OI type XIV
	AR	*BMP1*	OMIM as OI type XIII
	AR	*WNT1*	OMIM as OI type XV Variants may result in AD osteoporosis.
	AR	*CREB3L1*	OMIM as OI type XVI Ehlers-Danlos-like
	AR	*SPARC*	OMIM as OI type XVII
	AR	*TENT5A*	OMIM as OI type XVIII
	XLR	*MBTPS2*	OMIM as OI type XIX
	AR	*MESD*	OMIM as OI type XX
	AR	*KDELR2*	OMIM as OI type XXL
	AR	*CCD134*	OMIM as OI type XXII
Osteogenesis imperfecta, moderate form (Sillence type 4)	AD	*COL1A1, COL1A2, IFITM5*	OMIM as OI type IV
	AR	*WNT1*	OMIM as OI type XV
	AR	*CRTAP*	OMIM as OI type VII
	AD	*PP1B*	OMIM as OI type IX
	AR	*FKBP10*	OMIM as OI type XI
	AR	*SP7*	OMIM as OI type XII
Osteogenesis imperfecta with calcification of interosseous membranes and/or hypertrophic callus (OI type 5)	AD	*IFITM5*	May mimic progressively deforming or moderate OI (Sillence types 3 and 4)
Osteogenesis imperfecta with craniosynostosis (Cole- Carpenter syndrome)	AD	*P4HB*	Craniosynostosis is not well documented.
	AR	*SEC24D*	Most patients do not have craniosynostosis but rather large fontanels.
Osteoporosis – X-linked form	XL	*MBTPS2*	OMIM as OI type XIX
Osteoporosis – dominant form	AD	*WNT1*	OMIM as OI type XV

Data from Unger S, Ferreira CR, Mortier GR, et al: Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet* 2023;191A:1164-1209 (Table 1, Group 26, pp. 1187-1190).

Osteogenesis Imperfecta Type II (Perinatal Lethal)

Infants with OI type II may be stillborn or die in the first years of life. Birthweight and length are small for gestational age. There is extreme fragility of the skeleton and other connective tissues. There are multiple intrauterine fractures of long bones, which have a crumpled appearance on radiographs. There are striking micromelia and bowing of extremities; the legs are held abducted at right angles to the body in the frogleg position. Multiple rib fractures create a beaded appearance, and the small thorax contributes to respiratory insufficiency. The skull is large for body size, with enlarged anterior and posterior fontanels. Sclerae are dark blue-gray. The cerebral cortex has multiple neuronal migration and other defects (agyria, gliosis, periventricular leukomalacia).

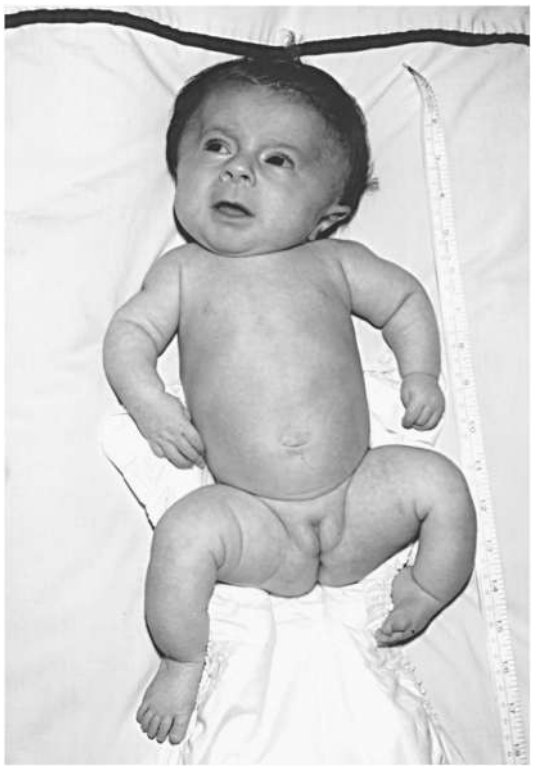

Fig. 742.1 Infant with type III osteogenesis imperfecta displays shortened bowed extremities, thoracic deformity, and relative macrocephaly.

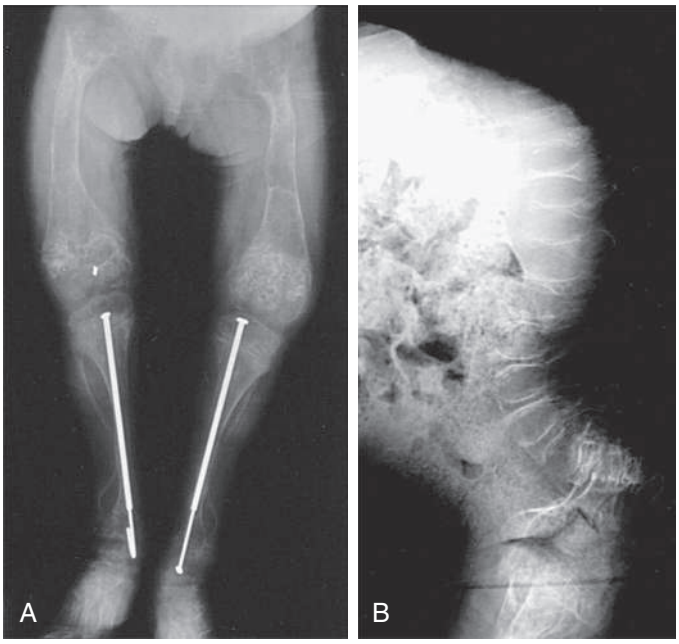

Fig. 742.2 Typical features of type III osteogenesis imperfecta radiographs in a 6-yr-old child. **A,** Lower long bones are osteoporotic, with metaphyseal flaring, "popcorn" formation at growth plates, and placement of intramedullary rods. **B,** Vertebral bodies are compressed and osteoporotic.

Osteogenesis Imperfecta Type III (Progressive Deforming)

OI type III is the most severe nonlethal form of OI and results in significant physical disability. Birthweight and length are often low normal. Fractures usually occur in utero. There is relative macrocephaly and triangular facies (Fig. 742.1). Postnatally, fractures occur from inconsequential trauma and heal with deformity. Disorganization of the bone matrix results in a "popcorn" appearance at the metaphyses (Fig. 742.2). The rib cage has flaring at the base, and pectus deformity is frequent. Virtually all type III patients have scoliosis and vertebral compression. Growth falls below the curve by the first year; all type III patients have extreme short stature. Scleral hue ranges from white to blue. Dentinogenesis imperfecta, hearing loss, and kyphoscoliosis may be present or develop over time.

Osteogenesis Imperfecta Type IV (Moderately Severe)

Patients with OI type IV can present at birth with in utero fractures or bowing of lower long bones. They can also present with recurrent fractures after ambulation and have normal to moderate short stature. Most children have moderate bowing even with infrequent fractures. Children with OI type IV require orthopedic and rehabilitation intervention, but they are usually able to attain community ambulation skills. Fracture rates decrease after puberty. Radiographically, they are osteoporotic and have metaphyseal flaring and vertebral compressions. Scleral hue may be blue or white.

Defects in the Processing of Type I Procollagen Propeptides

Autosomal dominant pathogenic variants in the C-propeptide cleavage site of procollagen or recessive defects in BMP1, the enzyme responsible for its cleavage, cause bone fragility with normal or elevated dual-energy x-ray absorptiometry bone density *z* scores. Individuals with dominant pathogenic variants have normal stature, white sclerae and teeth, and mild to moderate OI. Null pathogenic variants in *BMP1* lead to a more severe skeletal phenotype with short stature, scoliosis, and bone deformity because *BMP1* has other substrates in addition to type I collagen.

Defects in removal of the type I procollagen N-propeptide cause a distinctive combination of Ehlers-Danlos syndrome and OI. Deletion of exon six, containing the cleavage site, causes EDS type VII. Glycine substitutions near the cleavage site impair processing by altering the site configuration, causing hyperextensibility of large and small joints and variable bone fragility.

Osteogenesis Imperfecta Type V (Hyperplastic Callus) and Type VI Hyperosteoidosis (Mineralization Defect)

Types V and VI OI patients clinically have OI similar in skeletal severity to types IV and III, respectively, but they have distinct findings on bone histology. Type V patients also usually have some combination of hyperplastic callus, calcification of the interosseous membrane of the forearm, and/or a radiodense metaphyseal band. They constitute <5% of OI cases. All type V OI patients are heterozygous for the same pathogenic variant in *IFITM5*, which generates a novel start codon for the bone protein BRIL. Ligamentous laxity may be present; blue sclera or dentinogenesis imperfecta are not present. Patients with type VI OI have progressive deforming OI that does not manifest at birth. They have distinctive bone histology with broad osteoid seams and fish-scale lamellation under polarized light, caused by deficiency of pigment epithelium derived factor, encoded by *SERPINF1*. Types V and VI are connected in intracellular osteoblast pathways—*SERPINF1* transcripts are increased in type V OI, while *IFITM5* transcripts are decreased in type VI OI.

Osteogenesis Imperfecta Types VII, VIII, and IX (Autosomal Recessive)

Types VII and VIII patients overlap clinically with types II and III OI but have distinct features including white sclerae, rhizomelia, and small to normal head circumference. Surviving children have severe osteochondrodysplasia with extreme short stature and dual-energy x-ray absorptiometry L1-L2 *z* score in the −6 to −7 range. Type IX OI is very rare; most cases are lethal, but some have moderate skeletal severity without rhizomelia, and white sclerae.

Osteogenesis Imperfecta Types X and XI (Autosomal Recessive)

There have been several reports of severe to lethal type X OI caused by defects affecting the serine-type endopeptidase inhibitor domain of HSP47. This domain is responsible for the HSP47 chaperone function that helps to maintain the folded state of procollagen heterotrimers. HSP47 and FKBP65, the protein responsible for type XI OI, cooperate in collagen synthesis. Type XI OI is a more prevalent recessive form with a moderate to severe skeletal phenotype, including white sclerae and normal teeth. Congenital contractures of large joints may occur with the same pathogenic variants that cause only skeletal fragility, even in sibships. At the opposite end of the spectrum, a deletion of a single tyrosine residue causes Kuskokwim syndrome, a congenital contracture disorder with very mild vertebral findings and osteopenia. Defects in *FKBP10* decrease collagen crosslinking in matrix because FKBP65 is the foldase for lysyl hydroxylase 2, which hydroxylates collagen telopeptide residues important for cross linking.

Defects in Osteoblast Differentiation (Types XIII-XXII OI)

The most recent functional grouping of genes causing recessive OI (types XIII to XXII) affect osteoblast differentiation and are collagen related. *SP7* (type XIII OI) regulates osteoblast differentiation and is critical for bone formation. *TMEM38B* (type XIV OI) defects are clinically indistinguishable from type IV OI. *TMEM38B* encodes the endoplasmic reticulum membrane cation channel TRIC-B, which affects calcium flux from the endoplasmic reticulum to the cytoplasm. Since many enzymes involved in collagen metabolism are calcium dependent, collagen synthesis is globally dysregulated in the absence of TRIC-B, with significant intracellular retention. Collagen posttranslational modification is also impaired, leading to underhydroxylation of the collagen helix. Recessive *WNT1* (type XV OI) defects cause severe progressive deforming OI. Notably, Wnt signaling pathway activation through the Frizzled receptor on the osteoblast surface increases bone mass, and deficiency of Wnt decreases it. SPARC (type XVII OI), also known as osteonectin, is a glycoprotein component of extracellular matrix. Defects in residues important for SPARC binding to collagen were reported in two cases of moderate to severe OI.

The genes *MBTPS2* and *CREB3L1*, causing types XVIII and XVI OI, respectively, encode proteins involved in regulated intramembrane proteolysis (RIP). *MBTPS2* encodes the transmembrane Golgi protein site-2 protease (S2P), that acts in succession with S1P to activate regulatory molecules in times of cell stress. OASIS, encoded by *CREB3L1*, is an RIP substrate.

Interestingly, missense substitutions in S2P in OI patients result in underhydroxylation of the collagen lysine residue important for crosslinking of collagen in matrix, thus impairing bone strength. In OASIS-null mice, collagen transcription has been shown to be impaired.

Defects in *TENT5A, MESD, KDELR2,* and *CCDC134* have been reported in small numbers of individuals with lethal or severe OI skeletal phenotypes. The products of these genes are not known to interact directly with collagen. *TENT5A* encodes FAM46A, a cytoplasmic poly(A) polymerase with an unexpected role in bone mineralization, likely related to its role as a binding partner for SMADs, modulating BMP signaling. *MESD* acts along the Wnt pathway, serving as an endoplastic reticulum chaperone for the low-density lipoprotein receptors LRP5 and LRP6. Oligodontia and intellectual disability occur in some patients. Bone histology shows enlarged osteocytes and irregular matrix mineralization.

Pathogenic variants in *KDELR2* cause neurodevelopmental and severe skeletal defects. Pathogenic variants in *CCDC134* add to the skeletal effects by impacting the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway. Expression of type I collagen is reduced, as is osteoblast in vitro mineralization, but histomorphometry is atypical for OI.

LABORATORY FINDINGS

DNA sequencing is the first diagnostic laboratory test, and several Clinical Laboratory Improvement Amendments (CLIA)-certified sequencing labs offer panels to test for dominant and recessive OI. Pathogenic variant identification is useful to determine the type with certainty and to facilitate family screening and prenatal diagnosis. It is also possible to screen for type VI OI by the determination of serum pigment epithelium-derived factor level, which is severely reduced in this type.

If dermal fibroblasts are obtained, they can be useful for determining the level of transcripts of the candidate gene and for collagen biochemical testing, which is positive for overmodification in most cases of types I-IV and IX OI, and in all cases of VII/VIII OI, and for undermodification in type XIV. In OI type I, the reduced amount of type I collagen results in an increase in the ratio of type III to type I collagen on gel electrophoresis.

Severe OI can be detected prenatally by level II ultrasonography as early as 16 weeks of gestation. OI and thanatophoric dysplasia may be confused. Fetal ultrasonography might not detect OI type IV and rarely detects OI type I. For recurrent cases, chorionic villus biopsy can be used for biochemical or molecular studies. Amniocytes produce false-positive biochemical studies but can be used for molecular studies in appropriate cases.

In the neonatal period, the normal to elevated alkaline phosphatase levels present in OI distinguish it from hypophosphatasia. During the school-age period, children with type VI OI have notably elevated serum alkaline phosphatase.

COMPLICATIONS

The morbidity and mortality of OI are cardiopulmonary. Recurrent pneumonias and declining pulmonary function occur in childhood, and cor pulmonale is seen in adults.

Neurologic complications include basilar invagination, brainstem compression, hydrocephalus, and syringohydromyelia. Many children with OI types III and IV have basilar invagination, but brainstem compression is uncommon. Basilar invagination is best detected with spiral CT of the craniocervical junction (Fig. 742.3).

TREATMENT

There is no cure for OI. For severe nonlethal OI, active physical rehabilitation in the early years allows children to attain a higher functional level than orthopedic management alone. Children with OI type I and

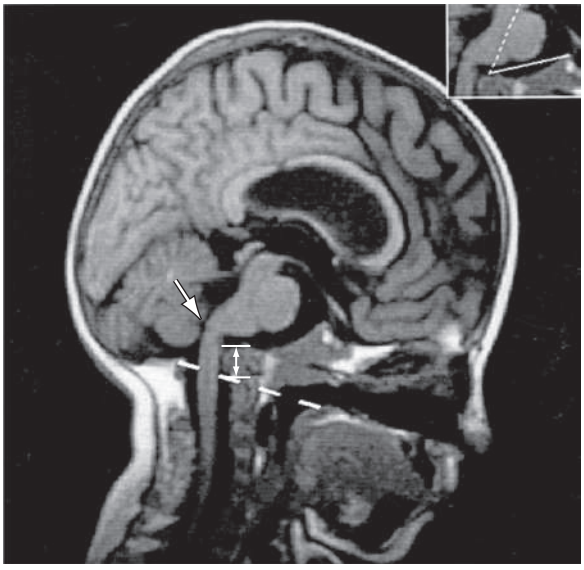

Fig. 742.3 Typical feature of basilar invagination shown in the sagittal MRI of an asymptomatic child with type III osteogenesis imperfecta. There is invagination of the odontoid above the Chamberlain line, causing compression and kinking at the pontomedullary junction *(arrow)*.

some with type IV are spontaneous ambulators. Children with types III, IV, V, VI, and XI OI benefit from gait aids and a program of swimming and conditioning. Severely affected patients require a wheelchair for community mobility but can acquire transfer and self-care skills. Teens with OI can require psychologic support with body image issues. Growth hormone improves bone histology in growth-responsive children (usually types I and IV).

Orthopedic management of OI is aimed at fracture management and correction of deformity to enable function. Fractures should be promptly splinted or cast; OI fractures heal well, and cast removal should be aimed at minimizing immobilization osteoporosis. Correction of long-bone deformity requires an osteotomy procedure and placement of an intramedullary rod.

A several-year course of treatment of children with OI with bisphosphonates (IV pamidronate or oral olpadronate or risedronate) confers some benefits. Bisphosphonates decrease bone resorption by osteoclasts; OI patients have increased bone volume that still contains the defective collagen. Bisphosphonates are more beneficial for vertebrae (trabecular bone) than long bones (cortical bone). Treatment for 1-2 years results in increased L1-L4 dual-energy x-ray absorptiometry and, more importantly, improved vertebral compressions and area. However, follow-up of bisphosphonate-treated children has shown that the incidence of scoliosis is unchanged even in children treated early, although there was a modest delay in progression in type III OI. The relative risk of long-bone fractures is modestly decreased by several years of bisphosphonates. However, the material properties of long bones are weakened by prolonged treatment and nonunion after osteotomy is increased. There is no effect of bisphosphonates on mobility scores, muscle strength, or bone pain. Limiting treatment duration to 2-3 years in mid-childhood can maximize the benefits and minimize the detriment to cortical material properties. Benefits appear to persist several years after the treatment interval, and alternation of treatment intervals and drug holidays may be beneficial. Side effects include abnormal long-bone remodeling, increased incidence of fracture nonunion, and osteopetrotic-like brittleness to bone.

Antibodies to sclerostin and TGF-β stimulate osteoblasts to produce bone matrix. They have shown promise in murine models for OI and are currently in trials for children with OI. TGF-beta signaling may be a pathogenic mechanism in OI. Fresolimumab, a TGF-beta neutralizing antibody, treatment in adults with OI type IV demonstrated increases in lumbar spine bone mineral density.

PROGNOSIS

OI is a chronic condition that may limit both life span and functional level. Infants with OI type II usually die within months to 1 year of life. An occasional child with radiographic type II and extreme growth deficiency survives to the teen years. Persons with OI type III have a reduced life span with clusters of mortality from pulmonary causes in early childhood, the teen years, and the 40s. OI types I, IV, and V OI are compatible with a full life span. The oldest reported individuals with type VIII are in their third decade, and some with type XI are in their fourth decade. The long-term prognosis for most recessive types is still emerging, and many adults with OI have not had molecular testing.

Individuals with OI type III are usually wheelchair dependent. With aggressive rehabilitation, they can attain transfer skills and household ambulation. OI type IV children usually attain community ambulation skills either independently or with gait aids.

GENETIC COUNSELING

For autosomal dominant OI, the risk of an affected individual passing the gene to the individual's offspring is 50%. An affected child usually has about the same severity of OI as the parent; however, there is variability of expression, and the child's condition can be either more or less severe than that of the parent. The empirical recurrence risk to an apparently unaffected couple of having a second child with OI is 5–7%; this is the statistical chance that one parent has germline mosaicism. The collagen pathogenic variant in the mosaic parent is present in some germ cells and may be present in somatic tissues. If a parent is a mosaic carrier, the risk of recurrence may be as high as 50%.

For recessive OI, the recurrence risk is 25% per pregnancy. No known individual with severe nonlethal recessive OI has had a child. For X-linked type XVIII OI, the risk to male offspring of carrier women is generally 50%.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 4

Connective Tissue Disorders

Chapter 743

Marfan Syndrome

Jefferson J. Doyle and Harry C. Dietz III

Marfan syndrome (MFS) is an inherited systemic, connective tissue disorder caused by pathogenic variants in the *FBN1* gene encoding the extracellular matrix (ECM) protein fibrillin-1. It is primarily associated with skeletal, cardiovascular, and ocular pathology. The diagnosis is based on clinical findings, some of which are age dependent.

EPIDEMIOLOGY

The incidence is estimated at 1 in 10,000 live births, and approximately 25% of cases are sporadic. The disorder shows autosomal dominant inheritance, with high penetrance but variable expression. Both interfamilial and intrafamilial clinical variation are common. There is no racial or gender preference.

PATHOGENESIS

MFS is associated with abnormal production, matrix deposition, and/or stability of fibrillin-1, a 350-kd ECM protein that is the major constituent of microfibrils, with prominent disruption of microfibrils and elastic fibers in diseased tissues. The fibrillin-1 *(FBN1)* gene is composed of 65 exons. Linkage analysis has suggested an absence of locus heterogeneity, and the involvement of *FBN1* is demonstrated in >90% of cases, with more than 1,000 disease-causing pathogenic variants identified to date (the majority of which are pathogenic missense variants unique to a given family). With the exception of early-onset and severe presentations of the disease associated with pathogenic variants in exons 26-27 and 31-32, no clear genotype-phenotype correlation has been identified. Given that there is considerable intrafamilial variability, genetic, epigenetic, environmental, or other unidentified factors may influence expression of the disease.

The transforming growth factor beta (TGF-β) family of cytokines influences a diverse repertoire of cellular processes, including cell proliferation, migration, differentiation, survival, and synthetic activity. The TGF-β ligands (TGF-β1, TGF-β2, or TGF-β3) are synthesized as inactive precursor complexes and sequestered by ECM proteins, including fibrillin-1. Mice heterozygous for a pathogenic variant in the fibrillin-1 gene, typical of those that cause MFS in humans, display many of the classic features of MFS, including aortic root aneurysm, which associates with a tissue signature for increased TGF-β signaling, suggesting that pathogenic variants in fibrillin-1 lead to increased TGF-β activation and signaling. Furthermore, pharmacologic antagonism

of TGF-β signaling initiated after the first few weeks of life ameliorates aortic aneurysm in mouse models of MFS, demonstrating that high TGF-β signaling is a cause rather than a consequence of disease progression.

Increased TGF-β signaling has been observed in other tissues in MFS mice, including the developing lung, mitral valve, and skeletal muscle. Treatment of these mice with agents that antagonize TGF-β attenuates or prevents pulmonary emphysema, myxomatous degeneration of the mitral valve, and skeletal muscle myopathy. The prominent role of TGF-β dysregulation in the pathogenesis of MFS was further validated by the discovery and characterization of another related aortic aneurysm syndrome, **Loeys-Dietz syndrome (LDS)**, in which patients have pathogenic variants in the genes encoding positive effectors of TGF-β signaling, including the ligands TGF-β2 or TGF-β3, either subunit of the TGF-β receptor (TβRI or TβRII) or the intracellular signaling intermediates SMAD2 or SMAD3. Patients with LDS share many overlapping clinical features with MFS (see the section on "Differential Diagnosis"). This is further supported by data showing that **Shprintzen-Goldberg syndrome (SGS)**, which shows phenotypic overlap with both MFS and LDS, is caused by pathogenic variants in *SKI*, a known repressor of the TGF-β transcriptional response.

CLINICAL MANIFESTATIONS

MFS is a multisystem disorder, with cardinal manifestations in the skeletal, cardiovascular, and ocular systems.

Skeletal System

Overgrowth of the long bones **(dolichostenomelia)** is often the most obvious manifestation of MFS and may produce a reduced upper segment–to–lower segment ratio (UL/LS) or an arm span–to–height ratio >1.05 times. Abnormal ratios are US/LS <1 for age 0-5 years, US/LS <0.95 for 6-7 years, US/LS <0.9 for 8-9 years, and US/LS <0.85 above age 10 years. Anterior chest deformity is likely the result of excessive rib growth, pushing the sternum either outward **(pectus carinatum)** or inward **(pectus excavatum)**. Abnormal curvatures of the spine (most commonly thoracolumbar scoliosis) may also partly result from increased vertebral growth. Other skeletal features include an inward bulging of the acetabulum into the pelvic cavity (protrusio acetabuli), flat feet (pes planus), and joint hypermobility (Fig. 743.1) or joint contractures. Long and slender fingers in relation to the palm of the hand **(arachnodactyly)** are generally a subjective finding. The combination of arachnodactyly and hypermobile joints is examined by the Walker-Murdoch or wrist sign, which is positive if there is full overlap of the distal phalanges of the thumb and fifth finger when wrapped around the contralateral wrist (see Fig. 743.1), and the Steinberg or thumb sign, which is present when the distal phalanx of the thumb fully extends beyond the ulnar border of the hand when folded across the palm (see Fig. 743.1). Contracture of the fingers **(camptodactyly)** and elbows is commonly observed. A selection of craniofacial manifestations may be present, including a long narrow skull (dolichocephaly), deeply set eyes (enophthalmos), recessed lower mandible (retrognathia) or small chin (micrognathia), flattening of the midface **(malar hypoplasia)**, a high-arching palate, and downward-slanting palpebral fissures (Fig. 743.2).

Cardiovascular System

Thickening of the atrioventricular valves is common and often associated with valvular prolapse. Variable degrees of regurgitation may be present. In children with early-onset and severe MFS, insufficiency of the mitral valve can lead to heart failure, pulmonary hypertension, and death in infancy. This manifestation is the leading cause of morbidity and mortality in young children with the disorder. Supraventricular arrhythmias may be seen in association with mitral valve dysfunction. Ventricular dysrhythmias have also been described in children with MFS, and there is an increased prevalence of prolonged QT interval. Dilated cardiomyopathy occurs with increased prevalence in patients with MFS, most often attributed to volume overload imposed by valve regurgitation. Aortic valve dysfunction is generally a late occurrence and attributed to stretching of the aortic annulus by an expanding aortic root aneurysm.

Aortic aneurysm, **dissection**, **and rupture**, principally at the level of the sinuses of Valsalva (also known as the aortic root), remain the most life-threatening manifestations of MFS, prompting lifelong monitoring by echocardiography or other imaging modalities. In severe cases, the aneurysm may be present in utero, but in mild examples it may be absent or never exceed dimensions that require clinical intervention. Aortic dimensions must be interpreted in comparison to age-dependent nomograms. The most important risk factor for aortic dissection is the maximal aortic root size and a positive family history. The characteristic histologic findings from aortas of patients with MFS include cystic medial necrosis of the tunica media and disruption of

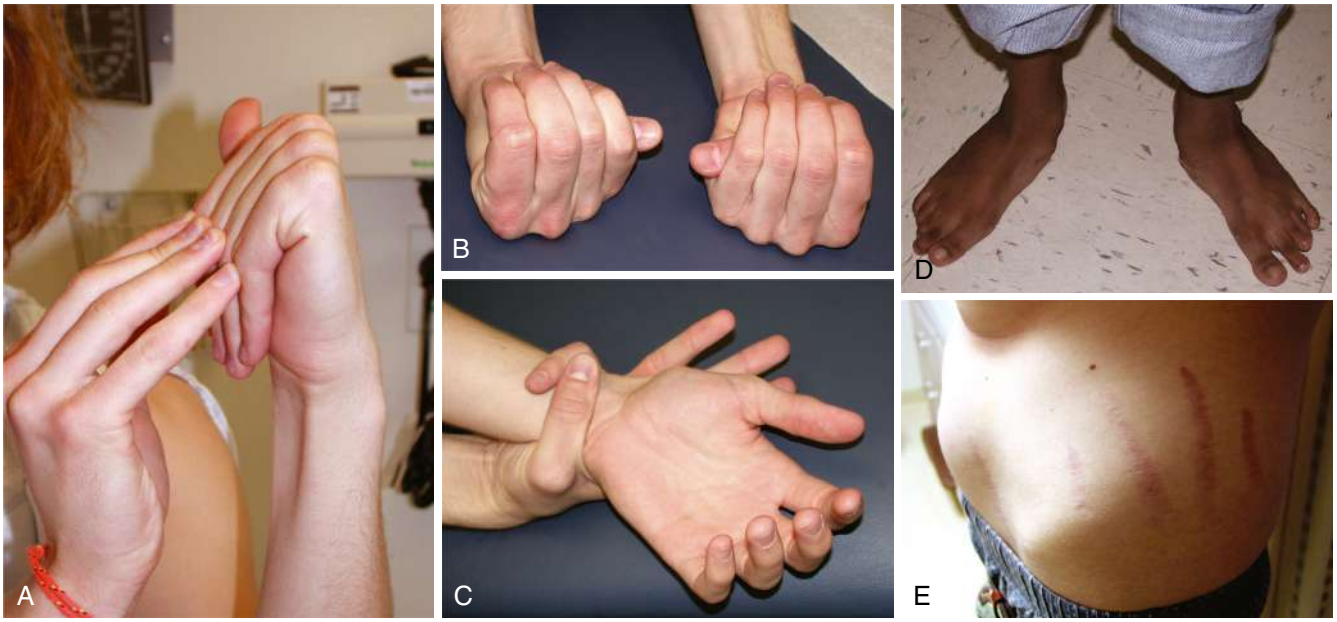

Fig. 743.1 Marfan syndrome. Note the joint laxity (A), Steinberg thumb sign (B), ability to join thumb and fifth finger around the wrist (Walker-Murdoch sign) (C), pes planus (D), and striae over hips and back (E). *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier, 2022; Fig. 2, p. 664.)*



Fig. 743.2 Marfan syndrome. Note the long slim limbs, pectus excavatum, narrow face, and reduced elbow extension. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier, 2022: Fig. 1A, p. 662.)*

elastic lamellae. Cystic medial necrosis describes the focal apoptosis and disappearance of vascular smooth muscle cells and elastic fibers from the tunica media of the aortic wall, and subsequent deposition of mucin-like material in the cystic space. These changes produce a thicker, less distensible and stiffer aorta, which is more prone to aortic dissection. Most patients experiencing acute aortic dissection present with classic symptoms, including sudden-onset, severe, tearing chest pain, often radiating into the back. The dissection typically starts at the aortic root and may remain confined to the ascending aorta (type II) or continue into the descending aorta (type I). Acute-onset heart failure may occur if aortic valve function is compromised, and patients may suffer cerebrovascular injury, depending on the involvement of the carotid arteries. Involvement of the coronary arteries may herald sudden cardiac death, secondary to myocardial infarction or rupture into the pericardial sac with subsequent pericardial tamponade. Chronic aortic dissection usually occurs more insidiously, often without chest pain. Dilatation of the main pulmonary artery is common but does not typically cause any clinical sequelae. Enlargement of the descending thoracic or abdominal aorta can also occur, although relatively rarely.

Ocular System

Dislocation of the ocular lens **(ectopia lentis, EL)** occurs in around 60–70% of patients, although it is not unique to the disorder. Other ocular manifestations include early and severe myopia, thin and flat cornea, increased axial length of the globe, and iris dilator muscle hypoplasia, which results in poor dilation (miosis). Patients are also predisposed to retinal detachment, early cataracts, glaucoma, strabismus, and amblyopia.

Table 743.1 Diagnostic Criteria for Marfan Syndrome

IN THE ABSENCE OF A FAMILY HISTORY OF MFS, A DIAGNOSIS CAN BE ESTABLISHED IN FOUR DISTINCT SCENARIOS:
1. Aortic root *z* score ≥2 AND ectopia lentis*
2. Aortic root *z* score ≥2 AND a bona fide *FBN1* pathogenic variant (see Table 743.2)
3. Aortic root *z* score ≥2 AND a systemic score ≥7* (see Table 743.3)
4. Ectopia lentis AND a bona fide *FBN1* pathogenic variant known to cause aortic disease
IN THE PRESENCE OF A FAMILY HISTORY OF MFS, A DIAGNOSIS CAN BE ESTABLISHED IN THE PRESENCE OF:
1. Ectopia lentis
2. A systemic score ≥7*
3. Aortic root *z* score ≥2 if older than 20 years or ≥3 if younger than 20 years*
IN THE ABSENCE OF A FAMILY HISTORY OF MFS, ALTERNATIVE DIAGNOSES INCLUDE:
1. Ectopia lentis ± systemic score AND *FBN1* pathogenic variant not known to associate with aortic aneurysm or no *FBN1* pathogenic variant = Ectopia lentis syndrome
2. Aortic root *z* score <2 AND a systemic score ≥5 (with at least one skeletal feature) without ectopia lentis = MASS phenotype
3. Mitral valve prolapse AND aortic root *z* score <2 AND a systemic score <5 without ectopia lentis = Mitral valve prolapse syndrome

*Denotes caveat that features suggestive of an alternative diagnosis must be excluded and appropriate alternative molecular testing should be performed. Other syndromes include Shprintzen-Goldberg, Loeys-Dietz, or vascular Ehlers Danlos (see Table 743.4 for genes).

Other Systems

There is an increased incidence of pulmonary disease in MFS; progressive anterior chest deformity or thoracic scoliosis may contribute to a restrictive pattern of lung disease. Furthermore, a widening of the distal airspaces predisposes patients to spontaneous pneumothorax, which occurs in up to 15% of patients. Assessment of pulmonary volumes and function should account for long-bone overgrowth affecting the lower extremities, which can lead to a reduction in the normalized forced vital capacity and total lung capacity. If normalized to thoracic size or sitting height, pulmonary function testing is often normal in patients with the disorder.

MFS patients typically have normal skin texture and elasticity. The most common skin finding is stretch marks—pinkish, scarlike lesions that later become white **(striae atrophicae)**, which occur in about one third of patients (Fig. 743.1). These may occur in the absence of obesity, rapid gain in muscle mass, or pregnancy, and at sites not associated with increased skin distention (i.e., the anterior shoulder or lower back). Another common manifestation is congenital or acquired inguinal hernia. There is also an increased risk of surgical and recurrent hernias in the Marfan population.

Widening of the dural sac or root sleeves (dural ectasia) is present in 63–92% of MFS patients. Although dural ectasia can result in lumbar back pain, it is often asymptomatic and should be assessed by lumbosacral imaging with CT or MRI.

DIAGNOSIS

Given the complexity of the clinical examination in MFS and the relevant differential diagnoses, evaluation should be coordinated by a professional with extensive experience, such as a geneticist, cardiologist, or ophthalmologist. The diagnosis is based on a defined set of clinical criteria drawn up by an international panel of experts (the revised Ghent nosology for the MFS; Table 743.1).

In the absence of a conclusive family history of MFS, the diagnosis can be established in four distinct scenarios:

1. The presence of either aortic root dilatation when standardized to age and body size (an aortic root *z* score ≥2) or aortic dissection combined with ectopia lentis allows for the unequivocal diagnosis of MFS, irrespective of the presence or absence of any systemic features (see Table 743.1), except when these are indicative of an alternative diagnosis.

Table 743.2 Criteria for Causal *FBN1* Pathogenic Variant

- Pathogenic variant previously shown to segregate in a Marfan family
- Any one of the following de novo pathogenic variants (with proven parentage and absence of disease in parents):
  - Nonsense pathogenic variant
  - In-frame and out-of-frame deletion/insertion
  - Splice site pathogenic variants affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
  - Missense pathogenic variant affecting/creating cysteine residues
  - Missense pathogenic variant affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with *m* and *n* representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
  - Other missense pathogenic variants: segregation in family if possible AND absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes
  - Linkage of haplotype for $n \geq 6$ meioses to the *FBN1* locus

From Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet*. 2010;47:476–485.

Table 743.3 Scoring of Systemic Features in Points

- Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hind foot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, midface hypoplasia, retrognathia)
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1

Maximum total: 20 points; score ≥7 indicates systemic involvement.
US/LS, Upper segment/lower segment ratio.

2. The presence of aortic root dilatation (*z* score ≥2) or aortic dissection and the identification of a bona fide *FBN1* pathogenic variant (Table 743.2) are sufficient to establish the diagnosis even if ectopia lentis is absent.
3. When aortic root dilatation (an aortic root *z* score ≥2) or aortic dissection is present, but ectopia lentis is absent and the *FBN1* status is either unknown or negative, the diagnosis may be confirmed by the presence of sufficient systemic findings (a systemic score ≥7 points; Table 743.3). However, features suggestive of an alternative diagnosis must be excluded, and the appropriate alternative molecular testing should be performed.
4. In the presence of ectopia lentis, but absence of aortic root dilatation or aortic dissection, an *FBN1* pathogenic variant, which has previously been associated with aortic disease, is required before the diagnosis can be made. If the *FBN1* pathogenic variant is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as "isolated ectopia lentis syndrome" (see the section on "Differential Diagnosis").

Despite these diagnostic criteria, on occasion sporadic cases in individuals <20 years old may not fit in one of the four proposed scenarios detailed above. If insufficient systemic features (systemic score <7) and/or borderline aortic root measurements (*z* score <3) are present without documented evidence of a bona fide *FBN1* pathogenic variant, the term "nonspecific connective tissue disorder" is recommended. In those instances in which an *FBN1* pathogenic variant is identified, the term *potential MFS* should be used instead.

In an individual with a positive family history of MFS (in which a family member has been independently diagnosed using the previously described criteria), the diagnosis can be established in the presence of:

1. Ectopia lentis
2. A systemic score ≥7 points (see Table 743.3)
3. Aortic root dilatation with *z* score ≥2 in adults (≥20 years old) or *z* score ≥3 in individuals <20 years old

In the case of scenarios 2 and 3, previously, features suggestive of an alternative diagnosis must again be excluded and appropriate alternative molecular testing should be performed.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of MFS includes disorders with aortic aneurysm (LDS, familial thoracic aortic aneurysm syndrome, and SGS), ectopia lentis (ectopia lentis syndrome, Weil-Marchesani syndrome, and homocystinuria), or systemic manifestations of MFS (congenital contractural arachnodactyly [CCA] and mitral valve, aorta, skin, skeletal [MASS] phenotype); Table 743.4).

Aortic Aneurysm Syndromes

LDS is a systemic connective tissue disorder characterized by the triad of arterial tortuosity and aggressive aneurysm disease, hypertelorism, and bifid uvula or cleft palate, as well as many of the craniofacial and skeletal features found in MFS. Distinction between MFS and LDS is important because aneurysms tend to dissect at younger ages and smaller dimensions in LDS patients, necessitating more aggressive management. LDS was originally classified into type 1 or type 2, depending on whether the pathogenic variant is present in the *TGFBR1* or *TGFBR2* gene, which encode the type 1 or type 2 TGF-β receptor subunits, respectively. LDS type 3 is caused by heterozygous pathogenic variants in the gene encoding the TGF-β–dependent intracellular signaling molecule SMAD3. LDS type 4 is caused by heterozygous pathogenic variants in the extracellular TGF-β receptor ligand TGF-β2, whereas LDS type 5 is caused by heterozygous pathogenic variants in the extracellular TGF-β receptor ligand TGF-β3. LDS type 6 is caused by heterozygous pathogenic variants in the gene encoding the TGF-β–dependent intracellular signaling molecule SMAD2. As a general rule, the severity of disease associated with the different forms of LDS can be summarized: LDS1 = LDS2 > LDS3 > LDS4 = LDS5 > LDS6. There are exceptions to this rule, mandating careful monitoring of all patients with LDS. Notably, there can be wide clinical variation within each subtype, including between family members harboring the identical pathogenic variant.

Like MFS, **familial thoracic aortic aneurysm syndrome** segregates as an autosomal dominant trait characterized by aortic root aneurysm and dissection. However, other systemic manifestations of MFS are typically absent, and the disorder has reduced penetrance. Disease-causing heterozygous pathogenic variants have been identified in several genes with roles in the vascular smooth muscle contractile apparatus, including *MYH11*, *ACTA2*, and *MYLK*, which encode smooth muscle myosin heavy chain 11, vascular smooth muscle α-actin, and myosin light chain kinase. However, these genes account for only a fraction of cases of *nonsyndromic* familial thoracic aortic aneurysm. In most cases, the management principles that have been generated for MFS have proved effective for this form of familial aortic aneurysm.

SGS is a systemic connective tissue disorder that includes virtually all the craniofacial, skeletal, skin, and cardiovascular manifestations of MFS and LDS, with the additional findings of developmental delay and severe skeletal muscle hypotonia. Most cases are caused by heterozygous pathogenic variants in the *SKI* gene, which encodes an intracellular repressor of TGF-β signaling. Vascular involvement tends to be less prevalent and less severe when compared with MFS or LDS.

Table 743.4 Differential Diagnosis of Marfan Syndrome

DIFFERENTIAL DIAGNOSIS (GENES)	CARDIAC FEATURES	VASCULAR FEATURES	SYSTEMIC FEATURES
AORTIC ANEURYSM SYNDROMES			
Loeys-Dietz syndromes (types I-V) (OMIM: 609192) *TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3*	• Patent ductus arteriosus • Atrial septal defect • Bicuspid aortic valve	• Aortic root aneurysm • Arterial tortuosity • Widespread aneurysms • Vascular dissection at relatively young ages and small aortic dimensions	• Hypertelorism • Cleft palate • Broad or bifid uvula • Craniosynostosis • Midface hypoplasia • Blue sclerae • Arachnodactyly • Pectus deformity • Scoliosis • Joint hypermobility • Pes planus • Rarely easy bruising • Dystrophic scars • Translucent skin • Rarely developmental delay
Familial thoracic aortic aneurysm (OMIM: 132900) *TGFBR2, ACTA2,* others	• Generally none • Rare forms with patent ductus arteriosus	• Aortic root aneurysm • Ascending aortic aneurysm	• Generally none • Rarely livedo reticularis and iris flocculi
Shprintzen-Goldberg syndrome (OMIM: 182212) *SKI,* unknown others	None	Aortic root aneurysm	• Hypertelorism • Craniosynostosis • Arched palate • Arachnodactyly • Pectus deformity • Scoliosis • Joint hypermobility • Developmental delay
Bicuspid aortic valve with aortic aneurysm (OMIM: 109730) *ACTA2*	Bicuspid aortic valve	• Aortic root aneurysm • Ascending aortic aneurysm	
Ehlers-Danlos syndrome, type IV (OMIM: 130050) *COL3A1*	Mitral valve prolapse	• Aneurysm and rupture of any medium to large muscular artery • No predisposition for aortic root enlargement	• Joint hypermobility • Atrophic scars • Translucent skin • Easy bruising • Hernias • Rupture of hollow organs
ECTOPIA LENTIS SYNDROMES			
Familial ectopia lentis (OMIM: 129600) *FBN1, LTBP2, ADAMTSL4*	None	None	Nonspecific skeletal features
Homocystinuria (OMIM: 236200) *CBS*	Mitral valve prolapse	Intravascular thrombosis	• Tall stature • Ectopia lentis • Long-bone overgrowth • Developmental delay
SYNDROMES WITH SYSTEMIC MANIFESTATIONS OF MFS			
MASS (mitral valve, aorta, skeleton, skin) phenotype (OMIM: 604308) *FBN1*	Mitral valve prolapse	Borderline or nonprogressive	• Nonspecific skin and skeletal findings • Myopia

Ectopia Lentis Syndromes

Both **ectopia lentis syndrome** and **Weill-Marchesani syndrome (WMS)** may also be caused by heterozygous pathogenic variants in *FBN1*. Compound heterozygous or homozygous pathogenic variants at a second locus, *ADAMTSL4* cause ectopia lentis syndrome associated with slightly younger age at diagnosis. Interestingly, some *FBN1* pathogenic variants can be associated with classic MFS, ectopia lentis syndrome, and ectopia lentis combined with skin, but not cardiovascular, manifestations of MFS, suggesting that these presentations are part of a spectrum of clinical features of the same disease, and highlighting the potential contribution of genetic modifiers of disease.

WMS is a systemic connective tissue disorder characterized by skin, skeletal, and ocular abnormalities, including microspherophakia, ectopia lentis, and myopia. Features inconsistent with the diagnosis of MFS include short stature and brachydactyly. In addition to *FBN1* pathogenic variants (type 2), the syndrome may be caused by biallelic pathogenic variants in *ADAMTS10* (type 1) or in *LTBP2* (type 3), which encode ADAM metallopeptidase with thrombospondin type 1 motif 10 and latent TGF-β binding protein 2, respectively.

Homocystinuria is a metabolic disorder caused by homozygous or compound heterozygous pathogenic variants in the gene encoding cystathionine β-synthase, which leads to increases in both homocysteine and methionine. The clinical features of untreated homocystinuria include ectopia lentis and skeletal abnormalities resembling MFS. However, in contrast to MFS, affected persons often suffer from developmental delay, a predisposition to

thromboembolic events, and a high incidence of coronary artery disease. Patients with homocystinuria are not at increased risk for aortic aneurysm.

Syndromes with Systemic Manifestations of MFS

Congenital contractural arachnodactyly (CCA) is a connective tissue disorder caused by heterozygous pathogenic variants in the gene encoding fibrillin-2 *(FBN2)*. There are a number of clinical features overlapping with MFS, including dolichostenomelia, anterior chest deformity, scoliosis, joint contractures, and arachnodactyly, as well as some craniofacial malformations, including highly arched palate and retrognathia. In addition, both may suffer from severe cardiovascular abnormalities leading to premature death, but the specific cardiac anomalies are different; valvular insufficiency and aortic root dilation are common with MFS, whereas congenital heart defects are more common in CCA. Patients with CCA also suffer from crumpled auricular helices (a hallmark of this condition).

Many patients referred for possible MFS are found to have evidence of a systemic connective tissue disorder, including long limbs, deformity of the thoracic cage, striae atrophicae, mitral valve prolapse, and borderline but nonprogressive dilatation of the aortic root, but do not meet diagnostic criteria for MFS. This constellation of features is referred to by the acronym **MASS phenotype**, emphasizing the *m*itral, *a*ortic, *s*kin, and *s*keletal manifestations. The MASS phenotype can segregate in large pedigrees and remain stable over time. The diagnosis is particularly challenging in the context of a young, sporadic patient in whom careful follow-up is needed to distinguish MASS phenotype from early MFS. Familial mitral valve prolapse syndrome can also be caused by pathogenic variants in the gene encoding fibrillin-1 and include subdiagnostic systemic manifestations.

LABORATORY FINDINGS

Laboratory studies should document a negative urinary cyanide nitroprusside test or specific amino acid studies to exclude cystathionine β-synthase deficiency (homocystinuria). Although it is estimated that most, if not all, people with classic MFS have a *FBN1* pathogenic variant, the large size of this gene and the extreme allelic heterogeneity in MFS have frustrated efficient molecular diagnosis. The yield of pathogenic variant screening varies based on technique and clinical presentation. It remains unclear whether the "missing" pathogenic variants are simply atypical in character or location within *FBN1* or located in another gene. Other differential diagnoses, such as MASS phenotype, EL, and WMS have been associated with pathogenic variants in the *FBN1* gene. Furthermore, it is often difficult or impossible to predict the phenotype from the nature or location of a *FBN1* pathogenic variant in MFS. Hence molecular genetic techniques can contribute to the diagnosis, but they do not substitute for comprehensive clinical evaluation and follow-up. Consequently, the absence or presence of a *FBN1* pathogenic variant is not sufficient to exclude or establish the diagnosis, respectively.

MANAGEMENT

Management focuses on preventing complications and genetic counseling. Referral to a multidisciplinary center where a geneticist with experience in MFS works in concert with subspecialists to coordinate a rational approach to monitoring and treatment is advisable, given the complex nature of some patients' disease. Yearly evaluations for cardiovascular disease, scoliosis, or ophthalmologic problems are imperative.

CURRENT THERAPIES

Most therapies currently available or under investigation aim to diminish cardiovascular complications, which can be categorized into activity restrictions, aortic surgery, endocarditis prophylaxis, and current pharmacologic approaches.

Activity Restrictions

Physical therapy can improve cardiovascular performance, neuromuscular tone, and psychosocial health, and so aerobic exertion in moderation is recommended. However, strenuous physical exertion, competitive or contact sports, and particularly isometric activities such as weightlifting, which invoke a Valsalva maneuver, should be avoided.

Aortic Surgery

Surgical outcome is more favorable if undertaken on an elective rather than an urgent or emergent basis (mortality of 1.5% vs 2.6% and 11.7%, respectively). Therefore aortic surgery should be recommended for adult patients when their aortic root diameter approaches 50 mm, and early intervention should be considered for those with a rapid rate of enlargement (>5-10 mm/yr) or a family history of early aortic dissection. There are no definitive criteria guiding the timing of surgery in children in whom dissection is extremely rare, irrespective of aortic size. This has prompted many centers to adopt the adult criterion of 50 mm, although early surgery may be undertaken in the presence of a rapid rate of growth (>10 mm/yr) or the emergence of significant aortic regurgitation. Preserving the native aortic valve at the time of repair is desirable to avoid the need for lifelong anticoagulation. Mitral valve repair or replacement is advised for severe mitral valve regurgitation with associated symptoms or progressive left ventricular dilatation or dysfunction.

Pregnancy

There is higher risk of aortic dissection during pregnancy and particularly in the early postpartum period in women with MFS. However, improved awareness and data have indicated the risk is low in patients with an aortic root diameter <40 mm. Prophylactic aortic root replacement can minimize the risk of aortic dissection and death in women with MFS who wish to become pregnant, but the risk of more distal ascending or descending aortic dissection would not be modified by this intervention. Work in mouse models of MFS and other vascular connective tissue disorders has associated postpartum aortic rupture with lactation and specifically the activity of the hormone oxytocin. This complication can be diminished or even avoided in some mouse models by avoiding lactation through pup removal or a pharmacologic antagonist of the oxytocin receptor. Although more work needs to be done in this area, we discuss the potential negative implications of lactation with women with MFS that choose to become pregnant and are deemed to be at particularly high risk based on the personal or family history.

Endocarditis Prophylaxis

The Professional Advisory Board of the National Marfan Foundation believes that patients with MFS should continue to receive prophylaxis for bacterial endocarditis, in part because it remains unknown, but possible, that the myxomatous valves typical of MFS are a preferred substrate for bacterial infection.

Current Pharmacologic Approaches

β-Blockers

β-Adrenergic receptor blockers have historically been considered the standard of care in MFS, and multiple small observational studies have suggested there is a protective effect on aortic root growth, with the dose typically titrated to achieve a heart rate <100 beats/min during submaximal exercise. Given the putative role of hemodynamic stress in aortic dilatation and aortic dissection in MFS, these effects are attributed to the negative inotropic and chronotropic effects of β-blockade.

Angiotensin II Receptor Type 1 Blockers

There is extensive evidence linking angiotensin II signaling to TGF-β activation and signaling. In a mouse model of MFS, the angiotensin II receptor type 1 blocker (ARB) losartan was shown to completely prevent pathologic aortic root growth and to normalize both aortic wall thickness and architecture, findings that were absent in placebo-treated and propranolol-treated mice. These data suggest the potential for productive aortic wall remodeling in MFS after TGF-β inhibition.

In support of its relevance to humans, a retrospective study assessing the effect of ARBs in a small cohort of pediatric patients with MFS who had severe aortic root enlargement despite previous alternative medical therapy, showed that ARBs significantly slowed the rate of aortic root and sinotubular junction dilatation (both of which occur in MFS), whereas the distal ascending aorta (which does not normally become dilated in MFS) remained unaffected. Further evidence of a beneficial effect from losartan therapy has been provided by three prospective clinical trials demonstrating that losartan treatment alone or in combination with β-blockade slowed the progression of aortic root dilation in patients with MFS.

A comparison clinical trial assessing the therapeutic benefit of losartan versus atenolol in patients with MFS concluded that both drugs provided significant protection against aortic growth, with no significant difference in therapeutic effect between the two drugs despite the use of conventional dose losartan (FDA-approved dose for hypertension) and an atypically high dose of atenolol (average dose of atenolol was 1.5 times and the maximum dose was 2 times the FDA approved upper limit for the treatment of hypertension). Both treatment arms in this trial showed a very slow rate of aortic root growth and a significant decline in aortic root *z* score over time, a performance superior to that observed in untreated Marfan patients or in patients treated with conventional dose atenolol (1–2 mg/kg/day). These data strongly suggest that both modalities have therapeutic roles in patients with MFS.

Additional prospective studies have demonstrated therapeutic benefit of ARBs. A meta-analysis integrating seven randomized prospective trials and over 1,500 patients concluded that ARBs are both efficacious and safe in MFS, either when used alone (in comparison to placebo) or in combination with β-blockers (in comparison to β-blockers alone). An 8-year follow-up of a Dutch study exploring the use of ARBs in adults with MFS suggested that this treatment not only suppressed pathologic aortic growth but also positively influenced important patient outcomes, including risk of surgery, aortic dissection, and all-cause mortality.

PROGNOSIS

The major cause of mortality is aortic root dilatation, dissection, and rupture, with the majority of fatal events occurring in the third and fourth decades of life. A reevaluation of life expectancy in MFS suggested that early diagnosis and refined medical and surgical management has greatly improved the prognosis for patients with the condition. Nevertheless, MFS continues to be associated with significant morbidity, and selected subgroups are refractory to therapy and continue to show early mortality. In a review of 54 patients diagnosed during infancy, 89% had serious cardiac pathology, and cardiac disease was progressive despite standard care (22% died during childhood, 16% before age 1 year). In the classic form of MFS, it is estimated that more than 90% of individuals will have a cardiovascular event during their lifetime, placing both physical and mental stresses on patients and their families. Awareness of these issues and referral for support services can facilitate a positive perspective toward the condition.

GENETIC COUNSELING

The heritable nature of MFS makes recurrence risk (genetic) counseling mandatory. Fathers of these sporadic cases are, on average, 7-10 years older than fathers in the general population. This paternal age effect suggests that these cases represent new dominant pathogenic variants with minimal recurrence risk to additional future offspring of the normal parents. Owing to rare reports of gonadal mosaicism in a phenotypically normal parent, the recurrence risk for parents of a sporadic case can be reported as low but not zero. Each child of an affected parent, however, has a 50% risk of inheriting the MFS pathogenic variant and thus being affected. Recurrence risk counseling is best accomplished by professionals with expertise in the issues surrounding the disorder.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 744

Ehlers-Danlos Syndrome

Donald Basel

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of heritable connective tissue disorders that are grouped into three broad pathoetiologic categories and more specifically divided into fourteen subtypes (Table 744.1). Affected individuals are considered to have an overlapping phenotype of abnormally soft, extensible skin, which often heals poorly, in association with joint hypermobility and occasional instability believed to be rooted in a disruption of normal collagen function (Tables 744.2 and 744.3). All organ systems contain connective tissue elements, and many of these elements are involved in supporting the function of feedback receptors such as mechanoreceptors in lumen or vessel walls or stretch receptors in tendons. The myriad of symptoms, variability of expression, modes of inheritance, and unique phenotypic elements distinguish the subtypes from one another while establishing their common origins. The hypermobility type (hEDS) is the most common form and has no clear molecular etiology.

The connective tissue matrix is complex (Fig. 744.1), and the interplay of cells, collagen and elastin fibers, proteins, and cell signaling molecules remains poorly understood. However, dysfunction at both structural and functional levels more than likely explains the complex medical associations typically encountered in this population, with complaints ranging from joint instability and tissue fragility to chronic pain, autonomic dysfunction, and chronic fatigue (see Table 744.3).

CLASSIFICATION OF THE SIX MOST COMMON SUBTYPES OF EHLERS-DANLOS SYNDROME

Classic (Genes: *COL5a1, COL5a2, COL1a1;* Previously EDS Type I—Gravis, EDS Type II—Mitis)

Classic EDS is the second most common form of EDS and is an autosomal dominant connective tissue disorder characterized by skin hyperelasticity (Fig. 744.2), widened atrophic scars (skin fragility), and joint hypermobility. Other features include easy bruising, which is often associated with hemosiderin staining of the tissues (particularly over regions exposed to frequent trauma, like the shins). The skin is "velvet" to the touch and is particularly fragile, with minor lacerations forming gaping wounds that leave broad, atrophic, papyraceous ("cigarette paper") scars (Fig. 744.3; see also Table 744.2). Additional cutaneous manifestations include molluscoid pseudotumors over pressure points from accumulations of connective tissue and piezogenic papules (Fig. 744.4). Joints are hypermobile, often with joint instability (Fig. 744.5). Scoliosis frequently presents in adolescence, and mitral valve prolapse is common. Life expectancy is generally not reduced, although rare rupture of large arteries has been reported. Similar noncutaneous nonarticular comorbidities, as seen in hypermobile EDS, are found, in particular pain and gastrointestinal dysfunction (see Table 744.3). Premature birth caused by rupture of membranes of an affected offspring is not uncommon. The diagnosis is made by clinical findings and sequencing of *COL5A1* and *COL5A2* genes.

Hypermobile (Cause Unknown, Previously EDS Type III)

Hypermobile EDS (hEDS) is the most prevalent form of EDS with an estimated population frequency of between 0.75–3%. It is an autosomal dominant disorder, but the causative molecular pathoetiology remains elusive. Fewer than 3% of patients with a hEDS phenotype are associated with heterozygous tenascin X gene loss of function, and likewise, only a minority of cases are linked to other findings, such as the association with mosaic type 1 collagen

Table 744.1 Classification of Ehlers-Danlos Syndrome

TYPE	GENE	SKIN FINDINGS	JOINT CHANGES	INHERITANCE	OTHER COMMENTS
Classic	*COL5A1, COL5A2* (usually haploinsufficiency)	Hyperextensibility, bruising, velvety skin, widened atrophic scars, molluscoid pseudotumors, spheroids	Hypermobility and its complications, joint dislocations	AD	Mitral valve prolapse, hernias
	COL1A1 Specific pathogenic variant; c.934C>T			AD	Blue sclerae, short stature, osteopenia/fractures; may have late arterial rupture
CLASSIC VARIANTS					
Cardiac valvular	Biallelic loss of function for *COL1A2*	Classic EDS features		AR	Severe cardiac valve issues as adult
Periodontal	*C1R* *C1S*	Can have classic EDS features	Can have hypermobility	AD	Periodontitis, marfanoid habitus, prominent eyes, short philtrum
Classic-like	*TNXB*	Hyperextensibility, marked hypermobility, severe bruising, velvety skin, no scarring tendency	Hypermobility	AR	Parents (especially mothers) with one *TNXB* pathogenic variant; can have joint hypermobility
	AEBP1	Joint hypermobility, extensible and redundant skin, abnormal scarring	Hypermobility	AR	Biallelic loss of function variants. Highly variable.
Hypermobility	Unknown	Mild hyperextensibility, scarring, textural change	Hypermobility, chronic joint pain, recurrent dislocations	AD	Sometimes confused with joint hypermobility syndrome
Vascular	*COL3A1* Rare variants in *COL1A1*	Thin, translucent skin, bruising, early varicosities, acrogeria	Small joint hypermobility	AD	Abnormal type III collagen secretion; rupture of bowel, uterus, arteries; typical facies; pneumothorax
Kyphoscoliosis	*PLOD* (deficient lysyl hydroxylase) *FKBP14*	Soft, hyperextensible skin, bruising, atrophic scars	Hypermobility	AR	Severe congenital muscle hypotonia that improves a little in childhood; congenital kyphoscoliosis, scleral fragility and rupture, marfanoid habitus, osteopenia, sensorineural hearing loss
VARIANTS WITH KYPHOSCOLIOSIS					
Spondylocheirodysplastic form	*SLC39A13,* which encodes the ZIP13 zinc transporter *B4GALT7* or *B3GALT6,* encoding galactosyltransferase I or II, key enzymes in GAG synthesis	Similar to kyphoscoliotic form		AR	Spondyloepimetaphyseal dysplasia; can have bone fragility and severe progressive kyphoscoliosis without congenital hypotonia; moderate short stature, loose facial skin, wrinkled palms with thenar and hypothenar atrophy, blue sclerae, curly hair, alopecia
Brittle cornea syndrome	ZNF469 or PRDM5	Skin hyperextensibility	Joint hypermobility	AR	Kyphoscoliosis; characteristic thin, brittle cornea, ocular fragility, blue sclera, keratoconus
Musculocontractural	*CHST14* (encoding dermatan 4-O-sulfotransferase) *DSE* (encoding dermatan sulfate epimerase)	Fragile, hyperextensible skin with atrophic scars and delayed wound healing	Hypermobility	AR	Progressive kyphoscoliosis; adducted thumbs in infancy, clubfoot, arachnodactyly, contractures, characteristic facial features, hemorrhagic diathesis
Myopathic	*COL12A1*	Soft, hyperextensible	Hypermobile small joints, large joint contractures (hip, knees, elbows)	AD or AR	Characterized by muscle hypotonia and weakness

Table 744.1 Classification of Ehlers-Danlos Syndrome—cont'd

TYPE	GENE	SKIN FINDINGS	JOINT CHANGES	INHERITANCE	OTHER COMMENTS
Arthrochalasis	Exon 6 deletion of *COL1A1* or *COL1A2*	Hyperextensible, soft skin with or without abnormal scarring	Marked hypermobility with recurrent subluxations	AD	Congenital hip dislocation, arthrochalasis, multiplex congenita, short stature
Dermatosparaxis	Type I collagen N-peptidase *ADAMTS2*	Severe fragility, sagging, redundant skin		AR	Also occurs in cattle

AD, Autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome; GAG, glycosaminoglycan.
From Malfait F, Francomano C, Byers P, et al. The 2017 International Classification of the Ehlers–Danlos syndromes. *Am J Med Genet C Semin Med Genet.* 2017;175(1):8–26.

Table 744.2 Common and Uncommon Features of Classic Ehlers-Danlos Syndrome

SKIN
Hyperextensible
Velvety
Fragile, thin, poor tensile strength
Atopic scarring ("cigarette-paper" scars)
Striae
Bruising and bleeding (hemosiderin staining of skin)
Piezogenic papules, subcutaneous sphenoids
Wound dehiscence/incisional hernia
MUSCULOSKELETAL/JOINTS
Hypermobile ± joint dislocations
Pes planus
Chronic musculoskeletal pain, sprains
Late walking, hypotonia
OTHER ORGAN INVOLVEMENT
Chiari type I malformation
Gastrointestinal (nausea, reflux, constipation)
Umbilical hernia
Hiatal hernia
Mitral valve prolapse
Aortic root dilation
CSF leak/headache
Pelvic organ prolapse
Premature rupture of fetal membranes
Cervical incompetence
Stress incontinence
Hyperkyphosis
Scoliosis
High arched palate
Femur anteversion ("W" sitting position)
Hollow organ rupture, diverticula
Occipitoatlantoaxial hypermobility

Table 744.3 Associated Features in Ehlers-Danlos/Hypermobility Spectrum Disorders

AUTONOMIC AND NEUROLOGIC DYSFUNCTION
Postural orthostatic tachycardia syndrome (POTS)
Dizziness
Palpitations
Gastroparesis
Diarrhea
Constipation
Sleep dysfunction
Chronic fatigue
Headache (migraine, new daily headache)
Urinary stress incontinence
Somatosensory amplification
Irritable bowel syndrome
Neuropathic pain
MUSCULOSKELETAL PAIN
Chronic regional pain syndrome
Fibromyalgia

defects. There are currently no diagnostic biomarkers, and the inter- and intrafamilial variation has clouded the ability to clearly define large study populations with sufficient phenotypic alignment. An editorial highlighted the impact of sex hormones and associations of certain symptom complexes to environmental exposures or "trigger events," which begs the question of a more complex gene-environment or epigenetic influence.

The primary clinical finding in hEDS is generalized joint hypermobility with less prominent skin manifestations. There is inconsistency in the literature as to what defines hypermobility, but generally a score of ≥6 on the Beighton hypermobility scale (Fig. 744.6, Table 744.4) would qualify as hypermobility in prepubertal children and adolescents, ≥5 for postpubertal individuals up to the age of 50, and ≥4 for all adults beyond the age of 50. Children <6 years of age generally tend toward a hypermobile state, and the Beighton score may not be a reliable indicator of connective tissue laxity in these children (Table 744.5). Joint instability with frequent dislocations is common but not universal; joints are predisposed to osteoarthritis in adults.

Patients with hEDS have significant nonarticular comorbidities associated with functional disorders. These present as complex pain, dysautonomia, chronic fatigue, anxiety, and sleep dysfunction (see Table 744.3). The complexity of hEDS most likely originates from the fact that it is genetically heterogeneous and represents an overlapping spectrum of disorders. Although joint hypermobility is the common denominator, symptoms may range from isolated familial joint hypermobility to the extreme multisystem disorder, which significantly impacts daily quality of life. Life expectancy is not reduced. Mild aortic root dilatation has been reported in up to 20% of affected adults. However, this mild dilatation is nonprogressive and not associated with aortic root dissection.

Vascular (vEDS) (Gene: *COL3A1*; Previously EDS Type IV)

vEDS is an autosomal dominant disorder that shows the most pronounced dermal thinning of all types of EDS. Consequently, the skin is translucent, and the underlying venous network is prominent, most notably over the chest region. The skin has minimal hyperextensibility but has a "velvet" texture and is often described as "doughy." The joints show increased mobility, often with instability. Congenital club foot and hip dislocation are frequently associated. Tissue fragility and arterial rupture cause significant morbidity and mortality. The majority of affected individuals experience a major vascular event before 20 years of age. Premature birth, extensive ecchymoses from trauma, a high incidence of bowel rupture (especially the colon), uterine rupture during pregnancy (~5% risk), rupture of the great vessels (80% by 40 years of age), dissecting aortic aneurysm, and stroke all contribute to the increased morbidity and

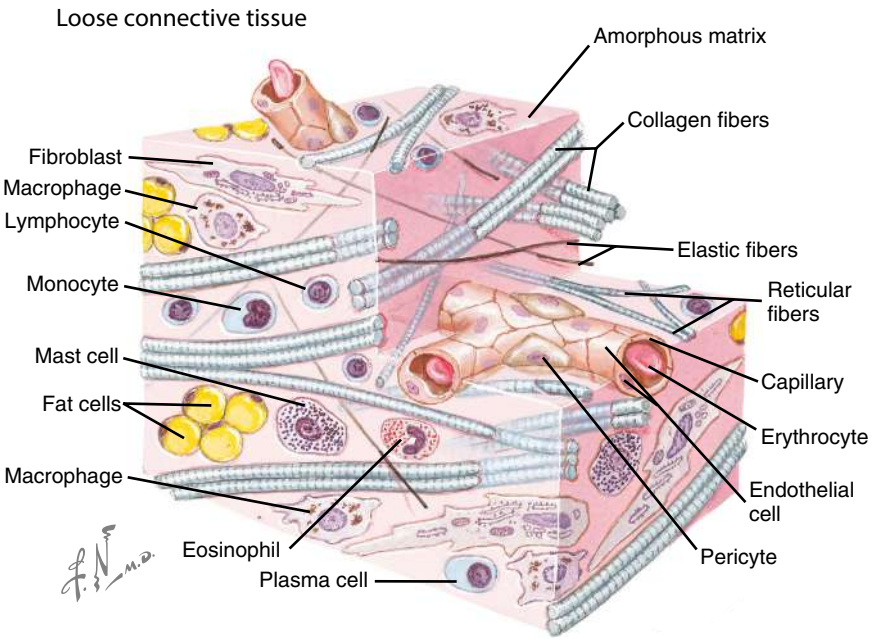

Fig. 744.1 Complex connective tissue macroenvironment illustrated by intermingled collagen and elastin fibers, nerves, mast cells, and capillaries. Both structure and function can be impacted by an abnormal connective tissue matrix. *(Courtesy Netter Images, Image ID 13192. https://netterimages.com/loose-connective-tissue-ovalle-histology-figure-31-labeled-ovalle-histology-frank-h-netter-13192.html)*



Fig. 744.2 Ehlers-Danlos syndrome (EDS). Skin hyperextensibility on the arm. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier, 2016: Fig. 6.1, p. 121.)*



Fig. 744.3 Ehlers-Danlos syndrome (EDS). The Gorlin sign is 5 times more common in EDS than in normal individuals. Note the scars on the forehead. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier, 2016: Fig. 6.2, p. 121.)*



Fig. 744.4 Piezogenic papules on the medial aspects of the heels in a 41-yr-old patient with Ehlers-Danlos syndrome *(top)* and his 2-yr-old daughter *(bottom)*. *(From Poppe H, Hamm H. Piezogenic papules in Ehlers-Danlos syndrome. J Pediatr. 2013;63:1788.)*

shortened life span associated with this condition. The median age of death is estimated at 50 years. Patients are generally counseled regarding the risks associated with pregnancy and advised to avoid activities that raise intracranial or intrathoracic pressure as a result of a Valsalva maneuver (such as weight training or trumpet playing). Skin protection in childhood is important to minimize trauma (shin guards). Celiprolol, a β1 antagonist and a β2 agonist (vasodilator), may reduce vascular events but is not approved by the U.S. Food and Drug Administration (FDA) for use in the United States. The diagnosis is clinical and confirmed by gene sequencing of *COL3A1*.

Kyphoscoliosis (Gene: *PLOD* [Lysyl Hydroxylase Deficiency]; Previously EDS Type VI)

The kyphoscoliotic form of EDS is distinguished by the severe kyphoscoliosis that develops early in childhood. It is an autosomal recessive disorder with phenotypic overlap with the classical type of EDS in that the skin is soft and fragile, joints are hyperextensible, and easy bruising is notable from a young age. Unique characteristics include marked hypotonia and keratoconus, with corneal fragility and globe rupture also reported. In addition, there is a higher risk for rupture of medium-sized arteries. The severity of the kyphoscoliosis may lead to restrictive lung disease with secondary pulmonary hypertension and reduced life expectancy. The diagnosis is clinical and confirmed by urine screening for an increased ratio of deoxypyridinoline to pyridinoline cross linking as well as gene sequencing of *PLOD*.



Fig. 744.5 Despite joint hyperextensibility, this patient does not meet Beighton score criteria for the extreme hypermobility seen with hypermobile Ehlers-Danlos syndrome.

Arthrochalasia (Gene: *COL1a1*, *COL1a2*; Previously EDS Types VIIA and B)

This type of EDS is inherited as an autosomal dominant disorder and characterized by severe joint instability in infancy. Joints show marked hyperextensibility with painless dislocation; the skin bruises easily and is soft and hyperextensible. Congenital hypotonia with gross motor delay is common, and kyphoscoliosis can develop in childhood. The diagnosis is clinical and confirmed by gene sequencing of *COL1A1* and *COL1A2*.

Dermatosparaxis (Type 1 Collagen N-Peptidase; Previously EDS Type VIIC)

This type of EDS is a rare autosomal recessive condition characterized by redundant skin that is soft, fragile, and bruises easily. Affected children often have a characteristic facial appearance, with skin sagging into jowls and fullness around the eyes ("puffy"). Premature rupture of membranes is common; closure of fontanels is delayed. Additional unique features reported in this group include short limbs with brachydactyly (short fingers), frequent



Fig. 744.6 Beighton score. The range of motion of several key small and large joints is measured to provide an overview of joint hypermobility. Instability is not assessed. Scoring: 2 points for each bilateral measure in Nos. ***1*** to ***4*** and 1 point for No. ***5***, equaling a total possible score of 9. Hypermobility is considered significant with a score of ≥6 between the ages of 6 and 35. *(Modified from Smits-Engelsman B, Klerks M, Kirby A. Beighton Score: a valid measure for generalized hypermobility in children. J Pediatr 2011;158:119–123.e4.)*

Table 744.4 The Nine-Point Beighton Hypermobility Score

THE ABILITY TO:	RIGHT	LEFT
1. Passively dorsiflex the fifth metacarpophalangeal joint to ≥90 degrees	1	1
2. Oppose the thenar aspect of the thumb to the volar aspect of the ipsilateral forearm	1	1
3. Hyperextend the elbow to ≥10 degrees	1	1
4. Hyperextend the knee to ≥10 degrees	1	1
5. Place hands flat on the floor without bending the knees	1	
		Total: 9

One point may be gained for each side for maneuvers 1-4, so the hypermobility score will have a maximum of 9 points if all are positive.
From Hakim A, Grahame R. Joint hypermobility. *Best Pract Res Clin Rheumatol.* 2003;17:989–1004, Table 1.

Table 744.5 A Five-Part Questionnaire for Identifying Hypermobility

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes *or* could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself double-jointed?

Answers in the affirmative to two or more questions suggest hypermobility with sensitivity 80–85% and specificity 80–90%.

From Hakim A, Grahame R. Joint hypermobility. *Best Pract Res Clin Rheumatol.* 2003;17:989–1004. Table 3.

Table 744.6 Genetic / Mendelian Conditions Presenting with Joint Hypermobility

HEREDITARY (SOFT/NONOSSIFIED) CONNECTIVE TISSUE DISORDERS
Ehlers-Danlos syndromes and related disorders
Fibrillinopathies (Marfan and Beals syndromes) and other disorders of the transforming growth factor-b pathway (e.g., Loeys-Dietz syndrome, Shprintzen-Goldberg syndrome)
Hereditary cutis laxae
SKELETAL DYSPLASIAS
Achondroplasia and hypochondroplasia
Dysplasias with multiple dislocations (e.g., Larsen and Desboquis syndromes, *CST3*-related and gPAPP-related disorders)
Some spondyloepimetaphyseal dysplasias
Some *COL2A1*-related and *COL11*-related disorders
Diastrophic dysplasia
Trichorhinophalangeal dysplasia
HEREDITARY MYOPATHIES
COL6-related disorders
SEPN1-related and *RYR1*-related disorders
MYH7-related and *TTN*-related disorders
Limb girdle muscular dystrophy 2E with joint hypermobility and contractures
CHROMOSOMAL AND GENOMIC DISORDERS
Trisomy 21
47,XXY and 47,XXX
Some microdeletion and microduplication syndromes
MULTIPLE CONGENITAL ANOMALIES/INTELLECTUAL DISABILITY DISORDERS (SELECTED)
RASopathies
Kabuki syndrome
FG syndrome
Fragile X syndrome

From Castori M, Hakim A. Contemporary approach to joint hypermobility and related disorders. *Curr Opin Pediatr.* 2017;29:640–649. Table 3.

hernias (umbilical, inguinal), blue sclerae, and bladder rupture. Joints are hypermobile. The diagnosis is confirmed by sequencing of *ADAMTS2*.

DIFFERENTIAL DIAGNOSIS

EDS represents a portion of the hereditary connective tissue disorders, many of which have unique features that enable clinical differentiation. The primary differential diagnosis would include Loeys-Dietz syndrome, which has features of both vEDS and Marfan syndrome (see Chapter 743). EDS has also been confused with MASS syndrome (mitral valve prolapse, aortic root dilation, skeletal changes, skin changes), cutis laxa (see Chapter 745), and pseudoxanthoma elasticum. In general, the skin of patients with cutis laxa hangs in redundant folds, whereas the skin of those with EDS is hyperextensible and snaps back into place when stretched. Other disorders that impact the integrity of the connective tissues—such as exposure to corticosteroids and osteogenesis imperfecta or mild myopathic disorders (Bethlem myopathy, Ullrich congenital muscular dystrophy)—can be indistinguishable in the early stages of disease (Table 744.6).

GENERAL APPROACH TO MANAGEMENT

In addition to the EDS type-specific therapies discussed under each disease, there are general approaches to help improve symptoms and avoid complications.

Musculoskeletal pain, which initially involves the joints, eventually may become generalized and requires a combination of physical therapy and nonpharmacologic approaches (Fig. 744.7). Physical therapy should focus on enhancing the strength of the muscles supporting the affected joints. With severe recurrent sprains or dislocations, bracing may be necessary. Pain medication for low- to moderate-intensity pain could include nonsteroidal antiinflammatory drugs (however, their platelet-inhibiting action may increase the risk of cutaneous bleeding). Higher-intensity pain may require other agents, such as selective serotonin receptor inhibitors or low-dose tricyclic antidepressants. Muscle relaxants or antiepileptic agents should be avoided because they may increase fatigue. Surgery for joint dislocations should be avoided if possible as should prolonged periods of inactivity (which result in rapid muscle deconditioning) (Table 744.7). If surgery is needed for any complication, the sutures should approximate the margins, suture tension should be avoided, and the sutures should be retained longer than usual. Other approaches to pain include cognitive behavioral therapy, acupuncture, and transepidermal electrical nerve stimulation (TENS).

Chronic fatigue should be approached by supporting good sleep hygiene and avoiding sedating medications (see Table 744.7). Patients at risk for arterial bowel or uterine rupture should be counseled about preventive measures, appropriate medications (see specific subtype), and early warning signs of organ rupture.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

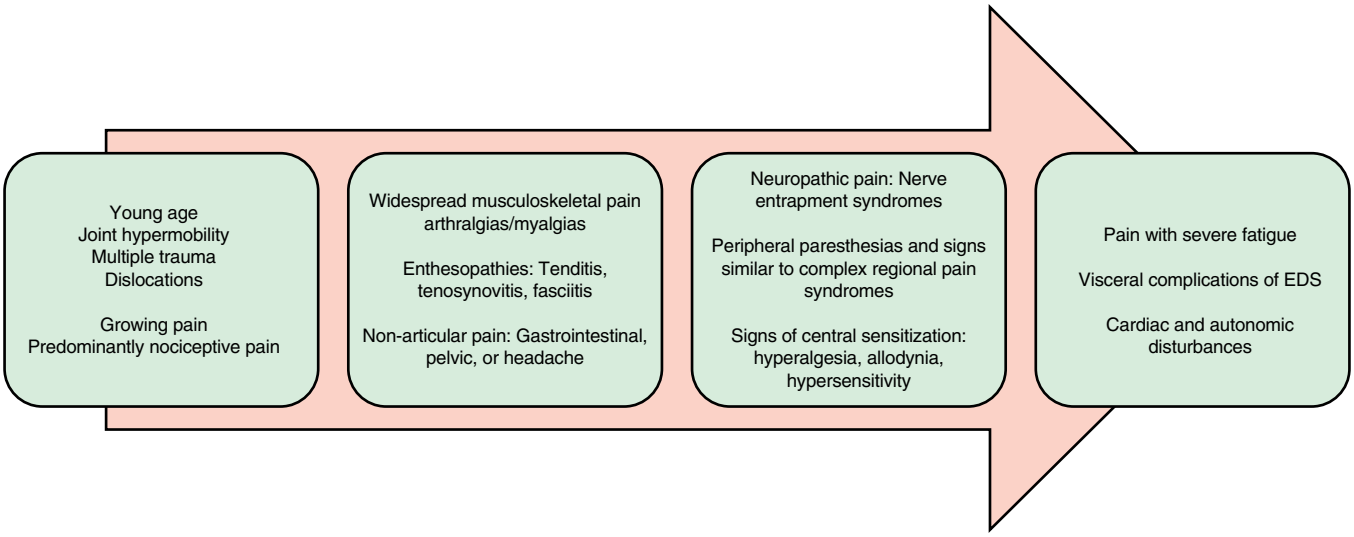

Fig. 744.7 Characteristics of pain in Ehlers-Danlos syndrome that progress in clinical stages. *(From Zhou Z, Rewari A, Shanthanna H. Management of chronic pain in Ehlers-Danlos syndrome. Medicine. 2018;97:e13115.)*

Table 744.7 Lifestyle Recommendations for Hypermobile Ehlers-Danlos Syndrome

Promote regular aerobic fitness
Promote fitness support with strengthening, gentle stretching, and proprioception exercise
Promote postural and ergonomic hygiene, especially during sleep, at school, and in the workplace
Promote weight control (body mass index [BMI] <25)
Promote daily relaxation activities
Promote lubrication during sexual intercourse
Promote early treatment of malocclusion
Avoid high-impact sports/activities
Avoid low environmental temperatures
Avoid prolonged sitting positions and prolonged recumbency
Avoid sudden head-up postural change
Avoid excessive weightlifting/carrying
Avoid large meals (especially of refined carbohydrates)
Avoid hard foods intake and excessive jaw movements (e.g., ice, gums)
Avoid bladder irritant foods (e.g., coffee and citrus products)
Avoid nicotine and alcohol intake

Note: these recommendations are intended as flexible indications for ameliorating quality of life and do not represent lifesaving solutions.
Adapted from Castori M, Morlino S, Celletti C, et al. Management of pain and fatigue in the joint hypermobility syndrome (aka Ehlers-Danlos syndrome, hypermobility type): principles and proposal for a multidisciplinary approach. *Am J Med Genet.* 2012;158:2055–2070.

Chapter 745

Cutis Laxa

Leah Lalor

Cutis laxa syndromes encompass a group of rare multisystem disorders that include loose redundant skinfolds as hallmark clinical feature (Fig. 745.1). Cutis laxa results from impaired elastic fiber assembly and homeostasis, and the known underlying gene defects affect different extracellular matrix proteins, intracellular trafficking, or cellular metabolism.

Cutis laxa (CL) may present in **autosomal recessive** (ARCL1A, ARCL1B, ARCL1C, ARCL2A, ARCL2B), **autosomal dominant** (ADCL), **X-linked** or acquired forms (Fig. 745.2, Tables 745.1 and 745.2). Acquired CL may develop after a febrile illness, inflammatory skin diseases such as lupus erythematosus or erythema multiforme, amyloidosis, urticaria, angioedema, hypersensitivity reactions to penicillin, or in neonates born to women who were taking penicillamine.



Fig. 745.1 Pendulous folds of skin of an infant with cutis laxa.

CLINICAL MANIFESTATIONS

CL may demonstrate widespread folds of **loose skin**, or changes may be mild and limited in extent, resembling anetoderma. Patients with severe cutis laxa have characteristic facial features; they present with an aged appearance with sagging jowls ("bloodhound" appearance; see Fig. 745.1), a hooked nose with everted nostrils, a short columella, a long upper lip, and everted lower eyelids. The skin is also lax elsewhere on the body and has been described as resembling an ill-fitting suit. Hyperelasticity and hypermobility of the joints as seen in the Ehlers-Danlos syndromes are not present. Many infants have a hoarse cry, probably as a result of laxity of the vocal cords. Tensile strength of the skin is normal. Other features are noted in Table 745.3.

The **autosomal dominant** form of CL (ADCL) is typically caused by pathogenic variants in *ELN*, which encodes elastin, an essential extracellular matrix protein responsible for maintenance of skin elasticity. ADCL has predominant skin involvement but can have risk for aortic aneurysm and emphysema. It typically manifests in infancy; it may be associated with intrauterine growth restriction, ligamentous laxity, and delayed closure of the fontanels.

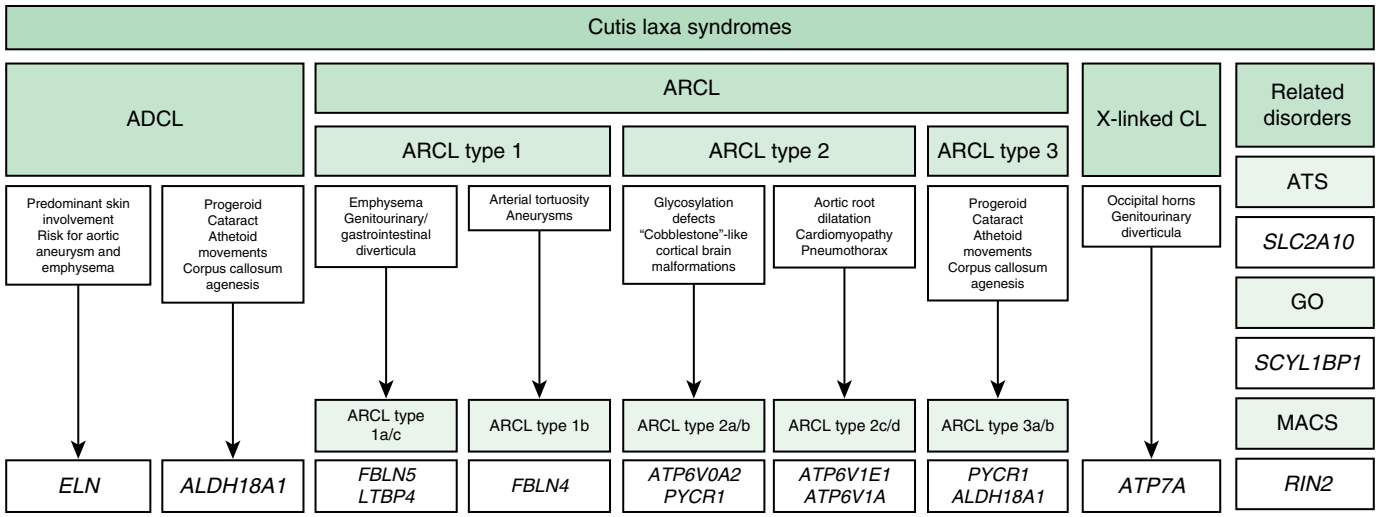

Fig. 745.2 The spectrum of cutis laxa disorders. ADCL, Autosomal dominant cutis laxa; ARCL, autosomal recessive cutis laxa; ATS, arterial tortuosity syndrome; GO, geroderma osteodysplasticum; MACS, macrocephaly-alopecia-cutis laxa-scoliosis. *(From Beyens A, Boel A, Symoens S, et al. Cutis laxa: a comprehensive overview of clinical characteristics and pathophysiology. Clin Genet. 2021;99:53–66. Fig.1.)*

Table 745.1 Disorders to Consider in the Differential Diagnosis of Cutis Laxa

				CLINICAL FINDINGS			
DISEASE NAME	**GENE SYMBOL**	**MIM #**	**INHERITANCE**	**CUTIS LAXA**	**EMPHYSEMA**	**ANEURYSMS**	**DEVELOPMENTAL DELAY**
ALDH18A1-related cutis laxa	*ALDH18A1*	612652	AR	+	–	–	++
FBLN5 -related cutis laxa	*FBLN5*	219100	AR	+++	+++	–	–
EFEMP2-related cutis laxa	*EFEMP2 (FBLN4)*	219100	AR	++	++	+++	–
Autosomal recessive cutis laxa type 2A	*ATP6V0A2*	278250 219200	AR	++	–	–	++
Autosomal dominant cutis laxa	*ELN or FBLN5*	123700	AD	+	+	+	–
Gerodermia osteodysplastica	*GORAB*	231070	AR	+ +	–	–	–
De Barsy syndrome (*PYCR1*-related progeroid syndrome)	*PYCR1*	219150	AR	+	–	–	+++
Autosomal recessive cutis laxa type 2B	*PYCR1*	612940	AR	+	–	_	+++
LTBP4-related cutis laxa	*LTBP4*	613177	AR	+	++	+	+
RIN2-related cutis laxa	*RIN2*	613075	AR	+	–	–	±

Reproduced with permission from Van Maldergem L, Dobyns W, Kornak U. ATP6V0A2-Related Cutis Laxa. 2009 Mar 19 [Updated 2011 May 10]. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews[Internet]. Seattle (WA): University of Washington, Seattle; 1993. Available from http://www.ncbi.nlm.nih.gov/books/NBK5200/

Pathogenic variants in *ALDH18A1*, which encodes delta-1-pyrroline-5-carboxylate synthetase (P5CS), a key enzyme in the synthesis of proline (an abundant amino acid in elastin), can cause autosomal dominant or recessive CL. Notably, pathogenic variants in *PYCR1*, which encodes pyrroline-carboxylate reductase 1, another enzyme in this pathway, cause recessive CL (ARCL3). Each of these proline synthesis-related CL subtypes can also present with progeroid features, cataracts, athetoid movements, and corpus callosum anomalies.

Autosomal recessive CL is divided into three general subtypes: type 1 (ARCL1), with cardiopulmonary complications, type 2 (ARCL2), with CNS and skeletal anomalies, and type 3 (ARCL3; de Barsy syndrome), which adds ocular findings to the type 2 features. Overall, these individuals can present with multiple hernias, rectal prolapse, diaphragmatic

Table 745.2 Associations with Acquired Cutis Laxa

Infections
Toxocara canis (cat-scratch)
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Onchocerca volvulus (onchocerciasis)
Medications
Isoniazid
Penicillins
D-penicillamine
Inflammatory diseases
Celiac disease
Sarcoidosis
Dermatitis herpetiformis
Sweet syndrome
Rheumatic disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Others
α_1-antitrypsin deficiency
Mastocytosis
Nephrotic syndrome
Amyloidosis
Malignancy

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier, 2022: Box 6.6, p. 151.

Table 745.3 Most Common Other Features of Cutis Laxa

- Facial dysmorphism
- Aortic dilatation
- Pulmonary artery stenosis
- Pulmonary emphysema
- Diverticulae: gastrointestinal, genitourinary
- Uterine or rectal prolapse
- Ventral, hiatal, inguinal hernias

Modified from Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier, 2022: Box 6.4, p. 148.

atony, diverticula of the gastrointestinal and genitourinary tracts, cor pulmonale, emphysema, pneumothoraces, peripheral pulmonary artery stenosis, and aortic dilation. Characteristic facial features include downward-slanting palpebral fissures, a broad, flat nose, and large ears. Skeletal anomalies, dental caries, growth retardation, and developmental delay also occur. Such patients often have a shortened life span.

ARCL1 is comprised of three subtypes. Subtypes ARCL1a and ARCL1c (Urban-Rifkin-Davis syndrome), caused by dominant pathogenic variants in *FBLN5* and *LTPB4*, respectively, are similar disorders and, in addition to skin findings, more frequently develop emphysematous lung changes and mechanical insufficiency of the gastrointestinal and genitourinary tract wall. Subtype ARCL1b, caused by pathogenic variants in *FBLN4*, in addition to skin findings, typically develops elongation, tortuosity, and aneurysms of the large- and middle-sized arteries.

ARCL2 often presents with delays in neuromotor development and can include epilepsy and cortical or cerebellar malformations. Recessive pathogenic variants in *ATP6V0A2* (ARCL 2a) are more common and include N- or O-glycosylation defects and pathogenic variants *PYCR1* (ARCL2b).

ARCL2 with recessive pathogenic variants in ATP6V1E1 (ARCL2c) and ATP6V1A (ARCL2d), genes encoding key enzymes in acidification of intracellular organelles, can include N- or O-glycosylation defects and demonstrate increased frequency of aortic root dilatation, cardiomyopathy, and pneumothorax.

X-linked CL, also referred to as **occipital horn syndrome**, is caused by pathogenic variants of *ATP7A* that encodes a Cu^{2+}-transporting adenosine triphosphatase, α-polypeptide. This clinical presentation is allelic with Menkes disease (see Chapter 639.5) but is at the milder end of that spectrum.

Cutis laxa–like skin changes may also be seen in association with multiple other syndromes, including Lenz-Majewski syndrome, hyperostotic dwarfism, SCARF (**s**keletal abnormalities, **c**utis laxa, craniostenosis, **a**mbiguous genitalia, **r**etardation, **f**acial abnormalities) syndrome, wrinkling skin syndrome, arterial tortuosity syndrome (ATS), gerodermia osteodysplasia, macrocephaly alopecia cutis laxa scoliosis syndrome (MACS), and Costello syndrome.

HISTOLOGY

Histologically, elastic tissue is reduced throughout the dermis, with fragmentation, distention, and clumping of the elastic fibers. This often results in bare microfibrils of random directionality. The light microscopic appearance of elastic fibers in CL patients is typically not able to discern between different subtypes as they appear reduced and fragmented in all.

TREATMENT

Treatment of the skin findings in cutis laxa is largely supportive, although textural improvement and symptomatic relief using resurfacing lasers for acquired CL has been reported.

Regarding medical management, as a general rule, unrelated to the underlying subtype, elastic fiber defects warrant regular assessment of pulmonary, cardiovascular, and urinary systems. Yearly echocardiography is recommended in dominant CL, ARCL1a/c, and ARCL2c. More intensive echocardiographic follow-up is needed in ARCL1b and ATS (every 3 months in ARCL1b; every 3 months until the age of 5 in ATS), while in the remaining subtypes an examination every 3-5 years is sufficient. In ARCL1, MRI head-to-pelvis should be repeated yearly (ARCL1b) or every 3-5 years (ARCL1a/c and ATS).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Section 5
Metabolic Bone Disease

Chapter 746
Bone Structure, Growth, and Hormonal Regulation

Rebecca J. Gordon and Catherine M. Gordon

See also Chapters 69 and 610.

Bone is a rigid organ but metabolically active in that it is constantly being formed **(modeled)** and reformed **(remodeled)**. It is capable of rapid turnover, bearing weight, and withstanding the stresses of various physical activities. Bone is the major body reservoir for calcium, phosphorus, and magnesium. Other functions of bone include organ protection, structure, movement, and sound transmission. It is also an endocrine organ that produces fibroblast growth factor 23 (FGF23), which regulates renal phosphate handling. Disorders that affect this organ and the process of mineralization are designated **metabolic bone diseases**.

The human skeleton consists of a protein matrix, largely composed of a collagen-containing protein, osteoid, on which is deposited a crystalline mineral phase. Collagen-containing osteoid accounts for 90% of bone protein; other proteins, including osteocalcin, which

contains γ-carboxyglutamic acid, are also present. Synthesis of osteocalcin depends on vitamin K and vitamin D; in states with high bone turnover, serum osteocalcin values are often elevated. Osteocalcin appears to enhance insulin secretion and sensitivity and reduce fat stores.

The microfibrillar matrix of osteoid permits deposition of highly organized calcium phosphate crystals, including hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] and octacalcium phosphate [$Ca_8H_2(PO_4)_6{\cdot}5H_2O$], plus less-organized amorphous calcium phosphate, calcium carbonate, sodium, magnesium, and citrate. Hydroxyapatite is deep within bone matrix, whereas amorphous calcium phosphate coats the surface of newly formed or remodeled bone.

Because bone growth and turnover rates are high during childhood, many clinical and osseous features of metabolic bone diseases are more prominent in children than in adults. The growth pattern of bones is an acceleration of bone growth (length) of the limbs during prepubescence, increased growth (length) of the trunk (spine) during early adolescence, and increased bone mineral deposition in late adolescence.

The use of dual-energy x-ray absorptiometry (DXA) or quantitative CT permits measurement of both mineral content and bone density in healthy subjects and children with metabolic bone disease. DXA exposes the patient to less radiation than a chest radiograph and significantly less than quantitative CT and is therefore most commonly used in clinical practice (see Chapter 749). **Bone growth** occurs in children by the process of calcification of the cartilage cells present at the ends of bone. In accord with the prevailing extracellular fluid calcium and phosphate concentrations, mineral is deposited in chondrocytes or cartilage cells set to undergo mineralization. The main function of the vitamin D–parathyroid hormone (PTH)–FGF23–endocrine axis is to maintain the extracellular fluid calcium and phosphate concentrations at appropriate levels to permit mineralization.

Other hormones also appear to regulate the growth and mineralization of cartilage, including growth hormone acting through insulin-like growth factors, thyroid hormones, insulin, leptin, ghrelin, and androgens and estrogens during the pubertal growth spurt. Supraphysiologic concentrations of glucocorticoids impair cartilage function and bone growth and augment bone resorption.

Rates of bone formation are coordinated with alterations in mineral metabolism in both the intestine and kidneys, where a number of hormones regulate the processes. Inadequate dietary intake or intestinal absorption of calcium causes a fall in serum levels of calcium and its ionized fraction. This decrease serves as the signal for PTH synthesis and secretion, resulting in greater bone resorption (which raises the serum calcium level) and enhanced distal tubular reabsorption of calcium. It also promotes higher rates of renal synthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol, the most active metabolite of vitamin D (Fig. 746.1). **Calcium homeostasis** is thus controlled by the intestine because the availability of 1,25$(OH)_2$D ultimately determines the fraction of ingested calcium that is absorbed.

Phosphate homeostasis is regulated by the kidneys because intestinal phosphate absorption is nearly complete, and renal excretion determines the serum level of phosphate. Excessive intestinal phosphate absorption causes a fall in serum levels of ionized calcium and a rise in PTH secretion, resulting in phosphaturia, thus lowering the serum phosphate level and permitting the calcium level to rise. Hypophosphatemia blocks PTH secretion and promotes renal 1,25$(OH)_2$D synthesis. This latter compound also promotes greater intestinal phosphate absorption. The important role of FGF23 in phosphate homeostasis is described later.

Vitamin D can be synthesized in the skin under the influence of ultraviolet (UV) irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D3 (vitamin D3) in the liver and then further converted by the kidney. The skin contains 7-dehydrocholesterol, which is converted to vitamin D3 [25(OH)D3] by UV radiation; other inactive vitamin D sterols are also produced (see Chapter 69). Vitamin D3 is then transported in the bloodstream to the liver by a vitamin D–binding protein (DBP); DBP binds all forms of vitamin D. The plasma concentration of free or nonbound vitamin D is much lower than the level of DBP-bound vitamin D metabolites.

Vitamin D also can enter the metabolic pathway by ingestion of dietary vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol), the latter of which is more potent, and both of which are absorbed from the intestine because of the action of bile salts. After absorption, ingested vitamin D is transported by chylomicrons to the liver, where, along with skin-derived vitamin D3, it is converted to 25-hydroxyvitamin D [25(OH)D]. The 25(OH)D is next transported by DBP to the kidneys, where it undergoes further metabolism. 25(OH)D is the main circulating vitamin D metabolite in humans (Table 746.1). Because the synthesis of 25(OH)D is weakly regulated by feedback, its plasma level rises in summer and decreases during winter. High vitamin D intake raises the plasma level of 25(OH)D to many times above normal, but the parent vitamin D compound itself is absorbed by adipose tissue.

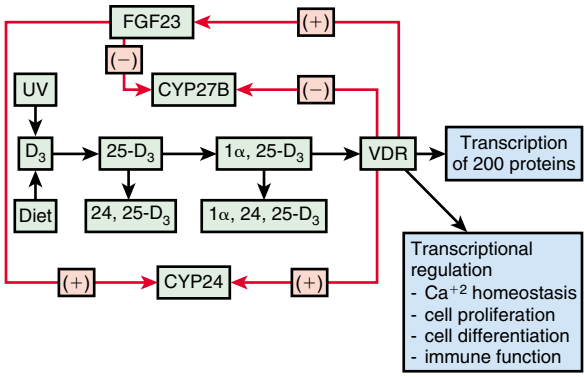

Fig. 746.1 Vitamin D metabolism. Vitamin D can be synthesized in the skin under the influence of ultraviolet (UV) irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D3 (vitamin D3) in the liver and then further converted by the kidney. The enzyme cytochrome P450 (CYP) 27B converts 25(OH)D3 to 1α,25-$(OH)_2$D3. 1,25$(OH)_2$D3 binds to vitamin D receptor (VDR), which, after transport to the nucleus, acts to induce the transcription of more than 200 proteins. The functions of some of the proteins are indicated. VDR activation leads to productions of fibroblast growth factor 23 (FGF23). FGF23 induces phosphaturia (not shown), upregulates CYP 24, and downregulates CYP 27B.

In the kidneys, 25(OH)D undergoes further hydroxylation, depending on the prevailing serum concentration of calcium, phosphate, PTH, and FGF23. If the calcium or phosphate level is reduced or the PTH level is elevated, the enzyme 25(OH)D-1-hydroxylase is activated and 1,25$(OH)_2$D is formed. 1,25$(OH)_2D_3$ binds to a vitamin D receptor, which after transport to the nucleus, acts to induce the transcription of 200-400 proteins and peptides. The functions of some of the proteins are known.

Another class of proteins important in the regulation of mineral balance and vitamin D synthesis are the **phosphatonins**. Among these are FGF23, sFRP-4 (secreted Frizzled-related protein 4), and MEPE (matrix extracellular phosphoglycoprotein). Overexpression of FGF23 results in hypophosphatemia, phosphaturia, reduced serum 1,25$(OH)_2$D values, and some forms of rickets. Disorders of phosphate balance, including hyper- and hypophosphatemia, can relate to loss or gain of function of these phosphatonins (see Fig. 746.1).

Vitamin D receptor activation by 1,25$(OH)_2$D leads to production of FGF23. FGF23 is produced by osteocytes and targets another organ, the kidney, to promote phosphaturia. FGF23 reduces expression/insertion of two sodium phosphate transporters into the renal proximal tubule, resulting in higher levels of urinary phosphate excretion. This bone-derived hormone also inhibits renal hydroxylase activity (CYP 27B1) and promotes 24-hydroxylase activity, with resultant decrease in 1,25$(OH)_2$D levels.

The active metabolite, 1,25$(OH)_2$D, circulates at a level that is only 0.1% of the level of 25(OH)D (see Table 746.1) and acts on the intestine to increase the active transport of calcium and stimulate phosphate absorption. Because 1α-hydroxylase is a mitochondrial enzyme that is tightly feedback regulated, the synthesis of 1,25$(OH)_2$D declines after serum calcium or phosphate values return to normal. Excessive 1,25$(OH)_2$D is converted to an inactive metabolite. In the presence of normal or elevated serum calcium or phosphate concentrations, the renal 25(OH)D-24-hydroxylase is activated, producing 24,25-dihydroxyvitamin D [24,25$(OH)_2$D], which is a pathway for the removal of excess vitamin D; serum levels of 24,25$(OH)_2$D (1-5 ng/mL) increase after ingestion of large amounts of vitamin D (see Fig. 746.1) or in the presence of increased concentrations of FGF23. Although hypervitaminosis D and production of

Table 746.1 Vitamin D Metabolic Values in Plasma of Normal Healthy Subjects

METABOLITE	PLASMA VALUE
Vitamin D2	1-2 ng/mL
Vitamin D3	1-2 ng/mL
25(OH)D2	4-10 ng/mL
25(OH)D3	26-70 ng/mL
TOTAL 25(OH)D	20-80 ng/mL*
24,25(OH)2D	1-4 ng/mL
1,25(OH)2D	
Infancy	70-100 pg/mL
Childhood	30-50 pg/mL
Adolescence	40-80 pg/mL
Adulthood	20-35 pg/mL

*The Institute of Medicine states that a value of 25(OH)D of 20 ng/mL is the lower limit of normal for the general population. In contrast, the Endocrine Society defines vitamin D *deficiency* as having a serum level of less than 20 ng/mL, and *insufficiency* as a serum level between 21-29 ng/mL.

inactive metabolites can occur after oral dosing, extensive skin exposure to sunlight does not usually produce toxic levels of 25(OH)D3, suggesting natural regulation of the production of this metabolite in cutaneous tissue.

Serum 1,25(OH)$_2$D levels are higher in children than in adults, are not as subject to seasonal variability, and peak during the first year of life and again during the adolescent growth spurt. These values must be interpreted in light of the prevailing serum calcium, phosphate, and PTH values, and with regard to the entire vitamin D metabolite profile.

Mineral deficiency prevents the normal process of bone mineral deposition. If mineral deficiency occurs at the growth plate, growth slows and bone age is retarded, a condition called **rickets**. Poor mineralization of trabecular bone resulting in a greater proportion of unmineralized osteoid is the condition of osteomalacia. Rickets is found only in growing children before fusion of the epiphyses, whereas osteomalacia is present at all ages. All patients with rickets have osteomalacia, but not all patients with osteomalacia have rickets. These conditions should not be confused with osteoporosis, a condition of equal loss of bone volume and mineral (see Chapter 749).

Rickets may be classified as calcium-deficient or phosphate-deficient rickets. Because both calcium and phosphate ions constitute bone mineral, the insufficiency of either type in the extracellular fluid that bathes the mineralizing surface of bone results in rickets and osteomalacia. The two types of rickets are distinguishable by their clinical manifestations (Table 746.2). Rickets can also occur in the face of mineral

Table 746.2 Clinical Variants of Rickets and Related Conditions

TYPE	SERUM CALCIUM LEVEL	SERUM PHOSPHORUS LEVEL	ALKALINE PHOSPHATASE ACTIVITY	URINE CONCENTRATION OF AMINO ACIDS	GENETICS	GENE DEFECT KNOWN
CALCIUM DEFICIENCY WITH SECONDARY HYPERPARATHYROIDISM*						
Lack of Vitamin D						
Lack of exposure to sunlight	N or L	L	E	E		
Dietary deficiency of vitamin D	N or L	L	E	E		
Congenital	N or L	L	E	E		
Other Deficiencies						
Malabsorption of vitamin D	N or L	L	E	E		
Liver diseases	N or L	L	E	E		
Anticonvulsant drug	N or L	L	E	E		
Renal osteodystrophy	N or L	E	E	V		
Vitamin D–dependent type I	L	N or L	E	E	AR	Y
PRIMARY PHOSPHATE DEFICIENCY (NO SECONDARY HYPERPARATHYROIDISM)						
Genetic primary hypophosphatemia	N	L	E	N	XL, AD, AR	Y
X-linked hypophosphatemic rickets					XL	Y
Autosomal dominant hypophosphatemic rickets					AD	Y
Autosomal recessive hypophosphatemic rickets					AR	Y
Fanconi Syndrome						
Cystinosis	N	L	E	E	AR	Y
Tyrosinosis	N	L	E	E	AR	Y
Lowe syndrome	N	L	E	E	XL	Y
Acquired	N	L	E	E		
Phosphate Deficiency or Malabsorption						
Parenteral hyperalimentation	N	L	E	N		
Low phosphate intake	N	L	E	N		

Continued

Table 746.2 Clinical Variants of Rickets and Related Conditions—cont'd

TYPE	SERUM CALCIUM LEVEL	SERUM PHOSPHORUS LEVEL	ALKALINE PHOSPHATASE ACTIVITY	URINE CONCENTRATION OF AMINO ACIDS	GENETICS	GENE DEFECT KNOWN
Other						
Renal tubular acidosis, type II proximal	N	L	E	N		Y
Tumor-induced osteomalacia	N	L	E	N		Y
END-ORGAN RESISTANCE TO $1,25(OH)_2D3$						
Vitamin D-dependent type II (several variants)	L	L or N	E	E	AR	Y
RELATED CONDITIONS RESEMBLING RICKETS						
Hypophosphatasia	N	N	L	Phosphoethanolamine elevated	AR	Y
Metaphyseal Dysostosis						
Jansen type	E	N	E	N	AD	Y
Schmid type	N	N	E	N	AD	Y

*Deficiency of vitamin D; low 25(OH)D and no stimulation of higher $1,25(OH)_2D$ values.
AD, Autosomal dominant; AR, autosomal recessive; E, elevated; L, low; N, normal; V, variable; XL, X-linked; Y, yes.

deficiency, despite adequate vitamin D stores. True dietary calcium deficiency rickets are found in some parts of Africa but rarely in North America or Europe. A form of phosphate-deficiency rickets can occur in infants, given prolonged administration of phosphate-sequestering aluminum salts as a treatment for colic or gastroesophageal reflux. This results in the phosphate depletion syndrome.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 747

Hypophosphatasia

Nourah N. Almutlaq and Linda A. DiMeglio

Hypophosphatasia (HPP) is a rare inborn error of metabolism in which tissue-nonspecific (liver, bone, kidney) alkaline phosphatase isoenzyme (TNSALP) activity is deficient, although activity of the intestinal and placental isoenzymes is normal. Decreased serum alkaline phosphatase (ALP) concentrations are the hallmark of HPP.

Pathogenic variants in the *ALPL* gene reduce the TNSALP enzyme activity to below the level essential for normal bone and teeth mineralization. More than 340 variants have been identified to date. Missense variants are the most common; however, splice-site, small deletions, and frameshift variants also have been found. The high heterogeneity of the disease is related to the inheritance pattern and different missense variants' varied TNSALP activity effects. Although the genotype/phenotype correlation is not very consistent, the more severe forms are recessively inherited and milder disease is dominantly inherited.

The clinical spectrum of HPP ranges from a very severe, typically lethal, perinatal form to a mild form with late-adult onset presenting with nonpathognomonic symptoms such as arthropathy and musculoskeletal pain. A nosology describing seven forms of the condition, ranging from neonatal lethal disease to odontohypophosphatasia, which only affects teeth with no skeletal deformities, is employed. (Subtypes and features of HPP are shown in Table 747.1.) The most common signs across subtypes are bone demineralization and premature loss of teeth with intact roots in the setting of low ALP.

The most severe **perinatal HPP** cases are lethal in utero or shortly after birth in untreated newborns. Infants have profound skeletal hypomineralization with short bones that lead to chest deformities and subsequent hypoplastic lungs. Infants may also have anemia with intracranial hemorrhage, periodic apnea, and pyridoxine-dependent seizures (Fig. 747.1A). **Infantile HPP** is next on the continuum. These infants present before 6 months of age with overlapping symptoms to perinatal HPP, including respiratory distress from severe lung hypoplasia. They can also have irritability and failure to thrive explained by the hypercalcemia/hypercalciuria (leading to nephrocalcinosis) and premature craniosynostosis (can lead to increased intracranial pressure). X-rays reveal irregular ossification, punched-out areas, and metaphyseal cupping. Before the availability of enzyme replacement therapy with asfotase alfa, mortality was estimated at 50% and survivors had significant disability. This subset of patients can also improve spontaneously as affected children mature, although early death from renal failure or flail chest leading to pneumonia can occur.

Of note, a **benign prenatal** form of hypophosphatasia also exists. It is seen in newborns with low ALP and skeletal abnormalities in utero or at birth that improve spontaneously over time.

The next category of hypophosphatasia manifests in childhood (after 6 months of life) or late adolescence **(hypophosphatasia tarda)** (see Fig. 747.1B). These children present with premature exfoliation of primary teeth (with the root intact because of poorly mineralized dental cementum), mild skeletal deformities, fracture, and variable short stature. Some children have symptoms of skeletal pain and muscle weakness. Long bones can have characteristic "tongues" of radiolucency (Fig. 747.2).

An **adult hypophosphatasia** form manifests in middle age (although some patients recount a history of early deciduous tooth loss or rickets). It is characterized by nonspecific symptoms and a milder course than pediatric forms. This form may be diagnosed after affected individuals present with osteopenia/osteoporosis, recurrent metaphyseal stress fractures (particularly of the metatarsals and tibiae), and femoral pseudofractures. Affected individuals can also have psychiatric symptoms (depression/anxiety) chondrocalcinosis, osteoarthritis, myopathy, nephrocalcinosis, and permanent tooth loss between 40-60 years of age.

Rarely, patients presenting with identical clinical and radiographic patterns have normal serum alkaline phosphatase activity but increased concentrations of phosphoethanolamine, inorganic phosphate, and pyridoxal-5-phosphate. Their disease has been labeled **pseudohypophosphatasia** and might represent the presence of a variant alkaline

Table 747.1 Hypophosphatasia Main Subtypes and Features

SUBTYPE	ONSET	INHERITANCE	CLINICAL FEATURES
Perinatal severe	Perinatal	Recessive	• Lethal in all cases without enzyme replacement • Prenatal US: absent skeletal mineralization, bowed/short long bones, fractures, osteochondral spurs, and pretibial dimpling • Death from respiratory distress from chest deformities and lung hypoplasia • Vitamin B6-dependent seizures
Prenatal benign	Perinatal	Dominant and recessive	• Skeletal deformity in utero without fractures ("bent not broken") • Improves spontaneously, benign course
Infantile	≤ 6 mo	Recessive	• Lethal in approximately 50% of cases without enzyme replacement • Appear normal at birth • Severe bone demineralization leads to rachitic chest deformities and resultant pulmonary hypoplasia • Hypercalcemic hypercalciuria (leads to nephrocalcinosis) • Craniosynostosis
Childhood	6 mo-18 yr	Dominant and recessive	• Premature loss of deciduous teeth with root intact in children <5 yr • Rickets/fractures/skeletal deformities • "Tongues" of radiolucency on x-ray • Chronic joint/bone pain • Short stature
Adult	Adulthood	Dominant and recessive	• Mild • Osteoporosis • Stress fractures, osteomalacia, and chondrocalcinosis
Odontohypophosphatasia	Childhood	Dominant and recessive	• Mildest form of HPP • No skeletal deformities; premature exfoliation of primary and/or permanent teeth • Severe dental caries

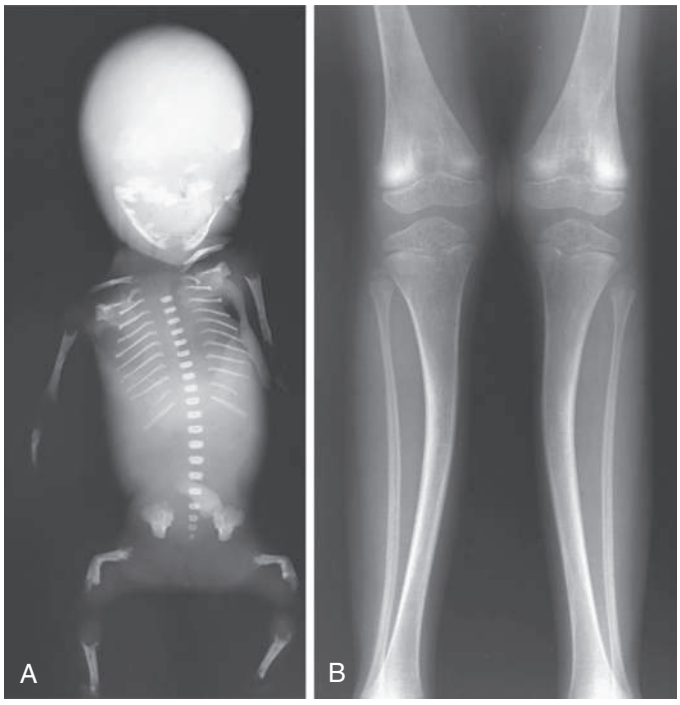

Fig. 747.1 A, Fetus with congenital lethal hypophosphatasia showing thin wavy ribs, platyspondyly, missing cervical vertebrae, ossification, and bent femurs. B, A 7-yr-old with hypophosphatasia tarda showing osteopenia, bent tibias, and punched-out metaphyseal lesions.

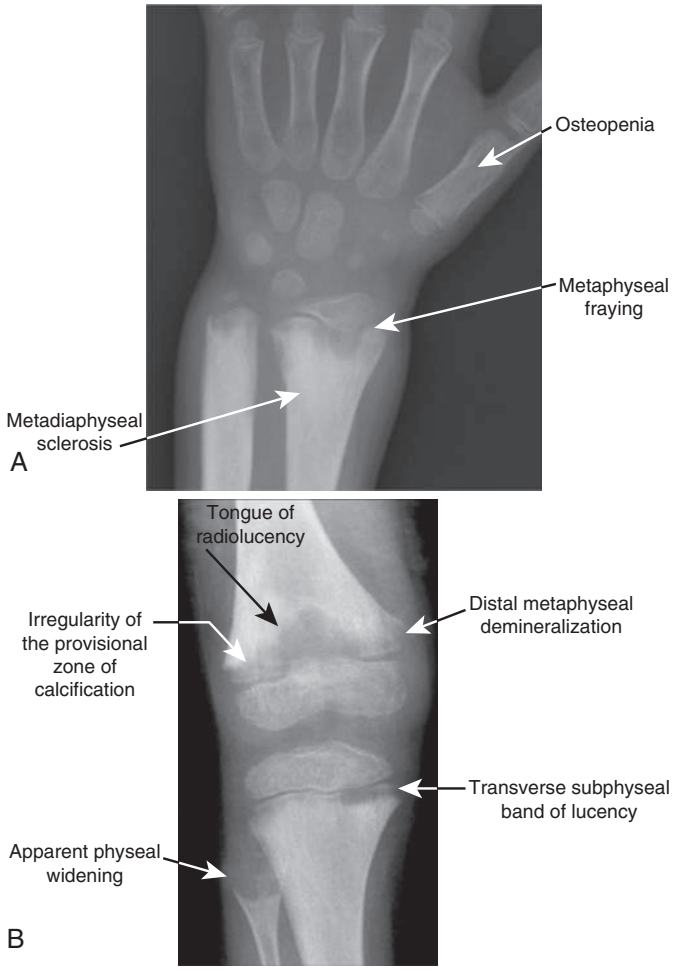

Fig. 747.2 Skeletal features of untreated hypophosphatasia. Untreated, the radiographic features of hypophosphatasia of the wrist (A) and knee (B) in children include osteopenia, metaphyseal fraying, metaphyseal flaring, metadiaphyseal sclerosis, characteristic "tongues" of radiolucency, irregularity of the provisional zone of calcification, distal metaphyseal demineralization, transverse subphyseal band of lucency, and apparent physeal widening. *(From Whyte MP, Madson KL, Phillips D, et al. Asfotase alfa therapy for children with hypophosphatasia. JCI Insight.2016;1:e85971, Fig. 2.)*

phosphatase isoenzyme that catalyzes artificial substrates in an alkaline environment (e.g., a test tube), but not in vivo with natural substrates.

Because of the heterogenous clinical manifestations of HPP, which often mimics other skeletal disorders, delays and misdiagnosis are common. Clinical features and radiologic findings in the setting of low ALP for age or other biomarkers of the disorder should raise suspicion. Initially the diagnosis might be suspected in the presence of a low serum ALP (adjusted for age and natal sex) and supported with an increased urinary phosphoethanolamine PEA level or high vitamin B6 concentrations. However, other etiologies for low ALP should be ruled out (Fig. 747.3 and Table 747.2).

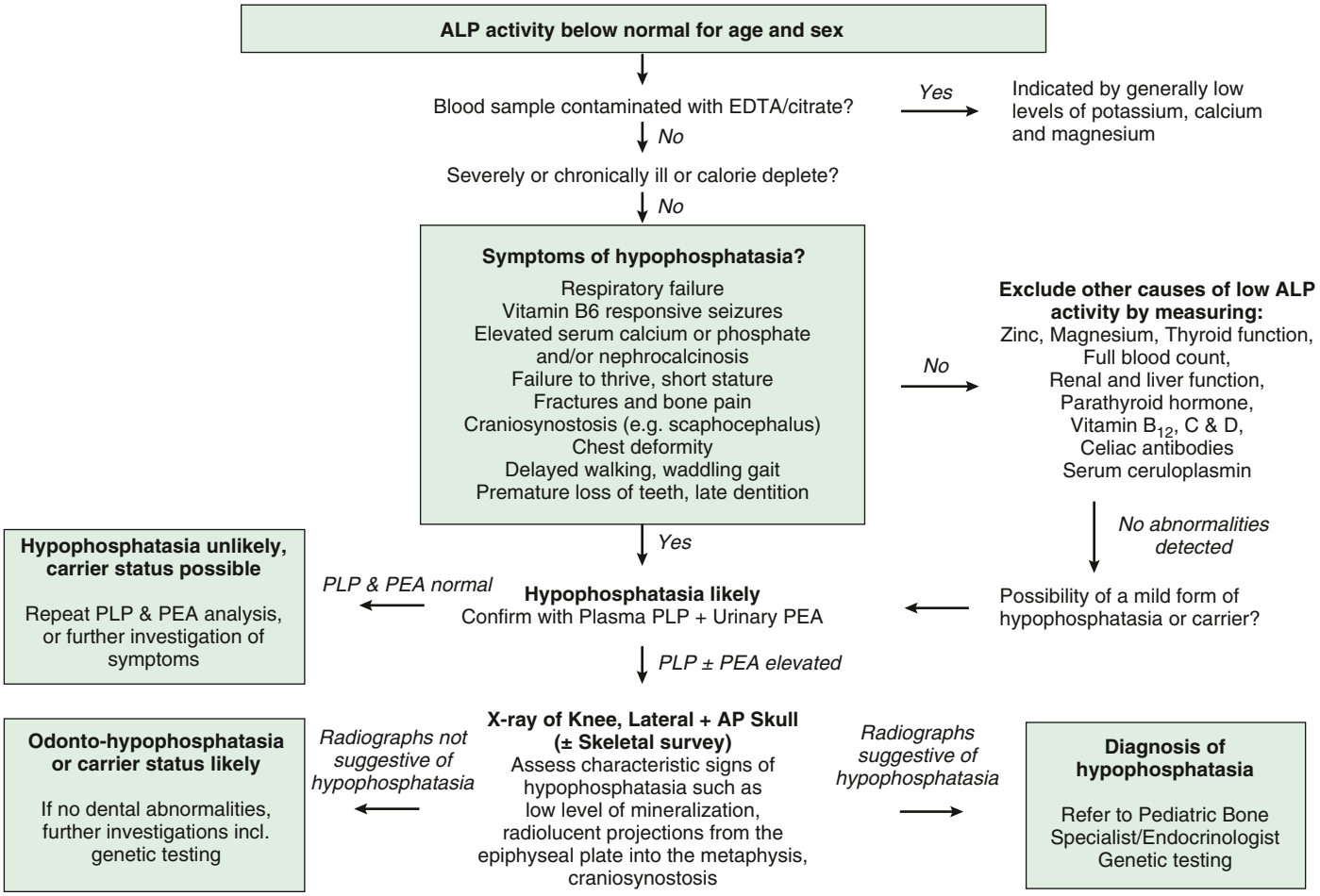

Fig. 747.3 Diagnostic algorithm for the investigation of children presenting with low ALP activity and/or symptoms of hypophosphatasia. For patients with low ALP, other conditions such as nutritional deficiencies (protein/calorie, zinc, folic acid, magnesium, vitamins B6, B12, and C), vitamin D excess, hypothyroidism, hypoparathyroidism, celiac disease, recent significant blood transfusions, renal osteodystrophy, cardiac surgery and cardiopulmonary bypass, posthepatic resection and transplantation, achondroplasia, and Wilson disease need to be excluded. AP, Anteroposterior; PEA, phosphoethanolamine; PLP, pyridoxal-5′-phosphate. *(From Saraff V, Narayanan VK, Lawson AJ, et al. A diagnostic algorithm for children with low alkaline phosphatase activities: lessons learned from laboratory screening for hypophosphatasia. J Pediatr. 2016;172:181–186. Fig. 3.)*

Table 747.2 Causes of Hypophosphatasemia

Cardiac bypass surgery	Milk-Alkali syndrome
Celiac disease	Multiple myeloma
Clofibrate therapy	Osteogenesis imperfecta, type II
Cleidocranial dysplasia	Pernicious or profound anemia
Cushing syndrome	Radioactive heavy metals
Hypophosphatasia	Starvation
Hypothyroidism	Vitamin C deficiency
Improperly collected blood (oxalate, EDTA)	Vitamin D intoxication
Inappropriate reference range	Wilson's disease
Massive transfusion	Zn^{++} or Mg^{++} deficiency

EDTA, Ethylenediaminetetraacetic acid
From Whyte MP. Hypophosphatasia: an overview for 2017. *Bone.* 2017;102:15–25. Table 1.

Some mild HPP forms require only symptomatic and supportive treatment. The primary treatment for more severe HPP is enzyme replacement therapy with recombinant human TNSALP (asfotase alfa). This therapy decreases the mortality rate in prenatal HPP and improves skeletal healing and mineral content, pulmonary status, and overall physical activity in other symptomatic forms.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 748

Hyperphosphatasia

Nourah N. Almutlaq and Linda A. DiMeglio

Hyperphosphatasia is a set of conditions characterized by hyperphosphatasemia (elevated serum alkaline phosphatase [ALP]). Increases in alkaline phosphatase are most commonly because of hepatobiliary disease or bone disorders characterized by high osteoblast activity, including nutritional rickets. Distinguishing liver from bone etiologies requires fractionating alkaline phosphatase isoenzymes or measuring bone-specific alkaline phosphatase as well as other laboratory assessments of liver function and bone turnover/vitamin D status. ALP activity varies by age and gender; therefore, specific reference ranges should be employed. It is usually higher in pediatric populations than adults, peaking at times of high bone formation including in the first 6 months and during pubertal growth.

In children younger than 5 years, marked increases in alkaline phosphatase without clinical or laboratory evidence of liver or bone disease is most often because of **benign transient hyperphosphatasemia** generally detected as an incidental finding during screening laboratory evaluations or evaluations performed to assess a specific complaint. The cause may be related to excess sialylation of alkaline phosphatase, which slows clearance. Cases often follow viral illness, including SARS-CoV-2 infection. Serum alkaline phosphatase values as high as 3,000-6,000 IU/L may be encountered. Liver and bone isoenzyme fractions are both elevated; there are no other clinical or laboratory signs of hepatic or bone disease. Diagnosis is confirmed by a careful clinical history plus laboratory assessments of calcium, phosphorus, creatine, AST, ALT, GGT, bilirubin, PTH, and 25-hydroxyvitamin D. A CBC should also be drawn to rule out oncologic processes. Alkaline phosphatase should be followed serially (every 2-3 months) until resolution is documented. The condition usually resolves within 16 weeks without intervention and does not recur.

Juvenile Paget disease (familial hyperphosphatasemia, idiopathic hyperphosphatasia or IHH) is a rare autosomal recessive bone disease hallmarked biochemically by marked serum ALP activity elevation. Most cases are because of loss-of-function variants in the tumor necrosis factor receptor superfamily, member 11B gene (TNFRSF11B) that encodes osteoprotegerin (OPG). OPG inhibits osteoclastogenesis and osteoclast activity by preventing receptor activator of nuclear factor κ-B (RANK) ligand (RANKL) from binding to its receptor RANK. Affected children are asymptomatic at birth and gradually develop progressive long bone deformity (including kyphoscoliosis), bone pain, and significant fractures. X-rays show bowing and diaphyseal thickening, along with osteopenia (Fig. 748.1). Radiographically, the bony texture is variable; dense areas (showing a teased cotton-wool appearance) are interspersed with radiolucent areas and general demineralization. Long bones appear cylindrical, lose metaphyseal modeling, and contain pseudocysts that show a dense, bony halo. Children with juvenile Paget disease have short stature, large skulls with a thickened cranium (widened diploë) that may be deformed, and progressive and profound hearing loss. There is substantial phenotype variability; some cases are diagnosed in infancy and others in late childhood. This disorder is distinct from adult Paget disease (osteitis deformans) because bone histology reveals a lack of normal cortical bone remodeling and an absence of the classic mosaic pattern of lamellar bone found in the adult condition. Given the rarity of this disorder, there is no strong evidence surrounding optimal clinical management; however, antiresorptive therapy with bisphosphonates is associated with clinical, biochemical, and radiographic improvement.



Fig. 748.1 Juvenile Paget disease showing bowing and thickening of the diaphyses and osteopenia. *(From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby, 2008. Fig. 167–226, p. 2744.)*

Other rare forms of hyperphosphatasia include **expansile skeletal hyperphosphatasia (ESH)** caused by dominant variants in the *TNFRSF11A* gene encoding receptor activator of RANK, which regulates osteoclastogenesis, and **hyperphosphatasia-mental retardation syndrome** caused by recessive variants in *PIGV* in the glycosylphosphatidylinositol (GPI)-anchor biosynthesis pathway.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 749

Osteoporosis

Rebecca J. Gordon and Catherine M. Gordon

Osteoporosis, the most common bone disorder in adults, is relatively uncommon in children and adolescents; the criteria that underlie this diagnosis in young patients are a source of debate. This disorder is characterized by diminished bone volume and a marked increase in the prevalence of fractures. In contrast to osteomalacia, which shows undermineralization and normal bone volume, histologic sections of bone in all forms of osteoporosis reveal a normal degree of mineralization but a reduction in the volume of bone, especially trabecular bone (vertebral bone). The **diagnosis of osteoporosis in children and adolescents** requires evidence of skeletal fragility with: (1) a clinically significant fracture history, which is defined as at least two long bone fractures in children less than 10 years old, at least three long bone fractures by 19 years old, or any vertebral fractures; and (2) low bone density, with age, sex, and ancestry-matched bone mineral density (BMD) Z-score ≤ –2.0, assessed by dual-energy x-ray absorptiometry (DXA).

Blood values of minerals (e.g., calcium, phosphorus), vitamin D metabolites, alkaline phosphatase, and parathyroid hormone are usually normal. Evaluation of bone mineral content and areal bone density by DXA is the clinical gold standard for measuring BMD. DXA evaluation in patients 15 years of age or younger includes total body less head and lumbar spine, and in those 16 years and older includes lumbar spine and hip. In certain clinical scenarios, it may be useful to obtain alternative sites, such as the distal femur or forearm scan. Additional research modalities allow for the assessment of bone microarchitecture (e.g., trabecular versus cortical bone), quality, and strength, such as peripheral quantitative CT and trabecular bone score.

In the pediatric age group, osteoporosis may be primary or secondary (Table 749.1, Fig. 749.1). The primary osteoporoses can be divided into heritable disorders of connective tissue, including osteogenesis imperfecta (see Chapter 742), Bruck syndrome, osteoporosis-pseudoglioma syndrome, Ehlers-Danlos syndrome (see Chapter 744), Marfan syndrome (see Chapter 743), homocystinuria, and idiopathic juvenile osteoporosis. Secondary forms of osteoporosis include various neuromuscular disorders, chronic illness, endocrine disorders, and drug-induced and inborn errors of metabolism, including lysinuric protein intolerance and Gaucher disease.

When no obvious primary or secondary cause can be detected, **idiopathic juvenile osteoporosis** should be considered, especially if the following clinical features are evident: onset before puberty, long bone and lower back pain, vertebral fractures, long bone and metatarsal fractures, a washed-out appearance of the spine and appendicular skeleton on standard radiographs, and improvement of bone density after puberty. Trabecular bones such as the spine and metatarsals are particularly affected by atraumatic fractures. Several modes of therapy (including oral calcium supplements, calcitriol, bisphosphonates, and calcitonin) have been used with some success in individual conditions, but the effect of these treatments is difficult to gauge because spontaneous recovery occurs after the onset of puberty in more than 75% of cases.

Osteoporosis-pseudoglioma syndrome is an autosomal recessive disorder manifested by variable age at onset, low bone mass, fractures in childhood, and abnormal eye development. It is caused by pathogenic loss of function variants in *LRP5*, which encodes the low-density lipoprotein receptor-related protein 5. Interestingly, gain-of-function pathogenic variants to this gene result in increased bone density.

The life-cycle implications of either significant demineralization or osteoporosis in childhood need to be stressed. Events in childhood influence peak bone mass, and late adolescence is a period of rapid bone mineral accretion. Peak bone mass is typically achieved by 20-25 years of age (depending on the bone measured), and the contribution during childhood is considerable. A number of measures influence bone mass including adequate calcium intake, vitamin D sufficiency, weight-bearing physical activity, and body mass index (BMI) within a healthy range. General recommendations include achieving the recommended daily allowance (RDA) of calcium for age. Excellent and convenient sources of dietary calcium include dairy products, but also bony fish, green vegetables, and calcium-supplemented drinks (e.g., orange juice). Yogurt and hard cheeses can be used in many lactase-deficient children. Also, a serum 25-hydroxyvitamin D level between 30-50 ng/mL in those with known threats to bone health can be beneficial to maximize calcium absorption and ensure normal range parathyroid hormone. Weight-bearing exercise

Table 749.1 Diagnoses That Confer Increased Risk for Osteoporosis

ENDOCRINE DISORDERS
Female Hypogonadism
Turner syndrome
Hypothalamic amenorrhea (female athletic triad)
Anorexia nervosa
Premature ovarian insufficiency
Depot medroxyprogesterone acetate therapy
Estrogen receptor α (ESR1) pathogenic variants
Hyperprolactinemia
Male Hypogonadism
Primary gonadal failure (Klinefelter syndrome)
Secondary gonadal failure (idiopathic hypogonadotropic hypogonadism)
Delayed puberty
Hyperthyroidism
Hyperparathyroidism
Hypercortisolism (therapeutic or Cushing disease)
Growth hormone deficiency
Thyrotoxicosis
INFLAMMATORY DISORDERS
Dermatomyositis
Chronic hepatitis
Juvenile idiopathic arthritis
Systemic lupus erythematosus
GASTROINTESTINAL DISORDERS
Malabsorption syndromes (cystic fibrosis, celiac disease, biliary atresia)
True or perceived lactose intolerance
Inflammatory bowel disease
Chronic obstructive jaundice
Primary biliary cirrhosis and other cirrhoses
Alactasia
Subtotal gastrectomy
BONE MARROW DISORDERS
Bone marrow transplant
Lymphoma
Leukemia
Hemolytic anemias (sickle cell anemia, thalassemia)
Systemic mastocytosis
CONNECTIVE TISSUE/BONE DISORDERS
Idiopathic juvenile osteoporosis
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Marfan syndrome
Homocystinuria
Fibrous dysplasia
Previous or recurrent low impact fractures
Early-onset osteoporosis with *WNT1* pathogenic variants
X-linked osteoporosis with fractures with *PLS3* pathogenic variants
DRUGS
Alcohol
Heparin
Glucocorticoids
Thyroxine
Anticonvulsants
Gonadotropin-releasing hormone agonists
Cyclosporine
Chemotherapy
Tobacco cigarettes
MISCELLANEOUS DISORDERS
Immobilization (cerebral palsy, spinal muscular atrophy, Duchenne muscular dystrophy)
Chronic renal disease
Glycogen storage disease type 1
Chronic hepatitis
Hypophosphatasia
Low calcium dietary intake
Gaucher disease
Severe congenital neutropenia

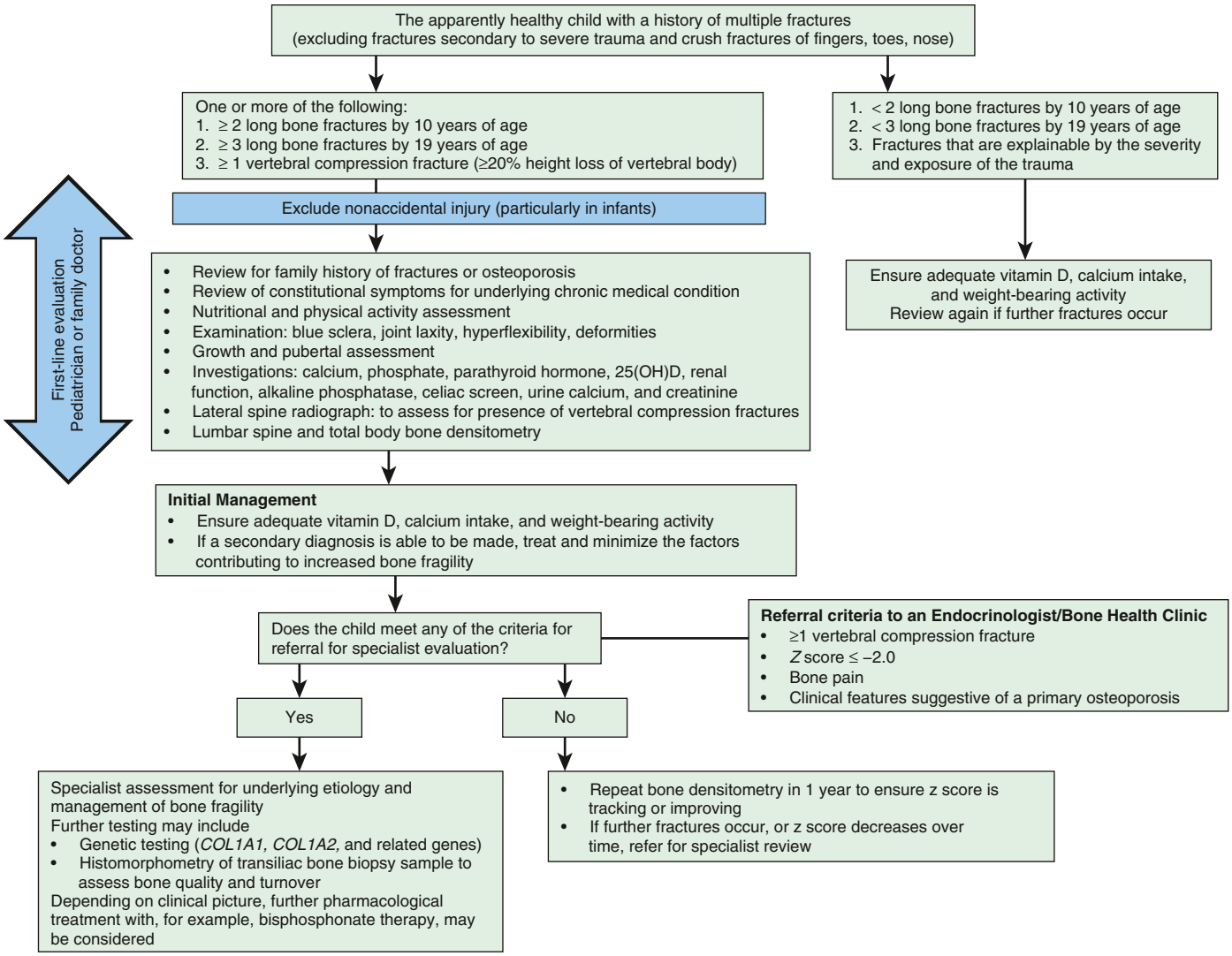

Fig. 749.1 An algorithm for the management of a child presenting with a clinically significant fracture history. The algorithm outlines the initial evaluation, management, and when to consider referral for specialist review. *(Data from Mayranpaa MK, Viljakainen HT, Toiviainen-Salo S, et al. Impaired bone health and asymptomatic vertebral compressions in fracture-prone children: a case-control study. J Bone Miner Res. 2012;27:1413–1424; and Bishop N, Arundel P, Clark E, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions. J Clin Densitom. 2014;17:275–280.)*

enhances bone formation and reduces bone resorption. Factors that can prevent acquisition of peak bone mass include the use of alcohol and tobacco. Because it appears that adult-onset osteoporosis stems primarily from genetic factors, representing a complex trait interaction, specific interventions during childhood to augment bone mass are not available.

The treatment of secondary osteoporosis is best achieved by treating the underlying disorder when feasible (see Fig. 749.1). Hypogonadism should be treated with hormone replacement therapy, but in adolescent girls, nutritional issues should first be addressed and, ultimately, prescription of transdermal over oral estrogen (see Chapter 732). Calcium intake should be increased to 1,500-2,000 mg/day. In glucocorticoid-induced osteoporosis, an emphasis is placed on the lowest possible dose to prevent disease activity (e.g., in children with inflammatory bowel disease) with alternate-day dosing or, when appropriate, topical (e.g., eczema) or inhaled (e.g., asthma) glucocorticoids. Special diets for inborn errors of metabolism are also appropriate, as well as enzymatic replacement for diseases such as hypophosphatasia, a genetic disorder leading to deficient endogenous alkaline phosphatase production and defective bone mineralization. Screening for celiac disease should be carried out in unexplained cases of low bone mass, as adherence to a gluten-free diet can significantly enhance bone health in these patients (see Chapter 384).

Treatment with bisphosphonates that inhibit bone resorption in certain secondary (e.g., glucocorticoid-induced) and adult-onset osteoporosis has been successful. Bisphosphonate therapy can also be beneficial for children and adolescents and has historically been used with osteogenesis imperfecta and cerebral palsy. The use of bisphosphonates has expanded to additional patient populations with secondary osteoporosis, such as recurrent fractures and low bone mineral density, and high risk for skeletal fragility because of their underlying medical conditions. In consultation with a metabolic bone expert, bisphosphonate treatment should be considered in the following patient populations: Duchenne muscular dystrophy, spinal muscular atrophy, and other nonambulatory patients (i.e., cerebral palsy, metabolic disorders). All modifiable risk factors should be addressed, including adequate calcium intake; sufficient vitamin D; weight-bearing physical activity, such as time within a stander and physical therapy; healthy range BMI; and evaluation of overall heath (i.e., regular menstrual periods in adolescent girls, no other endocrinopathies, and optimizing the treatment status of the underlying medical condition).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Rehabilitation Medicine

PART XXXI

Chapter 750

Rehabilitation for Traumatic Brain Injury

Chong-Tae Kim and J. Michael King

Traumatic brain injury (TBI) is a major cause of pediatric disability in children older than 1 year old in the United States (see Chapter 82). According to data from the Centers for Disease Control and Prevention (2006–2010), TBI due to falls (72.8%) is most common in the 0-4 age range. **Nonaccidental TBI** remains a significant cause of TBI at this age (20-30 cases/100,000) (see Chapter 17). Falls (35.1%) and being struck by or against an object (34.9%) are most common in those 5-14 years of age. Assaults, falls, and motor vehicle injuries make up to 85% of the TBI experienced in those 15-24 years of age. TBI is more common in males than females at all ages.

PATHOPHYSIOLOGY

TBI is the consequence of primary and secondary injury (see Chapter 82). Primary injury results from direct physical impact. Secondary injury is the consequence of aberrant neurochemical homeostasis after primary injury (Fig. 750.1). This injury mechanism helps explain why individuals may experience global dysfunction of the brain despite relatively small or focal brain lesions on imaging studies. Minimizing secondary injury is critical to preventing further brain insult after the primary injury.

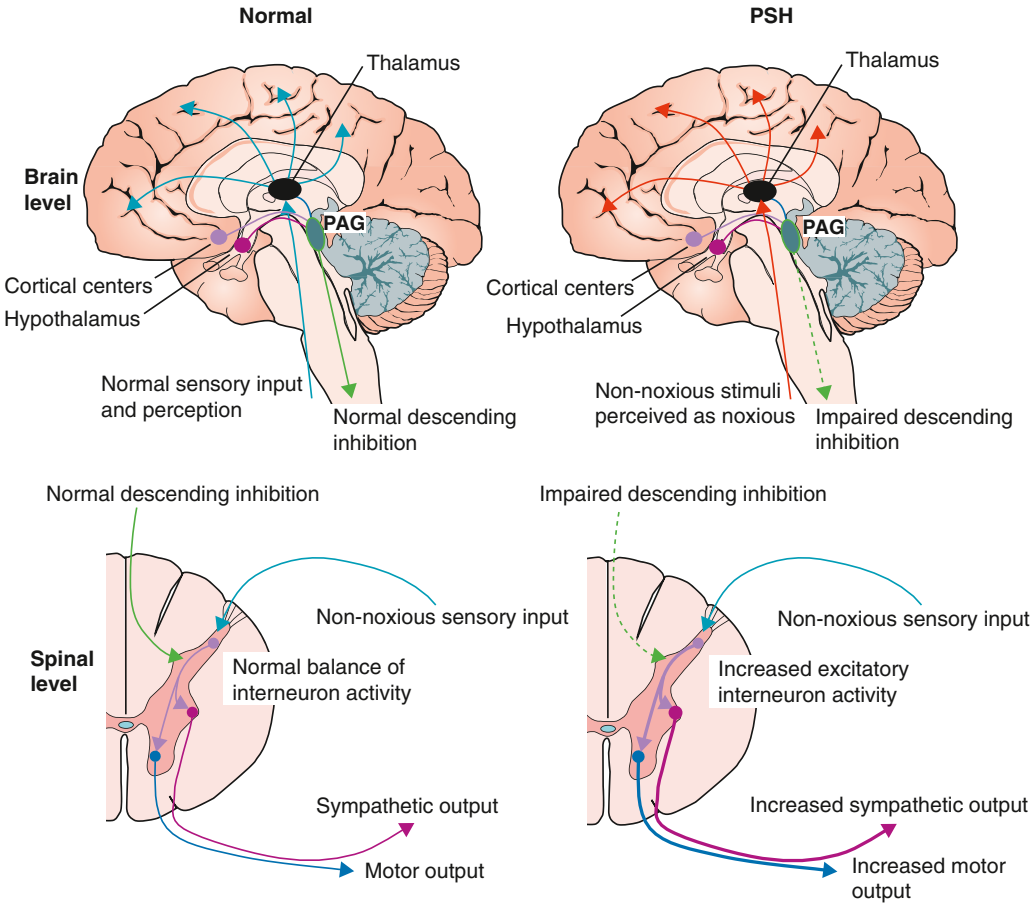

Fig. 750.1 Excitatory:inhibitory ratio model of the pathogenesis of PSH. In normal circumstances, various cortical, hypothalamic, thalamic, and other subcortical inputs modulate activity within brainstem centers—the PAG is shown here as one of the key brainstem hubs in this process. These brainstem nuclei provide inhibitory drive to spinal-reflex arcs, thereby maintaining balance between inhibitory and excitatory interneuron influences on motor and sympathetic efferents, allowing normal sensory stimuli to be perceived as nonnoxious. In the excitatory:inhibitory ratio model of PSH, disconnection of descending inhibition produces maladaptive dendritic arborization and spinal-circuit excitation, with nonnoxious stimuli triggering increased motor and sympathetic output (spinally) and potentially becoming perceived as noxious (centrally). PAG, Periaqueductal grey. PSH, paroxysmal sympathetic hyperactivity. *(From Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. Lancet. 16:721–729, 2017 [Fig. 2].)*

Very young children who have not yet closed their cranial sutures accommodate some increase in intracranial pressure that may result from TBI. However, young children have a relatively large head size compared with their body, higher brain water content, and less myelination, all of which may contribute to greater brain distortion and injury than from a comparable injury experienced by an adult.

SEVERITY

The acute severity of TBI is typically classified with the **Pediatric Glasgow Coma Scale** (GCS) (see Chapter 82). GCS scores of 13-15 are considered mild TBI, 9-12 moderate TBI, and 3-8 severe TBI. Additional parameters may be helpful in classifying severity. The longer the duration of loss of consciousness (i.e., <30 min, <24 hr, or >24 hr), the more severe the TBI. Longer duration of posttraumatic amnesia (<1 day, 1-7 days, or >7 days) is also reflective of a more severe TBI. Biomarkers (chemicals sensitive to nerve tissues) are being investigated as potential indicators of severity.

MEDICAL COMPLICATIONS

Disorders of Consciousness

Children with severe TBI manifest various levels of altered consciousness (Table 750.1). They may progress from coma to unresponsive wakefulness syndrome (formerly vegetative state) and/or minimally conscious state. The longer the period of impaired consciousness, the poorer the functional recovery. Rapid transition from coma/unresponsive wakefulness syndrome to a minimally conscious state increases the possibility of better recovery. As patients recover from impaired consciousness, they may have altered circadian sleep–wake patterns. In this phase, it is particularly important to **avoid overstimulation at night**, such as with procedures, and to avoid sedative medications during the day. **A sleep diary** over a period of several days to a week is a useful measure to monitor sleep patterns and determine the effectiveness of medications. **Neurostimulators** (e.g., amantadine, bromocriptine, methylphenidate, or L-dopa) may be used to improve arousal during the day. Trazodone or melatonin may help facilitate sleep onset or maintenance at night, respectively. Modafinil or donepezil can be tried if the above neurostimulators are ineffective. Paradoxically zolpidem has been reported to improve alertness in several cases.

Cognitive-Behavioral Disorders

The management and outcome of mild TBI (concussion) are discussed in Chapter 729. As patients with severe TBI recover from initial low levels of consciousness, they may demonstrate significant cognitive-behavioral disorders, such as agitation, aggression, decreased frustration tolerance, impulsivity, inattention, emotional lability, perseveration, impaired working memory, and poor safety awareness and judgement. Agitation is common in the early stages of recovery. The first line of management for agitation is to decrease excessive environmental, visual, auditory, and tactile stimulation. Physical constraint is typically implemented as a last resort to prevent harm to the patient and others, and it should be removed as soon as the danger has resolved. The **Rancho Los Amigo scale** (RLAS) (Table 750.2) may be used to evaluate the level of this impairment. It is important to exclude potential exacerbating factors or medical causes of impaired mental status and behavior, including electrolyte abnormalities, infection, and concomitant injuries in patients who incur multiple traumas including severe TBI. Posttraumatic amnesia can be particularly debilitating because it may limit the acquisition and retention of new learning skills. The **Children's Orientation and Amnesia Test** may be helpful in determining when a patients' posttraumatic amnesia has ended, after which these children may be candidates for cognitive rehabilitation. This test assesses **general orientation** (name, age, birthdate, school, etc.), **temporal orientation** (current time, day of the week, year, etc.), and **memory** (verbal and nonverbal).

Most patients who have moderate or severe TBI will have varying degrees of long-term residual cognitive impairments, which can include impaired judgment, attention deficits, and impaired working memory (see Chapter 49). The most rapid recovery in cognitive skills tend to occur in the first year after the TBI. Children with more severe injuries and children from lower socioeconomic status (SES) families tend to have more significant long-term deficits after a TBI.

Table 750.1 Level of Consciousness

	COMA	UNRESPONSIVE WAKEFULNESS SYNDROME	MINIMALLY CONSCIOUS STATE (–)	MINIMALLY CONSCIOUS STATE (+)
Eye opening	None	Spontaneous or to stimulus	Spontaneous	Spontaneous
Brain stem reflexes	None	Present	Present	Present
Orientation	None	None	Inconsistent	Consistent
Purposeful response	None	None	Trivial responses with localization (visual fixation or tracking, localization to pain)	Evident reliable responses with verbal, behavioral, and/or motor

Table 750.2 Rancho Los Amino Scale

LEVEL	COGNITIVE-BEHAVIORAL CHARACTERISTICS	CLINICAL FEATURES
I	No response	Comatose state
II	Generalized response	Nonpurposeful, reflexive, stereotyped response to simulations
III	Localized response	Specifically localized (head turn, blink eye, grasp), consistent response to stimulations
IV	Confused-agitated	Confused and hyperactive or bizarre behavior
V	Confused-inappropriate	Less agitated and able to follow simple instructions consistently but difficult to follow complicated ones
VI	Confused-appropriate	Still impaired recent memory, needs assistance for unfamiliar situations
VII	Automatic-appropriate	Able to do daily routine independently but has difficulty solving problems
VIII	Purposeful-appropriate	Independent and functional in activities at home and community but may have some difficulties in stressful situations

Posttraumatic Seizure

The incidence of posttraumatic seizure (PTS) is dependent on injury severity and age. About 30–35% of children with severe TBI will experience a PTS. Very early-onset PTS may develop within 24 hours after a TBI, early-onset PTS within 7 days, and late onset more than 7 days after a TBI. Early-onset PTS is more common in children, and late-onset PTS is more common in adults. The risk of late-onset PTS is increased in particularly severe TBI, those caused by penetrating injury, the presence of subdural hematoma, in injuries occurring in children younger than 5 years, and in patients with a history of early-onset PTS. Prophylactic treatment with an antiepileptic medication for 7 days after a TBI is commonly prescribed (see Chapter 82). However, treatment with an antiepileptic medication beyond 1 week offers no further benefit as a prophylactic agent. The risk of PTS decreases to the same incidence as in the general population after 5 years from TBI.

Paroxysmal Sympathetic Hyperactivity

Paroxysmal sympathetic hyperactivity (PSH) is a constellation of symptoms manifested by hyperthermia, tachycardia, tachypnea, diaphoresis, and increased tone, including dystonic posturing. It is primarily attributable to autonomic dysregulation. The mechanism has not been clearly defined but is thought to be because of disruption of the inhibitory function of the mesencephalon on the diencephalon (see Fig. 750.1). Some drug-related symptoms may mimic the features of PSH and may require discontinuation and the use of alternative medication; for example, haloperidol and chlorpromazine may cause neuroleptic malignant syndrome, and phenytoin may precipitate a fever. The assessment measure pediatric PSH-AM is suggested to improve diagnostic sensitivity (Tables 750.3, 750.4, and 750.5). There is no current established standard of care for management of PSH, but bromocriptine, propranolol or labetalol, clonidine, amantadine, intrathecal baclofen, morphine, benzodiazepine, and gabapentin have been prescribed with variable success. Morphine, fentanyl, propofol, propranolol, and gabapentin have consistently been effective in adult patients for both prevention and treatment. Most patients require more than one class of medication (opioid, beta blockers, alpha 2 agonists, neuromodulators, benzodiazepines, sarcolemmal calcium release blockers). Oral baclofen, Dilantin, and carbamazepine are reported to be ineffective for PSH. PSH is a negative factor for short-term but not long-term functional outcomes.

Neuroendocrine Disorders

Hypothalamic-pituitary injury that occurs with TBI can cause various endocrine disorders. Growth hormone deficiency is the most common and results in growth retardation. Precocious puberty, more common in females than males, may result from loss of neural inhibition on gonadotropin release. Three different types of salt and water metabolism derangements, diabetes insipidus (DI), syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and cerebral salt wasting (CSW) can develop after a severe TBI (see Chapter 82).

Spasticity

Spasticity is a major complication that develops in children with severe TBI (see Chapter 752).

OUTCOME ASSOCIATED WITH SEVERE TRAUMATIC BRAIN INJURY

Given different mechanisms of injury, younger children who incur a severe brain injury tend to have better functional outcomes than older children. However, given the same severity of TBI, the outcome of very young children is poorer than that of older children. The age defined as "very young children" (2-5 years) is variable depending on the studies. The specific reason for this difference in outcomes has not been identified, but a plausible explanation is that although very young children demonstrate a higher potential for neuroplasticity with focal brain injuries, their immature and developing brains are more vulnerable to the diffuse effects on the brain of most forms of TBI.

The GCS score is a strong prognostic factor for mortality and functional outcome in the acute injury phase but not for functional outcome in the subacute or chronic phase for children within the severe TBI group. Duration of posttraumatic amnesia or time to follow commands are better prognostic factors for long-term functional outcomes.

Cognitive and behavioral impairments (poor memory-learning and executive skills, hyperactivity, depression, awareness deficits) are the most common and long-lasting sequelae of TBI. These deficits can inhibit successful school reentry and participation in social activities.

Given the same severity, the long-term functional outcome of children who sustain nonaccidental (inflicted) trauma is worse than that of children with other forms of TBI. Children who incur nonaccidental trauma are typically very young. If developmentally delayed before their brain injury, they are likely to have poorer long-term functional outcomes. The

Table 750.3 Pediatric PSH-AM Pediatric Clinical Feature Scale (PCFS)

	AGE (YR)	0	1	2	3
Heart rate	1-4	<110	100-124	125-139	≥140
	5-15	<100	100-119	120-139	≥140
Respiratory rate	1-4	<30	30-34	35-39	≥40
	5-15	<25	25-29	30-34	≥35
Systolic BP	1-4	<100	100-109	110-119	≥120
	5-15	<120	120-129	130-139	≥140
Diastolic BP	1-4	<65	65-72	73-79	≥80
	5-15	<75	75-82	83-89	≥90
Temperature		37	37-37.9	38-38.9	≥39
Sweating		Normal	Increased sweating	Localized diaphoresis	Generalized diaphoresis
Posturing (muscle tone) during episode		None	Mild increase	Neat increase	Generalized spasticity/opisthotonos

Severity of CF (subtotal score of PCFS): Nil =0, Mild 1-6, Moderate 7-12, Severe ≥13
BP, Blood pressure; PSH-AM, paroxysmal sympathetic hyperactivity-assessment measure.

Table 750.4 Pediatric Diagnosis Likelihood Tool (PDLT)

	PRESENT/ABSENT (1/0)
1. Clinical features occur simultaneously	
2. Episodes are paroxysmal in nature	
3. Sympathetic overactivity to normally nonpainful stimuli	
4. Features persist > 3 consecutive days	
5. Features persist > 1 week postinjury	
6. Features persist despite treatment of alternative differential diagnoses	
7. At least single episode daily	
8. Medication administered to decrease sympathetic features	
9. Absence of parasympathetic features during episodes	
10. Absence of other presumed cause of features	
11. Antecedent acquired brain injury	

Table 750.5 Pediatric PSH-AM

PSH DIAGNOSTIC LIKELIHOOD	COMBINED TOTAL (PCFS + PDLT)
Unlikely	<8
Possible	8-16
Probable	>17

PSH-AM, paroxysmal sympathetic hyperactivity assessment measure; PCFS, pediatric clinical feature scale; PDLT, pediatric diagnosis likelihood tool.

long-term functional outcome of children who sustain a TBI is better than those who sustain a nontraumatic (anoxic) brain injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 751

Spinal Cord Injury and Autonomic Dysreflexia Management

Ashlee M. Jaffe and Abigail Case

See Chapter 81.

Individuals from birth to 21 years of age account for 25% of all cases of traumatic **spinal cord injury (SCI)**. Children are more susceptible to lap-belt injuries, upper cervical injuries, SCIs without radiologic abnormalities **(SCIWORA)**, and delayed onset of neurologic deficits, ranging from 30 minutes to 4 days. A population-based study found the epidemiology of pediatric spinal injury in the US varies greatly by age, ethnicity, and payor. Low-income populations are more likely to sustain spinal cord injury due to firearms than other populations.

The most accurate way to evaluate a patient who has sustained an SCI is by performing a standardized physical examination, as endorsed by the International Standards for Neurological and Functional Classification of SCI, recommended for children 6 years of age and older (Fig. 751.1). Life expectancy is related to the neurologic level of injury and the American Spinal Injury Association (ASIA) impairment scale classification.

CLINICAL MANIFESTATIONS

Immediately after an SCI, there is typically a period of **spinal shock** with low tone and absent reflexes. Eventually, signs of an **upper motor neuron** lesion may emerge, including spasticity and involuntary muscle spasms. However, if there is a substantial segment of spinal cord infarction present, patients may have persistent flaccid paralysis.

Children with neurologic levels of injury at T6 or above are at particular risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, **autonomic dysreflexia (AD)**. AD is a sustained sympathetic response as a result of a noxious stimulus *below* the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of the skin above the level of injury, although vague symptoms such as fatigue, irritability, or crying may be the presenting symptoms in younger patients. Noxious stimuli resulting from bladder or rectal distention is a common cause of AD, but there are a large number of other causes that need to be considered (Table 751.1). Children and adolescents with cervical and upper thoracic level SCI have lower baseline blood pressures (BPs) compared with the general population. Therefore caution should be used when referencing age-appropriate BPs because BP elevations of even 20-40 mm Hg above this lower baseline may be suggestive of AD. *Identification and treatment of the noxious stimulus is typically associated with resolution of symptoms without the use of antihypertensive medication.* If necessary, antihypertensive agents with a rapid onset and short duration, such as nifedipine and nitropaste, are advocated to treat elevated BP while the underlying cause is identified (Fig. 751.2). Emergent management of AD is necessary because of the risk of stroke and additional organ damage resulting from sustained hypertension. Consideration of a medical alert bracelet, education of supervising adults, and carrying of an AD emergency reference card is recommended (Fig. 751.3).

Patients with SCI are particularly vulnerable to **deep venous thrombosis** and **pulmonary embolism** because of immobilization of their affected limbs and venous stasis during the first 90 days after an injury. Deep venous thromboses are more common in postpubertal children >14 years old than in younger children. Mechanical prophylaxis (graduated compression stockings and sequential calf compression devices) are recommended for all children with acute SCI; adolescents should also start anticoagulant thromboprophylaxis, especially if additional risk factors like lower extremity fractures are present (unless contraindicated because of the risk of bleeding or prior allergic response). Late-occurring deep venous thrombosis most commonly occurs with prolonged immobilization related to illness or surgery, and prophylactic measures should be continued during these situations as well.

Consequent of SCI, patients often present with varying degrees of bowel and bladder incontinence. After an SCI, the bladder can be areflexic or hyperreflexic, and detrusor sphincter dyssynergia may occur. Clean intermittent catheterization (CIC) of the bladder is typically performed up to 4-6 times/day to prevent urinary retention and vesicoureteral reflux. Constipation can negatively impact the success of a CIC program. Anticholinergic medications may improve bladder storage capacity and prevent urinary incontinence between bladder catheterizations. *Antibiotics are only recommended for symptomatic urinary tract infections; asymptomatic bacteriuria, without vesicoureteral reflux, is generally due to colonization and typically not treated.* If intermittent catheterization is required, one can begin teaching the skills necessary for independent catheterization as early as 3 years of age with a goal of obtaining complete independence by 5-7 years old reflecting the progression toward independent bladder management of the child's able-bodied peers.

Bowel continence programs can be successfully introduced around 2-4 years old. There should be an attempt to distinguish between upper motor neuron (UMN) and lower motor neuron (LMN) bowel dysfunction because the management and bowel agents chosen may vary

Table 750.4 Pediatric Diagnosis Likelihood Tool (PDLT)

	PRESENT/ABSENT (1/0)
1. Clinical features occur simultaneously	
2. Episodes are paroxysmal in nature	
3. Sympathetic overactivity to normally nonpainful stimuli	
4. Features persist > 3 consecutive days	
5. Features persist > 1 week postinjury	
6. Features persist despite treatment of alternative differential diagnoses	
7. At least single episode daily	
8. Medication administered to decrease sympathetic features	
9. Absence of parasympathetic features during episodes	
10. Absence of other presumed cause of features	
11. Antecedent acquired brain injury	

Table 750.5 Pediatric PSH-AM

PSH DIAGNOSTIC LIKELIHOOD	COMBINED TOTAL (PCFS + PDLT)
Unlikely	<8
Possible	8-16
Probable	>17

PSH-AM, paroxysmal sympathetic hyperactivity assessment measure; PCFS, pediatric clinical feature scale; PDLT, pediatric diagnosis likelihood tool.

long-term functional outcome of children who sustain a TBI is better than those who sustain a nontraumatic (anoxic) brain injury.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 751

Spinal Cord Injury and Autonomic Dysreflexia Management

Ashlee M. Jaffe and Abigail Case

See Chapter 81.

Individuals from birth to 21 years of age account for 25% of all cases of traumatic **spinal cord injury (SCI)**. Children are more susceptible to lap-belt injuries, upper cervical injuries, SCIs without radiologic abnormalities **(SCIWORA)**, and delayed onset of neurologic deficits, ranging from 30 minutes to 4 days. A population-based study found the epidemiology of pediatric spinal injury in the US varies greatly by age, ethnicity, and payor. Low-income populations are more likely to sustain spinal cord injury due to firearms than other populations.

The most accurate way to evaluate a patient who has sustained an SCI is by performing a standardized physical examination, as endorsed by the International Standards for Neurological and Functional Classification of SCI, recommended for children 6 years of age and older (Fig. 751.1). Life expectancy is related to the neurologic level of injury and the American Spinal Injury Association (ASIA) impairment scale classification.

CLINICAL MANIFESTATIONS

Immediately after an SCI, there is typically a period of **spinal shock** with low tone and absent reflexes. Eventually, signs of an **upper motor neuron** lesion may emerge, including spasticity and involuntary muscle spasms. However, if there is a substantial segment of spinal cord infarction present, patients may have persistent flaccid paralysis.

Children with neurologic levels of injury at T6 or above are at particular risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, **autonomic dysreflexia (AD)**. AD is a sustained sympathetic response as a result of a noxious stimulus *below* the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of the skin above the level of injury, although vague symptoms such as fatigue, irritability, or crying may be the presenting symptoms in younger patients. Noxious stimuli resulting from bladder or rectal distention is a common cause of AD, but there are a large number of other causes that need to be considered (Table 751.1). Children and adolescents with cervical and upper thoracic level SCI have lower baseline blood pressures (BPs) compared with the general population. Therefore caution should be used when referencing age-appropriate BPs because BP elevations of even 20-40 mm Hg above this lower baseline may be suggestive of AD. *Identification and treatment of the noxious stimulus is typically associated with resolution of symptoms without the use of antihypertensive medication.* If necessary, antihypertensive agents with a rapid onset and short duration, such as nifedipine and nitropaste, are advocated to treat elevated BP while the underlying cause is identified (Fig. 751.2). Emergent management of AD is necessary because of the risk of stroke and additional organ damage resulting from sustained hypertension. Consideration of a medical alert bracelet, education of supervising adults, and carrying of an AD emergency reference card is recommended (Fig. 751.3).

Patients with SCI are particularly vulnerable to **deep venous thrombosis** and **pulmonary embolism** because of immobilization of their affected limbs and venous stasis during the first 90 days after an injury. Deep venous thromboses are more common in postpubertal children >14 years old than in younger children. Mechanical prophylaxis (graduated compression stockings and sequential calf compression devices) are recommended for all children with acute SCI; adolescents should also start anticoagulant thromboprophylaxis, especially if additional risk factors like lower extremity fractures are present (unless contraindicated because of the risk of bleeding or prior allergic response). Late-occurring deep venous thrombosis most commonly occurs with prolonged immobilization related to illness or surgery, and prophylactic measures should be continued during these situations as well.

Consequent of SCI, patients often present with varying degrees of bowel and bladder incontinence. After an SCI, the bladder can be areflexic or hyperreflexic, and detrusor sphincter dyssynergia may occur. Clean intermittent catheterization (CIC) of the bladder is typically performed up to 4-6 times/day to prevent urinary retention and vesicoureteral reflux. Constipation can negatively impact the success of a CIC program. Anticholinergic medications may improve bladder storage capacity and prevent urinary incontinence between bladder catheterizations. *Antibiotics are only recommended for symptomatic urinary tract infections; asymptomatic bacteriuria, without vesicoureteral reflux, is generally due to colonization and typically not treated.* If intermittent catheterization is required, one can begin teaching the skills necessary for independent catheterization as early as 3 years of age with a goal of obtaining complete independence by 5-7 years old reflecting the progression toward independent bladder management of the child's able-bodied peers.

Bowel continence programs can be successfully introduced around 2-4 years old. There should be an attempt to distinguish between upper motor neuron (UMN) and lower motor neuron (LMN) bowel dysfunction because the management and bowel agents chosen may vary

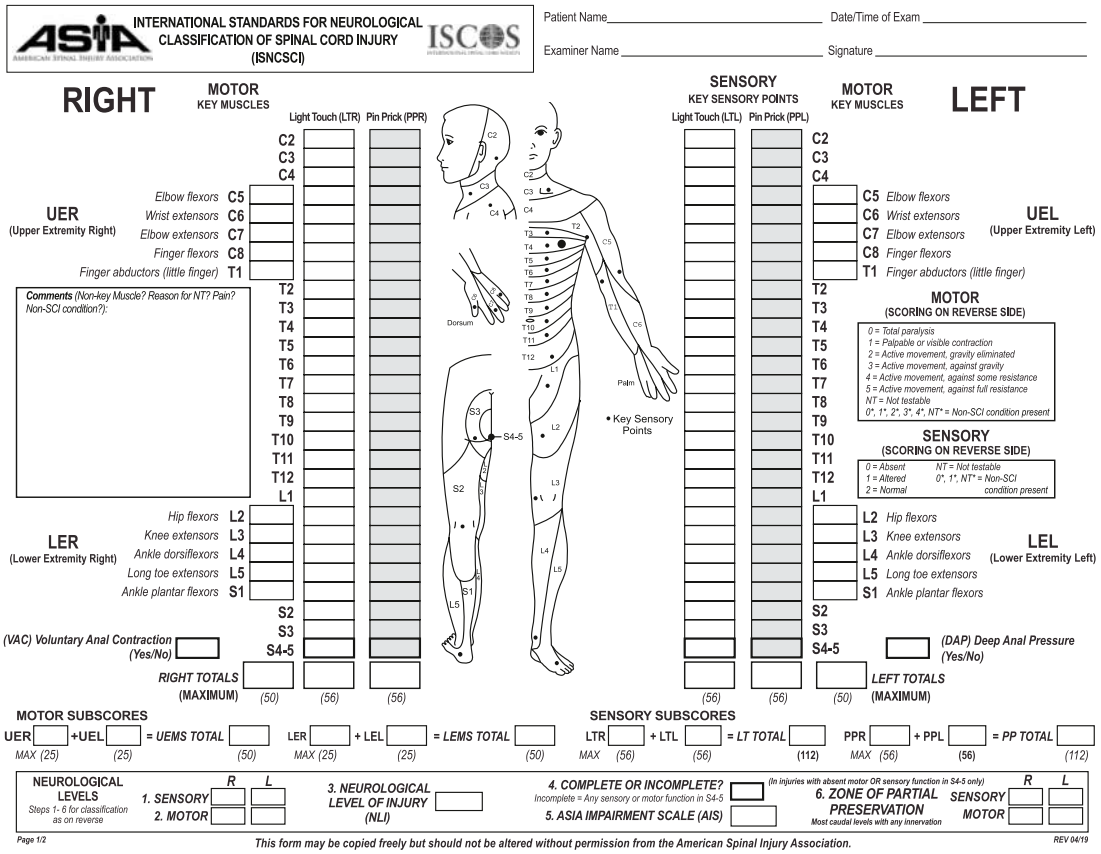

Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present [a]

Sensory Grading

0 = Absent **1** = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal **NT** = Not testable

0*, 1*, NT* = Non-SCI condition present [a]

[a] Note: Abnormal motor and sensory scores should be tagged with a '*' to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No**, then injury is **Complete**. Otherwise, injury is **Incomplete**.*

5. Determine ASIA Impairment Scale (AIS) Grade.
Is injury Complete? If YES, AIS=A
NO ↓
Is injury Motor Complete? If YES, AIS=B
NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?
NO ↓ AIS=C **YES ↓ AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Fig. 751.1 American Spinal Injury Association standards worksheet. *(From the American Spinal Injury Association: International standards for neurological and functional classification of spinal cord injury [ISNCSCI]. Richmond, Virginia, 2019, https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/.)*

Table 751.1 Potential Etiologies of Noxious Stimuli Causing Autonomic Dysreflexia

URINARY SYSTEM
• Bladder distention
• Bladder or kidney stones
• Blocked/kinked catheter
• Detrusor sphincter dyssynergia
• Urinary tract infection
• Urologic instrumentation
• Shock wave lithotripsy
GASTROINTESTINAL SYSTEM
• Bowel distention
• Bowel impaction
• Gallstones
• Appendicitis
• Gastric ulcers
• Gastritis
• Gastrointestinal instrumentation
• Hemorrhoids
INTEGUMENTARY SYSTEM
• Constrictive clothing, shoes, or orthotics
• Blisters
• Burns, sunburn, or frostbite
• Ingrown toenail
• Insect bites
• Pressure ulcers
MUSCULOSKELETAL SYSTEM
• Fractures
• Heterotopic ossification
• Functional electrical stimulation
REPRODUCTIVE SYSTEM—MALE
• Epididymitis
• Scrotal compression (sitting on scrotum)
• Sexual intercourse
• Sexually transmitted infections
REPRODUCTIVE SYSTEM—FEMALE
• Menstruation
• Pregnancy, especially labor and delivery
• Vaginitis
• Sexual intercourse
• Sexually transmitted infections
HEMATOLOGIC SYSTEM
• Deep vein thrombosis
• Pulmonary embolus
OTHER SYSTEMIC CAUSES
• Boosting (an episode of autonomic dysreflexia intentionally caused by an athlete with spinal cord injury in an attempt to enhance physical performance)
• Excessive alcohol intake
• Excessive caffeine or diuretic intake
• Over-the-counter or prescribed stimulants
• Substance abuse

From Consortium for Spinal Cord Medicine: Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities, Washington, DC, 2001, Paralyzed Veterans of America, 10–11.

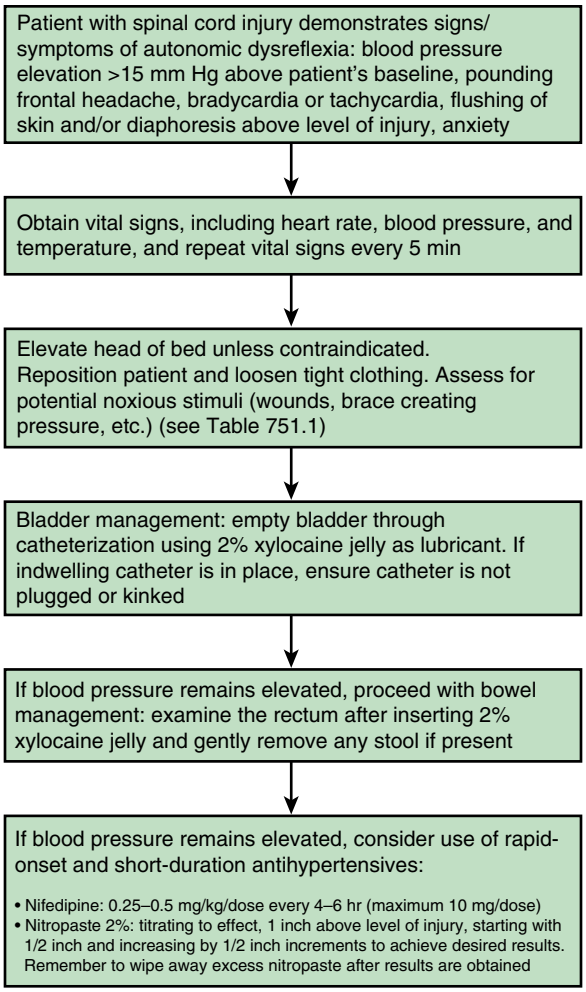

Fig. 751.2 Algorithm for the management of autonomic dysreflexia.

significantly. Lesions at or proximal to the conus medullaris typically result in UMN bowel dysfunction, whereas lesions distal to the conus typically result in LMN bowel dysfunction characterized by an areflexic bowel lacking peristalsis. Management of **bowel incontinence** requires the use of diet modifications, bowel medications, and planned evacuations. Emptying is facilitated by use of the gastrocolic reflex, digital stimulation, suppositories, and enemas in those with UMN bowel dysfunction. Individuals with LMN bowel dysfunction often require manual removal because peristalsis and reflexes are not intact.

Individuals with SCI have increased risk for dysphagia, delayed gastric emptying, ileus, gastric ulcerations, pancreatitis, and superior mesenteric artery syndrome. Presentation of an acute abdomen in SCI is challenging to identify because a patient may be incapable of feeling the pain intensity typically associated with an intraabdominal disorder. As a result, an acute abdomen may be manifested by nonspecific signs and symptoms, such as vomiting, poorly localized dull pain, restlessness, fever, and leukocytosis.

Frequent monitoring for **skin breakdown** and **pressure ulcers** is necessary, both acutely as well as lifelong. Pressure ulcers may heal more slowly in patients with SCI and can significantly impact function. Common locations include the occiput, elbows, sacrum, ischium, and heels. Devices such as halo vests and splints increase the risk of developing a pressure sore. Frequent inspection and repositioning for pressure relief when in bed and when sitting are important measures to minimize the risk of pressure ulcer development.

Depending on the level of the lesion, paralysis of the diaphragm or intercostal and abdominal muscles can result in restrictive ventilatory impairment and ineffective coughing. Respiratory muscle training, abdominal binders, and noninvasive ventilation and airway clearance devices, such as the insufflator–exsufflator cough assist device, should be considered in select patients.

Spasticity typically increases with noxious stimulation and can interfere with sleep, comfort, positioning, and care (see Chapter 752). Untreated spasticity can lead to contracture development and functional limitations. Management includes pharmacologic therapy, stretching, splinting, and positioning to reduce tone. Focal spasticity can be treated with chemodenervation by injecting botulinum toxin into select hypertonic muscles or phenol perineurally. Intrathecal baclofen may be an option for severe generalized spasticity or spasticity that is predominately in the lower extremities.

Increased bone resorption occurs as a result of prolonged immobilization. If excessive calcium is not adequately excreted by the kidneys, insidious onset of abdominal pain, nausea, vomiting, lethargy, polydipsia, polyuria, and behavior changes may occur. This **immobilization**

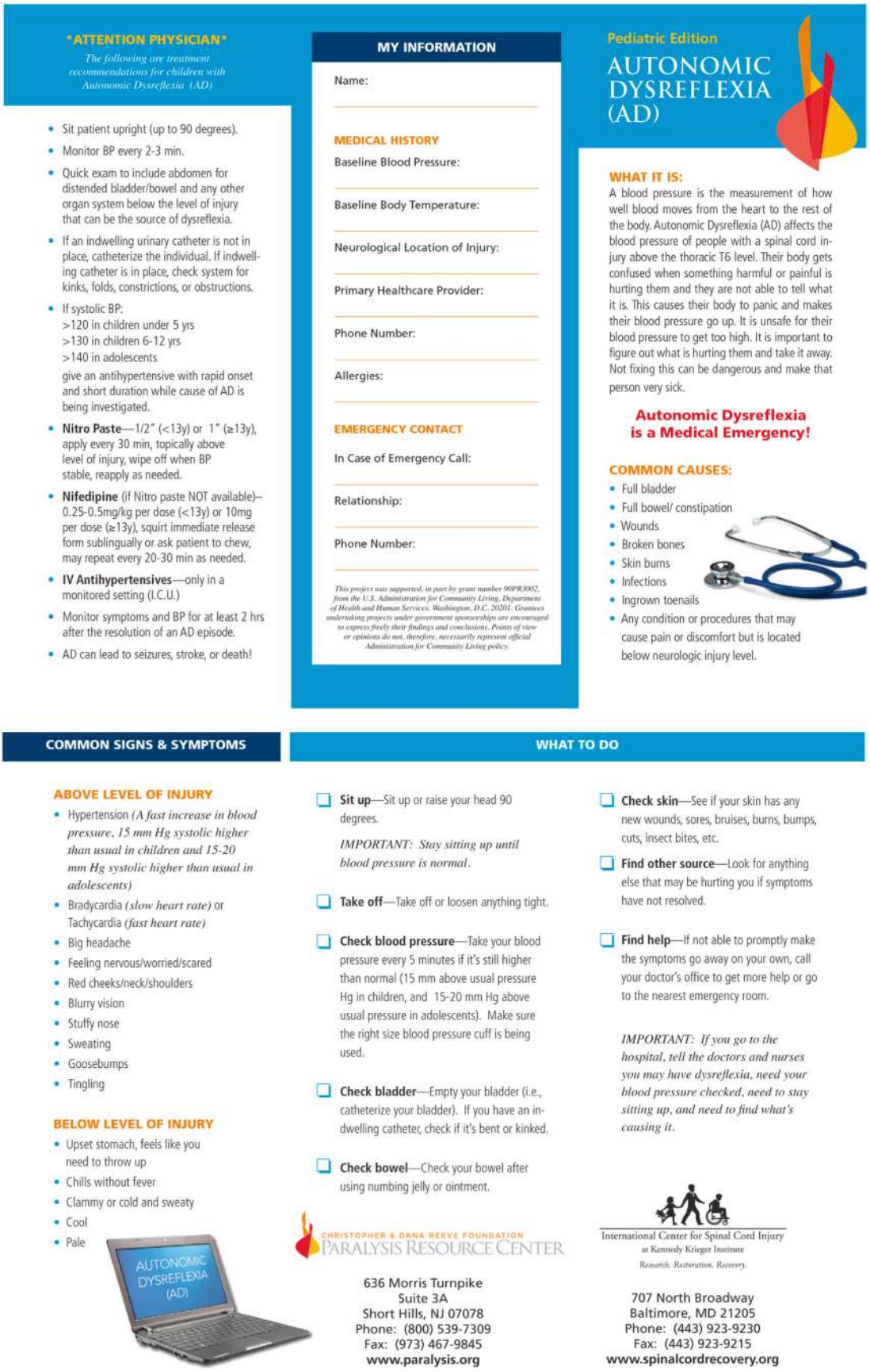

ATTENTION PHYSICIAN

The following are treatment recommendations for children with Autonomic Dysreflexia (AD)

- Sit patient upright (up to 90 degrees).
- Monitor BP every 2-3 min.
- Quick exam to include abdomen for distended bladder/bowel and any other organ system below the level of injury that can be the source of dysreflexia.
- If an indwelling urinary catheter is not in place, catheterize the individual. If indwelling catheter is in place, check system for kinks, folds, constrictions, or obstructions.
- If systolic BP:
  >120 in children under 5 yrs
  >130 in children 6-12 yrs
  >140 in adolescents
  give an antihypertensive with rapid onset and short duration while cause of AD is being investigated.
- **Nitro Paste**—1/2" (<13y) or 1" (≥13y), apply every 30 min, topically above level of injury, wipe off when BP stable, reapply as needed.
- **Nifedipine** (if Nitro paste NOT available)–0.25-0.5mg/kg per dose (<13y) or 10mg per dose (≥13y), squirt immediate release form sublingually or ask patient to chew, may repeat every 20-30 min as needed.
- **IV Antihypertensives**—only in a monitored setting (I.C.U.)
- Monitor symptoms and BP for at least 2 hrs after the resolution of an AD episode.
- AD can lead to seizures, stroke, or death!

MY INFORMATION

Name:

MEDICAL HISTORY

Baseline Blood Pressure:

Baseline Body Temperature:

Neurological Location of Injury:

Primary Healthcare Provider:

Phone Number:

Allergies:

EMERGENCY CONTACT

In Case of Emergency Call:

Relationship:

Phone Number:

This project was supported, in part by grant number 90PR3002, from the U.S. Administration for Community Living, Department of Health and Human Services, Washington, D.C. 20201. Grantees undertaking projects under government sponsorships are encouraged to express freely their findings and conclusions. Points of view or opinions do not, therefore, necessarily represent official Administration for Community Living policy.

Pediatric Edition

AUTONOMIC DYSREFLEXIA (AD)

WHAT IT IS:

A blood pressure is the measurement of how well blood moves from the heart to the rest of the body. Autonomic Dysreflexia (AD) affects the blood pressure of people with a spinal cord injury above the thoracic T6 level. Their body gets confused when something harmful or painful is hurting them and they are not able to tell what it is. This causes their body to panic and makes their blood pressure go up. It is unsafe for their blood pressure to get too high. It is important to figure out what is hurting them and take it away. Not fixing this can be dangerous and make that person very sick.

Autonomic Dysreflexia is a Medical Emergency!

COMMON CAUSES:

- Full bladder
- Full bowel/ constipation
- Wounds
- Broken bones
- Skin burns
- Infections
- Ingrown toenails
- Any condition or procedures that may cause pain or discomfort but is located below neurologic injury level.

COMMON SIGNS & SYMPTOMS

ABOVE LEVEL OF INJURY

- Hypertension *(A fast increase in blood pressure, 15 mm Hg systolic higher than usual in children and 15-20 mm Hg systolic higher than usual in adolescents)*
- Bradycardia *(slow heart rate)* or Tachycardia *(fast heart rate)*
- Big headache
- Feeling nervous/worried/scared
- Red cheeks/neck/shoulders
- Blurry vision
- Stuffy nose
- Sweating
- Goosebumps
- Tingling

BELOW LEVEL OF INJURY

- Upset stomach, feels like you need to throw up
- Chills without fever
- Clammy or cold and sweaty
- Cool
- Pale

WHAT TO DO

- ☐ **Sit up**—Sit up or raise your head 90 degrees.
  IMPORTANT: Stay sitting up until blood pressure is normal.
- ☐ **Take off**—Take off or loosen anything tight.
- ☐ **Check blood pressure**—Take your blood pressure every 5 minutes if it's still higher than normal (15 mm above usual pressure Hg in children, and 15-20 mm Hg above usual pressure in adolescents). Make sure the right size blood pressure cuff is being used.
- ☐ **Check bladder**—Empty your bladder (i.e., catheterize your bladder). If you have an indwelling catheter, check if it's bent or kinked.
- ☐ **Check bowel**—Check your bowel after using numbing jelly or ointment.
- ☐ **Check skin**—See if your skin has any new wounds, sores, bruises, burns, bumps, cuts, insect bites, etc.
- ☐ **Find other source**—Look for anything else that may be hurting you if symptoms have not resolved.
- ☐ **Find help**—If not able to promptly make the symptoms go away on your own, call your doctor's office to get more help or go to the nearest emergency room.

IMPORTANT: If you go to the hospital, tell the doctors and nurses you may have dysreflexia, need your blood pressure checked, need to stay sitting up, and need to find what's causing it.

CHRISTOPHER & DANA REEVE FOUNDATION
PARALYSIS RESOURCE CENTER

636 Morris Turnpike
Suite 3A
Short Hills, NJ 07078
Phone: (800) 539-7309
Fax: (973) 467-9845
www.paralysis.org

International Center for Spinal Cord Injury
at Kennedy Krieger Institute
Research. Restoration. Recovery.

707 North Broadway
Baltimore, MD 21205
Phone: (443) 923-9230
Fax: (443) 923-9215
www.spinalcordrecovery.org

Fig. 751.3 Example of pediatric autonomic dysreflexia emergency card, which can be downloaded in multiple languages for free from the Christopher & Dana Reeve Foundation Paralysis Resource Center website (https://www.christopherreeve.org/living-with-paralysis/free-resources-and-downloads/wallet-cards).

hypercalcemia is managed with IV normal saline and the bisphosphonate pamidronate. Failure to manage the immobilization hypercalcemia may result in nephrocalcinosis, urolithiasis, or renal failure. Loss of bone mineral density begins immediately after an SCI occurs and osteopenia plateaus 6-12 months later. This may result in **pathologic fractures,** with the most common sites of fracture including the supracondylar region of the femur and the proximal tibia. Precautions are necessary because fractures may occur with minor trauma, range of motion exercises, and gait training. Treatment should include the use of removable splints or casts that are well padded over bony prominences to prevent skin breakdown, which is more likely with insensate skin under the cast. Prevention through progressive weight bearing, if feasible and safe, and calcium and vitamin D supplementation is encouraged.

The risk of development of spinal deformities and scoliosis is about 25% in patients sustaining SCI both before and during puberty, and some of these children will require surgical correction. Because of the high incidence of scoliosis in patients younger than 15 at the time of their injury, radiographs of the thoracolumbar-sacral spine should generally be obtained every 6 months before skeletal maturity and every 12 months thereafter. Children who sustain injuries before puberty are also susceptible to hip dislocation and require periodic screening for this condition. Although neurologic **heterotopic ossification** is less prevalent in children compared with adults, it may occur on average about 4 months, but up to 14 months, after the initial injury. The most common site of heterotopic ossification is the hip, but it may also occur in the knee, elbow, and shoulder.

Children and adolescents with SCI are at risk for decreased muscle mass, insulin resistance, decreased glucose transport, dyslipidemia, obesity, and decreased bone health as they age. Long term, patients with SCI have a 3-5-fold greater odds of cardiovascular disease compared with able-bodied individuals. Nutrition education and monitoring are important for decreasing long-term morbidities. Promoting exercise and physical activity and fitness are important for well-being. Youth with SCI may develop latex allergy thought to be a result of repeated, early exposure to latex products; thus a latex-free environment and degree of suspicion for allergies to bananas, kiwis, avocados, or chestnuts is advised.

Psychologic adjustment to SCI is influenced by the developmental age at the time of injury. SCI will impact the child's psychosocial development, so adjustment should be monitored closely. Long-term outcomes related to coping, depression, and anxiety are better in adults who sustained their injury during childhood, compared with those who sustained their injuries in adulthood. Positive coping strategies and strong social supports are associated with greater social participation. Education regarding sexual development and function with SCI injury should be provided.

PROGNOSIS

Prognosis for functional recovery after an SCI depends on the neurologic level of injury and the level of completeness. Examination at least 72 hours after injury has been determined to be a better indicator of the prognosis than earlier examinations. Reexamination after recovery from spinal shock provides additional prognostic information. It is prudent for those determining and communicating the diagnosis to understand the limitations of the anorectal examinations, and thus completeness of injury, unique to children. Those individuals with an initial incomplete injury have an increased likelihood of eventual neurologic recovery. The neurologic level of injury can be helpful in determining the level of independence with functional activities (Table 751.2). The use of technology in rehabilitation encourages the pediatric patient to become more engaged in their own care and advance their

Table 751.2 Projected Functional Outcomes at 1 Year After Injury and/or Diagnosis According to Neurologic Level of Injury

	C1-C4	C5	C6	C7	C8- T1
Feeding	Dependent	Independent with adaptive equipment	Independent	Independent	Independent
Dressing—Upper Body	Dependent	Independent with adaptive equipment	Independent	Independent	Independent
Dressing—Lower Body	Dependent	Independent with adaptive equipment	Independent with adaptive equipment	Independent with adaptive equipment	Independent with adaptive equipment
Bathing	Dependent	Dependent	Dependent	Some assistance to independent with equipment	Independent
Bed mobility	Dependent	Dependent	Some assistance to independent	Independent	Independent
Transfers— Level Surface	Dependent	Dependent	Some assistance to independent	Independent	Independent
Wheelchair Propulsion	Independent with power; dependent with manual	Independent with power; may be independent with manual on level surfaces	Independent	Independent	Independent
Driving	Dependent	May be independent with adaptations	Independent	Independent	Independent
	T2-T9		**T10-L2**		**L3-L5**
Activities of daily living (feeding, dressing bathing)	Independent		Independent		Independent
Transfers	Independent		Independent		Independent
Ambulation	Standing in frame, tilt table, or standing wheelchair Exercise only		Household ambulation with orthosis		Community ambulation is possible

Adapted from Hornyak J, Wernimont C: Spinal cord injuries. In: Murphy K, McMahon M, Houtrow A eds. Pediatric Rehabilitation: Principles and Practice, 6th ed. New York: Demos Medical Publishing, 2021.

independence, which is correlated with higher quality of life. Common technology includes therapeutic and functional stimulation, EMG biofeedback and EMG-triggered stimulation, assistive technology for computer access, and implanted functional electrical stimulation system including phrenic nerve stimulators.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 752

Spasticity

Joyce L. Oleszek and Loren T. Davidson

Spasticity is a component of the upper motor neuron syndrome characterized by velocity-dependent resistance to passive range of motion, resulting in tonic stretch reflexes and accompanied by exaggerated tendon jerks. Spasticity management is determining what degree of spasticity may be tolerable and of functional benefit versus detrimental.

When devising a treatment plan, both the positive and negative effects of spasticity on function must be considered. Treatment should maximize function, independence, comfort, and quality of life while minimizing sedation and adverse effects. Management strategies including systemic medications, injections, and surgery are reviewed.

SYSTEMIC MEDICATIONS

Systemic medications are used as a treatment for generalized spasticity (Table 752.1). Although efficacy of certain antispasmodics has been demonstrated, their use should be contingent on functional benefit because adverse effects are quite common. Frequently used medications include baclofen, benzodiazepines, dantrolene sodium, tizanidine, clonidine, and trihexyphenidyl.

GABAergic Medications

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system. The two most relevant GABA receptors for the purposes of pharmacologic management of spasticity are $GABA_A$ and $GABA_B$. **Benzodiazepines** exert their effect by increasing the affinity of GABA for the $GABA_A$ receptor. This results in presynaptic inhibition and a net inhibitory effect at both spinal and supraspinal levels. Of the benzodiazepines, diazepam is a commonly used medication to treat spasticity because of its long half-life and need for less frequent administration. In children younger than 2 years of age, clonazepam is a good option because of the availability of a liquid formulation and dosing guidelines. Sedation and cognitive slowing limit the usefulness of this class of medications in children. However, benzodiazepines can be helpful for dystonic storms or disturbed sleep in children with cerebral palsy (CP). The use of benzodiazepines may lead to physiologic dependence; thus abrupt discontinuation should be avoided to prevent withdrawal.

Baclofen is a $GABA_B$ agonist and a preferred agent in the treatment of spasticity of spinal origin. Baclofen exerts an inhibitory effect on both monosynaptic and polysynaptic spinal reflexes, but its supraspinal receptor sites can result in sedation as is common to all GABAergic medications. Daytime dosing of oral baclofen is often better tolerated than benzodiazepines with regard to sedation. Intrathecal administration of baclofen via an intrathecal baclofen (ITB) pump (see later) allows greater selectivity of spasticity reduction while minimizing adverse cognitive effects. Oral baclofen is considered a first-line medication for the management of dystonia in CP with common indications including pain or difficulty sleeping associated with dystonia. Abrupt cessation of oral or ITB baclofen must be avoided because of withdrawal potential.

α_2-Adrenergic Agents

Clonidine and **tizanidine** are examples of centrally acting α_2-adrenergic agonists that decrease spasticity and have an antinociceptive effect. Clonidine is used more frequently as an antihypertensive. Clonidine exerts its effect on spasticity via both presynaptic inhibition of sensory afferents as well as release of glutamate at the level of the spinal cord. In comparison to clonidine, tizanidine has less-potent hemodynamic effects, which is desirable when used primarily for spasticity reduction. However, tizanidine is extensively metabolized by the liver, so hepatic impairment may have a significant effect on its pharmacokinetics. Although clonidine and tizanidine are used widely as antispasmodics in practice, there is limited evidence for their use in reducing spasticity in children with CP. Tizanidine's antispasticity effect has been demonstrated in adults with multiple sclerosis and spinal cord injury. Clonidine has been shown to be effective for disturbed sleep associated with severe hypertonia. The adverse effect profile of these agents can limit their use.

Peripherally Acting Calcium Blockers

Dantrolene sodium works at the level of skeletal muscle to block calcium release from the sarcoplasmic reticulum. Despite its peripheral site of action, dantrolene may induce sedation, although to a lesser degree than other centrally acting agents. A few small studies have shown that dantrolene decreases clonus and spasticity but can also decrease strength. Dantrolene is often well tolerated in children, but its risk of hepatotoxicity requires monitoring of liver function tests. Hepatotoxicity risk increases with age, increasing dose, and female gender (see Table 752.1).

INJECTION MANAGEMENT

Injection management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative options. Combining treatment options such as injections and systemic medications can be very effective.

Botulinum toxin (BoNT) and phenol injections are used to treat localized spasticity. OnabotulinumtoxinA (Botox) and AbobotulinumtoxinA (Dysport) have obtained U.S. Food and Drug Administration (FDA) approval for both upper and lower limb spasticity in pediatrics. RimabotulinumtoxinB (Myobloc) and IncobotulinumtoxinA (Xeomin) both have FDA approval but neither have a pediatric indication. BoNT is derived from the bacteria *Clostridium botulinum,* and there are seven immunologically distinct serotypes designated A through G. Its mechanism of action involves a light chain protein binding to synaptobrevin at the neuromuscular junction, inhibiting vesicles from anchoring to the cell membrane and preventing acetylcholine release from the presynaptic membrane. This interferes with nerve impulse transmission and results in weakness of the muscle injected. Onset of action is within 2 weeks of administration, duration is 3-6 months, and effects wane as the neuromuscular junction reestablishes its original function. Injections should be administered no more frequently than every 3 months to reduce neutralizing antibody formation, which occurs in 1–2% of treated individuals. BoNT-A is a safe and effective treatment for spasticity in the upper and lower extremities in children with CP, but the effects on long-term functional improvement with repeated injections are less well known. The combination of BoNT-A injections to the gastrocnemius muscles and serial casting has been shown to improve ankle range of motion and gait. BoNT-A can also improve ease of care and comfort in nonambulatory children with CP. The most common adverse events (AEs) include localized pain and weakness, unsteadiness and increased falls, fatigue, urinary incontinence, and dysphagia. Systemic AEs

independence, which is correlated with higher quality of life. Common technology includes therapeutic and functional stimulation, EMG biofeedback and EMG-triggered stimulation, assistive technology for computer access, and implanted functional electrical stimulation system including phrenic nerve stimulators.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 752

Spasticity

Joyce L. Oleszek and Loren T. Davidson

Spasticity is a component of the upper motor neuron syndrome characterized by velocity-dependent resistance to passive range of motion, resulting in tonic stretch reflexes and accompanied by exaggerated tendon jerks. Spasticity management is determining what degree of spasticity may be tolerable and of functional benefit versus detrimental.

When devising a treatment plan, both the positive and negative effects of spasticity on function must be considered. Treatment should maximize function, independence, comfort, and quality of life while minimizing sedation and adverse effects. Management strategies including systemic medications, injections, and surgery are reviewed.

SYSTEMIC MEDICATIONS

Systemic medications are used as a treatment for generalized spasticity (Table 752.1). Although efficacy of certain antispasmodics has been demonstrated, their use should be contingent on functional benefit because adverse effects are quite common. Frequently used medications include baclofen, benzodiazepines, dantrolene sodium, tizanidine, clonidine, and trihexyphenidyl.

GABAergic Medications

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system. The two most relevant GABA receptors for the purposes of pharmacologic management of spasticity are $GABA_A$ and $GABA_B$. **Benzodiazepines** exert their effect by increasing the affinity of GABA for the $GABA_A$ receptor. This results in presynaptic inhibition and a net inhibitory effect at both spinal and supraspinal levels. Of the benzodiazepines, diazepam is a commonly used medication to treat spasticity because of its long half-life and need for less frequent administration. In children younger than 2 years of age, clonazepam is a good option because of the availability of a liquid formulation and dosing guidelines. Sedation and cognitive slowing limit the usefulness of this class of medications in children. However, benzodiazepines can be helpful for dystonic storms or disturbed sleep in children with cerebral palsy (CP). The use of benzodiazepines may lead to physiologic dependence; thus abrupt discontinuation should be avoided to prevent withdrawal.

Baclofen is a $GABA_B$ agonist and a preferred agent in the treatment of spasticity of spinal origin. Baclofen exerts an inhibitory effect on both monosynaptic and polysynaptic spinal reflexes, but its supraspinal receptor sites can result in sedation as is common to all GABAergic medications. Daytime dosing of oral baclofen is often better tolerated than benzodiazepines with regard to sedation. Intrathecal administration of baclofen via an intrathecal baclofen (ITB) pump (see later) allows greater selectivity of spasticity reduction while minimizing adverse cognitive effects. Oral baclofen is considered a first-line medication for the management of dystonia in CP with common indications including pain or difficulty sleeping associated with dystonia. Abrupt cessation of oral or ITB baclofen must be avoided because of withdrawal potential.

α_2-Adrenergic Agents

Clonidine and **tizanidine** are examples of centrally acting α_2-adrenergic agonists that decrease spasticity and have an antinociceptive effect. Clonidine is used more frequently as an antihypertensive. Clonidine exerts its effect on spasticity via both presynaptic inhibition of sensory afferents as well as release of glutamate at the level of the spinal cord. In comparison to clonidine, tizanidine has less-potent hemodynamic effects, which is desirable when used primarily for spasticity reduction. However, tizanidine is extensively metabolized by the liver, so hepatic impairment may have a significant effect on its pharmacokinetics. Although clonidine and tizanidine are used widely as antispasmodics in practice, there is limited evidence for their use in reducing spasticity in children with CP. Tizanidine's antispasticity effect has been demonstrated in adults with multiple sclerosis and spinal cord injury. Clonidine has been shown to be effective for disturbed sleep associated with severe hypertonia. The adverse effect profile of these agents can limit their use.

Peripherally Acting Calcium Blockers

Dantrolene sodium works at the level of skeletal muscle to block calcium release from the sarcoplasmic reticulum. Despite its peripheral site of action, dantrolene may induce sedation, although to a lesser degree than other centrally acting agents. A few small studies have shown that dantrolene decreases clonus and spasticity but can also decrease strength. Dantrolene is often well tolerated in children, but its risk of hepatotoxicity requires monitoring of liver function tests. Hepatotoxicity risk increases with age, increasing dose, and female gender (see Table 752.1).

INJECTION MANAGEMENT

Injection management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative options. Combining treatment options such as injections and systemic medications can be very effective.

Botulinum toxin (BoNT) and phenol injections are used to treat localized spasticity. OnabotulinumtoxinA (Botox) and AbobotulinumtoxinA (Dysport) have obtained U.S. Food and Drug Administration (FDA) approval for both upper and lower limb spasticity in pediatrics. RimabotulinumtoxinB (Myobloc) and IncobotulinumtoxinA (Xeomin) both have FDA approval but neither have a pediatric indication. BoNT is derived from the bacteria *Clostridium botulinum,* and there are seven immunologically distinct serotypes designated A through G. Its mechanism of action involves a light chain protein binding to synaptobrevin at the neuromuscular junction, inhibiting vesicles from anchoring to the cell membrane and preventing acetylcholine release from the presynaptic membrane. This interferes with nerve impulse transmission and results in weakness of the muscle injected. Onset of action is within 2 weeks of administration, duration is 3-6 months, and effects wane as the neuromuscular junction reestablishes its original function. Injections should be administered no more frequently than every 3 months to reduce neutralizing antibody formation, which occurs in 1–2% of treated individuals. BoNT-A is a safe and effective treatment for spasticity in the upper and lower extremities in children with CP, but the effects on long-term functional improvement with repeated injections are less well known. The combination of BoNT-A injections to the gastrocnemius muscles and serial casting has been shown to improve ankle range of motion and gait. BoNT-A can also improve ease of care and comfort in nonambulatory children with CP. The most common adverse events (AEs) include localized pain and weakness, unsteadiness and increased falls, fatigue, urinary incontinence, and dysphagia. Systemic AEs

Table 752.1 Dosing Guidelines, Pharmacologic Actions, and Adverse Event Profile of Commonly Prescribed Oral Antispasmodic Medications for Children

MEDICATION/DOSING GUIDELINES	PHARMACOLOGIC ACTIONS	ADVERSE REACTIONS/PRECAUTIONS
BACLOFEN 0.125-1 mg/kg/day *2-7 yr:* 2.5-10 mg tid-qid (10-40 mg/day) *8-12 yr:* 5 mg-15 mg tid-qid (15-60 mg/day) *12-16 yr:* 5-20 mg tid-qid (20-80 mg/day) Note: Caution advised with renal impairment; consider reducing dose.	• Centrally acting, structural analog of GABA • Binds to $GABA_B$ receptors causing presynaptic inhibition of mono/polysynaptic spinal reflexes • Rapid absorption, blood level peaks in 1 hr, half-life 5.5 hr. • Renal excretion (70–80% unchanged) • Hepatic excretion (15%)	• CNS depression (sedation, fatigue) • Nausea • Headache • Dizziness • Confusion • Euphoria • Hallucinations • Hypotonia • Ataxia • Paraesthesias Note: Abrupt withdrawal may cause seizures, hallucinations, rebound muscle spasms, and hyperpyrexia.
DIAZEPAM 0.12-0.8 mg/kg/day *6 mo-12 yr:* 0.12-0.8 mg/kg/day PO divided q 6-8h *>12 yr:* 2-10 mg PO bid-qid Note: Starting a qhs dose only or proportionately larger dose at bedtime may limit excessive daytime sedation.	• Centrally acting, binds to $GABA_A$ receptors mediating presynaptic inhibition in brainstem reticular formation and spinal polysynaptic pathways • Rapid absorption, blood level peaks in 1 hr, with half-life of 30-60 hr	• CNS depression (sedation, impaired memory, and impaired attention) • Ataxia • Dependence/potential for substance abuse/overdose • Withdrawal syndrome (including anxiety, agitation, irritability, tremor, muscle twitching, nausea, insomnia, seizures, hyperpyrexia) • Increased potential for adverse effects with low albumin levels due to being 98% protein bound
DANTROLENE SODIUM 3-12 mg/kg /day *>5 yr:* 6-8 mg/kg/d PO divided bid-qid Start 0.5 mg/kg qd-bid for 7 days, then 0.5 mg/kg tid for 7 days, then 1 mg/kg tid for 7 days, then 2 mg/kg tid to a maximum of 12 mg/kg/d or 400 mg/day.	• Peripheral action, blocking release of calcium from sarcoplasmic reticulum with uncoupling of nerve excitation and skeletal muscle contraction • Blood level peaks in 3-6 hr (active metabolite 4-8 hr), half-life of approx. 15 hr	• Malaise • Fatigue • Nausea • Vomiting • Diarrhea • Muscle weakness with high dose **Note:** Hepatotoxicity (baseline liver function tests MUST be checked before starting dantrolene, tested weekly during dose titration and regularly every 1-2 months thereafter). Drug *should be discontinued promptly* if liver enzymes become elevated.
TIZANIDINE *<10 yr:* Initiate 1 mg orally at bedtime initially, increasing to 0.3-0.5 mg/kg in 4 divided doses *>10 yr:* Commence 2 mg orally at bedtime initially, increased according to response, maximum 24 mg/day in 3-4 divided doses	• Centrally acting, $alpha_2$ adrenoceptor agonist activity at both spinal and supraspinal sites. Prevents release of excitatory amino acids, facilitating presynaptic inhibition • Good oral absorption, blood level peaks in 1-2 hr, half-life of 2.5 hr	• Dry mouth • Drowsiness • Headache • Dizziness • Insomnia • Anxiety • Aggression • Mood swings • Visual hallucinations • Risk of hypotension (although 10 times less anti-hypertensive potency than clonidine) • Nausea/vomiting • Constipation • Liver function tests should be monitored; baseline and 1 month after maintenance dose achieved.
CLONIDINE 0.025-0.1 mg/day in 2-3 divided doses.	• Centrally acting, mixed alpha adrenoceptor agonist with predominant alpha-2 activity causing membrane hyperpolarization at multiple sites in brain, brainstem, and dorsal horns of spinal cord. • Rapidly absorbed orally, blood level peaks in 1-1½ hr, half-life of 6-20 hr.	• Drowsiness • Dry mouth • Bradycardia • Orthostatic hypotension • Abrupt cessation may result in rebound hypertension.

can occur in up to 3.6% of children with CP receiving BoNT-A, and those with a history of dysphagia and/or aspiration pneumonia are at increased risk. The FDA requires black box labeling on BoNT products, cautioning of a rare but potentially life-threatening complication of BoNT effects spreading beyond the injection site. Co-administration of BoNT and other agents interfering with neuromuscular transmission, such as aminoglycosides and curare-like agents, should be performed with caution because the effect of the toxin may be potentiated.

Phenol neurolysis can be used in combination with BoNT injections to allow treatment of more affected muscles while remaining within the safe dose range of BoNT. Phenol causes nonselective denaturing of proteins upon exposure to the nerve, thereby causing nerve injury by precipitating and dehydrating the protoplasm. This, in turn, interferes with nerve conduction and impairs innervation to muscles. Phenol injections are typically used to target nerves to large proximal muscles (musculocutaneous, obturator and sciatic nerves), and the duration of clinical effect may be longer than BoNT. There is limited evidence on the use of phenol in children with CP, but a few small studies show safety and efficacy. Phenol injection of the anterior branch of the obturator nerve in children with CP has been found to be safe and effective. AEs include pain, swelling and inflammation, and dysesthesias. The low cost of phenol incurs a significant advantage over BoNT, but the need for electrical stimulation or ultrasound guidance and general anesthesia may negate this benefit.

SURGICAL MANAGEMENT

Intrathecal baclofen (ITB) is approved to treat spasticity of cerebral origin. ITB is delivered to the intrathecal space by a catheter connected to a subfascially implanted pump. This mechanism of delivery produces much higher local concentrations in the cerebrospinal fluid at a fraction of the equivalent systemic dose of baclofen, thereby minimizing the CNS depressive effects. Catheter tips are typically positioned at C5-T2 but can be placed intraventricularly for severe dystonia. ITB pumps require refills at 2-6–month intervals depending on dose rate and pump size and need to be replaced every 5-7 years for end of battery life. The frequent maintenance required can be prohibitive to some families. Before ITB pump placement, a single bolus dose of baclofen can be delivered via lumbar puncture to evaluate responsiveness and impact on functional abilities. ITB is effective in reducing spasticity and dystonia in CP and may improve the ease of care and quality of life of children with CP. Continuous ITB treatment is superior to placebo on attainment of individual treatment goals in children with Gross Motor Function Classification System (GMFCS) level IV and V CP (Fig. 752.1). Serious AEs can occur with ITB. One 14-year study of 430 patients found at least one complication in 25% of patients: infection in 9.3%, CSF leak in 4.9%, catheter problem in 15.1%, and a pump-related problem in 1%. Electromagnetic interference and MRI may cause transient operational changes to the ITB pump and changes to the flow rate; thus the pump should be interrogated by a programmer after MRI as a precaution. **ITB withdrawal** is a medical emergency and needs to be identified early and managed aggressively. Sequelae can include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, can advance to rhabdomyolysis, multiple organ–system failure, and death. Caregivers need to be educated on the early symptoms of baclofen withdrawal. Prevention of abrupt discontinuation of ITB requires careful attention to programming and monitoring of the infusion system, refill scheduling, and pump alarms.

Selective dorsal rhizotomy (SDR) is a surgical procedure that decreases muscle spasticity by sectioning hyperexcitatory sensory nerve rootlets that innervate the lower extremities. The surgical technique involves single or multilevel osteoplastic laminectomies exposing the L2-S1 nerve roots, and sensory rootlets are chosen for sectioning using intraoperative electromyography. The most ideal candidates are thought to be children 3-8 years of age with spastic diplegic CP, minimal upper limb involvement, good selective motor control and strength with the ability to rise from the floor independently, minimal contractures, and good cognitive skills.

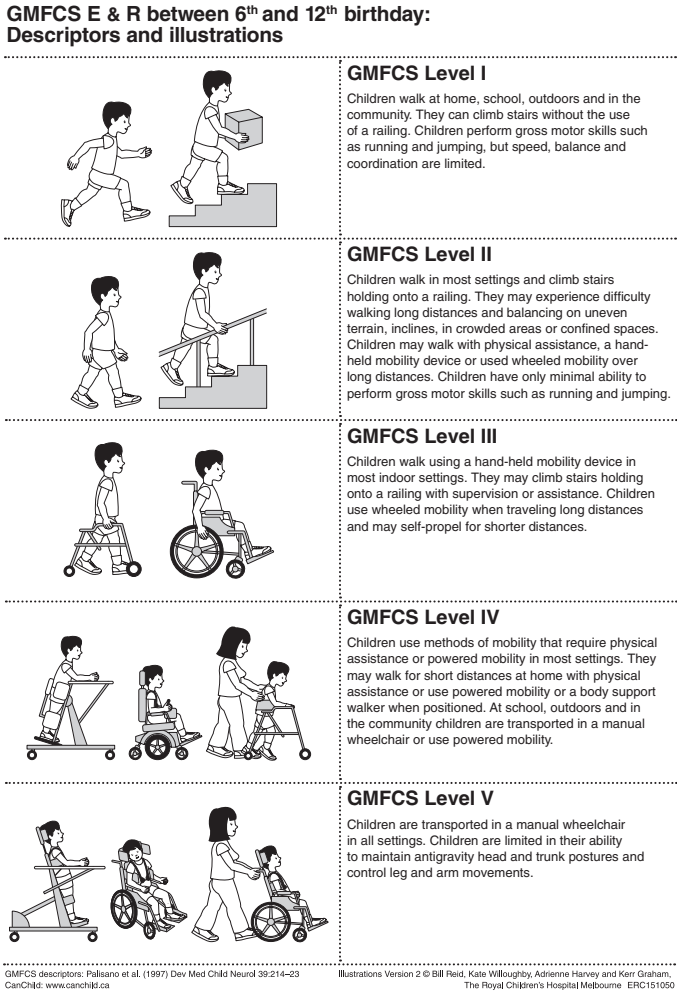

Fig. 752.1 Gross Motor Function Classification System Expanded and Revised (GMFCS E & R). *(Descriptors: ©Palisano et al, 1997 – Dev Med Child Neurol., 39:214-23 (CanChild: www.canchild.ca); Illustrations Version 2 © Bill Reid, Kate Willoughby, Adrienne Harvey and Kerr Graham, The Royal Children's Hospital Melbourne)*

Ambulatory children with CP have better function and quality of life in the 24 months after SDR. A prospective gait analysis study in adults with CP 20 years after SDR showed improved locomotor function with increased gait speed. SDRs are performed to a lesser extent in children with spastic quadriplegic CP, and goals in this population are often to decrease lower limb spasticity while improving comfort, care, and positioning. A study in nonambulatory children with severe CP showed improvements in daily care and comfort at a mean follow-up of 19 months after SDR, although unmasking of prior dystonia can occur. AEs after SDR include bladder or bowel dysfunction, sensory dysesthesias, and back pain; however, these occur infrequently and are typically transient. A systematic review of spinal deformities after SDR in children with CP found scoliosis to be the most common deformity occurring in approximately 30% of children, but this risk has never been satisfactorily shown to be higher than the risk in those children who have not undergone SDR. Studies have reported higher rates of spondylolysis and spondylolisthesis after SDR than would be expected in the general CP population. Spine radiographs should be obtained routinely after SDR to monitor for spinal deformity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 753

Birth Brachial Plexus Palsy

Maureen R. Nelson and Nicholas L. Fleming

Birth brachial plexus palsy (BBPP) may cause significant arm weakness and subsequent functional deficits in children. The nerves to the arm are affected with variable degrees of weakness and sensory loss. Most children will have good recovery spontaneously, but functional deficits will remain in 20–30% of children with BBPP.

The mechanism for BBPP is lateral stretch of the plexus for the vast majority of cases. Anatomic variations in bones, blood vessels, and tendons lead to a very small number of cases. The incidence of BBPP is reported as 0.5-4.6 per 1,000 live births, with variability thought to be attributable to the type of obstetric care and the size of infants around the world.

Risk factors for BBPP include prior infants with BBPP, shoulder dystocia, birthweight >4 kg, multiparous mothers, mothers with excessive weight gain, and diabetic mothers. Delivering twins or triplets, as well as cesarean sections, have been described as protective from BBPP. Factors with a higher risk of poor outcome are birthweight greater than 4 kg, Horner syndrome, cephalic presentation, and induction or augmentation of labor.

Nerve injuries include neurapraxia, neurotmesis, and axonotmesis. **Neurapraxia** is the least severe of these types and is a reversible loss of nerve conduction. This type will recover. **Neurotmesis** is the most severe and is a total and complete disruption of the nerve. An *avulsion* describes a **neurotmesis** that is a preganglionic lesion, and a *rupture* describes the same event for a postganglionic lesion. **Axonotmesis** is the intermediate form and the most difficult to delineate. There is disruption of the epineurium with variable injury to the axons creating the diagnostic and prognostic difficulties (Fig. 753.1). For these reasons, it is advisable to urgently seek out consultation from specialty clinics or specializing physicians in your geographic area for close monitoring and treatment considerations, including surgical candidacy.

Not only is there variability in the degree of nerve injury, but there is also variability in location. The brachial plexus consists of the anterior primary rami, or roots, from C5, C6, C7, C8, and T1. These roots will combine and then branch to form the trunks, divisions, and branches before separating distally to individual peripheral nerves as illustrated by Figure 753.2.

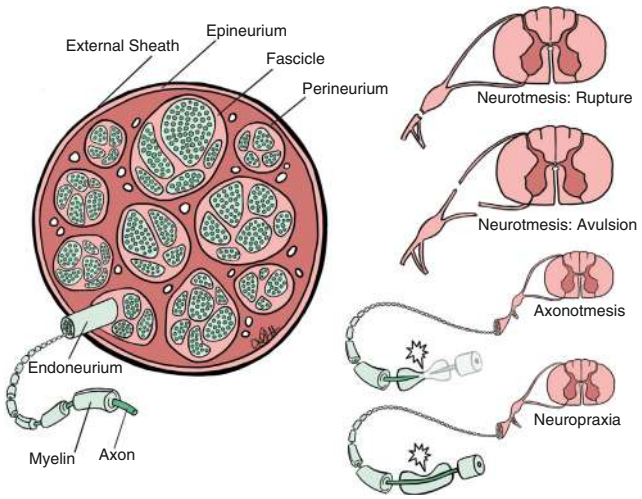

Fig. 753.1 Anatomy of peripheral nerve and injury type. *(Courtesy Kendall Hulk, DO.)*

There is variable impact on motor and sensory systems as well. The sensory fibers are relatively protected compared with the motor fibers because the sensory fibers run together until they are outside of the spinal cord into the dorsal root ganglion, where their cell bodies lie. The motor fibers have the cell bodies within the spinal cord and so are not as cohesive in their path. Therefore the sensory fibers may be spared, while motor fibers show clinical deficits.

Narakas is a commonly used classification system (Table 753.1). Erb palsy is generally described as the upper trunk or C5-C6 palsy. It is by far the most common injury seen in BBPP. When C7 is included in the injury, it may be referred to as *extended Erb palsy*. Together, these forms of Erb palsy make up 75% of all BBPP. These two groups also demonstrate the greatest recovery rate, at 80% and 60%, respectively, resulting in a functional arm. **Klumpke palsy**, C8-T1, is extremely rare in BBPP, likely not occurring except in the case of anatomic variation. If a baby presents with a C8-T1 deficit, the baby most likely originally had a complete C5-T1 BBPP and then had recovery of the upper portion of the plexus. This can happen because C4, C5, C6, and sometimes C7 are protected coming out from the spinal cord, held in a gutter along the transverse processes by connective tissue, whereas C8 and T1 are not. The phrenic nerve may also be involved with its innervation from C3, C4, and C5, with potential respiratory concerns. The differential diagnosis of an infant with a weak or less functional arm is broad, and there should be consideration for other neurologic injury (stroke, spinal cord injury, underlying congenital or metabolic diagnosis), musculoskeletal issues (fracture, muscular torticollis, anomalous rib impinging nerves), infection, tumor, and other sources of pain or pathology that could lead to developmental disregard or a learned nonuse of an extremity. **Phrenic nerve** (4th cervical and C3-C5) injury may also be present and result in ipsilateral diaphragm paralysis and respiratory distress.

PHYSICAL EXAMINATION

Motor movement evaluation is the focus of this exam. The Active Movement Scale is a reliable passive assessment of muscle strength that is widely used for infant examination of BBPP. Mallet scores, which assess shoulder abduction and external rotation deficits, are likewise useful but are more pertinent for examination of the toddler or older children. Examination for sensation, particularly sharp sensation, useful in its own right, will also frequently help with active motor evaluation in infants. Assessment of muscle stretch reflexes is important, in that infants with brachial plexus palsy will be areflexive or hyporeflexive in the involved arm. Evaluation of primitive reflexes, particularly the Moro reflex, is helpful, because most of these infants will have C5-C6 involvement, and therefore the Moro may show shoulder abduction and elbow flexion on one side but not the involved side. Range-of-motion examination is critical. Deficits are commonly seen because of the imbalance of muscles that are active and those that are not. Shoulder adduction and internal rotation is a common position, as is elbow flexion, forearm pronation, and wrist and finger flexion. Torticollis is commonly present and almost always with the face turned away from the involved arm. **Horner syndrome** (ptosis, miosis, and anhidrosis) may be present ipsilaterally and is an indicator of severity. In children with very severe deficits, the arm may be cooler because of the sympathetic nervous system outflow at T1. The size of the involved arm eventually is usually smaller, about 95% of the uninvolved arm, because of muscle atrophy and smaller diameter and length of the bone.

Among older infants and children, compensatory movements of the arm may be noted. Common examples are use of trunk momentum to move (particularly to rotate) the proximal arm, hyperlordosis of the lumbar spine to position the arm more advantageously, use of the pectoralis muscle to flex the shoulder, and use of the knee while sitting to physically flex the elbow. Examination of the back for symmetry, along with the scapulae for winging, is also relevant. Scapular winging can be problematic both socially and clinically. Having the older child manipulate buttons, snaps, or zippers, throw

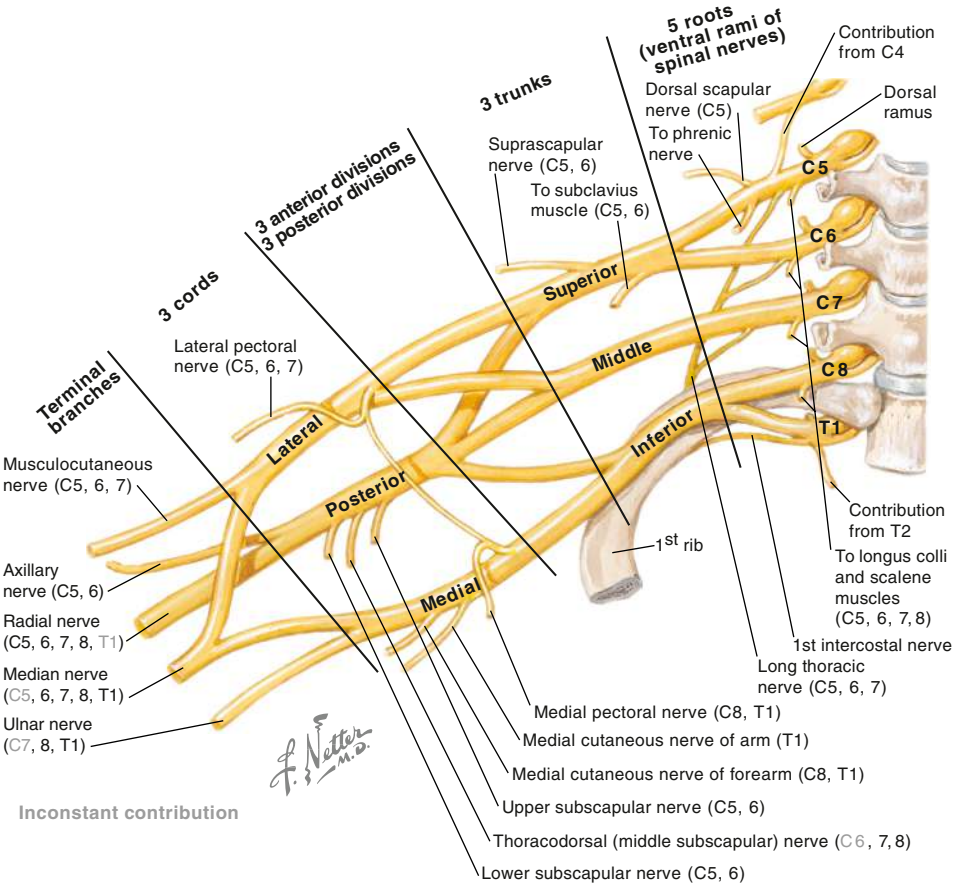

Fig. 753.2 Schematic of the brachial plexus. *(Netter illustration from www.netterimages.com. Elsevier Inc.)*

Table 753.1 Narakas Classification

GROUP	NAME	ROOTS	CLINICAL DESCRIPTION
I	Erb palsy	C5-6	Paralysis of shoulder and biceps with should abduction, external rotation, and elbow flexion
II	Extended Erb palsy	C5-7	As above with paralysis of wrist
III	Total palsy	C5-8, T1	Complete flaccid paralysis
IV	Total palsy with Horner syndrome	C5-8, T1	Complete flaccid paralysis with Horner syndrome

and catch a ball, and write, print, or color may be revealing, along with how they remove their shirt for examination.

When hand function was evaluated with testing of children with upper-plexus involvement, 80% of the children had significantly decreased performance compared with the contralateral hand. This indicates the hand function is impaired even in children who only have upper plexus involvement.

EVALUATION

Radiographic evaluation may be needed. Plain films can be viewed immediately if there is reason to consider clavicle or humerus fracture, infection, osteomyelitis, or tumor. Ultrasound (US) can be used to evaluate for shoulder dislocation. CT myelogram had been the mainstay diagnostic tool for brachial plexus evaluation despite its radiation dose and invasive lumbar puncture. However, MRI lacks these drawbacks and provides a more accurate and reliable evaluation.

US and electrodiagnostic evaluation (EDX) can also be helpful in evaluation of the brachial plexus. US is an ever-improving technology but does not yet evaluate the deeper nerve root avulsions or ruptures, making isolated US imaging inappropriate. However, US can be useful for postganglionic injury evaluation, specifically for the upper plexus. EDX may be supplemental and is especially helpful as a confirmatory test for lower plexus avulsion injuries given its strong specificity and MRI's weaker diagnostic accuracy for these lower plexus injuries.

EDX includes both nerve conduction studies (NCS) and electromyography (EMG) and should be performed by someone who is experienced in the examinations of infants and young children, both for the most precise evaluation and the most comfortable experience for the youngster. The following EDX pearls should be noted:

1. Normal electrical sensory response in areas where the child cannot feel indicates a *preganglionic neurotmesis* (avulsion).
2. Motor nerve conduction studies are useful to check for continuity of nerve fibers to muscles that are weak or paralyzed.
3. F waves are useful in evaluating proximally because these responses go from peripheral nerves to the spinal cord and back.
4. Somatosensory evoked potentials are difficult to perform on infants while awake, because of motor artifact obliterating the responses

with movement, and are imprecise because of overlapping responses to peripheral stimulation. These are useful intraoperatively because stimulation can be performed on the nerve roots themselves to determine proximal continuity.

5. EMG can show activation in muscles with paralysis or severe weakness.
6. The absence of biceps motor unit potentials at 1 month of age predicts future lack of clinical biceps recovery, although biceps EMG at 3 months has been reported to overestimate recovery potential.

TREATMENT

Early referral or consultation with a specialty clinic or specialized physician is paramount and should be completed as early as possible or by 1 month of age for close monitoring and consideration of possible microsurgery. Postoperative improvement in hand and arm function has been shown to have a negative correlation with age at time of primary surgery. Infants who do not show satisfactory improvement in muscle strength are candidates for such primary surgeries, which may include nerve transfers, in which branches from an uninvolved nerve are microsurgically transferred to the distal peripheral nerves supplied by the injured nerve roots and/or nerve grafting, in which one or more of the nonavulsed roots is attached distally to the trunk, cord, or peripheral nerve by means of an autogenous graft (commonly the sural nerve of the leg) or synthetic nerve conduits. There is general consensus that primary nerve surgeries should be performed at 3 months of age for Narakas type III and type IV. Those with upper-plexus (Narakas type I and type II) involvement are monitored closely, and there is surgical consideration for primary nerve surgery between 3 and 6 (or even 9) months of age. Classically, observed elbow flexion less than 3/5 at 6 months of age or a positive "cookie test" (child cannot bring cookie to mouth without bending neck forward more than 45 degrees) at 9 months would prompt decision to undergo primary surgery in these populations. The surgical focus for a complete palsy or "flail arm" is reinnervation of the hand, whereas the surgical goals of an upper-plexus reconstruction include, in descending priority, elbow flexion, glenohumeral abduction, shoulder stability, and shoulder external rotation. It should be noted that the goals of surgery are not to regain normal arm function but rather to have a more functional arm.

Regarding primary nerve surgeries, some have reported better outcomes with nerve transfer rather than nerve graft procedures. However, the heterogenous nature of BBPP, variable surgical techniques, and available nerve options often dictate what can be performed. Spinal accessory to suprascapular nerve transfer and radial nerve (long head of triceps branch) to axillary nerve transfer has been reported as the most common dual nerve transfer procedure. Other common nerve transfers include median or ulnar nerve to the musculocutaneous nerve (MCN), medial pectoral nerve to MCN, intercostal nerve to MCN, and contralateral or cross cervical nerve root transfers. Nerve graft procedures typically include harvesting of the sural (purely sensory) nerve or using synthetic nerve grafts. These grafts are typically used to reestablish the conduit of the suprascapular nerve, graft C5-to-posterior division, or graft C3/C4-to-upper trunk.

Regardless of whether primary surgery is pursued, treatment begins on the initial evaluation with instruction to the parents for positioning and early stretching exercises to begin at 2 weeks, or at 3-4 weeks if a humerus or clavicle fracture is present. They are also told of the critical task of maintaining infant awareness of the involved arm, initially by manually mimicking activities with the affected arm that the baby performs with the contralateral arm and by using a wrist rattle on the arm. Lack of awareness of the arm, sometimes called *developmental disregard*, in children can result in less active use of the arm, with functional loss, as a consequence. The parents also are informed of the higher risk of BBPP for future infants, and so the families are encouraged to speak with the obstetrician about optimal management in future deliveries.

The baby will start with occupational or physical therapy at approximately 2 weeks of age with focus on maintaining joint motion, maximizing strength, promoting sensory awareness, and supporting age-appropriate development. Parent education should be reinforced and a home program including daily stretching, positioning, and strengthening techniques should be constructed. Therapeutic taping may be done for supination, wrist extension, or, most commonly, for shoulder positioning to minimize an adducted, internally rotated posture. Neuromuscular electrical stimulation to the muscles minimizes atrophy and promotes increased size, and therefore strength, of muscle fibers. Ideal parameters for its use have not yet been determined, but a 20-30–minute twice-daily program is effective and has been shown to increase bone density.

The therapist or physician may consider a brace or splinting. Splints can be prescribed in conjunction with a physical or occupational therapist's guidance and are often worn the majority of the day (e.g., 22 hours/day). Common splinting strategies include supporting wrist extension with a baby with wrist-drop and/or extending the fingers and abducting the thumb as well, providing straps to assist with supination (Sup) of the forearm and even braces focused on positioning the shoulder in external rotation (ER). Protocols for splinting strategies such as the "Sup-ER orthosis" have been created and studied in small populations; however, there is currently no general consensus on implementation of such protocols. Early, close monitoring is not only important for surgical considerations, but it is also important for monitoring for secondary problems that can increase the negative impact of functional deficits in children with BBPP. Contractures of the elbow, shoulder, forearm, wrist, and fingers may occur. Although muscle imbalance and fibrosis can contribute to contracture, the evidence suggests a physiologic response related to muscle denervation leading to a failure of growth in the sarcomeres of these affected muscles. Early shoulder dislocations have been described in severe presentations. Botulinum toxin injections help balance out muscles that are overpowering weak muscles and such an intervention can minimize contractures and even prevent or help reduce a shoulder dislocation in these severe cases.

For older babies and children, muscle, tendon, and bony procedures are generally performed. These are often called *secondary surgeries*. Monitoring for shoulder deformity and dislocation is an important part of long-term follow-up. Because the shoulder joint develops as the infant and toddler grows, deficits frequently develop. Glenohumeral dysplasia, sometimes with shoulder dislocation, occurs in 60–80% of those with BBPP. Muscular imbalance across the developing shoulder results in deformity of the skeletally immature glenohumeral joint. The weakness of shoulder external rotation, combined with strong internal rotation, leads to this difficulty. The natural history of this deformity is progression if left untreated. This leads to further functional limitations, even with a strong hand. Treatment aims to minimize this progression. Treatment options include botulinum toxin injections, arthroscopic or open anterior capsule release or release of contracture, musculotendinous lengthening, tendon transfers (e.g., latissimus dorsi to increase external rotation and abduction strength), muscle transfers (e.g., gracilis muscle can be transferred to allow for elbow flexion and/or wrist extension), and, for severe deficits, a derotational humeral osteotomy.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 754

Meningomyelocele (Spina Bifida)

Pamela E. Wilson and Tess S. Simpson

See also Chapter 631.

Meningomyelocele, or spina bifida (SB), is a congenital neural tube defect that results in the malformation of the spine and a potential dysplastic spinal cord. The severity of defect ranges from SB occulta (see Chapter 631.2) upward to anencephaly (see Chapter 631.6). SB without anencephaly is the most prevalent nonchromosomal central nervous system (CNS) defect in the United States. For unknown reasons, Hispanic women have the highest rate of SB (3.80/10,000 live births), followed by non-Hispanic White women (3.09/10,000 live births); the lowest rate is in non-Hispanic Black women (2.73/10,000 live births).

ETIOLOGY

See Chapter 631.1.

PREVENTION

See Chapter 631.1.

PRENATAL SCREENING

Prenatal screening is recommended for all pregnant women to detect neural tube defects. A blood test is done in the second trimester to evaluate alpha-fetal protein (AFP). If a neural tube defect is present, the AFP is often elevated, and further screening using high-resolution ultrasound is indicated. Ultrasound may reveal not only the spinal defect but also abnormal brain development, suggested by the "lemon and banana signs." The lemon sign is a medial indentation and scalloping of the frontal bones in the skull, whereas the banana sign is associated with hindbrain herniation of the cerebellum into the foramen magnum. The importance in early identification allows families to plan for delivery and consider fetal interventions, mainly prenatal surgical closure of the defect. Prenatal closure decreases the need for a ventricular shunt and lowers the incidence of severe Arnold-Chiari malformations, along with improved motor outcomes. However, there is an increased incidence of preterm delivery and a risk for uterine dehiscence; these risks may be reduced with fetoscopic procedures.

CLINICAL IMPLICATIONS

Meningomyelocele is a multisystem condition that includes characteristic abnormalities within the CNS. The neurologic lesion is assessed by the most caudal intact nerve segment with a motor test of grade 3. Lesions associated with SB are often grouped together as thoracic, upper lumbar (L1-L2), midlumbar (L3), lower lumbar (L4-L5), and sacral. Based on this information, a clinician can make inferences on the functional capabilities of the child and answer pertinent questions during the initial encounters (Table 754.1). The most basic question all families ask is: "Will my child walk?"

Initial surgical interventions are related to closure of the open defect. This is generally done the first day of life. Once the back is closed, the child will be monitored to see if hydrocephalus develops. Hydrocephalus is very common and related to hindbrain herniation and obstruction of the fourth ventricle. Hydrocephalus may occur at any time but most frequently within the first few months. Ventricular dilation may precede a change in head circumference or signs of increased intracranial pressure. The occurrence of hydrocephalus is approximately 77–95% and does appear to have an association with level of lesion. Treatment of ventriculomegaly, if mild, may be limited initially to clinical observation. Surgical placement of a ventricular shunt or endoscopic third ventriculostomy is indicated when occipital frontal circumference (OFC) is increasing. The risk for shunt revision in the first 2 years is 30–50%, which then decreases to 10%.

Hindbrain herniation or the **Chiari type II malformation** is seen in 80–90% of individuals with meningomyelocele. The classic manifestations include caudal displacement of the cerebellum, pons, and medulla and elongation of the fourth ventricle. The Chiari II malformation can be symptomatic (from brainstem herniation/compression) in approximately 20% of children. Respiratory symptoms associated with a Chiari malformation include stridor, vocal cord dysfunction, and central or obstructive apnea. Swallowing and feeding problems may require gastrostomy tube placement. If the child has a symptomatic Chiari II malformation, surgical

Table 754.1 Prognosticating in Meningomyelocele

MOTOR LEVEL SPINAL CORD SEGMENT	CRITICAL MOTOR FUNCTION PRESENT	MOBILITY: SCHOOL AGE	RANGE: ADULT	ACTIVITY: ADOLESCENT
T12	Totally paralyzed lower limbs	Standing brace, wheelchair	Wheelchair	Wheelchair, no ambulation
L1-L2	Hip flexor muscles	Crutches, braces, wheelchair	Wheelchair, household ambulation	Wheelchair, nonfunctional ambulation
L3-L4	Quadriceps muscles	Crutches, braces, household ambulation, wheelchair	Crutches, household ambulation, wheelchair	50% Wheelchair, household ambulation with crutches
L5	Medical hamstrings, anterior tibial muscles	Crutches, braces, community ambulation	Crutches, community ambulation	Community ambulation with crutches
S1	Lateral hamstring and peroneal muscles	Community ambulation	Community ambulation	Community ambulation 50% crutch or cane
S2-S3	Mild loss of intrinsic foot muscles possible	Normal	Normal	Limited endurance because of late foot deformities

From Braddon RL, ed. *Physical Medicine & Rehabilitation*, 4th ed. Philadelphia: Saunders; 2011: Table 54.1.

decompression is indicated. All children with SB are at risk for **tethered cord syndrome** (see Chapter 646.1). After shunt malfunction, this is the second most common cause for neurologic decline. Clinical manifestations of tethered cord syndrome include any change in gait, change in bowel or bladder function, increasing scoliosis, back pain, or orthopedic changes. Surgical detethering procedures are indicated in those with neurologic decline, but the success rate is variable.

The **orthopedic complications** of myelomeningocele are common and have predictable patterns. The spine deformities include scoliosis, lordosis, and kyphosis (see Chapter 720). The development of scoliosis has an association with the neurologic level. Children with thoracic level meningomyeloceles have an 80–100% risk, whereas those with a sacral level are at very low risk. Spine deformities tend to increase more rapidly during growth, especially puberty. Treatment of scoliosis includes both nonsurgical and surgical options. Braces, such as thoracic-lumbar-sacral orthotics (TLSO), therapy, and proper seating options may be beneficial. Surgically implanted growing rods to support the developing spine have been used in younger children. Spine surgery should be considered if the scoliotic spine curvature reaches 45 degrees; the child who is nearing skeletal maturity is a better candidate for spine surgery. Realistic expectations need to be discussed with the child and family. Correction of the spine may improve sitting, posture, and pelvic obliquity but may have a negative impact on function and ambulation.

The **development of the hip** is also influenced by neurologic level (see Chapter 719). The risk for dislocation is highest for those with lesions at the L3 level, followed by L1-L2. Unilateral hip dislocations should be fixed surgically because they may result in pelvic obliquity and problems with sitting, whereas bilateral dislocations generally do not require interventions. Contractures of soft tissues are commonly seen in children with higher lesion levels. Hip flexors and knee flexors are commonly involved.

Abnormalities in the foot occur in approximately 90% of children and adolescents. The goal of treatment is to achieve a plantar grade foot for weight bearing and to allow shoe wear. Clubfoot deformities are common in babies, and treatment includes serial casting and orthotics (see Chapter 715.3). The results are often suboptimal, and surgery may be needed. In addition, congenital vertical talus (rocker-bottom feet) is often encountered and needs to be addressed (see Chapter 715.4).

Osteoporosis (see Chapter 749) begins to develop in childhood and is more severe in higher-level meningomyelocele. Fractures of the lower extremities are most common in the femur, followed by the tibia. Preventive treatment includes nutritional approaches such as the use of supplemental calcium and vitamin D. Those with documented fractures should undergo a diagnostic evaluation (see Table 749.1), including dual-energy x-ray absorptiometry (DEXA). The use of bisphosphonates may be considered if the diagnostic evaluation does not reveal other underlying causes. The utility of early weight bearing has been advocated, but passive standing may have little impact on bone density.

Neurogenic bladder and bowel can be anticipated. The goals of treatment interventions are to protect kidney function and achieve social continence. For continence of urine, clean intermittent catheterization (CIC) is the mainstay of management. It is not atypical for newborn babies to be started on a CIC program. Urodynamics and renal ultrasounds are routinely used to monitor for hydronephrosis and track intravesicular pressures. Medications may be used to reduce bladder contractions and improve volume capacity. Surgical techniques are being used to improve continence, including bladder augmentation, urethral surgeries, and catheterizable channels. Poor CIC technique and/or urinary reflux may lead to urinary tract infection (UTI), which is diagnosed by having two findings: a urinalysis with white cell count of >10 and urinary culture >100,000 cfu/mL. A multicomponent bowel program is generally needed to achieve bowel continence. Nonsurgical interventions include adequate hydration, dietary manipulation, fiber regulation, and use of laxatives and enemas. Surgical interventions, such as the antegrade continence enema (ACE), have improved continence in many children and adolescents with SB.

Latex allergies are common. The etiology is likely multifactorial, but increased early exposure may play a role in the development of severe reactions (see Chapter 190). Care providers need to be keenly aware of products that contain latex or that have a cross reactivity, such as foods mixed with avocado, bananas, or kiwi fruit. Radioallergosorbent testing is used for identification of potential severe allergens.

People with SB show a wide range of **neuropsychologic abilities**. Many show a complex neuropsychologic profile that includes strengths in some areas and weaknesses in other areas. Common areas of strengths include vocabulary, word reading, spelling, and certain types of memory. Common weaknesses include motor skills, attention, organization, math, reading comprehension, and executive functioning skills. Overall cognitive functioning typically falls within the average range for children with SB; however, neurologic factors such as a Chiari II malformation or the presence of hydrocephalus increase the risk for neuropsychologic challenges. Neuropsychologic assessment is recommended to identify any potential gaps in cognition and social or emotional skills. This assessment can provide helpful information related to a child or adolescent's education and employment needs and assist with development of an individualized educational plan (IEP) or vocational rehabilitation plan. Appropriate early intervention and support programs should be initiated through an IEP or 504 plan if indicated (see Chapter 56). Effective interventions both at school and the home should be structured, explicit, and individualized. Parents and teachers can support learning goals by progressing in an orderly fashion from one learning target to the next and by modeling how to approach problems or tasks, often with step-by-step instructions and supervised practice.

ADOLESCENCE AND TRANSITION TO ADULTHOOD

Improved and expanded clinical care has increased the life span of individuals with SB, with the majority of individuals now living well into adulthood. Secondary conditions associated with SB (e.g., UTIs, skin breakdown, learning challenges) and more difficulty accessing healthcare services compared with their age-matched peers make adolescents and young adults with SB less likely to achieve emerging adult milestones such as leaving home, attending college, or finding employment.

The primary care clinician, in conjunction with specialty services, plays a pivotal role in developing future planning. It is important to discuss early on strategies to encourage developmentally appropriate independence and self-management skills. Individualized, comprehensive transition care that includes care coordination, decision-making support, education and employment resources, and independent living support is recommended for providers caring for children and adolescents with SB.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 755

Upper and Lower Extremity Assistive Devices

Abigail Case and Sarah Helen Evans

Assistive devices, such as orthoses, prostheses, walkers, crutches, and wheelchairs, are key components of intervention for individuals with physical disabilities, and with the continued advancement in technology, robotic forms of these devices are also important to consider. The type of device chosen depends on the underlying diagnosis, functional abilities of the individual, prognosis for functional improvement or decline, tone abnormalities, range of motion, strength, and the overall gait pattern. Physicians, licensed independent practitioners, and physical therapists perform the evaluation of a child requiring an assistive device.

ORTHOSES

An **orthosis** is a device that is applied to the surface of the body to maintain alignment or position, to prevent or assist movement of the body part, or to provide support. Named for the body parts covered, orthoses can be static, made of rigid material, and designed to immobilize joints to inhibit movement, or they can be dynamic, allowing movement of the limb to occur. For example, **AFO** stands for *ankle-foot orthosis*, a brace worn on the foot that extends from the toes to the mid-calf position, supporting the foot and ankle joints (Fig. 755.1). Prefabricated orthoses are available, but many children require custom-made orthoses for optimal fit. Orthoses are modified or replaced during periods of growth or changes in function and can be obtained either directly through the orthotist or through the child's physical therapist. In most of the United States, braces must be prescribed by a physician or licensed independent practitioner to obtain insurance coverage, and it is best practice to have a prescription.

The use of an upper limb orthosis can be more conspicuous than its lower limb counterparts, and physicians should analyze the user's psychosocial well-being and tolerance for such device. In addition to patient goals and outcomes, the therapeutic intent of the upper limb orthosis must be considered. The efficacy of the orthosis may be measured by the reduction of the effects of the three Ps: paralysis, pain, and position.



Fig. 755.1 Hinged ankle-foot orthosis. *(Courtesy Ultraflex Systems, Inc., Pottstown, PA.)*

The type of lower-extremity orthosis prescribed is based on the child's diagnosis, functional status, prognosis, and the goals of treatment, with the prescription frequently modified over time as the child changes. Before writing a prescription, the provider performs an examination, which may include an evaluation of the child's gait, strength, tone, and range of motion. There are many types of braces that have specific functions to improve gait. Table 755.1 lists examples of these orthoses and their potential uses.

The most prescribed braces are solid and articulated AFOs. Solid AFOs are used for children with hypertonicity because they help to biomechanically reduce tone and provide stability with standing and walking. Children who are nonambulatory also benefit from wearing solid AFOs to maintain range of motion of the ankle.

Articulated (hinged) AFOs allow the child to have ankle dorsiflexion by permitting forward movement of the tibia and supporting the foot for heel strike. This design makes ambulating on uneven surfaces and using stairs easier because of the movement allowed at the ankle, while still supporting the foot position and maintaining medial-lateral stability of the ankle. Articulated AFOs should not be used in children with cerebral palsy, spina bifida, or other disorders if they have a crouched gait pattern because the hinge in the ankle joint may allow further crouching. In crouched gait, the hips and knees are held in flexion and ankles in dorsiflexion throughout the gait cycle, leading to an inefficient gait pattern.

PROSTHESES

A prosthesis is a device that replaces a missing body part, such as an arm or a leg. Lower-extremity prostheses are used to improve mobility, but upper-limb prostheses are not always needed to improve function because children can be quite independent with a single upper limb. Children with congenital upper limb amputations or deficiencies need to have prosthetic devices fit at the time they begin to sit for them to use the prosthesis functionally, and because, developmentally, young children are not ready to learn to use complicated devices, teaching them to use a mechanical prothesis requires intensive occupational therapy. Myoelectric protheses are too heavy and too hard to use at this age. Children with acquired upper limb amputations may be more likely to adjust to the use of a prosthetic arm.

Lower-limb prostheses are used in children with acquired amputations as a result of trauma or cancer and also in congenital transverse amputations or for those who have undergone surgical correction, as often occurs with longitudinal fibular deficiency or proximal femoral focal deficiency.

There are multiple components to lower-limb prostheses, which include the socket and foot, but may also include a hip and knee joint, depending on the level of amputation. A prosthetist works with the child and family to fabricate the prosthesis. A physician or licensed independent practitioner with experience in prostheses provides the prescription for this device.

The type of prosthesis depends on the age of the child, the level of the amputation, and the status of the residual limb. In very young children, use of a lower-extremity prosthesis follows developmental milestones, with the first prosthesis prescribed at the time the child should be pulling to stand. Addition of joints to the prosthesis also occurs when developmentally appropriate, such as use of a knee joint around the age of 3 years when the child is learning to use stairs.

Advances in technology are helping children who use prostheses achieve a fluid gait pattern that makes their prosthetic use virtually undetectable to the untrained eye. New components and designs allow amputees to lead active lifestyles that may include running, swimming, biking, and mountain climbing.

ASSISTIVE MOBILITY DEVICES

The function of assistive mobility devices is to provide a wider base of support to improve stability during ambulation, reduce the possibility

Table 755.1 Orthotic Options

ORTHOSIS	FUNCTION	COMMENTS
Neoprene thumb abductor	Places thumb in abduction to promote functional use of hand	Will not overcome severe cortical thumb position
Thumb spica	Immobilizes and protects the thumb and provides a stable post against which the index finger can pinch	Need to allow for full metacarpophalangeal (MCP) flexion of the fingers
Resting hand	Preserves balance between extrinsic and intrinsic musculature and provides joint stability; prevents contracture	Pressure at the MCP joint or proximal phalanx should be avoided because it can injure the MCP joint. This splint is to be used for positioning, not function
Wrist cock-up	Supports, immobilizes, or stabilizes wrist in extension, which allows for mechanical advantage in grasp	Must maintain full MCP flexion and thumb motion
Elbow extension	Increases extensor end range of motion (ROM)	Not for severe flexor tone with contracture or fluctuating tone; in that case, use a drop out cast or splint
Gunslinger	Supports shoulder girdle and prevents subluxation	Make sure the edges of splint are not cutting into hip area; check in standing and supine
Myomo	Sensor-activated, power-driven upper limb orthosis can train the arm and hand while providing assistance with bimanual activities	Heavy Minimal growth with a child
Foot orthosis (FO)	Provides support of foot only to keep ankle in subtalar neutral	Not typically customized but can be with a UCBL*
Supramalleolar orthosis (SMO)	Provides medial-lateral support of foot to prevent excessive pronation, supination, or instability	Appropriate for children with low tone such as in Down syndrome. Also useful for young children with equinovarus posture or mediolateral instability
Ankle-foot orthosis (AFO)	Provides support at the ankle and reduces foot drop or plantarflexion tone by keeping the ankle in a neutral position	Commonly used for ambulatory and nonambulatory children Assists with dorsiflexion and inhibits plantarflexion. Requires rocker bottom shoe for rollover in gait
FES activated AFO	Uses functional electrical stimulation to assist dorsiflexion at the appropriate time in the gait cycle	Cannot inhibit plantarflexion Less restrictive than a solid or hinged AFO Can be used with an SMO to provide mediolateral stability at the ankle
Ground reaction ankle-foot orthosis (GRAFO)	Provides knee extension moment to reduce crouching or collapsing into dorsiflexion during standing or walking	Appropriate for children with spina bifida or who have weakness in the plantar flexors who crouch when walking
Knee-ankle-foot orthosis (KAFO)	Provides support at the knee when there is quadriceps weakness to promote an upright posture with standing or walking	Less commonly used because of large size of brace but may be appropriate for child with spina bifida or spinal cord injury
Walking assistance exoskeleton	Bionic robot for use in paraplegic patients	Heavy. Very expensive. Does not grow with a patient. Cannot be used in patients with spared sensation in the legs

*UCBL – University of California Berkley Laboratories, where this maximum control foot orthosis was developed.

of falls, and improve efficiency of gait. The least supportive device is a traditional single-point cane commonly used after an orthopedic injury. For most children with gait abnormalities secondary to neurologic disorders, this is not a functional option because a cane does not provide enough stability. More supportive gait aids, such as forearm (Lofstrand) crutches, are appropriate in children with neurologic disorders; however, use of these devices requires good coordination and strength. Children with cerebral palsy and spina bifida may benefit from these devices.

Walkers provide more support than crutches and canes; they do not require as much strength and coordination to operate. Children with cerebral palsy, for example, may use a reverse walker, which they pull behind them. This reverse configuration provides a wide base of support and stability, helps maintain an erect posture, and allows the child to engage with the environment without the barrier of the walker in front of them. Having the walker behind them also reduces the risk for more serious injury from a forward fall.

For children who require a significant amount of support because of poor head and trunk control, **gait trainers** are often used. These devices allow the child to work on leg movements while the trunk and pelvis are stabilized (Fig. 755.2). Although gait trainers provide a child with moderate to severe motor impairments upright supportive mobility, "gait trainer" is a misnomer in that it is not intended to train a child to walk independently.

WHEELCHAIR

Wheelchairs should be considered as a means of mobility when ambulation is not possible or is difficult outside of the home setting. Children with spinal cord injuries, spina bifida, neuromuscular diseases, or cerebral palsy may benefit from the use of a wheelchair. The goal is to provide a wheelchair that will allow the child to move independently about the environment, including home, school, and the community. Children as young as age 2 years can self-propel a manual wheelchair and operate a power wheelchair. The type of wheelchair prescribed will depend on the child's underlying diagnosis, cognition, vision, motor skills (such as head and trunk control), strength and endurance of upper limbs, musculoskeletal deformities, if present, and medical comorbidities. One must also consider future growth or



Fig. 755.2 Gait trainer. *(Photo copyright 2013 by Rifton Equipment, http://www.rifton.com.)*

anticipated changes in function over time, as well as the family's ability to transport the chair. An important consideration when ordering a pediatric wheelchair is the adjustability to accommodate growth. A typical wheelchair may last 3-5 years with periodic adjustments to growth by a seating specialist. There are many components that can be added to provide more support in the wheelchair, including head rests, lateral trunk support, hip guides, antitippers that prevent the wheelchair from tipping backward, and specialized tires. The seating system is considered a separate item from the wheelchair itself and is, in fact, a seating orthosis. It should be properly fit for the child's current size and seating needs. The function of a seating system is to promote the upright positioning of the head and trunk as well as control of the position of the legs, especially the hips, in sitting. Children with good trunk control will require a simple seat back, while a child with poor trunk control, such as someone with a high cervical spinal cord injury, will require a system that includes a head rest and lateral thoracic supports. The seat itself must be customized to provide a stable base on which the trunk can align. Restraint at the pelvis, such as a seatbelt or bar, helps maintain proper positioning in the chair. Specialized cushions are needed for those with decreased sensation to prevent pressure-related skin sores.

ROBOTIC DEVICES

Rehabilitation robotics is a subspecialty field that is helping to increase independence for individuals with disabilities. Robots are currently defined as machines programmable by a computer and capable of carrying out a complex series of activities automatically. Although there is a wide range of the types of robots used in rehabilitation, a subset of robots provide assistance in the form of adaptive equipment. Most of these robots are wearable; notable exceptions are fully automated voice-controlled feeding systems and speech generating devices. Lower limb devices are designed to help a child progress toward a typical gait pattern and range in complexity from exoskeletons to programable AFOs that provide electrical stimulation to muscles that control foot position and strength across the ankle joint. Upper limb devices are designed to increase the use of a minimally functional arm and hand. Programmable prostheses, such as myoelectric arms and hands, respond to input from the user's neuromuscular system while bionic limbs respond to sensors implanted in the brain. The use of robotic assistive devices is less common than mechanical devices, in part because of availability and in part because of higher cost. The advantage of most robotic assistive devices compared with their mechanical counterparts is the ability of the device to train the user to need it less while providing the assistance required in the moment.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 756

Health and Wellness for Children with Disabilities

Meghan A. Klawonn, David M. Kanter, and Margaret A. Turk

DISABILITY

Children with Special Healthcare Needs

The expansion of the *disability* definition to include children with special healthcare needs (CSHCN), chronic conditions, and activity limitations from any cause (e.g., limitations in usual daily activities such as age-appropriate self-care, mobility, communication, and cognition) has made the health issues of the more *traditional* childhood disability types (e.g., cerebral palsy, intellectual disability, spina bifida, congenital musculoskeletal disorders) more difficult to identify. U.S. data note continued increasing prevalence of developmental disabilities and identify developmental, emotional, and behavioral conditions as the leading conditions. Physical health conditions comprise a smaller proportion of disabilities, although mobility and motor control issues may be noted among the aforementioned developmental, behavioral, and emotional conditions. These disabilities contribute to continued economic and health problems into adulthood. Childhood and adolescent health promotion interventions can decrease functional impairment across the life span. Monitoring children with disabilities throughout their development is essential for identifying times when support to children, adolescents, and/or their families is needed to promote positive health outcomes.

Health Promotion Definitions and Background for Disability

The World Health Organization (WHO) defines *health promotion* as "the process of enabling people to increase control over, and to improve, their health." For people with disabilities, this concept is important because they are both underserved and have comparatively large health disparities. The WHO further defines health promotion approaches as including more than health education and consisting of community action, supportive and accessible environments, policy changes, health service modifications, and development of personal skills. Health and wellness programs also include traditional preventive management strategies, such as anticipatory guidance. There is ample evidence that engaging in specific areas of health promotion results in improvement, although the evidence for its influence on adult health is less robust.

Children with disabilities encounter many barriers to healthy behaviors (Table 756.1). Both broad and focused health promotion programs consider severity of condition, barriers and resources, and self-efficacy to achieve health-promoting behaviors. Children with disabilities may also require modeling or assistance to apply healthy behaviors to their particular disability or economic, social, and environmental circumstances.

Individuals with disabilities and their families often view health differently than those without disabilities. Disability may influence health and

Table 756.1 Barriers and Facilitators for Children to Engage in Healthy Behaviors

SELF	FAMILY	INSTITUTION
BARRIERS	BARRIERS	BARRIERS
1. Lack of knowledge and skills 2. Fear of injury or failure 3. Personal choices 4. Fatigue 5. Lack of initiative 6. Limited functional capability	1. Negative attitudes by parents, peers, healthcare providers 2. Limited parental healthy behaviors 3. Stress in the close family network 4. Economic restrictions	1. Inaccessible facilities or resources 2. Needing adult or aide assistance 3. Policies and procedures of facilities or programs 4. Noninclusive providers 5. Transport challenges
FACILITATORS	FACILITATORS	FACILITATORS
1. Education or knowledge about heathy behaviors 2. Engaging child in discussions and decisions 3. Desire to be active 4. Making activities a part of the routine—repetition and consistency promote ongoing activities	1. Promotion of activities by rehabilitation and other healthcare professionals 2. Family support and participation 3. Involvement of friends and peers in activities 4. Models or directions for participation with adaptions 5. Creative and knowledgeable professionals	1. Accessible facilities and opportunities with knowledgeable staff 2. Policies and resources promoting participation 3. Welcoming and inclusive providers: Adaptable approaches

vice versa, but their perception of their own health and wellness does not equate with their level of disability. Experiences as a child with a disability often foreshadow adult behaviors, especially negative attitudes toward therapy, exercise, and activity. Beliefs of parents, families, and healthcare providers also influence the views of health by children with disabilities. Health promotion programs for these children must (1) understand and support the role and well-being of parents, (2) recognize that parents of children with more functional limitations may require more resources and support, (3) involve children with disabilities in the design of programs and decisions about participation, and (4) address barriers to participation, perceived and real (see Table 756.1).

An effective health and wellness program should involve multiple approaches and opportunities for success by considering novel and inclusive approaches, including partnerships with families, school staff, and rehabilitation providers. Effectiveness requires addressing any mismatch between the child's positive sense of health and well-being and that expected by the healthcare providers; recognizing limitations of an education-only model; engaging the child in discussions about the importance of healthy behaviors, ways to engage in healthy behaviors related to the child's disability and circumstances, and decisions about participation; promoting self-efficacy and self-management of health and wellness in preparation for adult healthcare when possible; and parent and family involvement coupled with sensitivity for the high level of support a family may already be providing for a child with a disability.

Anticipatory Guidance, Counseling, and Preventive Care

Preventive healthcare through health education, anticipatory guidance, and participation in screening and immunization schedules is the mainstay of pediatric public health programs (see Chapter 12). *Bright Futures*, developed by the American Academy of Pediatrics and their collaborators and supported by the Maternal and Child Health Bureau, Health Resources, and Services Administration, provides a knowledge base for pediatric healthcare providers and the public about anticipatory guidance, health promotion, and prevention for children and adolescents with a section in the 4th edition titled "Promoting Health for Children and Youth with Special Health Care Needs." For the general population, 25% of parents receive no information, and <50% receive all recommended guidance. Although parents of CSHCNs report similar or better receipt of general preventive information, it is not clear whether those with higher severity of functional limitations receive this guidance or counseling, and whether it is provided in the context of disability and other circumstances.

CSHCNs require typical prevention, as well as more specific counseling or screening related to their disability. Some of this more specific counseling can be managed by specialty care providers, although CSHCNs often have difficulty obtaining appropriate specialty outpatient services. Additional barriers to care, especially with increasing age of the child, are the lack of accessible medical equipment and facilities. Planning for transitions to adult care should begin early, with consideration of environmental access, preparedness for self-management when possible, and knowledge and skills of local healthcare providers. Although discussions of health risks with adolescents about smoking, drinking, and protected sexual activity should be undertaken, the discussions may require a different focus for adolescents with disabilities. Higher violence and abuse rates toward children with disabilities are reported, for which providers must be vigilant. Internet and social media use increases the risk of bullying and other negative experiences. It appears adolescent females with disabilities are more vulnerable than males to this victimization.

The recommendation is to recognize the need for modifications to typical guidance and to be alert for any signs of emotional disturbances. CSHCNs experience family issues with separation/divorce, mental health and substance abuse problems, incarceration, domestic or neighborhood violence, discrimination, parental death, and maltreatment more than those without special needs. Counseling should be broadened to include questions and discussions about conditions associated with the specific disabilities (e.g., epilepsy or cognitive impairments often seen with cerebral palsy, or neurogenic bladder and bowel in spinal cord dysfunction) or secondary conditions, such as pain, osteoporosis/fractures, or the fatigue seen in many CSHCNs. Early recognition of emotional and psychiatric disorders, at early ages and especially during times of transition, can help to address nationally acknowledged unmet mental healthcare needs. There are also signs of comorbidities commonly seen in adulthood, such as cardiovascular and renal conditions, in children with disability.

Physical Activity and Exercise

National health guidelines recommend at least 60 minutes of physical activity daily for children, but any activity increase from sedentary levels to even moderate activity (30-40 minutes of moderate intensity or 20 minutes of more strenuous activity) provides some health benefit. Health professionals should give specific advice about how children with disabilities can increase their level of activity. Exercise and activity increase aerobic capacity, functional ability, and quality of life for children with many kinds of disabilities and chronic diseases. National 24-hour movement guidelines have been established in Canada and Australia, with age-specific recommendations regarding lengths of time to sleep, perform physical activity, and sedentary time. It has been shown that individuals with disabilities meet the 24-hour movement guidelines at lower rates compared to the general population, which in turn may affect mental health. And yet, many healthcare providers and families accept sedentary lifestyles for children and adolescents with disabilities, whatever their functional abilities. Video gaming systems that involve movement can help to overcome this lack of activity because they can provide another way to increase movement. For children with disabilities, school physical education and recess programs can support activities at or greater than the recommendation, and school requirements can reinforce activity expectations; however, there should be monitoring for possible negative affect, poor sense of belonging, and presence of victimization during open recess opportunities. School-based interventions for adolescents with intellectual and developmental disabilities have been shown to increase healthy behaviors, such as engagement in physical activity and increased consumption of fruit and vegetables. Healthy behaviors are in turn associated with improvement in mental health. The need for exercise beyond physical therapy should be clarified to help children understand the benefits and purpose of both. The activities in which youth with disabilities wish to participate can be supported, and shared decision-making should be invoked. Children with disabilities who participate in physical activities report social benefits, such as developing friendships, building a support system, gaining knowledge of self, and acquiring a sense of accomplishment. These factors also contribute to higher adherence to activities. Children with disabilities may also be more likely to participate in physical activities when those activities are supervised and organized, as opposed to free play in an open room. For children with disabilities to engage in physical activity in supported environments, school and public playgrounds must be made sufficiently accessible to support community physical activity. A number of agencies have endorsed the Commit to Inclusion campaign to promote building healthy, inclusive communities for people of all ages with disability (e.g., the President's Council on Fitness, Sports, and Nutrition, along with the National Center on Health, Physical Activity, and Disability; the American Association on Health and Disability; and the Center on Disability at the Public Health Institute).

Physical activity for children and adolescents improves fitness and quality of life for youth with developmental disabilities (Table 756.2). These exercise and fitness programs require 2-3 months of participation, at least twice a week, to achieve any changes, and many of the changes achieved are longer lasting than expected. These programs are not traditional therapy, and participation in therapy is not a substitute. These focused fitness and

Table 756.2 Examples of Effective Exercise Programs for Children with Disabilities

CENTER-BASED FITNESS PROGRAM AND HOME PROGRAM	GROUP AQUATIC AEROBICS	GROUP TRAINING CLASS	ONLINE EXERCISE PRESCRIPTION TOOL
• Children with a variety of disabilities • Group exercise: 2×/wk for 14 wk, warm-up, aerobics, strengthening, cool-down • Home program: 2×/wk for 12 wk using video exercises • *Outcomes:* improved walking efficiency, strength, general function[a]	• Children with a variety of disabilities, 50% able to walk 2×/wk • Recreation to achieve target heart rate; aquatic strengthening program • *Outcomes:* improved walk/run[b]	• Children with cerebral palsy able to walk 2×/wk for 14 wk • Warm-up, circuit training stations (treadmill, balance stairs, closed-chain exercises) • *Outcomes:* improved muscle strength, mobility, function[c]	• Children with a variety of disabilities • 8 wk home exercise program delivered using Physitrack, an online exercise prescription tool • *Outcomes:* equivalent adherence to traditional paper-based method, more easily accessible[d,e]
• Strength • Training	• Walking-jogging program	• Treadmill training program	• Skill-related fitness (SRF)
• Children with cerebral palsy including a majority able to walk with assistive devices 3×/wk for 6 wk • Progressive training program, conducted in the home • *Outcomes:* improved perceptions of strength, walking, stair management, improved psychologic benefits[f]	• Children with down syndrome • 3×/wk for 10 wk, 30 min sessions, achieving 65–70% peak heart rate • *Outcomes:* improved peak exercise time and grade, improved walking capacity[g]	• Children with intellectual disabilities daily for 2 months • Progressive treadmill use with goal of 20-30 min • *Outcomes:* improved heart rate with and without activities[h]	• Adolescents with intellectual disabilities • SRF is a physical fitness component related to sports performance, used to enhance participation with peers in leisure activities • *Outcomes:* positive exercise training effects on agility, power RT, and speed[i]

[a]From Fragala-Pinkham MA, Haley SM, Rabin J, Kharasch VS. A fitness program for children with disabilities. *Phys Ther.* 2005;85(11):1182–1200.
[b]From Fragala-Pinkham M, Haley SM, O'Neil ME. Group aquatic aerobic exercise for children with disabilities. *Dev Med Child Neurol* 2008;50(11):822–827.
[c]From Blundell SW, Shepherd RB, Dean CM, Adams RD, Cahill BM. Functional strength training in cerebral palsy: A pilot study of a group circuit training class for children age 4-8 years. *Clin Rehabil* 2003;17(1):48–57.
[d]From Johnson RW, Williams SA, Gucciardi DF, Bear N, Gibson N. Can an online exercise prescription tool improve adherence to home exercise programmes in children with cerebral palsy and other neurodevelopmental disabilities? A randomised controlled trial. *BMJ Open.* 2020;10(12):e040108.
[e]From Johnson RW, Williams SA, Gucciardi DF, Bear N, Gibson N. Evaluating the effectiveness of home exercise programmes using an online exercise prescription tool in children with cerebral palsy: protocol for a randomised controlled trial. *BMJ Open.* 2018;8(1):e018316.
[f]From McBurney H, Taylor NF, Dodd KJ, Graham HK. A qualitative analysis of the benefits of strength training for young people with cerebral palsy. *Dev Med Child Neurol.* 2003;45(10):658–663.
[g]From Millar AL, Fernhall B, Burkett LN. Effects of aerobic training in adolescents with Down syndrome. *Med Sci Sports Exerc.* 1993;25(2):270–274.
[h]From Lotan M, Isakov E, Kessel S, Merrick J. Physical fitness and functional ability of children with intellectual disability: effects of a short-term daily treadmill intervention. *Sci World J* 2004;4:449–457.
[i]From Jeng SC, Chang C-W, Liu W-Y, Hou Y-J, Lin Y-H. Exercise training on skill-related physical fitness in adolescents with intellectual disability: A systematic review and meta-analysis. *Disabil Health J.* 2017;10(2):198–206.

exercise programs generally require the support and direction of rehabilitation professionals, although programs can be community based in nonmedical surroundings.

Recreation and organized sports are other areas where children and adolescents with disabilities can engage successfully, at times with modifications. Participation improves cardiopulmonary parameters, motor function, social competence, and general sense of well-being. Many children with disabilities require 1-on-1 instruction for development of skills, with a goal of participation in activities with their peers. Perceived barriers to participation in sports differ based on the source: children were concerned about dependency; parents required more information about possible sport participation. Programs through Special Olympics International are an opportunity for children and adolescents to engage in supportive and monitored environments for sport and recreation.

Rehabilitation professionals can assist with problem-solving activity participation, such as by using computerized technologies for "exergaming" (e.g., Wii, Xbox, PlayStation), developing individual or group challenges with mobile devices (e.g., activity trackers), adapting equipment (e.g., modified upper-limb prosthesis to allow baseball glove use or modified bicycle equipment), and knowing of adapted recreation programs in the area (e.g., horseback riding, winter/water sports). Technologies that allow for exercise as part of gaming provide new opportunities for moderate to vigorous exercise in people with disabilities, especially in those with limited use of the lower limbs. Youth with greater functional limitations may not be able to achieve moderate to vigorous exercise, but even light intensity exercise may be enough to give them some health benefits. "Exergaming" programs are viewed as more fun than traditional exercises, which may increase likelihood of participation.

Sleep and Pain

Poor sleep quality or the presence of pain will have an impact on physical activity and general performance in children and youth with disabilities. Regular inquiry about sleep and pain is important because of the higher prevalence of problems in these areas in children with disabilities. Common sleep disturbances include difficulty initiating sleep, frequent sleep disruptions, and reduced sleep duration. Causes are often complex and multifactorial, with some associations with disability type (e.g., obstructive sleep apnea with Down or Prader-Willi syndromes, disrupted sleep patterns with autism, negative bedtime behaviors with attention-deficit/hyperactivity disorder, pain as trigger with cerebral palsy) and comorbidities (e.g., epilepsy, gastroesophageal reflux). Frontline approaches are sleep hygiene and behavioral interventions, and further evaluation may be warranted for targeted interventions (see Chapter 31).

Pain has been described as a cause for behavioral changes, poor sleep, activity interference, and change in school performance in children with a variety of disabilities. Children with cerebral palsy have been most closely studied, with high prevalence of both acute and chronic pain. Routine screening is important for early identification and evaluation for cause, and interventions should be tailored to address the biopsychosocial model of pain management.

Nutrition and Obesity

See also Chapter 65.

Managing the combination of nutrition and physical activity is the key ingredient of weight control. Estimates suggest that children with physical activity limitations were twice as likely as the general population to be overweight, and youth with cognitive impairments are at increased risk. It is unclear if obesity is a cause for the activity limitations or is a result of the limited activity, which may be an important distinction in developing interventions. The concern with obesity contrasts with early life weight gain needs of many children with disabilities, and it may be confusing for parents and families when the focus changes to weight decrease. Confounding factors related to monitoring percent body fat in children with disability include (1) the propensity for some disabilities, often those that are genetically mediated, to be associated with obesity; (2) standards of measurement may not be appropriate for certain diagnoses or disability types (e.g., inaccurate weight [limb deficiencies/amputation, scale inaccessibility], inaccurate height [unable to stand, contractures], no standards related to short stature or muscle wasting); (3) obesity may be a side effect of medication, and this effect must be balanced against the drug benefits (e.g., antipsychotics, steroids); and (4) the social network of family, friends, schools, and healthcare providers may unwittingly negatively influence health habits, including use of food as reward for behavior management. Both children and their parents should be a part of the conversations related to obesity or any weight-related topic. Information must be presented in a direct and understandable way and modified for the child's and parents' needs. Discussion of promoting health through nutrition and physical activity, while problem solving challenges to participation, may be a better approach than explaining body composition and metabolic pathways.

Emotional Health and Leisure Activities

Emotional health is often overlooked in children with disabilities. Youth and adolescents with disabilities appear to be at higher risk for feeling low, stressed, or anxious (especially those with higher levels of limitations), and those with mental health needs may have lower adaptive functioning or a family history of mental illness. While children and young adults diagnosed with autism have received much attention related to emotional support needs, there are increasing reports of this need with most childhood-onset disability conditions, including at ages before teenage years. Sexuality, gender identity, and other sex-related issues can also be reasons for emotional turmoil. Adolescents with physical disabilities participate in fewer social activities, have fewer close or intimate friends, and have fewer plans for ongoing education. There is a risk for continued isolation into adulthood. Passive social media use may exacerbate this problem. Novel programs to improve self-concept and build resilience based on psychoeducational therapy principles, typically developed through interdisciplinary teams, and involving peer groups, parents, and family members, have been shown to successfully promote positive outcomes. Medications may be considered, but effectiveness is not guaranteed, and unwanted side effects may produce more health challenges. Counseling requires insurance support or discretionary funding. There is some early work on using apps to try and help track mental health issues.

Leisure and recreational activities provide social supports, additional stress-coping mechanisms, and ability to develop social skills and a stronger personal identity. Although the negative aspects of social media are often discussed, there are also positive aspects. Adolescents with disabilities may more easily communicate and socialize with peers online, improving their mental well-being. Females with disabilities tend to engage in social or skill-based activities, and males in physical activities, with decreasing participation with increasing age. In general, encouraging socialization through leisure activities, recreation, or sports and physical activity can be a part of counseling in a routine health visit.

Dental Care

Dental care is a frequently unmet healthcare need for children with disabilities, especially for those in low-income families or with more severe impairments. The principal deficits are in receipt of specific dental care (not preventive services). Condition severity may also predict the degree to which parents are interested in oral health–related education and actually engage in oral health efforts. Parents and caregivers play a critical role in oral health support. Challenging behaviors often limit dental care, and the use of behavior management techniques and education programs have been effective in allowing dental care. Dental treatment under anesthesia may be necessary to provide effective oral healthcare.

Role of Healthcare Providers

Primary care and other healthcare providers should be mindful of discussing and promoting health and healthy behaviors with children and adolescents with disabilities and their families (Table 756.3). Initial discussions and preventive screening, including exploration for early signs of cardiovascular or renal diseases and assessing the need for emotional support, are a responsibility of primary care providers individually or in conjunction with specialty care providers. Children with a wide range of impairments should be included in multi-method inclusive research. Innovative strategies for engaging

Table 756.3 Targeting Healthy Behaviors for Children with Disabilities

GENERAL PREVENTION	PHYSICAL ACTIVITY	NUTRITION AND OBESITY
• Recognize risks for less healthy behaviors and facilitators of behavior changes and participation. • Cover typical topics for all children counsel regarding disability or situation context. • Specifically monitor for abuse and violence. • Provide typical age-appropriate adolescent information about smoking, drinking, substance abuse, sexual contacts; refer if unable to provide. • Monitor for disability-specific health conditions; many require referral.	• Promote exercise and activity with an expectation for activity. • Ensure that family and child/adolescent are knowledgeable about benefits and possible adaption. • Review need for possible dietary changes. • Consider referral to community programs and/or rehabilitation professionals	• Recognize obesity can cause limitations and can be the result of poor dietary habits and limited activity. • Follow percent body fat in a consistent way, recognizing the need for accurate measures or limitations of measures (e.g., weight, body mass index [BMI], skinfold thickness, other traditional measures) in many disability conditions. • Ensure that family and child/adolescent are knowledgeable about healthy nutrition. • Consider referral to nutritionist or other professional to engage patient and family in education and behavior change counseling • Review need for increased activity level with dietary intervention.
EMOTIONAL	**HEALTH, RECREATION, AND LEISURE**	**DENTAL**
• Question for sense of anxiety/feeling low, stress management and ability to adapt, and social supports. • Consider medications and counseling based on expected effect, monitor effects/side effects; consider referral, making sure that insurance/payment coverage is available. • Consider recreation and leisure activities to promote social support and ability to develop social skills. • Recommend use of social media in positive ways to enhance connections.	• Question about social activities outside the home: highlight the importance of developing social skills, sense of self, and support networks • Consider referral to community programs or rehabilitation professionals. • Consider recommending online support groups, social groups.	• Discuss more than preventive dental care. • Suggest behavior strategies if there are problems engaging in dental appointments and refer for this service as needed.

children with disabilities have been identified and offer much hope for the future. Parents are more likely to positively engage with a referral to healthcare professionals with expertise in providing a more tailored approach to health promotion after initial advice and support. Strategizing with parents about accessible environments or opportunities can promote inclusive community opportunities for participation. Providers should be willing to discuss intimate relationships and sex-related issues at appropriate times as they do with youth without disabilities—and refer when unable to meet those needs. Family-centered and coordinated care, commonly found in medical homes, can support healthy behaviors and emergency planning for unforeseen events.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Environmental Health

PART XXXII

Chapter 757

Overview of Environmental Health and Children

Ruth A. Etzel

GLOBAL CLIMATE CHANGE

Pediatricians' primary goal is prevention. One dominant prevention challenge of the 21st century is the climate crisis. The Intergovernmental Panel on Climate Change concluded that the Earth is undergoing adverse global climate change and that anthropogenic (human-made) contributions are significant. These climate changes are creating conditions that have already affected public health, with disproportionate impacts on certain life stages, including children. Children are especially vulnerable to the impacts of climate change because their bodies are growing and developing, they have unique behaviors and interactions with their environment, and they must rely on parents or caregivers to provide for their basic needs. Climate change affects children's health as a result of their exposure to elevated temperatures; more frequent, severe, or longer-lasting extreme weather events; transmission rates of food-borne, waterborne, and vector-borne diseases; increases in air pollution from molds, pollens, and the burning of fossil fuels; and mental health stressors (Fig. 757.1). Natural disasters such as floods and hurricanes, damp housing, and mycotoxin-related illnesses are worsening as temperatures and sea levels rise. The impacts are being felt most among young children and those who are living in poverty. The need to reduce carbon dioxide in the environment has compelled many countries to sign the Paris Agreement. This agreement promises to keep the global temperature rise well below 2°C above preindustrial levels, and to try to limit the temperature increase to 1.5°C. Even though the Paris Agreement began in 2016, its promises have not been kept and the temperature is already 1.2°C higher than in the preindustrial era. Individual actions are another necessary step in carbon dioxide reduction. Parents and caregivers can work to reduce their family's burning of fossil fuels. They also can protect children's health by checking the air quality index and pollen counts and considering a limit to children's outdoor play time if levels are high. Parents can watch for signs of dehydration or overheating in their children and can prevent tick and mosquito bites by using insect repellent and protective clothing. Pediatricians and those who care for children can be highly effective advocates for an urgent governmental response to the climate crisis by speaking out at the community, national, and international level.

LOCALIZED ENVIRONMENTAL HAZARDS

Localized exposures to a wide variety of chemical, biologic, and physical agents can also harm children. Numerous epidemics of disease from chemical, biologic, and physical agents (both natural and human-made) over the past 80 years have documented a variety of adverse outcomes among children (Table 757.1). Some epidemics, such as those caused by the nighttime release of methyl isocyanate from a factory in Bhopal, India, the nuclear meltdown in Chernobyl, and the melamine contamination of infant formula in China, received widespread attention and heightened the awareness of parents and pediatricians about hazards in the environment. For many people, the word *epidemic* conjures up images of hospital isolation wards, poor sanitation, and rapidly spreading infectious diseases. Epidemics of environmental origin often have served to elucidate new hazards for children. Many of the routinely used chemicals understood to be toxic to children were initially identified when a cluster of children was exposed and developed symptoms during a relatively short period of time. Unfortunately, the children served as the "canaries in the coal mine" to indicate that specific chemicals (including thallium, mercury, arsenic, and lead) contained in products for children such as diaper rinses, teething powders, and depilatory agents, posed a threat to their health. The comparison of children to canaries is apt: following underground mine explosions, canaries were used by miners throughout recent history to help detect elevated levels of carbon monoxide gas. Canaries were useful "carbon monoxide detectors" because of their rapid breathing rate and high metabolism, making them more sensitive to the effects of gases, including carbon monoxide. Likewise, young children have a rapid breathing rate and a high metabolic rate and may be more sensitive than adults to chemicals in the environment.

Table 757.1 summarizes major incidents of environmental poisoning that affected children. The characteristics of environmental exposure and the age and developmental stage of the child affect the likelihood of developing health problems. After the release of methyl isocyanate (used in the production of some pesticides) at Bhopal in 1984, an estimated 200,000 children living near the Bhopal chemical plant were affected by the gas release (see Table 757.1). Methyl isocyanate gas is 1.4 times heavier than air; thus higher concentrations of the gas were found near the ground or floor. Because of their short stature, children's breathing zones are closer to the ground or floor than adults' breathing zones; therefore children likely inhaled higher concentrations of the toxic gas. Children exposed to the same levels of methyl isocyanate as adults may have received larger doses because they have relatively greater lung surface area to body weight ratios and higher minute volume to weight ratios. Based on each of the poisoning events listed in Table 757.1, additional precautions were taken to avoid children's unnecessary exposure to the specific product or chemical implicated.

Although major poisonings such as those listed in Table 757.1 have caused substantial morbidity and mortality among children, environmental health hazards may also result in more subtle effects that may not manifest until later in life. In addition to the exposures received during large outbreaks, children receive smaller doses of chemicals on an almost daily basis through the water they drink, the food they eat, and the air they breathe. Because of their unique vulnerability, they may exhibit symptoms from these exposures earlier than do adults.

TOXINS VERSUS TOXICANTS

A toxin is a poisonous substance produced naturally by a living organism (e.g., aflatoxin). A toxicant is a poisonous substance made by humans or introduced into the environment by human activity (e.g., dioxins). Synthetic chemicals are referred to as toxicants.

MYCOTOXINS

Children's exposures to mycotoxins, the toxins produced by certain fungi on grains, nuts, and other crops, will likely increase as the

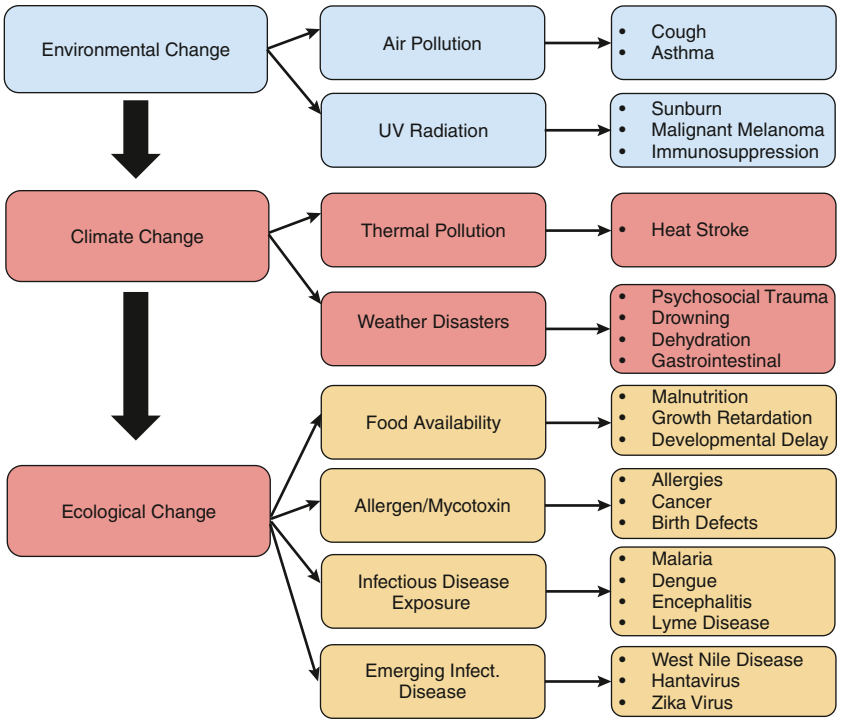

Fig. 757.1 The relationship between environmental change, climate change, ecologic change, and child health. *(Adapted from Bunyavanich S, Landrigan CP, McMichael AJ, et al. The impact of climate change on child health. Ambul Pediatr. 2003;3:44–52. Fig. 2.)*

Table 757.1 Epidemics of Environmental Disease Affecting Children

CONTAMINANT	VEHICLE	DATE	COUNTRY	APPROX. # SICKENED	ILLNESS	APPROX. # WHO DIED
Thallium	Depilatory agents	1930	Grenada	16	Thallotoxicosis	13
Methylmercury	Fish and shellfish	1956	Japan	2,265	Cerebral palsy	1,784
Arsenic	Contaminated milk powder	1955	Japan	11,778	Fever, diarrhea darkened skin, swollen abdomen	113
Hexachlorobenzene	In human milk after pregnant women ate HCB-treated seed grain	1957	Turkey	~200	Pembe yara (pink sore) rash, weakness convulsions	<2 yr ~200
Methyl isocyanate	Leak from chemical plant	1984	India	<15 yr: 200,000	Coughing, eye irritation choking death	All ages 2,500-5,000
Dioxin	Chemical plant explosion	1976	Italy	193 (88%)	Chloracne	0
Radiation	Chernobyl	1986	Ukraine	<18 yr: 4,000	Thyroid cancer	~8
Radiation	Scrapped medical machine stolen from hospital	1987	Goiânia, Brazil	249	Acute radiation syndrome	4 (1 child)
Fungi	Water-damaged homes	1990s	Ohio, US	30	Pulmonary hemorrhage	5
Aflatoxin	Grain	2004	Kenya	317	Aflatoxicosis	125
Melamine	Infant formula	2008	China	290,000	Kidney stones	6
Lead	Small-scale gold mining	2010	Nigeria	>2,000	Seizures, death	200

climate changes because their production is influenced by temperature, humidity, and rainfall. Exposure to mycotoxins results in different health outcomes dependent on the route of exposure. Exposure from eating or drinking may lead to gastrointestinal illness, tremors, and cancer in adulthood; exposure via breathing may result in acute respiratory illness during infancy. There also is emerging evidence linking mycotoxin exposures among children, especially those in developing countries, to stunted growth.

Pediatric Conditions Linked to Mycotoxin Exposures

Exposures to mycotoxins have been linked to at least two conditions that affect children: neural tube defects and acute pulmonary hemorrhage.

Neural Tube Defects

Studies of an epidemic of birth defects in 1990 in south Texas suggested an association between maternal ingestion during pregnancy of high levels of fumonisin, universally present in corn and in corn-based products, and birth defects such as anencephaly and spina bifida. Fumonisins are known to interfere with cellular folate uptake.

Infant Pulmonary Hemorrhage

Several studies of a 1994 epidemic of acute pulmonary hemorrhage in Cleveland, Ohio, documented a novel association between life-threatening pulmonary hemorrhage and the presence of the toxigenic mold *Stachybotrys* in the water-damaged homes in which the infants were living. *Stachybotrys* produces mycotoxins that are lipid soluble and readily absorbed by the airways, as well as a hemolysin and several proteinases that can degrade vascular collagen. In subsequent years, *Stachybotrys* and other toxigenic fungi including *Trichoderma* have been associated with acute pulmonary hemorrhage among infants in other areas of the United States, Canada, and New Zealand. The rapidly growing lungs of infants are especially vulnerable to the effects of the trichothecene mycotoxins produced by *Stachybotrys* and *Trichoderma*.

FOOD-BORNE DISEASES CAUSED BY ENVIRONMENTAL EXPOSURES

Contamination of food with viruses and bacteria is a major cause of childhood food-borne diseases (see Chapter 387), and children are also at risk from a variety of noninfectious food-borne hazards in the environment, which include natural hazards such as mycotoxins and synthetic persistent organic pollutants such as dioxins (see Chapter 759; Table 757.2).

Table 757.2 Food-Borne Illnesses (Noninfectious)

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Antimony	5 min to 8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine; may cause eosinophilia	Gastric lavage BAL (dimercaprol)
Cadmium	5 min to 8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr	**GI:** abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish, grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol; children more vulnerable
	3 hr	**Neurologic:** paresthesias, reversal of hot and cold, pain, weakness				
	2-5 days	**Cardiovascular:** bradycardia, hypotension, increase in T-wave abnormalities				
Copper	5 min to 8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and developing fetuses are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (museinol, muscarine, psilocybin, coprius artemetaris, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction	Self-limited	Wild mushrooms (cooking may not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care

Continued

Table 757.2 Food-Borne Illnesses (Noninfectious)—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Mushroom toxin, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate brown–colored blood	Usually self-limited	Cured meals, any contaminated foods, spinach exposed to excessive nitrification	Analysis of food, blood	Supportive care, methylene blue
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, and meiosis	Usually self-limited	Any contaminated food	Analysis of food, blood	Atropine: 2-PAM (pralidoxime) is used when atropine is not able to control symptoms and is rarely necessary in carbamate poisoning
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min to 3 hr	Flushing, rash, burning sensation of skin, mouth, and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning (DSP)—30 min to 2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning (NSP)—few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning (ASP)—24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				
Shellfish toxins (paralytic shellfish poisoning)	30 min to 3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth, lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support

Table 757.2 Food-Borne Illnesses (Noninfectious)—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with sodium fluoride–containing insecticides and rodenticides	Testing of vomitus or gastric washings, analysis of food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated foods	Urine, hair	Supportive care
Tin	5 min to 8 hr, usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of food	Supportive care
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of food, blood, and feces, saliva, or urine	Supportive care

BAL, Bronchoalveolar lavage; GI, gastrointestinal; IV, intravenous.
Adapted from Centers for Disease Control and Prevention. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. *MMWR.* 2004;53(No. RR-4):1–33.

Aflatoxins

Aflatoxins are poisonous substances that are formed as a result of mold growth on peanuts, corn, figs, oil-seeds, tobacco, and other products. The International Agency for Research on Cancer (IARC) has classified aflatoxin B1 as a group I carcinogen (known to be carcinogenic to humans). Ingestion of elevated levels of aflatoxin also can result in acute aflatoxicosis, characterized by vomiting, abdominal pain, hepatitis, and sometimes death.

Ochratoxin A

The mycotoxin ochratoxin A, produced by many different species of *Aspergillus* molds, is toxic to the kidneys. Ochratoxin A contaminates many foods, including barley, rye, and other cereals, cereal-derived foods, dry fruits, beans, cocoa, coffee, beer, wine, poultry, eggs, pork, and milk. Ochratoxin A is teratogenic, immunotoxic, genotoxic, and mutagenic. The IARC has indicated that ochratoxin is a possible human carcinogen (category 2B).

Fumonisins

Fumonisins are mycotoxins that may contaminate cornmeal and cereals. The fumonisins are known to interfere with sphingolipid metabolism. Consuming foods contaminated with fumonisins during pregnancy has been linked to an increased risk of having a child with a neural tube defect and an increased risk of esophageal cancer in adulthood.

Deoxynivalenol

This mycotoxin, often called *vomitoxin* because its predominant effect is vomiting, can be present in foods made from wheat and corn. Even after the grain is baked or cooked, vomitoxin retains its toxicity. Multiple epidemics of vomiting illness that occurred in China during 1961 to 1985 were associated with ingesting grain contaminated with vomitoxin. In India in 1987, almost 100 people started vomiting after they ate wheat products that contained vomitoxin and other mycotoxins. For infants, the estimated tolerable daily intake is 1.5 µg/kg body weight. A suspected epidemic of vomitoxin-related illness that affected about 1,700 school children in the United States in 1997-98 was linked to burritos that had measurable levels of vomitoxin of 0.3 parts per million (ppm; the advisory level set by the U.S. Food and Drug Administration for adults is 1 ppm).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 758

Biologic Effects of Ionizing Radiation on Children

Samuel L. Brady and Donald P. Frush

DIAGNOSTIC IMAGING, RADIATION THERAPY

Ionizing radiation is produced when energy is absorbed within an atom such that a bound electron is liberated, and the atom becomes ionized. Exposure to ionizing radiation is characterized by three

categories: (1) **absorbed dose**, (2) **equivalent dose**, and (3) **effective dose**. In terms of radiation interaction with humans, absorbed dose is defined as the energy imparted (i.e., absorbed) within a mass of tissue from a radiation source. Absorbed dose is calculated based on the attenuation properties of the irradiated tissue (e.g., attenuation is greater in bony tissue due to its higher electron density and mass than water equivalent, soft tissue organs). The units of absorbed dose, as defined by the International Commission of Radiation Units, are the **Gray** (Gy), the preferred unit, and the older radiation absorbed dose **(rad)**. There are different types of radiation including x-ray, γ-ray, α particles (helium nucleus stripped of all electrons), β particles (unbound electrons), neutrons, and protons. Not all radiation has the same effect on biologic tissue for a given absorbed dose; for example, β particles are quite superficial, protons deposit most of their energy deeper within the body, and α particles and neutrons cause significantly more damage than x-rays or γ-rays. Diagnostic imaging uses x-rays and γ-rays. The therapeutic use of radiation for cancer treatment primarily uses x-rays, β particles, and protons depending on their application and location of disease within the body. **Equivalent dose** is a term used to define the relative effectiveness to cause biologic damage. The International Commission on Radiological Protection (ICRP) gives x-rays, γ-rays, and β particles a relative weighting of 1, protons a weighting of 2, neutrons a weighting of 2.5-20 (neutron weighting factor depends on the energy of the neutron), and α particles a weighting of 20. Thus, for the same level of radiation exposure to an organ, the equivalent dose, i.e., the relative level of biologic damage, would be higher for absorbed doses from protons compared with x-rays. **Effective dose** is a term that represents "the sum of the weighted [applying organ and tissue weighting factors] equivalent doses for the radiosensitive tissues and organs of the body" (National Council on Radiation Protection and Measurements). A list of relative organ and tissue weighting factors defined by the ICRP is provided in Table 758.1. Equivalent dose and effective dose are measured in units of **sievert** (Sv), with levels in diagnostic imaging typically in millisieverts (mSv), and the **rem** (older unit) (Table 758.2). Effective dose is not applied as a metric of dose to an individual but is a population average. Effective dose is not adjusted based on real or potential radiation susceptibilities for tissues for either gender or age.

Nuclear medicine and PET imaging examinations are described by the amount of radioactivity given, commonly injected intravenously. Administered radioactivity is referred to as the administered radiopharmaceutical dose, commonly defined in millicuries (mCi) or megabecquerels (MBq). Radiopharmaceutical dose may be converted to effective dose by applying correction factors provided in ICRP reports 53, 80, 106, and 128.

Table 758.1 Tissue Radiosensitive Weighting Factors; ICRP Report 103

TISSUE	TISSUE WEIGHTING FACTOR (W_T)	$\sum w_T$
Red bone marrow, colon, lung, stomach, breast, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
Total		1.00

*Remainder tissues: Adrenal glands, extrathoracic region, gallbladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix

For the average adult, ionizing radiation exposure occurs from both natural (60%) and medical (40%) sources, and for the average pediatric-age individual, ionizing radiation exposure occurs primarily from natural sources (91%) as compared to medical sources (9%) (National Council on Radiation Protection and Measurements). Radon gas accounts for the majority of natural radiation exposure. For the adult population, the percentage contribution from medical imaging to the total ionizing radiation exposure had been increasing in the late 20th and early 21st century, but is now declining since 2006. As of 2016, for the average adult, CT imaging comprised 63% of the total of ionizing radiation procedures (Fig. 758.1A), but medical imaging accounted for only 42% of the average adult population exposure to ionizing radiation; this has decreased slightly in the past decade due to technologic advances in imaging equipment and how we use the equipment in practice. For the pediatric patient population, CT remains the primary source of medical radiation exposure, accounting for 84% of the total medical exposure (annual per capita exposure) from ionizing radiation (see Fig. 758.1B). Despite efforts to educate the medical community and the public on radiation safety and the guiding principle of keeping radiation dosing "as low as reasonably achievable (ALARA)," understanding of sources, amounts, and potential risks of ionizing radiation can still be limited. Some imaging procedures do not produce ionizing radiation (Table 758.3), and not all ionizing radiation-producing modalities expose a child to the same amount of radiation (Table 758.4). To facilitate choosing the appropriate imaging modality for a patient's clinical indications, American College of Radiology appropriateness criteria have been published (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria) to assist referring physicians in making the most appropriate imaging or treatment decision for a specific clinical condition.

BIOLOGIC EFFECTS OF RADIATION

Biologic effects of radiation are divided into **tissue reactions** (previously known as **deterministic effects**) and **stochastic effects**. Tissue reactions do not occur below a threshold absorbed dose, and severity is directly related to the magnitude once the threshold is exceeded. No evidence of tissue reactions has been demonstrated from radiation dose levels typical of diagnostic imaging examinations (i.e., <100 mGy), but complicated interventional procedures have on rare occasions led to these effects. Typical tissue reactions can present as temporary hair loss (epilation) and skin reddening (erythema), which occur in regions of peak dose of >2 Gy (Table 758.5). Cataracts have been reported to occur with acute exposure of >0.5 Gy.

The second type of biologic effect is the **stochastic effects** that are of concern because they are assumed to potentially occur at any dose; that is, there is no threshold. Stochastic effects are most commonly discussed as cancer risk but also include heritable effects. The probability of a stochastic effect increases with rising level of absorbed dose, but not the severity. Cancer, if radiation induced, is not more severe with higher doses. It is generally accepted by the scientific and medical community that stochastic effects may be caused by any level of radiation striking vulnerable tissue (most importantly DNA, but cytoplasm also may be at risk) and causing irreversible damage. The most widely accepted model representing stochastic effects is the **linear no (dose) threshold (LNT) model**. This model maintains that any level of radiation dose has a potential risk, although this risk is currently uncertain at effective dose levels below 50-100 mSv. Greater than this range, there is a recognized, although very small, statistically significant risk of a stochastic effect. In the LNT model, no level of radiation exposure is assumed to be safe.

Table 758.2 Radiation Measurements

UNITS	RADIOACTIVITY	ABSORBED DOSE	EFFECTIVE DOSE	EXPOSURE
Common units	Curie (Ci)	rad	rem	Roentgen (R)
SI units*	Becquerel (Bq)	Gray (Gy)	Sievert (Sv)	Coulombs/kg

CONVERSION EQUIVALENTS
1 millicurie (mCi) = 37 megabecquerels (MBq)
100 rad = 1 Gy (1 rad = 1 cGy)
100 rem = 1 Sv (1 rem = 10 mSv)
Background radiation dose is approximately 10 μGy/day (1 millirad/day)

*SI units: International System of Units.

Radiation can cause permanent cell injury leading to carcinogenesis, genetic variants, or cell death. The biologic effects of radiation result primarily from damage to DNA. **Direct effect** reactions occur mainly through interactions of high **linear energy transfer (LET)** particles, such as α particles or neutrons, directly with the DNA structure. A similar mechanism also can occur with x-ray or γ-ray photons by directly liberating an electron from atoms (called a recoil electron) near the DNA structure. The kinetic energy of the recoil electron or high LET particles may directly cleave chemical bonds in the DNA structure.

An **indirect effect** is caused by the formation of free radicals. This is the more common mechanism with x-rays and γ-rays used in medical imaging. Approximately 80% of the cell is water, so most of the energy deposited in a cell results in the production of aqueous free radicals. This occurs when the absorbed x-ray or γ-ray photon energy is converted to recoil electrons that create ion radicals (H_2O^+ and H_2O^-). The ion radicals promptly decay (10^{-18} to 10^{-3} seconds) into free radical species (OH^-, H^+, H_3O^+). Approximately two thirds of DNA damage is believed to be caused by this indirect effect through creation of hydroxyl (OH^-) free radicals, which then primarily reacts with DNA by attaching to the hydrogen bound to the deoxyribose carbon resulting in a base release from the DNA structure and strand break of the DNA helix. The biochemical changes that follow either direct or indirect effects take hours or days to manifest, whereas the physiologic changes leading to the likely complex cascade of a variety of factors for cancer induction may take years to decades to manifest.

The results from DNA injury are variable. The cell containing the damaged DNA almost always repairs itself and continues as a viable cell for miotic division. In some instances, the cell might die; one form of cell death is called **apoptosis**, which is a common pathway to eliminate heavily damaged and potentially mutable cells. Damage to a single base pair from radiation exposure is the most prevalent and least significant effect. Ninety percent of single-strand DNA breaks are repaired within an hour by naturally occurring DNA repair processes; therefore they usually have little biologic significance because each strand is repaired with use of the opposite strand as a template. Though less likely, a pathogenic variant can result from single-strand break repair if inaccurate repairs occur; however, large regions of the DNA genome on somatic cells are not active or do not have genes that are expressed. Inaccurate repair in these regions of the genome lead to minimal biologic effect and are sufficient to produce viable cells.

Breakage of both strands of DNA (i.e., double-strand break) is the least common event, but more problematic. The ultimate outcome for cell viability depends on the proximity of the break in each strand. If widely separated (greater than 10 base pairs), which is essentially two remote single-strand breaks, repairs occur rather seamlessly. If the breaks in the two strands are opposite or near each other (separated by less than 10 base pairs), repair is more difficult as there is no reciprocal base pair to serve as a "memory" template. Radiation-induced double-stranded breaks generally lead to cell death or **chromosomal misrepair,** potentially leading to pathogenic gene variants that may result in carcinogenesis.

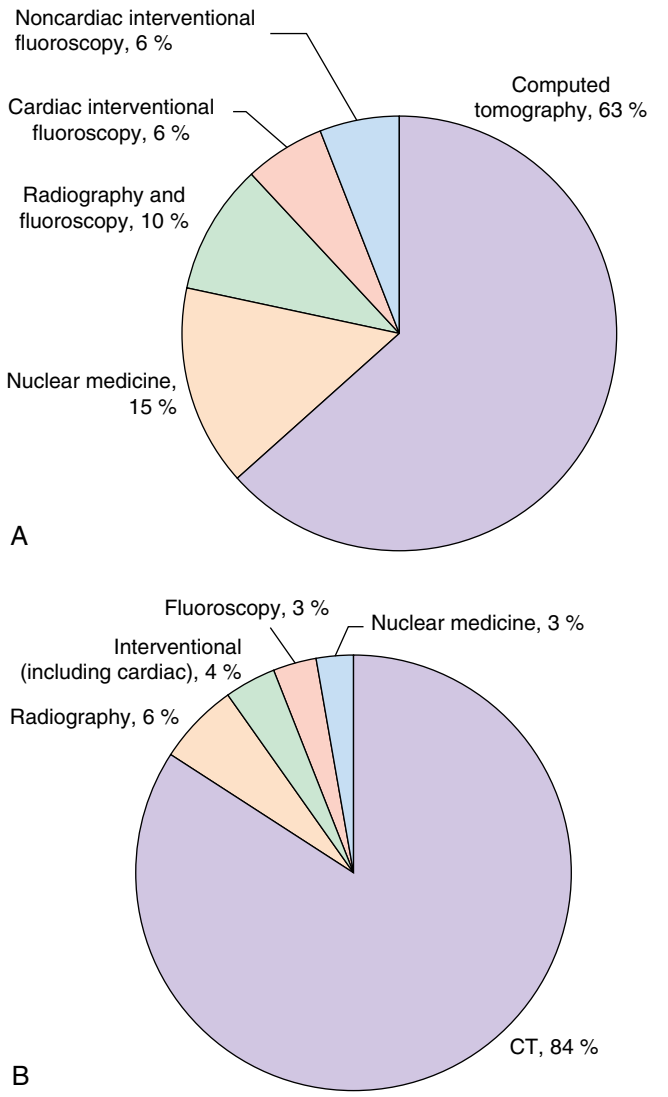

Fig. 758.1 Percentage radiation exposure by diagnostic imaging modality for (A) adult and (B) pediatric populations. *(Adapted with permission of the National Council on Radiation Protection and Measurements, Report 184: Medical Radiation Exposure of Patients in the United States, 2019. Figs. 14.3 and 12.2.)*

When misrepaired DNA damage occurs, aberrations may then be produced in chromosomes, resulting in an *unstable aberration* (usually lethal to dividing cells) or a *stable aberration.* Stable aberrations can result in failure of chromosomes to reunite (leading to deletions) or in abnormal rearrangement of chromosomes, such

as reciprocal translocation or aneuploidy. Although it is logical to think that these abnormalities in chromosomes lead to variants that can activate oncogenes or protooncogenes, or cause variants in tumor-suppressor genes (see Chapter 541), few radiation-induced cancers show specific translocations such as would be associated with activation of specific oncogenes or known tumor-suppressor genes. An exception is the radiation induction of papillary thyroid carcinoma in children, which probably results from activation of the RET oncogene (see Chapter 607).

A longitudinal study of the lifetime risks of excess cancer mortality to irradiation has been evaluated in atomic bomb survivors. More than 120,000 survivors since 1950 have been followed since exposure; additionally, 3,600 in utero survivors and their 77,000 progeny have been followed since 1945. Individual radiation doses were estimated by considering the person's location in relation to distance from the epicenter and individual shielding situations (such as line of sight with respect to buildings and terrain). Radiation types were mixed, and most of the exposure was direct gamma irradiation; neutron exposure was out to approximately 2,000 m. Age at exposure, lifestyle, and other factors were considered in the analytic models when calculating cancer occurrence (Fig. 758.2).

The pediatric population is approximately two to three times more sensitive to radiation-induced carcinogenesis compared with middle-age adults; however, the risk even in this population is indirectly related to age where the neonate is more sensitive than the older child to an identical radiation exposure. Because of the higher risks associated with breast and thyroid cancer, females are also more sensitive than males. It must be understood that cancer rates in this study are mortality figures; the incidence of cancer is approximately twice that of the mortality incidence for all ages. The Centers for Disease Control and Prevention (CDC) reports no scientific evidence demonstrating noncancerous effects (e.g., malformations, growth, intellectual disability, etc.) from in utero exposure <50 mGy, an exposure level that is greater than essentially any single diagnostic examination using ionizing radiation. Additionally, noncancerous effects may only increase slightly with exposure levels between 50 and 500 mGy. In utero radiation exposure is associated with an excess risk of developing (all types) childhood cancer: 1% (<100 mGy), 1–6% (100-500 mGy), and >6% (>500 mGy) as compared to 0.7% naturally. Children are at increased risk of stochastic risks for identical levels of exposure seen in adults because (1) children are growing rapidly, with many

Table 758.3 Imaging Modalities

MODALITY	SOURCE
Radiography (digital plain film x-ray)	Radiation (x-ray)
Fluoroscopy and fluoroscopically guided procedures	Radiation (x-ray)
Ultrasonography	Sound beams
Computed tomography	Radiation (x-ray)
Magnetic resonance imaging	Magnetic field with radiofrequency
Nuclear medicine (including positron emission tomography)	Radiation (administered isotope)

Table 758.4 Average Radiation Dose by Imaging Test for Pediatric Population*

EXAMINATION (0-18 YEARS)	EFFECTIVE DOSE (mSv)
Interventional fluoroscopy: AP and lateral abdomen	0.2-1.1 mSv/min
Interventional fluoroscopy: head	0.02-0.08 mSv/min
Interventional fluoroscopy: cardiac	0.1-1 mSv/min
Digital radiography: 2-view chest	0.04-0.06
Digital radiography: 2-view abdomen	0.1-0.6
Computed tomography: brain	0.8-2
Computed tomography: chest	0.5-4
Computed tomography: abdomen/pelvis†	1-9
Nuclear medicine (^{99m}Tc methylene diphosphonate: bone)	2-5
Positron emission tomography (^{18}F-FDG; whole body)	2-11

*Background radiation reference = 0.01 mSv/day or 3 mSv/yr.
†Radiation dose upper limit includes young adult age population.

Table 758.5 Tissue Reaction Dose Levels

INJURY	APPROXIMATE THRESHOLD
SKIN	
Transient erythema	2 Gy (200 rad)
Dry desquamation	8 Gy (800 rad)
Moist desquamation	15 Gy (1,500 rad)
Temporary epilation	2 Gy (200 rad)
Permanent epilation	7 Gy (700 rad)
EYES	
Cataracts (acute)	2 Gy (200 rad)*

*Has been reported as occurring between 0.5 and 1 Gy.

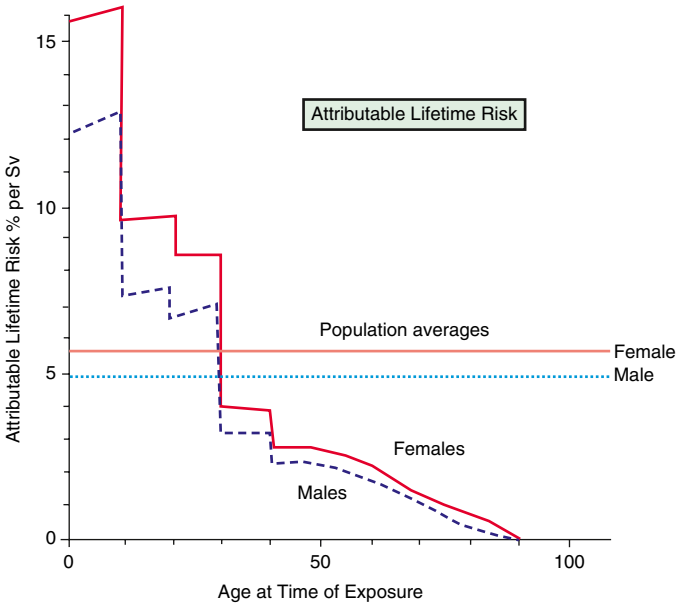

Fig. 758.2 Lifetime risk of excess cancer per sievert (Sv) as a function of age at the time of exposure. Data from the atomic bomb survivors. The average risk across all ages in a population is approximately 5% per Sv, but the risk varies considerably with age: children are much more sensitive than adults. At early ages, girls are more sensitive than boys. *(From Hall EJ. Introduction to session I: Helical CT and cancer risk. Pediatr Radiol. 2002;32:225–227.)*

Table 758.6 Inherited Human Syndromes Associated with Sensitivities to X-Rays

Ataxia-telangiectasia	Fanconi anemia
Basal cell nevoid syndrome	Gardner syndrome
Cockayne syndrome	Nijmegen breakage syndrome
Down syndrome	Usher syndrome

Modified from Davis JT, Frush DP. Biologic effects of diagnostic radiation on children. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: p. 5; and Hall EJ. *Radiobiology for the Radiologist*, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2006: p. 41.

cells undergoing mitotic activity dependent on undamaged DNA and chromosomes, and (2) radiation-induced tumors (except leukemia) take a relatively long time to develop and children have a longer lifetime. Policies relating to the use of therapeutic abortion have been established by the ICRP and American College of Obstetricians and Gynecologists, which state that fetal doses <100 mGy should not be considered a reason for terminating pregnancy, and that every woman should be counseled that exposure from a single diagnostic procedure does not result in tissue effects to the fetus.

Most childhood tumors occur sporadically, but 10–15% of cases have a strong familial association. Familial tumors have specific chromosomal deletions in common. In some of these tumors (e.g., retinoblastoma), the two-hit hypothesis is apparent (see Chapter 541). Individuals with certain congenital diseases are at higher risk for the development of tumors after irradiation. Table 758.6 lists diseases that are associated with sensitivity to radiation.

RADIATION EXPOSURE IN DIAGNOSTIC IMAGING OF CHILDREN

Imaging modalities utilizing ionizing radiation for diagnostic purposes (e.g., CT, nuclear medicine, PET, radiography, and fluoroscopy or fluoroscopically guided procedures) are commonly utilized; however, increased awareness of the long-term risk for cancer induction and mortality has led to declining pediatric CT use over the past decade. The European EPI-CT study found a significant dose-response relationship between CT-related radiation exposure and brain cancer as well as hematologic malignancies in a large international study cohort, supporting the concept that stochastic effects are a dose-dependent probability, with the probability of an effect increasing with radiation dose. Therefore it is important that we use the lowest dose necessary to get sufficient diagnostic images. Various federal agencies, healthcare accrediting bodies, and national professional organizations support this goal and provide recommendations or requirements for all imaging examinations to have some retrievable radiation dose estimate, and for institutions and clinics that provide ionizing radiation imaging services to track and review patient examination dose levels annually, comparing these dose levels with expected dose ranges and external benchmarks.

Dose reporting and aggregating software provides the ability to collect and analyze individual examination doses and gives healthcare providers a powerful tool to correct outlier examinations (i.e., over exposures), over utilization, and address other systemic errors present in imaging clinics (such as radiation dose creep with time).

DECREASING UNNECESSARY DIAGNOSTIC RADIATION IN CHILDREN WHILE STILL OBTAINING DIAGNOSTIC IMAGES

Ultimately, the lowest radiation dose examination is the imaging examination performed without ionizing radiation. For an increasing number of indications, utilization of nonionizing radiation modalities such as ultrasound or MRI may be the first consideration for diagnosis. Selecting the correct examination is the responsibility of the requesting healthcare provider and may involve consultation with the radiologist, preferably with pediatric expertise. Clinical decision support algorithms are also available to assist with examination appropriateness (e.g., American College of Radiology's Appropriateness Criteria). The risk of using ionizing radiation for imaging should be weighed against other risks during imaging. CT (depending on the indication and region examined) may detect as many abnormalities as MRI, but CT involves ionizing radiation. However, sedation is often required to successfully obtain MRI imaging in young children; in these cases, consideration of the relative risks of cognitive impairment from moderate sedation and anesthetic versus potential radiation risks use should come into play.

Reducing Radiation from the CT Examination

The most common source of medical radiation for all ages is CT. CT offers the ability to acquire high-quality volumetric imaging datasets in seconds. For many years, adult parameters for CT settings were used for children, which led to dosages for children much higher than the dosage for adults. This occurs because lower energy x-rays that would have been absorbed in the near field in an adult pass into the entire child, with relatively greater organ irradiation for the same exposure. When comparing dosages given to newborns and adults during CT scanning of the head, with the same parameters in both groups, the dosage given to newborns can be four times that of the dosage given to adults; with abdominal imaging, the dosage is increased by 60%. It is the role of the radiologist and technologist, with the help of a medical physicist, to develop and monitor protocols that tailor the examination to the individual indication and for the variabilities in sizes found in the pediatric population.

Modern CT scanners have many tools to help administer the appropriate amount of radiation dose to a pediatric patient and acquire the necessary diagnostic image quality from the imaging examination. Radiologists should work in conjunction with medical physicists and vendor supplied application specialists to tailor specific examination protocols to the pediatric patient population by establishing appropriate scan parameters such as the kilovoltage (kV). Scan range should be limited to only the necessary area for diagnosis (e.g., a chest only scan should begin at the lung apices and extend to no more than a little below the lowest lung base). Multiphasic scanning should be only obtained when justified; for example, in pediatric abdominopelvic CT multiple phases should be necessary in no more than approximately 5% of examinations.

Technologic advances for modern CT scanners are using reconstruction algorithms, such as statistical iterative reconstruction (IR), model-based IR, and deep learning reconstruction (DLR), as well as photon counting technology. These algorithms have been shown to allow the reduction of radiation dose for IR algorithms by 15-30% and DLR algorithms by 44-83% in some patient populations while maintaining equivalent diagnostic confidence to the pre-dose reduced image datasets. Other practical steps to reduce pediatric population radiation dose include replacing older CT scanners with technologically advanced scanners; monitoring institution dose values, which can be compared with available benchmarks, such as **diagnostic reference levels (DRLs)**; and performing only examinations that are justified. Advances in technology and attention to proper performance of examinations have contributed to overall reductions in pediatric patient population doses by >50% during the past two decades.

RADIATION THERAPY: ACUTE AND LATE EFFECTS

Radiation therapy uses high doses to kill malignant cells. The sensitivity of normal cells is quite close to that of malignant cells, and to achieve significant cure rates, radiation oncologists must accept a given percentage of serious complications (5–10%). Radiation causes tissue loss plus injury to the underlying vasculature. The vascular change may be progressive, leading to arteriocapillary fibrosis and irreparable injury, in turn leading to further tissue loss.

The acute effects of therapy (occurring less than 3 months after therapy begins) are usually related to the area of the body being irradiated (except fatigue, which can begin during this time period). These acute effects include radiation-induced pneumonitis, dermatitis, mucositis and esophagitis, cerebral edema, and swelling of the organ irradiated. There may be changes in bowel movement patterns. Of these, one of the most severe acute reactions is pneumonitis. It can manifest within

Table 758.7 Late Effects of Radiation Therapy in Children Treated for Cancer

SYSTEM	LATE EFFECT	DOSE (GY)
Musculoskeletal	Muscular hypoplasia	>20
	Scoliosis, kyphosis, lordosis	>20
	Osteocartilaginous exostosis/ osteochondroma	>12
Neuroendocrine (cranial or cranial spinal)	Impaired growth hormone	>15
	Adrenocorticotropic hormone deficiency	>30
	Thyrotropin-releasing deficiency	>40
	Precocious puberty (females mostly)	>18
	Gonadotropin deficiency	>30
Gonad failure	Ovarian failure	>10
	Testicular failure	>3
Central nervous system dysfunction	Structured changes	>18
	Cognitive changes/Processing speed	Variable
Other	Pulmonary fibrosis	>15
	Nephropathy	>20
	Liver disease	>30 (>60% liver volume)
	Cerebral arteriopathy	>50
	Eye impairment (cataracts, legally blind, double vision, dry eyes)	>5
	Hearing loss	>30
	Dental abnormalities	>20
	Cardiac impairment	>30

24 hours of irradiation when there is an exudation of proteinaceous material into the alveoli and interalveolar edema. Most often, however, radiation pneumonitis begins 2-6 months after the beginning of radiation with a clinical presentation of fever, cough, congestion, and pruritic pain. The late effects of therapy (beginning more than 3 months after therapy) are numerous (Table 758.7). The most common are abnormalities of musculoskeletal development, endocrine/reproductive function, pulmonary function, neurocognition, hearing loss, cardiac function, eye impairment, and dental abnormalities.

As of 2020, there are more than 500,000 childhood cancer survivors in the United States. The risk of developing a second cancer among cancer survivors is over fivefold higher than the general population. Second cancers account for 2.3% of all cancers in children; this reflects an overall standard incidence rate (SIR) of 5.5%. Primary malignancies with the highest cumulative incidence of a second neoplasm in the order of frequency are retinoblastoma (10.4%), CNS cancers (7.4%), cancers of bone (7.2%), soft tissue sarcomas (6.5%), hepatic cancer (5.9%), and neuroblastoma (5.9%) [data from the U.S. Surveillance, Epidemiology, and End Results program (SEER)]. Table 758.8 relates second cancers to primary cancer and latency period. Almost 70% of the second neoplasms are in the field of the original irradiation. Radiation therapy increases the risk of second cancers in a dose-dependent manner for nongenetic neoplasms.

The exact complications depend on the location of the treatment field. In children, because of the location of many childhood tumors, the normal brain is commonly in the treatment field. Standard irradiation of the brain in children results in cortical atrophy in more than half of patients who receive 20-60 Gy; 26% are left with white matter changes (leukoencephalopathy) and 8% with calcifications. The younger the child is at the time of irradiation, the greater the atrophy. Some patients also demonstrate mineralizing microangiopathy. Radiation-induced changes of the brain are potentiated by methotrexate administered before, during, or after radiation therapy.

Cerebral necrosis is a serious complication of radiation-induced vascular disease. It is usually diagnosed 1-5 years after irradiation but can occur up to a decade later. Brain necrosis may manifest as headache, increased intracranial pressure, seizures, sensory deficits, and psychotic changes.

Spinal cord irradiation may result in **radiation myelitis,** which may be either transient or permanent. Acute transient myelitis often appears 2-4 months after irradiation. Patients with myelitis usually present with **Lhermitte sign,** a sensation of little electrical shocks radiating down the spine into the arms and legs, occurring with neck flexion or other movements that stretch the spinal cord. Reversal of transient myelopathy usually occurs between 8 and 40 weeks and does not necessarily progress to delayed necrosis.

Delayed myelopathy occurs after a mean latent period of 20 months but can occur earlier if the total dose or the dose per fraction is high. It usually manifests as discontinuous deterioration and is irreversible. In the cervical and thoracic regions, sensory dissociation develops, followed by spastic and then flaccid paresis. In the lumbar cord, flaccid paresis is dominant. The mortality for high thoracic and cervical lesions reaches 70% with death commonly being due to pneumonia and urinary tract infections.

CNS irradiation may affect growth by compromising function of the pituitary-hypothalamic axis and leading to diminishing growth hormone production and release. Non–growth hormone tropins may also be affected by CNS irradiation, leading to gonadotropin deficiency or precocious puberty. Central hypothyroidism can also develop. CNS irradiation also compromises bone mineral deposition both locally (in the radiation field) and systemically.

Irradiation has other effects specific to children. Scoliosis and hypoplasia of bones may occur if fractionated treatment schemes exceed 4,000 rad. Fractionated doses higher than 25 Gy can result in slipped capital femoral epiphyses. An increase in the incidence of benign osteochondromas has been reported after childhood irradiation. Chest wall irradiation in females (besides causing breast cancer) may impair breast development and/or cause fibrosis and atrophy of breast tissue.

WHOLE BODY IRRADIATION

Uncontrolled Large- or Small-Scale Exposure to Radiation

Large-scale exposure to radiation can occur in an event of nuclear accidents, war, or terrorist attacks (Fig. 758.3). Radiation as well as explosive and thermal injury need to be considered.

Clinical Manifestations

A large single exposure of penetrating radiation can result in **acute radiation syndrome** (Table 758.9). The signs and symptoms of this syndrome result from damage to major organ systems that have different levels of radiation sensitivity, modulated by the rate at which the radiation exposure occurred. Delivery of 1 Gy in 1 minute would be symptomatic, but delivery of 1 cGy/day for 100 days would not be symptomatic.

The **hematopoietic syndrome** results from acute whole body doses >0.7-10 Gy; where healthy patients will almost always recover from doses <2 Gy. The dose that kills 50% of a population in 60 days is approximately 3.5-4.5 Gy, where effective blood transfusions and antibiotics may extend the dose range to 5-8 Gy. Doses >8 Gy almost always lead to hematopoietic-induced death. Symptoms of exposure consist of a *prodromal phase* during which the patient will experience nausea/vomiting, diarrhea, and fatigue within the first 12 hours, with symptoms usually lasting up to 48 hours. A *latent period* of 2-3 weeks, during which patients may feel quite well, follows. Although patients are asymptomatic, bone marrow impairment has occurred. The most obvious laboratory finding is lymphocyte depression (Table 758.10). Maximal bone marrow depression occurs approximately 30 days after exposure, when hemorrhage and infection can be major problems. If the bone marrow was not completely eradicated, a *recovery phase* then ensues. This radiation effect is similar to what occurs when whole body irradiation (given as 12 Gy in two treatments) is used

Table 758.8 Second Cancers and Their Relationship with Primary Cancers

SECOND CANCERS	PRIMARY CANCERS	LATENCY (MEDIAN IN YEARS)	RISK FACTORS
Brain tumors	ALL; brain tumors; HD	9-10	Radiation; younger age
Myelodysplastic syndromes/ acute myelogenous leukemia	ALL; HD; bone tumors	3-5	Topoisomerase II inhibitors; alkylating agents
Breast cancer	HD; bone tumors; soft tissue sarcomas; ALL; brain tumors; Wilms tumors; NHL	15-20	Radiation; female gender
Thyroid cancer	ALL: HD; neuroblastoma; soft tissue sarcomas; bone tumors; NHL	13-15	Radiation; younger age; female gender
Bone tumors	Retinoblastoma (heritable); other bone tumors; Ewing sarcoma; soft tissue sarcomas; ALL	9-10	Radiation; alkylating agents; removal of the spleen
Soft tissue sarcomas	Retinoblastoma (heritable); soft tissue sarcomas; HD; Wilms tumors; bone tumors; ALL	10-11	Radiation; younger age; anthracyclines

ALL, Acute lymphocytic leukemia; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma.
From Bhatia S, Sklar S. Second cancers in survivors of childhood cancer. *Nat Rev Cancer.* 2002;2:124–132.

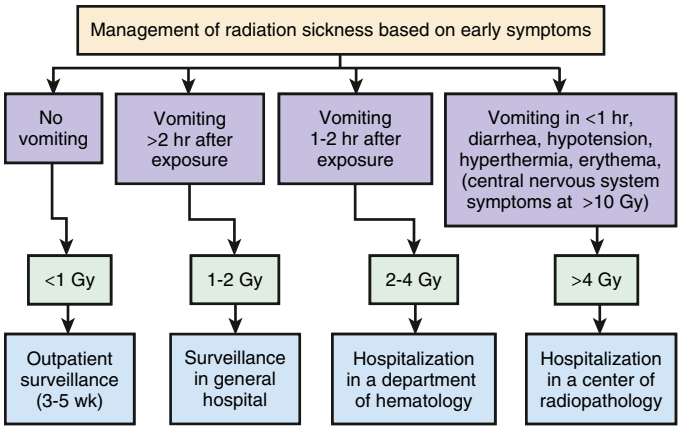

Fig. 758.3 Management algorithm for radiation sickness at different levels of medical care, depending on the appearance of early symptoms and the estimated radiation dose to the whole body. *(From Turai I, Veress K, Günalp B, et al. Medical response to radiation incidents and radionuclear threats. BMJ. 2004;328:568–572.)*

to obliterate the bone marrow in children with leukemia before bone marrow transplantation.

The **gastrointestinal (GI) syndrome** occurs from acute whole body doses >6-10 Gy. Prompt onset of nausea, vomiting, and diarrhea follows. There is a latent period of approximately 1 week if intense medical treatment is administered. Following the latent period, recurrence of GI symptoms, sepsis, and electrolyte imbalance occurs, which results in death at about 2 weeks postexposure from GI tract and bone marrow destruction.

At dose levels exceeding 20-50 Gy, the **cardiovascular/CNS syndrome** predominates. Nausea, vomiting, prostration, hypotension, ataxia, and convulsions are almost immediate. The latent period occurs between 4 and 6 hours postexposure followed by severe manifestation of the initial illness stage leading to eventual coma and death within 2-3 days.

Treatment

For the hematopoietic and GI syndromes, treatment is supportive involving transfusions and Neupogen (filgrastim), Neulasta (pegfilgrastim) and other hematopoietic growth factors, fluids, and, if infected antibiotics and antiviral agents. Stem cell (bone marrow) transplantation may be needed in severe cases.

Localized Irradiation

Clinical Manifestations

Because localized exposure involves a small amount of tissue, systemic manifestations may be less severe, and patients may survive even if locally absorbed doses are very high. The hand is the most common site for accidental localized irradiation injuries, usually as a result of picking up or playing with lost radiation sources. The second most common accidental site is the thigh and buttocks, predominantly from placing unsuspected highly radioactive sources in the pockets.

Table 758.11 lists the skin changes that occur after a single acute, localized irradiation. As opposed to other forms of thermal burns, signs of irradiation appear a period of days *after* the exposure. Vascular insufficiency may appear months to years later and cause ulcerations or necrosis in formerly healed areas. The penetrability of the radiation is an important factor in the outcome of local radiation injury. Beta particles from heavy radiation fallout can cause superficial skin burns because they have low penetrability.

Some tissues that may receive localized radiation exposure are relatively radiosensitive. **Cataract formation** (see Chapter 668) may occur with single γ-ray exposures in the range of <1 Gy. Such cataracts usually take from 2 months to several years to develop. **Oligospermia** may take up to 2 months to develop. Transient infertility in men may result from doses as low as 0.15 Gy, and permanent sterility may occur in males at dose levels between 3 and 6 Gy.

Treatment

Skin therapy is directed at prevention of infections. Treatment of localized injuries usually involves class II to III topical steroids and plastic surgery and grafting, if the radiation exposure was not deeply penetrating (see Chapter 89). The nature of the surgery depends on the dose at various depths in tissue and the location of the lesion. The full expression of radiation injury often is not apparent for 1-2 years due to slow arteriolar narrowing that can cause delayed necrosis. After relatively penetrating radiation, amputation may be necessary because of obliterative changes in small vessels.

INTERNAL CONTAMINATION

Epidemiology

Accidents involving internal contamination are rare and are usually the result of misadministration in hospital settings or voluntary ingestion of unsuspected contaminated radioactive materials. Other possible causes of internal contamination of children include ingestion of breast milk from mothers who have had diagnostic nuclear medicine scans and radiation exposure when a parent or sibling receives a therapeutic dose of iodine-131.

Table 758.9 Acute Radiation Syndrome

SYNDROME	DOSE*	PRODROMAL STAGE	LATENT STAGE	MANIFEST ILLNESS STAGE	RECOVERY
Hematopoietic (bone marrow)	>0.7 Gy (>70 rads) *(mild symptoms may occur as low as 0.3 Gy or 30 rads)*	• Symptoms are anorexia, nausea and vomiting • Onset occurs 1 hr to 2 days after exposure • Stage lasts for minutes to days	• Stem cells in bone marrow are dying, although patient may appear and feel well • Stage lasts 1-6 wk	• Symptoms are anorexia, fever, and malaise • Drop in all blood cell counts occurs for several weeks • Primary cause of death is infection and hemorrhage • Survival decreases with increasing dose • Most deaths occur within a few months after exposure	• In most cases, bone marrow cells will begin to repopulate the marrow • There should be full recovery for a large percentage of individuals from a few weeks up to 2 yr after exposure • Death may occur in some individuals at 1.2 Gy (120 rads) • The $LD_{50}/60$† is about 2.5-5 Gy (250-500 rads)
Gastrointestinal (GI)	>10 Gy (>1,000 rads) *(some symptoms may occur as low as 6 Gy or 600 rads)*	• Symptoms are anorexia, severe nausea, vomiting, cramps, and diarrhea • Onset occurs within a few hours after exposure • Stage lasts about 2 days	• Stem cells in bone marrow and cells lining GI tract are dying, although patient may appear and feel well • Stage lasts <1 wk	• Symptoms are malaise, anorexia, severe diarrhea, fever, dehydration, and electrolyte imbalance • Death is due to infection, dehydration, and electrolyte imbalance • Death occurs within 2 wk of exposure	• The LD_{100}‡ is about 10 Gy (1,000 rads)
Cardiovascular (CV)/ central nervous system (CNS)	>50 Gy (5,000 rads) *(some symptoms may occur as low as 20 Gy or 2,000 rads)*	• Symptoms are extreme nervousness and confusion; severe nausea, vomiting, and watery diarrhea; loss of consciousness; and burning sensations of the skin • Onset occurs within minutes of exposure • Stage lasts for minutes to hours	• Patient may return to partial functionality • Stage may last for hours but often is less	• Symptoms are return of watery diarrhea, convulsions, and coma • Onset occurs 5-6 hr after exposure • Death occurs within 3 days of exposure	• No recovery is expected

*The absorbed doses quoted here are "gamma equivalent" values. Neutrons or protons generally produce the same effects as γ-, β-, or x-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.
†The $LD_{50}/60$ is the dose necessary to kill 50% of the exposed population in 60 days.
‡The LD_{100} is the dose necessary to kill 100% of the exposed population.
From Centers for Disease Control and Prevention. Acute radiation syndrome: a fact sheet for clinicians. Table 1. https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm.

Table 758.10 Expected Outcome Based on Absolute Lymphocyte Count After Acute Penetrating Whole Body Irradiation

MINIMAL LYMPHOCYTE COUNT WITHIN FIRST 48 HR AFTER EXPOSURE	PROGNOSIS
1,000-3,000 (normal range)	No significant injury
1,000-1,500	Significant but probably nonlethal injury, good prognosis
500-1,000	Severe injury, fair prognosis
100-500	Very severe injury, poor prognosis
<100	Lethal without compatible bone marrow donor

Clinical Manifestations

The hazards from internal contamination depend on the nature of both the radionuclide (particularly in terms of its solubility in water, half-life, biologic half-life, and radioactive emission) and the chemical compound.

Treatment

The most effective treatment requires knowledge of both the radionuclide and the chemical form. Treatment must be instituted quickly to be effective (Table 758.12). **Removal treatment** involves cleaning a contaminated wound and performing gastric lavage or administration of cathartics in the case of ingestion. Administration of alginate-containing antacids (e.g., Gaviscon) also usually helps in removal by decreasing absorption in the GI tract. An example of **blocking therapy** is the administration of potassium iodine or other stable iodine-containing compounds to patients with known internal contamination with radioactive iodine. The stable iodine effectively blocks the thyroid, although its effectiveness decreases rapidly as time elapses after the contamination. The recommended dose of potassium iodine is 16 mg

for neonates (up to 1 month of age); 32 mg for children ages 1 month to 3 years; 65 mg for children ages 3-18 years (if less than 70 kg), and 130 mg for adults and adolescents >70 kg. Each dose protects for only 1 day. **Dilution therapy** is used in cases of tritium (radioactive hydrogen as water) contamination. Forcing fluids promotes excretion. Cases of internal contamination with transuranic elements (americium and plutonium) may require **chelation therapy** with calcium diethylenetriamine pentaacetate.

Prussian blue is a drug approved by the FDA for patients with internal contamination with cesium or thallium. It can speed fecal elimination of radioactive cesium from the body. It acts by intercepting the cesium coming into the gut from the bile. Prussian blue prevents

Table 758.11 Skin Changes After a Single, Acute, Localized Radiation Exposure

APPROXIMATE THRESHOLD (GY)	CHANGE
2-4	Primary erythema within hours of exposure (appears more quickly after larger doses)
3	Second phase erythema (develops during the manifestation phase of local radiation injury); appears 14-21 days after exposure
3	Temporary epilation (14-18 days after exposure)
7	Definitive epilation (25-30 days after exposure)
10	Dry desquamation (20-28 days after exposure)
15	Moist desquamation, possible ulceration (15-25 days after exposure)
25	Desquamation with blistering, ulceration, and necrosis (>21 days after exposure)

Data from the International Atomic Energy Agency. *Safety Reports Series, No. 101: Medical management of radiation injuries*, 2020. https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1891_web.pdf

Table 758.12 Decontamination of Common Elements in Industrial and Medical Accidents

ELEMENT	EMISSIONS	CRITICAL ORGAN	EFFECTIVE $T_{1/2}$*	DECONTAMINATION
Cesium-137	Beta, gamma	Total body	70 days	Prussian blue (Radiogardase) 3 g po 3 times/day (adults and adolescents); 1 g po 3 times/day (2-12 yr old); consider lavage and purgatives
Cobalt-60	Beta, gamma	Total body	10 days	Lavage, purgatives, penicillamine
Iodine-125, iodine-131	Beta, gamma	Thyroid	Iodine-125, 42 days; iodine-131, 8 days	Potassium iodide: 0-1 mo, 16 mg/day >1 mo to 3 yr, 32 mg/day >3 mo to 3 yr, 32 mg/day >3 to 12 yr and <70 kg, 65 mg/day adults or ≥70 kg, 130 mg/day; consider lavage
Iridium-192	Beta, gamma	Lung	74 days	Lavage for large quantities
Technetium-99 m	Gamma	Total body	5 hours	Potassium perchlorate to reduce thyroid dose
Tritium-3	Beta	Total body	12 days	Forced fluids
Uranium-235, uranium-238	Alpha	Kidney,† bone, liver, lung	Can be permanent if in bone	Bicarbonate to alkalinize the urine

*Effective $t_{1/2}$ combines radioactive and chemical properties and rates of elimination without decontamination efforts.
†The kidney is most vulnerable to large amounts of uranium because of the chemical properties of this heavy metal. Uranium can ultimately be deposited in bone.
po, Per os; *qd*, once per day.
Data from U.S. Food and Drug Administration. Prussian blue, Radiogardase, package insert. Available at: http://www.fda.gov/cder/drug/infopage/prussian_blue/default.htm; U.S. Food and Drug Administration. Guidance: Potassium iodide as a thyroid blocking agent in radiation emergencies. Available at: http://www.fda.gov/cder/guidance/4825fnl.htm; *Management of Persons Accidentally Contaminated with Radionuclides*. NCRP Report No. 65. Bethesda, MD: National Council on Radiation Protection and Measurements; 1980; and Jarrett D, ed. *Medical Management of Radiation Casualties: Handbook*. 2nd ed. AFRRI Special Publication 03-1. Bethesda, MD: Armed Forces Radiobiology Research Institute; 2003. Available at: http://www.afrri.usuhs.mil.
From Linder JA, Linder LS: Radiation accident—dispersed exposure. In Ciottone GR (ed). *Ciottone's Disaster Medicine*, 2nd ed. Philadelphia: Elsevier, 2016. Table 108-1.

Table 758.13 Nuclear Regulatory Commission Guidelines on Breastfeeding During the Period During a Nuclear Medicine Examination

RADIOPHARMACEUTICAL	BREASTFEEDING CESSATION
^{11}C, ^{13}N, ^{15}O, ^{82}Rb	None
^{18}F-labeled	12 hr
^{68}Ga-labeled	12 hr
^{99m}Tc-labeled	24 hr
^{123}-I Sodium iodide	7 days
^{111}In-leukocytes	7 days
^{99m}-Tc labeled	No interruption*
^{201}Tl chloride	14 days
^{67}Ga and ^{89}Zr	28 days
^{177}Lu, diagnostic	35 days
^{131}I-NaI	Stop breastfeeding
^{177}Lu, therapeutic	Stop breastfeeding
^{223}Ra and all alpha emitters	Stop breastfeeding

*The guideline for ^{99m}Tc compounds is a 24-hr interruption for >1110 MBq administered, 12 hr for 444-1110 MBq, and no interruption for <444 MBq administered. The normally administered activity is below activities that require any interruption.

From Dilsizian V, Metter D, Palestro C, Zanaonico P. The Advisory Committee on Medical Uses of Isotomes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, 2018, p. 12. https://www.nrc.gov/docs/ML1803/ML18033B034.pdf

cesium from being absorbed again from the gut. Prussian blue can be given days after ingestion, unlike potassium iodine, which must be given initially in the first 12-24 hours after exposure.

In the case of breastfeeding after a nuclear medicine procedure, two primary concerns are considered: (1) the internal dose to the infant passed through the excreted milk and (2) the dose from the radiopharmaceutical absorption in the female breast that exposes the infant to external γ-rays while undergoing decay. Most imaging radiopharmaceuticals are below the activity calculated to expose the infant to a dose of 1 mSv via either internal or external mode of exposure. Table 758.13 provides a comprehensive list of radiopharmaceuticals and the recommended period for breastfeeding cessation by the U.S. Nuclear Regulatory Commission. In the case of delaying breastfeeding, pumped milk may be stored for the times indicated in Table 758.13, after which they will be safe to feed the infant.

EXTERNAL CONTAMINATION

The presence of external radioactive contamination on a patient's skin is not an immediate medical emergency. Management involves removing and controlling the spread of radioactive materials. If a patient has suspected surface contamination and no physical injuries, decontamination can be performed relatively easily. If substantial physical trauma or other life-threatening injuries are combined with external contamination, surface decontamination should proceed only after the patient has been stabilized physiologically. In many accident situations, essential medical care may be delayed inappropriately by hospital emergency staff because of fear of radiation or spread of contamination in the hospital. After a radiation accident, triaging of patients is critical and is based on exposure and symptoms (see Fig. 758.3).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 759

Chemical Pollutants

Joel A. Forman and Lauren M. Zajac

More than 85,000 new synthetic chemicals have been developed in the past 75 years. These chemicals are used in millions of products, ranging from food packaging to clothing, building materials, motor fuels, cleaning products, cosmetics, medical products, toys, and baby bottles.

Synthetic chemicals are widely disseminated in the environment. The Toxic Release Inventory of the U.S. Environmental Protection Agency (EPA) reports that in 2021, of 29.3 billion pounds of production-related chemical waste managed, nearly 3.3 billion pounds (11%) were discharged into air, water, and land in the United States. These chemicals are detected today in even the most remote corners of the planet, such as the polar icecaps and in the ocean depths.

All people are at daily risk of exposure to synthetic chemicals, and children are especially likely to be exposed to the nearly 3,000 chemicals that are produced in amounts of 1 million pounds or more per year, designated by the EPA as high-production-volume chemicals. Biomonitoring data on blood and urine levels of more than 400 high-production-volume chemicals are obtained annually by the Centers for Disease Control and Prevention in a sample of the U.S. population through the National Health and Nutrition Examination Survey (NHANES). These data document that most Americans, including children, are routinely exposed to scores of synthetic chemicals; exposure often falls disproportionately on poor children and children of color. Examples are wide ranging and include lead, air pollutants, endocrine disrupting chemicals like phthalates, and many others.

Toxic chemicals are exported in ever-increasing quantities to the world's poorer countries as these countries undergo industrial development. Environmental safeguards in those countries are typically not as stringent as in high-income countries, and the potential for serious exposure is therefore high. Examples of tragedies that have resulted from the movement of toxic chemicals to low- and middle-income countries include the Bhopal disaster in India, in which hundreds were killed and thousands injured by methylisocyanate gas released by an explosion in a pesticide production facility, and the ongoing export each year of more than 2 million tons of newly produced asbestos to the world's poorest countries, where this asbestos is responsible for nearly 200,000 deaths annually from asbestosis, lung cancer, and malignant mesothelioma.

SYNTHETIC CHEMICALS AND HUMAN HEALTH

A recurrent pattern is that chemicals are brought to market with great enthusiasm, presumed harmless, and undergo little or no premarket safety testing. Then years or decades later, after they had come into wide use, the chemicals were found to be harmful to children's health.

Often the first cases of disease caused by these chemicals are clinically severe, but as time passes, evidence of widespread subclinical toxicity comes to light.

Classic historical examples of epidemics caused by inadequately tested toxic chemicals include the following:

- *Tetraethyl lead:* This was added to gasoline in the United States from the early 1920s until 1980. It was responsible for widespread lead poisoning, initially evident as an epidemic of acute toxicity manifesting as encephalopathy, seizures, and even death, but later demonstrated to have caused subclinical neurotoxicity and reduction in IQ across two generations of U.S. children (see Chapter 761).
- *Dichlorodiphenyltrichloroethane (DDT):* This pesticide very nearly led to extinction of the osprey and the American bald eagle and more recently has been linked to increased risk for breast cancer among women exposed decades ago in utero.

- *Polychlorinated biphenyls (PCBs)*: These are highly persistent pollutants banned from production in the United States in 1977, which continue today to contaminate major lakes and rivers and have been found also to be responsible for loss of IQ and disruption of behavior in children.
- *Chlorofluorocarbons:* These destroy the ozone.

Other examples of synthetic chemicals that came into wide use with little assessment of their safety and are now recognized as causing harm to children's health include the following:

- *Phthalates:* These chemicals are added to plastics, cosmetics, medical equipment like intravenous tubing, and common household products that are now linked to increased risk for reproductive abnormalities in male infants and heightened risk of behavioral abnormalities such as attention-deficit/hyperactivity disorder (see Chapter 50).
- *Polybrominated diphenyl ethers:* These are used as flame retardants in carpets, furniture, and electronic equipment and are now linked to persistent loss of intelligence and disruption of behavior in children.
- *Bisphenol A:* A plastics chemical linked to neurodevelopmental disorders.

These chemicals are all produced in volumes of millions of tons per year, are widely disseminated in the environment, and are detectable in the bodies of nearly all Americans. Only decades after their introduction are these chemicals' risks to children beginning to be recognized.

CHILDREN'S UNIQUE SUSCEPTIBILITY TO SYNTHETIC CHEMICALS

The health effects of synthetic chemicals are especially serious when exposure occurs during windows of vulnerability in early life such as during pregnancy, infancy, and early childhood. Children are highly vulnerable to chemical pollutants for several reasons:

1. Children have proportionally greater exposure to environmental pollutants than adults. Because they drink more water, eat more food, and breathe more air per kilogram of body weight, children are more heavily exposed to pollutants in water, food, and air. Children's hand-to-mouth behavior and their play close to the ground further magnify their exposures.
2. Children's metabolic pathways, especially in the first few months after birth, are immature. Although in some instances children are better able than adults to cope with environmental toxicants because they cannot metabolize these chemicals to their active forms, more commonly children are not as able as adults to detoxify and excrete chemical pollutants.
3. Infants and children are growing and developing, and their complex, fast-moving, and highly choreographed developmental processes are exquisitely sensitive to disruption by chemical pollutants. Exposures to even minute doses of toxic chemicals during windows of vulnerability in early development have been shown to cause a wide array of diseases in childhood and to increase risk for chronic disease and disability lifelong (Table 759.1).
4. Because children have many future years of life, they have time for the development of multistage chronic diseases that may be triggered by early exposures.

Table 759.1 Effects of Selected Chemical Pollutants on Infants and Children

CHEMICAL POLLUTANT	EFFECT(S)
Air pollution	Asthma, other respiratory diseases, sudden infant death syndrome
Asbestos	Mesothelioma and lung cancer
Benzene, nitrosamine, vinyl chloride, ionizing radiation	Cancer
Environmental tobacco smoke	Increased risk of sudden infant death syndrome and asthma
Ethyl alcohol	Fetal alcohol syndrome after intrauterine exposure
Lead	Neurobehavioral toxicity from low-dose exposure
Methyl mercury	Developmental neurotoxicity
Organophosphate insecticides	Developmental neurotoxicity
Per- and poly-fluoroalkyl substances (PFAS)	Increased cholesterol levels, altered liver function tests, decreased antibody response to childhood vaccines
Polychlorinated biphenyls	Developmental neurotoxicity
Polybrominated diphenyl ethers	Developmental neurotoxicity
Phthalates	Developmental neurotoxicity and reproductive impairment
Trichloroethylene	Elevated risk of leukemia after intrauterine exposure

SAFETY TESTING OF SYNTHETIC CHEMICALS

Legally mandated testing of chemicals for safety and toxicity coupled with strict controls on dangerous chemicals are the linchpins of chemical safety. Strong chemical safety policies are needed to protect children against disease and death caused by chemicals. A fundamental problem in environmental pediatrics today is that chemical safety policies in many countries are weak. Only approximately 65% of high-production-volume chemicals have been tested for their safety or potential hazard to human health, and fewer than 30% have been assessed for their pediatric or developmental toxicity.

Failure to test chemicals for safety and toxicity reflects the chemical industry's unwillingness to take responsibility for the products they produce coupled with long-standing failure of the previous U.S. federal law on chemical safety, the Toxic Substances Control Act (TSCA). Only five chemicals were banned or controlled under the original TSCA law: PCBs, the ozone-destroying chlorofluorocarbons, and three known human carcinogens—dioxin, asbestos, and hexavalent chromium.

To address the problem of exposure to untested chemicals, countries have enacted stronger chemical safety legislation. In 2007, the European Union enacted the Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) legislation. This law places responsibility on industry to generate data on potential risks of commercial chemicals and to register this information with the European Chemical Agency in Helsinki. The European Union is using this information to craft regulations to protect children's health. Since 2009 REACH has restricted more than 1,000 toxic substances.

In June 2016, the United States passed legislation to revamp TSCA. This law—the Frank R. Lautenberg Chemical Safety for the 21st Century Act—requires the EPA to assess the safety of any new chemical before it is allowed to enter the market, to prioritize safety testing of existing chemicals, and to use a risk-based standard to evaluate chemical safety that considers only hazards to health and is blind to the costs of protective action. This law holds much promise for improving the protection of children's health against toxic chemicals, but it also includes a federal preemption clause that could inhibit state-based protective regulations. Transparency, oversight, and advocacy is critical to ensuring that the law is implemented in a timely manner that is true to the intent to prioritize children's health.

The UN Environment Programme (UNEP) is the United Nations agency responsible for chemical safety. UNEP has called for "a global commitment to the sound management of chemicals. The agency supports and tracks the progress of international agreements and treaties limiting the manufacture, environmental release and global transport of persistent pollutants, pesticides, hazardous waste, and mercury." The Strategic Approach to International Chemicals Management, a program supported by UNEP, provides a platform for coordinating international control of toxic chemicals and hazardous waste across a broad

range of stakeholders. UNEP has worked closely with the World Health Organization (WHO) to coordinate the removal of lead from gasoline in countries around the world.

SYNTHETIC CHEMICALS AND DISEASE IN CHILDREN

A large and growing body of evidence documents that toxic chemicals can cause disease, disability, and death in children. High-dose exposures can cause acute, clinically evident disease. Lower-dose exposures can cause subclinical injury (injury that is very real but detectable only through special testing), such as decreases in intelligence, shortening of attention span, reductions in fertility, and slowing of lung growth. When exposure to a neurotoxic pollutant is widespread, the resulting widespread subclinical neurotoxicity can reduce the intelligence, creativity, and economic productivity of entire societies.

Exposures to toxic chemicals in early life are linked not only to increased risks of disease in childhood, but also to increased risks of disease in later life. This recognition, termed the *developmental origins of health and disease concept*, derives from studies conducted by Barker and colleagues who found that undernutrition in utero is associated decades later with increased risks for hypertension, obesity, diabetes, and cardiovascular disease. Epigenetic programming of gene expression during windows of vulnerability in early development appears to be the underlying mechanism. Increased risks for disease in adult life have now been associated also with early-life exposures to toxic chemicals and appear to be mediated through epigenetic changes in gene expression. Among the health problems linked to toxic chemical exposures in early life are decreased cognition in adults who were exposed as children to lead, neurobehavioral disorders in children exposed to a range of developmental neurotoxicants, and cancer.

CHEMICAL POLLUTANTS OF MAJOR CONCERN

Air Pollutants

Air pollution—ambient air pollution and household air pollution—is the world's largest environmental threat to health and, according to the WHO, is responsible for an estimated 6.7 million deaths each year. The air pollutants of greatest concern for children's health are particulate matter (especially fine particulates less than 2.5 microns in aerodynamic diameter), photochemical oxidants (especially ozone), oxides of nitrogen, sulfur oxides, and carbon monoxide; these are the "criteria air pollutants" regulated by the U.S. EPA in the Clean Air Act. In the United States, approximately 60% of children live in areas that do not meet national ambient air quality standards (NAAQS), most commonly particulate matter and ozone. Globally, ambient levels of air pollutants can be magnitudes higher than the United States.

Fuel combustion is the principal source of air pollution. In high- and middle-income countries, combustion of fossil fuels—coal, oil, and gas—accounts for most air pollution. In low-income and lower middle-income countries, the major source is burning of biomass, such as wood, dung, straw, and charcoal. Coal is the single most highly polluting fossil fuel and the most important source of the greenhouse gas emissions that drive global climate change, but fixed and mobile oil and gas combustion are also major contributors. As the climate changes, wildfires are becoming more common and are further contributing to air pollution and climate change.

Elevated levels of ambient air pollutants are associated with respiratory problems in children, including decreased expiratory volume, wheezing, exacerbations of asthma, and slowed lung growth. Slowed lung growth leads to decreased lung volume and increases risk for respiratory disease in childhood, adolescence, and adult life. Long-term improvements in ambient air quality, especially reductions in levels of particulates and oxides of nitrogen, are associated with statistically and clinically significant improvements in lung growth in children, effects that appear likely to persist into adulthood and to reduce lifetime risk of pulmonary and cardiovascular disease.

Aside from the criteria air pollutants, other pollutants emitted from mobile, stationary, and area sources are considered *hazardous air pollutants* (HAPs), which are known or suspected to cause cancer, reproductive effects, or birth defects. Some common examples are metals such as mercury (neurotoxin), asbestos (mesothelioma, lung cancer), and volatile organic compounds such as polychloroethylene (reproductive effects, cancer). Diesel exhaust is a particularly concerning source of air pollution as it contains fine and ultrafine particulates (capable of reaching alveoli and getting absorbed into bloodstream) and multiple HAPs (e.g., formaldehyde), and has been classified by the International Agency for Research on Cancer as a known human carcinogen.

The effects of household air pollution on children's health are magnified by the fact that many children spend 80–90% of their time indoors, and pollutant levels can be 2-5 times higher indoors especially in poorly ventilated spaces. In 2020, the WHO estimated that 237,000 children <5 years old died from illnesses attributable to household air pollution. Secondhand tobacco smoke (SHS) is an especially hazardous constituent of indoor air pollution and a powerful trigger for asthma (see Chapter 759.1). Household products, particularly some disinfectants, cleaners, paints, and floor finishes, have also been connected to respiratory tract irritation and increased asthma morbidity. Allergens in indoor air can contribute to respiratory problems and include cockroach, mite, mold, and cat and dog allergens.

HEALTH HAZARDS OF UNCONVENTIONAL NATURAL GAS DEVELOPMENT (FRACKING)

Unconventional natural gas development (UNGD) using high-volume horizontal hydraulic fracturing (fracking) has made possible the cost-effective extraction of natural gas from previously inaccessible underground shale deposits and has catalyzed a 16-fold increase in fracking wells in the United States between 2000 and 2020. Natural gas has surpassed coal to become the major source of electricity generation in North America.

In fracking, large volumes of water containing a mix of chemicals (whose composition is a closely guarded secret) are injected at very high pressure through deep wells into shale deposits to break apart the rock and allow release of gas. The gas is brought up to the wellhead through return pipes, collected, and sent to market. In some areas, gas and oil occur together, and the gas may be burned off (flared) at the wellhead while the more valuable oil is piped to market.

The hazards of fracking to children's health include:

- *Toxic air pollution by volatile organic compounds released from fracking wells such as benzene, ethyl-benzene, hydrogen sulfide (H_2S), n-hexane, and methane:* Benzene and ethyl-benzene are known human carcinogens, H_2S and n-hexane are neurotoxicants, and methane is a climate pollutant that contributes to greenhouse gas emissions.
- *Traffic-related air pollution resulting from the large volumes of diesel truck traffic required to bring piping, chemicals, and water to drilling operations:* Diesel exhaust contains coarse and fine particulates, polycyclic aromatic hydrocarbons (PAHs), and formaldehyde, and has been classified by the International Agency for Research on Cancer as a known human carcinogen.
- *Water pollution by toxic chemicals:* Leaks of toxic materials into waterways occur commonly during fracking operations; in addition, much of the water injected into the wells returns to the surface containing proprietary injected chemicals, along with high concentrations of salt dissolved from underground deposits and naturally occurring radioactive materials. These chemicals have been shown to contaminate both ground and surface waters. Water pollution is a particularly severe problem in arid regions with limited water supplies.
- *Radon released from underground deposits:* Radon has been shown to contaminate air near wellheads, and high concentrations of radon have been identified in shipped gas. Additional, nonchemical hazards of fracking include incessant noise, high risk of vehicular injury to children from fast-moving heavy trucks on poorly maintained rural roads, societal disruption in rural communities, and extensive degradation of the environment.

Lead

See Chapter 761.

Mercury

See Chapter 760.

Asbestos

Between 1947 and 1973, asbestos was sprayed as insulation on classroom walls and ceilings in approximately 10,000 schools in the United States. It was also widely utilized in homes as pipe insulation and in floor tiles. Subsequent deterioration or unsafe removal of this asbestos can release asbestos fibers into the air. Asbestos is not a health hazard so long as it is intact, but once it becomes airborne, it can be inhaled by children to produce adverse health effects. Asbestos is a human carcinogen, and the two principal cancers caused by asbestos are lung cancer and mesothelioma. U.S. federal law requires that all schools be inspected periodically for asbestos and that the results be made public. Removal by an EPA-certified contractor is required only when asbestos is visibly deteriorating or is within the reach of children. In most cases, placement of barriers (drywall walls or drop ceilings) provides appropriate protection.

Pesticides

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and rodents, and are used in large quantities in agriculture, homes, schools, parks, gardens, and recreational areas. Children are at risk of exposure when pesticides are used inside or outside in places where children live, learn, and play, and in rural areas they can be exposed to pesticide drift from fields that have been sprayed. Children employed in agriculture or living in migrant farm camps are at risk of direct exposure to pesticides. Diet is another major route of exposure because children are exposed to residual levels of multiple pesticides on fruit and vegetables, especially fruits and vegetables imported from countries where pesticide use is heavier than in the United States. Children can be acutely overexposed to pesticides and clinically evident poisoning results. High-dose exposure to neurotoxic insecticides such as the organophosphate and carbamate pesticides can cause acute neurotoxicity. Both classes of pesticides act through inhibition of acetylcholinesterase and are responsible for the largest number of acute poisoning cases. Symptoms include meiosis, excess salivation, abdominal cramping, vomiting, diarrhea, and muscle fasciculation. In severe cases, the child may experience loss of consciousness, cardiac arrhythmias, and death by respiratory arrest. The war gas sarin is an organophosphate. See Chapter 94 for treatment of poisoning from drugs, chemicals, and plants.

Pesticides can also cause a range of chronic toxic effects that include polyneuropathy and central nervous system (CNS) dysfunction (organophosphates), hormonal disruption and reproductive impairment (DDT, kepone, dibromochloropropane), cancer (aldrin, dieldrin, chlorophenoxy herbicides [2,4,5-T]), and pulmonary fibrosis (paraquat).

Prenatal exposure to the organophosphate pesticide **chlorpyrifos** at levels that produce no evident toxicity in pregnant women has been associated with neurodevelopmental disability in children with reduced cognitive function (lowered IQ), disordered executive function, and functional and anatomic changes in the brain discernible by functional magnetic resonance imaging (fMRI).

Two classes of pesticides of concern are synthetic herbicides and the neonicotinoid insecticides. Herbicides account for about 48% of total pesticide use, and their application is increasing. A major use of herbicides is in production of *genetically modified (GM) food crops*, mainly corn and soybeans that are engineered to be tolerant to **glyphosate (Roundup)**, the most used herbicide worldwide. Herbicides can be sprayed on herbicide-resistant crops throughout the growing season, and glyphosate-resistant, "Roundup-Ready," GM crops account for more than 90% of all corn and soybeans planted in the United States.

Studies of agricultural workers exposed occupationally to glyphosate and other herbicides have found evidence for increased incidence of non-Hodgkin lymphoma. On the basis of these studies and convergent results from toxicologic studies, the International Agency for Research on Cancer has determined that glyphosate is a "probable human carcinogen." Measurable levels of glyphosate metabolites are commonly detected in the urine of Americans.

The **neonicotinoids** are a class of neurotoxic pesticides developed in the 1980s to replace the organophosphates and carbamates. Use of neonicotinoids rose dramatically in the early 2000s, and the neonicotinoid insecticide, imidacloprid, is one of the most widely used insecticides in the world. A growing body of evidence indicates that neonicotinoids are toxic to bees and other pollinators at concentrations found currently in agricultural areas, and neonicotinoids are suspected of contributing to bee colony collapse disorder. In 2020, the EPA proposed a number of restrictions and precautions for neonicotinoid use. More than a dozen states have also introduced legislation limiting neonicotinoids, and several European countries have banned or severely restricted their use. Almost no information is available on the possible developmental or pediatric toxicity of the neonicotinoids. This is another example of a new pesticide in widespread use without prior testing for health impacts on children.

Children's exposures to pesticides can be reduced by minimizing applications to lawns, gardens, schools, and playgrounds; adapting techniques of integrated pest management; and reducing pesticide applications to food crops. Pediatricians and parents can look to resources including the National Pesticide Information Center (NPIC) and the EPA for guidance on integrated pest management and safer use of pesticides in and around the home. Consumption of organic produce has been shown to dramatically reduce pesticide exposure in school-age children. Families can choose organic produce when available and cost-competitive but should not avoid a diet rich in fruits and vegetables if organic options are not feasible.

Persistent Organic Pollutants: Per- and Poly-fluoroalkyl Substances and Chlorinated Hydrocarbons

Per- and Poly-fluoroalkyl Substances. Per- and poly-fluoroalkyl substances (PFAS) are a group of synthetic chemicals that have been used in industrial processes and consumer products because they are resistant to water and heat, and do not break down in the environment. In addition, they can move through soil into drinking water sources and can build up in fish and wildlife (bioaccumulate). They may make clothing stain resistant and also reduce friction. PFAS are also known as "forever chemicals" due to their persistence in the environment, as their strong carbon-fluorine chain is resistant to degradation. NHANES has documented universal exposure to some PFAS due to their ubiquity in consumer products (e.g., nonstick pans, take-out food containers, water-resistant textiles) and the food chain. PFAS have also been detected in drinking water sources (both municipal systems and private wells) across the United States. In March 2023, the EPA proposed a draft of enforceable maximum contaminant levels (MCLs) for six different PFAS chemicals in public drinking water systems; the final regulations are expected by the end of 2023. Several states have enacted their own MCLs for various PFAS compounds; these state MCLs will have to become at least as stringent as the federal MCLs (once finalized).

Ingestion of contaminated food, water, or household dust is the major route of exposure to these chemicals. PFAS can cross the placenta and enter breastmilk. The half-life in the body can be days to decades, depending on the specific PFAS compound. Epidemiologic studies suggest a link between PFAS exposure and increased cholesterol levels, altered liver function tests, decreased antibody response to childhood vaccines, increased risk of preeclampsia/high blood pressure during pregnancy, and cancer (kidney and testicular). Health outcome studies in highly exposed communities are ongoing.

Chlorinated Hydrocarbons. The chlorinated hydrocarbons are a large and diverse class of chemicals that include insecticides (DDT), plastics (polyvinyl chloride), electrical insulators (PCBs), and solvents (trichloroethylene). Highly toxic chlorinated dioxins and furans are formed during synthesis of chlorinated herbicides or as by-products of plastic combustion. These materials are widely dispersed and highly persistent in the environment. Dioxins and furans are known human carcinogens. Brominated flame retardants are used in carpets, furniture, and computers and are environmentally persistent.

The embryo, fetus, and young child are at particularly high risk of injury from halogenated hydrocarbons. All of these compounds are lipid soluble. They readily cross the placenta, and they accumulate in breast milk. Intrauterine exposure to PCBs and brominated flame retardants has been linked to persistent neurobehavioral dysfunction

in children manifested by cognitive impairment (reduced IQ), shortening of attention span, and behavioral disorders.

Consumption of fish from contaminated waters is a major source of children's exposure to PCBs. Children can be exposed in utero or through breast milk. To protect children and pregnant women against PCBs in fish, government agencies have issued advisories concerning fish consumption for certain lakes and rivers. Combustion of medical wastes containing polyvinyl chloride and the use of chlorine to bleach paper products are major preventable sources of environmental dioxin emissions and should be discouraged. Older fluorescent light ballasts that were installed decades ago in schools in the United States are another source of PCB exposure. PCB-containing ballasts should be removed from schools as soon as possible to prevent environmental contamination. Removal must be performed by trained workers.

Endocrine Disruptors

Endocrine disruptors are synthetic chemicals that mimic, block, or alter the actions of normal hormones such as estrogen, testosterone, growth hormone, insulin, and thyroid hormone. Synthetic endocrine disruptors are manufactured in volumes of millions of pounds per year. They include phthalates, bisphenol A, perchlorate, certain pesticides, brominated flame retardants, certain metals, and dioxins. These chemicals are widespread today in consumer products such as soaps, shampoos, perfumes, and plastics. They are widely disseminated in the environment and encountered in air, food, and drinking water.

Exposures to endocrine disruptors in early human development are especially hazardous. Even extremely low-dose exposures during critical early periods can lead to lasting impairments in organ function and to increased risk of disease. Reproductive effects are one consequence of early life exposures to endocrine disruptors. Endocrine disruption is implicated in the epidemiologic observations of a trend toward earlier thelarche and menarche in females, with rising rates of testicular cancer and hypospadias, and with diminishing sperm counts. Among the most clearly documented reproductive effects of early life exposures to endocrine disruptors are adenocarcinoma of the vagina in women and cryptorchidism in men whose mothers took diethylstilbestrol (DES). Another well-documented effect is shortening of the anogenital distance, a measure of in utero feminization, in infant males whose mothers had elevated exposures to phthalates during pregnancy.

Early life exposures to endocrine disruptors can have adverse effects on brain development. Prenatal exposure to low molecular weight phthalates is associated with shortening of attention span in children 4-9 years old, as well as with increased risk for autistic behaviors. Prenatal exposure to bisphenol A has also been linked to behavioral anomalies.

Endocrine disruptors have been reported to have adverse impacts on lipid metabolism and to increase the risk for obesity. Higher urinary levels of bisphenol A are associated with obesity-related outcomes, such as cardiovascular disease, in a cross-sectional analysis of NHANES 2003-2004 data in adults.

Early life exposures to endocrine disruptors, most notably DDT, are linked with increased risk for cancer. A long-term epidemiologic study of women in California found that those who were exposed in utero to high levels of DDT have increased risk for breast cancer in adult life 40-50 years later.

Environmental Carcinogens

Leukemia and brain cancer, the two most common forms of pediatric malignancy in the United States, both increased in incidence from 1972 to 2018, despite declining mortality. The cumulative increase in incidence for childhood leukemia was more than 20%, and for brain and CNS cancer more than 40%. In the same time period, testicular cancer in young men, ages 15-30 years, more than doubled in incidence and is occurring at younger ages. These increases are too rapid to be of genetic origin and are not likely due to better diagnostic capabilities. They are most probably the result of still undefined exposures in the environment. Cancer is now the second-leading cause of death in American children, surpassed only by injuries.

Children may be exposed to carcinogenic pollutants in utero or after birth. Children appear more sensitive than adults to certain chemical carcinogens and also to ionizing radiation (see Chapter 758). The potential for chemical carcinogenesis in utero was initially recognized with the discovery that clear cell adenocarcinoma of the vagina could develop in young women who were exposed in utero to DES.

Carcinogenesis may be associated with exposures in the home and community. Children of asbestos workers and children who have grown up near asbestos plants have been found to have an elevated incidence of mesothelioma. Children who attended elementary school in communities containing synthetic rubber plants have been shown to be at increased risk of leukemia as a result of their exposure to 1,3-butadiene, a known human carcinogen and a major component of synthetic rubber. Children who grow up on farms have elevated rates of leukemia; pesticides are suspected of playing an etiologic role. Intrauterine exposure to trichloroethylene via contaminated drinking water has been associated with an increased incidence of leukemia among females living near an industrial facility and industrial waste site.

Routes of Exposure

Transplacental. Heavy metals such as lead and mercury, fat-soluble compounds such as PCBs and DDT, and endocrine disruptors such as phthalates, readily cross the placenta. They may have serious and irreversible toxic effects on the developing nervous, endocrine, and reproductive organs, even at very low levels. The American College of Obstetricians and Gynecologists have recognized the hazards of environmental exposures during pregnancy and provide detailed guidance for counseling to reduce these exposures in their 2021 statement Reducing Prenatal Exposure to Toxic Environmental Agents (Table 259.2).

Water. Approximately 200 chemicals have been detected at various levels in water supplies including contaminants like lead, solvents, pesticides, and emerging chemicals like PFAS. Lead is an especially common contaminant. Water supplies are generally lead-free at the source but can become contaminated by lead that dissolves from lead pipes and from lead-containing plumbing fixtures. Lead is especially likely to dissolve from pipes and plumbing when the water is acidic, as happened in Flint,

Table 759.2 Toxic Chemicals or Pollutants and Reported Association with Adverse Reproductive Health Outcomes*

CHEMICAL OR POLLUTANT WITH REPORTED ADVERSE ASSOCIATION	POTENTIAL HEALTH EFFECT
Antineoplastic drugs, bisphenol A (BPA), cigarette smoke, ethylene oxide, formaldehyde, polybrominated diphenyl ether (PBDE) flame retardants, solvents	Infertility and miscarriage
Air pollutants from fracking, ambient air pollutants, antineoplastic drugs, cigarette smoke, ethylene oxide, formaldehyde, perfluorochemicals (PFAS),* pesticides, phthalates, PBDEs, toluene	Preterm birth and low birthweight
Ambient air pollutants, BPA, lead, mercury, pesticides, phthalates, PBDE flame retardants, polychlorinated biphenyls (PCBs)	Neurodevelopmental impairment

*Associations noted are from reports of animal and limited human studies. Although there are reported associations between exposures and adverse obstetric outcomes, an association does not necessarily mean that the exposure is a cause of the outcome. More research is needed to understand if there is causality and, if so, at what level of exposure or use of a specific product.

Modified from American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Reducing prenatal exposure to toxic environmental agents: ACOG Committee Opinion, Number 832. *Obstet Gynecol.* 2021;138(1):e40–e54. Table 1.

Michigan, in 2014. The highest levels of lead occur in water that has been standing in lead pipes overnight. It is wise therefore to run water for 2-3 minutes each morning before making up infant formula. Solvents and components of gasoline such as methyl tertiary-butyl ether and benzene are commonly encountered in groundwater. Chemical contaminants from gas drilling can contaminate water in areas where fracking is taking place. Herbicides, such as glyphosate and atrazine, are commonly found contaminants in drinking water in agricultural areas.

In the United States, the EPA regulates approximately 90 drinking water contaminants including organic chemicals, inorganic chemicals, radionuclides, and infectious agents in public water systems. The municipal water systems are responsible for ensuring that the regulated contaminants are below MCLs and will notify customers of any exceedance and steps to address the issue. Those families using private wells, however, are responsible for testing their water on a regular basis. Families with well water can be directed to the EPA private well website or their local health department for guidance on the recommended tests.

Air. Vehicular emissions are the major source of urban air pollution, notably ground-level ozone and particulate matter. Diesel exhaust is a human carcinogen. Coal-fired power plants are another major source of outdoor air pollution. In rural areas, wood smoke can contribute to air pollution. Pediatricians and parents can follow local air quality alerts that include recommendations to reduce risk especially for sensitive groups (airnow.gov). Children living in the vicinity of smelters and chemical production plants can be exposed to toxic industrial emissions such as lead, benzene, and 1,3-butadiene. Specific information about toxic air pollution release in a community can be obtained via the Toxics Release Inventory (www.epa.gov/toxics-release-inventory-tri-program).

Food. Many chemicals are intentionally added to food to improve appearance, taste, texture, or preservation, but many such chemicals have been poorly tested for potential toxicity. Residues of many pesticides are found in both raw and processed foods. Levels of pesticides are lower in organic produce than in conventionally grown fruits and vegetables. Children who consume organic produce have substantially lower urinary pesticide levels than children who eat conventional produce. Elevated levels of methylmercury can be found in large predator fish such as swordfish, shark, king mackerel, and tuna sushi; families should be encouraged to follow fish advisories. Baby foods can contain trace amounts of metals, and rice and rice-based products (especially those made of brown rice) can have inorganic arsenic.

Breast Milk. Breast milk provides many benefits to infants including protection from illness, reduction in allergic diseases like asthma, and reduced risk of obesity, among many others. Breast milk can also be a route of exposure to environmental chemicals including fat-soluble persistent organic pollutants, pesticides, and metals. In almost all situations, the benefits of breastfeeding outweigh the risks of these exposures, and numerous professional organizations support breast milk as the first choice for infant feeding. In addition, chemical regulation can further reduce unnecessary exposure through this route.

Work Clothes. Illnesses in children sometimes may be traced to contaminated dust from parents' work clothes; toxicity from lead, beryllium, dioxin, organophosphate pesticides, and asbestos has occurred. Such exposure (termed *fouling the nest*) can be prevented by providing facilities at work for changing and showering. If facilities are not available, caregivers can be advised to change clothes and shoes before returning home and wash work clothes separately from household laundry. Some work activities and hobbies that occur at home can also expose children to toxins including metals like lead and solvents.

School. Children may be exposed in schools, kindergartens, and nurseries to lead paint, molds, asbestos, tobacco smoke, pesticides, and hazardous arts and crafts materials. Substantial opportunities for prevention exist in the school environment, and pediatricians are often consulted for advice. The EPA has school related environmental health materials (www.epa.gov/schools) that can be shared with stakeholders.

Child Labor. Four to five million children and adolescents in the United States work for pay, and child labor is widespread around the world. Working children are at high risk of physical trauma and injury. They also may be exposed to a wide range of toxic chemicals, including pesticides in agriculture and lawn work, asbestos in construction and building demolition, and benzene in pumping gasoline.

THE PHYSICIAN'S ROLE

Pediatricians have time and again played key roles in the initial recognition of diseases caused by toxic chemicals. Every pediatrician needs to be an "alert clinician" open to the possibility of discovering new diseases in children caused by hazardous exposures in the environment. In considering the origins of noninfectious disease, pediatricians should ask about the home environment, parental occupation, unusual exposures, and neighborhood factories. An environmental cause is particularly likely when several unusual cases of disease or constellations of findings occur together. Any adolescent with a traumatic injury may have been injured at work.

The history is the single most important instrument for obtaining information on environmental exposures (Table 759.3). Information about current and past exposures (including questions about work and travel to or residence in developing countries) should be sought routinely for every new patient. The age of the patient can help focus questions and provide anticipatory guidance on key exposures of concern, such as screening for common sources of lead exposure in young children. Patients with asthma should be evaluated for exposure to common allergens (mold, cockroaches, dust mites) and irritants (tobacco smoke, strong odors). Children with neurodevelopmental disorders should be assessed for pica and other behaviors that increase their risk of toxic exposures. Consider targeted environmental health history questions in patients with illness of unclear causation. Changes in patterns of exposure or new exposures may be especially important. If suspicious information is elicited, more detailed follow-up should be pursued. Referral to a state or local health department or to a Pediatric Environmental Health Specialty Unit may be indicated (https://www.pehsu.net/). Accurate diagnosis of an environmental cause of disease can lead to better care of sick children and prevention of disease in other children.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

759.1 Tobacco

Judith A. Groner

Cigarette smoking is the single most preventable cause of morbidity and mortality, contributing to over 480,000 annual deaths in the United States. The most common reason that people smoke is nicotine addiction, and people who start smoking at an earlier age are more likely to develop a severe addiction than those who start when they are older. In 2022, 4.5% of middle school students and 16.5% of high school students reported current tobacco use (see Chapter 157.2). While youth use a variety of tobacco products, e-cigarettes are the most common. E-cigarettes work by heating liquid to produce an aerosol that is then inhaled into the lungs; this process is called **vaping**. While the long-term health effects of vaping are still being evaluated, the 2019 E-cigarette or Vaping Use-Associated Lung Injury (EVALI) epidemic drew attention to the dangers associated with e-cigarette use (see Chapter 450).

COMPOSITION OF SECONDHAND SMOKE AND TOXICITIES

Along with active tobacco use, secondhand tobacco smoke (SHS) exposure is a very serious health hazard for both children and adults. SHS is a mixture of approximately 7,000 chemicals and is made up of the mainstream smoke exhaled by the smoker and side-stream smoke expelled from the end of a lit tobacco product. At least 70 carcinogens have been identified in SHS, along with 250 chemicals that are toxic to the CNS, immune system, heart, and liver.

SHS also contains particulate matter, which is an independent health hazard. Particulate matter is microscopic solid and liquid matter suspended in air, which can be inhaled and enter the circulation. The most studied of these include polycyclic aromatic hydrocarbons (PAHs) and the tobacco-specific nitrosamines, which are both carcinogenic. Most particulate matter in side-stream smoke is unfiltered by the smoker

Table 759.3 Clinical Tools for Incorporating Environmental Health into Patient Care

Tips for implementing a focused environmental health history:

1. *Age:* Patient age can help direct screening questions and anticipatory guidance on key exposures of concern, such as lead screening questions for young children. Refer to American Academy of Pediatrics (AAP) Bright Futures or the Pediatric Environmental Health Toolkit for age-specific information.
2. *Location*: Local environmental conditions can help direct environmental guidance. For example, in rural communities with high prevalence of private wells for drinking water, families can be counseled on the importance of routine well water testing.
3. *Symptoms*: Consider environmental exposures in the differential diagnosis. For example, carbon monoxide exposure should be on the differential for families presenting with headaches and flulike symptoms (afebrile, no cough).
4. *Asthma*: assess for common environmental asthma triggers in the home such as mold, cockroaches, mice, environmental tobacco smoke, furry pets, cleaning chemicals, strong odors/fragrances
5. *Neurodevelopmental disorders*: assess for pica behavior and other risk factors that may increase the likelihood of exposures (e.g., lead); assess for use of alternative medications

Components of environmental health history (can be adapted based on patient scenario):

General home health and safety:
- Age and condition of home (lead paint in pre-1978 home)
- Carbon monoxide and fire alarms
- Heat and cooking sources (stove ventilation, safe space heater use)
- Tobacco smoke
- Radon (test basement and first/second floors)
- Cleaning products-safe storage and use (e.g., bleach)

Common indoor allergens:
- Water leaks/mold
- Pests (cockroaches, mice) and pesticide use

Water and food:
- Drinking water source (well water requires routine testing)
- Fish advisories (methylmercury) for pregnant persons and children
- Fresh produce (rinse well before eating)
- Rice-based products (vary grains to reduce arsenic exposure)

Jobs and hobbies:
- Caregiver jobs (contaminant transfer from clothing, shoes)
- Adolescent jobs (safety)
- Hobbies in the home (paints, chemicals)
- Sun protection outdoors
- Noise from headphones, toys

Resources and tools for clinical practice:

Environmental history forms:
- National Environmental Education Foundation (NEEF) has a general environmental history and an asthma-focused environmental history (English and Spanish): www.neefusa.org/resource/pediatric-environmental-history
- World Health Organization (WHO) Paediatric Environmental Health History (Green Page) provides a series of concise questions to assess potential exposures: https://www.who.int/publications/m/item/children-s-environmental-record--green-page

Evidence-based clinical resources:
- The Green Book: American Academy of Pediatrics. *Pediatric Environmental Health*. 4th ed. Etzel RA, Balk SJ, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2019.
- Pediatric Environmental Health Specialty Unit (PEHSU). One PEHSU is located in each of the 10 federal regions in the United States. The PEHSUs provide online classroom materials, resources, and access to network of experts in pediatric and reproductive environmental health: www.pehsu.net
- The Pediatric Environmental Health Toolkit is an online clinical tool that providers can use to access information on common exposures, including identification of sources of exposure and provision of targeted anticipatory guidance: https://peht.ucsf.edu.
- Bright Futures provides guidance for well child care for children and adolescents (includes key environmental anticipatory guidance): https://brightfutures.aap.org/.
- American College of Obstetricians and Gynecologists (ACOG). Reducing Prenatal Exposure to Toxic Environmental Agents: https://pubmed.ncbi.nlm.nih.gov/34259492/

Resources for patients:
- Prescriptions for Prevention are tools that link patients to evidence-based simple steps to reduce or prevent common environmental exposures (English and Spanish): https://nyscheck.org/rx
- National Institute of Environmental Health Sciences (NIEHS). Environmental health topics: https://www.niehs.nih.gov/health/topics/index.cfm

and is in the submicron (<1 μm diameter) range, meaning that it is classified as fine particulate matter. These are smaller than the particles in mainstream smoke and can penetrate deeper into the lungs, resulting in higher toxicity through oxidative stress and inflammation. Short- and long-term exposure to fine particulate matter contributes to the aggravation of asthma and other respiratory diseases, lung and other cancers, cardiovascular disease, and death.

SHS concentration in the indoor environment depends on the number of cigarettes smoked in a period, the volume of the room, the ventilation rate, and other processes that eliminate pollutants from the air. There are multiple mechanisms by which SHS causes injury to the respiratory tract, and injury to the cardiovascular system is due to endothelial cell dysfunction due to smoke exposure and its prothrombotic effects.

THIRDHAND SMOKE

Thirdhand smoke (THS) was defined in 2011 as consisting of the residual tobacco smoke pollutants that remain on surfaces and in dust after tobacco has been smoked. These toxins are reemitted into the gas phase or react with oxidants and other compounds in the environment to yield secondary pollutants. These residual pollutants can be detected in the indoor environment well after being generated. About half the particulate matter from SHS is still airborne after 5-6 hours. Many chemicals, such as nicotine and some PAHs, exist in both the gaseous and the particulate phase of SHS. Classified as "semi-volatile," their ability to change form according to environmental conditions means that they remain detectable in the indoor environment for longer periods after active smoking has ceased. These components in dust and on surfaces can be ingested, inhaled, or even absorbed through the skin. The health implications of THS are not well understood, but there is growing evidence both in vitro and in vivo of health harms of THS exposure, particularly respiratory symptoms. Young children are at higher risk of health issues due to THS absorption because of their hand to mouth behaviors, crawling near surfaces, time spent in the home, and increased respiratory rate.

TOBACCO USE AND EXPOSURE IS A HEALTH RISK DISPARITY

Tobacco use, and hence childhood exposure, is found disproportionately among socially disadvantaged low-income populations, who can least afford tobacco and SHS-related illness and evidenced-based treatment for nicotine addiction. There has been a profound decrease in smoking rates among the middle and upper classes within the United States since the 1960s (83% decrease), but the rate of decrease is much less (39%) among lower income groups. The smoking rate for the overall U.S. population is approximately 12.5%, but it is as high as 32% among adults with a high school equivalency degree. Because of these disparities in smoking rates among adults, children born into low-income homes are more likely to be exposed to SHS. More than 38% of U.S. children age 3-11 years were exposed to tobacco smoke from 2017 to 2018, based on a biologic marker of exposure, serum cotinine levels. Children from low-income homes have the highest rates of biologically measured SHS exposure; for every decrease in family income ratio, serum cotinine levels increase by 1.18 ng/L among children. Having a parent who smokes has also been shown to be an independent risk factor for food insecurity in children.

MATERNAL SMOKING DURING PREGNANCY AND TOBACCO SMOKE EXPOSURE DURING PREGNANCY

The effects of maternal smoking on the fetus are profound and can be divided into pregnancy-related and long-term effects. Fetal exposure is one of the most important modifiable risk behaviors for childhood and long-term health.

Pregnancy-Related Effects

Maternal smoking increases the risk of placenta-associated complications of pregnancy, with an increased rate of placental abruption and placenta previa among maternal smokers. Both active maternal smoking and secondhand maternal tobacco smoke exposure have been shown to reduce birthweight and to increase the risk of preterm birth. In utero tobacco exposure from either maternal active tobacco product use or maternal SHS exposure increases the rate of stillbirth. Smoking both during and after pregnancy is a risk factor for **sudden infant death syndrome (SIDS)**; one study found that any smoking during pregnancy was associated in a doubling of SIDS risk and that there was a linear correlation between the average number of cigarettes smoked daily and an increased risk for SIDS. These associations are modifiable by public policy. Several countries in Europe have shown decreased perinatal complications after comprehensive smoke-free laws; within the United States, pregnancy complications and SIDS are inversely related to tobacco taxation levels.

Long-Term Effects

Maternal smoking in early pregnancy is considered causal for orofacial clefts (Surgeon General Report 2014).

Both active smoking during pregnancy and SHS exposure of the mother increases the *child's* later risk of being overweight or obese. This finding may appear surprising due to the long-known relationship between smoking during pregnancy and low birthweight. This relationship has been shown in multiple epidemiologic studies and is robust to adjustment for potential confounders, such as parental body mass index (BMI), breastfeeding, family diet, and lifestyle.

Maternal smoking during pregnancy has been associated with both an increased risk of learning problems and neurobehavioral issues during childhood. The adverse effects of prenatal smoking on child neurodevelopment include poor language development and reduction in cognitive functioning. Prenatal exposure to smoking may also reduce the child's motor performance, mental development (measured by the Bayley Scales of Infant Development), IQ scores, and language development through age 3 years. This exposure may also increase the risks of several child behavioral problems, including externalization of aggressive and hyperactive behavior, prolonged periods of verbal or physical aggression and socially undesirable behavior (conduct disorder) throughout childhood, and delinquency in later childhood. In one study, a dose-response relationship with increasing severity of poor school performance was related to the number of cigarettes the mother smoked during pregnancy.

Maternal Smoking During Pregnancy and Lung Development

Smoking during pregnancy is associated with poor lung growth and function in the offspring and with a greater risk for wheezing between age 2-4 years. According to the Surgeon General Report (2014), there is sufficient evidence to consider this relationship to be causal.

POSTNATAL SECONDHAND SMOKE EXPOSURE—EFFECTS ON THE CHILD

Respiratory

Children exposed to SHS have a higher rate of asthma prevalence and greater asthma severity. The Surgeon General Report (2006) concluded that there is a causal relationship between parental smoking and cough, phlegm, wheezing, and breathlessness, along with asthma, among school-age children. Children with SHS exposure have a weakened response to inhaled corticosteroids. Children with asthma who are SHS-exposed are more likely to have an acute care visit, an overnight hospital stay, and a higher number of hospital admissions than children with asthma and no SHS exposure. The rate of hospital readmissions for asthma has been associated with the level of the child's saliva cotinine, a biomarker of smoke exposure, and this is true even at very low levels of exposure.

Tobacco smoke exposure is a cause of lower respiratory tract infection in children. Findings of the Surgeon General in 2006 were updated by a systemic review of parental and household smoking and risk of lower respiratory tract infections in infancy in 2011. The strongest relationship was for bronchiolitis, where the risk of any household smoke exposure was increased in the first two years of life.

SHS exposure during childhood increases the rate of middle ear disease, including acute, recurrent otitis media and chronic middle ear effusion. The Surgeon General Report (2006) rated this evidence as sufficient to infer a causal relationship between parental smoking and middle ear disease in children.

Cardiovascular Effects

Tobacco smoke exposure during adulthood has been linked to an increased risk of cardiovascular disease. Evidence links childhood exposure to findings of preclinical atherosclerosis. These include increased carotid intima-media thickness and decreased flow-mediated dilation, both indirect tests for preclinical changes leading to atherosclerosis during adulthood. Other findings have included increased inflammation as measured by C-reactive protein, abnormal lipid profiles, higher blood pressure, and increased rates of metabolic syndrome among SHS-exposed children and youth.

Infection

Childhood exposure to SHS is related to increased rates of invasive meningococcal disease in children less than 5 years old. SHS in the home doubled the risk of invasive meningococcal disease with some evidence of a dose-response relationship. The strongest effect was seen in children under 5 years, with SHS exposure more than doubling the rate of meningococcal disease. This relationship was seen both with prenatal smoking and postnatal exposure.

SHS exposure has also been shown to increase the severity of influenza among children hospitalized for the disease. Children with SHS exposure were 4.7 times more likely to be admitted to intensive care and had a 70% longer length of stay than nonexposed children, after controlling for multiple potential confounding factors.

Healthcare Utilization

Children and teens age 3-19 years who are SHS-exposed had higher healthcare utilization compared with nonexposed peers based on an analysis of NHANES data from 2009–2012. Children with high SHS exposure based on serum cotinine were almost three times more likely to have an overnight hospital stay and two times as likely to have a higher number of total hospital admissions as children with no exposure.

Special Vulnerable Pediatric Populations

There is evidence that SHS exposure exacerbates disease processes among children with significant chronic health conditions. Children with sickle cell disease who are exposed to SHS have increased morbidity, specifically increased rates of emergency department visits, and hospitalizations for vasoocclusive crisis and acute chest syndrome (see Chapter 511.1). In addition, tobacco smoke exposure is also associated with pulmonary function abnormalities among children with sickle cell disease, independent of their baseline disease.

Children with cystic fibrosis (CF) are another vulnerable population in which SHS exposure presents an additive threat to overall health. Core health issues for this group of children include problems with growth, lung function, and pulmonary infections (see Chapter 454). SHS-exposed children with CF had decreased growth between 4 and 12 months compared with non–SHS exposed infants. Furthermore, tobacco smoke exposure was associated with increased bronchodilator responsiveness and air trapping, and with increased methicillin-resistant *Staphylococcus aureus* and anaerobic growth on respiratory culture. Tobacco smoke exposure can be considered a modifiable risk factor for children with sickle cell disease and CF.

TREATMENT FOR TOBACCO USE AND SECONDHAND TOBACCO SMOKE EXPOSURE

There is no risk-free level of youth tobacco use or SHS exposure. Thus the best method to treat tobacco use and SHS exposure is to eliminate this exposure by helping adolescents and their caregivers quit smoking. Methods to reduce exposure such as "smoking outside" or wearing a "smoking jacket" have not been shown to eliminate biochemically confirmed SHS exposure. A meta-analysis of six controlled trials aimed specifically at SHS exposure reduction for children (not parental smoking cessation) showed some reduction in tobacco smoke pollution post intervention. However, all homes had significant tobacco-related air pollution at the end of the study period.

The pediatric office has long been considered an excellent venue for pediatricians to screen for youth tobacco use as well as children's SHS exposure and to intervene with youth and their caregivers. The American Academy of Pediatrics (AAP) recommends that providers:

1. Inquire about tobacco use and tobacco smoke exposure as part of health supervision visits and visits for diseases that may be caused or exacerbated by tobacco smoke exposure.
2. Include tobacco use prevention as part of anticipatory guidance.
3. Address parent/caregiver tobacco dependence as part of pediatric healthcare.
4. Offer tobacco dependence treatment and/or referral to adolescents who want to stop smoking.

The United States Preventative Services Task Force also recommends that primary care clinicians provide school-age children and adolescents who have not started to use tobacco with interventions (including education or brief counseling) to prevent initiation of tobacco use. The "Ask-Counsel-Treat" (ACT) model developed by the AAP provides tips on addressing youth tobacco use in the office (available at https://www.aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/tobacco-use-considerations-for-clinicians/); it is recommended that screening begin at age 11. The Clinical Effort Against Secondhand Smoke Exposure (CEASE) is a program that trains pediatricians and their office staff to systematically provide cessation counseling and interventions to caregivers who smoke. The CEASE model is (1) **ask** if anyone in the home or who cares for the child smokes; (2) **assist** the patient or caregiver with quitting by providing brief counseling, pharmacotherapy, or appropriate referrals; and (3) **refer** the smoker to evidence based cessation treatments, including telephone-based Quitlines or Text to Quit services. The CEASE model (found at https://www.massgeneral.org/children/cease-tobacco) involves training pediatricians to provide smoking cessation pharmacotherapy to caregivers who wish to quit smoking; it includes tools to both identify caregivers who smoke and facilitate pediatric healthcare providers' delivery of counseling, medications, and referral for tobacco treatment.

Despite the AAP recommendations for pediatricians to incorporate these methods into practice, a meta-analysis in 2016 of controlled trials in routine healthcare settings of child SHS exposure reduction did not show an intervention effect. However, three controlled trials of maternal postpartum smoking relapse prevention did demonstrate beneficial outcomes of the intervention.

Decreasing smoking initiation among youth will prevent the children of the future from SHS exposure. Ninety percent of smokers initiate use before 19 years of age, and 80% of youth who are smokers persist in smoking in adulthood. Of those, half will die earlier than their nonsmoking peers. After many years of individual states working to enact stricter tobacco laws, new federal legislation known as Tobacco 21 was signed in 2019 that raised the minimum age for sale of tobacco products from 18 to 21 years nationwide. By increasing the age of tobacco purchase to 21 years, there is hope that a whole generation of smoking can be prevented.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

759.2 Marijuana Smoke Exposure

Karen M. Wilson

Unlike tobacco smoke exposure, which has long been recognized as a cause of morbidity and mortality among nonsmokers, marijuana smoke exposure is far less well studied. In 2021, 13.2 million persons age 12 years or older used marijuana on a daily or almost daily basis in the past 12 months, an increase from the 5.7 million daily or almost daily users in 2013 (see Chapter 157.3). The use of marijuana has been increasing in both acceptability and legality in the past 20 years. Current use of marijuana is more common among males and younger adults (18-34 years vs 35 years or older), and those with less than a high school degree. As of 2023, 38 states allow the legal use of marijuana for medical reasons, and 24 states plus Washington DC and Guam have legalized its recreational use. Analysis of poison control center calls for exposure to marijuana for children under 6 years of age showed an increase of 148% from 2006 to 2013; from 4.2/1 million children to 10.4/1 million. Tobacco-smoking parents with young children residing in the home are four times more likely to use marijuana as compared with nontobacco smoking parents. About 38% of young children in the United States are exposed to tobacco smoke, compared to an estimate of 15% of children exposed to marijuana smoke. Studies examining the presence of biomarkers of marijuana smoke exposure have found an exposure prevalence of 16% in young children hospitalized for bronchiolitis in Colorado, and 21% in children 0-3 years being seen at a clinic in New York City.

COMPONENTS OF MARIJUANA SMOKE

While marijuana can also be aerosolized or ingested as hash oil or leaf, combusted marijuana is still the most common form. A recent analysis of data from the U.S. National Health and Nutrition Examination Survey (NHANES) finds that daily marijuana users have higher levels of combustion biomarkers (e.g., volatile organic compounds and polycyclic aromatic hydrocarbons (PAHs) than nonusers. In addition to the particulates and other chemicals of combustion, marijuana comprises two primary active chemicals: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Exposure to combustion products likely extends to adjacent nonusers, as has been shown for tobacco smoke. Most states with legal marijuana use do not have any restrictions on combustible marijuana use in the presence of children.

IMPACT OF MARIJUANA SMOKE EXPOSURE

While there is clear research on the dangers of secondhand tobacco smoke (SHS), there have been very few studies examining the impact of marijuana smoke exposure. Secondhand marijuana smoke contains particulate matter that is known to be harmful when inhaled, in addition to other toxic and carcinogenic chemicals such as volatile organic compounds, PAHs, and aromatic amines. Studies in adults have demonstrated that it is possible to get a "contact high" from intense exposure. Even brief exposures have been found to impair vascular endothelial function in animal models. Children can be exposed to secondhand and thirdhand marijuana smoke when parents or other household contacts smoke indoors, similar to children living with tobacco smokers. Also similar to tobacco, children could be exposed to marijuana smoke through incursions from neighboring apartments; in a New York City sample, 31% of parents reported marijuana incursions, whereas 34% reported tobacco incursions. Neonates can be exposed to marijuana prenatally or through breast milk. Prenatal exposure has been linked to growth restriction and neonatal intensive care admissions, as well as behavioral issues such as impulsivity. Prenatal exposure has also been linked to impaired executive functioning in young adulthood. One study examined the role of indoor cannabis smoke and health; although they found increased particulates in homes with cannabis use, there was no statistically significant difference in health outcomes.

TREATMENT

In the absence of convincing data showing that marijuana is not harmful, parents should be counseled to avoid exposing their children to marijuana smoke, to lock marijuana in a safe place out of reach of any children, to avoid edibles in appealing or non–child proof packaging, and to be cautious about their own level of impairment if they do choose to use legal marijuana.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 760

Heavy Metal Intoxication

Prashant V. Mahajan

Lead, mercury, arsenic, and cadmium, four of the World Health Organization's (WHO) "Ten chemicals of greatest public health concern," are the heavy metals posing the greatest threats to humans. The most prevalent of these exposures is lead (see Chapter 761).

Heavy metal intoxication results in multiorgan toxicity through widespread disruption of vital cellular functions. A meticulous history of environmental exposure may be necessary to correctly identify heavy metals as the source of the protean manifestations associated with such exposure. Arsenic exposure can occur from contaminated food or water; globally, more than 140 million people are estimated to be chronically exposed to drinking water containing high arsenic levels. Mercury exposure occurs primarily through food; fish is a major source of methyl mercury exposure.

ARSENIC

Arsenic is a metalloid that exists in four forms: elemental arsenic, arsine gas, inorganic arsenic salts (pentavalent arsenate form or trivalent arsenite form), and organic arsenic compounds. Toxic manifestations are higher in the more soluble and higher-valence compounds. **Arsine gas** is the most toxic form of arsenic. Mass poisonings from exposure to arsenic have occurred throughout history, including one in 1998 in Wakayama, Japan, in which 70 people were poisoned. Children may be poisoned after exposure to inorganic arsenic found in pesticides, herbicides, dyes, homeopathic medicines, and certain contaminated folk remedies from China, India, and Southeast Asia (see Chapter 94). Soil deposits contaminate artesian well water. Groundwater contamination with arsenic is a common problem in developing countries and has been reported to be a common well contaminant in many areas of the United States as well (Fig. 760.1). The Southwest has the highest arsenic concentrations in the country with more than 16% of sampled wells exceeding the maximum contaminant level. Food products (e.g., rice, organic brown rice syrup, fruit juices) cooked in contaminated water may absorb arsenic, thus concentrating it in the food (Fig. 760.2). The WHO and United States Environmental Protection Agency (EPA) have set 10 μg/L as the upper limit of safety. In many parts of Asia and South America, this limit is frequently exceeded. Arsenic concentrations in a quarter of the wells in Bangladesh exceed 50 μg/L, and 35-77 million of the 125 million inhabitants of Bangladesh regularly consume arsenic-contaminated water. Occupational exposure may occur in industries involved in the manufacturing, mining, smelting, or refining of glass, pottery, electronic and semiconductor components, and lasers. Although arsenic is no longer produced in the United States, it is produced in many countries and is imported into the United States for industrial use. Organic arsenic compounds may be found in seafood, pesticides, and some veterinary pharmaceuticals. In contrast to mercury, the organic forms of arsenic found in seafood are nontoxic.

Pharmacokinetics

Elemental arsenic is insoluble in water and bodily fluids, and thus is insignificantly absorbed and nontoxic. Inhaled arsine gas is rapidly absorbed through the lungs. The inorganic arsenic salts are well absorbed through the gastrointestinal tract, lungs, and skin. The organic arsenic compounds are well absorbed through the gastrointestinal tract. After acute exposure, arsenic initially is bound to the protein portion of hemoglobin in the red blood cells (RBCs) and rapidly distributed to all tissues. Inorganic arsenic is methylated and is eliminated predominantly by the kidneys, with approximately 95% excreted in the urine and 5% excreted in the bile. Most of the arsenic is eliminated in the first few days, with the remainder slowly excreted over a period of several weeks. Arsenic concentrates in hair, nails, and skin. Arsenic can also accumulate in the fetus, as it can cross the placenta. Measurement of the distance of **Mees lines** (transverse white striae on the nail) from the nailbed can provide an estimate of time of exposure (nails grow at the rate of 0.4 mm/day) (Fig. 760.3).

Pathophysiology

After exposure to arsine gas, absorbed arsine enters RBCs and is oxidized to arsenic dihydride and elemental arsenic. Complexing of these derivatives with red cell sulfhydryl groups results in cell membrane instability and massive hemolysis. The inorganic arsenic salts poison enzymatic processes vital to cellular metabolism. Trivalent arsenic binds to sulfhydryl groups, resulting in decreased production of

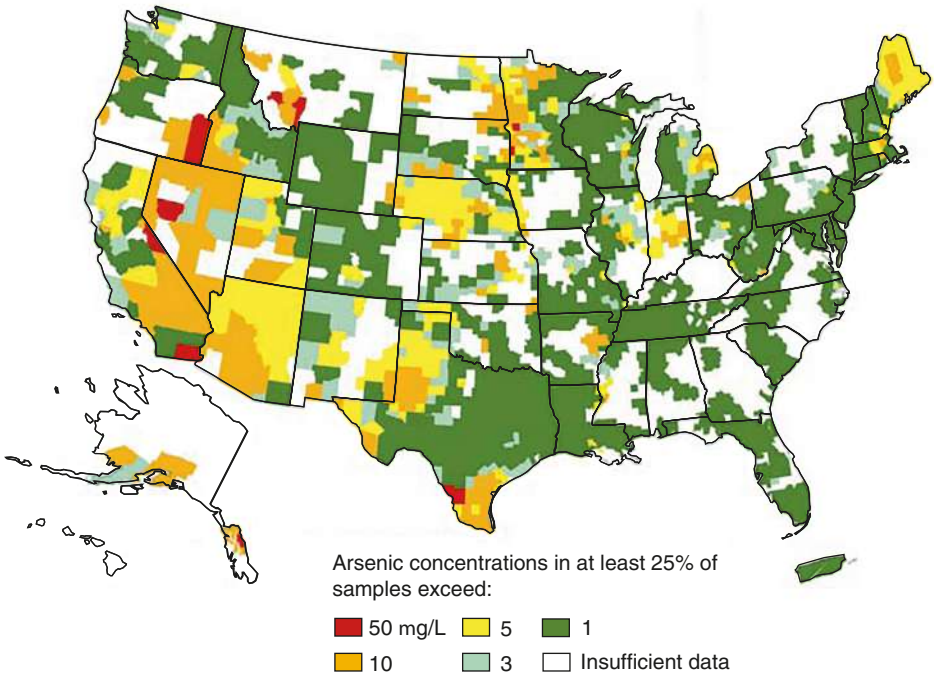

Fig. 760.1 U.S. Geological Survey map of arsenic in groundwater. Groundwater may also contain elevated concentrations of arsenic from agricultural runoff, contamination from runoff from wood preservatives containing arsenic, improperly disposed arsenical chemicals, or mining. For the latest on the US Geological survey: https://www.usgs.gov/mission-areas/water-resources/science/arsenic-and-drinking-water#overview. *(Modified from Agency for Toxic Substances and Disease Registry: Arsenic toxicity. What Are the Routes of Exposure for Arsenic? Fig 1.* https://www.atsdr.cdc.gov/csem/arsenic/what_routes.html.*)*

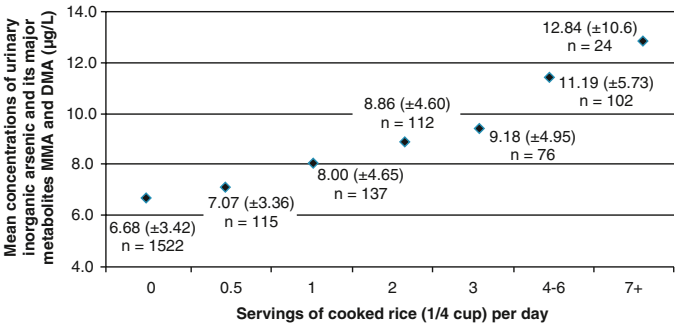

Fig. 760.2 Mean concentrations of urinary inorganic arsenic and its major metabolites monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) by categories of rice intake in children ages 6-17, National Health and Nutrition Examination Survey (NHANES) 2003-2008, excluding subjects with recent seafood consumption. *(From Lai PY, Cottingham KL, Steinmaus C, et al. Arsenic and rice: Translating research to address health care providers' needs. J Pediatr. 2015;167[4]:797–803. Fig. 1.)*

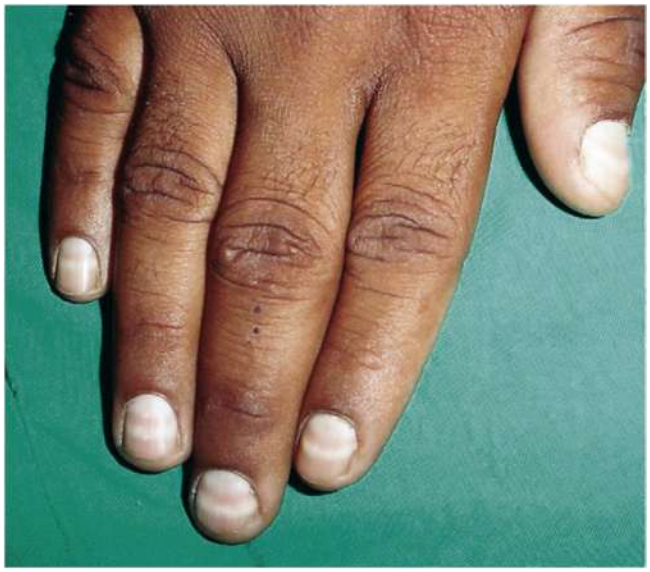

Fig. 760.3 Mees lines. Transverse white bands are clearly visible on the nails. *(From Chauhan S, D'Cruz S, Singh R, et al. Mees' lines. Lancet. 2008;372[9647]:1410.)*

adenosine triphosphate through the inhibition of enzyme systems such as the pyruvate dehydrogenase and α-ketoglutarate complexes. Pentavalent arsenic may be biotransformed to trivalent arsenic or substituted for phosphate in the glycolytic pathway, resulting in uncoupling of oxidative phosphorylation.

Clinical Manifestations

Arsine gas is colorless, odorless, nonirritating, and highly toxic. Inhalation causes no immediate symptoms. After a latent period of 2-24 hours, exposed individuals experience massive hemolysis, malaise, headache, weakness, dyspnea, nausea, vomiting, abdominal pain, hepatomegaly, pallor, jaundice, hemoglobinuria, and renal failure (Table 760.1). Acute ingestion of arsenic produces gastrointestinal toxicity within minutes to hours and is manifested as nausea, vomiting, abdominal pain, and diarrhea. Hemorrhagic gastroenteritis with extensive fluid loss and third spacing may result in hypovolemic shock. Cardiovascular toxicity includes QT interval prolongation, polymorphous ventricular tachycardia, congestive cardiomyopathy, pulmonary edema, and cardiogenic shock. Acute neurologic toxicity includes delirium, seizures, cerebral edema, encephalopathy, and coma. Lethal doses of arsenates are 5-50 mg/kg; lethal doses of arsenites are <5 mg/kg.

Table 760.1 Effects of Arsenic on Organ Systems

ORGAN SYSTEM	EFFECTS OF ARSENIC
Gastrointestinal system	Submucosal vesicles, watery or bloody diarrhea, severe hematemesis, pancreatitis, jaundice, toxic hepatitis
Cardiovascular system	Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias, torsades de pointes, pericarditis Vasodilation, hypotension, shock
Kidneys	Hematuria, proteinuria, oliguria, renal failure
Nervous system	Toxic encephalopathy with seizures, headache, cerebral edema, and coma Chronic exposure: peripheral painful sensorimotor neuropathy, paresthesias
Hematologic and lymphatic system	Anemia, leukopenia, and thrombocytopenia; acute hemolysis with arsine gas, basophilic stippling
Liver	Fatty degeneration with central necrosis
Skin	Desquamation, alopecia, hyperkeratosis, nail changes (Mees lines), brown pigmentation Chronic exposure: hyperkeratosis, hyperpigmentation
Teratogenic	Neural tube defects in the fetus
Oncologic	Urologic cancer, other malignancies

Late sequelae include hematuria, proteinuria, and acute kidney injury. A delayed sensorimotor peripheral neuropathy may appear days to weeks after acute exposure, secondary to axonal degeneration. Neuropathy manifests as painful dysesthesias followed by diminished vibratory, pain, touch, and temperature sensation; decreased deep tendon reflexes; and in the most severe cases, an ascending paralysis with respiratory failure mimicking Guillain-Barré syndrome (see Chapter 656). Adult survivors of infant arsenic poisoning experience higher mortality from disorders of the nervous system compared with adults without such exposure.

Subacute toxicity is characterized by prolonged fatigue, malaise, weight loss, headache, chronic encephalopathy, peripheral sensorimotor neuropathy, leukopenia, anemia, thrombocytopenia, chronic cough, and gastroenteritis. Mees lines in the nails become apparent 1-2 months after exposure in approximately 5% of patients. Dermatologic findings include alopecia, oral ulceration, peripheral edema, a pruritic macular rash, and desquamation.

Chronic arsenic toxicity causes significant morbidity in children resulting in skin lesions, lung disease, and deficits in intellectual function. **Chronic exposure** to low levels of arsenic is usually from environmental or occupational sources. Over the course of years, dermatologic lesions develop, including hyperpigmentation, hypopigmentation, hyperkeratoses (especially on the palms and soles), squamous and basal cell carcinomas, and **Bowen disease** (cutaneous squamous cell carcinoma in situ). Encephalopathy and peripheral neuropathy may be present. Hepatomegaly, hypersplenism, noncirrhotic portal fibrosis, and portal hypertension occur. **Blackfoot disease** is an obliterative arterial disease of the lower extremities associated with chronic arsenic exposure that has been described in Taiwan. Carcinogenicity of chronic arsenic exposure is reflected in increased rates of cancers of the skin, lung, liver, bladder, and kidney as well as of angiosarcomas. Arsenic is carcinogenic, possibly through epigenetic dysregulation. The effects of prenatal exposure to arsenic are uncertain but may include low birthweight.

Laboratory Findings

The diagnosis of arsenic intoxication is based on characteristic clinical findings, a history of exposure, and elevated urinary arsenic values, the last of which confirm the exposure. A spot urine arsenic level should be determined for symptomatic patients before chelation, although initially the result may be negative. Because urinary excretion of arsenic is intermittent, definitive diagnosis depends on a 24-hour urine collection. Concentrations greater than 50 µg/L in a 24-hour urine specimen are consistent with arsenic intoxication (Table 760.2). Urine specimens must be collected in metal-free containers. Ingestion of seafood containing nontoxic arsenobetaine and arsenocholine can cause elevations of urinary arsenic. Blood arsenic levels rarely are helpful because of their high variability and the rapid clearance of arsenic from the blood in acute poisonings. Elevated arsenic values in the hair or nails must be interpreted cautiously because of the possibility of external contamination. Abdominal radiographs may demonstrate ingested radiopaque arsenic.

Later in the course of illness, a complete blood cell count may show anemia, thrombocytopenia, and leukocytosis, followed by leukopenia, karyorrhexis, and basophilic stippling of RBCs. The serum concentrations of creatinine, bilirubin, and transaminases may be elevated; urinalysis may show proteinuria, pyuria, and hematuria; and examination of the cerebrospinal fluid may show protein elevations.

MERCURY

Mercury exists in three forms: elemental mercury, inorganic mercury salts, and organic mercury (Table 760.3). **Elemental mercury** is present in thermometers, sphygmomanometers, barometers, batteries, gold or silver smelting processes, and some latex paints produced before 1991. Workers in industries producing these products may expose their children to the toxin when mercury is brought home on contaminated clothing. Vacuuming of carpets contaminated with mercury and breaking of mercury fluorescent light bulbs may result in elemental mercury vapor exposure. Severe inhalation poisonings have resulted from attempts to separate gold from gold ore by heating mercury and forming a gold-mercury amalgam. Elemental mercury has been used in folk remedies by Asian and Mexican populations for chronic stomach pain, by Latin Americans and Caribbean natives in occult practices, and as a skin-lightening agent. Dental amalgams containing elemental mercury release trace amounts of mercury. An expert panel for the National Institutes of Health concluded that existing scientific evidence does not indicate that dental amalgams pose a health risk and should not be replaced merely to decrease mercury exposure. A 2009 WHO expert panel concluded that a global near-term ban on amalgam would be problematic for public and dental health. However, this committee recommended that alternatives to amalgam should be sought as part of a phase-out of the use of mercury-containing amalgams.

Inorganic mercury salts are found in pesticides, disinfectants, antiseptics, pigments, dry batteries, and explosives and as preservatives in some medicinal preparations. **Organic mercury** in the diet, especially fish containing methyl mercury, is a major source of mercury exposure among the general population. Industries that may produce mercury-containing effluents include chlorine and caustic soda production, mining and metallurgy, electroplating, chemical and textile manufacturing, paper and pharmaceutical manufacturing, and leather tanning. Mercury compounds in the environment are methylated to methyl mercury by soil and water microorganisms. Methyl mercury in the water rapidly accumulates in fish (swordfish, king mackerel, fresh tuna, tile fish, shark) and other aquatic organisms, which are in turn consumed by humans. To address concerns that maternal consumption of large quantities of fish during pregnancy may expose the fetus to concentrations of mercury with adverse consequences, the longitudinal Seychelles Child Development Study has been ongoing since the late 1980s. The first cohort of the study involved nearly 800 mother–child pairs, with subsequent cohorts enrolled. Despite a high maternal fish intake (mean of 12 fish meals per week), follow-up of children at least through 9 years of age has revealed no consistent adverse developmental effects. Well-known large outbreaks of methyl mercury intoxication include the incidents in Japan in the 1950s (**Minamata disease,** from consumption of contaminated seafood) and in Iraq in 1971 (from consumption of grain treated with a methyl mercury fungicide).

Thimerosal is a mercury-containing preservative used in some vaccines. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. During an ongoing review of biologic products in response to the U.S. Food and Drug Administration (FDA) Modernization Act of 1997, the FDA determined that infants who received thimerosal-containing vaccines at multiple visits might have been exposed to more mercury than recommended by federal guidelines. As a precautionary measure, the American Academy of Pediatrics, American Academy of Family Physicians, Advisory Committee on Immunization Practices, and U.S. Public Health Service issued a joint recommendation in 1999 that thimerosal be removed from vaccines as quickly as possible. *In the United States, thimerosal has been removed from all vaccines in the recommended childhood immunization schedule.* Infants and children who have received thimerosal-containing vaccines do not need to undergo blood, urine, or hair testing for mercury because the concentrations of mercury would be quite low and would not require treatment. The larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines. Studies do *not* demonstrate a link between thimerosal-containing vaccines and autism spectrum disorders (see Chapter 58), and no evidence supports a change in the standard of practice regarding administration of thimerosal-containing vaccines in areas of the world where they are used. A rise in blood mercury levels following a single dose of hepatitis vaccine was seen in preterm infants, but the clinical significance is unknown.

Pharmacokinetics

Inhaled elemental mercury vapor is 80% absorbed by the lungs and is distributed rapidly to the central nervous system because of its high lipid solubility. The elemental mercury is oxidized by catalase to the mercuric ion, which is the reactive form that causes cellular toxicity. Elemental mercury liquid is poorly absorbed from the gastrointestinal tract, with less than 0.1% being absorbed. The half-life of elemental mercury in the tissues is approximately 60 days, with most of the excretion occurring in the urine.

Inorganic mercury salts are approximately 10% absorbed from the gastrointestinal tract and cross the blood-brain barrier to a lesser extent than elemental mercury. Mercuric salts are more soluble than mercurous salts and therefore produce greater toxicity. Elimination occurs primarily in the urine, with a half-life of approximately 40 days.

Table 760.2 Acceptable and Toxic Levels of Arsenic and Mercury

	ARSENIC	MERCURY
Molecular weight	74.9 Da	200.59 Da
Acceptable blood level	<5 µg/L (<0.665 nmol/L)	<10 µg/L (<50 nmol/L)
Acceptable urine level	<50 µg/L (<6.65 nmol/L) 24-hr urine sample	<20 µg/L (<100 nmol/L)
Intervene at blood level		>35 µg/L (>175 nmol/L)
Intervene at urine level	>100 µg/L (>13.3 nmol/L) 24-hr urine sample	>150 µg/L (>750 nmol/L)

Table 760.3 Differential Characteristics of Mercury Exposure

	ELEMENTAL	INORGANIC (SALT)	ORGANIC (ALKYL)
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Blood (transient, acute), kidney, CNS (delayed)	CNS, kidney, liver, blood, hair
Clearance	Kidney, GI	Kidney, GI	Methyl: GI Aryl: kidney, GI
CLINICAL EFFECTS CNS	Tremor	Tremor, erethism (irritability)	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	—	—
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (acute tubular necrosis)	+
Acrodynia	+	++	—
Therapy	BAL, succimer	BAL, succimer	Succimer (early)

+, mild; ++, moderate; +++, severe; BAL, British antilewisite (also known as dimercaprol); CNS, central nervous system; GI, gastrointestinal.
From Sue YJ. Mercury (heavy metals). In: Nelson LS, Howland MA, Lewin NA, et al., eds. *Goldfrank's Toxicologic Emergencies,* 11th ed. New York: McGraw-Hill; 2019: Table 95.3.

Methyl mercury is the most avidly absorbed of the organic mercury compounds, with approximately 90% absorbed from the gastrointestinal tract. The lipophilic, short-chain alkyl structure of methyl mercury allows it to distribute rapidly across the blood-brain barrier and placenta. Methyl mercury is approximately 90% excreted in the bile, with the remainder being excreted in the urine. The half-life is 70 days.

Pathophysiology

After absorption, mercury is distributed to all tissues, particularly the central nervous system and kidneys. Mercury reacts with sulfhydryl, phosphoryl, carboxyl, and amide groups, resulting in disruption of enzymes, transport mechanisms, membranes, and structural proteins. Widespread cellular dysfunction or necrosis results in the multiorgan toxicity characteristic of mercury poisoning.

Clinical Manifestations

Five syndromes describe the clinical presentation of mercury poisoning. **Acute inhalation of elemental mercury vapor** results in rapid onset of cough, dyspnea, chest pain, fever, chills, headaches, and visual disturbances. Gastrointestinal findings include metallic taste, salivation, nausea, vomiting, and diarrhea. Depending on the severity of the exposure, the illness may be self-limited or may progress to necrotizing bronchiolitis, interstitial pneumonitis, pulmonary edema, and death from respiratory failure. Younger children are more susceptible to pulmonary toxicity. Survivors may demonstrate restrictive lung disease. Renal dysfunction and neurologic disturbances (ataxia, persistent weakness, emotional lability) may develop subacutely. Chronic exposure to volatilized elemental mercury in dental amalgams has not been found to be of any clinical significance.

Acute ingestion of inorganic mercury salts (typically secondary to ingestion of a button battery) can manifest in a few hours as corrosive gastroenteritis, signified by metallic taste, oropharyngeal burns, nausea, hematemesis, severe abdominal pain, hematochezia, acute tubular necrosis, cardiovascular collapse, and death.

Chronic inorganic mercury intoxication produces the classic triad consisting of tremor, neuropsychiatric disturbances, and gingivostomatitis. The syndrome may result from long-term exposure to elemental mercury, inorganic mercury salts, or certain organic mercury compounds, all of which may be metabolized to mercuric ions. The tremor starts as a fine intention tremor of the fingers that is abolished during sleep but that may later involve the face and progress to choreoathetosis and spasmodic ballismus. Mixed sensorimotor neuropathy and visual disturbances may also be present. The neuropsychiatric disturbances include emotional lability, delirium, headaches, memory loss, insomnia, anorexia, and fatigue. Renal dysfunction ranges from asymptomatic proteinuria to nephrotic syndrome.

Acrodynia, or **pink disease**, is a rare idiosyncratic hypersensitivity reaction to mercury that occurs predominantly in children exposed to mercurous powders. The symptom complex includes generalized pain, paresthesias, and an acral (hands, feet) rash that may spread to involve the face. The rash typically is red-pink, papular, pruritic, and painful; it may progress to desquamation and ulceration. Morbilliform, vesicular, and hemorrhagic variants have been described. Other important features include anorexia, apathy, photophobia, and hypotonia, especially of the pectoral and pelvic girdles. Irritability, tremors, diaphoresis, insomnia, hypertension, and tachycardia may be present. Some cases initially were diagnosed as pheochromocytoma. The outcome is good after removal of the source of mercury exposure.

Methyl mercury intoxication (also known as **Minamata disease** after the widespread mercury poisoning that occurred at Minamata Bay in Japan in people who had ingested contaminated fish) manifests as delayed neurotoxicity that appears after a latent period of weeks to months. It is characterized by ataxia; dysarthria; paresthesias; tremors; movement disorders; impairment of vision, hearing, smell, and taste; memory loss; progressive dementia; and death. Infants exposed in utero are the most severely affected, with low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures. Although there is significant residual morbidity from methyl mercury neurotoxicity, observations on long-term follow-up of children exposed in Iraq reveal complete or partial resolution in most cases.

Laboratory Findings

The diagnosis of mercury intoxication is based on characteristic clinical findings, a history of exposure, and elevation of whole blood or urine mercury values, the last of which confirms the exposure. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Blood should be collected in special tubes for trace elements from laboratories that capably perform those tests. Levels <10 μg/L in whole blood and <20 μg/L in a 24-hour urine specimen are considered normal (see Table 760.2). Although blood mercury levels may reflect acute exposure, they decrease as mercury redistributes into the tissues. Urine mercury levels are most useful for identifying long-term exposures, except in the case of methyl mercury, which undergoes minimal urinary excretion. Urinary mercury levels are used in monitoring efficacy of chelation therapy, whereas blood levels are used primarily in monitoring organic mercury poisonings. Hair analysis for mercury is not reliable because hair reflects

both endogenous and exogenous mercury exposure (hair avidly binds mercury from the environment). Abdominal radiographs may demonstrate ingested radiopaque mercury.

Urinary markers of early nephrotoxicity include microalbuminuria, retinol-binding protein, β_2-microglobulin, and *N*-acetyl-β-D-glucosaminidase. Early neurotoxicity may be detected with neuropsychiatric testing and nerve conduction studies, whereas severe central nervous system toxicity is apparent on CT or MRI.

TREATMENT OF ARSENIC AND MERCURY INTOXICATION

The principles of management for arsenic and mercury intoxication include prompt removal from the source of poisoning, aggressive stabilization and supportive care, decontamination, and chelation therapy when appropriate. Once the diagnosis is suspected, the local poison control facility should be contacted, and care coordinated with physicians who are familiar with the management of heavy metal poisoning.

Supportive care for patients exposed to arsine gas requires close monitoring for signs of hemolysis, including evaluation of the peripheral blood smear and urinalysis. Transfusion of packed RBCs may be necessary, as may administration of intravenous fluids, sodium bicarbonate, and mannitol to prevent renal failure secondary to the deposition of hemoglobin in the kidneys. After inhalation of elemental mercury vapor, patients require careful monitoring of respiratory status, which may include pulse oximetry, arterial blood gas analysis, and chest radiography. Supportive care involves administration of supplemental oxygen and, in severe cases, intubation and mechanical ventilation.

Acute ingestion of inorganic arsenic and mercury salts results in hemorrhagic gastroenteritis, cardiovascular collapse, and multiorgan dysfunction. Fluid resuscitation, pressor agents, and transfusion of blood products may be required for management of cardiovascular instability. Severe respiratory distress, coma with loss of airway reflexes, intractable seizures, and respiratory paralysis are indications for intubation and mechanical ventilation. Renal function must be monitored carefully for signs of renal failure and the need for hemodialysis.

Gastrointestinal decontamination after ingestion of inorganic arsenic and mercury salts has not been well studied. Because of the corrosive effects of these compounds, induced emesis is not recommended, and endoscopy may be considered before gastric lavage. Arsenic and mercury are not well adsorbed to activated charcoal, but its use may be helpful if coingestants are suspected. Whole bowel irrigation is used to remove any radiopaque material remaining in the gastrointestinal tract.

Chelation for acute arsenic and mercury poisoning is most effective when administered as soon as possible after exposure. Chelation should be continued until 24-hour urinary arsenic or mercury levels return to normal (<50 μg/L for arsenic and <20 μg/L for mercury), the patient is symptom-free, or the remaining toxic effects are believed to be irreversible. The efficacy of chelation in long-term exposures is reduced because heavy metal in the tissue compartment is relatively nonexchangeable and some degree of irreversible toxicity has already occurred.

Dimercaprol, also known as *2,3-dimercaptopropanol* or *British antilewisite (BAL)*, is the chelator of choice for a patient who cannot tolerate oral therapy, as often is true for critically ill patients and after ingestion of the corrosive inorganic arsenic and mercury salts. Dimercaprol is available in 3-mL ampules at a concentration of 100 mg/mL for deep intramuscular (IM) injection. It is formulated in a peanut oil and benzyl benzoate suspension; as such, it is not suitable for patients with peanut allergy. For **arsenic poisoning**, the recommended regimen of dimercaprol is 2.5 mg/kg IM q4 hours for six doses, then every 6 hours for four doses, then every 8 hours for three doses, then every 12 hours for two doses, followed by once daily for 10 days. For severe arsenic poisoning, the dose of dimercaprol is increased to 3.5-5 mg/kg; the same dosing interval is followed. The dose of dimercaprol for **inorganic mercury poisoning** is 5 mg/kg every 4 hours IM for 24-48 hours, and then 2.5 mg/kg IM q12 hours for 10 days. The dimercaprol–heavy metal complex is excreted in the urine and bile. A period of 5 days between courses of chelation is recommended. Adverse effects of dimercaprol include pain at the injection site, hypertension, tachycardia, diaphoresis, nausea, vomiting, abdominal pain, a burning sensation in the oropharynx, and a feeling of constriction in the chest. Dimercaprol may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals. It is important to note that dimercaprol is contraindicated for chelation of methyl mercury because dimercaprol redistributes methyl mercury to the brain from other tissue sites, resulting in increased neurotoxicity.

Oral chelating agents are used to replace the painful dimercaprol injections when the patient is stable enough to tolerate oral therapy and prolonged chelation is necessary. **Succimer**, also known as *2,3-dimercaptosuccinic acid* (DMSA), is an orally administered water-soluble derivative of dimercaprol. DMSA is available in 100 mg capsules. The recommended regimen of DMSA for both arsenic and mercury poisoning is 10 mg/kg orally every 8 hours for 5 days followed by 10 mg/kg orally every 12 hours for 14 days. The DMSA–heavy metal complex is excreted in the urine and bile. A period of 2 weeks between courses of chelation is recommended. Mild adverse effects include nausea, vomiting, diarrhea, loss of appetite, and transient elevations in liver enzyme levels. DMSA also may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient patients.

D-**Penicillamine** is an orally administered chelator that has been used in the past for less-severe mercury poisoning or as an adjunct to dimercaprol therapy in arsenic poisoning. Its use is largely restricted because of the potential for significant leukopenia, thrombocytopenia, and proteinuria along with the improved tolerability of succimer.

Patients with ingestion of elemental mercury require no follow-up unless there is an underlying disease that decreases the gastrointestinal transit time. Serial abdominal radiographs to document the progression of the metal are recommended. Acute inhalation of mercury fumes and ingestion of inorganic mercury require hospitalization to monitor the respiratory and gastrointestinal status, respectively. Therapeutic abortion may be considered in pregnant patients because of the teratogenic effect of mercury.

Strategies to reduce arsenic exposure in rice are noted in Table 760.4.

Table 760.4 Potential Strategies for Reducing Exposure of Arsenic in Rice

1. Diversify the diet
   - Eat a well-balanced diet and a variety of grains[†,‡,§]
   - Identify children at risk for high consumption of rice and rice products (e.g., gluten-free diets, highly allergic)
2. Consider alternatives to rice for first food
   - Start infants on barley, oats, or other grains[†,‡]
   - If rice cereal must be used for infants, limit to one serving per day[§]
3. Adopt strategies that help minimize exposure
   - Rinse rice in a colander before cooking[§]
   - Cook rice like pasta, with plenty of extra water[§]
   - Choose lower-arsenic varieties of rice (e.g., basmati)[§]
   - Avoid or limit use of rice milk or other rice beverages for infants[‡] and children under 5 yr old[§,¶]
   - Read labels of processed foods: choose alternatives to foods sweetened with brown rice syrup or thickened with rice products
4. Regulatory action
   - Federal agencies should establish regulatory limits for arsenic content in rice and rice products[§]

[†]U.S. Food and Drug Administration.
[‡]American Academy of Pediatrics.
[§]Consumer Reports.
[¶]United Kingdom Food Standard Agency.
From Lai PY, Cottingham KL, Steinmaus C, et al. Arsenic and rice: translating research to address health care providers' needs. *J Pediatr.* 2015;167(4):797–803.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 761

Lead Poisoning

Morri Markowitz

Lead is a metal that exists in four isotopic forms. Clinically it is purely a toxicant; no organism has an essential function that is lead dependent. Chemically its low melting point and ability to form stable compounds have made it useful in the manufacture of hundreds of products; this commercial attractiveness has resulted in the processing of millions of tons of lead ore, leading to widespread dissemination of lead in the human environment.

The **blood lead level (BLL)** is the gold standard for determining risk of health effects. The threshold level at which lead begins to cause biochemical, subclinical, or clinical disturbance remains to be determined. In 2021, the Centers for Disease Control and Prevention (CDC) designated 3.5 μg/dL as the *"reference value based on the 97.5th percentile of the population of US children aged 1-5 years."* It is the BLL that identifies the 2.5% of children with the highest BLLs. As a measure of the distribution of BLLs in young American children rather than a toxicity threshold, this number will change in a manner dependent on the epidemiology of BLLs. Surveillance by the CDC has shown that the prevalence of elevated BLLs has declined markedly. Approximately 500,000 U.S. children ages 1-5 years currently have BLLs ≥3.5 μg/dL. Fortunately, children with levels high enough to be life-threatening (>100 μg/dL) are rarely seen in the United States, though deaths continue to occur in other areas of the world. Although BLL ≥3.5 μg/dL is stated as a reference value, it is likely that clinicians and departments of health will consider this a threshold for action.

PUBLIC HEALTH HISTORY

In the late 1970s, nearly all preschool-age children in the United States had BLLs above the current reference value of 3.5 μg/dL. Over the next 25 years, government regulations resulted in the significant reduction of three main contributors to lead exposure by means of (1) the elimination of the use of tetraethyl lead as a gasoline additive, (2) the banning of lead-containing solder to seal food- and beverage-containing cans, and (3) the application of a federal rule that limited the amount of lead allowed in paint intended for household use to less than 0.06% by weight (further reduced by the Consumer Product Safety Commission to 0.009% in 2008). Factors identified by the CDC in the late 1970s that indicate increased risk of lead poisoning, in addition to preschool age, include low socioeconomic status; living in older housing, built primarily before 1960; urban location; and Black race. Another high-risk group that has been identified consists of recent immigrants from less wealthy countries, including adoptees. These risk factors largely persist currently, as indicated by an analysis of over 1 million BLLs obtained from U.S. children between October 2018 and February 2020 and analyzed in a commercial lab. In addition, these data indicated that over half of the children still have measurable BLLs, i.e., ≥1 μg/dL.

Progress is also being made globally. In Mexico, the introduction of unleaded gasoline in 1990 was associated with a decline in BLLs among first-grade students, from 17 μg/dL in 1990 to 6.2 μg/dL in 1997. Algeria, the last country to use leaded gasoline for cars and trucks, phased out its use in 2021. In Malta, after the import of red lead paint was banned and the use of lead-treated wood for fuel in bakeries was prohibited, mean BLLs of pregnant women and newborns decreased by 45%. After it was documented that children living in the neighborhood of a battery factory in Nicaragua had a mean BLL of 17.2 μg/dL, but children in the control community had a mean BLL of 7.4 μg/dL, the factory was closed. Despite these advances, in 2021 the World Health Organization (WHO), citing research for UNICEF by the Institute for Health Metrics and Evaluation, estimated that 815 million children globally may have elevated BLLs above 5 mg/dL. The majority live in developing countries, where in some regions BLLs may be 10- to 20-fold higher than in developed countries.

Unfortunately, local lead-related harms continue to occur. When the water source for Flint, Michigan, was changed (2014) to the Flint River and utilized a water treatment plant with poor corrosion control, the lead level of Flint tap water increased, as did the BLLs of children <5 years of age. Flint is not unique; many other cities have lead pipes that can result in water contamination. In 2021 the US government allocated $15 billion for lead pipe removal.

In 2010, the CDC and WHO identified numerous lead-contaminated villages in northern Nigeria. The grinding of ore to extract gold caused widespread leaded dust dissemination. It is likely that hundreds of children died because of this activity, and all remaining children in some of the villages assessed were lead poisoned, with 97% having a BLL ≥45 μg/dL, the threshold for chelation therapy in the United States. Unfortunately, such disasters continue to occur in Nigeria and neighboring countries from similar metal extraction activities.

SOURCES OF EXPOSURE

Lead poisoning may occur in utero because lead readily crosses the placenta from maternal blood. The spectrum of toxicity is similar to that experienced by children after birth. The source of maternal blood lead content is either redistribution from endogenous stores (i.e., the mother's skeleton) or lead newly acquired from ongoing environmental exposure.

Several hundred products contain lead, including paint, batteries, cable sheathing, cosmetics, mineral supplements, plastics, toys (Table 761.1), and traditional medicines (Table 761.2). Major sources of exposure vary among and within countries; the major source of exposure in the United States remains old lead-based paint. Approximately 34.6 million homes, mainly built before 1950, have lead-based paint (2021 estimate), of which the CDC has estimated that 22.3 million are in a hazardous state. As paint deteriorates, it chalks, flakes, and turns to dust. Improper rehabilitation work of painted surfaces (e.g., sanding) can result in dissemination of lead-containing dust throughout a home. The dust can coat all surfaces, including children's hands. All of these forms of lead can be ingested. If heat is used to strip paint, then lead vapor concentrations in the room can reach levels sufficient to cause lead poisoning via inhalation. There is an increased awareness that tap water in both homes and schools may have substantial amounts of lead. The latter arose from the discovery of contaminated water in most New York City public schools. Moreover, this occurrence raised questions about the safety of the US Environmental Protection Agency (EPA) lead-in-water-standard of 15 parts per billion (ppb; μg of Pb/L of water) that water distribution companies must meet in at least 90% of homes in their service areas. This standard was not based on achieving health safety but rather on what the water companies felt was financially feasible. After review, in 2021 the EPA recommended lowering the "trigger" level to 10 ppb. Breaching this value requires water companies to prepare an intervention plan should the level subsequently go over 15 ppb. It does not require action to reduce the amount of lead in that water supply. Even 10 ppb is still much greater than the 1 ppb recommended by the American Academy of Pediatrics as the limit for allowable lead in drinking water. It should be noted that the EPA lead in water standard does not apply to schools, although many states have set their own standards.

In other parts of the world, especially in poorer countries, additional sources can be found. These include contaminated neighborhoods as the result of car/truck battery lead recycling, aluminum cookware made with recycled metals, spices, and traditional medicines.

METABOLISM

The nonnutritive hand-to-mouth activity of young children is the most common pathway for lead to enter the body. In most cases, lead is ingested either as a component of dust licked off of surfaces or in swallowed paint chips, through water contaminated by its flow through lead pipes or brass fixtures, or from otherwise contaminated foods or liquids. Cutaneous contamination with inorganic lead compounds, such as those found in pigments, does not result in a substantial amount of absorption. Organic lead compounds, such as tetraethyl lead, may penetrate through skin; however, these are rarely encountered.

The percentage of lead absorbed from the gut depends on several factors: particle size, pH, other material in the gut, and nutritional status of

Table 761.1 Sources of Lead

Paint chips
Dust
Soil
Parent's or household contact's occupational exposure (auto repair, smelting, construction, remodeling, plumbing, gun/bullet (firing range) exposure, painting, e-scrap)
Glazed ceramics
Herbal remedies (e.g., Ayurvedic medications)
Home remedies, including antiperspirants, deodorants (litargirio)
Jewelry (toys or parents')
Stored battery casings or recycling (or living near a battery smelter)
Lead-based gasoline (in aviation fuel for propeller planes)
Moonshine alcohol
Mexican candies; Ecuadorian chocolates
Ceremonial spices
Indoor firing ranges
Retained bullet fragments
Imported spices (svanuri marili, zafron, kuzhambu)
Lead-based cosmetics (kohl, surma, kajal)
Lead plumbing (water)
Imported foods in lead-containing cans
Domestic foods (applesauce pouches, others)
Imported toys
Home renovations
Antique toys or furniture
Kratom

Table 761.2 Cases of Lead Encephalopathy Associated with Traditional Medicines by Type of Medication

TRADITIONAL MEDICAL SYSTEM	NO. (%) CASES OF LEAD ENCEPHALOPATHY	NO. (%) PEDIATRIC CASES WITHIN CAM SYSTEM OR MEDICATION
Ayurveda	5 (7)	1 (20)
Ghasard	1 (1)	1 (100)
Traditional Middle Eastern practices	66 (87)	66 (100)
Azarcon and Greta	2 (3)	2 (100)
Traditional Chinese medicine	2 (3)	2 (100)
Total	76 (100)	72 (95)

CAM, Complementary and alternative medicines.
From Karri SK, Saper RB, Kales SN. Lead encephalopathy due to traditional medicines. *Curr Drug Saf.* 2008;3:54–59.

essential elements. Large paint chips are difficult to digest and are mainly excreted; this chemical characteristic of lead compounds is fortunate, as a single chip may contain a potentially lethal dose of lead. Fine dust can be dissolved more readily, especially in an acid medium. Lead eaten on an empty stomach is better absorbed than that taken with a meal. The presence of **calcium** and **iron** may decrease lead absorption by direct competition for binding sites; iron (and probably calcium) deficiency results in enhanced lead absorption, retention, and toxicity.

After absorption, lead is disseminated throughout the body via blood. It circulates bound to erythrocytes; approximately 97–99% of lead in blood is bound on or in the red blood cells. The plasma fraction is too small to be measured by conventional techniques employing atomic absorption spectroscopy or anodic stripping voltammetry; it is presumably the plasma portion that may leave the blood compartment to enter cells and induce toxicity. Thus clinical laboratories report the BLL, not the serum or plasma lead level. The increasing availability and decreasing cost of inductively coupled plasma mass spectrometry, which is capable of measuring lead in ng/dL quantities, may eventually result in clinical availability of tools to measure plasma lead, a more proximal measure to where toxicity is actually occurring.

Most retained lead accumulates in bone, where it resides for years. But in all cells, lead has multiple effects. It binds to enzymes, particularly those with available sulfhydryl groups, changing the contour and diminishing function. For example, three of eight enzymes in the ubiquitously distributed heme pathway are susceptible to lead inhibitory effects. The accumulation of excess amounts of heme precursors is also toxic. The last enzyme in this pathway, ferrochelatase, enables protoporphyrin to chelate iron, thus forming heme. **Erythrocyte protoporphyrin (EP)** levels higher than 35 μg/dL (laboratory dependent) are abnormal and are consistent with lead poisoning, iron deficiency, or recent inflammatory disease. Measurement of the EP level is thus a useful tool for monitoring biochemical lead toxicity. EP levels begin to rise several weeks after BLLs have reached 20 μg/dL in a susceptible portion of the population and are elevated in nearly all children with BLLs higher than 50 μg/dL. A drop in EP levels also lags behind a decline in BLLs by several weeks because it depends on both cell turnover and cessation of further overproduction by marrow red blood cell precursors. The test can be ordered either as the free EP or the zinc protoporphyrin. Results are reported in μg/dL. When reported in μmol/mmol this likely indicates that the analysis has been standardized to a hematocrit of 45, an unwarranted assumption in young children.

A second mechanism of lead toxicity works via its competition with calcium. Many calcium-binding proteins have a higher affinity for lead than for calcium. Lead bound to these proteins may alter function, resulting in abnormal intracellular and intercellular signaling. Neurotransmitter release is, in part, a calcium-dependent process that is adversely affected by lead.

Although these two mechanisms of toxicity may be reversible, a third mechanism prevents the development of the normal tertiary brain structure. In immature mammals the normal neuronal pruning process that results in elimination of multiple intercellular brain connections is affected by lead. Failure to construct the appropriate tertiary brain structure during infancy and childhood may result in a permanent abnormality. In a longitudinal study of childhood lead poisoning, MRI examinations of the participants when in their 20s found smaller areas of brain in the prefrontal cortex and hippocampus regions, areas involved in decision-making and memory formation.

CLINICAL EFFECTS

The BLL is the best-studied measure of the lead burden in children. Although subclinical and clinical findings correlate with BLLs in populations, there is considerable interindividual variability in this relationship. **Lead encephalopathy** is more likely to be observed in children with BLLs higher than 100 μg/dL; however, one child with a BLL of 300 μg/dL may have no symptoms, whereas another with the same level may be comatose. Susceptibility may be associated with polymorphisms in genes coding for lead-binding proteins, such as Δ-aminolevulinic acid dehydratase, an enzyme in the heme pathway.

Several **subclinical effects** of lead have been demonstrated in cross-sectional epidemiologic studies. Hearing and height are inversely related to BLLs in children; in neither case, however, does the lead effect reach a level that would bring an individual child to medical attention. As BLLs increase in the study populations, more sound (at all frequencies) is needed to reach the hearing threshold. Children with higher BLLs are shorter than those with lower levels; for every 10 μg increase in the BLL, the children are 1 cm shorter. Chronic lead exposure also may delay puberty.

Several longitudinal studies have followed cohorts of children for decades after birth and examined the relationship between BLLs and cognitive test scores over time. In general, there is agreement that BLLs, expressed either as levels obtained concurrently with cognitive testing or as a measure that integrates multiple BLLs drawn from subjects over time, are inversely related to cognitive test scores. From these studies, no BLL above 0 μg/dL appears safe. On average, for each 1 μg/dL elevation in BLL, the cognitive score is approximately 0.25-0.50 points lower, though the relationship is not linear across the BLL spectrum.

Because the BLLs from early childhood are predictors of the cognitive test results performed years later, this finding implies that the effects of lead can be permanent.

The effect of in utero lead exposure is less clear. Scores on the Bayley Scale of Mental Development were obtained repeatedly every 6 months for the first 2 years of life in a cohort of infants born to middle-class families. Results correlated inversely with cord BLLs, a measure of in utero exposure. However, after 2 years of age, all other cognitive tests performed on the cohort over the next 10 years correlated with the BLLs at age 2 years but not with cord BLLs, indicating that the effects of prenatal lead exposure on brain function were superseded by early childhood events and later BLLs. Later studies, performed in cohorts of Mexican children monitored from the prenatal period, confirm the association between in utero lead exposure and later cognitive outcomes. In these studies, maternal plasma lead levels, obtained especially during the first trimester, were more strongly associated with cognitive scores in the offspring than with the traditionally measured maternal whole BLLs.

Behavior also is adversely affected by lead exposure. Hyperactivity is noted in young school-age children with histories of lead poisoning or with concurrent elevations in BLL. Older children with higher bone lead content are more likely to be aggressive and to have behaviors that are predictive of later juvenile delinquency. One report supports the concept of long-term effects of early lead exposure. In this longitudinal study, the mothers of a cohort were enrolled during their pregnancies. BLLs were obtained early in pregnancy, at birth, and then multiple times in the offspring during the first 6 years. The investigators report that the later relative rate of arrests, especially for violent crimes, increased significantly in relationship to the presence of these BLLs early in life. For every 5 μg/dL increase in BLL, the adjusted arrest rate was 1.40 for prenatal BLLs and 1.27 for 6-year BLLs. Epidemiologic data support the findings in this observational study. In an analysis that combined two national datasets, total annual leaded gasoline use (U.S. Geological Survey) and total reported violent criminal acts (U.S. Department of Justice), the amount of leaded gasoline used yearly was found to be strongly associated with violent criminal behavior with a lag time of 23 years; that is, early childhood exposure was followed two decades later by violent behavior rising and falling in close tandem. A similar association was found, this time between urban air lead levels and later violent crime, with a similar best-fit model employing a lag of approximately 22 years.

An intervention study, in which children with moderate lead poisoning and initial BLLs of 20-55 μg/dL were aggressively managed over 6 months, addressed the issue of the effects of treatment on cognitive development. Components of treatment included education regarding sources of lead and its abatement, nutritional guidance, multiple home and clinic visits, and for a subset, chelation therapy. Average BLLs declined, and cognitive scores were inversely related to the change in BLLs. For every 1 μg/dL fall in BLLs, cognitive scores were 0.25 point higher. A randomized placebo-controlled treatment study of 2-year-old children with initial BLLs of 20-44 μg/dL that employed the chelating agent succimer administered over 6 months found no difference in mean cognitive scores at age 4 years. However, as in the earlier treatment study, regression analysis did find an inverse relation between *change* scores; that is, a change in BLLs was associated with an inverse change in cognitive scores.

Whether the behavioral effects of lead are reversible is unclear. In one small, short-term study, 7-year-old hyperactive children with BLLs in the 20s were randomly allocated to receive a chelating agent (penicillamine), methylphenidate, or placebo. Teacher and parent ratings of behavior improved for the first two groups but not the placebo group. BLLs declined only in the chelated group. Two-year-old lead-poisoned children enrolled in a placebo-controlled trial of the chelating agent succimer showed no mean difference in behavior at 4 or 7 years of age. However, mean BLLs were also not different in the two groups at those ages.

These studies support the concept that early exposure to lead can result in long-term deficits in cognition and behavior; they also hold out the possibility that reductions in lead burden may be associated with improvement in cognitive test scores.

CLINICAL SYMPTOMS

Gastrointestinal symptoms of lead poisoning include anorexia, abdominal pain, vomiting, and constipation, often occurring and recurring over a period of weeks. Children with BLLs higher than 20 μg/dL are twice as likely to have gastrointestinal complaints as those with lower BLLs. **Central nervous system** symptoms are related to worsening cerebral edema and increased intracranial pressure. Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death are rarely seen at levels lower than 100 μg/dL but have been reported in children with a BLL as low as 70 μg/dL. The last-reported death directly attributable to lead toxicity in the United States was in 2006 in a child with a BLL of 180 μg/dL. There is no clear cutoff BLL value for the appearance of hyperactivity, but it is more likely to be observed in children who have levels higher than 20 μg/dL.

Other organs also may be affected by lead toxicity, but symptoms usually are not apparent in children. At high levels (>100 μg/dL), renal tubular dysfunction is observed. Lead may induce reversible Fanconi syndrome. In addition, at high BLLs, red blood cell survival is shortened, possibly contributing to a hemolytic anemia, although most cases of anemia in lead-poisoned children are a result of other factors, such as iron deficiency and hemoglobinopathies. Older patients may develop peripheral neuropathy leading to wrist drop and foot drop, as well as hypertension.

DIAGNOSIS

Screening

It is estimated that 99% of lead-poisoned children are identified by screening procedures rather than through clinical recognition of lead-related symptoms. Until 1997, universal screening by blood lead testing of all children at ages 12 and 24 months was the standard in the United States. Given the national decline in the prevalence of lead poisoning, the recommendations have been revised to target blood lead testing of high-risk populations. High risk is based on an evaluation of the likelihood of lead exposure. Departments of health are responsible for determining the local prevalence of lead poisoning, as well as the percentage of housing built before 1950, the period of peak leaded paint use. When this information is available, informed screening guidelines for practitioners can be issued. For instance, in New York State, where a large percentage of housing was built before 1950, the Department of Health mandates that all children be tested for lead poisoning via blood analyses. *In the absence of such data, the practitioner should continue to test all children at both 12 and 24 months*. In areas where the prevalence of lead poisoning and old housing is low, targeted screening may be performed on the basis of a risk assessment. Three questions form the basis of most published questionnaires (Table 761.3), and items that are pertinent to the locale or individual may be added. If there is a lead-based industry in the child's neighborhood, the child is a recent immigrant from a country that until recently still permitted the use of leaded gasoline, or the child has **pica** (pattern of eating non-food materials) or developmental delay, blood lead testing would be appropriate. All Medicaid-eligible children should be screened by blood lead testing. Venous sampling is preferred to capillary sampling because the chances of false-positive and false-negative results are less with the former. However, capillary screening can be performed rapidly in the office with a point of care (POC) instrument; use of such instruments in primary care offices substantially increases screening rates. Other screening guidelines vary by federal, state, and even local governmental agencies. Contacting your local Department of Health is one way to determine local primary care obligations.

The threshold for lead effects and the reference level for risk management purposes are not the same. Laboratory issues make the interpretation of values more difficult at low levels. Most labs achieve quality control of ±2 μg/dL for reports of BLL, but federal regulations allow laboratories that perform BLL testing to operate with an allowable error of ±4 μg/dL. A capillary screening value ≥3.5 μg/dL requires a venous sample for confirmation (Table 761.4). If the diagnostic (venous) test

Table 761.3 Minimum Personal Risk Questionnaire

1. Does the child live in or regularly visit a house that was built before 1950? (Include settings such as daycare, babysitter's, or relative's home.)
2. Does the child live in or regularly visit a house built before 1978 with recent (past 6 months) or ongoing renovations or remodeling?
3. Does the child have a sibling or playmate who has or did have lead poisoning?

From Screening young children for lead poisoning. Guidance for state and local public health officials. Atlanta: Centers for Disease Control and Prevention, 1997.

Table 761.4 Recommended Schedule for Obtaining a Confirmatory Venous Sample

BLOOD LEAD LEVEL (µg/dL)	TIME TO CONFIRMATION TESTING*
≥3.5-9	Within 3 mo
10-19	Within 1 mo
20-44	Within 2 wk
≥45	Within 48 hr

*The higher the blood lead level is on the initial screening capillary test, the more urgent it is to get a venous sample for confirmatory testing.
Courtesy Centers for Disease Control and Prevention, 2022. https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm#anchor_86654

confirms that the BLL is elevated, then further testing is required by the recommended schedule (Table 761.5). A confirmed venous BLL of 45 µg/dL or higher requires prompt chelation therapy.

Other Tools for Assessment

BLL determinations remain the gold standard for evaluating children because of ready availability and its correlation with health outcomes in populations. Techniques are available to measure lead in other tissues and body fluids. Experimentally, the method of x-ray fluorescence (XRF) allows direct and noninvasive assessment of bone lead stores. XRF methodology was used to evaluate a population that had long-term exposure to lead from a polluting battery-recycling factory. The study found that the school-age children had elevated lead levels in bone but not in venous blood, a finding that is consistent with our understanding of the slow turnover of lead in bone, which is measurable in years, in contrast to that in blood, which is measurable in weeks. It also indicates that children may have substantial lead in their bodies that is not detected by routine blood lead testing. This stored lead may be released to toxic levels if bone resorption rates suddenly increase, as occurs with prolonged immobilization of longer than a week and during pregnancy. Thus children with histories of elevated BLLs are potentially at risk for recrudescence of lead toxicity long after ingestion has stopped and may pass this lead to the next generation. XRF methodology is not available for clinical use in children.

Lead also can be measured in urine. Spontaneous excretion, even in children with high BLLs, is usually low. Lead excretion may be stimulated by treatment with chelating agents, and this property of these drugs forms the basis of their use as a component of lead treatment. It also has been used to develop a test that differentiates children with lead burdens responsive to chelation therapy, the **lead mobilization test**. In this test, a timed urine collection follows one or two doses of chelating agent, and the lead content is determined. However, this test is no longer recommended.

Lead in hair, nails, and saliva also is measurable but has problems of contamination and interpretability; thus these have no clinical utility. Radiographs of long bones may show dense bands at the metaphyses ("**lead lines**"), which may be difficult to distinguish from growth arrest

Table 761.5 Schedule for Follow-Up Blood Lead Testing

VENOUS BLOOD LEAD CONCENTRATIONS (µg/dL)	EARLY FOLLOW-UP TESTING (2-4 TESTS AFTER INITIAL TEST ABOVE SPECIFIC VENOUS BLLs)	LATER FOLLOW-UP TESTING AFTER BLL DECLINING
≥3.5-9	3 mo*	6-9 mo
10-19	1-3 mo*	3-6 mo
20-44	2 wk to 1 mo	1-3 mo
≥45	As soon as possible	As soon as possible

BLL, Blood lead level.
Courtesy Centers for Disease Control and Prevention, 2022. https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm



Fig. 761.1 Anteroposterior radiograph of the abdomen demonstrates retention of radiopaque lead-based paint chips within bowel, predominantly clustered in the ascending colon. Other etiologies resembling "paint chips" include certain medications, eggshells, other heavy metals including iron- and calcium-containing supplements. Dense "lead lines" are noted in the proximal femoral metaphyses. *(From Swenson DW, Walters MM. Musculoskeletal imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.50, p. 214.)*

lines but, if caused by lead, are indicative of months to years of exposure (Fig. 761.1). For children with acute symptoms, when a BLL result is not immediately available, a **kidneys-ureters-bladder (KUB) radiograph** may reveal **radiopaque flecks** in the intestinal tract, a finding that is consistent with recent ingestion of lead-containing plaster or paint chips (see Fig. 761.1). However, the absence of radiographic findings does not rule out lead poisoning.

Because BLLs reflect recent ingestion or redistribution from other tissues but do not necessarily correlate with the body burden of lead or lead toxicity in an individual child, tests of lead effects also may be useful. After several weeks of lead accumulation and a BLL higher than 20 µg/dL, increases in EP values to more than 35 µg/dL may occur. An elevated EP value that cannot be attributed to iron deficiency or recent inflammatory illness is both an indicator of lead effect and a useful means of assessing the success of the treatment; the EP level will begin to fall a few weeks after successful interventions that reduce lead ingestion and increase lead excretion. Because EP is light sensitive, whole blood samples should be covered in aluminum foil (or equivalent) until analyzed.

TREATMENT

All BLLs ≥3 μg/dL should be reported to state or local health departments. Once lead is in bone, it is released slowly and is difficult to remove even with chelating agents. Because the cognitive/behavioral effects of lead may be irreversible, the main effort in treating lead poisoning is to prevent it from occurring and to prevent further ingestion by already-poisoned children. The main components in the effort to eliminate lead poisoning are universally applicable to all children (and adults) and are as follows: (1) identification and elimination of environmental sources of lead exposure, (2) behavioral modification to reduce nonnutritive hand-to-mouth activity, and (3) dietary counseling to ensure sufficient intake of the essential elements calcium and iron and their supporting vitamins, D and C. For the small minority of children with more severe lead poisoning, drug treatment is available that enhances lead excretion. How effective these interventions may be at reducing BLLs or improving cognitive function remains unclear at the lower BLLs commonly observed currently in young children in the United States.

During health maintenance visits a limited risk assessment is warranted, which includes questions pertaining to the most common sources of lead exposure: the condition of old paint, secondary occupational exposure via an adult living in the home, and/or proximity to an industrial source of pollution. If such a source is identified, its elimination usually requires the assistance of public health and housing agencies as well as education for the parents. It would be safest for the family to move out of a lead-contaminated apartment until repairs are completed. During repairs, repeated washes of surfaces and the use of high-efficiency particle accumulator (HEPA) vacuum cleaners help reduce exposure to lead-containing dust. Careful selection of a contractor who is certified to perform lead abatement work is necessary. Sloppy work can cause dissemination of lead-containing dust and chips throughout a home or building and result in further elevation of a child's BLL. After the work is completed, dust wipe samples should be collected from floors and windowsills or wells to verify that the risk from lead has abated. The standards for what are considered acceptable lead dust levels have recently been modified by the EPA to lower limits that are more protective.

A single case of lead poisoning is often discovered in a household with multiple family members, including other young children, and even in a household with a common source of exposure such as peeling lead-based paint. The mere presence of lead in an environment does not produce lead poisoning. Parental efforts at reducing the hand-to-mouth activity of the affected child are necessary to reduce the risk of lead ingestion. Handwashing with soap and water effectively removes lead, but in a home with lead-containing dust, lead rapidly begins to reaccumulate on the child's hands after washing. Therefore handwashing is best limited to the period immediately before nutritive hand-to-mouth activity occurs.

Because there is competition between lead and essential metals, it is reasonable to promote a healthy diet that is sufficient in calcium and iron. The recommended daily intakes of these metals vary somewhat with age. In general, for children 1 year of age and up, a calcium intake of about 1 g/day is sufficient and convenient to remember (roughly the calcium content of a quart of milk [~1,200 mg/qt] or calcium-fortified orange juice). Calcium absorption is vitamin D dependent; milk is fortified with vitamin D, but other nutritional sources of calcium often are not. A multivitamin containing vitamin D may be prescribed for children who do not drink sufficient milk or who have inadequate sunlight exposure. Iron requirements also vary with age, ranging from 6 mg/day for infants to 12 mg/day for adolescents. For children identified biochemically as being iron deficient, therapeutic iron at a daily dose of up to 5-6 mg/kg/day for 3 months is appropriate. Iron absorption from vegetables is enhanced when iron is ingested with vitamin C (ascorbic acid), which is found in citrus juices. Giving additional calcium or iron above the recommended daily intake to mineral-sufficient children has not been shown to be of therapeutic benefit in the treatment of lead poisoning.

For children with BLLs of ≥20 μg/dL, an abdominal x-ray should be considered to check for lead-based paint chips or leaded foreign bodies, if not already obtained. If radiopaque fragments are visualized on imaging, bowel decontamination (typically with whole bowel irrigation) should be initiated (see Chapter 94).

Drug treatment to remove lead is lifesaving for children with lead encephalopathy. In nonencephalopathic children, it prevents symptom progression and further toxicity. Guidelines for **chelation** are based on the BLL. *A child with a venous BLL of 45 μg/dL or higher should be treated.* Four drugs have been used in the United States: 2,3-dimercaptosuccinic acid (DMSA [**succimer**]), $CaNa_2EDTA$ (versenate), British anti-lewisite (BAL [dimercaprol]), and penicillamine. DMSA and penicillamine can be given orally, whereas $CaNa_2EDTA$ and BAL can be administered only parenterally. The choice of agent is guided by the severity of the lead poisoning, the effectiveness of the drug, and the ease of administration (Table 761.6). Children with BLLs of 44-70 μg/dL may be treated with a single drug, preferably DMSA. Those with BLLs of 70 μg/dL or greater require two-drug treatment: $CaNa_2EDTA$ in combination with either DMSA or BAL for those without evidence of encephalopathy, or $CaNa_2EDTA$ and BAL for those with encephalopathy. Published data on the combined treatment with $CaNa_2EDTA$ and DMSA for children with BLLs higher than 100 μg/dL are very limited. However, anecdotal information derived from the treatment of hundreds of severely lead-poisoned children in northern Nigeria indicates that single-drug treatment with DMSA is lifesaving, although the degree of long-term residual damage in survivors has not been reported.

Drug-related toxicities are minor and reversible. These include gastrointestinal distress, transient elevations in transaminases, active urinary sediment, and neutropenia. These types of events are least common for $CaNa_2EDTA$ and DMSA, and more common for BAL and penicillamine. All of the drugs are effective in reducing BLLs when given in sufficient doses and for the prescribed time. These drugs also may increase lead absorption from the gut and should be administered to children in lead-free environments. Some authorities also recommend the administration of a cathartic immediately before or concomitant with the initiation of chelation to eliminate any lead already in the gut.

None of these agents removes all lead from the body. Within days to weeks after completion of a course of therapy, the BLL rises, even in the absence of new lead ingestion. The source of this rebound in the BLL is believed to be release from bone. Serial examinations of bone lead content have shown that chelation with $CaNa_2EDTA$ is associated with a decline in bone lead levels, but that residual bone lead remains detectable even after multiple courses of treatment.

Repeat chelation is indicated if the BLL rebounds to 45 μg/dL or higher. Children with initial BLLs higher than 70 μg/dL are likely to require more than one course. A minimum of 3 days between courses is recommended to prevent treatment-related toxicities, especially in the kidney.

The indication for chelation therapy for children with BLLs <45 μg/dL is less clear. Although use of these drugs in children with BLLs from 20-45 μg/dL will result in transiently lowered BLLs, and in some cases reversal of lead-induced enzyme inhibition, few such children increase their excretion of lead significantly during chelation, raising the question of whether any long-term benefit is achieved. A study of 2-year-old children with BLLs of 20-44 μg/dL who were randomized to receive either DMSA or placebo found that the drop in BLLs was greater in the first 6 months after enrollment in the DMSA-treated group, but the levels converged by 1 year of follow-up. Mean cognitive test scores obtained at 4 and 7 years of age were not statistically different between the groups. Chelation with DMSA (and $CaNa_2EDTA$) is not recommended for all children with BLLs <45 μg/dL. Further work needs to be done to determine whether there are subgroups of children with BLLs <45 μg/dL who might benefit from chelation. It also remains to be demonstrated whether other chelating agents available in the United States or elsewhere are effective at either substantially reducing body stores (bone) of lead or reversing the cognitive deficits attributable to lead at these BLLs.

Table 761.6 Chelators Used for Lead Poisoning

CHELATOR	DOSAGE	INDICATIONS	CONTRAINDICATIONS	ADVERSE EFFECTS
Succimer (DMSA)	1050 mg/m^2/day divided into 3 doses for 5 days, then 700 mg/m^2/day divided into 2 doses for 14 days (maximum 500 mg per dose for children)	BLL >45 µg/dL	None	Nausea, vomiting Diarrhea Metallic taste Transient increase in AST/ALT
$CaNa_2EDTA$	1,500 mg/mm^2/day continuous intravenous (IV) infusion for encephalopathy *Otherwise:* 1,000 mg/m^2/day divided in 2 to 4 doses for up to 5 days, IV or IM	BLL >70 µg/dL (starting after first dose of BAL or succimer) May substitute for succimer if that drug is not tolerated	Severe renal disease Hepatitis	Nephrotoxicity Transient increase in AST/ALT Arrythmia (bradycardia)
Dimercaprol (BAL)	4 mg/kg deep IM injection every 4 hours for 5 days in children and adults	BLL >70 µg/dL and encephalopathy Consider succimer as alternative	Peanut allergy Organic mercury poisoning Hepatic insufficiency	Pain at injection site Hypertension and tachycardia Nausea, vomiting Headache Fever (especially in children) Nephrotoxicity in the setting of an acidic urine
D-Penicillamine	1-1.5 g/day (children: 20-30 mg/kg/day), in 3 or 4 divided doses for 1-6 months To minimize adverse reactions, start at 250 mg/day (children: 10 mg/kg/day) and increase to 50% during week 2 and to a full dose by week 3 Maximum adult daily dose is 2 g	BLL of 45 to 69 µg/dL AND succimer not tolerated	Penicillin allergy	Leukopenia Thrombocytopenia Enuresis Abdominal pain Rashes

Note: Indications for chelation and dosing regimens may change. Consult with a medical toxicologist or regional poison center for the most up-to-date recommendations.
BAL, British antilewisite; BLL, blood lead level; $CaNa_2EDTA$, calcium disodium ethylenediaminetetraacetic acid; DMSA, 2,3-dimercaptosuccinic acid; IM, intramuscular; AST, alanine transaminase; ALT, aspartate transaminase.
Modified from Theobald JL, Mycyk MB. Iron and heavy metals. In: Walls RM, ed. *Rosen's Emergency Medicine*, 10th ed. Philadelphia: Elsevier; 2023: Table 146.5.

With successful intervention, BLLs decline, with the greatest fall in BLL occurring in the first 2 months after therapy is initiated. Subsequently, the rate of change in BLL declines slowly, so that by 6-12 months after identification, the BLL of the average child with moderate lead poisoning (BLL >20 µg/dL) will be 50% lower. Children with more markedly elevated BLLs may take years to reach the current CDC reference level, 3.5 µg/dL, even if all sources of lead exposure have been eliminated, behavior has been modified, and nutrition has been maximized. Early screening remains the best way of avoiding and therefore obviating the need for the treatment of lead poisoning.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 762 Nonbacterial Food Poisoning

762.1 Mushroom Poisoning

Diane P. Calello and Katherine Baranowski

Mushrooms are an ideal food. They are low in calories, fat free, and high in protein, making them a great source of nutrition. Unfortunately, some are highly toxic if ingested. Picking (foraging) and consumption of wild mushrooms are increasingly popular in the United States. This rise in popularity has led to increased reports of severe and fatal mushroom poisonings.

The clinical syndromes produced by mushroom poisoning are divided according to the rapidity of onset of symptoms and the predominant system involved (Table 762.1). The symptoms are caused by the principal toxin present in the ingested mushrooms. The eight major toxins produced by mushrooms are categorized as cyclopeptide *(amatoxin and phallotoxin),* gyromitrin, muscarine, coprine, ibotenic acid and muscimol, psilocybin, orellanine, and gastrointestinal tract–specific irritants. The edible wild mushroom *Tricholoma equestre* is associated with delayed rhabdomyolysis, and *Clitocybe amoenolens* and *Clitocybe acromelalga* have been reported to cause erythromelalgia, although toxins responsible for these effects are unknown.

Symptoms after eating mushrooms may not be the direct effect of a toxin but may be an allergic reaction or a toxic effect of pesticides or other contaminants. In addition, all who ate the same mushroom may not become sick, or if they do, they may become sick at different intervals. Table 762.2 lists general principles of management. Wherever possible, identification of the implicated mushroom is encouraged via mycologist or regional Poison Control Center.

GASTROINTESTINAL

Rapid Onset

Many mushrooms from various genera (such as *Chlorophyllum* species) produce local gastrointestinal manifestations. The causative toxins are diverse and largely unknown. Within 1 hour of ingestion, patients experience acute abdominal pain, nausea, vomiting, and diarrhea. Symptoms may last hours to days, depending on the species of mushroom.

Treatment is mainly supportive. Children with large fluid losses may require parenteral fluid therapy. It is imperative to differentiate ingestion of mushrooms of this class from ingestion of *Amanita* and

Table 762.1 Summary of Common Mushroom-Associated Syndromes

TOXIN	SYNDROME	CLINICAL COURSE	TYPICAL CAUSATIVE MUSHROOM(S)
Cyclopeptides, principally amatoxins	Delayed gastroenteritis followed by hepatic failure	*Stage 1:* 6-24 hr after ingestion: onset of nausea, vomiting, profuse cholera-like diarrhea, abdominal pain, hematuria *Stage 2:* 12-48 hr after ingestion: apparent recovery; levels of hepatic enzymes are rising during this stage *Stage 3:* 24-72 hr after ingestion: progressive hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, death	"Deadly *Amanitas*," *(A. phalloides, A. bisporigera)* *Galerina* species
General gastrointestinal irritants	Early gastroenteritis, may be severe	30 min to 2 hr after ingestion: nausea, vomiting, abdominal cramping, diarrhea; may recover without treatment	*Chlorophyllum molybdites*, backyard mushrooms ("little brown mushrooms"), many others
Gyromitrin	Delayed gastroenteritis with central nervous system toxicity, seizures	6-24 hr after ingestion: nausea, vomiting, diarrhea, abdominal pain, muscle cramps, delirium, convulsions, coma; hemolysis, and methemoglobinemia may occur	*Gyromitra esculenta* ("false morel")
Orellanine	Delayed onset gastroenteritis and renal failure	Abdominal pain, anorexia, vomiting starting over 30 hr after ingestion, followed by progressive renal failure 3-14 days later	*Cortinarius* species
Muscarine	Cholinergic syndrome	30 min to 2 hr after ingestion: bradycardia, bronchorrhea, bronchospasm, salivation, perspiration, lacrimation, convulsions, coma	*Clitocybe* species, *Inocybe* species, *Boletus* species, some *Amanita* species
Coprine	Disulfiram-like reaction with ethanol	30 min after drinking ethanol (may occur up to 1 week after eating coprine-containing mushrooms): flushing of skin of face and trunk, hypotension, tachycardia, chest pain, dyspnea, nausea, vomiting, extreme apprehension	*Coprinus atramentarius*
Ibotenic acid and muscimol	Hyperactivity, delirium, coma	30 min to 2 hours after ingestion: delirium, hallucinations, and coma	*Amanita muscaria, Amanita pantherina*
Psilocybin	Hallucinations	30 min to 3 hr after ingestion: hallucinations, euphoria, drowsiness, compulsive behavior, agitation	*Psilocybe* species

Modified from Brent J, Palmer RB: Mushrooms. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: WB Saunders; 2007: Table 23-1.

Table 762.2 General Management of Mushroom Ingestion

1. Determine history of ingestion: how many types of mushrooms ingested, what time, if anyone else ate them, and what symptoms are present.
2. Attempt to determine which of the possible syndromes (see Table 762.1) the patient may have. For example, gastrointestinal symptoms occurring more than 6 hr after ingestion strongly suggest cyclopeptide, gyromitrin, or *Cortinarius* poisoning.
3. Administer activated charcoal. If the patient has diarrhea, do not give a cathartic. If a cathartic is used, give it only with the first dose of activated charcoal. Use repeated doses of activated charcoal for suspected amatoxin poisonings.
4. If feasible and when indicated, send gastric aspirate or emesis, along with any remaining mushrooms, to a mycologist for identification.
5. Try to perform a preliminary identification of mushroom and spores. Start to develop a spore print as soon as possible.
6. Maintain supportive measures, including airway support, intravenous fluids, and vasopressors (if needed). Monitor volume status.
7. Avoid antispasmodics for gastrointestinal symptoms.
8. Anticipate the clinical course.

From Brent J, Palmer RB: Mushrooms. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: WB Saunders; 2007: Box 23.1.

Galerina species containing cyclopeptide toxins, which present with symptoms after 6 hours of ingestion.

Delayed Onset

Cyclopeptide (Amatoxin) Poisoning

Poisonings by species of *Amanita* (death cap mushroom) and *Galerina* account for 95% of the fatalities from mushroom intoxication; the mortality rate for this group is 5–10%. Most species produce two classes of **cyclopeptide toxins:** (1) **phallotoxins,** which are heptapeptides believed to be responsible for the early symptoms of *Amanita* poisoning, and (2) **amatoxins,** octapeptides that inhibit nuclear RNA polymerase II and subsequent production of messenger RNA leading to impaired protein synthesis and cell death. Cells with high turnover rates, such as those in the gastrointestinal mucosa, kidneys, and liver, are the most severely affected. Other suggested toxin effects are induction of apoptosis, glutathione depletion in the liver, and oxygen free radical formation. Acute yellow atrophy of the liver and necrosis of the proximal renal tubules are found in lethal cases.

The clinical course of poisoning with *Amanita* or *Galerina* species is biphasic. Nausea, vomiting, and severe abdominal pain ensue 6-24 hours after ingestion. Profuse watery diarrhea follows shortly thereafter and may last for 12-24 hours or longer. During this time, patients become severely dehydrated. From 24 to 48 hours

after poisoning, jaundice, hypertransaminasemia (peaking at 72-96 hours), renal failure, and coma occur. Death occurs 4-7 days after the ingestion. A prothrombin time less than 10% of control is a poor prognostic factor. Of note, there are species of Amanita mushrooms that may present with earlier onset of symptoms and confound diagnosis, such as *Amanita smithiana,* which grows in the Pacific Northwest.

Treatment

Treatment for *Amanita* poisoning is both supportive and specific. Fluid loss from severe diarrhea during the early course of the illness is profound, requiring aggressive correction of fluid loss, electrolytes, and acid-base disturbances. In the late phase of the disease, management of renal and hepatic failure is also necessary.

Specific therapy for *Amanita* poisoning is designed to remove the toxin rapidly and to block binding at its target site. Oral activated charcoal is recommended as part of the initial treatment for children with *Amanita* poisoning. For significant ingestions, intravenous silibinin or intravenous penicillin G may be considered after discussion with a toxicologist or Poison Control Center. Silibinin and penicillin G inhibit binding of both toxins, interrupt enterohepatic recirculation of amatoxin, and protect the liver from further injury, although their effectiveness is controversial. *N*-acetylcysteine should be given for hepatoprotective effect. Hemodialysis or hemoperfusion may be beneficial in removing toxin. Orthotopic liver transplantation may be required for children with severe hepatic failure.

Gyromitrin Poisoning

Species of *Gyromitra* contain **gyromitrin,** which decomposes in the stomach to form **monomethylhydrazine** (CH_3NHNH_2) and inhibits central nervous system (CNS) enzymatic production of γ-aminobutyric acid (GABA). Monomethylhydrazine also oxidizes iron in hemoglobin, resulting in methemoglobinemia. Children with *Gyromitra* poisoning often experience vomiting, diarrhea, and abdominal pain within 6-24 hours of ingestion of the toxin. CNS symptoms such as vertigo, diplopia, headache, ataxia, and seizures develop later in the clinical course. Hemolysis and methemoglobinemia (see Chapter 511.6) are rare but potential life-threatening complications of gyromitrin poisoning.

Treatment

Hypovolemia from gastrointestinal fluid losses and seizures require supportive intervention. **Pyridoxal phosphate,** the coenzyme that catalyzes the production of GABA, can reverse the effects of monomethylhydrazine when administered in high doses. Pyridoxine hydrochloride (25 mg/kg infused over 30 minutes) is given at a frequency that is dependent on clinical improvement. Diazepam is given for persistent seizures. Parenteral administration of methylene blue is indicated if the methemoglobin concentration exceeds 30%. Blood transfusions may be required for significant hemolysis.

RENAL

Orellanine Poisoning

Species of *Cortinarius* mushrooms contain the heat-stable toxin bipyridyl **orellanine,** which causes severe nonglomerular renal injury characterized by interstitial fibrosis and acute tubular necrosis. Although the exact mechanism of injury is not fully understood, a metabolite of orellanine is thought to inhibit renal protein synthesis. *Cortinarius* poisoning is characterized by delayed onset of nausea, vomiting, and diarrhea that manifest 36-48 hours after ingestion. Although the initial symptoms may be trivial, more serious renal toxicity occurs in several days. Acute renal failure occurs in 30–50% of those affected, beginning with polyuria and progressing to renal failure (see Chapter 572).

Treatment

Treatment for orellanine poisoning is supportive. Early presentation, within 4-6 hours after ingestion, can be treated with activated charcoal and gastric lavage. Hemodialysis may be needed in patients suffering from renal failure. Most patients recover within 1 month, but chronic renal insufficiency develops in one third to one half of patients who subsequently require renal transplantation.

AUTONOMIC NERVOUS SYSTEM

Muscarine Poisoning

Mushrooms of the genera *Inocybe* and, to a lesser degree, *Clitocybe* contain **muscarine** or muscarine-related compounds. These quaternary ammonium derivatives bind to postsynaptic receptors, producing an exaggerated cholinergic response.

The onset of symptoms is rapid (30 minutes to 2 hours after consumption), and intoxication is characterized by symptoms of cholinergic excess: diaphoresis, excessive lacrimation, salivation, miosis, bradycardia, hypotension, urinary and fecal incontinence, and vomiting. Respiratory distress caused by bronchospasm and increased bronchopulmonary secretions is the most serious complication. The symptoms subside spontaneously within 6-24 hours.

Treatment

Atropine sulfate, the specific antidote, is administered intravenously (0.01 mg/kg; maximum: 2 mg). This is repeated until the pulmonary symptoms resolve or the patient becomes overtly tachycardic.

Coprine Poisoning

Coprinus atramentarius and *Clitocybe clavipes* contain **coprine.** Like disulfiram (Antabuse; Odyssey Pharmaceuticals, Inc.), coprine inhibits the metabolism of acetaldehyde after ethanol ingestion. The clinical manifestations result from accumulation of acetaldehyde.

Coprine intoxication becomes apparent after ethanol ingestion and may be delayed up to 5 days after consumption of the mushroom. Hyperemia of the face and trunk, tingling of the hands, metallic taste, tachycardia, and vomiting occur acutely. Hypotension may result from intense peripheral vasodilation.

The syndrome typically is self-limited and lasts only several hours. No specific antidote is available. If hypotension is severe, vascular reexpansion with isotonic parenteral solutions may be required.

CENTRAL NERVOUS SYSTEM

Ibotenic acid and Muscimol Poisoning

Although *Amanita muscaria* and *Amanita pantherina* may contain muscarine, the toxins responsible for the CNS symptoms after ingestion of these mushrooms are primarily **muscimol** and **ibotenic acid,** the heat-stable derivatives of the isoxazoles. Muscimol, a hallucinogen, and ibotenic acid, an insecticide, act as GABA agonists. From 30 minutes to 3 hours after ingestion, CNS symptoms appear: obtundation, alternating lethargy and agitation, and occasionally seizures. Nausea and vomiting are uncommon. If large amounts of muscarine are contained in the mushroom, symptoms of cholinergic crisis also may occur.

Specific therapy must be carefully selected, and in most cases supportive care will suffice. If an exaggerated cholinergic response is observed, atropine should be administered. Conversely, because ingestions of *A. muscaria* or *A. pantherina* may cause anticholinergic findings, the acetylcholinesterase inhibitor physostigmine can be used to reverse the delirium and coma. Benzodiazepines also are used for the agitation and delirium. Seizures can be controlled with diazepam. In the majority of patients, however, early supportive care and close observation are all that is required.

Psilocybin Intoxication

Mushrooms belonging to the genus *Psilocybe* ("magic mushrooms") contain **psilocybin and psilocin,** two psychotropic compounds. Within 30 minutes after ingestion, patients experience euphoria and hallucinations, often accompanied by tachycardia and mydriasis. Fever and seizures have also been observed in children with psilocybin poisoning. These symptoms are short-lived, usually lasting for 6 hours after consumption of the mushroom. Treatment consists of rest and observation in a quiet environment. Severely agitated patients may respond to diazepam.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

762.2 Solanine Poisoning

Katherine Baranowski and Diane P. Calello

Solanine is an alkaloid found in plants of the nightshade family (Solanaceae), specifically tomatoes, eggplant, paprika and pepper-based spices, and most significantly, white potatoes. The majority of solanine poisoning reported has arisen from the ingestion of greened potatoes. When exposed to light and allowed to turn green and/or sprout, potatoes produce several alkaloid glycosides containing the cholesterol derivative *solanidine*. Two of these glycosides, α-solanine and α-chaconine, are found in highest concentration in the peels and sprouts. Some solanine can be removed by boiling but not by baking. The major effect of α-solanine and α-chaconine is the reversible inhibition of cholinesterase. Cardiotoxic and teratogenic effects have also been reported.

Clinical manifestations of solanine and chaconine poisoning occur within 7-19 hours after ingestion. The most common symptoms are vomiting, abdominal pain, and diarrhea; in more severe instances of poisoning, neurologic symptoms, including drowsiness, apathy, confusion, weakness, and vision disturbances, are rarely followed by coma or death.

Treatment of solanine poisoning is largely supportive. In the most severe cases, symptoms resolve within 1-2 weeks.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for a Bibliography.

762.3 Seafood Poisoning

Diane P. Calello and Katherine Baranowski

CIGUATERA FISH POISONING

The most frequently reported seafood toxin illness in the world is ciguatera fish poisoning. Grouper is the most commonly identified source of the toxin, followed by snapper, kingfish, amberjack, dolphin, eel, and barracuda. Poisoning has also been associated with farm-raised salmon.

The dinoflagellate ***Gambierdiscus toxicus,*** a microscopic unicellular organism found along coral reefs, produces high concentrations of **ciguatoxin** and **maitotoxin.** The toxins are passed along the food chain from small herbivorous fish that consume the dinoflagellate to larger predatory fish and then to humans. These toxins are harmless in fish but produce distinct clinical symptoms in humans.

Ciguatoxins are odorless, colorless, and tasteless and are not destroyed by cooking or freezing. Ciguatoxins increase the sodium ion permeability of excitable membranes and depolarize nerve cells, actions that are inhibited by calcium and tetrodotoxin.

Between 2 and 30 hours after ingestion, ciguatera fish poisoning typically produces a biphasic illness. The initial symptoms are nonspecific and are of gastrointestinal origin (diarrhea, vomiting, nausea, and abdominal pain). The second phase occurs within a few days of ingestion and consists of intense itching, anxiety, myalgias, painful intercourse, feeling of loose teeth, and rash on palms and soles; the neurologic symptoms of **circumoral dysesthesias** and **cold allodynia** (reversal of hot and cold sensation) are characteristic of this disease and may last for months. Tachycardia, bradycardia, hypotension, and death occur very infrequently. Eating fish organs, roe, or viscera is associated with greater symptom severity. The diagnosis of ciguatera fish poisoning is based on clinical presentation and a compatible epidemiologic history; the diagnosis is confirmed by testing the ingested fish for toxin. There is no human biomarker to confirm ciguatera fish poisoning.

Treatment

Treatment of ciguatera fish poisoning is supportive. Intravenous fluids may be required for severe diarrhea, and careful observation for hypovolemic shock is advised. Once adequate hydration is established, mannitol (0.5-1.0 g/kg intravenously over 30-45 minutes), given within 48-72 hours of the toxic fish ingestion, is recommended for reduction of acute symptoms (especially neurologic symptoms) and possible prevention of chronic neurologic symptoms. Various other medications and herbal remedies have been tried, with variable results. Most cases are self-limited with a favorable prognosis.

SCOMBROID (PSEUDOALLERGIC) FISH POISONING

Ingestion of members of the **Scombridae** families, including albacore, mackerel, tuna, bonito, and kingfish, have been linked to major outbreaks of pseudoallergic fish poisoning. Non-scombroid fish such as mahi-mahi (dolphin fish), swordfish, and bluefish also are associated with poisoning.

The bacterial transformation of histidine to histamine is responsible for the clinical syndrome. Histidine is found in high concentrations in the flesh of scombroid fish; if refrigeration is inadequate, the action of bacterial decarboxylases during putrefaction converts histidine to histamine. Fish containing more than 20 mg of histamine per 100 g of flesh are toxic. In patients receiving isoniazid, a potent histaminase blocker, ingestion of fish flesh containing a lower concentration of histamine may be toxic.

The onset of clinical manifestations is acute and occurs within 10 minutes to 2 hours of ingestion. The most common symptoms and signs are diarrhea, erythema, sweating, flushing, diaphoresis, urticaria, nausea, and headache (Fig. 762.1). Abdominal pain, tachycardia, oral burning or numbness, dizziness, respiratory distress, hives, and facial swelling also occur. The illness is usually self-limited, terminating within 8-24 hours.

Treatment

Treatment is mainly supportive. With severe diarrhea, fluid replacement may be necessary. Antihistamines and antiemetics have been variably successful.

PARALYTIC SHELLFISH POISONING

Mussels, clams, oysters, scallops, and other filter-feeding mollusks may become contaminated during dinoflagellate blooms or **"red tides."** During periods of contamination, water in coastal areas can be colored red by the algae; this sign is the origin of the term *red tide*. (Such discoloration does not necessarily indicate the presence of toxin, and toxin may be present in high quantities without discoloration. Nonetheless, discolored water should be regarded with suspicion.) The dinoflagellates *Alexandrium* spp. and *Gymnodinium catenatum* often are responsible for these red tides and contain several potent neurotoxins. Paralytic shellfish poisoning is a distinctive neurologic illness caused by 20 closely related heat-stable paralytic shellfish toxins, generally referred to as **saxitoxins.** These compounds prevent nerve conduction by inhibiting the sodium-potassium pump. Consumption of bivalves, such as mussels, scallops, and clams, is the usual pathway of intoxication, although crustaceans and fish have been implicated as well.

The onset of clinical manifestations of paralytic shellfish poisoning occurs rapidly, 30 minutes to 2 hours after ingestion. Abdominal pain and nausea are common. Paresthesias are common and occur circumorally or in a stocking-glove distribution, or both. Perioral numbness or tingling, diplopia, ataxia, dysarthria, and the sensation of floating are seen less commonly. In severe cases, respiratory failure from diaphragmatic paralysis may result. Swimming in the water during a red tide episode does not appear to have neurologic sequelae, although skin or mucosal irritation may result.

Treatment

No antidote for paralytic shellfish poisoning is known. Supportive care, including mechanical ventilation, may be needed. Although the symptoms are usually self-limited and short-lived, weakness and malaise may persist for weeks after ingestion.

NEUROTOXIC SHELLFISH POISONING

Neurotoxic shellfish poisoning is a rare disease that occurs after consumption of molluscan shellfish contaminated with brevetoxins. Shellfish harvested along the Gulf of Mexico during or right after a red tide are at risk of contamination with brevetoxins produced by the

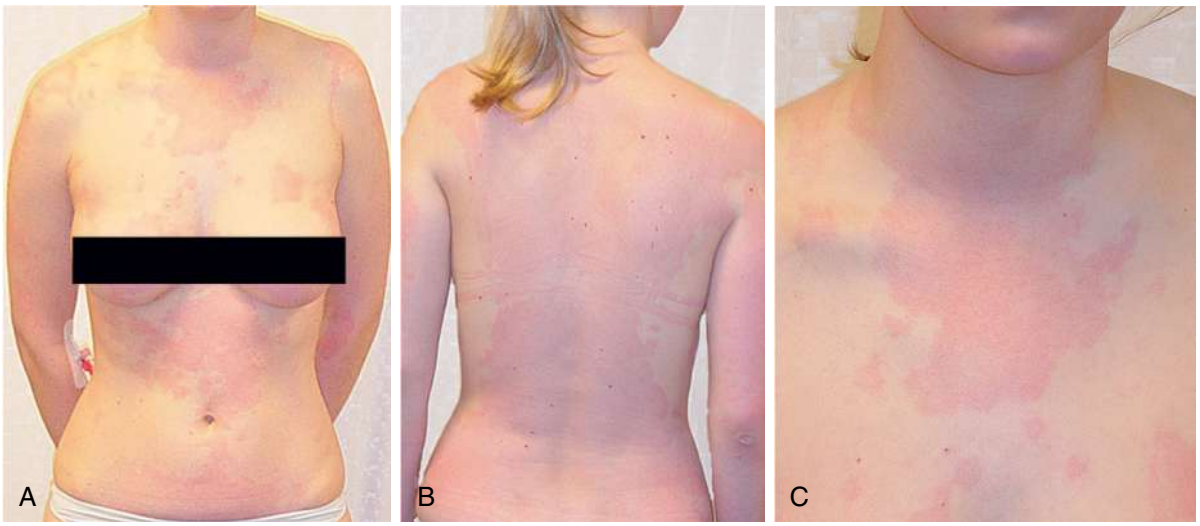

Fig. 762.1 Scombroid fish poisoning. A and B, Widespread erythematous rash predominantly on the face (not shown) and trunk of patient 1. C, Close-up view of the upper chest area. Note the absence of wheals. *(Modified from Jantschitsch C, Kinaciyan T, Manafi M, et al. Severe scombroid fish poisoning: an underrecognized dermatologic emergency. J Am Acad Dermatol. 2011;65[1]:246–247. Fig. 1.)*

dinoflagellate *Karenia brevis;* some raphidophytes (*Chattonella* spp.) also produce brevetoxins. **Brevetoxins** are a group of more than 10 lipid-soluble neurotoxins that activate sodium ion channels, causing nerve membrane depolarization. Shellfish are not affected by brevetoxins. Rinsing, cleaning, cooking, and freezing do not destroy the toxins, which also cannot be detected by taste or smell.

The onset of clinical manifestations of neurotoxic shellfish poisoning occurs from within a few minutes up to 18 hours after consumption. Most symptoms are gastrointestinal (nausea, vomiting, and diarrhea) or neurologic (numbness and tingling of the lips, mouth, face, and extremities, ataxia, partial limb paralysis, reversal of hot and cold sensation, slurred speech, headache, and fatigue). Neurotoxic shellfish poisoning is similar to a mild case of paralytic shellfish poisoning.

Treatment

There are no specific antidotes for brevetoxins. Treatment involves mostly supportive care. Brevenal, a natural antagonist of brevetoxin produced by *K. brevis,* may be used as a form of treatment in the future.

DIARRHETIC SHELLFISH POISONING

Several outbreaks of diarrhetic shellfish poisoning have been reported in Europe after consumption of mussels, cockles, and other shellfish. The dinoflagellates *Dinophysis* and *Prorocentrum* produce **okadaic acid** and its derivatives, the **dinophysistoxins.** These compounds inhibit protein phosphatases. The intracellular accumulation of phosphorylated proteins causes increased fluid secretion by gut cells via calcium influx, which is mediated by cyclic adenosine monophosphate and prostaglandins.

Patients have severe diarrhea. Care is supportive and directed at rehydration. The illness is self-limited, and recovery occurs in 3-4 days; few patients require hospitalization.

AMNESIC SHELLFISH POISONING

Amnesic shellfish poisoning has been identified after consumption of shellfish from the United States, Spain, and the United Kingdom. The responsible toxin, **domoic acid,** comes from a diatom, *Pseudonitzschia multiseries,* and is a potent glutamate agonist, disrupting neurochemical transmission in the brain. It also binds to glutamate receptors, which increase calcium influx, producing neuronal swelling in the hippocampal area of the brain and death.

The initial clinical manifestations are gastrointestinal with nausea, vomiting, diarrhea, and abdominal cramps within 24 hours of ingestion. Neurologic symptoms may follow including headache, confusion, and short-term memory loss. Memory loss is closely related to advanced age with those >50 years more likely to suffer from memory loss lasting months to years.

PUFFERFISH POISONING

The consumption of pufferfish (blowfish) in certain geographic areas such as Japan and the Indo-Pacific Ocean is associated with a lethal neurotoxic illness due to **tetrodotoxin**. Fugu, a Japanese delicacy, is sought after in part because of the subtle neurotoxic effects experienced upon eating, including perioral paresthesias and a dissociative feeling. While a trained fugu chef will remove the most toxic parts of the fish, the toxin is still found in varying degrees.

Tetrodotoxin, which is also found in the blue-ringed octopus, causes a paralytic illness due to the blockade of voltage-dependent sodium channels. Early symptoms include paresthesias, nausea, and dizziness, which progresses to weakness, numbness, and incoordination. Autonomic compromise may also occur with bradycardia and hypotension. In the most severe of cases, respiratory compromise requires assisted ventilation.

There is no specific antidote for tetrodotoxin pufferfish poisoning.

AZASPIRACID POISONING

The azaspiracids are a class of algal toxins associated with **harmful algal blooms (HABs).** Azaspiracid poisoning results from ingestion of contaminated bivalve shellfish, especially mussels. Azaspiracid toxins are distributed throughout the muscle tissue in the shellfish. Azaspiracid is cytotoxic to cells and an inhibitor of Ca^{2+} channels in plasma membranes. Symptoms start 6-18 hours after ingestion and include nausea, vomiting, severe stomach cramps, and diarrhea, which often persist up to 5 days.

Cyanobacteria (blue-green algae) also produce HABs; exposure is usually during recreational water sports and may be cutaneous or gastrointestinal. Symptoms include rash, cough, abdominal pain, diarrhea, nausea, emesis, muscle aches, watery eyes, weakness, or sore throat.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

762.4 Melamine Poisoning

Katherine Baranowski and Diane P. Calello

Melamine (1,3,5-triazine-2,4,6-triamine, or $C_3H_6N_6$) is found in many plastics, adhesives, laminated products, cement, cleansers, fire retardant paint, and more. Melamine poisoning from food products was unheard of until 2007, when melamine-tainted pet food caused the death of many dogs and cats in the United States. In 2008, feeding of melamine-tainted infant formula to more than 300,000 children resulted in urolithiasis and resultant kidney injuries, 50,000 hospitalizations, and 6 deaths in China. This was the first reported epidemic of melamine-tainted milk products.

Melamine contains 66% nitrogen by mass. The illegal addition of melamine to infant formula can give the formula a milky appearance and falsely raise the protein content as measured by nitrogen testing. Melamine, combined with cyanuric acid, forms cyanurate crystals in the kidneys. Along with protein, uric acid, and phosphate, melamine forms renal calculi. The melamine stones and gravel can be treated with hydration, alkalinization, or lithotripsy. Acute renal failure requires supportive care and dialysis if needed.

Clinical manifestations are initially subtle and nonspecific. The severity is dose related. The first symptoms in affected infants are unexplained crying (especially when urinating), vomiting, and discolored urine caused by the formation of stones and gravel in the urinary tract. Urinary obstruction and acute renal failure follow. In the absence of a specific diagnosis, death from renal failure may occur. Whether children with melamine-induced renal failure will have chronic renal sequelae is currently unknown.

In addition to the more well-known renal toxicity, cognitive defects can be seen after acute, chronic, or prenatal exposure. Dissolved and insoluble melamine and its insoluble metabolites all have the potential to cause neurotoxicity.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 763

Biological and Chemical Terrorism

*Theodore J. Cieslak, Jonathan Newmark, and Mark G. Kortepeter**

In April of 2017, an attack on the town of Khan Shaykhun in Syria employed a poisonous "nerve agent" (likely sarin) that resulted in the deaths of at least 92 civilians, many of them young children. The attack intentionally targeted civilian neighborhoods at the time children were getting ready for school, which is strong evidence that its purpose was terror, not warfare. Terrorist actions targeting children are not novel. Brought to the forefront of American consciousness by Timothy McVeigh's references to child fatalities as "collateral damage" during the Oklahoma City bombing in April 1995, the intentional targeting of children became a global reality with the attack upon a school in Beslan, Russia, in September 2004. The attack, which left 334 dead (including 186 children), presaged additional attacks specifically directed against children. School shootings have become an all too frequent occurrence in the United States with over 175 children dying from mass shootings on school grounds since 1999.

Paralleling the targeting of children is an apparent trend toward the use of "unconventional" weapons of terror. In 1984, members of the Rajneeshee cult employed *Salmonella typhi* in a wave of intentional poisonings that affected 751 persons, including 142 teenage patrons of a popular pizza parlor. In 1995, the Aum Shinrikyo cult killed 12 and sickened thousands by intentionally releasing sarin nerve agent in the Tokyo subway system. A disgruntled scientist allegedly deployed anthrax spores via the U.S. mail in October 2001, killing 5 and injuring 17 in an attack upon a nation already reeling in the wake of the 9/11 attacks. Conflicts in Afghanistan, Syria, and Iraq from 2012 to 2016 led to another spike in chemical attacks.

These developments remind us that terrorists can strike at any time, utilizing any number of unconventional weapons, including biologic and chemical agents. Children will not be spared in these attacks on civilians, and indeed schools and daycare sites may be the targets of these actions.

ETIOLOGY

Although terrorists may choose to use **weapons of opportunity,** agents that are readily available to some member of the terrorist group, the motives of terrorists often are obscure and difficult to predict. Prevention and response strategies should thus concentrate not on those agents most likely to be used but, rather, on those agents that, if used, would constitute the gravest potential threats to public health and security.

Biologic threat agents, including pathogens and toxins, have been divided by the Centers for Disease Control and Prevention (CDC) into three categories, with **category A** including diseases caused by those six agents posing the greatest threat: anthrax, plague (see Chapter 249.3), tularemia (see Chapter 252), smallpox, botulism (see Chapter 256), and the viral hemorrhagic fevers, including Ebola (see Chapter 317).

Terrorists could also procure and release a vast array of potentially harmful chemicals. The Chemical Threat Risk Assessment prepared by the U.S. Department of Homeland Security lists over 170 chemical compounds as potential threats in accidental or deliberate scenarios. Tank cars full of flammable industrial gases and liquids, corrosive industrial acids and bases, poisonous compounds such as cyanides and nitrites, pesticides, dioxins, and explosives traverse our railways and roads daily. Four classes of "military-grade" chemicals with a history of use in warfare or manufactured specifically for use as weapons include the organophosphate-based nerve agents, vesicants, cyanides (misleadingly referred to as "blood agents"), and certain pulmonary irritants or "choking agents."

EPIDEMIOLOGY AND PEDIATRIC-SPECIFIC CONCERNS

Large-scale attacks on civilian targets will likely involve pediatric victims. Children may be more susceptible than adults to the effects of certain biologic and chemical agents (see Chapter 759). A thinner and less-keratinized epidermis makes dermally active agents, such as mustard or trichothecene mycotoxins, a greater risk to children than to adults. A larger surface area per unit volume further increases the problem. A small relative blood volume makes children more susceptible to the volume losses associated with enteric infections such as cholera and to gastrointestinal intoxications such as might be seen with exposure to the staphylococcal enterotoxins. The high minute ventilation of children, compared with that of adults, increases the threat of agents delivered via the inhalational route. The fact that children live "closer to the ground" compounds this effect when heavier-than-air chemicals are involved.

*The views expressed herein are those of the authors and do not necessarily reflect the position of the University of Nebraska, the U.S. Department of Defense, Health and Human Services, and Veterans' Affairs, or their component entities.

An immature blood-brain barrier may heighten the risk of central nervous system toxicity from nerve agents. Developmental considerations make it less likely that a child would readily flee an area of danger, thereby increasing exposure to these various adverse effects. Moreover, children are more likely to be terrified at the sight of responders in personal protective ensembles.

Children appear to have a unique susceptibility to certain agents that might be used by terrorists. Although adults generally suffer only a brief, self-limited incapacitating illness after infection with Venezuelan equine encephalitis virus, young children are more likely to experience seizures, permanent neurologic sequelae, and death. In the case of smallpox, waning herd immunity may disproportionately affect children. Vaccine-induced immunity to smallpox diminishes significantly after 3-10 years. Although most adults are considered susceptible to smallpox given that routine civilian immunization ceased in the early 1970s, older adults may have some residual protection from death, if not from the development of disease. Today's children are among the first to grow up in a world without any individual or herd immunity to smallpox.

Children also may experience unique disease manifestations not seen in adults. Suppurative parotitis is a common characteristic finding among children with melioidosis but is not generally seen in adults with *Burkholderia pseudomallei* infection (see Chapter 251.2). Seizures, often the presenting symptom of cyanide or nerve agent poisoning, may be much more difficult to recognize clinically in children than in adults, more likely presenting as unresponsiveness or change in mental status than tonic-clonic episodes.

Pediatricians are likely to experience unique problems in managing childhood victims of a biologic or chemical attack. Many of the drugs useful in treating such casualties are unfamiliar to pediatricians or have relative contraindications in childhood. The fluoroquinolones and tetracyclines are commonly cited as agents of choice in the treatment and prophylaxis of anthrax, plague, tularemia, brucellosis, and Q fever. Both drug classes are often avoided in children, although the risk of morbidity and mortality from diseases induced by agents of bioterrorism far outweighs the minor risk associated with short-term use of these agents. Ciprofloxacin received, as its first licensed pediatric indication, approval from the FDA for use in the prophylaxis of anthrax after inhalational exposure during a terrorist attack; doxycycline and levofloxacin are licensed specifically in children for the same indication. Levofloxacin is also licensed for postexposure prophylaxis of children against plague, and moxifloxacin is considered an acceptable alternative to first-line therapies for the treatment of plague in those less than 18 years of age. Immunizations potentially useful in preventing biologic agent–induced diseases are often not approved for use in pediatric patients. The available anthrax vaccine is licensed only for those between 18 and 65 years. The plague vaccine, currently out of production and probably ineffective against inhalational exposures, was approved only for individuals ages 18-61 years. The live replicating smallpox vaccine (ACAM2000), a live vaccine employing vaccinia virus, can cause fetal demise when given to pregnant women. A nonreplicating smallpox (and mpox) vaccine (Jynneos) was introduced in 2019.

Many otherwise useful pharmaceutical agents are not available in pediatric dosing regimens. The military distributes nerve agent antidote kits consisting of prefilled autoinjectors designed for the rapid administration of atropine and pralidoxime. Many emergency departments and some ambulances stock these kits. The doses of agents contained in the nerve agent antidote kit are calculated for soldiers and thus are inappropriate for young children, and pediatric pralidoxime autoinjectors are not yet available. Atropine autoinjectors specifically formulated for children are approved by the FDA, although their availability is limited. Unfortunately, there is no pediatric combination autoinjector containing atropine and pralidoxime, the backbone of acute nerve agent treatment in adults. Moreover, children smaller than 7 kg (15 pounds) are too small for safe use of atropine autoinjectors, while obtaining venous access may be time-consuming and extremely difficult in a contaminated environment.

Although physical protective measures and devices (e.g., "gas masks") are likely to be of little utility in a civilian terrorism setting, such commercially available devices are not often available in pediatric sizes. The Israeli experience during the first Gulf War suggests that frightened parents may improperly use such masks on their children, resulting in inadvertent suffocation.

In the event of a large-scale terrorist attack, there may be an insufficient number of pediatric hospital beds. In any large disaster, excess bed capacity might potentially be provided at civilian and veterans hospitals under the auspices of the National Disaster Medical System. Although that system now specifically tracks pediatric beds, none of these would be found in the Veterans Administration system and few are likely to exist elsewhere. The situation is even more dire regarding burn unit beds, which may be needed in an attack with vesicants such as sulfur mustard.

CLINICAL MANIFESTATIONS

Should a terrorist attack occur, clinicians may be called on to make prompt diagnoses and render rapid lifesaving treatments before the results of confirmatory diagnostic tests are available. Although each potential agent of terrorism produces its own unique clinical manifestations, it is useful for the frontline clinician to consider their effects in terms of a limited number of distinct clinical syndromes. This approach helps clinicians make prompt, rational decisions regarding empirical therapy. Casualties resulting from a terrorist attack would either experience symptoms immediately upon exposure to an agent (or within the first several hours after exposure) or would see their symptoms develop slowly over a period of days to weeks. In the former case, the sinister nature of the event is often obvious and the etiology more likely to be conventional or chemical in nature.

Biologic agents differ from conventional, chemical (see Chapter 759), and nuclear (see Chapter 758) weapons in that they have inherent incubation periods. Consequently, patients are likely to present distant in time and place from the point of an unannounced and unnoticed exposure to a biologic agent. Whereas traditional first responders, such as firefighters and paramedics, may be at the forefront of a conventional or chemical terrorism response, the primary care physician or emergency room is likely to constitute the first line of defense against the effects of a biologic agent.

Casualties can thus be categorized as either immediate or delayed in presentation. Within each of these categories, patients can be further classified as having primarily respiratory, neuromuscular, or dermatologic manifestations (Table 763.1). A limited number of agents may cause each particular syndrome, permitting institution of empiric therapy targeted at a short list of potential etiologies. The viral hemorrhagic fevers might manifest as fever and a bleeding diathesis; these agents are considered separately in Chapter 317. In most cases, supportive care is the mainstay of hemorrhagic fever treatment, although two drugs (Inmazeb, Ebanga) have recently been licensed for the treatment of adults and children with Ebola.

Sudden-Onset Neuromuscular Syndrome: Nerve Agents

The very rapid onset of neuromuscular symptoms after an exposure should lead the clinician to consider nerve agent intoxication. The nerve agents (*tabun, sarin, soman, and VX)* are **organophosphate** analogs of common pesticides that act as potent inhibitors of the enzyme acetylcholinesterase. The so-called "Novichok" agents, used in deliberate attacks upon Russian targets in Salisbury, UK (2018) and Tomsk, Russia (2020), also belong to this agent class. The nerve agents are hazardous via ingestion, inhalation, or cutaneous absorption (see Chapter 94).

The inhibition of cholinesterase by these compounds results in the accumulation of acetylcholine at neural and neuromuscular junctions, causing excess stimulation. The resultant **cholinergic**

Table 763.1 Diseases Caused by Agents of Chemical and Biologic Terrorism, Classified by Syndrome

	NEUROMUSCULAR SYMPTOMS PROMINENT	RESPIRATORY SYMPTOMS PROMINENT	DERMATOLOGIC FINDINGS PROMINENT
Sudden-onset or intermediate-onset	Nerve agents	Chlorine Phosgene Cyanide	Mustard Lewisite
Delayed-onset	Botulism	Anthrax Plague Tularemia Ricin	Smallpox

syndrome involves central, nicotinic, and muscarinic effects. Central effects are both muscarinically and nicotinically mediated and include altered mental status progressing rapidly to lethargy and coma, as well as ataxia, convulsions, and central respiratory depression. Studies on pesticide exposure suggest that children may be more prone to central neurologic dysfunction with organophosphate toxicity than adults. The most lethal effects are respiratory, which result not only from central effects but also from direct paralysis of the diaphragm and other respiratory muscles (nicotinic effects), as well as bronchospasm and bronchorrhea (muscarinic effects). Nicotinic effects include muscle fasciculations and twitching, followed by weakness, which can progress to flaccid paralysis as muscles fatigue. Importantly, flaccid paralysis is not present initially, as in a patient with botulinum toxin poisoning. In botulinum toxin poisoning, neurotransmitter cannot be released from the presynaptic terminal, whereas in nerve agent poisoning, excess neurotransmitter accumulates because acetylcholinesterase, the enzyme that turns off the transmitter, is inhibited. Muscarinic effects include miosis (the clinical hallmark of a patient who has suffered a non–life-threatening nerve agent challenge), visual blurring, profuse lacrimation, and watery rhinorrhea. Bronchospasm and increased bronchial secretions lead to cough, wheezing, dyspnea, and cyanosis. Cardiovascular manifestations include bradycardia, hypotension, and atrioventricular block. Flushing, sweating, salivation, nausea, vomiting, diarrhea, abdominal cramps, and urinary incontinence are also seen. In the absence of prompt intervention, death can quickly result from a combination of central effects and respiratory muscle paralysis.

The classic neuromuscular syndrome of extremely acute symptoms most commonly results from an aerosol or vapor exposure, the most likely route in a terrorist attack. But nerve agents are liquids at standard temperature and pressure and do not cause immediate irritation to skin. Liquid nerve agent may thus pass through the skin and enter the systemic circulation, causing cholinergic crisis. This can be delayed by minutes to hours, depending upon dose and body site. In children, because the stratum corneum of the skin forms only gradually, skin transit time will be reduced. Miosis may be a late development. *If the clinician suspects that the child may have been exposed to nerve agent via the cutaneous route, they should immediately treat, even if miosis has not yet developed.*

Cyanide poisoning is a major differential diagnosis of nerve agent poisoning in an attack scenario. Cyanide poisons cytochrome a3 in the mitochondrial electron transport chain and can cause an almost immediate and rather similar syndrome of loss of consciousness, immediate rapid breathing, status epilepticus, and rapid progression to cardiac arrest. Important clinical differential points include miosis, which is usually absent in cyanide poisoning, and the usual lack of cyanosis (ironically) due to the tissues' inability to use oxygen from the blood, causing venous blood to retain oxygen and remain red. In an emergency, it may be necessary to treat for both nerve agent and cyanide poisoning until the cause is definitively identified.

Delayed-Onset Neuromuscular Syndrome: Botulism

The delayed onset (hours to days after exposure) of neuromuscular symptoms is characteristic of botulism. Botulism, an intoxication rather than an infection, occurs after exposure to one of eight related neurotoxins produced by certain strains of *Clostridium botulinum,* a strictly anaerobic, spore-forming, gram-positive bacillus commonly found in soil. Naturally occurring botulism (see Chapter 256) usually follows ingestion of preformed toxin (food poisoning) or results from intestinal toxin production (infantile botulism). An aerosol exposure to the toxin would likely result in a case of clinical botulism indistinguishable from that caused by natural exposures.

Following exposure to botulinum toxin, clinical manifestations typically begin with bulbar palsies, causing patients to complain of ptosis, photophobia, and blurred vision resulting from difficulty in accommodation. Symptoms can progress to include dysarthria, dysphonia, dysphagia, and finally, a descending symmetric paralysis. Sensation and sensorium are typically not affected. In the absence of intervention, death often results from respiratory muscle failure. The mechanism of action of botulinum toxin is, in many ways, the opposite of that of nerve agent intoxication. Seizures, loss of consciousness, and peripheral twitching and fasciculations, typical of nerve agent poisoning, are not seen in botulism.

Sudden-Onset Respiratory Syndrome: Chlorine, Phosgene, and Cyanide

The acute onset of respiratory symptoms shortly after exposure should prompt the clinician to consider a range of potential chemical agents. Of note, nerve agents, discussed previously, may affect respiration via massive bronchial hypersecretion, bronchospasm, and respiratory muscle paresis. However, the nerve agent casualty will likely have generalized muscle involvement and central nervous system manifestations. In contrast, the toxic inhalants chlorine and phosgene produce respiratory distress without neuromuscular involvement or other features of cholinergic crisis. Several other pulmonary toxicants may produce similar clinical toxidromes.

Chlorine is a dense, acrid, yellow-green gas that is heavier than air. After mild to moderate exposure, ocular and nasal irritation occurs, followed by cough, a choking sensation, bronchospasm, and substernal chest tightness. Pulmonary edema, mediated by hydrochloric acid and free oxygen radical generation, follows moderate to severe exposures within 30 minutes to several hours. Hypoxemia and hypovolemia secondary to noncardiogenic pulmonary edema are the factors responsible for death.

Phosgene, like chlorine, is a common industrial compound that was used as a weapon on the battlefields of World War I. Its odor has been described as similar to "new-mown hay." Like chlorine, phosgene exposure also is thought to result in the generation of hydrochloric acid, contributing particularly to upper airway, nasal, and conjunctival irritation. Acylation reactions caused by the effects of phosgene on the pulmonary alveolar-capillary membrane lead to pulmonary edema. Phosgene lung injury also may be mediated, in part, by an inflammatory reaction associated with leukotriene production. Patients with mild to moderate exposures to phosgene

may be asymptomatic, a fact that may cause victims to remain in a contaminated area. Noncardiogenic pulmonary edema or "dry land drowning" occurs 4-24 hours after exposure and is dose dependent, with heavier exposures causing earlier symptoms. Dyspnea may precede radiologic findings. In severe exposures, pulmonary edema may be so marked as to result in hypovolemia and hypotension. As in the case of chlorine, death results from hypoxemia and asphyxia.

Cyanide, by contrast, is a cellular poison capable of causing protean clinical manifestations, not a pulmonary toxicant. Initially, cyanide toxicity is most likely to manifest as tachypnea and hyperpnea, progressing rapidly to apnea in cases with significant exposure (see Chapter 94). The efficacy of cyanide as a chemical terrorism agent is limited by its volatility in open air and relatively low lethality compared with nerve agents. Released in a closed room, however, cyanide could have devastating effects, as evidenced by its use in the Nazi gas chambers during World War II. Cyanide inhibits cytochrome a3, interfering with normal mitochondrial oxidative metabolism and leading to cellular anoxia and lactic acidosis. In addition to respiratory distress, early findings among cyanide victims include tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. With greater exposure, seizures, coma, apnea, and cardiac arrest may follow within minutes. An elevated anion gap metabolic acidosis is typically present and decreased peripheral oxygen utilization leads to an elevated mixed venous oxygen saturation value.

Delayed-Onset Respiratory Syndrome: Anthrax, Plague, Tularemia, and Ricin

A delayed onset of respiratory symptoms (days after exposure) is characteristic of several infectious diseases and at least one toxin that might be adapted for sinister purposes by terrorists. Among the most threatening and problematic of these are anthrax, plague, tularemia, and ricin.

Anthrax is caused by infection with the gram-positive spore-forming rod *Bacillus anthracis*. Its ability to form a spore enables the anthrax bacillus to survive for long periods in the environment and enhances its potential as a weapon.

The vast majority of naturally occurring anthrax cases are cutaneous, acquired by close contact with the hides, wool, bone, and other by-products of infected ruminants (principally cattle, sheep, and goats). Cutaneous anthrax is amenable to therapy with a variety of antibiotics and is readily recognizable to experienced clinicians in endemic areas; consequently, it is rarely fatal. Although it is common in parts of Asia and sub-Saharan Africa, only two cases of cutaneous anthrax had occurred in the United States in the 9 years that preceded the attacks of 2001 (when 11 cutaneous cases were seen). Gastrointestinal anthrax has been described only once in the United States, in a drum circle participant whose drum heads were made from imported animal hides. In general, however, it occurs after the ingestion of contaminated meat. In the past, inhalational anthrax, or **woolsorters' disease,** was an occupational hazard of abattoir and textile workers. Now eliminated as a naturally occurring disease in the United States, it is this inhalational form of anthrax that poses the greatest terror threat. Following an inadvertent release in 1979 from a bioweapons facility at Sverdlovsk in the former Soviet Union, 66 of 77 (86%) known adult victims of inhalational anthrax died. In the 2001 attacks involving contaminated mail in the United States, 5 of 11 (46%) patients with inhalational anthrax died. Whether better intensive care modalities, changes in antibiotic therapy, or earlier recognition accounted for this improved mortality rate remains unknown.

Symptomatic *inhalational* anthrax typically begins 1-6 days after exposure, although incubation periods of up to several weeks have been reported. The disease begins as a flulike illness, characterized by fever, myalgia, headache, and cough. A brief intervening period of improvement sometimes follows, but rapid deterioration then ensues; high fever, dyspnea, cyanosis, and shock mark this second phase. Hemorrhagic meningitis occurs in up to 50% of cases. Chest radiographs obtained late in the course of illness may reveal a widened mediastinum or prominent mediastinal lymphadenopathy; pleural effusions also may be seen. Bacteremia is often so profound that Gram stains of peripheral blood may demonstrate the organism at this stage. Prompt treatment is imperative. Death occurs in as many as 95% of inhalational anthrax cases if such treatment is begun more than 48 hours after the onset of symptoms.

Whereas inhalational anthrax is a disease primarily of mediastinal lymphatic tissue, exposure to aerosolized plague bacilli typically leads to a primary pneumonia. Endemic **plague** is usually transmitted via the bites of fleas and is discussed in Chapter 249.3. The causative organism of all forms of human plague, *Yersinia pestis,* is a bipolar-staining, gram-negative facultative intracellular bacillus. An ability to survive within the macrophage aids its dissemination to distant sites following inoculation or inhalation. "Buboes," markedly swollen, exquisitely tender regional lymph nodes in the distribution of a bite, are the hallmark feature of bubonic plague. Fever and malaise are typically present, and septicemia often develops as bacteria gain access to the circulation. Petechiae, purpura, and overwhelming disseminated intravascular coagulopathy commonly occur, and 80% of bubonic plague victims ultimately have positive blood cultures. Plague is extremely lethal, as illustrated by the fact that the "Black Death" eliminated one-third of the population of Europe during the Middle Ages.

Intentional aerosol dissemination of *Y. pestis* would likely result in a preponderance of pneumonic plague cases. Pneumonic plague may also arise secondarily after seeding of the lungs of septicemic patients. Symptoms include fever, chills, malaise, headache, and cough. Chest radiographs may reveal a patchy consolidation, and the classic clinical finding is blood-streaked sputum. Disseminated intravascular coagulation and overwhelming sepsis typically develop as the disease progresses. Untreated pneumonic plague has a fatality rate approaching 100%.

Tularemia is a highly infectious disease caused by the gram-negative coccobacillus *Francisella tularensis.* Naturally occurring tularemia is discussed in Chapter 252. The high degree of infectivity of *F. tularensis* (<10 organisms are thought to be necessary to produce infection via inhalation), as well as its survivability in the environment, contributes to its inclusion on the CDC's list of Category A agents. Several clinical forms of endemic tularemia are known, but inhalational exposure resulting from a terrorist attack would likely lead to a plaguelike primary pneumonia or to typhoidal tularemia, manifesting as a variety of nonspecific symptoms, including fever, malaise, and abdominal pain.

Ricin is a protein toxin derived from the castor bean plant *(Ricinus communis)* that inhibits ribosomal protein synthesis. It is highly toxic in animal studies when inhaled and may result in the delayed onset of respiratory distress, pulmonary edema, and acute respiratory failure. If injected, it may cause a sepsis-like syndrome that may progress to multiorgan system failure; ingestion can lead to severe gastroenteritis. Ricin-containing letters were mailed to a U.S. Senate office building in 2004, to President Obama and New York City Mayor Bloomberg in 2013, and to President Trump in 2020, although no persons were sickened in any of the attacks.

Intermediate-Onset Dermatologic Syndrome: Mustard and Lewisite

The development of skin lesions within hours to days of exposure is characteristic of the chemical vesicants. These compounds, often referred to as **blistering agents**, are cellular poisons and include the alkylating agent mustard and the organic arsenical agent lewisite. Injury to rapidly reproducing cells begins within minutes of contact with these agents. Clinical effects typically become evident several hours after exposure to mustard, whereas patients exposed to lewisite feel immediate pain. Both mustard and lewisite affect the eyes and respiratory tract, and their inadvertent ingestion may produce significant gastrointestinal symptoms. Mustard exposure may lead, several days later, to bone marrow suppression. With

a large inhalational challenge, mustard may also cause an acute respiratory syndrome, particularly affecting the upper airway and presenting with laryngospasm and stridor.

Delayed-Onset Dermatologic Syndrome: Smallpox

The appearance of an exanthem days to weeks after exposure is likely to be a presenting feature of smallpox. Caused by infection with variola virus, a member of the *Orthopoxvirus* family, smallpox has an incubation period of 7-17 days. This would likely permit the wide dispersal of asymptomatic exposed persons, thus contributing to the spread of an outbreak. During the incubation period, the virus replicates in the upper respiratory tract. A primary viremia ensues, during which time seeding of the liver and spleen occurs. A secondary viremia then develops, the skin is seeded, and the classic exanthem of smallpox appears.

Symptoms of smallpox begin abruptly during the phase of secondary viremia and include fever, rigors, vomiting, headache, backache, and extreme malaise. Within 2-4 days, macules appear on the face and extremities and then progress in synchronous fashion to papules, pustules, and finally scabs. As the scabs separate, survivors often are left with disfiguring, depigmented scars. The synchronous nature of the rash and its centrifugal distribution distinguish smallpox from chickenpox, which has a centripetal distribution. Historically, smallpox had a 30% mortality rate, with death typically resulting from visceral organ involvement.

DIAGNOSIS

In some cases, the terrorist nature of a chemical or biologic attack may be obvious; for example, a chemical attack in which victims succumb in close temporal and geographic proximity to a dispersal device or when terrorists announce their attack. In other instances, the clinician may need to rely on epidemiologic clues to suspect an intentional release of chemical or biologic agents. The presence of large numbers of victims clustered in time and space should raise the index of suspicion, as should cases of unexpected death or unexpectedly severe disease. Diseases unusual in a given locale, in a given age group, or during a certain season likewise may warrant further investigation. Simultaneous outbreaks of a disease in noncontiguous areas should cause one to consider an intentional release (as in the 2001 mail-borne anthrax attacks), as should outbreaks of multiple diseases in the same area. Even a single case of a rare disorder such as anthrax or certain viral hemorrhagic fevers would be suspicious, and a single case of smallpox would almost certainly be the result of an intentional dissemination. Large numbers of dying animals might provide evidence of an unnatural aerosol release, as would evidence of disparate attack rates between those known to be indoors and outdoors at a given time.

In a mass casualty setting, diagnoses may be made largely on clinical grounds. The diagnosis of nerve agent intoxication is based primarily on clinical recognition and patient response to antidotal therapy. Several simple rapid detection devices developed for military use can detect the presence of nerve agents in the environment. Some of these are now commercially available and are stocked in certain emergency departments and public safety vehicles. Measurements of acetylcholinesterase in plasma or erythrocytes of nerve agent victims may be helpful in long-term prognostication, but the correlation between cholinesterase levels and clinical effects is often poor, and the test is rarely available on an emergency basis.

Botulism should be suspected clinically among patients presenting with a symmetric, descending, flaccid paralysis. Although the differential diagnosis of botulism includes other uncommon neurologic disorders, such as myasthenia gravis and the Guillain-Barré syndrome, the presence of multiple casualties with similar symptoms should aid in the determination of a botulism outbreak. Electromyography is useful in supporting the diagnosis.

Initially the diagnosis of cyanide poisoning also will likely be made on clinical grounds in the presence of the appropriate toxidrome. An unusually high anion gap metabolic acidosis with elevated serum lactate and an oxygen concentration greater than expected in mixed venous blood lend support to the clinical diagnosis. Elevated blood cyanide concentrations can confirm the clinical suspicion.

Of all the chemical and biological agents, the only ones for which immediate therapy without waiting for definitive diagnosis is potentially lifesaving and mandatory are nerve agents and cyanide poisoning. If these are suspected, they should be treated before waiting for further diagnostic certainty.

Anthrax should be suspected upon finding gram-positive bacilli in skin biopsy material (in the case of cutaneous disease), blood smears, pleural fluid, or spinal fluid. Chest radiographs demonstrating a widened mediastinum in the context of fever and constitutional signs and, in the absence of another obvious explanation (e.g., blunt trauma or postsurgical infection), should also lead one to consider the diagnosis. Confirmation can be obtained by blood culture.

A diagnosis of plague can be suspected on finding bipolar "safety-pin"–staining bacilli in Gram or Wayson stains of sputum or aspirated lymph node material; confirmation is obtained by culturing *Y. pestis* from blood, sputum, or lymph node aspirate. The organism grows on standard blood or MacConkey TRA agars, but it is often misidentified by automated systems. *F. tularensis,* the causative agent of tularemia, grows poorly on standard media; its growth is enhanced on media containing cysteine. Because of its extreme infectivity, however, many laboratories prefer to make a diagnosis via polymerase chain reaction or serologically using an enzyme-linked immunosorbent assay or serum agglutination assay.

Smallpox should be suspected on clinical grounds and can be confirmed by culture or electron microscopy of scabs or vesicular fluid, although the manipulation of clinical material from suspected smallpox victims should be attempted only at public health laboratories able to employ maximum biocontainment (Biosafety Level 4) precautions. Similar caution should be exercised with specimens from patients with various viral hemorrhagic fevers.

PREVENTION

Preventive measures can be considered in both a preexposure and a postexposure context. **Preexposure protection** against a chemical or biologic attack may consist of physical, chemical, or immunologic measures. **Physical protection** against primary attack often involves gas masks and protective suits; such equipment is used by the military and by certain hazardous materials response teams, but it is unlikely to be available to civilians at the precise moment that a release occurs. Medical personnel need to understand the principles of physical protection as they apply to infection control and the spread of contamination.

Pneumonic plague is spread through respiratory droplets. Droplet precautions, including the use of simple surgical masks, are thus warranted for providers caring for patients with plague. Smallpox is transmitted by droplet nuclei. Airborne precautions, including (ideally) a high-efficiency particulate air filter mask, are thus warranted with smallpox victims. Patients with certain viral hemorrhagic fevers, such as those caused by filoviruses (Ebola, Marburg) and arenaviruses, should be managed using a combination of droplet and contact precautions, ideally in a specialized biocontainment unit. Most other biologic agent victims can be safely cared for with the use of standard precautions. In the case of chemical agents, residual mustard or nerve agent on the skin or clothing of victims might potentially pose a hazard to medical personnel. For such victims, whenever possible, clothing should be removed, and the patients decontaminated using copious amounts of water before extensive medical care is rendered. Most other chemical agents are volatile enough that spread of an agent among patients or from patient to caregiver is unlikely.

Preexposure chemical prophylaxis might be used on the basis of credible intelligence reports. Should officials deem that the threatened release of a specific biologic agent appears imminent, antibiotics might be distributed to a population before exposure. Opportunities to employ such a strategy are likely to be limited, although federal and state officials are examining various mechanisms for such employment. In military settings, pyridostigmine is FDA-approved as pretreatment against expected nerve agent attack. It is not approved for use in children, and it is not likely to be recommended in civilian settings.

Although licensed vaccines **(preexposure immunologic measures)** against anthrax and smallpox have been developed, widespread use of either vaccine is likely to be problematic, especially in children. The anthrax vaccine is licensed only for those persons age 18 years and older, is given as a five-dose series over 18 months, and requires annual booster doses. These considerations make civilian employment of the current anthrax vaccine on a large scale unlikely, although recombinant anthrax vaccines requiring fewer doses are in development.

Significant obstacles to the widespread employment of smallpox vaccine also exist, although public health officials have contemplated the resumption of a smallpox vaccination campaign. Whereas in the past, the live replicating smallpox vaccine (prepared from vaccinia virus, an *Orthopoxvirus* related to variola) was used safely and successfully in young infants, it has a relatively high rate of serious complications in certain patients. *Fetal vaccinia* and demise can occur when pregnant women are vaccinated. *Vaccinia gangrenosa*, an often fatal complication, can occur when immunocompromised persons are vaccinated. *Eczema vaccinatum* occurs in those with preexisting dermatoses (atopic dermatitis). Severe vaccine-related encephalitis was well known during the era of widespread vaccination; because it occurs only in primary vaccines, it would disproportionately affect pediatric patients. Autoinoculation can occur when the virus present at the site of vaccination is manually transferred to other areas of skin or to the eye. Young children would presumably be at greater risk for such inadvertent transmission. Myocarditis has been reported following vaccinations of military recruits. A new nonreplicating vaccine may alleviate some of these concerns.

To manage complications associated with use of the replicating vaccine, vaccinia immune globulin should be available when one is undertaking a vaccination campaign. Vaccinia immune globulin (6000 U/kg intravenously) may be given to vaccine recipients who experience severe complications or to significantly immunocompromised individuals exposed to smallpox and in whom vaccination would be unsafe. In 2018, tecovirimat was approved by the FDA for the treatment of persons (including children) experiencing severe complications from vaccine. Vaccine, as well as vaccinia immune globulin and tecovirimat, can be obtained as needed upon consultation with officials at the CDC. In addition to a potential role in preexposure prophylaxis, vaccination may be effective in postexposure prophylaxis if given within the first 4 days after exposure.

Anthrax vaccine might similarly be employed in a postexposure setting. Some authorities recommend three doses of this vaccine as an adjunct to postexposure chemoprophylaxis after documented exposure to aerosolized anthrax spores. Nonetheless, postexposure administration of oral antibiotics constitutes the mainstay of management for asymptomatic victims believed to have been exposed to anthrax as well as to other bacterial agents such as plague and tularemia. Table 763.2 lists appropriate prophylactic regimens for various biologic exposures.

TREATMENT

Although Tables 763.2, 763.3, and 763.4 provide recommended therapies for overt diseases caused by various chemical and biologic agents, it is likely that the clinician attending to victims will need to make therapeutic decisions before the results of confirmatory diagnostic tests are available and in situations in which the diagnosis is not known with certainty. In particular, decontamination by hospital personnel in appropriate personal protective equipment is required for patients exposed to chemical agents who have not been adequately decontaminated in the prehospital setting (see Table 763.4). In such cases, it is useful to note that many diseases and symptoms caused by chemical and biologic agents will resolve with supportive care. Most cases of chlorine or phosgene exposure can be successfully managed by providing meticulous attention to oxygenation and fluid balance. Mustard victims may require intensive multisystem support, but no specific antidote or therapy is available. Many viral diseases, including most viral hemorrhagic fevers, as well as equine encephalitides, are also managed supportively.

In addition to ensuring adequate oxygenation, ventilation, and hydration, the clinician may need to provide specific empiric therapies on an urgent basis. Patients suffering from the sudden onset of severe neuromuscular symptoms may have nerve agent intoxication and should be given atropine (0.05-0.1 mg/kg) promptly for its antimuscarinic effects. Although atropine relieves bronchospasm and bradycardia, reduces bronchial secretions, and ameliorates the gastrointestinal effects of nausea, vomiting, and diarrhea, it does not improve skeletal muscle paralysis. 2-Pralidoxime chloride (*2-PAM*) cleaves the organophosphate moiety from cholinesterase and regenerates intact enzyme if "aging" has not occurred. The effect is most prominent at the neuromuscular junction and leads to improved muscle strength. Its prompt use (at a dose of 25-50 mg/kg) as an adjunct to atropine is recommended in all serious cases.

Ideally, both atropine and pralidoxime should be administered intravenously (IV) in severe cases, although the intraosseous route is acceptable. In the field, as time is of the essence in treating nerve agent poisoning, first responders are trained to administer atropine IM via autoinjector. Some experts also recommend that atropine be given IM in the presence of hypoxia to avoid arrhythmias associated with IV administration. Many emergency management services stock military-style autoinjector kits consisting of atropine and 2-PAM for IM injection. Pediatric atropine autoinjectors containing 0.5 or 1 mg of atropine are licensed and held in the Strategic National Stockpile, although kits intended for adults (with 2 mg of atropine and 600 mg of pralidoxime) may be used in children >2-3 years of age (Table 763.5). Autoinjectors cannot easily be used in the smallest infants.

Animal studies support the routine prophylactic administration of anticonvulsant doses of benzodiazepines, even in the absence of observable convulsive activity. Although diazepam has long been employed for this purpose, midazolam was recently granted FDA approval, and animal studies have shown it to have superior efficacy in treating acute nerve agent poisoning. Military and civilian stocks of diazepam autoinjectors are being replaced by midazolam autoinjectors.

Delayed neuromuscular symptoms in the setting of terrorism might be due to botulism. Supportive care, with meticulous attention to ventilatory support, is the mainstay of botulism treatment. Such support may be necessary for several months, making the management of a large-scale botulism outbreak especially problematic in terms of medical resources. A licensed heptavalent antitoxin (types A-G) is available through the CDC (1-800-232-4636). Administration of this antitoxin is unlikely to reverse disease in symptomatic patients but may prevent further progression. In addition, a pentavalent product (containing antibody against toxin types A-E but licensed only for treatment of type A or B intoxication), Botulism Immune Globulin Intravenous (Human; BabyBIG), is available through the California Department of Health Services (1-510-231-7600) specifically for the treatment of infant botulism.

The *rapid onset of respiratory symptoms* may signal an exposure to chlorine, phosgene, cyanide, or a number of other toxic industrial chemicals. Although the mainstay of therapy in virtually all of these exposures consists of removal to fresh air and intensive supportive care, cyanide intoxication often requires the administration of specific antidotes.

Table 763.2 CDC Category A Agents of Bioterrorism

DISEASE	CLINICAL FINDINGS	INCUBATION PERIOD (DAYS)	ISOLATION PRECAUTIONS	INITIAL TREATMENT	PROPHYLAXIS
Anthrax (inhalational) Patients who are clinically stable after 14 days can be switched to a single oral agent (as described in the prophylaxis section of this table) to complete a 60-day course	Febrile prodrome with rapid progression to mediastinal lymphadenitis and mediastinitis, sepsis, shock, and meningitis	1-5	Standard	See Table 763.3.	**Ciprofloxacin 30 mg/kg/day PO divided q12h*** (max 500 mg/dose) *or* **doxycycline 4.4 mg/kg/day PO divided q12h** (max 100 mg/dose) *or* clindamycin 30 mg/kg/day PO divided q8h (max 900 mg/dose) *or* levofloxacin 16 mg/kg/day PO divided q12h (max 250 mg/dose) *or* **amoxicillin 75 mg/kg/day PO divided q8h†** (max 1 g/dose) or penicillin VK 50-75 mg/kg/day divided q6-8h
Plague (pneumonic)	Febrile prodrome with rapid progression to fulminant pneumonia, hemoptysis, sepsis, disseminated intravascular coagulation	2-3	Droplet (for first 3 days of therapy)	Gentamicin** 1.25- 2.5 mg/kg IV q8h *or* doxycycline 2.2 mg/kg IV q12h *or* ciprofloxacin 15 mg/kg IV q12h *or* levofloxacin 8 mg/kg IV/PO q12h	Doxycycline 2.2 mg/kg PO q12h *or* ciprofloxacin 20 mg/kg PO q12h *or* levofloxacin 8 mg/kg PO q12h
Tularemia	Pneumonic: abrupt onset of fever with fulminant pneumonia Typhoidal: fever, malaise, abdominal pain	2-10	Standard	Options same as for plague‡, gentamicin preferred	Same as for plague‡
Smallpox	Febrile prodrome with synchronous, centrifugal, vesiculopustular exanthema	7-17	Airborne (+ contact)	Tecovirimat *Oral dosage by body weight:* 13 kg to <25 kg: 200 mg q12h 25 kg to <40 kg: 400 mg q12h 40 kg to <120 kg: 600 mg q12h ≥120 kg: 600 mg q8h *Intravenous infusion dosage by body weight:* 3 kg to <35 kg: 6 mg/kg q12h by IV infusion over 6 hr 35 kg to <120 kg: 200 mg q12h by IV infusion over 6 hr ≥120 kg: 300 mg q12h by IV infusion over 6 hr	Vaccination may be effective if given within the first several days after exposure
Botulism	Afebrile descending symmetric flaccid paralysis with cranial nerve palsies	1-5	Standard	Supportive care; antitoxin (see text) may halt the progression of symptoms but is unlikely to reverse them	No licensed preexposure prophylaxis is available; postexposure administration of antitoxin may prevent the development of symptoms
Viral hemorrhagic fevers	Febrile prodrome with rapid progression to shock, purpura, and bleeding diatheses	4-21	Contact (consider airborne in cases of massive hemorrhage)	Supportive care; ribavirin may be beneficial in treating Lassa fever, and perhaps other arenaviral hemorrhagic fevers	Ribavirin has been shown to be efficacious in the postexposure prophylaxis of Lassa fever

*Preferred drugs are shown in **bold**.
**Some experts say 4.5-7.5 mg/kg/day.
†Penicillin and amoxicillin should only be used when the strain of *Bacillus anthracis* is known to be susceptible.
‡Levofloxacin (as well as moxifloxacin) is licensed by the U.S. Food and Drug Administration for the prophylaxis and treatment of plague in the setting of a bioterror attack, but not tularemia.
PO, By mouth; IV, intravenously.

Table 763.3 Treatment of Inhalational Anthrax in Children

WHEN MENINGITIS PRESENT OR HAS NOT RULED OUT*	WHEN MENINGITIS CAN BE RULED OUT*
1. A bactericidal fluoroquinolone: **Ciprofloxacin 30 mg/kg/day IV divided q8h**† (max 400 mg/dose) *or* Levofloxacin 24 mg/kg/day IV divided q12h (max 250 mg/dose) *or* Moxifloxacin 12 mg/kg/day IV divided q12h (max 200 mg/dose; for children 3 mo to 2 yr); 10 mg/kg/day IV divided q12h (for children 2-5 yr); 8 mg/kg/day IV divided q12h (for children 6-11 yr); 400 mg IV qd (for children >12 yr and >45 kg)	1. A bactericidal antimicrobial: **Ciprofloxacin 30 mg/kg/day IV divided q8h** (max 400 mg/dose) *or* Levofloxacin 20 mg/kg/day IV divided q12h (max 250 mg/dose) *or* Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) *or* Vancomycin 60 mg/kg/day IV divided q8h *or* **Penicillin G 400,000 U/kg/day IV divided q4h** (max 4 MU/dose) [if PCN sensitive] *or* Ampicillin 200 mg/kg/day IV divided q6h (max 3 g/dose)
2. A second bactericidal antimicrobial: **Meropenem 120 mg/kg/day IV divided q8h** (max 2 g/dose) *or* Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) *or* Doripenem 120 mg/kg/day IV divided q8h (max 1 g/dose) *or* Vancomycin 60 mg/kg/day IV divided q8h *or* **Penicillin G** 400,000 U/kg/day IV divided q4h**‡ (max 4 MU/dose) [if PCN sensitive] *or* Ampicillin 400 mg/kg/day IV divided q6h (max 3 g/dose)	
3. A protein synthesis inhibitor: **Linezolid 30 mg/kg/day IV divided q8h** (for children <12 yr); 30 mg/kg/day IV divided q12h (for children >12 yr; max 600 mg/dose) *or* Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose) *or* Rifampin 20/mg/kg/day IV divided q12h (max 300 mg/dose) *or* Chloramphenicol 100 mg/kg/day IV divided q6h	2. A protein synthesis inhibitor: **Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose)** *or* Linezolid 30 mg/kg/day IV divided q8h (for children <12 yr); 30 mg/kg/day IV divided q12h (for children >12 yr; max 600 mg/dose) *or* Rifampin 20/mg/kg/day IV divided q12h (max 300 mg/dose) *or* Doxycycline 4.4 mg/kg/day IV loading dose (for children <45 kg; max 200 mg), followed by 4.4 mg/kg/day IV divided q12h; 200 mg IV loading dose, followed by 100 mg IV q12h (for children >45 kg)

*Meningitis occurs in approximately 50% of patients with inhalational anthrax.
**Some experts provide a range of 400,000–600,000 U/kg/d.
†Preferred drugs are shown in **bold**.
‡Penicillin and amoxicillin should only be used when the strain of *Bacillus anthracis* is known to be susceptible.
IV, Intravenous; qd, every day; PCN, penicillin.
Data from Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. *Pediatrics*. 2014;133:e1411–e1436. Appendices 3 & 4.

The classic **cyanide antidote** utilizes a nitrite along with sodium thiosulfate and is given in two stages. The methemoglobin-forming agent (e.g., sodium nitrite) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 5-10 minutes. A sulfur donor, such as sodium thiosulfate, is given next. This compound is used as a substrate by the hepatic enzyme rhodanese, which converts cyanide to thiocyanate, a less toxic compound excreted in the urine. Thiosulfate treatment itself is efficacious and relatively benign and may be used alone for mild to moderate cases. Sodium nitrite and sodium thiosulfate are packaged together in standard antidote kits, along with amyl nitrite, a sodium nitrite substitute that can be inhaled in prehospital settings in which IV access is not available.

Many first responder agencies in the United States have replaced the traditional two-part cyanide antidote kit with hydroxocobalamin, which exchanges its hydroxy group for cyanide, forming harmless cyanocobalamin (vitamin B_{12}) that is subsequently excreted by the kidneys. Hydroxocobalamin use is not complicated by the potential for nitrite-induced hypotension or methemoglobinemia, and it has low toxicity. The recommended dose is 5 g in adults or 70 mg/kg in children, administered IV over 15 minutes. A second dose (5 g in adults; 70 mg/kg in children) may be repeated in severely affected patients. Side effects include modest hypertension and reddening of skin, mucous membranes, and urine that may last several days. Although no human controlled trials are currently available to compare hydroxocobalamin with nitrite/thiosulfate-based therapies, many authorities believe that hydroxocobalamin's efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context. To use hydroxocobalamin, however, the solution must be mixed immediately before use, in the field if need be, so first responders need to be properly trained to employ it.

Animal research suggests a modest benefit of steroid therapy in mitigating lung injury after chlorine inhalation; thus steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those with bronchospasm and/or a history of asthma. Symptomatic relief has also been reported following chlorine exposure with nebulized 3.75% sodium bicarbonate therapy, though the impact of this regimen on pulmonary damage is unknown. Animal models have also suggested a benefit from antiinflammatory agents, including ibuprofen and *N*-acetylcysteine, which appear to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), although the results of such interventions have not yet been reported in clinical trials.

In cases in which the delayed onset of respiratory symptoms may be the result of a terrorist attack, consideration should be given to the empirical administration of an antibiotic effective against anthrax, plague, and tularemia. Ciprofloxacin (10-15 mg/kg IV q12 hours), levofloxacin (8 mg/kg IV q12 hours), or doxycycline (2.2 mg/kg IV q12 hours) is a reasonable choice. Although naturally occurring strains of *B. anthracis* usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of *B. anthracis* exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of *Y. pestis* and *F. tularensis*. Concerns about inducible β-lactamases in *B. anthracis* have led experts to recommend one to two additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, and imipenem are reasonable choices based on in vitro sensitivity data. Because *B. anthracis* relies on the production of two protein toxins, edema toxin and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningeal involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. The treatment of anthrax is detailed in Table 763.3.

Table 763.4 Critical Chemical Agents of Terrorism

AGENT	TOXICITY	CLINICAL FINDINGS	ONSET	DECONTAMINATION*	MANAGEMENT
NERVE AGENTS					
Tabun, sarin, soman, VX	Anticholinesterase: muscarinic, nicotinic, central nervous system effects	Vapor: miosis, rhinorrhea, dyspnea Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea	Seconds: vapor Minutes to hours: liquid	Vapor: fresh air, remove clothes, wash hair Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation	ABCs. Atropine: 0.05-0.1 mg/kg IV†, IM‡ (min: 0.1 mg, max: 5 mg), repeat q2-5 min prn for marked secretions, bronchospasm AND Pralidoxime: 25-50 mg/kg IV, IM§ (max: 1 g IV; 2 g IM), may repeat within 30-60 min prn, then again q1h for one or two doses prn for persistent weakness, high atropine requirement AND Diazepam: 0.3 mg/kg (max: 10 mg) IV *or* Lorazepam: 0.1 mg/kg IV, IM (max: 4 mg) *or* Midazolam: 0.2 mg/kg (max: 10 mg) IM prn for seizures or severe exposure
VESICANTS					
Mustard	Alkylation	Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation	Hours	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Symptomatic care
Lewisite	Arsenical		Immediate pain	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Possibly British antilewisite (BAL) 3 mg/kg IM q4-6h for systemic effects of lewisite in severe cases
PULMONARY AGENTS					
Chlorine, phosgene	Liberate hydrochloric acid, alkylation	Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene)	Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema	Fresh air Skin: water	Symptomatic care (see text)
CYANIDE					
	Cytochrome oxidase	Tachypnea, coma, seizures, apnea	Seconds	Fresh air	ABCs, 100% oxygen
	Inhibition: cellular anoxia, lactic acidosis			Skin: soap and water	Na bicarbonate prn metabolic acidosis; hydroxocobalamin 70 mg/kg IV (max: 5 g) *or* nitrite/thiosulfate, given as follows (see text): *Na nitrite (3%): dose (mL/kg)* (max: 10 mL) — *Estimated hemoglobin concentration (g/dL)* 0.27 — 10 0.33 — 12 (estimated for average child) 0.39 — 14 Followed by Na thiosulfate (25%): 1.65 mL/kg (max: 50 mL)

*Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.
†Intraosseous route is likely equivalent to intravenous.
‡Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 741.5.
§Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army's Mark 1 autoinjector concentration) to effect a reasonable volume for injection. See also Table 741.5.
ABCs, Airway, breathing, and circulatory support; IM, intramuscularly; IV, intravenously; max, maximum; min, minimum; prn, as needed.
Adapted from Henretig FH, Cieslak TJ, Eitzen EM. Biological and chemical terrorism. *J Pediatr.* 2002;141:311–326.

Table 763.5 Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care*

ATROPINE AUTOINJECTOR THERAPY		
APPROXIMATE AGE	**APPROXIMATE WEIGHT (KG)**	**AUTOINJECTOR SIZE (MG)**
<6 mo	<7.5	0.25
6 mo to 4 years	7.5-18	0.5
5-10 years	18-30	1.0
>10 years	>30	2.0

PRALIDOXIME AUTOINJECTOR THERAPY			
APPROXIMATE AGE (YEARS)	**APPROXIMATE WEIGHT (KG)**	**NUMBER OF AUTOINJECTORS**	**PRALIDOXIME DOSE (MG/KG)**
3-7	13-25	1	24-46
8-14	26-50	2	24-46
>14	>50	3	<35

*Consider adult pralidoxime autoinjector use for severely affected mass casualties when intravenous (IV) access or more precise mg/kg intramuscular (IM) dosing is logistically impractical. The initial dose using atropine autoinjectors is one autoinjector of each recommended size. The initial dose using pralidoxime autoinjectors is the recommended number of (adult-intended, 600 mg) autoinjectors. These latter may also be injected into an empty sterile vile; the contents redrawn through a filter needle into a small syringe may then provide a ready source of concentrated (300 mg/mL) pralidoxime solution for IM injection to infants. Autoinjectors may become available that provide adult doses of both atropine and pralidoxime in one injector; these could be used in children ≥3 years in lieu of two individual injectors and dosed as noted above for pralidoxime alone.

Raxibacumab, a monoclonal antibody that inhibits anthrax antigen binding to cell receptors, thus preventing toxins from entering cells, is approved for the treatment of inhalation anthrax in combination with antibiotics, as is obiltoxaximab, which neutralizes anthrax toxins. The adult dose of raxibacumab is 40 mg/kg given IV over 2 hours and 15 minutes. The dose for children is weight based: ≤15 kg, 80 mg/kg; >15-50 kg, 60 mg/kg; >50 kg, 40 mg/kg. Premedication with diphenhydramine IV or by mouth (PO) is recommended 1 hour before the infusion.

In patients with an established diagnosis of tularemia, gentamicin (5 mg/kg IV/IM divided 2 or 3 times/day) is the preferred choice for therapy due to the limited availability of streptomycin (15 mg/kg IM q12 hours). Bioterrorism-related plague should be treated with two distinct antibiotic classes until sensitivity patterns are known; gentamicin, streptomycin, ciprofloxacin, and levofloxacin are all approved agents for treatment of pneumonic plague in children (see Table 763.2). To be effective, therapy for pneumonic plague must be initiated within 24 hours of the onset of symptoms. There is little clinical experience with ricin-induced pulmonary injury. The mainstay of therapy is expected to be supportive care.

The management of **vesicant-induced injury** is similar to that for burn victims and is largely symptomatic (see Chapter 89). The major difference between thermal burns and vesicant burns is that vesicant casualties do not need the large volumes of fluid required by thermal burn victims, as their epidermis remains intact. These patients are at risk of overhydration if treated using thermal burn protocols. Mustard victims will benefit from the application of soothing skin lotions such as calamine and the administration of analgesics. Early intubation of severely exposed patients is warranted to guard against edematous airway compromise. Oxygen and mechanical ventilation may be needed, and meticulous attention to hydration is of paramount importance. Ongoing research suggests a role for oral *N*-acetylcysteine in mitigating chronic pulmonary effects due to mustard injury. Lewisite victims can be managed in much the same manner as mustard victims. Dimercaprol (British antilewisite) in peanut oil, given IM, may help ameliorate the systemic effects of lewisite, although few hospitals or pharmacies are likely to have this drug on hand.

The management of symptomatic smallpox victims also is largely supportive, with attention to pain control, hydration status, and respiratory sufficiency of primary importance. The parenteral antiviral compound cidofovir, licensed for the treatment of cytomegalovirus retinitis in HIV-infected patients, has in vitro efficacy against variola and other orthopoxviruses. Its utility in treating smallpox victims is untested. Moreover, in the face of a large outbreak of disease, wide parenteral use of this drug would be problematic. Tecovirimat demonstrates excellent in vitro activity against orthopoxviruses, but its utility in treating patients with smallpox is likewise untested.

In all chemical casualties, but especially if a liquid agent such as VX or mustard is suspected, decontamination is crucial and should be considered a primary medical intervention. Although this has been part of casualty doctrine in the civilian and military environments for decades, a 2016 study showed that disrobing eliminated 90% of contamination in normal volunteers; following this with showering using water or soap and water eliminated 99% of contamination. This has huge implications for the hospital management of possibly contaminated casualties, including children, and hospitals must plan to execute the decontamination mission at all levels.

For those faced with an acute chemical emergency, especially a mass casualty situation, a useful resource is the Chemical Hazard Emergency Medical Management website (https://chemm.hhs.gov), maintained by the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. Among its features is a decision support tool, CHEMM-IST, which aids in identification of the chemical a patient was exposed to.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 764

Mass Psychogenic Illness

Jonathan W. Mink

Mass psychogenic illness refers to the rapid spread of illness signs and symptoms affecting members of a cohesive group, originating from a nervous system disturbance involving excitation, loss, or alteration of function, whereby physical complaints that are exhibited unconsciously have no corresponding organic etiology. Mass psychogenic illness shares features in common with **conversion disorder (functional neurologic system disorder)** (see Chapter 35) in that the symptoms are not consciously produced and are typically sensorimotor in nature. The physical symptoms are associated with significant distress and impairment; they commonly interfere with function at school or home and affect peer relationships. Some experts have argued that "functional" is a better used term than "psychogenic" because it does not imply etiology and does not reinforce dualist thinking about the mind being separate from the brain.

Much less is known about the biologic underpinnings and clinical features of mass psychogenic illness than is known about conversion disorder and other somatic symptom disorders. However, there are some important features in common with conversion disorder. These include sudden abrupt onset, inconsistency with known anatomy and physiology, atypical features, and inconsistency of symptoms over time. Specific features of mass psychogenic illness are the occurrence of these symptoms in a cohesive group; the presence of increased anxiety; spread of symptoms via sight, sound, or oral communication (including social media); and a high female:male ratio.

CLINICAL FEATURES AND DIAGNOSIS

There are many examples of mass psychogenic illness throughout history. The best known is perhaps that of the Salem "witches." Most widely reported examples of mass psychogenic illness are in adults, but there are several reports in children as well. In 2004, 10 teenage females from a school in rural North Carolina developed paroxysmal episodes resembling epilepsy or syncope. These females were from a cohesive social group (school-age students in a small school) and had similar symptoms. The symptoms were shown not to be consistent with either syncope or epilepsy, and they eventually resolved after a two-week holiday break from school. Another episode in Le Roy, New York, was an outbreak of a "tic-like" illness among high school students. The symptoms were atypical for tics because they were not preceded by a premonitory urge and could not be suppressed with effort. In addition, the symptoms were remarkably similar across the affected patients. Symptoms resolved over time. In the Le Roy example, there was likely an exacerbating role of both social media and mass media, which amplified the cohesiveness of the group. There has been a surge of cases of "tic-like" symptoms in adolescents during the COVID-19 pandemic. It has been suggested that social media, especially videos presented on the TikTok platform, has played an important role in the spread of these symptoms.

In a study of 280 environmental chemical incidents in the United Kingdom between 2007 and 2008, 7% were classified as mass psychogenic illness according to five diagnostic criteria: (1) presence of somatic (bodily) symptoms, (2) preexisting social connection between two or more of the affected people, (3) epidemic spread of symptoms, (4) attribution of symptoms by affected individuals (or by their parents or caregivers) to a threatening external agent of a physical (usually chemical, biologic, or radiologic) or spiritual nature, and (5) symptoms and signs that are not compatible with the environmental exposure specified by the affected individuals nor with any other environmental exposure that could reasonably be expected to have been present at the time of (or shortly before) the onset of symptoms.

One study has examined experimentally induced mass psychogenic illness. In a randomized controlled experiment, participants were assigned to one of three groups to study the effects of a simulated biologic threat and elements of social contagion. The three groups were (1) no-intervention control group, (2) psychogenic illness induction group, and (3) psychogenic illness induction plus media group. Groups 2 and 3 were told that the purpose of the study was to test the side effects of a carrier compound for an antiinfluenza medication. They were told that the compound did not produce serious side effects but was being evaluated with regard to mild side effects. In groups 2 and 3, professional actors were placed among the participants to feign illness during the study with symptoms of nausea, dizziness, and headache. Group 3 was also shown a documentary about the 1918 flu pandemic. The video contained interviews with survivors and vivid images of death and illness. The two psychogenic induction groups had 11 times more symptoms than did the control group. If a subject had a lifetime history of a traumatic event or depression, he or she was more likely to have symptoms. The documentary viewing was not associated with a higher rate of symptoms. This study confirmed the role of **"social contagion"** in mass psychogenic illness and provided a model for future studies of factors leading to such contagion.

TREATMENT STRATEGIES

Mass psychogenic illness is usually self-limited, but treatment requires careful reassurance and communication between physician and patient. Explanation models should be communicated in a sensitive manner so as not to appear dismissive of symptoms. When doctors and patients do not agree on the "reality" of the illness, the prognosis is worse. Thus media attention, medical and scientific disagreement, and legal proceedings must be managed in a way that does not exacerbate the symptoms or the illness.

In the Le Roy illness, treatment varied across individuals. The treatment strategies included cognitive-behavioral therapy, supportive psychotherapy, education, pharmacotherapy for coexisting anxiety, and alteration of social setting. Many of the patients sought multiple medical opinions. There were frequent discussions among public health and other medical officials and the local media outlets. Reduced media attention seemed to lead to more rapid improvement of symptoms in some patients.

It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either physically *or* psychologically based. In contrast, a biobehavioral continuum of disease better characterizes illness as occurring across a spectrum ranging from a predominantly biologic etiology on one end to a predominantly psychosocial etiology on the other. It is beneficial to the patient for the treating physician to try to shift the emphasis from understanding the etiology to a path toward recovery.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 765

Animal and Human Bites

David A. Hunstad

Many animals, besides domestic and stray dogs and cats, inflict bites on humans. The profile of such bites varies by country and region, based on community and living conditions, indigenous species, and opportunity for encounter.

EPIDEMIOLOGY

Worldwide there are tens of millions of dog bites each year, resulting in nearly 60,000 deaths annually from rabies (see Chapter 320). **Dog bites** represent approximately 80–90% of all bites in the United States, while 5–15% are from cats, 2–5% from rodents, and the remainder from rabbits, ferrets, farm animals, monkeys, and reptiles. An estimated 4.5 million persons in the United States are bitten by dogs annually; over 800,000 of those seek medical care. Bites from dogs are also most common in Bangladesh, India, Pakistan, and Myanmar, whereas in Nepal cattle and buffalo account for more than half of bites, followed by dogs, pigs, and horses. Approximately 1% of dog bite wounds and 6% of cat bite wounds in the United States require hospitalization. During the past three decades, there have been several dozen deaths per year in the United States from dog-inflicted injuries; the majority of these occurred in children under 11 years of age. Various studies have examined the incidence of dog bite injuries by dog breed. Compared with other breeds, bites by pit bull terriers and mixed-breed dogs account for higher rates of hospital admission, lower Glasgow Coma Scores at admission, and an increased risk of death. Unaltered male dogs account for approximately 75% of attacks, while nursing female dogs may inflict injury when humans attempt to handle their puppies.

The majority of dog attacks on children in the United States occur between the ages of 6 and 11 years, with a slight predominance in males. Approximately 65% of attacks occur around the home, 75% of biting animals are known by the children, and 50% of attacks are said to be unprovoked. Similar statistics apply in Canada, where 70% of all bites reported in one study were sustained by children age 2-14 years; 65% of dogs involved in biting were part of the family or extended family.

Of the approximately 450,000 reported **cat bites** per year occurring in the United States, nearly all are inflicted by known household animals. Because rodent bites (rat, mouse, gerbil) do not represent reportable conditions, little is known about the epidemiology of these injuries or the incidence of infection after rodent-inflicted bites or scratches.

Few data exist on the incidence and demographics of **human bite** injuries in pediatric patients; however, preschool and early school-age children appear to be at greatest risk of sustaining an injury from a human bite, often in daycare or preschool settings. In some series, the proportion of human bites is highest among adolescents, an age group in which fist-to-teeth injuries (so-called "fight bites") become more common.

CLINICAL MANIFESTATIONS

Dog bite–related injuries can be divided into three categories of almost equal incidence: abrasions, puncture wounds, and lacerations with or without an associated avulsion of tissue. Bites from larger dogs may also involve crush injury to tissues. In contrast, the most common type of injury from cat bites is a puncture wound, often penetrating deep into tissue or joint spaces. Human bite injuries are of two types: an occlusion injury that is incurred when the upper and lower teeth come together on a body part, or a clenched-fist injury that occurs when the injured fist, usually on the dominant hand, strikes the teeth of another individual.

DIAGNOSIS

Management of the bite victim should begin with a thorough history and physical examination. Careful attention should be paid to the circumstances surrounding the bite event (e.g., species and number of animals, type of animal [domestic or wild], whether the attack was provoked or unprovoked, location of the attack), a history of drug allergies, and the immunization status of the child (tetanus) and animal (rabies). During physical examination, meticulous attention should be paid to the type, size, and depth of the injury; the presence of any foreign material in the wound; the status of underlying structures; and, when the bite is on an extremity, the exact location of the injury, an assessment of possibly involved structures, and the range of motion of the affected area. Photographs of the injury should be recorded in the patient's medical record. Radiographs of the affected part should be considered if it is likely that a bone or joint was penetrated or fractured or if foreign material is present in the wound. The possibility of a fracture or penetrating injury of the skull should particularly be considered in infants who have sustained dog bite injuries to the face or head.

COMPLICATIONS

Infection is the most common complication of bite injuries regardless of the species of biting animal. In most cases, culture specimens from a fresh dog bite wound are not likely to be clinically useful. Although potentially pathogenic bacteria have been isolated from up to 80% of dog bite wounds that are brought to medical attention within 8 hours of the bite, the infection rate for wounds receiving medical attention in <8 hours is relatively low (2.5–20%). Cultures should be obtained from the wound if there is clinical evidence of infection or if the patient is immunocompromised. *Capnocytophaga canimorsus* is isolated from approximately 5% of infected wounds in immunocompromised patients (especially asplenia) and can cause serious systemic infection in these individuals. In contrast to dogs, the infection rate in cat bite wounds, even those that receive prompt medical attention, is >50%; therefore cat bites should be closely monitored for signs of infection.

The rate of infection after rodent bite injuries is not known. Most of the oral flora of rats is similar to that of other mammals; however, up to 50% of rats, depending on worldwide geography, may harbor strains of *Streptobacillus moniliformis* and *Spirillum minus,* both of which cause rat bite fever (see Chapter 766).

All human bite wounds, regardless of the mechanism of injury, should be considered high risk for infection. Current recommendations do not support obtaining cultures at the time of the bite as it does not change empiric antibiotic therapy; however, any infected wounds should be cultured.

Table 765.1 lists common causes of soft tissue bacterial infections after dog, cat, or other animal bites. Bites of humans or cats, those in which treatment is delayed, those in immunocompromised patients, and those associated with deep puncture wounds or significant crush injury carry a higher risk for infection. An elevated risk for infection is also present if the bite is to certain anatomic regions (e.g., hand, foot, or genitals) or there is penetration of bone or tendons.

TREATMENT

Table 765.2 outlines the management of human or animal bite wounds to reduce risk for infection. The wound should be anesthetized, cleaned, and irrigated with sterile saline using moderate pressure. Irrigation with antibiotic-containing solutions provides no advantage over saline alone and may cause local irritation of the tissues. Puncture wounds should be thoroughly cleansed and

Table 765.1 Microorganisms Associated with Animal Bites

DOG BITES
Staphylococcus species
Streptococcus species
Eikenella species
Pasteurella species
Proteus species
Klebsiella species
Haemophilus species
Enterobacter species
Capnocytophaga canimorsus
Bacteroides species
Moraxella species
Corynebacterium species
Neisseria species
Fusobacterium species
Prevotella species
Porphyromonas species

CAT BITES
Pasteurella species
Actinomyces species
Propionibacterium species
Bacteroides species
Fusobacterium species
Clostridium species
Wolinella species
Peptostreptococcus species
Staphylococcus species
Streptococcus species

HERBIVORE BITES
Actinobacillus lignieresii
Actinobacillus suis
Pasteurella multocida
Pasteurella caballi

SWINE BITES
Pasteurella aerogenes
Pasteurella multocida
Bacteroides species
Proteus species
Actinobacillus suis
Streptococcus species
Flavobacterium species
Mycoplasma species

RODENT BITES
Streptobacillus moniliformis
Spirillum minus (in Asia)

PRIMATE BITES
Bacteroides species
Fusobacterium species
Eikenella corrodens
Streptococcus species
Enterococcus species
Staphylococcus species
Enterobacterales
Herpes B virus

LARGE REPTILE (CROCODILE, ALLIGATOR) BITES
Aeromonas hydrophila
Pseudomonas pseudomallei (in Asia)
Pseudomonas aeruginosa
Proteus species
Enterococcus species
Clostridium species

Adapted from Perkins Garth A, Harris NS, Spanierman CS. Animal bites in emergency medicine. Available at: http://emedicine.medscape.com/article/768875-overview, updated October 7, 2021; accessed November 27, 2021. Reprinted with permission from eMedicine.com.

Table 765.2 Initial Management of Bite Wounds

HISTORY
Animal bite: Ascertain the type of animal, whether the bite was provoked or unprovoked, and the situation/environment in which the bite occurred. Follow rabies guidelines (see Chapter 320) for details on management of bites that carry a risk of rabies.
Patient: Obtain information on antimicrobial allergies, current medications, splenectomy, liver disease, or immunosuppressive conditions.

PHYSICAL EXAMINATION
If possible, photograph the wound and record its location, type, and approximate depth; range of motion; possibility of joint penetration; presence of edema or crush injury; nerve and tendon function; and signs of infection.

CULTURE
Aerobic and anaerobic cultures should be taken from infected wounds (not from fresh wounds).

IRRIGATION AND DEBRIDEMENT
Irrigate with water or sterile saline and debride devitalized or necrotic tissue.

RADIOGRAPHS
Plain radiographs should be obtained if bony penetration is possible or suspected; radiographs can also provide a baseline for future evaluation of osteomyelitis.

WOUND CLOSURE
Primary wound closure is usually not advocated unless wounds are extensive and closure is necessary for cosmetic or functional reasons, especially large facial or neck wounds or those overlying the joints. When possible, delayed primary closure or allowing the wound to close by secondary intention is recommended.

ANTIMICROBIAL THERAPY
Early presenting (uninfected) wounds: provide prophylactic antimicrobials for (1) moderate-to-severe injuries, especially if preexisting edema or significant crush injury is present; (2) bone or joint space penetration; (3) deep hand wounds; (4) immunocompromised patients; (5) wounds adjacent to prosthetic material; and (6) wounds in close proximity to the genital area. In most cases, coverage should include *Pasteurella* (*Eikenella* in human bites), *Staphylococcus, Streptococcus,* and anaerobes including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* spp. See Table 765.3 for recommended antibiotics.
Infected wounds: See Table 765.3 for oral antibiotic recommendations. In cases where intravenous antibiotics are deemed necessary, antimicrobial choices include ampicillin/sulbactam, piperacillin-tazobactam, cefoxitin, or ertapenem.

HOSPITALIZATION
Indications include signs and symptoms of systemic toxicity and worsening infection.

IMMUNIZATIONS
Provide tetanus and rabies immunization, if indicated.

ELEVATION
Elevation may be required if edema is present. Lack of elevation is a common cause of therapeutic failure.

IMMOBILIZATION
For significant injuries, immobilize the extremity, especially the hands, with a splint.

FOLLOW-UP
Patients should be reminded to follow up within 48 hours or sooner for worsening or unresolved infections and continued pain.

REPORTING
Reporting the incident to a local health department may be required.

Adapted from Goldstein EJC, Abrahamian FM. Bites. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 315-3.

Table 765.3 Recommended Empirical Oral Antibiotics for Bite Wound Prophylaxis and Treatment

ANTIBIOTIC	RECOMMENDED ADULT DOSE	RECOMMENDED CHILD DOSE*
AGENT OF CHOICE (A) Amoxicillin-clavulanate	875/125 mg twice daily	45 mg/kg per dose (amoxicillin component) twice daily
ALTERNATE COMBINATION THERAPY: B OR C (WITH ANAEROBIC ACTIVITY) PLUS E, F, G, H, OR I		
(B) Metronidazole	500 mg three times daily	10 mg/kg per dose three times daily
Or:		
(C) Clindamycin	450 mg three times daily	10 mg/kg per dose three times daily
PLUS, ONE OF THE FOLLOWING: (D) Doxycycline	100 mg twice daily	Not for use in children <8 yr old
(E) Trimethoprim-sulfamethoxazole	160/800 mg (1 DS tab) twice daily	4 to 5 mg/kg (trimethoprim component) per dose* twice daily
(F) Penicillin V potassium	500 mg four times daily	12.5 mg/kg per dose four times daily
(G) Cefuroxime	500 mg twice daily	10 mg/kg per dose twice daily
(H) Moxifloxacin	400 mg once daily	Use with caution in children

*Child dose should not exceed recommended adult dose.
From Phillips LL, Semple J: Bites and injuries inflicted by wild and domestic animals. In Auerbach PS, Cushing TA, Harris NS (editors): *Auerbach's Wilderness Medicine*, 7th ed, vol 1. Philadelphia: Elsevier, 2017; Table 30.3, p. 623.

gently irrigated with a catheter or blunt-tipped needle; blind, high-pressure irrigation should not be employed. Avulsed or devitalized tissue should be debrided and any fluctuant areas incised and drained.

Surgical approaches to management of bite wounds may include primary closure, delayed primary closure (i.e., in 3-5 days), or healing by secondary intention. Factors to be considered are the type, size, and depth of the wound; the anatomic location; the presence of infection; the time since the injury; and the potential for cosmetic disfigurement. Appropriate surgical consultation (e.g., general pediatric surgery; plastic, hand, or orthopedic surgery) should be obtained promptly for all patients with deep or extensive wounds; wounds involving the hands, face, or bones and joints; and infected wounds that require open drainage. Although there is general agreement that visibly infected wounds and those that are more than 24 hours old should not be sutured, there is a spectrum of practice regarding the closing of wounds <8 hours old with no evidence of infection. Because all bite wounds to the hand are at high risk for infection, particularly if there has been disruption of the tendons or penetration of the bones, surgical consultation is almost always indicated, and delayed primary closure is recommended for many bite wounds of the hands. Facial lacerations are at lower risk for secondary infection because of the excellent blood supply to this region. Given this fact and cosmetic considerations, many plastic surgeons advocate primary closure of facial bite wounds that have been brought to medical attention within 8 hours.

Similarly, there are few comparative trials addressing the efficacy and selection of antimicrobial agents for **prophylaxis** of bite injuries. The bacteriology of bite wound infections is more often a reflection of the oral flora of the biting animal than the skin flora of the victim (see Table 765.1). Because many aerobic and anaerobic bacterial species colonizing the oral cavity of the biting animal have the potential to invade local tissue, multiply, and cause tissue destruction, most bite wound infections are polymicrobial.

Despite substantial homology in the oral bacterial flora of humans, dogs, and cats, important differences exist among the biting species, reflected in the types of wound infections that occur. The predominant bacterial species isolated from infected dog bite wounds are *Staphylococcus aureus* (20–30%), *Pasteurella multocida* (20–30%), *Staphylococcus intermedius* (25%), and *C. canimorsus;* approximately one-half of dog bite wound infections also contain mixed anaerobes. Similar species are isolated from infected cat bite wounds; however, *P. multocida* is the predominant species in at least 50% of cat bite wound infections. At least 50% of rats harbor *S. moniliformis* in the oropharynx, and approximately 25% in Asia harbor *S. minus,* a small, uncultivatable gram-negative organism. In infected human bite wounds, nontypable strains of *Haemophilus influenzae, Eikenella corrodens, S. aureus,* α-hemolytic streptococci, and β-lactamase–producing aerobes (~50%) are the predominant species. Clenched-fist injuries are particularly prone to infection by *Eikenella* spp. (25%) and other anaerobes (50%).

The choice between oral and parenteral antimicrobial therapy should be based on the severity of the wound, the presence and degree of overt infection, signs of systemic toxicity, and the patient's immune status. **Amoxicillin-clavulanate is an excellent choice for empiric oral therapy** for human and animal bite wounds because of its activity against most bacteria that are isolated from infected bites (Table 765.3). Similarly, **ampicillin-sulbactam or piperacillin-tazobactam is preferred for patients who will receive empiric parenteral therapy**. Penicillin G is the drug of choice for prophylaxis and treatment of rat bite injuries, as this agent has excellent activity against *S. moniliformis* and *S. minus*. Because first-generation cephalosporins have limited activity against *P. multocida* and *E. corrodens,* they should not be used for prophylaxis or empiric therapy of bite wound infections. Therapeutic alternatives for bite wound infections in penicillin-allergic patients are limited; clindamycin plus trimethoprim-sulfamethoxazole is the most commonly suggested regimen for these patients. Tetracycline is the drug of choice for penicillin-allergic patients who have sustained rat bite injuries.

Although **tetanus** occurs only rarely after human or animal bite injuries, it is important to obtain a detailed immunization history and to provide tetanus toxoid to all patients who are incompletely immunized or who received their most recent tetanus immunization more than five years prior. The need for postexposure **rabies** vaccination in victims of dog and cat bites depends on whether the biting animal is known to have been vaccinated and, most importantly, on local experience with rabid animals in the community. Bites from bats, foxes, skunks, and raccoons should be considered

high risk for rabies, and postexposure prophylaxis is uniformly indicated. For dogs, cats, and other animals that are known or captured, observation for 7-10 days by the local animal control department is indicated, and rabies prophylaxis can be delayed as long as the animal remains asymptomatic. If a biting dog or cat has escaped, a decision about rabies prophylaxis can be based on the circumstances surrounding the bite and advice from local infectious disease specialists and/or health department officials. Worldwide, animal bites and contacts result annually in more than 10 million courses of rabies postexposure prophylaxis.

In human bites where the biter's blood may have contaminated the wound, risk for hepatitis B, hepatitis C, and HIV infections should be considered (see Chapters 322 and 406).

PREVENTION

It is possible to reduce the risk of animal bite injury with anticipatory guidance. Parents should be routinely counseled during prenatal visits and routine health maintenance examinations about the risks of having potentially biting pets in the household. All patients should be cautioned against harboring exotic animals as pets. All young children should be closely supervised, particularly when in the presence of animals, and from a very early age should be taught to respect animals and to be aware of their potential to inflict injury. Reduction of the rate of human bite injuries, particularly in daycare centers and schools, can be achieved by good surveillance of the children and adequate teacher-to-child ratios.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 766

Rat Bite Fever

David A. Hunstad

ETIOLOGY

Rat bite fever is a generic term that has been applied to at least two distinct clinical syndromes, each caused by a different microbial agent. Rat bite fever caused by *Streptobacillus moniliformis* is most commonly reported in the United States as well as in Brazil, Canada, Mexico, Paraguay, Great Britain, and France; it has been identified elsewhere in Europe and in Australia. *S. moniliformis* is a gram-negative bacillus that is present in the nasopharyngeal flora of many laboratory and wild rats. Infection with *S. moniliformis* most commonly occurs following the bite of a rat; however, infection has also been reported in individuals who have been scratched by rats, in those who have handled dead rats, and in those who have ingested milk contaminated with the bacterium (termed **Haverhill fever**). Rat bite fever may also be transmitted by bites from wild mice. Rat bite fever caused by *Spirillum minus,* called **sodoku** (after the Japanese for "rat" and "poison"), is most commonly reported in Asia. *S. minus* is a small, spiral, aerobic gram-negative organism. Reports of rat bite fever from Africa are rare, suggesting under recognition rather than absence of the disease.

CLINICAL COURSE

The incubation period for the streptobacillary form of rat bite fever is variable, ranging from 3-10 days. The illness is characterized by an *abrupt* onset of fever up to 41°C (105.8°F) in over 90% of reported cases, as well as severe throbbing headache, intense myalgias, chills, and vomiting. In virtually all instances, the lesion at the cutaneous inoculation site has healed by the time that systemic systems first appear. Shortly after the onset of the fever, a polymorphous rash occurs in up to 75% of patients. In most patients, the rash consists of blotchy red maculopapular lesions that often have a petechial component; the distribution of the rash is variable, but it is typically most dense on the extremities (Fig. 766.1). Hemorrhagic vesicles may develop on the hands and feet and are very tender to palpation (Fig. 766.2).



Fig. 766.1 Morbilliform rash on the hands/palms (A) and feet (B) of a patient with rat bite fever. *(From Vetter NM, Feder HM Jr, Ratzan RM. Rat bite fever caused by a kiss. Am J Emer Med. 2015;34:1190.e3–1190.e4. Figs. 1 and 3.)*



Fig. 766.2 Hemorrhagic vesicles on the first and third toes of a patient with advanced rat bite fever. *(From Elliott SP. Rat bite fever and Streptobacillus moniliformis. Clin Microbiol Rev. 22007;20:13–22. Fig. 3.)*

Approximately 50% of patients have arthritis, which first manifests toward the end of the first week of disease; early on, the arthritis may be migratory. If untreated, fever, rash, and arthritis last from 14-21 days, often with a biphasic pattern to the fever and arthritis. A wide range of complications are reported in patients with rat bite fever, the most common being pneumonia, persistent arthritis, brain and soft tissue abscesses, and, less commonly, myocarditis or endocarditis. The mortality rate in untreated rat bite fever is estimated to be 10–15%.

The incubation period of sodoku is longer (14-21 days) than that of the streptobacillary form of disease. The hallmark of *Spirillum*-induced disease is fever associated with an indurated, often suppurative, nonhealing lesion at the bite site. Lymphadenitis and lymphadenopathy are invariably present in the regional nodes that drain the inoculation site, and many patients have a generalized macular rash most prominent

when fever is present. In untreated patients, sodoku has a relapsing and remitting course; symptoms abate after 5-7 days of chills and fever but recur 7-10 days later. There may be multiple cycles if the disease is not recognized and treated.

DIAGNOSIS

Diagnosis of the streptobacillary form of rat bite fever is difficult because the disease is uncommon and can be confused with Rocky Mountain spotted fever or (less commonly) meningococcemia. Furthermore, *S. moniliformis* is difficult both to isolate and to identify with classic bacteriologic techniques. The organism is fastidious and is inhibited by sodium polyanethol sulfonate, an additive present in many commercial blood culture bottles. Therefore the clinical microbiology laboratory should be notified when this infection is suspected so that additional media can be inoculated. A definitive diagnosis is made when *S. moniliformis* is recovered from blood or joint fluid or is identified in human samples by polymerase chain reaction (PCR), which has been used successfully in humans.

Diagnosis of sodoku is made on clinical grounds because there are no diagnostic serologic tests and culture of *S. minus* has not been achieved in laboratory media. Rarely, the organism may be visualized in Gram-stained smears of pus from the inoculation site. Approximately 50% of patients exhibit a false-positive Venereal Disease Research Laboratory (VDRL) test.

TREATMENT

Penicillin is the drug of choice for both forms of rat bite fever. Intravenous penicillin G or intramuscular penicillin G procaine is recommended for 7-10 days; a regimen of IV penicillin G for 5-7 days followed by oral penicillin V for an additional 7 days has also been used. Doxycycline, gentamicin, or streptomycin represent effective alternatives for penicillin-allergic patients. Patients with endocarditis caused by *S. moniliformis* require high-dose penicillin G for 4 weeks; the addition of streptomycin or gentamicin might be helpful.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 767

Mpox (Monkeypox)

David A. Hunstad

Since the eradication of **smallpox** (variola), mpox (formerly known as monkeypox) virus has, for humans, become the most important member of the genus ***Orthopoxvirus***. Monkeys are the predominant host for the virus; however, it may be endemic in African rainforest squirrels and is present in African rats, mice, domestic pigs, hedgehogs, and opossums. It has also been identified in and transmitted by imported prairie dogs in the United States and has affected elephants in zoos. Severity of infection varies by viral strain and by host; for example, disease is relatively mild in cynomolgus monkeys but severe in orangutans.

Mpox was first observed in humans from West and Central Africa in the 1970s at the time that smallpox had been eradicated from the area. In the 1970s, the secondary attack rate was around 3% (a stark comparison to the 80% seen in unvaccinated smallpox contacts). Few cases were observed over the next 2 decades; however, during a subsequent outbreak in the 1990s, when immunity to smallpox was no longer prevalent in the population, the secondary attack rate exceeded 75%. Mpox was introduced into the United States in 2003, presumably through rodents from Ghana that infected prairie dogs that were subsequently distributed as pets. Before 2022, primary transmission of the disease was from infected animal to human by bite or by human contact with an infected animal's blood, wound discharge, or other body fluids. Human-to-human transmission was previously thought to be uncommon, but a global outbreak in 2022 was linked to a shift to human-to-human transmission.

As of early 2023, nearly 87,000 cases were documented globally. Although children have comprised up to 40% of cases in previous outbreaks, the epidemiology of the current outbreak is different; less than 700 cases (<2%) have been reported in children and adolescents ≤20 years old. Mpox is currently spread predominantly through close human-to-human contact. The most recent outbreak has affected mostly gay, bisexual, and other men who have sex with men. Patients living with advanced HIV (with low CD4 counts) are at increased risk for severe disease. Although children typically acquire mpox from household contact, sexual contact is the primary route of transmission for adolescents. Mpox virus can persist on surfaces in households with an affected person.

CLINICAL COURSE

The classic clinical signs, symptoms, and course of mpox are similar to those of smallpox, although typically milder. After an incubation period of 10-14 days, during which the mpox virus replicates in lymphoid tissues, humans experience an abrupt onset of malaise, fever, myalgia, headache, and severe backache. Nonproductive cough, nausea, vomiting, and abdominal pain may be present. Generalized lymphadenopathy, a finding unusual in smallpox, is invariably present during the acute stages of mpox illness. After a prodrome of 2-4 days, an exanthem appears on the face and progresses inferiorly, including the palms and soles. As the rash spreads, fevers begin to abate. The rash is initially macular but transforms within hours to firm papules that rapidly vesiculate and become pustular over 2-3 days (Table 767.1). Unlike smallpox lesions but similar to chickenpox lesions, the lesions of mpox tend to occur in crops (Fig. 767.1). Late into the second week of illness, the lesions begin to desiccate, crust, scab, and fall off. During the 2022 global outbreak, lesions often occurred in the genital and anorectal areas and in the mouth (Fig. 767.2); cutaneous lesions are

Table 767.1 Mpox: Lesion Progression Through the Scab Stage

STAGE	STAGE DURATION (DAYS)*	CHARACTERISTICS
Enanthem		Sometimes, lesions first form on the tongue and in the mouth.
Macules	1-2	Macular lesions appear.
Papules	1-2	Lesions typically progress from macular (flat) to papular (raised).
Vesicles	1-2	Lesions then typically become vesicular (raised and filled with clear fluid).
Pustules	5-7	Lesions then typically become pustular (filled with opaque fluid) – sharply raised, usually round, and firm to the touch (deep seated). Finally, lesions typically develop a depression in the center (umbilication). The pustules will remain for approximately 5-7 days before beginning to crust.
Scabs	7-14	By the end of the second week, pustules have crusted and scabbed over. Scabs will remain for about a week before beginning to fall off.

*This is a typical timeline, but timelines can vary.
From Centers for Disease Control and Prevention. Key Characteristics for identifying Mpox. https://www.cdc.gov/poxvirus/mpox/clinicians/clinical-recognition.html



Fig. 767.1 A, Legs and feet of an mpox (endemic) patient. B, Legs and feet of a smallpox patient at an analogous stage of rash (pustular). *(A, Courtesy Joseph M. Harvey, MD. B, Courtesy J. Nobel, Jr., MD, Centers for Disease Control and Prevention.)*



Fig. 767.2 Clinical presentation of mpox. A, Pustules in the genital and pubic region, in which the initial umbilication has progressed to necrotic crust with central depression. B, Three semiconfluent pustular lesions with a depressed center located on the left side of the tongue dorsum. C, Pearly acral vesicles embedded in the thick stratum corneum of the palmar skin, shotty on palpation. D, Scattered papules, pustules, and umbilicated pustules surrounded by an erythematous halo on the lateral aspect of the chest and left arm. E, Pustules circumferentially distributed on the anal margin and perianal skin. F, A pustular lesion with a crusted center on the semimucosa of the lower lip, close to the right oral commissure. G, Primary inoculation site with a large, crusted lesion on the right cheek. H, The right palatine tonsil is reddened and enlarged and has a fibrin-covered ulcer. I, The penile glans and foreskin have lesions of varying sizes and stages of evolution, with edema surrounding the larger ulcer. *(From Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. Lancet. 2022;400[10353]:661–669. Fig. 1; Photos A–C, E–G, I taken by Eloy José Tarín-Vicente, MD; Photos D, H by Maria Ubals, MD.)*

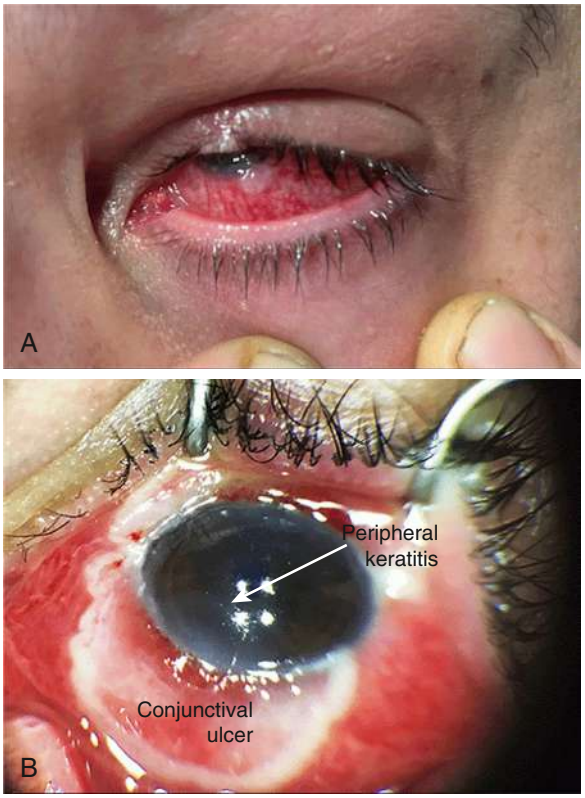

Fig. 767.3 Left eye in a patient with HIV-associated immunocompromise and ocular mpox, with conjunctivitis and conjunctival lesion earlier in the course of mpox illness (**A**), and with conjunctival ulcer and peripheral keratitis later in the course of mpox illness (**B**) — United States, August–September 2022. (*A courtesy Nathanael Adjei-Kyeremeh. B courtesy Dharmendra R. Patel; From Cash-Goldwasser S, Labuda SM, McCormick DW, et al. Ocular monkeypox – United States, July–September 2020. MMWR. 2022;71:1343–1347. Fig. 2.)*

less often disseminated with occasionally only a single lesion noted. Additionally, fever and other systemic symptoms may occur before the rash, *after* the rash, or *not at all*. Disseminated systemic or focal disease may include encephalitis, pharyngitis, myocarditis, arthritis, proctitis, lymphadenopathy, pneumonia, and ocular involvement (Fig. 767.3).

Mpox should be suspected in any child or adolescent who has the characteristic prodrome associated with a poxlike eruption and a history of close contact with someone who has been diagnosed with mpox, residence in Africa, or contact with prairie dogs or exotic mammals such as Gambian rats and rope squirrels. Diagnosis is by isolation of mpox viral DNA by polymerase chain reaction (PCR) from a skin lesion, including exudate or lesion crust. Oropharyngeal swabs may be considered in high-risk contacts of known or probable cases who have not yet developed a rash that can be swabbed (Table 767.2).

Cowpox, another *Orthopoxvirus*, often acquired from a pet rat, may produce similar cutaneous lesions. Regional lymphadenopathy and mild system features may also be present. Diagnosis is confirmed by a specific cowpox virus PCR.

PREVENTION AND TREATMENT

In 2019, the U.S. Food and Drug Administration (FDA) approved a new live-attenuated, replication-deficient vaccinia virus vaccine (branded Jynneos in the United States and Imvamune in the European Union [EU]; Bavarian Nordic) for use in patients ≥18 years old who are at risk for mpox acquisition. Despite evidence that preexposure administration of classical smallpox vaccine is 85% effective in preventing or attenuating mpox disease, the rarity of mpox infection does not warrant universal vaccination. However, following the recent 2022 outbreak, the U.S. Centers for Disease Control and Prevention recommends vaccinating high-risk patients (Table 767.3). This vaccine has a very low side effect profile and can be safely used in immunocompromised individuals, a significant advantage over classical (replication-competent) live smallpox vaccines.

For most immunocompetent patients with mild to moderate disease, supportive care is recommended. However, treatment should be considered for those with severe disease (hemorrhagic disease, large number of confluent lesions, necrotic lesions, severe lymphadenopathy that is necrotic or obstructing, involvement of multiple organ systems and comorbidities, or those who require hospitalization) or those with involvement of anatomic areas where scarring or stricture might cause serious sequelae (Fig. 767.4). In addition, treatment may be considered in patients at high risk for severe disease, including children less than 1 year old, immunocompromised or pregnant patients, or those with reduced skin integrity (e.g., eczema). Treatment options include tecovirimat, brincidofovir, cidofovir, or trifluridine ophthalmic solution; these medications were originally developed for treatment of other viral infections and

Table 767.2 Mpox Case Definitions

CLINICAL AND LABORATORY CLASSIFICATION	CRITERIA
Suspected	New characteristic rash* **OR** Meets one of the epidemiologic criteria and has high clinical suspicion† for mpox
Probable	No suspicion of other recent *Orthopoxvirus* exposure (e.g., vaccinia virus in ACAM2000 vaccination) AND demonstration of the presence of • *Orthopoxvirus* DNA by polymerase chain reaction testing of a clinical specimen **OR** • *Orthopoxvirus* using immunohistochemical or electron microscopy testing methods **OR** • Demonstration of detectable levels of anti-*Orthopoxvirus* IgM antibody during the period of 4-56 days after rash onset
Confirmed	Demonstration of the presence of mpox virus DNA by polymerase chain reaction testing or next-generation sequencing of a clinical specimen **OR** Isolation of mpox virus in culture from a clinical specimen
EPIDEMIOLOGIC CLASSIFICATION	
Within 21 days of illness onset:	Reports having contact with a person or persons with a similar appearing rash or with a person who has received a diagnosis of confirmed or probable mpox **OR** Had close or intimate in-person contact with persons in a social network experiencing mpox infections. This includes MSM who meet partners through an online website, digital application ("app"), or social event (e.g., a bar or party) **OR** Traveled, within 21 days of illness onset outside the United States to a country with confirmed cases of mpox or where mpox virus is endemic **OR** Had contact with a dead or live wild animal or exotic pet that is an African endemic species, or used a product derived from such animals (e.g., game meat, creams, lotions, powders, etc.)
EXCLUSIONS	
A case might be excluded as a suspected, probable or confirmed case if:	An alternative diagnosis* can fully explain the illness **OR** A person with symptoms consistent with mpox does not develop a rash within 5 days of illness onset **OR** A case where high-quality specimens do not demonstrate the presence of *Orthopoxvirus* or mpox virus or antibodies to *Orthopoxvirus*

*The characteristic rash associated with mpox lesions involves the following: deep-seated and well-circumscribed lesions, often with central umbilication; and lesion progression through specific sequential stages: macules, papules, vesicles, pustules, and scabs. The rash can sometimes be confused with other diseases that are more commonly encountered in clinical practice (e.g., syphilis, herpes, and varicella-zoster). Historically, sporadic accounts of patients co-infected with mpox virus and other infectious agents (e.g., varicella-zoster, syphilis) have been reported; so patients with a characteristic rash should be considered for *Mpox virus* testing, even if tests for other infectious agents are positive.

†Clinical suspicion may exist if lesions consistent with those from more common infections (e.g., syphilis, herpes, and varicella-zoster) coexist with lesions that may be characteristic of mpox.

From Centers for Disease Control and Prevention. Updated case-finding guidance: Mpox outbreak – United States, 2022. https://emergency.cdc.gov/han/2022/han00468.asp#:~text

Table 767.3 Mpox Vaccination Basics

Centers for Disease Control and Prevention recommends vaccination against mpox if:

- You had known or suspected exposure to someone with mpox
- You had a sex partner in the past 2 weeks who was diagnosed with mpox
- You are a gay, bisexual, or other man who has sex with men or a transgender, nonbinary, or gender-diverse person who in the past 6 months has had any of the following:
  - A new diagnosis of one or more sexually transmitted diseases (e.g., chlamydia, gonorrhea, or syphilis)
  - More than one sex partner
- You have had any of the following in the past 6 months:
  - Sex at a commercial sex venue (like a sex club or bathhouse)
  - Sex related to a large commercial event or in a geographic area (city or county for example) where mpox virus transmission is occurring
  - Sex in exchange for money or other items
- You have a sex partner with any of the above risks
- You anticipate experiencing any of the above scenarios
- You have HIV or other causes of immune suppression and have had recent or anticipate future risk of mpox exposure from any of the above scenarios
- You work in settings where you may be exposed to mpox:
  - You work with orthopoxviruses in a laboratory
  - You are part of an *Orthopoxvirus* and healthcare worker response team

From Centers for Disease Control and Prevention. Mpox Vaccination Basics. https://www.cdc.gov/poxvirus/mpox/vaccines/index.html

are thought to complement the immune response by reducing replication, maturation, and spread of mpox. Vaccinia immune globulin intravenous (VIGIV) may be considered in immunocompromised patients who cannot mount an appropriate immune response to clear the virus. In addition to antiviral medications, careful attention should be paid to skin hygiene, maintenance of adequate nutrition and hydration, and prompt implementation of local or systemic therapy for secondary bacterial infection that may occur. Pain management is a common reason for hospitalization because both cutaneous and mucosal lesions can be very painful. For prevention of human-to-human spread of disease, a combination of contact, droplet, and airborne infection control procedures should be implemented.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

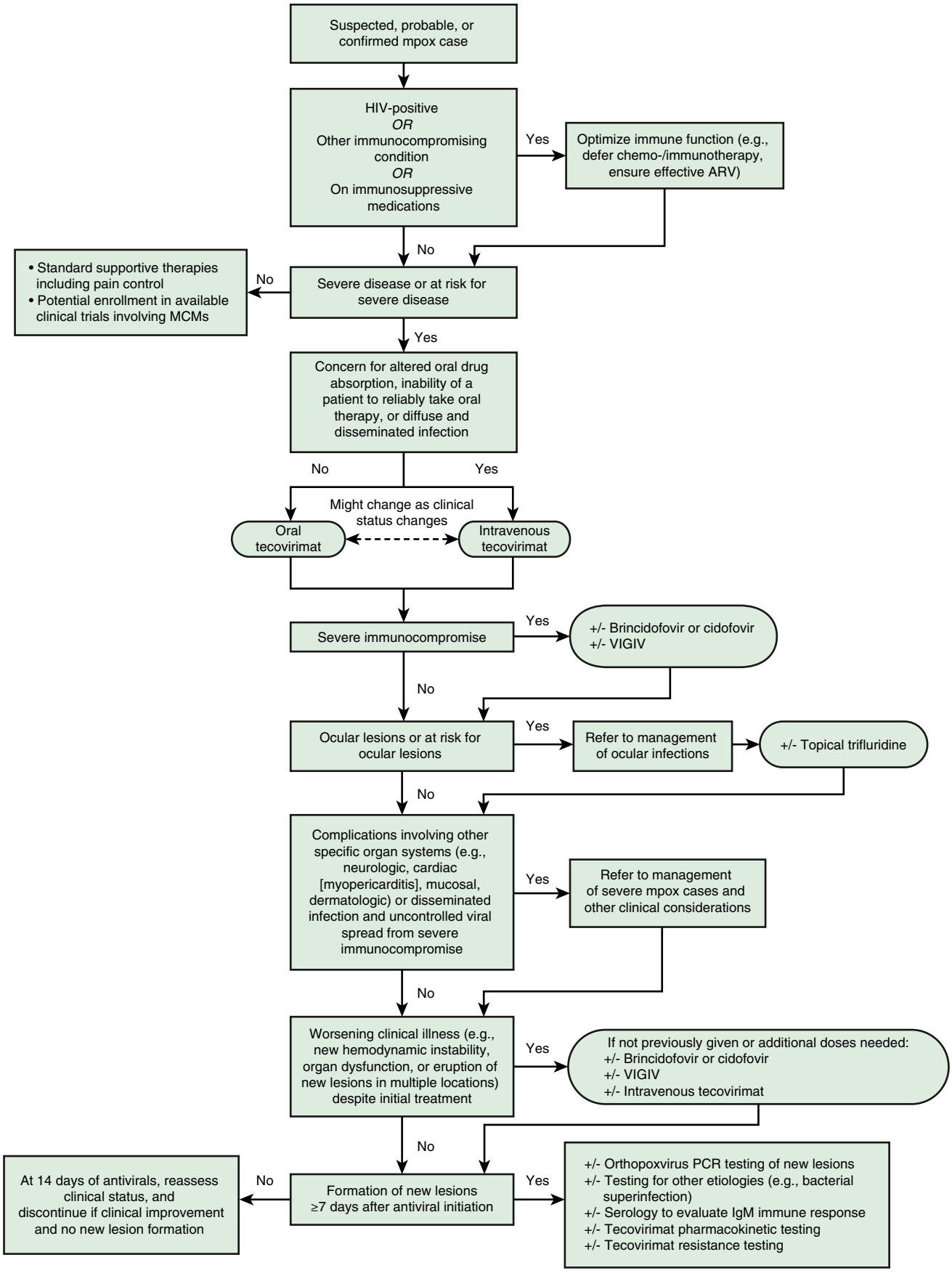
Suspected, probable, or confirmed mpox case
HIV-positive
OR
Other immunocompromising condition
OR
On immunosuppressive medications
Yes
Optimize immune function (e.g., defer chemo-/immunotherapy, ensure effective ARV)
No
Severe disease or at risk for severe disease
No
• Standard supportive therapies including pain control
• Potential enrollment in available clinical trials involving MCMs
Yes
Concern for altered oral drug absorption, inability of a patient to reliably take oral therapy, or diffuse and disseminated infection
No
Yes
Might change as clinical status changes
Oral tecovirimat
Intravenous tecovirimat
Severe immunocompromise
Yes
+/- Brincidofovir or cidofovir
+/- VIGIV
No
Ocular lesions or at risk for ocular lesions
Yes
Refer to management of ocular infections
+/- Topical trifluridine
No
Complications involving other specific organ systems (e.g., neurologic, cardiac [myopericarditis], mucosal, dermatologic) or disseminated infection and uncontrolled viral spread from severe immunocompromise
Yes
Refer to management of severe mpox cases and other clinical considerations
No
Worsening clinical illness (e.g., new hemodynamic instability, organ dysfunction, or eruption of new lesions in multiple locations) despite initial treatment
Yes
If not previously given or additional doses needed:
+/- Brincidofovir or cidofovir
+/- VIGIV
+/- Intravenous tecovirimat
No
Formation of new lesions ≥7 days after antiviral initiation
No
At 14 days of antivirals, reassess clinical status, and discontinue if clinical improvement and no new lesion formation
Yes
+/- Orthopoxvirus PCR testing of new lesions
+/- Testing for other etiologies (e.g., bacterial superinfection)
+/- Serology to evaluate IgM immune response
+/- Tecovirimat pharmacokinetic testing
+/- Tecovirimat resistance testing

Fig. 767.4 Algorithmic approach to treatment*,†,‡ of patients with severe§ or at risk¶ for severe manifestations of mpox** : United States, February 2023.††

* Treatment includes MCMs (i.e., tecovirimat, brincidofovir, cidofovir, VIGIV, and trifluridine) and supportive therapies, including pain management. https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html

† Most immunocompetent patients should display signs of clinical improvement within 4 days of antiviral initiation (i.e., tecovirimat, brincidofovir, cidofovir, and trifluridine). Tecovirimat is expected to reach steady-state concentrations by day 6 of dosing in healthy volunteers; therefore worsening clinical illness after 7 days of treatment in patients with severe illness could prompt additional evaluations.

‡ Concern for altered drug absorption includes the inability to tolerate or take oral therapy (e.g., nothing by mouth), or possibility that the oral drug absorption might be altered because of inability to consume a high-fat meal, severity of symptoms (e.g., systemic illness), comorbidities (e.g., history of gastric bypass or underlying GI disease), or other factors that might alter oral drug absorption.

§ Hemorrhagic disease, a large number of confluent or necrotic lesions, severe lymphadenopathy that is necrotizing or obstructing (e.g., of the upper airway causing airway compromise or of the GI tract necessitating parenteral feeding), edema that is obstructing (e.g., of the lower GI tract), extradermatologic manifestations (e.g., pulmonary nodules, encephalitis, myopericarditis, or ocular infections), and sepsis. Detailed characteristics of severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

¶ Persons with underlying medical conditions (e.g., severe or moderate immunocompromise [https://www.cdc.gov/poxvirus/monkeypox/clinicians/people-with-HIV.html]); bacterial superinfections; or complications, including strictures, edema, and infections of the penile foreskin, vulva, urethral meatus, or anorectum, which could require procedural intervention (e.g., urethral catheterization, colostomy, or surgical debridement). This also includes those with or at risk for ocular lesions (i.e., presence of eyelid lesions, facial lesions near the eyes, or finger or hand lesions in patients unable to avoid touching their eyes [for whom autoinoculation is a concern]). Detailed characteristics of persons at risk for severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

** https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html

†† This figure is a comprehensive synthesis of heterogeneous evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline.

ARV, Antiretroviral medications; GI, gastrointestinal; IgM, immunoglobulin M; MCM, medical countermeasure; PCR, polymerase chain reaction; VIGIV, vaccinia immune globulin intravenous. *(From Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations of severe manifestations of Mpox – United States, February 2023. MMWR. 2023;72:232–243.)*

Chapter 768

Envenomations

Sing-Yi Feng

Envenomations due to snakes, spiders, scorpions, and other venomous animals can cause significant morbidity and mortality, although the majority cause only localized pain and swelling. In the 2020 report of the American Association of Poison Control Centers, approximately 42,800 out of 2.1 million phone consultations were related to bites and stings of various creatures, with approximately 14,000 involving children <20 years of age.

Not every bite from a venomous creature is harmful. In many cases, no venom is injected; these are called **dry bites**. A dry bite may occur for many reasons, including failure of the venom delivery mechanism and depletion of venom. Up to 20% of pit viper, 80% of coral snake, and approximately 50% of all venomous snake bites are dry.

GENERAL APPROACH TO THE ENVENOMATED CHILD

Children may be bitten or stung as they play and explore their environment. The evaluation may be hampered by an unclear history of the circumstances and the possible offending organism, particularly with preverbal children. The overall effects of some venomous bites and stings may be relatively more severe in children than in adults because children generally receive a similar venom load from the offending animal yet have less circulating blood volume to dilute its effects.

General Management

The majority of envenomations require local wound care, pain control, and reassurance. However, the severely envenomated child may require advanced life support interventions including endotracheal intubation and mechanical ventilation. Intravenous access should be obtained in an unaffected extremity if possible (see Chapters 91 and 92) to provide fluids and vasopressors as needed. Early hypotension is usually due to vasodilation and should be treated with volume expansion using appropriate infusion of intravenous crystalloid solution (normal saline boluses of 20 mL/kg; repeated as needed up to three times). Shock unresponsive to volume repletion may require addition of a vasopressive agent such as epinephrine or norepinephrine (in addition to antivenom administration if appropriate). If the presentation is suspicious for an anaphylactic reaction to venom, treatment (including epinephrine) should be initiated as soon as possible (see Chapter 190) along with the appropriate **antivenom**.

The affected body part should be immobilized in a position of function and any areas of edema should be marked, measured, and monitored. If antivenom is available for the envenomation, efforts should be initiated to locate and secure an adequate amount to treat the patient. In the United States, regional poison control centers are available via the national phone number 1-800-222-1222 to facilitate this effort, especially if the species is exotic. Guidance in dosing the antivenom should be obtained from experienced toxicologists via the regional poison center.

General Wound Care

Bites and stings require basic wound care, including copious tap water or normal saline irrigation under pressure when possible. For small puncture wounds, this is impractical, but the skin should still be thoroughly cleansed with soap and water. Tetanus immunization should be updated as needed. Intact bullae should be left to act as a natural sterile dressing to prevent infection, whereas ruptured bullae should be debrided. Exposed tissue should be covered with wet to dry dressings. Necrotic wounds, as seen in some snake and spider bites, should be judiciously debrided, with removal of only clearly necrotic tissue. Reconstructive surgery with skin grafts or muscle/tendon grafts may be necessary later. Prophylactic antibiotics are usually not necessary because venom is bacteriostatic. Antibiotics should generally be reserved for signs of established secondary infection.

SNAKE BITES

Most snake bites are inflicted by nonvenomous species and are of no more consequence than a potentially contaminated puncture wound. Anatomic features including head shape, pupil shape, and anal plate arrangement can be used to differentiate venomous and nonvenomous snakes (Fig. 768.1). Medically important venomous snakes in the United States belong to two families: **Crotalinae** and **Elapidae** (Table 768.1). Most snakebites occur

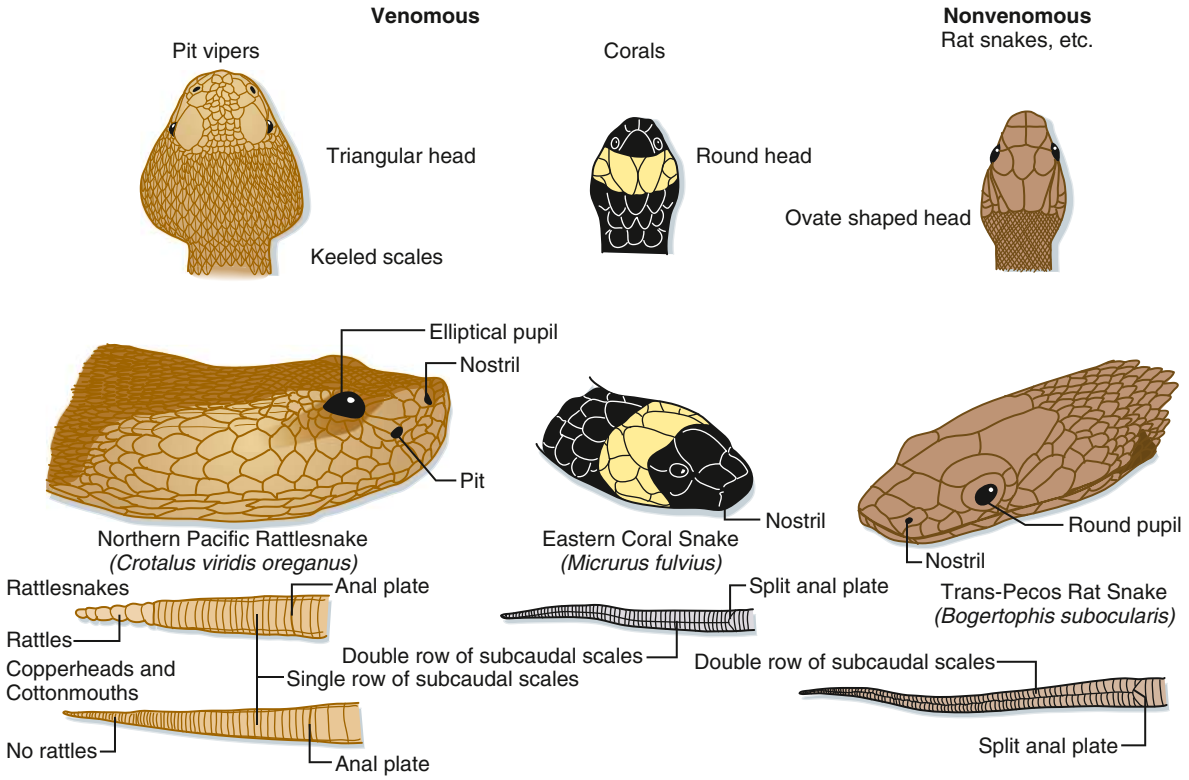

Fig. 768.1 Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States. *(Modified from Adams JG, ed. Emergency Medicine. Philadelphia: WB Saunders; 2008. Drawing by Marlin Sawyer.)*

Table 768.1 Important Venomous Snake Families in the United States

FAMILY	EXAMPLES	TOXIN EFFECTS/OTHER COMMENTS	ANTIVENOM
Crotalinae (pit vipers)	Rattlesnakes (*Crotalus* and *Sistrurus* spp.), cottonmouths and copperheads (*Agkistrodon* spp.)	Heat-sensing "pit" between each eye and nostril Toxins cause tissue damage, coagulopathy, cardiovascular collapse Exception: Mojave rattlesnake (*Crotalus scutulatus*) – neurotoxic venom	*Crotalinae* polyvalent immune Fab
Elapidae	Coral snakes (*Micrurus* spp.)	Venom is neurotoxic	Antivenin *(Micrurus fulvius)*

from April through September, when snakes are at their most active. Males sustain 75% of bites and children <5 years of age account for 10–15%. Bites are usually located on extremities, although other parts of the body have been reported. In the United States, approximately 98% of venomous snake bites are inflicted by pit vipers (Crotalinae). A small fraction of bites are caused by coral snakes (Elapidae) in the southern and southwestern states and by exotic pet snakes that have been imported.

Venoms and Effects

Snake venoms are complex mixtures of proteins including enzymes that cause local tissue destruction and other enzymes that have potentially lethal systemic effects including coagulopathy and neurotoxicity. The symptoms and severity of an envenomation vary according to the type of snake, the amount of venom injected, and the location of the bite. About 25% of snakebites are **"dry bites,"** where the patient has fang marks and puncture wounds but no pain, swelling, or systemic effects as no venom was injected. Most pit viper bites cause significant local pain, swelling, and ecchymosis and may result in necrosis of the affected extremity (Fig. 768.2). Pain and swelling typically begin quickly after the bite and may progress over hours to days. Serious envenomation may result in a consumptive coagulopathy, hypotension, and respiratory distress. In contrast, venom from the Elapidae is neurotoxic with little or no local tissue damage. These bites cause variable local pain, and the onset of systemic effects can be delayed for hours. Manifestations of neurotoxicity generally are caused by curare-like blockade at the neuromuscular junction. Symptoms usually begin with cranial nerve palsies such as ptosis, dysarthria, and dysphagia and may progress to respiratory failure and complete paralysis. Some pit vipers, including the Southern Pacific rattlesnake *(Crotalus oreganus helleri),* western diamondback rattlesnake *(Crotalus atrox),* timber rattlesnake *(Crotalus horridus),* and Mojave rattlesnake *(Crotalus scutulatus),* can also cause significant neurotoxicity, like the Elapidae. Regional poison control centers and toxicologists should be consulted early in the course of treatment.

Management

Prehospital care should focus on rapid transport to the emergency department while providing supportive care. Constrictive clothing, jewelry, and watches should be removed, and the injured body part should be immobilized in a position of function at the level of the heart. Many popularized field treatments for snake bites, such as



Fig. 768.2 Southern Pacific rattlesnake bite *(Crotalus oreganus helleri)* in a 2-yr-old child. Note the fang marks, swelling, and bruising of the tissues (photograph taken 2 hours following the bite). *(Courtesy Sean Bush, MD.)*

tourniquets, ice, electric shock, incision, and suction, have proven ineffective or deleterious.

At the hospital, supportive care should be continued as an effort is made to identify the offending snake and secure the appropriate antivenom (if applicable). In severe envenomations, advanced respiratory support may be required, including endotracheal intubation and mechanical ventilation. Intravenous access should be established in an unaffected extremity, intravenous fluids administered as needed, and standard laboratory specimens obtained, including complete blood count, coagulation studies, fibrinogen concentration, and serum chemistry analysis including total creatine kinase. Laboratory studies should initially be repeated every 4-6 hours to monitor the patient's progress and response to therapy. If tourniquets are placed in the field, they should be cautiously removed after venous access is obtained due to possible adverse effects that may follow from a sudden release of venom into the systemic circulation. The bitten extremity should be marked with the leading edge of the erythema and edema as well as the time to monitor progression of the swelling.

Assessment of the severity of the envenomation in the field and at the hospital is essential in determining the appropriateness of antivenom therapy for the snakebite victim (Table 768.2). Antivenoms are relatively specific for the genus of snake whose venom they are designed to neutralize. If it is determined that the patient requires antivenom, appropriating the correct antivenom should begin as soon as possible by discussing the matter with the hospital pharmacy, regional poison control center, and perhaps local zoos and museums that keep captive snakes because they often stock exotic snake antivenom.

Table 768.3 lists the indications for administering antivenom. CroFab, a Crotalinae polyvalent immune Fab antivenom (FabAV), is approved by the U.S. Food and Drug Administration (FDA) for use in crotalid envenomations. FabAV is derived from sheep (ovine) antibodies to crotalid snake venom, and side effects include both immediate and delayed hypersensitivity reactions. FabAV is derived from four snakes, three from the genus *Crotalus* (the eastern diamondback rattlesnake, the western diamondback rattlesnake, and the Mojave rattlesnake) and one from the genus *Agkistrodon* (the cottonmouth or water moccasin). It is effective against the venoms of all Crotalinae snakes in the United States. There is cross reactivity with FabAV against venom from copperhead snakes *(Agkistrodon contortrix)*. However, copperhead bites often do not require treatment with antivenom because they cause fewer systemic effects and less severe local tissue damage. Most copperhead envenomations cause only local tissue swelling, ecchymosis, and pain and generally do well with good supportive care and pain control. Any child with evidence of systemic toxicity should receive FabAV.

Initial dosing of FabAV is aimed at control of symptoms (progressive tissue swelling, thrombocytopenia, coagulopathy, neurotoxicity, or systemic toxicity). The dose is repeated until initial control of toxicity is achieved (see Table 768.3). Subsequent maintenance dosing may be needed to prevent or treat recurrence of venom effects because, due to its small molecular size, the half-life of FabAV is considerably shorter than that of crotalid venom constituents. Patients with significant envenomation should be followed for late hematologic abnormalities (coagulopathy) that can occur up to 2 weeks after the bite. Although these tend to be mild laboratory coagulopathies without clinical bleeding, rare cases of severe delayed bleeding have been reported. Further antivenom therapy should be considered for such delayed or recurrent coagulopathy as outlined in Table 768.4.

In April 2021, the U.S. FDA approved a crotaline immune Fab2 antivenin (Fab2AV) to treat adult and pediatric patients with North American Crotaline envenomations marketed as AnaVIP. This antidote is an equine-derived antivenin and, due to it being a Fab2 fragment, has a longer half-life than the FabAV. It has a similar side effect profile as the FabAV including anaphylactoid and hypersensitivity reactions. Initial dosing is 10 vials given intravenously over 60 minutes. If the symptoms continue to progress, then 10 vials can be given every hour until there is no further progression of symptoms. Patients should be observed for a minimum of 18 hours after the Fab2AV infusion. If a patient has reemerging symptoms including coagulopathies, then an additional four vials of the Fab2AV can be infused (Table 768.5).

Envenomation of the extremities can mimic compartment syndrome, with severe pain and swelling. It is important to treat these patients aggressively with FabAV or Fab2AV and pain control to control the severe pain and swelling. Although fasciotomy was once advocated for the treatment of crotalid snakebites of the extremities, it is now a treatment of last resort only if aggressive FabAV or Fab2AV treatment is unable to stop the progression of pain and swelling and true compartment syndrome is documented with measurement of intracompartmental pressure.

The antivenom for coral snakes *(Micrurus fulvius)* has been the recommended treatment for envenomation by the eastern coral snake *(M. fulvius)* and the Texas coral snake *(Micrurus tener)*. Indications for this antivenom are the development of any neurologic signs and symptoms of coral snake envenomation including paresthesias, slurred speech, respiratory difficulties, muscle weakness, and fasciculations. Due to it being equine in origin, its side effect profile includes anaphylaxis and allergic reactions. Most hospitals do not carry this antivenom and local poison centers should be notified to help locate supplies. Respiratory supportive care including endotracheal intubation and mechanical ventilation for respiratory failure remains the mainstay of treatment.

Disposition

If, after observation for 6-8 hours, a patient exhibits only fang-induced puncture marks with no local or systemic symptoms, the wounds can be considered dry bites and the patient can be safely discharged home. Patients with significant toxicity and those requiring treatment with antivenom should be admitted to the hospital. Patients with a history of eastern or Texas coral snakebite should be admitted to a monitored setting for 24 hours to observe for neurologic toxicity so that respiratory support can be provided as needed. Children should be admitted to an intensive care setting if they develop severe and progressive local tissue toxicity or evidence of systemic toxicity including coagulopathy, neurotoxicity, hemodynamic instability, or respiratory difficulties.

SPIDER BITES

In the United States, 18 genera of spiders have been identified that cause clinically significant envenomation. The spiders of importance in the United States include the *Latrodectus* species (the widow spiders) and the *Loxosceles* species (the recluse spiders).

Table 768.2 Pit Viper Envenomation Classification

GRADE	CLINICAL FEATURES	ANTIVENOM	DISPOSITION
0 (None)	No evidence of envenomation. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 hr after the bite. No laboratory changes occur.	No	Observe for 8-12 hr. May be discharged if repeat labs are normal and no signs of envenomation develop.
I (Minimal)	Pain is moderate or throbbing and localized to the fang wound, surrounded by 1-5 inches of edema and erythema. No evidence of systemic involvement is present after 12 hr of observation. No laboratory changes occur.	No	Admission for 12-24 hr. Repeat labs every 6 hr. May be discharged if repeat labs are normal and no signs of envenomation develop.
II (Moderate)	There is more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.	Yes	Admission to intensive care unit.
III (Severe)	This may initially resemble a grade I or II; however, within 12 hr, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.	Yes	Admission to intensive care unit.
IV (Very severe)	Sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 min of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.	Yes	Admission to intensive care unit.

From Curtis AM, Erickson TB. Venomous animal injuries. Walls RM, ed. *Rosen's Emergency Medicine*, 10th ed. Philadelphia: Elsevier; 2023: Table 53.2, p. 696.

Table 768.3 Crotaline Fab Antivenom Dosing Guidelines

DOSE	RECOMMENDATIONS
Initial dose: four to six vials IV	• Reconstitute each vial of FabAV in 18 mL normal saline for injection and mix with continuous manual inversion at the rate of one to two inversions per second until no solid material is visible in the vial. • Further dilute four to six vials of reconstituted FabAV in 250 mL normal saline. • Infuse FabAV over 1 hr IV. • Start with slow infusion rate of 25-50 mL/hr for 10 min. • If no acute allergic reaction occurs, increase rate to 250 mL/hr to complete infusion. • The volume of the infusion may be decreased for the very small child or volume-sensitive patient. • Observe 1 hr after initial dose to assess for control of envenomation. • Repeat four to six vials of FabAV as needed to gain initial control.
Maintenance dose: two vials IV every 6 hr × 3 doses	• Monitor for delayed or recurrent toxicity requiring additional FabAV. • Antivenom dose requirements vary depending on the individual patient's response and clinical course. • Patients with mild envenomation may not require maintenance dosing beyond the initial dose.

Adapted from Goto CS, Feng SY. Crotalidae polyvalent immune Fab for the treatment of pediatric crotaline envenomations. *Ped Emerg Care*. 2009;25(4):273–279; and from Crofab Package Insert (revised 2018).

Table 768.4 Indications for Administration of Additional Antivenom in Patients with Recurrent Coagulopathy or Thrombocytopenia After Initial Control

- Evidence of clinically significant bleeding
- Platelet count below 25,000/mm^3
- International normalized ratio (INR) >3
- Activated partial thromboplastin time (aPTT) >50 seconds
- Fibrinogen <50 mg/dL
- Presence of multicomponent coagulopathy
- Worsening trend in a patient with prior severe coagulopathy
- High-risk behavior for trauma
- Certain comorbid conditions (e.g., systemic vasculitis, seizure disorders, prior stroke)

From Norris RL, Bush SP, Cardwell MD. Bites by venomous reptiles in Canada, the U.S. and Mexico. In: Auerbach PS, ed. *Wilderness Medicine*, 7th ed. Philadelphia: Elsevier; 2017.

Latrodectus Spiders

The *Latrodectus* species are found throughout the United States and include *L. mactans* (Fig. 768.3; **black widow** spider), *L. hesperus* (western black widow), *L. bishop* (red widow spider), *L. variolus,* and *L. geometricus* (brown widow spider). They are indigenous to every state except Alaska. The classic hourglass-shape marking is found only in *L. mactans*. They like to live close to the ground in secluded and dimly lit areas such as barns, sheds, and garages.

Venoms and Effects

Latrodectus spiders possess venoms that act at neuromuscular and autonomic nervous system synapses, resulting in excessive release of

Table 768.5	Crotaline Fab2 Antivenom Dosing Guidelines
Initial Dose: 10 vials (*no known maximum dose of Crotaline Fab2 antivenom)	• Reconstitute 10 vials for less than 1 min each using 10 mL sterile normal saline per vial • Combine all vials and dilute to a total volume of 250 mL sterile normal saline • Infuse at 25-50 mL/hr for 10 min; if tolerated at 250 mL/hr to completion
Evaluate for control	60 minutes after infusion, check for: • Local injury not progressing • Coagulation parameters improving • Systemic effects resolved
Observe	• Observe for at least 18 hr after initial control • If symptoms reemerge, can administer four vials in 250 mL

Adapted from AnaVIP package insert.



Fig. 768.3 Female black widow spider *(Latrodectus mactans).* Note the red hourglass-shaped marking on the underside of her abdomen. *(From The Centers for Disease Control and Prevention Public Health Image Library, Image #5449.)*

neurotransmitters. All of the widow spiders possess similar venoms, with the most important neurotoxin being α-latrotoxin.

Bites by the neurotoxic spiders tend to be very painful, and the offending spider is often seen. Systemic effects may include hypertension, tachycardia, bradycardia, hypersalivation, diaphoresis, and diffuse muscle spasm. Nausea, vomiting, abdominal pain, and abdominal rigidity may mimic appendicitis or another acute abdominal emergency.

Management

The management of a neurotoxic spider envenomation centers on sound supportive care. Generous doses of opioid analgesics and benzodiazepines should be utilized to ease severe pain and muscle spasm. *Latrodectus* antivenom (Wyeth) is equine-derived and may be considered to reverse severe systemic effects of widow spider envenomation. Although effective, it is associated with anaphylaxis, serum sickness, and anaphylactoid reactions and should be reserved for high-risk patients such as pregnant women at risk of spontaneous abortion due to the severe pain. One vial is administered via intravenous infusion. Efficacy is usually noted within 1 hour of administration, with reversal of systemic toxicity and relief of pain. Occasionally a second vial is necessary. Due to the possibility of severe or life-threatening reactions, the risks and benefits should be carefully considered and the antivenom infused slowly with continuous monitoring and preparation to treat anaphylaxis should it occur.



Fig. 768.4 Male recluse spider (*Loxosceles* spp.). Note the distinct violin-shaped marking on the dorsum of the cephalothorax. *(Courtesy Michael Cardwell/Extreme Wildlife Photography)*

Loxosceles Spiders

Venoms and Effects

The spiders most notorious for their dermonecrotic potential are the recluse spiders of the genus *Loxosceles*. The best-known member of this genus is the **brown recluse** (*Loxosceles reclusa*; Fig. 768.4), found in the midwestern and southern regions of the United States. The venom of *Loxosceles* spiders contains a phospholipase enzyme, sphingomyelinase D, as well as hyaluronidase. Hyaluronidase is the spreading factor that enables the venom to penetrate tissues, but it does not induce tissue damage. Sphingomyelinase D causes necrosis, red blood cell hemolysis, and platelet serotonin release. The bite of this spider is generally painless and initially goes unnoticed. A few hours after the bite, the area begins to blister and bleed and become painful. Within a day or two, the site will ulcerate and develop violaceous necrosis with surrounding ecchymosis and a rim of pale ischemia ("red, white, and blue" reaction). The lesion may gradually expand over a period of days to weeks until necrotic tissue sloughs and healing begins (Fig. 768.5).

Rare cases of systemic loxoscelism appear to be more common in young children. Patients present with systemic toxicity, including fever, chills, nausea, malaise, diffuse macular rash, and petechiae; they may experience hemolysis, coagulopathy, and renal failure.

In cases of necrotic dermal lesions with no identified spider as the culprit, a broad differential diagnosis must be considered to ensure appropriate management. The differential diagnosis includes skin infections (particularly methicillin-resistant *Staphylococcus aureus;* see Chapter 227), pyoderma gangrenosum, or ecthyma gangrenosum.

Management

The management of necrotizing spider bites includes good wound care, updating of tetanus status, and administration of antibiotics if there is secondary bacterial infection. Daily wound cleansing and splinting of the affected area should be provided until the wound has healed.

No therapy has been definitively proven effective in limiting the extent of necrosis after a recluse spider bite, including steroids, dapsone, colchicine, cyproheptadine, nitroglycerin, hyperbaric oxygen, and early excision of tissue. Meticulous wound care is the mainstay of treatment, and large lesions may require delayed secondary closure with skin grafting after clear tissue demarcation has occurred.

Patients with signs and symptoms of systemic loxoscelism should be admitted to the hospital for supportive treatment of hypovolemia, coagulopathy, hemolysis, and acute kidney injury. There is no commercially available antivenom in the United States for the management of necrotizing spider bites such as those from *Loxosceles* species.



Fig. 768.5 Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt. Ulceration and necrosis at day 1 (A), day 9 (B), day 16 (C), and day 25 (D). *(From Isbister G, Fan HW. Spider bite. Lancet. 2011;378:2039–2046. Fig. 3. Photographs by Ceila MS Malaque.)*

Disposition

Victims with necrotic skin lesions should be monitored with frequent outpatient wound checks to determine progression of the lesion. Children with rapidly progressive dermonecrosis or systemic toxicity should be admitted to the hospital for supportive therapy, which may include intensive care admission for hemolysis, coagulopathy, renal failure, or hypotension.

SCORPION STINGS

There are more than 650 species of scorpions worldwide, some of which are capable of causing severe or lethal envenomation. In the United States, there are two clinically significant scorpions: ***Centruroides exilicauda*** (the bark scorpion) and ***Centruroides vittatus.*** Most scorpion envenomations occur in the southwestern United States, and fatalities are rare. In other regions of the world, especially Latin America, Africa, the Middle East, and Asia, a number of scorpions regularly cause fatalities.

Venoms and Effects

Centruroides scorpion venom contains phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins, resulting in severe pain and paresthesia as well as systemic symptoms of excessive nerve depolarization and release of acetylcholine and catecholamines. The manifestations of scorpion stings in children vary from mild to severe and can include autonomic and somatic toxicity. Autonomic toxicity includes hypertension, tachycardia, hypersalivation, emesis, diaphoresis, and bronchoconstriction, although respiratory failure is rare. Somatic motor toxicity includes ataxia, fasciculations, myoclonus, and opsoclonus. Patients are often restless or agitated, and cranial nerve dysfunction may occur.

Management

Most scorpion stings do not produce severe effects and require only wound care and orally administered pain medications. However, patients with more severe symptoms may require intravenous opioids for analgesia and benzodiazepines for severe muscle spasm or agitation.

A bark scorpion–specific antivenom, Anascorp (Bioclon, Mexico), is approved by the FDA. This antivenom is recommended for critically ill patients with neurotoxicity or other severe symptoms, including intractable pain that is not responsive to adequate doses of opioid analgesics. Small children are more likely than adults to develop such severe symptoms. It is best to discuss antivenom therapy with the regional poison control center for guidance.

Disposition

Patients who have had mild scorpion stings with only local effects can be safely discharged home with wound care instructions, analgesics, and close outpatient follow-up. Patients with evolving symptoms, intractable pain, neurotoxicity, or other systemic toxicity should be admitted to the hospital, especially if scorpion antivenom is being considered. Those with severe toxicity should be admitted to an intensive care unit.

HYMENOPTERA STINGS

The insect order Hymenoptera includes the stinging ants, bees, and wasps, which are characterized by the presence of a modified ovipositor (the "sting" or "stinger") at the end of the abdomen through which venom is injected. Various members of the order can be found throughout the world.

Venoms and Effects

Hymenoptera venom is a complex mixture of proteins, enzymes, and vasoactive substances that result in local tissue injury and inflammation. Most stings cause only local pain, redness, and swelling followed by itching and resolution. Some patients experience a large local reaction in which swelling progresses beyond the sting site, possibly involving the entire extremity. Approximately 0.4–0.8% of children and 3% of adults are at risk for acute, life-threatening allergic reactions as a result of Hymenoptera venom sensitivity; anaphylaxis due to Hymenoptera envenomation causes an average of 62 deaths annually in the United States (see Chapter 187). Rare cases of delayed serum sickness can follow Hymenoptera stings (see Chapter 191). Africanized honeybees *(Apis mellifera scutellata)*, an aggressive hybrid of western honeybee species with African bee species, can cause massive stinging episodes resulting in systemic venom toxicity with hypotension, respiratory failure, shock, hemolysis, and renal failure.

Management

Patients with typical local reactions can be treated with supportive care including analgesics and antihistamines as needed. Patients with large local reactions should also receive a course of oral corticosteroids and a prescription for an epinephrine autoinjection kit including instructions in its use before discharge. Patients presenting with urticaria, angioedema, wheezing, or hypotension should be treated with aggressive supportive care including standard therapy for anaphylaxis such as intramuscular epinephrine, corticosteroids, antihistamines, intravenous fluids, oxygen, and airway management as needed (see Chapter 190). Patients suffering massive stinging episodes may also require critical care resuscitation.

Disposition

Patients with local reactions can be discharged with continued outpatient care that may include analgesia and antihistamines. More difficult disposition decisions are involved for children with systemic manifestations. Children with only diffuse urticaria who are stable after a period of observation can be discharged home to continue a short course of antihistamines and steroids and to carry an epinephrine self-administration kit. These children are at low risk for progressing to systemic anaphylaxis with future stings. Children suffering more than simple urticaria (e.g., wheezing, evidence of laryngeal edema or cardiovascular instability) should be treated aggressively and admitted for at least 24 hours of observation. They should receive a referral to allergy/immunology to test for Hymenoptera venom sensitivity and possible immunotherapy. Immunotherapy reduces the risk of systemic anaphylaxis from future stings in high-risk patients from 30–60% to <5%.

MARINE ENVENOMATION

The classes of venomous marine animals that cause the most morbidity and mortality in humans are the **Cnidaria** (including jellyfish, the Portuguese man-of-war, Pacific blue bottle, fire coral, sea nettles, anemones, and others), Mollusca (blue-ringed octopus and cone snails), Chondrichthyes (stingrays), and members of the family Scorpaenidae (lionfish, scorpionfish, and stonefish).

Venoms and Effects

All members of the Cnidaria have unique stinging cells called nematocysts. These cells contain a highly folded tubule that discharges on contact, penetrates the skin, and injects venom. The venom is antigenic and can be dermonecrotic, hemolytic, cardiotoxic, or neuropathic, depending on the species. The **Pacific box jellyfish** *(Chironex fleckeri)* of Australia, with its cardiotoxic venom, is known to cause stings that are rapidly fatal due to cardiac arrest and pulmonary edema. Although fatal anaphylaxis to jellyfish stings has been reported in coastal waters of the United States, these events are rare. For clinicians in the Americas, the primary concern with Cnidaria envenomation is localized pain that may be associated with paresthesias or pruritus. Occasionally, victims may have systemic symptoms such as nausea, vomiting, headache, and chills.

The phylum **Mollusca** includes octopi and cone snails (*Conus* sp.). The **octopus** of toxicologic significance is the *Hapalochlaena maculosa* (blue-ringed octopus), which is primarily found in Australian waters. The blue-ringed octopus secretes **tetrodotoxin** (the same toxin found in pufferfish) in its salivary gland. The beak of the octopus punctures the skin and delivers the tetrodotoxin. Tetrodotoxin blocks sodium channels in neurons, leading to paralysis. The venom also contains other toxins, including vasoactive agents and enzymes that cause local tissue injury. Cone snails have a hollow proboscis with a tooth that can be extended to inject venom into the victim. Venom of the *Conus* species contains conotoxins that target multiple receptors, including voltage, ligand, and G-mediated receptors. Conotoxins cause a variety of symptoms including severe pain, weakness, tissue ischemia, cyanosis, and numbness. Systemic symptoms are usually neurologic and include aphonia, aphasia, weakness, paralysis, respiratory failure, cardiovascular collapse, and ultimately death.

The **stingray** has a sharp, retroserrated spine and associated venom gland at the base of its tail. Envenomation often occurs when the victim steps on the animal hidden in the surf and the tail is whipped around to puncture the lower extremity. Injuries involve jagged lacerations from the spine, often with retained debris (spine fragments, glandular tissue, and sand). The venom has vasoconstrictive properties that can result in tissue necrosis and poor wound healing. Stingray envenomations are noteworthy for immediate and intense pain at the site of injury that lasts 24-48 hours. Some patients experience nausea, vomiting, and muscle cramps. Rarely, hypotension or seizures occur.

The Scorpaenidae have venomous dorsal, pelvic, and anal spines that become erect when the animal is threatened. The venom glands associated with these spines contain multiple toxins, enzymes, and vasoactive substances. Envenomation causes immediate severe pain that may persist for hours or days. Victims may experience local tissue destruction, and superinfections are common. Systemic symptoms include diaphoresis, nausea, vomiting, diarrhea, abdominal pain, muscle cramping, and headache. In severe cases, paralysis, respiratory failure, hypotension, dysrhythmias, and cardiovascular collapse have been reported.

Management

Treatment of Cnidaria stings should begin immediately after envenomation. Dousing the sting site with vinegar has been shown to inhibit nematocyst discharge. If vinegar is not immediately available, the area should be washed with seawater; freshwater should be avoided as it is thought to stimulate firing of remaining nematocysts. Visible tentacle fragments should be removed with a gloved hand or forceps, and microscopic fragments may be removed by gently shaving the affected area. Folk remedies such as rubbing the sting with sand and applying urine are not helpful and cause more irritation. Meat tenderizer is usually not effective. Antihistamines and corticosteroids are indicated for swelling and urticaria. An acute anaphylactic reaction should be treated with intramuscular epinephrine. Antibiotics are usually not necessary.

Patients who have been envenomated by Mollusca are treated supportively. There are no antivenoms available for either the blue-ringed octopus or the cone snails. Adequate pain control should be provided as needed. Cardiovascular support may be required, and severe neurologic toxicity such as respiratory failure should be managed via airway management and mechanical ventilation.

Treatment of stingray and Scorpaenidae stings is similar. These toxins are heat-labile, and immersion in hot water (approximately 42°C [107.6°F]) for 30-60 minutes denatures the protein constituents and decreases pain significantly. The wounds should be thoroughly cleansed and explored with use of local or regional anesthesia to rule out retention of spine or integument fragments. Stingray spines are radiopaque and may be seen on radiographs or identified by ultrasonography. Lacerations should be treated with delayed primary closure or allowed to heal by secondary intention. Systemic analgesia should be provided as needed. Because of the risk of secondary bacterial infection, there should be a low threshold for administering prophylactic antibiotics to cover *Staphylococcus, Streptococcus,* and *Vibrio* species, and wounds should be rechecked at 3 and 7 days postinjury. An equine Fab stonefish antivenom is available for severe stonefish envenomation with systemic toxicity or intractable pain.

Disposition

After wound care and effective analgesia, most victims can be discharged home. If there are significant systemic effects, the patient should be admitted for monitoring and further care as needed.

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

Chapter 769

Laboratory Testing in Infants and Children

Stanley F. Lo and Stephen M. Roper

Normal values **(reference intervals)** are difficult to establish within the pediatric population. Differences in genetic composition, physiologic development, environmental influences, and subclinical disease are variables that need to be considered when developing reference intervals. Other considerations for further defining reference intervals include partitioning based on sex and age. The most commonly used reference range is generally given as the **mean** of the reference population ±2 standard deviations (SD). This is acceptable when the distribution of results for the tested population is essentially gaussian (normal). The serum sodium concentration in children, which is tightly controlled physiologically, has a distribution that is essentially gaussian; the mean value ±2 SD gives a range very close to that actually observed in 95% of children (Table 769.1). However, not all analytes have a gaussian distribution. The serum creatine kinase level, which is subject to diverse influences and is not actively controlled, does not show a gaussian distribution, as evidenced by the lack of agreement between the range actually observed and that predicted by the mean value ±2 SD. In these cases, a reference interval defining the 2.5-97.5 percentiles is typically used.

Reference cutoffs are typically established from large studies with a healthy reference population. Examples of these cutoffs are illustrated by reference cutoffs established for cholesterol, lipoproteins, and neonatal bilirubin. Patient results exceeding these cutoffs have a future risk of acquiring disease. A final modification needed for reporting reference intervals is referencing the Tanner stage of sexual maturation (sexual maturity rating scale), which is most useful in assessing pituitary and gonadal function.

The establishment of common reference intervals remains an elusive target. Although some patient results are directly comparable between laboratories and methods, most are not. Careful interpretation of patient results must consider when testing was performed and what method was used. **Higher-order methods**, methods that are more accurate and precise, continue to be slowly developed. These will be critical to the standardization of tests and the establishment of common reference intervals.

COMMON CHALLENGES IN PEDIATRIC LABORATORY MEDICINE

There are several challenges in pediatric lab medicine that are encountered infrequently, are less consequential, or do not apply to adult populations. For example, the rate of in-vitro hemolysis is increased in children because of the use of inappropriate needle or tubes sizes, applying too much pressure to the site of a finger or heel-stick collection, or simply drawing a specimen rapidly to minimize the discomfort of the child. Hemolyzed specimens can lead to inaccurate results for several analytes because of spectrophotometric interference caused by hemoglobin, dilution effects, or because of the release of other red blood cell components (e.g., lactate dehydrogenase [LDH]). A related issue is the frequent occurrence of physiologic jaundice. Like hemoglobin, bilirubin can absorb light and influence with spectrophotometric analyses. Although many chemistry analyzers can detect these interferences and suppress affected results, specimens frequently must be recollected. Likewise, the increased hematocrit common in the first month of life can lead to decreased amount of plasma/serum from a given blood volume. This phenomenon can result in the need for repeat phlebotomy or larger starting volumes of whole blood. In addition to blood, urine is another difficult fluid to work with in children. Noninvasive urine collections from infants often require special collection techniques (bags, cotton balls) that may only capture small volumes. Coupled with the relatively dilute urine typically produced by newborns, urine specimens may require concentration, or analyzer measurement ranges may need to be adjusted to provide useful information. Other challenges in pediatric lab medicine include, but are not limited to, the use of small ("bullet") blood collection tubes that are incompatible with automated sample handlers, the need for specialized testing (e.g., sweat test, newborn screening), and working with specimens drawn from indwelling catheters that may be contaminated with IV or total parenteral nutrition (TPN) fluid.

ACCURACY AND PRECISION OF LABORATORY TESTS

Technical accuracy, or trueness, is an important consideration in interpreting the results of a laboratory test. Because of improvements in methods of analysis and elimination of analytic interference, the accuracy of most tests is limited primarily by their precision. **Accuracy** is a measure of the nearness of a test result to the actual value, whereas **precision** is a measure of the reproducibility of a result. No test can be more accurate than it is precise. Analysis of precision by repetitive measurements of a single sample gives rise to a gaussian distribution with a mean and an SD. The estimate of precision is the coefficient of variation (CV):

$$CV = \frac{SD}{Mean} \times 100$$

The CV is not likely to be constant over the full range of values obtained in clinical testing, but it is approximately 5% in the normal range. The CV is generally not reported but is always known by the laboratory. It is particularly important in assessing the significance of changes in laboratory results. For example, a common situation is the need to assess hepatotoxicity incurred because of the administration of a therapeutic drug and reflected in the serum alanine transaminase (aminotransferase) (ALT) value. If serum ALT increases from 25 units/L to 40 units/L, is the change significant? The CV for ALT is 7%. Using the value obtained ±2 × CV to express the extremes of imprecision, a value of 25 units/L is unlikely to reflect an actual concentration of >29 units/L, and a value of 40 units/L is unlikely to reflect an actual concentration of <34 units/L. Therefore the change in the value as obtained by testing is likely to reflect a real change in circulating ALT levels. Continued monitoring of serum ALT is indicated, even though both values for ALT are within normal limits. *Likely* in this case is only a probability. Inherent biologic variability is such that the results of two successive tests may suggest a trend that will disappear on further testing.

Table 769.1 Gaussian and Nongaussian Laboratory Values in 458 Normal Schoolchildren 7-14 Years Old

	SERUM SODIUM (MMOL/L)	SERUM CREATINE KINASE (UNITS/L)
Mean	141	68
Standard deviation (SD)	1.7	34
Mean ±2 SD	138-144	0-136
Actual 95% range	137-144	24-162

The precision of a test may also be indicated by providing *confidence limits* for a given result. Usually, 95% confidence limits are used, indicating that it is 95% certain that the value obtained lies between the two limits reported. Confidence limits are calculated using the mean and SD of replicate determinations:

$$95\%\ \text{confidence limits} = \text{Mean} \pm t \times \text{SD}$$

where t is a constant derived from the number of replications. In most cases, $t = 2$.

Accuracy is expressed by determining the difference, or **bias**, between results from a comparative method and a definitive or reference method. A **definitive** or **reference** method provides results with increased precision and accuracy compared with the clinical laboratory. When these methods are used, along with highly purified materials (i.e., Standard Reference Materials from the National Institute of Standards and Technology) to establish values for assay calibrators used in the clinical laboratory, the accuracy of patient results is improved. Creatinine, hemoglobin A_{1c}, and neonatal bilirubin are examples in which the accuracy of these tests has been improved.

SENSITIVITY, ACCURACY, AND ANALYTIC TESTING

In some circumstances, the sensitivity and accuracy of an analysis are reduced or increased as functions of clinical purpose. For example, ion exchange chromatography of plasma amino acids for the diagnosis of inborn errors of metabolism is usually performed at an analytic sensitivity that allows measurement of all the amino acids with a single set of standards. The range of values is approximately 20-800 µmol/L, and accuracy is poor at values ≤20 µmol/L. The detection of homocysteine in this type of analysis suggests an inborn error of methionine metabolism. If the analysis is adjusted to achieve greater analytic sensitivity, it is possible to measure homocysteine accurately in normal plasma (3-12 µmol/L). This more sensitive test is used to assess cobalamin and folate status.

PREDICTIVE VALUE OF LABORATORY TESTS

Predictive value (PV) theory deals with the usefulness of tests as defined by their clinical **sensitivity** (ability to detect a disease) and **specificity** (ability to define the absence of a disease).

$$\text{Sensitivity} = \frac{\text{Number positive by test}}{\text{Total number positive}} \times 100$$

$$\text{Specificity} = \frac{\text{Number negative by test}}{\text{Total number without disease}} \times 100$$

$$\text{PV of positive test result} = \frac{\text{True-positive results}}{\text{Total positive results}} \times 100$$

$$\text{PV of negative test result} = \frac{\text{True-negative results}}{\text{Total negative results}} \times 100$$

The problems addressed by PV theory are *false-negative* and *false-positive* test results. Both are major considerations in interpreting the results of screening tests in general and neonatal screening tests in particular.

Testing for human immunodeficiency virus (HIV) seroreactivity illustrates some of these considerations. If it is assumed that approximately 1,100,000 of 284,000,000 residents of the United States are infected with HIV (prevalence = 0.39%) and that 90% of those infected demonstrate antibodies to HIV, then we can consider the usefulness of a simple test with 99% sensitivity and 99.5% specificity (see Chapter 322). If the entire population of the United States were screened, it would be possible to identify most of those infected with HIV:

$$1{,}100{,}000 \times 0.9 \times 0.99 = 980{,}100\ \ (89.1\%)$$

However, there will be 119,900 false-negative test results. And even with 99.5% specificity, the number of false-positive test results would be larger than the number of true-positive results:

$$284{,}000{,}000 \times 0.005 = 1{,}420{,}000$$

In addition, there will be 281,480,000 true-negative results:

$$\text{PV of positive test result} = \frac{980{,}100}{(980{,}100 + 1{,}420{,}000)} \times 100 = 41\%$$

$$\text{PV of negative test result} = \frac{281{,}480{,}000}{(281{,}480{,}000 + 119{,}900)} \times 100 = 99.96\%$$

Given the high cost associated with follow-up and the anguish produced by a false-positive result, it is easy to see why universal screening for HIV seropositivity received a low priority immediately after the introduction of testing for HIV infection.

By contrast, we can consider the screening of 100,000 individuals from groups at increased risk for HIV in whom the overall prevalence of disease is 10%, with all other considerations being unchanged.

$$\text{True-positive results} = 0.9 \times 0.99 \times 10{,}000 = 8{,}910$$

$$\text{False-positive results} = 0.005 \times 90{,}000 = 450$$

$$\text{False-negative results} = 10{,}000 - 8{,}910 = 1{,}090$$

$$\text{PV of positive test result} = \frac{8{,}910}{8{,}910 + 450} \times 100 = 95\%$$

$$\text{PV of negative test result} = \frac{89{,}500}{89{,}550 + 1{,}090} \times 100 = 99\%$$

These two hypothetical testing strategies show that the diagnostic efficiency of testing depends heavily on the prevalence of the disease being tested for, even with a superior test, such as the test for HIV antibodies. Because the treatment of pregnant women infected with HIV is effective in preventing vertical transmission, screening has now been expanded to all pregnant women. The proven effectiveness of current therapy in preventing neonatal infection has intensified screening for HIV early in pregnancy.

However, because of the long time needed to test for HIV antibodies, it was difficult to screen women during labor and provide the necessary therapy. Rapid HIV antibody testing procedures using a fingerstick or venipuncture to obtain whole blood, plasma, or serum, and tests using oral fluid were approved (Table 769.2). The HIV test results are usually obtained in <20 minutes. The collection of oral fluid samples provides an alternative for individuals who avoid HIV testing because of their dislike of needlesticks. HIV testing using whole blood or oral fluid is classified as a waived test under the **Clinical Laboratory Improvement Amendments of**

Table 769.2 Rapid HIV Antibody Tests and Status Under CLIA

RAPID HIV TEST	SPECIMEN TYPE	CLIA CATEGORY	TIME FOR PERFORMING ASSAY	WAIT TIME TO READ RESULTS	MANUFACTURER
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	Oral fluid Whole blood (fingerstick or venipuncture)	Waived Waived	<5 min	20-40 min	OraSure Technologies www.orasure.com
	Plasma	Moderate complexity			
Uni-Gold Recombigen HIV-1	Whole blood (fingerstick or venipuncture)	Waived	<5 min	10-12 min	Trinity Biotech www.trinitybiotech.com
	Serum and plasma	Moderate complexity			
Reveal G4 Rapid HIV-1 Antibody Test	Serum and plasma	Moderate complexity	<5 min	Read result immediately	MedMira www.medmira.com
MultiSpot HIV-1/HIV-2 Rapid Test	Serum and plasma	Moderate complexity	10-15 min	Result can be read immediately or up to 4 hr later	BioRad Laboratories www.bio-rad.com
Clearview HIV 1/2 STAT-PAK and Clearview COMPLETE HIV 1/2	Whole blood (fingerstick or venipuncture)	Waived	5 min	15-20 min	Alere www.alere.com
	Serum and plasma	Waived	5 min	15-20 min	Alere
Clearview Determine HIV1/2 Ag/Ab Combo	Whole blood (fingerstick or venipuncture)	Waived	5 min	20 min	Alere
	Serum and plasma	Waived	5 min	20 min	Chembio Diagnostic Systems; distributed by Alere

Ag/Ab, Antigen/antibody; CLIA, Clinical Laboratory Improvement Amendments of 1988; HIV, human immunodeficiency virus.

1988 (CLIA), and these tests are allowed in a point-of-care setting. *Waived tests* are laboratory procedures that use methodologies that are so simple and accurate as to render the likelihood of an erroneous result by the user negligible. A positive rapid HIV test result is then confirmed by nucleic acid amplification testing or immunofluorescence assay.

According to the U.S. Centers for Disease Control and Prevention (CDC), 174 infants were born with HIV in 2014 in the United States. Rapid HIV testing during labor allows for implementation of antiretroviral therapy for HIV-infected women who have not been tested or are unaware of their HIV status. The initiation of therapy at the time of labor or within the first 12 hours of an infant's birth significantly reduces the risk of mother-to-child transmission. In the mother–infant rapid intervention at delivery study, it was shown that the sensitivity and specificity of a rapid whole blood test for HIV during labor were 100% and 99.9%, respectively, with a positive PV of 90%. The median turnaround time for obtaining results from blood collection to patient notification was only 66 minutes. The performance of the rapid blood test was better than that of the standard HIV enzyme immunoassay, which had a sensitivity and specificity of 100% and 99.8%, respectively, with a positive PV of 76%. In addition, the median turnaround time from blood collection to patient notification was 28 hours. As a result, rapid whole blood HIV testing is now the standard of care for women in labor with undocumented HIV status.

Rapid HIV testing can also be used in developing countries. In resource-poor settings, because of the lack of properly equipped laboratories, skilled technologists, and basic resources, such as electricity and water, these self-contained, point-of-care HIV tests are very attractive. In areas of Asia and Africa where HIV is epidemic, screening pregnant women with rapid HIV tests and offering antiretroviral therapy can significantly reduce the transmission of HIV to hundreds of thousands of infants.

NEONATAL SCREENING TESTS

Almost all the diseases detected in neonatal screening programs have a very low prevalence, and for the most part, the tests are *quantitative* rather than qualitative. In general, the strategy is to use the initial screening test to separate a highly suspect group of patients from normal infants (i.e., to increase the prevalence) and then to follow this suspect group aggressively. Two common strategies are used to detect congenital hypothyroidism (see Chapter 603): one uses thyroid-stimulating hormone for the initial screen, and the other uses thyroxine. In the **thyroxine** strategy for congenital hypothyroidism, which has a prevalence of 25 in 100,000 liveborn infants, the initial test performed is for thyroxine in whole blood. Infants with the lowest 10% of test results are considered suspect. If all infants with hypothyroidism were included in the suspect group, the prevalence of disease in this group would be 250 in 100,000 infants. The original samples obtained from the suspect group are retested for thyroxine and are tested for thyroid-stimulating hormone. This second round of testing results in an even more highly suspect group composed of 0.1% of the infants screened and having a prevalence of hypothyroidism of 25,000 in 100,000 individuals. This final group is aggressively pursued for further testing and treatment. Even with a 1,000-fold increase in prevalence, 75% of the aggressively tested population is euthyroid. The justifications advanced for the program are that treatment is easy and effective and that the alternative if congenital hypothyroidism is undetected and untreated—long-term custodial care—is both unsatisfactory and expensive.

At its inception, newborn screening was driven by the selection of genetic diseases whose clinical manifestations developed postnatally, such as phenylketonuria, galactosemia, and hypothyroidism. Diseases selected for screening typically had to meet certain criteria. The prevalence of disease had to meet a minimum, typically 1 in 100,000. Disease selection required demonstrated reduction in morbidity and mortality in the neonatal period. Effective therapies needed to be available, and the cost of screening and the feasibility of laboratory testing were also considerations in this selection process.

More common diseases have also become targets for neonatal screening programs. **Sickle cell disease** (see Chapter 511.1), easily detected using liquid chromatography or isoelectric focusing, can be treated more effectively if it is diagnosed before clinical signs appear. In addition, the results of neonatal screening for **cystic fibrosis** (CF; see Chapter 454) show clear benefits associated with preclinical diagnosis but also some inherent difficulties associated with genetic screening for complex autosomal recessive diseases that are common and are caused by a rather large number of pathogenic variants (>1,500) of a single gene. The definitive diagnostic test for CF is the measurement of concentrations of chloride in sweat, a test that is not practical during the first week of life. Neonates with CF generally have elevations in whole blood trypsinogen. This test allows the identification of a group of neonates at risk for CF. Unfortunately, trypsinogen as an initial screening test has a high false-positive rate, an unfavorable characteristic that creates unnecessary anxiety among newborn parents and families and is costly because of the time and expense for medical follow-up. Performing DNA analysis for common variants that cause CF reduces the size of the suspect group and identifies neonates with a higher likelihood of disease. This two-tiered strategy identifies a manageable number of infants for whom to perform sweat tests. Problems include the following: (1) uncommon variants are not included in the screening panel, and cases of CF caused by these variants can be missed; (2) common variants that cause clinically innocent elevations of whole blood trypsinogen in heterozygous neonates cause potentially alarming false-positive findings; and (3) CF in patients with normal sweat test results is rare but is likely to be missed.

Tandem mass spectrometry (MS/MS) is a technically advanced method in which many compounds are initially ionized and separated by molecular weight. Each compound is then fragmented, and the identification of compounds is based on characteristic fragments. The process requires approximately 2 minutes per sample and can detect 20 or more inborn errors of metabolism. The effects of prematurity, neonatal illness, and intensive neonatal management on metabolites in blood complicate the interpretation of results. The PV of a positive screening result is likely to be <10%; that is, 90% of positive results are not indicative of a genetic disorder of metabolism. Nonetheless, MS/MS permits a diagnosis to be made before clinical illness develops and has revolutionized the purpose and ability of newborn screening. MS/MS is not directed toward diseases defined as treatable, but it is directed toward all the diseases, each of which is rare, that the technique can identify.

MS/MS permits the detection of rare inborn errors of metabolism and has been introduced as a newborn screening tool worldwide. Since 1998, when mass spectrometry was implemented in Australia, the rate of detection per 100,000 births has been 15.7, significantly higher than the rate of 8.6-9.5 in the six preceding 4-year periods. Disorders of fatty acid oxidation, particularly medium-chain acyl coenzyme A dehydrogenase deficiency (see Chapter 106.1), accounted for the majority of increased diagnoses. Expanded newborn screening programs using MS/MS increase the detection of inherited metabolic disorders. All states in the United States use MS/MS in their neonatal screening programs; the metabolic conditions screened range from 31 to >50.

In an attempt to standardize newborn screening programs, the American College of Medical Genetics (ACMG) recommended that every baby born in the United States be screened for a core panel of 29 disorders (Table 769.3). An additional 25 conditions were recommended as secondary targets because they may be identified while screening for the core panel disorders. The March of Dimes and the American Academy of Pediatrics also endorse the ACMG recommendations. However, expansion of the screening test menu raises several issues. The cost of implementation can be significant because many states will need multiple MS/MS systems. Staffing the laboratory with qualified technical personnel to run the MS/MS system and qualified clinical scientists to interpret the profiles can be a challenge. A number of false-positive results will also be obtained with these newborn screening programs. Many of these findings are the result of parenteral nutrition, biologic variation, or treatment and are *not* the result of an inborn error of metabolism. Consequently, qualified staff will be needed to ensure that patients with abnormal results are contacted and receive follow-up testing and counseling, if needed. Even with these concerns, the ACMG report is a step in the right direction toward standardizing guidelines for state newborn screening programs.

TESTING IN REFINING A DIFFERENTIAL DIAGNOSIS

The use of laboratory tests in refining a differential diagnosis satisfies PV theory because a correct differential diagnosis should result in a relatively high prevalence of the disease under consideration. An example of testing in refining a differential diagnosis is the measurement of urinary vanillylmandelic acid (VMA) for the diagnosis of **neuroblastoma** (see Chapter 547). A simple spot test for VMA is not useful in general screening programs because of the low prevalence of neuroblastoma (3 cases/100,000) and the low sensitivity of the test (69%). Even though the specificity of urinary VMA is 99.6%, testing of 100,000 children would produce 2 true-positive test results, 400 false-positive results, and 1 false-negative result. The PV of a positive result in this setting is 0.5%, and the PV of a negative result is 99.99%, not much different from the assumption

Table 769.3 American College of Medical Genetics Core Panel of Neonatal Screening Tests

Isovalericacidemia
Glutaric aciduria type 1
3-Hydroxy-3-methylglutaricaciduria
Multiple coenzyme A (CoA) carboxylase deficiency
Methylmalonic acidemia (mutase deficiency)
3-Methylcrotonyl CoA carboxylase deficiency
Methylmalonic acidemia (cobalamin [Cbl] A, B)
Propionic acidemia
β-Ketothiolase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake deficiency
Phenylketonuria
Maple syrup urine disease
Homocystinuria (because of cystathionine β-synthase deficiency)
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type 1
Sickle cell anemia (Hb SS disease)
Hemoglobin (Hb) S/β-thalassemia
Hb S/C disease
Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia (21-hydroxylase deficiency)
Classic galactosemia
Hearing loss
Cystic fibrosis

that neuroblastoma is not present. Testing for urinary VMA in a 3-year-old child with an abdominal mass, however, gives a useful result because the prevalence of neuroblastoma is at least 50% in 3-year-old children with abdominal masses. If 100 such children are tested and the prevalence of neuroblastoma in the group is assumed to be 50%, a satisfactory PV is obtained.

$$\text{PV of positive test result} = \frac{0.69 \times 50}{0.69 \times 50 + (0.004 \times 50)} \times 100 = 99\,\%$$

$$\text{PV of negative test result} = \frac{0.996 \times 50}{0.996 \times 50 + (0.31 \times 50)} \times 100 = 76\,\%$$

Thus, in this situation, a test with low sensitivity is powerful in refining the differential diagnosis because the PV of a positive result is almost 100% in the setting of high prevalence.

Serologic Testing

Using laboratory testing to refine a differential diagnosis poses problems, as exemplified by serologic testing for **Lyme disease**, which is a tick-borne infection by *Borrelia burgdorferi* that has various manifestations in both early and late stages of infection (see Chapter 268). Direct demonstration of the organism is difficult, and serologic test results for Lyme disease are not reliably positive in young patients presenting early with erythema chronicum migrans. These results become positive after a few weeks of infection and remain positive for a number of years. In an older population being evaluated for late-stage Lyme disease, some individuals will have recovered from either clinical or subclinical Lyme disease, and some will have active Lyme disease, with both groups having true-positive serologic test results. Of individuals without Lyme disease, some will have true-negative serologic test results, but a significant percentage will have antibodies to other organisms that cross-react with *B. burgdorferi* antigens.

This set of circumstances gives rise to a number of problems. First, the protean nature of Lyme disease makes it difficult to ensure a high prevalence of disease in persons to be tested. Second, the most appropriate antibodies to be detected are imperfectly defined, leading to a wide variety of tests with varying false-positive and false-negative rates. Third, the natural history of the antibody response to infection and the difficulty of showing the causative organism directly combine to make laboratory diagnosis of early Lyme disease difficult. Fourth, in the diagnosis of late-stage Lyme disease in older individuals, the laboratory diagnosis is plagued by misleading positive (either false-positive or true-positive, but not clinically relevant) results, typically an enzyme-linked immunosorbent assay (ELISA) that uses whole *B. burgdorferi* organisms. In a review of 788 patients referred to a specialty clinic with the diagnosis of Lyme disease, the diagnosis was correct in 180 patients, 156 patients had true seropositivity without active Lyme disease, and 452 had never had Lyme disease, even though 45% of them were found to be seropositive by at least one test before referral.

A two-step approach, similar to that used in HIV testing, is often used: a screening test that has high sensitivity (e.g., ELISA) and excellent negative PV, followed by a very specific confirmatory test for verification of positive screening test results (e.g., Western blot to detect antibodies to selected bacterial antigens). Negative screening test results and negative verification test results are reported as negative. Positive verification test results are reported as positive. However, standardization of the testing procedures is difficult in North America, where only one pathogenic strain of *B. burgdorferi* is found, and is more difficult elsewhere in the Northern hemisphere, where as many as three pathogenic strains are present. Identification of microbial DNA in body fluids by polymerase chain reaction is definitive but invasive.

Table 769.4 Laboratory Profile as a Review of Systems

LABORATORY TEST	ASSESSMENT FACILITATED BY TESTS
Complete blood cell count and platelets	Nutrition, status of formed elements
Complete urinalysis	Renal function/genitourinary tract inflammation
Albumin and cholesterol	Nutrition
ALT, bilirubin, GGT	Liver function
BUN, creatinine	Renal function, nutrition
Sodium, potassium, chloride, bicarbonate	Electrolyte homeostasis
Calcium and phosphorus	Calcium homeostasis

ALT, Alanine transaminase; BUN, blood urea nitrogen; GGT, γ-glutamyltransferase.

Laboratory Screening

Screening profiles are used as part of a complete review of systems, to establish a baseline value, or to facilitate patient care in specific circumstances, such as (1) when a patient clearly has an illness, but a specific diagnosis remains elusive; (2) when a patient requires intensive care; (3) for postmarketing surveillance and evaluation of a new drug; and (4) when a drug is used that is known to have systemic adverse effects. Laboratory screening tests should be used in a targeted manner to supplement, not supplant, a complete history and physical examination (Table 769.4).

Bibliography

American Academy of Pediatrics. American Thyroid Association: newborn screening for congenital hypothyroidism. *Pediatrics*. 1987;80:745–749.

Bulterys M, Jamieson DJ, O'Sullivan MJ, et al. Rapid HIV-1 testing during labor: a multicenter study. *JAMA*. 2004;292:219–223.

Clayton EW. Issues in state newborn screening programs. *Pediatrics*. 1992;90:641–646.

Farrell PM, Kosrok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics*. 2001;107:1–13.

Galen RS, Gambino SR. *Beyond Normality*. New York: Academic Press; 1975.

Hu LT, Klempner MS. Update on the prevention, diagnosis, and treatment of Lyme disease. *Adv Intern Med*. 2001;46:247–275.

Minamitani K, Inomata H. Neonatal screening for congenital hypothyroidism in Japan. *Pediatr Endocrinol Rev*. 2012;10(suppl 1):79–88.

National Newborn Screening and Genetic Resource Center. Newborn screening information. http://genes-r-us.uthscsa.edu.

Rinaldo P, Tortorelli S, Matern D. Recent developments and new applications of tandem mass spectrometry in newborn screening. *Curr Opin Pediatr*. 2004;16:427–433.

Steere AC, Taylor E, McHugh GL, et al. The overdiagnosis of Lyme disease. *JAMA*. 1993;269:1812–1826.

Sun A, Lam C, Wong DA. Expanded newborn screening for inborn errors of metabolism: overview and outcomes. *Adv Pediatr*. 2012;59(1):209–245.

Watson MS, Mann MJ, Lloyd-Puryear MA, et al. Newborn screening: towards a uniform screening panel and system. *Genet Med*. 2006;8(Suppl):S12–S252.

Wilcken B, Wiley V, Hammond J, et al. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. *N Engl J Med*. 2003;348:2304–2312.

Zytkovicz TH, Fitzgerald EF, Marsden D, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. *Clin Chem*. 2001;47:1945–1955.

Chapter 770

Reference Intervals for Laboratory Tests and Procedures

Stanley F. Lo and Stephen M. Roper

In Tables 770.1-770.5, the reference intervals apply to infants, children, and adolescents when possible. For many analyses, separate reference intervals for children and adolescents are not well delineated. When interpreting a test result, the reference interval supplied by the laboratory performing the test should always be used because these intervals are instrument and/or method dependent. Figures 770.1 and 770.2 provide estimations related to dosages. Figure 770.3 is a nomogram for risk assessment of hyperbilirubinemia.

Table 770.1 Prefixes Denoting Decimal Factors in Table 770.5

PREFIX	SYMBOL	FACTOR
mega-	M	10^6
kilo-	k	10^3
hecto-	h	10^2
deka-	da	10^1
deci-	d	10^{-1}
centi-	c	10^{-2}
milli-	m	10^{-3}
micro-	μ	10^{-6}
nano-	n	10^{-9}
pico-	p	10^{-12}
femto-	f	10^{-15}

Table 770.2 Abbreviations Used in Table 770.5

Ab	Absorbance	mm^3	Cubic millimeter, microliter (μL)
AU	Arbitrary unit	mm Hg	Millimeters of mercury
BB	Brain isoenzyme of creatine kinase	mmol	Millimole
cap	Capillary	mo	Month, months
CH_{50}	Dilution required to lyse 50% of indicator red blood cells; indicates complement activity	mol	Mole
		mOsm	Milliosmole
		MW	Relative molecular weight
Cr	Creatinine	ND	Not detected
CSF	Cerebrospinal fluid	nm	Nanometer (wavelength)
F	Female	Pa	Pascal(s)
g	Gram, grams	pc	Postprandial
G6PD	Glucose-6-phosphate dehydrogenase	RBC	Red blood cell(s), erythrocyte(s)
Hb	Hemoglobin	RT	Room temperature
HbCO	Carboxyhemoglobin	SD	Standard deviation
hpf	High-power field	sec	Second, seconds
hr	Hour, hours	Tr	Trace
IU	International unit(s) of hormone activity	U	International unit(s) of enzyme activity
L	Liter	V	Volume
M	Male	WBC	White blood cell(s)
MB	Heart isoenzyme of creatine kinase	WHO	World Health Organization
mEq/L	Milliequivalents per liter	wk	Week, weeks
min	Minute, minutes	yr	Year, years

Table 770.3 Abbreviations for Specimens in Table 770.5

S	Serum
P	Plasma
(H)	Heparin
(LiH)	Lithium heparin
(E)	Ethylenediaminetetraacetic acid (EDTA)
(C)	Citrate
(O)	Oxalate
W	Whole blood
(NH_4H)	Ammonium heparinate

Table 770.4 Key to Comments Section of Table 770.5

30°C, 37°C	Temperature of enzymatic analysis (Celsius)	l	Fluorometric method
a	Values obtained are significantly method dependent	m	Fluorescence-activated cell sorting (FACS)
b	Values in older males are higher than those in older females	n	Fluorescence polarization
c	Values in older females are higher than those in older males	o	Gas chromatography
d	Atomic absorption	p	High-performance liquid chromatography (HPLC)
e	Borate affinity chromatography	q	Indirect fluorescence antibody (IFA) assay
f	Cation-exchange chromatography	r	Ion-selective electrode
g	Vitros, a proprietary analytic system of Ortho Clinical Diagnostics	s	Nephelometry
i	Electrophoresis	t	Optical density
j	Enzymatic assay	u	Radial immunodiffusion (RID)
k	Enzyme-amplified immunoassay	v	Radioimmunoassay (RIA)
		w	Spectrophotometry

Table 770.5 Reference Intervals*

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
COMPLETE BLOOD COUNT						
Hematocrit (HCT, Hct)	*W(E)*		*% of packed red cells (V red cells/V whole blood cells × 100)*		*Volume fraction (V red cells/V whole blood)*	
Calculated from mean corpuscular volume (MCV) and RBC count (electronic displacement or laser)		0-30 days	44-70%	×0.01	0.44-0.70	
		1-23 mo	32-42%		0.32-0.42	
		2-9 yr	33-43%		0.33-0.43	
		10-17 yr M	36-47%		0.36-0.47	
		F	35-45%		0.35-0.45	
		>18-99 yr M	42-52%		0.42-0.52	
		F	37-47%		0.37-0.47	
Hemoglobin (Hb)	*W(E)*		*g/dL*		*mmol/L*	
		0-30 days	15.0-24.0	×0.155	2.32-3.72	MW Hb = 64,500
		1-23 mo	10.5-14.0		1.63-2.17	
		2-9 yr	11.5-14.5		1.78-2.25	
		10-17 yr M	12.5-16.1		1.93-2.50	
		F	12.0-15.0		1.86-2.32	
		>18-99 yr M	13.5-18.0		2.09-2.79	
		F	12.5-16.0		1.93-2.48	
	P(H)	*See Chemical Elements*				
Erythrocyte indices (RBC indices)						

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Mean corpuscular hemoglobin (MCH)	*W(E)*		*pg/cell*		*fmol/cell*	
		0-30 days	33-39	×0.0155	0.51-0.60	
		1-23 mo	24-30		0.37-0.46	
		2-9 yr	25-31		0.39-0.48	
		10-17 yr M	26-32		0.26-0.32	
		F	26-32		0.26-0.32	
		>18-99 yr M	27-31		0.27-0.31	
		F	27-31		0.27-0.31	
Mean corpuscular hemoglobin concentration (MCHC)	*W(E)*		*% Hb/cell or g Hb/dL RBC*		*mmol Hb/L RBC*	
			32-36	×0.155	4.96-5.58	
Mean corpuscular volume (MCV)	*W(E)*		*μm³*		*fL*	
		0-30 days	99-115	×1	99-115	
		1-23 mo	72-88		72-88	
		2-9 yr	76-90		76-90	
		10-17 yr	78-95		78-95	
		>18-99 yr	78-100		78-100	
Leukocyte count (WBC count)	*W(E)*	*×1,000 cells/mm³ (μL)*			*×10⁹ cells/L*	
		0-30 days	9.1-34.0	×1	9.1-34.0	
		1-23 mo	6.0-14.0		6.0-14.0	
		2-9 yr	4.0-12.0		45.0-12.0	
		10-17 yr	4.0-10.5		4.0-10.5	
		18-99 yr	4.0-10.5		4.0-10.5	
Leukocyte differential	*W(E)*	*%*			*Number fraction*	
Myelocytes		0%		×0.01	0	
Neutrophils ("bands")		3-5%			0.03-0.05	
Neutrophils ("segs")		54-62%			0.54-0.62	
Lymphocytes		25-33%			0.25-0.33	
Monocytes		3-7%			0.03-0.07	
Eosinophils		1-3%			0.01-0.03	
Basophils		0-0.75%			0-0.0075	
		Cells/mm³ (μL)			*×10⁶ cells/L*	
Myelocytes		0		×1	0	
Neutrophils ("bands")		150-400			150-400	
Neutrophils ("segs")		3,000-5,800			3,000-5,800	
Lymphocytes		1,500-3,000			1,500-3,000	
Monocytes		285-500			285-500	
Eosinophils		50-250			50-250	
Basophils		15-50			15-50	
Platelet count (thrombocyte count)	*W(E)*	*×10³/mm³ (μL)*			*×10⁹/L*	
		Newborn 84-478 (after 1 wk, same as adult)		×10⁶	84-478	(Buck, 1996)
		Adult 150-400			150-400	

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Reticulocyte count	*W(E,H,O)*	*Adults 0.5-1.5% of erythrocytes or 25,000-75,000/mm³ (μL)*		*×0.01 ×10⁶*	*0.005-0.015 (number fraction) or 25,000-75,000 × 10⁶/L*	
			%		*Number fraction*	
	W(cap)	1 day	0.4-6.0	×0.01	0.004-0.060	
		7 days	<0.1-1.3		<0.001-0.013	
		1-4 wk	<1.0-1.2		<0.001-0.012	
		5-6 wk	<0.1-2.4		<0.001-0.024	
		7-8 wk	0.1-2.9		0.001-0.029	
		9-10 wk	<0.1-2.6		<0.001-0.026	
		11-12 wk	0.1-1.3		0.001-0.013	
Alanine transaminase (aminotransferase) (ALT, SGPT)	*S*	*0-7 days*	*6-40 U/L*	*×1*	*6-40 U/L*	37°C,[bgw] (Soldin, Savwoir, Guo, 1997; Lockitch Halstead, Albersheim, 1988)[g] (Meites, 1989; Soldin and Morse, 1998; Lockitch Halstead, Albersheim, 1988)
		8-30 days M	10-40		10-40	
		F	8-32		8-32	
		1-12 mo	12-45		12-45	
		1-19 yr	5-45		5-45	
Albumin (BCG)	P	Premature 1 day	1.8-3.0 g/dL	×10	18-30 g/dL	
		Full term <6 days	2.5-3.4		25-34	
		8 days-1 yr	1.9-4.9		19-49	
		1-3 yr	3.4-4.2		34-42	
		4-19 yr	3.5-5.6		35-56	
Ammonia	P		11-35 μmol/L	×1	11-35 μmol/L	[g]
Amylase	S,P	1-19 yr	30-100 U/L	×1	30-100 U/L	(Lockitch Halstead, Albersheim, 1988; Gillard et al, 1983)
			% pancreatic fraction		*% pancreatic fraction*	
Amylase isoenzymes	S,P(H)	Cord-8 mo	0-34%	×0.01	0-0.34%	
		9 mo-4 yr	5-56%		0.05-0.56%	
		5-19 yr	23-59%		0.23-0.59%	
Anion gap (sodium – [chloride + bicarbonate])	P(H)	7-16 mEq/L		×1	7-16 mEq/L	
Antideoxyribonuclease B titer (anti-DNase B titer)	*S*	*Age*	*Upper limit of normal*		*Upper limit of normal*	
		4-6 yr	240-480 U	×1	240-480 U	(Kaplan et al, 1998)
		7-12 yr	480-800 U		480-800 U	
Antidiuretic hormone (hADH, vasopressin)	*P(E)*	*Plasma osmolarity (mOsm/kg)*	*Plasma ADH (pg/mL)*		*Plasma ADH ng/L*	
		270-280	<1.5	×1	<1.5	
		280-285	<2.5		<2.5	
		285-290	1-5		1-5	
		290-295	2-7		2-7	
		295-300	4-12		4-12	

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†		COMMENTS
Antistreptolysin-O titer (ASO titer)	*S*	*Age*	*Upper limit of normal*		*Upper limit of normal*		
		2-5 yr	120-160 Todd units	×1	120-160 Todd units		(Kaplan et al, 1998)
		6-9 yr	240 Todd units		240 Todd units		
		10-12 yr	320 Todd units		320 Todd units		
Aspartate transaminase (aminotransferase) (AST, SGOT)	*S*		*U/L*		*U/L*		
		0-7 days M	30-100	×1	35-100		37°C,[9] (Soldin, Savwoir, Guo, 1997; Lockitch Halstead, Albersheim, 1988)
		F	24-95		24-95		
		8-30 days	22-71		22-71		
		1-12 mo	22-63		22-63		
		1-3 yr	20-60		20-60		
		3-9 yr	15-50		15-50		
		10-15 yr	10-40		10-40		
		16-19 yr M	15-45		15-45		
		F	5-30		5-30		
Base excess	*W(H)*		*mmol/L*		*mmol/L*		
		Newborn	(−10)-(−2)	×1	(−10)-(−2)		
		Infant	(−7)-(−1)		(−7)-(−1)		
		Child	(−4)-(+2)		(−4)-(+2)		
		Thereafter	(−3)-(+3)		(−3)-(−3)		
Bicarbonate	*S,P*		*mmol/L*		*mmol/L*		
		Arterial	21-28	×1	21-28		
		Venous	22-29		22-29		
Bilirubin, total	*S*		*mg/dL*		*μmol/L*		
		Newborn	See Bhutani nomogram (Fig. 770.3)	×17.1			(Bhutani et al, 1999)
		1 mo-adult	<1.0		<17		
C-reactive protein (high sensitivity)	*S*						*(Soldin et al, 2004)*
			M (mg/dL)	*F (mg/dL)*		*M (mg/L)*	*F (mg/L)*
		0-90 days	0.08-1.58	0.09-1.58	×10	0.8-15.8	0.9-15.8
		91 days-12 mo	0.08-1.12	0.05-0.79		0.8-11.2	0.5-7.9
		13 mo-3 yr	0.08-1.12	0.08-0.79		0.8-11.2	0.8-7.9
		4-10 yr	0.06-0.79	0.5-1.0		0.6-7.9	0.5-10.0
		11-14 yr	0.08-0.76	0.06-0.81		0.8-7.6	0.6-8.1
		15-18 yr	0.04-0.79	0.06-0.79		0.4-7.9	0.6-7.9
Calcium, ionized (Ca)	*S,P(H),W(H)*		*mg/dL*		*mmol/L*		
		Cord blood	5.0-6.0	×0.25	1.25-1.50		
		Newborn, 3-24 hr	4.3-5.1		1.07-1.27		
		24-48 hr	4.0-4.7		1.00-1.17		
		Thereafter	4.8-4.92		1.12-1.23		
		or	2.24-2.46 Eq/L	×0.5	1.12-1.23		

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Calcium, total	*S*		*mg/dL*		*mmol/L*	
		Cord blood	9.0-11.5	×0.25	2.25-2.88	
		Newborn, 3-24 hr	9.0-10.6		2.3-2.65	
		24-48 hr	7.0-12.0		1.75-3.00	
		4-7 days	9.0-10.9		2.25-2.73	
		Child	8.8-10.8		2.20-2.70	
		Thereafter	8.4-10.2		2.10-2.55	
Carbon dioxide, partial pressure (Pco_2)	*W(H)*		*mm Hg*		*kPa*	
		Newborn	27-40	×0.1333	3.6-5.3	
		Infant	27-41		3.6-5.5	
		Thereafter M	35-48		4.7-6.4	
		F	32-45		4.3-6.0	
Carbon monoxide (carboxyhemoglobin)	W(E)	Nonsmoker	<2% HbCO	×0.01	HbCO fraction <0.02	
		Smoker	<10%		<0.10	
		Lethal	>50%		>0.5	
Chloride	S,P(H)	Cord blood	96-104 mmol/L	×1	96-104 mmol/L	
		Newborn	97-110		97-110	
		Thereafter	98-106		98-106	
Chloride, sweat	*Sweat*		*mmol/L*			(Farrell et al, 2008)
			≤29	CF unlikely		
			30-59	Intermediate		
			≥60	Indicative of CF		
Cortisol	*S,P(H)*		*μg/dL*		*nmol/L*	
		Newborn	1-24	×27.59	28-662	
		Adults, 8 AM	5-23		138-635	
		4 PM	3-15		82-413	
		8 PM	<50% of 8 AM	×0.01	Fraction of 8 AM	
					≤0.50	
Creatine kinase	S	Cord blood	70-380 U/L	×1	70-380 U/L	30°C,[b] (Jedeikin et al, 1982)
		5-8 hr	214-1,175		214-1,175	
		24-33 hr	130-1,200		130-1,200	
		72-100 hr	87-725		87-725	
		Adult	5-130		5-130	
Creatine kinase isoenzymes	*S*		*% MB*	*% BB*		
		Cord blood	0.3-3.1	0.3-10.5		
		5-8 hr	1.7-7.9	3.6-13.4		
		24-33 hr	1.8-5	2.3-8.6		
		72-100 hr	1.4-5.4	5.1-13.3		
		Adult	0-2	0		

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†		COMMENTS
Creatinine (IDMS)							
Enzymatic	*S,P*		*mg/dL*		*μmol/L*		[9]
		0-4 yr	0.03-0.50	×88.4	2.65-44.2		
		4-7 yr	0.03-0.59		2.65-52.2		
		7-10 yr	0.22-0.59		19.4-52.2		
		10-14 yr	0.31-0.88		27.4-77.8		
		>14 yr	0.50-1.06		44.2-93.7		
Creatinine clearance (endogenous)	S,P,U	Newborn 40-65 mL/min/1.73 m^2					
		<40 yr, M 97-137					
		F 88-128					
		Decreases <6.5 mL/min/decade					
Ferritin	*S*		*ng/mL*		*μg/L*		
		0-6 wk	0-400	×1	0-400		
		7 wk-365 days	10-95		10-95		
		1-9 yr	10-60		10-60		
		10-18 yr M	10-300		10-300		
		F	10-70		10-70		
Folate	S	Newborn 7.0-32 ng/mL		×2.265	15.9-72.4 nmol/L		
		Thereafter 1.8-9.0			4.1-20.4		
	W(E)	150-450 ng/mL RBCs			340-1,020 nmol/L cells		
Glucose	*S*		*mg/dL*		*mmol/L*		
		Cord blood	45-96	×0.0555	2.5-5.3		
		Premature	20-60		1.1-3.3		
		Neonate	30-60		1.7-3.3		
		Newborn					
		1 day	40-60		2.2-3.3		
		>1 day	50-90		2.8-5.0		
		Child	60-100		3.3-5.5		
		Adult	70-105		3.9-5.8		
	W(H)	Adult	65-95		3.6-5.3		
Glucose tolerance test (GTT) (see Chapter 629)	*S*		*mg/dL*			*mmol/L*	
Oral dose							
Adult: 75 g			*Normal* *Diabetic*			*Normal* *Diabetic*	
Child: 1.75 g/kg of ideal weight, up to a maximum of 75 g		Fasting	70-105 ≥126	×0.0555		3.9-5.8 ≥7.0	(Diabetes Care, 2019)
		120 min	70-120 ≥200			3.9-6.7 ≥11	
G6PD in erythrocytes		W(E,H,C)					
Bishop, modified		Adult			Adult		
		3.4-8.0 U/g Hb		×0.0645	0.22-0.52 mU/mol Hb		
		98.6-232 $U/10^{12}$ RBCs		$\times 10^{-3}$	0.10-0.23 $nU/10^{6}$ RBCs		
		1.16-2.72 U/mL RBC		×1	1.16-2.72 kU/L RBC		
		Newborn: 50% higher			Newborn: 50% higher		

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
γ-Glutamyl transpeptidase (GGT, GGTP)	*S*		*U/L*		*U/L*	
		Cord blood	37-193	×1	37-193	37°C,[b] (Knight and Haymond, 1981)
		0-1 mo	13-147		13-147	
		1-2 mo	12-123		12-123	
		2-4 mo	8-90		8-90	
		4 mo-10 yr	5-32		5-32	
		10-15 yr	5-24		5-24	
Immunoglobulin A (IgA)	*S*		*mg/dL*		*mg/L*	
		Cord blood	1.4-3.6	×10	14-36	[s] (Meites, 1989)
		1-3 mo	1.3-53		13-530	
		4-6 mo	4.4-84		44-840	
		7 mo-1 yr	11-106		110-1,060	
		2-5 yr	14-159		140-1,590	
		6-10 yr	33-236		330-2,360	
		Adult	70-312		700-3,120	
Immunoglobulin D (IgD)	S	Newborn: none detected			None detected	
		Thereafter: 0-8 mg/dL		×10	0-80 mg/L	
Immunoglobulin E (IgE)	S	M 0-230 IU/mL		×1	0-230 kIU/L	
		F 0-170			0-170	
Immunoglobulin G (IgG)	S		mg/dL		g/L	
		Cord blood	636-1,606	×0.01	6.36-16.06	[s] (Meites, 1989)
		1 mo	251-906		2.51-9.06	
		2-4 mo	176-601		1.76-6.01	
		5-12 mo	172-1,069		1.72-10.69	
		1-5 yr	345-1,236		3.45-12.36	
		6-10 yr	608-1,572		6.08-15.72	
		Adult	639-1,349		6.39-13.49	
Immunoglobulin M (IgM)	*S*		*mg/dL*		*mg/L*	
		Cord blood	6.3-25	×10	63-250	[s](Meites, 1989)
		1-4 mo	17-105		170-1,050	
		5-9 mo	33-126		330-1,260	
		10 mo-1 yr	41-173		410-1,730	
		2-8 yr	43-207		430-2,070	
		9-10 yr	52-242		520-2,420	
		Adult	56-352		560-3,520	
Iron	P	All ages	22-184 μg/dL	×0.1791	4-33 μmol/L	(Lockitch Halstead, Wadsworth, 1988)
Iron-binding capacity, total (TIBC)	S	Infant 100-400 μg/dL		×0.179	17.90-71.60 μmol/L	
		Thereafter 250-400			44.75-71.60	
L-lactate (perchloric acid)	*W*		*mg/dL*		*mmol/L*	
		1-12 mo	10-21	×1	1.1-2.3	(Bonnefont et al, 1990)
		1-7 yr	7-14		0.8-1.5	
		7-15 yr	5-8		0.6-0.9	
D-lactate	P(H)					[j](Rosenthal and Pesce, 1985)
		6 mo-3 yr	0.0-0.3	×1	0.0-0.3	

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†			CONVERSION FACTOR	REFERENCE VALUES (SI)†			COMMENTS
Lactate dehydrogenase (LDH)	*S*		*U/L*			*U/L*			
		<1 yr	170-580		×1	170-580			37°C,[a] (Meites, 1989)
		1-9 yr	150-500			150-500			
		10-19 yr	120-330			120-330			
Isoenzymes	*S*		*% of total activity*						
			1-6 yr	7-19 yr					
		LD1	20-38	20-35					
		LD2	27-38	31-38					
		LD3	16-26	19-28					
		LD4	5-16	7-13					
		LD5	3-13	5-12					
Lead	*W(H)*		*μg/dL*			*mmol/L*			
		Child	<3.5*		×0.0483	<0.0024			
		Initiate chelation therapy	≥70			≥3.38			
Lipase	P,S	1-18 yr	145-216 U/L		×1	145-216 U/L			(Ghoshal and Soldin, 2003)
Magnesium	P(H)		mg/dL			mmol/L			
		0-6 days	1.2-2.6		×0.411	0.48-1.05			[gw](Meites, 1989)
		7 days-2 yr	1.6-2.6			0.65-1.05			
		2-14 yr	1.5-2.3			0.60-0.95			
		0.78 ± 0.37% of total Hb			×0.01	0.0078 ± 0.0037 (mass fraction)			
Osmolality	S	Child, adult							
		275-295 mOsm/kg H_2O							
Phosphatase, alkaline	*S*		*U/L*			*U/L*			
		1-9 yr	145-420		×1	145-420			37°C,[aw]
		10-11 yr	140-560			140-560			
			M	F			M	F	
		12-13 yr	200-495	105-420			200-495	105-420	
		14-15 yr	130-525	70-230			130-525	70-230	
		16-19 yr	65-260	50-130			65-260	50-130	
Phosphorus, inorganic	S,P(H)		mg/dL			mmol/L			
		0-5 days	4.8-8.2		×0.3229	1.55-2.65			[w](Meites, 1989)
		1-3 yr	3.8-6.5			1.25-2.10			
		4-11 yr	3.7-5.6			1.20-1.80			
		12-15 yr	2.9-5.4			0.95-1.75			
		16-19 yr	2.7-4.7			0.90-1.50			
Potassium	*S*		*mmol/L*			*mmol/L*			
		0-1 wk	3.2-5.5		×1	3.3-5.5			(Greeley et al, 1993) Increased by hemolysis; serum values systematically higher than plasma values
		1 wk-1 mo	3.4-6.0			3.4-6.0			
		1-6 mo	3.5-5.6			3.5-5.6			
		6 mo-1 yr	3.5-6.1			3.5-6.1			
		>1 yr	3.3-4.6			3.3-4.6			
	P(H)	3.5-4.5 mmol/L				3.5-4.5 mmol/L			

*https://www.cdc.gov/nceh/lead/prevention/blood-lead-levels.htm

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Prealbumin (transthyretin)	*S*		*mg/dL*		*mg/L*	
		0-5 days	6.0-21.0	×10	60-210	[s](Lockitch, Halstead, Quigley, 1988)
		1-5 yr	14.0-30.0		140-300	
		6-9 yr	15.0-30.0		150-300	
		10-13 yr	20.0-36.0		200-360	
		14-19	22.0-45.0		220-450	
Protein, total	*S*		*g/dL*		*g/L*	
		Premature	4.3-7.6	×10	43-76	(Meites, 1989)
		Newborn	4.6-7.4		46-74	
		1-7 yr	6.1-7.9		61-79	
		8-12 yr	6.4-8.1		64-81	
		13-19 yr	6.6-8.2		66-82	
Pyruvate (perchloric acid)	W	7-17 yr	0.076 ± 0.026 mmol/L	×1	0.076 ± 0.026 mmol/L	(Pianosi et al, 1995)
Sodium	*S,P (LiH, NH_4H)*		*mmol/L*		*mmol/L*	
		Newborn	133-146	×1	133-146	[g](Greeley et al, 1993)
		Infant	134-144		134-144	
		Child	134-143		134-143	
		Thereafter	135-145		135-145	
Thyroid-stimulating hormone (TSH)	*S*		*mIU/L*		*mIU/L*	
		0-3 days	1.00-20.00	×1	1.0-20.00	[g](Dugaw et al, 2001)
		4-30 days	0.5-6.5		0.50-6.50	
		1-5 mo	0.5-6.0		0.5-6.0	
		6 mo-18 yr	0.5-4.5		0.5-4.5	
Thyrotropin-releasing hormone (TRH)	P	5-60 pg/mL		×2.759	14-165 pmol/L	
Thyroxine-binding globulin (TBG)	*S*		*mg/dL*		*mg/L*	
		Cord blood	1.4-9.4	×10	14-94	
		1-4 wk	1.0-9.0		10-90	
		1-12 mo	2.0-7.6		20-76	
		1-5 yr	2.9-5.4		29-54	
		5-10 yr	2.5-5.0		25-50	
		10-15 yr	2.1-4.6		21-46	
		Adult	1.5-3.4		15-34	
Thyroxine (T_4), total	*S*		*μg/dL*		*nmol/L*	
		0-3 days	8.0-20.0	×12.9	103-258	[g](Dugaw et al, 2001)
		3-30 days	5.0-15.0		64-193	
		31-365 days	6.0-14.0		77-180	
		1-5 yr	4.5-11.0		58-142	
		6-18 yr	4.5-10.0		58-129	

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Thyroxine (T_4), free	*S*		*ng/dL*		*pmol/L*	
		0-3 days	2.00-5.00	×12.9	25.7-64.3	[9](Dugaw et al, 2001)
		3-30 days	0.90-2.20		11.6-28.3	
		31 days-18 yr	0.7-2.00		9.0-25.7	
Thyroxine (T_4), total	W	Newborn screen (filter paper) 6.2-22.0 µg/dL		×12.9	80-283 nmol/L	
Triiodothyronine (T_3), free	*S*		*pg/dL*		*pmol/L*	
		Cord blood	20-240	×0.01536	0.3-3.7	
		1-3 days	200-610		3.1-9.4	
		6 wk	240-560		3.7-8.6	
		Adult (20-50 yr)	230-660		3.5-10.0	
Triiodothyronine (T_3), total	*S*		*ng/dL*		*nmol/L*	
		0-3 days	60-300	×0.0154	0.9-4.7	
		4-365 days		90-260		1.4-4.0
		1-6 yr	90-240		1.4-3.7	
		7-11 yr	90-230		1.4-3.6	
		12-18 yr	100-210		1.5-3.3	[9](Dugaw et al, 2001)
Urea nitrogen	S,P		mg/dL		mmol/L	
		Cord blood	21-40	×0.357	7.5-14.3	
		Premature (1 wk)	3-25		1.1-9.0	
		Newborn	3-12		1.1-4.3	
		infant or child	5-18		1.8-6.4	
		Thereafter	7-18		2.5-6.4	
Uric acid	*S*		*mg/dL*		*µmol/L*	
		1-3 yr	1.8-5.0	×59.48	100-300	
		4-6 yr	2.2-4.7		130-280	
		7-9 yr	2.0-5.0		120-295	
		10-11 yr M	2.3-5.4		135-320	(Lockitch Halstead, Albersheim, 1988)
		10-11 yr F	3.0-4.7		180-280	
		12-13 yr M	2.7-6.7		160-400	
		14-15 yr M	2.4-7.8		140-465	
		12-15 yr F	3.0-5.8		180-345	
		16-19 yr M	4.0-8.6		235-510	
		16-19 yr F	3.0-5.9		180-350	

*In preparing the reference range listings, a number of abbreviations, symbols, and codes were used (see Table 770.2).
†Reference values are shown in SI units (International System of Units) and U.S. units (Traditional Units).

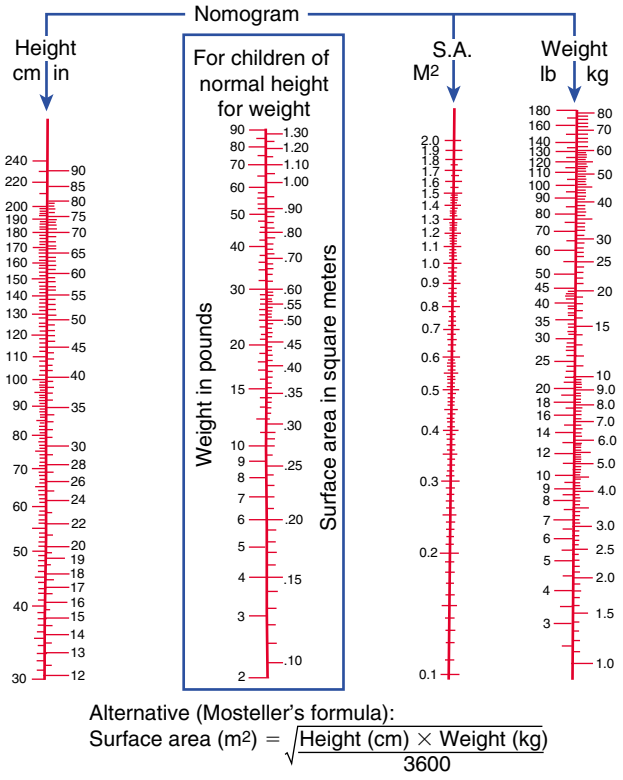

Fig. 770.1 Nomogram for the estimation of surface area. The surface area is indicated where a straight line that connects the height and weight levels intersects the surface area column, or if the patient is roughly of average size, from the weight alone *(enclosed area)*. *(Nomogram modified from the data of E. Boyd by CD West. See also Briars GL, Bailey BJ. Surface area estimation: pocket calculator v nomogram. Arch Dis Child. 1994;70:246–247.)*

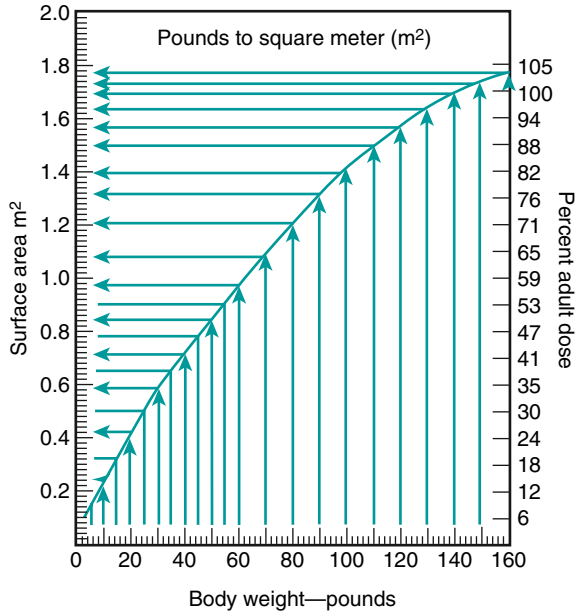

Fig. 770.2 Relationships between body weight (lb), body surface area, and adult dosage. The surface area values correspond with those set forth by Crawford JD, Terry ME, Rourke GM. Simplification of drug dosage calculation by application of the surface area principle. *Pediatrics*. 1950;5:783–790. Note that the 100% adult dose is for a patient weighing approximately 140 lb and having a surface area of approximately 1.7 m². *(From Talbot NB, Richie RH, Crawford JH. Metabolic homeostasis: a syllabus for those concerned with the care of patients. Cambridge, MA: Harvard University Press, 1959.)*

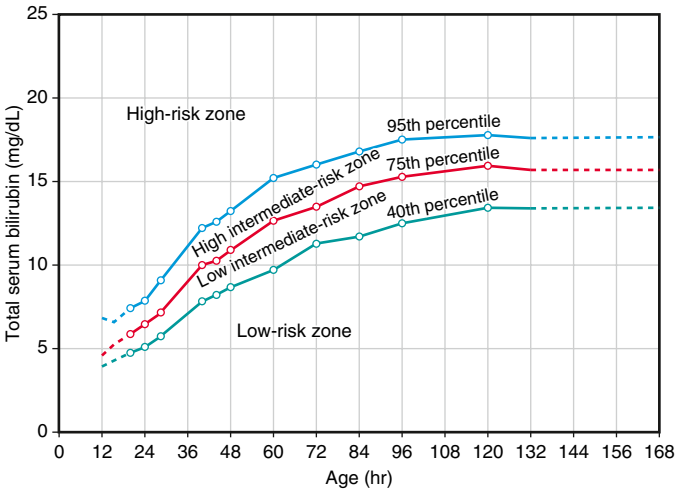

Fig. 770.3 Nomogram for risk assessment of hyperbilirubinemia. *(From Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics. 1999;103:6–14. Fig 2.)*

Bibliography (for Table 770.5)

American Diabetes Association. Classification and diagnosis of Diabetes: Standards of Medical care in Diabetes - 2019. *Diabetes Care*. 2019;42:S13–S28.

Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6–14.

Bonnefont JP, Specola NB, Vassault A, et al. The fasting test in children: application to the diagnosis of pathological hypo- and hyperketotic state. *Eur J Pediatr*. 1990;150:80–85.

Buck ML. Anticoagulation with warfarin in infants and children. *Ann Pharmacother*. 1996;30:1316–1322.

Diaz J, Tornel PL, Martinez P. Reference intervals for blood ammonia in healthy subjects, determined by microdiffusion. *Clin Chem*. 1995;41:1048.

Dugaw KA, Jack RM, Rutledge J. Pediatric reference ranges for TSH, free T_4, total T_4, total T_3 and T_3 uptake on the VitrosECi analyzer. *Clin Chem*. 2001;47:A108.

E. Endocrinology, C. Hills, CA 91301.

Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr*. 2008;153:S4–S14.

Ghoshal A, Soldin S. Evaluation of the Dade Behring dimension R × L: integrated chemistry system, pediatric reference ranges. *Clin Chim Acta*. 2003;331:135–146.

Gillard BK, Simbala JA, Goodglick L. Reference intervals for amylase isoenzymes in serum and plasma of infants and children. *Clin Chem*. 1983;29:1119–1123.

Greeley C, Snell J, Colaco A, et al. Pediatric reference ranges for electrolytes and creatinine. *Clin Chem*. 1993;39:1172.

Jedeikin R, Makela SK, Shennan AT, et al. Creatine kinase isoenzymes in serum from cord blood and the blood of healthy full-term infants during the first three postnatal days. *Clin Chem*. 1982;28:317–322.

Kaplan EL, Rothermel CD, Johnson DR. Antistreptolysin O and antideoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. *Pediatrics*. 1998;101:86–88.

Knight JA, Haymond RE. γ-Glutamyltransferase and alkaline phosphatase activities compared in serum of normal children and children with liver disease. *Clin Chem*. 1981;27:48–51.

Lockitch G, Halstead AC, Albersheim S, et al. Age- and sex-specific pediatric reference intervals for biochemistry analytes as measured with the Ektachem-700 analyzer. *Clin Chem*. 1988;34:1622–1625.

Lockitch G, Halstead AC, Quigley G, et al. Age- and sex-specific pediatric reference intervals: study design and methods illustrated by measurement of serum proteins with the Behring LN nephelometer. *Clin Chem*. 1988;34:1618–1621.

Lockitch G, Halstead AC, Wadsworth L, et al. Age- and sex-specific pediatric reference intervals and correlations for zinc, copper, selenium, iron, vitamins A and E, and related proteins. *Clin Chem*. 1988;34:1625–1628.

Meites S, ed. *Pediatric Clinical Chemistry, Reference (normal) Values*. 3rd ed. Washington, DC: American Association for Clinical Chemistry; 1989.

Muntau A, Streiter M, Kappler M, et al. Age-related reference values for serum selenium concentrations in infants and children. *Clin Chem*. 2002;48:555–560.

Nichols I. Diagnostics. San Juan Capistrano, CA 92675.

Nir A, Bar-Oz B, Perles Z, et al. N-terminal pro-B-type natriuretic peptide: reference plasma levels from birth to adolescence: elevated levels at birth and in infants and children with heart diseases. *Acta Paediatr*. 2004;93:603–607.

Pianosi P, Seargeant L, Haworth JC. Blood lactate and pyruvate concentrations, and their ratio during exercise in healthy children: developmental perspective. *Eur J Appl Physiol Occup Physiol*. 1995;71:518–522.

Rosenthal P, Pesce MA. Long-term monitoring of d-lactic acidosis in a child. *J Pediatr Gastroenterol Nutr*. 1985;4:674–676. 1985.

Sherry B, Jack RM, Weber A, et al. Reference interval for prealbumin for children 2 to 36 months old. *Clin Chem*. 1988;34:1878–1880.

Soldin SJ, Morse AS. Pediatric reference ranges for albumin and total protein in children <1 year old using the Vitros 500 analyzer. *Clin Chem*. 1998;44:A15.

Soldin SJ, Savwoir TV, Guo Y. Pediatric reference ranges for alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase in children less than 1 year old on the Vitros 500. *Clin Chem*. 1997;43:S199.

Soldin SJ, Brugnara C, Wong ED, eds. *Pediatric Reference Intervals*. 5th ed. Washington, DC: American Association for Clinical Chemistry; 2005.

Soldin O, Bierbower L, Choi J, et al. Serum iron, ferritin, transferrin, total iron binding capacity, hs-CRP, LDL cholesterol and magnesium in children: new reference intervals using the Dade Dimension Clinical Chemistry System. *Clin Chim Acta*. 2004;342:211–217.

Soldin SJ, Hicks JM, Bailey J, et al. Pediatric reference ranges for 25-hydroxy vitamin D during the summer and winter. *Clin Chem*. 1997;43:S200.